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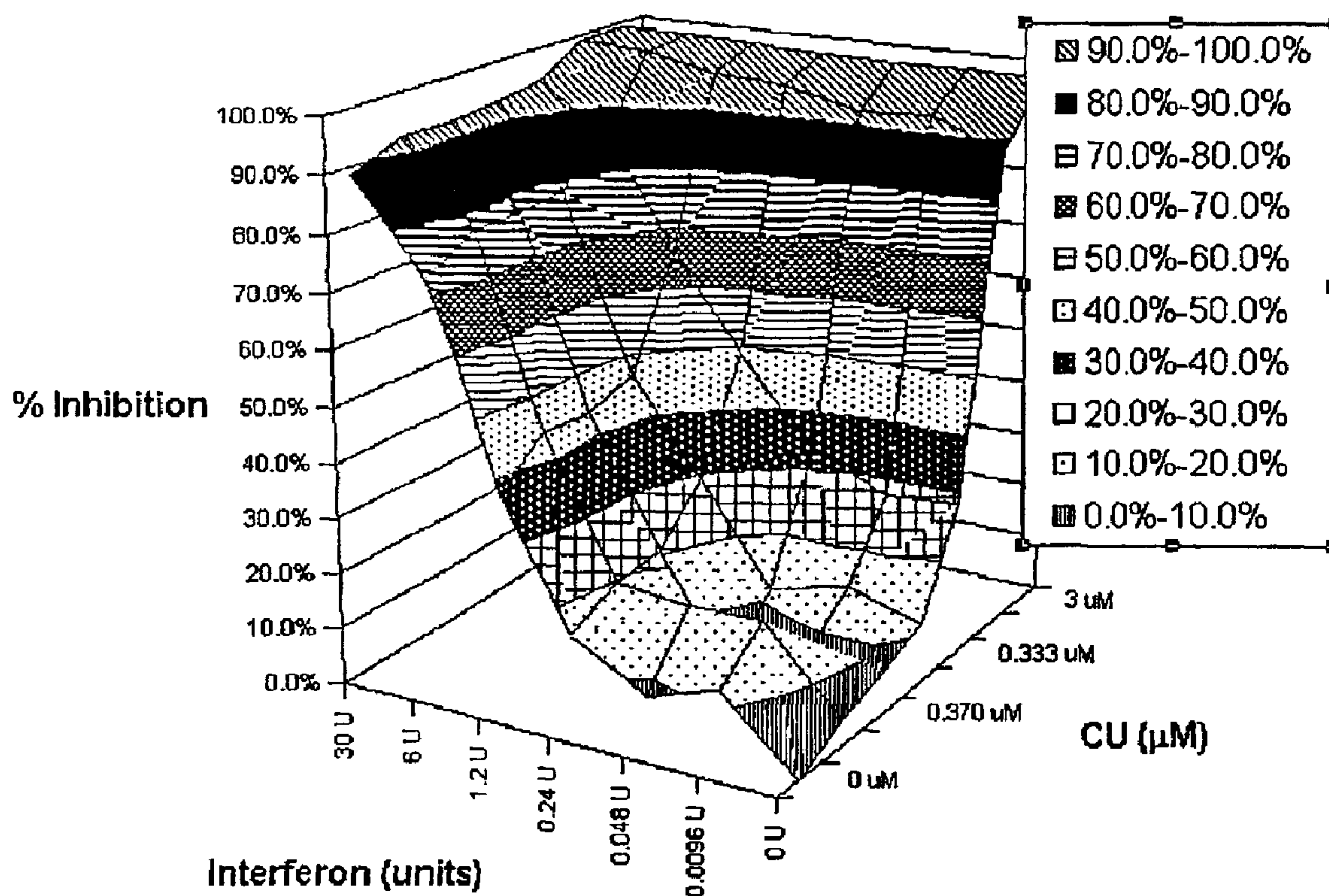
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(54) Titre : INHIBITEURS PEPTIDOMIMETIQUES DE PROTEASE

(54) Title: PEPTIDOMIMETIC PROTEASE INHIBITORS

Combination treatment with Interferon alpha-2B and Compound CU



(57) Abrégé/Abstract:

The present invention relates to peptidomimetic compounds useful as protease inhibitors (1), particularly as serine protease inhibitors and more particularly as hepatitis C NS3 protease inhibitors; intermediates thereto; their preparation including novel

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(57) **Abrégé(suite)/Abstract(continued)**:

stereoselective processes to intermediates. The invention is also directed to pharmaceutical compositions and to methods for using the compounds for inhibiting HCV protease or treating a patient suffering from an HCV infection or physiological condition related to the infection. Also provided are pharmaceutical combinations comprising, in addition to one or more HCV serine protease inhibitors, one or more interferons exhibiting anti-HCV activity and/or one or more compounds having anti HCV activity and a pharmaceutically acceptable carrier, and methods for treating or preventing a HCV infection in a patient using the compositions. The present invention is also directed to a kit or pharmaceutical pack for treating or preventing HCV infection in a patient.

ABSTRACT

The present invention relates to peptidomimetic compounds useful as protease inhibitors (1), particularly as serine protease inhibitors and more particularly as hepatitis C NS3 protease inhibitors; intermediates thereto; their preparation including novel stereoselective processes to intermediates. The invention is also directed to pharmaceutical compositions and to methods for using the compounds for inhibiting HCV protease or treating a patient suffering from an HCV infection or physiological condition related to the infection. Also provided are pharmaceutical combinations comprising, in addition to one or more HCV serine protease inhibitors, one or more interferons exhibiting anti-HCV activity and/or one or more compounds having anti HCV activity and a pharmaceutically acceptable carrier, and methods for treating or preventing a HCV infection in a patient using the compositions. The present invention is also directed to a kit or pharmaceutical pack for treating or preventing HCV infection in a patient.

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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THIS IS VOLUME __1__ OF __2__

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Peptidomimetic Protease Inhibitors

This invention is directed to peptidomimetic compounds and intermediates thereto, their preparation including stereoselective synthetic processes to intermediates, pharmaceutical compositions containing the peptidomimetic compounds, and the use of the peptidomimetic compounds or compositions thereof as protease inhibitors, particularly as serine protease inhibitors, and more particularly as hepatitis C virus ("HCV") NS3 protease inhibitors. The peptidomimetic compounds, as HCV NS3 protease inhibitors, are particularly useful in interfering with the life cycle of the hepatitis C virus and in treating or preventing an HCV infection or physiological conditions associated therewith. The present invention is also directed to methods of combination therapy for inhibiting HCV replication in cells, or for treating or preventing an HCV infection in patients using the peptidomimetic compounds or pharmaceutical compositions, or kits and pharmaceutical packs therefor. According to the present invention included as pharmaceutical compositions are those comprising an inhibitor of HCV serine protease in combination with an interferon having anti-HCV activity; an inhibitor of HCV serine protease in combination with a compound, other than an interferon, having anti-HCV activity; or an inhibitor of HCV serine protease in combination with both an interferon having anti-HCV activity and a compound, other than an interferon, having anti-HCV activity. Further the present invention is directed to stereoselective methods for preparing chiral bicycloproline intermediates useful in the synthesis of the peptidomimetic compounds.

Background of the Invention

Infection by the HCV is a compelling human medical problem and is now recognized as the causative agent for most cases of non-A, non-B hepatitis.

The HCV is thought to infect chronically 3% of the world's population [A. Alberti et al., "Natural History of Hepatitis C," *J. Hepatology*, **31**, (Suppl. 1), 17-24 (1999)]. In the United States alone the infection rate is 1.8% or 3.9 million people [M.J. Alter, "Hepatitis C Virus Infection in the United States," *J. Hepatology*, **31**, (Suppl. 1), 88-91 (1999)]. Of all patients infected over 70% develop a chronic infection that is believed to be a major cause of cirrhosis and hepatocellular carcinoma. [D. Lavanchy, "Global Surveillance and Control of Hepatitis C," *J. Viral Hepatitis*, **6**, 35-47 (1999)]

The replication of the HCV encompasses genomic encoding a polyprotein of 3010-3033 amino acids [Q.-L. Choo, et al., "Genetic Organization and Diversity of the Hepatitis C Virus", *Proc. Natl. Acad. Sci. USA*, **88**, 2451-2455 (1991); N. Kato et al., "Molecular Cloning of the

Human Hepatitis C Virus Genome From Japanese Patients with Non-A, Non-B Hepatitis", Proc. Natl. Acad. Sci. USA, 87, 9524-9528 (1990); A. Takamizawa et al., "Structure and Organization of the Hepatitis C Virus Genome Isolated From Human Carriers", J. Virol., 65, 1105-1113 (1991)]. The HCV nonstructural (NS) proteins are presumed to provide the essential catalytic machinery for viral replication. The NS proteins are derived by proteolytic cleavage of the polyprotein [R. Bartenschlager et al., "Nonstructural Protein 3 of the Hepatitis C Virus Encodes a Serine-Type Proteinase Required for Cleavage at the NS3/4 and NS4/5 Junctions", J. Virol., 67, 3835-3844 (1993); A. Grakoui et al. "Characterization of the Hepatitis C Virus-Encoded Serine Proteinase: Determination of Proteinase-Dependent Polyprotein Cleavage Sites", J. Virol., 67, 2832-2843 (1993); A. Grakoui et al., Expression and Identification of Hepatitis C Virus Polyprotein Cleavage Products", J. Virol., 67, 1385-1395 (1993); L. Tomei et al., "NS3 is a serine protease required for processing of hepatitis C virus polyprotein", J. Virol., 67, 4017-4026 (1993)]. In fact, it is the first 181 amino acids of NS3 (residues 1027-1207 of the viral polyprotein) have been shown to contain the serine protease domain of NS3 that processes all four downstream sites of the HCV polyprotein [C. Lin et al., "Hepatitis C Virus NS3 Serine Proteinase: *Trans*-Cleavage Requirements and Processing Kinetics", J. Virol., 68, 8147-8157 (1994)].

The HCV NS protein 3 (NS3) contains a serine protease activity that helps in the processing of the majority of the viral enzymes, and thus is considered essential for viral replication and infectivity. The essentiality of the NS3 protease was inferred from the fact that mutations in the yellow fever virus NS3 protease decreases viral infectivity [T.J. Chambers et al., "Evidence that the N-terminal Domain of Nonstructural Protein NS3 From Yellow Fever Virus is a Serine Protease Responsible for Site-Specific Cleavages in the Viral Polyprotein", Proc. Natl. Acad. Sci. USA, 87, 8898-8902 (1990)]. More recently, it was demonstrated that mutations at the active site of the HCV NS3 protease could completely abolish the HCV infection in a chimpanzee model [C.M. Rice et al. "Hepatitis C virus-encoded enzymatic activities and conserved RNA elements in the 3'-nontranslated region are essential for virus replication in vivo." J. Virol., 74(4) 2046-51 (2000)]. The HCV NS3 serine protease is also considered essential for viral replication as it and its associated cofactor, NS4A, help in the processing of all of the viral enzymes. This processing appears to be analogous to that carried out by the human immunodeficiency virus ("HIV") aspartyl protease. In addition, the demonstrated use of HIV protease inhibitors as potent antiviral agents in man demonstrates that interrupting a protease protein processing stage in the viral life cycle does result in therapeutically active agents. Consequently, the protease enzyme is an attractive target for drug discovery.

Several potential HCV protease inhibitors have been described. PCT Publications Numbers WO 00/09558, WO 00/09543, WO 99/64442, WO 99/07733, WO 99/07734, WO 99/50230, WO98/46630, WO 98/17679 and WO 97/43310, United States Patent No. 5,990,276, M. Llinás-Brunet et al., Bioorg. Med. Chem. Lett., 8, 1713-1718 (1998), W. Han et al., Bioorg. Med. Chem. Lett., 10, 711-713 (2000), R. Dunsdon et al., Bioorg. Med. Chem. Lett., 10, 1571-1579 (2000), M. Llinás-Brunet et al., Bioorg. Med. Chem. Lett., 10, 2267-2270 (2000), and S. LaPlante et al., Bioorg. Med. Chem. Lett., 10, 2271-2274 (2000) each describe potential HCV NS3 protease inhibitors. Unfortunately, there are no serine protease inhibitors available currently as anti-HCV agents.

In fact, there are no anti-HCV therapies except interferon- α , interferon- α /ribavirin combination and more recently pegylated inteferon- α . The sustained response rates for the interferon- α therapies and interferon- α /ribavirin however tend to be low (<50%) and the side effects exhibited by the therapies tend to be significant and severe [M.A. Walker, "Hepatitis C Virus: an Overview of Current Approaches and Progress," DDT, 4, 518-529 (1999); D. Moradpour et al., "Current and Evolving Therapies for Hepatitis C," Eur. J. Gastroenterol. Hepatol., 11, 1199-1202 (1999); H.L.A. Janssen et al., "Suicide Associated with Alfa-Interferon Therapy for Chronic Viral Hepatitis," J. Hepatol., 21, 241-243 (1994); and P.F. Renault et al., "Side effects of alpha interferon", Seminars in Liver Disease 9, 273-277, (1989)]. Furthermore, the interferon therapies only induce long term remission in only a fraction (~ 25%) of cases [O. Weiland, "Interferon Therapy in Chronic Hepatitis C Virus Infection", FEMS Microbiol. Rev., 14, 279-288 (1994)]. The aforesaid problems with the interferon- α therapies has even led to the development and clinical study of pegylated derivatized interferon- α compounds as improved anti-HCV therapeutics.

In view of the current situation regarding anti-HCV therapeutics, it is clear that there is a need for more effective and better tolerated therapies.

Furthermore, synthesis of complex peptidomimetic compounds has long been hampered by the nonstereoselective nature of most synthetic organic processes. It is well known that the therapeutic activity of enantiomers of peptidomimetic compounds varies widely. It is therefore of great benefit to provide such stereospecific synthetic processes.

Previous attempts to synthesize chirally specific bicycloprolinate intermediates, useful in the synthesis of the present therapeutic peptidomimetic protease inhibitors have suffered from being non enantioselective, or diastereoselective, or long encompassing synthetic pathways, or being unsuitable for preparing large quantities of product. Thus, there is also a need for a means of

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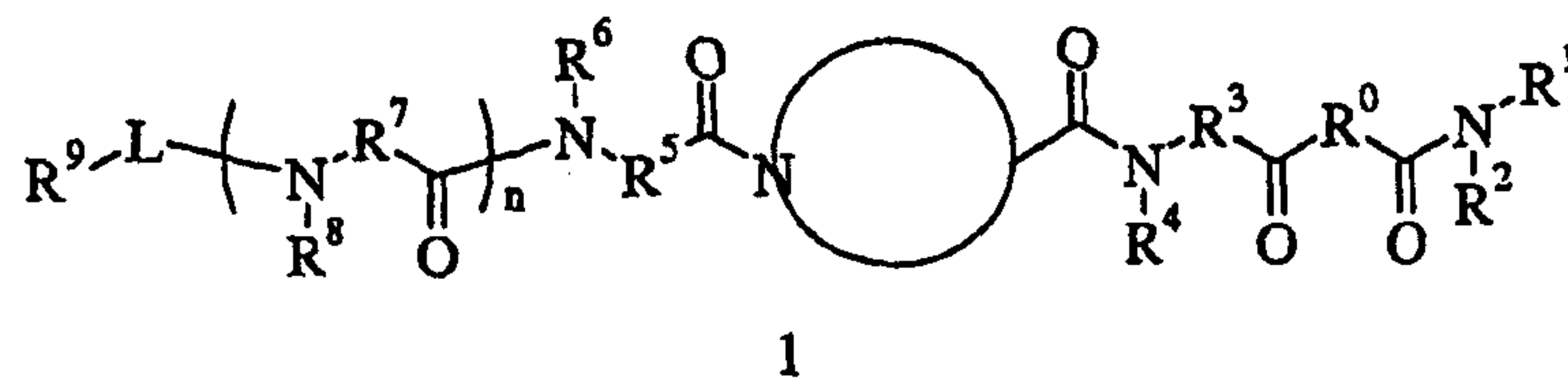
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preparing large quantities of bicycloprolinates in a diastereoselective manner and enantiomerically enriched form.

Summary of the Invention

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The present invention relates to a peptidomimetic compound of formula 1



wherein:

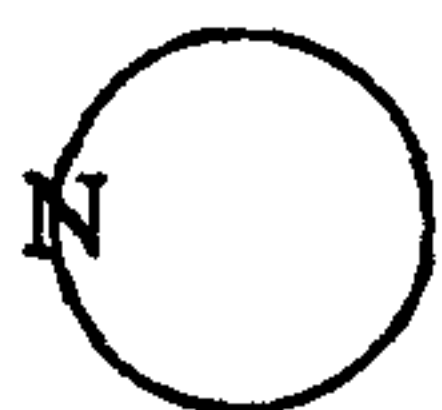
R^0 is a bond or difluoromethylene;

10 R^1 is hydrogen, optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group;

R^2 and R^9 are each independently optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group;

15 R^3 , R^5 and R^7 are each independently (optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group)(optionally substituted methylene or optionally substituted ethylene), optionally substituted (1,1- or 1,2-)cycloalkylene or optionally substituted (1,1- or 1,2-)heterocyclylene;

R^4 , R^6 , R^8 and R^{10} are each independently hydrogen or optionally substituted aliphatic group;



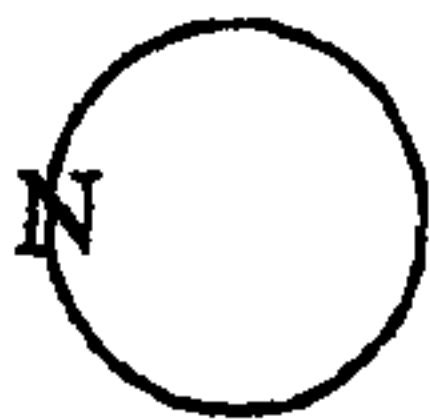
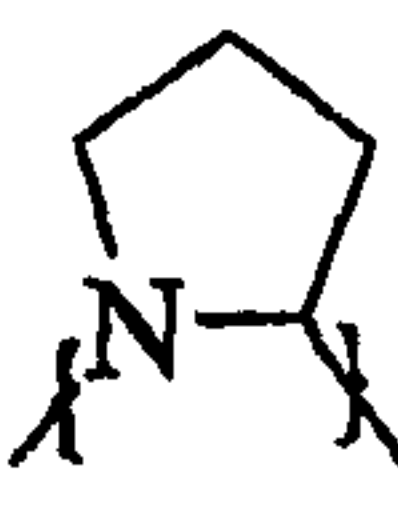
20 is substituted monocyclic azaheterocyclyl or optionally substituted multicyclic azaheterocyclyl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturation is in the ring distal to the ring bearing the R^9 -L-(N(R^8)- R^7 -C(O)-) $_n$ N(R^6)- R^5 -C(O)-N moiety and to which the -C(O)-N(R^4)- R^3 -C(O)C(O)NR ^{2} R ^{1} moiety is attached;

L is -C(O)-, -OC(O)-, -NR ^{10} C(O)-, -S(O) $_2$ -, or -NR ^{10} S(O) $_2$ -; and

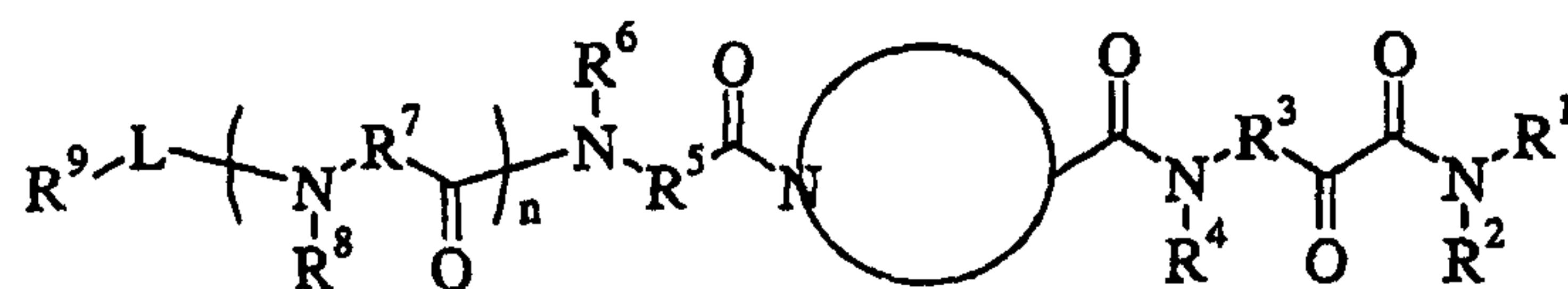
n is 0 or 1, or

25 a pharmaceutically acceptable salt or prodrug thereof, or a solvate of such a compound, its salt or its prodrug,

provided

when  is substituted , then L is $-\text{OC}(\text{O})-$ and R^9 is optionally substituted aliphatic, or at least one of R^3 , R^5 and R^7 is (optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group)(optionally substituted ethanediyl), or R^4 is optionally substituted aliphatic.

5 This inventions also provides a compound having the structural formula:



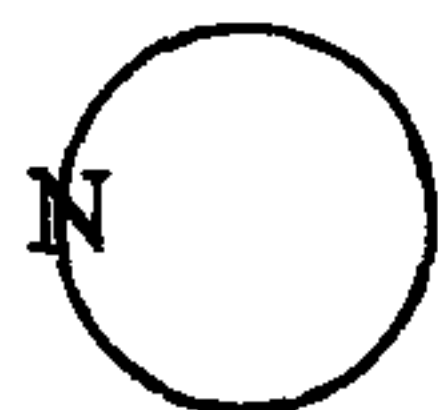
wherein:

R^1 is hydrogen, optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group;

10 R^2 and R^9 are each independently optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group;

R^3 , R^5 and R^7 are each independently (optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group)(optionally substituted methanediyl or optionally substituted ethanediyl);

15 R^4 , R^6 , R^8 and R^{10} are each independently is hydrogen or optionally substituted aliphatic group;



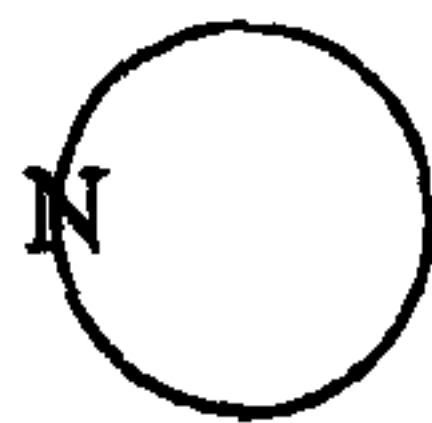
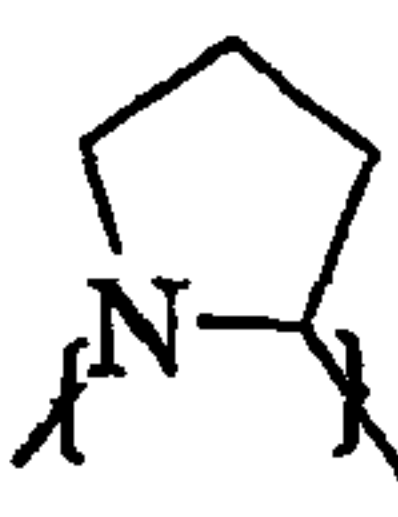
is substituted monocyclic azaheterocyclyl or optionally substituted multicyclic azaheterocyclyl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturation is in the ring distal to the ring bearing the $\text{R}^9\text{-L-(N(R}^8\text{)-R}^7\text{-C(O)-)}_n\text{N(R}^6\text{)-R}^5\text{-C(O)-N}$ moiety and to which the $-\text{C(O)-N(R}^4\text{)-R}^3\text{-C(O)C(O)NR}^2\text{R}^1$ moiety is attached;

20 L is $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{NR}^{10}\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, or $-\text{NR}^{10}\text{S}(\text{O})_2-$; and

n is 0 or 1, or

a pharmaceutically acceptable salt or prodrug thereof, or a solvate of such a compound, its salt or its prodrug,

provided

25 when  is substituted , then L is $-\text{OC}(\text{O})-$ and R^9 is optionally substituted aliphatic, or at least one of R^3 , R^5 and R^7 is (optionally substituted aliphatic group, optionally

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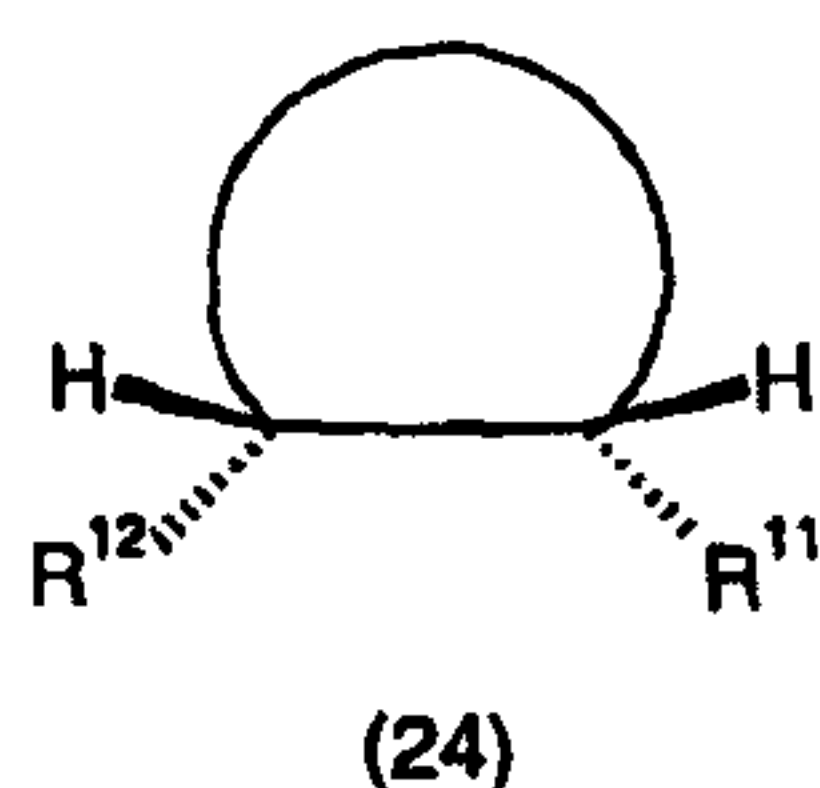
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substituted cyclic group or optionally substituted aromatic group)(optionally substituted ethanediyl), or R^4 is optionally substituted aliphatic.

The invention is also directed to a pharmaceutical composition comprising a compound of formula 1, and method for using the compound of formula 1 for inhibiting HCV protease, or
5 treating or preventing an HCV infection in patients or physiological condition related to the infection.

The invention is also directed to a stereoselective process for preparing a chiral bicycloprolinate compound that is an intermediate useful in preparing a compound of formula 1. The synthetic process comprises the steps of:

10 (a) cleaving and cyclizing a compound of formula 24



wherein:



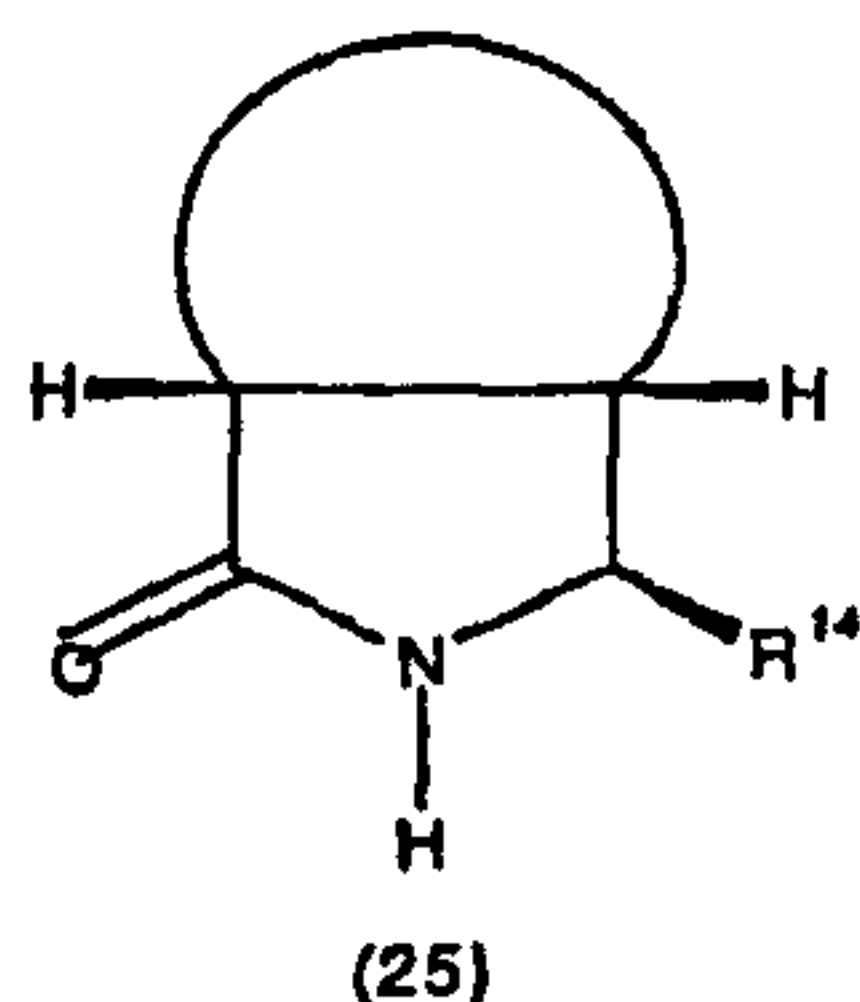
is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

15 R^{11} is $-\text{CO}_2R^{13}$;

R^{12} is an iminic glycinimide adduct;

R^{13} is acid protecting group or optionally substituted aliphatic group;

under cleaving and cyclizing conditions to form a compound of formula 25



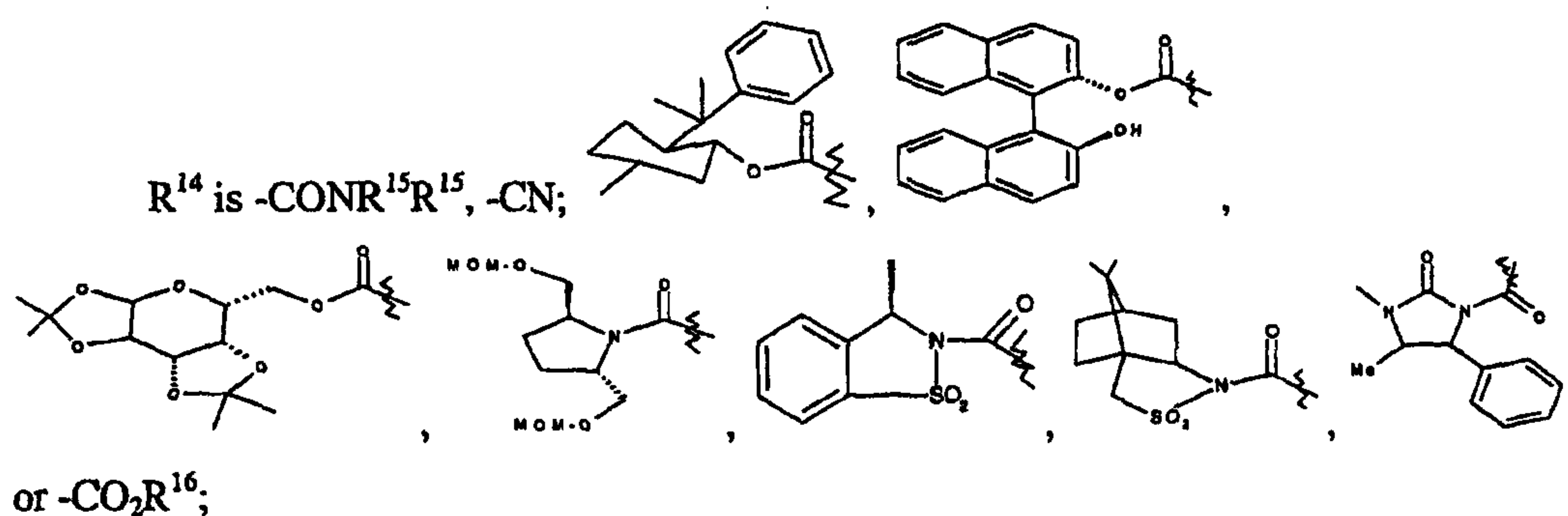
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wherein:

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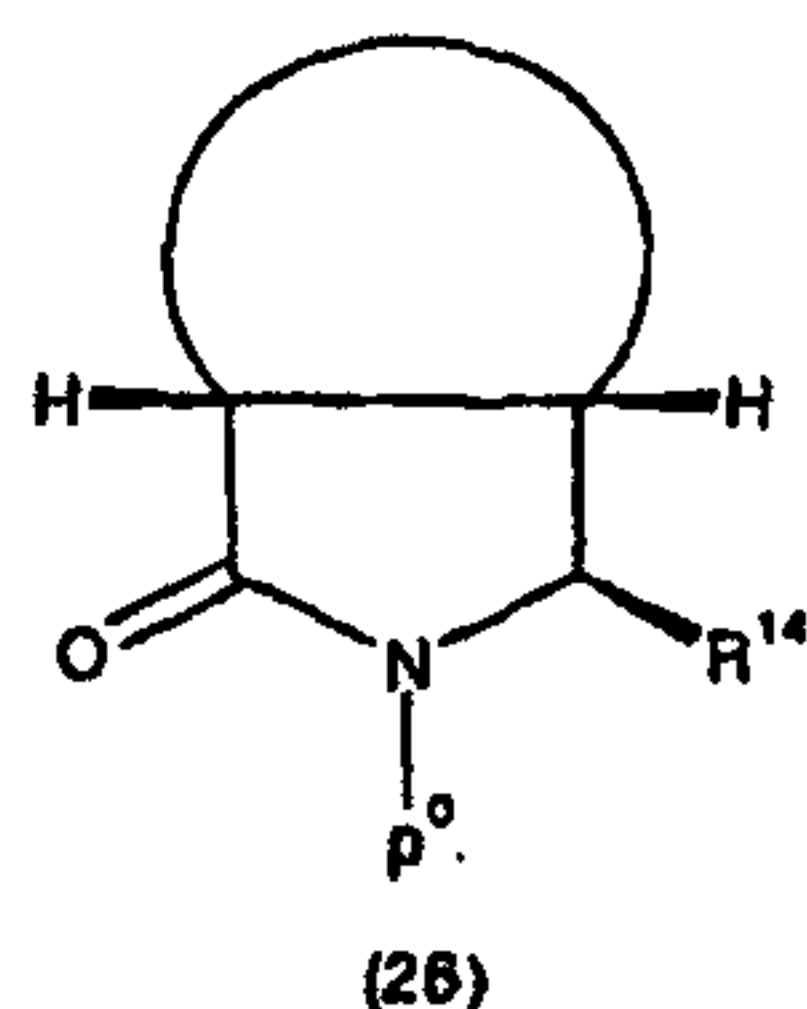
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R^{15} is optionally substituted aliphatic group;

5 R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group; and

(b) protecting the nitrogen of the lactam moiety in the compound of formula 25 with an amide protecting group to form a compound of formula 26

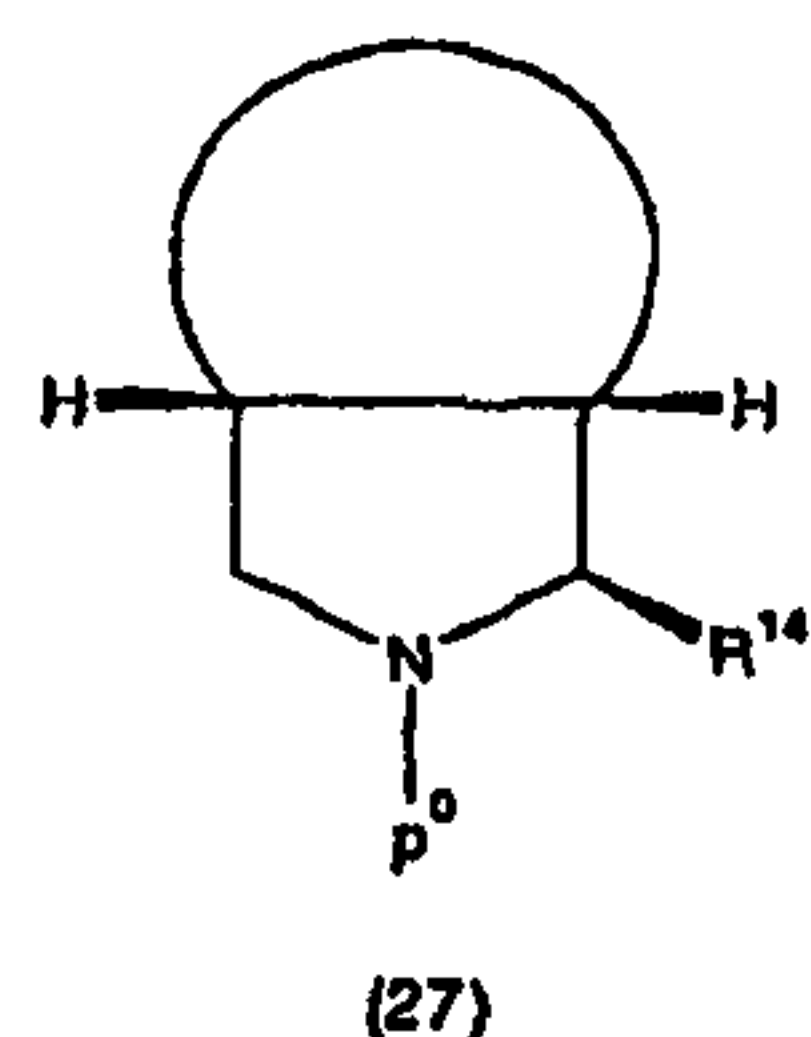


10 wherein:

p^O is amide protecting group;

R^{14} is as described herein; and

(c) reducing the compound of formula 26 under reducing conditions to form a compound of formula 27



15

wherein:

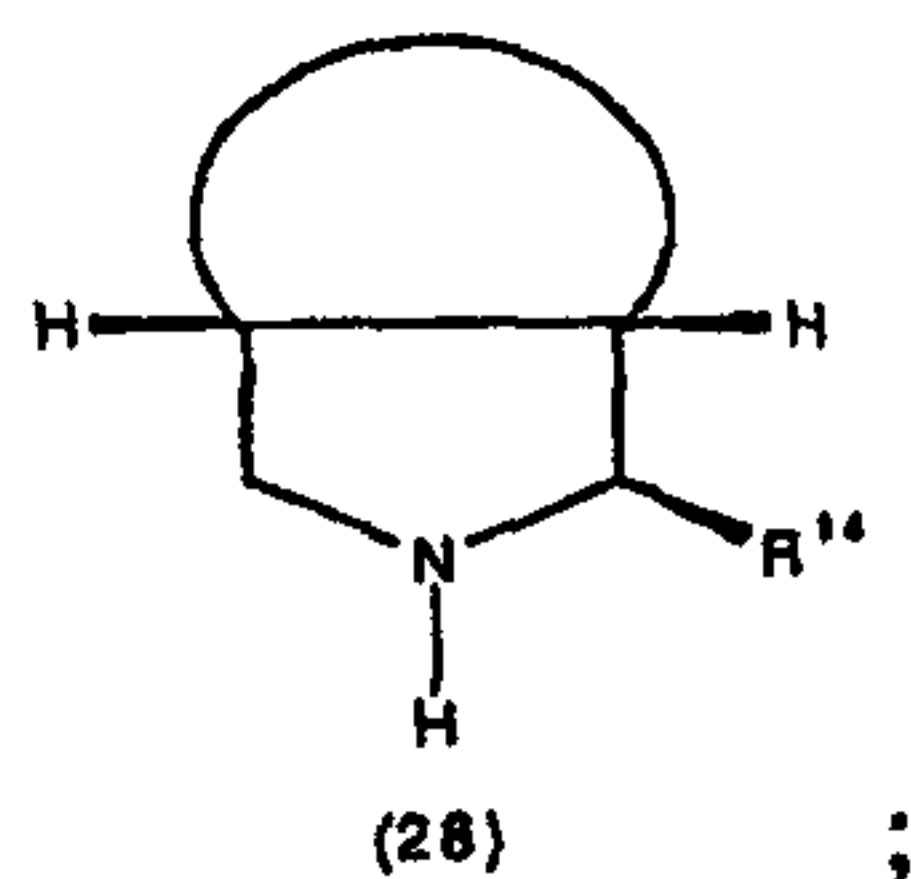
p^O and R^{14} are as described herein; and

(d) deprotecting the compound of formula 27 under deprotecting conditions to form a compound of formula 28

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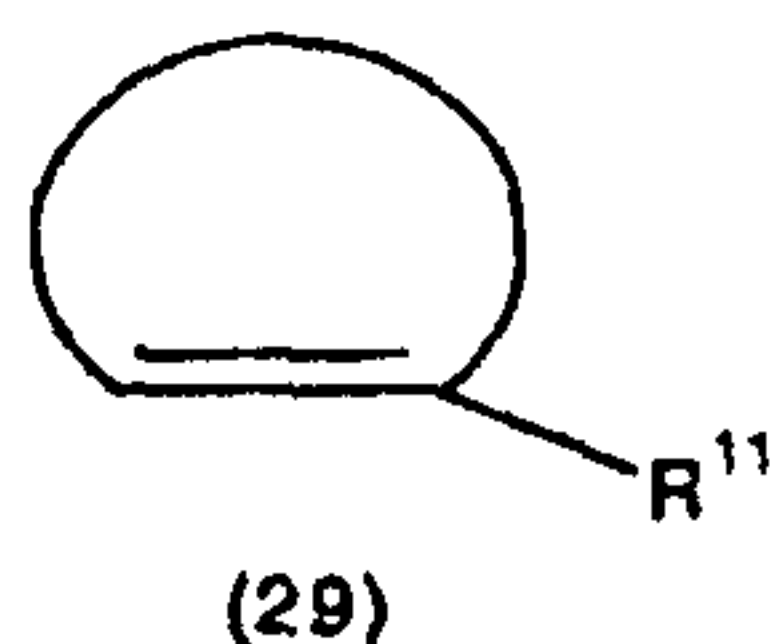
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wherein:

 R^{14} is as described herein.

The invention is also directed to the above synthetic process further comprising the step
 5 wherein the compound of formula 24 is prepared by effecting a Michael addition with an iminic
 glycinimide compound on a compound of formula 29



wherein:



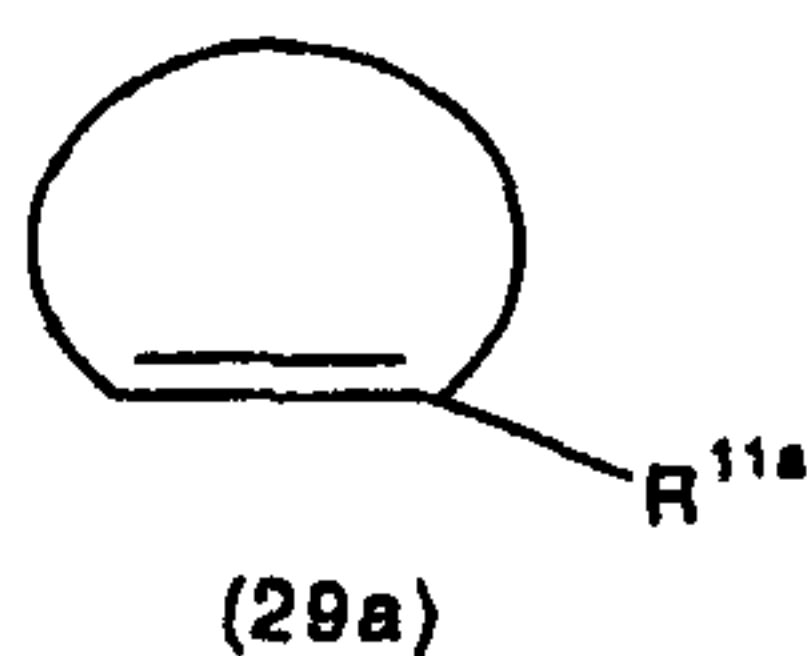
is optionally substituted cycloalkenyl or optionally substituted fused

10 arylcycloalkenyl;

 R^{11} is $-\text{CO}_2\text{R}^{13}$;

wherein:

the compound of formula 29 may be prepared by esterifying a compound of formula 29a



15

wherein:



is optionally substituted cycloalkenyl or optionally substituted fused

arylcyloalkenyl;

 R^{11a} is $-\text{CHO}$, $-\text{COR}^{15}$, $-\text{C}\equiv\text{N}$, or $-\text{CONR}^{15}\text{R}^{15}$; and R^{15} is as described herein.

20

Notably, one skilled in the art would know that conversion of ketones to esters may be
 accomplished, for example, by a Bayer-Villiger reaction. Conversion of nitriles and amides to
 esters may be accomplished, for example, by aqueous hydrolysis followed by further

esterification. Conversion of aldehydes to esters may be accomplished, for example, by oxidation of the aldehyde followed by esterification.

Another aspect of the invention is a compound of formula 1 wherein the substituents are selected from a combination of preferred or particular embodiments as defined herein.

5 Another aspect of the invention is a compound of formulae 24-29 wherein the substituents are selected from a combination of preferred or particular embodiments as defined herein.

Another aspect of the invention are pharmaceutical compositions comprising, in addition to one or more HCV serine protease inhibitors, one or more interferons or compounds that induce the production of interferons that exhibit anti-HCV activity and/or one or more compounds
10 having anti HCV activity, including immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity, and a pharmaceutically acceptable carrier.

Another aspect of the invention are methods of treating or preventing a HCV infection in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a combination of one or more HCV serine protease inhibitors; one or more interferons
15 or compounds that induce the production of an inteferon that exhibit anti-HCV activity; and/or one or more compounds having anti-HCV activity, including immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity.

The invention is also directed to the use of one or more HCV serine protease inhibitors in combination with one or more interferons or compounds that induce the production of an
20 inteferon that exhibit anti-HCV activity and/or one or more compounds having anti-HCV activity, including immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity, to prepare a medicament for treating or preventing a HCV infection in a patient in need thereof.

The present invention is also directed to a kit or pharmaceutical pack for treating or
25 preventing HCV infection in a patient, wherein the kit or pharmaceutical pack comprises a plurality of separate containers, wherein at least one of said containers contains one or more HCV serine protease inhibitors (alone or in combination with a pharmaceutically acceptable carrier or diluent), at least another of said containers contains one or more interferons or compounds that induce the production of an inteferon that exhibit anti-HCV activity, (alone or in combination
30 with a pharmaceutically acceptable carrier or diluent) and, optionally, at least another of said containers contains one or more compounds having anti-HCV activity (alone or in combination with a pharmaceutically acceptable carrier or diluent), including immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity.

The amount of the HCV serine protease inhibitor(s), interferon(s), or anti-HCV
35 compound(s) in any of the foregoing applications can be a pharmaceutically effective amount, a

subclinical anti-HCV effective amount, or combinations thereof, so long as the final combination of HCV serine protease inhibitor(s), interferon(s), or compounds that induce the production of an interferon that exhibit anti-HCV activity, and/or anti-HCV compound(s) comprises a pharmaceutically effective amount of compounds that is effective in treating or preventing HCV infection in a patient.

Brief Description of the Drawings

The above and other aspects, features, and advantages of the present invention will be better understood from the following detailed description taken in conjunction with the accompanying drawings, all of which are given by way of illustration only, and are not limitative of the present invention, in which:

Figure 1 shows the inhibition of HCV replicon RNA accumulation after 48 hour treatment of replicon-containing cells with Compound CU and interferon-alpha 2B, individually or in combination.

Figure 2 graphically shows the isobol concavity exhibited by compounds used in combination that are antagonistic, additive, and synergistic according to the synergy calculation methods of Greco, Park and Rustom ((1990) Application of a New Approach for the Quantitation of Drug Synergism to the Combination of cis-Diamminedichloroplatinum and 1-β-D-Arabinofuranosylcytosine, *Cancer Research*, 50, 5318-5327).

Figure 3 shows the geometric relationship between α and the amount of curvature in the isobol. A hypothetical isobol at the $E = 50\%$ effect level is displayed with a straight line isobol that would be expected under additivity. M is the point of intersection of the line $y = x$ and the hypothetical isobol. N is the point of intersection of the line $y = x$ and the straight line isobol. O is the origin (0,0). S gives a measure of the amount of curvature in the isobol, where $S = ON/OM$. ON is the distance from O to N and OM is the distance from O to M. The parameter α is related to S by the equation $\alpha = 4(S^2 - S)$.

Figure 4 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound CU and interferon alpha-2B (Schering-Plough) using 6 dilutions of each compound in Experiment 1

Figure 5 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound CU and interferon alpha-2A using 6 dilutions of each compound in Experiment 2.

Figure 6 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound CU and interferon alpha-2B (Schering-Plough) using 8 dilutions of each compound in Experiment 3.

5 Figure 7 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound CU and interferon alpha-2A using 8 dilutions of each compound in Experiment 4.

Figure 8 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound CU and ovine interferon tau using 8 dilutions of each compound in Experiment 5.

10 Figure 9 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound EC and interferon alpha-2B (Schering-Plough) using 8 dilutions of each compound in Experiment 6.

Figure 10 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound EC and interferon alpha-2A using 8 dilutions of each compound in
15 Experiment 7.

Figure 11 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of compound CU and interferon beta using 8 dilutions of each compound in Experiment 8.

Figure 12 shows the isobol calculations using the method of Greco et al., *supra*, for the
20 combination of compound EP and interferon alpha-2B (Schering-Plough) using 8 dilutions of each compound in Experiment 9.

Figure 13 shows the isobol calculations using the method of Greco et al., *supra*, for the combination of Ribavirin and interferon alpha-2B (Schering-Plough) using 8 dilutions of each compound in Experiment 10.

25 Figure 14 shows inhibition of HCV replicon RNA accumulation caused by treatment of replicon cells with either (A) Ribavirin alone or (B) interferon alpha-2B alone. In both panels, the measured inhibition as well as the inhibition corrected for cytotoxicity of the compounds is shown.

30 Detailed Description of the Invention

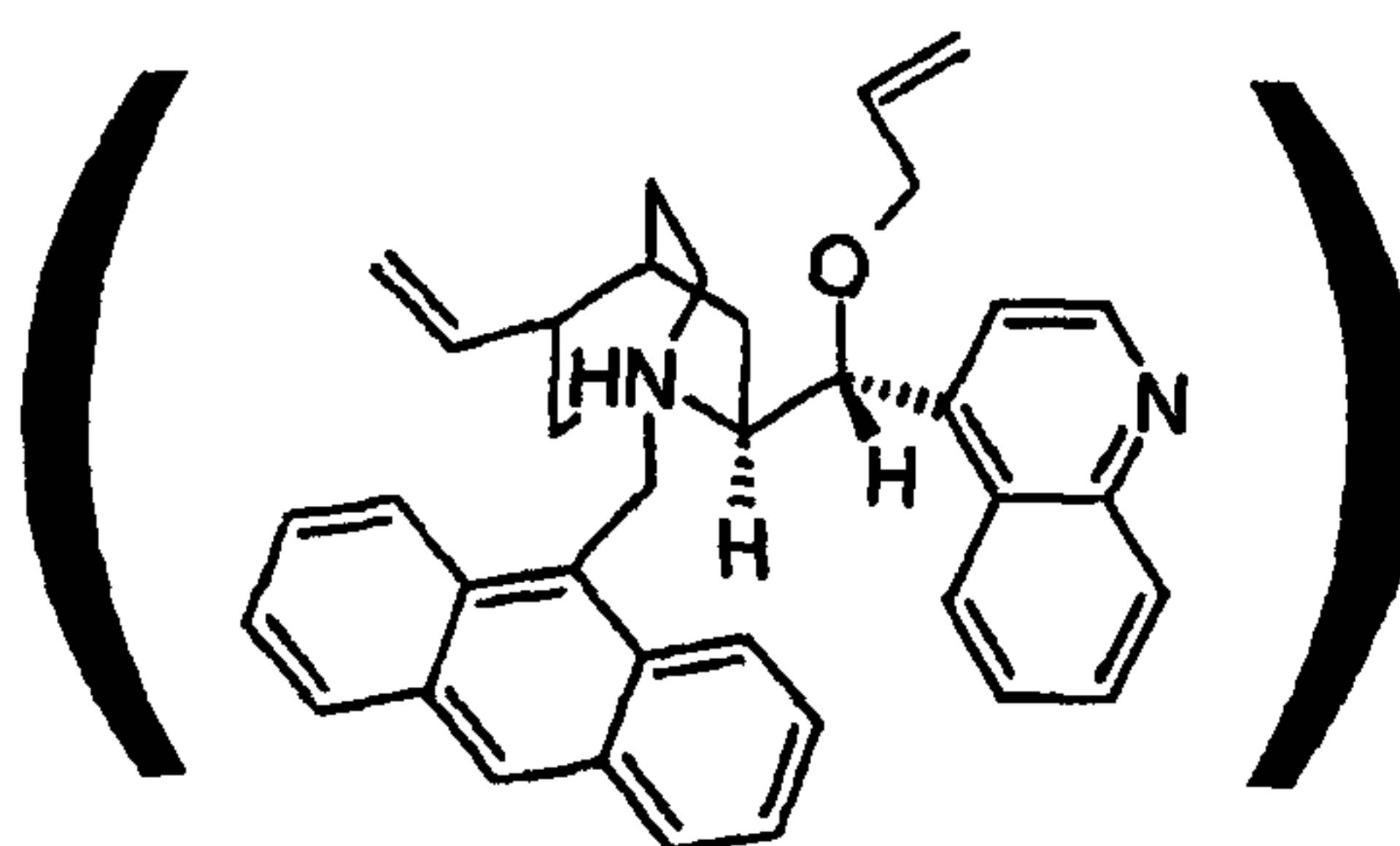
As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:-

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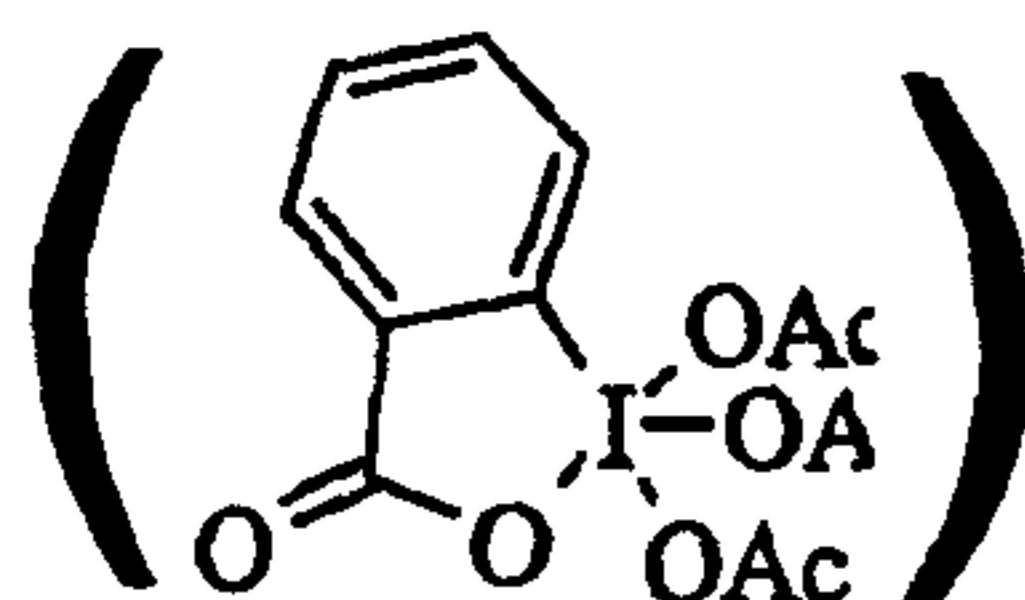
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	<u>Designation</u>	<u>Reagent or Fragment</u>
	ACN	acetonitrile
	AIBN	2,2'-azobisisobutyronitrile
5	BOC or Boc	<i>tert</i> -butyl carbamate
	BOP	benzotriazol-1-yl-oxytris (dimethylamino)phosphonium hexafluorophosphate
	n-Bu ₃ SnH	tri-n-butyltin hydride
	t-Bu	<i>tert</i> -butyl
10	Cbz	benzyl carbamate
	chiral PTC	chiral phase transfer catalyst



	DAST	(diethylamino)sulfur trifluoride (Et ₂ NSF ₃)
15	DCC	dicyclocarbodiimide
	DCM	dichloromethane (CH ₂ Cl ₂)
	DIBAL-H	Diisobutylaluminum hydride
	DIC	1,3-diisopropylcarbodiimide
	DIPEA	diisopropylethylamine
20	DMAP	4-(N,N-dimethylamino)pyridine
	DMP reagent	Dess-Martin Periodinane reagent

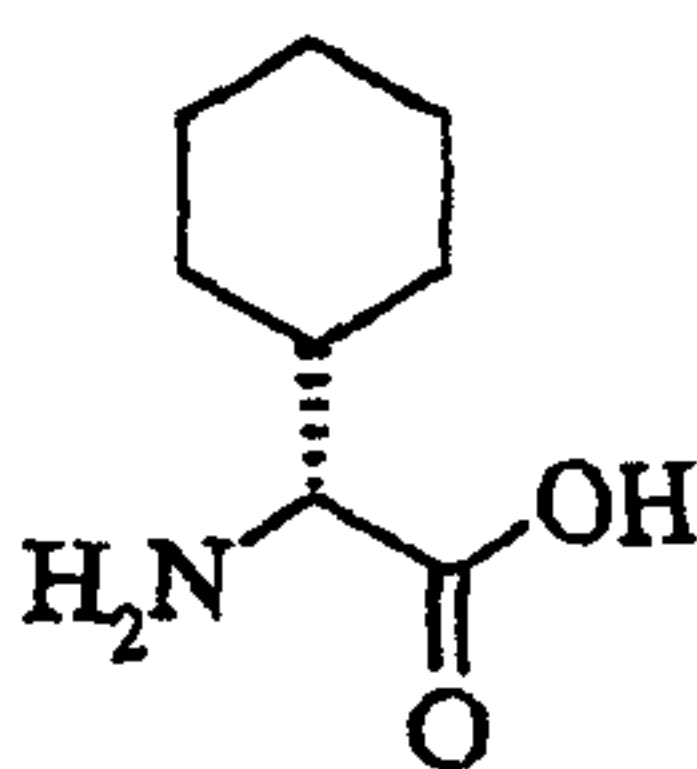


	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
25	EA	elemental analysis
	EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl

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	eq	equivalent(s)
	Et	ethyl
	Et ₂ O	diethyl ether
	EtOH	ethanol
5	EtOAc	ethyl acetate
	Et ₃ Si	triethylsilane
	Fmoc	9-fluorenylmethoxycarbonyl
		
	H-Chg-OH	
	HOAt	1-hydroxy-7-azabenzotriazole
10	HOBT	1-hydroxybenztriazole
	HOSu	N-hydroxysuccinamide
	HPLC	high performance liquid chromatography
	LAH	lithium aluminum anhydride
	Me	methyl
15	MeI	methyliodide
	MeOH	methanol
	MeOC(O)Cl	methyl chloroformate
	MOMCl	methoxymethylchloride
	MOM	methoxymethyl
20	MS	mass spectroscopy
	NaBH ₄	sodium borohydride
	Na ₂ C ₄ H ₄ O ₆	sodium tartrate
	NMP	N-methyl pyrrolidinone
	NMR	nuclear magnetic resonance
25	P-	Polymer bond
	PyBOP	benzotriazole-1-yl-oxytris-pyrrolidino-phosphonium hexafluorophosphate
	TBD	1,5,7-triazabicyclo[4.4.0]-dec-5-ene
	RP-HPLC	reverse phase – high pressure liquid chromatography
30	TBSCl	<i>tert</i> -butyldimethylsilyl chloride
	TCA	trichloroacetic acid

	TFA	trifluoroacetic acid
	Tf ₂ O	triflate anhydride
	THF	tetrahydrofuran
	THP	tetrahydropyran
5	TLC	thin layer chromatography

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Acid bioisostere" means a group which has chemical and physical similarities producing broadly similar biological properties to a carboxy group (see Lipinski, Annual Reports in Medicinal Chemistry, "Bioisosterism In Drug Design" 21, 283 (1986); Yun, Hwahak Sekye, "Application Of Bioisosterism To New Drug Design" 33, 576-579, (1993); Zhao, Huaxue Tongbao, "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design" 34-38, (1995); Graham, Theochem, "Theoretical Studies Applied To Drug Design:ab initio Electronic Distributions In Bioisosteres" 343, 105-109, (1995)). Exemplary acid bioisosteres include -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbonyl, tetrazolyl, arylsulphonylcarbonyl, N-methoxycarbonyl, heteroarylsulphonylcarbonyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl and the like.

"Acidic functional group" means a moiety bearing an acidic hydrogen. Exemplary acid functional groups include carboxyl (-C(O)OH), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbonyl, tetrazolyl, arylsulphonylcarbonyl, N-methoxycarbonyl, heteroarylsulphonylcarbonyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, imidazolyl, mercapto, and the like, and an appropriate hydroxy such as an aromatic hydroxy, e.g., hydroxyphenyl.

"Acid protecting group" means an easily removable group that is known in the art to protect an acidic hydrogen of a carboxyl group against undesirable reaction during synthetic procedures, e.g., to block or protect the acid functionality while the reactions involving other functional sites of the compound are carried out, and to be selectively removable. Such acid protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups, as described in U.S. Pat. No. 3,840,556 and 3,719,667.

For suitable acid protecting

groups, see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John

Wiley and Sons, 1991. Acid protecting group also includes hydrogenation labile acid protecting group as defined herein. Exemplary acid protecting groups include esters such as substituted and unsubstituted C₁-8 lower alkyl, e.g., methyl, ethyl, *t*-butyl, methoxymethyl, methylthiomethyl, 2,2,2-trichloroethyl and the like, tetrahydropyranyl, substituted and unsubstituted phenylalkyl such as benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like, cinnamyl, dialkylaminoalkyl, e.g., dimethylaminoethyl and the like, trimethylsilyl, substituted and unsubstituted amides and hydrazides, e.g., amides and hydrazides of N,N-dimethylamine, 7-nitroindole, hydrazine, N-phenylhydrazine and the like, acyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like, aroyloxyalkyl such as benzoyloxyethyl and the like, alkoxycarbonylalkyl such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl and the like, alkoxycarbonyloxyalkyl such as *t*-butyloxycarbonyloxymethyl and the like, alkoxycarbonylaminoalkyl such as *t*-butyloxycarbonylaminomethyl and the like, alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like, acylaminoalkyl such as acetylaminomethyl and the like, heterocyclylcarbonyloxyalkyl such as 4-methylpiperazinyl-carbonyloxymethyl and the like, dialkylaminocarbonylalkyl such as dimethylaminocarbonyl-methyl and the like, (5-(lower alkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl such as (5-*t*-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like, and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

“Acid labile amine protecting group” means an amine protecting group as defined herein which is readily removed by treatment with acid while remaining relatively stable to other reagents. A preferred acid labile amine protecting group is BOC.

“Aliphatic” means alkyl, alkenyl or alkynyl as defined herein.

“Aliphatic group substituent(s)” mean substituents attached to an aliphatic group as defined herein inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio,

heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene ($H_2C=$), oxo ($O=$), thioxo ($S=$), Y^1Y^2N- , $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$, $Y^1Y^2NSO_2-$, or $Y^3SO_2NY^1-$ wherein R^2 is as defined herein, Y^1 and Y^2 are independently hydrogen, alkyl, aryl or heteroaryl, and Y^3 is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y^1Y^2N- , then one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$ or $Y^1Y^2NSO_2-$, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl. Acidic/amide aliphatic group substituents are carboxy (acid), $-C(O)-NHOH$, $-C(O)-CH_2OH$, $-C(O)-CH_2SH$, $-C(O)-NH-CN$, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl and Y^1Y^2NCO- . Non-acidic polar aliphatic group substituents are hydroxy, oxo ($O=$), thioxo ($S=$), acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, thiol, Y^1Y^2N- , $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$ or $Y^1Y^2NSO_2-$. Exemplary aliphatic groups bearing an aliphatic group substituent include methoxymethoxy, methoxyethoxy, ethoxyethoxy, (methoxy-, benzyloxy-, phenoxy-, or ethoxy-)carbonyl(methyl or ethyl), benzyloxycarbonyl, pyridylmethyloxy-carbonylmethyl, methoxyethyl, ethoxymethyl, *n*-butoxymethyl, cyclopentylmethyloxyethyl, phenoxypropyl, phenoxyallyl, trifluoromethyl, cyclopropyl-methyl, cyclopentylmethyl, carboxy(methyl or ethyl), 2-phenethenyl, benzyloxy, 1- or 2-naphthyl-methoxy, 4-pyridyl-methyloxy, benzyloxyethyl, 3-benzyloxyallyl, 4-pyridylmethyl-oxyethyl, 4-pyridylmethyl-oxyallyl, benzyl, 2-phenethyl, naphthylmethyl, styryl, 4-phenyl-1,3-pentadienyl, phenyl-propynyl, 3-phenylbut-2-ynyl, pyrid-3-ylacetylenyl and quinolin-3-ylacetylenyl, 4-pyridyl-ethynyl, 4-pyridylvinyl, thienylethenyl, pyridylethenyl, imidazolyl-ethenyl, pyrazinylethenyl, pyridylpentenyl, pyridylhexenyl and pyridylheptenyl, thienyl-methyl, pyridylmethyl, imidazolylmethyl, pyrazinylmethyl, tetrahydropyranylmethyl, tetrahydropyranyl-methyloxymethyl, and the like.

"Acyl" means an $H-CO-$ or (aliphatic or cyclyl)- $CO-$ group wherein the aliphatic group is as herein described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include

formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl, palmitoyl, acryloyl, propynoyl, cyclohexylcarbonyl, and the like.

"Alkenoyl" means an alkenyl-CO- group wherein alkenyl is as defined herein.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain that may be straight or branched. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, cyclohexylbutenyl, decenyl, and the like.. "Substituted alkenyl" means an alkenyl group as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary alkenyl aliphatic group substituents include halo or cycloalkyl groups

"Alkenyloxy" means an alkenyl-O- group wherein the alkenyl group is as herein described. Exemplary alkenyloxy groups include allyloxy, 3-butenyloxy, and the like.

"Alkoxy" means an alkyl-O- group wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, heptoxy, and the like.

"Alkoxycarbonyl" means an alkyl-O-CO- group, wherein the alkyl group is as herein defined. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, *t*-butyloxycarbonyl, and the like.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain, more preferred is lower alkyl as defined herein. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain that may be straight or branched. "Substituted alkyl" means an alkyl group as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different, and are as defined herein.

"Alkylsulfinyl" means an alkyl-SO- group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulfonyl" means an alkyl-SO₂-group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulphonylcarbamoyl" means an alkyl-SO₂-NH-C(=O)- group wherein the alkyl group is as herein described. Preferred alkylsulphonylcarbamoyl groups are those wherein the alkyl group is lower alkyl.

"Alkylthio" means an alkyl-S- group wherein the alkyl group is as herein described.

5 Exemplary alkylthio groups include methylthio, ethylthio, *i*-propylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain that may be straight or branched. The alkynyl group may be substituted by one or more halo. Exemplary alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl, decynyl, and the like. "Substituted alkynyl" means alkynyl as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different, and are as defined herein.

"Amine protecting group" means an easily removable group that is known in the art to protect a nitrogen moiety of an amino or amide group against undesirable reaction during synthetic procedures and to be selectively removable. The use of amine/amide protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, for example, T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991). Amine/amide protecting group also includes "acid labile amine/amide protecting group" and "hydrogenation labile amine/amide protecting group". Exemplary amine/amide protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, *o*-nitrophenylacetyl, *o*-nitrophenoxy-acetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, *o*-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxy-carbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxy-carbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butoxycarbonyl (BOC), 1,1-dimethyl-propynyloxycarbonyl, benzyloxycarbonyl (CBZ), *p*-nitrobenzyloxycarbonyl, 2,4-dichloro-benzyloxycarbonyl, and the like.

"Amide protecting group" means an easily removable group that is known in the art to protect a nitrogen moiety of an amide group against undesirable reaction during synthetic procedures and to be selectively removable after its conversion to the amine. The use of amide protecting groups is well known in the art for protecting groups against undesirable reactions

during a synthetic procedure and many such protecting groups are known, for example, T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley & Sons, New York (1991). Amide protecting group also includes

“acid labile amide protecting group” and “hydrogenation labile amide protecting group”.

- 5 Exemplary amide protecting groups are *o*-nitrocinnamoyl, picolinoyl, aminocaproyl, benzoyl and the like, and acyloxy including methoxy-carbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxy-carbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 1,1-dimethyl-propynyloxycarbonyl, benzyloxycarbonyl (CBZ), *p*-nitrobenzyloxycarbonyl, 2,4-dichloro-benzyloxycarbonyl, and the like.

- 10 “Amino acid” means an amino acid selected from the group consisting of natural and unnatural amino acids as defined herein. Amino acid is also meant to include α -amino acids having L or D stereochemistry at the α -carbon. Preferred amino acids are those possessing an α -amino group. The amino acids may be neutral, positive or negative depending on the substituents in the side chain. “Neutral amino acid” means an amino acid containing uncharged
- 15 side chain substituents. Exemplary neutral amino acids include alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine and cysteine. “Positive amino acid” means an amino acid in which the side chain substituents are positively charged at physiological pH. Exemplary positive amino acids include lysine, arginine and histidine. “Negative amino acid” means an amino acid in which the side chain substituents
- 20 bear a net negative charge at physiological pH. Exemplary negative amino acids include aspartic acid and glutamic acid. Preferred amino acids are α -amino acids. Exemplary natural amino acids are isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid and glutamic acid. Unnatural amino acid” means an amino acid for which there is no nucleic acid codon.
- 25 Exemplary unnatural amino acids include, for example, the D-isomers of the natural α -amino acids as indicated above; Aib (aminobutyric acid), β Aib (3-amino-isobutyric acid), Nva (norvaline), β -Ala, Aad (2-aminoadipic acid), β Aad (3-aminoadipic acid), Abu (2-aminobutyric acid), Gaba (γ -aminobutyric acid), Acp (6-aminocaproic acid), Dbu (2,4-diaminobutryic acid), α -aminopimelic acid, TMSA (trimethylsilyl-Ala), alle (allo-isoleucine), Nle (norleucine), *tert*-Leu,
- 30 Cit (citrulline), Orn, Dpm (2,2'-diaminopimelic acid), Dpr (2,3-diaminopropionic acid), α - or β -Nal, Cha (cyclohexyl-Ala), hydroxyproline, Sar (sarcosine), and the like; cyclic amino acids; N^x -alkylated amino acids such as MeGly (N^x -methylglycine), EtGly (N^x -ethylglycine) and EtAsn (N^x -ethylasparagine); and amino acids in which the α -carbon bears two side-chain substituents. The names of natural and unnatural amino

acids and residues thereof used herein follow the naming conventions suggested by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in "Nomenclature of α -Amino Acids (Recommendations, 1974)" Biochemistry, 14(2), (1975). To the extent that the names and abbreviations of amino acids and residues thereof employed in this specification and appended claims differ from those noted, differing names and abbreviations will be made clear.

"Amino acid protecting group" mean a group that protects an acid or amine moiety of the amino acid or other reactive moiety on the side chain of an amino acid, e.g., hydroxy or thiol. For examples of "corresponding protected derivatives" of amino acid side chains, see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Protecting groups for an acid group in an amino acid are described herein, for example in the sections "acidic functional group" and "hydrogenation labile acid protecting group". Protecting groups for an amine group in an amino acid are described herein, for example in the sections "amine protecting group", "acid labile amine protecting group" and "hydrogenation labile amine protecting group".

"Amino acid residue" means the individual amino acid units incorporated into the compound of the invention.

"Amino acid side chain" means the substituent found on the carbon between the amino and carboxy groups in α -amino acids. Exemplary α -amino acid side chains include isopropyl, methyl, and carboxymethyl for valine, alanine, and aspartic acid, respectively.

"Amino acid equivalent" means an amino acid that may be substituted for another amino acid in the peptides according to the invention without any appreciable loss of function. In making such changes, substitutions of like amino acids are made on the basis of relative similarity of side chain substituents, for example regarding size, charge, hydrophilicity, hydrophobicity and hydrophobicity as described herein.

"Aromatic group" means aryl or heteroaryl as defined herein. Exemplary aromatic groups include phenyl, halo substituted phenyl, azaheteroaryl, and the like.

"Aroyl" means an aryl-CO- group wherein the aryl group is as herein described. Exemplary aroyl groups include benzoyl, 1- and 2-naphthoyl, and the like.

"Aryl" means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms, preferably of about 6 to about 10 carbon atoms. Encompassed by aryl are fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl and fused arylheterocyclyl as defined herein when bonded through the aryl moiety thereof. The aryl is optionally substituted with one or more "ring group substituents" which may be the same or different, and are as defined herein. Exemplary aryl groups include phenyl or naphthyl, or phenyl substituted or naphthyl

substituted. "Substituted aryl" means an aryl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein.

5 "Aryldiazo" means an aryl-diazo- group wherein the aryl and diazo groups are as defined herein.

"Arylene" means an optionally substituted 1,2-, 1,3-, 1,4-, bivalent aryl group, wherein the aryl group is as defined herein. Exemplary arylene groups include optionally substituted phenylene, naphthylene and indanylene. A particular arylene is optionally substituted phenylene. "Substituted arylene" means an arylene group as defined above which is substituted with one or
10 more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein.

"Aryloxy" means an aryl-O- group wherein the aryl group is as defined herein.

Exemplary aryloxy groups include phenoxy and 2-naphthyloxy.

"Aryloxycarbonyl" means an aryl-O-CO- group wherein the aryl group is as defined
15 herein. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfonyl" means an aryl-SO₂- group wherein the aryl group is as defined herein.

"Arylsulphonylcarbamoyl" means an aryl-SO₂-NH-C(=O)- group wherein the aryl group is as herein described. An exemplary arylsulphonylcarbamoyl group is phenylsulphonylcarbamoyl.

20 "Arylsulfinyl" means an aryl-SO- group wherein the aryl group is as defined herein.

"Arylthio" means an aryl-S- group wherein the aryl group is as herein described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Basic nitrogen atom" means a sp² or sp³ hybridized nitrogen atom having a non-bonded pair of electrons which is capable of being protonated. Exemplary basic nitrogen atoms include
25 optionally substituted imino, optionally substituted amino and optionally substituted amidino groups.

"Carboxy" means an HO(O)C- (carboxylic acid) group.

"Coupling agent" means a compound that reacts with the hydroxyl moiety of a carboxy moiety thereby rendering it susceptible to nucleophilic attack. Exemplary coupling agents include
30 DIC, EDCI, DCC, and the like.

"Cycloalkenyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which contains at least one carbon-carbon double bond. Encompassed by cycloalkenyl are fused arylcycloalkenyl and fused heteroaryl-cycloalkenyl as defined herein when bonded through the cycloalkenyl moiety
35 thereof. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and

such preferred ring sizes are also referred to as "lower". "Substituted cycloalkenyl" means an cycloalkenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. An exemplary multicyclic cycloalkenyl is norbornenyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". Encompassed by cycloalkyl are fused arylcycloalkyl and fused heteroaryl cycloalkyl as defined herein when bonded through the cycloalkyl moiety thereof. "Substituted cycloalkyl" means a cycloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary monocyclic cycloalkyl include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Exemplary multicyclic cycloalkyl include 1-decalin, norbornyl, adamant-(1- or 2-)yl, and the like.

"Cycloalkylene" means a bivalent cycloalkyl group as defined herein having about 4 to about 8 carbon atoms. Preferred ring sizes of the cycloalkylene include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". The points of binding on the cycloalkylene group include 1,1-, 1,2-, 1,3-, or 1,4- binding patterns, and where applicable the stereochemical relationship of the points of binding is either cis or trans. Exemplary cycloalkylene groups include (1,1-, 1,2- or 1,3-)cyclohexylene and (1,1- or 1,2-)cyclopentylene. "Substituted cycloalkylene" means an cycloalkylene group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein

"Cyclic" or "Cyclyl" means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl as defined herein. The term "lower" as used in connection with the term cyclic is the same as noted herein regarding the cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

"Cyclyloxy" means a cyclyl-O- group wherein the cyclyl group is as herein described. Exemplary cycloalkoxy groups include cyclopentyloxy, cyclohexyloxy, quinuclidyloxy, pentamethylenesulfideoxy, tetrahydropyranyloxy, tetrahydrothiophenyloxy, pyrrolidinyloxy, tetrahydrofuranyloxy or 7-oxabicyclo[2.2.1]heptanyloxy, hydroxytetrahydropyranyloxy, hydroxy-7-oxabicyclo[2.2.1]heptanyloxy, and the like.

"Cyclylsulfinyl" means a cyclyl-S(O)- group wherein the cyclyl group is as herein described.

“Cyclylsulfonyl” means a cyclyl-S(O)₂- group wherein the cyclyl group is as herein described.

“Cyclylthio” means a cyclyl-S- group wherein the cyclyl group is as herein described.

“Diazo” means a bivalent -N=N- radical.

5 “Displaceable moiety” means a group that where associated with L as defined herein is subject to being displaced by nucleophilic attack by a mono- or di-substituted amine moiety with or without the presence of an agent that facilitates said attack, e.g., coupling agent. Exemplary displaceable moieties include hydroxy, aliphatic oxy, halo, N-oxy succinimide, acyloxy, and the like.

10 “Effective amount” is means an amount of a compound/composition according to the present invention effective in producing the desired therapeutic effect.

“Fused arylcycloalkenyl” means a fused aryl and cycloalkenyl as defined herein. Preferred fused arylcycloalkenyls are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkenyl as a variable
15 may be bonded through any atom of the ring system thereof capable of such. “Substituted fused arylcycloalkenyl” means a fused arylcycloalkenyl group as defined above which is substituted with one or more “ring group substituents” (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary fused arylcycloalkenyl include 1,2-dihydronaphthylene, indene, and the like.

20 “Fused arylcycloalkyl” means a fused aryl and cycloalkyl as defined herein. Preferred fused arylcycloalkyls are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. “Substituted fused arylcycloalkyl” means a fused arylcycloalkyl group as defined above which is substituted with one or more “ring group
25 substituents” (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary fused arylcycloalkyl includes 1,2,3,4-tetrahydro-naphthylene, and the like.

“Fused arylheterocyclenyl” means a fused aryl and heterocyclenyl as defined herein. Preferred fused arylheterocyclenyls are those wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclenyl as a variable
30 may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heterocyclenyl portion of the fused arylheterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. “Substituted fused arylheterocyclenyl” means a fused arylheterocyclenyl group as defined above which is substituted with one or more “ring group substituents” (preferably 1 to 3) which may be
35 the same or different and are as defined herein. The nitrogen atom of a fused arylheterocyclenyl

may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl portion of the fused arylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclenyl include 3H-indolinyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl, 1,2-di-hydroquinolyl, 3,4-dihydroquinolyl, 1,2-dihydroisoquinolyl, 3,4-dihydroisoquinolyl, and the like.

“Fused arylheterocyclyl” means a fused aryl and heterocyclyl as defined herein. Preferred fused arylheterocyclyls are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heterocyclyl portion of the fused arylheterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. “Substituted fused arylheterocyclyl” means a fused arylheterocyclyl group as defined above which is substituted with one or more “ring group substituents” (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused arylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl portion of the fused arylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 1H-2,3-dihydroisoindol-2-yl, 2,3-dihydrobenz[f]isoindol-2-yl, 1,2,3,4-tetrahydrobenz[g]-isoquinolin-2-yl, and the like.

“Fused heteroarylcyaloalkenyl” means a fused heteroaryl and cycloalkenyl as defined herein. Preferred fused heteroarylcyaloalkenyls are those wherein the heteroaryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused heteroaryl-cycloalkenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heteroaryl portion of the fused heteroarylcyaloalkenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. “Substituted fused heteroarylcyaloalkenyl” means a fused heteroarylcyaloalkenyl group as defined above which is substituted with one or more “ring group substituents” (preferably 1 to 30 which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylcyaloalkenyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcyaloalkenyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcyaloalkenyl include 5,6-dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalyl, 5,6-dihydroquinazolyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-di-hydrobenzoxazolyl, and the like.

“Fused heteroarylcyaloalkyl” means a fused heteroaryl and cycloalkyl as defined herein. Preferred fused heteroarylcyaloalkyls are those wherein the heteroaryl thereof consists of about 5

to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused heteroarylcyaloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heteroaryl portion of the fused heteroarylcyaloalkyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused heteroarylcyaloalkyl" means a fused heteroarylcyaloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylcyaloalkyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcyaloalkyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcyaloalkyl include 5,6,7,8-tetrahydroquinoliny, 5,6,7,8-tetrahydroisoquinoliny, 5,6,7,8-tetrahydroquinoxaliny, 5,6,7,8-tetrahydroquinazoliny, 4,5,6,7-tetrahydro-1H-benzimidazoliny, 4,5,6,7-tetrahydrobenzoxazoliny, 1H-4-oxa-1,5-diazanaphthalen-2-ony, 1,3-dihydroimidazole-[4,5]-pyridin-2-ony, and the like.

"Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl as defined herein. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylhetero-cyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused heteroarylheterocyclenyl" means a fused heteroarylheterocyclenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylazaheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl portion of the fused heteroarylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide. The nitrogen or sulfur atom of the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused heteroarylheterocyclenyl include 7,8-dihydro[1,7]naphthyridiny, 1,2-dihydro[2,7]-naphthyridiny, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, 1,2-dihydro-1,5-naphthyridiny, 1,2-dihydro-1,6-naphthyridiny, 1,2-dihydro-1,7-naphthyridiny, 1,2-dihydro-1,8-naphthyridiny, 1,2-dihydro-2,6-naphthyridiny, and the like.

"Fused heteroarylheterocyclyl" means a fused heteroaryl and heterocyclyl as defined herein. Preferred fused heteroarylheterocyclyls are those wherein the heteroaryl thereof consists

of about 5 to about 6 ring atoms and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused heteroarylheterocyclyl" means a fused heteroarylheterocyclyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide. The nitrogen or sulfur atom of the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused heteroarylheterocyclyl include 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2-yl, 2,3-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2-yl, 5,6,7,8-tetrahydro[1,7]naphthyridyl, 1,2,3,4-tetrahydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa[4,6]diazanaphthalenyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro[5,8]diazanaphthalenyl, 1,2,3,4-tetrahydro[1,5]-naphthyridinyl, 1,2,3,4-tetrahydro[1,6]naphthyridinyl, 1,2,3,4-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrahydro[1,8]naphthyridinyl, 1,2,3,4-tetrahydro[2,6]naphthyridinyl, and the like.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Heteroaroyl" means an heteroaryl-CO- group wherein the heteroaryl group is as herein described. Exemplary heteroaroyl groups include thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl, 1- and 2-naphthoyl, pyridinoyl, and the like. "

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferably the ring system includes 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. Encompassed by heteroaryl are fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl and fused heteroarylheterocyclyl as defined herein when bonded through the heteroaryl moiety thereof. "Substituted heteroaryl" means a heteroaryl group as defined above which is substituted

with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. A nitrogen atom of an heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. Exemplary heteroaryl and substituted heteroaryl groups include

5 pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxaliny, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, azaindolyl, benzimidazolyl, benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, benzoazaindolyl, 1,2,4-triazinyl, benzthiazolyl, furanyl,

10 imidazolyl, indolyl, indoliziny, isoxazolyl, isoquinoliny, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazoliny, quinoliny, 1,3,4-thiadiazolyl, thiazolyl, thienyl, triazolyl, and the like. A preferred heteroaryl group is pyrazinyl.

"Heteroaryldiazo" means an heteroaryl -azo- group wherein the heteroaryl and azo groups are as defined herein.

15 "Heteroarylidy" means a bivalent radical derived from a heteroaryl, wherein the heteroaryl is as described herein. An exemplary heteroaryldiyl radical is optionally substituted pyridinediyl.

"Heteroarylsulphonylcarbonyl" means a heteroaryl-SO₂-NH-C(=O)- group wherein the heteroaryl group is as herein described.

20 "Heterocyclenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Preferably, the ring includes 1 to 3

25 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". Encompassed by heterocyclenyl are fused arylheterocyclenyl and fused heteroarylheterocyclenyl as defined herein when bonded through the heterocyclenyl moiety thereof. The designation of the aza, oxa or thia as a prefix before heterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present,

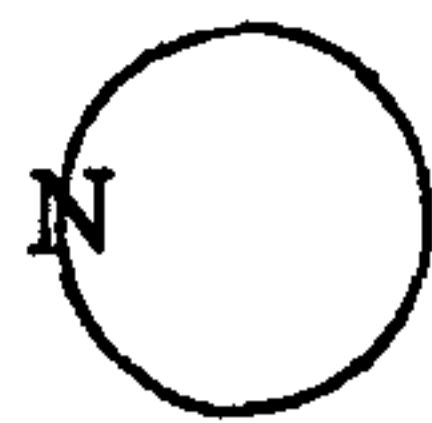
30 respectively, as a ring atom. "Substituted heterocyclenyl" means a heterocyclenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of an heterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

35 Exemplary monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydrohydropyridine,

1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetra-hydropyridine, 1,4,5,6-tetrahydro-pyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazoliny, 2-pyrazoliny, and the like. Exemplary oxaheterocyclenyl groups include 3,4-dihydro-2*H*-pyran, dihydrofuranyl, and fluorodihydro-furanyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl.

5 Exemplary monocyclic thiaheterocyclenyl rings include dihydrothiophenyl and dihydrothiopyranyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for
 10 example nitrogen, oxygen or sulfur. Preferably, the ring system contains from 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". Encompassed by heterocyclyl are fused arylheterocyclyl and fused heteroarylheterocyclyl as defined herein when bonded through the heterocyclyl moiety thereof. The designation of the aza, oxa or thia as a prefix before
 15 heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. "Substituted heterocyclyl" means a heterocyclyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of an heterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl may also be optionally oxidized to
 20 the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and



the like. as substituted monocyclic azaheterocyclyl is substituted directly or through a linker by at least one substituent that is, or encompasses, or is substituted by an aromatic group as
 25 defined herein; for example aryl, heteroaryl, aryloxy, heteroaryloxy, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, aroyloxy, heteroaroyloxy, aryloxycarbonyl, heteroaryloxycarbonyl, arylsulfonyl, heteroarylsulfonyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aryldiazo, heteroaryldiazo, Y^1Y^2N- , $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$ or $Y^1Y^2NSO_2-$ wherein at least one of Y^1 and Y^2 is, encompasses or is
 30 substituted by an aryl or heteroaryl moiety. Preferred linkers include $-C(O)-$, $-OC(O)-$, lower alkyl, lower alkoxy, lower alkenyl, $-O-$, $-S-$, $-C(O)C(O)-$, $-S(O)-$, $-S(O)_2-$, $-NR^{80}-$, where R^{80} is hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl or heteroaryl. Particularly preferred linkers are $-C(O)-$ and $-OC(O)-$. "Substituted multicyclic azaheterocyclyl" means a multicyclic

azaheterocyclyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. "Substituted multicyclic azaheterocyclenyl" means a multicyclic azaheterocyclenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein.

"Heterocyclylene" means a bivalent heterocyclyl group as defined herein having about 4 to about 8 carbon atoms. Preferred ring sizes of the heterocyclylene include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". The points of binding on the cycloalkylene group include 1,1-, 1,2-, 1,3-, or 1,4- binding patterns, and where applicable the stereochemical relationship of the points of binding is either cis or trans. Exemplary heterocyclylene groups include (1,1-, 1,2- or 1,3-)piperidinylene and (1,1- or 1,2-)tetrahydrofuranylene. "Substituted heterocyclylene" means a heterocyclylene group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein.

"Hydrate" means a solvate wherein the solvent molecule(s) is/are H₂O.

"Hydrogenation labile amine protecting group" means an amine protecting group as defined herein which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile amine protecting group is Cbz.

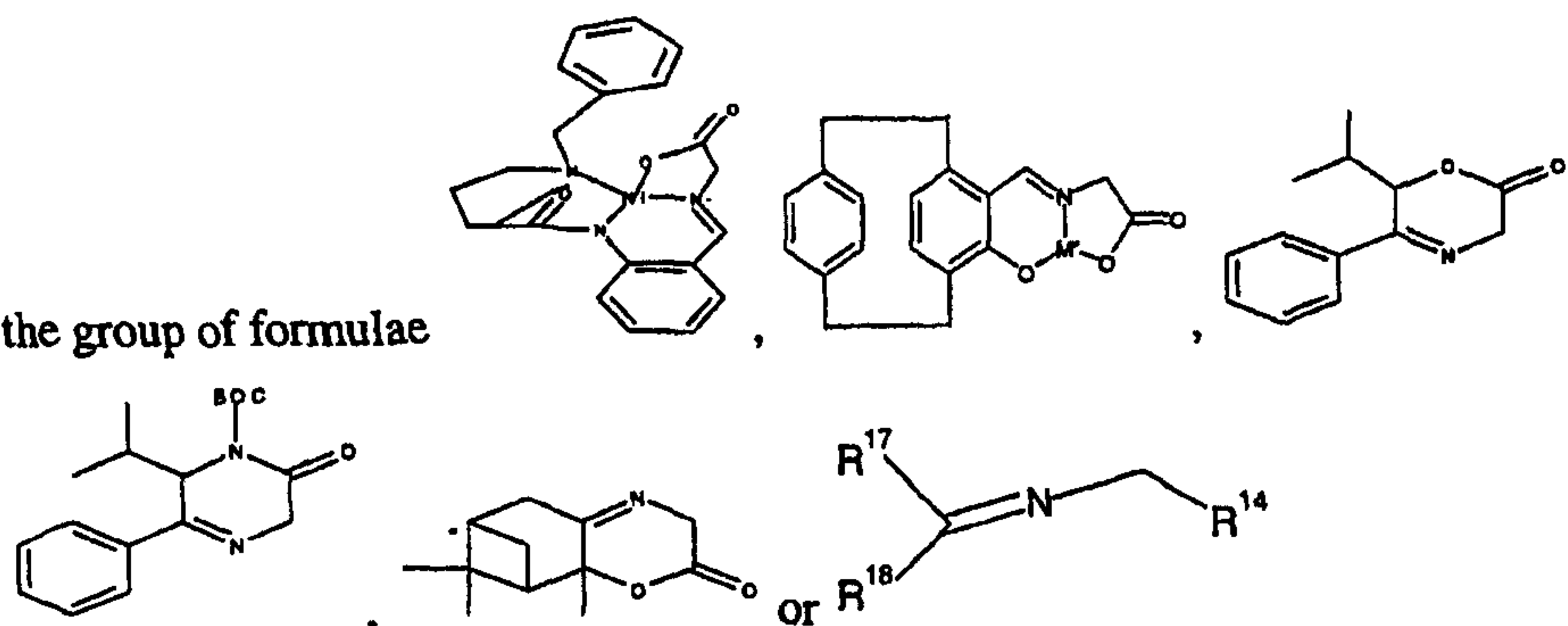
"Hydrogenation labile acid protecting group" means an acid protecting group as defined herein which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile acid protecting group is benzyl.

"Hygroscopicity" means sorption, implying an acquired amount or state of water sufficient to affect the physical or chemical properties of the substance (Eds. J. Swarbrick and J.C. Boylan, *Encyclopedia of Pharmaceutical Technology*, 10, 33).

"Iminic glycinimide derivative" means an iminic Schiff base of a glycine that is useful in the synthesis of α -amino acids, both natural and unnatural. The iminic ester functionality may contain one or more asymmetric centers that may aid in stereinduction during the bond forming process. In addition, these iminic glycinimide derivatives may be incorporated onto polymeric supports to facilitate combinatorial synthesis. Iminic glycinimide derivatives may be prepared by condensing a glycine ester with the appropriate ketone in the presence of an acid catalyst. The reaction is facilitated by the removal of water. Iminic glycinimide derivatives are well known in the art for use in Michael Addition synthetic procedures, for example as disclosed by Guillena, G., *et al.*, *J. Org. Chem.* 2000, 65, 7310-7322. Particular examples of iminic glycinimide derivatives according to the invention include one selected from

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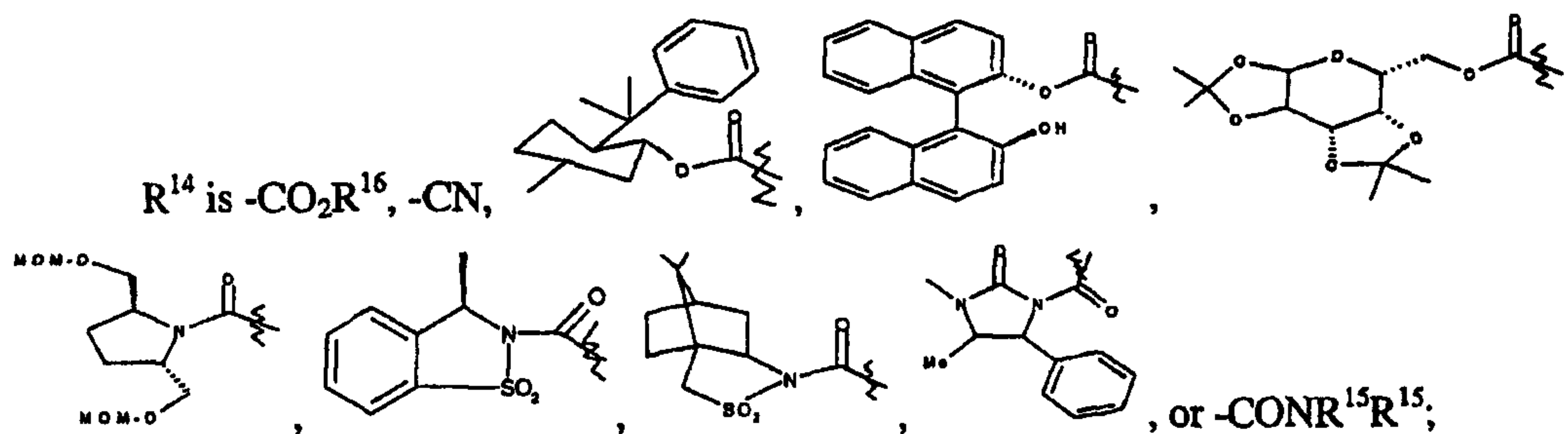
the group of formulae



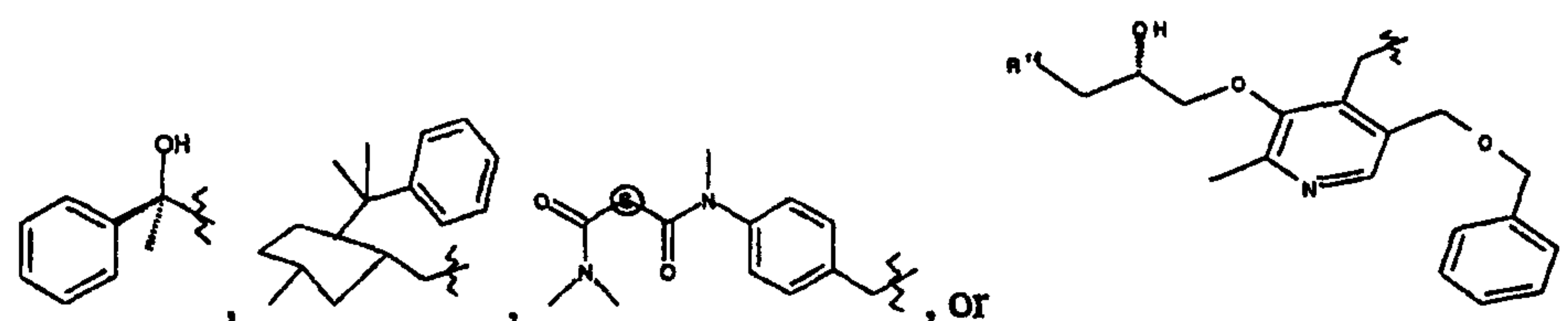
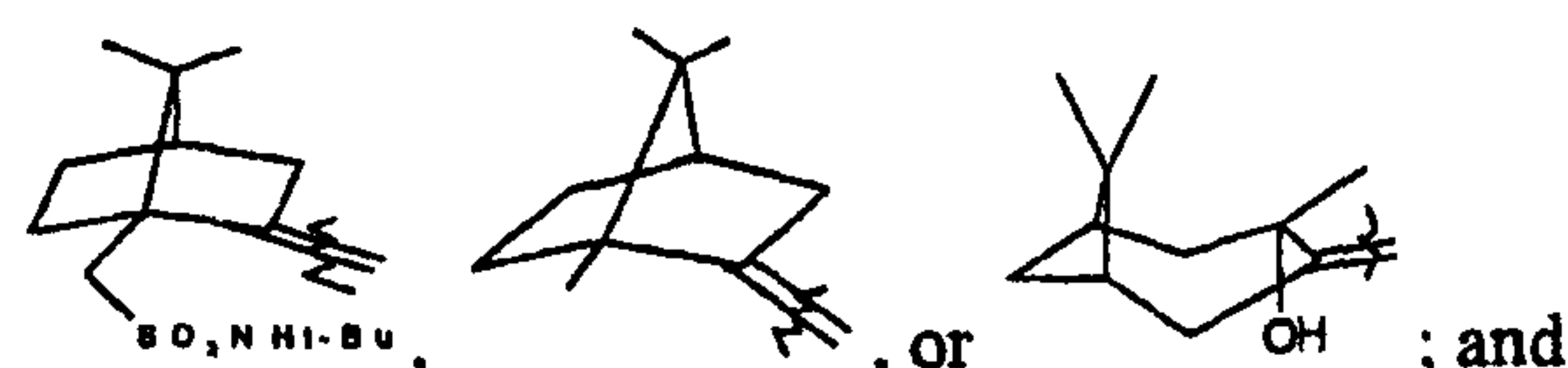
wherein:

M* is a transition metal, preferably CU, more preferably CU^{II}.

5

R¹⁵ is optionally substituted aliphatic group;R¹⁶ is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group;

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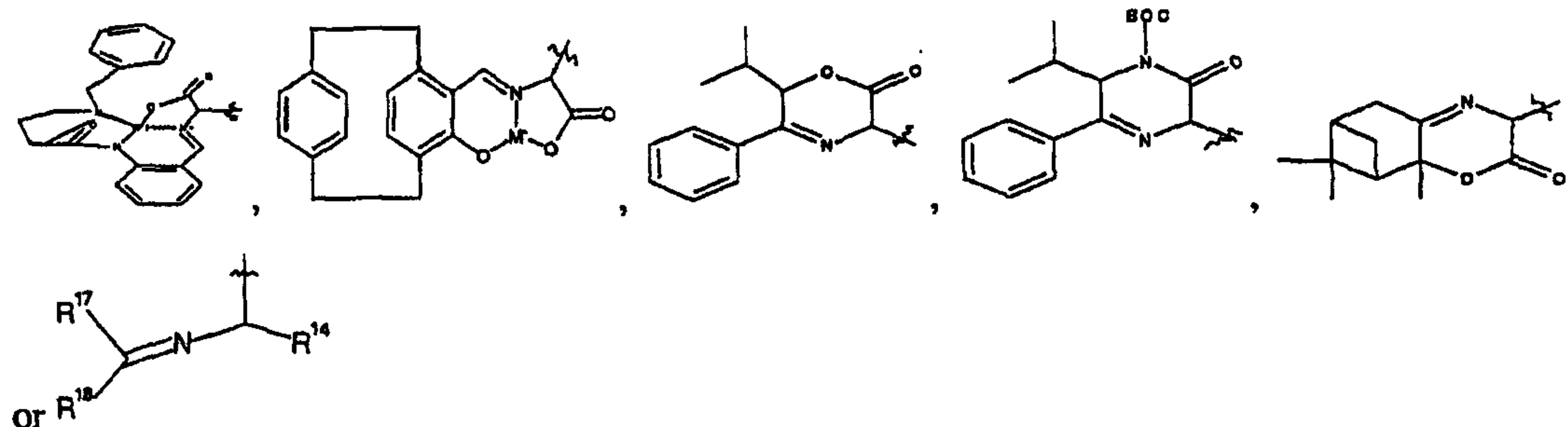
R¹⁷ is optionally substituted aryl, optionally substituted aliphatic group,R¹⁸ is hydrogen, alkyl, or alkylthio; or optionally substituted aryl;R¹⁷ and R¹⁸ taken together with the carbon to which R¹⁷ and R¹⁸ are attached

15

Ⓢ is a solid phase.

"Iminic glycinimide derivative adduct" means the resulting compound where an α -hydrogen to the nitrogen and carbonyl moiety of the Schiff base portion is removed and used to form an attachment for the bond formation thereto. Particular examples of iminic glycinimide

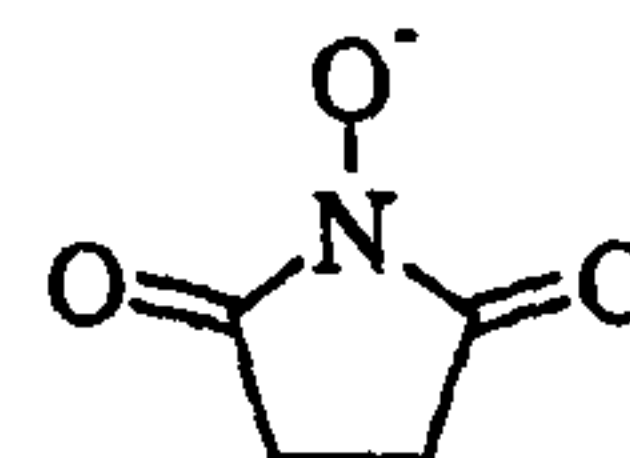
derivative adducts according to the invention include one selected from the group of formulae



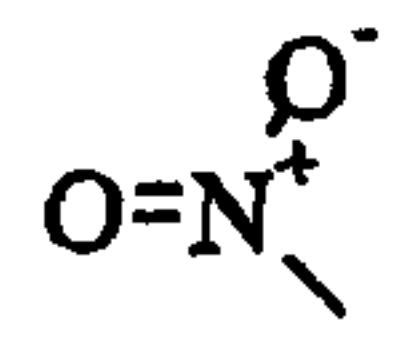
wherein:

- 5 R^{14} , R^{17} , and R^{18} are defined as described in the definition of iminic glycinimide derivative herein.

"N-oxysuccinimide" means a moiety of the following structure



"N-oxide" means a moiety of the following structure



"Patient" includes both human and other mammals.

- 10 "Peptidomimetic" mean a polymer encompassing amino acid residues joined together through amide bonds.

"Pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Exemplary esters include formates, acetates, propionates, butyrates, acrylates, ethylsuccinates, and the like.

- 20 "Pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. Functional groups that may be rapidly transformed, by metabolic cleavage, *in vivo* form a class of groups reactive with the carboxyl group of the compounds of this invention. They

include, but are not limited to such groups as alkanoyl (such as acetyl, propanoyl, butanoyl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds of this invention are cleaved *in vivo*, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion is provided in Design of Prodrugs, H. Bundgaard, ed., Elsevier (1985); Methods in Enzymology; K. Widder et al, Ed., Academic Press, 42, 309-396 (1985); A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bandaged, ed., Chapter 5; "Design and Applications of Prodrugs" 113-191 (1991); Advanced Drug Delivery Reviews, H. Bundgard, 8, 1-38, (1992); J. Pharm. Sci., 77, 285 (1988); Chem. Pharm. Bull., N. Nakeya et al, 32, 692 (1984); Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, 14 A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, E.B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987.

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, sulphamates, malonates, salicylates, propionates, methylene-bis- β -hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quaternary laurylsulphonate salts, and the like. See, for example S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977).

Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. The sodium and potassium salts are preferred. Suitable inorganic base addition salts are

prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide and the like. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and preferably include those amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e.g., lysine and arginine, and dicyclohexylamine, and the like.

"Ring group substituents" mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y¹Y²N-, Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, wherein Y¹, Y² and Y³ are independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of Y¹ and Y² is as defined previously, or for where the substituent is Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl. When a ring system is saturated or partially saturated, the "ring group substituents" further include, methylene (H₂C=), oxo (O=) and thioxo (S=). Acidic/amide ring group substituents are carboxy (acid), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl,

arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydroxy-1-methylpyrazolyl and Y^1Y^2NCO- . Non-acidic polar ring group substituents are hydroxy, oxo ($O=$), thioxo ($S=$), acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, thiol, Y^1Y^2N- , $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$ or $Y^1Y^2NSO_2-$.

“Solvate” means a physical association of a compound of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, methanolates, and the like.

Embodiments

With reference to inventions described herein, below are particular and preferred embodiments are related thereto.

A particular embodiment according to the invention is where R^0 is a bond.

Another particular embodiment according to the invention is where R^0 is difluoromethylene.

A particular embodiment according to the invention is where R^1 is hydrogen or optionally substituted lower aliphatic group.

Another particular embodiment according to the invention is where R^1 is hydrogen or lower alkyl.

A preferred embodiment according to the invention is where R^1 is hydrogen.

A particular embodiment according to the invention is where R^2 is optionally substituted lower aliphatic group or optionally substituted monocyclic group.

Another particular embodiment according to the invention is where R^2 is optionally substituted lower alkyl, optionally substituted lower alkenyl, or optionally substituted monocyclic cycloalkyl.

Further particular embodiment according to the invention is where R^2 is carboxymethyl, 1-carboxy-2-phenylethyl, cyclopropyl, cyclobutyl, 1-cyclohexylethyl, 1-phenylethyl, but-2-yl, 1-pyrid-4-ylethyl, propen-3-yl or 3-methylbut-2-yl; more preferred cyclopropyl.

A particular embodiment according to the invention is where R^3 is optionally substituted lower aliphatic group methylene.

Another particular embodiment according to the invention is where R^3 is optionally halo substituted lower (alkyl or alkenyl)methylene.

5 A preferred embodiment according to the invention is where R^3 is propylmethylene, 2,2-difluoroethylmethylene, 2,2,2-trifluoromethylene or propen-3-ylmethylene; more preferred R^3 is propylmethylene or 2,2-difluoroethylmethylene; further preferred R^3 is propylmethylene.

A particular embodiment according to the invention is where R^4 is hydrogen or optionally substituted lower aliphatic group.

10 Another particular embodiment according to the invention is where R^4 is hydrogen or lower alkyl.

A preferred embodiment according to the invention is where R^4 is hydrogen.

A particular embodiment according to the invention is where R^5 is optionally substituted lower aliphatic group methylene.

15 Another particular embodiment according to the invention is where R^5 is optionally (phenyl, carboxy, carboxamido or alkoxycarbonyl) substituted lower (alkyl or alkenyl) methylene.

A preferred embodiment according to the invention is where R^5 is methylmethylene, isopropylmethylene, *t*-butylmethylene, but-2-ylmethylene, butylmethylene, benzylmethylene, 3-methylbutylmethylene, 2-methylpropyl-methylene, carboxymethylmethylene, carboxamidomethylmethylene, benzyloxycarbonylmethylmethylene, benzyloxycarbonylpropylmethylene, or phenylpropen-3-ylmethylene; more preferred R^5 is isopropylmethylene or *t*-butyl-methylene.

A particular embodiment according to the invention is where R^6 is hydrogen or optionally substituted lower aliphatic group.

25 Another particular embodiment according to the invention is where R^6 is hydrogen or lower alkyl.

A preferred embodiment according to the invention is where R^6 is hydrogen.

A particular embodiment according to the invention is where R^7 is optionally substituted lower aliphatic group methylene, optionally substituted lower cyclic group methylene or optionally substituted monocyclic (aryl or heteroaryl) methylene.

30 Another particular embodiment according to the invention is where R^7 is optionally substituted lower alkylmethylene, optionally substituted lower cycloalkylmethylene or optional substituted phenylmethylene.

A preferred embodiment according to the invention is where R^7 is methylmethylene, isopropylmethylene, *n*-propylmethylene, phenylmethylene, cyclohexylmethylene,

35

cyclopentylmethylene, *t*-butylmethylene, *s*-butylmethylene, cyclohexylmethylmethylene, or phenylmethylmethylene; more preferred is isopropylmethylene, cyclohexylmethylene, cyclopentylmethylene, *t*-butylmethylene or *s*-butylmethylene.

5 A preferred embodiment according to the invention is also wherein each of R^3 , R^5 , and R^7 is mono substituted methylene.

A preferred embodiment according to the invention is also wherein R^3 is mono substituted methylene and has an (S) configuration on the carbon attached to the $-C(O)-R^0-C(O)-NR^1R^2$ moiety.

10 A particular embodiment according to the invention is where R^8 is hydrogen or optionally substituted lower aliphatic group.

Another particular embodiment according to the invention is where R^8 is hydrogen or lower alkyl.

A preferred embodiment according to the invention is where R^8 is hydrogen.

15 A particular embodiment according to the invention is where R^9 is optionally substituted lower aliphatic group or optionally substituted monocyclic aromatic group.

Another particular embodiment according to the invention is where R^9 is optionally substituted lower alkyl or optionally substituted monocyclic heteroaryl.

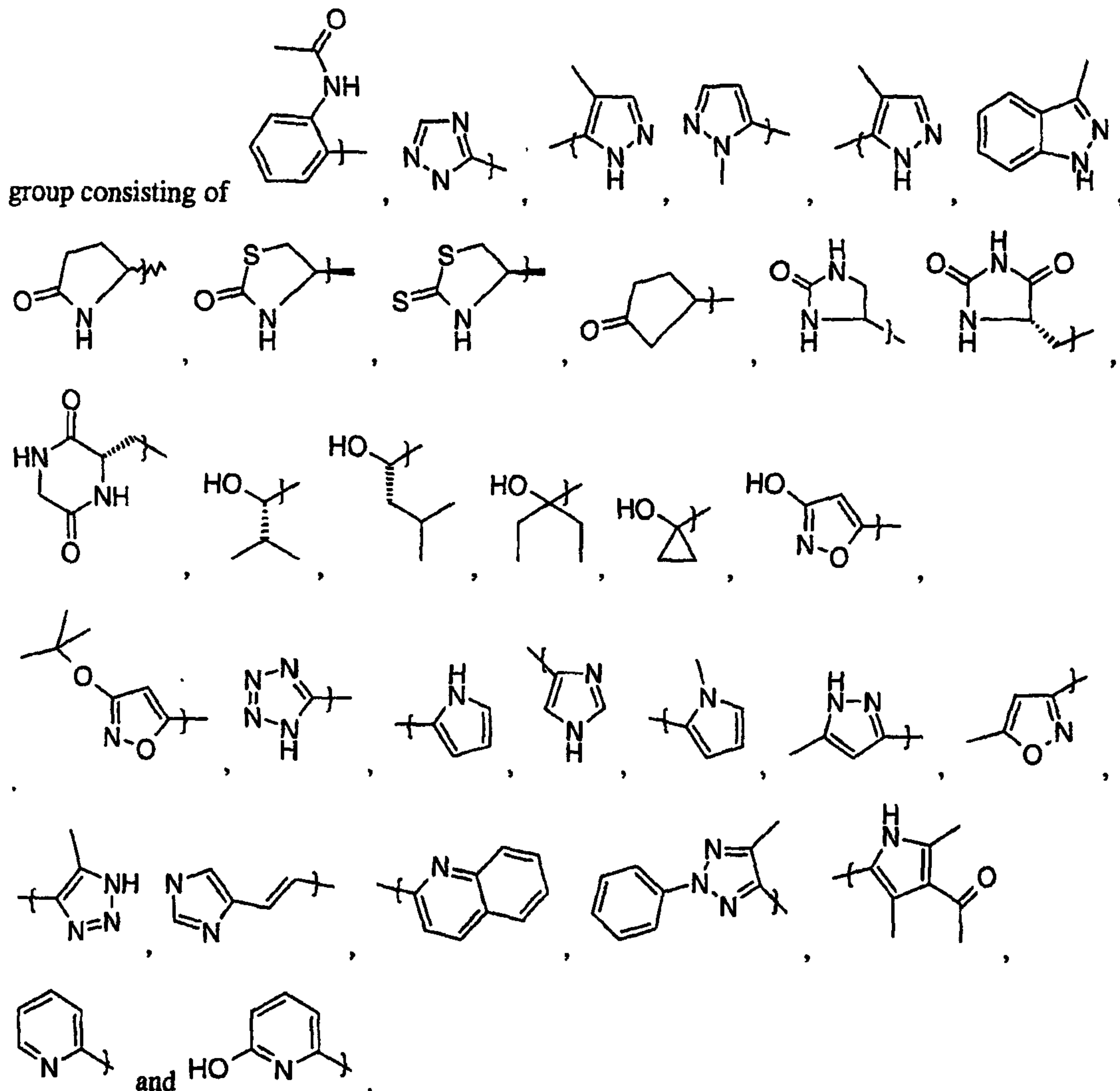
20 Another particular embodiment according to the invention is where R^9 is optionally (carboxy, (loweralkyl)SO₂NH-, (lower alkyl)HNCO-, hydroxy, phenyl, heteroaryl, or (lower alkyl)OC(O)NH-)substituted lower alkyl, or optionally substituted monocyclic heteroaryl.

A further preferred embodiment according to the invention is where R^9 is lower alkyl substituted by (mono- or di-)MeOC(O)NH-; more preferred is 1,2-di(MeOC(O)NH)ethyl or 1-(MeOC(O)NH)ethyl.

25 A preferred embodiment according to the invention is where R^9 is (carboxy, (lower alkyl)HNCO- or tetrazolyl)substituted lower alkyl; more preferred 3-carboxypropyl, 2-tetrazol-5ylpropyl, 3-(N-methylcarboxamido)propyl or 3-carboxy-2,2-dimethylpropyl; further preferred is 3-carboxypropyl, 2-tetrazol-5ylpropyl or 3-(N-methylcarboxamido)propyl.

30 Another preferred embodiment according to the invention is where R^9 is optionally substituted lower alkyl; more preferred is 1-hydroxy-2-phenylethyl, methyl, isopropyl or *t*-butyl; further preferred is methyl, isopropyl or *t*-butyl.

Another preferred embodiment according to the invention is where R^9 is selected from the



Yet another preferred embodiment according to the invention is where R⁹ is pyrazinyl.

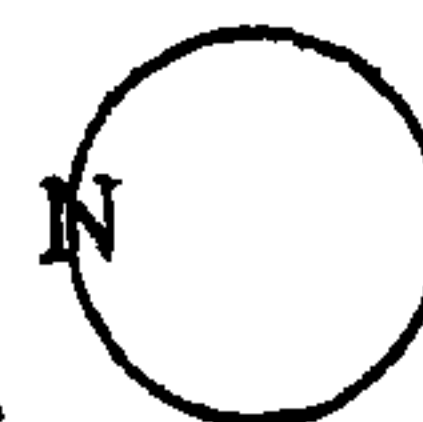
A particular embodiment according to the invention is where R^{10} is hydrogen or optionally substituted lower aliphatic group.

Another particular embodiment according to the invention is where R^{10} is hydrogen or lower alkyl.

A preferred embodiment according to the invention is where R¹⁰ is hydrogen.

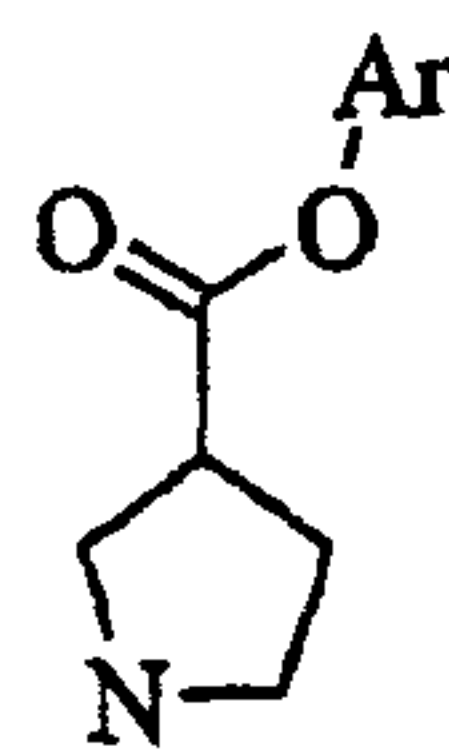
A preferred embodiment according to the invention is where  as a substituted
15 monocyclic azaheterocyclyl is substituted pyrrolidinyl.

A preferred embodiment according to the invention is where

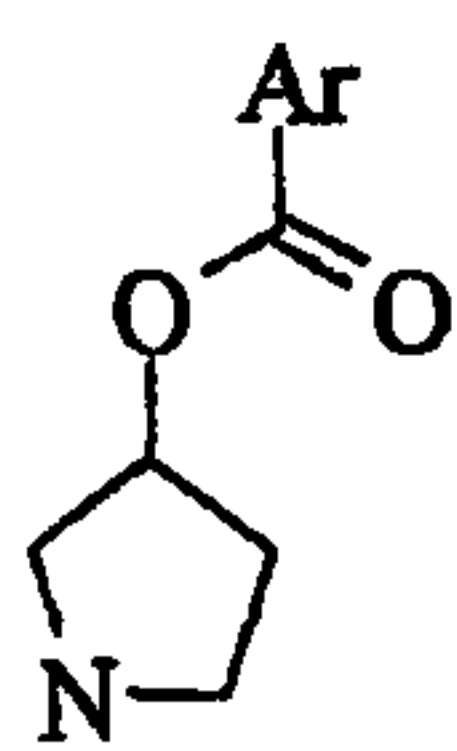


as a substituted

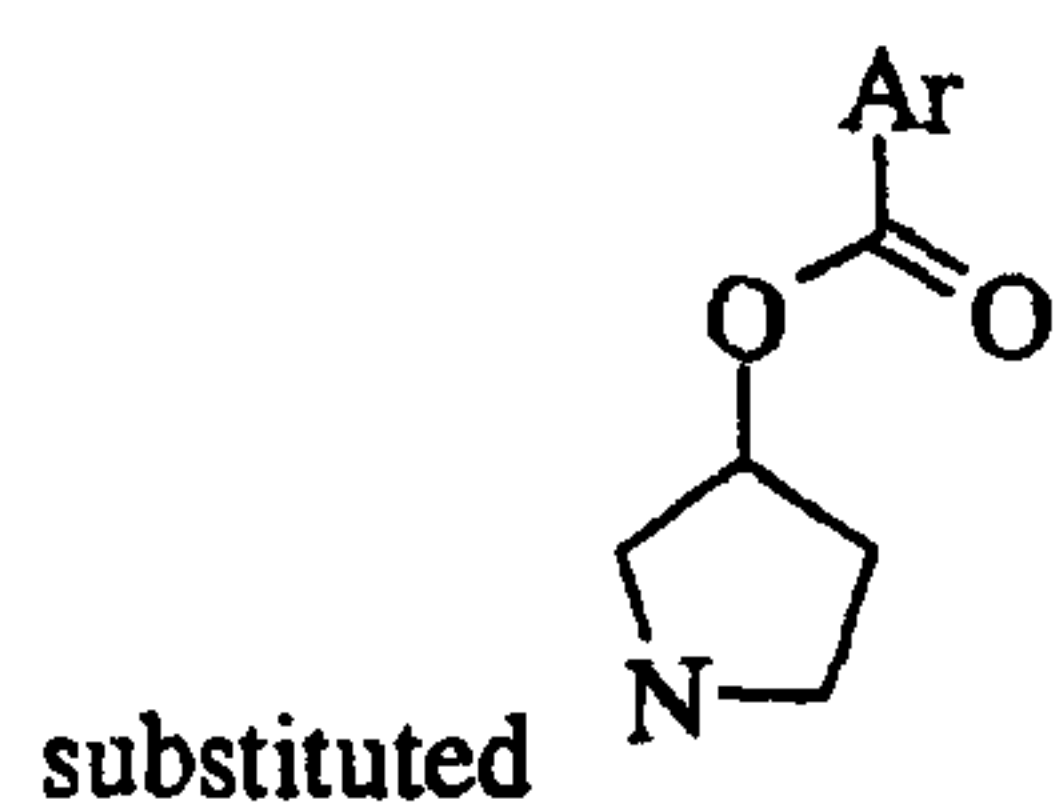
monocyclic azaheterocyclyl is optionally substituted



or optionally substituted

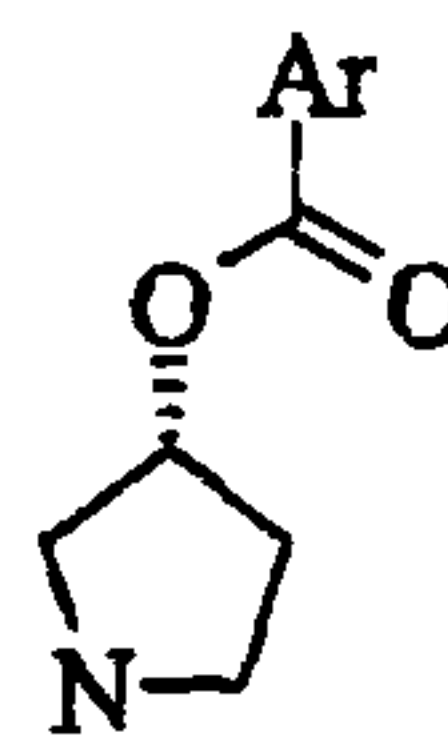


,wherein Ar is R² that comprises an aromatic moiety; more preferred is optionally



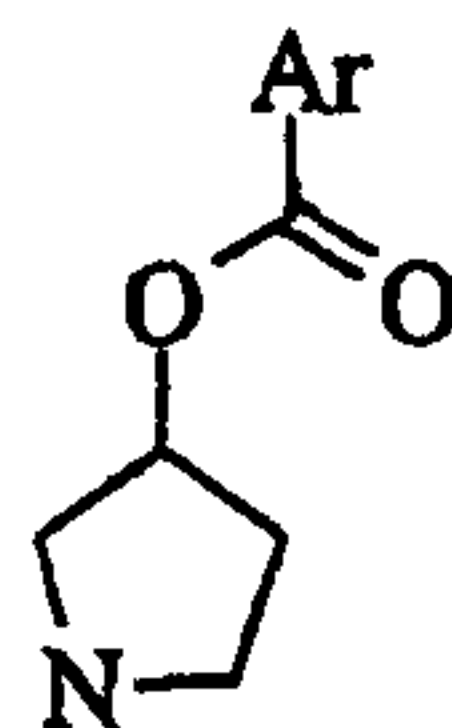
substituted

; further preferred is optionally substituted

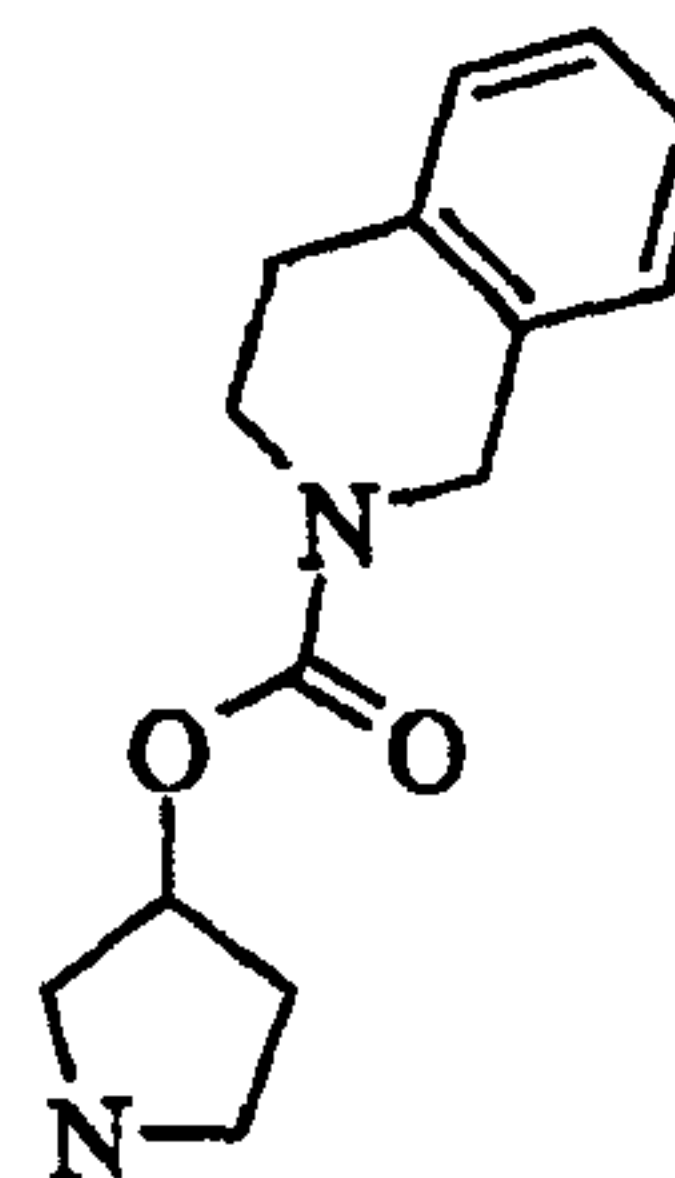


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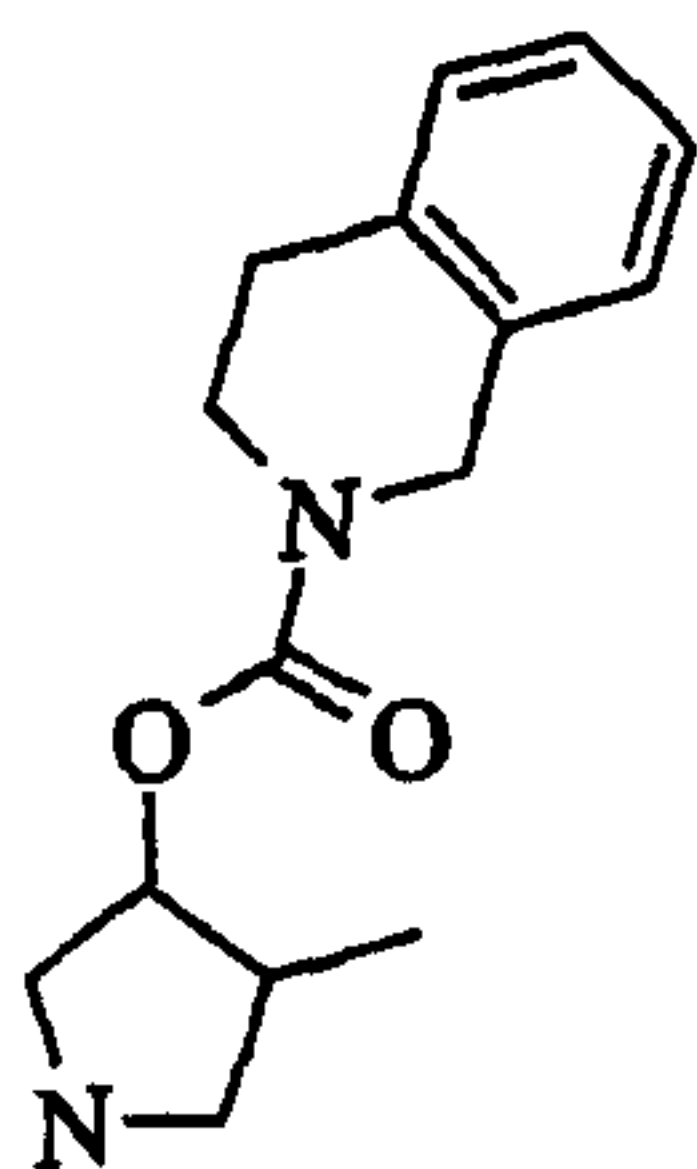
Further preferred optionally substituted



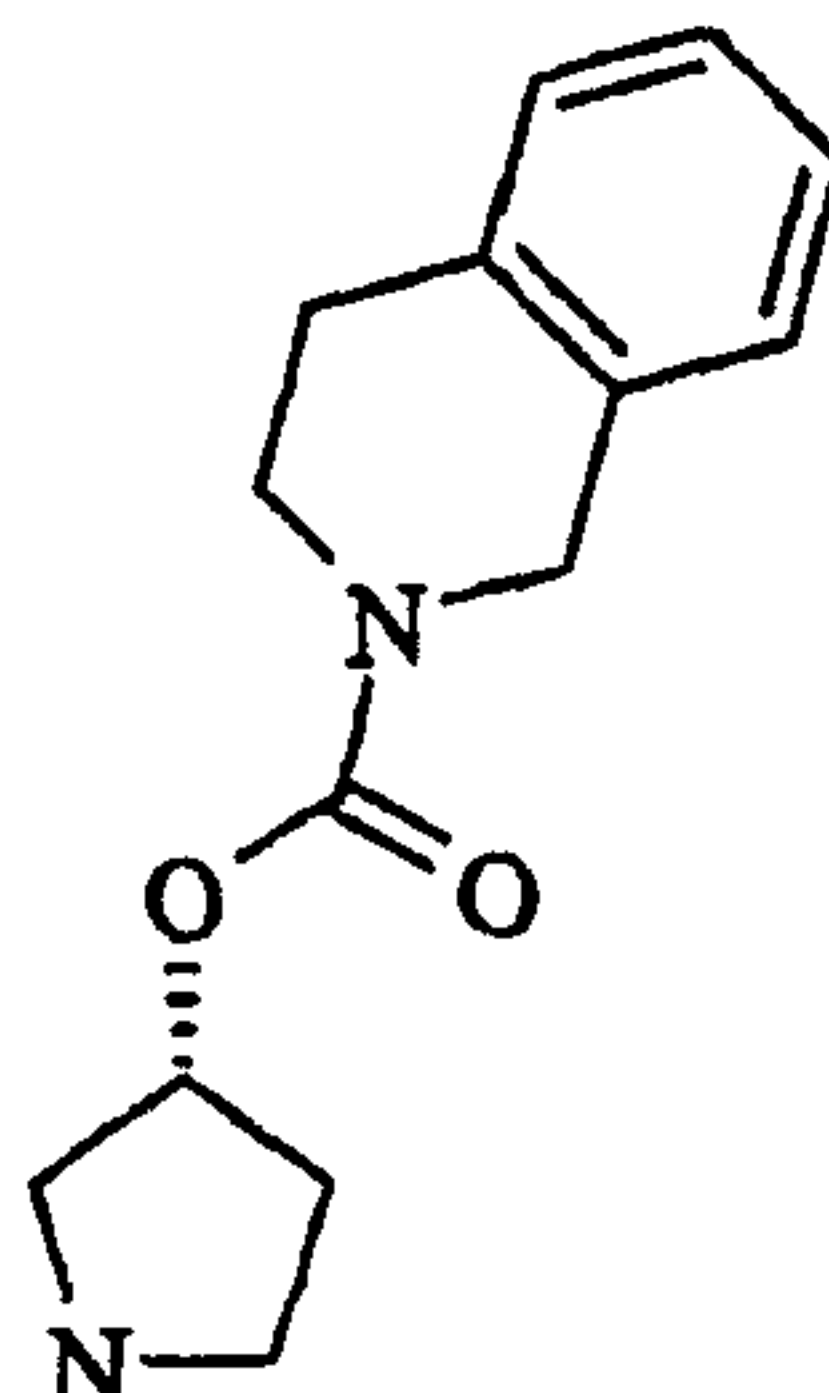
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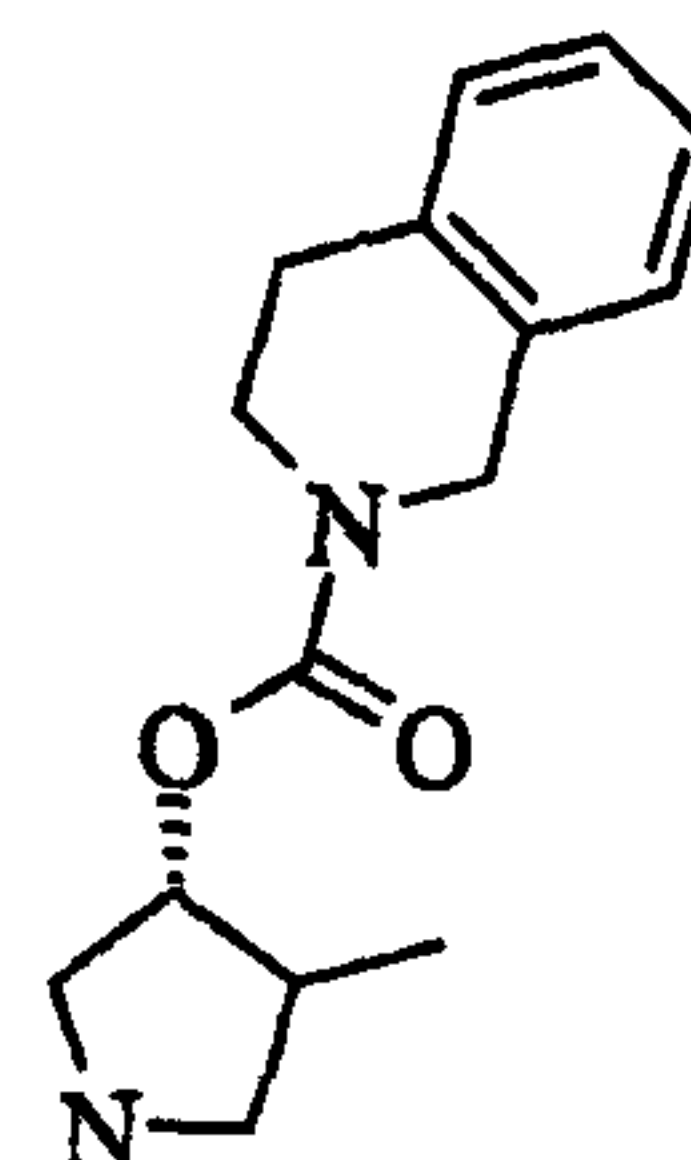
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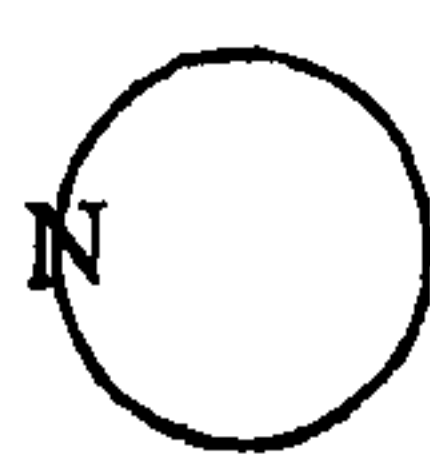
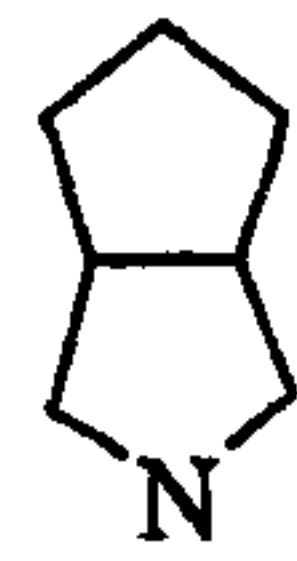
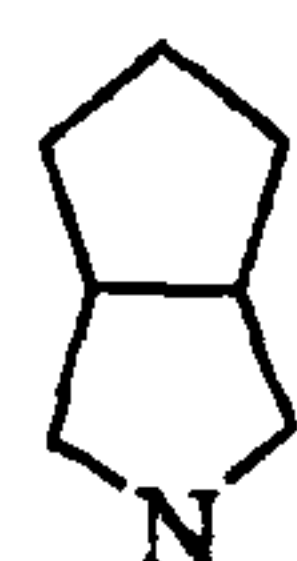


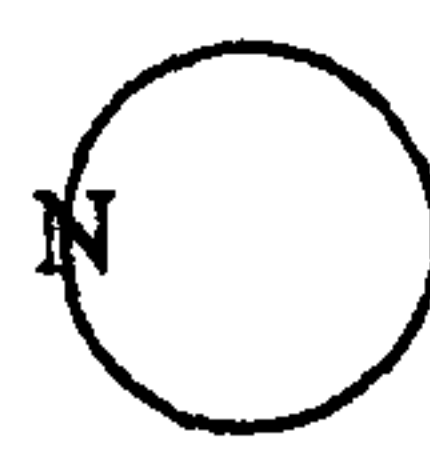
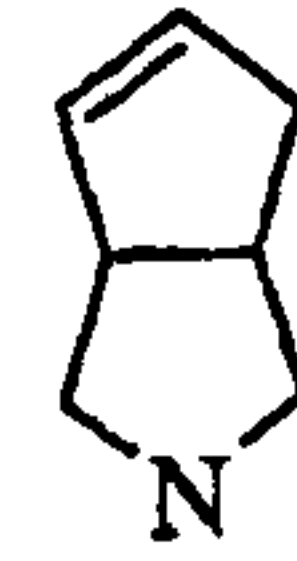
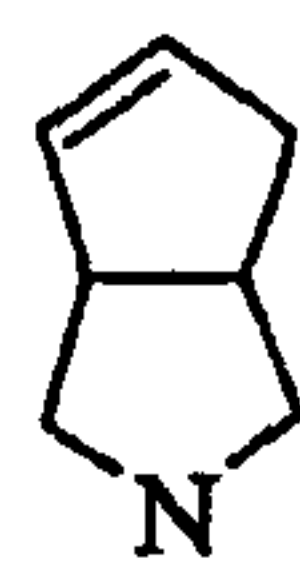
; yet further preferred

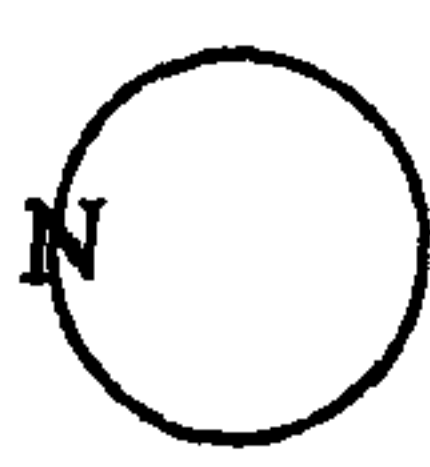
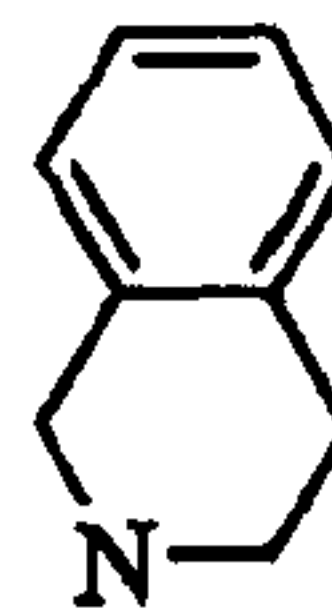


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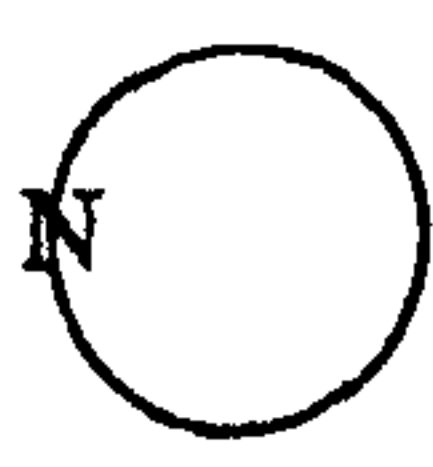


Another preferred embodiment according to the invention is where  as an optionally substituted multicyclic azaheterocyclyl is optionally substituted ; more preferred is optionally substituted . Particular substituents for  are hydroxy, fluoro or oxo.

5 Another preferred embodiment according to the invention is where  as an optionally substituted multicyclic azaheterocyclenyl is optionally substituted ; more preferred is ; further preferred is .

Another preferred embodiment according to the invention is where  as an optionally substituted multicyclic azaheterocyclenyl is optionally substituted .

10 A preferred embodiment according to the invention is where the $-\text{C}(\text{O})-\text{N}(\text{R}^4)-\text{R}^3-$

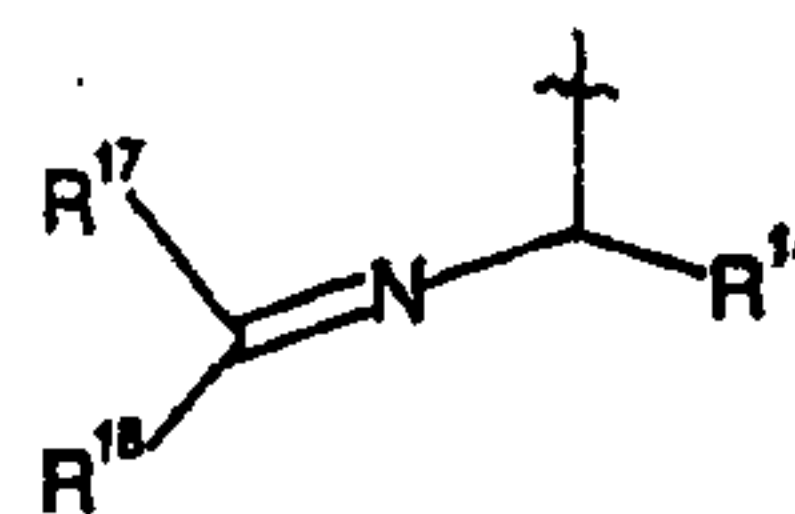
$\text{C}(\text{O})\text{R}^0\text{C}(\text{O})\text{NR}^2\text{R}^1$ moiety attached to  is attached a carbon α to the nitrogen atom.

A preferred embodiment according to the invention is where L is $-\text{C}(\text{O})-$ or $-\text{OC}(\text{O})-$.

A preferred embodiment according to the invention is where n is 0.

Another preferred embodiment according to the invention is where n is 1.

15 A preferred embodiment according to the invention is where R^{11} is $-\text{CO}_2\text{R}^{13}$.



A preferred embodiment according to the invention is where R^{12} is

A particular embodiment according to the invention is where R^{13} is an optionally substituted aliphatic group.

5 Another particular embodiment according to the invention is where R^{13} is an alkyl group.

A preferred embodiment according to the invention is where R^{13} is lower alkyl.

Another preferred embodiment according to the invention is where R^{13} is methyl.

A preferred embodiment according to the invention is where R^{14} is $-\text{CO}_2R^{16}$.

A particular embodiment according to the invention is where R^{15} is alkyl.

10 A preferred embodiment according to the invention is where R^{15} is lower alkyl.

A preferred embodiment according to the invention is where R^{15} is methyl.

A particular embodiment according to the invention is where R^{16} is optionally substituted aliphatic.

Another particular embodiment according to the invention is where R^{16} is alkyl.

15 A preferred embodiment according to the invention is where R^{16} is lower alkyl.

A preferred embodiment according to the invention is where R^{16} is t-Bu.

A particular embodiment according to the invention is where R^{17} is optionally substituted aryl.

A preferred embodiment according to the invention is where R^{17} is phenyl.

20 A particular embodiment according to the invention is where R^{18} is optionally substituted aryl.

A preferred embodiment according to the invention is where R^{18} is phenyl.

A particular embodiment according to the invention is where p^0 is selected from the group consisting of BOC, CBz, and $-\text{CO}_2\text{alkyl}$.

25 A preferred embodiment according to the invention is where p^0 is BOC.

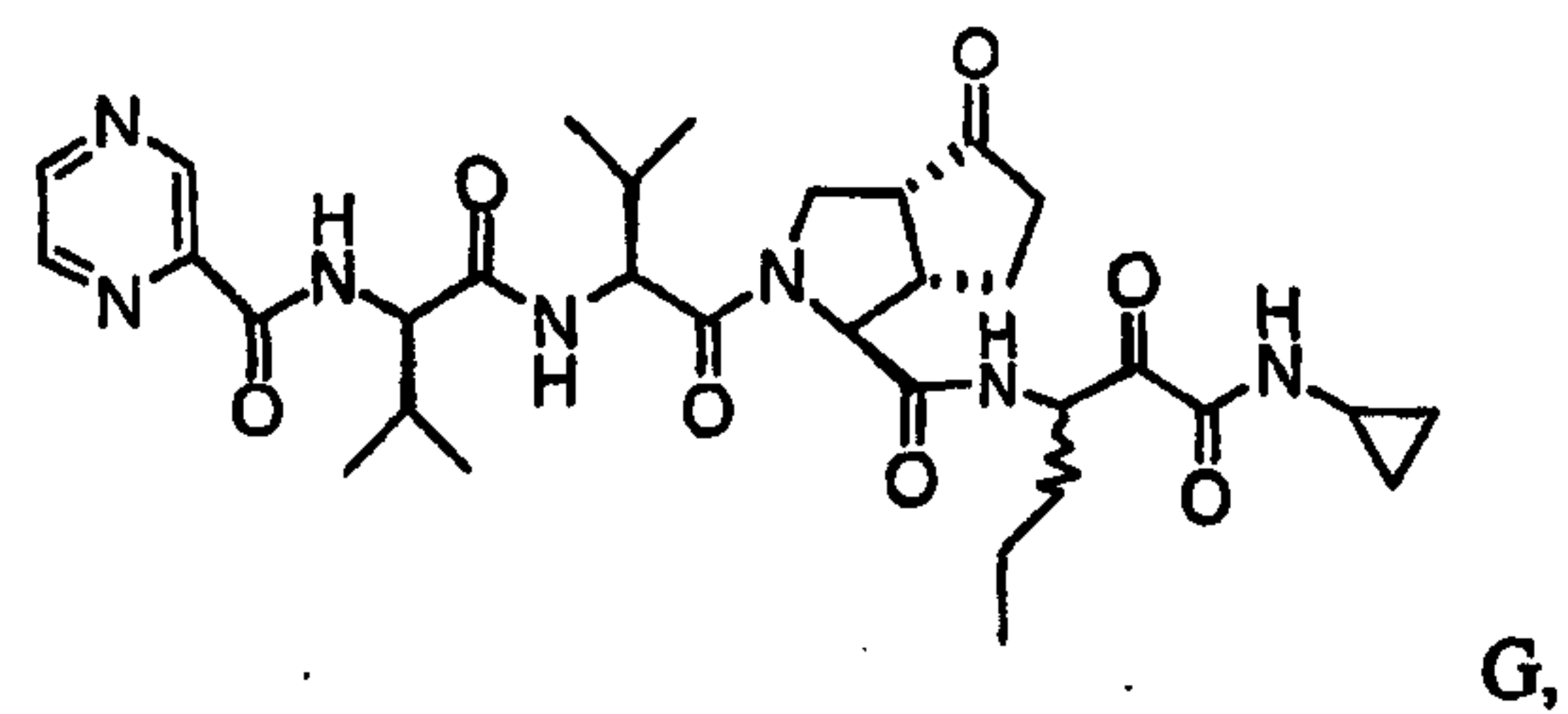
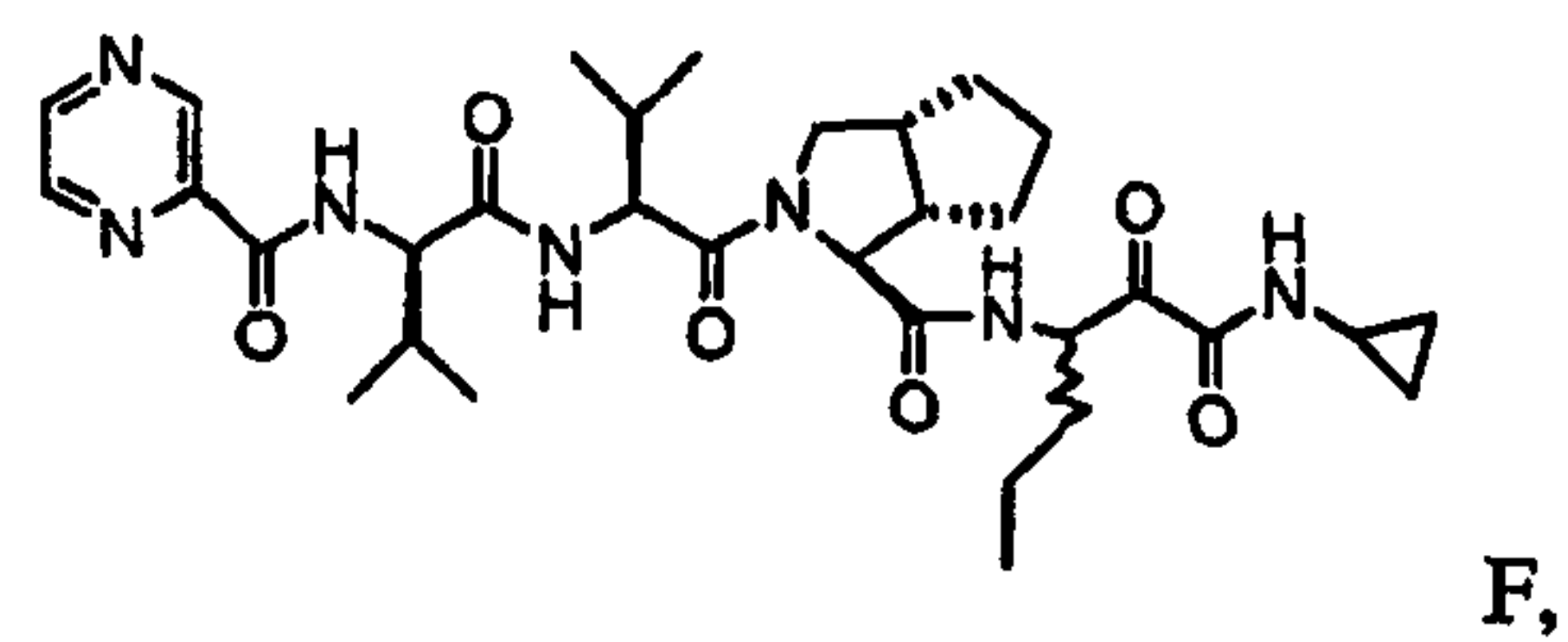
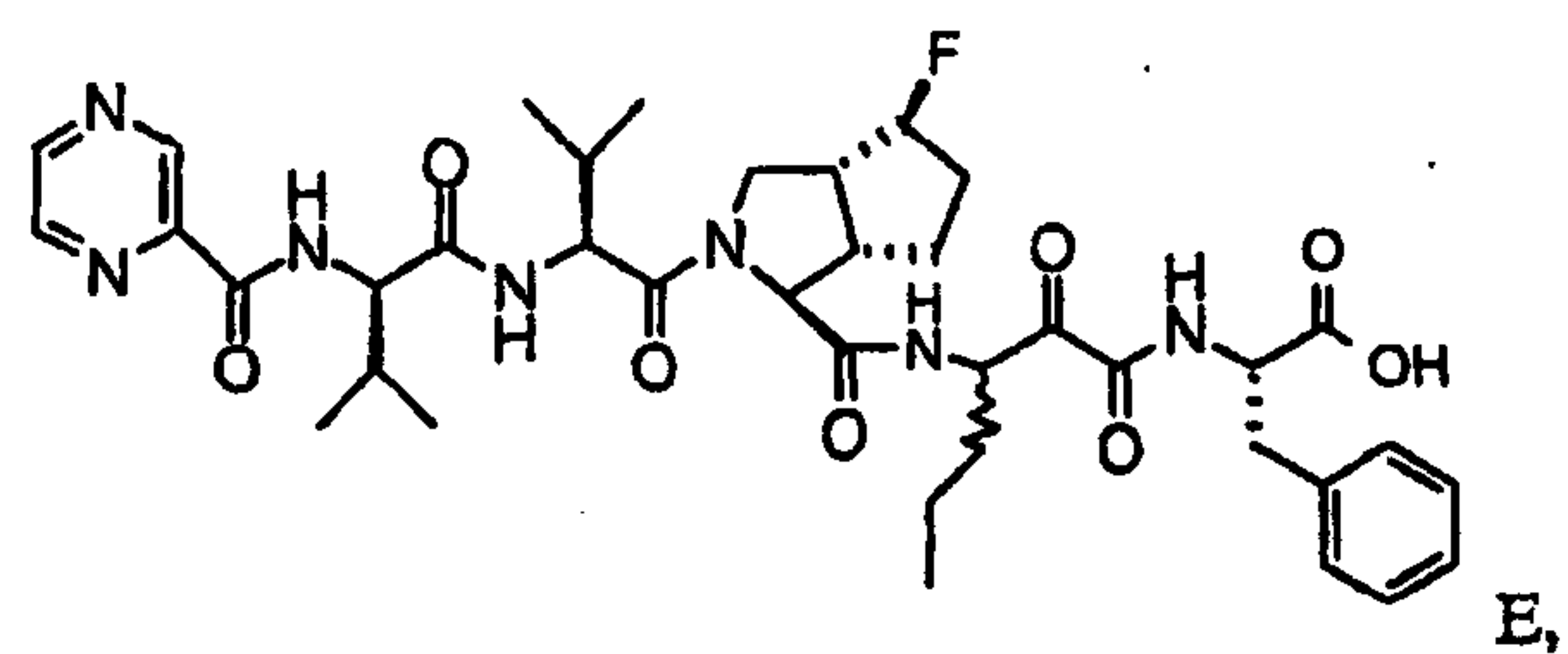
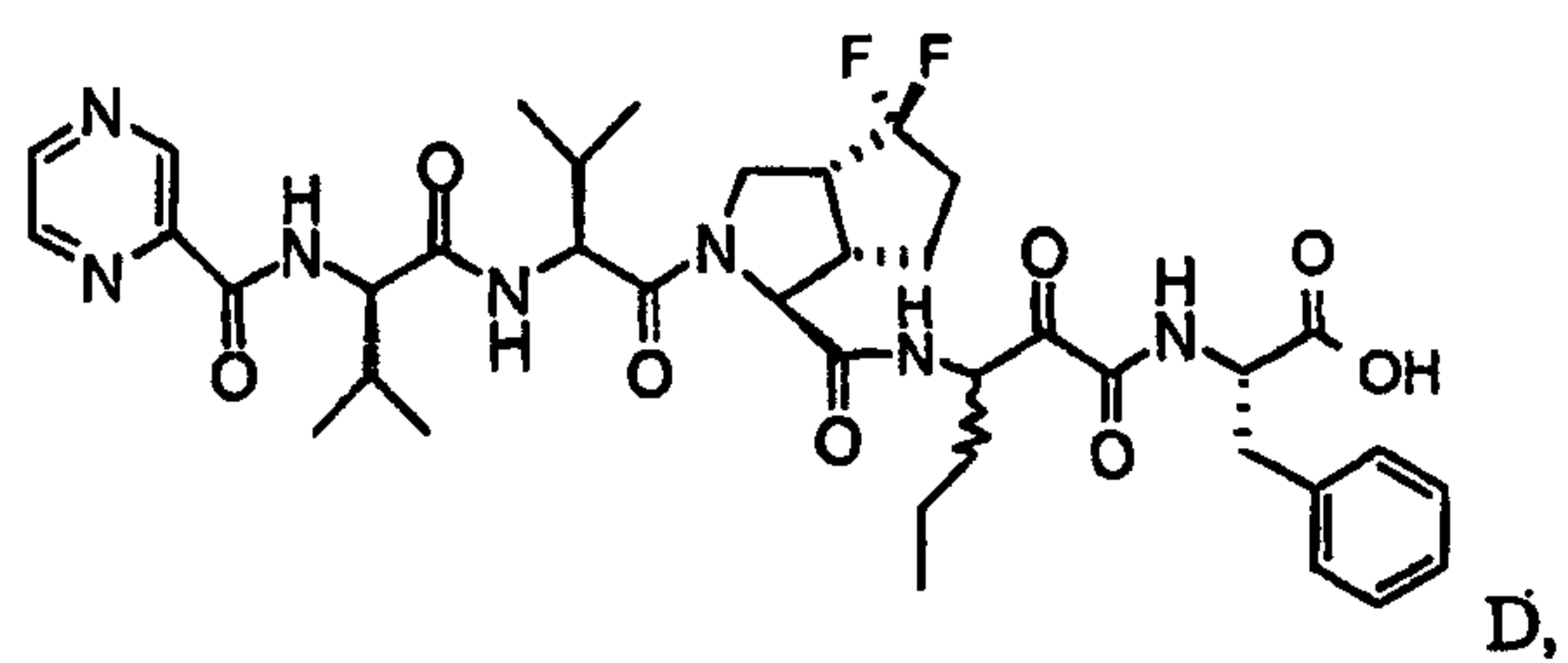
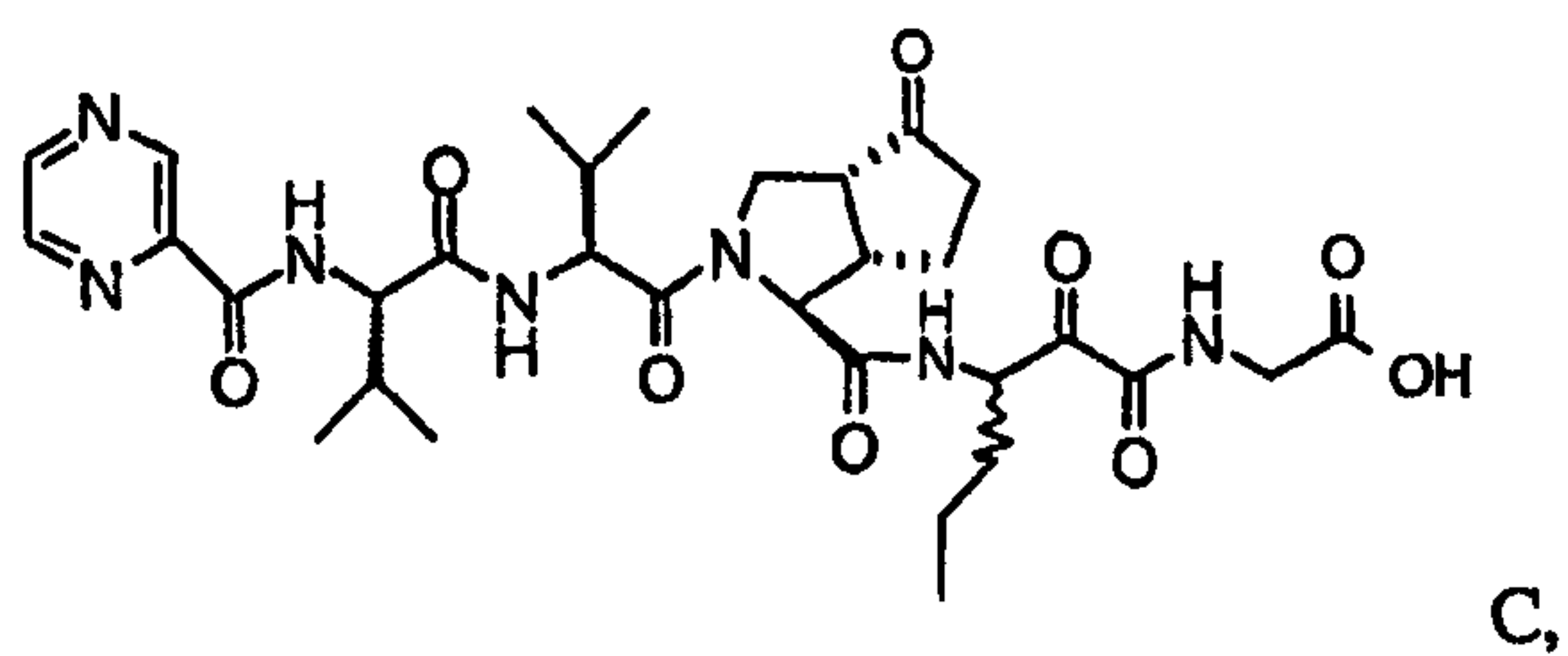
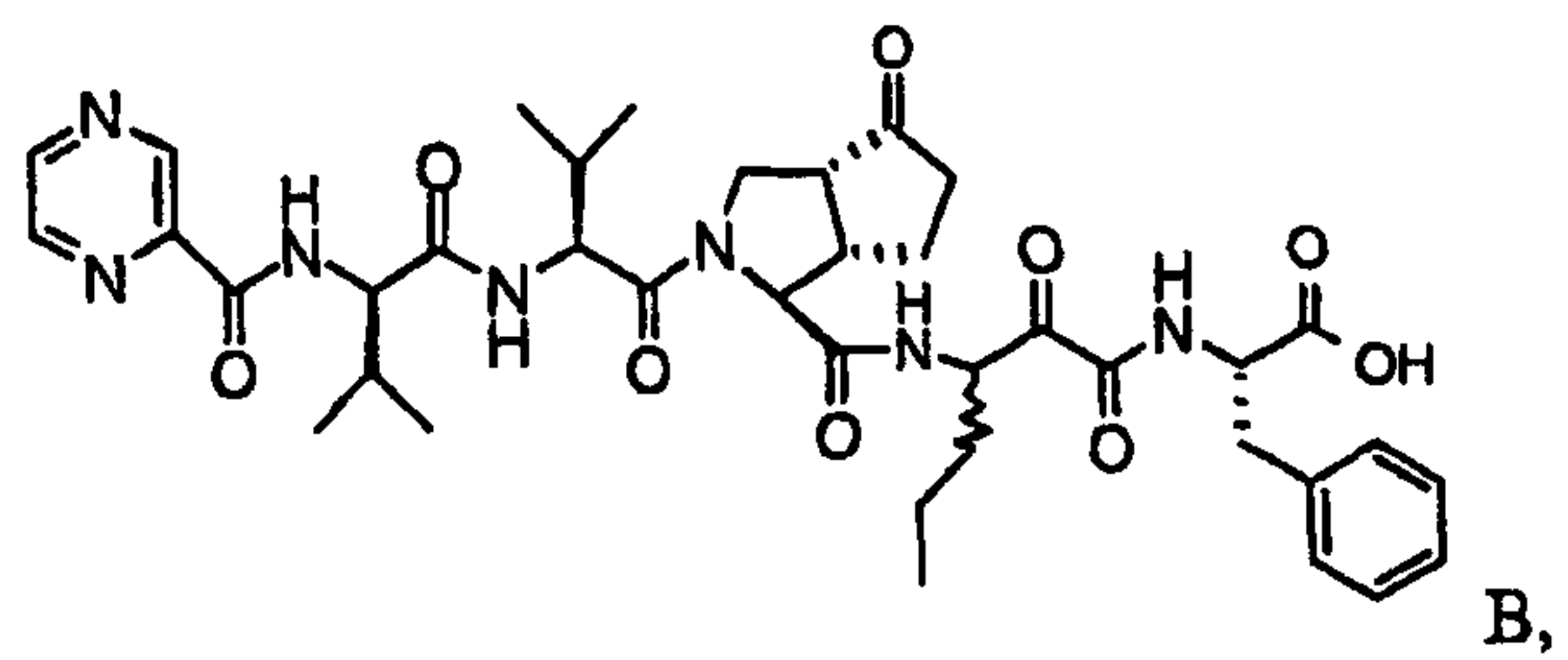
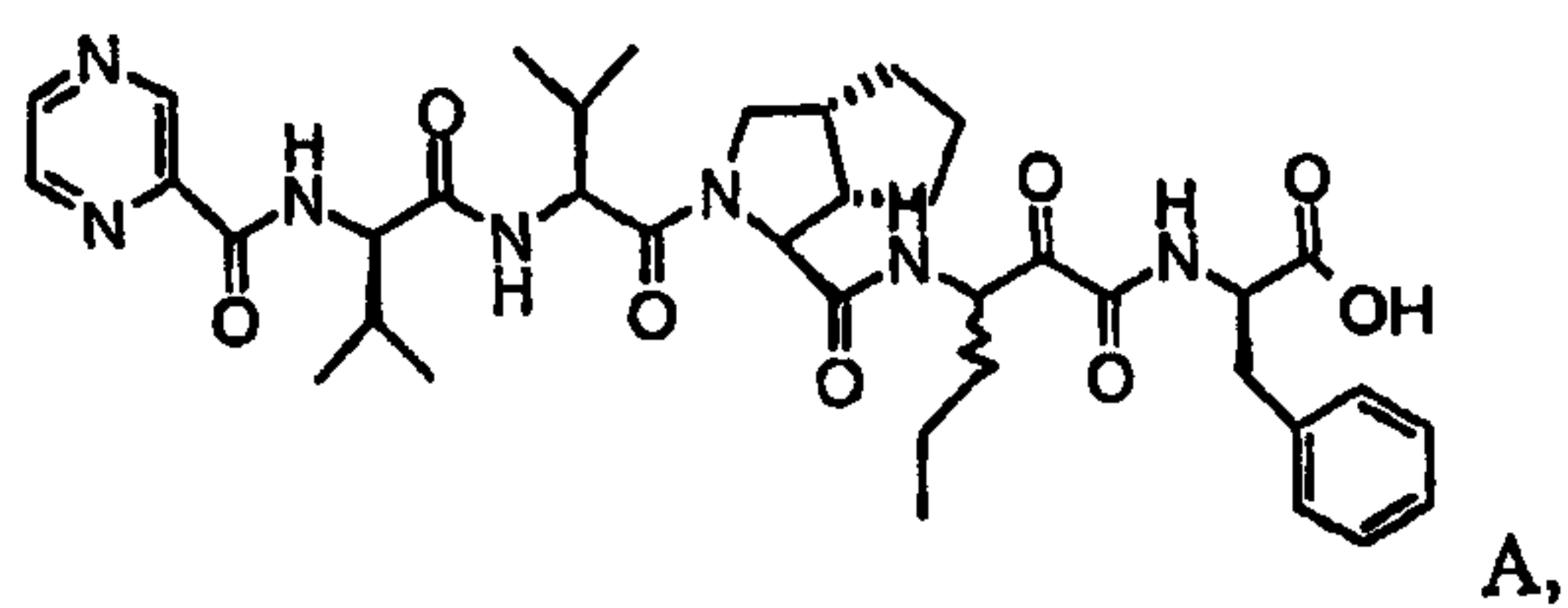
It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein.

Particular compounds according to the invention are selected from the group of compounds A-FH consecutively consisting of

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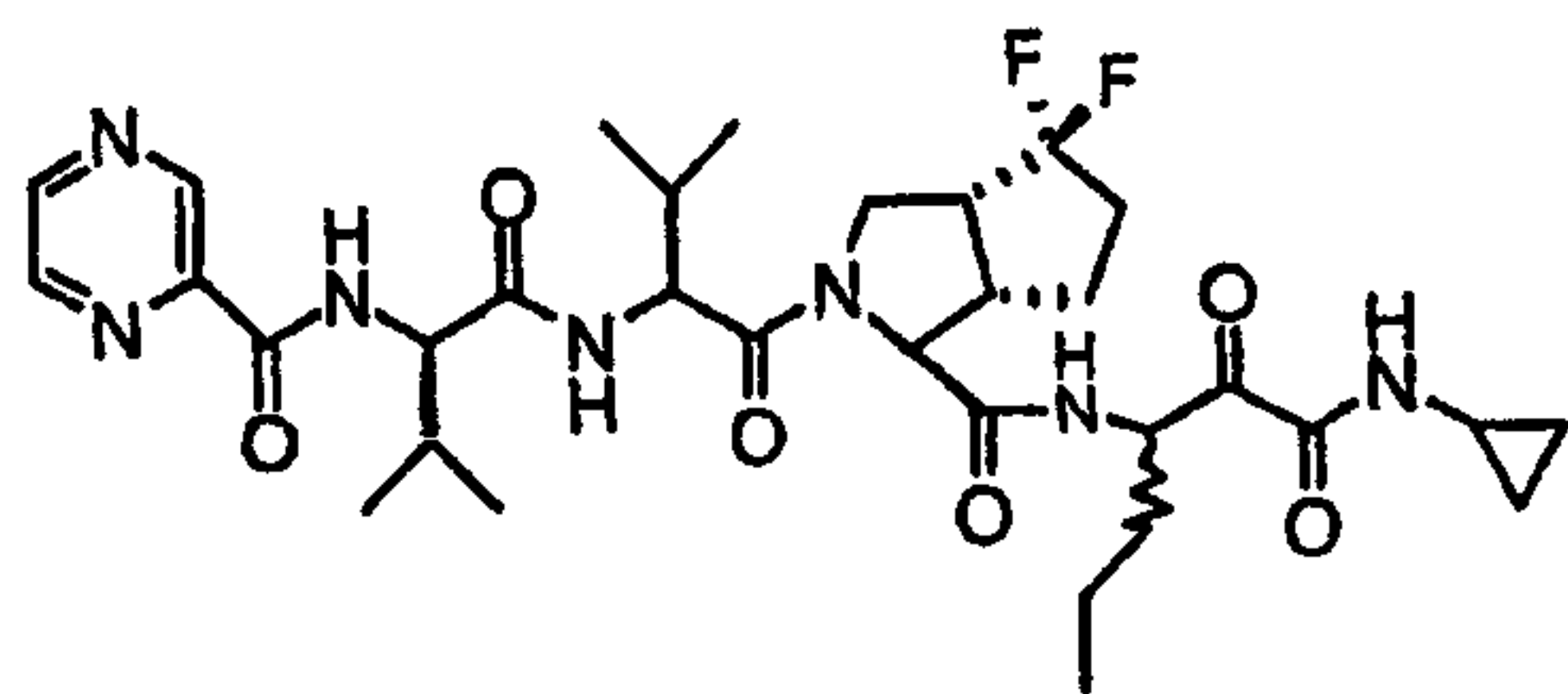


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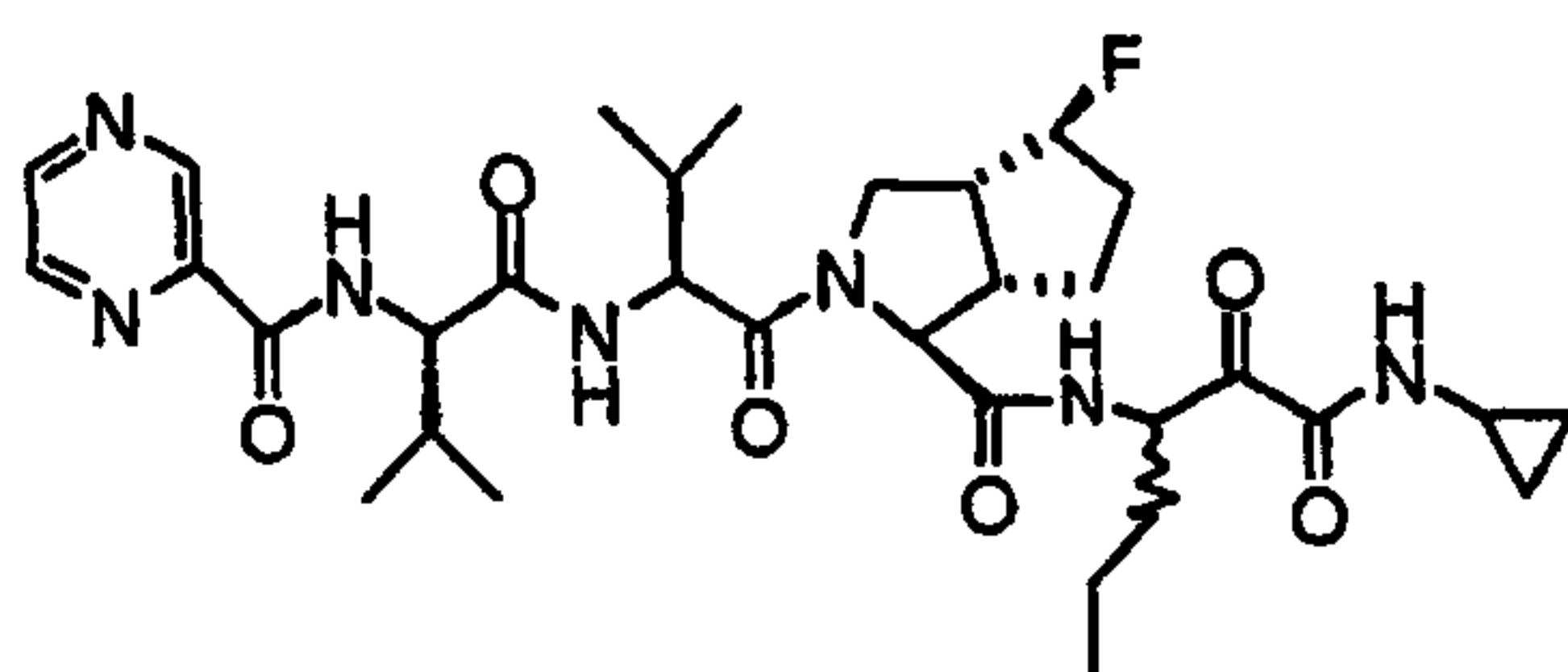
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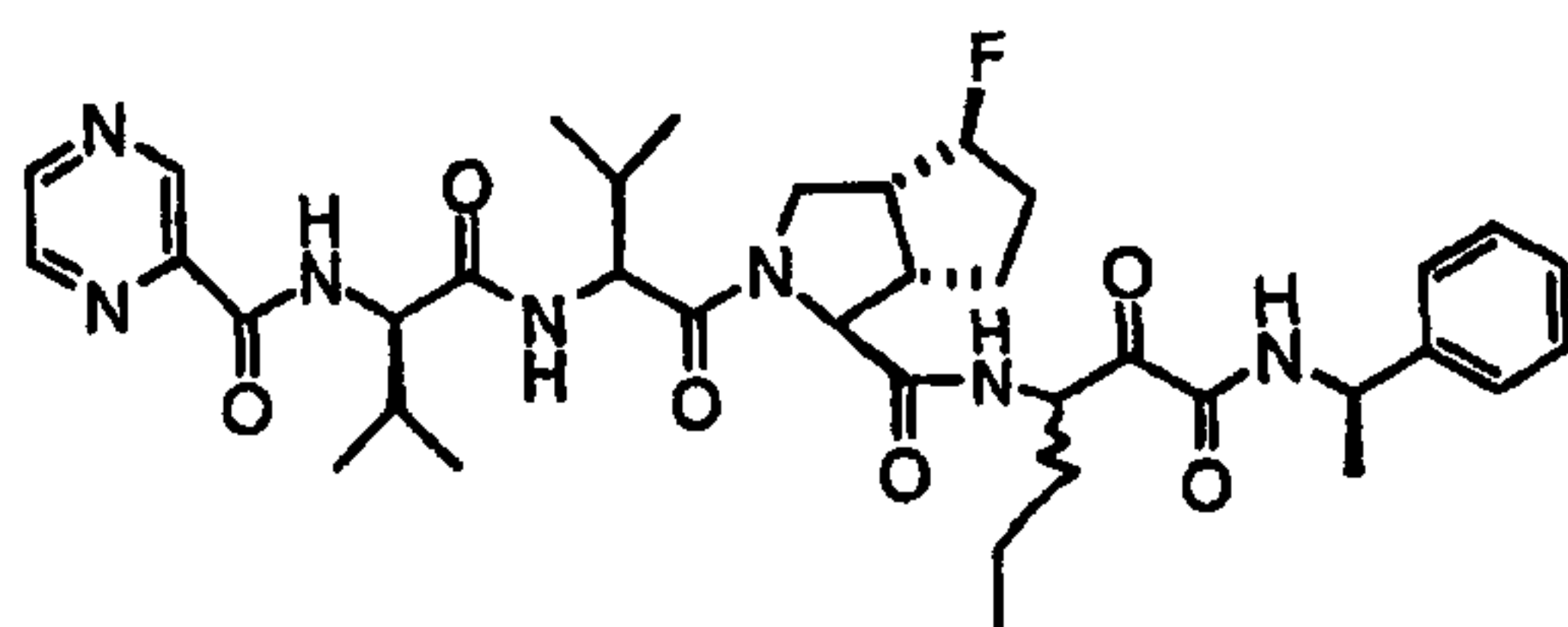
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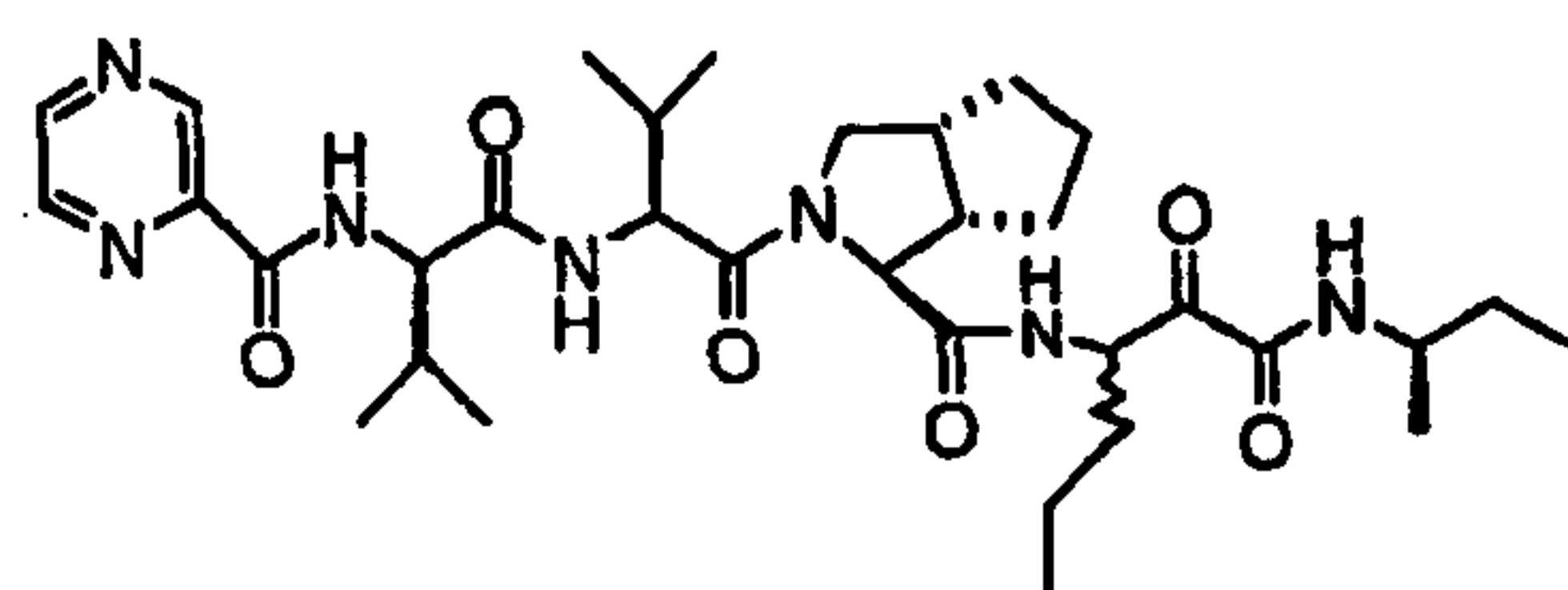
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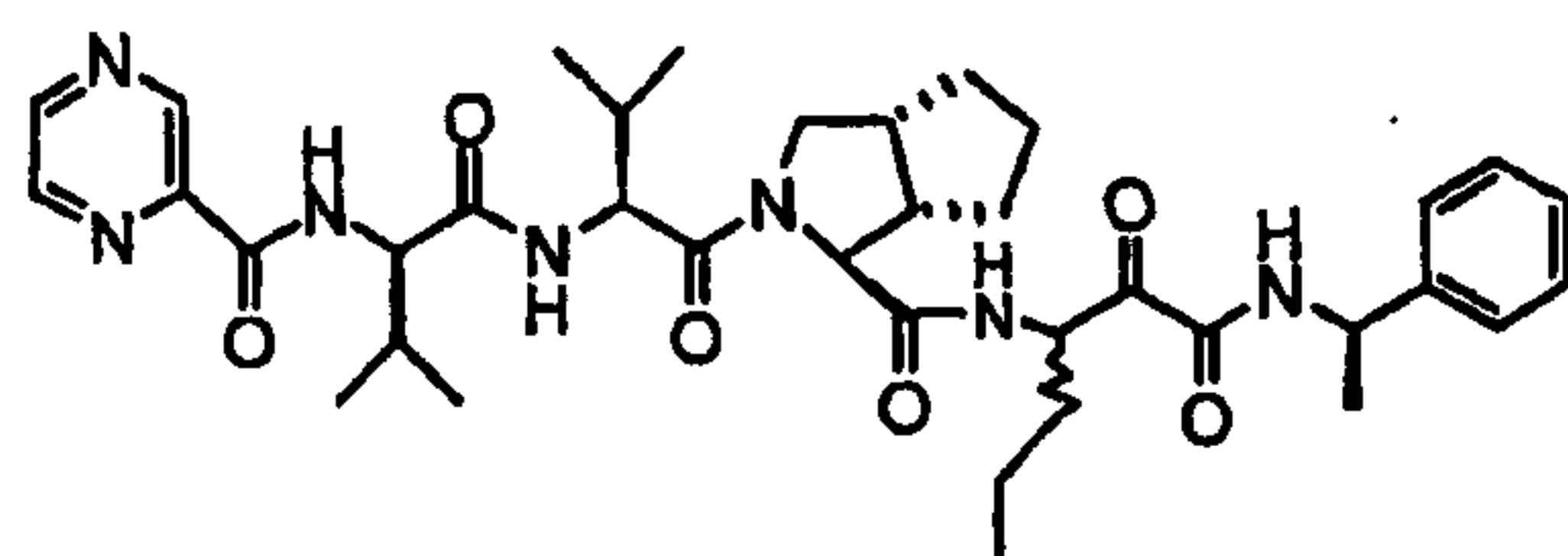
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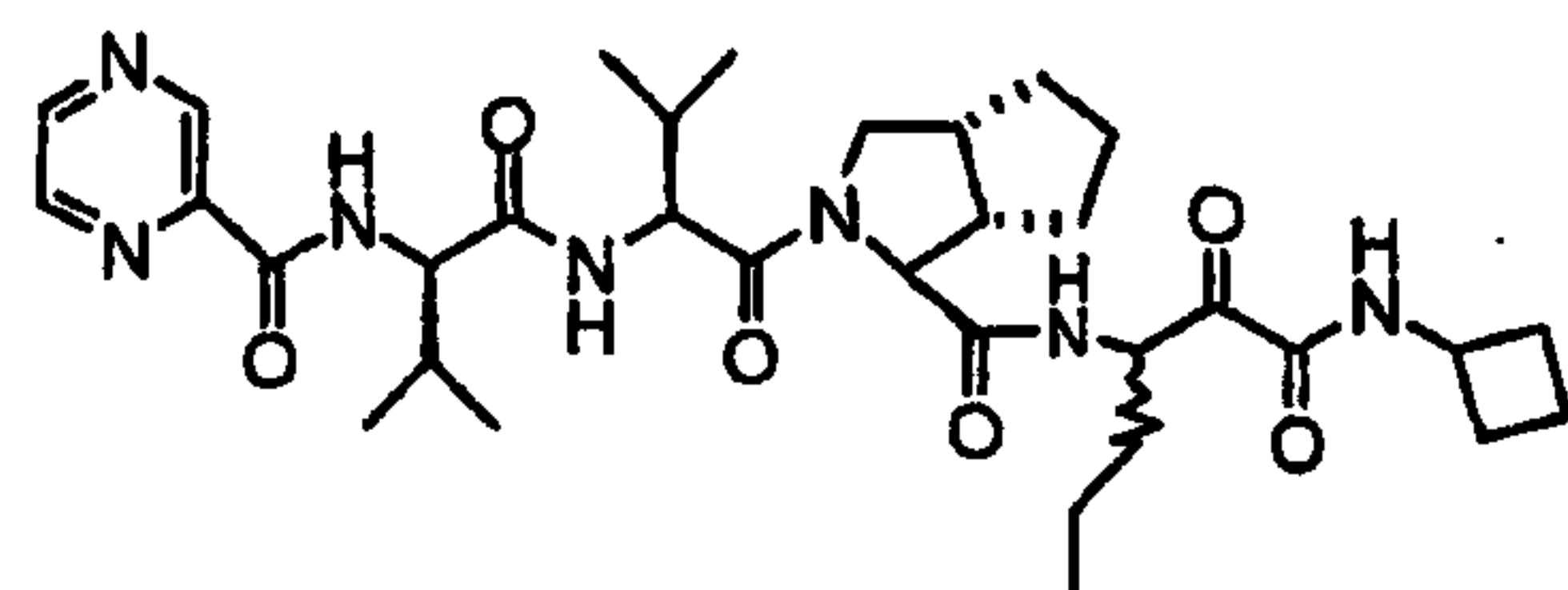


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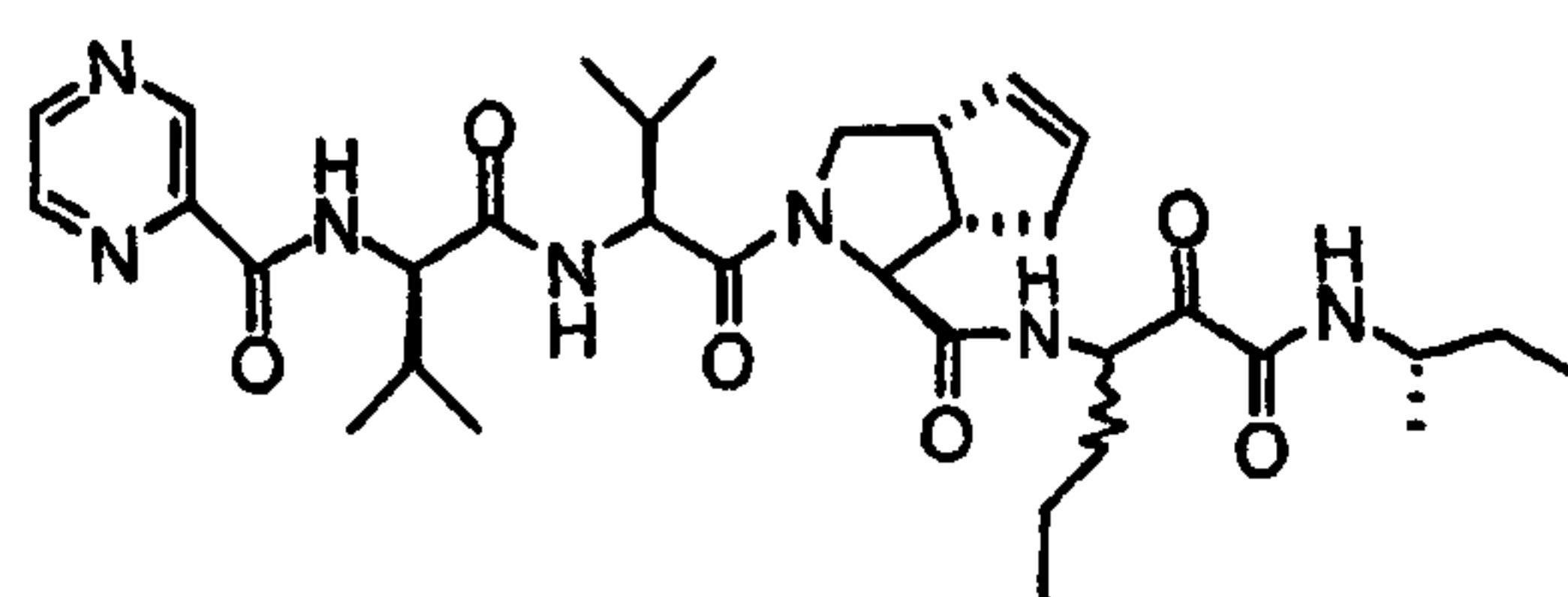


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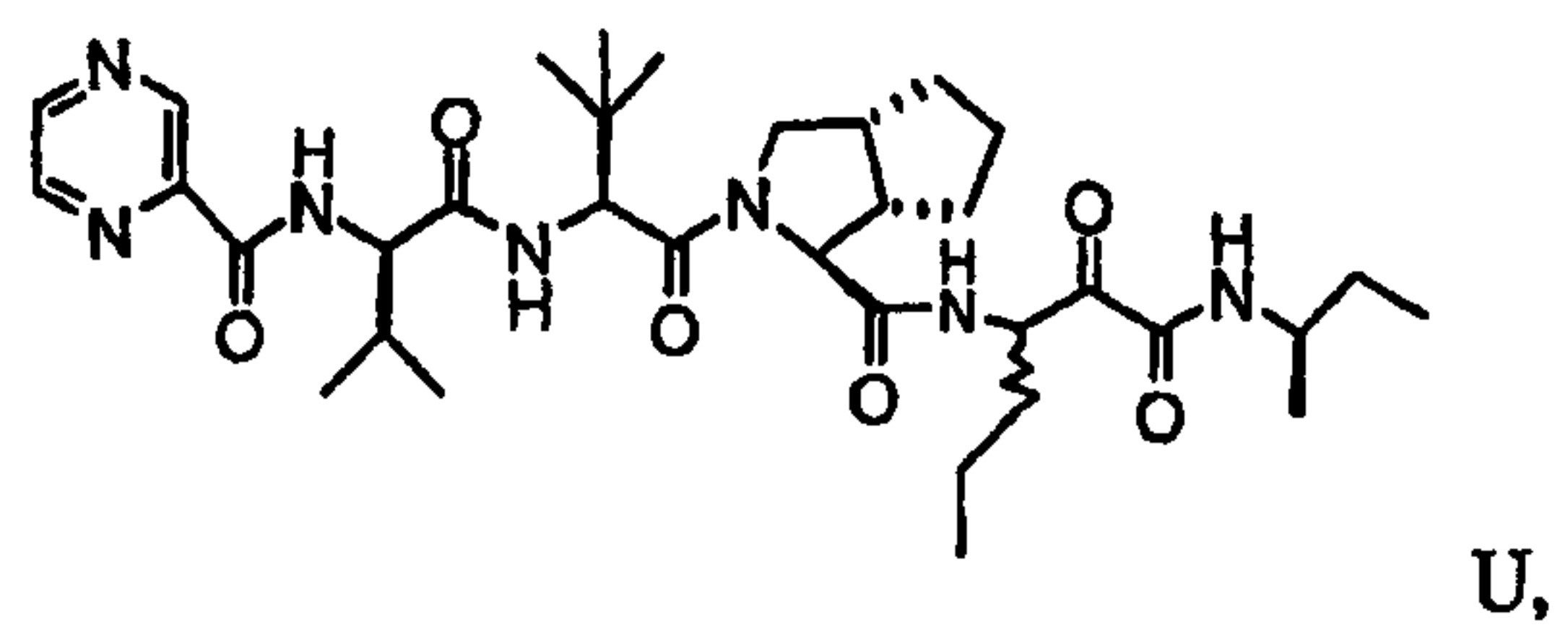
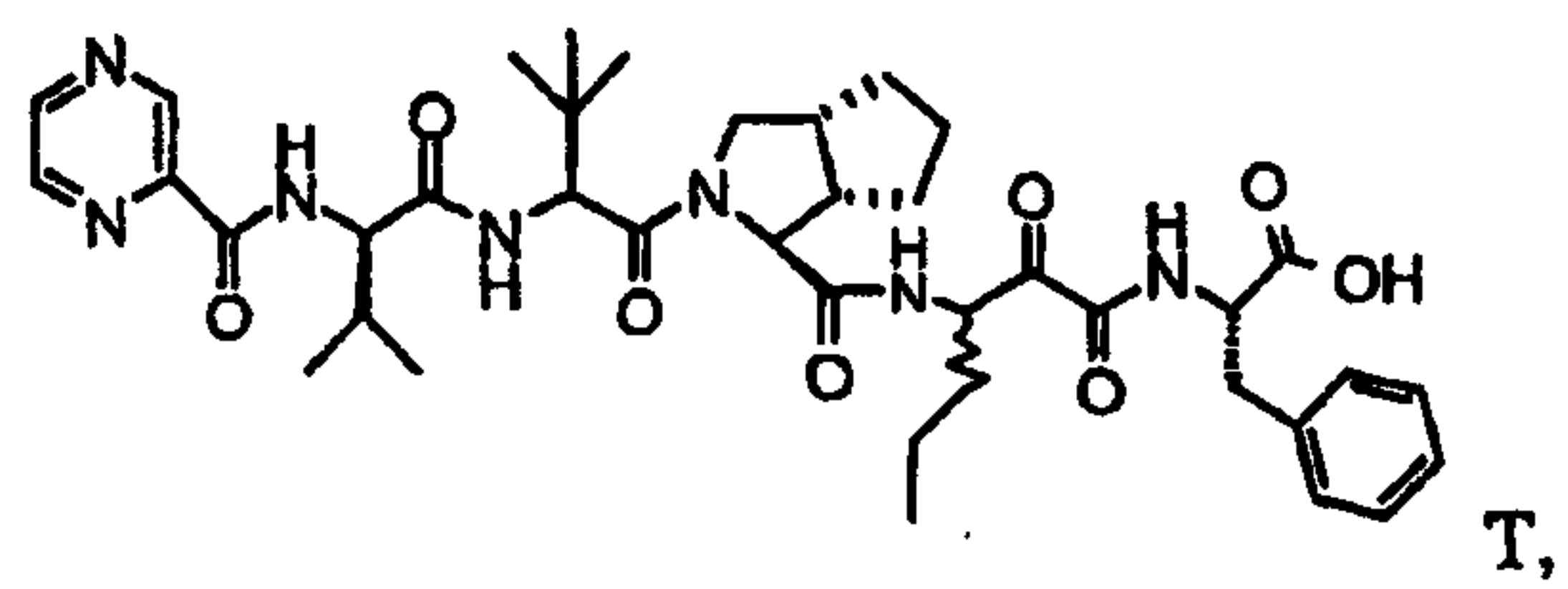
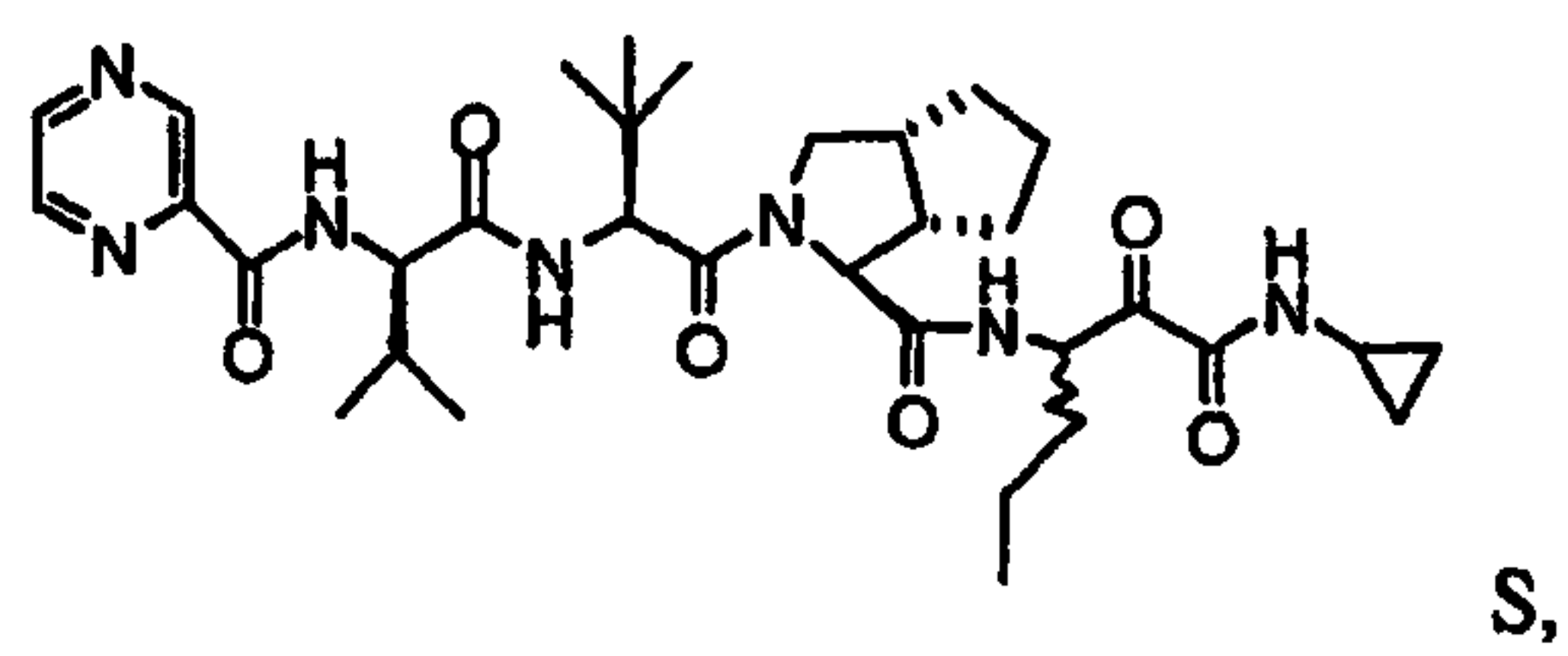
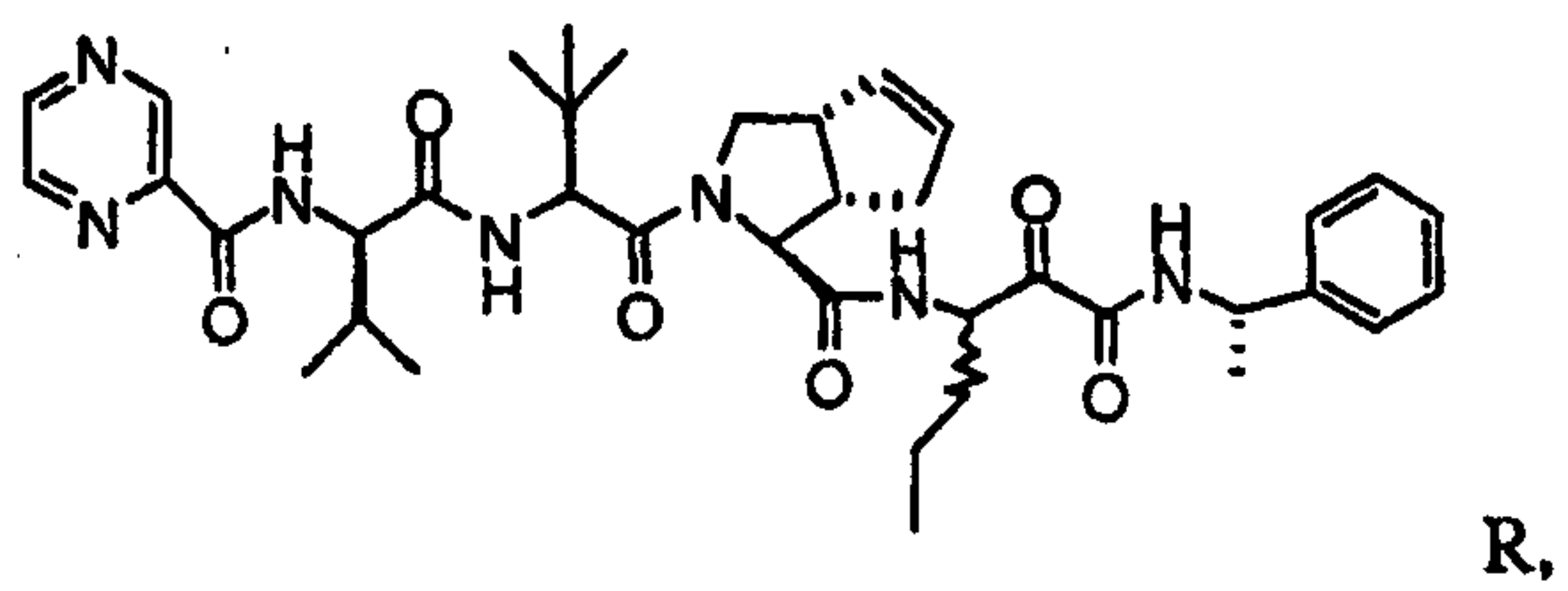
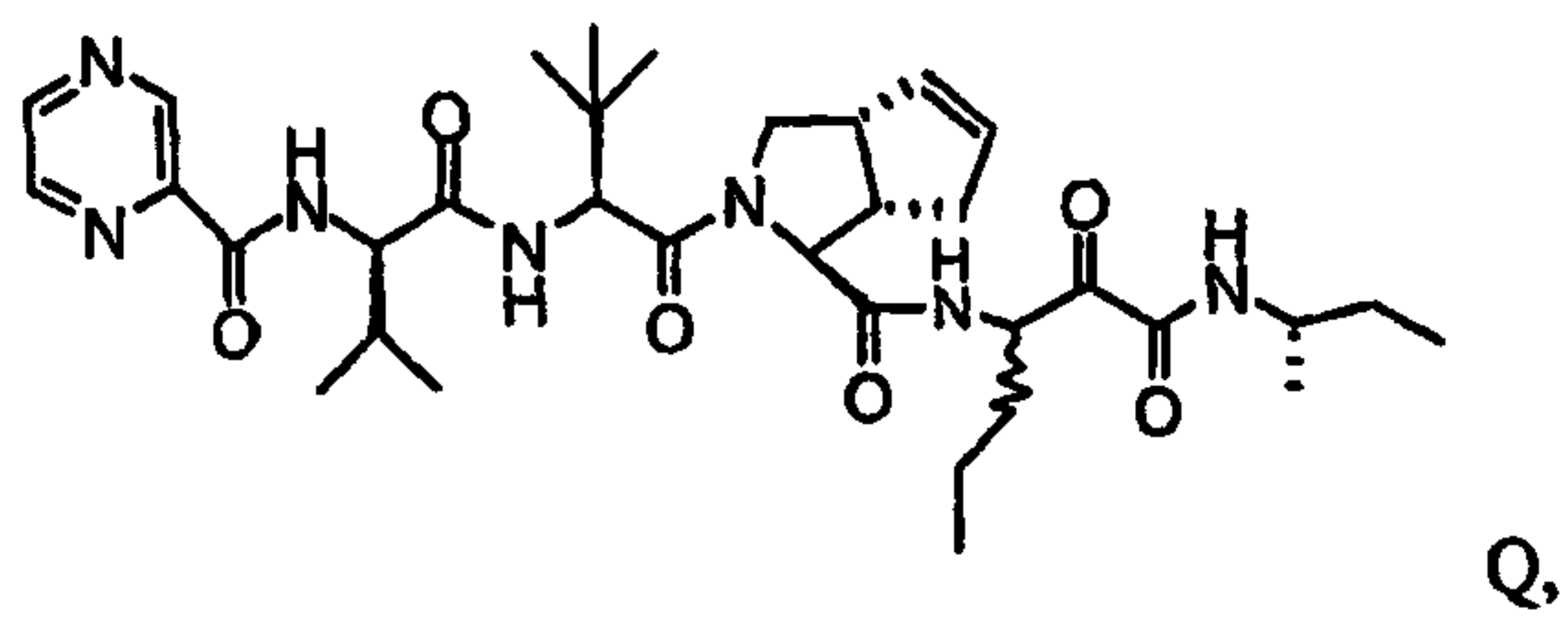
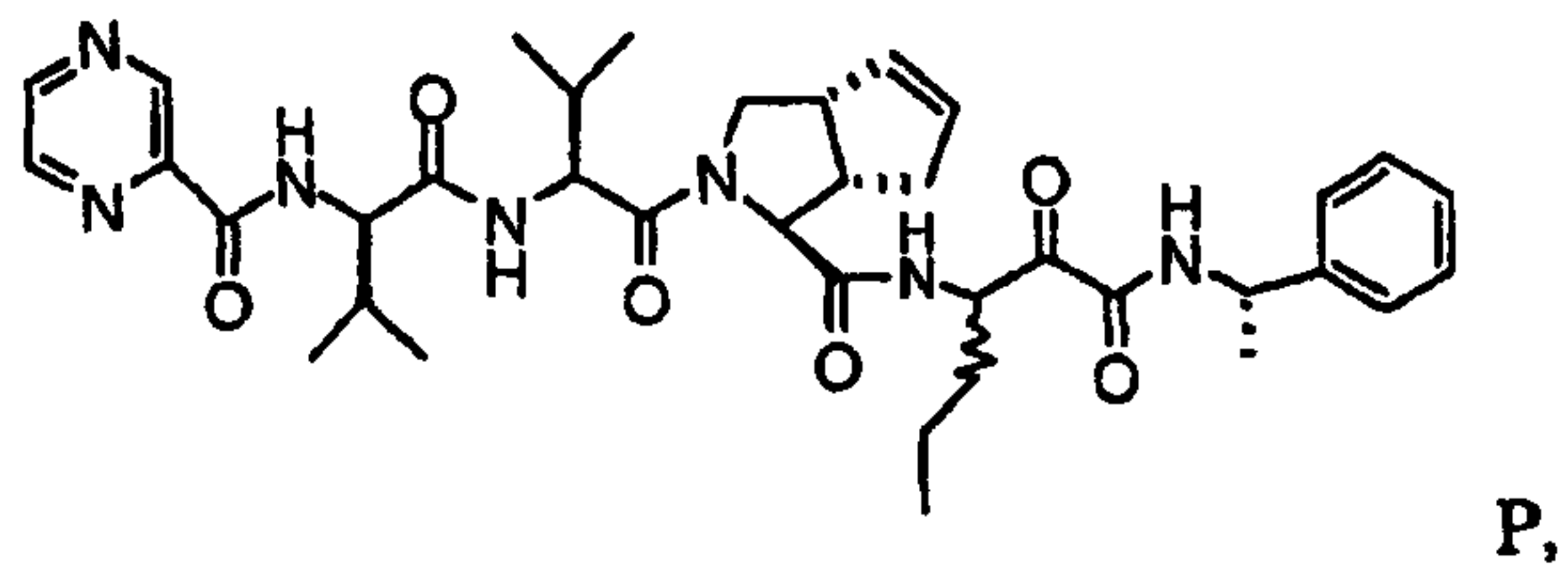
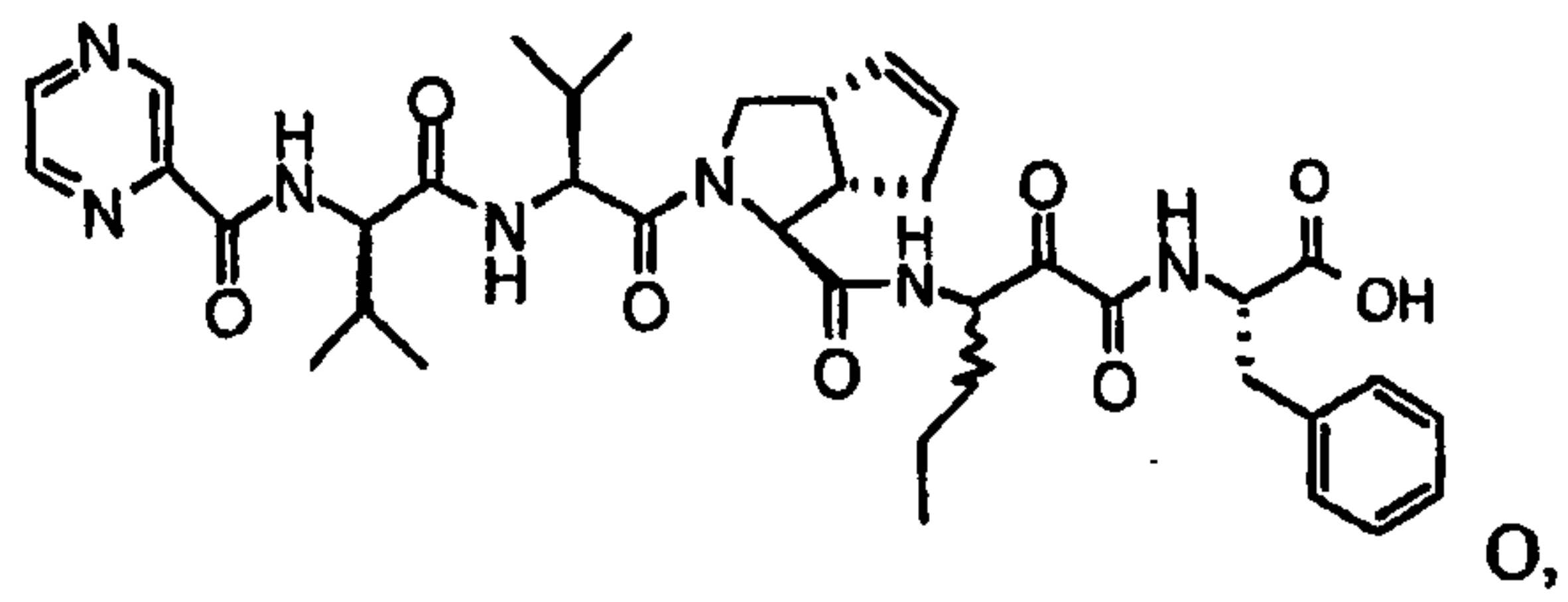


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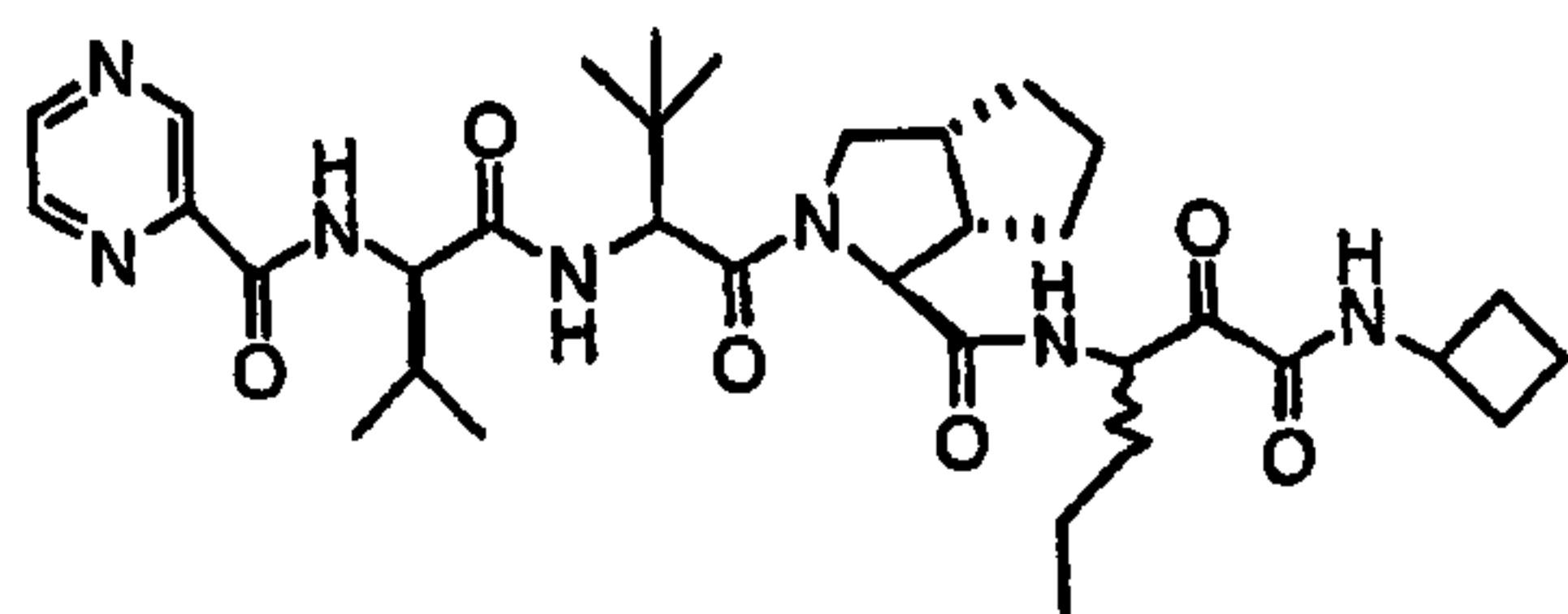


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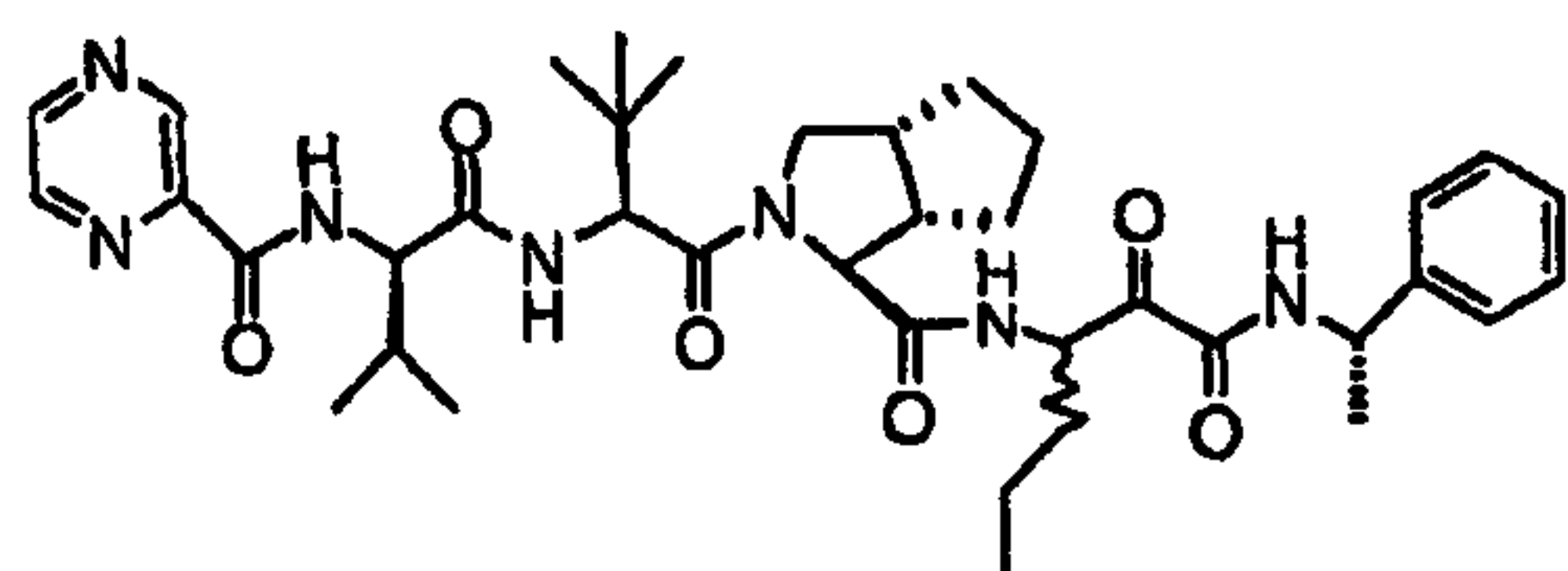
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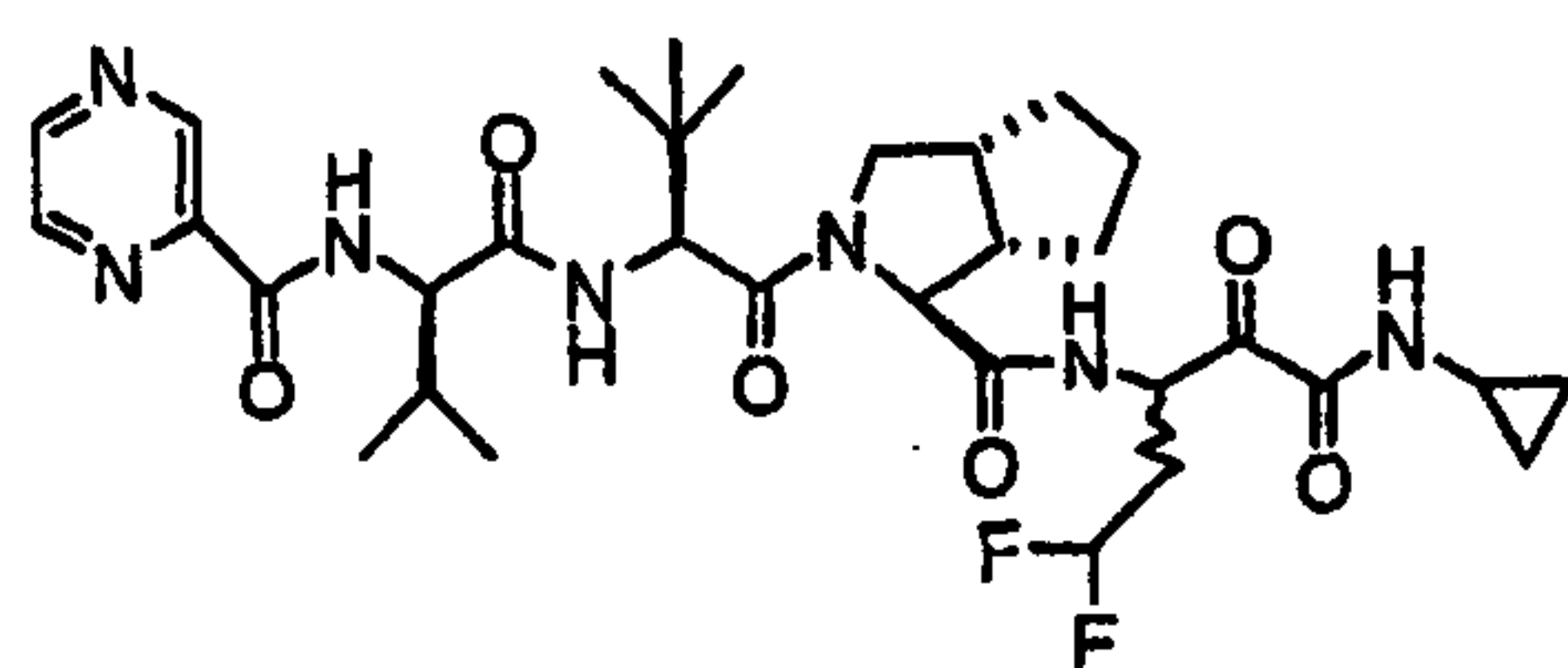
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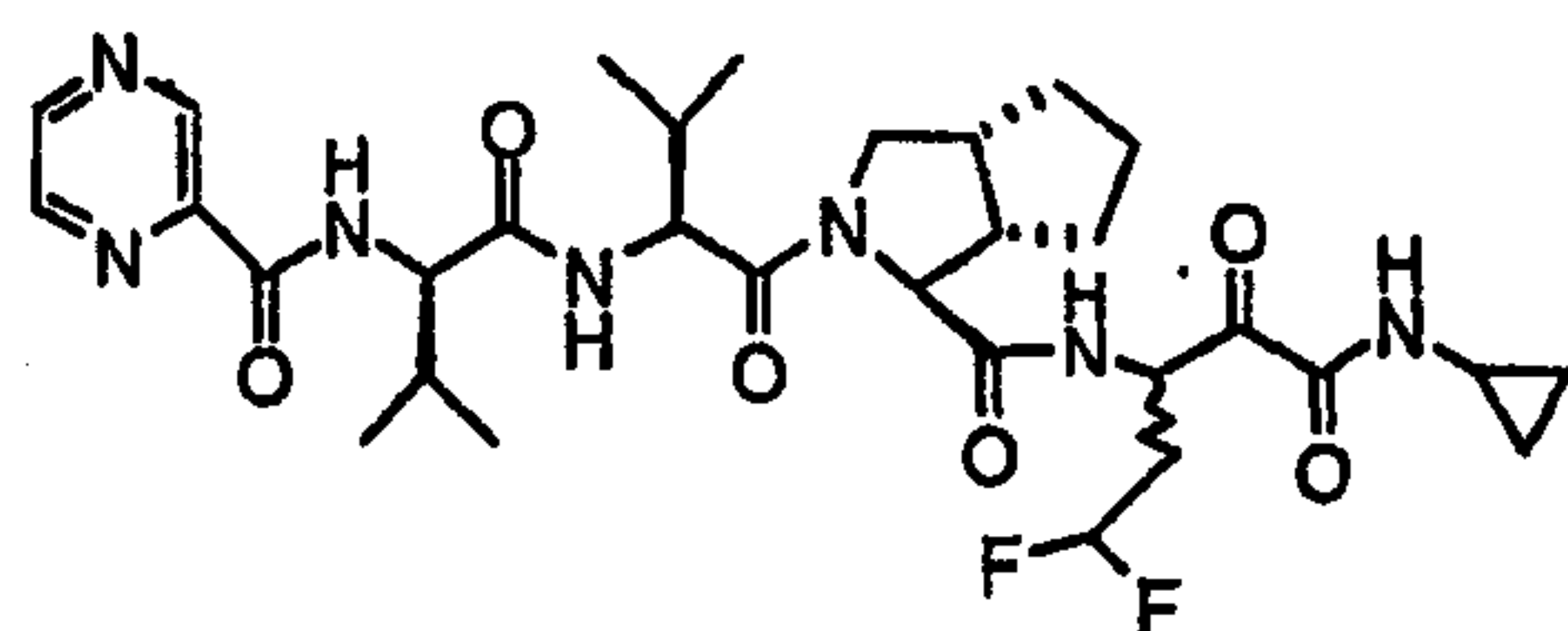
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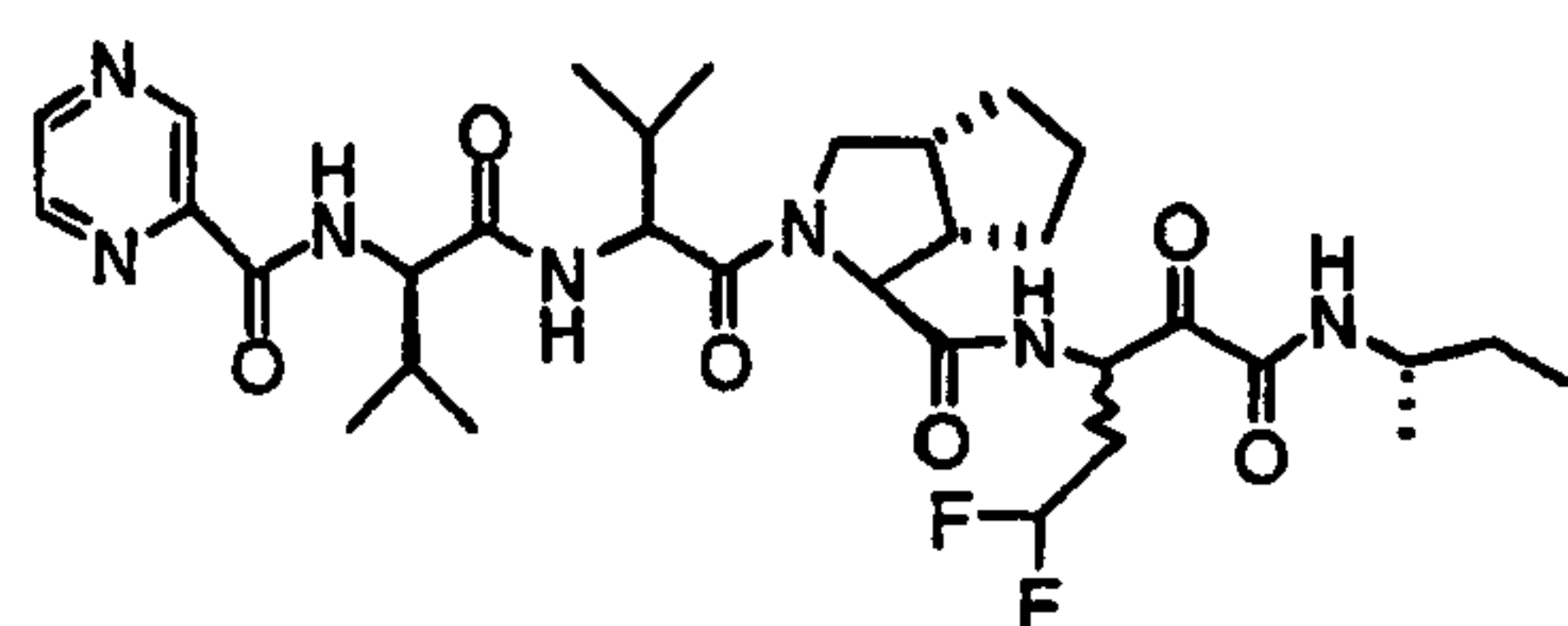
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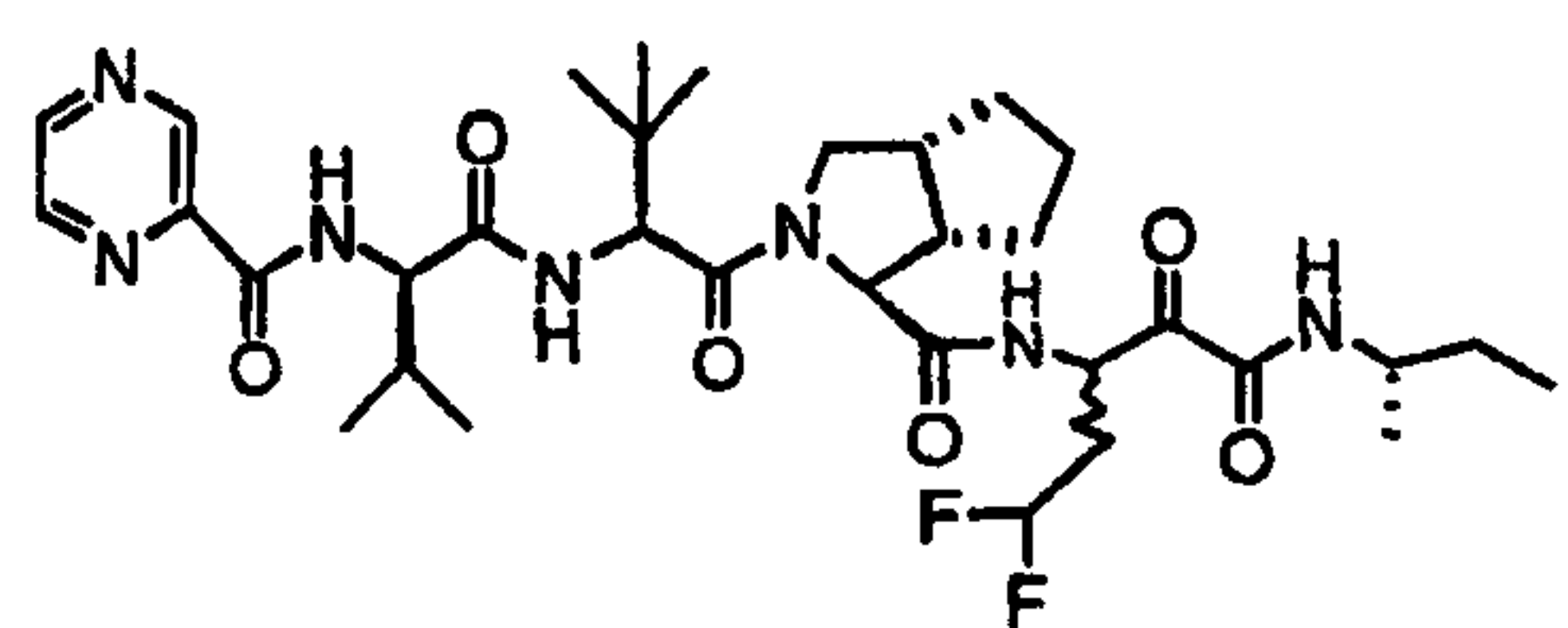
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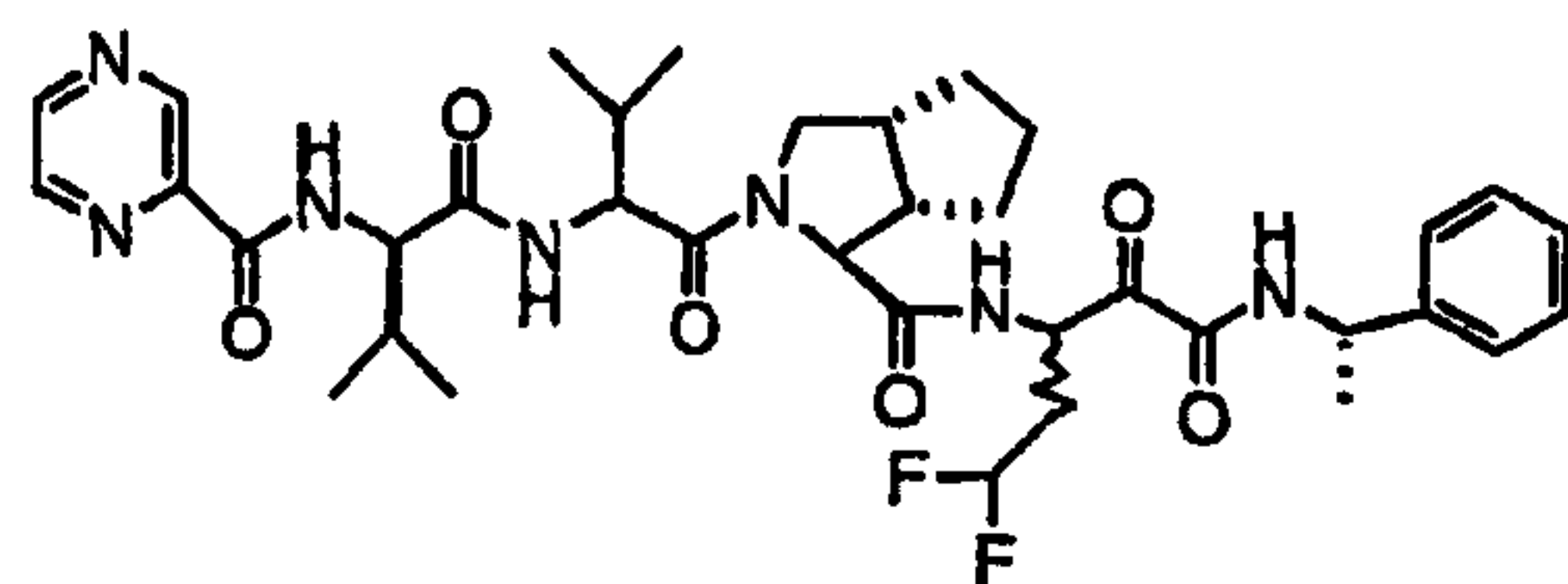
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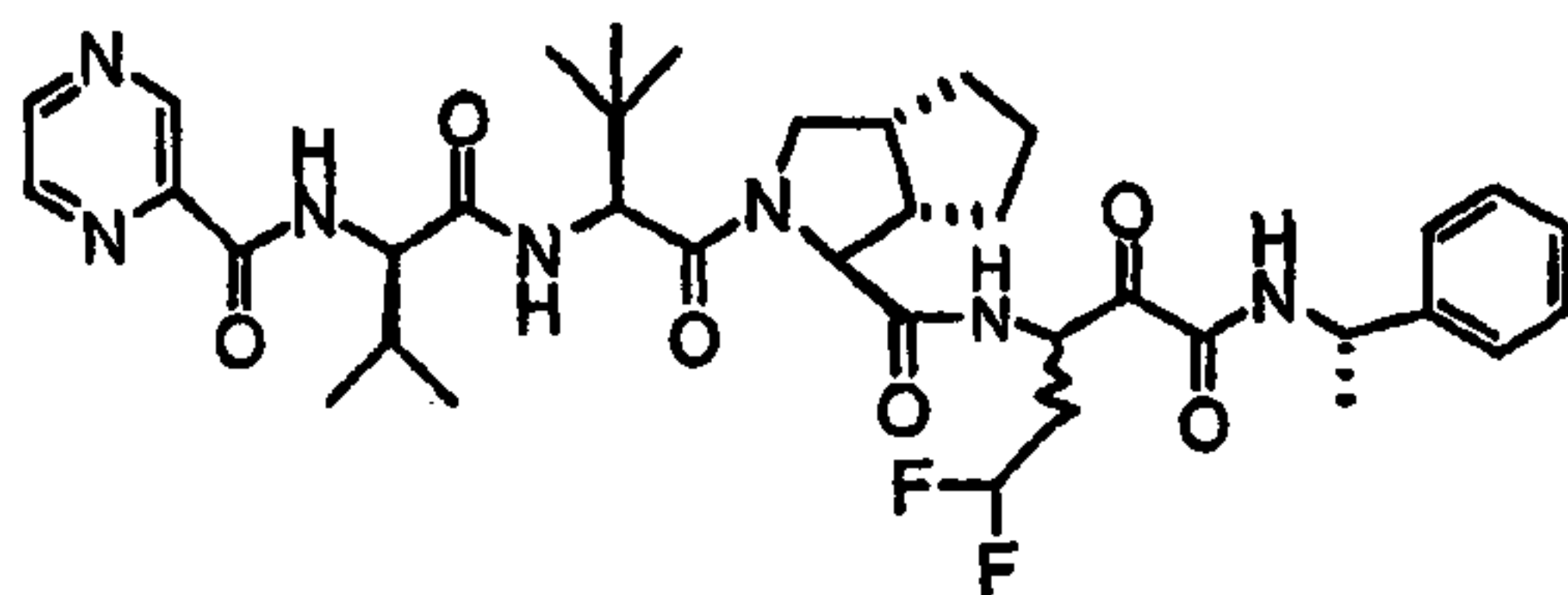
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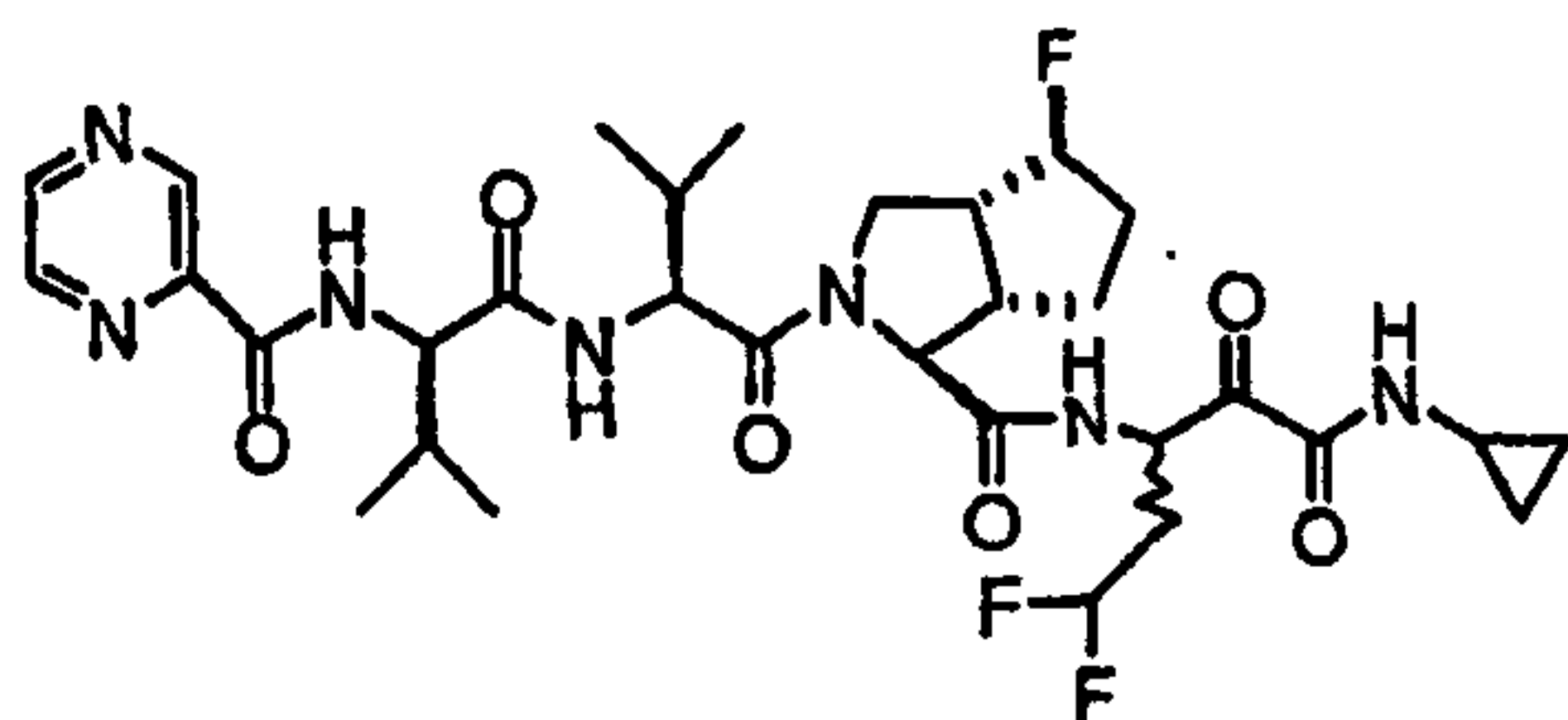
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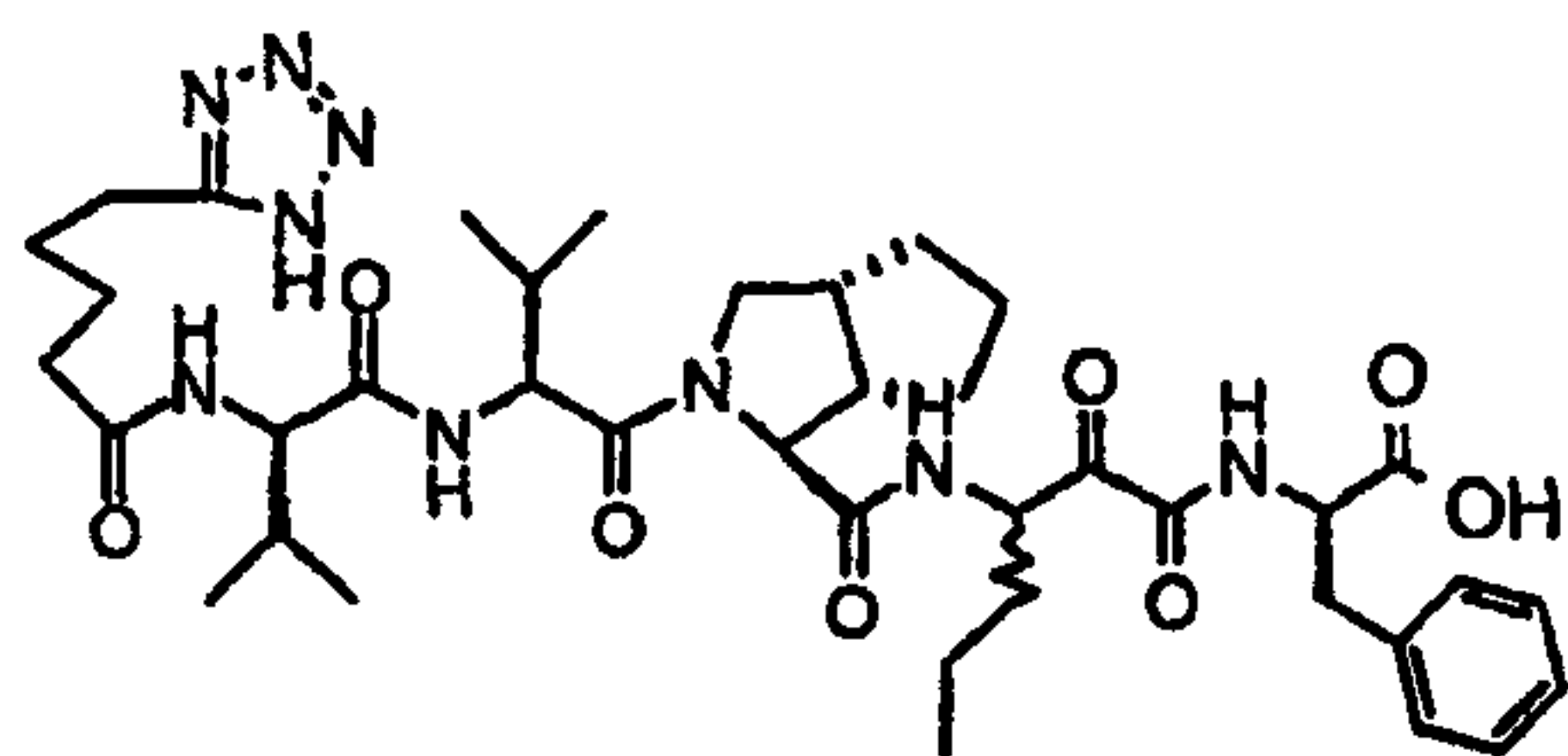
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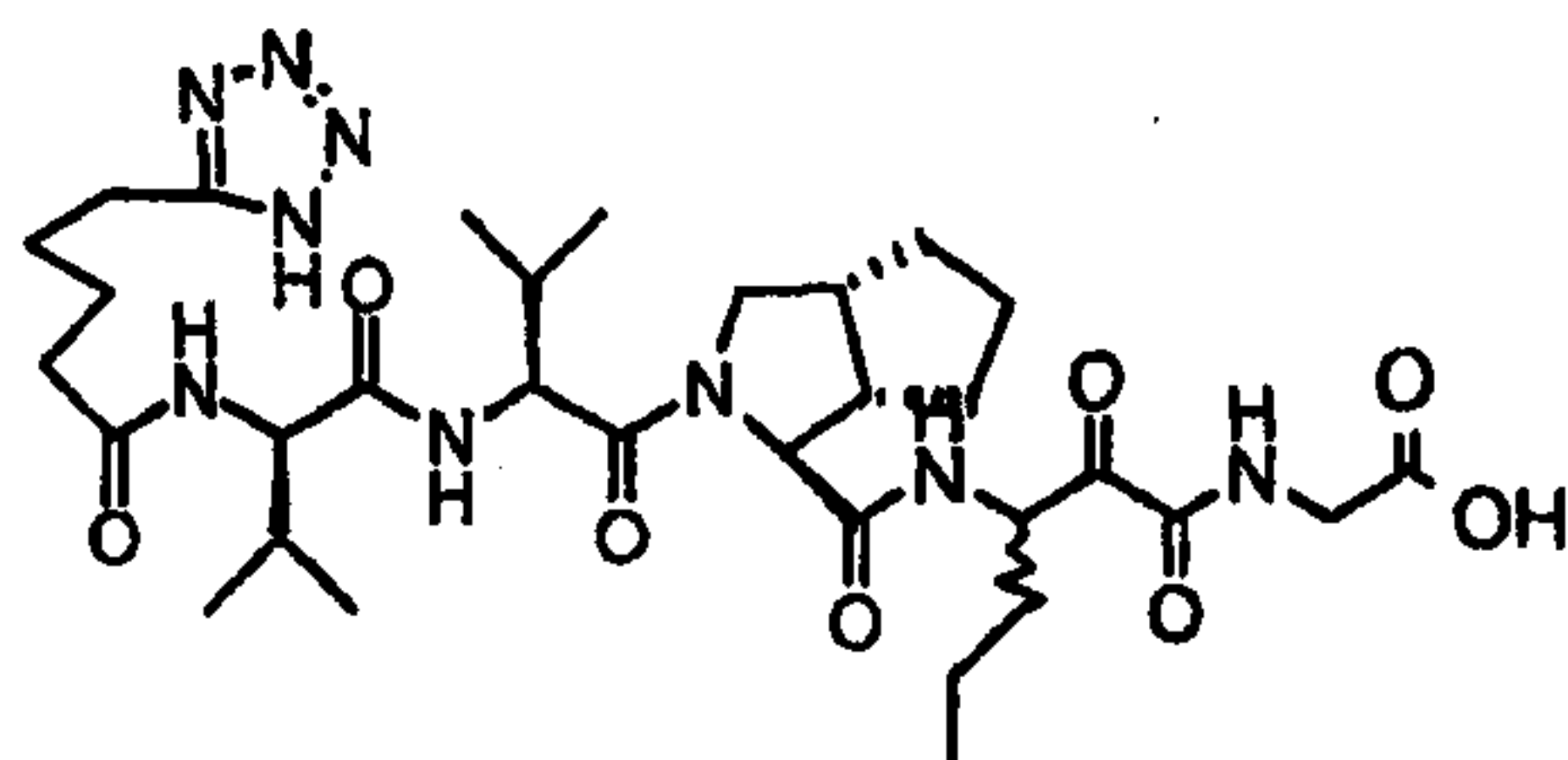
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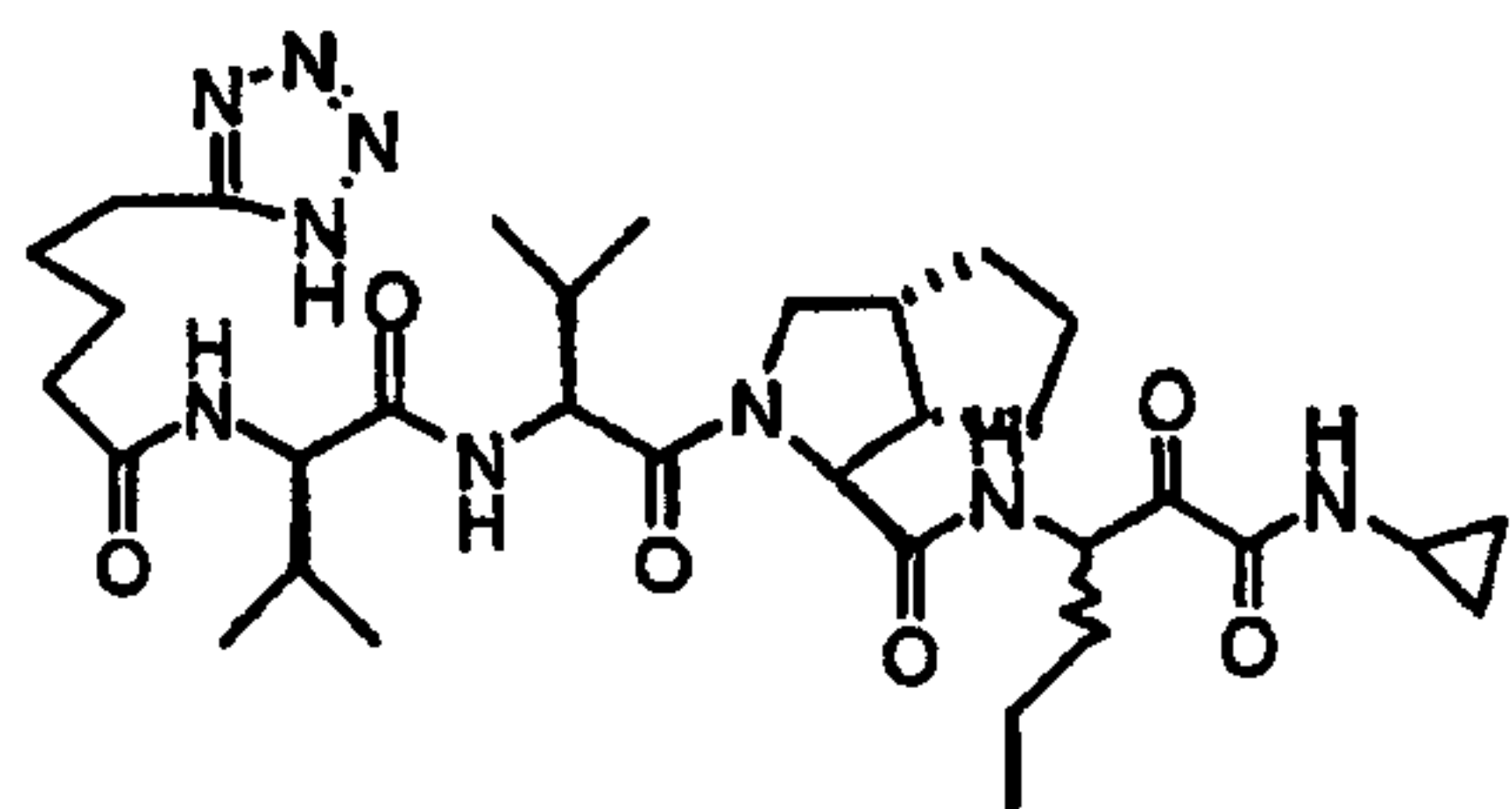
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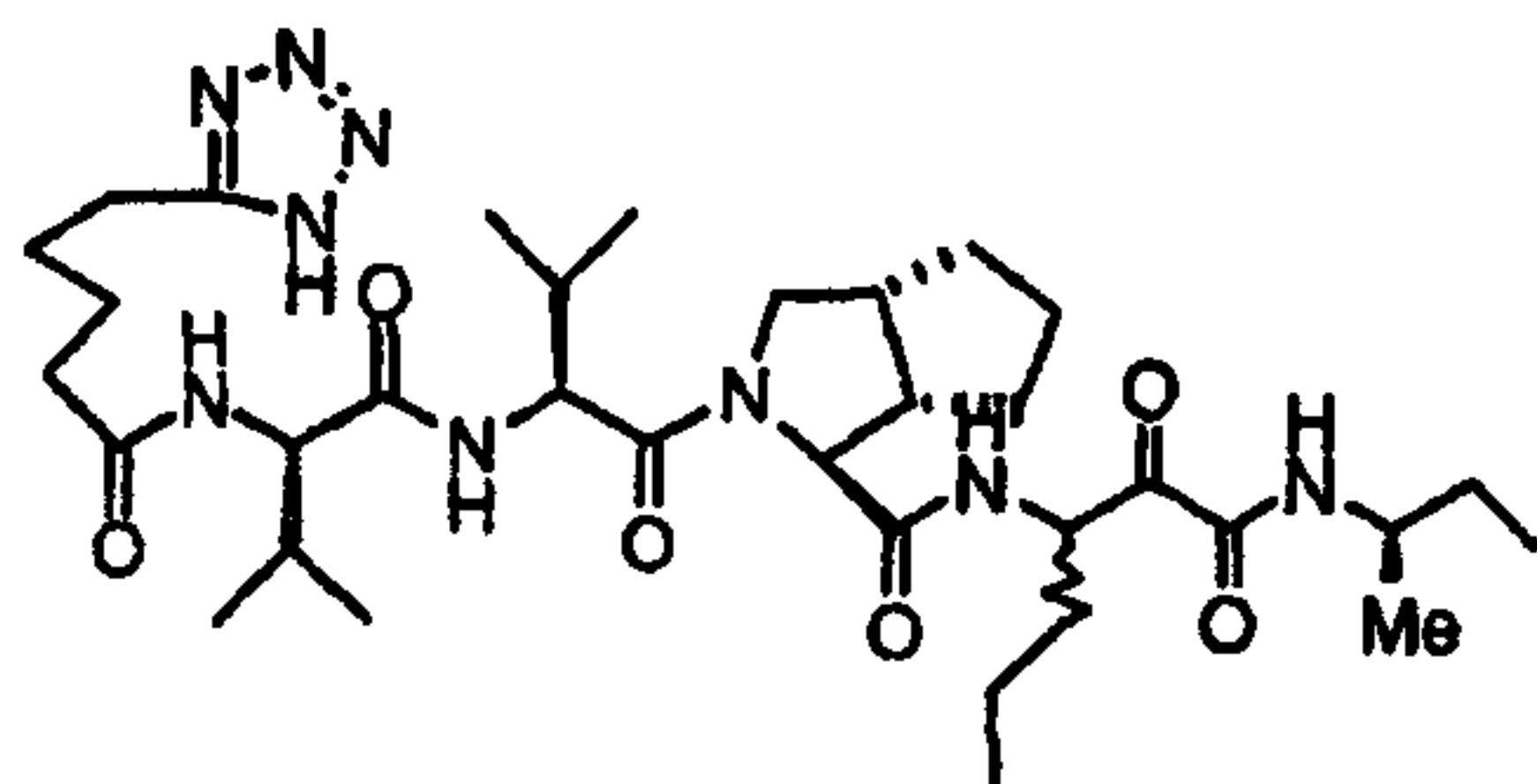
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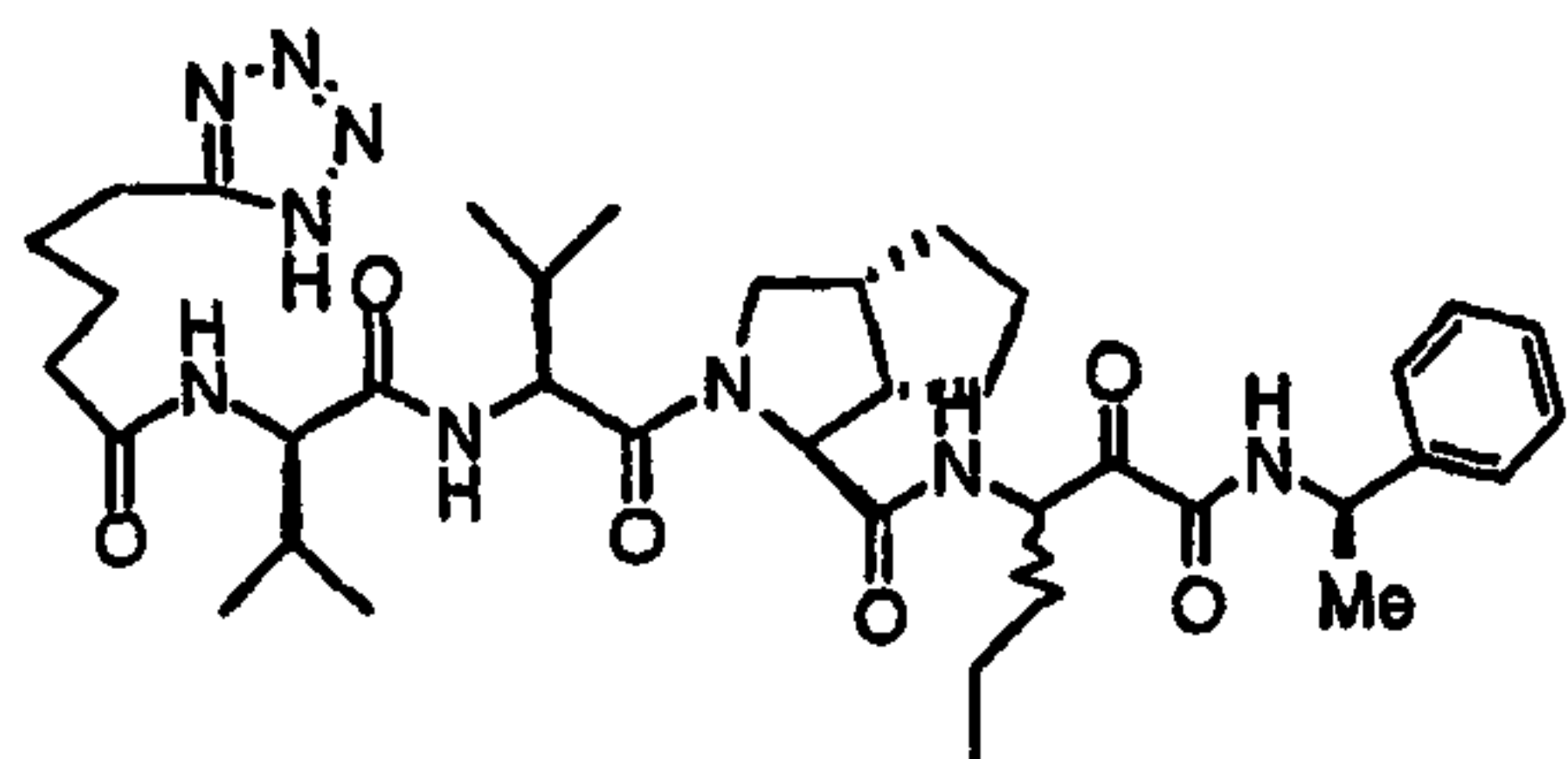
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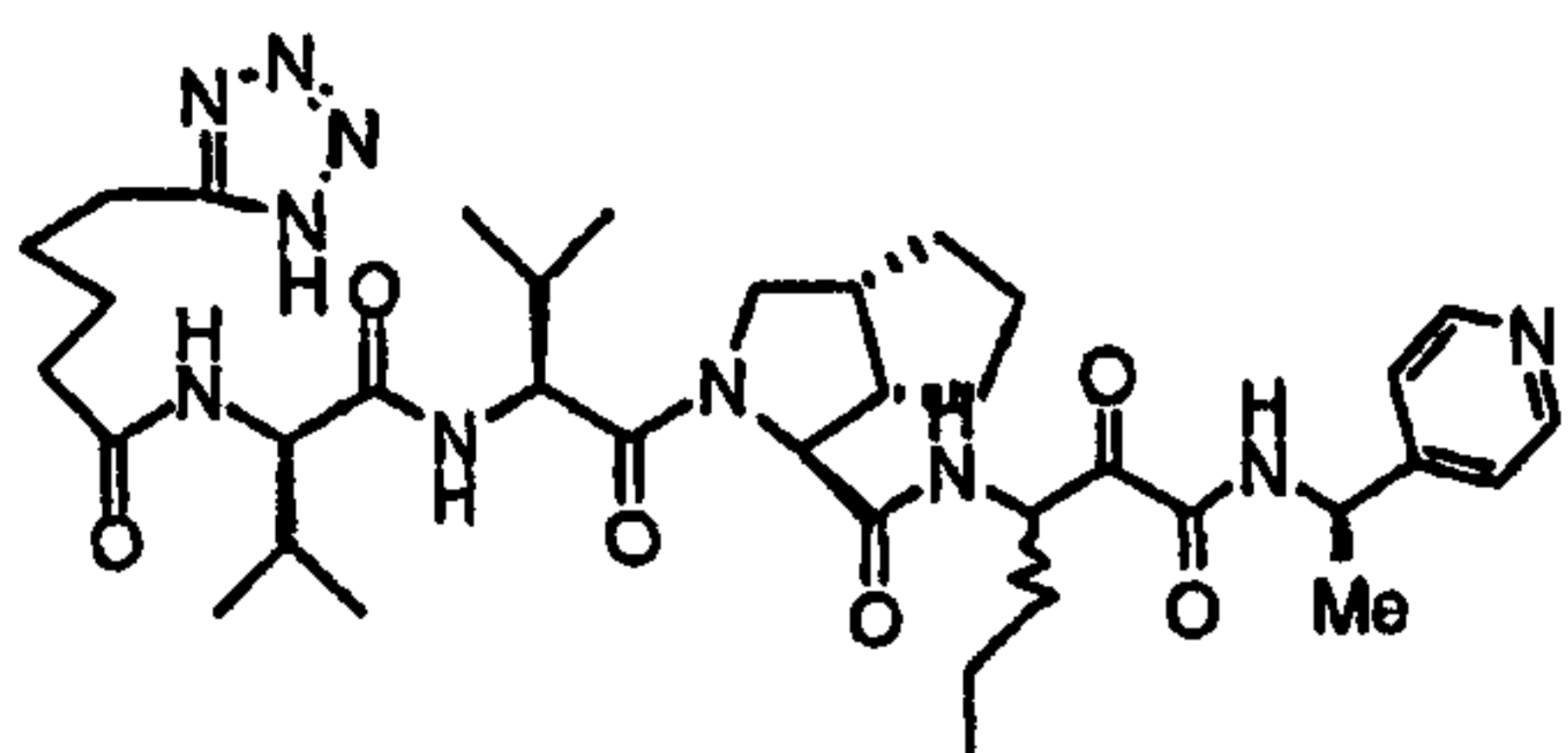
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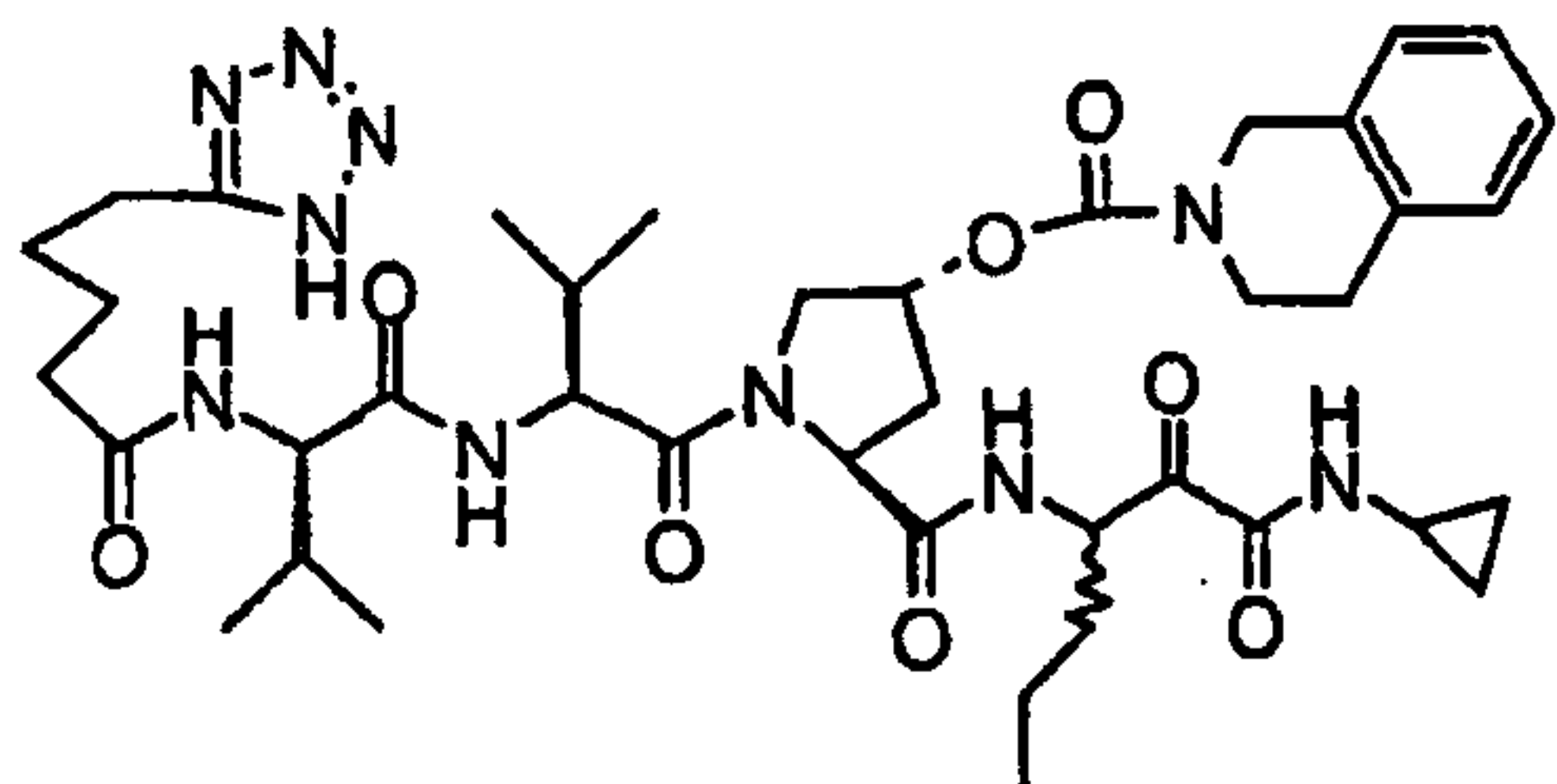
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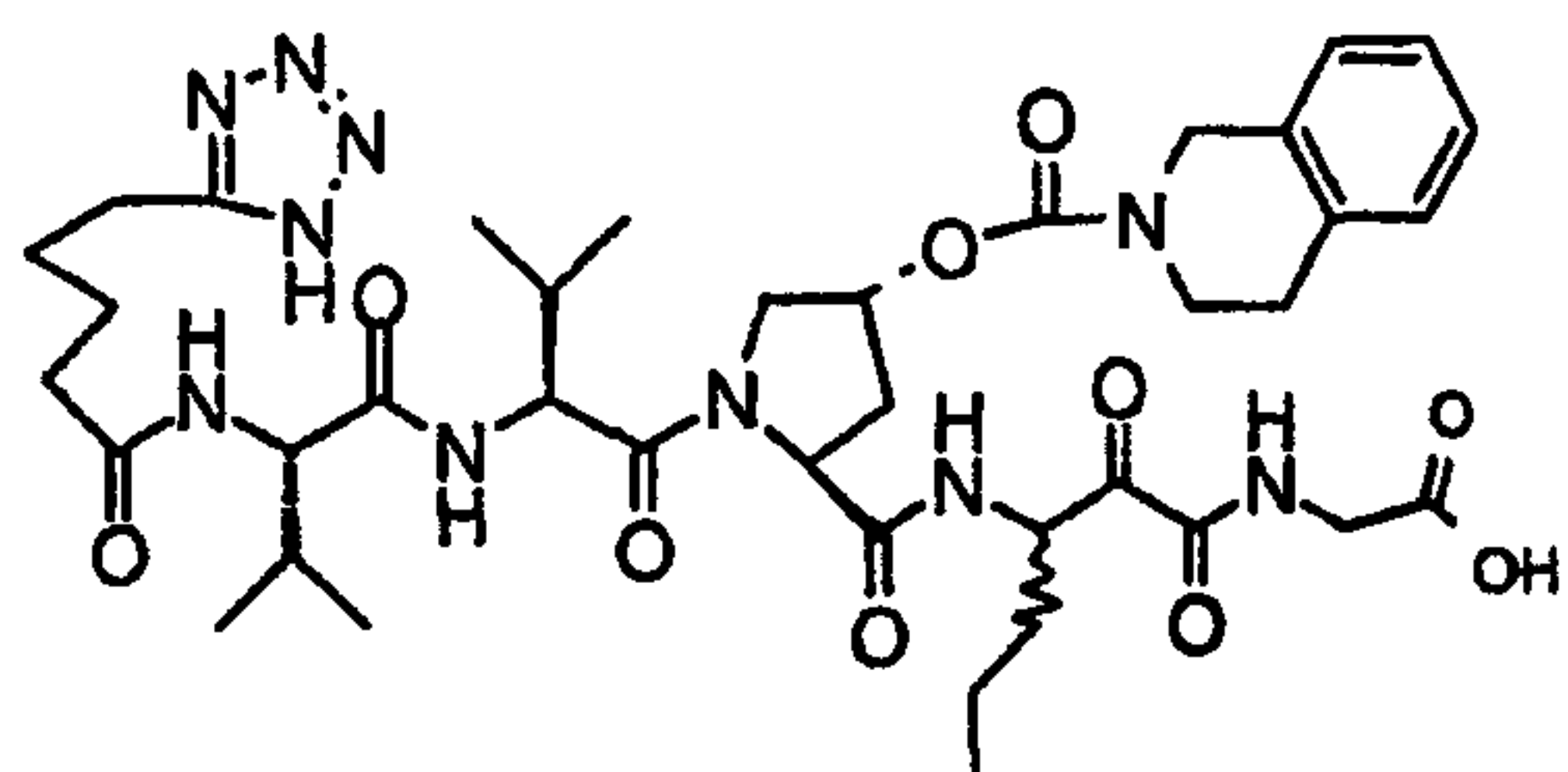
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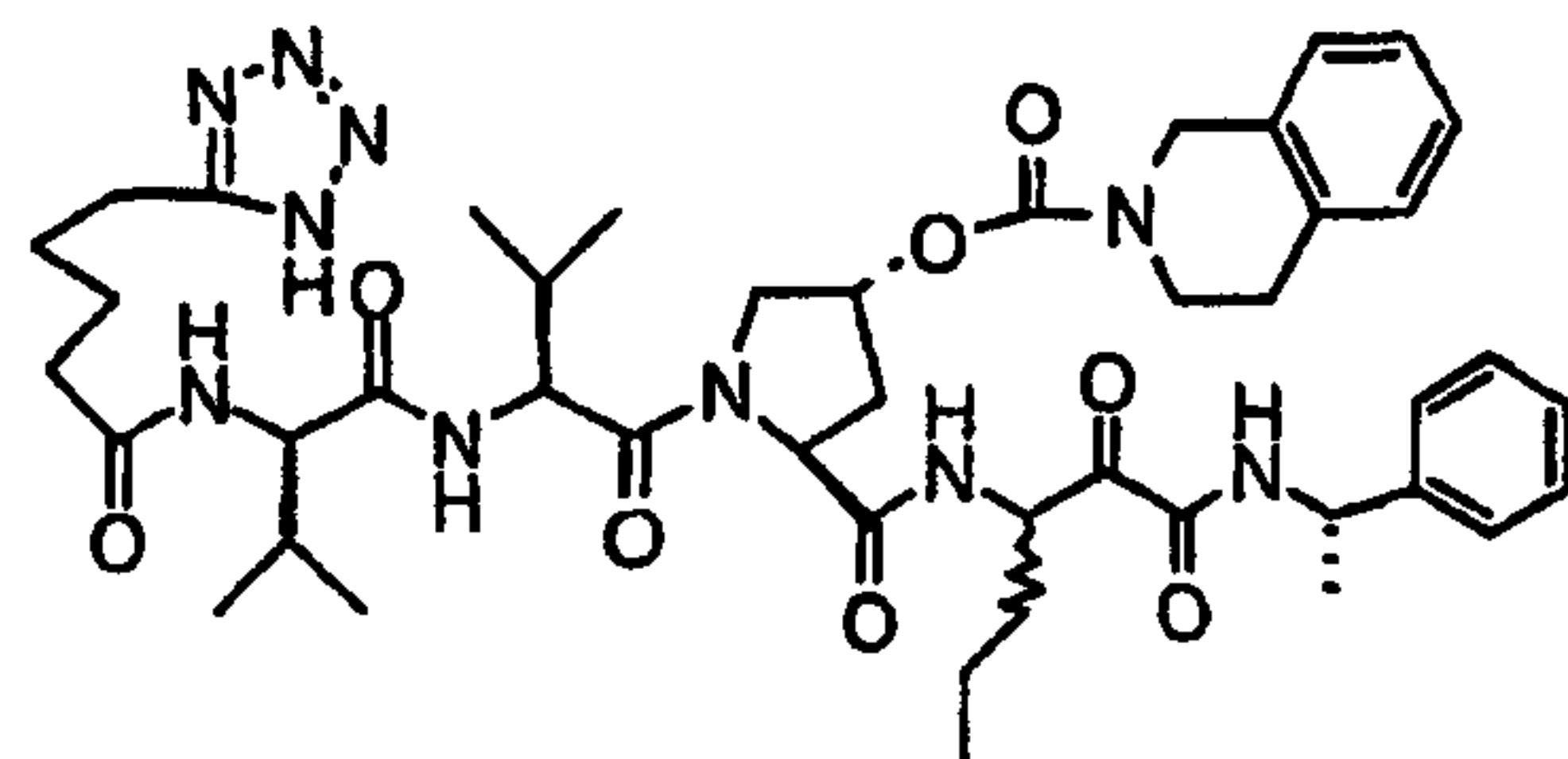
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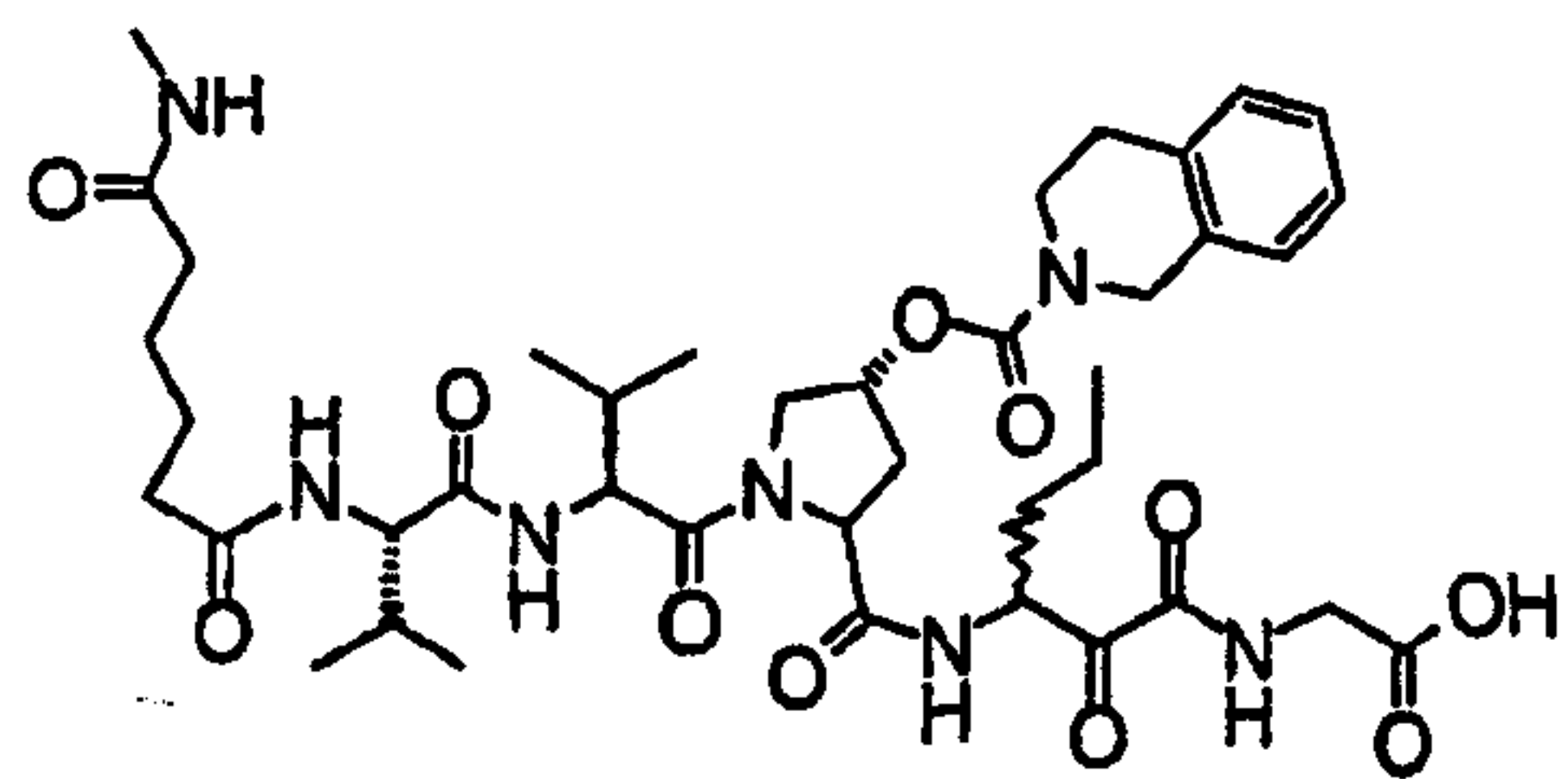


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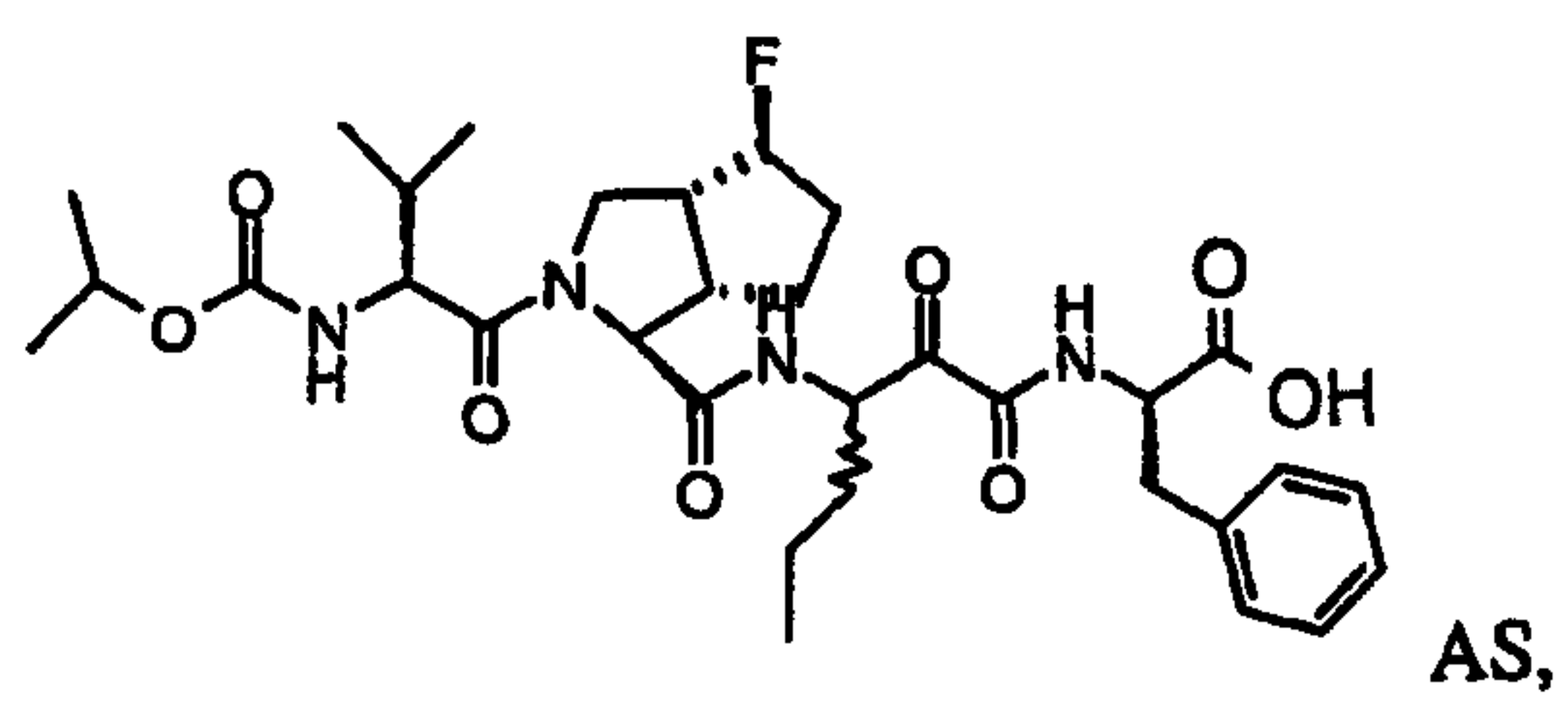
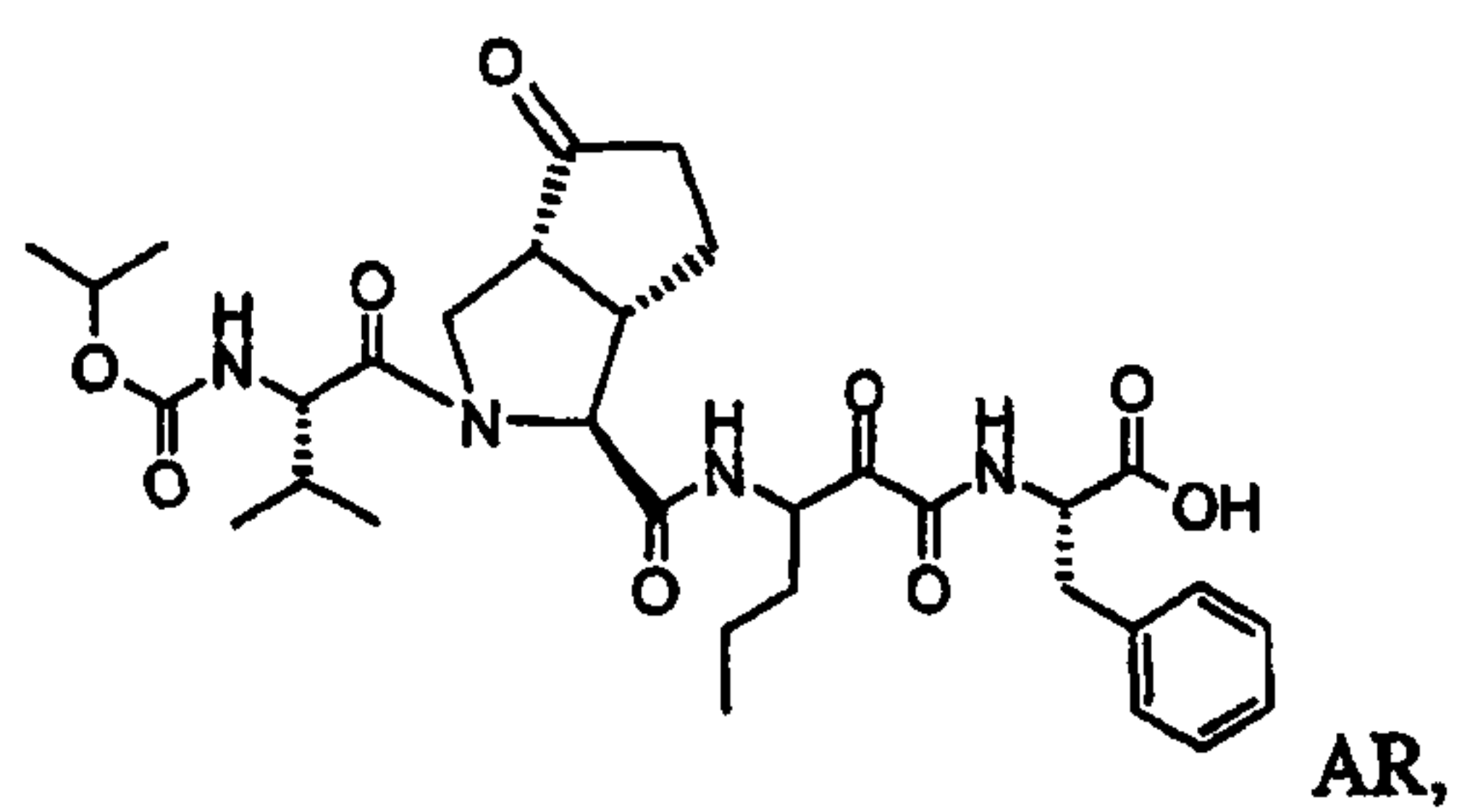
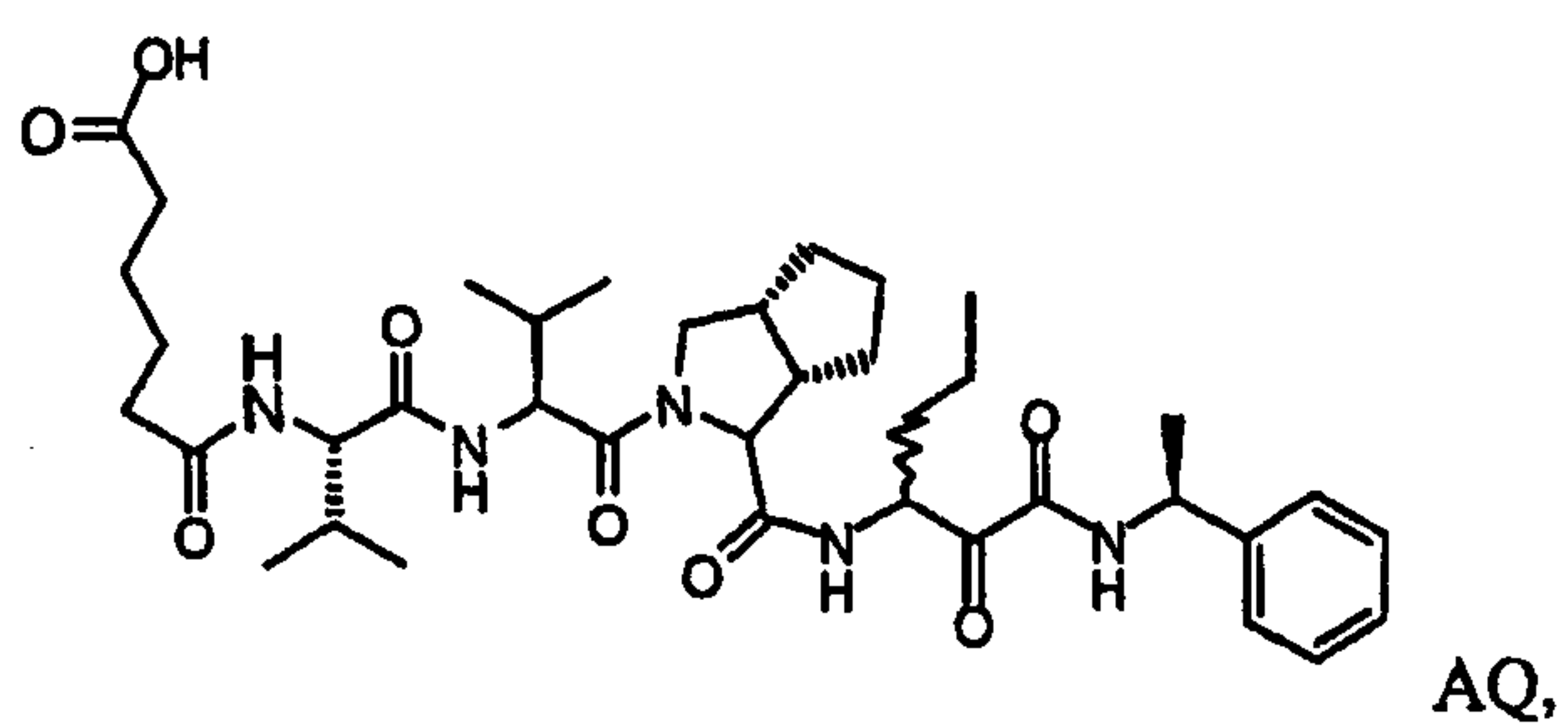
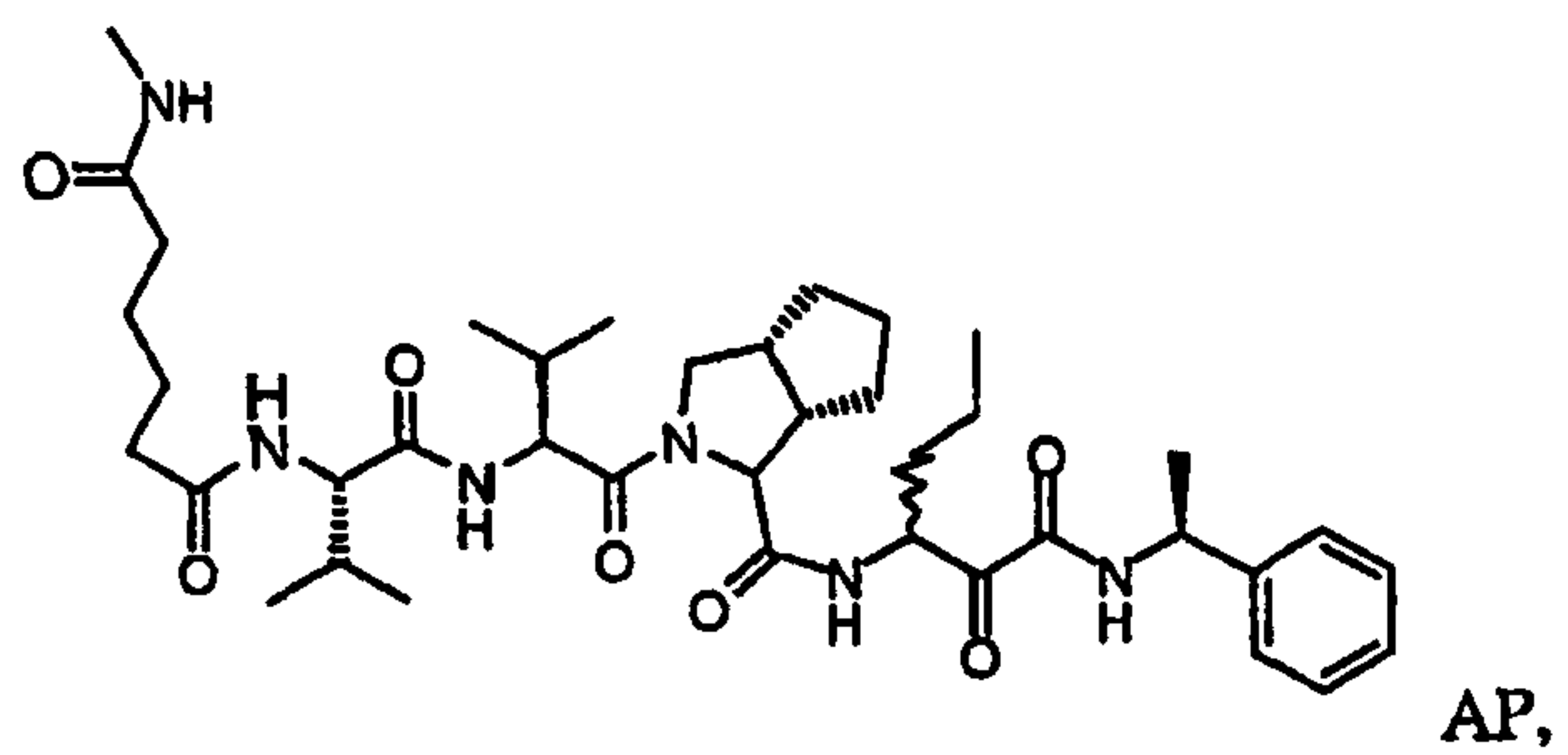
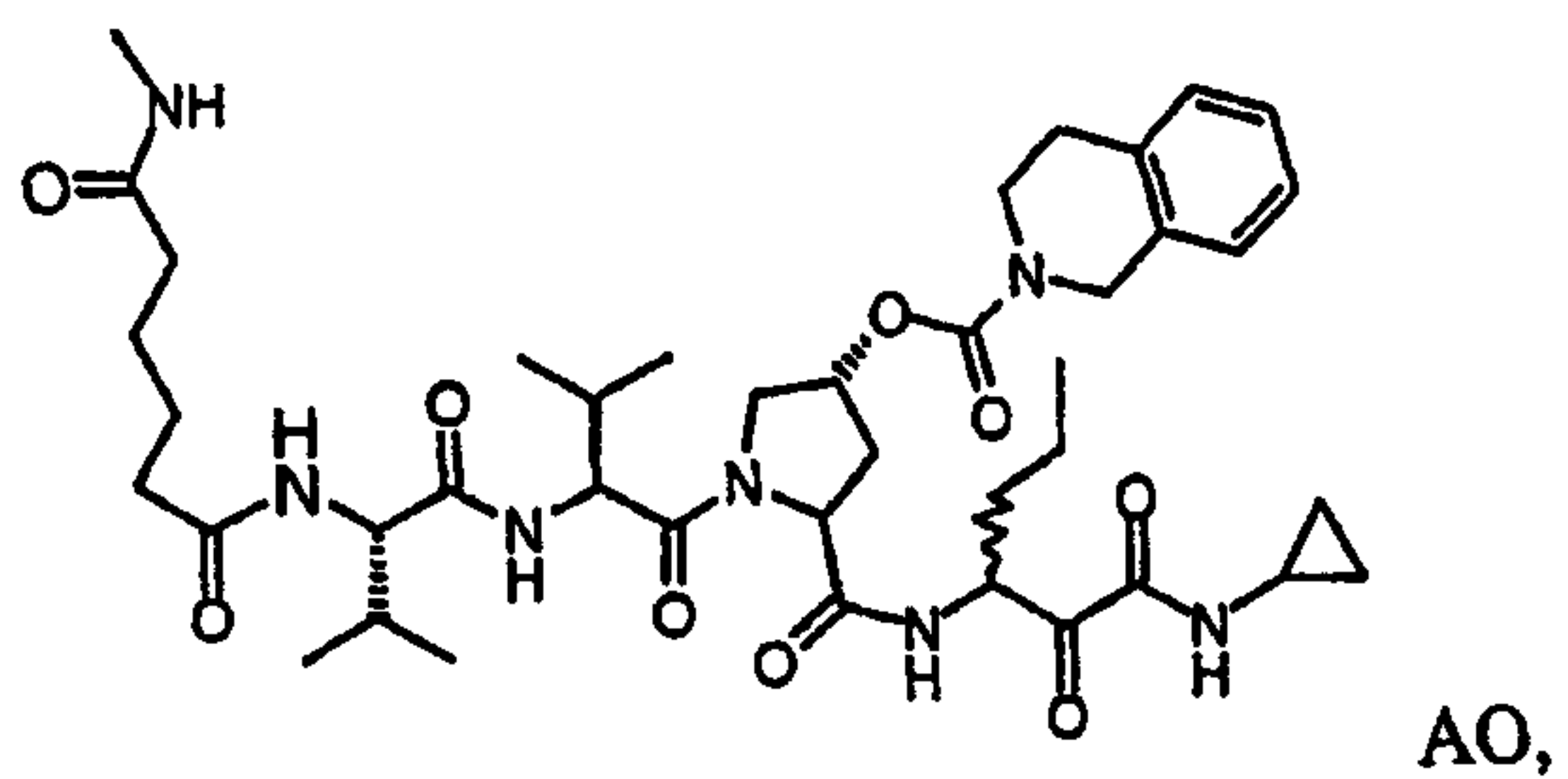


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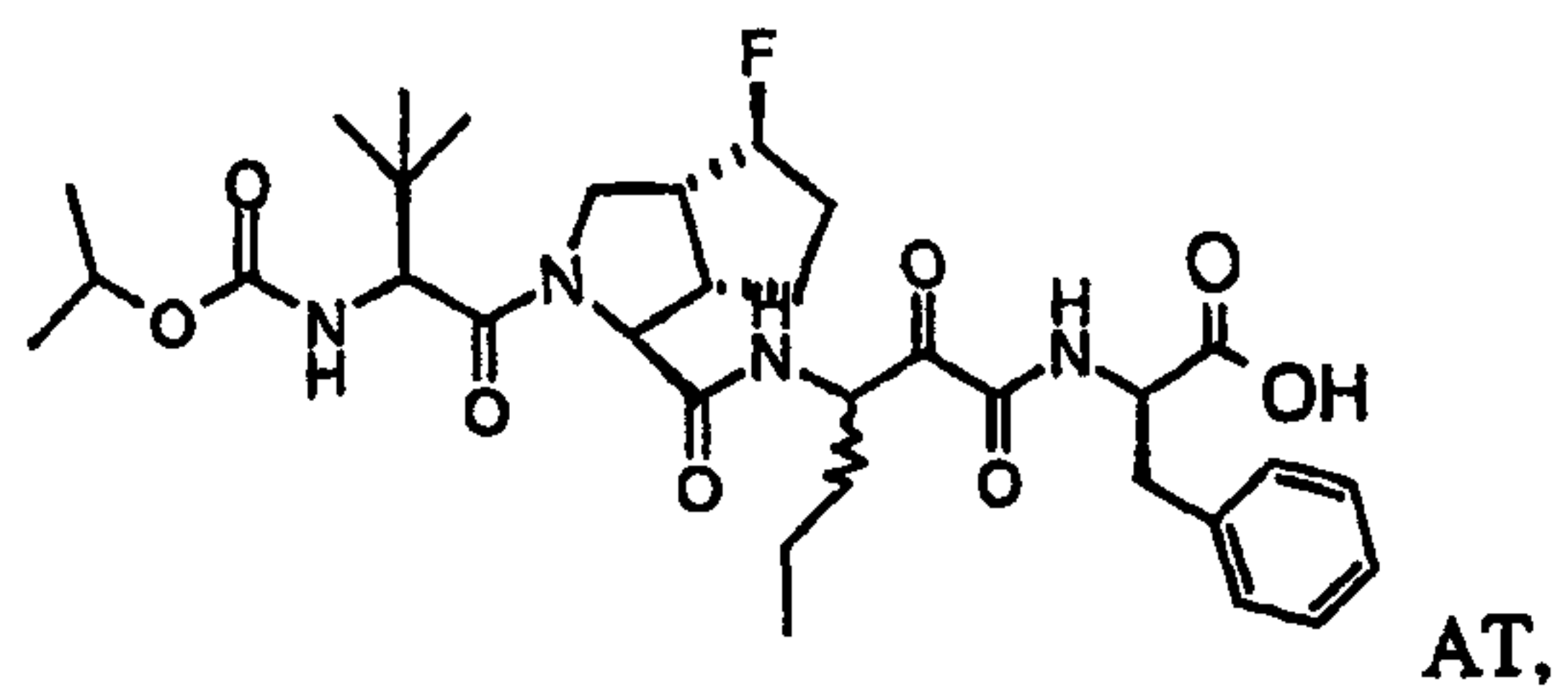
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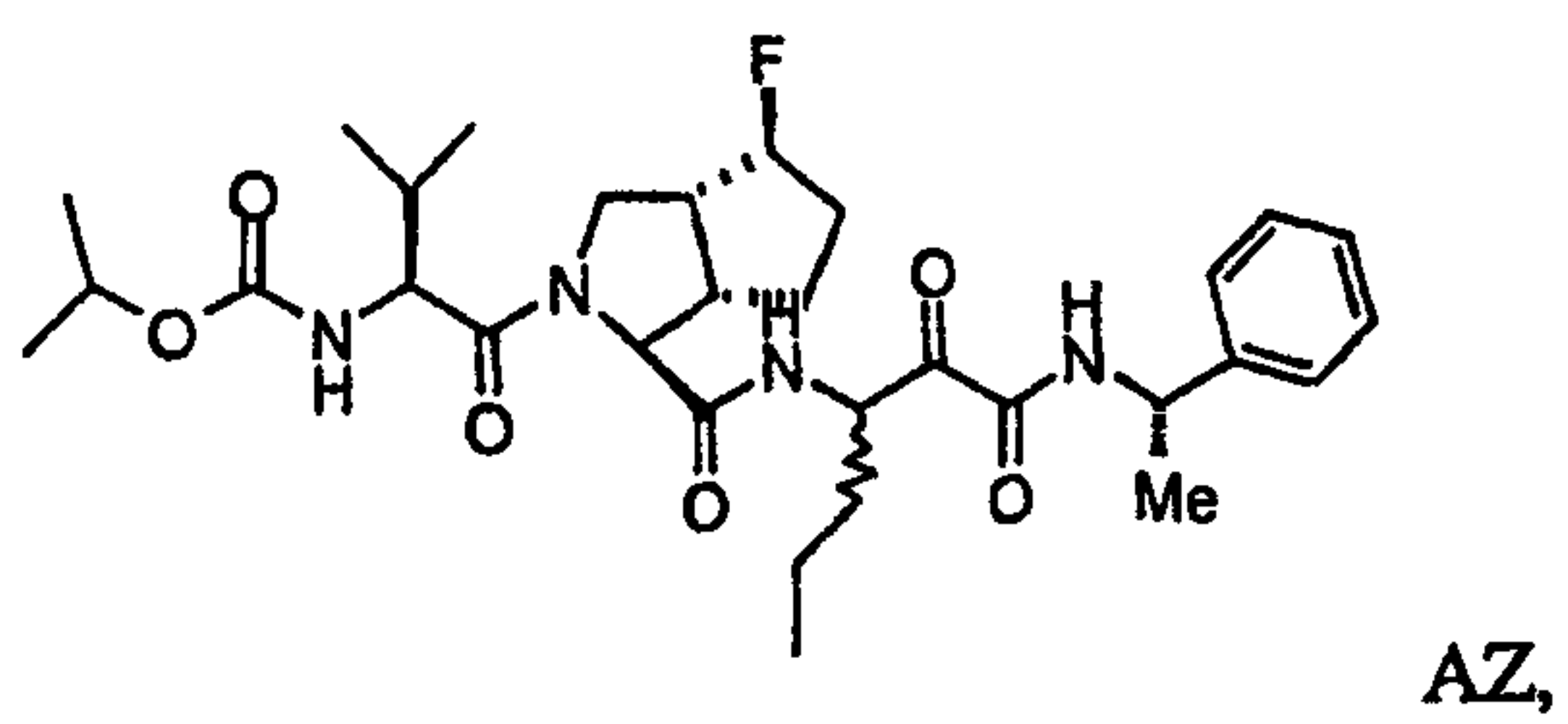
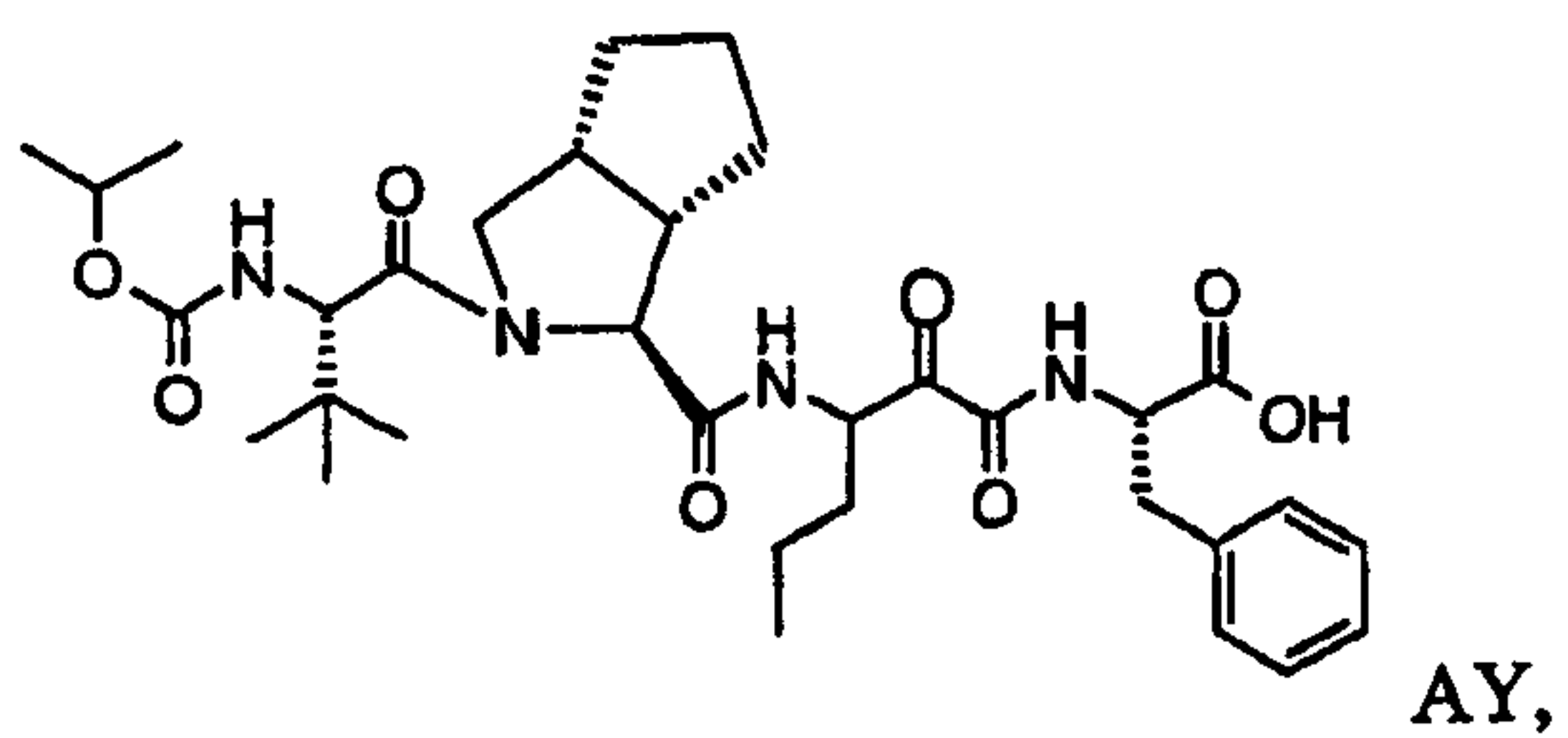
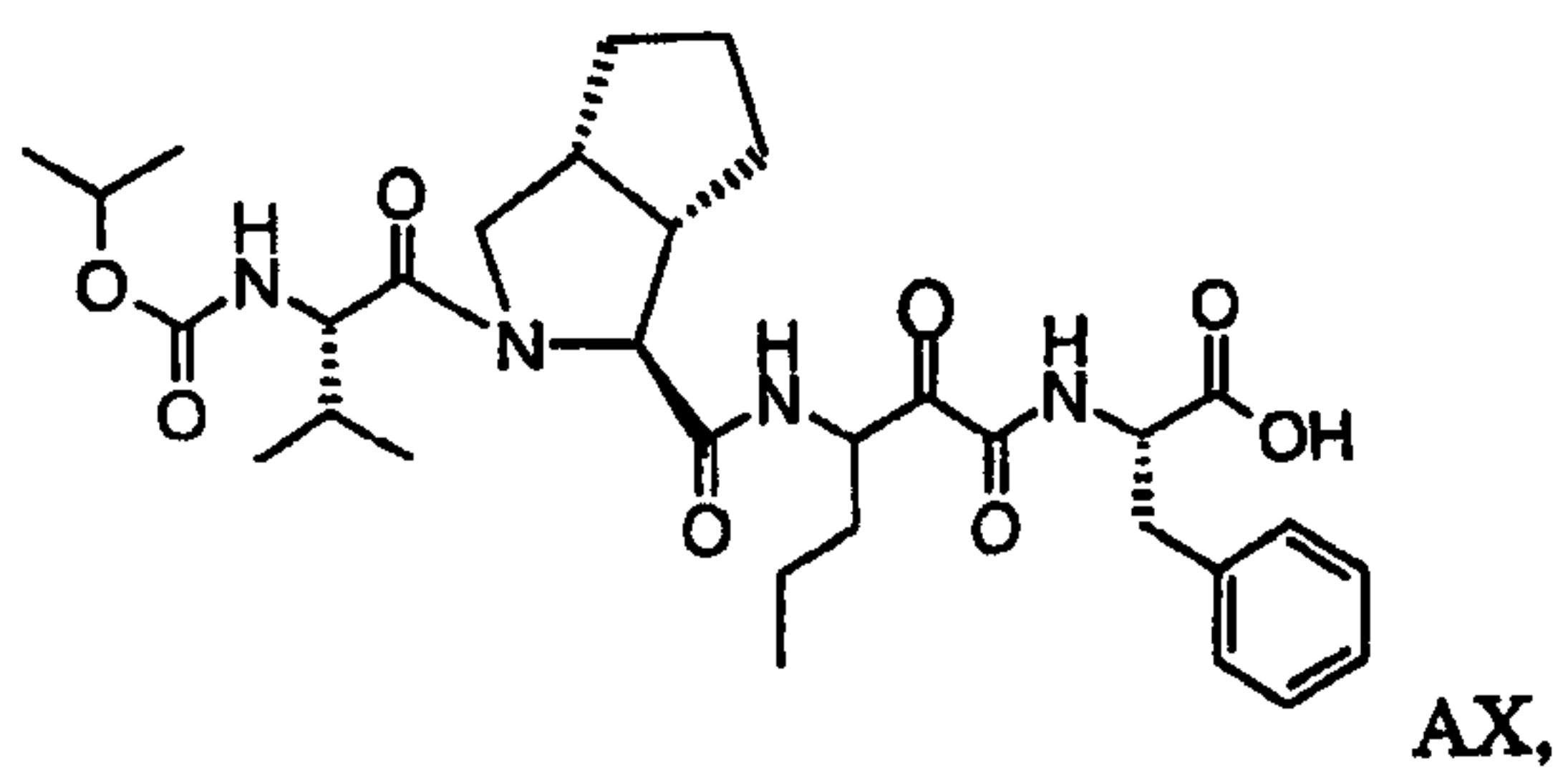
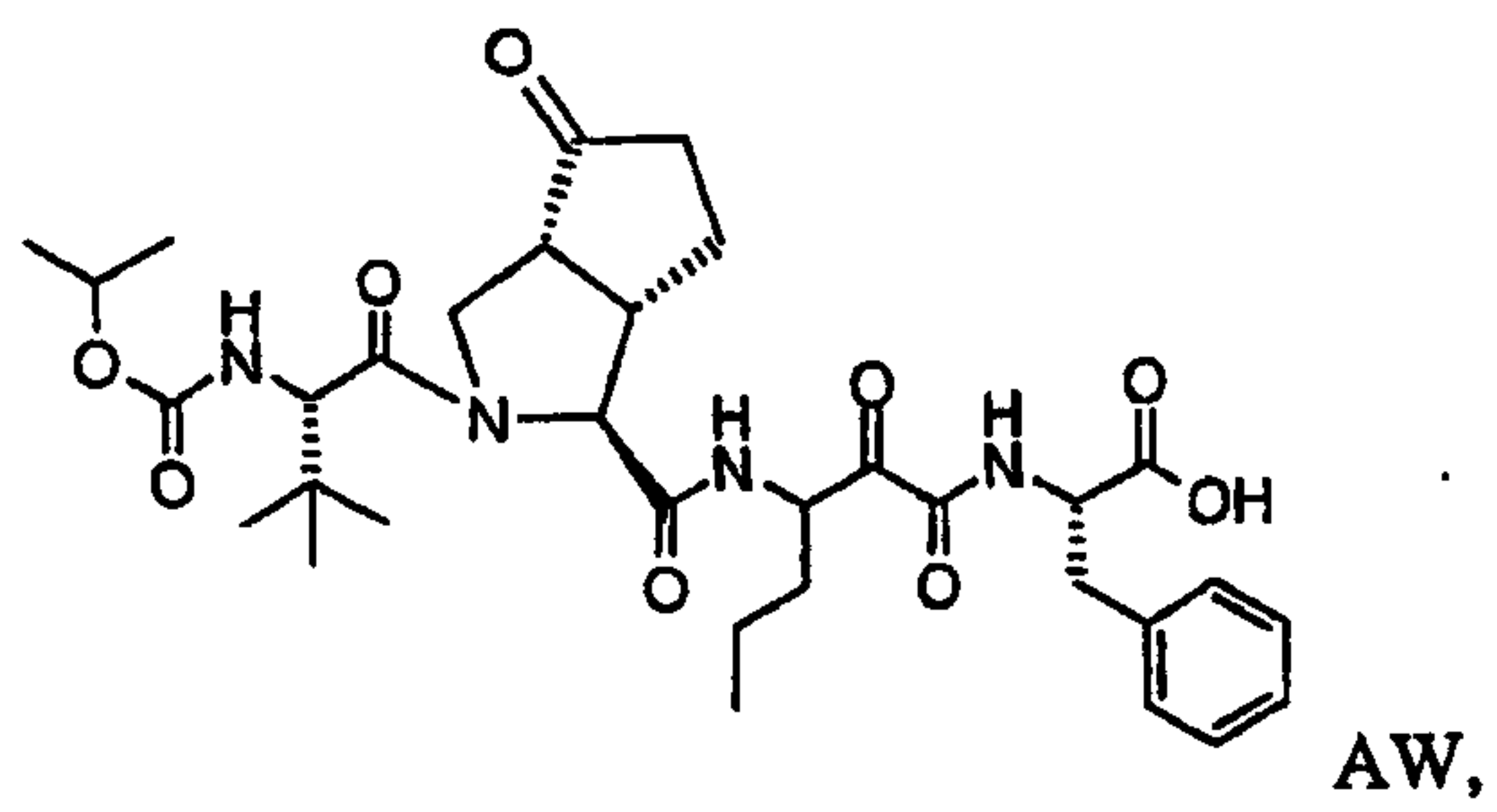
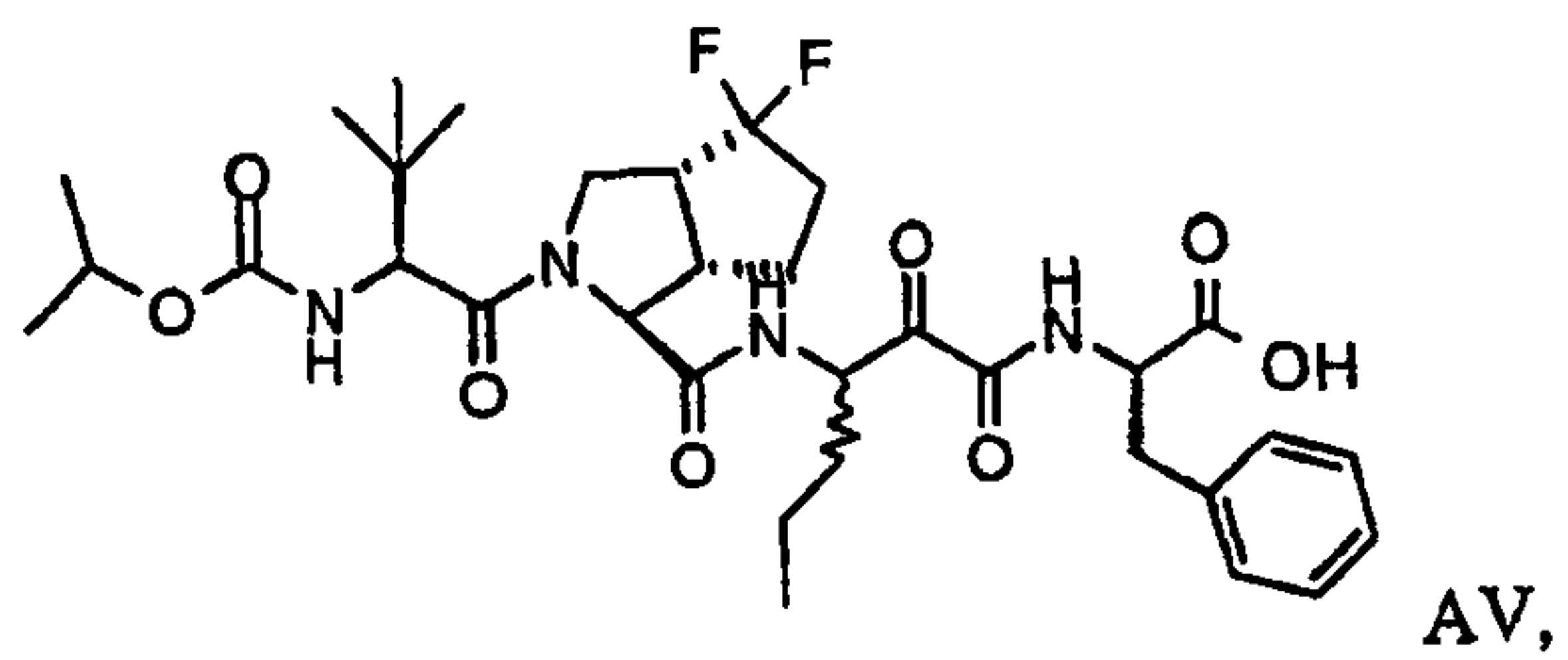
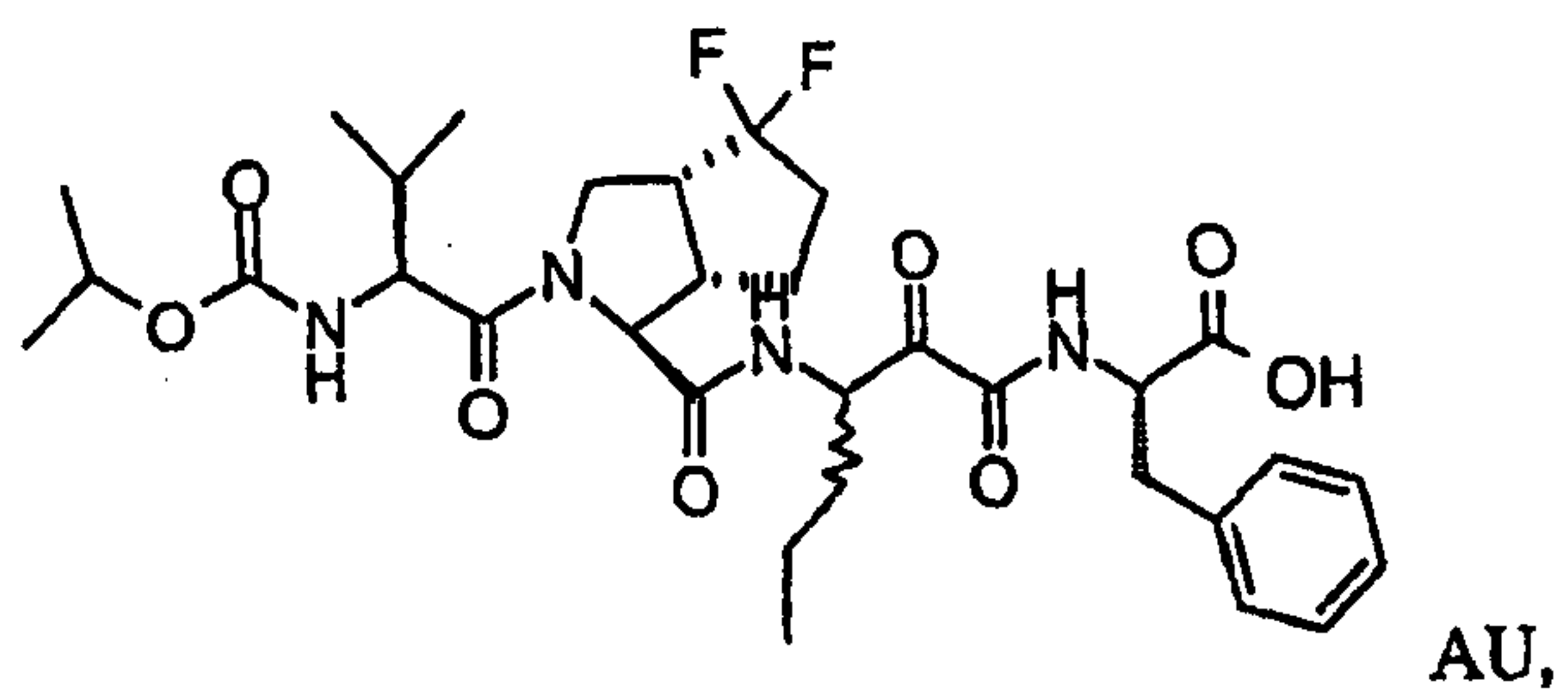
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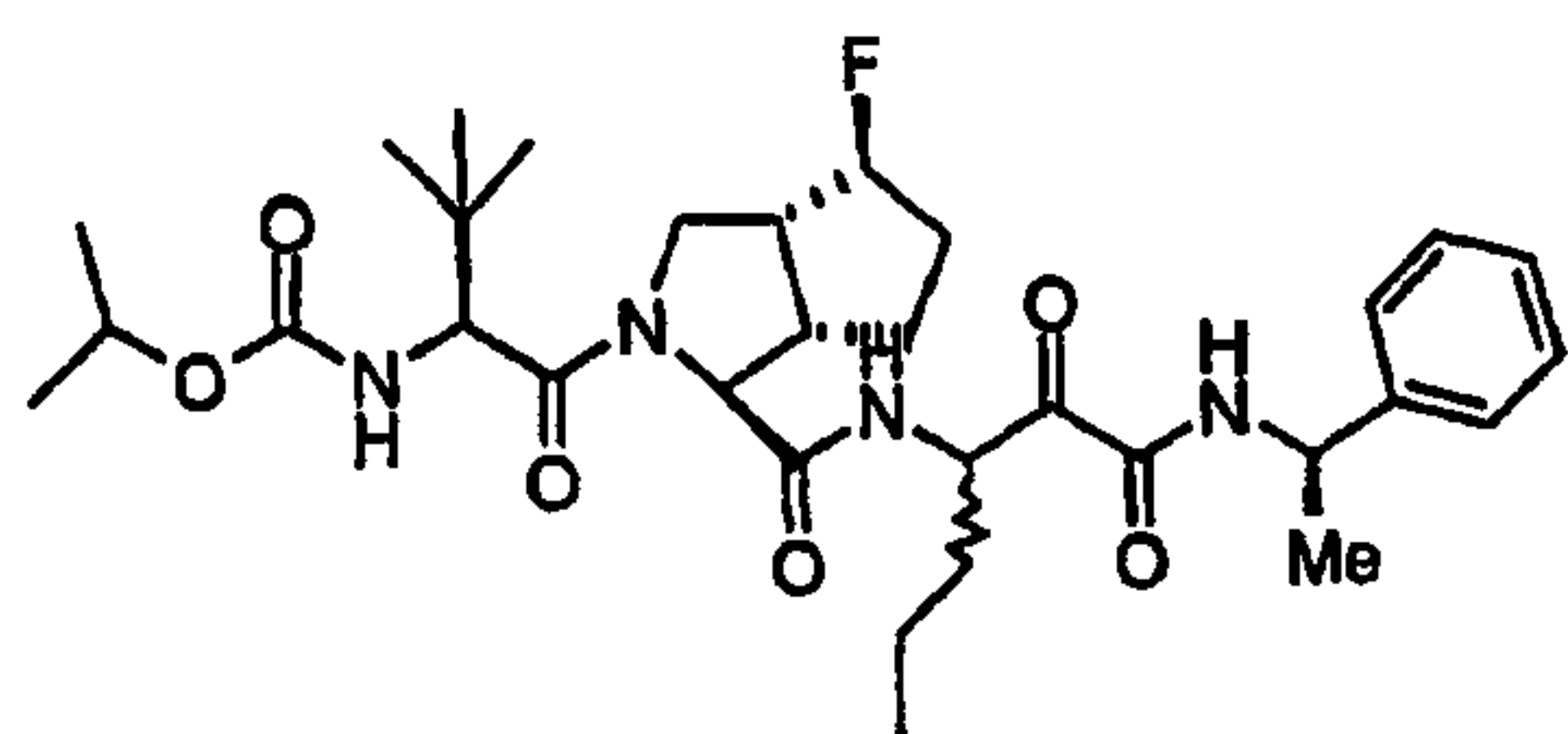


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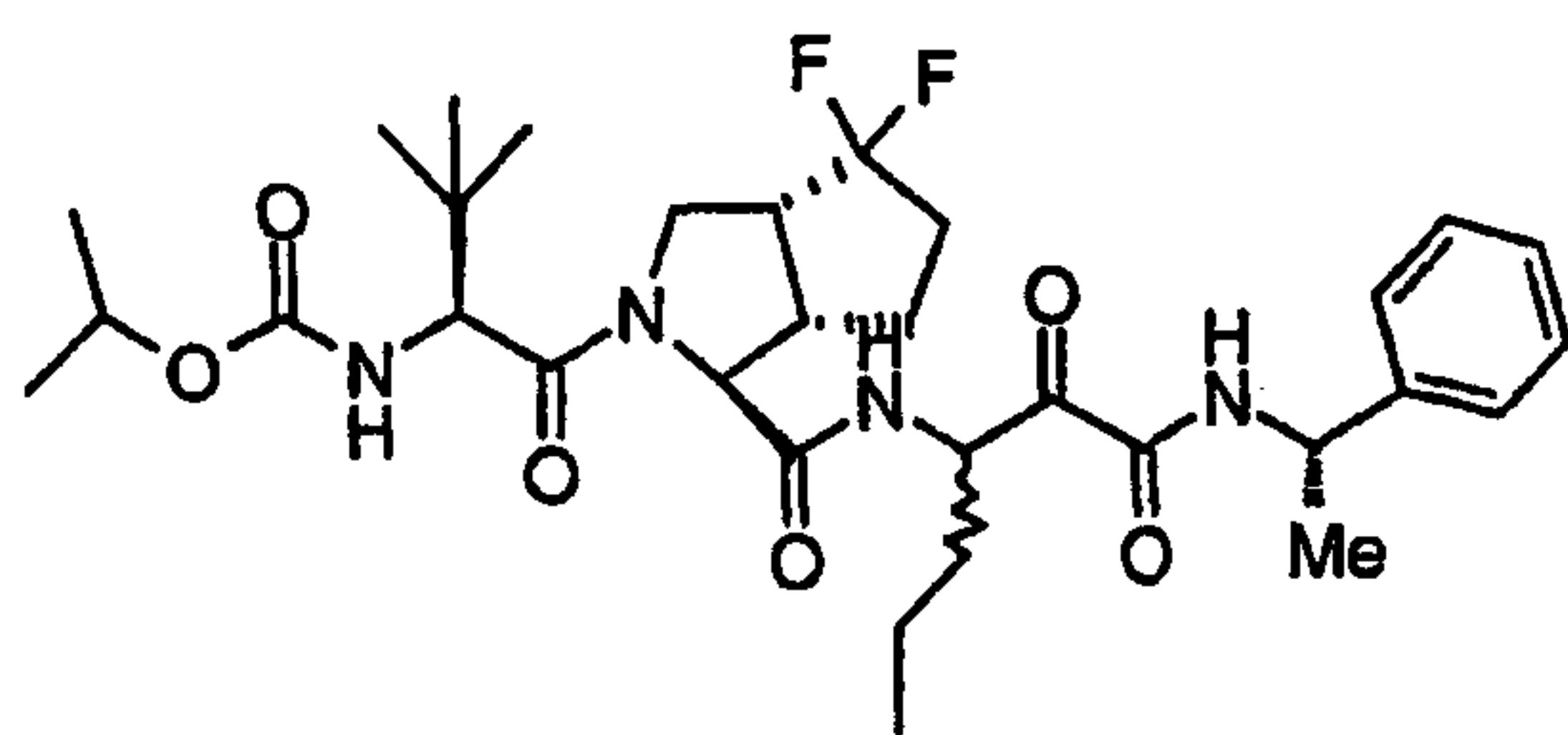
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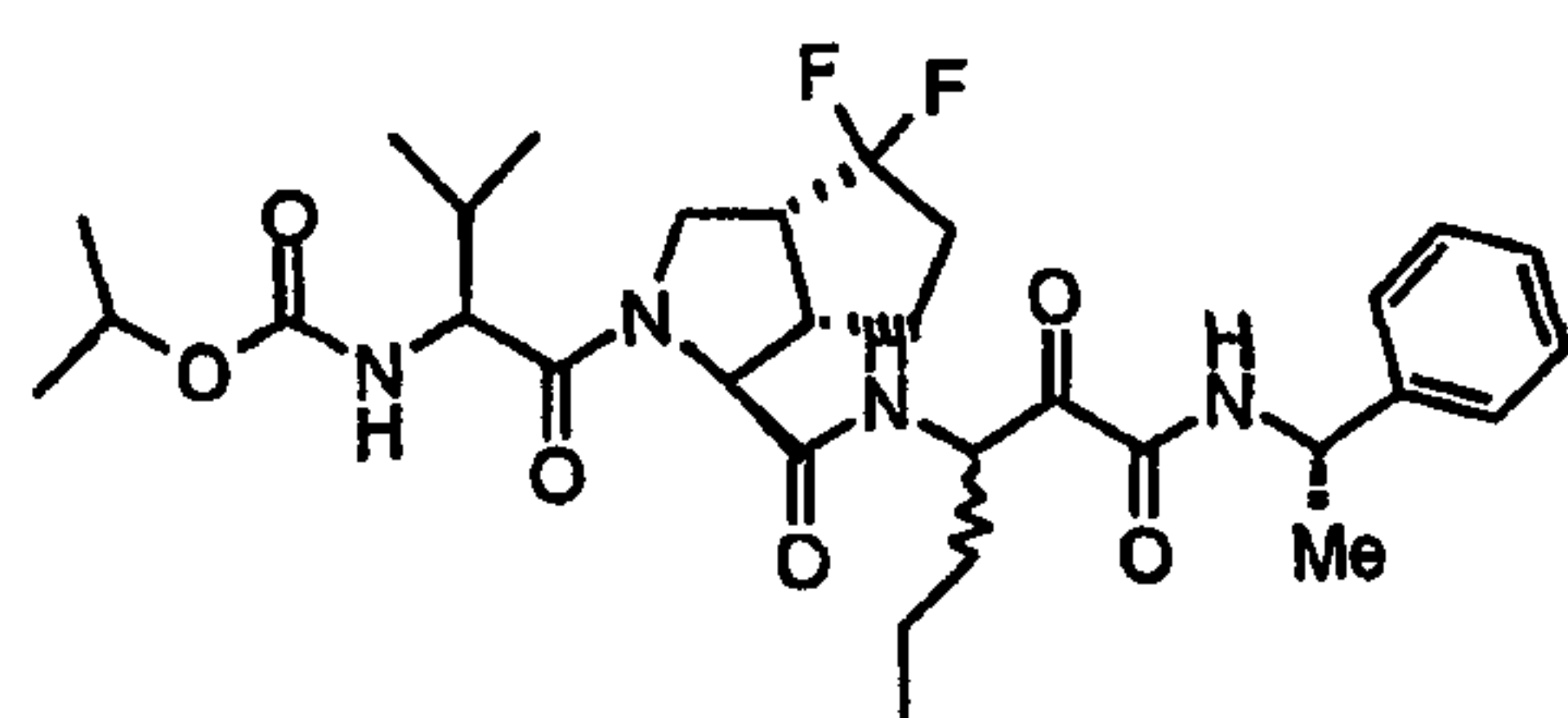
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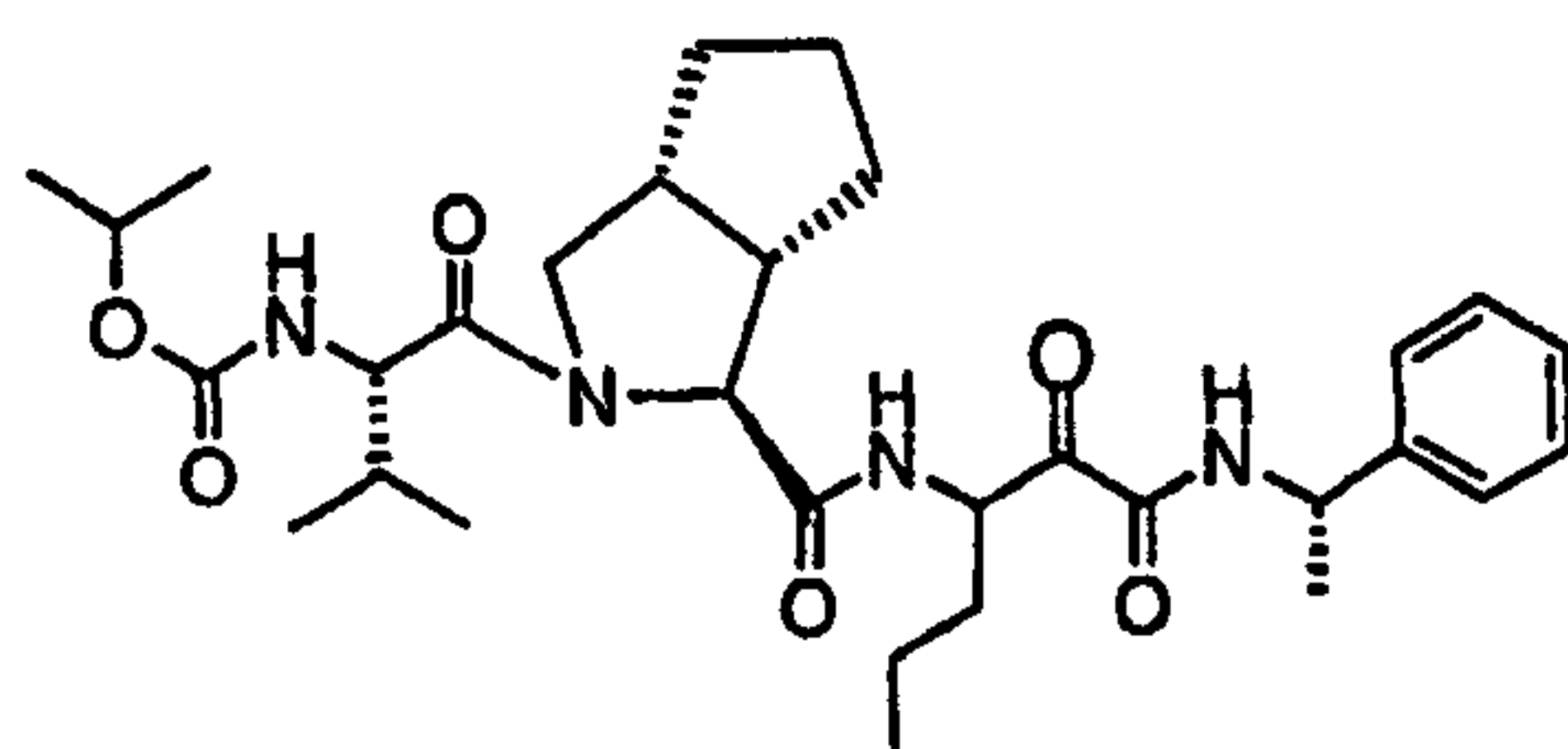
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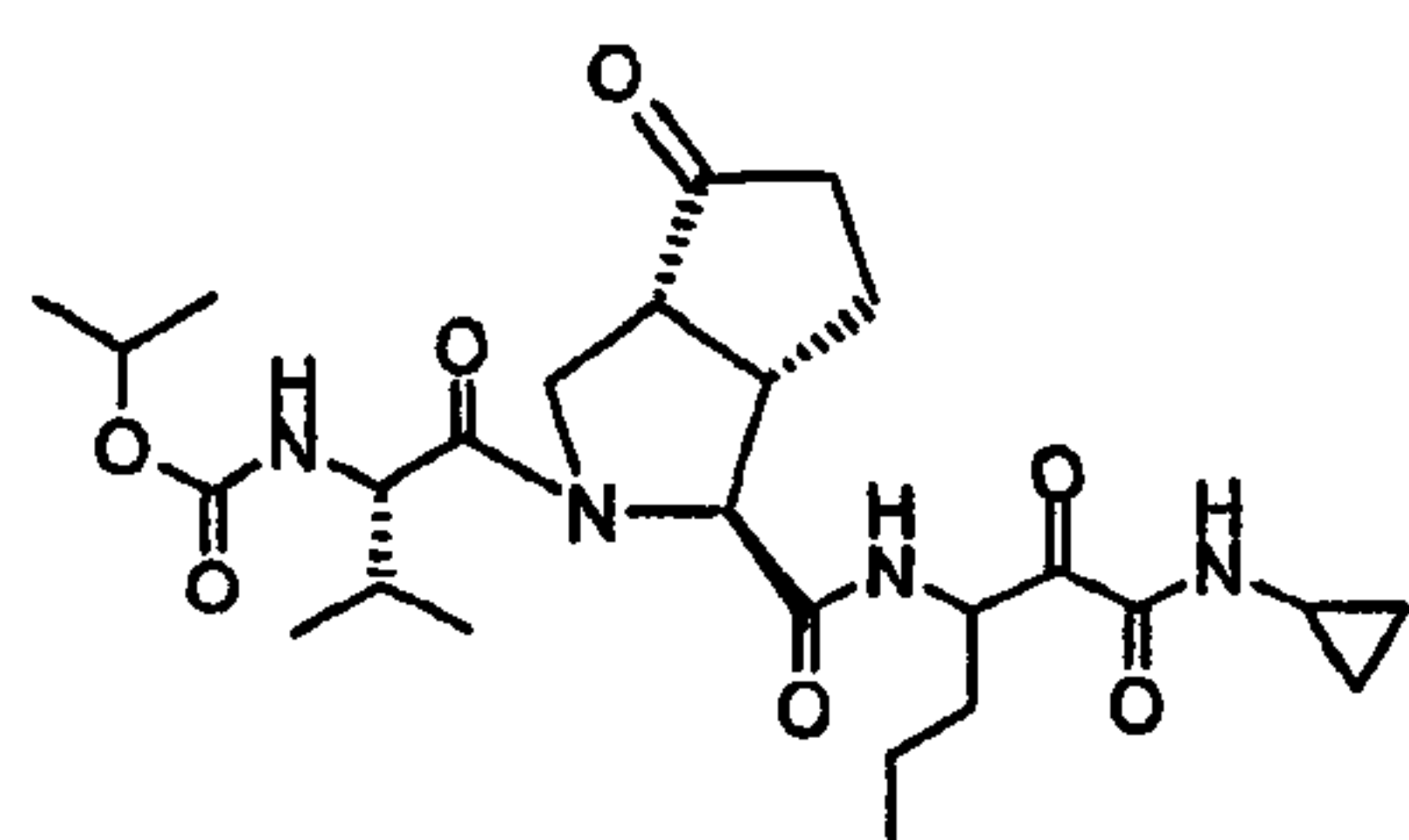
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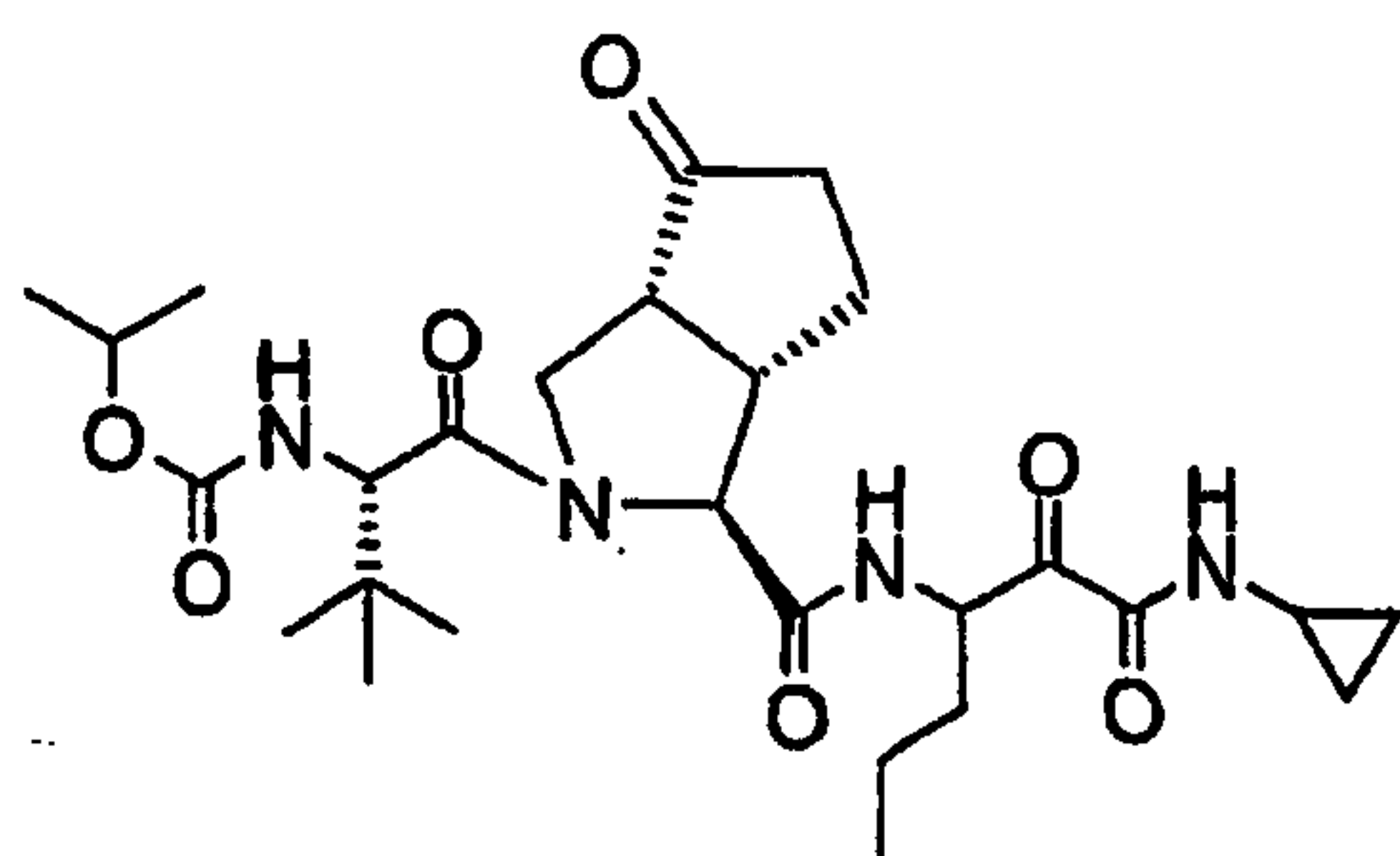
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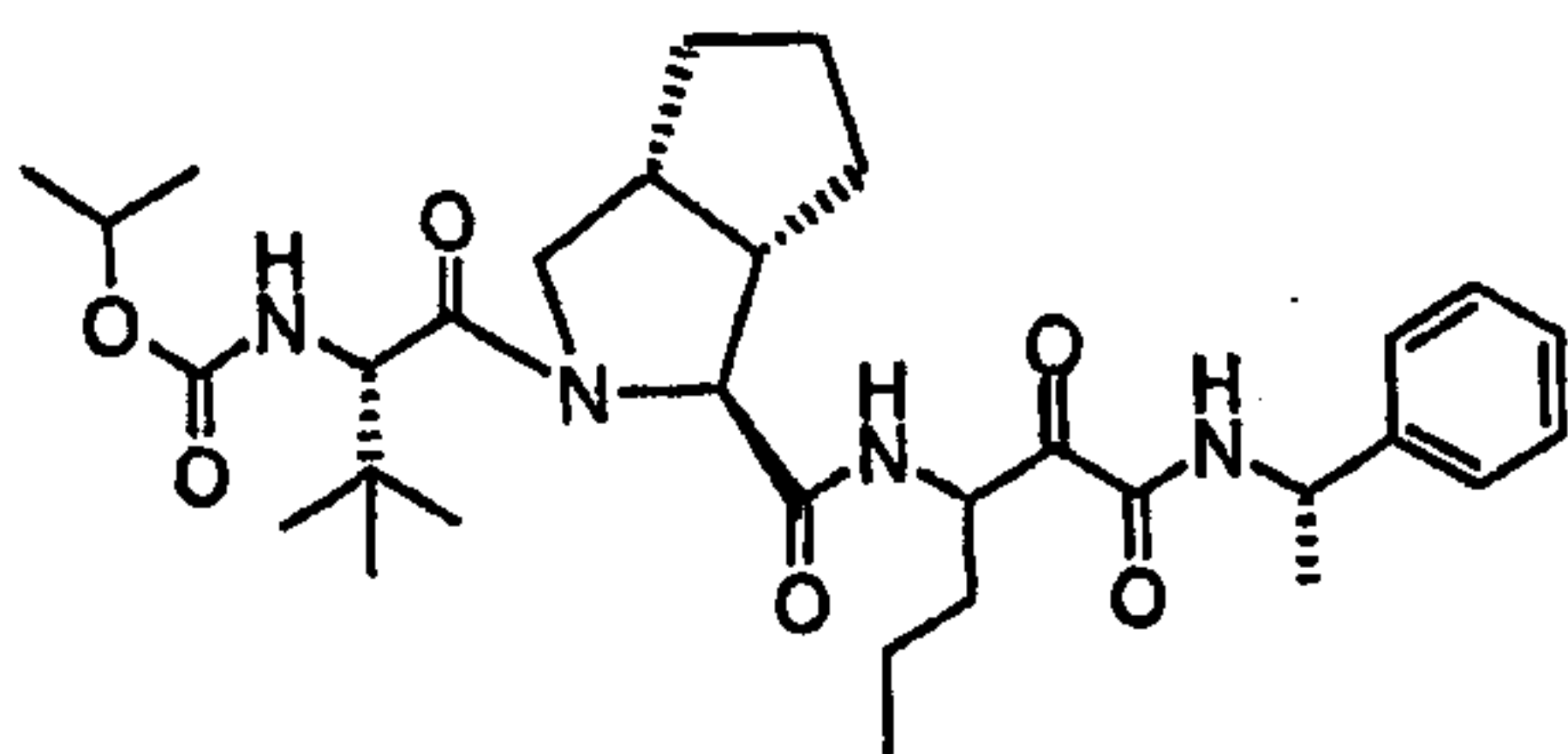


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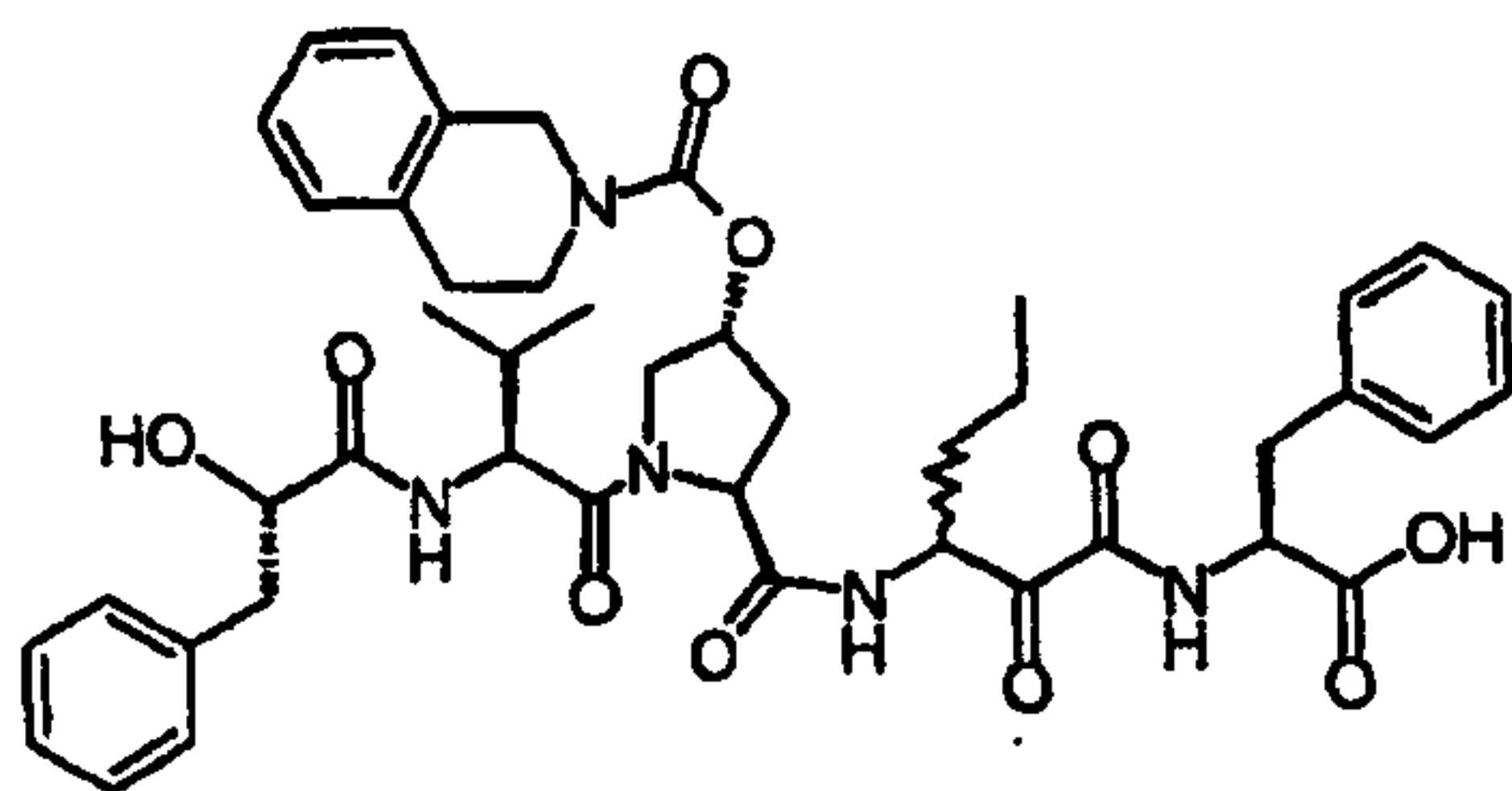
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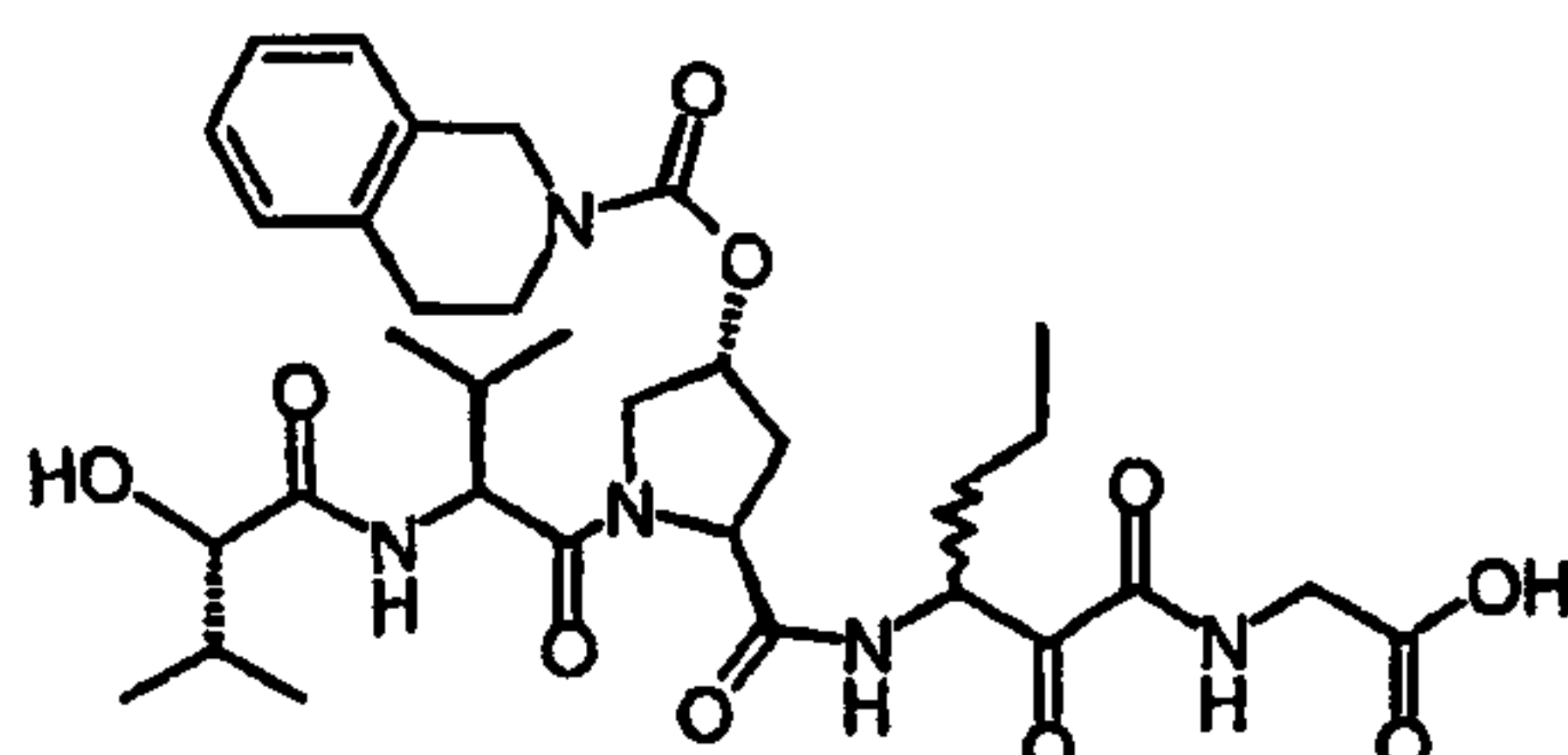
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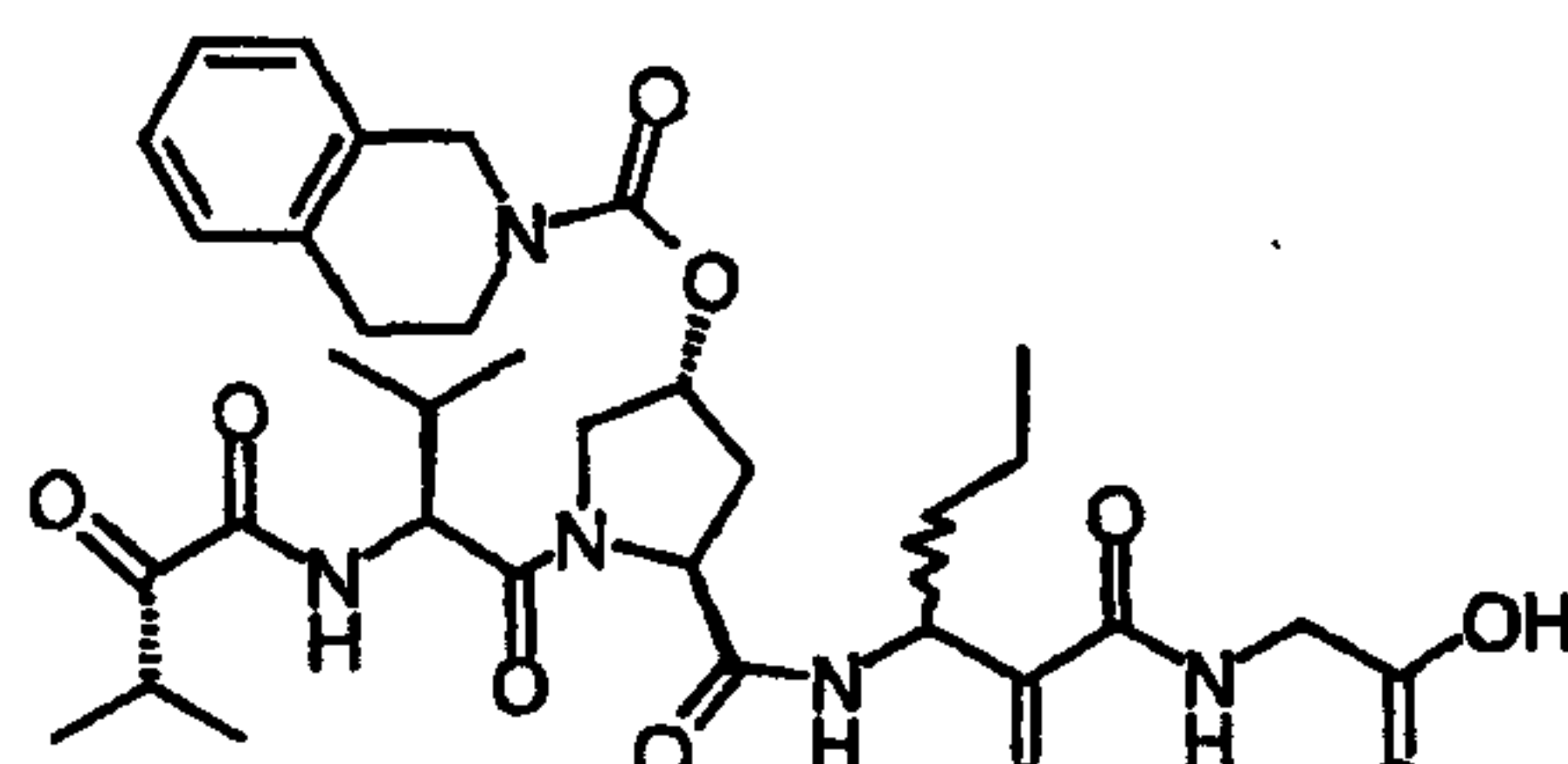
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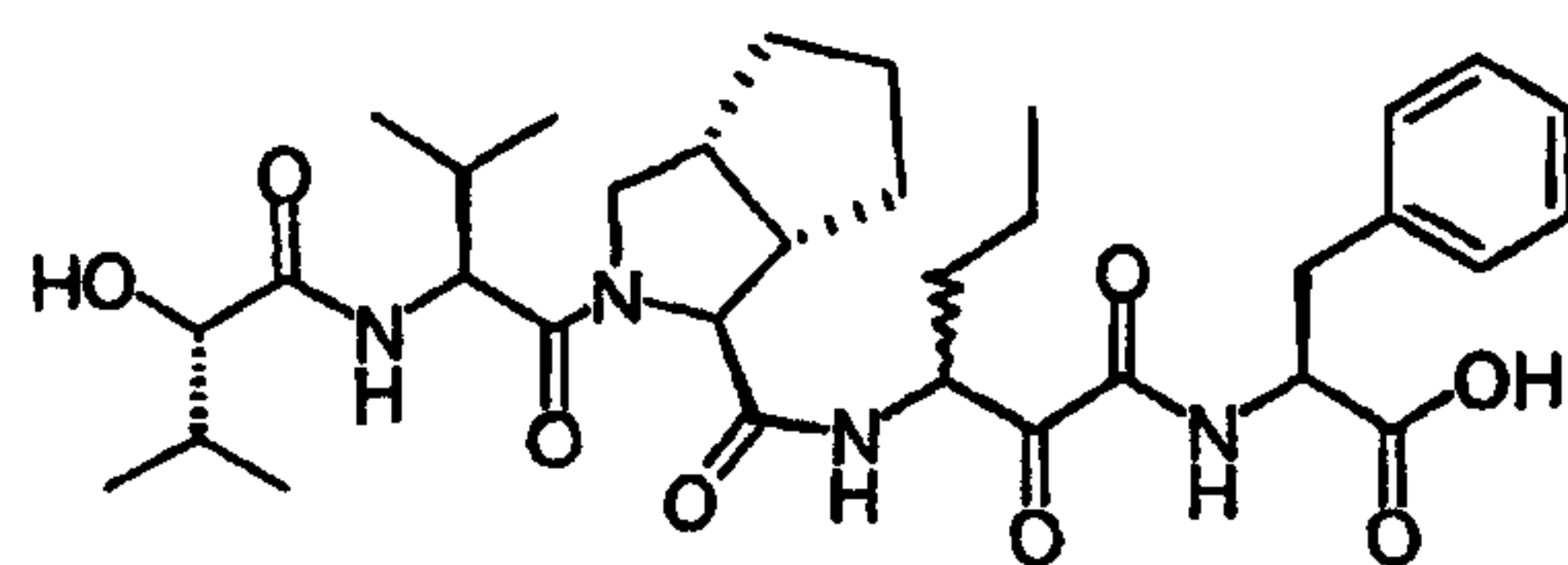
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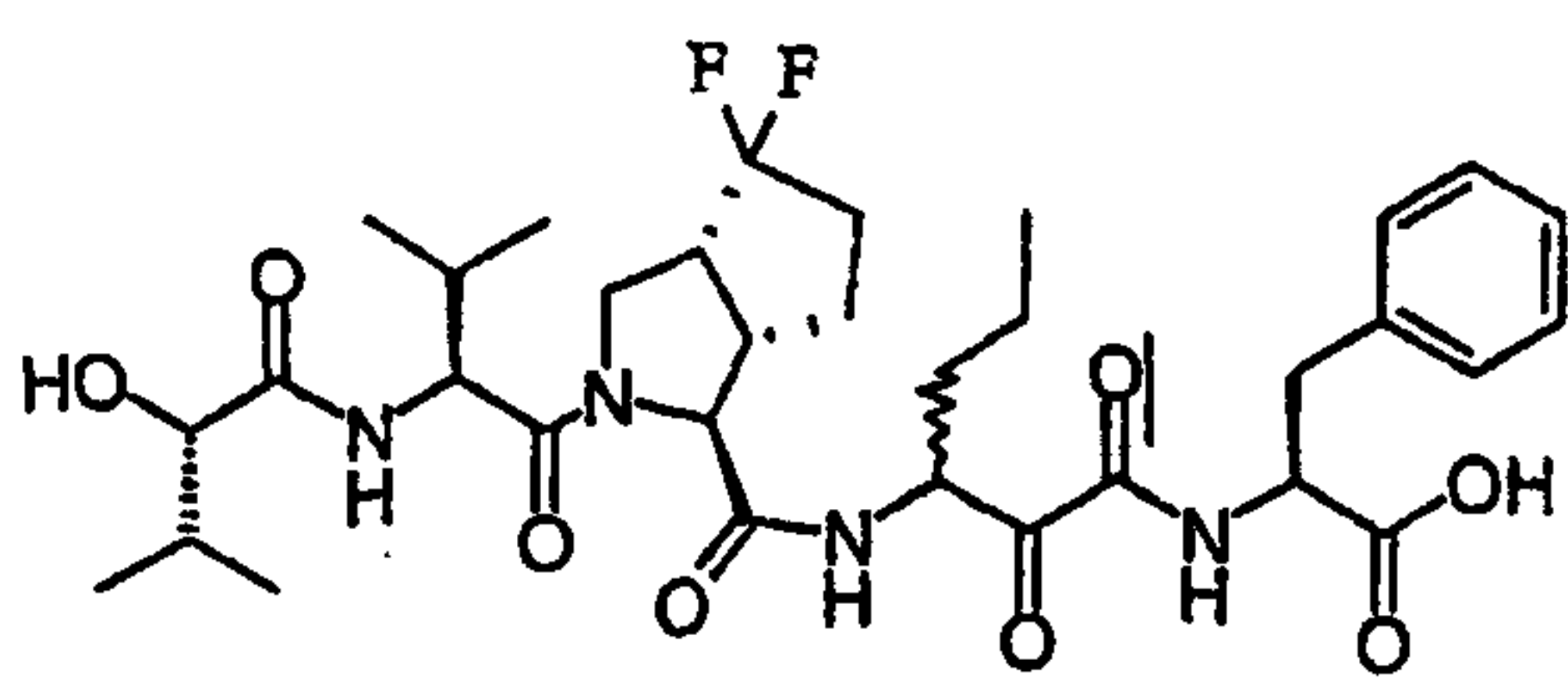


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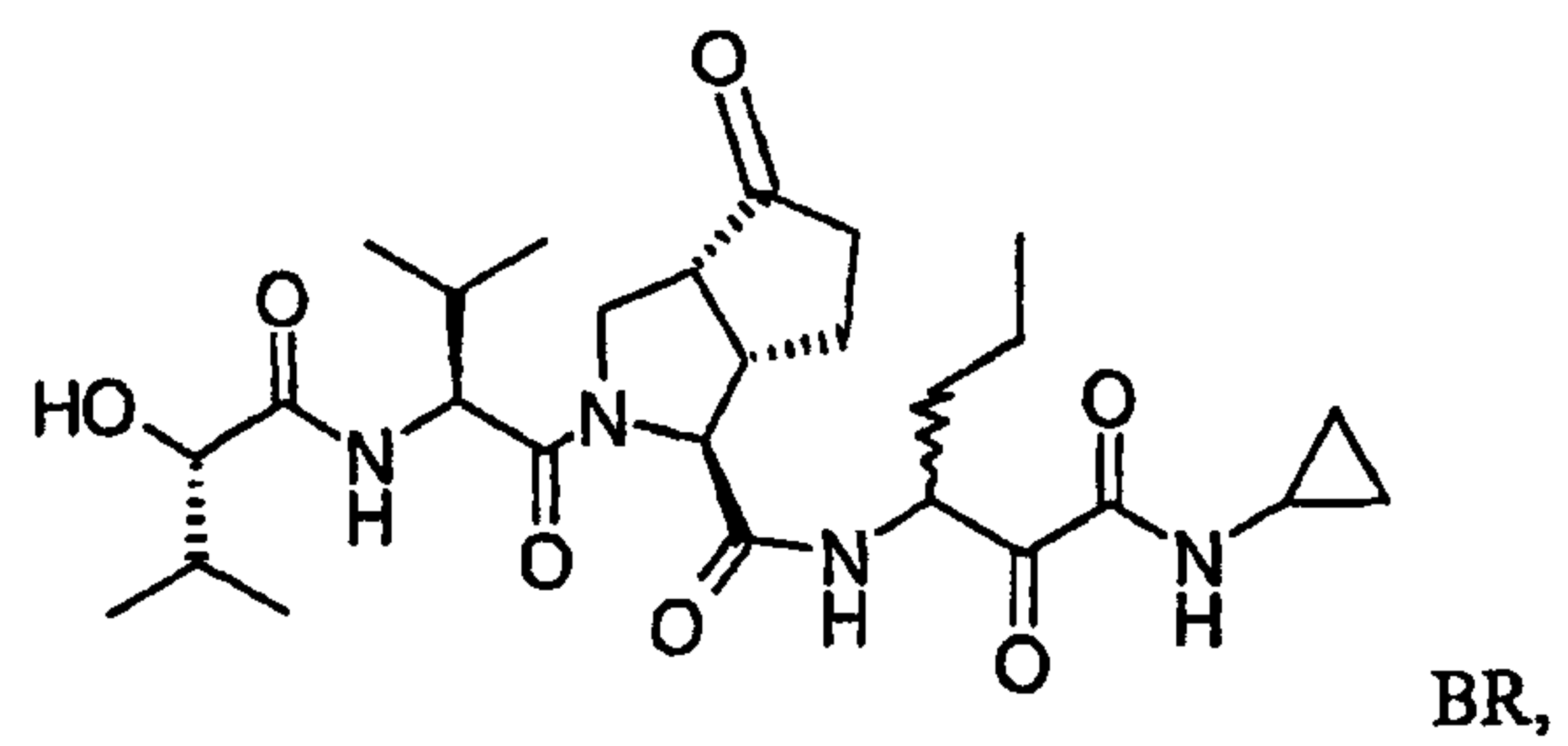
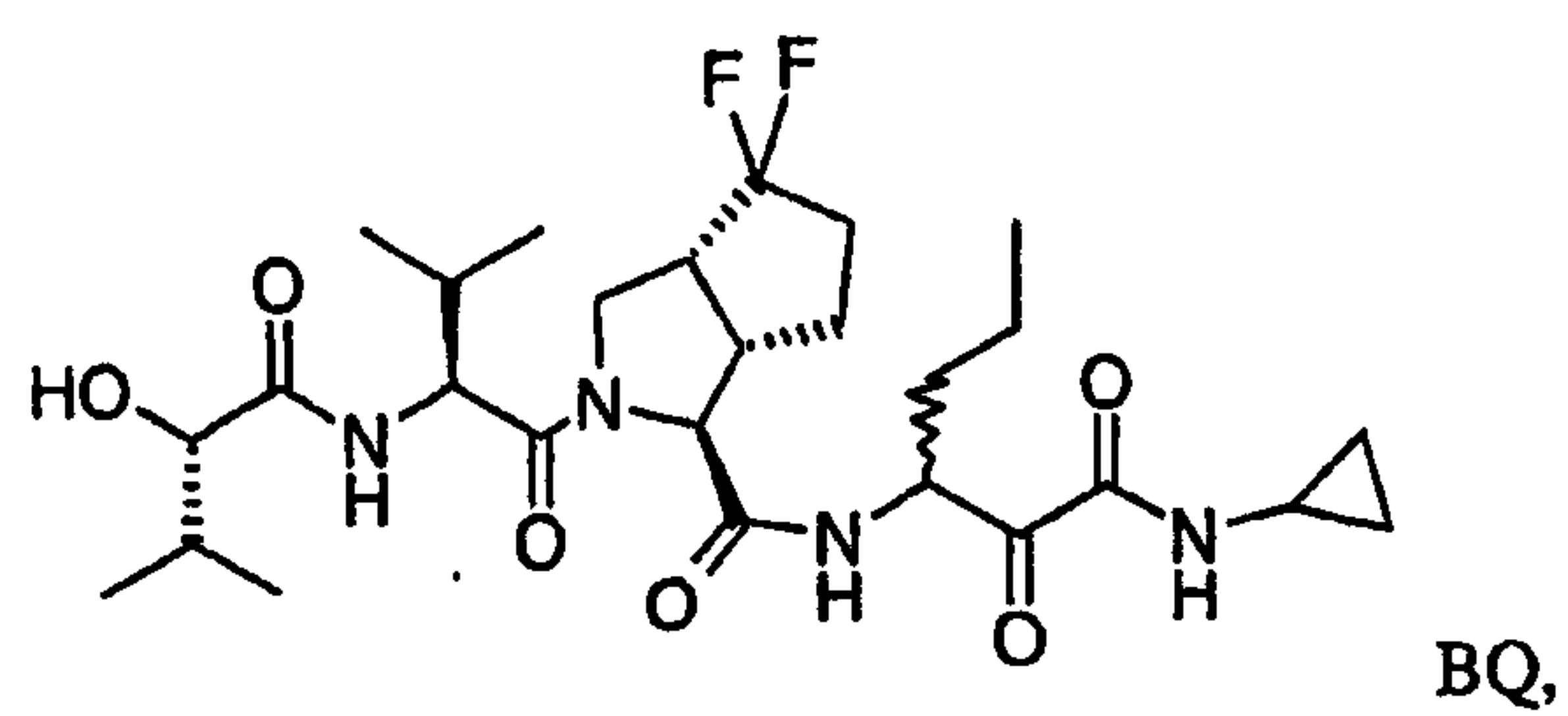
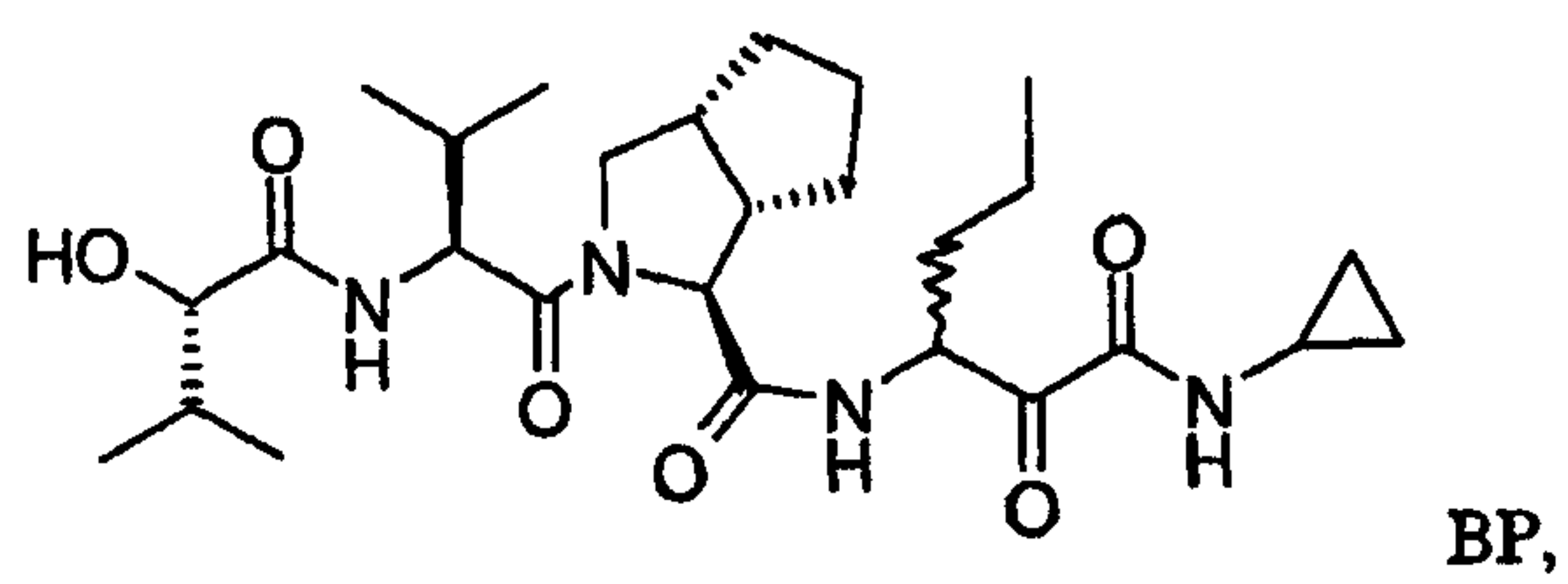
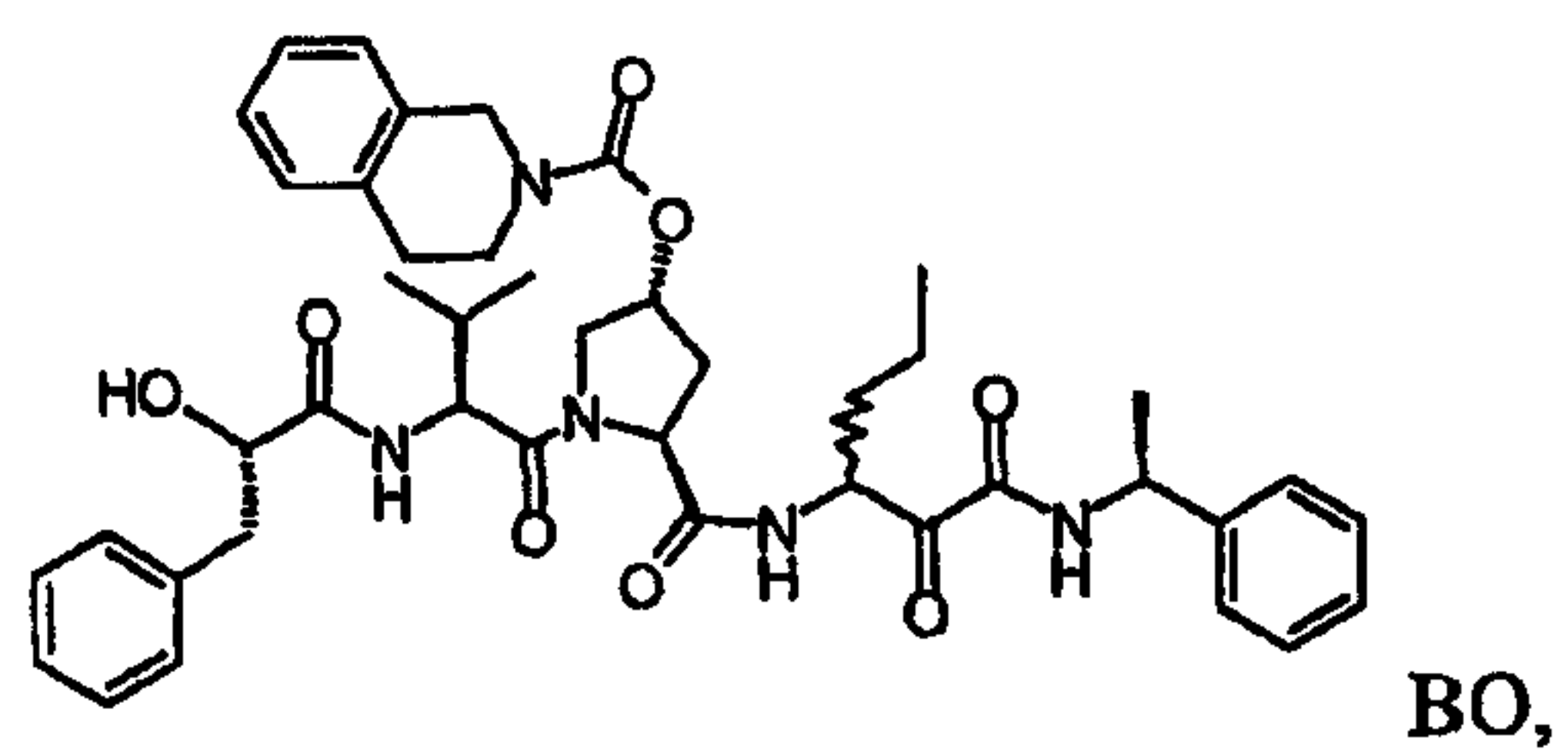
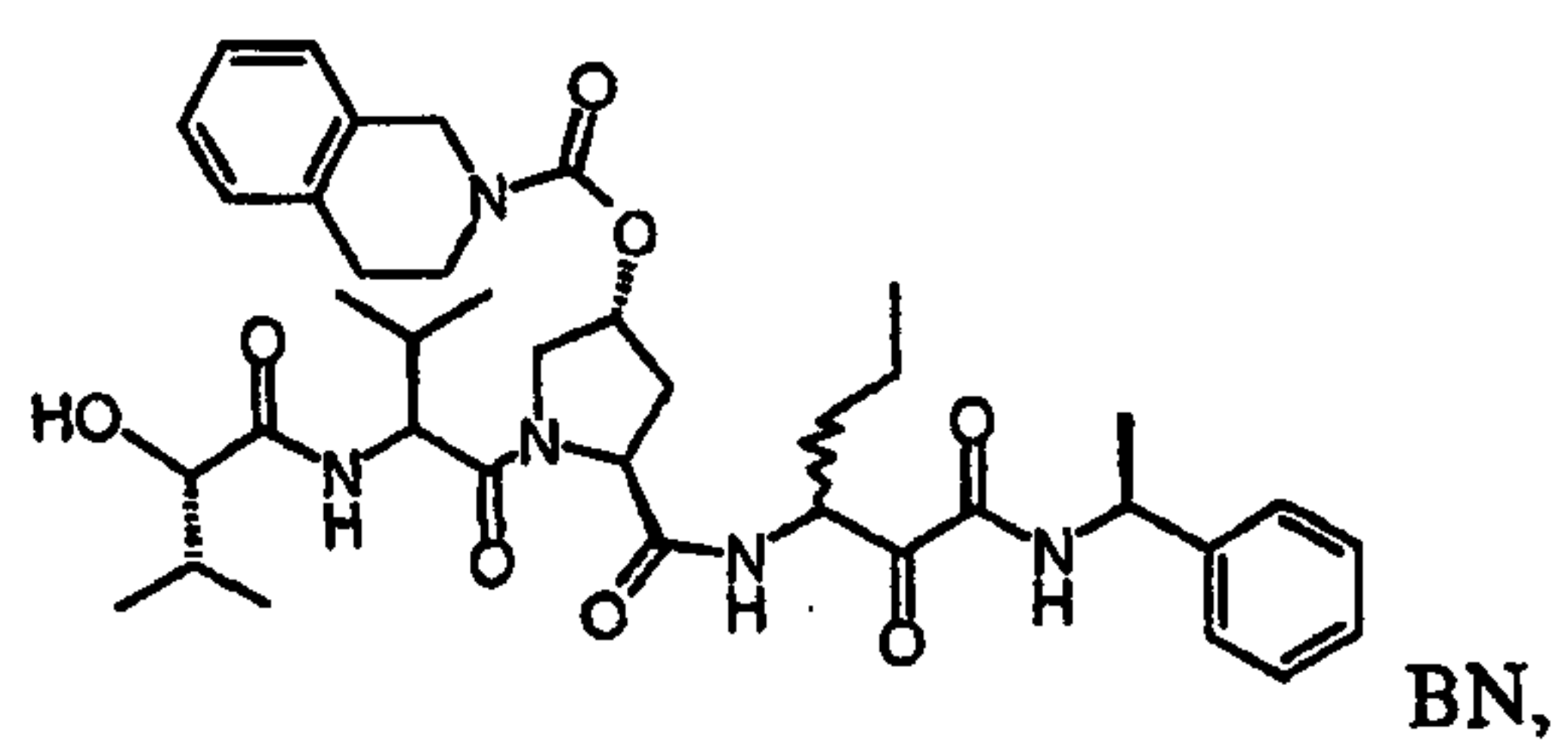
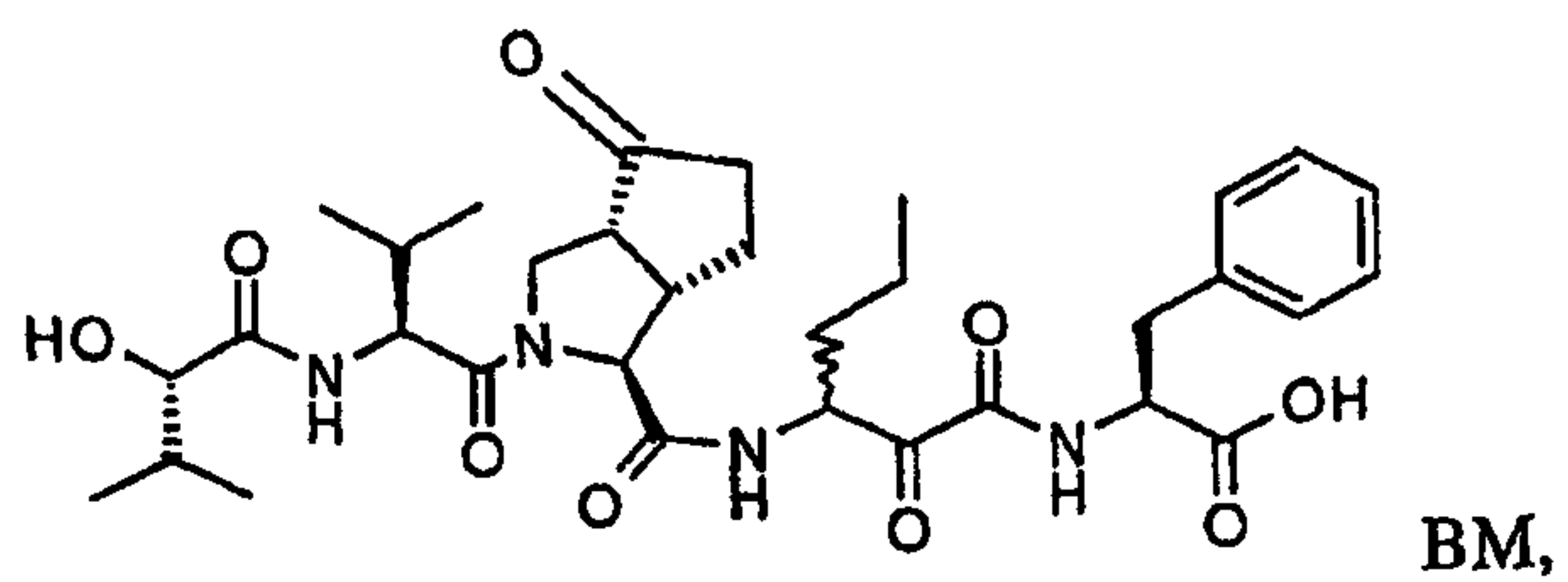


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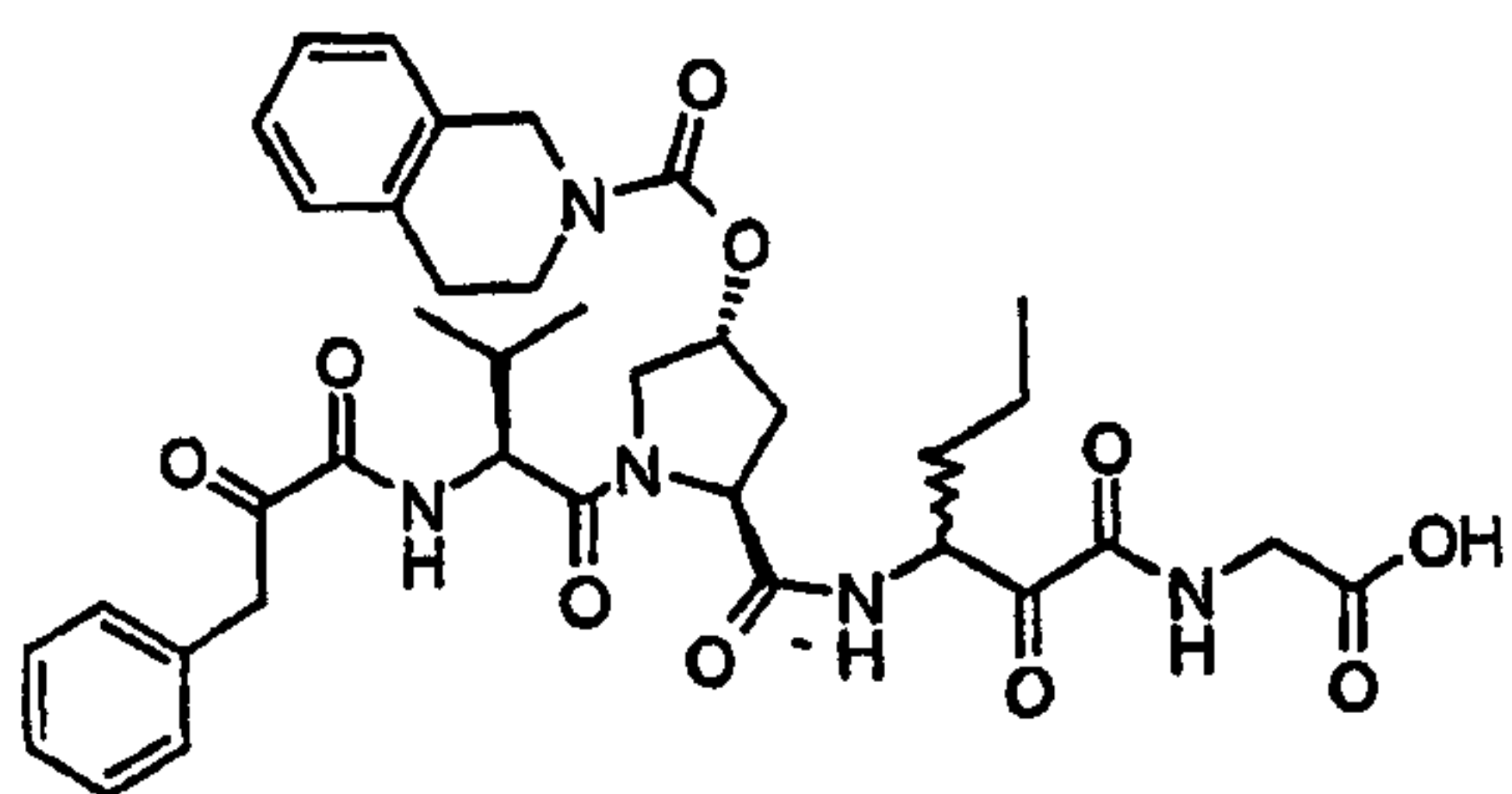
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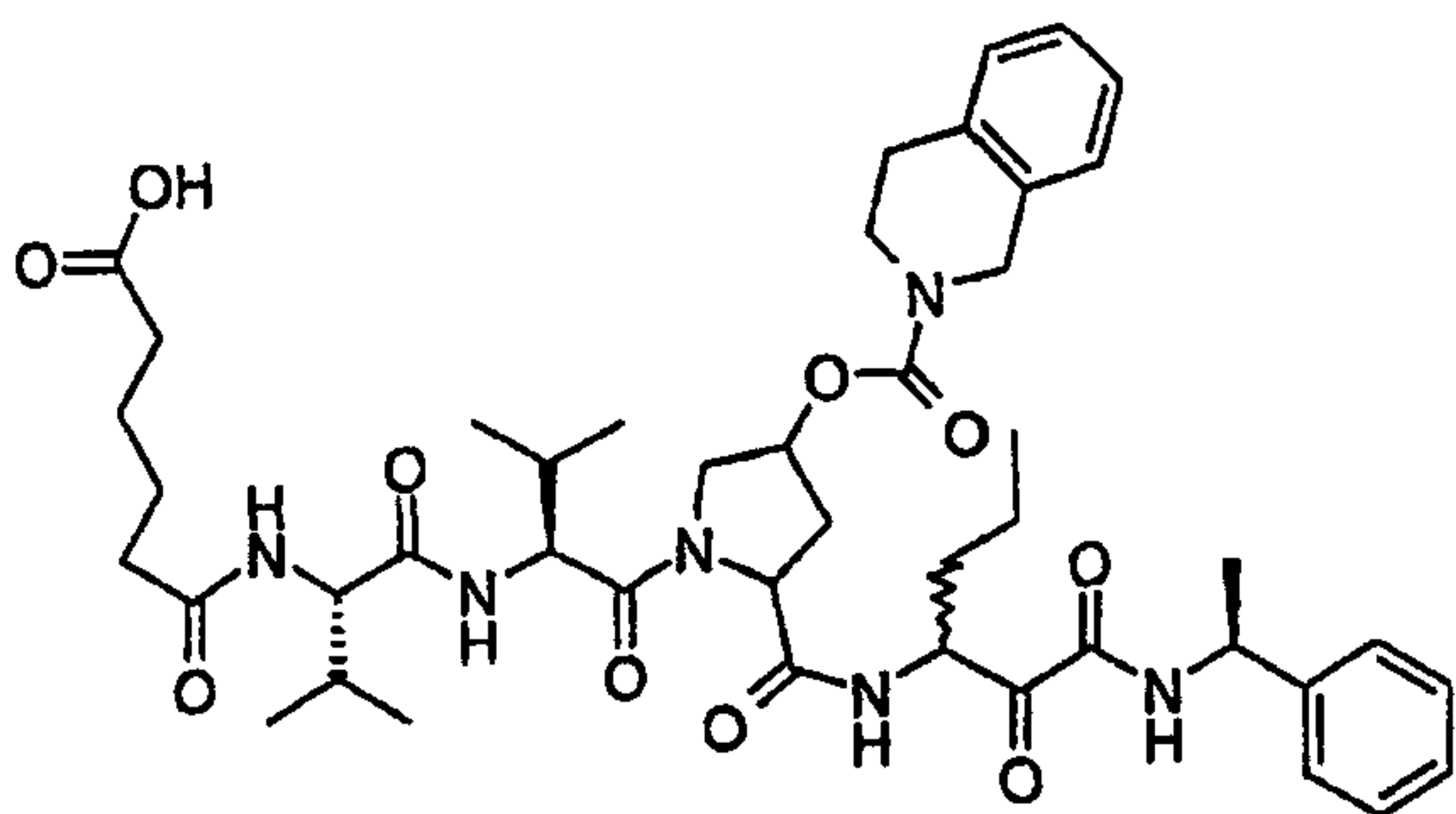
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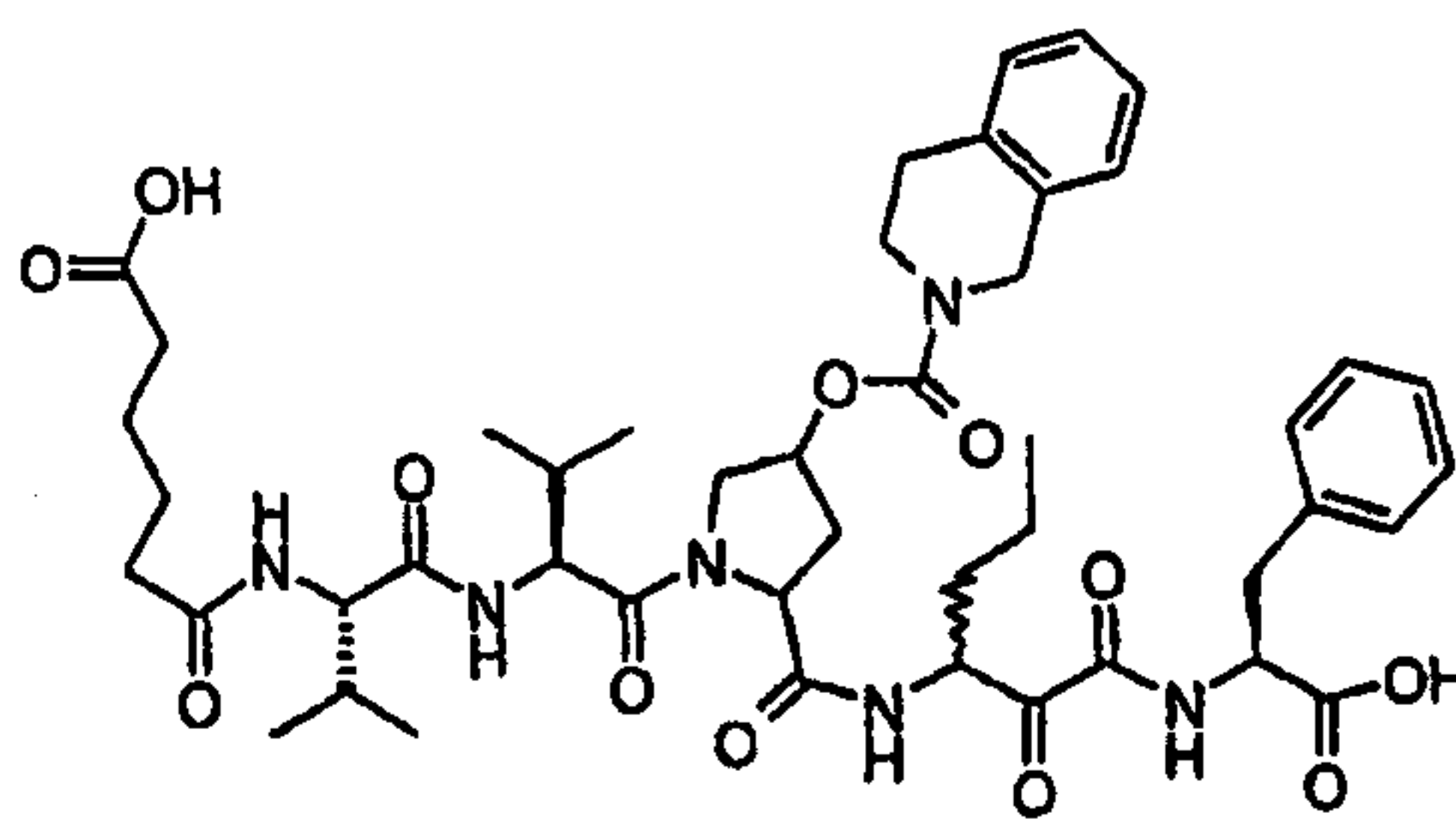
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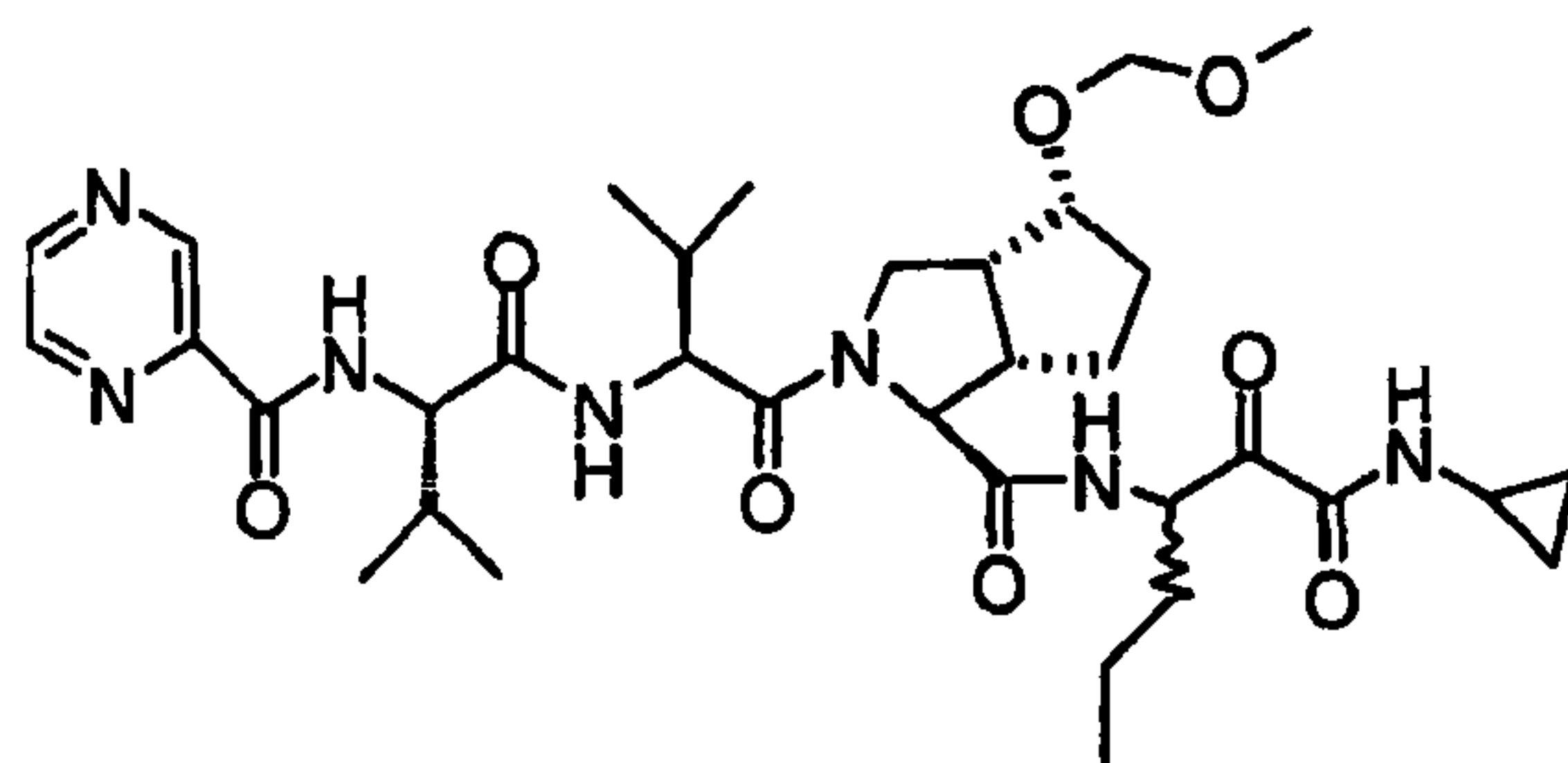
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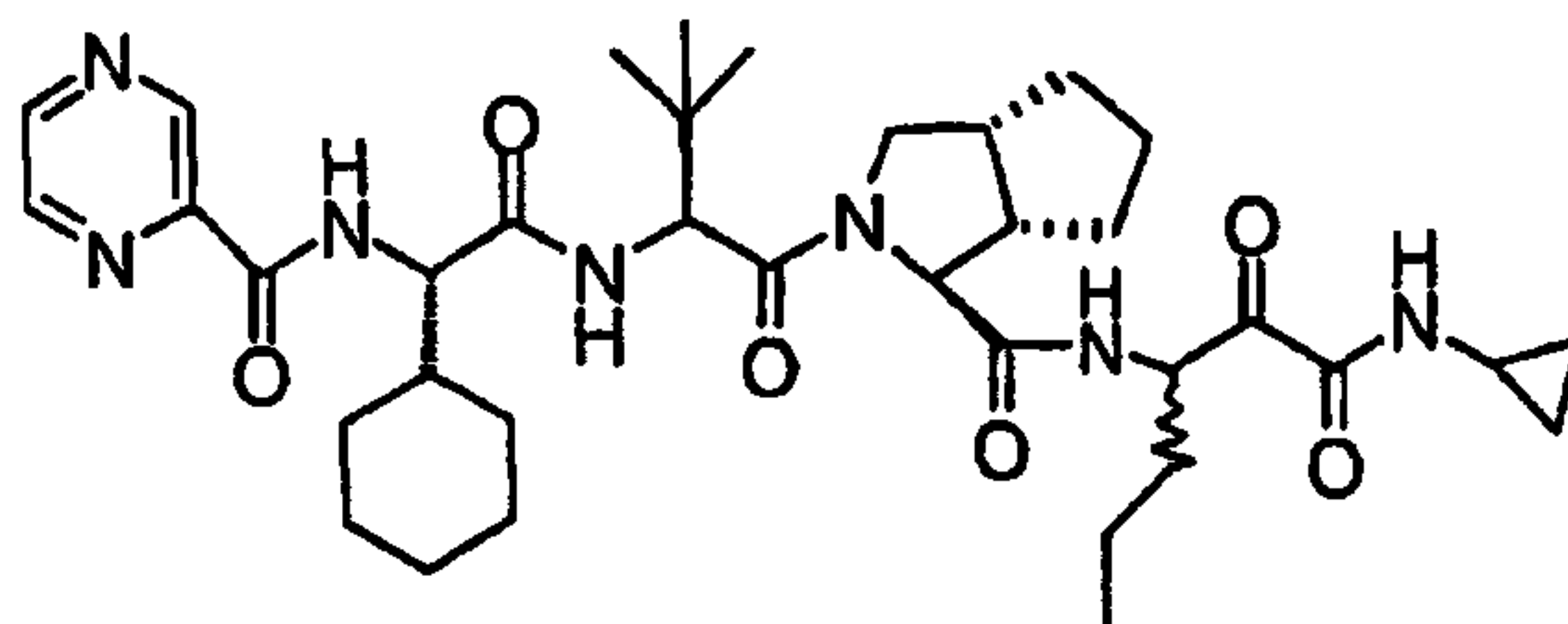
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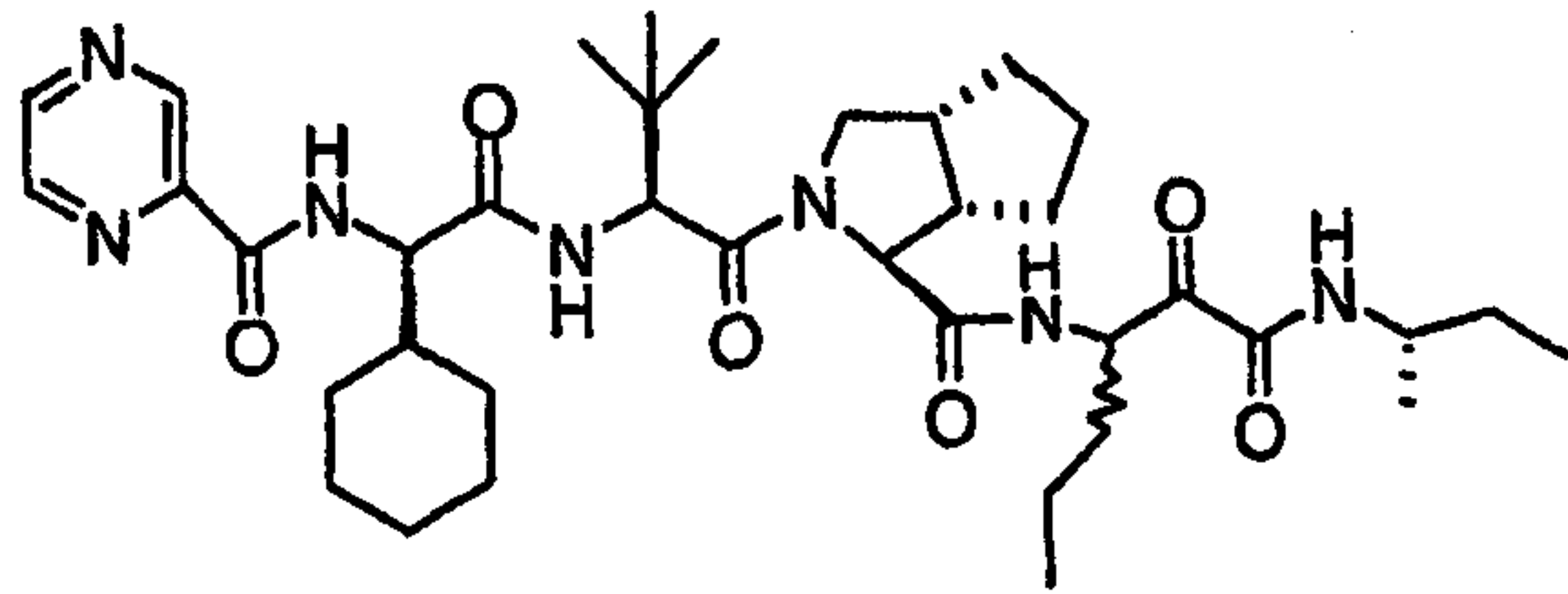


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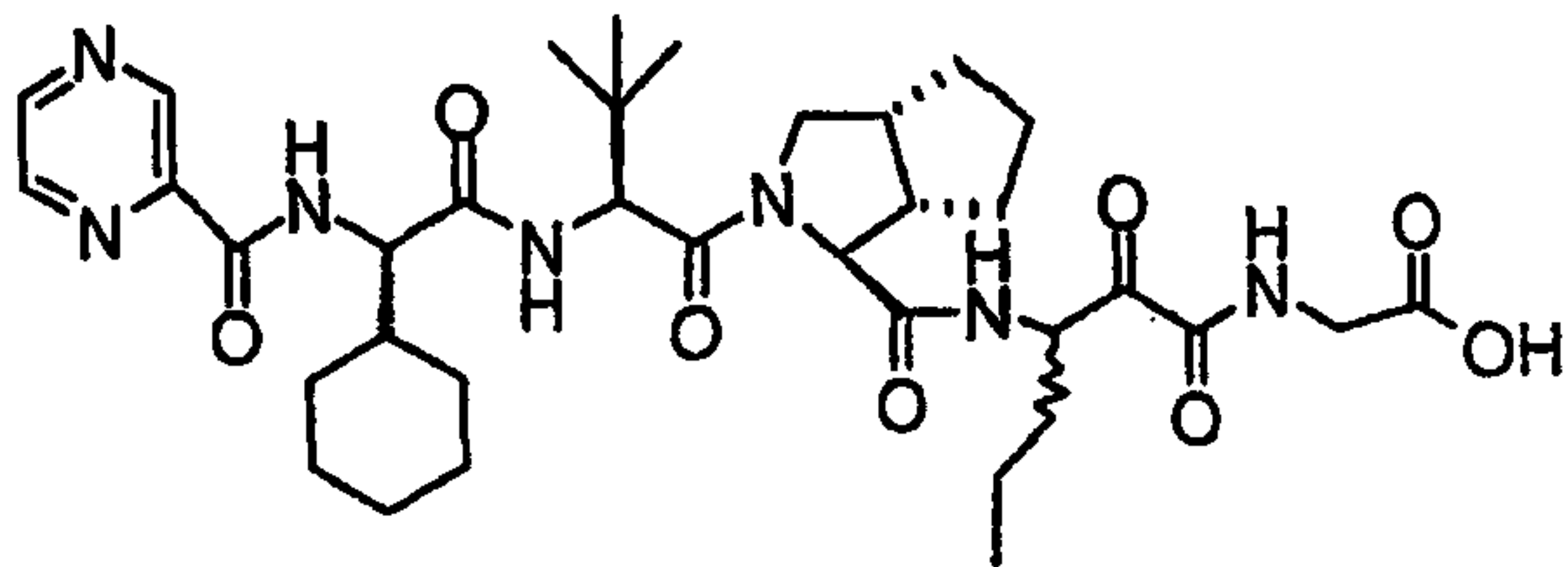
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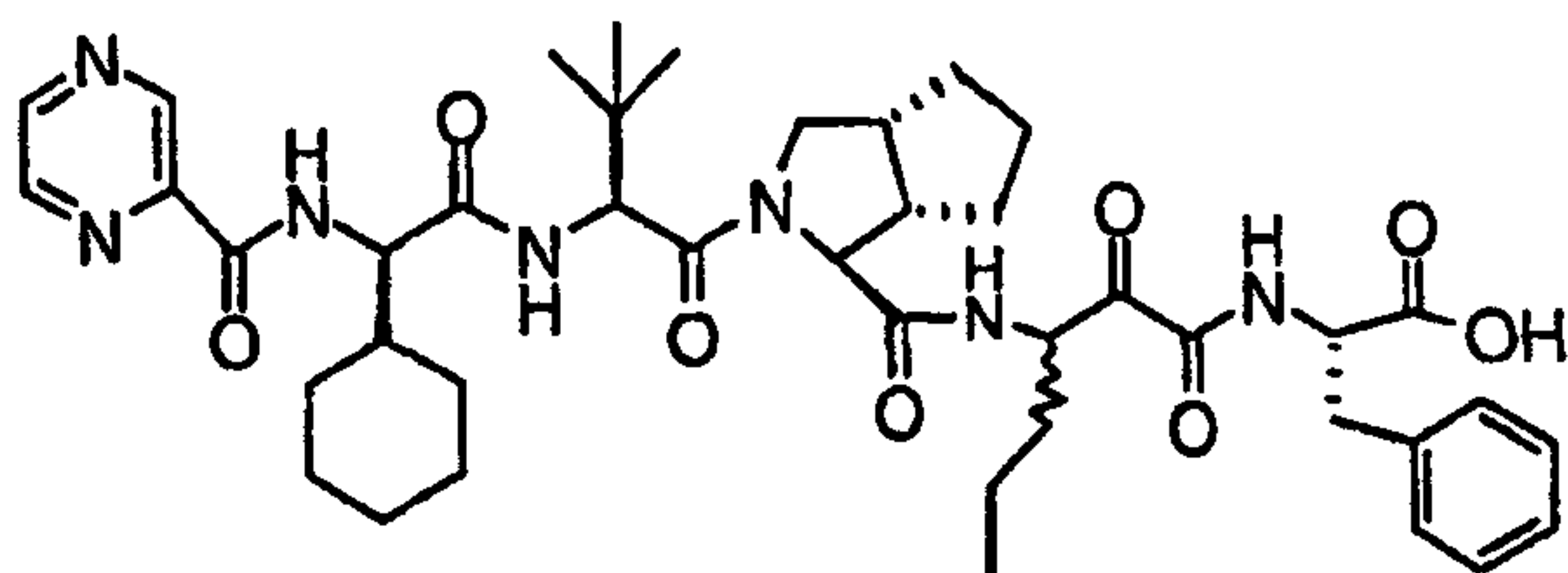
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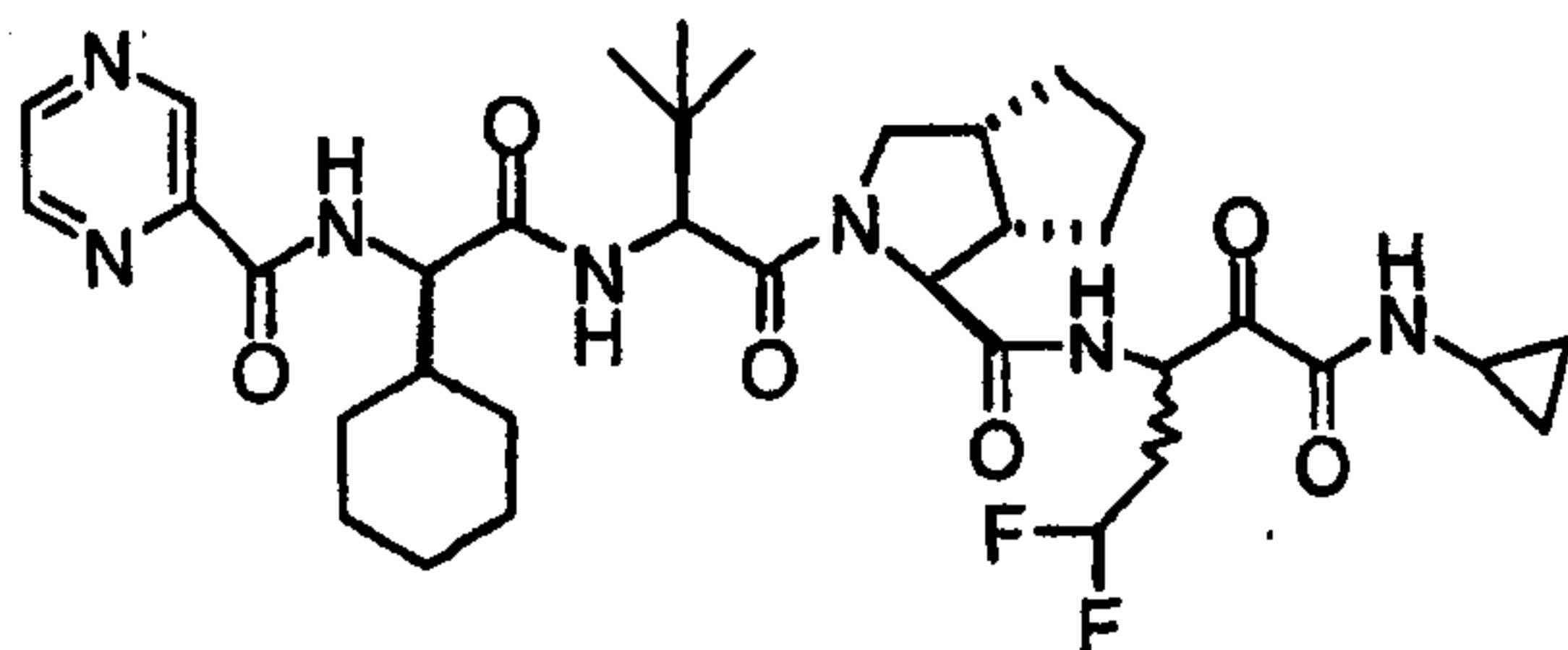
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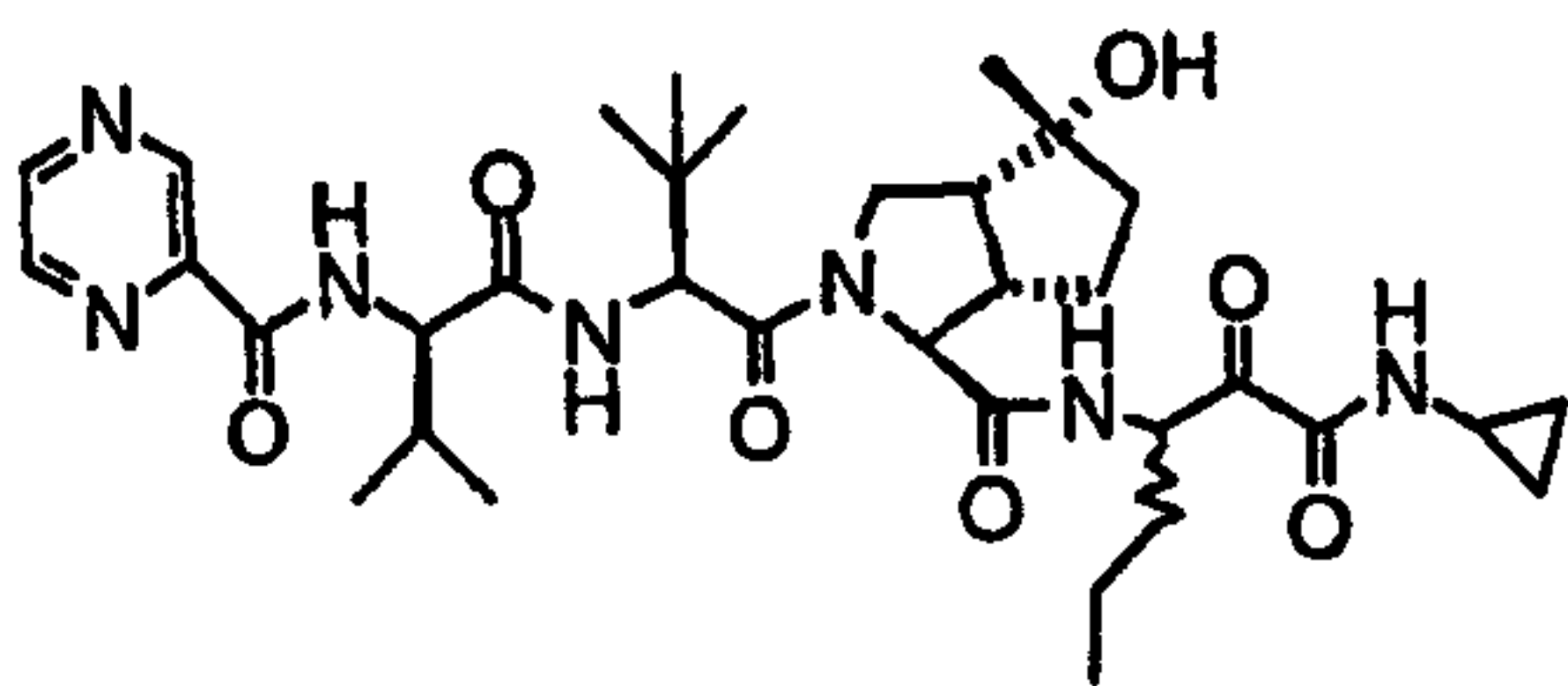
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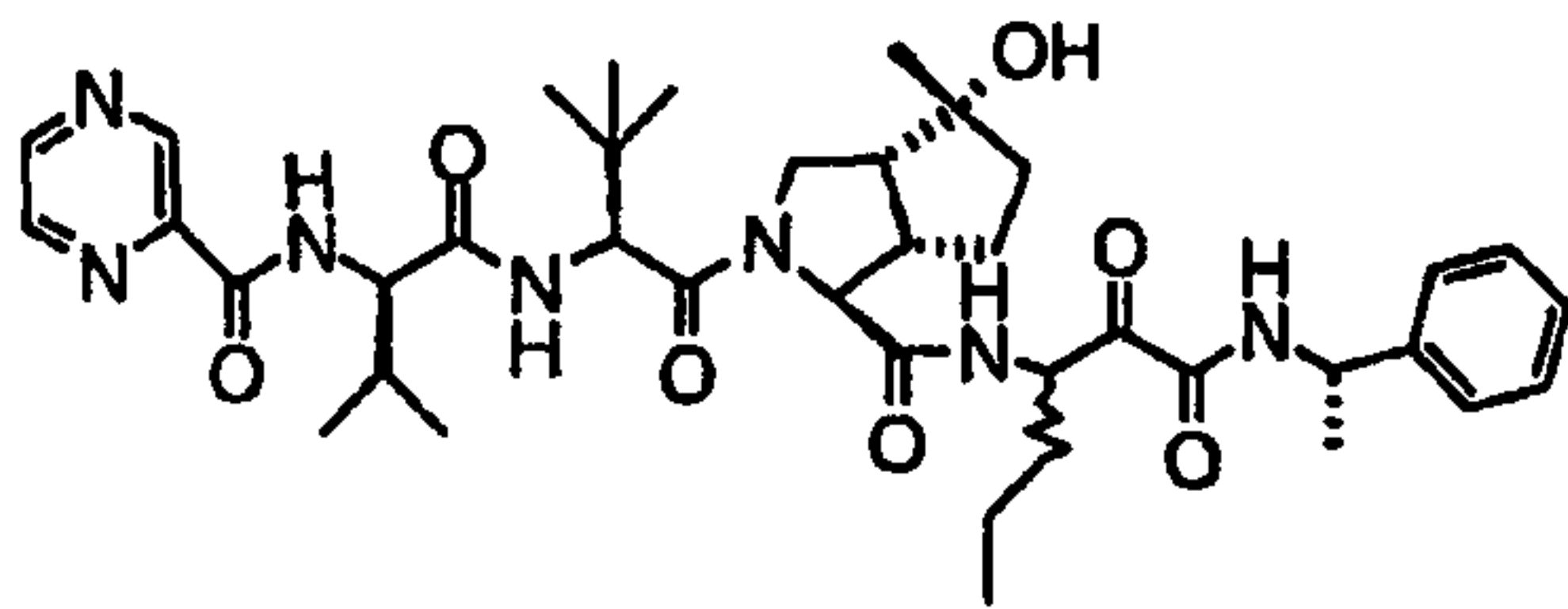
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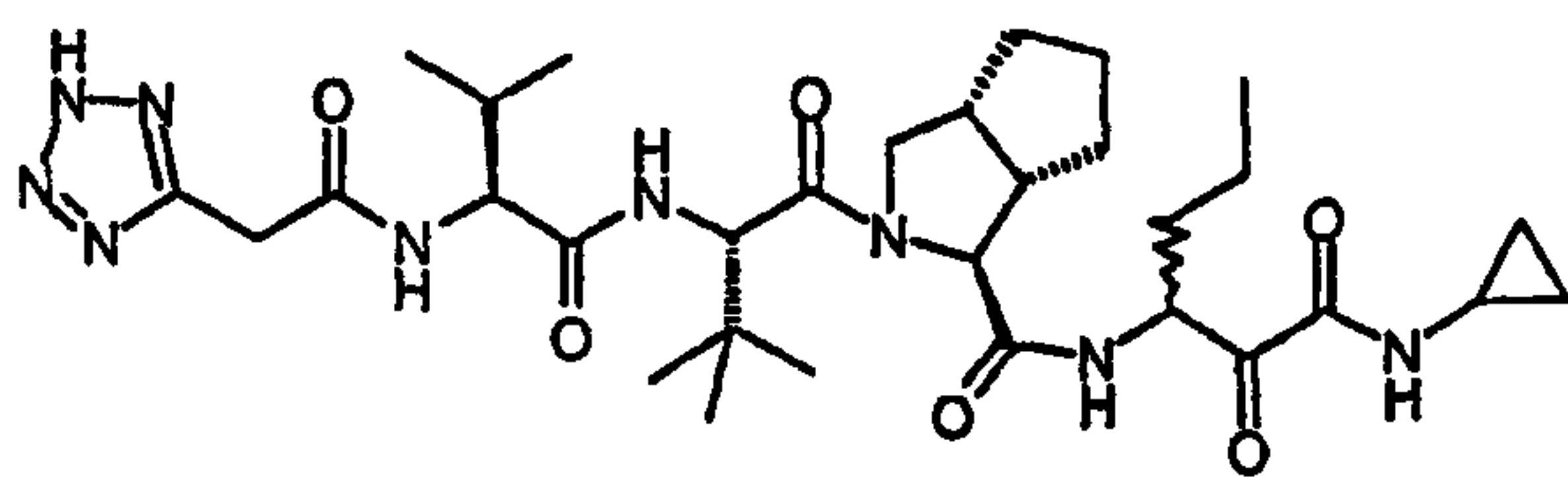
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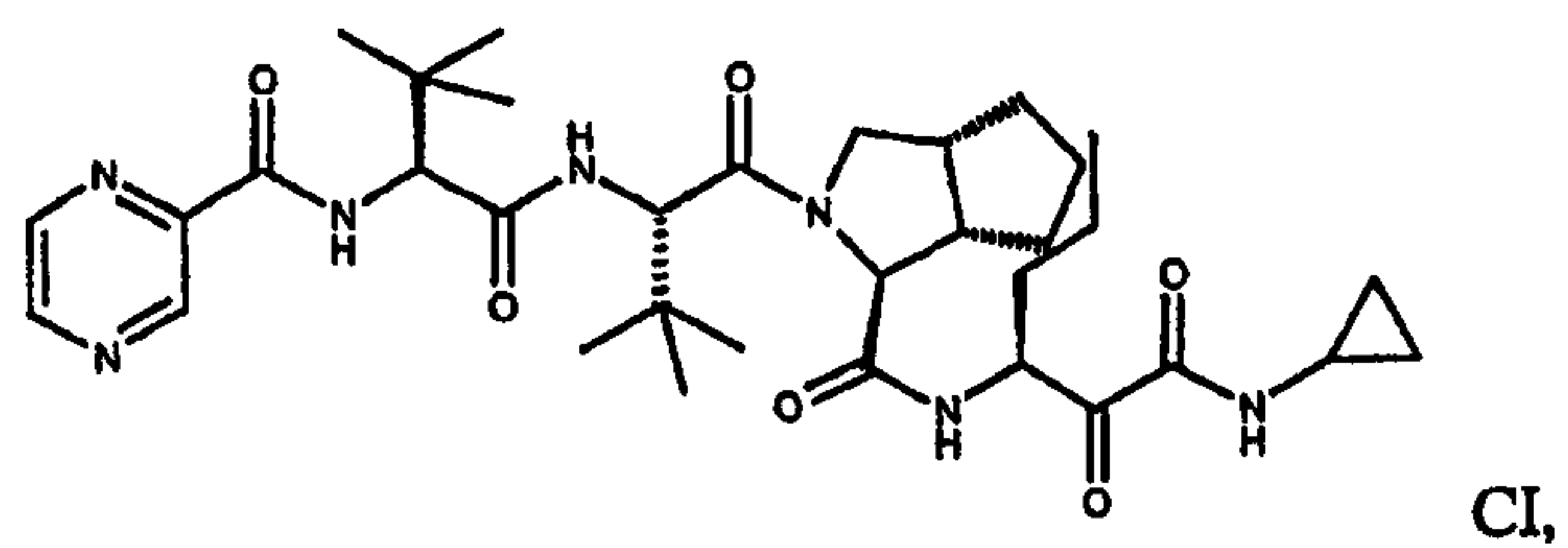
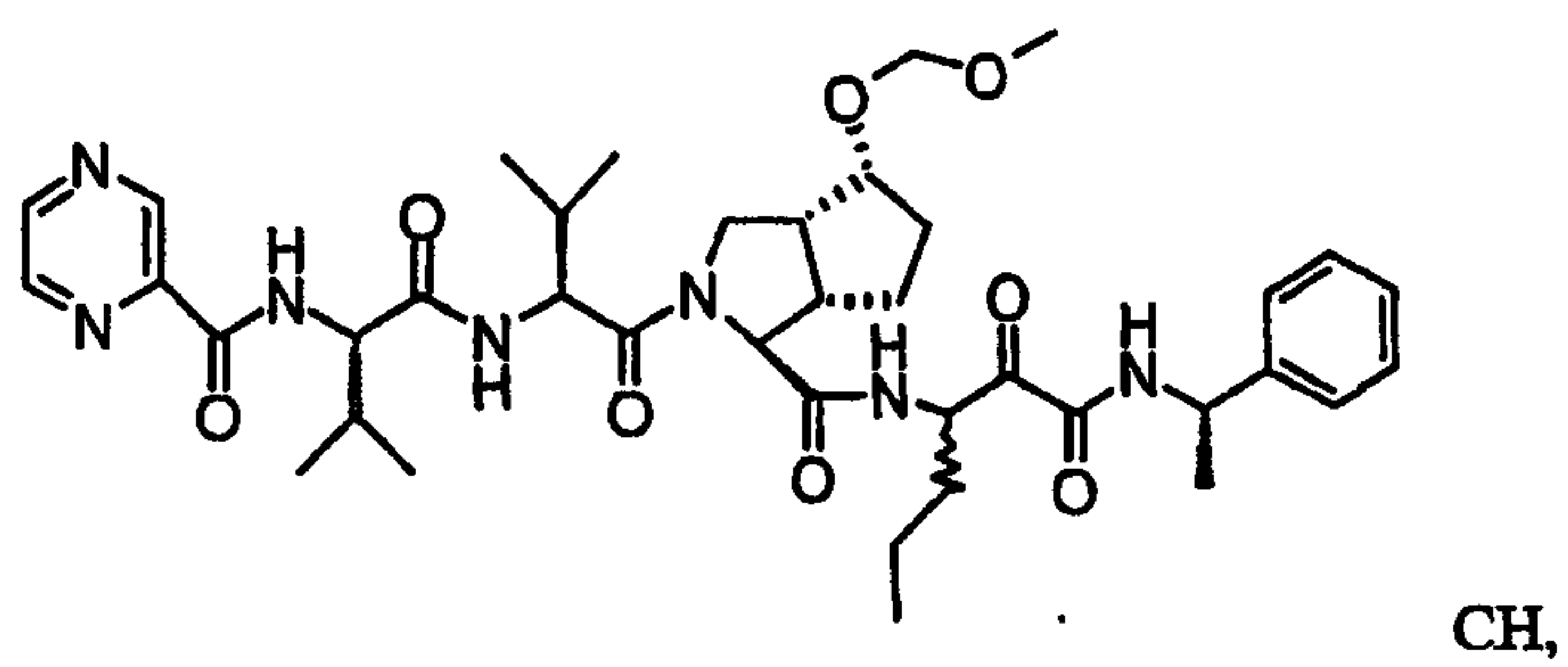
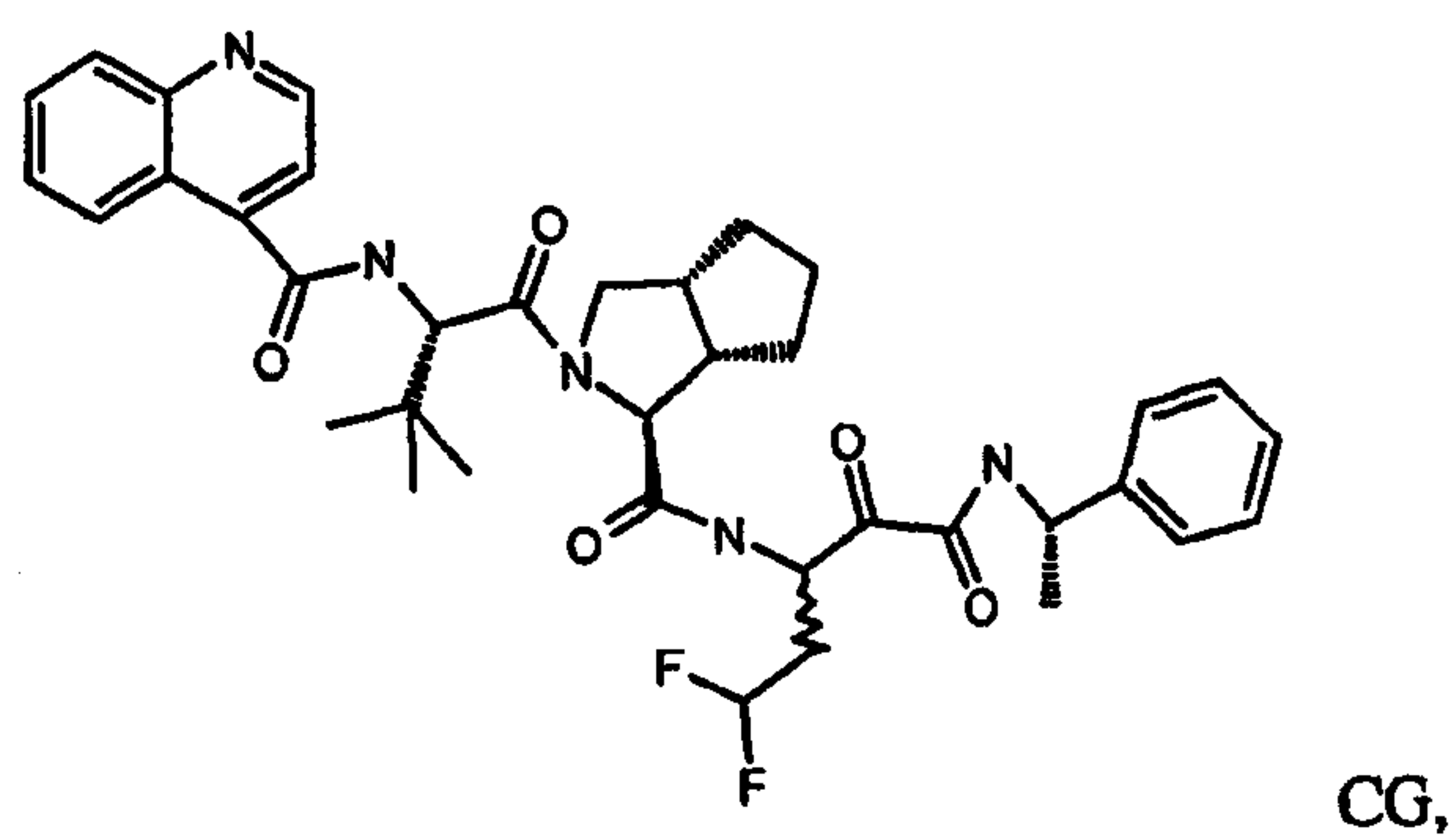
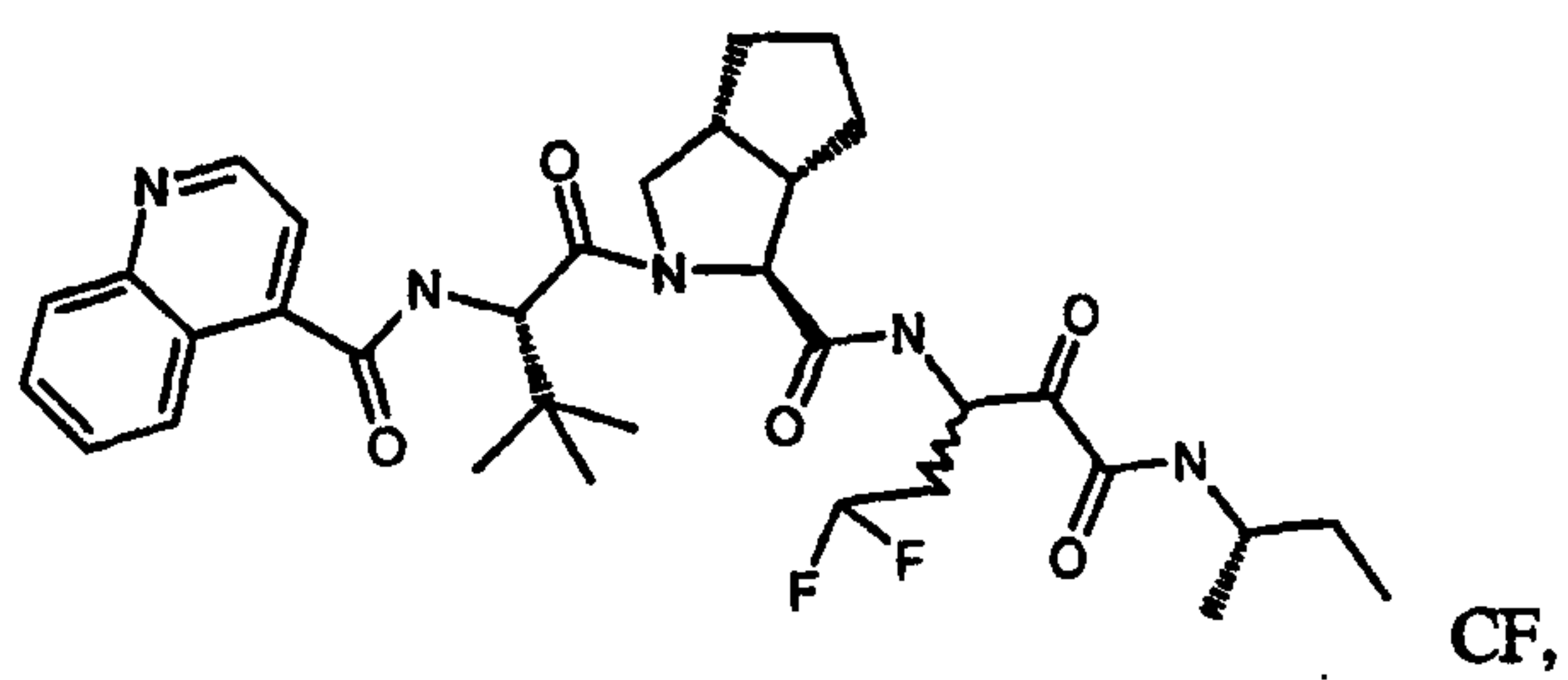
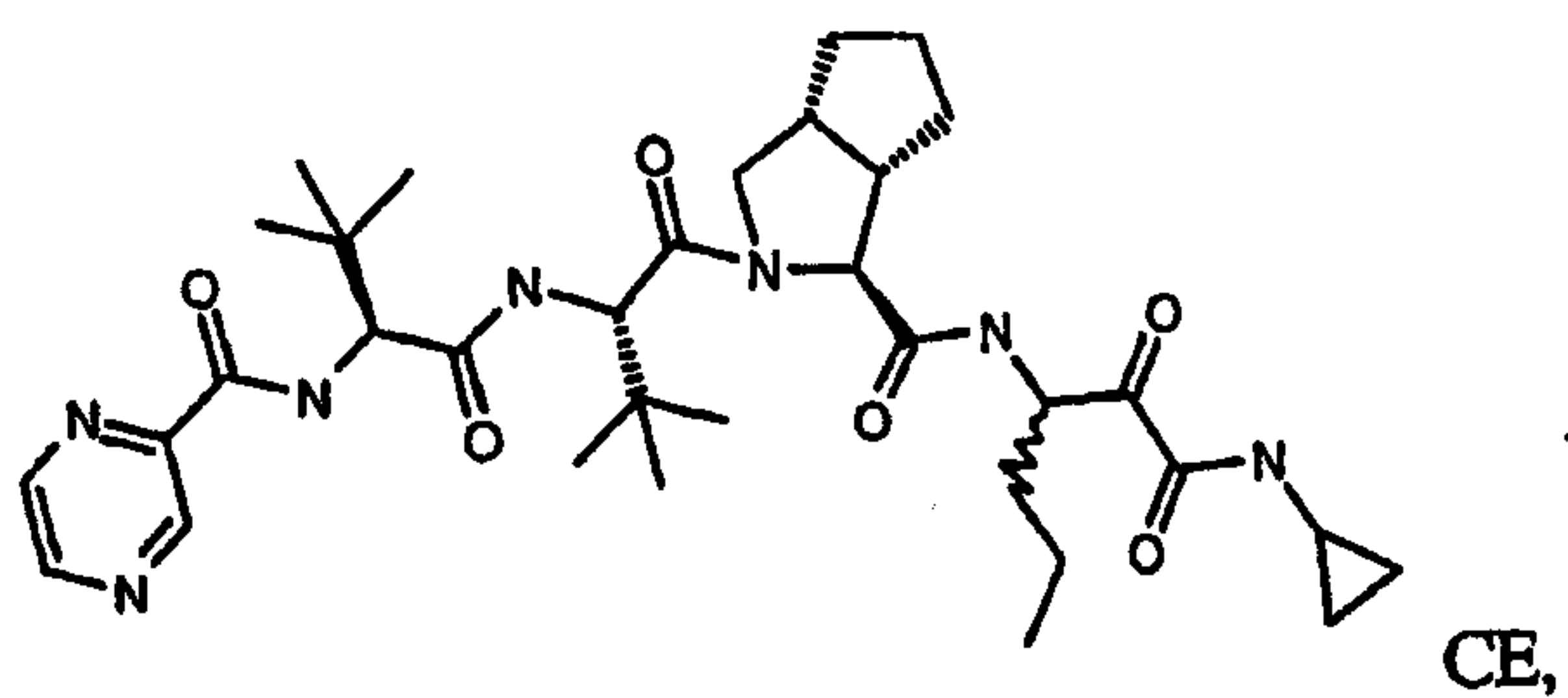


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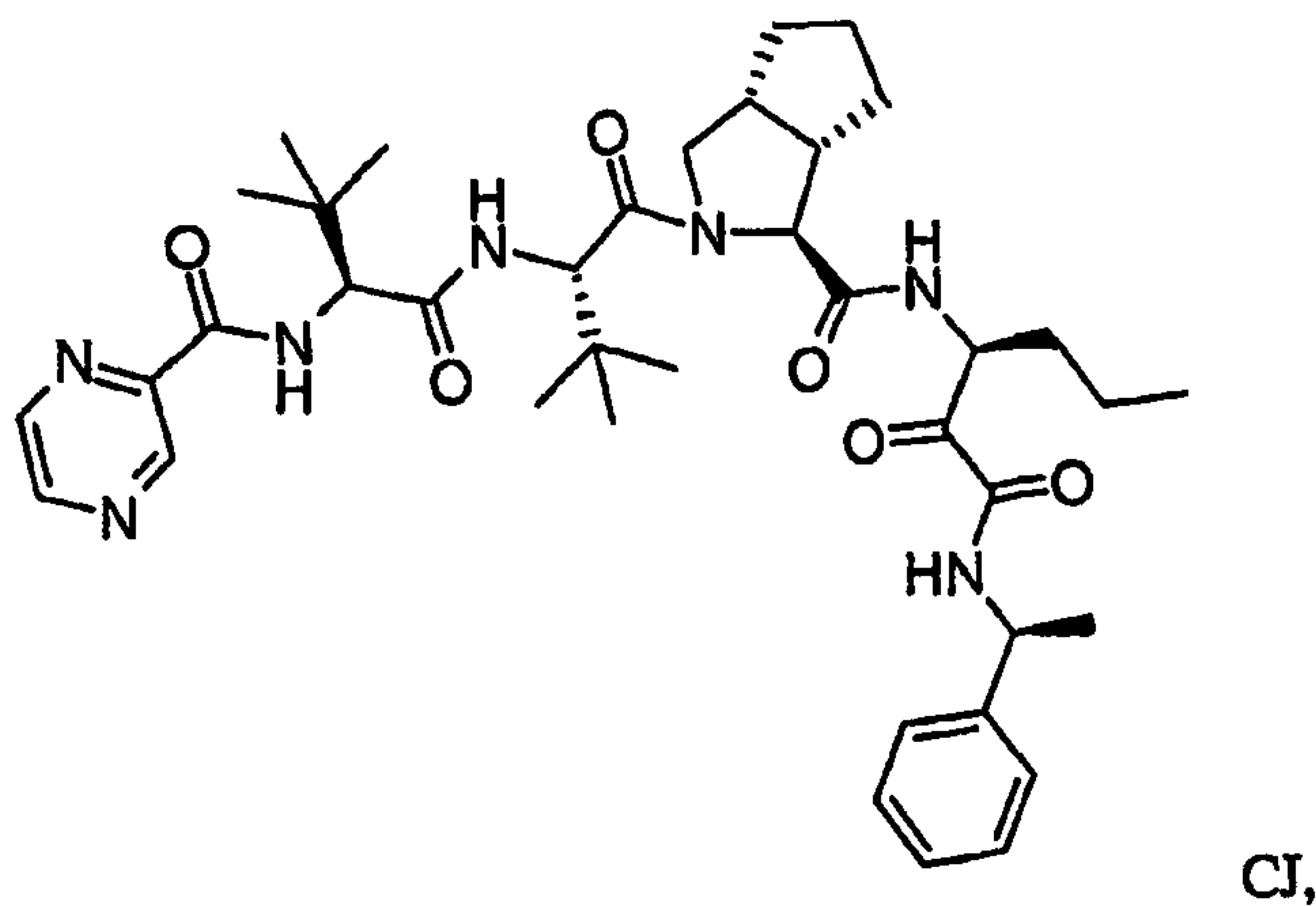
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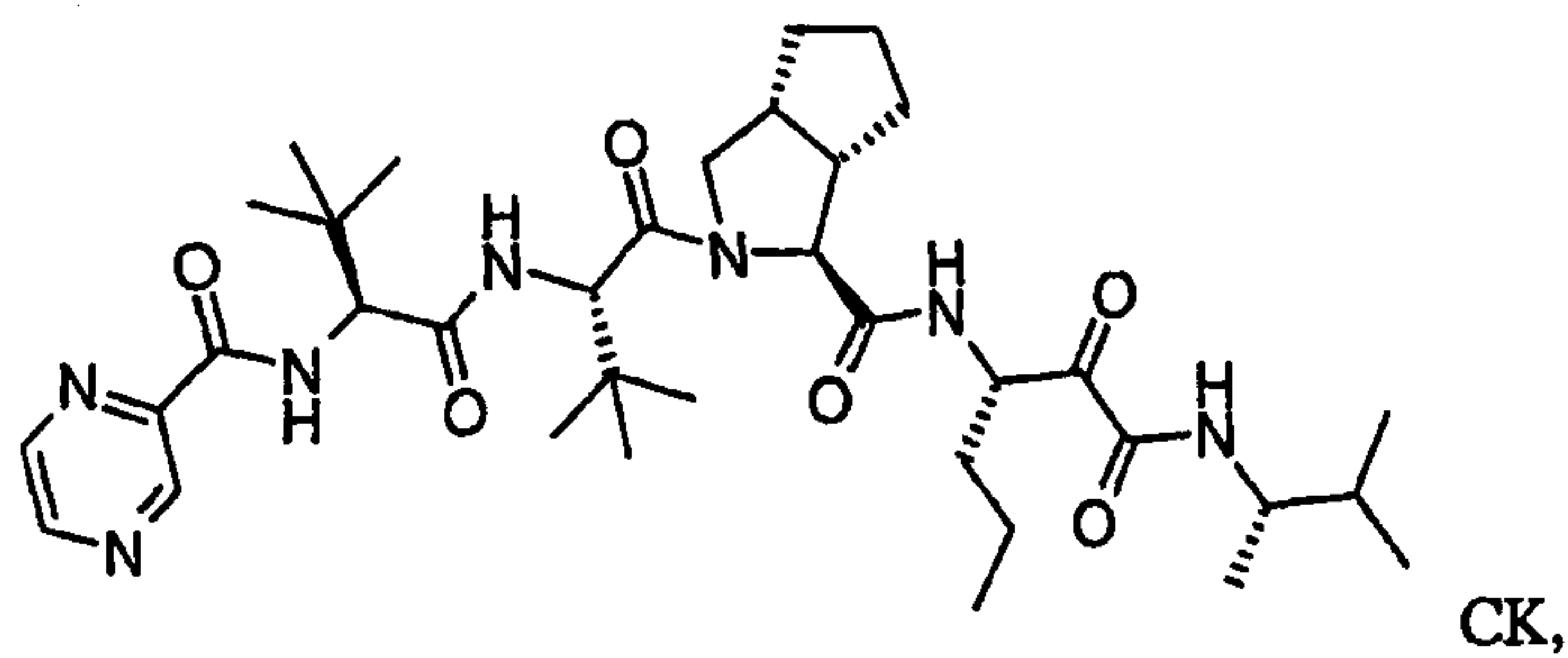
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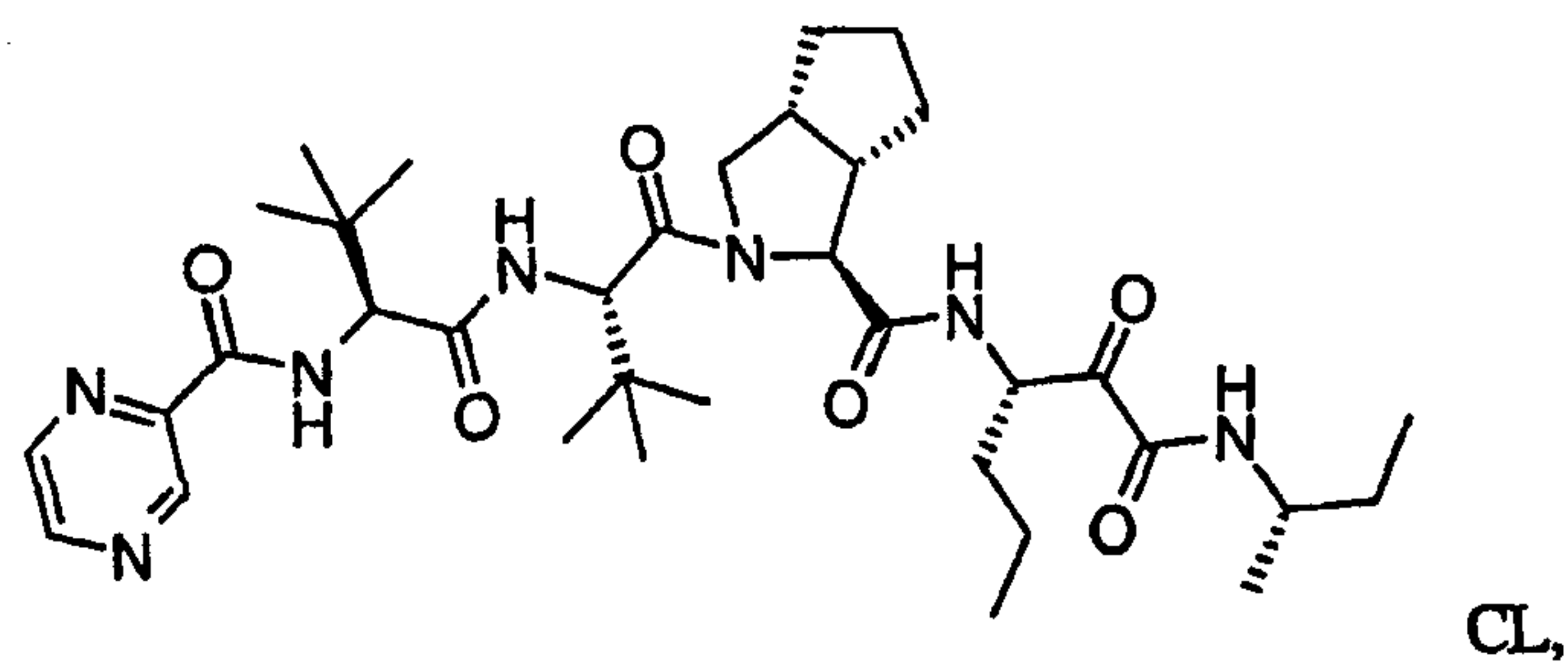
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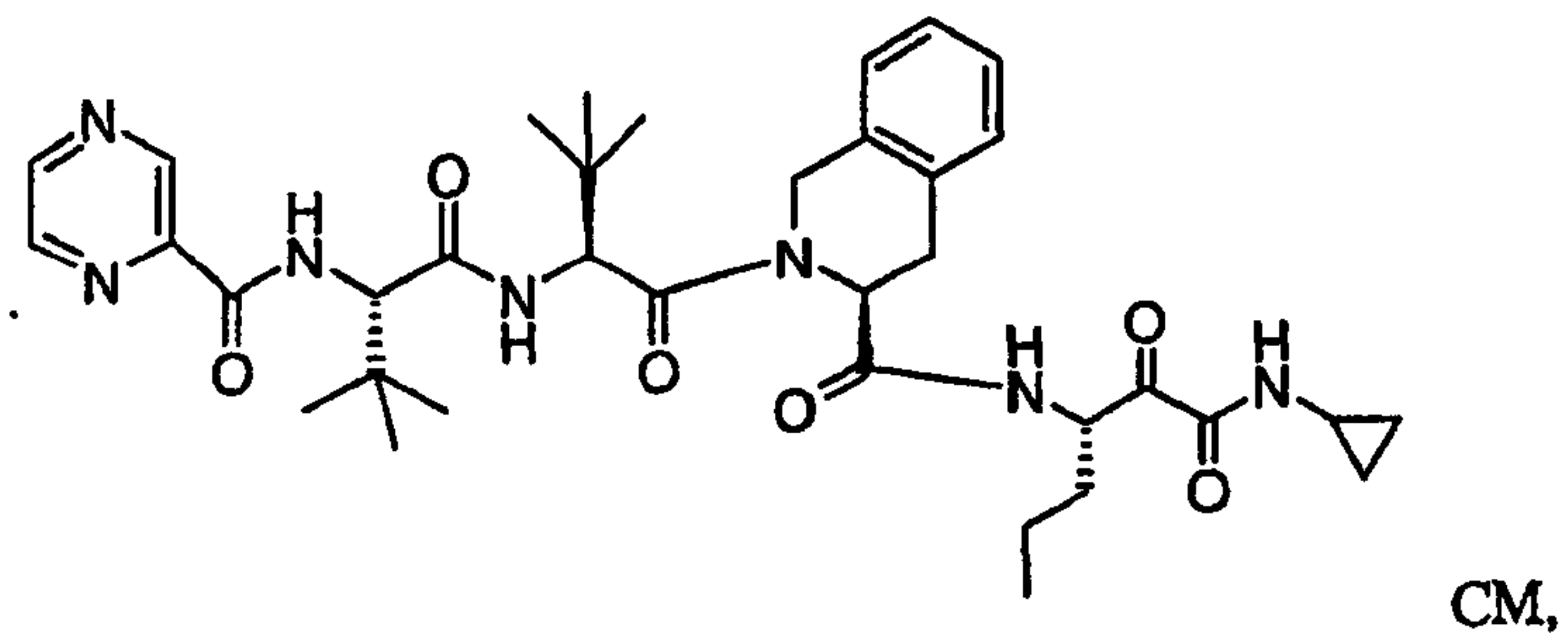
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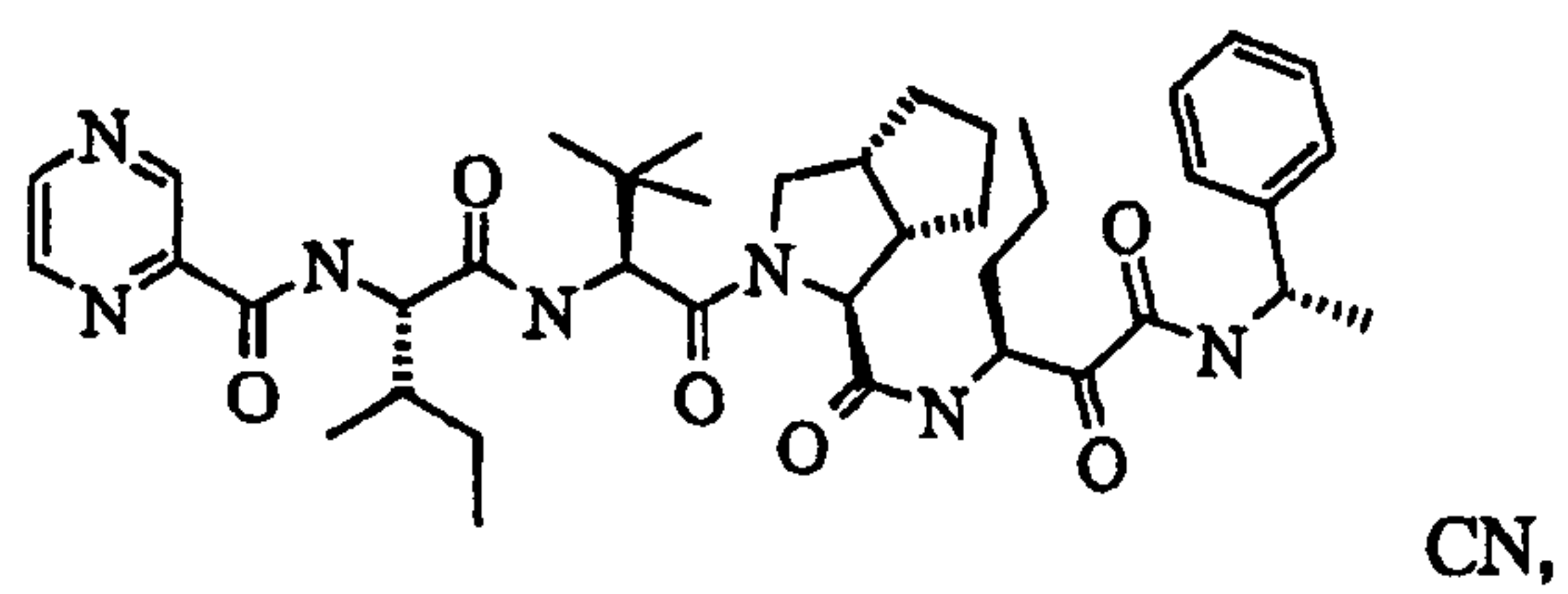
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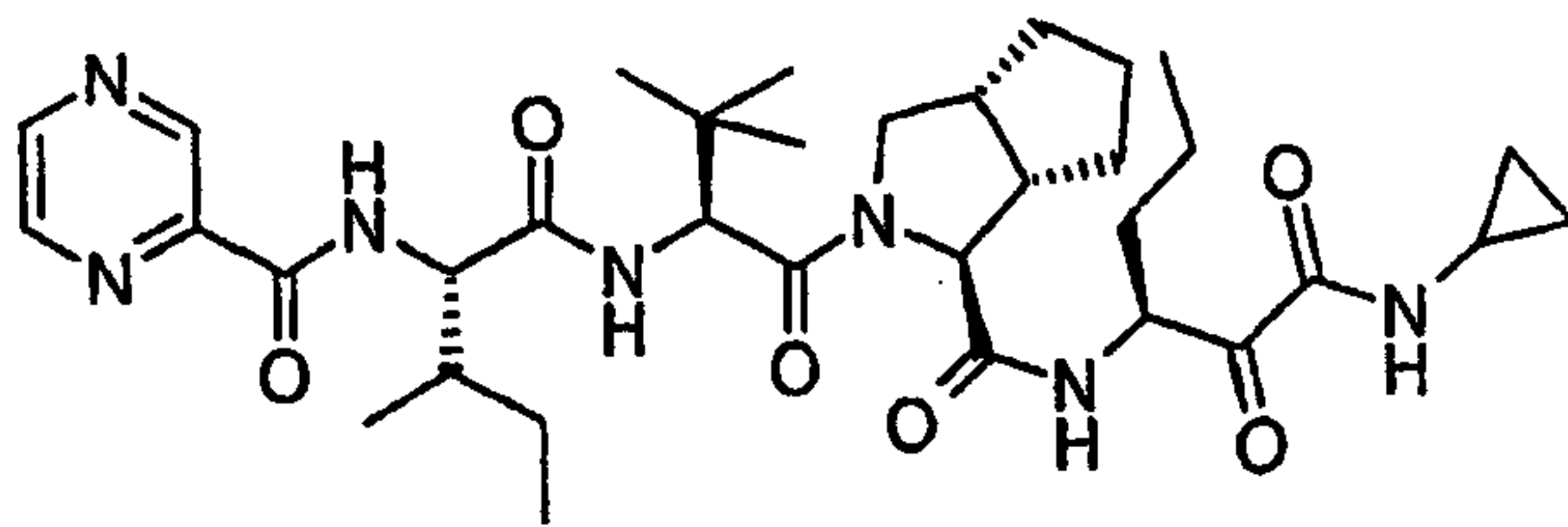


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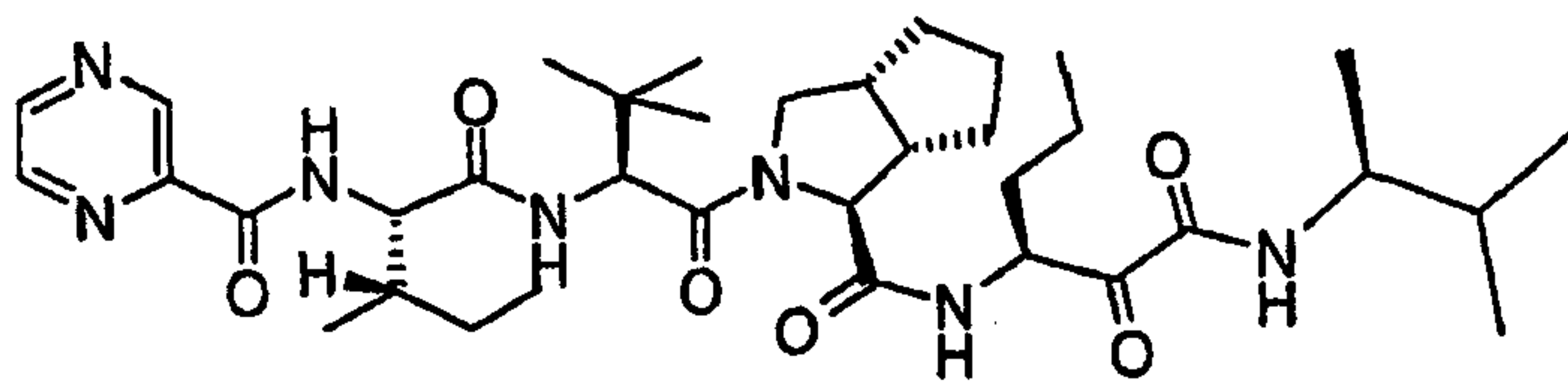
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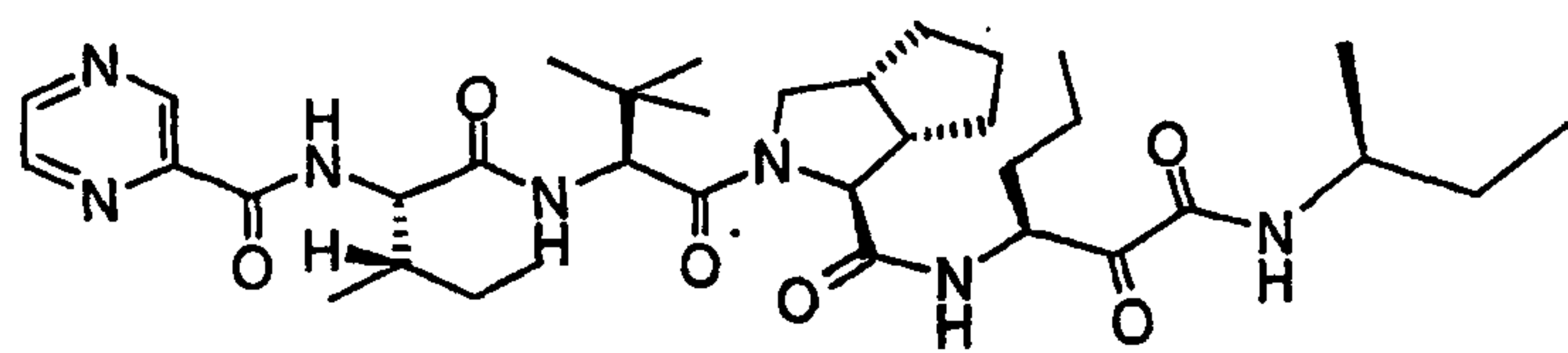
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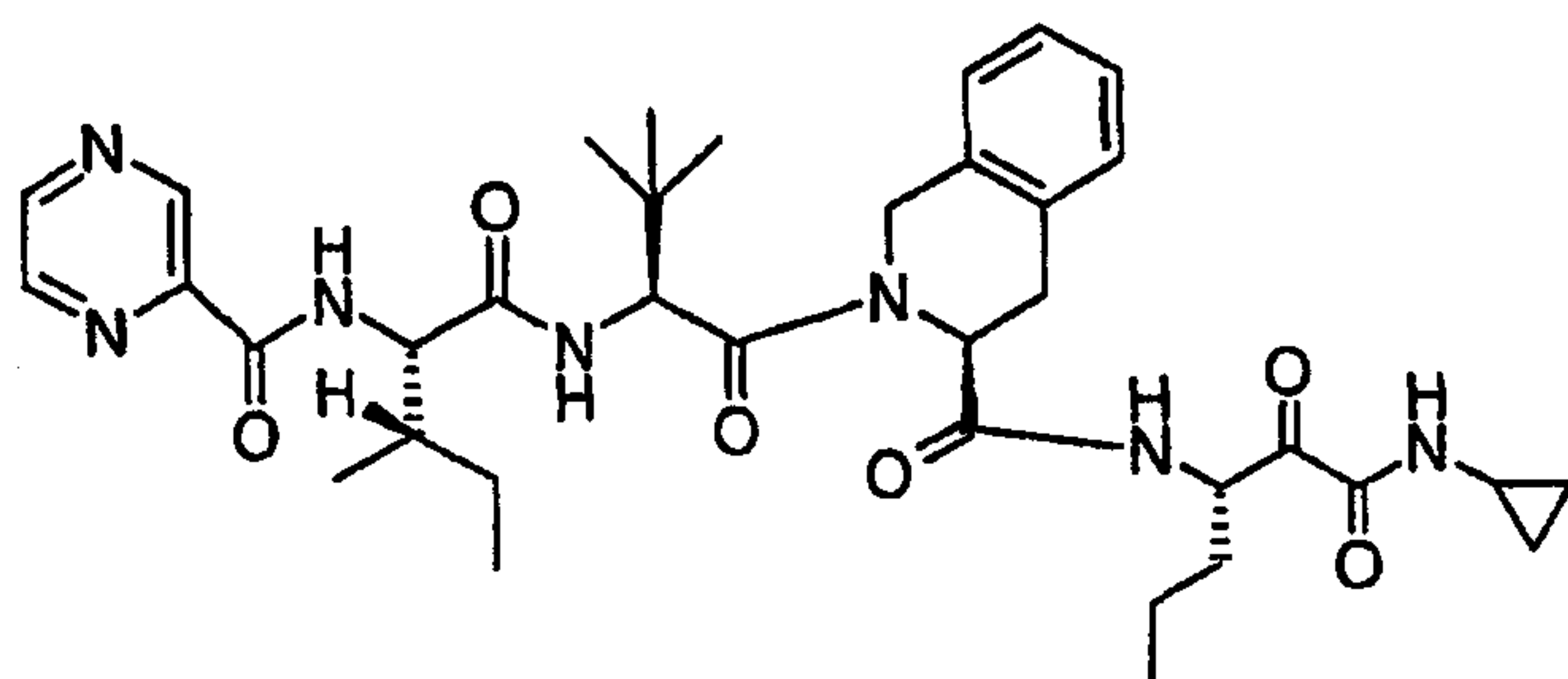
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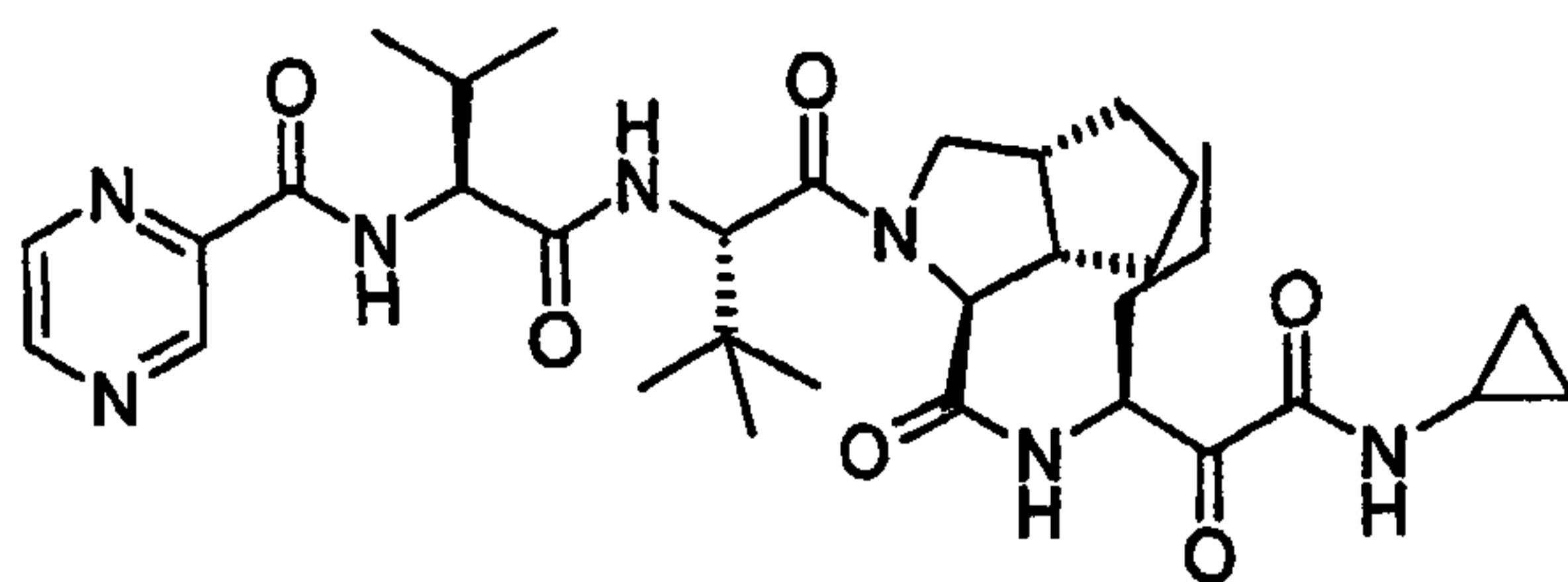
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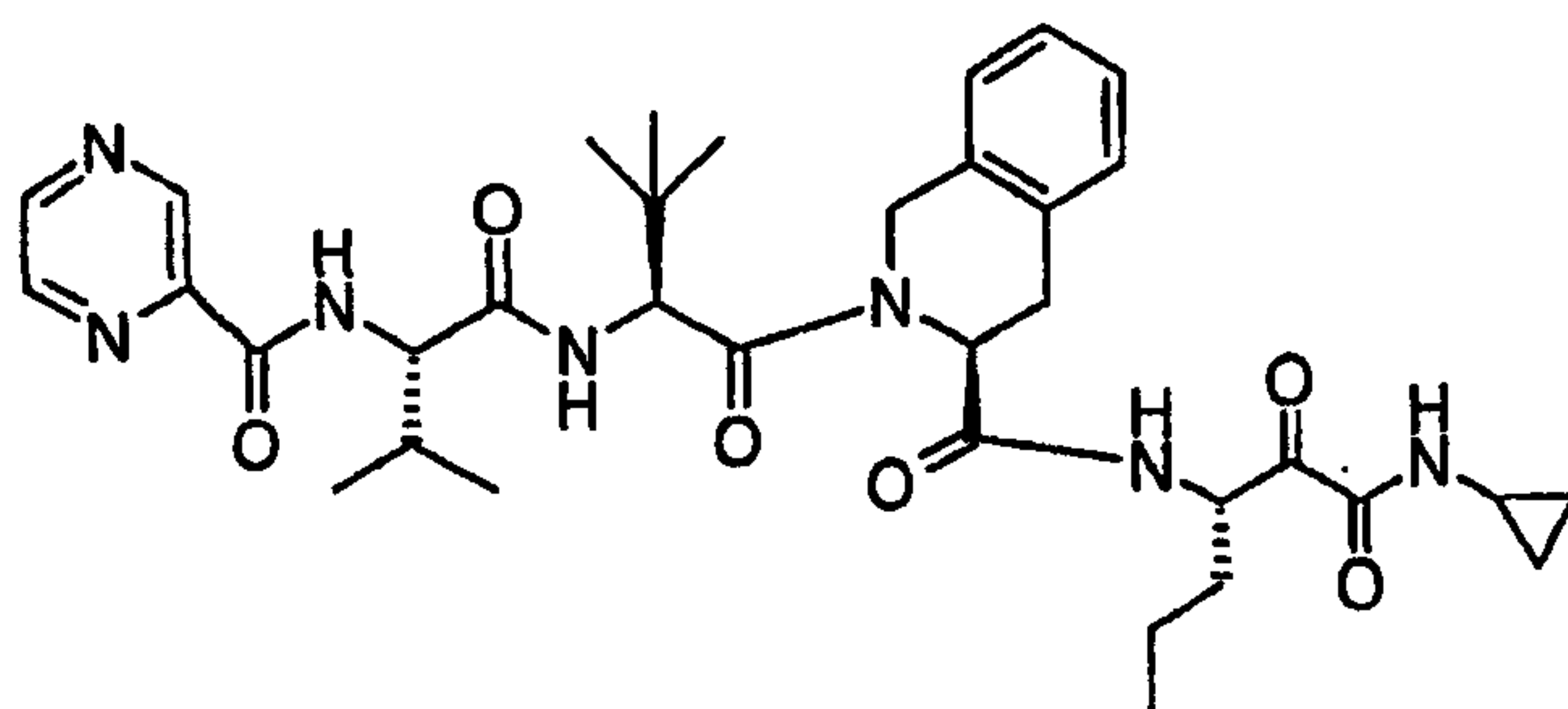
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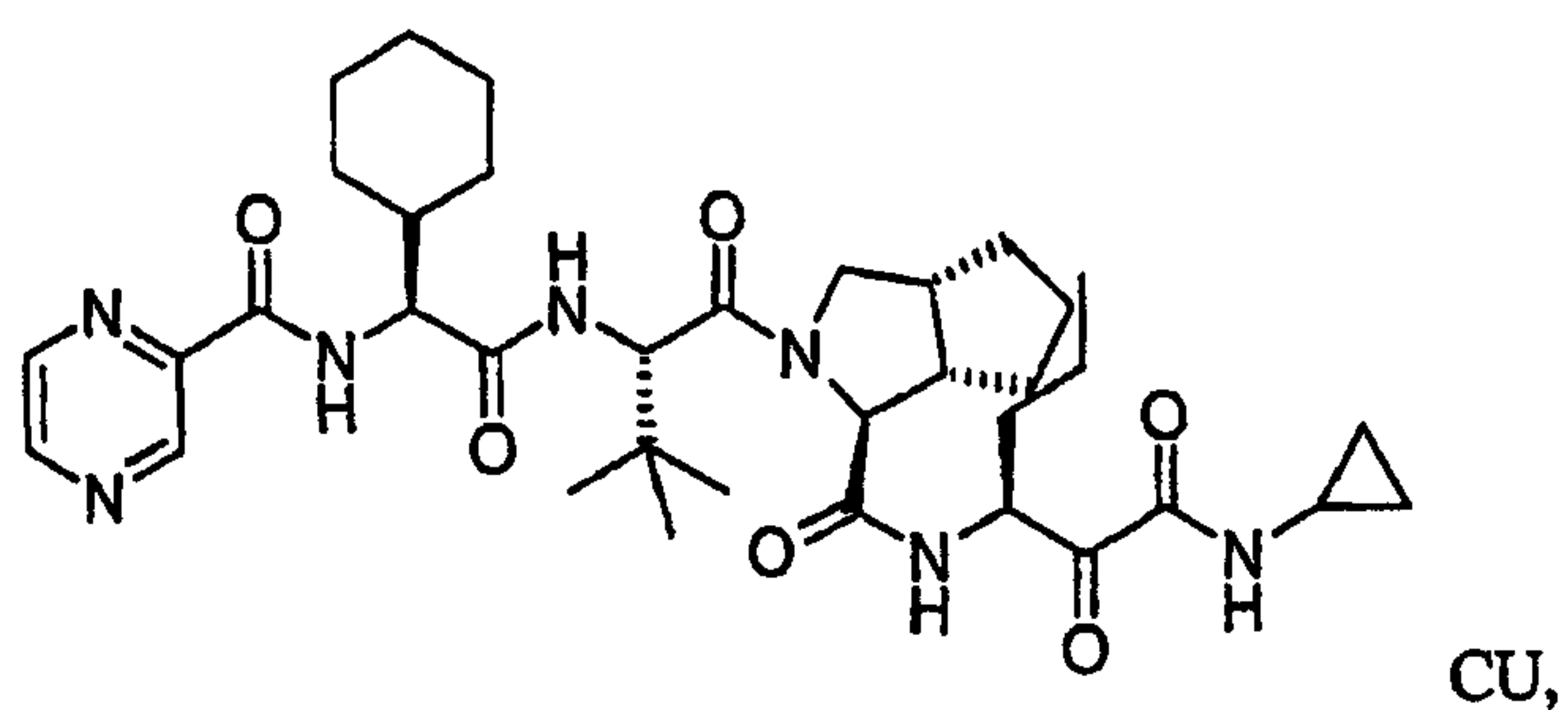


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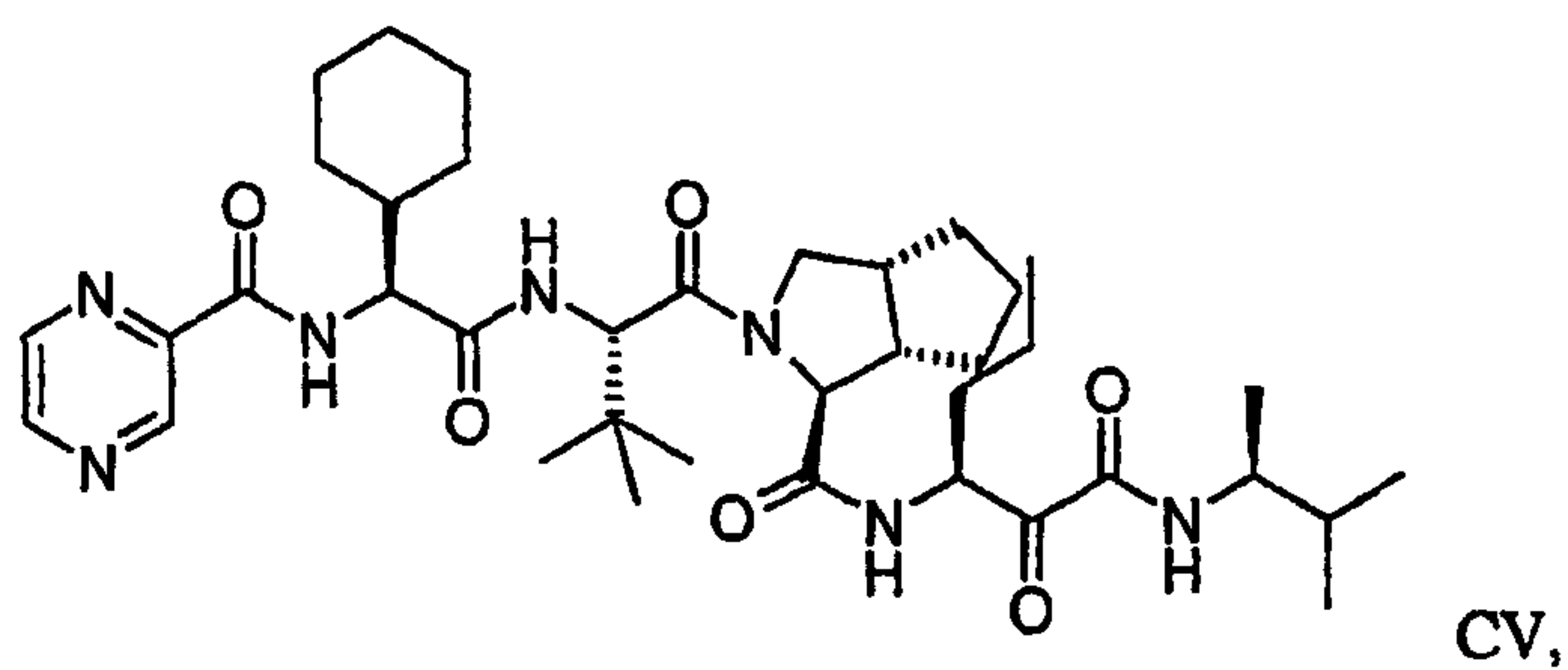


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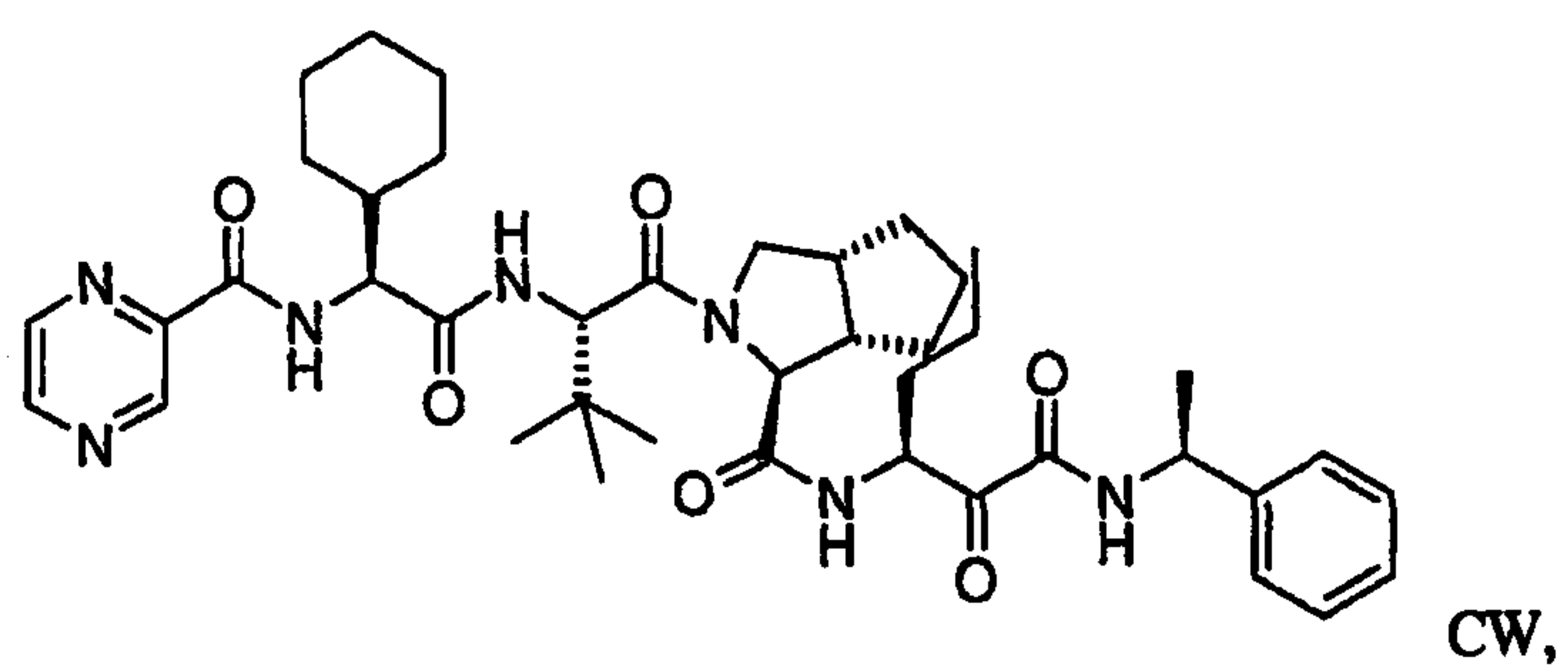
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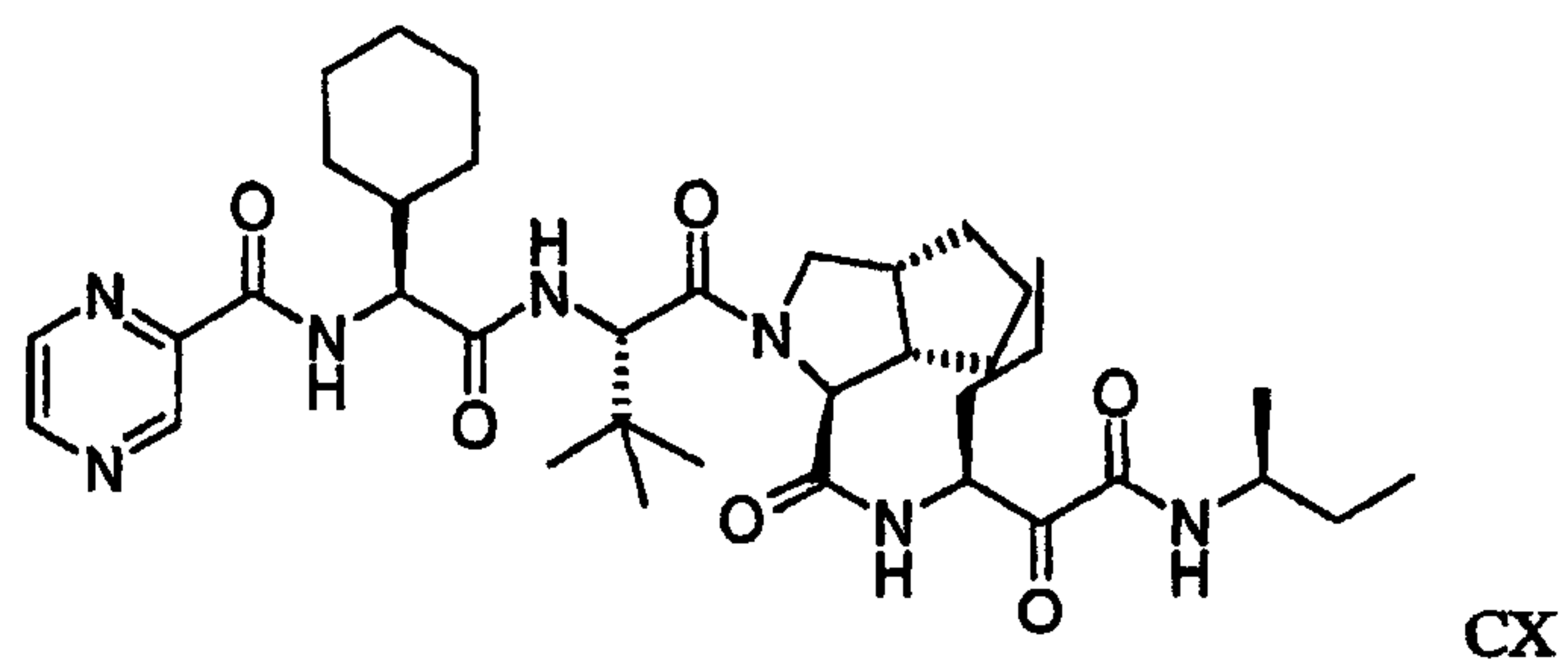
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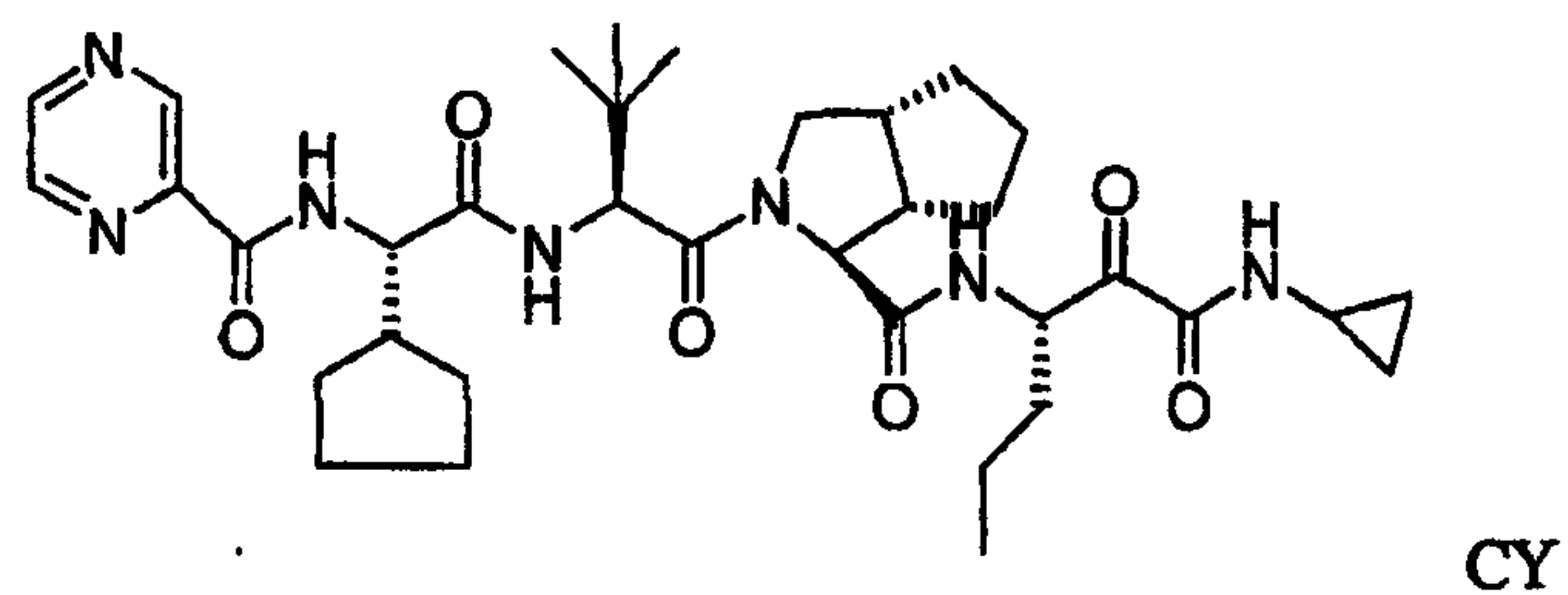
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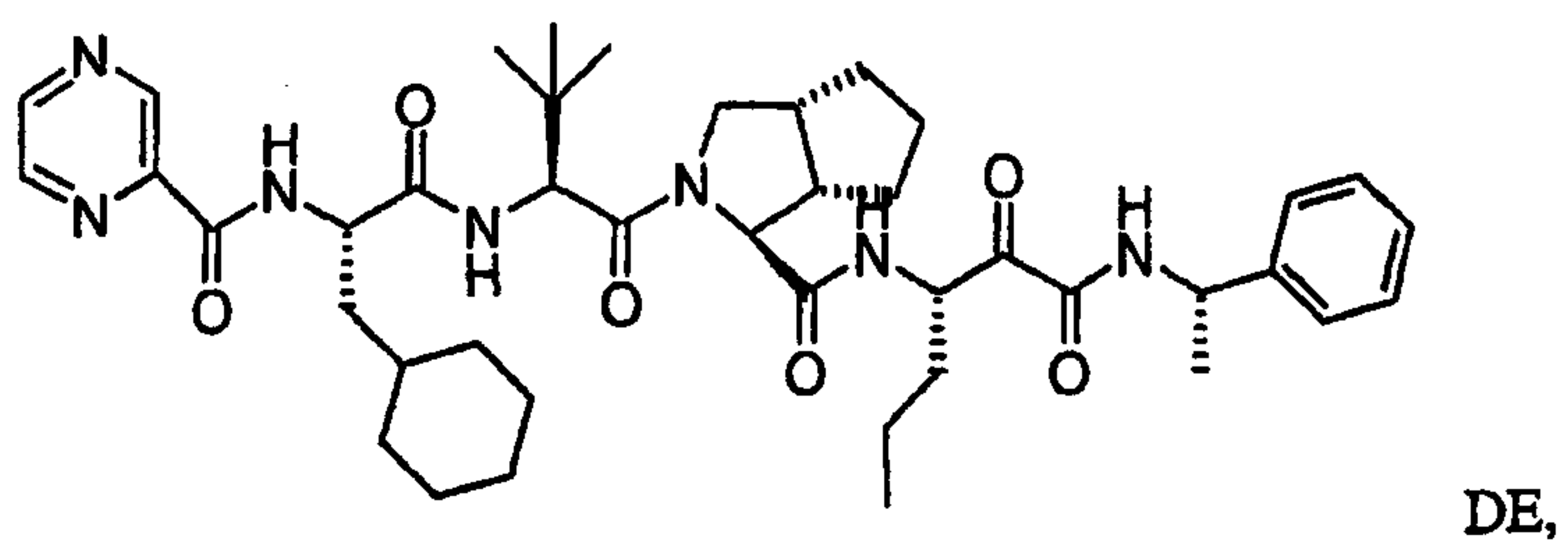
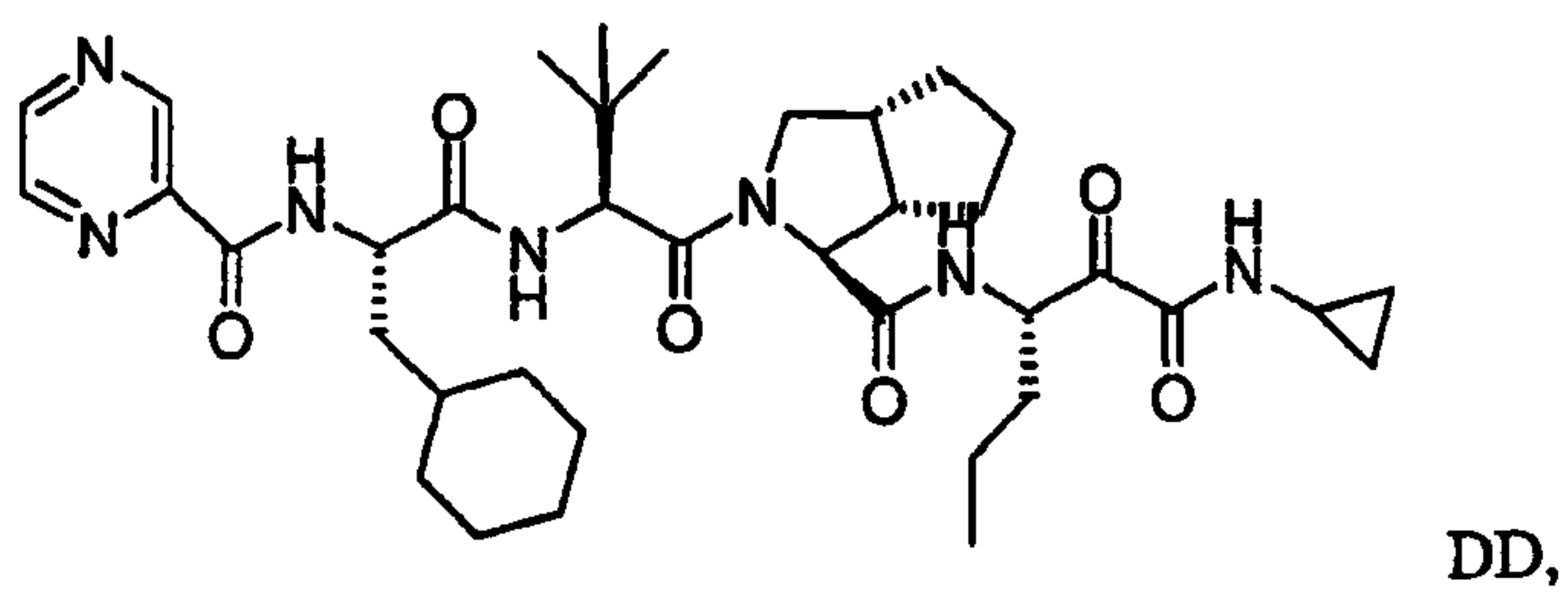
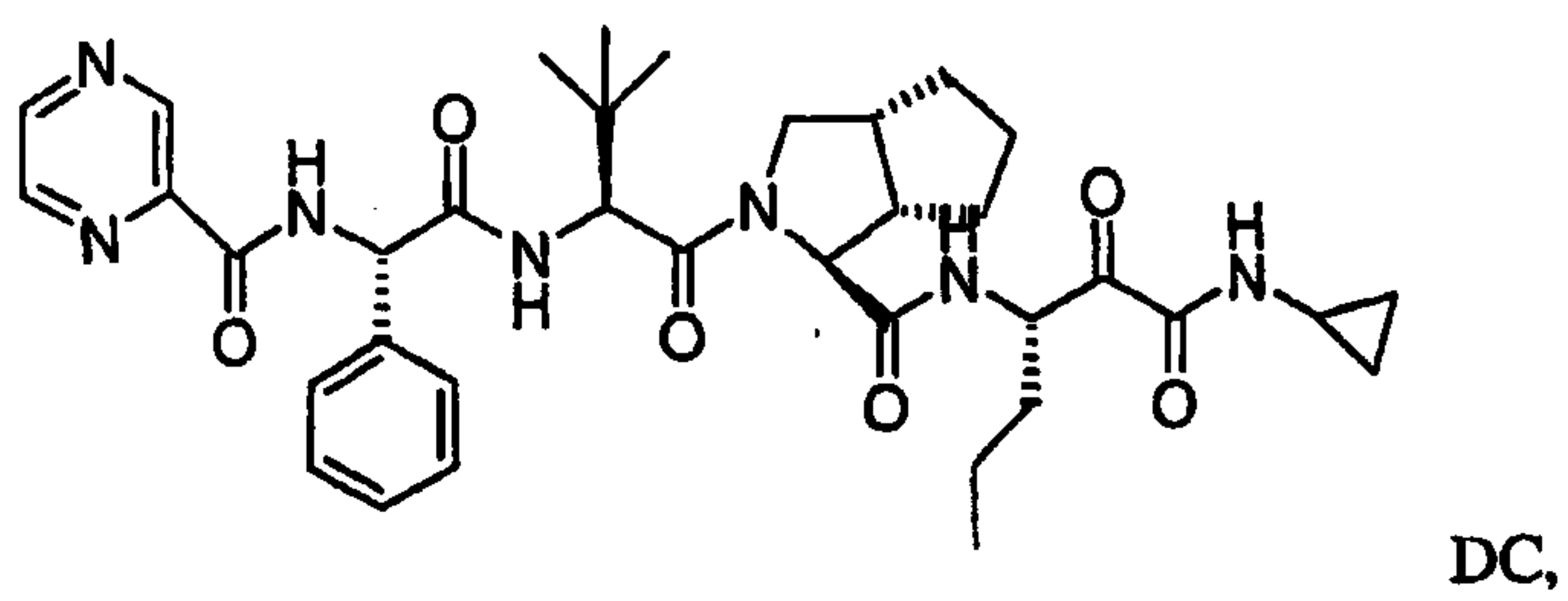
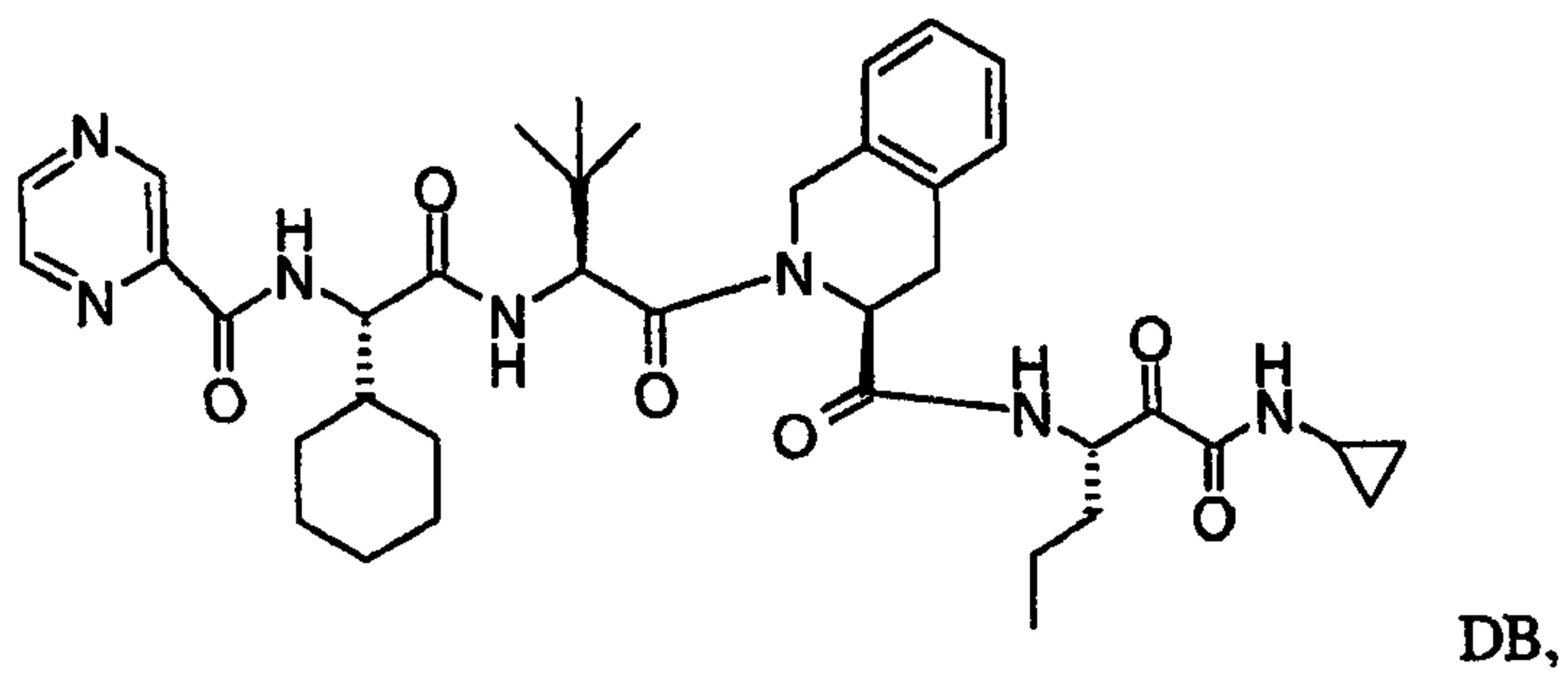
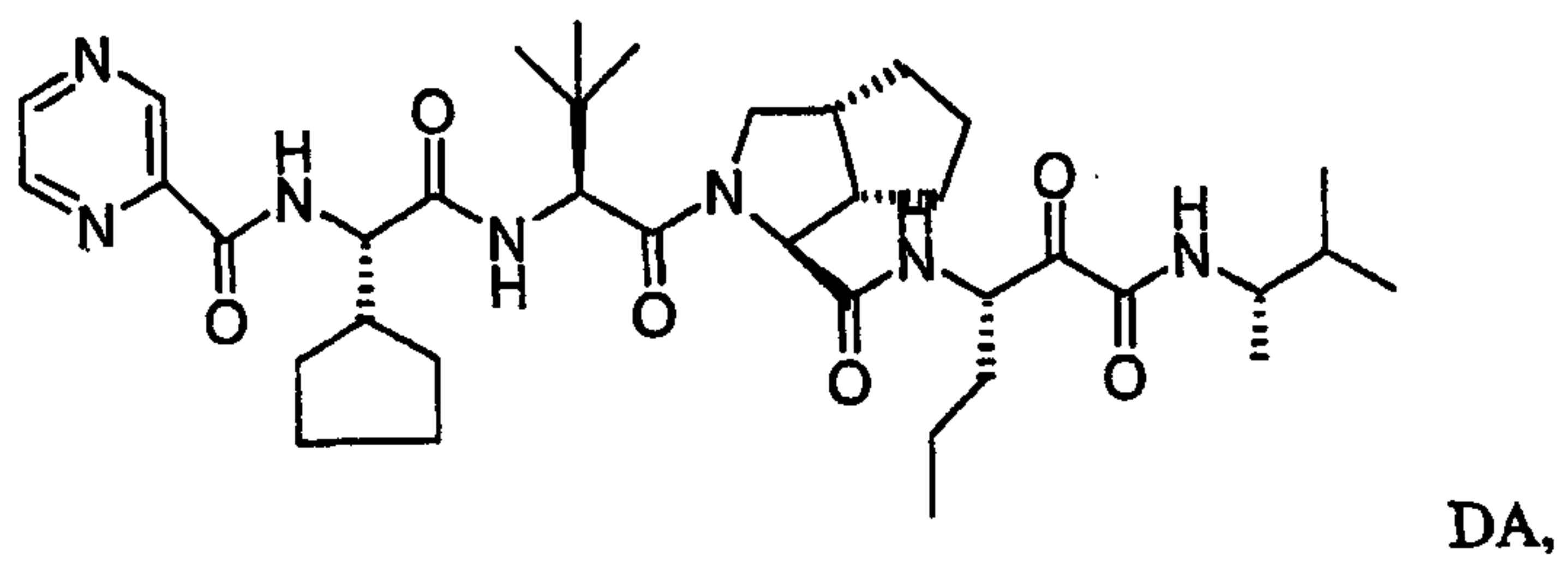
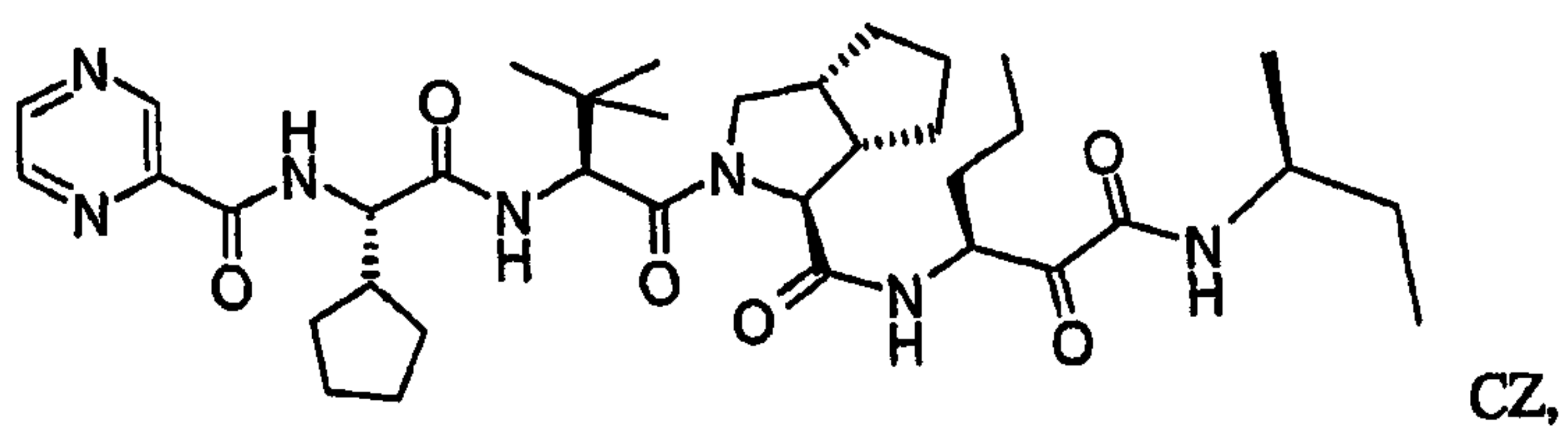


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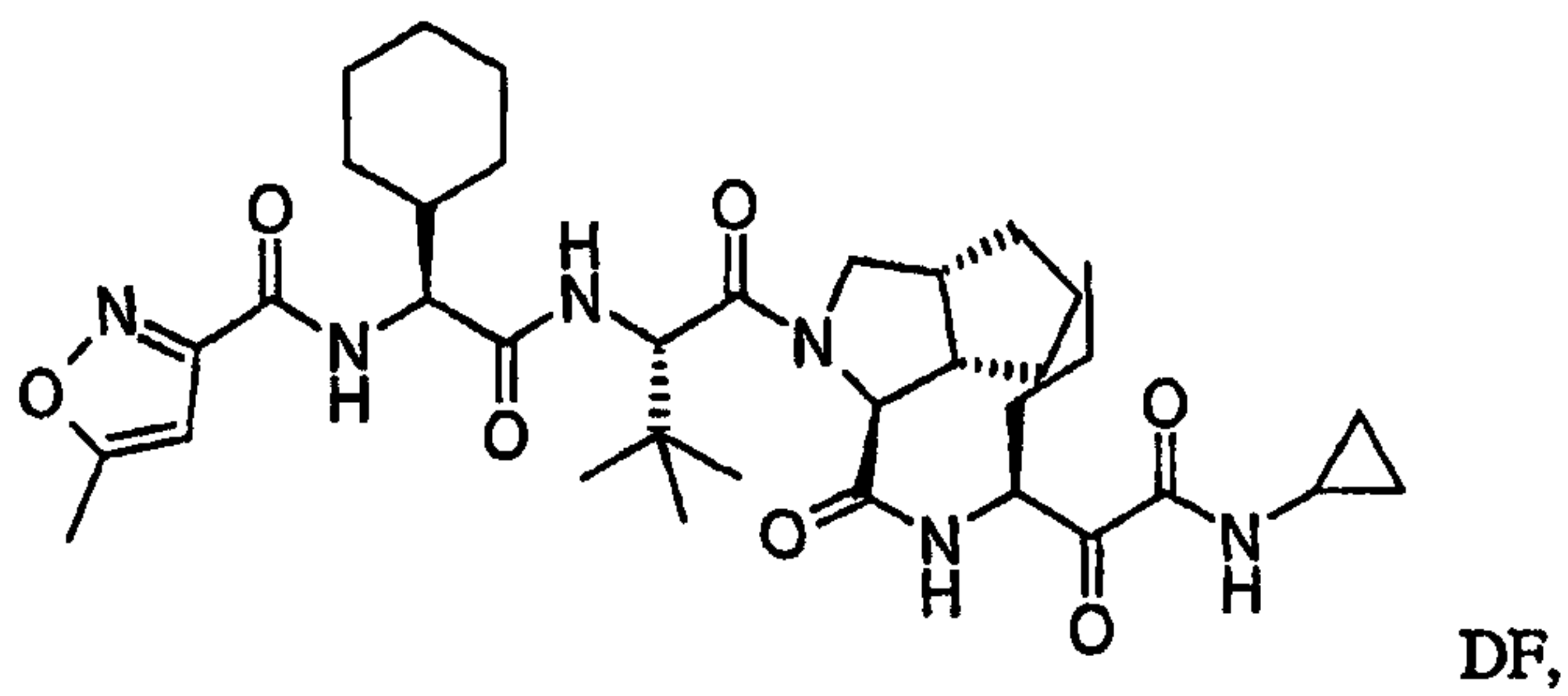
58



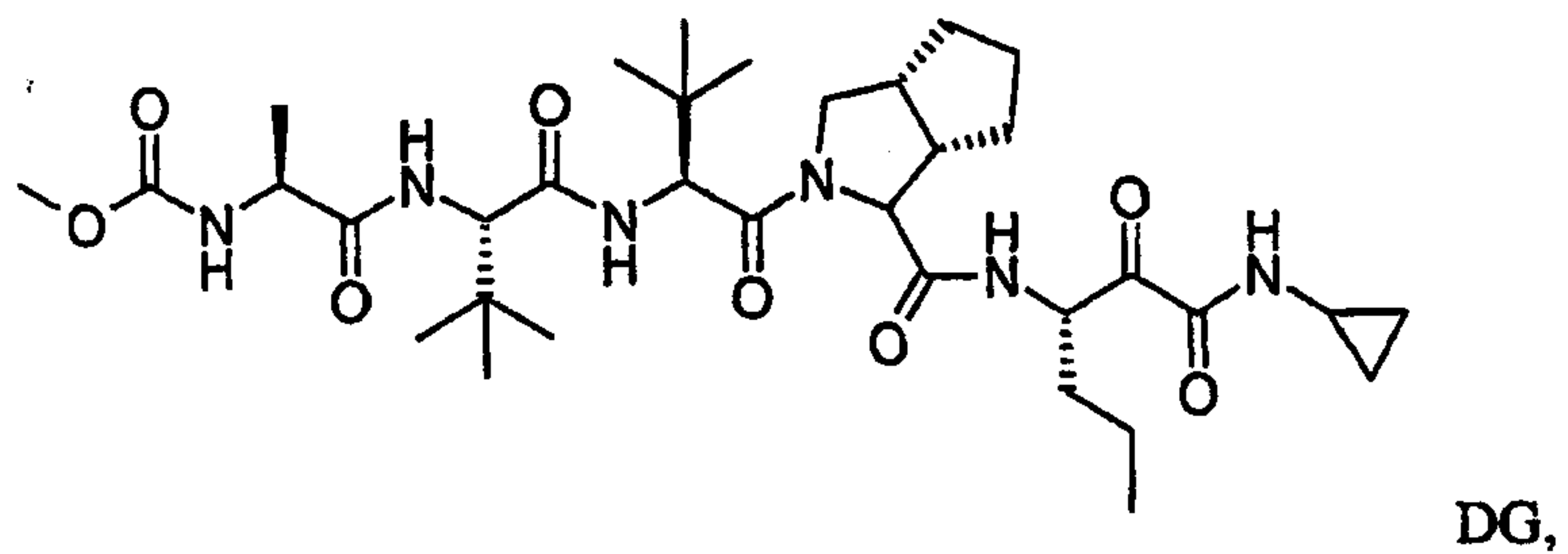
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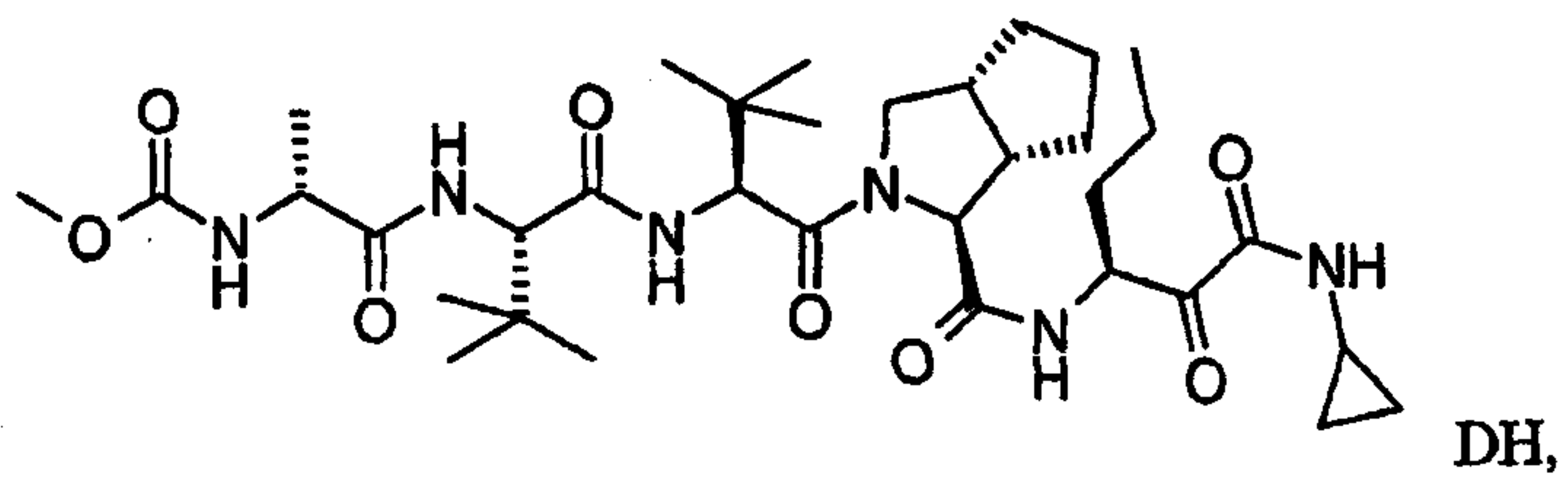
59



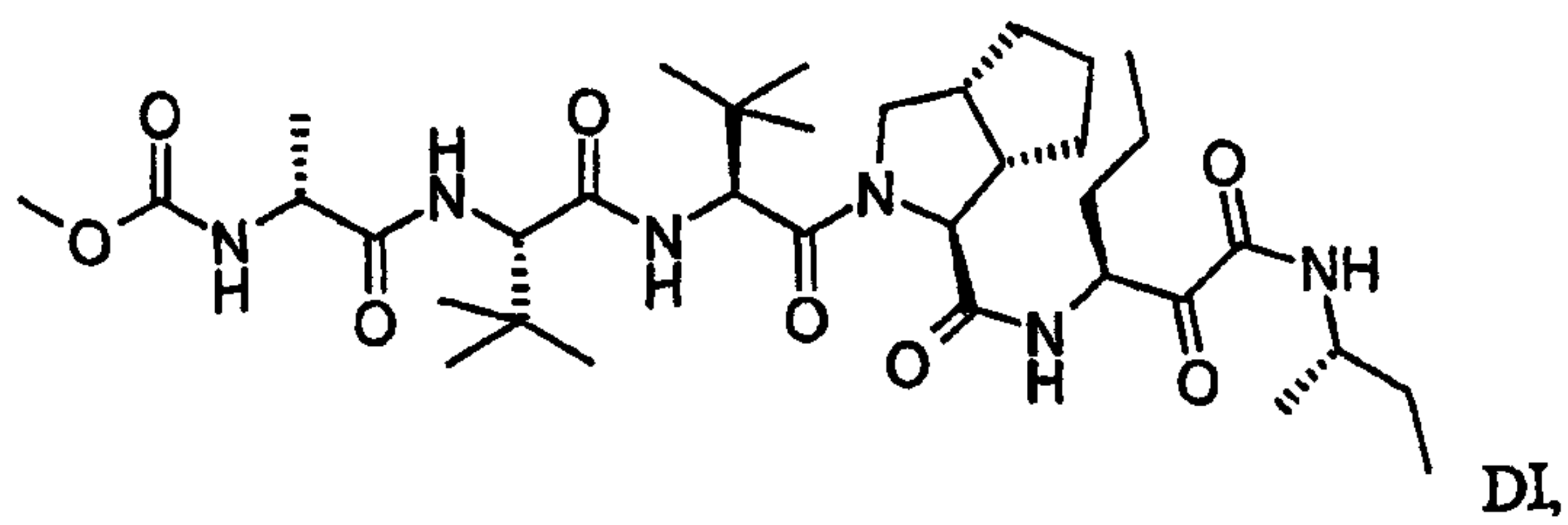
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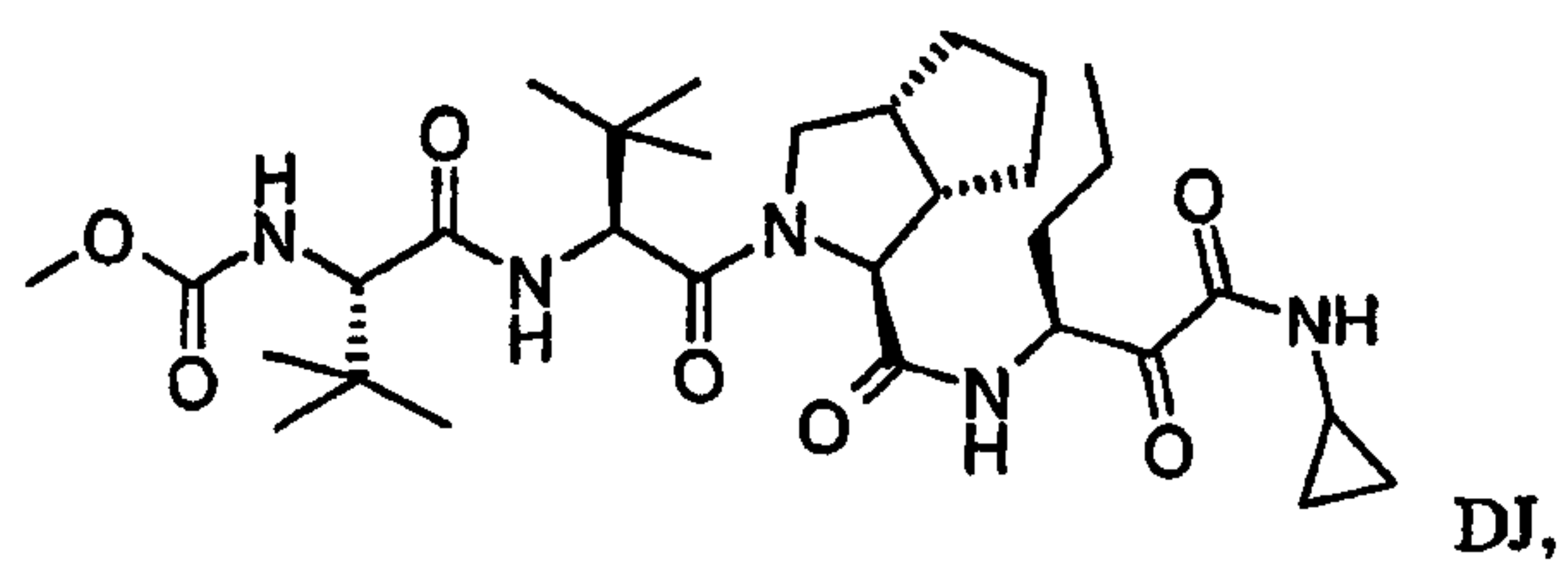
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DH,

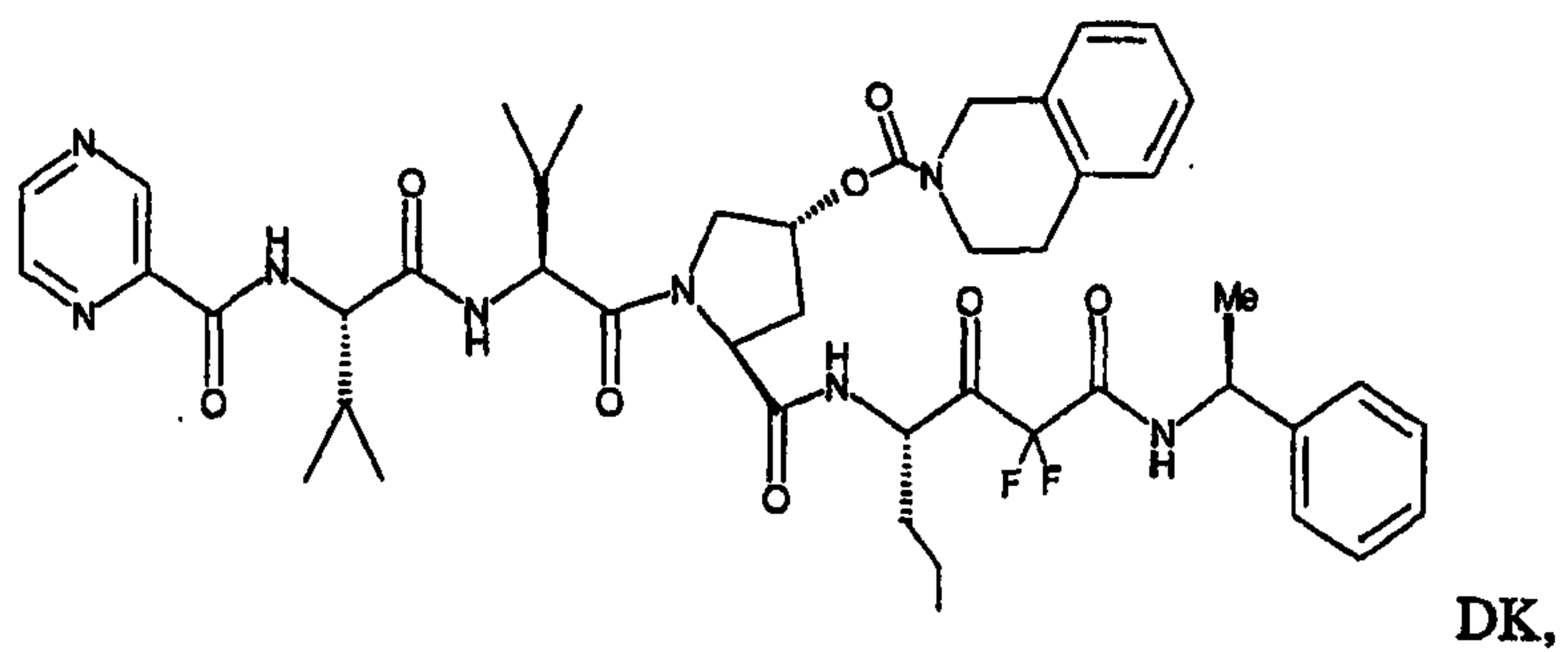


DL,



DJ,

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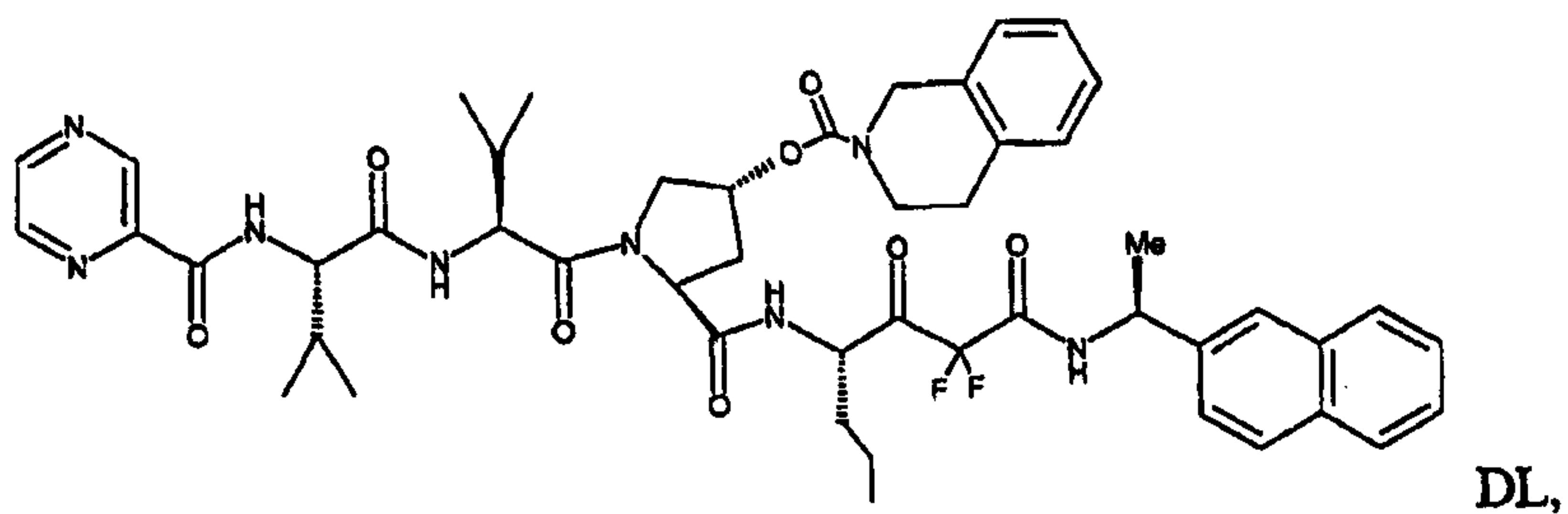


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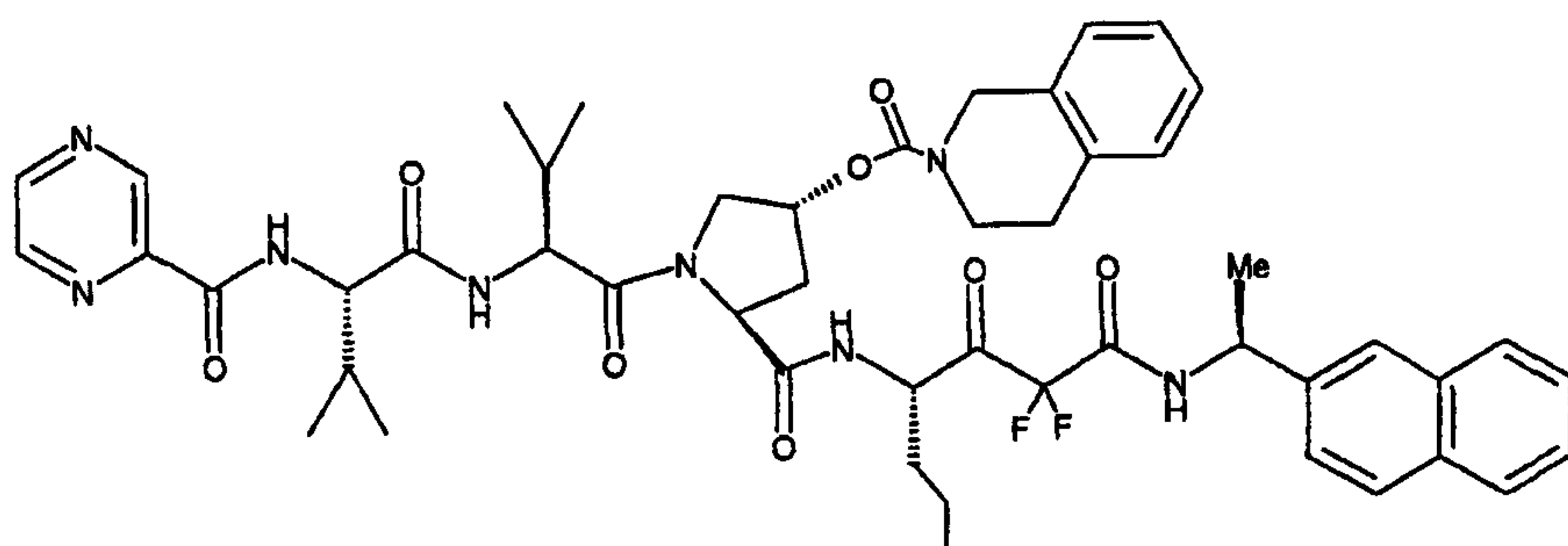
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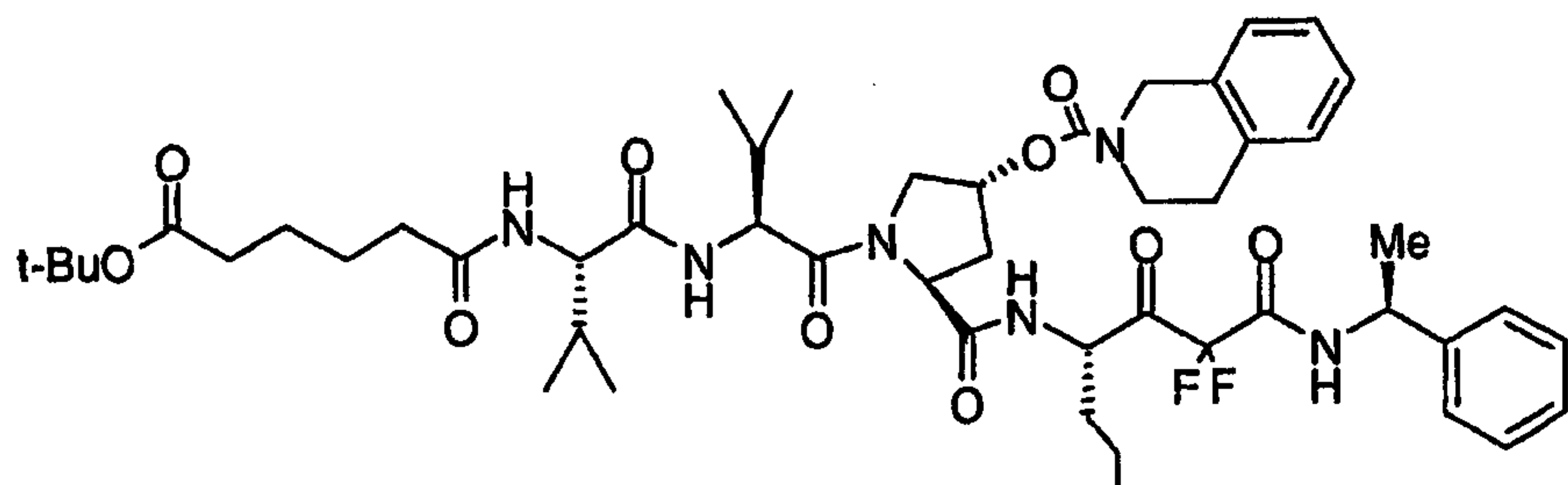
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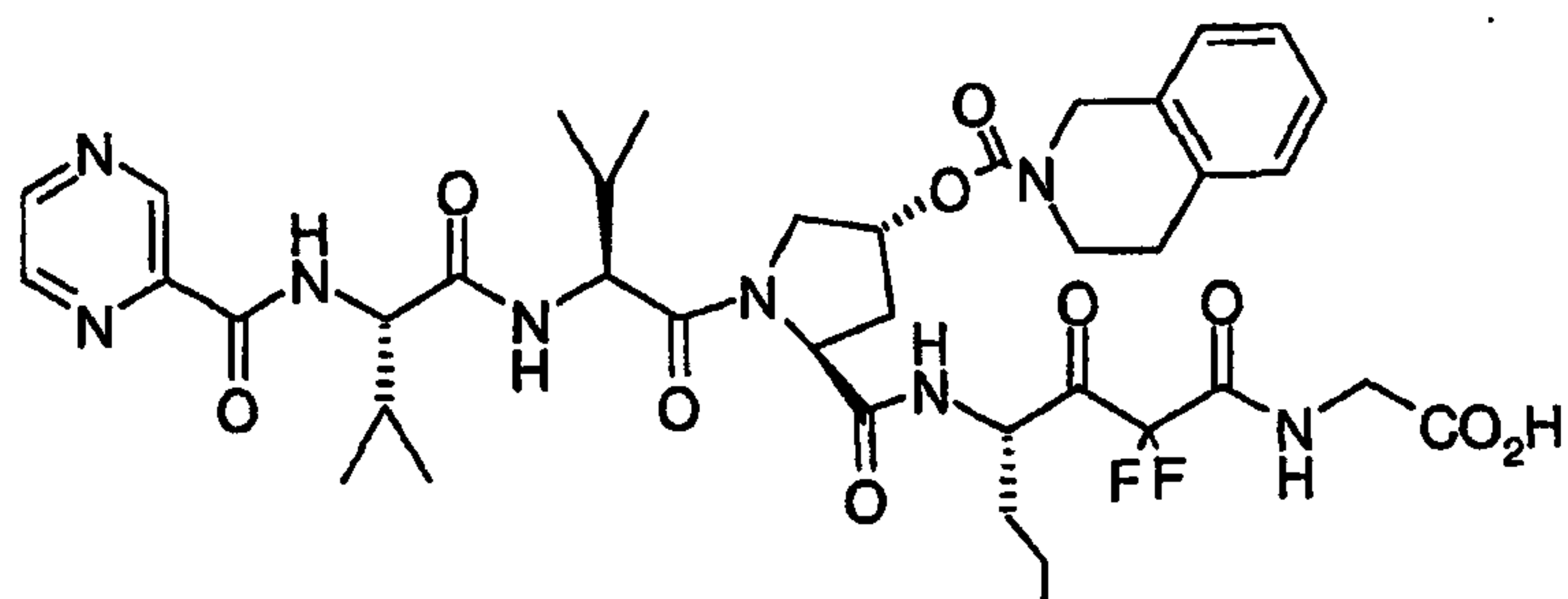
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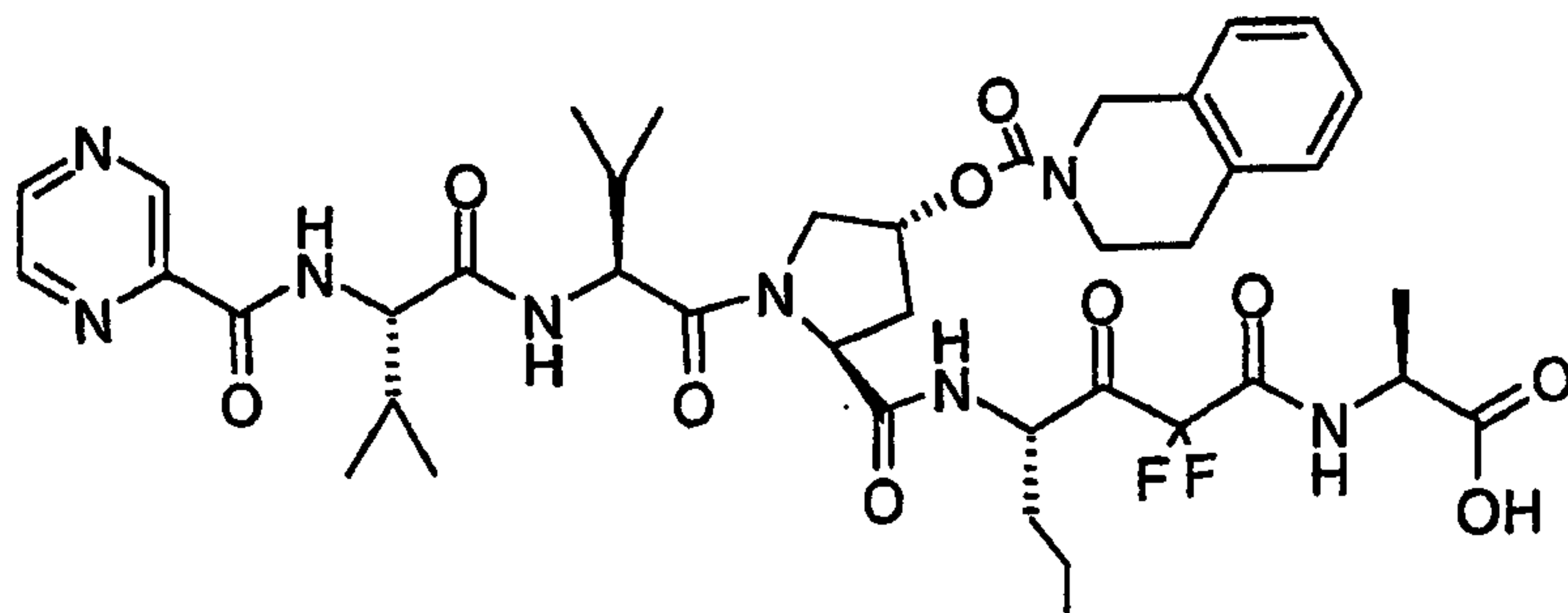
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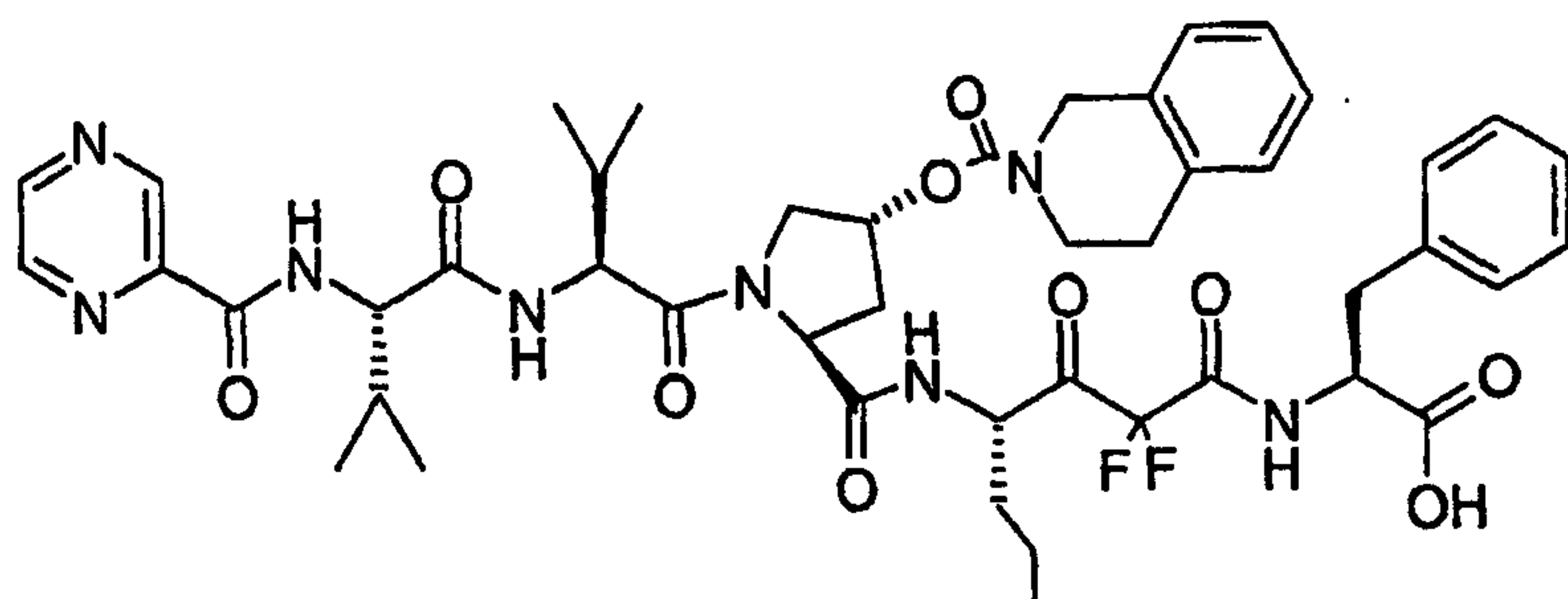


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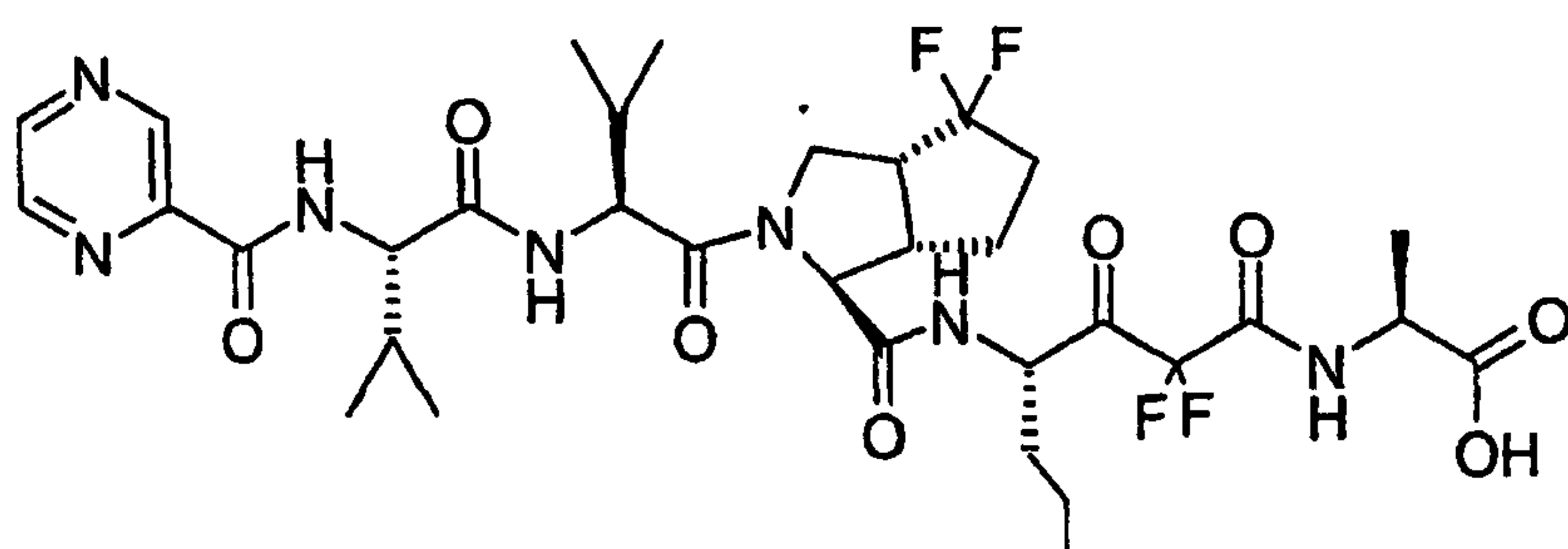
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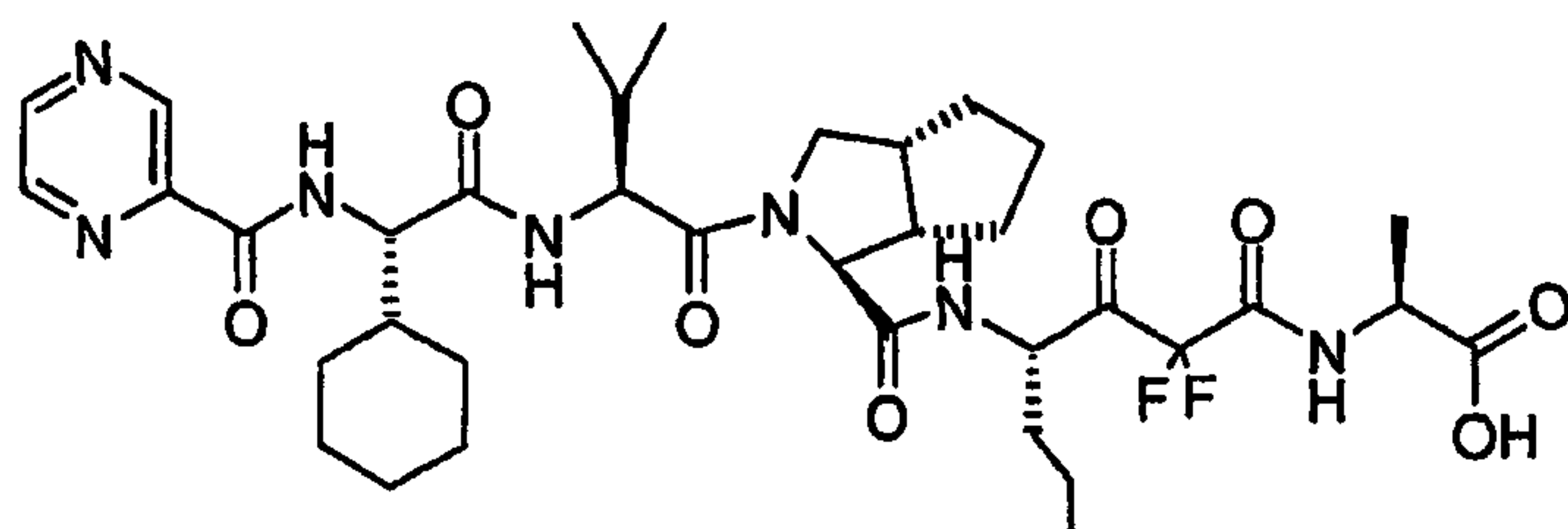
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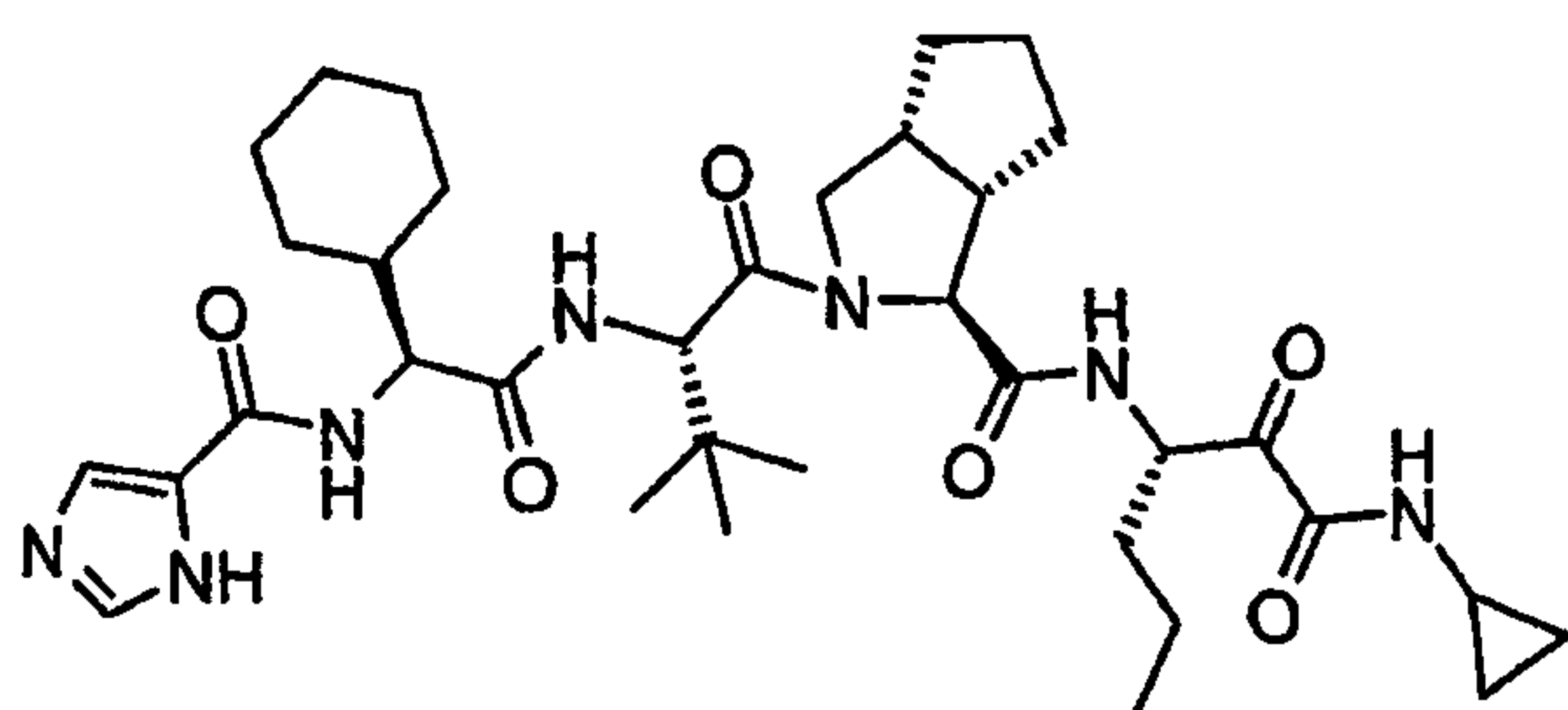
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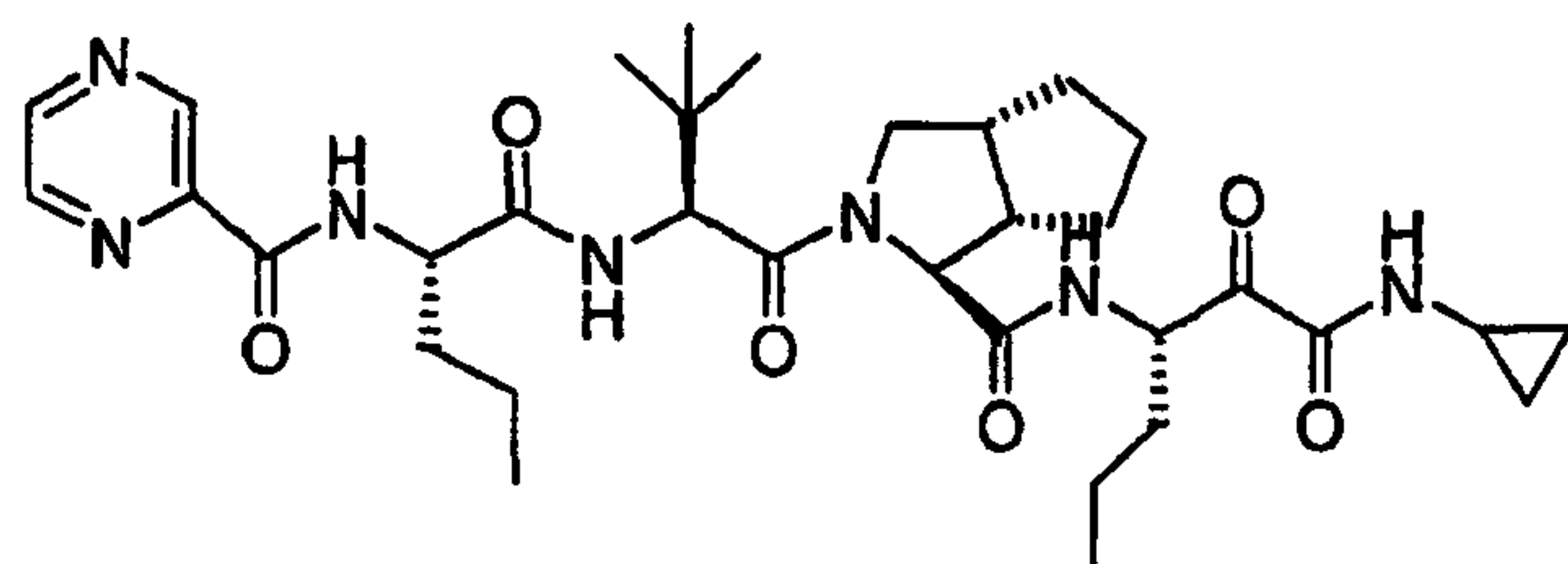
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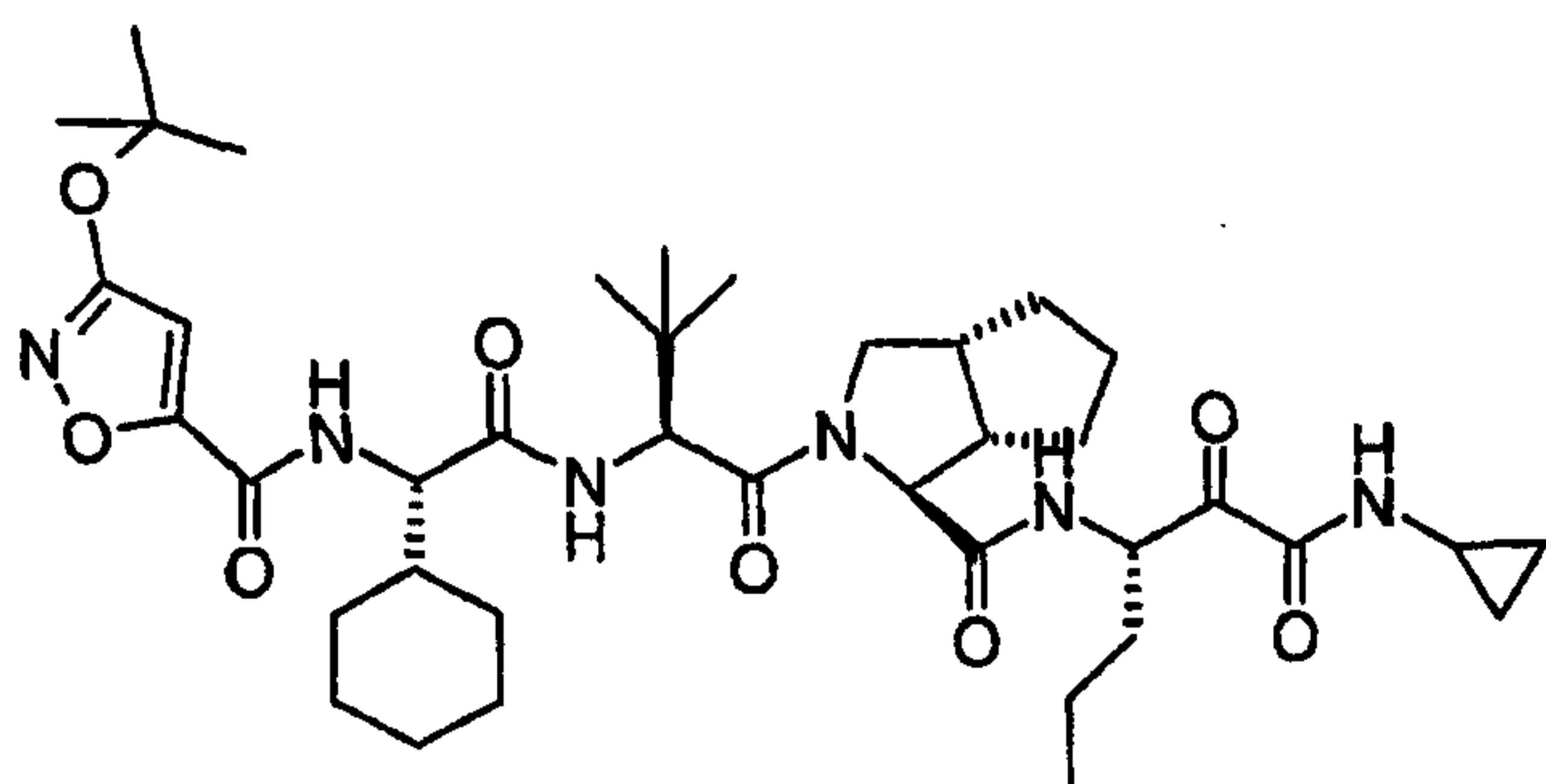


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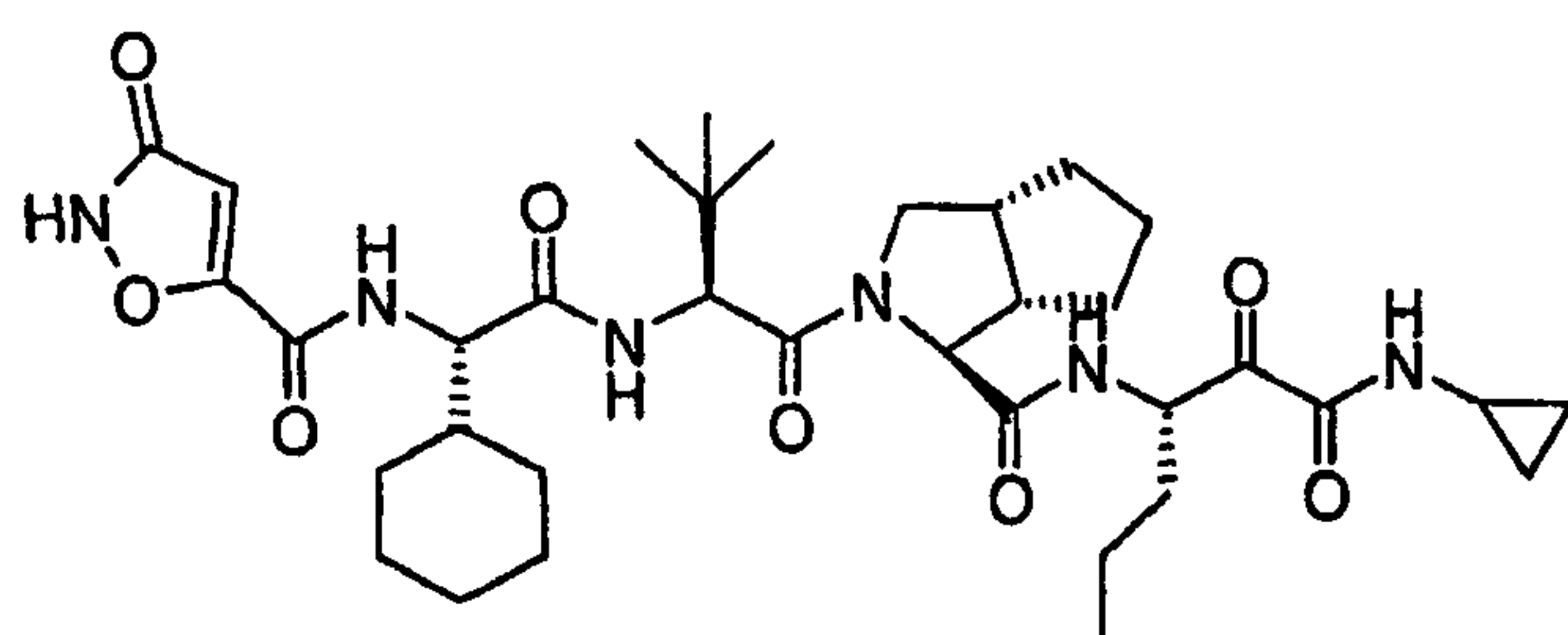
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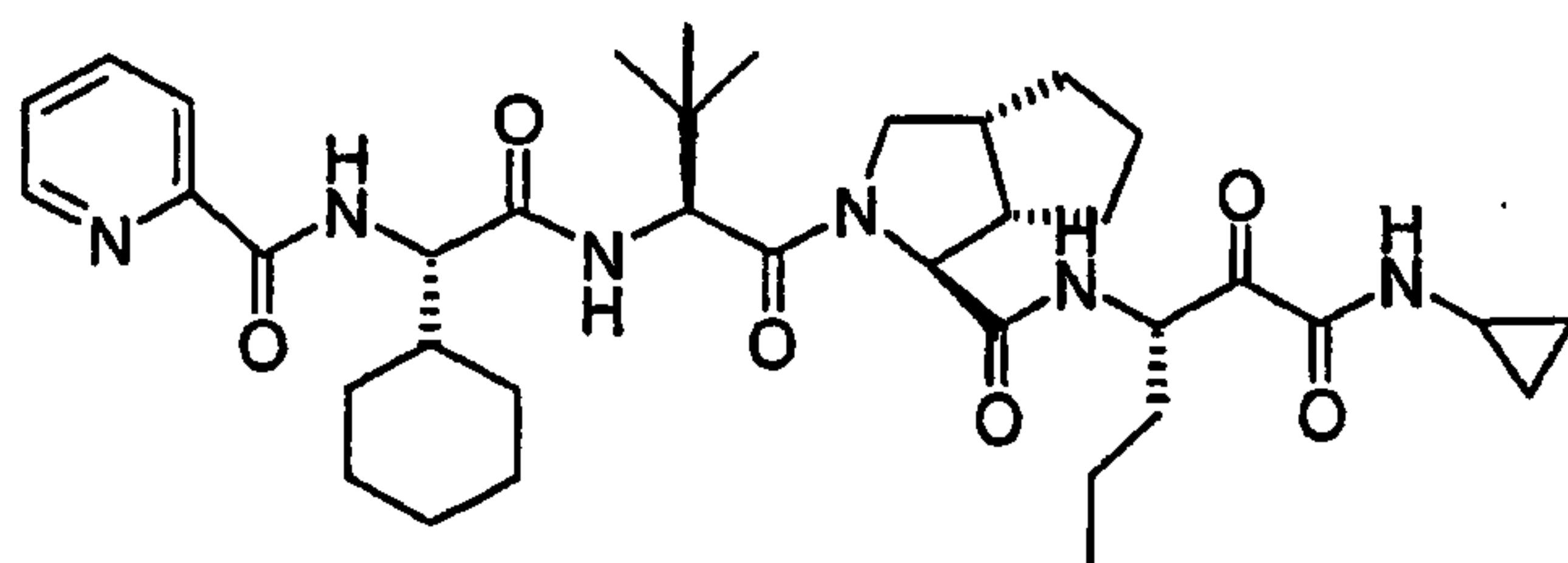
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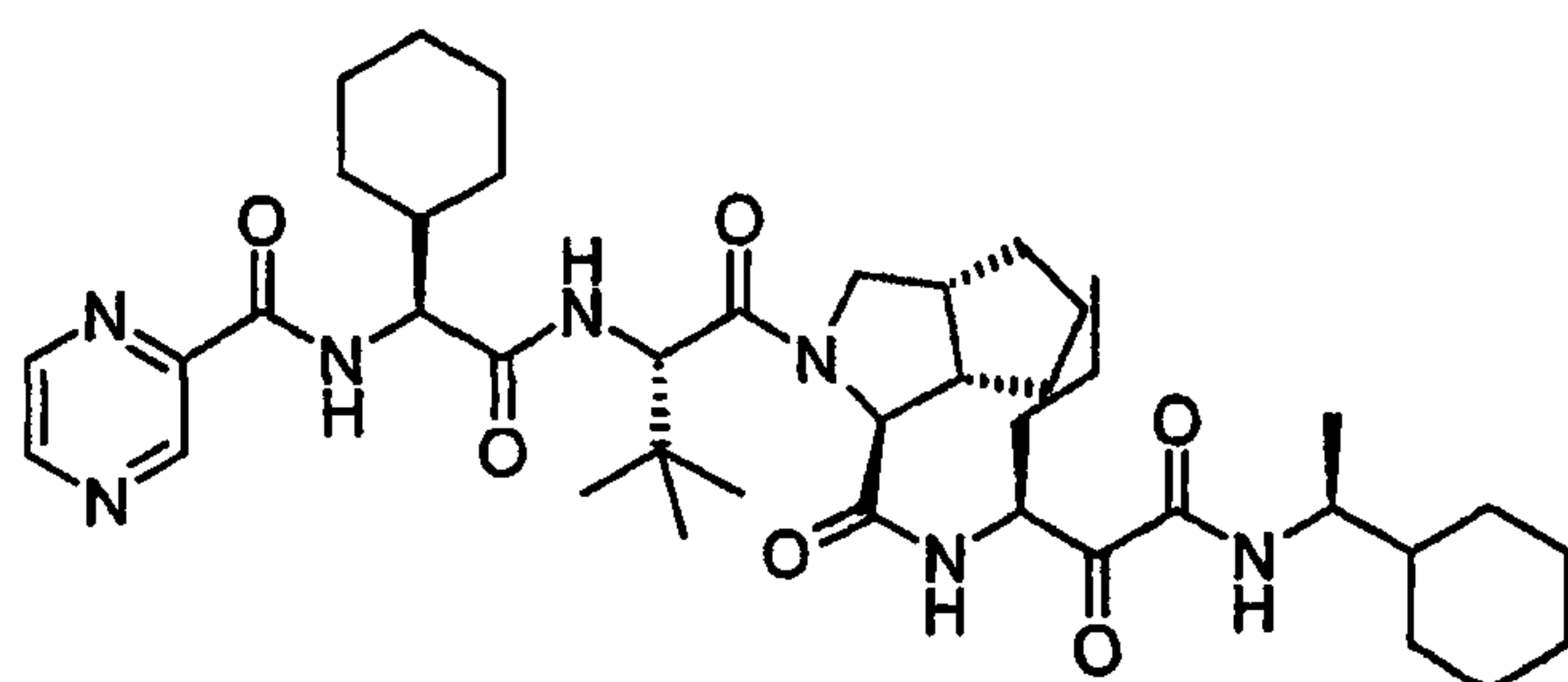
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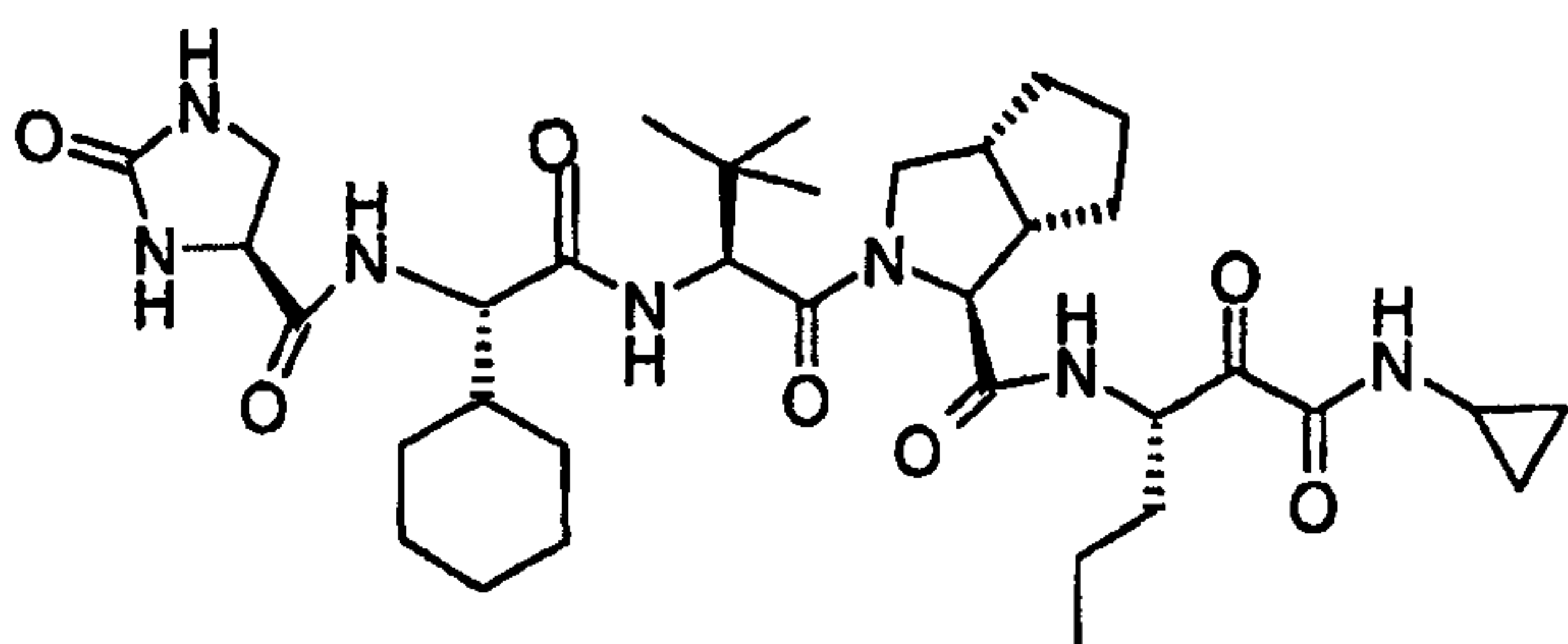
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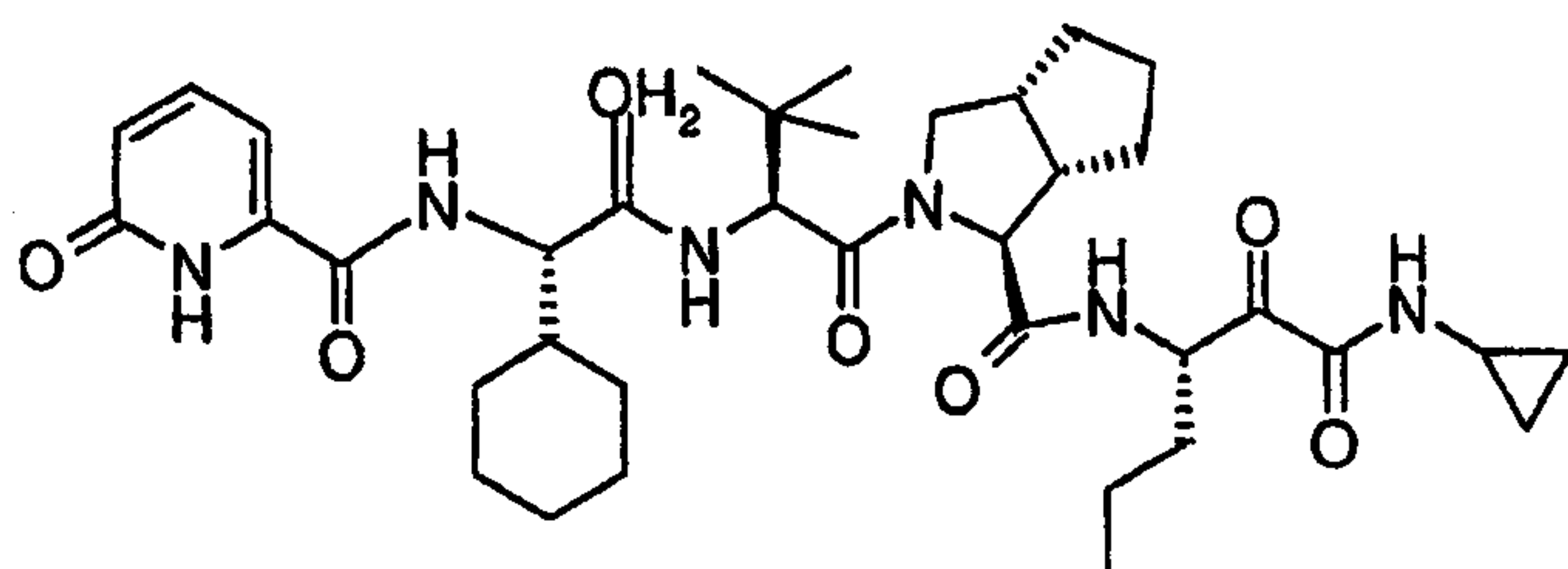


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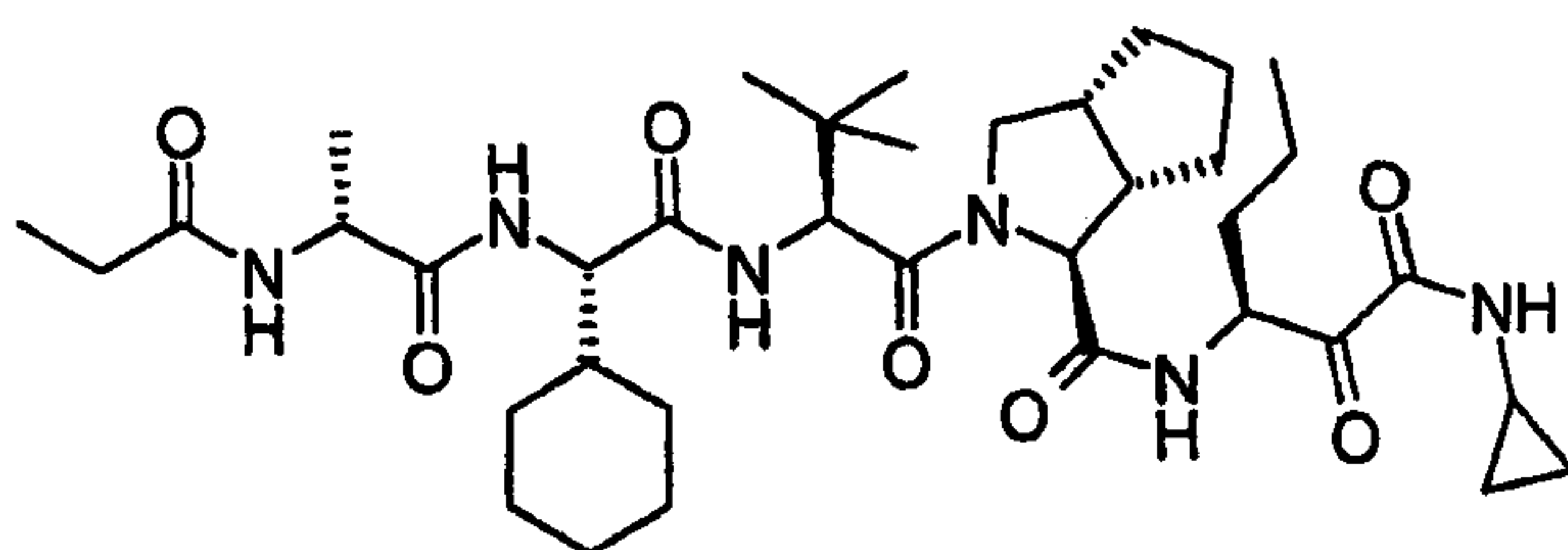
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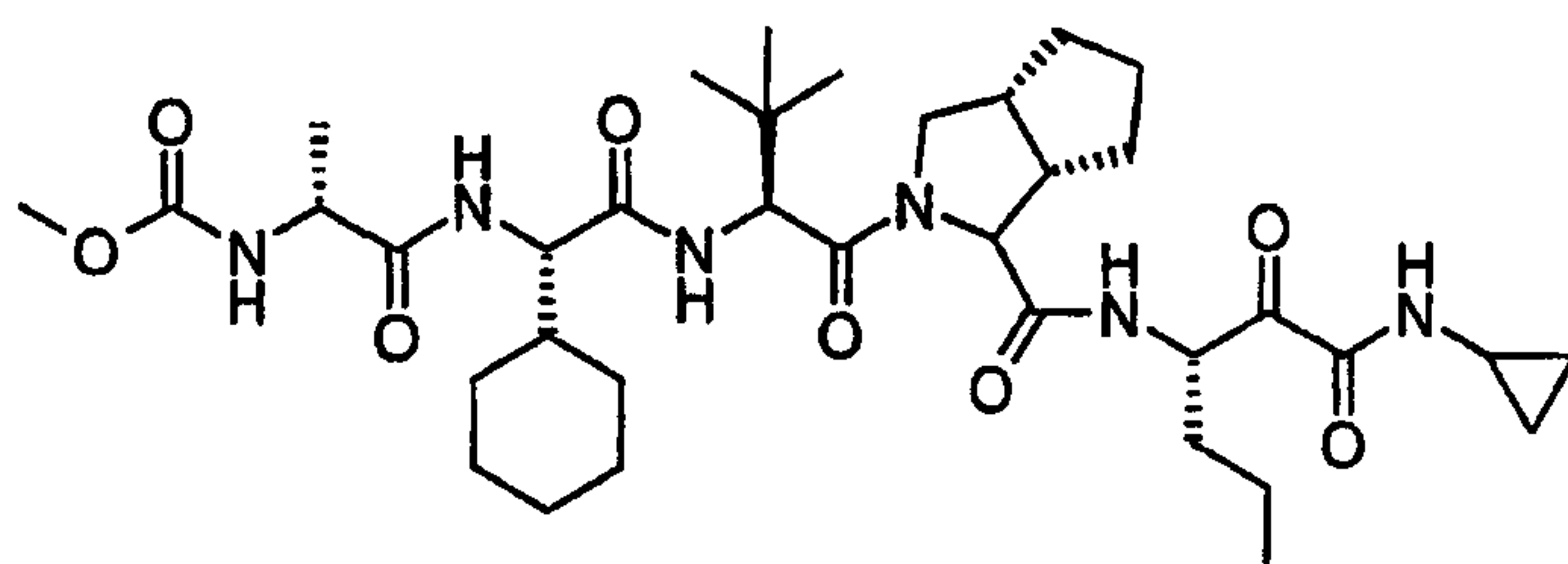
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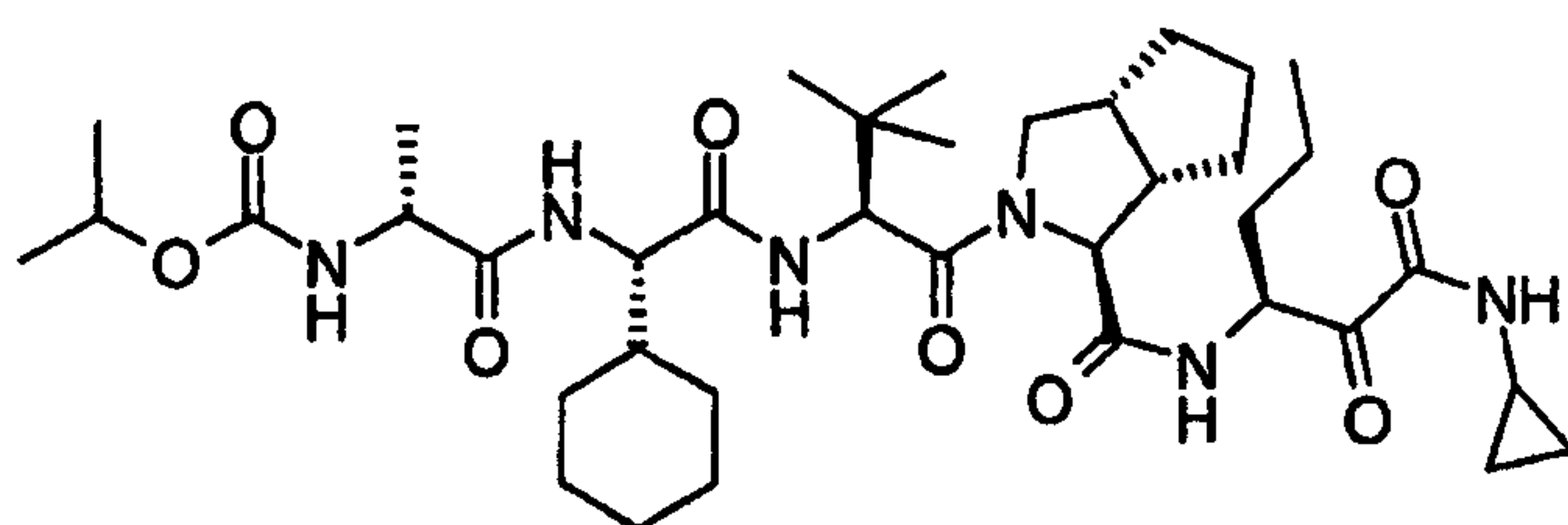
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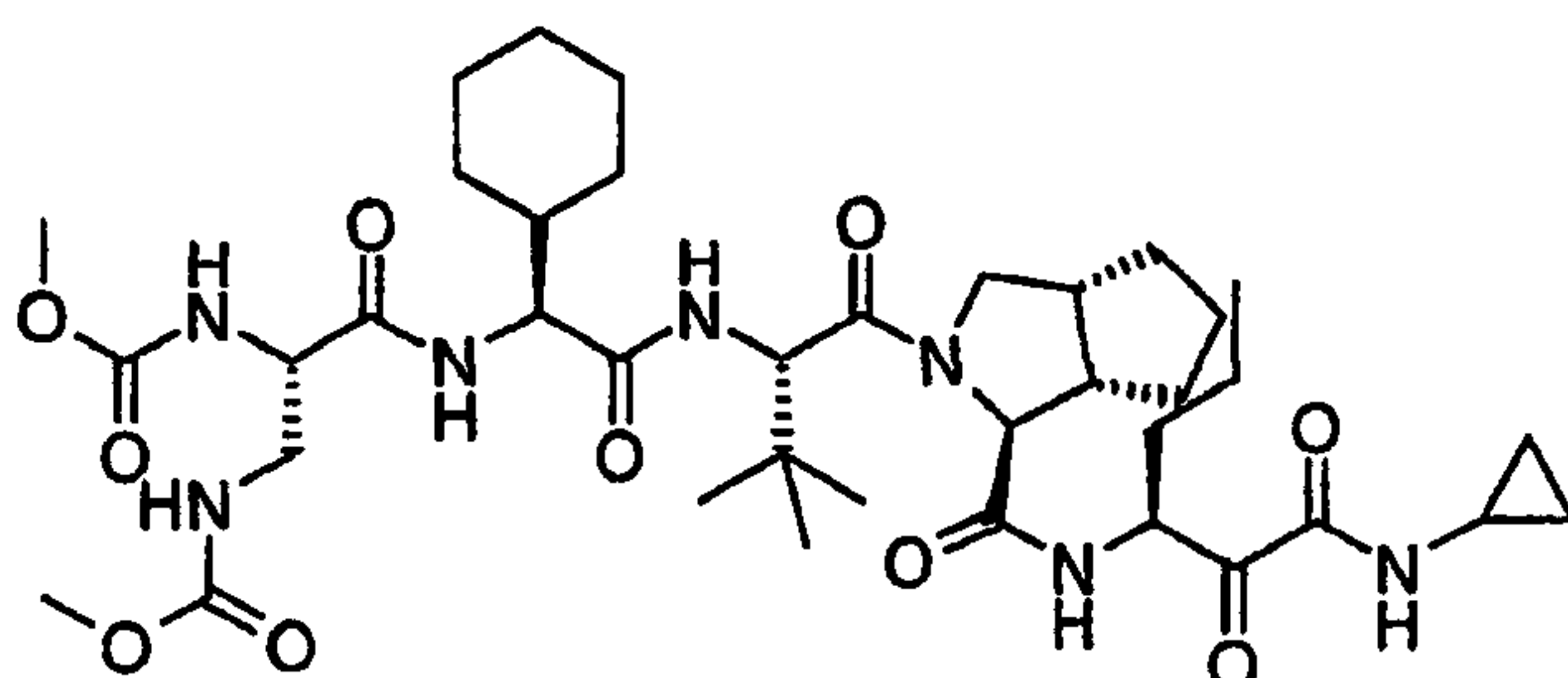
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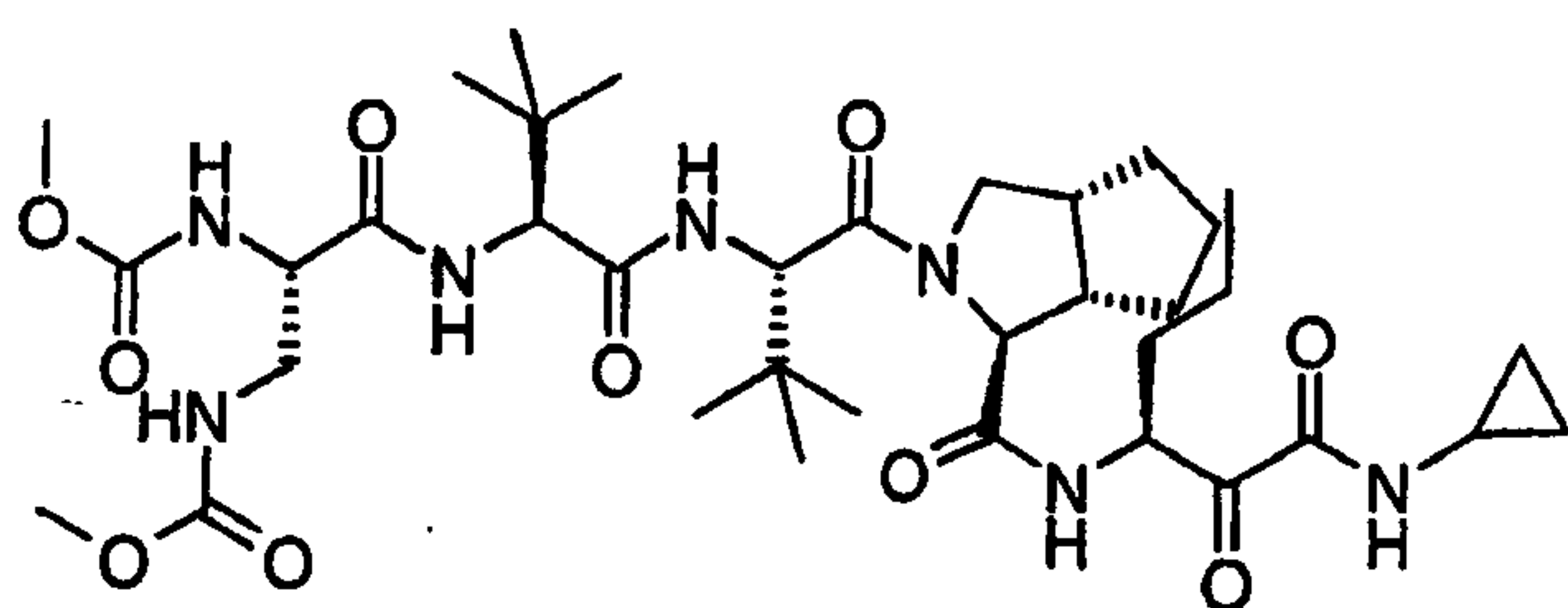
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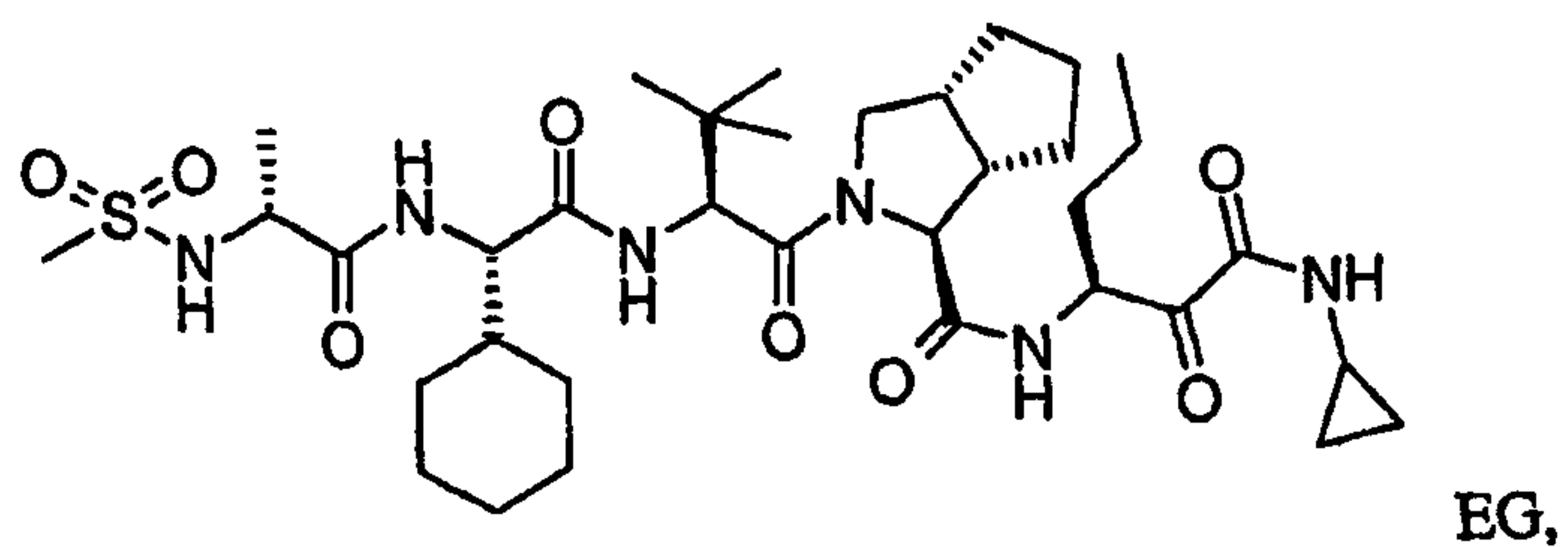


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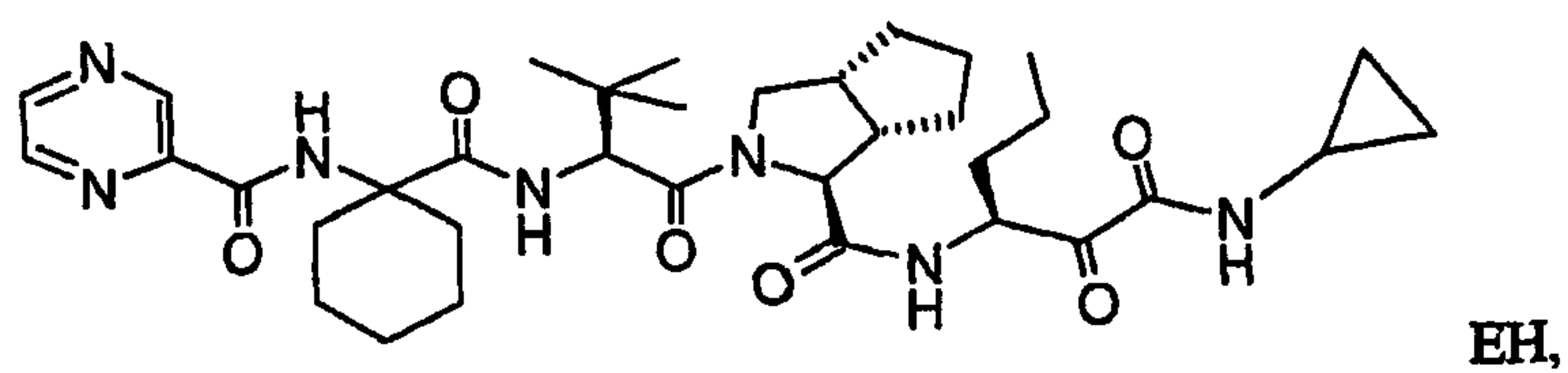
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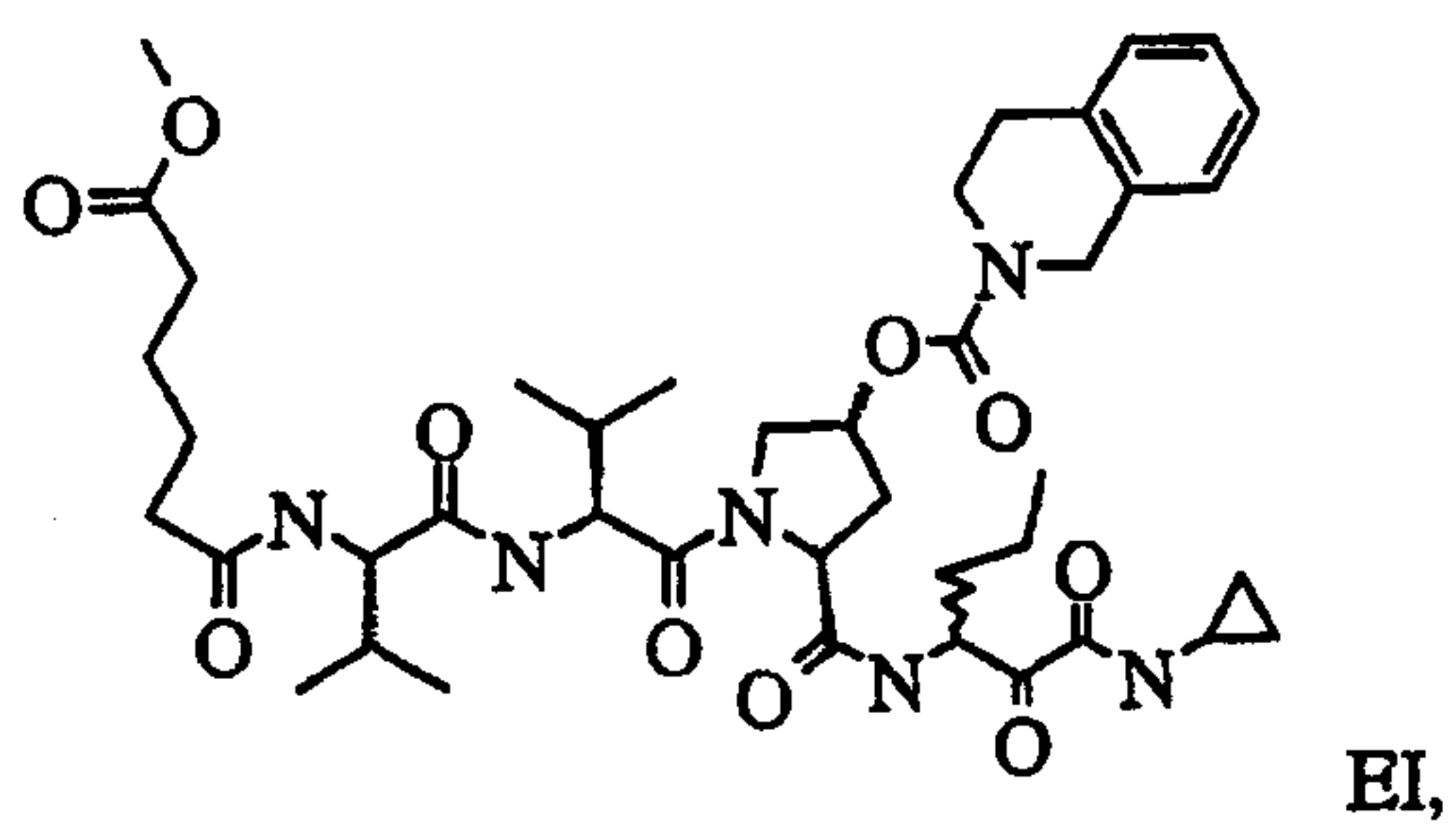


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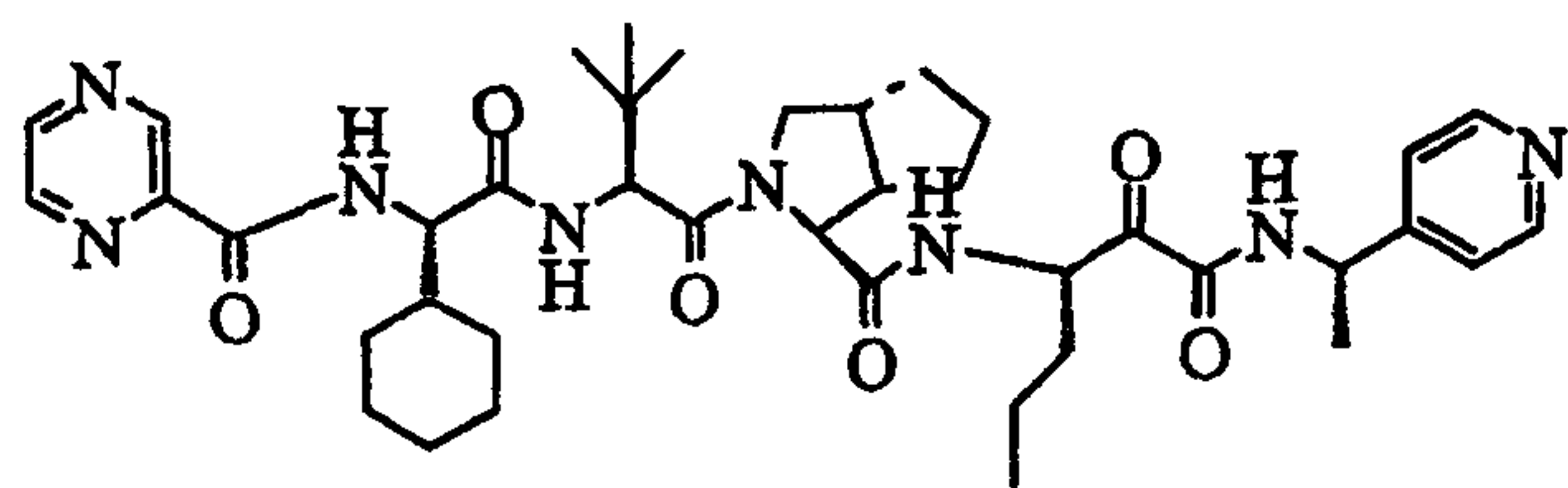


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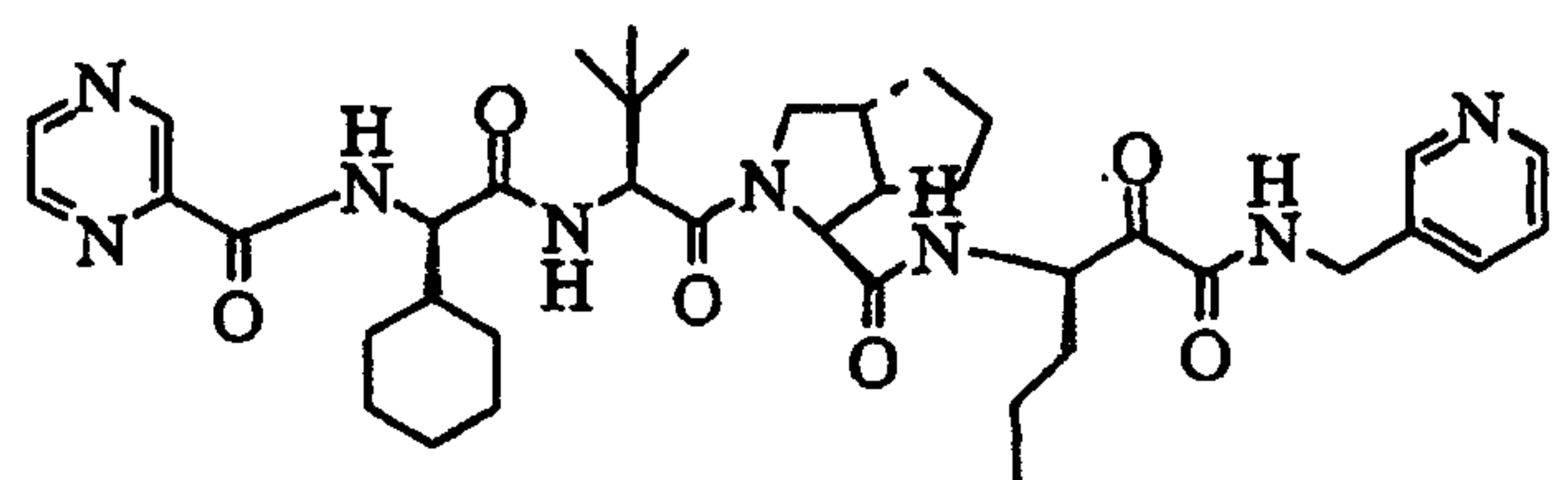


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EJ,

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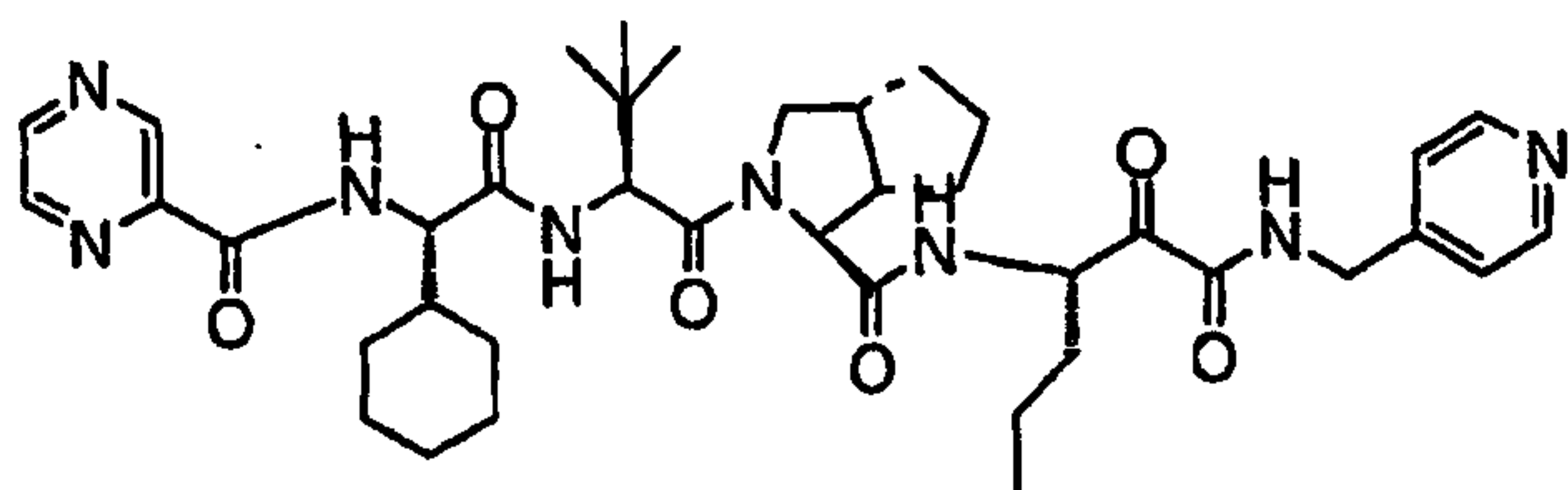


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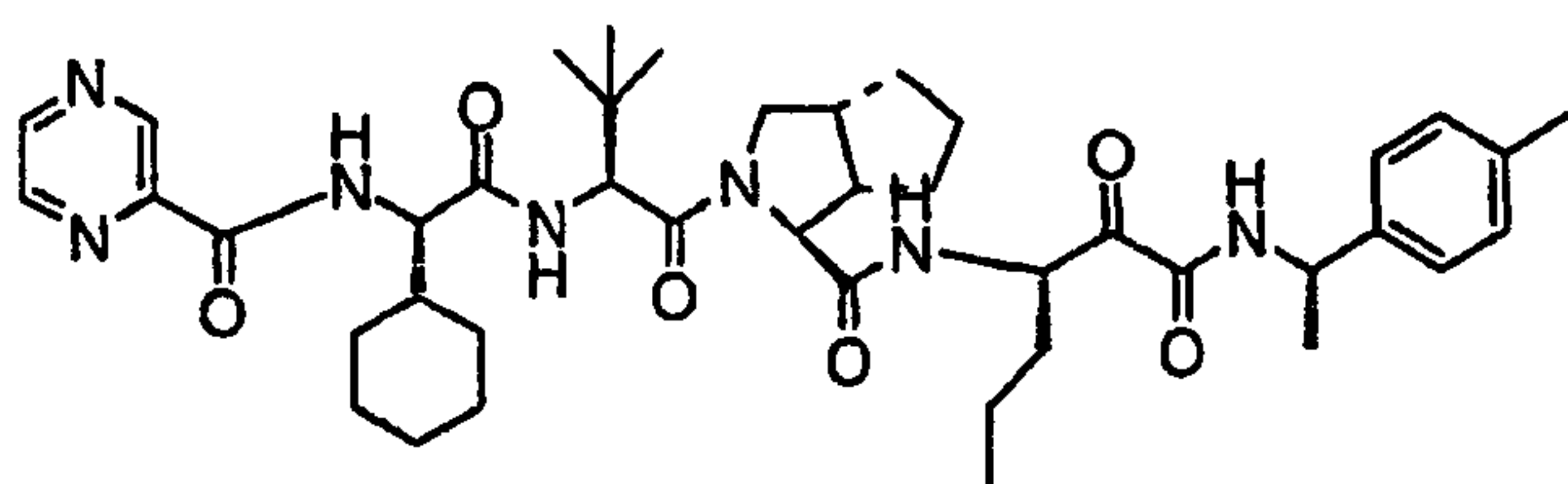
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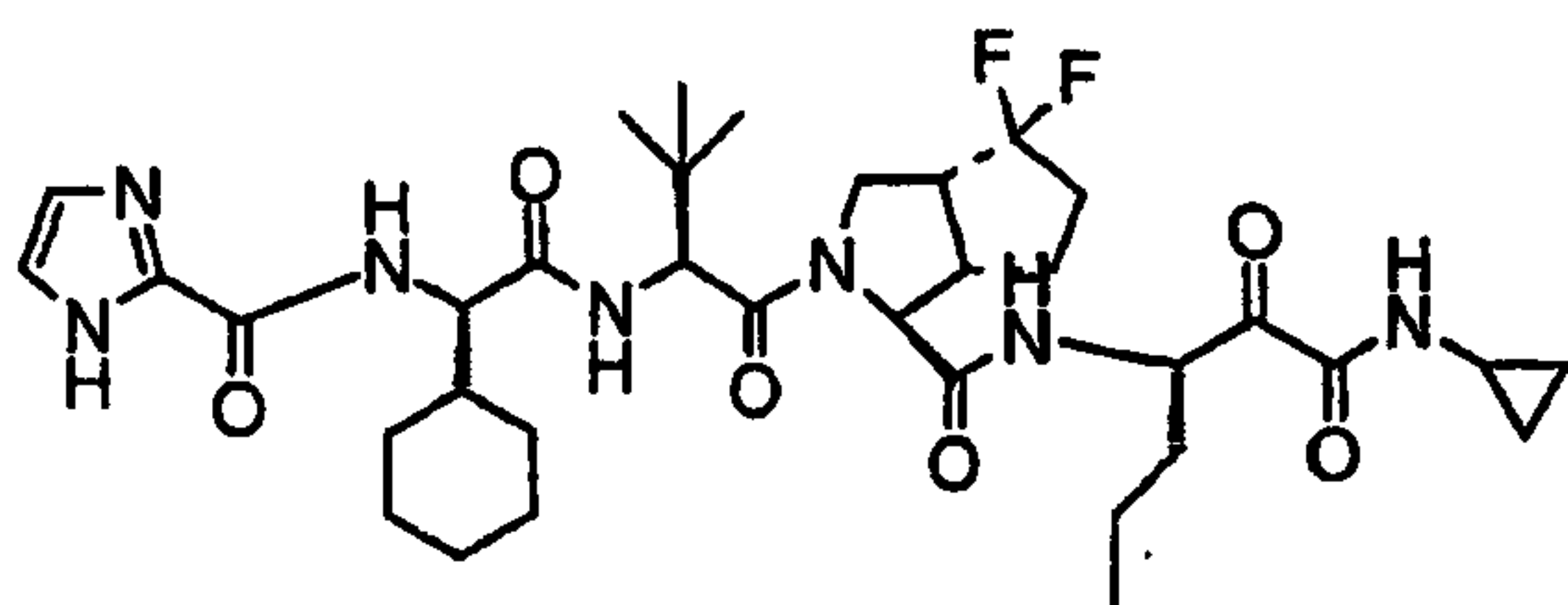


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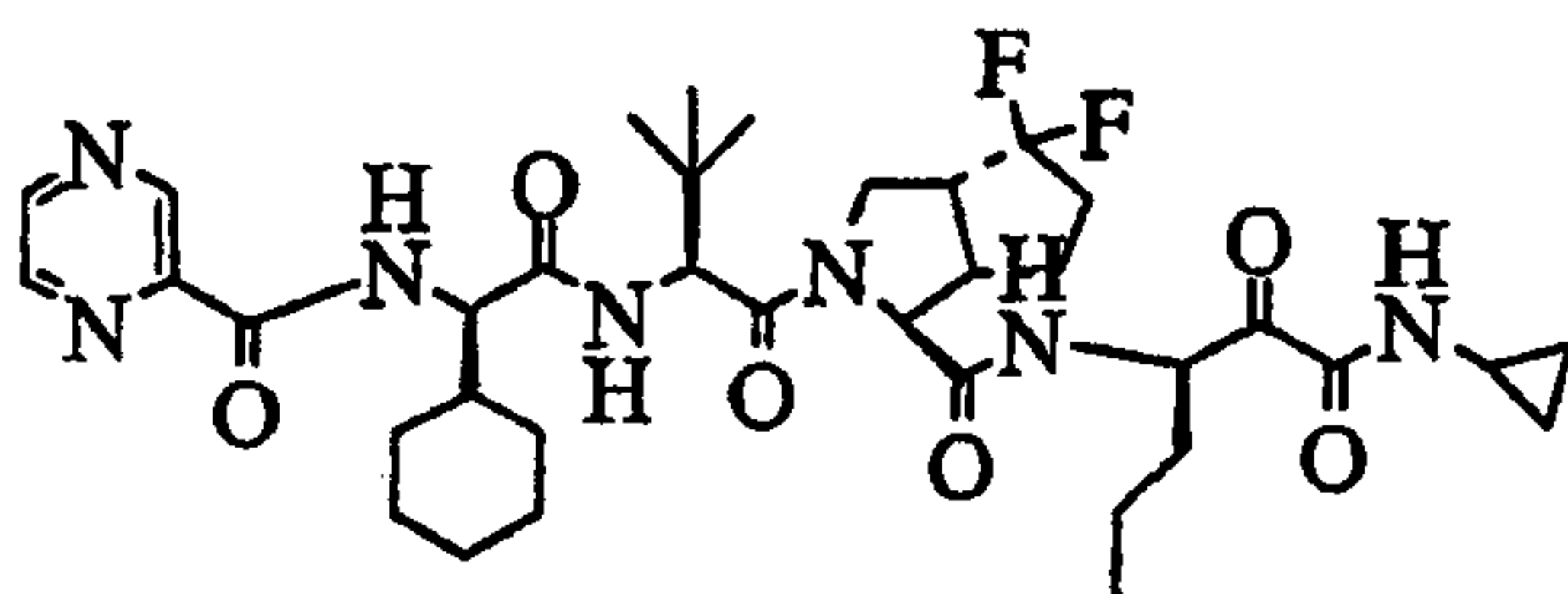


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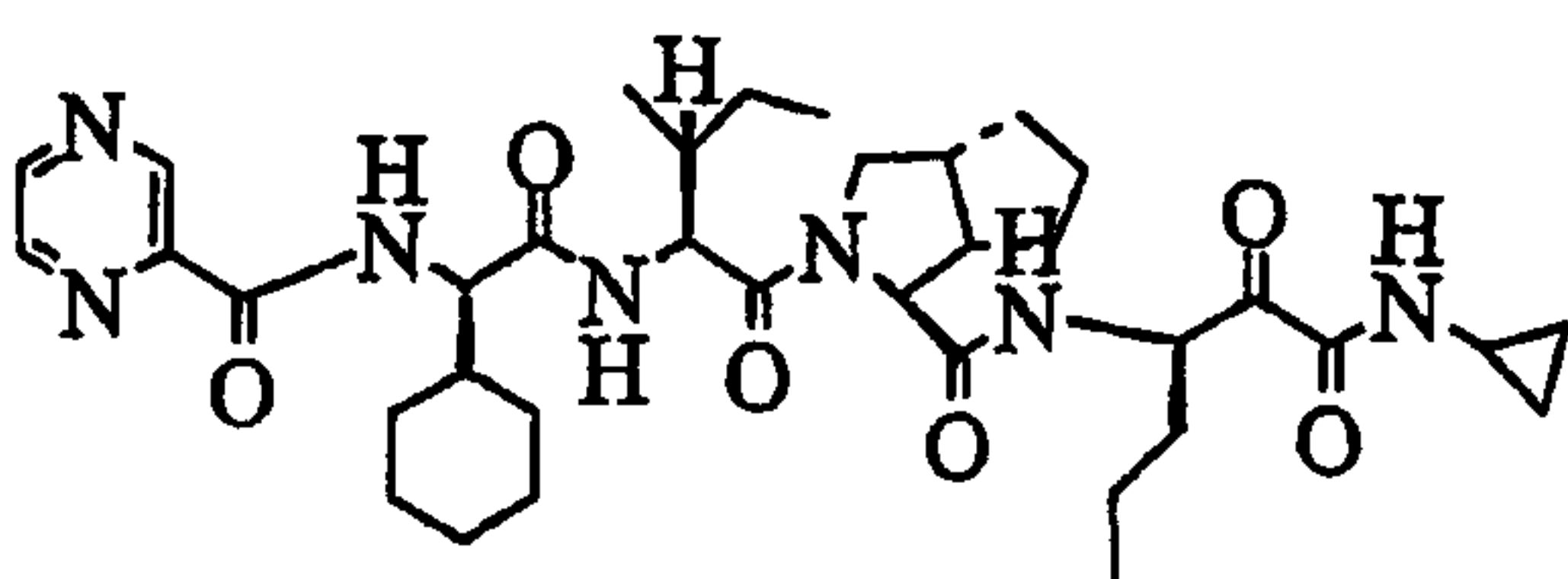
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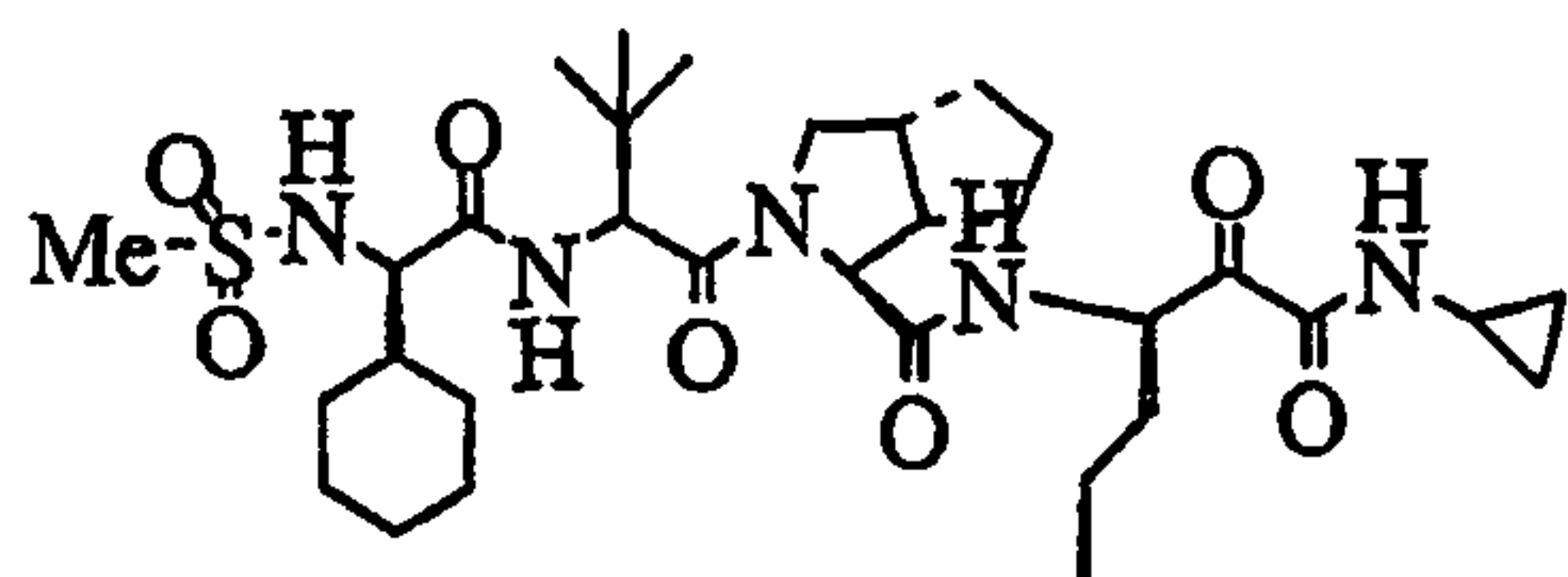
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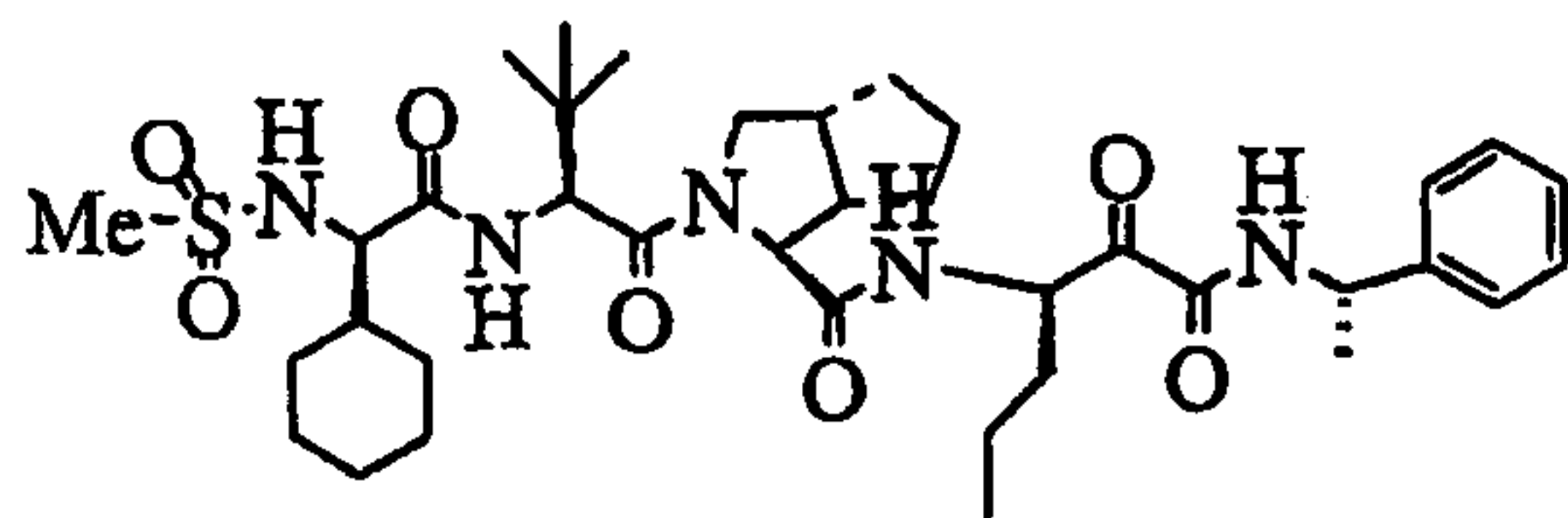
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66

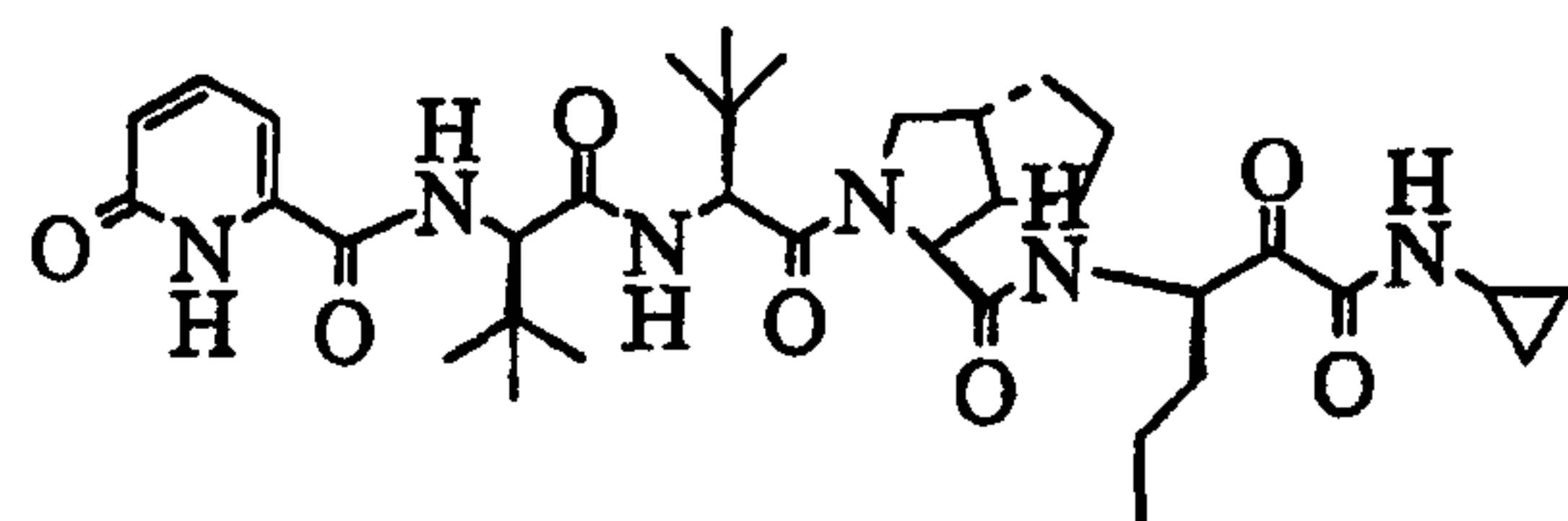


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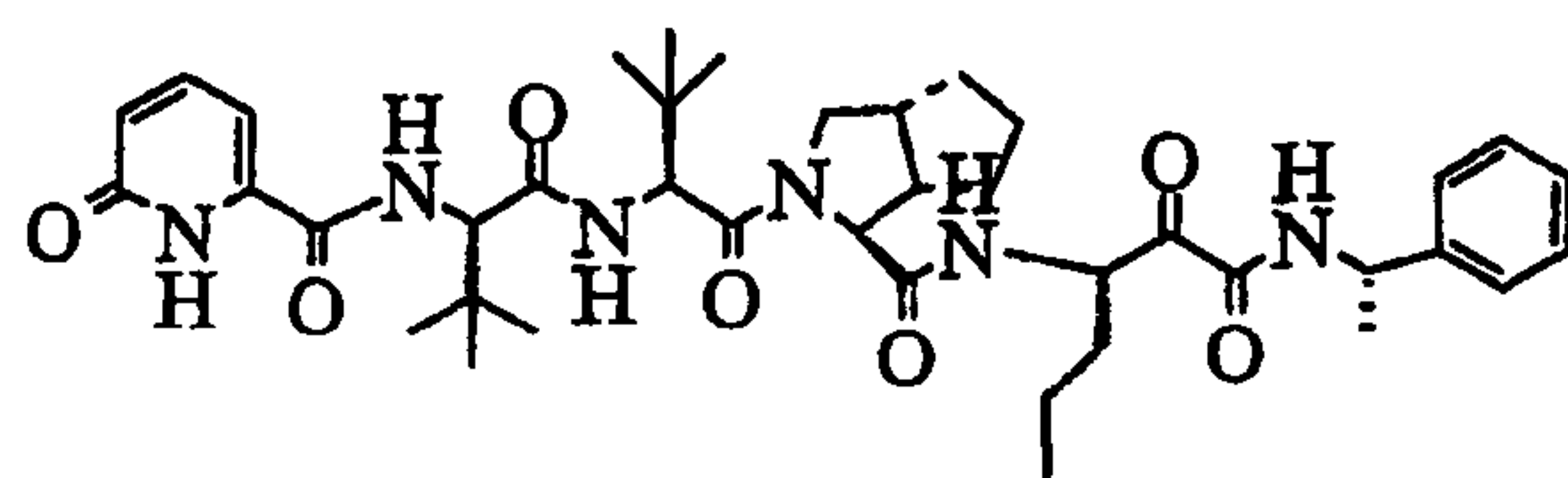
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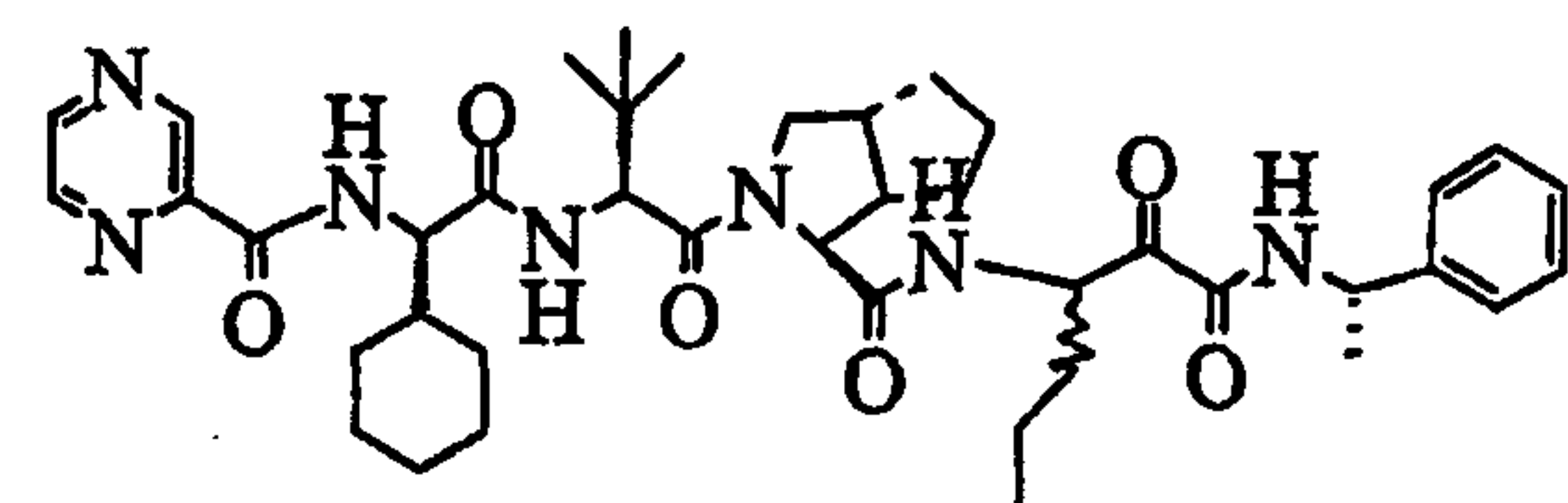
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ET,

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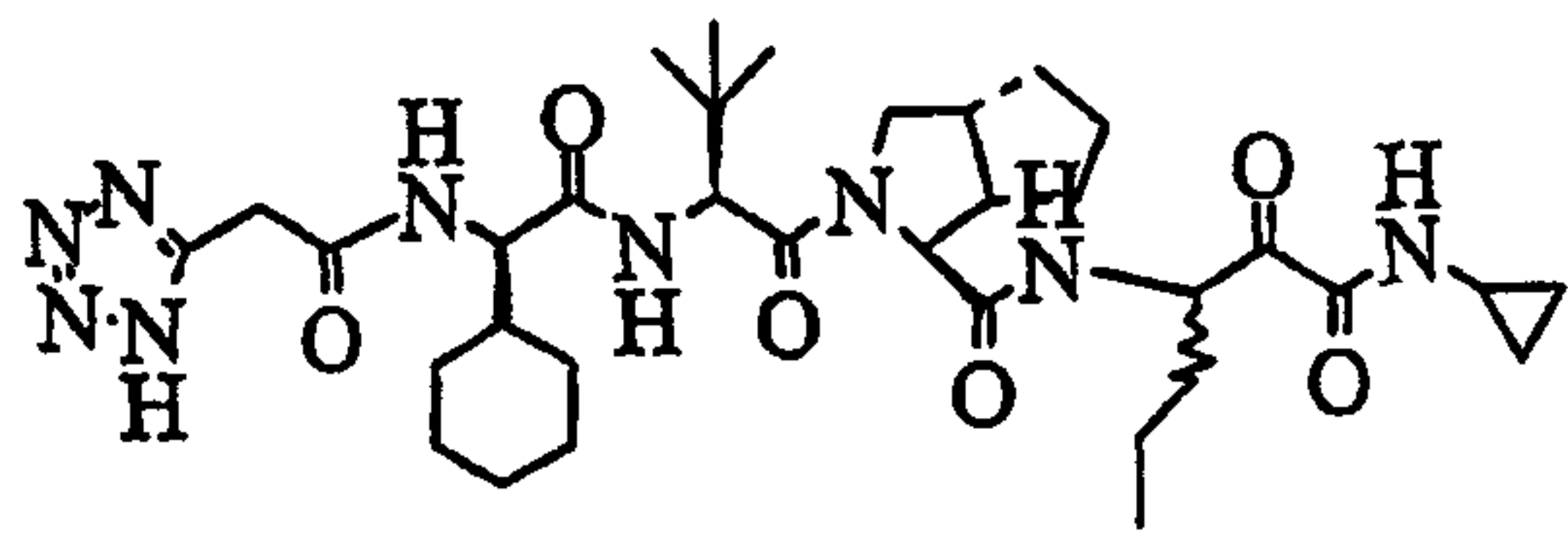


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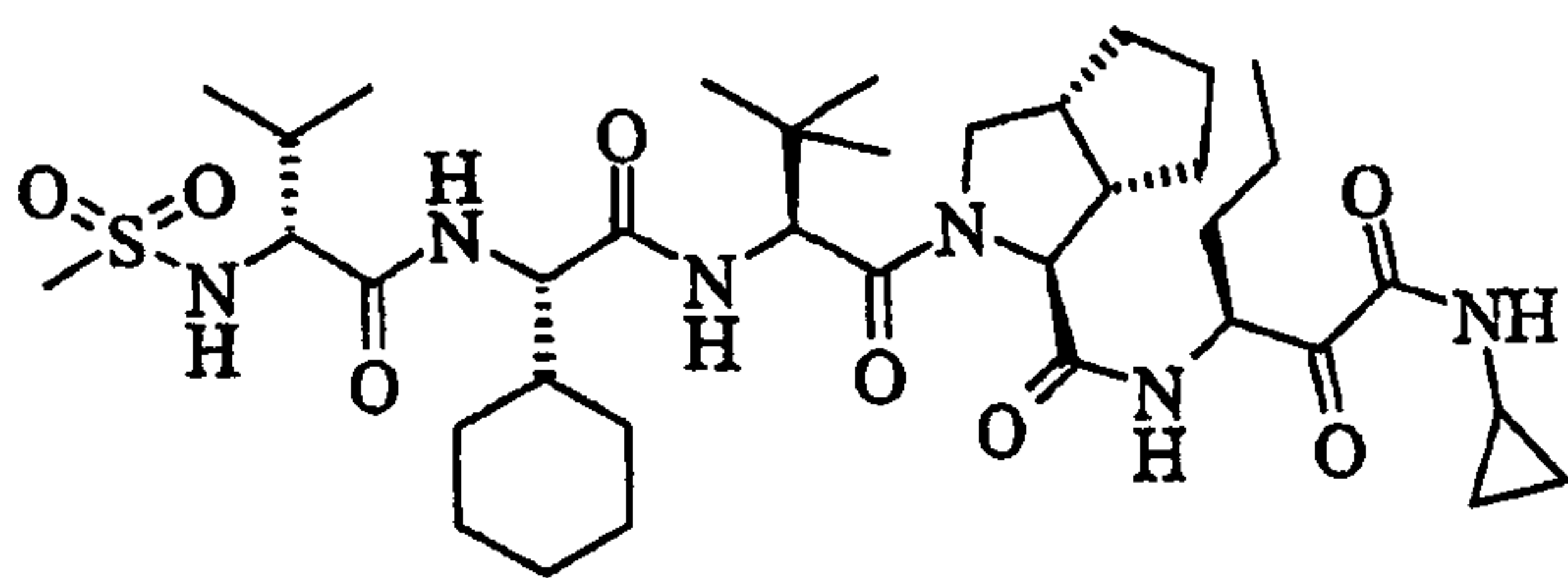
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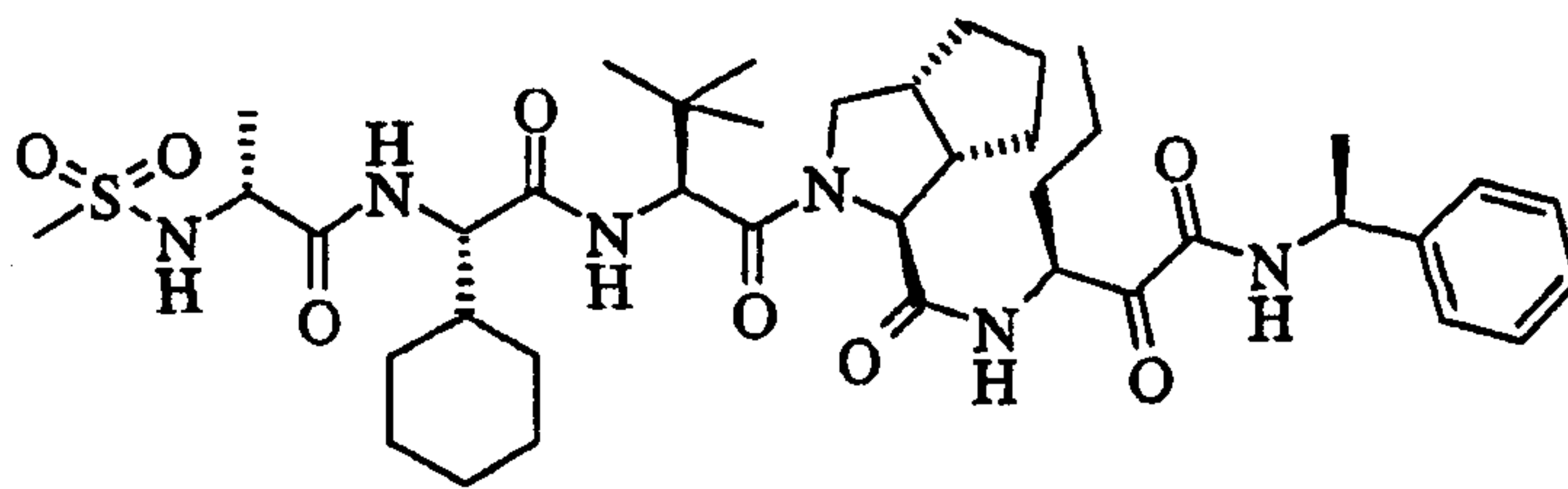


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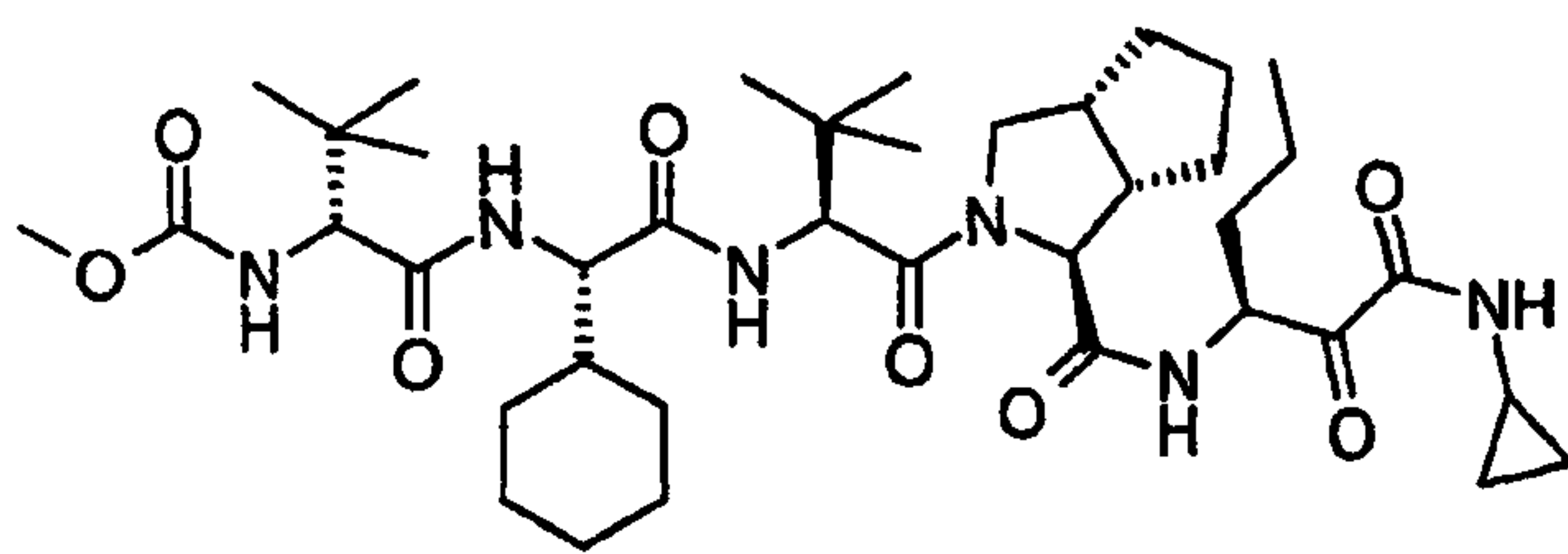


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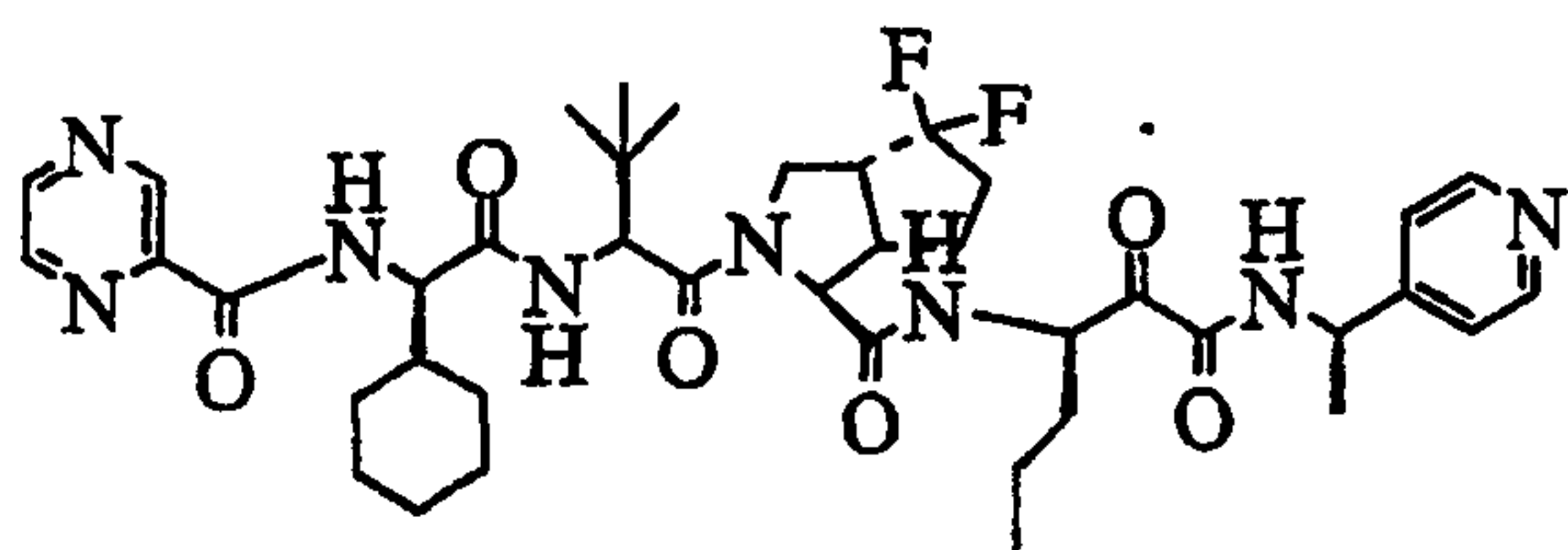


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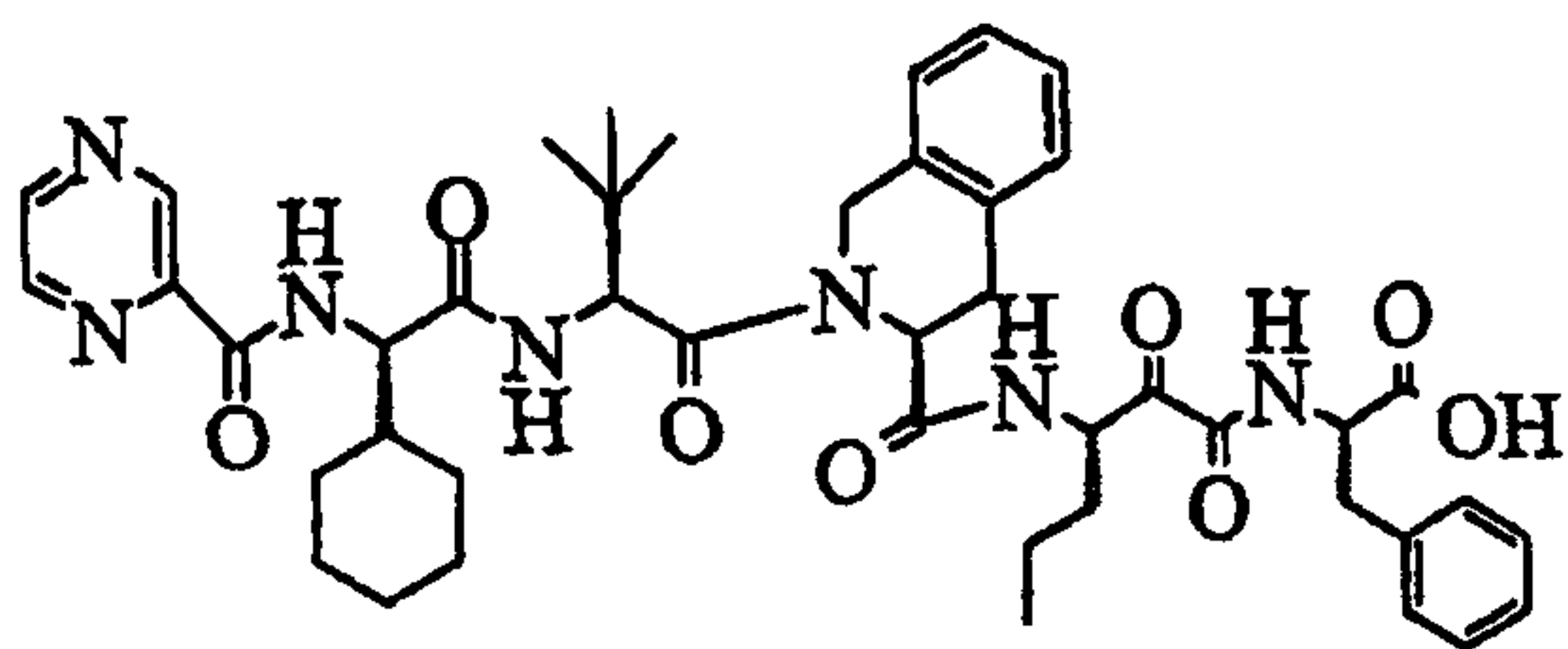


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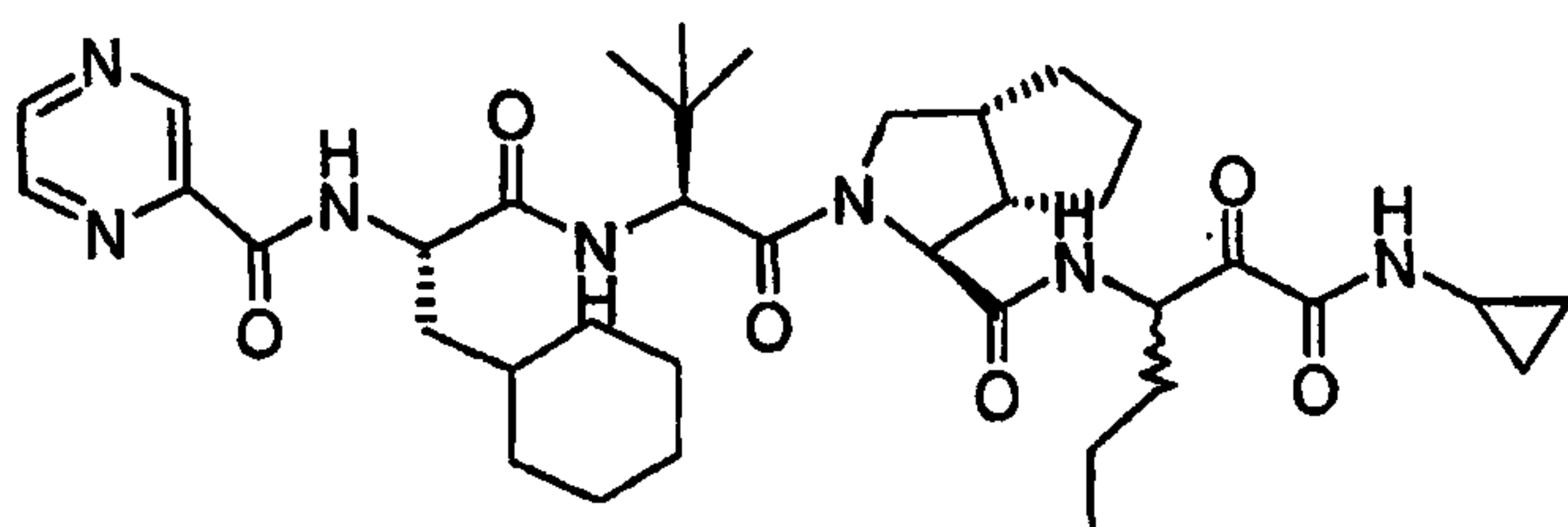
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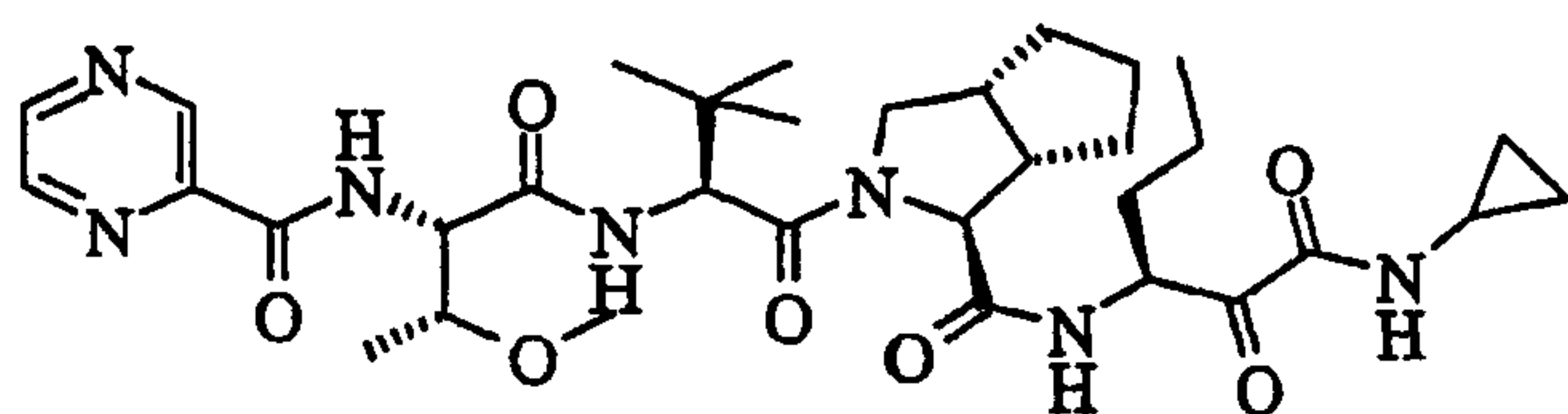


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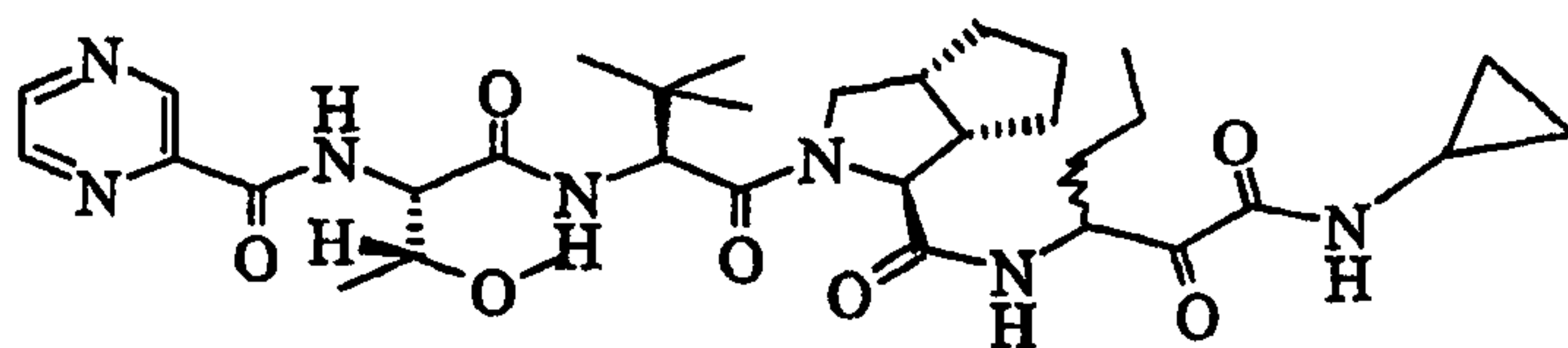


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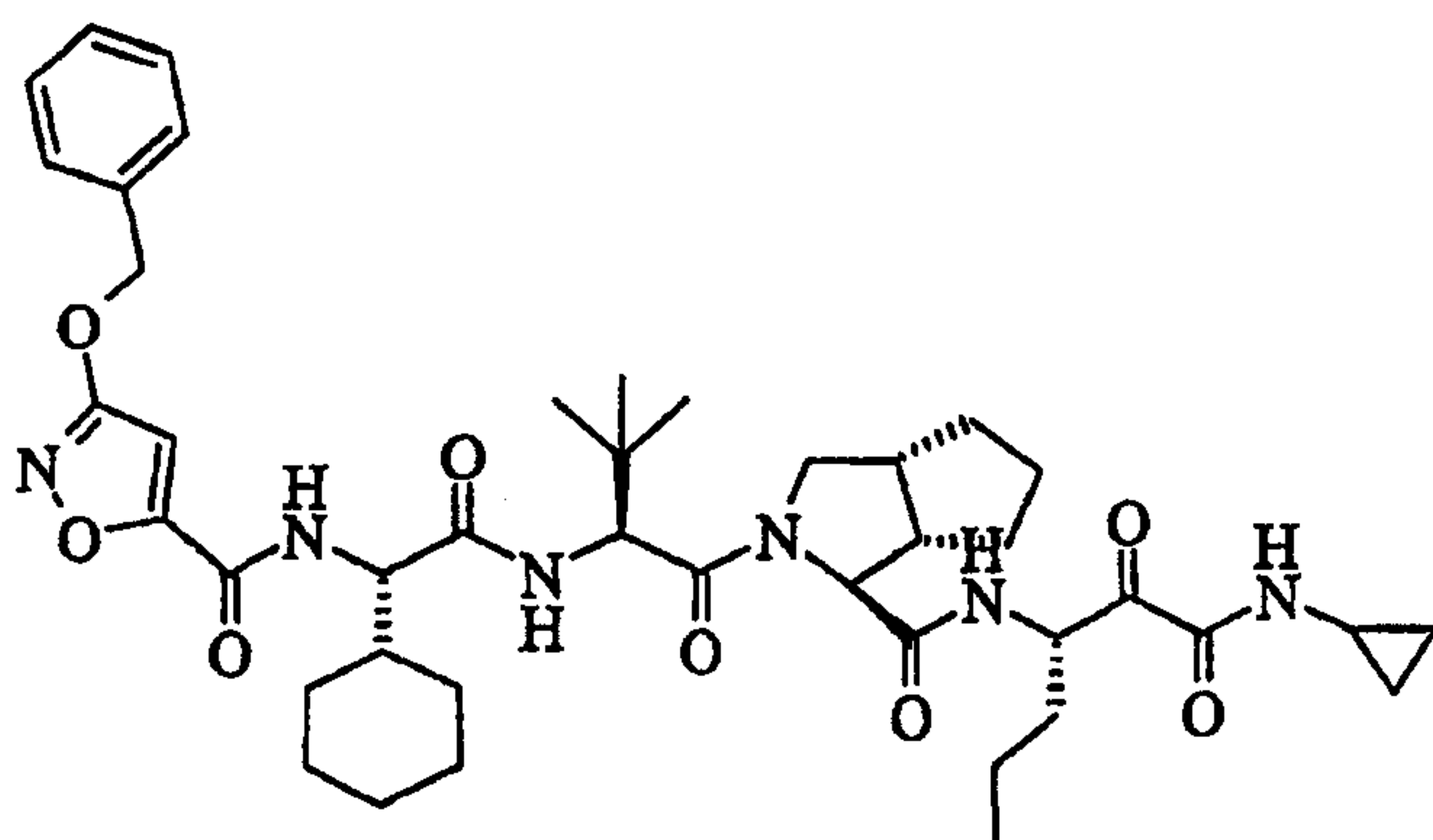


FC,



FD,

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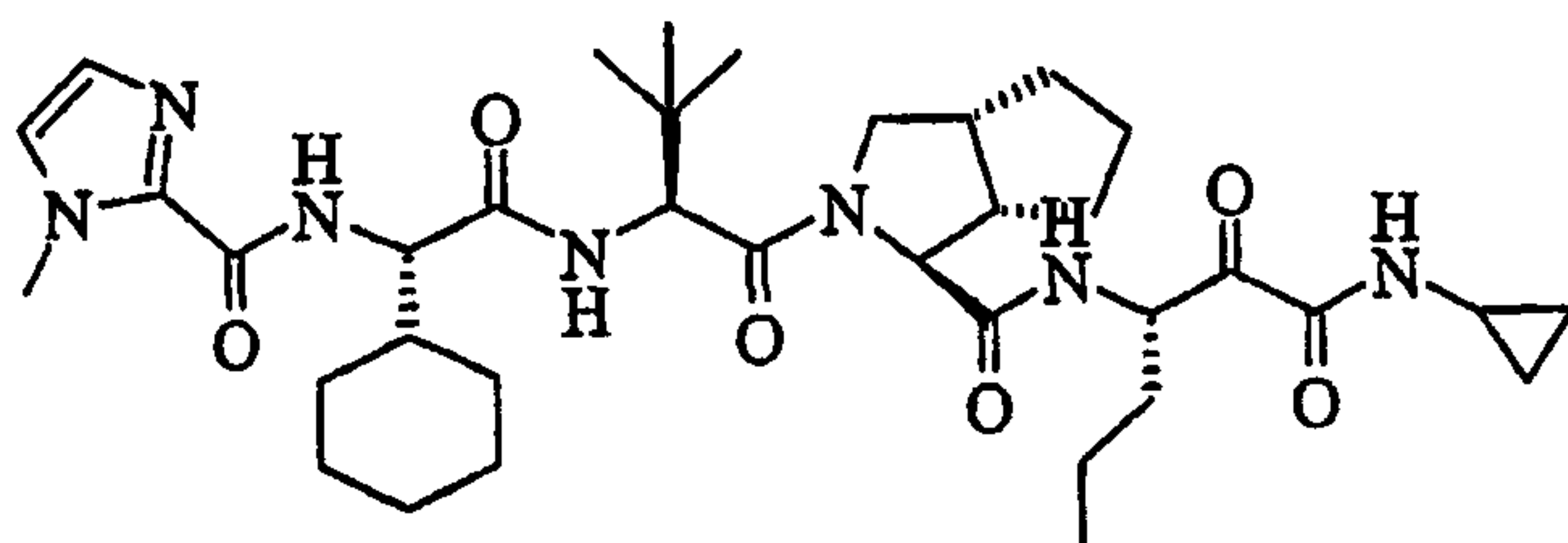


FE,

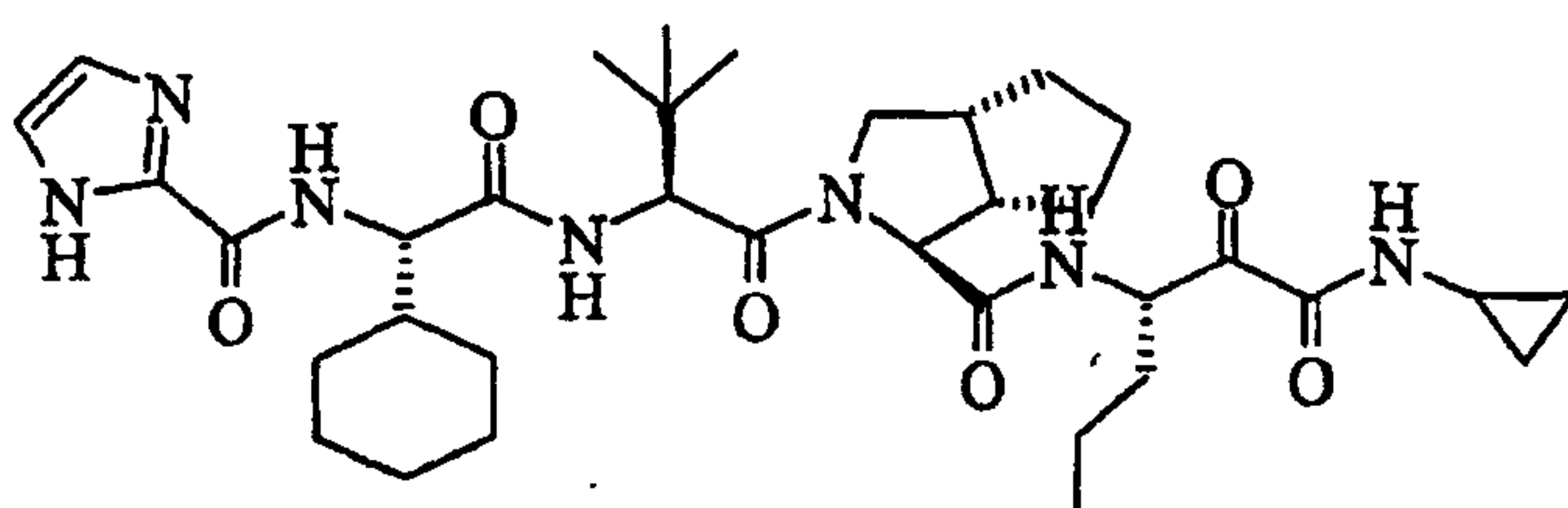
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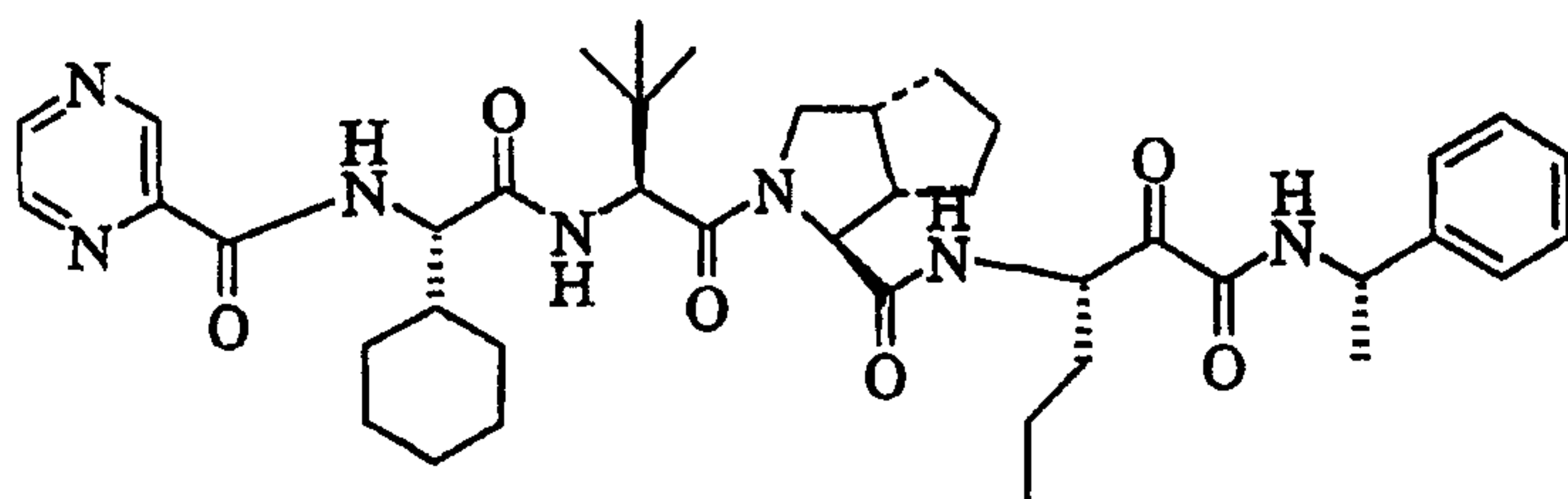


FF,



FG, and

5



FH,

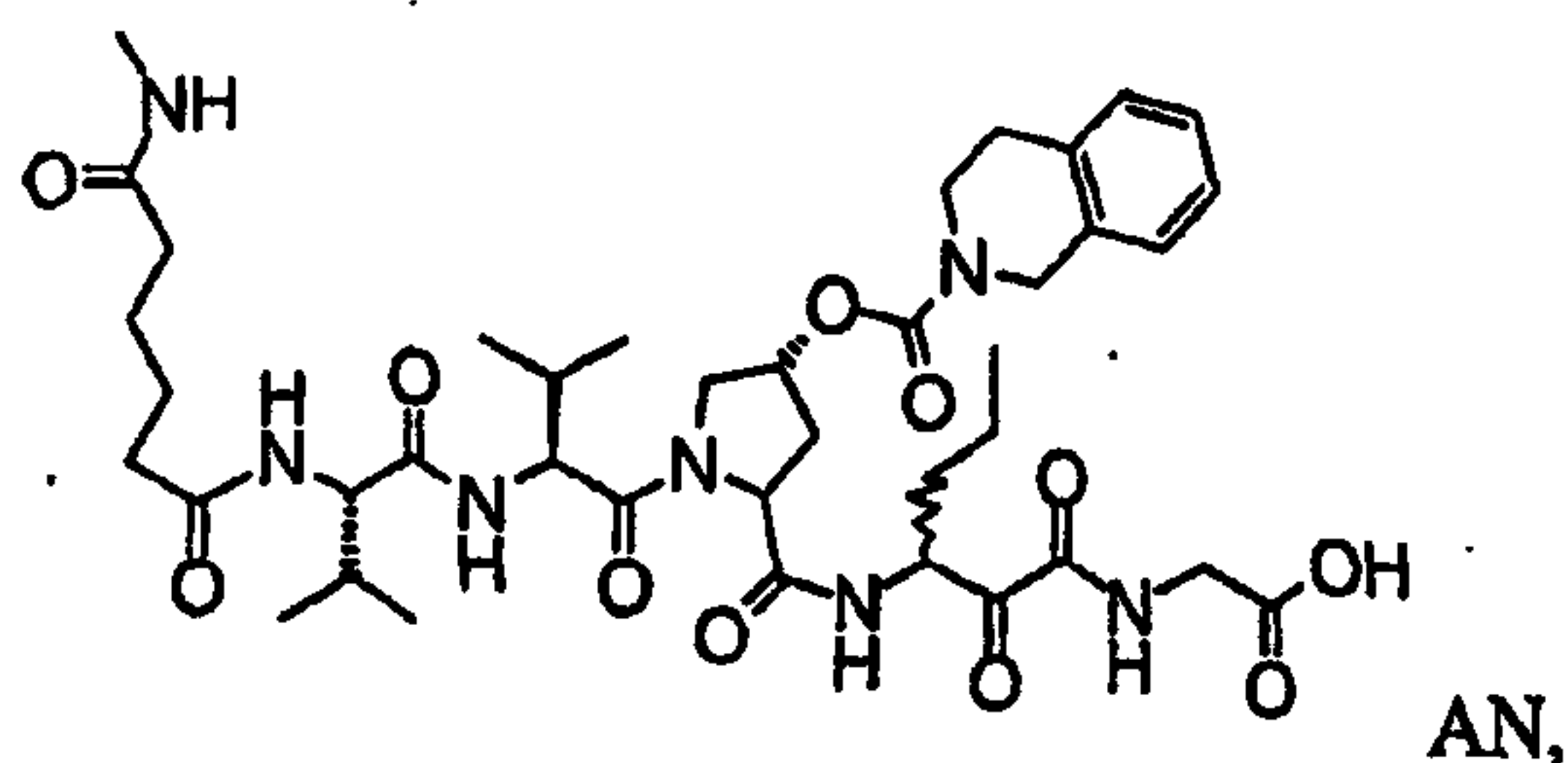
or a pharmaceutically acceptable salt or prodrug thereof, or a solvate of such a compound, its salt or its prodrug.

10

A preferred compound is one selected from the group consisting of S, U, BW, BX, BY, BZ, CE, CU, CW, CY, DZ, EA, EC, EJ, FH, EW, EO, EZ, FG and EN a pharmaceutically acceptable salt or prodrug thereof, or solvate of such compound, its salt or its prodrug.

15

Another preferred embodiment of the invention are selected from the following group of compounds:

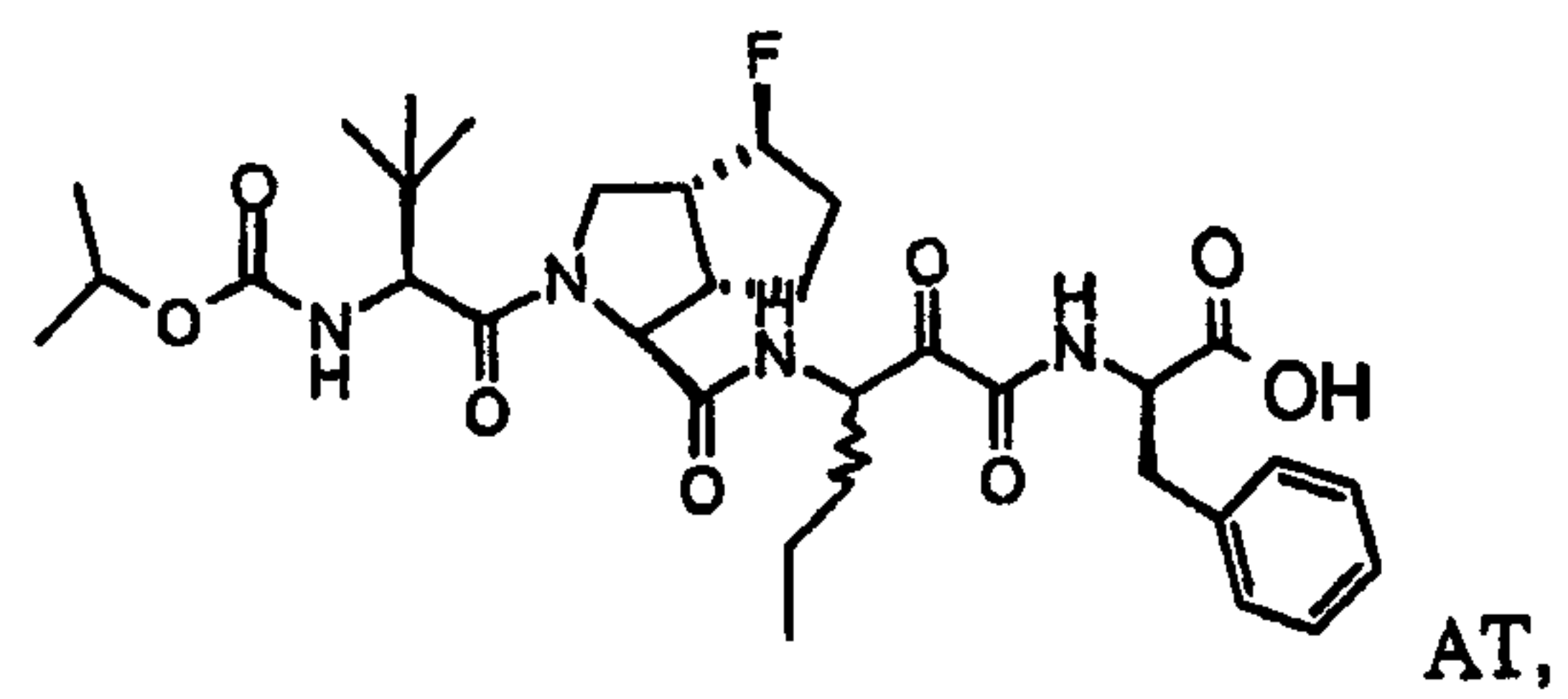
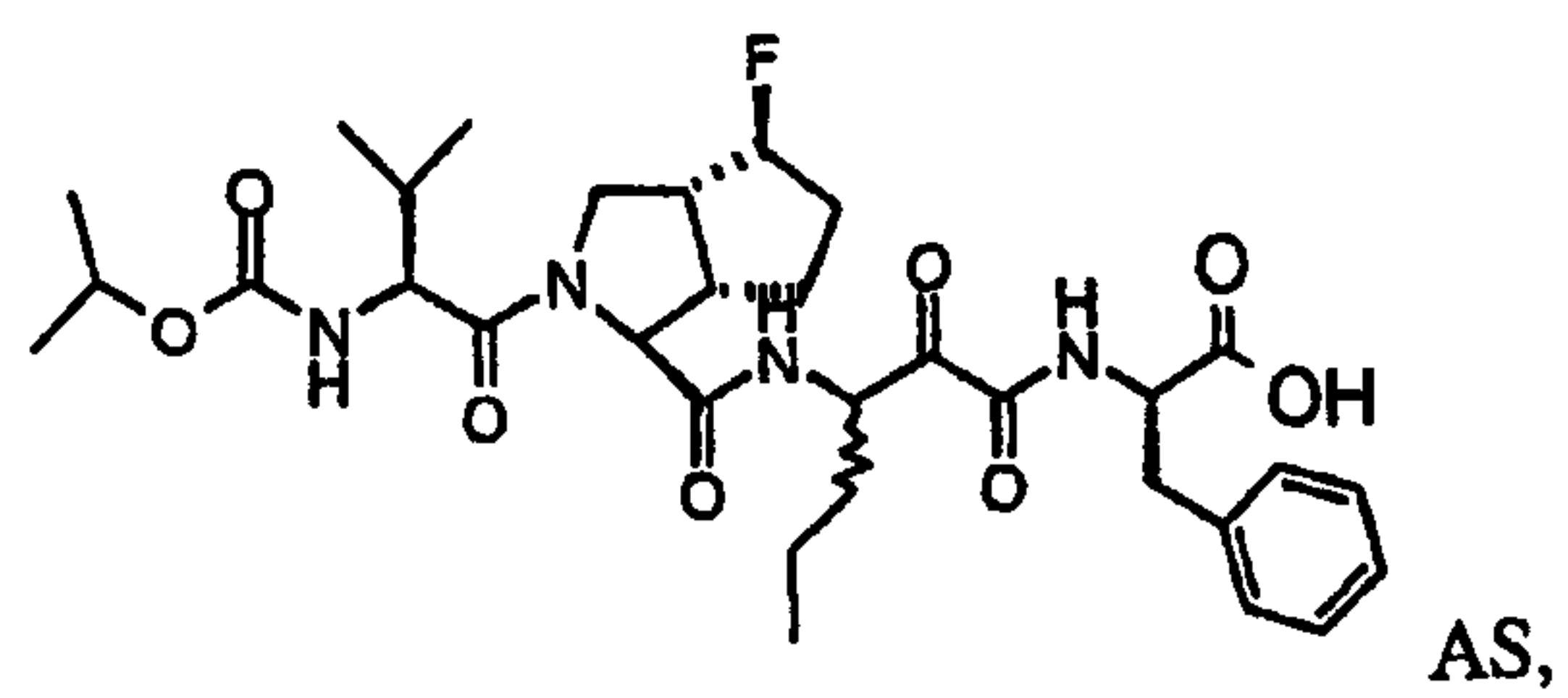
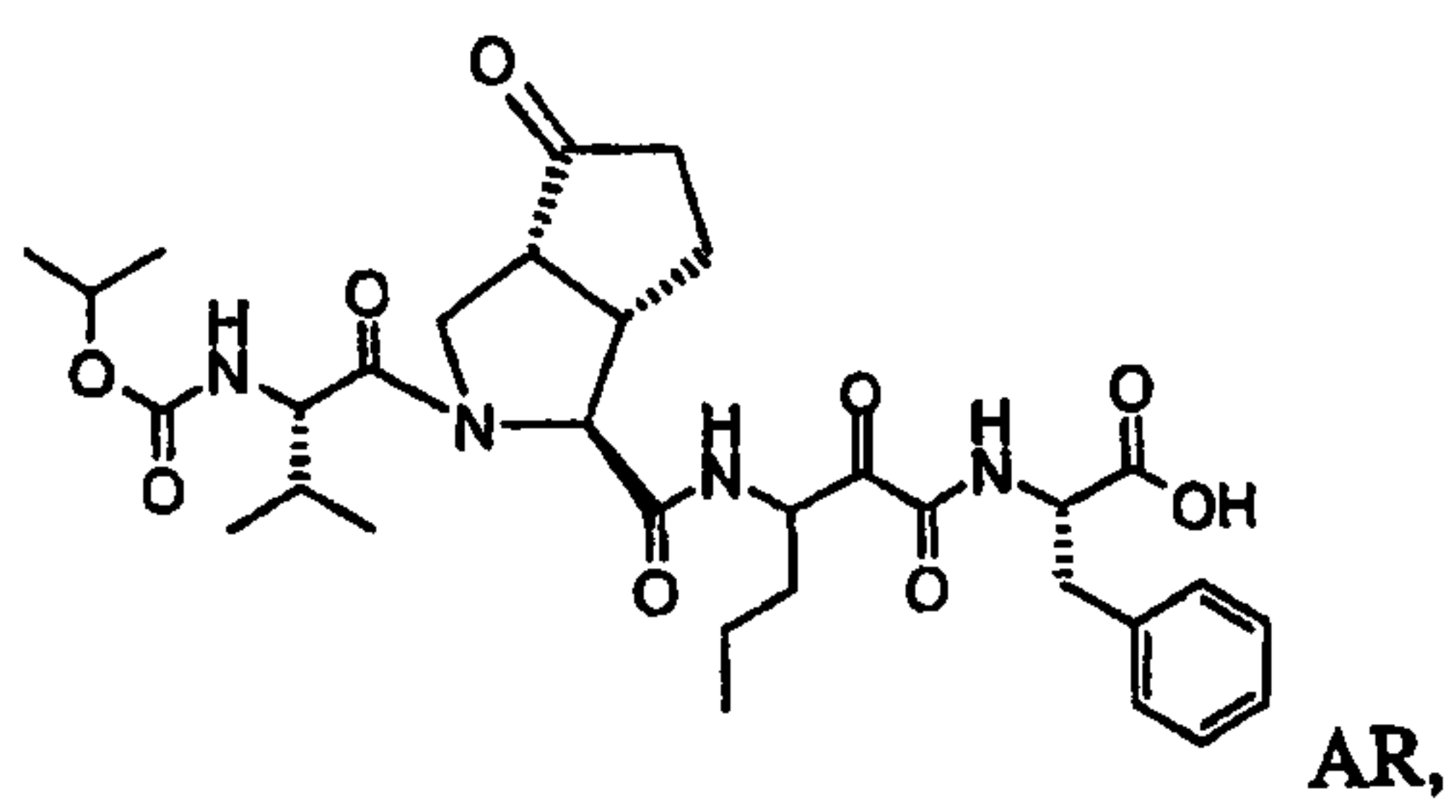
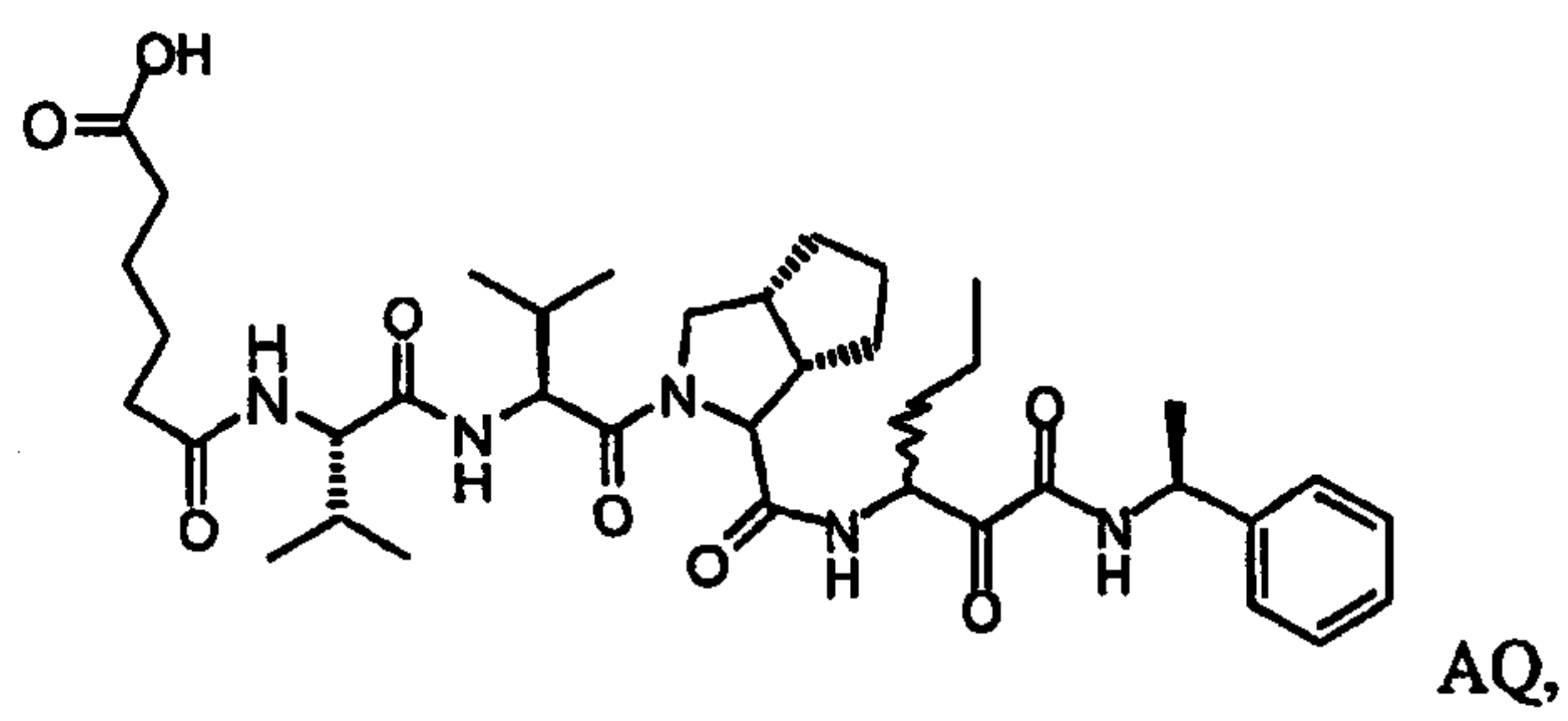
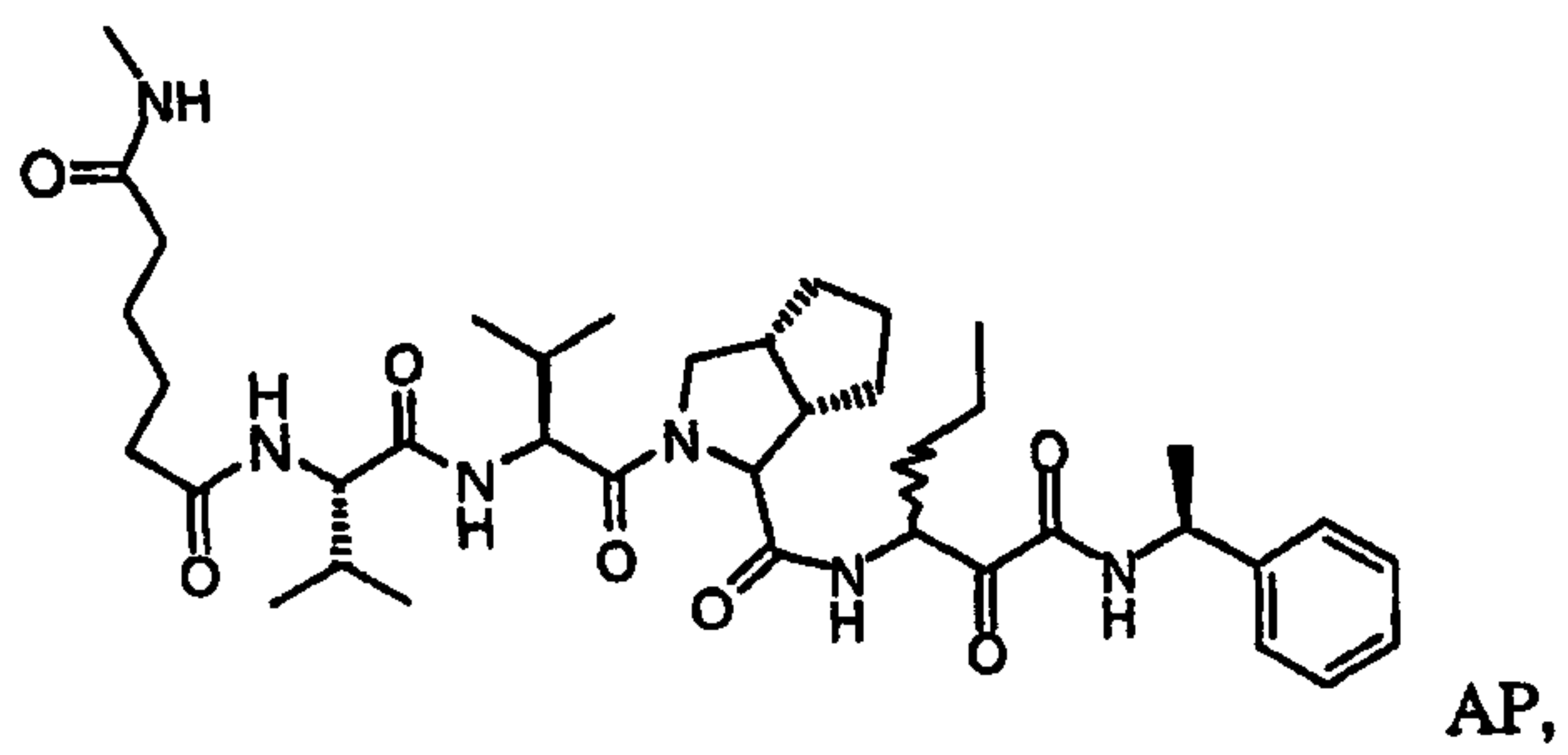
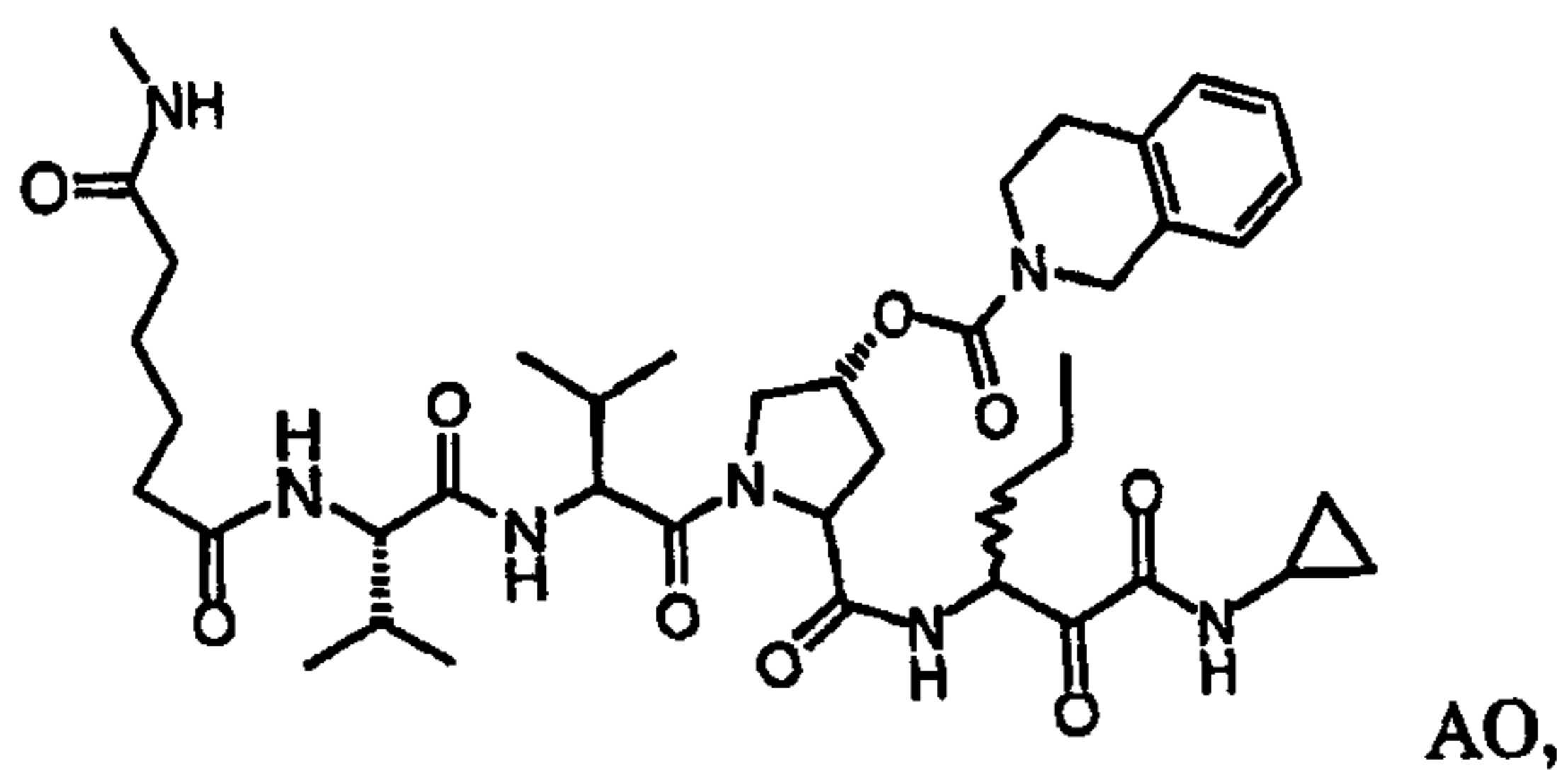


AN,

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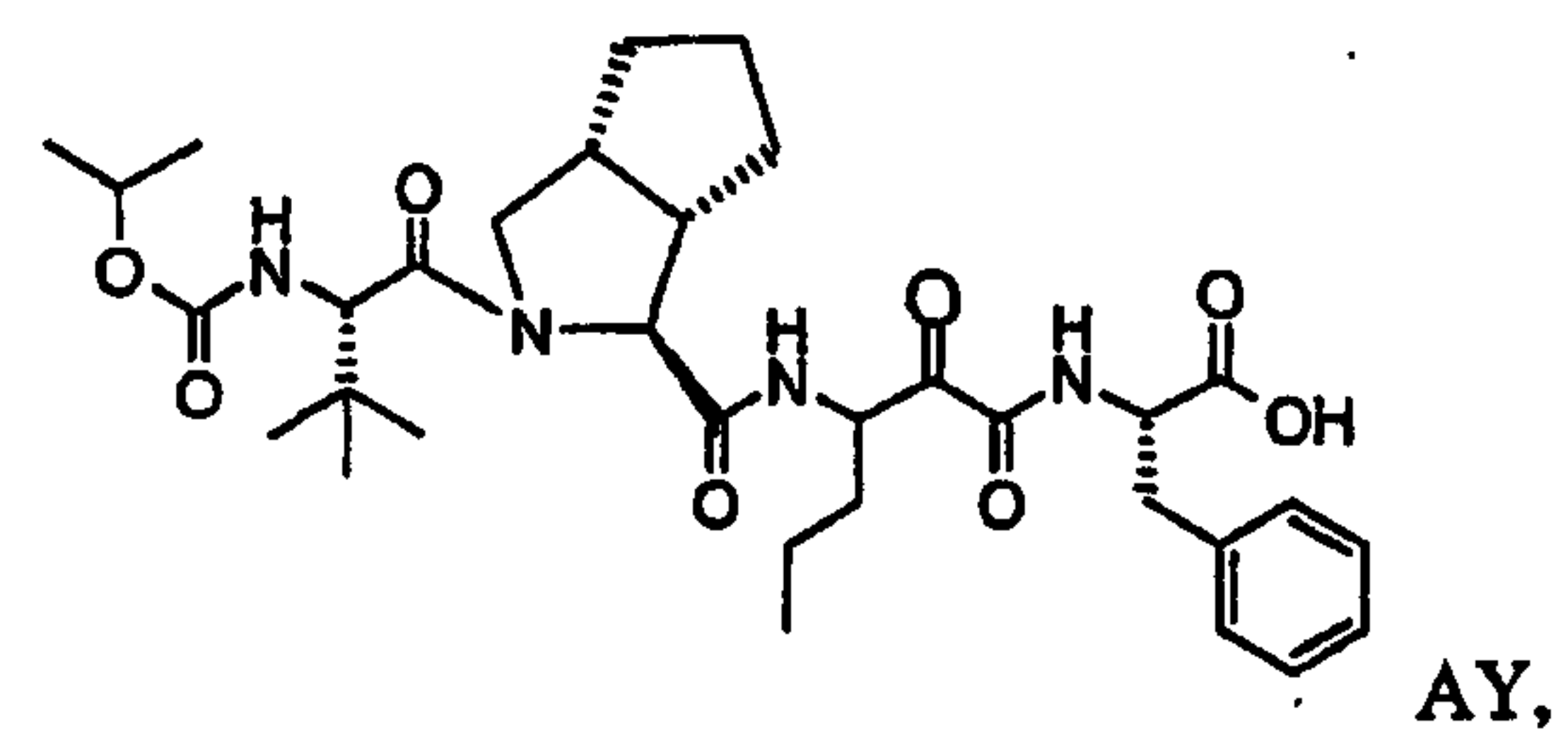
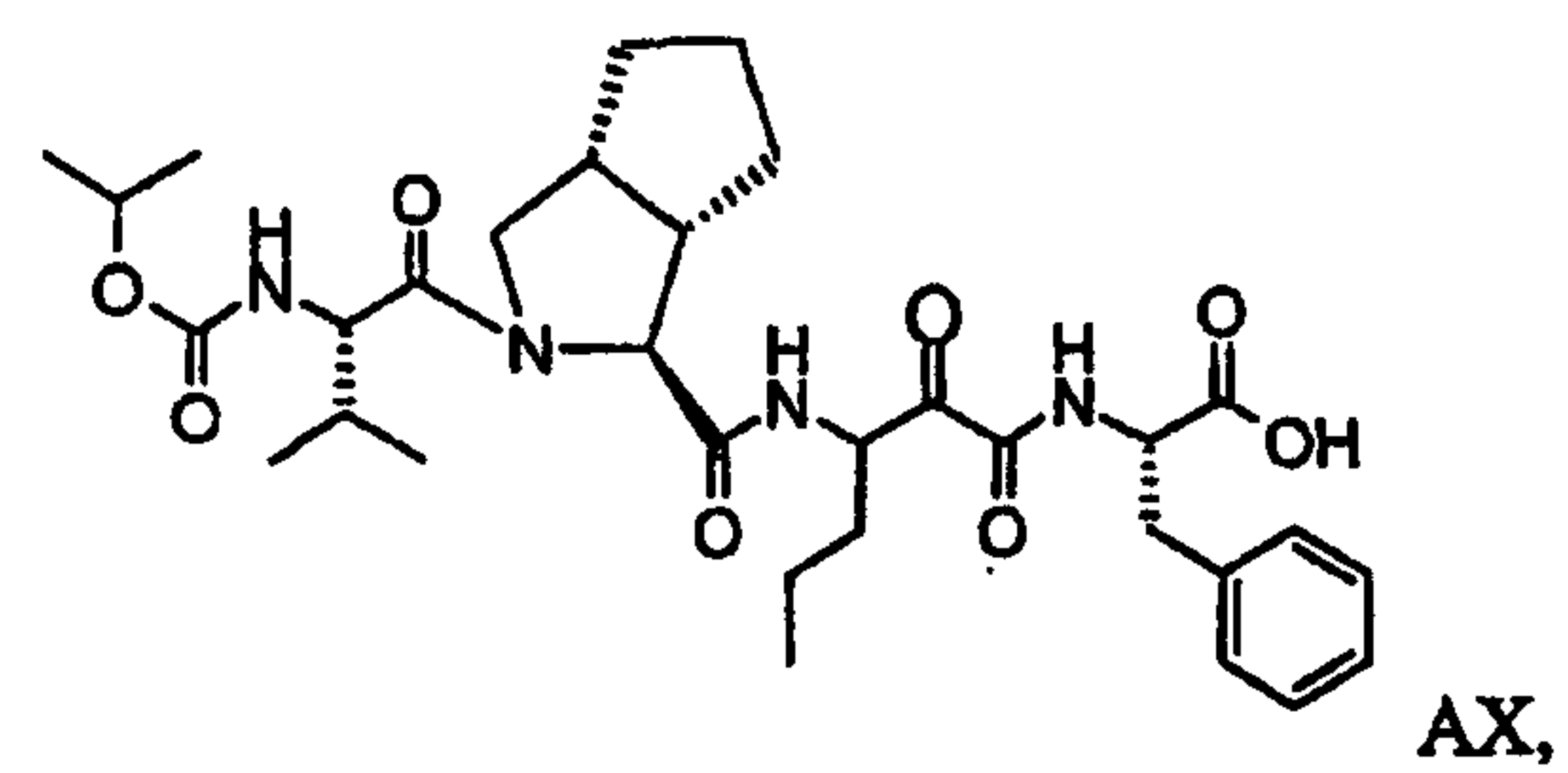
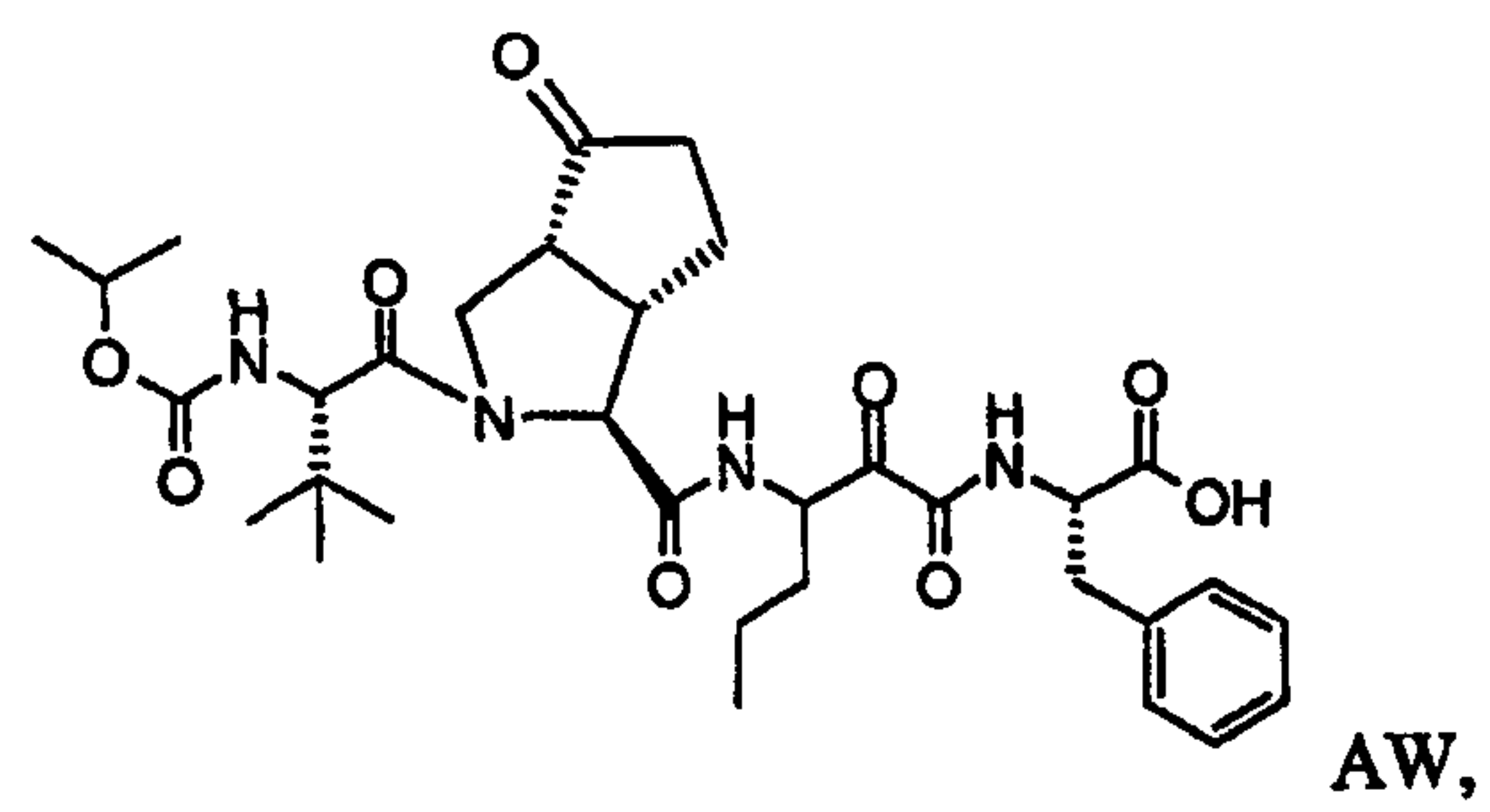
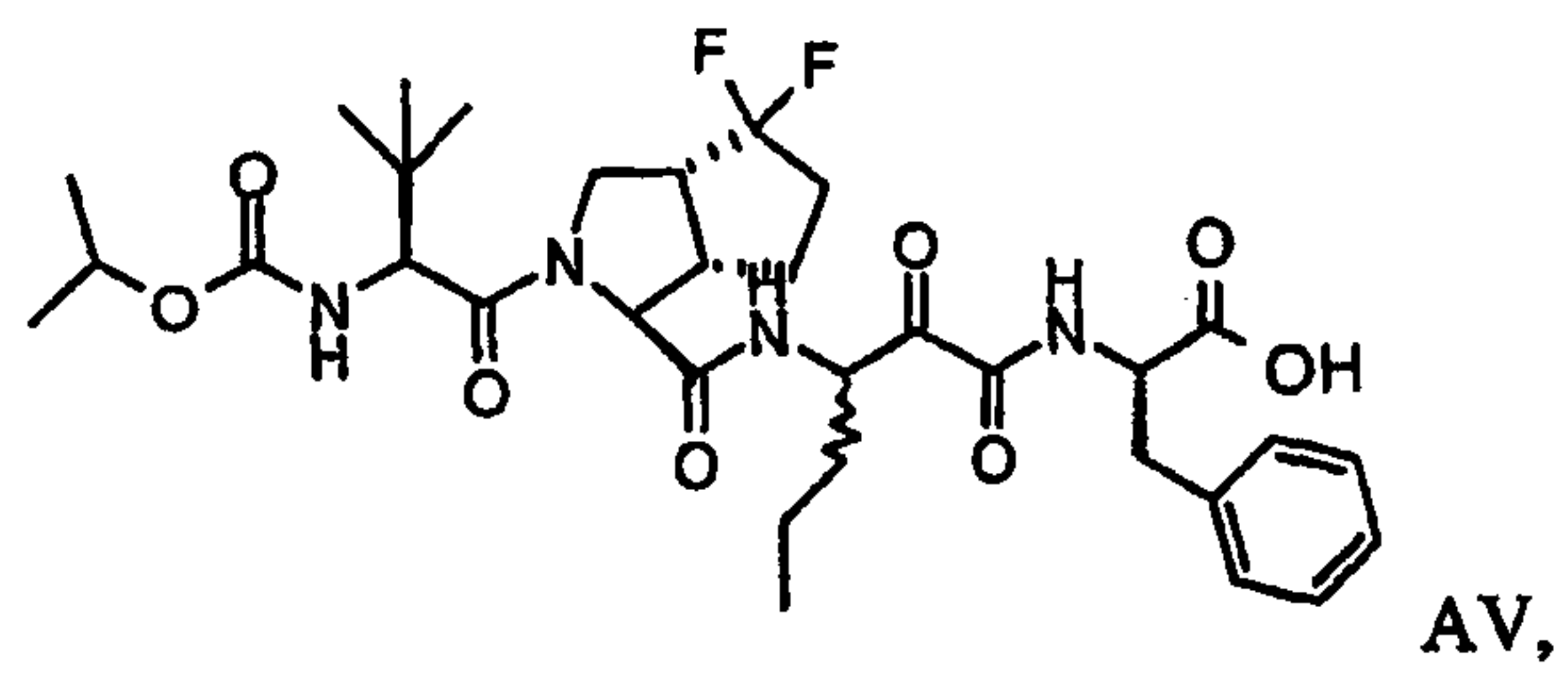
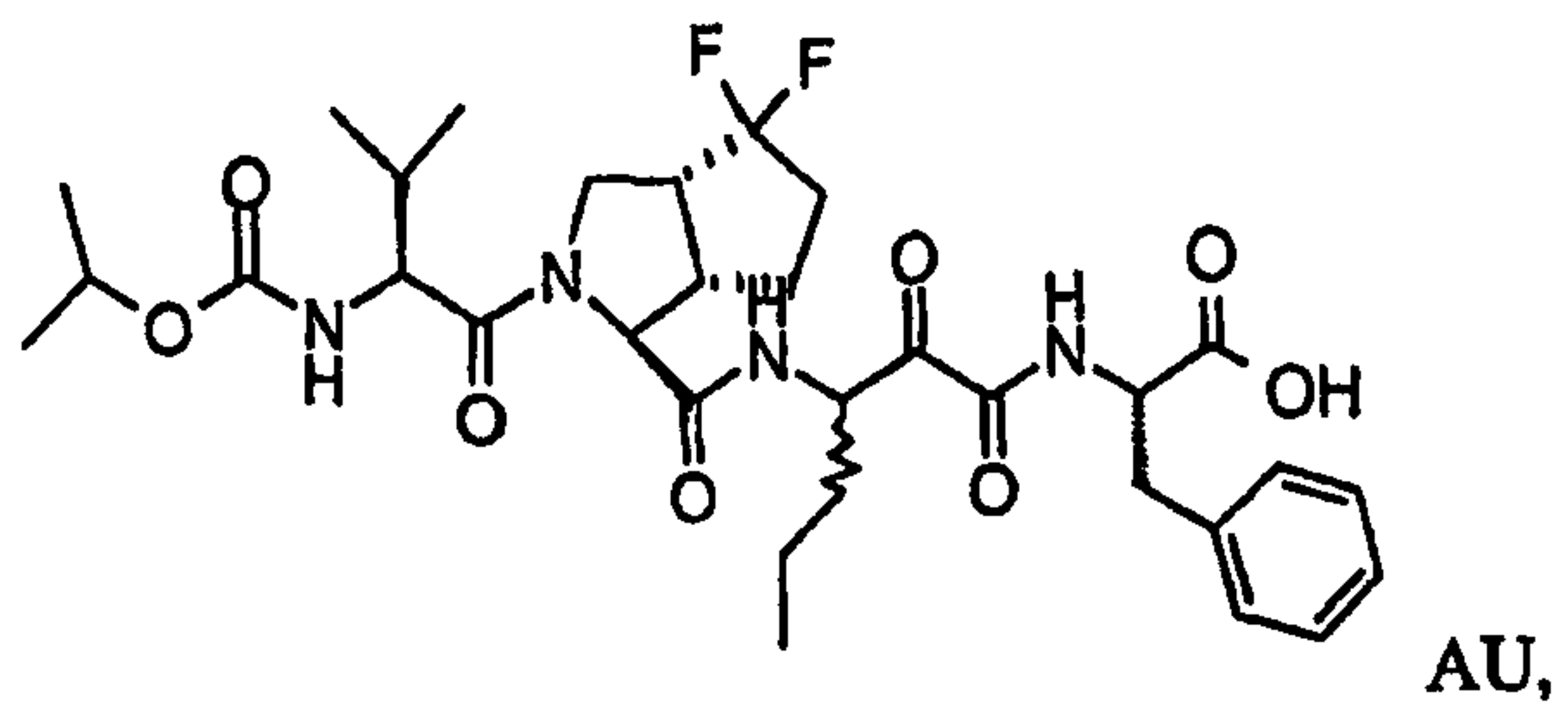
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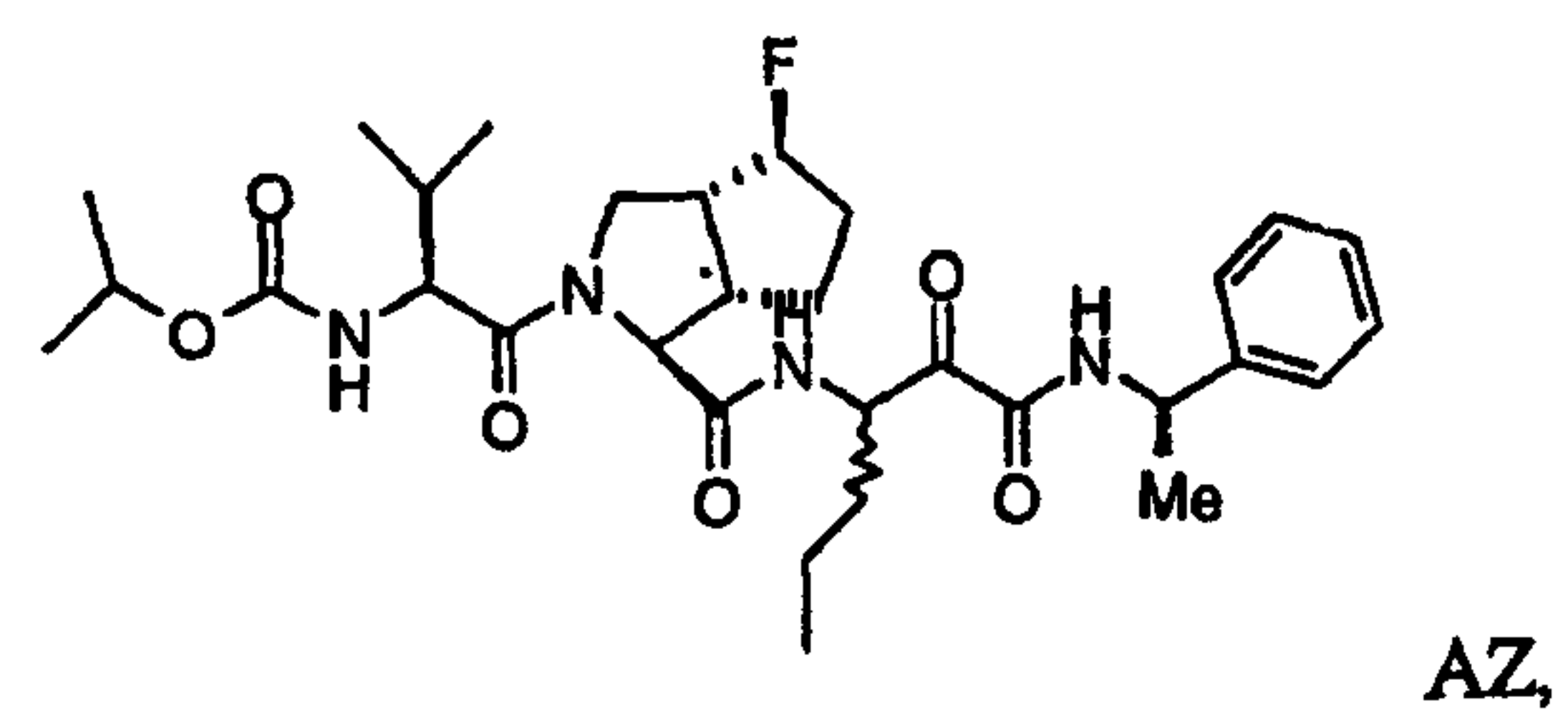
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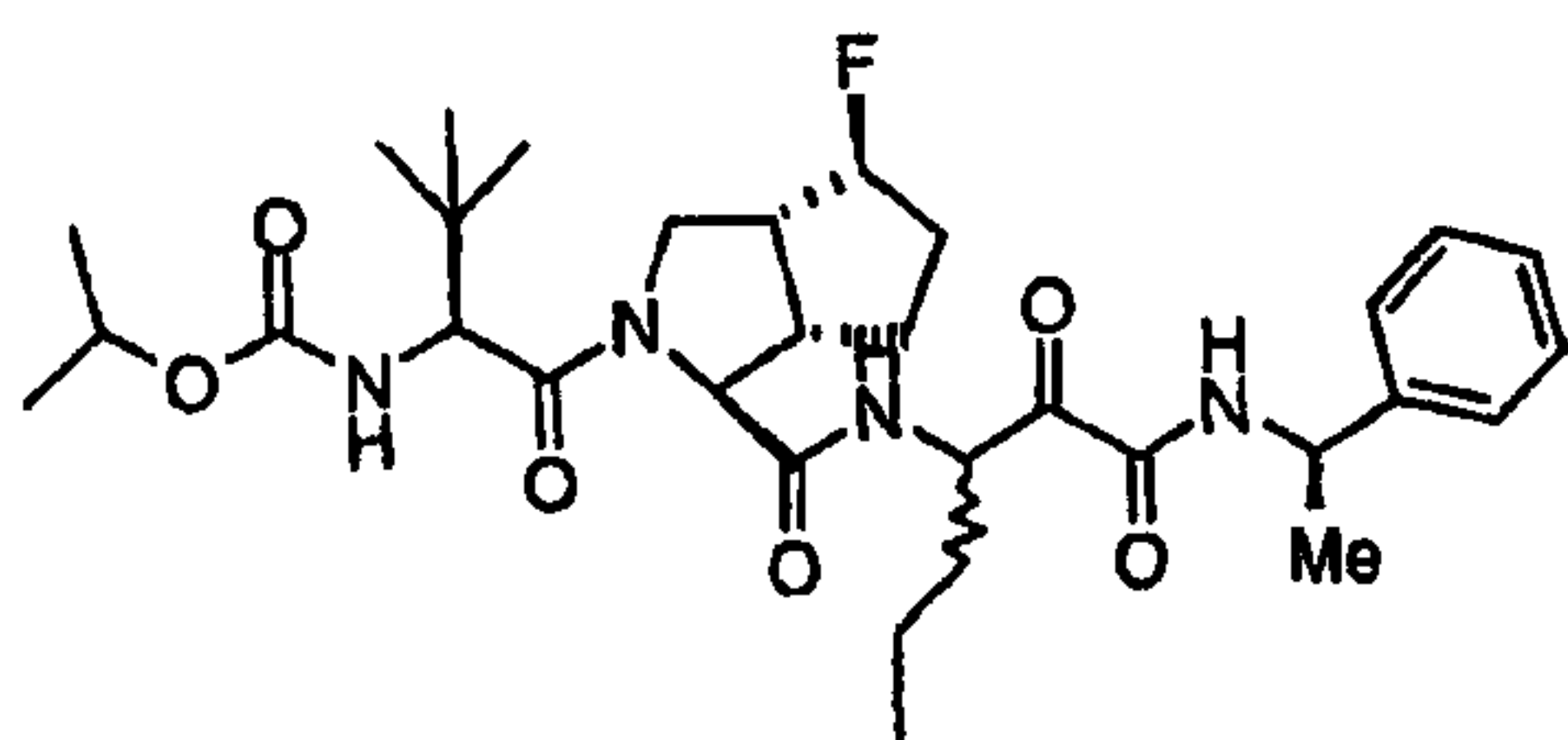
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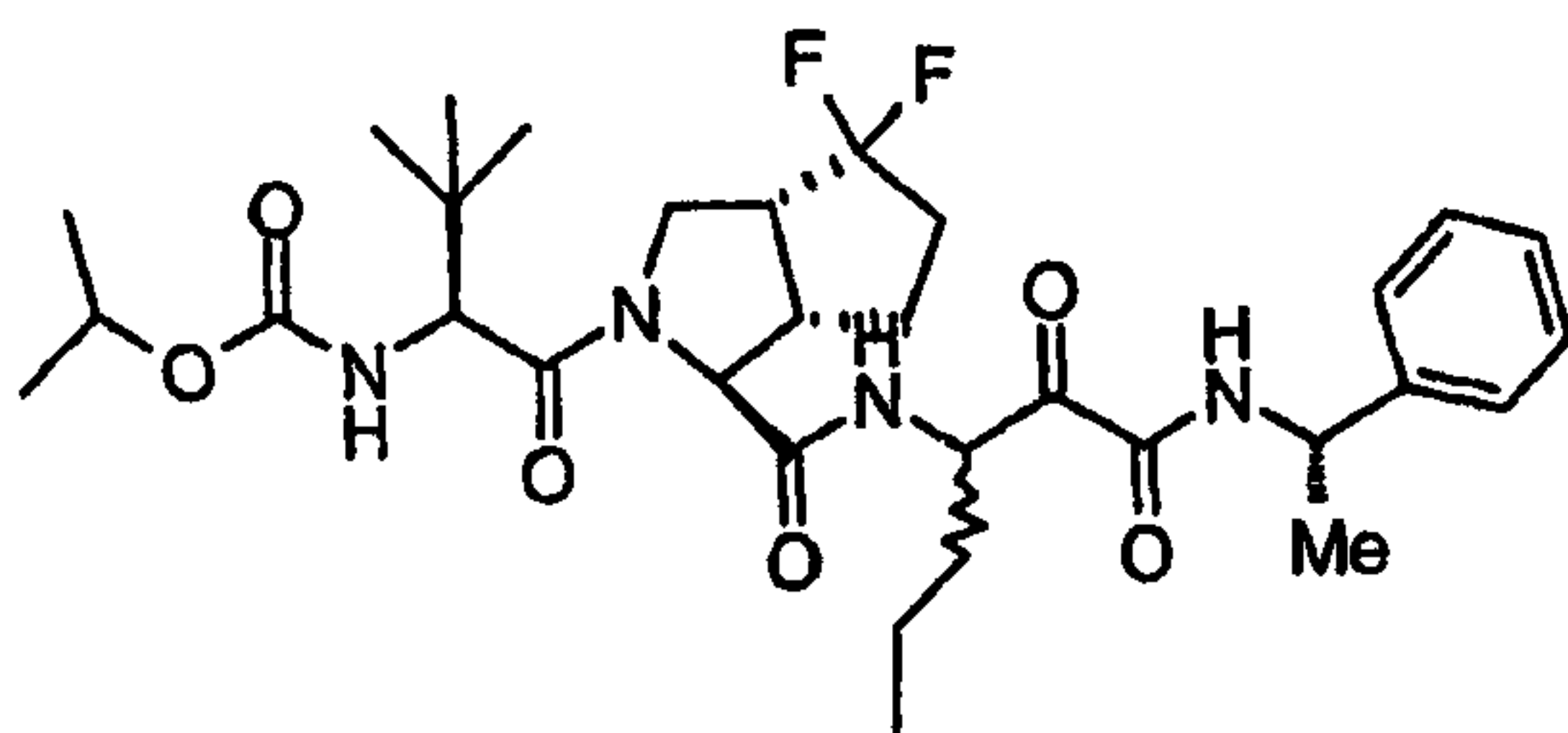
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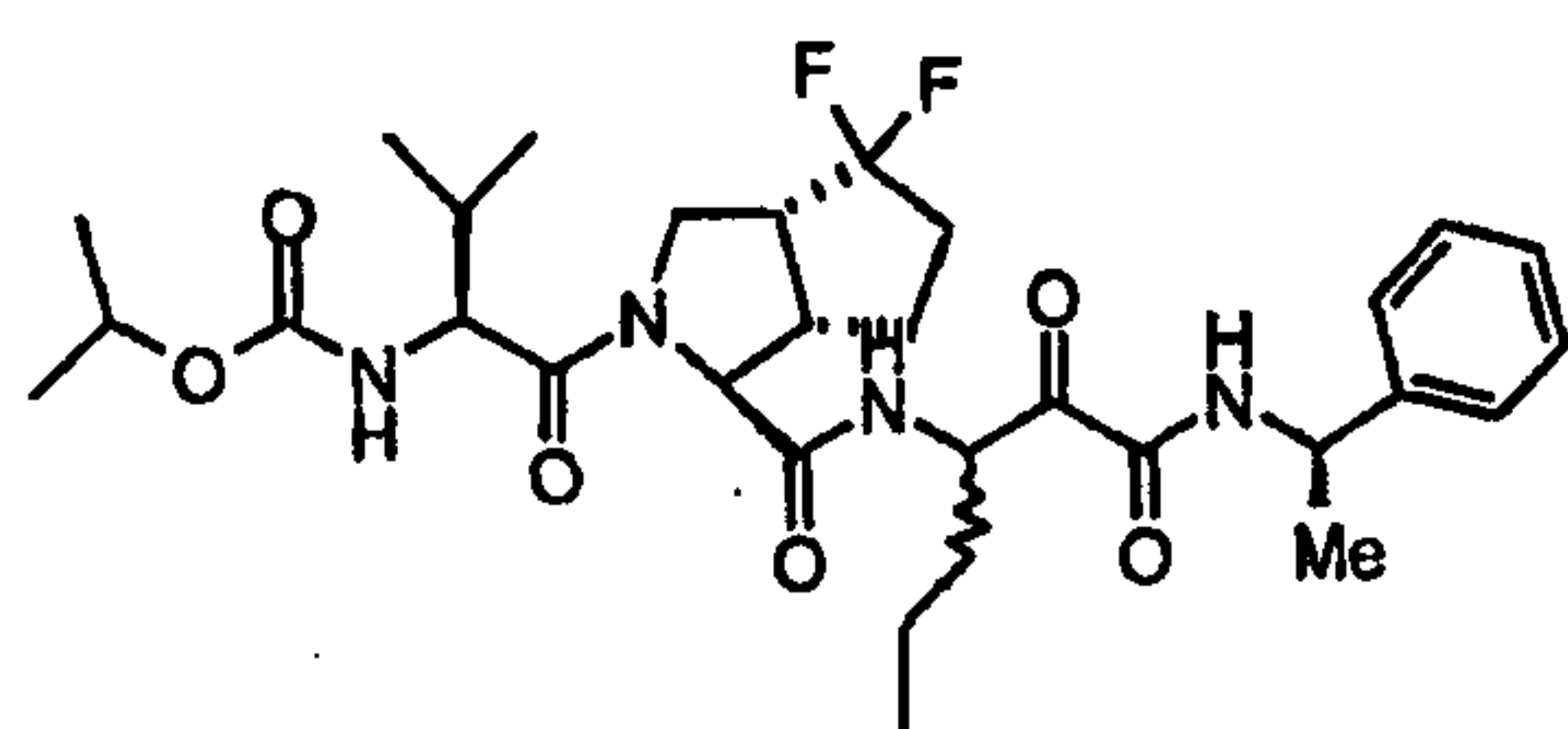
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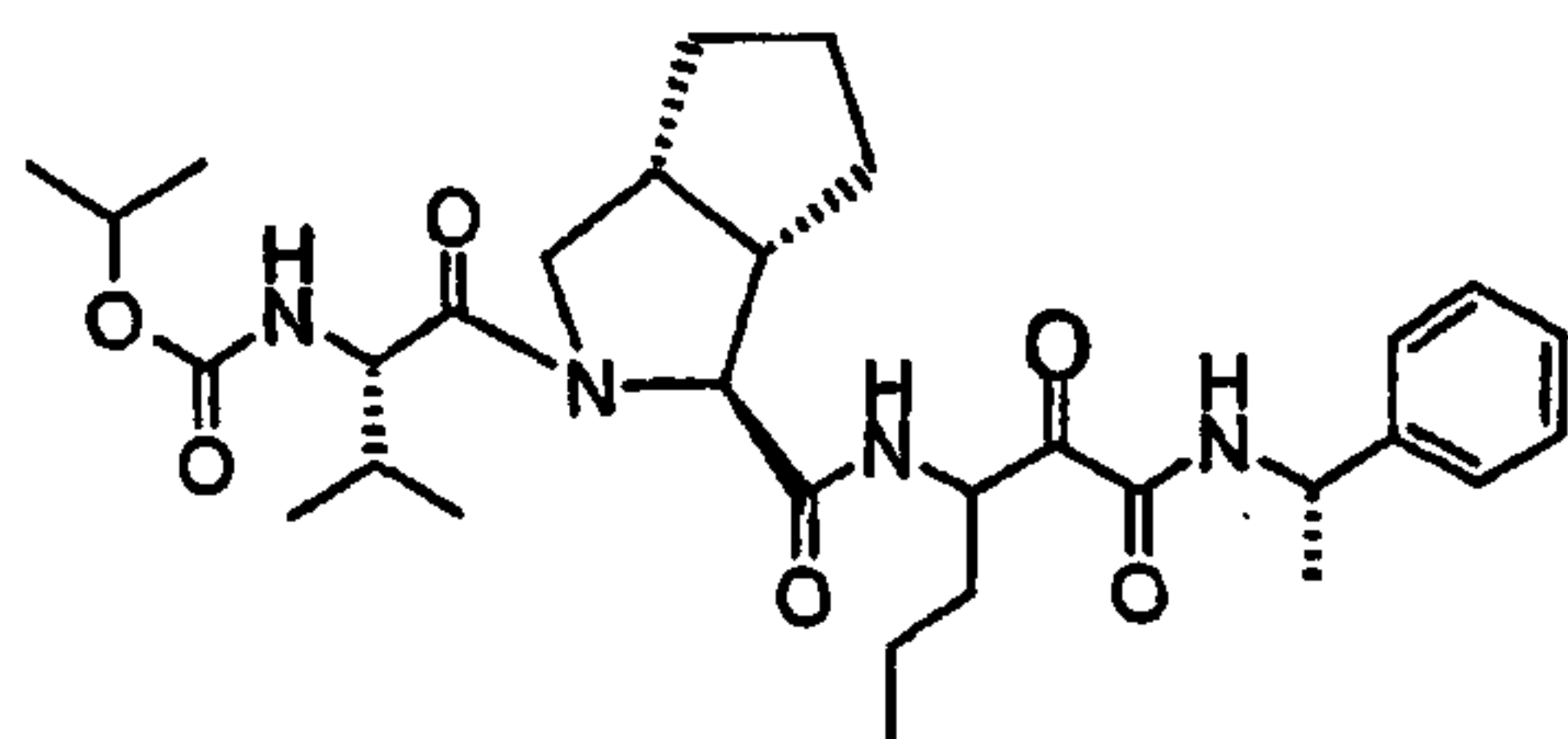
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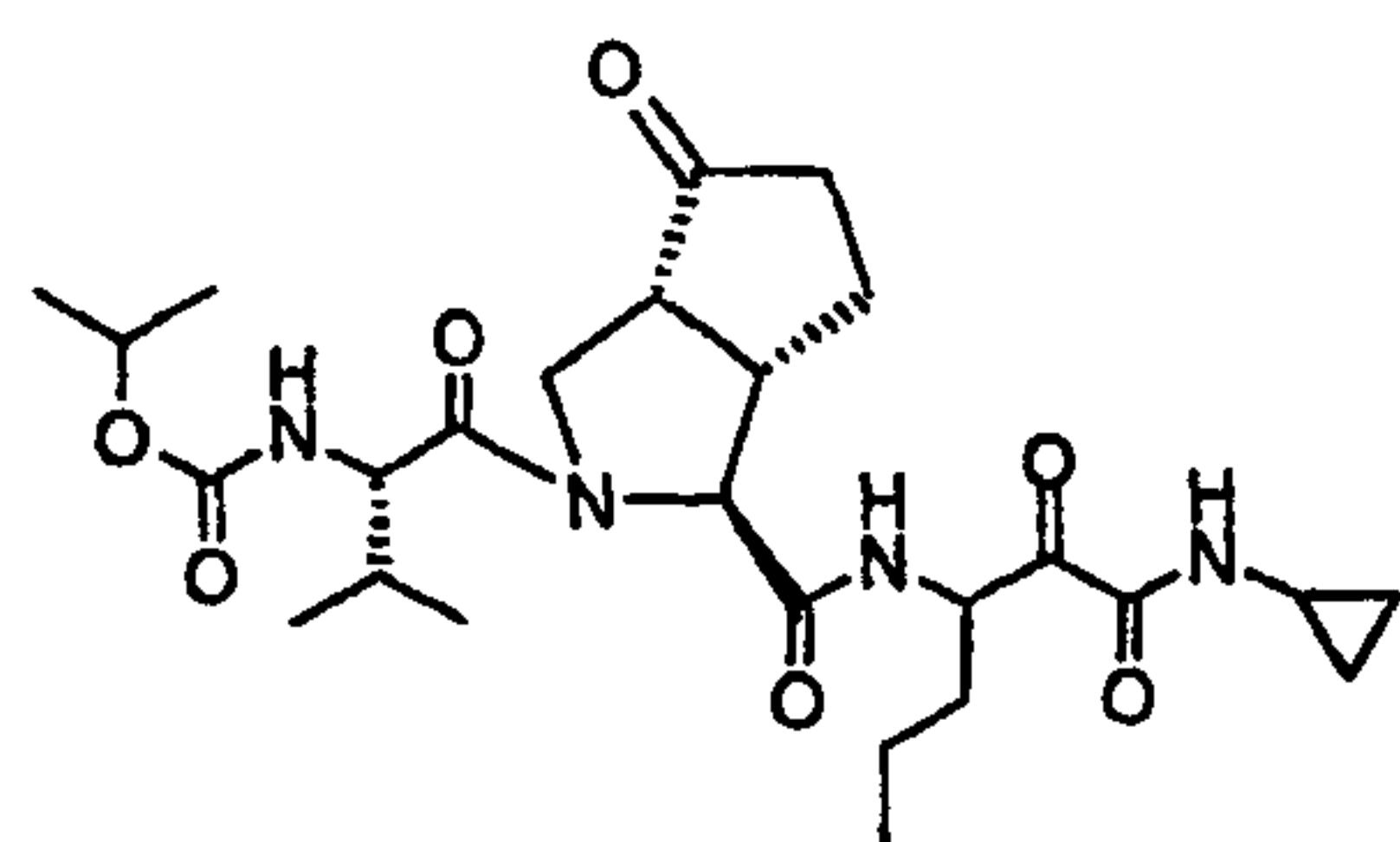
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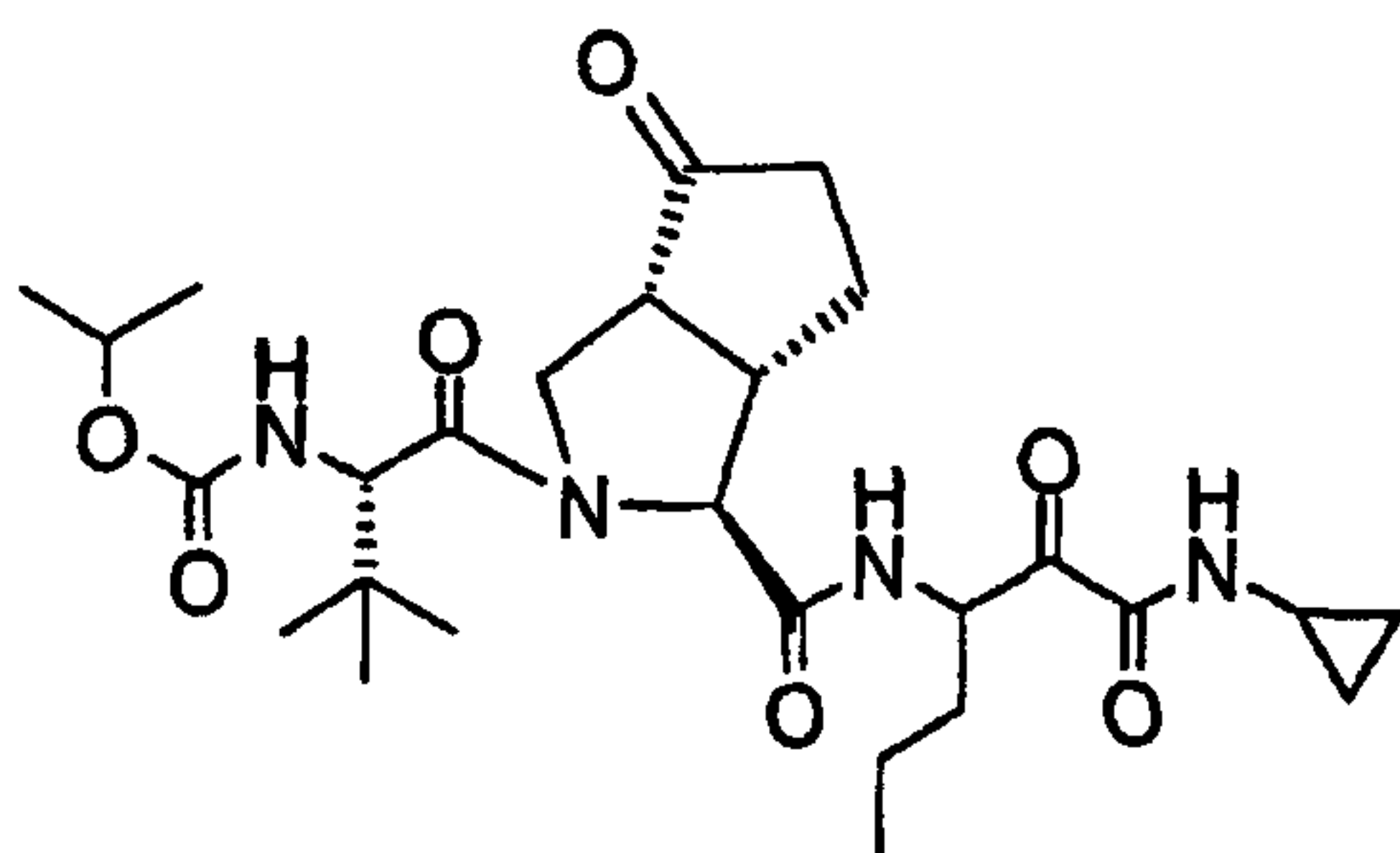
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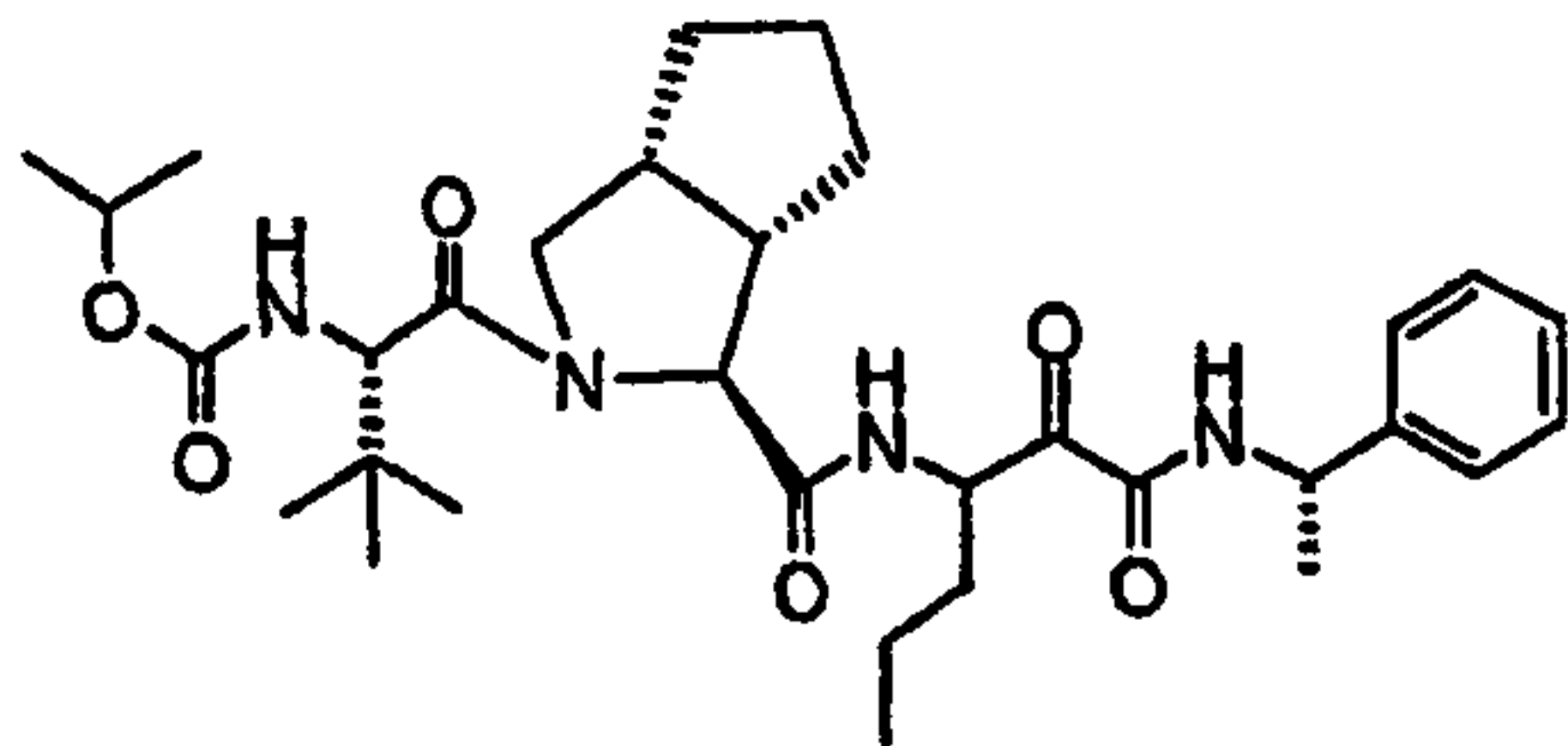


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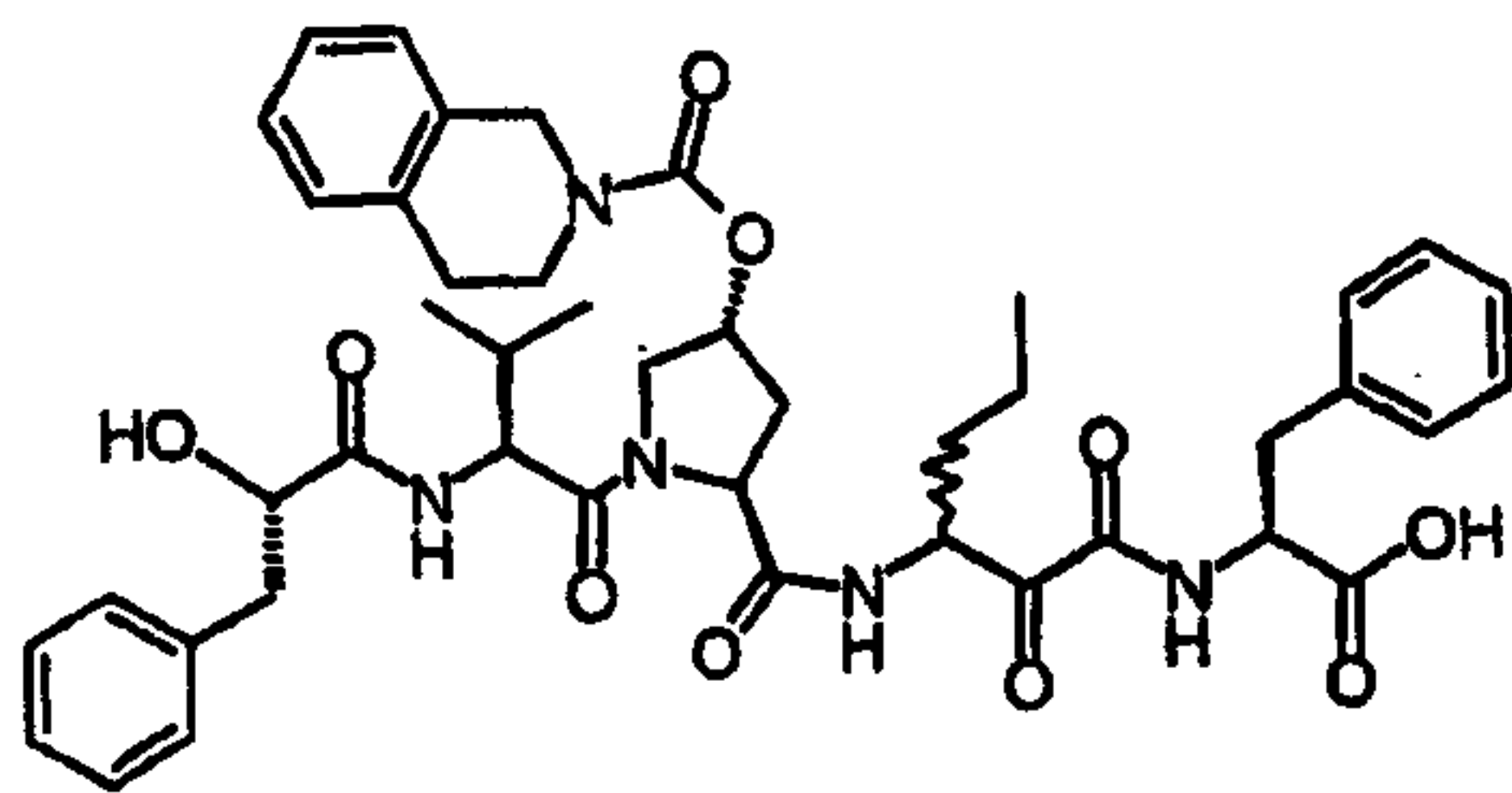
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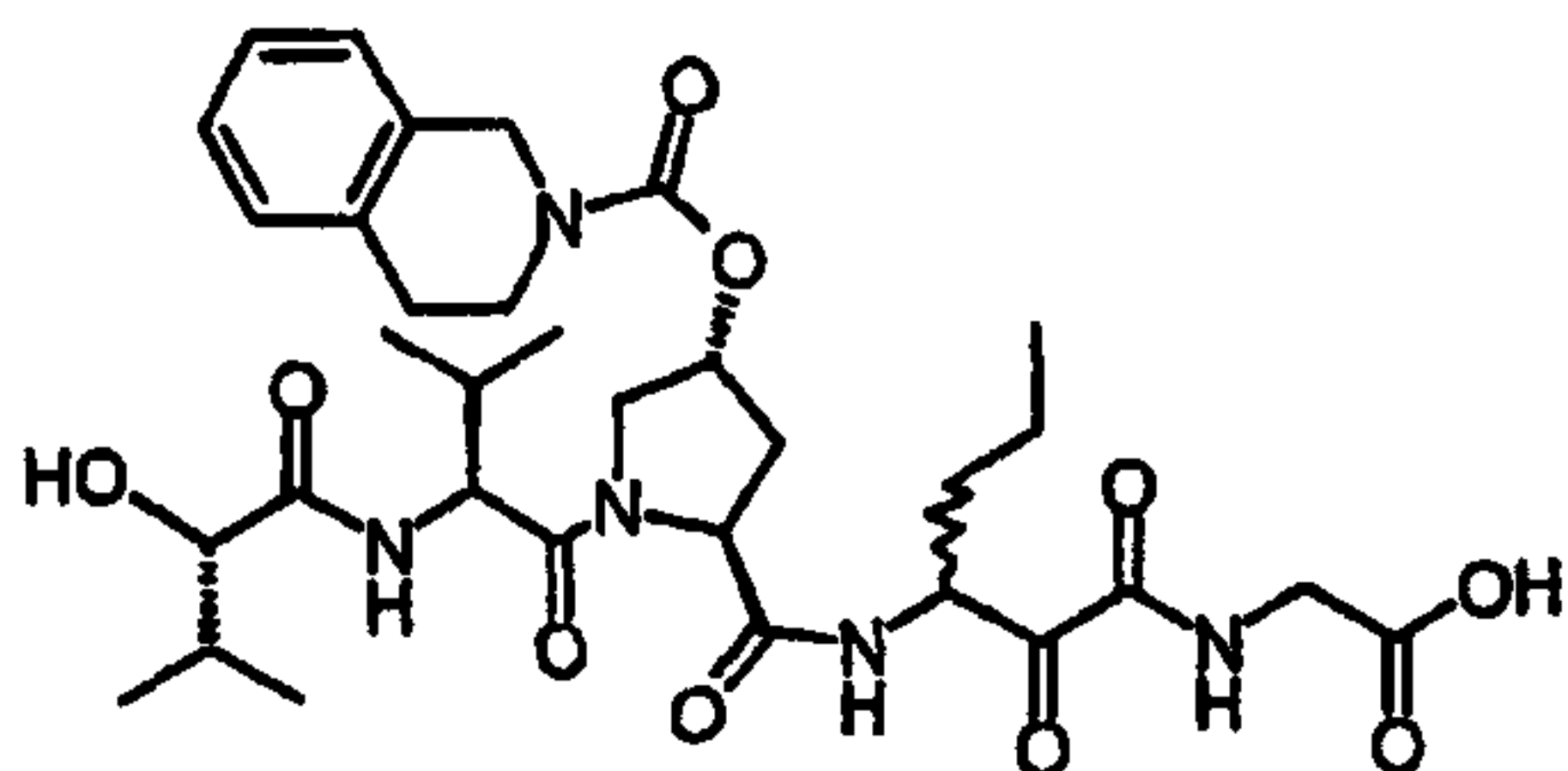
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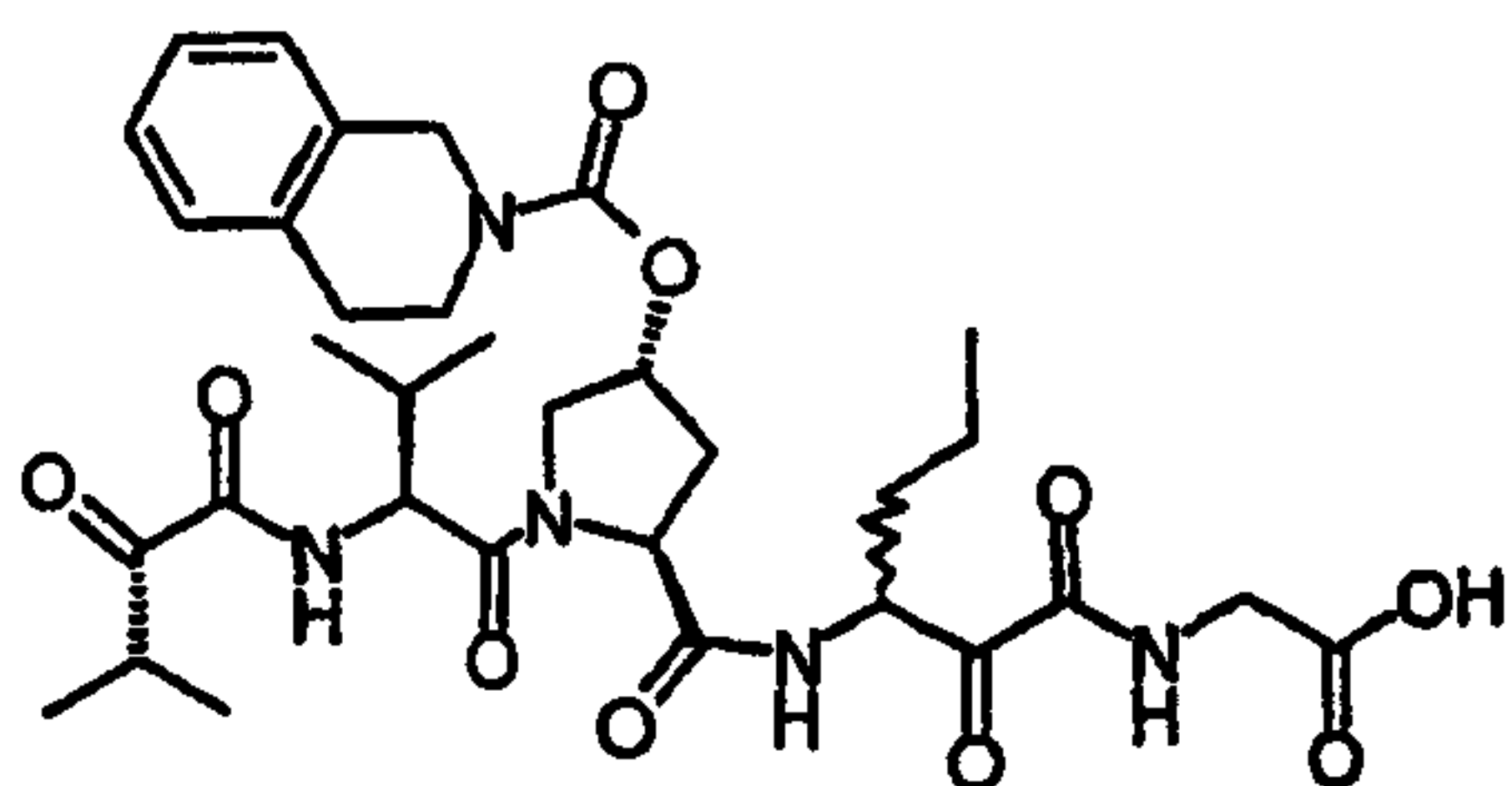
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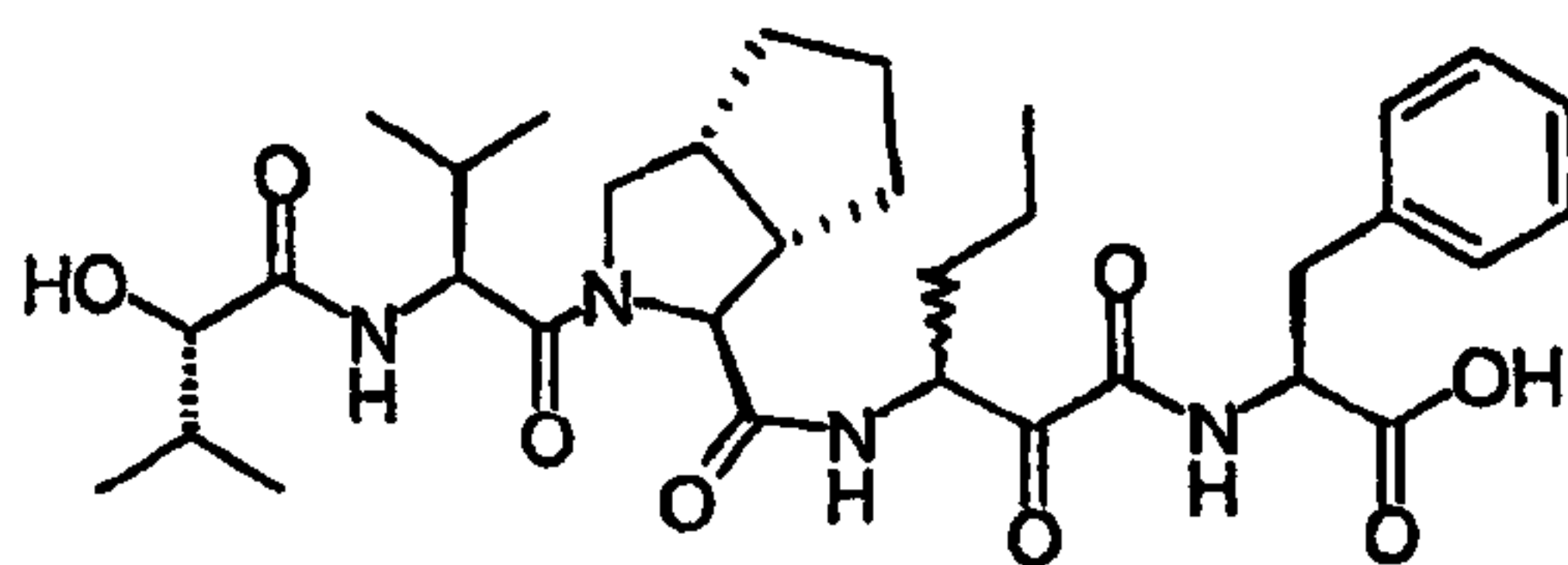
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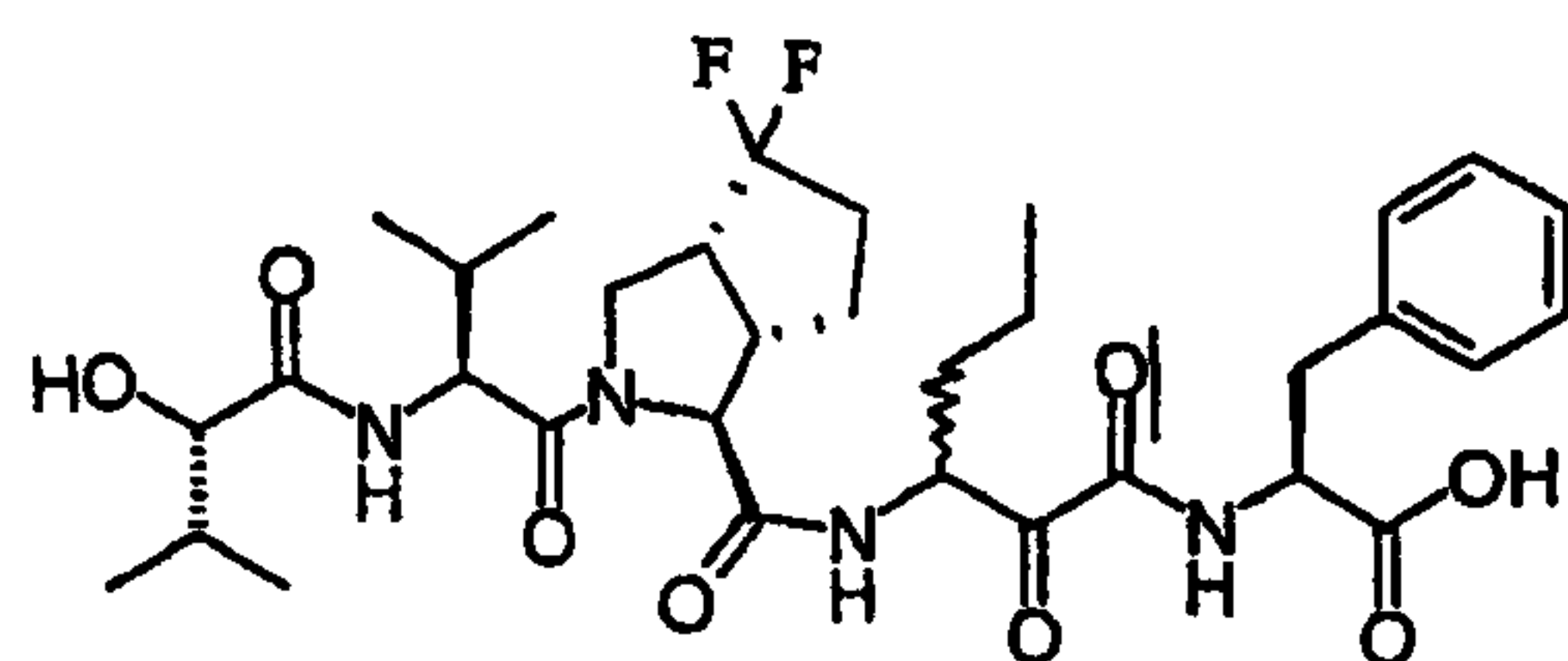


BJ,



BK,

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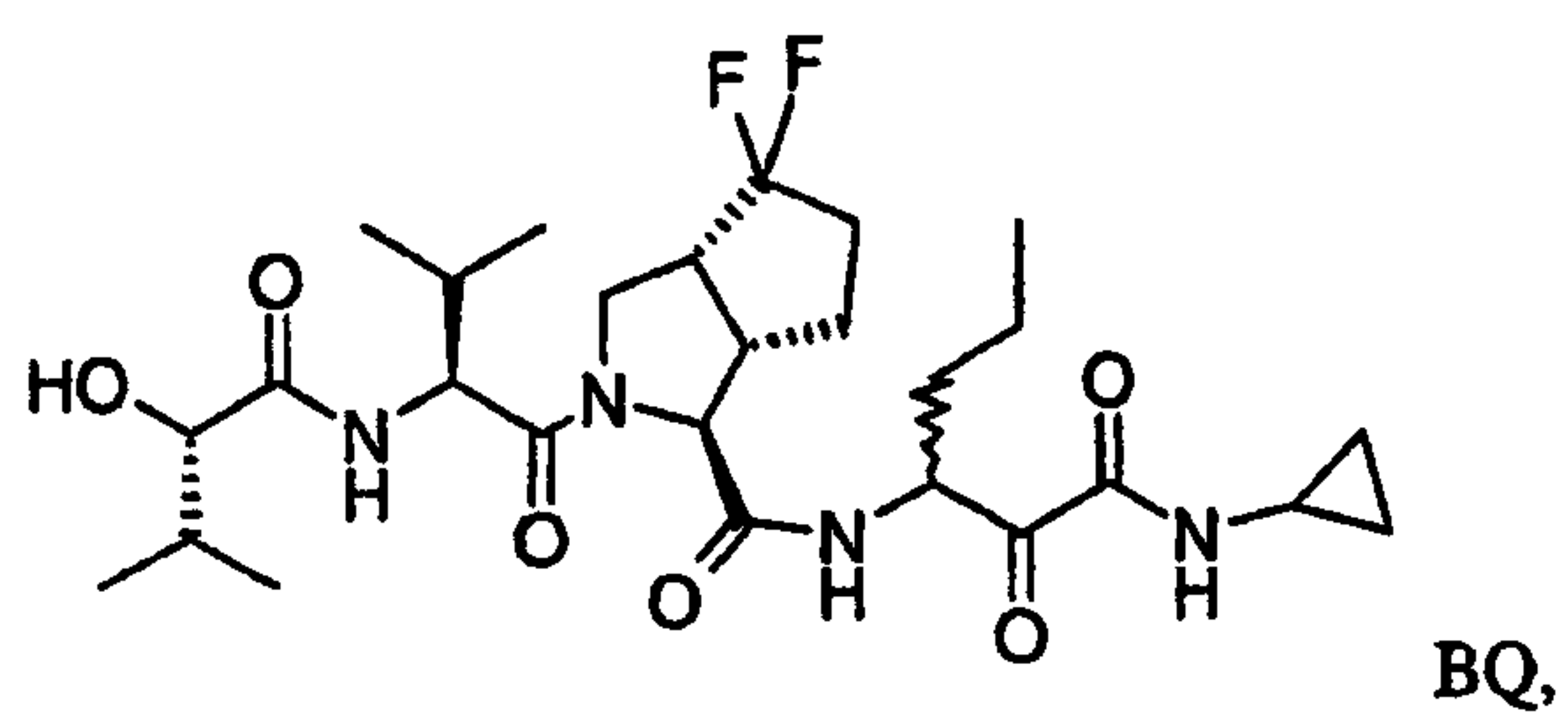
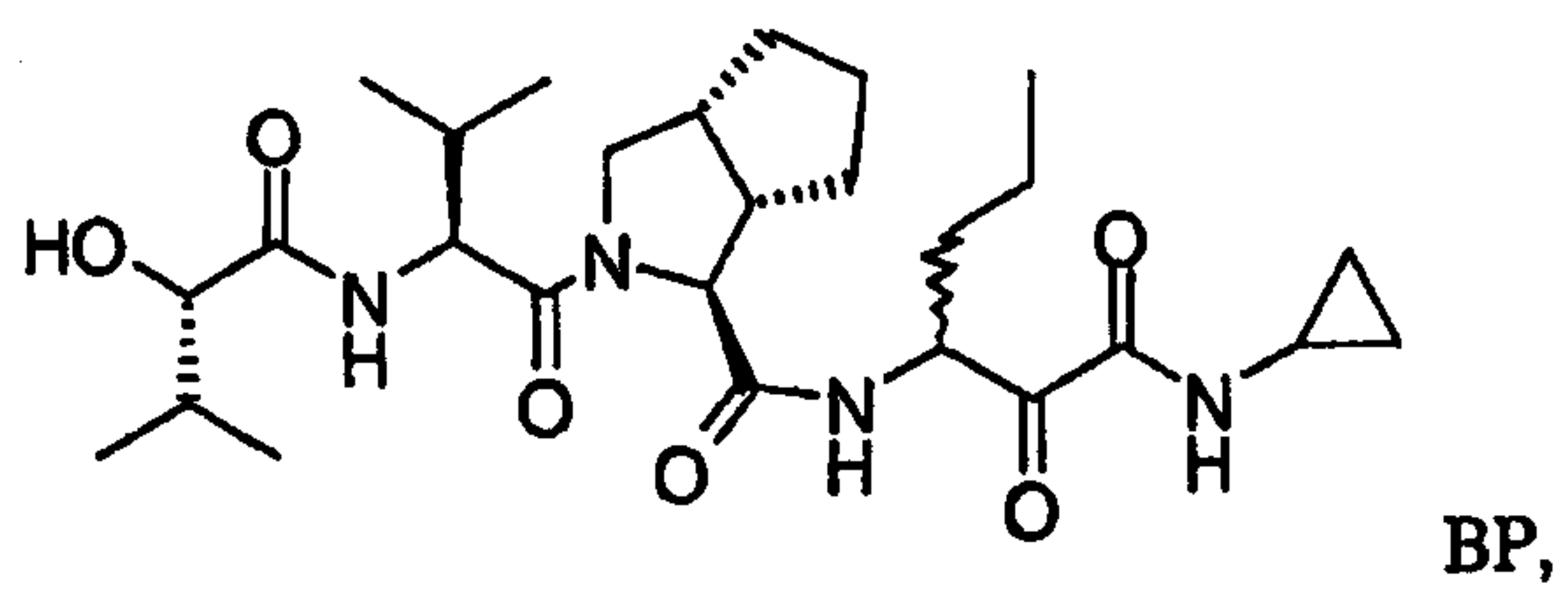
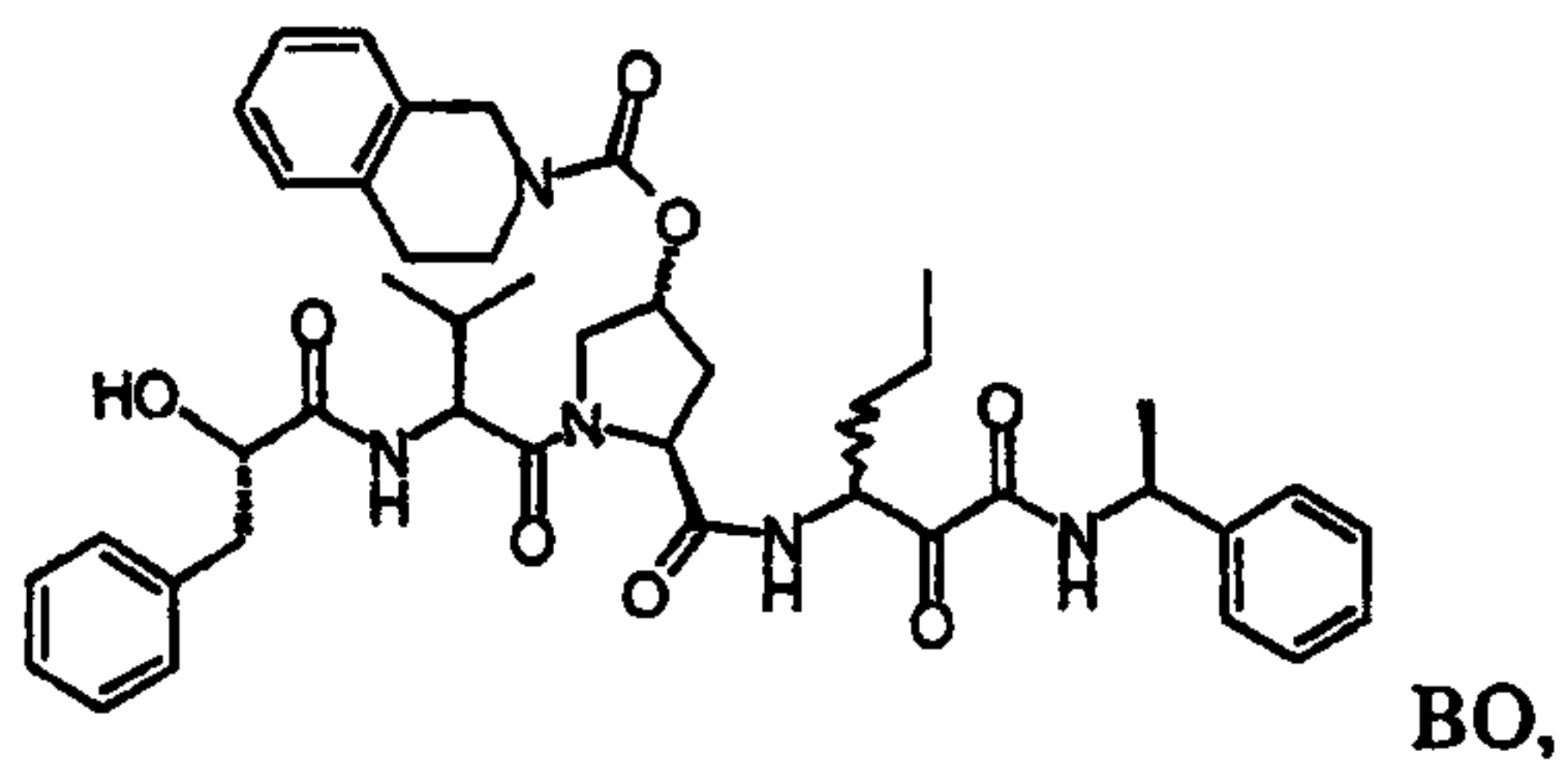
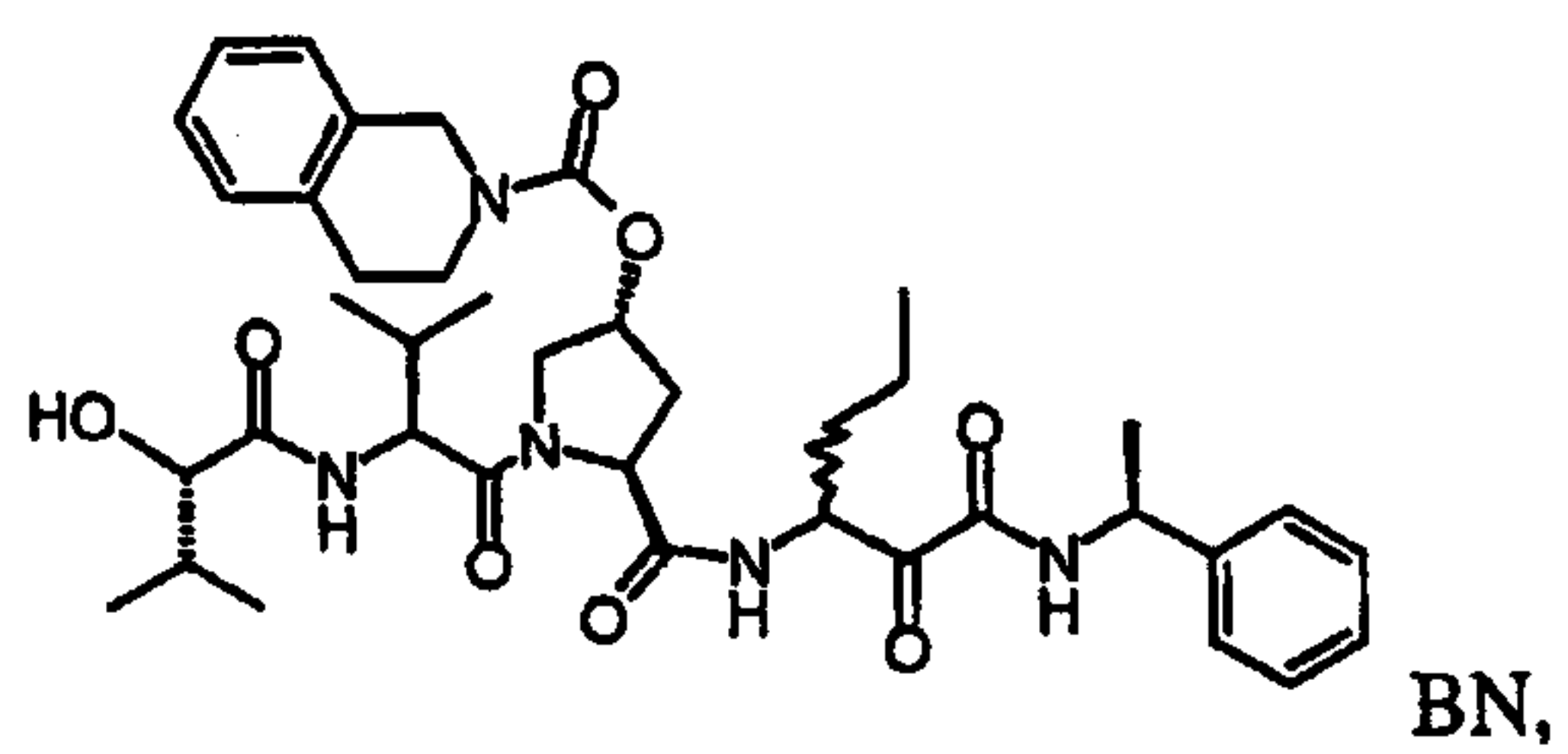
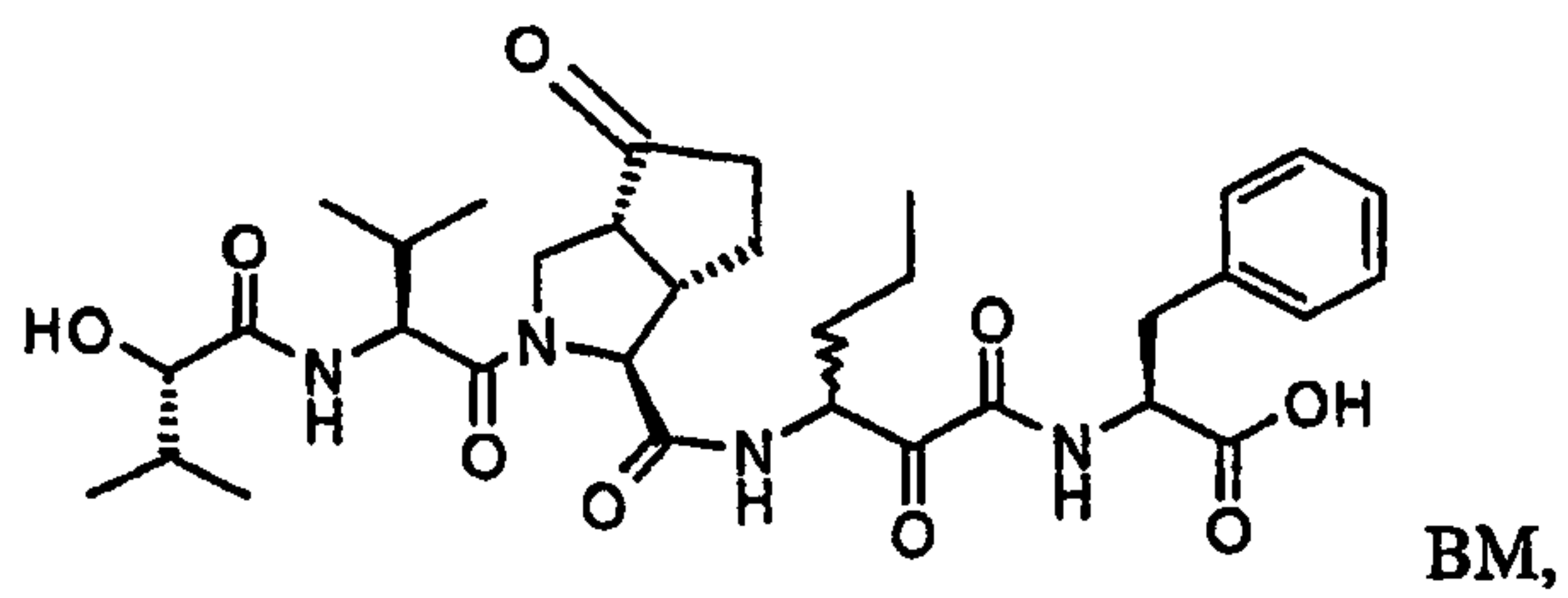


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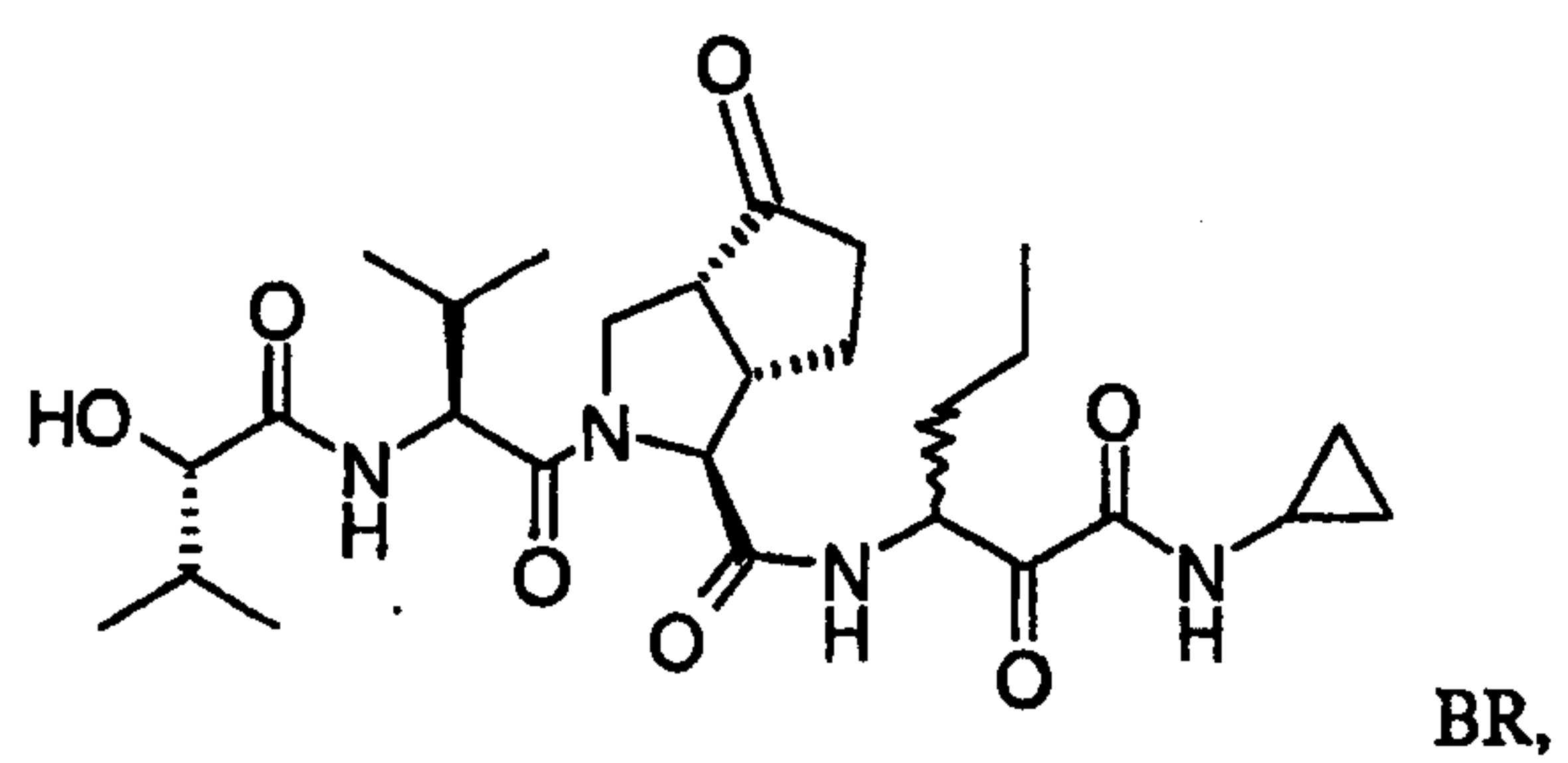
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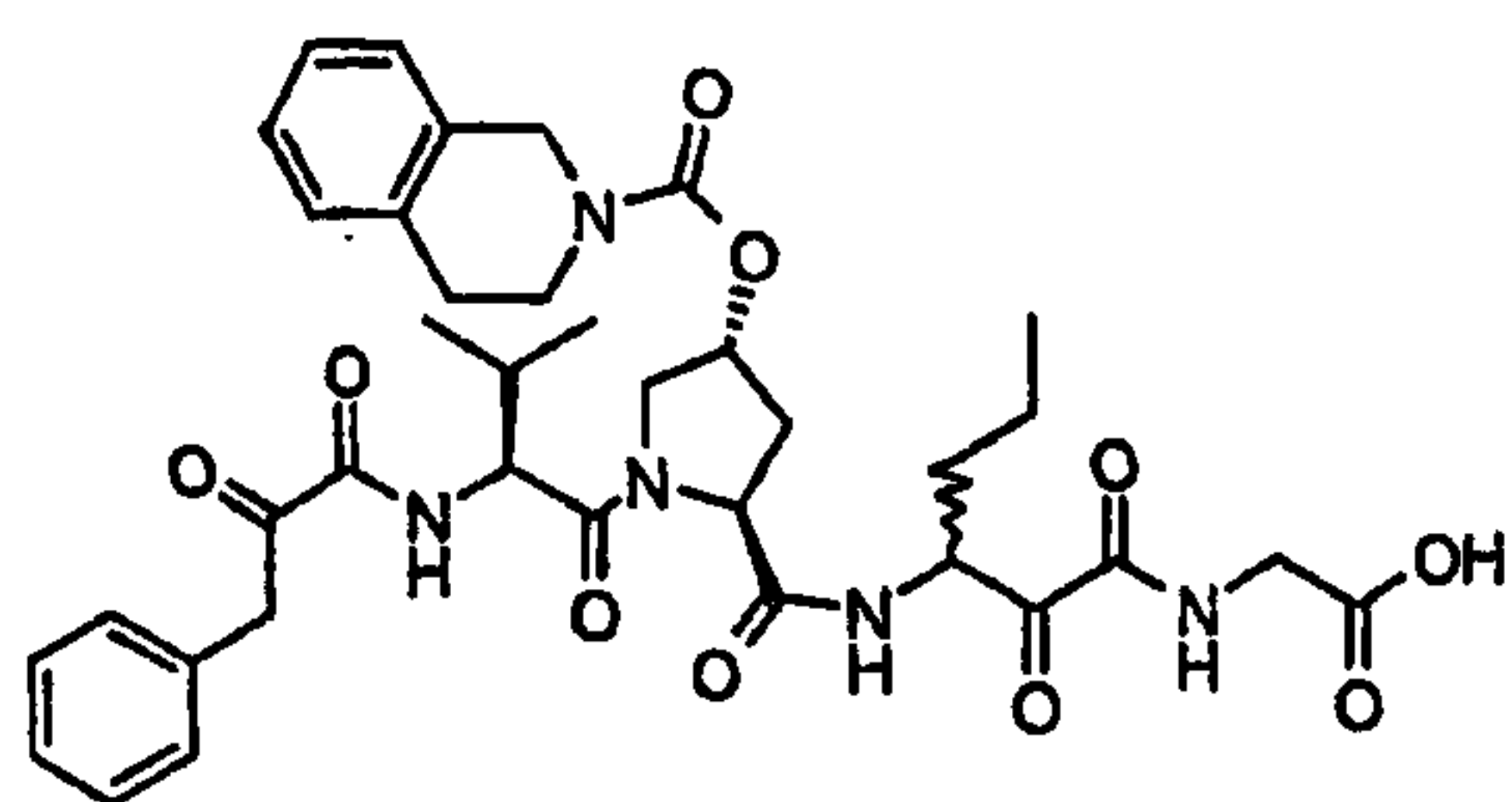
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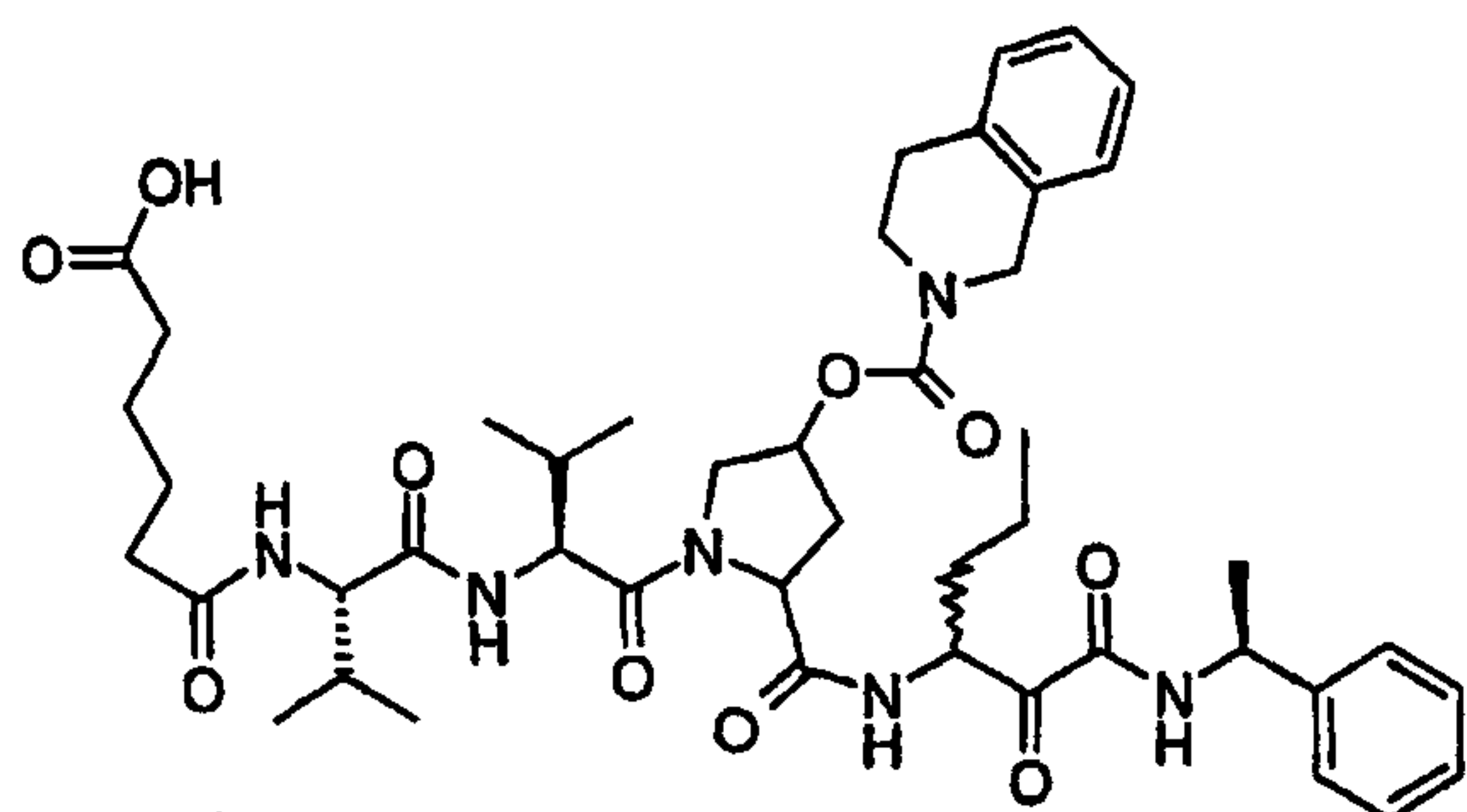
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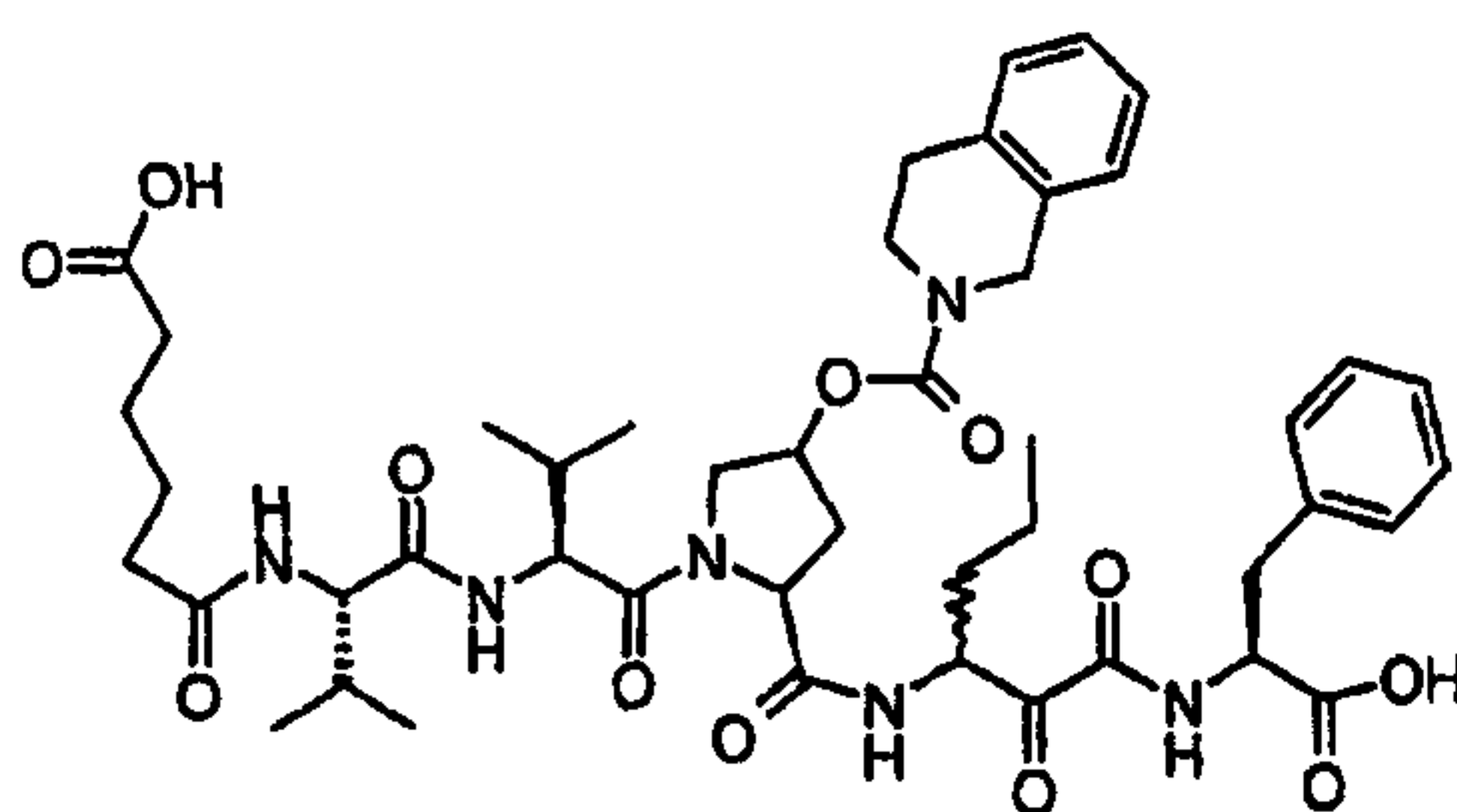
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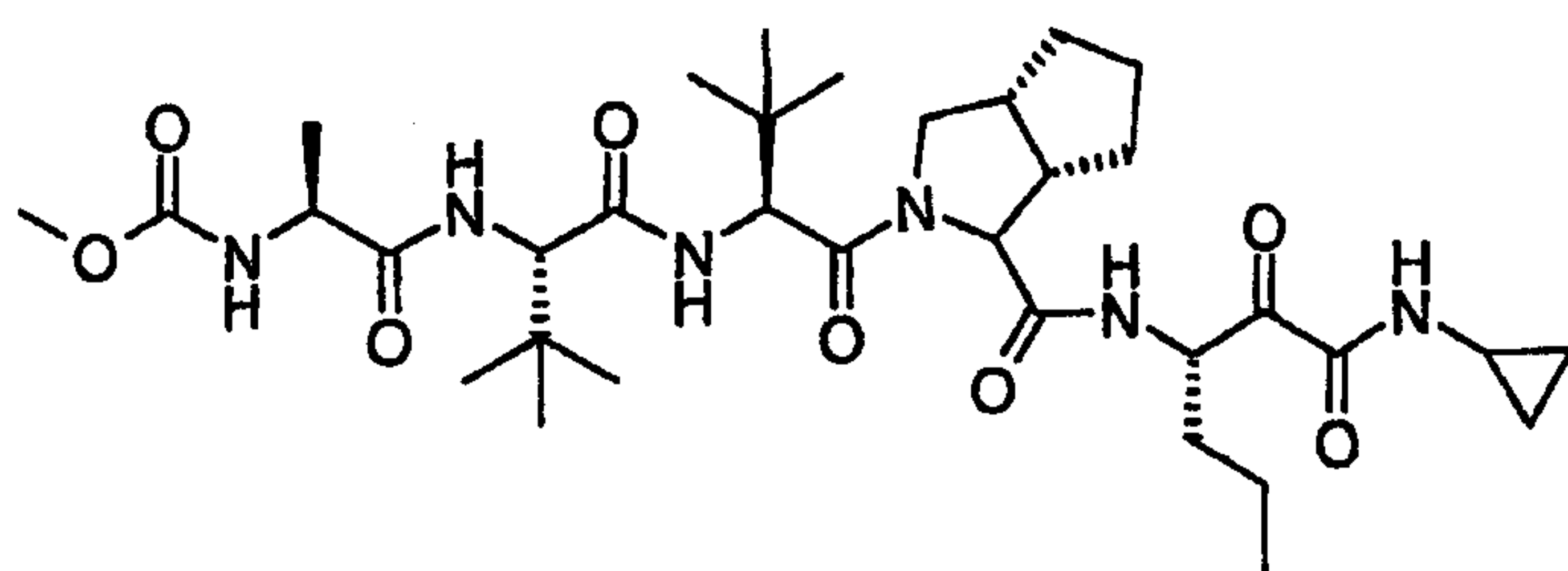
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BT,

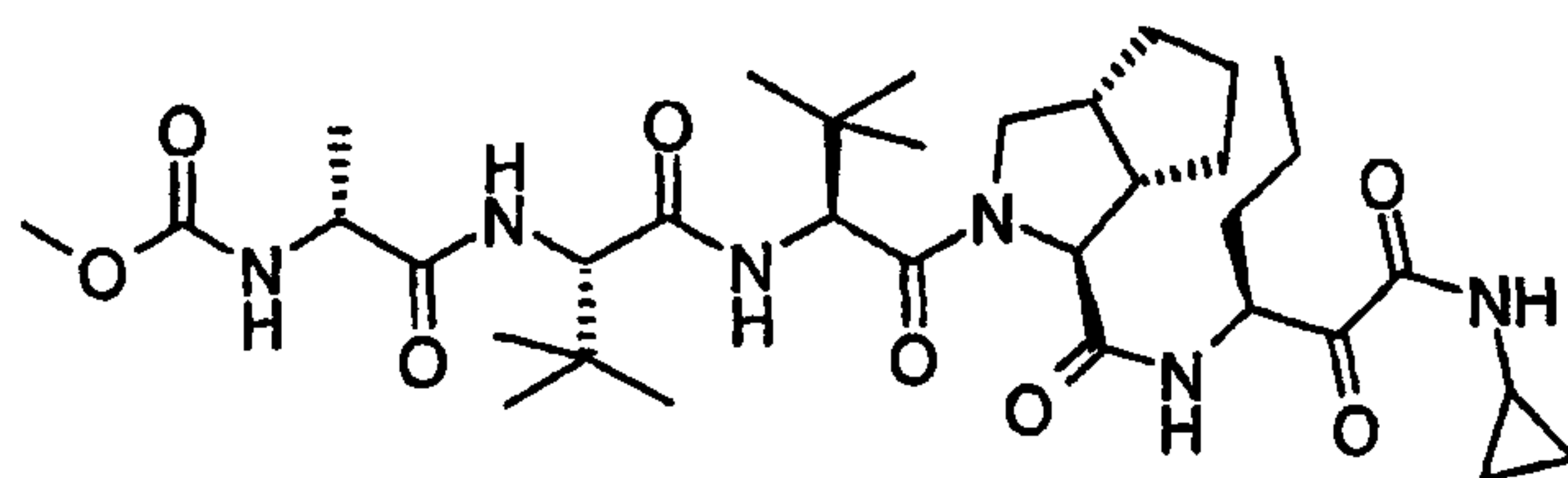


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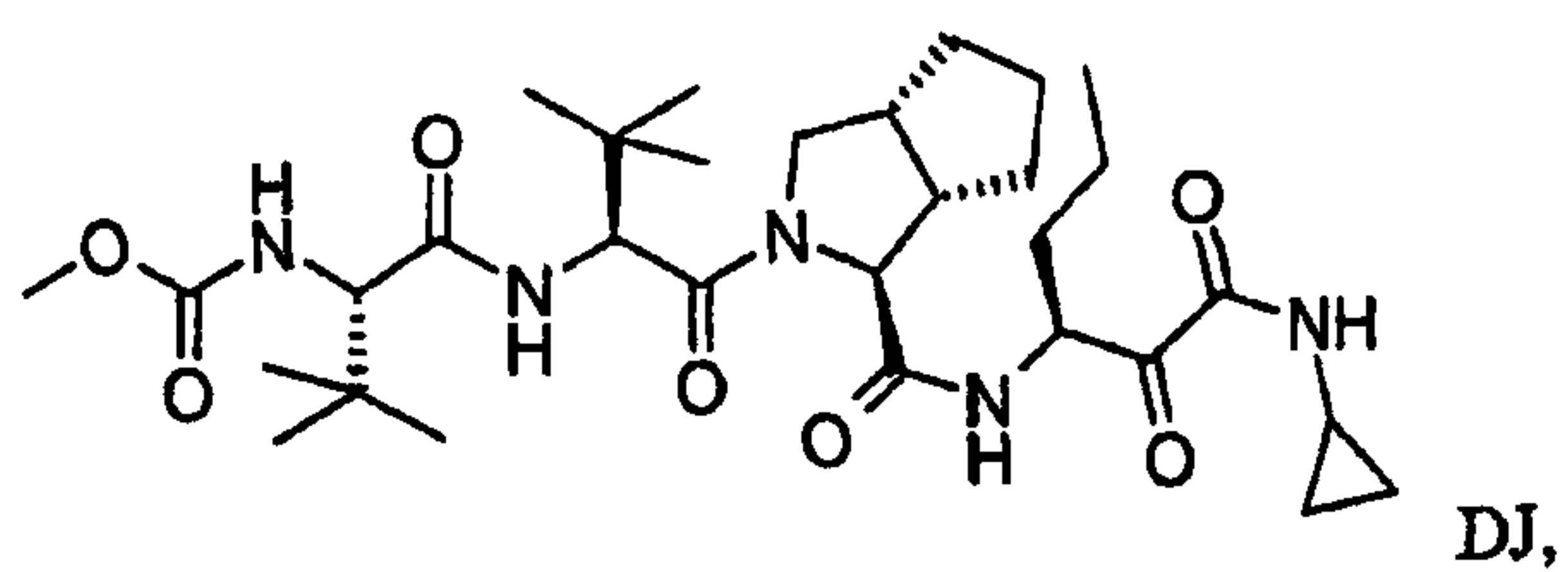
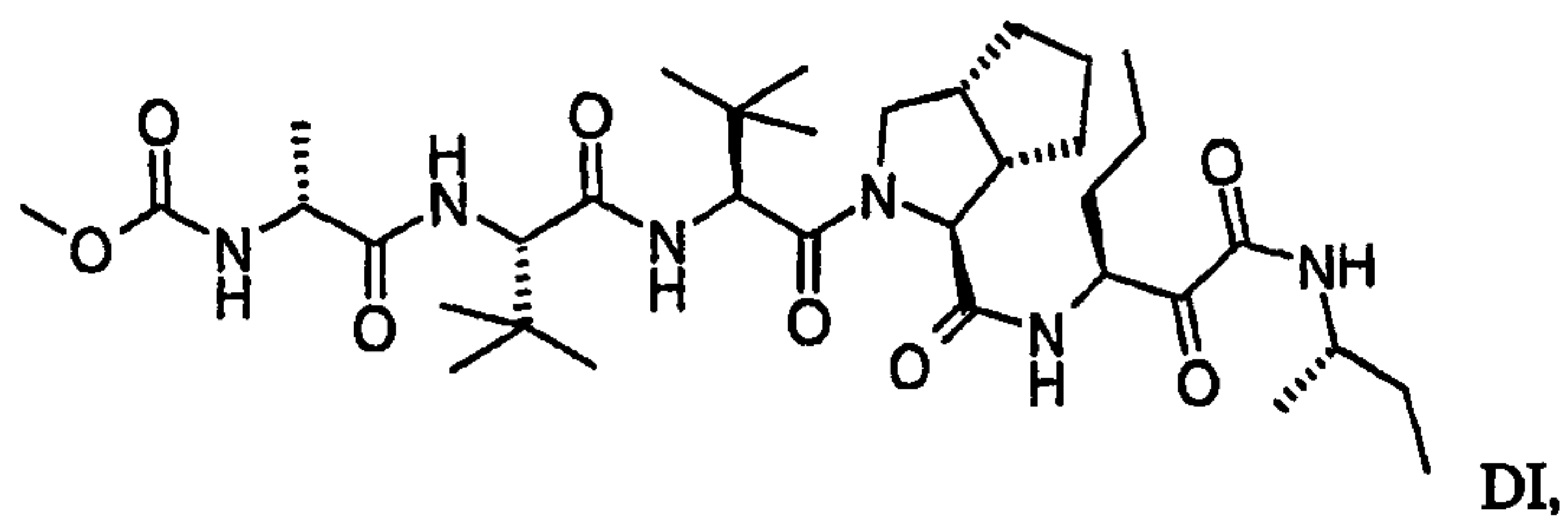


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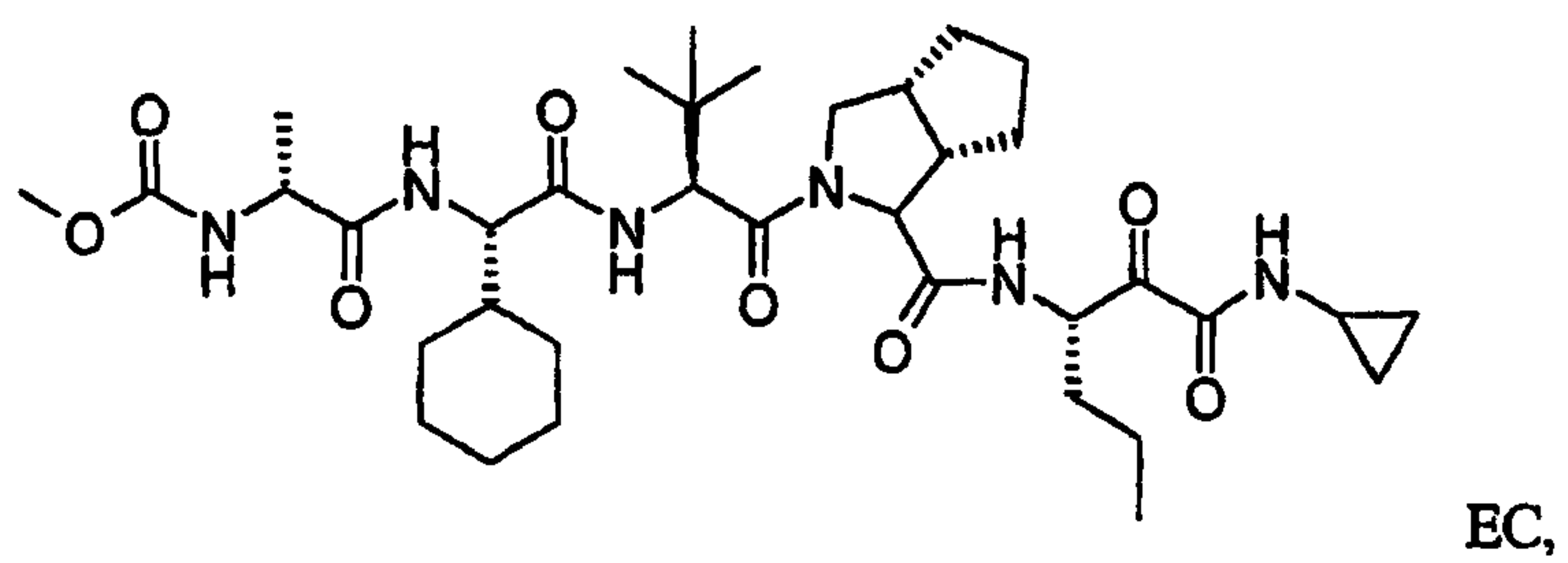
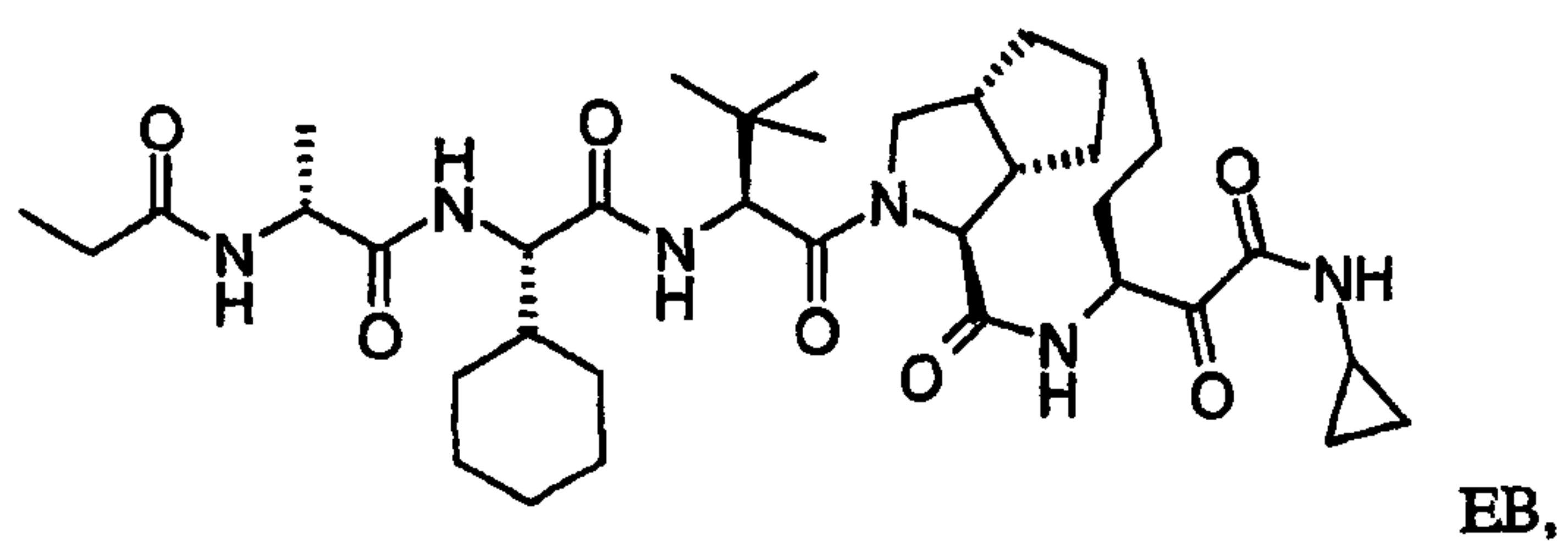
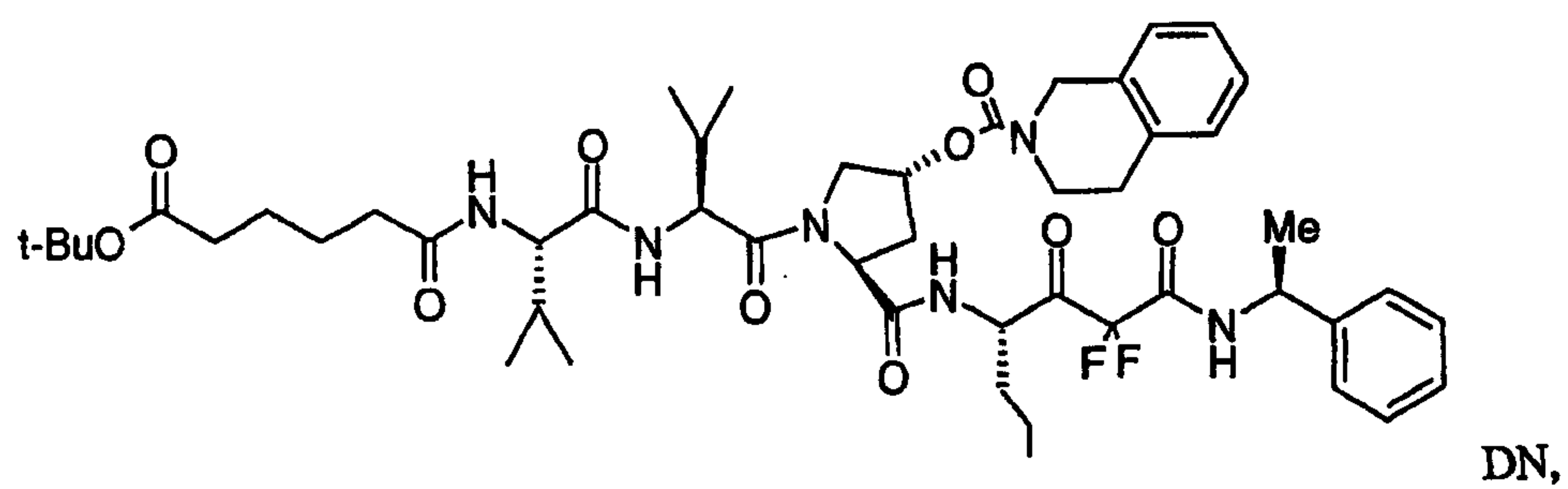
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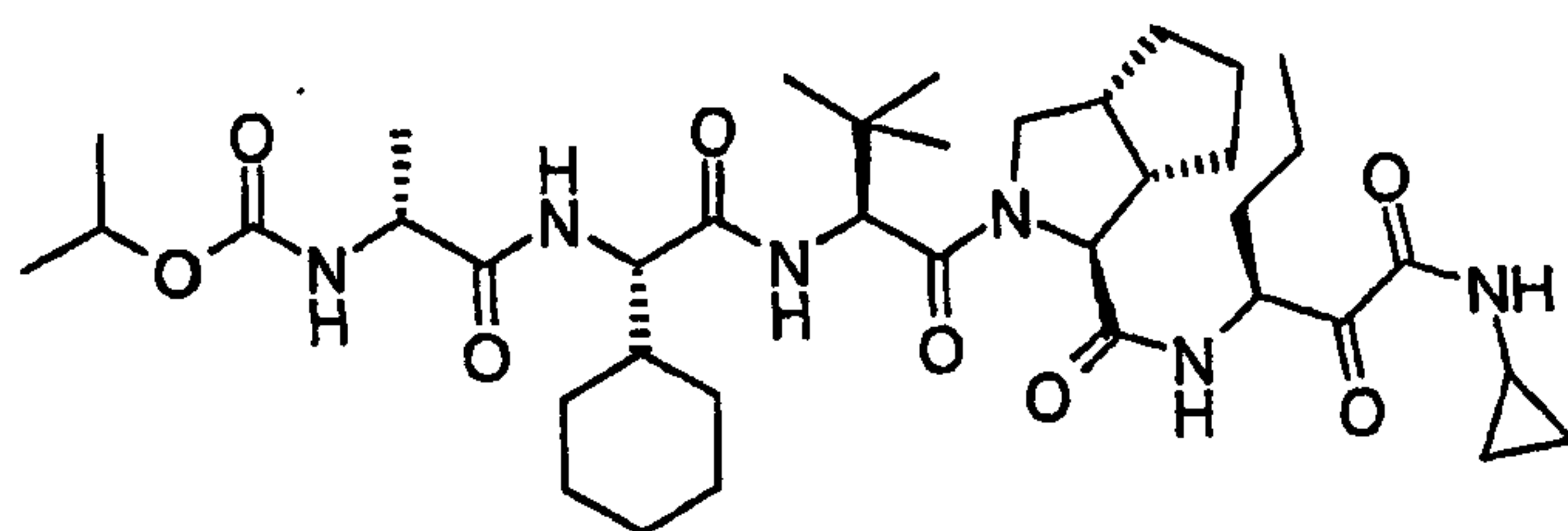
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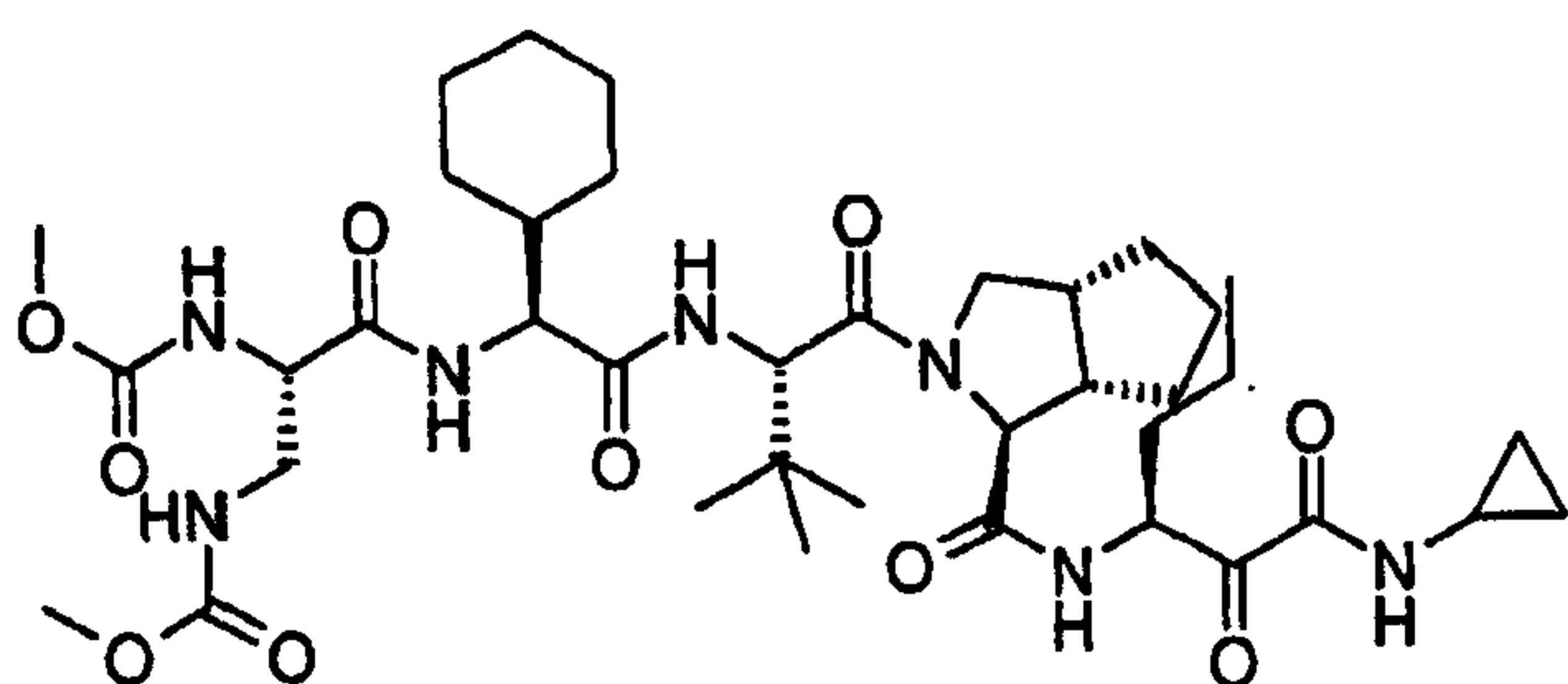
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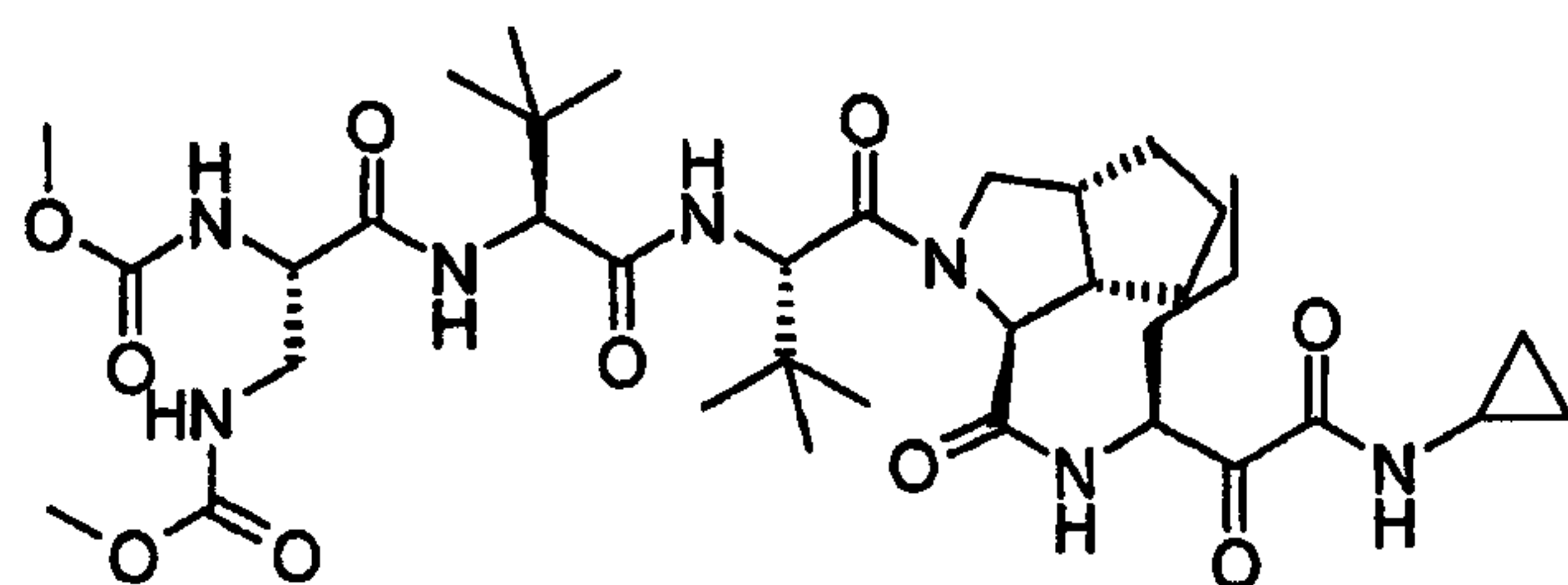
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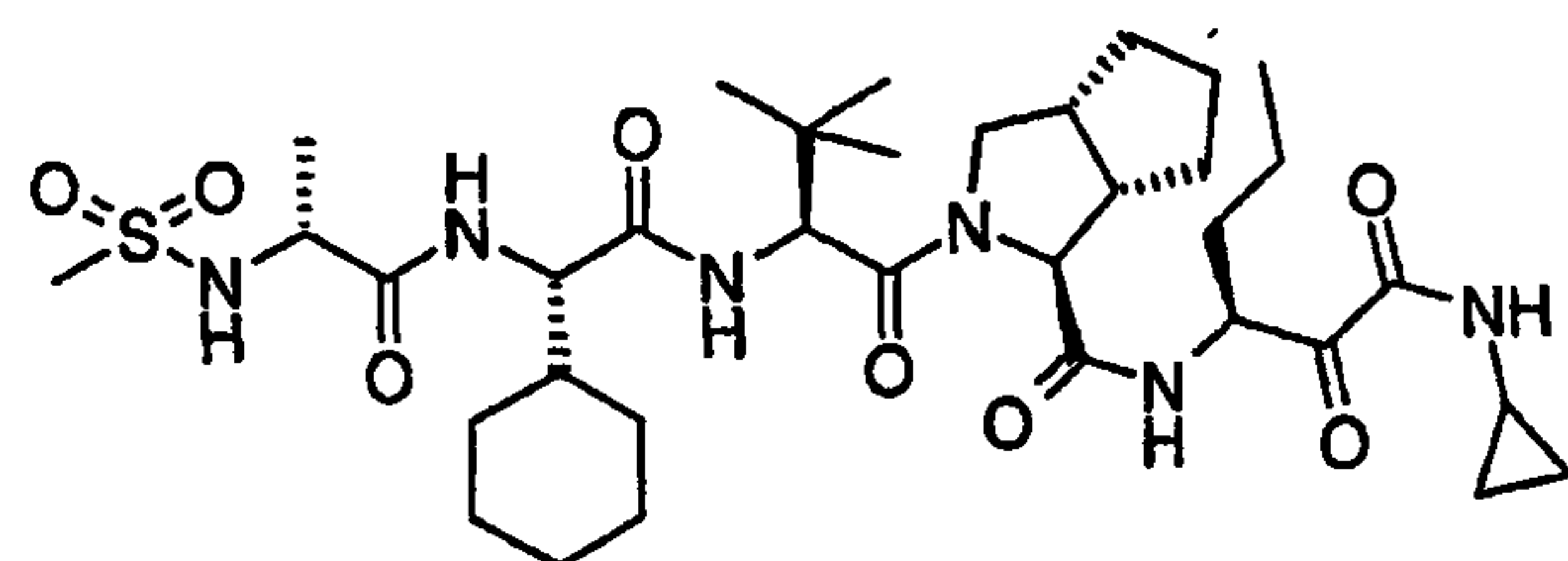
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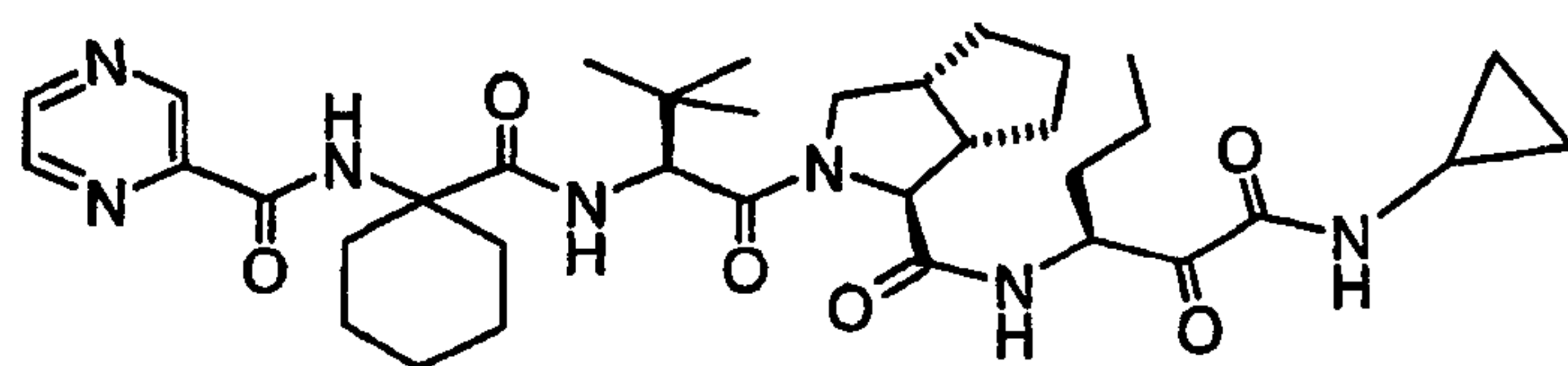
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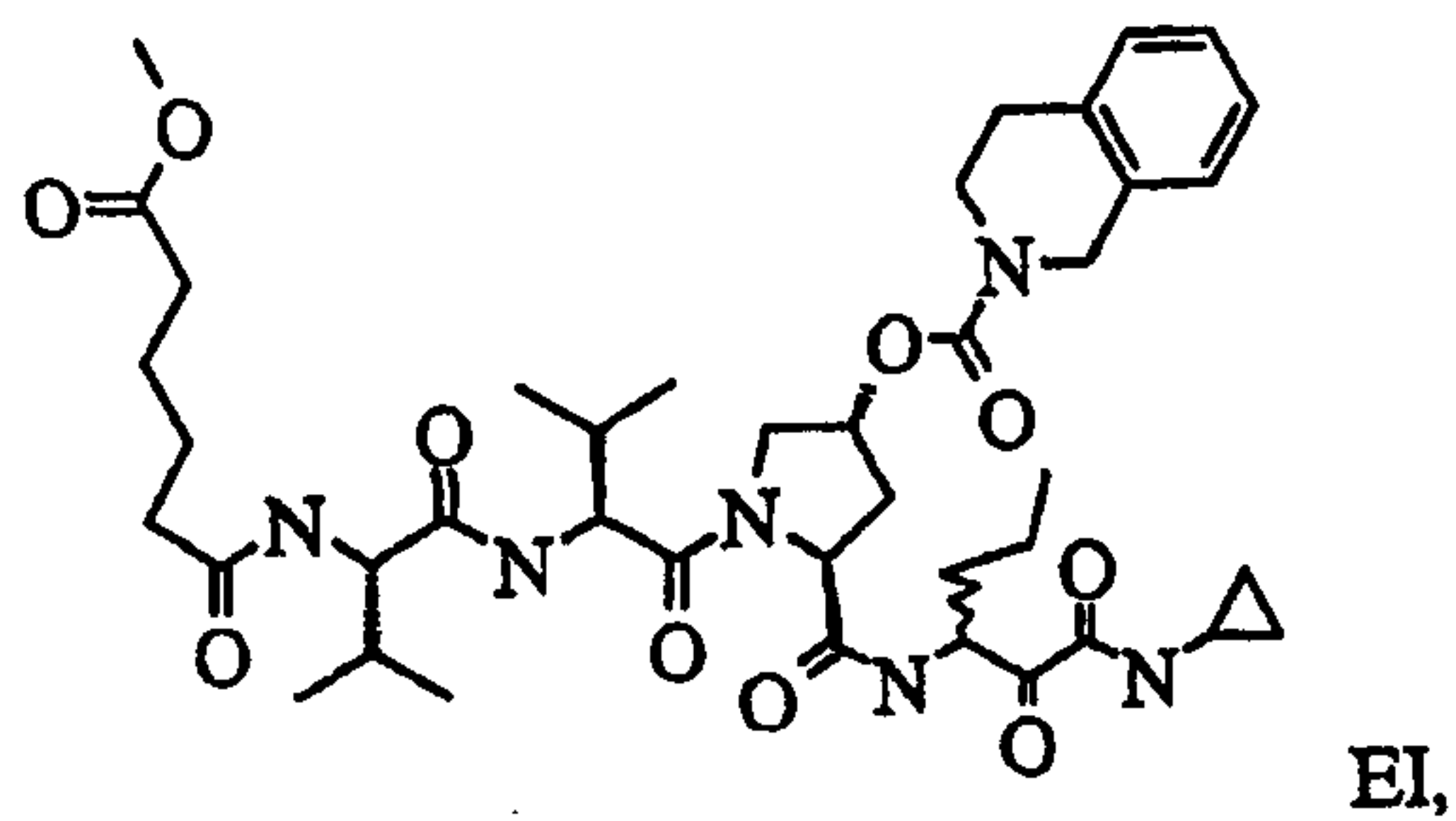


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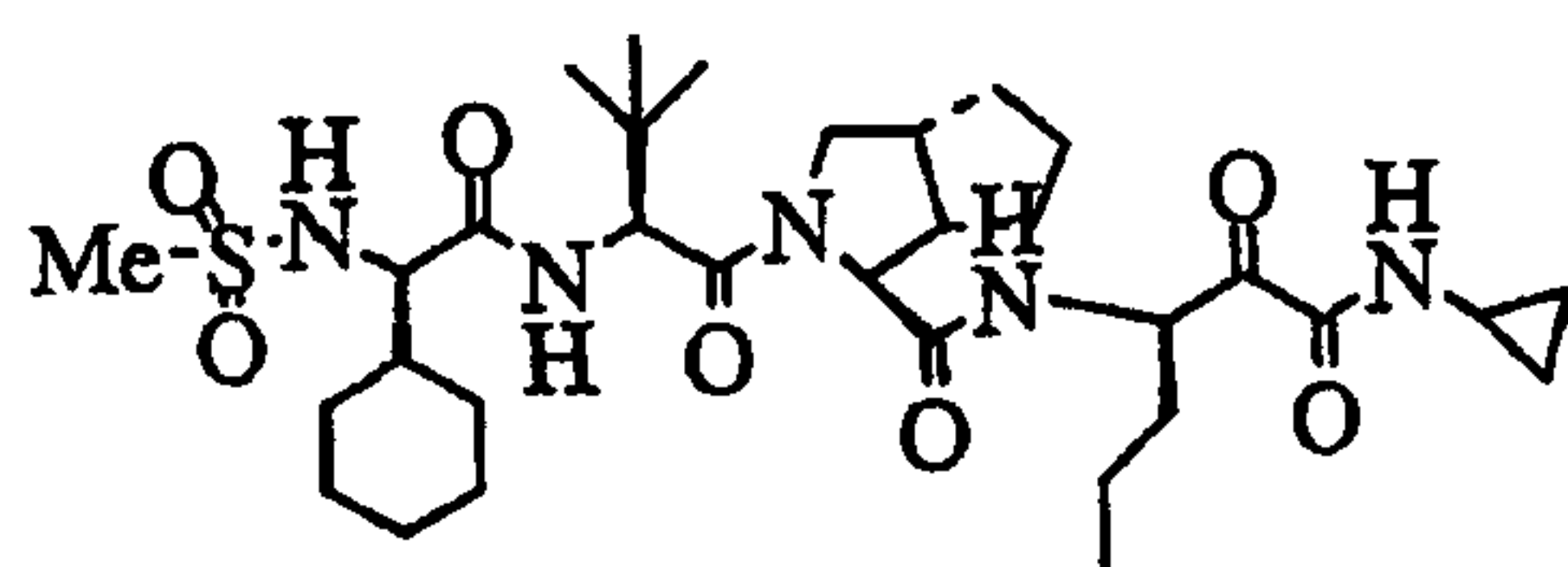
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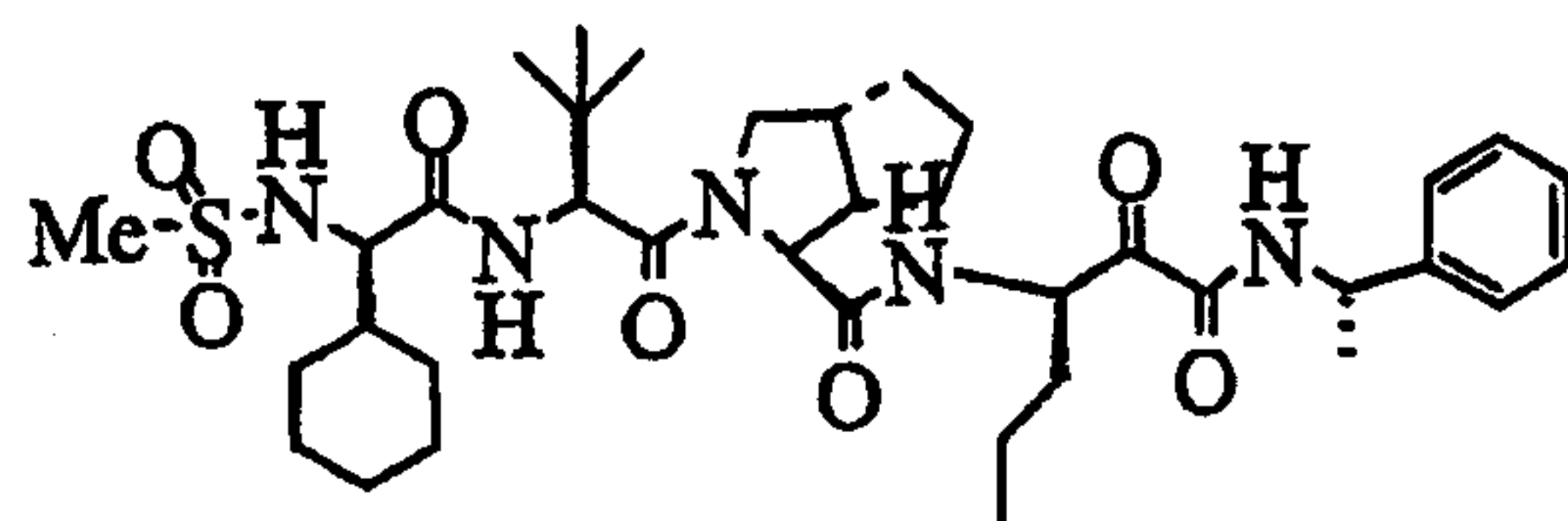


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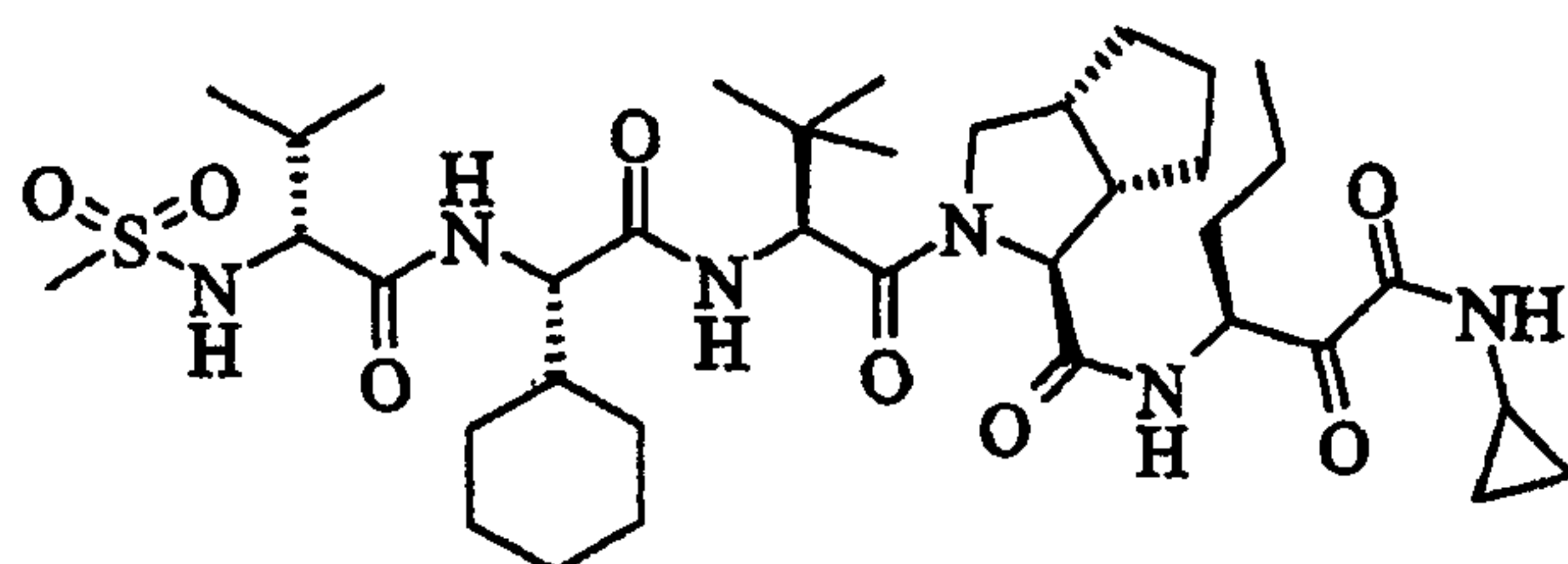


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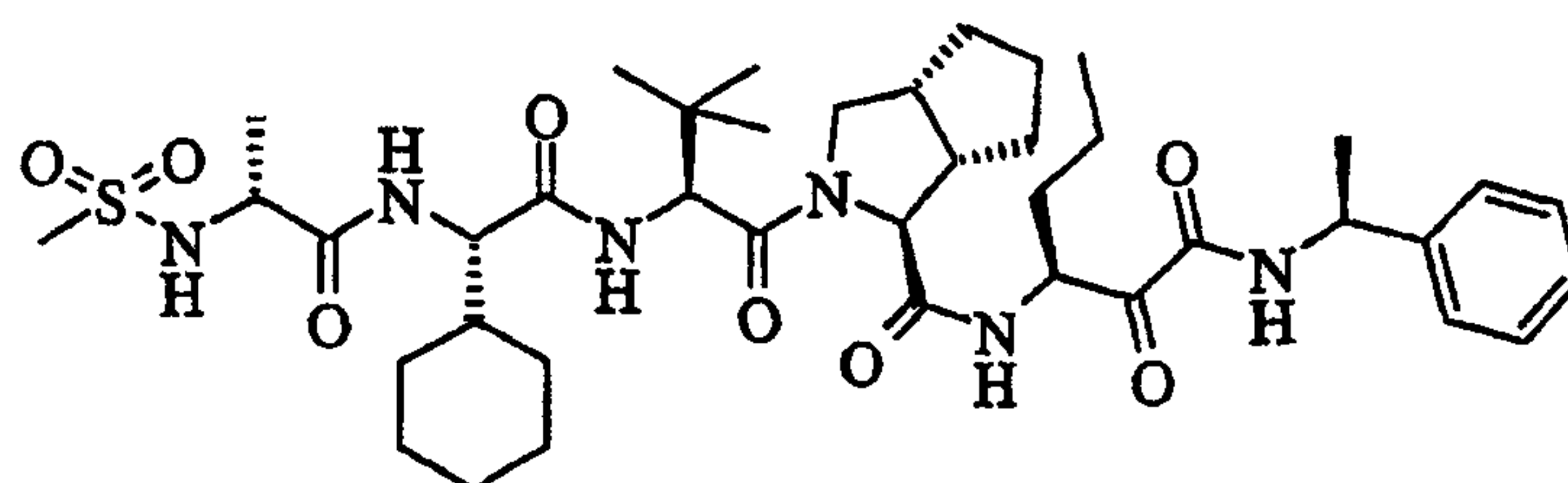


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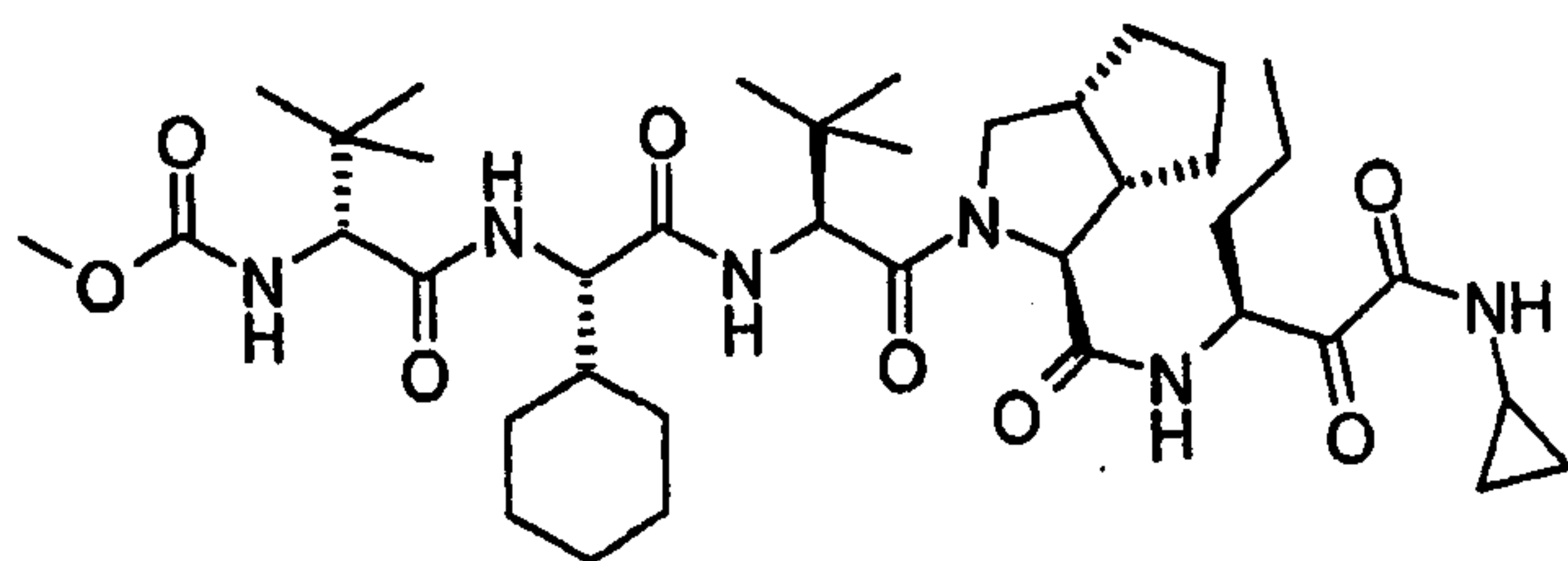


EX.

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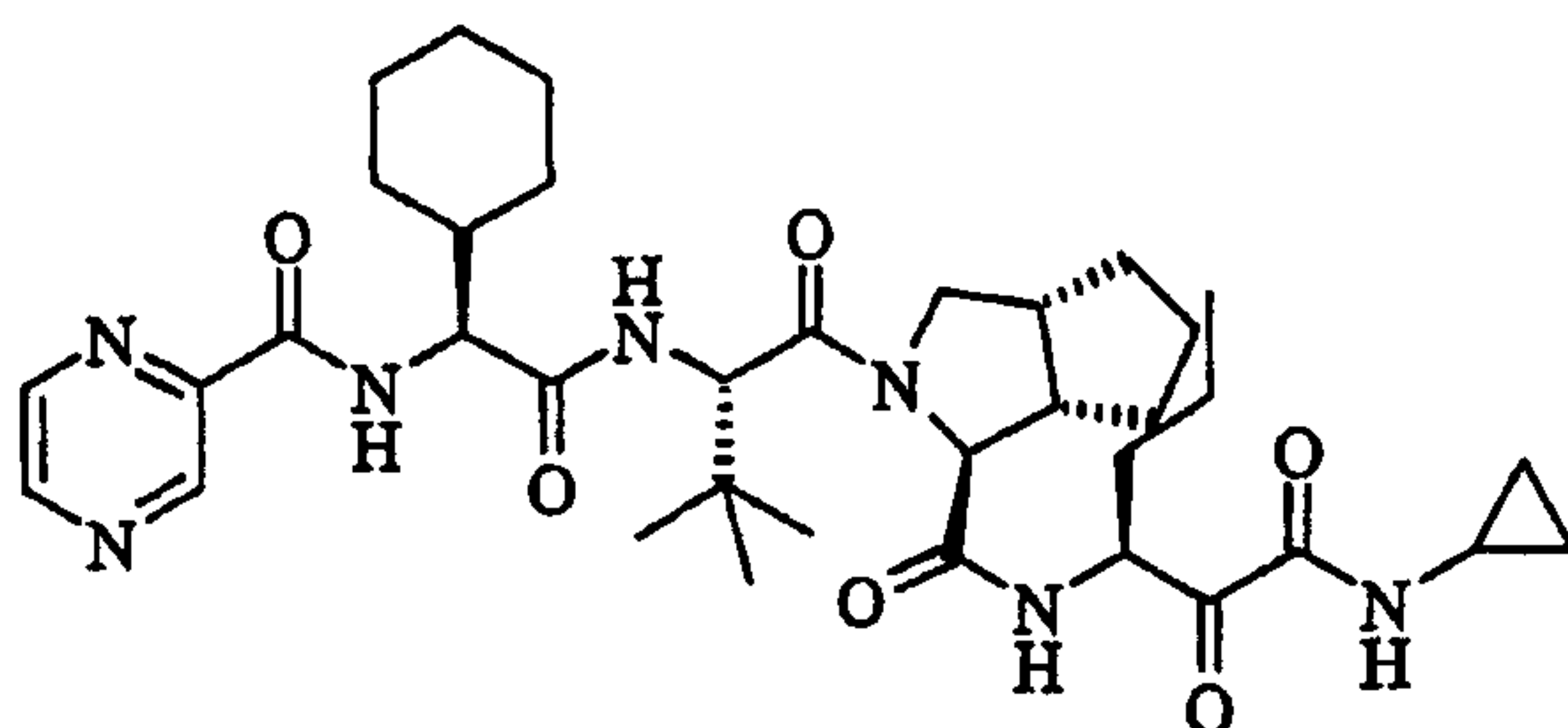
79



EY,

- 5 or a pharmaceutically acceptable salt or prodrug thereof, or a solvate of such a compound, its salt or its prodrug.

Another preferred embodiment of the invention is a compound of the formula



or a pharmaceutically acceptable salt or

prodrug thereof, or a solvate of such a compound, its salt or its prodrug.

- 10 Another preferred embodiment of the invention is compound of formula 1 wherein:

R^0 is a bond;

R^1 is hydrogen;

R^2 is lower alkyl optionally substituted with 1 to 3 aliphatic group substituents ;or

lower cycloalkyl optionally substituted with 1 to 3 cyclic group substituents;

- 15 R^3 and R^5 are each independently methylene optionally substituted with 1 to 3 aliphatic group substituents;

R^4 , R^6 , R^8 and R^{10} are hydrogen;

R^7 is methylene substituted with cycloalkyl, lower alkyl or aryl;or

or (1,1- or 1,2-)cycloalkenyl optionally substituted with cycloalkyl, lower alkyl or aryl;

- 20 R^9 is

lower alkyl optionally substituted with 1 to 3 aliphatic group substituents; or

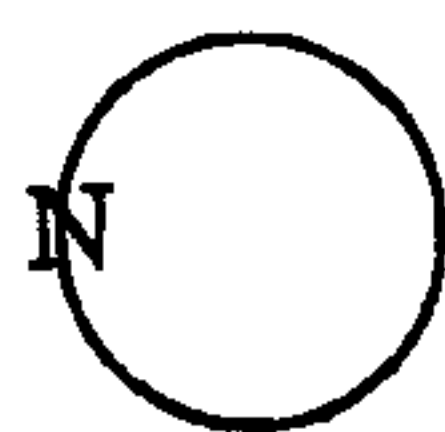
heteroaryl optionally substituted with 1 to 3 cyclic group substituents;

or heterocyclic optionally substituted with 1 to 3 cyclic group substituents;

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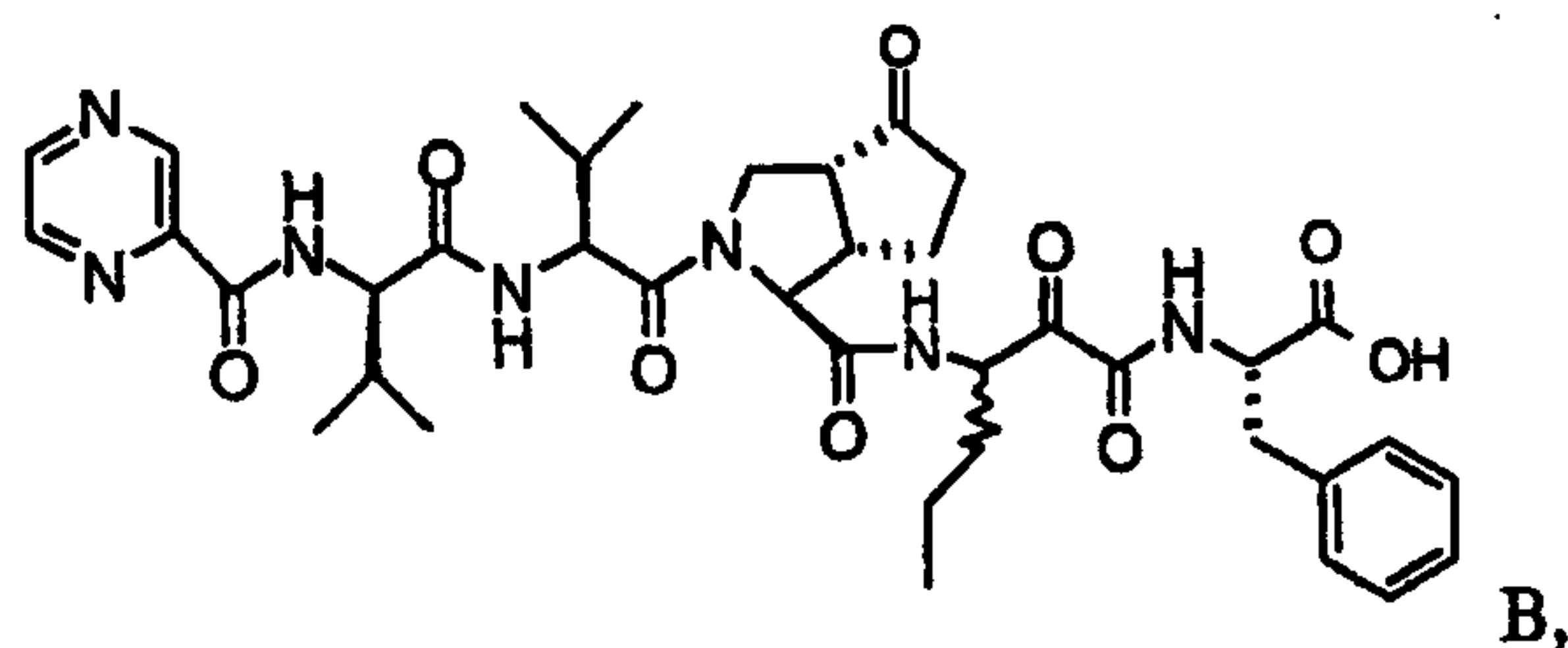
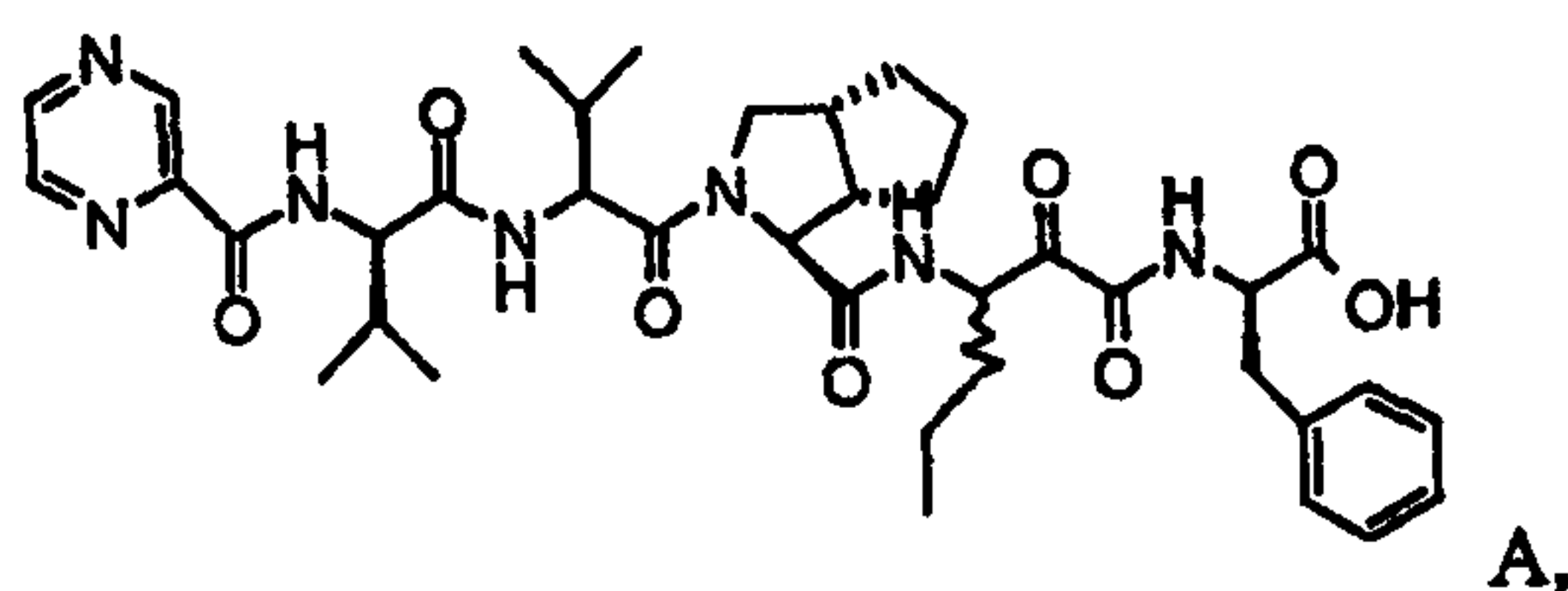
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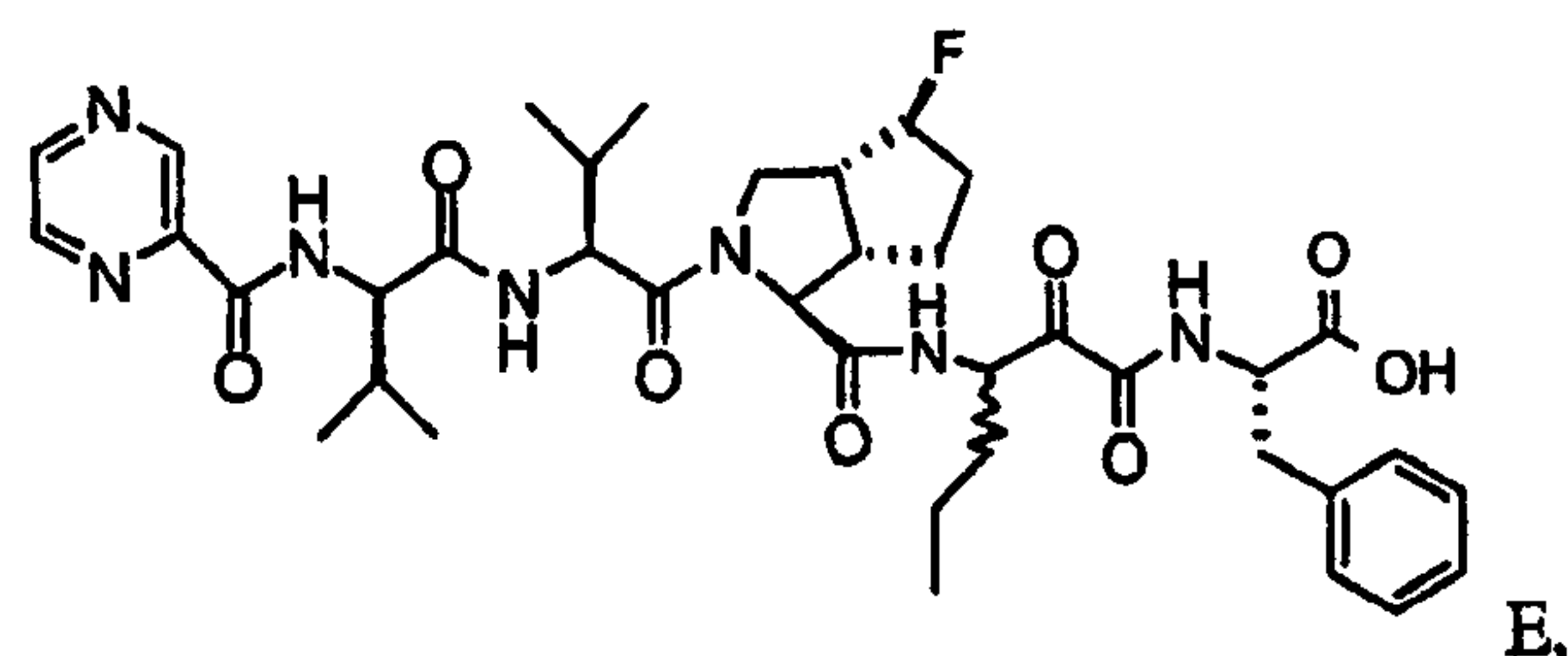
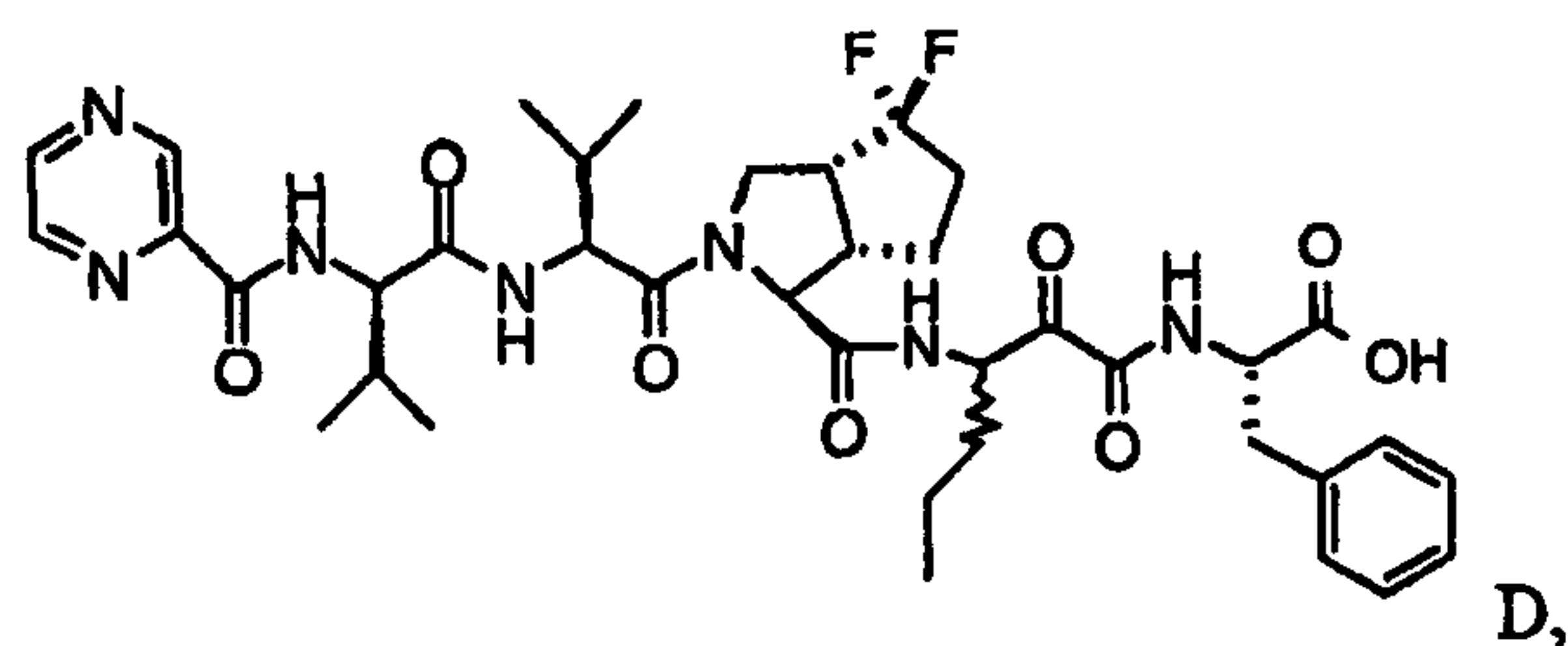
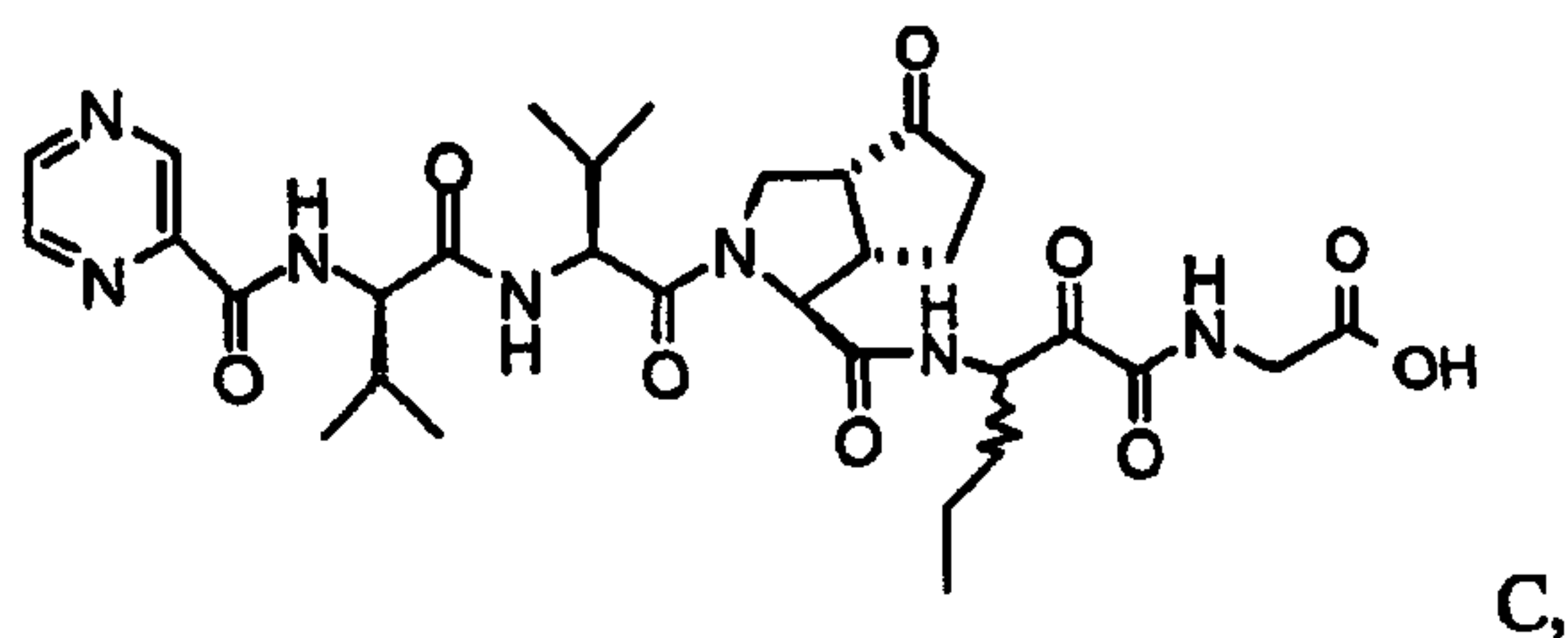


is monocyclic azaheterocyclyl, multicyclic azaheterocyclyl, or multicyclic azaheterocyclenyl optionally substituted with from 1 to 3 cyclic group substituents; and L is $-C(O)-$, $-OC(O)-$.

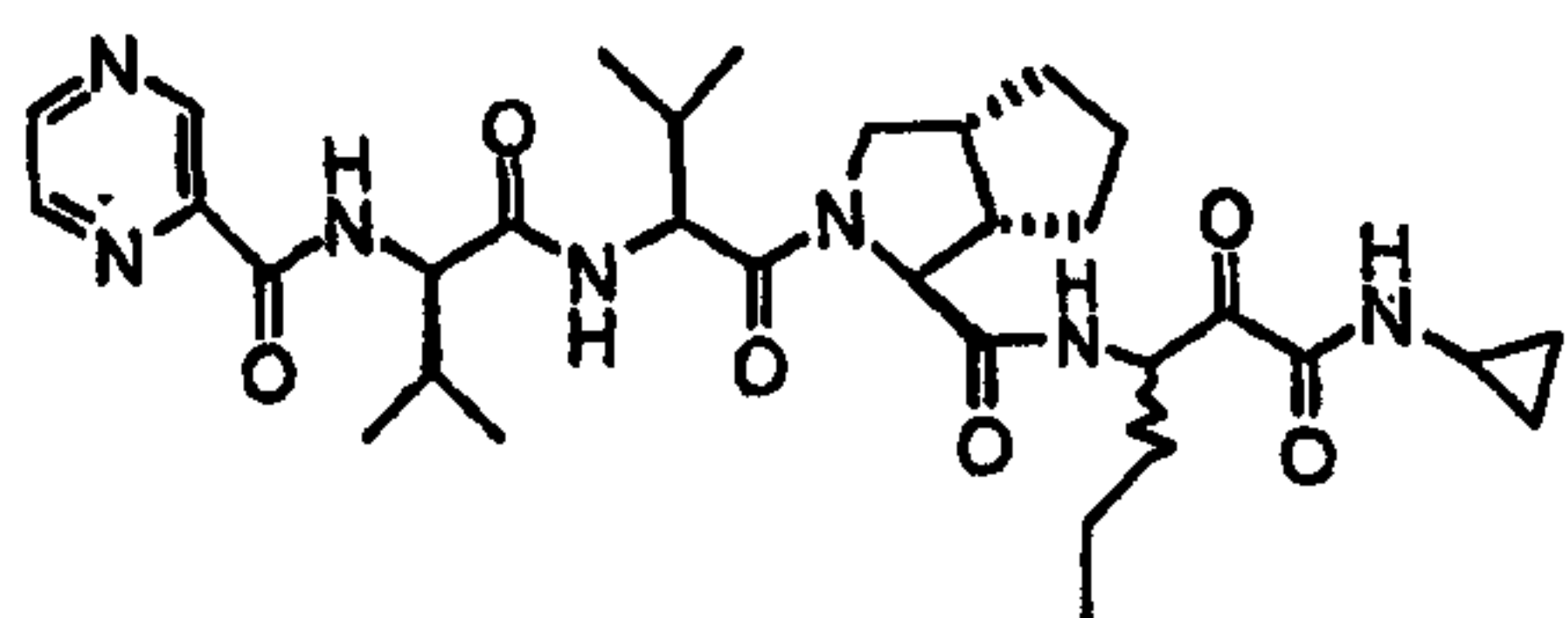
- 5 Another preferred embodiment of the invention is a compound selected from the group consisting of:



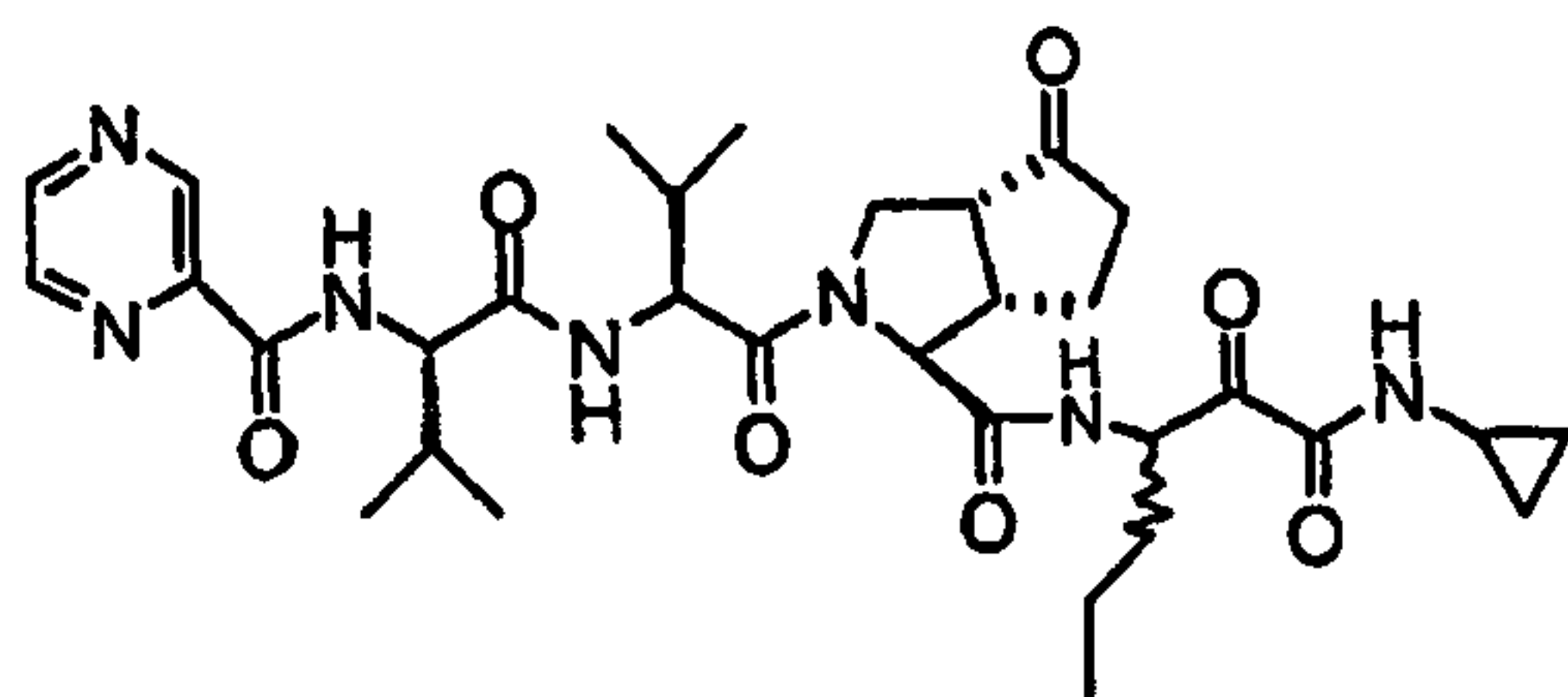
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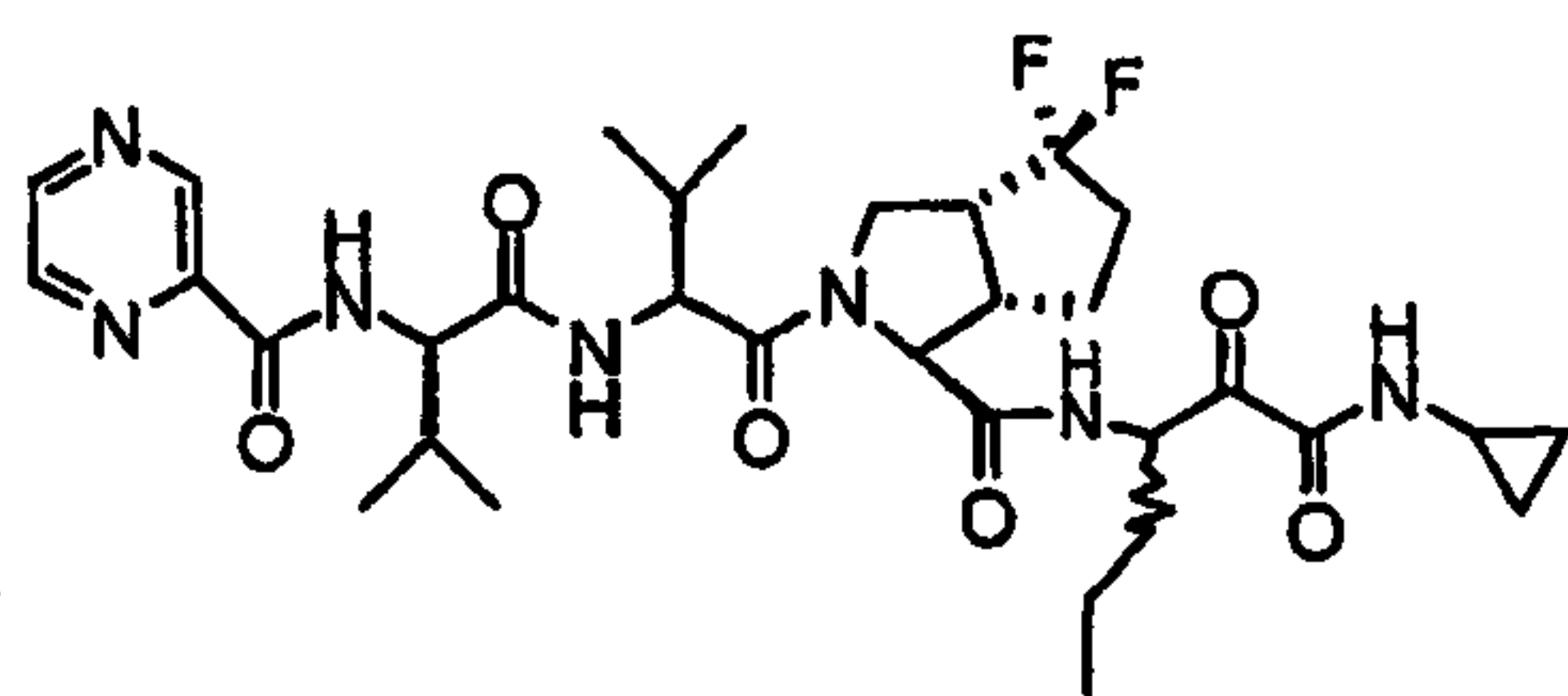
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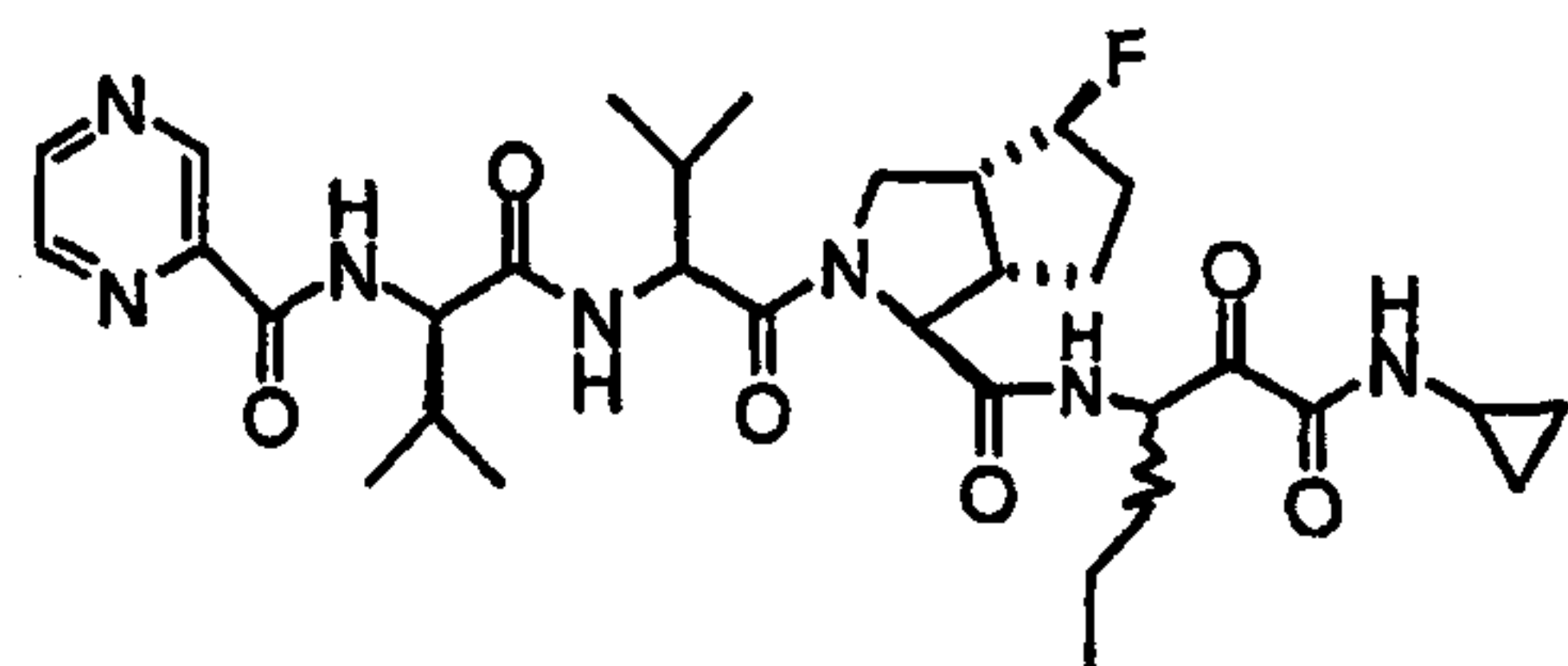
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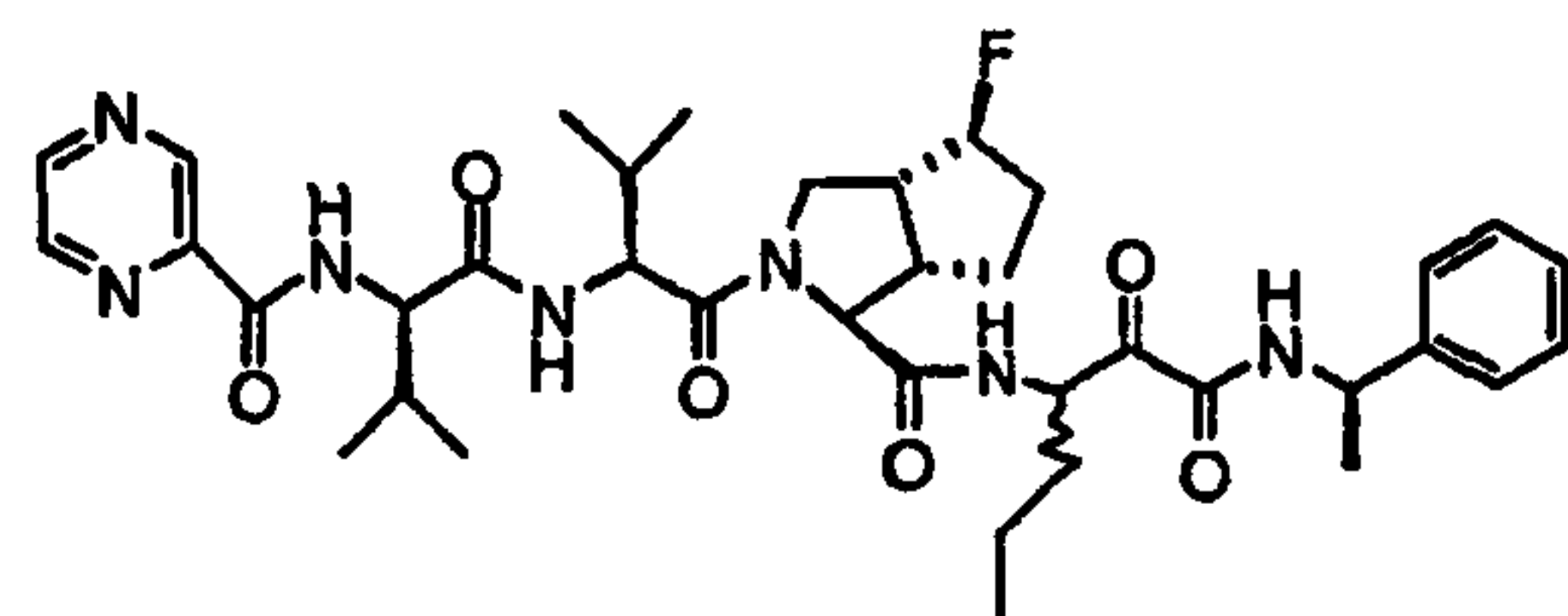
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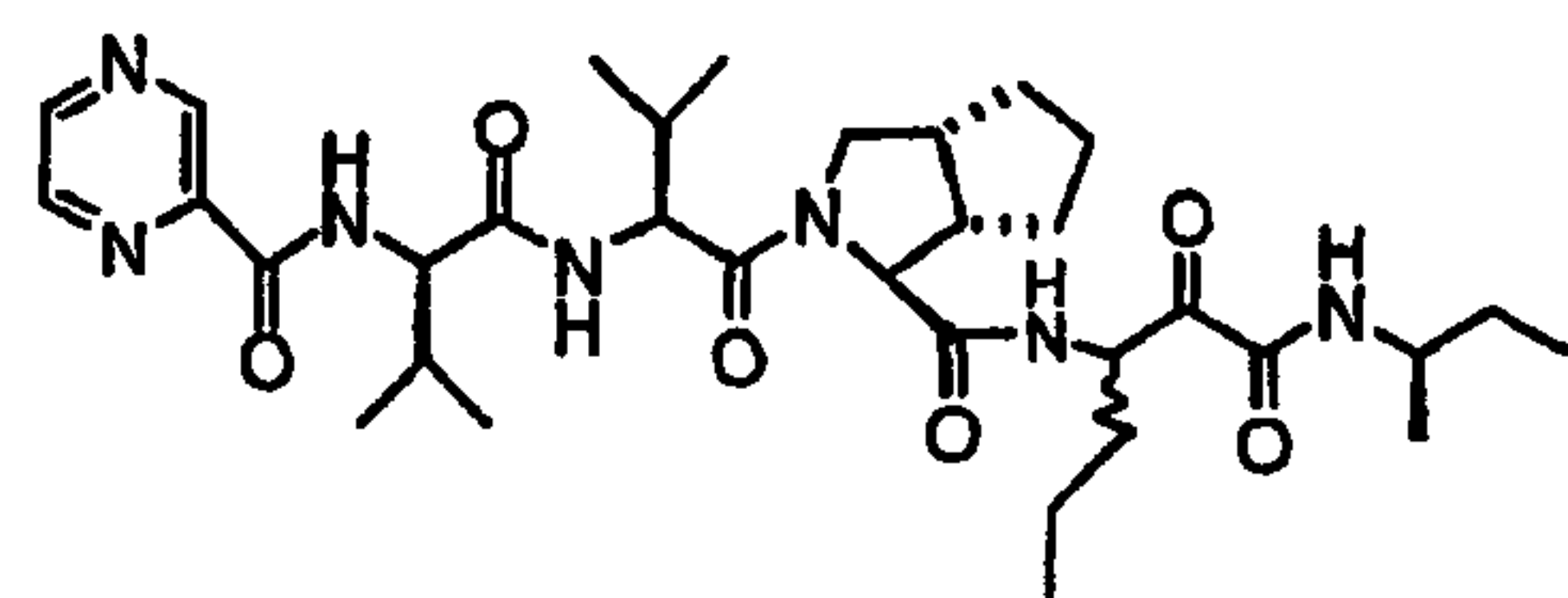


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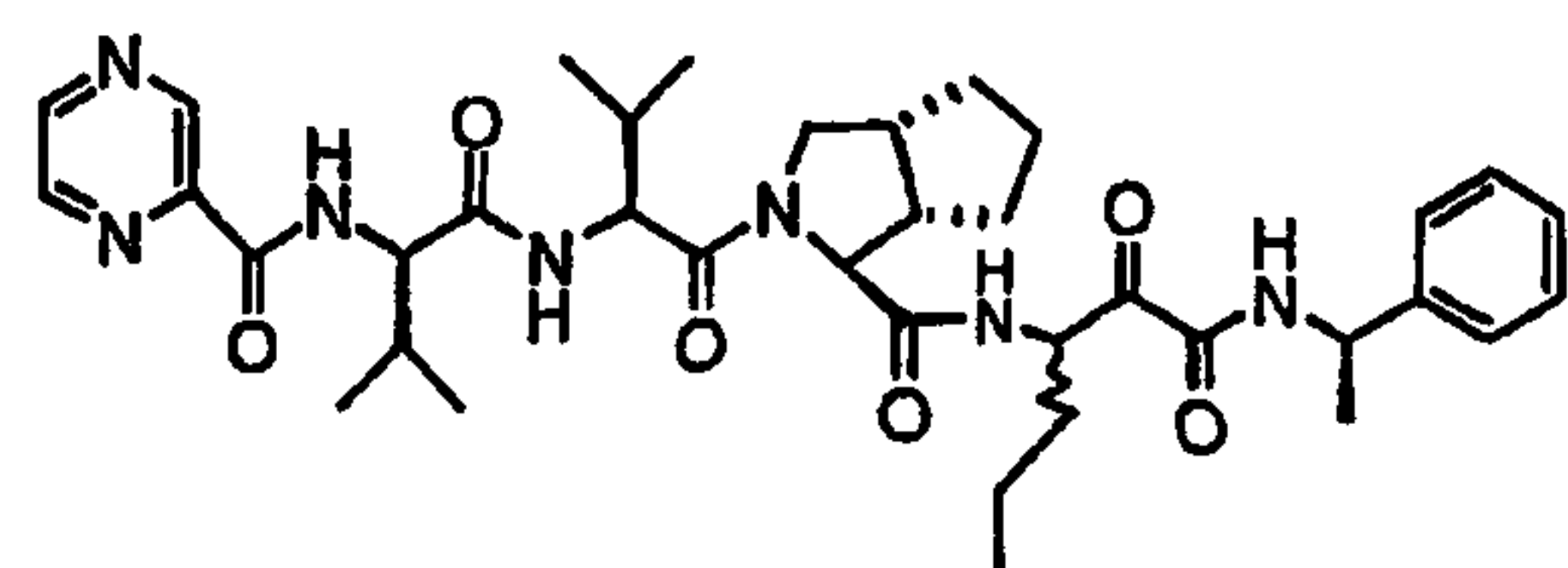


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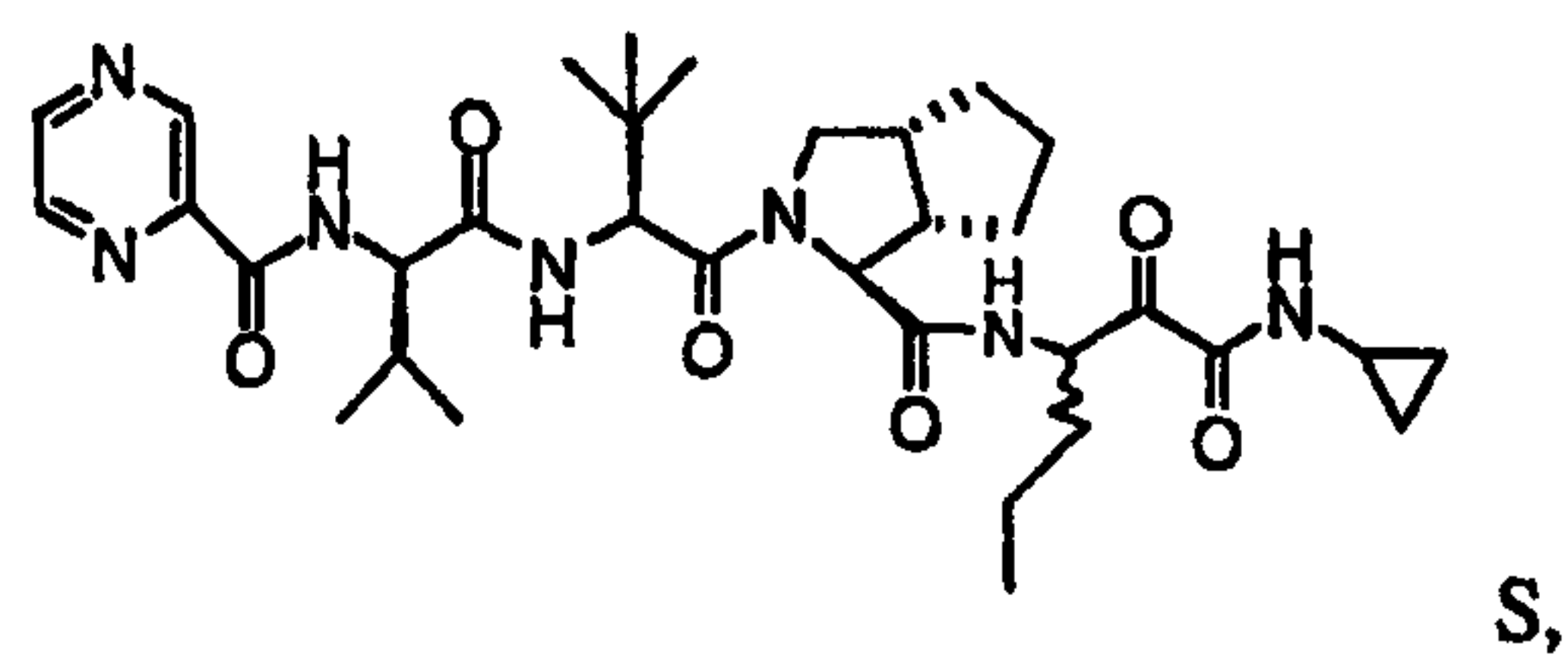
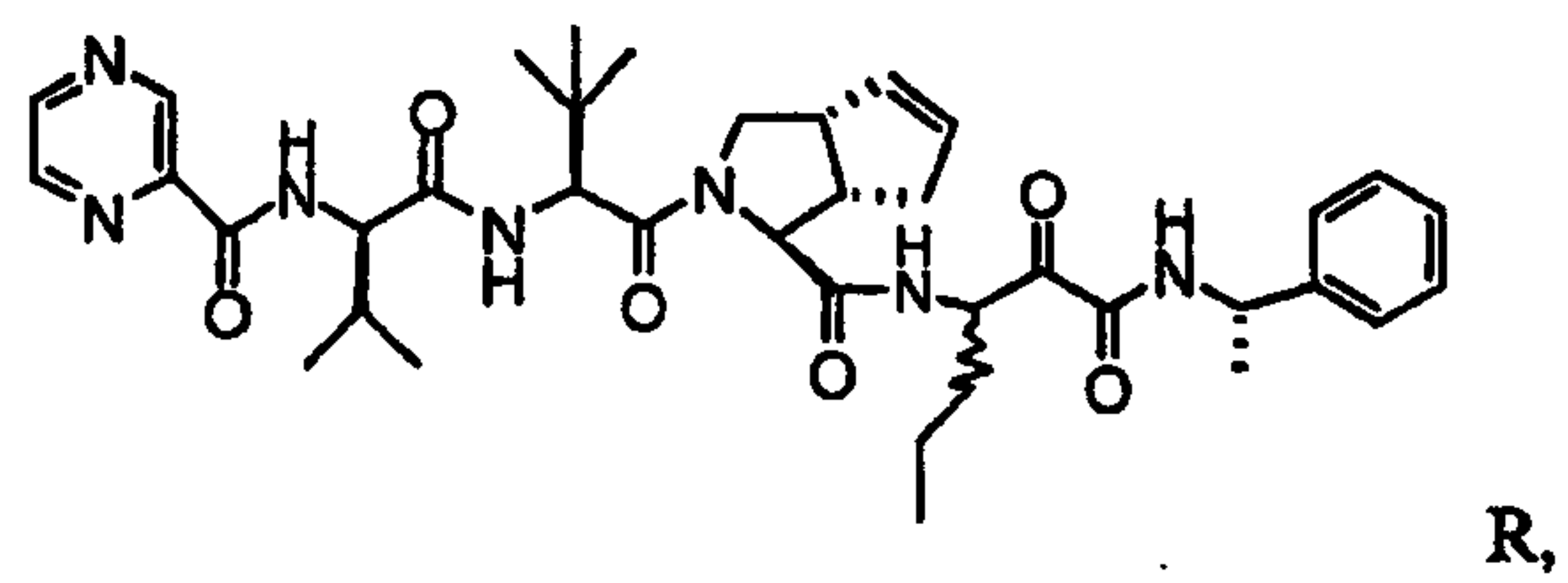
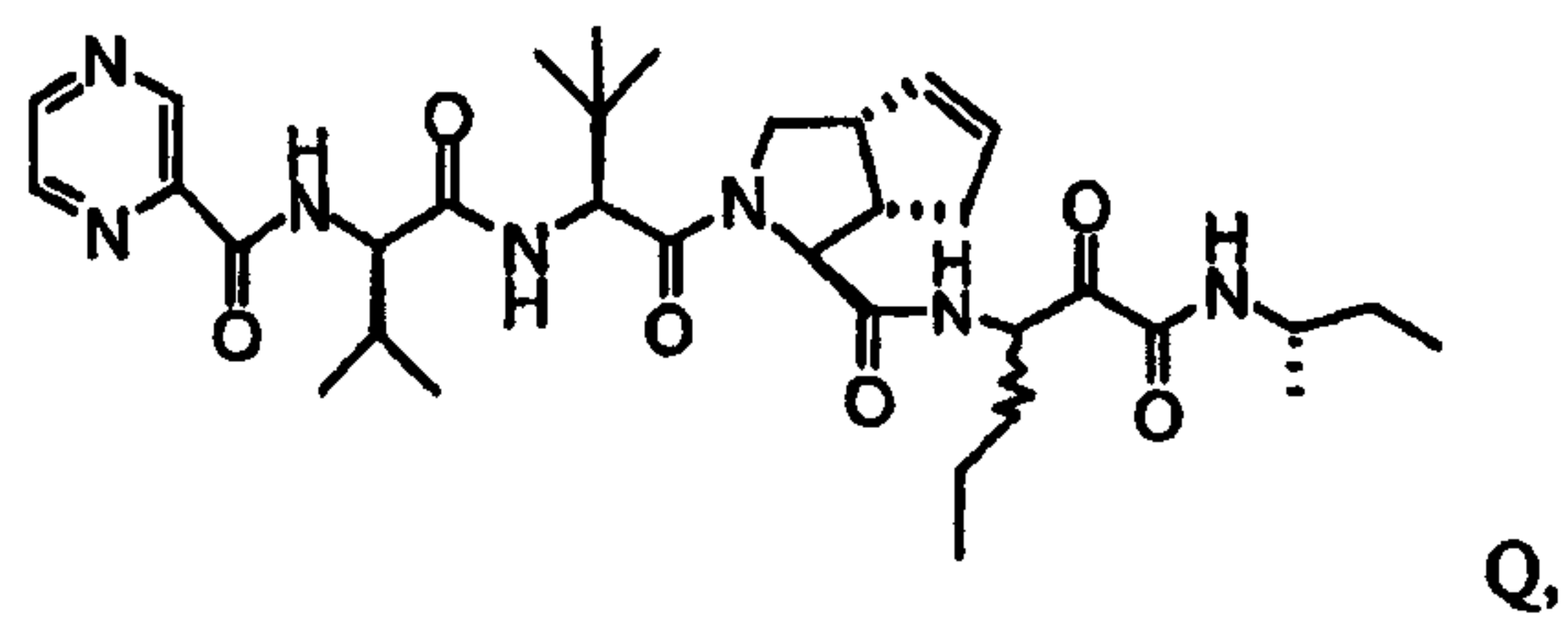
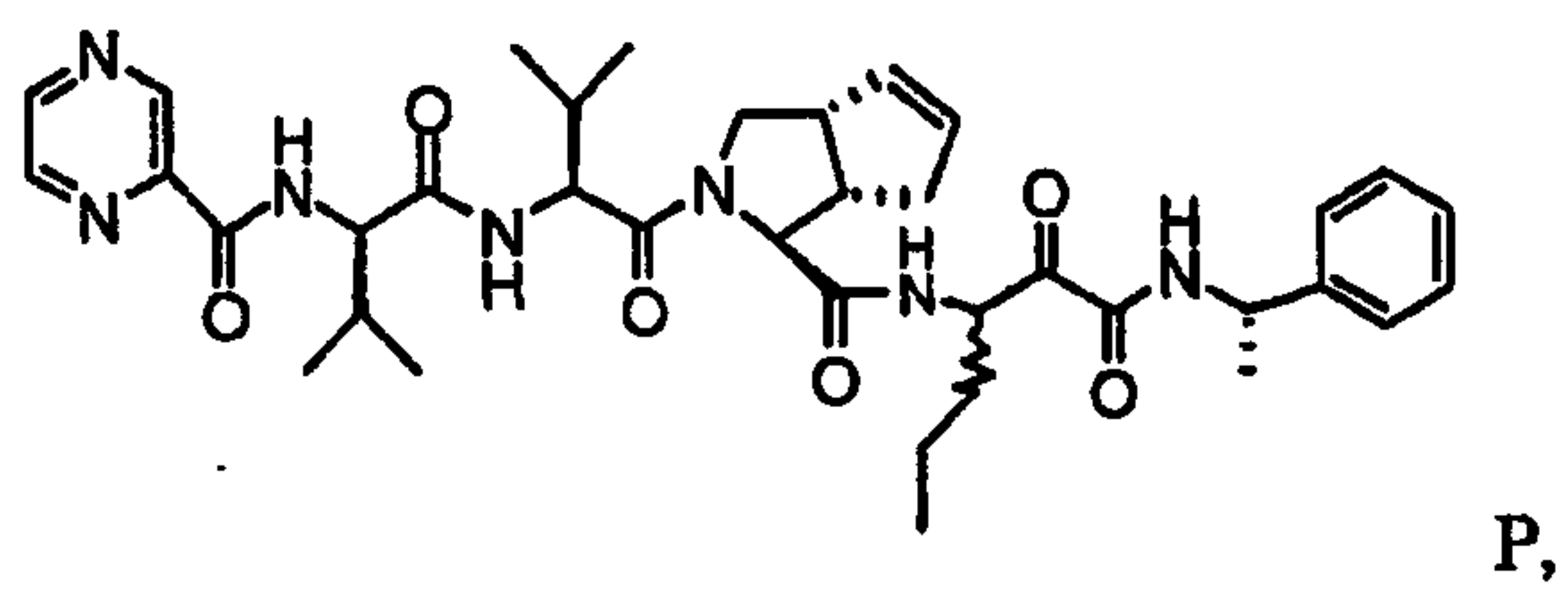
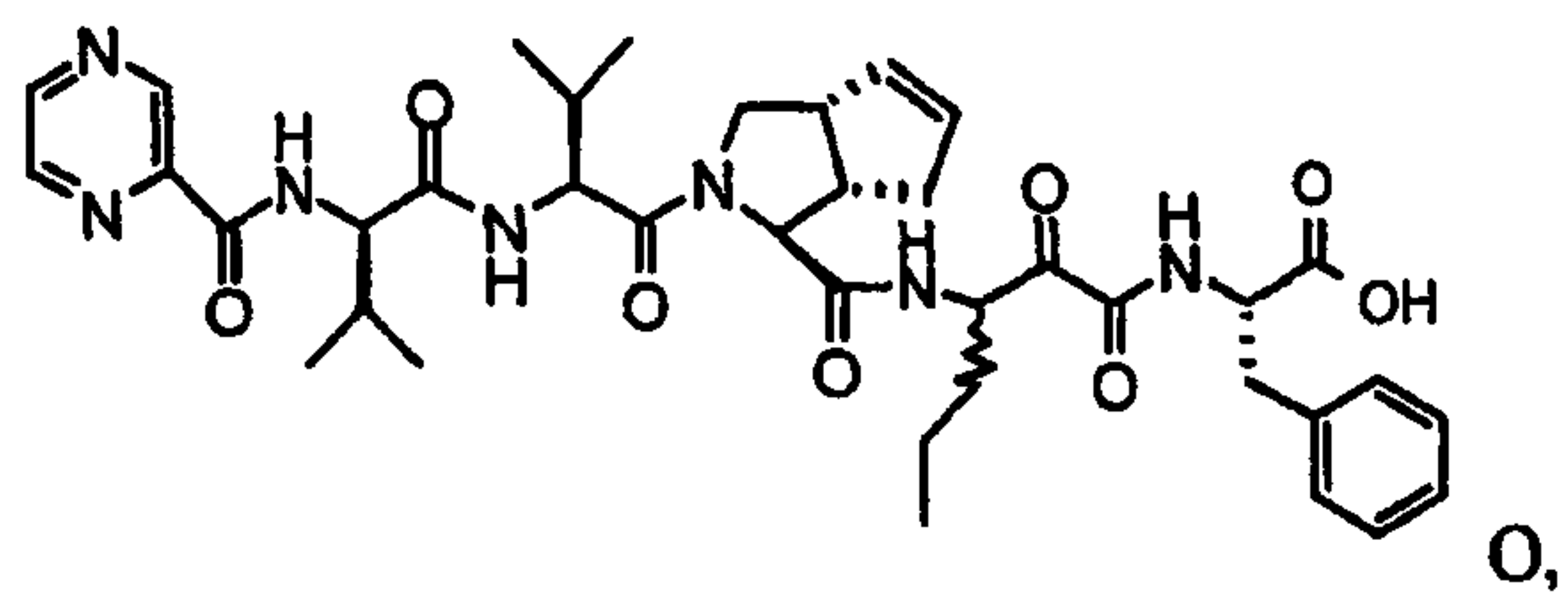
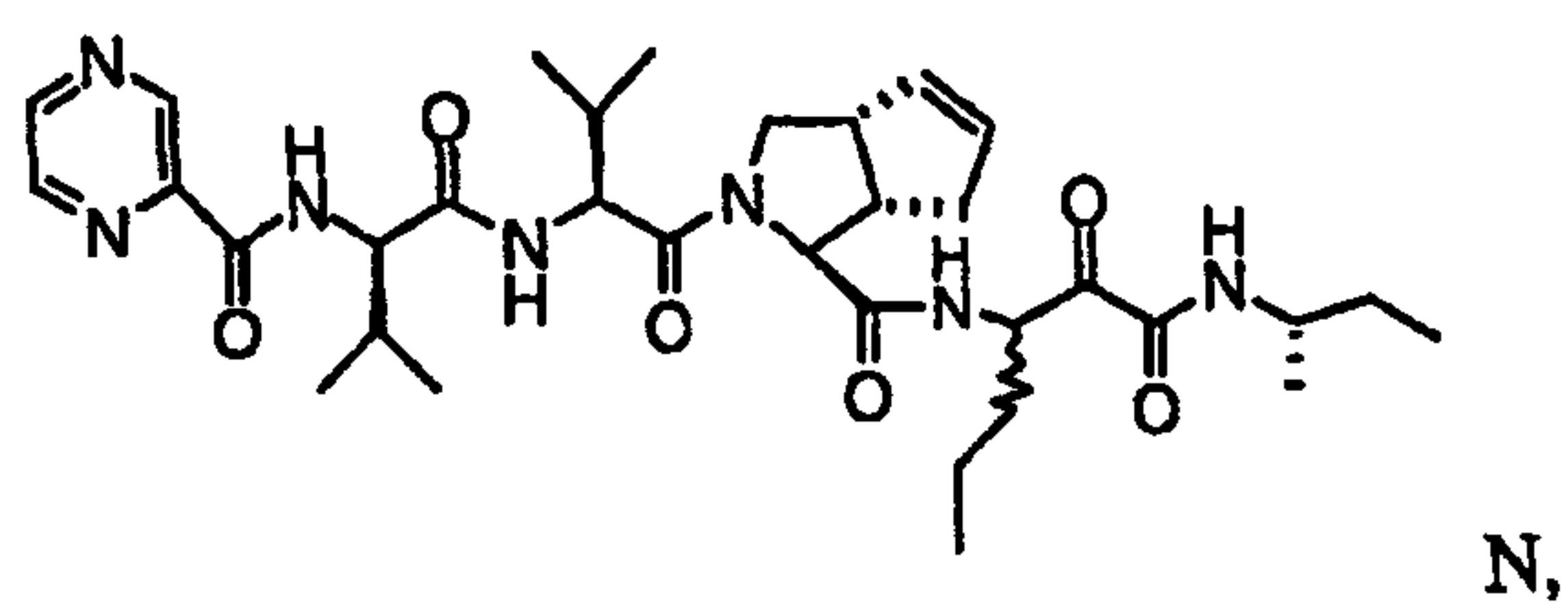
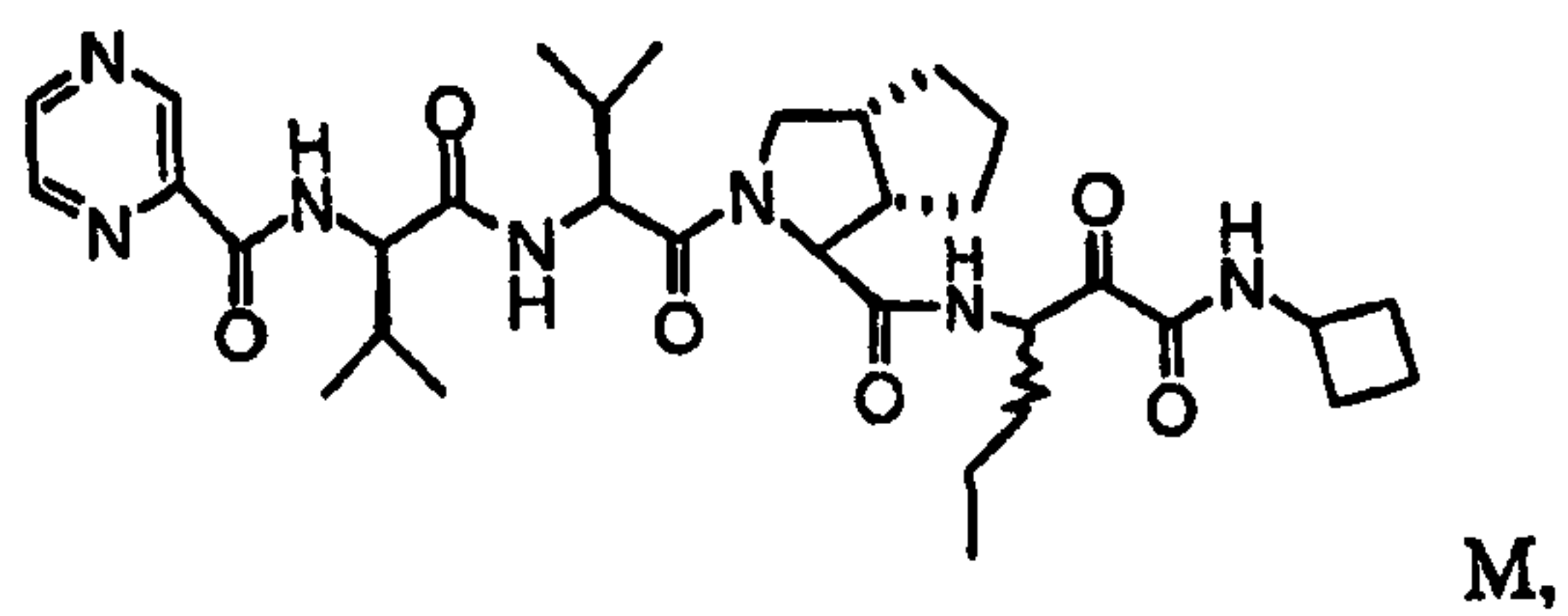


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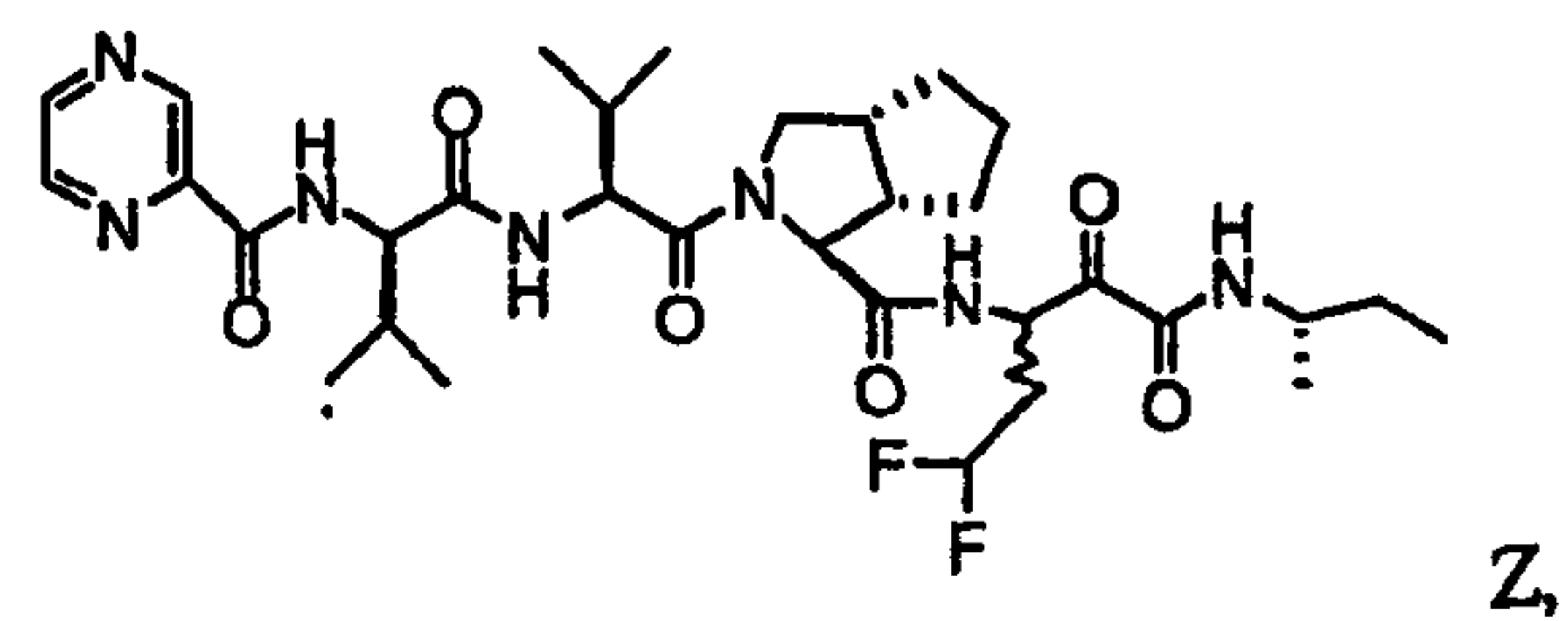
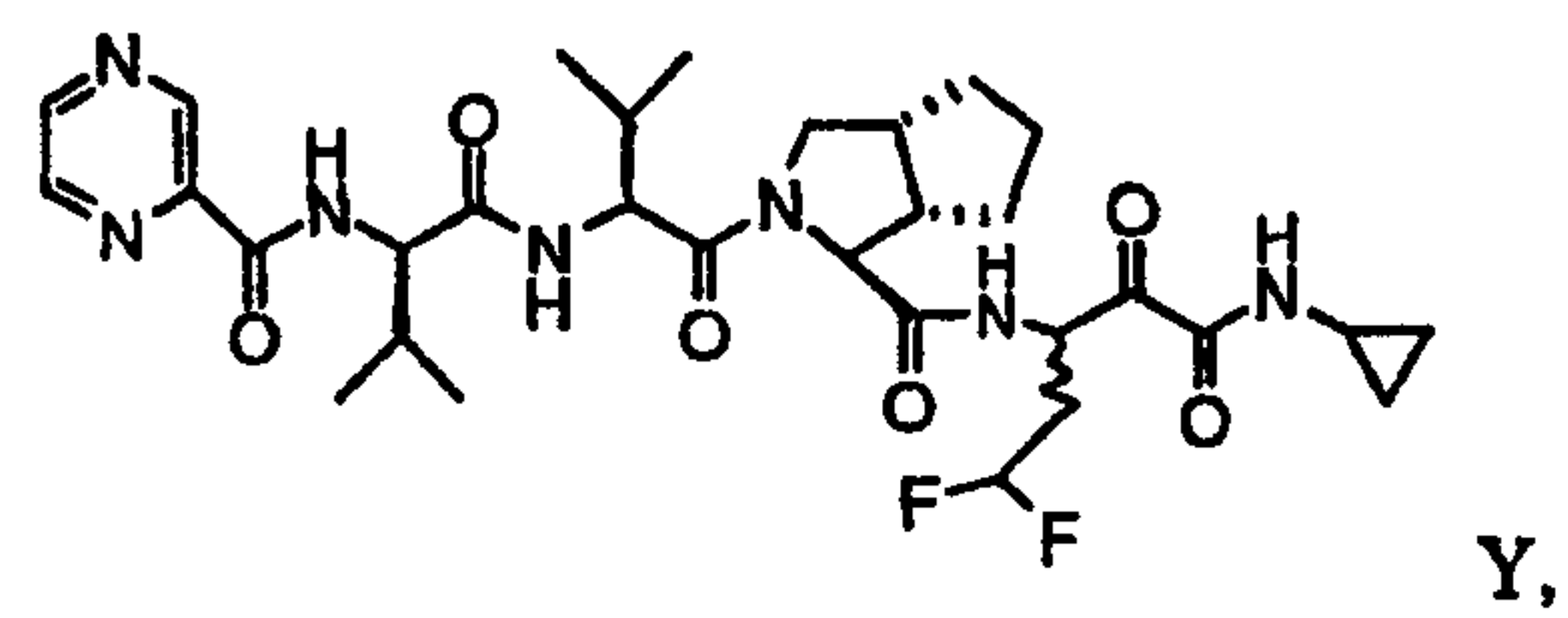
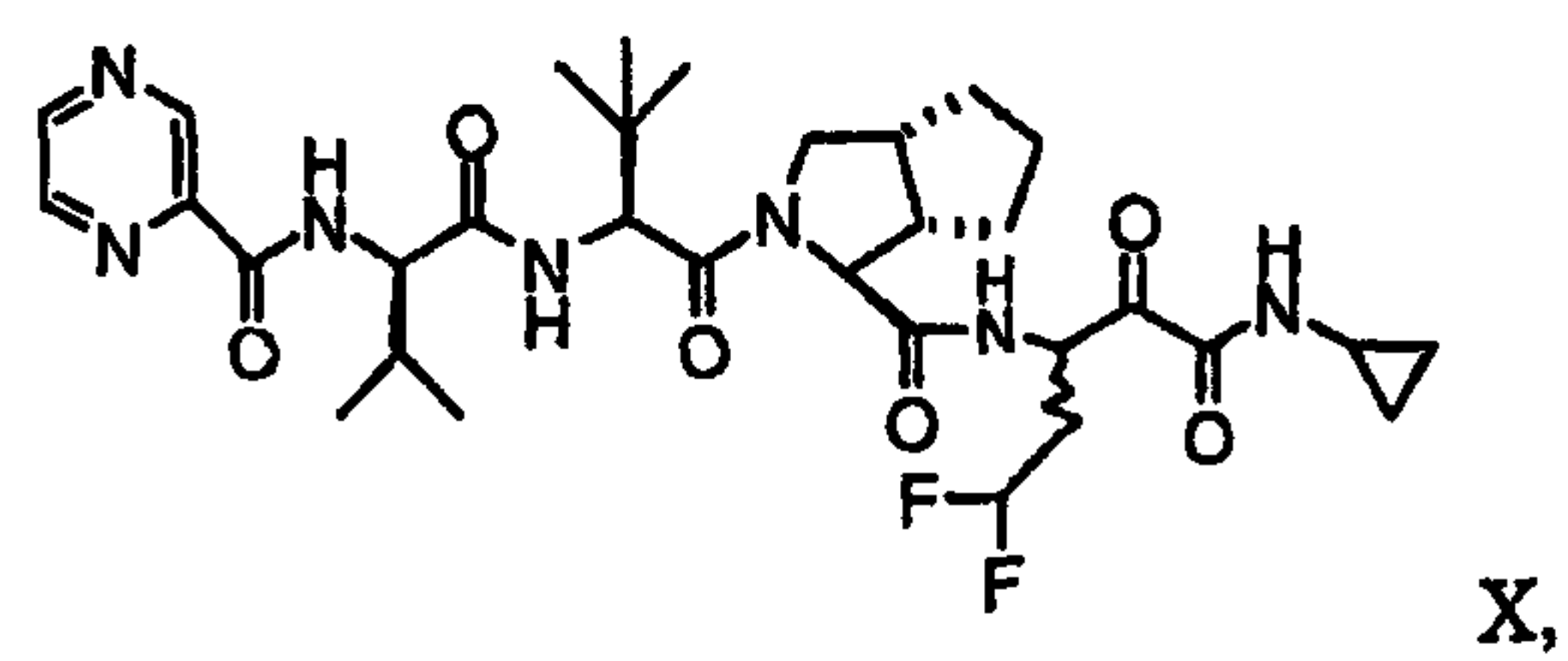
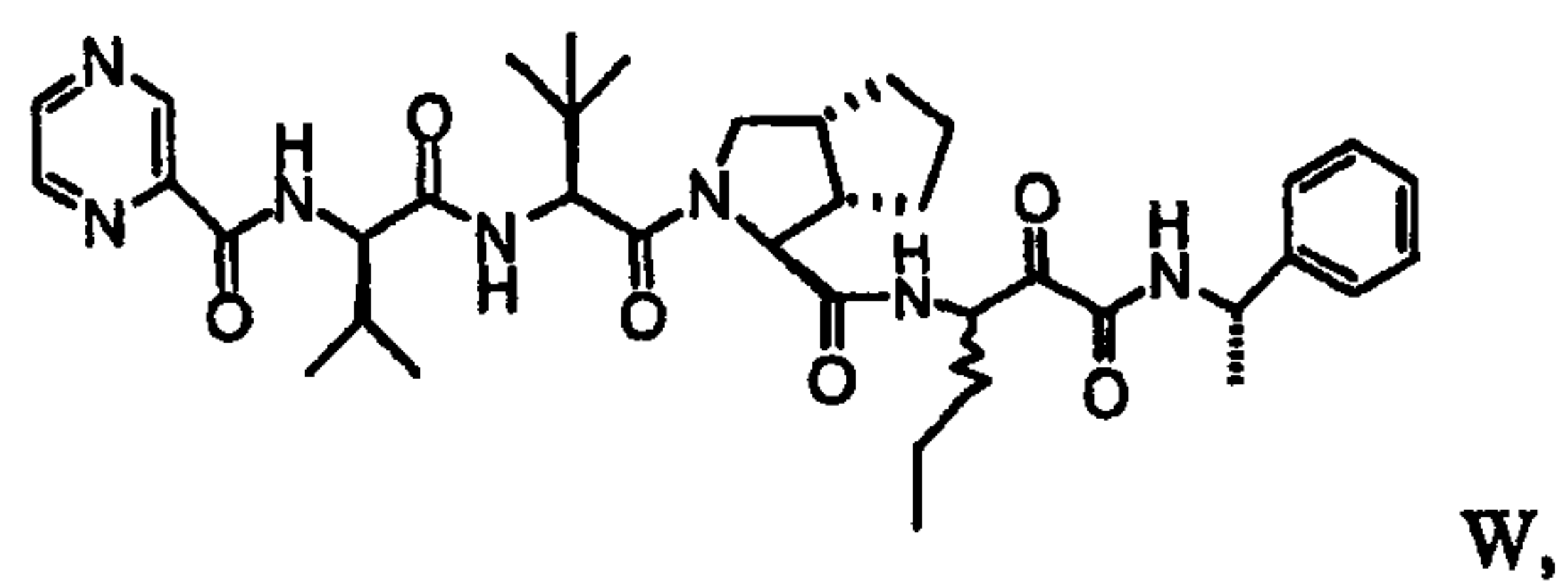
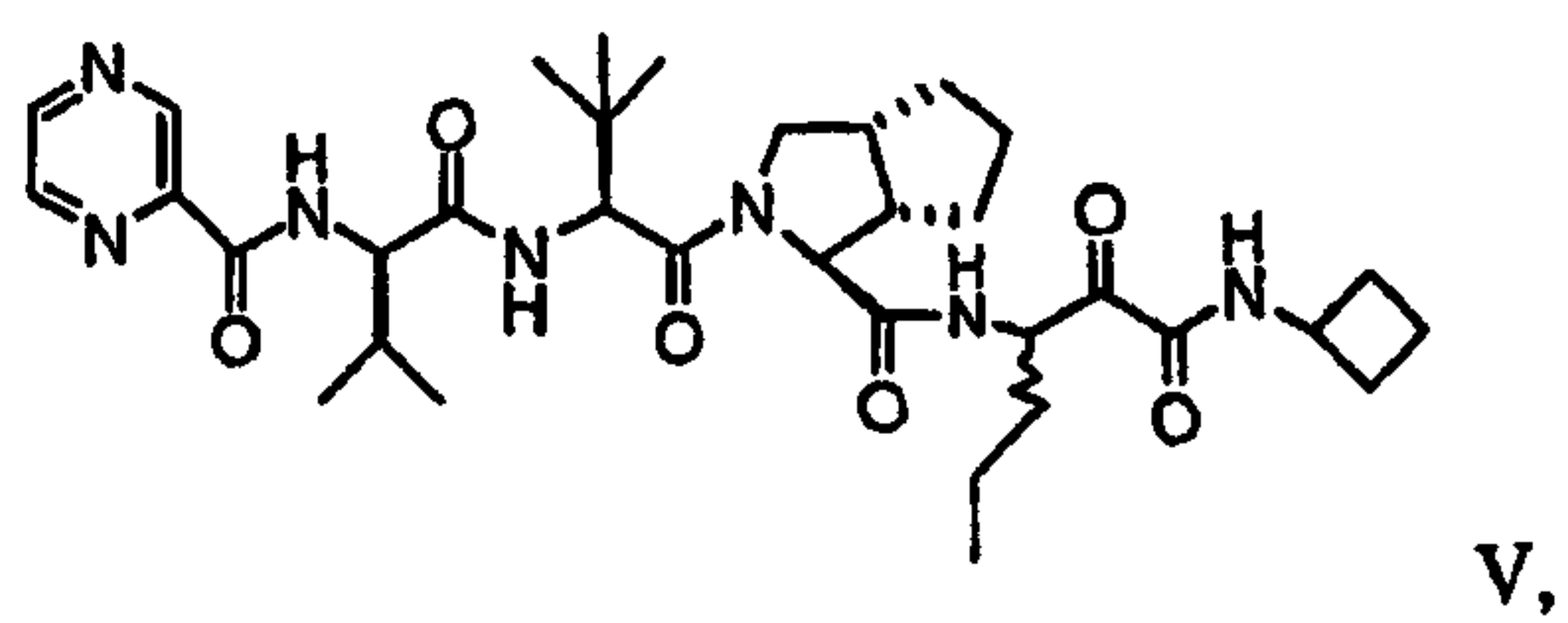
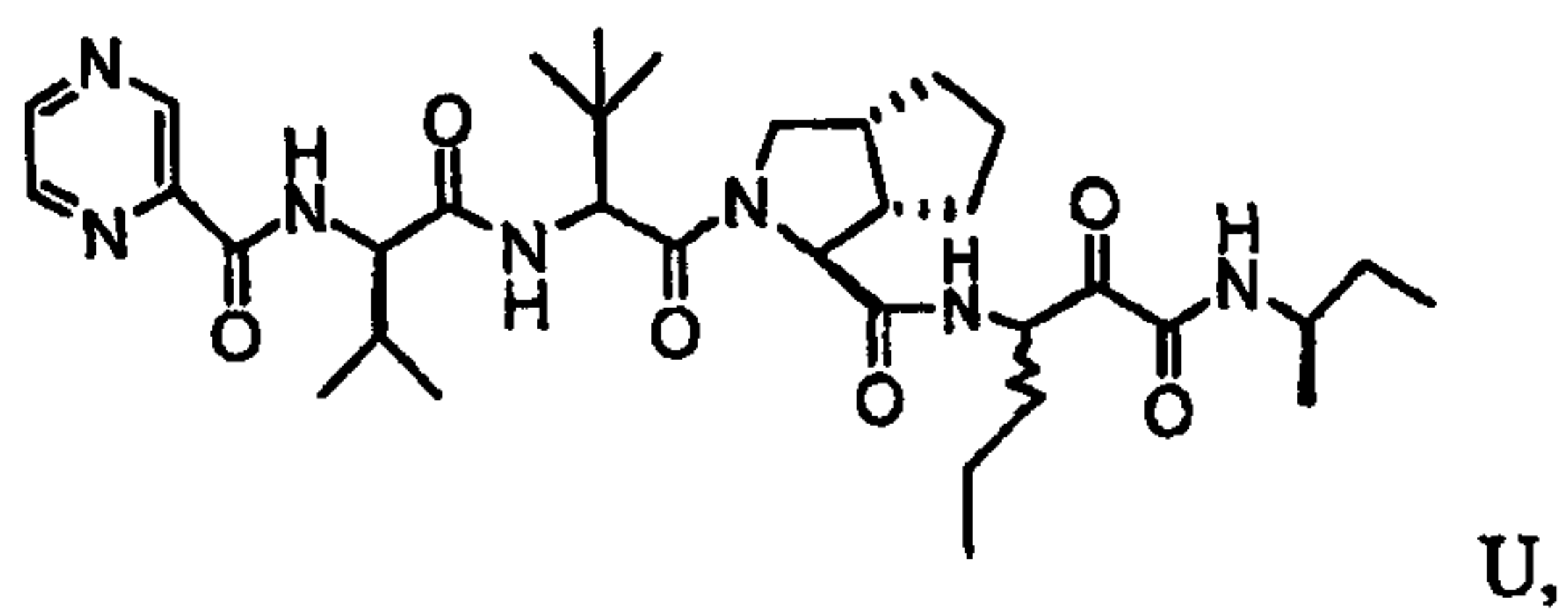
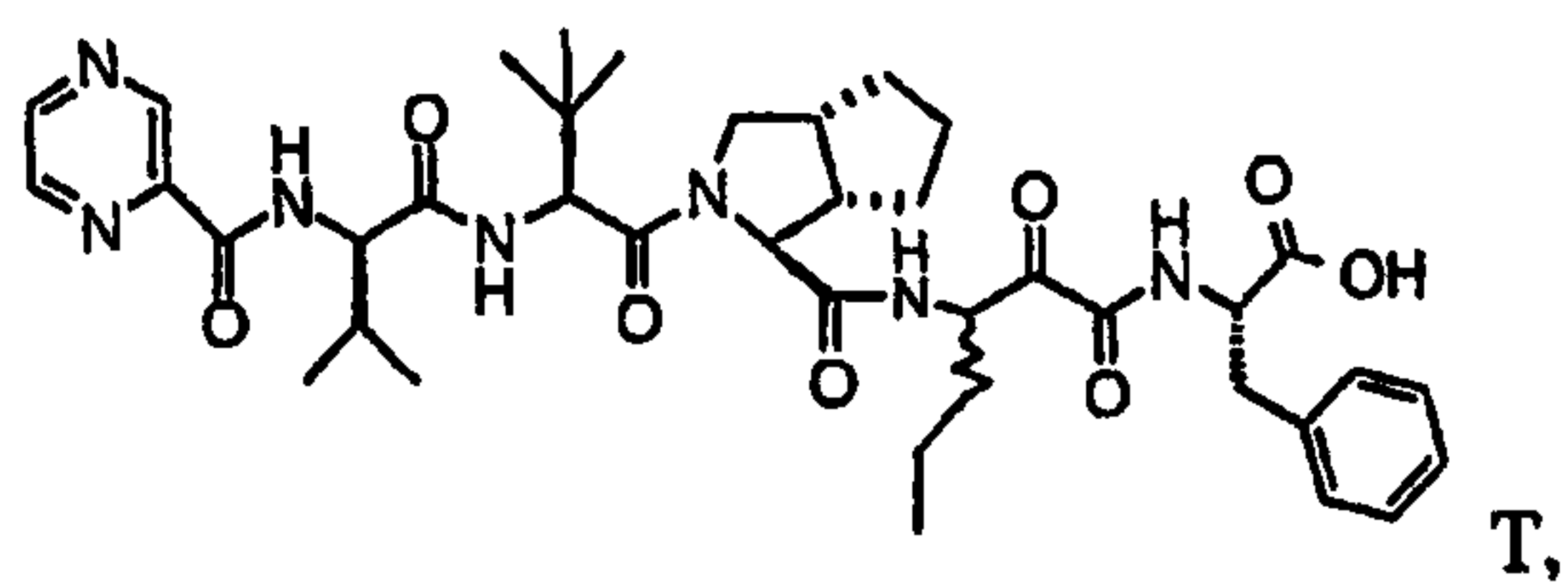
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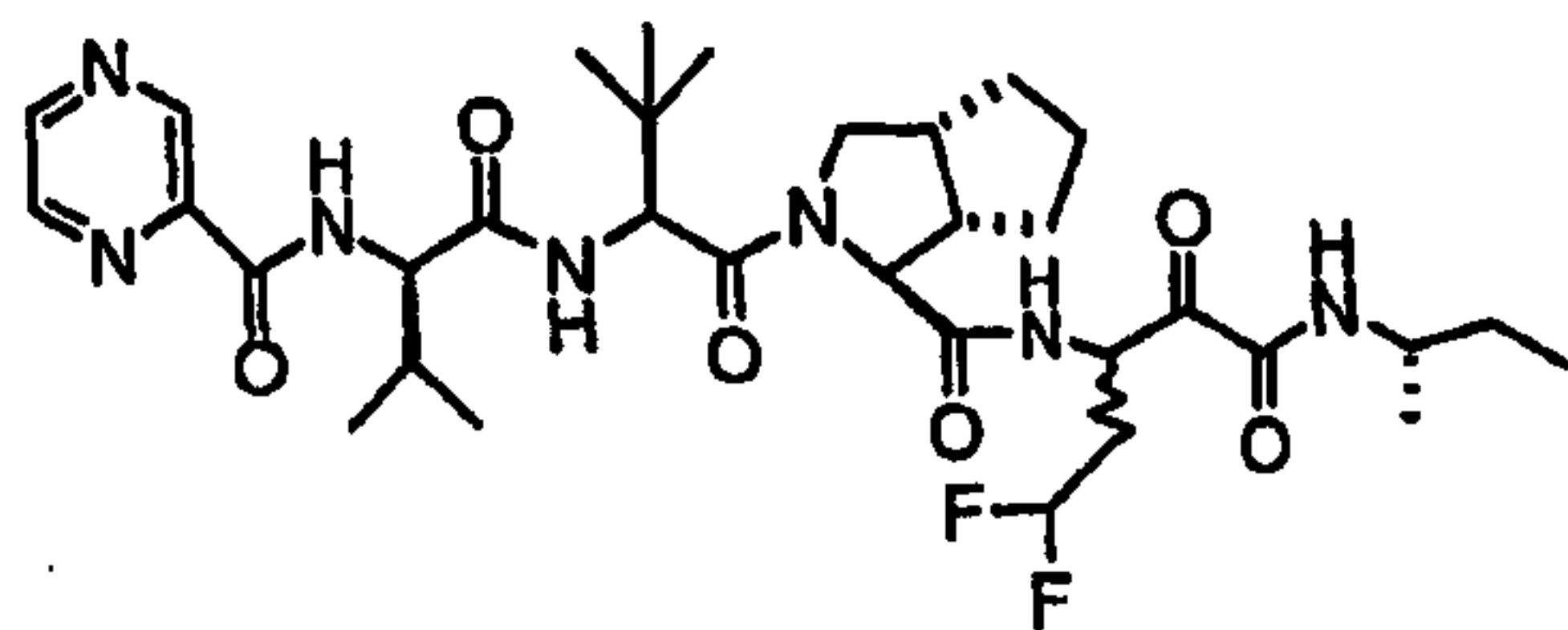


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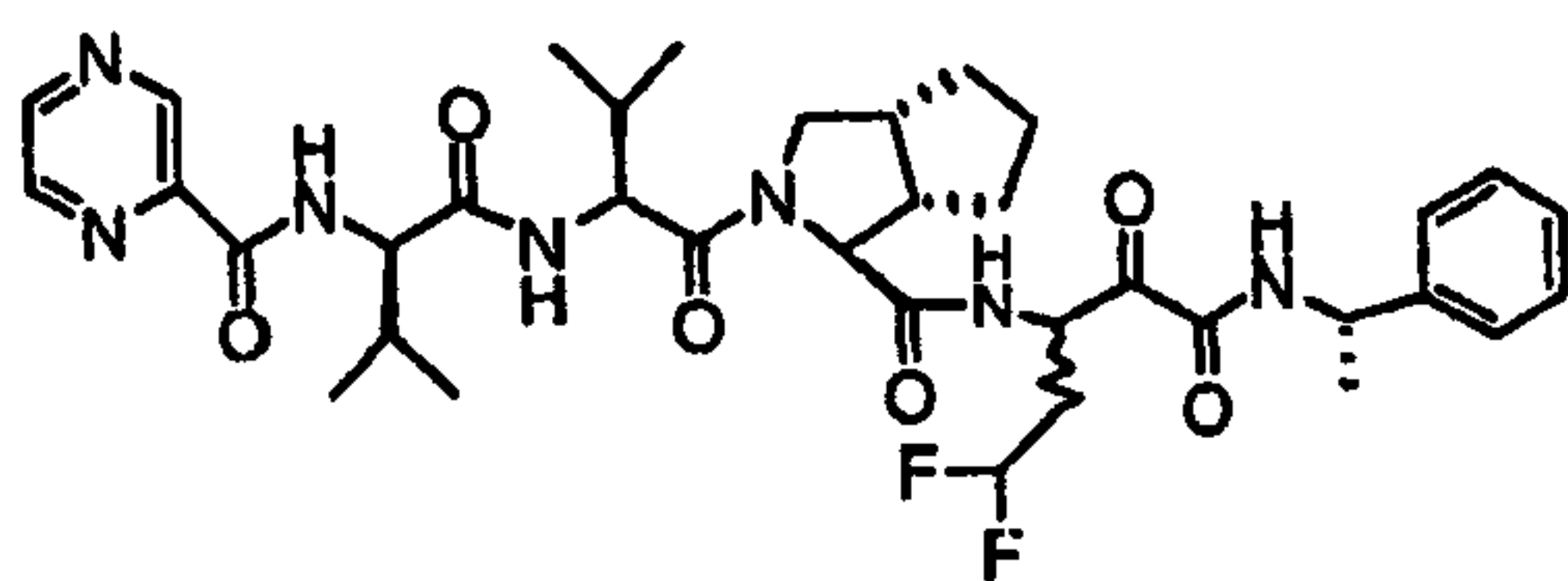
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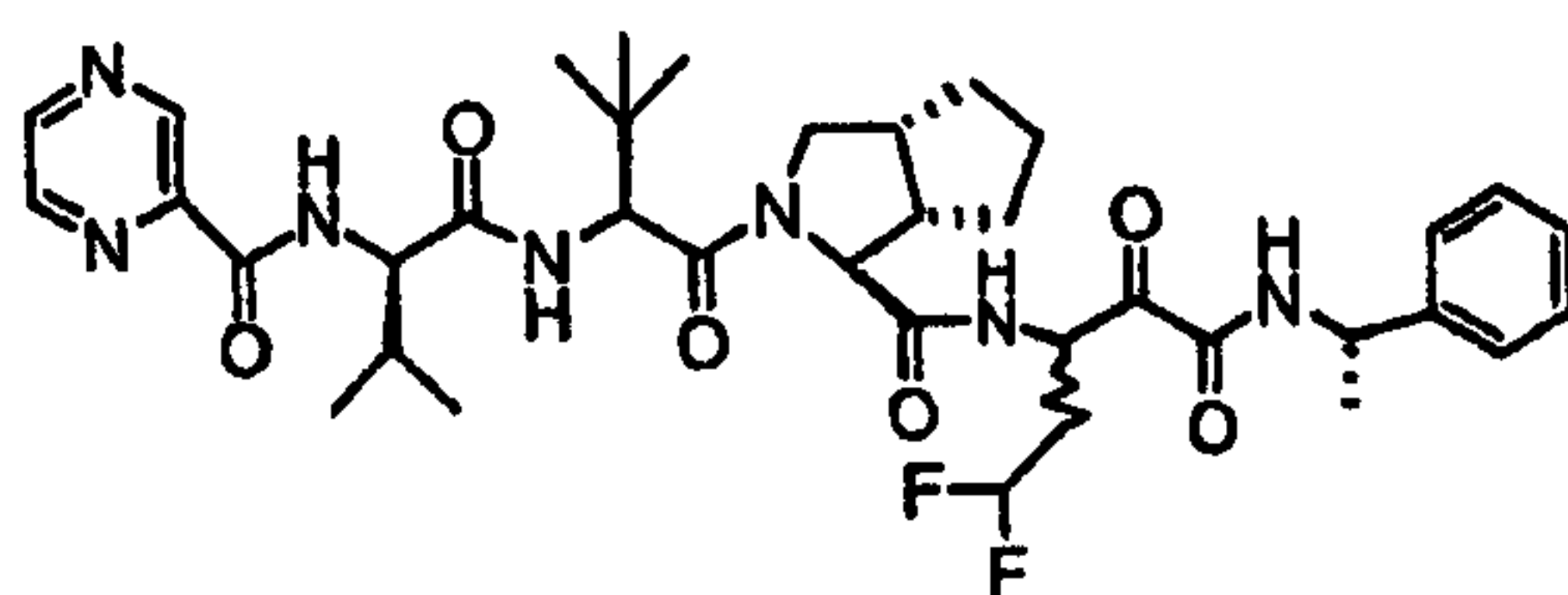
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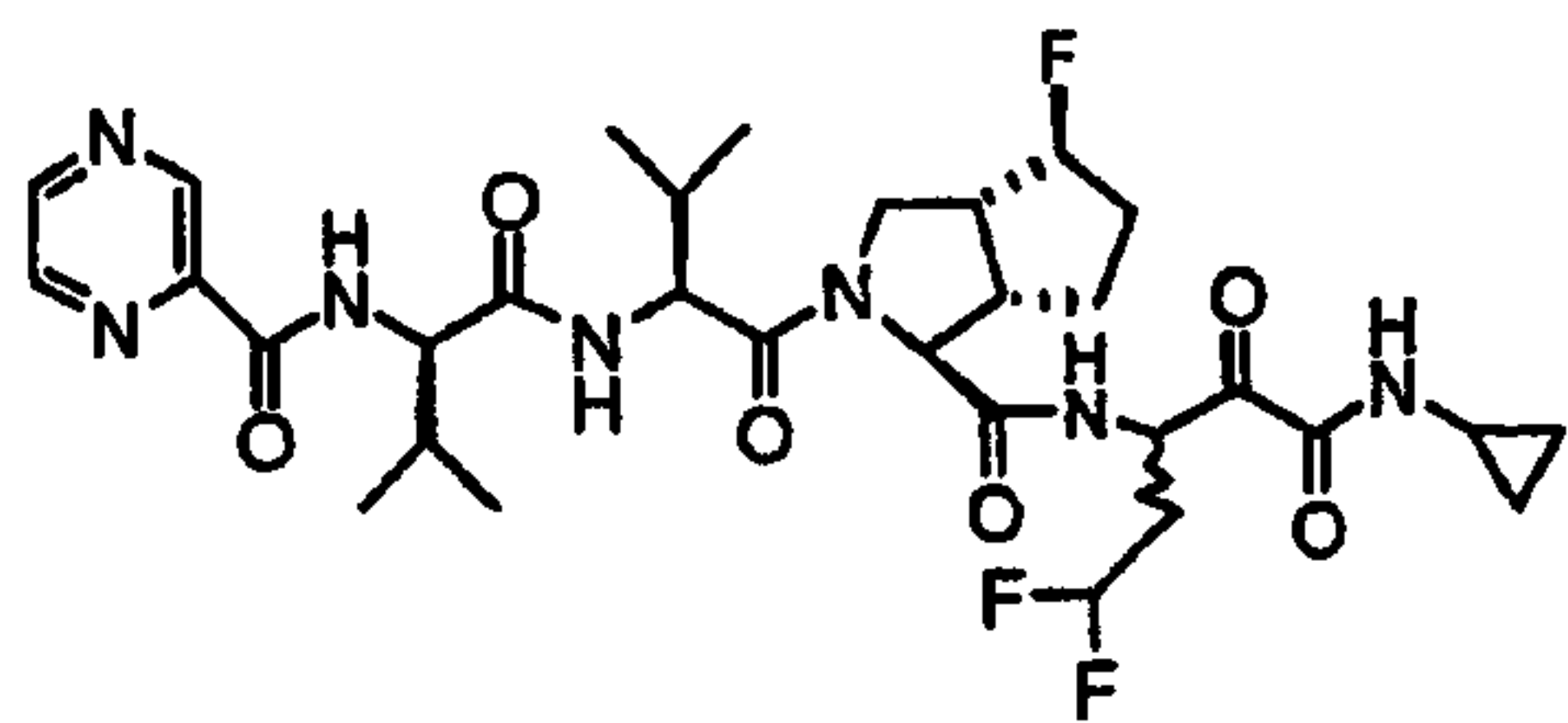
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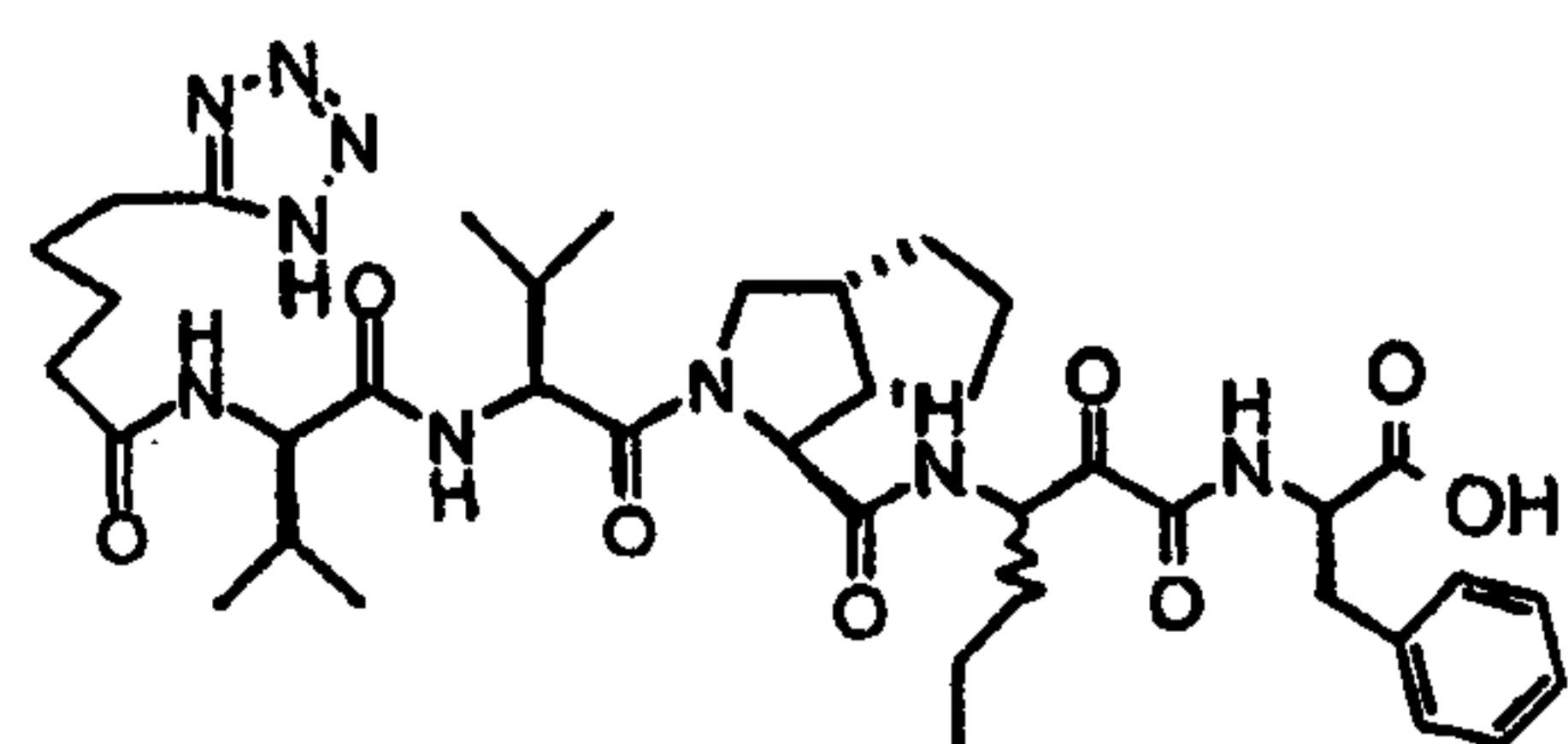
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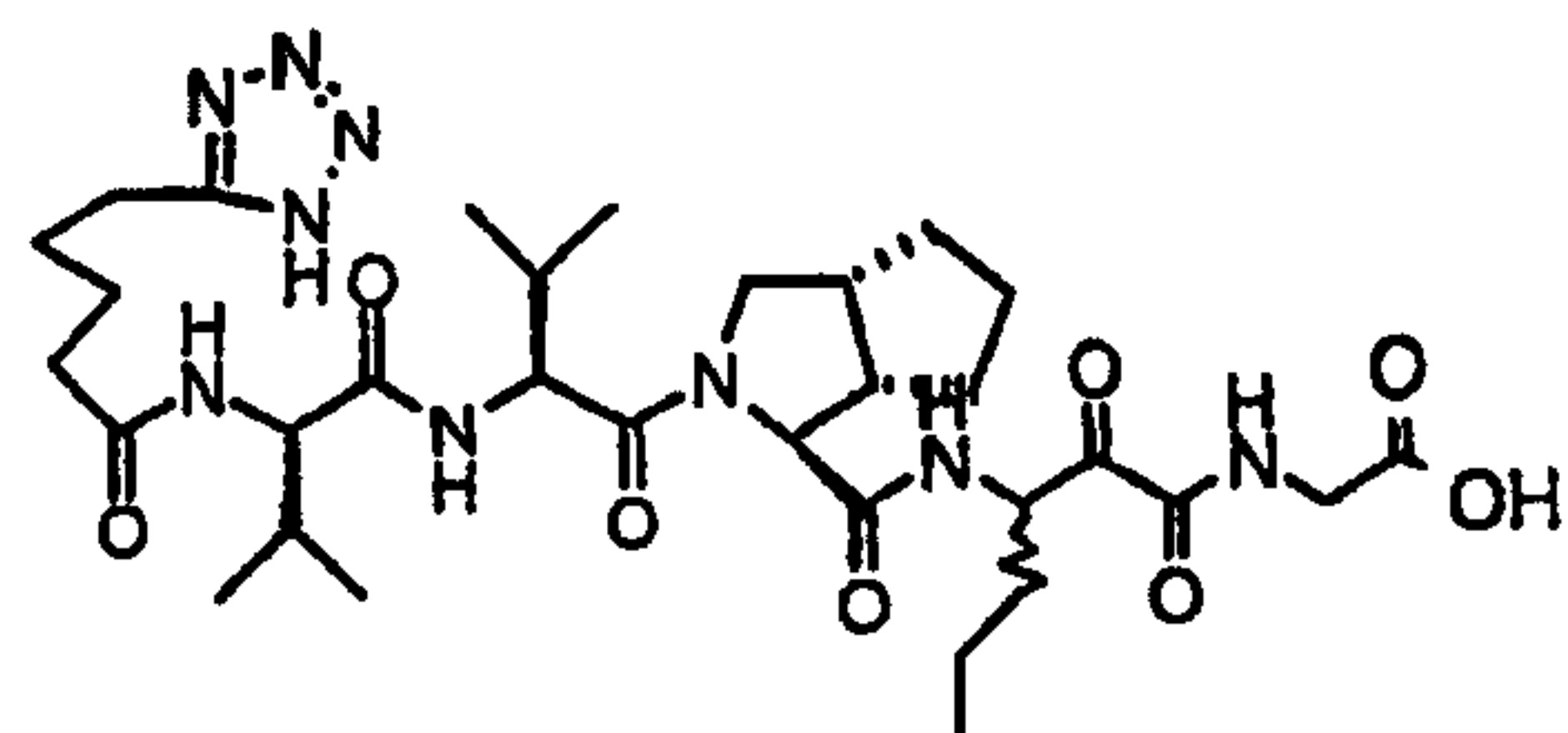
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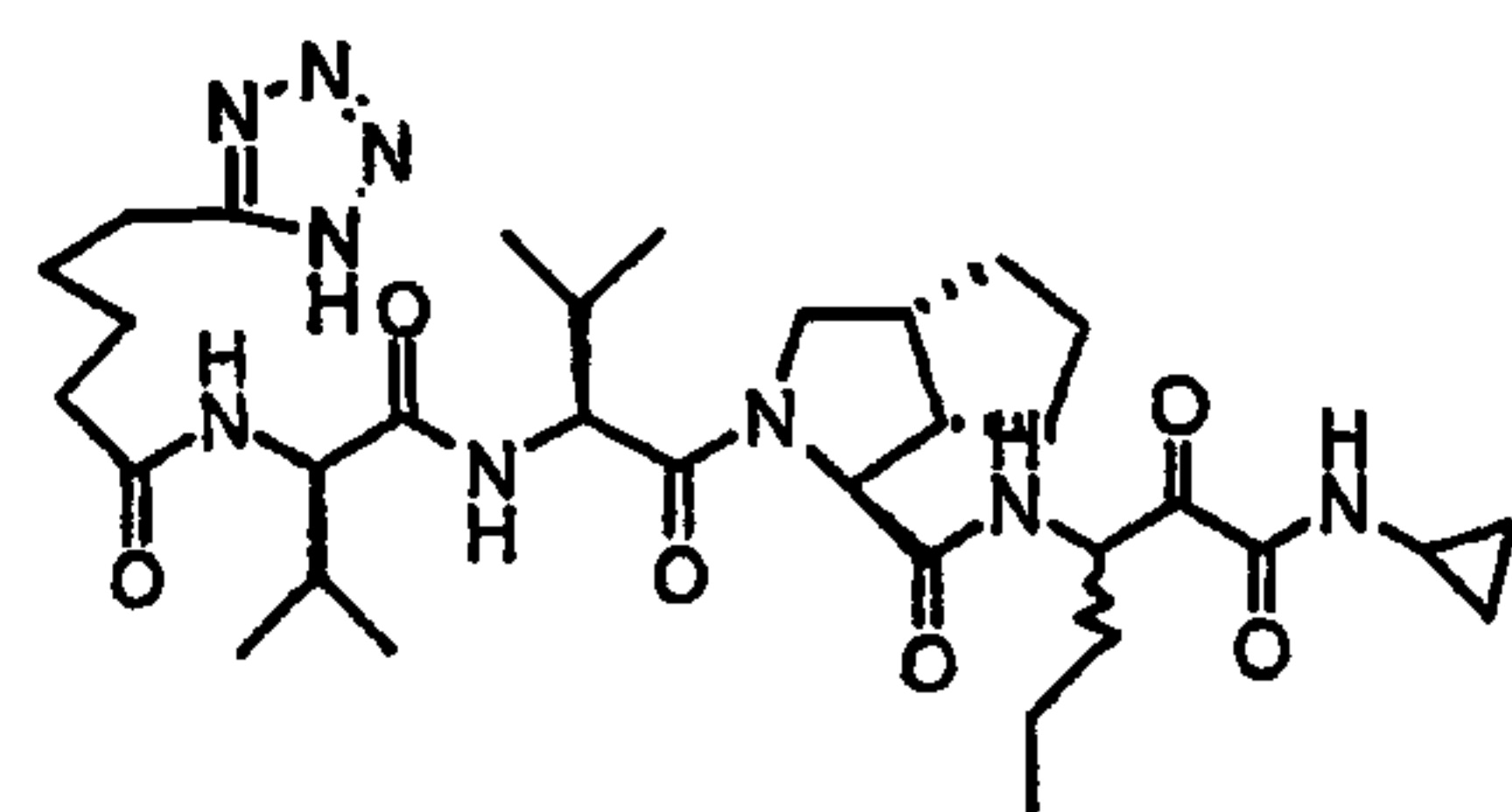
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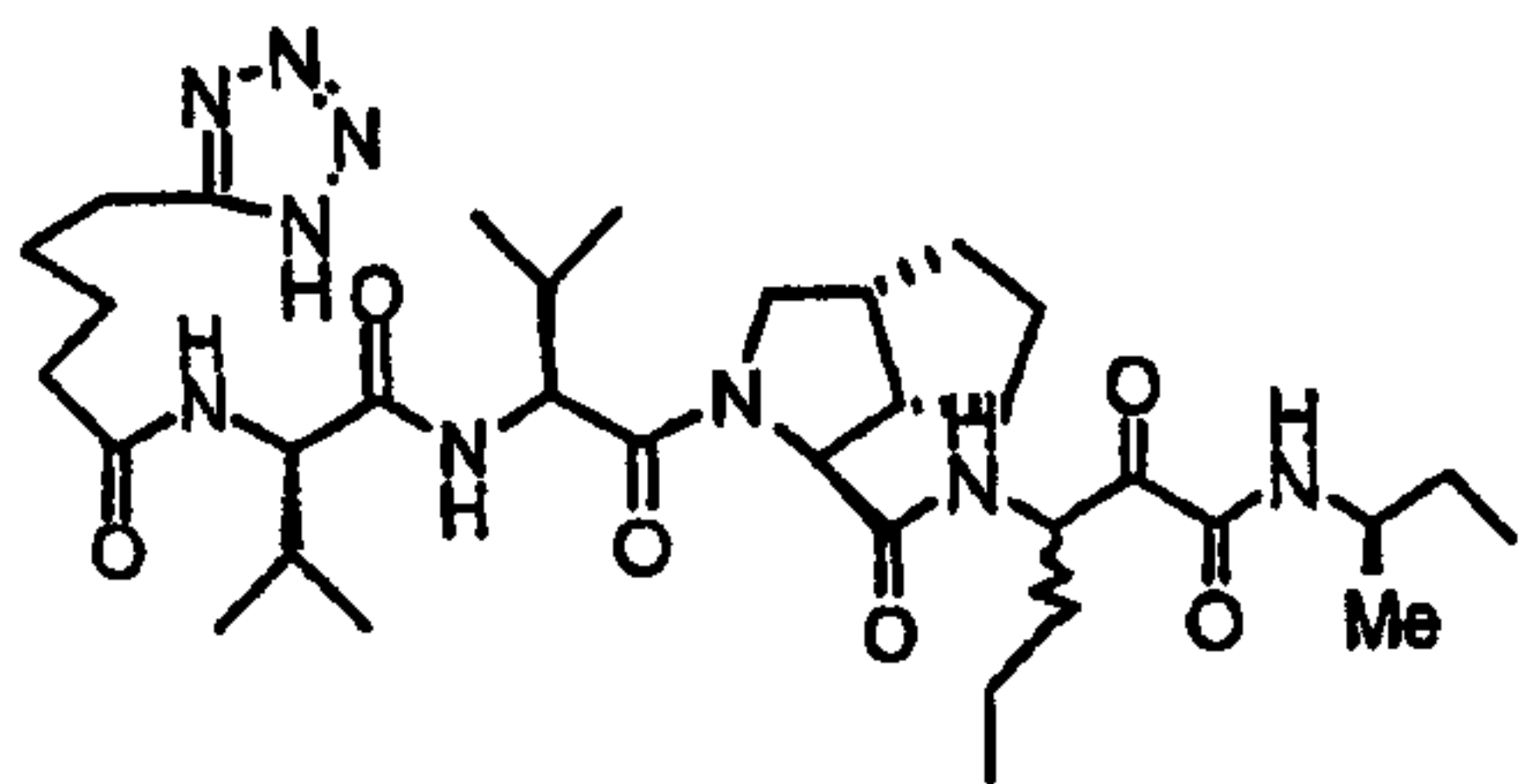


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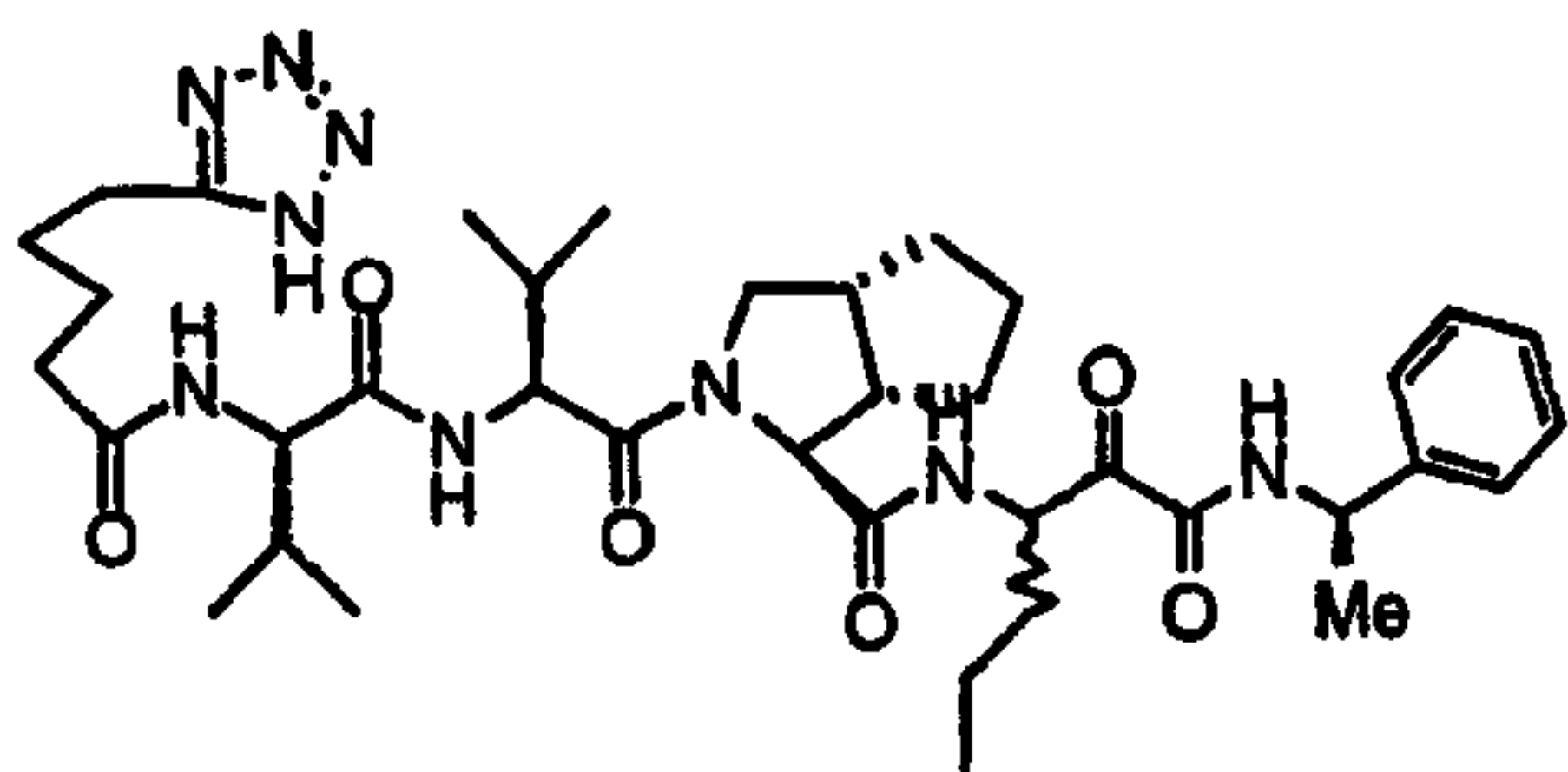
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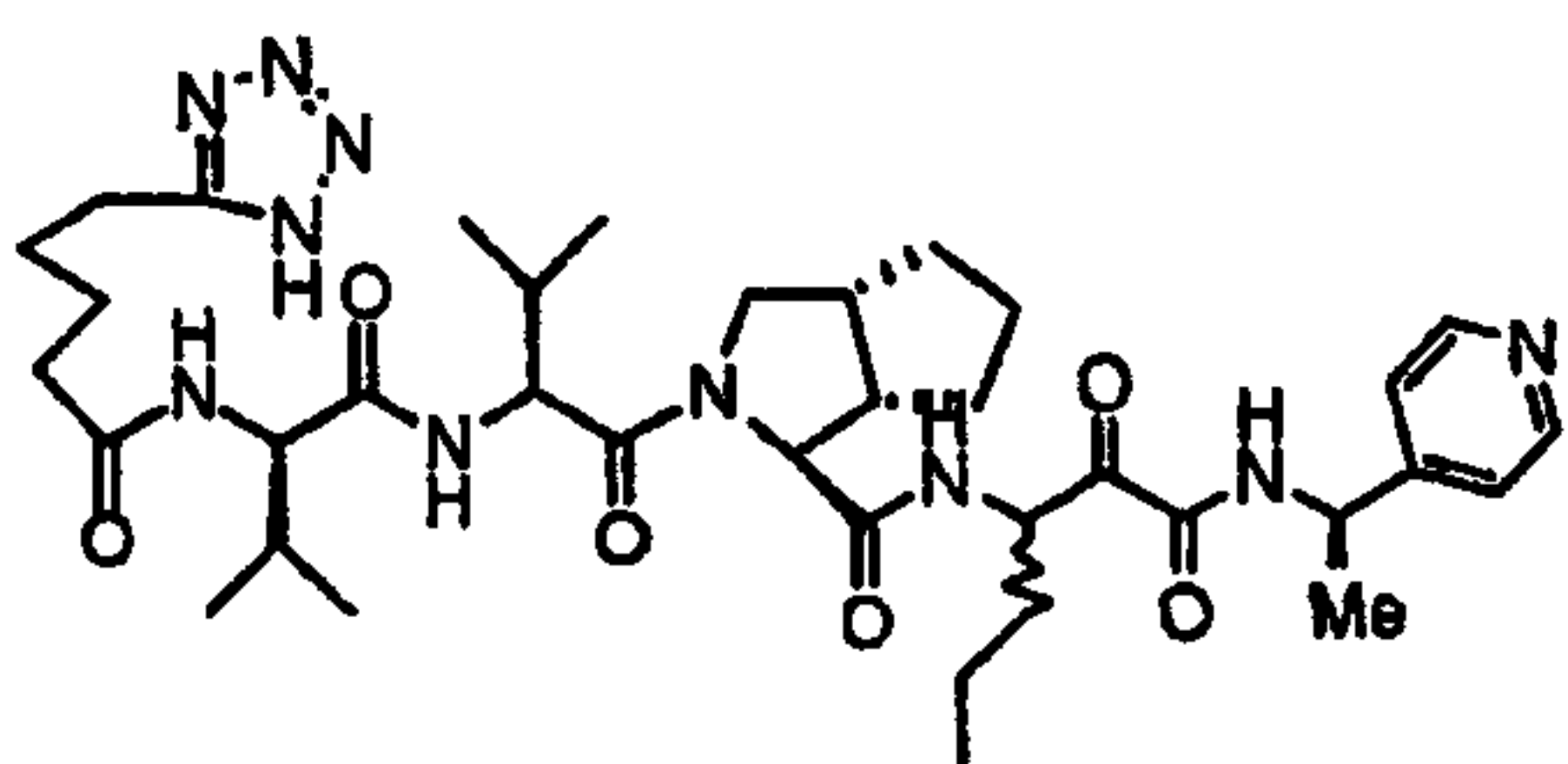
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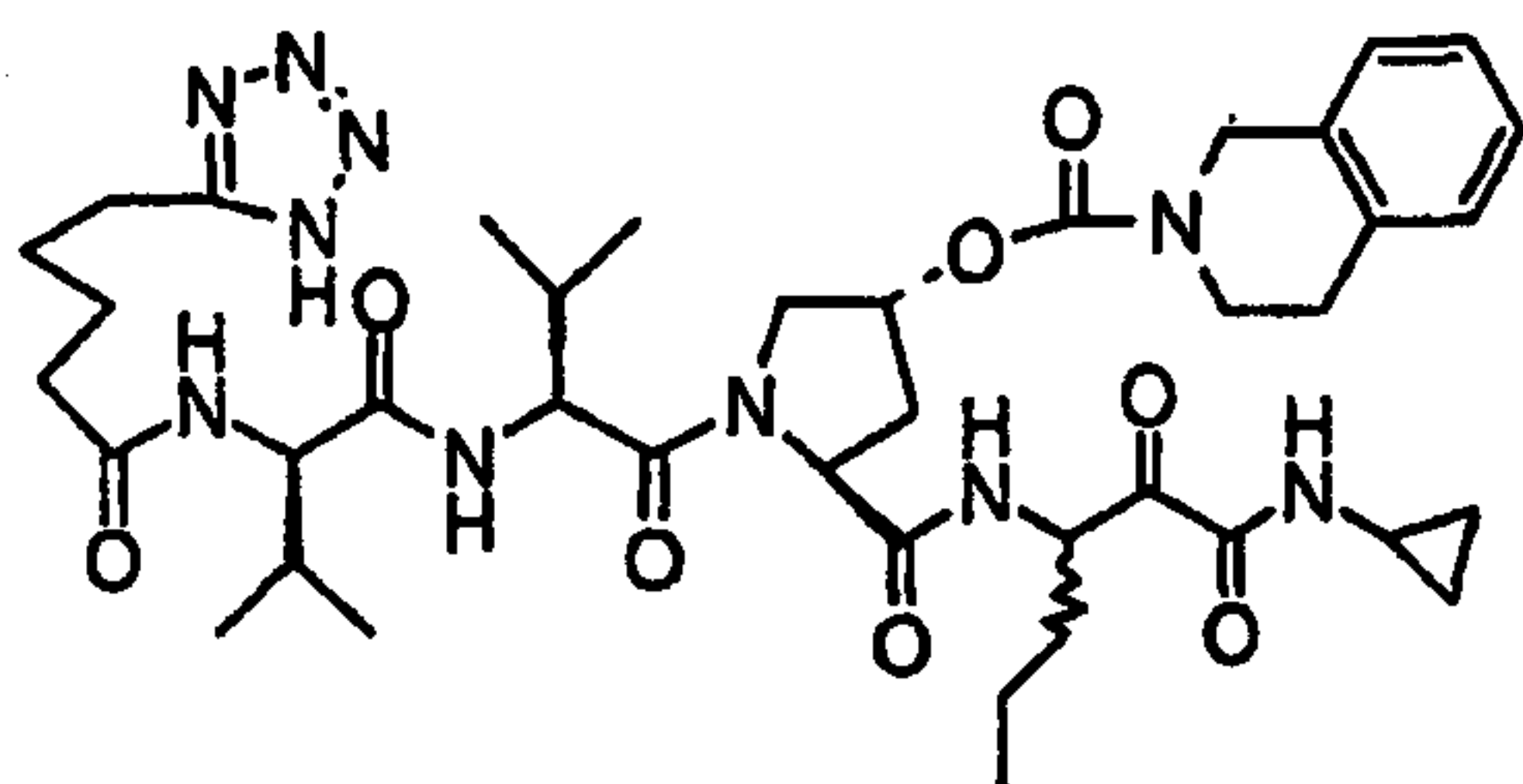
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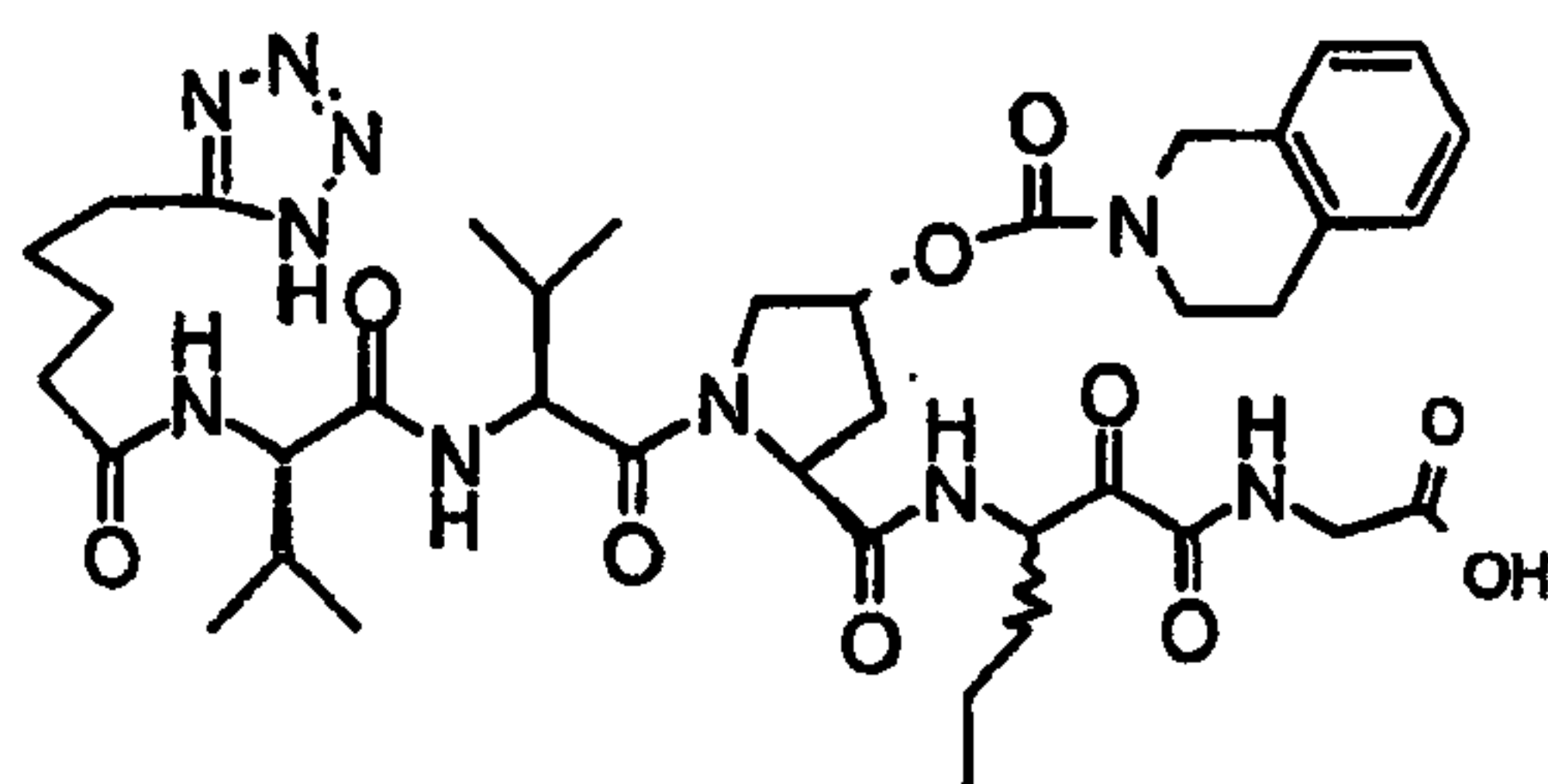
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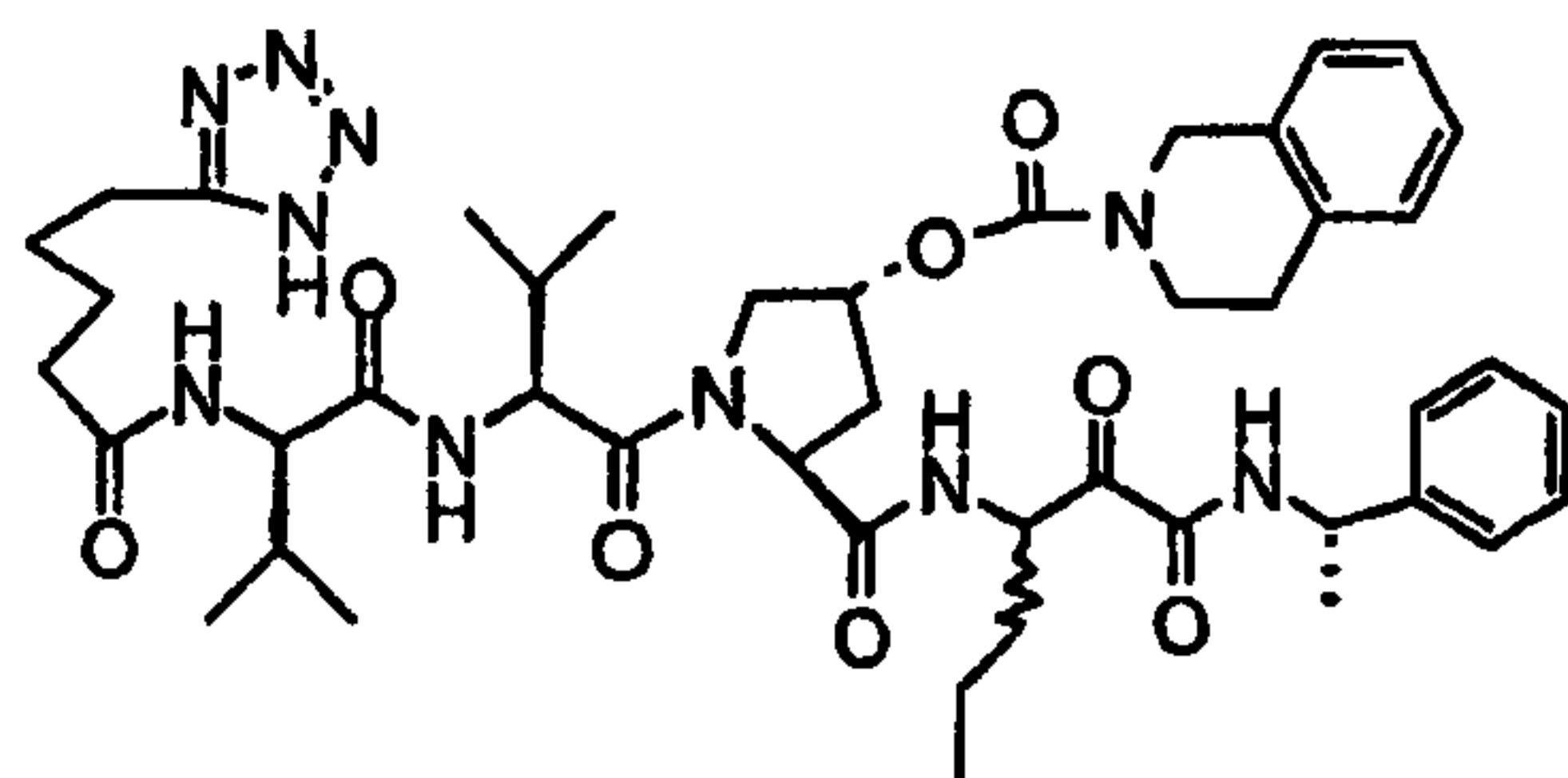
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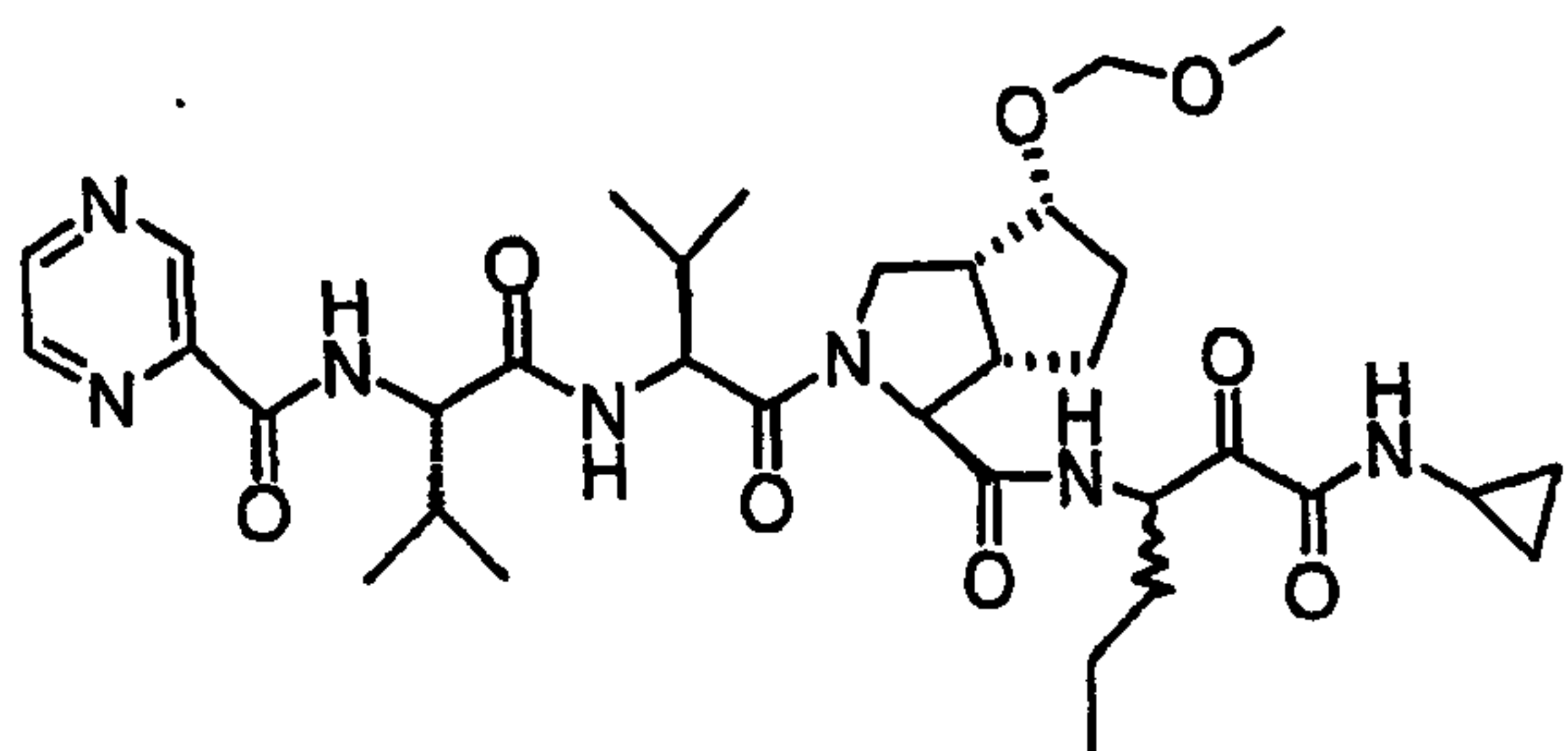


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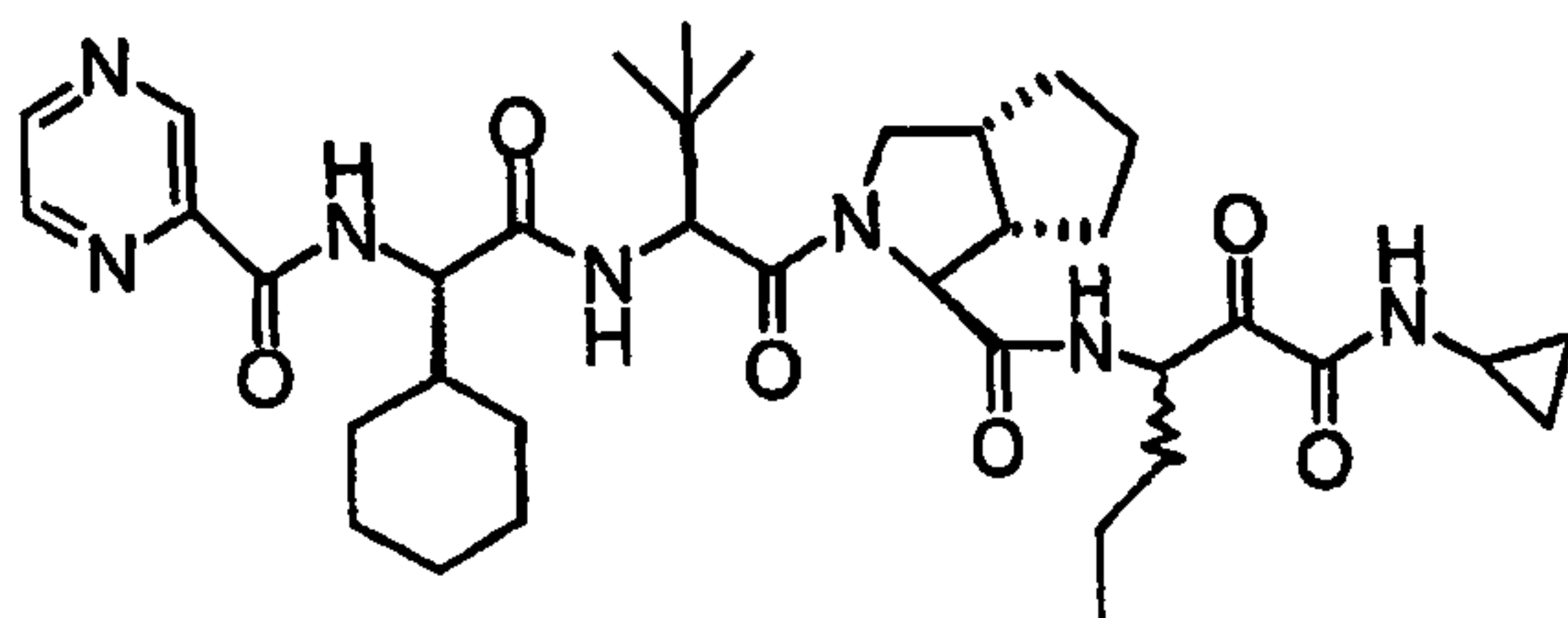
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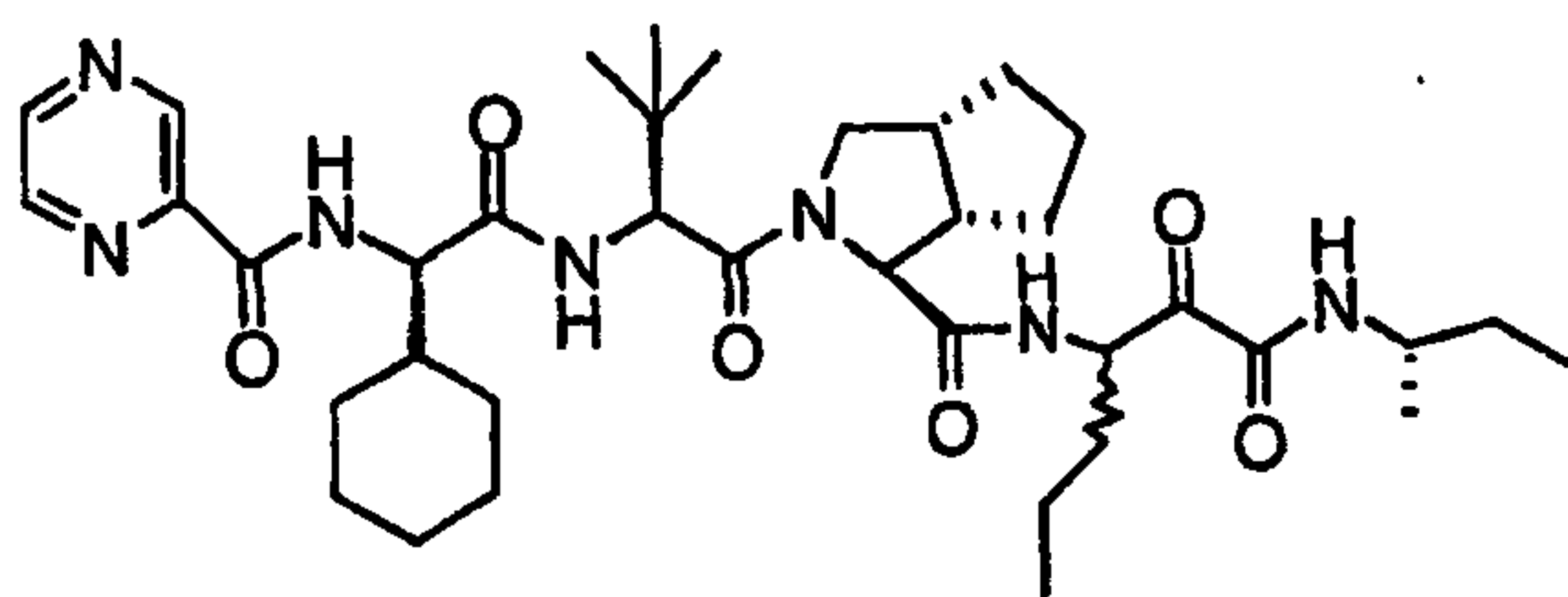
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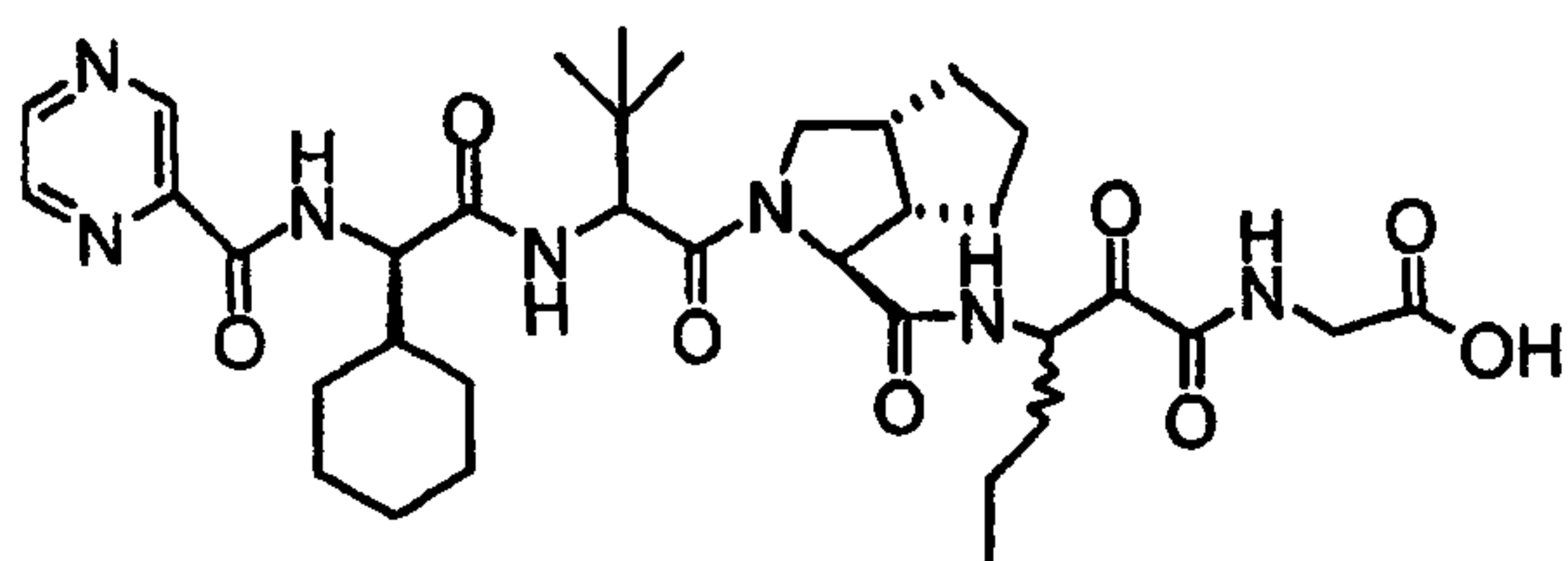
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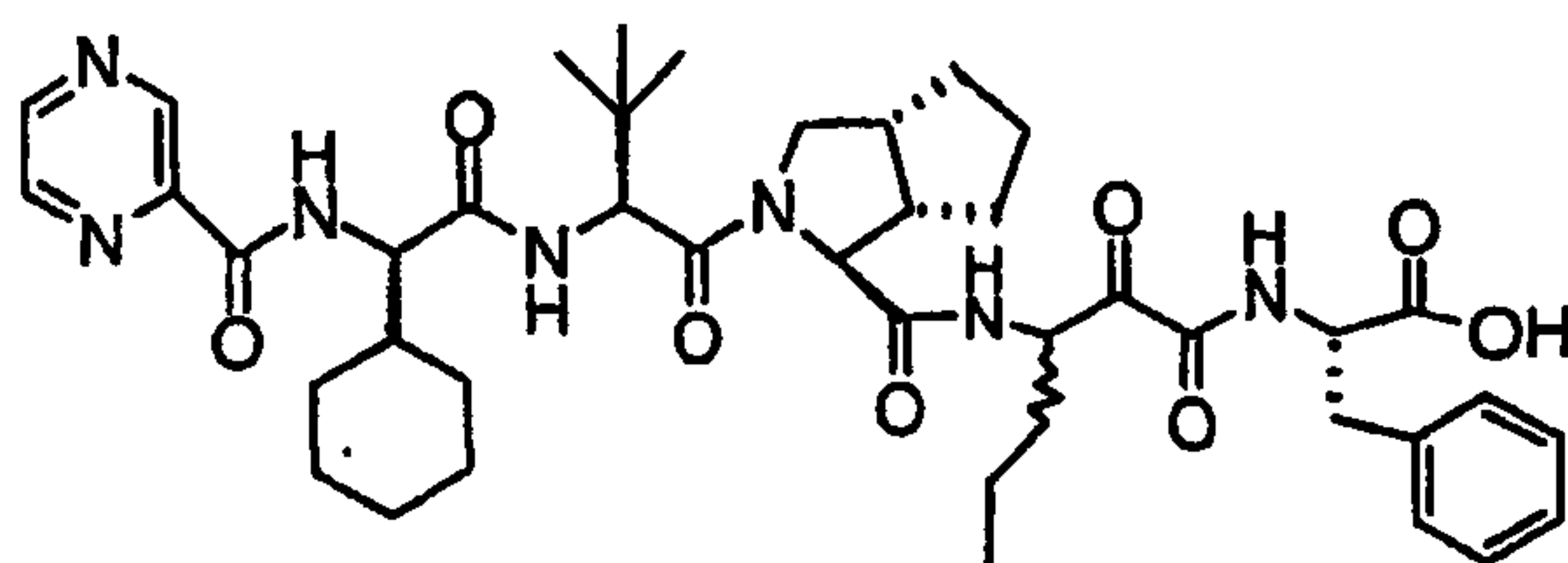
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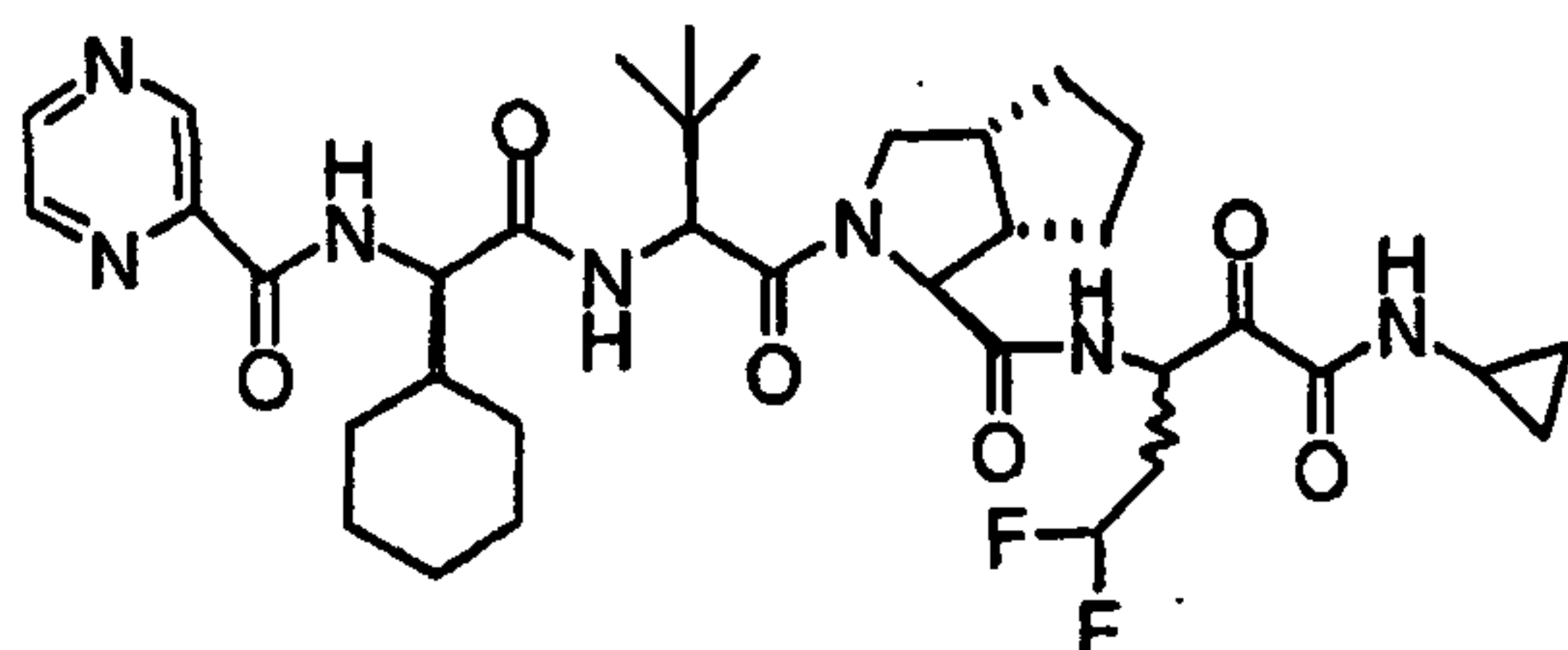


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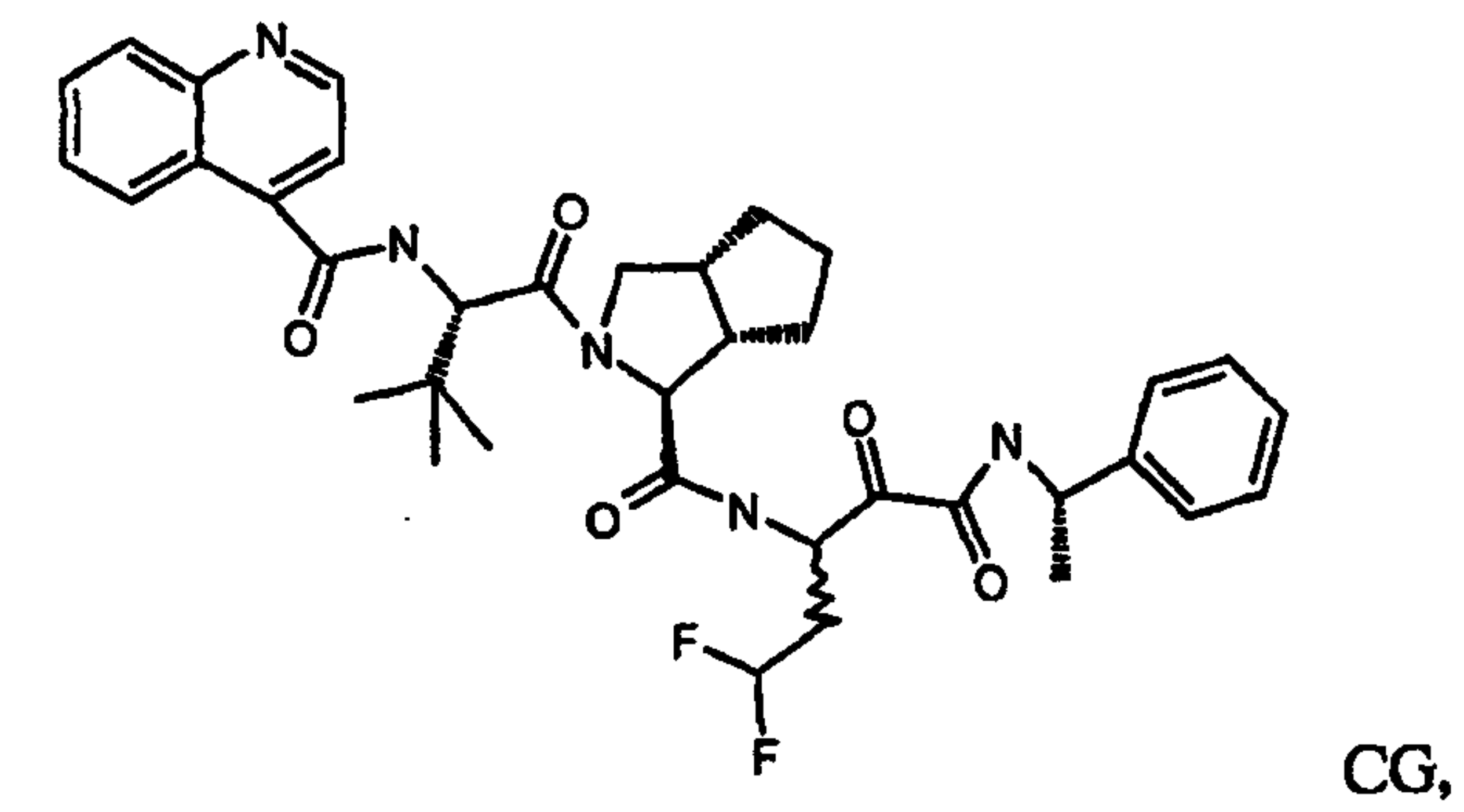
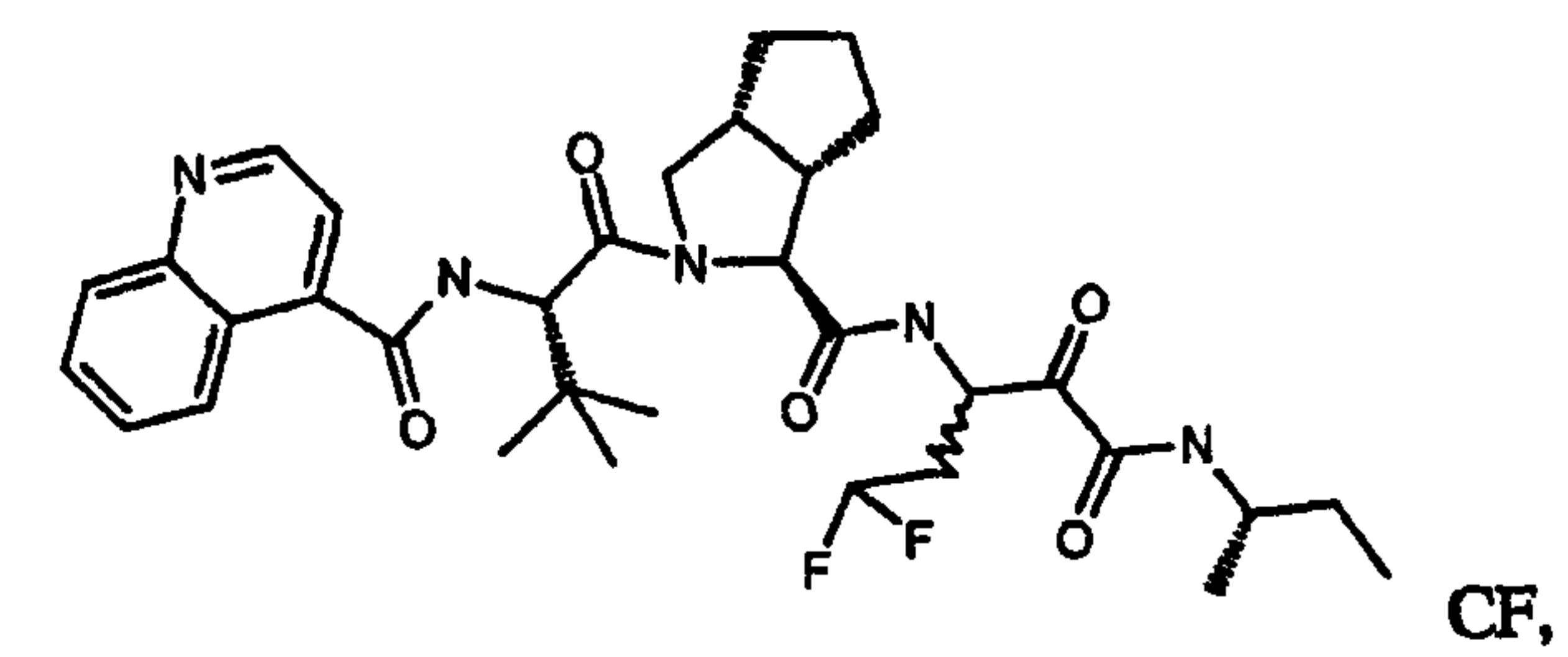
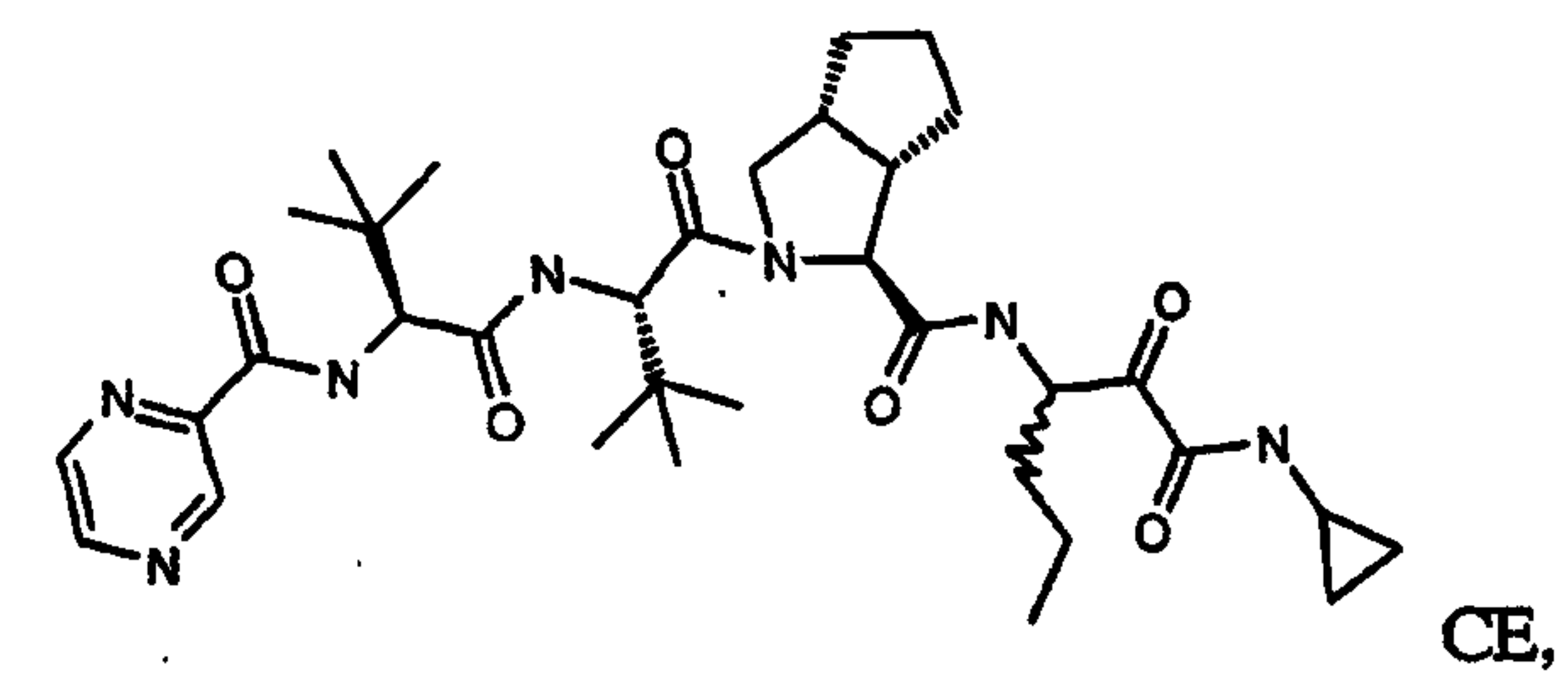
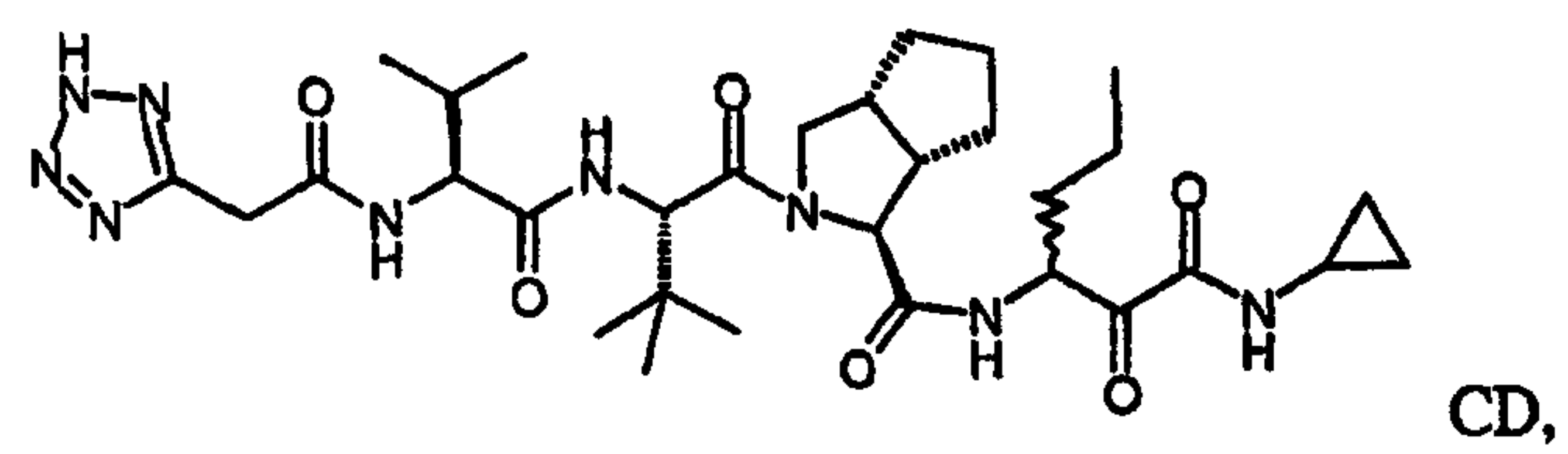
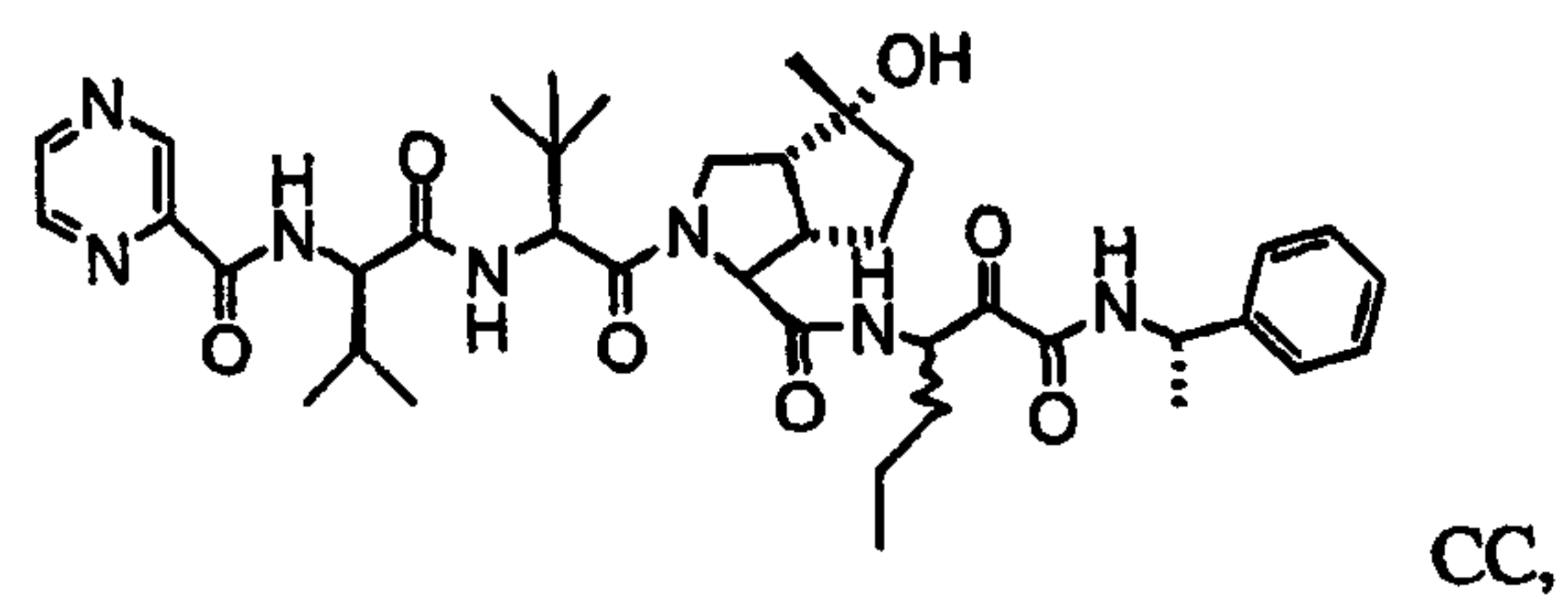
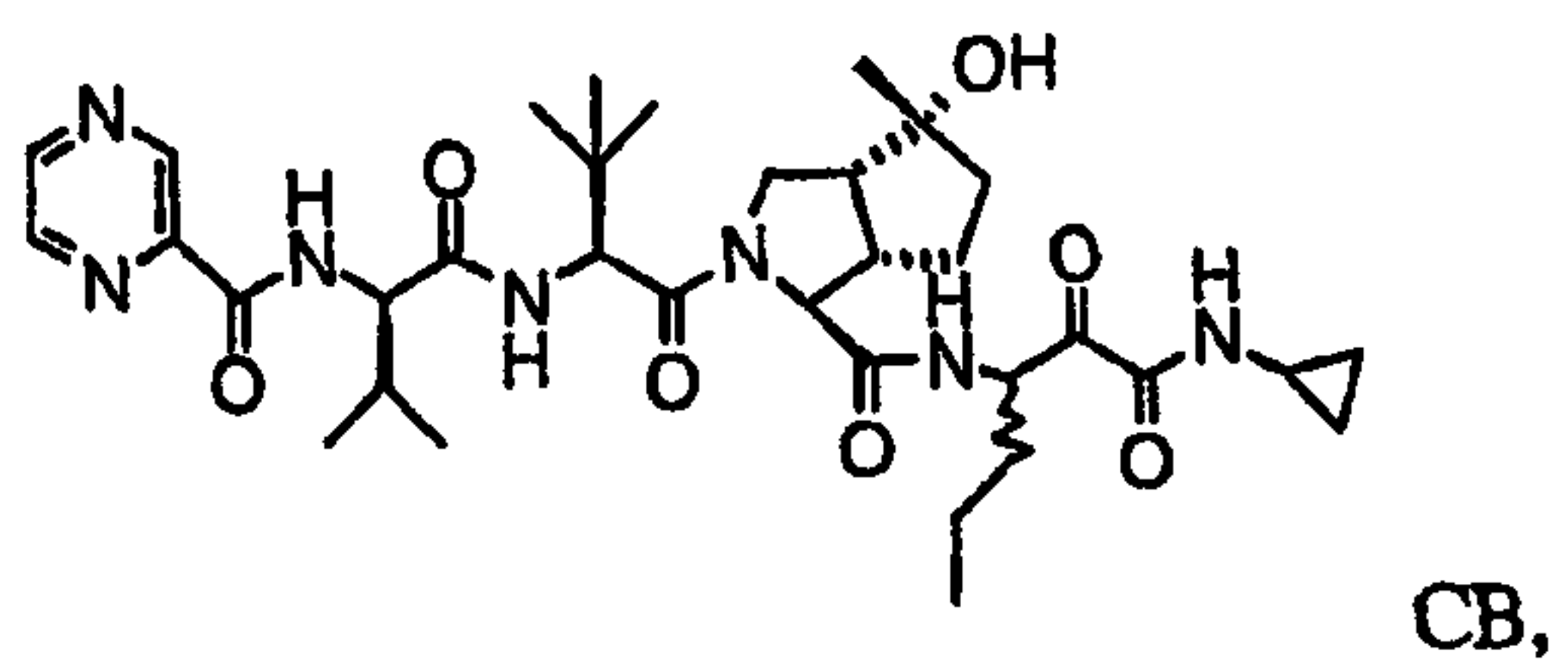


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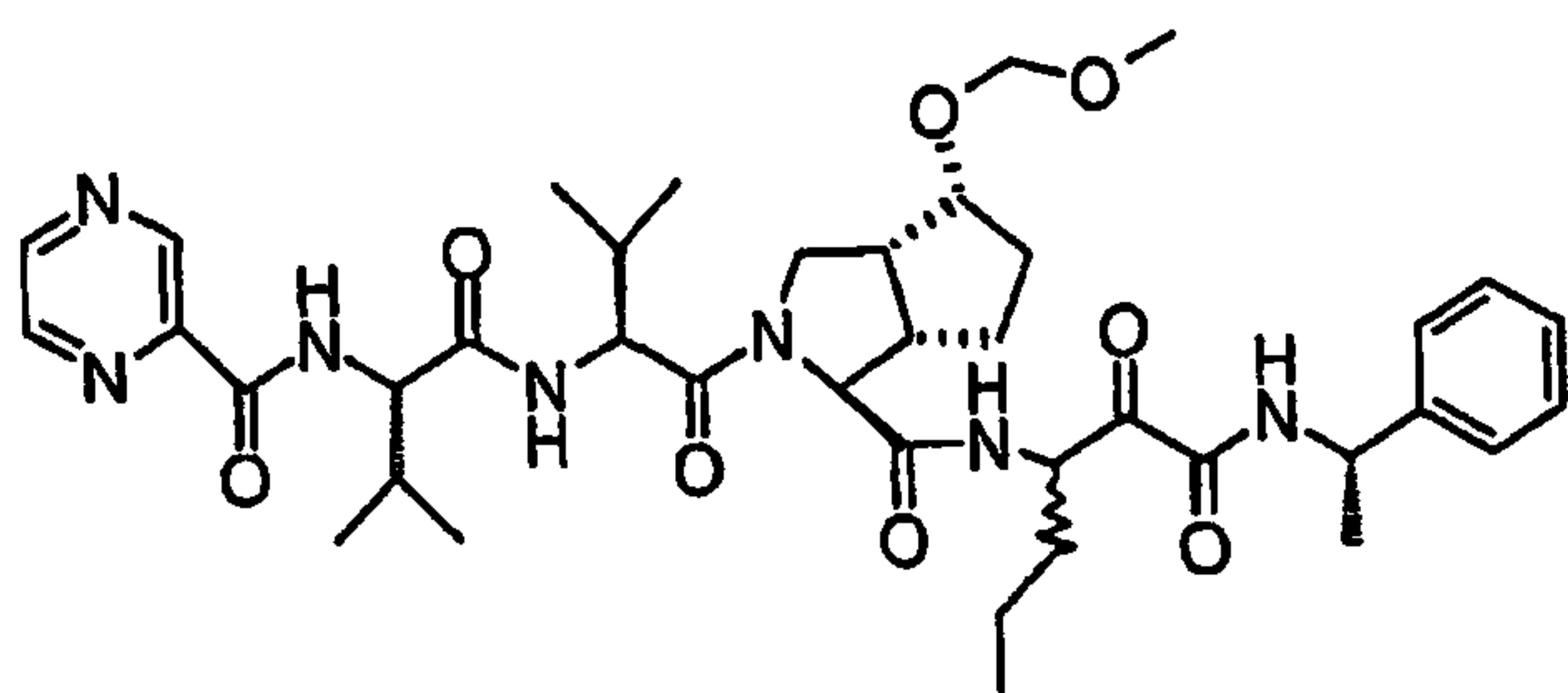


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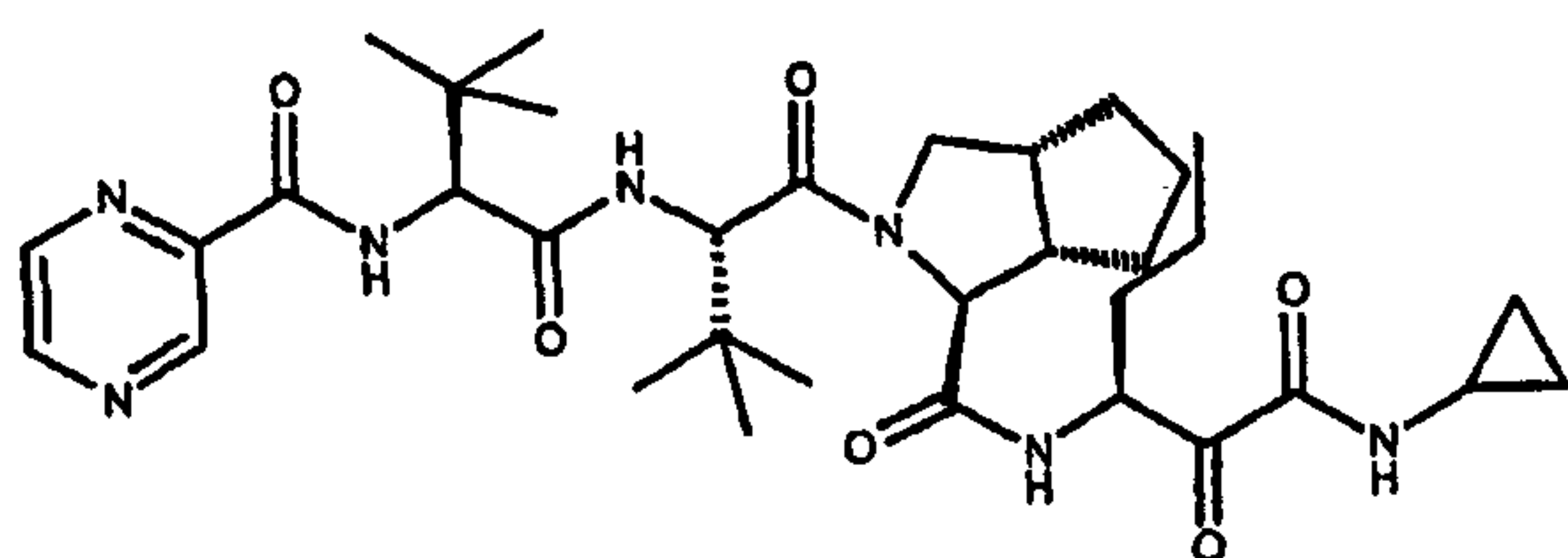
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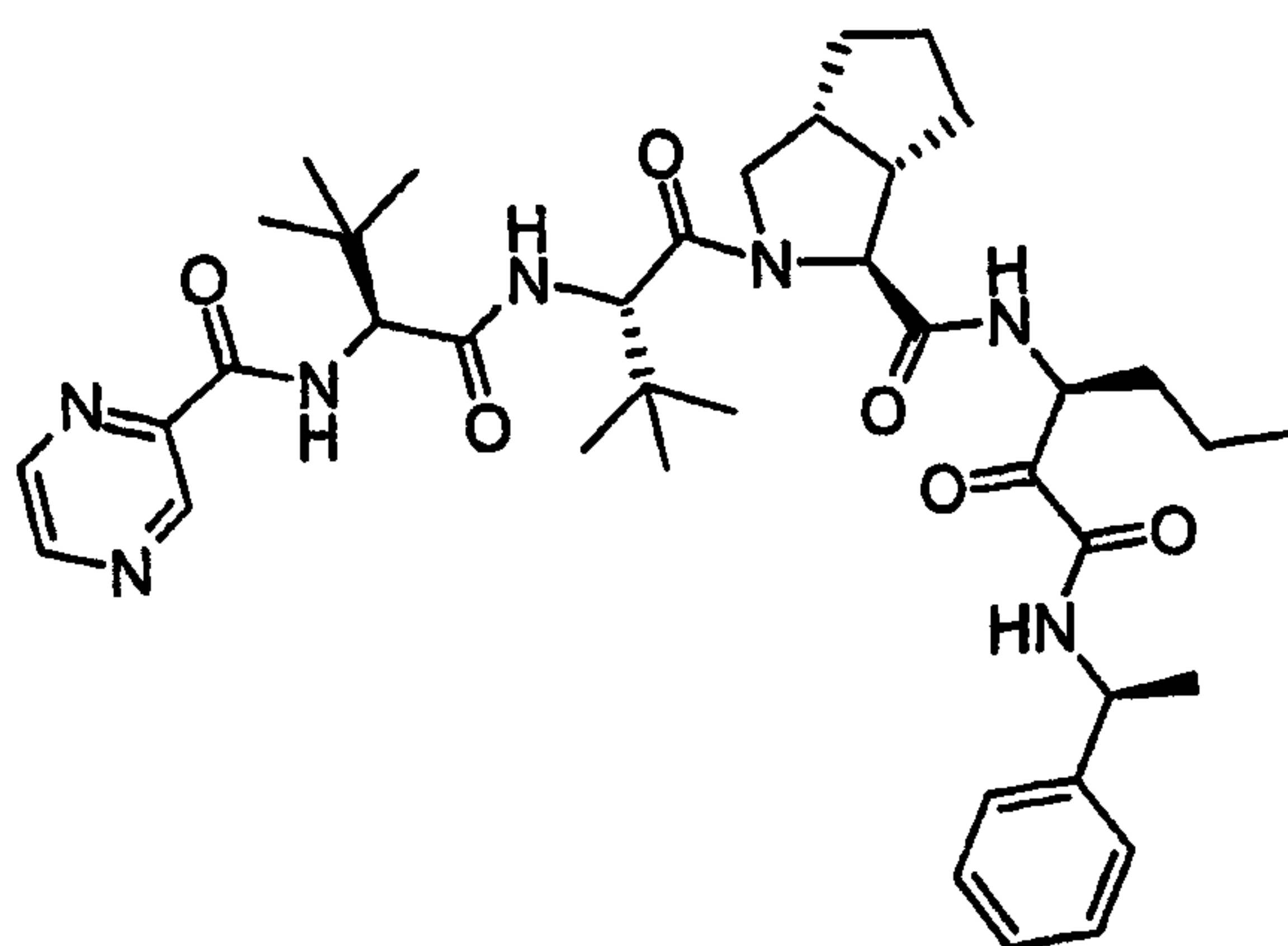
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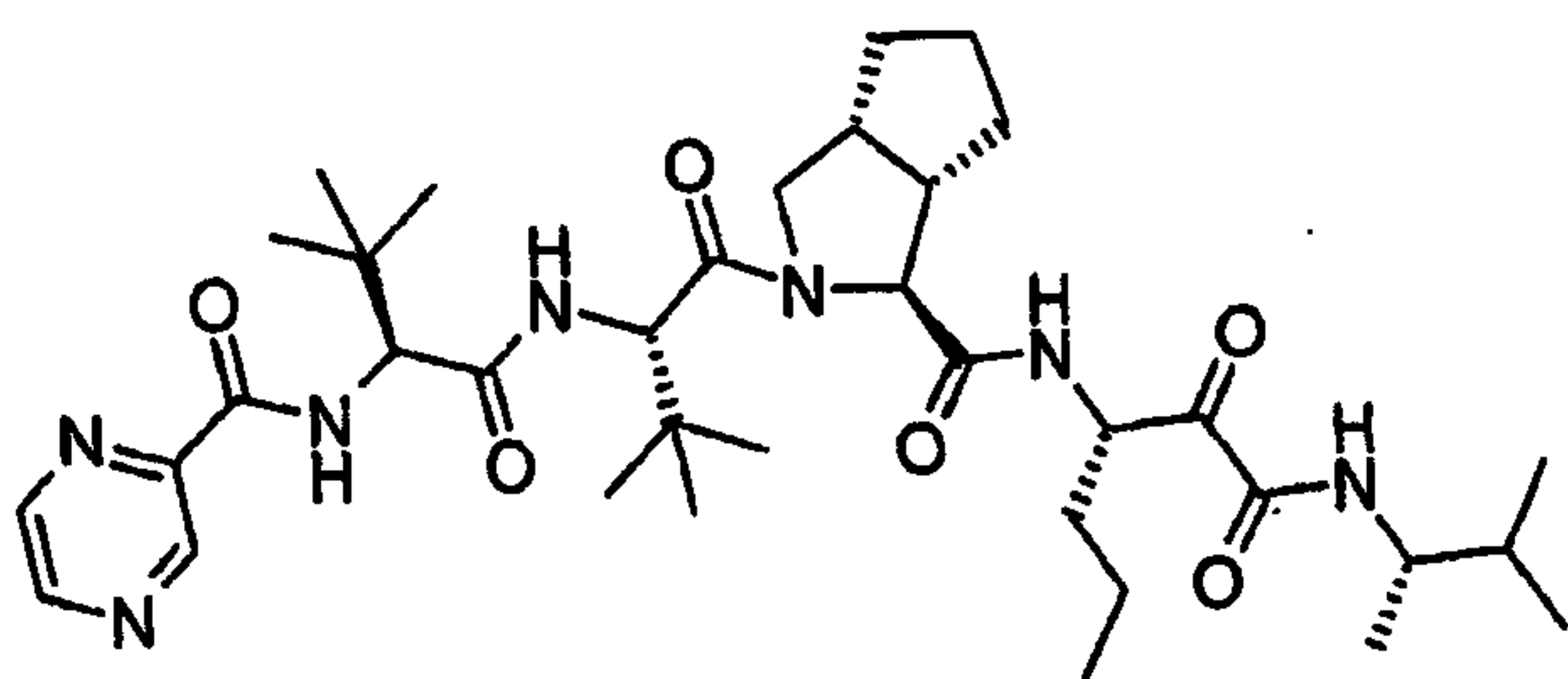
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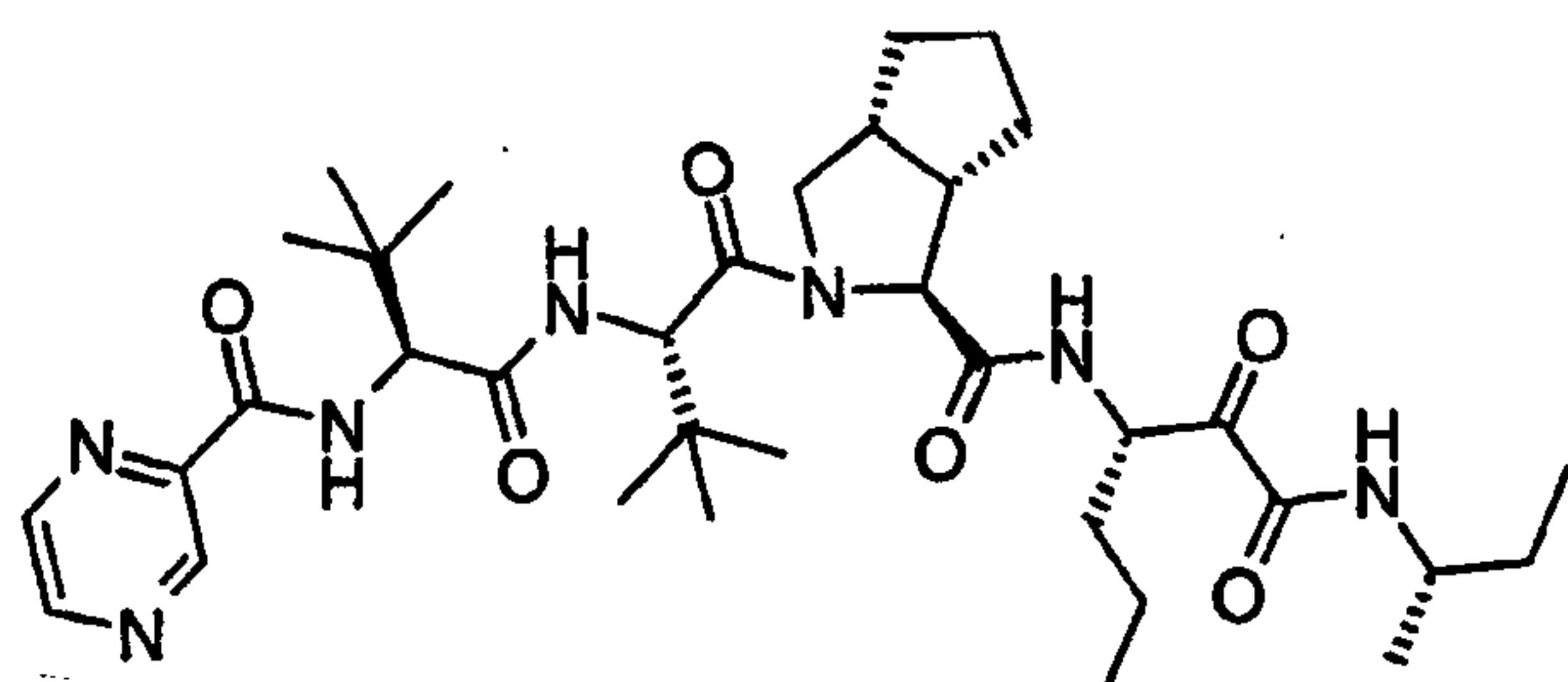
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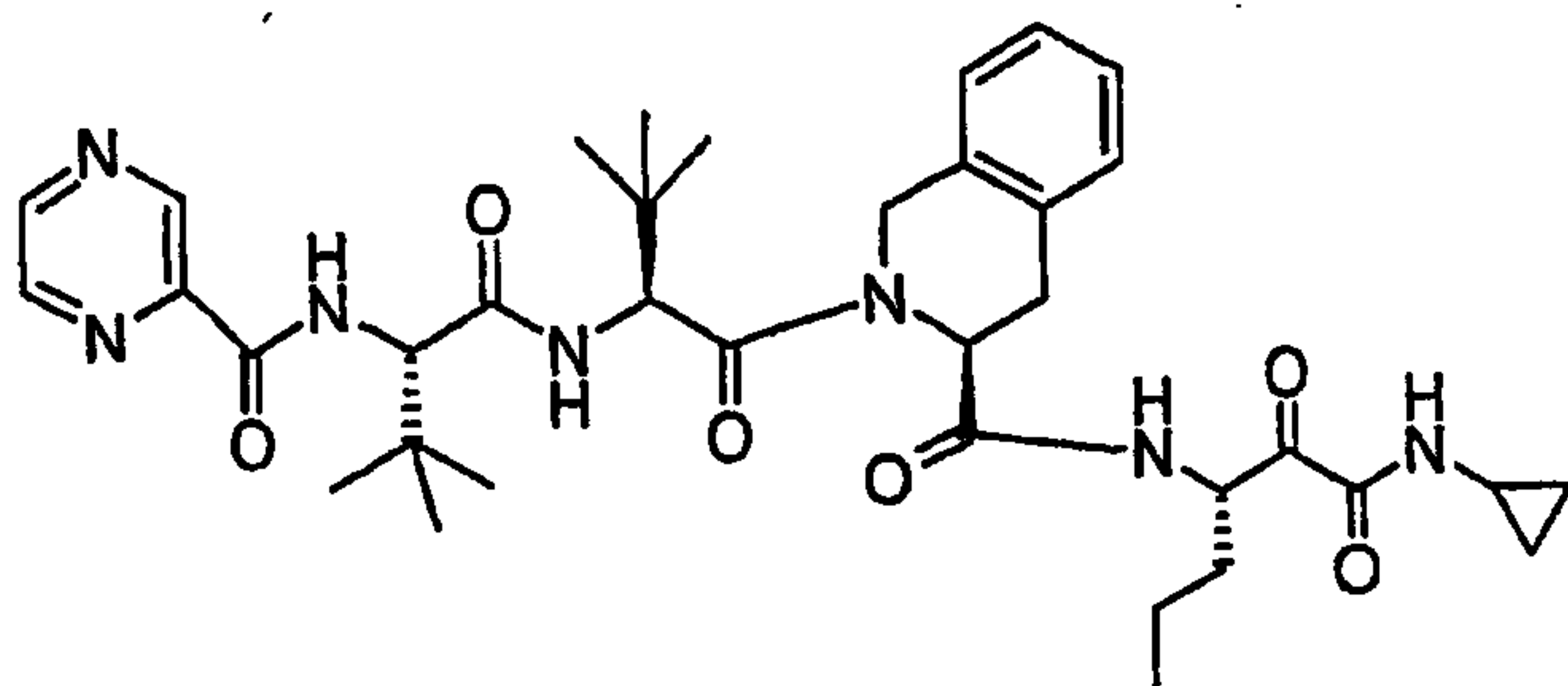


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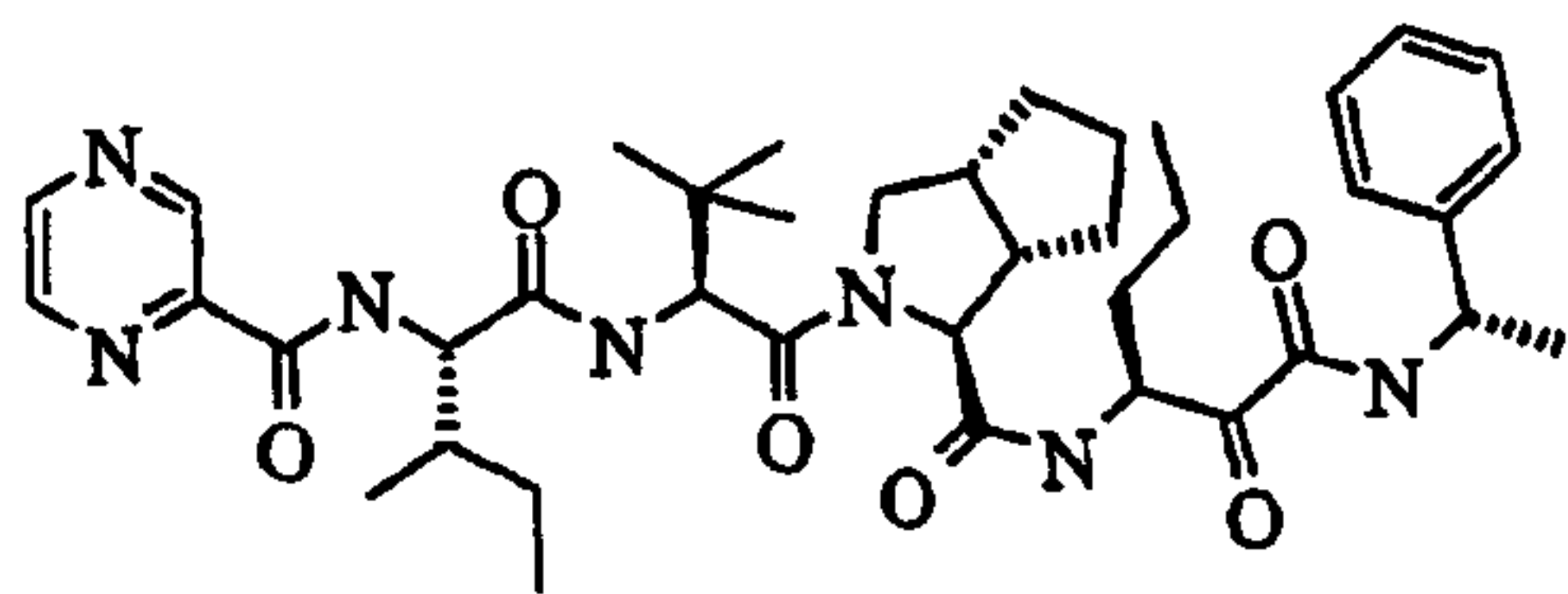
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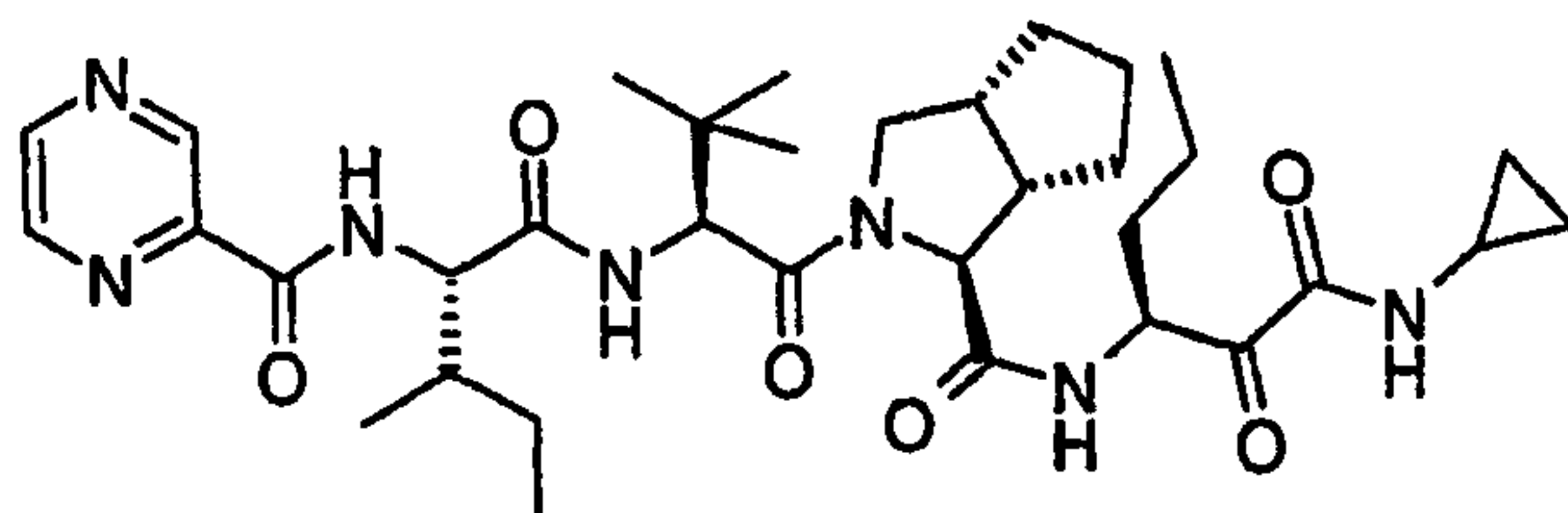
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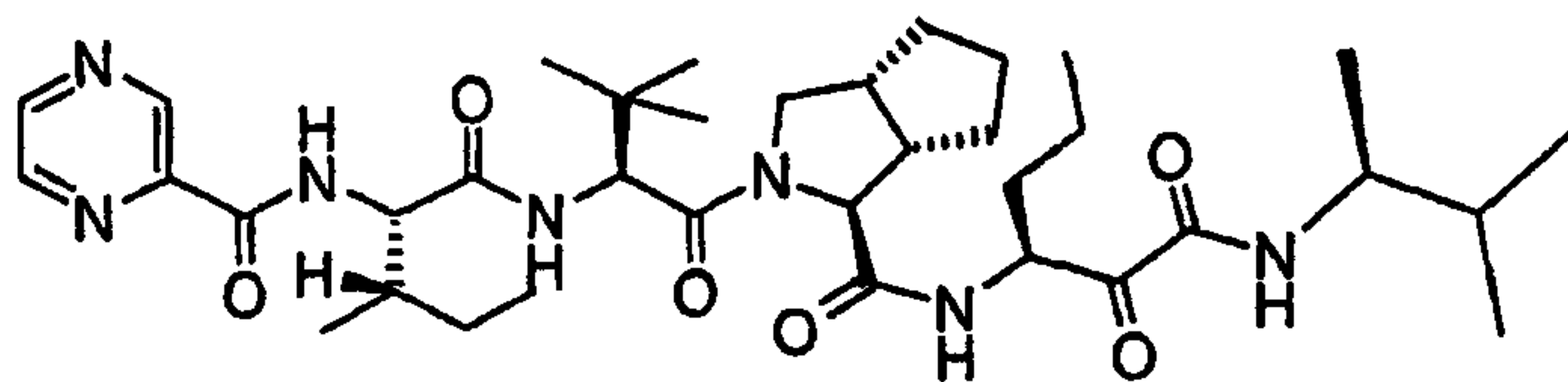
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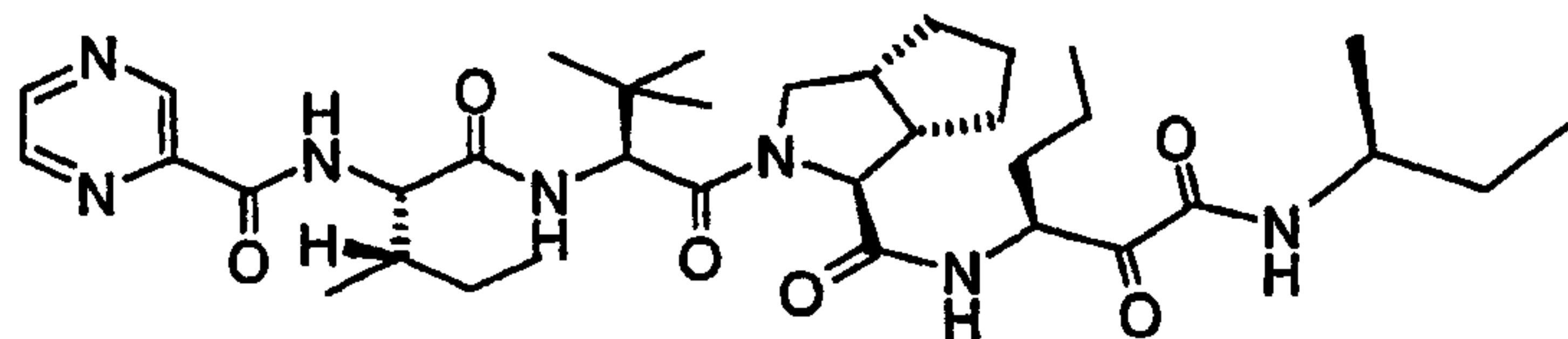
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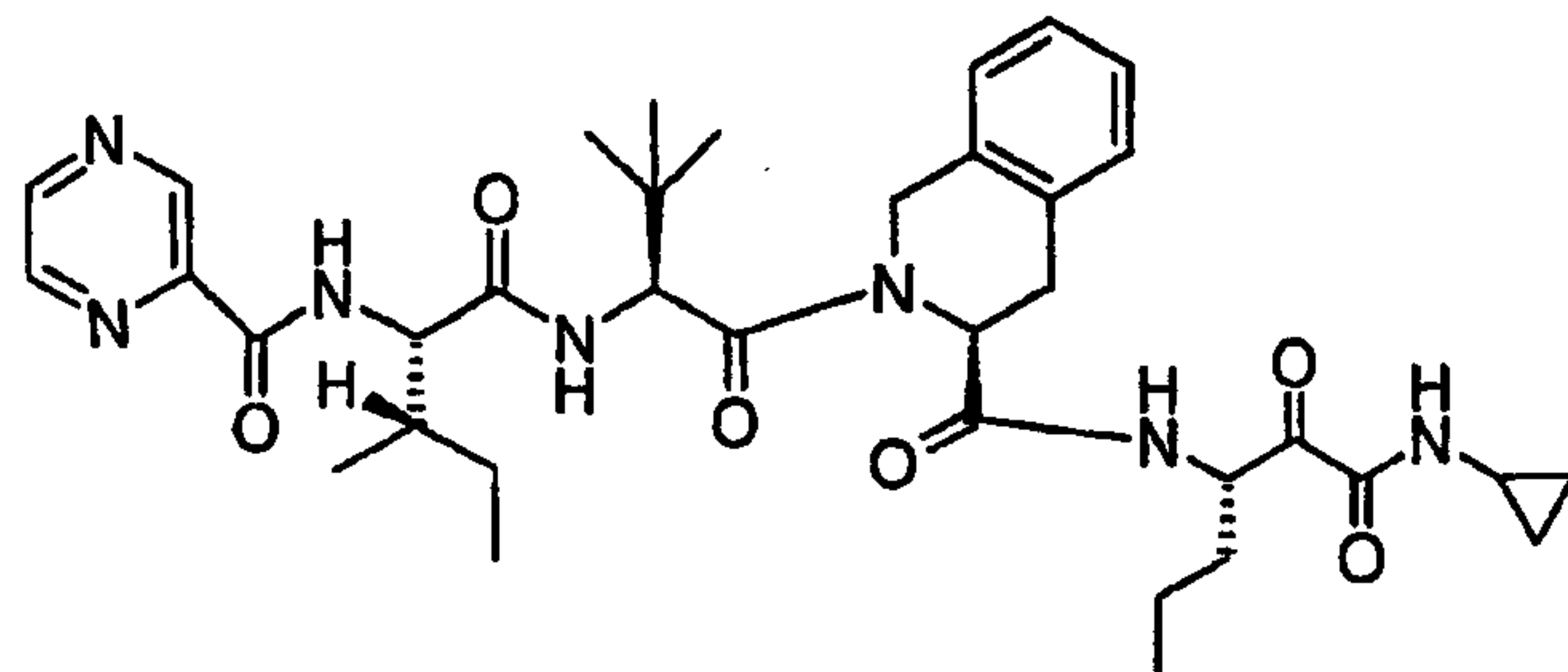


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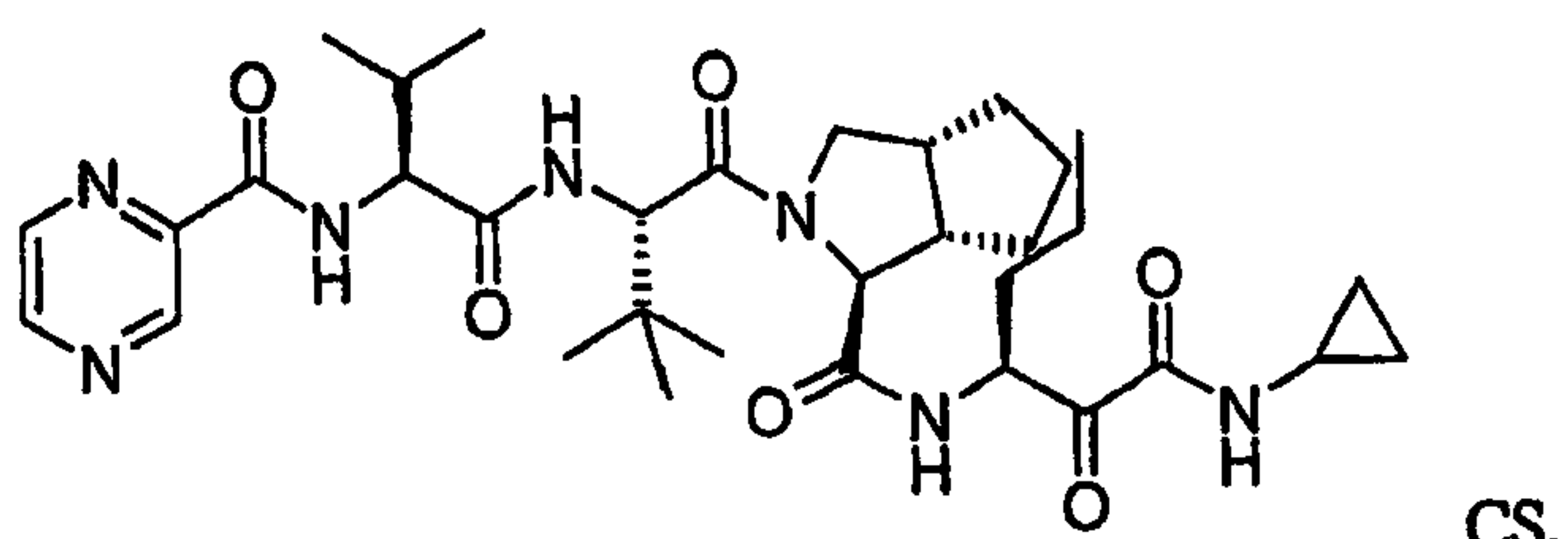


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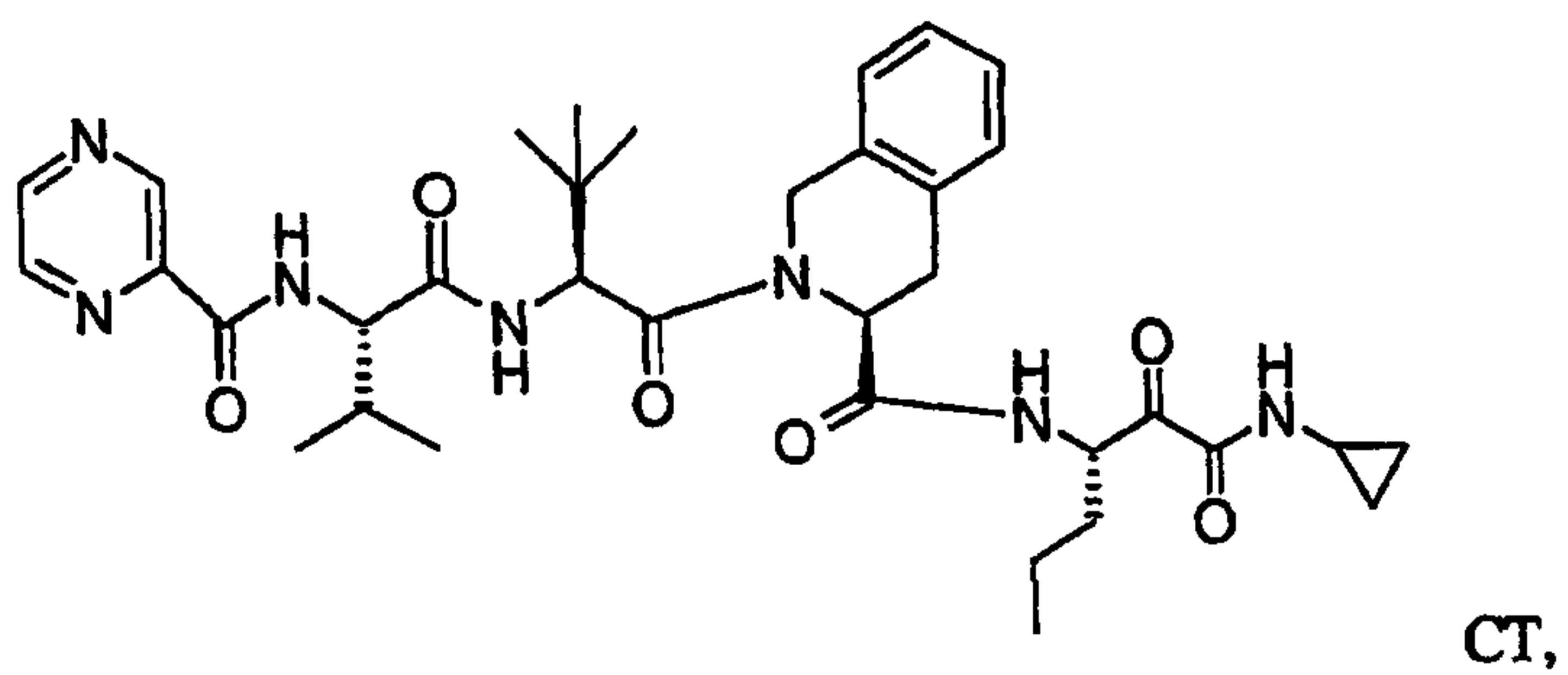
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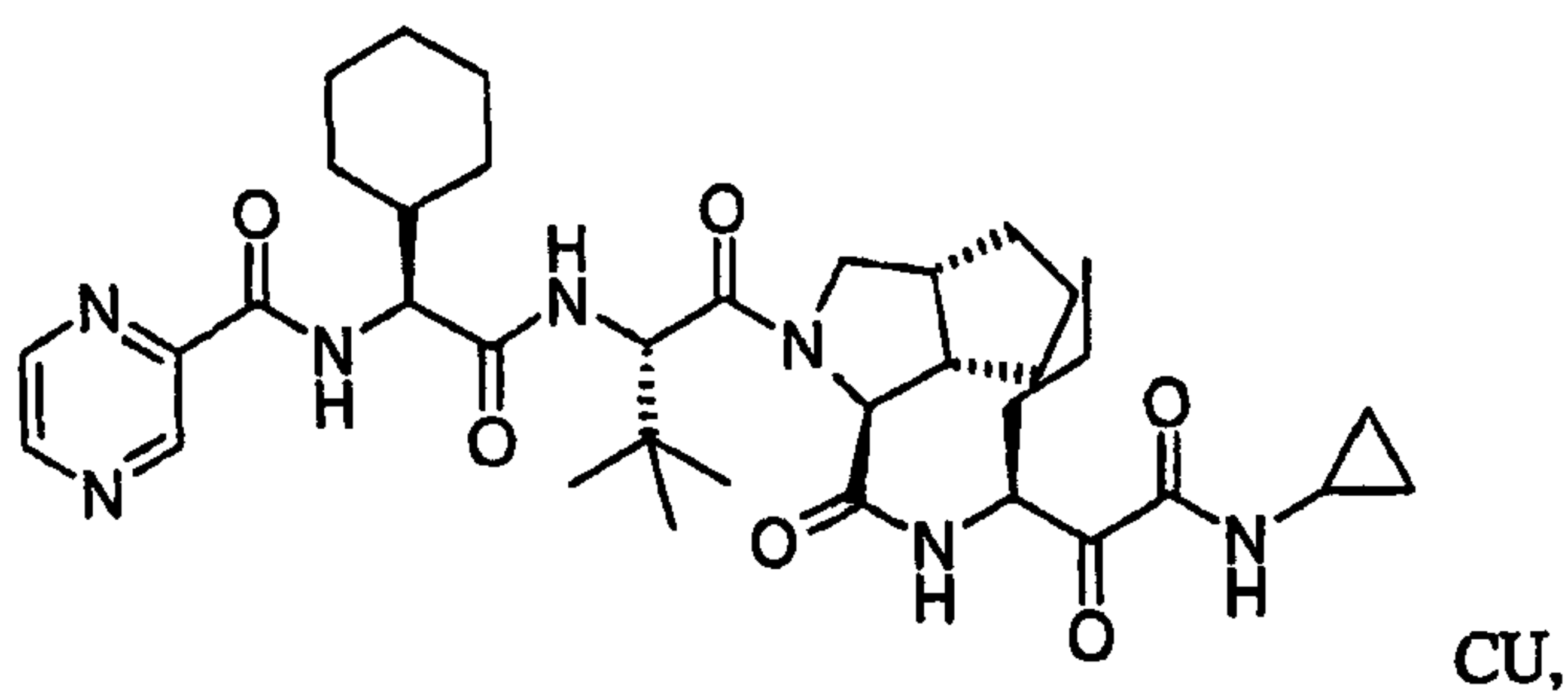
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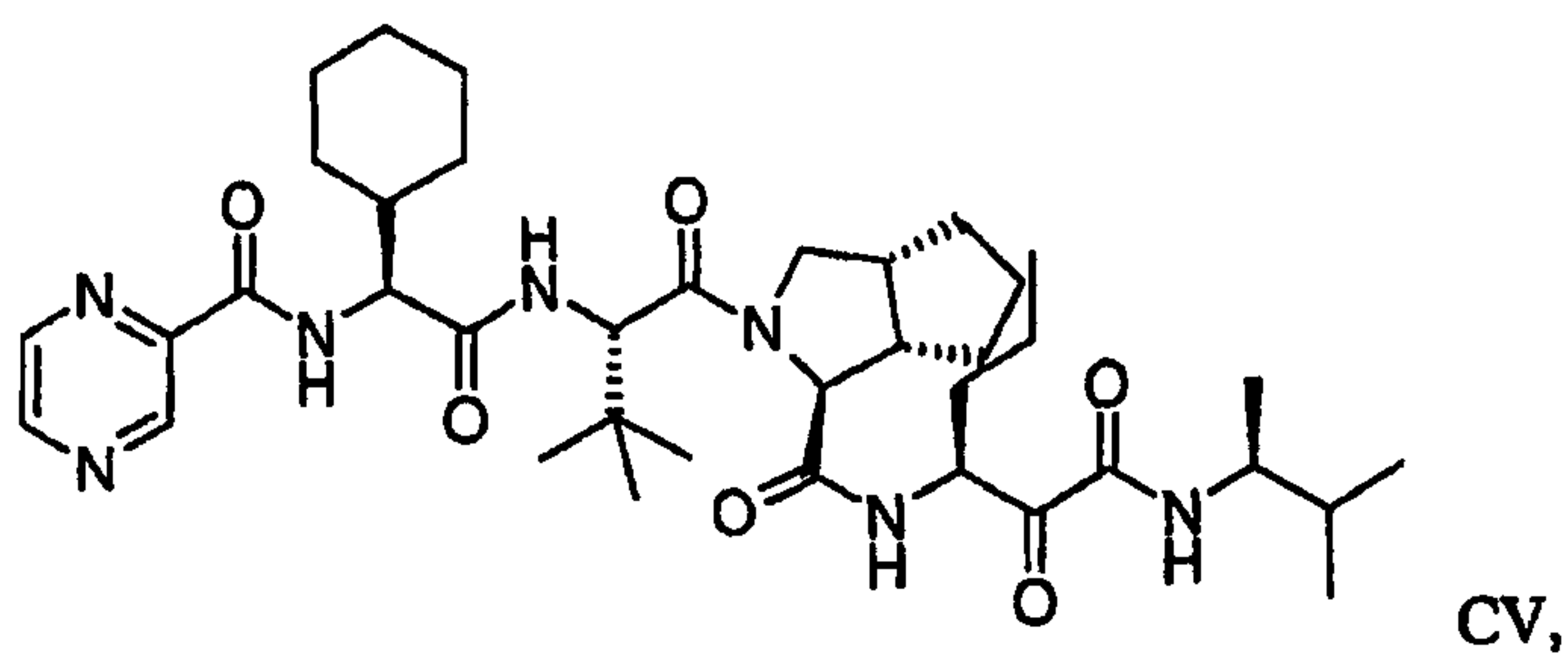
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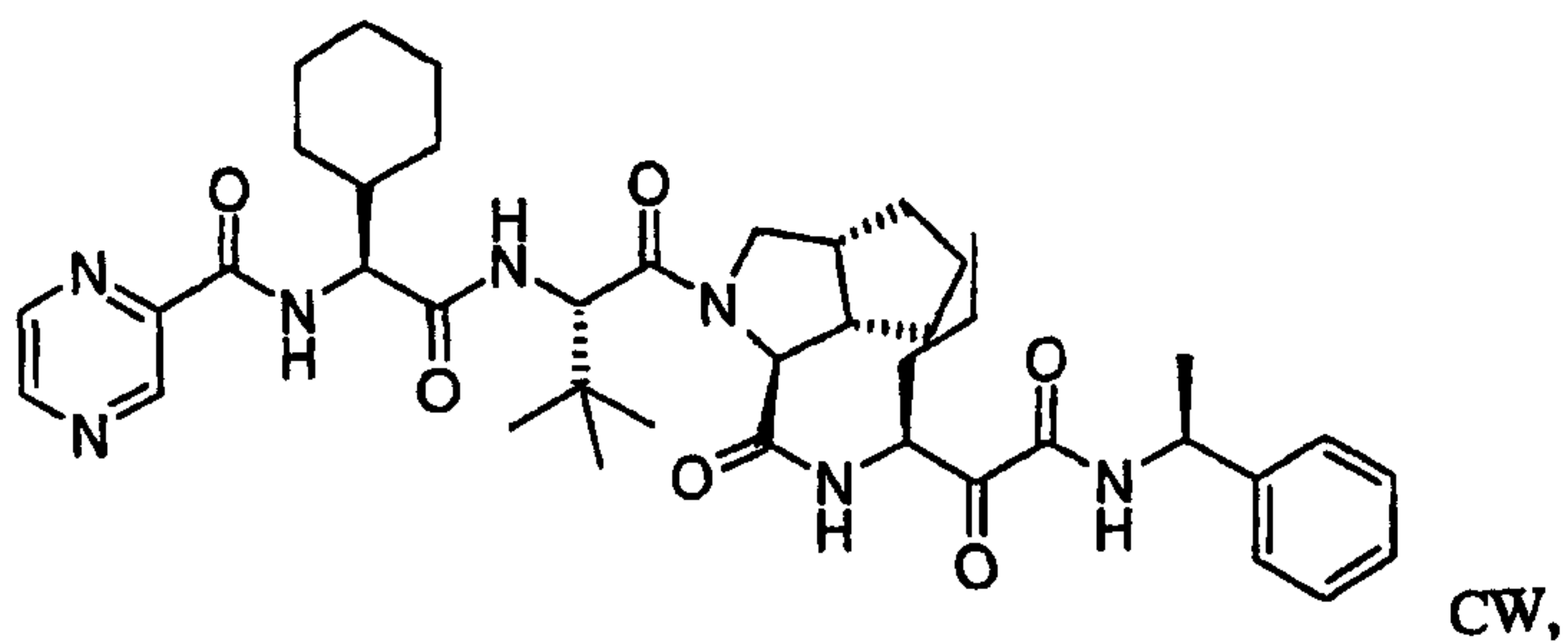
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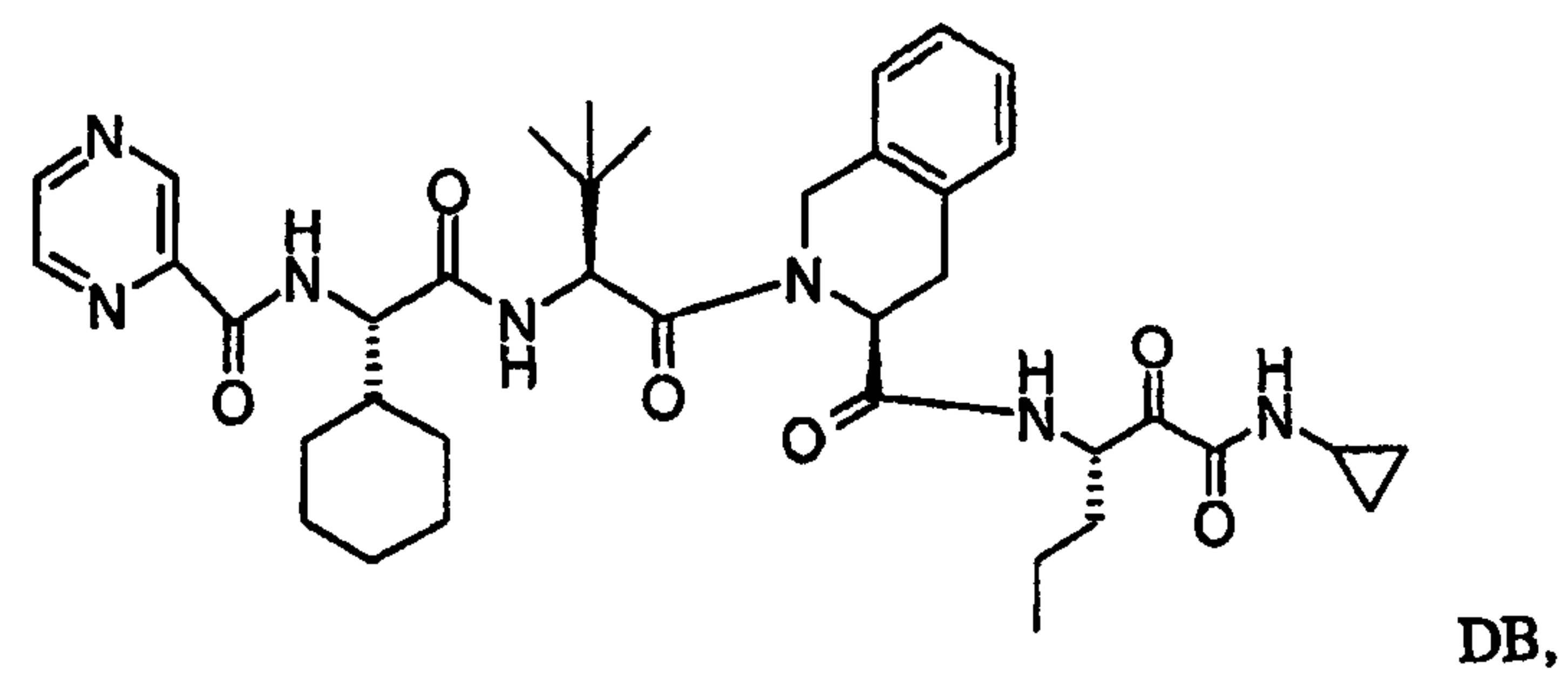
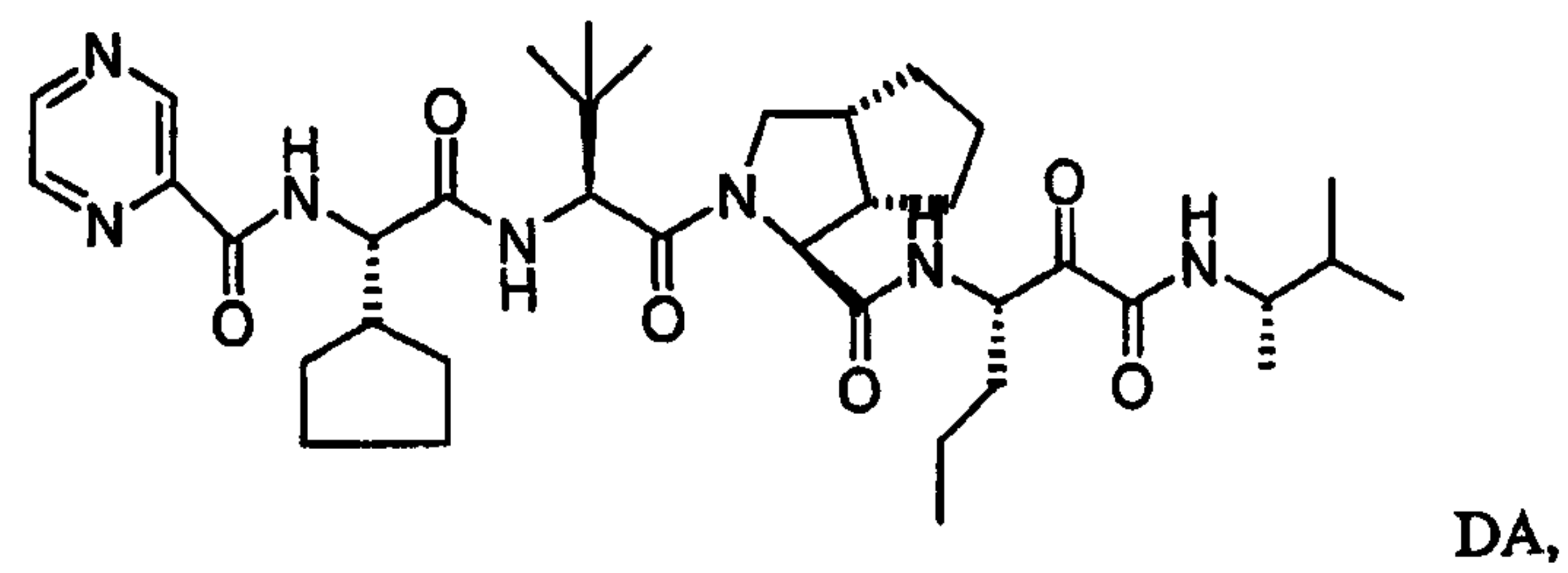
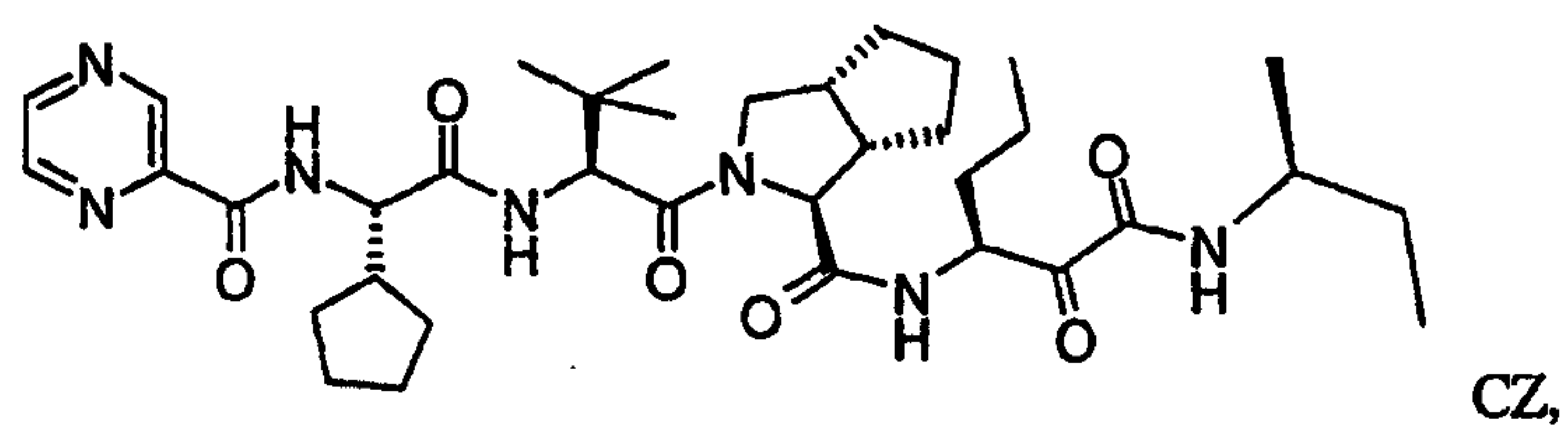
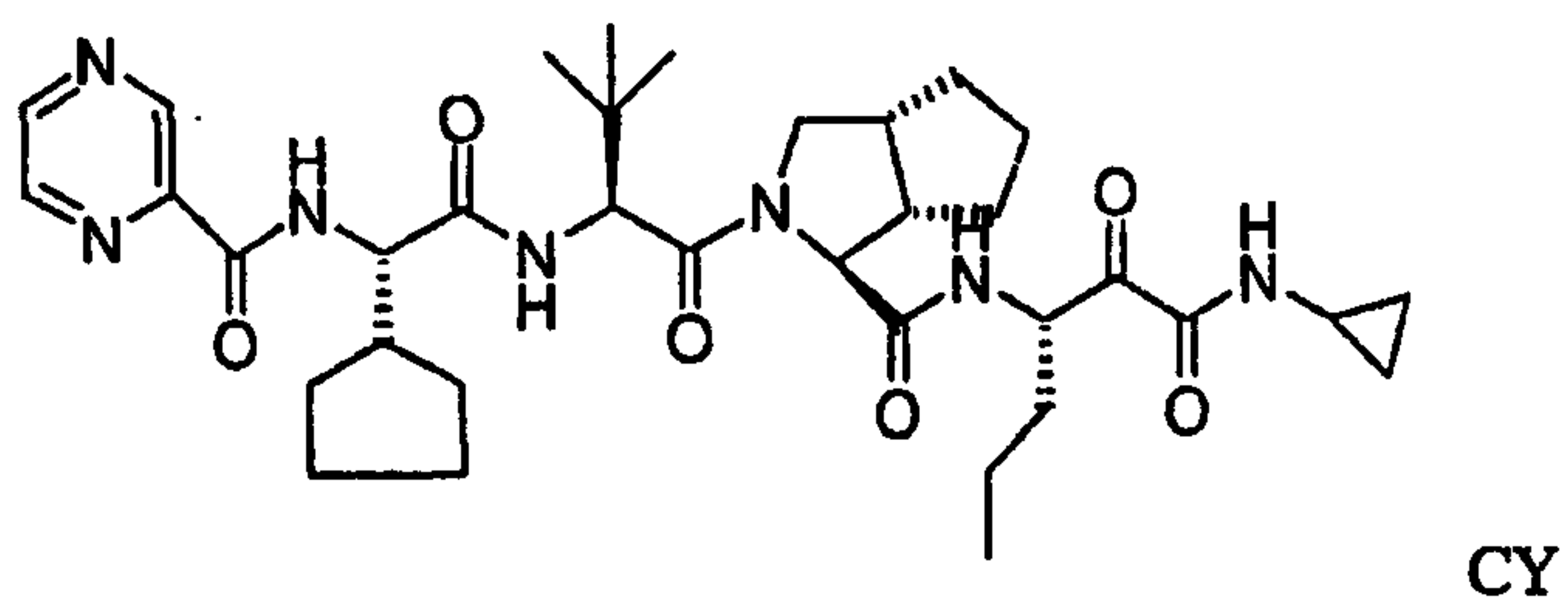
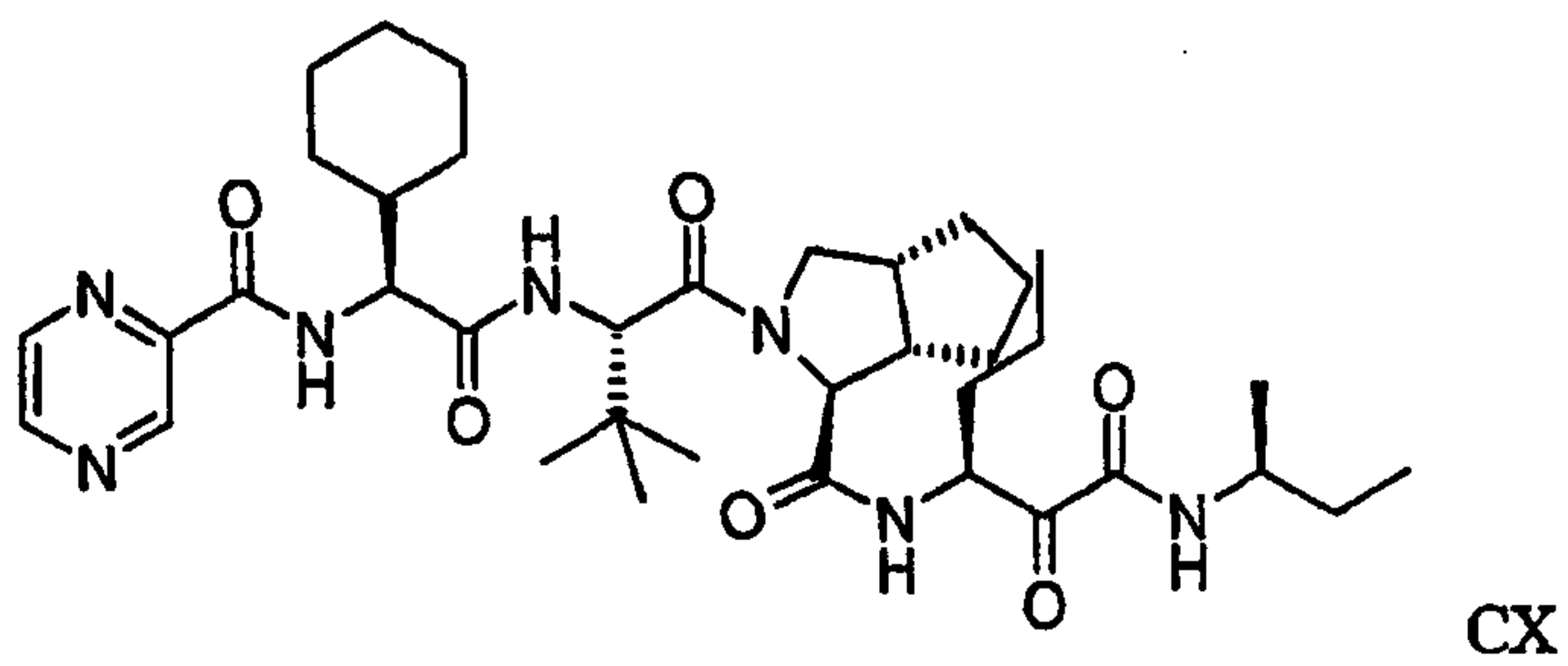


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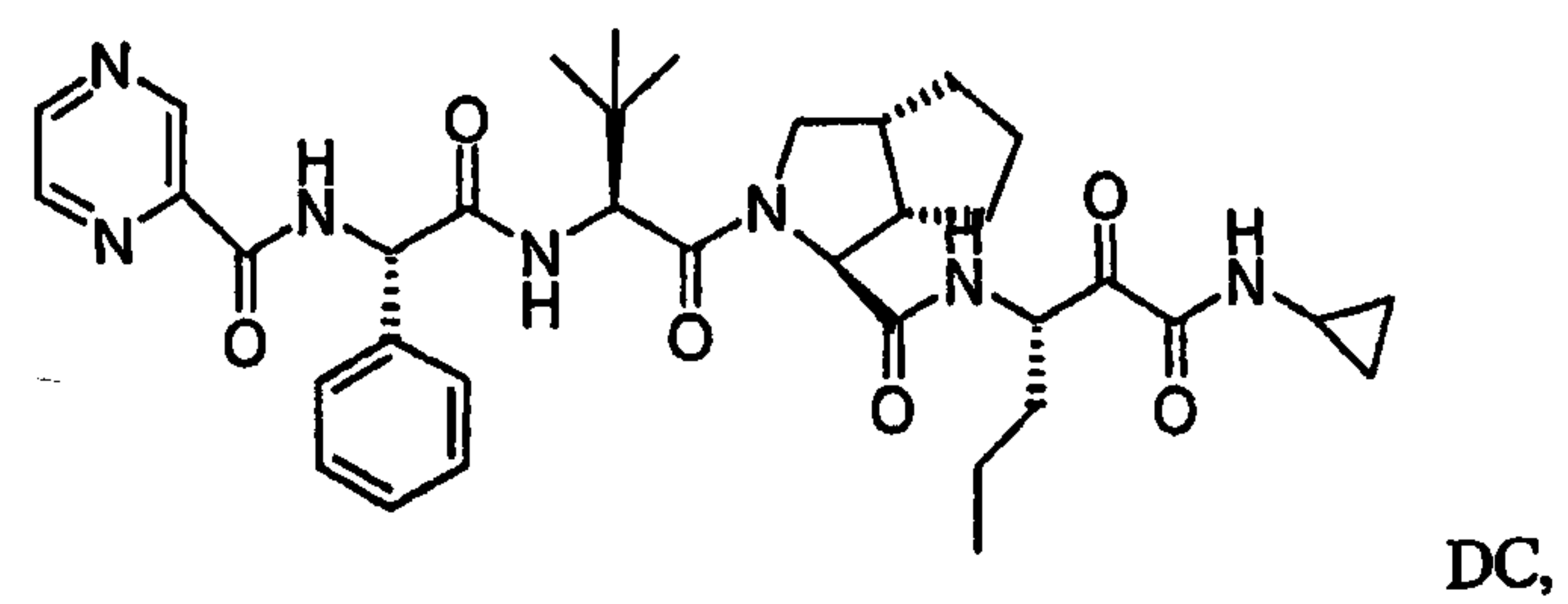
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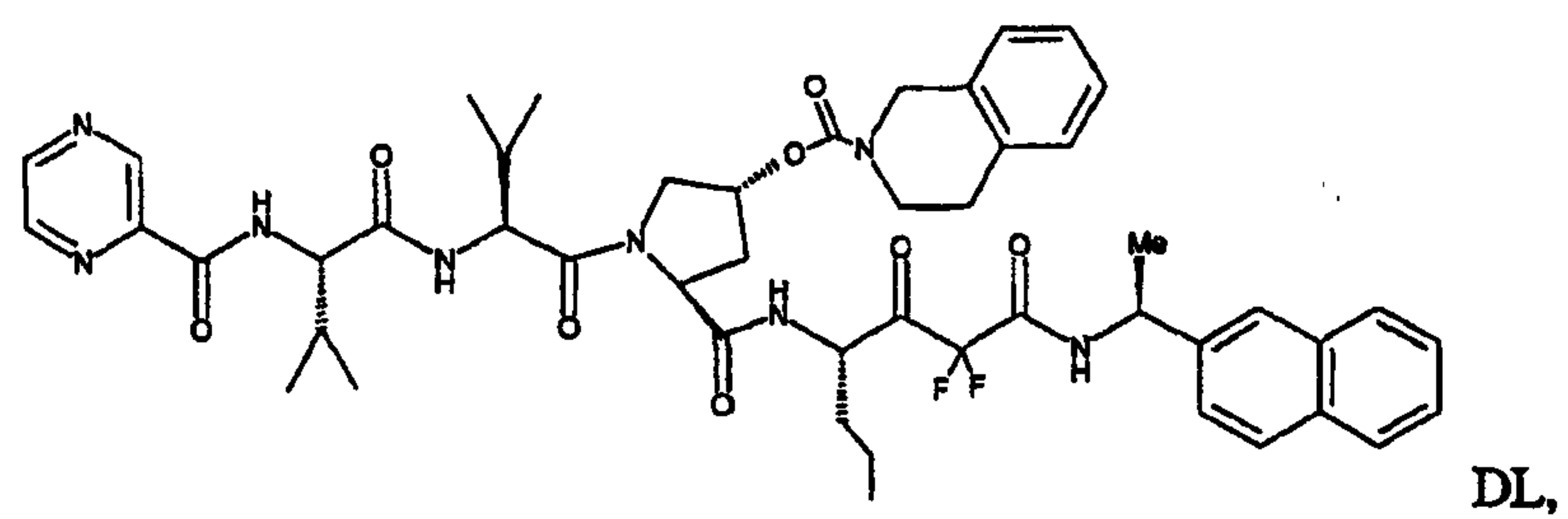
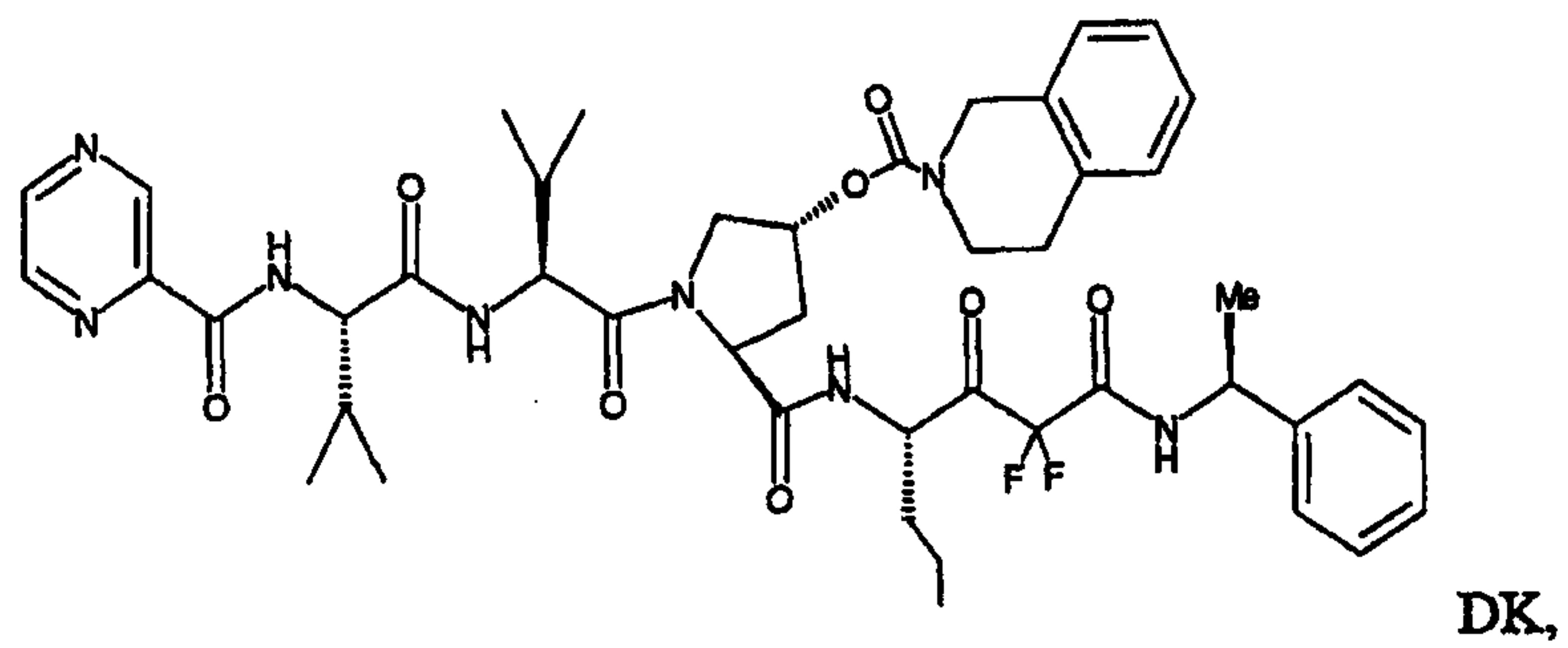
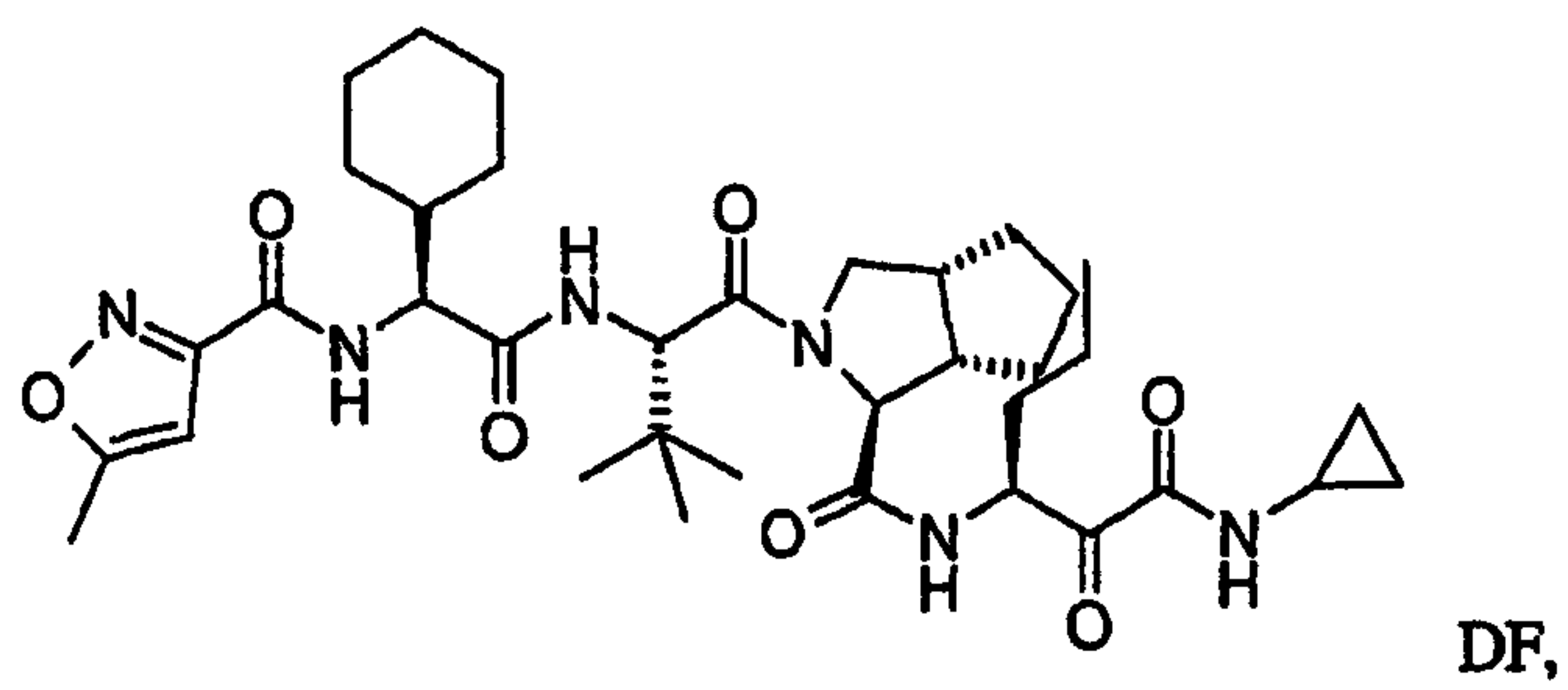
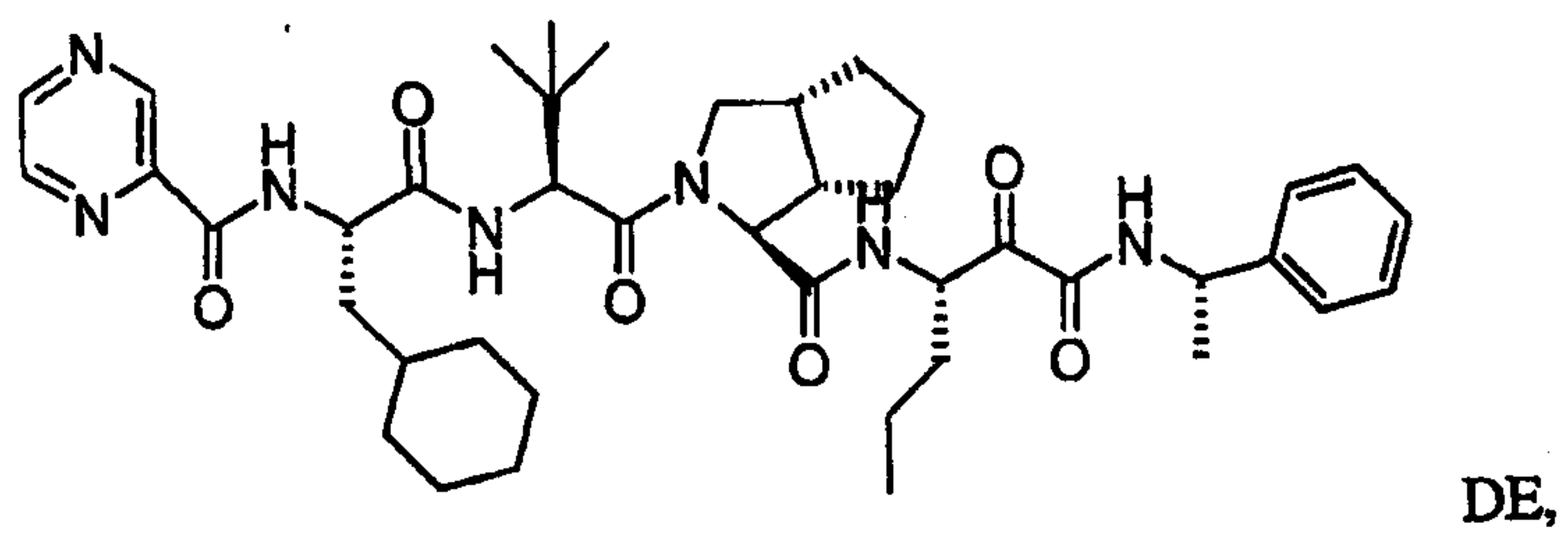
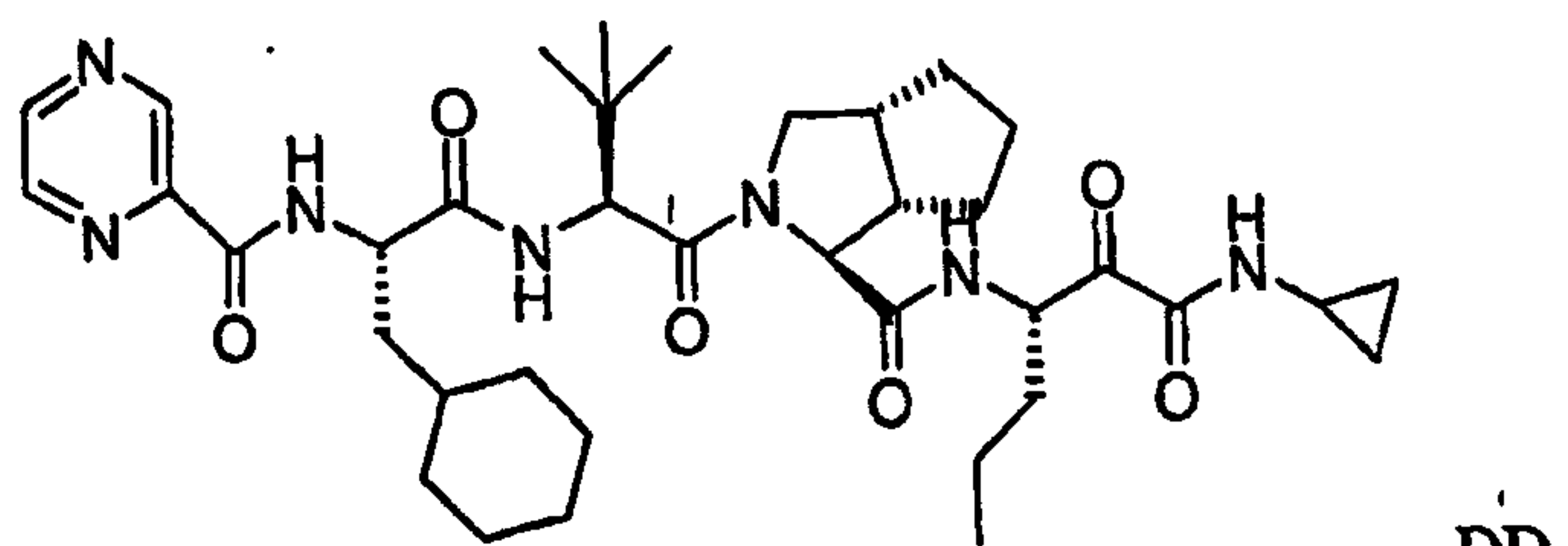
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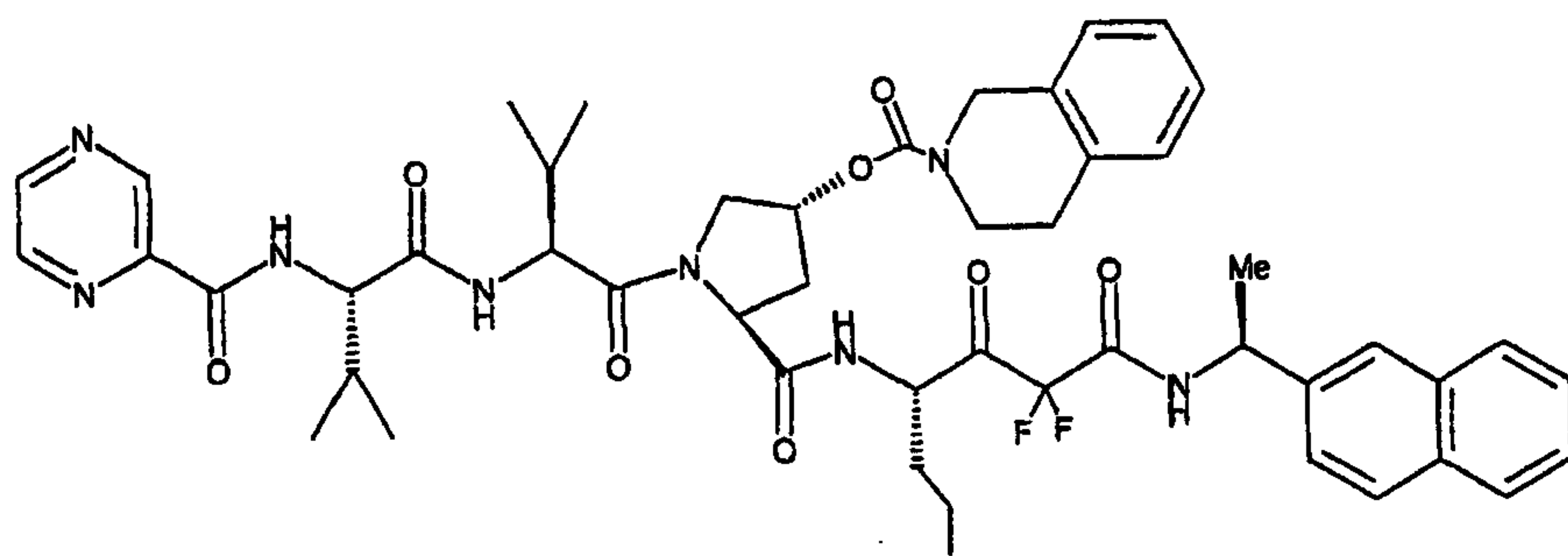
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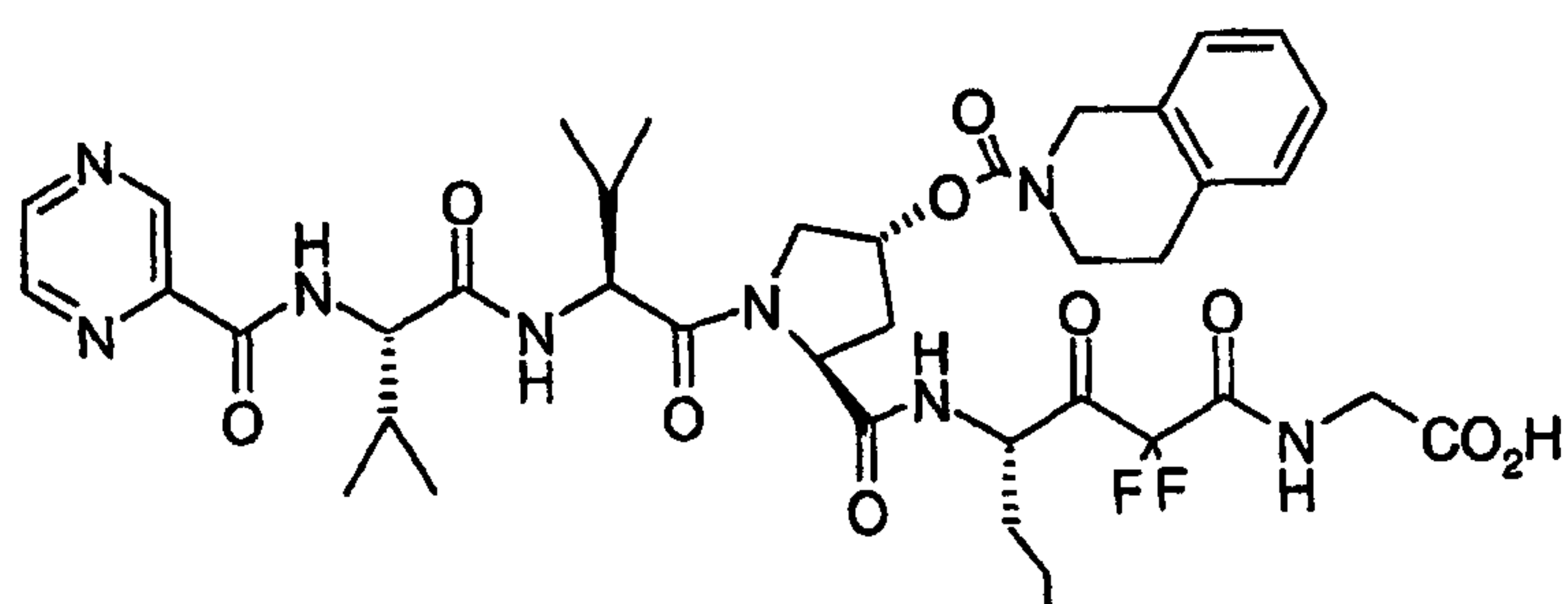
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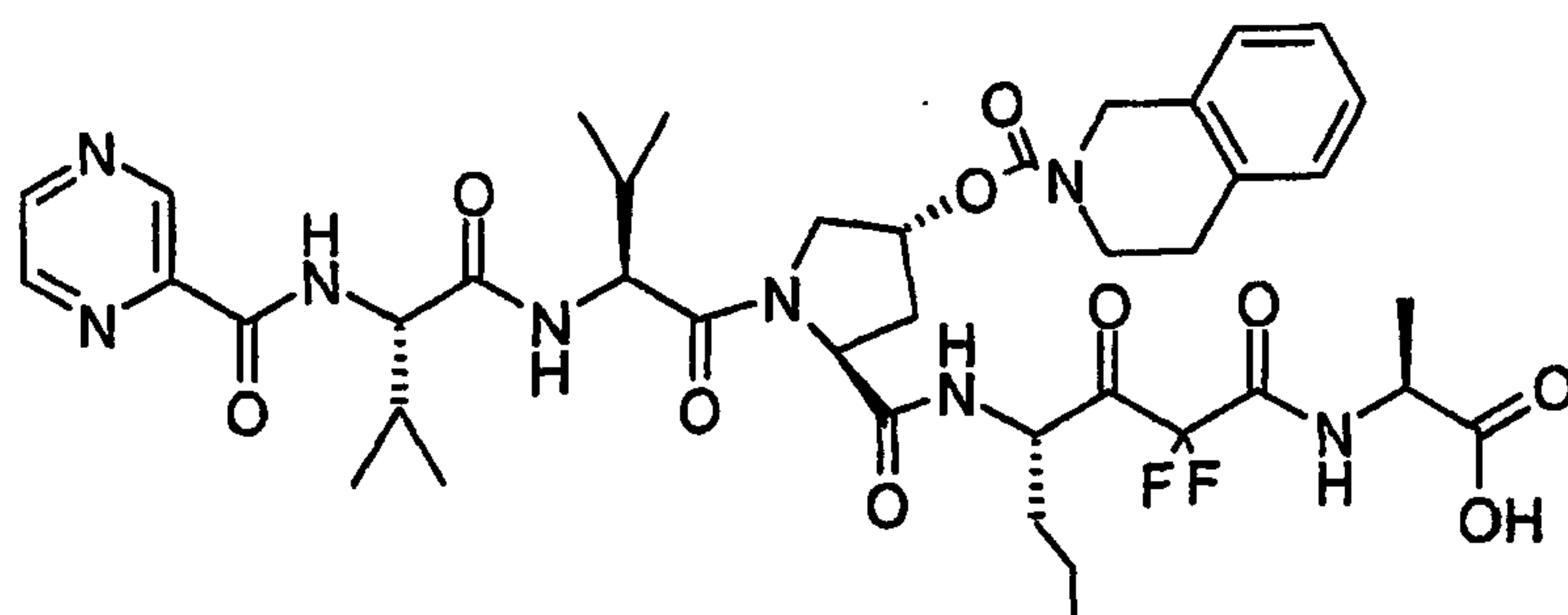
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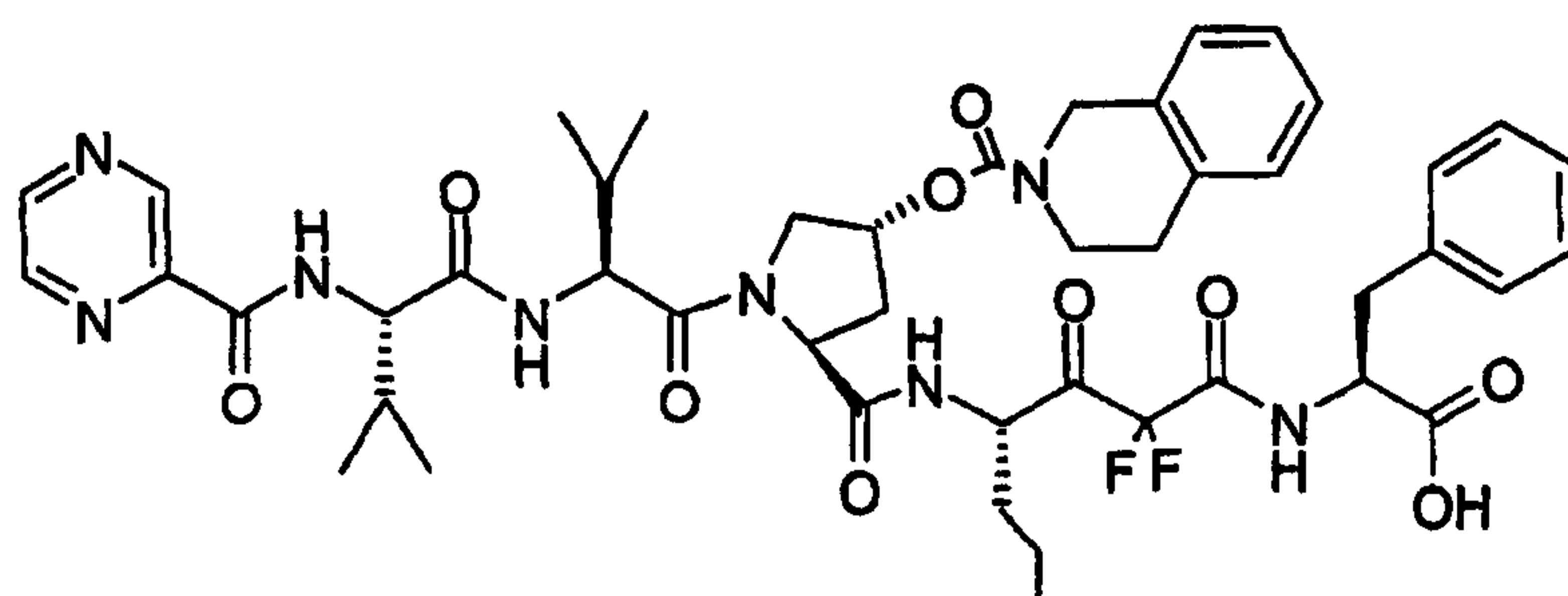
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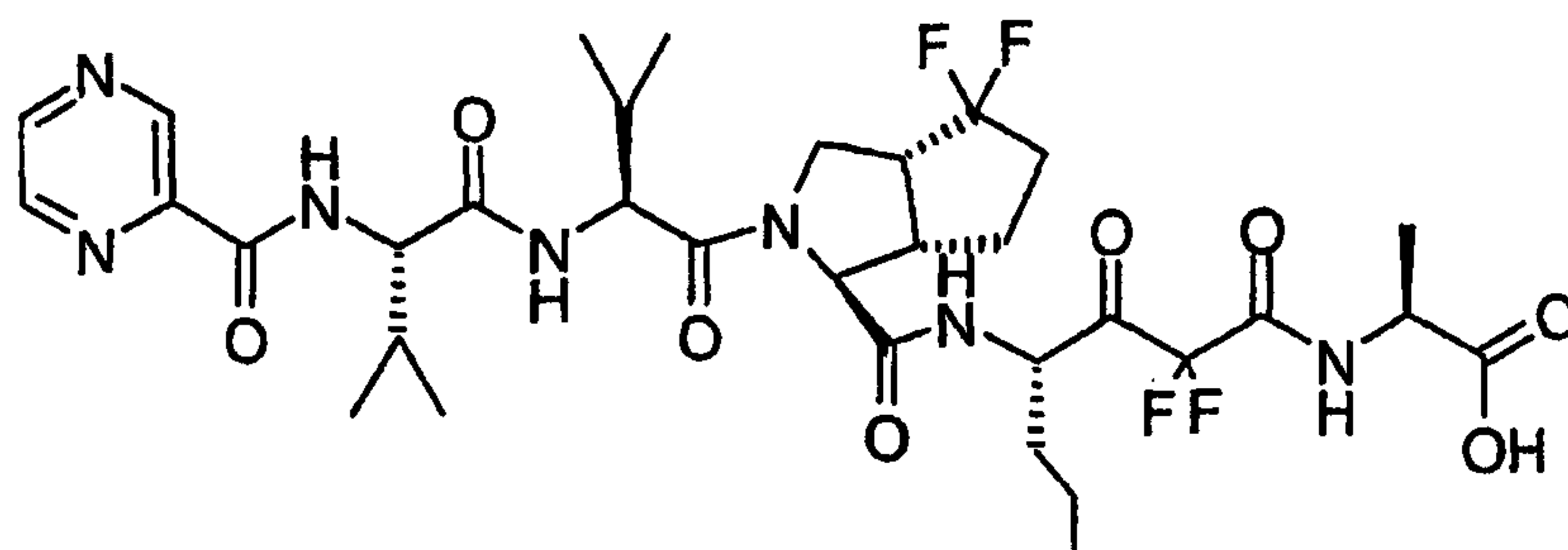
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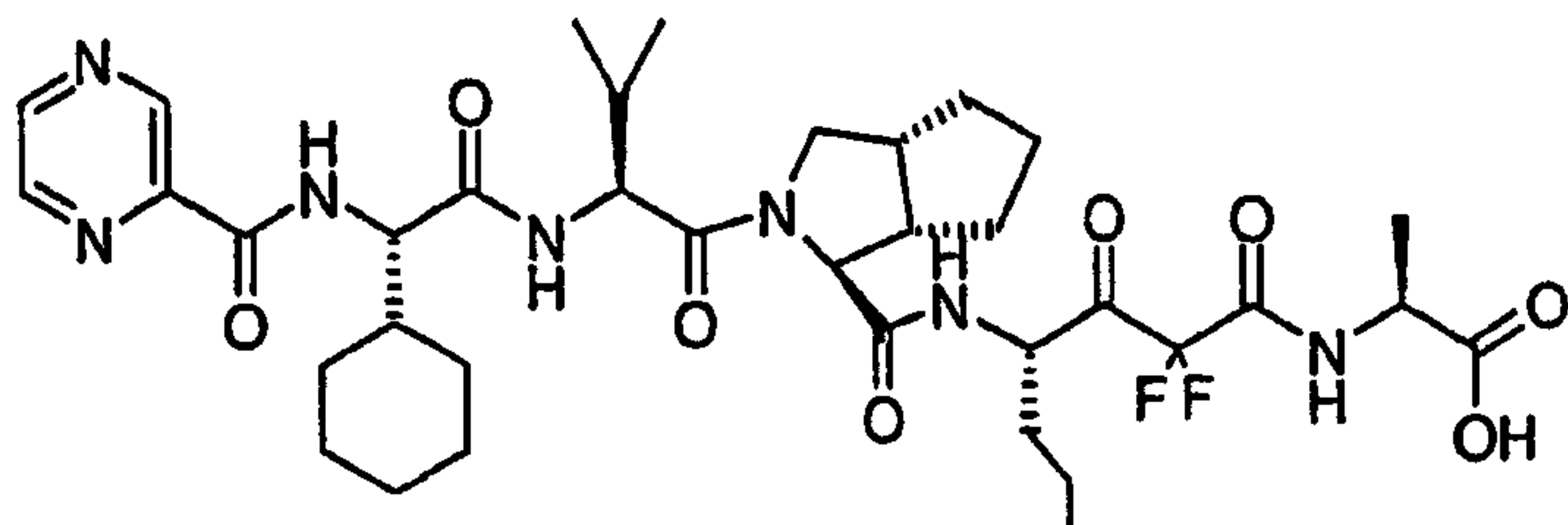


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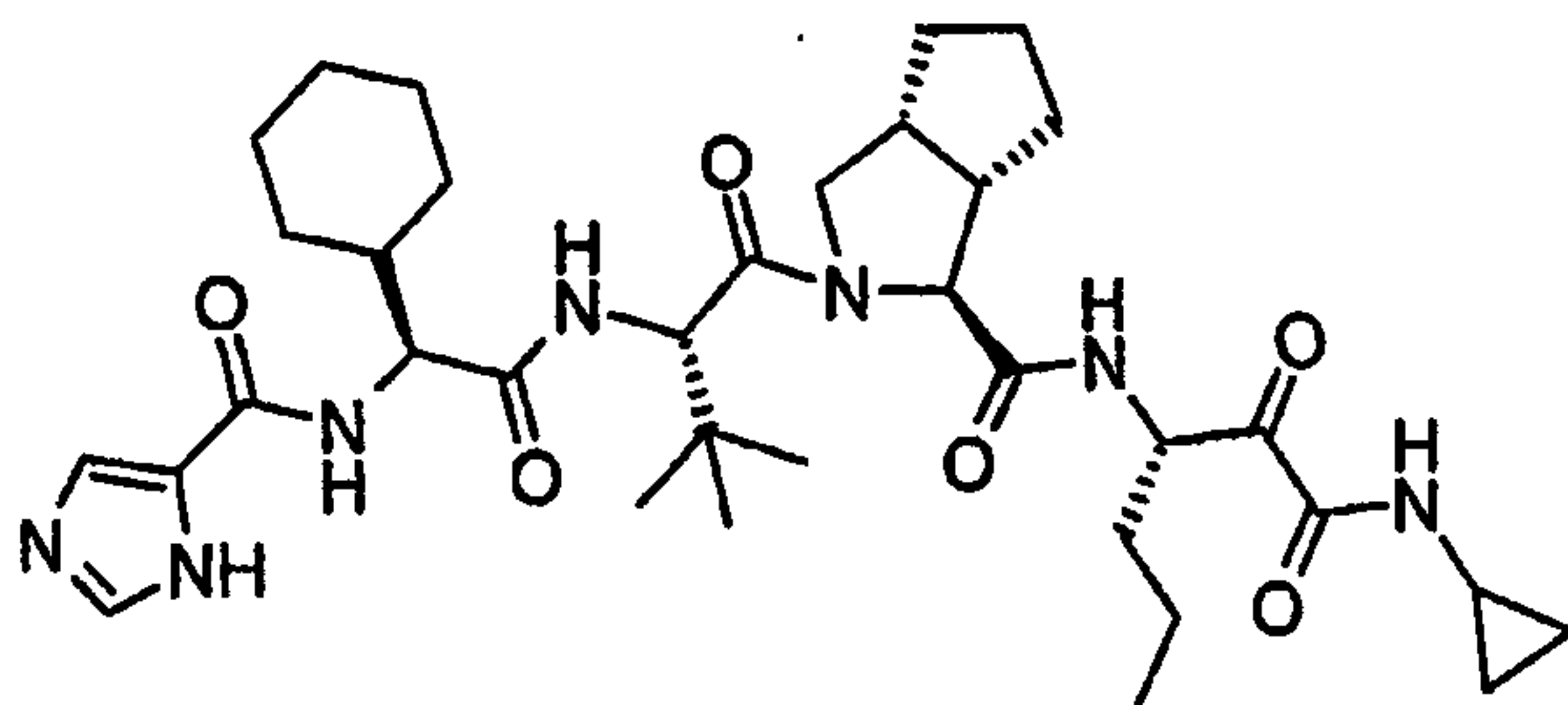
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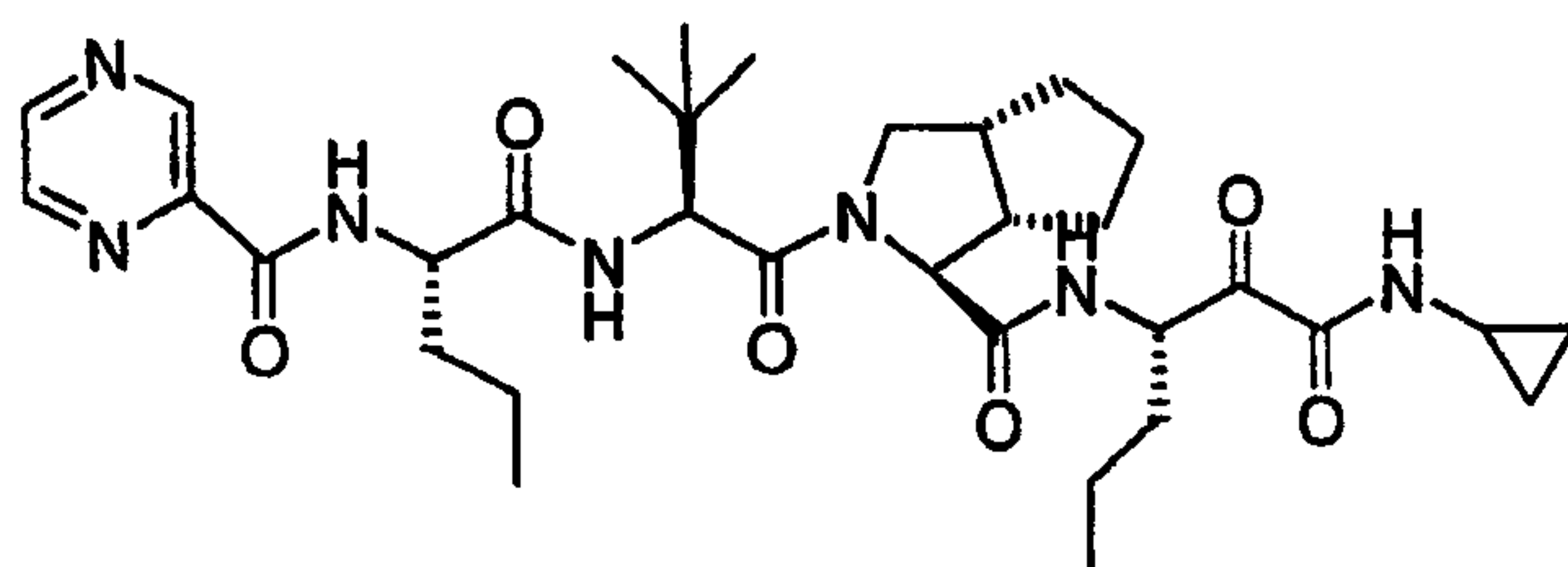
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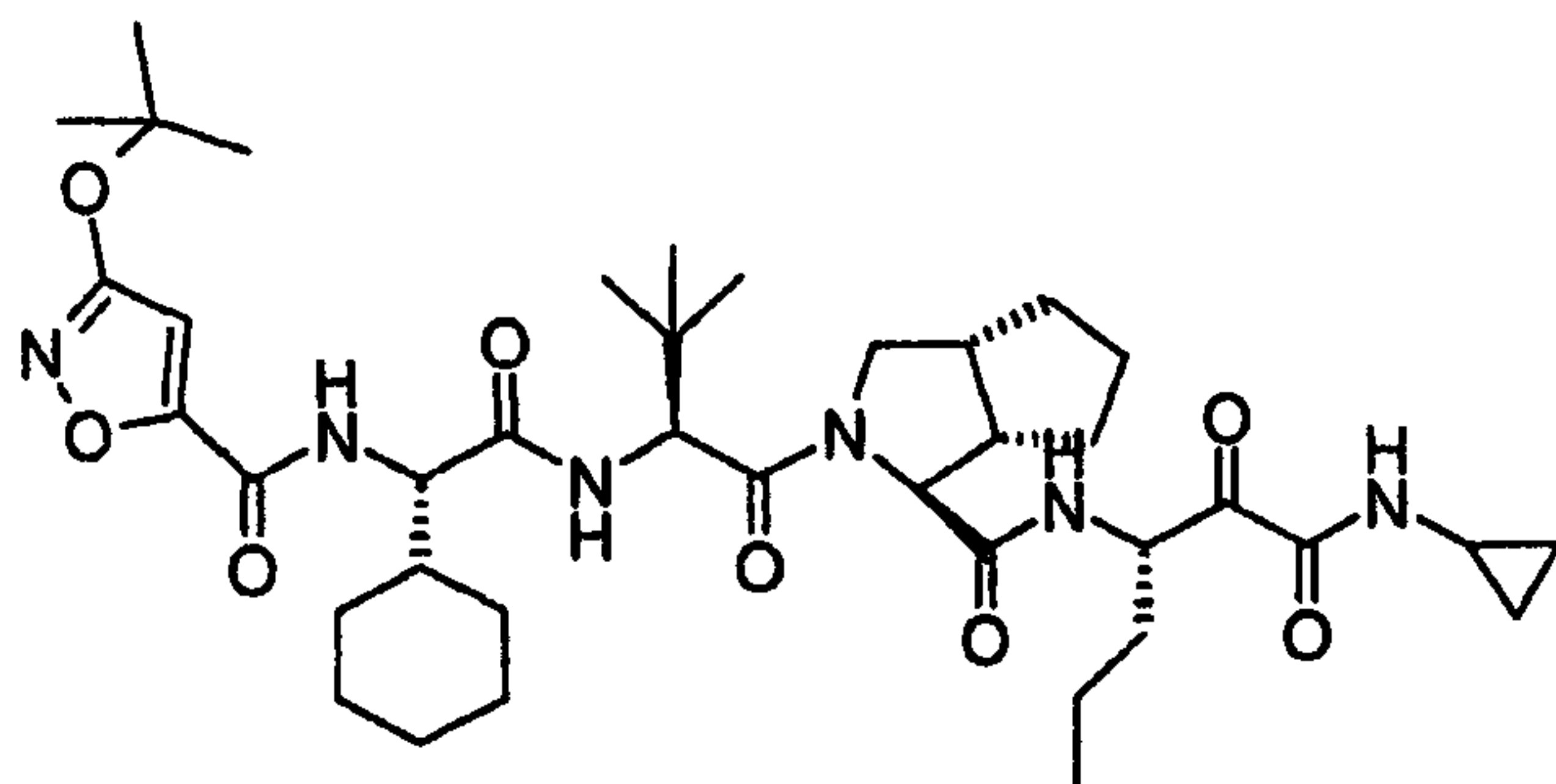
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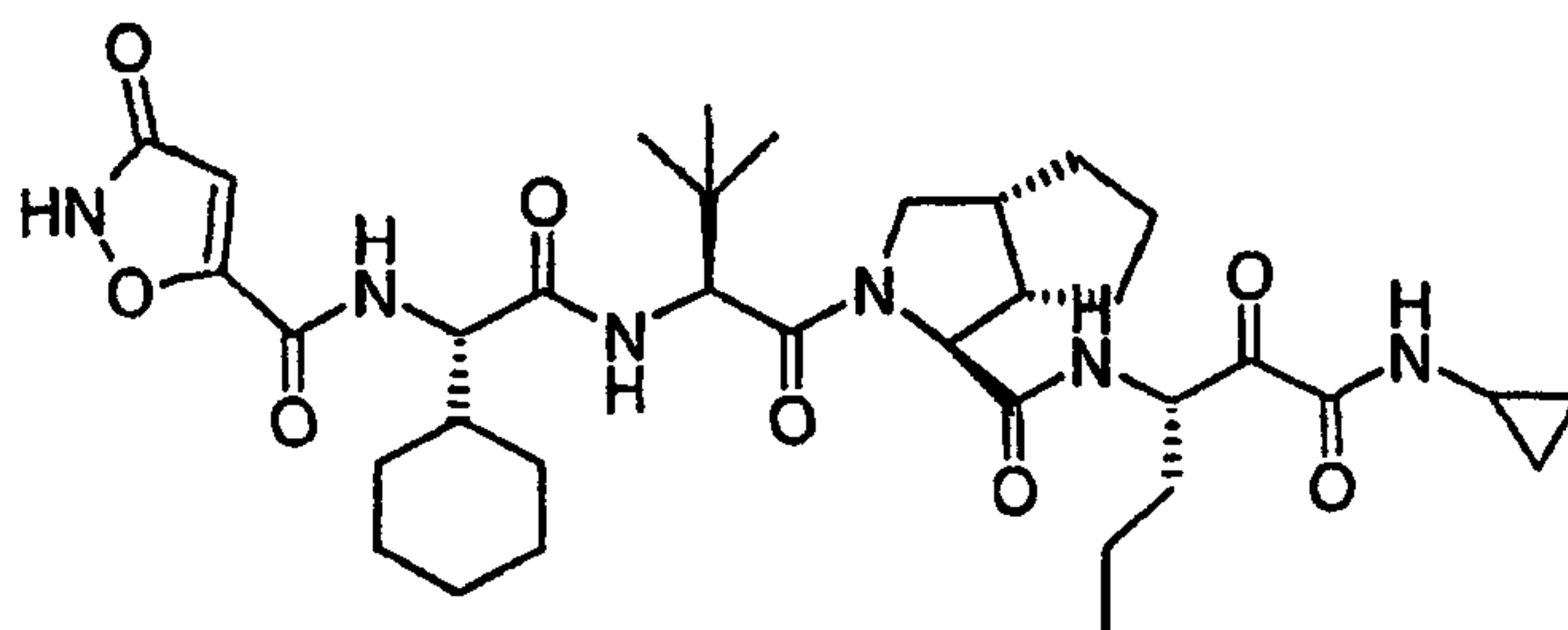
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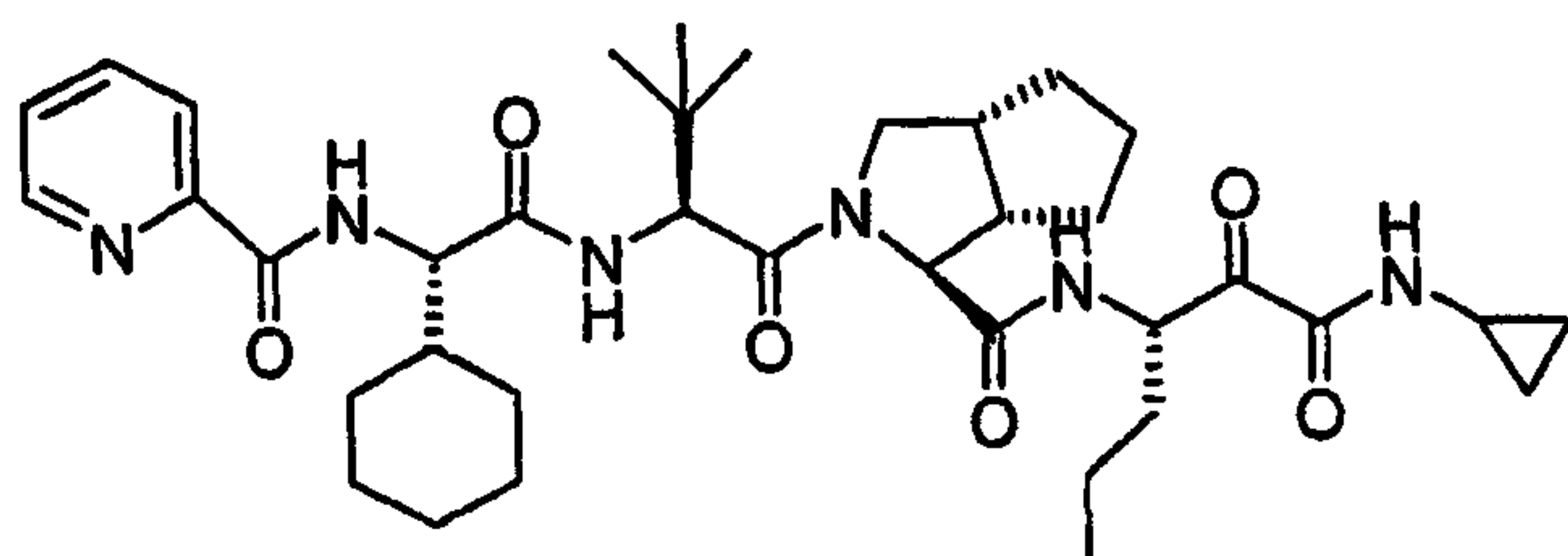


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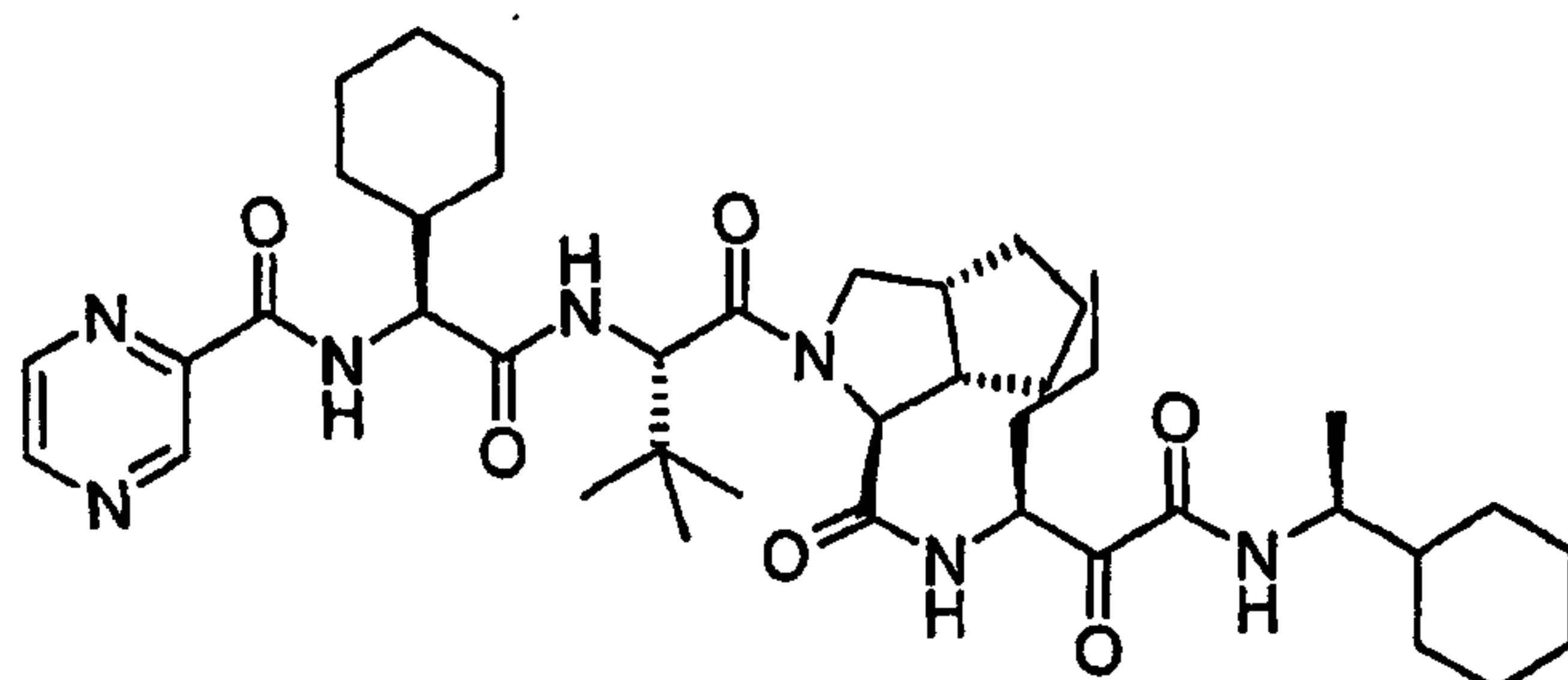
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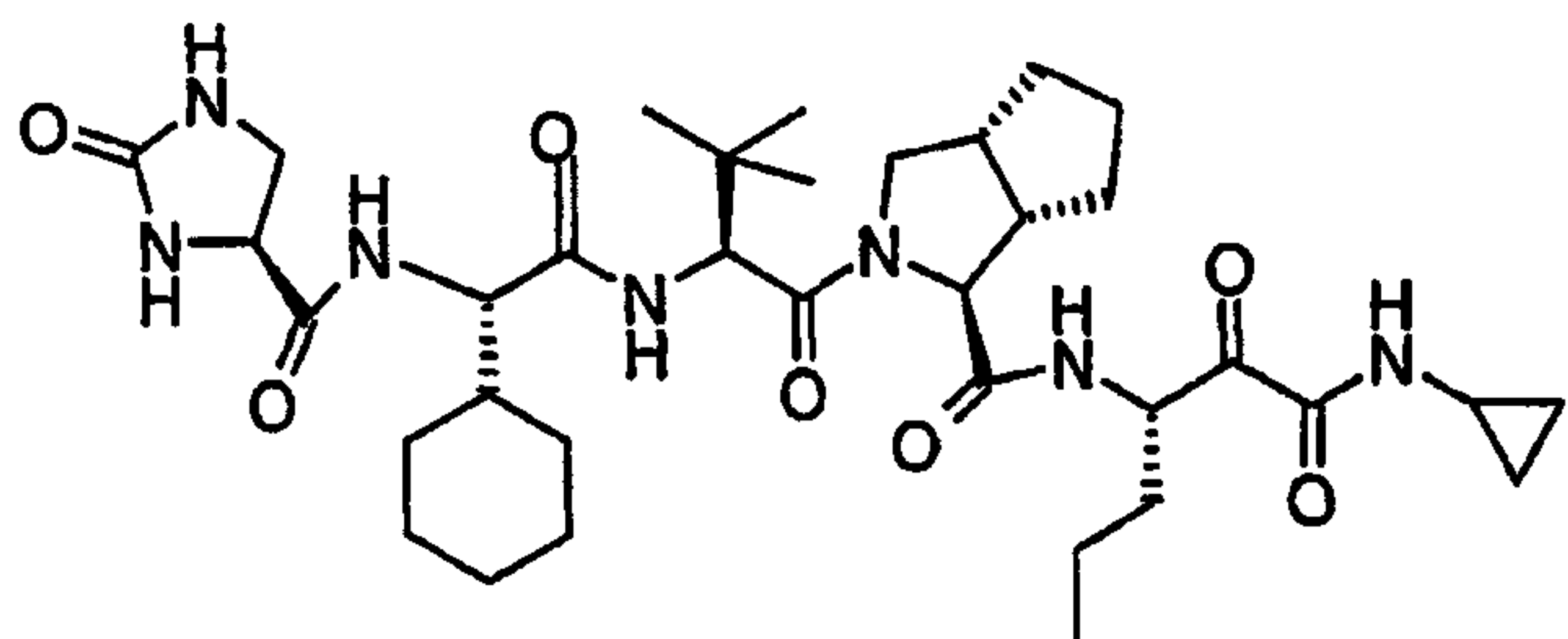
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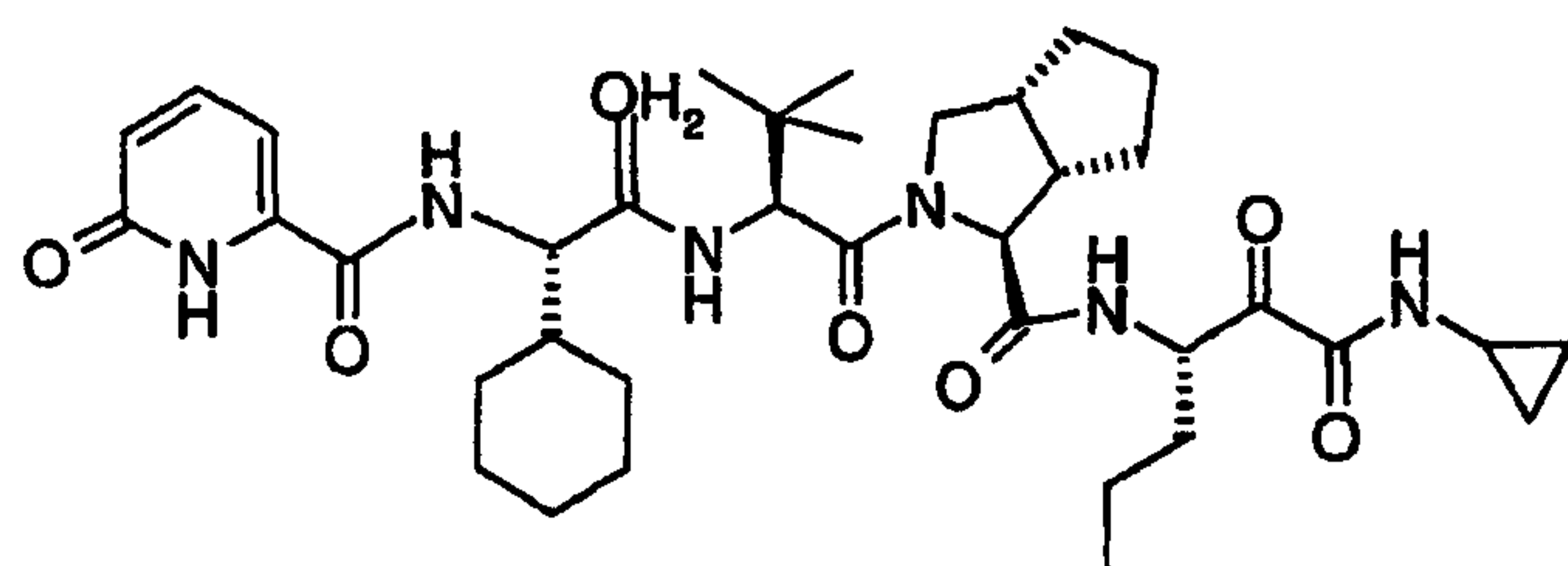
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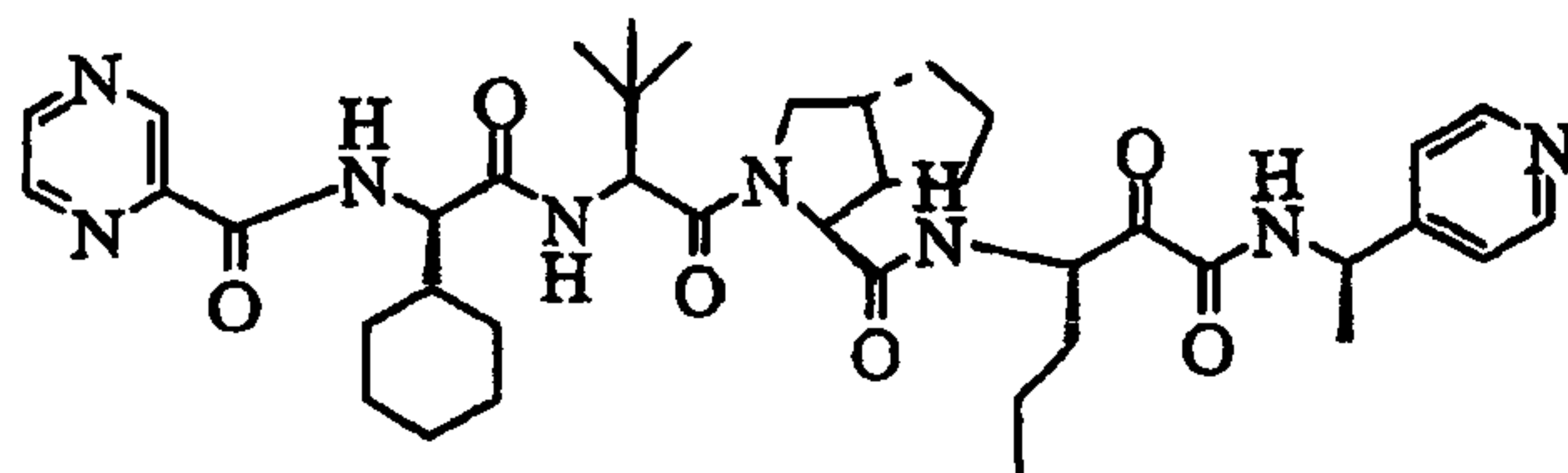


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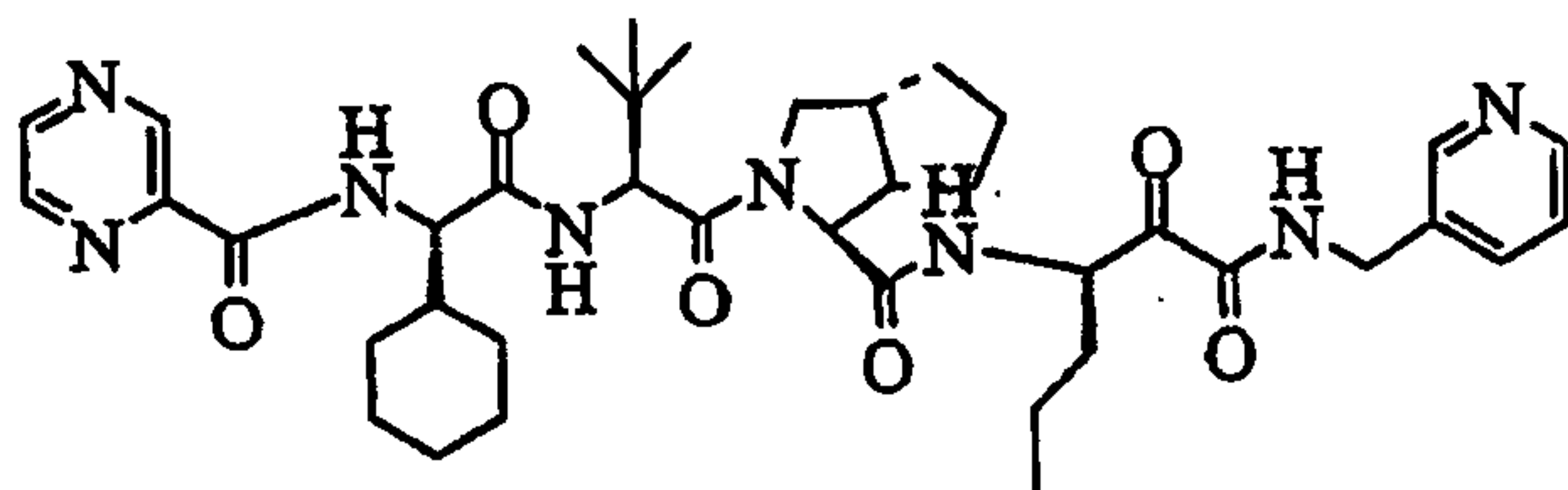


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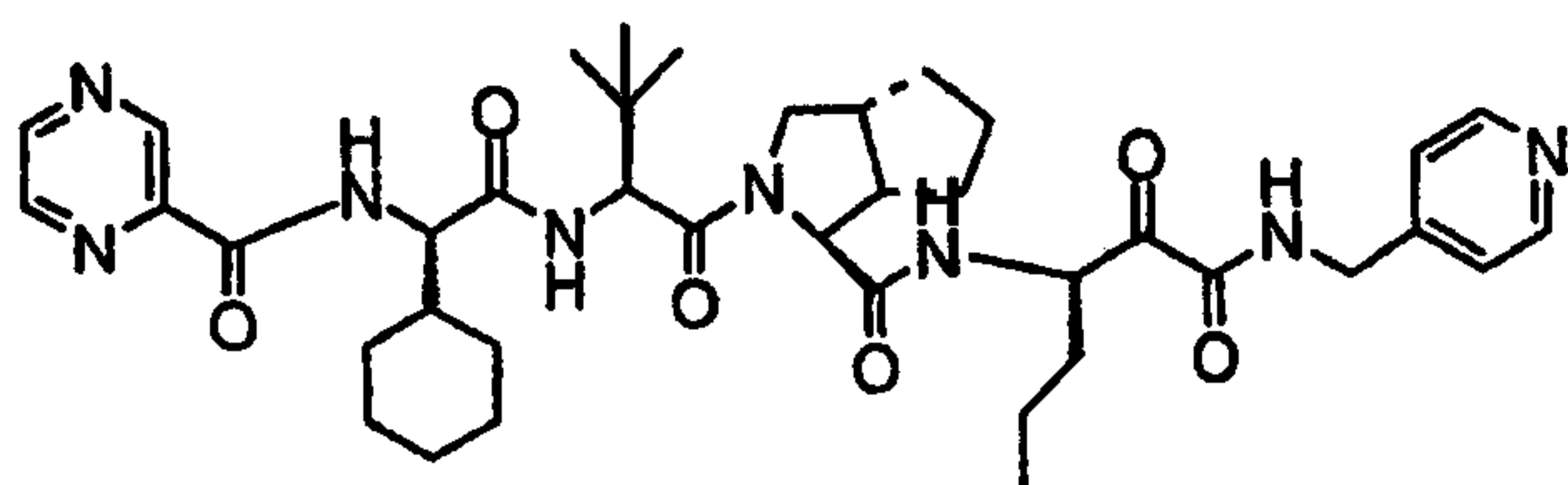
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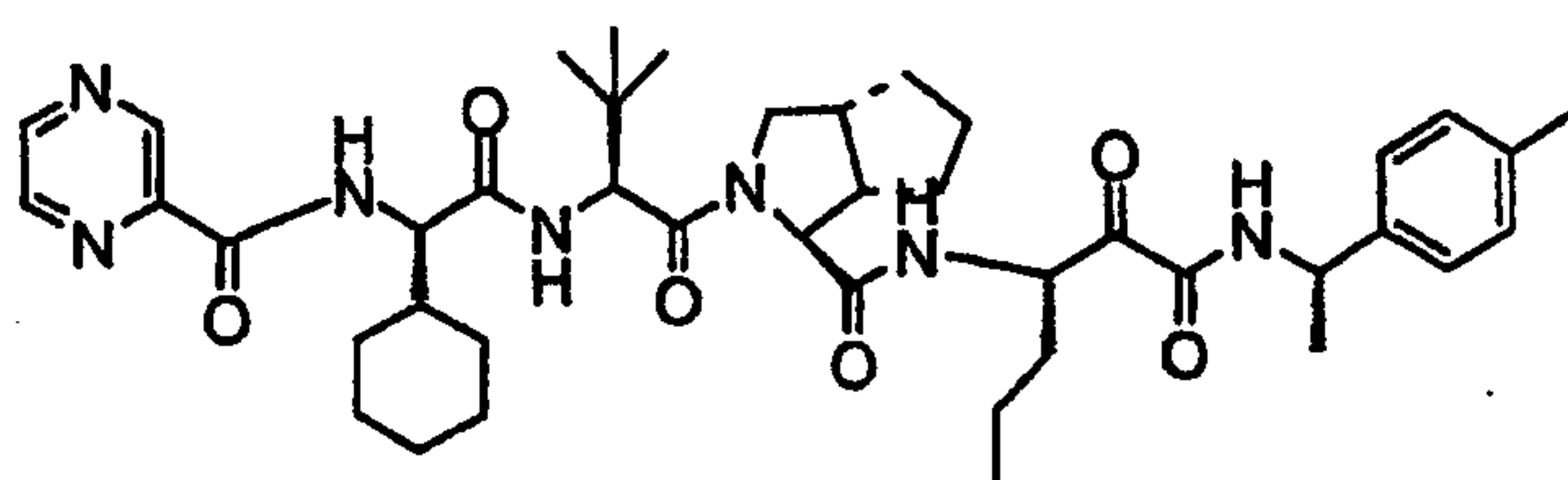


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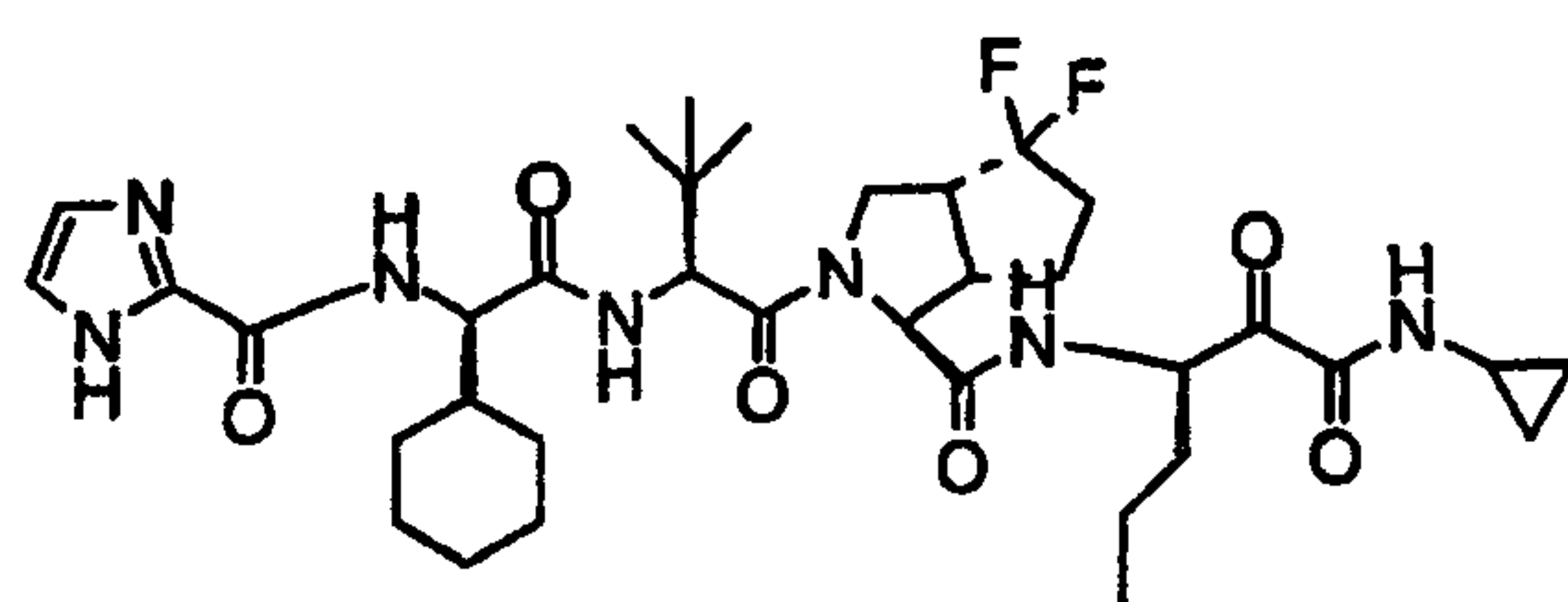
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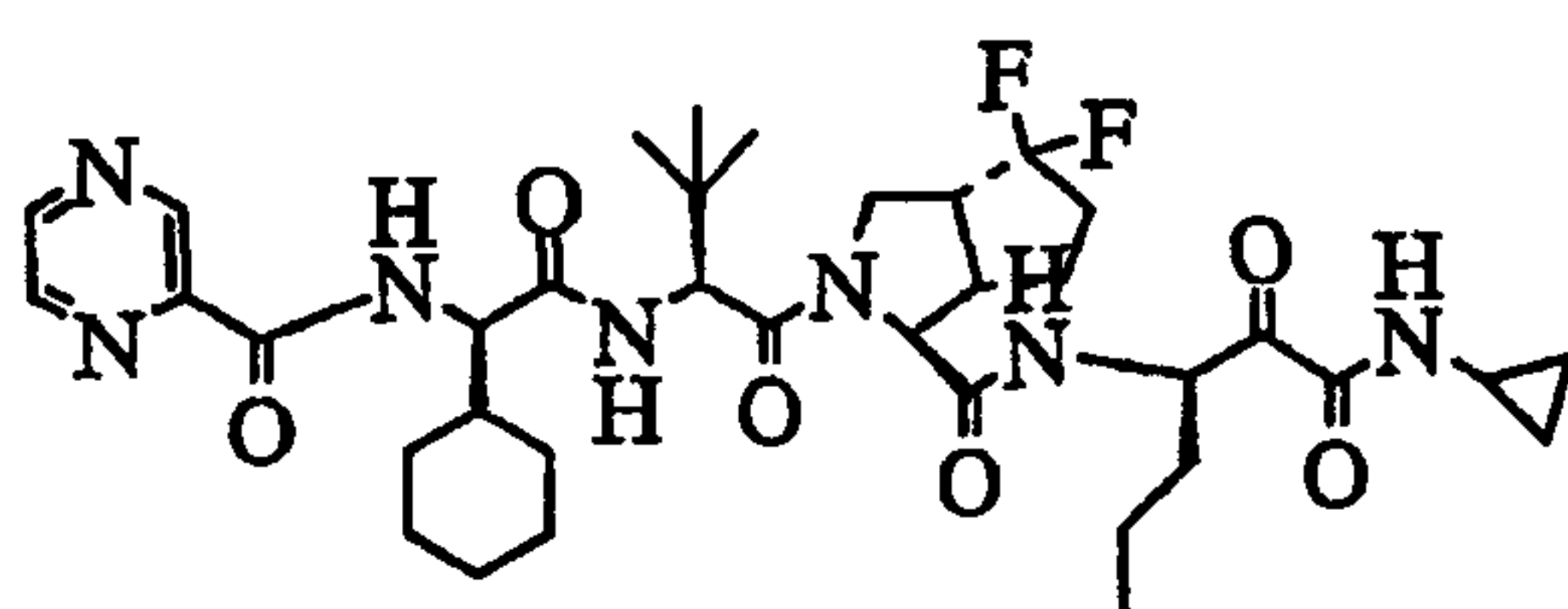


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EN,



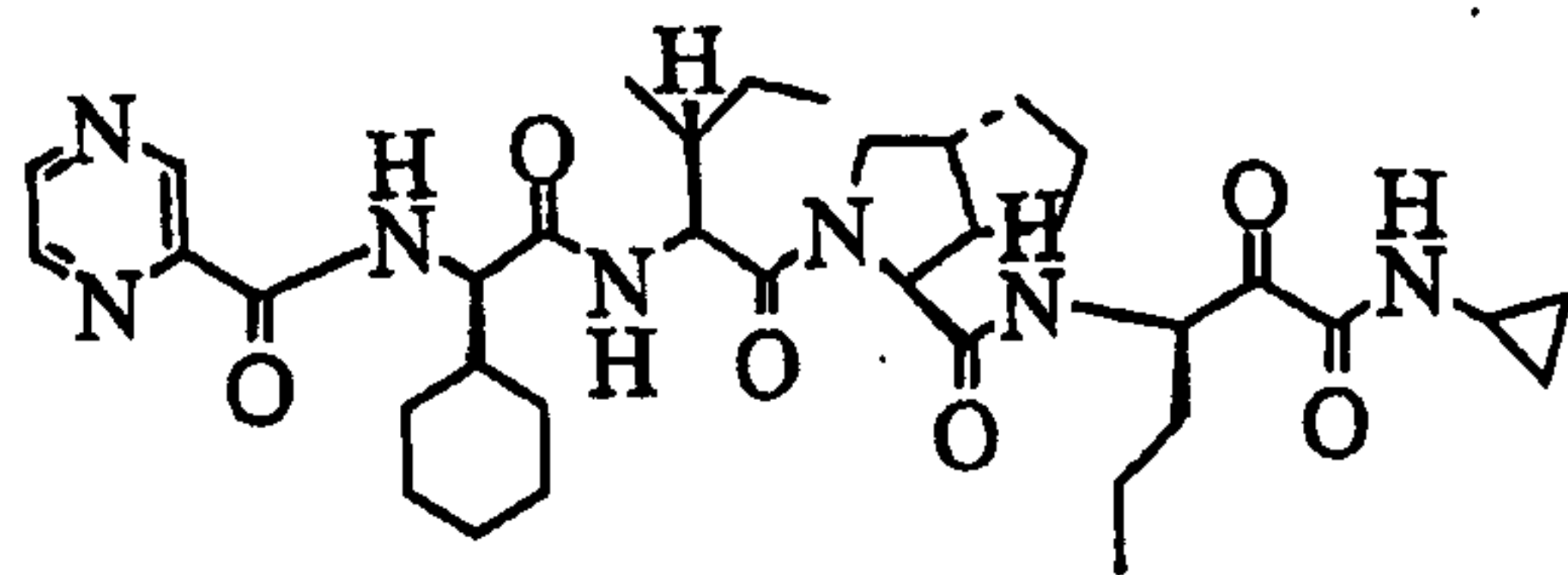
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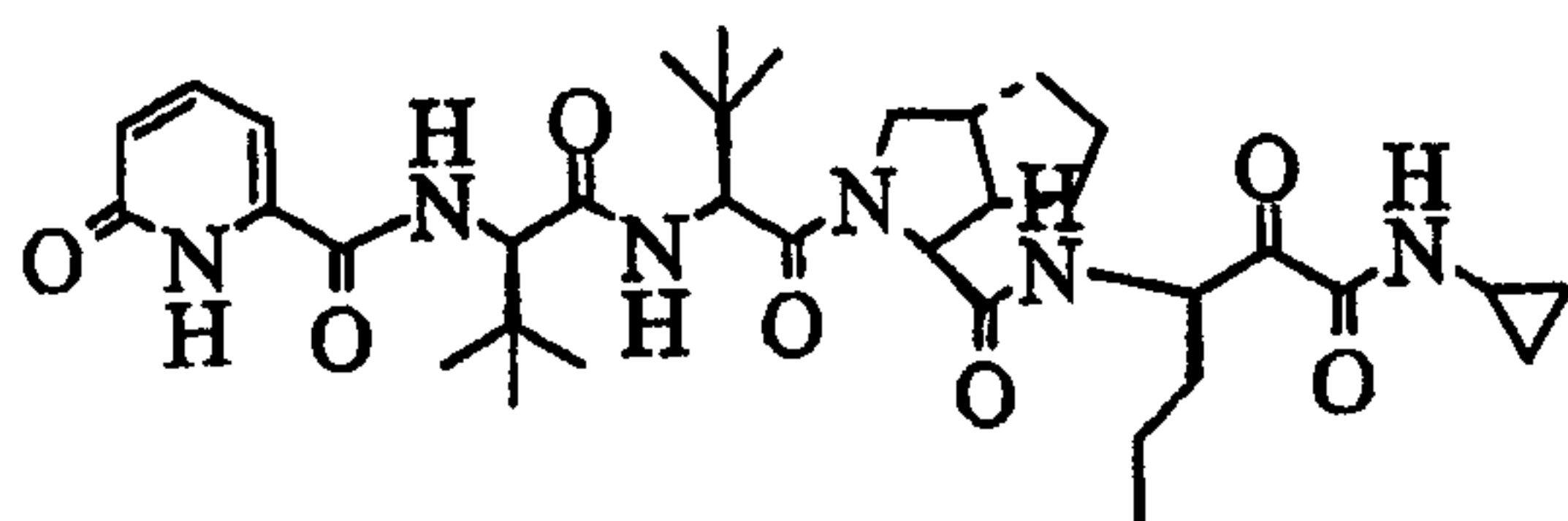
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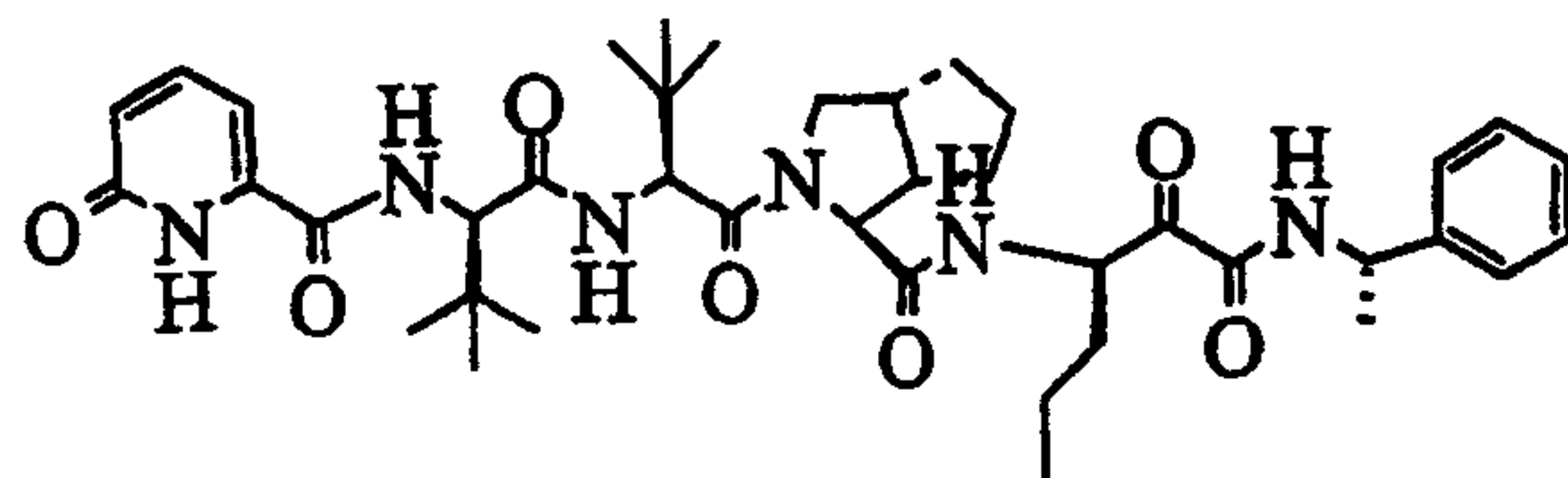
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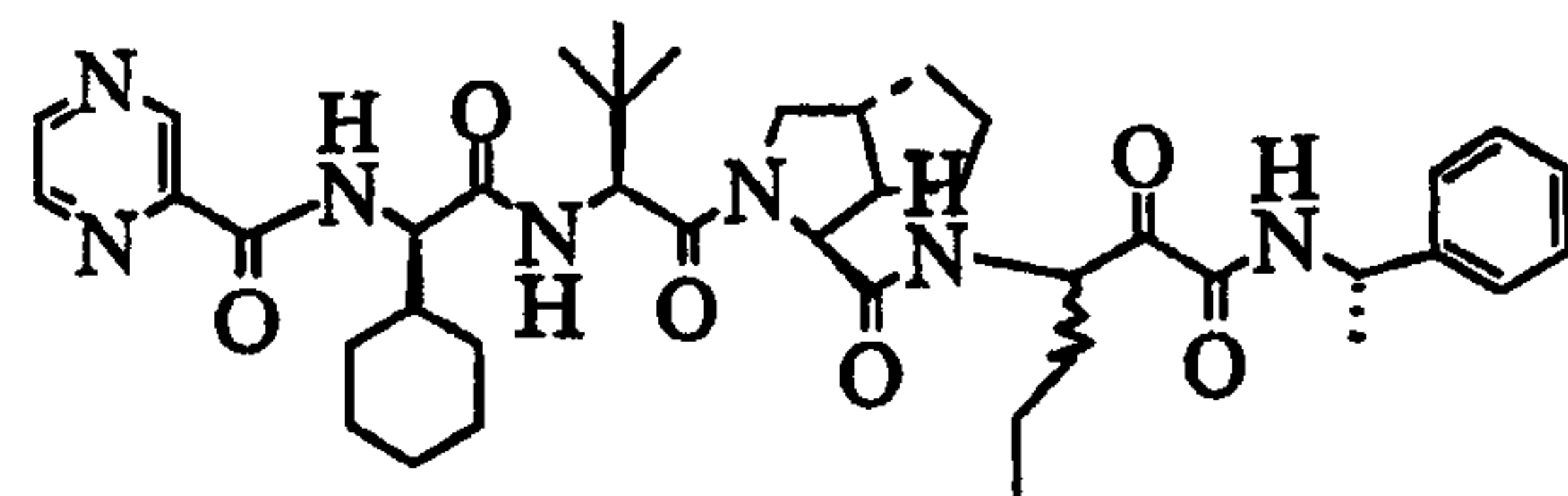


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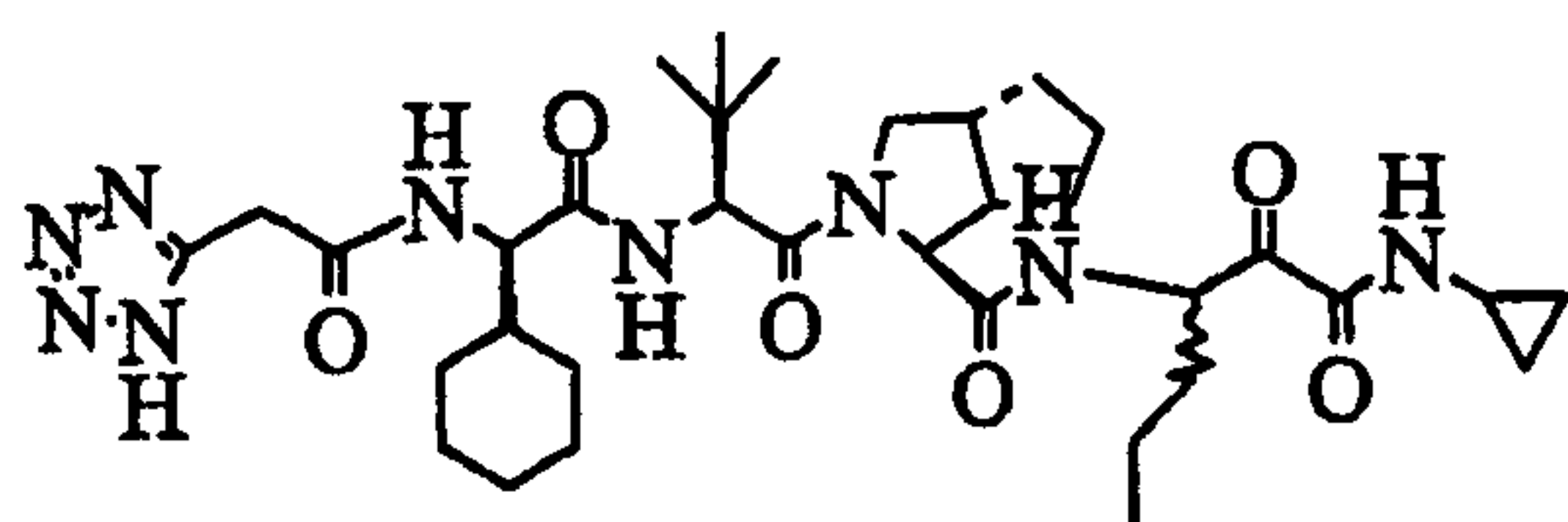


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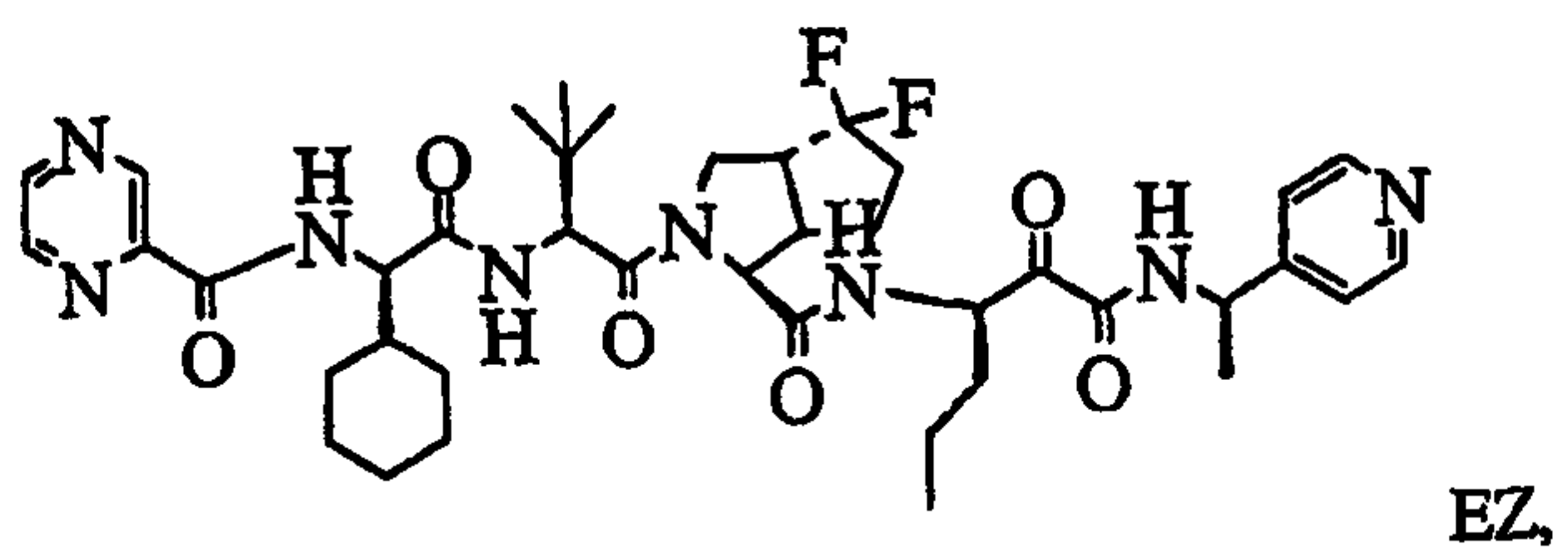


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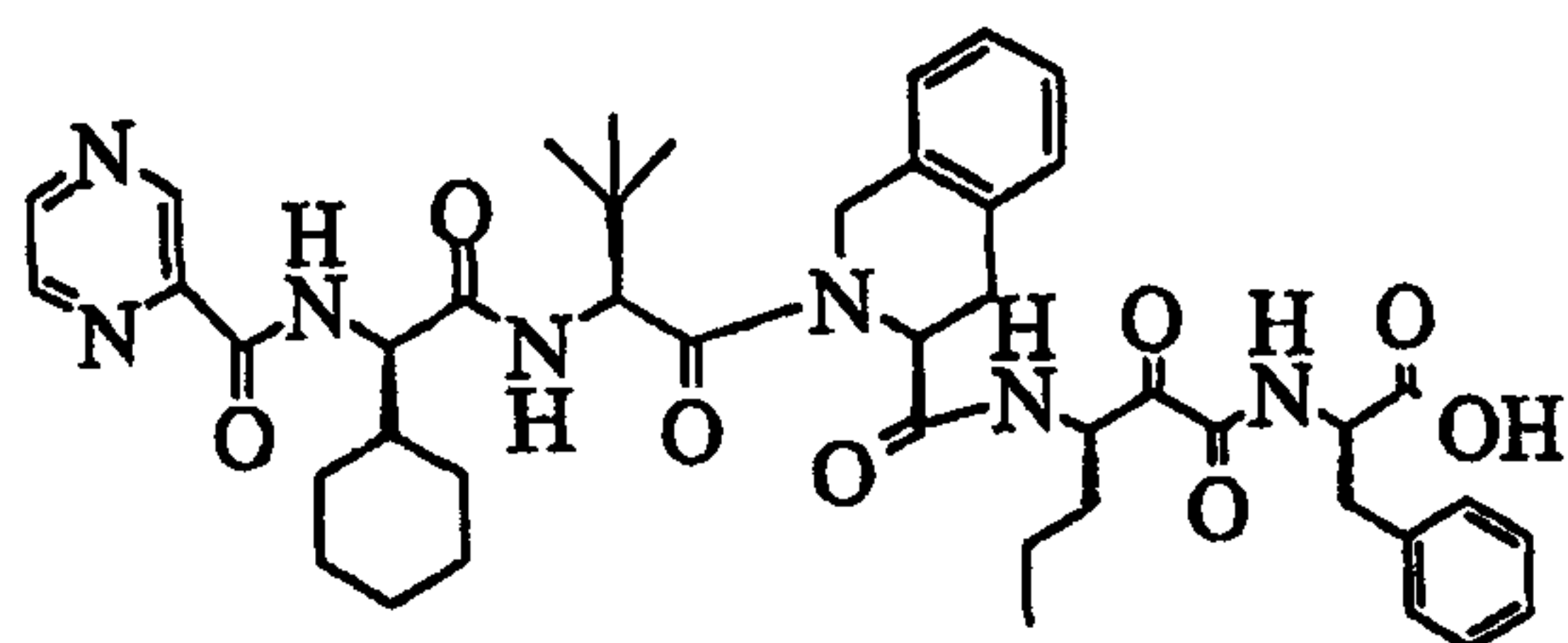
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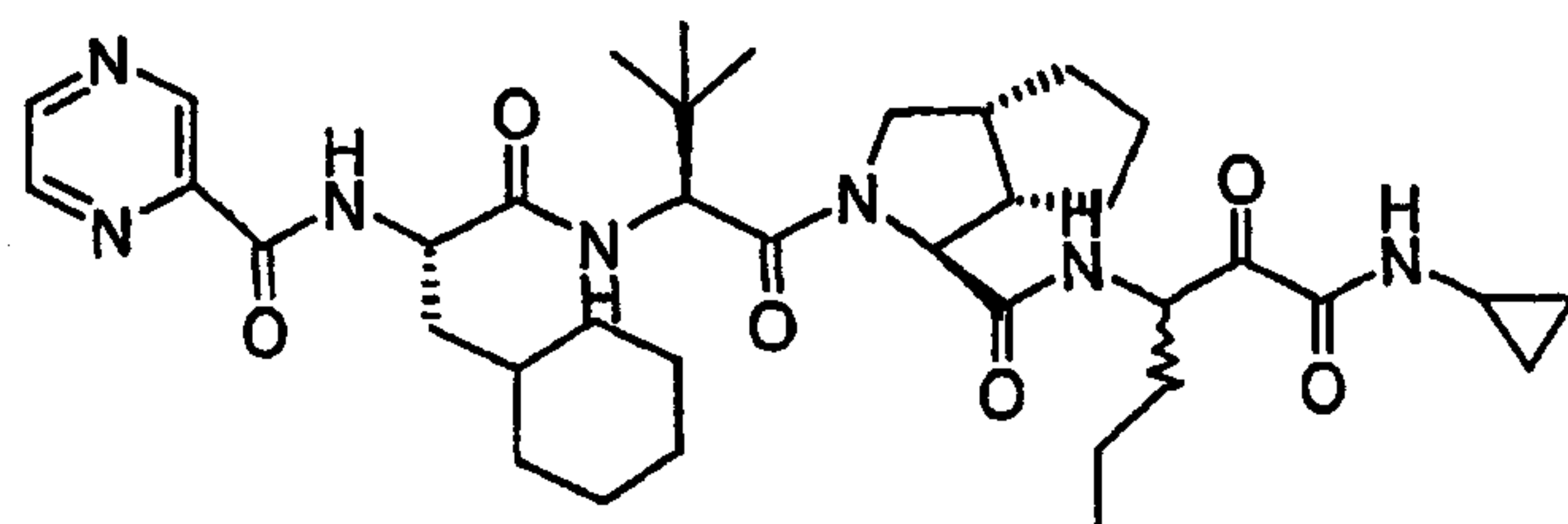
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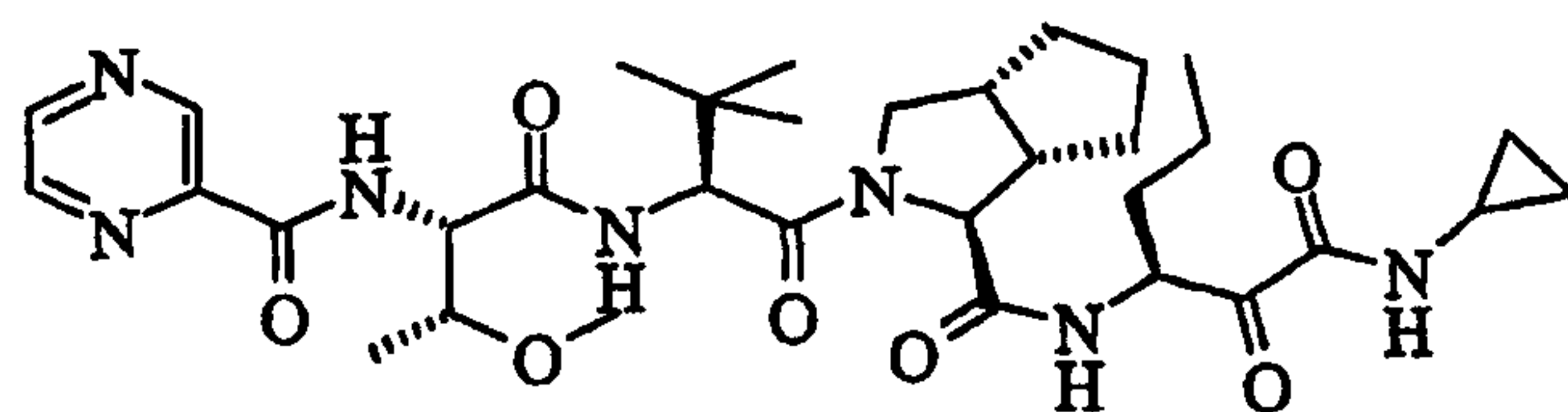
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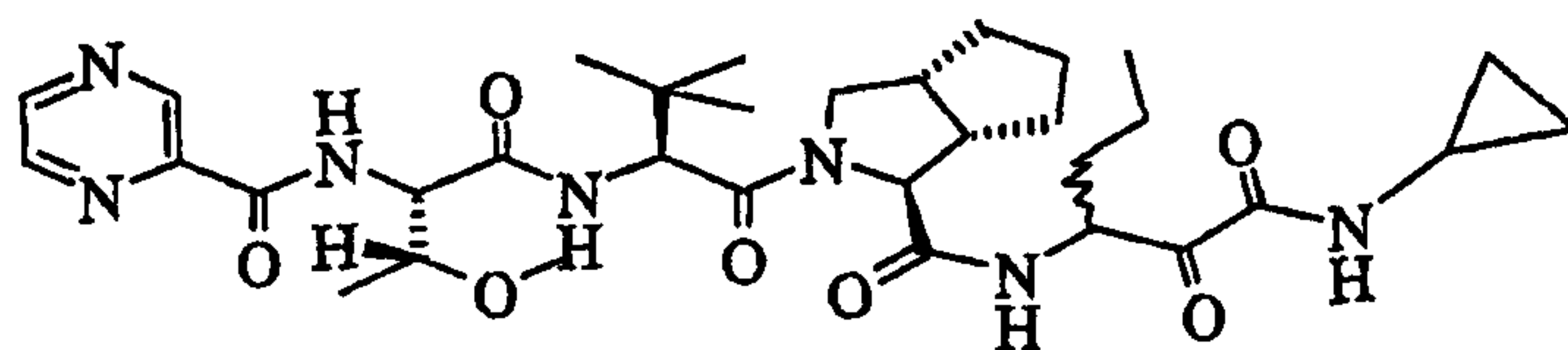
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FB,



FC,

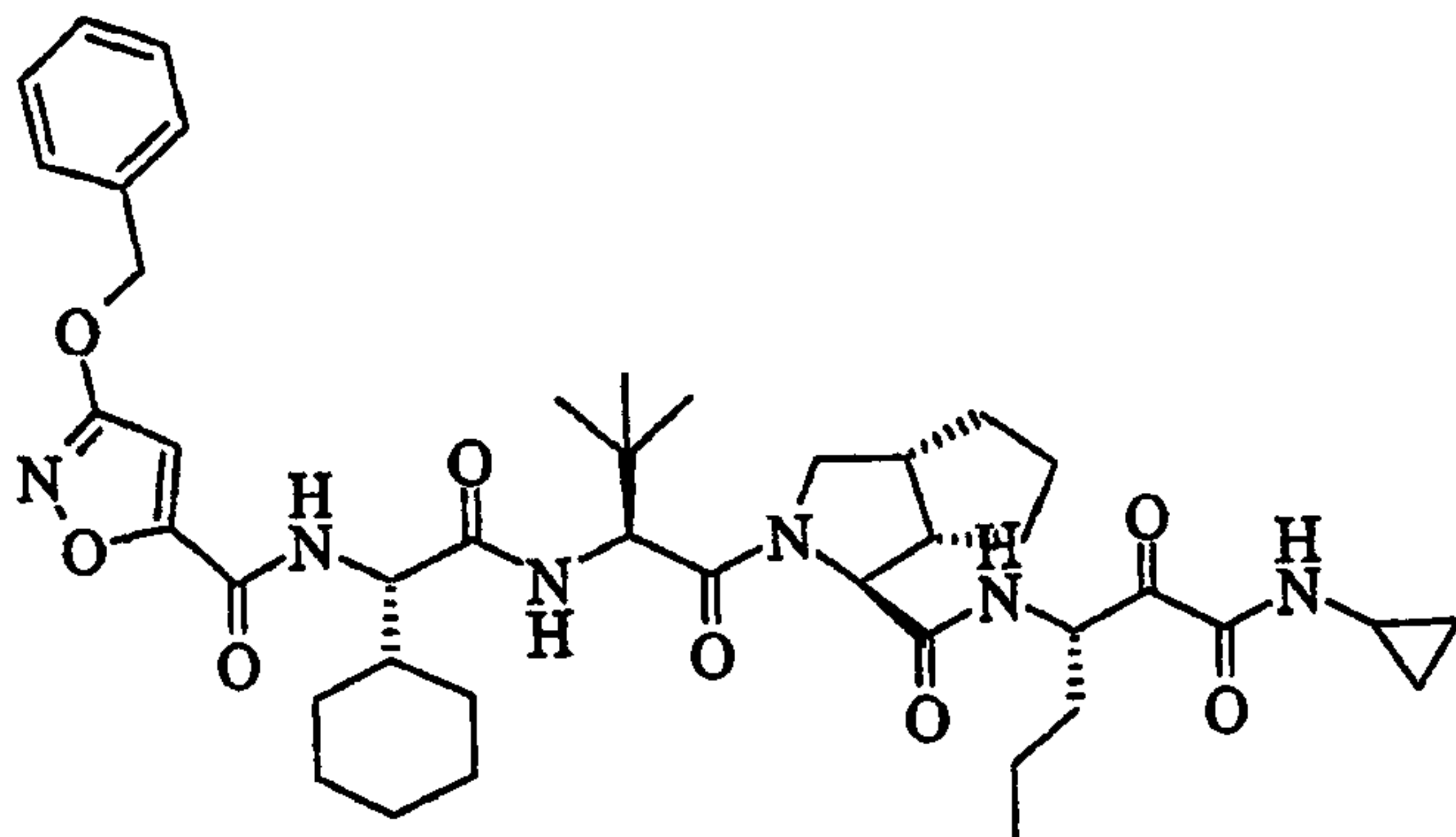


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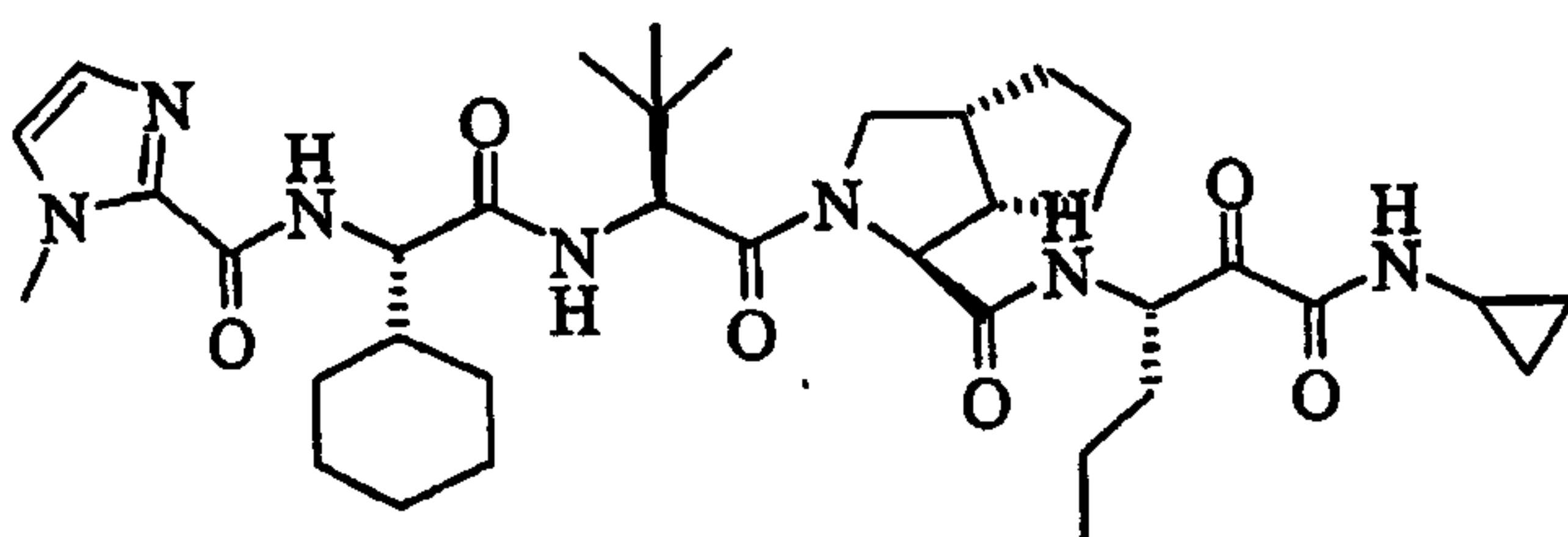
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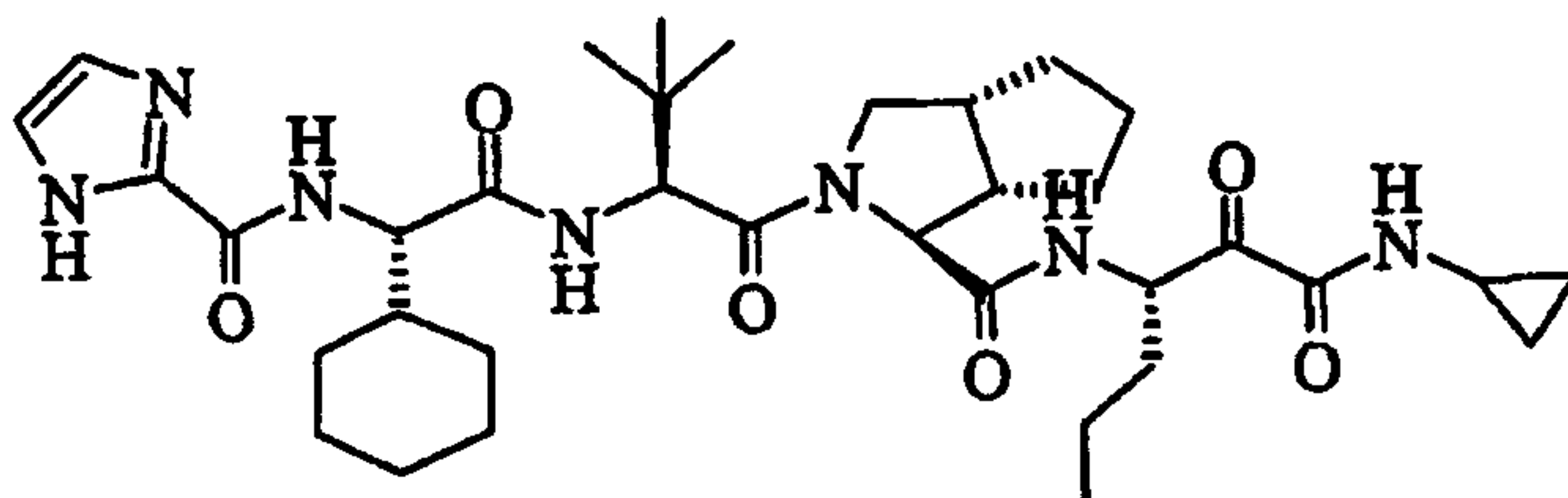


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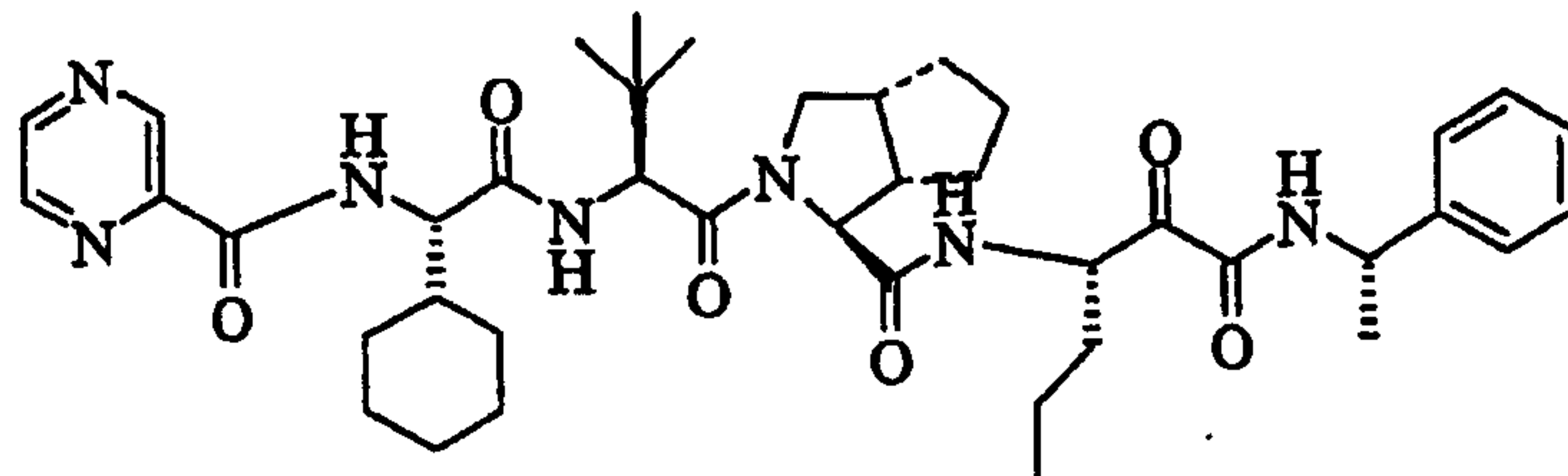


FF,

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FG, and



FH,

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or a pharmaceutically acceptable salt or prodrug thereof, or a solvate of such a compound, its salt or its prodrug.

Another preferred embodiment of the invention is a compound of formula 1 wherein the optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group of R^9 is substituted with at least one heteroaryl substituent.

Another preferred embodiment of the invention is a compound of formula 1 wherein the optionally substituted aromatic group of R^9 is optionally substituted heteroaryl.

Another preferred embodiment of the invention is a compound of formula 1 wherein the optionally substituted aliphatic group of R^9 is optionally substituted alkylheteroaryl.

Another preferred embodiment of the invention is a compound wherein the optionally substituted heteroaryl group of R^9 is pyrazinyl, tetrazolyl, quinolinyl, imidazolyl, isoxazolyl and pyradonyl, optionally substituted with a ring group substituent.

The compounds of the invention optionally are supplied as salts. Those salts that are pharmaceutically acceptable are of particular interest since they are useful in administering the foregoing compounds for medical purposes. Salts that are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of this invention. The latter is particularly true of amine salts prepared from optically active amines.

Where the compound of the invention contains a carboxy group, or a sufficiently acidic bioisostere, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form.

Also, where the compound of the invention contains a basic group, or a sufficiently basic bioisostere, acid addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form.

A preferred embodiment of a method according to the present invention is for treating a patient suffering from an HCV infection or physiological conditions related to the infection comprising administering to the patient a pharmaceutically effective amount of a compound of formula 1.

Another preferred embodiment of a therapeutic method according to the present invention is for treating a patient suffering from an HCV infection or physiological conditions related to the infection comprising administering a pharmaceutically effective amount of a compound of formula 1 in combination with a pharmaceutically effective amount of another anti-HCV therapeutic to the patient.

Another object of the present invention is to provide pharmaceutical compositions comprising, in addition to one or more HCV serine protease inhibitors, one or more interferons exhibiting anti-HCV activity and/or one or more compounds having anti HCV activity, including

immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity, and a pharmaceutically acceptable carrier or diluent.

It is another object of the invention to provide a pharmaceutical composition which is effective, in and of itself, for utilization in a beneficial combination therapy because it includes a plurality of active ingredients which may be utilized in accordance with the invention.

The invention also provides kits or single packages combining two or more active ingredients useful in treating or preventing an HCV infection in a patient. A kit may provide (alone or in combination with a pharmaceutically acceptable diluent or carrier), the compound of formula 1 and the additional active ingredient (alone or in combination with diluent or carrier) other anti-HCV therapeutic.

Compounds of formula 1 may be prepared by the application or adaptation of known methods as used heretofore or described in the literature, or by methods according to this invention herein.

Another object of the present invention is to provide methods of treating or preventing a HCV infection in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a combination of one or more HCV serine protease inhibitors; one or more interferons exhibiting anti-HCV activity; and/or one or more compounds having anti-HCV activity, including immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity.

Another object of the present invention is the use of one or more HCV serine protease inhibitors in combination with one or more interferons exhibiting anti-HCV activity and/or one or more compounds having anti-HCV activity, including immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity, to prepare a medicament for treating or preventing a HCV infection in a patient in need thereof.

A further object of the present invention is a kit or pharmaceutical pack for treating or preventing HCV infection in a patient, wherein the kit or pharmaceutical pack comprises a plurality of separate containers, wherein at least one of said containers contains one or more HCV serine protease inhibitors, at least another of said containers contains one or more interferons or compounds that induce the production of an inteferon that exhibit anti-HCV activity (alone or in combination with a pharmaceutically acceptable carrier or diluent), and, optionally, at least another of said containers contains one or more compounds having anti-HCV activity (alone or in combination with a pharmaceutically acceptable carrier or diluent), including immunomodulatory compounds such as immunostimulatory cytokines exhibiting HCV antiviral activity.

Yet another object of the present invention is to provide a method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell, a hepatitis C virus serine protease

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inhibitor, and optionally an interferon or compounds that induce the production of an interferon that have anti-hepatitis C virus activity.

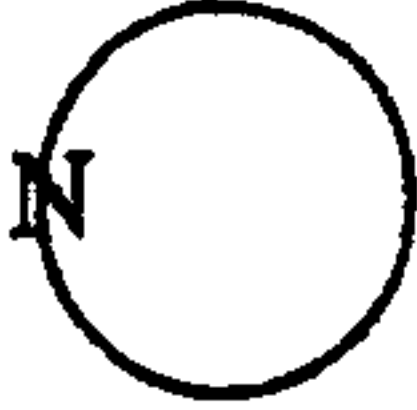
The amount of the HCV serine protease inhibitor(s), interferon(s), or anti-HCV compound(s) in any of the foregoing applications can be a pharmaceutically effective amount, a suboptimal anti-HCV effective amount, or combinations thereof, so long as the final combination of HCV protease inhibitor(s), interferon(s), and/or anti-HCV compound(s) comprises a pharmaceutically effective amount of compounds that is effective in treating or preventing HCV infection in a patient.

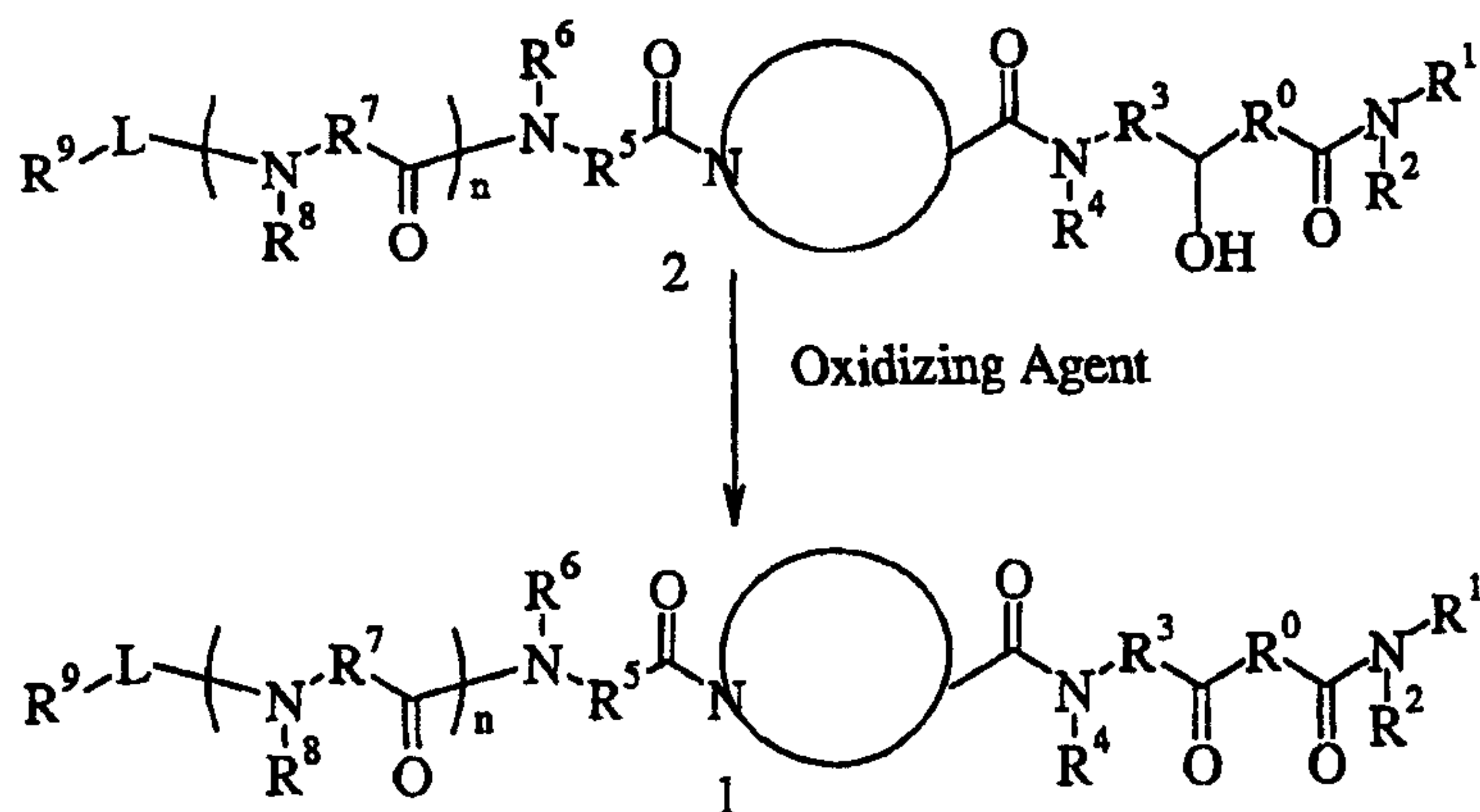
It is a further object of the invention to provide a method for preparing a chiral bicycloprolinate compound that is useful in preparing the compound of formula 1.

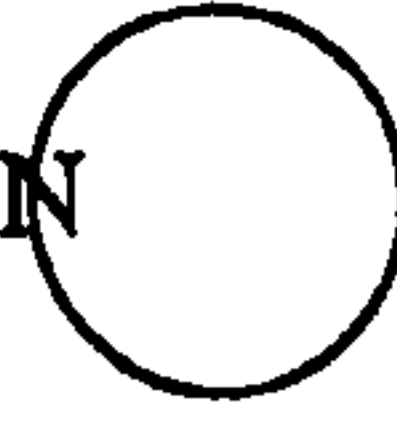
Preparation of Compounds of the Invention

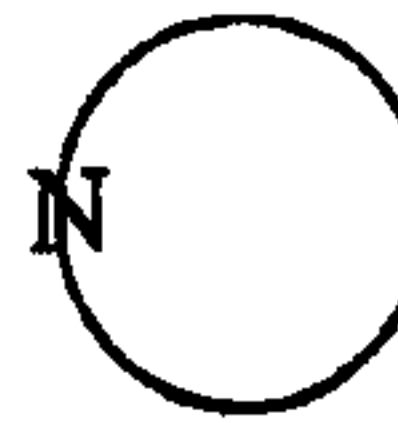
The starting materials and intermediates of compounds of the invention may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

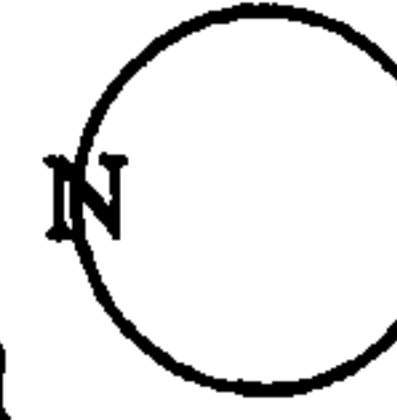
Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in Comprehensive Organic Transformations, VCH publishers (1989).

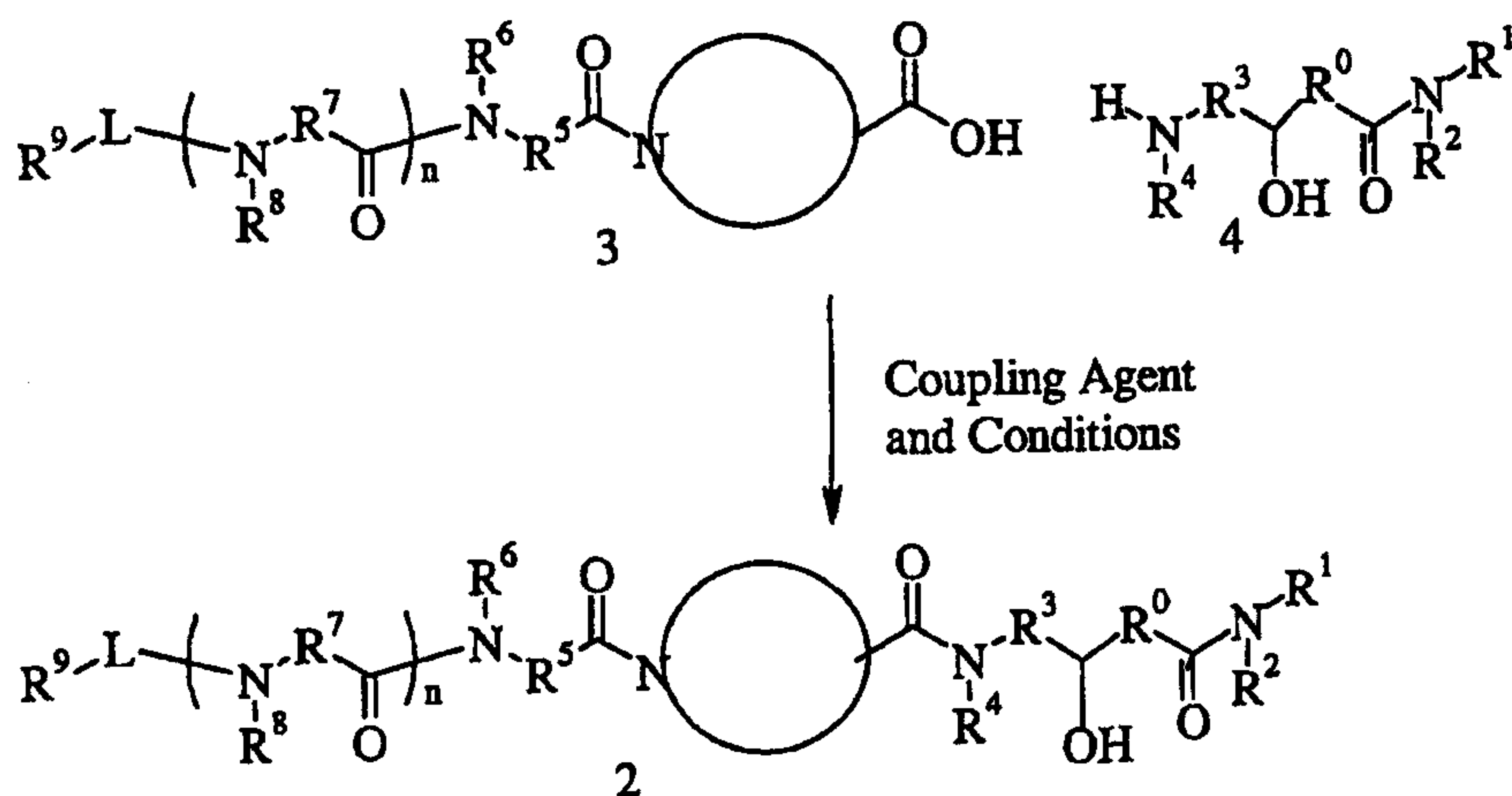
A compound of formula 1, wherein the variables and  moiety thereof are as described herein, may be prepared by treating a compound of formula 2, wherein the variables



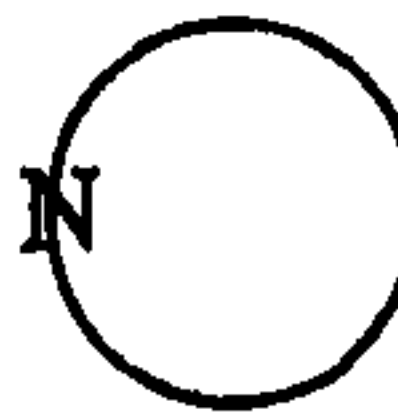
and  moiety thereof are as described herein, with an appropriate oxidizing agent and under appropriate conditions. A particular oxidizing agent is DMP reagent. Particular conditions include carrying out the oxidation in an appropriate organic solvent such as dichloromethane at about room temperature.

5 A compound of formula 2, wherein the variables and  moiety thereof are as described herein, may be prepared by coupling a compound of formula 3, wherein the variables

and  moiety thereof are as described herein, and a compound of formula 4, wherein the



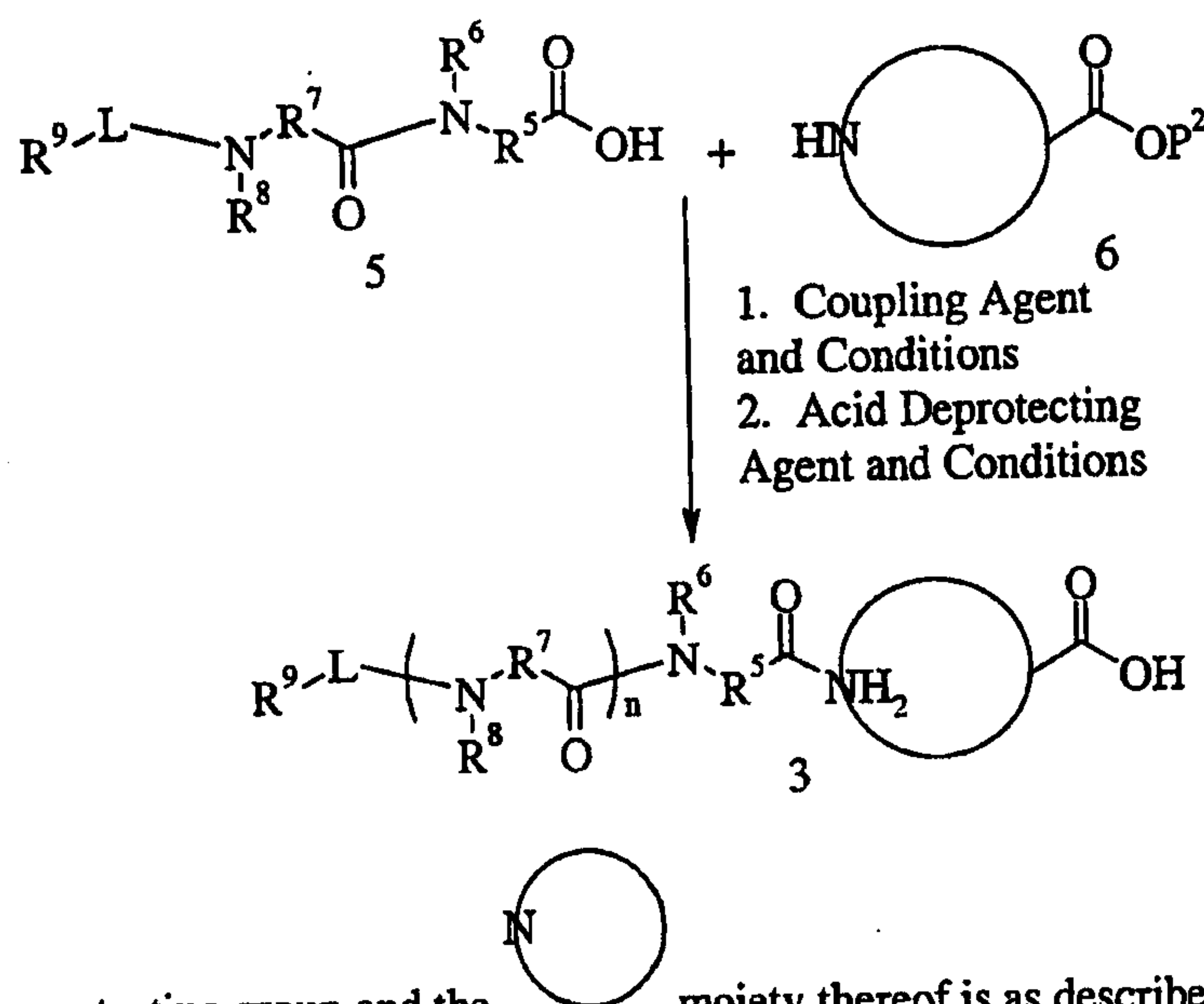
variables thereof are as described herein, with an appropriate coupling agent and under
 10 appropriate conditions. Particular coupling agent and conditions include using DIC and HOAt in
 an appropriate organic solvent such as DMF at about 0°C or using PyBop and DIPEA in an
 appropriate organic solvent such as dichloromethane at about room temperature.

A compound of formula 3, wherein the variables and  moiety thereof are as
 described herein, may be prepared by coupling a compound of formula 5, wherein the variables
 15 thereof are as described herein, and a compound of formula 6, wherein P² is an acid

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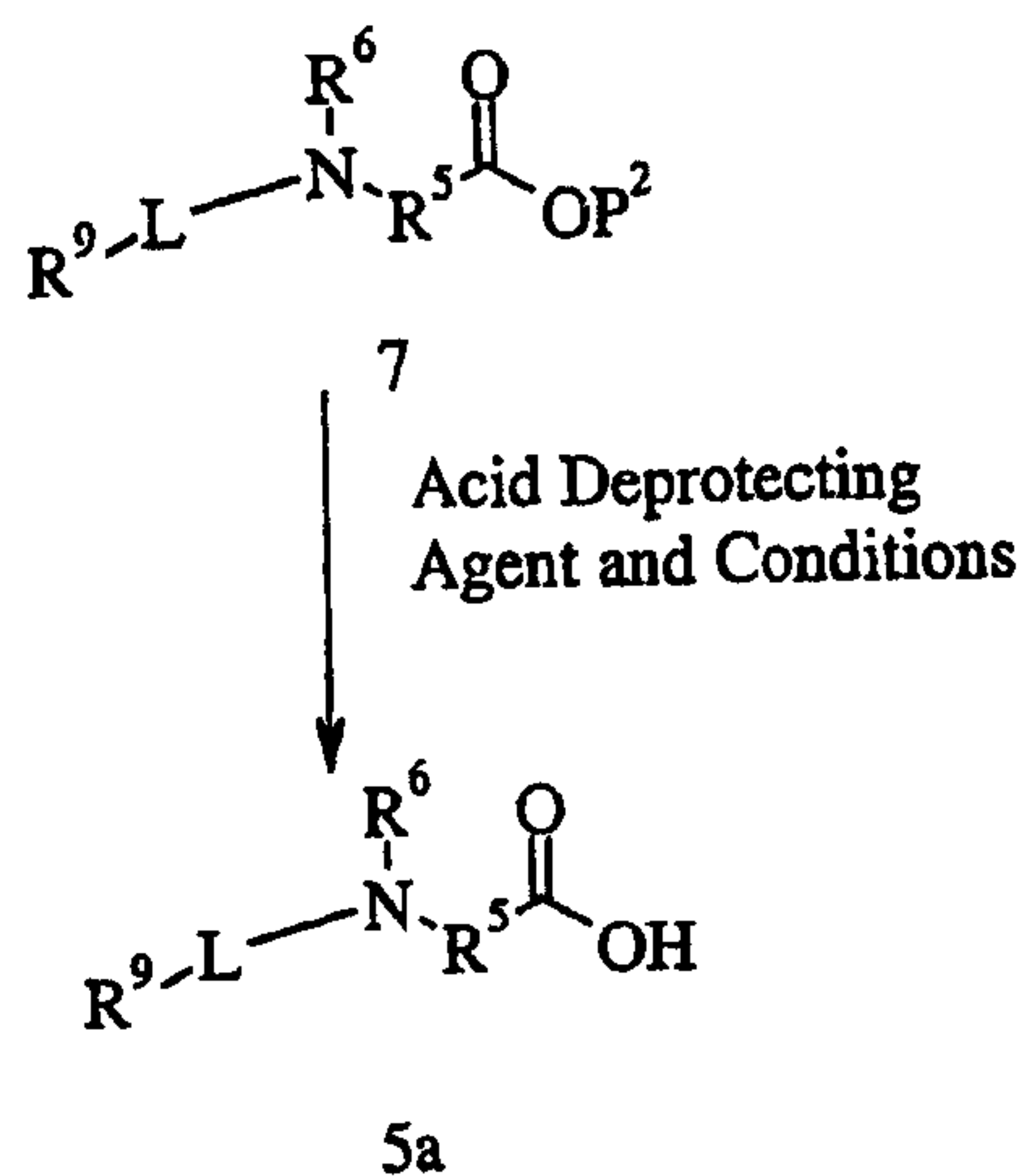
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protecting group and the moiety thereof is as described herein, with an appropriate coupling agent and under appropriate coupling conditions, followed by an appropriate deprotecting agent and under appropriate deprotecting conditions. Particular coupling agent and conditions include using DIC or DCC and HOAt in an appropriate organic solvent such as DMF or dichloromethane at about 0°C to about room temperature. The deprotecting is carried out using an appropriate deprotecting agent that depends on the nature of the protecting agent, i.e., whether it is removable (labile) under acid, base, or hydrogenation conditions, and other reactive moieties in the compound undergoing deprotection, i.e., a deprotecting agent is chosen to carry out the deprotection without effecting the other reactive moieties unless a concomitant reaction is desired. A particular acid protecting agent is C₁ to C₈ lower alkyl; more particular methyl. A particular deprotecting agent is an inorganic base such as an alkali hydroxide; more particular NaOH. Particular deprotection conditions encompass carrying out the deprotection in an alcoholic solvent such as methanol or ethanol at about room temperature.

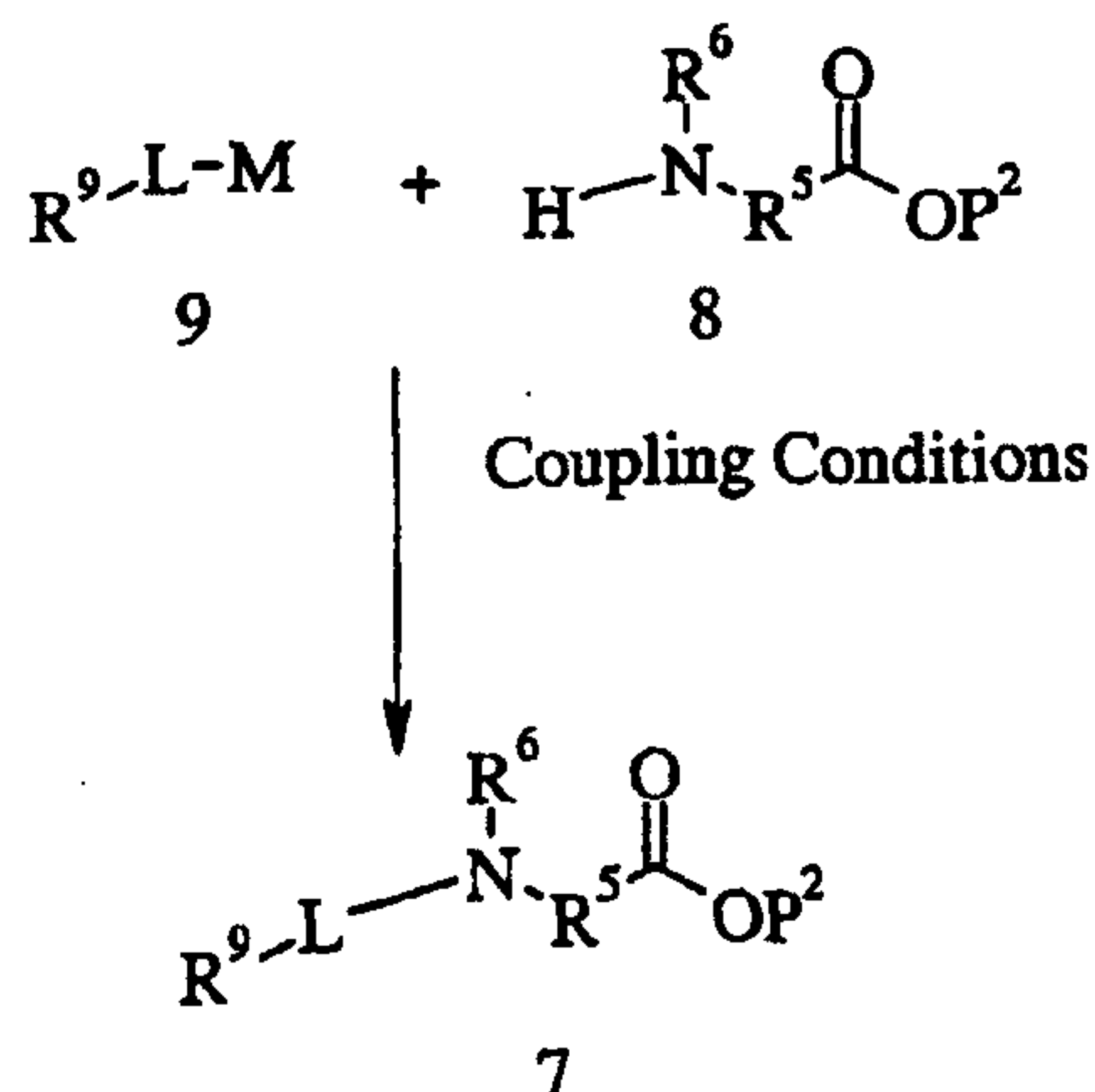
A compound of formula 5, wherein n is 0 and the other variables are as described herein, i.e., compound 5a, may be prepared by deprotecting a compound of formula 7,

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wherein P² is an acid protecting group and the other variables thereof are as described herein, with an appropriate deprotecting agent and under appropriate conditions. The deprotecting is carried out using an appropriate deprotecting agent that depends on the nature of the protecting agent, i.e., whether it is removeable (labile) under acid, base, or hydrogenation conditions, and other reactive moieties in the compound undergoing deprotection, i.e., a deprotecting agent is chosen to carry out the deprotection without effecting the other reactive moieties unless a concomitant reaction is desired. A particular acid protecting agent is C₁ to C₈ lower alkyl; more particular methyl. A particular deprotecting agent is an inorganic base such as an alkali hydroxide; more particular NaOH. Particular deprotection conditions encompass carrying out the deprotection in an alcoholic solvent such as methanol or ethanol at about room temperature.

A compound of formula 7, wherein the variables thereof are as described herein, may be prepared by acylating a compound of formula 8, wherein the variables thereof are as described herein, with a compound of formula 9, wherein M is a displaceable moiety and the other variables

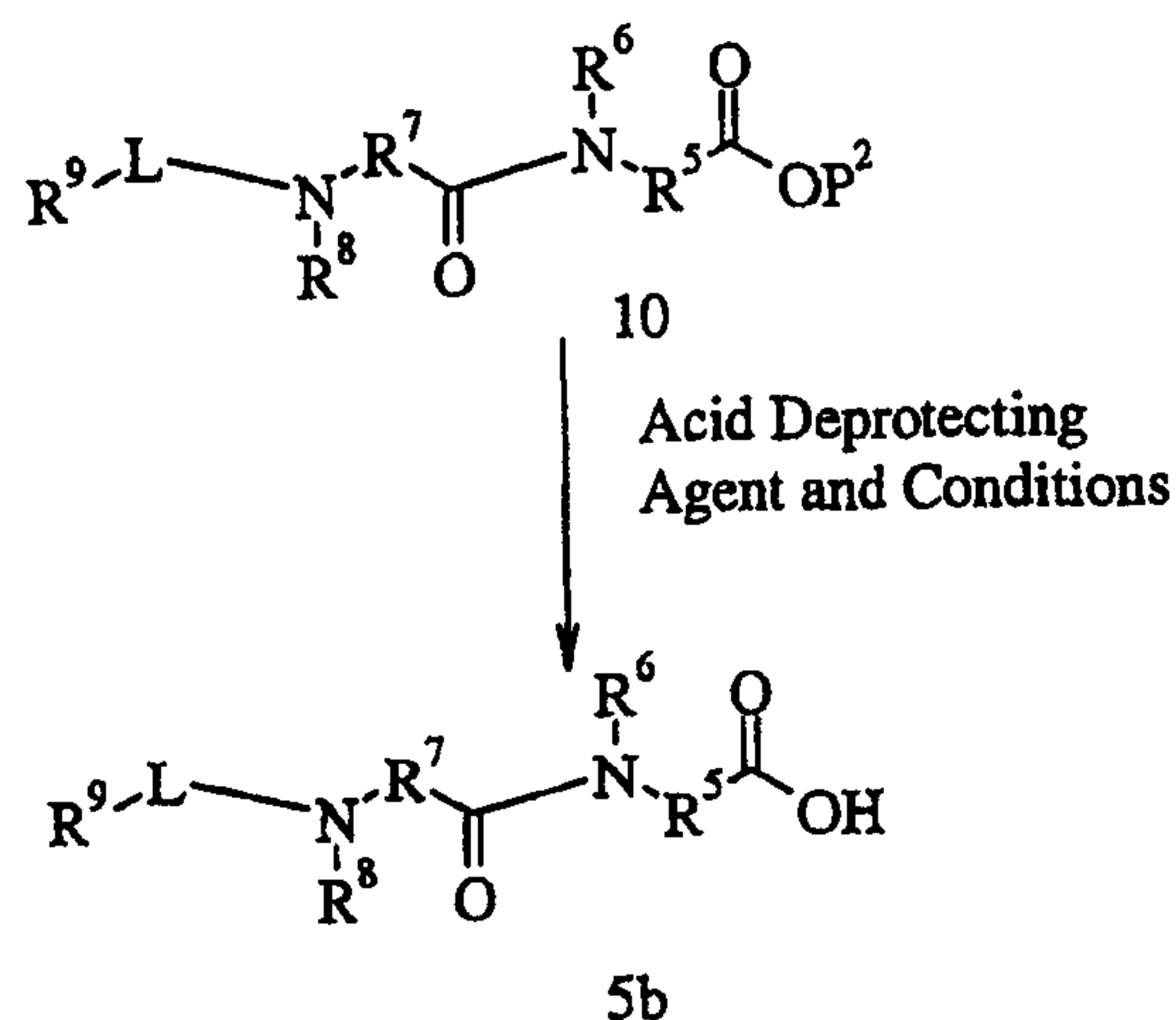


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thereof are as described herein, under appropriate conditions. Particular coupling conditions use DIC or DCC and HOAt in an appropriate organic solvent such as DMF or dichloromethane at

about 0°C to about room temperature, or PyBop and DIPEA in an appropriate organic solvent such as DMF or dichloromethane at about room temperature; and preferably the latter conditions. A particular L is carbonyl. A particular M is hydroxy or N-oxysuccinimide.

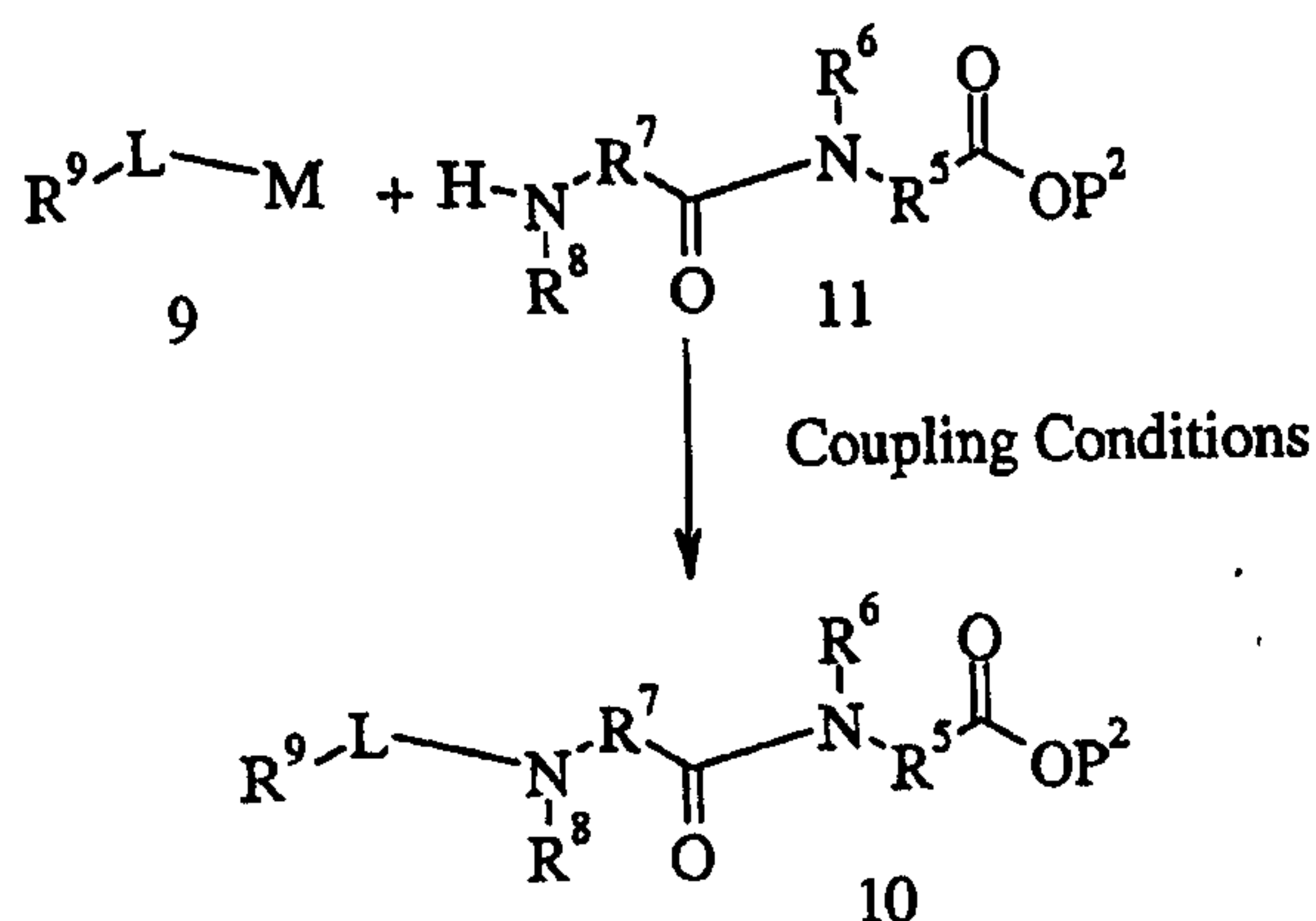
A compound of formula 5, wherein n is 1 and the other variables are as described herein,
 5 i.e., compound 5b, may be prepared by deprotecting a compound of formula 10, wherein P² is an



acid protecting group and the other variables thereof are as described herein, with an appropriate deprotecting agent and under appropriate conditions. The deprotecting is carried out using an appropriate deprotecting agent that depends on the nature of the acid protecting agent, i.e.,
 10 whether it is removeable (labile) under acid, base, or hydrogenation conditions, and other reactive moieties in the compound undergoing deprotection, i.e., a deprotecting agent is chosen to carry out the deprotection without effecting the other reactive moieties unless a concomitant reaction is desired. A particular acid protecting agent is C₁ to C₈ lower alkyl; more particular methyl. A particular deprotecting agent is an inorganic base such as an alkali hydroxide; more particular
 15 NaOH. Particular deprotection conditions encompass carrying out the deprotection in an alcoholic solvent such as methanol or ethanol at about room temperature.

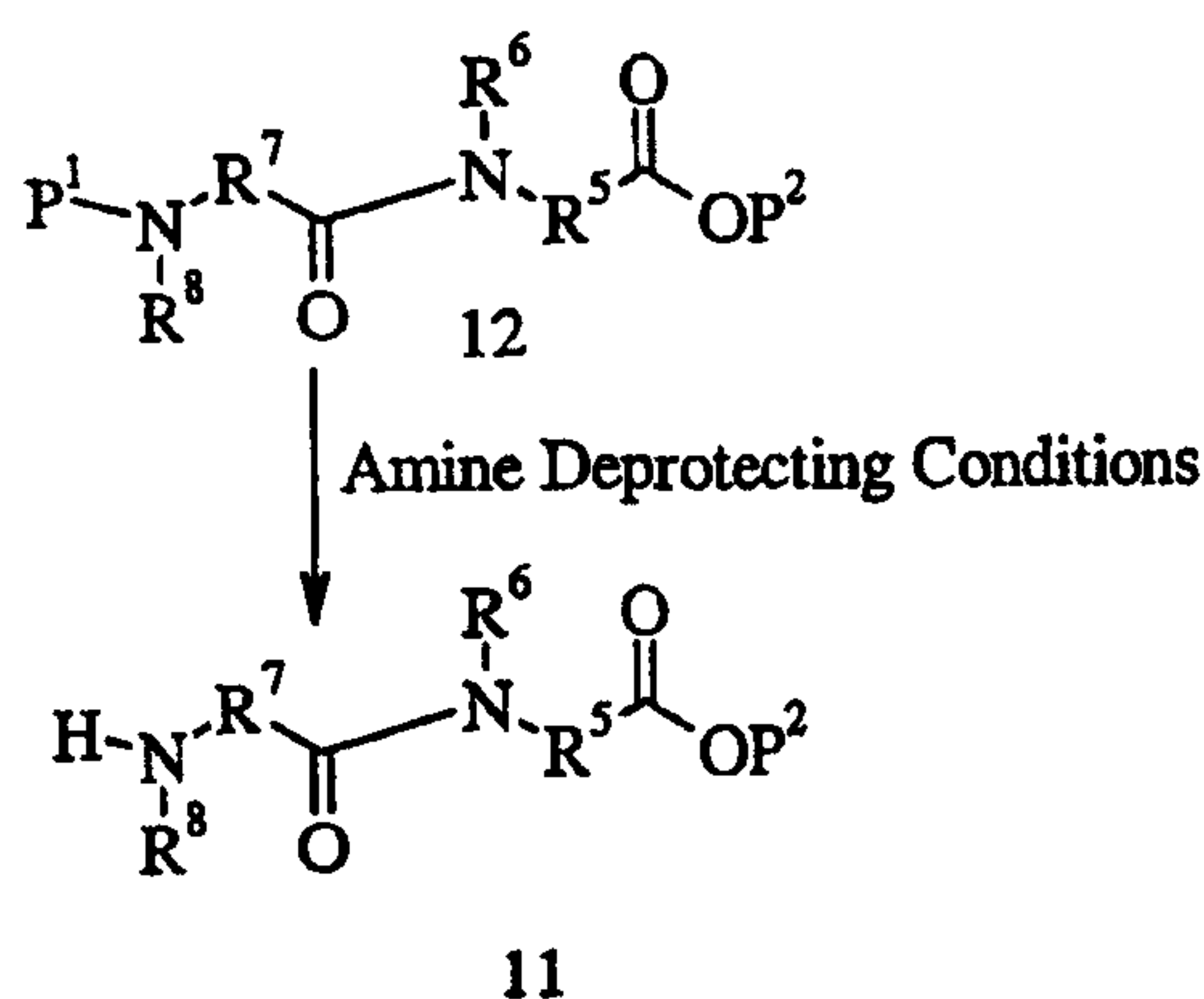
A compound of formula 10, wherein the variables thereof are as described herein, may be prepared by acylating a compound of formula 11, wherein the variables thereof are as described herein, with a compound of formula 9, wherein the variables thereof are as described herein,

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under appropriate conditions. Particular coupling conditions use DIC or DCC and HOAt in an appropriate organic solvent such as DMF or dichloromethane at about 0°C to about room temperature, or PyBop and DIPEA in an appropriate organic solvent such as DMF or dichloromethane at about room temperature; and preferably the latter conditions. A particular L is carbonyl. A particular M is hydroxy or N-oxysuccinimide.

A compound of formula 11, wherein the variables are as described herein, may be prepared by deprotecting a compound of formula 12, wherein P¹ is an amine protecting group

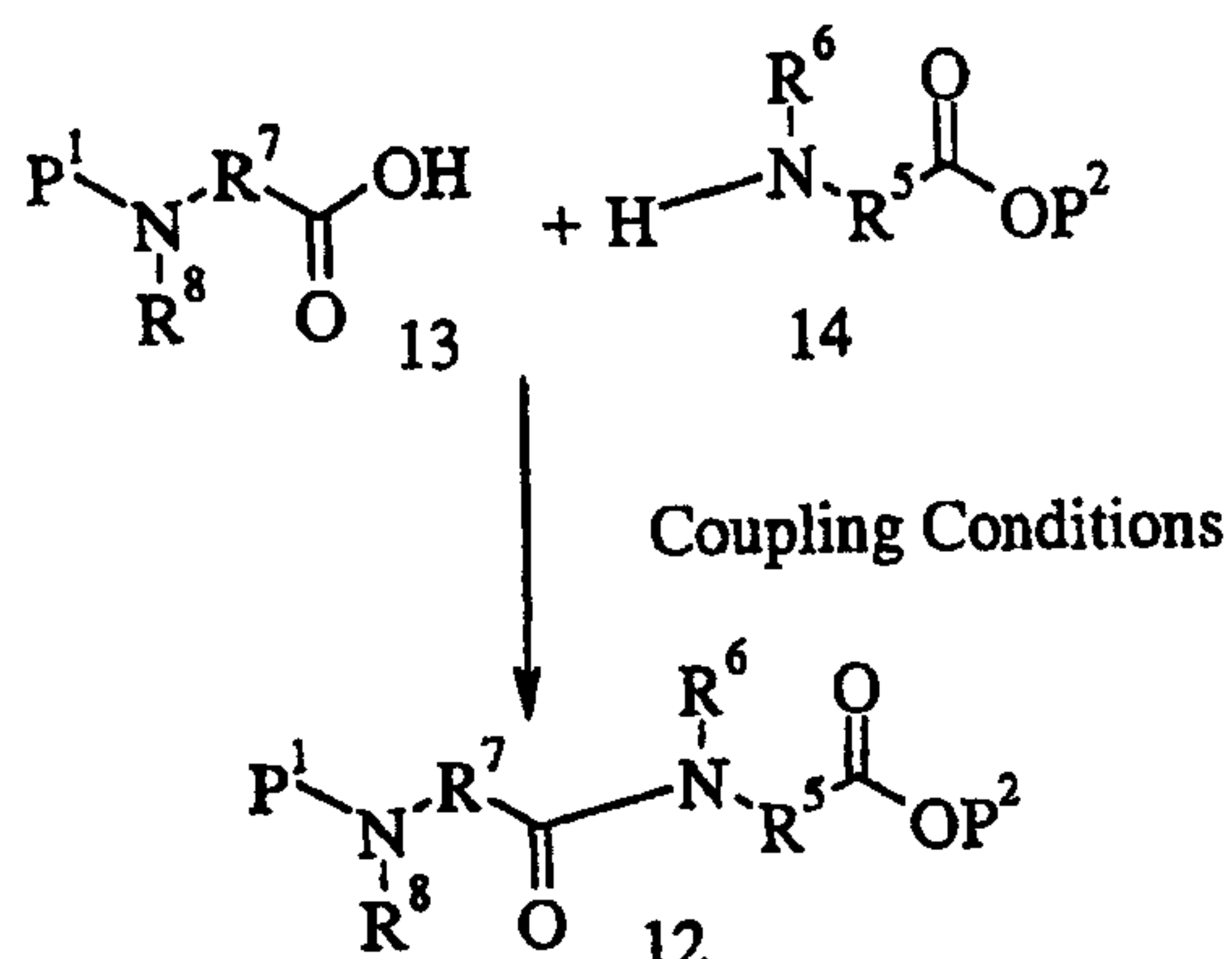


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and the other variables thereof are as described herein, with an appropriate deprotecting agent and under appropriate conditions. The deprotecting is carried out using an appropriate deprotecting agent that depends on the nature of the amine protecting agent, i.e., whether it is removeable (labile) under acid, base, or hydrogenation conditions, and other reactive moieties in the compound undergoing deprotection, i.e., a deprotecting agent is chosen to carry out the deprotection without effecting the other reactive moieties unless a concomitant reaction is desired. A particular amine protecting agent is Cbz or BOC; more particular Cbz. A particular deprotecting agent is acid such as HCl or H₂/Pd(OH)₂; more particular H₂/Pd(OH)₂. Particular

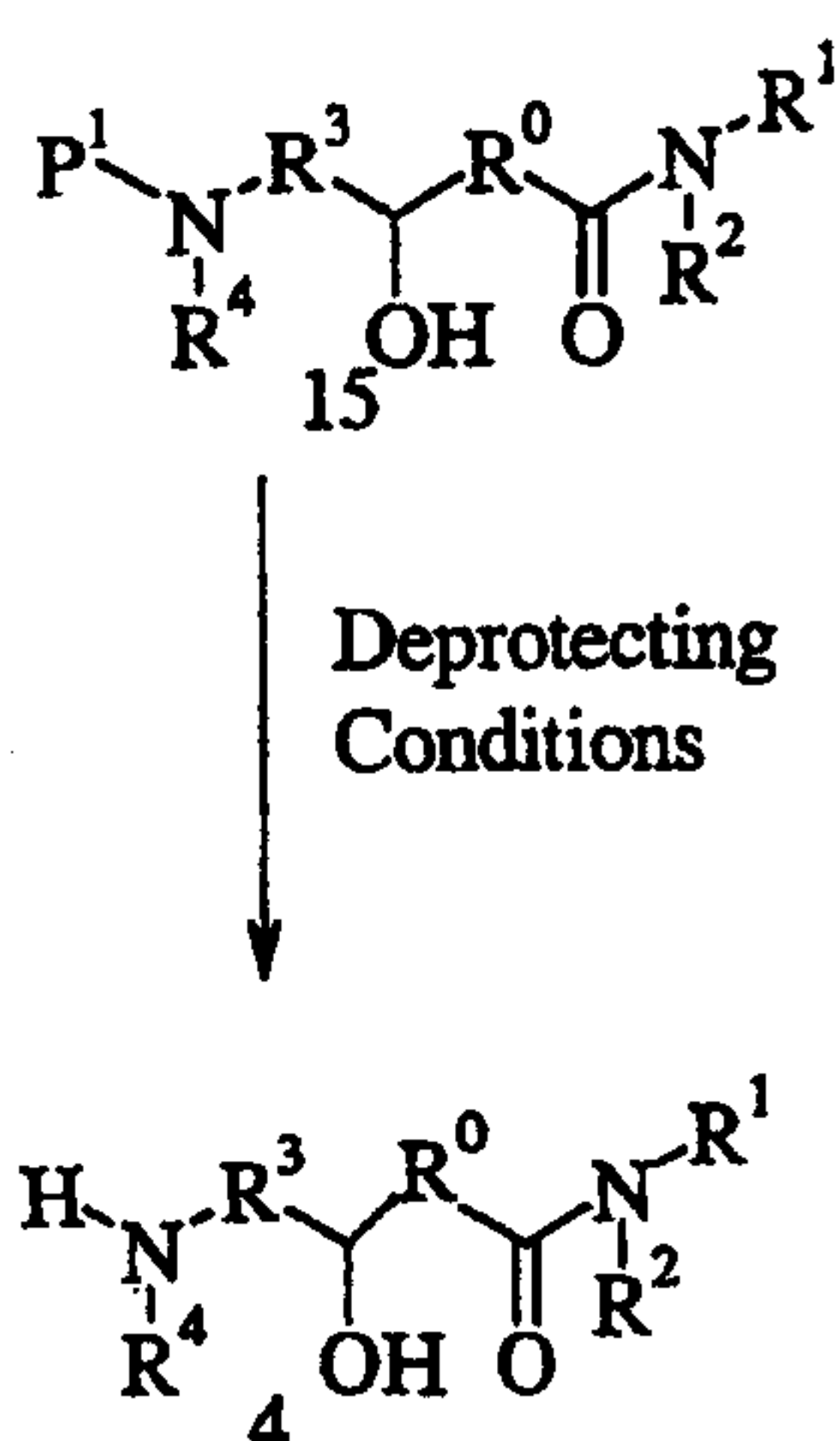
deprotection conditions encompass carrying out the deprotection in an alcoholic solvent such as methanol or ethanol or an alkyl alkanoate solvent such as ethyl acetate at about room temperature.

A compound of formula 12, wherein the variables thereof are as described herein, may be prepared by coupling a compound of formula 13, wherein the variables thereof are as described
 5 herein, with a compound of formula 14, wherein the variables thereof are as described herein,



under appropriate conditions. Particular coupling conditions use HOAt/DIC and DIPEA in an appropriate organic solvent such as THF at about room temperature.

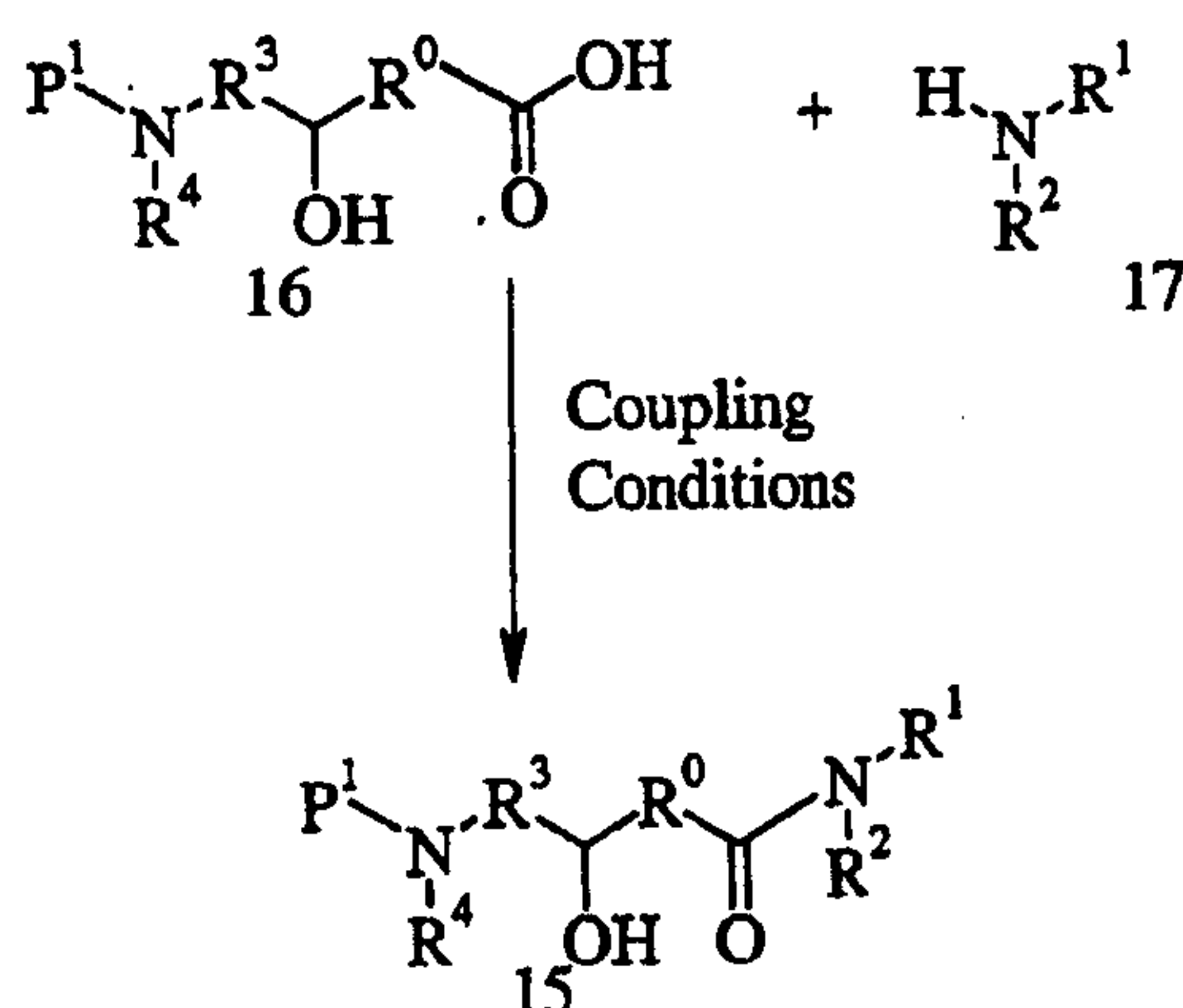
A compound of formula 4, wherein the variables are as described herein, may be prepared
 10 by deprotecting a compound of formula 15, wherein the variables thereof are



as described herein, with an appropriate deprotecting agent and under appropriate conditions. The deprotecting is carried out using an appropriate deprotecting agent that depends on the nature of
 15 the amine protecting agent, i.e., whether it is removeable (labile) under acid, base, or hydrogenation conditions, and other reactive moieties in the compound undergoing deprotection, i.e., a deprotecting agent is chosen to carry out the deprotection without effecting the other reactive moieties unless a concomitant reaction is desired. A particular amine protecting agent is

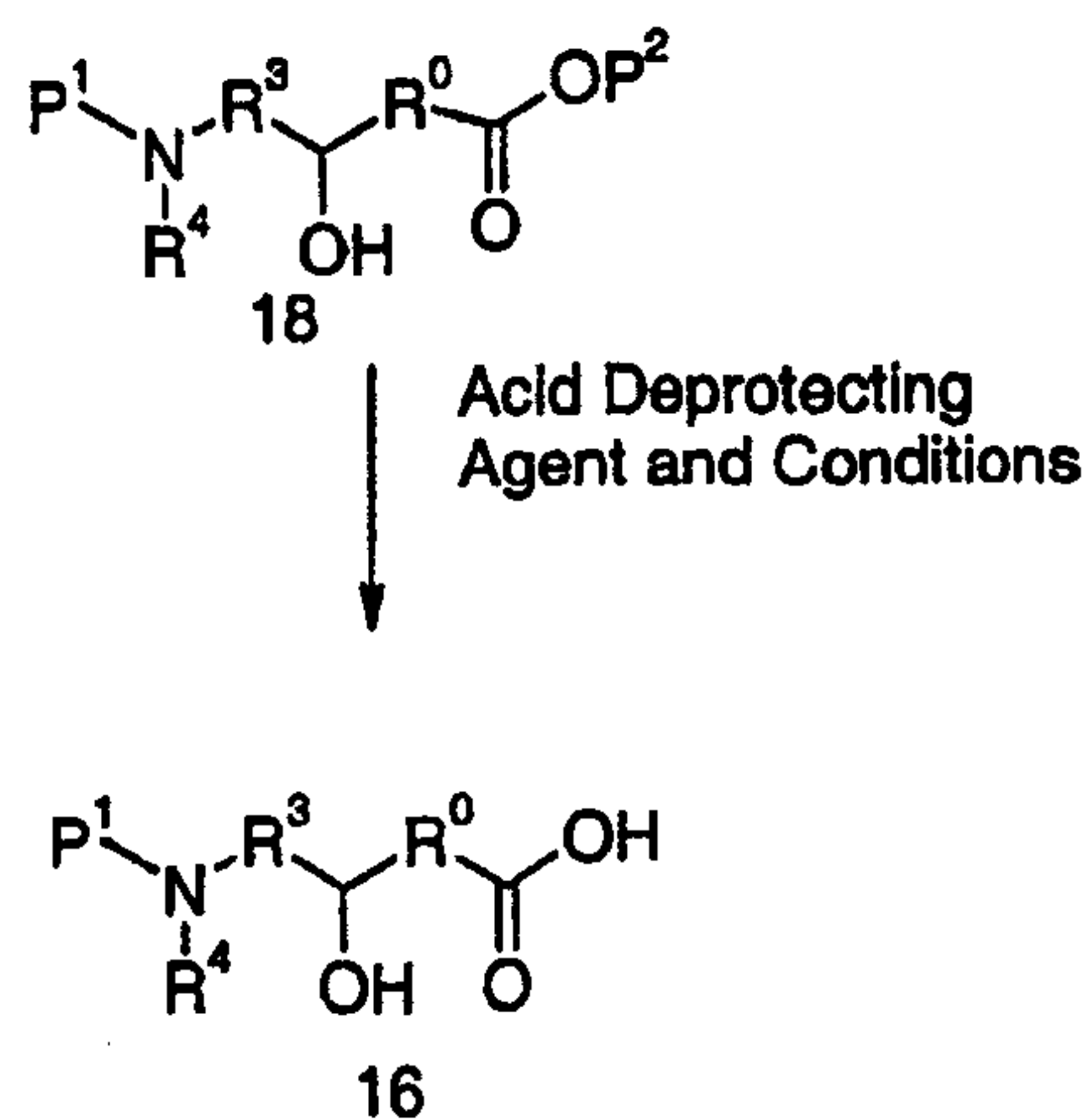
Cbz or BOC; more particular Cbz. A particular deprotecting agent is an acid such as HCl or $H_2/Pd(OH)_2$; more particular $H_2/Pd(OH)_2$. Particular deprotection conditions encompass carrying out the deprotection in an alcoholic solvent such as methanol or ethanol or an alkyl alkanoate solvent such as ethyl acetate at about room temperature.

- 5 A compound of formula 15, wherein the variables thereof are as described herein, may be prepared by coupling a compound of formula 16, wherein the variables thereof are as described herein, with a compound of formula 17, wherein the variables thereof are as described herein,



- under appropriate conditions. A particular amine protecting agent is Cbz or BOC; more particular Cbz. Particular coupling conditions use HOBT, PyBop and DIPEA in an appropriate organic solvent such as dichloromethane at about $0^\circ C$ to about room temperature.

A compound of formula 16, wherein the variables are as described herein may be prepared by deprotecting a compound of formula 18, wherein the other variables thereof are



- 15 as described herein, with an appropriate deprotecting agent and under appropriate conditions. The deprotecting is carried out using an appropriate deprotecting agent that depends on the nature of the acid protecting agent, i.e., whether it is removeable (labile) under acid, base, or hydrogenation conditions, and other reactive moieties in the compound undergoing deprotection, i.e., a deprotecting agent is chosen to carry out the deprotection without effecting the other reactive

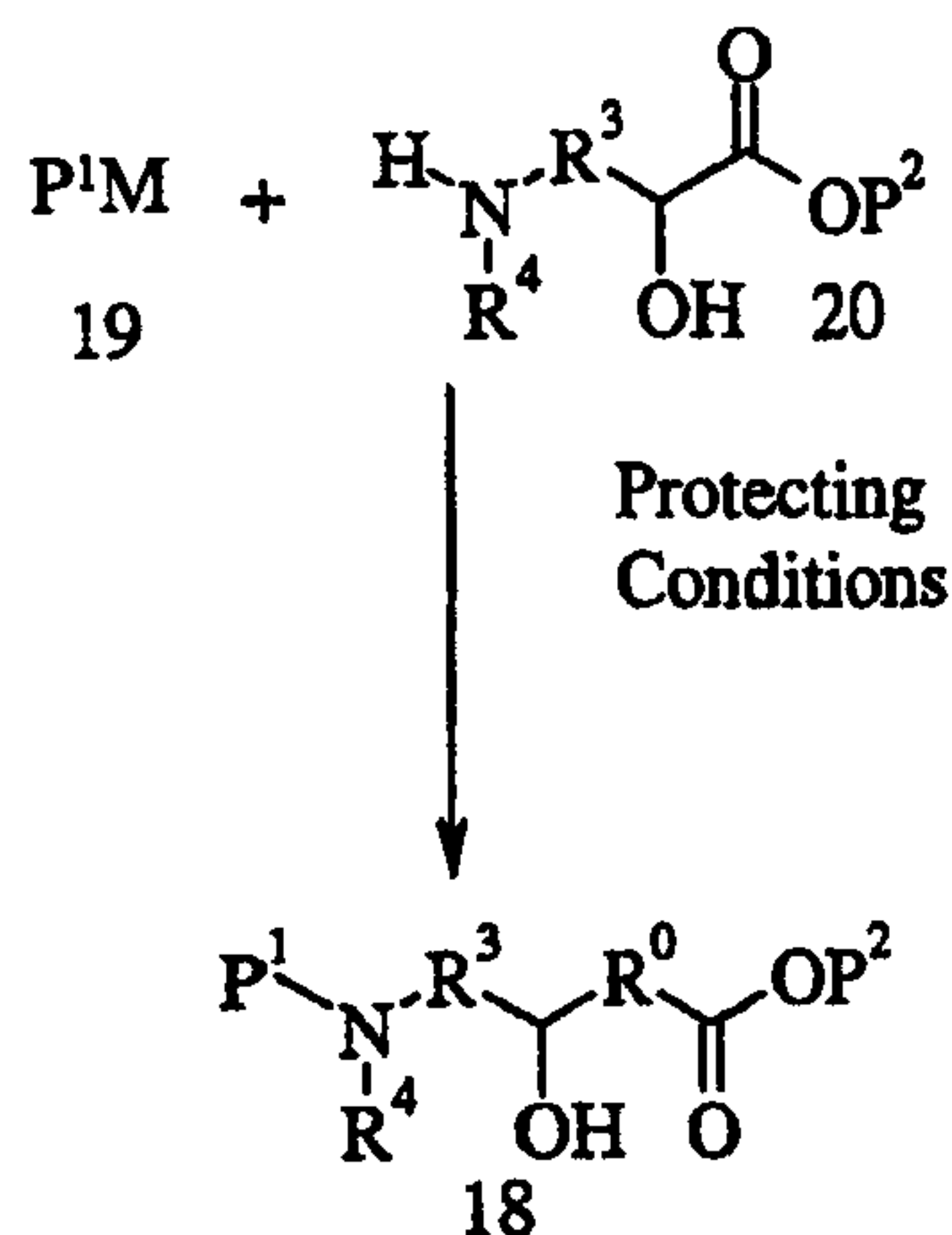
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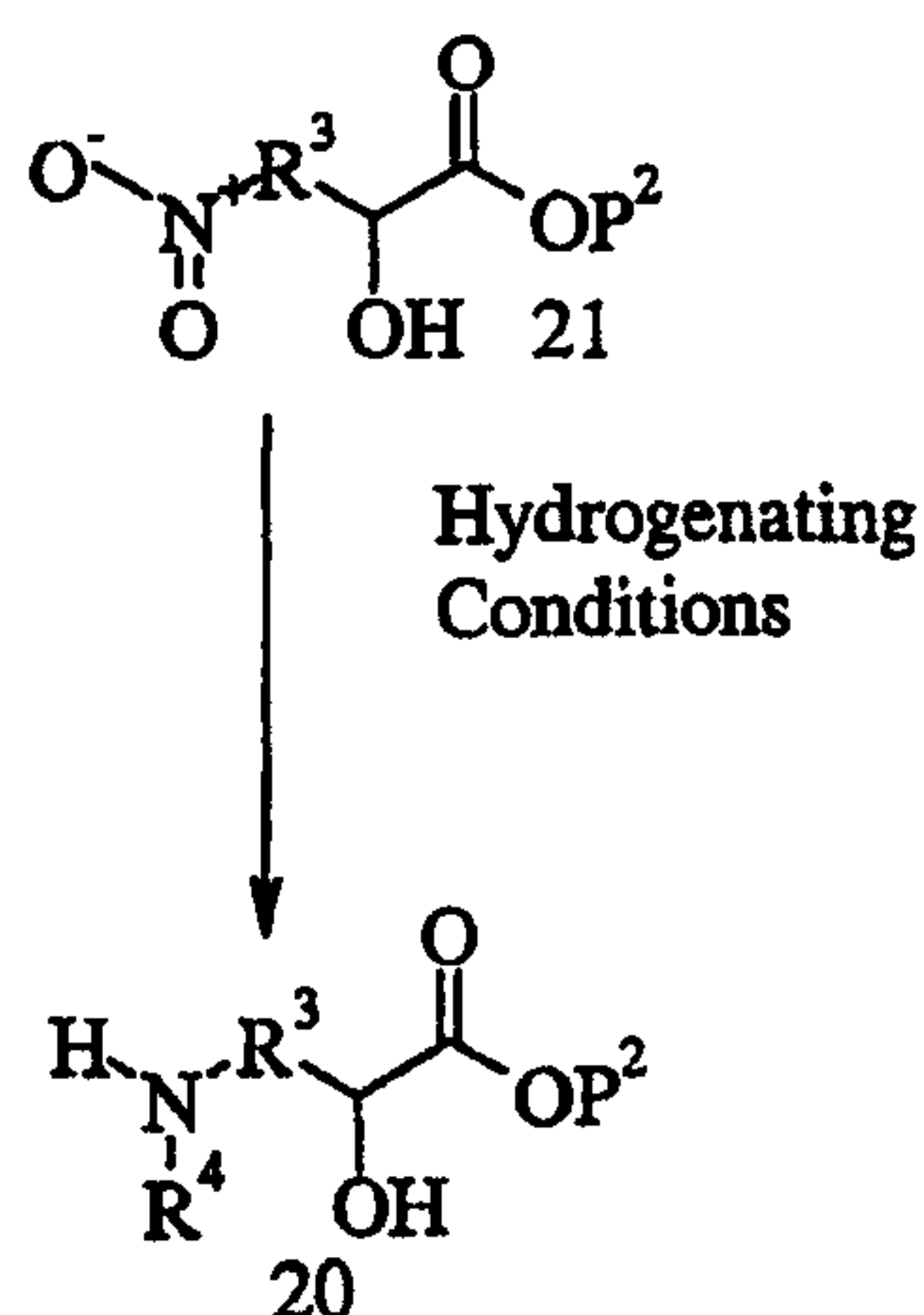
moieties unless a concomitant reaction is desired. A particular amine protecting agent is Cbz. A particular acid protecting agent is C₁ to C₈ lower alkyl; more particular methyl. A particular deprotecting agent is an inorganic base such as an alkali hydroxide; more particular NaOH. Particular deprotection conditions encompass carrying out the deprotection in an alcoholic solvent such as methanol or ethanol at about room temperature.

A compound of formula 18, wherein R⁰ is a bond and the other variables thereof are as described herein, may be prepared by protecting a compound of formula 20, wherein the variables thereof are as described herein, with a compound of formula 19, wherein the



variables thereof are as described herein, under appropriate conditions. A particular amine protecting agent is Cbz or BOC. Particular coupling conditions use an appropriate organic solvent such as dichloromethane at about 0°C to about room temperature.

A compound of formula 20, wherein R⁴ is hydrogen and the other variables are as described herein, may be prepared by hydrogenating a compound of formula 21, wherein the



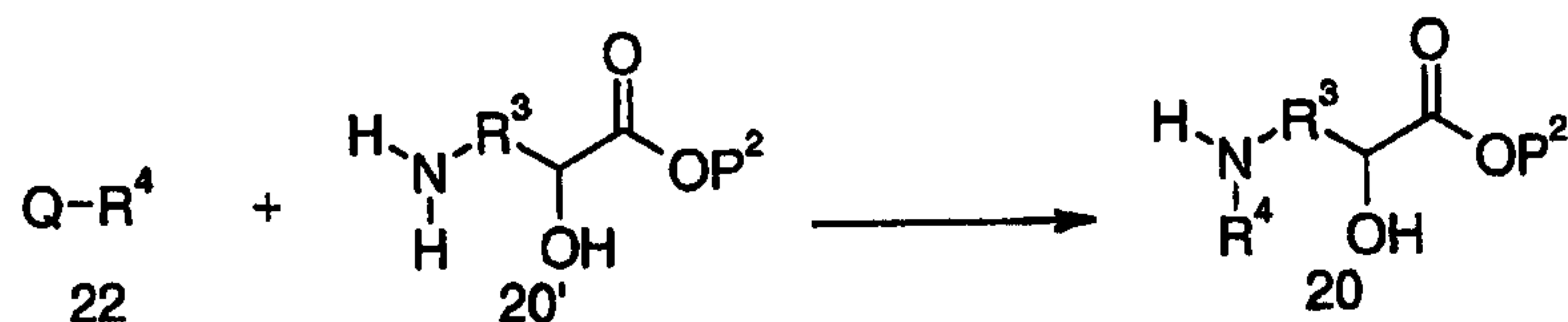
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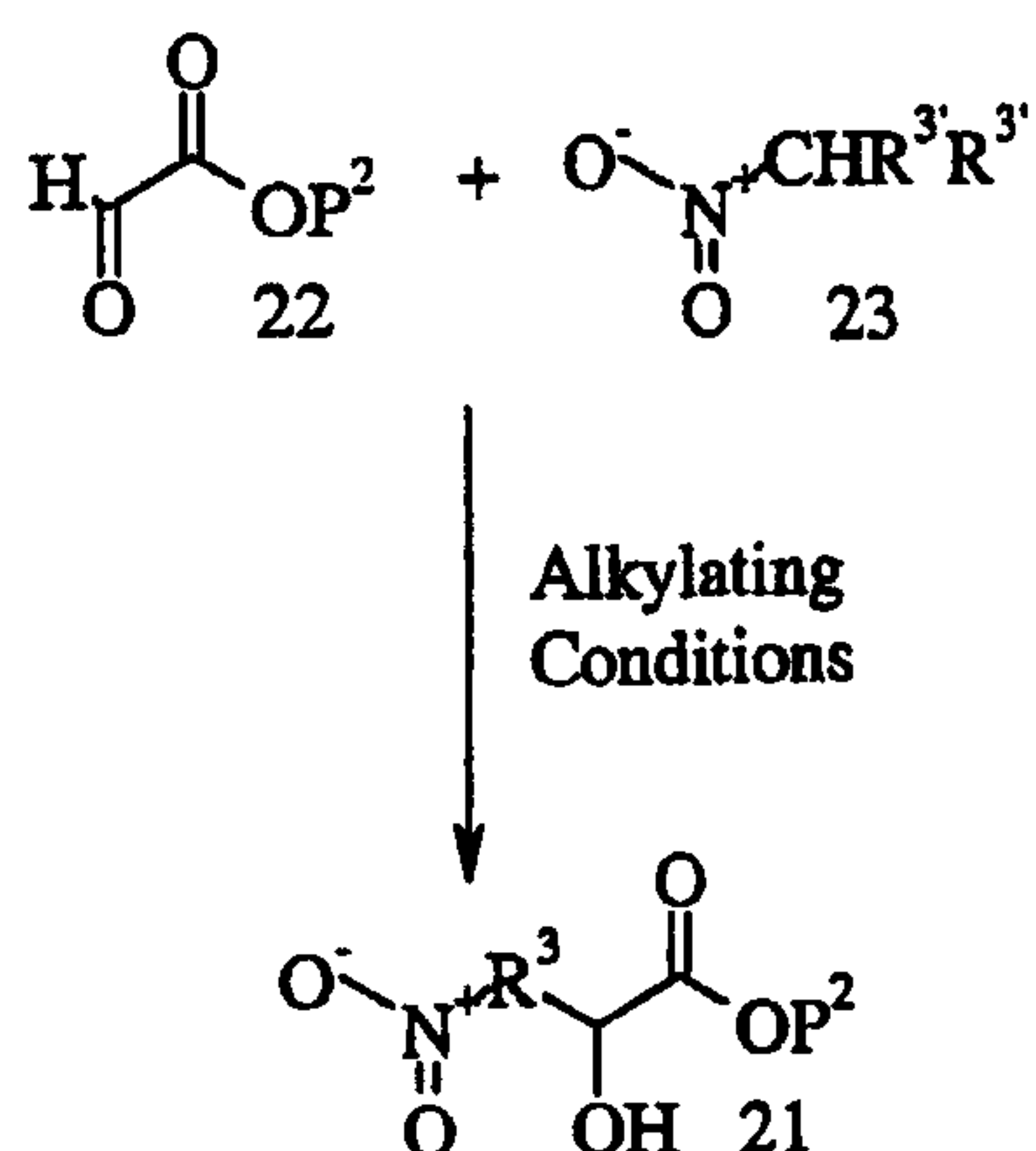
variables thereof are as described herein, with an appropriate hydrogenating agent and under appropriate conditions. A particular hydrogenating agent is $H_2/Pd(OH)_2$. Particular hydrogenating conditions encompass carrying out the hydrogenation in an alcoholic solvent such as methanol or ethanol or an alkyl alkanoate solvent such as ethyl acetate at about room temperature.

A compound of formula 20 wherein R^4 is optionally substituted aliphatic and the other variables are as described herein may be prepared by alkylating compound 20' wherein the variables are as described herein with compound 22 (alkylating agent) wherein R^4 is optionally substituted aliphatic and Q is a displaceable group such as a halides, tosylates or sulfonates, under appropriate conditions.



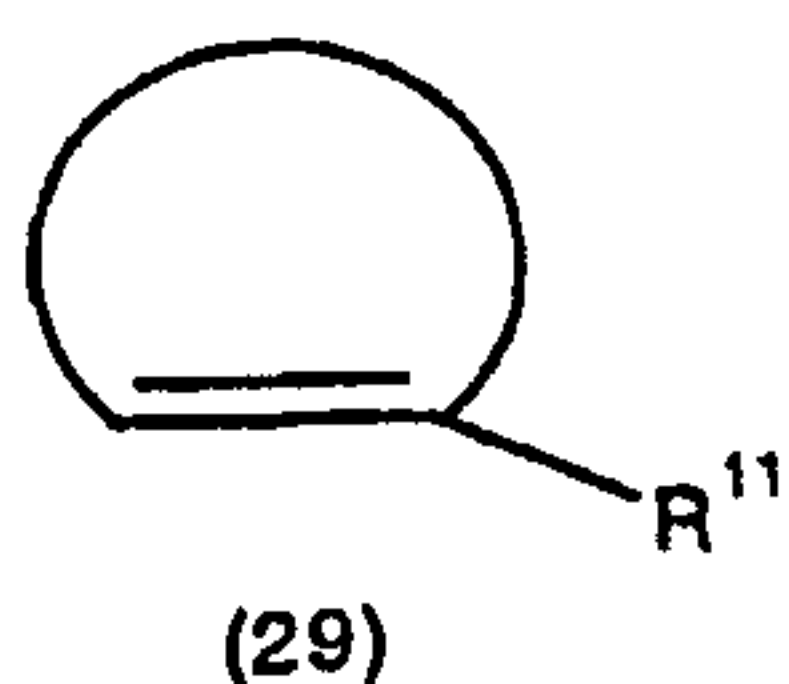
Appropriate alkylating agents include aliphatic (halides, tosylates or sulfonates). Appropriate alkylating conditions encompass carrying out to alkylation in an appropriate organic solvent such as an alcoholic solvent, e.g., methanol or ethanol, or etheric solvent, e.g., ether or tetrahydrofuran at about room temperature to about reflux.

A compound of formula 21, wherein the variables are as described herein, may be prepared by alkylating a compound of formula 22, wherein the variable thereof is as described herein, with a compound of formula 23, wherein the R^3 's independently are optionally



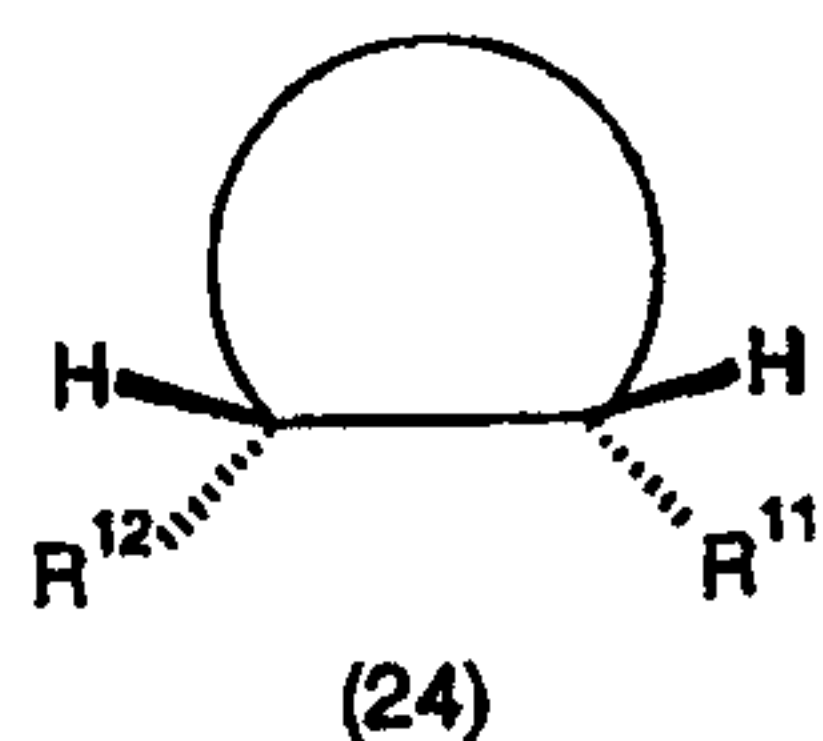
substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group as described herein, under appropriate conditions. Particular alkylating conditions encompass carrying out the alkylation using a strong base such as potassium *t*-butoxide in an alcoholic solvent such as methanol or ethanol at about room temperature.

A compound of formula 24 wherein the variables thereof are as described herein, may be prepared by effecting a Michael addition on a Michael acceptor of formula 29, wherein the variable thereof is as described herein, with an iminic glycinimide derivative.



5

↓ Michael Addition Conditions

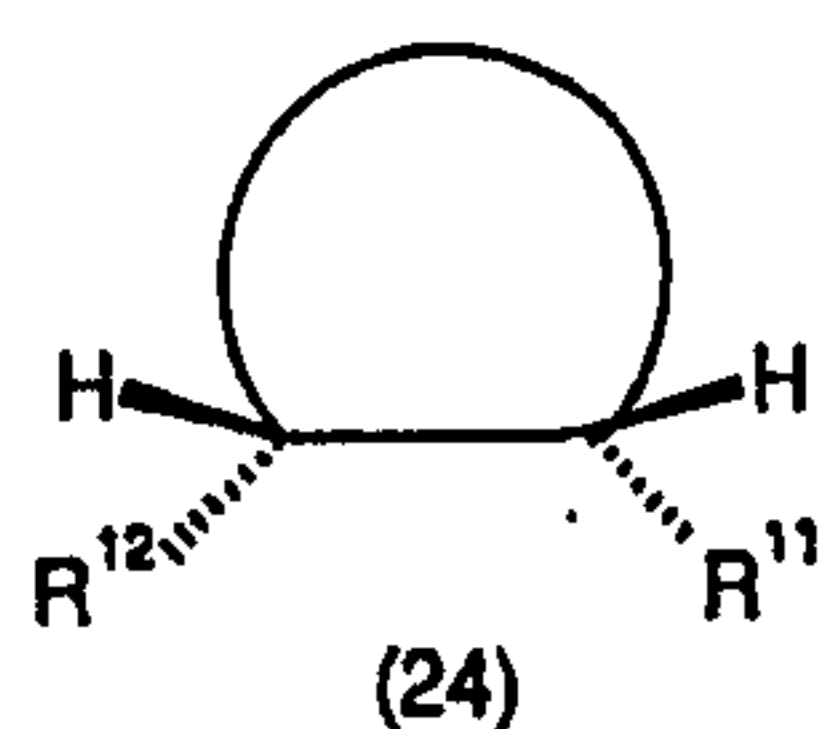


Michael additions comprise appropriate aprotic polar solvents, alkali methyl hydroxide bases, and appropriate temperatures. For Michael additions, see Corey, E.J.; Noe, M.C.; Xu, F. *Tetrahedron Letter* 1998, 39, 5347. For the synthesis of chiral phase transfer catalysts, see Corey, E.J.; Noe, M.C.; Xu, F. *J. Am. Chem. Soc.* 1997, 119, 12414. Appropriate solvents include DCM, ACN, or THF depending on the reaction conditions. Appropriate bases include CsOH, NaOH, KOH, and LiOH. Appropriate temperatures range from about -78°C to about 0°C, more particularly at about -60°C. Iminic glycinimides useful in the invention are described herein. A preferred iminic glycinimide is N-(diphenylmethylene)glycine tert-butyl ester. In addition, Michael addition conditions may be affected with or without a phase transfer catalyst (PTC) (chiral and nonchiral). A preferred PTC is O-[9] allyl-N-9-anthracenylmethylcinchonidium bromide.

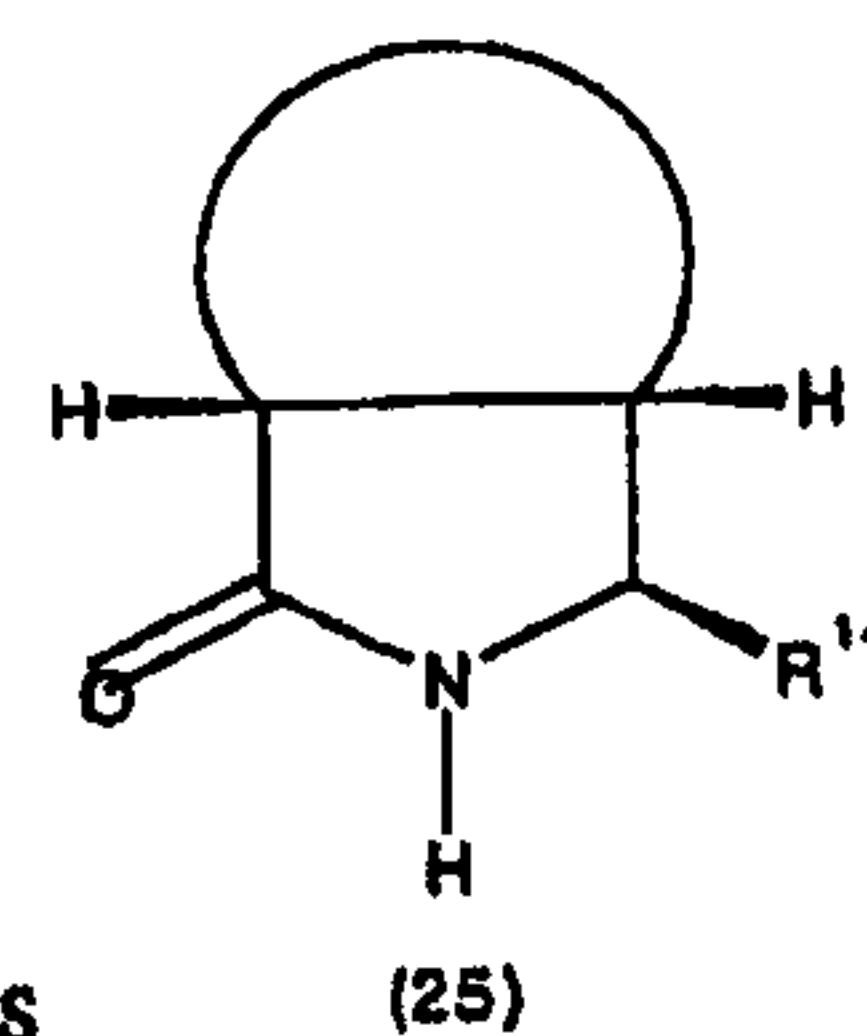
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A compound of formula 25, wherein the variables thereof are as described herein, may be prepared by imine cleavage and cyclizing of the compound of formula 24.

20



Cleavage and Cyclizing Conditions

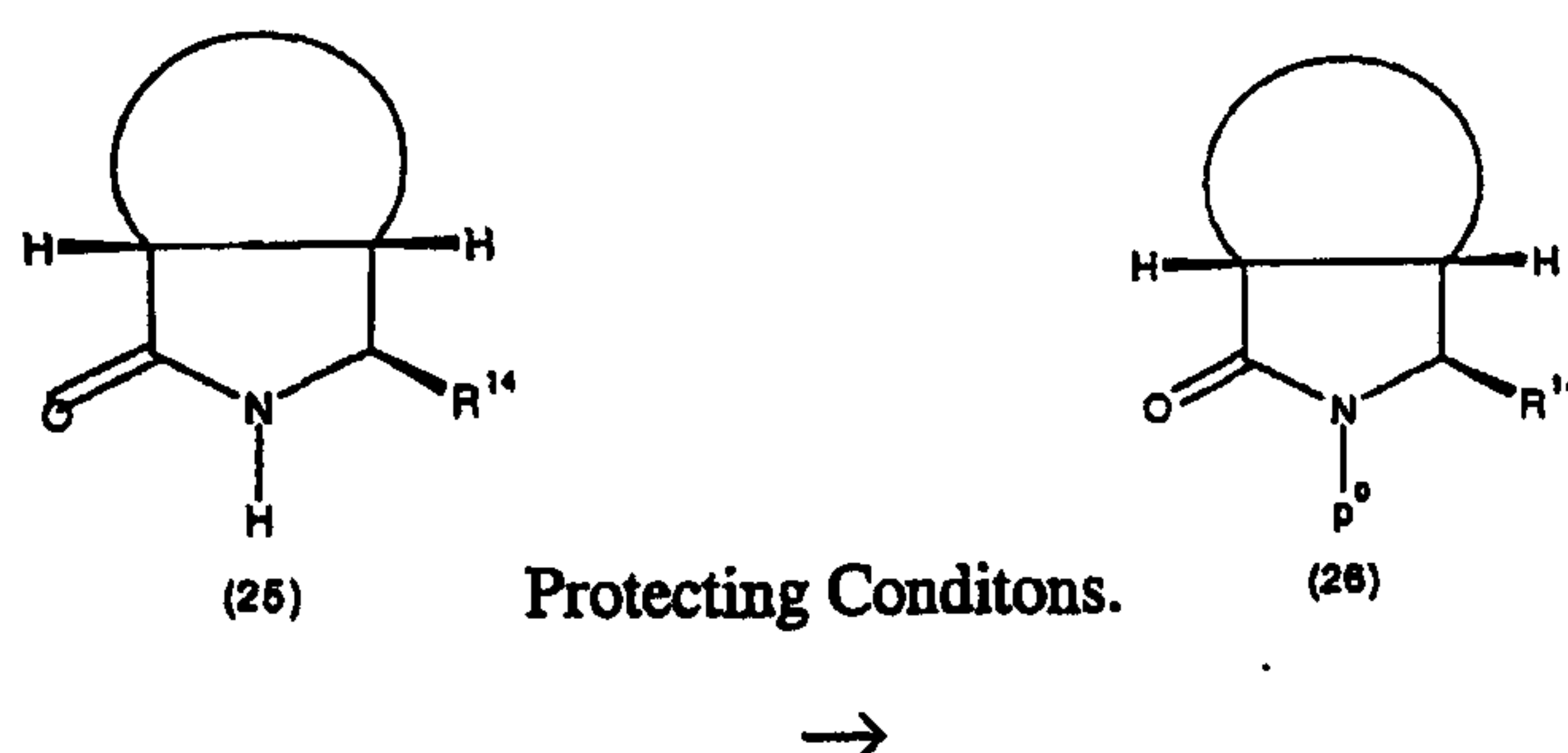


For cleavage and cyclization procedures, see Javidan, A.; Schfer, K.; Pyne, S. *Synlett* 1996, 100; Tatsukawa, A.; Dan, M.; Ohbatake, M.; Kawatake, K.; Fukata, T.; Wada, E.; Kanemase, S.; Kakei, S. *J. Org. Chem.* 1993, 58, 4221. Cleavage and cyclizing conditions include the use of polar solvents, acid reagents, and temperatures of about room temperature to about 150°C.

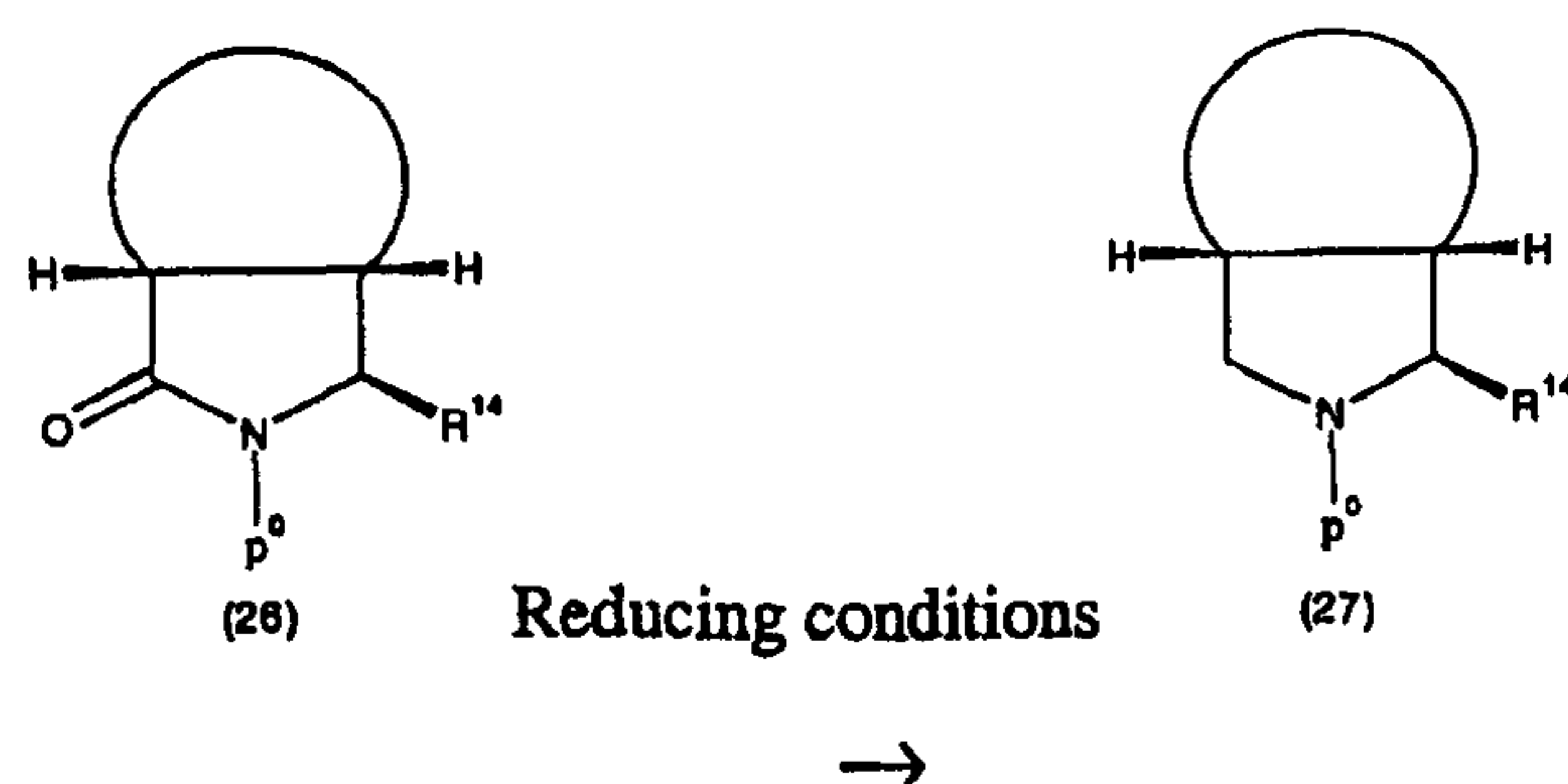
- 5 Preferred conditions include the use of EtOH, AcONa and $\text{NH}_2\text{OH}\cdot\text{HCl}$, and a temperature of about boiling point for the solvent used.

A compound of formula 26, wherein the variables thereof are as described herein, may be prepared by protecting the amide of the compound of formula 25, wherein the variables thereof are as described herein, with a suitable amide protecting group such as BOC. Other suitable
10 protecting groups include CBz, $-\text{CO}_2\text{alkyl}$. Also see, Greene, T.W.; P.G.M. in *Protective Groups in Organic Synthesis*, Wiley, New York, 1991 for other amine protecting groups. Protecting conditions include the use of aprotic polar solvents, organic bases as catalysts, and temperatures of about 0°C-100°C. Preferred conditions include the use of ACN, dimethyl amino pyridine, and a temperature of about room temperature.

15



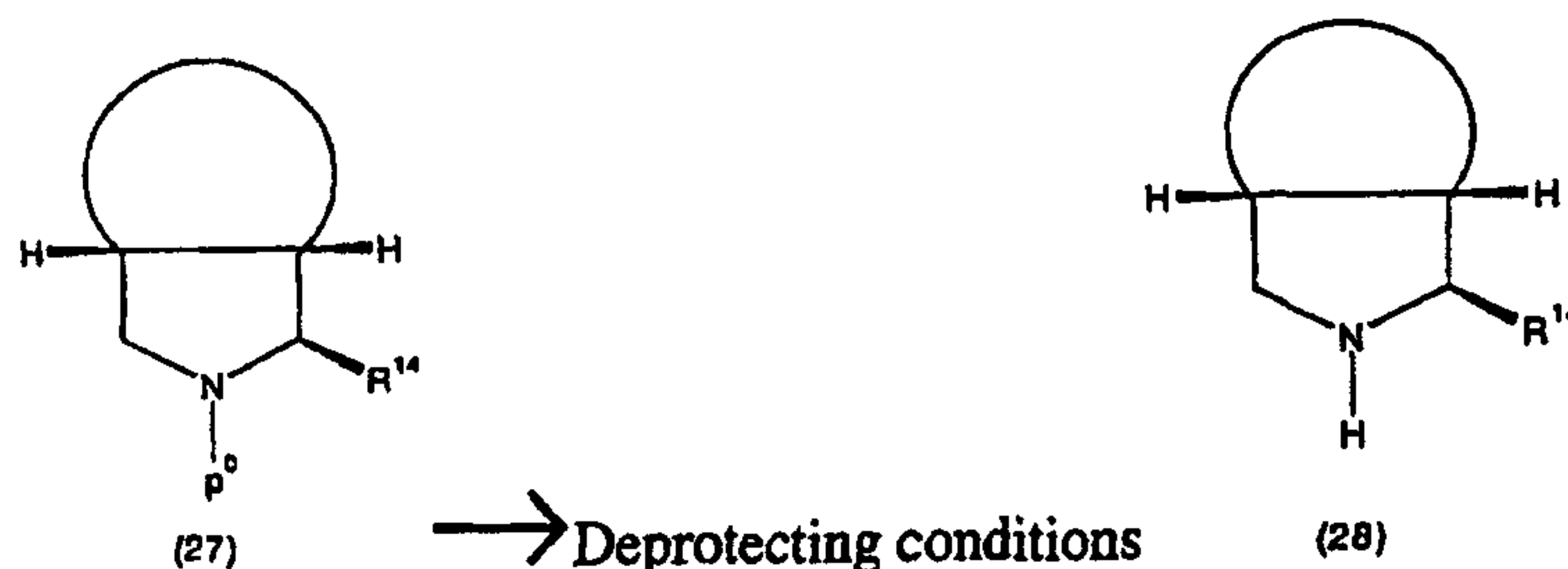
A compound of formula 27, wherein the variables thereof are as described herein, may be prepared by reducing the protected compound of formula 26, wherein the variables thereof are as
20 described herein.



Two reductions are, in fact, done. The first reduction is of the amide to a hemiaminal using DIBALH or superhydride $[\text{LiBEt}_3\text{H}]$. The second reduction is of the hemiaminal to the amine
25 using Et_3SiH and $\text{BF}_3\cdot\text{OEt}_2$. See Collado, I.; Ezquerra, J.; Mateo, A.I.; Rubio, A., *J. Org. Chem.*

1998, 63 1995-2001 and Ezqueera, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Carreno, M.C.;
Escribano, A.; Garcia Ruano, J.L. *J. Org. Chem.* 1995, 60,2925 for reducing conditions.. Other
usual conditions for converting pyroglutamates into pyrrolidines is the use of $\text{BH}_3 \cdot \text{SMe}_2$.

A compound of formula 28, wherein the variables thereof are as described herein, may be
5 prepared by deprotecting the compound of formula 27, wherein the variables thereof are as
described herein.



See Gibson, F.G.; Bermeier, S.C.; Rapoport, H., *J. Org Chem.* 1994, 59, 3216-3218 for the
conditions for selective removal of N-BOC protecting group in the presence of tert-butyl ester.
10 One skilled in the art would know that the deprotecting conditions will be dependent upon the
choice of the protecting group. For example, if CBz is used, hydrogenation or basic conditions
may be used. Preferably, if BOC is used, 1 N HCl in ethyl acetate may be used. See, Greene,
T.W.; P.G.M. in *Protective Groups in Organic Synthesis*, Wiley, New York, 1991.

The person of ordinary skill in the art will appreciate that a compound of formula 3 may
15 be prepared by coupling a compound of formula 5 with a compound of formula 28 under
conditions described above herein.

Methods for preparing R^3 , R^5 or R^7 as optionally substituted ethanediyl moieties include
those known to those skilled in the art, e.g., those methods described in "The organic Chemistry
of β -Lactams" edited by G. Georg, VCH Publishers, Inc. (1993), e.g., pages 240-241 and 303-
20 305.

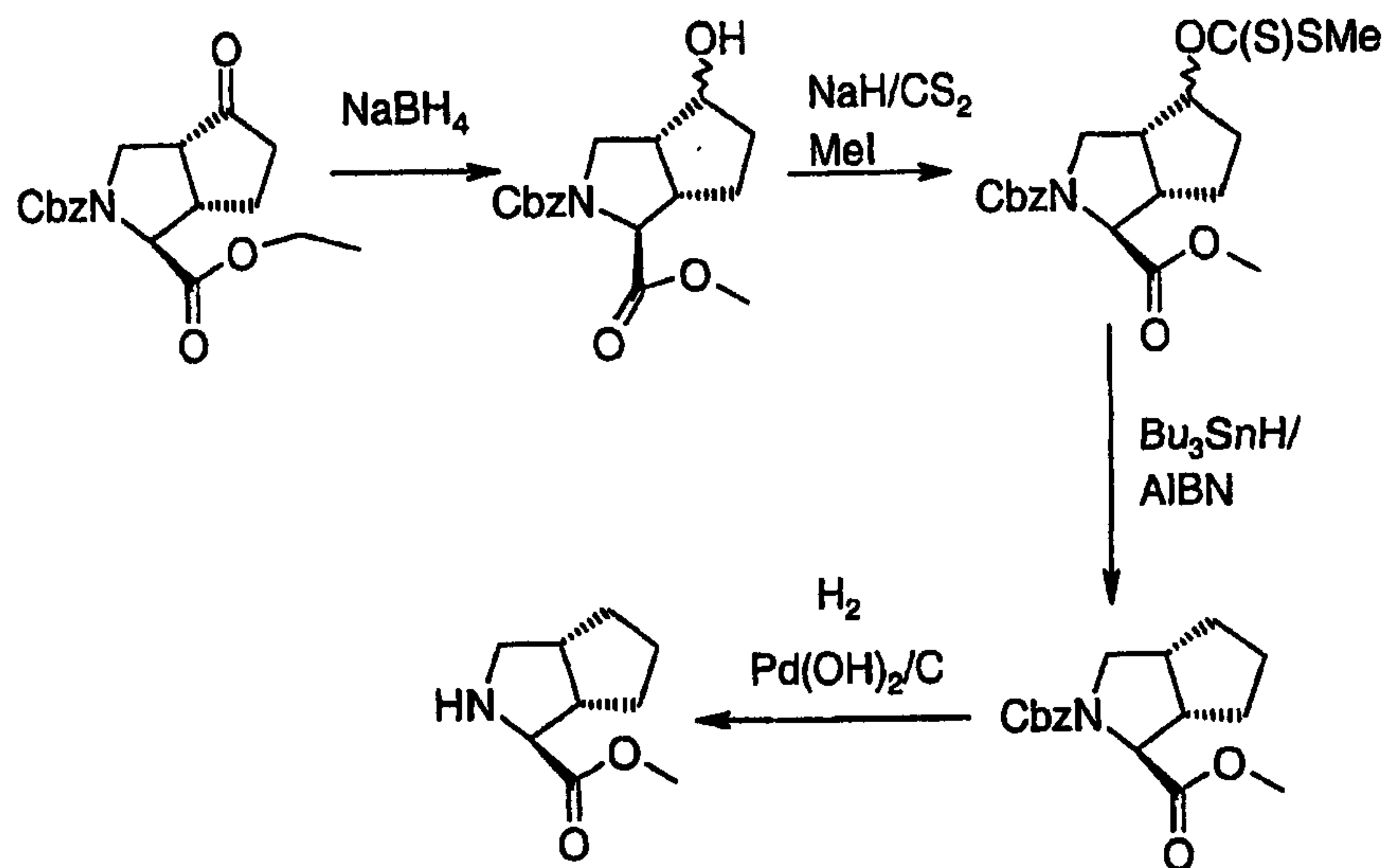
Schemes 1-11 that follow exemplify assorted methods for preparing an optionally
substituted multicyclic azaheterocyclyl. The methods in the schemes below are also applicable to
other optionally substituted multicyclic azaheterocyclyls comprising compatible like substituents.

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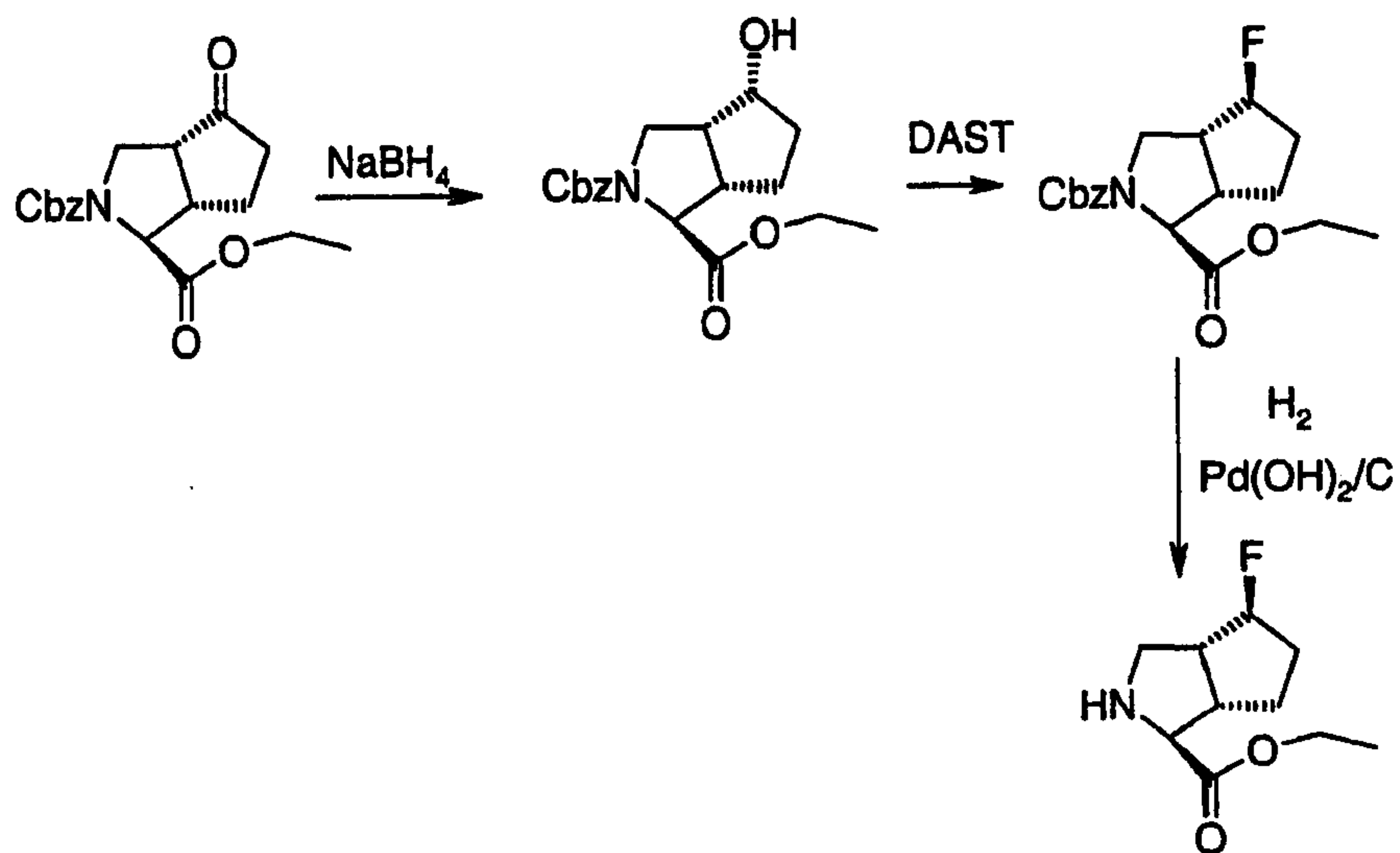
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SCHEME 1



SCHEME 2

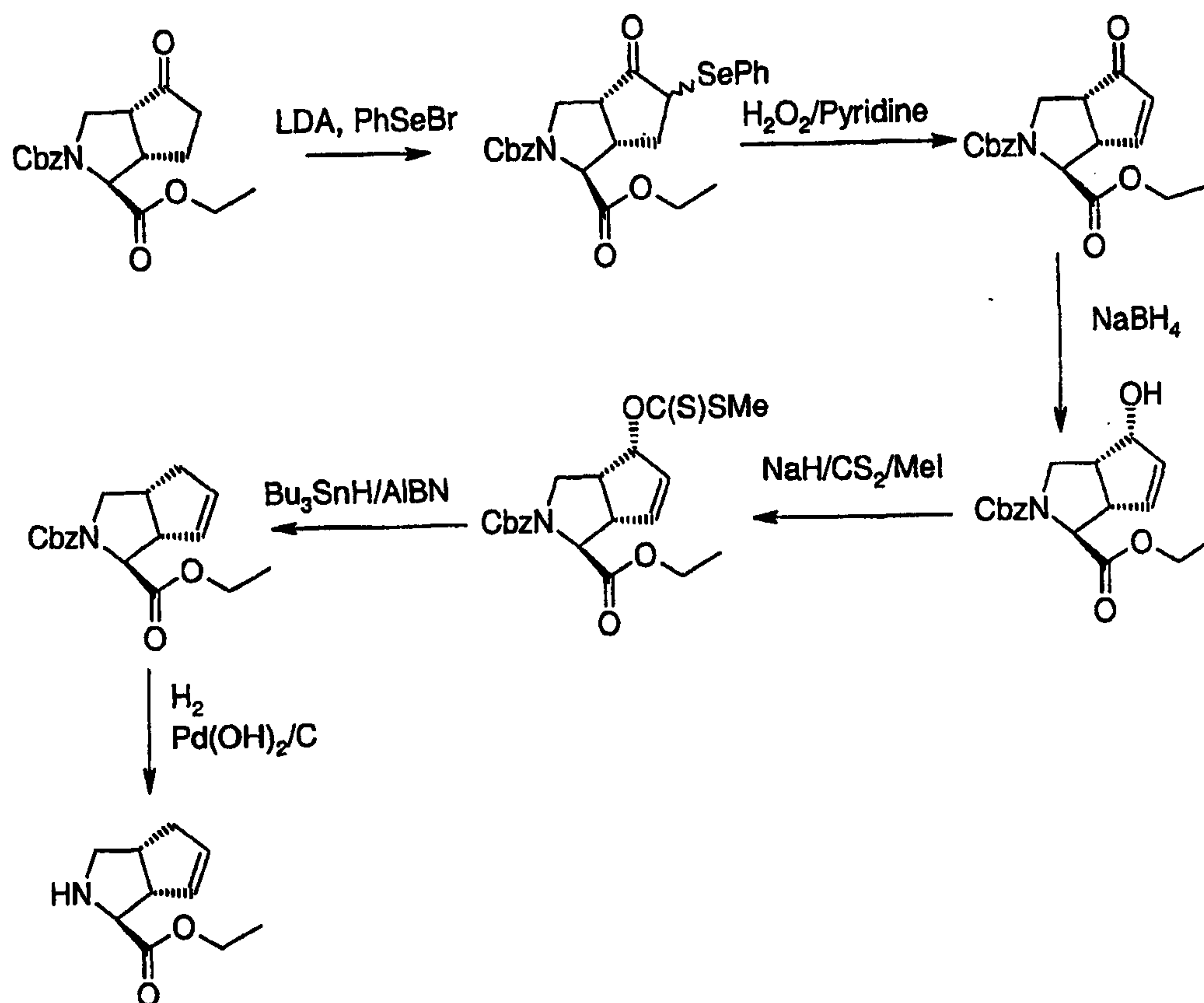


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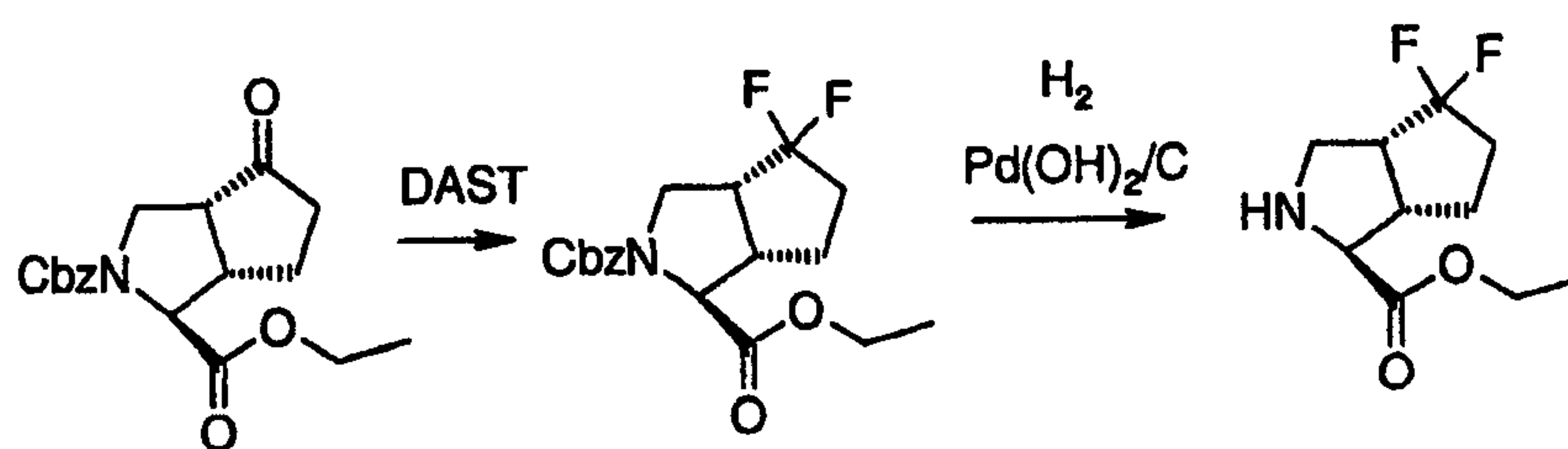
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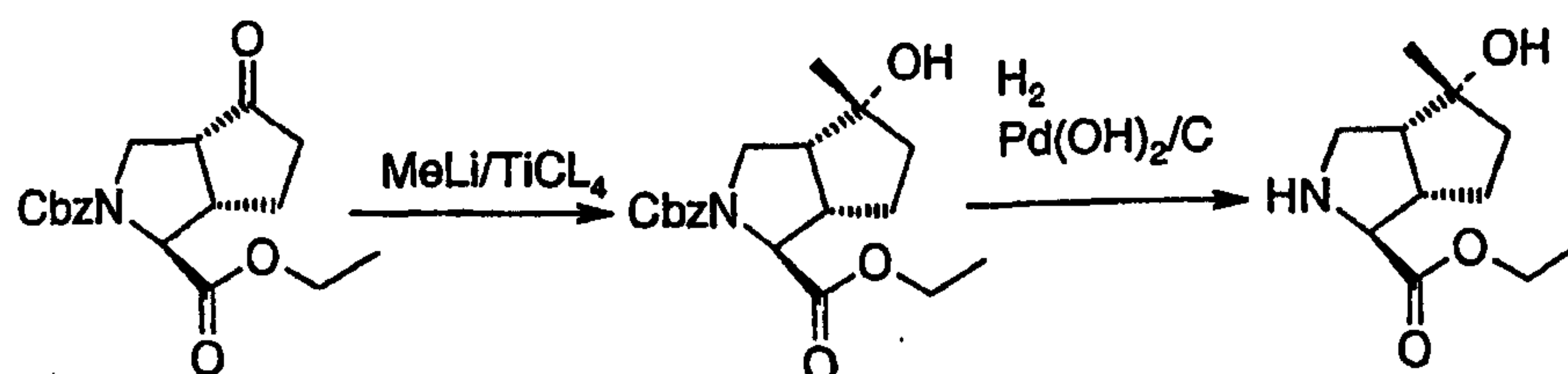
SCHEME 3



SCHEME 4



SCHEME 5

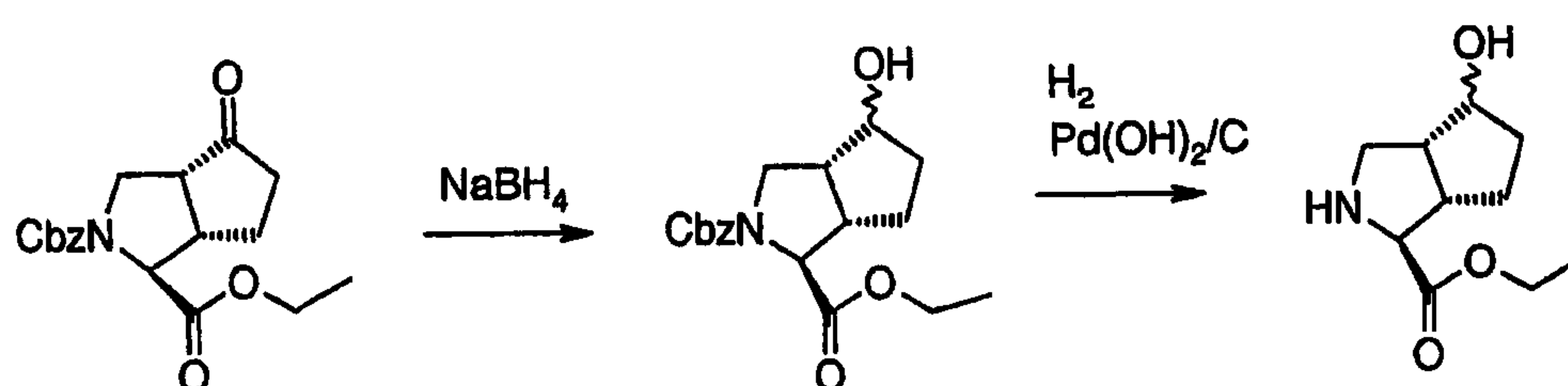


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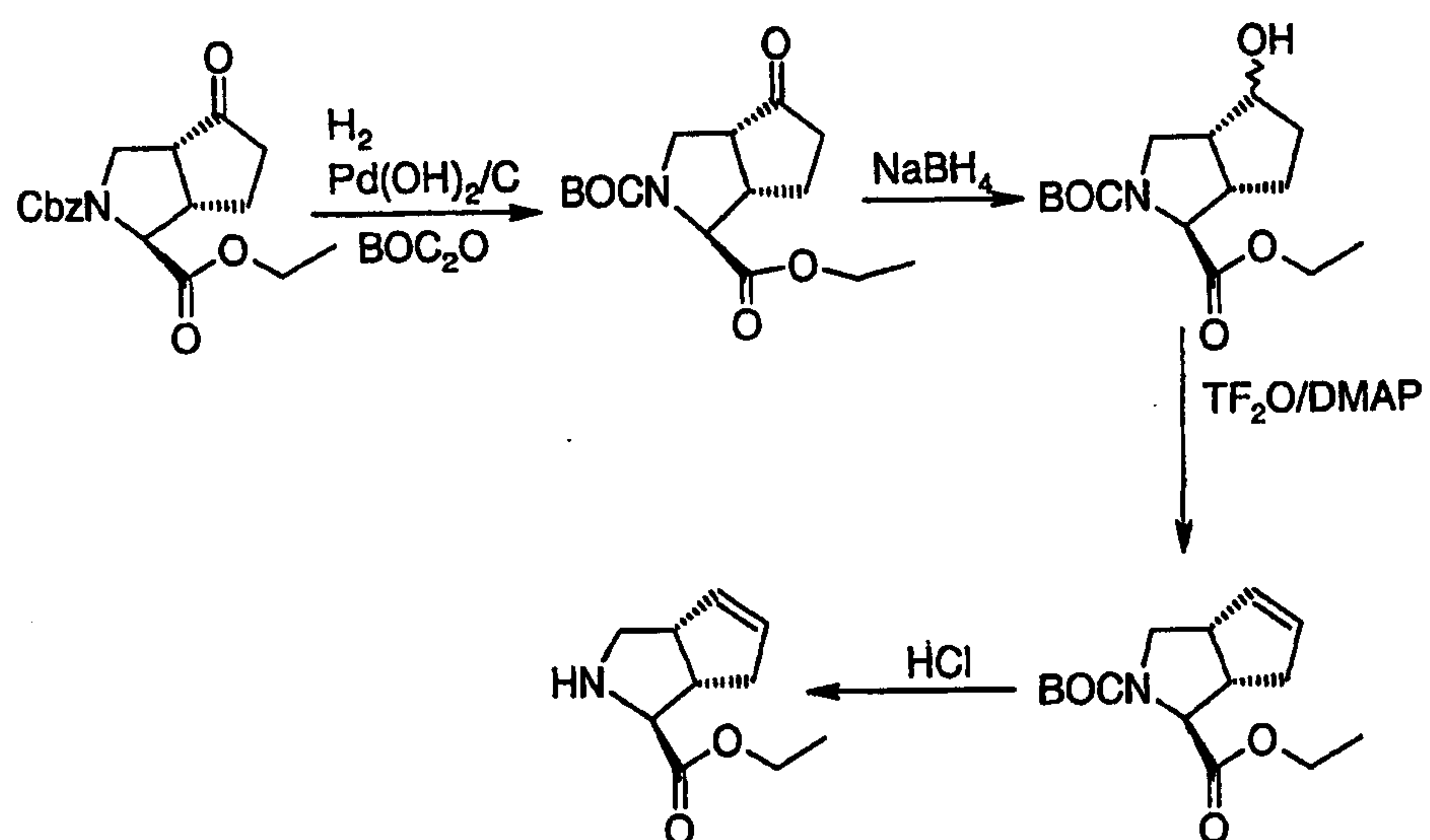
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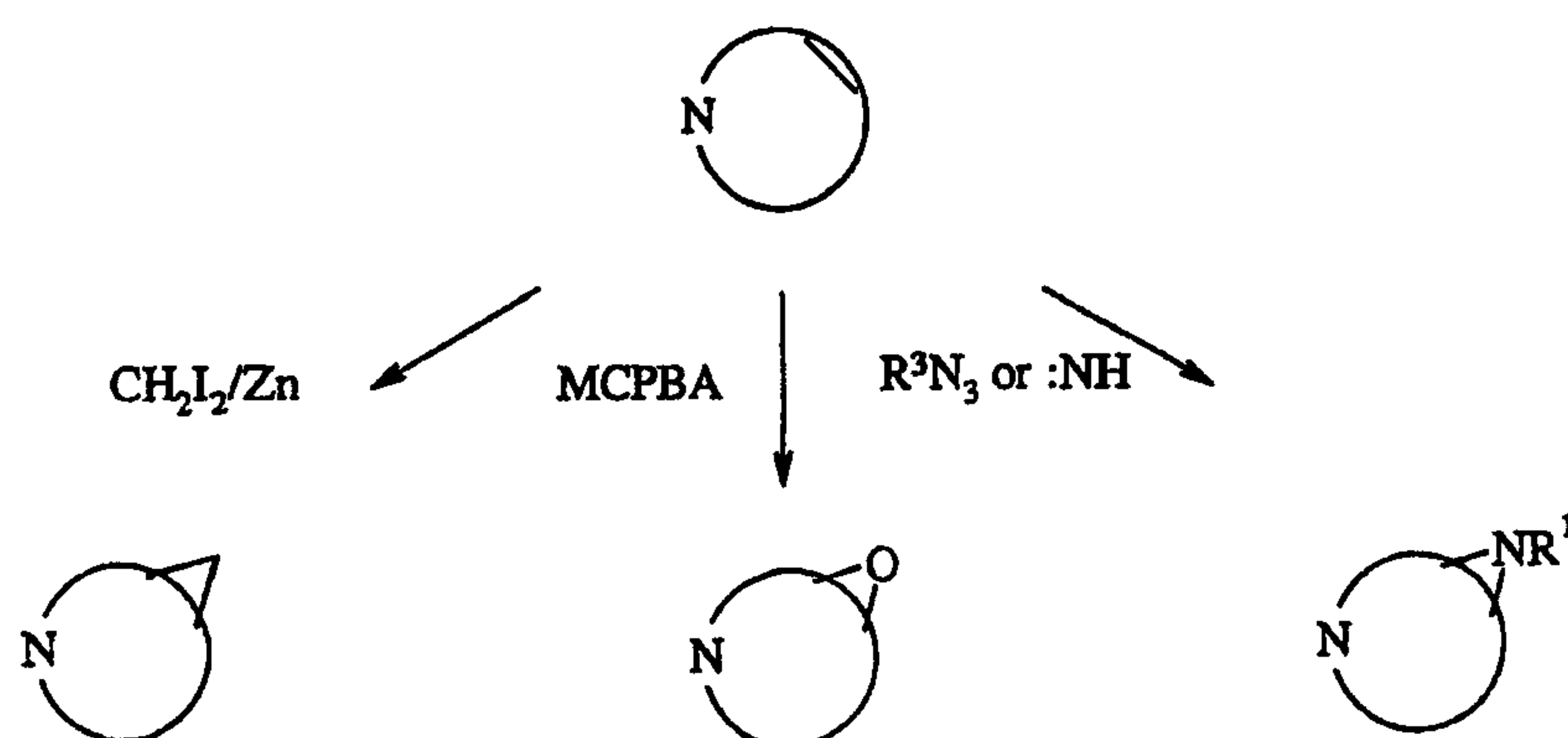
SCHEME 6



SCHEME 7



SCHEME 8

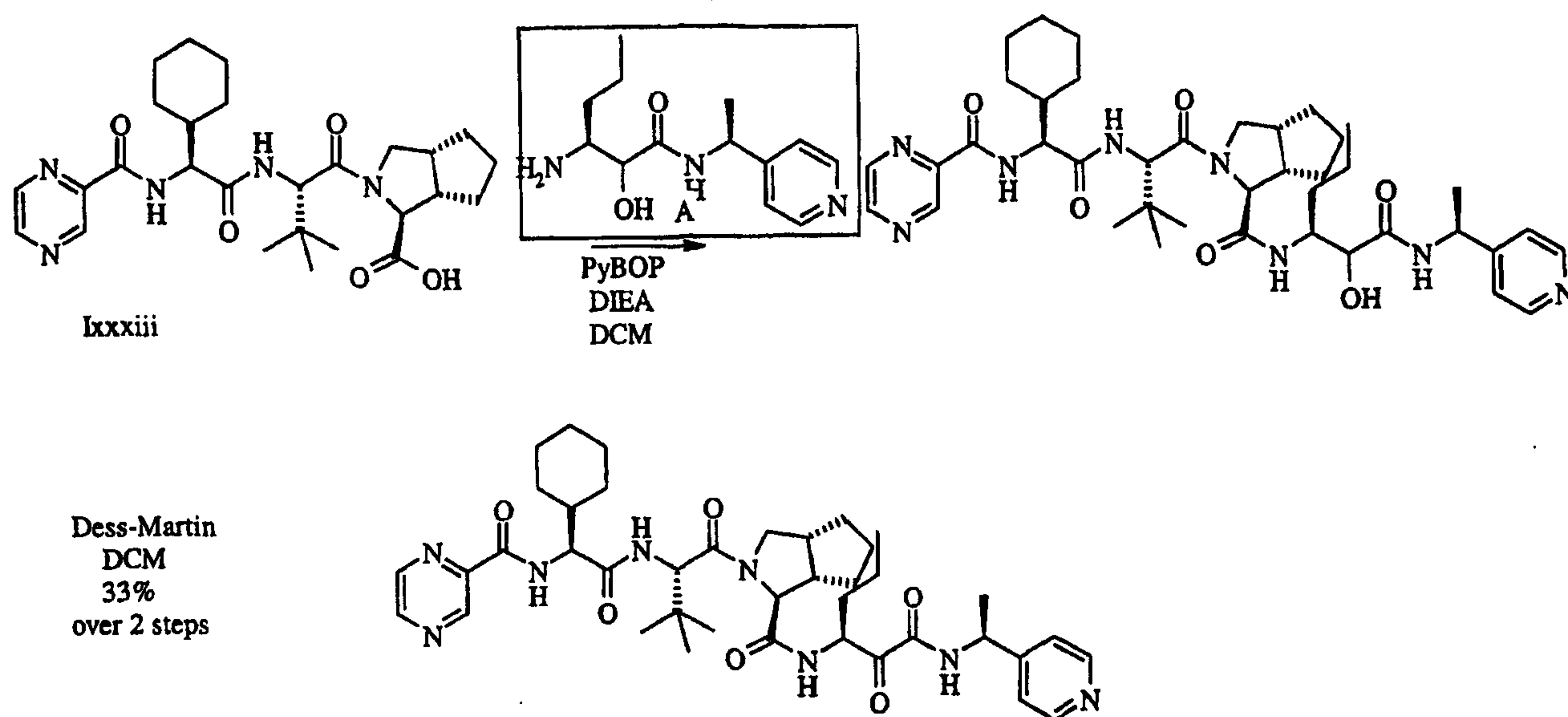


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Scheme 9

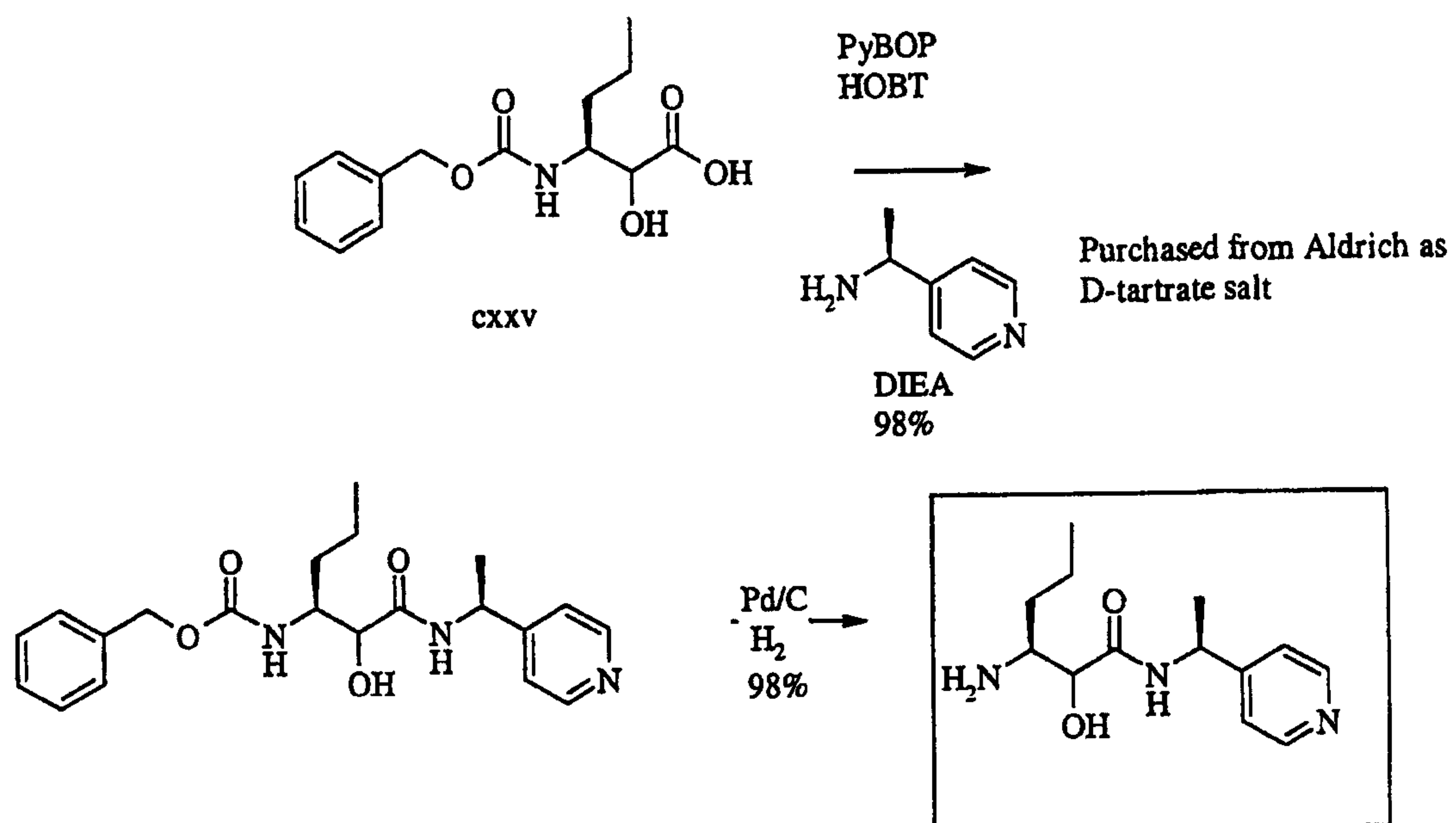


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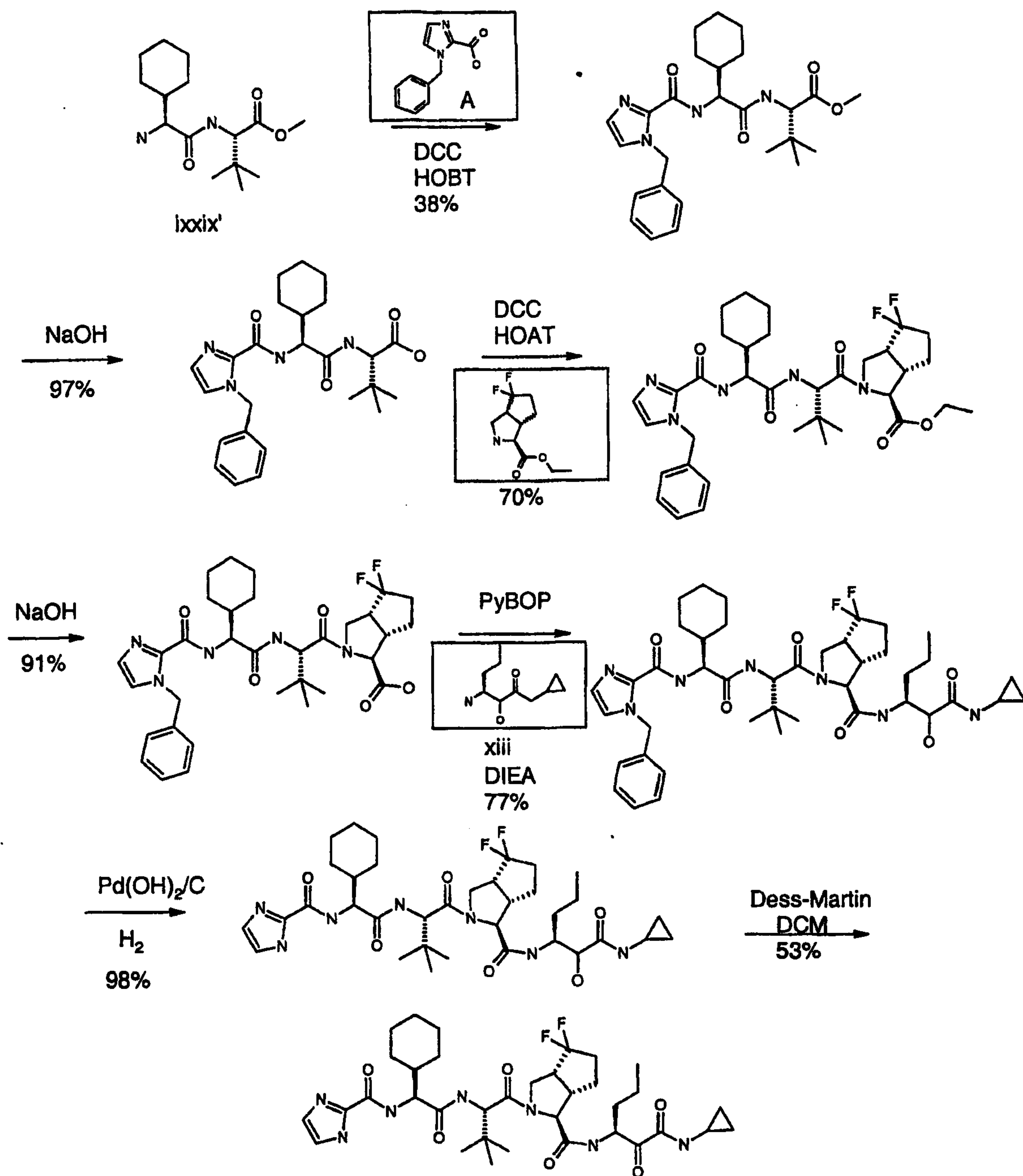
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SCHEME 10



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Scheme 11



A compound of formula 1 including a group containing one or more nitrogen ring atoms,
 5 preferably imine (=N-), may be converted to the corresponding compound wherein one or more
 nitrogen ring atoms of the group are oxidized to an N-oxide, preferably by reacting with a peracid,

for example peracetic acid in acetic acid or m-chloroperoxybenzoic acid in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons (1991); J.F.W. McOmie in "Protective Groups in Organic Chemistry" Plenum Press, 1973.

A compound that is prepared as described herein may be recovered from the reaction mixture by conventional means. For example, the compounds may be recovered by distilling off the solvent from the reaction mixture or, if necessary after distilling off the solvent from the reaction mixture, pouring the residue into water followed by extraction with a water-immiscible organic solvent and distilling off the solvent from the extract. Additionally, the product can, if desired, be further purified by various well techniques, such as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography or preparative thin layer chromatography.

According to a further feature of the present invention, compounds of the invention may be prepared by interconversion of other compounds of the invention.

As an example of the interconversion process, compounds of formula 1 containing sulphoxide linkages may be prepared by the oxidation of corresponding compounds containing -S- linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g., 3-chloroperbenzoic acid, preferably in an inert solvent, e.g., dichloromethane, preferably at or near room temperature, or alternatively by means of potassium hydrogen peroxomonosulphate in a medium such as aqueous methanol, buffered to about pH 5, at temperatures between about 0°C and room temperature. This latter method is preferred for compounds containing an acid-labile group.

As another example of the interconversion process, compounds of formula 1 containing sulphone linkages may be prepared by the oxidation of corresponding compounds containing -S- or sulphoxide linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g., 3-chloroperbenzoic acid, preferably in an inert solvent, e.g., dichloromethane, preferably at or near room temperature.

It will be understood that designation of aromaticity with respect to aryls and heteroaryls herein includes any highly resonant unsaturated ring structure. Alternatively, placement of double bonds, where indicated, represents one potential structure for the depicted compound but will be

understood to include other resonant states of the compound as well as protonated and charged species, only one of which may be shown.

It will be appreciated that compounds of the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds according to the invention. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates.

For the purpose herein it is understood that tautomeric forms are included in the recitation of a given group, e.g., thioxo/mercapto or oxo/hydroxyl.

Acid additional salts are formed with the compounds of the invention in which a basic function such as an amino, alkylamino, or dialkylamino group is present. The pharmaceutically acceptable, i.e., nontoxic, acid addition salts are preferred. The salts chosen are chosen optimally to be compatible with the customary pharmaceutical vehicles and adapted for oral or parenteral administration. Acid addition salts of the compounds of this invention may be prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention may be prepared either by dissolving the free base in water or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution. Some suitable acids for use in the preparation of such salts are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, various organic carboxylic and sulfonic acids, such as acetic acid, citric acid, propionic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid, malic acid, methanesulfonic acid, toluenesulfonic acid, fatty acids, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, cyclopentanepropionate, digluconate, dodecylsulfate, bisulfate, butyrate, lactate, laurate, lauryl sulfate, malate, hydroiodide, 2-hydroxy-ethanesulfonate, glycerophosphate, picrate, pivalate, pamoate, pectinate, persulfate, 3-phenylpropionate, thiocyanate, 2-naphthalenesulfonate, undecanoate, nicotinate, hemisulfate, heptonate, hexanoate, camphorate, camphersulfonate, and others.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the

invention can be regenerated from their acid addition salts by treatment with an alkali, e.g., aqueous sodium bicarbonate solution or aqueous ammonia solution.

Compounds of this invention can be regenerated from their base addition salts by the application or adaptation of known methods. For example, parent compounds of the invention
5 can be regenerated from their base addition salts by treatment with an acid, e.g., hydrochloric acid.

Base addition salts may be formed where the compound of the invention contains a carboxy group, or a sufficiently acidic bioisostere. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid,
10 pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including those derived from alkali and alkaline earth metal salts, within the scope of the invention include those derived from the following bases: sodium hydride, sodium hydroxide,
15 potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

20 Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxan, tetrahydrofuran or methanol.

The starting materials and intermediates may be prepared by the application or adaptation
25 of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

The compounds of the invention, their methods or preparation and their biological activity will appear more clearly from the examination of the following examples which are presented as an illustration only and are not to be considered as limiting the invention in its scope.

30 Samples were analyzed by TLC, NMR, RP-HPLC or EA.

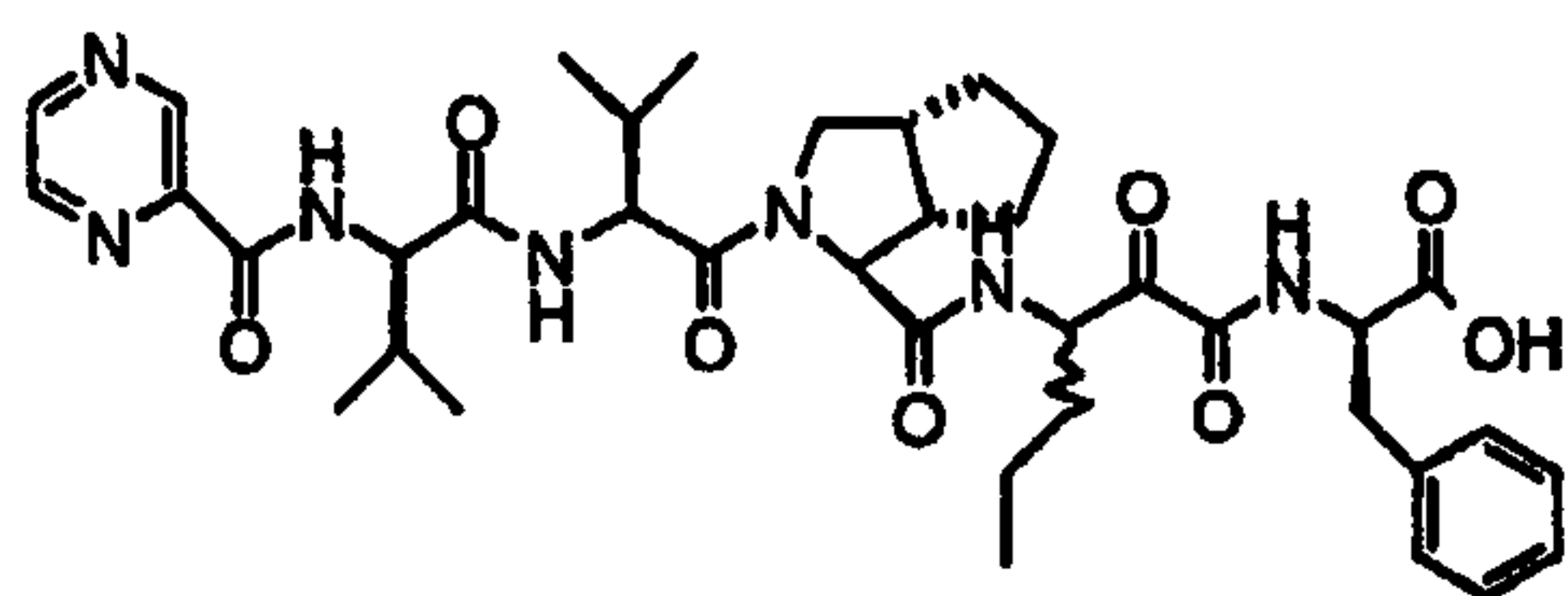
The compounds of the invention, their methods or preparation and their biological activity will appear more clearly from the examination of the following examples which are presented as an illustration only and are not to be considered as limiting the invention in its scope.

Samples were analyzed by TLC, NMR, RP-HPLC or EA.

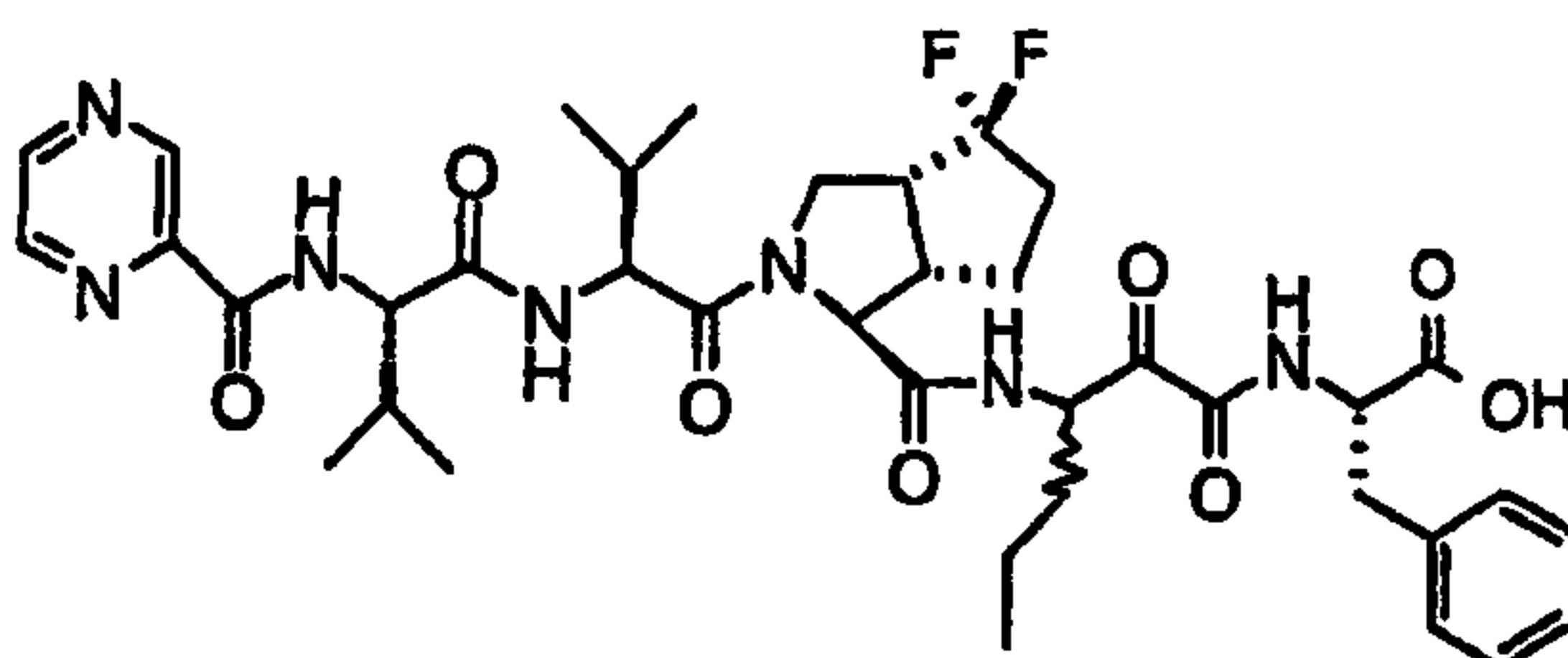
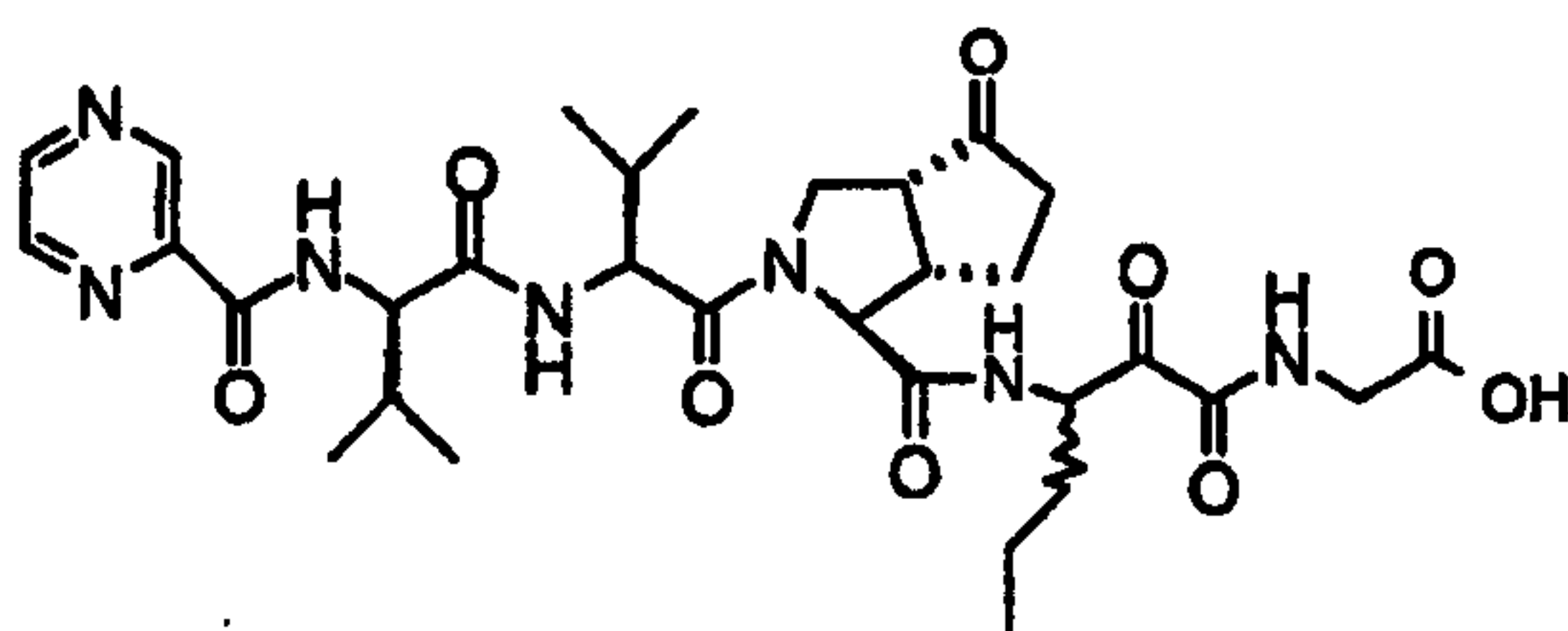
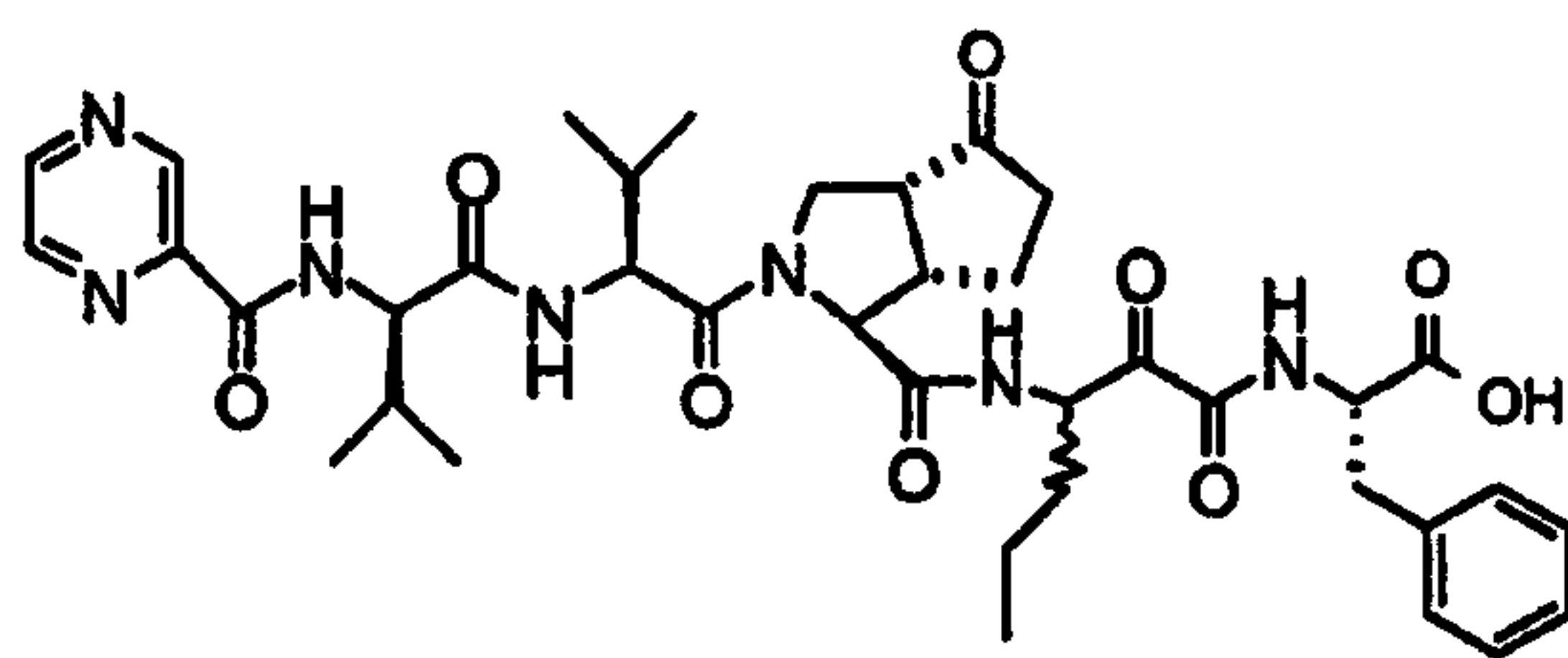
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Example 1 – Compounds A-E:

To a DCM solution (10 mL) of compound xi (310 mg, 0.39 mmol) is added TFA (4 mL). The reaction is stirred at about room temperature for 5 hours. At this point, the solvent is removed *in vacuo*. The resulting residue is purified by reverse phase HPLC to give 195 mg
10 (68%) of compound A,



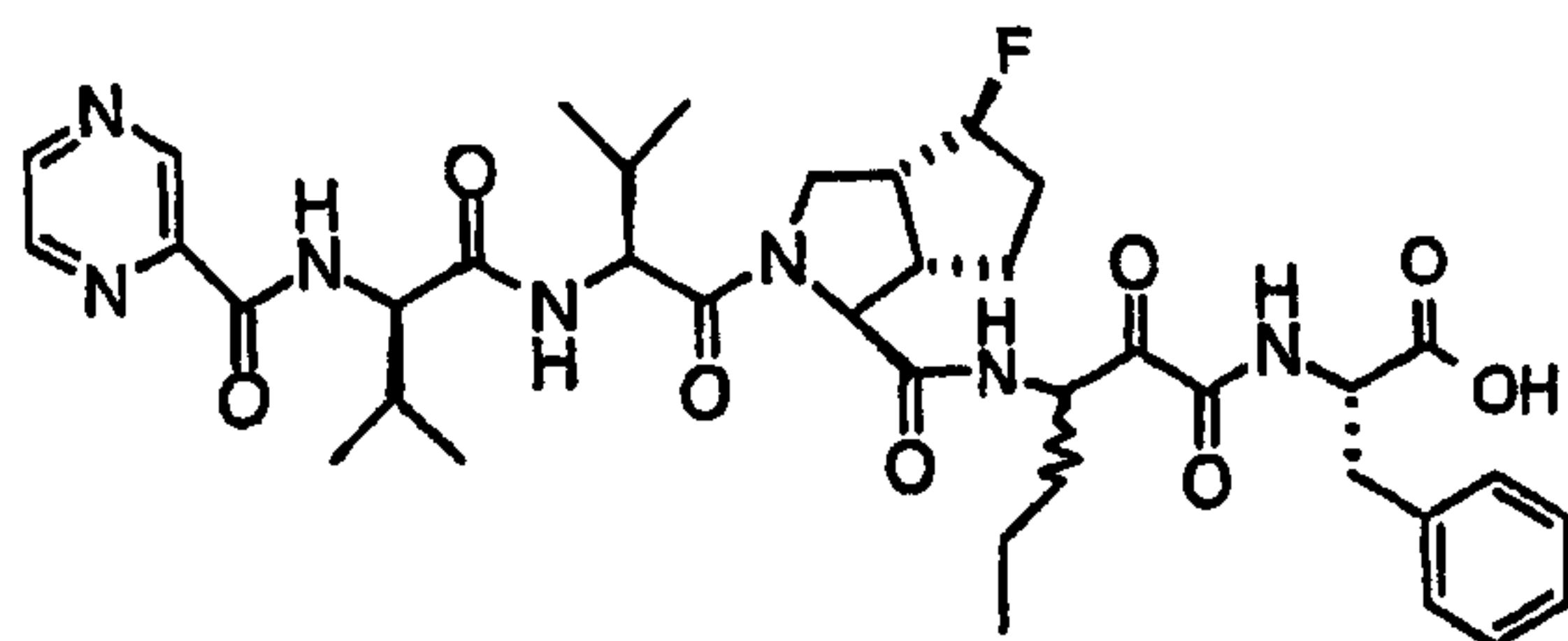
Following the above method and using the appropriate starting materials, the following
15 consecutive compounds B-E are prepared:



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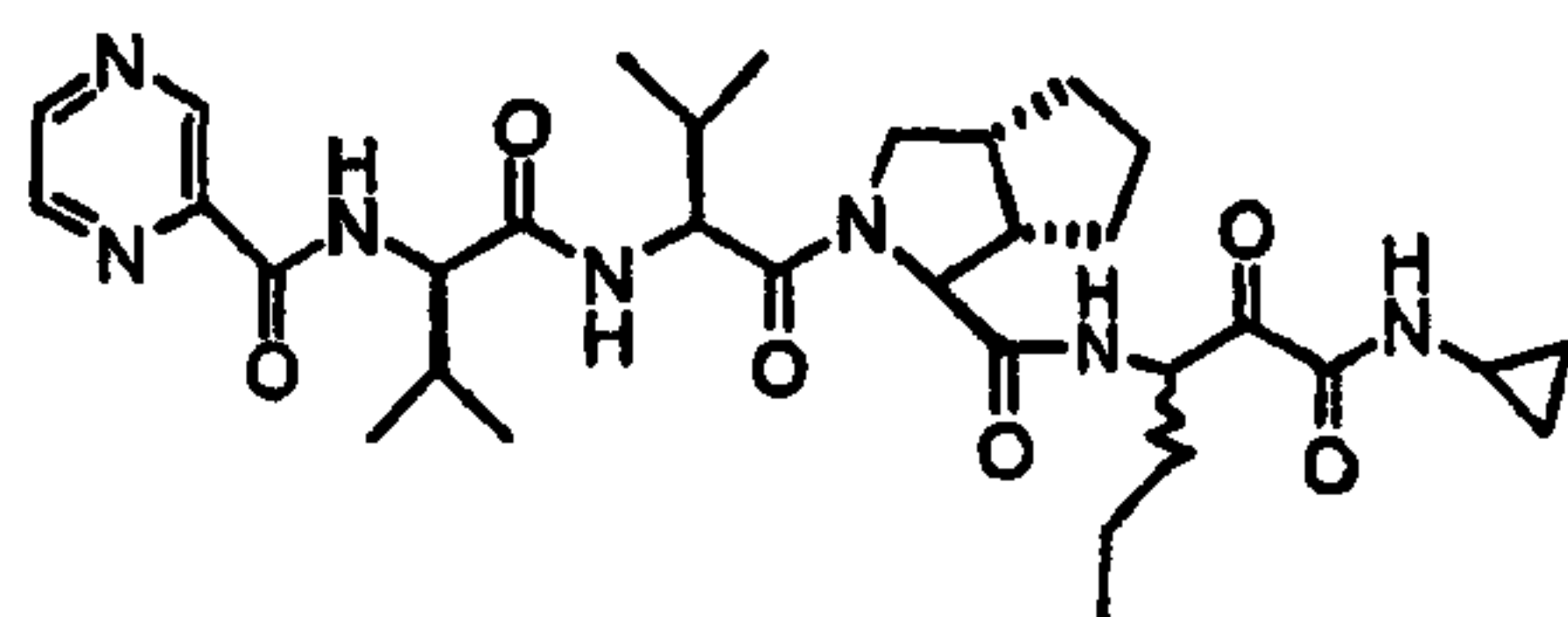
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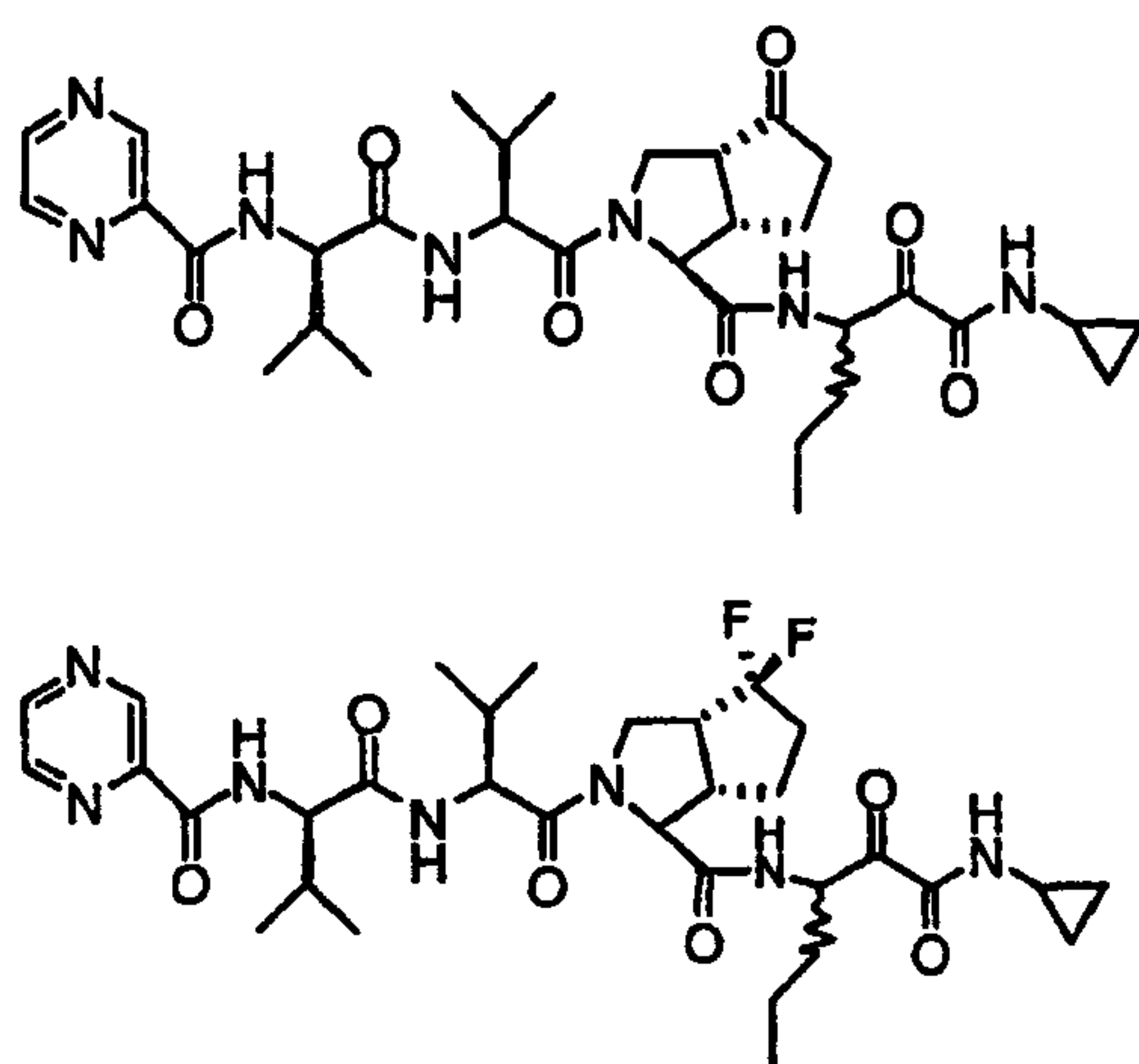
Example 2 – Compounds F-M:

To a DCM solution (10 mL) of compound xii (350 mg, 0.56 mmol) is added DMP reagent reagent (307 mg, 0.73 mmol). The reaction is stirred at about room temperature for 2
 5 hours and then quenched with 10% Na₂SO₃ for 30 minutes. The reaction mixture is then extracted with EtOAc (75 mL) and washed with brine. The organic layer is dried and concentrated *in vacuo*. The resulting residue is purified with silica gel chromatography (80-90% EtOAc/Hexanes) to give 248 mg (71%) of compound F



10

Following the above method and using the appropriate starting materials, the following consecutive compounds G-M are prepared:

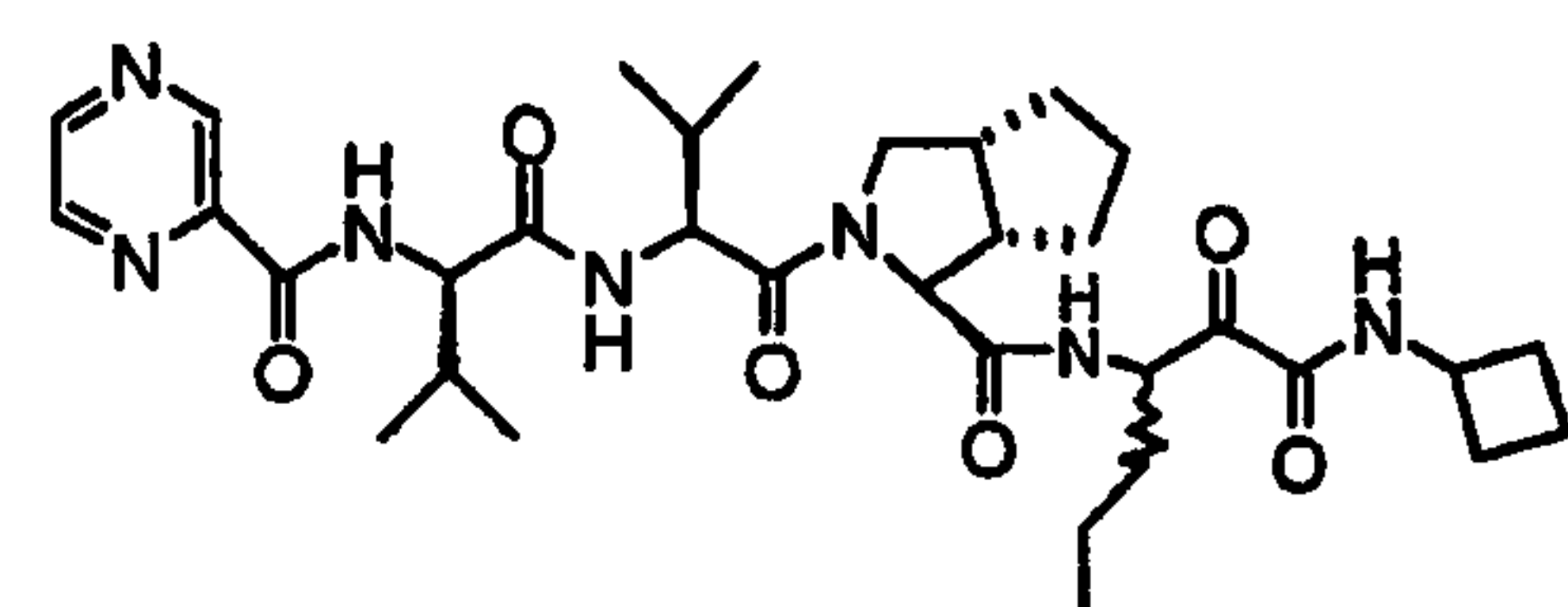
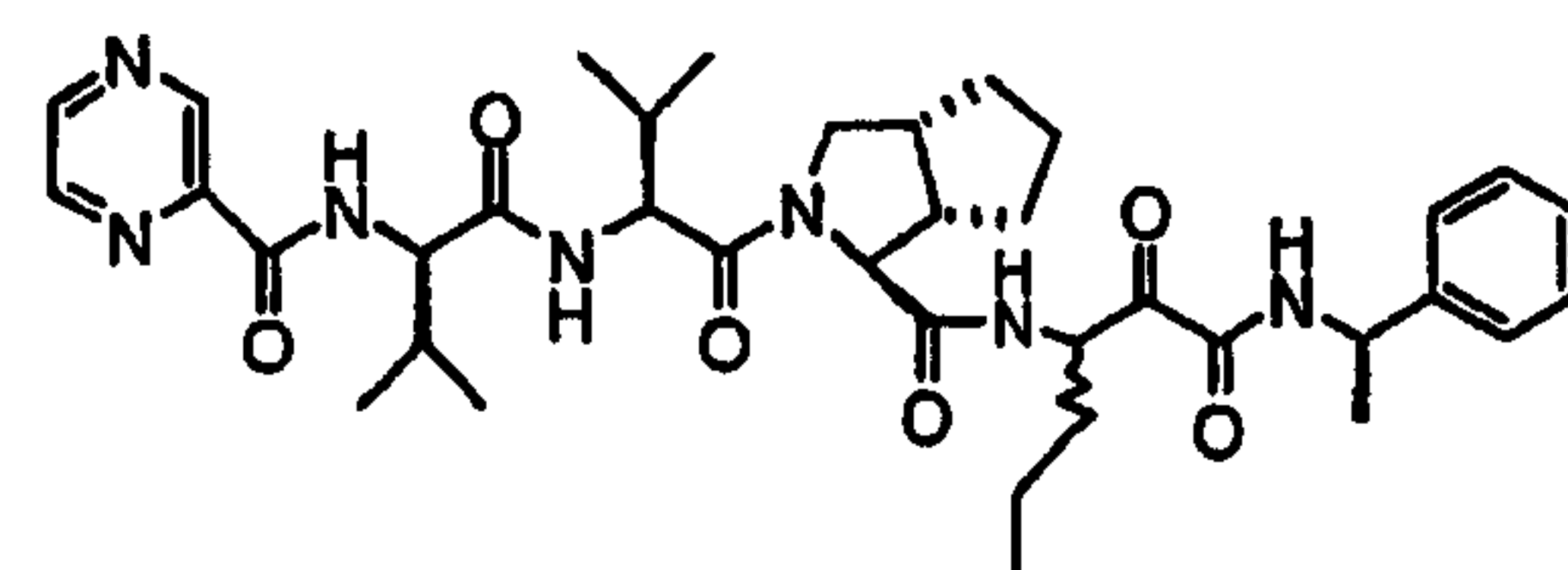
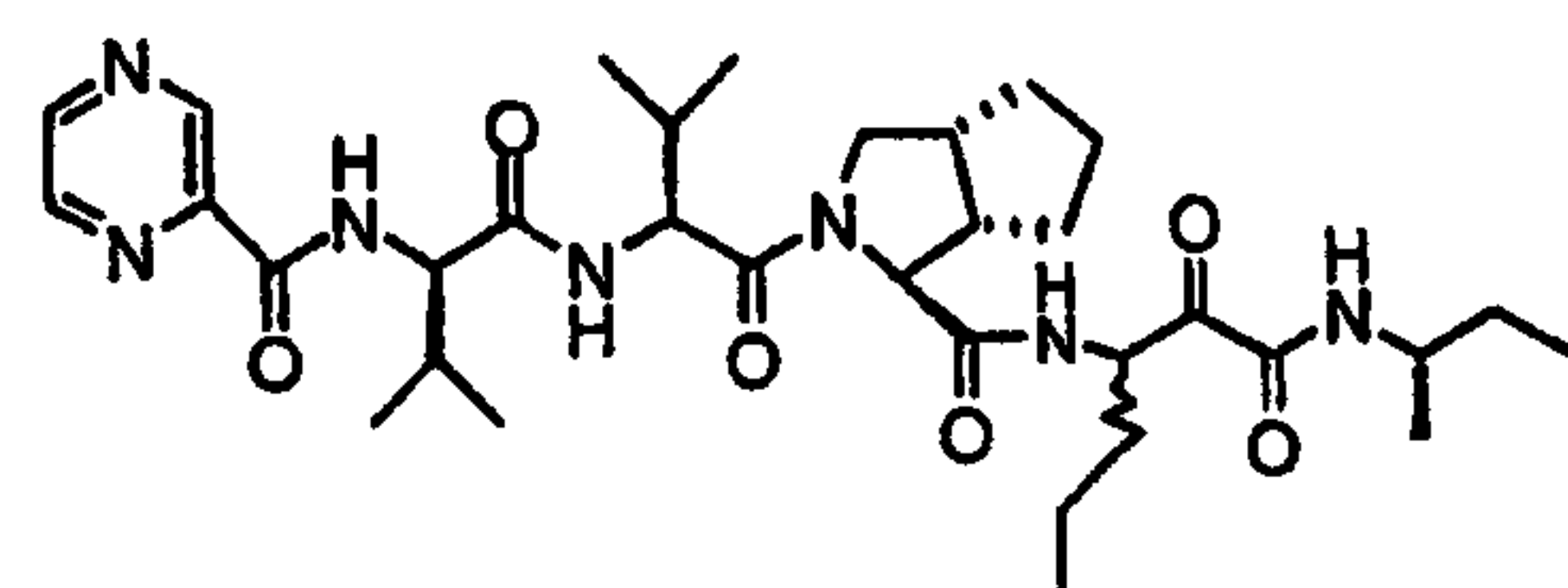
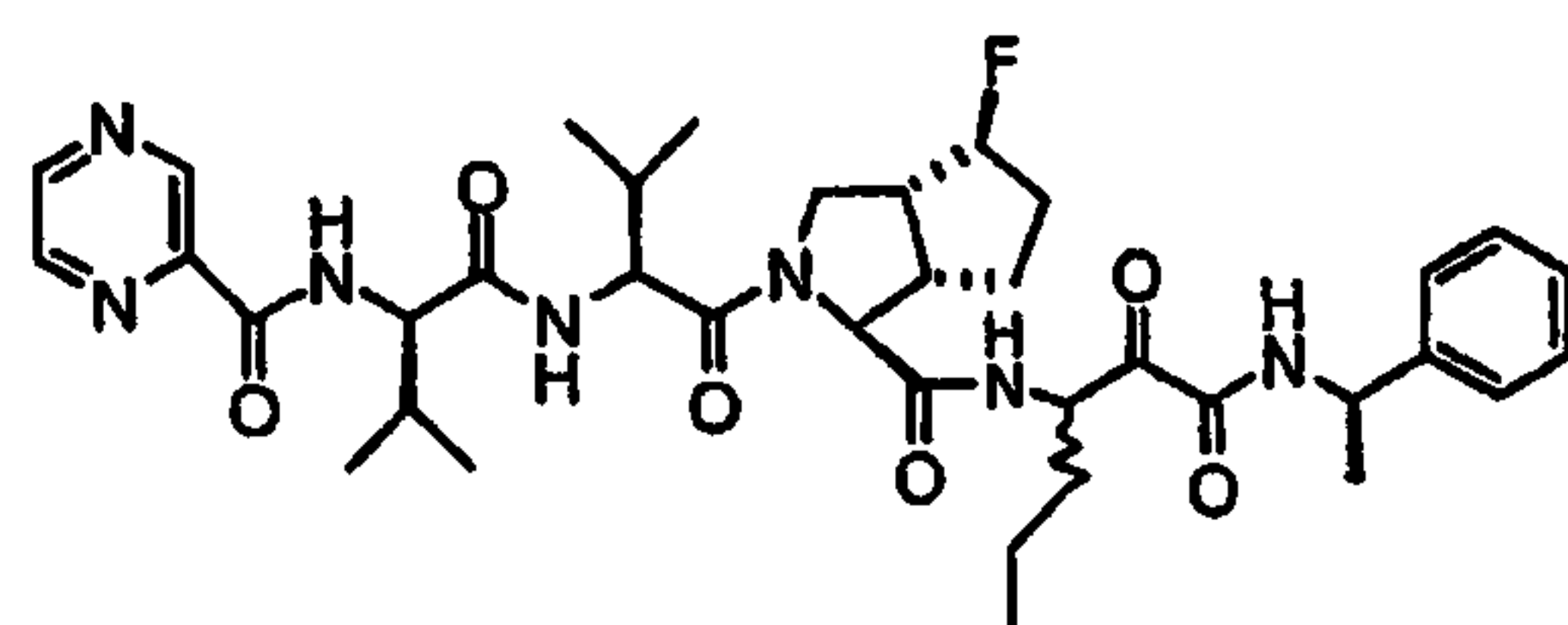
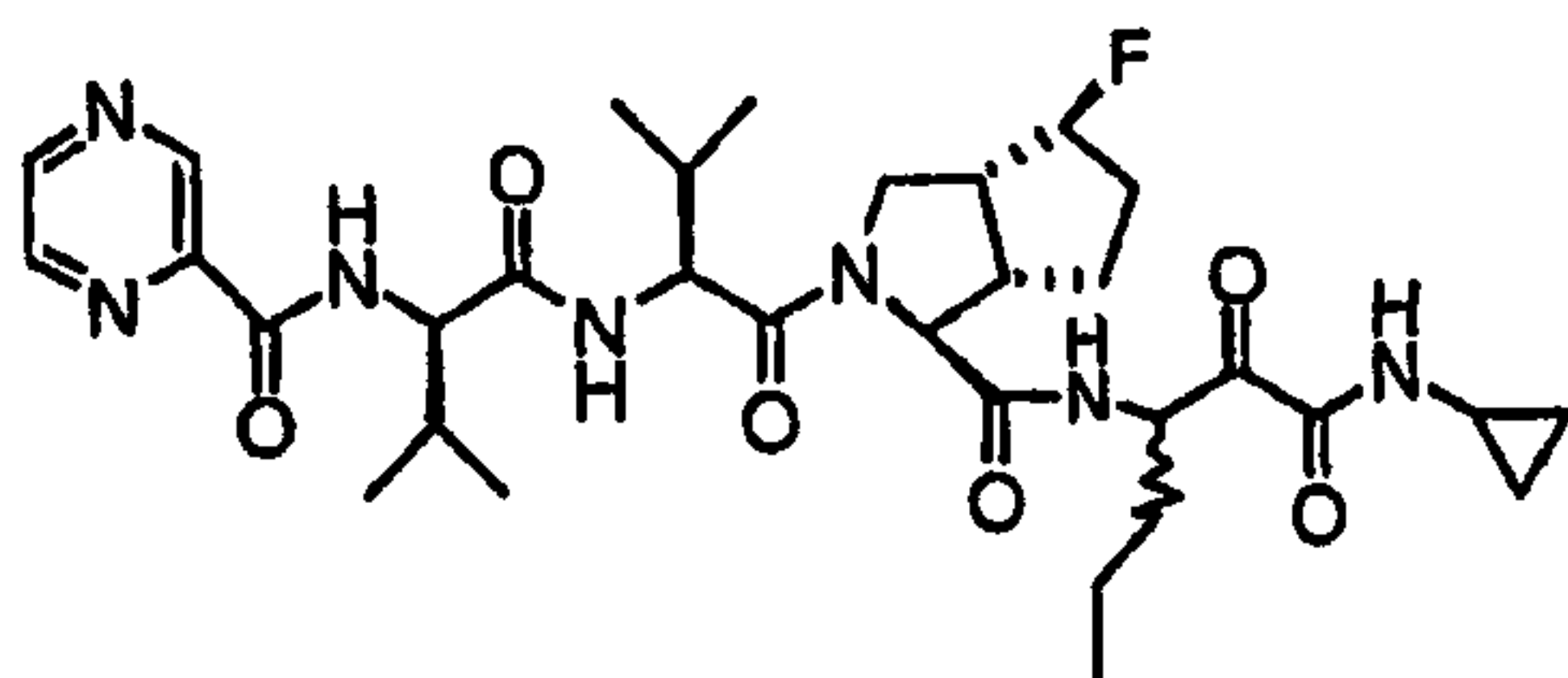


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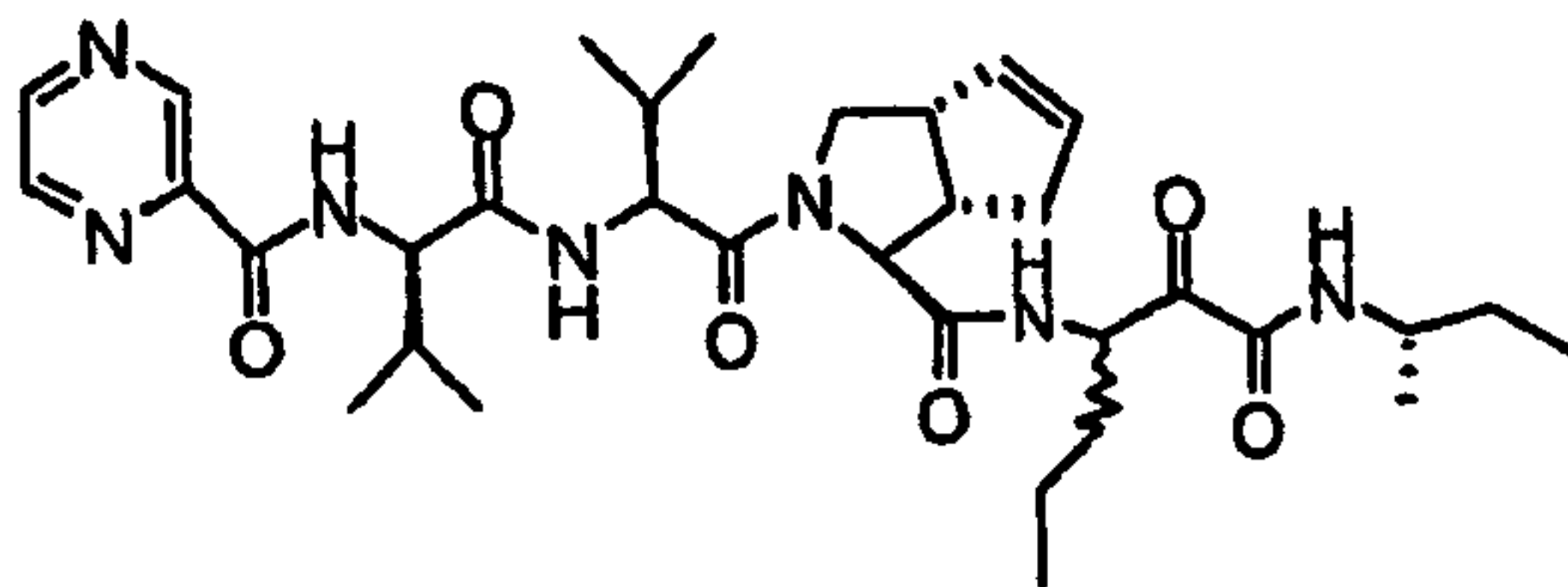
Example 3 – Compounds N-R:

To a DCM solution (4 mL) of compound xix (~0.22 mmol) is added DMP reagent reagent (146 mg, 0.34 mmol). After stirring at about room temperature for 2 hours, the reaction is
 10 quenched with 10% Na₂SO₃. The reaction mixture is then diluted with DCM. The organic layer is separated and washed with 10% Na₂SO₃ twice and brine. The resulting organic layer is dried and concentrated *in vacuo* to give a residue, which is purified by silica gel chromatography (5% EtOH/EtOAc) to provide 78 mg (56%) of the desired compound N

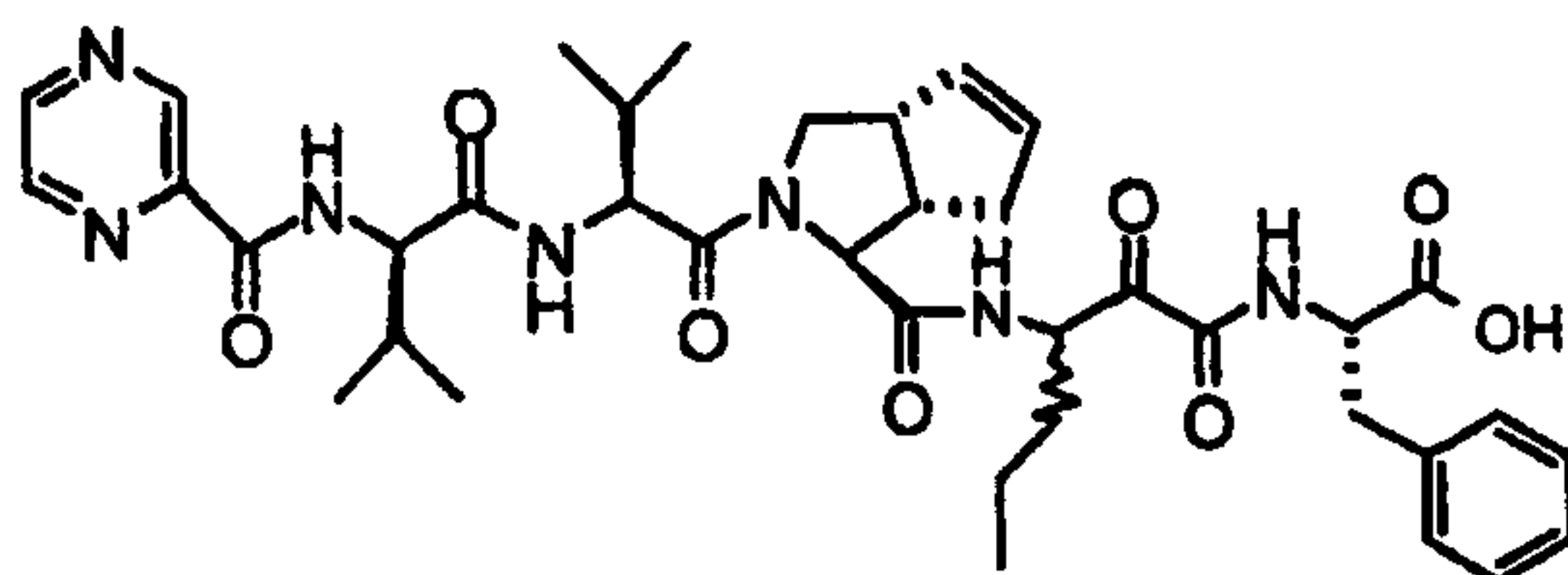
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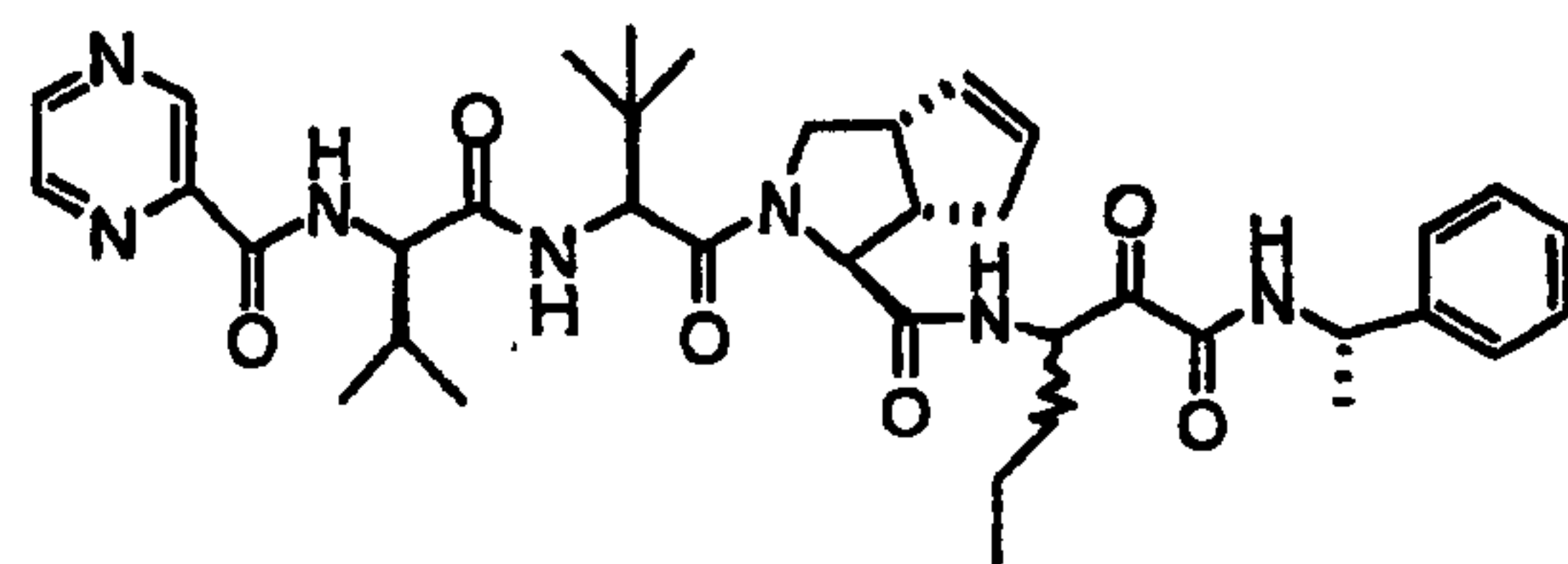
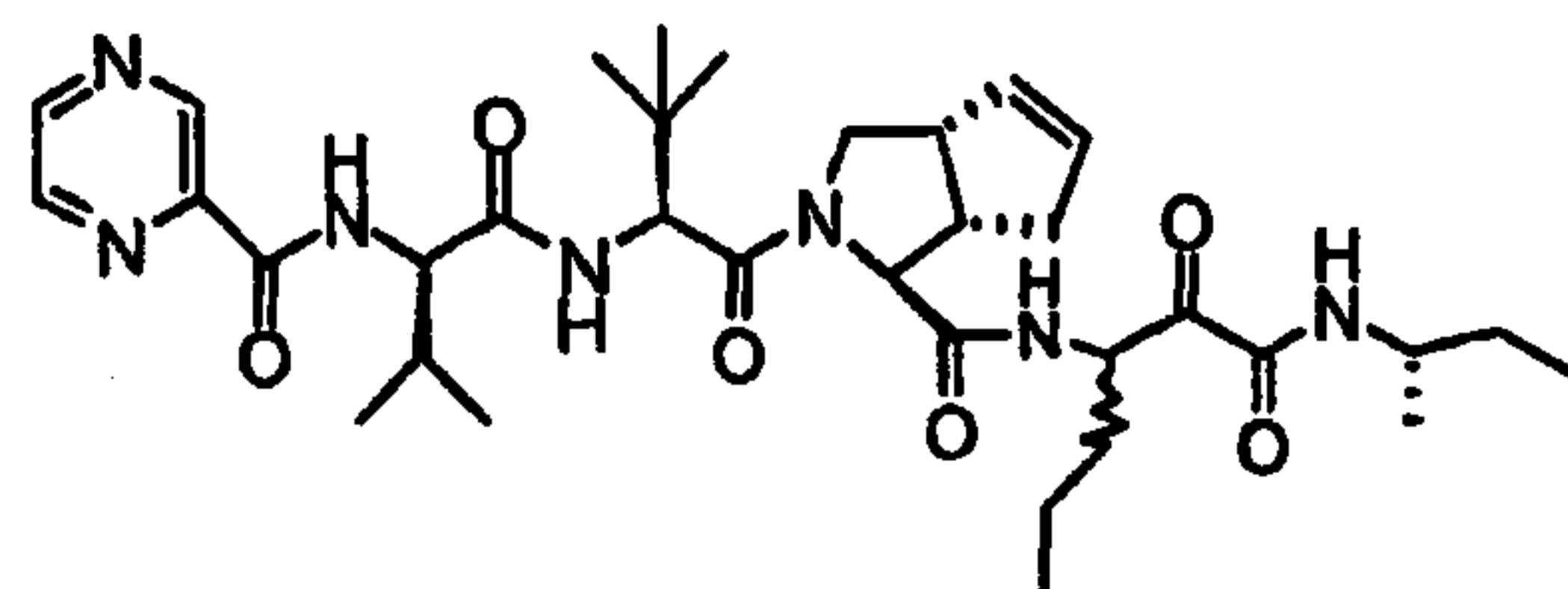
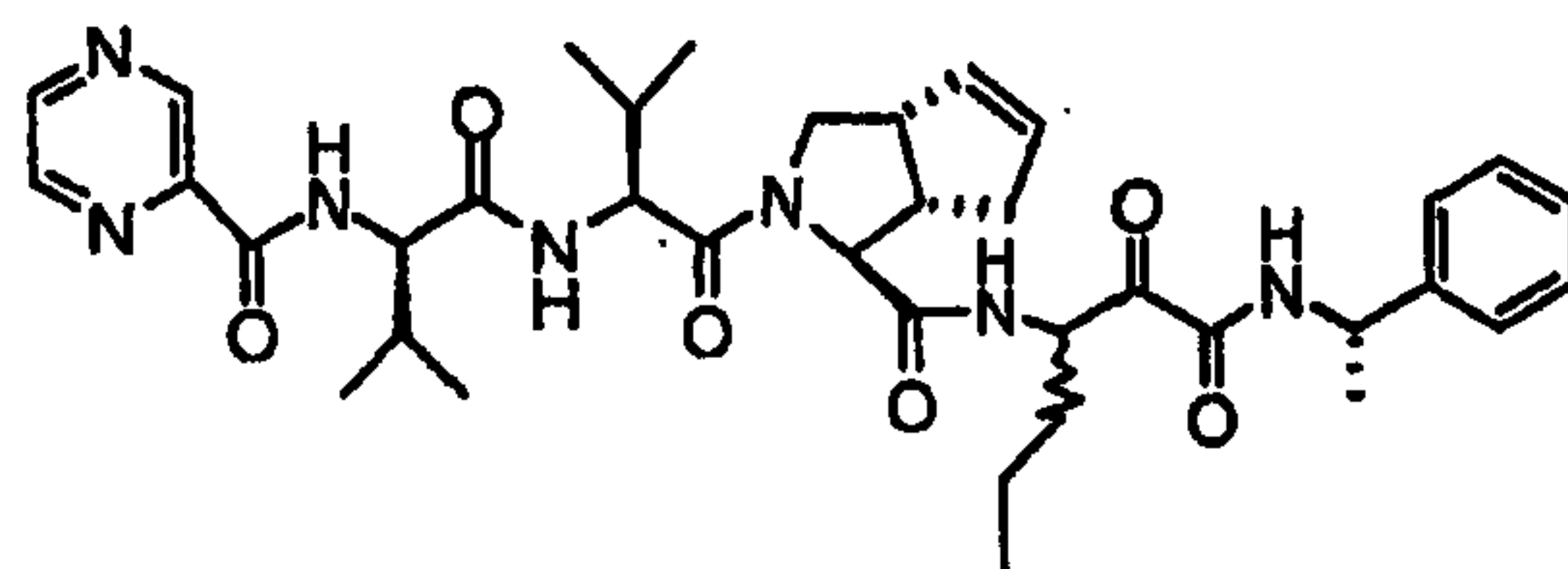
127



Following the above method and using the appropriate starting materials, the following consecutive compounds O-R are prepared:



5



Example 4 – Compounds S-W:

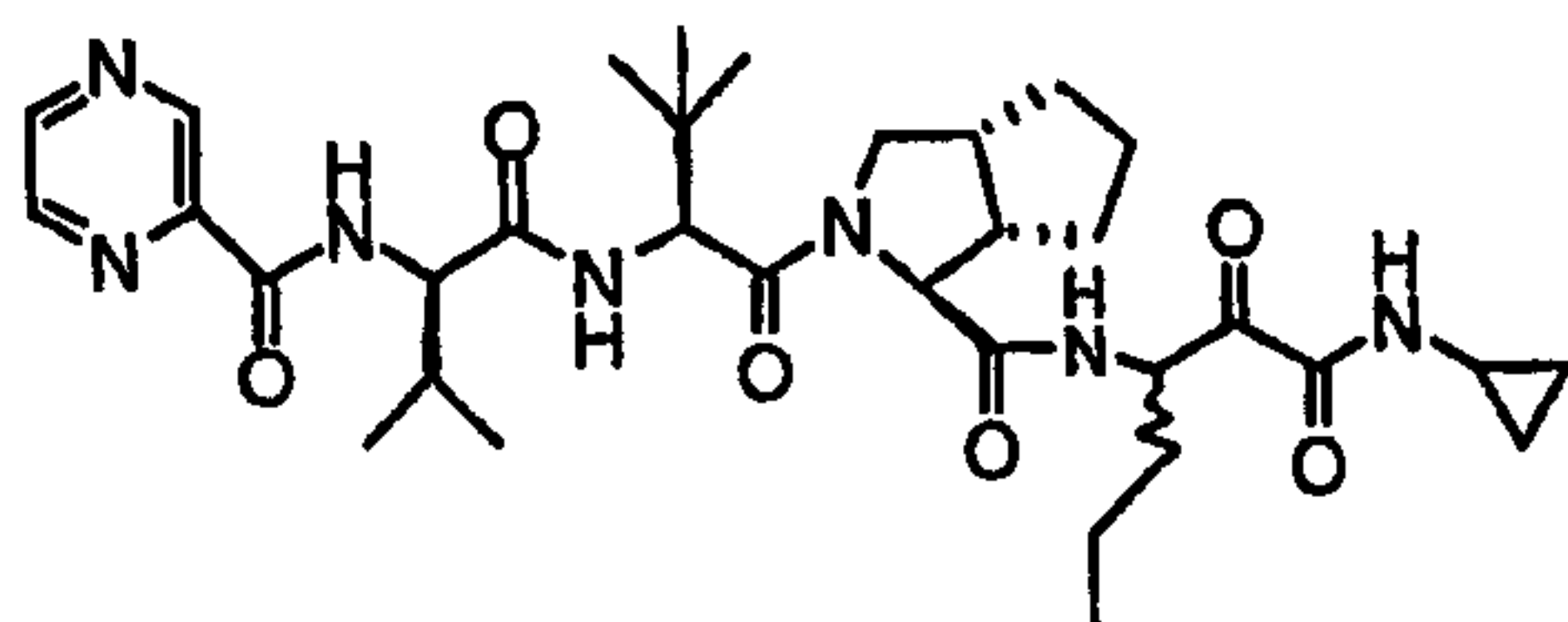
To a DCM solution (10 mL) of compound xxv (320 mg, 0.5 mmol) is added DMP reagent reagent (272 mg, 0.65 mmol). The reaction is stirred at about room temperature for 2 hours and quenched with 10% Na₂SO₃ for 20 minutes. The resulting mixture is then extracted with EtOAc. The organic layer is washed with brine, dried and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (80% EtOAc/Hexanes) to give 170 mg (53%) of compound S,

15

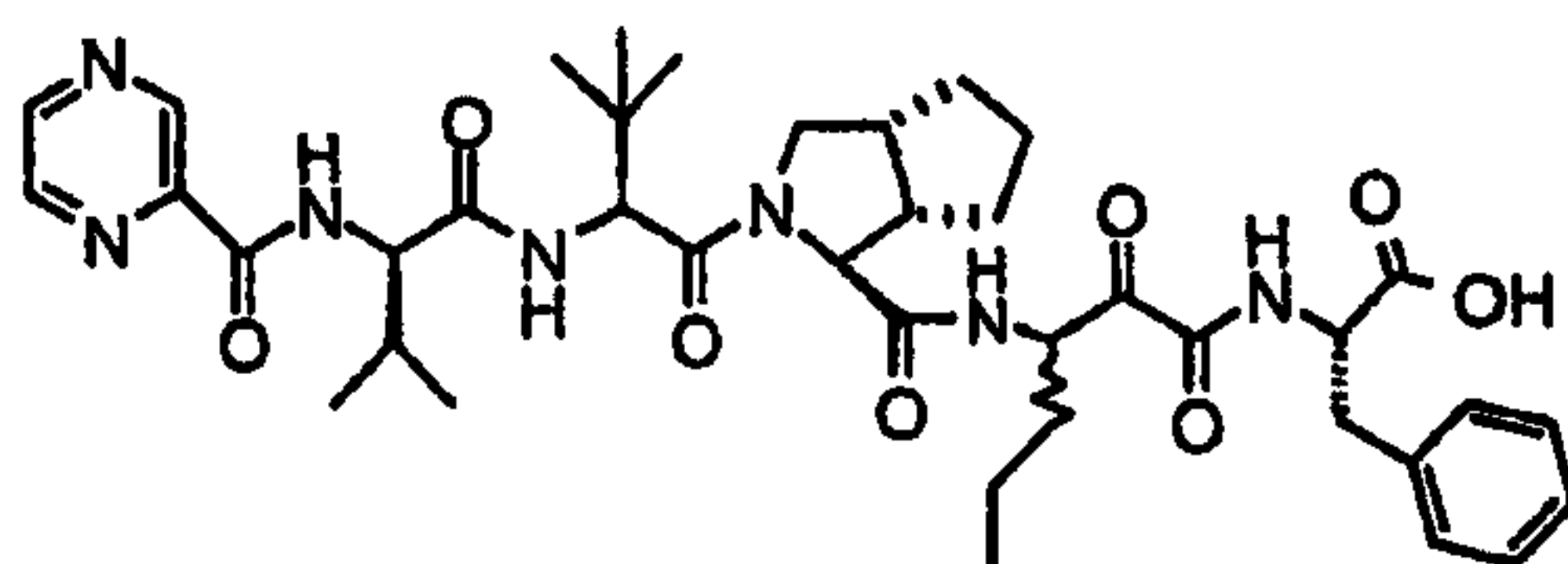
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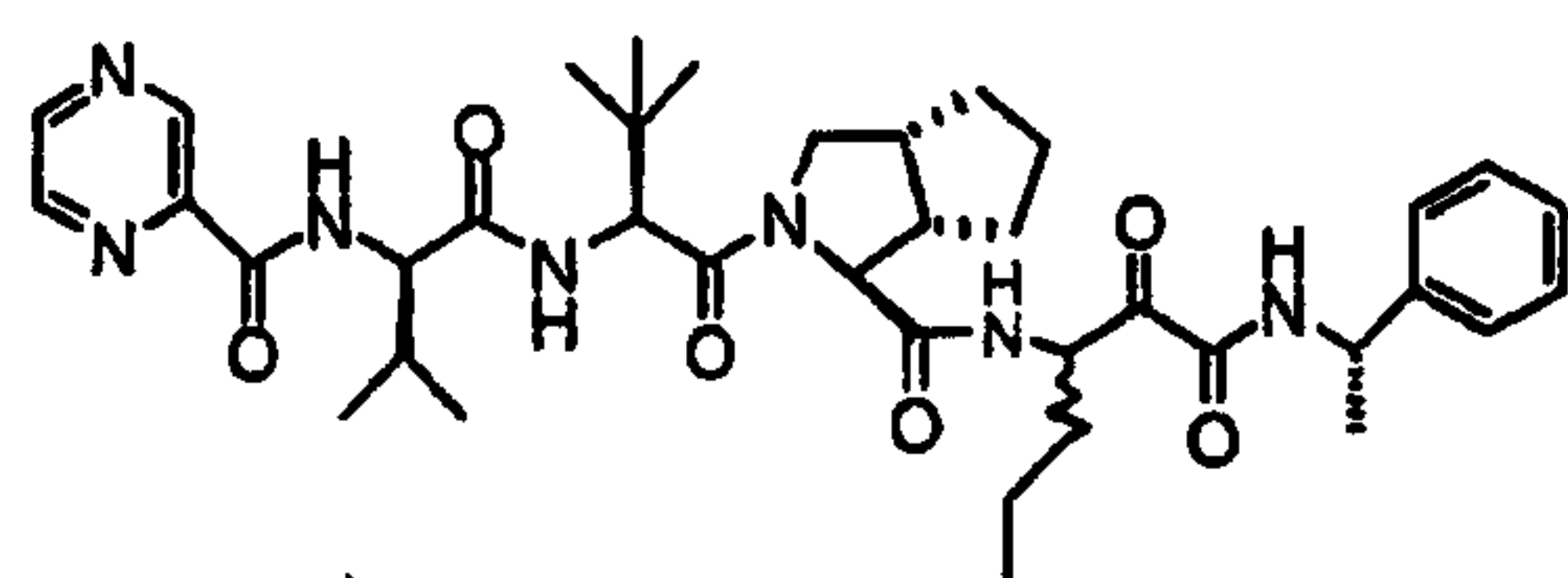
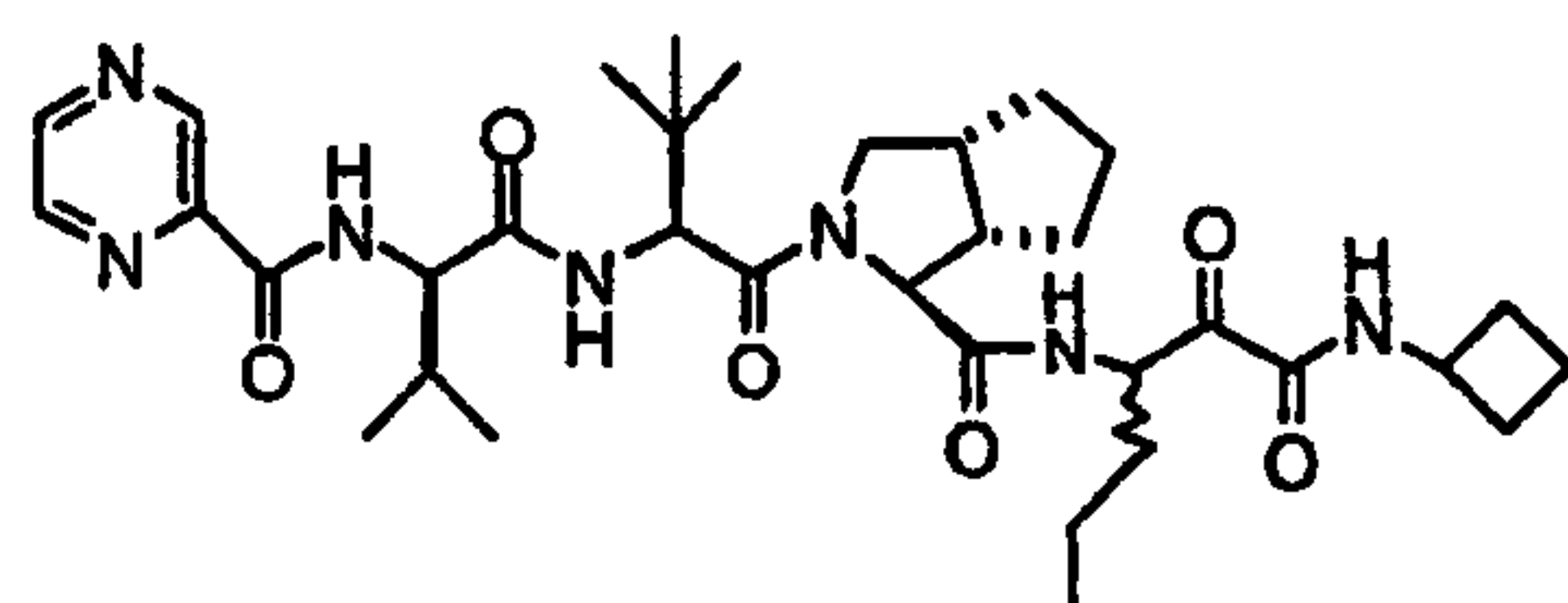
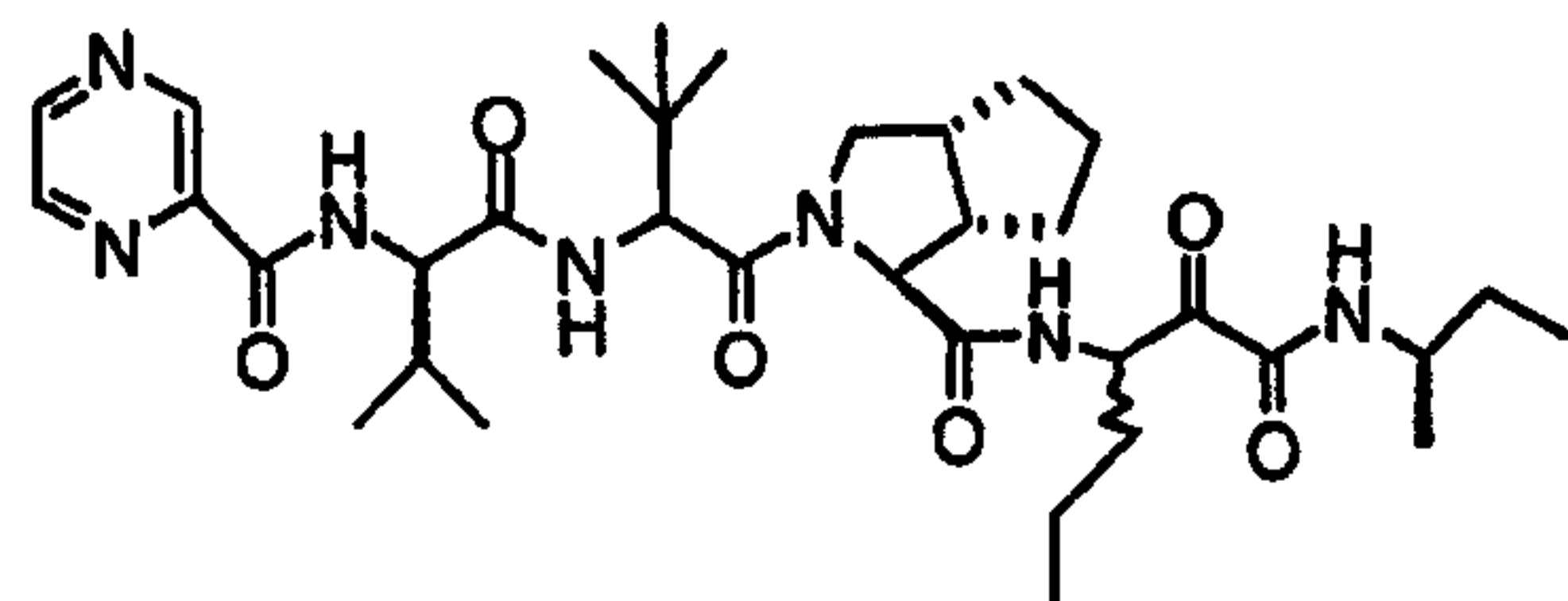
128



Following the above method and using the appropriate starting materials, the following consecutive compounds T-W are prepared:



5



10 Example 5 – Compounds X-AD:

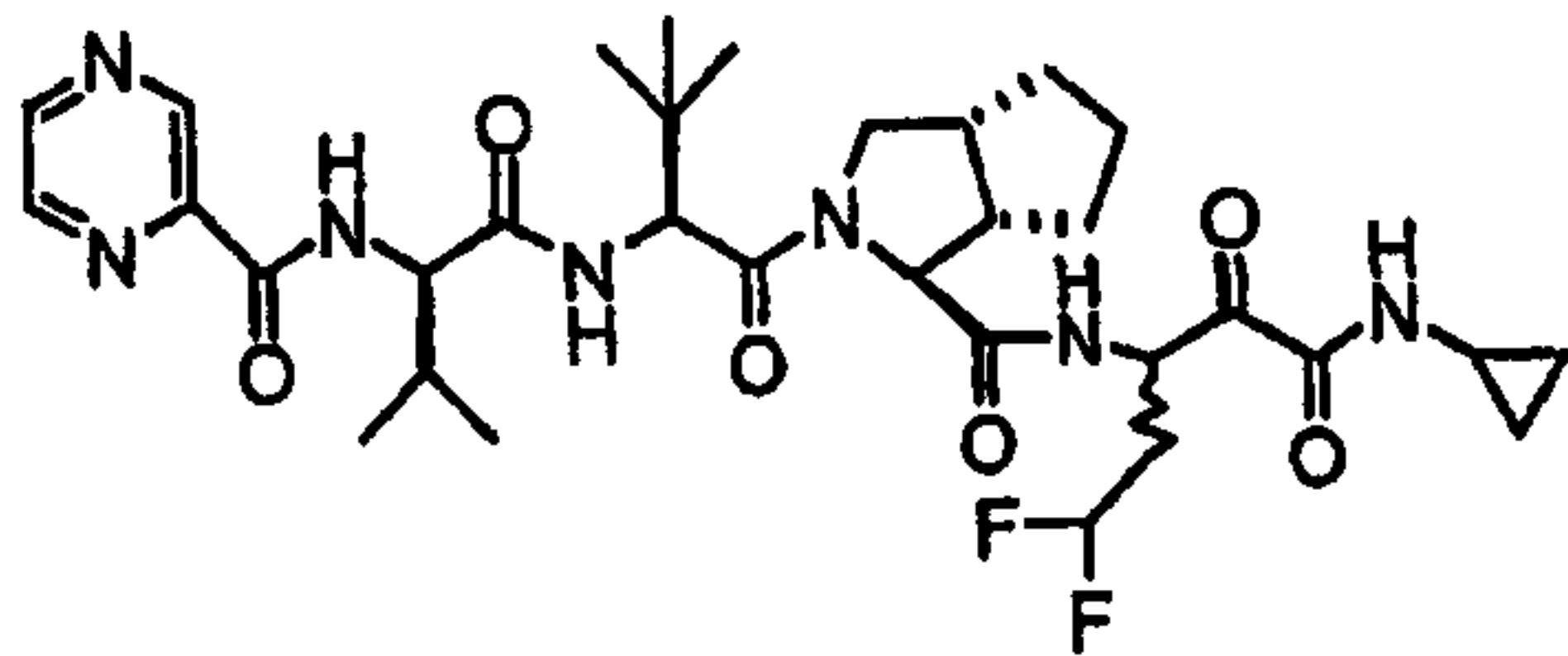
To a DCM solution (20 mL) of compound xxvi (400 mg, 0.6 mmol) is added DMP reagent reagent (329 mg, 0.78 mmol). The reaction is stirred at about room temperature for 1.5 hours and quenched with 10% Na₂SO₃ for 20 minutes. The resulting mixture is then extracted with EtOAc. The organic layer is washed with brine, dried and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (70-100% EtOAc/Hexanes) to give 210 mg (53%) of compound X,

15

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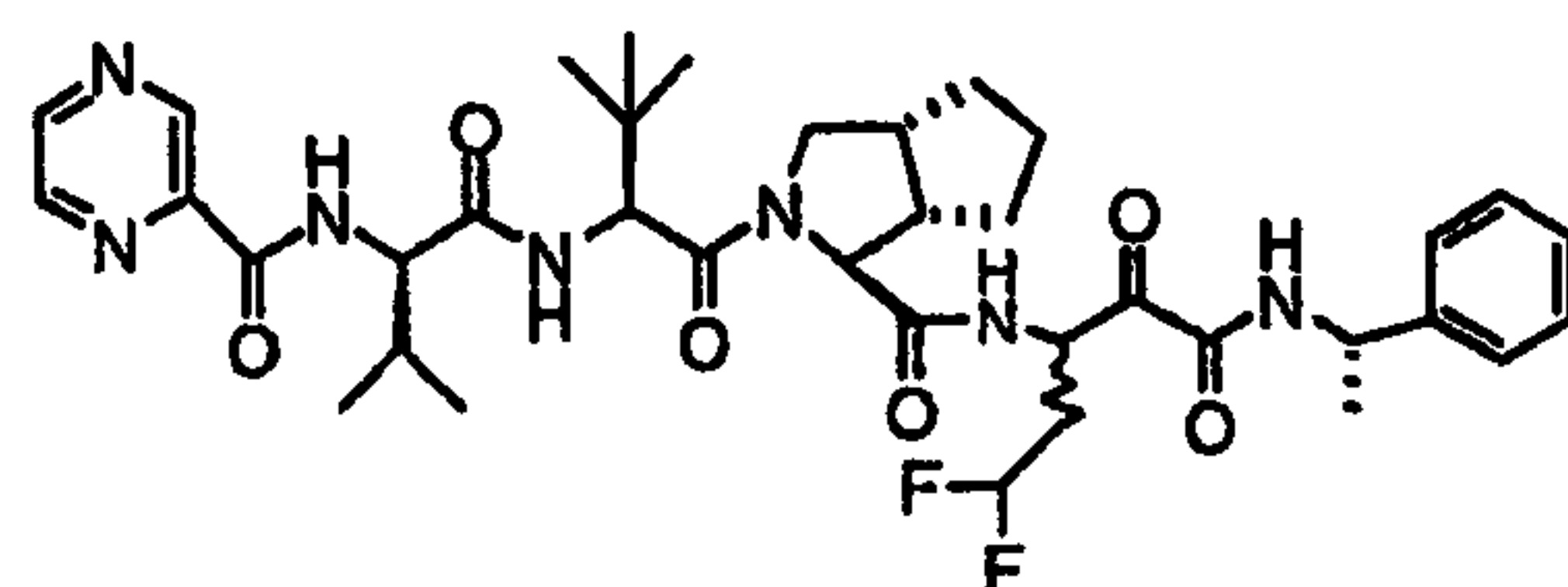
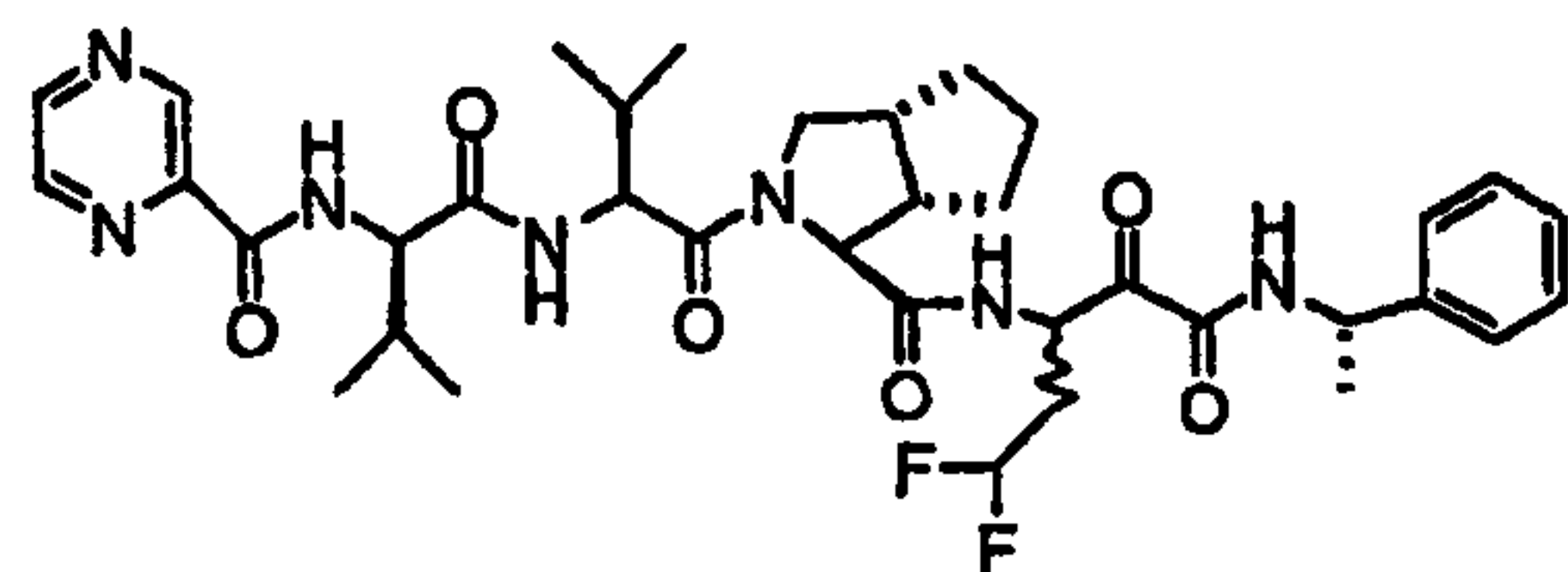
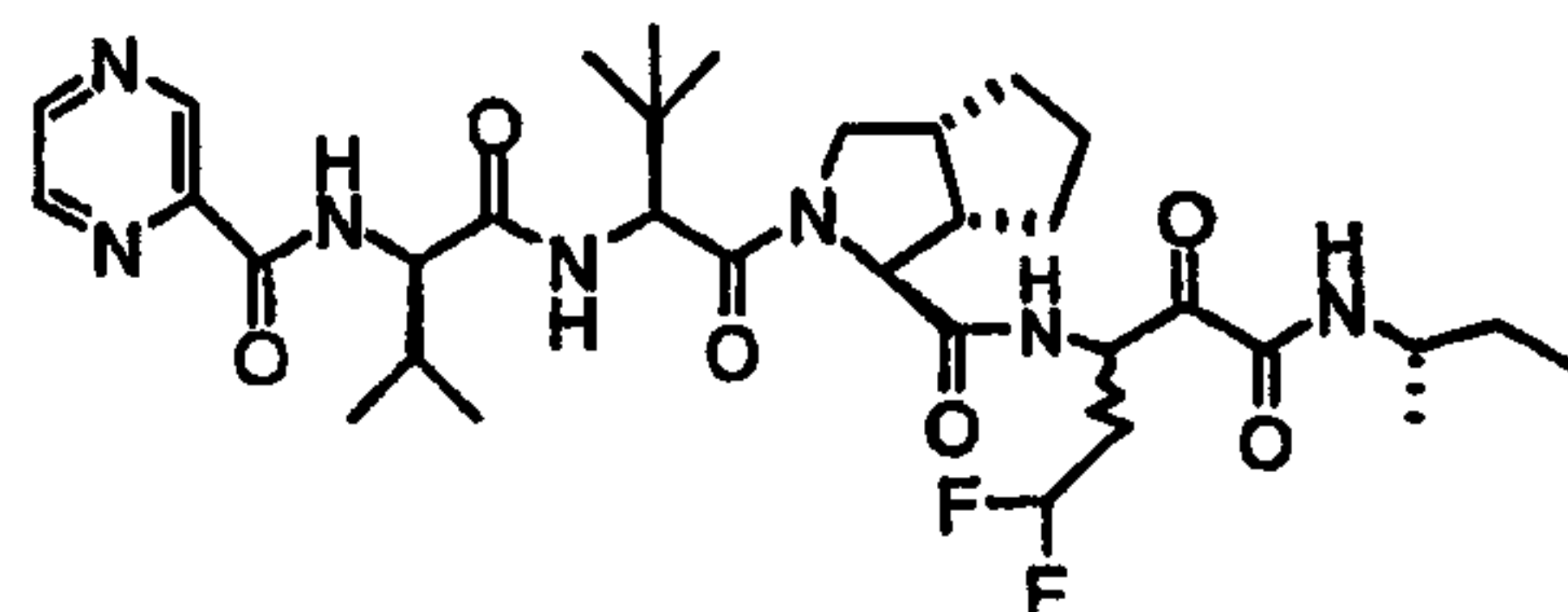
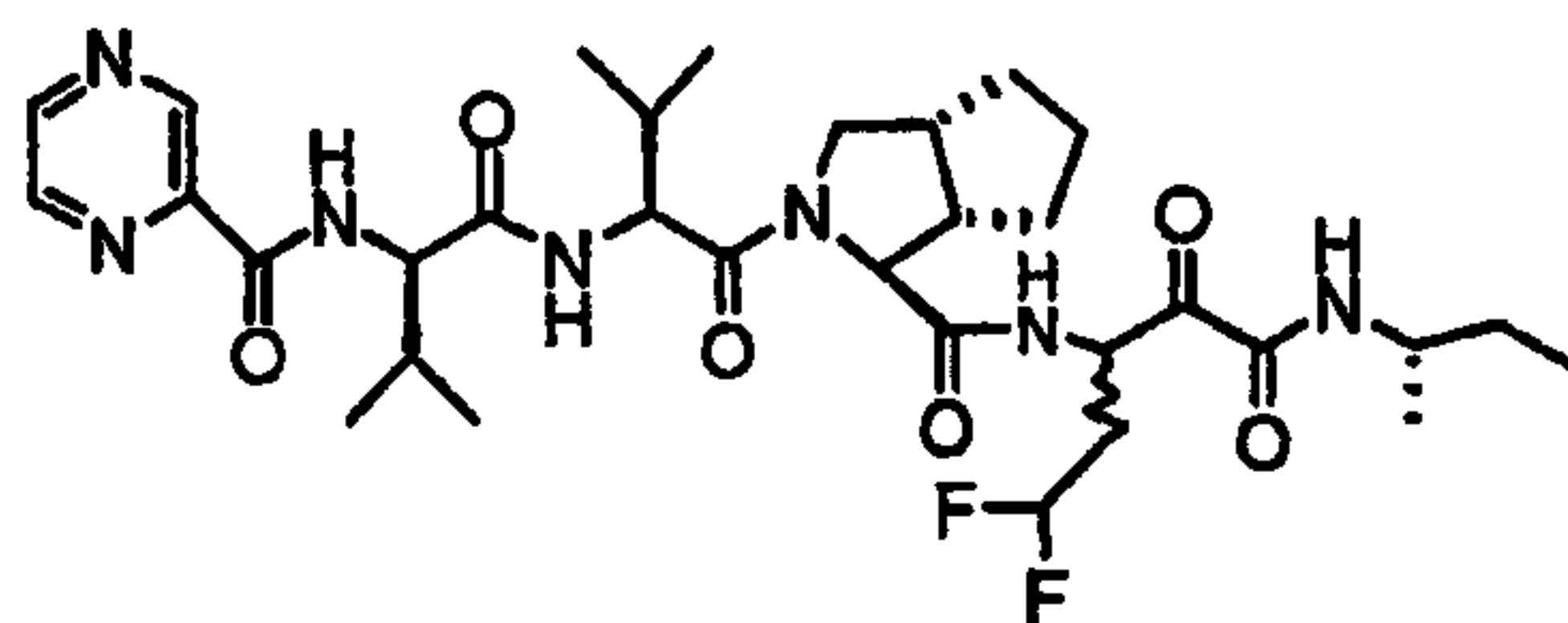
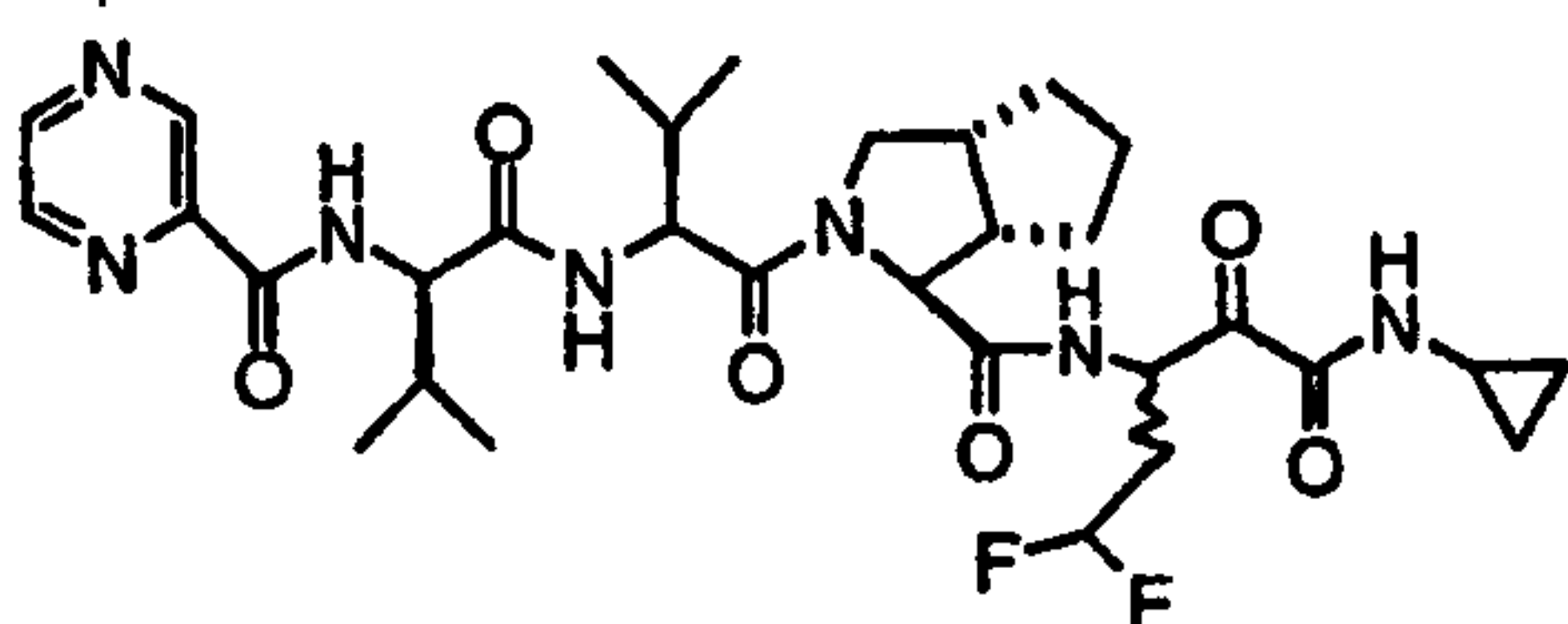
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Following the above method and using the appropriate starting materials, the following consecutive compounds Y-AD are prepared:

5

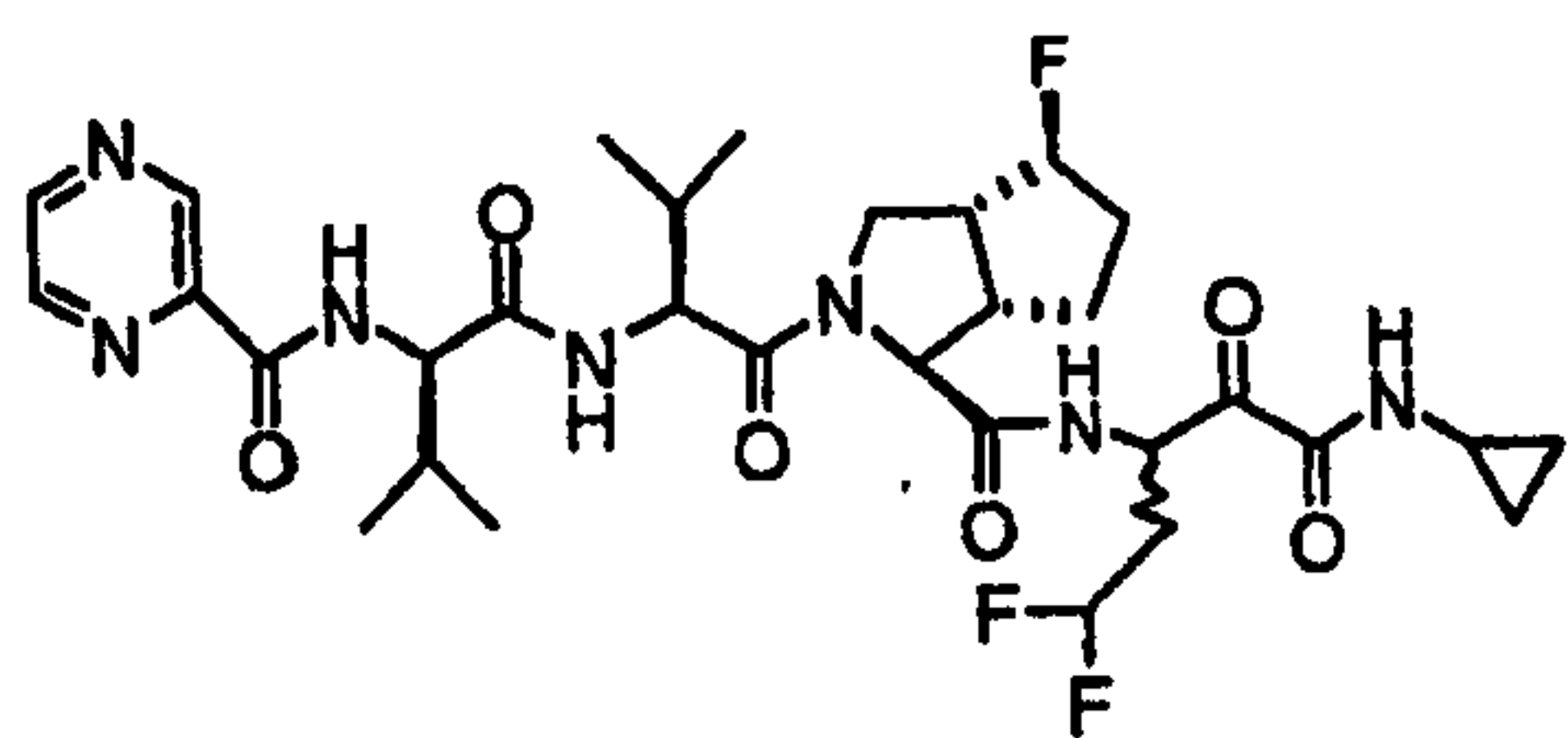


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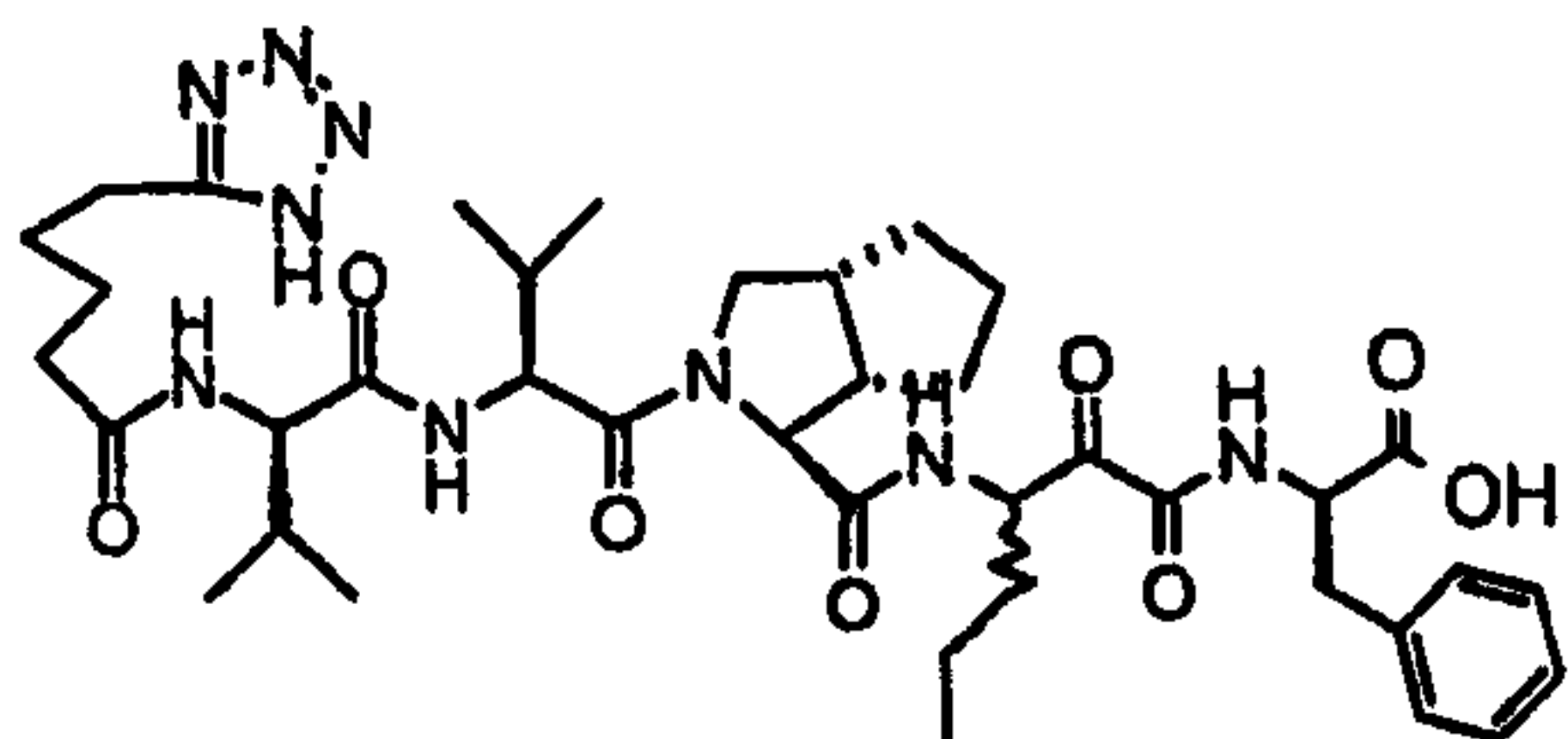
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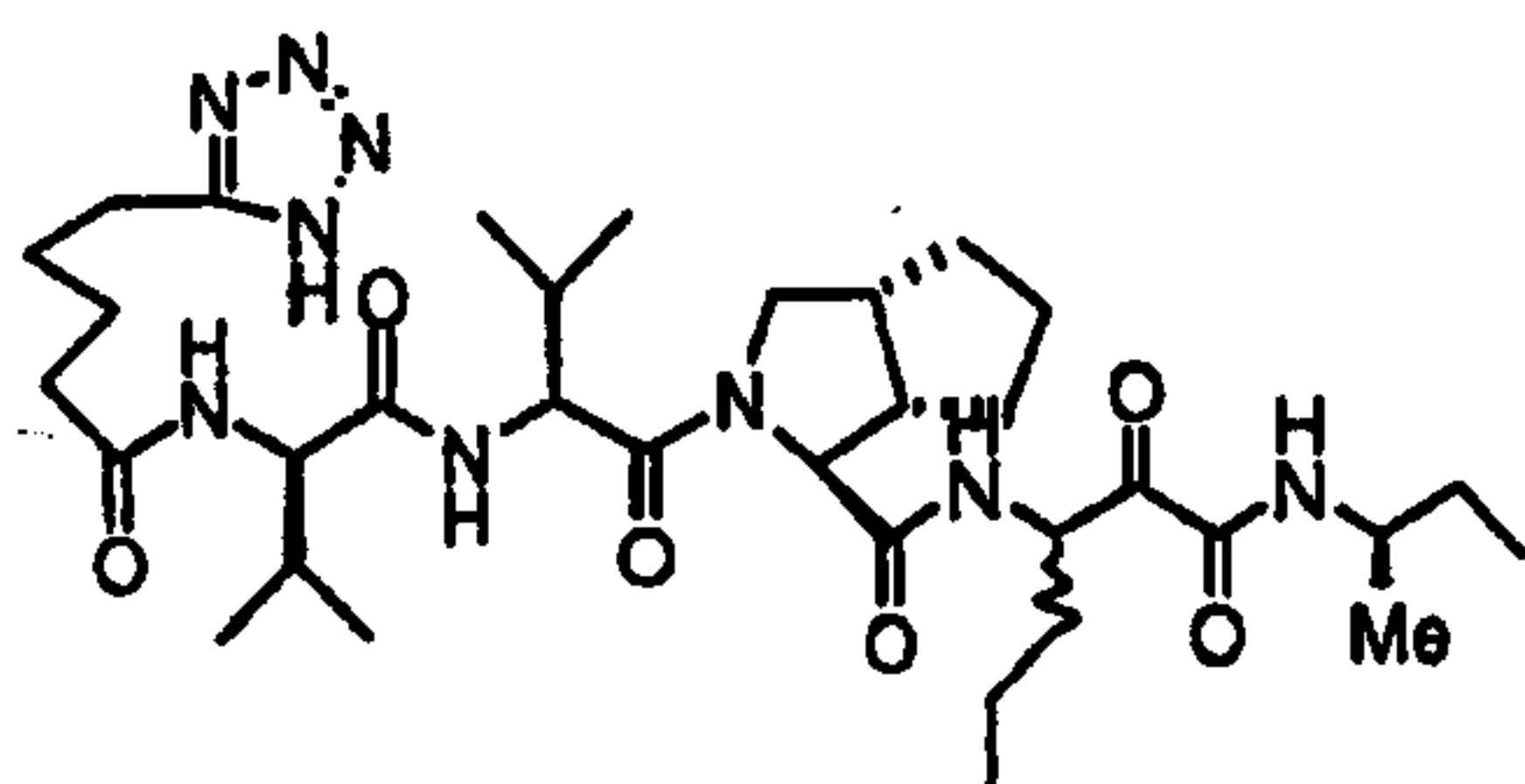
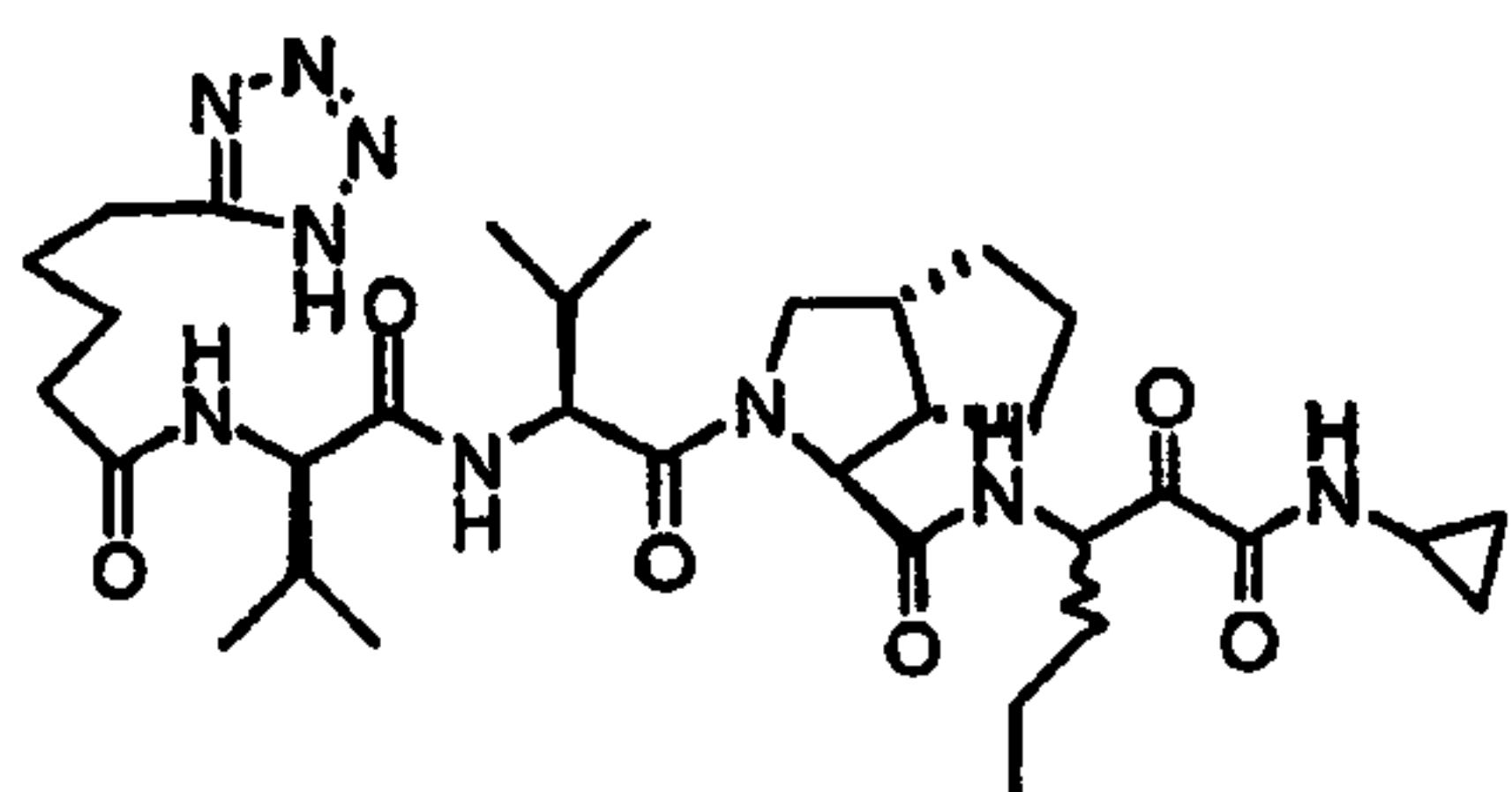
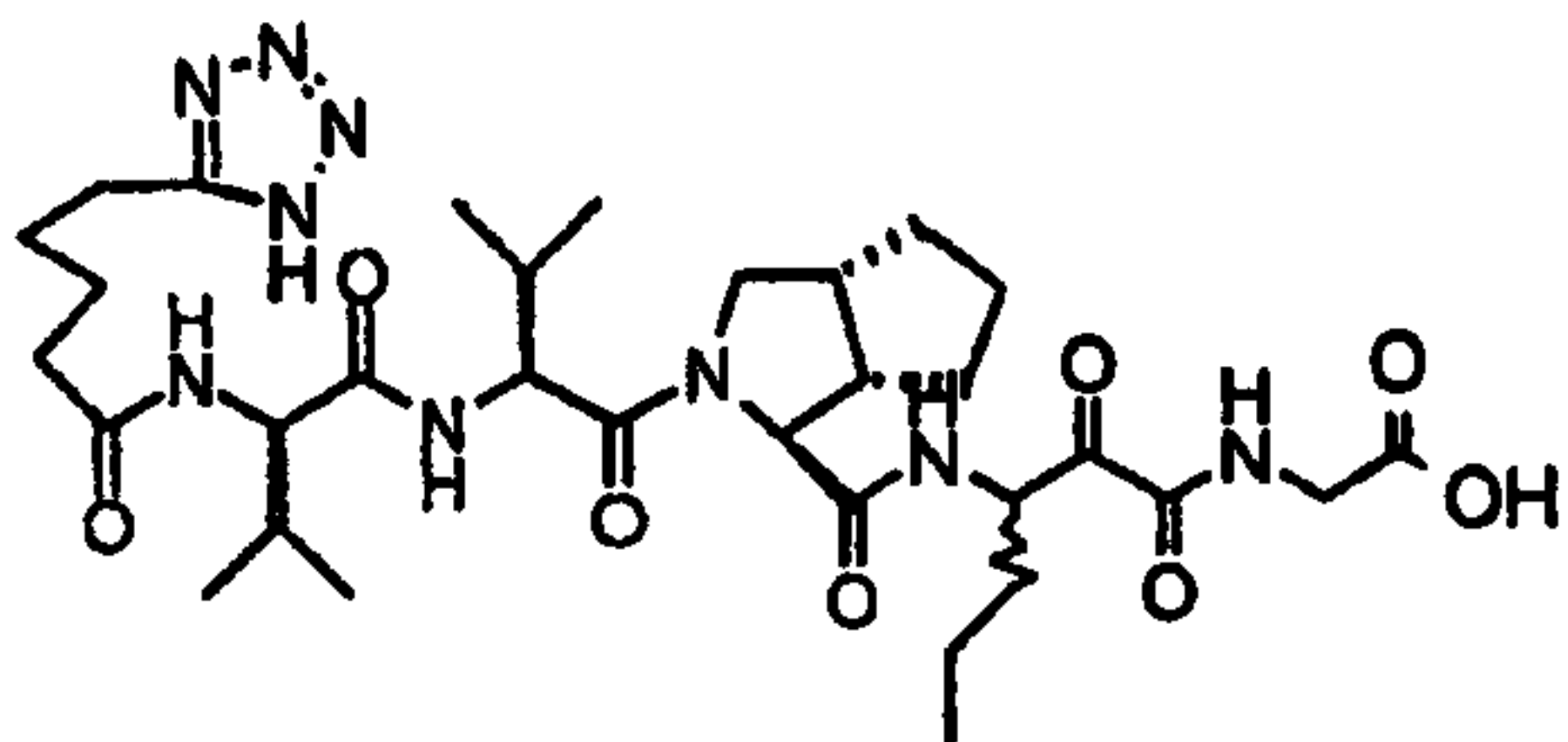
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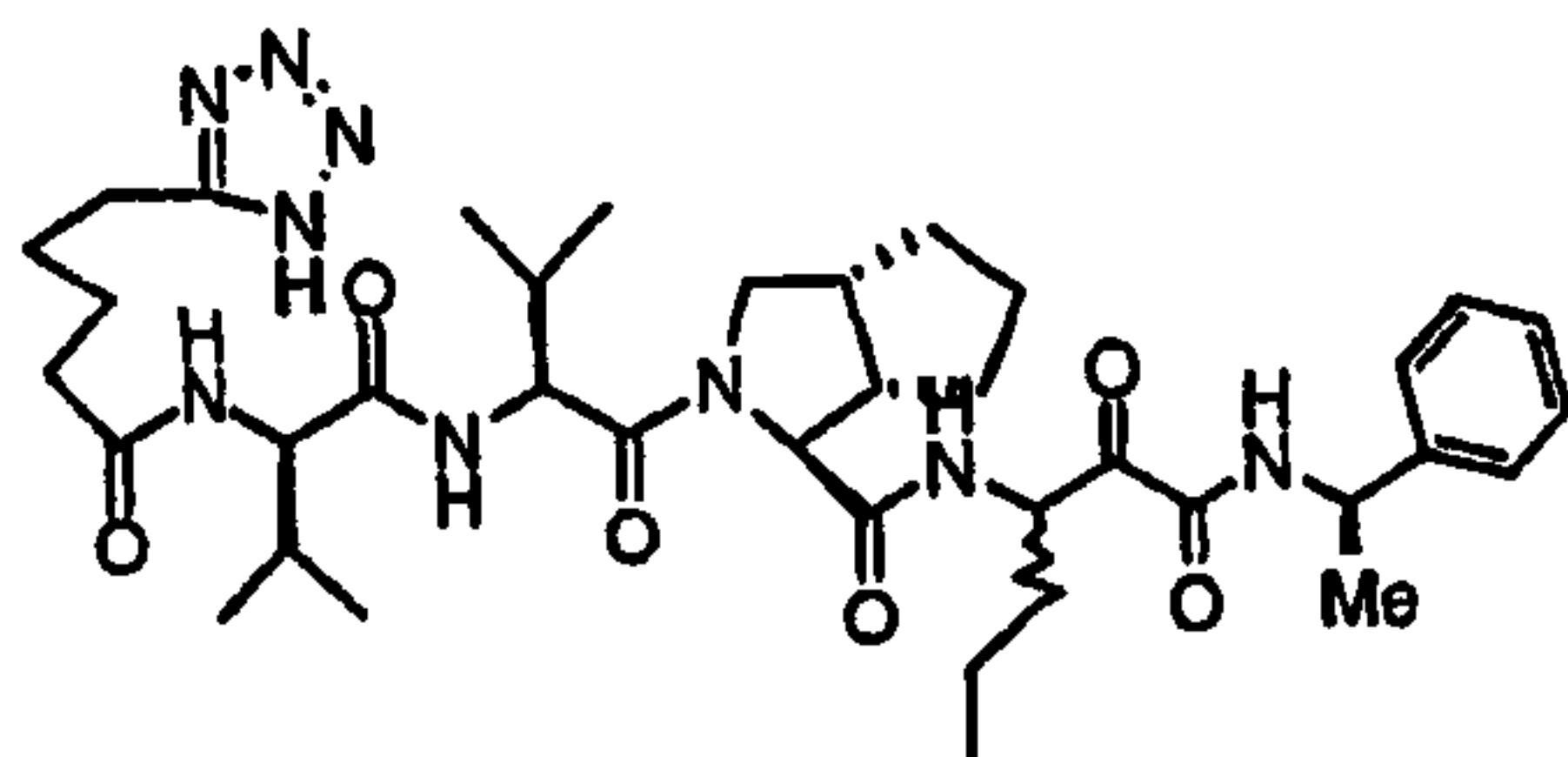
**Example 6 – Compounds AE-AI:**

Compound xxxiii (150 mg; 0.076 mmol) is dissolved in 5 mL TFA and stirred for two
5 days. The product is purified by RP-HPLC to yield 40 mg (33% yield) of compound AE,



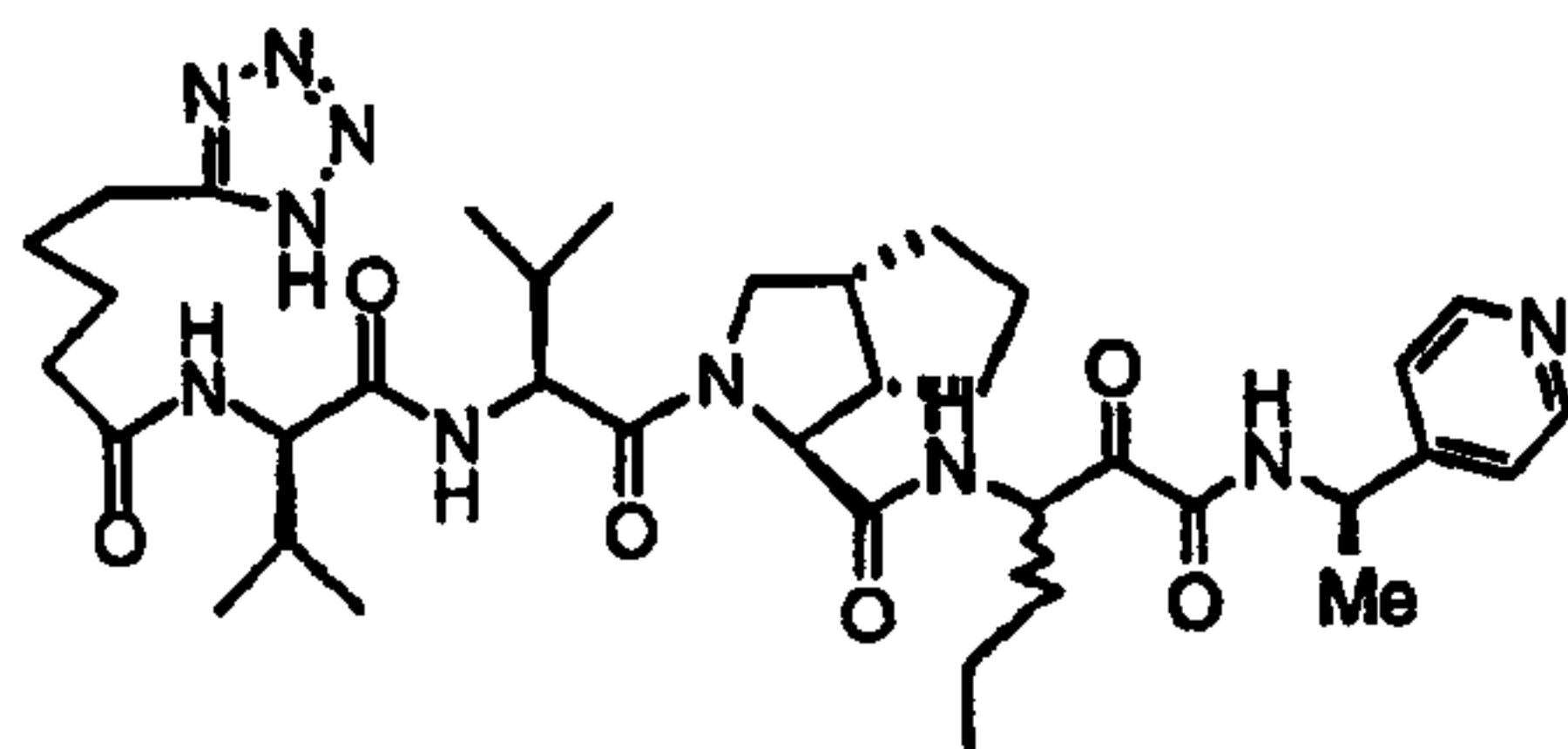
Following the above method and using the appropriate starting materials, the following
10 consecutive compounds AF-AI are prepared:





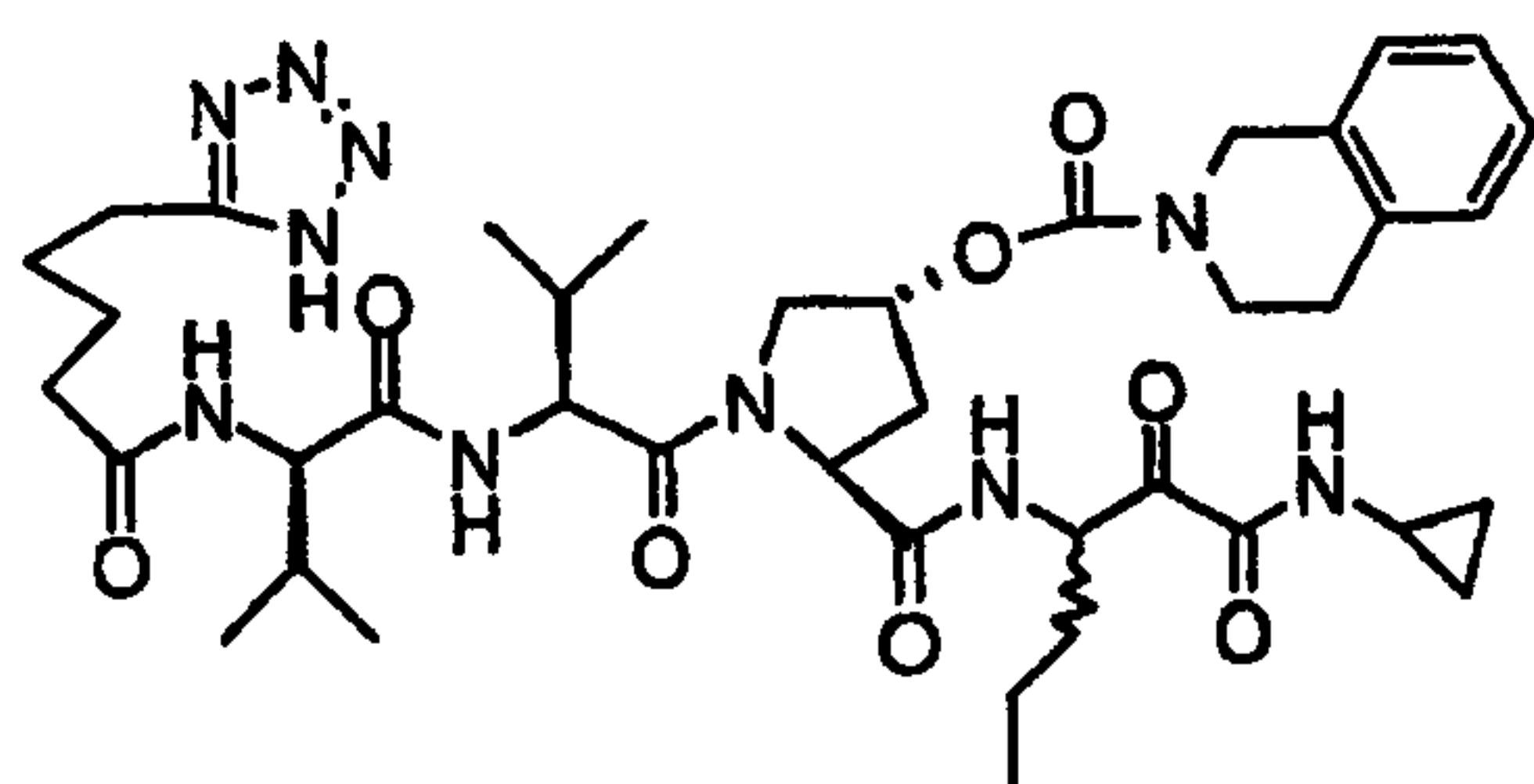
Example 7 – Compound AJ:

Compound xxxviii (180 mg, 0.21 mmol) is dissolved in neat TFA (5 mL) and left for 3
 5 day at about room temperature. At this point, the reaction mixture is concentrated *in vacuo* to
 give a residue, which is purified by reverse phase HPLC to give 50 mg (32%) of the compound
 AJ,



10 Example 8 – Compounds AK-AM:

Compound xxxxiii (150 mg; 0.16 mmol) is dissolved in 4.5 mL TFA and stirred for three
 days. The product is purified by RP-HPLC to yield 70 mg (54% yield) compound AK,

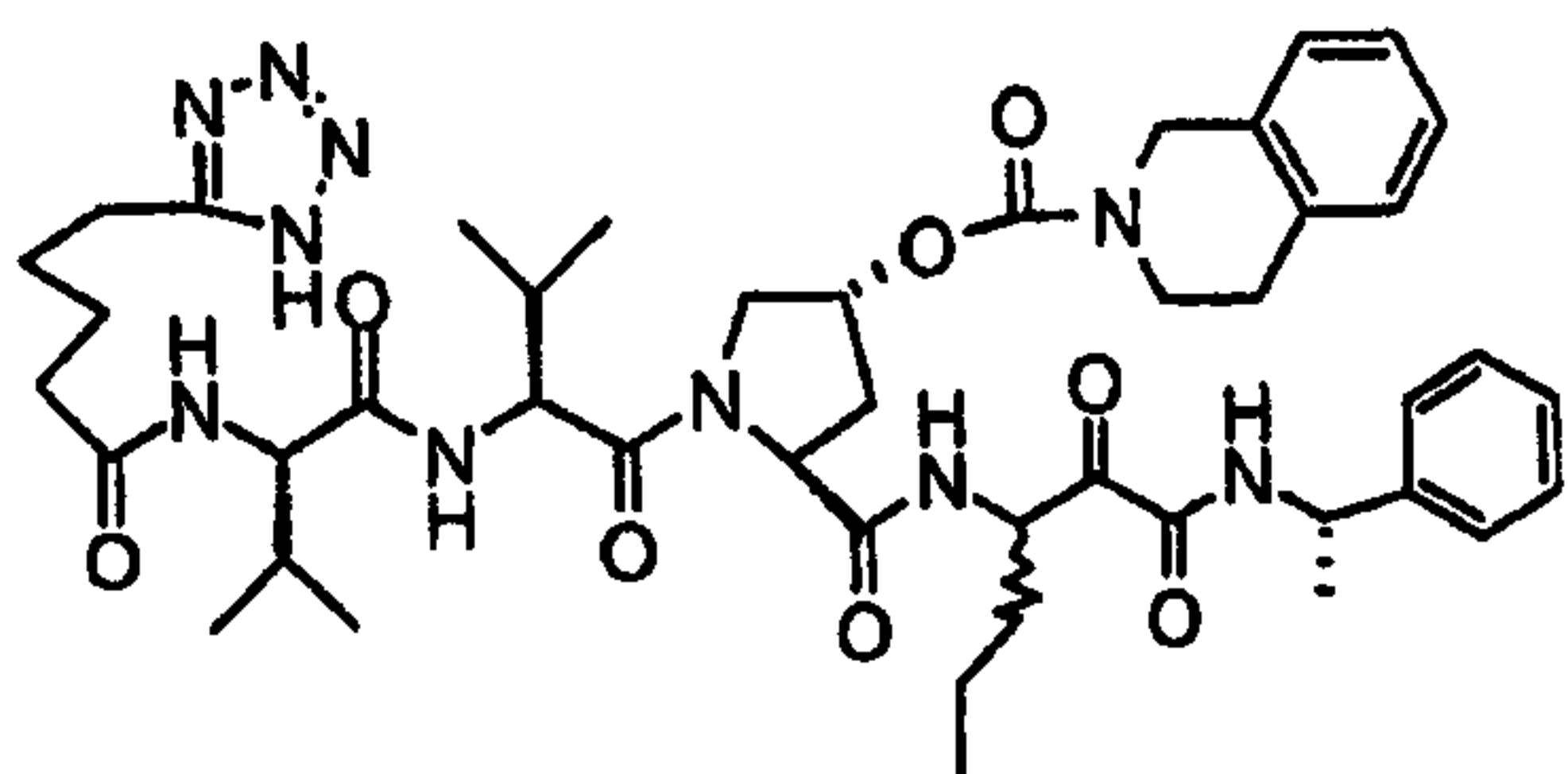
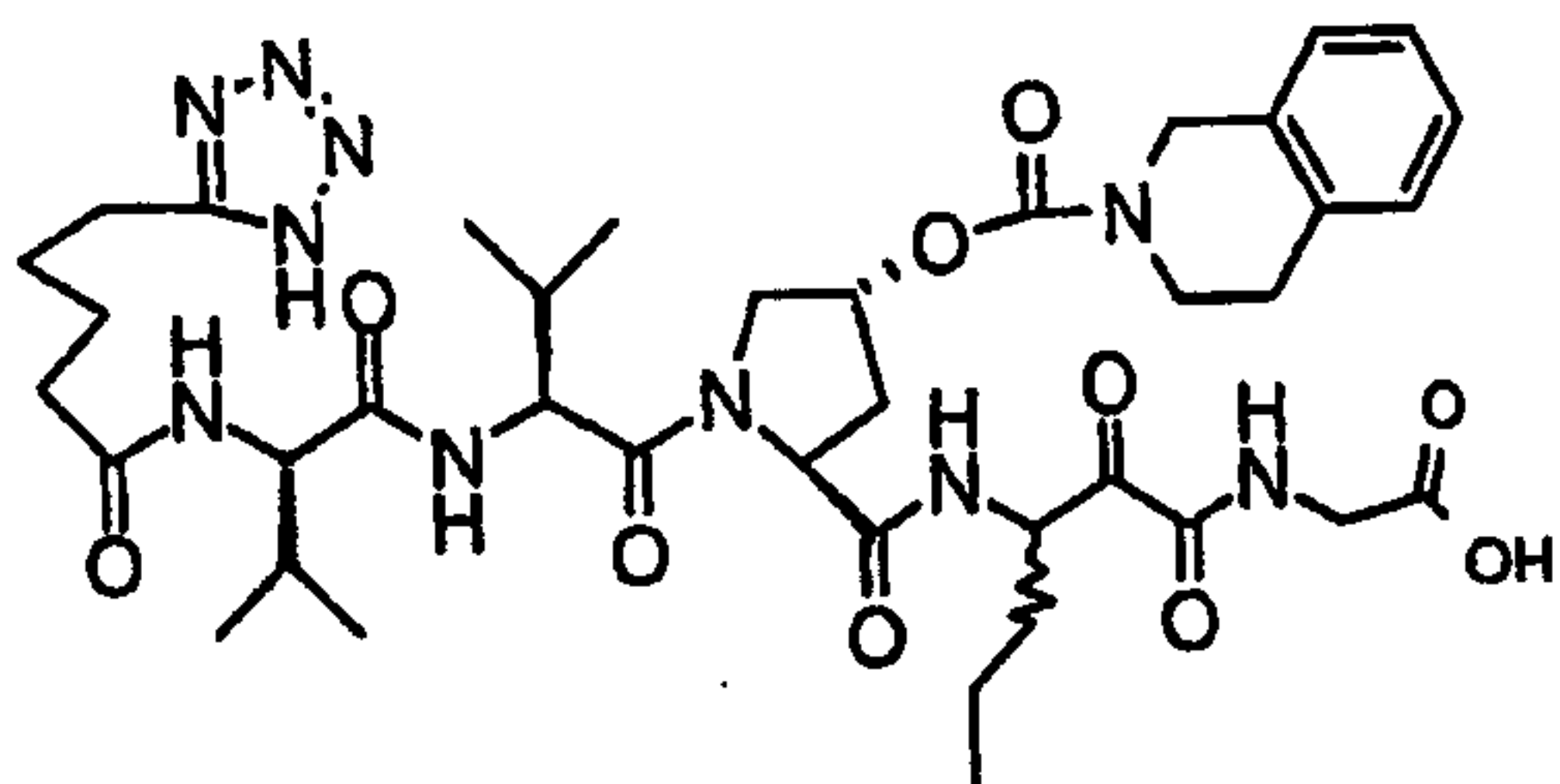


15 Following the above method and using the appropriate starting materials, the following
 consecutive compounds AL-AM are prepared:

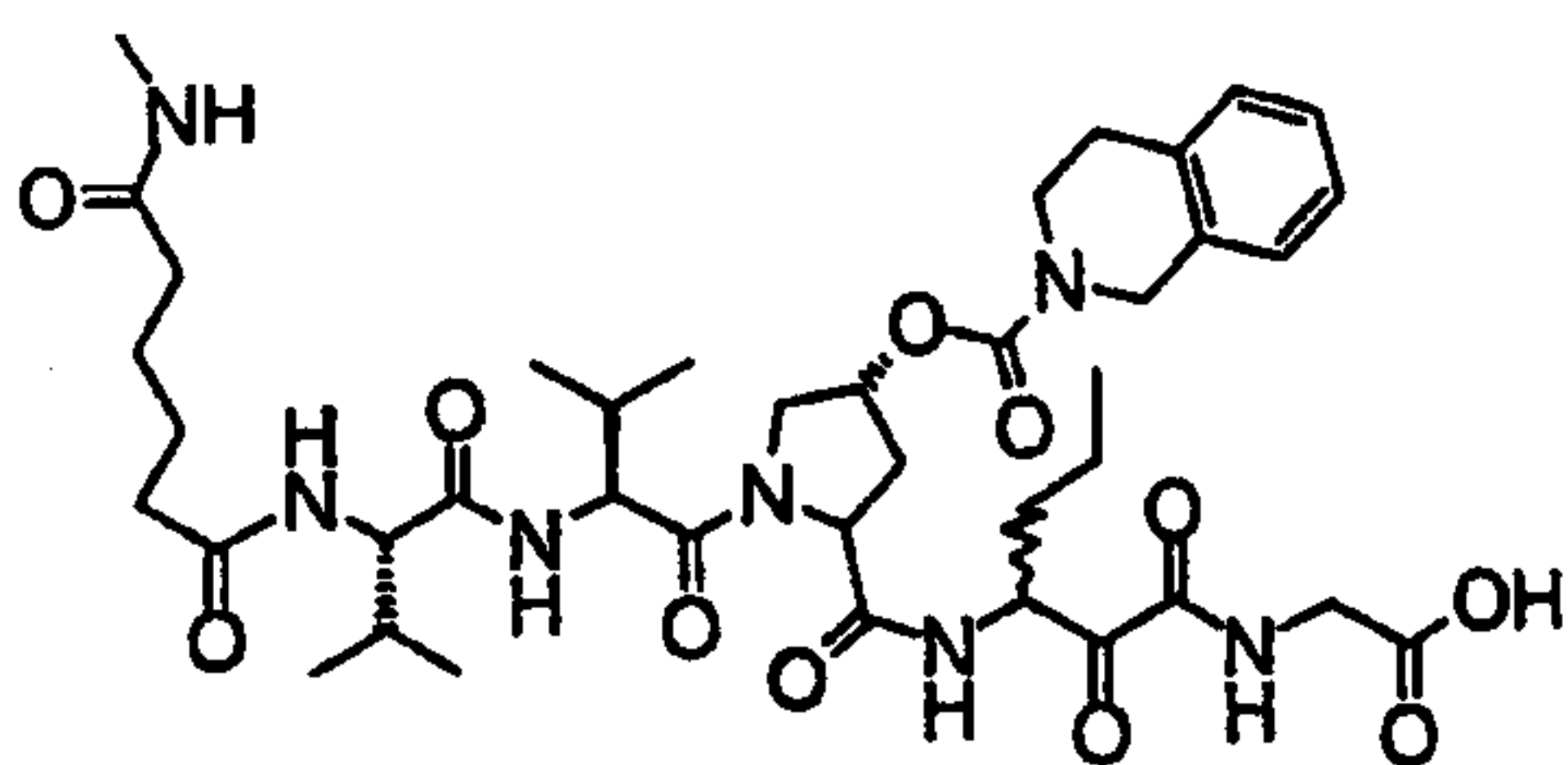
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**Example 9 – Compounds AN:**

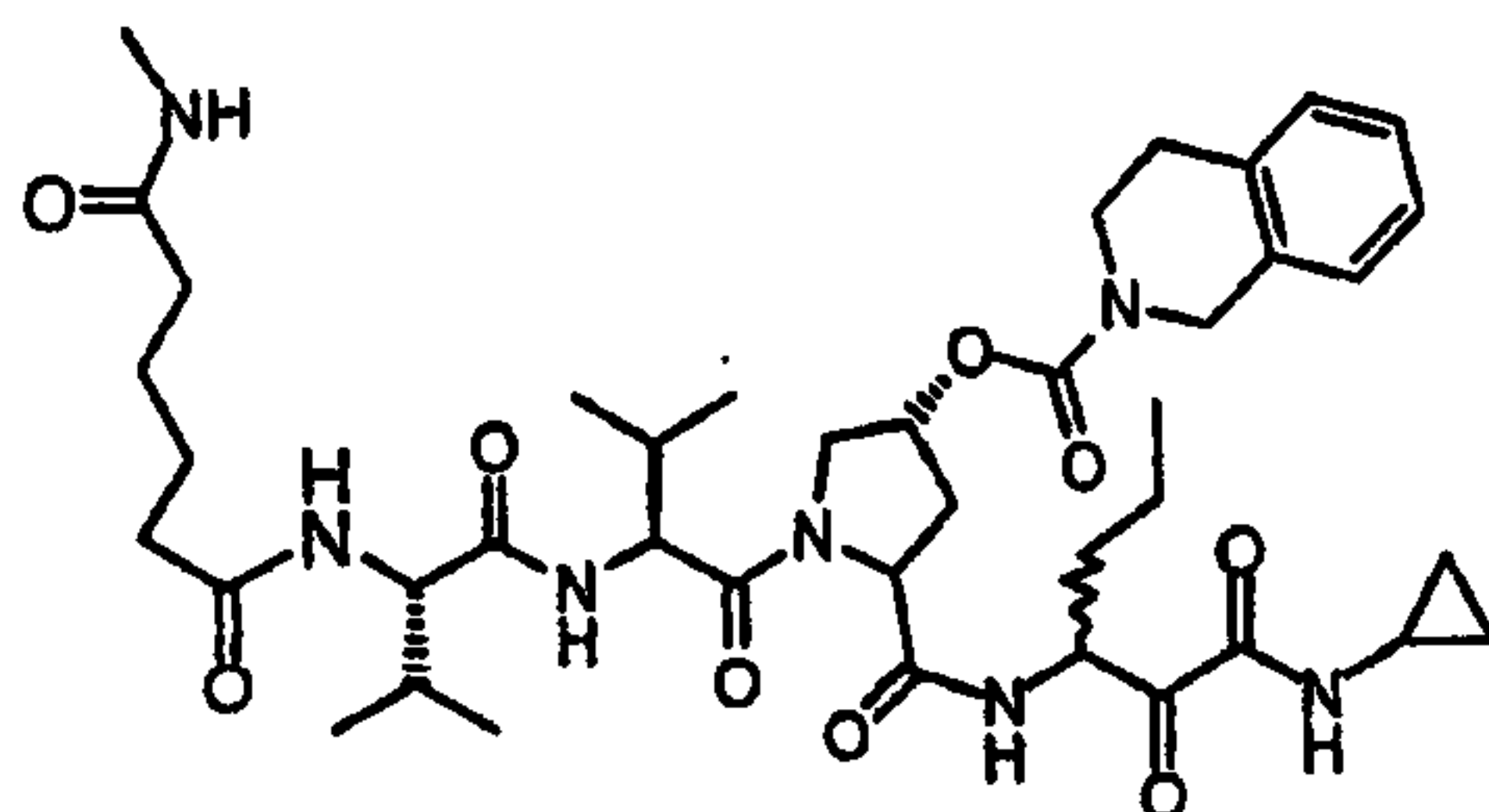
Compound lii (80 mg) is dissolved in 3 mL TFA and 3 mL DCM. The mixture is stirred
 5 at about room temperature for 5 hours. The solvent is removed by evaporation. The resulting
 residue is purified by HPLC to yield 62 mg (83%) of compound AN,



10

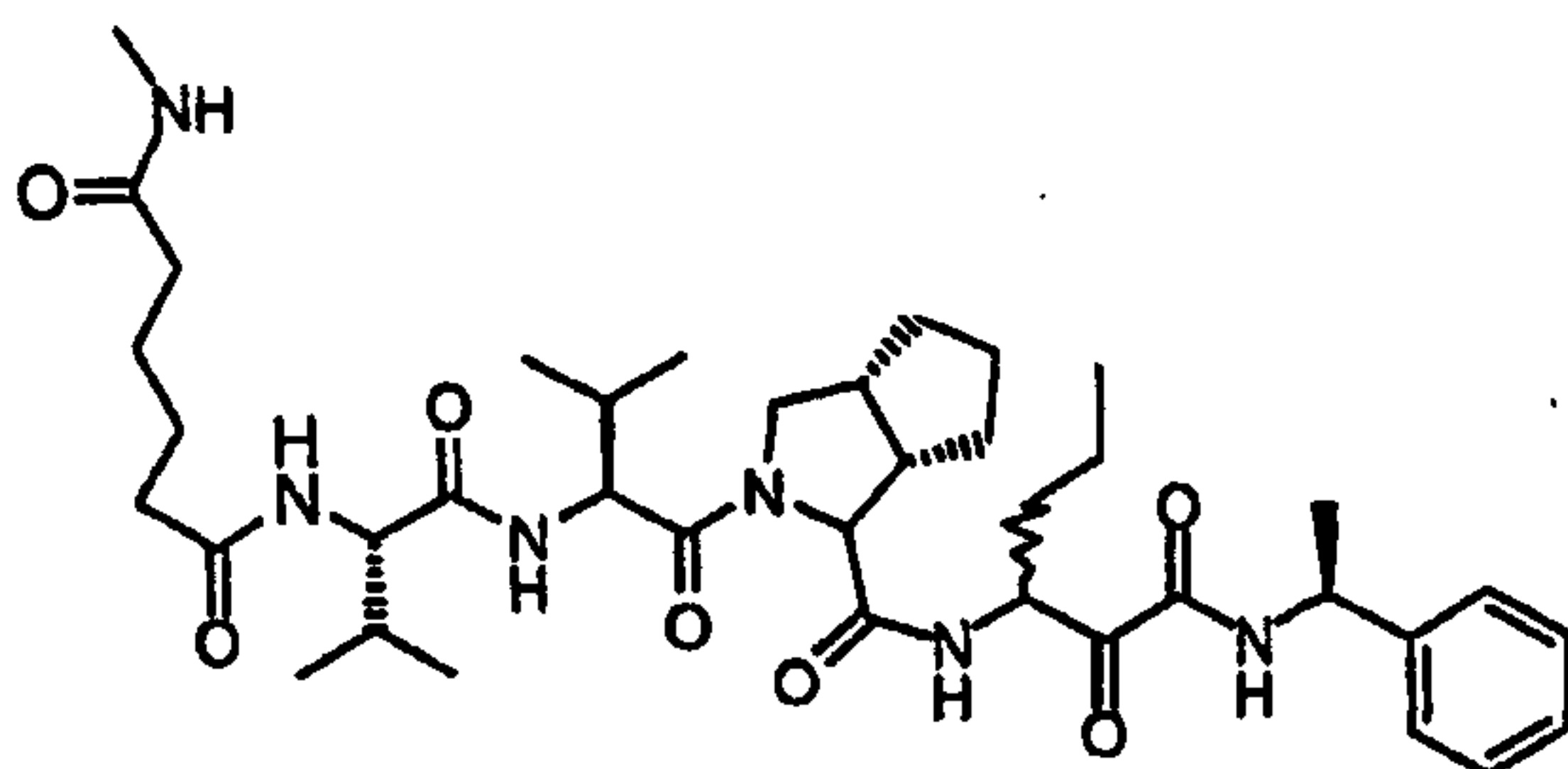
Example 10 – Compounds AO:

Compound liii (160 mg; 0.2 mmol) is dissolved in 5 mL DCM and DMP reagent reagent
 (170 mg; 0.4 mmol) is added. The mixture is stirred at about room temperature for three hours.
 The solvent is removed by evaporation and the residue is dissolved in 50% acetonitrile/water and
 15 purified by RP-HPLC to yield 51 mg (32%) of compound AO,



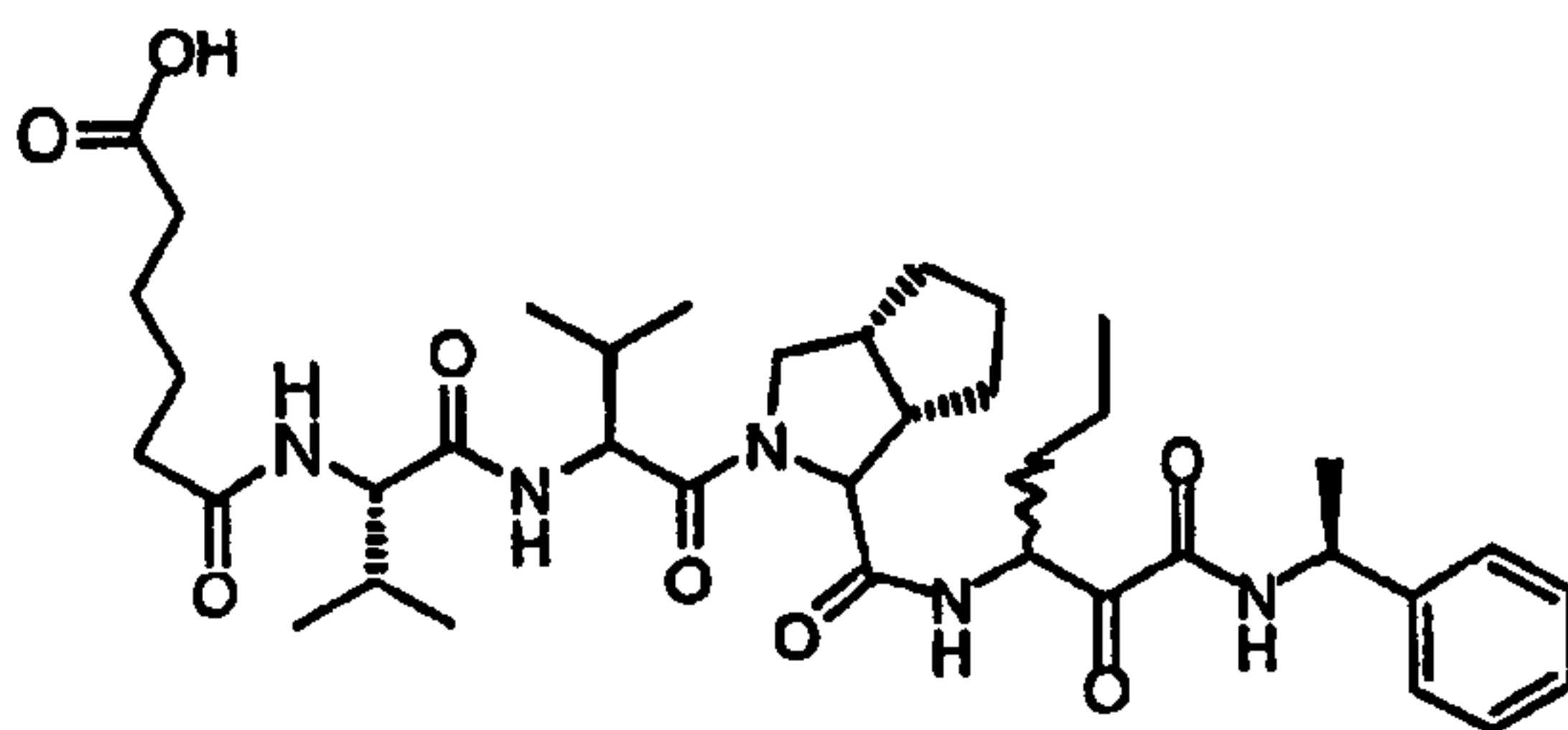
Example 11 – Compounds AP:

Compound lix (162 mg; 0.22 mmol) is dissolved in 8 mL of DCM and DMP reagent reagent (189 mg; 0.44 mmol) is added. The mixture is stirred at about room temperature for 3
5 hours. The solvent is removed by evaporation and product is purified by RP-HPLC to yield 41 mg (25%) of compound AP,



10 **Example 12 – Compounds AQ:**

Compound lx (70 mg; 0.09 mmol) is dissolved in 5 mL TFA and 5 mL DCM. The mixture is stirred at about room temperature for 3 hours. The solvent is removed by vacuum and the residue is dissolved in 50% acetonitrile/water and lyophilized to yield compound AQ as a
15 powder,

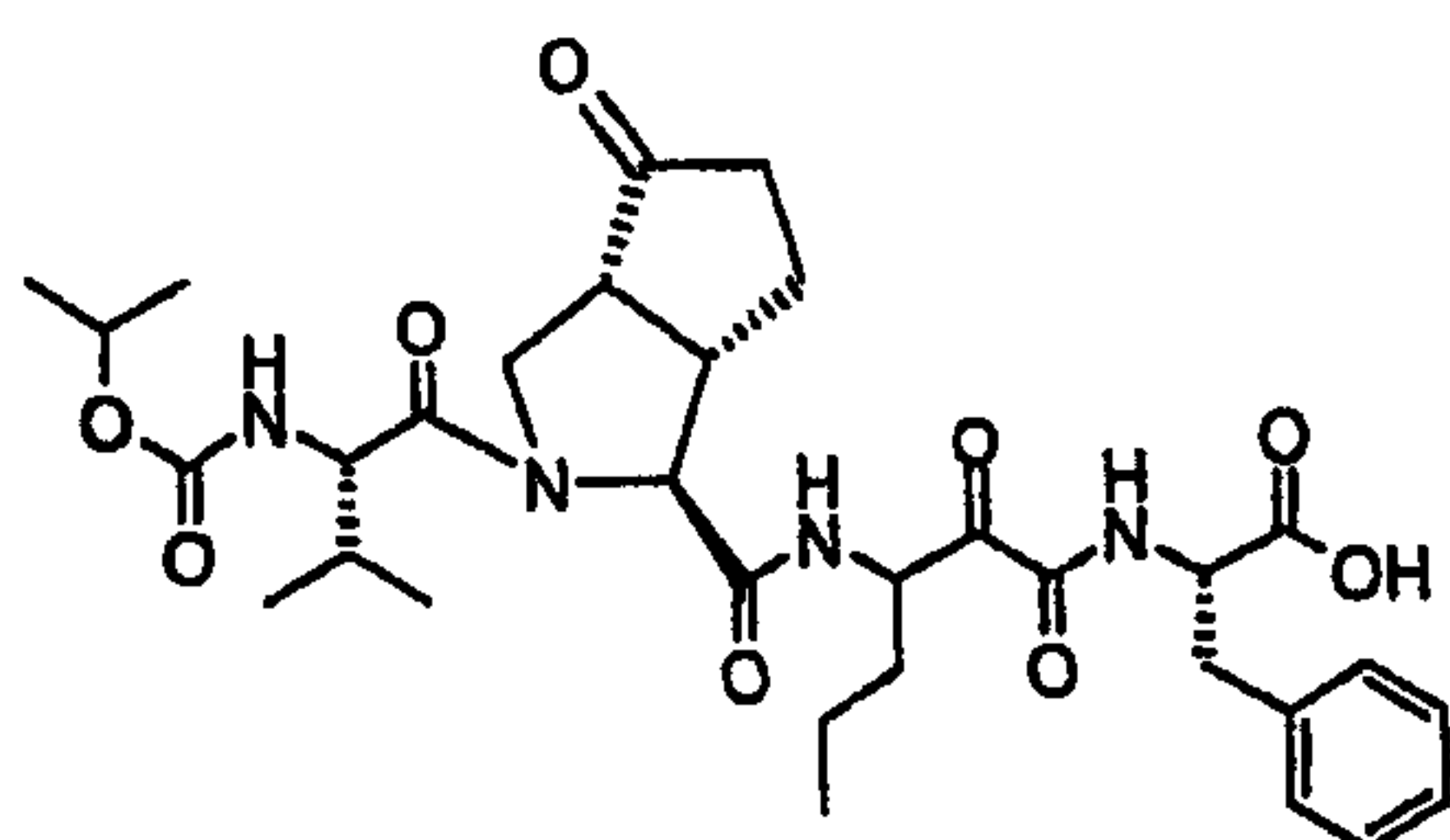
**Example 13 – Compounds AR-BG:**

Compound lxvi (223 mg, 0.326 mmol) is stirred in a solution of TFA (5 mL) and DCM (5 mL) for 4 hours. TLC (silica gel: 2% MeOH/EtOAc) showed complete conversion to the slower
20 product. The solvent is removed under reduced pressure and the product lyophilized to give 198 mg (97%) compound AR,

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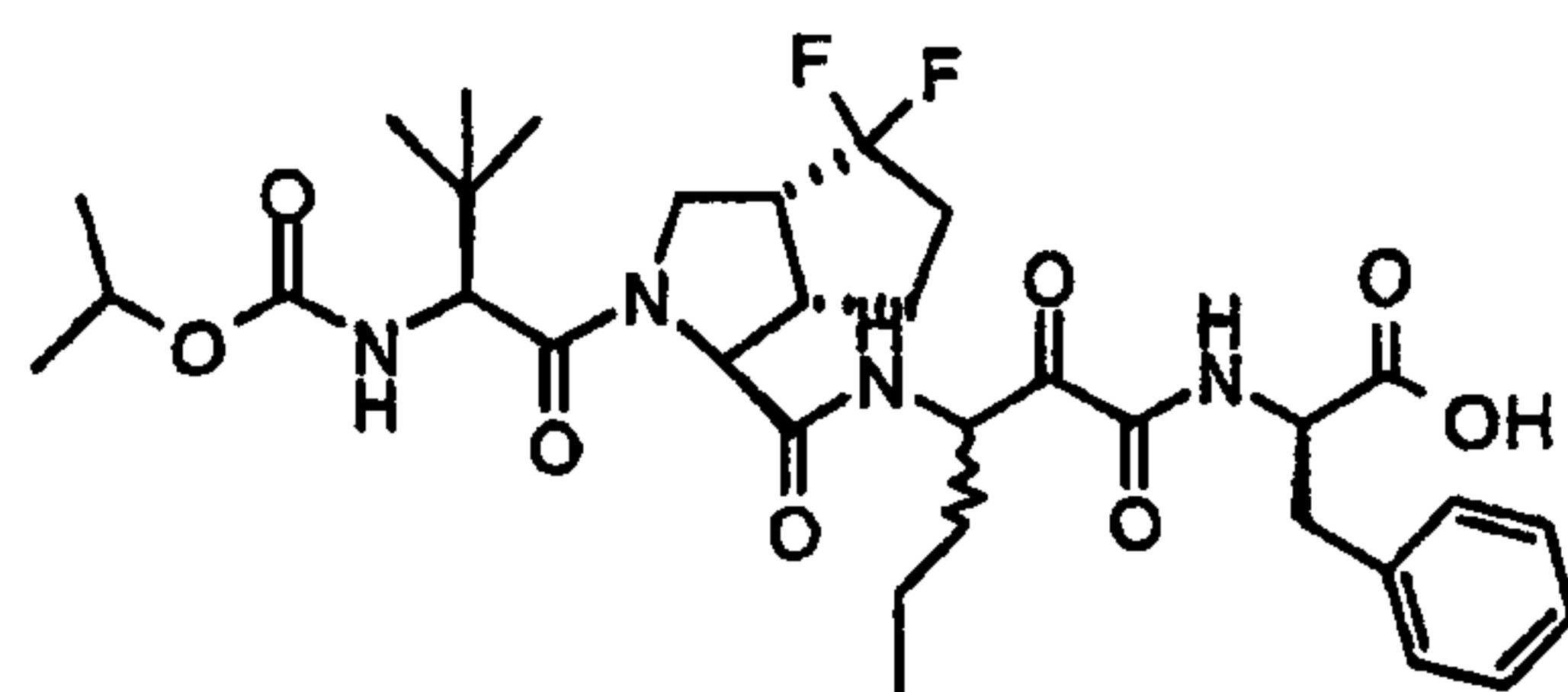
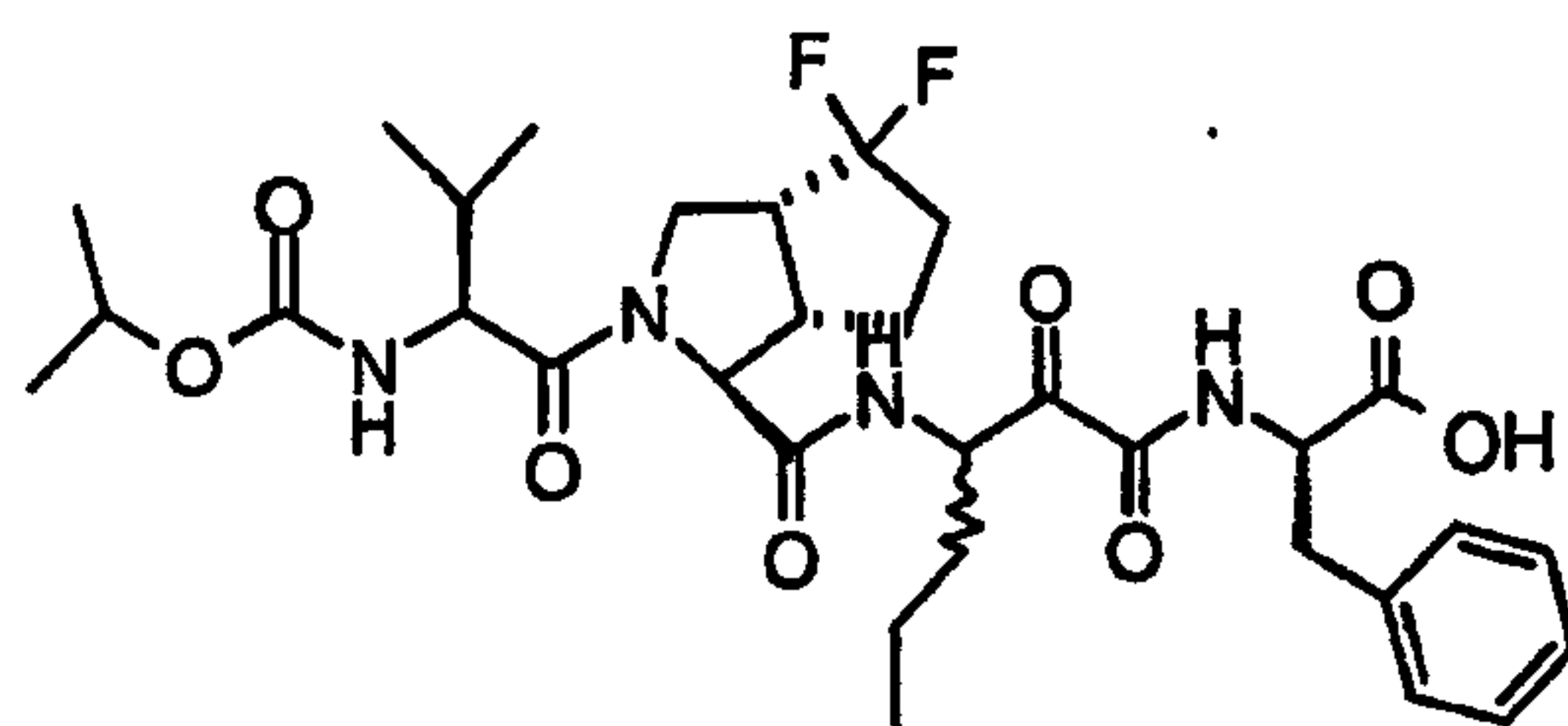
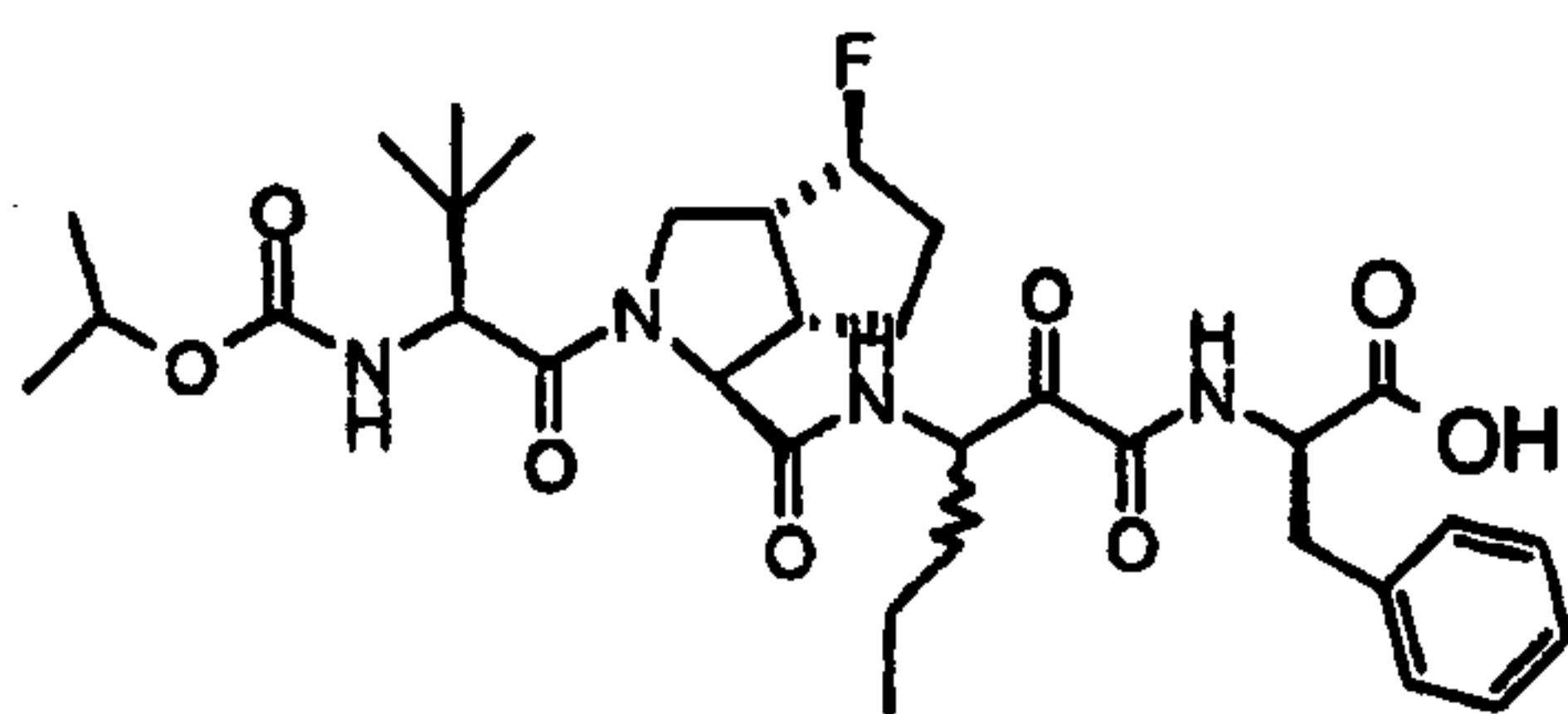
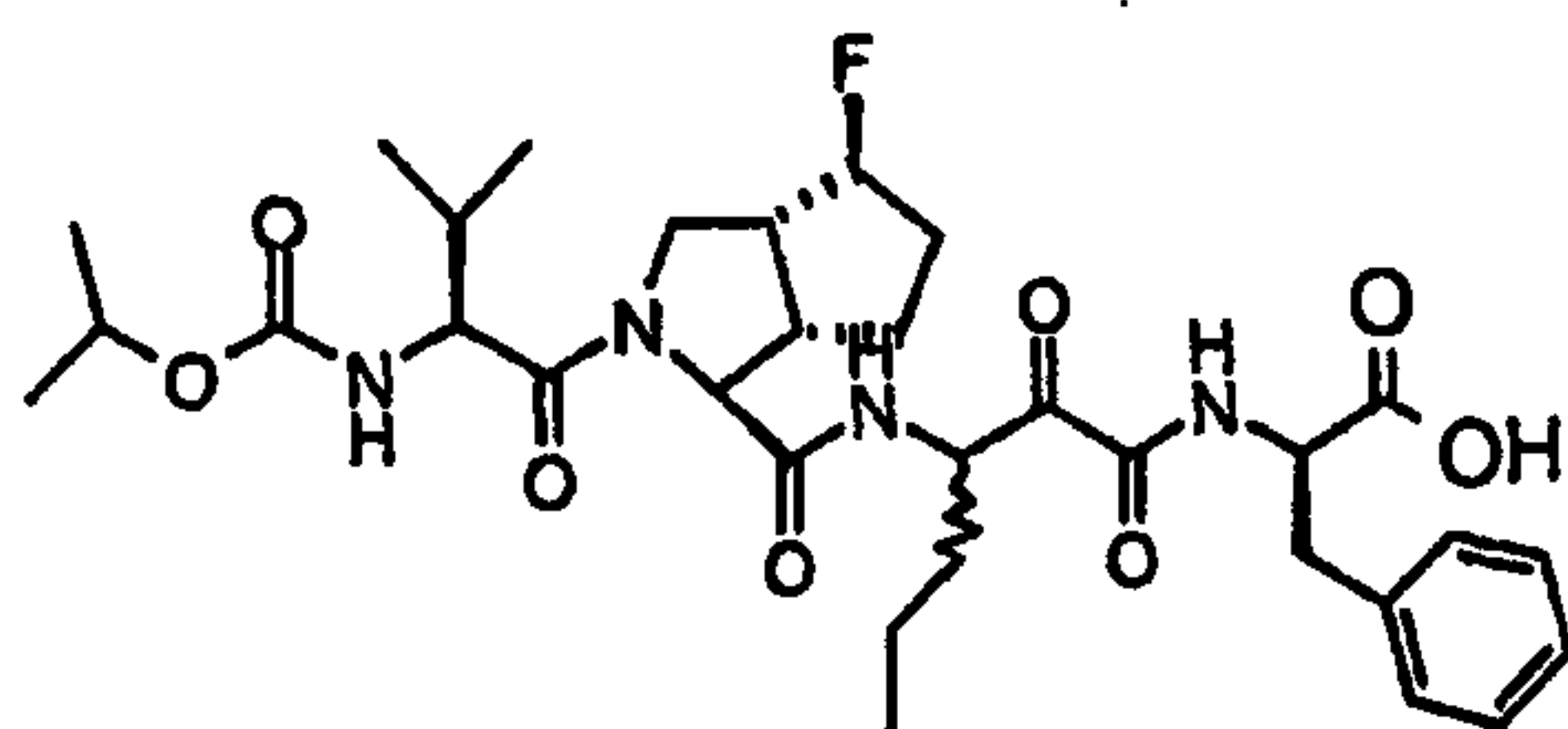
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Following the above method and using the appropriate starting materials, the following consecutive compounds AS-BG are prepared:

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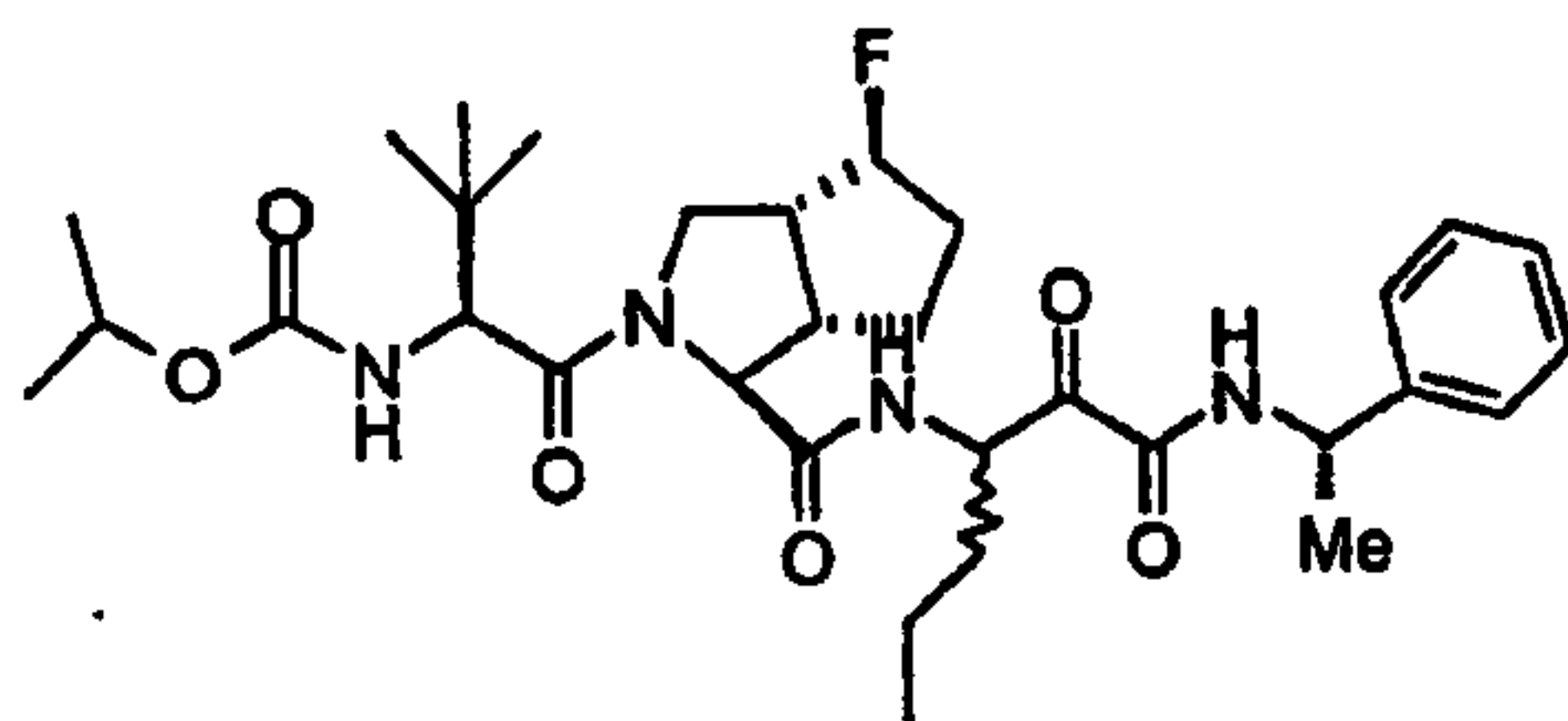
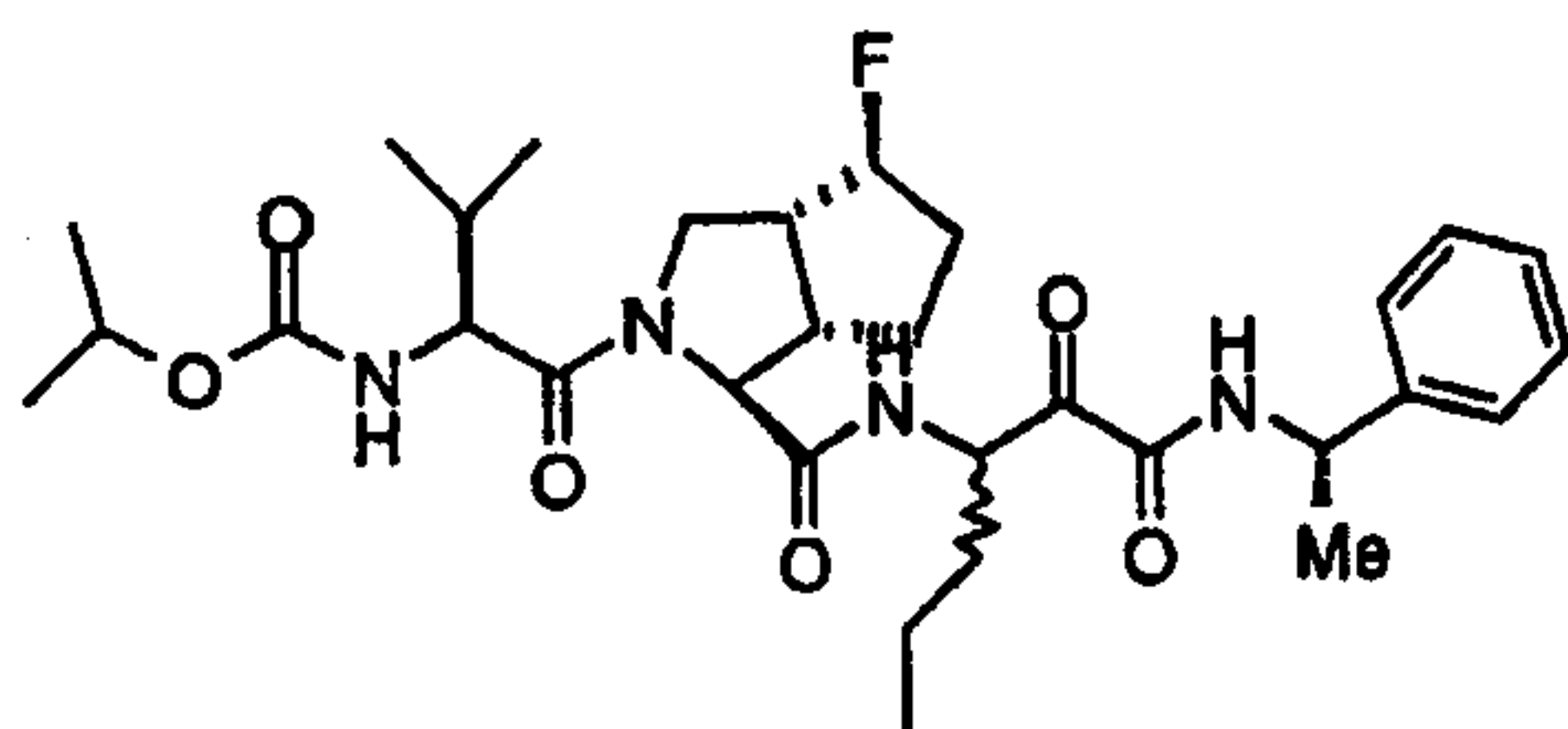
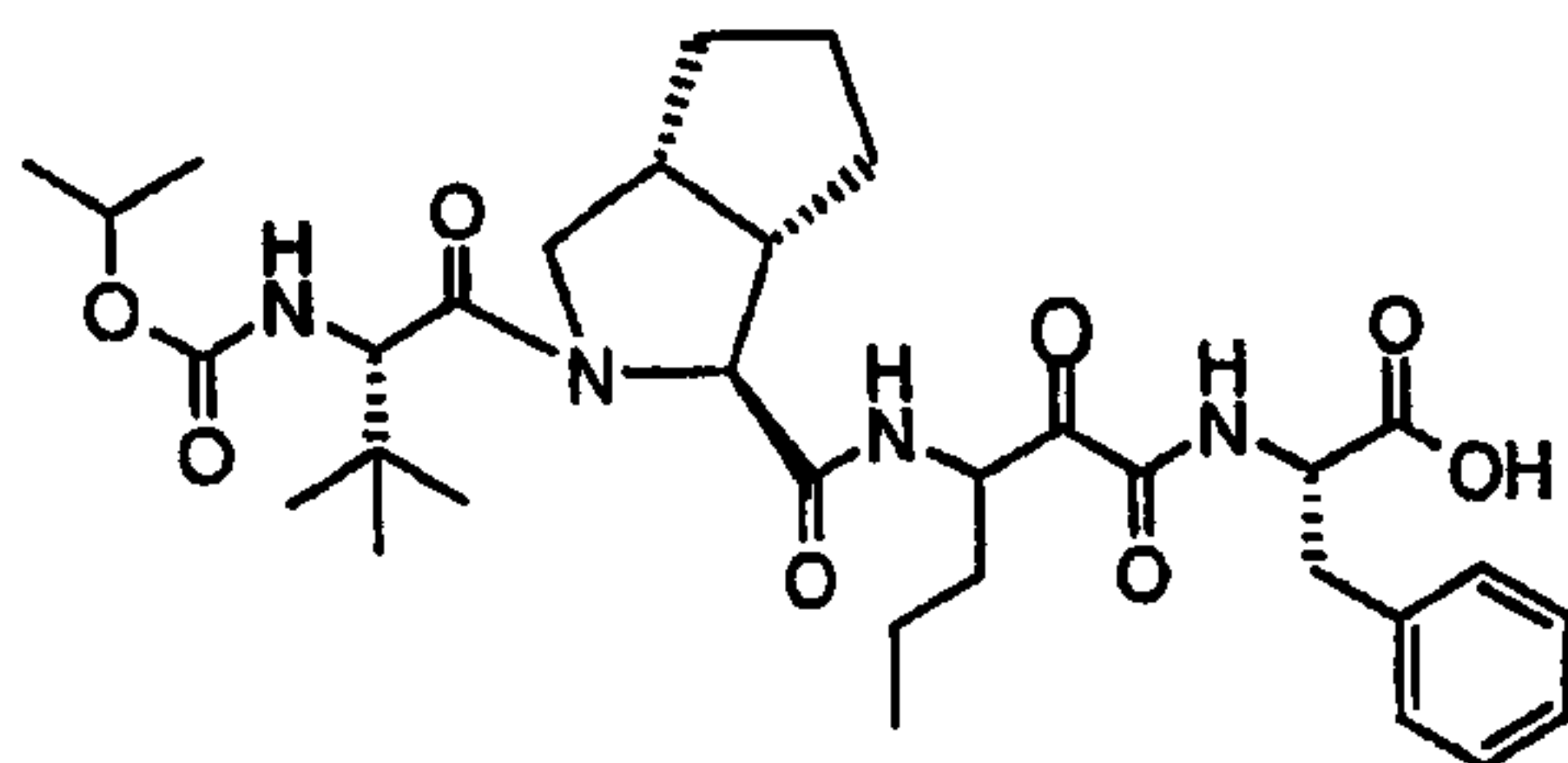
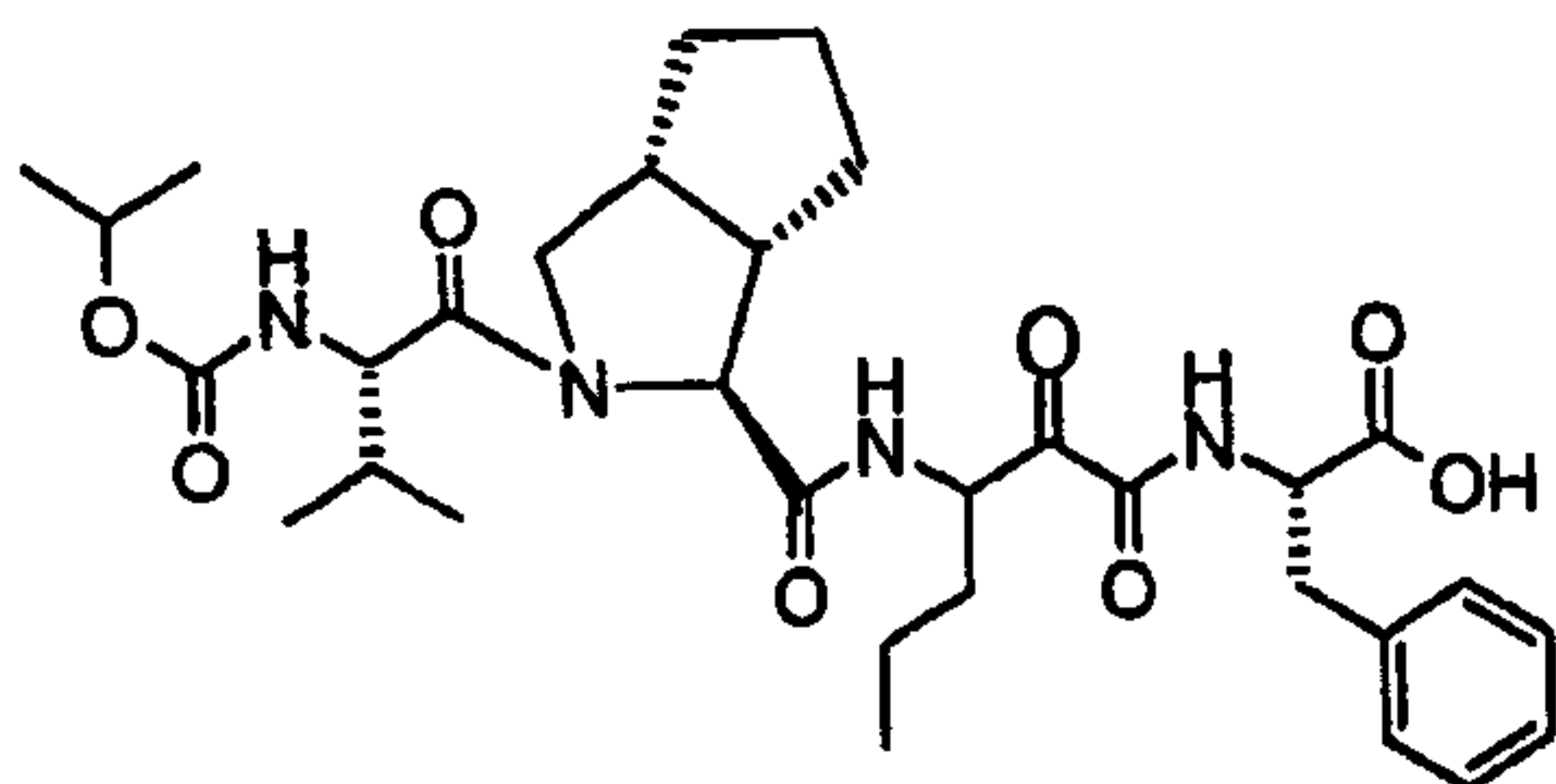
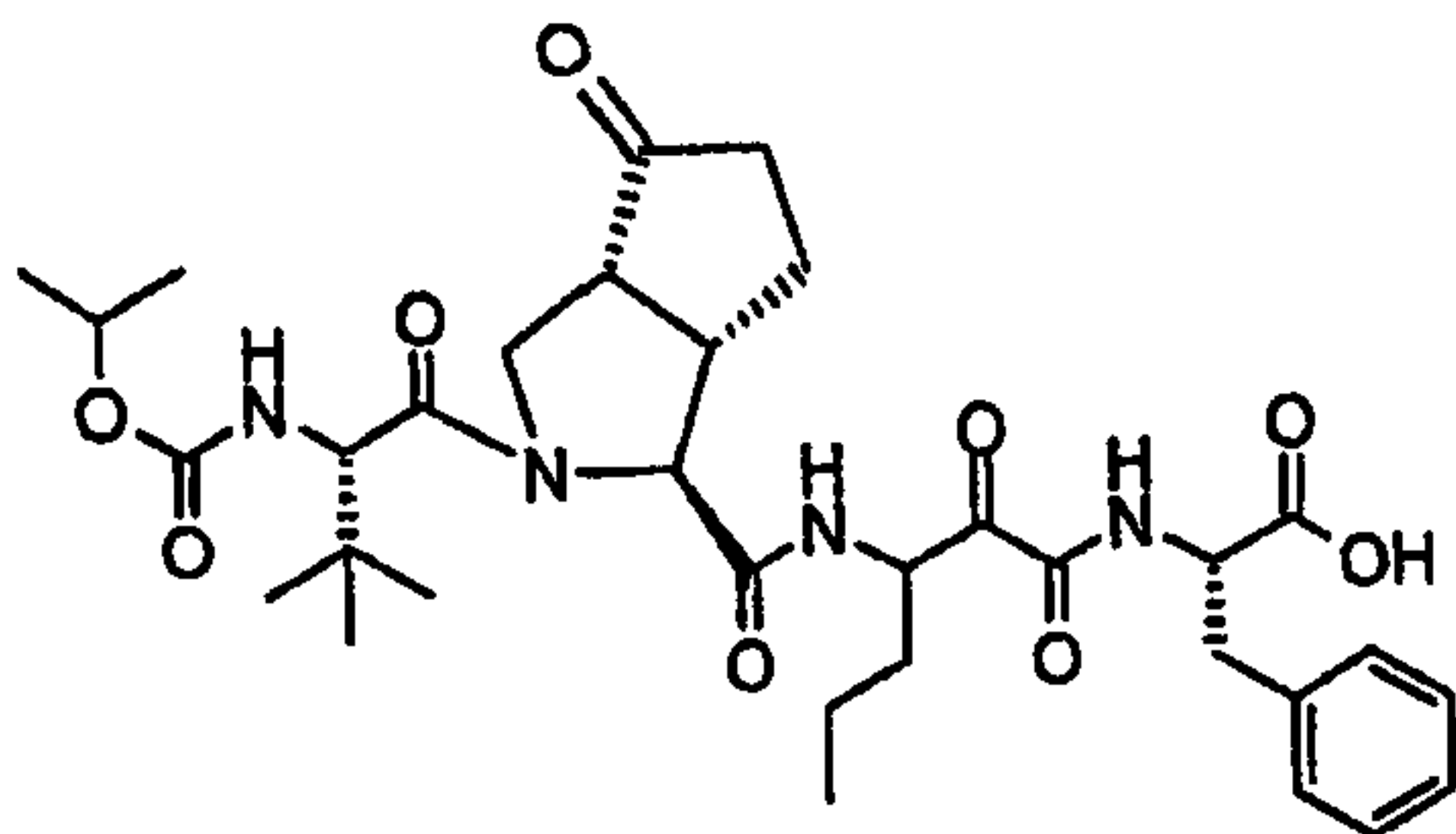


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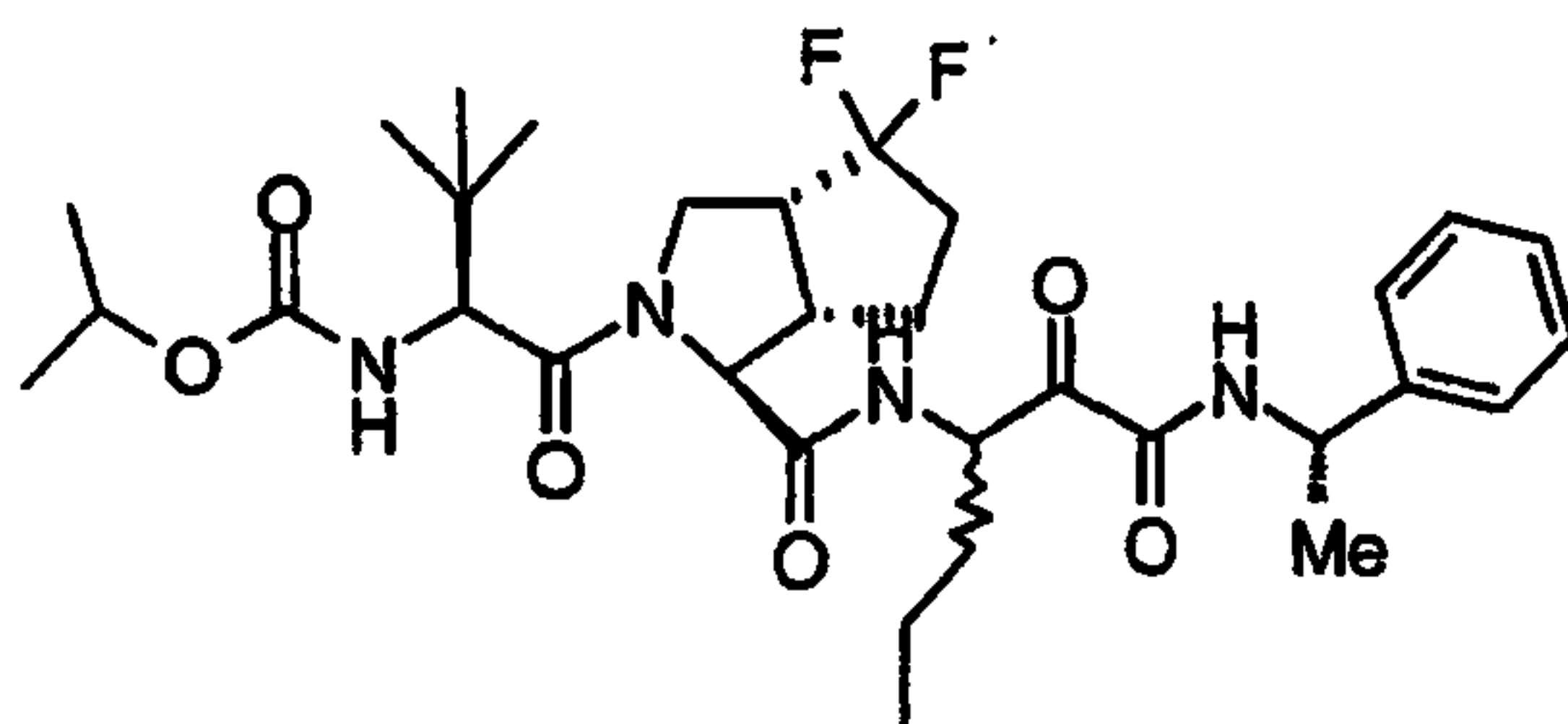
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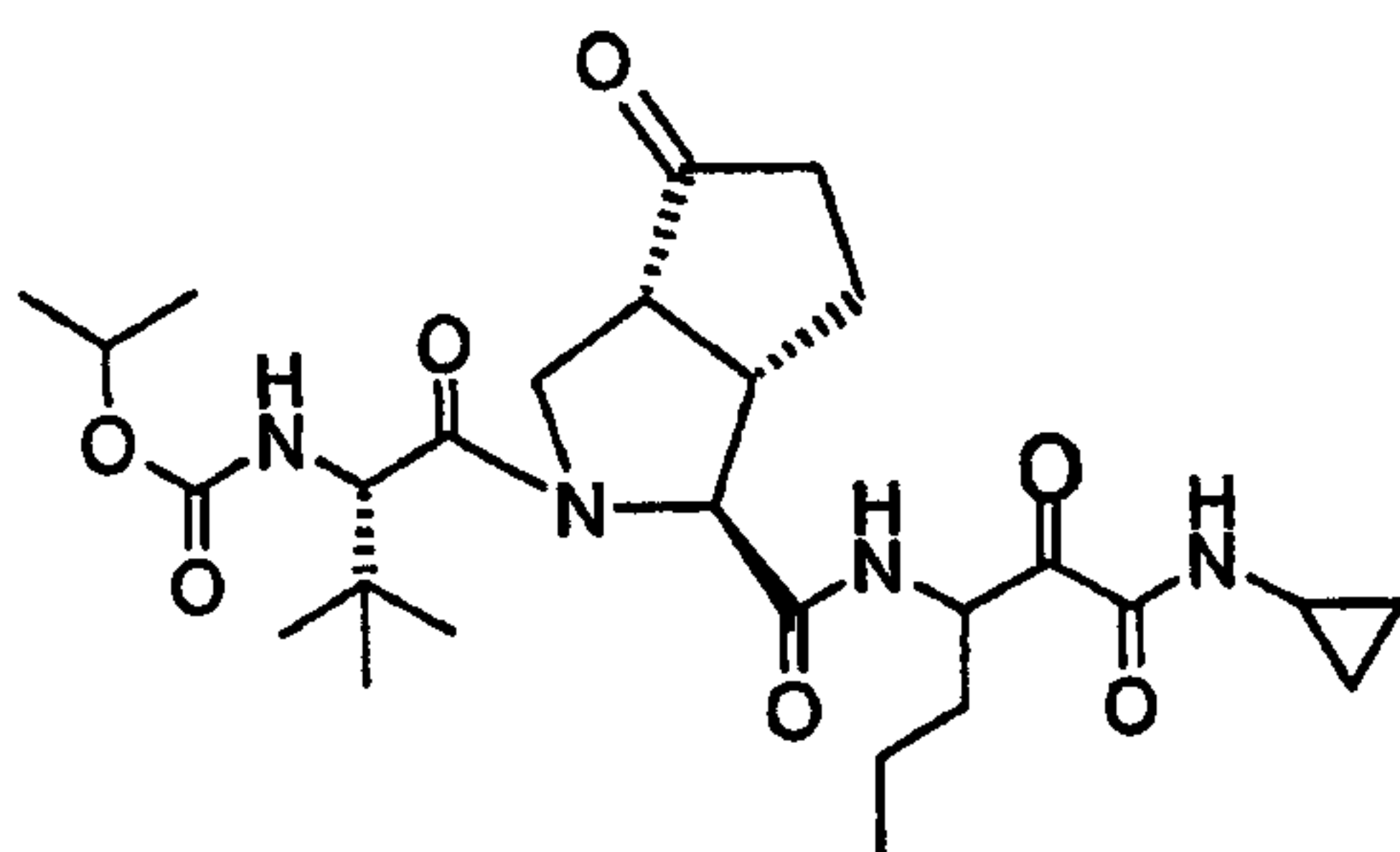
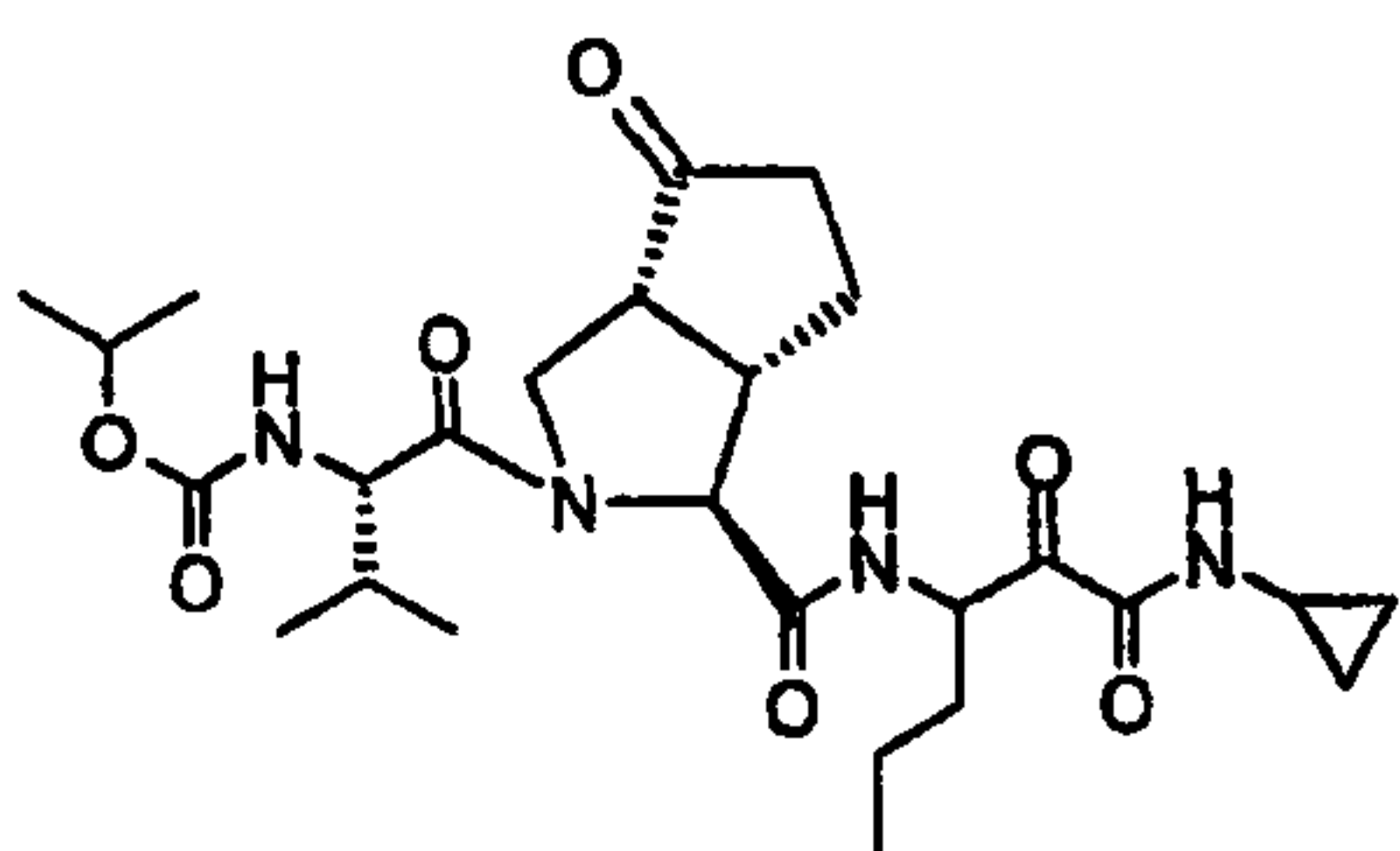
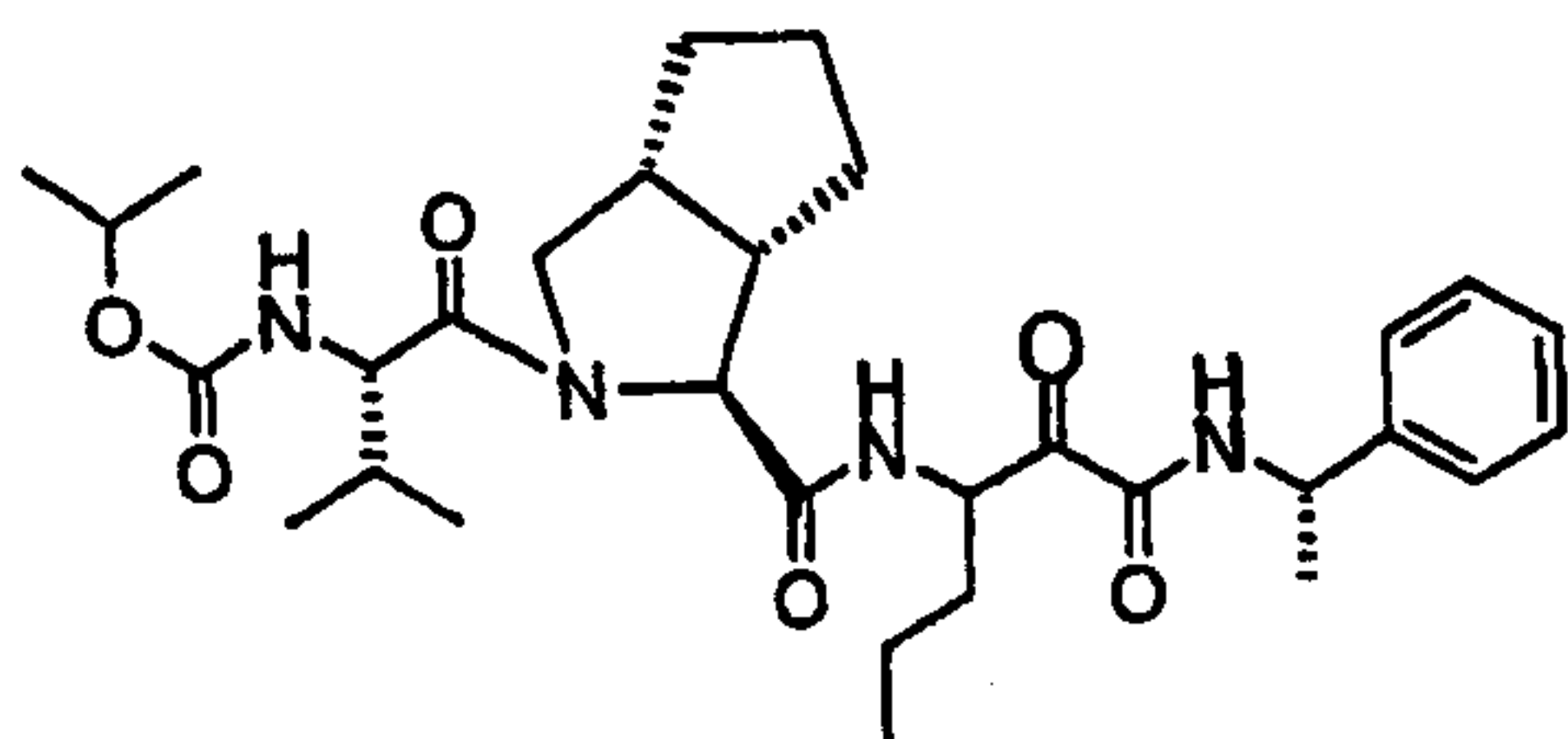
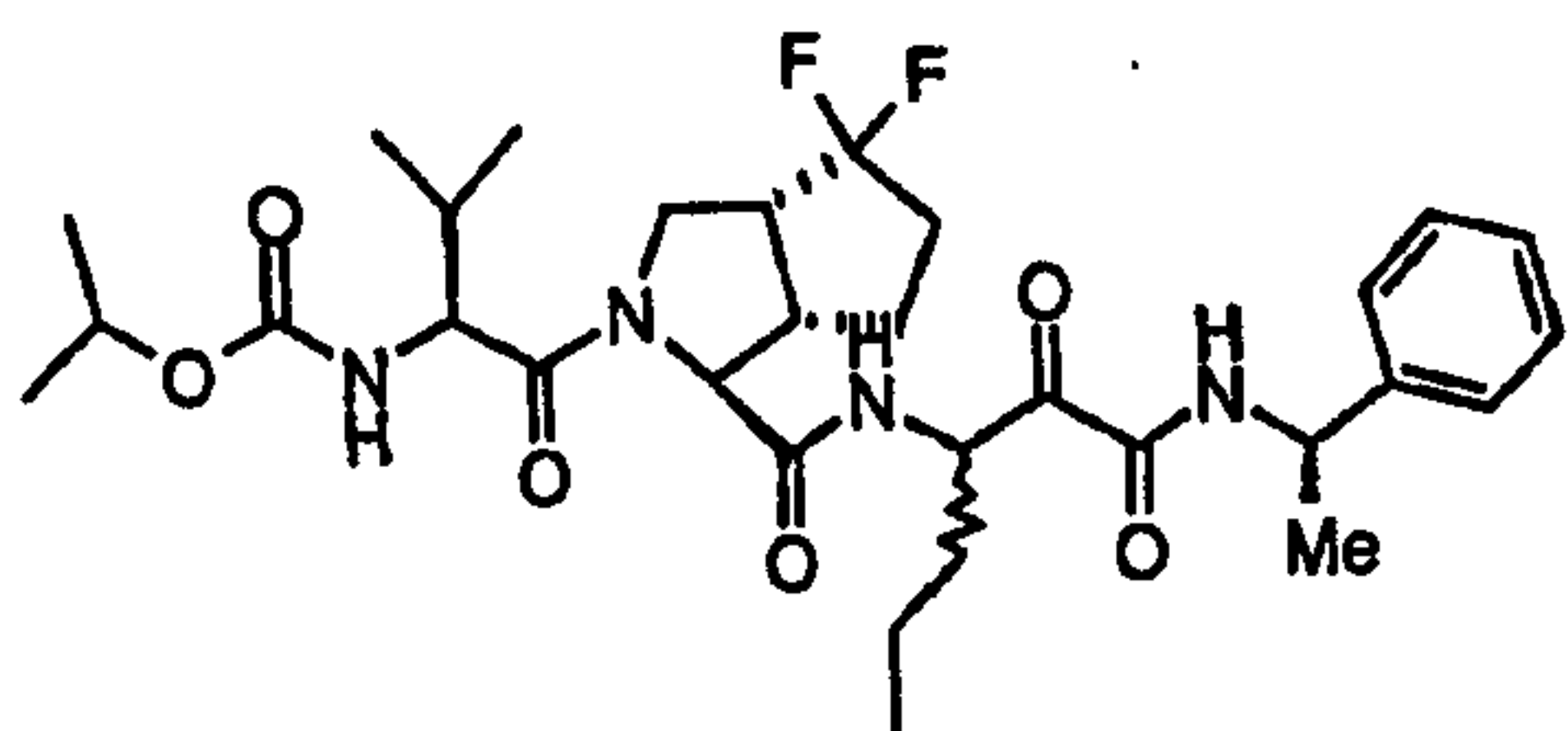
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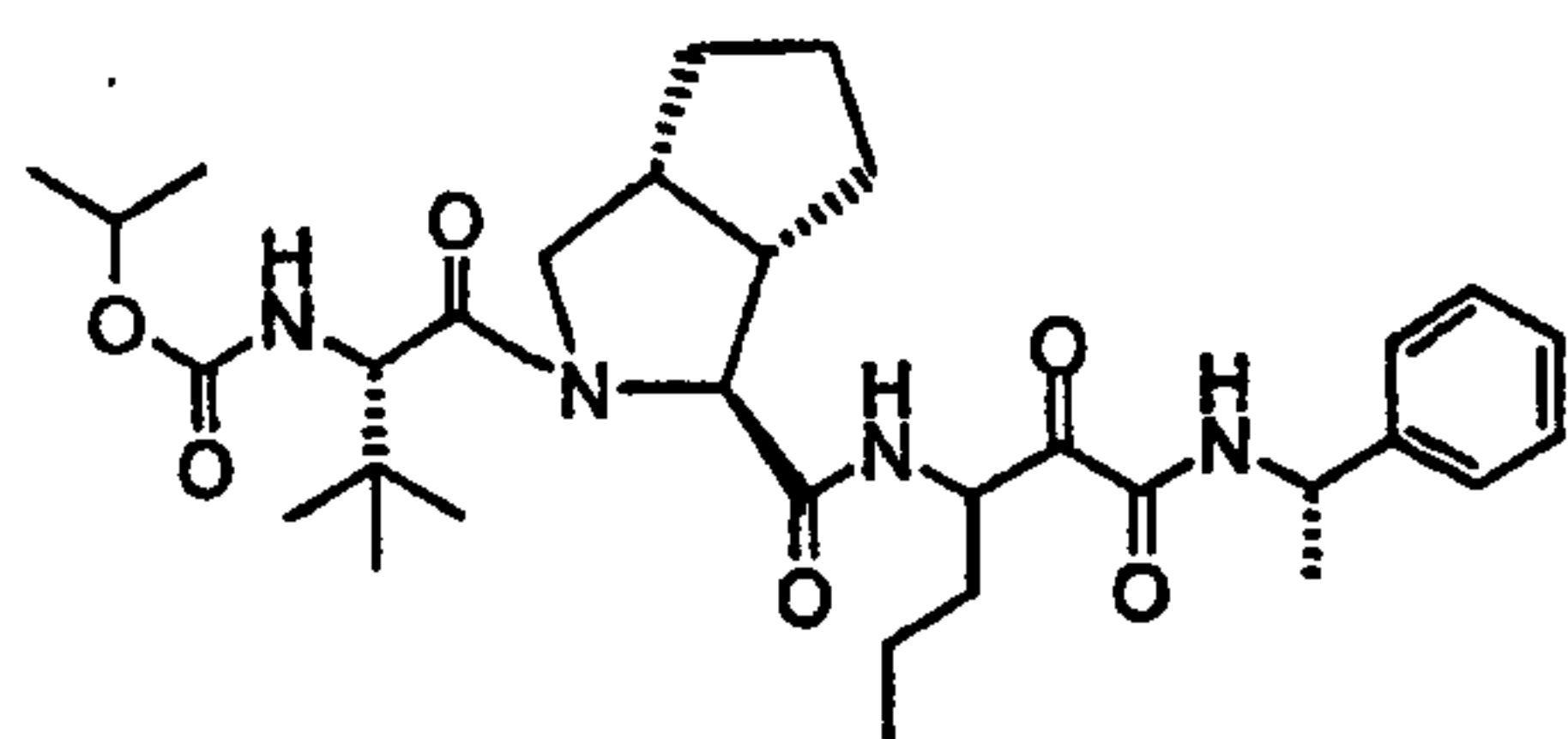
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10 Example 14 – Compounds BH-BS:

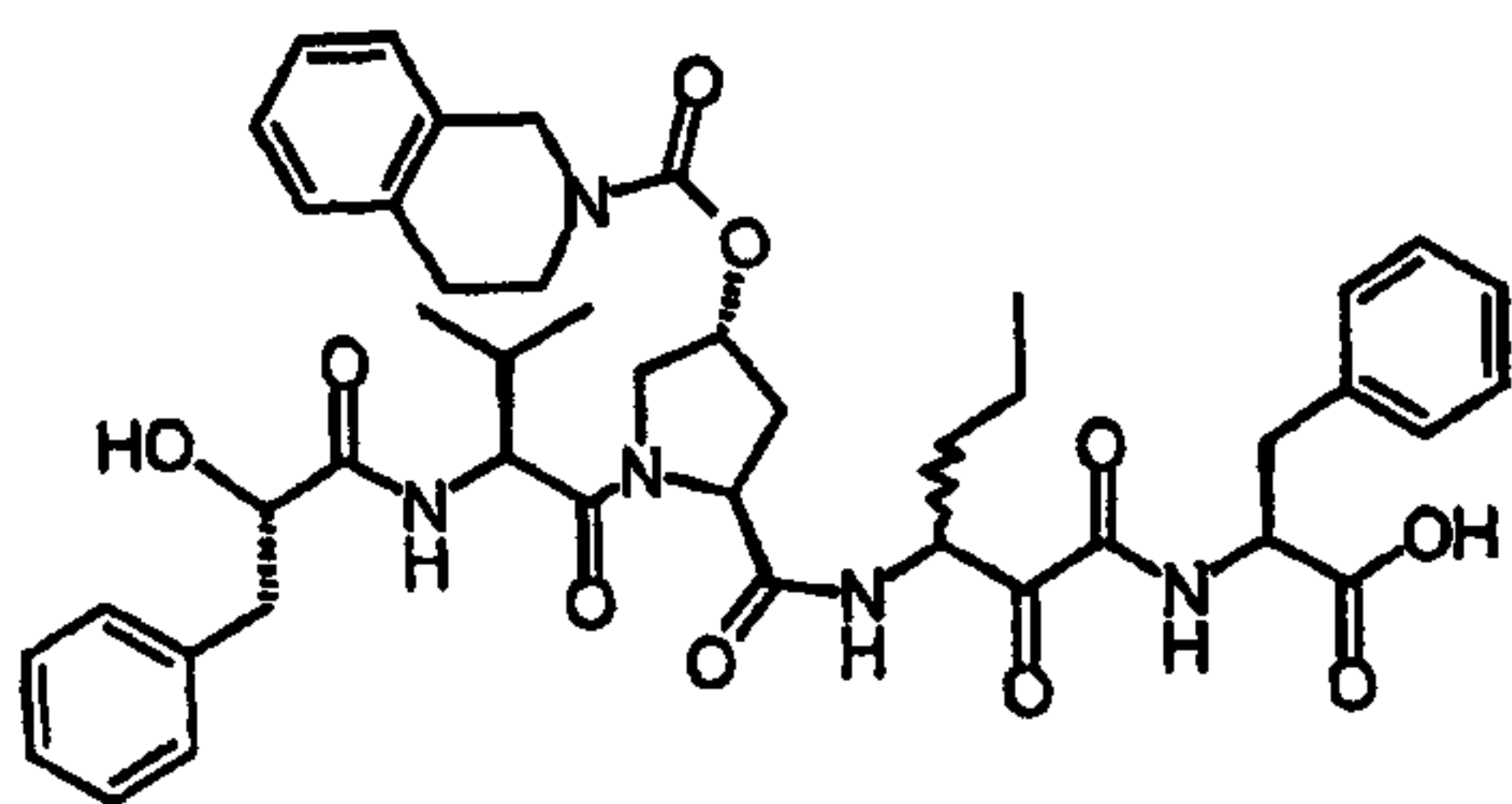
Compound lxxiii (150 mg, 0.15 mmol) is taken up in DCM (3 mL). To this solution is added TFA (1.5 mL). The resulting solution is stirred overnight. At this point, the reaction is

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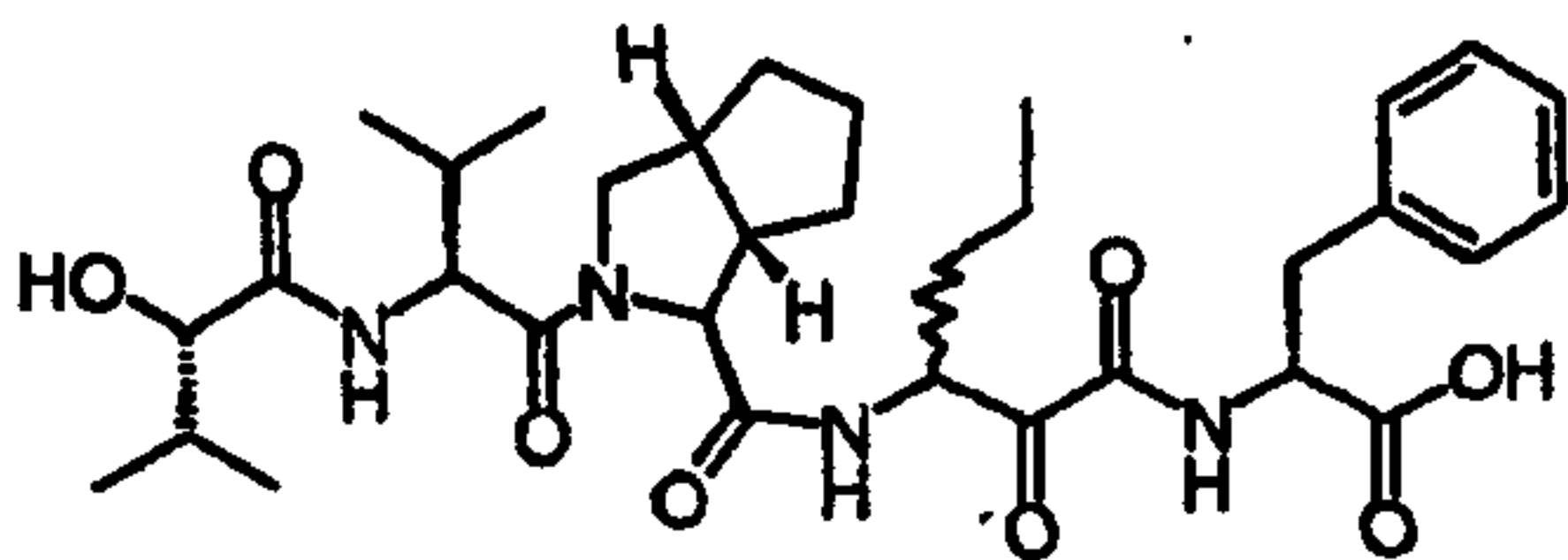
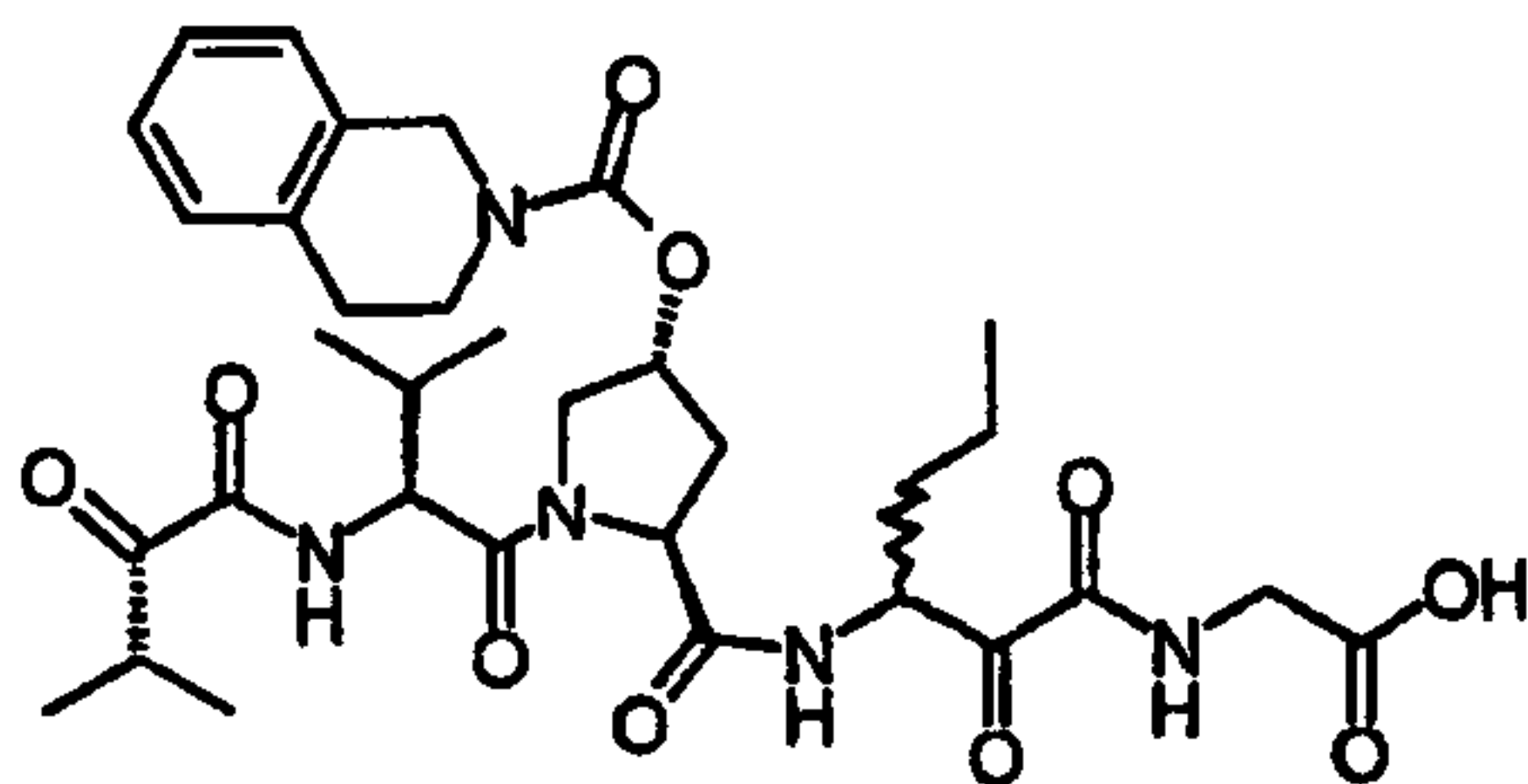
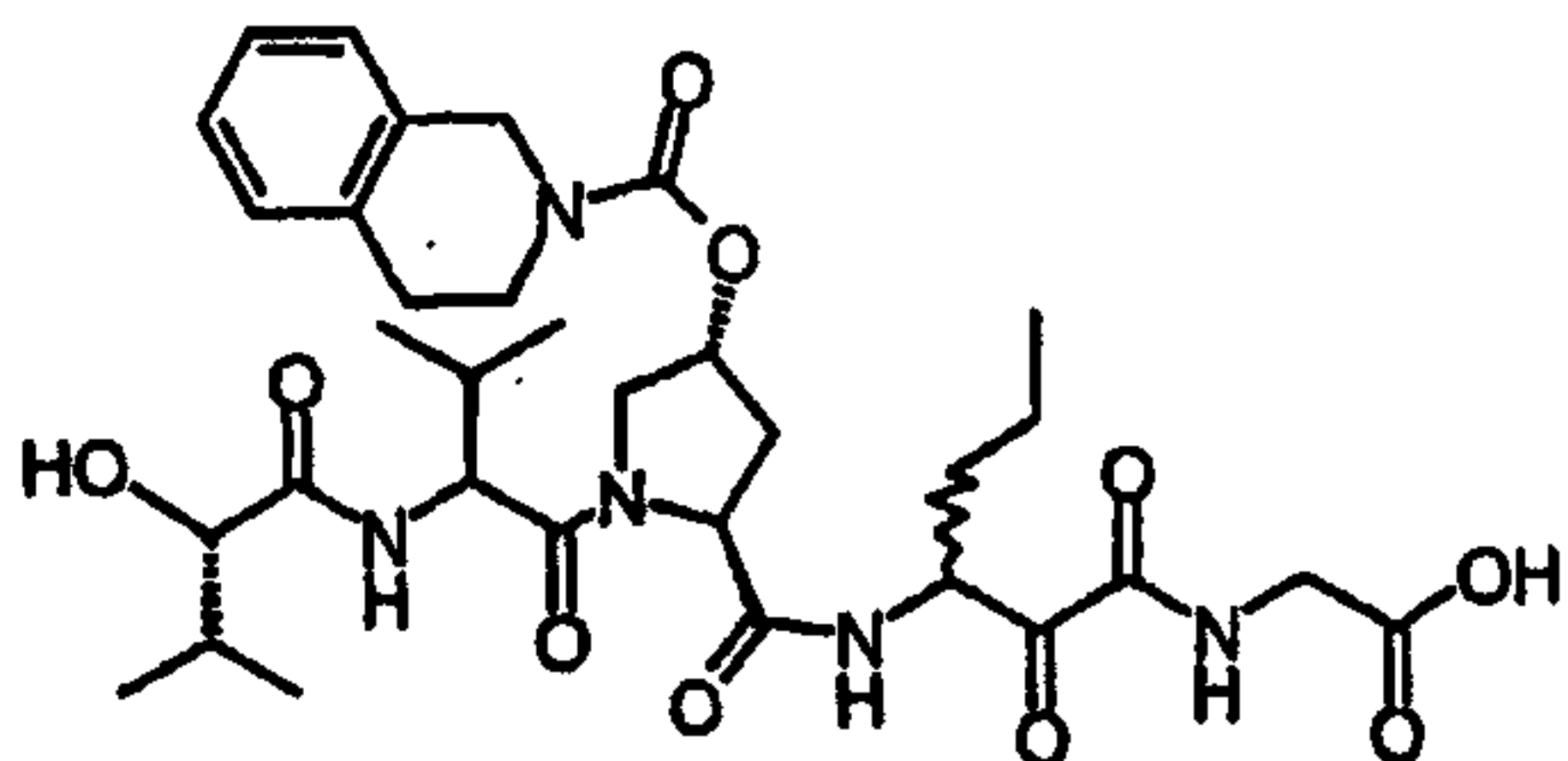
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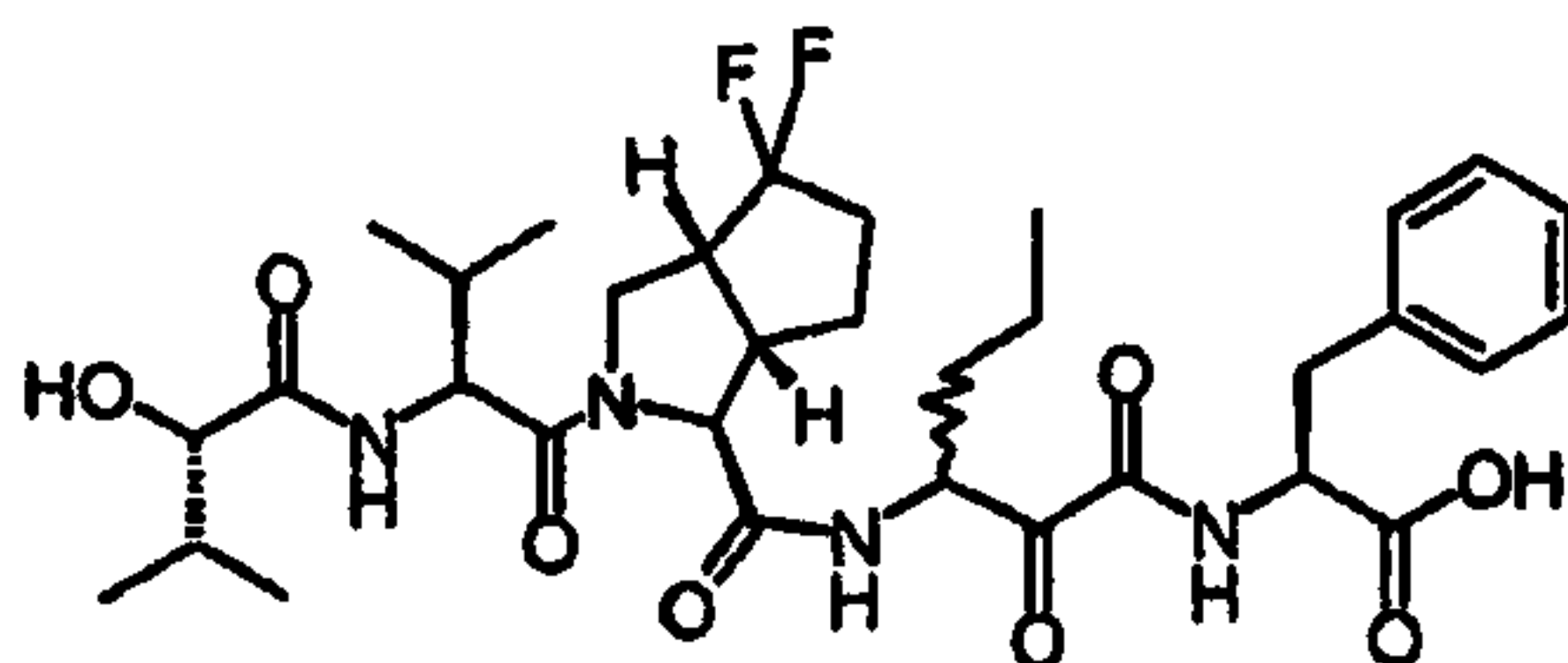
concentrated *in vacuo* to give a residue. The residue is purified by reverse phase HPLC and lyophilized to give 60 mg (50%) of compound BH,



- 5 Following the above method and using the appropriate starting materials, the following consecutive compounds BI-BS are prepared:



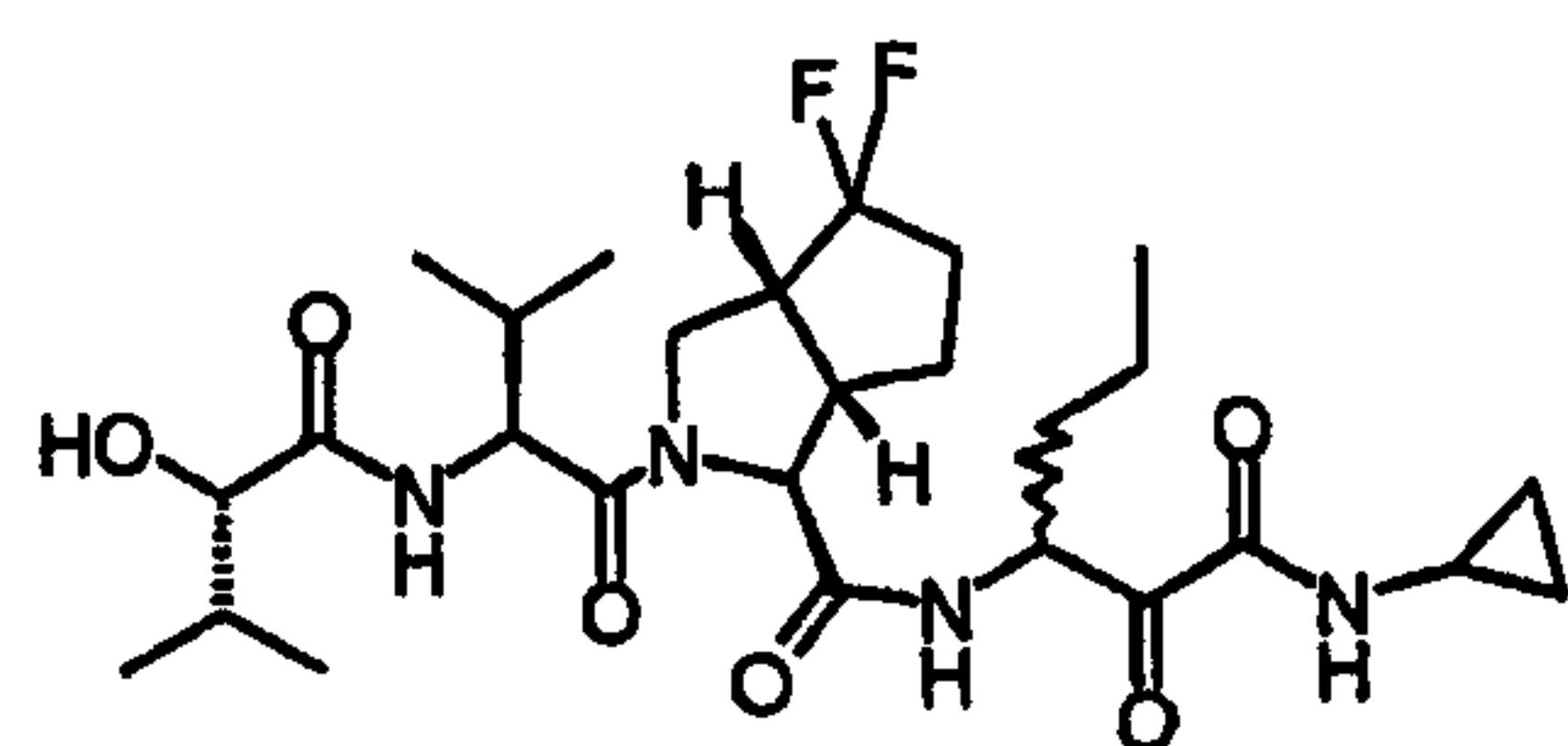
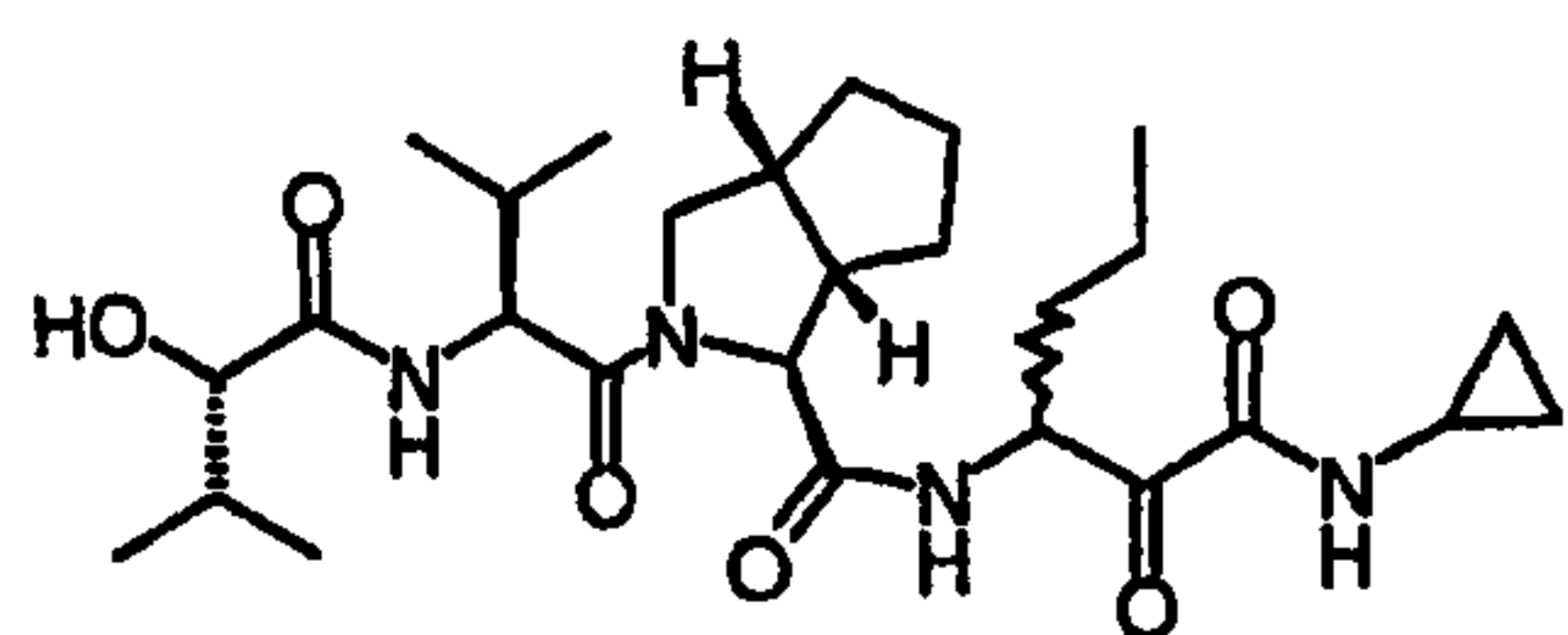
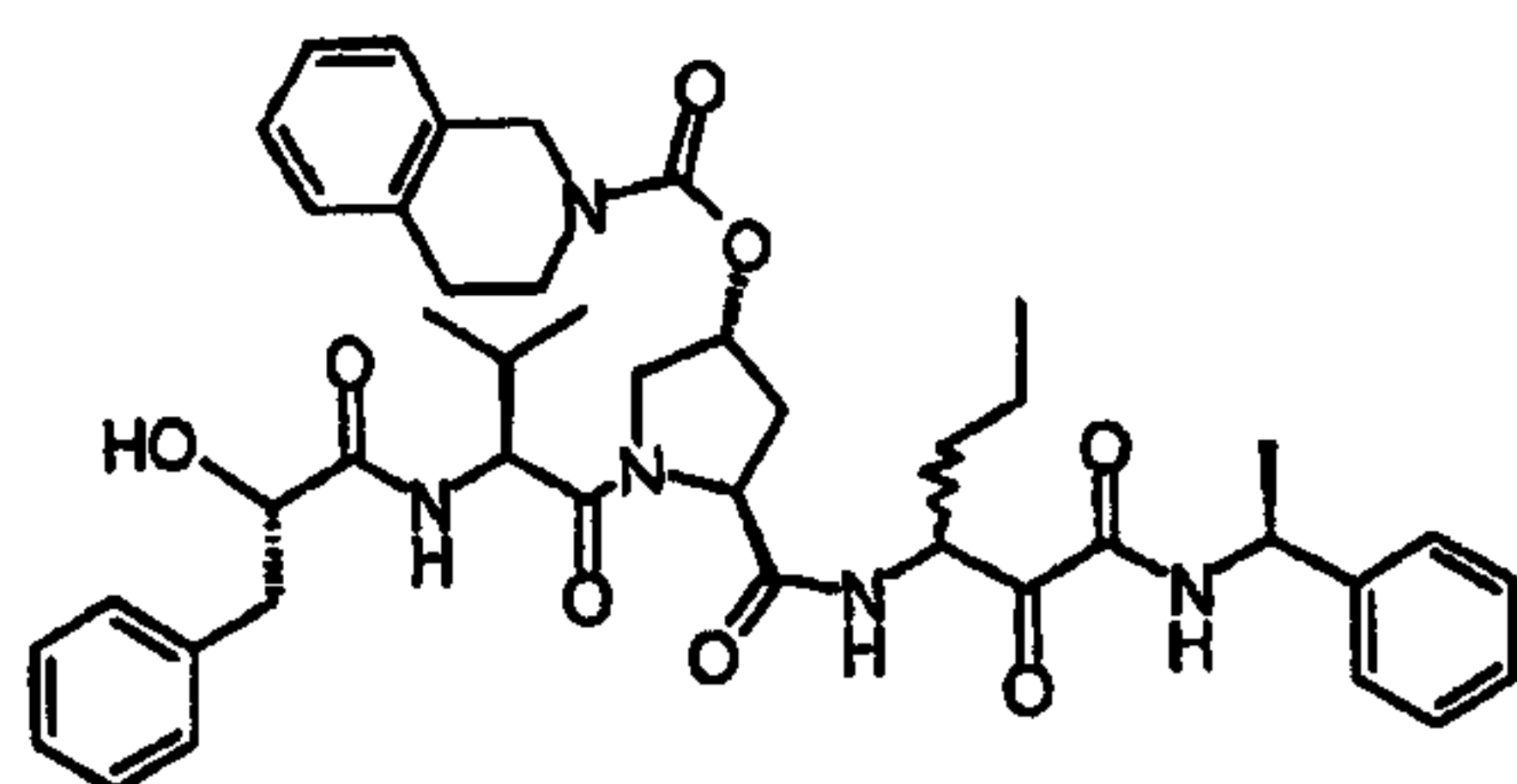
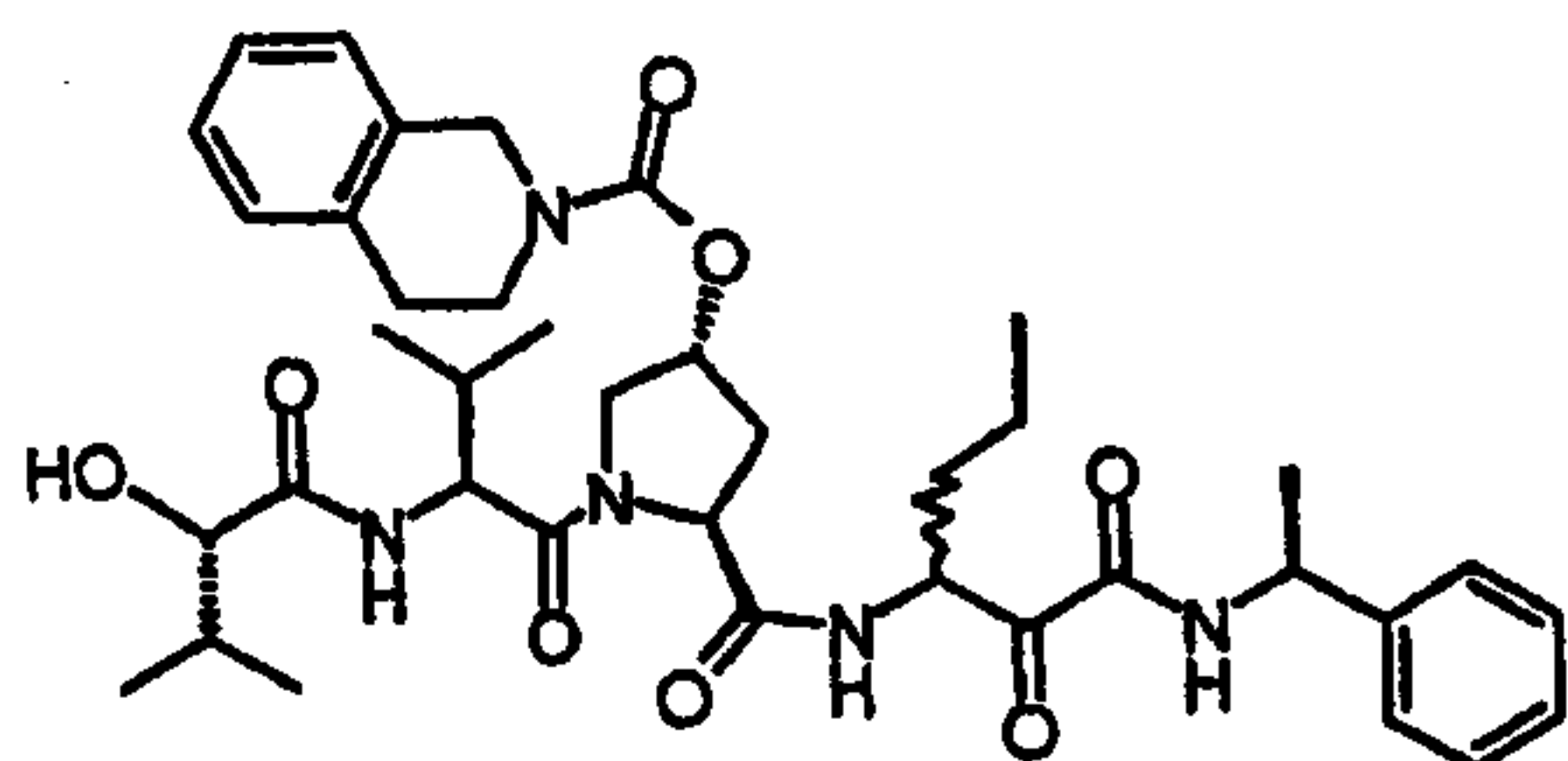
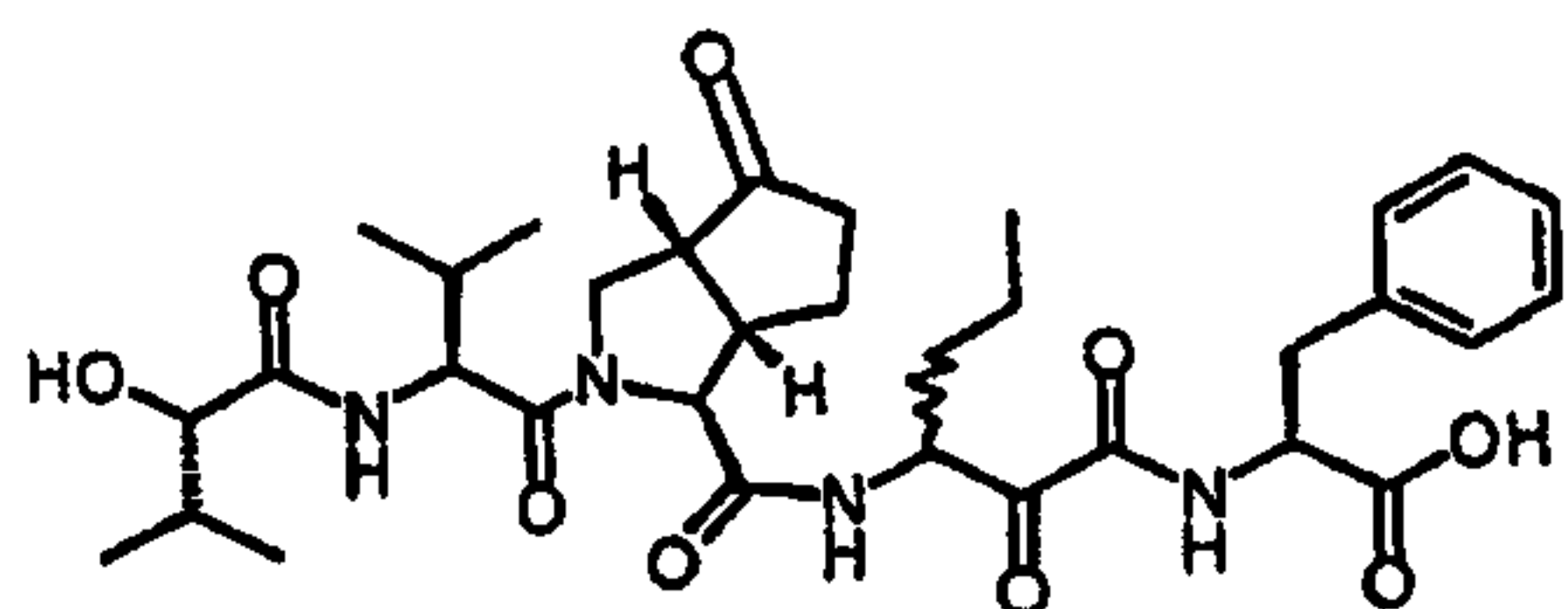
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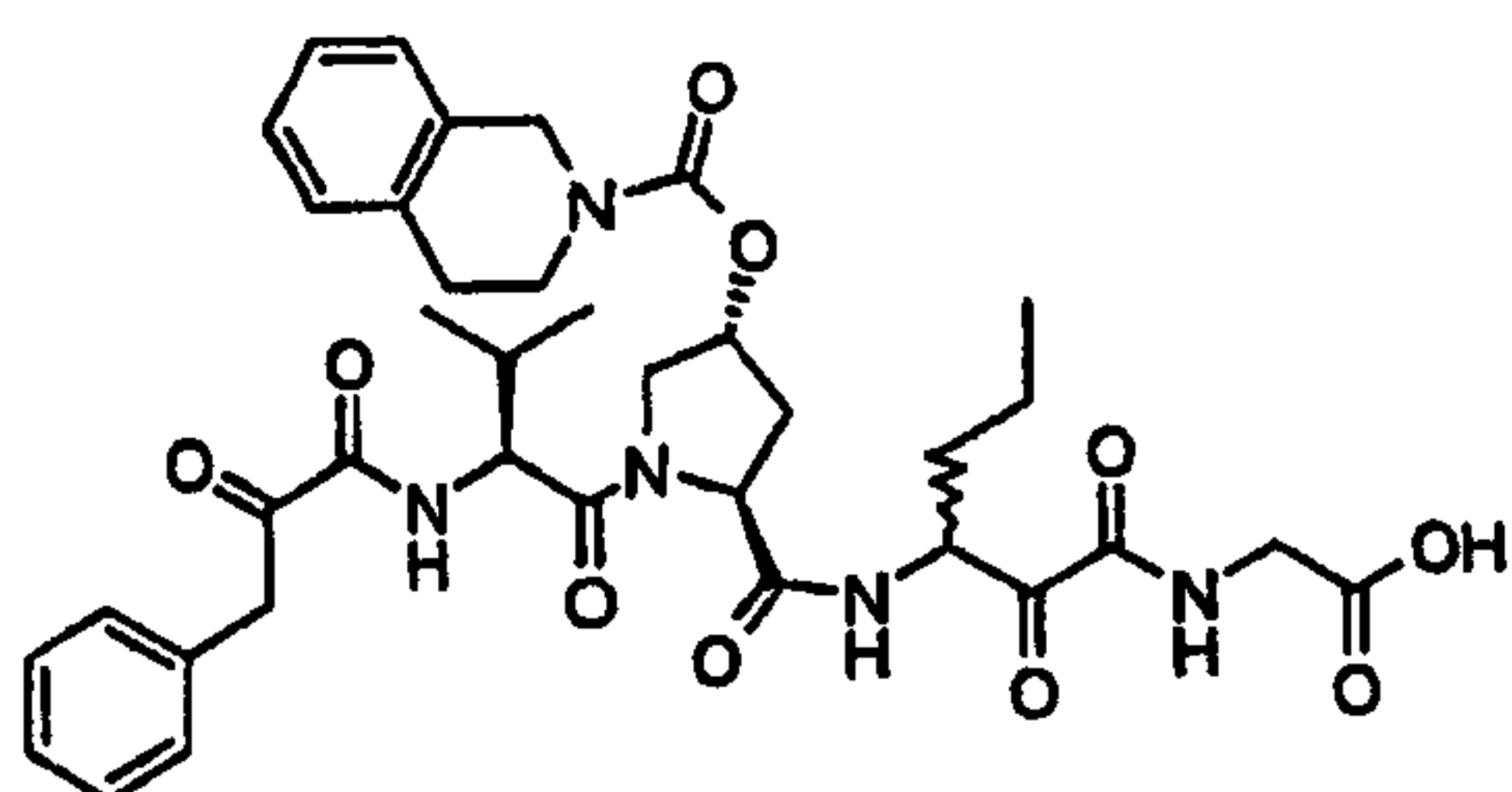
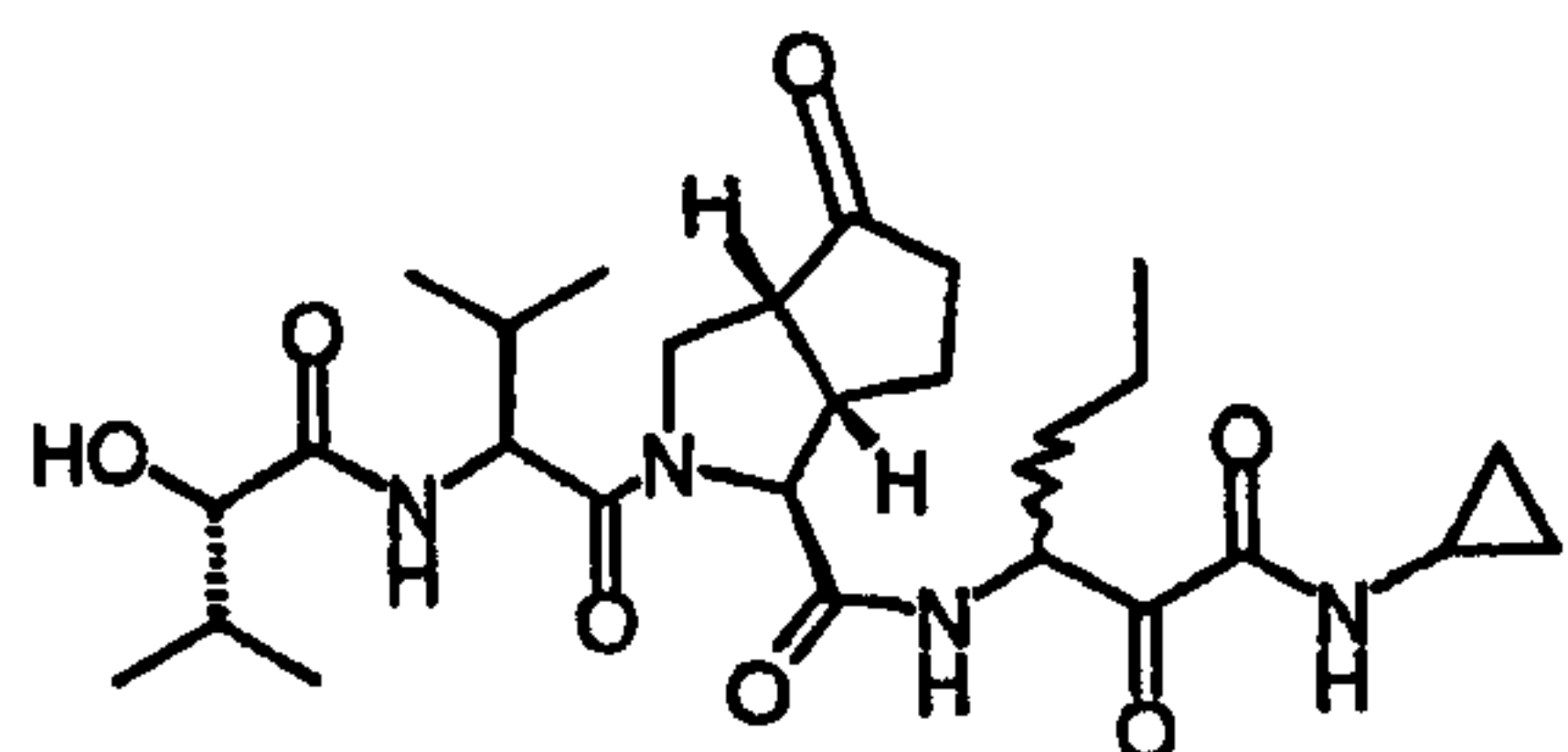
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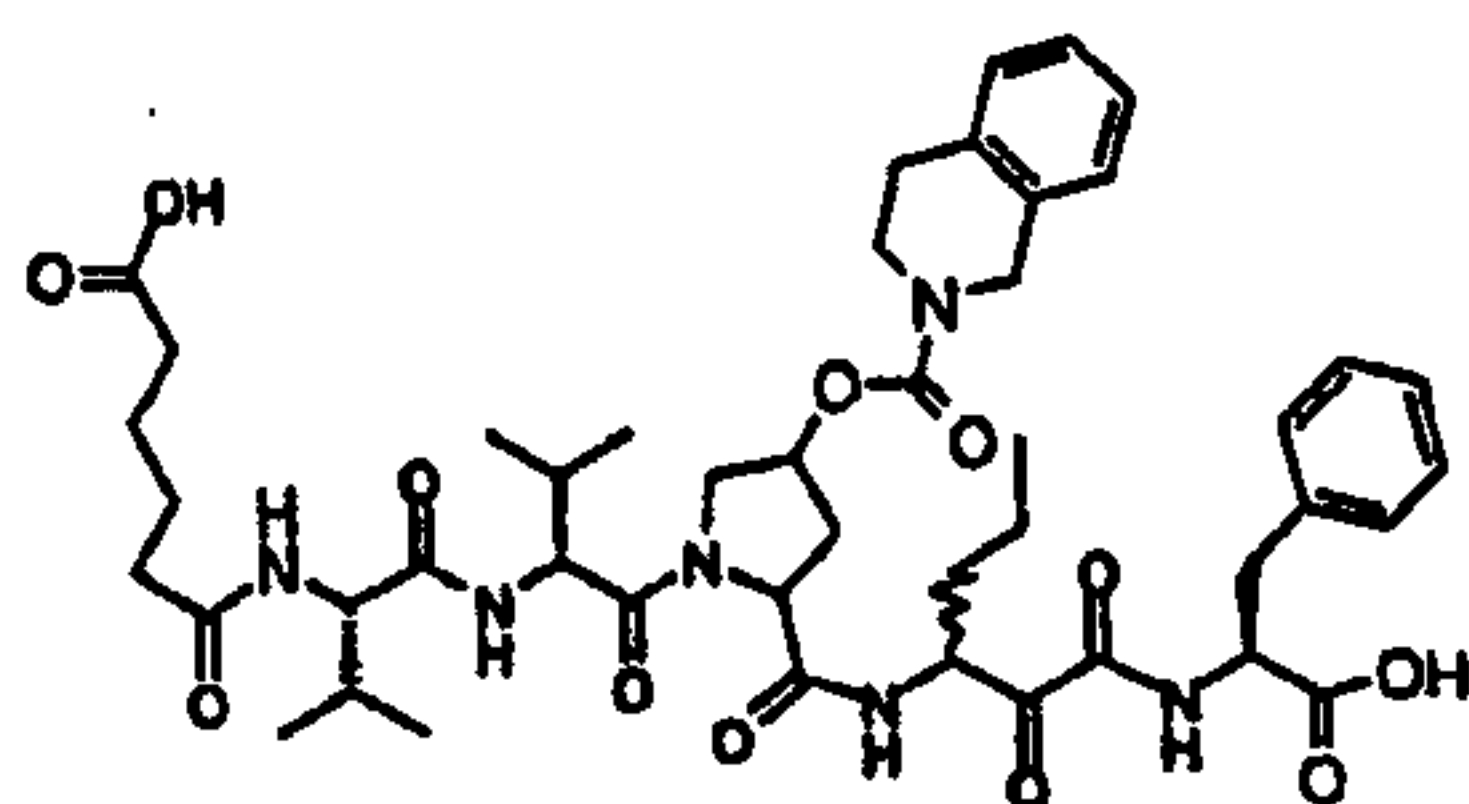
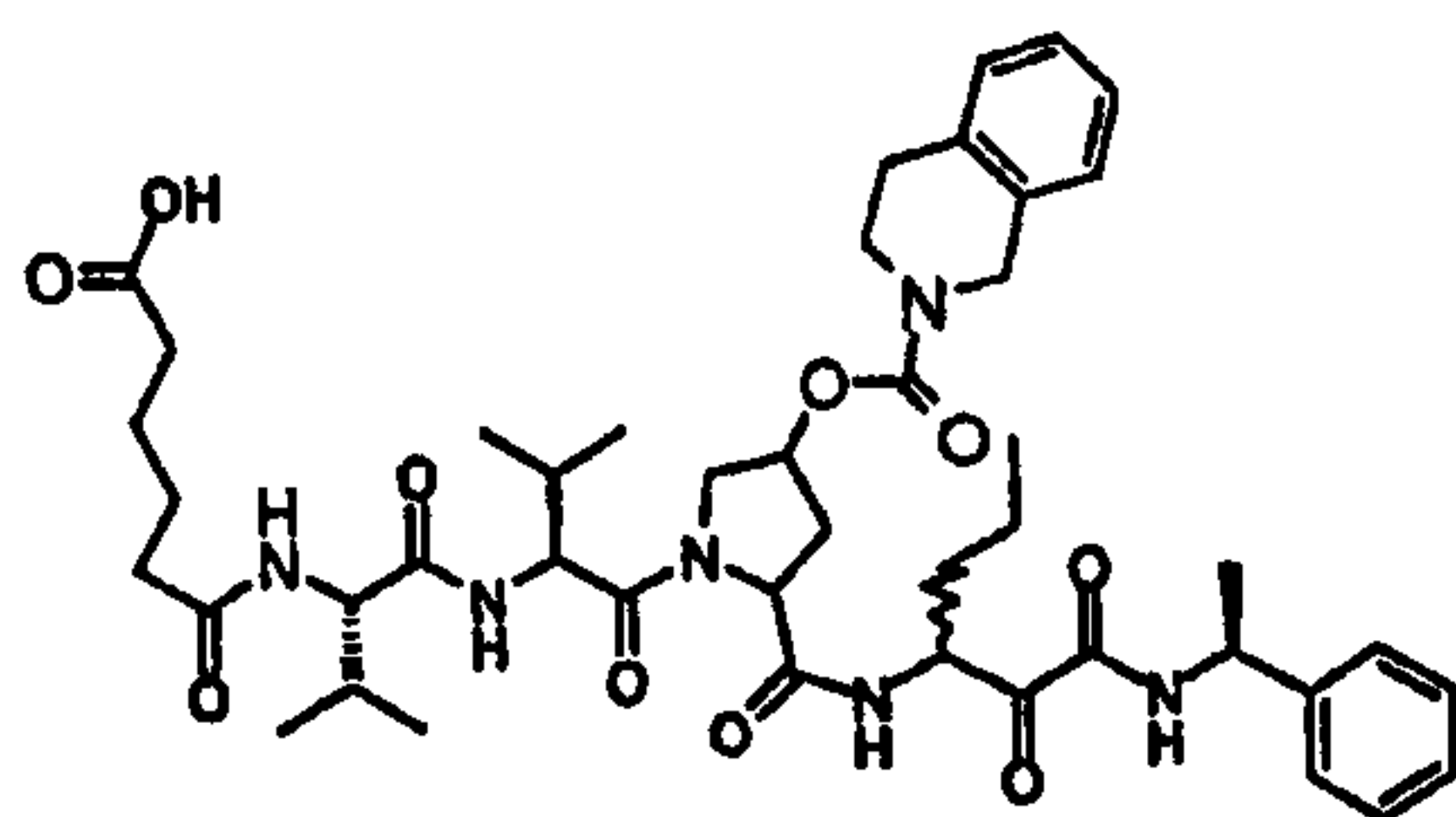


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Example 15 – Compounds BT-BU:

Following the method of Example 12 and using the appropriate starting materials, the following consecutive compounds BT-BU are prepared:

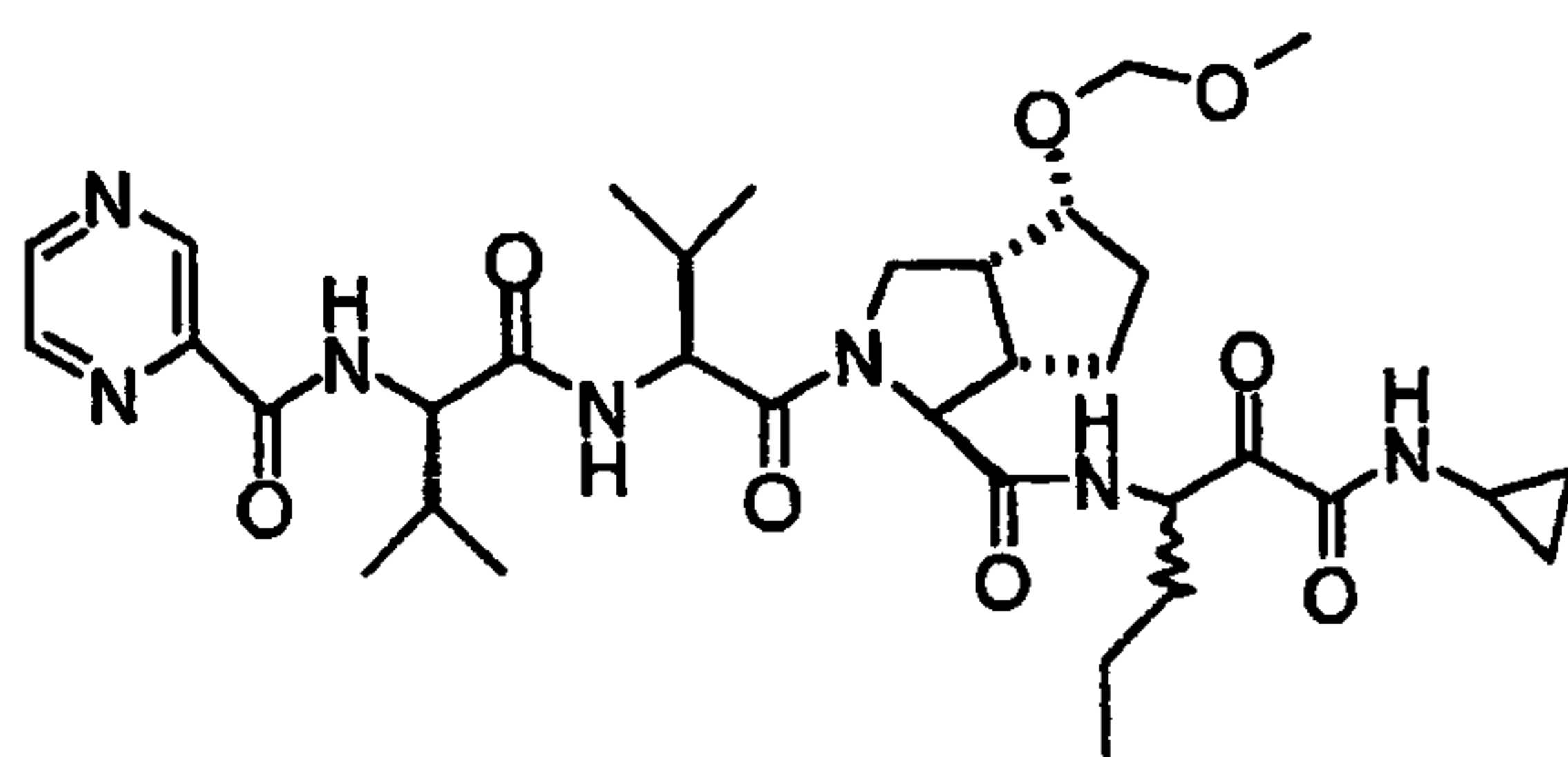


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Example 16 – Compound BV:

To a dichloromethane solution (4.2 mL) of compound lxxvii (143 mg, 0.21 mmol) is added DMP reagent reagent (165 mg, 0.39 mmol). The reaction is stirred at about room temperature for 2 hours and quenched with 10% Na₂SO₃ (aq.) for 20 minutes. The resulting mixture is extracted with EtOAc. The organic layer is washed with brine, dried over MgSO₄ and concentrated to a yellow oil. Purification by silica gel chromatography (5% EtOH/EtOAc) yielded 124 mg (79%) of compound BV,

10



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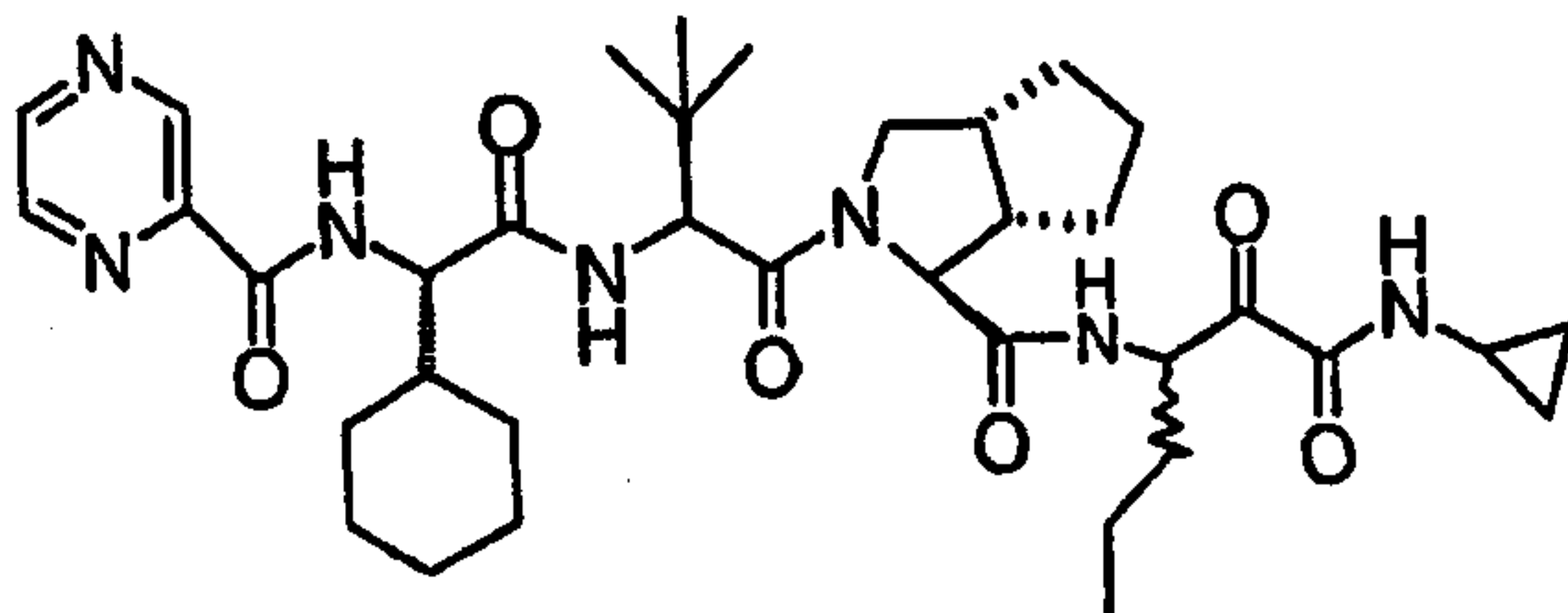
Example 17 – Compounds BW-CA:

To a dichloromethane solution (20 mL) of compound lxxxix (420 mg, 0.62 mmol) is added DMP reagent reagent (342 mg, 0.81 mmol). The reaction is stirred at about room temperature for 1 hour and quenched with 10% Na₂SO₃ for 20 minutes. The resulting mixture is then extracted with EtOAc. The organic layer is washed with brine, dried and concentrated in

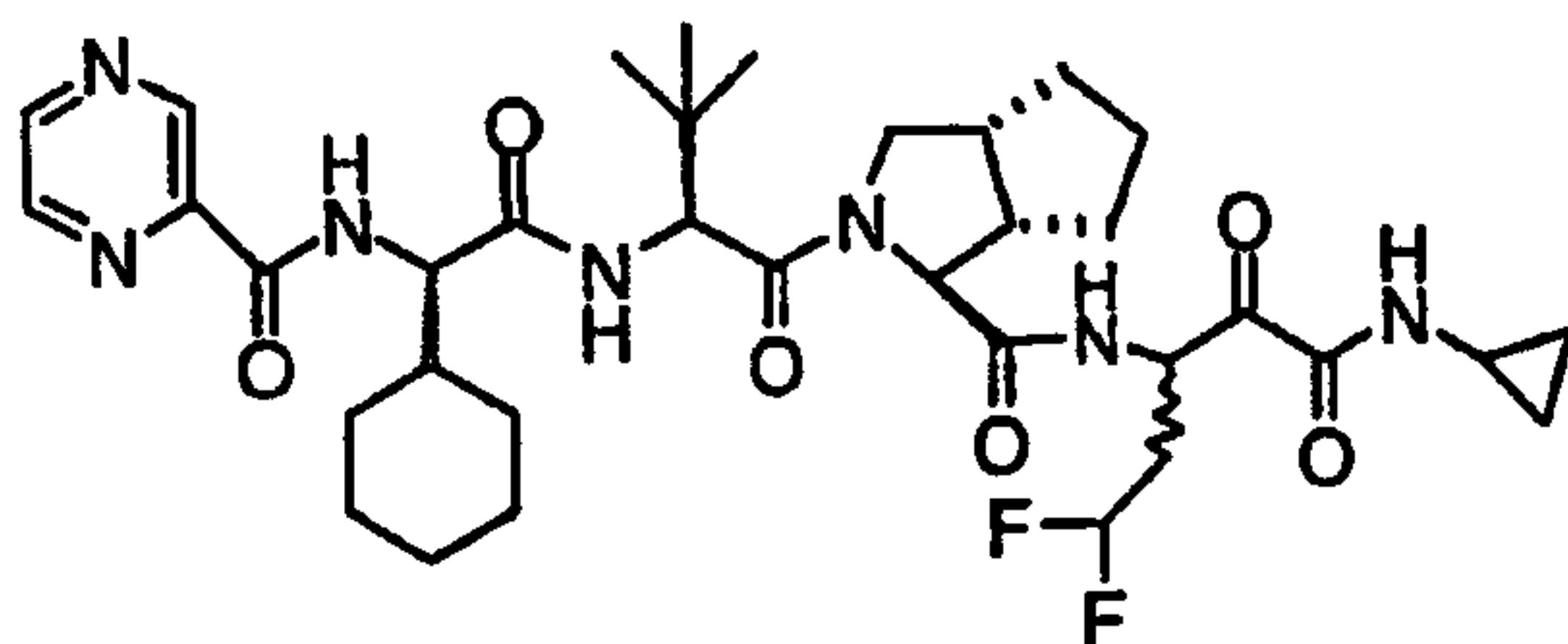
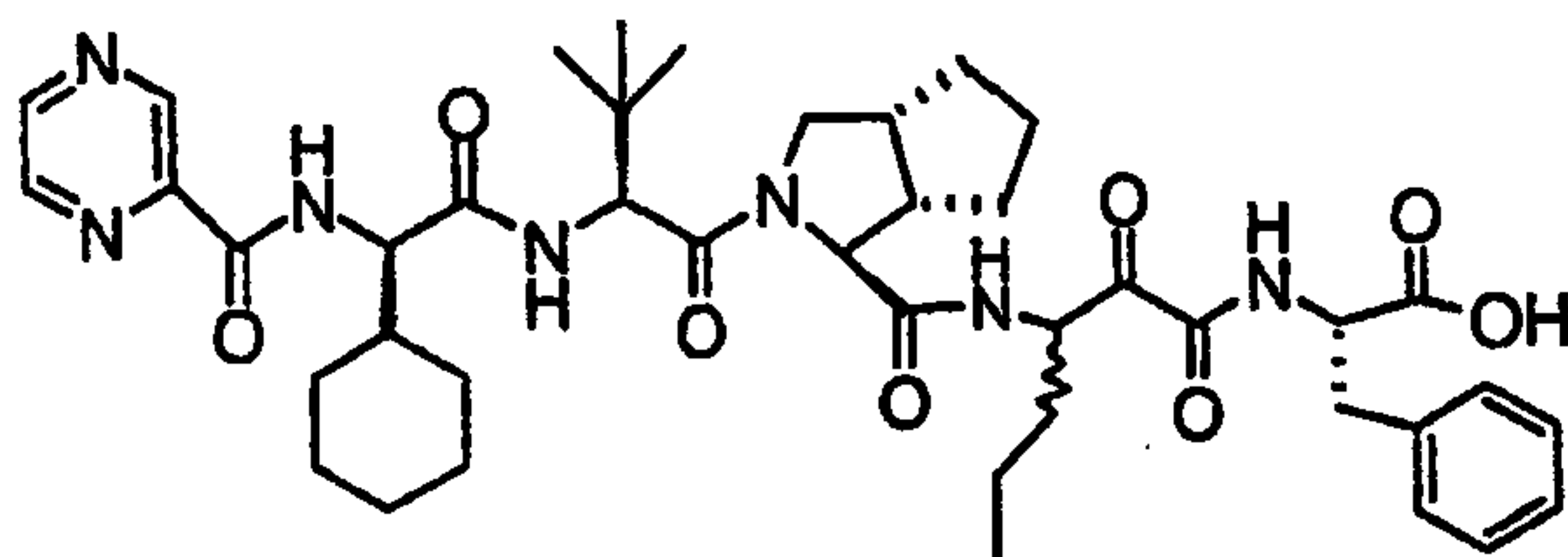
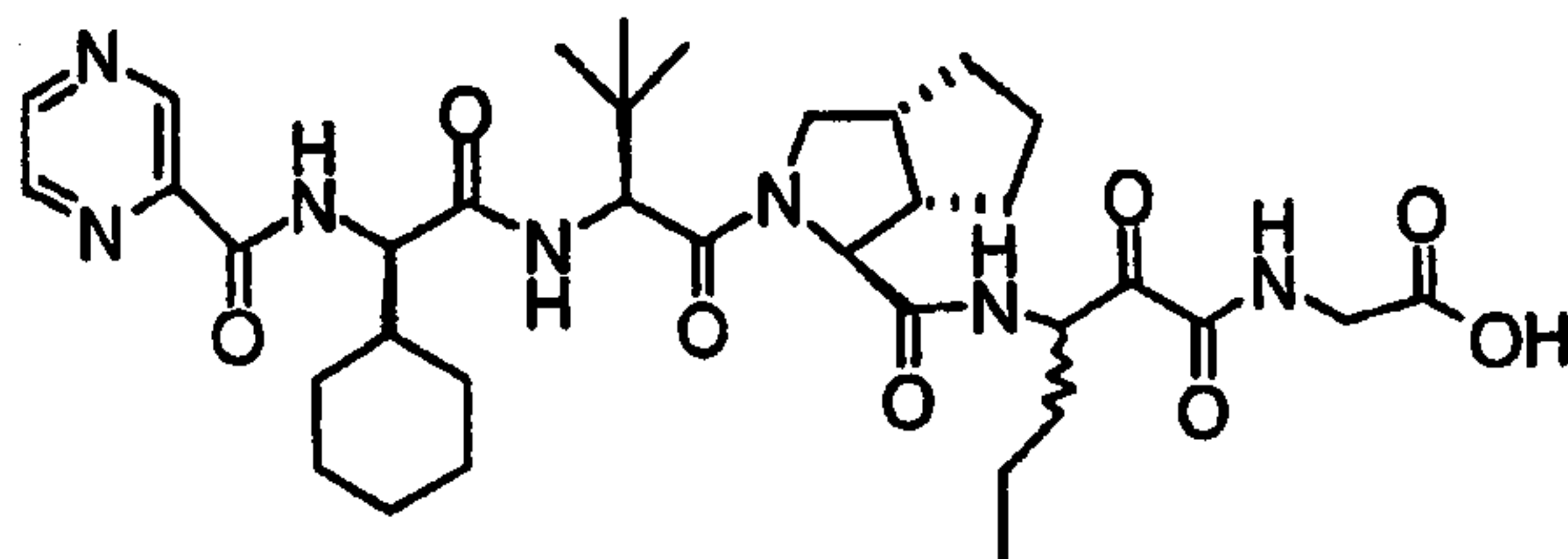
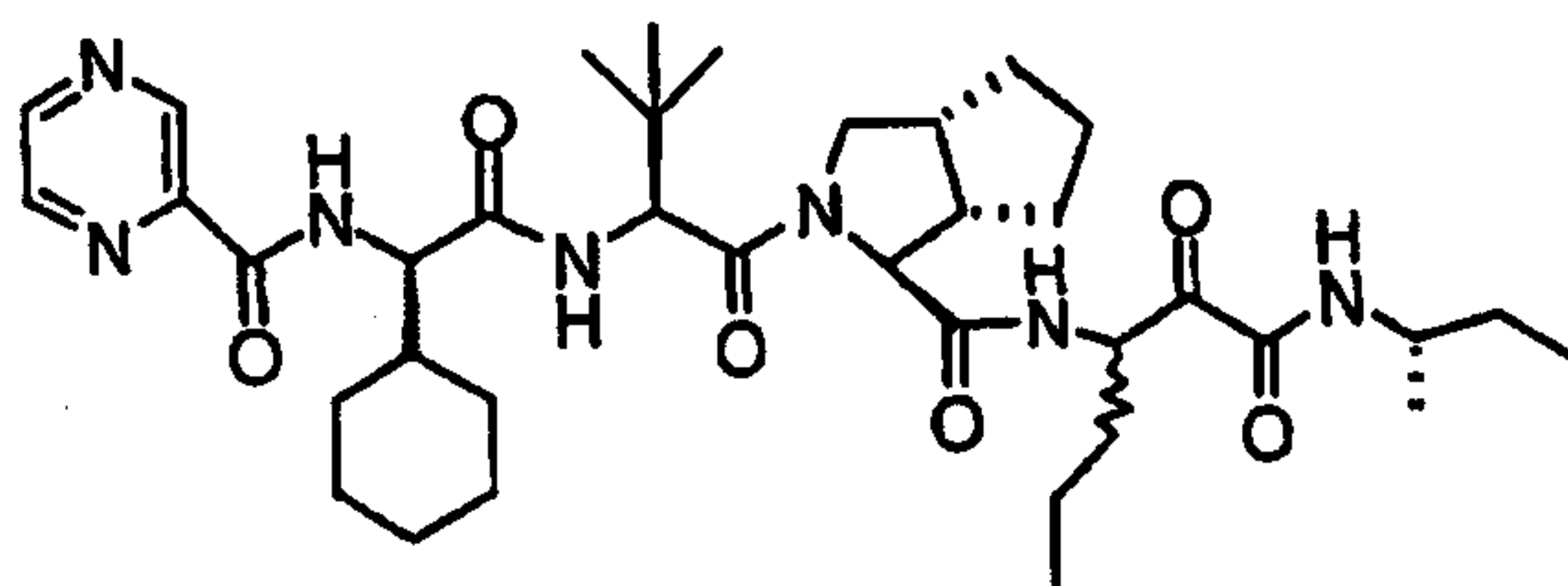
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vacuo. The resulting residue is purified by silica gel chromatography (80% EtOAc/Hexanes) to give 208 mg (50%) of compound BW,



Following the above method but using the appropriate starting materials, the following
5 consecutive compounds BX-CA are prepared:



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Example 18 – Compounds CB-CC:

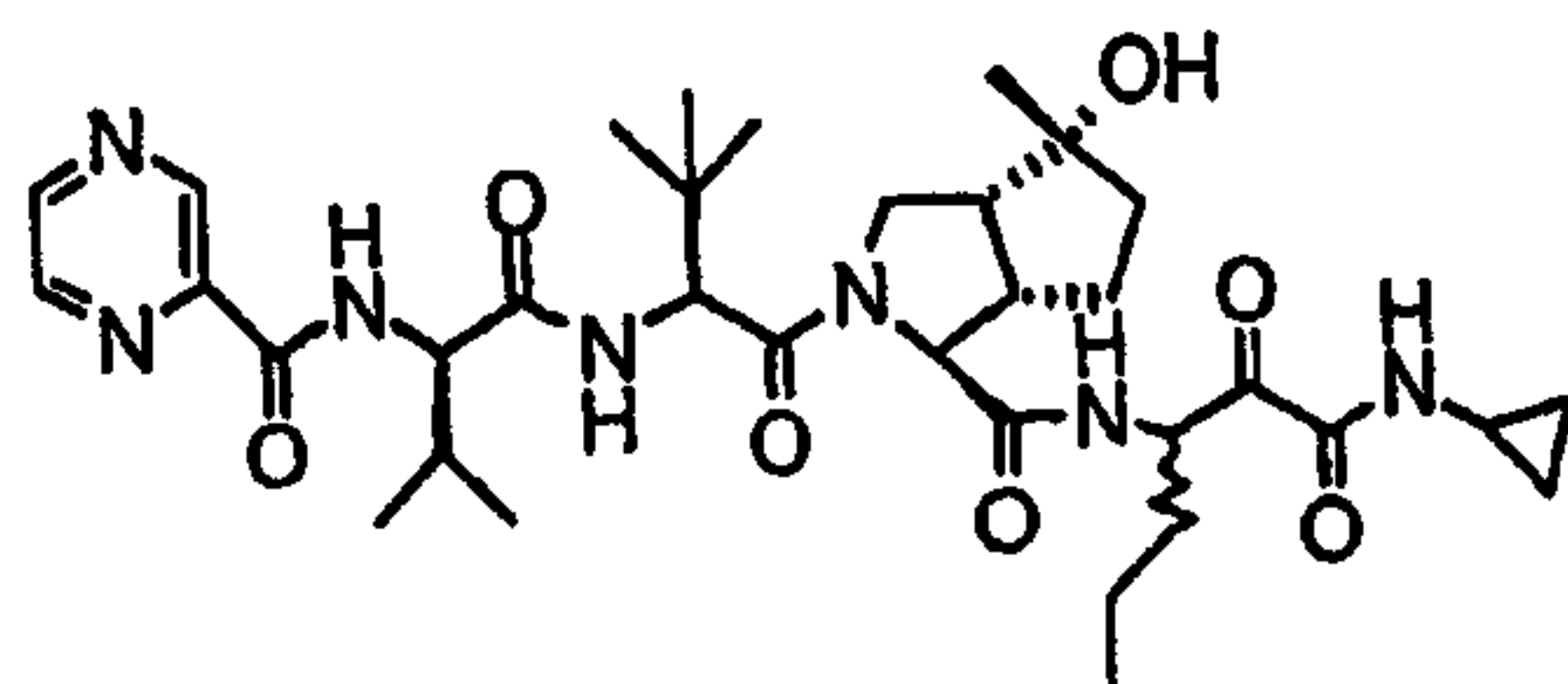
To a dichloromethane solution (6.5 mL) of compound lxxxvii (200 mg, 0.3 mmol) is added DMP reagent reagent (227 mg, 0.54 mmol). The reaction is stirred at about room

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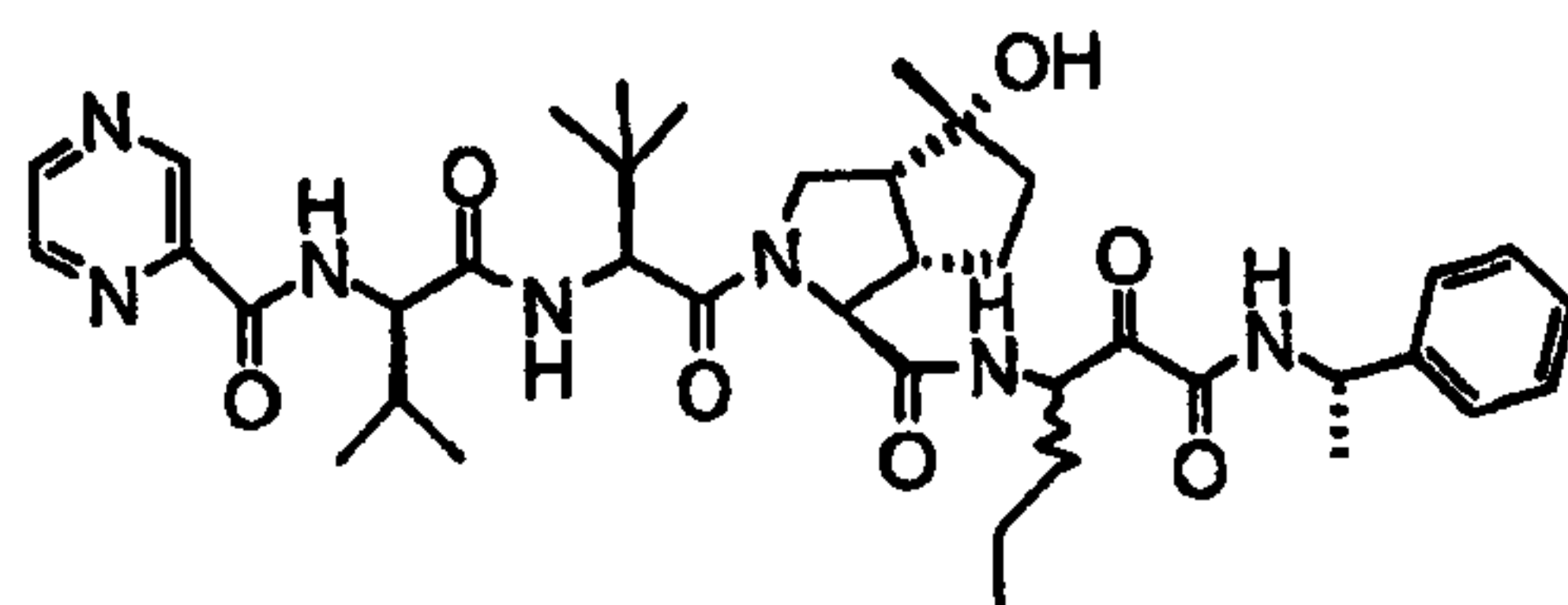
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temperature for 2 hours and quenched with 10% Na₂SO₃ (aq.) for 20 minutes. The resulting mixture is extracted with EtOAc. The organic layer is washed with brine, dried over MgSO₄ and concentrated to a yellow oil. Purification by silica gel chromatography (5% EtOH/EtOAc) yields 138 mg (70%) of compound CB,



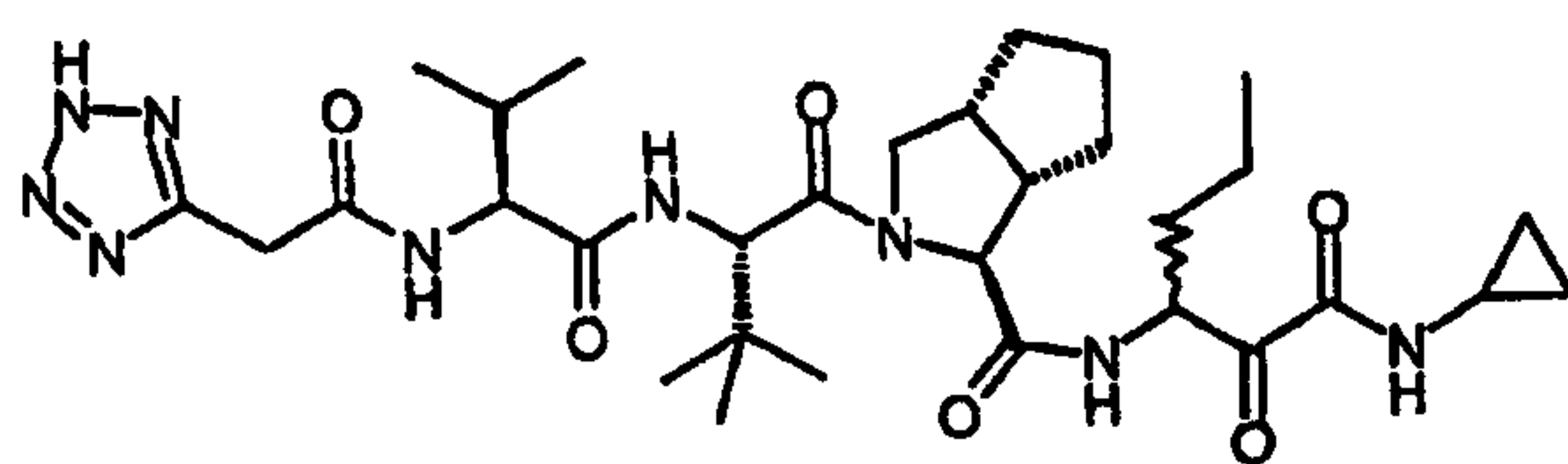
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Following the above method but using the appropriate starting materials, the following compound CC is prepared:



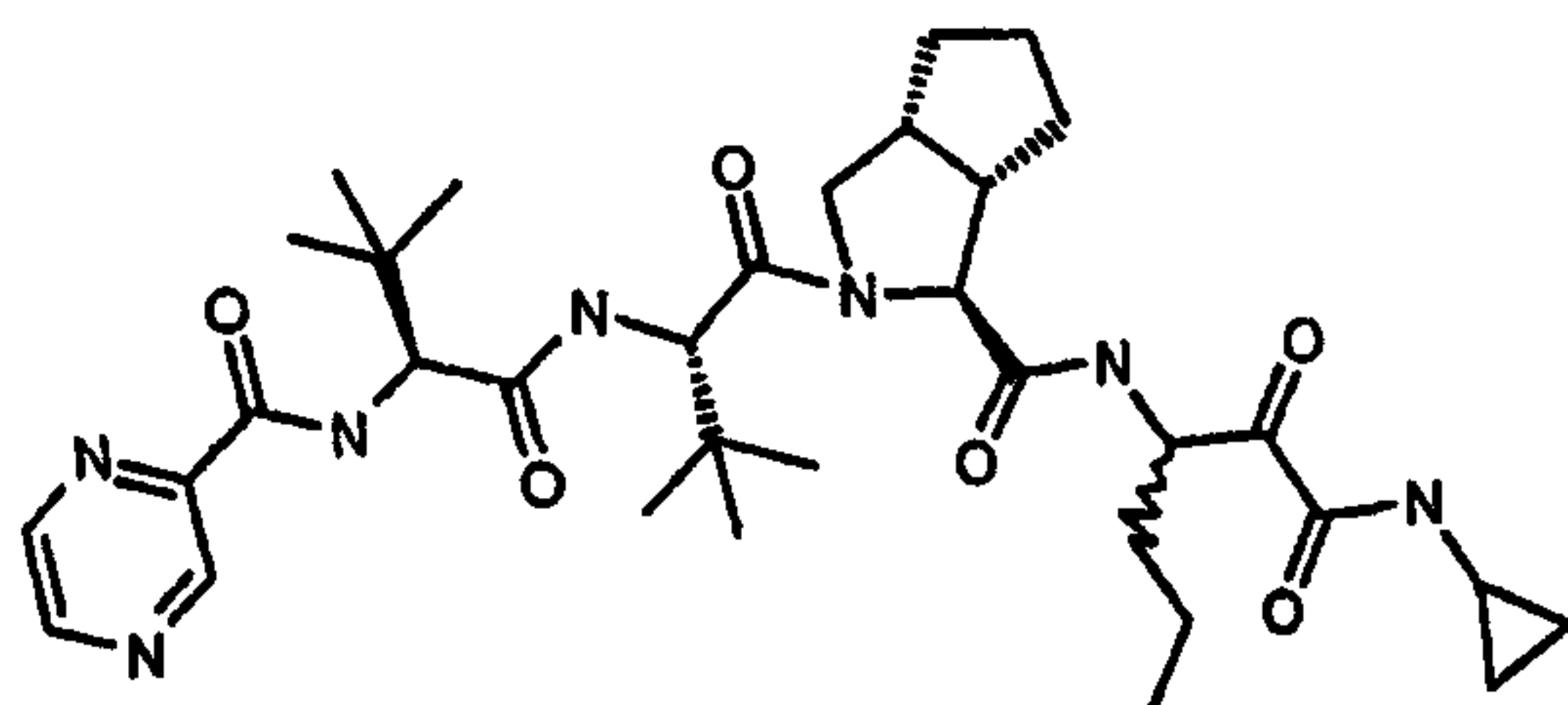
10 Example 19 – Compound CD:

Compound lxxxviii (40 mg, 0.05 mmol) is taken up in TFA (3 mL). The solution stirred over two nights and is concentrated. The residue is purified on reverse phase HPLC to give 25 mg (74%) of compound CD,



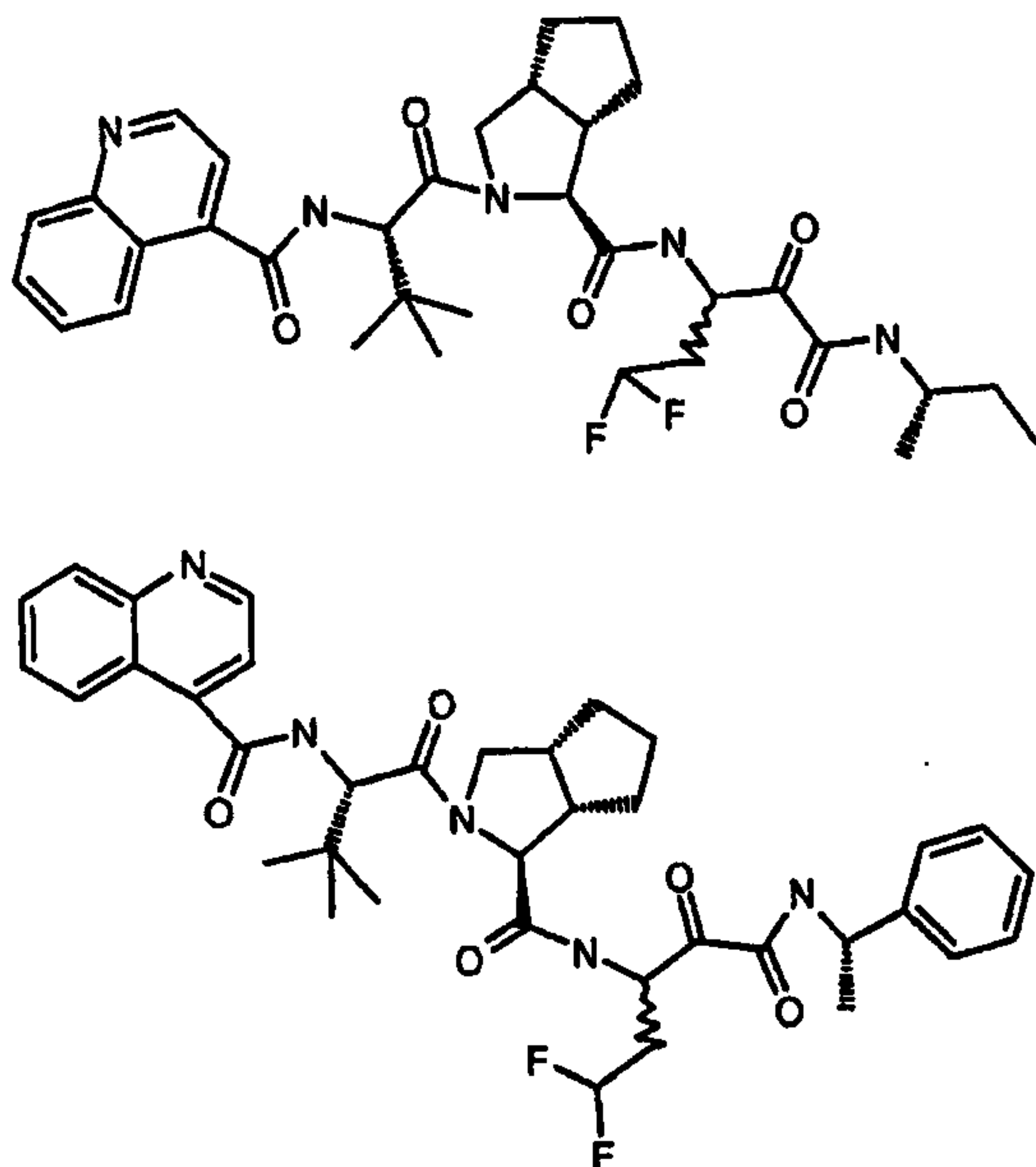
15 Example 20 – Compound CE:

Following the method of Example 17 and using the appropriate starting materials, the following compound CE is prepared:



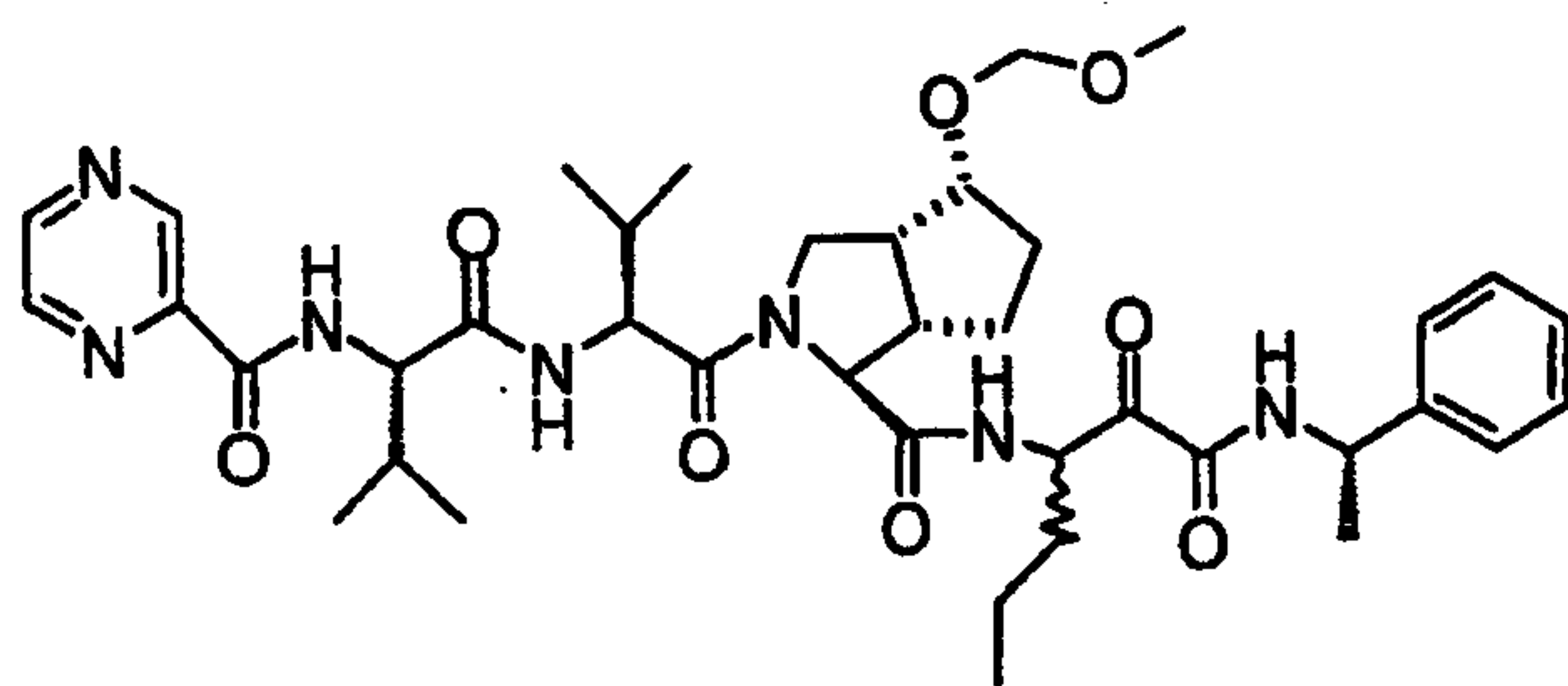
Example 21 – Compounds CF-CG:

Following the method of Example 14 and using the appropriate starting materials, the following consecutive compounds CF-CG are prepared:



5 Example 22 – Compound CH:

Following the method of Example 16 and using the appropriate starting materials, the following compound CH is prepared:



10 Example 23 – Compounds CI-CM

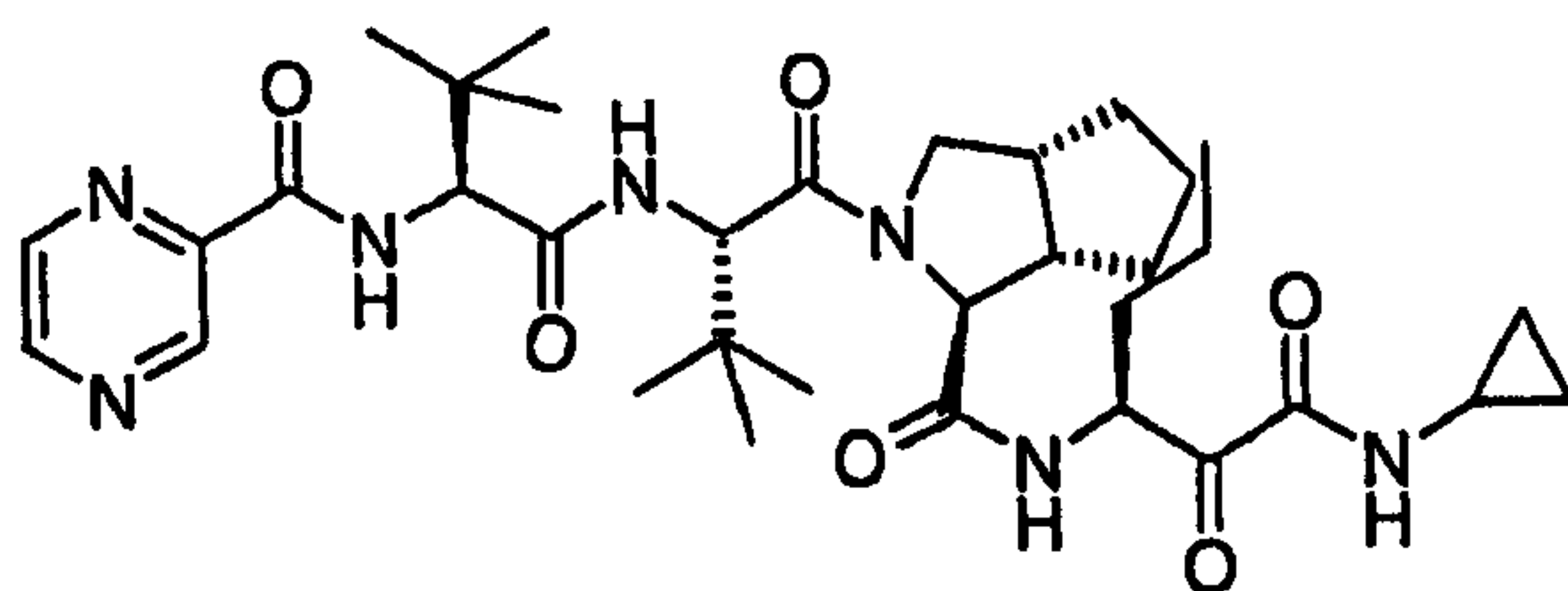
Compound cxi (490 mg, 0.75 mmol) is dissolved in DCM (6 mL). DMP reagent reagent (380 mg, 0.9 mmol) is added to this solution and stirred 1 hour. The reaction mixture is quenched with a 10% Na₂SO₃ solution, and then the organic phase is washed with saturated NaHCO₃ and brine. Following the concentration of the organic phase, the resultant residue is

15 chromatographically purified by 70% EtOAc/hexanes to yield compound CI (325 mg, 66.4%).

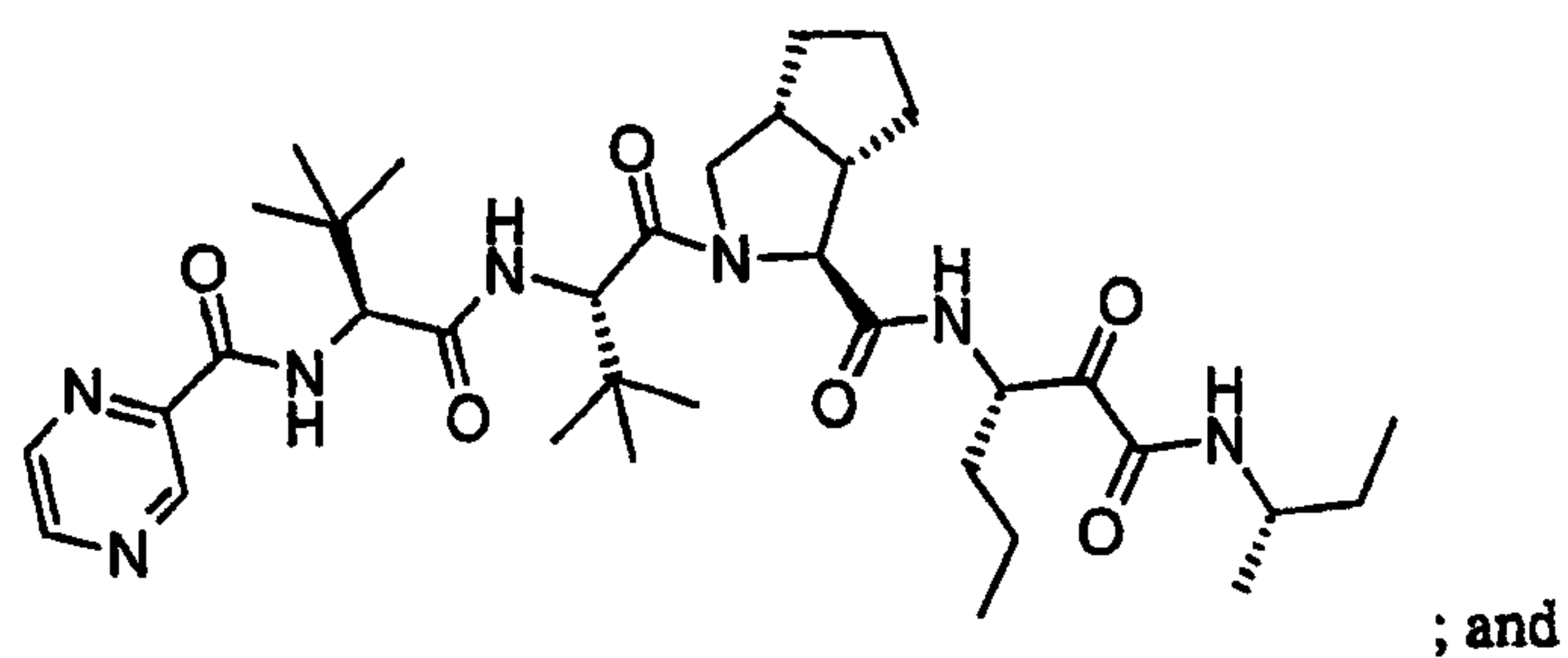
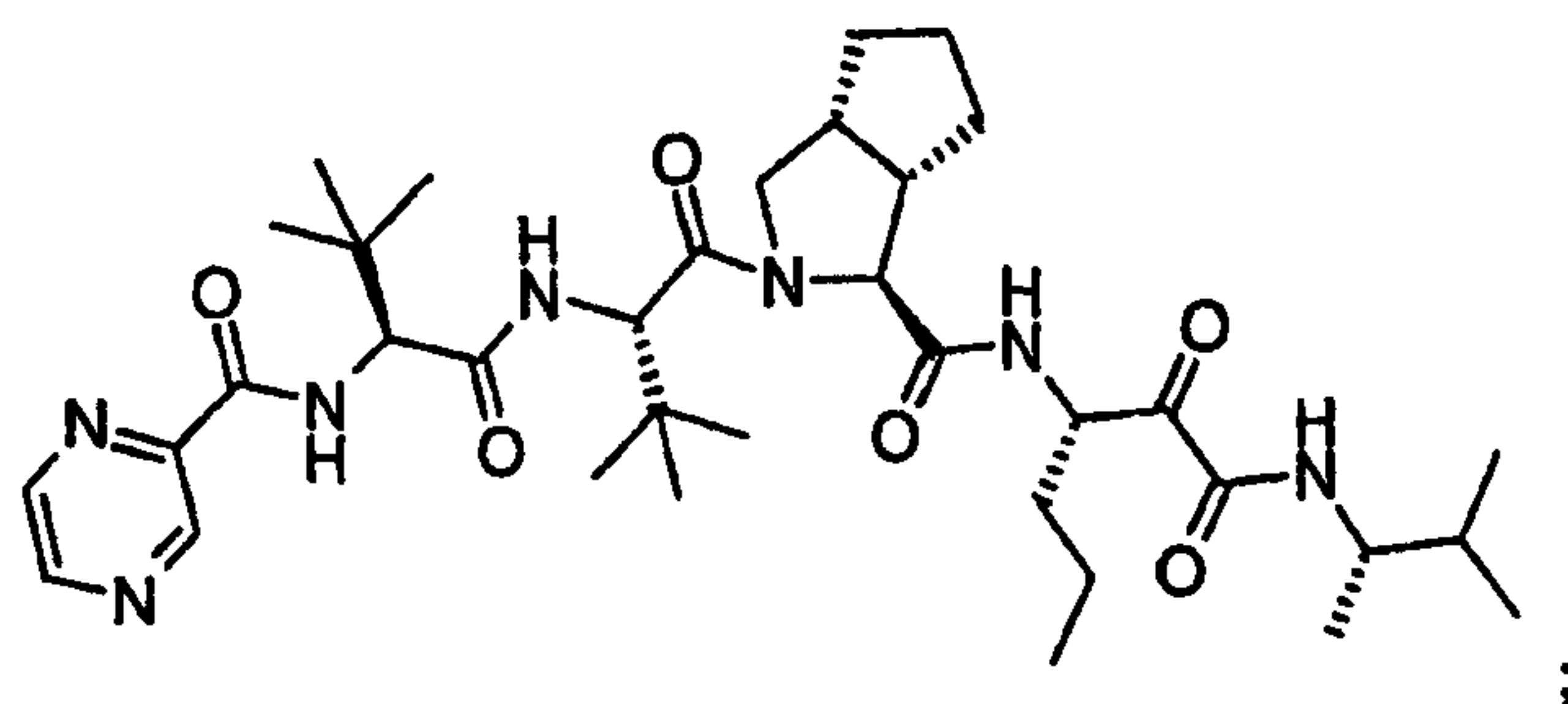
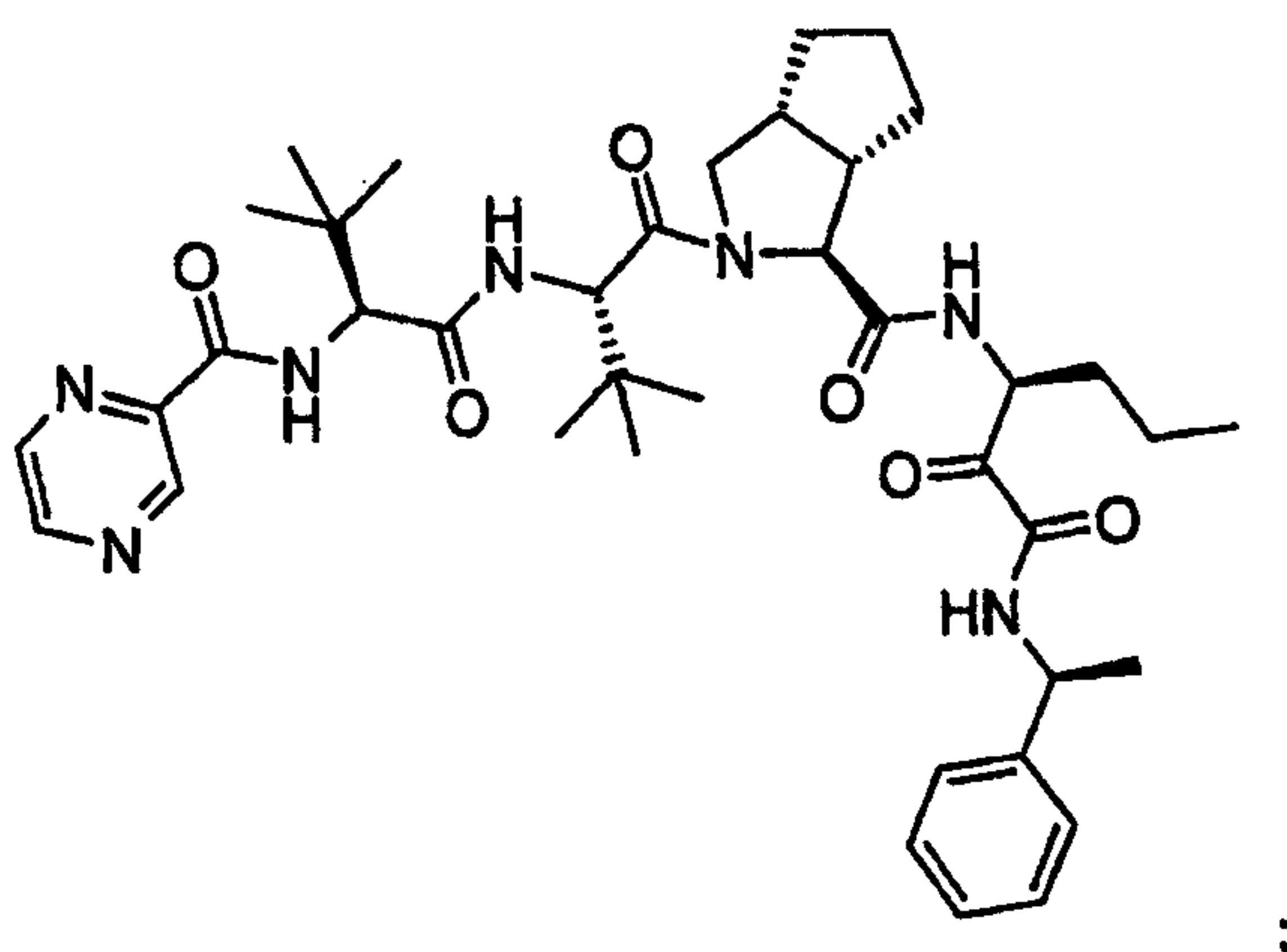
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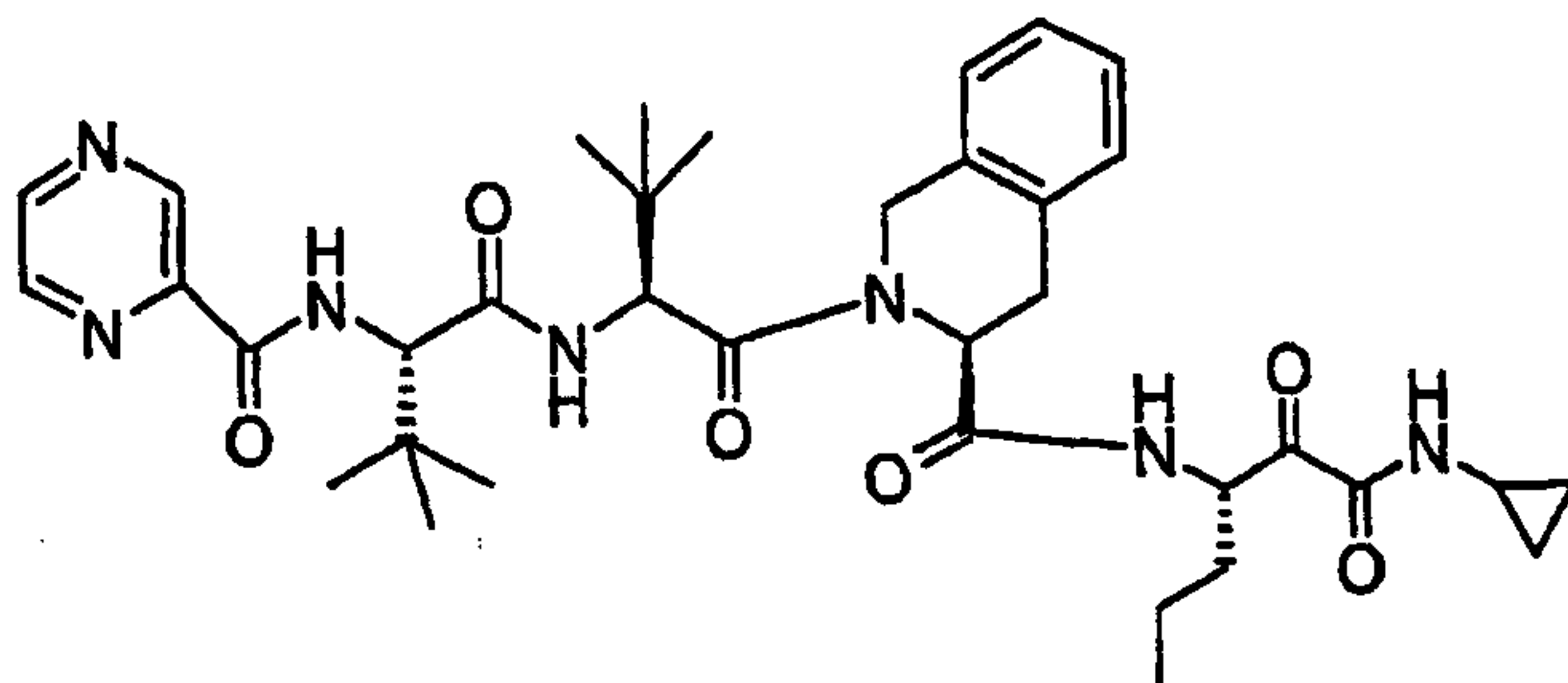
143



- Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following
- 5 consecutive compounds CJ-CM are prepared:

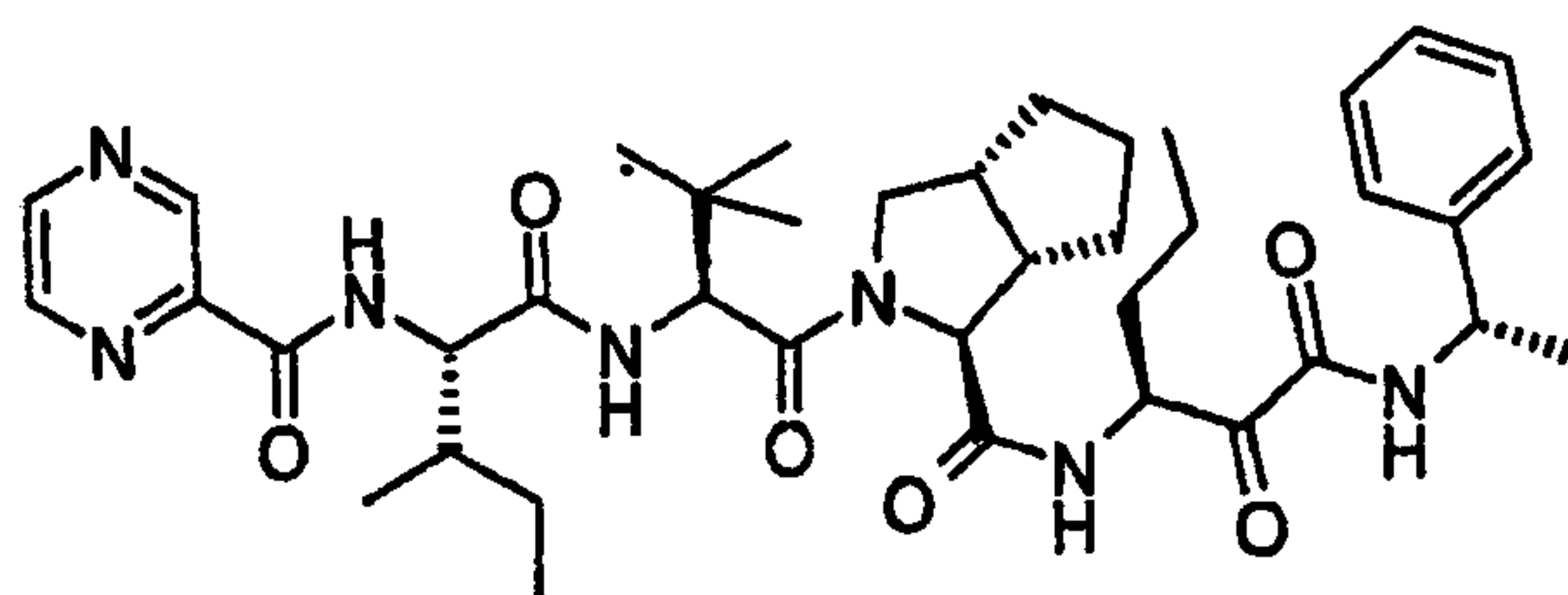


144



Example 24 – Compounds CN

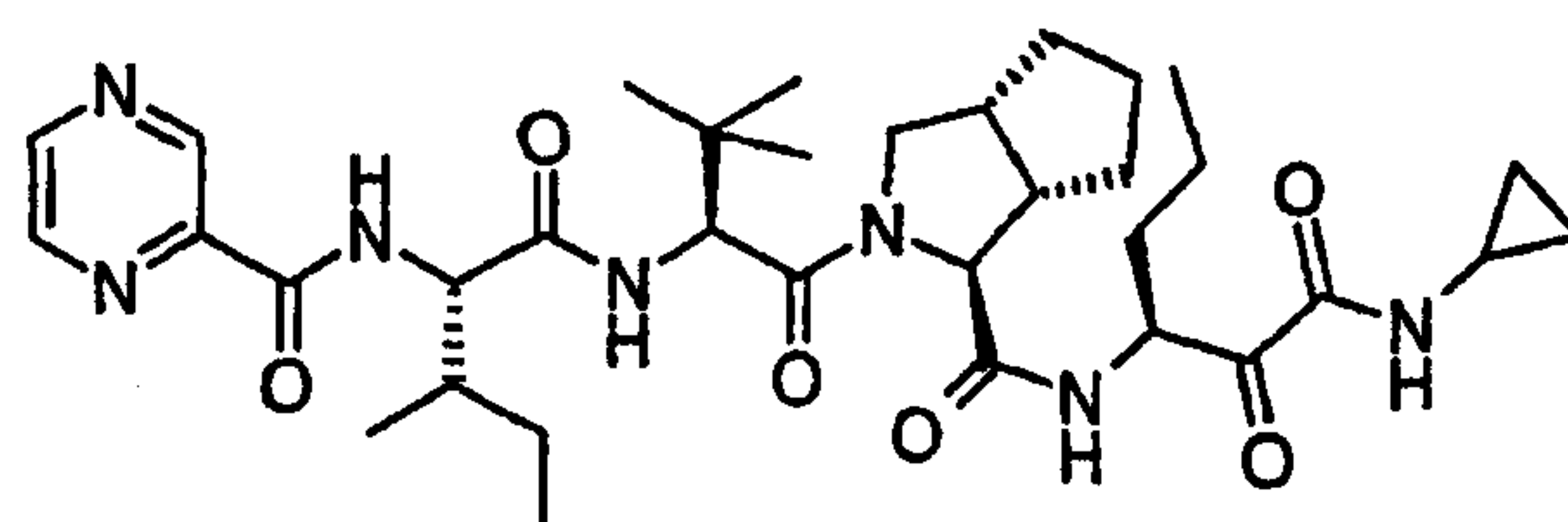
To a DCM/THF solution (3 mL/3 mL) of compound cxviii (335 mg, 0.46 mmol) is added
 5 DMP reagent reagent (300 mg, 0.69 mmol). The reaction mixture is stirred at room temperature
 for 2 hours and quenched with 10% Na₂SO₃ (aq.) for 20 minutes. The resulting mixture is
 extracted with EtOAc. The organic phase is washed with brine, dried over MgSO₄ and
 concentrated to yield a yellow oil. Purification by silica gel chromatography (80%
 EtOAc/hexanes) yields compound CN (220 mg, 67%).



10

Example 25 – Compounds CO-CR

To a DCM/THF solution (1.5 mL/1.5 mL) of compound cxix (164 mg, 0.25 mmol) is
 added DMP reagent reagent (159 mg, 0.38 mmol). The reaction mixture is stirred at room
 15 temperature for 2 hours and quenched with 10% Na₂SO₃ (aq.) for 20 minutes. The resulting
 mixture is extracted with EtOAc. The organic phase is washed with brine, dried over MgSO₄ and
 concentrated to yellow oil. Purification by silica gel chromatography (70% EtOAc/hexanes)
 yields compound CO (100 mg, 61%).



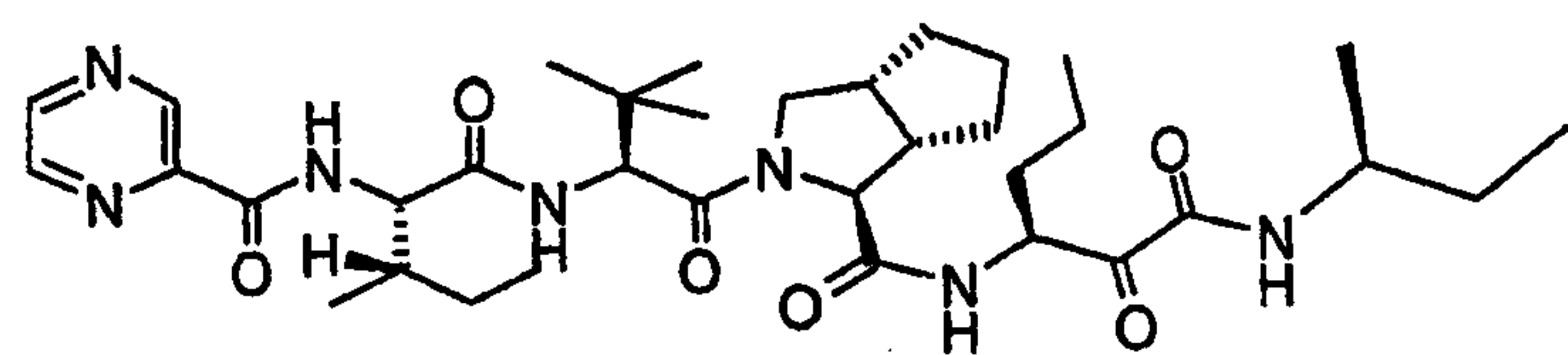
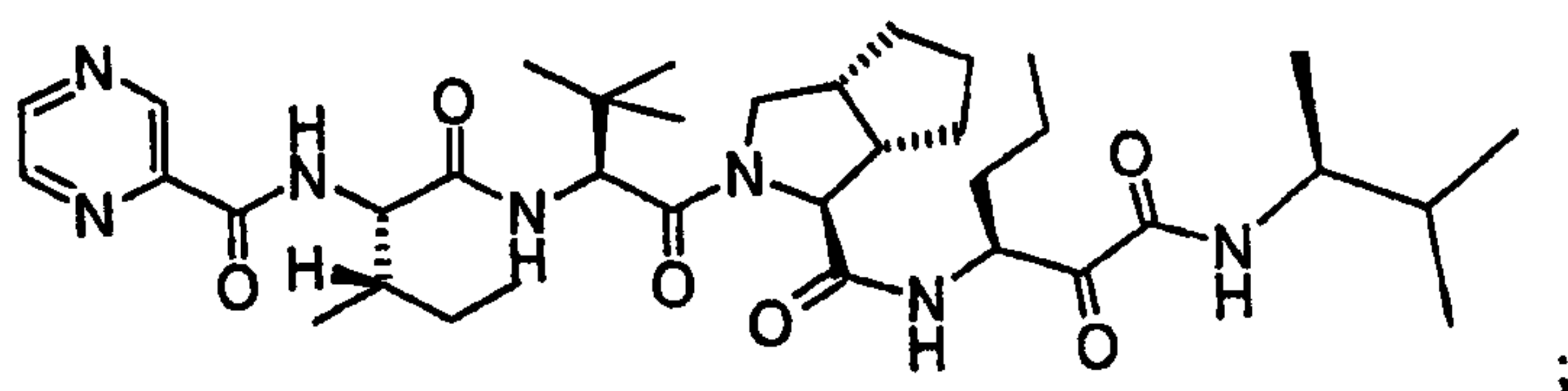
20

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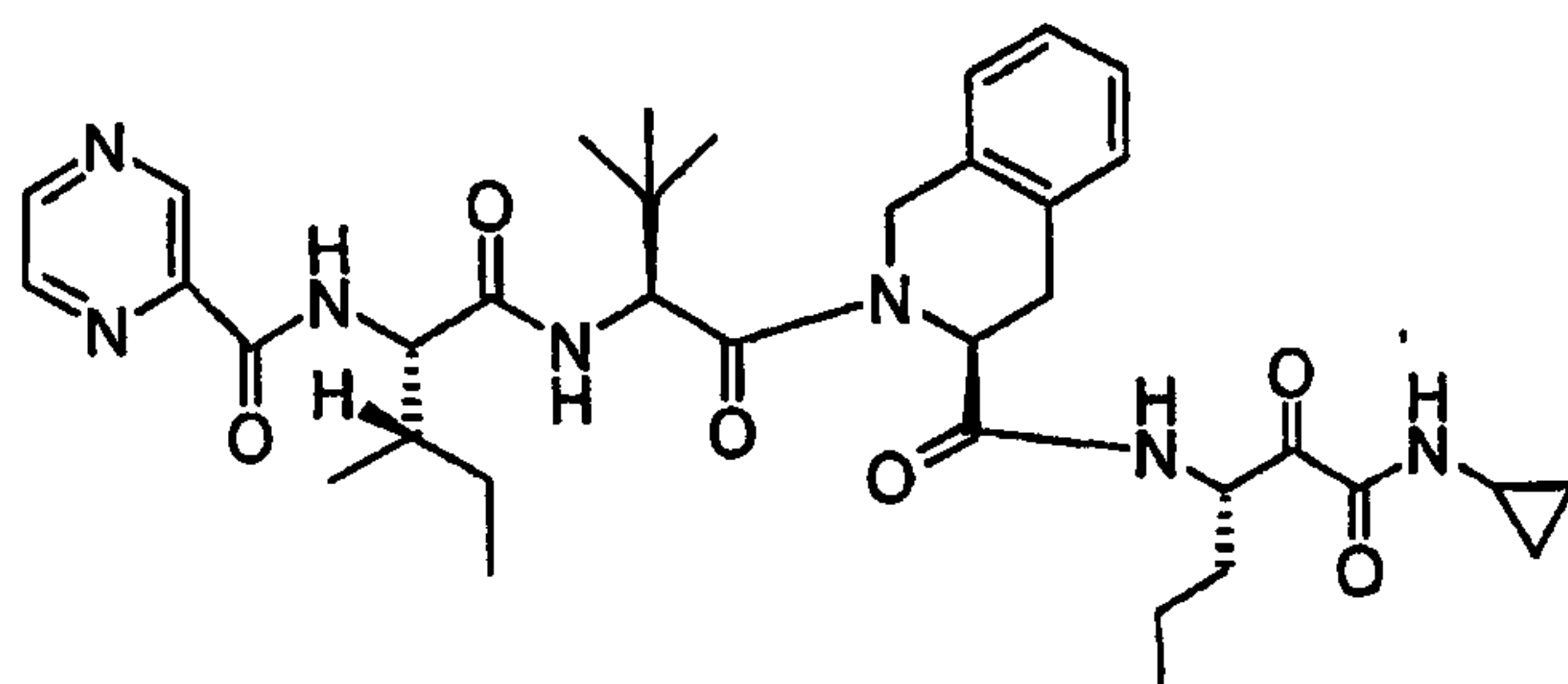
145

Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following consecutive compounds CP-CR are prepared:



5

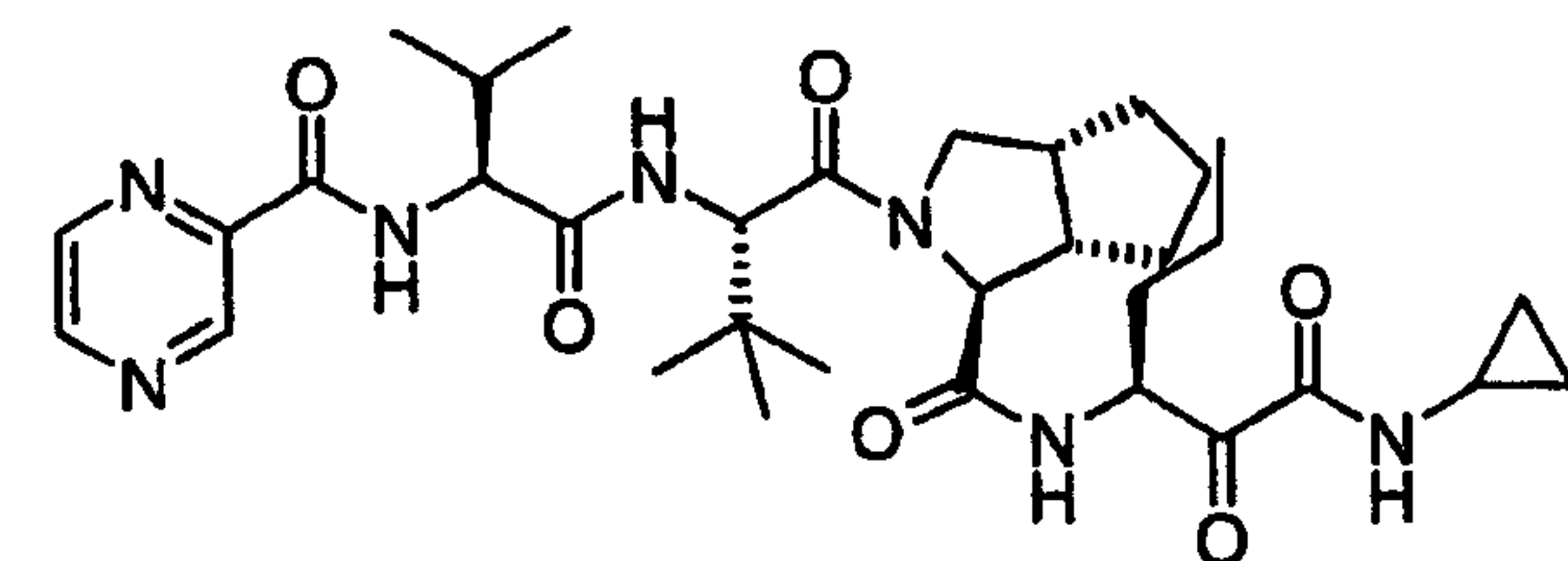
; and



Example 26 – Compounds CS-CT

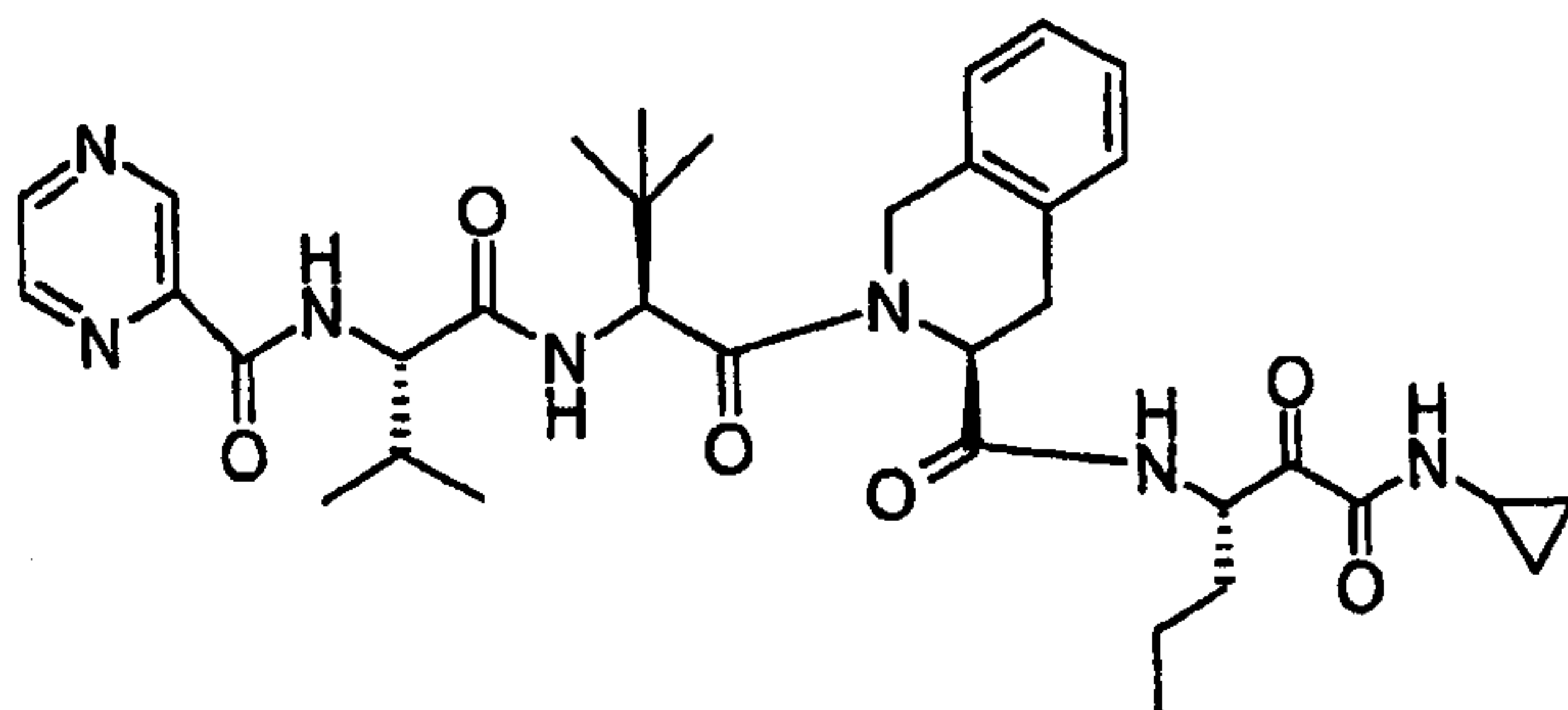
Compound cxx is dissolved in DCM (3 mL). DMP reagent reagent (180 mg, 0.41 mmol) is added to the solution, and then stirred for 1 hour. The reaction mixture is quenched with 10% Na_2SO_3 , and then the organic phase is washed with saturated NaHCO_3 and brine. Following the concentration of the organic phase, the residue is chromatographically purified by 100% EtOAc to yield compound CS (95 mg, 43.7%).

15



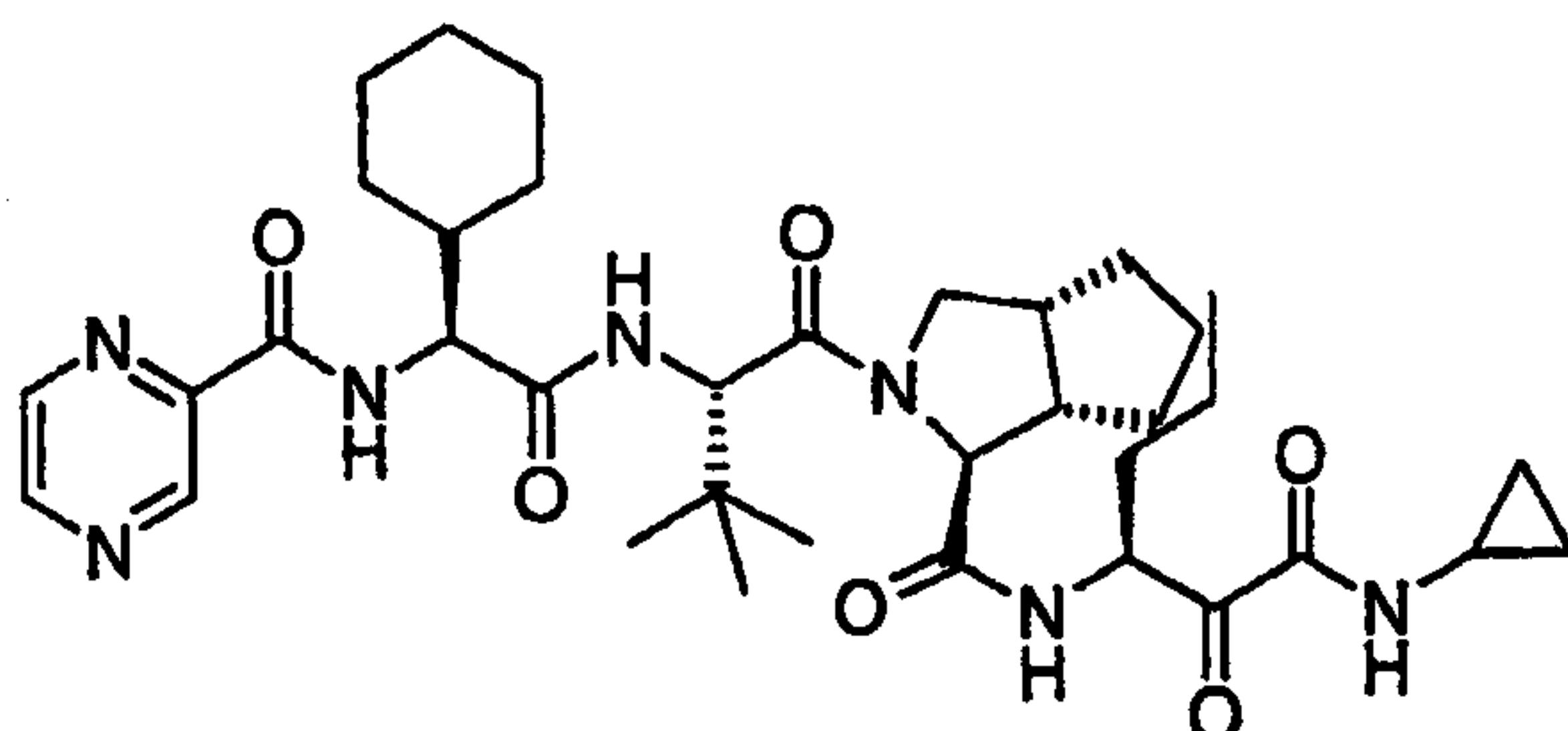
Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following compound CT is prepared:

146



Example 27 – Compounds CU, EI, EK-EM, EO-EZ, and FA-FG

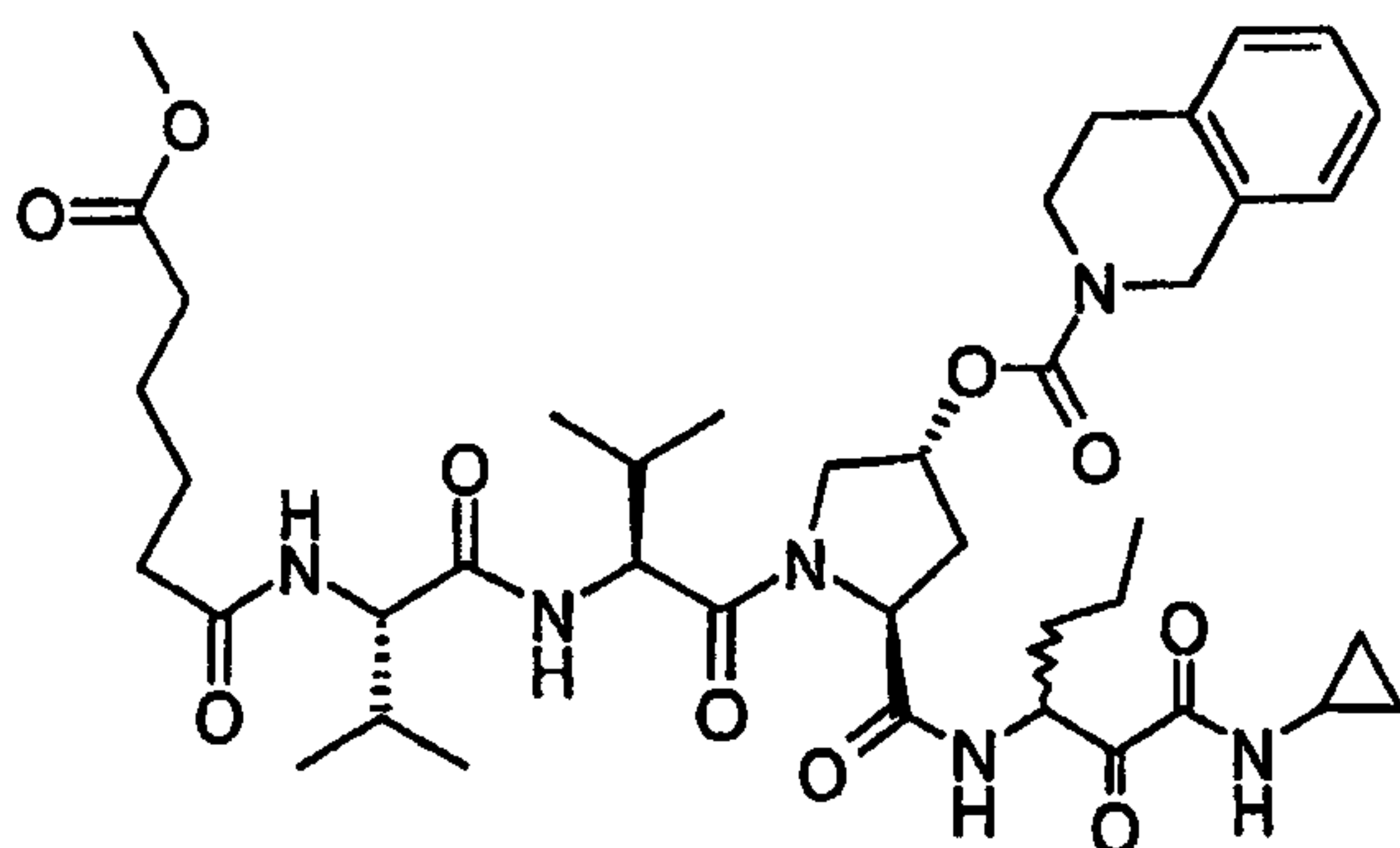
Compound cxxviii (356 mg, 0.52 mmol) is dissolved in DCM (5 mL). DMP reagent
 5 reagent (270 mg, 0.63 mmol) is added to this solution and stirred 1 hour. The reaction mixture is
 quenched with 10% Na₂SO₃, and then the organic phase is separated and washed with saturated
 NaHCO₃ and brine. Following the concentration of the organic solvent, the
 residue is chromatographically purified by 100% EtOAc to yield compound CU (200 mg, 56.3%).
 mp 225-235° C.



10

Following the above method for preparing the above compound and methods related to
 preparing the intermediate thereto, but using the appropriate starting materials the following
 consecutive compounds EI, EK-EM, EO-EZ and FA-FH are prepared:

15

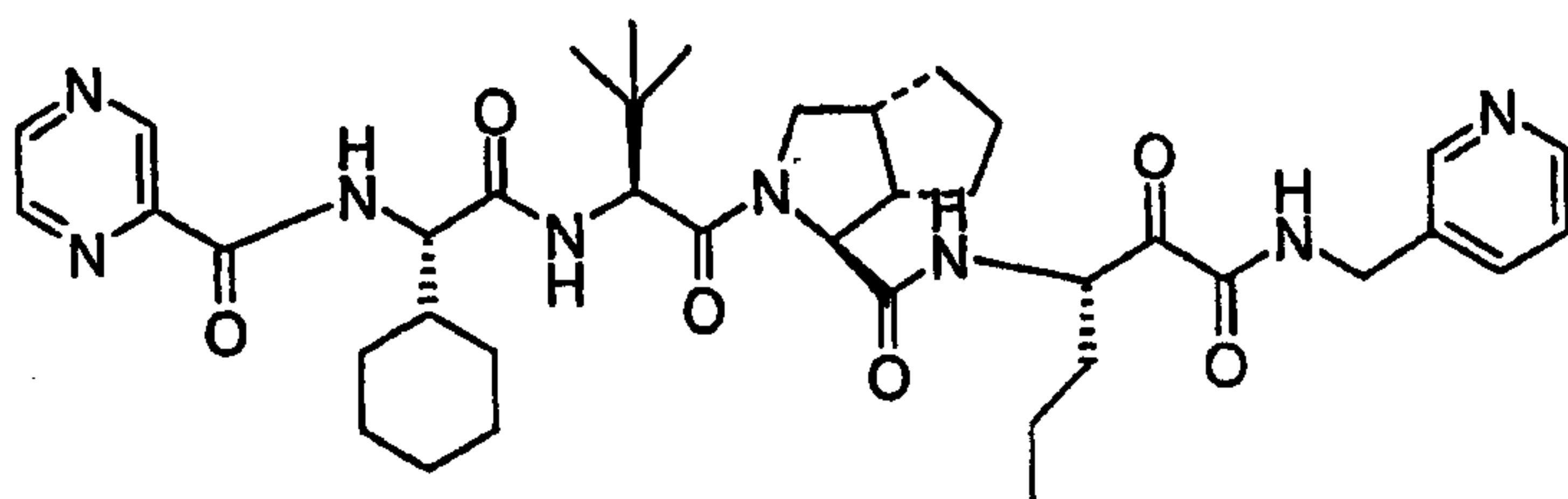


EI,

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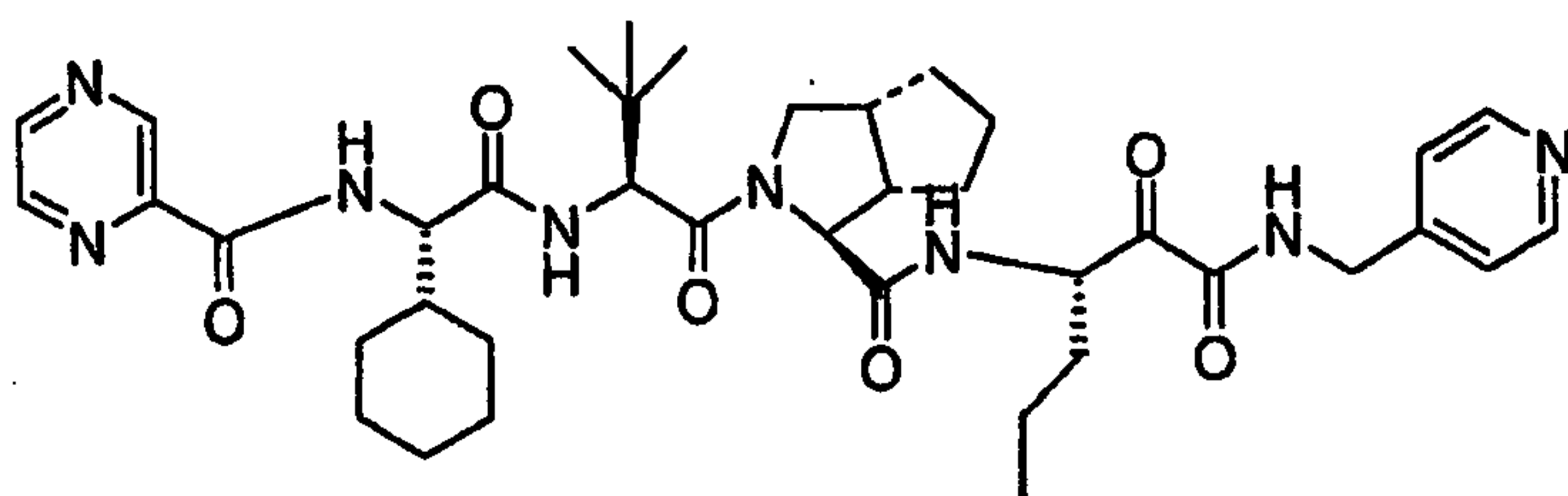
PCT/US01/26008

147



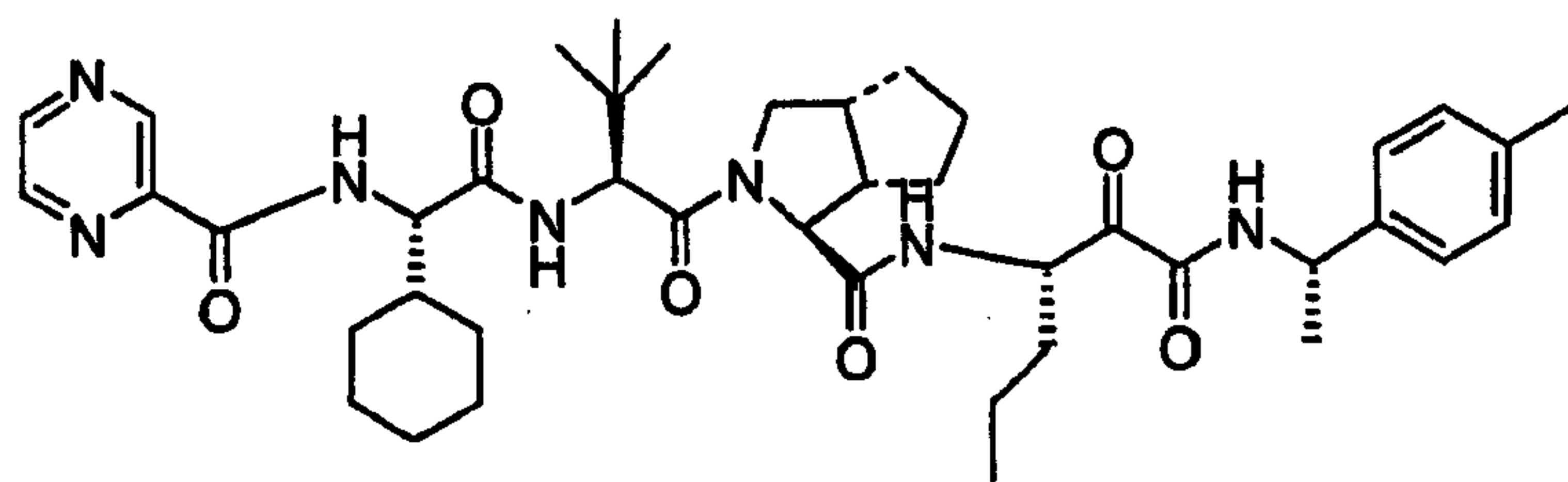
EK,

5

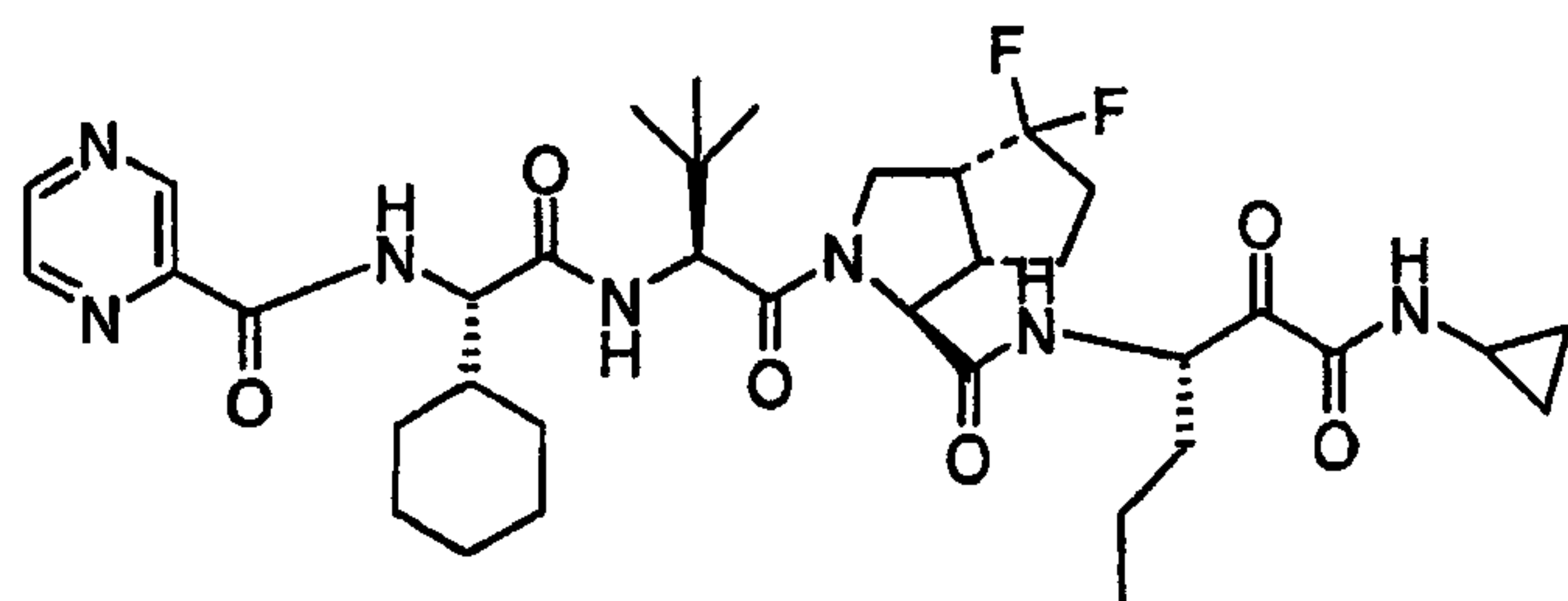


10

EL,



EM,



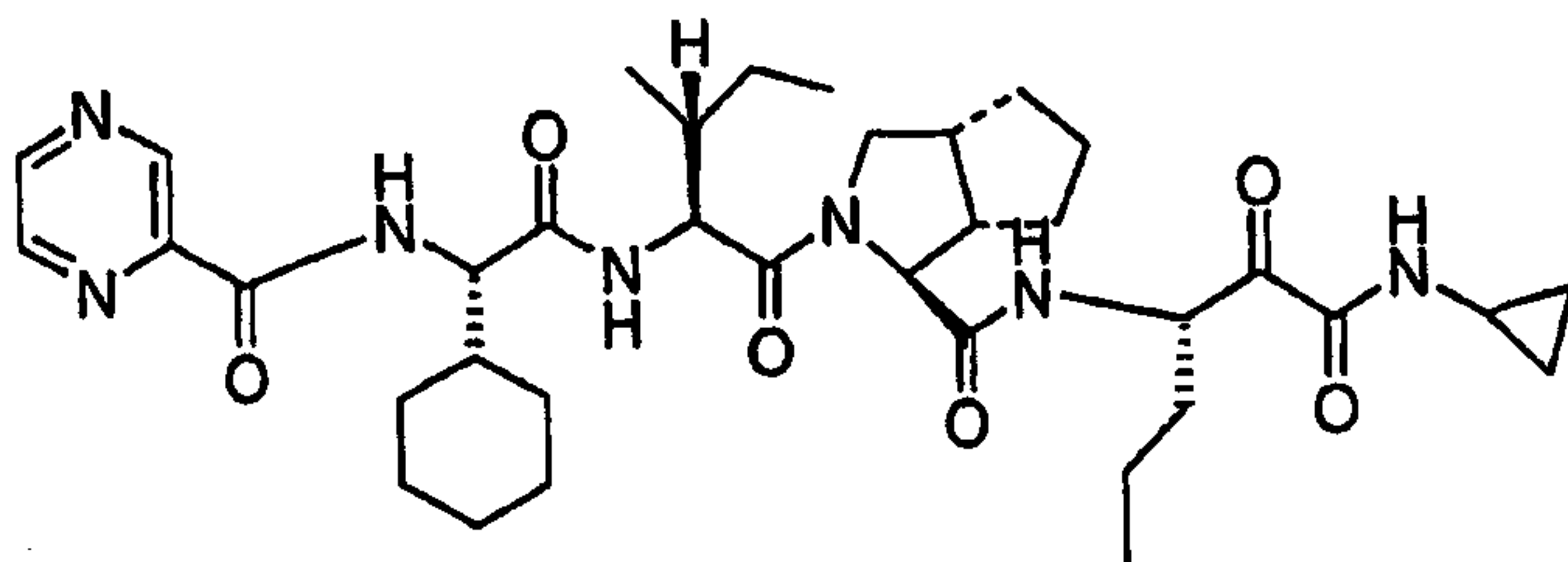
15

EO,

WO 02/18369

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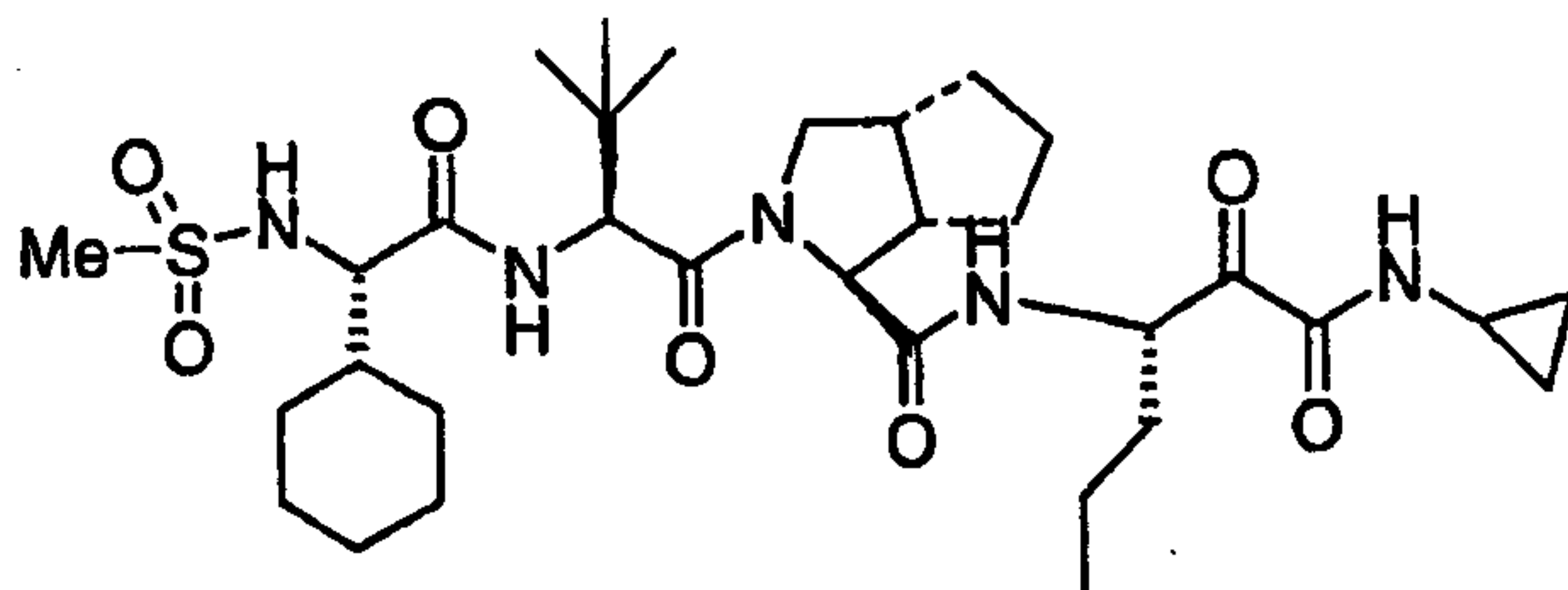
148



EP,

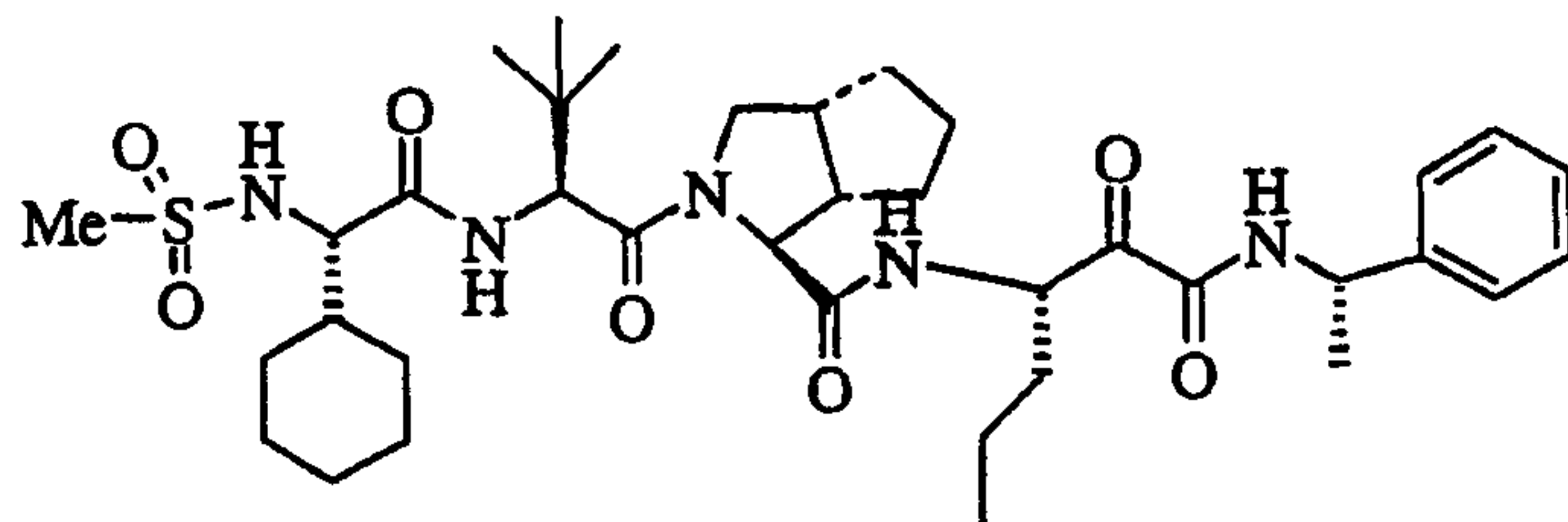
5

10



EQ,

15

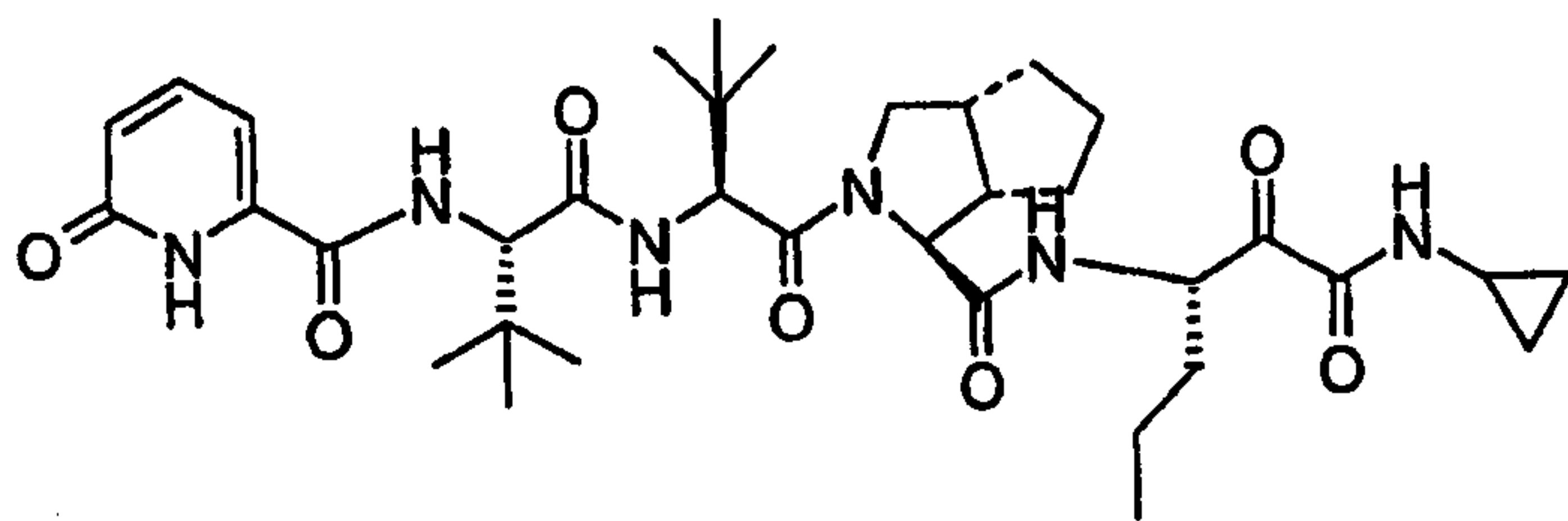


ER,

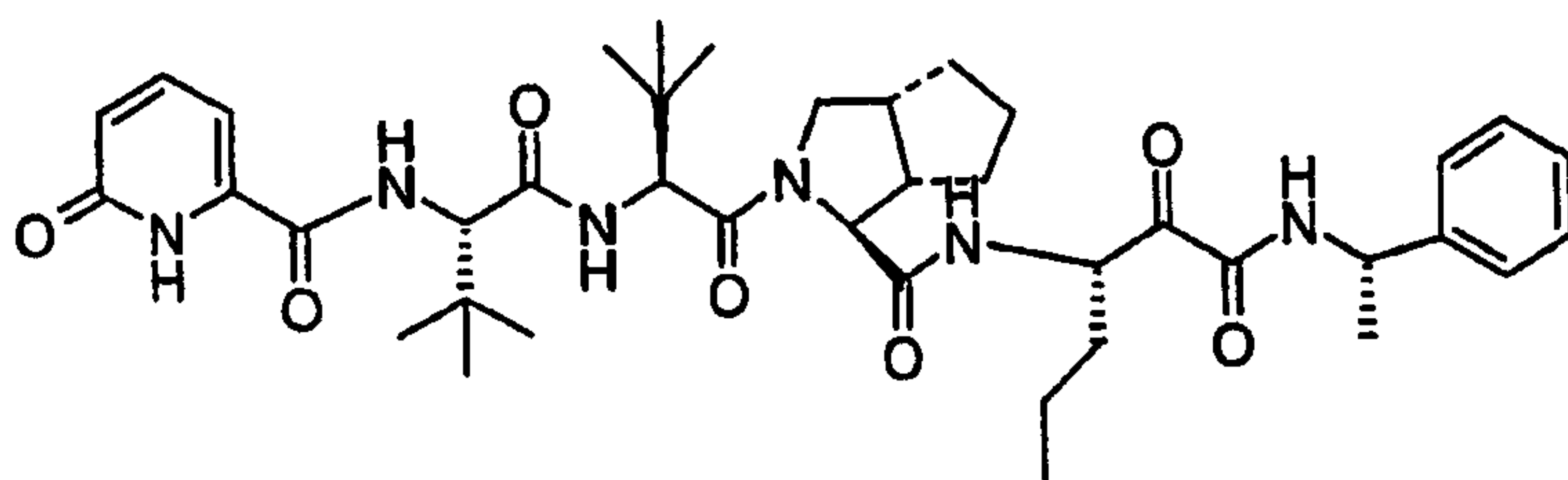
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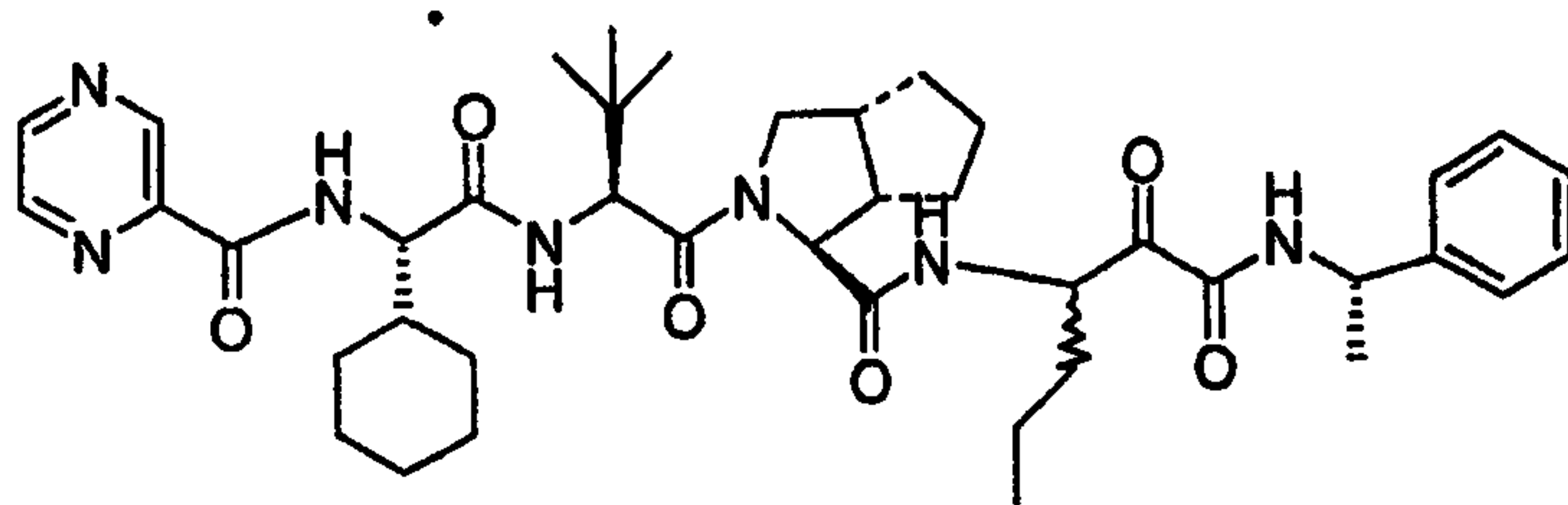


ES,



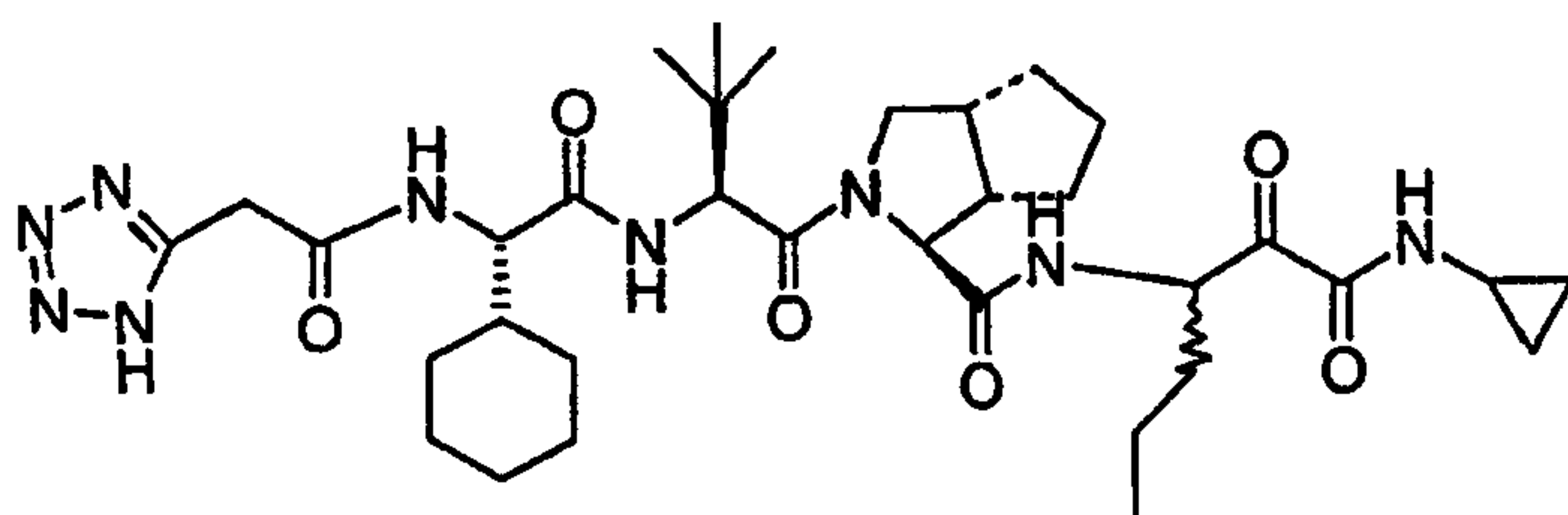
5

ET,



10

EU,



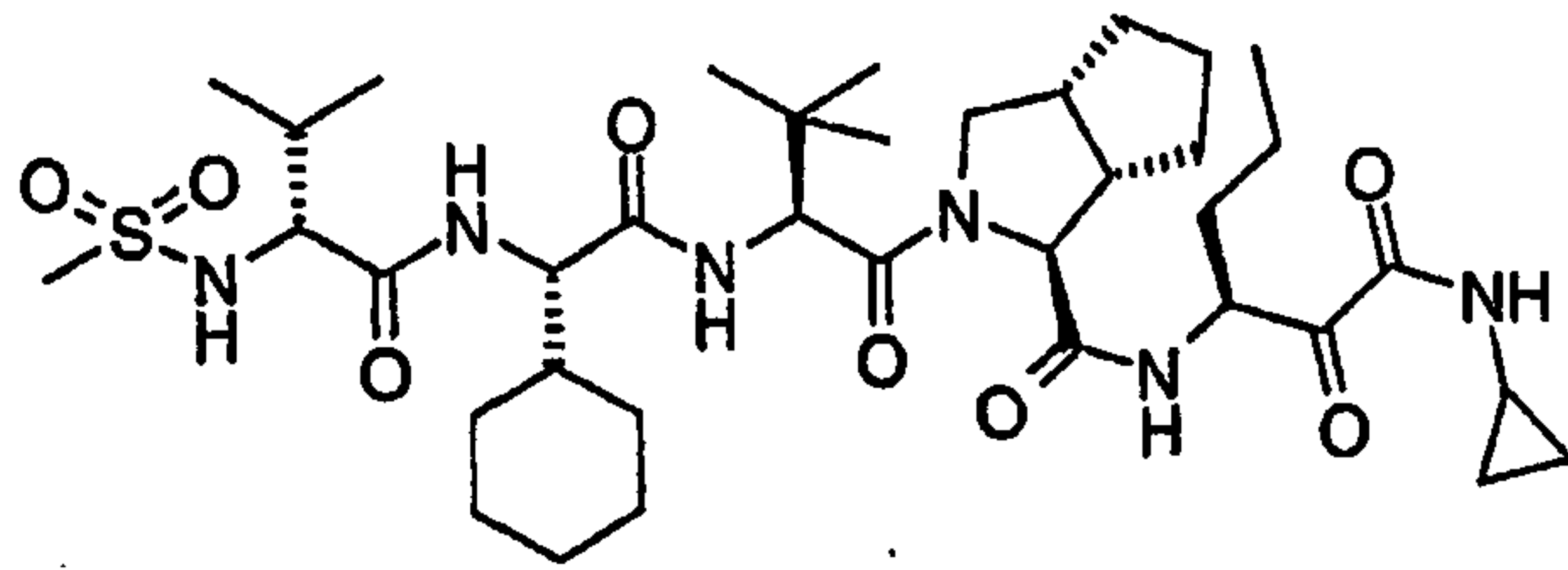
EV,

15

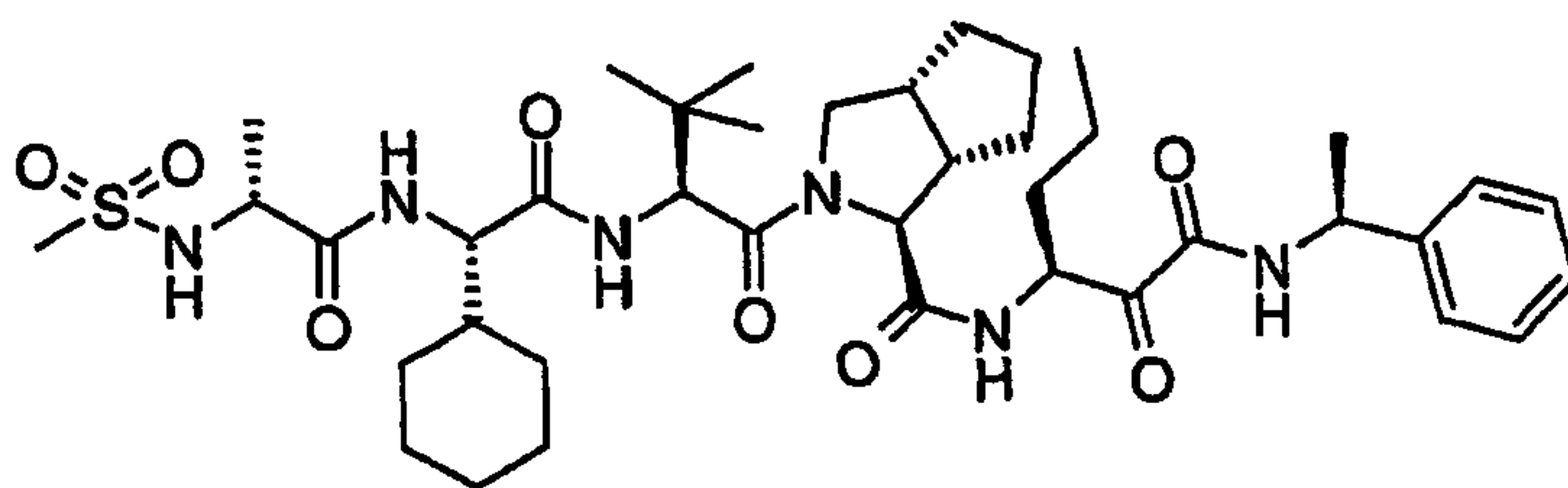
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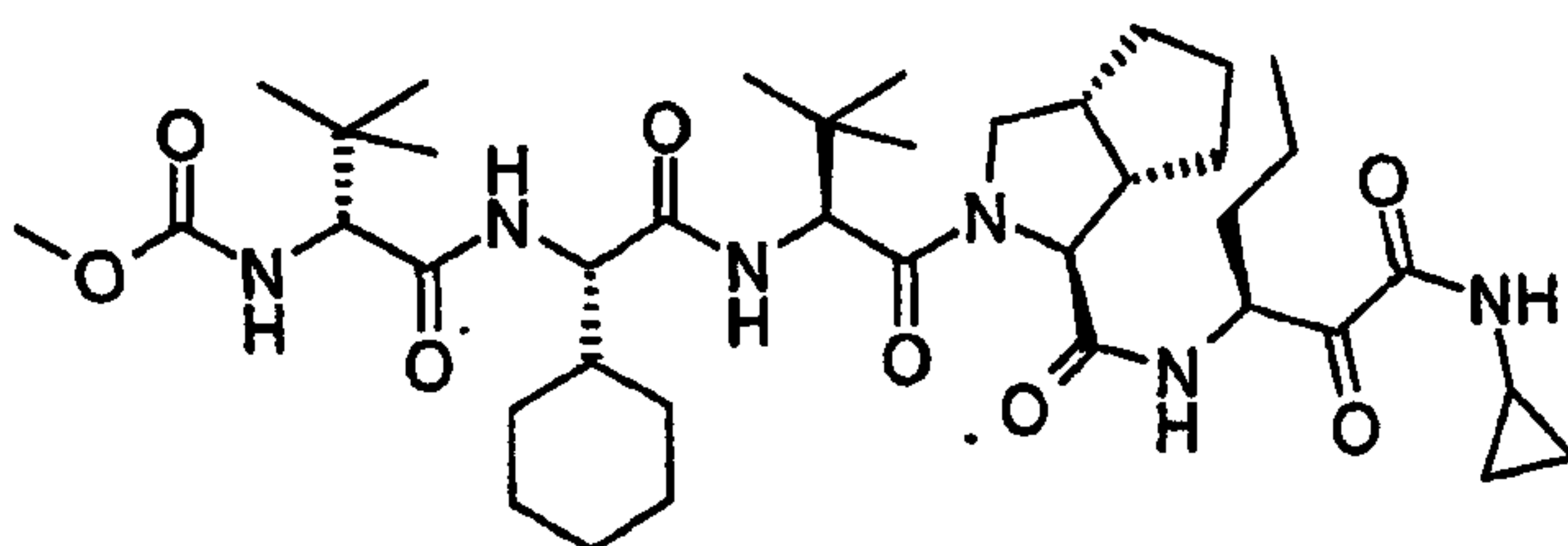


EW,



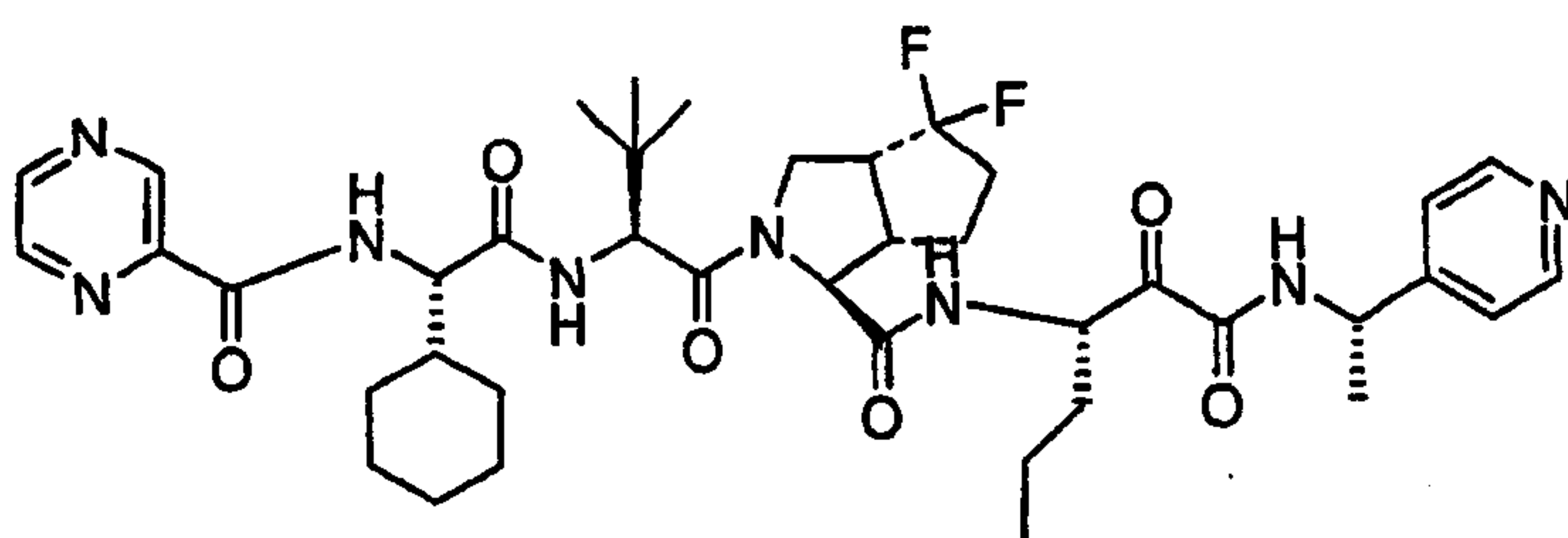
EX,

5



EY,

10

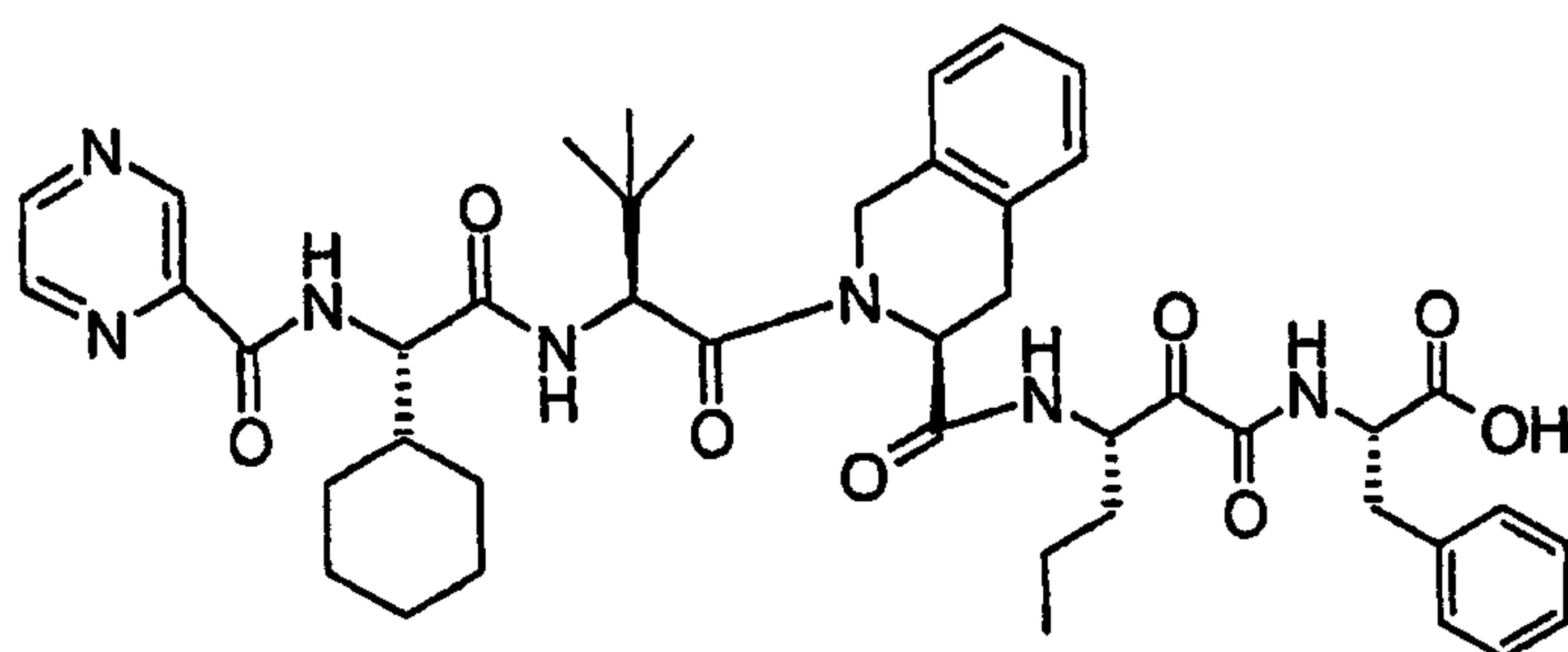


EZ,

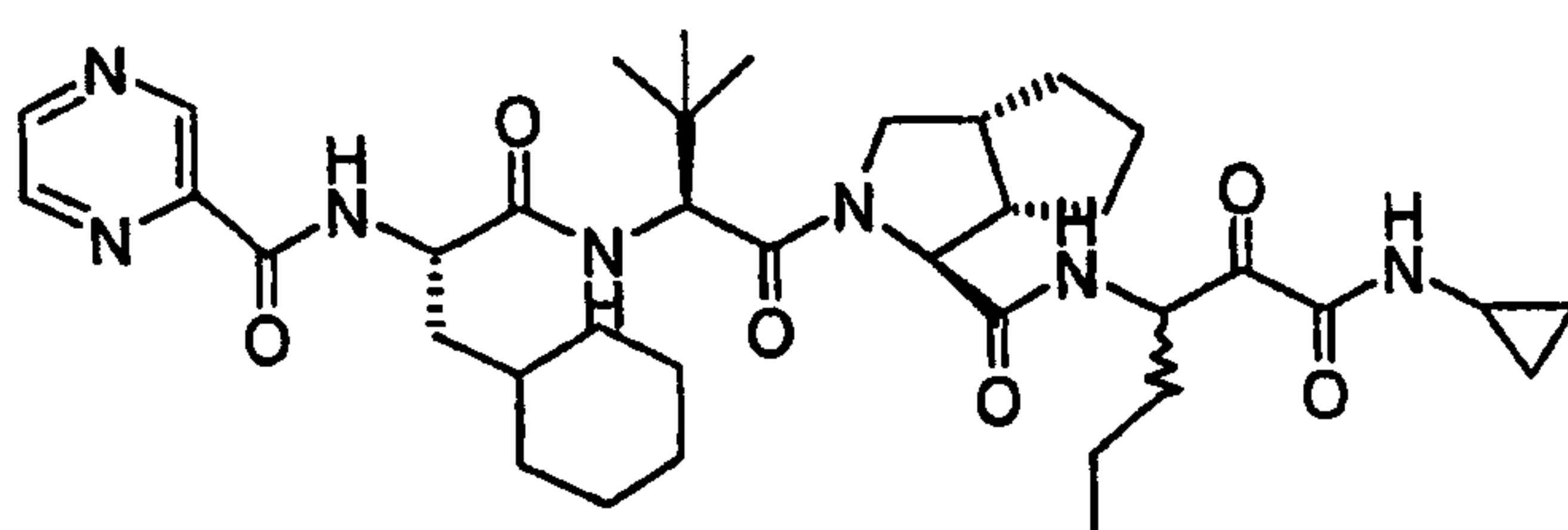
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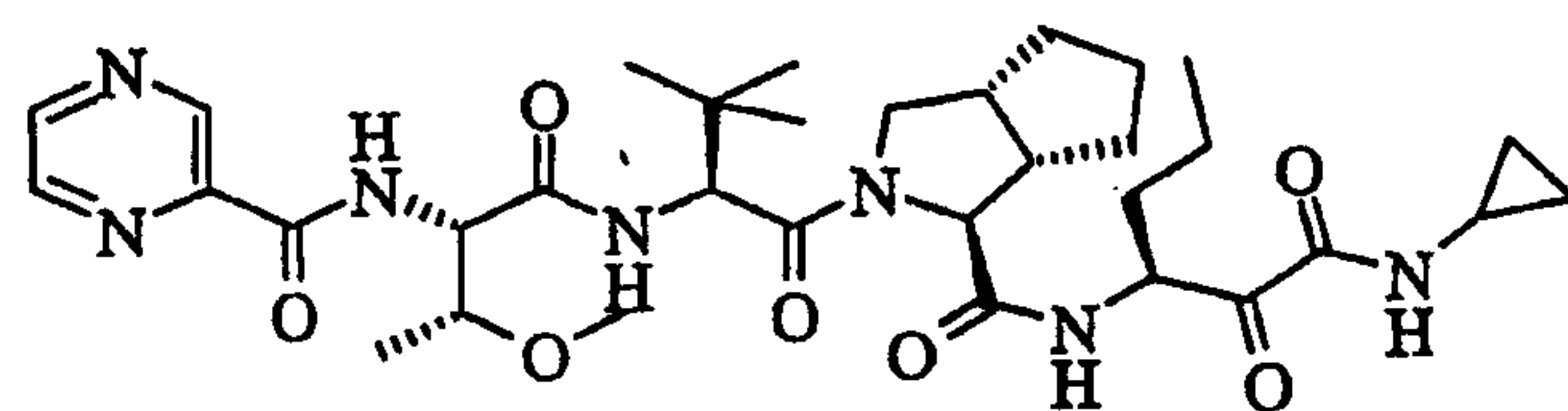
151



FA,

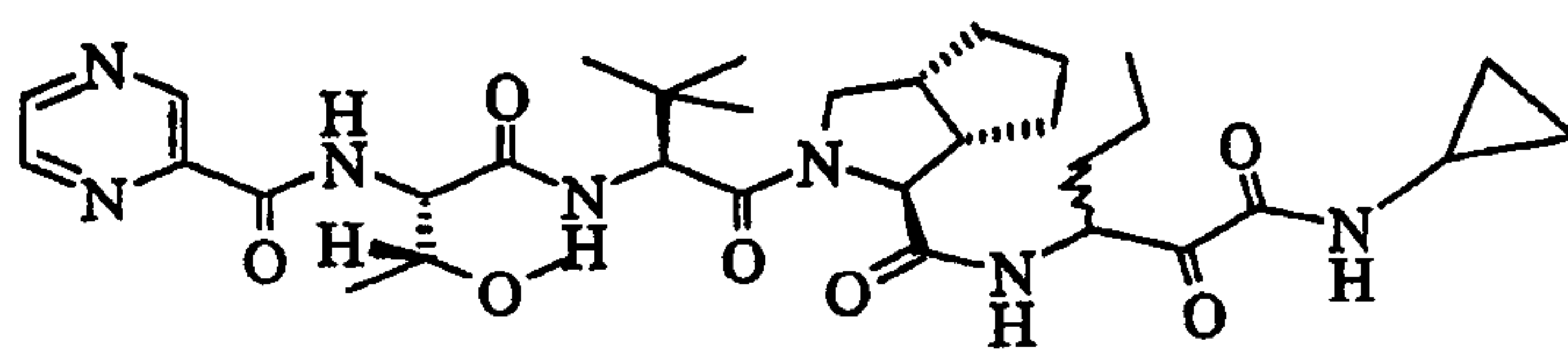


FB,



FC,

10

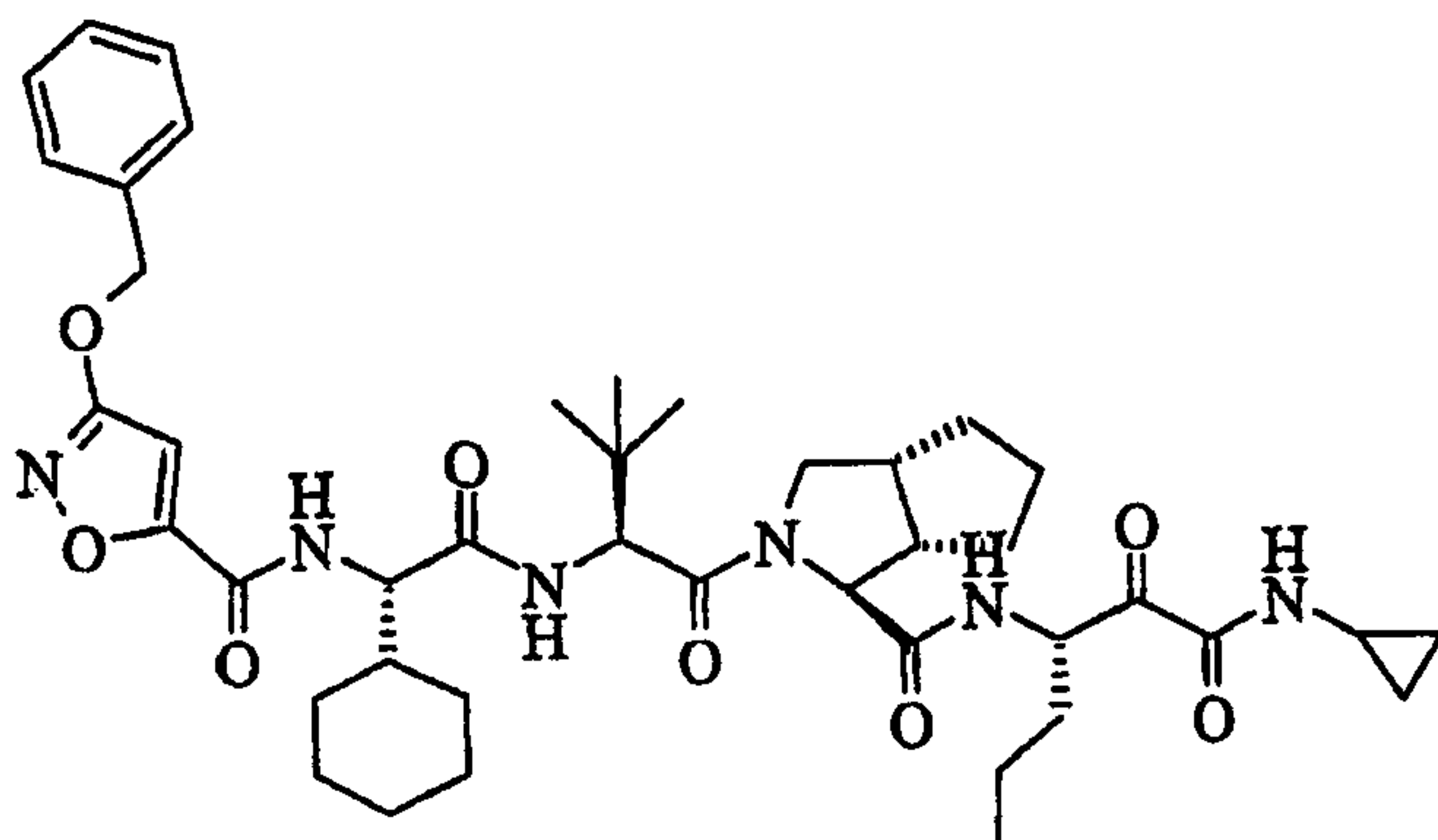


FD,

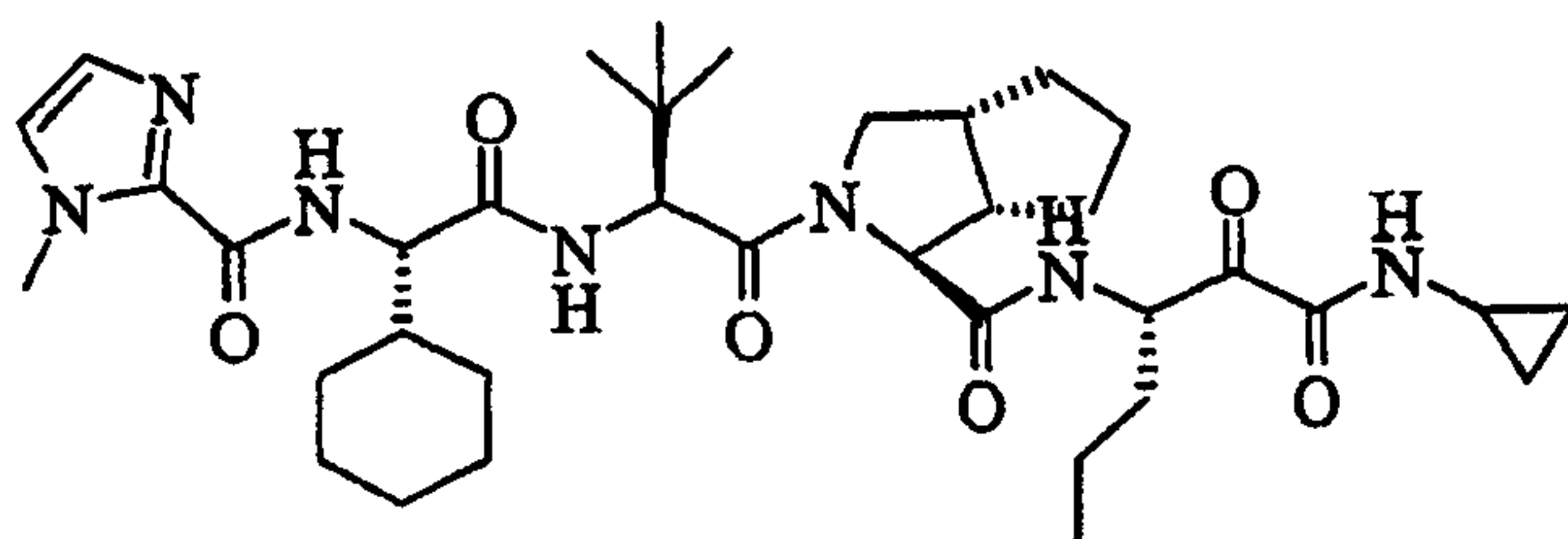
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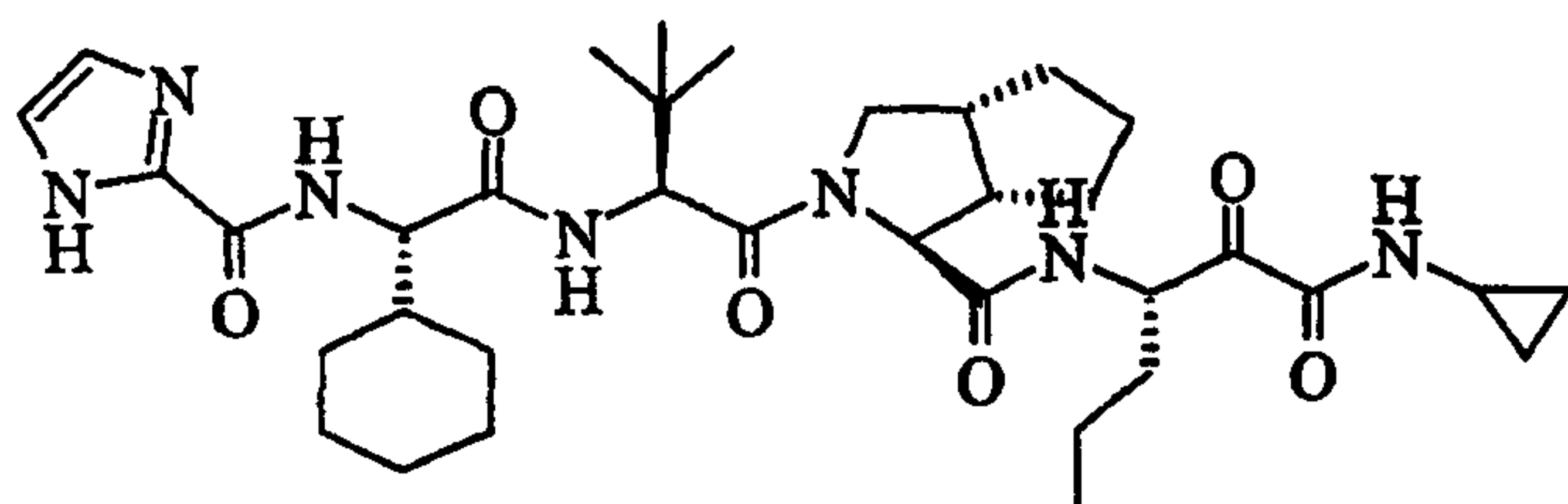
152



FE,



FF,



FG, and

5

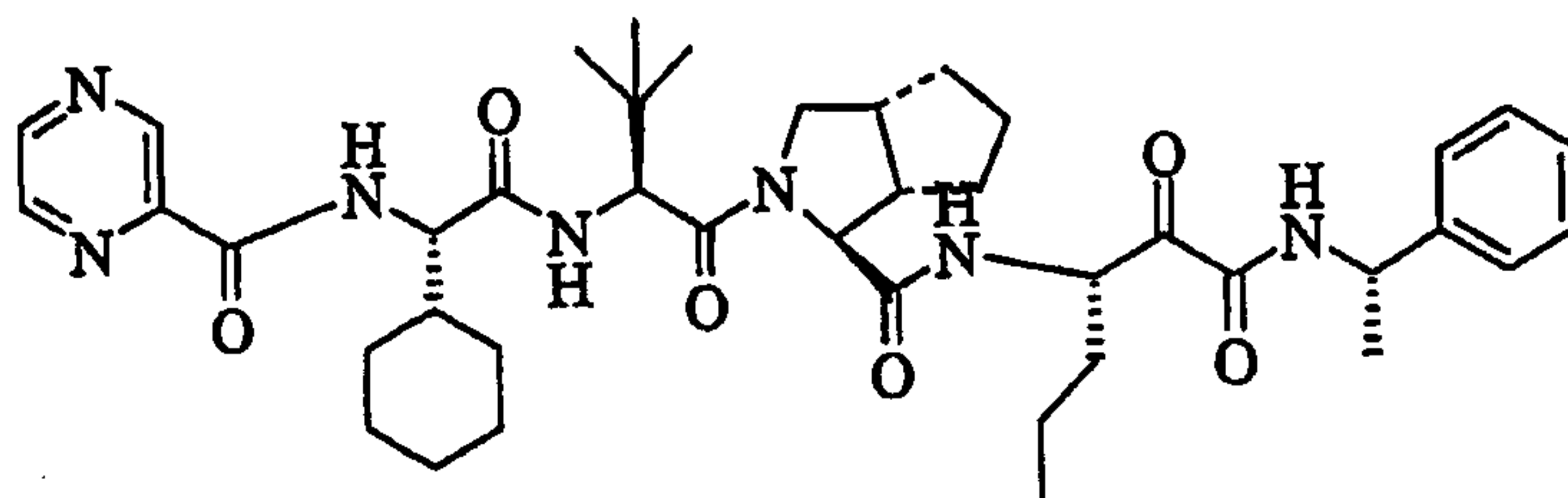
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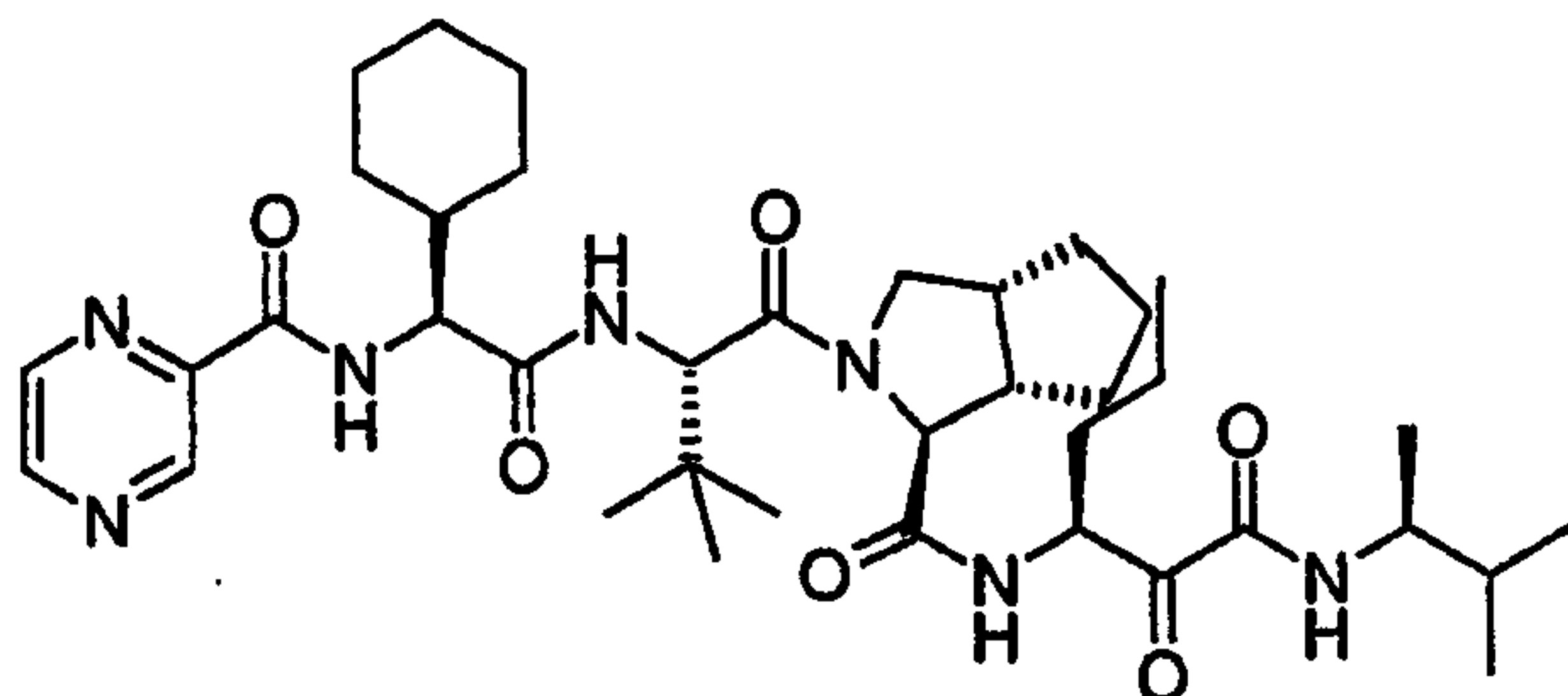


FH.

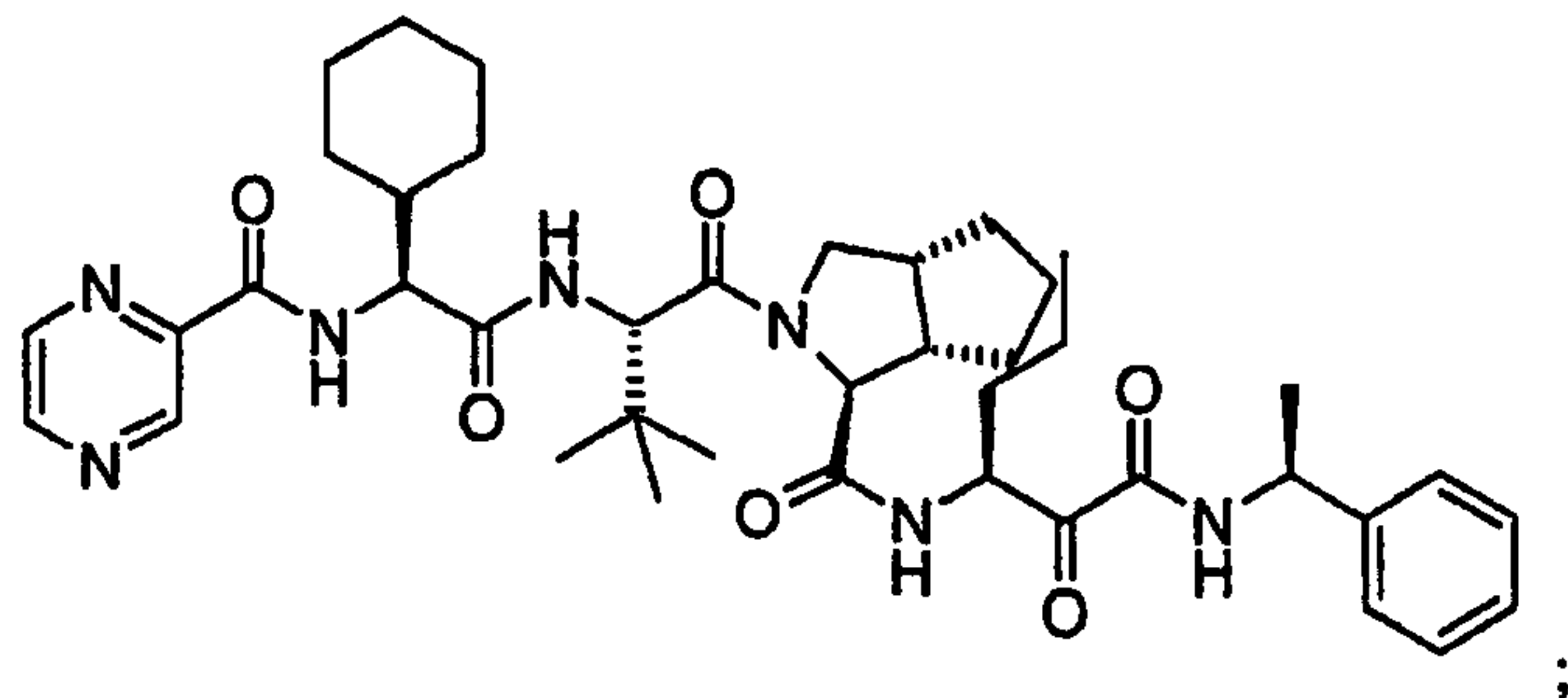
5 Example 28 – Compounds CV-DC

Compound cxxx (330 mg, 0.46 mmol) is dissolved in DCM (5 mL). DMP reagent reagent (240 mg, 0.56 mmol) is added to this solution and stirred 1 hour. The reaction mixture is quenched with a 10% Na₂SO₃, and the organic phase washed with saturated NaHCO₃ and brine.

Following the concentration of the organic phase, the resulting residue is
 10 chromatographically purified by 100% EtOAc to yield compound cxxx (280 mg, 85.9%).



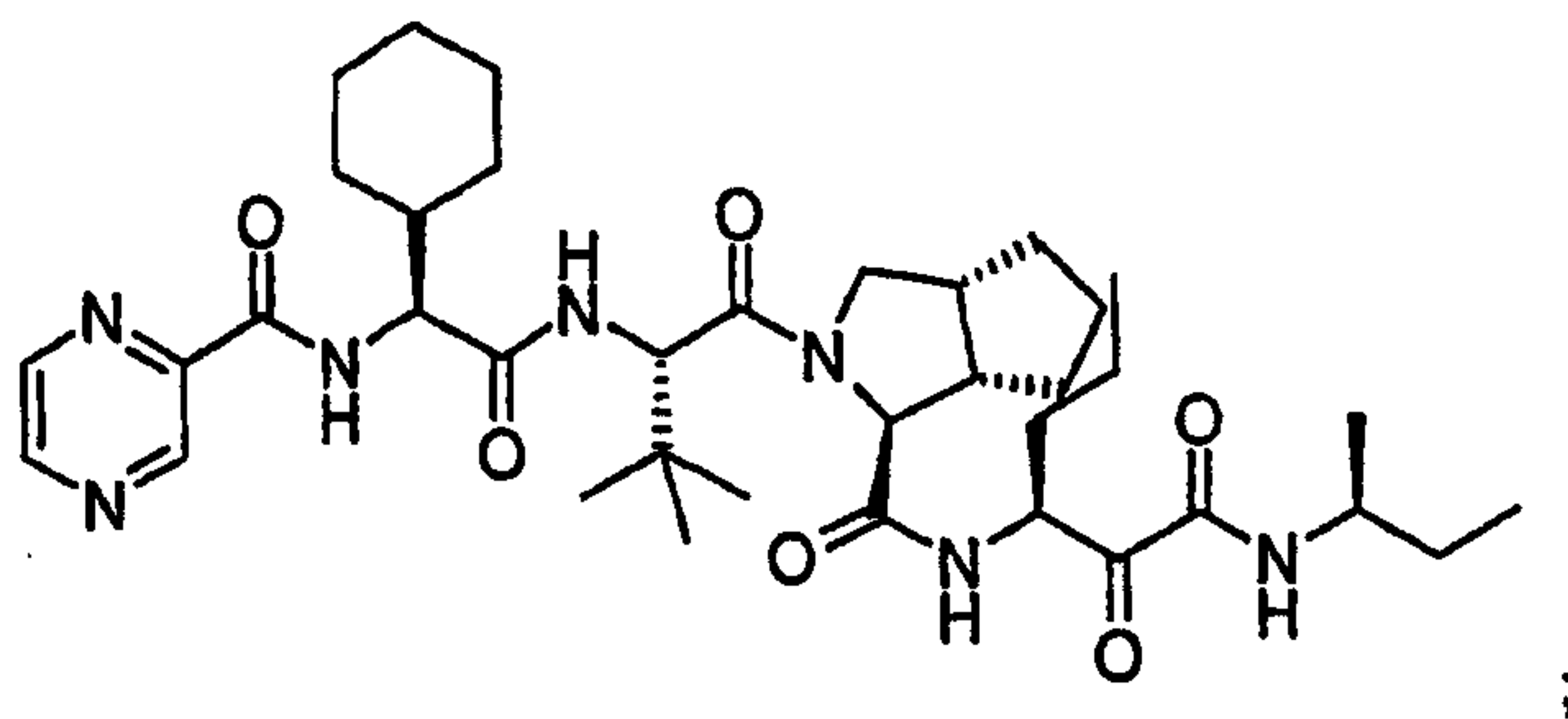
Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following
 15 consecutive compounds CW-DC are prepared:



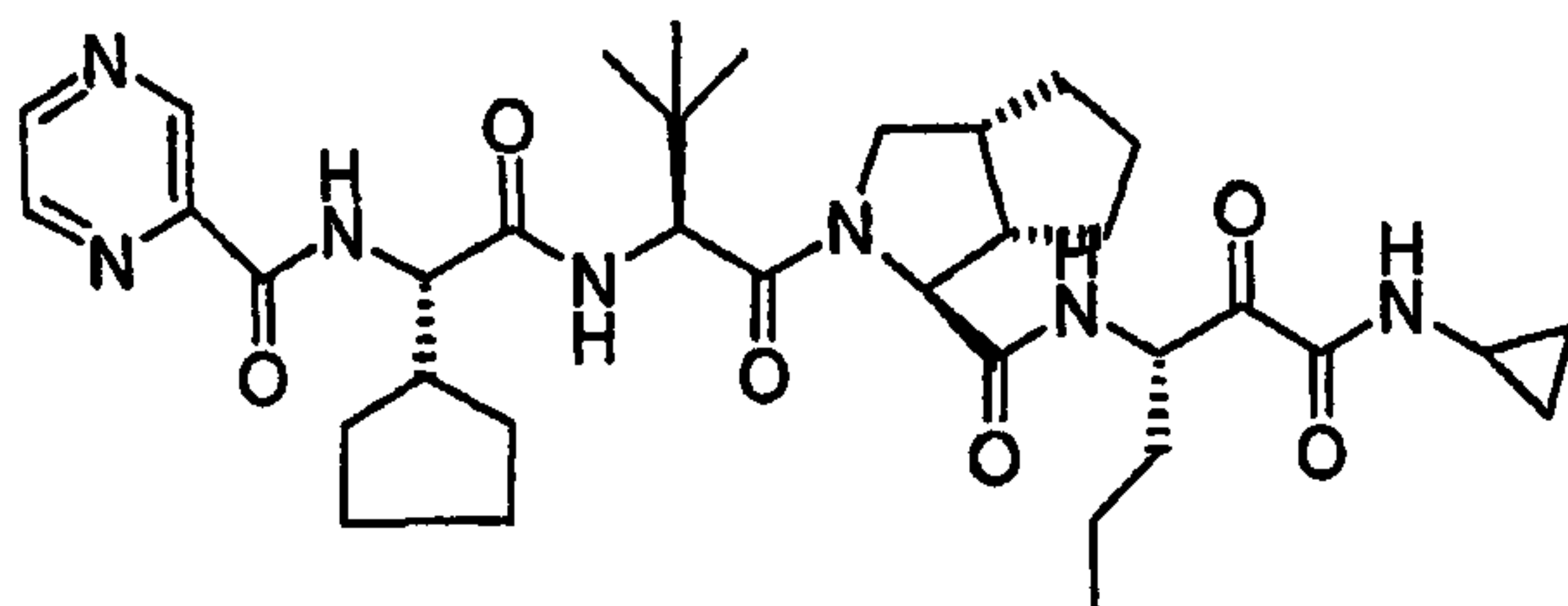
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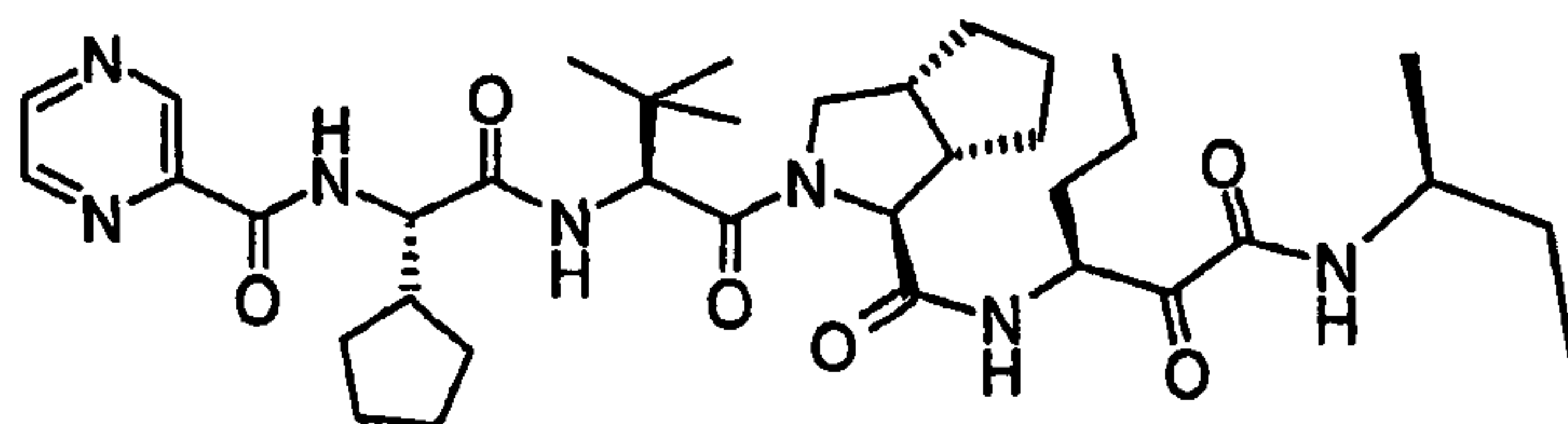
154



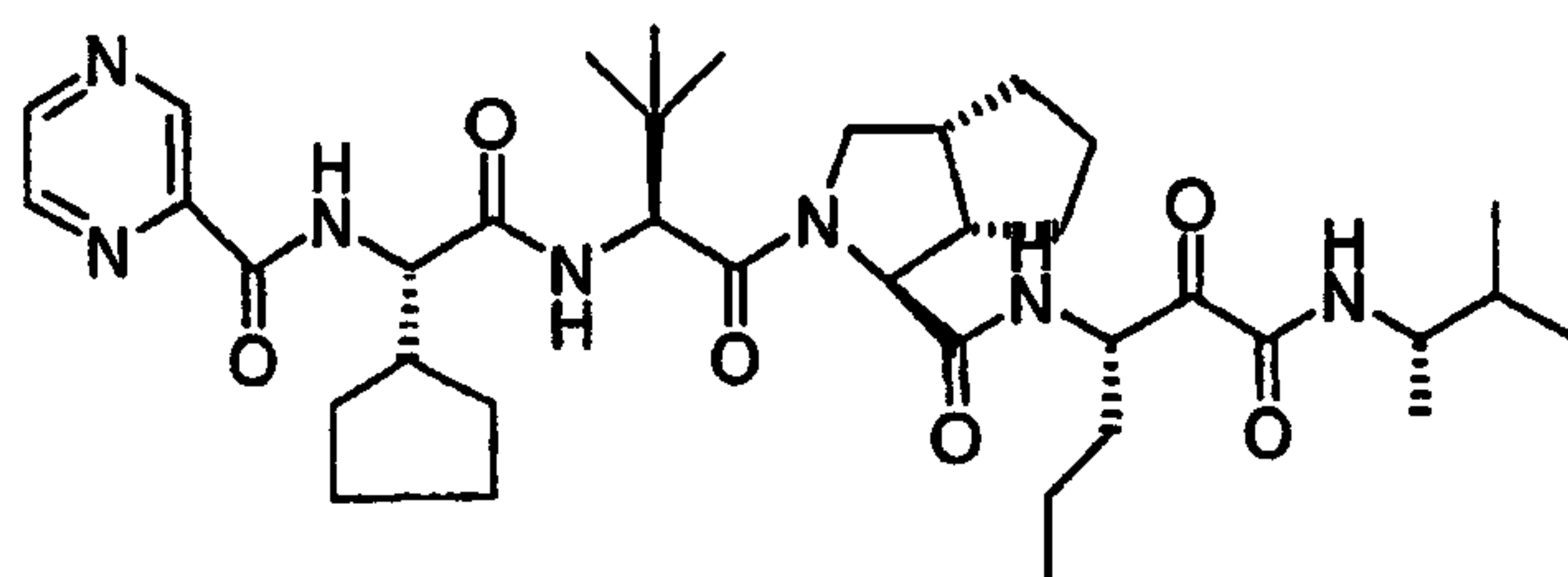
;



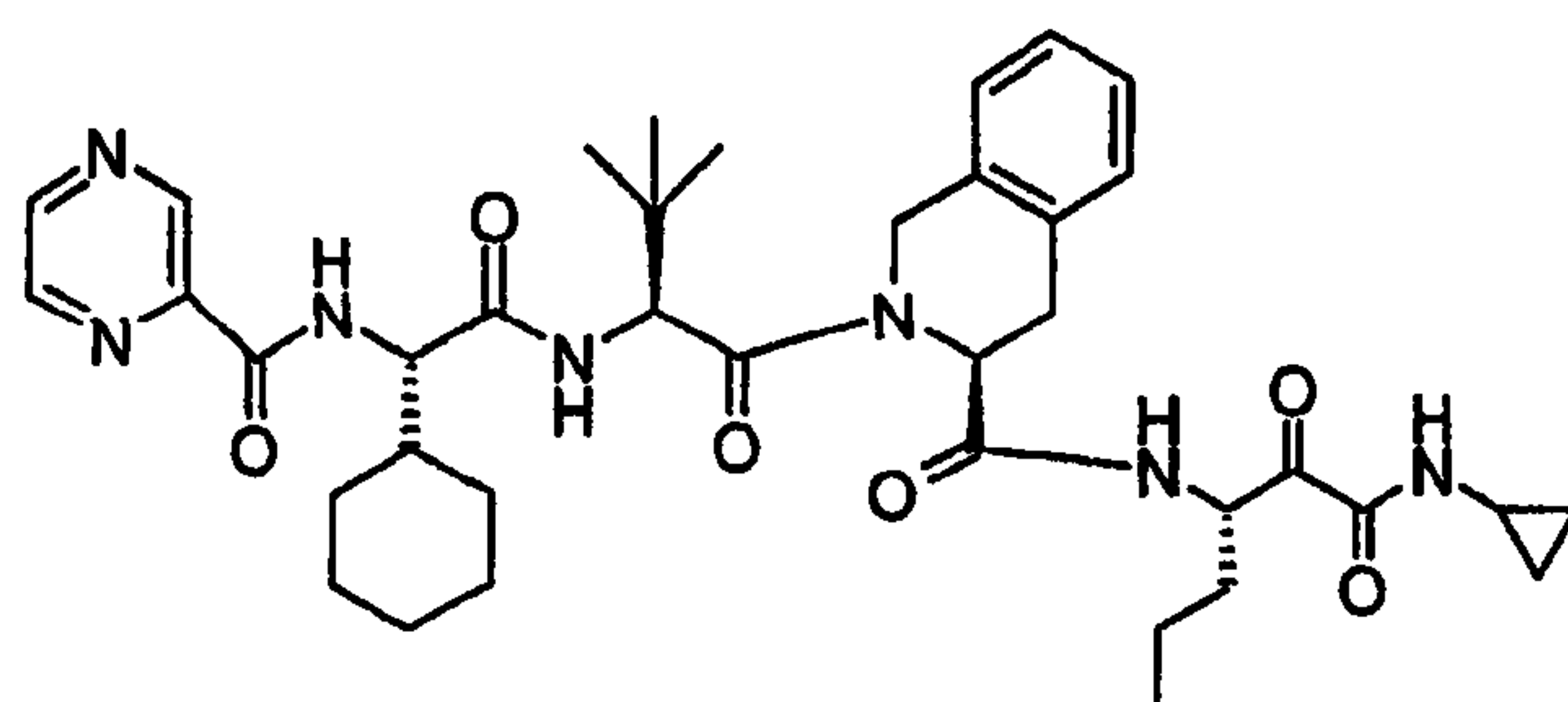
;



;

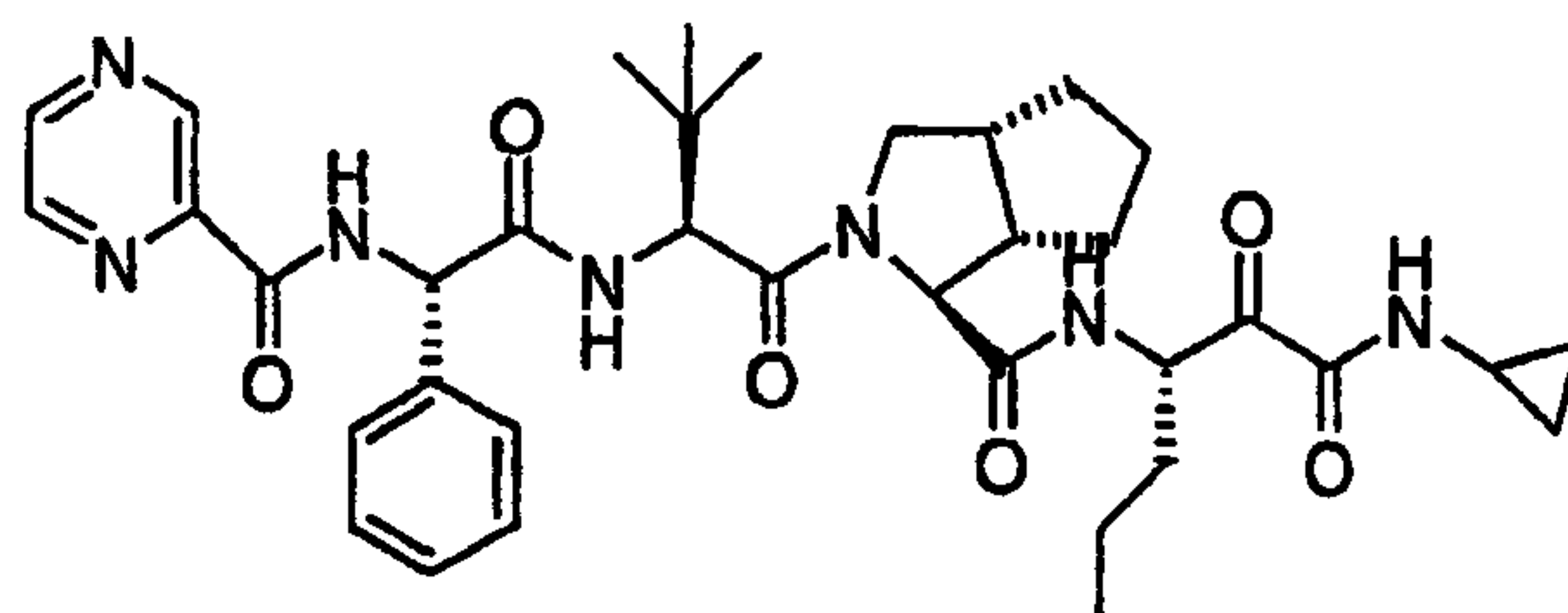


;



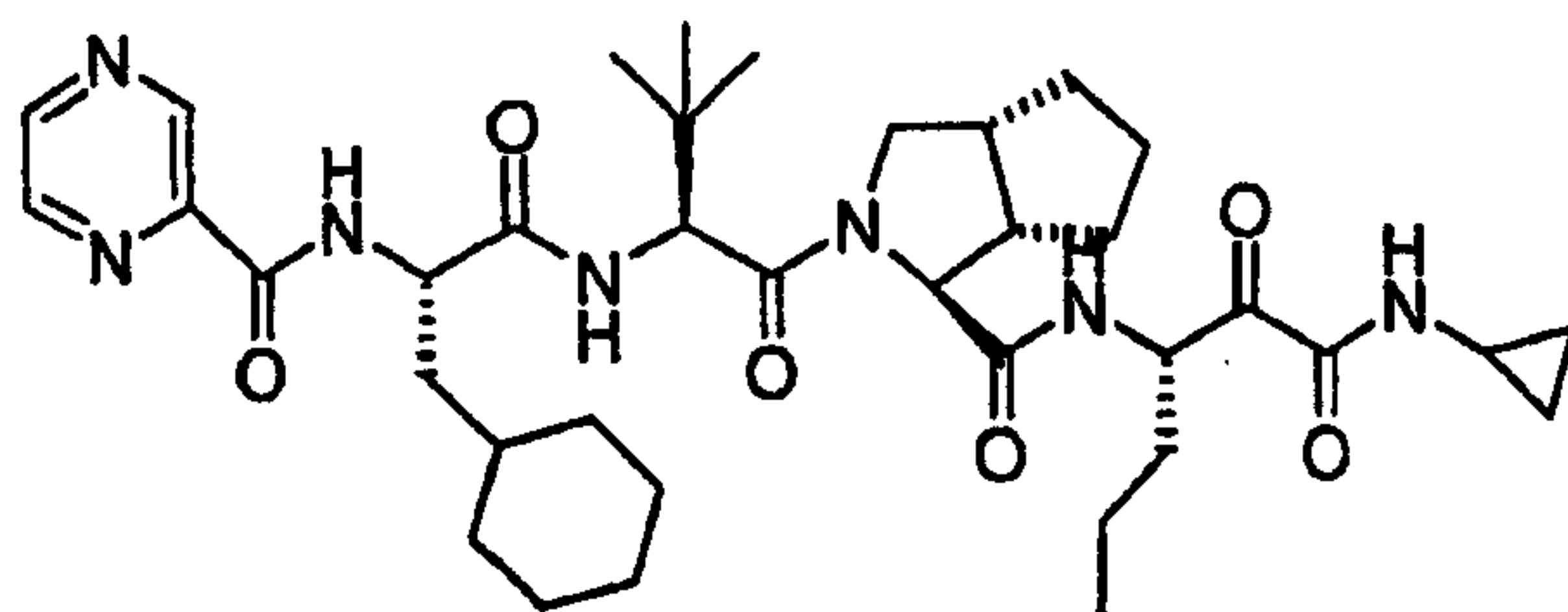
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; and

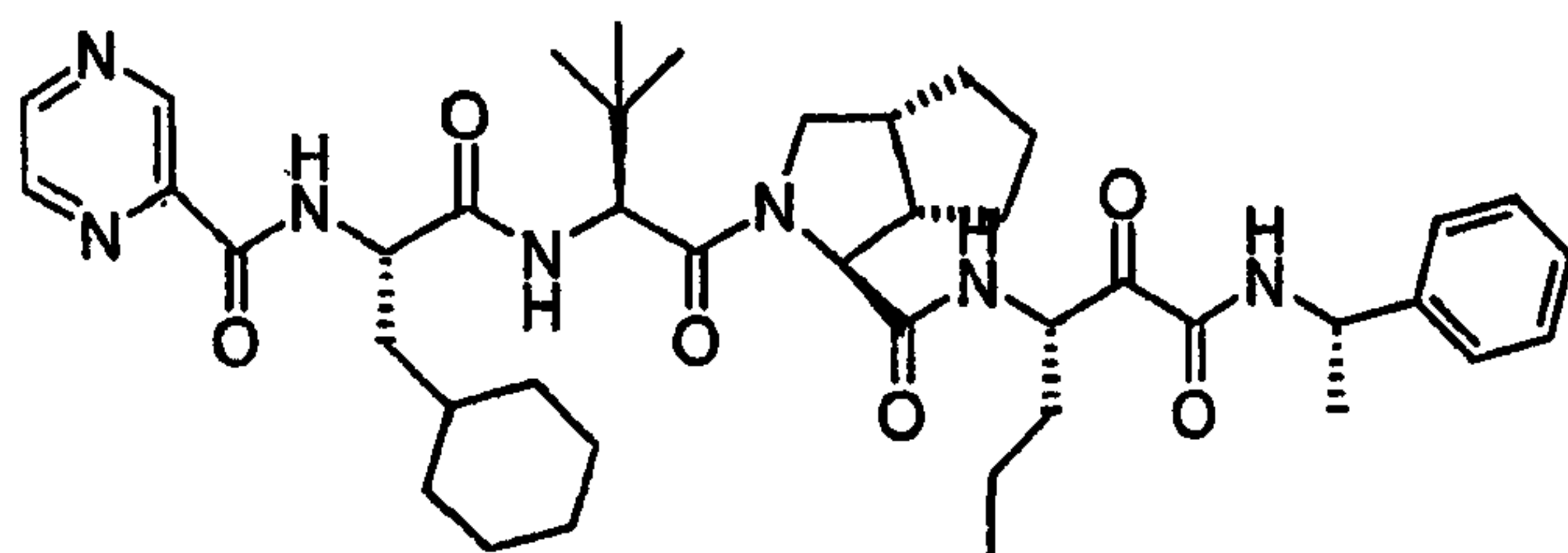


Example 29 – Compounds DD-DE

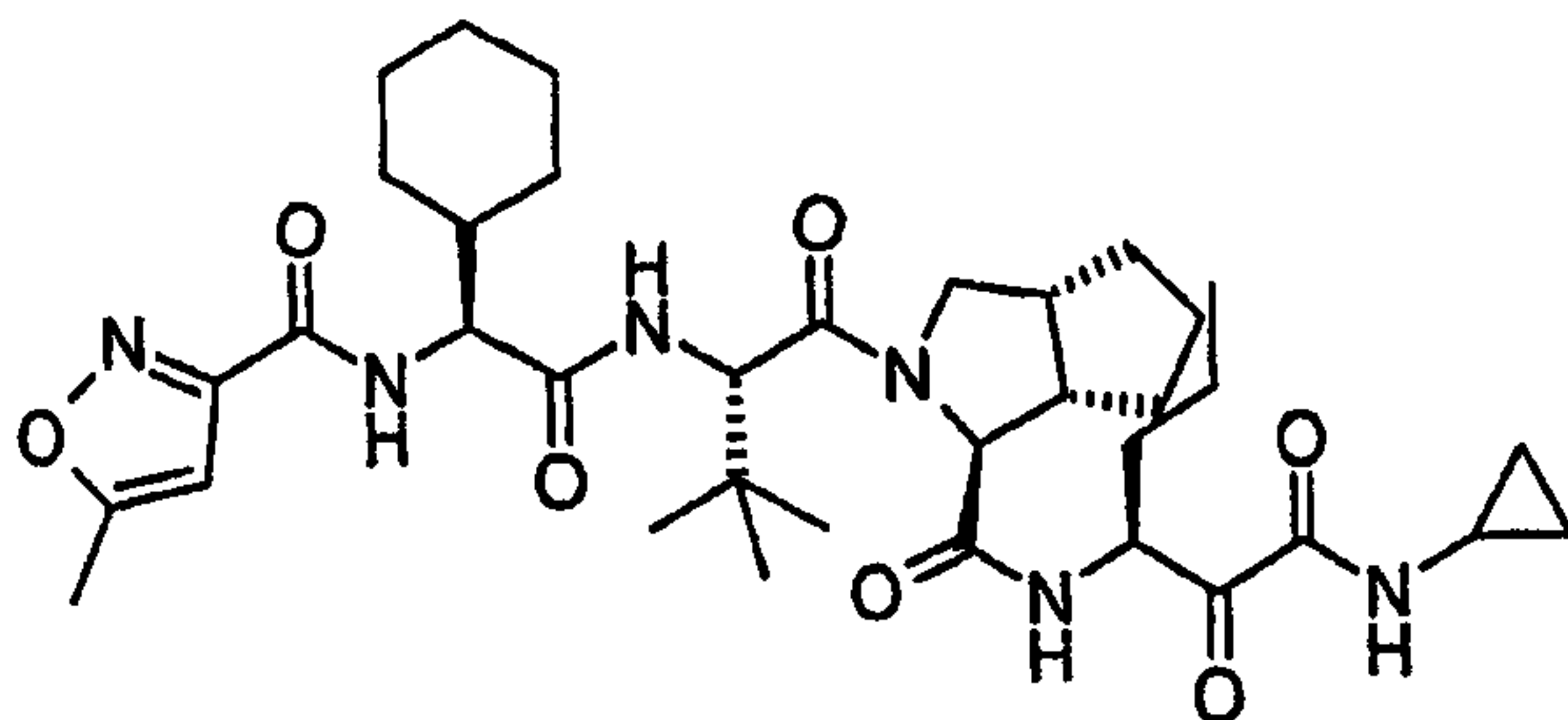
To a DCM solution (6 mL) of compound cxxxviii (400 mg, 0.57 mmol) is added DMP reagent reagent (362 mg, 0.85 mmol). The reaction mixture is stirred at room temperature for 2 hours and quenched with 10% Na₂SO₃ (aq.) for 20 minutes. The resulting mixture is extracted with EtOAc. The extracted organic phase is washed with brine, dried over MgSO₄ and concentrated to yield yellow oil. Purification by silica gel (70% EtOAc/hexanes) yields compound DD (201 mg, 51%).



Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following compound DE is prepared:

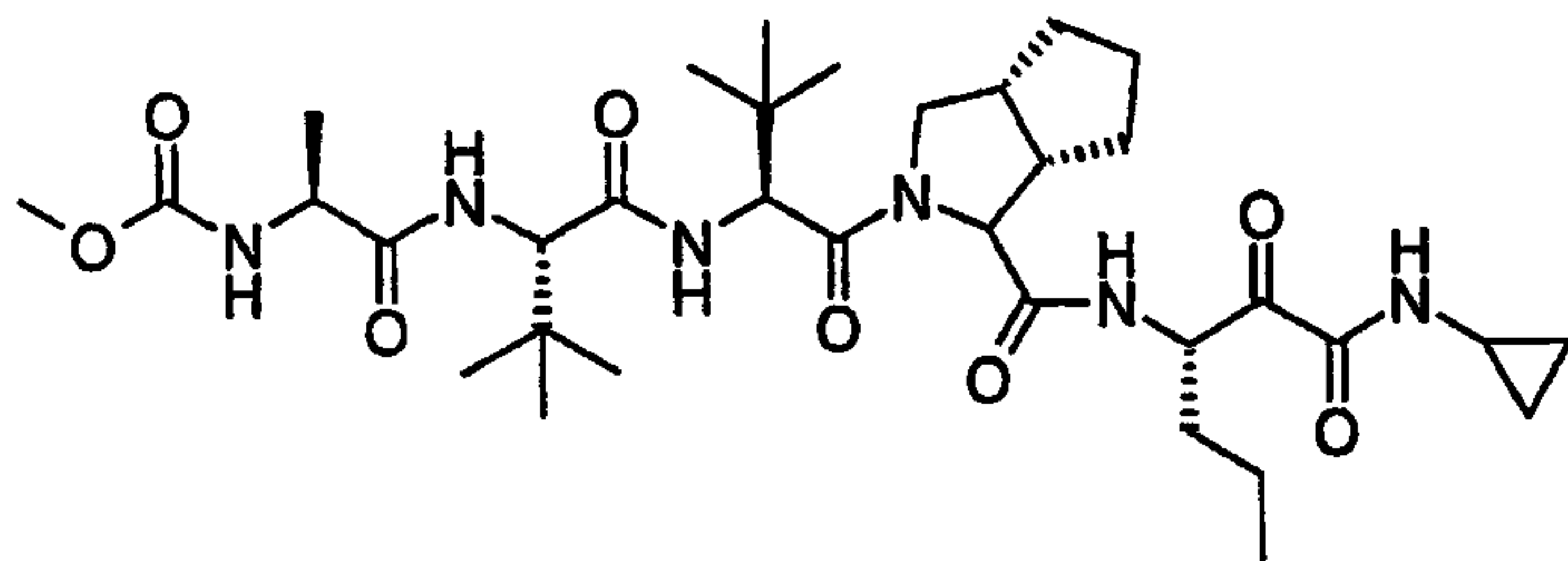
**Example 30 – Compound DF**

Compound cxxxiii (165 mg, 0.24 mmol) is dissolved in DCM (5 mL). DMP reagent reagent (125 mg, 0.29 mmol) is added to the solution and stirred 1 hour. The reaction mixture is quenched with a 10% Na₂SO₃, and the organic phase washed with saturated NaHCO₃ and brine. Following the concentration of the organic phase, the resultant residue is purified chromatographically by 70% EtOAc/hexanes to yield compound DF (108 mg, 65.6%).

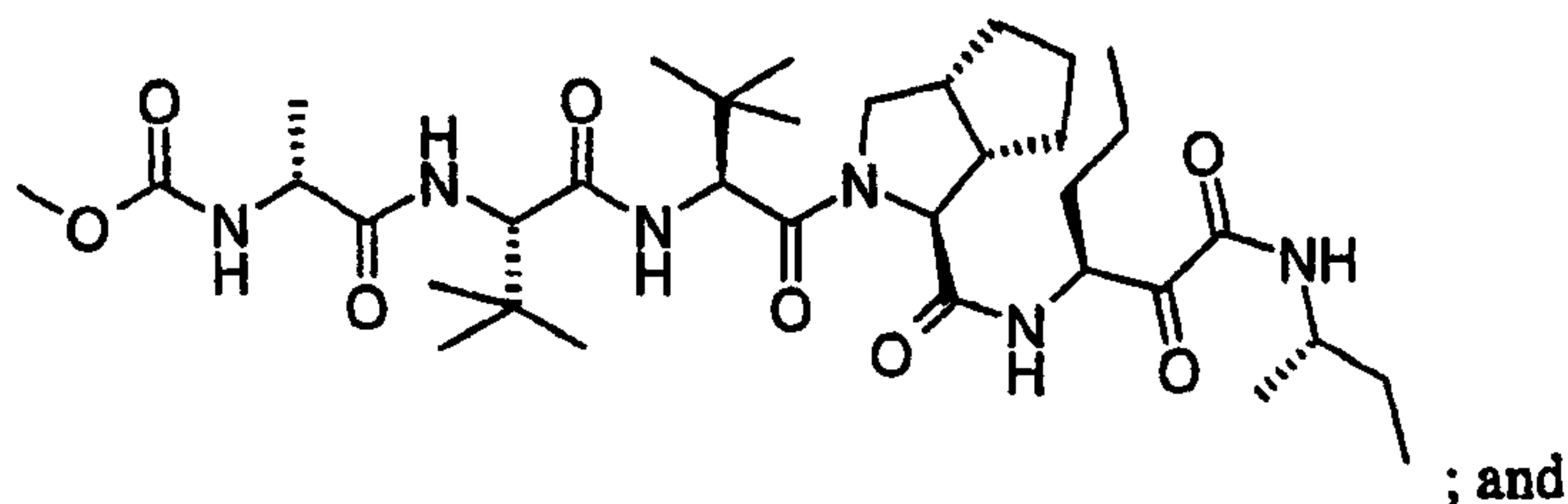
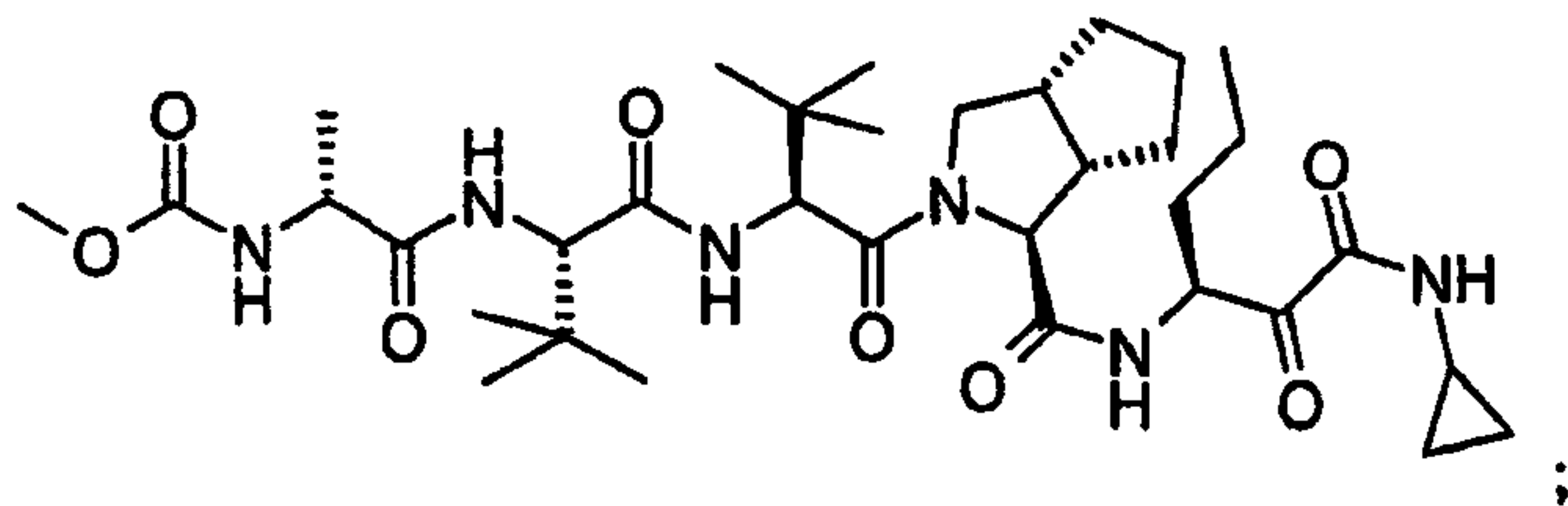


Example 31 – Compounds DG-DJ

To a solution of compound cil (0.350 g, 0.516 mmol) in DCM (15 mL) cooled by an ice
 5 bath is added DMP reagent reagent (0.281 g, 0.671 mmol). The mixture is stirred at room
 temperature for 2 hours, then quenched with 10% Na₂SO₃ solution and stirred for 20 minutes.
 The resulting mixture is extracted with DCM (3x20 mL) and the organic extract is dried (MgSO₄).
 After filtration to remove MgSO₄, the filtrate is concentrated and purified by column
 chromatography (70% Ethyl acetate/Hexanes) to yield the final compound DG (0.265 g, 76%) as
 10 white solid.



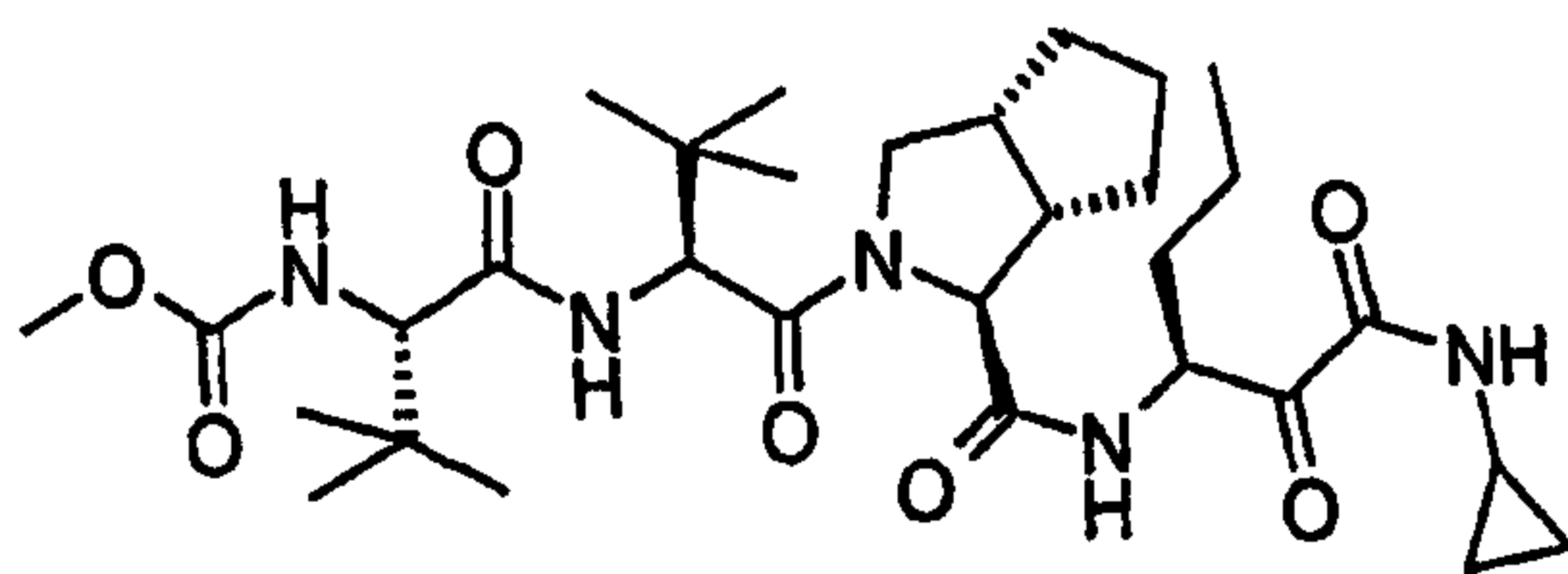
Following the above method for preparing the above compound and methods related to
 preparing the intermediate thereto, but using the appropriate starting materials the following
 15 consecutive compounds DH-DJ are prepared:



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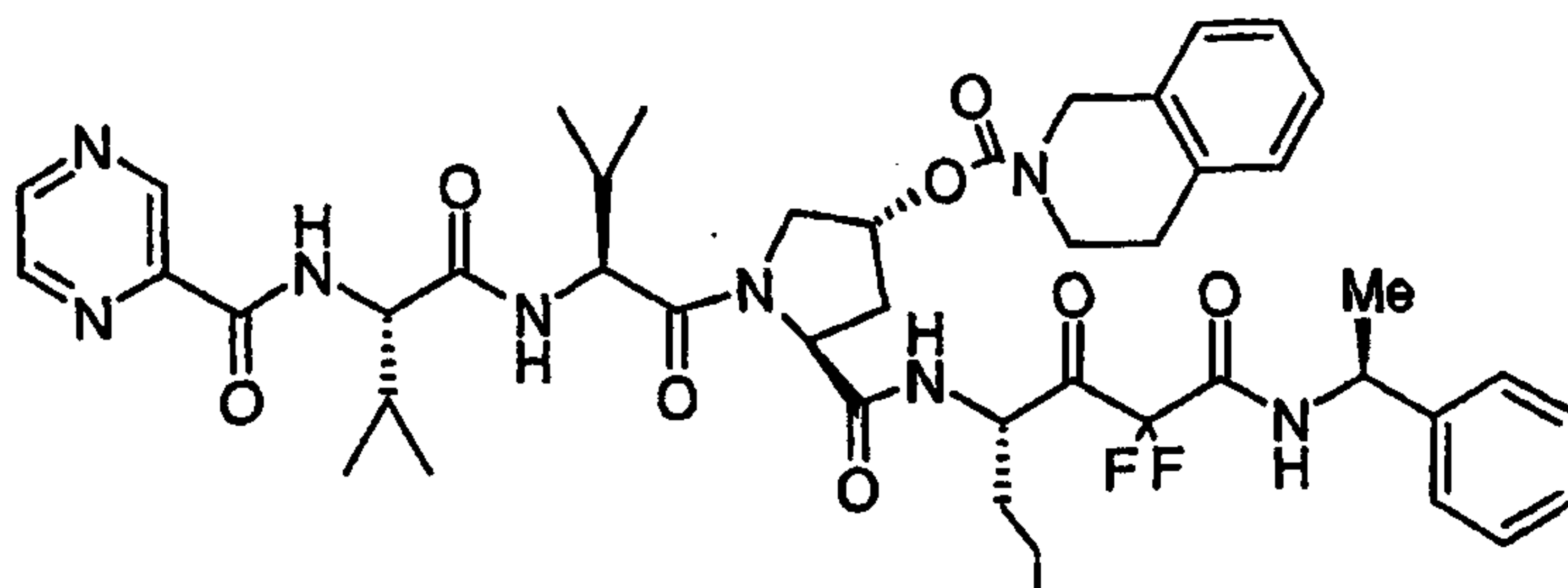
157



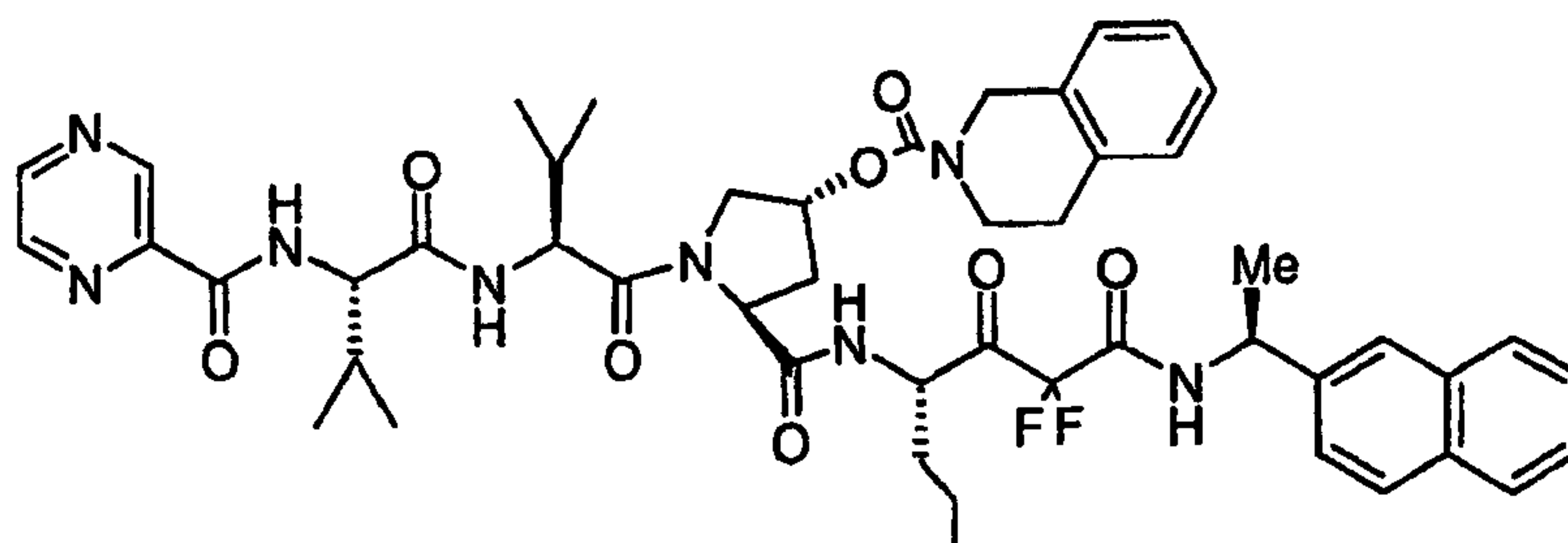
Example 32 – Compounds DK-DN

A DCM solution of compound clx (108 mg, 0.123 mmol) is treated with DMP reagent reagent
 5 (78 mg, 0.185 mmol). After stirring at room temperature for 1 hour, the reaction mixture is
 diluted with EtOAc (50 mL), and then quenched with 10% Na₂SO₃. After stirring for 30 minutes,
 the organic phase is separated and washed with NaHCO₃ and brine. The organic phase is dried
 and concentrated *in vacuo* to give a residue that is purified by silica gel chromatography (80%
 EtOAc/hexanes) to yield compound DK (84 mg, 78%).

10



Following the above method for preparing the above compound and methods related to
 preparing the intermediate thereto, but using the appropriate starting materials the following
 compounds DL-DN are prepared.

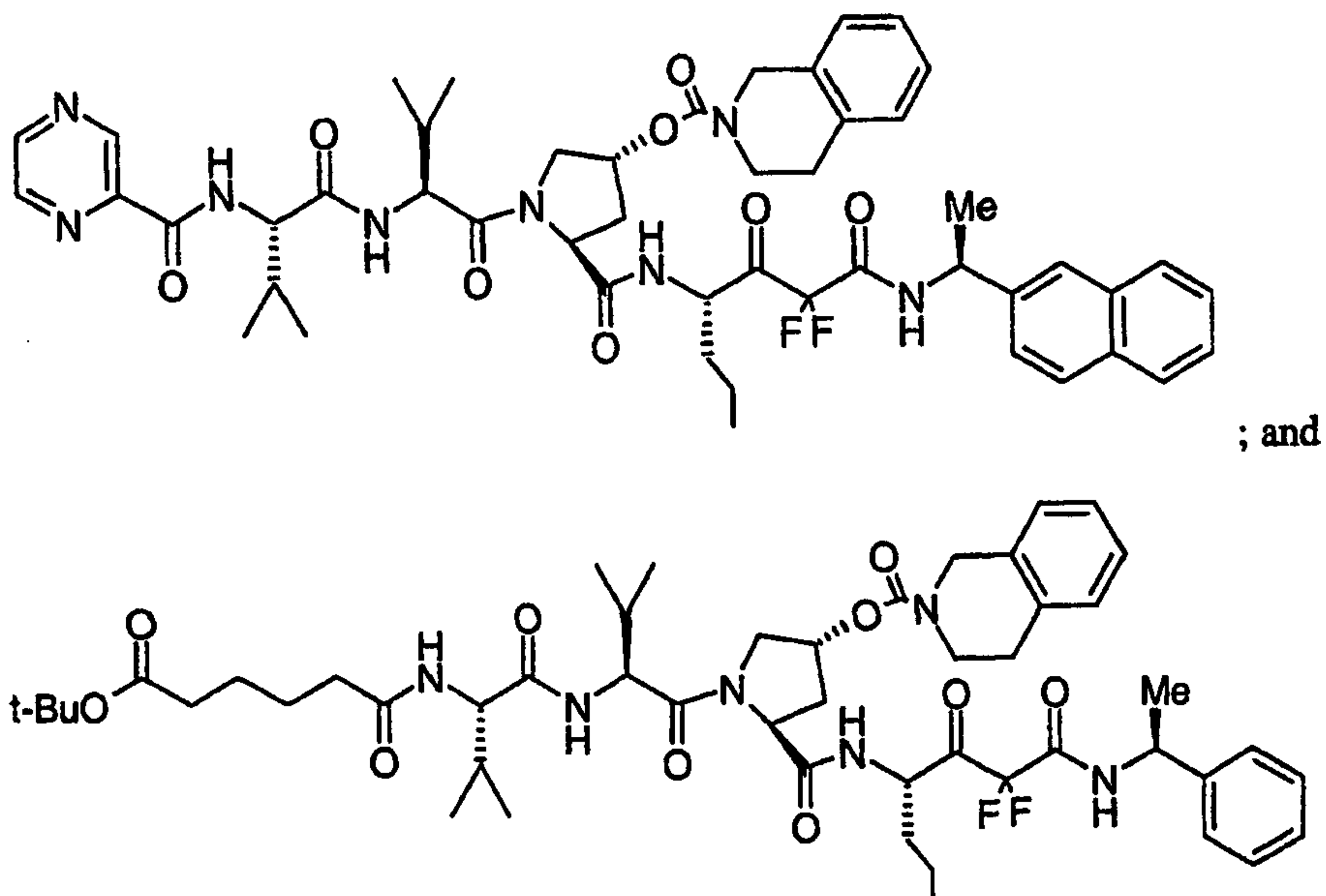


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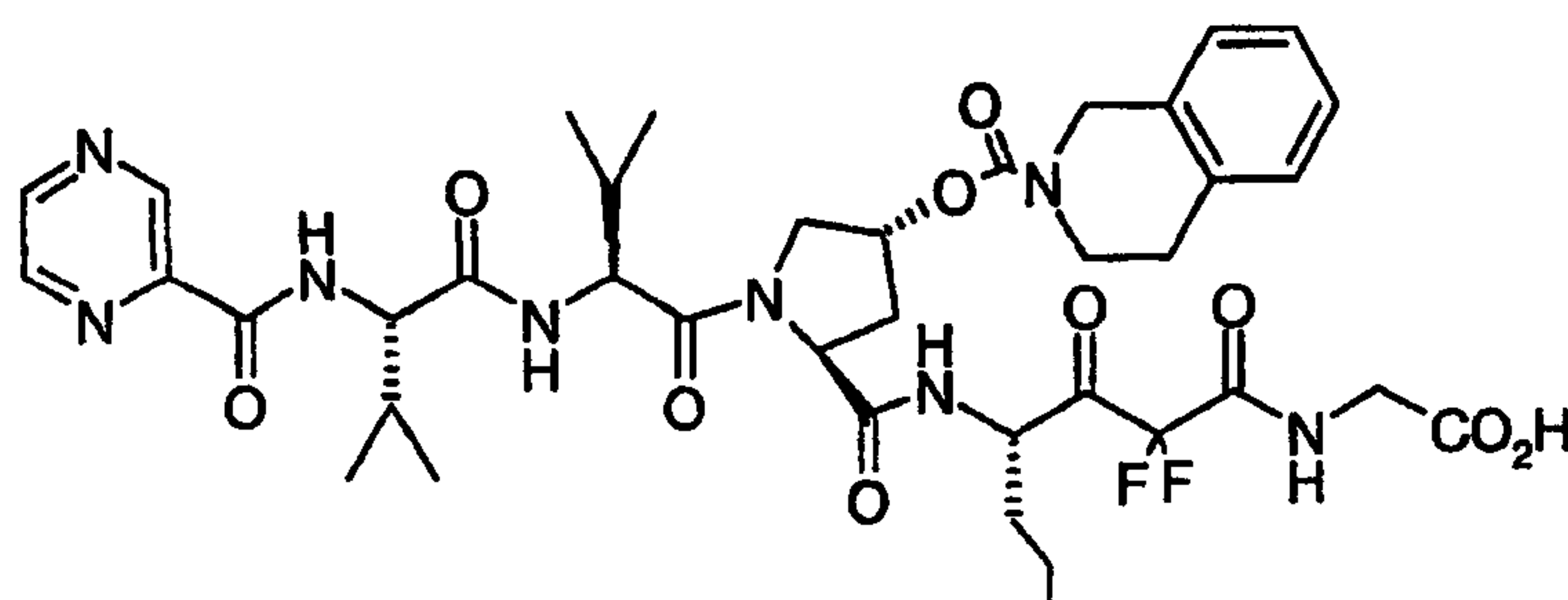
5

Example 33 – Compounds DO-DS

An EtOH solution (10 mL) of compound clxii (174 mg, 0.189 mmol) is hydrogenated using Pd/C (30% eq., 60 mg, 10% palladium content) for 2.5 hours. The catalyst is then filtered off.

The resulting filtrate is concentrated *in vacuo* to yield a residue that is purified by semi-

10 preparative reverse phase chromatography and lyophilized to afford compound DO in 70 % yield.

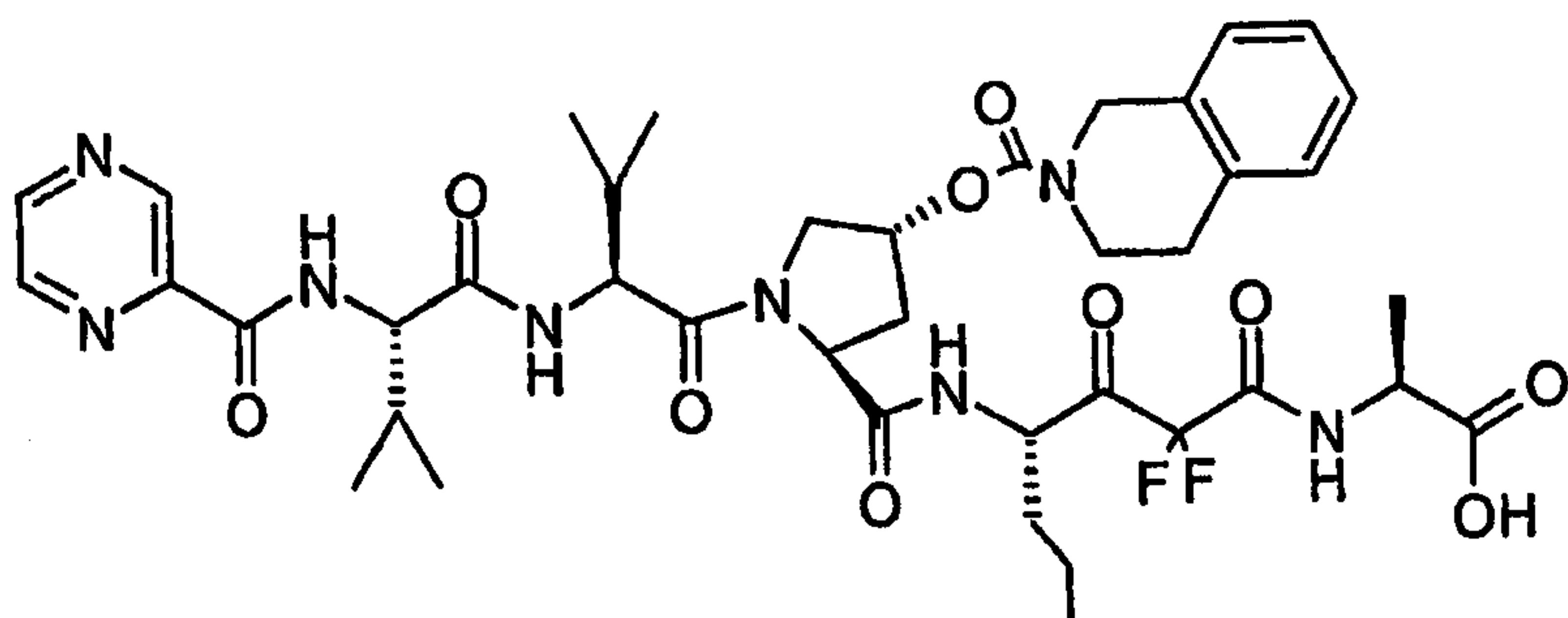


15 Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following consecutive compounds DP-DS are prepared.

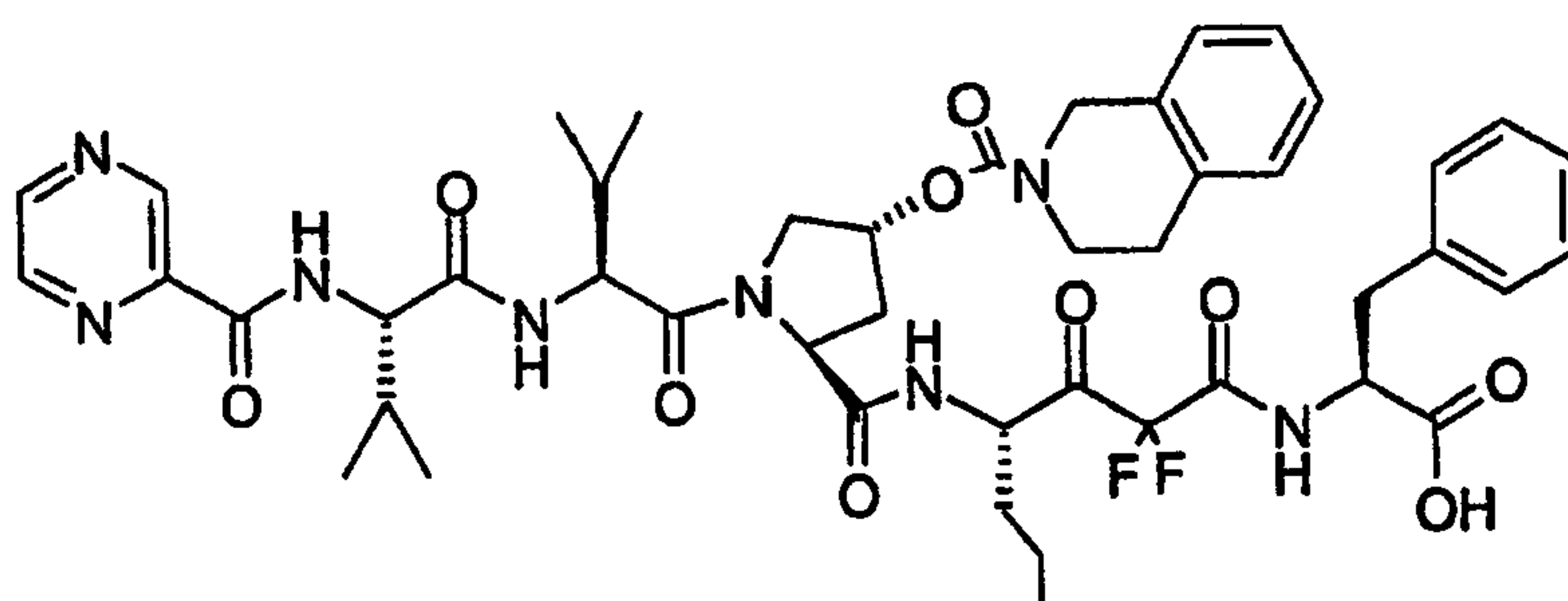
WO 02/18369

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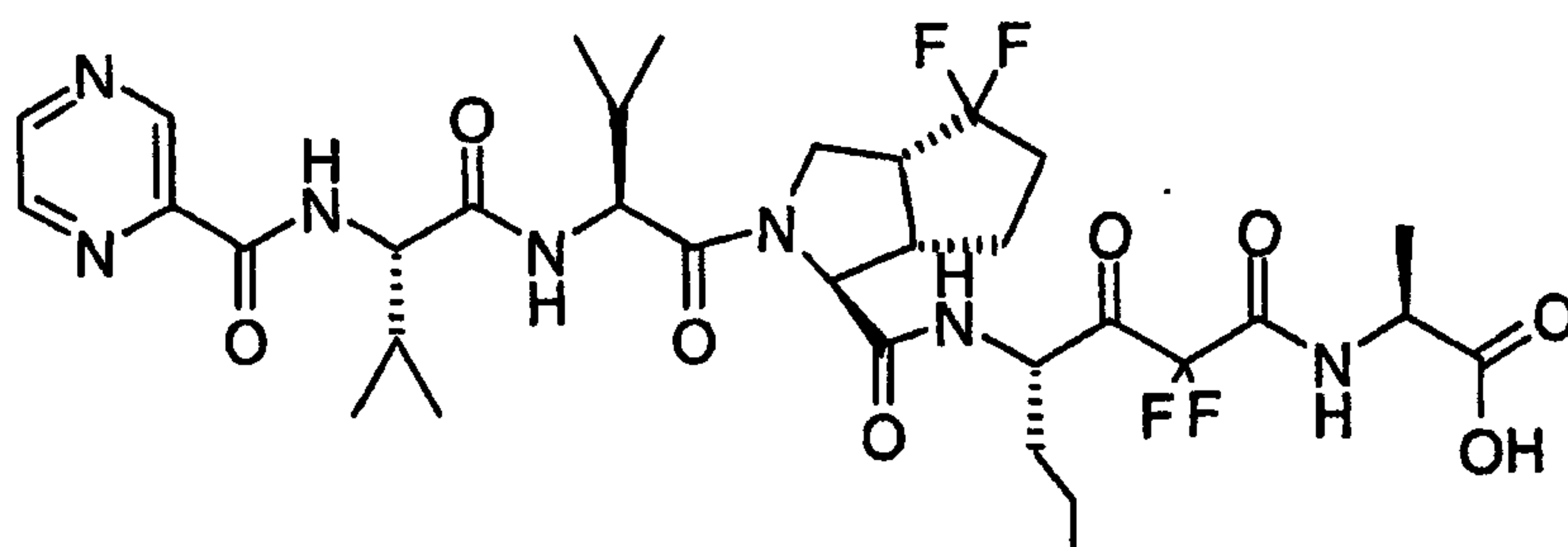
159



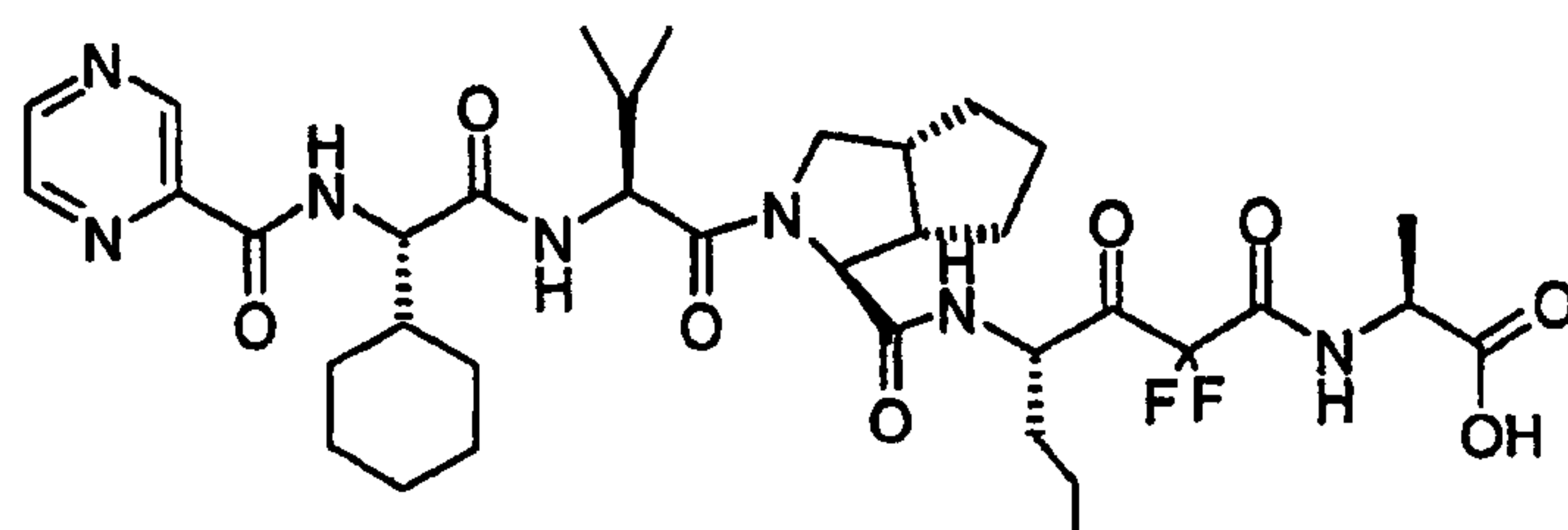
;



;



; and



5

Example 34 – Compound CW:

Compound clxiii (175 mg, 0.24 mmol) is taken up in DCM (3mL). DMP reagent (120 mg, 0.28 mmol) is added to this solution and stirred 1 hour. The reaction is quenched with a 10% Na_2SO_3 and washed with saturated NaHCO_3 and brine. Purification by 70% EtOAc yields

10

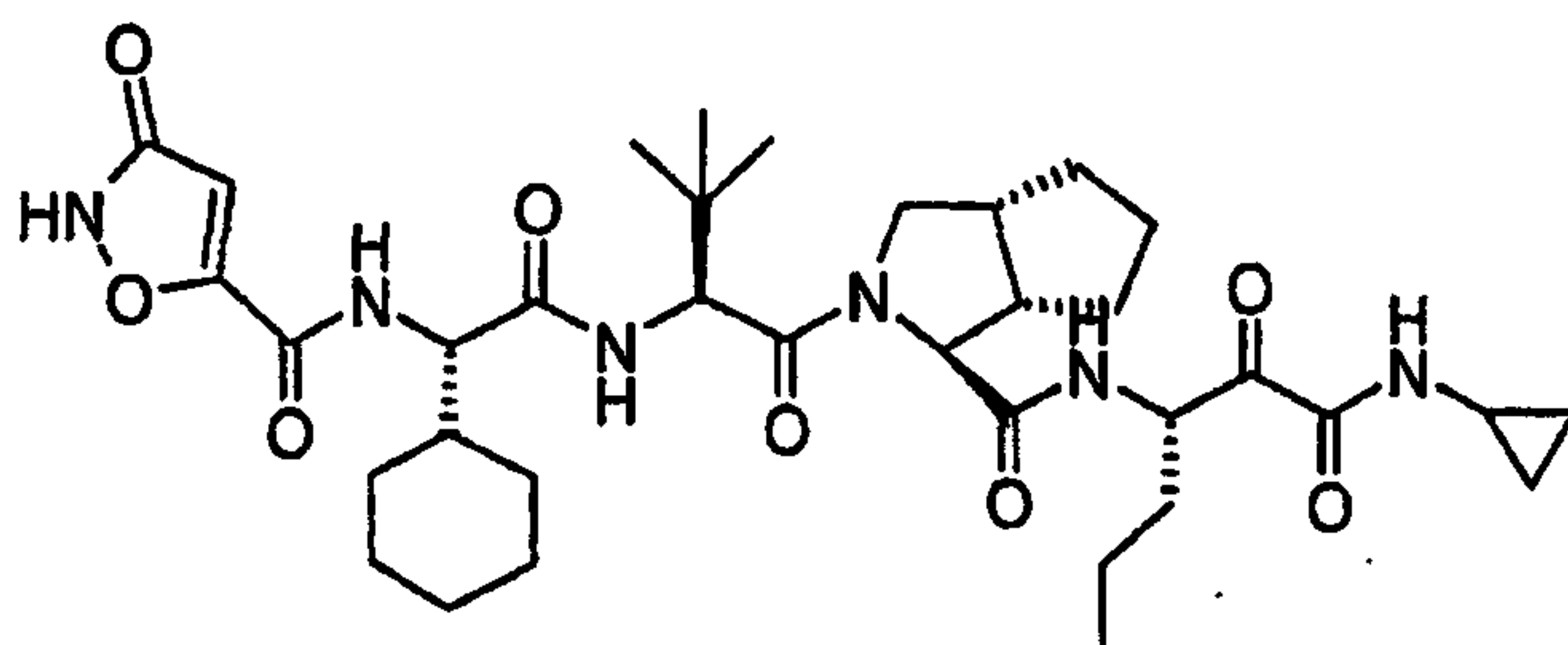
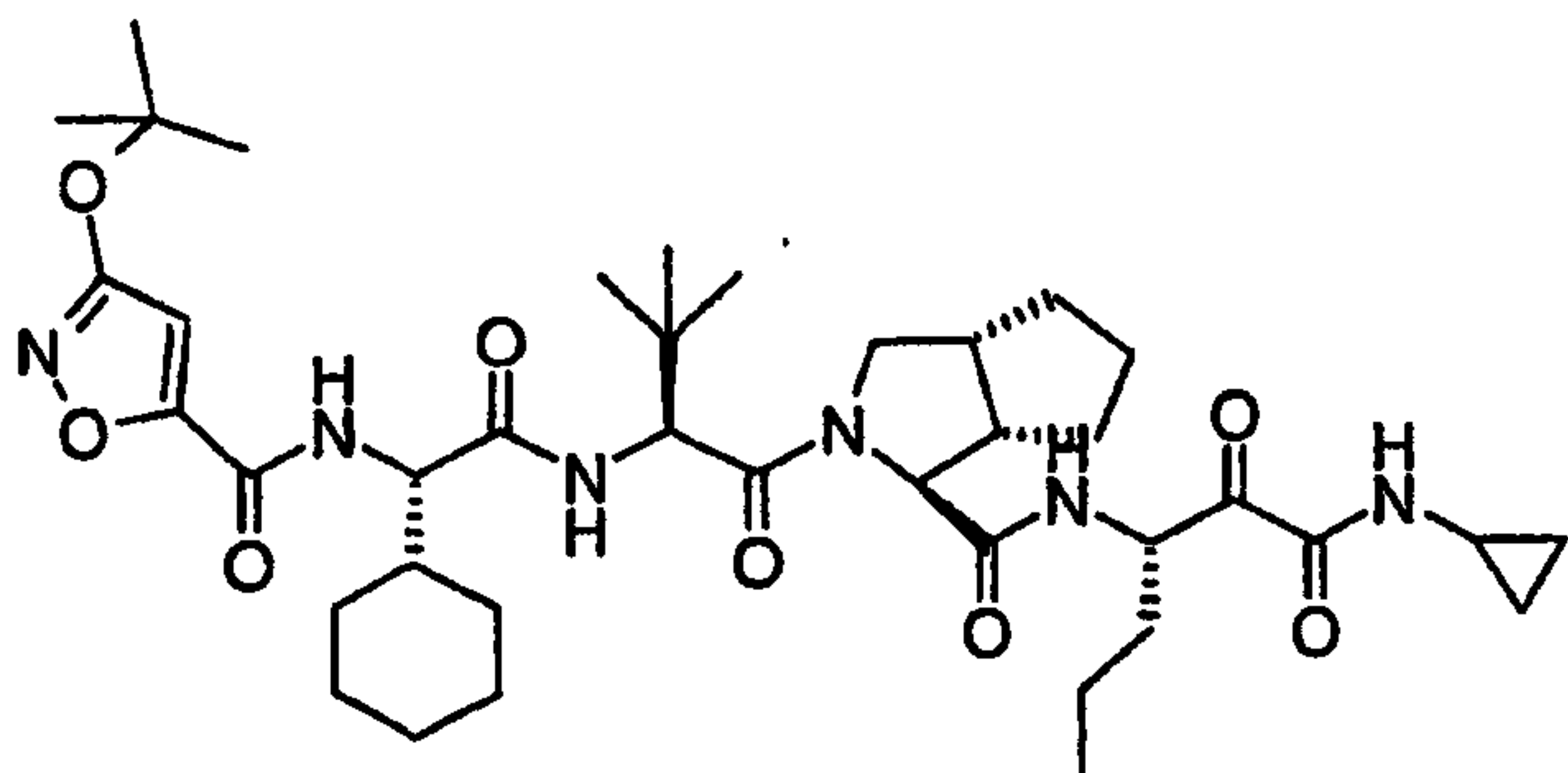
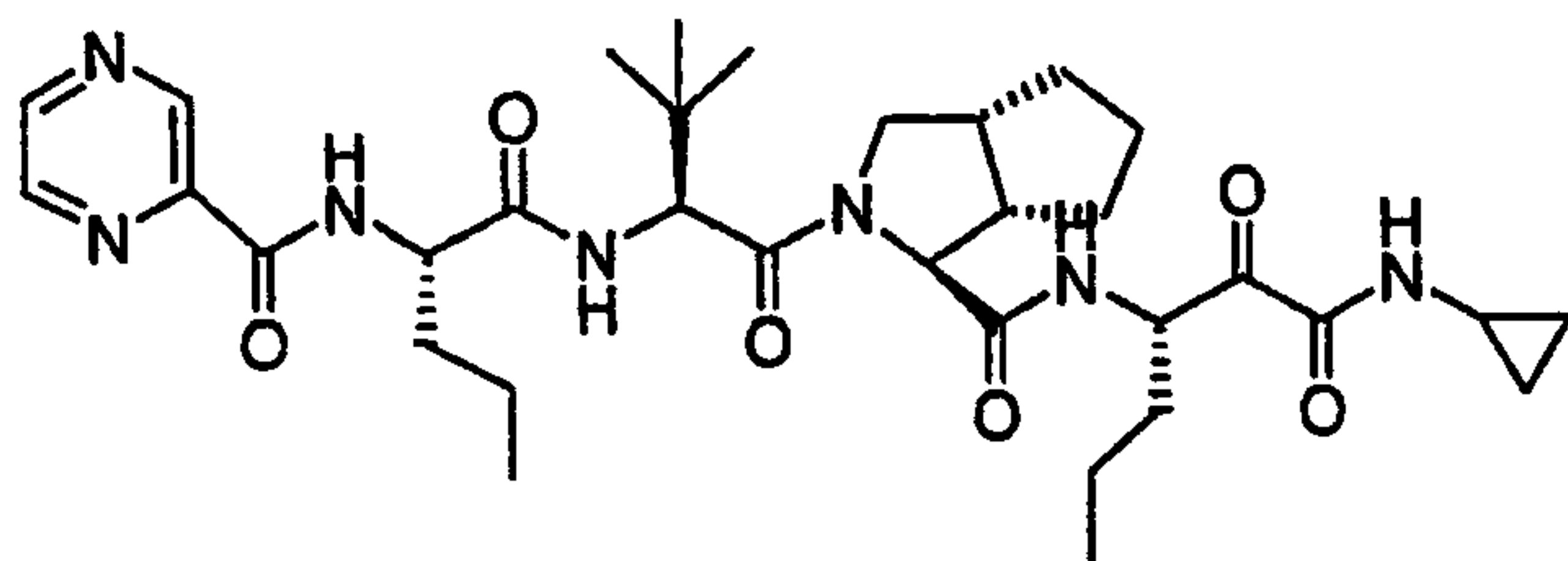
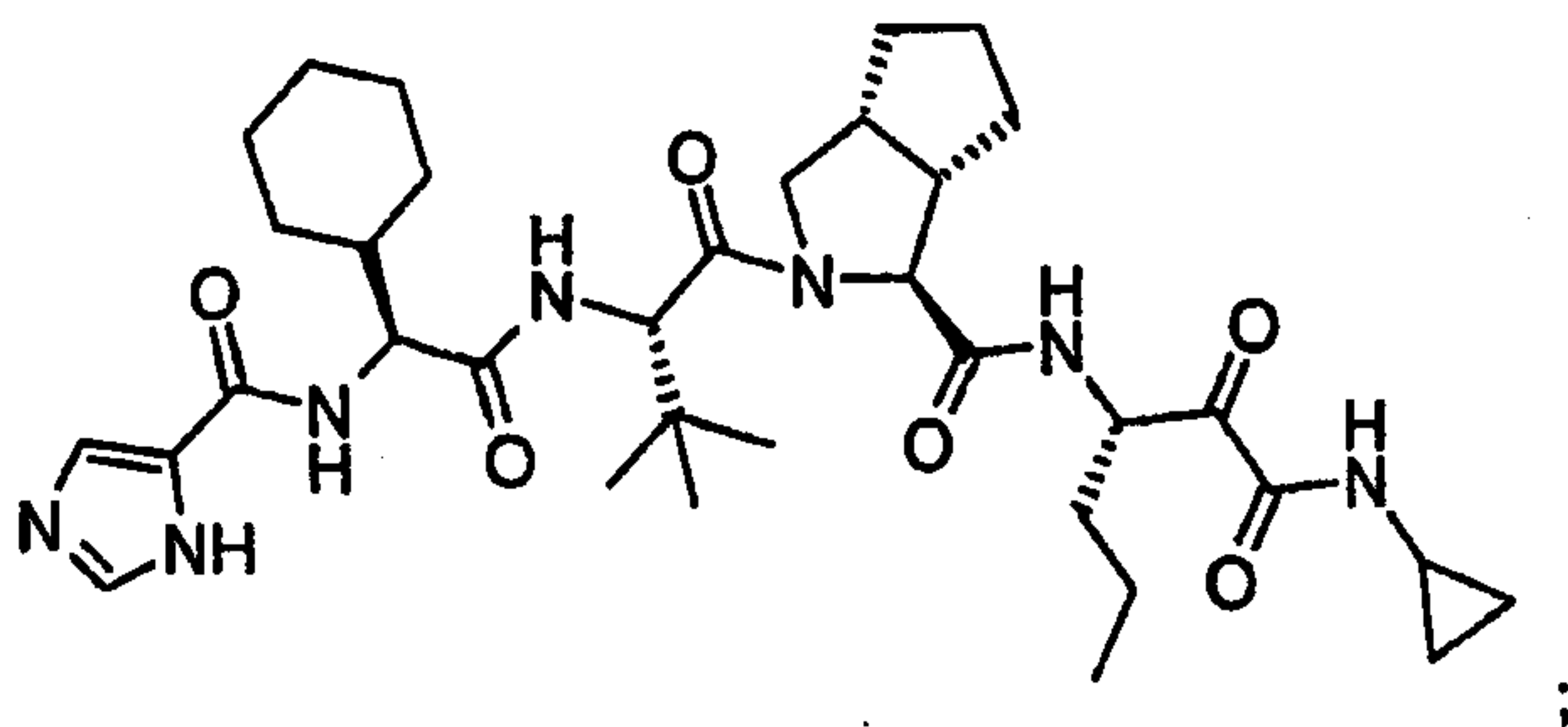
compound CW (134 mg, 75%).

Example 35 – Compounds CY and DT-DX:

To a DCM solution (15 mL) of clxxii (290 mg, 0.43 mmol) is added DMP reagent (239 mg, 0.56 mmol). The reaction is stirred at room temperature for 1 hour and quenched with 10% Na₂SO₃ for 20 minutes. The resulting mixture is then extracted with EtOAc. The organic layer is washed with brine, dried and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (8-100% EtOAc/Hexanes) to give compound CY (151 mg, 52%).

Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following consecutive compounds DT-DX are prepared.

10

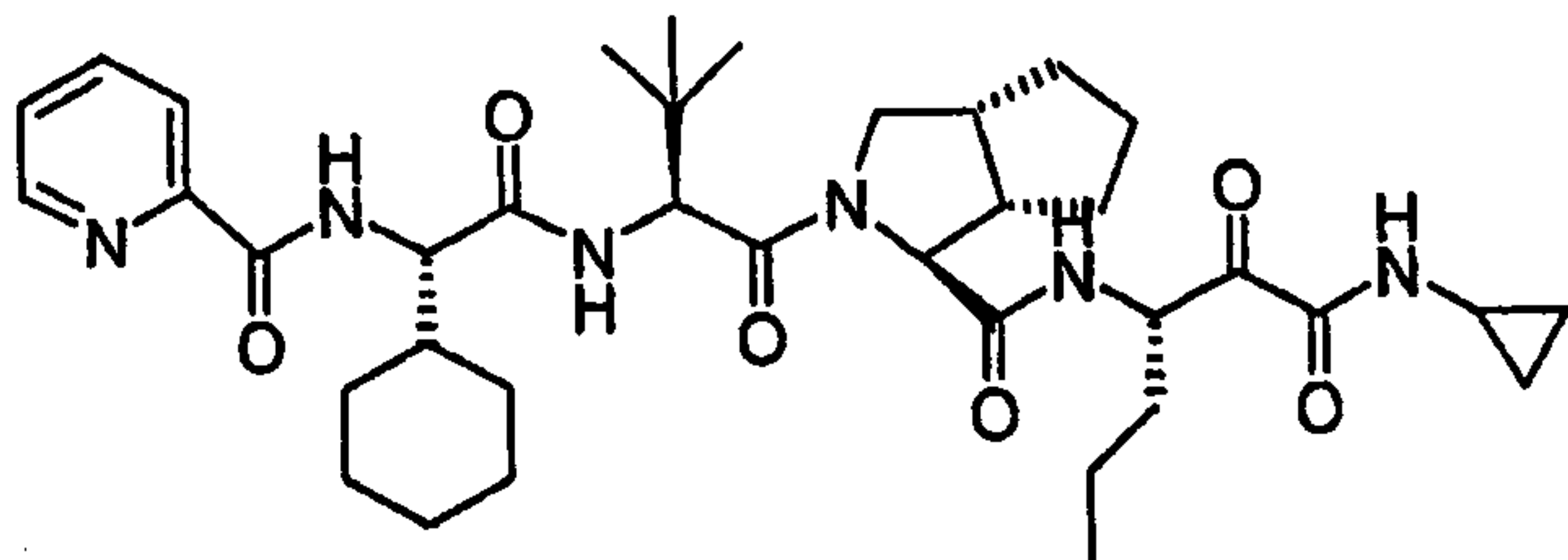


; and

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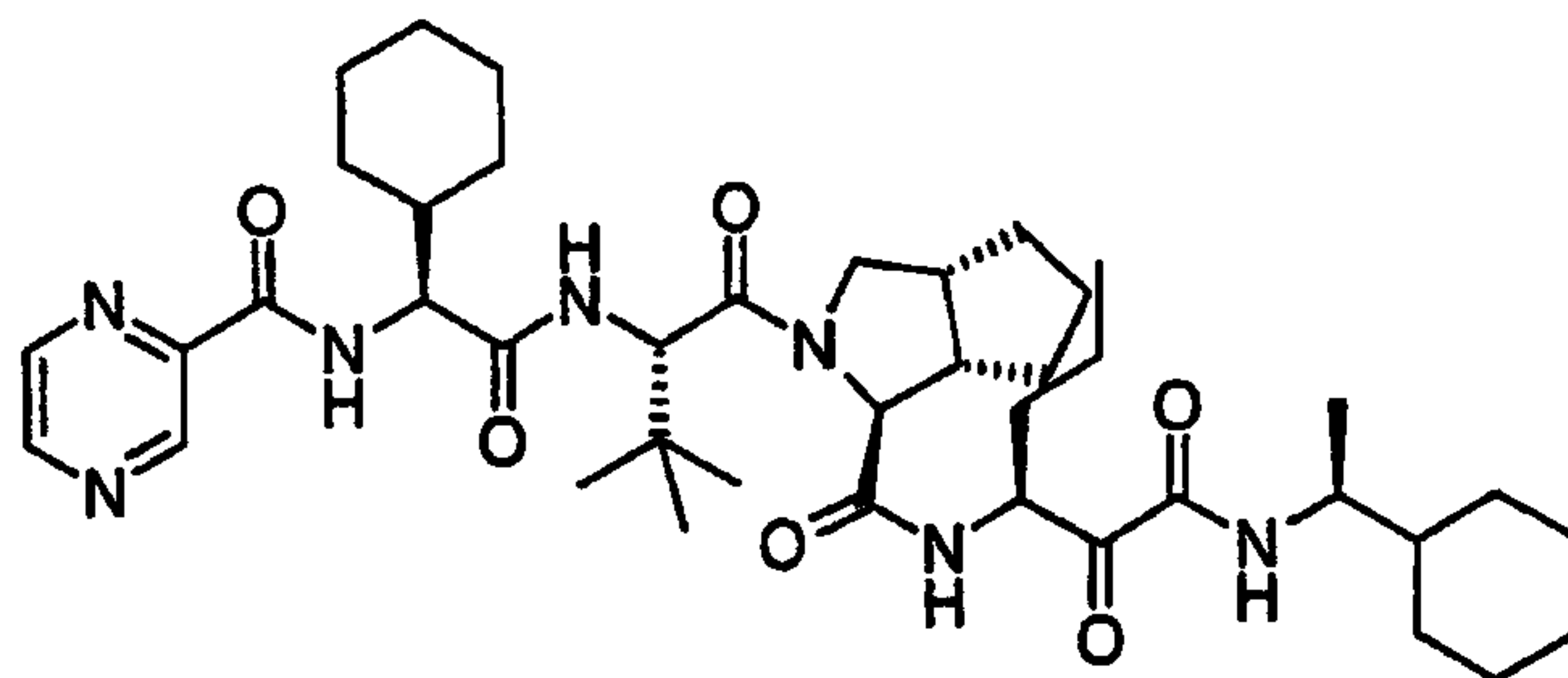
161



Example 36 – Compounds DY:

Compound lxxxv (1.17 mmol) is taken up in DCM (5mL). DMP reagent (545 mg, 1.3 mmol) is added to this solution and stirred 1 hour. The reaction is quenched with a P-Na₂SO₃ (1.5 mmol/g resin) and stirred one hour. P-TBD scavenger resin* (2.5 mmol/g resin) is added and stirred 45 minutes. The resulting mixture is filtered and purified by 50% EtOAc to give compound DY (440 mg, 50.2% over two steps).

*Reference for P-TBD scavenger resin: J. Parlow et al. *Tetrahedron*, **55**, 6785-6796 (1999).



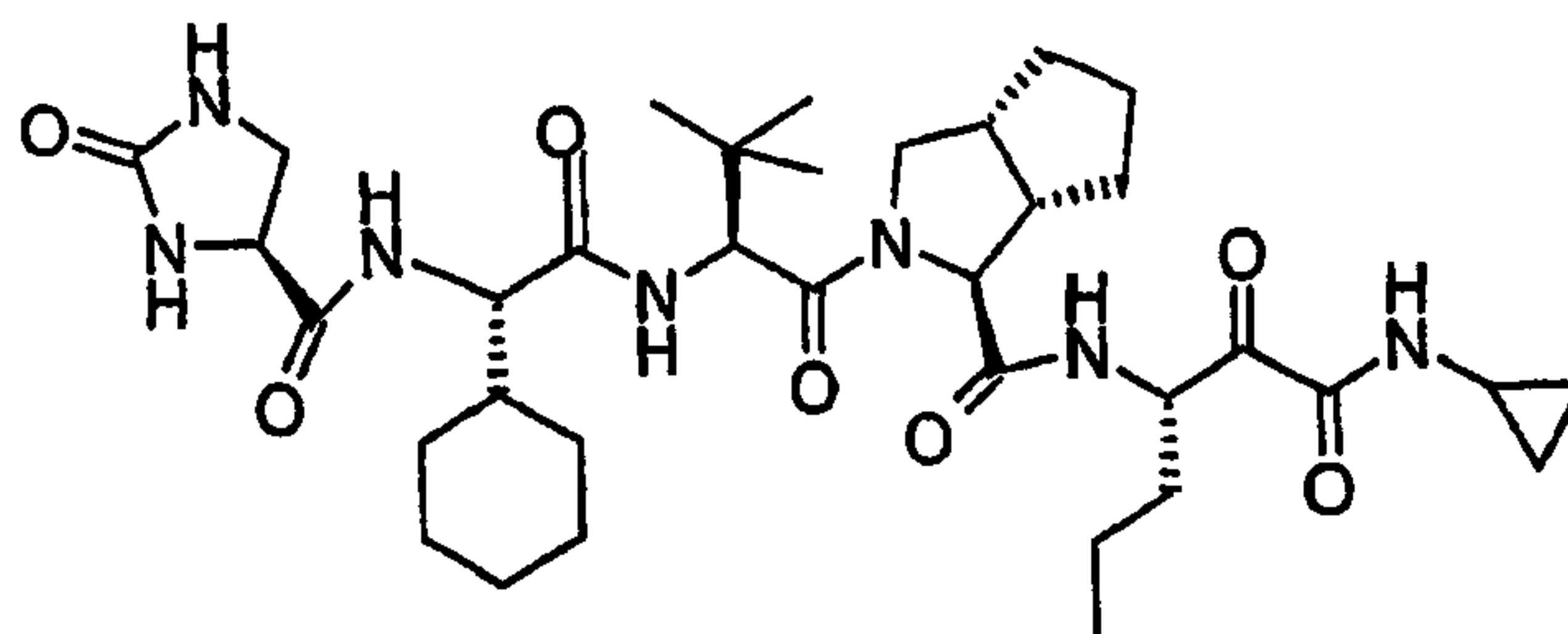
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Example 37 – Compound DZ:

The starting material compound clxxxxi (94 mg, 0.14 mmole) is dissolved in a mixture of THF (10 mL) and DCM (20 mL). The DMP reagent (118 mg, 0.28 mmol) is then added. After stirring at room temperature for 2 hours. The reaction is dumped in a separatory funnel containing Dri Solv THF (120 mL). The reaction is washed with 10% Na₂SO₃ (50 mL), and then brine (75 mL). The organic layer is then separated, dried over MgSO₄ and the solvent removed under reduced pressure. After chromatography (silica gel: elution with 50% Dri Solv THF/EtOAc, and then 4% MeOH/THF). Fractions are checked by MS. Appropriate fractions are lyophilized to yield compound DZ (38.8 mg, 41%).

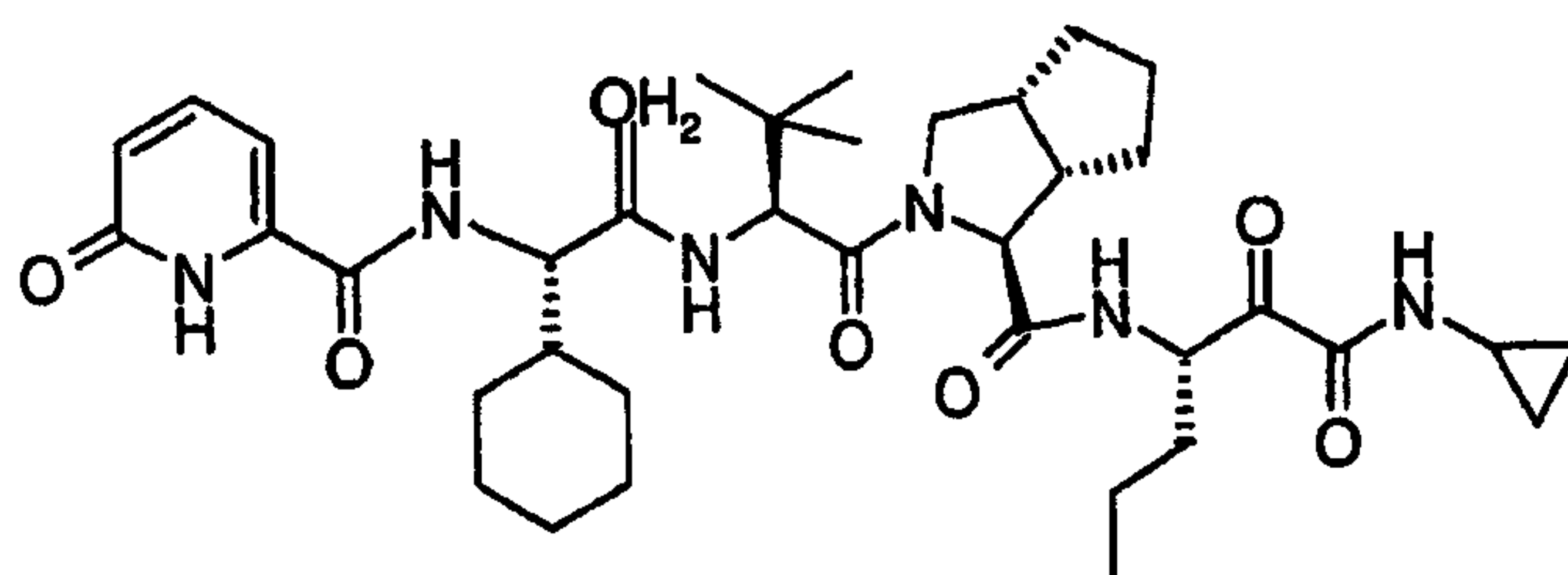
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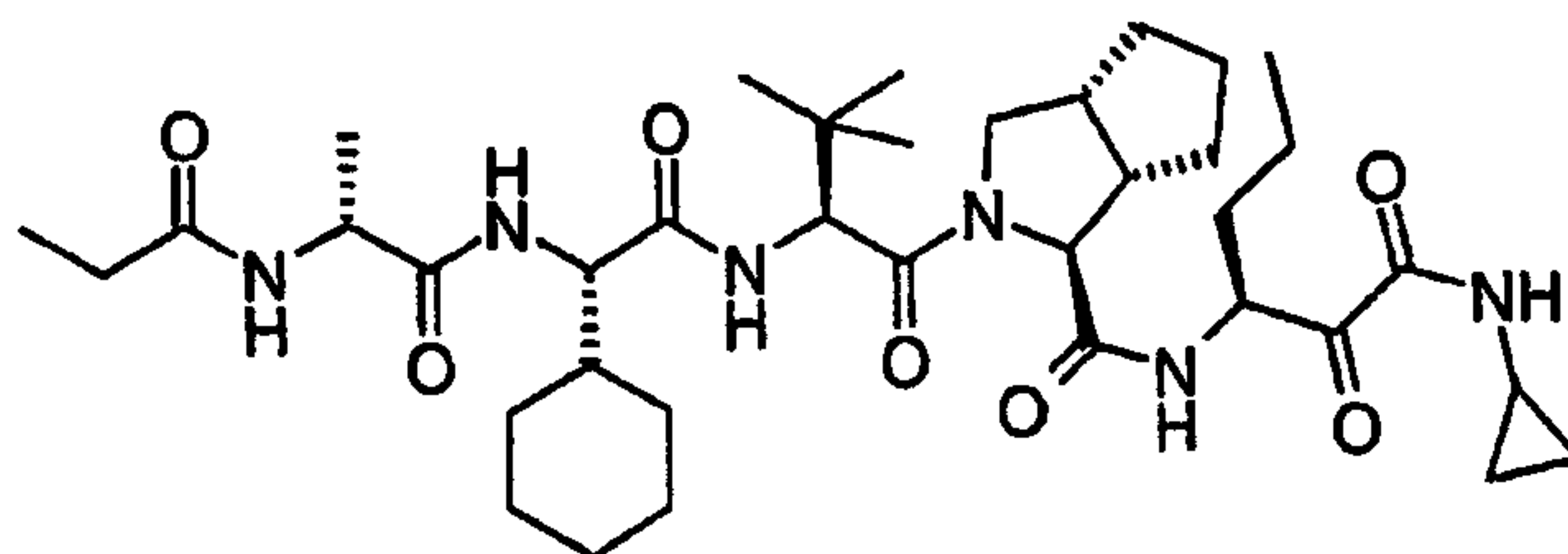


Example 38 – Compounds EA-EB:

The starting compound clxxxxv (185 mg, 0.26mmol) is dissolved in THF (20 mL). The
 5 DMP reagent (219 mg, 0.52 mmol) is then added. After stirring at room temperature for 1 hour.
 TLC shows complete conversion to ketone (5% MeOH/THF). The reaction is dumped in a
 separatory funnel containing Dri Solv THF (120 mL). The reaction is washed with 10% Na₂SO₃
 (50 mL), and then brine (75 mL). The organic layer is then separated, dried over MgSO₄ and
 solvent removed by reduced pressure to yield a residue that is purified by chromatography (silica
 10 gel: elution with 50% Dri Solv THF/EtOAc, and then 4% MeOH/THF) and fractions are checked
 by UV and MS. The appropriate fractions are lyophilized to yield compound EA (159 mg, 88%).



Following the above method for preparing the above compound and methods related to
 preparing the intermediate thereto, but using the appropriate starting materials the following
 15 compound EB is prepared:



Example 39 – Compounds EC-ED:

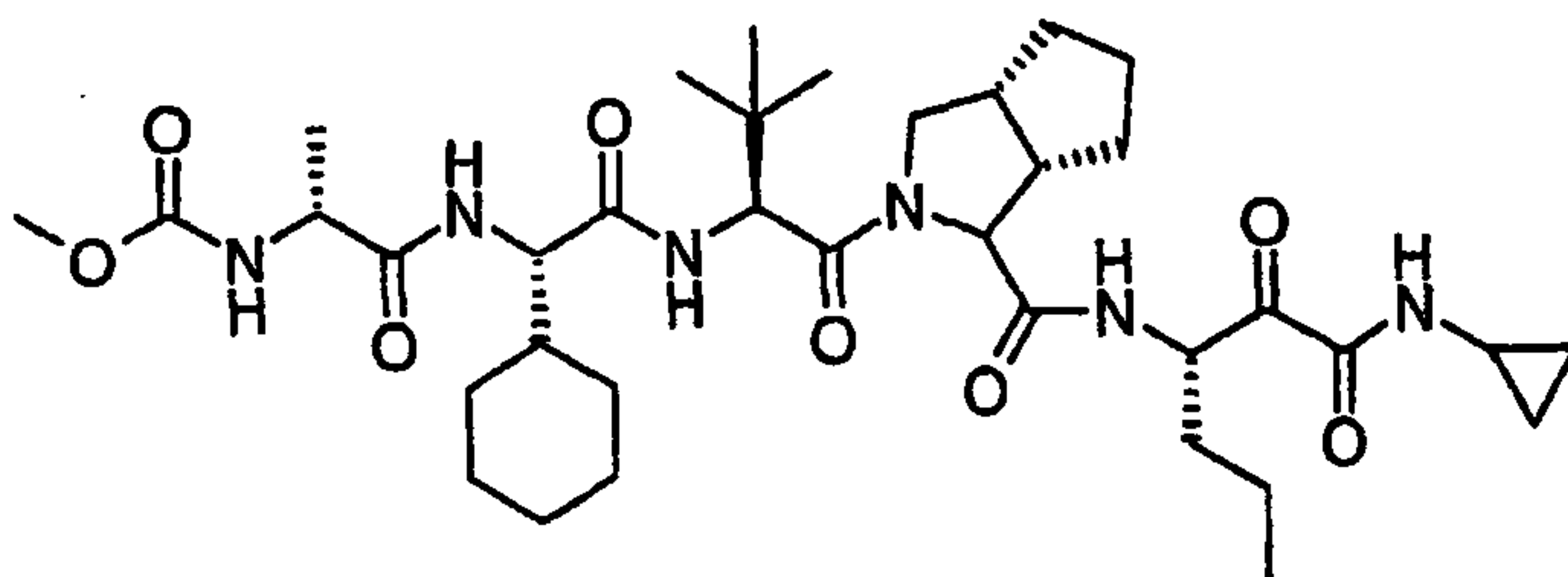
To a solution of compound clxxxxviii (0.341 g, 0.503 mmol) in DCM (15 mL) cooled in
 20 an ice bath is added DMP reagent (0.277 g, 0.654 mmol). The mixture is stirred at room
 temperature for 2 hours, then quenched with 10% Na₂SO₃ solution and stirred for 20 minutes.

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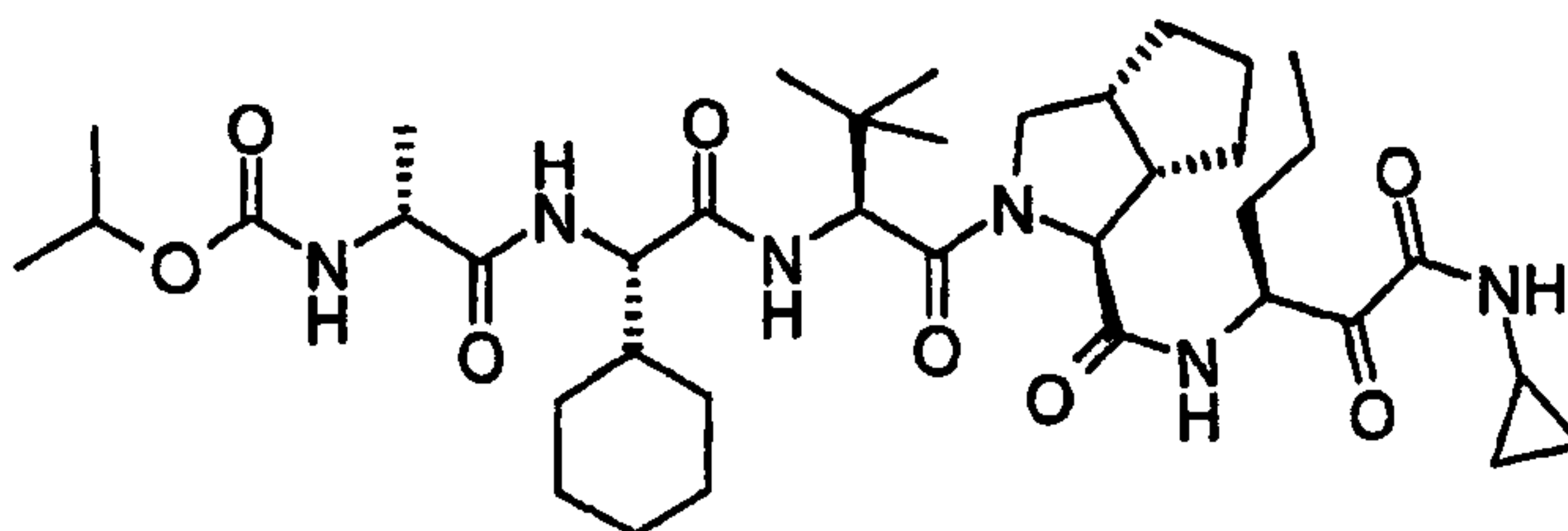
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The resulting mixture is extracted with DCM (3x20 mL) and the organic extract is dried (MgSO_4). After filtration to remove MgSO_4 , the filtrate is concentrated and purified by column chromatography (70% EtOAc/Hexane) to give compound EC (0.183 g, 54%) as white solid.

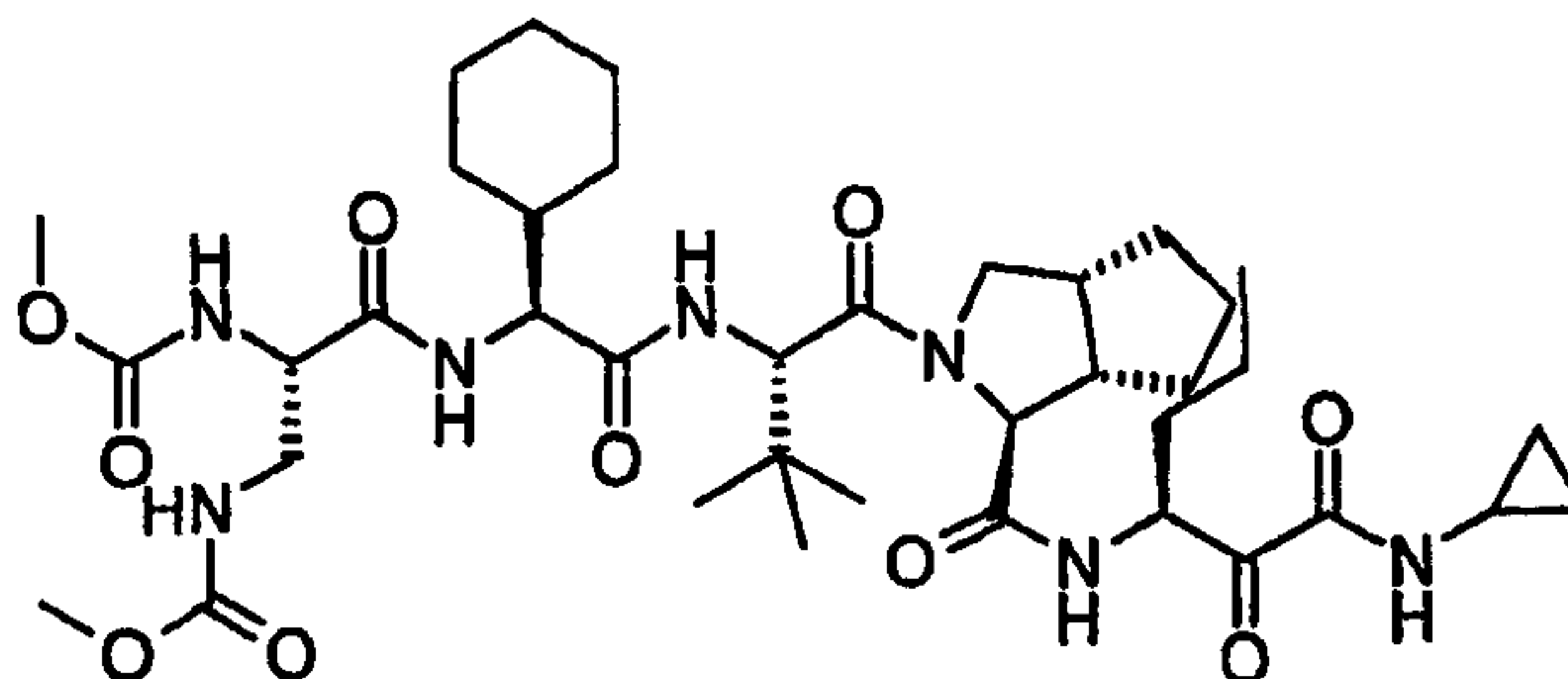


- 5 Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following compound ED is prepared:



10 Example 40 – Compounds EE-EG:

- Compound ccii (290 mg, 0.37 mmol) is taken up in DCM (5 mL). DMP reagent (175 mg, 0.41 mmol) is added to this solution and stirred 1 hour. The reaction is quenched with $\text{P-Na}_2\text{SO}_3$ (1.5 mmol/g resin) and stirred 1 hour. Quenched DMP reagent is scavenged with P-TBD (2.5 mmol/g resin) and stirred 1 hour. The resulting mixture is filtered, rinsed with DCM, before
15 being concentrated to a residue. The resulting residue is purified by 50% EtOAc/Hex to yield compound EE (440 mg, 28%).

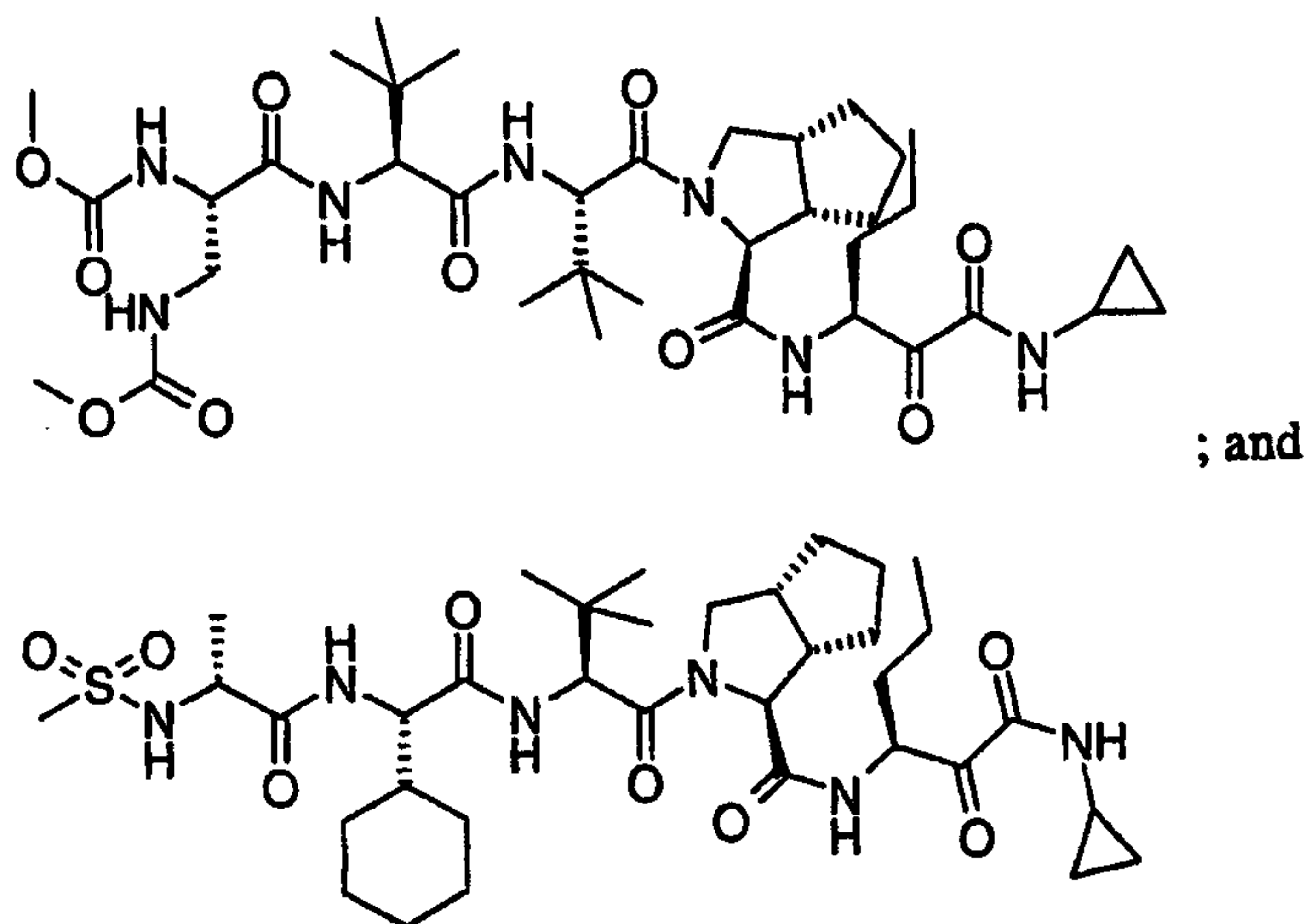


- 20 Following the above method for preparing the above compound and methods related to preparing the intermediate thereto, but using the appropriate starting materials the following compounds EF-EG are prepared:

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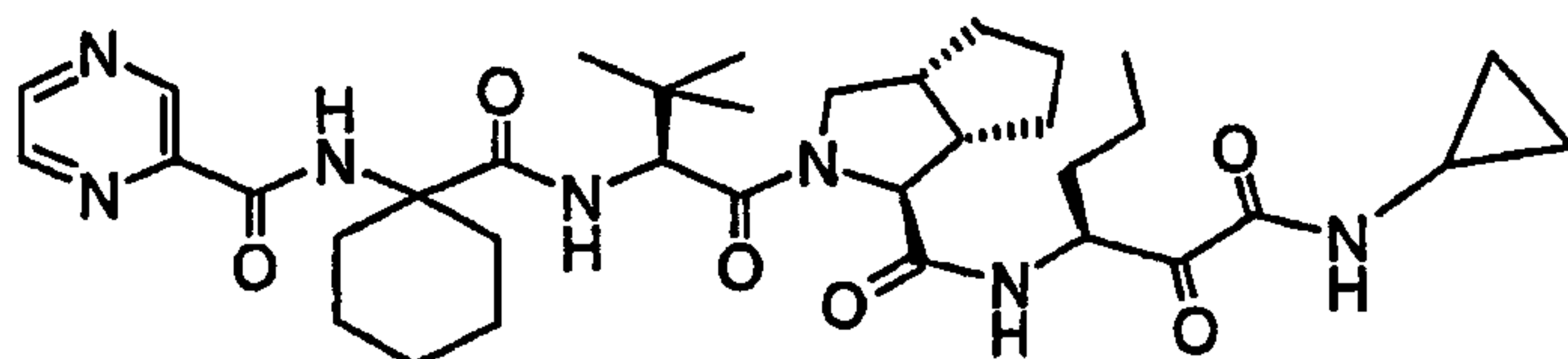
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Example 41 – Compound EH:

5 To a DCM solution (3 mL) of compound cciii (140 mg, 0.2 mmol) is added DMP reagent (133 mg, 0.3 mmol). The reaction is stirred at room temperature for 2 hours and quenched with 10% Na₂SO₃ (aq.) for 20 minutes. The resulting mixture is extracted with EtOAc. The organic layer is washed with brine, dried over MgSO₄, concentrated to a yellow oil that is purified by silica gel (70% EtOAc/hexane), and after lyophilized to yield compound EH (50 mg, 38%).



Example 42 – Compound EJ

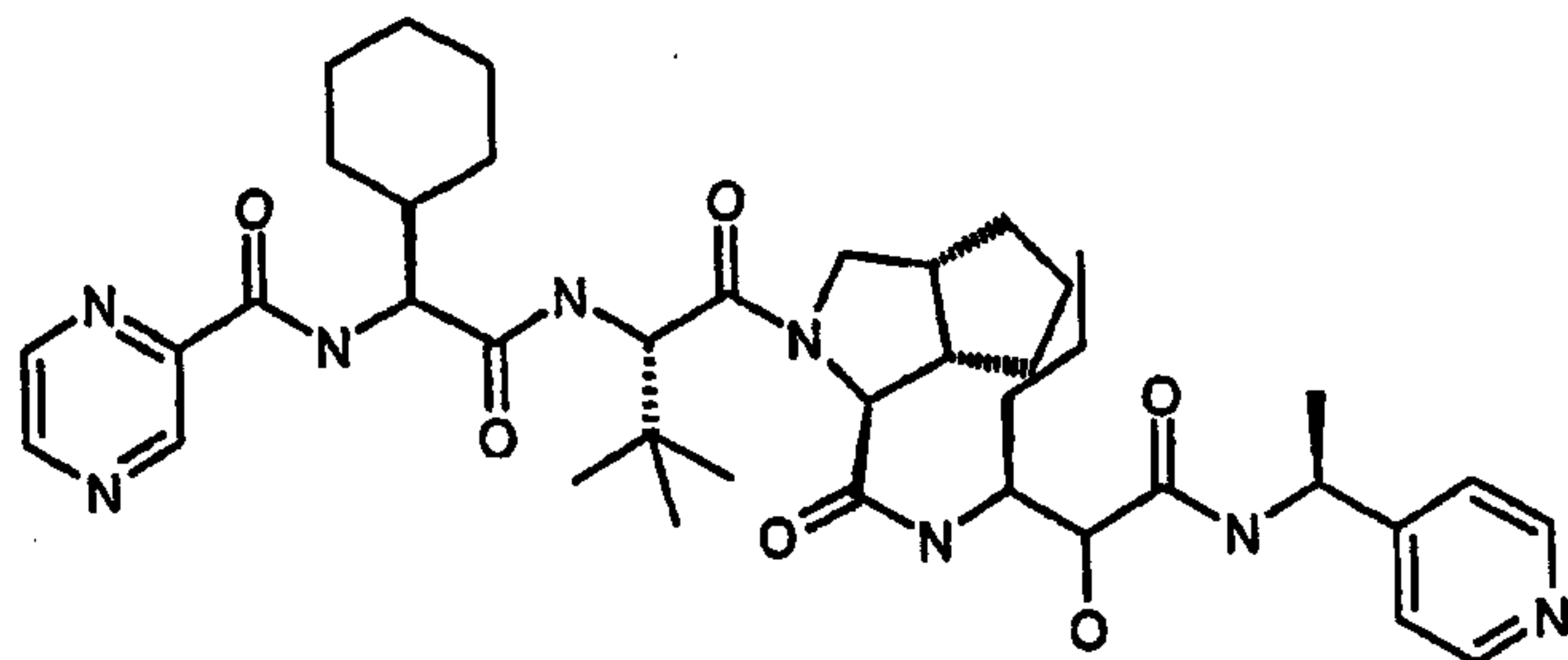
Compound ixiii (520 mg, 1 mmol) is taken up in DCM (5 mL). PyBOP (624 mg, 1.2 mmol) is added to the above solution and stirred for 5 minutes. Compound cdviii (300 mg, 1.2 mmol) in THF (5 mL) is added drop-wise to this solution, followed by DIPEA (0.22 ml, 1.2 mmol). The reaction is stirred at room temperature overnight under nitrogen. At this point, the reaction is diluted with EtOAc, washed with saturated NaHCO₃, and brine. The organic phase is dried with MgSO₄, filtered, and concentrated to give the crude coupled intermediate cdix.

20

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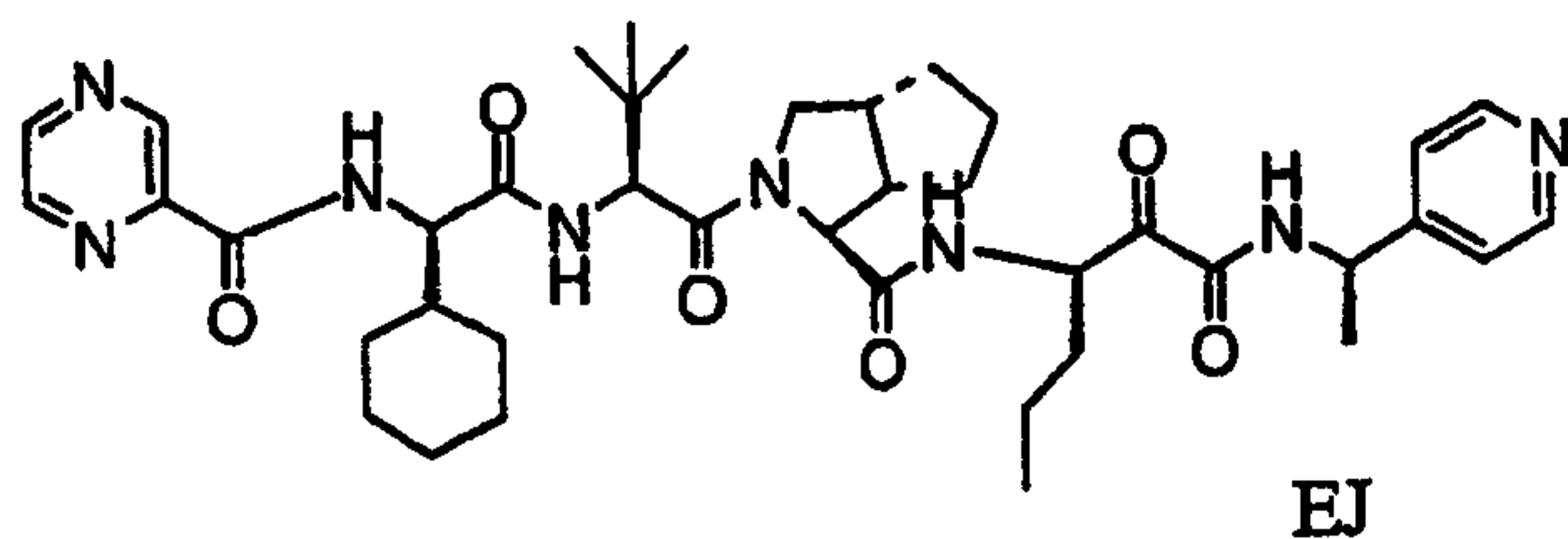
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cdix

This intermediate cdix (~1 mmol) is taken up in DCM (10 mL). Dess-Martin Periodinane (466 mg, 1.1 mmol) is added to this solution. After stirring for 1 hour at room temperature, the reaction is quenched with a polymer bound Na_2SO_3 (740 mg, 1.5 mmol DMP/ g resin) and stirred 45 minutes. Then, the reaction mixture is scavenged with polymer bound TBD resin (440 mg, 2.5 mmol DMP/ g resin). The resulting mixture is stirred for 45 minutes and then filtered. Purification is achieved in 5% EtOH/EtOAc to yield compound EJ (245 mg, 32% over 2 steps). Literature reference for the work-up procedure can be found in Tetrahedron 55 (1999) 6785-6796.



EJ

15

Example 43 – Compound EN

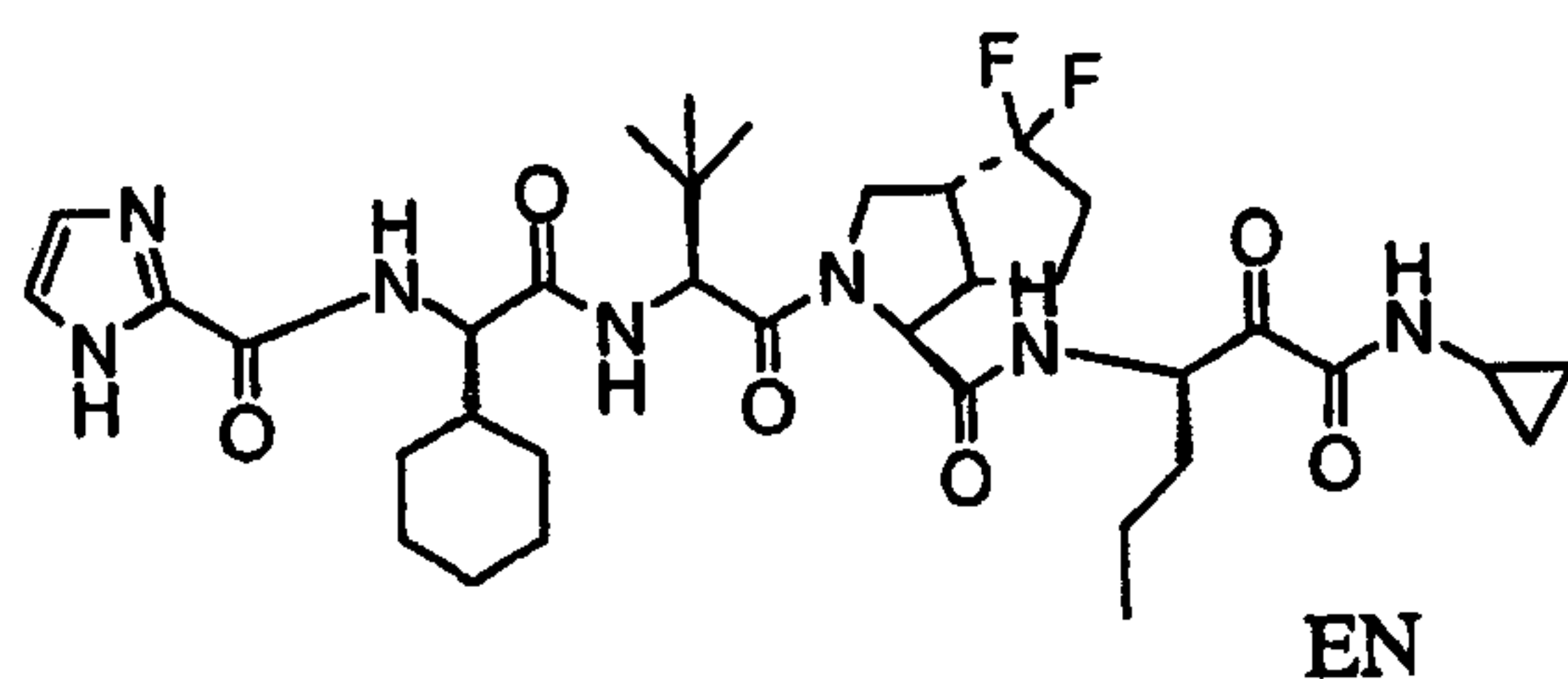
Intermediate compound cdvii (415 mg, 0.59 mmol) is taken up in DCM (10 mL) and THF (10 mL). *t*-BuOH (300 μL) is added followed by Dess-Martin Periodinane (750 mg, 1.77 mmol). The reaction is stirred 50 minutes and then quenched with P- Na_2SO_3 (1.5 mmol DMP / g resin). After stirring for 20 minutes at room temperature, the reaction mixture is scavenged with P-TBD (2.5 mmol DMP/ g resin). After stirring for 1 hour, the resulting mixture was filtered and

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concentrated. Product was purified by silica gel chromatography (50% to 70% EtOAc/Hexanes) to yield compound EN (220 mg, 53%).



Mass Spectra [M] were obtained for the following compounds as shown in Table 1 below.

5

TABLE 1

<u>LY#</u>	<u>Example</u>	<u>Mass Found</u>
10	A	733.3
	B	747.2
	C	657.2
	D	769.4
	E	733.4
15	F	625.4
	G	639.3
	H	661.4
	I	643.4
	J	707.3
20	K	641.3
	L	689.3
	M	639.3
	N	639.4
	O	731.4
25	P	687.4
	Q	653.4
	R	701.4
	S	639.3
	T	747.1
30	U	655.4
	V	653.4
	W	703.4
	X	661.3
	Y	647.3
35	Z	663.3
	AA	667.4
	AB	711.4
	AC	725.4
	AD	647.3
40	AE	779.4
	AF	689.3

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	AG	671.4
	AK	806.4
	AH	687.5
	AI	735.4
5	AJ	736.5
	AM	870.4
	AN	813.3
	AP	724.4
	AQ	653.4
10	AR	628.2
	AW	642.2
	AX	614.2
	AY	628.3
	BD	570.3
15	BE	520.2
	BF	534.3
	BG	584.3
	BU	890.3
	BV	685.4
20	BW	679.3
	BX	695.3
	BY	697.3
	BZ	787.4
	CA	701.3
25	CB	669.4
	CC	733.5
	CD	643.3
	CE	653.5
	CH	749.4
30	CI	653.3
	CJ	717.5
	CK	683.4
	CL	669.3
	CM	675.2
35	CN	717.2
	CO	653.3
	CP	683.3
	CQ	669.3
	CR	675.2
40	CT	661.8
	CS	639.3
	CU	679.2
	CV	709.3
	CW	743.3
45	CX	695.3
	CY	665.2
	CZ	681.3
	DA	695.3
	DB	701.2
50	DC	673.3
	DD	693.3
	DE	757.4

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	DF	682.3
	DG	676.3
	DH	676.2
	DI	692.5
5	DJ	605.2
	DK	874.4
	DL	924.5
	DM	924.2
	DN	952.7
10	DO	830
	DP	842.5
	DT	667.4
	DU	639.2
	DV	740.3
15	DW	684.2
	DX	678.5
	DY	749.3
	DZ	685.3
	EA	649.3
20	EB	700.3
	EC	702.3
	ED	730.3
	EE	775.3
	EF	749.3
25	EG	722.3
	EH	665.2
	EI	796.4
	EJ	744.3
	EK	730.5
30	EL	730.5
	EM	757.3
	EN	703.5
	EO	715.5
	EP	679.2
35	EQ	651.3
	ER	715.3
	ES	668.5
	ET	732.5
	EU	743.3
40	EV	683.3
	EW	750.4
	EX	786.4
	EY	744.5
	EZ	780.4
45	FB	693.4
	FC	655.3
	FD	655.3
	FE	774.4
	FF	681.5
50	FG	667.5

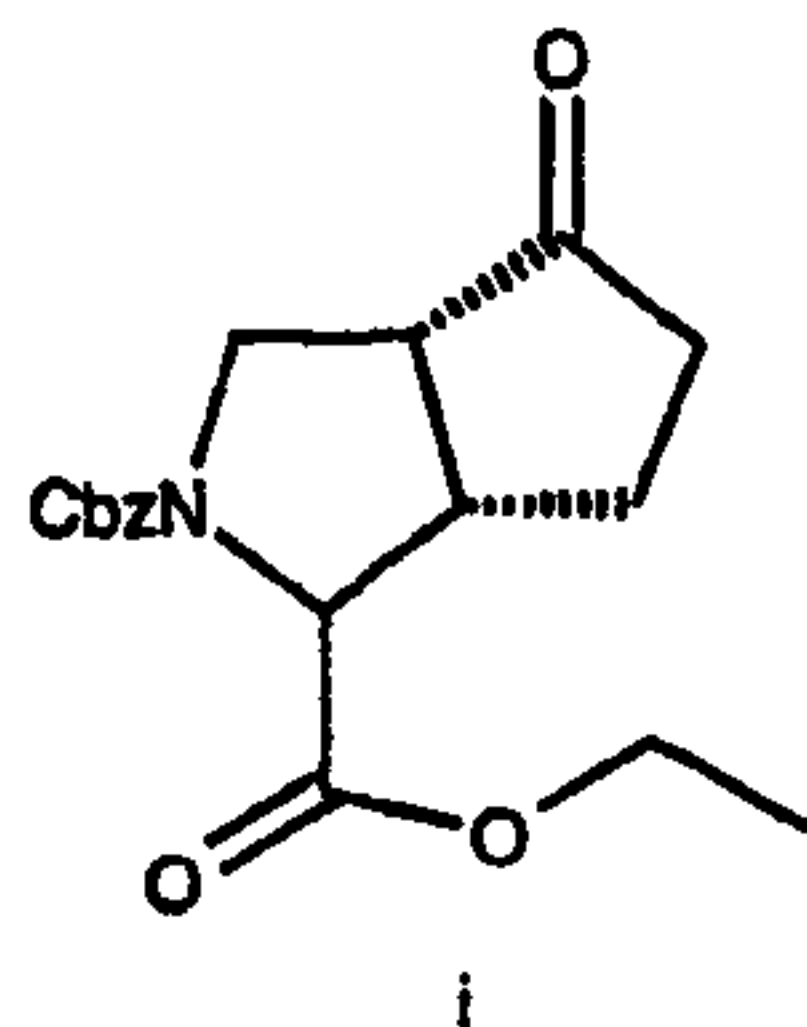
High Resolution Mass Spectra (HRMS) of the following compounds were obtained as shown in Table 2.

TABLE 2

Example	Molecular Formula (M+1)	Calculated MS (M+1)	Mass Found (M+1)
L	C ₃₇ H ₅₂ N ₇ O ₆	690.3979	690.3986
M	C ₃₃ H ₅₀ N ₇ O ₆	640.3822	640.3822
Z	C ₃₂ H ₄₈ F ₂ N ₇ O ₆	664.3634	664.3627
AB	C ₃₆ H ₄₈ F ₂ N ₇ O ₆	712.3634	712.3649
CE	C ₃₄ H ₅₂ N ₇ O ₆	654.3979	654.3967
EN	C ₃₅ H ₅₂ N ₇ O ₆ F ₂	704.3947	704.3945
EK	C ₃₇ H ₆₃ N ₆ O ₈ S	751.4428	750.4350 (M)
EC	C ₃₆ H ₅₉ N ₆ O ₈	703.4395	703.4382
CA	C ₃₅ H ₅₀ N ₇ O ₆ F ₂	702.3790	702.3801
EZ	C ₄₀ H ₅₅ N ₈ O ₆ F ₂	781.4213	781.4196
EU	C ₃₆ H ₅₂ N ₇ O ₆ F ₂	716.3947	716.3929
CY	C ₃₅ H ₅₂ N ₇ O ₆	666.3979	666.3966
BX	C ₃₇ H ₅₈ N ₇ O ₆	696.4448	696.4432
S	C ₃₃ H ₅₀ N ₇ O ₆	640.3823	640.3831
BW	C ₃₆ H ₅₄ N ₇ O ₆	680.4136	680.4126
CU	C ₃₆ H ₅₄ N ₇ O ₆	680.4136	680.4128
EJ	C ₄₀ H ₅₇ N ₈ O ₆	745.4401	745.4417
EM	C ₃₅ H ₅₄ N ₇ O ₆	668.4136	668.4139
None	C ₄₁ H ₅₈ N ₇ O ₆	744.4448	744.4691

Intermediate Example 1 – Compound ii

To an ethanol solution (40 mL) of compound i (8.1 g, 24.4 mmol) is added NaBH₄



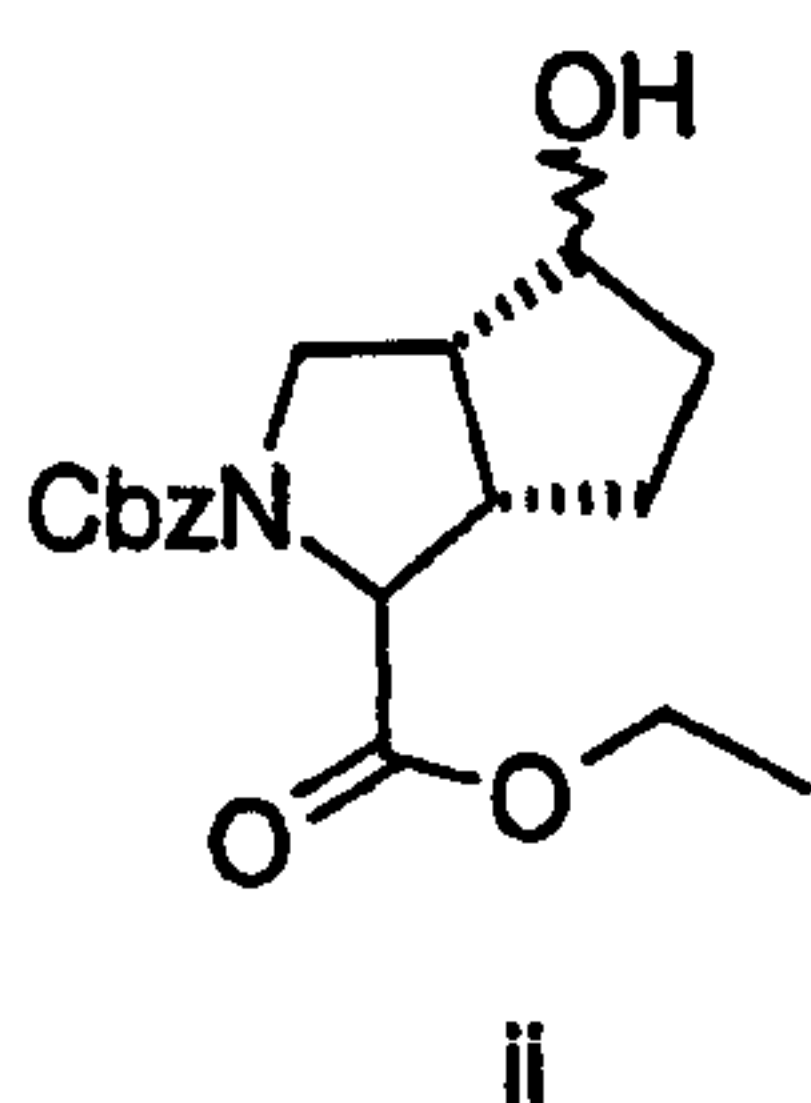
(924 mg, 24.4 mmol) at -10°C . The reaction is stirred at that temperature for 30 minutes, and then quenched with AcOH (3 mL). The reaction mixture is diluted with EtOAc (250 mL), and washed with NaHCO₃ and brine. The organic layer is dried and concentrated *in vacuo* to yield a

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residue that is purified by silica gel chromatography (50% EtOAc/Hexanes) to provide 7.85 g (97%) of compound ii,

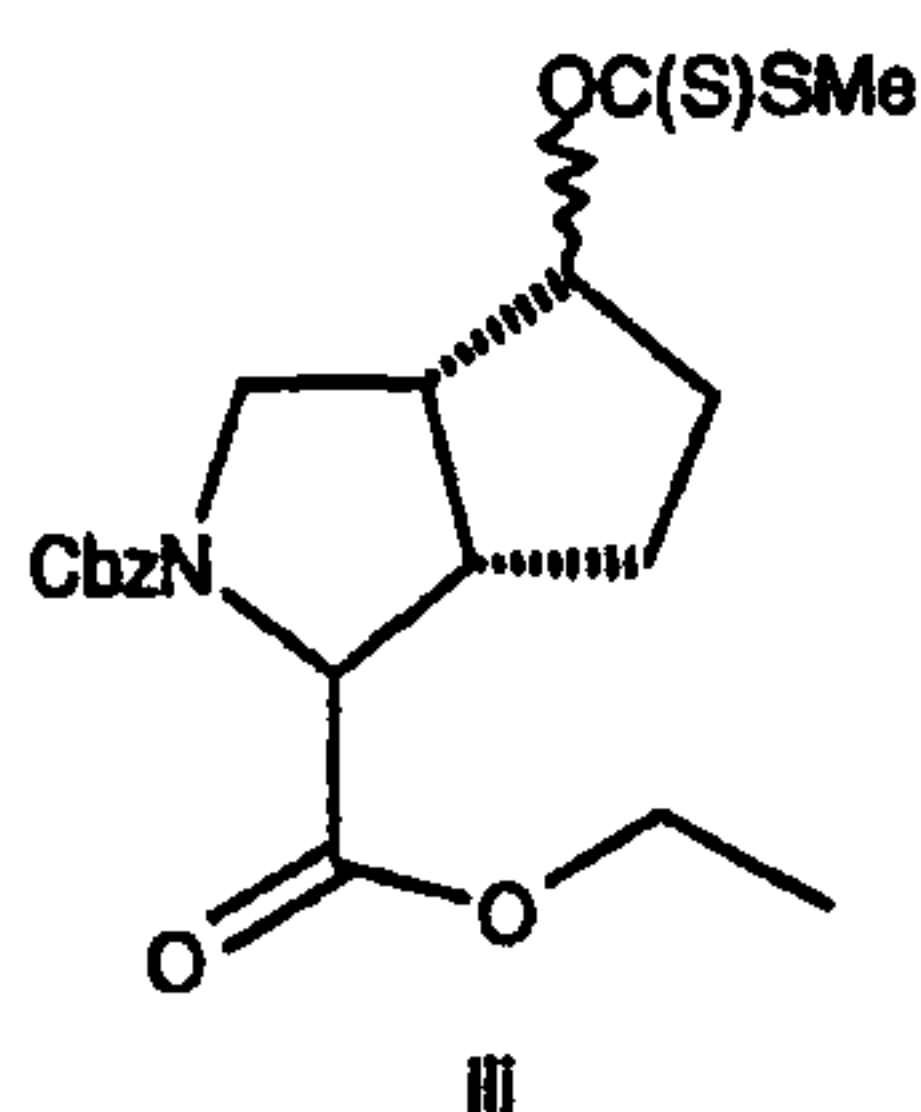


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Intermediate Example 2 – Compound iii

To a THF solution (70 mL) of compound ii (4.48 g, 13.4 mmol) is added at 0°C of NaH (699 mg, 60%, 17.42 mmol). After stirring at that temperature for 40 minutes, neat MeI (1.25 mL, 20.1 mmol) is added. The reaction is stirred at about room temperature overnight. At this point, the reaction is quenched carefully with saturated solution of NH₄Cl at 0°C. The reaction mixture is extracted with Et₂O and EtOAc. The organic layer is washed with water, brine and dried with Na₂SO₄. The organic layer thus obtained is concentrated *in vacuo* to provide the xanthate compound iii,

10



15

Intermediate Example 3 – Compound iv

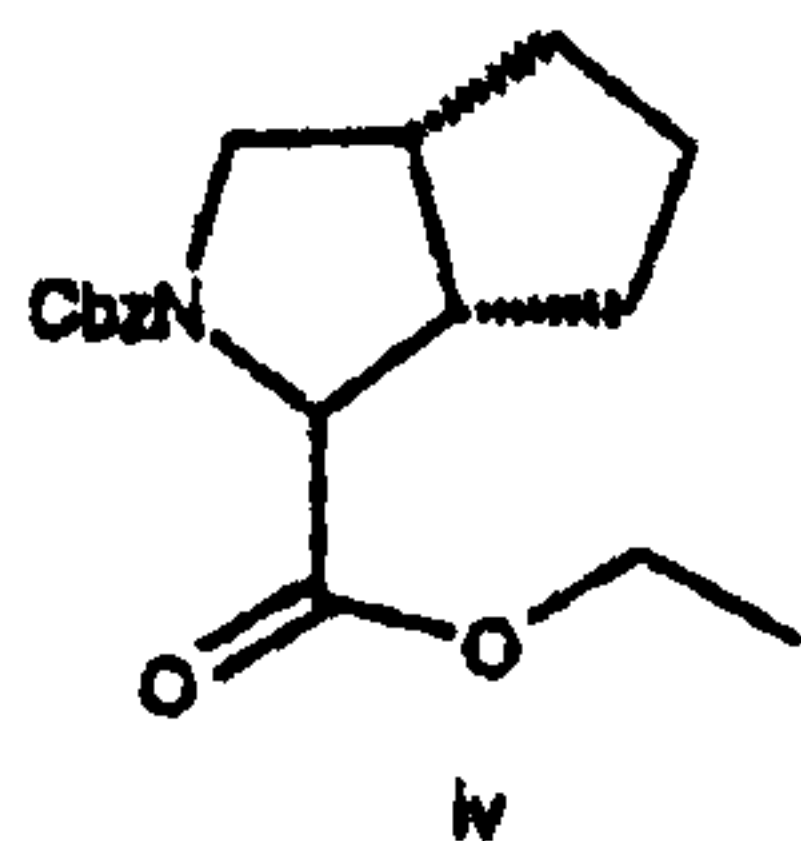
The xanthate compound iii (~13.4 mmol) is dissolved in toluene (100 mL). To this solution is added AIBN (216 mg, 1.34 mmol). The resulting solution is degassed with dry nitrogen and then treated with n-Bu₃SnH (5.4 mL, 20.1 mmol). The reaction mixture is heated at 90 °C for 3 hours. At this point, the reaction is cooled to room temperature and concentrated *in vacuo*. The resulting residue is purified with silica gel chromatography (15-20% EtOAc/Hexanes) to provide 2.8 g (66% overall from compound ii) of compound iv,

20

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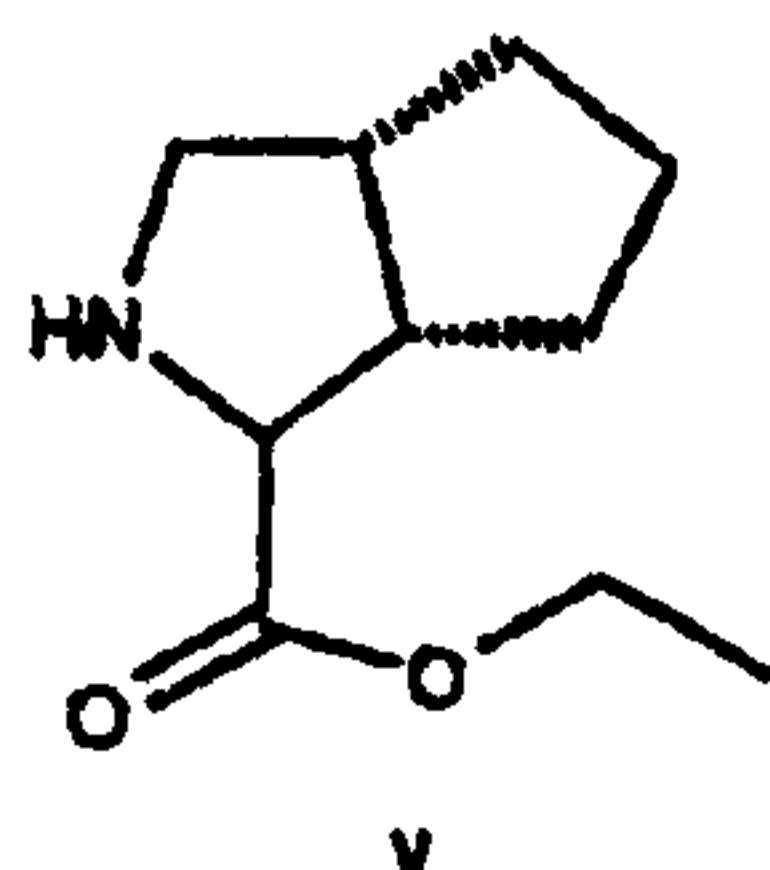
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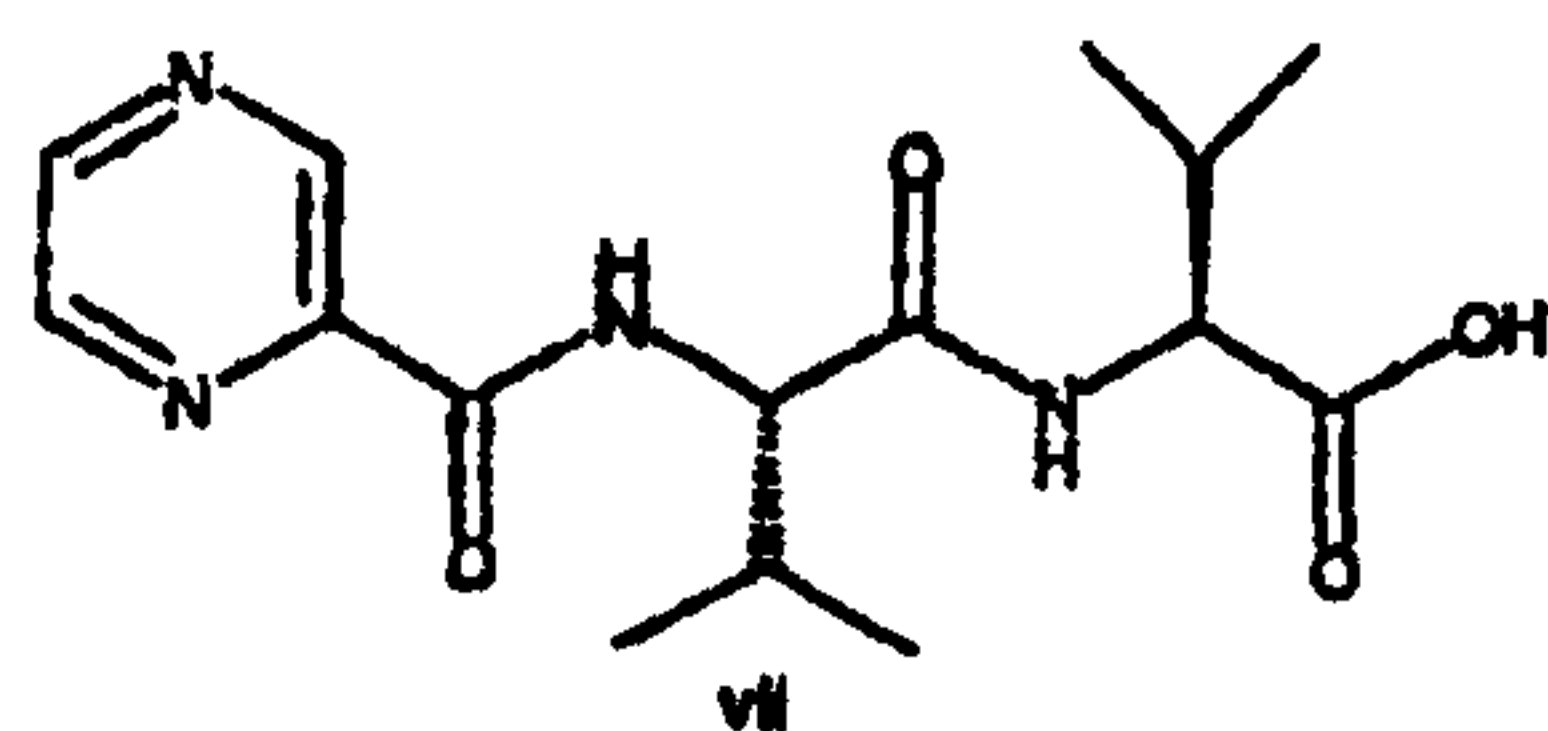
Intermediate Example 4 – Compound v

To an ethanol solution (21 mL) of compound iv (1 g, 3.15 mmol) is added Pd(OH)₂/C (655 mg, 20%, 0.95 mmol) under a stream of nitrogen. The resulting reaction mixture is subjected to standard hydrogenation (1.5 atm). After 5 hours, the hydrogen source is removed and the reaction is filtered. The filtrates are concentrated *in vacuo* to provide the free amine compound v,



Intermediate Example 5 – Compound vi

To a DCM solution (10 mL) of compound vii (629 mg, 1.95 mmol) is added at about



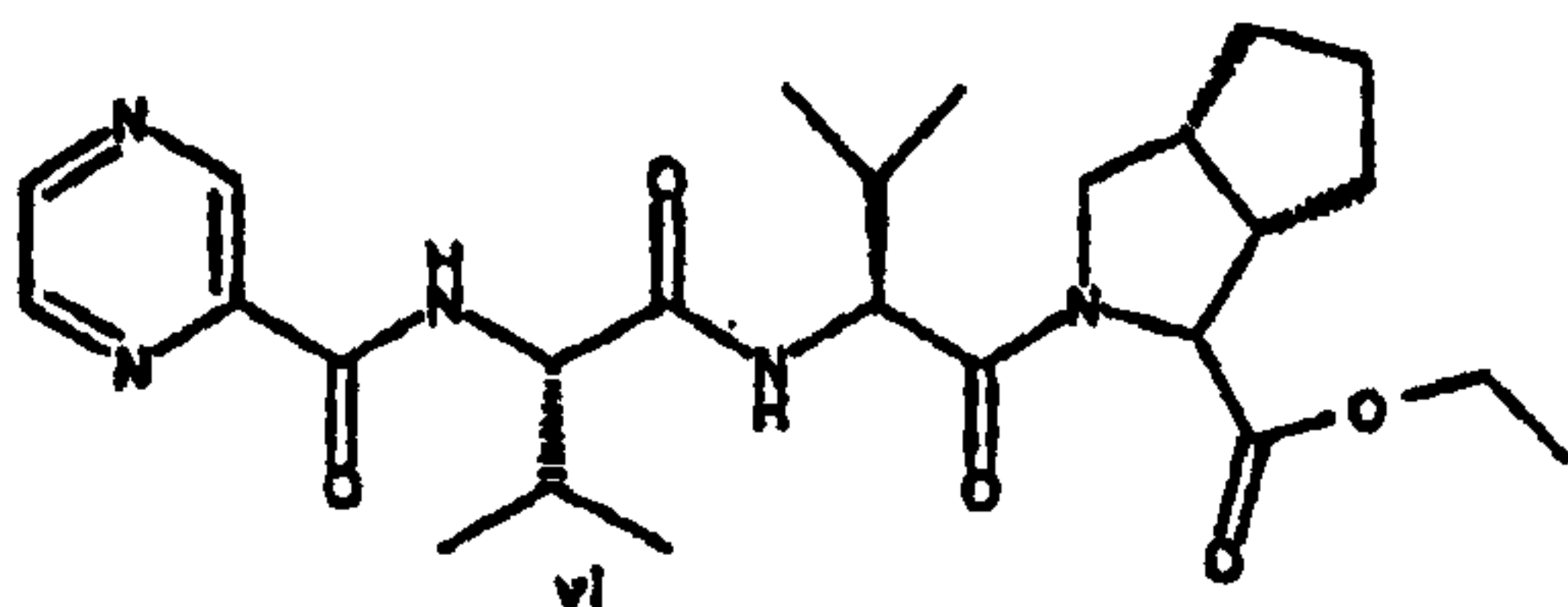
room temperature HOAt (265 mg, 1.95 mmol) and followed by 1 M DCC solution in DCM (1.95 mL, 1.95 mmol). After stirring for 30 minutes, a DCM solution (3 mL) of compound v (1.5 mmol) is added to the above HOAt-activated acid. The reaction is stirred at about room temperature overnight. At this point, the reaction is filtered through Celite.* The filtrates are diluted with EtOAc (75 mL) and washed with water and brine. The organic layer is dried and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (70-80% EtOAc/Hexanes) to afford 620 mg (85%) of compound vi,

* Trade-mark

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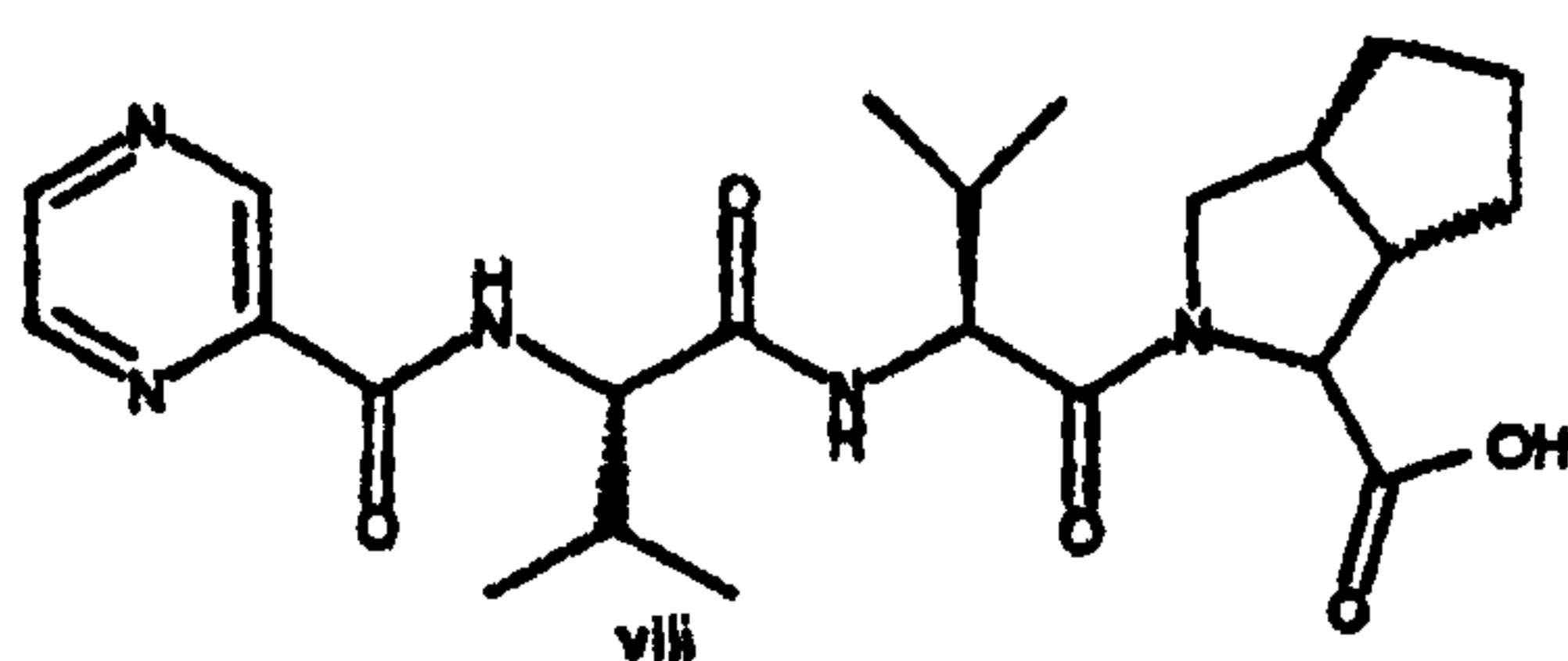
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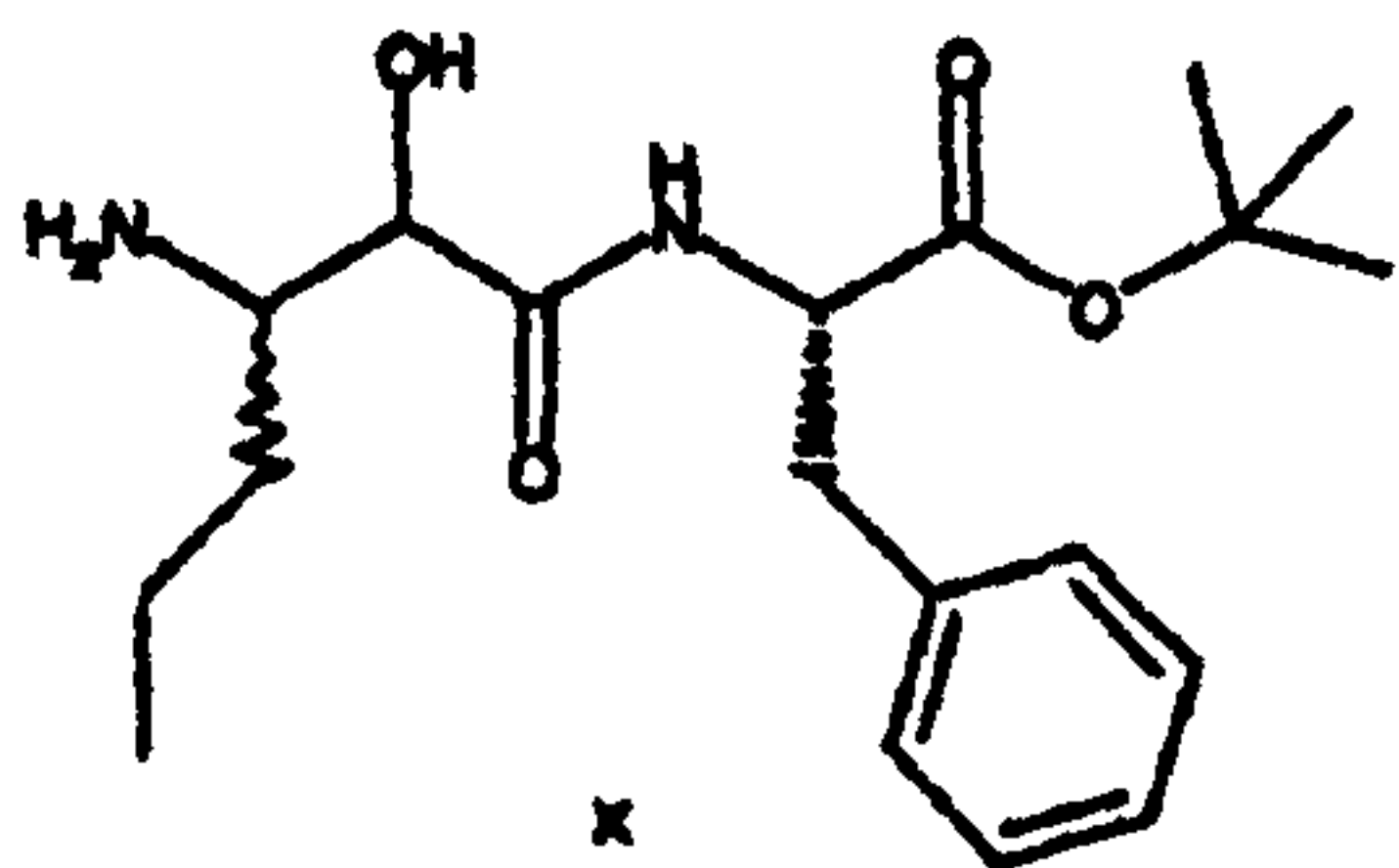
Intermediate Example 6 – Compound viii

To an ethanol solution (10 mL) of compound vi (615 mg, 1.26 mmol) is added 2 N NaOH aqueous solution (1.26 mL, 2.52 mmol). The reaction is stirred overnight at about room temperature and then acidified to pH 3 using Dowex acidic resins. The solids are filtered off and the filtrates are concentrated *in vacuo* to give a residue that is redissolved in 1:1 CH₃CN/H₂O. This solution is subjected to lyophilization to provide 495 mg (85%) of compound viii,



Intermediate Example 7 – Compound ix

To a DCM solution (10 mL) of compound viii (230 mg, 0.5 mmol) is added PyBop (417 mg, 0.8 mmol). The reaction is stirred at about room temperature for 30 minutes. To this solution is then added a THF solution (5.25 mL) of compound x (263 mg, 0.75 mmol) and followed by



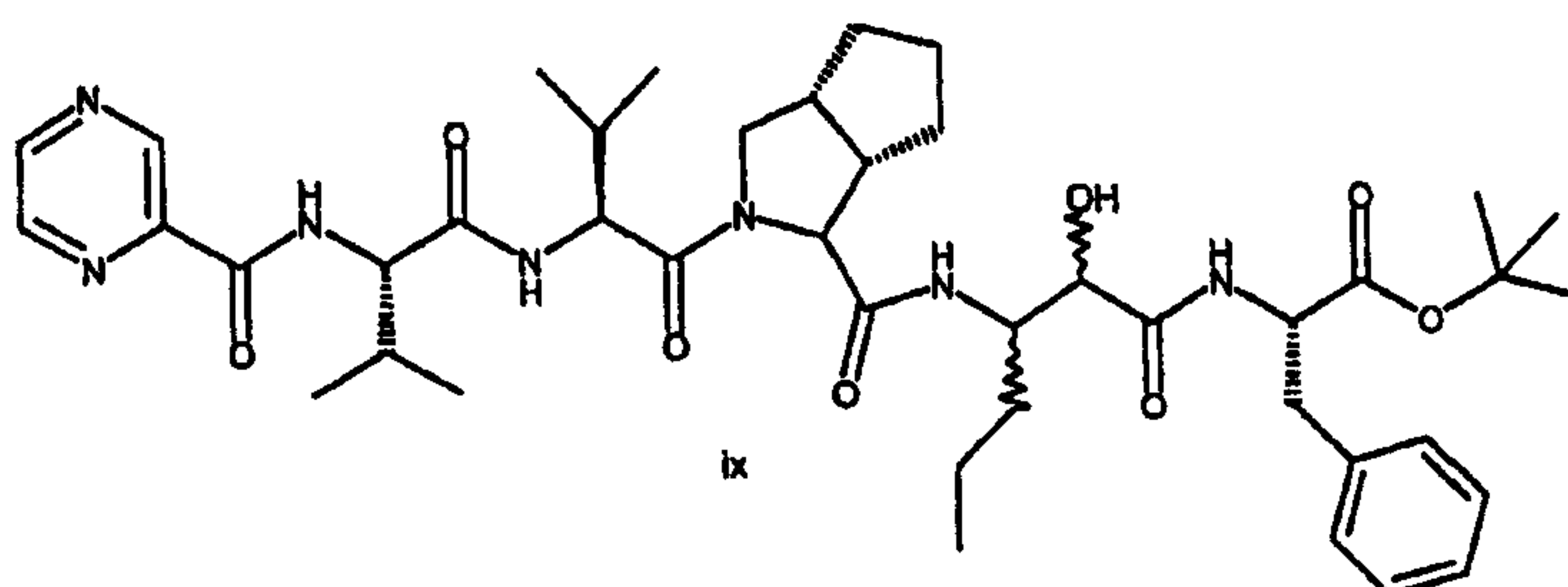
DIPEA (0.174 mL, 1 mmol). The reaction is stirred at about room temperature overnight and then quenched with water (30 mL) for 30 minutes. The reaction mixture is extracted with EtOAc (100 mL). The organic layer is washed with brine and dried and concentrated *in vacuo* to afford a residue that is purified via silica gel chromatography (5% EtOH/EtOAc) to give ~400 mg (100%) of compound ix,

* Trade-mark

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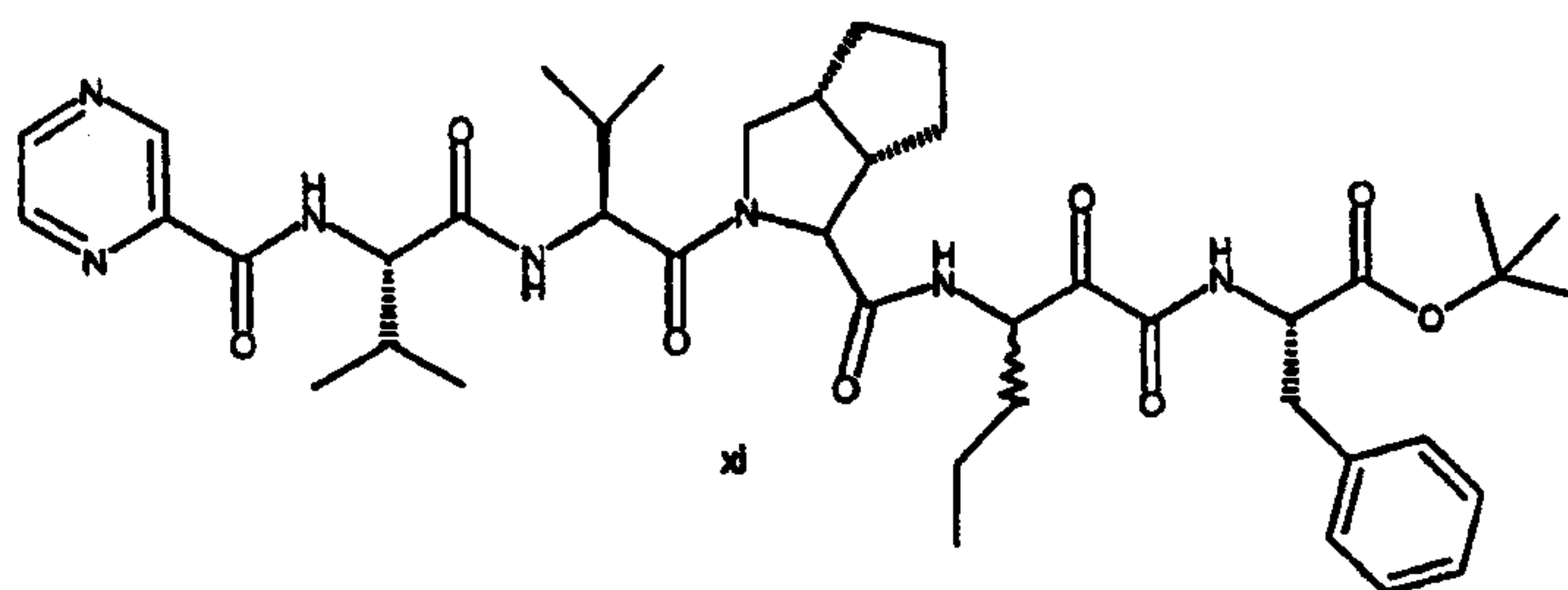
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5 Intermediate Example 8 – Compound xi

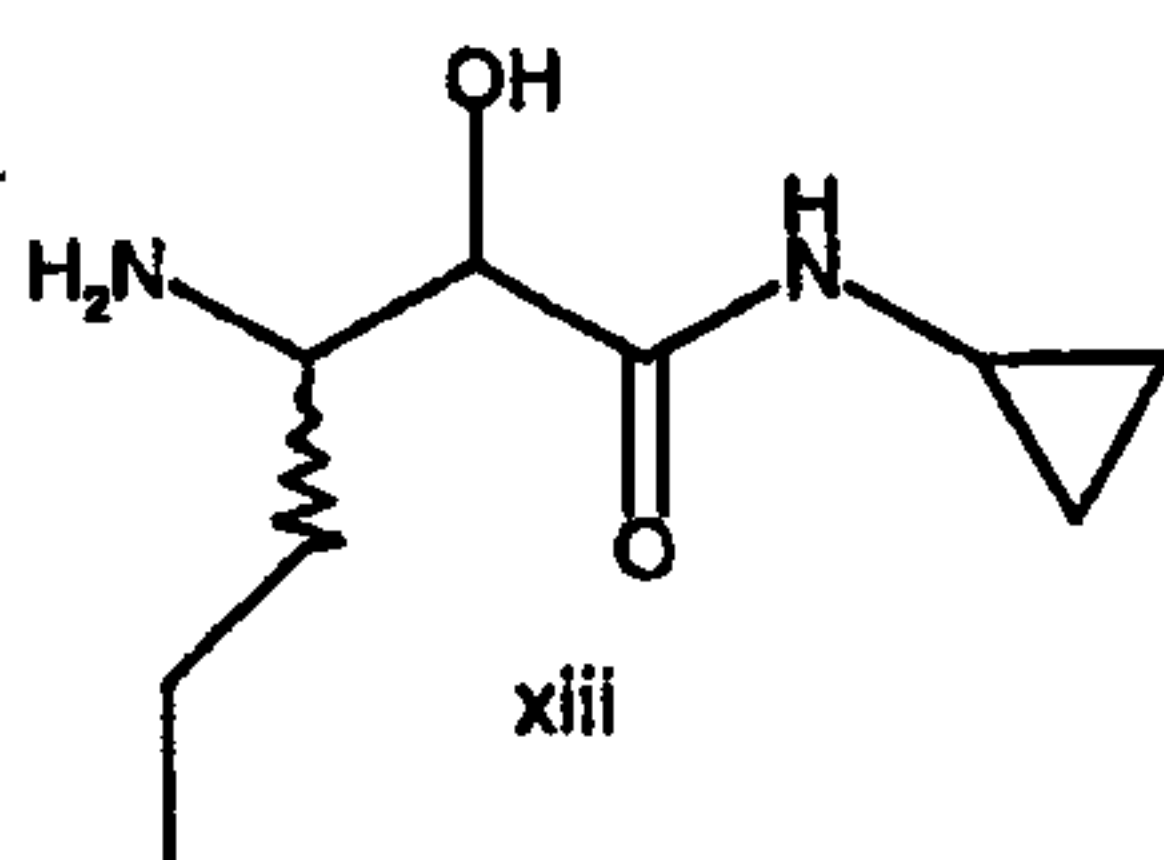
To a DCM solution (10 mL) of compound ix (396 mg, 0.5 mmol) is added DMP reagent reagent (278 mg, 0.65 mmol). The reaction is stirred at about room temperature for 1 hour and then quenched with 10% Na₂SO₃ for 30 minutes. The reaction mixture is then extracted with EtOAc (75 mL) and washed with brine. The organic layer is dried and concentrated *in vacuo*.

10 The resulting residue is purified with silica gel chromatography (70% EtOAc/Hexanes) to give 320 mg (81%) of compound xi,



Intermediate Example 9 – Compound xii

To a DCM solution (10 mL) of compound viii (230 mg, 0.5 mmol) is added PyBop (417 mg, 0.8 mmol). The reaction is stirred at about room temperature for 30 minutes. To this solution is then added a THF solution (3.5 mL) of compound xiii (140 mg, 0.75 mmol) and



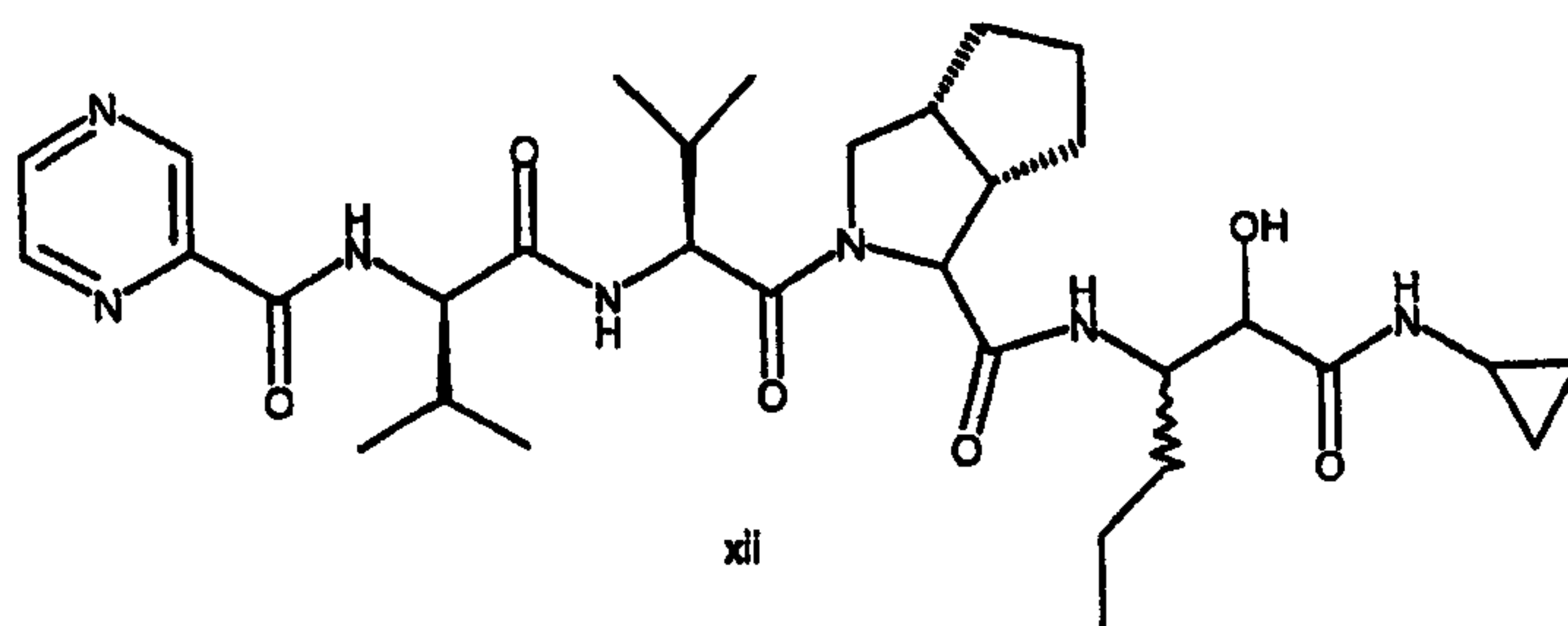
followed by DIPEA (0.174 mL, 1 mmol). The reaction is stirred at about room temperature overnight and then quenched with water (30 mL) for 30 minutes. The reaction mixture is
 20 extracted with EtOAc (75 mL). The organic layer is washed with brine and dried and

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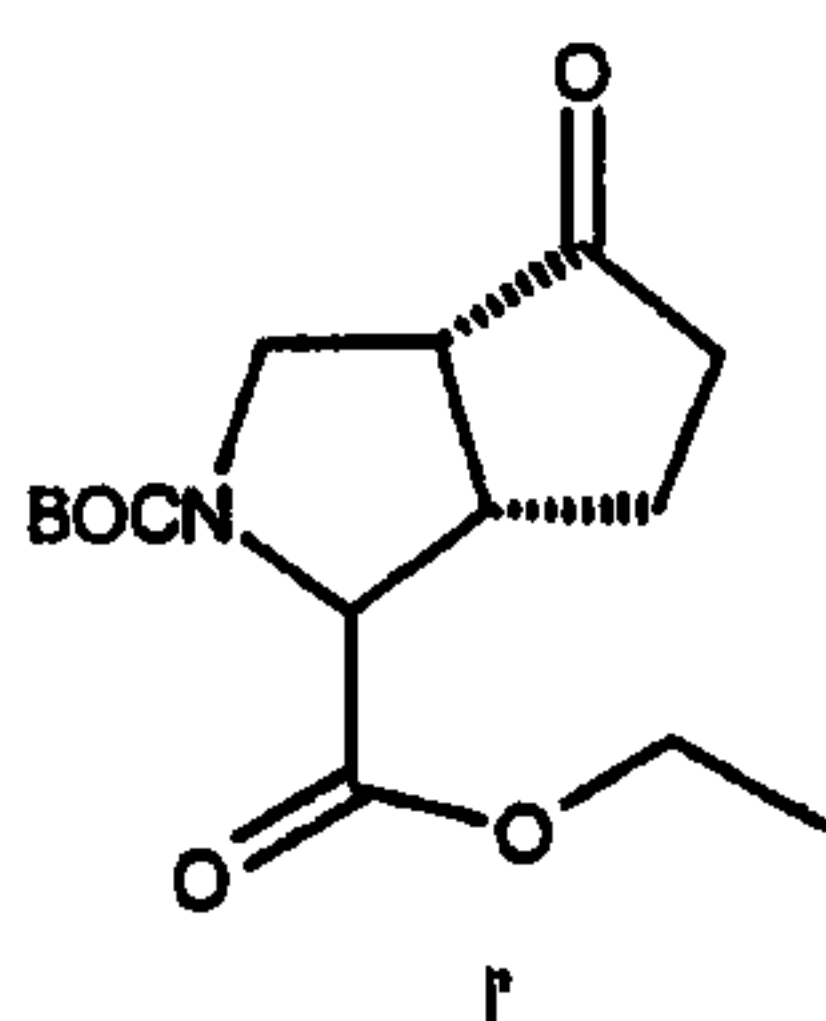
concentrated *in vacuo* to afford a residue that is purified via silica gel chromatography (5% EtOH/EtOAc) to give in quantitative yield compound xii,



5

Intermediate Example 10 – Compound i'

To a methanol solution (30 mL) of compound i (5 g, 15.1 mmol) is added (BOC)₂O (3.3 g, 15.1 mmol) and H₂/Pd(OH)₂/C (1.6 g, 10% Pd content). The reaction is stirred at about room temperature for 2 hours and then filtered through Celite twice. The Celite bed is rinsed with DCM. The combined filtrates are concentrated *in vacuo* to yield an oily residue that is purified by silica gel chromatography (40% EtOAc/Hexanes) to give 3.8 g (85%) of compound i',

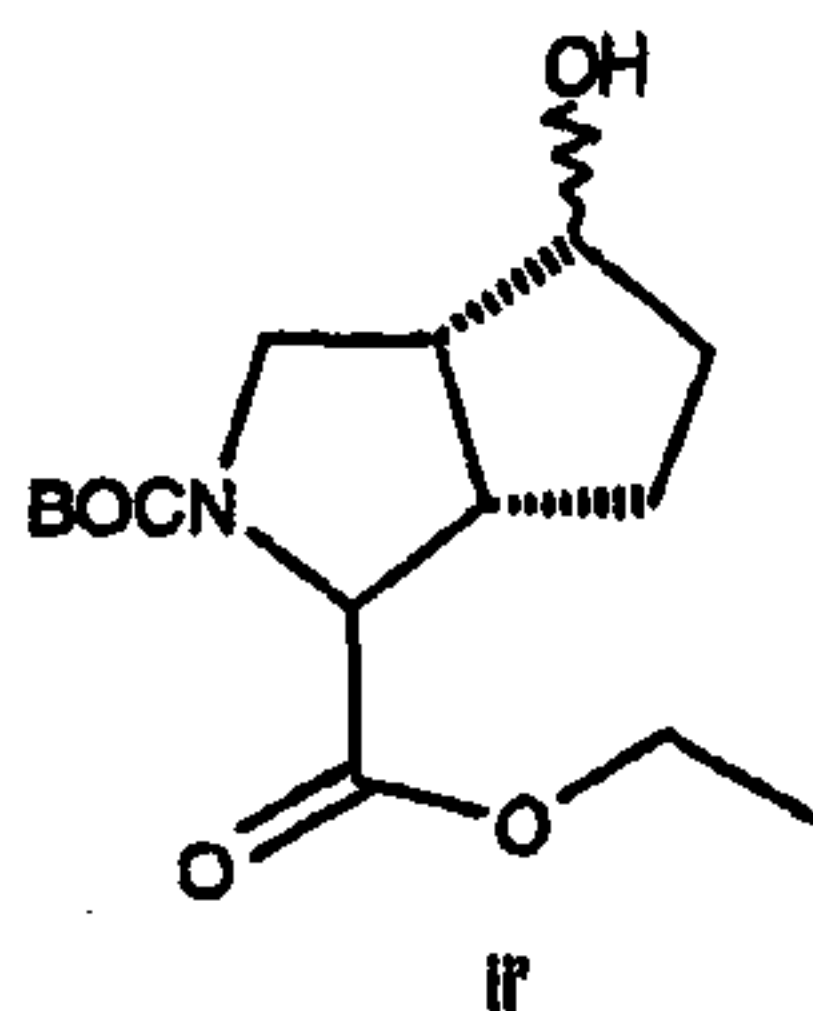


Intermediate Example 11 – Compound ii'

To a methanol solution (111 mL) of compound i' (3.7 g, 12.5 mmol) is added at 0°C NaBH₄ (0.805 g, 21 mmol). After stirring at 0 °C for 2.5 hours, the reaction solvent is evaporated slowly *in vacuo* to yield a residue that is diluted with EtOAc. This solution is then washed with water twice. The aqueous layer is extracted with EtOAc. The combined organic layers are dried with MgSO₄ and filtered and concentrated *in vacuo* to yield a residue that is purified with chromatography to provide 3.76 g (99%) of compound ii',

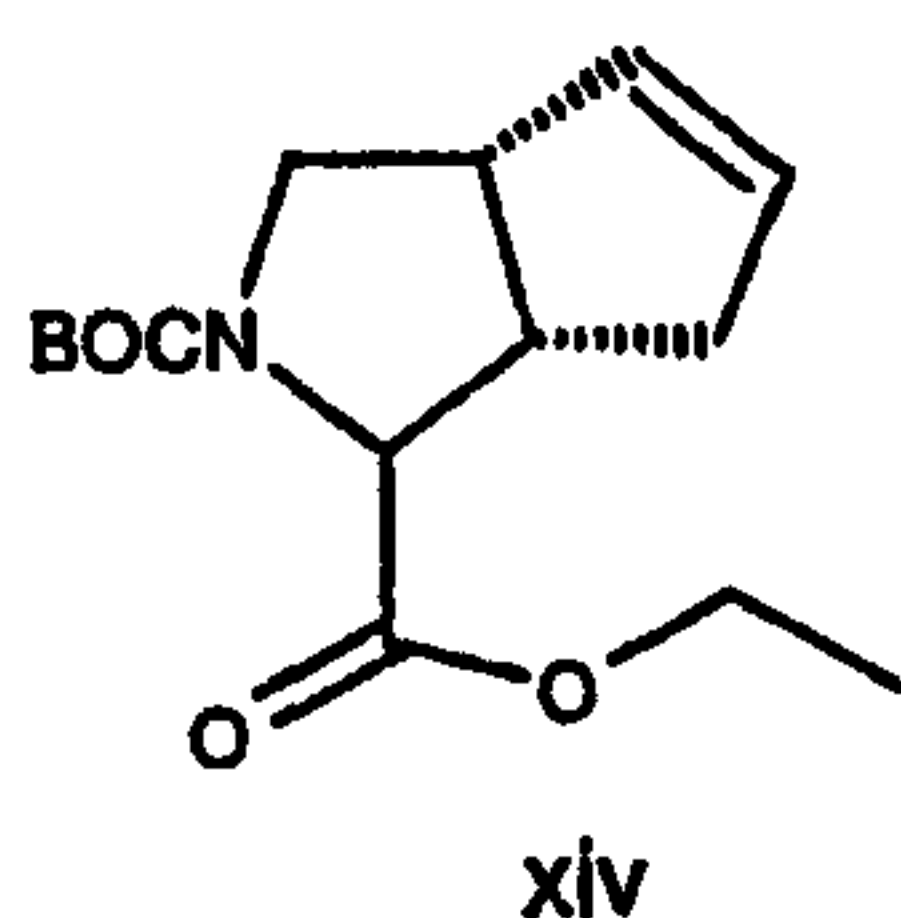
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Intermediate Example 12 – Compound xiv

To a DCM solution (180 mL) of compound ii' (3.76 g, 12.3 mmol) is added at 0 °C DMAP (5 g, 40.1 mmol) and then followed by Tf₂O (4 mL, 23.7 mmol). The reaction is stirred at 0 °C for 1 hour and at about room temperature for additional 1.5 hours. The reaction mixture is then washed twice with 5% NaHCO₃ and dried with MgSO₄. The organic layer thus obtained is concentrated *in vacuo* to provide the crude triflate. The resulting triflate (2.7 g, 6 mmol) is dissolved in DCM (120 mL). To this solution is added DMAP (2.5 g, 20.5 mmol). The resulting reaction mixture is heated to reflux overnight. At this point, the reaction is cooled to room temperature and washed with 5% NaHCO₃ twice. The reaction mixture is dried with MgSO₄ filtered and concentrated *in vacuo* to yield a brownish oily residue that is purified (1% MeOH/DCM) to give 500 mg (30%) of compound xiv,



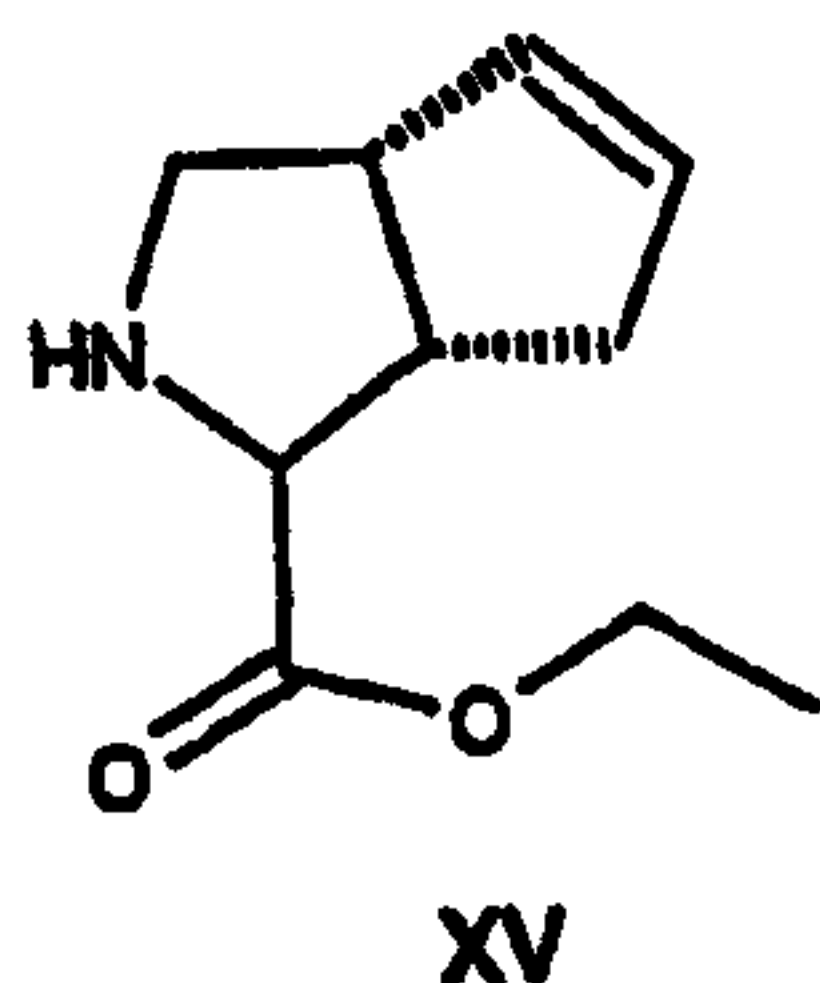
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Intermediate Example 13 – Compound xv

Compound xiv (500 mg, 1.8 mmol) is dissolved in 4 N HCl in dioxane (6.75 mL). The reaction is stirred at about room temperature for ~ 4 hours. At this point, the solvent is removed *in vacuo*. The resulting residue is titrated with diethylether twice to give in almost quantitative yield the HCl salt of compound xv,

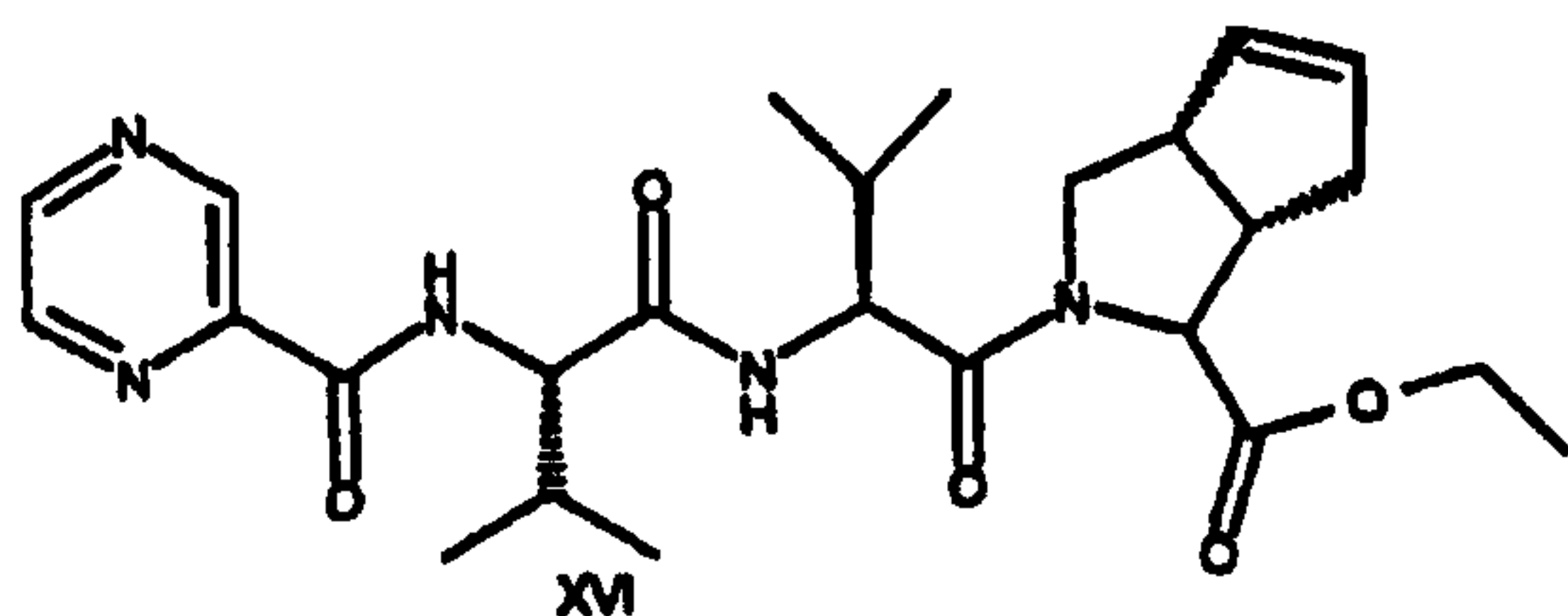
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Intermediate Example 14 – Compound xvi

To a THF solution (7 mL) of compound vii (579 mg, 1.8 mmol) is added HOAt (245 mg, 1.8 mmol) and DCC (1.8 mL, 1 M in DCM). A suspension is resulted. After stirring at about room temperature for 15 minutes, a THF solution (6 mL) of compound xv (1.8 mmol) and DIPEA (0.63 mL, 3.6 mmol) is added to the above suspension. Additional DIPEA (0.8 mL) is added later. The reaction mixture is stirred overnight at about room temperature. At that point, the white solids so formed are filtered off. The white solids are rinsed with THF. The combined filtrates and washings are concentrated *in vacuo* to give the crude product that is purified by silica gel chromatography (100% EtOAc) to provide 665 mg (76%) of compound xvi,



15

Intermediate Example 15 – Compound xvii

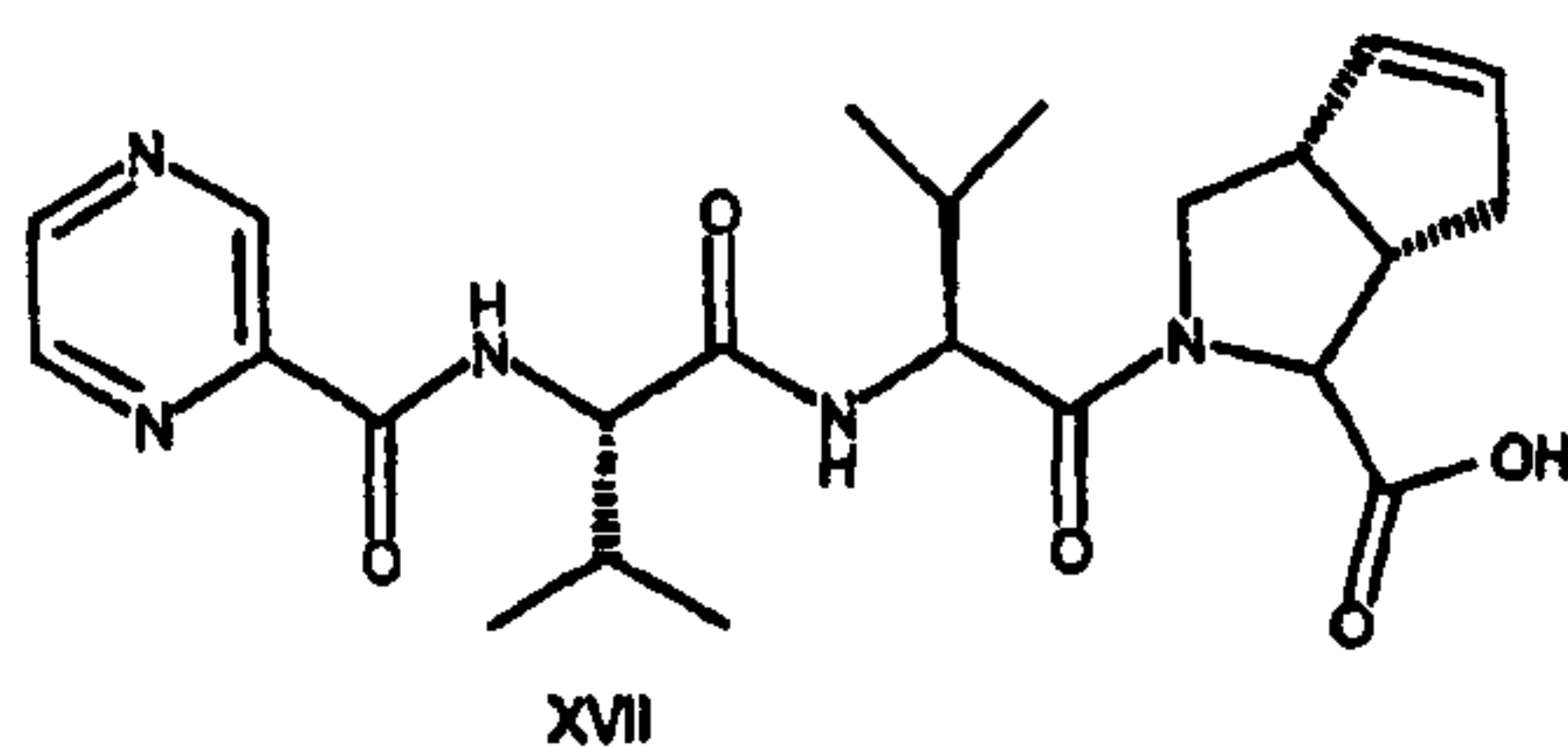
To an ethanol solution (8 mL) of 7 (665 mg, 1.37 mmol) is added 1 N aqueous NaOH (2.4 mmol) at 0°C. The reaction is stirred overnight at about room temperature, and then acidified to pH 3 using Dowex* acidic resins. The solids are filtered. The resulting filtrates are concentrated *in vacuo* to give a pale yellow residue that is redissolved in 1:1 CH₃CN/H₂O and lyophilized to give 467 mg (74%) of compound xvii,

* Trade-mark

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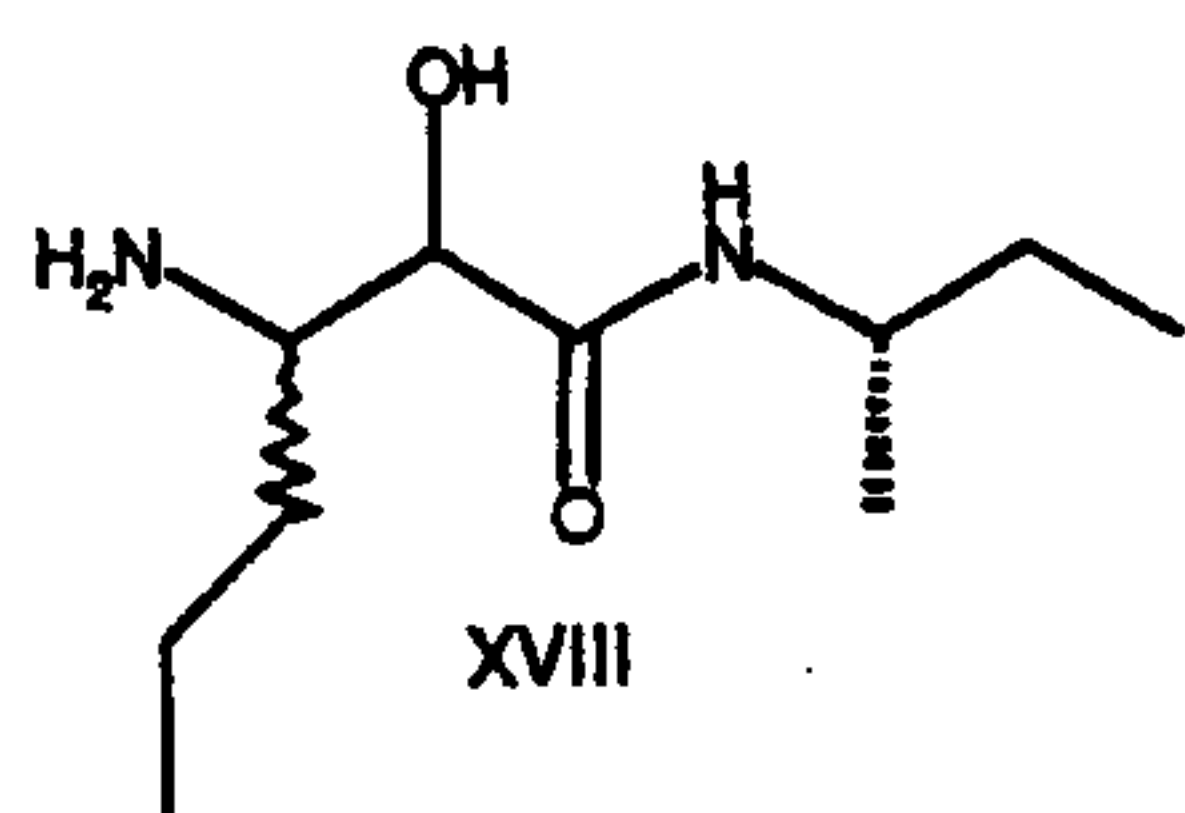
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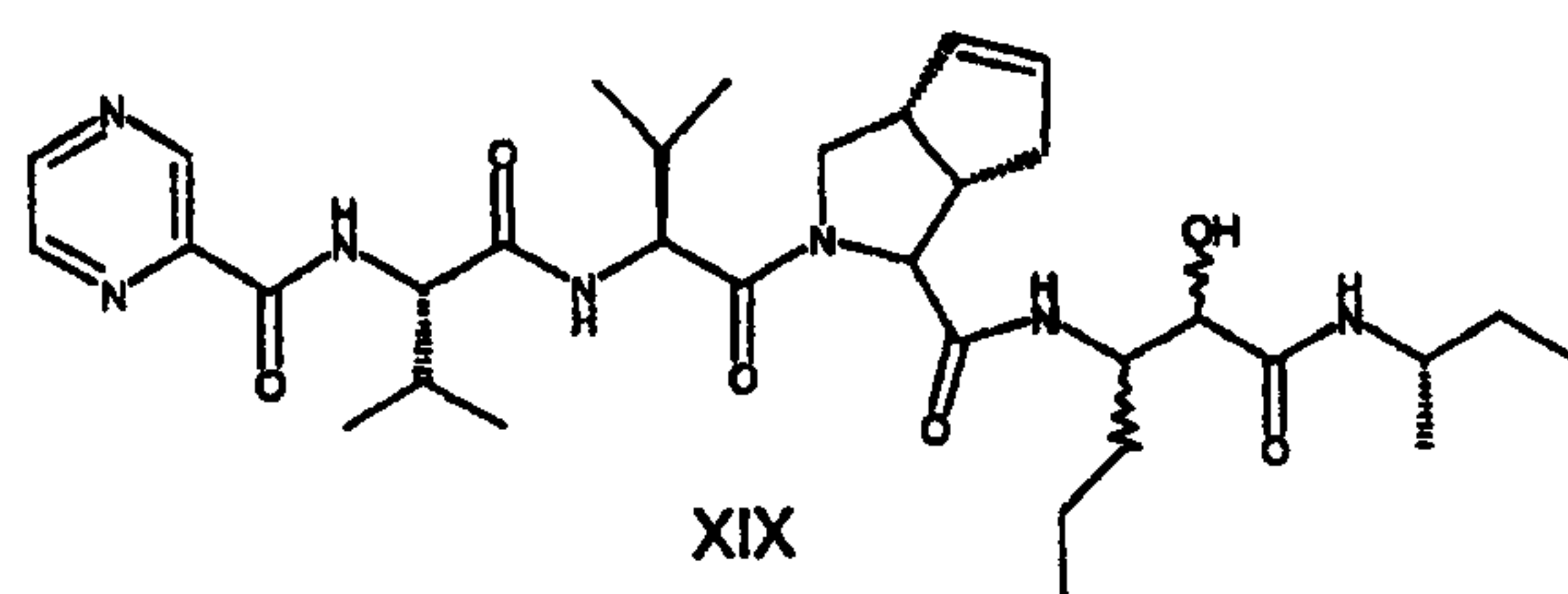


Intermediate Example 16 – Compound xix

A DCM solution (4 mL) of compound xvii (100 mg, 0.22 mmol) is treated with PyBop (207 mg, 0.4 mmol) at about room temperature for 20 minutes. At this point, the above solution is treated with a THF solution (2.6 mL) of compound xviii (65 mg, 0.32 mmol), followed by DIPEA



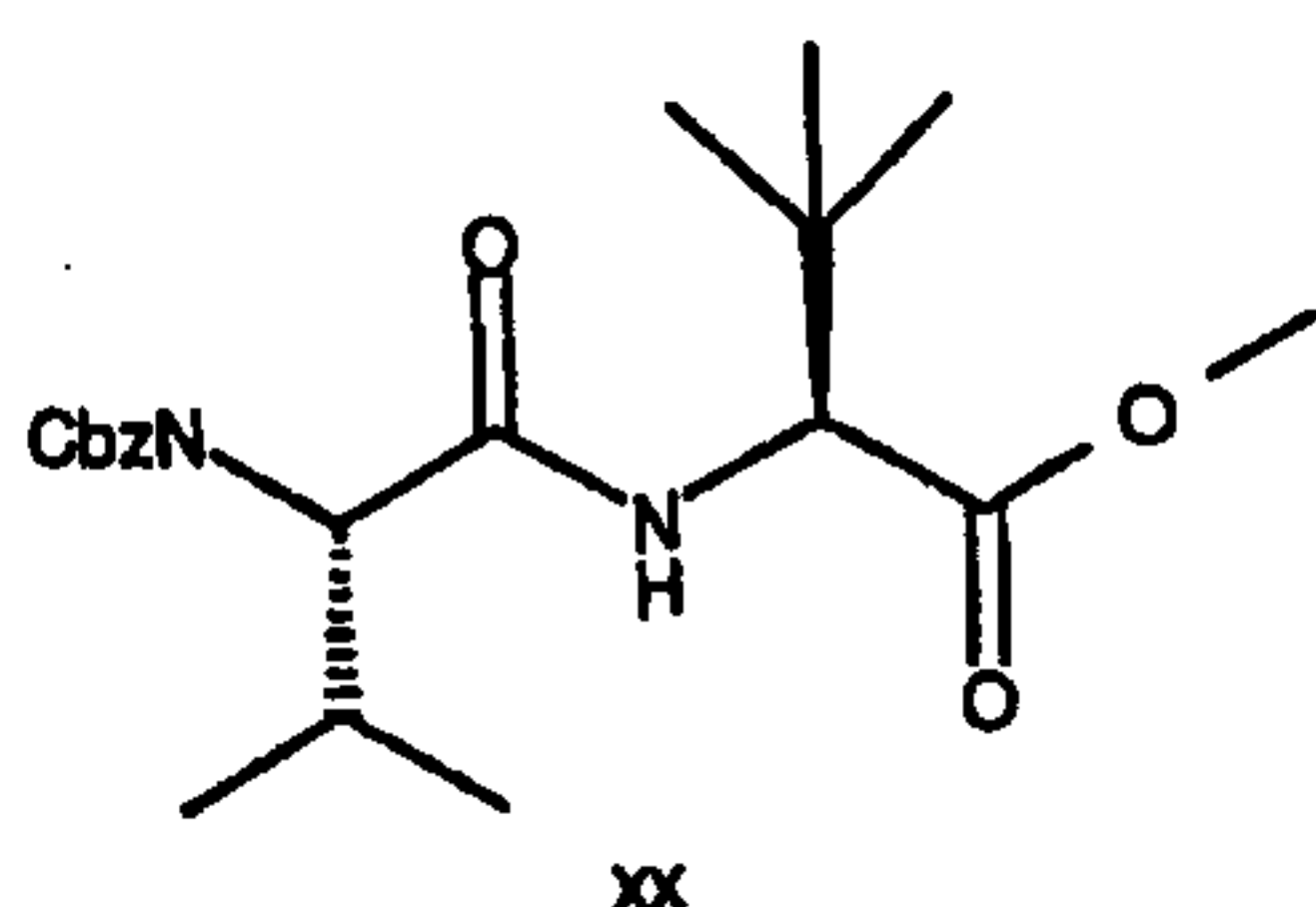
(0.076 mL). After stirring at about room temperature for 7 hours, the reaction is quenched with water. The reaction mixture is diluted with DCM (60 mL). The organic layer is separated and washed twice with brine and dried with MgSO_4 . Upon filtration, concentrated and silica gel chromatography (5% EtOH/EtOAc), 148 mg (~100%) of compound xix is obtained.



Intermediate Example 17 – Compound xx

To a THF solution (100 mL) of N-Cbz-L-valine (14.4 g, 57.2 mmol) is added HOBT (7.72 g, 57.2 mmol) and EDCI (10.98 g, 57.2 mmol). After stirring at about room temperature for 20 minutes, a THF solution (50 mL) containing tert-L-Leucine methyl ester-hydrochloride (10.4 g, 57.2 mmol) and DIPEA (11.9 mL, 68.7 mmol) is added to the above solution. The reaction is

stirring at about room temperature overnight. Upon standard aqueous work-up and silica gel chromatography (30% EtOAc/Hexanes) 14 g (64%) of compound xx is afforded.



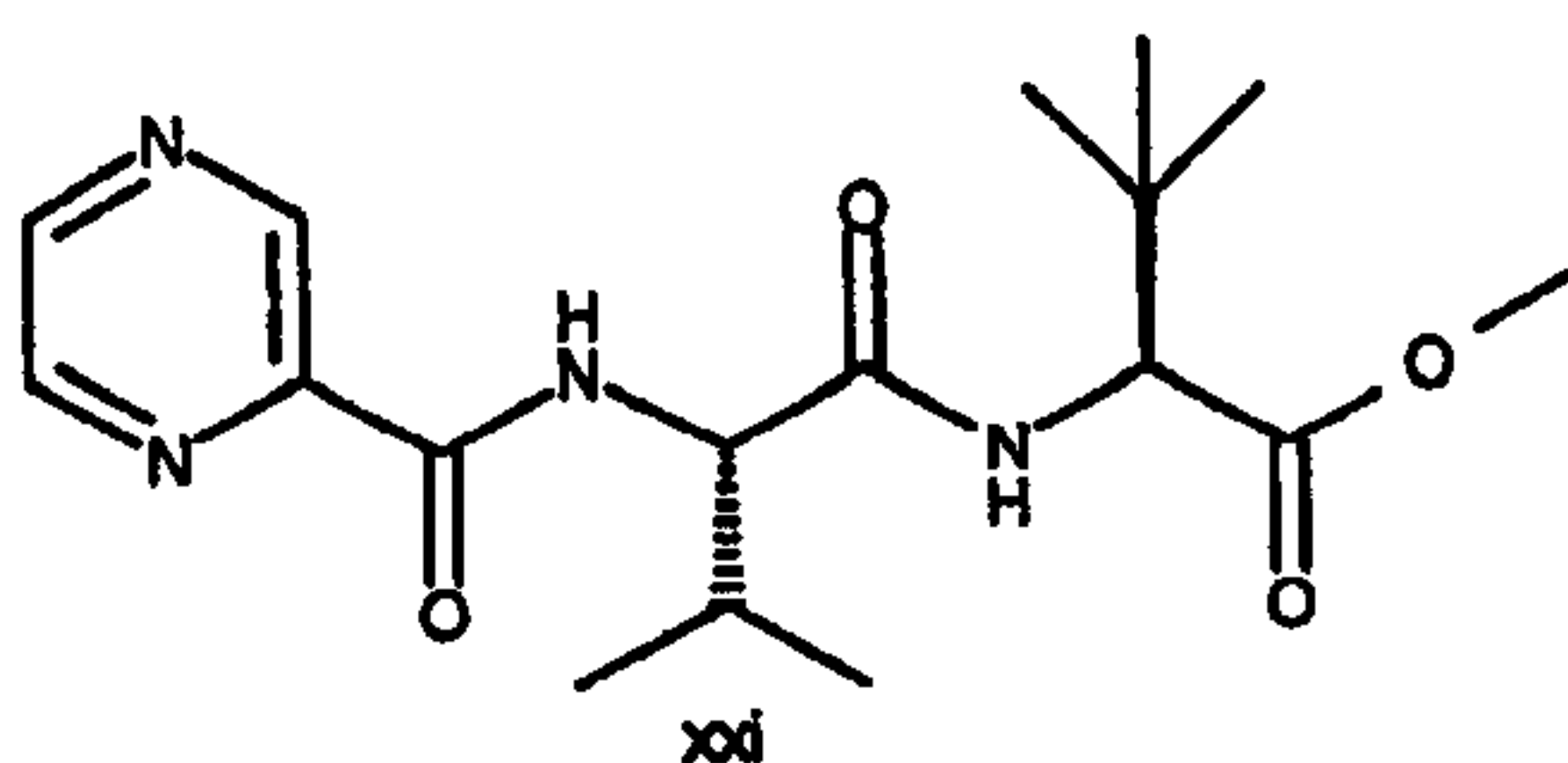
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Intermediate Example 18 – Compound xxi

To a methanol solution (80 mL) of xx (6.71 g, 17.7 mmol) is added (under a stream of N₂) Pd/C (1.88 g, 10% Pd content). The reaction vessel is subjected to hydrogenation (1 atm H₂) overnight at about room temperature. At this point, the reaction mixture is filtered through a pad of Celite and concentrated *in vacuo* to provide the corresponding crude free amine for next step.

10 A THF solution of this amine (~17.7 mmol) is added to a THF (46 mL) and DMF (5 mL) solution containing 2-pyrazinecarboxylic acid (2.85 g, 23 mmol), Hobbit (3.12 g, 23 mmol) and EDCI (4.41 g, 23 mmol). To the resulting mixture is then added DIPEA (3.08 g, 17.7 mmol). The reaction is stirred overnight at about room temperature and then quenched with water. The

15 reaction mixture is extracted with EtOAc. The organic layer is washed with brine and concentrated *in vacuo* to provide a residue that is purified by silica gel chromatography (40-50% EtOAc/Hexanes) to provide 3.9 g (63%) of compound xxi,

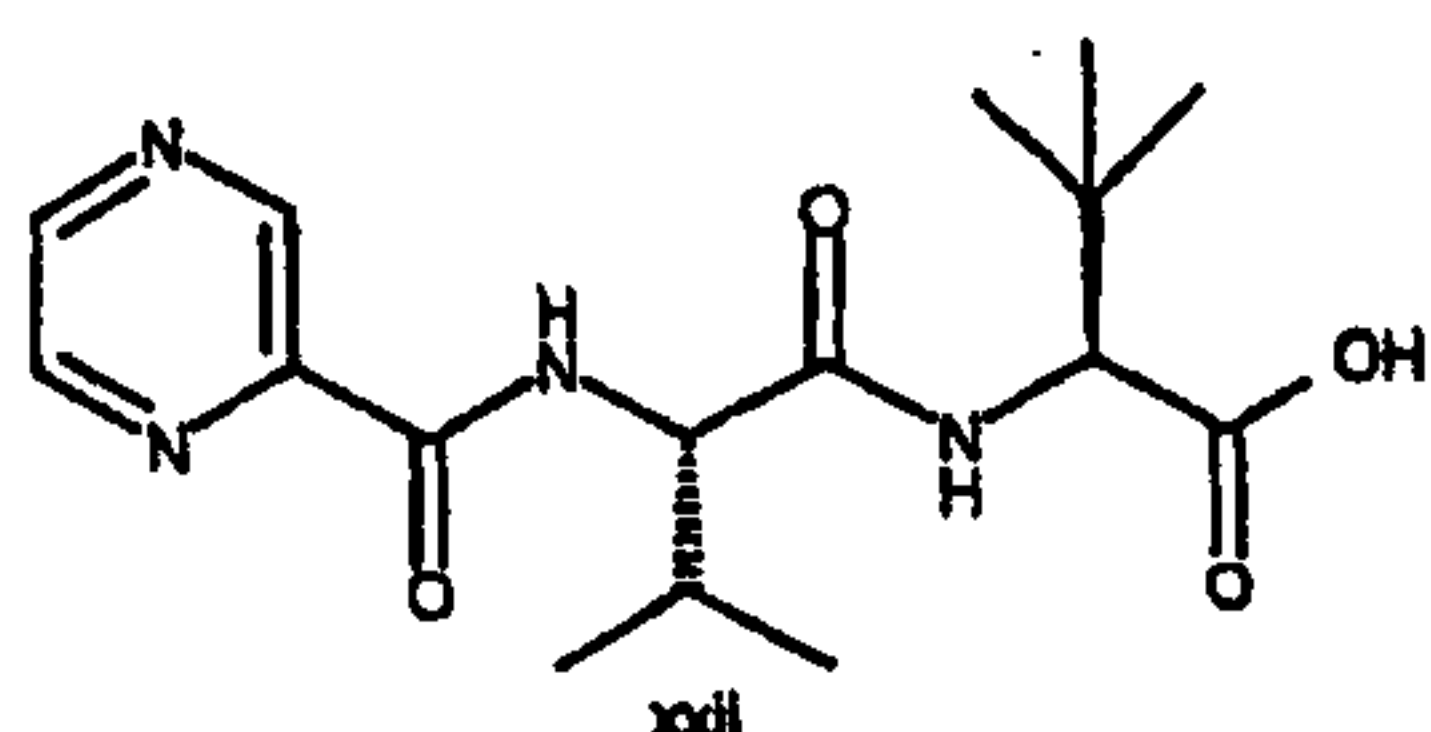


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Intermediate Example 19 – Compound xxii

To a methanol solution (40 mL) of compound xxi (4.67 g, 13.34 mmol) is added 2 N NaOH (10 mL, 20 mmol). The reaction is stirred at about room temperature for 2 hours. At this time, an additional amount of 2 N NaOH (3.3 mL, 6.67 mmol) is added to the reaction mixture. After stirring at about room temperature overnight, the reaction is acidified to pH 3 using acidic

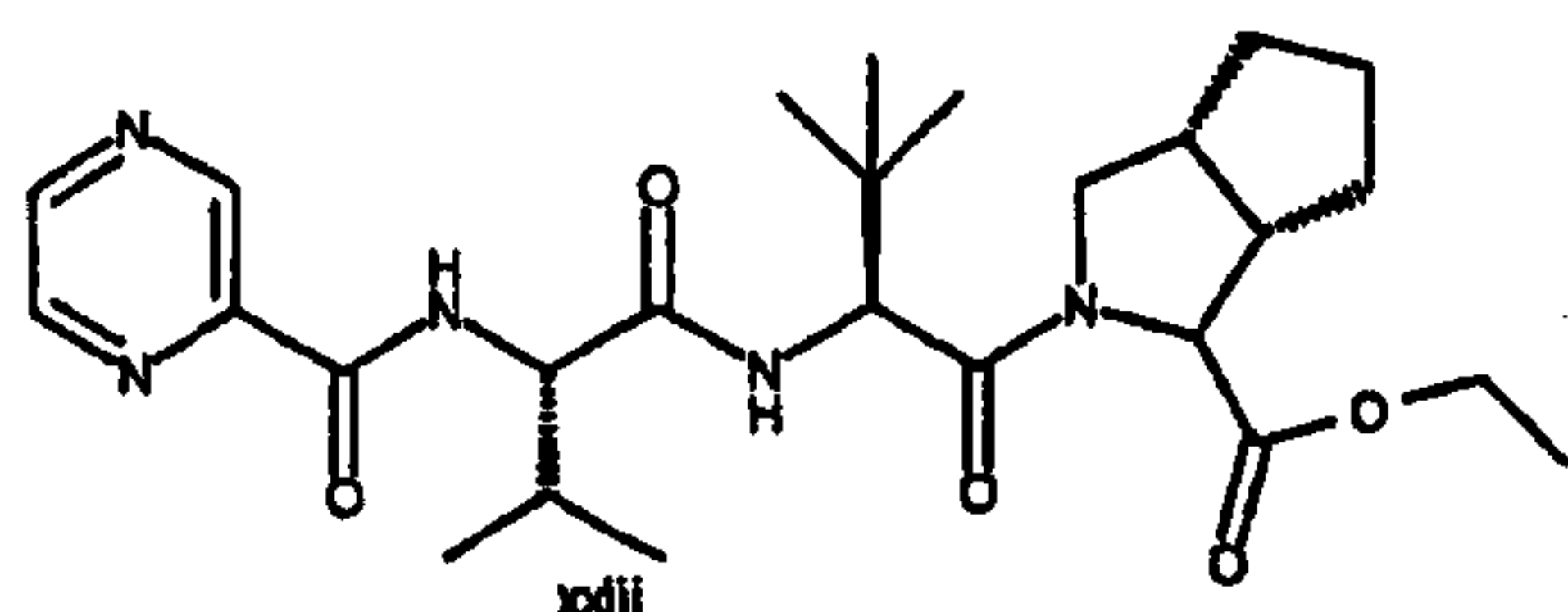
25 resin. The reaction is then filtered and the filtrates are concentrated *in vacuo* to yield a residue that is dissolved in 1:1 CH₃CN/H₂O for lyophilization. 4.15 g (93%) of compound xxii is obtained.



Intermediate Example 20 – Compound xxiii

A DCM solution (10 mL) of compound xxii (917 mg, 2.73 mmol) is treated with HOAt (371 mg, 2.73 mmol) and DCC (2.73 mL, 1 M, 2.73 mmol). After stirring for 30 minutes, the reaction mixture is treated with a THF solution (10 mL) of compound v (500 mg, 2.73 mmol). After stirring at about room temperature overnight, the white solids (urea) are filtered. The filtrates are concentrated *in vacuo* to give a residue that is purified by silica gel chromatography (60-70% EtOAc/Hexanes) to provide 1.06 g (77%) of compound xxiii,

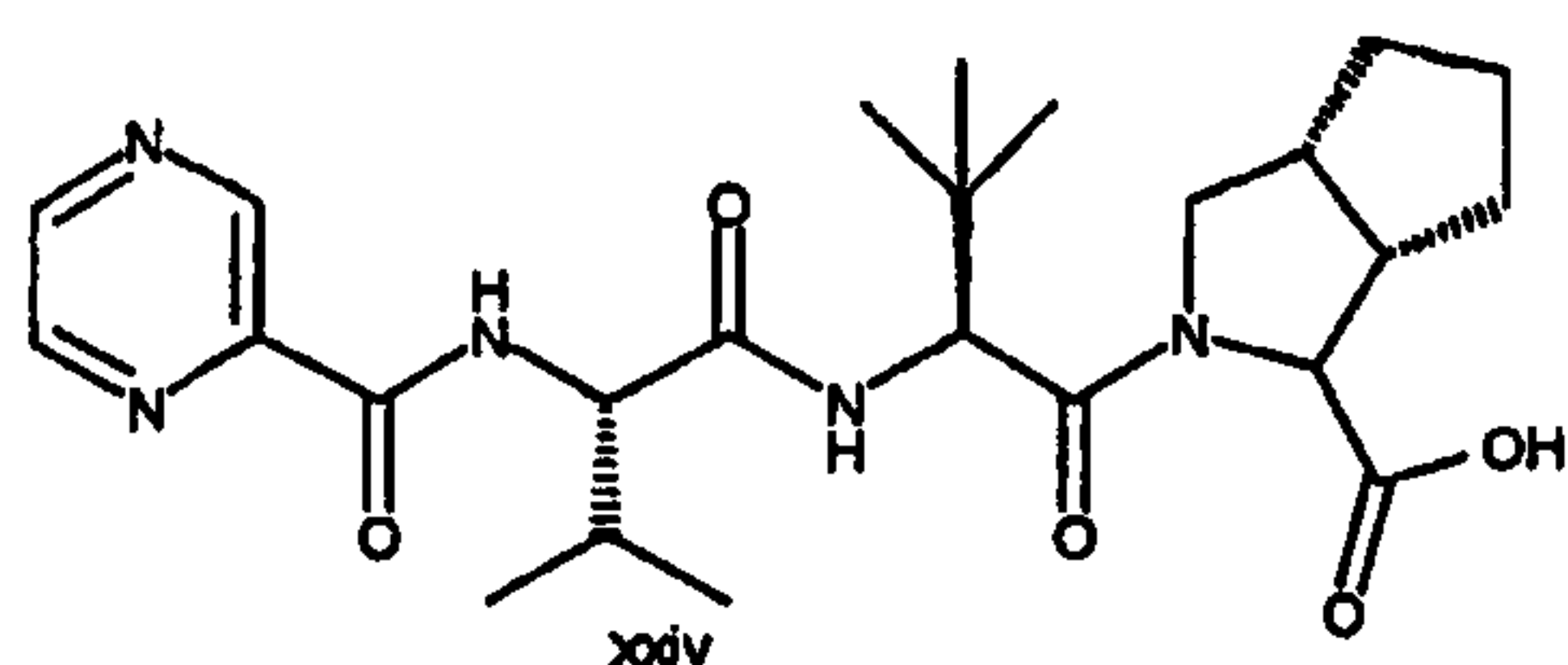
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Intermediate Example 21 – Compound xxiv

An ethanol solution (20 mL) of compound xxiii (1.06 g, 2.11 mmol) is treated with 2 N NaOH (2.11 mL, 4.23 mmol). After stirring at about room temperature overnight, the reaction mixture is acidified to pH 3 with acidic resin. The solids are filtered off. The resulting filtrates are concentrated *in vacuo* to give a residue that is lyophilized to give ~ 1 g (100%) of compound xxiv,

15



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Intermediate Example 22 – Compound xxv

A DCM solution (10 mL) of compound xxiv (236.7 mg, 0.5 mmol) is treated with PyBop (417 mg, 0.8 mmol). After stirring at about room temperature for 20 minutes, the reaction mixture is treated with a DMF solution (5.6 mL) of compound xiii (139.5 mg, 0.75 mmol), followed by DIPEA (0.174 mL, 1 mmol). After stirring at about room temperature for 8 hours,

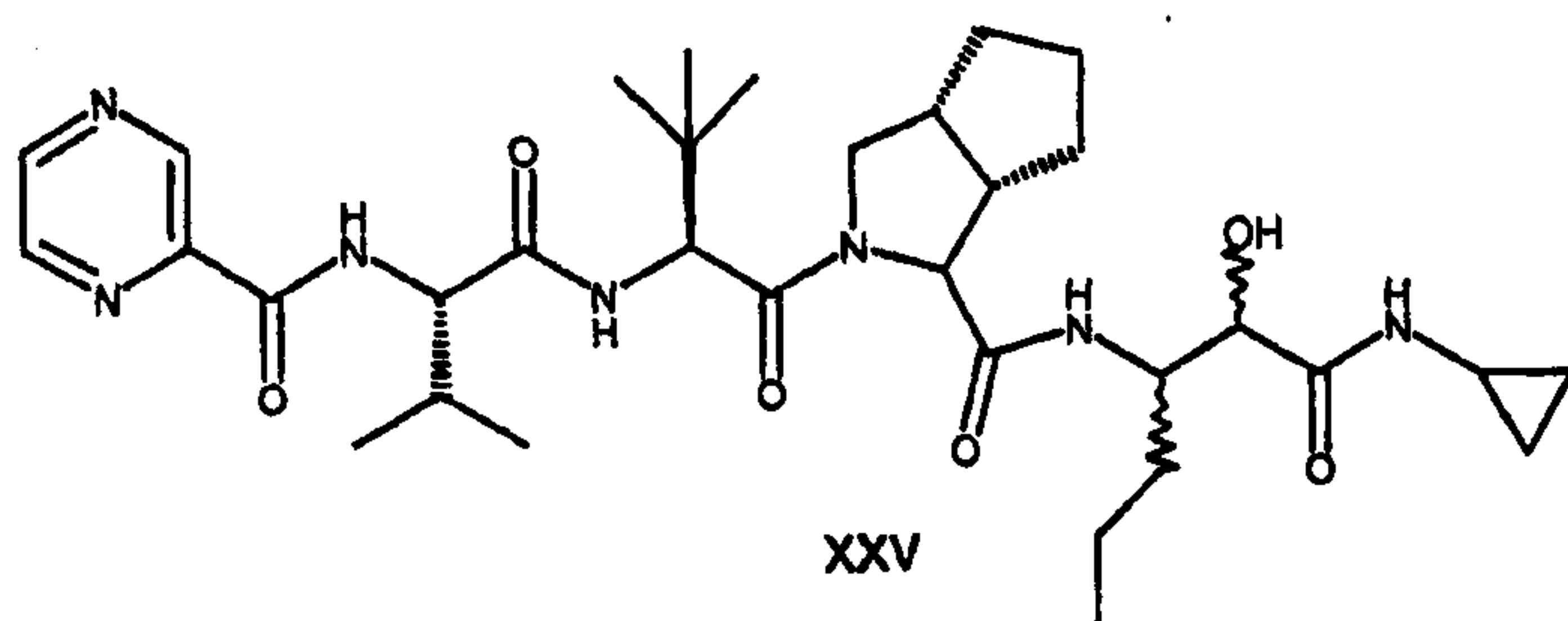
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the reaction is quenched with water and extracted with EtOAc. The resulting organic layer is washed with brine and dried and concentrated *in vacuo* to give a residue that is purified by silica gel chromatography (5% EtOH/EtOAc) to afford ~320 mg (100%) of compound xxv,

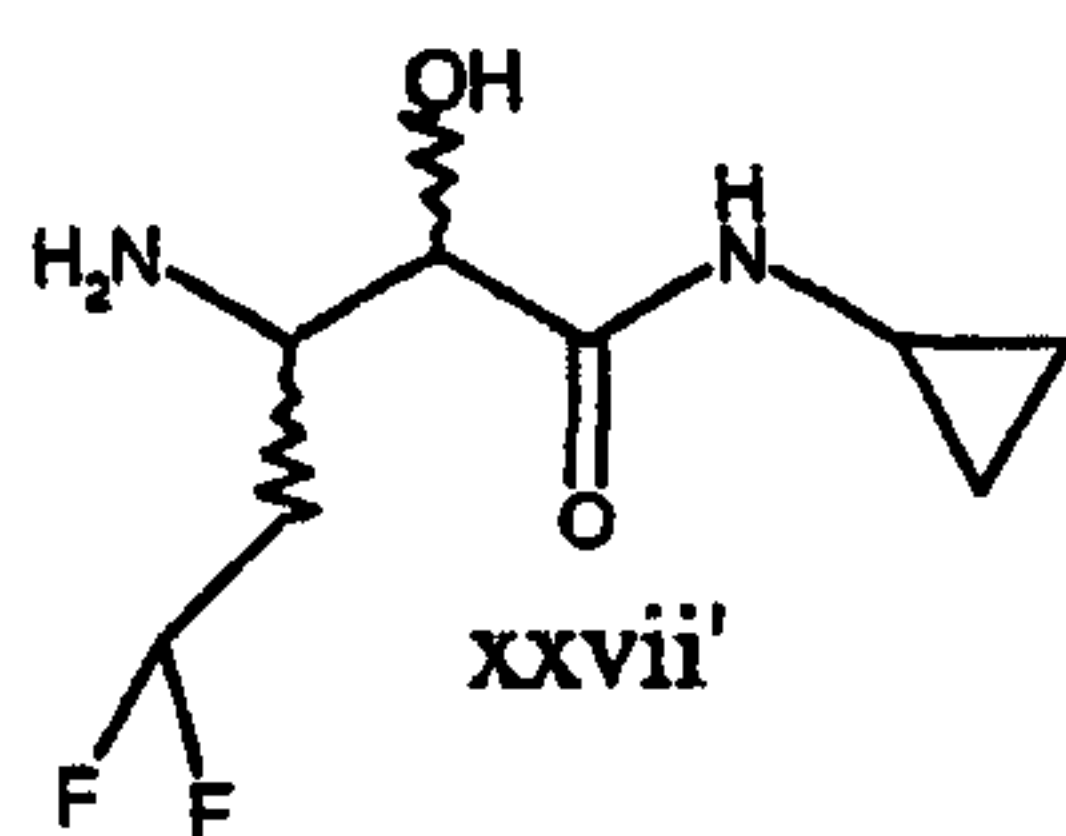


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Intermediate Example 23 – Compound xxvi

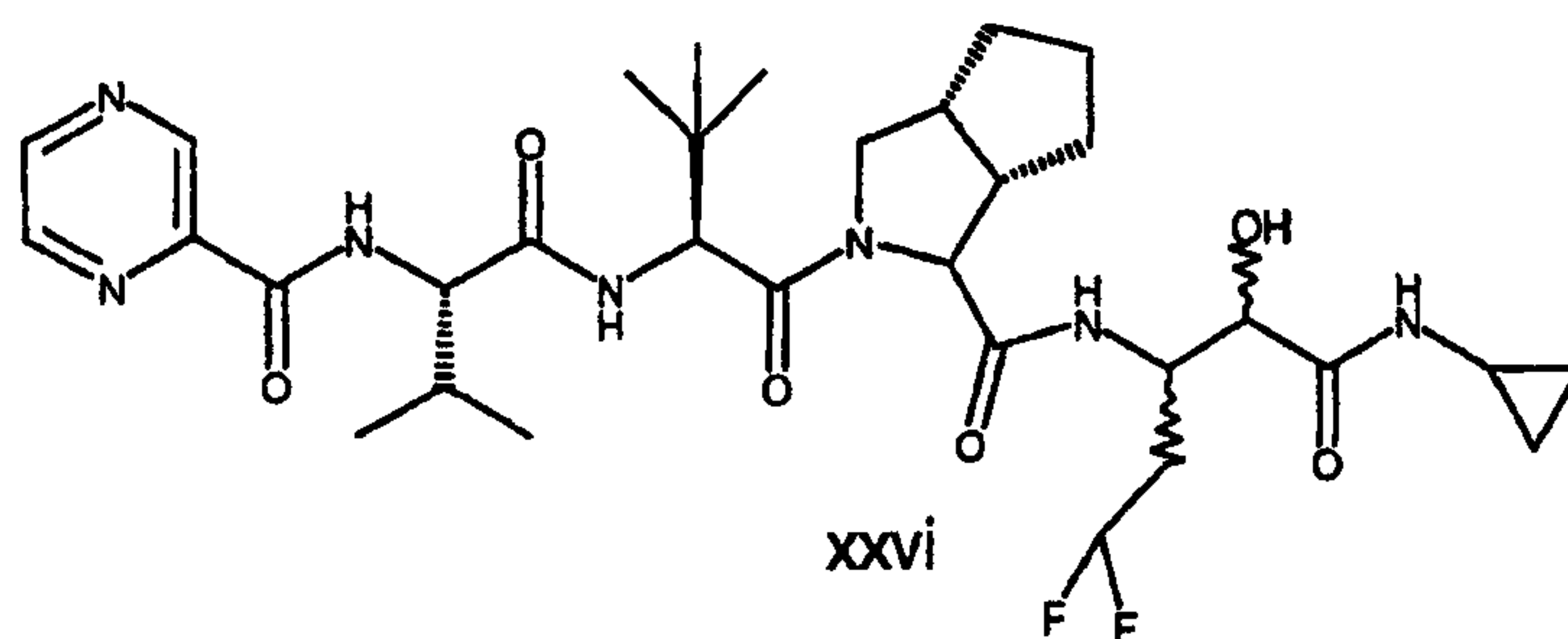
A DCM solution (15 mL) of compound xxiv (355 mg, 0.75 mmol) is treated with PyBop (622 mg, 1.2 mmol). After stirring at about room temperature for 20 minutes, the reaction mixture is treated with a THF solution (10 mL) of compound xxvii' (156 mg, 0.75

10



mmol), followed by DIPEA (0.26 mL, 1.5 mmol). After stirring at about room temperature overnight, the reaction is quenched with water and extracted with EtOAc. The resulting organic layer is washed with brine and dried and concentrated *in vacuo* to give a residue that is purified by silica gel chromatography (2% EtOH/EtOAc) to afford ~400 mg (80%) of compound xxvi,

15



Intermediate Example 24 – Methyl 5-cyanopentanoate

Potassium Cyanide (4 g, 61.44 mmol) is dissolved in 70 mL water and 200 mL methanol. To the solution 10 g (51.2 mmol) of methyl 5-bromopentanoate is added and the mixture is refluxed overnight. The reaction mixture is concentrated to dryness. To the residue, 100 mL of EtOAc is added to extract the product. The organic is washed with water three times, dried and concentrated to yield 5.37 g (74%) of methyl 5-cyanopentanoate as an oil.

Intermediate Example 25 – Methyl 5-tetrazol-5-ylpentanoate

Methyl 5-cyanopentanoate (4.8 g, 34 mmol) is dissolved in toluene, triethylammonium chloride (14 g, 102 mmol) and sodium azide (6.63, 102 mmol) is added. The mixture is heated to reflux for overnight. The reaction mixture is cooled to room temperature, water is added to extract (3x100 mL) methyl 5-tetrazol-5-ylpentanoate from the organic. To the aqueous phase, concentrate HCl is added to adjust pH to 2. The product is extracted from the aqueous solution with EtOAc (3x50 mL). The organic is combined, dried and concentrated to yield 4.25 g (68%) of methyl 5-tetrazol-5-ylpentanoate.

Intermediate Example 26 – Methyl 5-[N-(1,1-dimethylbenzyl)tetrazol-5-yl]pentanoate

Methyl 5-tetrazol-5-ylpentanoate (4.23 g, 23 mmol) and trichloroacetic acid (8.69 g, 53 mmol) are dissolved in 50 mL of CHCl_3 . α -Methylstyrene (2.72, 23 mmol) is added to the solution dropwise, and the reaction mixture is allowed to stirred at about room temperature for overnight. The reaction mixture is diluted with EtOAc to 200 mL, and organic layer is washed with 10% aqueous KOH and brine. The organic layer is dried, concentrated. The product is purified by flash column chromatography to yield 6.6 g (95%) methyl 5-[N-(1,1-dimethylbenzyl)tetrazol-5-yl]pentanoate.

Intermediate Example 27 – 5-[N-(1,1-dimethylbenzyl)tetrazol-5-yl]pentanoic acid

Methyl 5-[N-(1,1-dimethylbenzyl)tetrazol-5-yl]pentanoate (6.6 g, 21.8 mmol) is dissolved in methanol (100 mL) and 23 mL of 1 N aqueous NaOH is added. The mixture is stirred overnight and is concentrated to remove methanol. The residue is dissolved in water (100 mL) and the solution is neutralized by adding the same equivalent of 1 N aqueous HCl. The product is extracted with EtOAc (3x50 mL). The organic is dried and concentrated to yield 4.75g (75%) 5-[N-(1,1-dimethylbenzyl)tetrazol-5-yl]pentanoic acid.

Intermediate Example 28 – Compound xxviii

5-[N-(1,1-dimethylbenzyl)tetrazol-5-yl]pentanoic acid (4.75 g, 16.5 mmol) is dissolved in DCM (100 mL), 4.8 g (24.8 mmol) of EDCI and 6 mL of DIPEA are added. To the mixture, N-

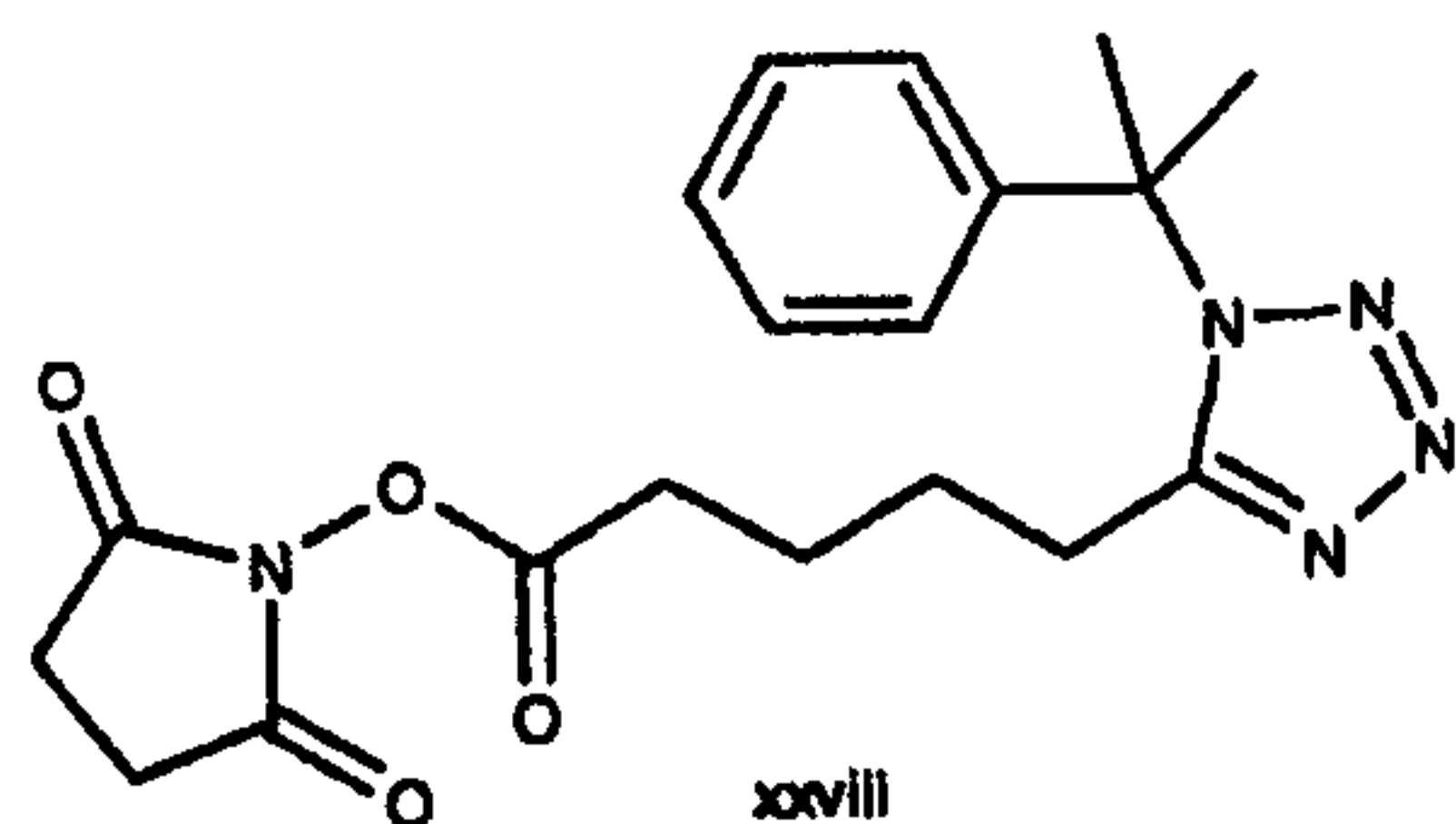
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hydroxylsuccinimide (3.8 g, 33 mmol) is added. The reaction mixture is stirred for three hours at about room temperature. The mixture is diluted with DCM to 200 mL and the solution is washed with water three times. The organic is dried and concentrated to yield 4.79 g (75%) of compound xxviii,

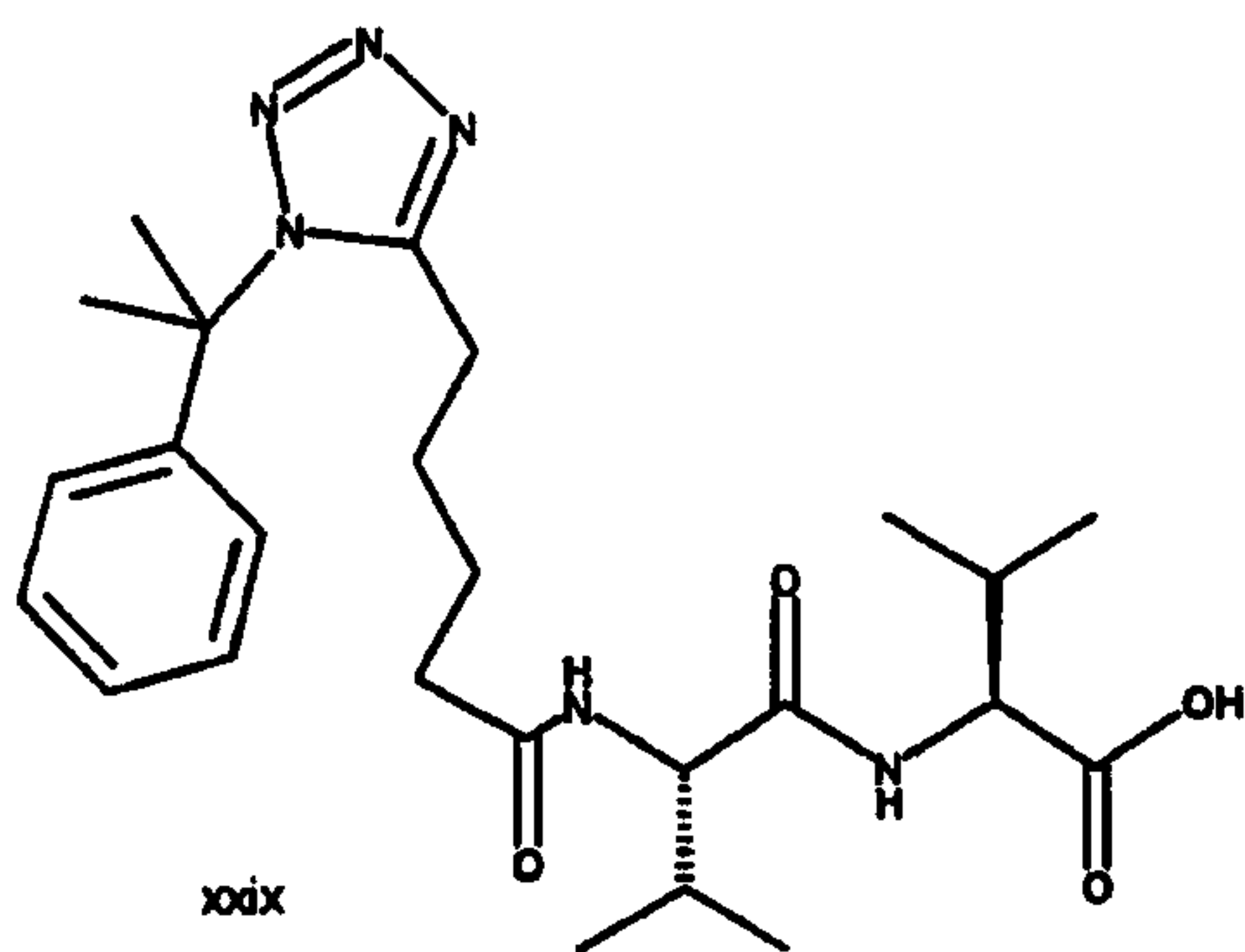
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Intermediate Example 29 – Compound xxix

The dipeptide H-Val-Val-OH (3.22 g, 14.9 mmol) is suspended in 50 mL of N,N-dimethylformamide (DMF) and 4.75 g (12.42 mmol) of compound xxviii is added followed the addition of 3.4 mL (18.63 mmol) of diisopropylethylamine (DIPEA). The mixture is warmed up to 40°C and stirred overnight. The solvent is evaporated under high vacuum. The residue is dissolved in EtOAc and washed with 1 N HCl and brine to yield 5.52 g (91%) of compound xxix,

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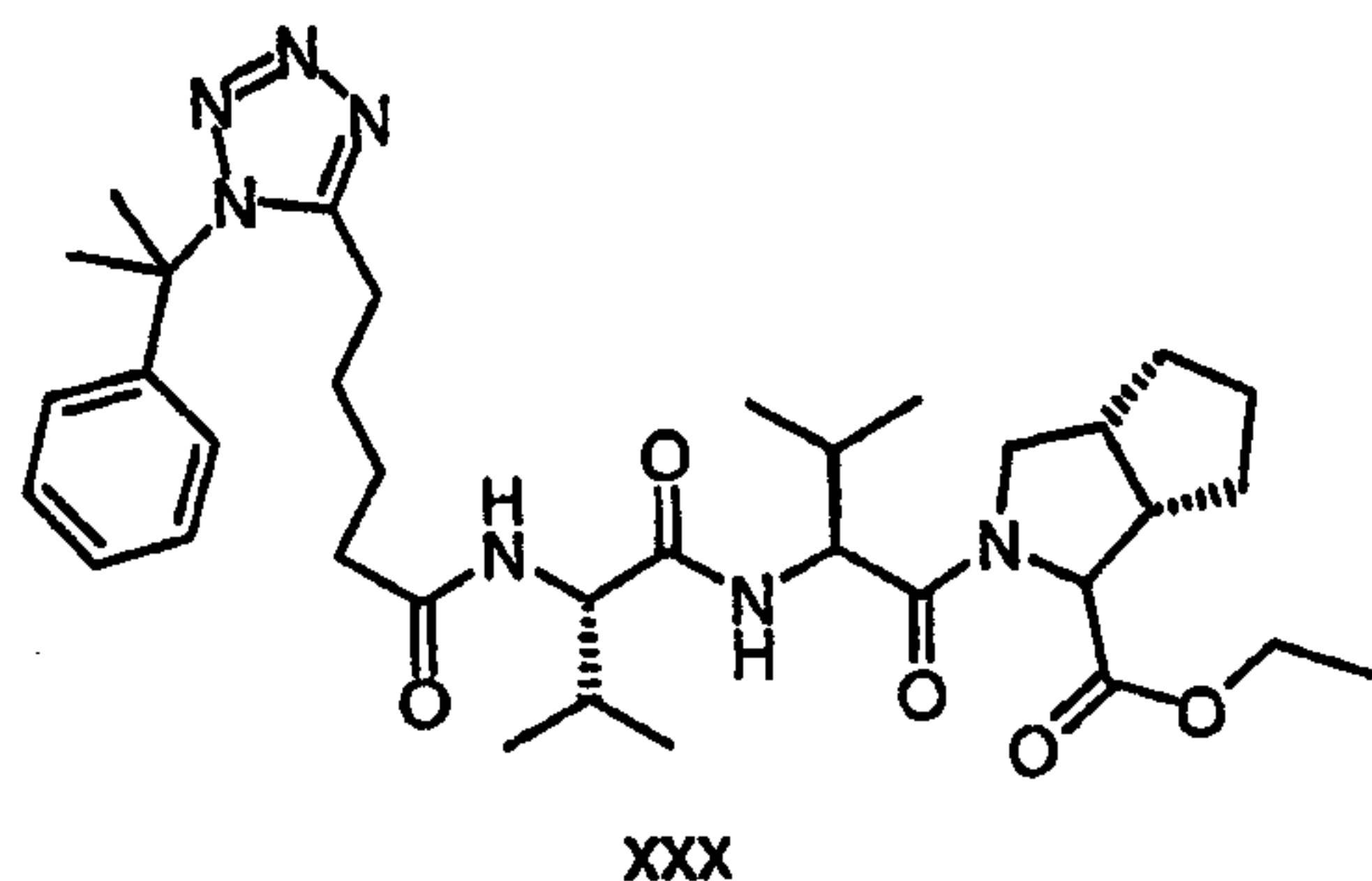


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Intermediate Example 30 – Compound xxx

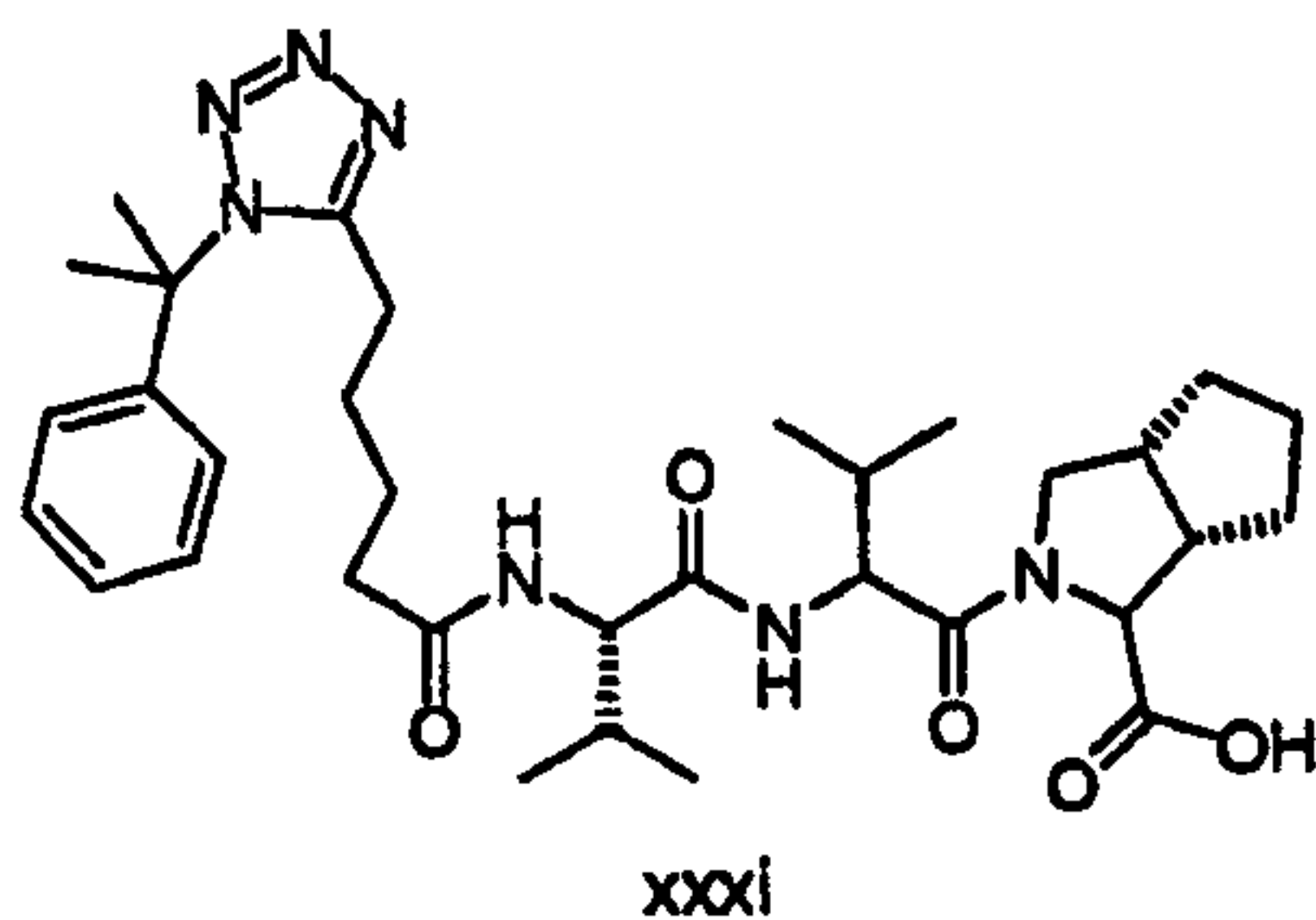
1.6 g (3.29 mmol) of compound xxix is dissolved in 20 mL of DCM, 3.3 mL of 1 M solution of DCC in THF is added. To the mixture, 500 mg (2.73 mmol) of compound v is added. The mixture is stirred at about room temperature overnight. The mixture is diluted with EtOAc to 100 mL and washed with 1 N HCl, NaHCO₃ and brine. Purified by column chromatography (50% EtOAc/hexane) to yield 1.02 g (58%) compound xxx,

20



Intermediate Example 31 – Compound xxxi

Compound xxx (1.02 g, 1.57 mmol) is dissolved in 10 mL MeOH and 2 mL of 1 N
 5 aqueous NaOH is added. The mixture is stirred overnight. The methanol is removed by
 evaporation and the residue is dissolved in water and neutralized with 2 mL HCl. Following
 extraction with EtOAc, 1.00g (~100%) of compound xxxi is afforded.



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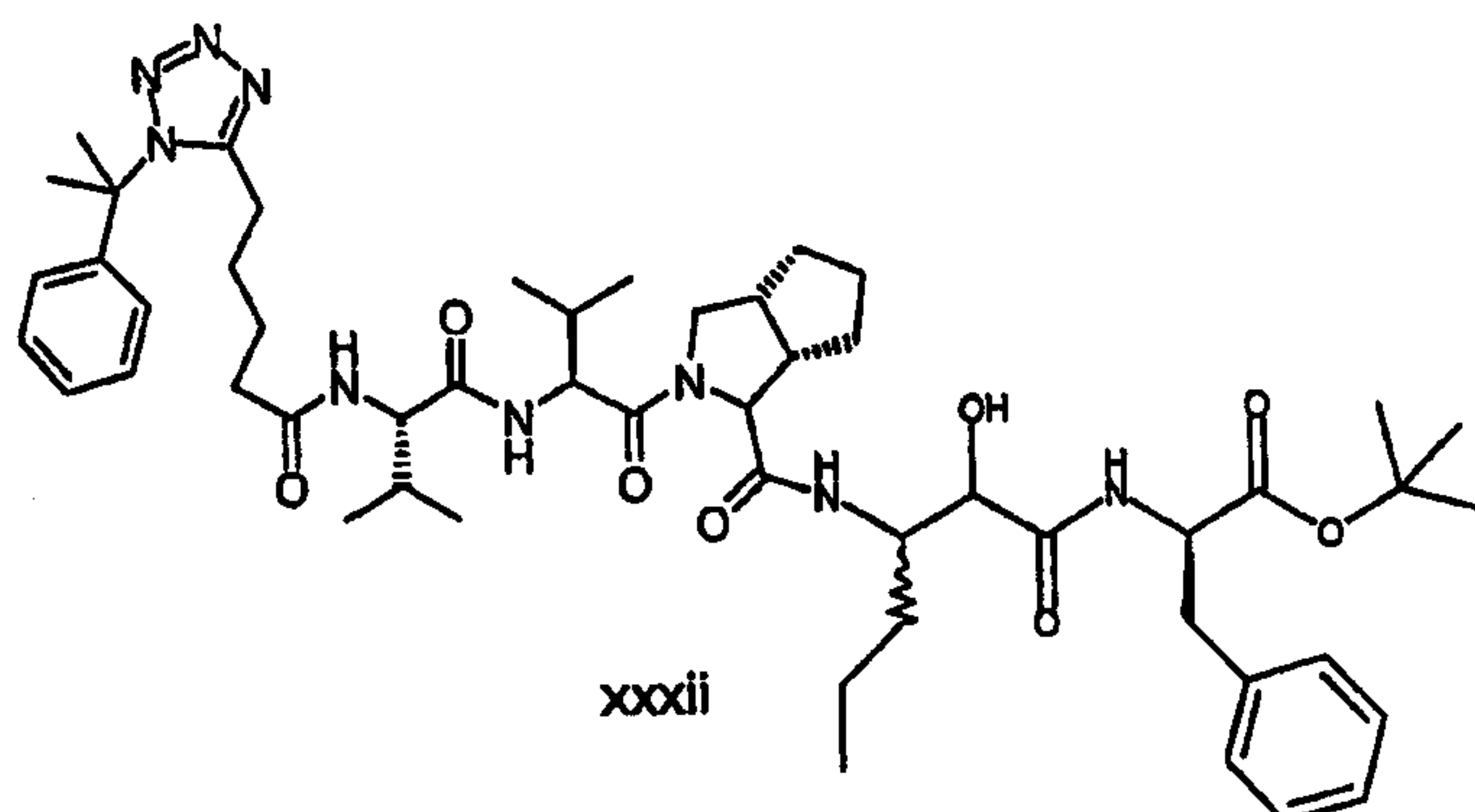
Intermediate Example 32 – Compound xxxii

Compound xxxi (300 mg, 0.48 mmol) and PyBop (300 mg, 0.58 mmol) are dissolved in
 10 mL DCM. To the solution, compound x (201 mg, 0.58 mmol) is added and then DIPEA (104
 15 μ l) is added. The mixture is stirred at about room temperature overnight. The reaction mixture is
 then diluted with EtOAc to 100 mL and washed twice with 1 N HCl, twice with NaHCO₃ and
 thrice with brine. The organic is dried and concentrated. The residue is purified by column
 chromatography (100% EtOAc) to yield 450 mg (98%) of compound xxxii,

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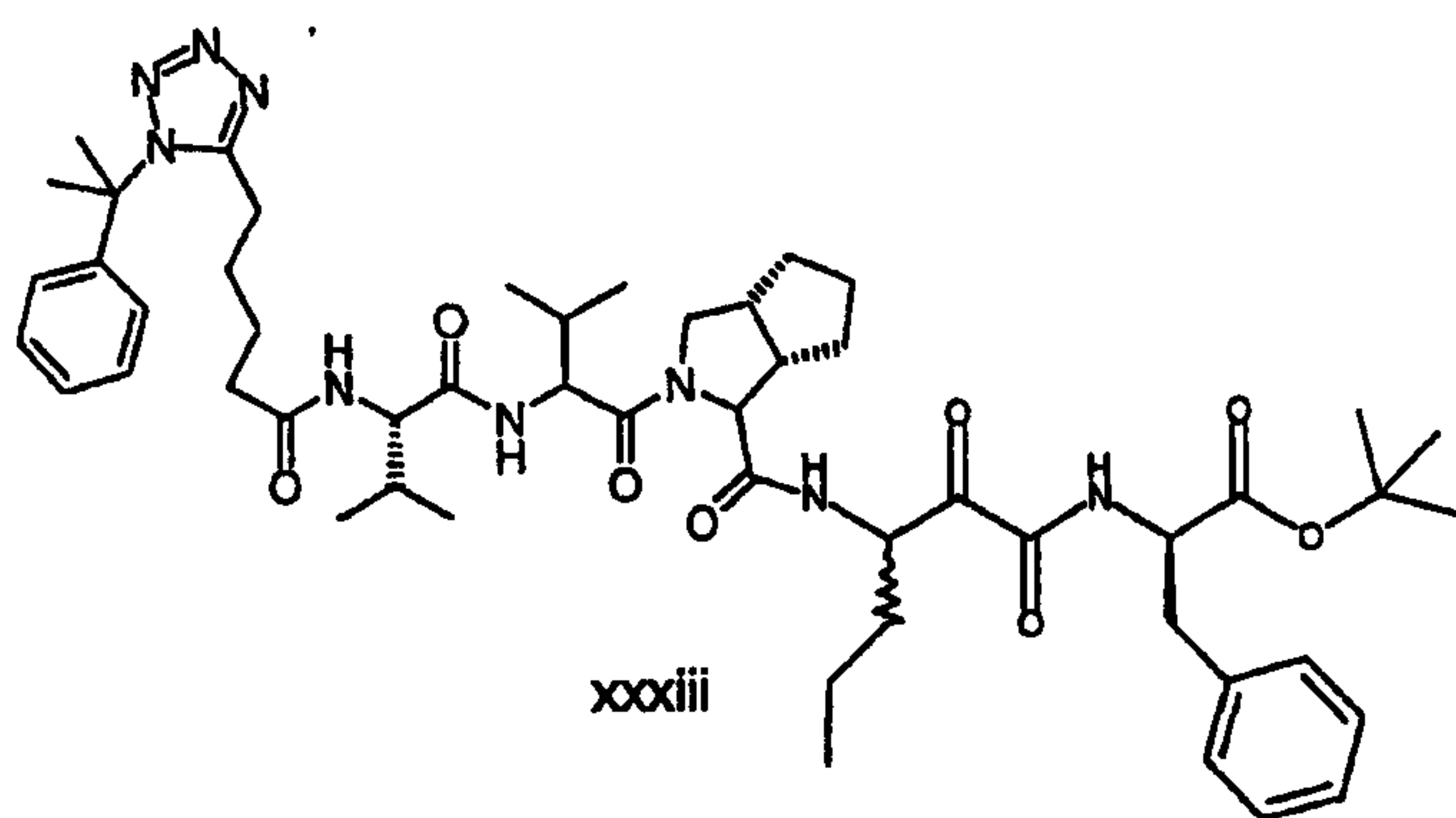
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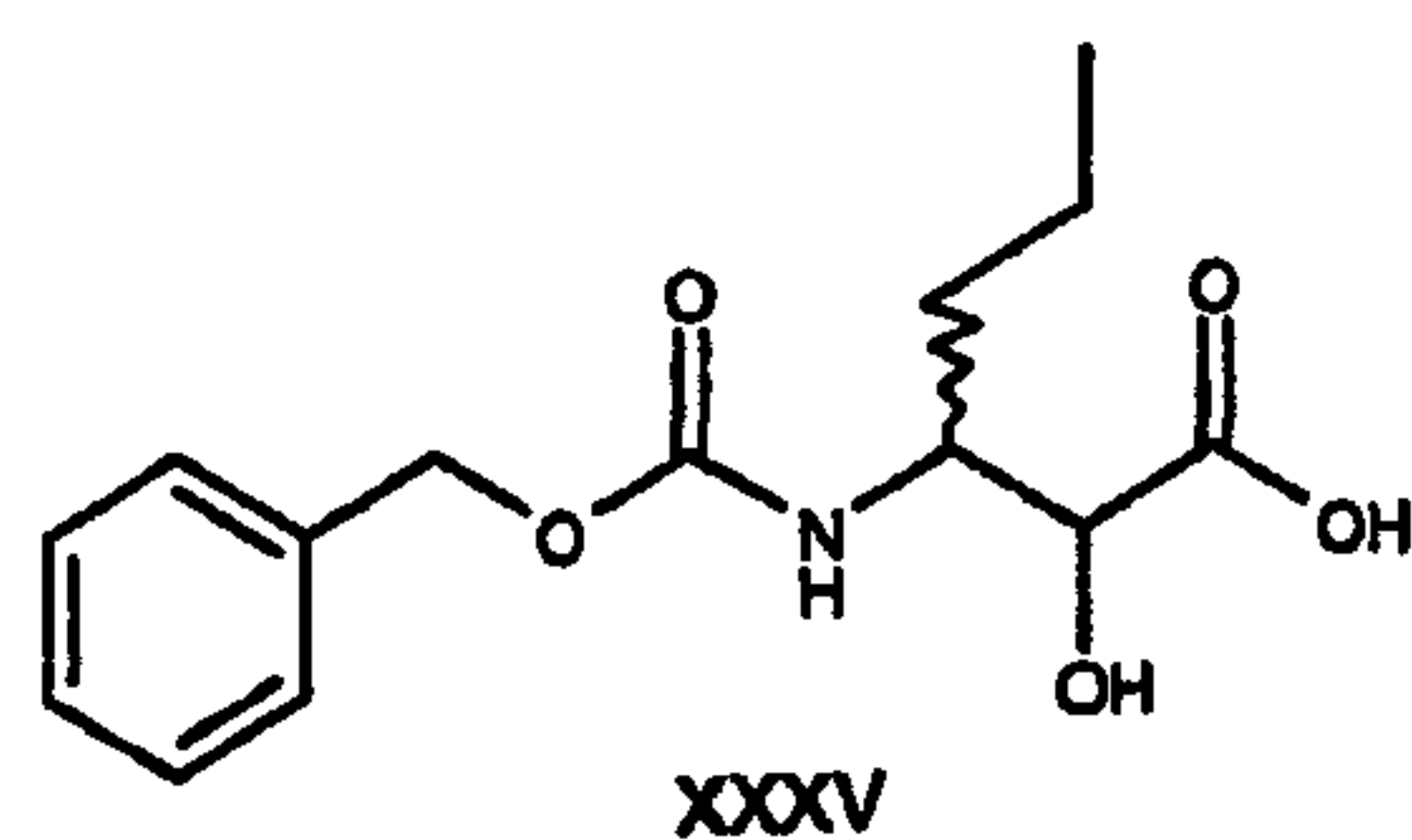
Intermediate Example 33 – Compound xxxiii

Compound xxxii 360 mg (0.38 mmol) is dissolved in 8 mL DCM and 240 mg (0.57 mmol) of DMP reagent is added. The mixture is stirred at about room temperature for three hours. The mixture is diluted with EtOAc to 50 mL and washed with brine three times. The product is purified by column chromatography (25% ethanol/EtOAc) to yield 300 mg (83%) of compound xxxiii,

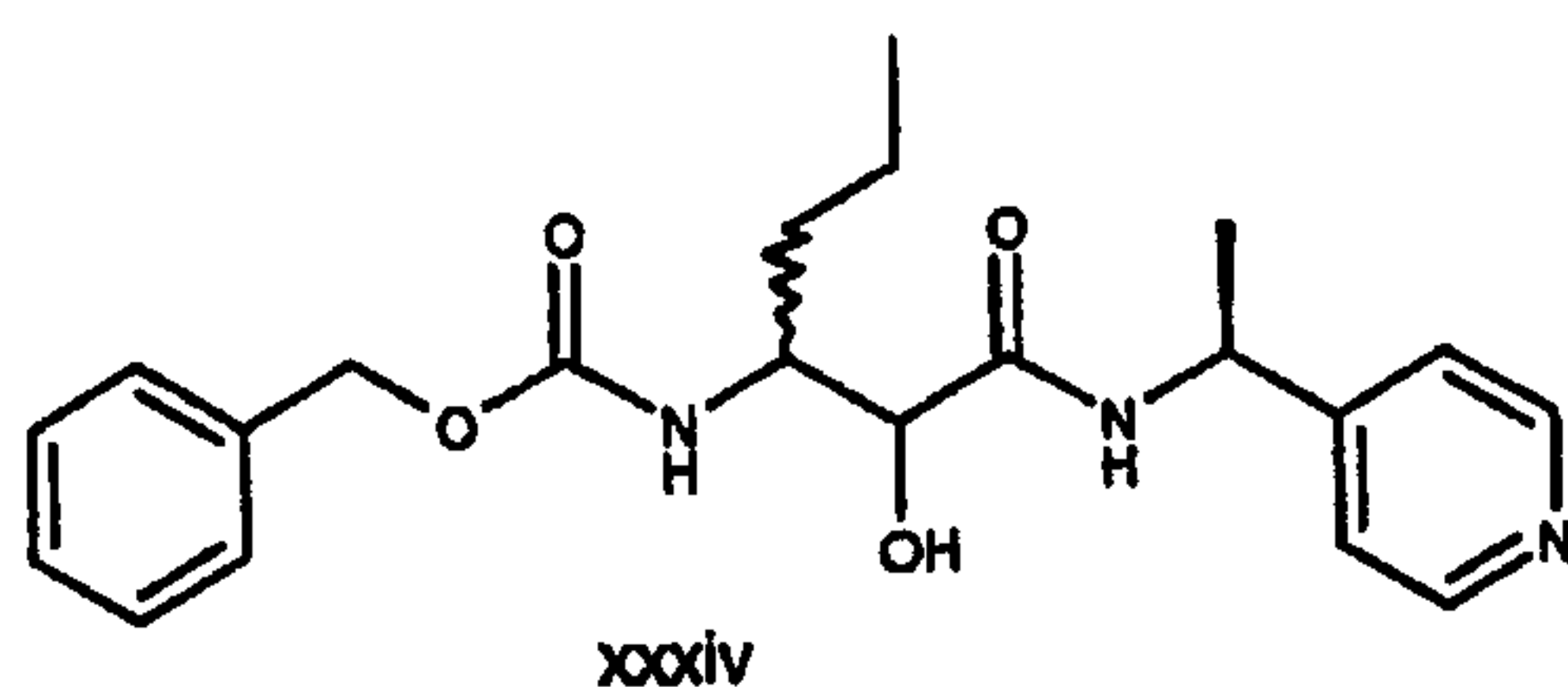


Intermediate Example 34 – Compound xxxiv

To a DCM solution (10 mL) of xxxv (790 mg, 2.80 mmol) is added PyBop (1.7 g,



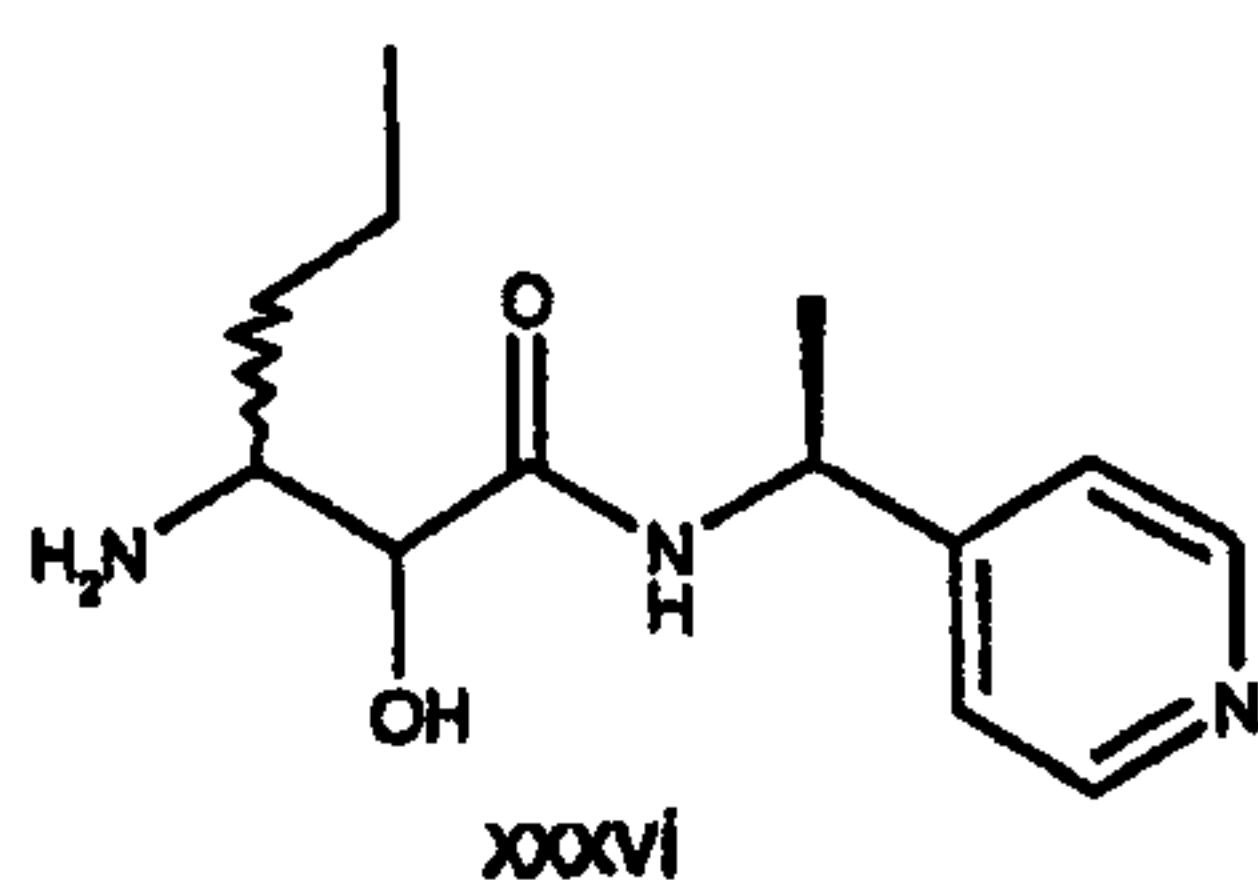
3.36 mmol) and Hobbit (450 mg, 3.36 mmol). The resulting solution is cooled to 0°C and treated with a DCM solution (3 mL) of (s)- α -(4-pyridyl)ethylamine (410 mg, 3.36 mmol). This is followed by the addition of DIPEA (0.5 mL, 3.36 mmol). The reaction is stirred overnight at about room temperature. At this point, the reaction mixture is diluted with EtOAc. The whole is washed with saturated NaHCO₃ and brine. The organic layer thus obtained is dried and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (5% EtOH/EtOAc) to provide 630 mg (58%) of compound xxxiv,



Note: (s)- α -(4-pyridyl)ethylamine is obtained from its D-tartrate salt by base wash (1 N NaOH) and subsequent EtOAc extraction. The recovery rate is 89%.

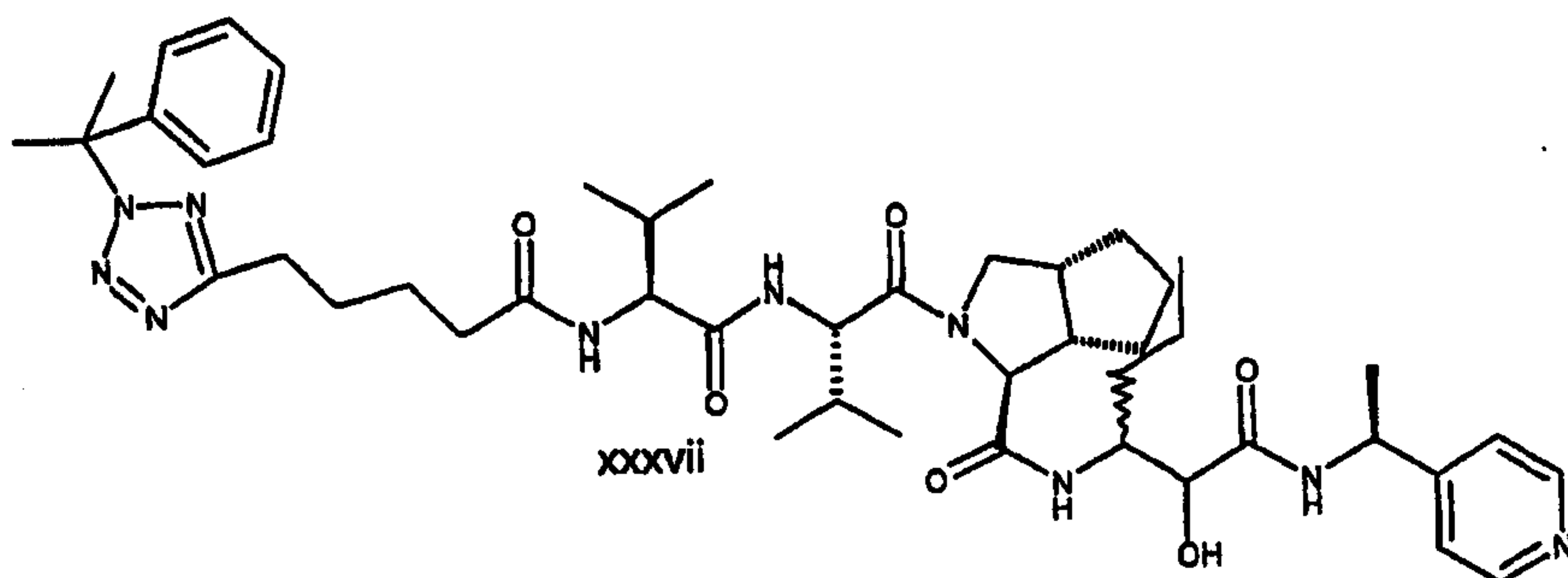
Intermediate Example 35 – Compound xxxvi

To a methanol solution (15 mL) of compound xxxiv (630 mg, 1.64 mmol) is added under N₂ Pd/C (150 mg, 10% palladium content). The reaction is stirred under H₂ overnight. The reaction mixture is filtered through a pad of Celite® 521. The filtrates are concentrated *in vacuo* to provide 420 mg (~100%) of compound xxxvi,



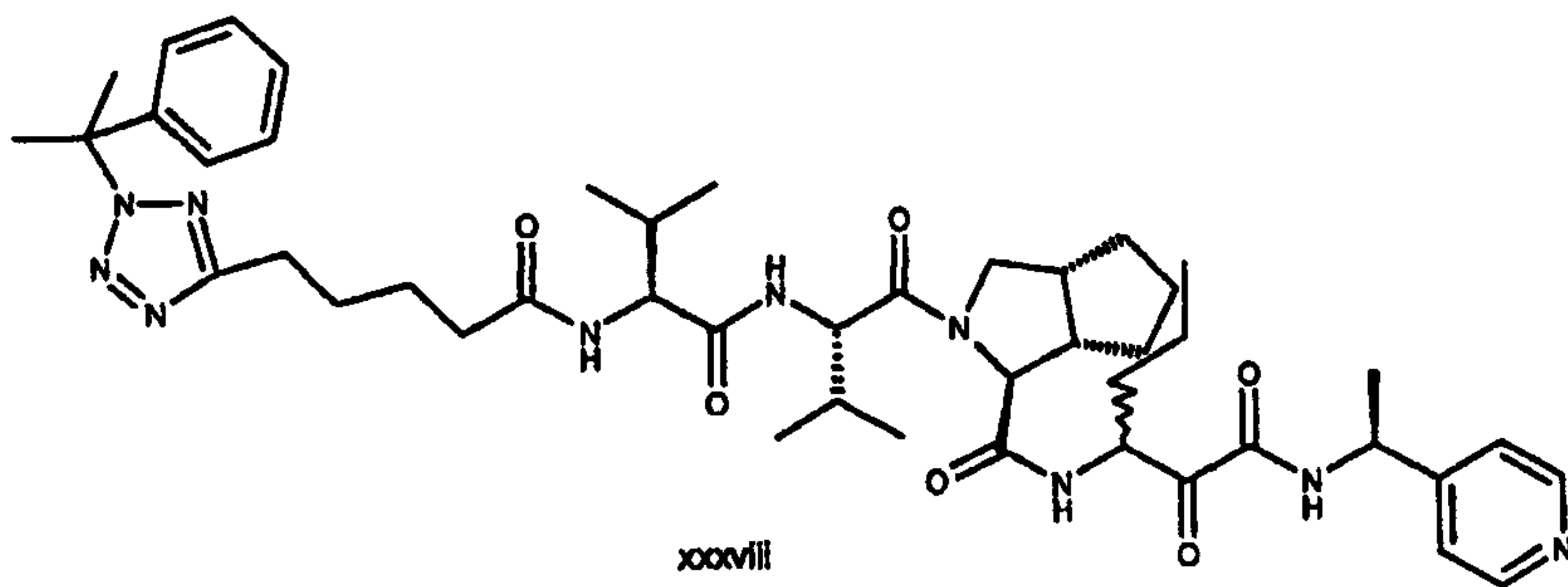
Intermediate Example 36 – Compound xxxvii

To a DCM solution (3 mL) of compound xxxi (270 mg, 0.43 mmol) is added PyBop (270 mg, 0.52 mmol). This is followed by addition of compound xxxvi (160 mg, 0.64 mmol) and DIPEA (0.09 mL, 0.52 mmol). The reaction is stirred at about room temperature overnight. At this point, the reaction is diluted with EtOAc and washed with 0.1N HCl, followed by saturated NaHCO₃ and brine. The resulting organic layer is dried and concentrated to give compound xxxvii (430 mg total mass) for next step



Intermediate Example 37 – Compound xxxviii

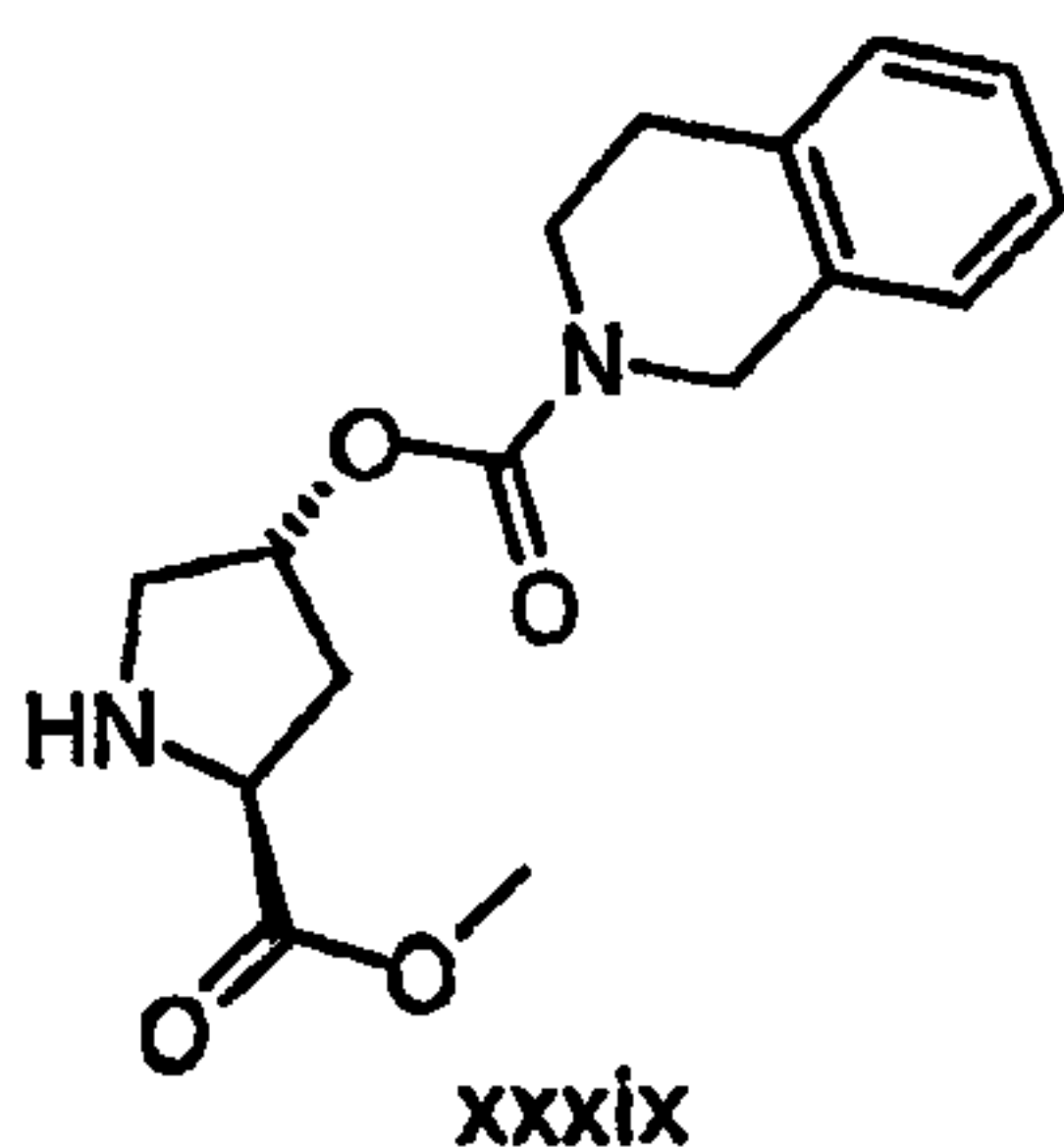
To a DCM solution (3 mL) of compound xxxvii (370 mg, 0.43 mmol) is added DMP reagent reagent (280 mg, 0.65 mmol). The reaction is stirred at about room temperature for 2 hours and then quenched with 10% Na₂SO₃. After stirring for 30 minutes, the reaction is
 5 extracted with EtOAc. The organic layer is washed with saturated NaHCO₃ and brine. The resulting organic layer is dried and concentrated *in vacuo* to give a residue that is purified by silica gel chromatography (5% EtOH/EtOAc) to provide 180 mg (49% for 2-steps) of compound xxxviii,



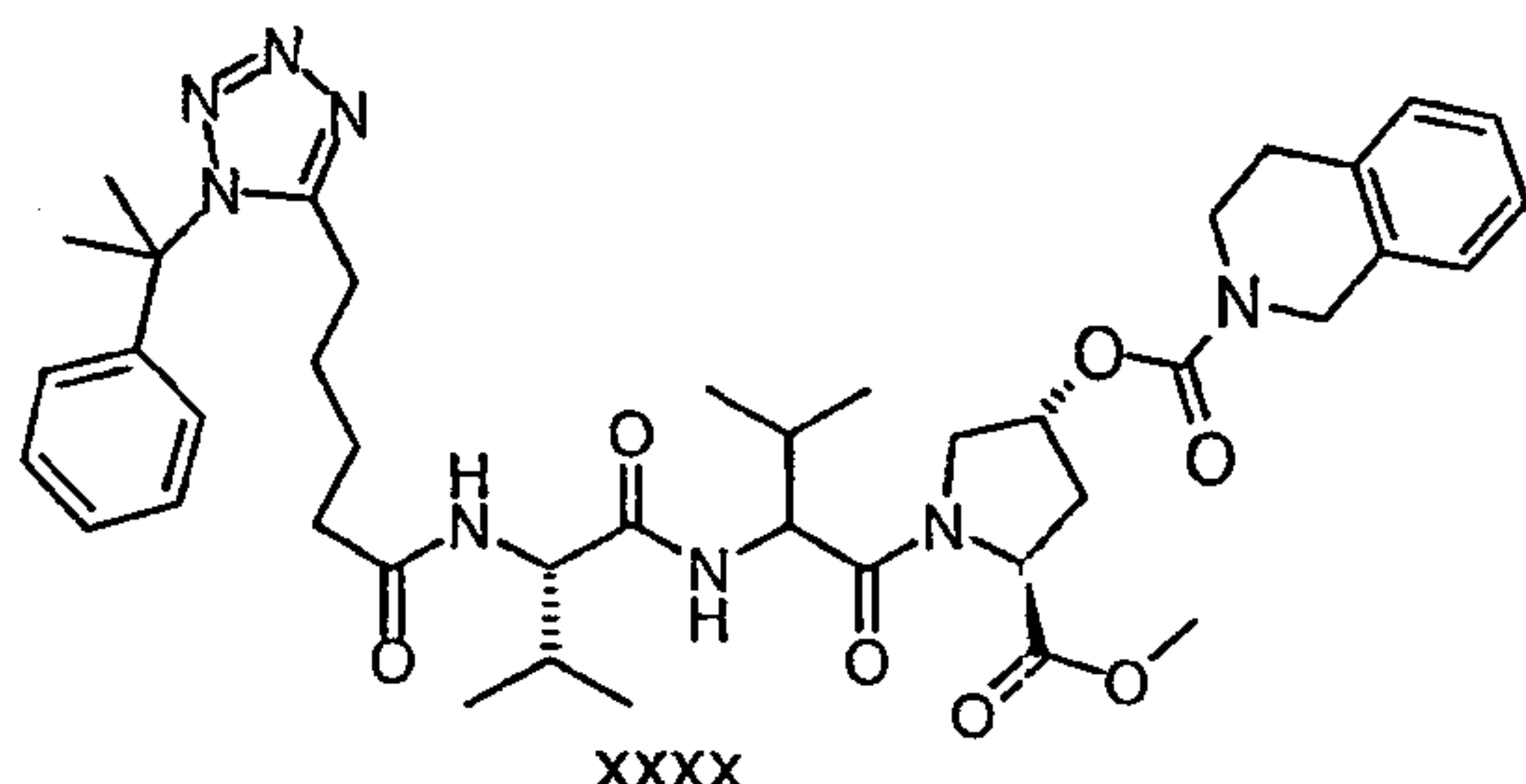
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Intermediate Example 38 – Compound xxxix

Compound xxix (2.5 g, 5 mmol) is dissolved in 40 mL of DCM, 5.1 mL of 1 M solution of DCC in THF is added to the solution. To the mixture, 1.08 g (3.53 mmol) of compound xxxix
 15 is added. The mixture is stirred at about room temperature overnight.

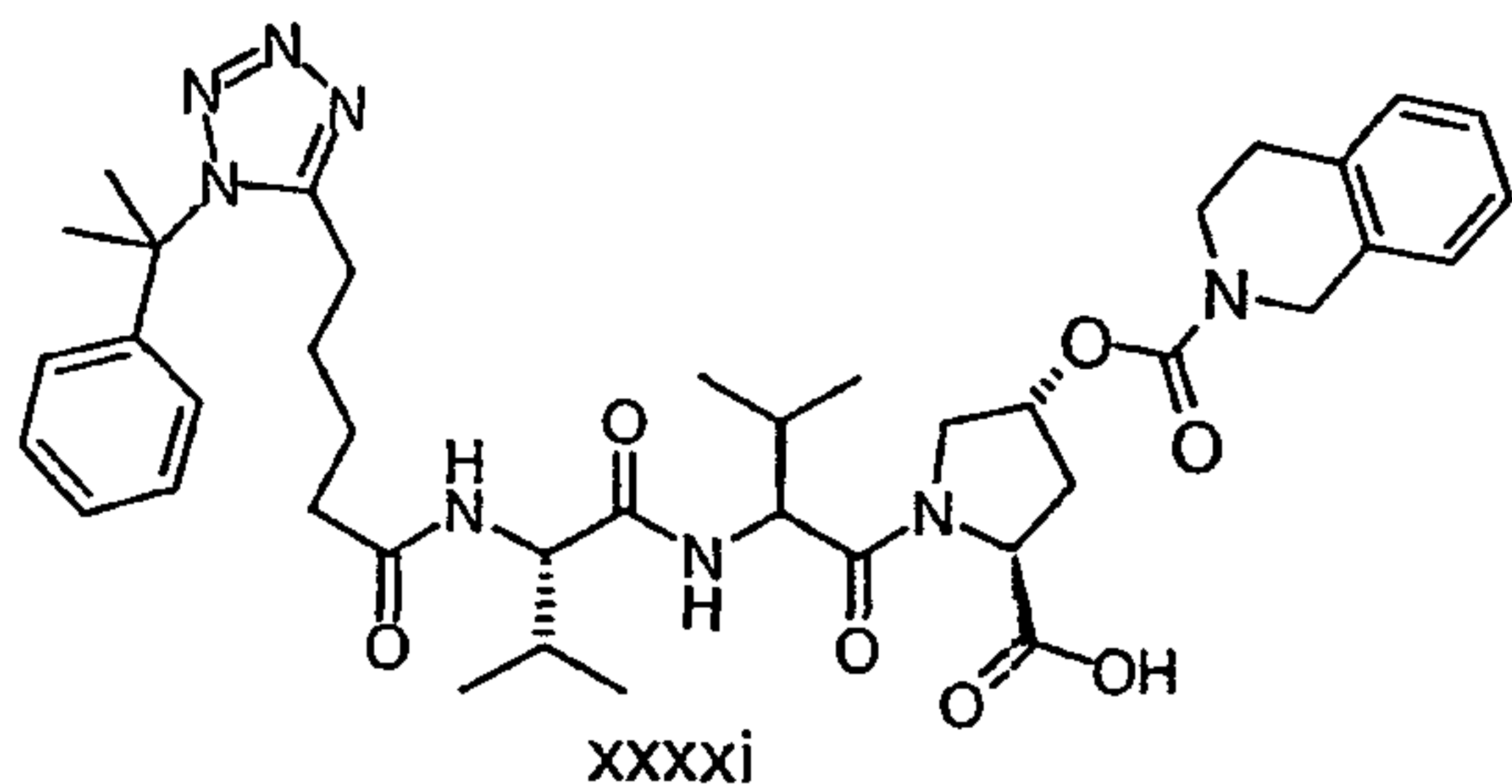


The mixture is diluted with EtOAc to 100 mL, washed sequentially with 1 N HCl, NaHCO₃ and brine, and then purified by column chromatography (80% EtOAc/hexane) to yield 2.59 g (95%) of compound xxxx,



5 Intermediate Example 39 – Compound xxxxi

Compound xxxx (2.59g, 3.35 mmol) is dissolved in 20 mL MeOH and 4 mL of 1 N aqueous NaOH is added. The mixture is stirred overnight and then rotary evaporated to leave a residue. The residue is dissolved in water and neutralized with 2 mL HCl. The neutralized solution is then extracted with EtOAc to yield 2.49 g (~100%) of compound xxxxi,



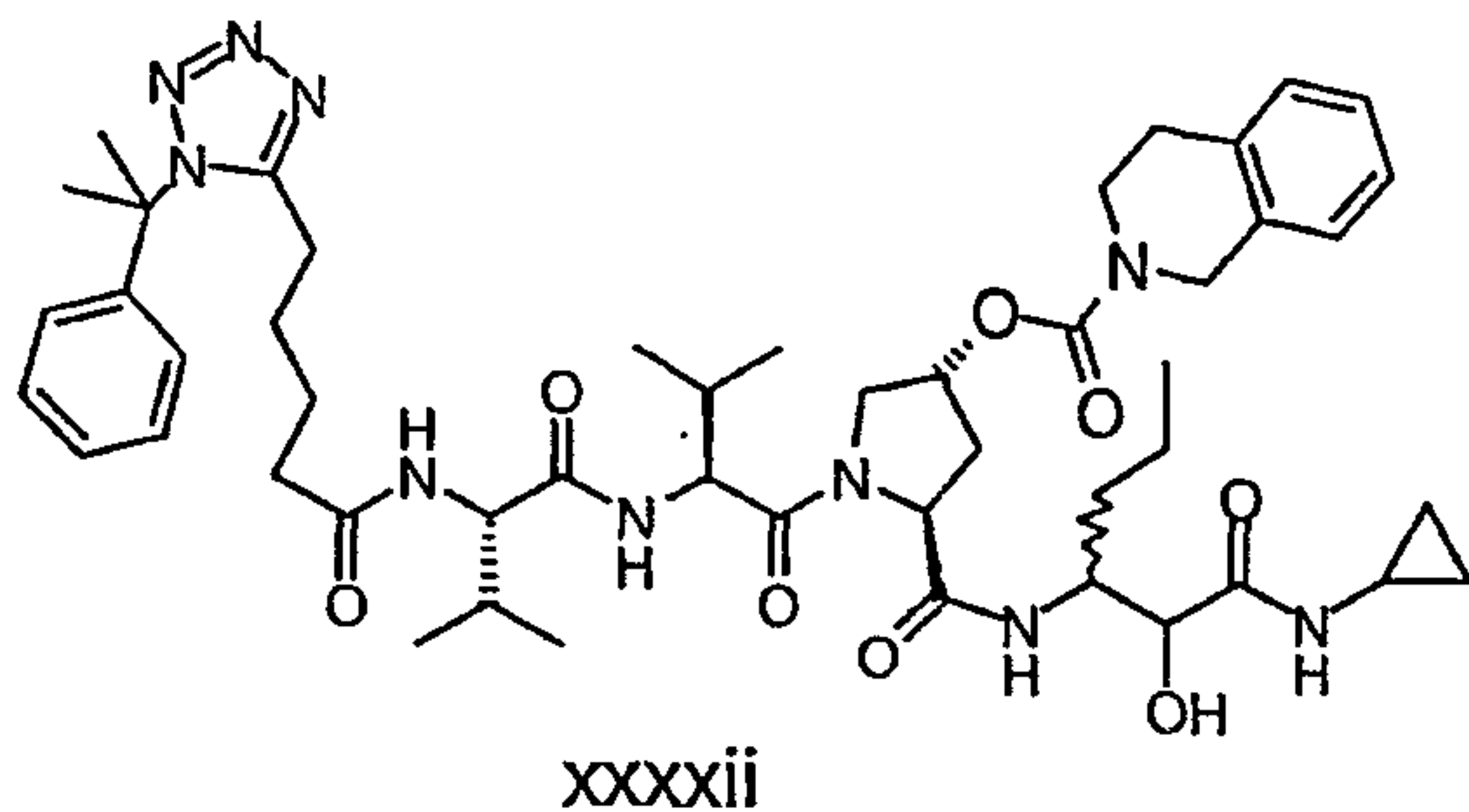
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Intermediate Example 40 – Compound xxxxii

Compound xxxxi (847 mg, 1.16 mmol) and 724 mg (1.39 mmol) of PyBop are dissolved in 10 mL DCM. To the solution, compound xiii (260 mg, 1.39 mmol) is added and then followed by the addition of DIPEA (209 µl). The mixture is stirred at about room temperature overnight.

15 The reaction mixture is then diluted with EtOAc to 100 mL and washed twice with 1 N HCl, twice with NaHCO₃ and thrice with brine. The organic is dried and concentrated. The residue is purified by column chromatography (5% ethanol/EtOAc) to yield 930 mg (86%) of compound xxxxii,

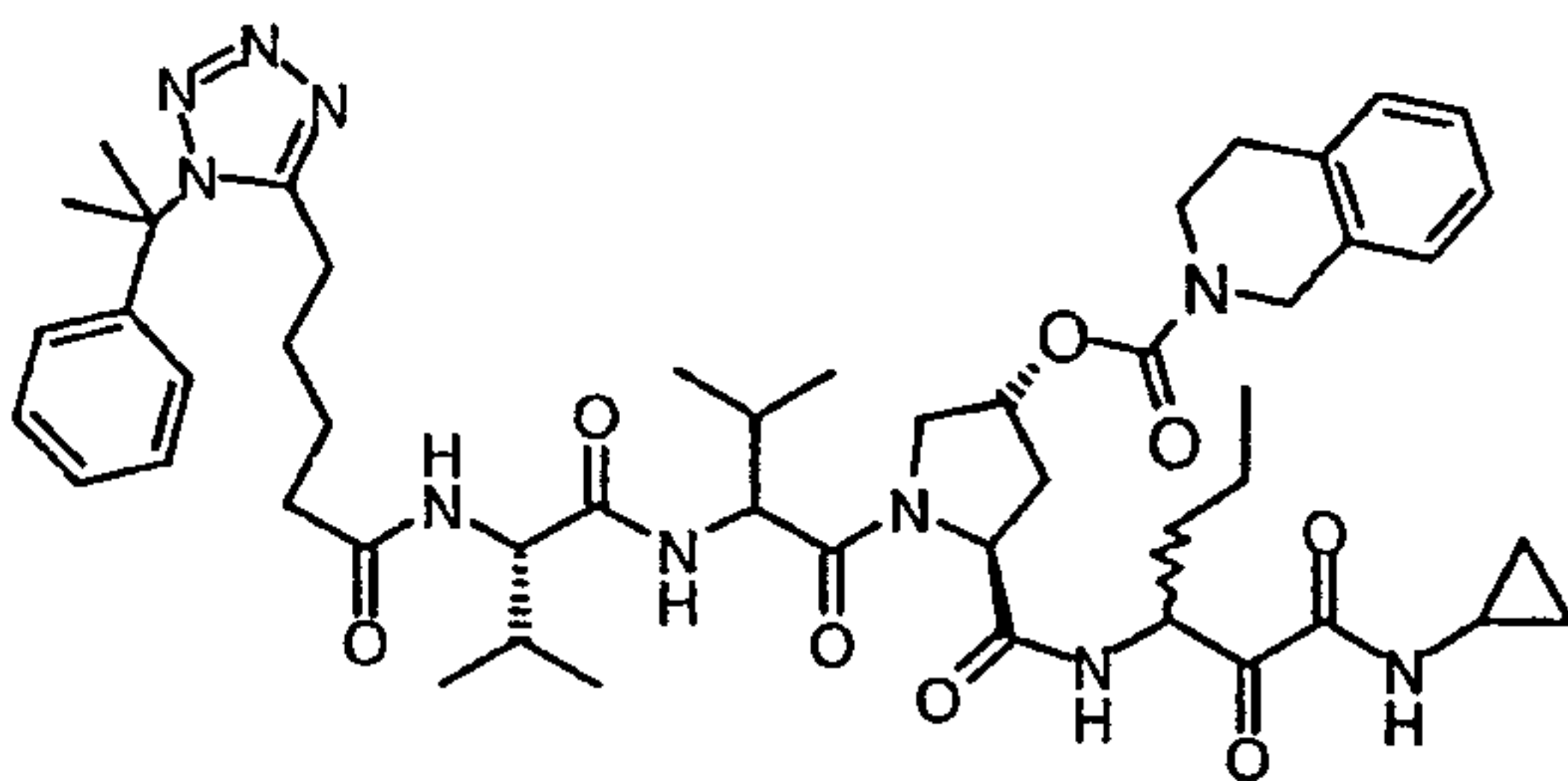
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xxxxii

Intermediate Example 41 – Compound xxxxi

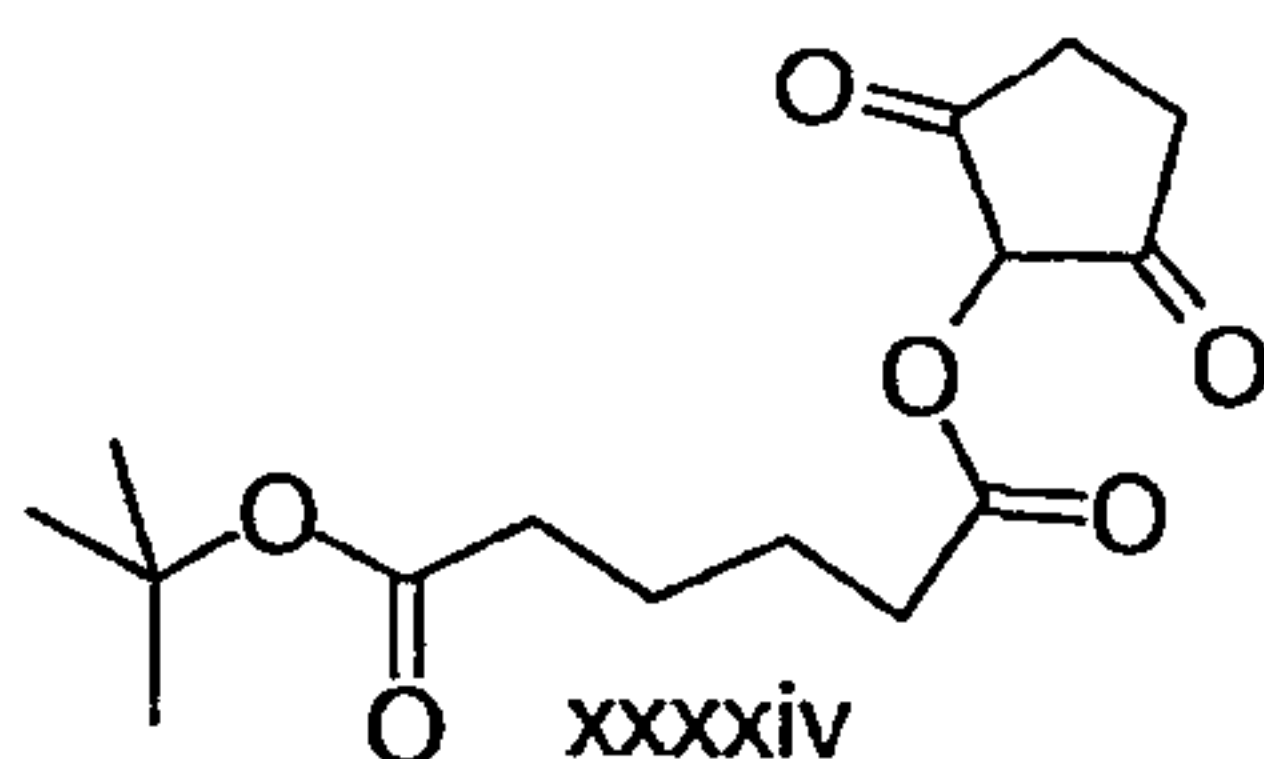
Compound xxxxi (350 mg, 0.38 mmol) is dissolved in 10 mL DCM and 242 mg (0.57 mmol) of DMP reagent reagent is added. The mixture is stirred at about room temperature for three hours. The mixture is diluted with EtOAc to 50 mL and washed thrice with brine. The product is purified by column chromatography (100% EtOAc) to yield 180 mg (51%) of compound xxxxi,



xxxxiii

Intermediate Example 42 – Compound xxxv

H-Val-Val-OH (5 g, 23 mmol) is suspended in 100 mL DMF, compound xxxiv



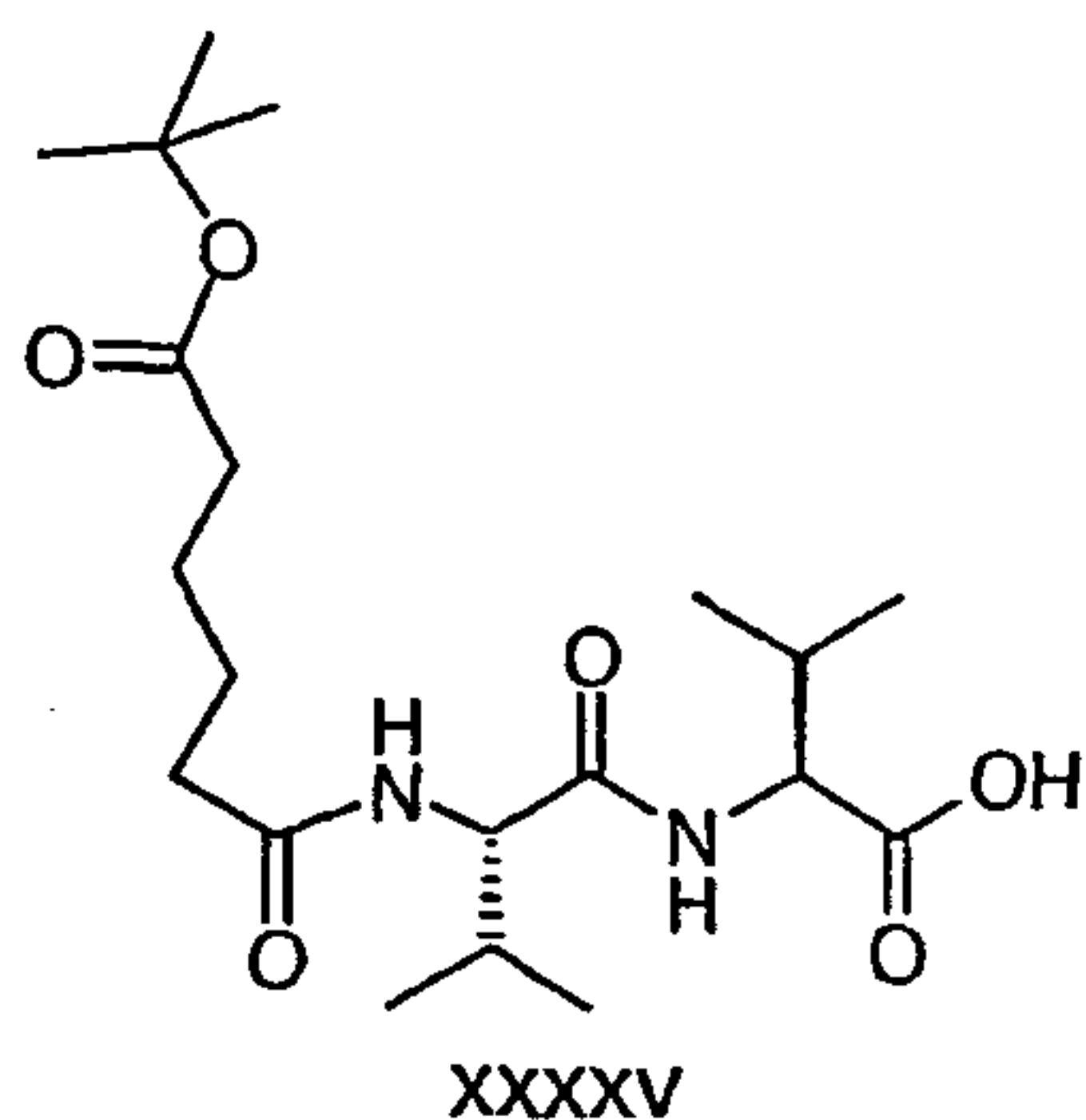
xxxxiv

(8.3 g, 27.6 mmol) is added, and then 6.2 mL (35.5 mmol) of DIPEA is added. The mixture is stirred at 40 °C for two days. The solvent is removed under high vacuum and the residue is dissolved in 100 mL EtOAc and washed thrice with 1 N HCl and twice with brine. 9.14 g (99%) of compound xxxv is afforded.

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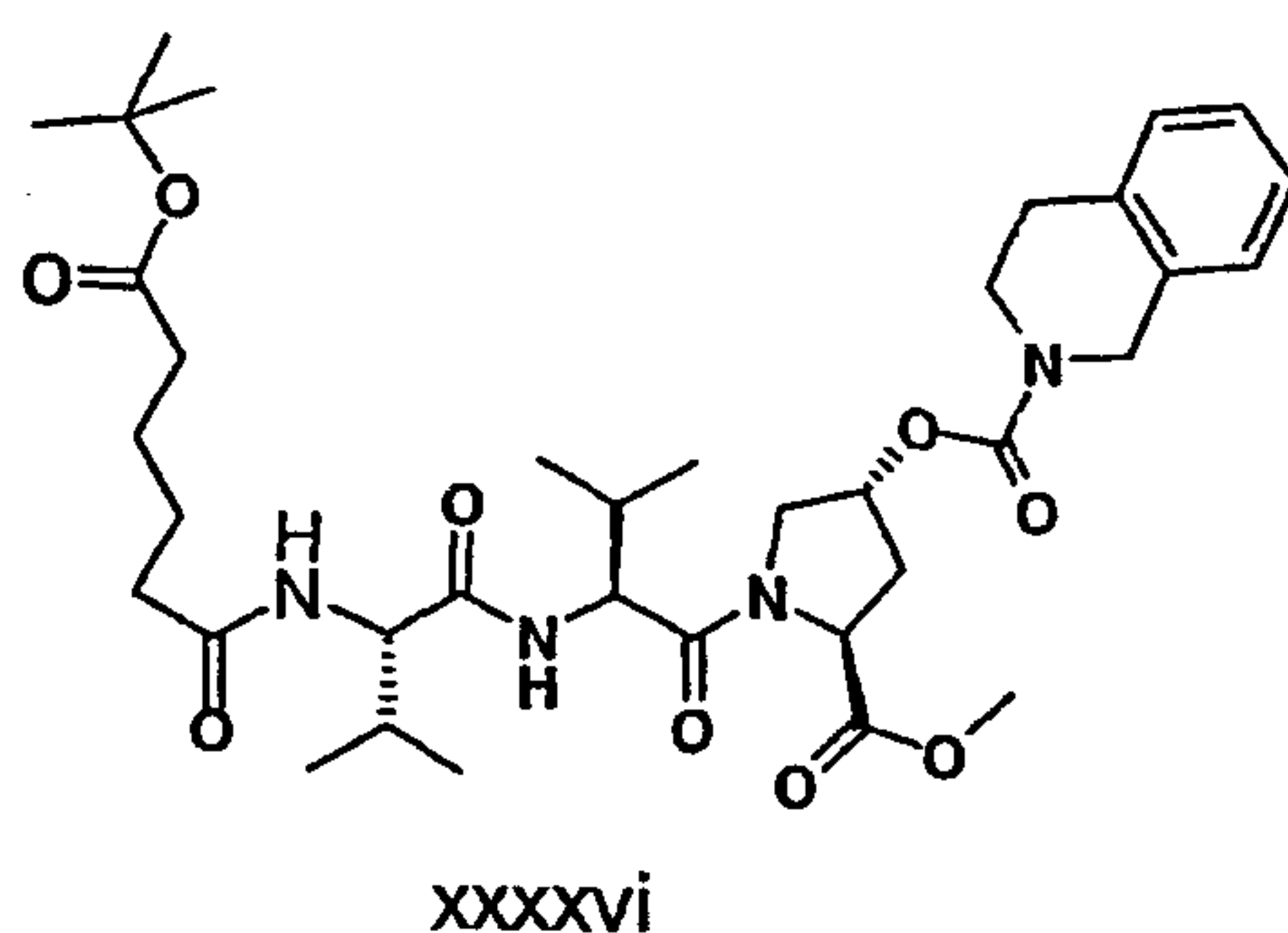
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Intermediate Example 43 – Compound xxxxvi

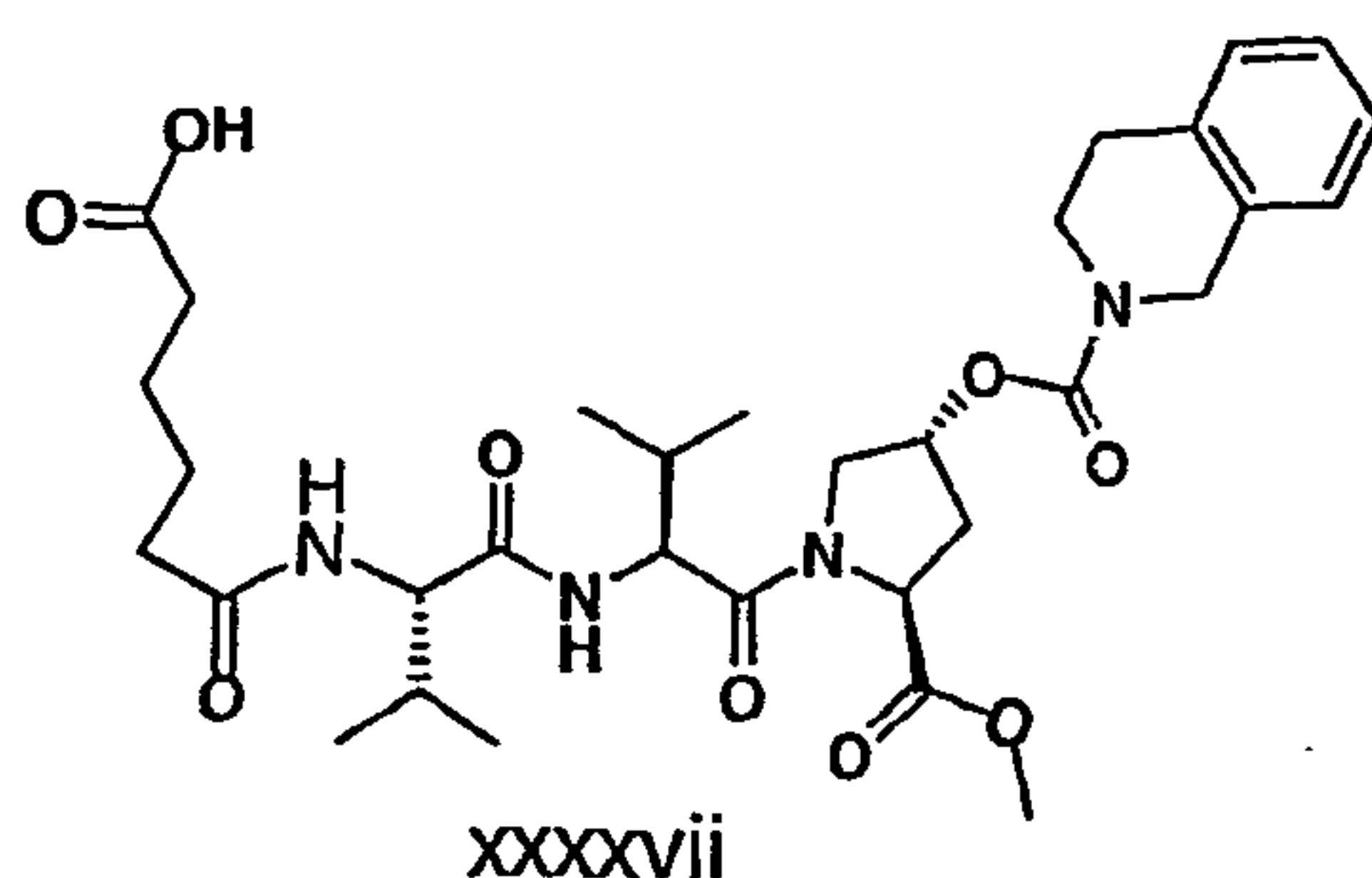
Compound xxxxv (2.8 g, 7 mmol) and 954 mg (7 mmol) of HOAt is dissolved in 100 mL DCM. 7 mL of 1 M DCC/DCM is added. To the reaction mixture, compound xxxix (2.15 g) is added and the reaction mixture is stirred at about room temperature for overnight. The mixture is concentrated to dryness and the residue is dissolved in EtOAc and purified by column chromatography (100% EtOAc) to yield 4.57 g (95%) of compound xxxxvi,



10 Intermediate Example 44 – Compound xxxxvii

Compound xxxxvi (4.57 g, 6.65 mmol) is dissolved in 10 mL TFA and 10 mL DCM. The mixture is stirred at about room temperature for 4 hours. The solvent is removed by vacuum and the residue is dissolved in 50:50 acetonitrile/water and lyophilized to yield as a powder compound xxxxvii,

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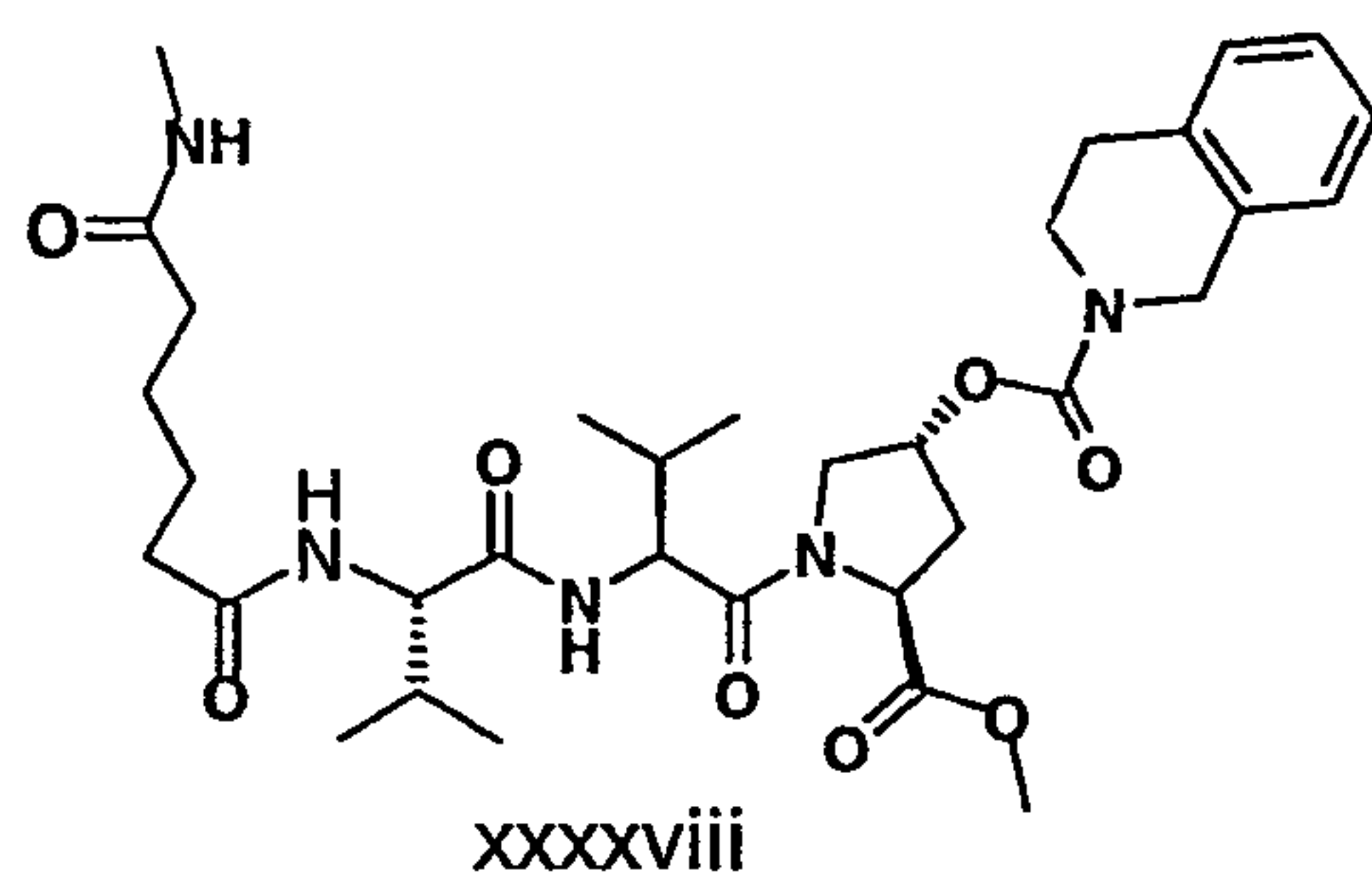
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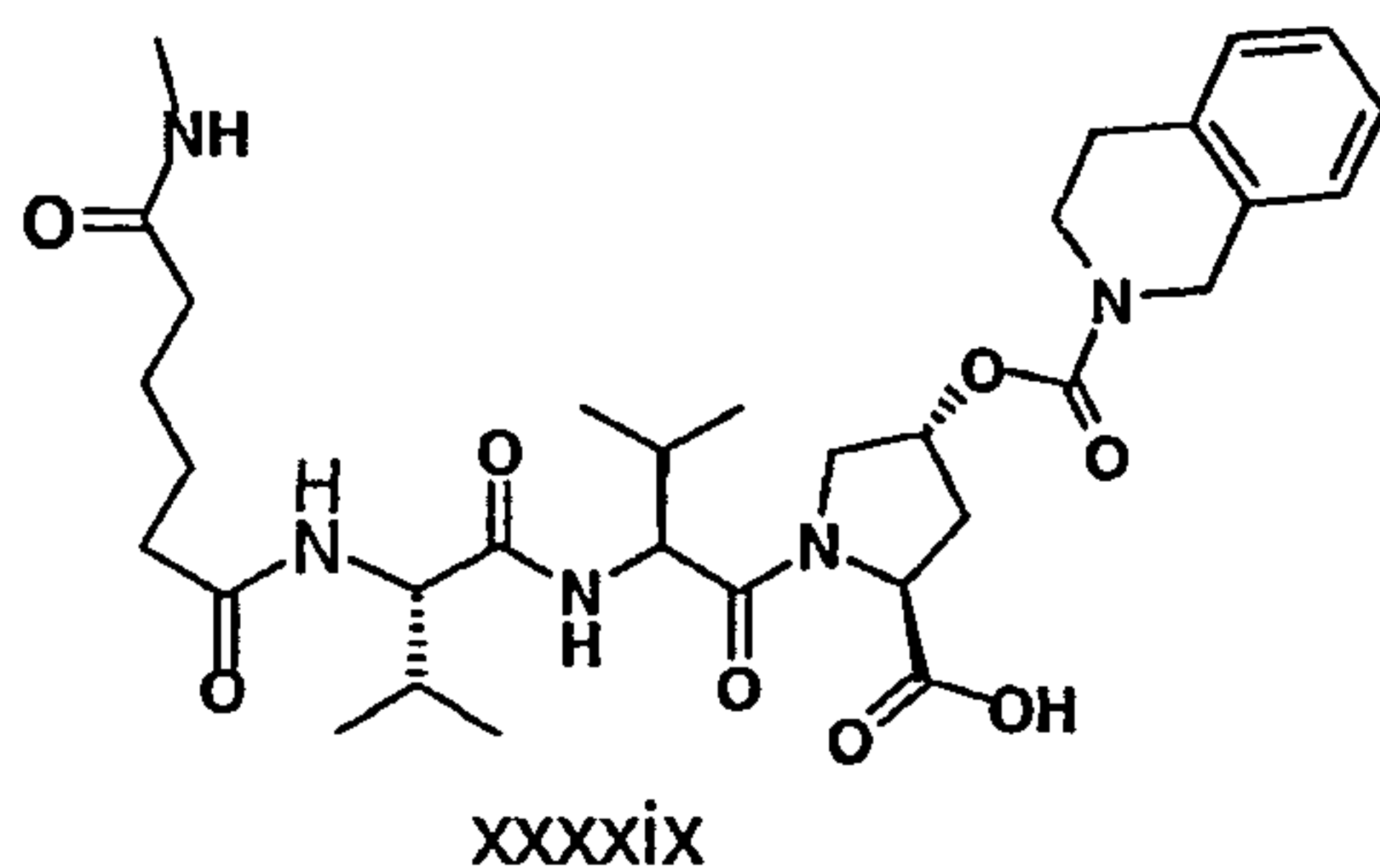
Intermediate Example 45 – Compound xxxviii

Compound xxxvii (1 g, 1.59 mmol) and 990 mg (2.28 mmol) of PyBop is dissolved in 20 mL DCM and 1.6 mL of 1 M methylamine in THF is added. The mixture is stirred at about room temperature for 4 hours. The reaction mixture is diluted to 100 mL with EtOAc and washed
 5 with 1 N HCl, NaHCO₃ and brine. The residue is purified by flash column chromatography (10% EtOH/EtOAc) to yield 1 g (98%) of compound xxxviii,



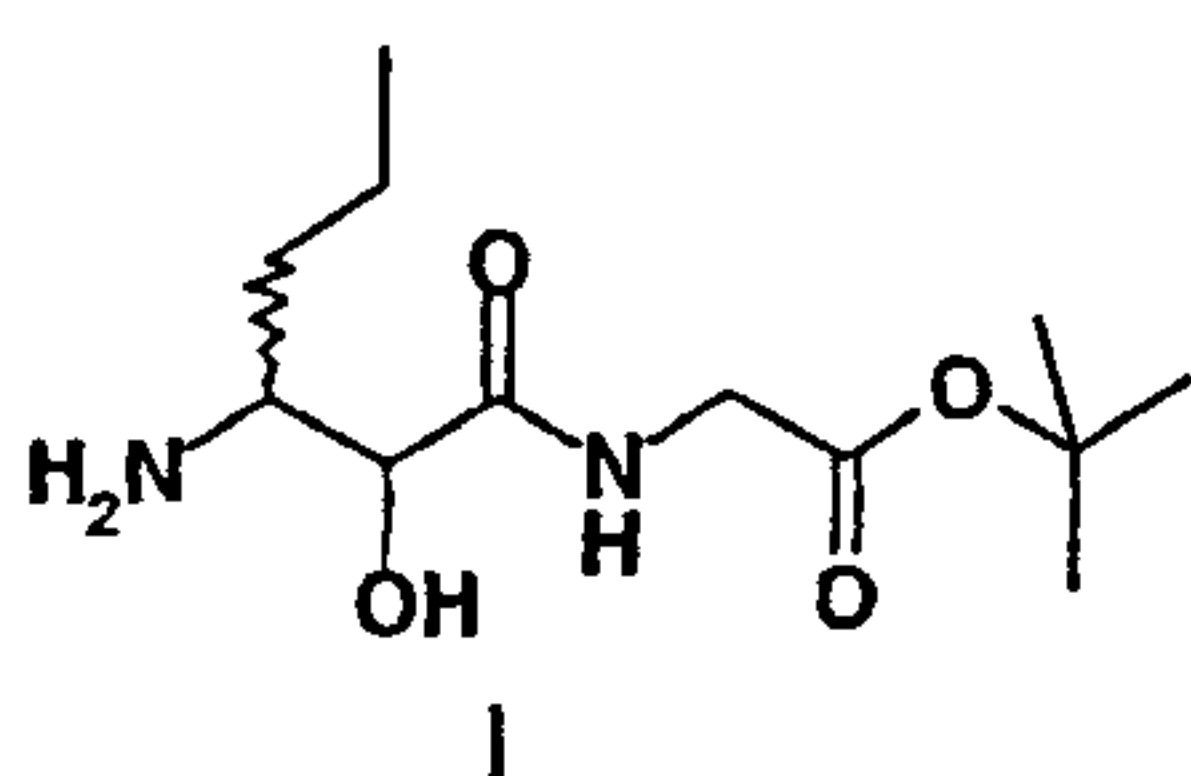
Intermediate Example 46 – Compound xxxix

Compound xxxviii (1 g, 1.55 mmol) is dissolved in 10 mL of MeOH and 2 mL 1 N NaOH is added. The mixture is stirred at about room temperature for overnight. The solvent is removed by evaporation. The residue is dissolved in water, neutralized and extracted with EtOAc to yield 960 mg (98%) of compound xxxix,



Intermediate Example 47 – Compound I

Compound xxxix (315 mg, 0.5 mmol) and 312 mg (0.6 mmol) of PyBop are dissolved in 10 mL DCM. Compound I (56 mg, 0.6 mmol) and 108 µl of DIPEA is added. The mixture



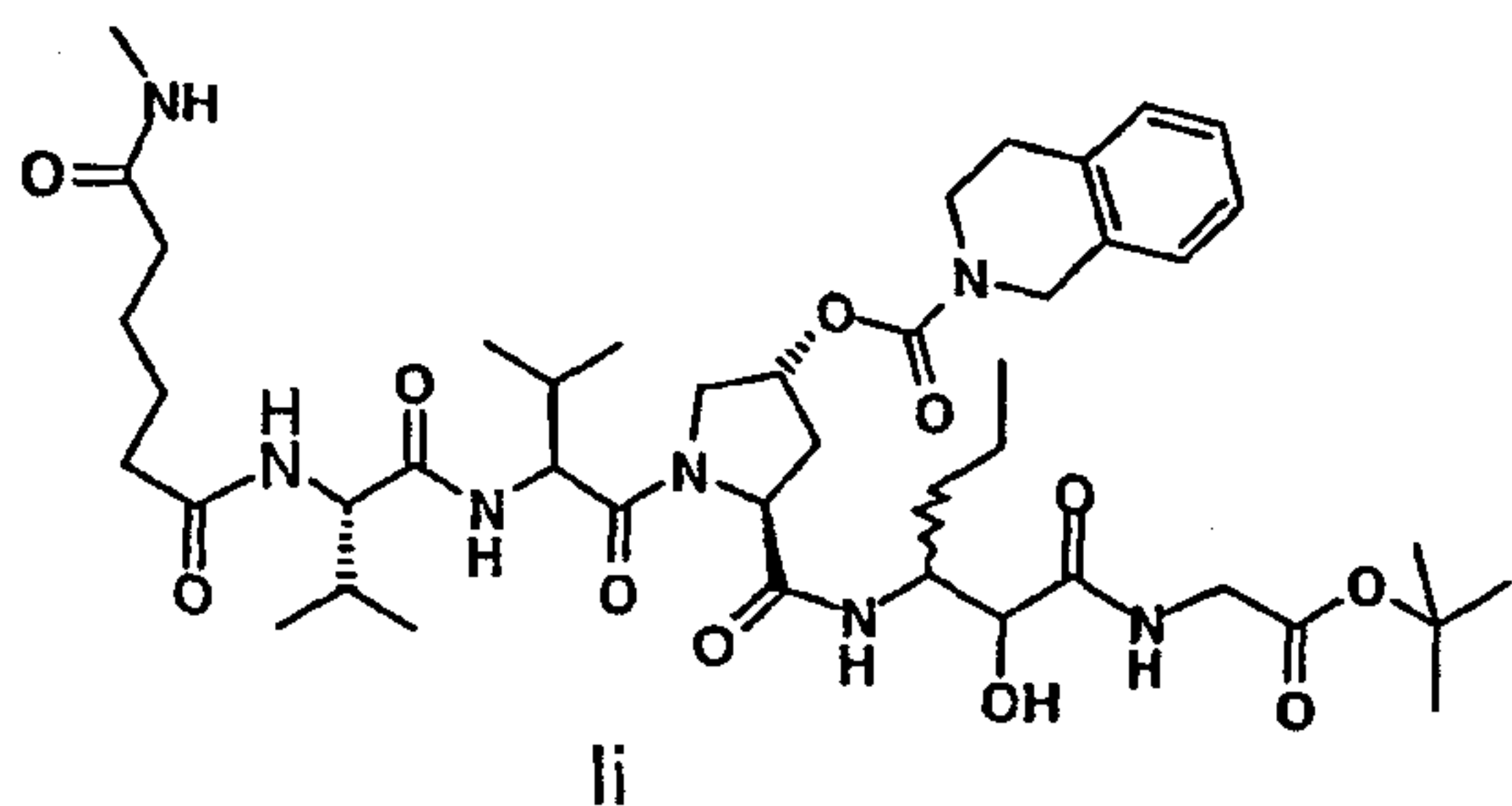
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is stirred at about room temperature overnight, and is diluted to 100 mL with EtOAc and washed with 1 N HCl, NaHCO₃ and brine. Purified by column chromatography (15% EtOH/EtOAc) to yield 400 mg (92%) of compound li,

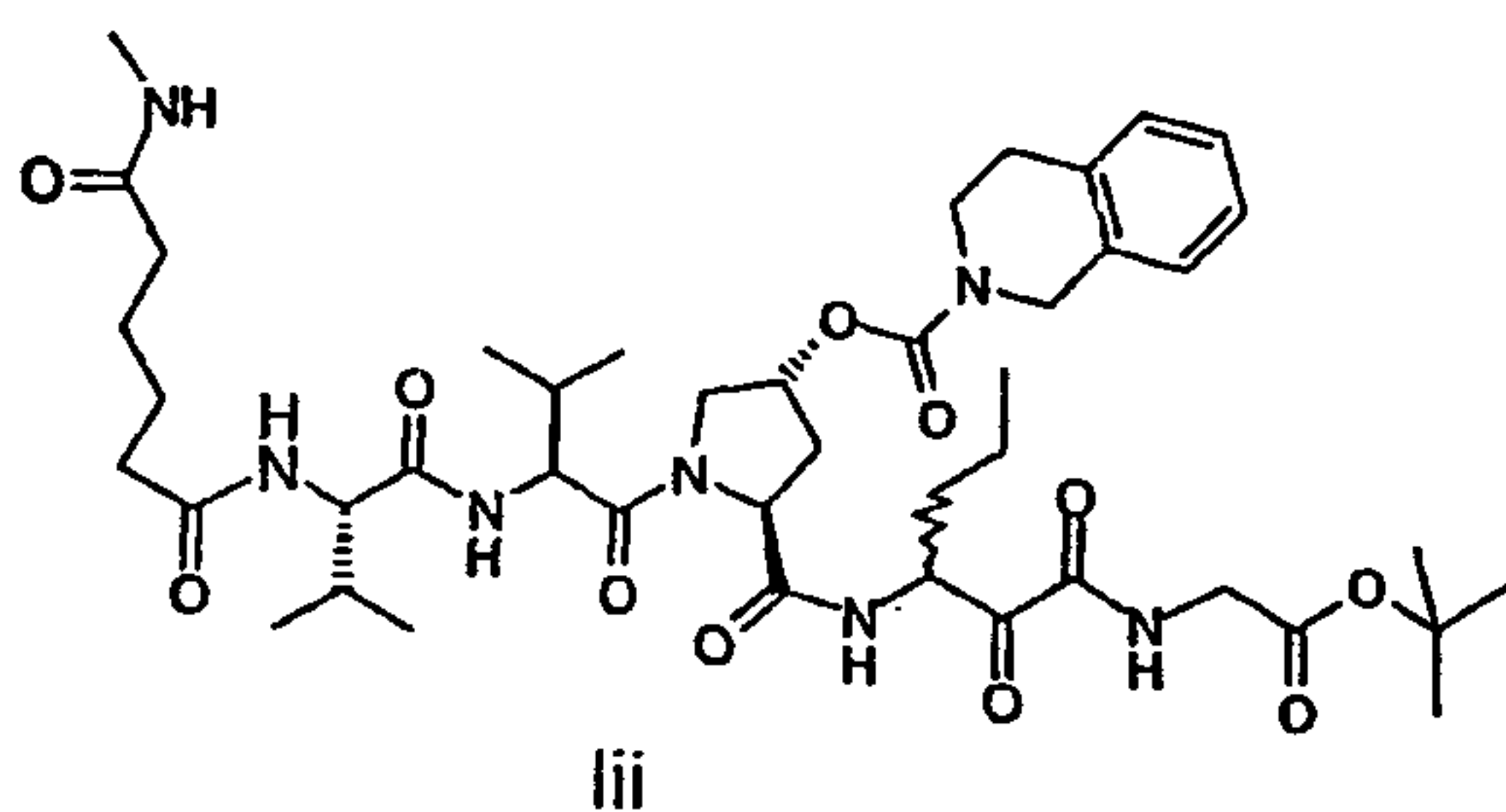


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Intermediate Example 48 – Compound lii

Compound li (400 mg, 0.46 mmol) is dissolved in 10 mL of DCM and 292 mg (0.69 mmol) DMP reagent reagent is added. The mixture is stirred at about room temperature for 3 hours. The solvent is removed by evaporation and product is purified by RP-HPLC to yield 130 mg (32%) of compound lii,

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Intermediate Example 49 – Compound liii

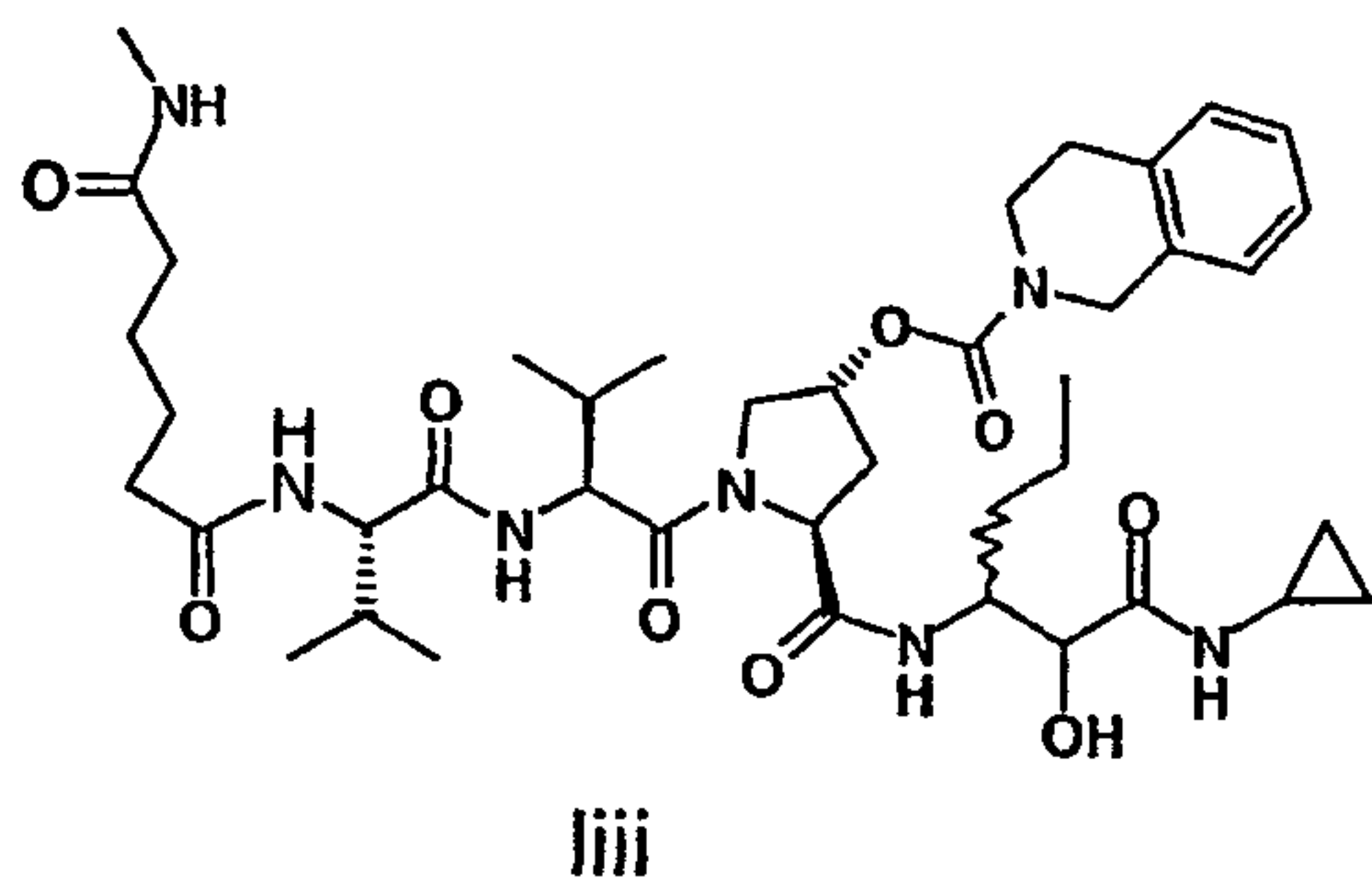
Compound xxxix (210 mg, 0.33 mmol) and 208 mg (0.4 mmol) of PyBop are dissolved in 10 mL DCM. Compound xiii (154 mg, 0.83 mmol) is added to the solution followed by the addition of DIPEA (72 μ l, 0.4 mmol). The mixture is stirred at about room temperature overnight. The reaction mixture is diluted to 100 mL with EtOAc, washed with 1 N HCl, NaHCO₃ and brine, and then purified by flash column chromatography (10% EtOH/EtOAc) to yield 250 mg (95%) of compound liii,

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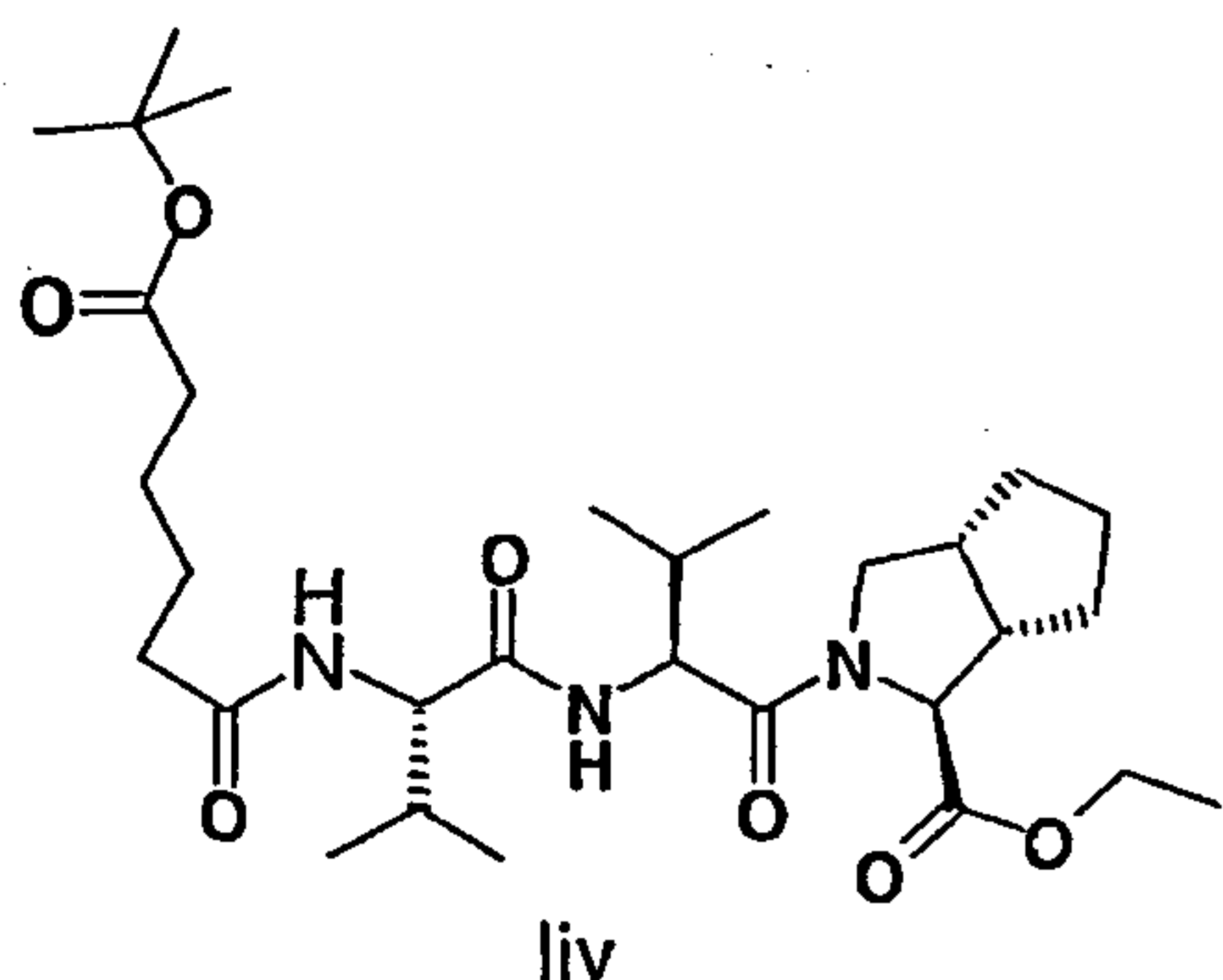
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Intermediate Example 50 – Compound liv

Compound xxxv (755 mg, 1.88 mmol) and 255 mg (1.88 mmol) of HOAt are dissolved in 20 mL DCM. 1.88 mL of 1 M DCC/DCM is added. To the reaction mixture, compound v (288 mg) is added and the reaction mixture is stirred at about room temperature for 2 hours. The mixture is concentrated to dryness and the residue is dissolved in EtOAc and purified by column chromatography (80% EtOAc/Hexanes) to yield 800 mg (90%) of compound liv,



10 Intermediate Example 51 – Compound lv

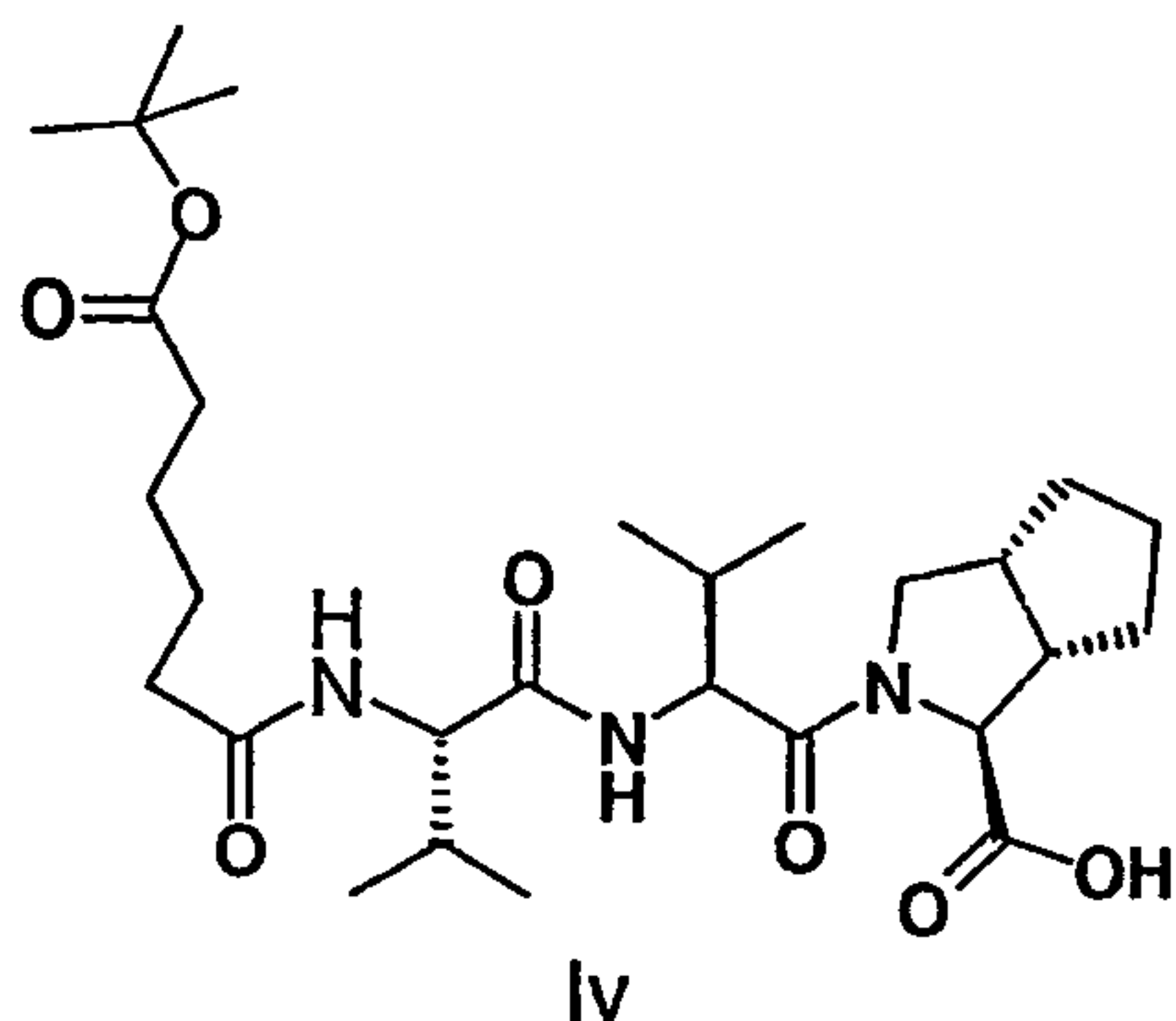
Compound liv (800 mg, 1.41 mmol) is dissolved in 10 mL MeOH and 2 mL NaOH is added. The mixture is stirred at about room temperature overnight. The solvent is removed by vacuum and the residue is dissolved in water and neutralized with 2 mL 1 N HCl. The product is extracted with EtOAc. Evaporation of the extraction solvent afforded 760 mg (~100%) lv,

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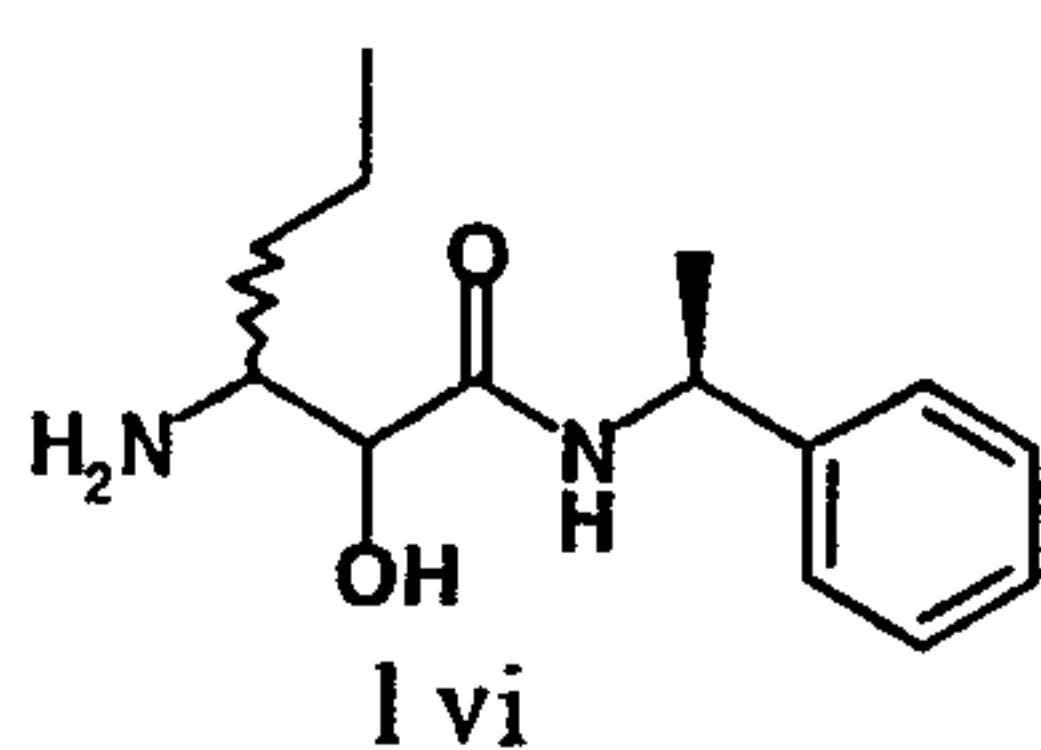
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Intermediate Example 52 – Compound lvii

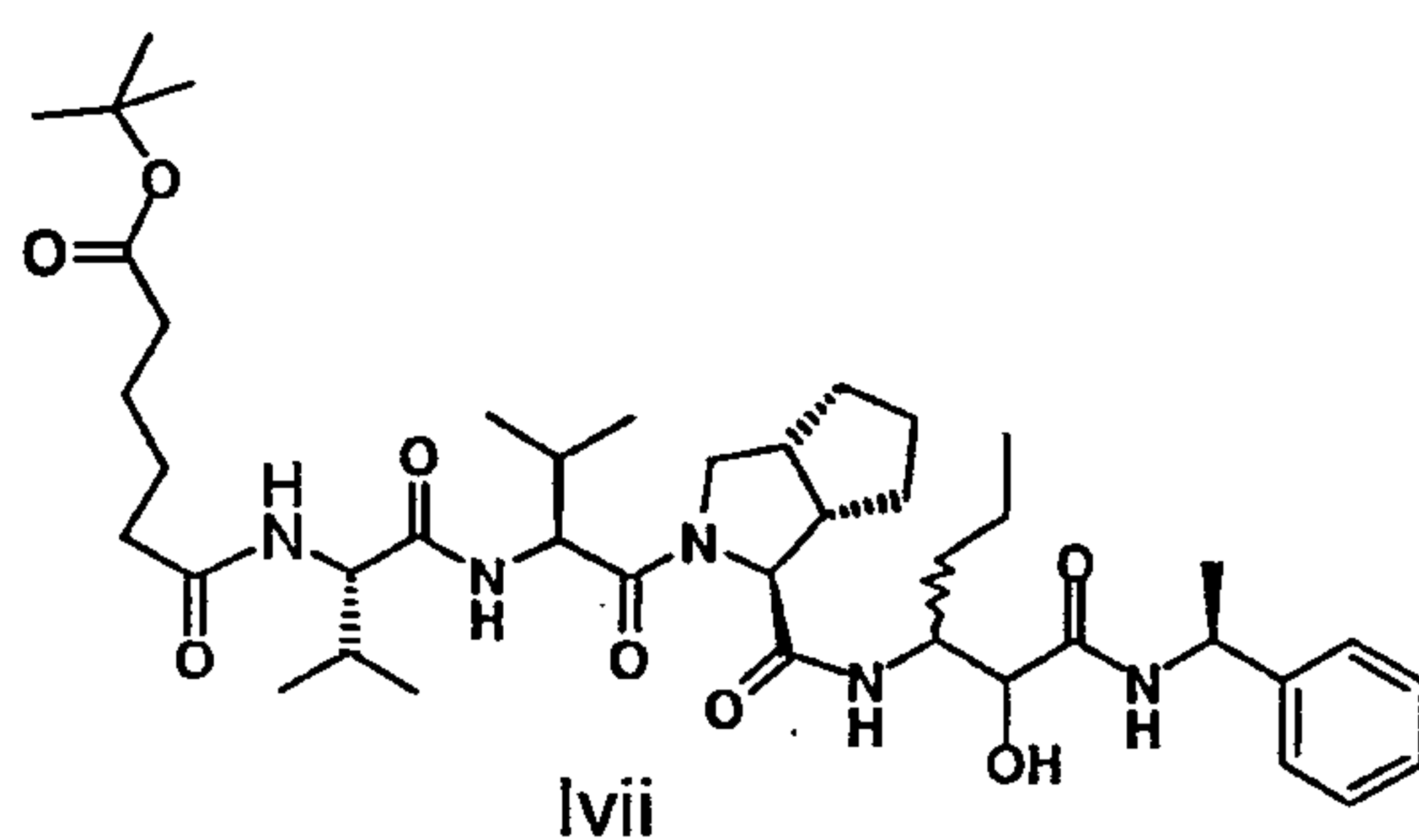
Compound lv (760 mg, 1.41 mmol) and 880 mg (1.69 mmol) of PyBop are dissolved in 5 mL DCM. Compound lvi (530 mg, 2.12 mmol) is added to the solution and then 0.31



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of DIPEA is added. The mixture is stirred at about room temperature overnight. The reaction mixture is diluted to 100 mL with EtOAc, washed with 1 N HCl, NaHCO₃ and brine, and then purified by flash column chromatography (100% EtOAc) to yield 870 mg (80%) of compound lvii,

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Intermediate Example 53 – Compound lviii

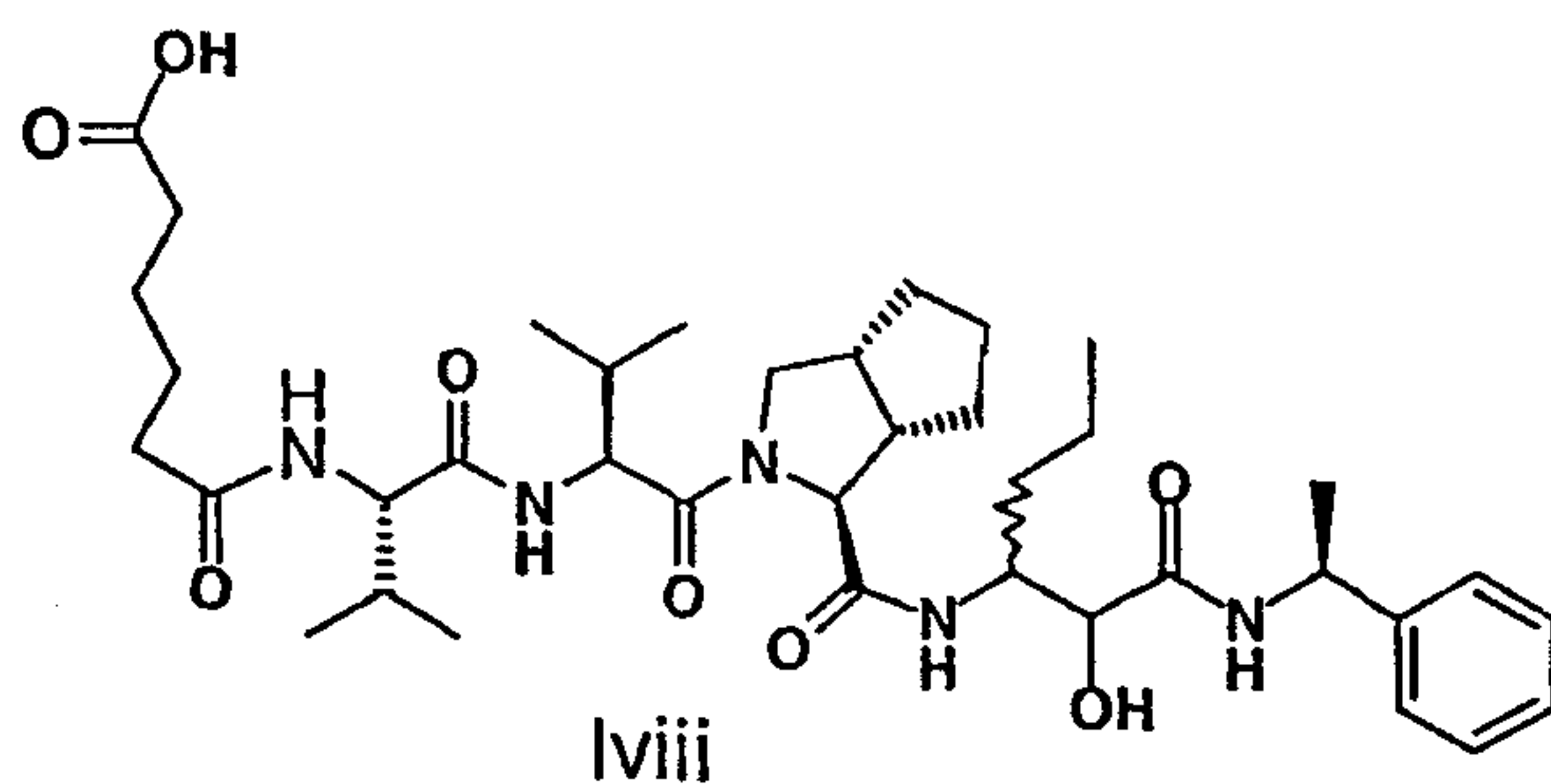
Compound lvii (350 mg, 0.45 mmol) is dissolved in 5 mL TFA and 5 mL DCM and the mixture is stirred at about room temperature for 3 hours. The solvent is removed by evaporation and the product is purified by RP-HPLC to yield 220 mg (69%) of compound lviii,

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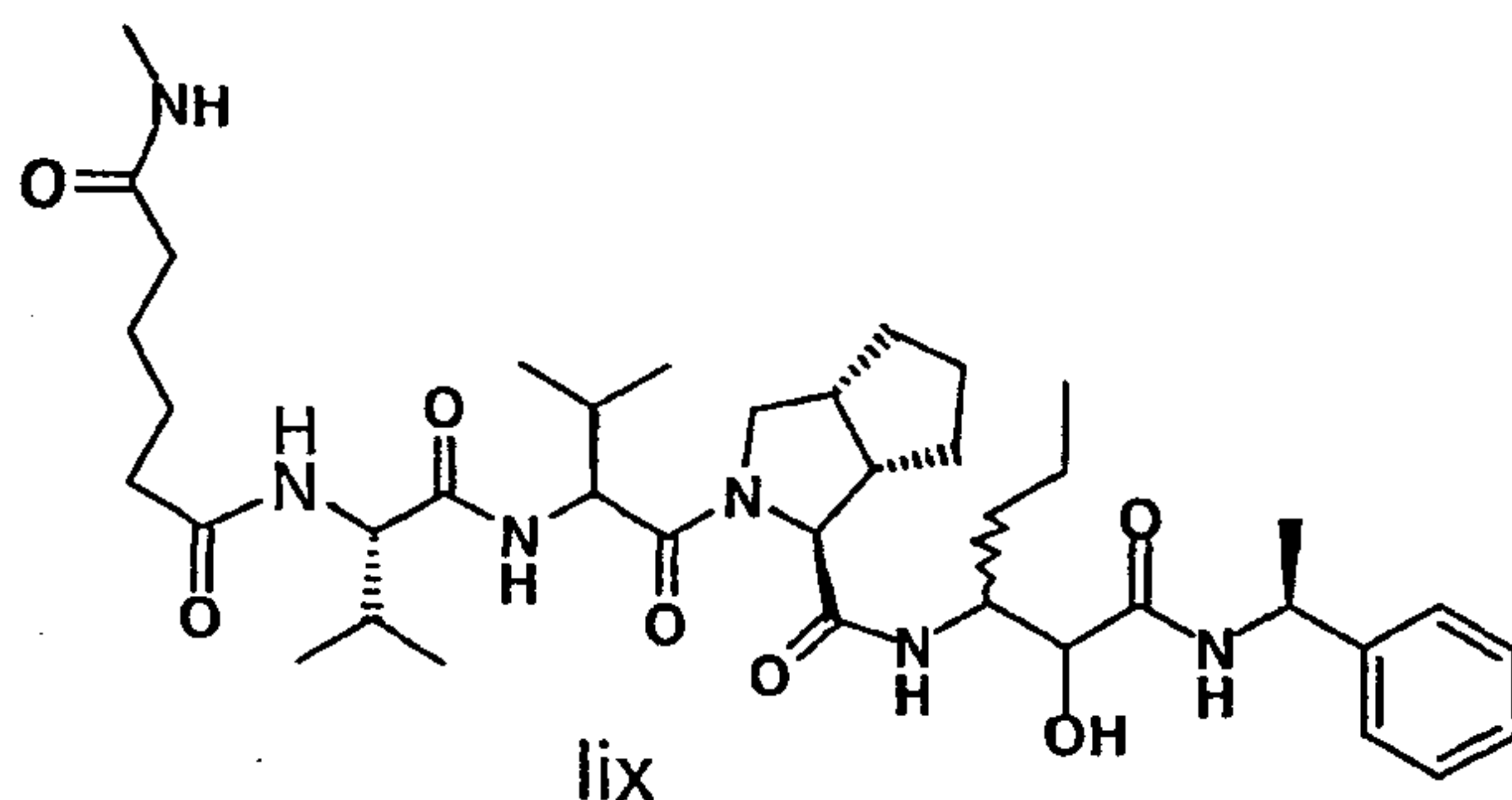
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Intermediate Example 54 – Compound lix

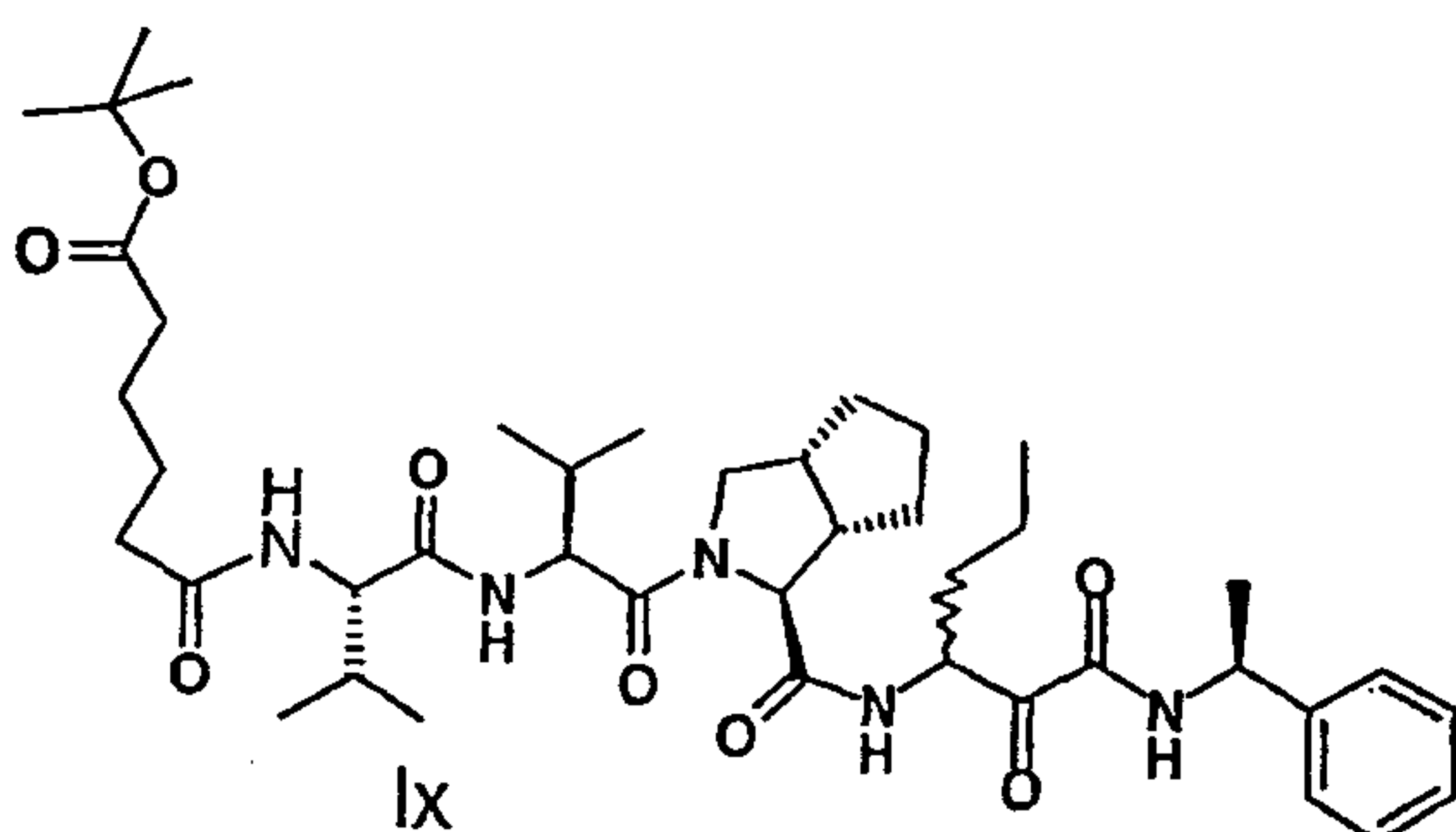
Compound lviii (200 mg, 0.28 mmol) and 218 mg (0.42 mmol) of PyBop are dissolved in 5 mL DCM. Methylamine (0.28 mL of 2 M in THF) is added. The mixture is stirred at about room temperature overnight. The mixture is diluted to 100 mL with EtOAc, washed with 1 N HCl, NaHCO₃ and brine, and then purified by column chromatography (15% EtOH/EtOAc) to yield 168 mg (79%) of lix,



10 Intermediate Example 55 – Compound lx

Compound lviii (200 mg, 0.26 mmol) is dissolved in 4 mL of DCM and 165 mg (0.39 mmol) of DMP reagent is added. The mixture is stirred at about room temperature for 3 hours. The solvent is removed by evaporation. The residue is dissolved in 50% acetonitrile/water, and filtered purified by RP-HPLC to yield 140 mg (70%) of compound lx,

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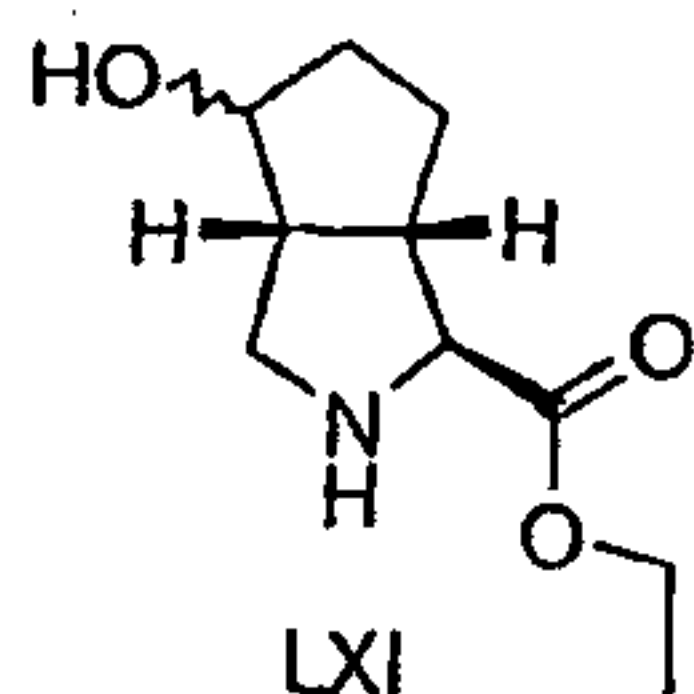


Intermediate Example 56 – Compound ii

A DCM (30 mL) and EtOH (30 mL) solution of compound i (4 g, 12.1 mmol), under N₂, is cooled down to –10° C. NaBH₄ (458 mg, 12.1 mmol) is added and the solution is stirred at –10° C for 50 minutes. TLC (50% EtOAc/Hexane) showed total conversion to a slower running spot. The reaction is carefully quenched with ice and then with a cold saturated solution of NH₄Cl (10 mL). The mixture is dumped in DCM (300 mL). The organic layer is washed once with saturated solution of NH₄Cl (60 mL) and twice with brine (60 mL). The organic layer is then separated, dried over MgSO₄ and concentrated *in vacuo*, to yield 3.5 g of compound ii (87%)

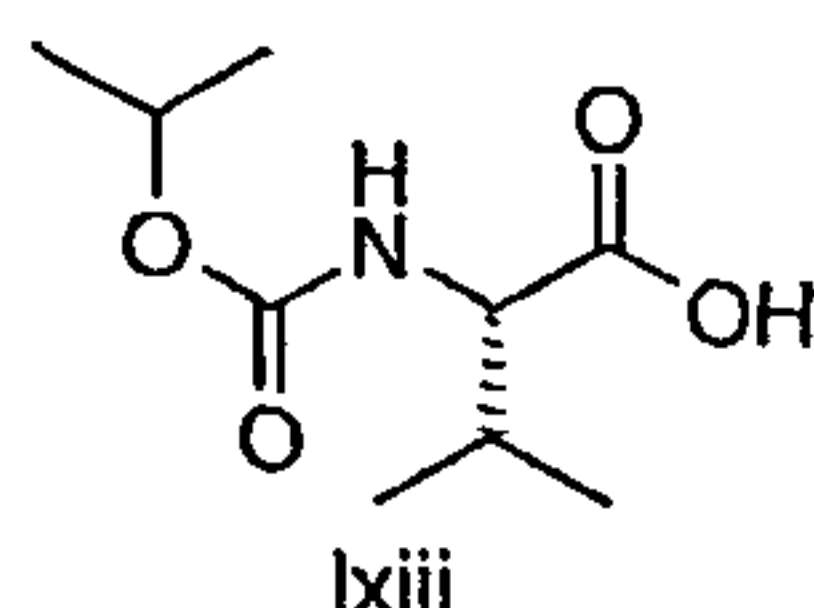
10 Intermediate Example 57 – Compound lxi

In a 250 mL round bottom flask equipped with a H₂ balloon, an ethanolic solution (50 mL) of compound ii (3.5 g, 10.5 mmol) is subjected to standard hydrogenation conditions [20% Pd(OH)₂/C (1.47 g, 2.1 mmol)] for 5 hours at about room temperature. The catalyst is filtered off through Celite and washed with DCM. The solvent is then removed under reduced pressure to yield 2 g (96%) of compound lxi,



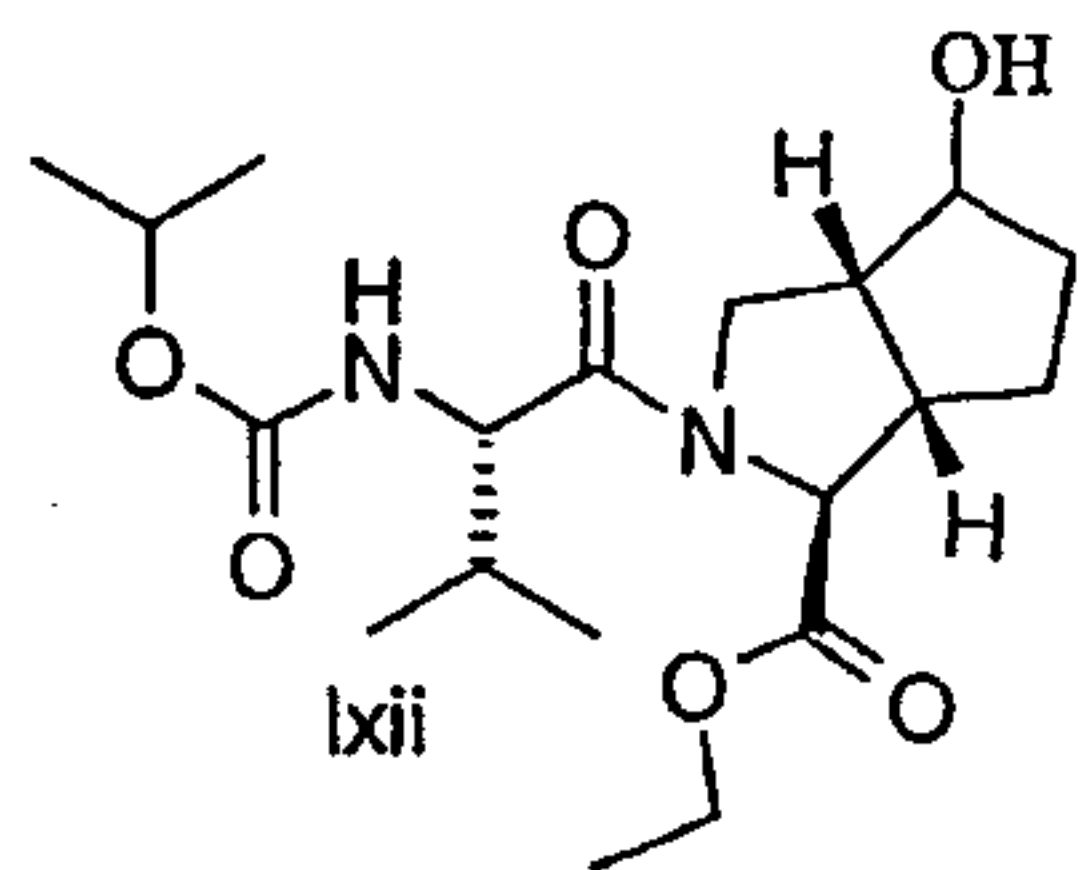
20 Intermediate Example 58 – Compound lxiii

Under inert atmosphere, a solution of compound lxi (200 mg, 1 mmol), compound lxiii,



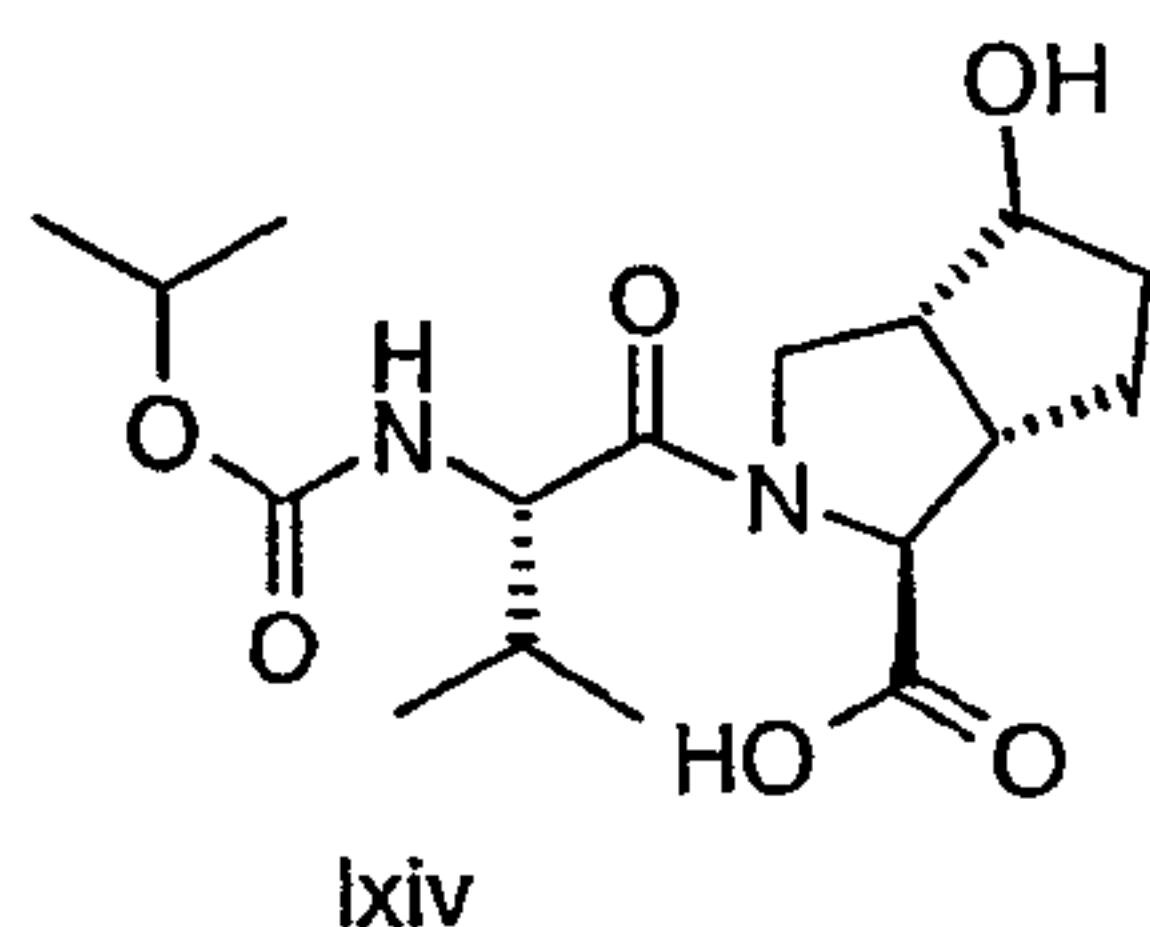
(233 mg, 1.1 mmol), HOAt (1-hydroxy-7-azabenzotriazole) (156 mg, 1.15 mmol) in anhydrous DMF (6 mL) is stirred for 20 minutes. The temperature is then taken down to 0°C, followed by the addition of DIC (0.18 mL, 1.15 mmol). The reaction is stirred overnight at about room temperature. The solution is diluted with EtOAc and then washed twice with 1 N HCl, twice with saturated aqueous NaHCO₃, and brine. The organic layer is separated dried over MgSO₄ and the

solvent removed under reduced pressure. The residue is cleaned by chromatography (silica gel: 70% EtOAc/DCM) to give in 45% yield compound lxii.



5 Intermediate Example 59 – Compound lxiv

A solution of compound lxii (777 mg, 2 mmol) in dioxane (6 mL) and 0.5 M NaOH (6 mL) is stirred for 5 hours at about room temperature. Examination by TLC (100% EtOAc) shows complete conversion to a spot at the origin. The reaction is cooled down with an ice bath followed by the addition of 1 N HCl (4 mL). Solid NaCl is then added and the whole mixture is
 10 extracted twice with EtOAc (2X150mL). The organic extracts are then combined, dried over MgSO₄ and the solvent removed under reduced pressure to give compound lxiv in 92% yield.

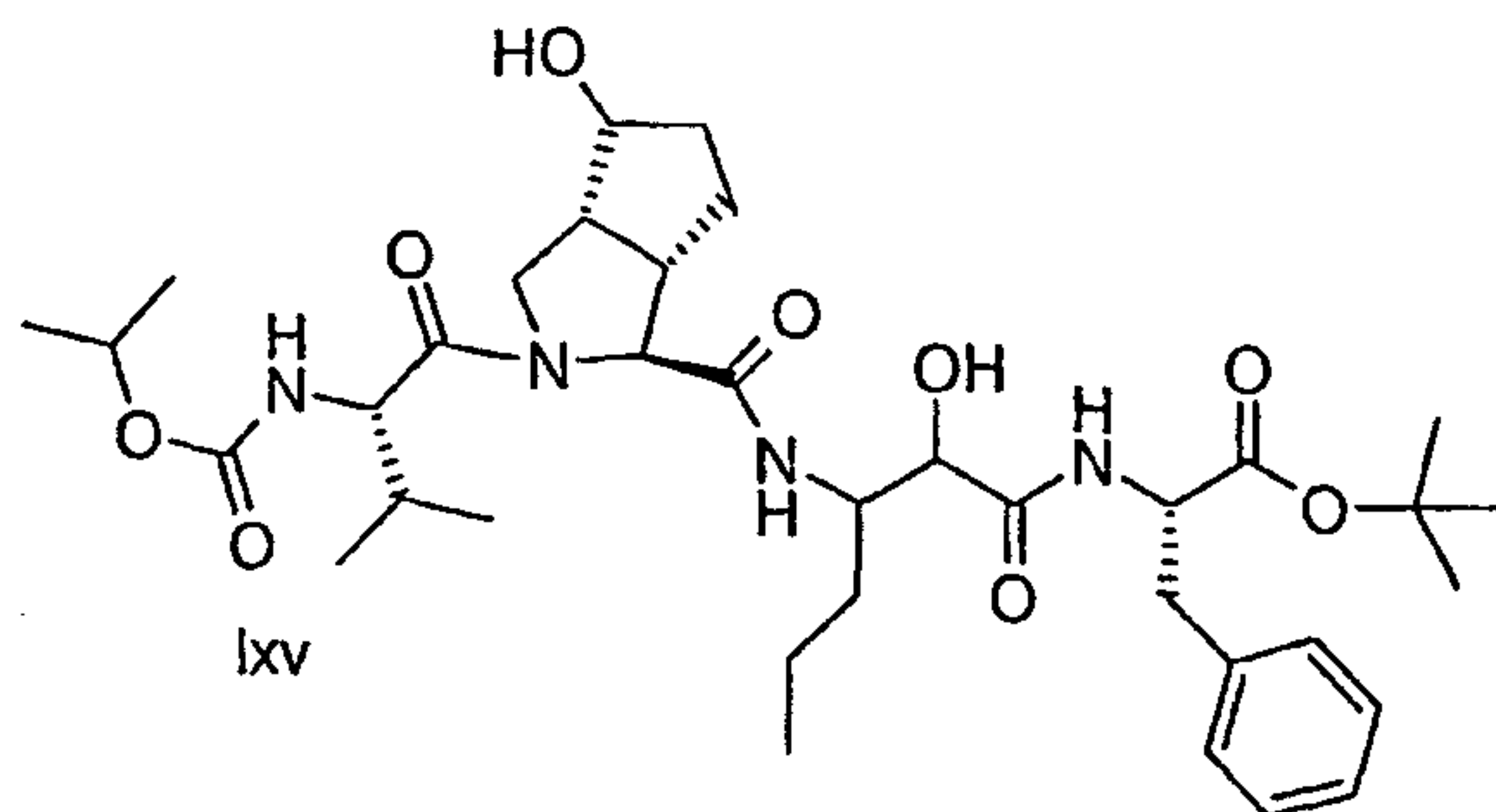


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Intermediate Example 60 – Compound lxv

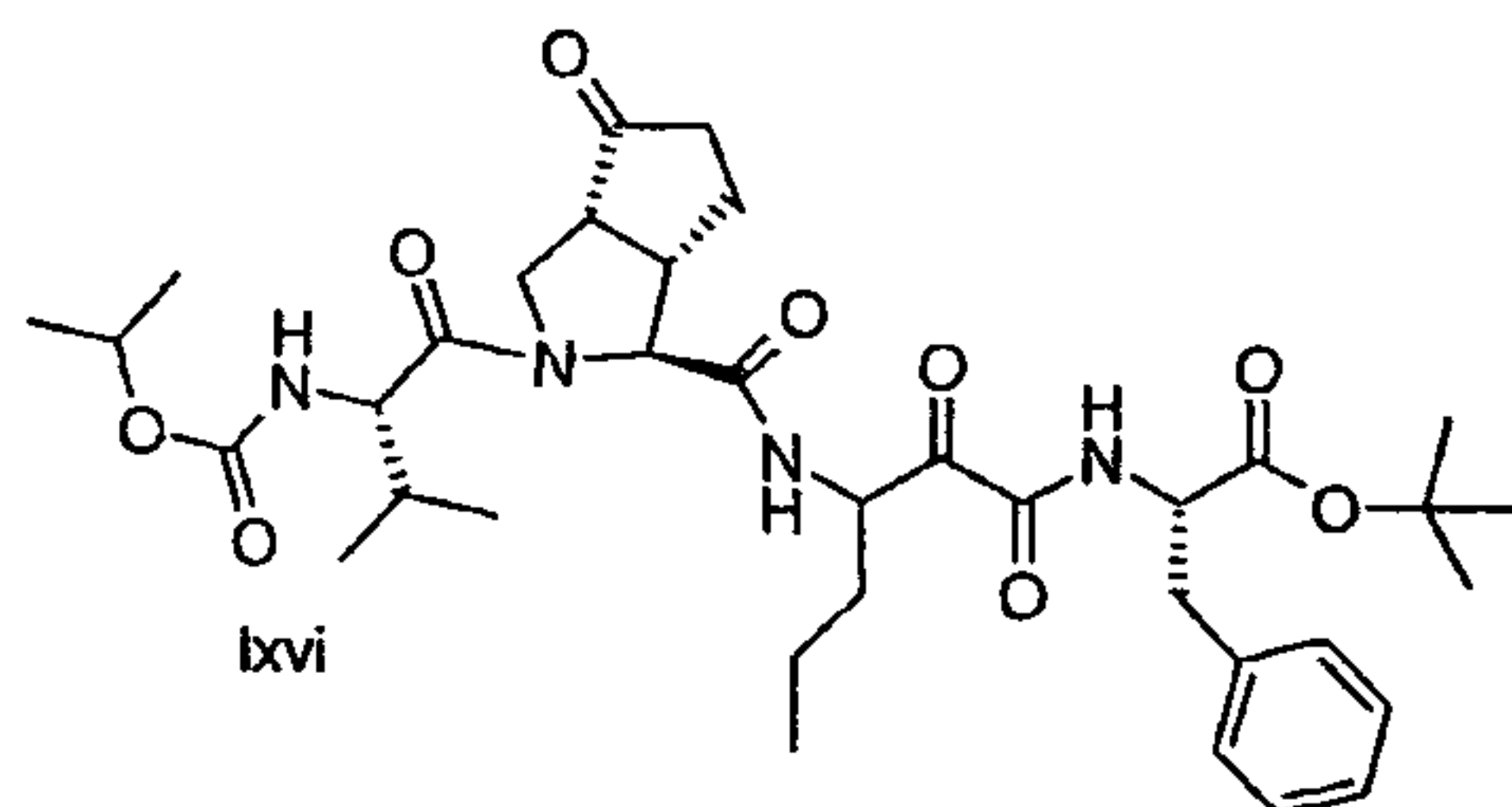
Under an inert atmosphere, a solution of compound x (203 mg, 0.58 mmol), compound lxiv (276 mg, 0.775 mmol), HOAt (1-hydroxy-7-azabenzotriazole) (126 mg, 0.93 mmol) in anhydrous DMF (6mL) is stirred for 20 minutes. The temperature is then taken down to 0°C, followed by
 20 the addition of DIC (0.14 mL, 0.93 mmol). The reaction is stirred overnight at about room temperature. The solution is diluted with EtOAc and then washed twice with 1 N HCl, twice with saturated aqueous NaHCO₃, and brine. The organic layer is separated dried over MgSO₄ and the solvent removed under reduced pressure. The residue is purified by chromatography (silica gel: 50% EtOAc/DCM to 80:19:1 EtOAc/DCM/MeOH) to give compound lxv in 62% yield.

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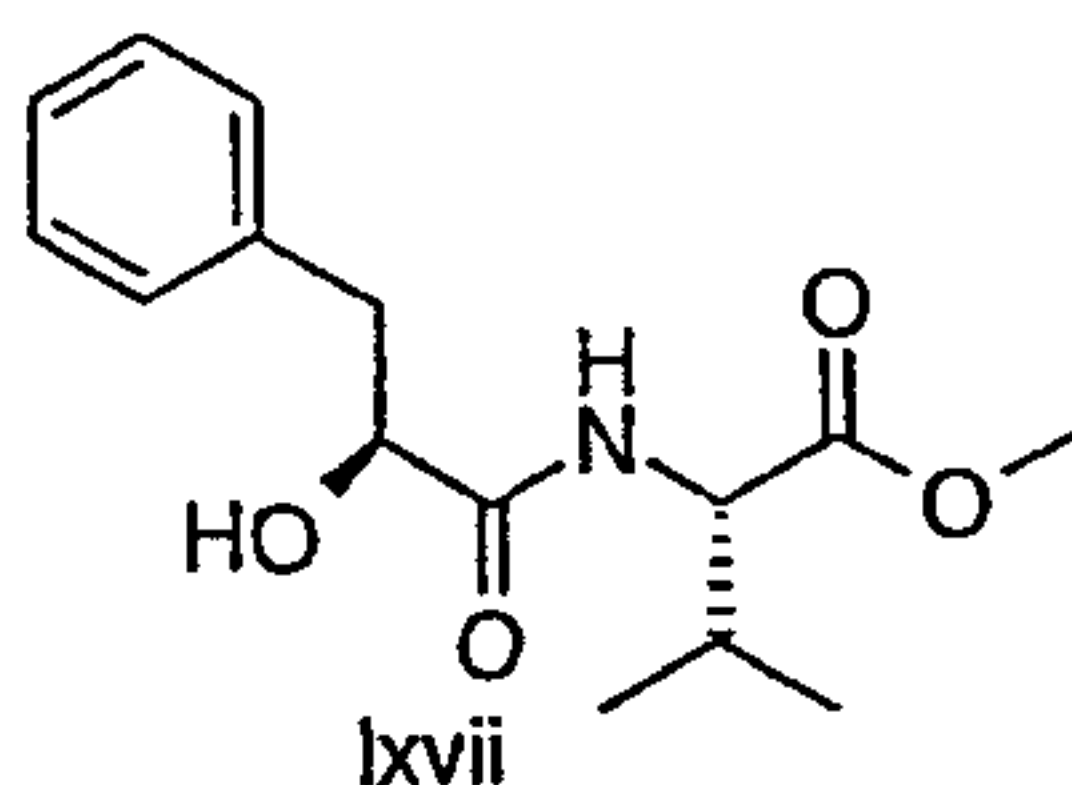
Intermediate Example 61 – Compound lxvi

Under an inert atmosphere, to a solution of compound lxv (287mg, 0.42 mmol) in anhydrous DCM (15mL) is added the DMP reagent reagent (605mg, 1.43 mmol). The reaction is stirred for 2 hours at about room temperature. (Note.- The doubling of the amount of the DMP reagent reagent and the reaction time is to assure that both alcohol groups are completely oxidized to the corresponding keto groups). Examination by TLC (silica gel: 2% MeOH/EtOAc) shows complete conversion to the faster product. The reaction is diluted with DCM (150 mL) and then washed twice with a 10% aqueous sodium sulfite solution (2X 50mL), twice with saturated aqueous NaHCO₃, and with brine. The organic layer is separated dried over MgSO₄ and the solvent removed under reduced pressure. The residue is purified by chromatography (silica gel: 50% EtOAc/DCM to 80:19:1 EtOAc/DCM/MeOH) to give in 77% yield compound lxvi.



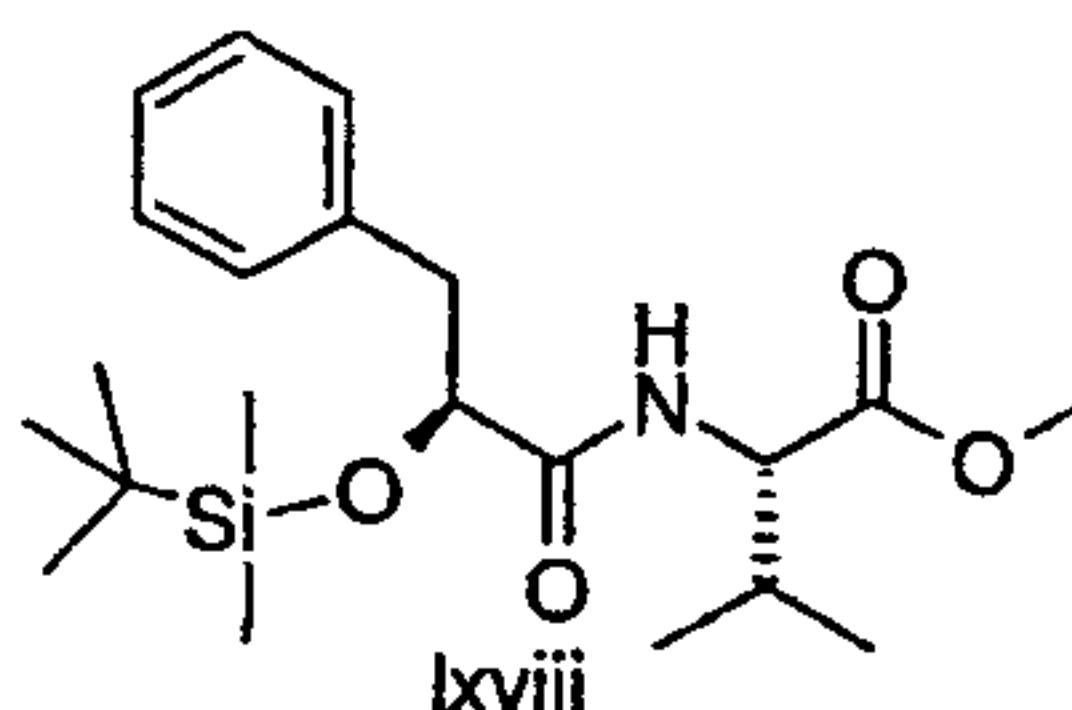
Intermediate Example 62 – Compound lxvii

To a DCM solution (60 ml) of L-3 phenyl lactic acid (2 g, 12 mmol) is added PyBOP (7.5 g, 14.4 mmol). To this solution is added a DCM solution (20 mL) containing L-valine methyl ester HCl (2.4 g, 14.4 mmol) and DIPEA (2.6 mL, 14.4 mmol). The resulting reaction mixture is stirred overnight at about room temperature. At this point, the reaction is diluted with EtOAc (30 mL), washed with NaHCO₃ (30 mL) and brine (15 mL). The organic layer is dried over Na₂SO₄, filtered and concentrated. Purification is achieved in 50% EtOAc/Hex on silica gel to give 2.97 g (89%) of compound lxvii,



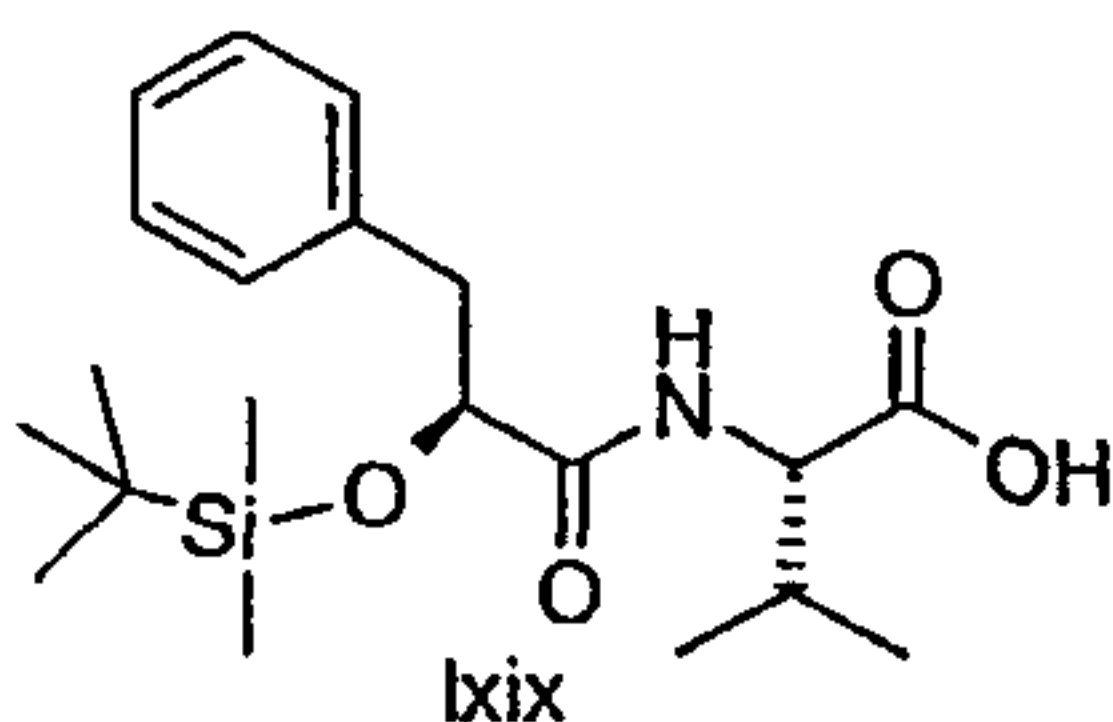
Intermediate Example 63 – Compound lxviii

Compound lxvii (2.97 g, 10.6 mmol) is taken up in DCM (50 mL) and cooled with an ice bath. TBSCl (2.1 g, 13.8 mmol) is added to this solution followed by imidazole (0.94 g, 13.8 mmol). The resulting solution is stirred overnight. The reaction is then diluted with EtOAc (50 mL), washed with NaHCO₃ and brine. The organic layer is dried over Na₂SO₄, filtered and concentrated. Purification is achieved in 20% EtOAc/Hexane on silica gel to give 3.79 g (90%) of compound lxviii,



10 Intermediate Example 64 – Compound lxix

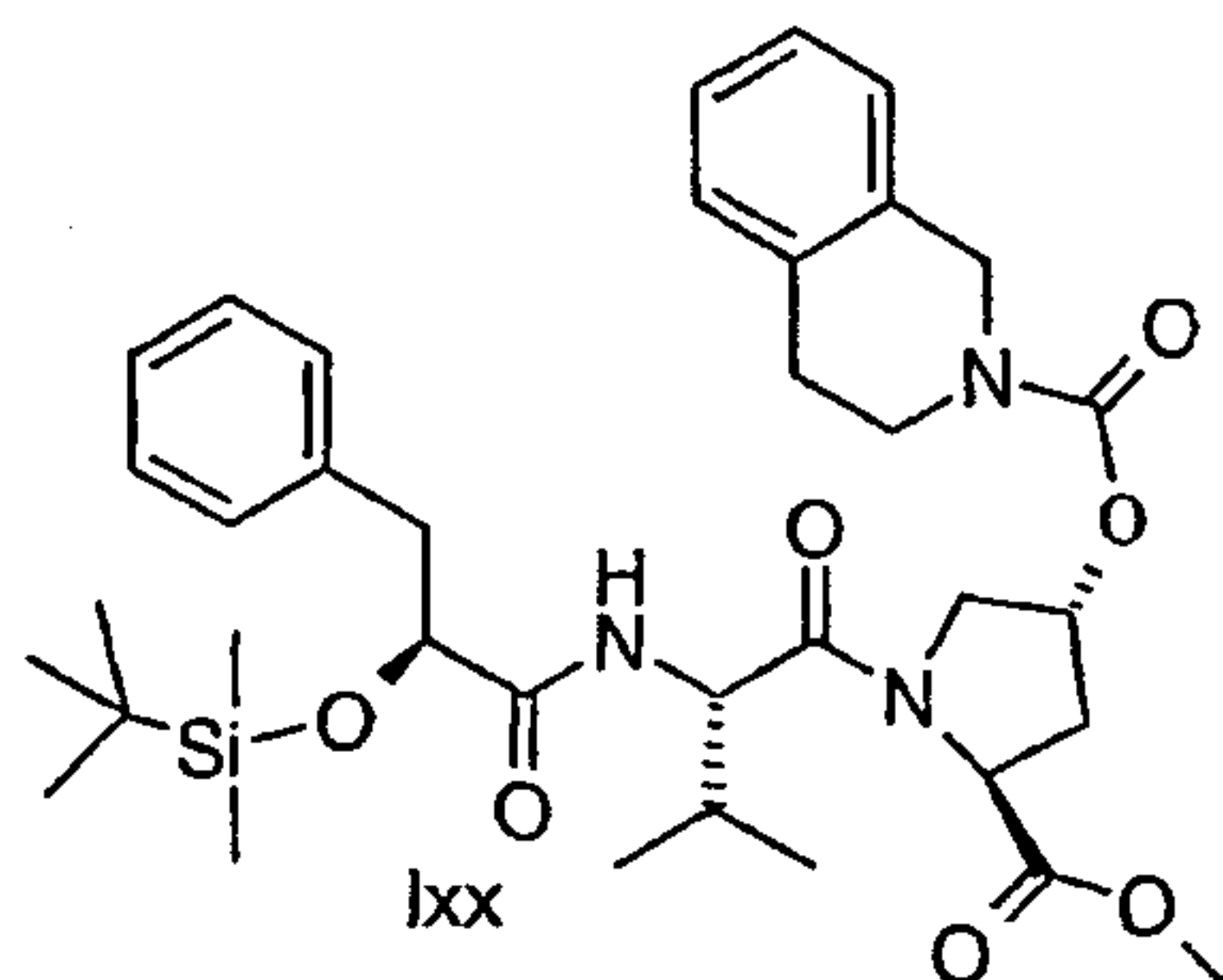
To a methanol (50 mL) solution of compound lxviii (3.78 g, 9.6 mmol) is added 1 N aqueous NaOH (14.4 mL, 14.4 mmol). The resulting solution is stirred overnight. The solvent is partially removed *in vacuo*. The pH of the reaction mixture is then lowered to 3 using 1 N HCl aqueous solution. The solution is diluted with EtOAc and brine. The desired product is extracted with EtOAc (3x50 mL). The organic layers are combined, dried over Na₂SO₄, filtered and concentrated to give 3.5 g (96%) of compound lxix,



Intermediate Example 65 – Compound lxx

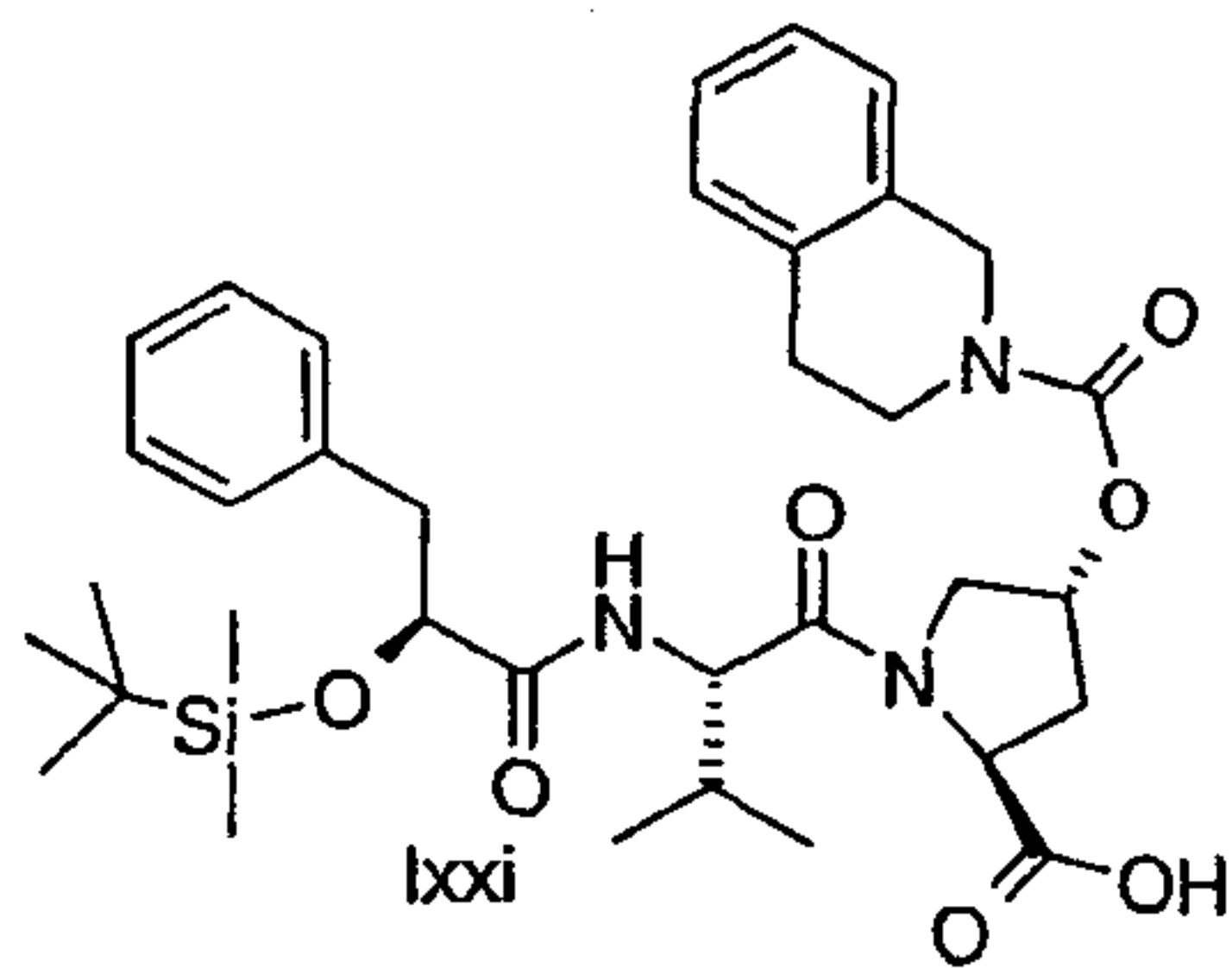
To a DCM (15 mL) solution containing compound lxix (1.1 g, 2.9 mmol) is added HOAt (0.44 g, 3.2 mmol) followed by a 1 M solution of DCC (3.2 mL, 3.2 mmol) in DCM. After stirring at about room temperature for 20 minutes, a DCM (15 mL) solution of compound xxxix (970 mg, 3.2 mmol) is added. This reaction is stirred overnight under N₂. The reaction is then diluted with EtOAc (30 mL), filtered through a pad of silica gel, washed with 0.1 N HCl,

NaHCO₃, and brine. The organic layer is dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification is achieved in 50% EtOAc/Hex on silica gel to give 1.5 g (77%) of compound lxx,



5 Intermediate Example 66 – Compound lxxi

To a methanol solution (30 mL) of compound xx (1.5 g, 2.4 mmol) is added 1 N aqueous NaOH (3.6 mL, 3.6 mmol). The resulting solution stirred overnight. At this point, the solvent is partially removed, and the pH of the reaction mixture is adjusted to 3 using 1 N aqueous HCl. The reaction is then diluted with EtOAc (50 mL) and brine (20 mL). The aqueous layer is
 10 extracted with EtOAc (3x50mL). The organic layers are combined, dried over Na₂SO₄, filtered and concentrated to provide 1.3 g (92%) of compound lxxi,



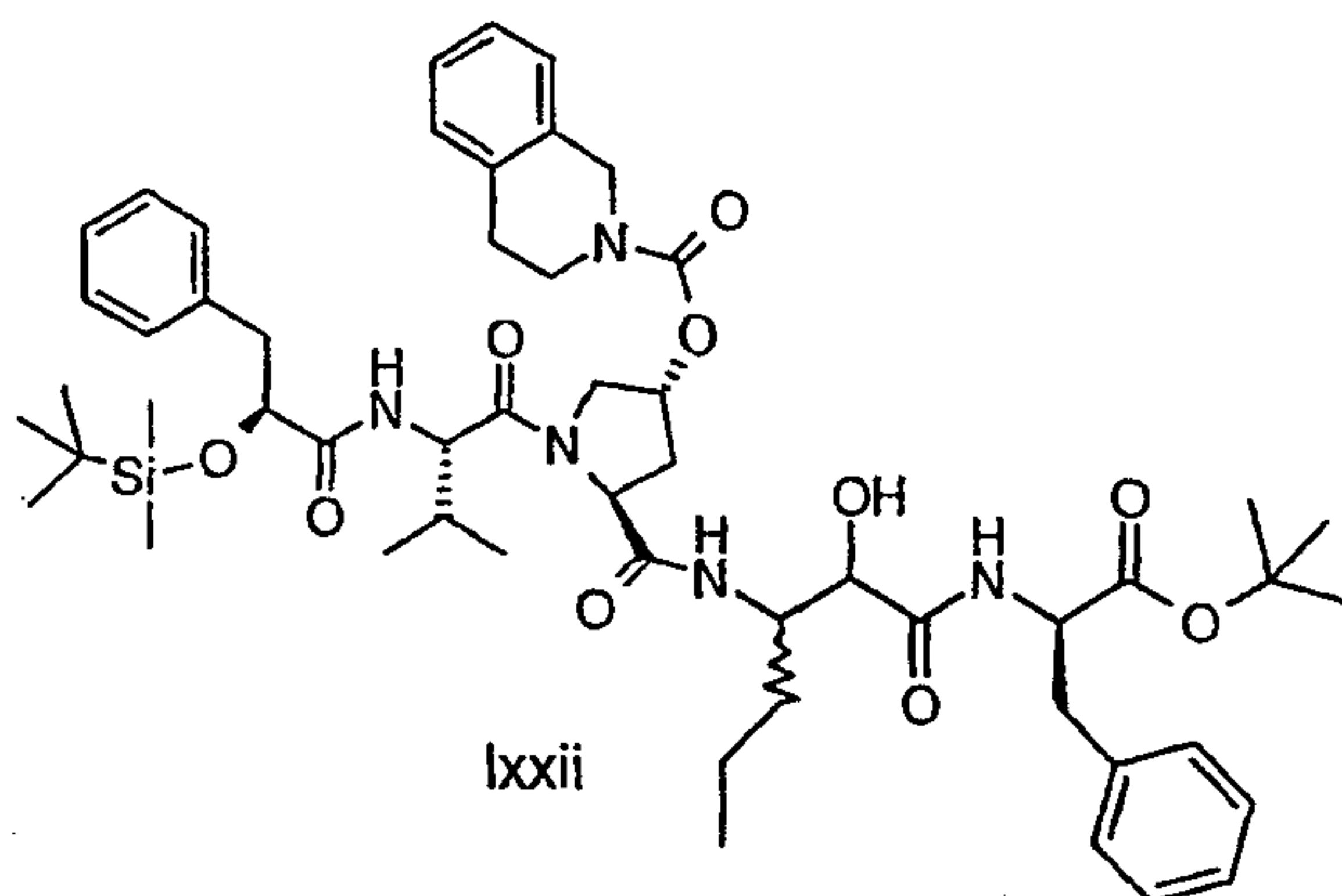
Intermediate Example 67 – Compound lxxii

15 To a solution of DCM (2 mL) containing compound lxxi (180 mg, 0.28 mmol) is added PyBOP (175 mg, 0.34 mmol) and DIPEA (0.06 mL, 0.34 mmol), followed by a DCM solution (3 mL) of compound x (150 mg, 0.41 mmol). The resulting solution is stirred overnight under N₂. The reaction is then diluted with EtOAc (30 mL), washed with NaHCO₃ and brine. The organic layer is dried over Na₂SO₄, filtered and concentrated. Purification is achieved in 100% EtOAc on
 20 silica gel to give 270 mg (98%) of compound lxxii,

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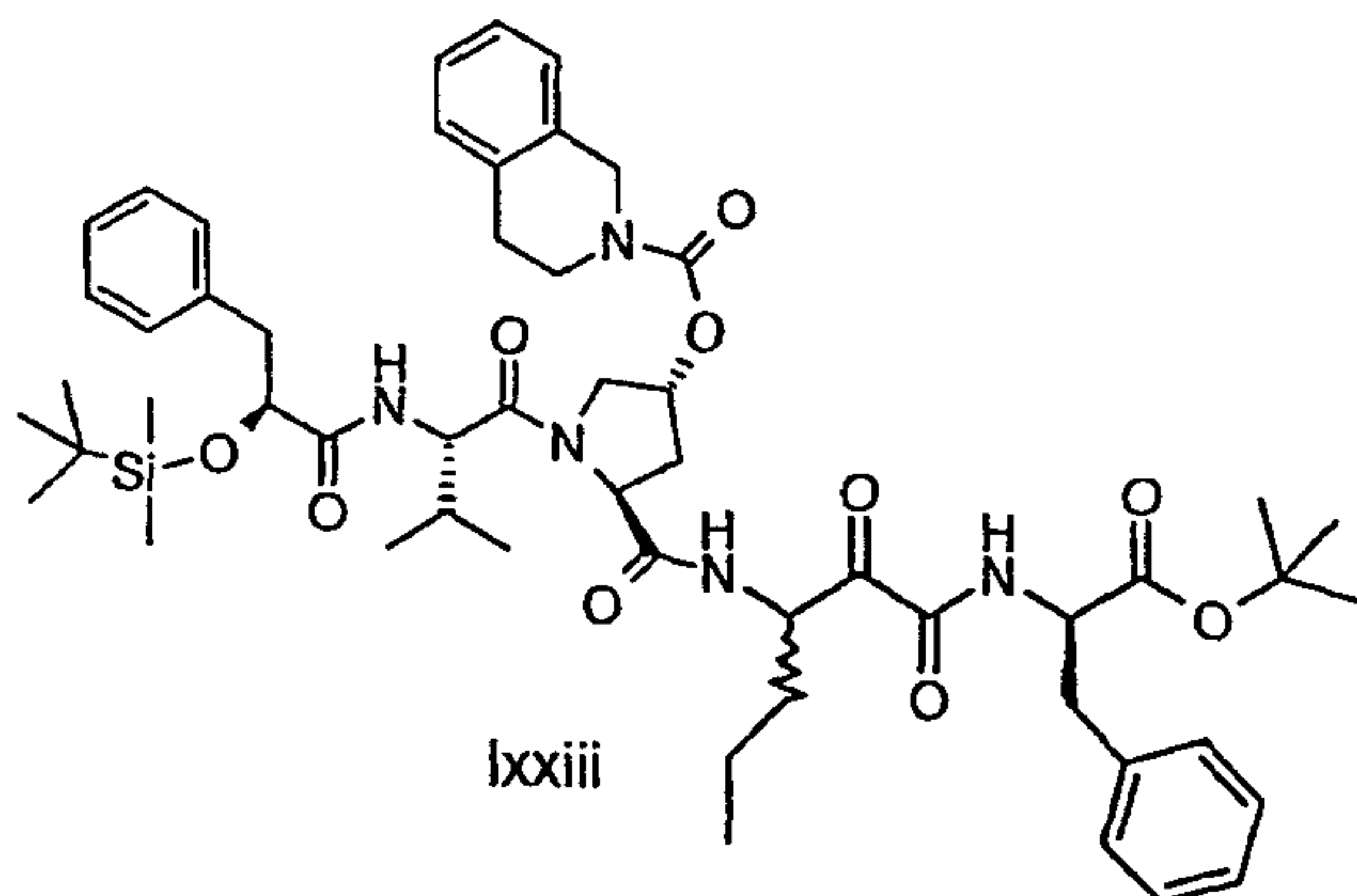
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Intermediate Example 68 – Compound lxxiii

To a DCM (3 mL) solution of compound lxxii (270 mg, 0.27 mmol) is added DMP reagent reagent (140 mg, 0.33 mmol). After stirring at about room temperature for 1.5 hours, the reaction is quenched with 10% Na₂SO₃ (10 mL). The reaction is diluted with EtOAc (30 mL) and stirred for 10 minutes. The organic layer is washed with NaHCO₃ and brine. The organic layer is dried over Na₂SO₄, filtered and concentrated. Purification is achieved in 60% EtOAc/Hex. to give 150 mg (56%) of compound lxxiii,



10 Intermediate Example 69 – Compound lxi

To an ethanol solution (50 mL) of compound ii (3.5 g, 10.5 mmol) is added under a stream of nitrogen Pd(OH)₂/C (1.47 g, 20% Pd content, 2.1 mmol). The reaction is subjected to hydrogenation under 1 atm pressure. Upon completion, the catalysts are filtered through a pad of Celite and washed with dichloromethane. The filtrates are concentrated *in vacuo* to give 2 g (96%) of compound lxi.

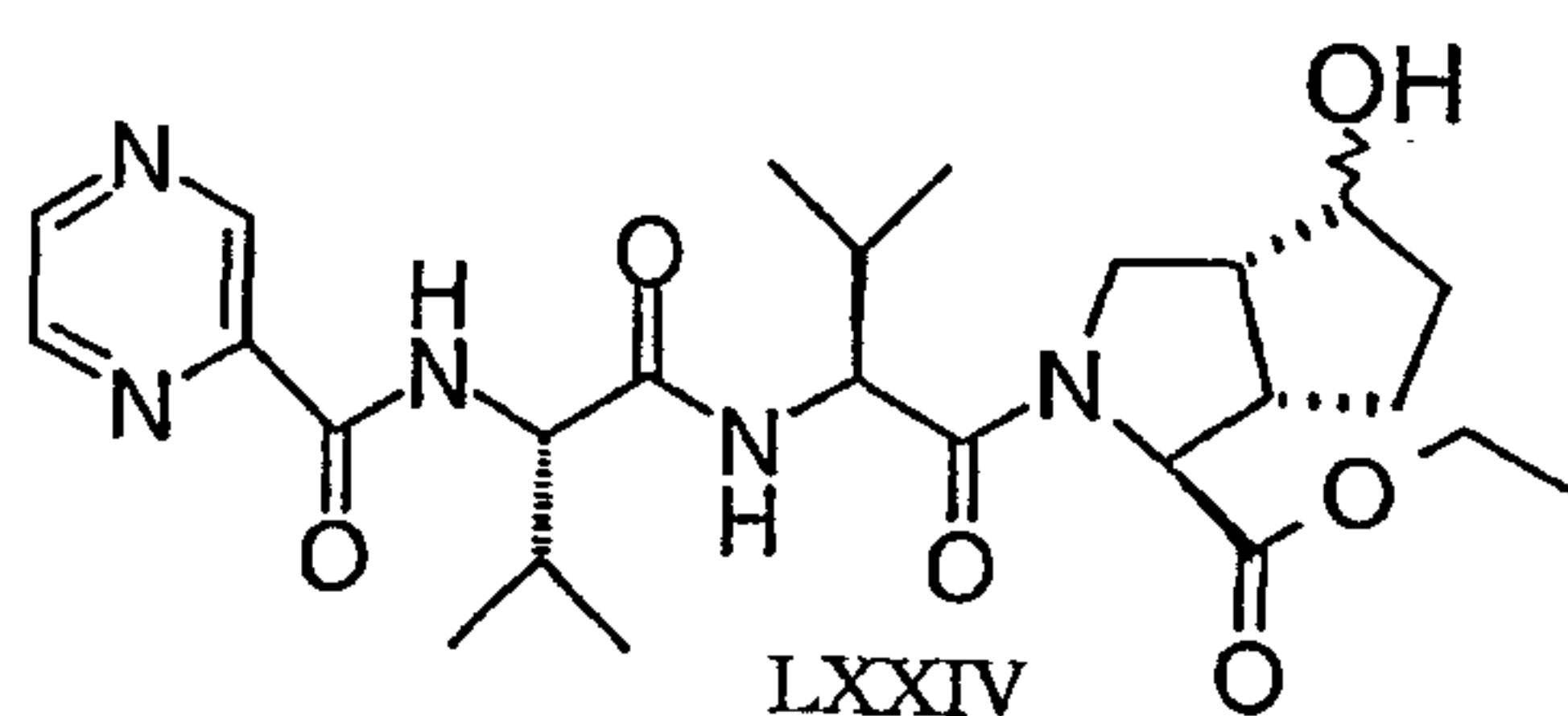
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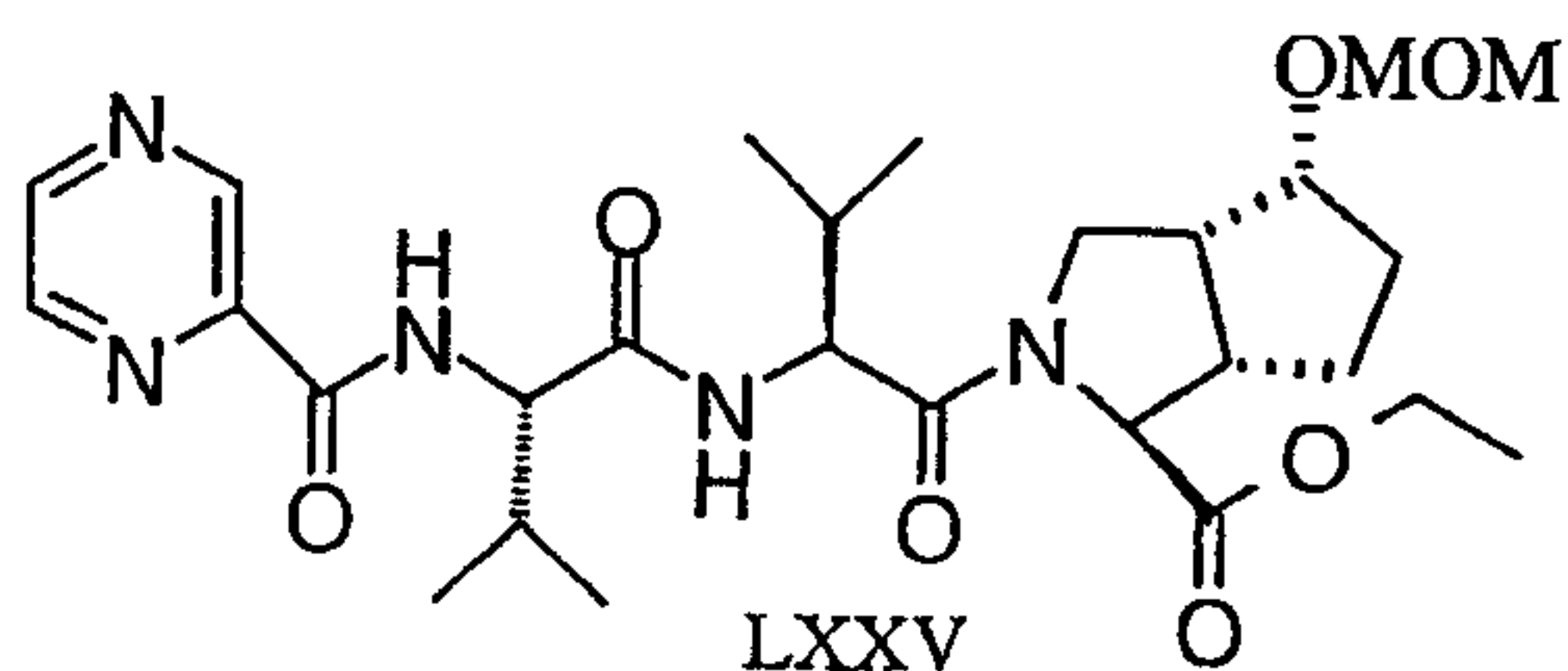
Intermediate Example 70 – Compound lxxiv

To a DMF solution (60 mL) of compound vii (9.1 g, 28.2 mmol) is added HOAt (4 g, 29.4 mmol) and 1,3-diisopropylcarbodiimide (3.7 g, 29.4 mmol). After stirring at about room temperature for 30 minutes, a DMF solution (10 mL) of compound lxi (5.1 g, 25.6 mmol) is added to the above solution. The reaction is stirred at about room temperature overnight. At this point, the white solids are filtered off. The filtrates are concentrated *in vacuo* to give a residue that is purified by silica gel chromatography to give 9.5 g (67%) of compound lxxiv,



10 Intermediate Example 71 – Compound lxxv

To a solution of compound lxxiv (1.5 g, 3 mmol) in anhydrous THF (25 mL) is added $\text{Et}_2\text{Pr}_2\text{N}$ (0.78 mL, 4.5 mmol) at about room temperature. The mixture is cooled to 0°C and MOMCl (1.5 mL, 19.7 mmol) is added in a dropwise fashion. The reaction is allowed to warm to room temperature and stirred overnight. The solution is then diluted with ether and washed with water (3 times). The aqueous layers are extracted further by ether and all the organic layers are dried over MgSO_4 before being concentrated to afford a yellow oil. The desired isomer of compound lxxv is isolated by silica gel chromatography (EtOAc/Hexanes



5/2) in 40% yield with clear separation of diastereomers.

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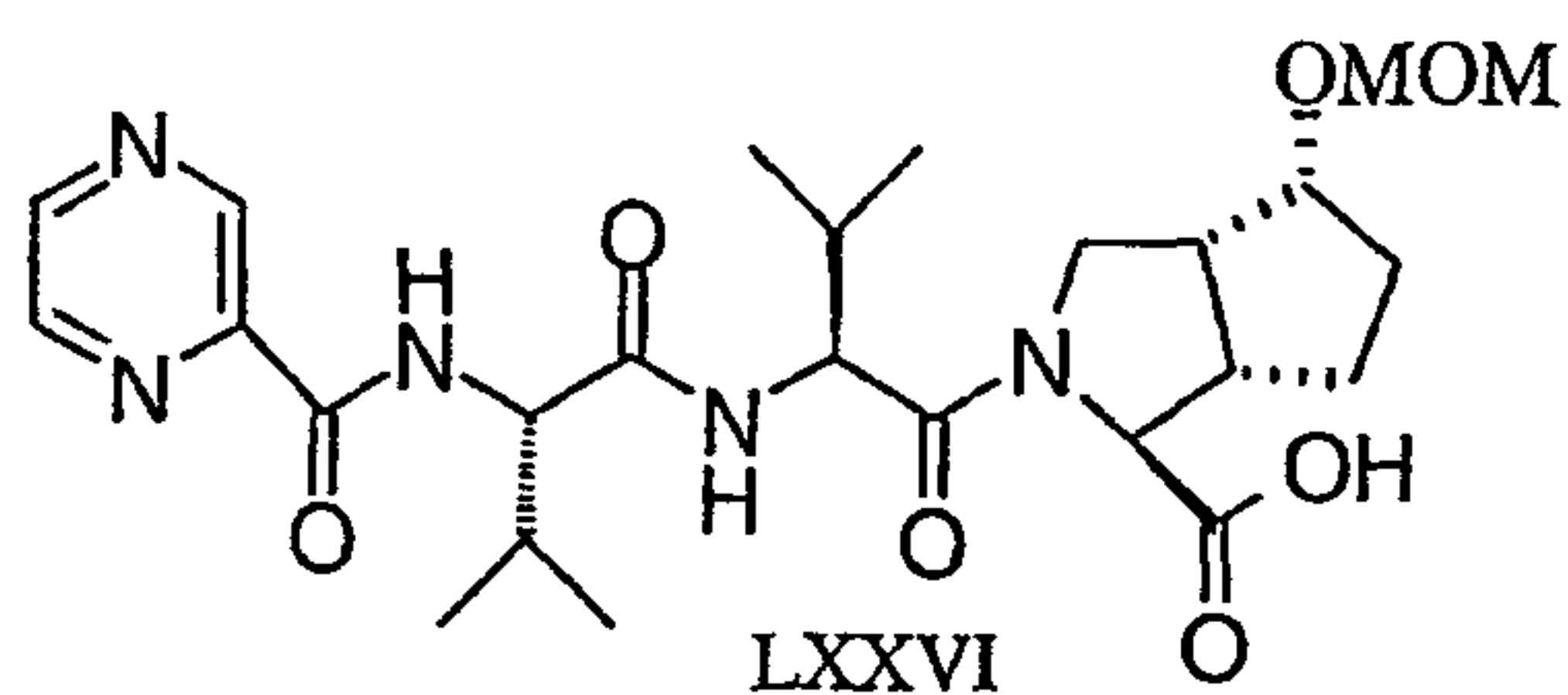
Intermediate Example 72 – Compound lxxvi

To a solution of compound lxxv (502 mg, 0.9 mmol) in EtOH (5 mL) is added 2 N aqueous NaOH (0.9 mL, 1.8 mmol) dropwise at 0°C. The reaction is allowed to warm to room temperature and stirred overnight. Upon completion of the saponification, the solution is acidified to pH 3 with Dowex 50W8X-200 acidic resin. The solids are filtered off and the resulting filtrate is concentrated *in vacuo* to give a oily residue that is lyophilized to give 370 mg (80 %) compound lxxvi,

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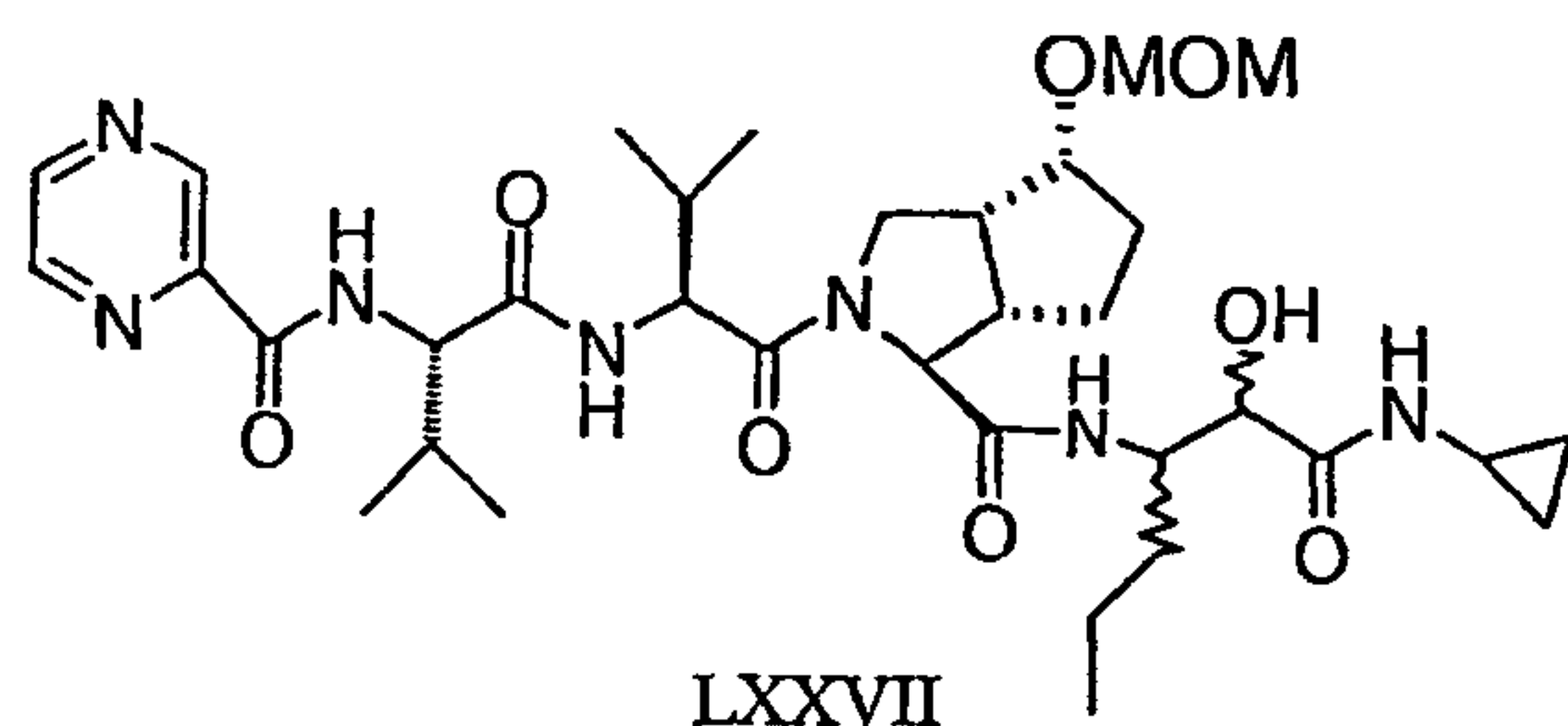
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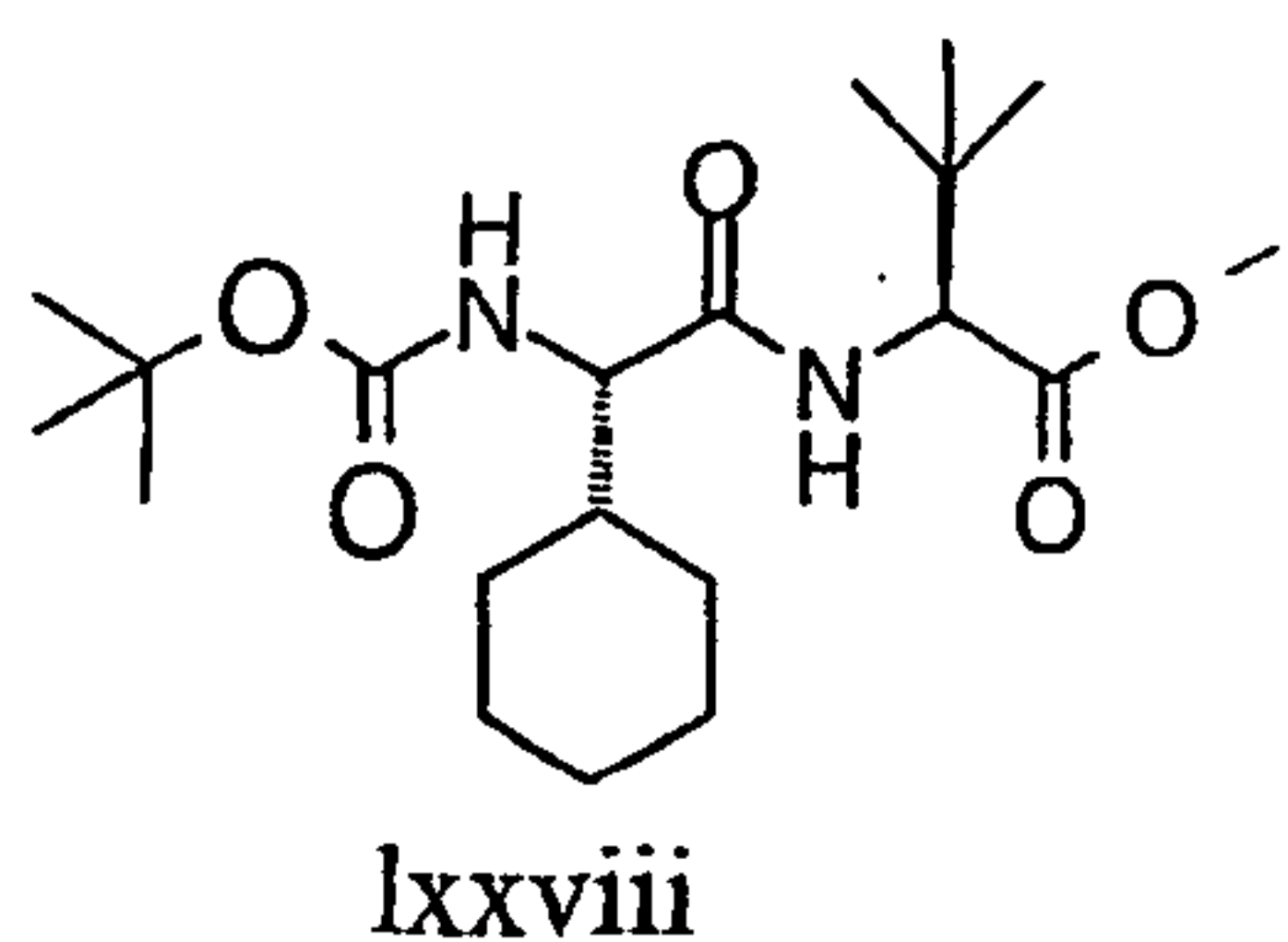
Intermediate Example 73 – Compound lxxvii

- 5 A dichloromethane solution (4 mL) of compound lxxvi (110 mg, 0.21 mmol) is treated with PyBOP (200 mg, 0.38 mmol). After stirring at about room temperature for 30 minutes, the reaction mixture is charged with a THF solution (3.2 mL) of compound xiii (60 mg, 0.32 mmol), followed by Et₃Pr₂N. After stirring overnight at about room temperature, the reaction is quenched with water and extracted with EtOAc. The resulting organic layer is washed with brine and dried
 10 over MgSO₄, before being concentrated to a yellow oil. Purification by silica gel chromatography (5% EtOH/EtOAc) yields 143mg (100%) of compound lxxvii,



Intermediate Example 74 – Compound lxxviii

- 15 To a THF solution (50 mL) of H-Chg-OH 2 (5 g, 19.4 mmol) is added HOBt (2.63 g, 19.4 mmol) and EDCI (3.72 g, 19.4 mmol). After stirring at about room temperature for 20 minutes, a THF (19 mL) and DMF (10 mL) solution containing tert-L-Leucine methyl ester-hydrochloride (19.4 mmol) and DIPEA (6.75 mL, 38.8 mmol) is added to the above solution. The reaction is stirred at about room temperature overnight. Standard aqueous work-up and silica gel
 20 chromatography (15 - 20% EtOAc/Hexanes) affords 2.27 g (30%) of compound lxxviii,



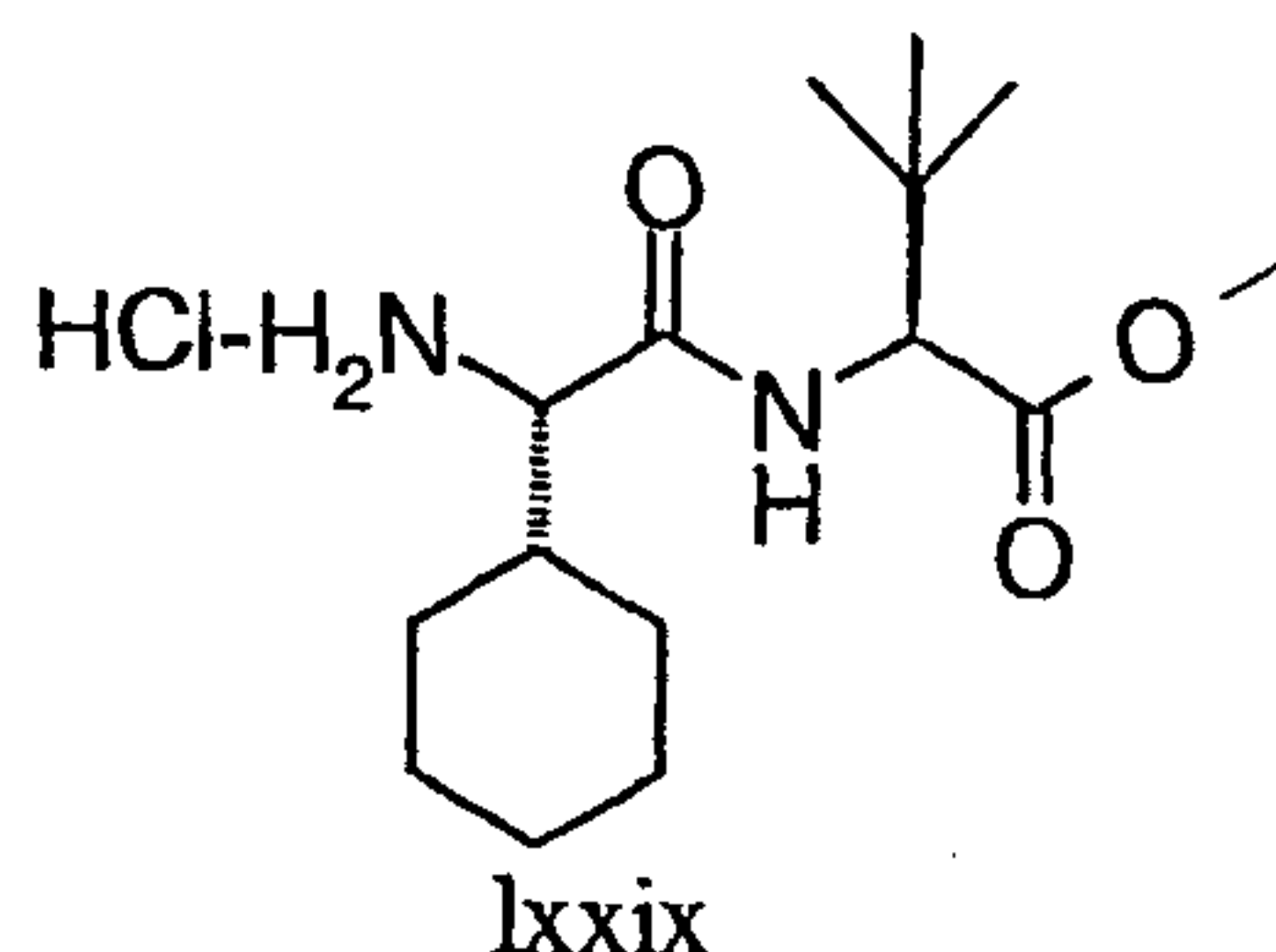
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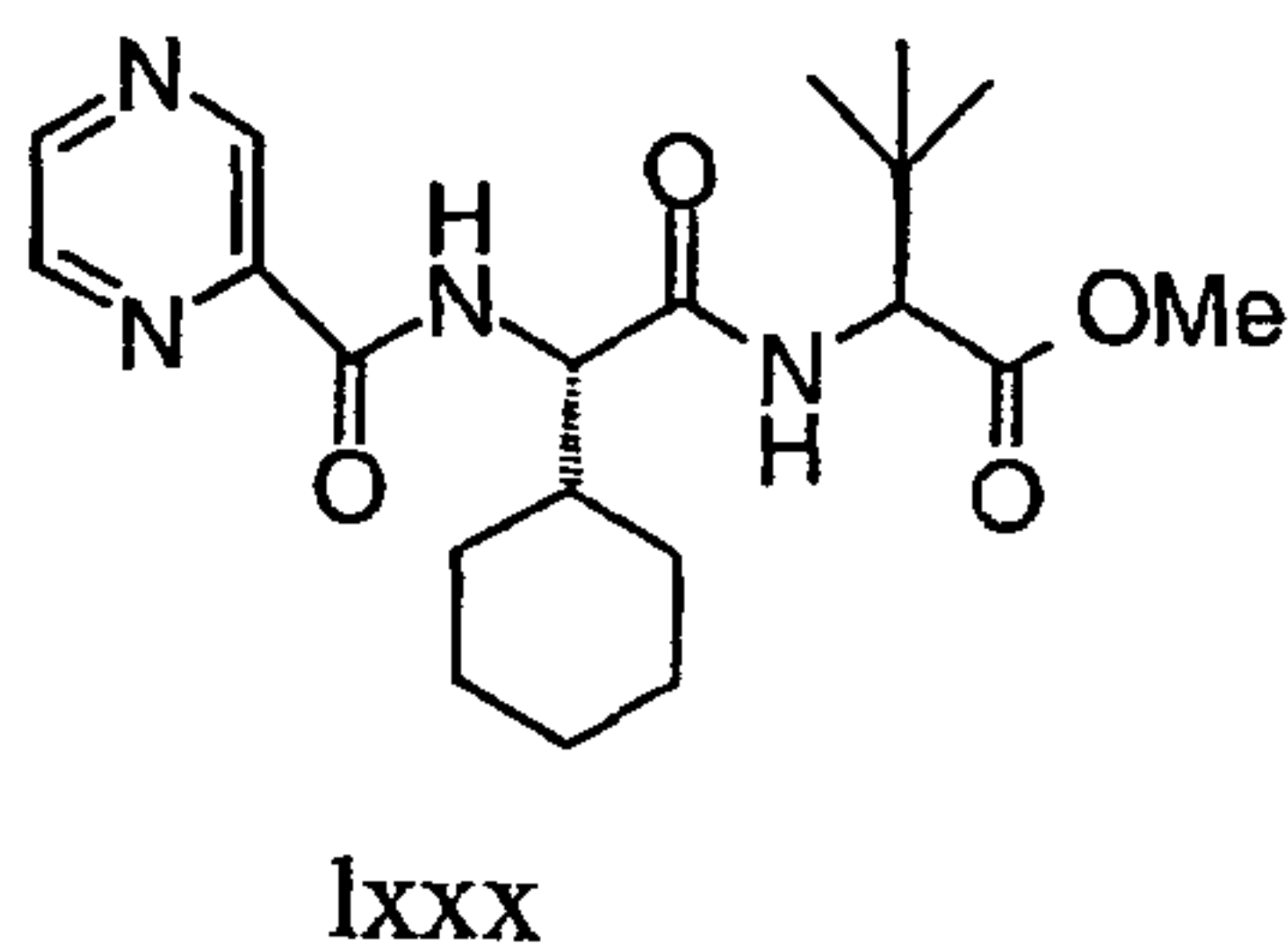
Intermediate Example 75 – Compound lxxix

To a THF solution (12 mL) of compound lxxviii (2.27 g, 5.91 mmol) is added 4 N HCl solution in dioxane (7.38 mL, 29.5 mmol). The reaction is stirred at about room temperature overnight. At this point, the solvent is removed under reduced pressure to yield the compound lxxix that is used directly for next reaction.



Intermediate Example 76 – Compound lxxx

To a THF solution of compound lxxix (5.9 mmol) is added to a THF (20 mL) solution containing 2-pyrazinecarboxylic acid (878 mg, 7.08 mmol), HOBt (957 mg, 7.08 mmol) and EDCI (1.36 g, 7.08 mmol). To the resulting mixture is then added DIPEA (2.05 mL, 11.8 mmol). The reaction is stirred overnight at about room temperature and then quenched with water. The reaction mixture is extracted with EtOAc. The organic layer is washed with brine and concentrated *in vacuo* to provide a residue that is purified by silica gel chromatography (40-50% EtOAc/Hexanes) to provide 1 g (36%) of compound lxxx,



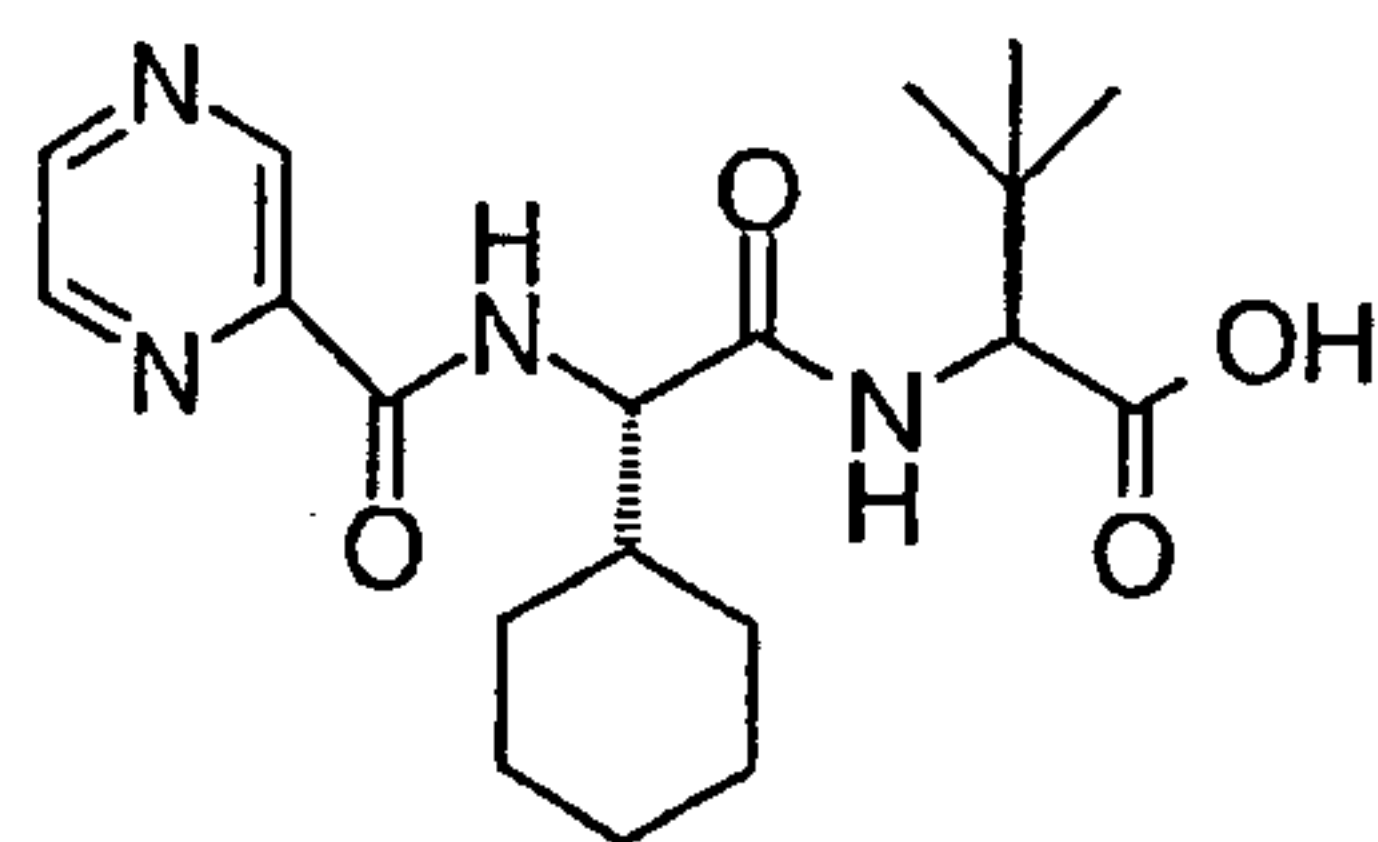
Intermediate Example 77 – Compound lxxxi

To a methanol solution (20 mL) of compound lxxx (1 g, 2.56 mmol) is added 2 N NaOH 3.2 mL, 6.4 mmol). The reaction is stirred at about room temperature overnight. At this point, the reaction is acidified to pH 3 using 5 N HCl. The reaction is diluted with EtOAc (75 mL), and washed with water and brine. The organic layer thus obtained is dried and concentrated *in vacuo* to give a residue that is dissolved in 1:1 CH₃CN/H₂O for lyophilization. A total of ~1 g (100%) of compound lxxxi is obtained.

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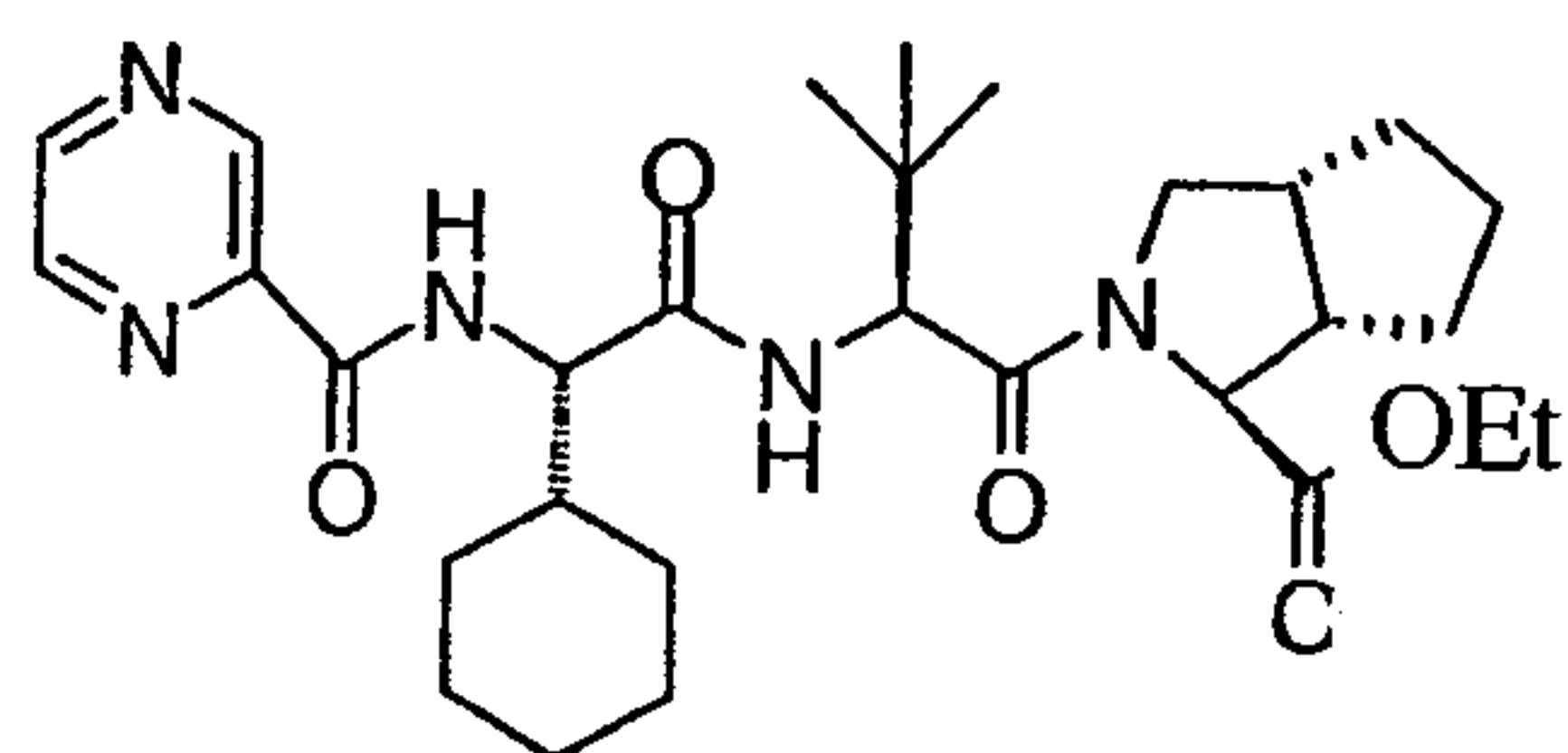
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lxxxix

Intermediate Example 78 – Compound lxxxii

A dichloromethane solution (10 mL) of compound lxxxix (2.56 mmol) is treated with HOAt (348 mg, 2.56 mmol) and DCC (2.56 mL, 1M, 2.56 mmol). After stirring for 30 minutes, the reaction mixture is treated with a THF solution (5 mL) of compound v (2.56 mmol). After stirring at about room temperature overnight, the white solids (urea) are removed by filtration. The filtrates are concentrated *in vacuo* to give a residue that is purified by silica gel chromatography to provide 1.4 g (100%) of the compound lxxxii,

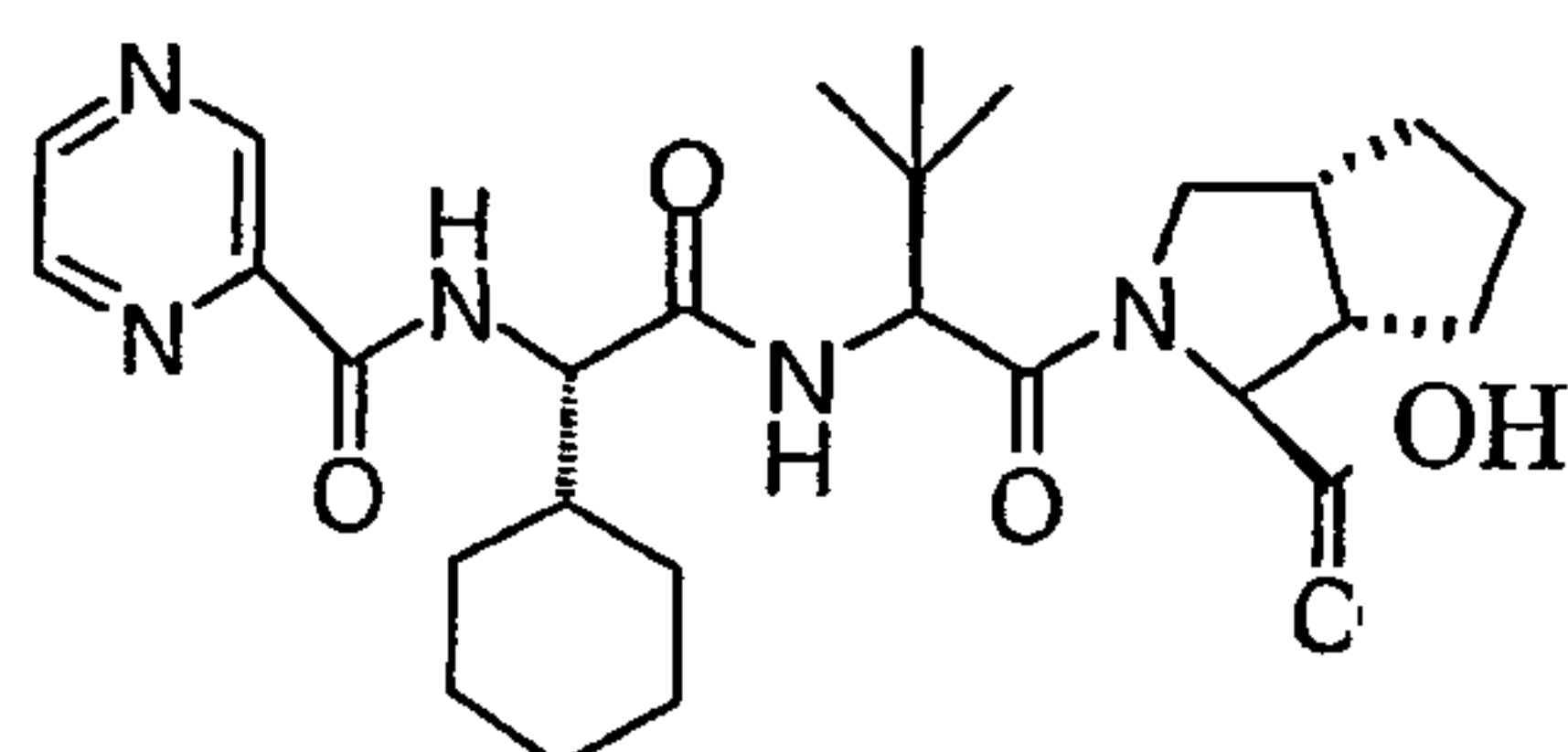


lxxxii

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Intermediate Example 79 – Compound lxxxiii

An ethanol solution (15 mL) of compound lxxxii (1.4 g, 2.58 mmol) is treated with 2 N NaOH (2.58 mL, 5.17 mmol). After stirring at about room temperature overnight, the reaction mixture is acidified to pH 3 with acidic resin. The solids are filtered off. The resulting filtrates are concentrated *in vacuo* to give a residue that is lyophilized to give 1.32 g (~100%) of compound lxxxiii,



lxxxiii

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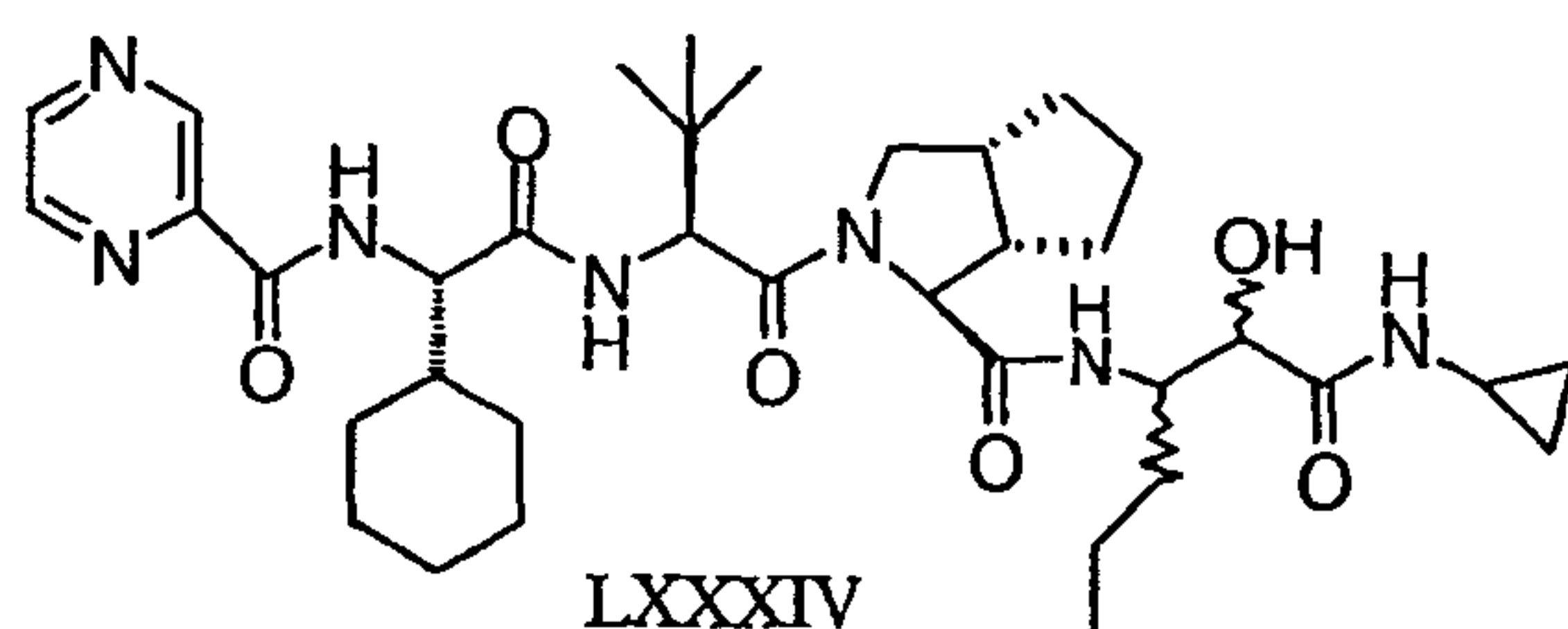
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Intermediate Example 80 – Compound lxxxiv

A dichloromethane solution (15 mL) of compound lxxxiii (360 mg, 0.7 mmol) is treated with PyBOP (582 mg, 1.12 mmol). After stirring at about room temperature for 20 minutes, the reaction mixture is treated with a THF solution (10 mL) of compound xiii (195.6 mg, 1.05 mmol), followed by DIPEA (0.25 mL, 1.40 mmol). After stirring overnight at about room temperature, the reaction is quenched with water and extracted with EtOAc. The resulting organic layer is washed with brine and dried and concentrated *in vacuo* to give a residue that is purified by silica gel chromatography (3% EtOH/EtOAc) to afford 420 mg (88%) of compound lxxxiv,

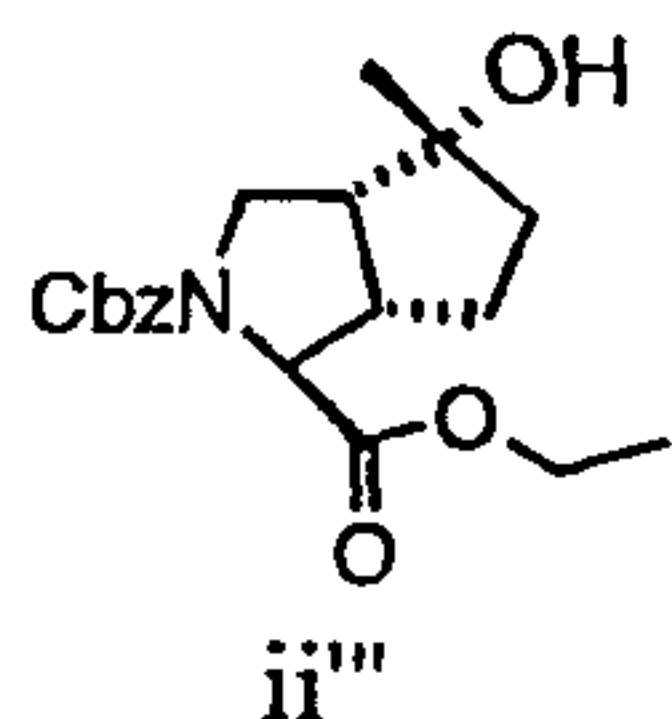


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Intermediate Example 81 – Compound ii'''

A mixture of anhydrous dichloromethane and ether (20 mL:20 mL) is cooled to -78°C under N_2 (g). To the solution is added TiCl_4 (1 M in dichloromethane, 10 mL, 10 mmol) and then MeLi (1.4 M in ether, 7.1 mL, 10 mmol) is added subsequently with stirring for another 30 minutes at -78°C . A solution of compound i (2 g, 6 mmol) in 10 mL dichloromethane is added to the mixture dropwise at the same temperature over 15 minutes. The solution is slowly warmed up to -40°C for 10 minutes and then stirred at 0°C for 2 hours. The reaction is quenched by pouring the mixture into a water/ether mixture (1:1) and then the layers are allowed to separate. The aqueous layer is further extracted by ether twice. All organic layers is washed by water, brine and dried over MgSO_4 before being concentrated to a yellow oil. The desired compound ii''' is isolated by silica gel chromatography (EtOAc/Hexanes 2/1) in 83%

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Intermediate Example 82 – Compound lxi'

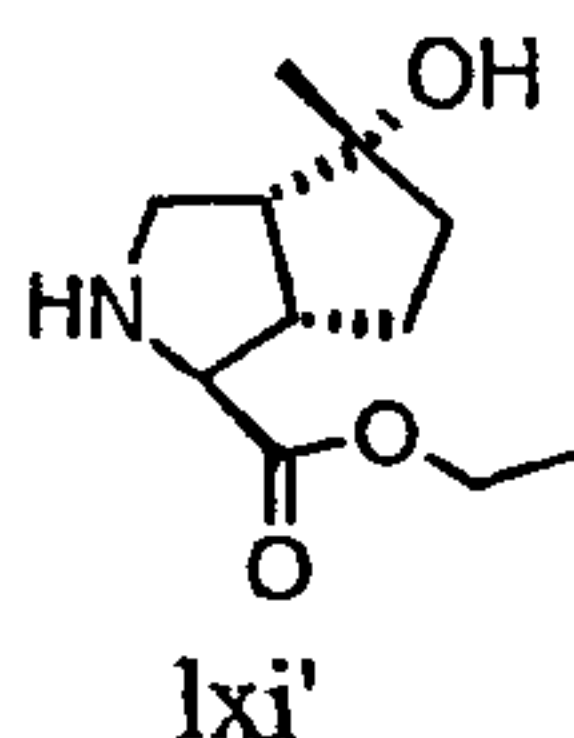
To the compound ii''' (1.7 g, 5 mmol) is added to 10 wt %Pd on C (0.53 g, 0.5 mmol), followed by addition of MeOH (17 mL). Hydrogen gas is flushed through the reaction mixture and hydrogen gas is maintained for reaction at 1 atm overnight. The reaction mixture is then filtered and concentrated to afford 929 mg (87%) of compound lxi' as a colorless oil.

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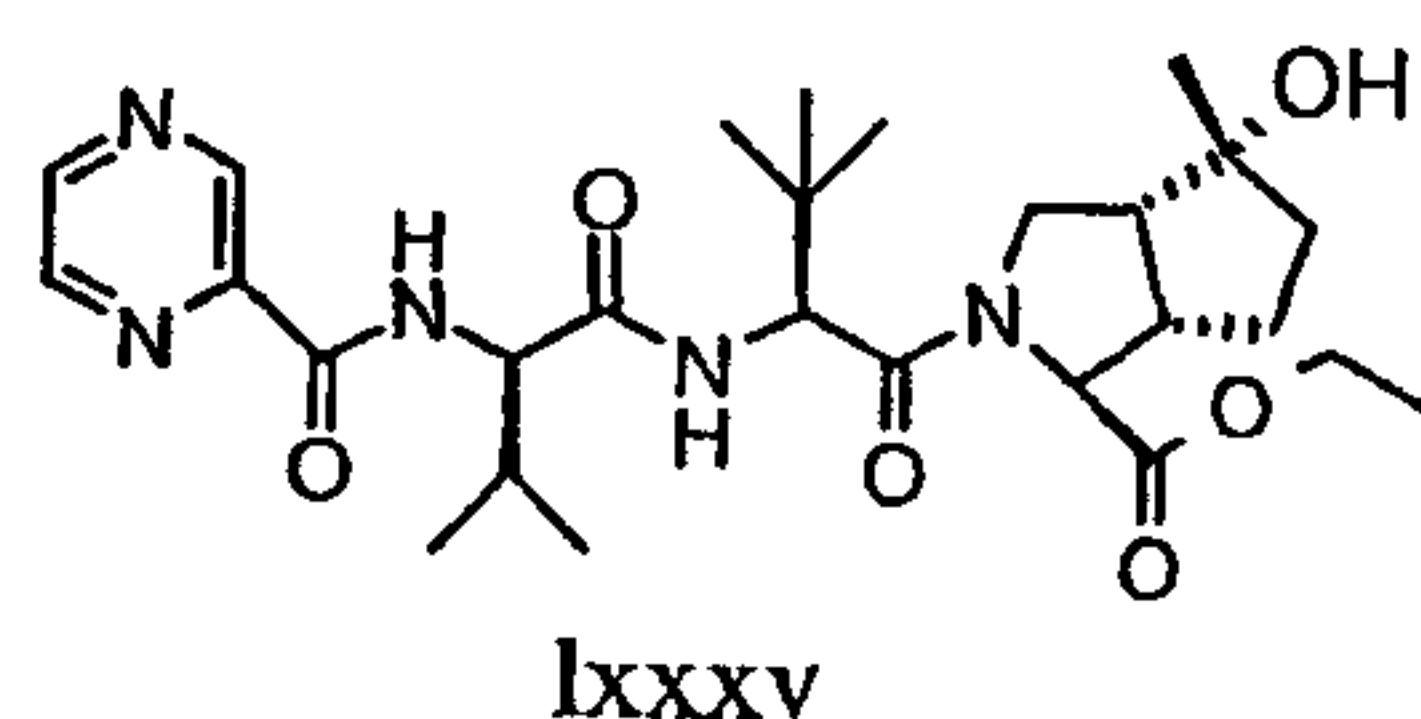
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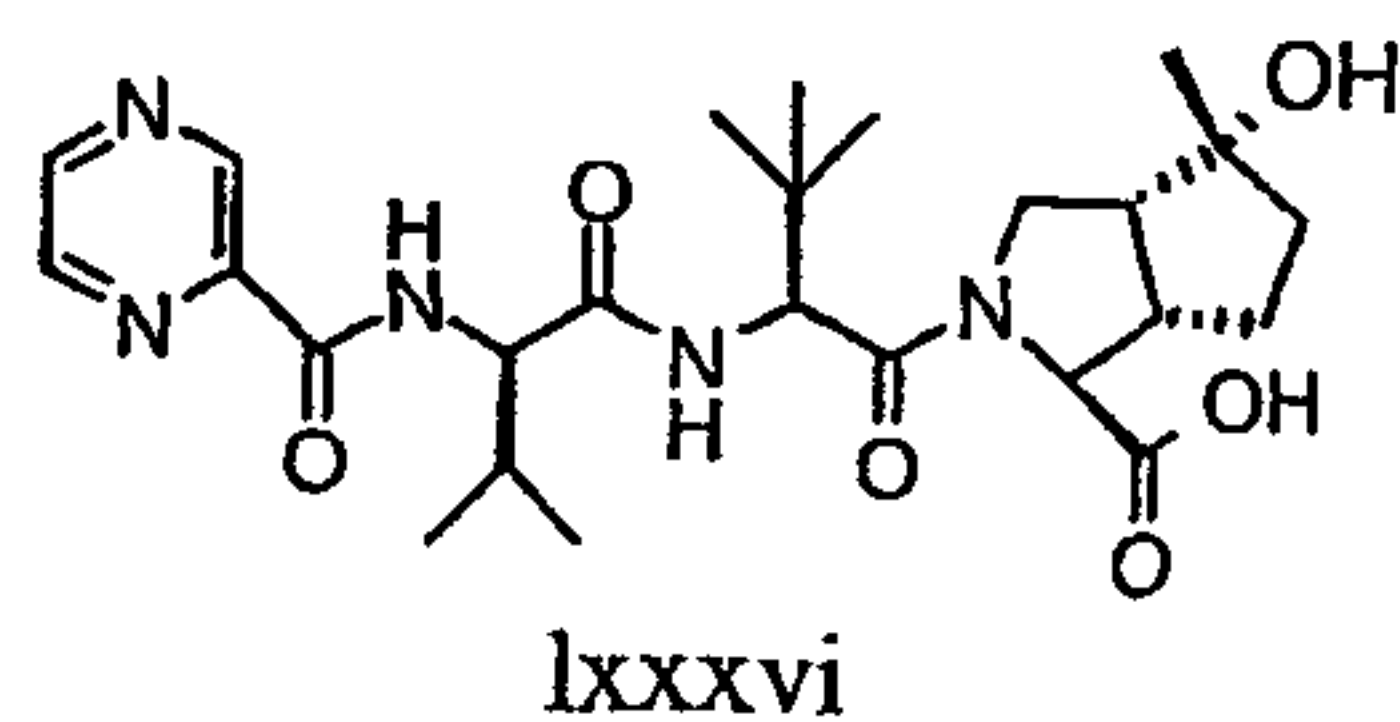
Intermediate Example 83 – Compound lxxxv

To a THF solution (16 mL) of compound xxii (1 g, 3 mmol) is added at about room temperature HOAt (0.41 g, 3 mmol) and followed by 1 M DCC solution of dichloromethane (3 mL, 3 mmol). After stirring for 30 minutes at about room temperature, a dichloromethane solution (6 mL) of compound lxi' is added to the above HOAt-activated acid. The reaction is stirred at about room temperature overnight. At this point, the reaction is filtered through Celite. The filtrate is diluted with EtOAc (120 mL) and washed with water and then brine. The organic layer is dried and concentrated to an yellow oil which is purified by silica gel chromatography (100% EtOAc) to yield 1 g (65%) of compound lxxxv,



Intermediate Example 84 – Compound lxxxvi

To an ethanol solution (8 mL) of compound lxxxv (920 mg, 1.7 mmol) is added 2 N NaOH aqueous solution (1.7 mL, 3.4 mmol). The reaction is stirred overnight at about room temperature and then acidified to pH 3 by Dowes acidic resin. The solids are filtered off and the filtrate is concentrated to give a colorless oil, which is redissolved in 1:1 CH₃CN/H₂O and lyophilized to provide 800 mg (93%) of compound lxxxvi. HPLC shows a single product peak.



Intermediate Example 85 – Compound lxxxvii

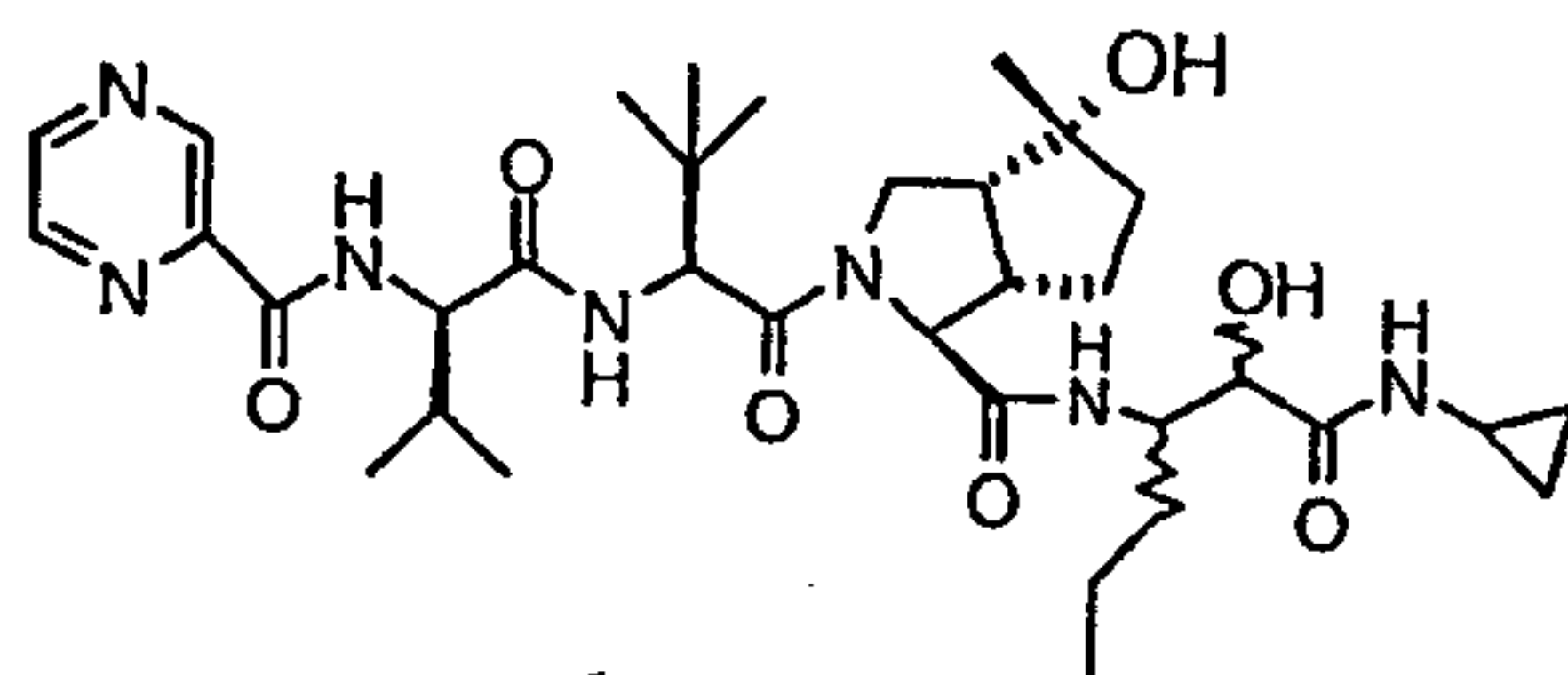
To a dichloromethane solution (4 mL) of compound lxxxvi (150 mg, 0.3 mmol) is added by PyBOP (250 mg, 0.47 mmol). The solution is stirred at about room temperature for 30 minutes. To this solution is then added a THF (4.5 mL) solution of compound xiii (84 mg, 0.45 mmol) followed by Et₃N (0.1 mL, 0.6 mmol). The reaction is stirred at about room

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temperature overnight and then quenched with water (25 mL) for 30 minutes. The mixture is then extracted with EtOAc. The resulting organic layer is washed with brine and dried over MgSO_4 , before being concentrated to a yellow oil. Purification by silica gel chromatography (5% EtOH/EtOAc) yields 200 mg (100%) of compound lxxxvii,

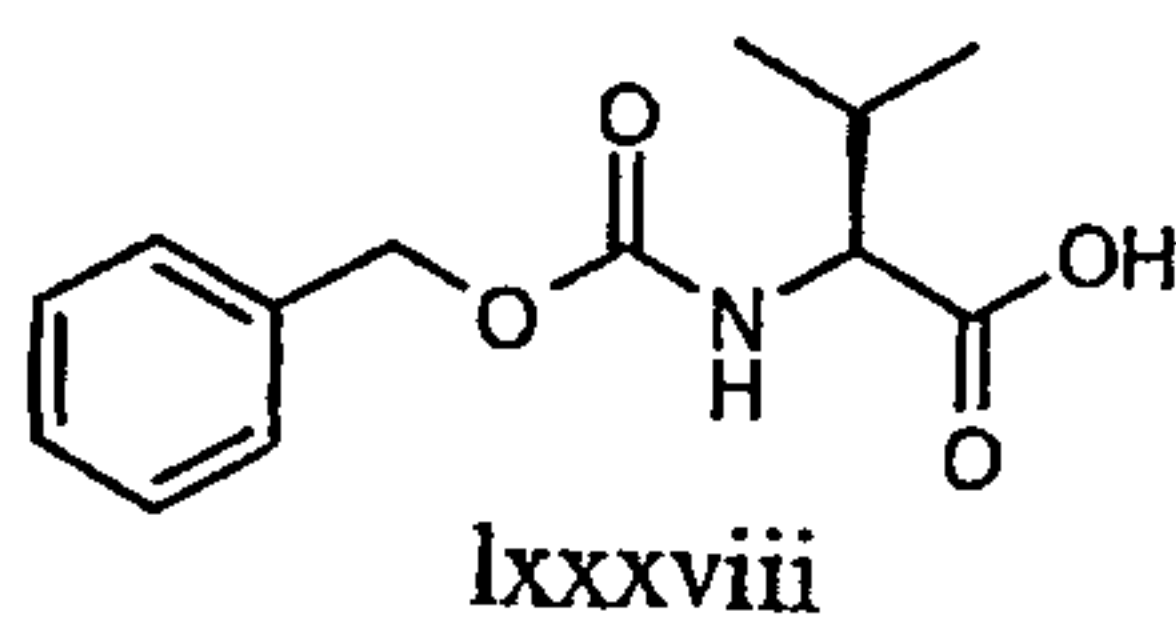


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lxxxvii

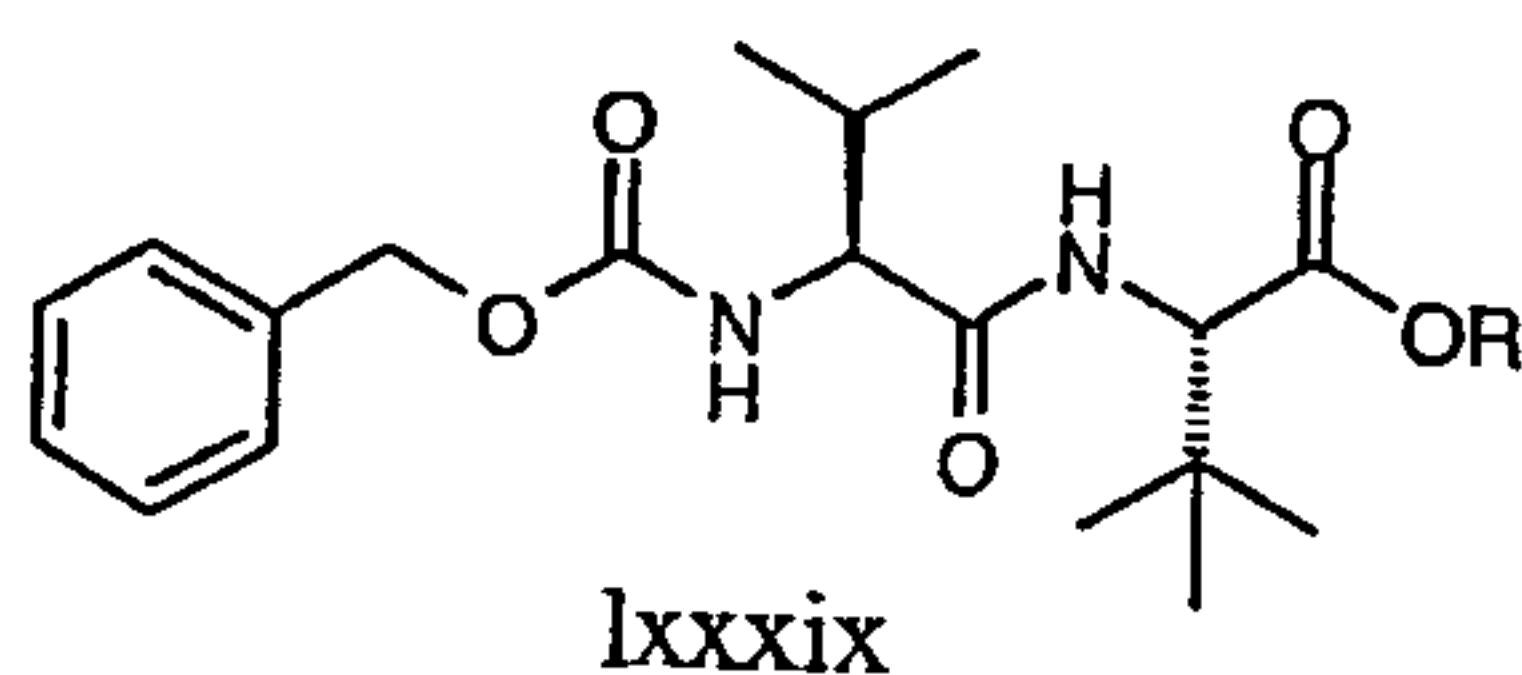
Intermediate Example 86 – Compound lxxxix

Compound lxxxviii, N-Cbz-L-Valine, (2.5 g, 9.9 mmol) is taken up in THF (30mL).



lxxxviii

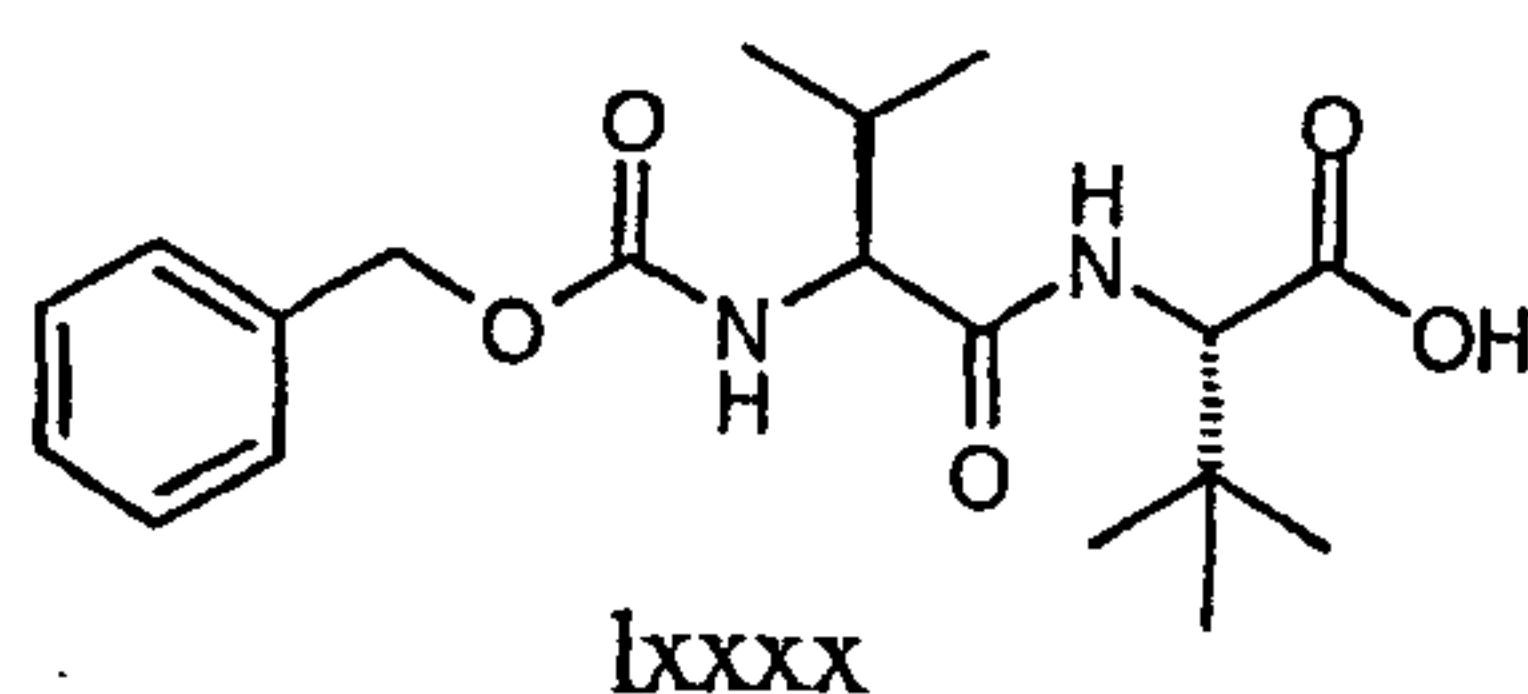
- EDCI (2.29 g, 11.9 mmol) and HOBT (1.62 g, 11.9 mmol) are added and the mixture stirred five minutes. *L-tert*-Leucine methyl ester hydrochloride (2.17 g, 11.9 mmol) is added in THF (23.9 mL) followed by DIPEA (2.1mL). The reaction mixture is stirred overnight under nitrogen. The reaction mixture is diluted with ethyl acetate, washed with 1 N HCl, saturated sodium bicarbonate, and brine. The organic phase is dried over sodium sulfate, filtered and concentrated. The concentrate residue is purified in 25% ethyl acetate/hexane to afford 1.1 g (29%) of compound lxxxix,



lxxxix

Intermediate Example 87 – Compound lxxxx

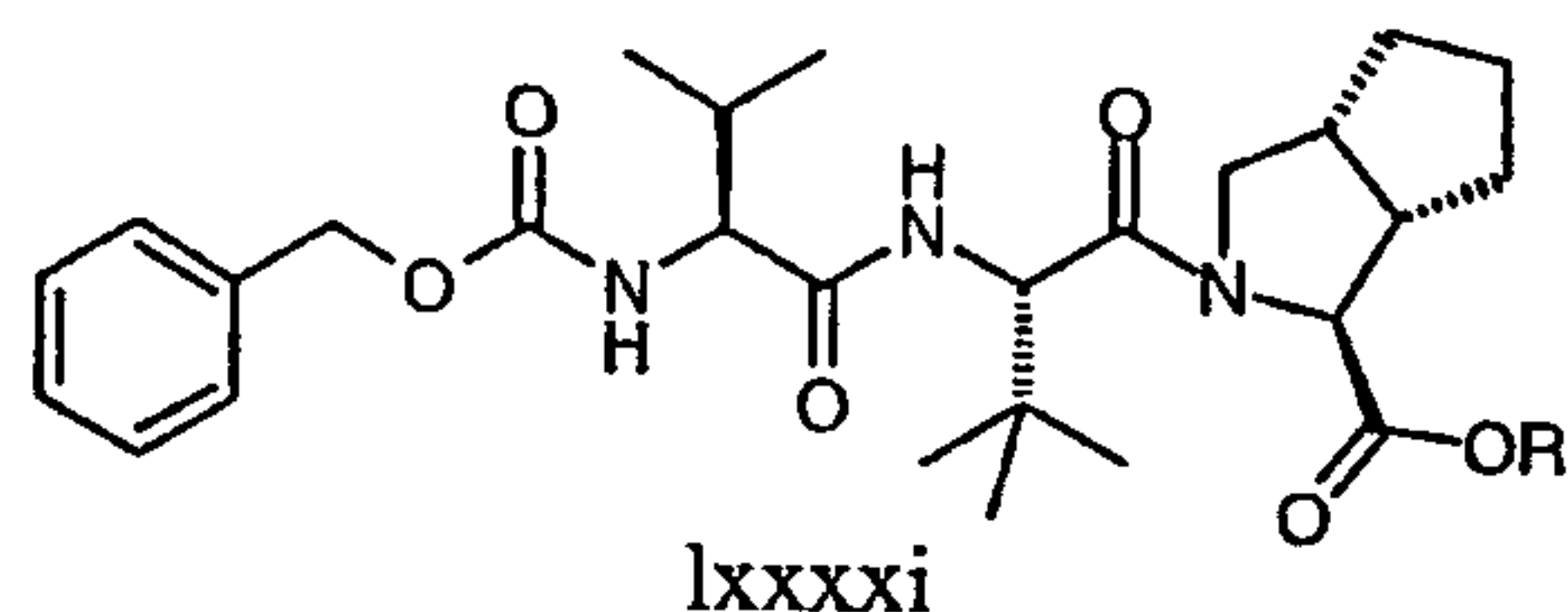
- Compound lxxxix is hydrolyzed under standard conditions using methyl alcohol (0.3 M) and 1 N NaOH (1.5 eq) to afford 1.03 g (95%) of compound lxxxx,



lxxxx

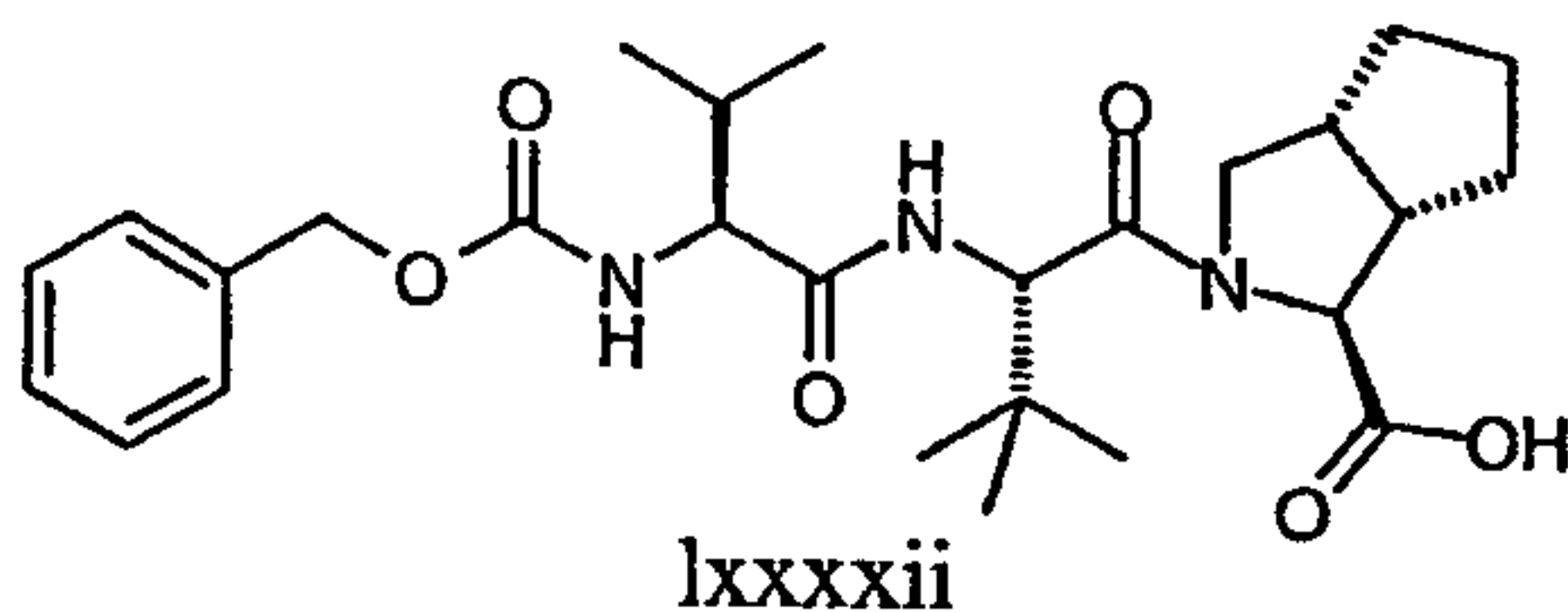
Intermediate Example 88 – Compound lxxxxi

Compound lxxxx (385mg, 1.06 mmol) is taken up in dichloromethane (3mL). DCC (1.4 mmol) is added followed by HOAt (190 mg, 1.4mmol). Compound v (260 mg, 1.4 mmol) is then added in dichloromethane (3 mL). The resulting mixture is stirred overnight under nitrogen. The reaction is diluted with ethyl acetate, filtered through silica gel, and concentrated. The residue is purified in 50% ethyl acetate / hexane to afford 440 mg (80%) of compound lxxxxi,



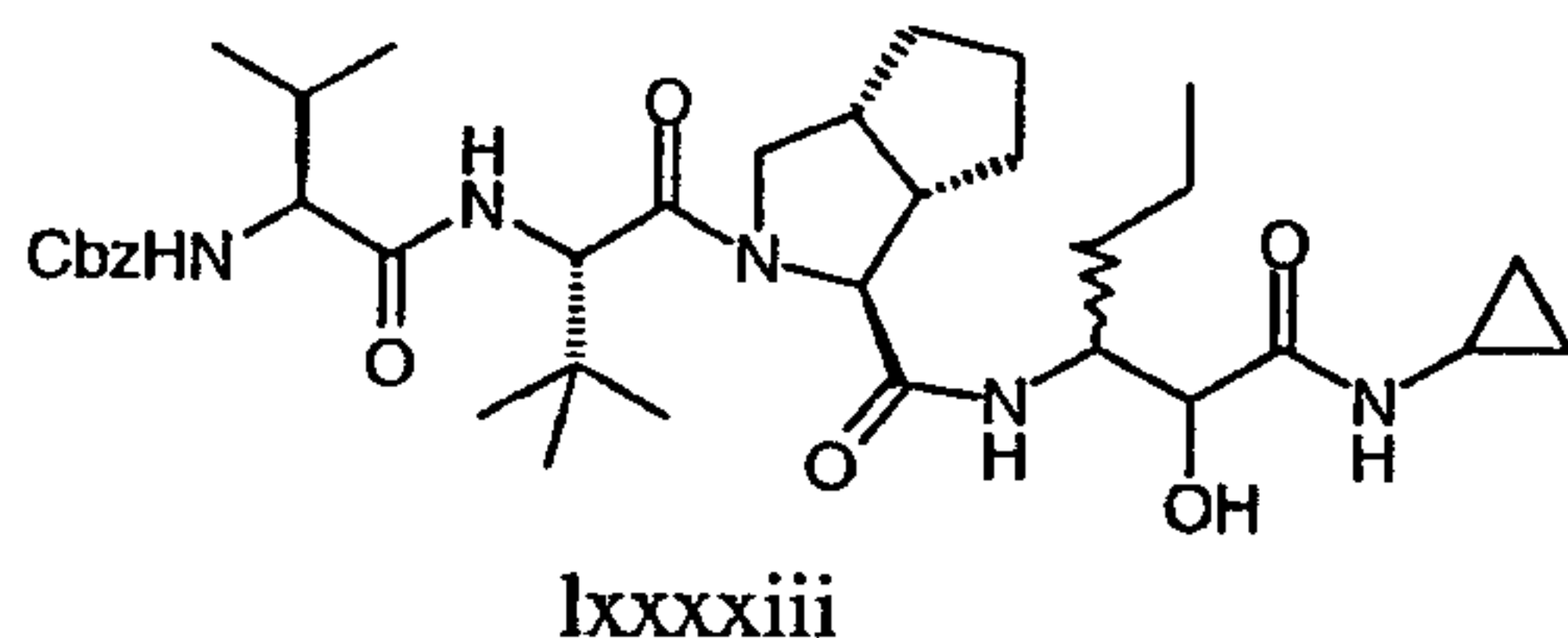
Intermediate Example 89 – Compound lxxxxii

Compound lxxxxi is hydrolyzed under standard conditions using ethyl alcohol (0.3 M) and 1 N NaOH (1.5eq) to afford 390 mg of compound lxxxx.ii,



Intermediate Example 90 – Compound lxxxxiii

Compound lxxxxii (350 mg, 0.7 mmol) is taken up in dichloromethane (3mL). PyBOP (480 mg, 0.91 mmol) is added followed by compound xiii (170 mg, 0.91 mmol). DIPEA (0.16 mL, 0.91mmol) is added and reaction mixture stirred overnight. The reaction mixture is concentrated and purified in 100% ethyl acetate to afford 420 mg (90%) of compound lxxxxiii,



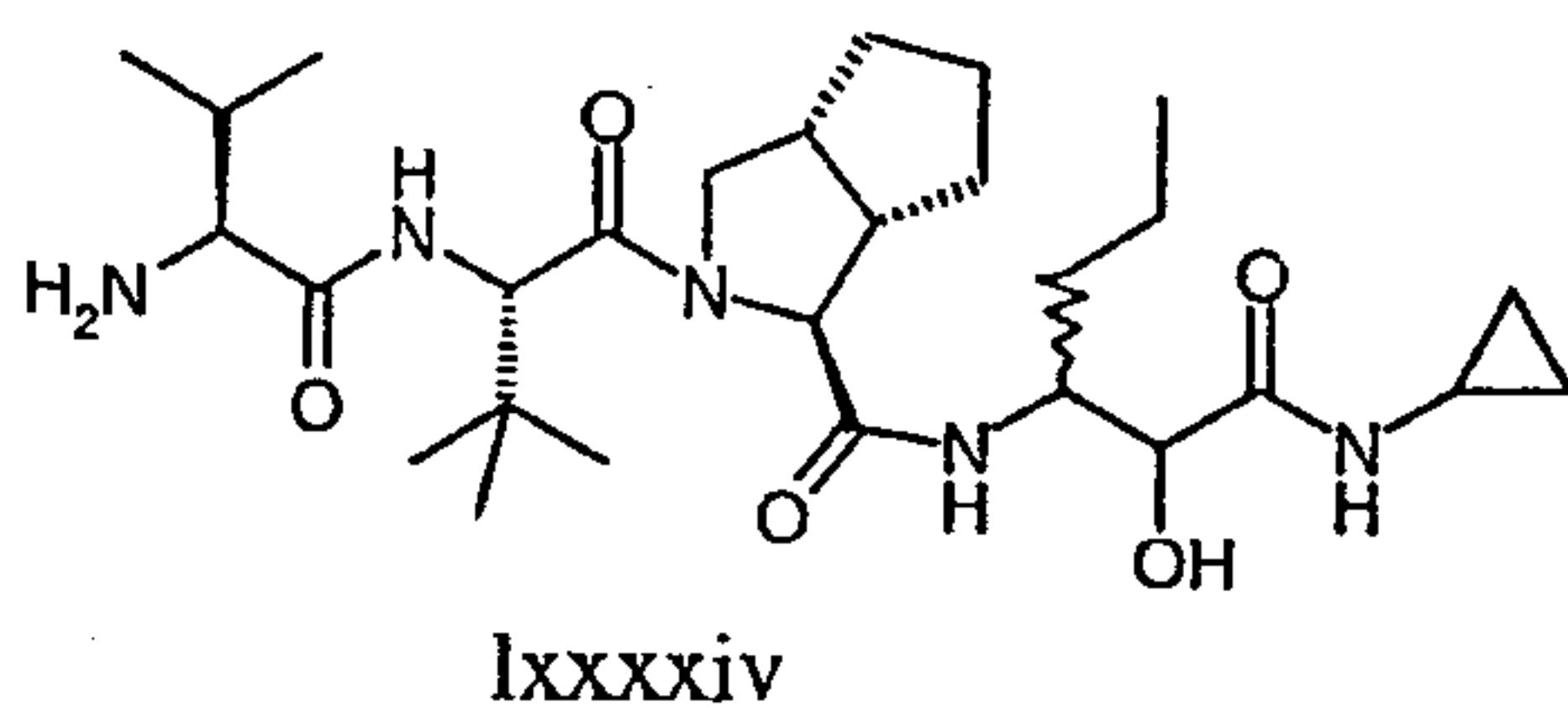
Intermediate Example 91 – Compound lxxxxiv

Compound lxxxxiii is hydrogenated using 10% Pd/C (1% mol) in methyl alcohol under hydrogen to afford 335 mg (100%) of compound lxxxxiv,

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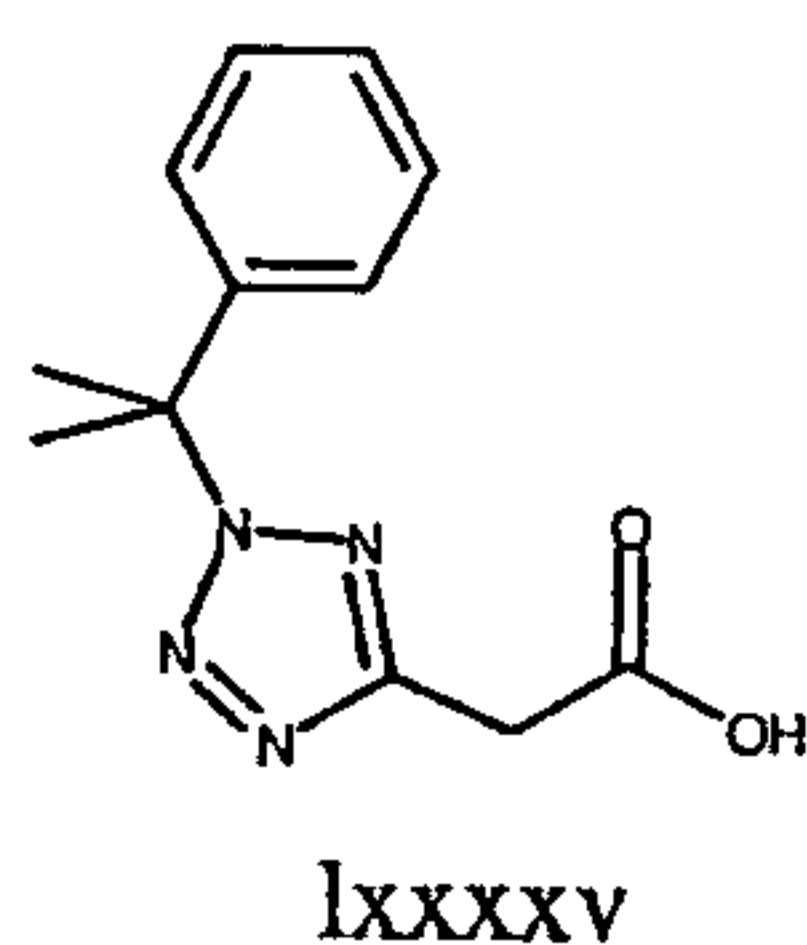
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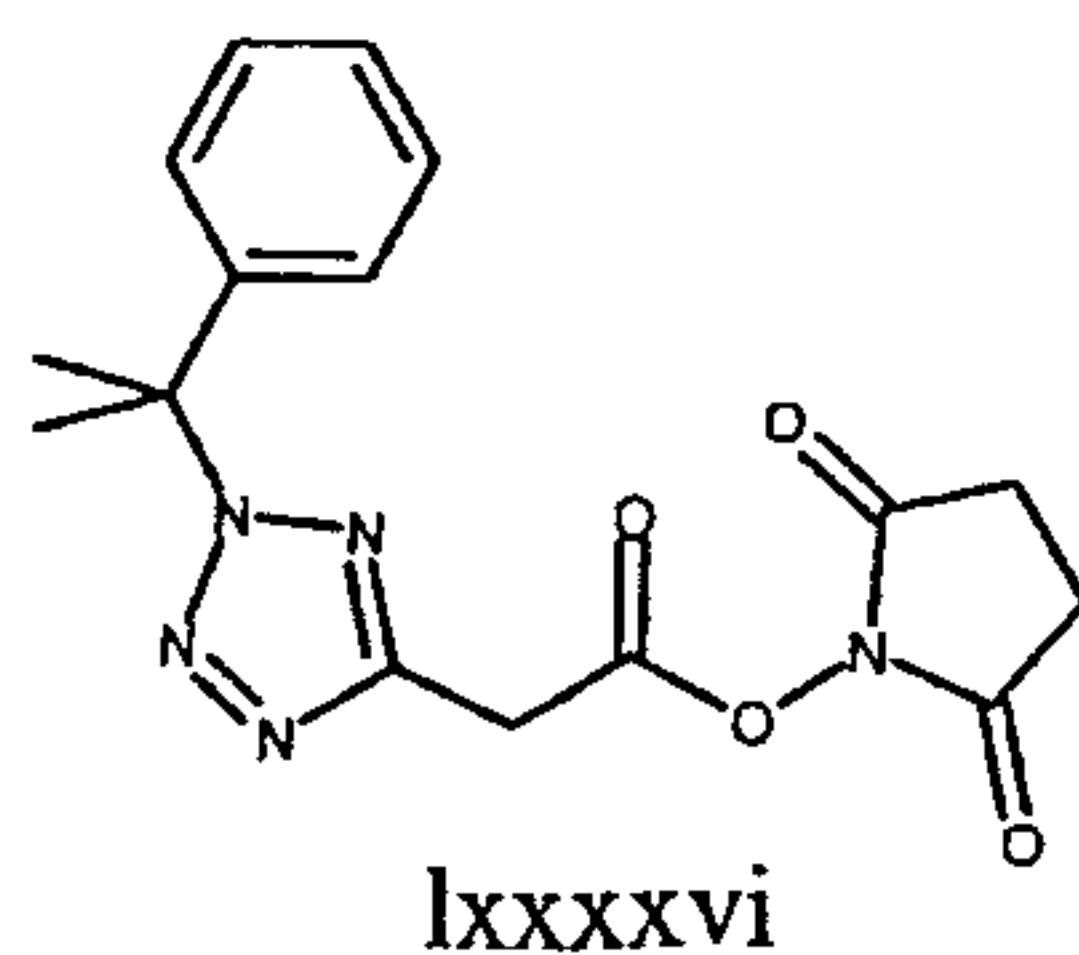
Intermediate Example 92 – Compound lxxxxv

- 5 Ethyl 1H-tetrazole-5-acetate (5 g, 32 mmol) is taken up in chloroform (80 mL). Trichloroacetic acid (12.03 g, 73.65 mmol) is added followed by alpha methyl styrene (3.78 g, 32 mmol). The reaction mixture is stirred overnight. The next day, the solution is diluted with ethyl acetate, washed with 10% KOH and brine. The organic phase is dried over magnesium sulfate, filtered and concentrated to afford 8 g (96%) of the corresponding
- 10 N-protected ethyl tetrazole-5-acetate. This material is subjected to standard hydrolysis conditions using ethyl alcohol (0.3 M) and 1 N NaOH (3 eq) to afford 7 g (99%) of compound lxxxxv,



Intermediate Example 93 – Compound lxxxxvi

- 15 Compound lxxxxv (3.62 g, 14.7 mmol) is taken up in dichloromethane (50 mL). EDCI (4.32 g, 22.1 mmol) and DIPEA (5.1 mL, 29.4 mmol) are added and stirred for five minutes. N-hydroxy succinimide (3.38 g, 29.4 mmol) is added and stirred three hours. The reaction is diluted with dichloromethane and washed with water three times. The organic phase is dried over sodium sulfate, filtered and concentrated to afford 3.66 g (73%) of compound lxxxxvi,



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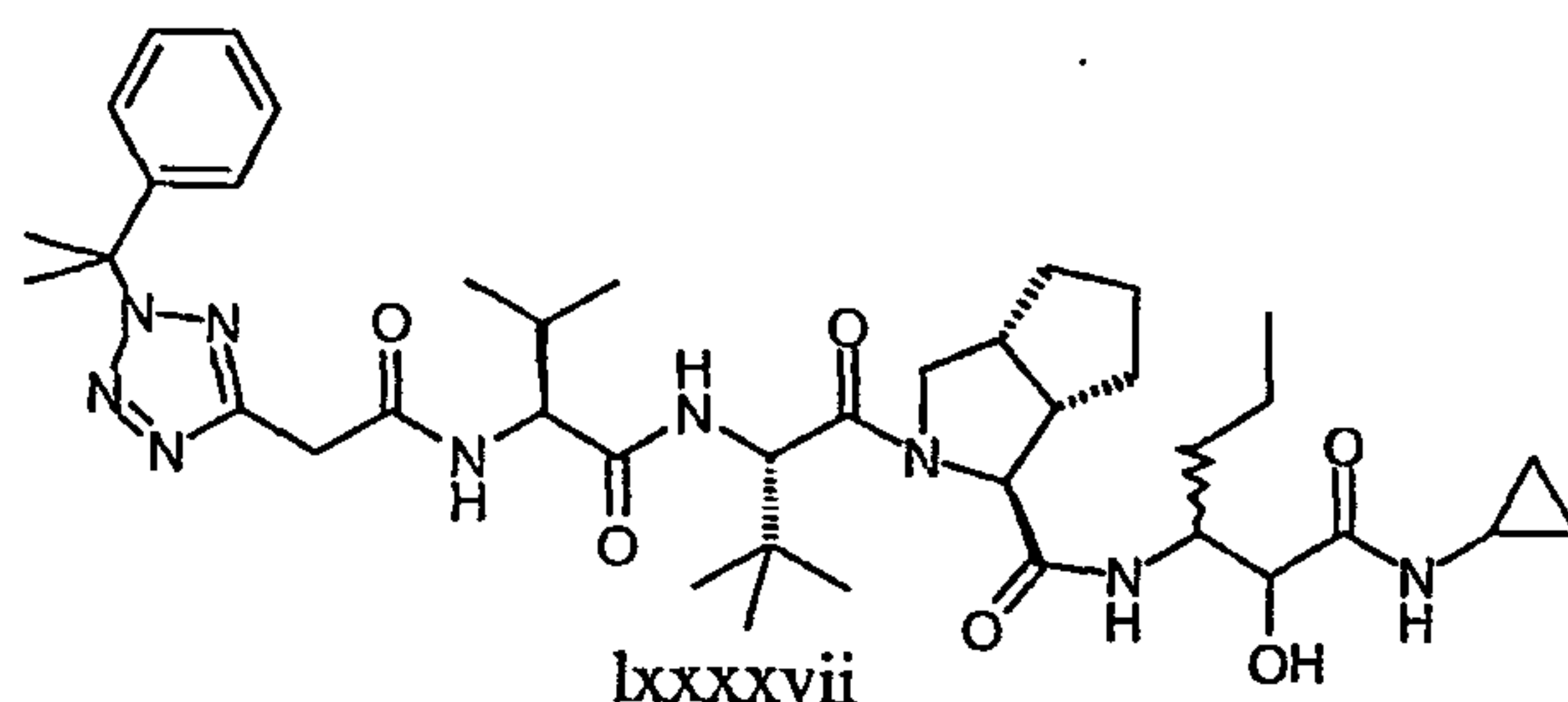
Intermediate Example 94 – Compound lxxxxvii

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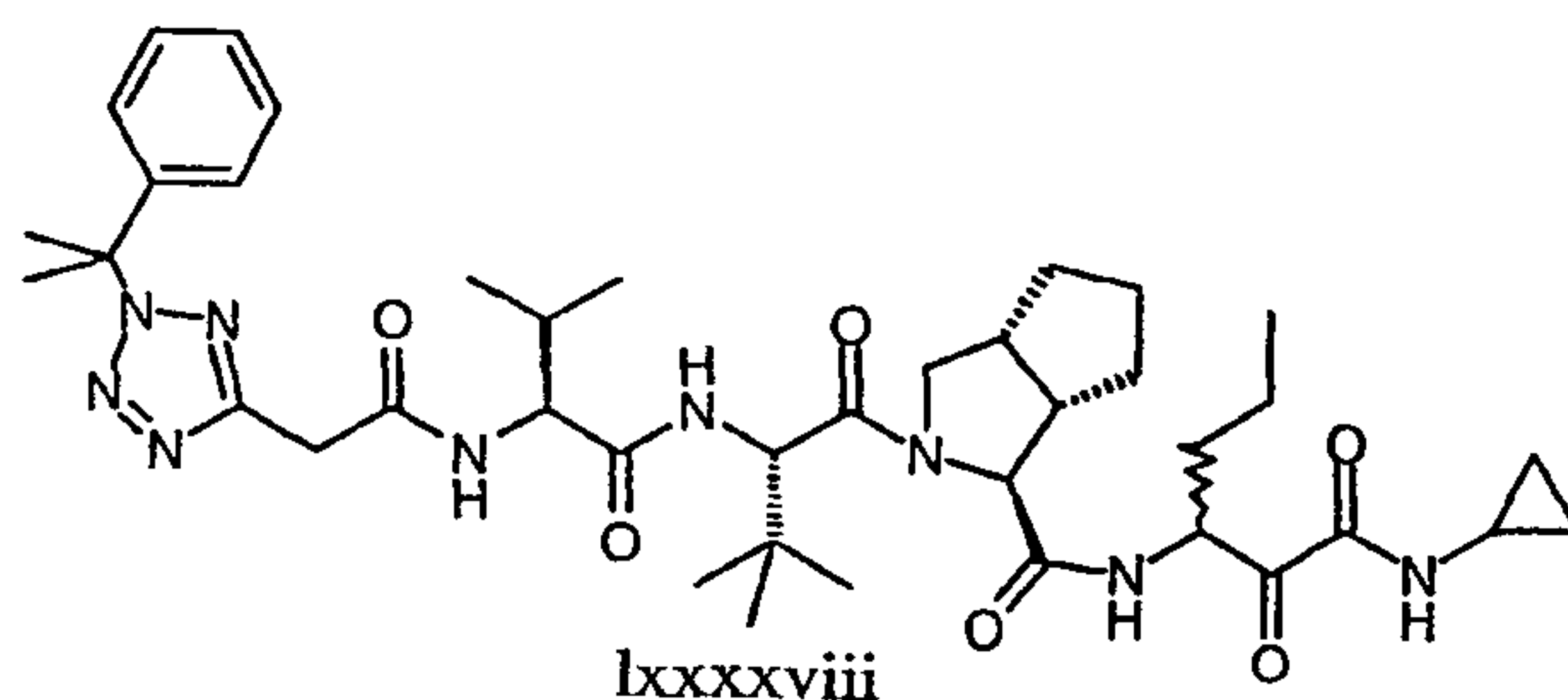
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Compound lxxxxiv (335 mg, 0.62 mmol) and compound lxxxxvi (343 mg, 1 mmol) are taken up in dichloromethane (6 mL). DIPEA (0.17 mL, 1 mmol) is added and reaction mixture stirred overnight. The reaction is diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine and concentrated. The residue is purified in 5% ethyl alcohol / ethyl acetate to give 80 mg (16%) of compound lxxxxvii,



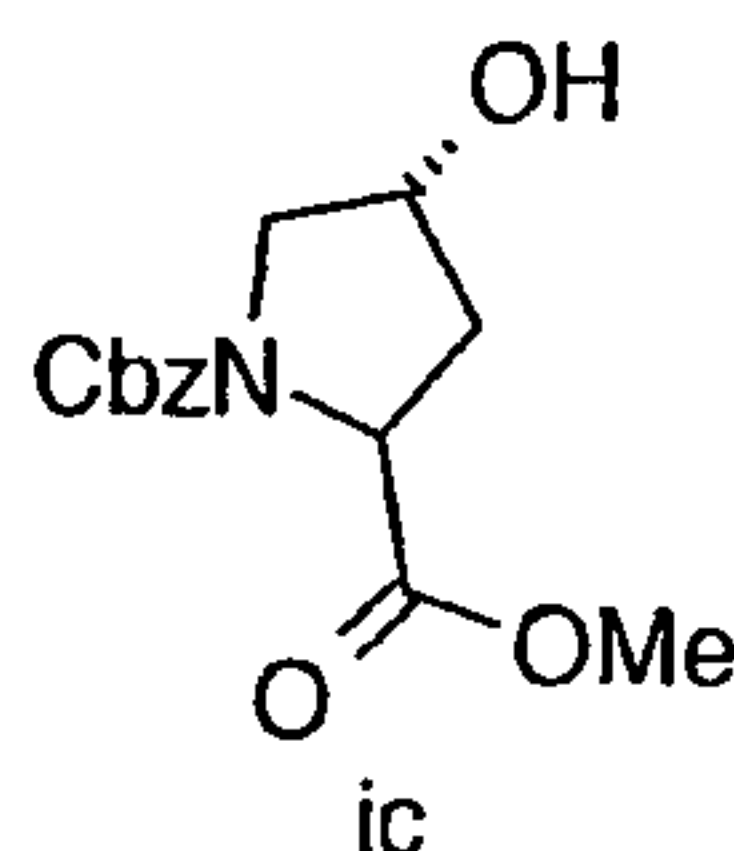
Intermediate Example 95 – Compound lxxxxviii

Compound lxxxxvii (80 mg, 0.11 mmol) is taken up in dichloromethane (3 mL). DMP reagent reagent (55 mg, 0.13 mmol) is added and stirred for one hour. The reaction mixture is diluted with ethyl acetate and quenched with 10% solution of sodium sulfite. The organic phase is washed with saturated sodium bicarbonate and brine. The organic phase is concentrated and the resulting residue is purified in 100% ethyl acetate to afford 40 mg (48%) of compound lxxxxviii,



Intermediate Example 96 – Compound xxxix

Compound ic, N-Cbz-4-Hydroxy Pro methyl ester, (2.1 g, 7.9 mmol) is prepared in

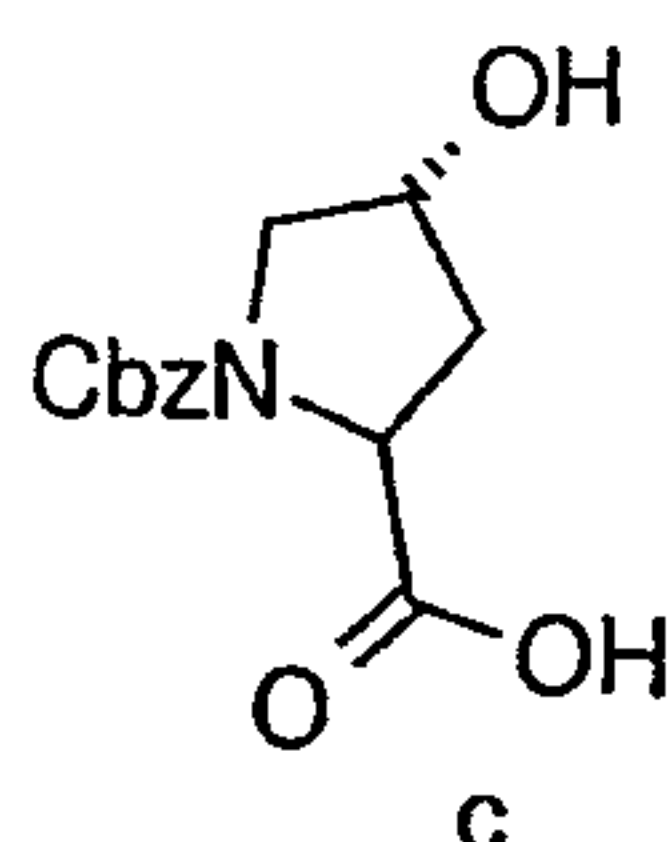


quantitative yield from compound c, N-Cbz-4-hydroxy Pro), is dissolved in DCM (25

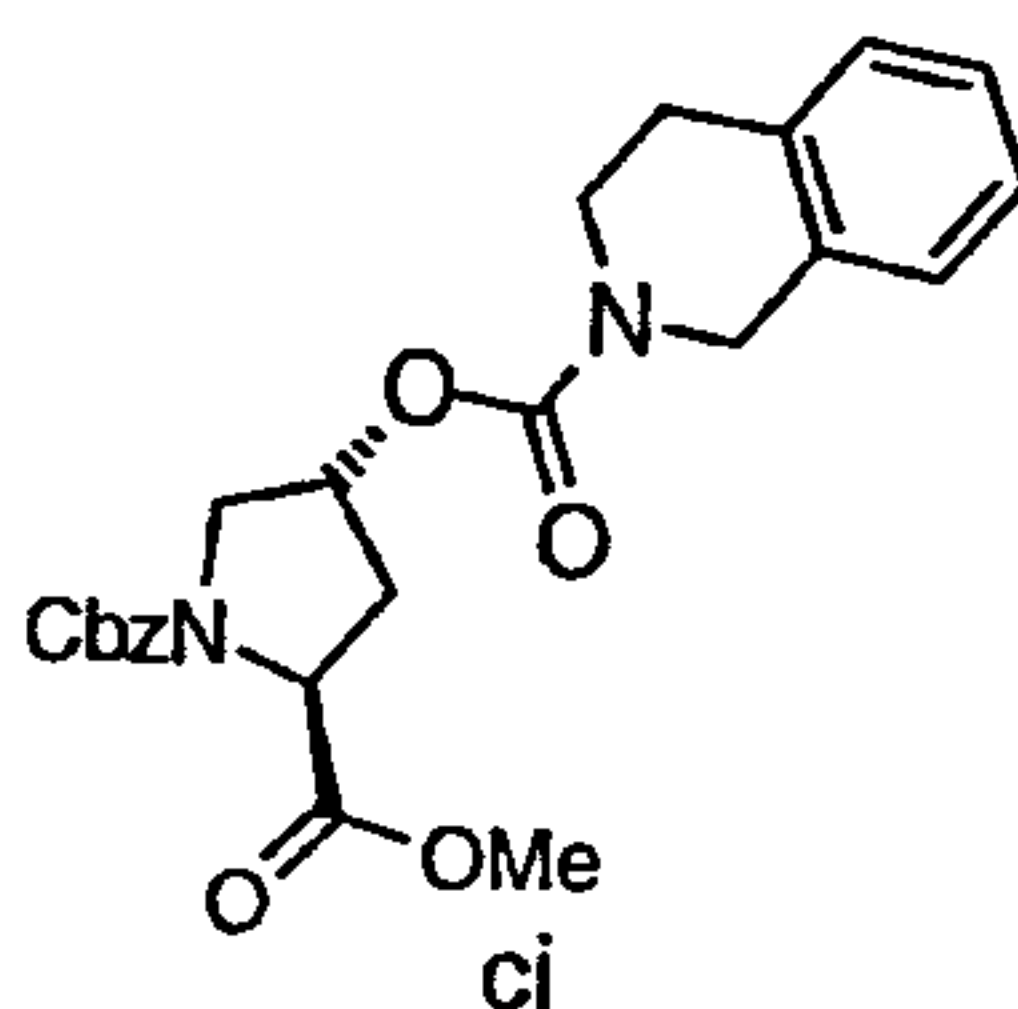
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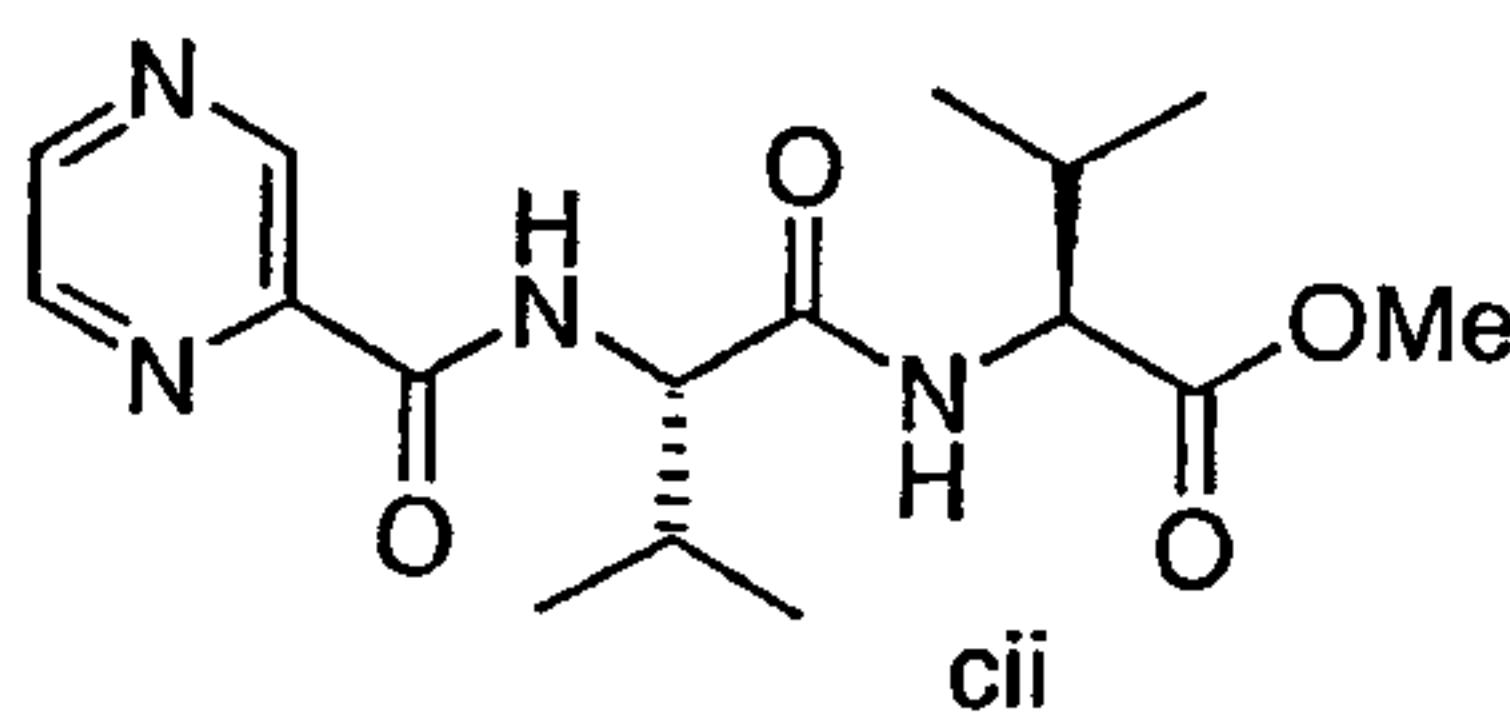
mL). CDI (1.54 g, 9.5 mmol) and DIPEA (1.7 mL, 9.5 mmol) are added to the solution and stirred for 10 minutes. 1,2,3,4-Tetrahydroisoquinoline (TIQ) (1.2 mL, 9.5 mmol) is added dropwise to the reaction mixture and stirred five hours. The organic phase is washed with water, 1 N HCl, and brine. Following the concentration of the organic phase, the resultant residue is chromatographically purified by 40% EtOAc/Hexanes to yield compound ci, N-Cbz-4-TIQ-carboxyloxy-Pro methyl ester, (2.5 g, 75%).



Compound ci (2.5 g, 5.9 mmol) is dissolved in MeOH (75 mL). The solution is flushed with N₂ and Pd/C (10%, 300 mg) is added. The reaction mixture is flushed with H₂ and stirred overnight. The reaction mixture is filtered through Celite and concentrated to yield compound xxxix, 4-(TIQ-carboxyloxy)-Pro, methyl ester, (1.49 g, 83%).

Intermediate Example 97 – Compound vii

Compound cii, N-pyrazin-2-ylcarbonyl-Val-Val methyl ester, (10.9 g, 32.4 mmol) is



dissolved in THF (80 mL), and then aqueous NaOH (48.6 mL, 48.6 mmol) is added. The resulting mixture is stirred 48 hours, and then additional NaOH (16.3 mL, 16.3 mmol) is added and mixture is heated to 40°C for three hours. The pH of the reaction mixture is then lowered to 3, and the aqueous phase extracted with EtOAc and then concentrated to yield crude compound vii, N-pyrazin-2-ylcarbonyl-Val-Val acid (10.6 g, 100%).

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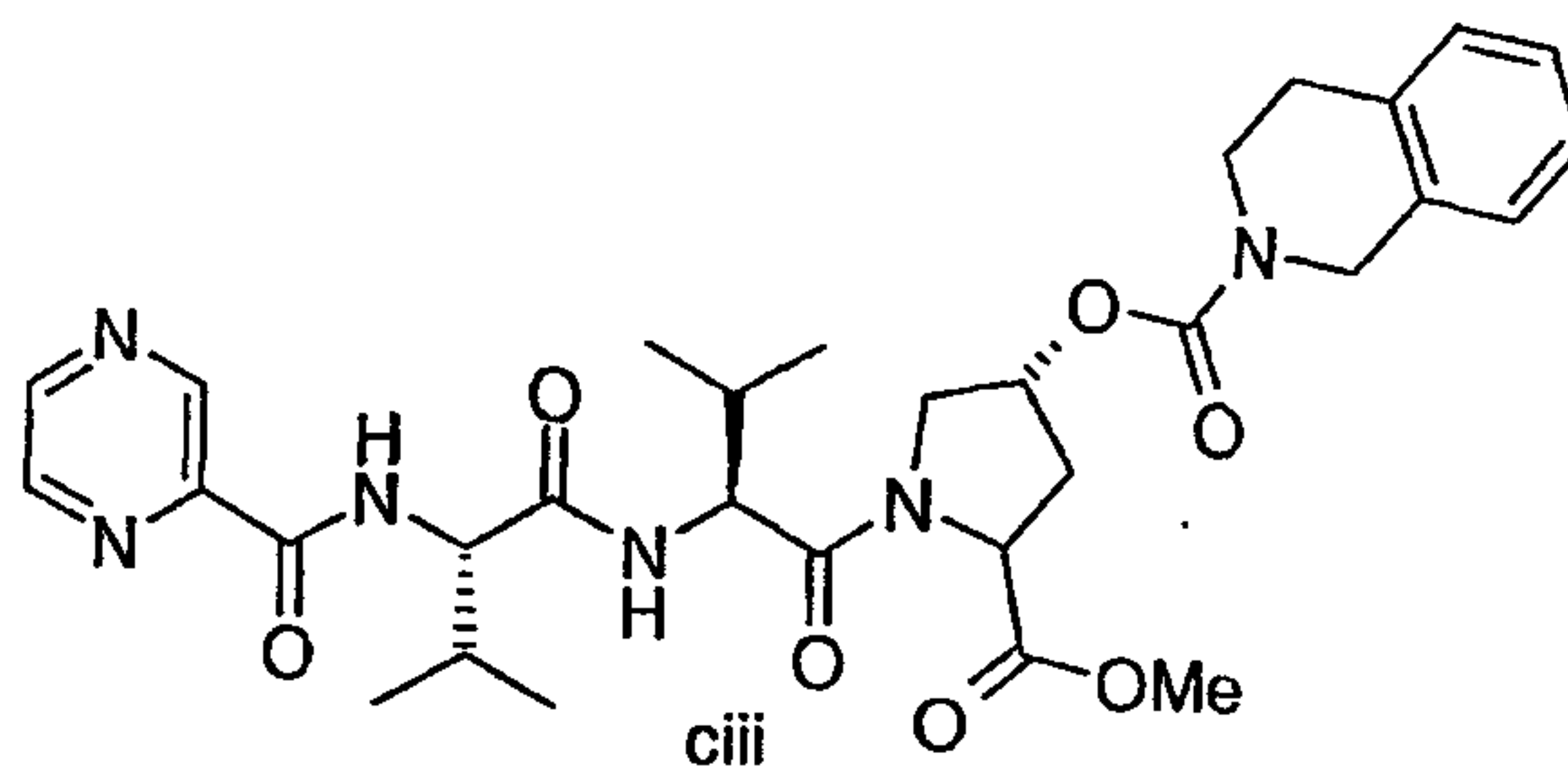
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Intermediate Example 98 – Compound ciii

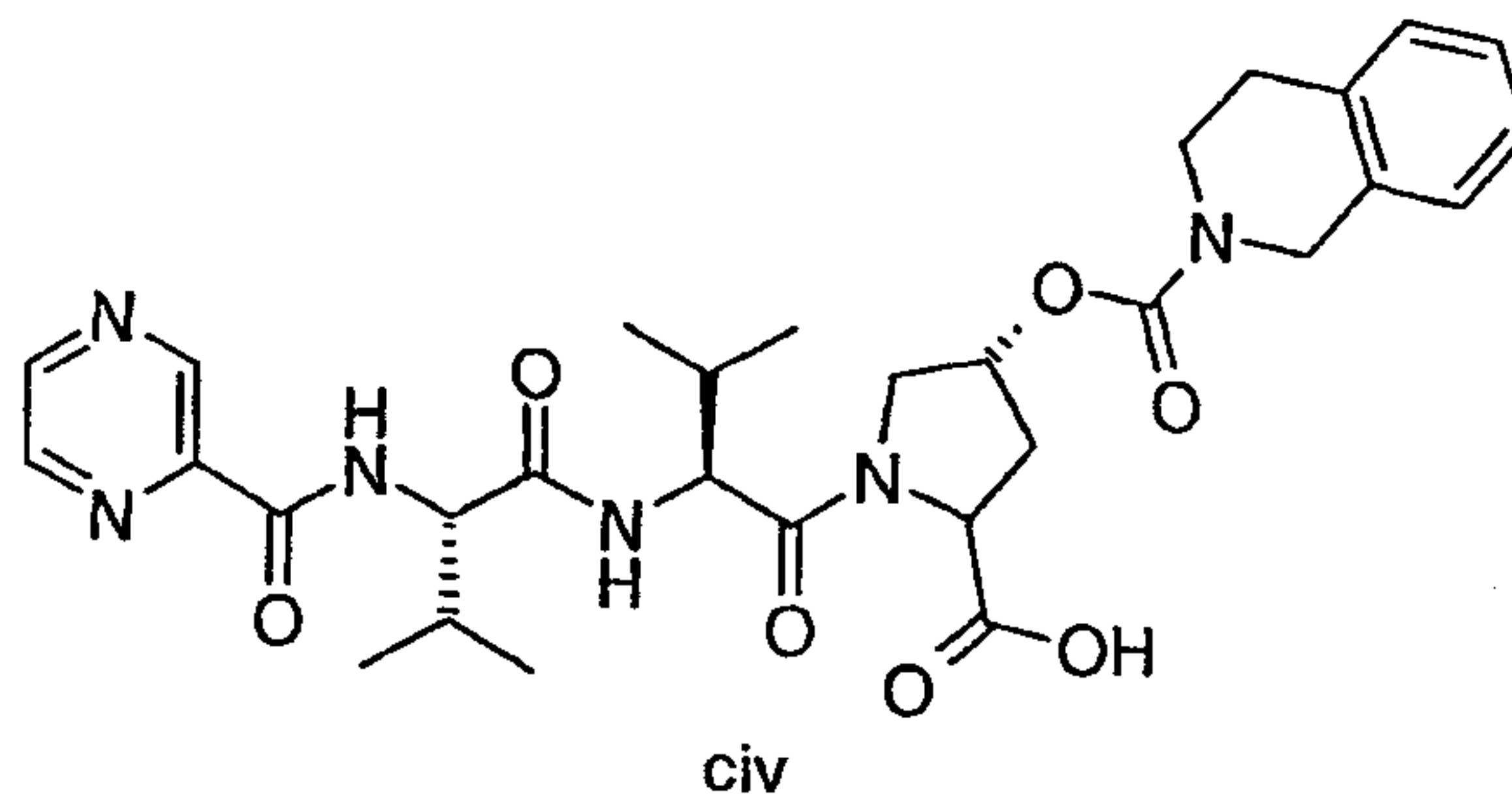
Compound cii (4.1 g, 12.7 mmol) is dissolved in DCM (20 mL). HOAt (1.73 g, 12.7 mmol) and DCC (12.7 mmol) are added to this solution, and the solution stirred for one hour. Compound xxxix (3.22 g, 10.6 mmol) is added to reaction mixture in DCM (10 mL). The resulting mixture is stirred overnight under N₂. The reaction mixture is filtered through silica gel and concentrated. The resulting residue is purified by silica gel chromatography (50% to 80% EtOAc/Hexanes gradient) to yield compound ciii,

N-pyrazin-2-ylcarbonyl-Val-Val-4-(TIQcarbonyloxy)-Pro methyl ester, (5.27 g, 81.7%).



Intermediate Example 99 – Compound civ

Compound ciii (650 mg, 1.29 mmol) is dissolved in THF (5 mL). Aqueous NaOH (1.42 mL, 1.42 mmol) is added to the solution and then stirred overnight. The pH of the solution is lowered to 3, and the organic phase is isolated and concentrated to yield a residue. The residue is purified using reverse phase HPLC in acetonitrile/water to yield compound civ, N-pyrazin-2-ylcarbonyl-Val-Val-4-(TIQcarbonyloxy)-Pro acid, (600 mg, 95%).



Intermediate Example 100 – Compound cv

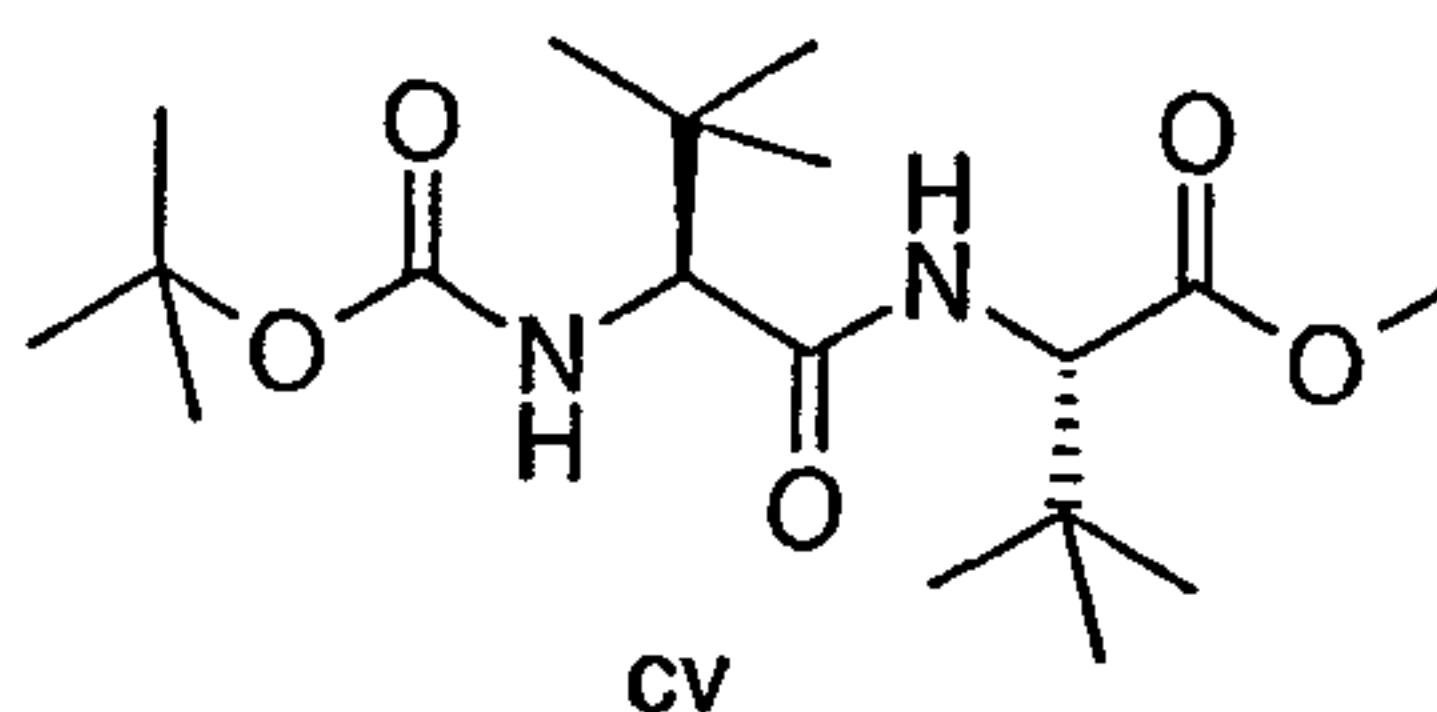
N-Boc-L-*tert*-Leucine (2.3 g, 10 mmol) and L-*tert*-Leucine methyl ester hydrochloride (2 g, 11 mmol) are combined in DMF (30 mL). HOAt (1.6 g, 11.5 mmol) is then added to the solution. The resulting mixture is stirred for 20 minutes under N₂ and then lowered to 0°C whereupon DIC (1.8 mL, 11.5 mmol) and 2,4,6-collidine (1.45 mL, 11 mmol) are added. The resulting solution is stirred overnight with warming to room temperature. The reaction mixture is

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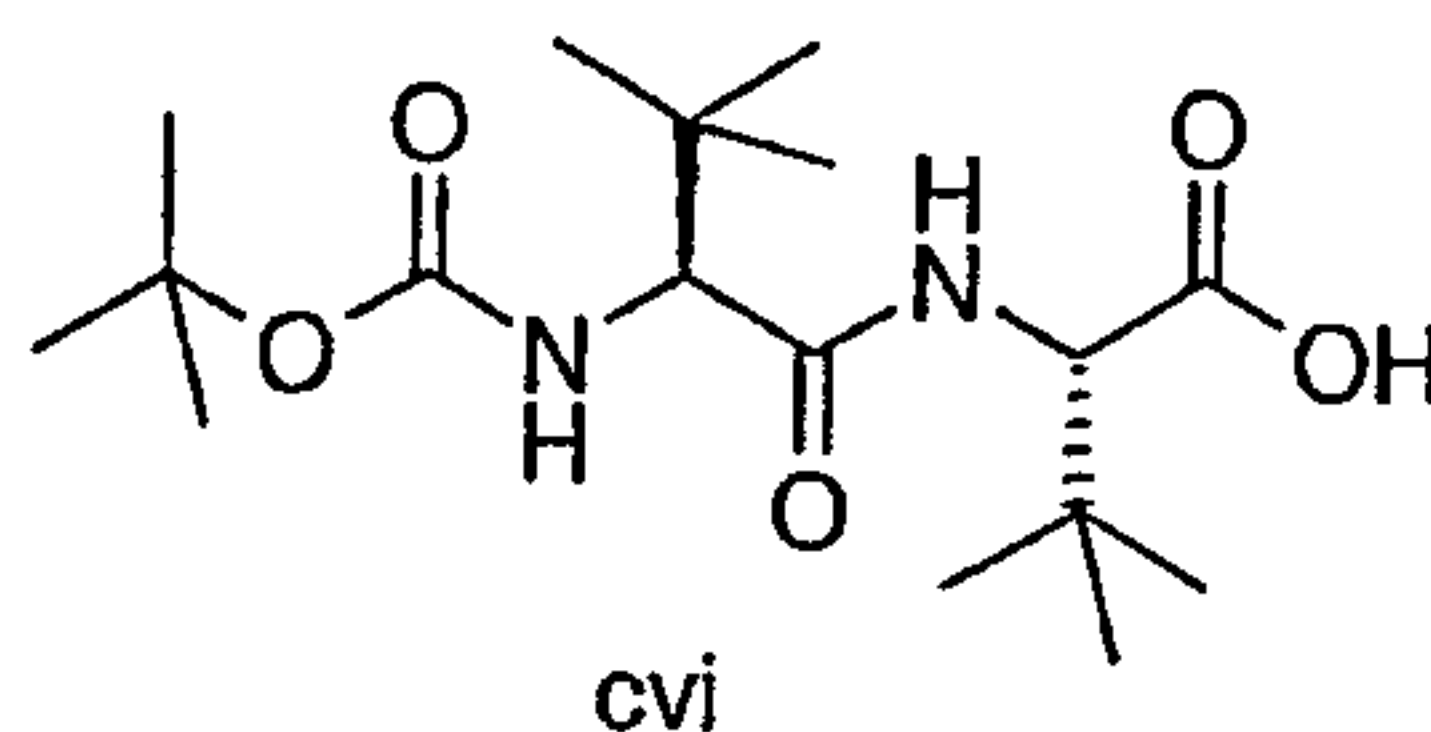
diluted with EtOAc, and the organic phase washed with 1 N HCl, saturated NaHCO₃ and brine. Following the concentration of the organic phase, the resultant residue is chromatographically purified by 20% - 30% EtOAc/hexanes gradient to yield compound cv (3.3 g, 92%).



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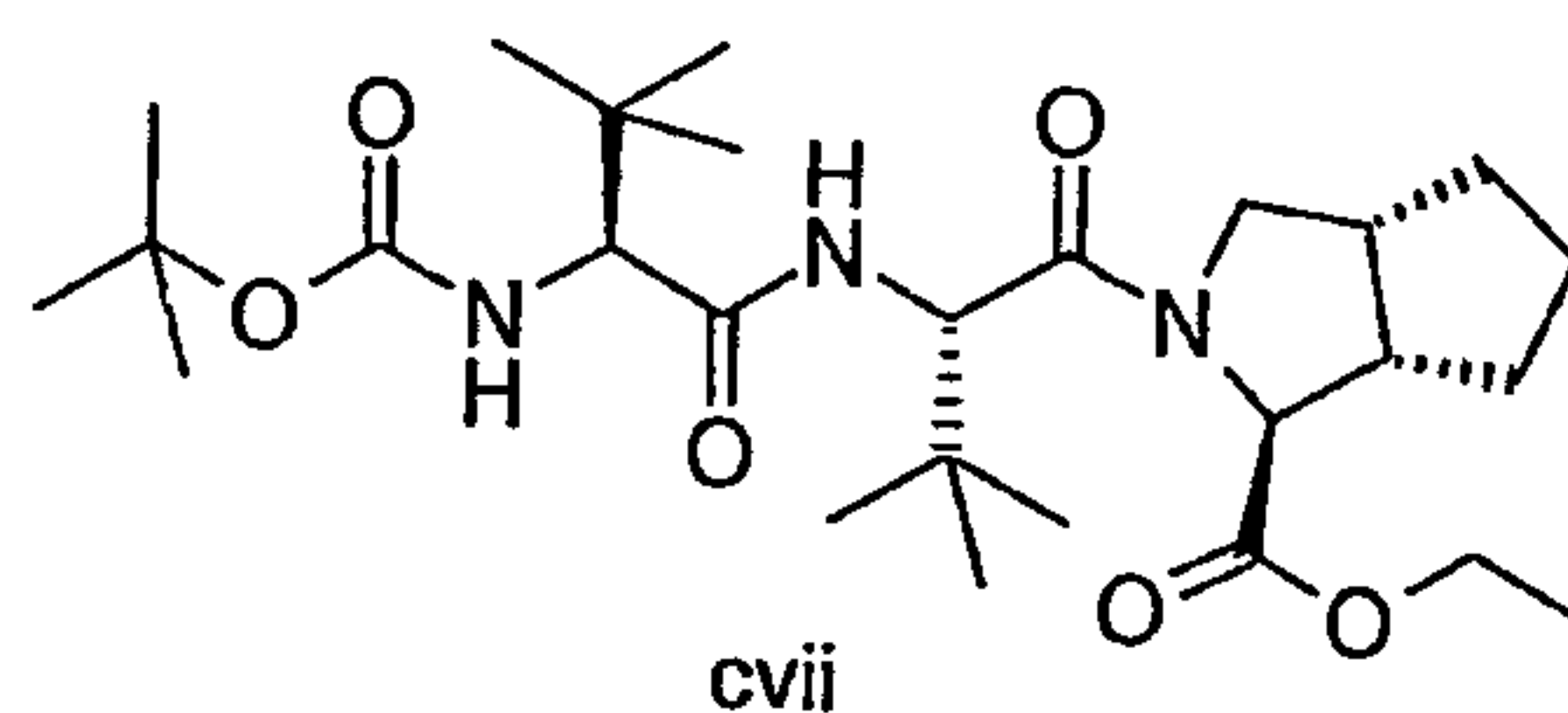
Intermediate Example 101 – Compound cvi

Compound cv (3.3 g, 9.2 mmol) is hydrolyzed using dioxane (40 mL) and 0.5 N NaOH (37 mL, 18.4 mmol) to yield compound cvi (2.9 g, 92%).



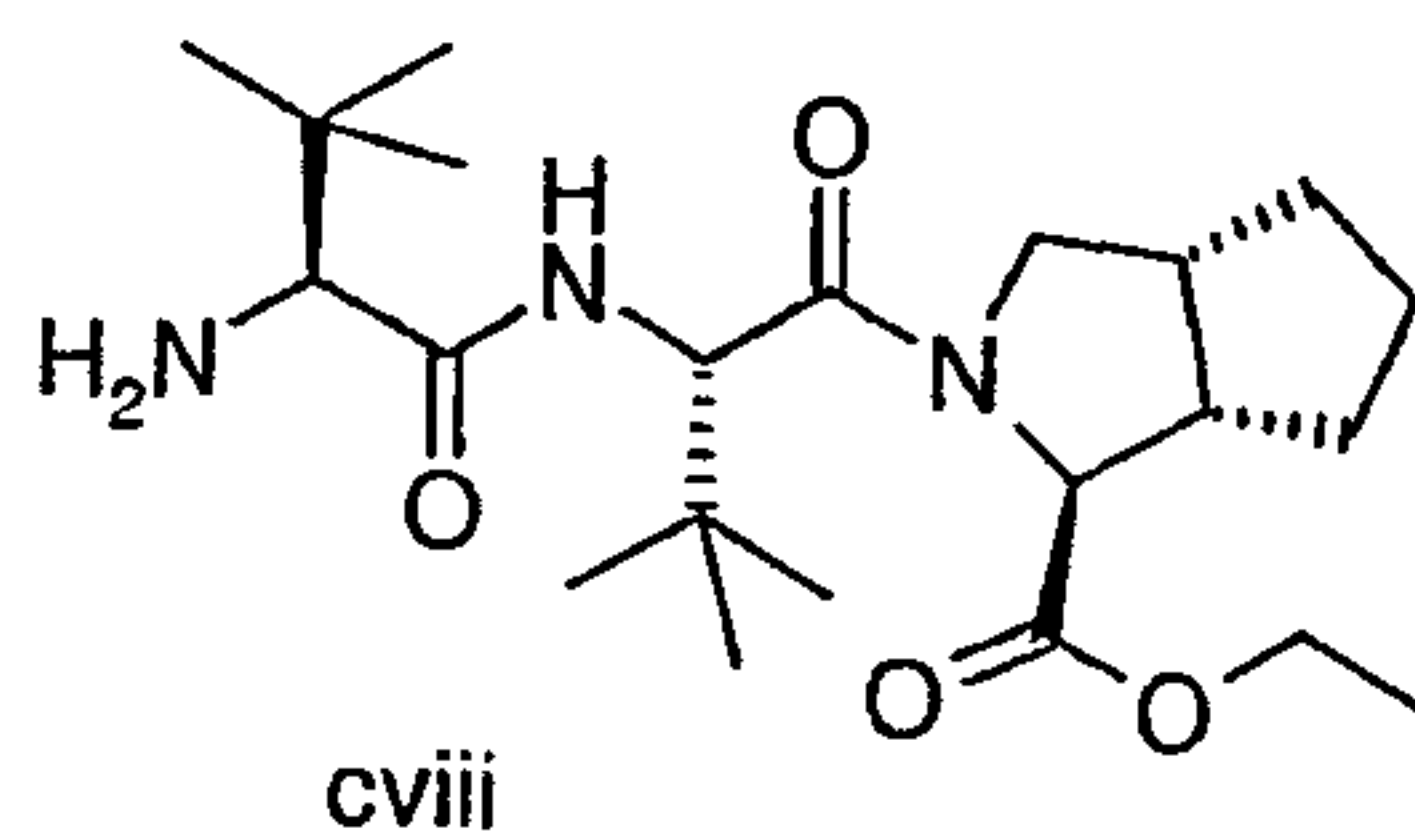
5 Intermediate Example 102 – Compound cvii

Compound cvi (2 g, 5.8 mmol) and compound v (1 g, 5.5 mmol) are dissolved in DMF (20 mL). HOAt (832 mg, 6.6 mmol) and DIC (1.1 mL, 6.6 mmol) are then added to the solution. The resulting solution is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, and the organic phase washed with 1 N HCl, saturated NaHCO₃ and brine. Following the
10 concentration of the organic phase, the resultant residue is chromatographically purified by 20%-30% EtOAc/hexanes gradient to yield compound cvii (2.4 g, 81%).



Intermediate Example 103 – Compound cviii

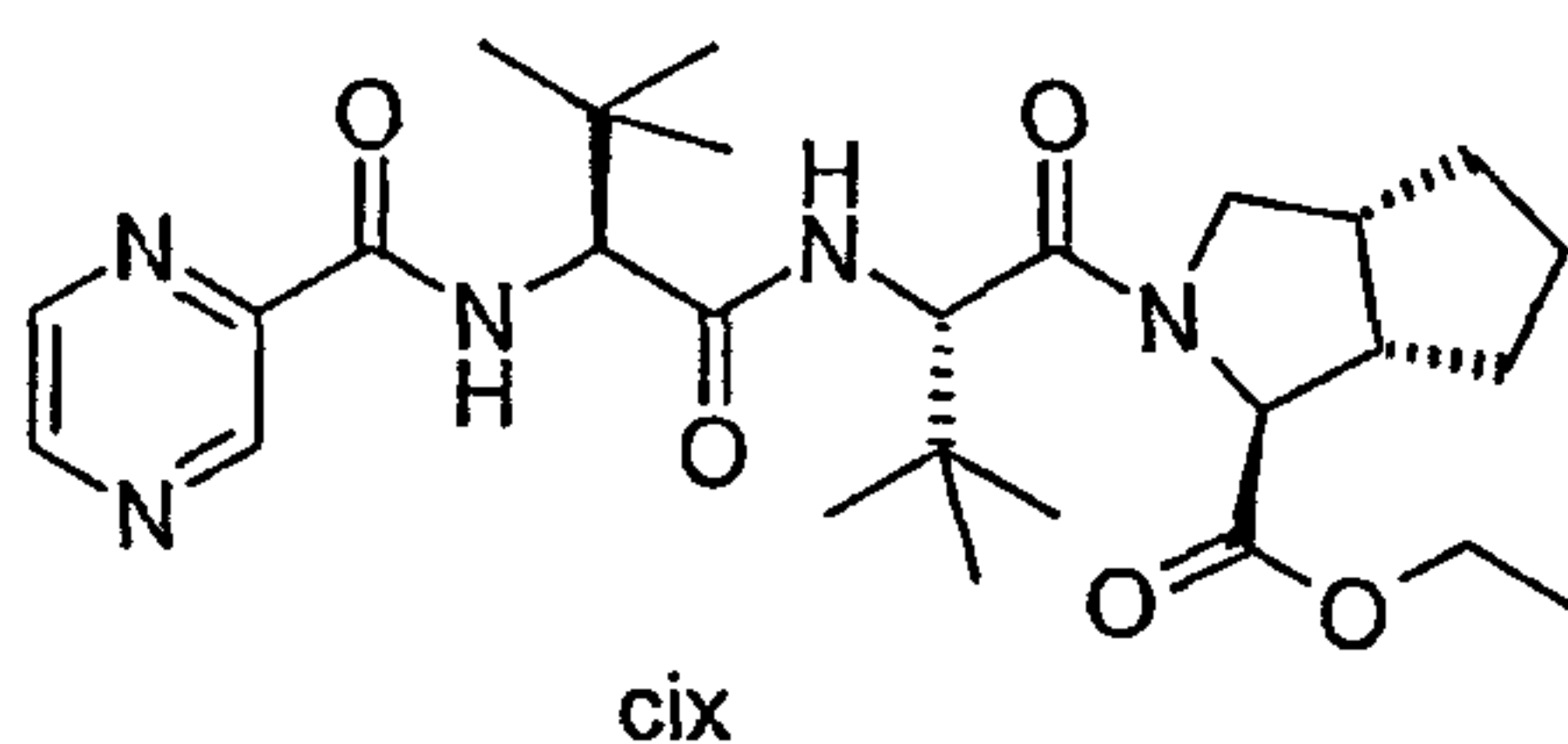
Compound cvii (2.4 g, 4.72 mmol) is dissolved in DCM (10 mL). TFA (10 mL) is added
15 to the solution. The resulting solution is stirred for 4 hours. The reaction mixture is concentrated, dissolved in EtOAc, and then the organic phase is washed with 1 N NaOH and brine. The organic phase is concentrated to yield compound cviii (1.084 g, 56.1%).



Intermediate Example 104 – Compound cix

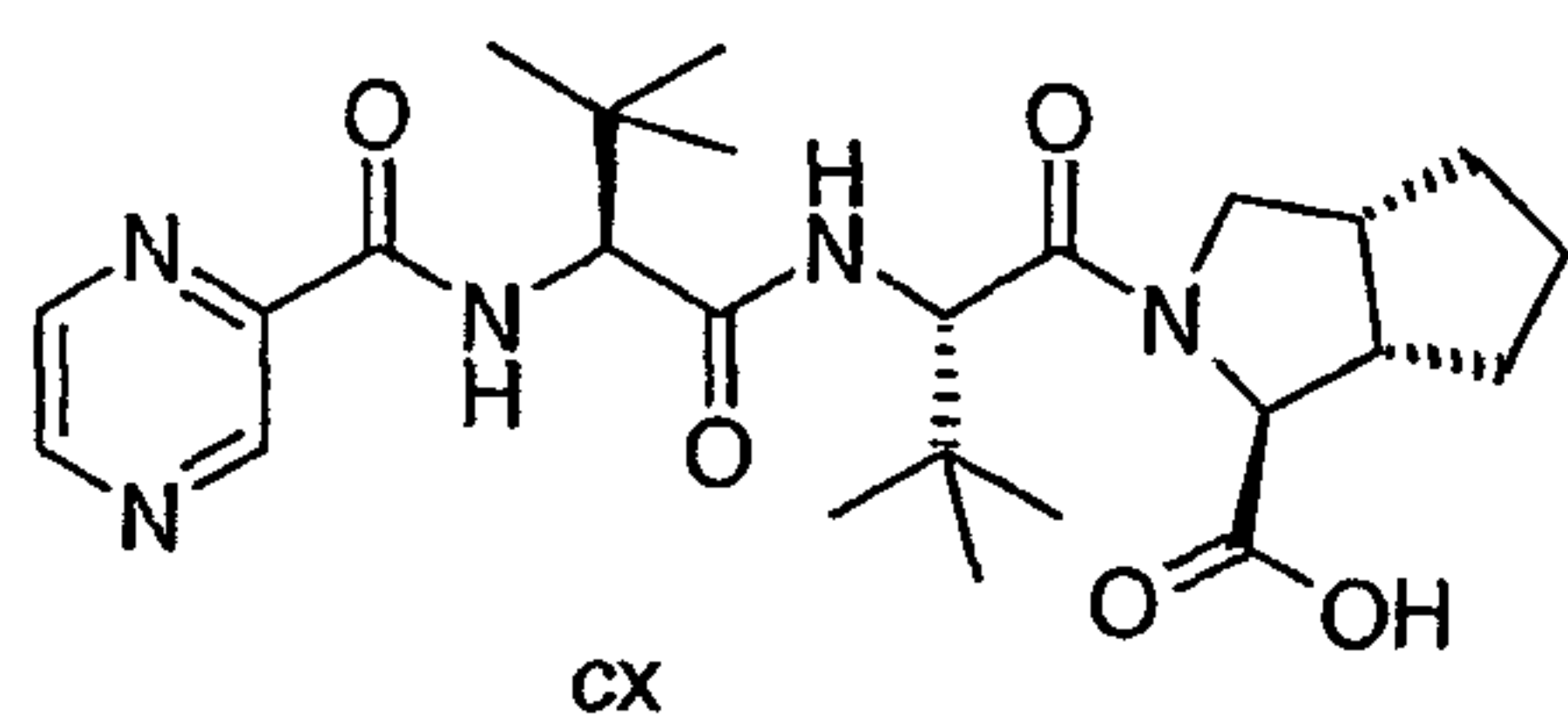
20 2-Pyrazinecarboxylic acid (181 mg, 1.46 mmol) and compound cviii (541 mg, 1.325

mmol) are dissolved in DMF (15 mL). HOAt (207 mg, 1.52 mmol) and DIC (0.24 mL, 1.52 mmol) are added to the solution. The resulting solution is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, and the organic phase washed with 1 N HCl, saturated NaHCO₃ and brine. Following the concentration of the organic phase, the resultant residue is chromatographically purified by 20%-30%-35% EtOAc/hexanes gradient to yield compound cix (430 mg, 63%).



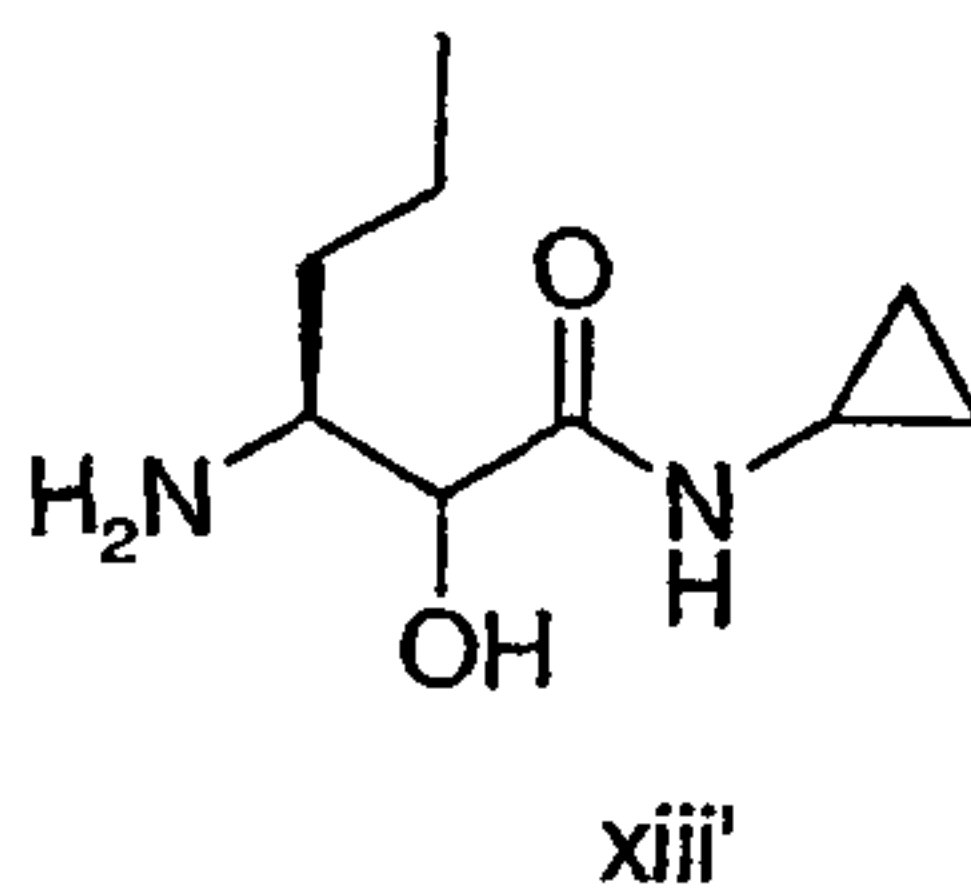
Intermediate Example 105 – Compound cx

Compound cix is hydrolyzed using EtOH (7 mL) and 1 N NaOH (4.7 mL, 4.7 mmol) to yield compound cx (700 mg, 91.6%).



Intermediate Example 106 – Compound cxi

Compound cx (690 mg, 1.42 mmol) is dissolved in DCM (9 mL). PyBOP (890 mg, 1.7 mmol) is then added to the solution, followed by the addition of Compound xiii' (320

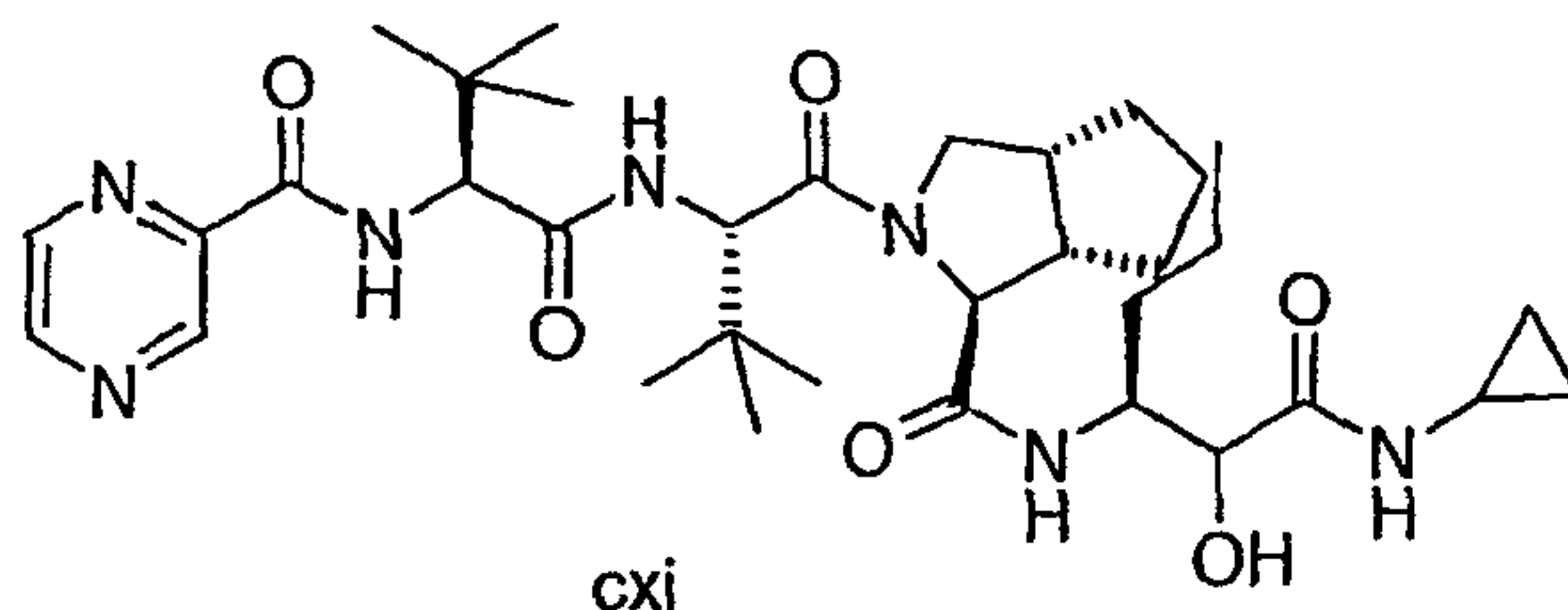


mg, 1.7 mmol). To the resulting mixture is added DIPEA (0.3 mL, 1.7 mmol). The reaction mixture is stirred overnight under N₂. The reaction mixture is then diluted with EtOAc, washed with saturated NaHCO₃, and brine. Following the concentration of the organic phase, the resultant residue is chromatographically purified by 100% EtOAc to yield compound cxi (490 mg, 52.7%).

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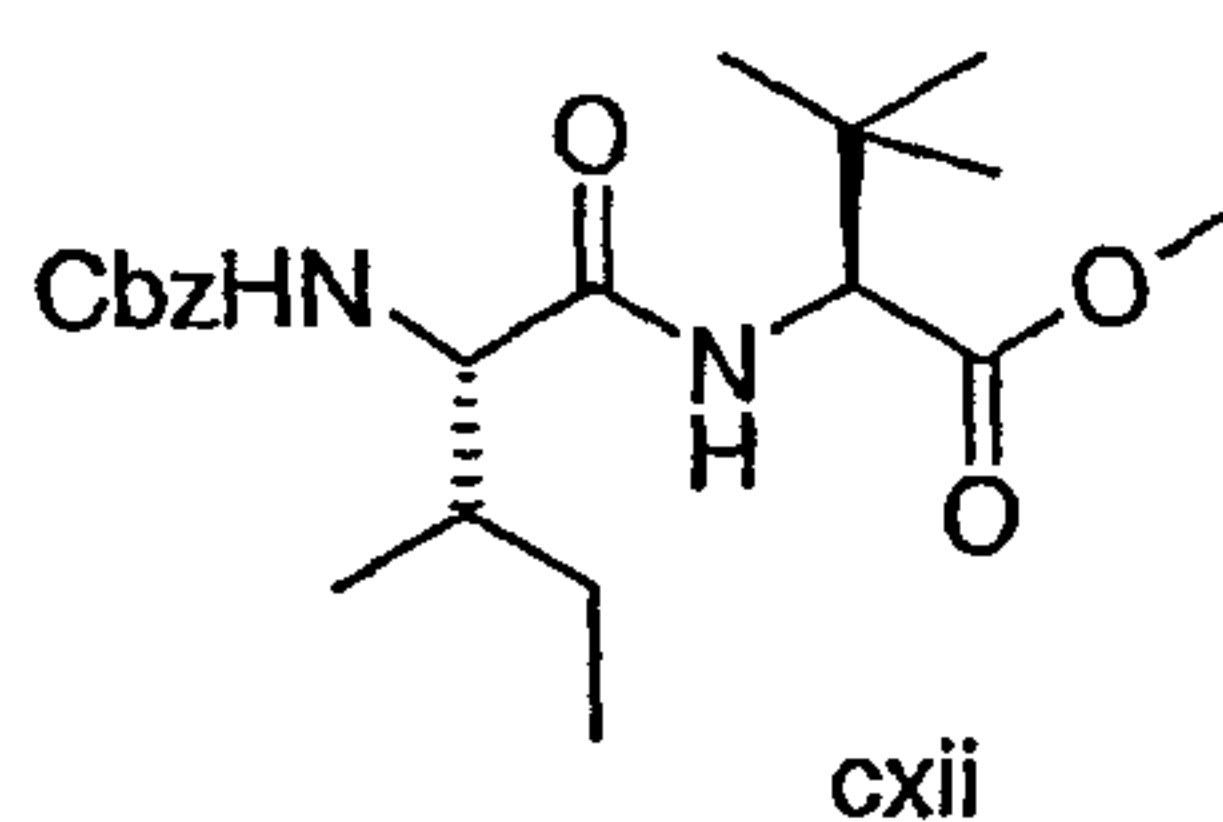
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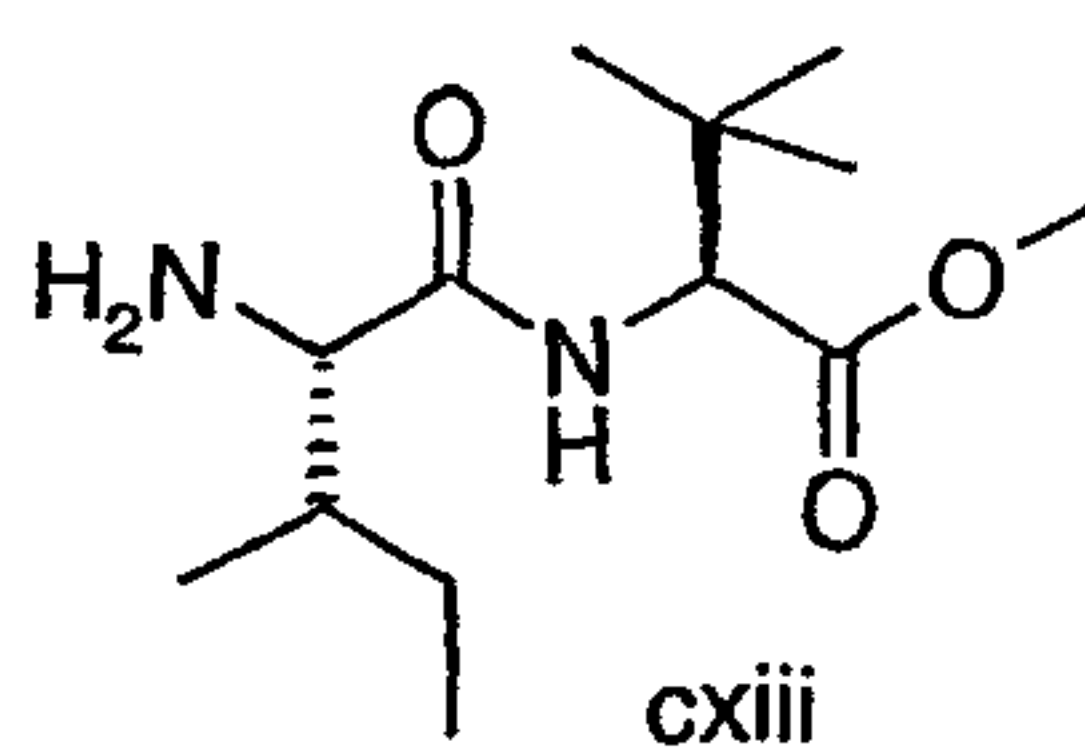


Intermediate Example 107 – Compound cxiv

Compound cxii (1.2 g, 3.06 mmol) is dissolved in MeOH (12 mL). After thoroughly

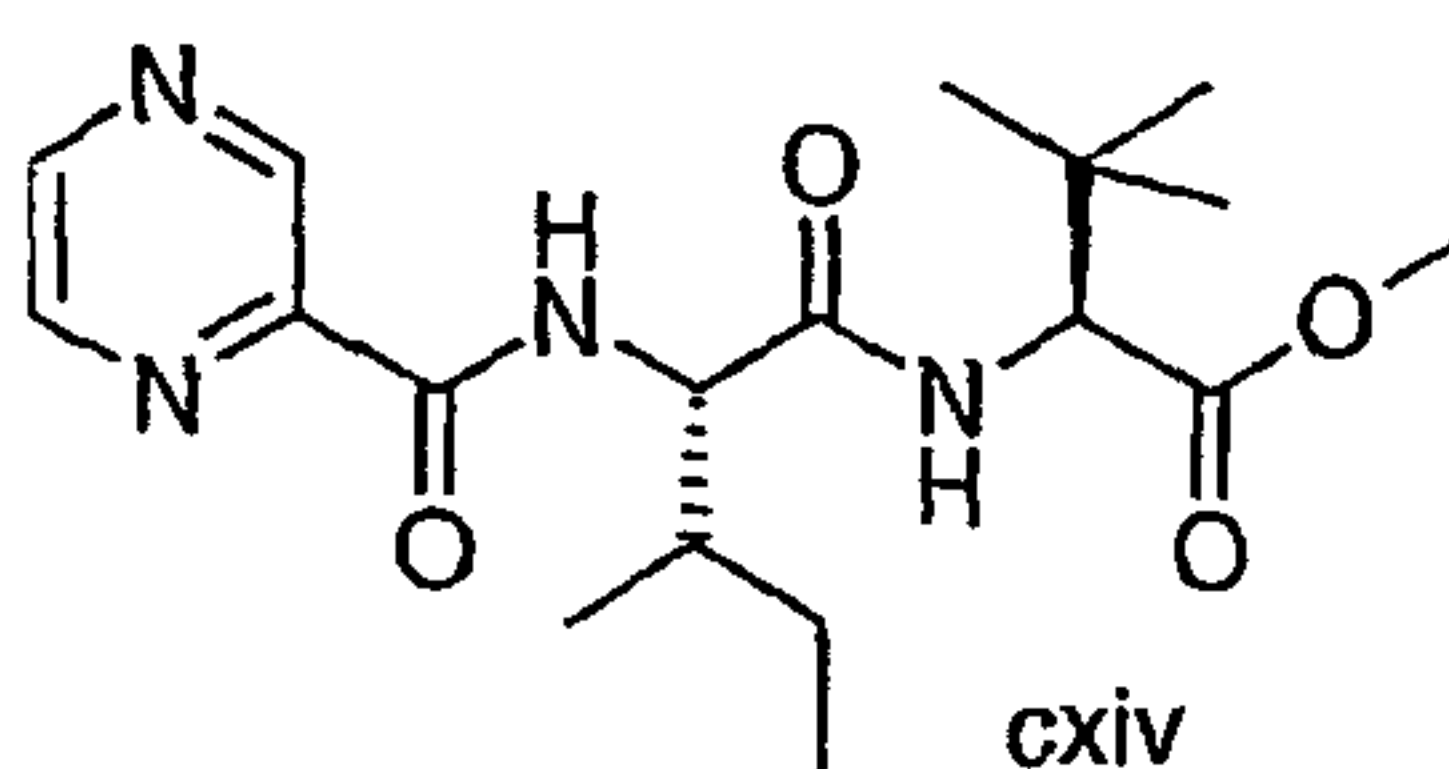


- 5 flushing with N₂, 10 wt% Pd(OH)₂ on carbon (0.6 g) is added and the mixture is hydrogenated for overnight, whereupon a complete reaction mixture is shown by TLC (30% EtOAc/hexanes). The solution is isolated from solid material by filtration and concentrated to the corresponding deprotected compound cxiiias a colorless oil (100%)



- 10 that is used in the next step without further purification.

- 2-Pyrazinecarboxylic acid (400 mg, 3.2 mmol, 1.1 eq) is dissolved in DCM/THF (4 mL/4 mL), and then HOAt (440 mg, 3.2 mmol) and DCC (343 mL, 1 M in DCM) are added. After stirring at room temperature for 20 minutes, the compound cxiii (0.96 g, 3.2 mmol) obtained previously is dissolved in DCM (6.4 mL) and added to the activated mixture. After stirring overnight at room temperature, the reaction mixture is filtered through Celite and compound cxiv is purified by column chromatography (30% EtOAc/hexanes)



to yield a white solid (0.8 g, 80%).

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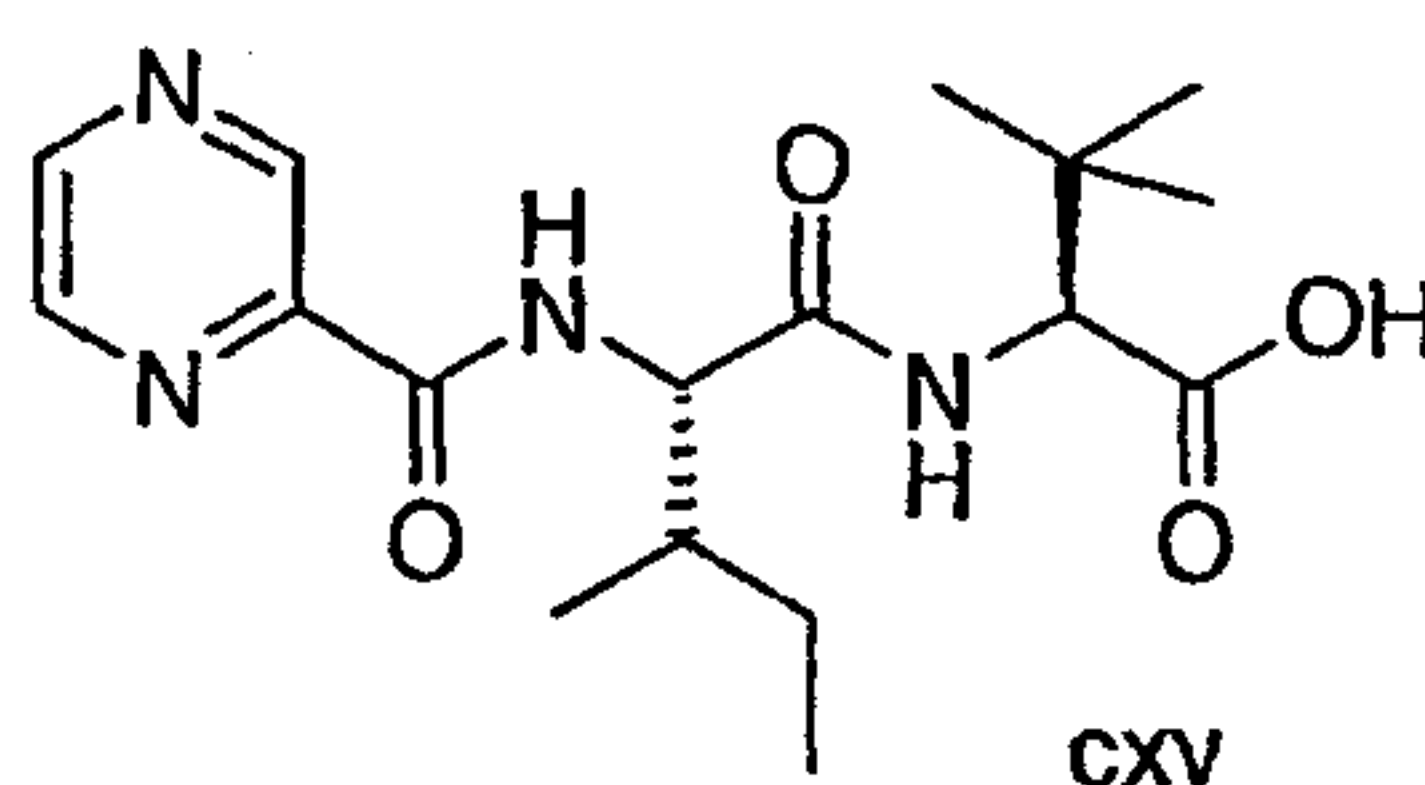
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Intermediate Example 108 – Compound cxv

Compound cxiv (0.8 g, 2.2 mmol) is dissolved in MeOH (10 mL), and then 2 N NaOH (aq) (3.3 mL, 6.6 mmol) is added. The solution is stirred at room temperature overnight, whereupon the completion of the reaction mixture is indicated by TLC (50% EtOAc/hexanes).

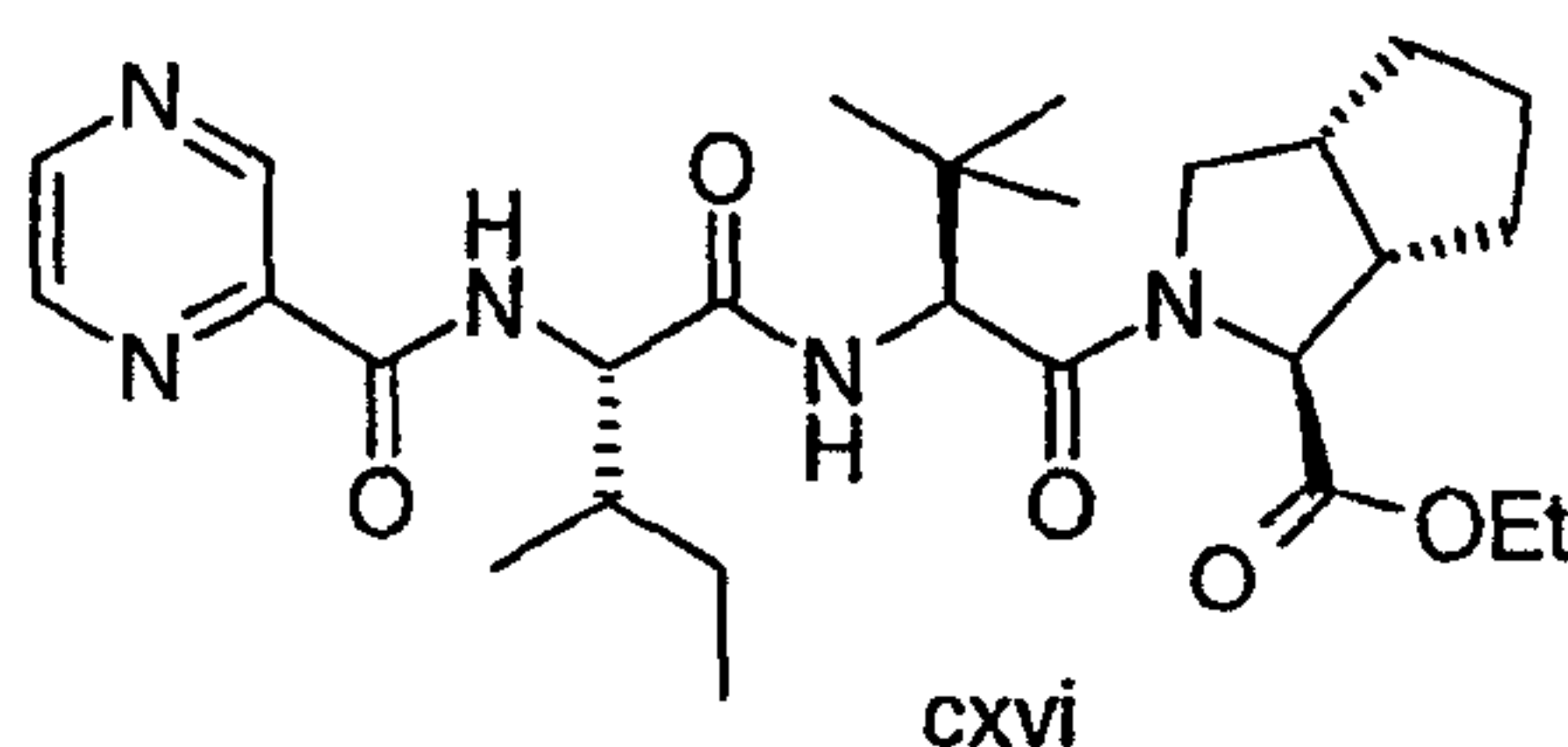
- 5 Acidification to pH 3 by 5 N HCl and diluted with EtOAc is followed by extraction of the organic phase. The extracted organic phase is washed with brine and dried over MgSO₄ to yield compound cxv (0.74, 95%) upon concentration.



Intermediate Example 109 – Compound cxvi

- 10 To a DCM solution (6 mL) of compound cxv (0.74 g, 2.1 mmol) at room temperature is added HOAt (290 mg, 2.1 mmol), followed by the addition of 1 M DCC solution in DCM (2.2 mL, 2.2 mmol). After stirring for 30 minutes at room temperature, a THF solution (10.5 mL, 0.2 M) of compound v (2.1 mmol) is added to the above HOAt-activated acid.

- The reaction mixture is stirred at room temperature overnight. At this point, the reaction mixture is filtered through celite. The filtrate is diluted with EtOAc (120 mL) and washed with water and brine. The organic phase is dried and concentrated to a yellow oil that is purified by silica gel chromatography (50% EtOAc/hexanes) to yield compound cxvi (0.714 g, 66%).
- 15



20 Intermediate Example 110 – Compound cxvii

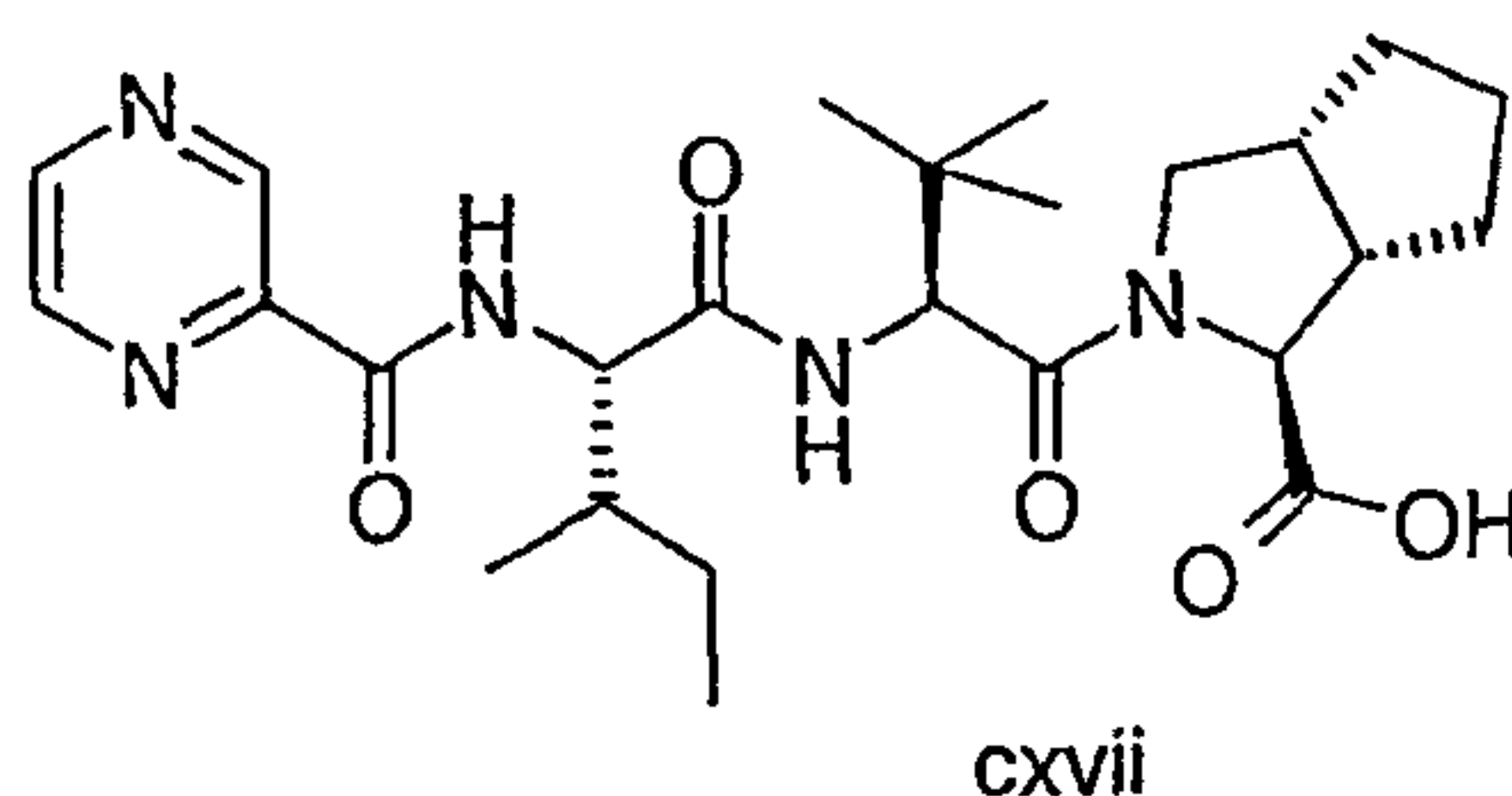
To an EtOH solution of compound cxvi (0.7 g, 1.4 mmol) is added 2 N NaOH aqueous solution (2 mL, 4 mmol). The reaction mixture is stirred overnight at room temperature, then acidified to pH 3 by 5 N HCl and diluted with EtOAc is followed by extraction of the organic phase. The extracted organic phase is washed with brine and dried over MgSO₄ to yield

- 25 compound cxvii (95%) upon concentration.

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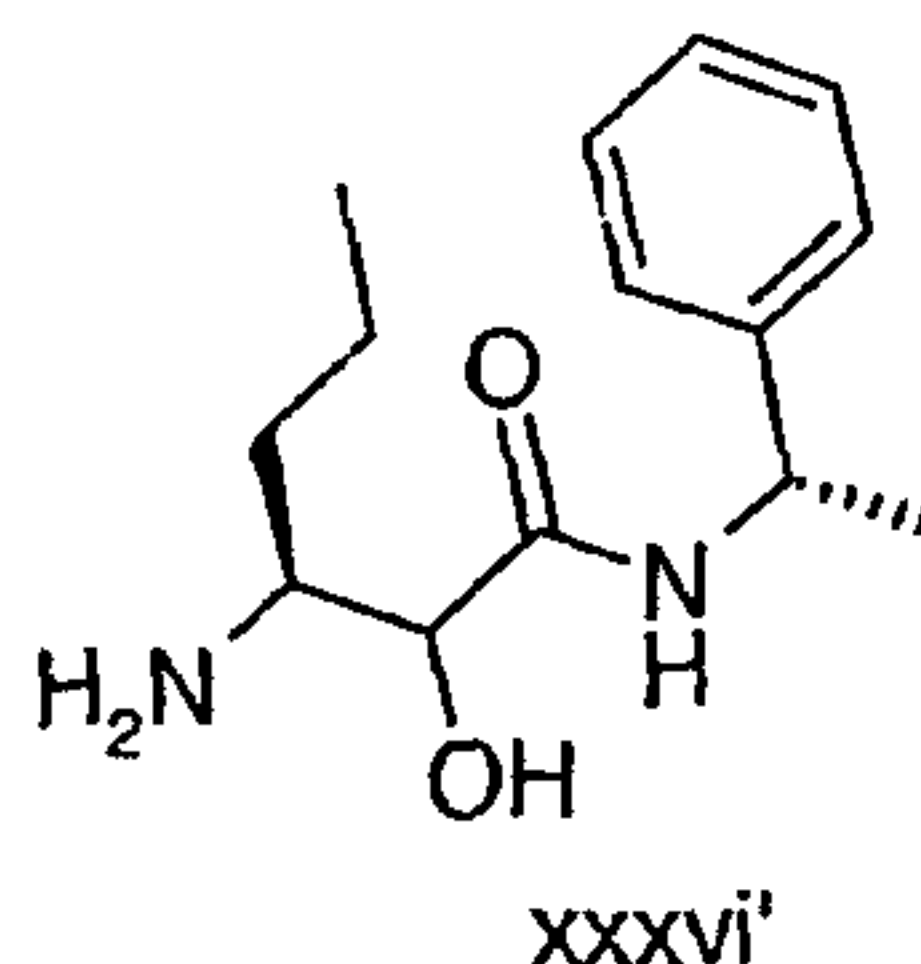
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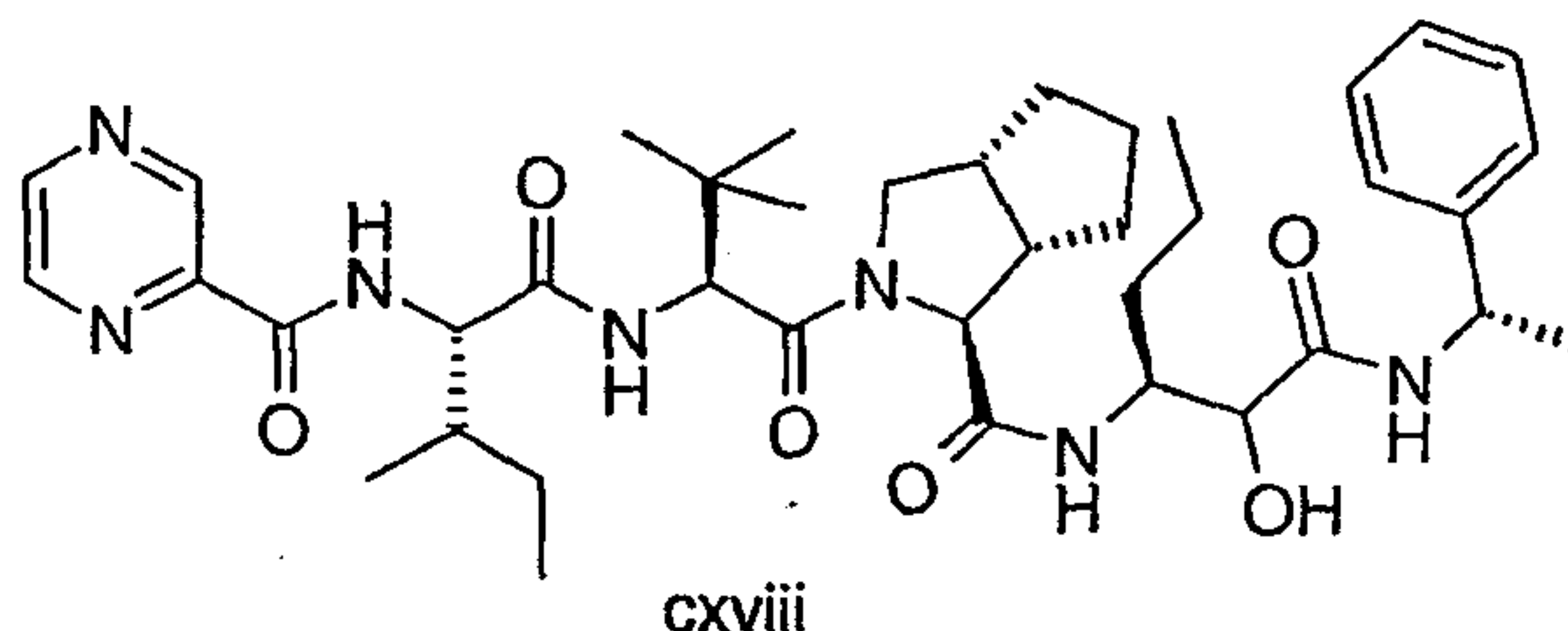


Intermediate Example 111 – Compound cxviii

- 5 To a DCM/THF solution (10 mL/2 mL) of compound cvii (300 mg, 0.6 mmol) is added PyBOP (416 mg, 0.8 mmol). The solution is stirred at room temperature for 30 minutes. To this solution is then added compound xxxvi' (200 mg, 0.8 mmol), followed by DIPEA



- (0.22 mL, 1.2 mmol). The reaction mixture is stirred at room temperature overnight and then
 10 quenched with water (25 mL) for 30 minutes. The mixture is then extracted with EtOAc. The resulting organic phase is washed with brine and dried over MgSO₄, before being concentrated to yield a yellow oil. Purification by silica gel chromatography (3-5% EtOH/EtOAc) yields compound cxviii (335 mg, 76%).

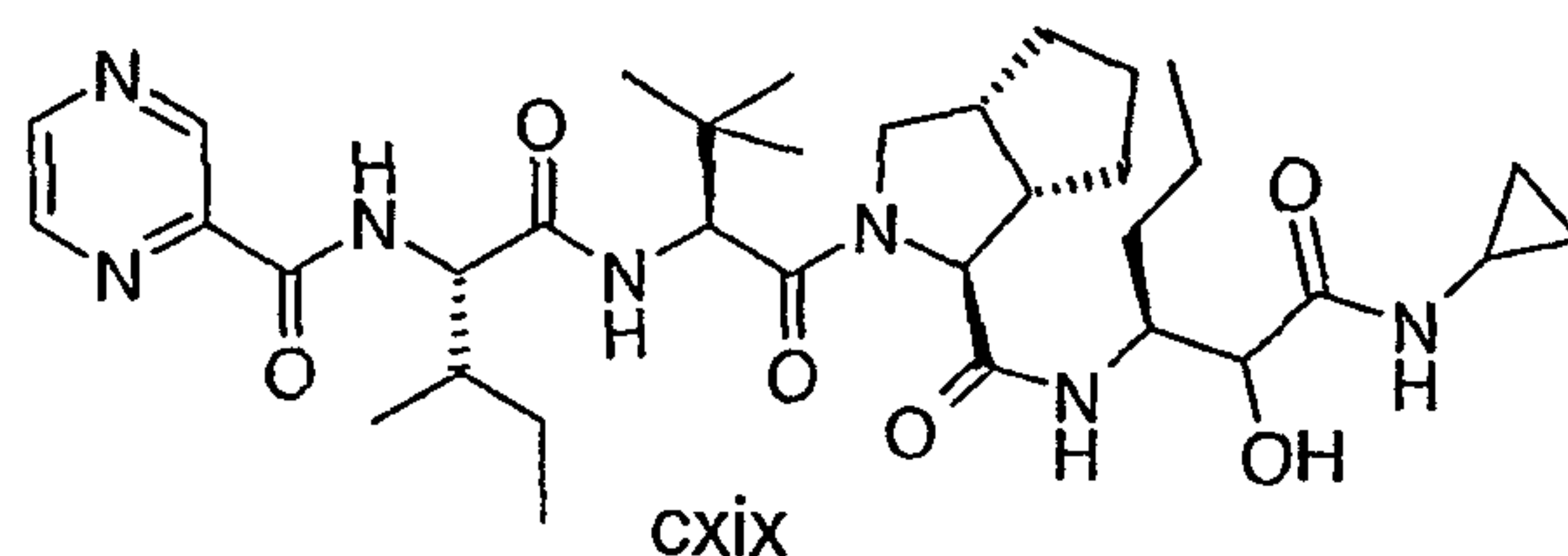


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Intermediate Example 112 – Compound cxix

- To a DCM solution (10 mL) of compound cxvii (340 mg, 0.6 mmol) is added PyBOP (470 mg, 0.9 mmol). The solution is stirred at room temperature for 30 minutes. To this solution is then added compound xiii' (170 mg, 0.9 mmol), followed by DIPEA (0.24 mL, 1.2 mmol). The
 20 reaction mixture is stirred at room temperature overnight and then quenched with water (25 mL) for 30 minutes. The mixture is then extracted with EtOAc. The resulting organic phase is washed

with brine and dried over MgSO_4 , before being concentrated to yellow oil. Purification by silica gel chromatography (3-5% EtOH/EtOAc) yields compound cxix (164 mg, 36%).

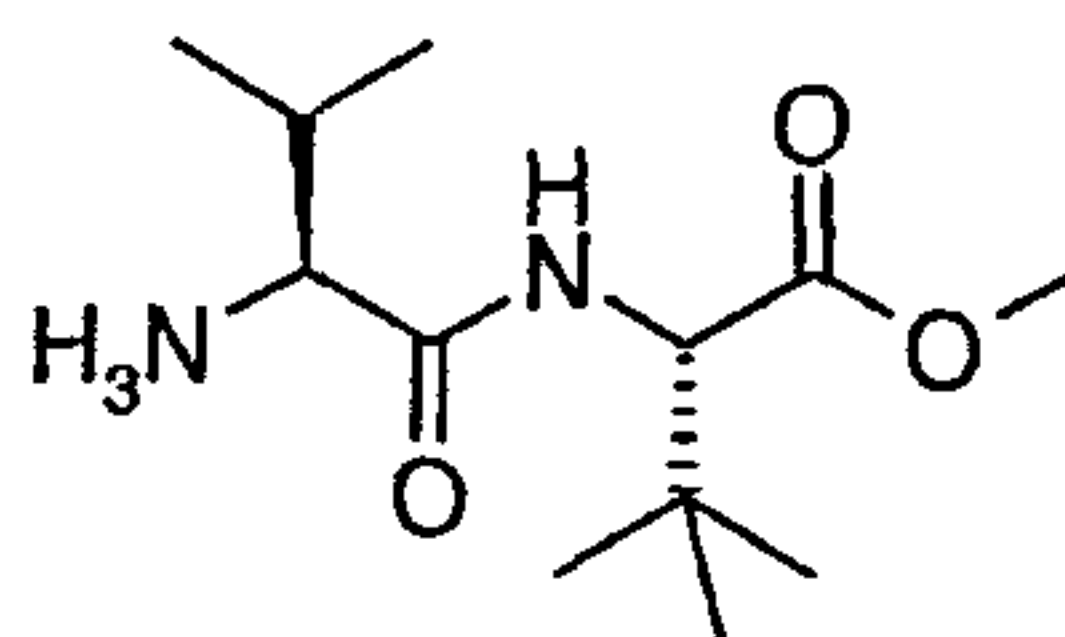


5 Intermediate Example 113 – Compound xx

N-Cbz-L-Valine (6.28 g, 25 mmol) is dissolved in DCM (30 mL). HOBT (3.38 g, 25 mmol) and DCC (25 mL, 1 M solution) are added to this solution and stirred five minutes. L-tert-Leucine methyl ester hydrochloride (25 mL, 1 M solution) is added to this mixture and stirred overnight under N_2 . The reaction mixture is diluted with EtOAc, washed with 1 N HCl, saturated
 10 NaHCO_3 , and brine. The organic phase is dried over Na_2SO_4 , filtered and concentrated. The residue is chromatographically purified by 20%-30% EtOAc/hexanes to yield compound xx (2.96g, 31%).

Intermediate Example 114 – Compound xxi

15 Compound xx (2.95 g, 7.8 mmol) is hydrogenated using 10% Pd/C (800 mg) in MeOH (40 mL) under H_2 to yield the below corresponding free amine (1.9g, 100%).

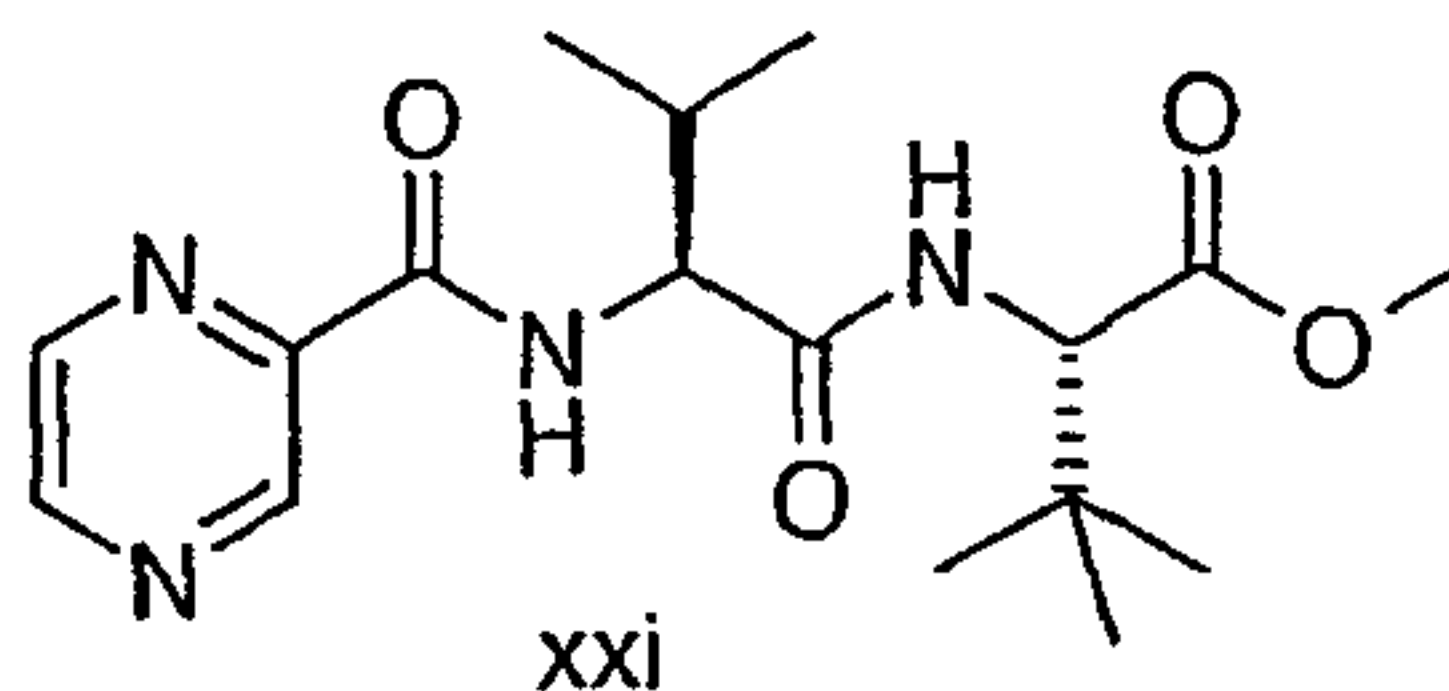


2-Pyrazine-carboxylic acid (970 mg, 7.8 mmol) is dissolved in DCM (20 mL). PyBOP (4.06 g, 7.8 mmol) is added to this solution. The free amine (1.9 g, 7.8 mmol) in DCM (15 mL) is added to the solution, and then DIPEA (1.36 mL, 7.8 mmol) is added. The resulting mixture is stirred overnight under N_2 . The reaction mixture is diluted with EtOAc, and the organic phase is washed with saturated NaHCO_3 and brine. Following the concentration of the organic phase, the residue is chromatographically purified by 30%-40% EtOAc/Hexanes to yield compound xxi (2.07g,
 20 75.8%).

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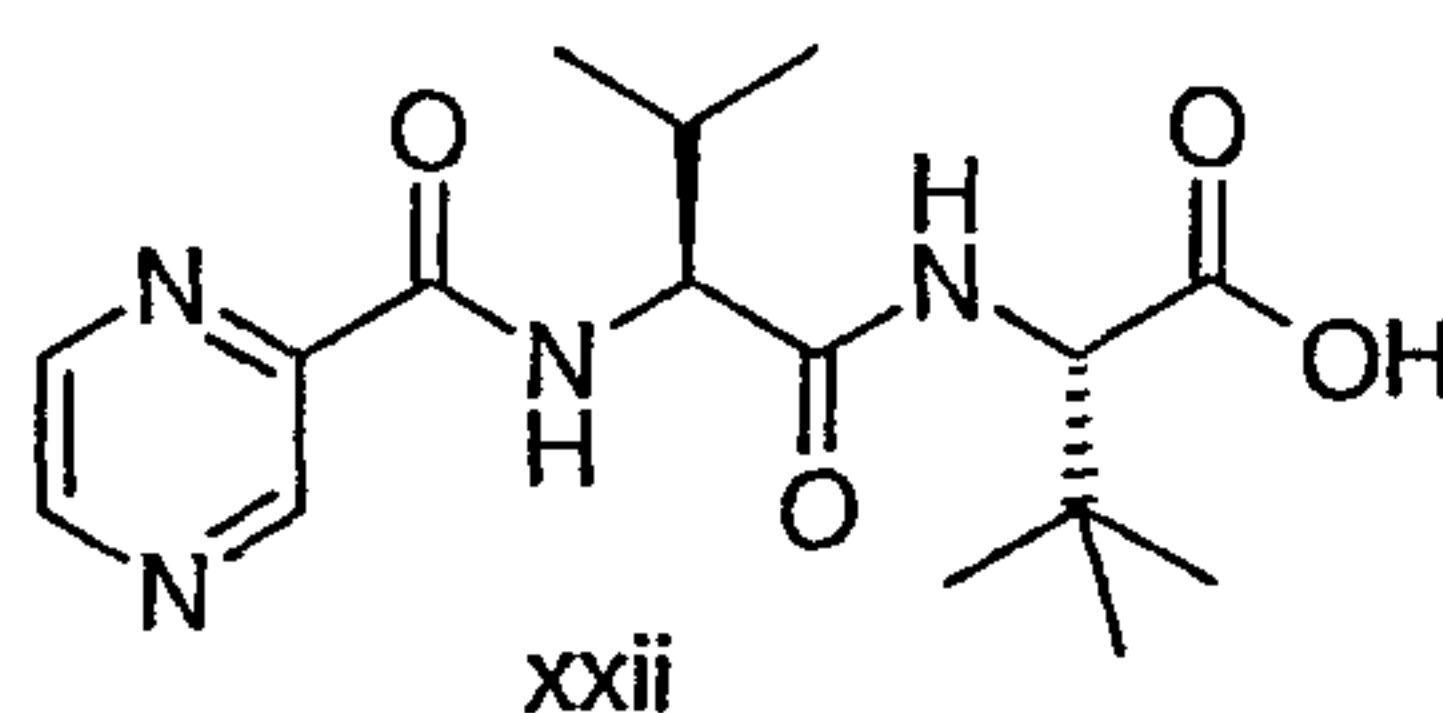
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Intermediate Example 115 – Compound xxii

Compound xxi is hydrolyzed using MeOH (20 mL) and 1 N NaOH (3 eq) to yield
 5 compound xxii (1.82g, 93.9%).



10

Intermediate Example 116 – Compound xxiii

Compound xxii (895 mg, 2.66 mmol) is dissolved in DCM (10 mL). DCC (3.2 mmol) is added to the solution, and then HOAt (435 mg, 3.2 mmol) is added. Compound v (3.2 mmol) in THF (16 mL) is then added. The resulting mixture is stirred overnight under N₂. The reaction
 15 mixture is diluted with EtOAc, filtered through silica gel, and concentrated. The resulting residue is chromatographically purified by 50% EtOAc/hexanes to yield compound xxiii (730 mg, 54.8%).

Intermediate Example 117 – Compound xxiv

Compound xxiii is hydrolyzed using EtOH (5 mL) and 1 N NaOH (1.5 eq) to yield compound
 20 xxiv (690 mg, 100%).

Intermediate Example 118 – Compound cxx

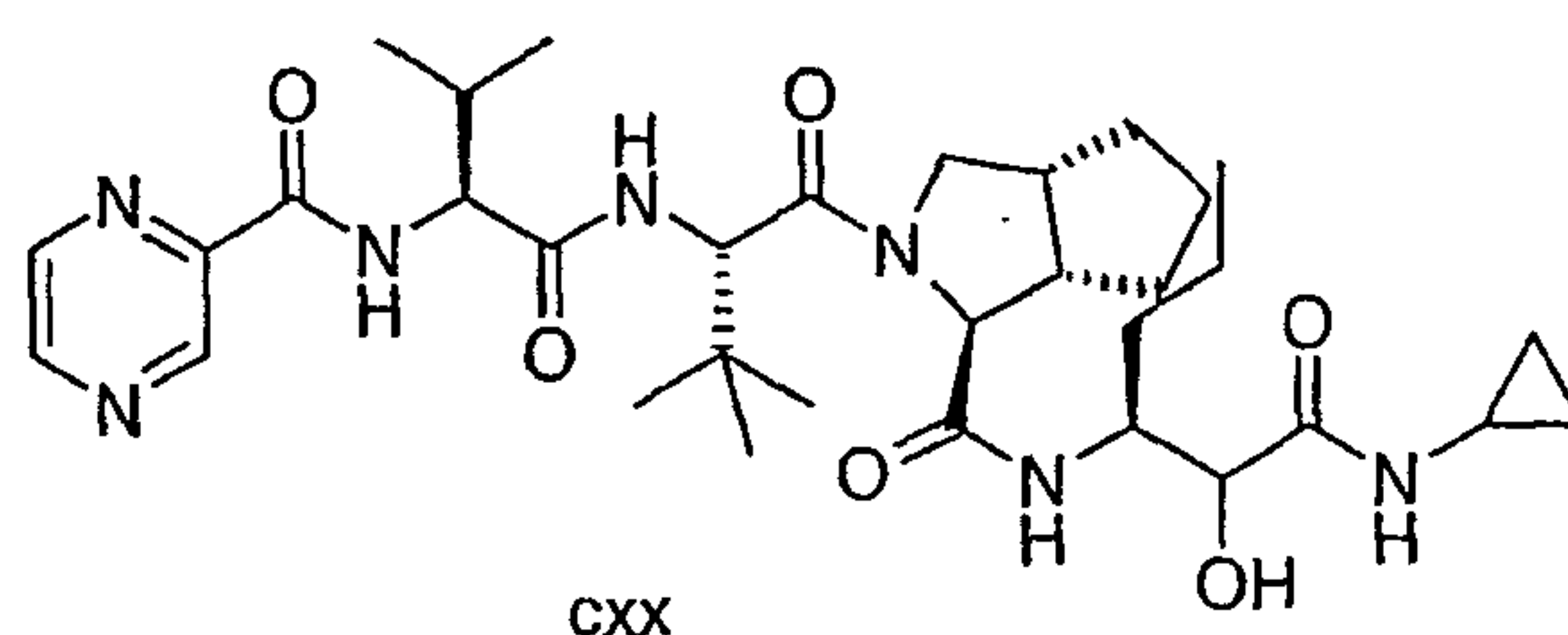
Compound xxiv (245 mg, 0.52 mmol) is dissolved in DCM (3 mL). PyBOP (330 mg, 0.62 mmol) is added to the solution, and then compound xiii' (120 mg, 0.62 mmol) is added. To the resulting mixture is added DIPEA (0.11 mL, 0.62 mmol). The reaction mixture is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, and the organic phase washed
 25

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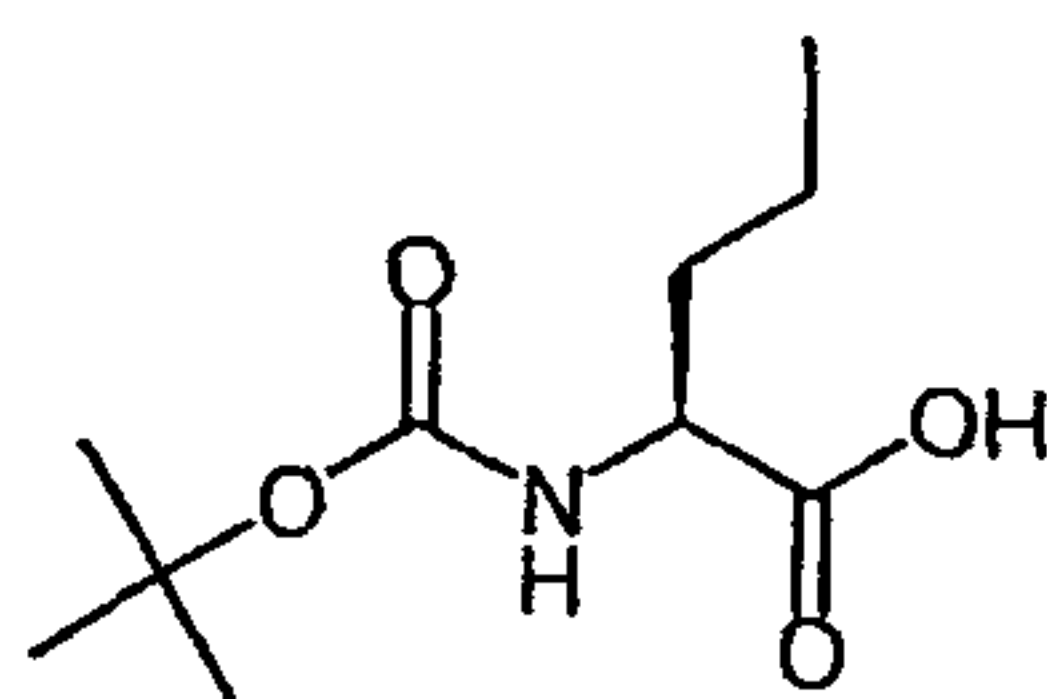
with saturated NaHCO_3 and brine. Following the concentration of the organic phase, the residue is chromatographically purified by 5% EtOH/EtOAc to yield compound cxx (220 mg, 60%).



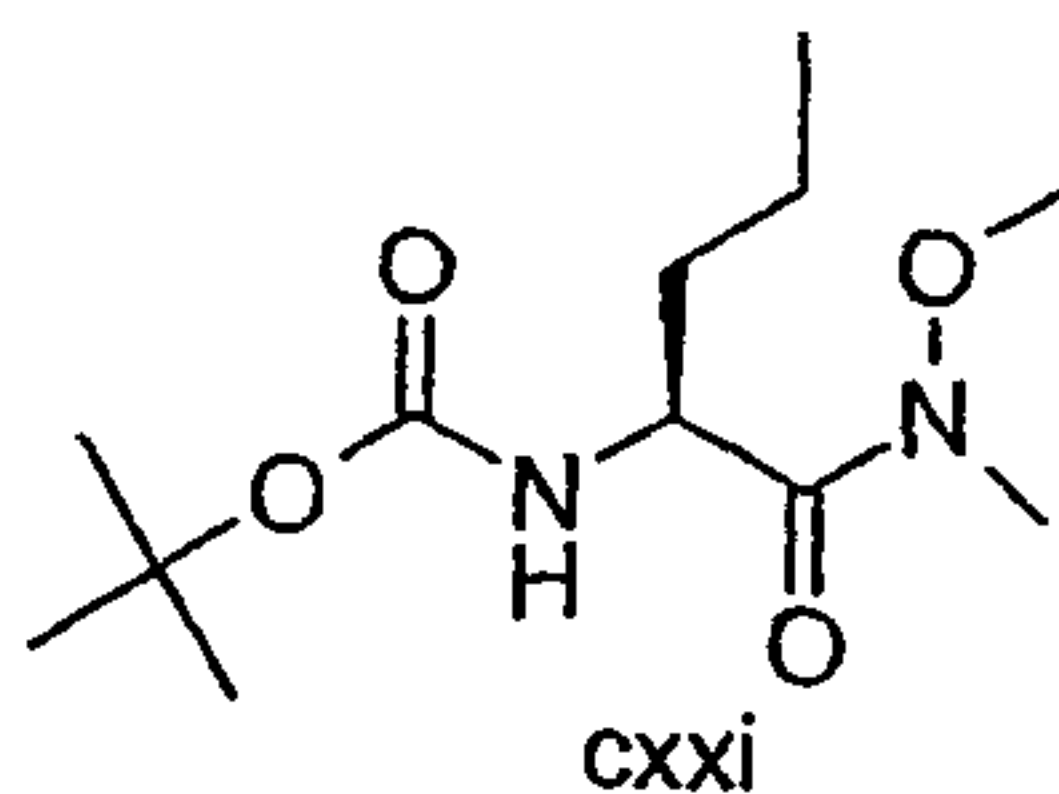
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Intermediate Example 119 – Compound xiii'

Boc-NVA-OH (24.96 g, 114.9 mmol) is dissolved in THF (200 mL). CDI (22.35, 137.8



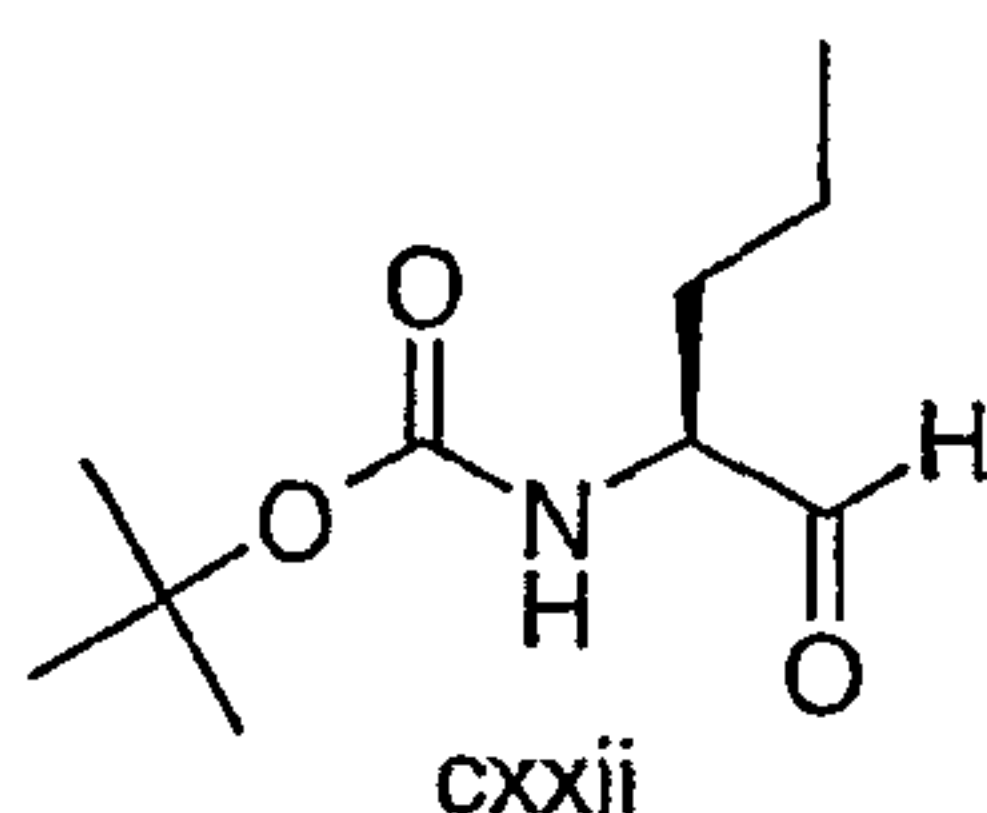
mmol) is added portion-wise to the solution, and the solution is stirred for 30 minutes. N,O-Dimethylhydroxylamine hydrochloride (12.33 g, 126.4 mmol) is dissolved in DMF (50 mL) and then DIPEA (22 mL, 126.4 mmol) is added to the solution. The DMF solution is allowed to stir at room temperature for 20 minutes and then added to THF solution. The resulting mixture is stirred over a weekend under N_2 . The reaction mixture is concentrated *in vacuo* to 100 mL total volume. This organic phase is washed with 1 N HCl, saturated NaHCO_3 and brine. The organic phase is concentrated to yield crude compound cxxi (25.3 g).



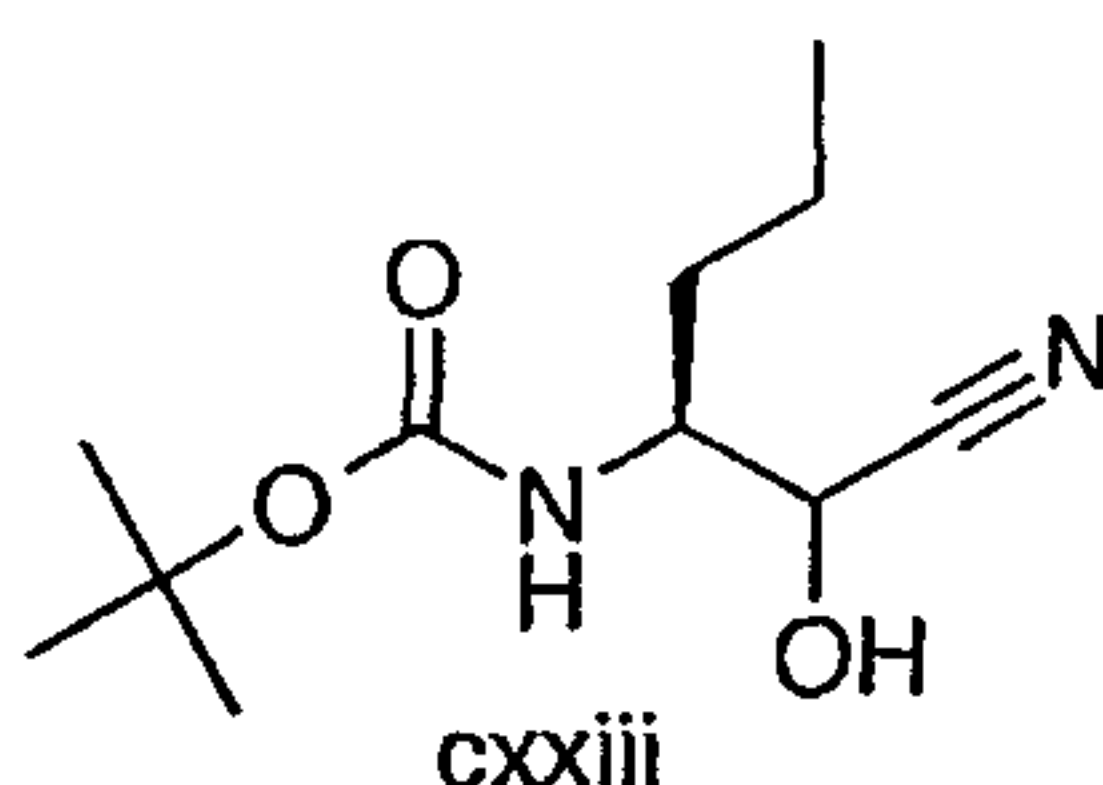
LAH (107.3 mmol) is added to a dry 1-L round bottom flask under N_2 in a 1 M Et_2O solution. This solution is lowered to 0°C , and then compound cxxi (97.5 mmol) is added drop-wise in Et_2O (100 mL). Upon completion of the addition, the resulting mixture is stirred for 30 minutes. The reaction mixture is quenched at 0°C by slowly adding EtOAc (50 mL), followed by slowly adding a 5% KHSO_4 (50 mL) solution. This mixture is stirred for 30 minutes. The

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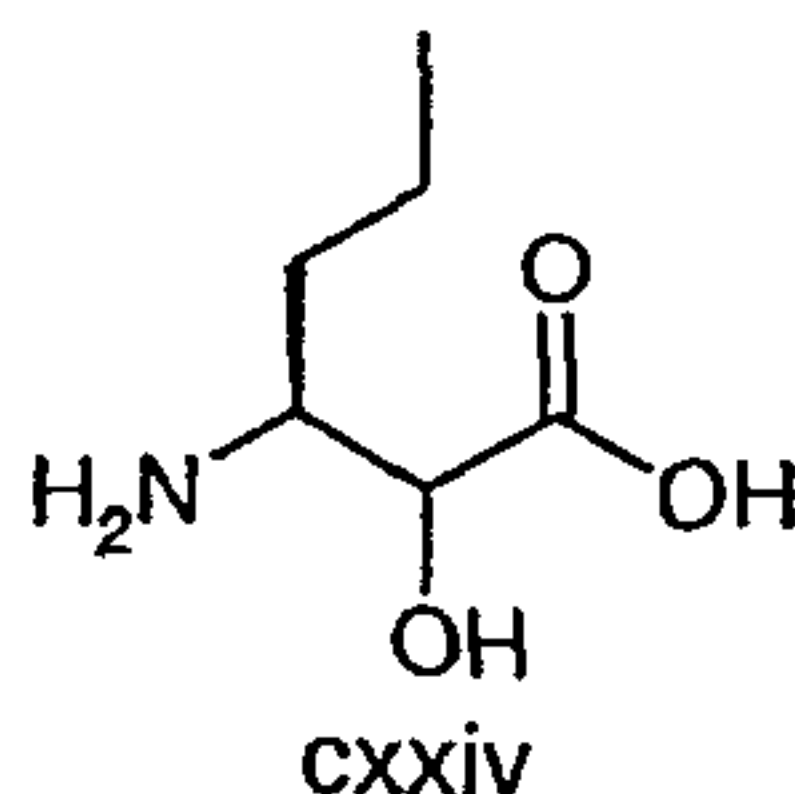
organic phase is washed with 1 N HCl, saturated NaHCO₃, and brine. The organic phase is concentrated to yield crude compound cxxii (22.28 g).



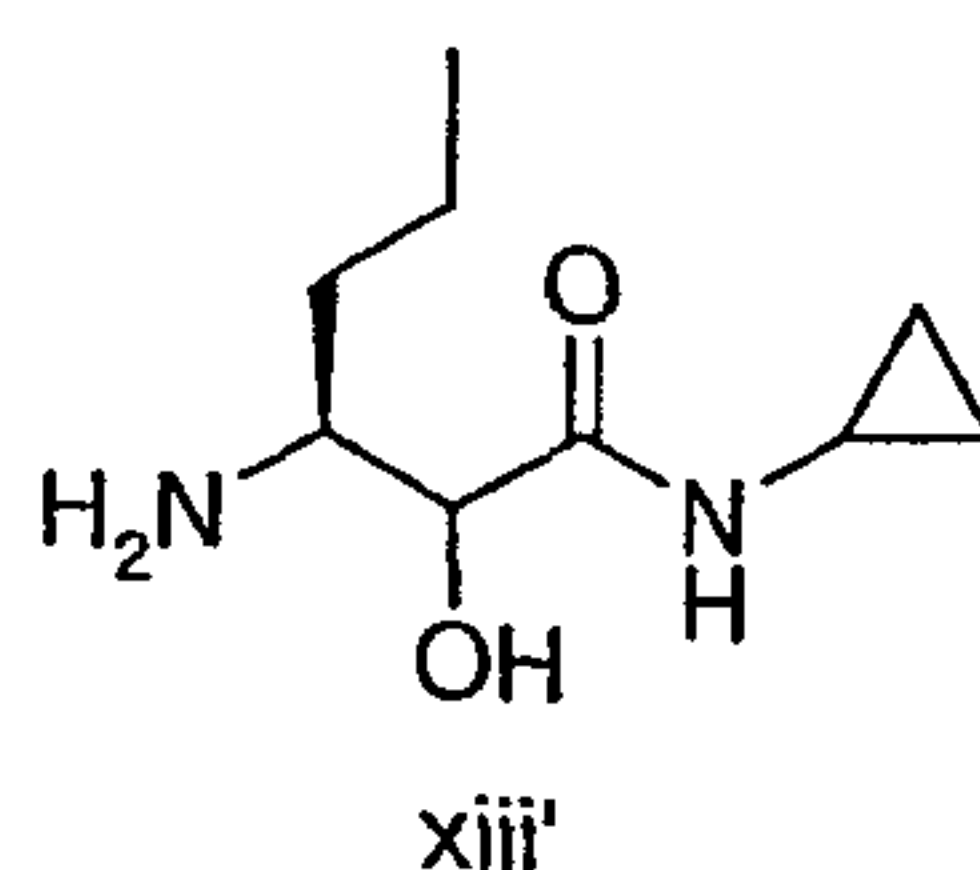
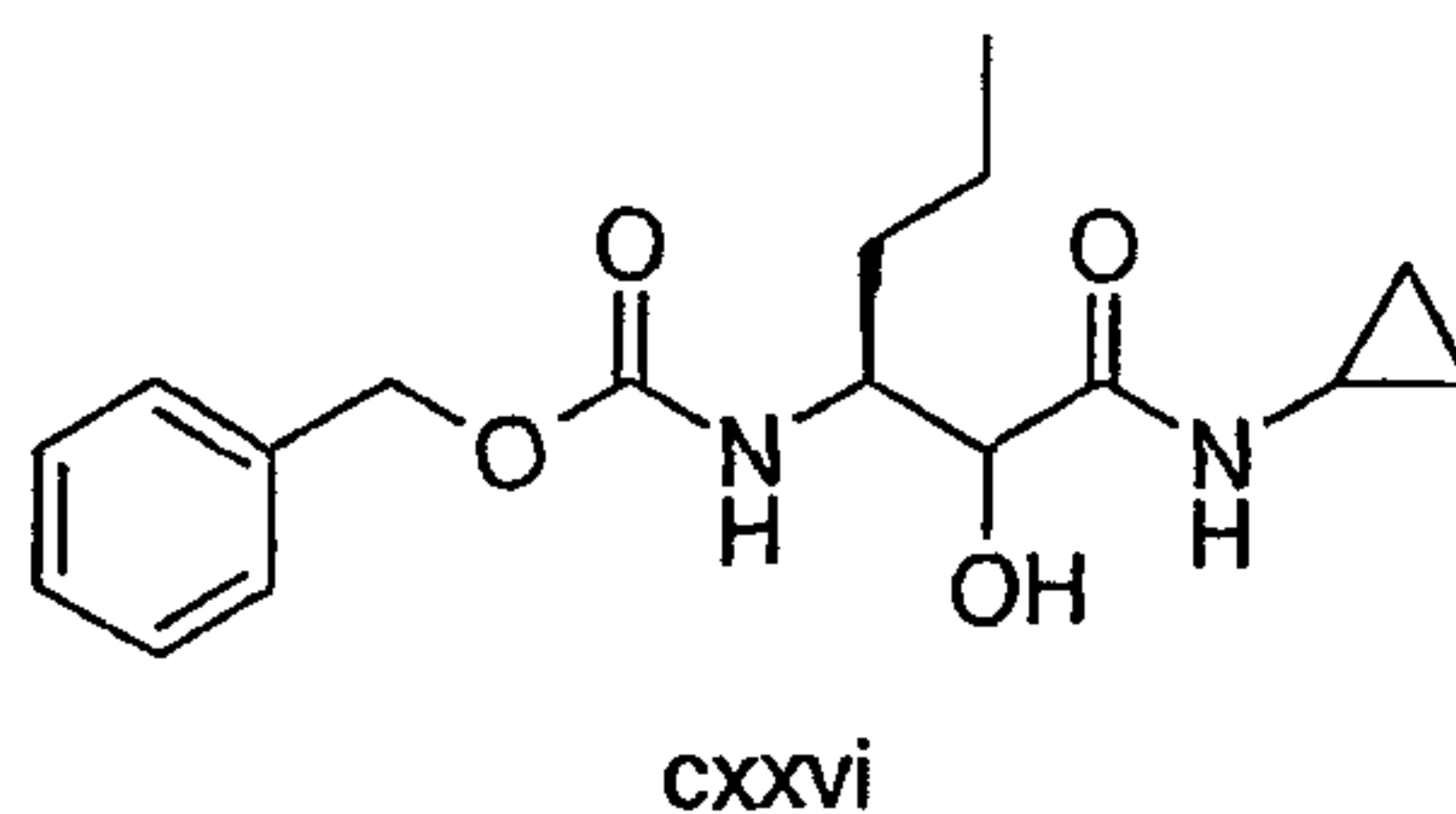
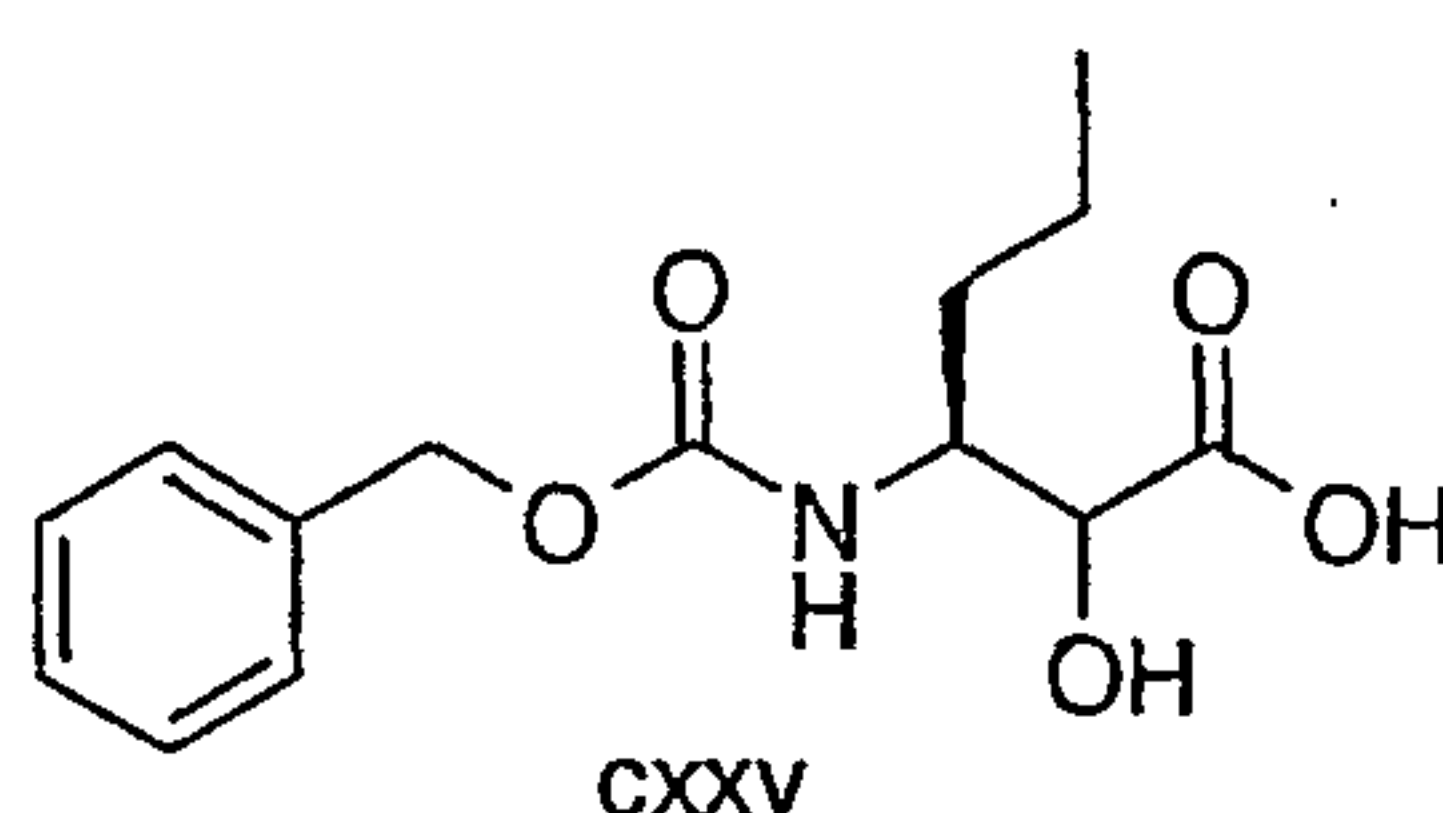
- 5 Compound cxxii is dissolved in MeOH (100 mL). Na₂S₂O₄ (16.82 g, 96.6 mmol) is dissolved in water (100 mL) and then added to solution of compound cxxii at 0°C. This mixture is stored in the refrigerator (5°C) overnight. KCN (7.53 g, 115.9 mmol) in water (100 mL) is added to reaction mixture and stirred for 1.5 hours at room temperature. The compound is extracted with EtOAc (3x100 mL). The organic phase is washed with brine (3x50 mL), dried over MgSO₄,
10 filtered and concentrated to yield crude compound cxxiii (15.86g).



- Compound cxxiii (15.86 g) is dissolved in dioxane (100 mL). Concentrated HCl (37%, 100 mL) is added to this solution followed by anisole (10 mL) and reflux is established (110°C).
15 The reaction stirred for 1.5 hours. When the reaction mixture is cooled to room temperature, the solvent is removed *in vacuo* to yield a dry paste. The residue is dried overnight under high vacuum to yield crude compound cxxiv.

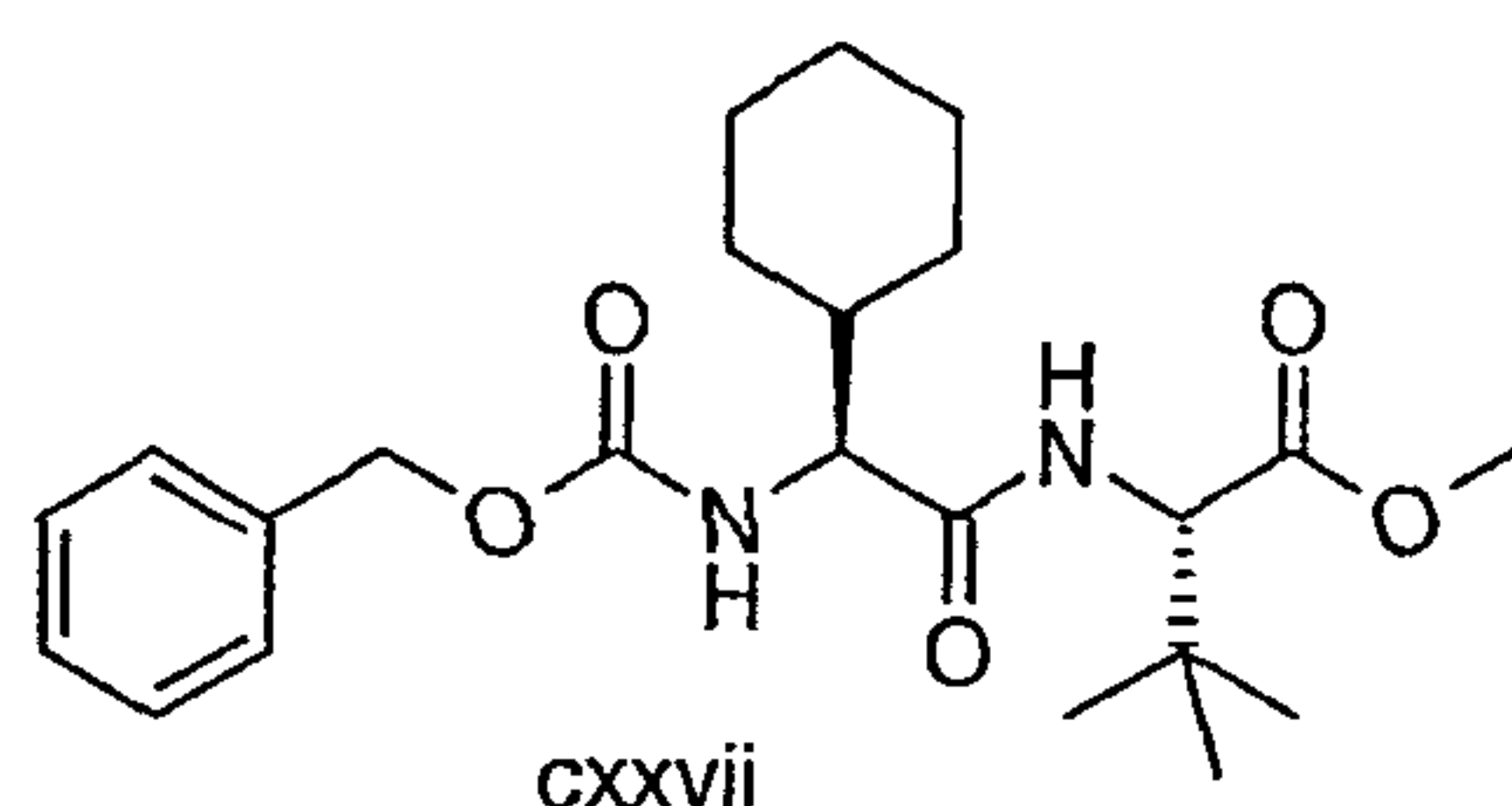


- 20 Compound cxxiv (69.6 mmol) is dissolved in DMF (60 mL) and THF (60 mL). N-(Benzyl-oxycarbonyloxy)succinimide (17.33 g, 69.6 mmol) is added to the mixture, followed by the addition of DIPEA (12.1 mL, 69.6 mmol). The reaction mixture is stirred overnight under N₂. The mixture is concentrated to a reduced volume (50 mL) and diluted with EtOAc. The organic



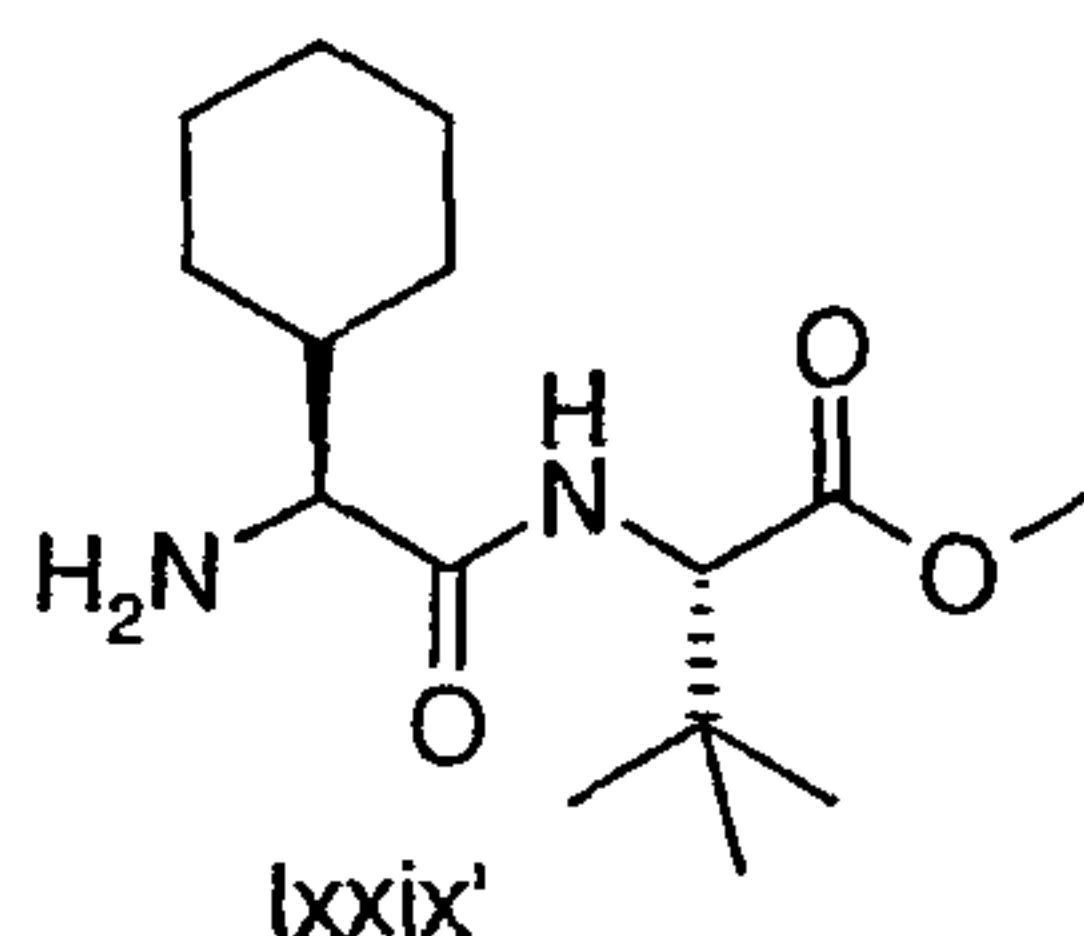
20 N-Cbz-L-Cyclohexylglycine (3 g, 10.3 mmol) is dissolved in DCM (36 mL). HOAt (1.5 g, 11.28 mmol) and DCC (11.28 mL, 11.28 mmol) are added to this solution and stirred five minutes. L-tert-Leucine methyl ester hydrochloride (103 mL, 1 M solution, 10.3 mmol) is added to this mixture and stirred overnight under N₂. The reaction mixture is filtered through celite,

rinsed with EtOAc and concentrated to a residue that is purified chromatographically using 20%-30% EtOAc/hexanes to yield compound cxxvii (2.2 g, 52%).



5 Intermediate Example 121 – Compound lxxix'

Compound cxxvii (2.2 g, 5.2 mmol) is hydrogenated using 20% Pd(OH)₂/C (1 g) in MeOH (15 mL) under H₂ to yield compound lxxix' (1.4 g, 98%).



2-Pyrazinecarboxylic acid (360 mg, 2.9 mmol) is dissolved in DCM (10 mL). PyBOP (1.81 g, 3.5 mmol) is added to the solution. Compound lxxix' (825 mg, 2.9 mmol) in THF (10 mL) is then added to the solution, followed by the addition of DIPEA (0.5 mL, 2.9 mmol). The resulting mixture is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, and the organic phase washed with saturated NaHCO₃ and brine. The residue resulting from the concentration of the organic phase is chromatographically purified by 30% EtOAc/Hexanes to yield Compound lxxx (780 mg, 69%).

Intermediate Example 123 – Compound lxxxi

20 Compound lxxx is hydrolyzed using MeOH (10 mL) and 1 N NaOH (3 eq) to yield compound lxxxi (615 mg, 81.8%).

Intermediate Example 124 – Compound lxxxii

25 Compound lxxxi (610 mg, 1.6 mmol) is dissolved in DCM (10 mL). DCC (1.94 mL, 1.94 mmol) is then added to the solution, followed by the addition of HOAt (270 mg, 1.94 mmol). Compound v (1.94 mmol) in THF (19.4 mL) is then added to the solution. The resulting mixture

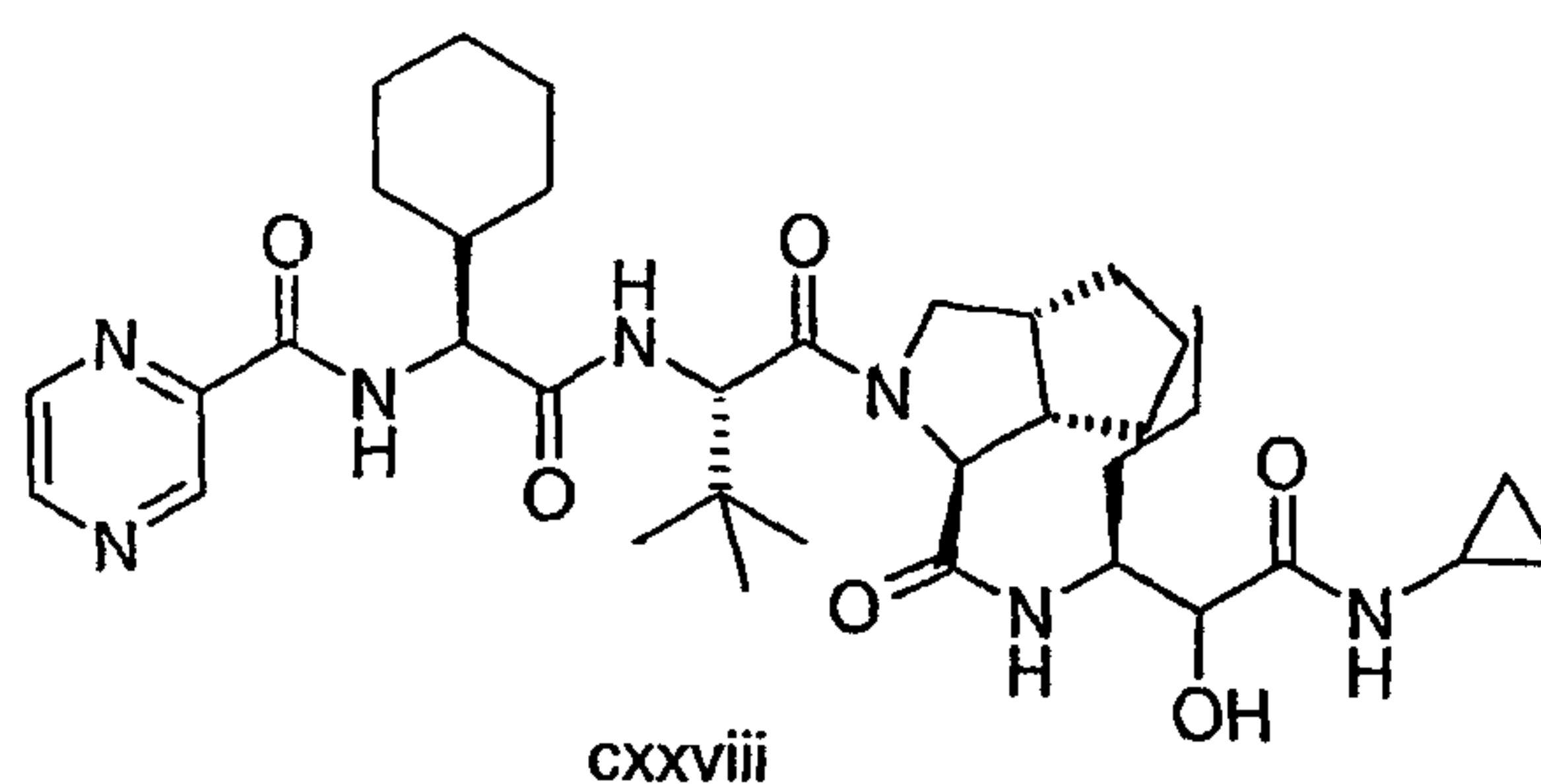
is stirred over two nights under N₂. The reaction mixture is diluted with EtOAc, filtered through silica gel, and concentrated. The resulting residue is purified chromatographically by 40% EtOAc/hexanes to yield compound lxxxii (450 mg, 83.4%).

5 Intermediate Example 125 – Compound lxxxiii

Compound lxxxi is hydrolyzed using EtOH (10 mL) and 1 N NaOH (3 eq) to yield compound lxxxiii (650 mg, 99%).

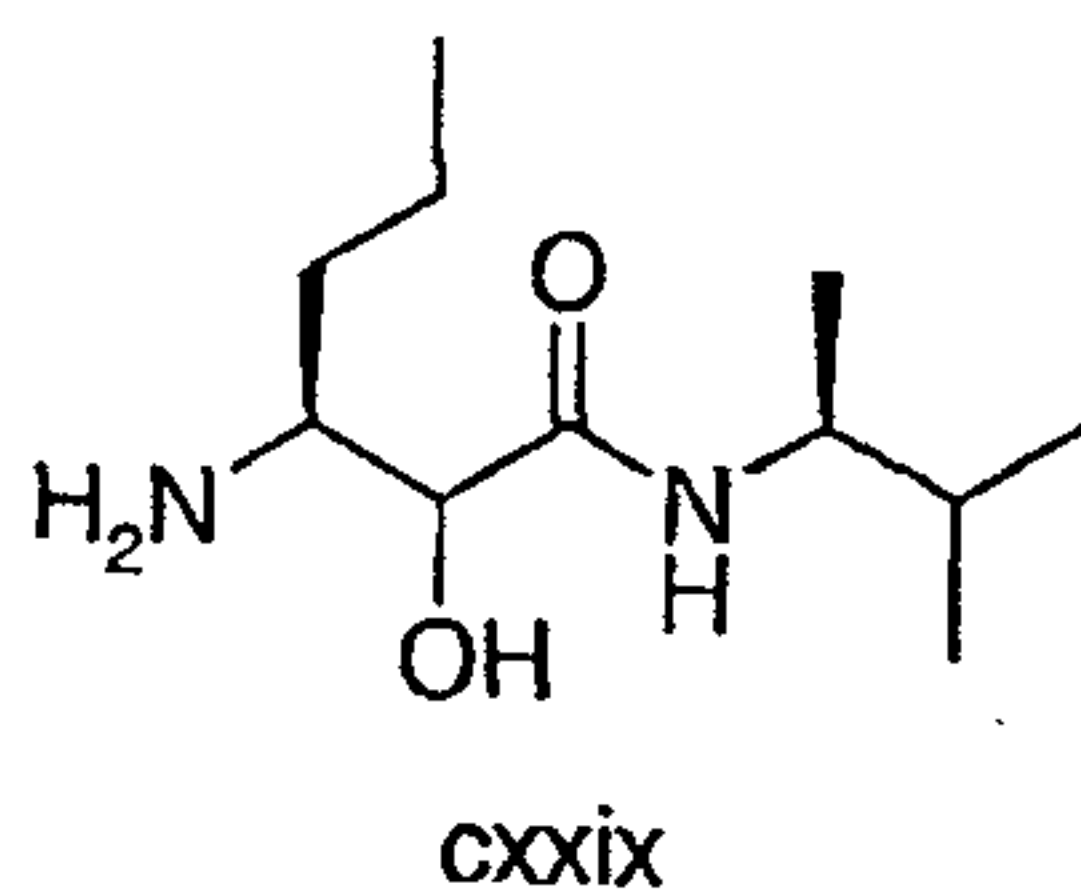
Intermediate Example 126 – Compound cxxviii

10 Compound lxxxiii (400 mg, 0.78 mmol) is dissolved in DCM (5 mL). PyBOP (610 mg, 1.2 mmol) is added to the solution, followed by Compound xiii' (230 mg, 1.2 mmol). To the resulting mixture is added DIPEA (0.2 mL, 1.2 mmol). The reaction mixture is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, and the organic phase washed with saturated NaHCO₃ and brine. Following the concentration of the organic phase, the residue is
15 chromatographically purified by 100% EtOAc to 5% EtOH/EtOAc gradient to yield compound cxxviii (365 mg, 68.7%).



20 Intermediate Example 127 – Compound cxxx

Compound lxxxiii (365 mg, 0.7 mmol) is dissolved in DCM (5 mL). PyBOP (440 mg, 0.84 mmol) is added to the solution, followed by the addition of compound cxxix (0.84



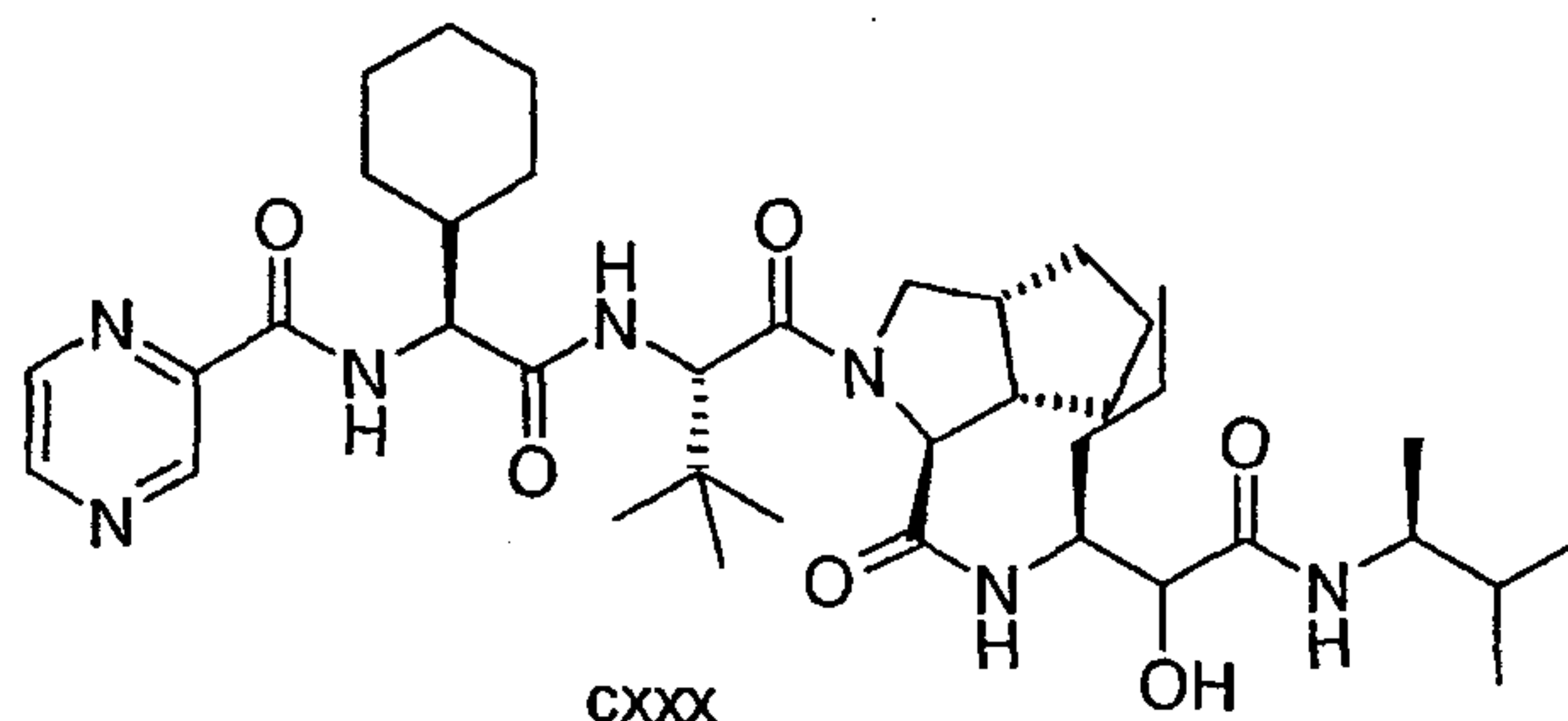
mmol) in THF (8.4 mL). To the resulting mixture is added DIPEA (0.1 mL, 0.84 mmol). The
25 reaction mixture is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, and

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the organic phase is washed with saturated NaHCO_3 and brine. Following the concentration of the organic phase, the resulting residue is chromatographically purified by 100% EtOAc to yield compound cxxx (350 mg, 70%).

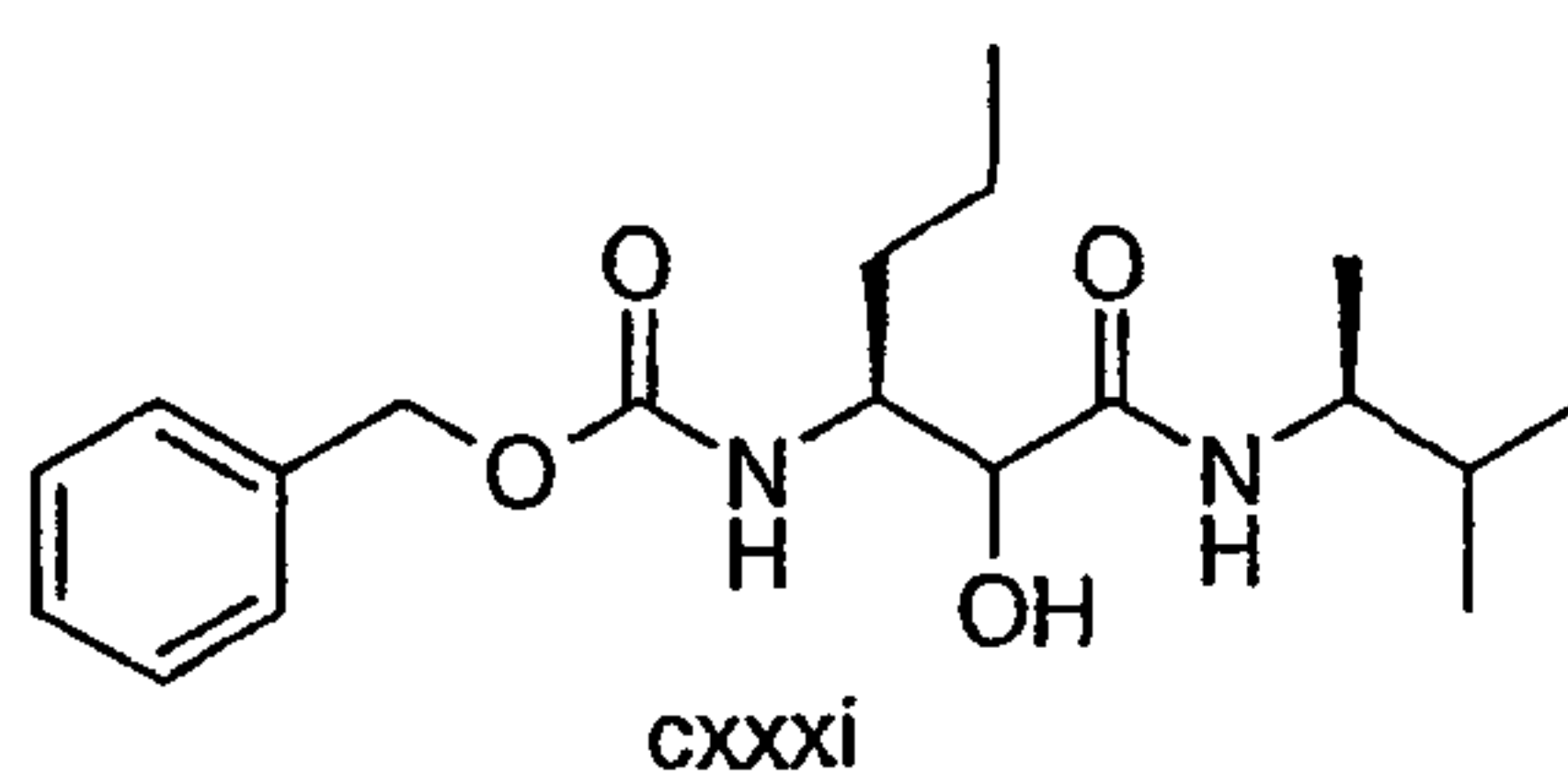


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Intermediate Example 128 – Compound cxxxi

Compound cxxv (2.54 g, 9.05 mmol) is dissolved in DCM (30 mL). PyBOP (5.65 g, 10.9 mmol) and HOBT (1.47 g, 10.9 mmol) are added to the solution and stirred five minutes. The resulting mixture is lowered to 0°C , whereupon (S)-(+)-3-Methyl-2-butylamine (1.27 mL, 10.9 mmol) and DIPEA (1.9 mL, 10.9 mmol) are added. The reaction mixture is stirred overnight with warming to room temperature. The organic phase is washed with 0.1 N HCl, saturated NaHCO_3 and brine. Following the concentration of the organic phase, the resultant residue is chromatographically purified by 30% EtOAc/hexanes to yield compound cxxxi (1.44 g, 45.5%).

15



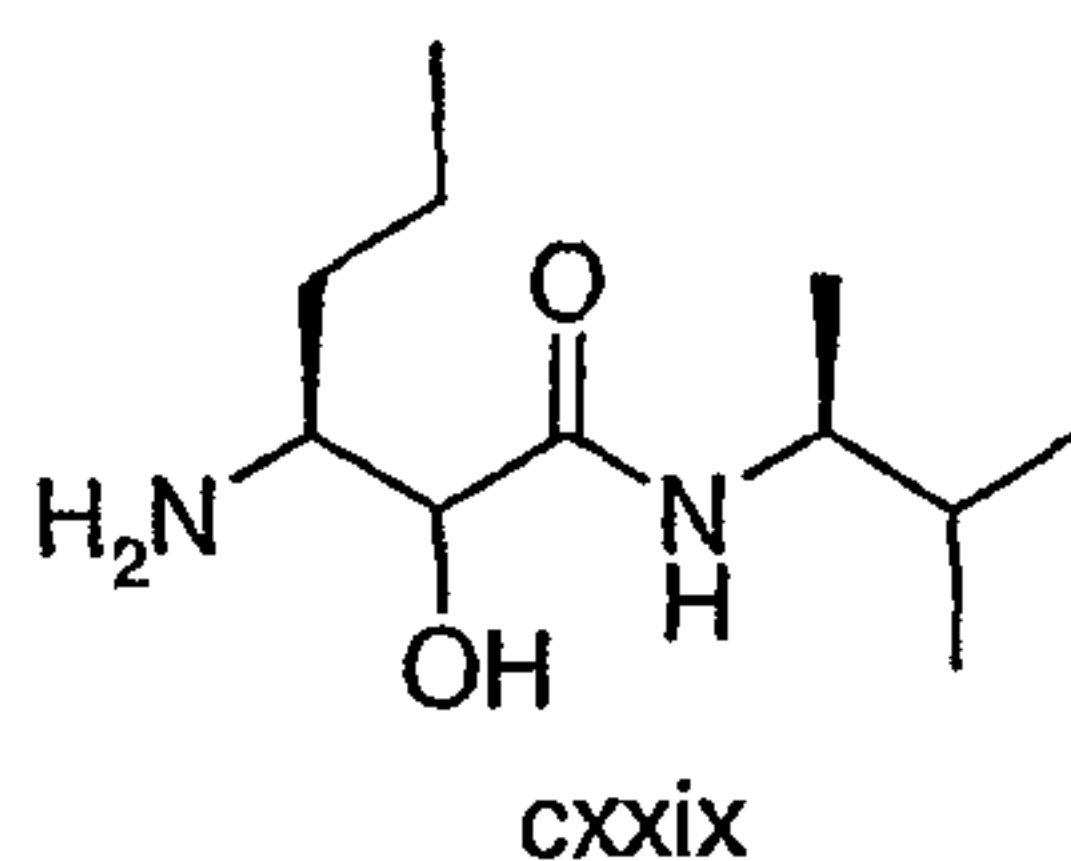
Intermediate Example 129 – Compound cxxix

Compound cxxxi (1.3 g, 3.7 mmol) is hydrogenated using 10% Pd/C (500 mg) in MeOH (40 mL). The reaction mixture is stirred overnight under H_2 . The reaction mixture is filtered through celite and the organic phase concentrated to yield crude compound cxxix (800 mg, 100%).

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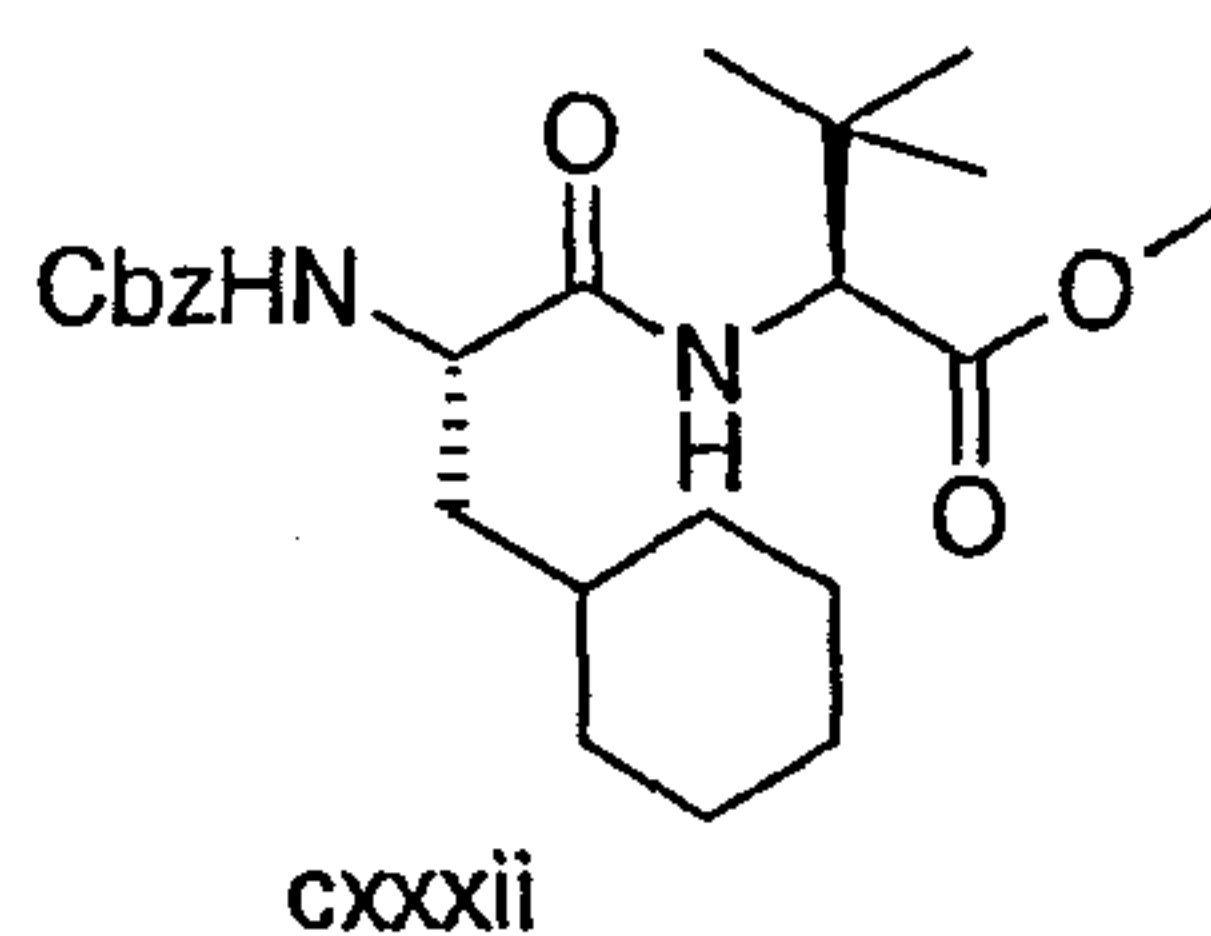
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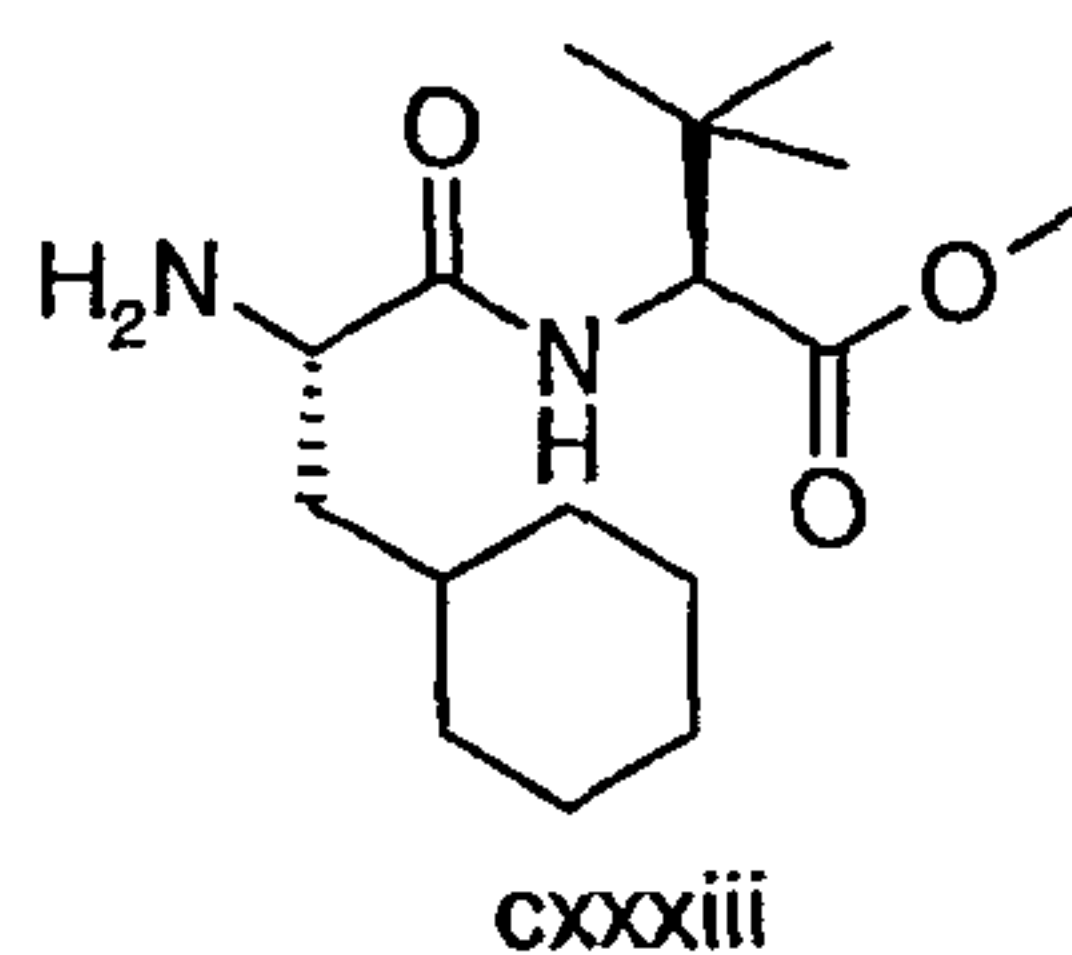


Intermediate Example 130 – Compound cxxxiv

Compound cxxxii (1.6 g, 3.7 mmol) is dissolved in MeOH (12 mL). After thoroughly

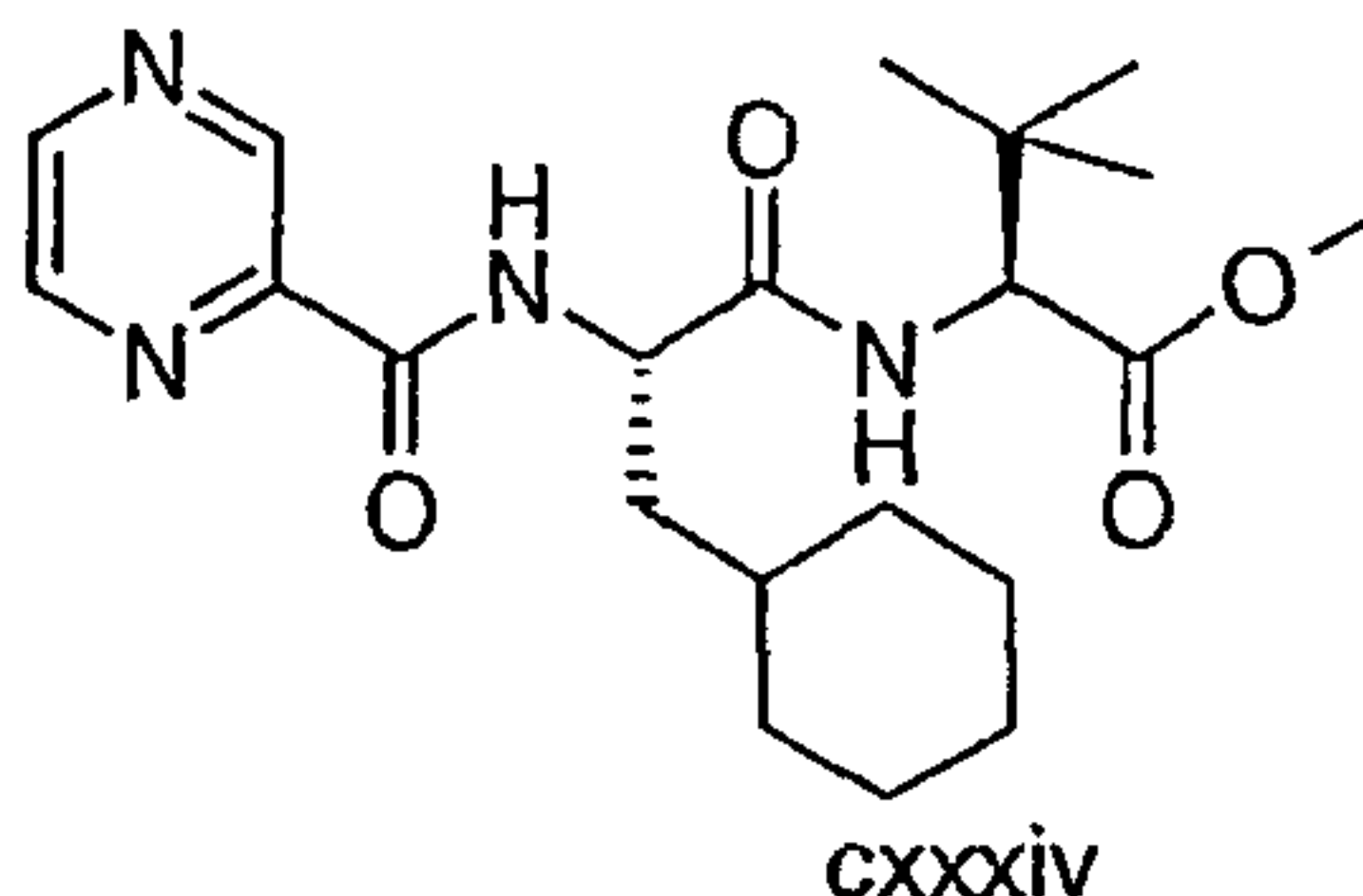


flushing with N₂, 10 wt% Pd(OH)₂ on carbon (0.74 g) is added and the mixture is hydrogenated overnight, whereupon a complete reaction mixture is shown by TLC (30% EtOAc/hexanes). The solution is isolated from solid material by filtration and concentrated to yield compound cxxxiii as colorless oil (100%) that is used in the next



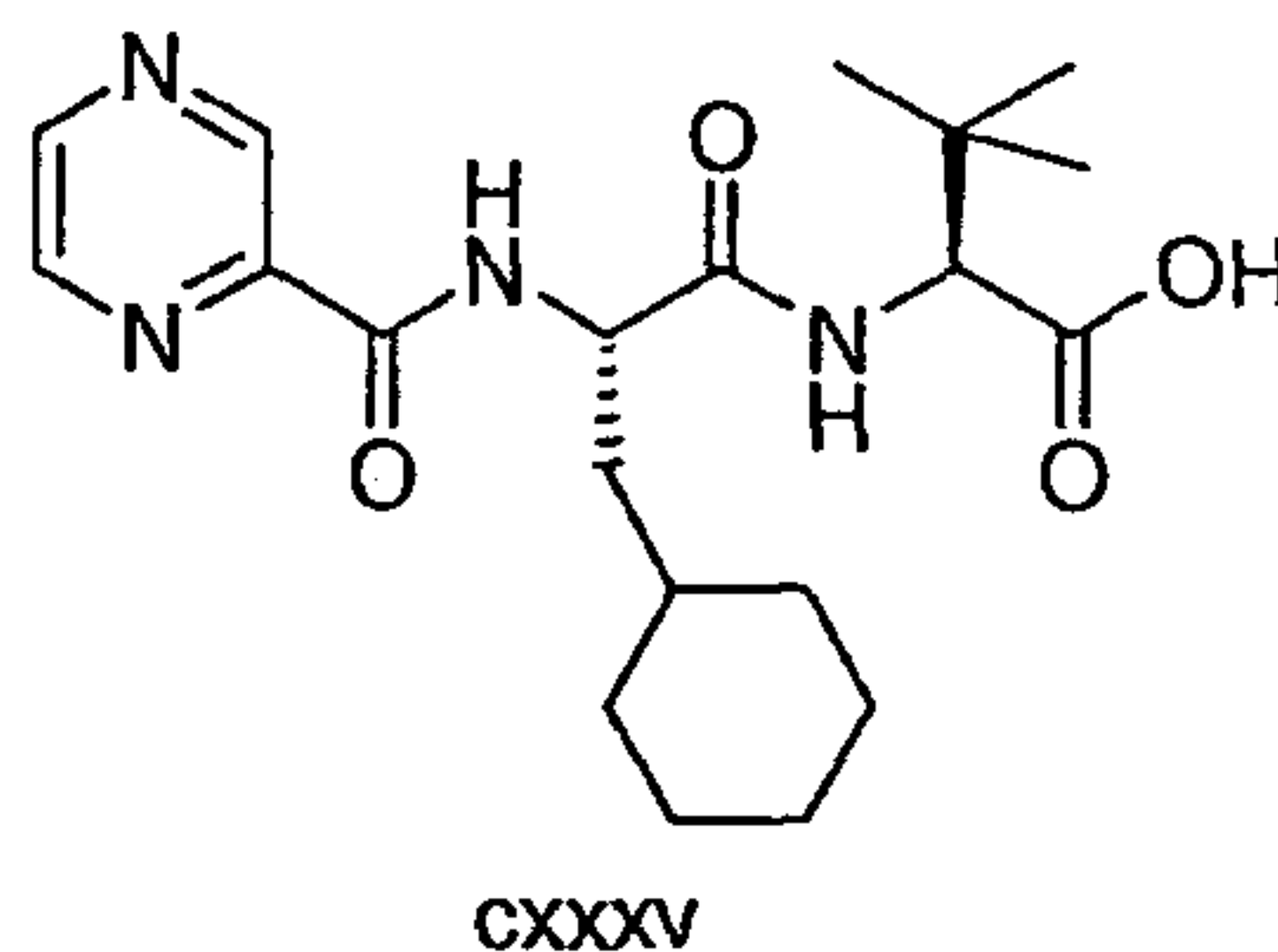
step without further purification. 2-Pyrazinecarboxylic acid (400 mg, 3.2 mmol, 1.1 eq) is dissolved in DCM/THF (4mL/4 mL), and then HOAt (440 mg, 3.2 mmol) and DCC (3.3 mL, 1 M in DCM) is added. After stirring at room temperature for 20 minutes, compound cxxxiii (0.96 g, 3.2 mmol) obtained previously is dissolved in DCM (6.4 mL) and added to the activated mixture. After stirring over 2 days at room temperature, the reaction mixture is filtered through Celite, and concentrated to a residue that is purified by column chromatography (50% EtOAc/hexanes) to yield compound cxxxiv as a white solid (1.06 g, 83%).

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Intermediate Example 131 – Compound cxxxv

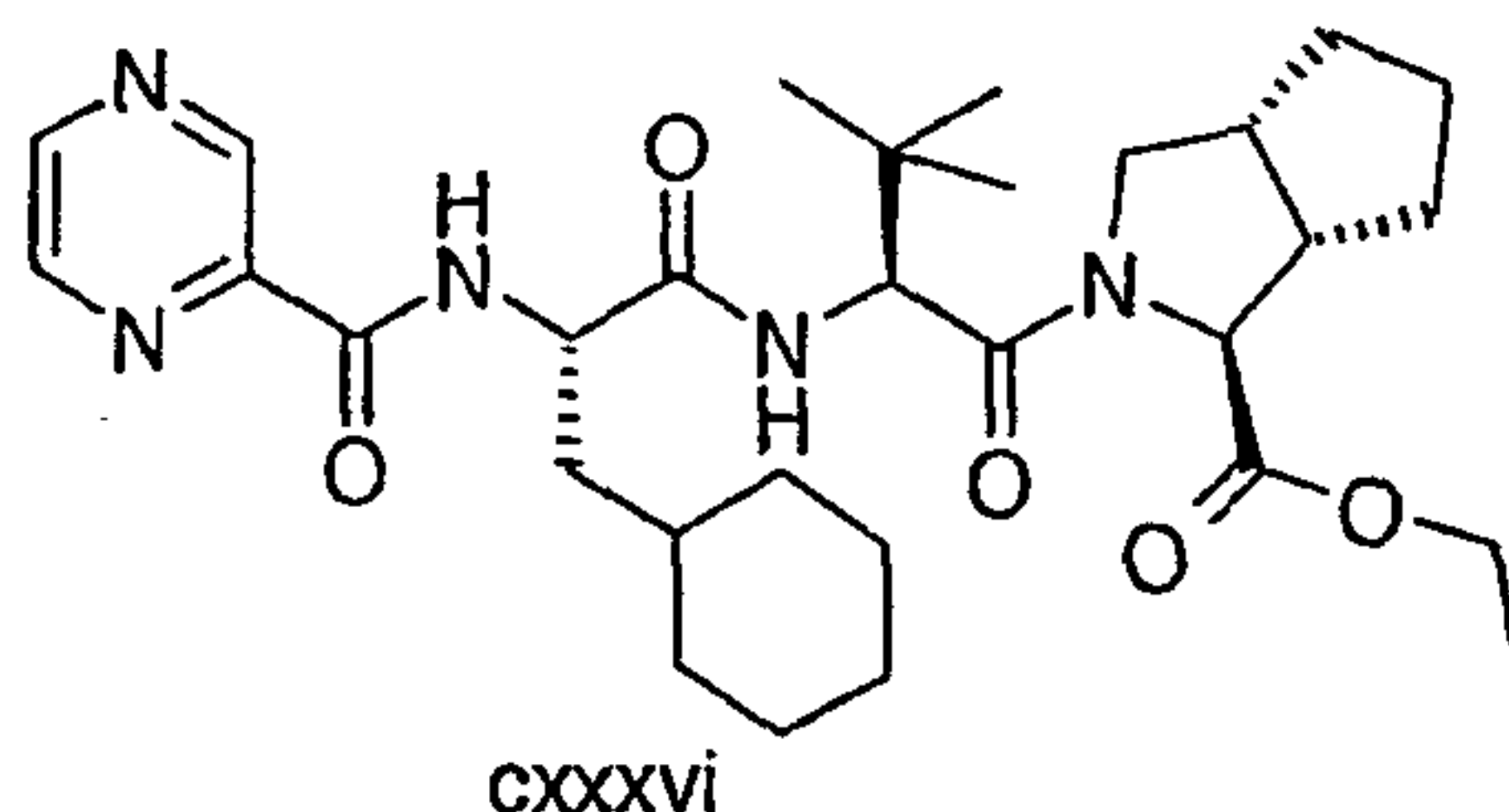
Compound cxxxiv (1.06 g, 2.6 mmol) is dissolved in MeOH (10 mL), and then 2 N
 5 NaOH (aq) (4 mL, 8 mmol) is added. The solution is stirred at room temperature overnight, whereupon the completion of the hydrolysis is indicated by TLC (50% EtOAc/hexanes). The solution is acidified to pH 3 by 5 N HCl, diluted with EtOAc and then the organic phase is extracted. The extracted organic phase is washed with brine and dried over MgSO₄ to yield compound cxxxv (100%) upon concentration.



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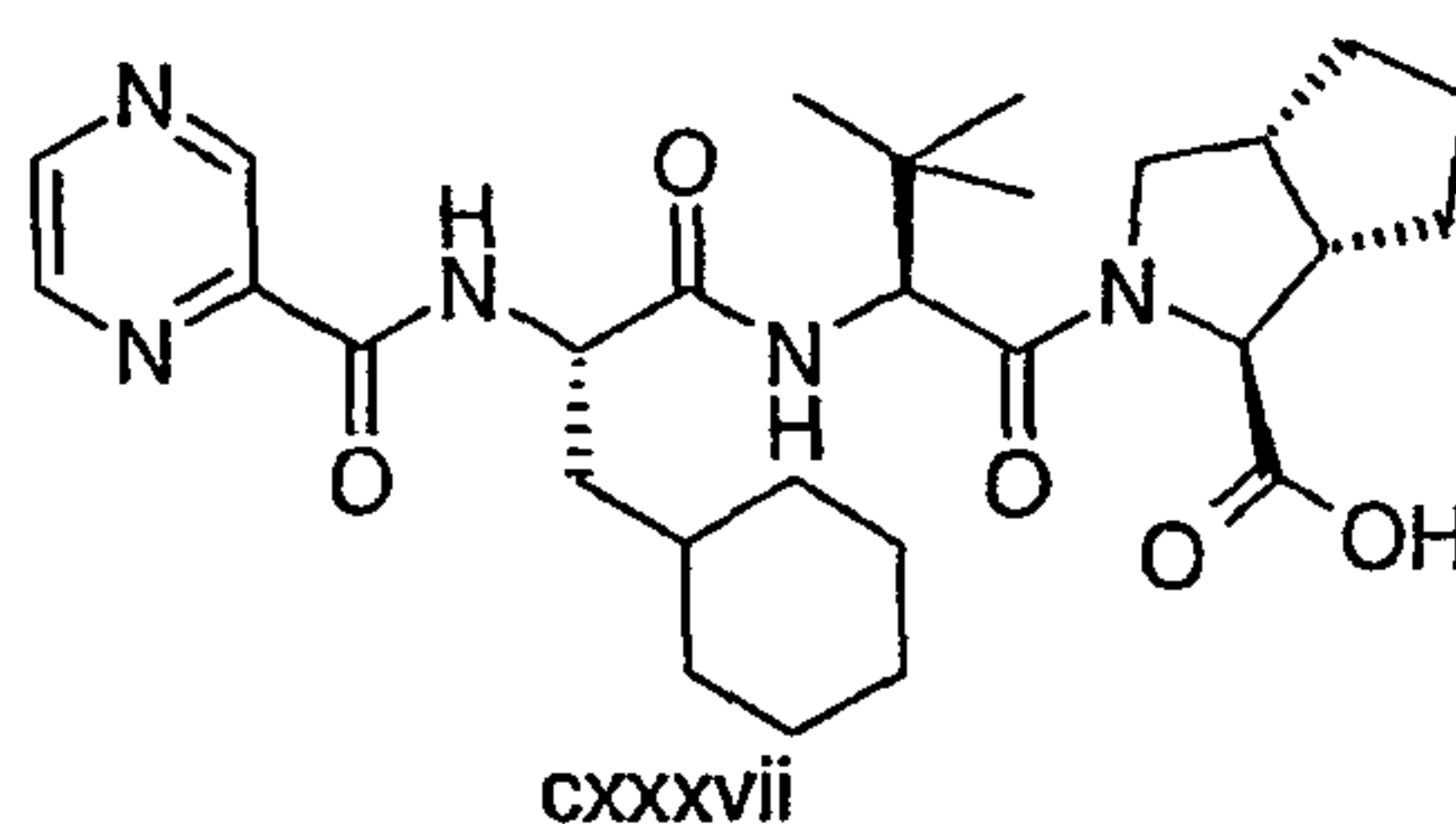
Intermediate Example 132 – Compound cxxxvi

To a DCM solution (8 mL) of compound cxxxv (1.44 g, 3.7 mmol) at room temperature is added HOAt (500 mg, 3.7 mmol), and then 1 M DCC solution in DCM (3.7 mL, 3.7 mmol) is
 15 added. After stirring for 30 minutes at room temperature, a THF solution (18.5 mL, 0.2 M) of compound v (3.7 mmol) is added to the above HOAt-activated acid. The reaction mixture is stirred at room temperature overnight. The reaction mixture is filtered through Celite. The filtrates are diluted with EtOAc (120 mL) and washed with water and brine. The organic phase is dried and concentrated to yield yellow oil that is purified by silica gel chromatography (70%
 20 EtOAc/hexanes) to yield compound cxxxvi (1 g, 71%).



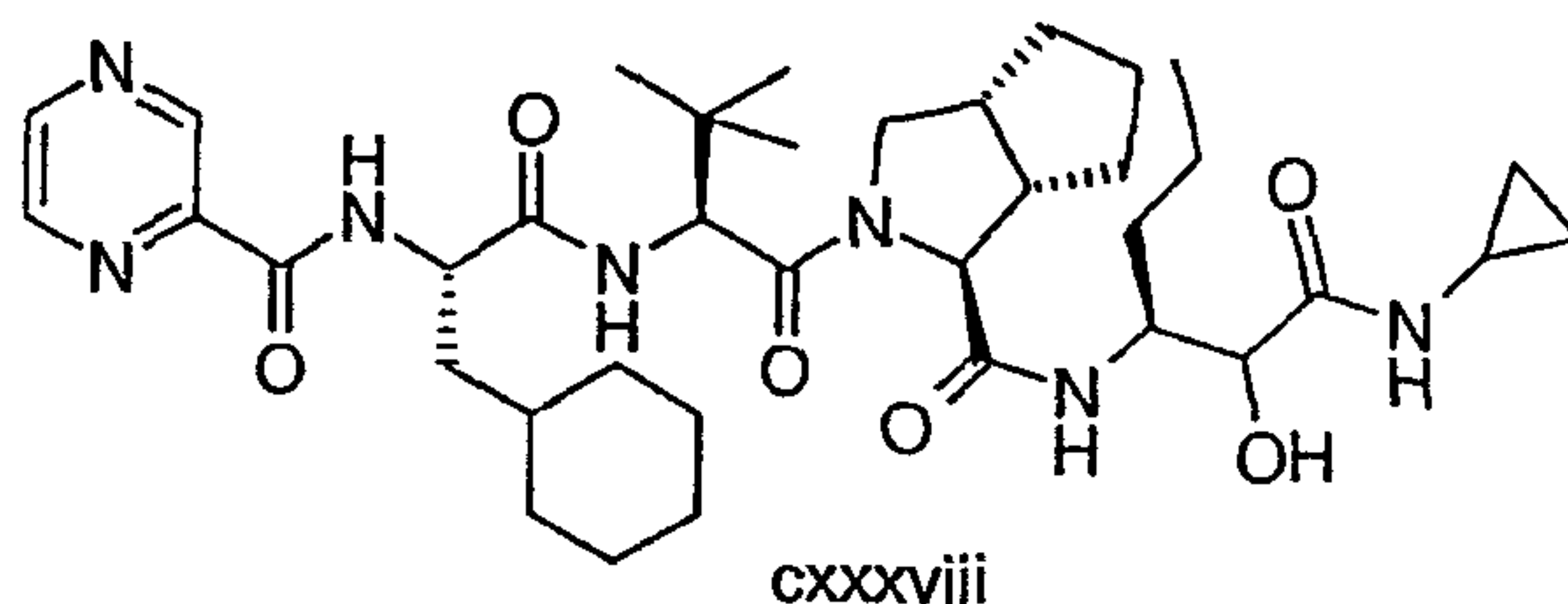
Intermediate Example 133 – Compound cxxxvii

To an EtOH solution (8 mL) of compound cxxxvi (1 g, 1.8 mmol) is added 2 N NaOH aqueous solution (2.7 mL, 5.4 mmol). The reaction mixture is stirred overnight at room temperature, then acidified to pH 3 by 5 N HCl, diluted with EtOAc, and then the organic phase is extracted. The extracted organic phase is washed with brine and dried over MgSO₄ to yield compound cxxxvii (88%) upon concentration.



Intermediate Example 133 – Compound cxxxviii

To a DCM solution (10 mL) of compound cxxxvii (350 mg, 0.6 mmol) is added PyBOP (450 mg, 0.86 mmol). The solution is stirred at room temperature for 30 minutes. To this solution is then added compound xiii' (160 mg, 0.86 mmol) followed by DIPEA (0.23 mL, 1.3 mmol). The reaction mixture is stirred at room temperature overnight and then quenched with water (25 mL) for 30 minutes. The mixture is then extracted with EtOAc. The extracted organic phase is washed with brine and dried over MgSO₄, before being concentrated to yield yellow oil. Purification by silica gel chromatography (5% EtOH/EtOAc) yields compound cxxxviii (407 mg, 88%).



Intermediate Example 134 – Compound cxxxix

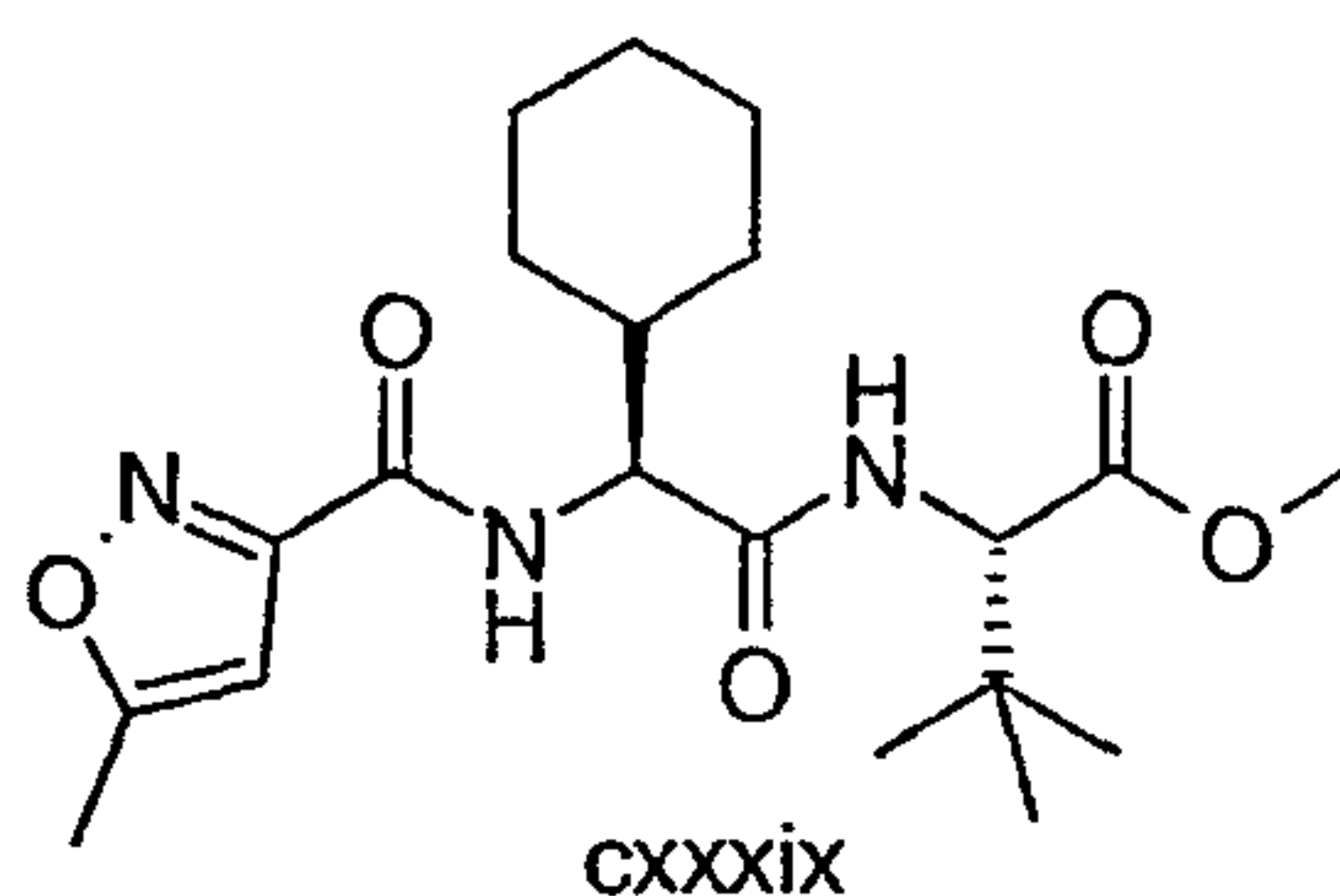
5-Methylisoxazole-3-carboxylic acid (200 mg, 2.05 mmol) is dissolved in DCM (5 mL). PyBOP (1.07 g, 2.05 mmol) is added to the solution. Compound lxxix' (582 mg, 2.05 mmol) in DCM (5 mL) is added to the solution, followed by the addition of DIPEA (0.36 mL, 2.05 mmol). The resulting mixture is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, and the organic phase washed with saturated NaHCO₃ and brine. The organic phase is

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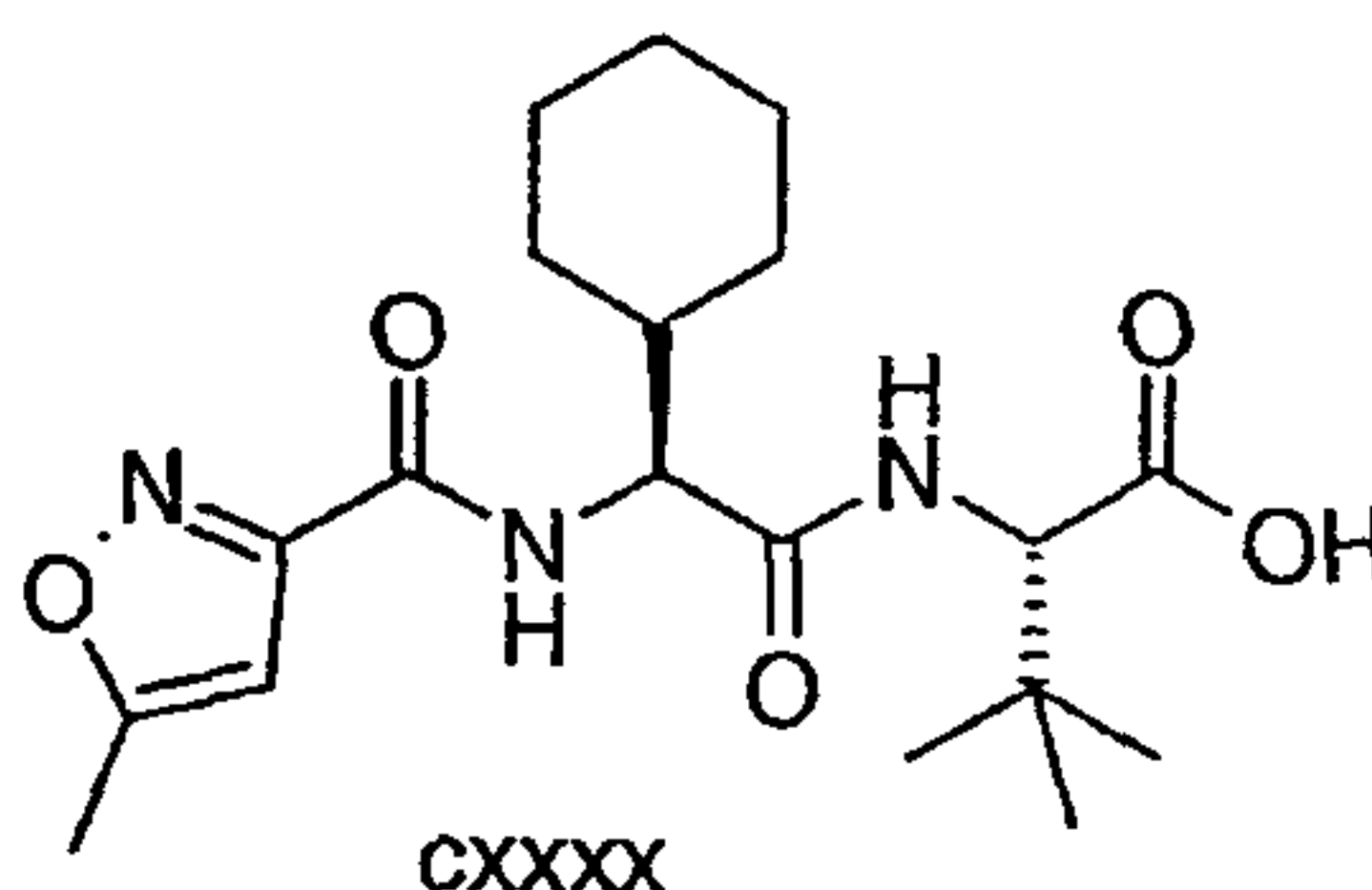
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concentrated, and the resultant residue is purified chromatographically by 30% EtOAc/hexanes to yield Compound cxxxix (495 mg, 61.4%).



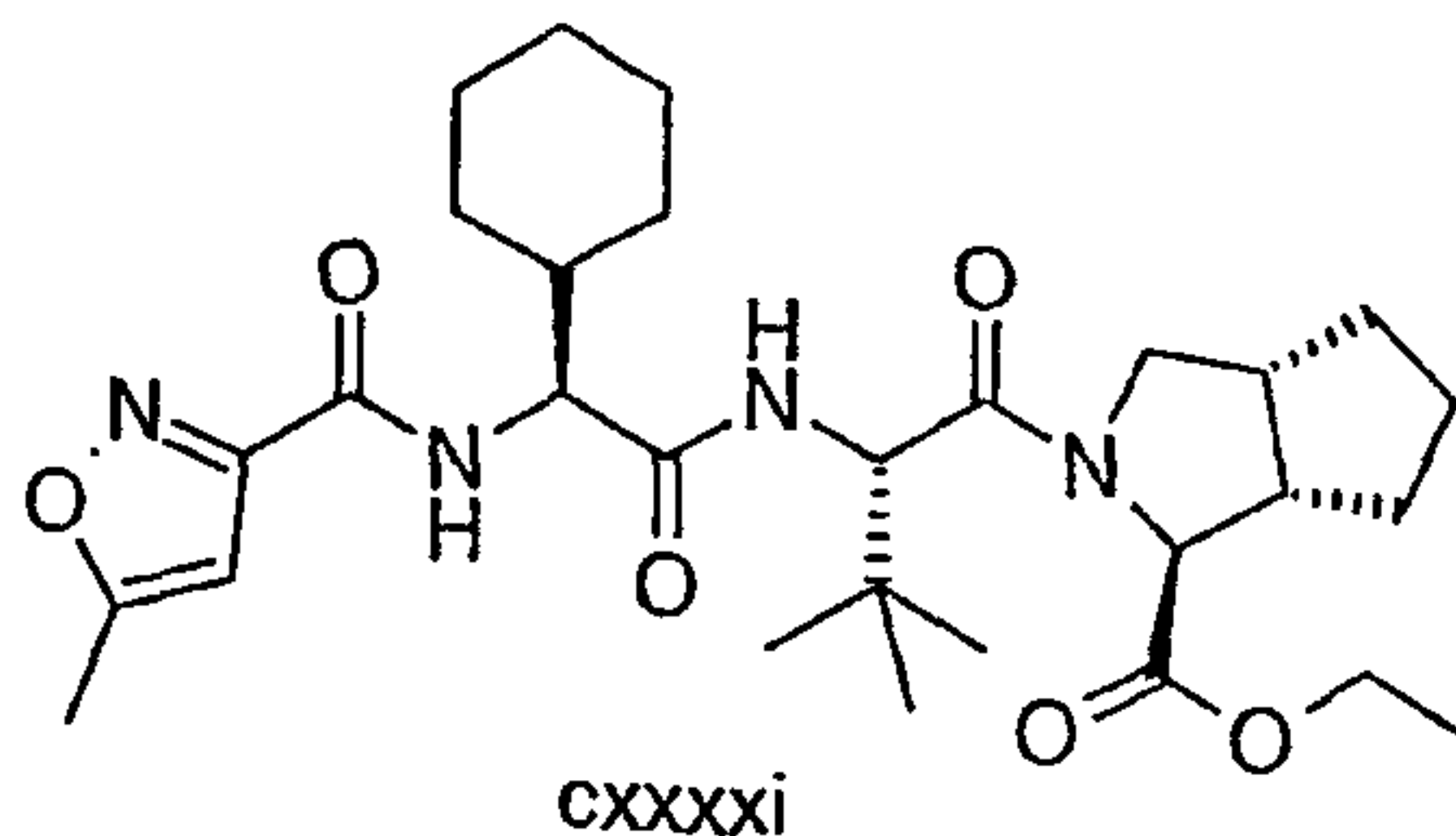
5 Intermediate Example 135 – Compound cxxxx

Compound cxxxix is hydrolyzed using MeOH (10 mL) and 1 N NaOH (3 eq) to yield compound cxxxx (430 mg, 90%).



10 Intermediate Example 136 – Compound cxxxxi

Compound cxxxx (380 mg, 1 mmol) is dissolved in DCM (5 mL). DCC (1.2 mmol) is then added to the solution, followed by the addition of HOAt (165 mg, 1.2 mmol). Compound v (1.2 mmol) is then added in THF (12 mL). The resulting mixture is stirred overnight under N₂. The reaction mixture is diluted with EtOAc, filtered through silica gel, and concentrated. The resultant residue is chromatographically purified by 35% EtOAc/hexanes to yield compound cxxxxi (320 mg, 58%).



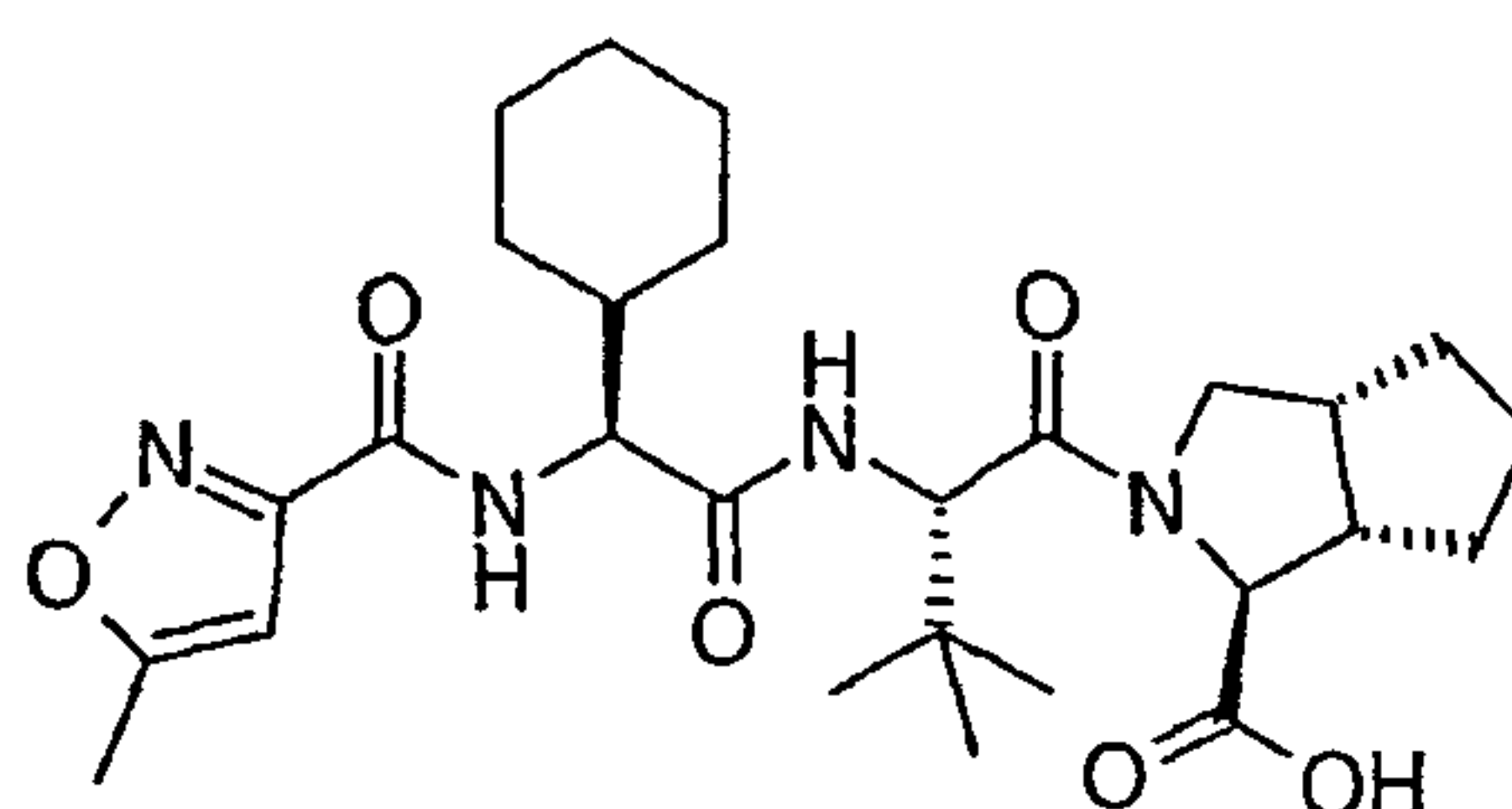
Intermediate Example 137 – Compound cxxxxii

20 Compound cxxxxi is hydrolyzed using EtOH (10 mL) and 1 N NaOH (3 eq) to yield compound cxxxxii (730 mg, 94.3%).

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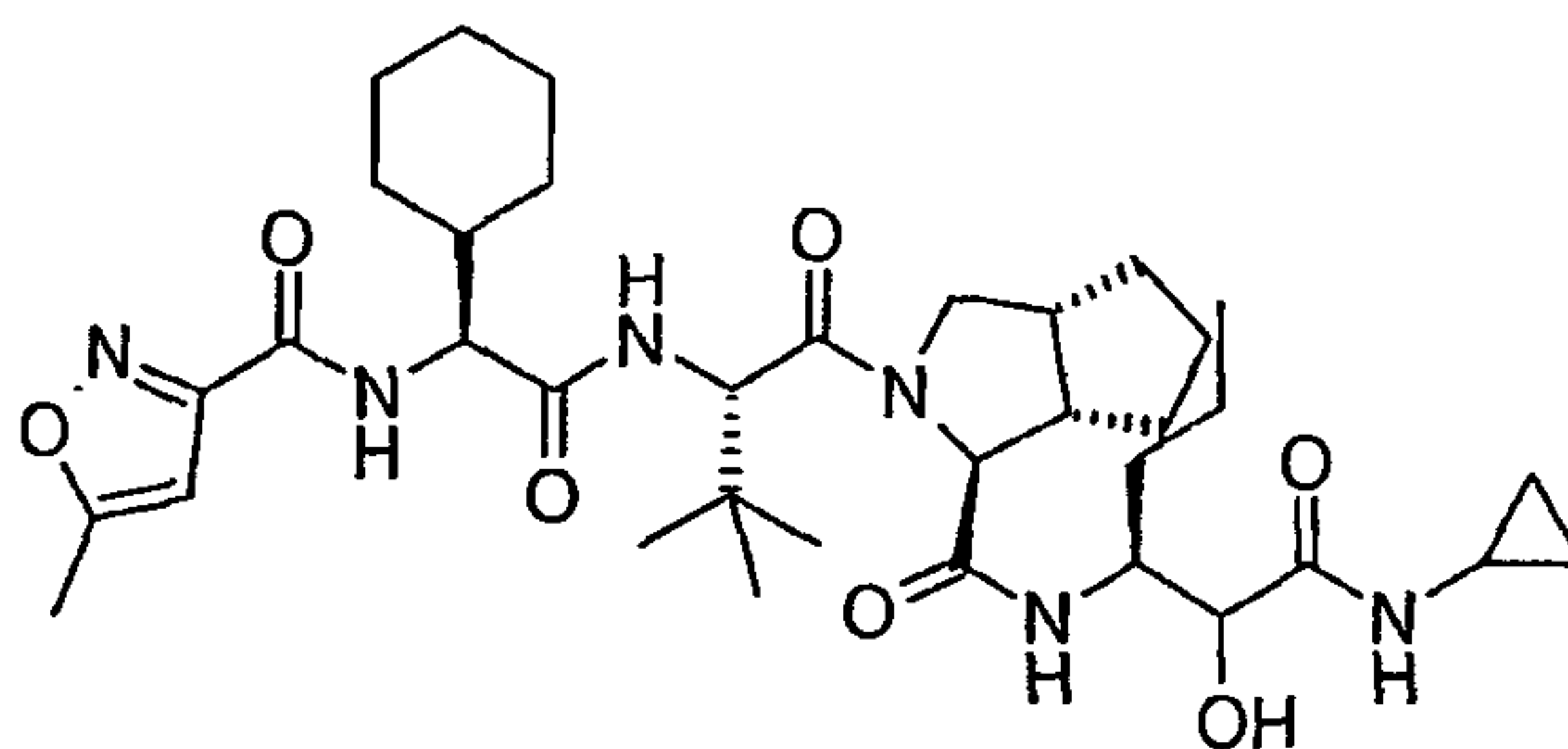
231



cxxxxii

Intermediate Example 138 – Compound cxxxxiii

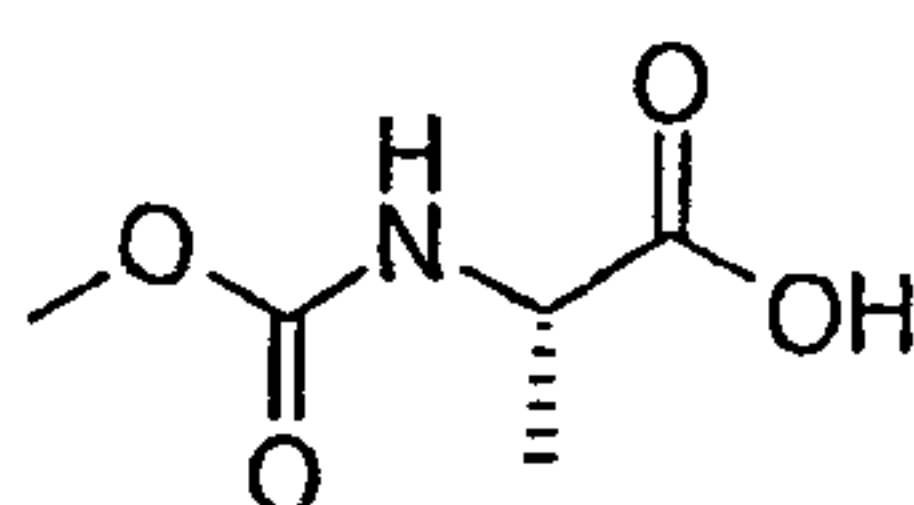
Compound cxxxxii (240 mg, 0.46 mmol) is dissolved in DCM (5 mL). PyBOP (295 mg, 0.56 mmol) is then added to the solution, followed by the addition of Compound xiii' (110 mg, 0.56 mmol). To the resulting mixture is added DIPEA (0.1 mL, 0.56 mmol). The reaction mixture is stirred over two nights under N₂. The reaction mixture is diluted with EtOAc, and the organic phase washed with saturated NaHCO₃ and brine. Following the concentration of the organic phase, the resultant residue is chromatographically purified by 90% EtOAc/hexanes to yield Compound cxxxxiii (168 mg, 53%).



cxxxxiii

Intermediate Example 139 – Compound cxxxxiv

To a solution of NaOH (2N, 42.1 mL, 84.2 mmol) at 5 °C is added L-alanine (5.00 g, 56.1 mmol). After stirring for 10 minutes, methyl chloroformate (6.5 mL, 84.2 mmol) and NaOH (2 N, 42.1 mL, 84.2 mmol) are added dropwise simultaneously. The solution is stirred in ice bath for 2 hours, then at room temperature for 1 hour. The mixture is washed with Et₂O (2 x 50 mL), the aqueous layer is neutralized to pH ~2 with 5 N HCl, and extracted with EtOAc (3 x 50 mL). The extracted organic phase is washed with brine, dried by MgSO₄ and concentrated to yield



cxxxxiv

compound cxxxxiv, N-carbomethoxy-L-alanine, (4.54 g, 54%) as colorless oil.

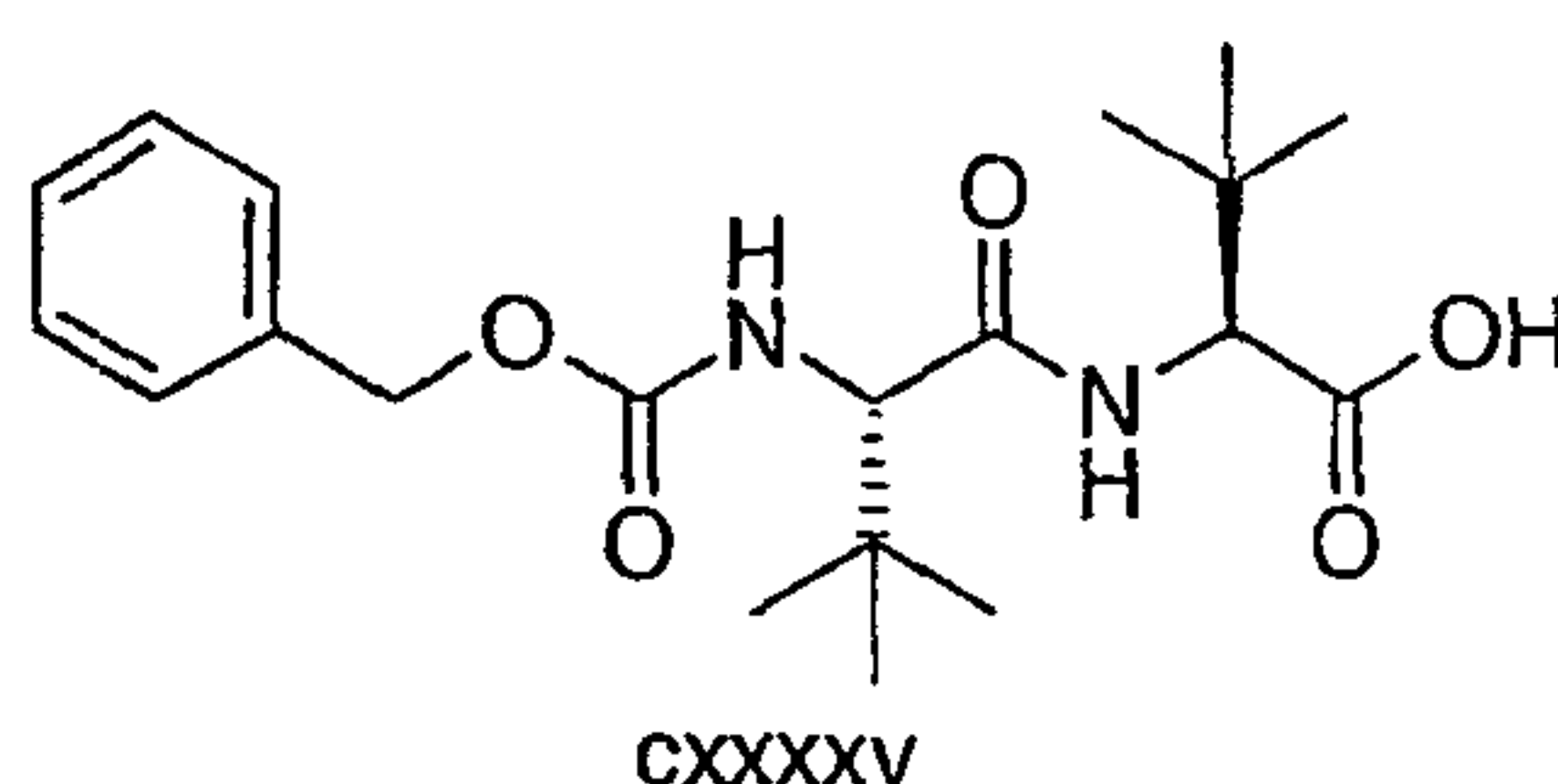
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Intermediate Example 140 – Compound cxxxxvi

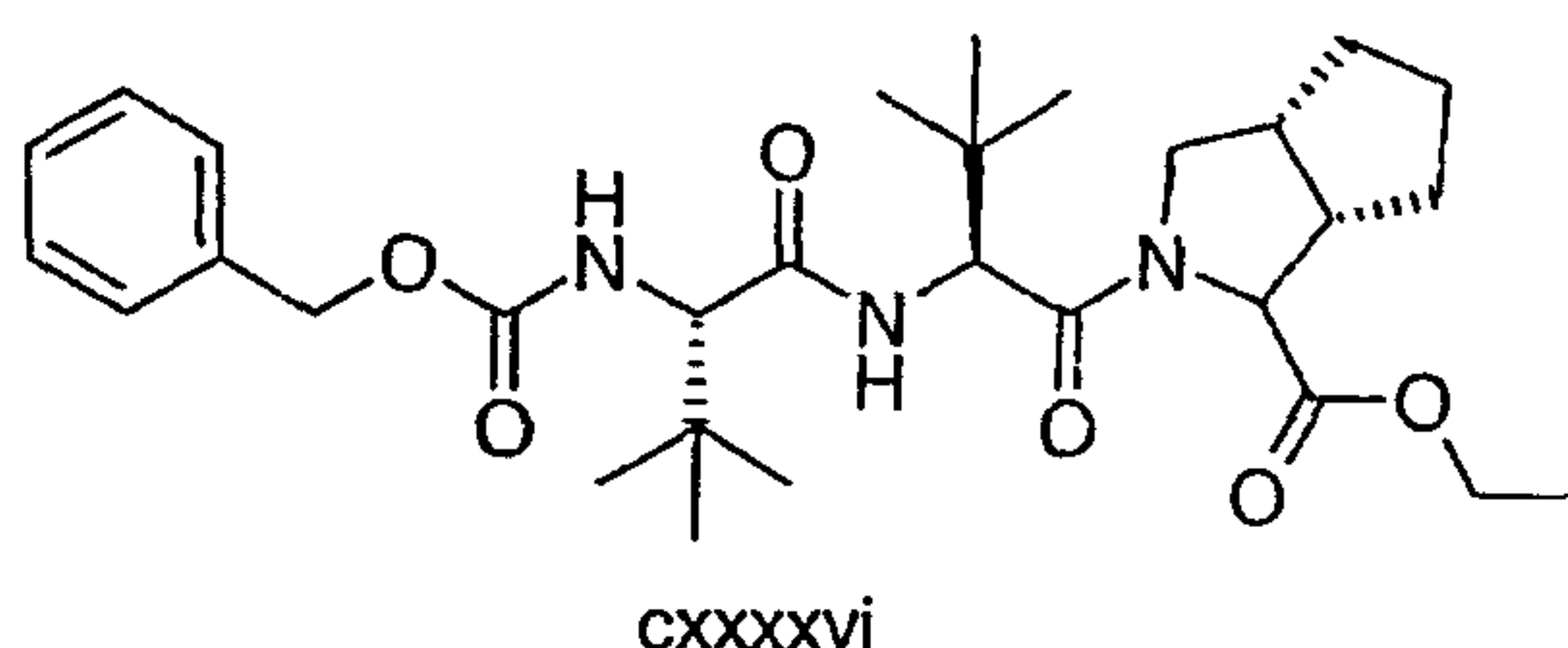
A solution of compound cxxxxv (3.57 g, 9.44 mmol) in THF at 5 °C is treated with HOAt



5

(1.28 g, 9.44 mmol), and then DCC (9.50 mL, 9.50 mmol) is added. After stirring in ice bath for 45 minutes, a solution of compound v (104 mL, 10.4 mmol) in THF is added. The mixture is stirred at room temperature overnight. The mixture is cooled to 5 °C and quenched with saturated NaHCO₃. After filtration to remove the precipitated DCU, the mixture is dissolved in EtOAc (100 mL), washed with saturated NaHCO₃, brine, and then dried by MgSO₄ and concentrated to a residue purified by silica column chromatography (25% EtOAc/Hexanes) to yield compound cxxxxvi (2.91 g, 57%) as gummy foam.

10



15 Intermediate Example 141 – Compound cviii

To a solution of compound cxxxxvi in MeOH (25 mL) cooled by an ice bath under a stream of N₂ is added slowly Pd/C. The mixture is hydrogenated at 1 atm overnight. The catalyst is removed by filtration, the filtrate is combined with 5 mL DMF and dried under vacuum to yield compound cviii.

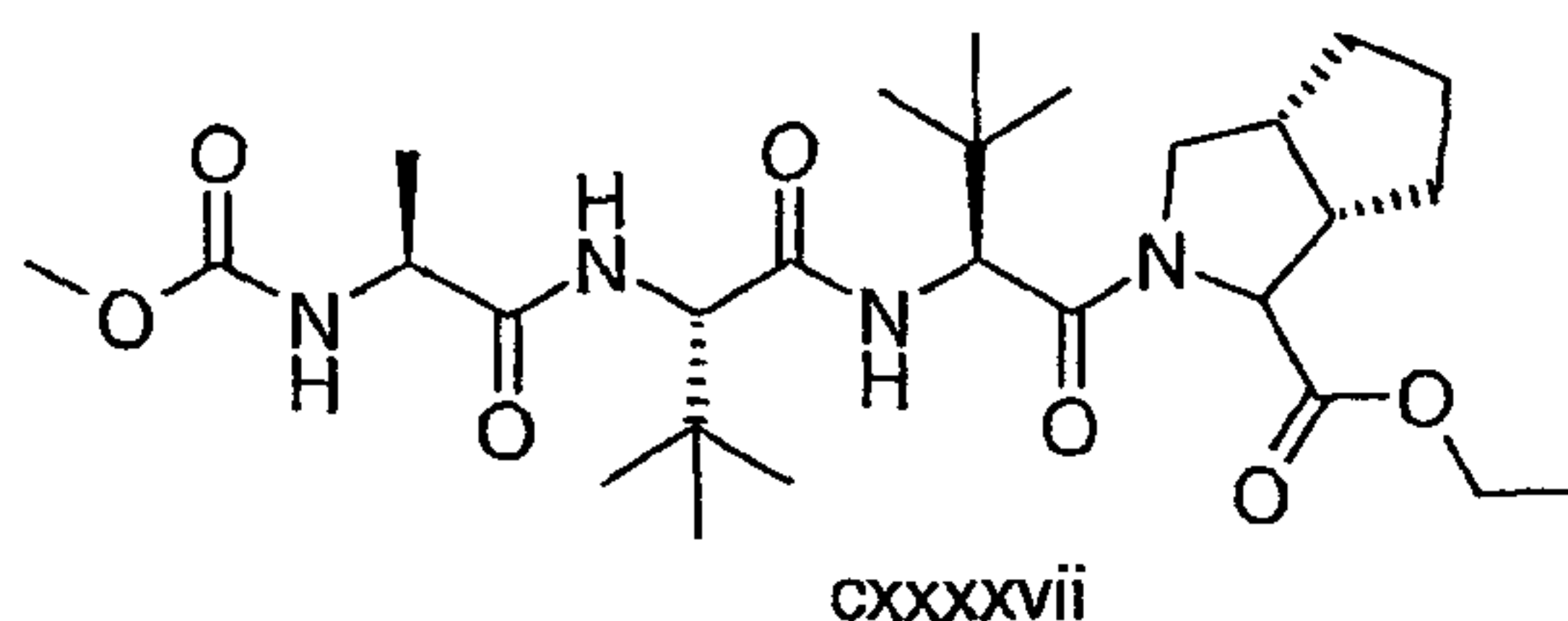
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Intermediate Example 142 – Compound cxxxxvii

To a solution of compound cxxxxiv (0.298 g, 2.03 mmol) and HOAt (0.276 g, 2.03 mmol) in THF cooled in ice bath is treated with DCC (2.05 mL, 2.05 mmol). After stirring in an ice bath for 0.5 hour, a solution of compound cviii in THF is added, and then DIPEA (0.39 mL, 2.2 mmol) is added. The mixture is stirred at room temperature overnight, then cooled in an ice bath, and quenched with saturated NaHCO₃. The precipitated DCU is filtered and the filtrate is

25

dissolved in EtOAc (100 mL). The organic phase is washed with saturated NaHCO₃, brine, and then dried by MgSO₄. After removal of the organic solvent, the residue is purified by silica column chromatography (60% EtOAc/Hexanes) to yield compound cxxxxvii (0.47 g, 48%) as gummy foam.

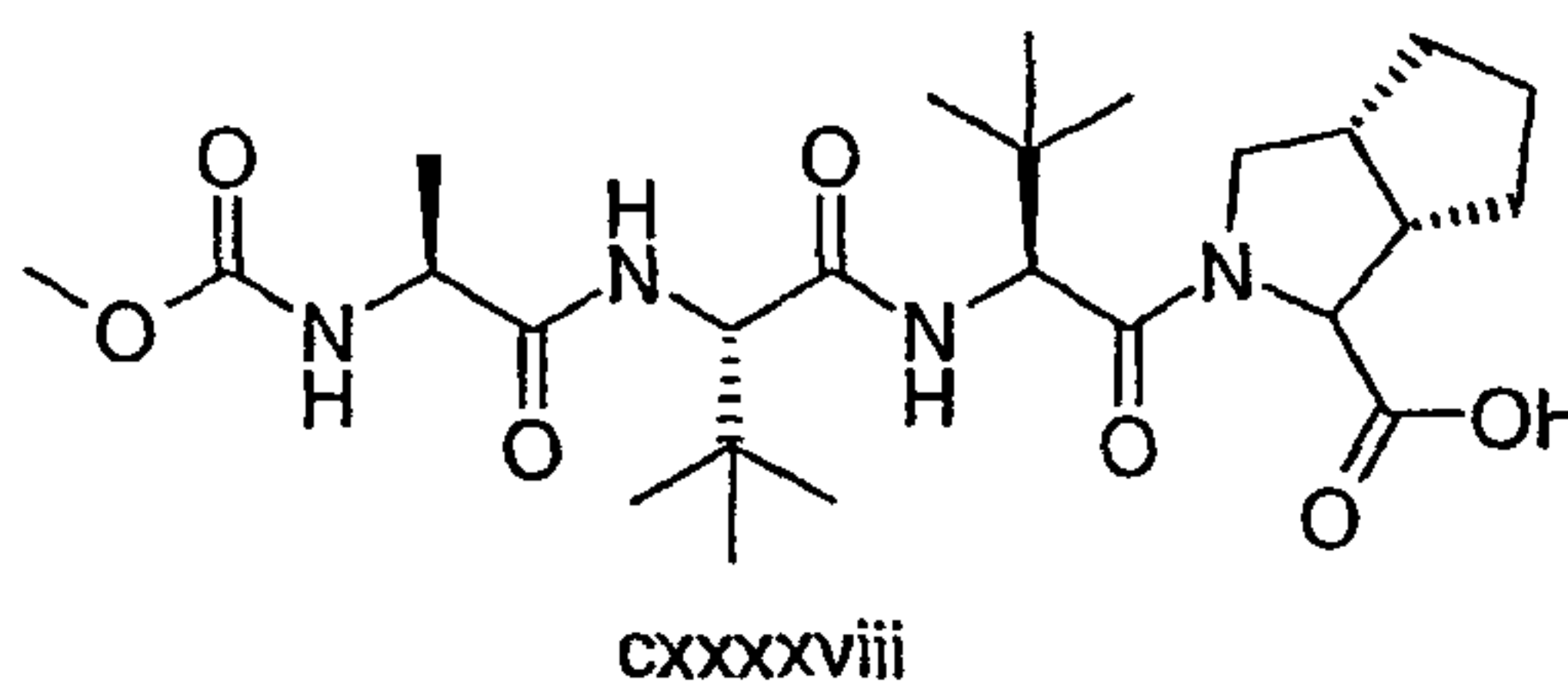


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Intermediate Example 143 – Compound cxxxxviii

To a solution of compound cxxxxvii (0.47 g, 0.847 mmol) in EtOH (5 mL) at 5 °C is added NaOH (2 N, 1.31 mL, 2.62 mmol). The mixture is stirred at room temperature for 4 hours. The solution is acidified to pH ~2 with HCl (1N) and the EtOH is removed by rotary evaporation. The mixture is extracted with EtOAc (3x30 mL) and the combined extract is washed with brine, and then dried by MgSO₄. The solvent is removed and the residue is dried under vacuum to yield compound cxxxxviii (0.366 g, 82%) as gummy foam.

10



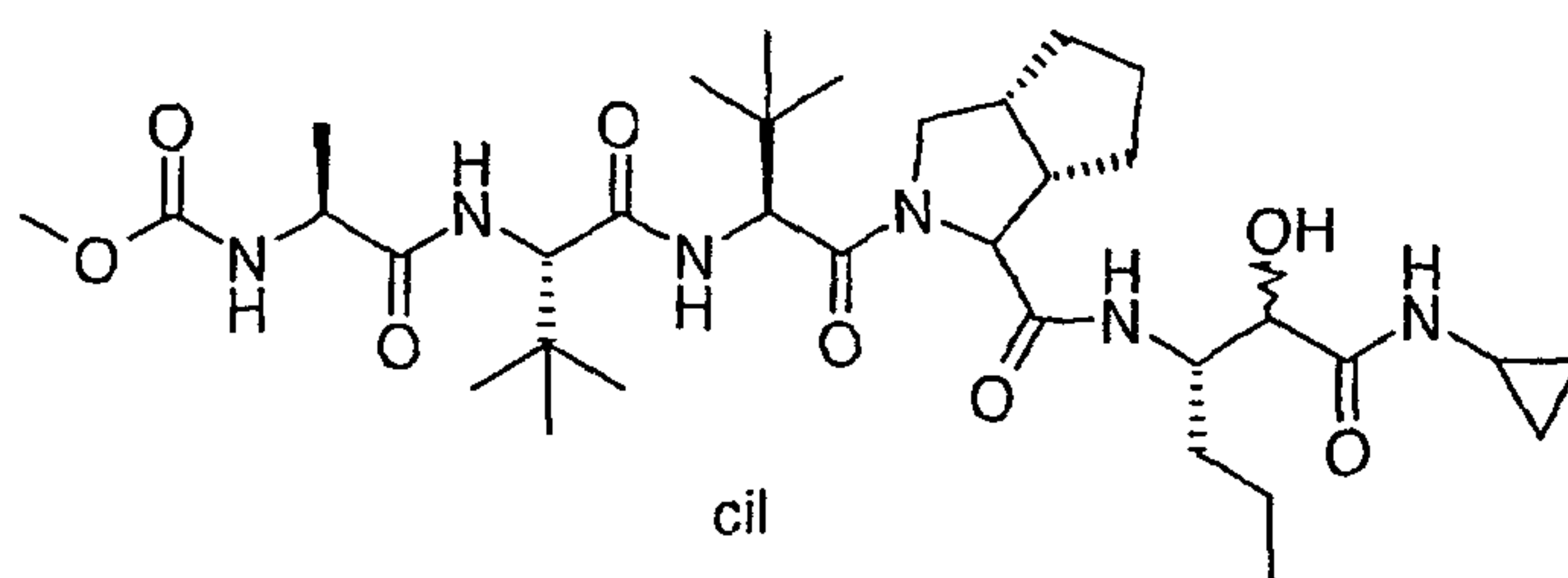
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Intermediate Example 144 – Compound cil

A solution of compound cxxxxviii (0.366 g, 0.718 mmol) in DCM is cooled in an ice bath and treated with PyBop (0.599 g, 1.15 mmol). After stirring at room temperature for 0.5 hour, the mixture is cooled by an ice bath and treated with a solution of compound xiii' (0.200 g, 1.08 mmol) in THF and DIPEA (0.250 mL, 1.44 mmol). The mixture is stirred at room temperature overnight and then quenched with NH₄Cl solution. The solvent is concentrated and the mixture is dissolved in EtOAc (100 mL). The organic phase is washed with saturated NaHCO₃, brine, and then dried by MgSO₄. After removal of the organic solvent, the residue is purified by column chromatography (5% EtOH/EtOAc) to yield compound cil (0.35 g, 72%)

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Intermediate Example 145 – Compound cxxi

- 5 To a THF solution (85 mL) of N-Boc-Nva-OH (compound 1) (8.68 g, 40 mmol) is added CDI (7.79 g, 48 mmol). After stirring at room temperature for 30 minutes, the above solution is treated with a DMF solution (25 mL) containing N,O-dimethyl-hydroxylamine hydrochloride (4.25 g, 44 mmol) and DIPEA (7.66 mL, 44 mmol). The reaction mixture is stirred overnight at room temperature. The reaction mixture is then concentrated *in vacuo*. The resulting
- 10 residue is diluted with EtOAc (300 mL). This solution is washed sequentially with 0.1 N HCl (50 mL), saturated NaHCO₃ (3 x 50 mL) and brine. The organic phase is concentrated *in vacuo* to yield a residue that is purified with silica gel chromatography (40% EtOAc/Hexanes) to compound cxxi (9.38 g, 94%).

15 Intermediate Example 146 – Compound cxxii

- To a diethyl Et₂O solution (50 mL) of compound cxxi (9.38 g, 31.9 mmol) cooled to 0°C is added (slowly) LAH (34.7 mL, 1 M, 34.7 mmol). The temperature of the reaction flask is maintained below 5 °C during LAH addition. Upon completion of the addition, EtOAc (20 mL) is added to the reaction to quench the excess LAH. Aqueous KHSO₄ (5%, 20 mL) is then added in a
- 20 dropwise fashion in order to keep the temperature below 5 °C. The organic phase is separated and then washed sequentially with 1 N HCl (3 x 30 mL), saturated NaHCO₃ (3 x 30 mL) and brine. The organic phase is concentrated and dried *in vacuo* to yield crude compound cxxii (5.18 g, 69%).

25 Intermediate Example 147 – Compound cl

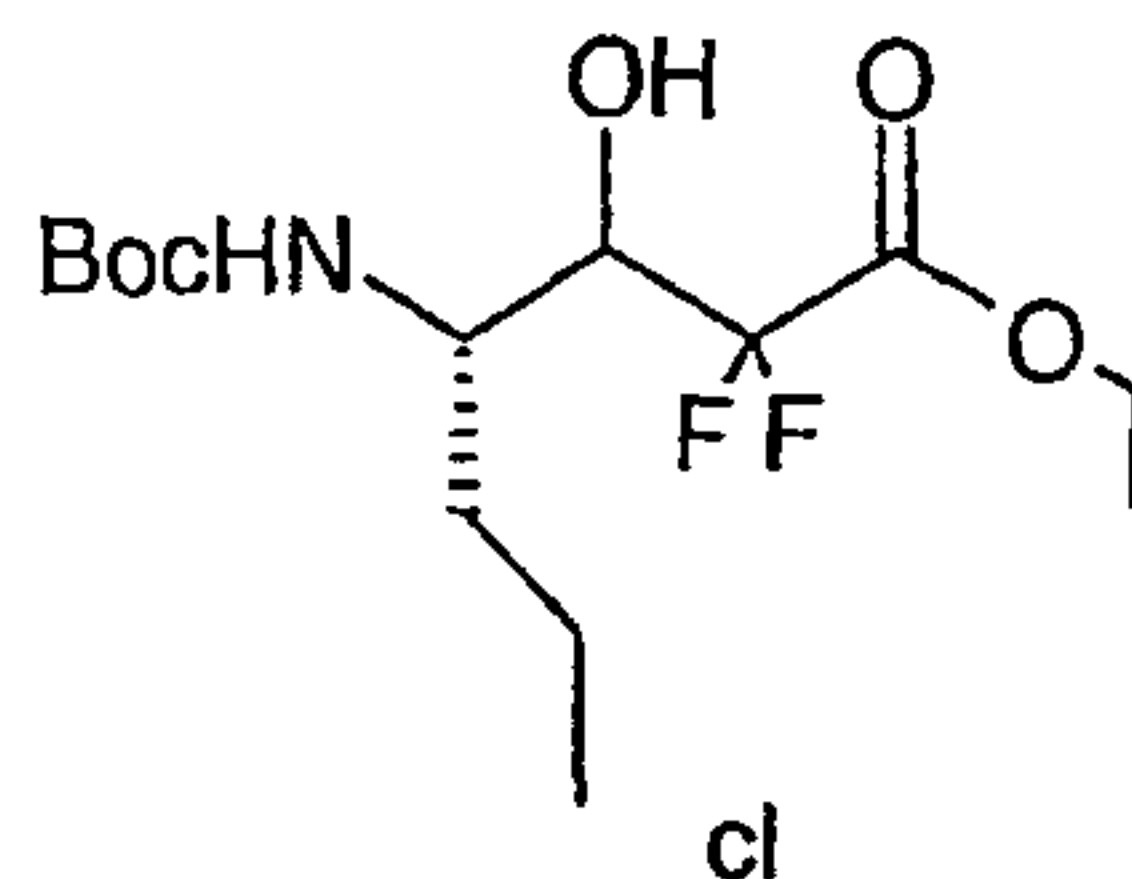
- To a THF (25 mL) suspension of Zn (2.75 g, 42 mmol) is added at reflux 0.2 mL of EtOC(O)CF₂Br. This is followed by slowly adding a THF solution (25 mL) of compound cxxii (3.05 g, 15.0 mmol) and EtOC(O)CF₂Br (4.84 mL, 37.5 mmol). Upon completion of the addition of both reagents, the reaction mixture is further refluxed for 30 minutes. The reaction mixture is

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cooled to room temperature and diluted with DCM (200 mL). The organic phase is washed with 1 N KHSO₄. The organic phase is concentrated and dried *in vacuo* to yield a residue that is purified by silica gel chromatography (20% EtOAc/Hexane) to yield compound cl (2.78 g, 57%).

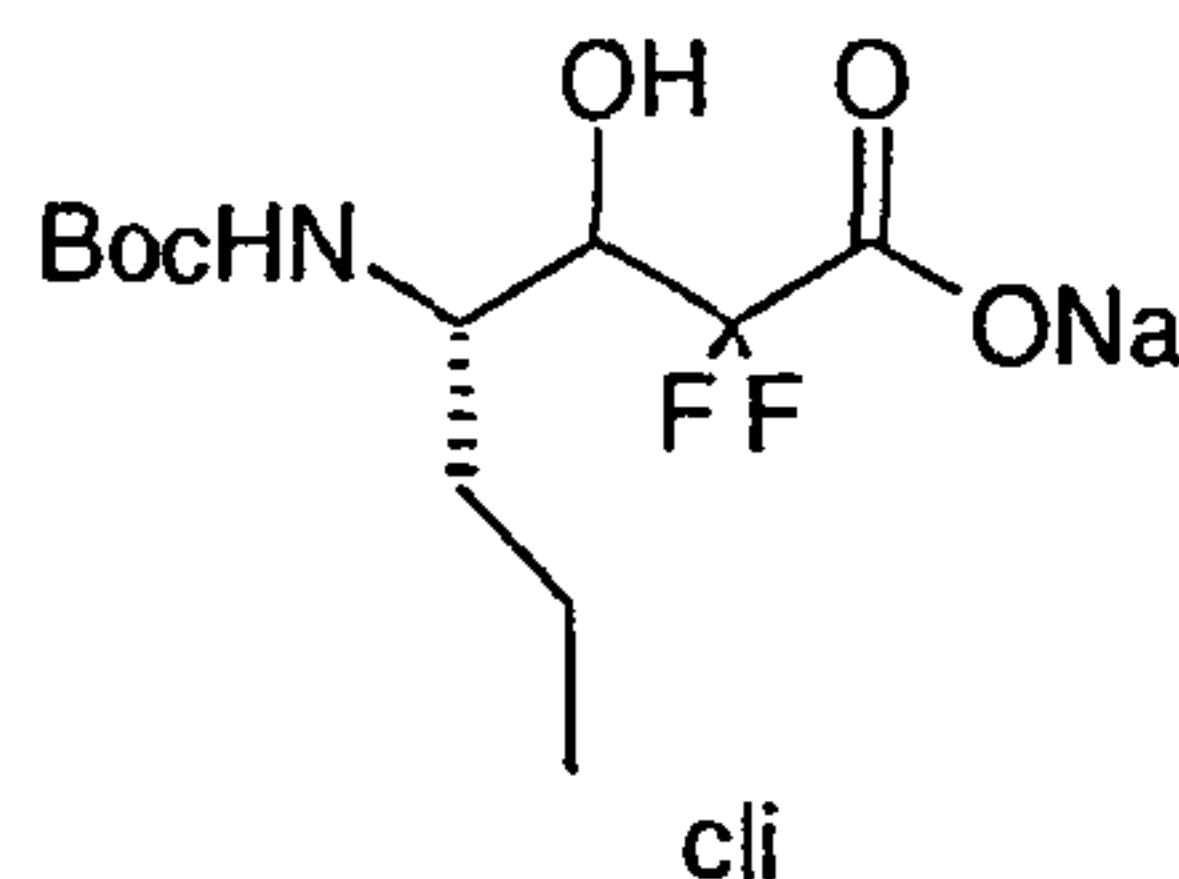


5

This preparation is essentially the same as that disclosed by Thaisrivongs et al., J. Med. Chem., 29, 2080-2087 (1986).

Intermediate Example 148 – Compound cli

- 10 A THF solution (40 mL) of compound cl (2.78 g, 8.53 mmol) is treated with 1 N NaOH (12.8 mL, 12.8 mmol). After stirring at room temperature overnight, the solvent is partially removed *in vacuo*. The remaining reaction mixture is diluted with water (50 mL) and lyophilized to yield crude compound cli (2.82 g, >100%) as its sodium salt.



15

This preparation is essentially the same as that disclosed by Thaisrivongs et al., J. Med. Chem., 29, 2080-2087 (1986).

Intermediate Example 149 – Compound clii

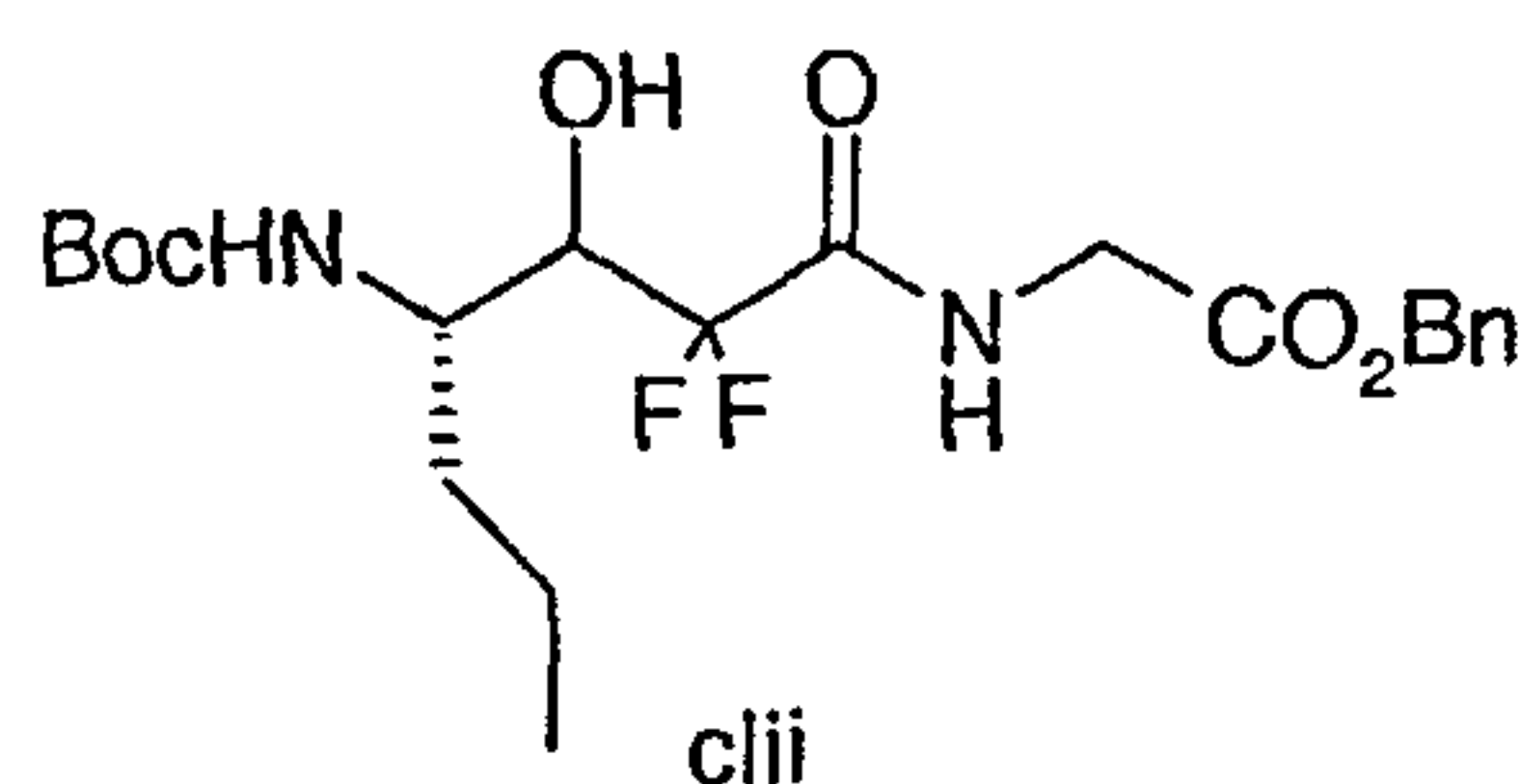
- 20 A DCM solution (10 mL) of the crude compound cli (516 mg, 1.61 mmol) is treated with HOBt (436 mg, 3.23 mmol) and DIC (0.328 mL, 2.09 mmol). After stirring at room temperature for 30 minutes, the reaction mixture is treated with a DCM solution (5 mL) containing glycine benzylester-TsOH salt (815 mg, 2.42 mmol) and DIPEA (0.422 mL, 2.42 mmol). After stirring at room temperature for 12 hours, the reaction mixture is quenched with water and extracted with
- 25 EtOAc. The organic phase is dried and concentrated *in vacuo* and purified by silica gel chromatography (40% EtOAc/hexanes) to yield compound clii (495 mg, 69%).

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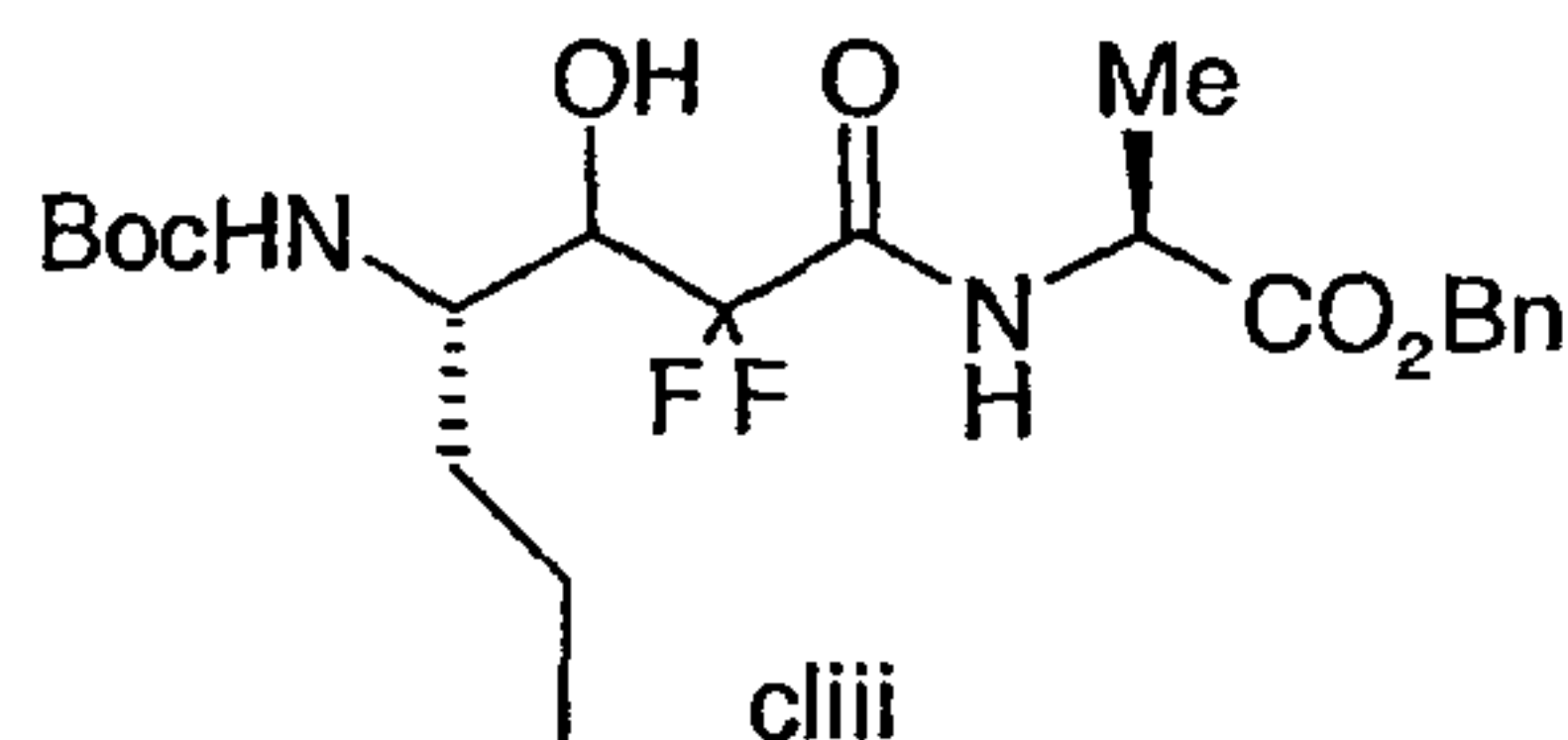
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¹H NMR of compound clii (400 MHz, CDCl₃): δ 7.29-7.21 (m, 5H), 5.16 (bs, 2H), 4.89 (bs, 1H), 4.20-3.90 (m, 4H), 3.80 (bs, 1H), 1.75-1.42 (m, 4H), 1.38 (s, 9H), 0.87 (m, 3H).



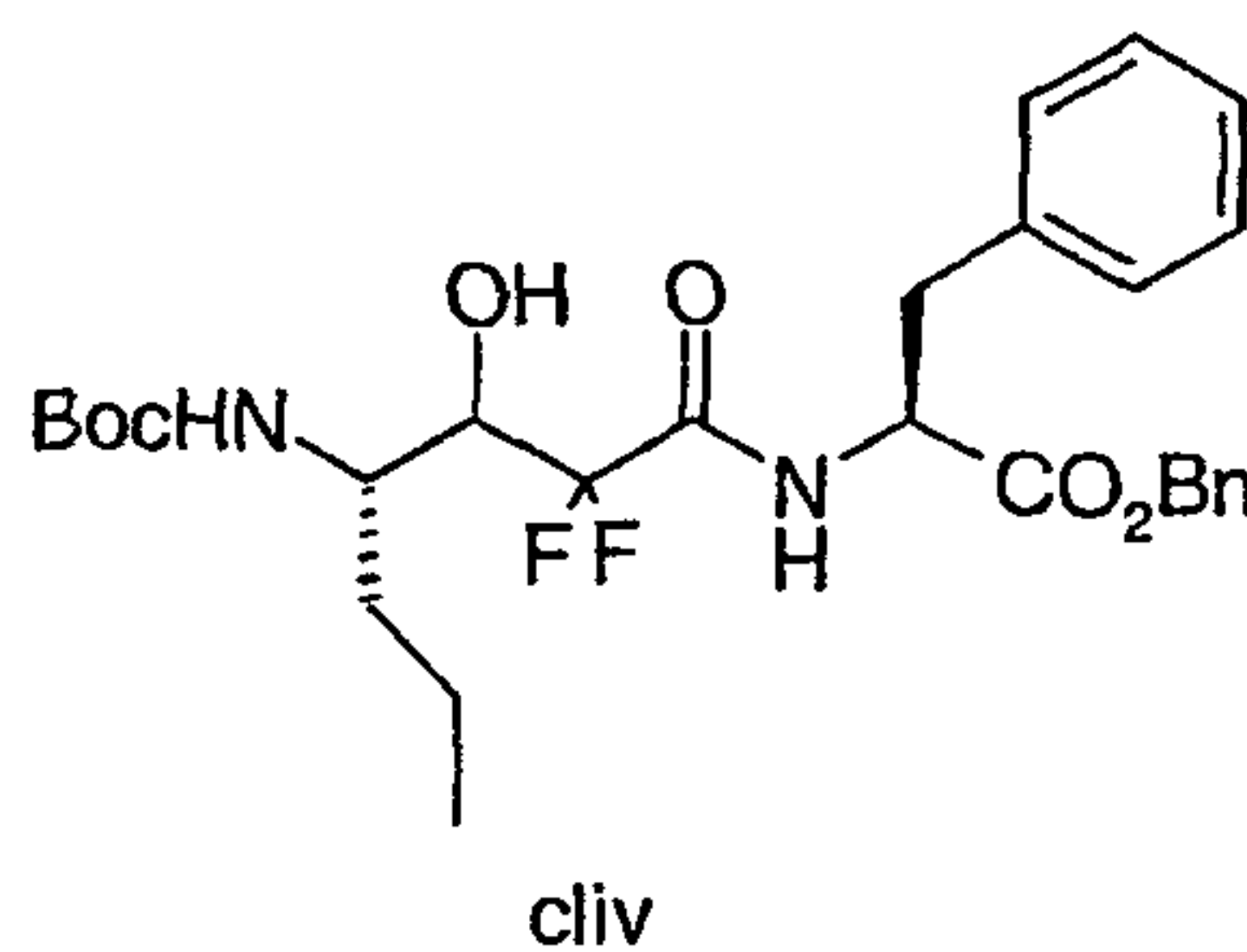
- 5 Starting from crude compound cli, compounds cliii (83%) and cliv (50%) are prepared in an identical method to that described for compound clii.

¹H NMR of compound cliii (400 MHz, CDCl₃): δ 7.49 (bs, 1H), 7.34-7.24 (m, 5H), 5.13 (AB q, J = 12.2 Hz, J' = 23.9 Hz, 2H), 4.88 (bd, J = 8.8 Hz, 1H), 4.53 (m, 1H), 3.98-3.91 (m, 2H), 3.82 (m, 1H), 1.65-1.20 [m, 16H, including singlet at 1.37 (9H)], 0.86 (t, J = 7.3 Hz, 3H).



10

¹H NMR of compound cliv (400 MHz, CDCl₃): δ 7.60-7.0 (m, 10H), 5.30-5.00 (m, 2H), 5.00-4.75 (m, 2H), 4.15-3.70 (m, 3H), 3.30-3.00 (m, 2H), 1.75-1.20 [m, 13H, including singlet at 1.36 (9H)], 0.86 (bs, 3H).



15

Intermediate Example 150 – Compound clv

To a DCM (10 mL) and THF (5 mL) solution of the crude compound cli (1 g, 3.13 mmol) is added HOBT (634 mg, 4.69 mmol) and EDCI (781 mg, 4.07 mmol), and then (s)-α-methylbenzylamine (0.604 mL, 4.69 mmol). The reaction mixture is stirred overnight at room temperature and then quenched with water. The reaction mixture is extracted with EtOAc. The organic phase is washed with brine and dried by Na₂SO₄. The organic phase is concentrated *in vacuo* to yield a residue that is purified by silica gel chromatography (20% EtOAc/hexanes) to

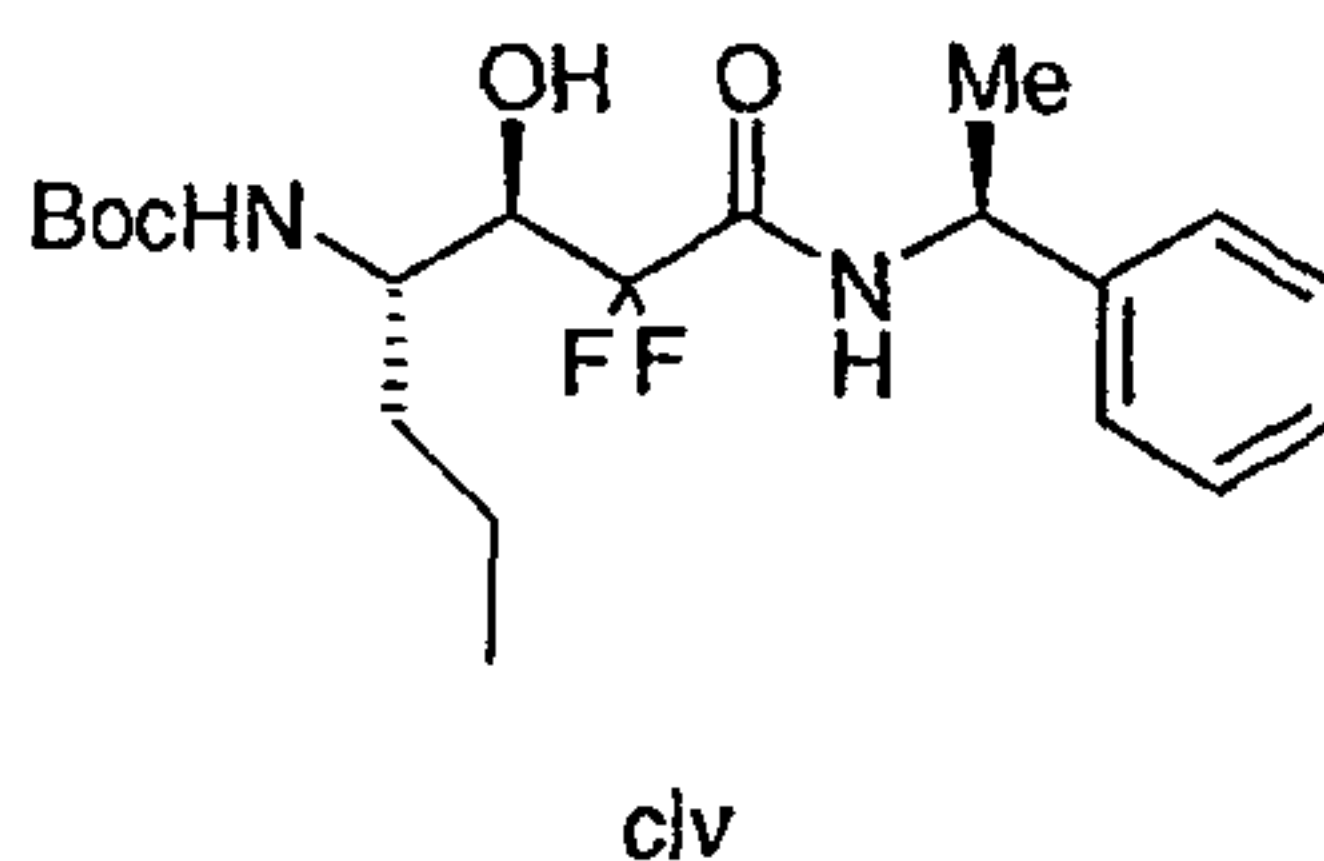
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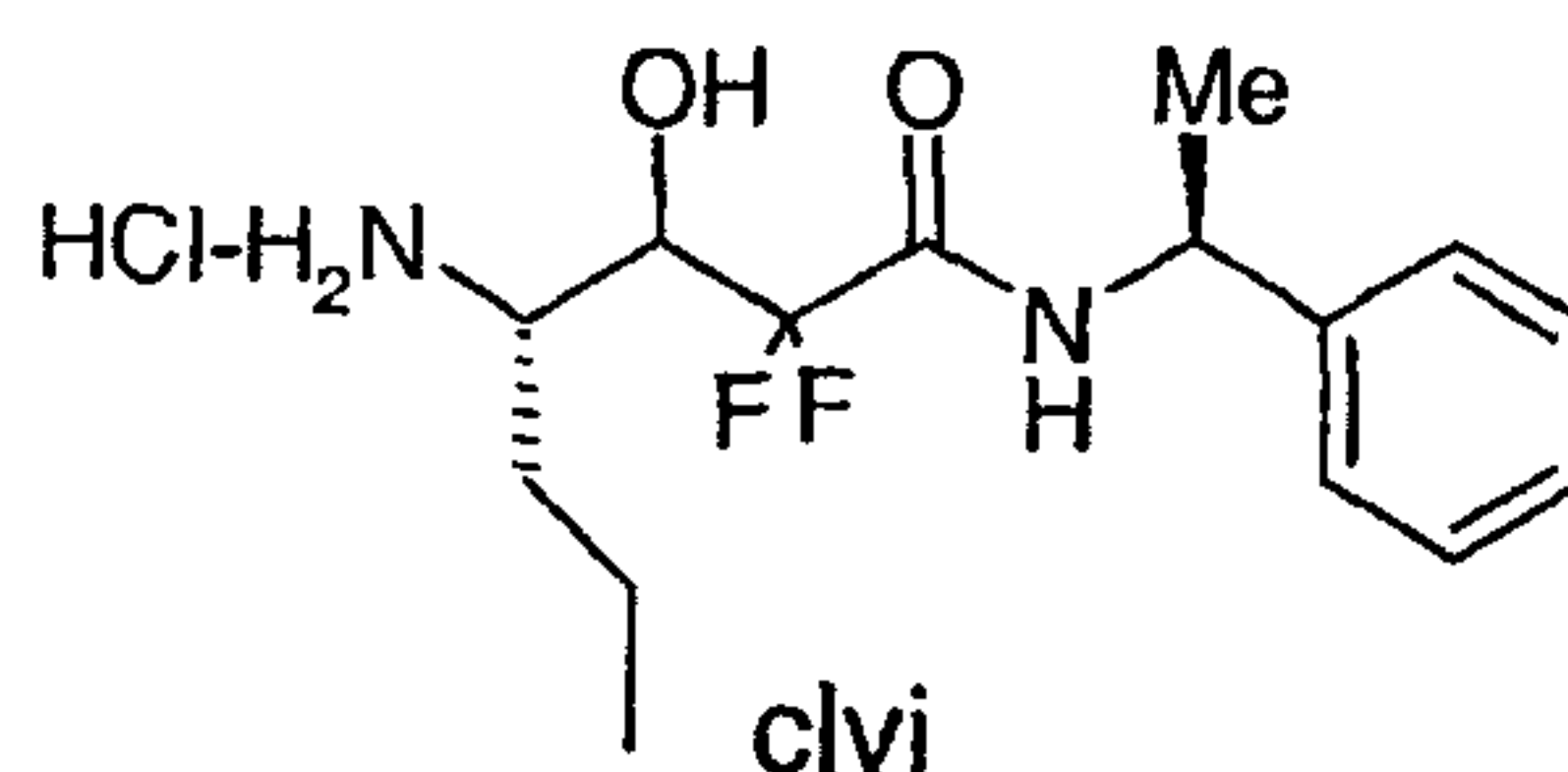
yield compound clv (459 mg, 37%). ^1H NMR of compound clv (400 MHz, CDCl_3): δ 7.32-7.21 (m, 6H), 5.00 (m, 1H), 4.75 (m, 1H), 3.94 (m, 2H), 3.70 (m, 1H), 1.65-1.15 [m, 16H, including doublet at 1.51 ($J=6.8$ Hz, 3H), singlet at 1.39 (9H)], 0.82 (m, 3H).



5

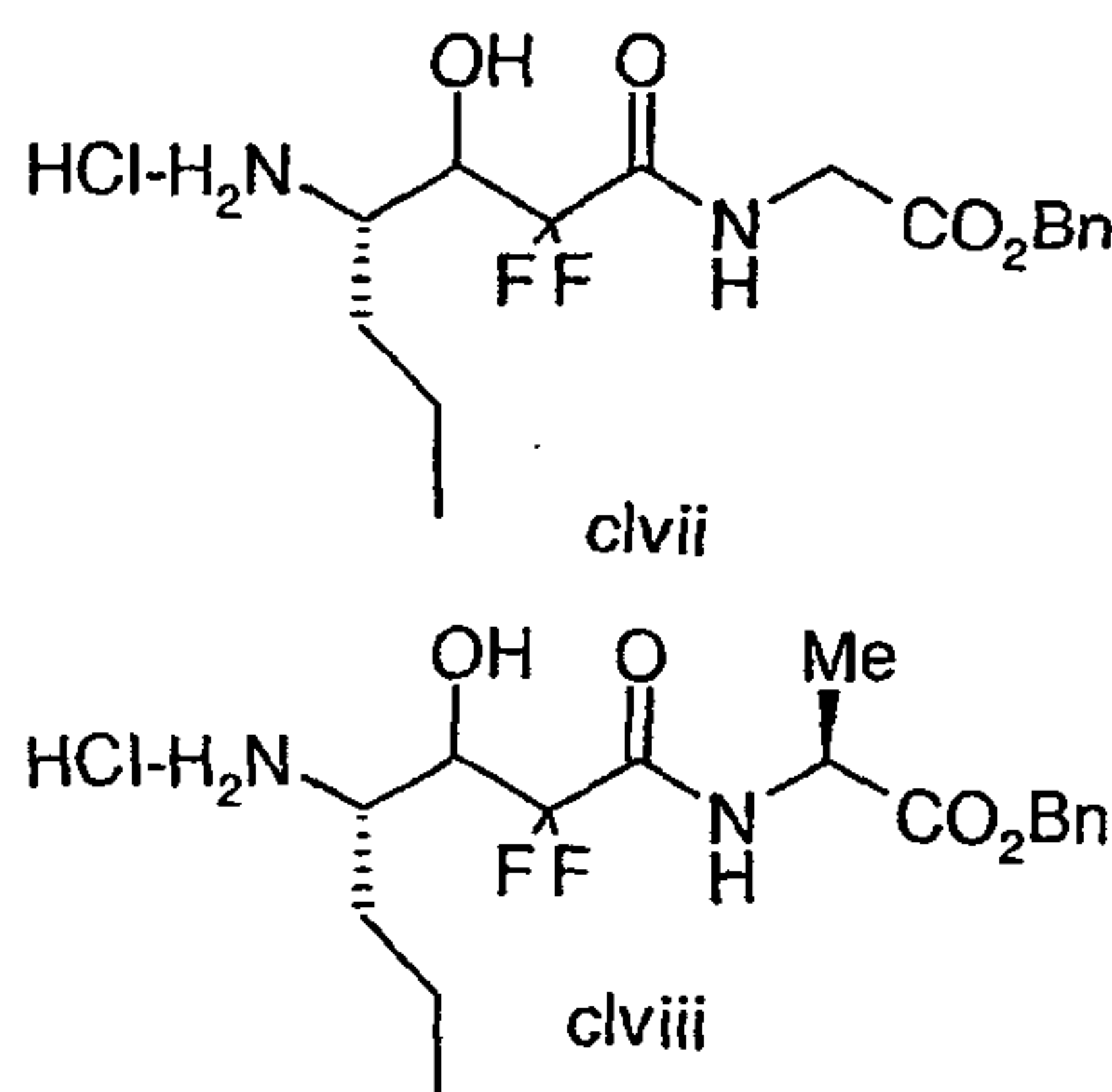
Intermediate Example 151 – Compound clvi

Compound clv (220 mg, 0.55 mmol) is dissolved in 4 N HCl in dioxane (10 mL). The reaction mixture is stirred at room temperature for 2 hours and then concentrated *in vacuo* to give the crude compound clvi (~100%) as its HCl salt.



Following the procedure described for preparing compound clvi, compounds clvii, clviii, and clix are prepared in almost quantitative yield from the crude compound cli.

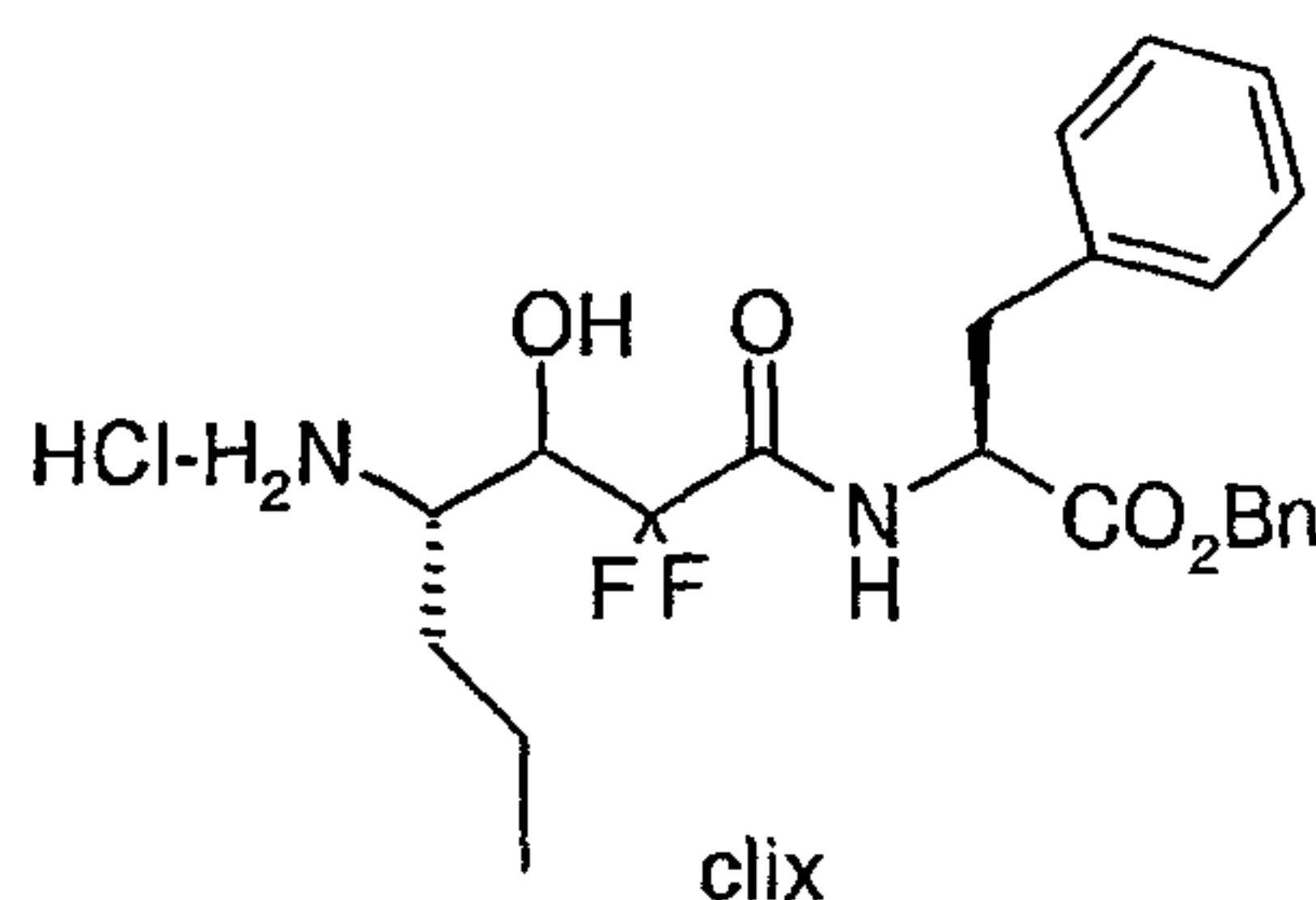
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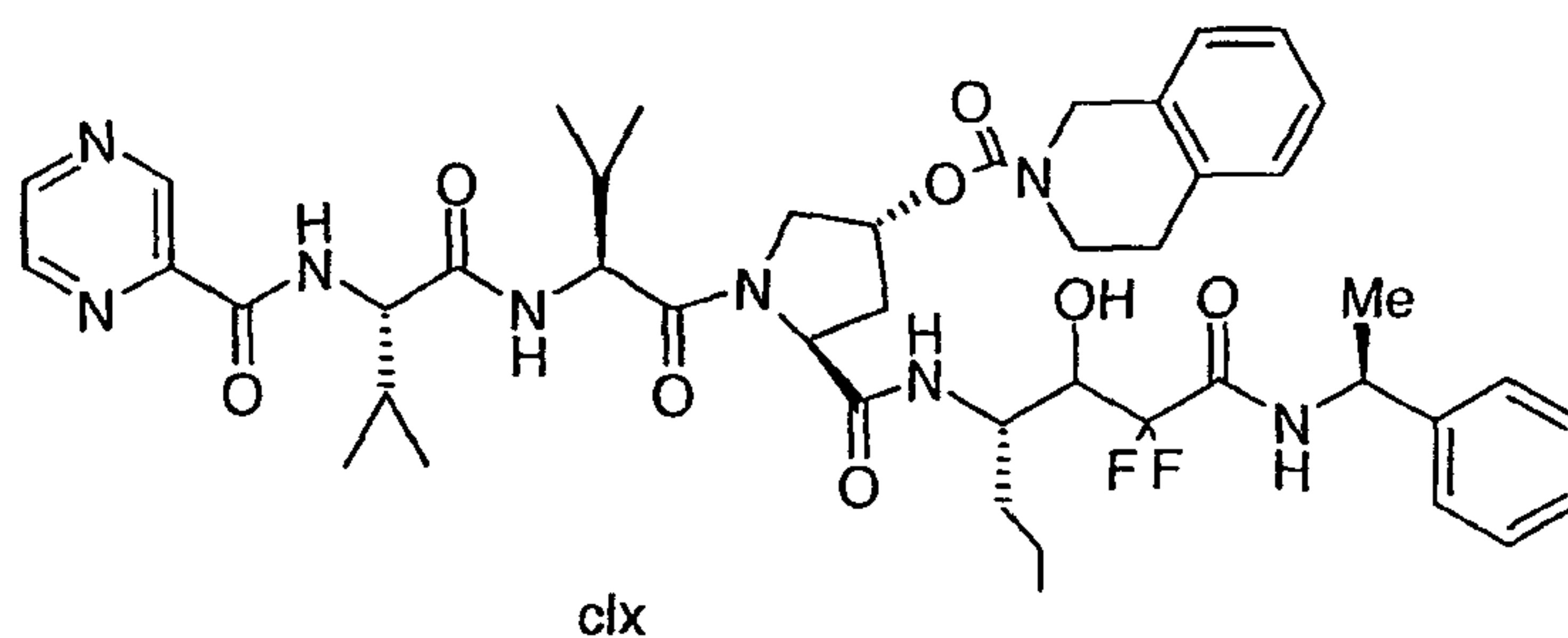
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Intermediate Example 152 – Compound clx

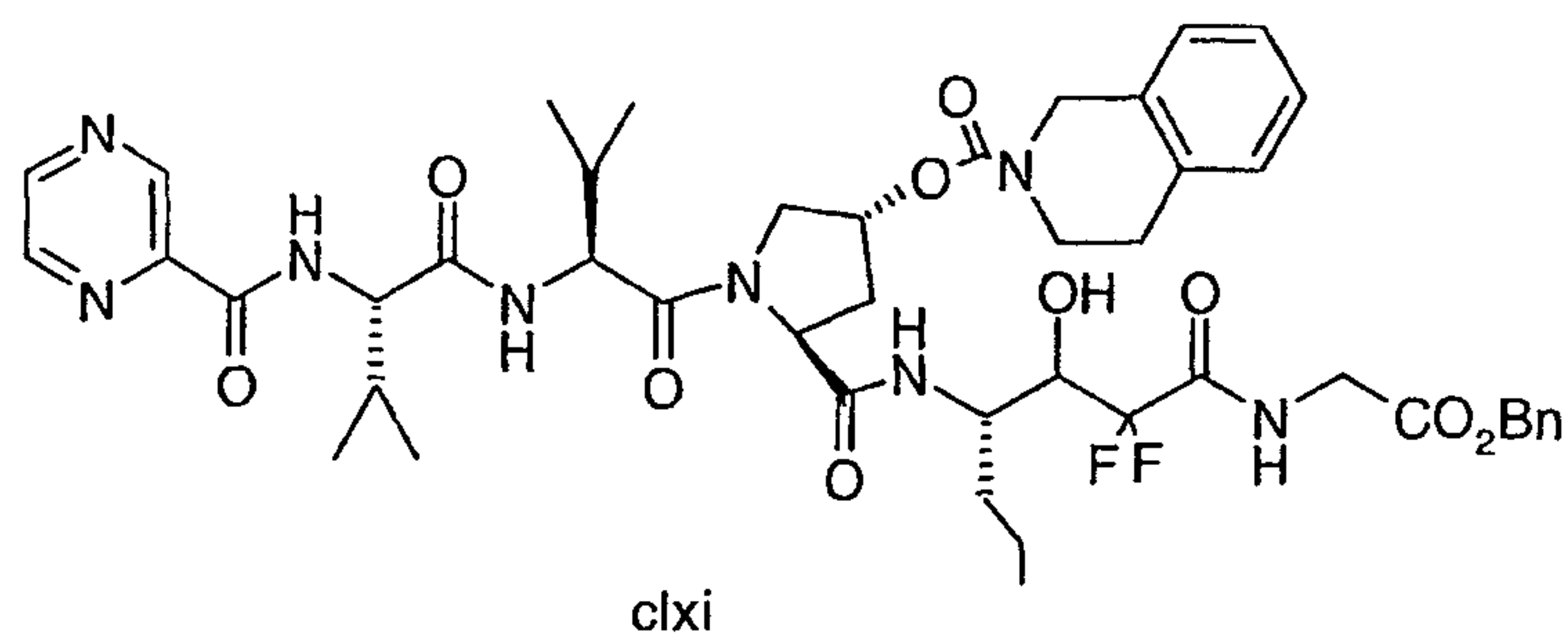
A DCM solution (4 mL) of the HCl salt of compound vii (96 mg, 0.144 mmol) is treated with
 5 PyBOP (120 mg, 0.23 mmol) and DIPEA (0.1 mL, 0.576 mmol). After stirring at room
 temperature for 30 minutes, the solution is treated with a THF solution (4 mL) containing
 compound clv (0.288 mmol) and DIPEA (0.2 mL, 1.152 mmol). The reaction mixture is stirred at
 room temperature overnight. The reaction mixture is then diluted with EtOAc (50 mL), and the
 organic phase then washed with NaHCO₃ and brine. The organic phase is concentrated *in vacuo*
 10 and the residue purified by silica gel chromatography (80% EtOAc/hexanes) to yield compound
 clx (113 mg, 89%).



Intermediate Example 153 – Compound clxi

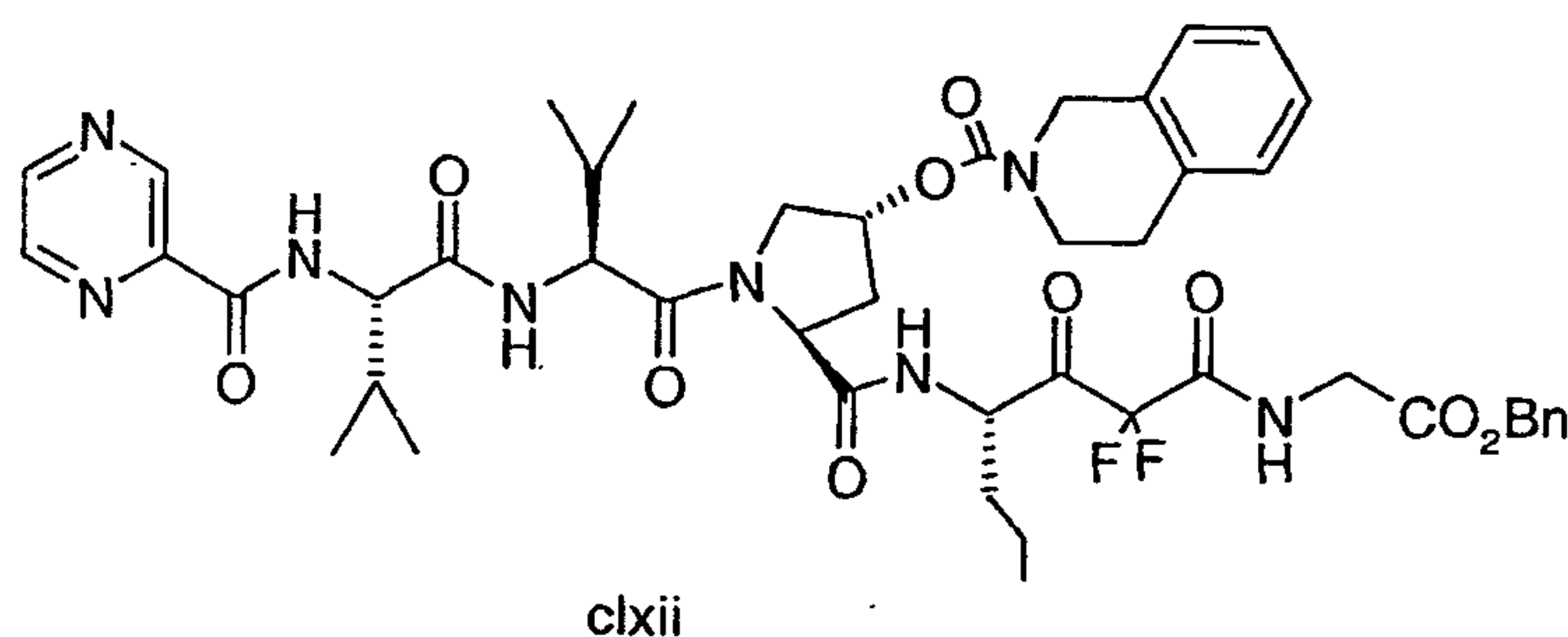
15 A DCM solution (6 mL) of compound vii (140 mg, 0.235 mmol) is treated with PyBOP
 (196 mg, 0.376 mmol) for 30 minutes. A THF solution (6 mL) of compound clvii (~0.47 mmol)
 and DIPEA (0.327 mL, 1.88 mmol) is then added to the above solution. The reaction mixture is
 stirred at room temperature overnight and quenched with water (30 minutes). The reaction
 mixture is extracted with EtOAc (50 mL). The organic phase is washed with NaHCO₃ and brine.
 20 The combined aqueous layers are back extracted with EtOAc (50 mL). The combined organic
 phases are dried and concentrated *in vacuo*. The resultant residue is purified by silica gel
 chromatography (80-100 EtOAc/hexanes) to yield compound clxi (104 mg, 48%).

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Intermediate Example 154 – Compound clxii

To a DCM solution (10 mL) of compound clxi (280 mg, 0.304 mmol) is added DMP reagent reagent (193 mg, 0.456 mmol). The reaction mixture is stirred at room temperature for 3 hours and quenched with 10% Na₂SO₃. The organic phase is washed with NaHCO₃ and brine. The resulting organic phase is dried and concentrated *in vacuo* to yield a residue that is purified with silica gel chromatography (80-100% EtOAc/hexanes) to yield compound clxii (271 mg, 97%).

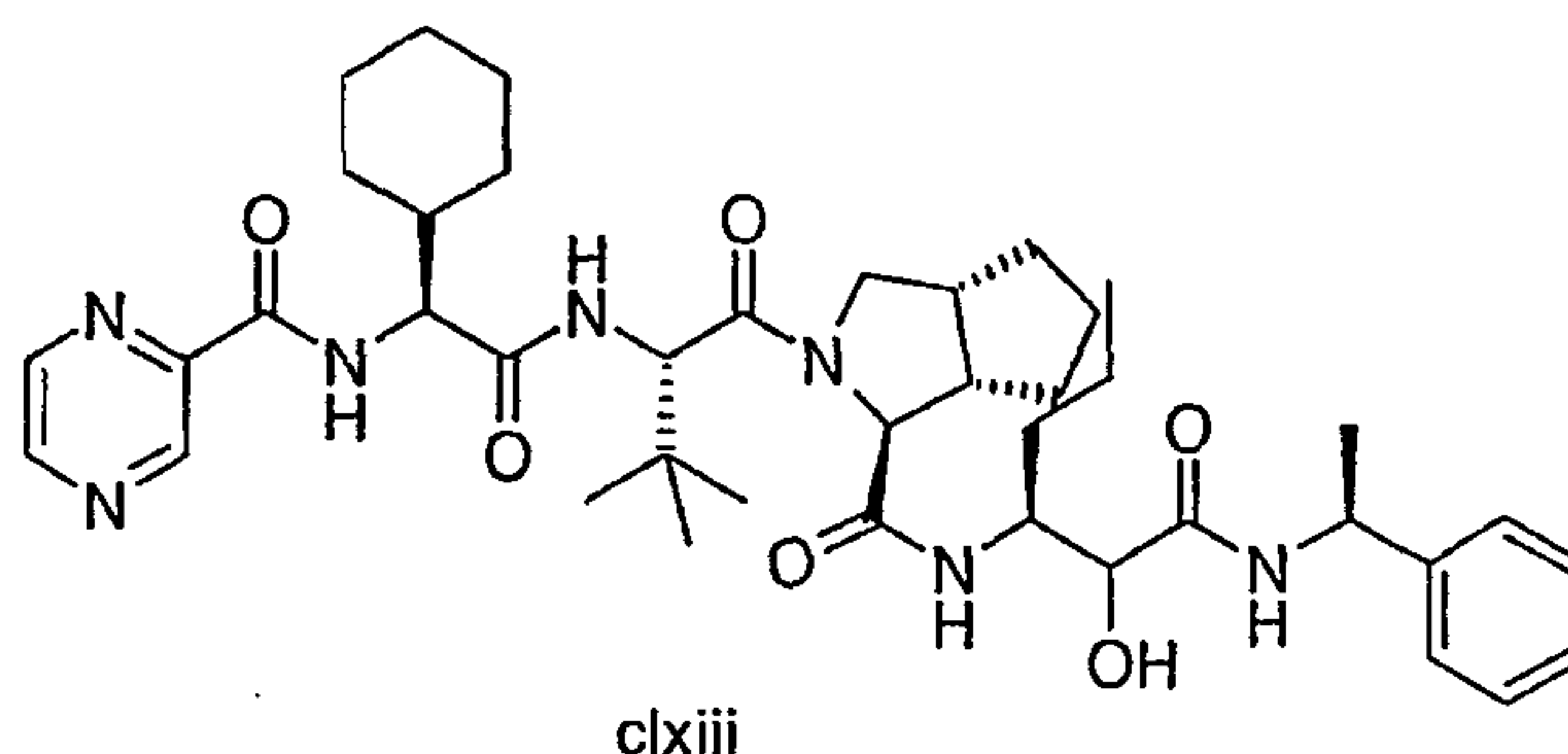


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Intermediate Example 155 – Compound clxiii

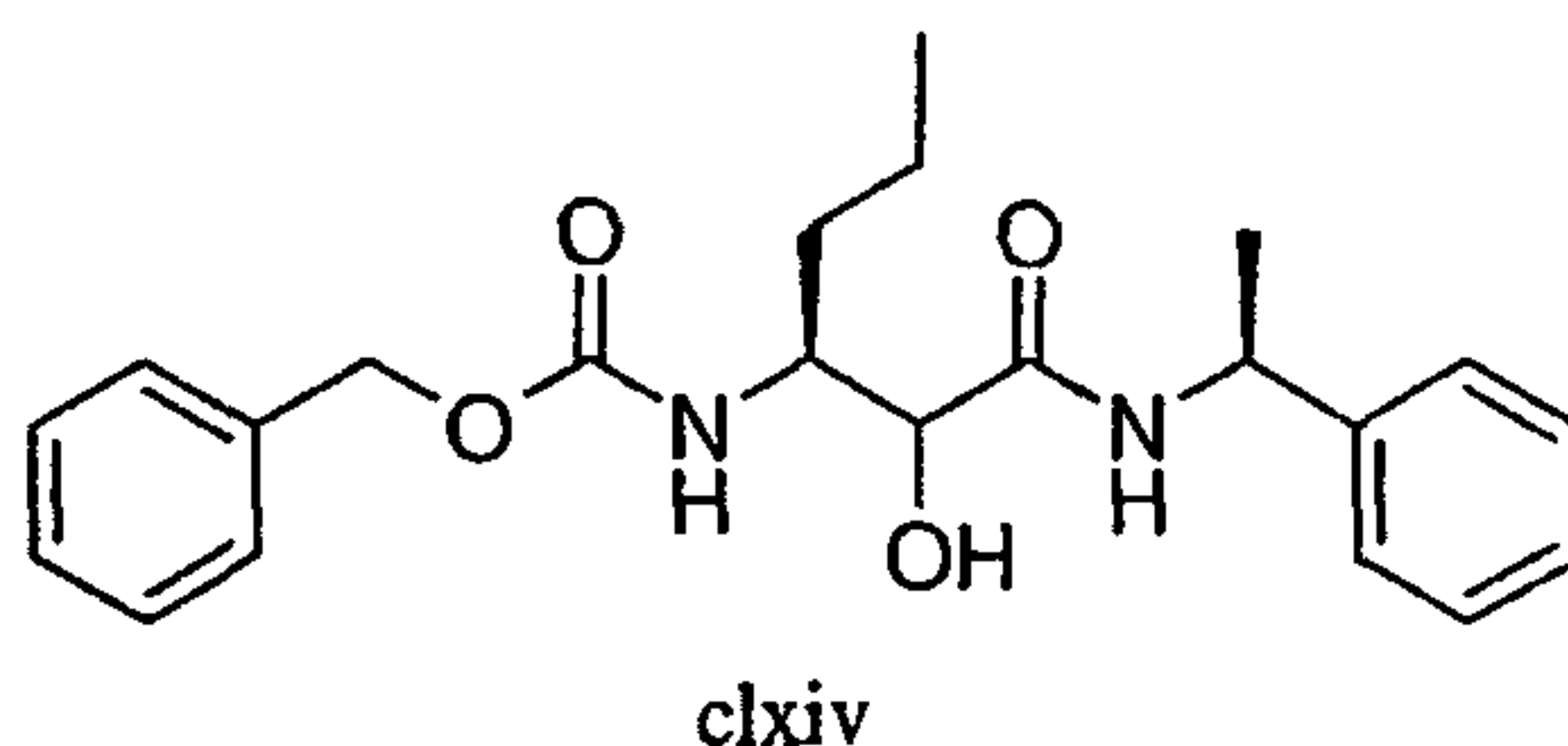
Compound lxxxiii (220 mg, 0.43 mmol) is taken up in DCM (5 mL). PyBOP (270 mg, 0.51 mmol) is added to the DCM solution and stirred 5 minutes. Compound xxxvi' (0.51 mmol) in THF (5.1 mL) is added drop-wise to this solution. DIPEA (0.09 mL, 0.51 mmol) is added to reaction mixture and stirred overnight under N₂. The next day, the reaction mixture is diluted with EtOAc, washed with saturated NaHCO₃, washed with brine. Purification by 70% to 90% EtOAc/Hexane gradient yields compound clxiii (180 mg, 56%).

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Intermediate Example 156 – Compound clxiv

Compound cxxv (2.09 g, 7.4 mmol) is taken up in DCM (20 mL). PyBOP (4.64 g, 8.9 mmol) and HOBt (1.2 g, 8.9 mmol) are added to this solution and stirred five minutes. The resulting mixture is lowered to 0°C where S(-)- α -Methylbenzylamine (1.15 mL, 8.9 mmol) and DIPEA (1.55 mL, 8.9 mmol) are added. The reaction is stirred overnight with warming to room temperature. The reaction mixture is washed with 0.1 N HCl, sat NaHCO₃, and brine. Purification by 30% EtOAc/Hexanes yields compound clxiv (1.6 g, 56.3%).

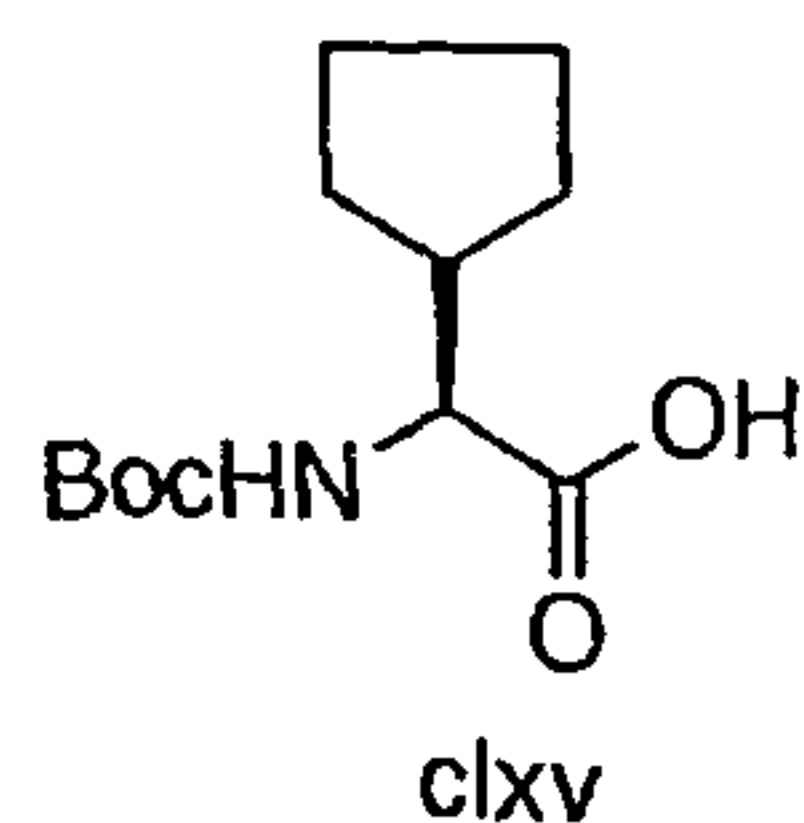


Intermediate Example 157 – Compound xxxvi'

Compound clxiv (1.48 g, 3.8 mmol) is hydrogenated using 10% Pd/C (300 mg) in MeOH (50 mL). The reaction mixture stirred overnight under H₂. The reaction mixture is filtered through celite and concentrated to give compound xxxvi' (895 mg, 94.2%).

Intermediate Example 158 – Compound clxvi:

To a DCM solution (15 mL) of compound clxv (2 g, 8.2 mmol) is added HOAt (1.34 g,



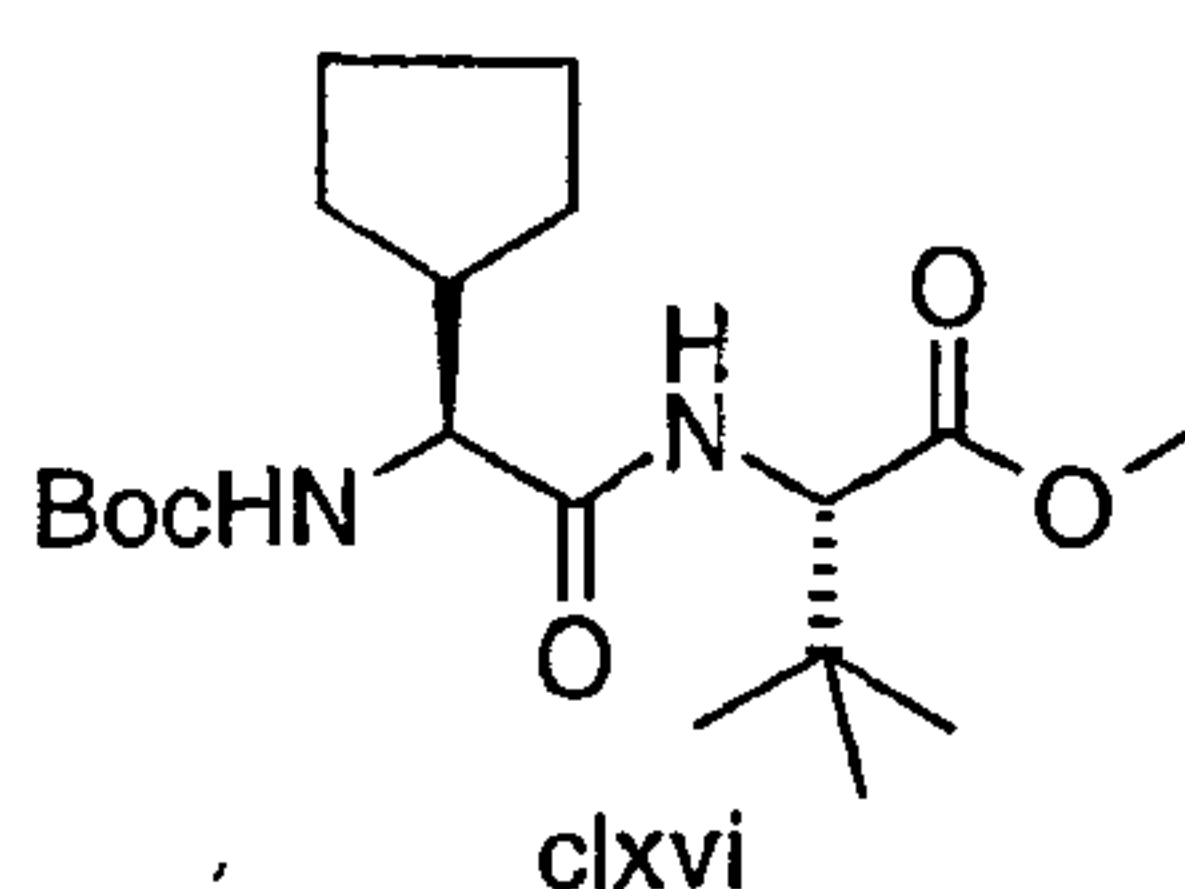
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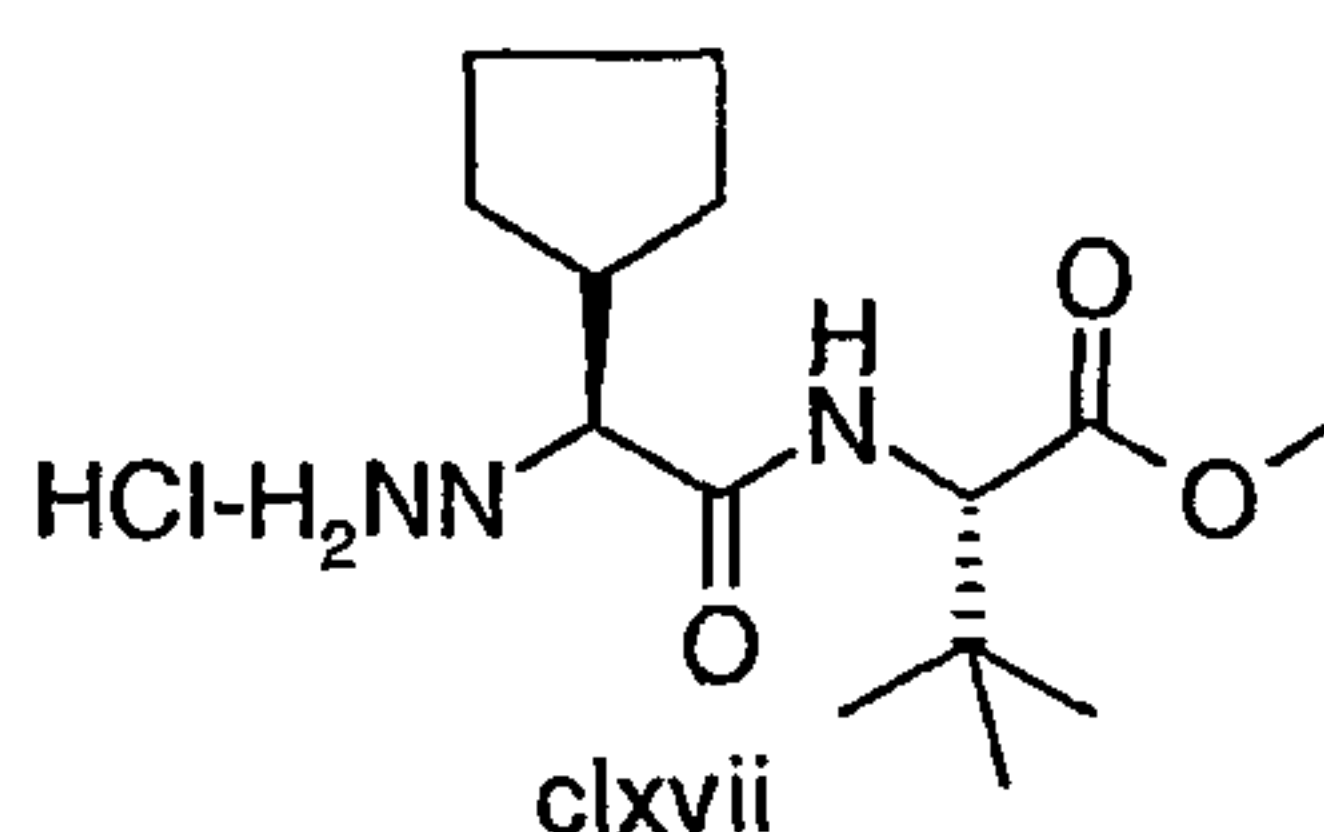
9.84 mmol) and DCC (9.84 mL, 1 M, 9.84 mmol). After stirring at room temperature for 20 minutes, a THF solution (9.84 mL) containing tert-L-Leucine methyl ester-hydrochloride (9.84 mmol) and DIPEA (1.72 mL, 9.84 mmol) is added to the above solution. Then DMAP (1 g, 8.2 mmol) is added at room temperature. The reaction is stirred at room temperature overnight.

- 5 Following standard aqueous work-up and silica gel chromatography (20% EtOAc/Hexanes), compound clxvi (1.75 g, 58%) is obtained.



Intermediate Example 159 – Compound clxvii:

- 10 To a THF solution (35 mL) of compound clxvi (1.75 g, 4.73 mmol) is added 4 N HCl solution in dioxane (11.8 mL, 47.3 mmol). The reaction is stirred at room temperature overnight. At this point, the solvent is removed under reduced pressure to yield crude clxvii (~100%), which is redissolved in DMF and used directly in the next reaction.



15

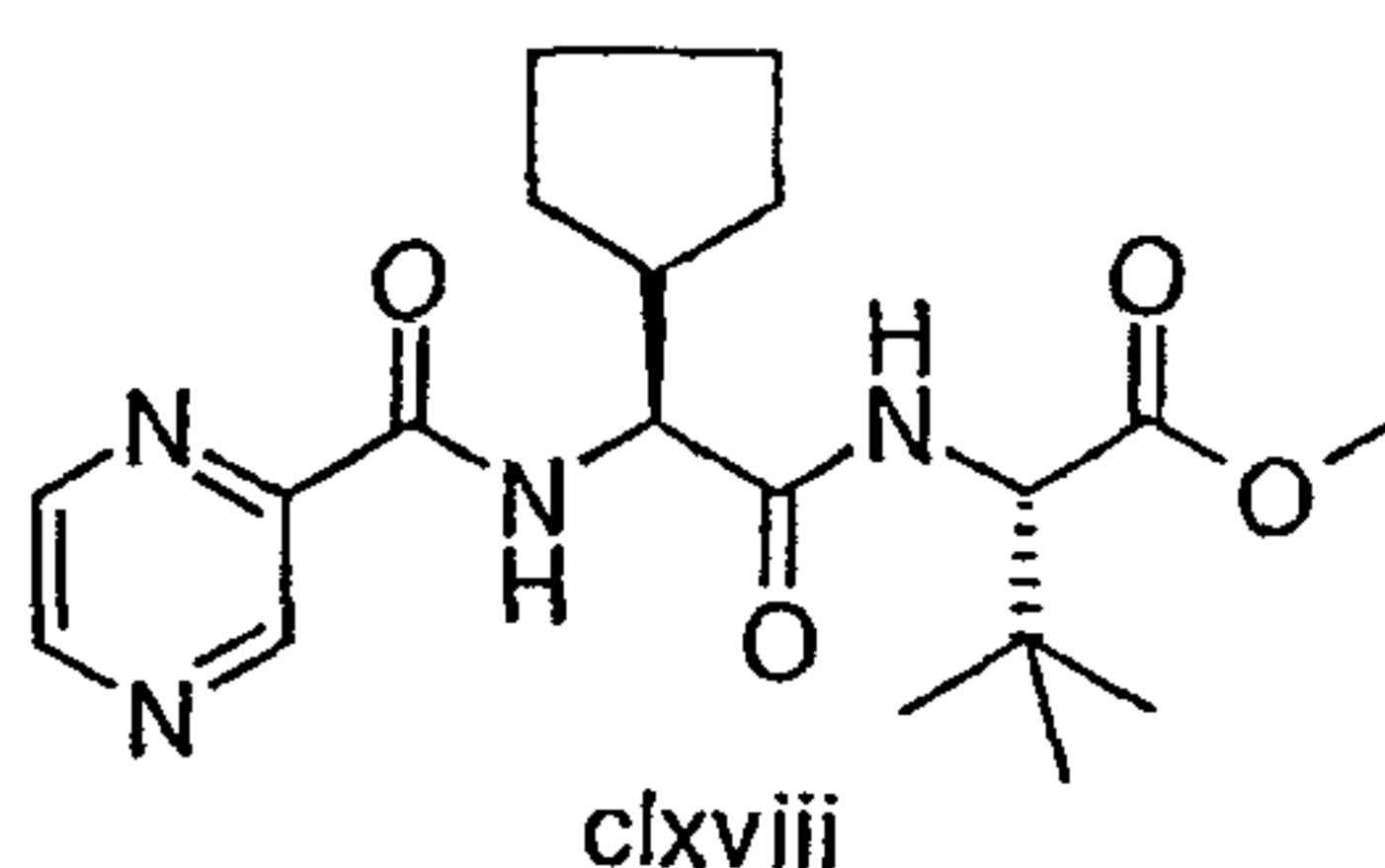
Intermediate Example 160 – Compound clxviii:

- To a DCM solution (15 mL) containing 2-pyrazinecarboxylic acid (447 mg, 3.6 mmol), PyBOP (1.87 g, 3.6 mmol) is added a DMF solution (15 mL) of compound clxvii (811 mg, 3 mmol). To the resulting mixture is then added DIPEA (0.63 mL, 3.6 mmol). The reaction is stirred overnight at room temperature and then quenched with water. The reaction mixture is extracted with EtOAc. The organic layer is washed with brine and concentrated *in vacuo* to provide a residue that is purified by silica gel chromatography (40% EtOAc/Hexanes) to yield compound clxviii (0.93 g, 82%).
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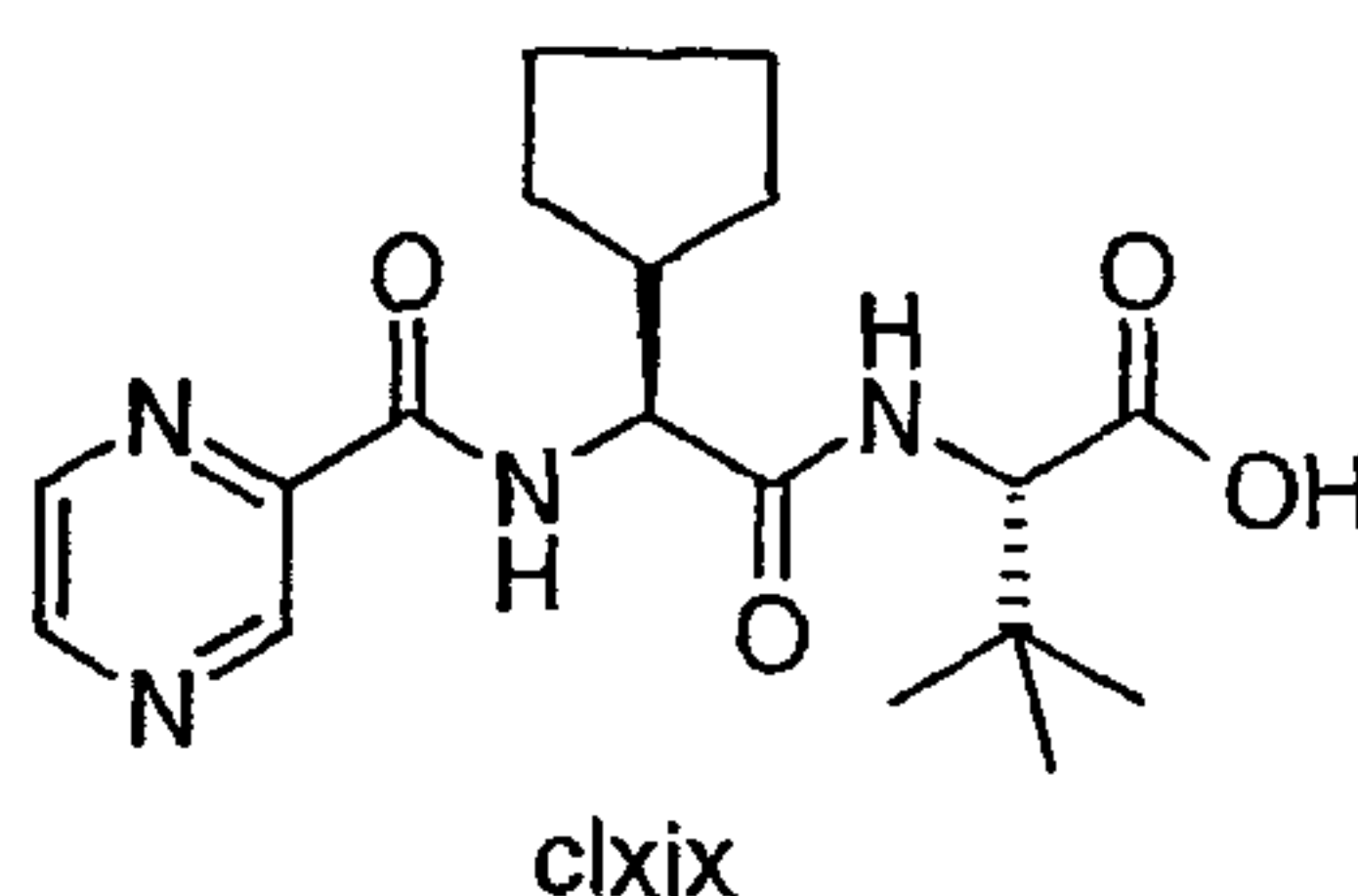
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Intermediate Example 161 – Compound clxix:

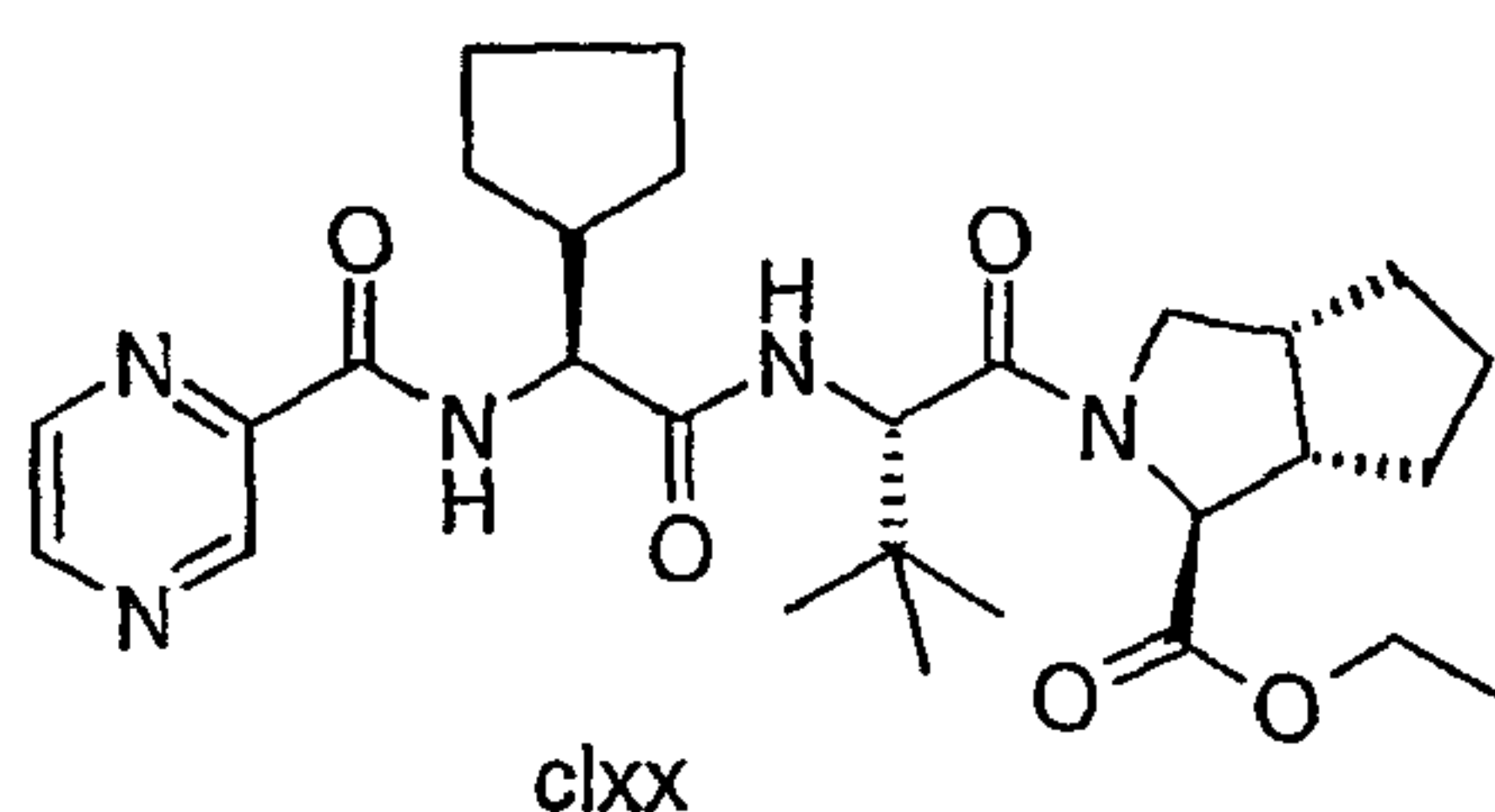
To a MeOH solution (10 mL) of compound clxviii (0.93 g, 2.47 mmol) is added 2 N NaOH (3.71 mL, 7.41 mmol). The reaction is stirred at room temperature overnight. Then the reaction is acidified to pH 3 using 1 N HCl. The reaction is diluted with EtOAc (75 mL), and washed with water and brine. The organic layer thus obtained is dried and concentrated *in vacuo* to give compound clxix (~100%).



10

Intermediate Example 162 – Compound clxx:

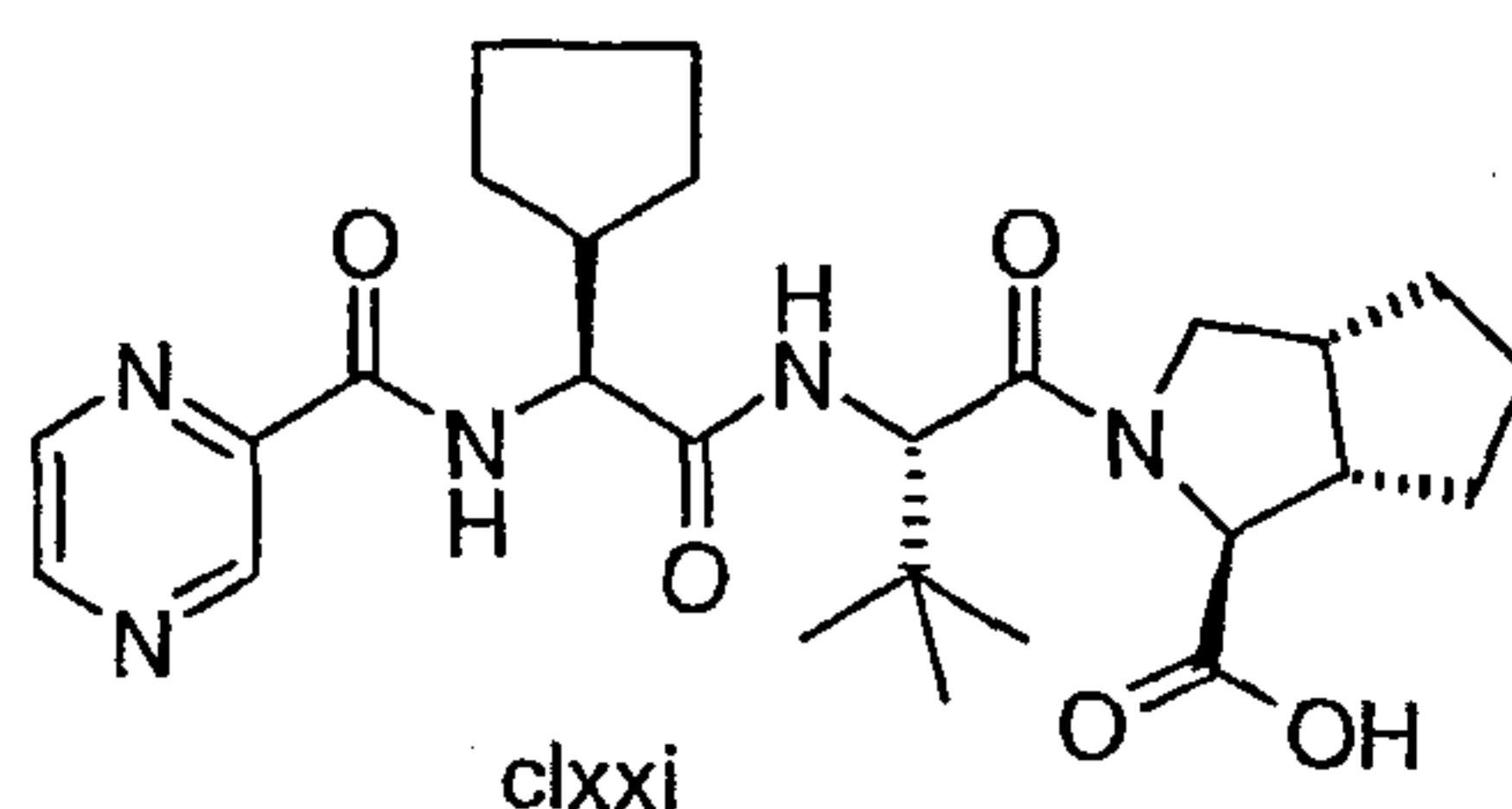
A DCM solution (10 mL) of compound clxix (2.47 mmol) is treated with HOAt (436 mg, 3.21 mmol) and DCC (3.2 mL, 1 M, 3.2 mmol). After stirring for 30 minutes, the reaction mixture is treated with a THF solution (13.6 mL) of compound v (499 mg, 2.72 mmol). After stirring at room temperature overnight, white solids (urea) are filtered. The filtrates are concentrated *in vacuo* to give a residue that is purified by silica gel chromatography to yield compound clxx (0.99 g, 76%).



20 Intermediate Example 163 – Compound clxxi:

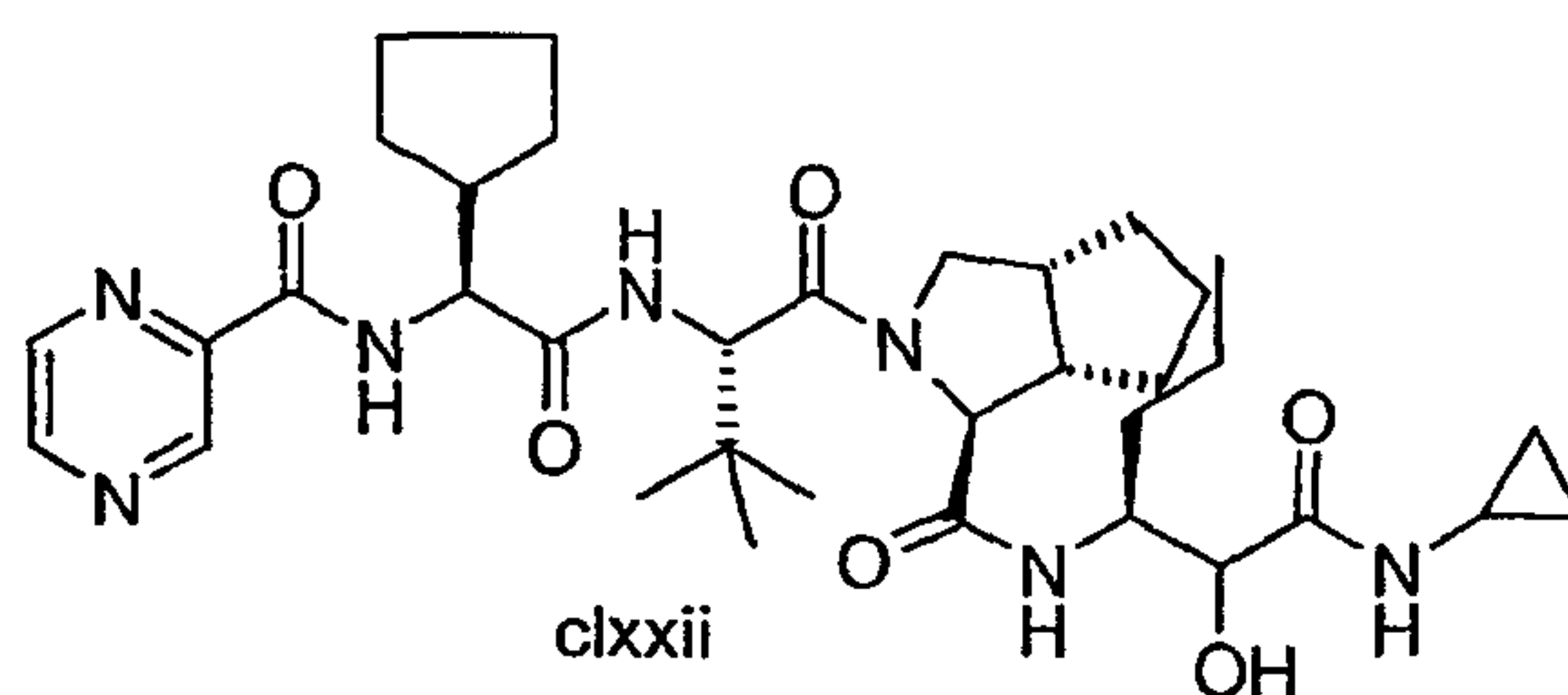
An EtOH solution (20 mL) of compound clxx (0.99 g, 1.88 mmol) is treated with 2 N NaOH (2.81 mL, 5.63 mmol). After stirring at room temperature overnight, the reaction mixture

is acidified to pH 3 with 1 N HCl. The reaction mixture is extracted with EtOAc (75 mL). The organic layer is dried and concentrated *in vacuo* to give compound clxxi (772 mg, 82%).



5 Intermediate Example 164 – Compound clxxi:

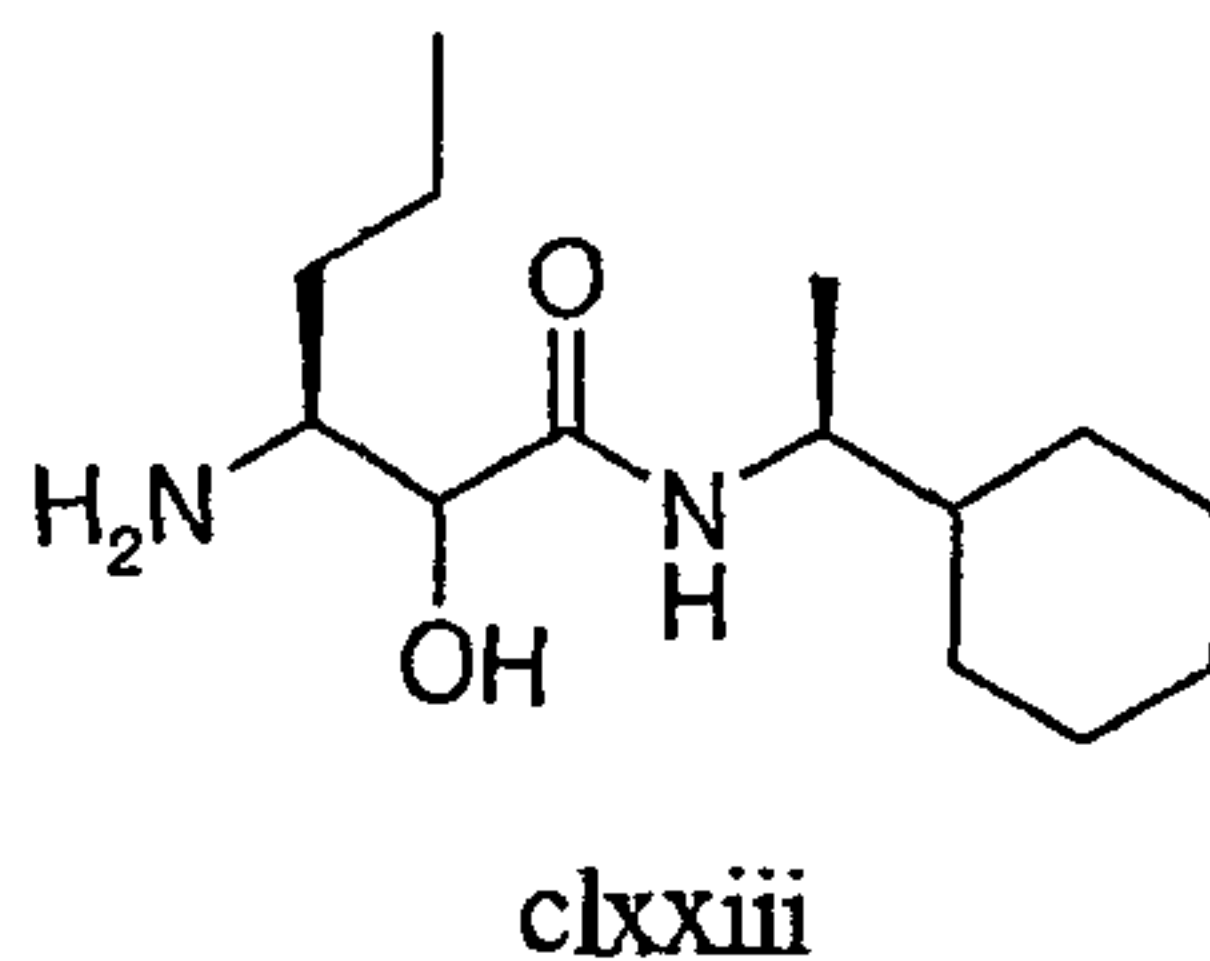
A DCM solution (10 mL) of compound clxxi (290 mg, 0.58 mmol) is treated with PyBOP (484 mg, 0.93 mmol). After stirring at room temperature for 20 minutes, the reaction mixture is treated with a THF solution (7.5 mL) of compound xiii' (140 mg, 0.75 mmol), followed by DIPEA (0.13 mL, 0.75 mmol). After stirring overnight at room temperature, the reaction is
 10 quenched with water and extracted with EtOAc. The resulting organic layer is washed with brine and dried and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (5% EtOH/EtOAc) to yield compound clxxii 290 mg (75%).



15

Intermediate Example 165 – Compound clxxiv:

Compound lxxxi (600 mg, 1.17 mmol) is taken up in DCM (4 mL). PyBOP (670 mg, 1.3 mmol) is added, stirred five minutes, and cooled to 0°C. Compound clxxiii (333 mg, 1.3
 20



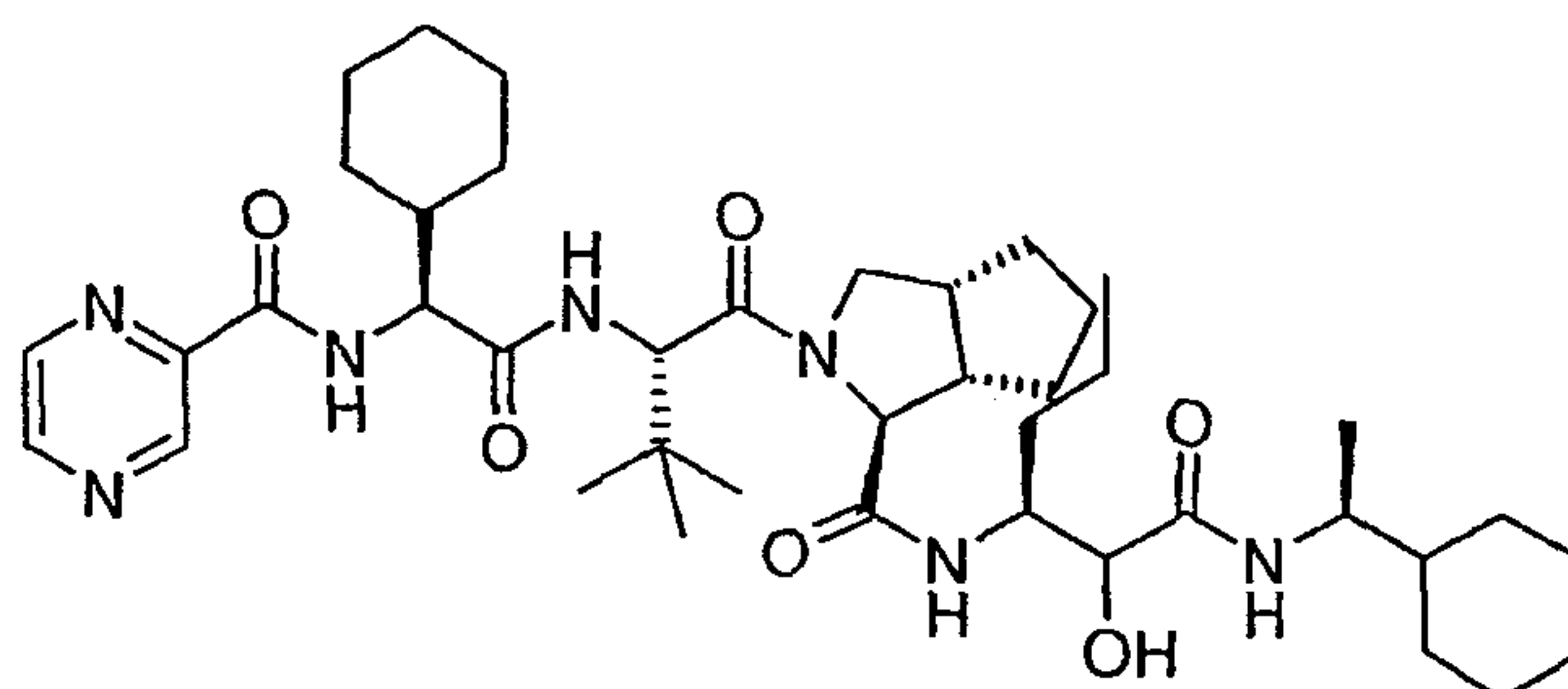
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mmol) in THF (13 mL) is added drop-wise to this solution. DIPEA (0.23 mL, 1.3 mmol) is added to reaction mixture and allowed to warm to ambient temperature with stirring for two nights. The next day, the reaction is concentrated and purified by 2% EtOH/EtOAc to give crude compound clxxiv (900 mg, excess of 100%).

5

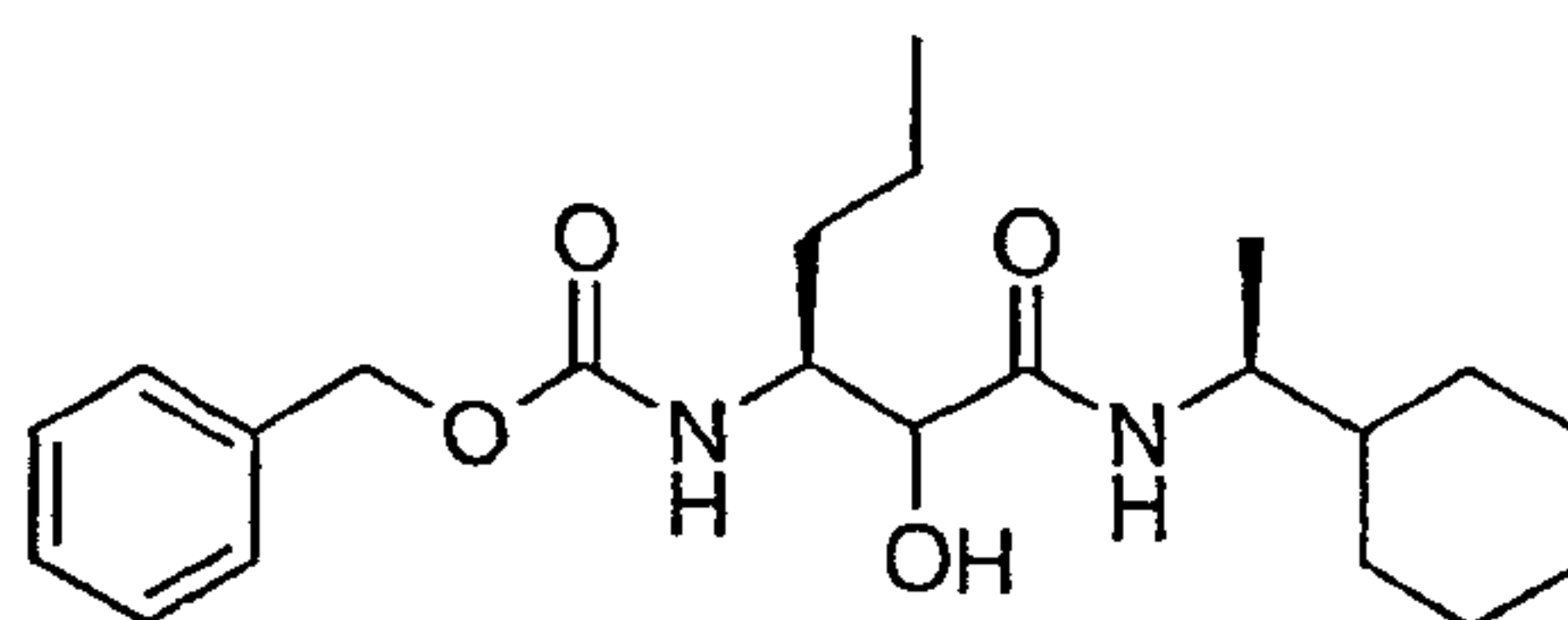


clxxiv

Intermediate Example 166 – Compound clxxxv:

Compound cxxv (3.01 g, 10.7 mmol) is taken up in DCM (30 mL) and the temperature lowered to -78°C . PyBOP (6.1g, 11.7 mmol) and HOBT (1.58 g, 11.7 mmol) are added to this solution followed by (S)-(+)-1-cyclohexylethylamine, compound clxxv, (1.74 mL, 11.7 mmol) and DIPEA (2.1 mL, 11.7 mmol). The resulting mixture stirred overnight at room temperature. The next day, the reaction mixture is diluted with EtOAc, washed with 0.1 N HCl, saturated NaHCO_3 , and brine. The product is purified in 40% EtOAc/Hex to give 2 g (47.8%) of compound clxxvi.

15



clxxvi

Intermediate Example 167 – Compound clxxiii:

Compound clxxvi (2 g, 5.13 mmol) is hydrogenated using 10% Pd/C (500 mg) in MeOH (40 mL). The reaction mixture stirred overnight under H_2 . The reaction mixture is filtered through celite and concentrated to give compound clxxiii (1.31 g, 99.8%).

20

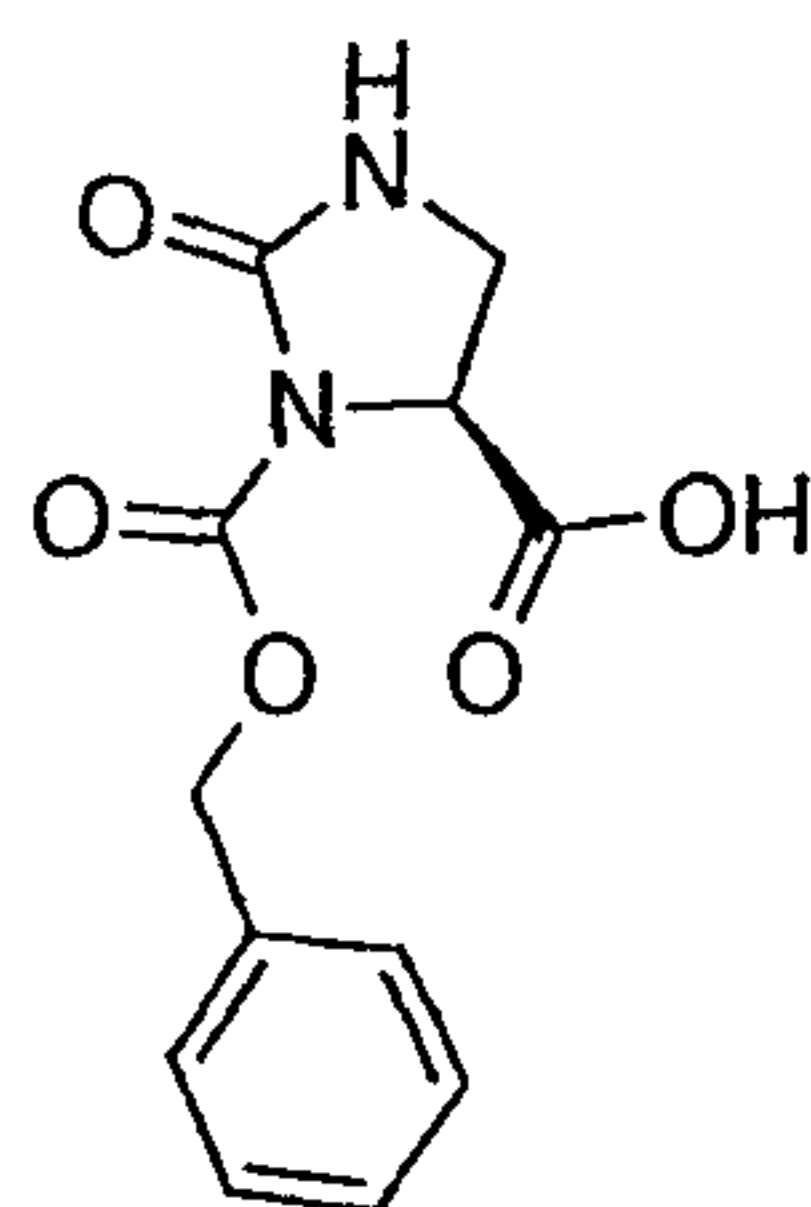
Intermediate Example 168 – Compound clxxix:

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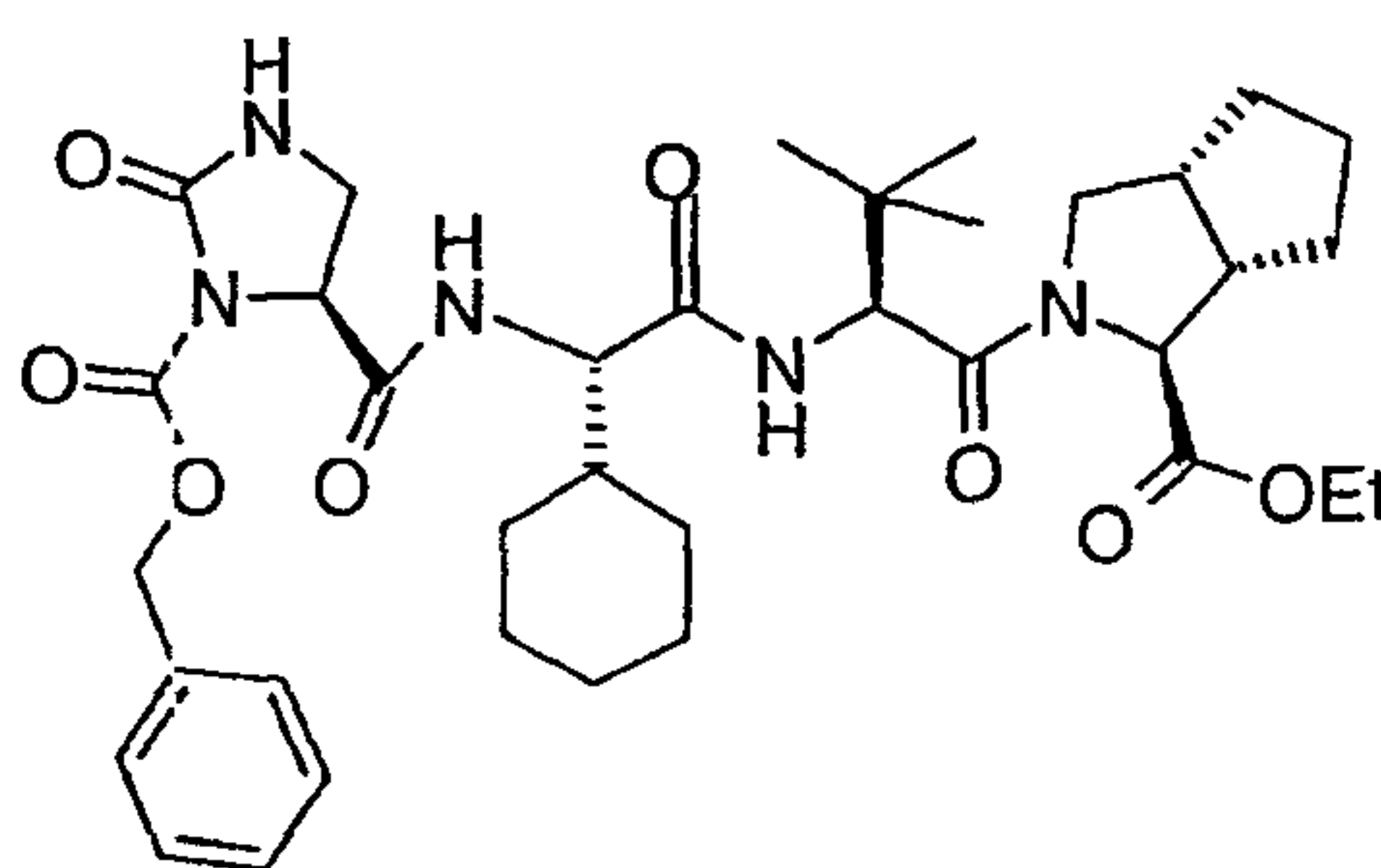
245

In a round bottom flask under inert atmosphere, compound clxxvii [(S)-(-)-2-oxo 1,5



clxxvii

imidazoline dicarboxylic acid 1-benzyl ester] (290 mg, 1.1 mmol) is dissolved in anhydrous
 5 DMF (6 mL). HOAt (151 mg, 1.2 mmol) is added and the reaction is stirred at room temperature
 for 25 minutes. The reaction is then cooled down in an ice bath. DIC (0.2 mL, 0.16 g, 1.2 mmol)
 is then added followed by the addition of compound clxxviii (1 mmol, 435 mg.) in anhydrous
 DMF (4 mL). The reaction is allowed to rise slowly to room temperature and stirred for 2 days.
 The reaction is then dumped in a separatory funnel containing 120 mL of EtOAc and washed 2X
 10 with 1 N HCl (50 mL) and 1X brine. The organic layer is separated, dried over MgSO₄. The
 solvent evaporated under reduced pressure and the residue purified by chromatography on silica
 gel (load in DCM and elute with 30% then 50% EtOAc/DCM then 2% MeOH/EtOAc) to yield
 product clxxix (434 mg, 64%).



clxxix

15

Intermediate Example 169 – Compound clxxx:

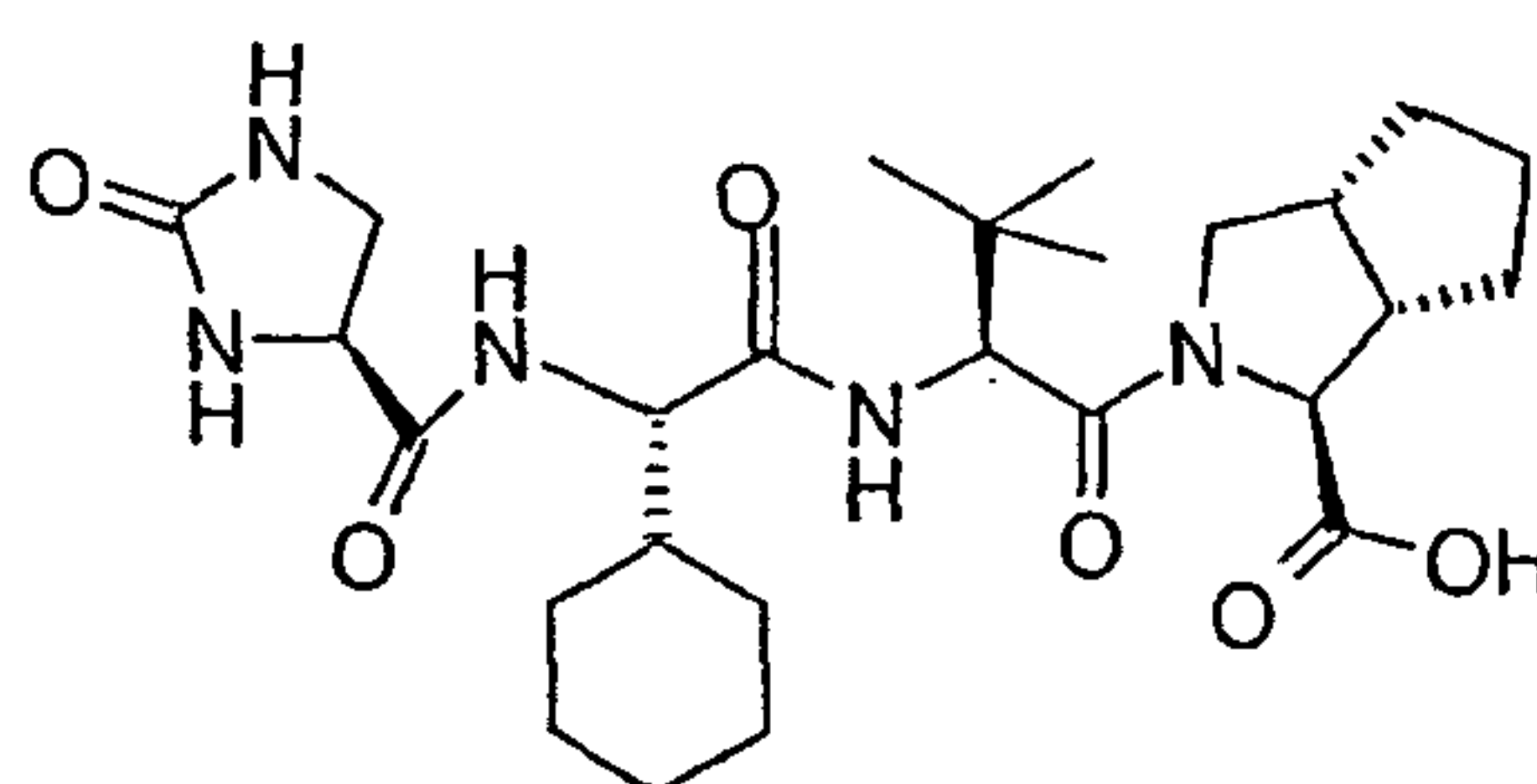
The starting material clxxix (434 mg, 0.64 mmol) is dissolved in Dioxane (6 mL) and 0.5
 20 M aqueous NaOH solution (4 mL, 3 eq.). The reaction is run overnight. TLC in 100% EtOAc
 (using PMA stain) shows in addition to the expected acid product at the origin, a faster running

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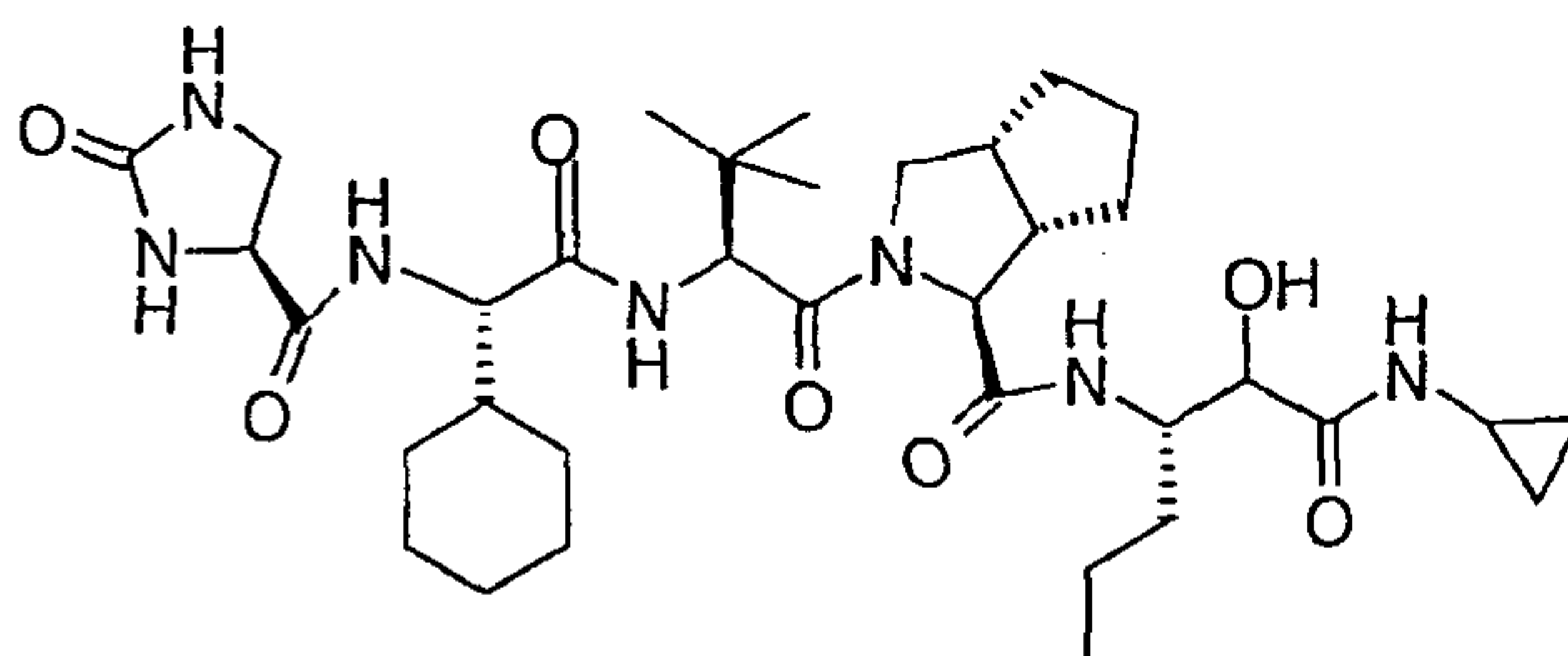
product. The reaction mixture is acidified to pH 2 with 1 N HCl, and then extracted 2X with EtOAc. Solid NaCl is added to the aqueous solution to facilitate the extraction. The organic extracts are then combined, dried over MgSO₄ and evaporated under reduced pressure. MS indicates that the CBZ group is removed by the hydrolysis. The resulting compound clxxx
 5 (quantitative yield) is used as is in the next step.



clxxx

Intermediate Example 170 – Compound clxxxi:

10 In a round bottom flask under inert atmosphere, compound clxxx (279 mg, 0.54 mmol) is dissolved in anhydrous DMF (6 mL). HOAt (82 mg, 0.65 mmol) is added and the reaction is stirred at room temperature for 25 minutes. The reaction is then cooled down in an ice bath. DIC (0.11 mL, 0.65 mmol) is then added, followed by the addition of compound xiii' (0.7 mmol) in anhydrous DMF (4 mL). The reaction is allowed to rise slowly to room temperature and stirred
 15 for 21 hours. The reaction is then dumped in a separatory funnel containing 120 mL of EtOAc and washed 2X with 1 N HCl (50 mL) and 1X brine. The organic layer is separated, dried over MgSO₄. The solvent evaporated by reduced pressure and the product cleaned by chromatography on silica gel (load in DCM and elute with 50% EtOAc/Hexane, then 3% MeOH/EtOAc, then 20% EtOH/EtOAc). After removal of solvent, the residue is redissolved in Dri Solv THF and filtered
 20 to remove any silica gel. Removal of the solvent then yields compound clxxxi (434 mg, 64% yield).



clxxxi

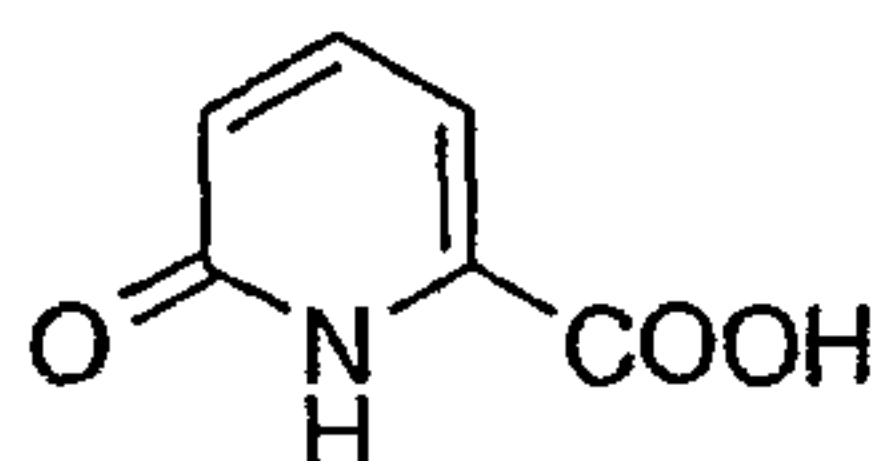
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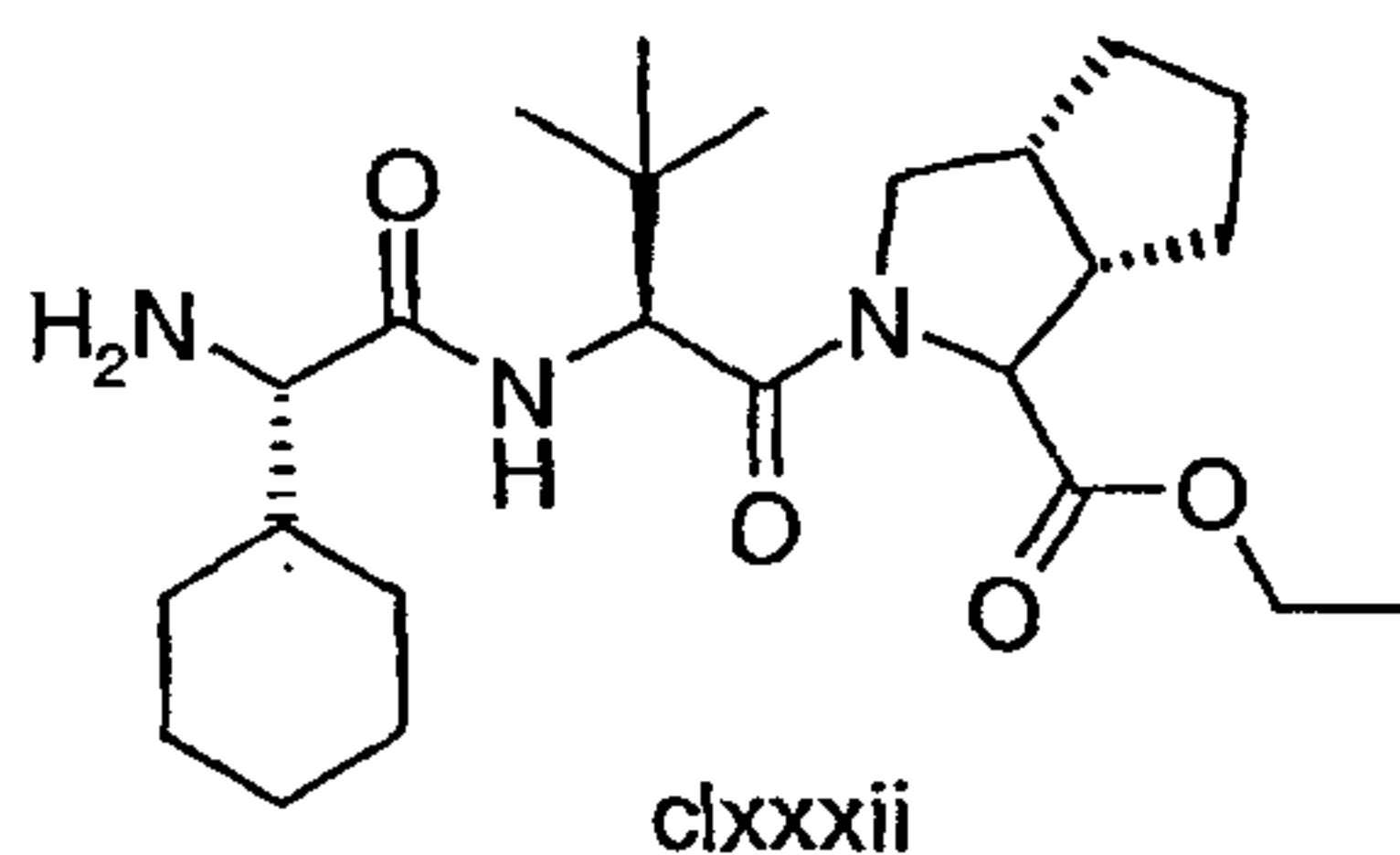
247

Intermediate Example 171 – Compound clxxxiii:

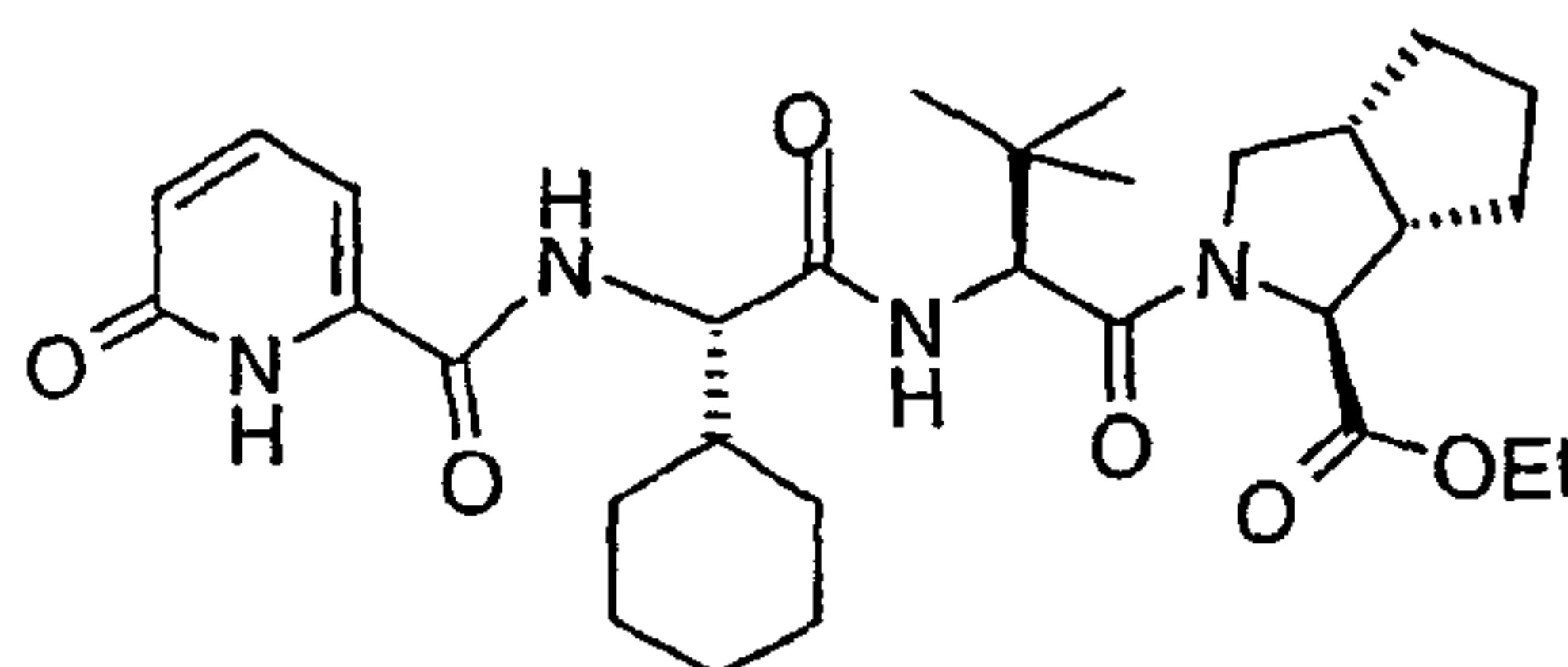
In a round bottom flask under inert atmosphere, 6-hydroxy picolinic



- 5 (153 mg, 1.1 mmol) is dissolved in anhydrous DMF (6 mL). HOAt (151 mg, 1.2 mmol) is added and then the reaction is stirred at room temperature for 25 minutes. The reaction is then cooled down in an ice bath. DIC (0.2 mL, 0.16 g, 1.2 mmol) is then added followed by the addition of the compound clxxxii (1.0 mmol, 435 mg.) in anhydrous DMF (4 mL). The



- 10 reaction is allowed to rise slowly to room temperature and stirred for 2 days. The reaction is then dumped in a separatory funnel containing 120 mL of EtOAc and washed 2X with 1 N. HCl (50 mL) and 1X with brine. The organic layer is separated, dried over MgSO₄. The solvent is evaporated by reduced pressure and the product purified by chromatography on silica gel (load in DCM, elute with 30%, then 50% EtOAc/DCM, and then 2% MeOH/EtOAc) to yield compound
- 15 clxxxiii collected (314 mg, 56%).



Intermediate Example 172 – Compound clxxxiv:

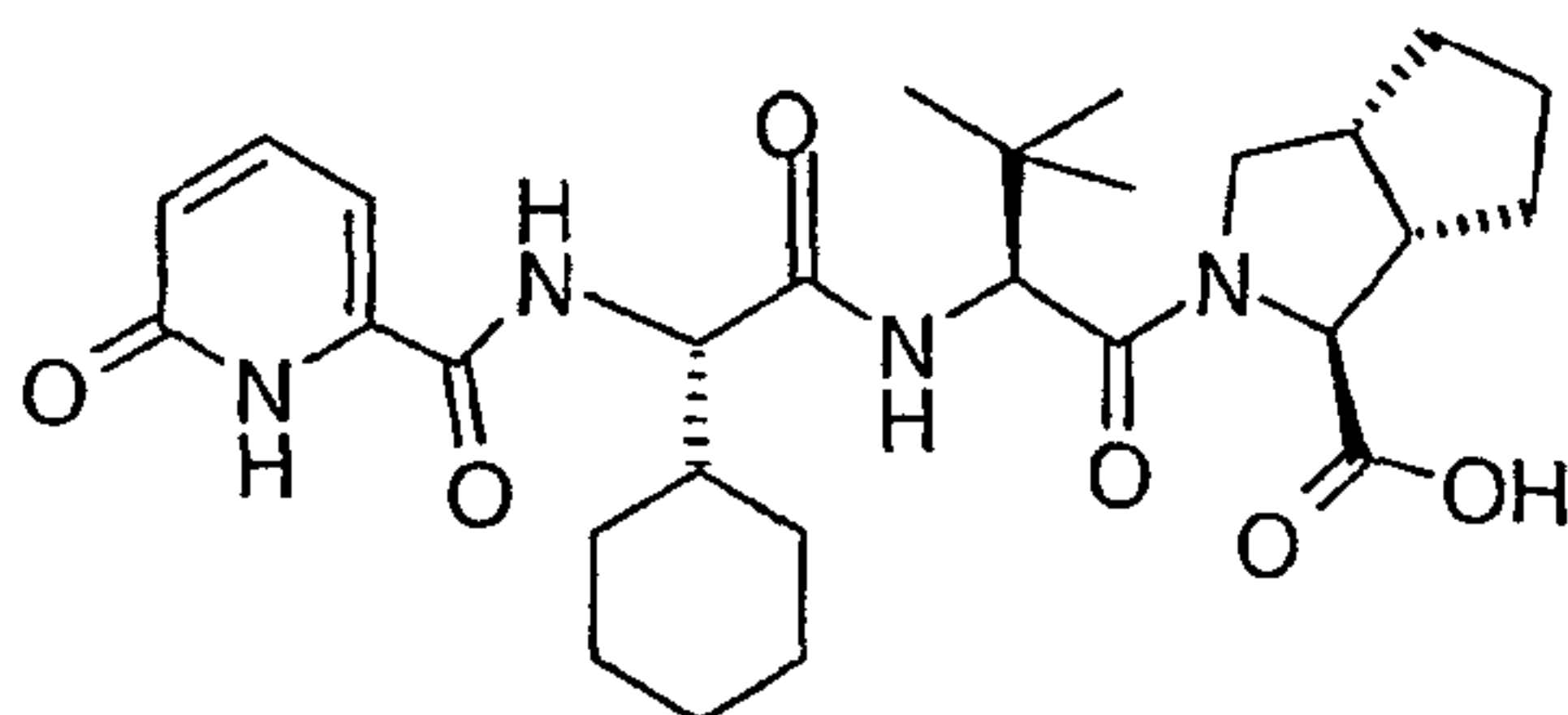
- 20 The starting material clxxxiii (314 mg, 0.56 mmol) is dissolved in dioxane (5 mL) and 0.5 M NaOH (3.4 mL, 3 eq). The reaction is run overnight. TLC in 100% EtOAc (using UV) shows complete conversion to the slow running acid product at the origin. The reaction is acidified to pH 2 with 1 N HCl, and then extracted 2X with EtOAc. Solid NaCl is added to the aqueous to

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facilitate the extraction. The organic extracts are then combined, dried over MgSO_4 , and then evaporated under reduced pressure to yield compound clxxxiv (0.5 mmol, 89%) that is used as is in the next step.



clxxxiv

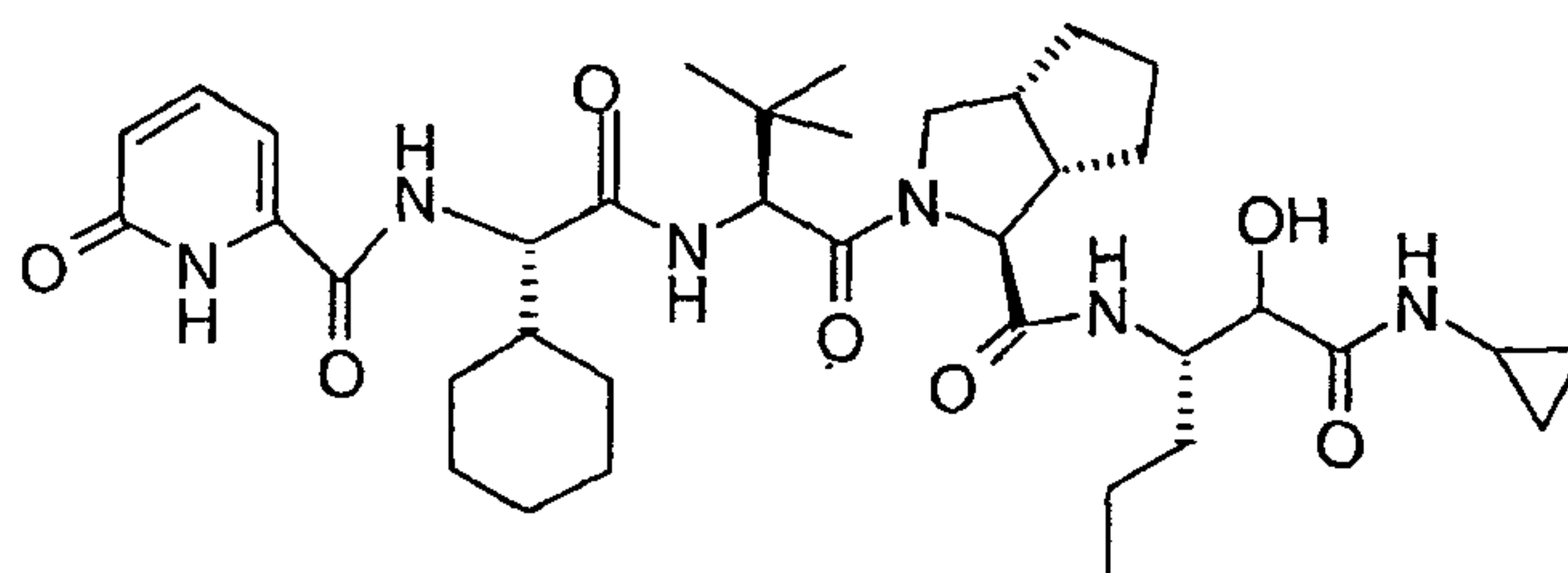
5

Intermediate Example 173 – Compound clxxxv:

In a round bottom flask under inert atmosphere, acid compound clxxxiv (265mg, 0.5 mmol) is dissolved in anhydrous DMF (6 mL). HOAT (75.6 mg, 0.6 mmol) is added and the reaction is stirred at room temperature for 25 minutes. The reaction is then cooled down in an ice bath. DIC (0.1 mL, 0.6 mmol) is then added followed by the addition of the compound xiii' (0.65 mmol) in anhydrous DMF (4mL). The reaction is allowed to rise slowly to room temperature and stirred for 21 hours. The reaction is then dumped in a separatory funnel containing EtOAc (120 mL) and washed 2X with 1 N HCl (50 mL) and 1X with brine. The organic layer is separated, dried over MgSO_4 . The solvent is evaporated by reduced pressure and the product purified by chromatography on silica gel (load in DCM, elute with 50% EtOAc/Hexane, then pure EtOAc, and then 4% MeOH/EtOAc) to yield product compound clxxxv (185 mg, 52%).

10

15



clxxxv

20

Intermediate Example 174 – Compound cxxxxiv':

To a solution of D-alanine (5 g, 56.1 mmol) in 1 N NaOH (152 mL, 152 mmol) at 0°C is added a solution of MeOC(O)Cl (6.5 mL, 84.2 mmol) in diethyl ether (30 mL). The mixture is stirred in ice bath for 3 hours and then adjusted to pH 9 with 1 N NaOH. After stirring at room

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

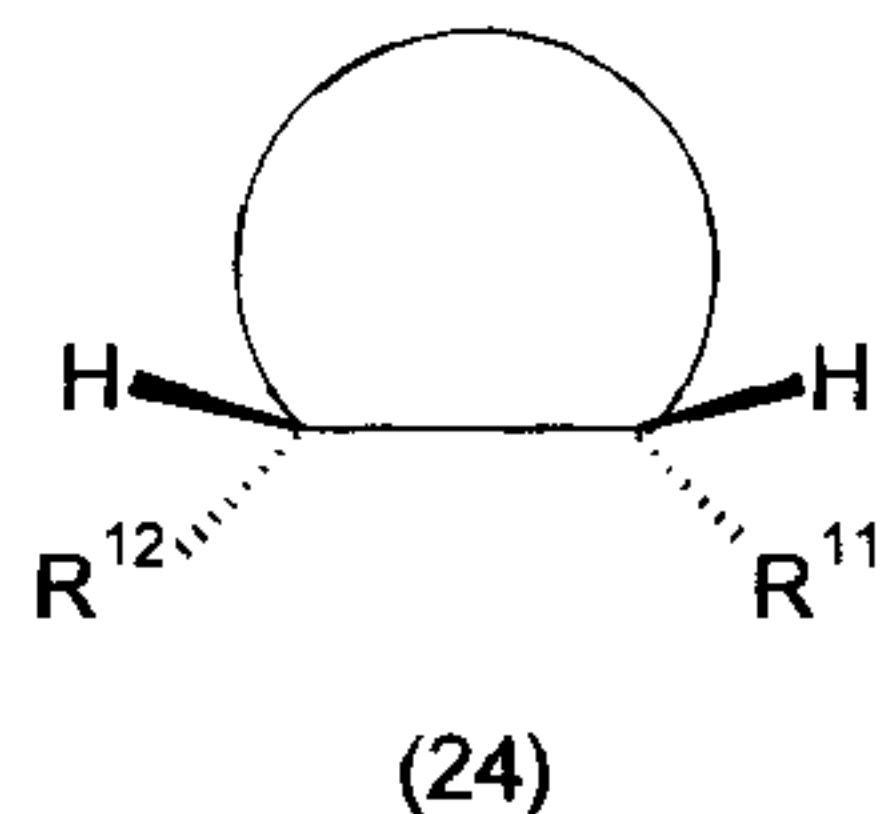
THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

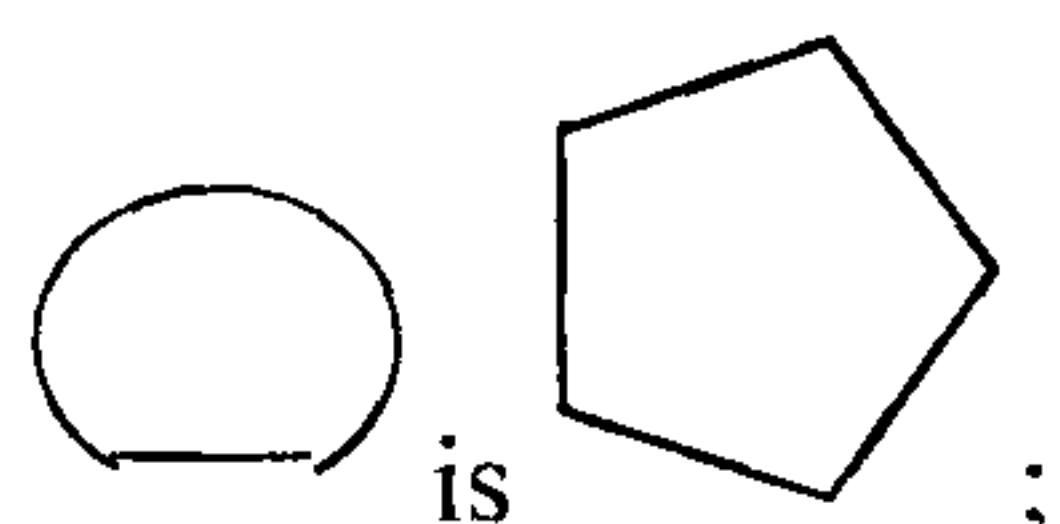
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CLAIMS:

1. A compound of formula 24



wherein:



R^{11} is $-\text{CO}_2R^{13}$;

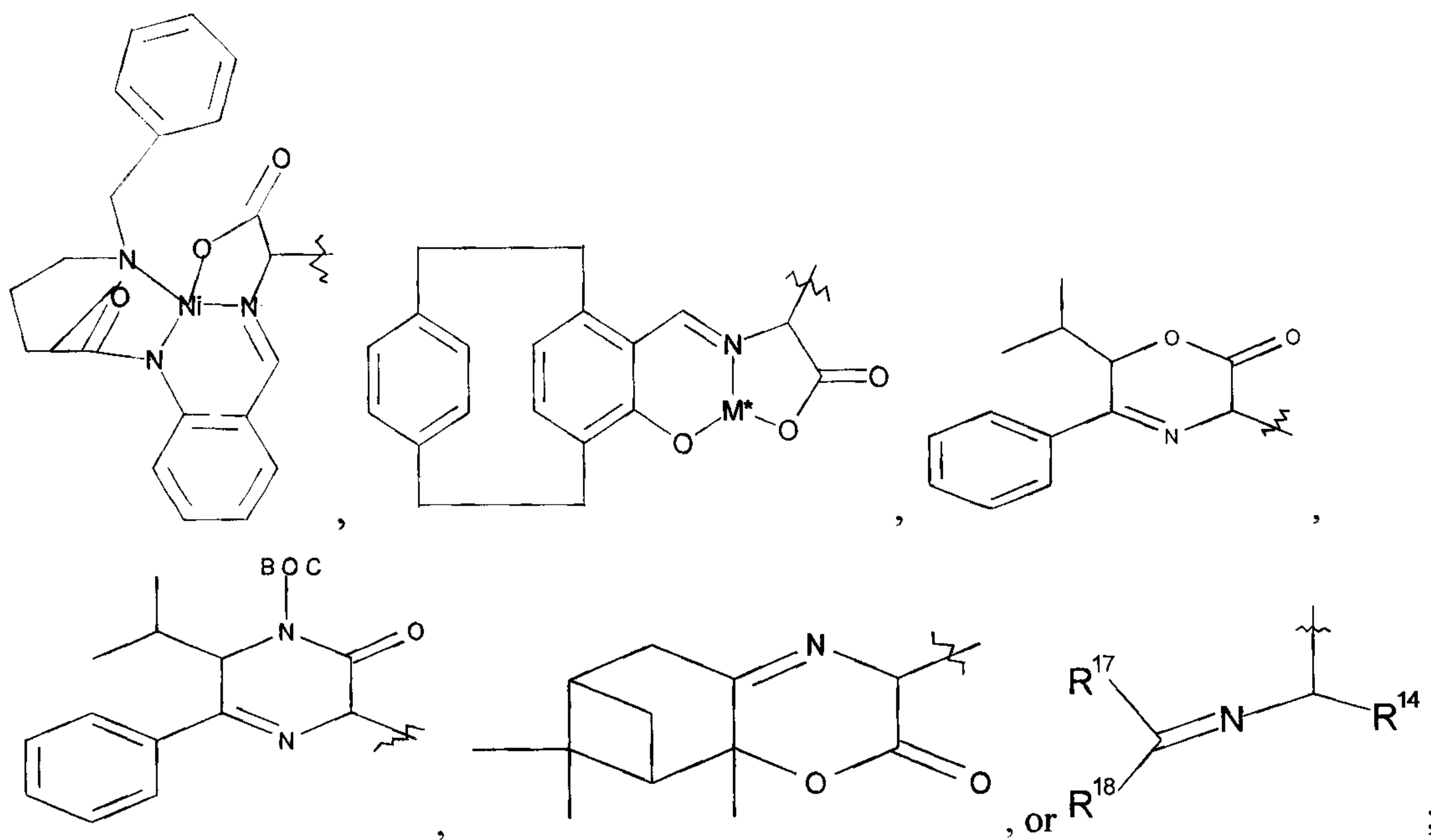
R^{12} is an iminic glycinimide derivative adduct; and

R^{13} is acid protecting group or optionally substituted aliphatic group.

2. A compound of claim 1 wherein:

optionally substituted aliphatic group are alkyl, alkenyl, or alkynyl optionally substituted with an aliphatic group substituent;

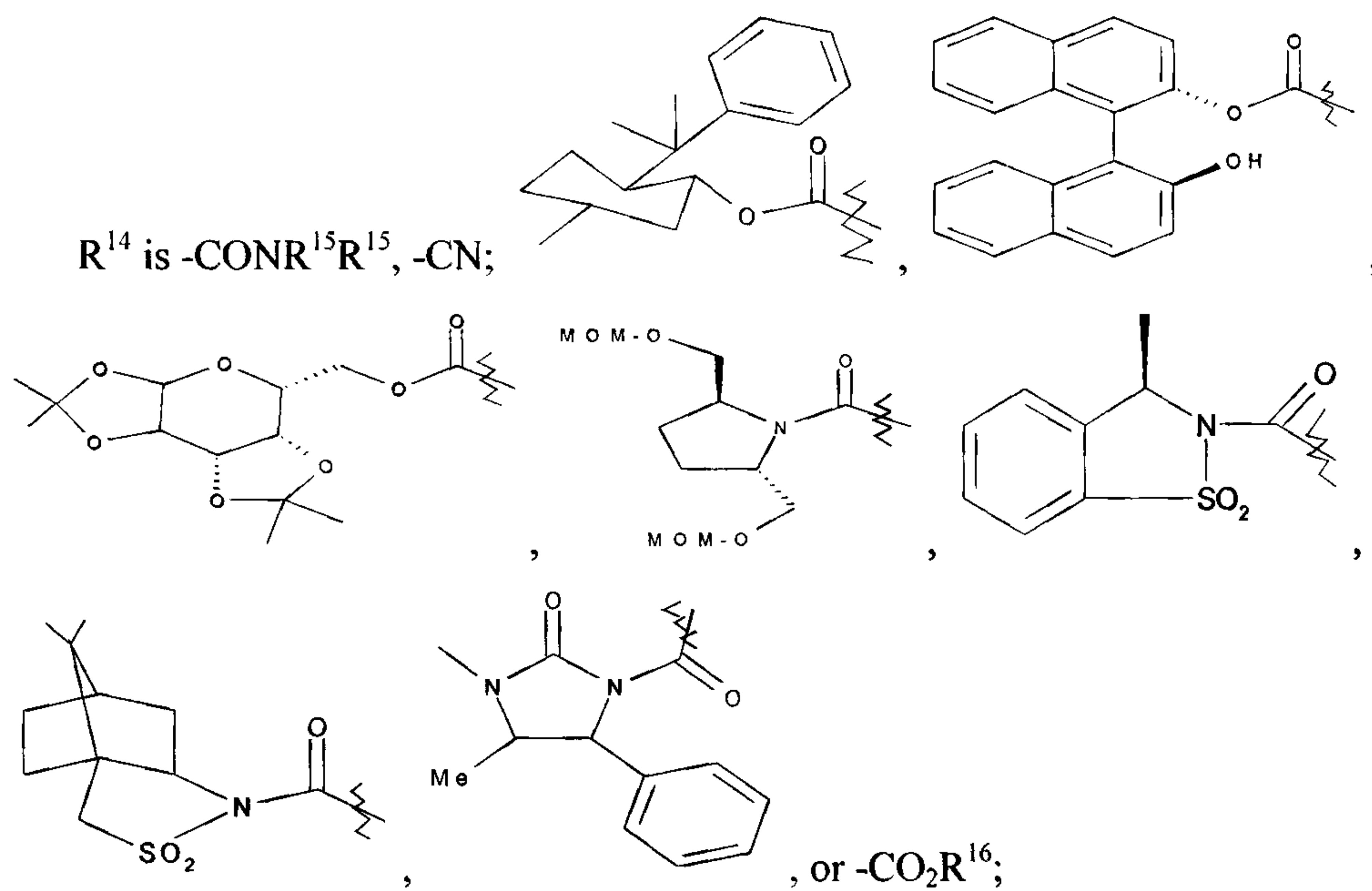
an iminic glycinimide derivative adduct is



wherein:

M^* is a transition metal;

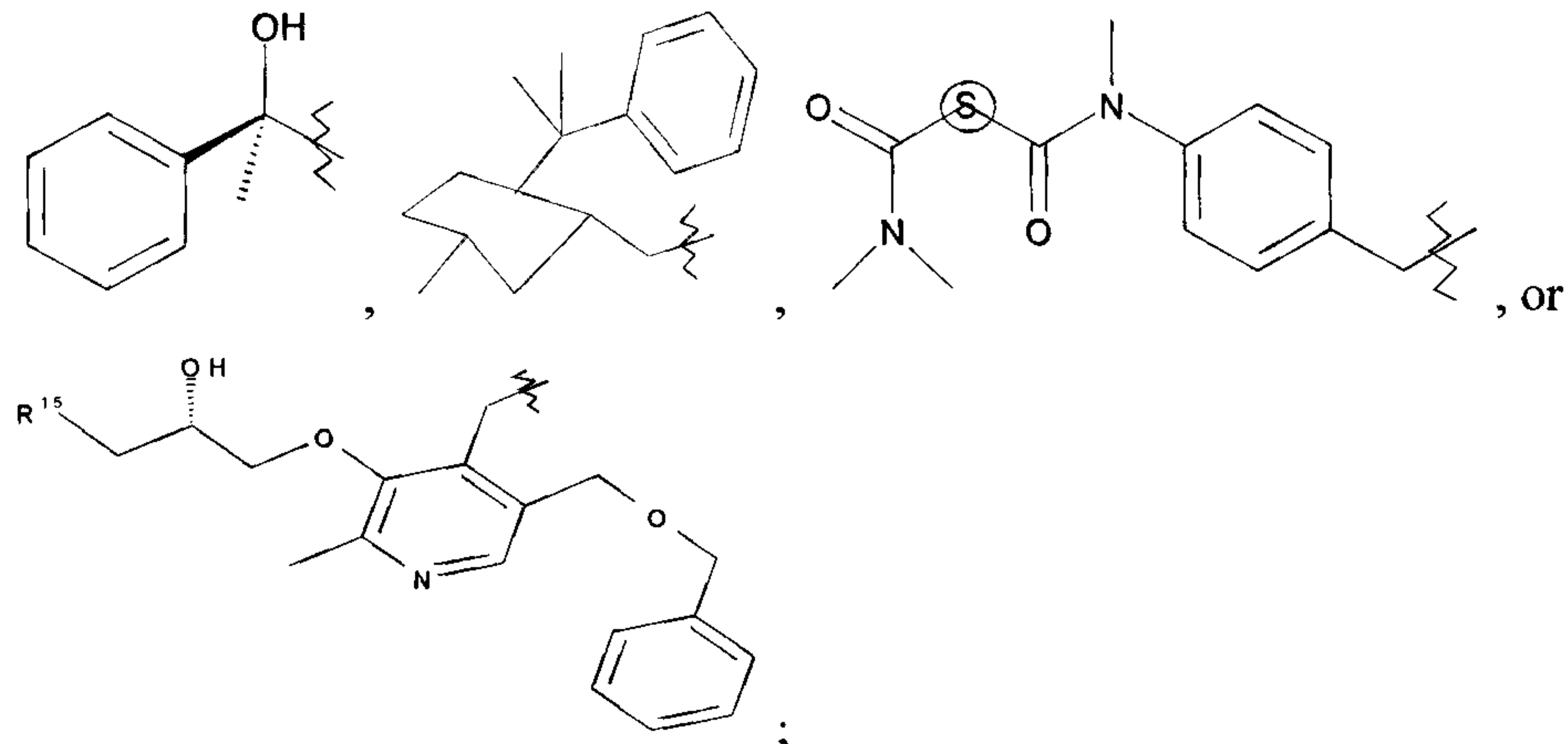
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R^{15} is an aliphatic group;

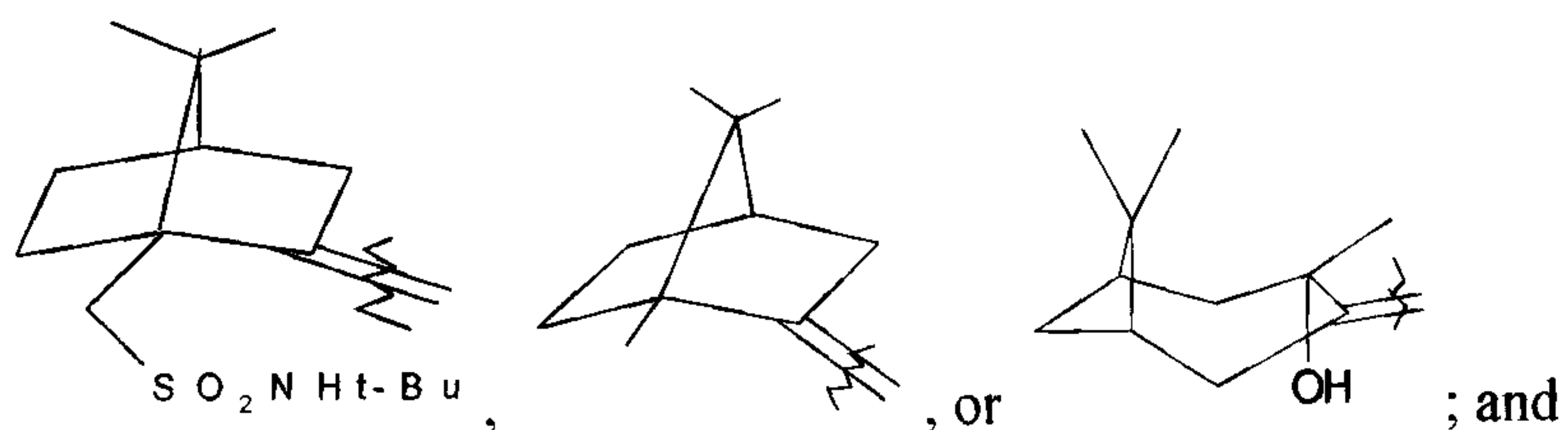
5 R^{16} is an acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group;

R^{17} is optionally substituted aryl, optionally substituted aliphatic group,



10 R^{18} is hydrogen, alkyl, or alkylthio, or optionally substituted aryl; or

R^{17} and R^{18} , taken together with the carbon to which R^{17} and R^{18} are attached, form



wherein:

Ⓢ is a solid phase;

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aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H₂C=), oxo (O=), thioxo (S=), Y¹Y²N-, Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³-, Y¹Y²NSO₂-, or Y³SO₂NY¹- wherein Y¹ and Y² are independently hydrogen, alkyl, aryl or heteroaryl, and Y³ is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, and the other of Y¹ and Y² is as defined previously, or for where the substituent is Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl;

aryl means an aromatic monocyclic or multicyclic ring system of 6 to 14 carbon atoms; and cyclyl means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

3. A compound according to claim 1 or claim 2 where aliphatic group substituents means heteroaryl and wherein heteroaryl is 3-hydroxyisoxazolyl or 3-hydroxy-1-methylpyrazolyl.

25 4. A compound according to any one of claims 1 to 3 where R¹¹ is -CO₂R¹³.

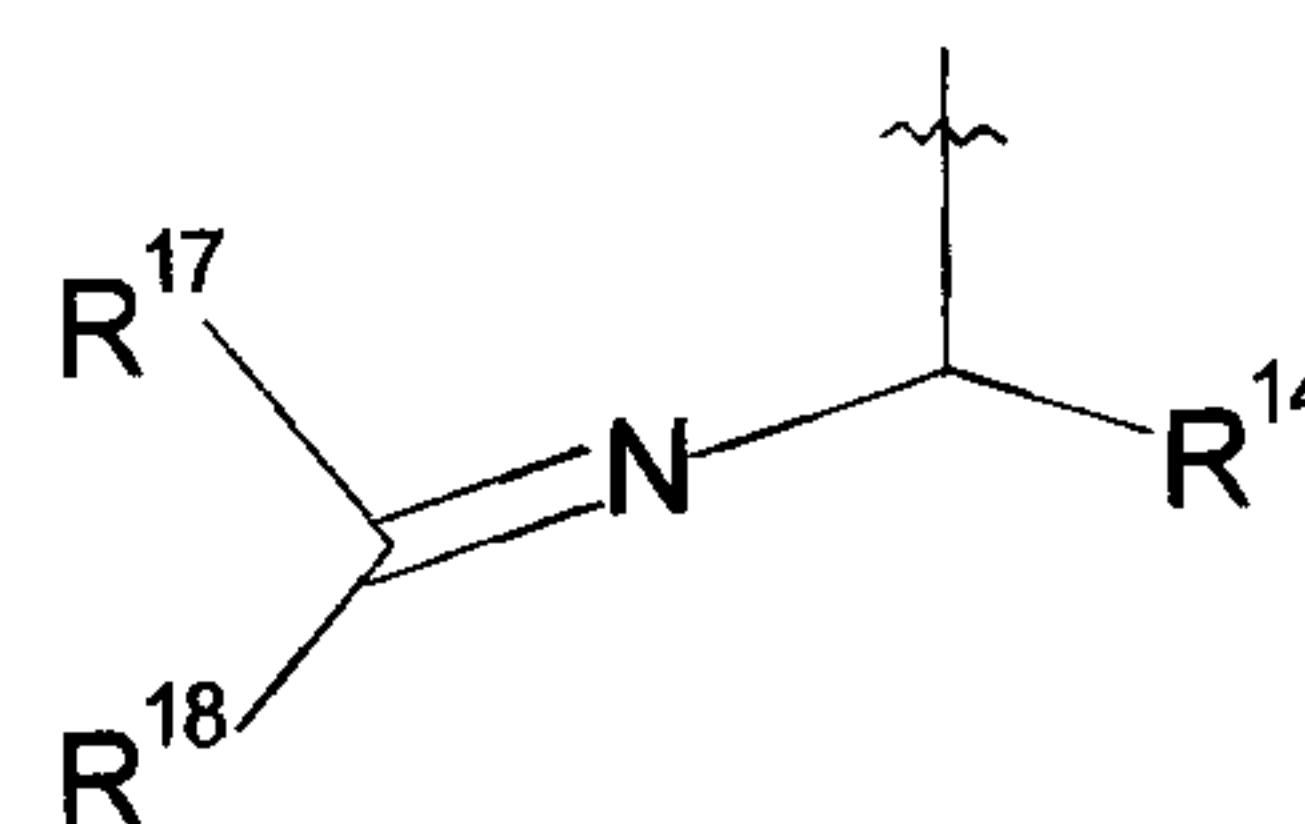
5. A compound according to any one of claims 1 to 4 where R¹³ is an optionally substituted aliphatic group.

6. A compound according to any one of claims 1 to 5 where R¹³ is an alkyl group.

7. A compound according to any one of claims 1 to 6 where R¹³ is lower alkyl.

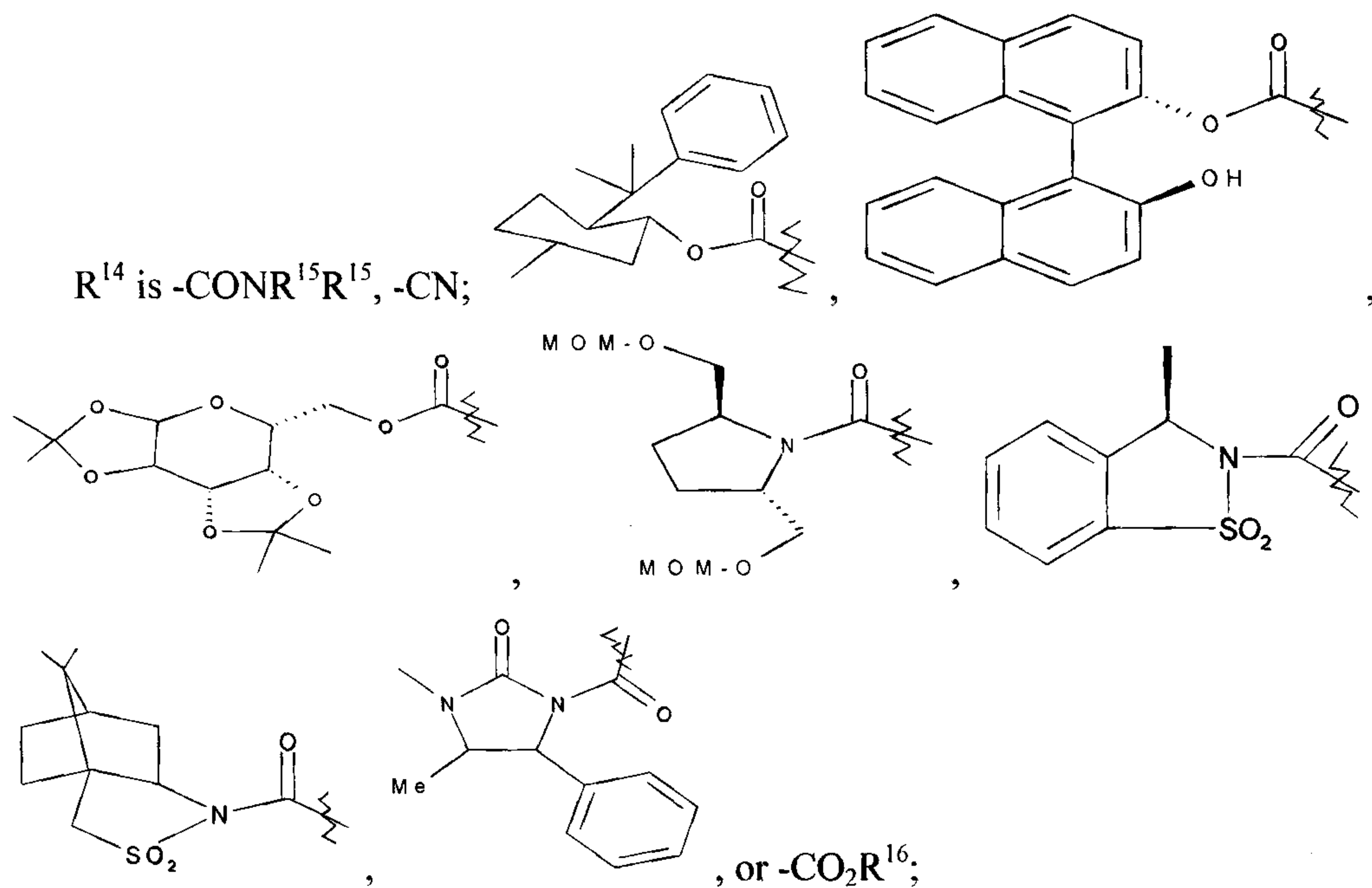
30 8. A compound according to any one of claims 1 to 7 where R¹³ is methyl.

9. A compound according to any one of claims 1 to 8 where R¹² is



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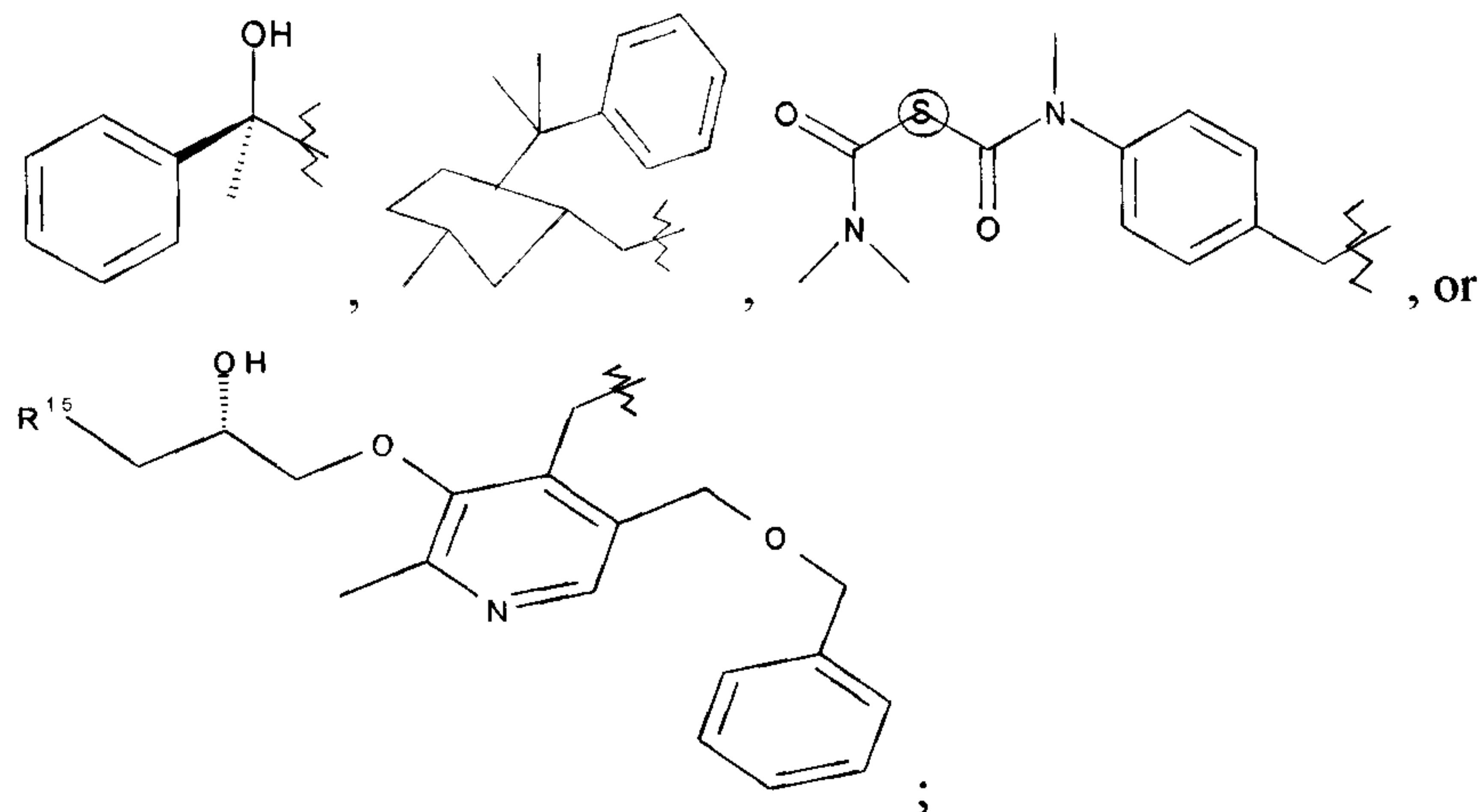
wherein:



R^{15} is optionally substituted aliphatic group;

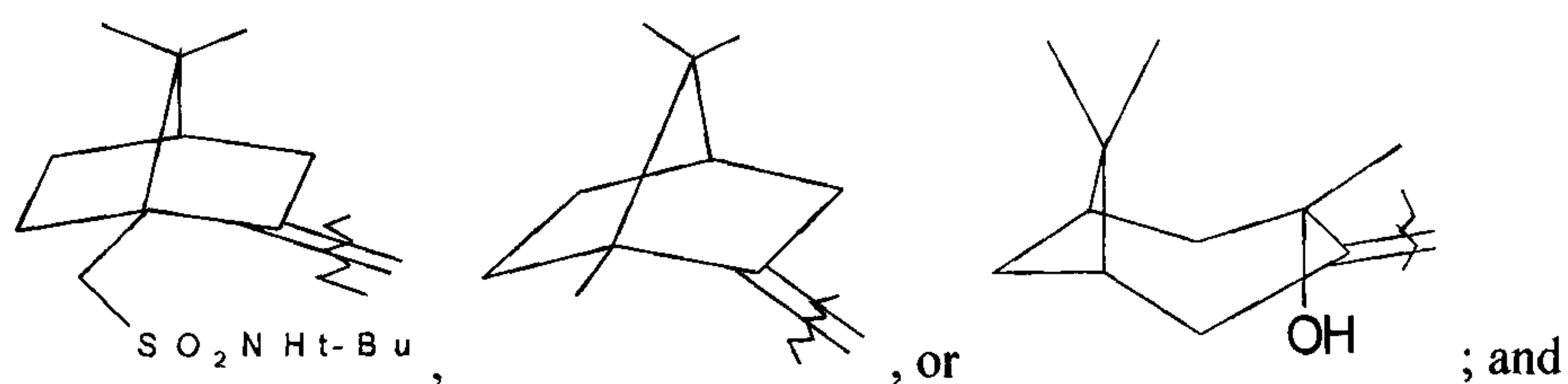
R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group;

R^{17} is optionally substituted aryl, optionally substituted aliphatic group,



R^{18} is hydrogen, alkyl, or alkylthio; or optionally substituted aryl; or

R^{17} and R^{18} taken together with the carbon to which R^{17} and R^{18} are attached form



10. A compound according to claim 9 where R^{14} is $-CO_2R^{16}$.

11. A compound according to claim 9 or 10 where R¹⁶ is optionally substituted aliphatic.

12. A compound according to any one of claims 9 to 11 where R¹⁶ is alkyl.

5 13. A compound according to any one of claims 9 to 12 where R¹⁶ is lower alkyl.

14. A compound according to any one of claims 9 to 13 where R¹⁶ is t-Bu.

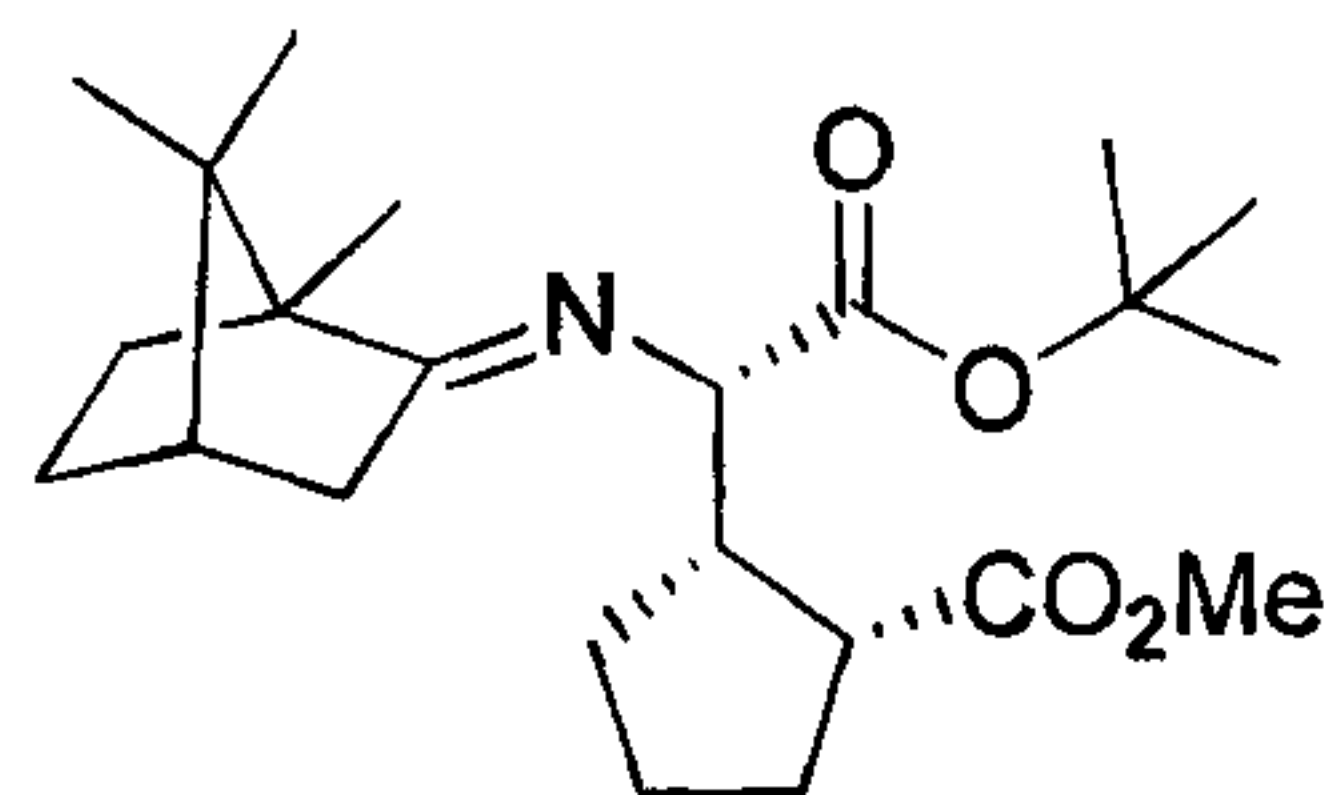
15. A compound according to any one of claims 9 to 14 where R¹⁷ is optionally substituted aryl.

16. A compound according to any one of claims 9 to 15 where R¹⁷ is phenyl.

17. A compound according to any one of claims 9 to 16 where R¹⁸ is optionally substituted aryl.

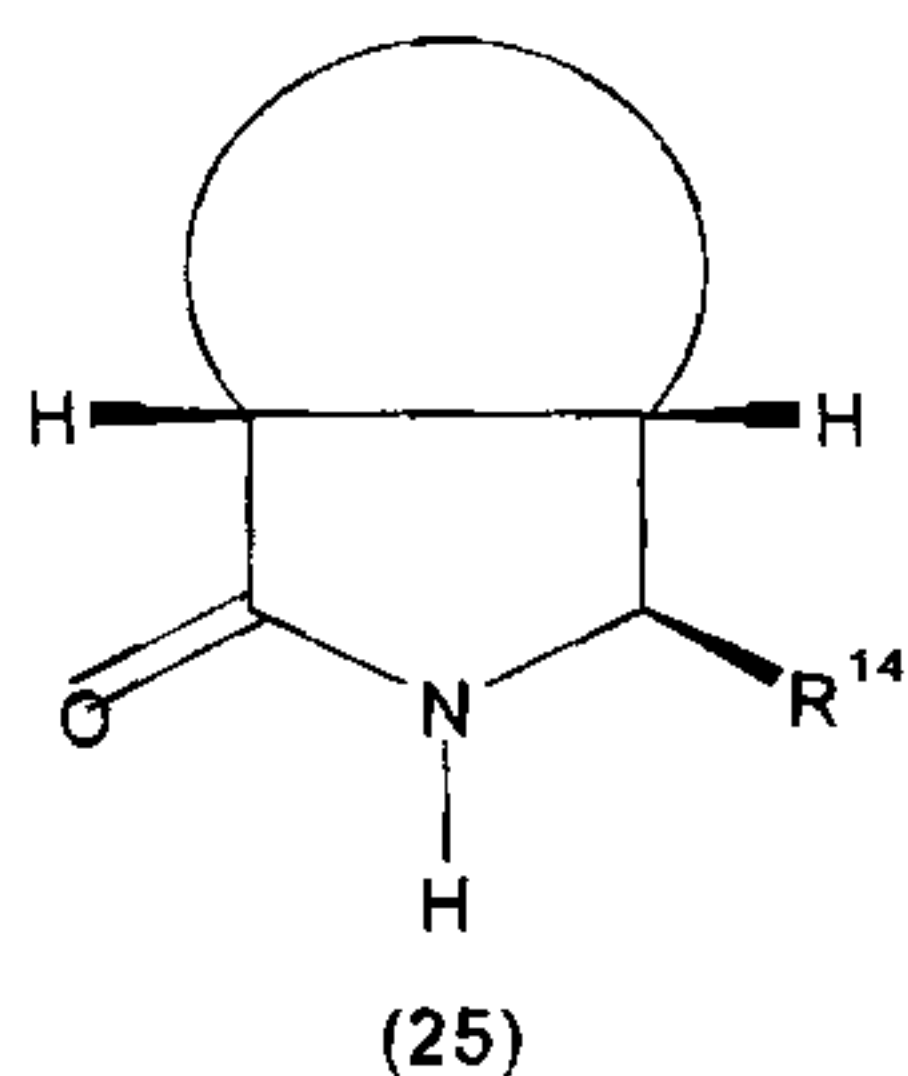
10 18. A compound according to any one of claims 9 to 17 where R¹⁸ is phenyl.

19. A compound according to any one of claims 9 to 14 where R¹⁷ and R¹⁸, taken together with



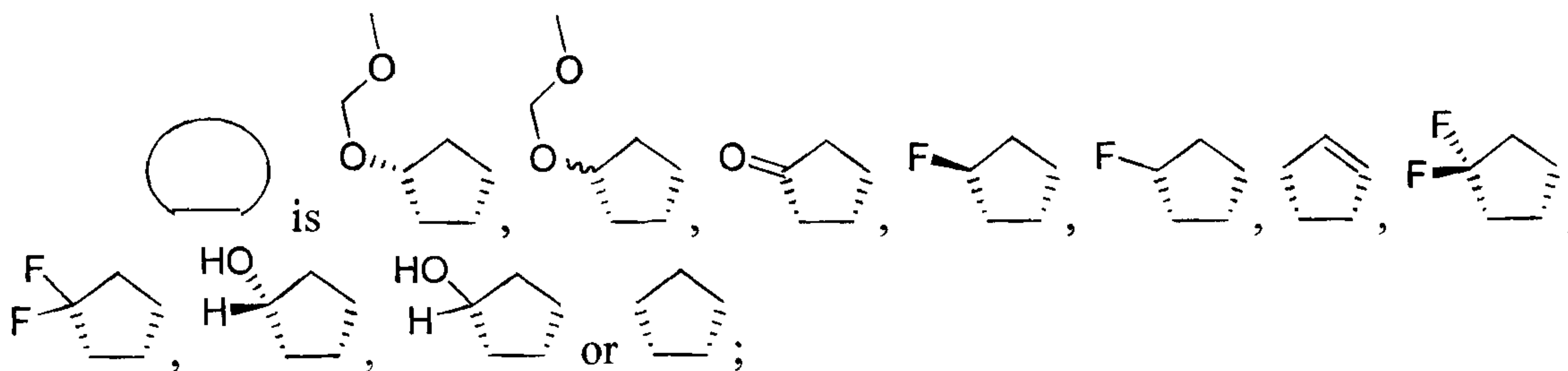
20. A compound according to claim 19, with the structure

21. A compound of formula 25

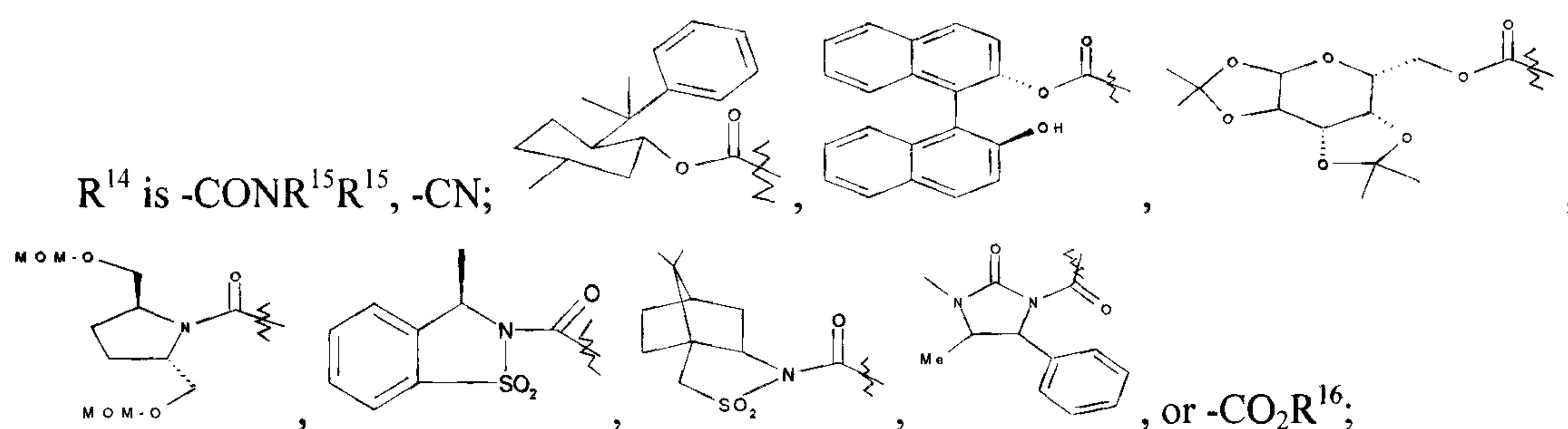


15

wherein:



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R^{15} is optionally substituted aliphatic group; and

R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group.

22. A compound according to claim 21 wherein:

optionally substituted aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;

optionally substituted aryl means an aromatic monocyclic or mylticyclic ring systems of 6 to 14

carbon atoms optionally substituted with one or more ring group substituents;

wherein;

ring group substituents mean substituents attached to aromatic or non-aromatic ring systems

inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue,

heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), $-\text{C}(\text{O})-\text{NHOH}$, $-\text{C}(\text{O})-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})-\text{CH}_2\text{SH}$, $-\text{C}(\text{O})-\text{NH}-$

CN , sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl, hydroxyheteroaryl, alkoxy carbonyl, cyclyloxycarbonyl,

aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl,

heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, $\text{Y}^1\text{Y}^2\text{N}-$,

$\text{Y}^1\text{Y}^2\text{NC}(\text{O})-$, $\text{Y}^1\text{Y}^2\text{NC}(\text{O})\text{O}$, $\text{Y}^1\text{Y}^2\text{NC}(\text{O})\text{NY}^3-$ or $\text{Y}^1\text{Y}^2\text{NSO}_2-$, wherein Y^1 , Y^2 and Y^3 are

independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is $\text{Y}^1\text{Y}^2\text{N}-$, then

one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy carbonyl,

cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and the other of Y^1 and Y^2 is

as defined previously, or for where the substituent is $\text{Y}^1\text{Y}^2\text{NC}(\text{O})-$, $\text{Y}^1\text{Y}^2\text{NC}(\text{O})\text{O}$,

$\text{Y}^1\text{Y}^2\text{NC}(\text{O})\text{NY}^3-$ or $\text{Y}^1\text{Y}^2\text{NSO}_2-$, Y^1 and Y^2 may also be taken together with the N atom

through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or

azaheterocyclenyl or when the ring system is saturated or partially saturated, the "ring group substituents" further include, methylene ($\text{H}_2\text{C}=\text{}$), oxo ($\text{O}=\text{}$) or thioxo ($\text{S}=\text{}$); and

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aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulfo, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H₂C=), oxo (O=), thioxo (S=), Y¹Y²N-, Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³-, Y¹Y²NSO₂-, or Y³SO₂NY¹- wherein Y¹ and Y² are independently hydrogen, alkyl, aryl or heteroaryl, and Y³ is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and the other of Y¹ and Y² is as defined previously, or for where the substituent is Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl; and

cyclyl means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

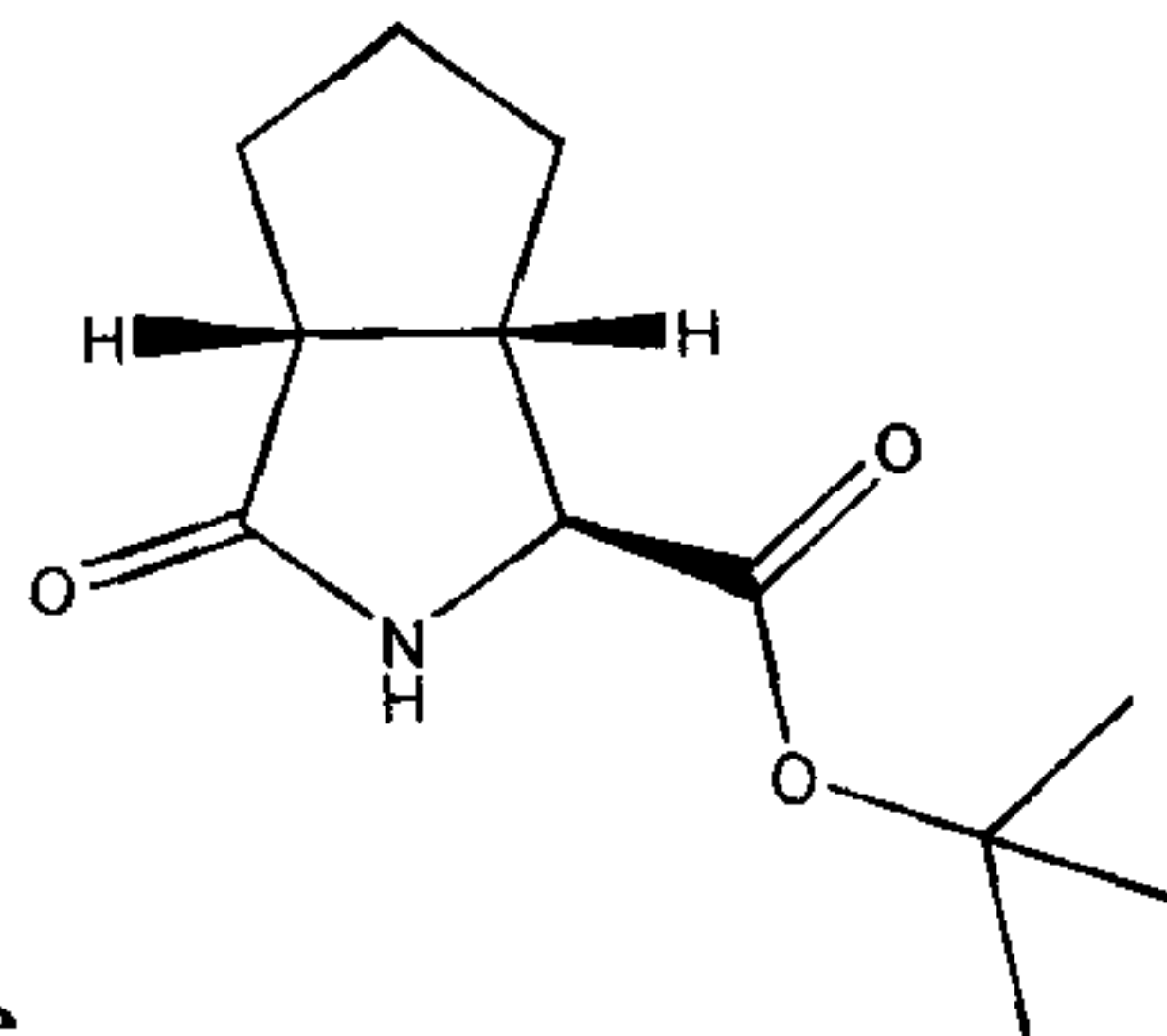
23. A compound according to claim 21 or 22 where R¹⁴ is -CO₂R¹⁶.

24. A compound according to any one of claims 21 to 23 where R¹⁶ is optionally substituted aliphatic.

25. A compound according to any one of claims 21 to 24 where R¹⁶ is alkyl.

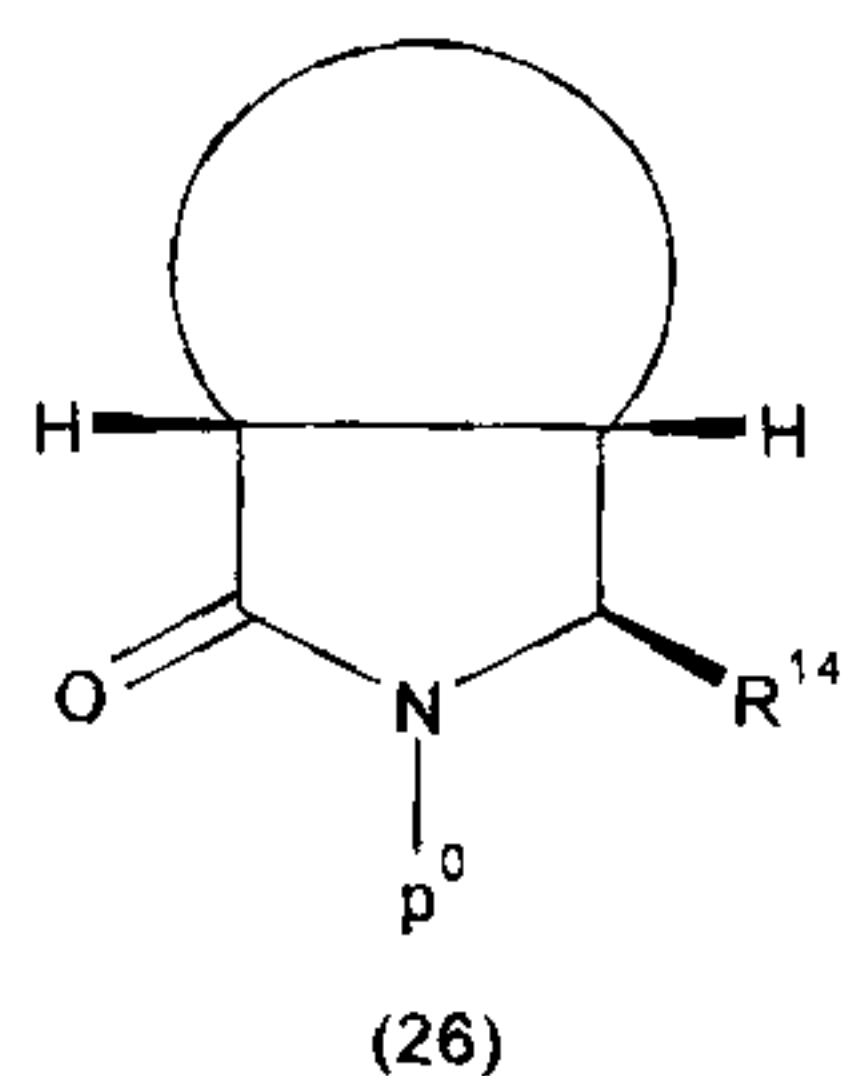
26. A compound according to any one of claims 21 to 25 where R¹⁶ is lower alkyl.

27. A compound according to any one of claims 21 to 26 where R¹⁶ is t-Bu.

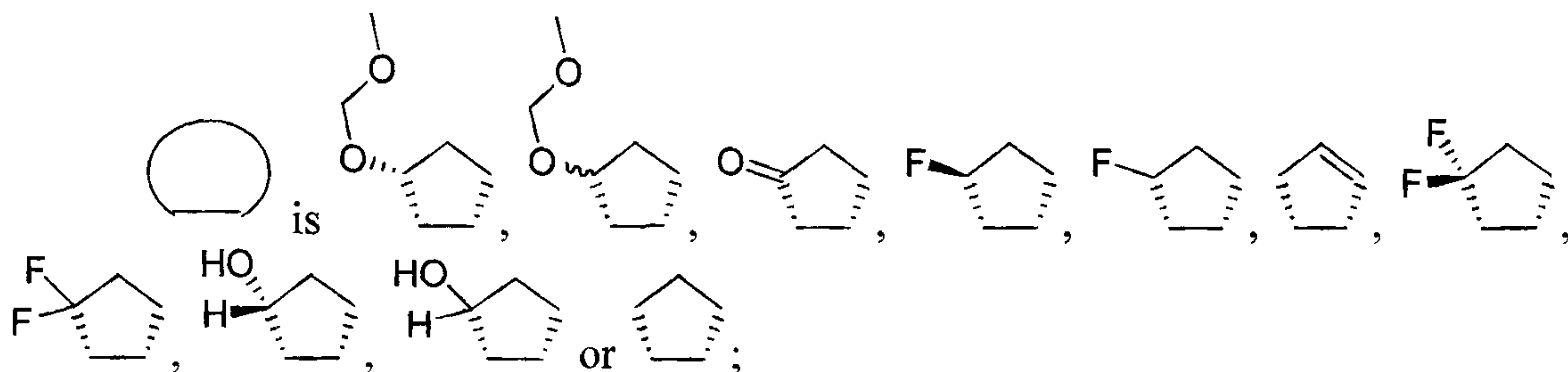


28. A compound according to claim 21, with the structure

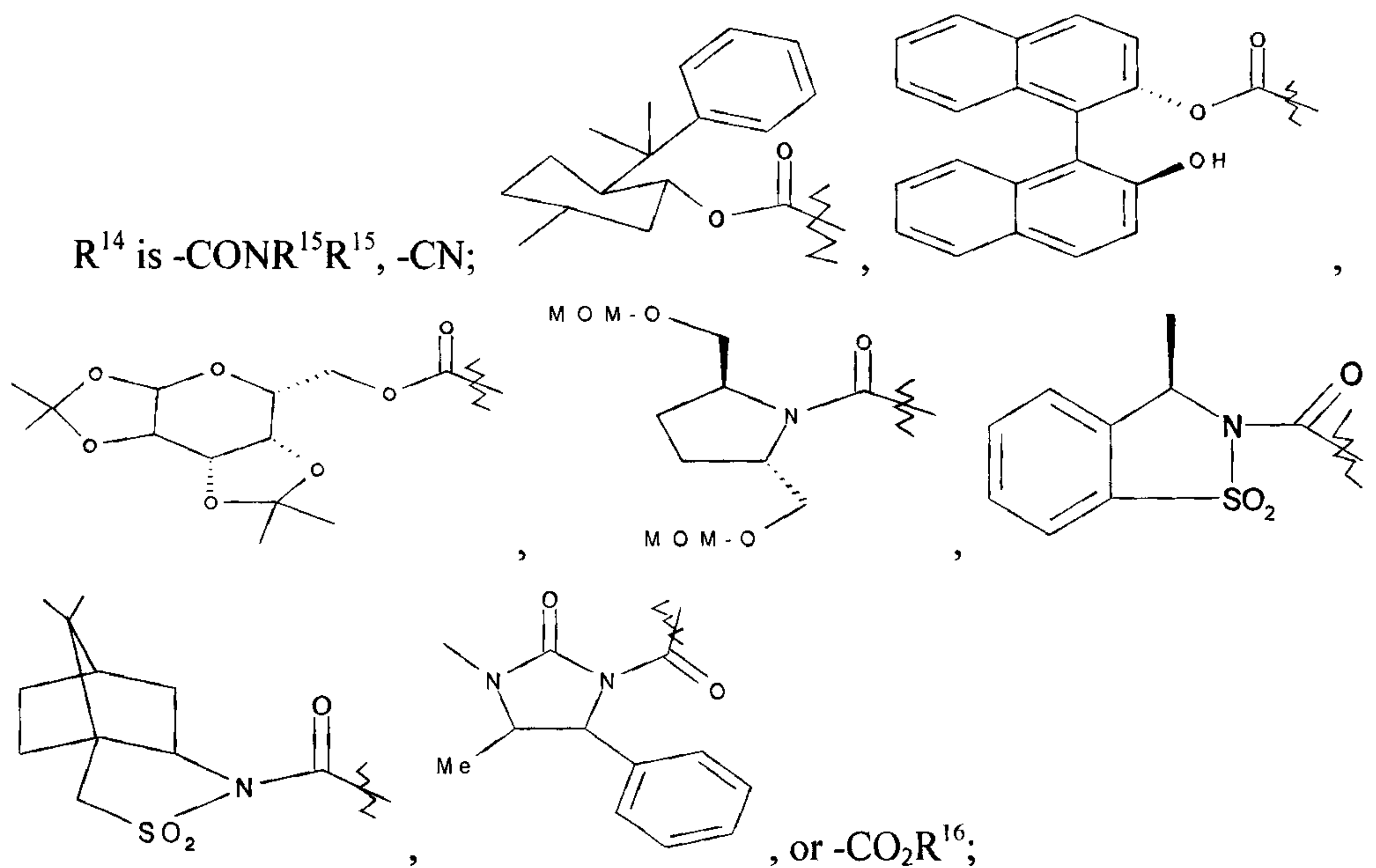
29. A compound of formula 26



wherein:



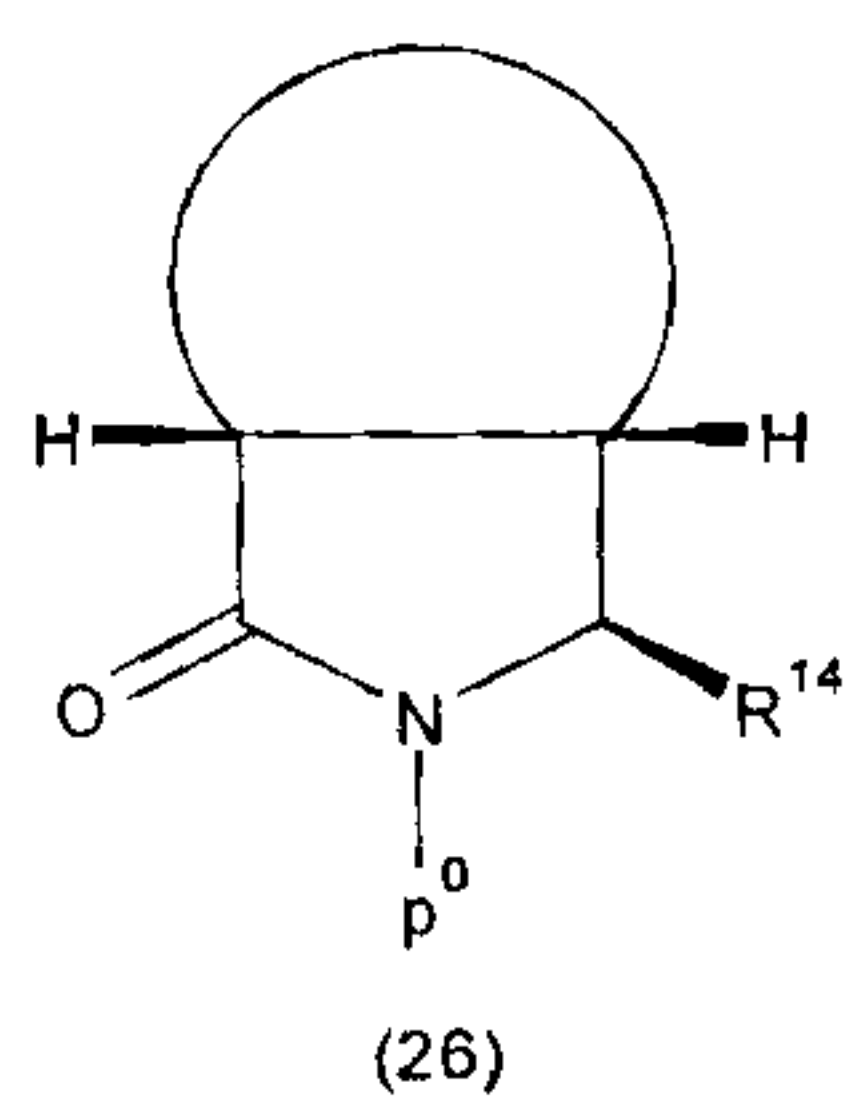
p^O is amide protecting group;



R¹⁵ is optionally substituted aliphatic group; and

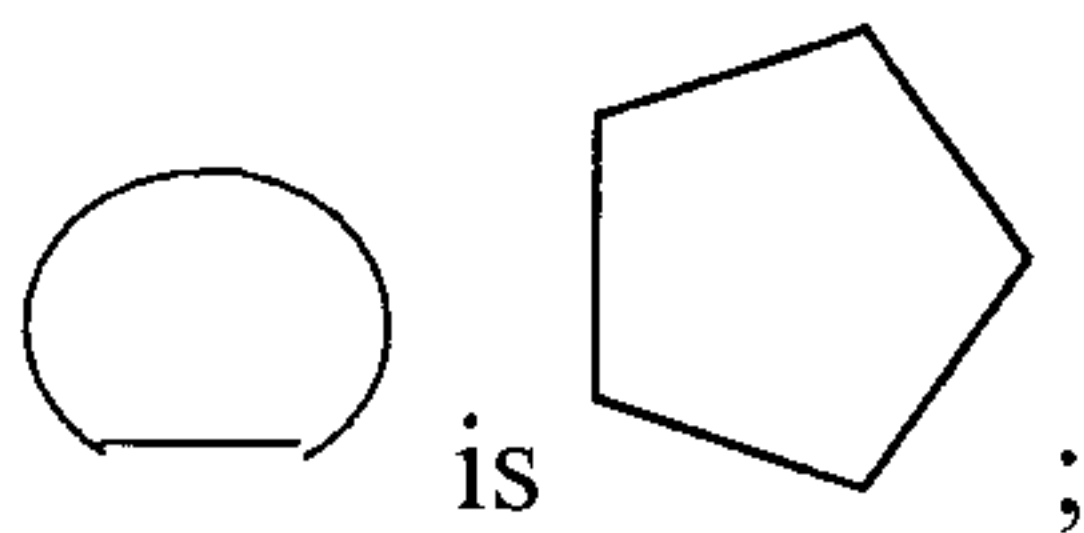
R¹⁶ is t-butyl.

30. A compound of formula 26

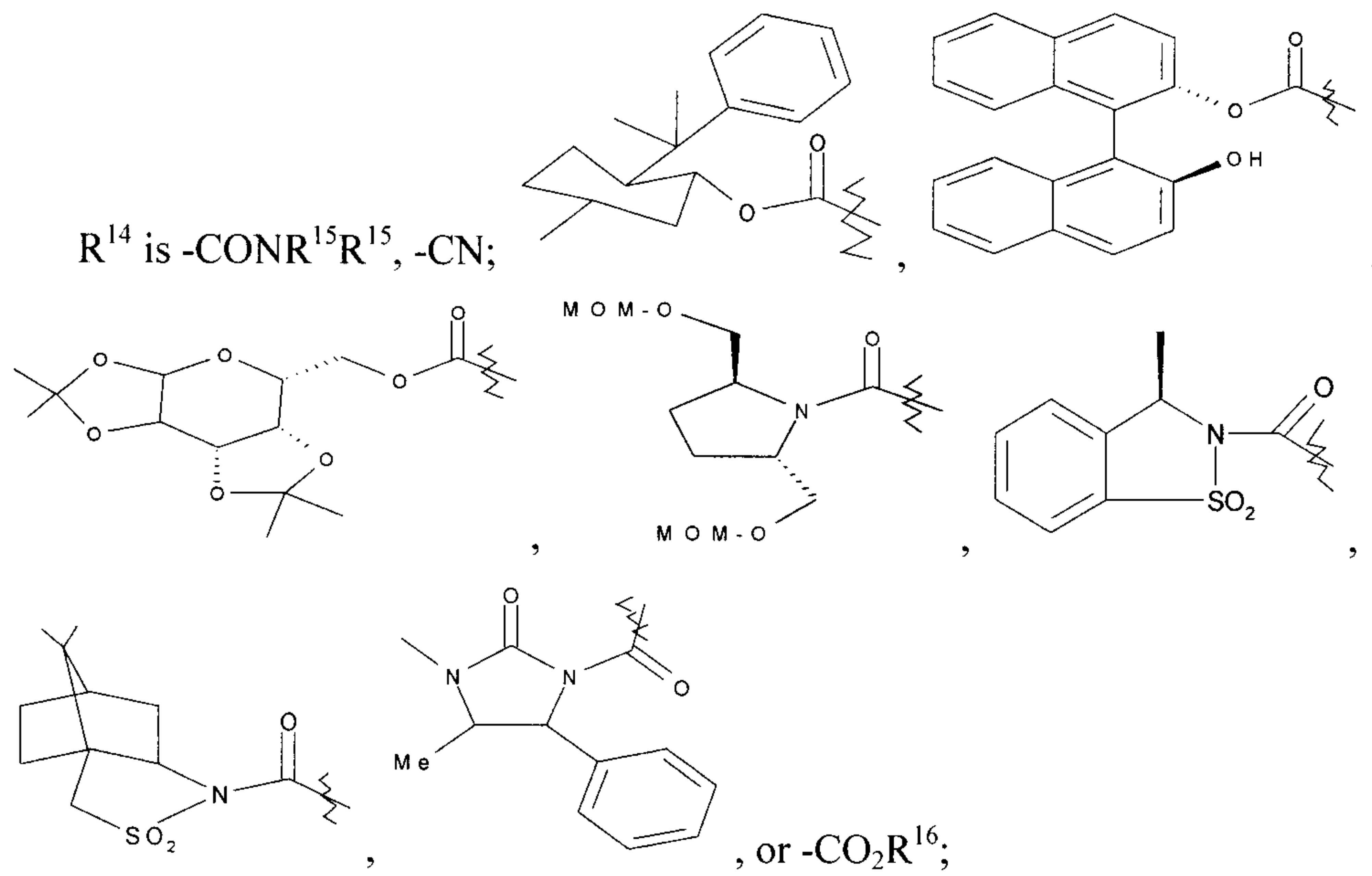


wherein:

- 320 -



p^O is amide protecting group;



R^{15} is optionally substituted aliphatic group; and

R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group.

10 31. A compound according to claim 29 or 30 wherein:

optionally substituted aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;

optionally substituted aryl means an aromatic monocyclic or mylticyclic ring systems of 6 to 14 carbon atoms optionally substituted with one or more ring group substituents;

15 wherein;

ring group substituents mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), $-\text{C}(\text{O})-\text{NHOH}$, $-\text{C}(\text{O})-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})-\text{CH}_2\text{SH}$, $-\text{C}(\text{O})-\text{NH}-$ 20 CN , sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl, hydroxyheteroaryl, alkoxy carbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl,

- 321 -

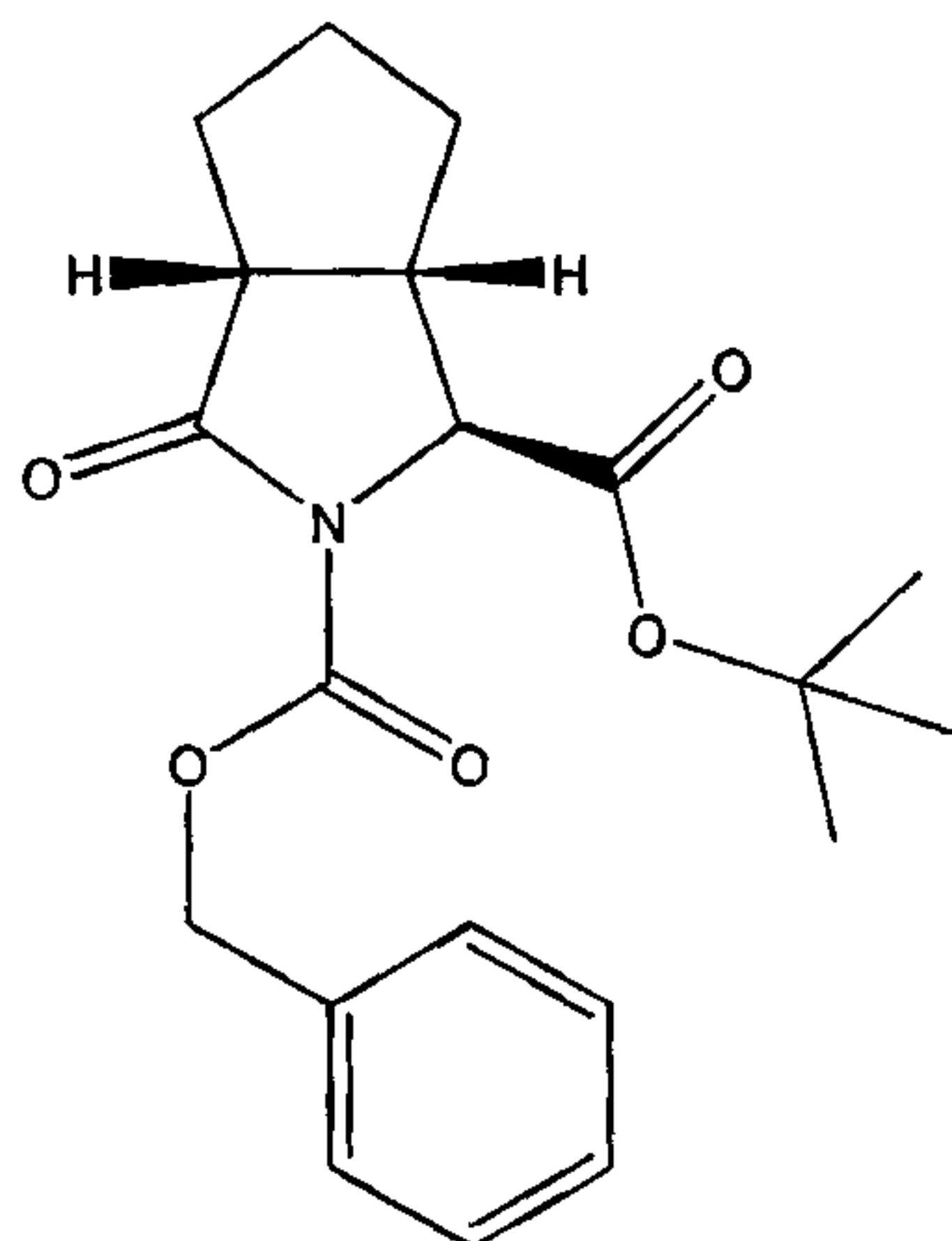
heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y^1Y^2N- , $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$ or $Y^1Y^2NSO_2-$, wherein Y^1 , Y^2 and Y^3 are independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is Y^1Y^2N- , then one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$ or $Y^1Y^2NSO_2-$, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl or when the ring system is saturated or partially saturated, the ring group substituents further include, methylene ($H_2C=$), oxo ($O=$) or thioxo ($S=$); and aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), $-C(O)-NHOH$, $-C(O)-CH_2OH$, $-C(O)-CH_2SH$, $-C(O)-NH-CN$, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene ($H_2C=$), oxo ($O=$), thioxo ($S=$), Y^1Y^2N- , $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$, $Y^1Y^2NSO_2-$, or $Y^3SO_2NY^1-$ wherein Y^1 and Y^2 are independently hydrogen, alkyl, aryl or heteroaryl, and Y^3 is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y^1Y^2N- , then one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is $Y^1Y^2NC(O)-$, $Y^1Y^2NC(O)O-$, $Y^1Y^2NC(O)NY^3-$ or $Y^1Y^2NSO_2-$, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl; and cyclyl means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

32. A compound according to any one of claims 29 to 31 where R^{14} is $-CO_2R^{16}$.

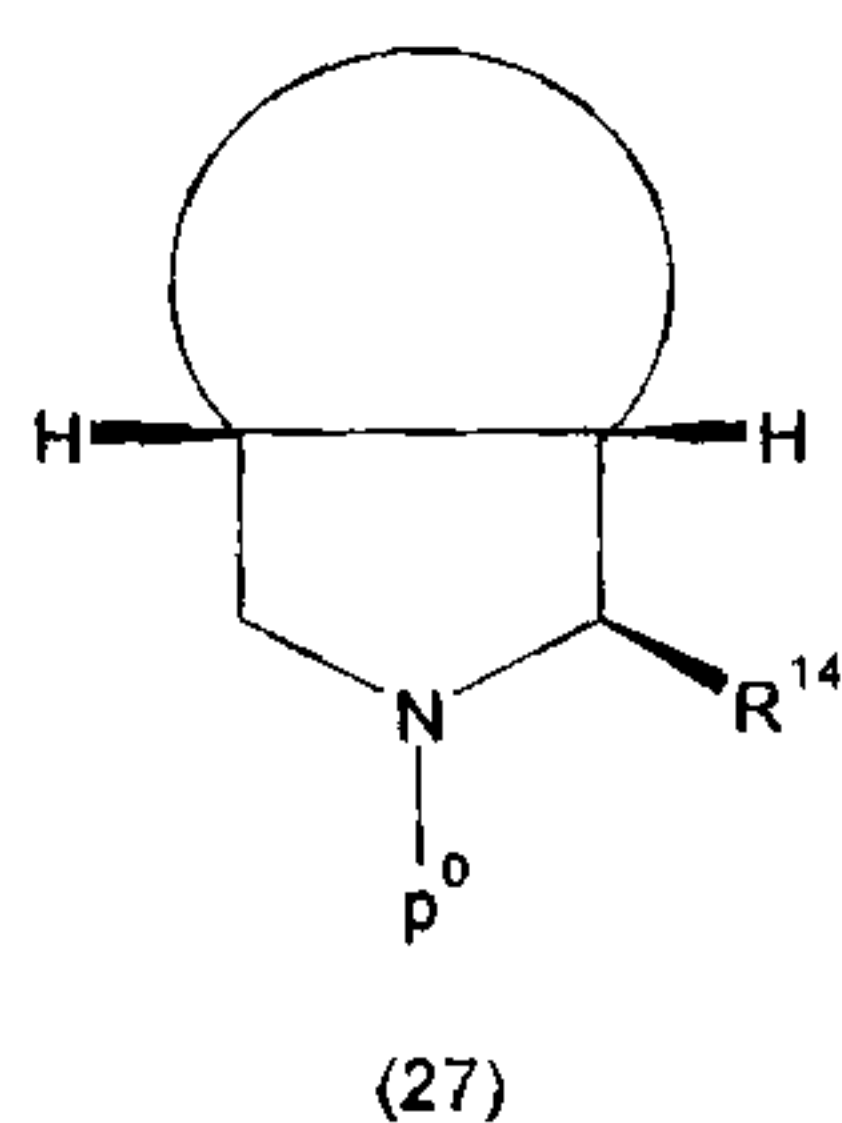
33. A compound according to any one of claims 29 to 32 where R^{16} is optionally substituted aliphatic.

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34. A compound according to any one of claims 29 to 33 where R^{16} is alkyl.
35. A compound according to any one of claims 29 to 34 where R^{16} is lower alkyl.
36. A compound according to any one of claims 29 to 35 where R^{16} is t-Bu.
37. A compound according to any one of claims 29 to 36 where p^0 is BOC, CBz, or $-\text{CO}_2\text{alkyl}$.
- 5 38. A compound according to claim 37 where p^0 is BOC.
39. A compound according to any one of claims 29 or 30 where the compound of formula 26 is



40. A compound of formula 27



10 wherein:



is an unsubstituted cycloheptyl ring;

p^0 is amide protecting group;

R^{14} is $-\text{CO}_2R^{16}$; and

R^{16} is aliphatic group.

- 15 41. A compound according to claim 40 wherein:

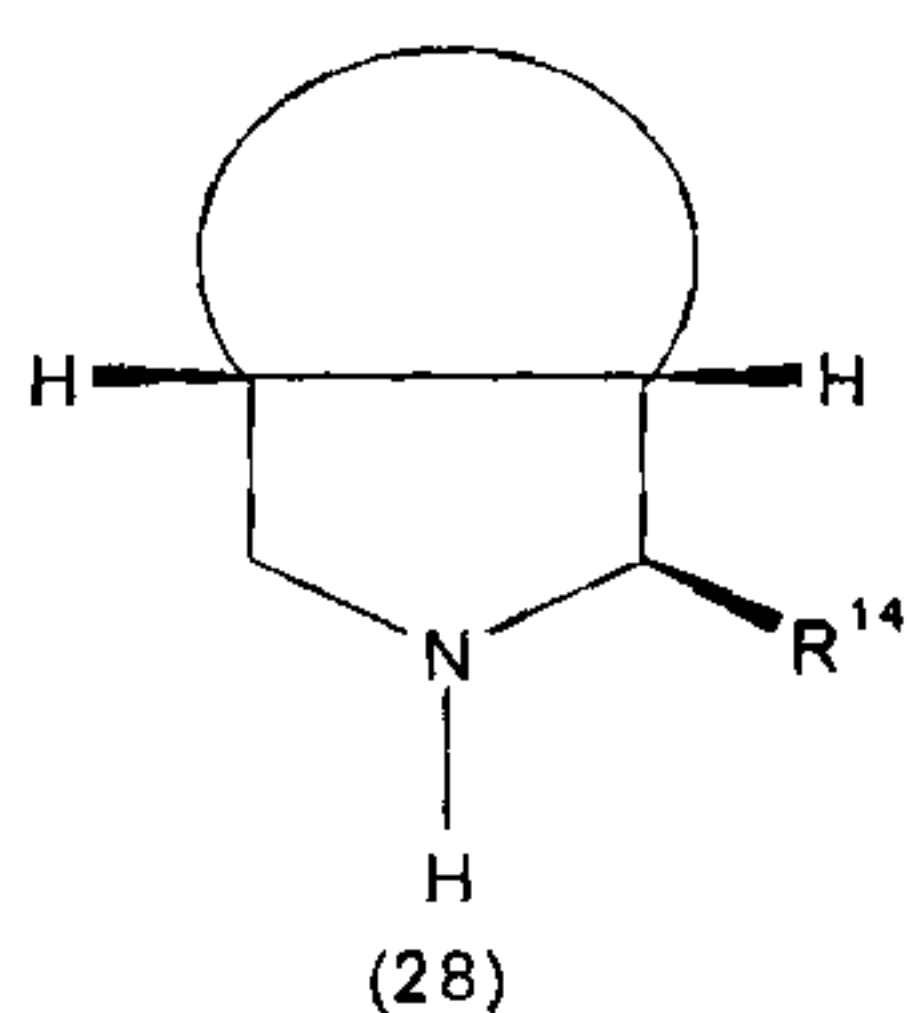
aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;

wherein;

20 aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cycloalkoxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), $-\text{C}(\text{O})-\text{NHOH}$, $-\text{C}(\text{O})-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})-$

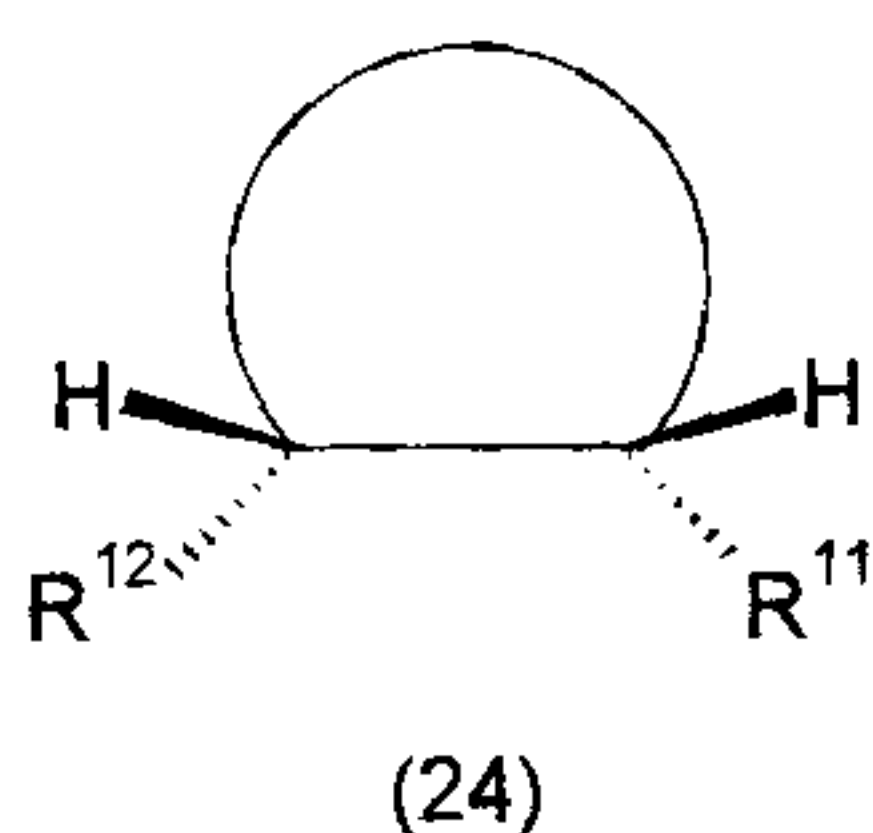
- 323 -

- CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl, hydroxyheteroaryl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H₂C=), oxo (O=), thioxo (S=), Y¹Y²N-, Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³-, Y¹Y²NSO₂-, or Y³SO₂NY¹-, Y¹ and Y² are independently hydrogen, alkyl, aryl or heteroaryl, and Y³ is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and the other of Y¹ and Y² is as defined previously, or for where the substituent is Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl.
42. A compound according to claim 40 or 41 where R¹⁶ is alkyl.
 43. A compound according to any one of claims 40 to 42 where R¹⁶ is lower alkyl.
 44. A compound according to any one of claims 40 to 43 where R¹⁶ is t-Bu.
 45. A compound according to any one of claims 40 to 44 where p⁰ is BOC, CBz, or -CO₂alkyl.
 46. A compound according to claim 45 where p⁰ is BOC.
 47. A process for preparing a chiral bicycloprolinate compound of formula 28



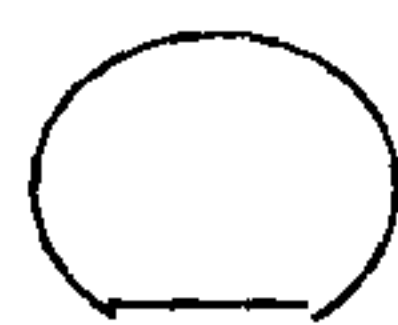
comprising the steps of:

- (a) cleaving and cyclizing a compound of formula 24



wherein:

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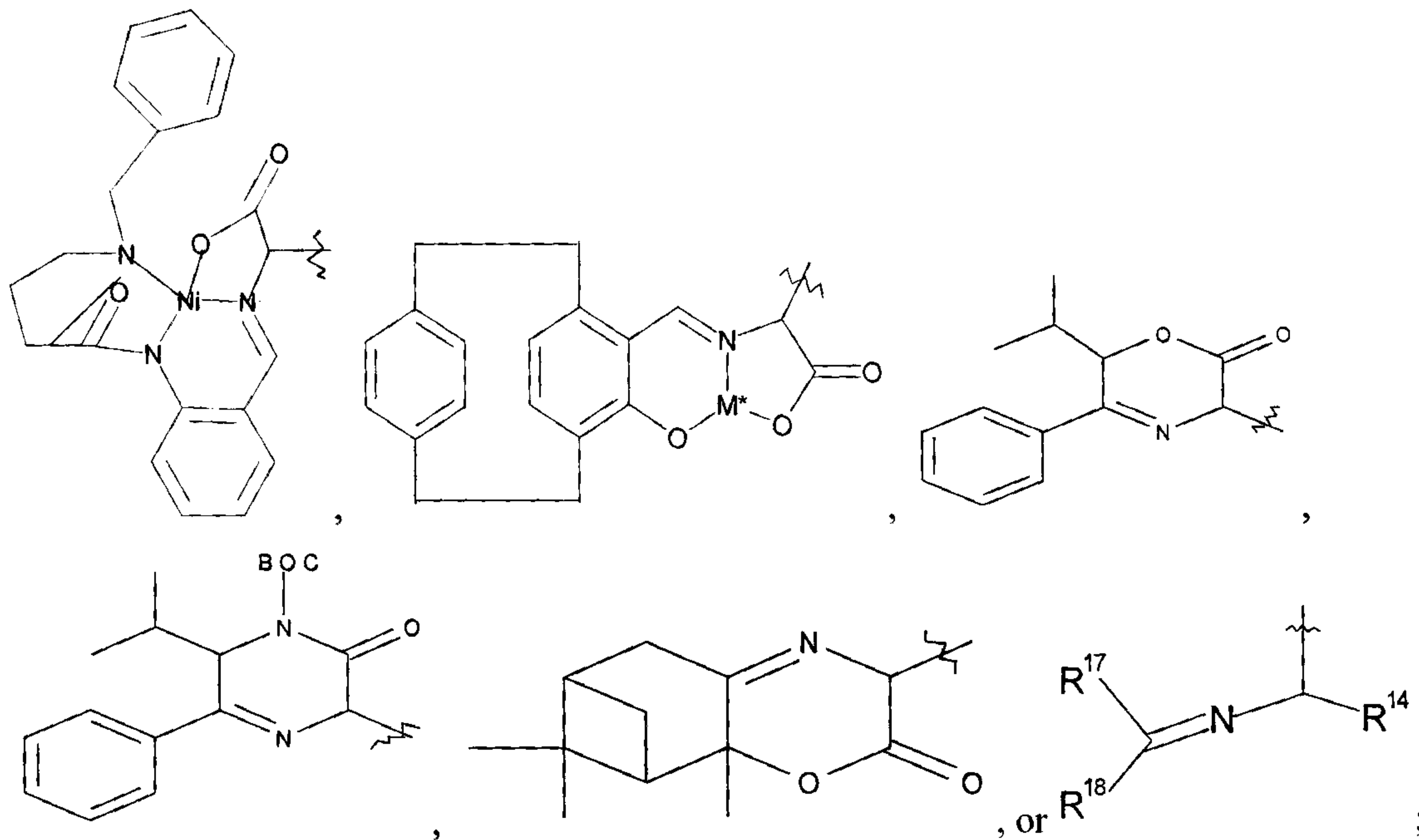
is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

R^{11} is $-\text{CO}_2R^{13}$;

R^{12} is an iminic glycinimide derivative adduct;

R^{13} is acid protecting group or optionally substituted aliphatic group;

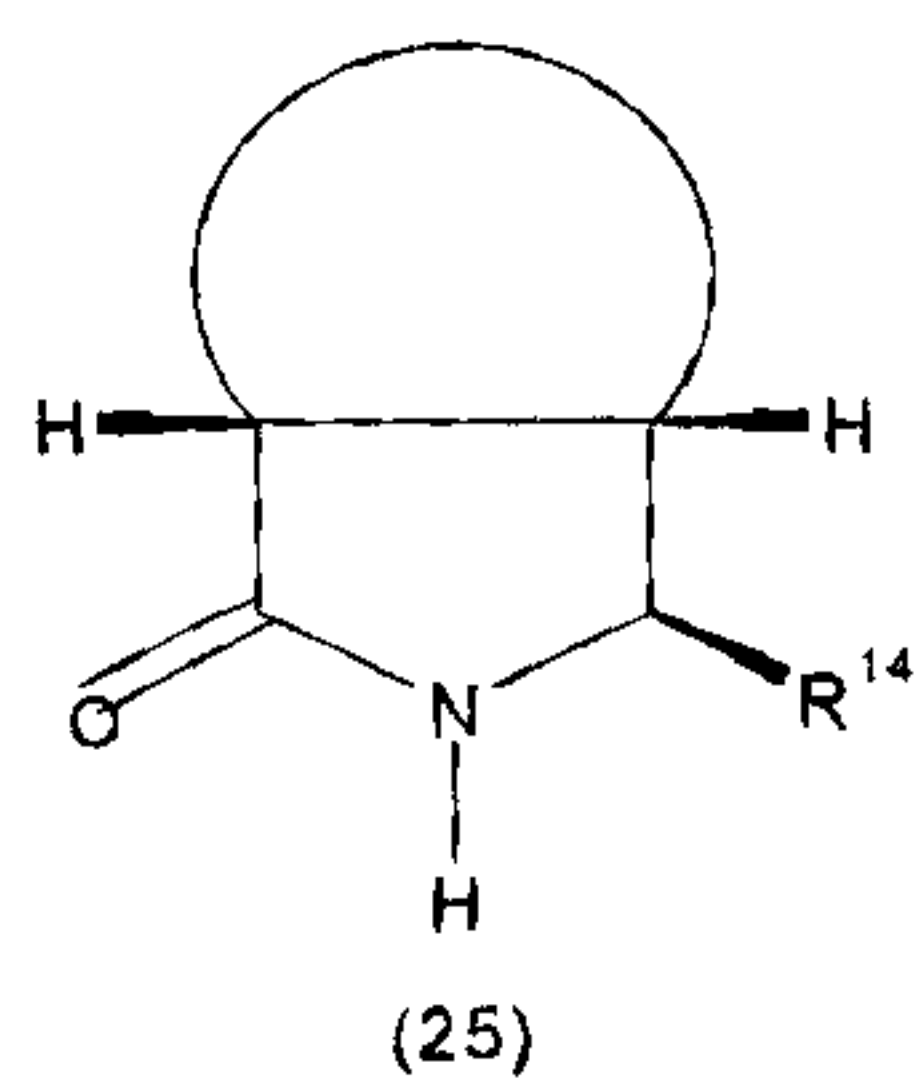
5 the iminic glycinimide derivative adduct is



wherein:

M^* is a transition metal;

10 under cleaving and cyclizing conditions to form a compound of formula 25

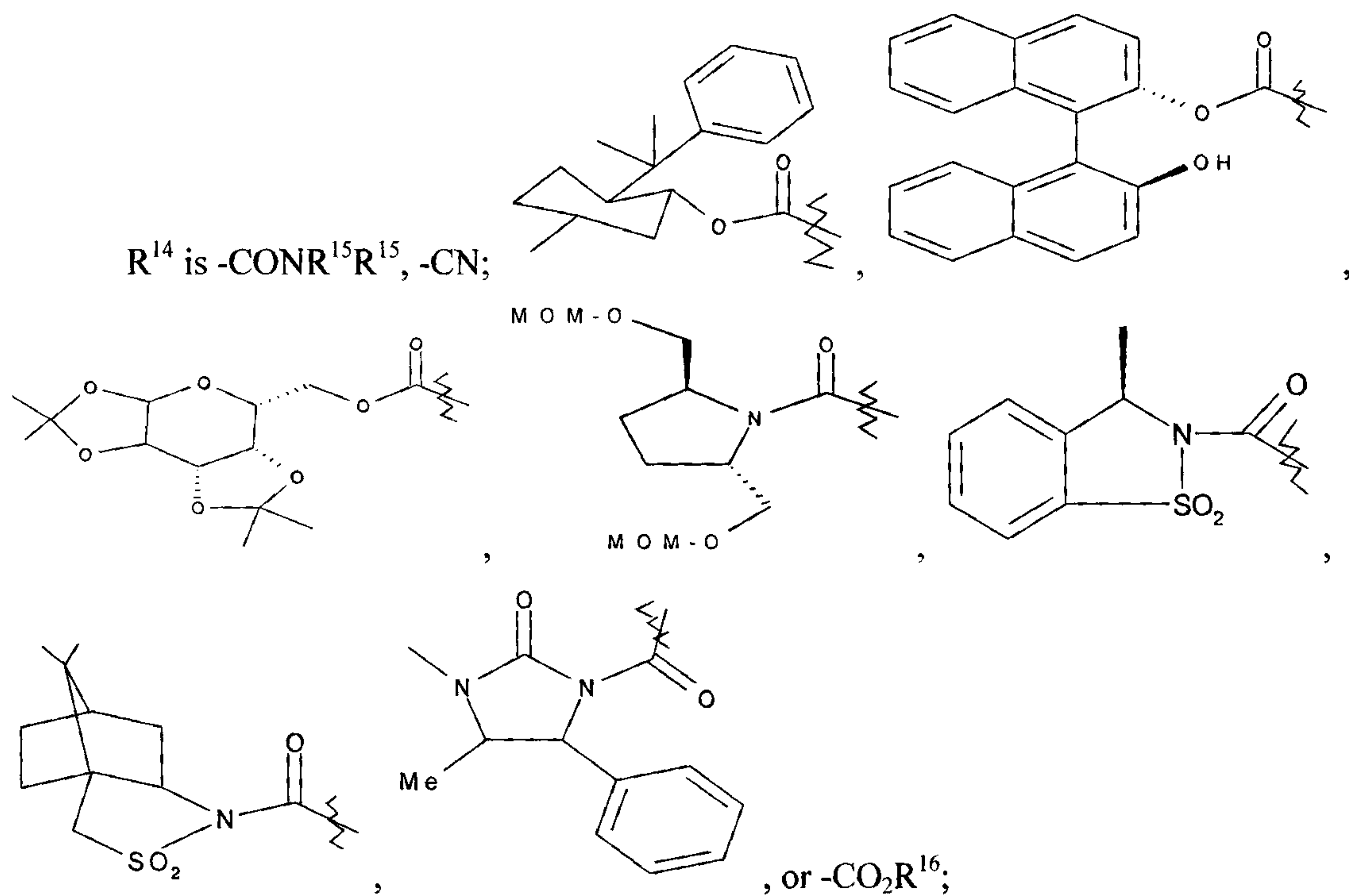


wherein:



is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

- 325 -



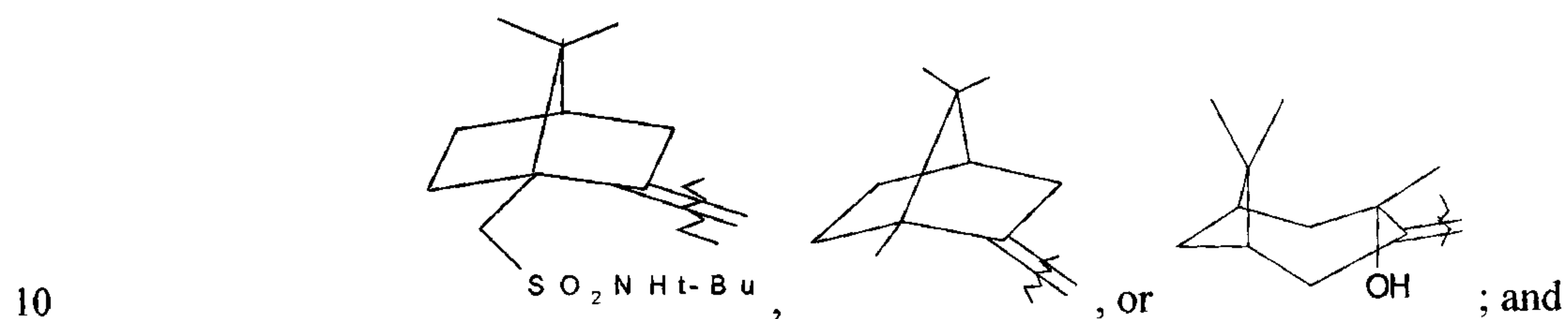
R^{15} is optionally substituted aliphatic group;

5 R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group; and

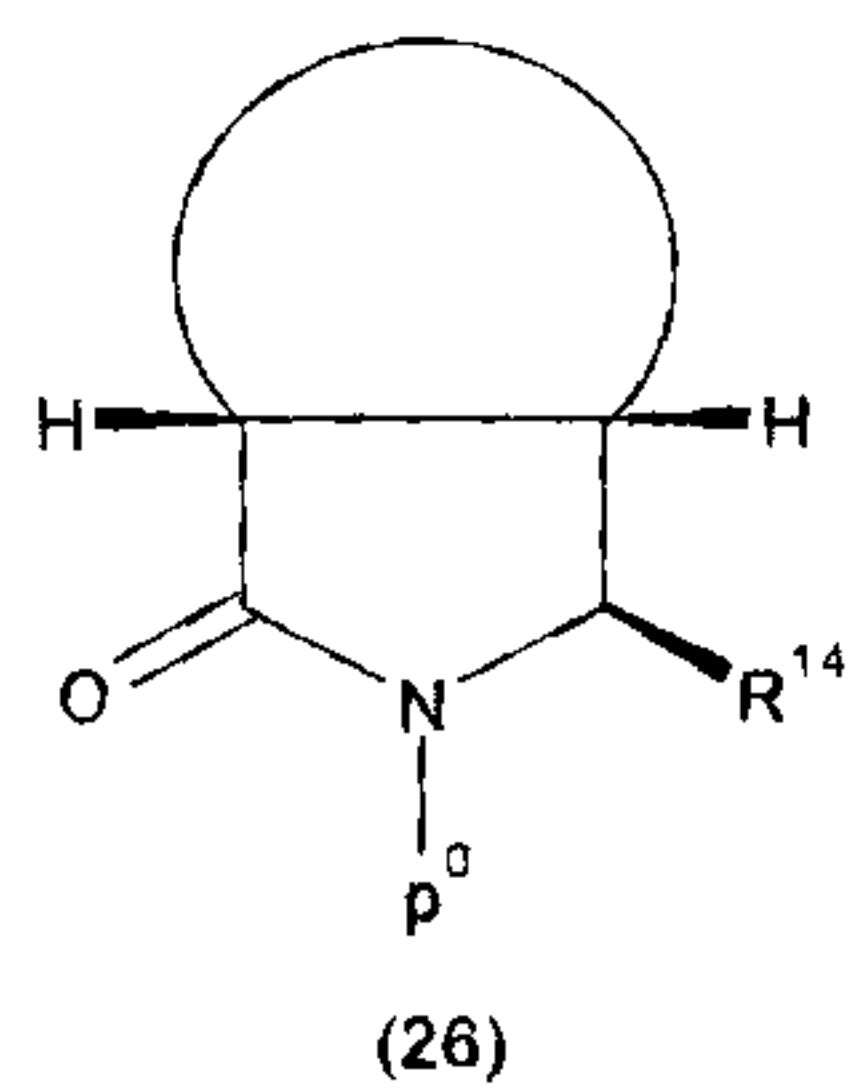
R^{17} is aryl;

R^{18} is aryl; or

R^{17} and R^{18} , taken together with the carbon to which R^{17} and R^{18} are attached, form

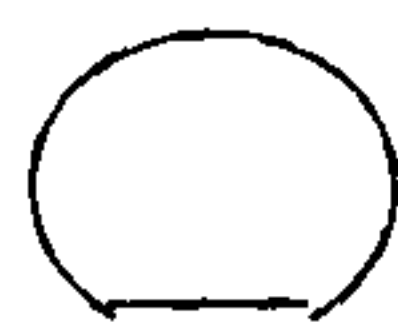


(b) protecting the nitrogen of the lactam moiety in the compound of formula 25 with an amide protecting group to form a compound of formula 26



15 wherein:

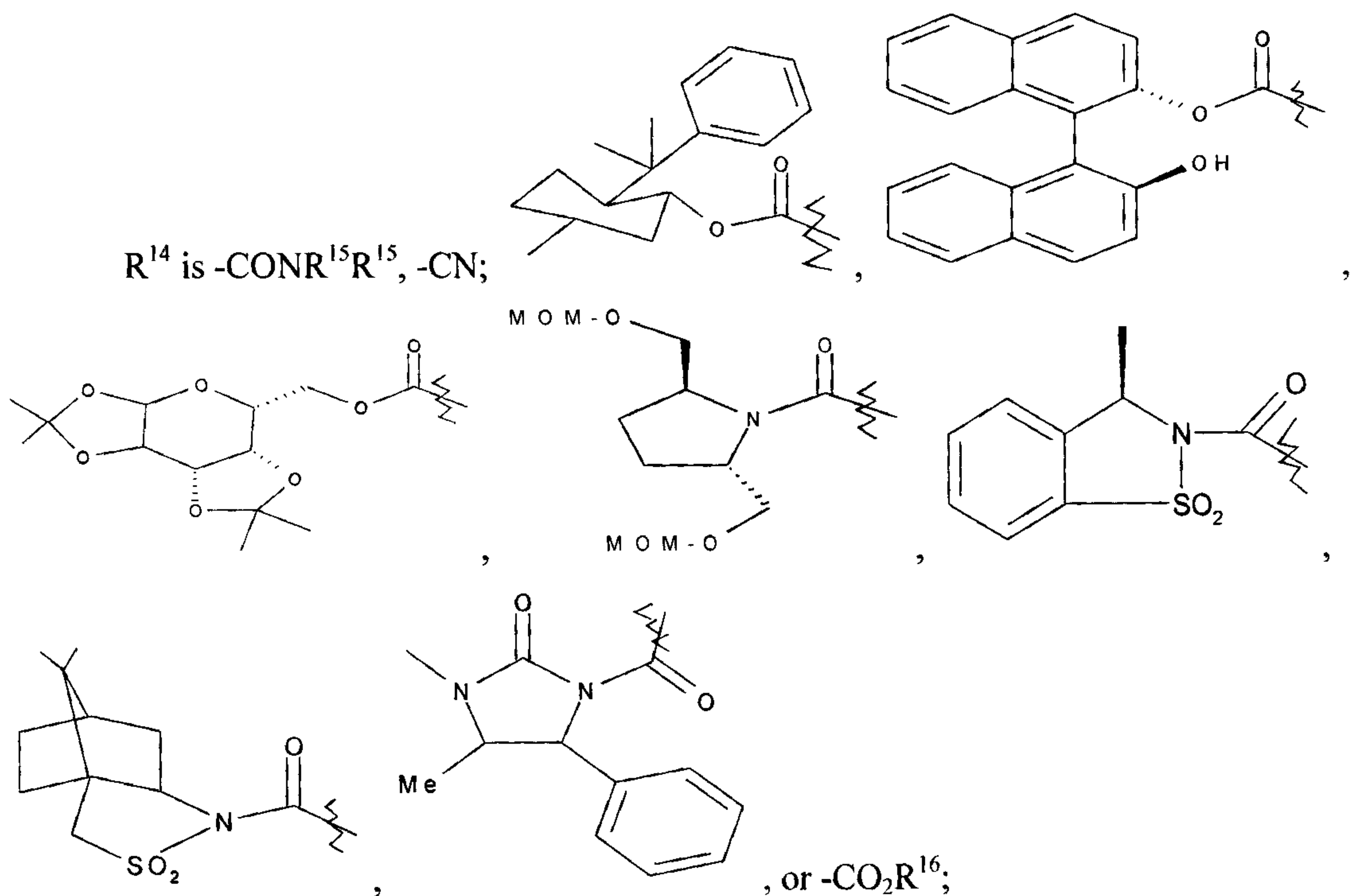
- 326 -



is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

p^O is amide protecting group;

R^{14} is $-\text{CONR}^{15}R^{15}$, $-\text{CN}$;



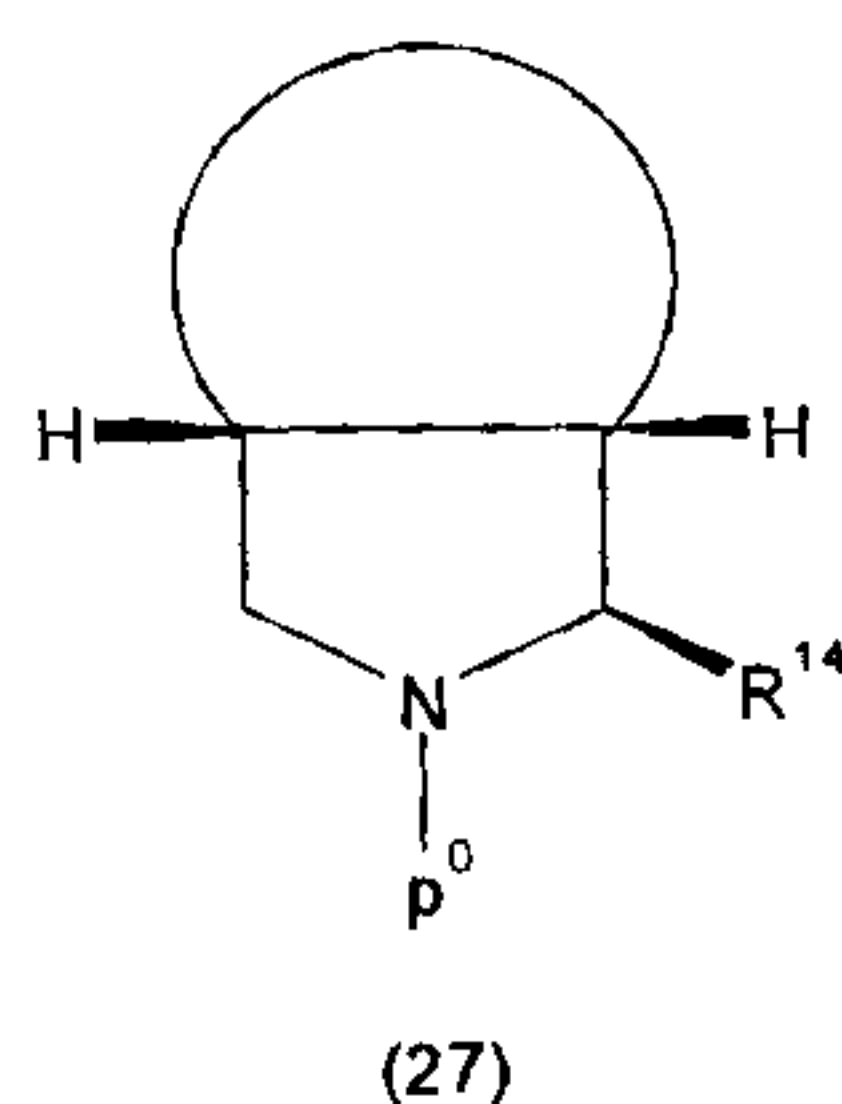
5

R^{15} is optionally substituted aliphatic group;

R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group; and

(c) reducing the compound of formula 26 under reducing conditions to form a compound

10 of formula 27



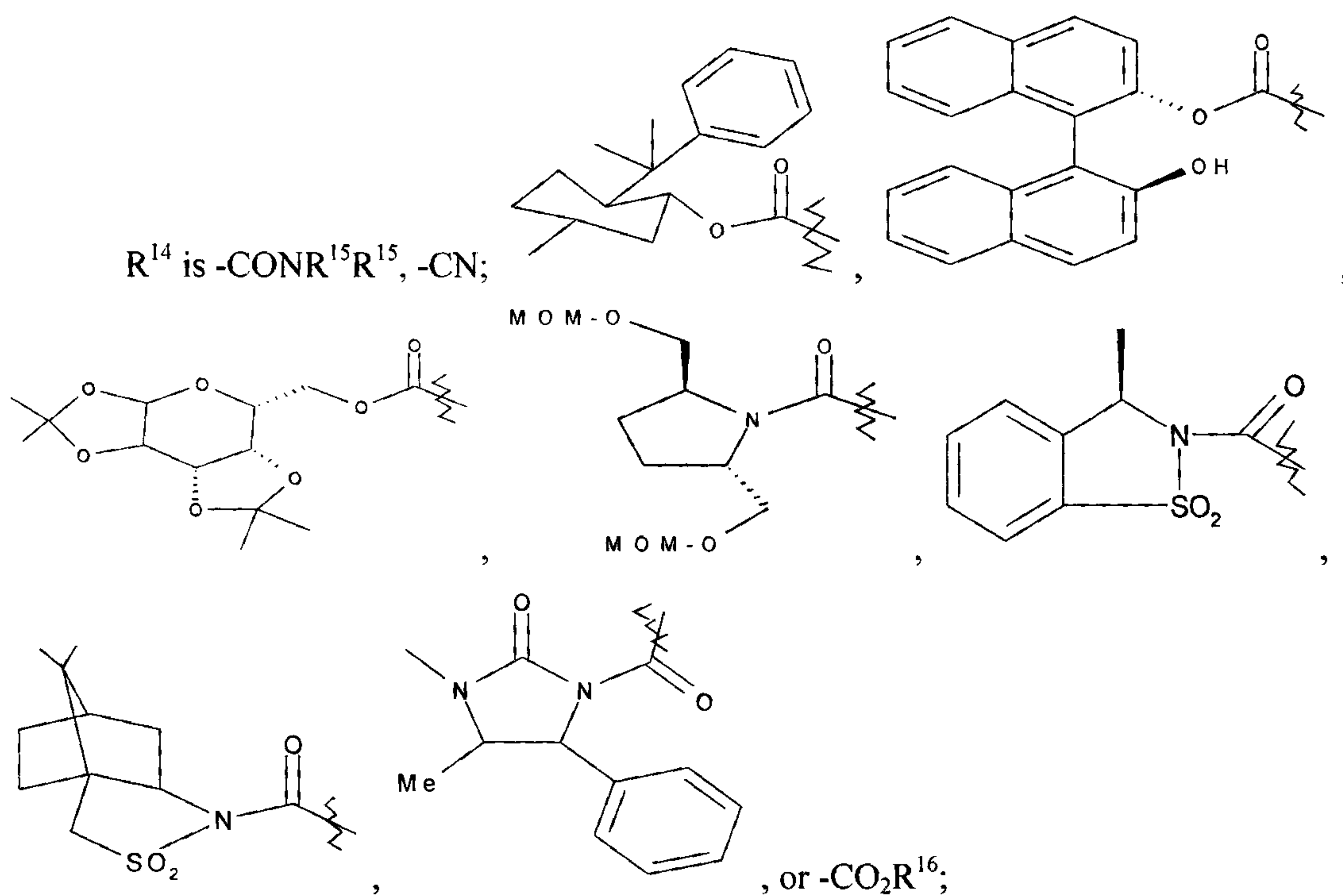
wherein:



is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

p^O is amide protecting group;

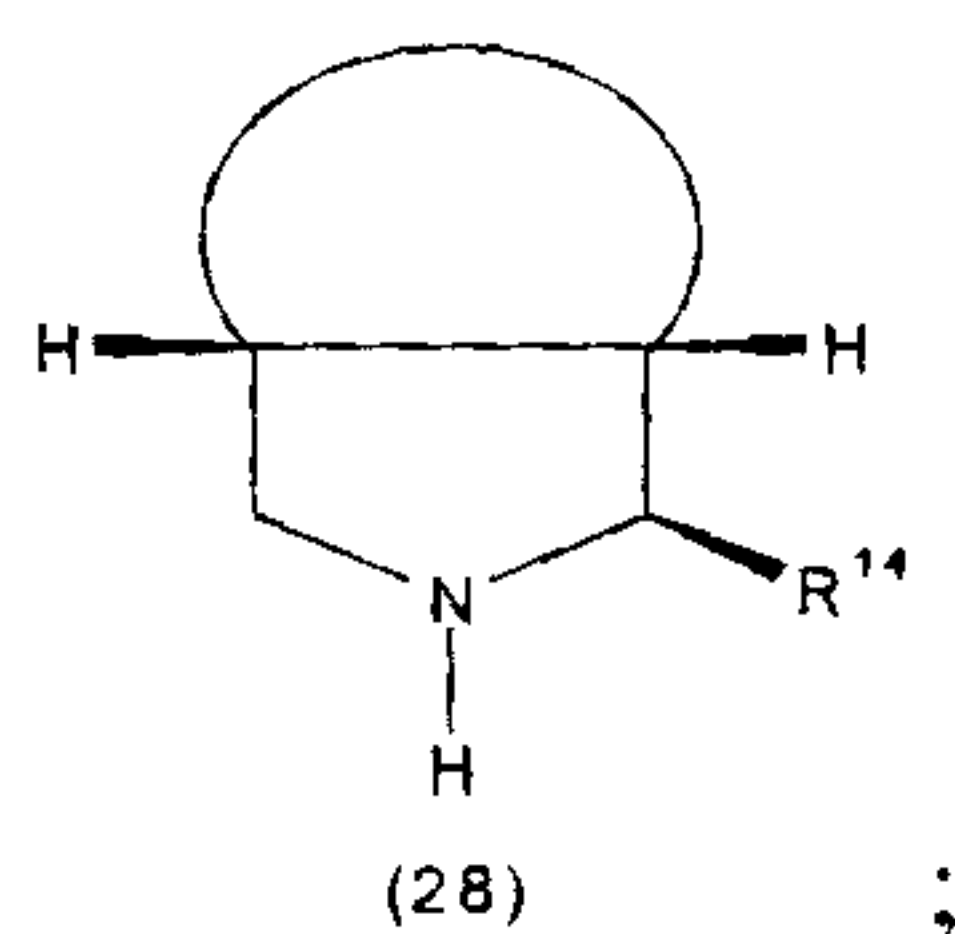
- 327 -



R^{15} is optionally substituted aliphatic group;

5 R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group; and

(d) deprotecting the compound of formula 27 under deprotecting conditions to form a compound of formula 28

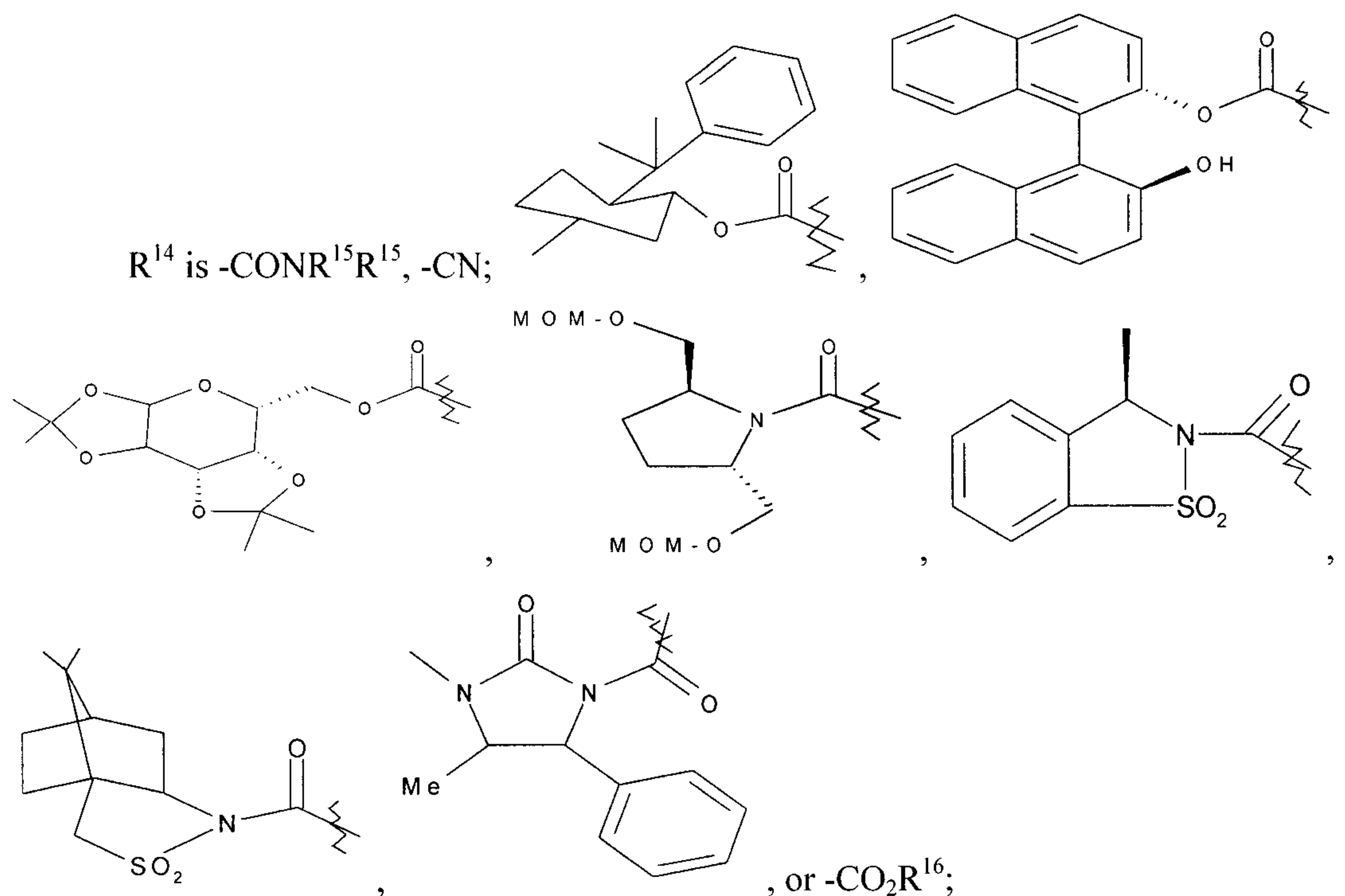


10 wherein:



is optionally substituted cycloalkyl or optionally substituted fused arylcycloalkyl;

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R^{15} is optionally substituted aliphatic group; and

5 R^{16} is acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group.

48. A process according to claim 47 wherein:

optionally substituted aliphatic groups are alkyl, alkenyl, or alkynyl optionally substituted with one or more aliphatic group substituents;

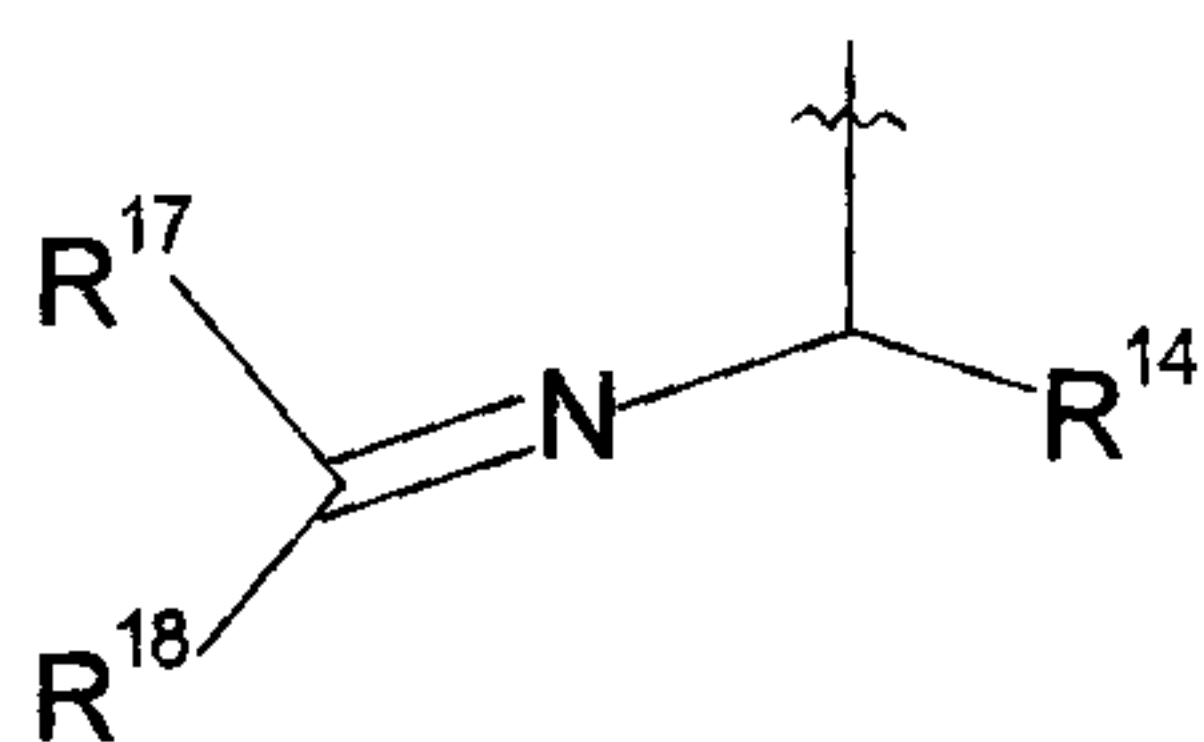
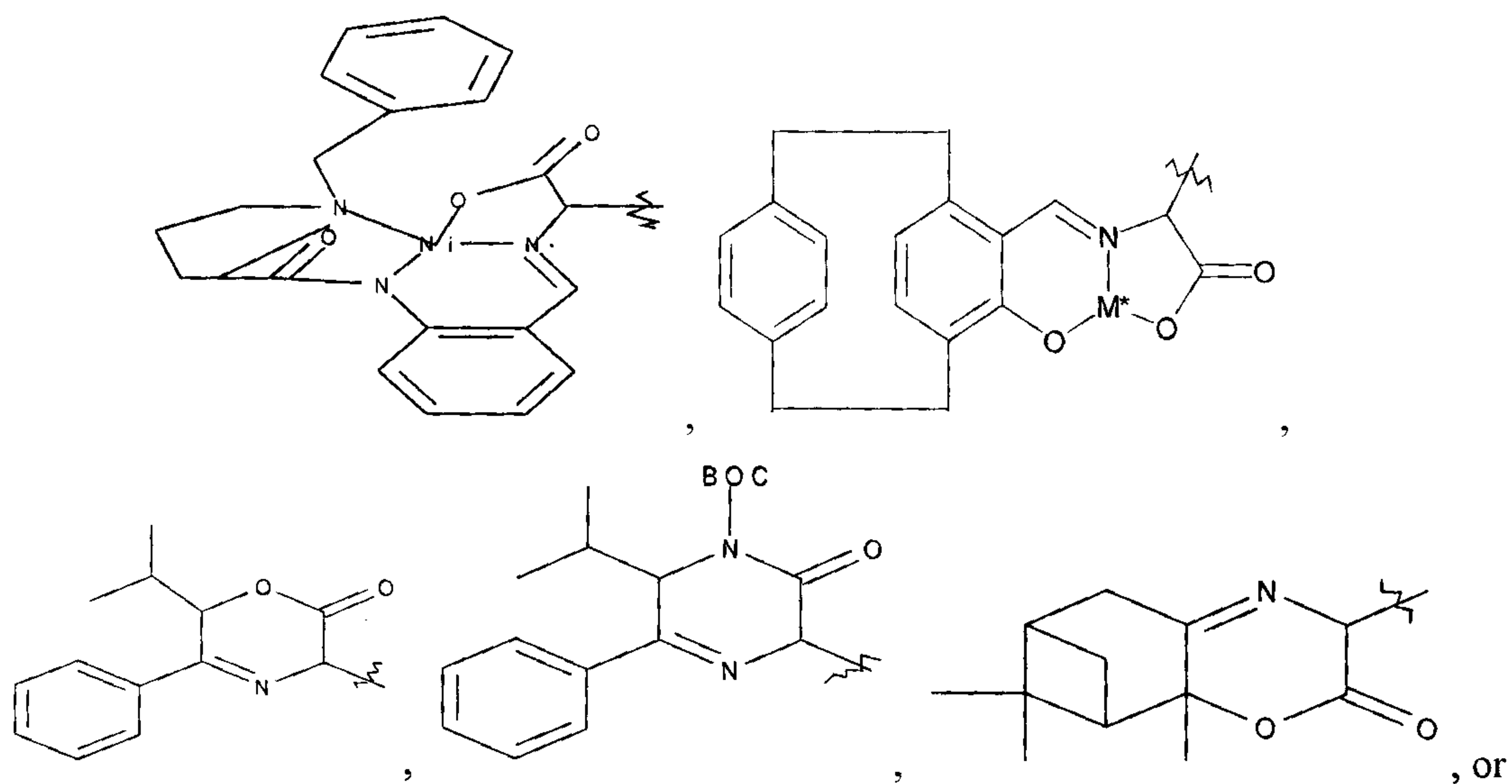
10 optionally substituted aryl means an aromatic monocyclic or mylticyclic ring systems of 6 to 14 carbon atoms optionally substituted with one or more ring group substituents;

optionally substituted cycloalkyl means a non-aromatic mono- or multicyclic ring system of 3 to 10 carbon atoms optionally substituted with one or more ring group substituents;

optionally substituted fused arylcycloalkyl means a fused arylcycloalkyl optionally substituted with

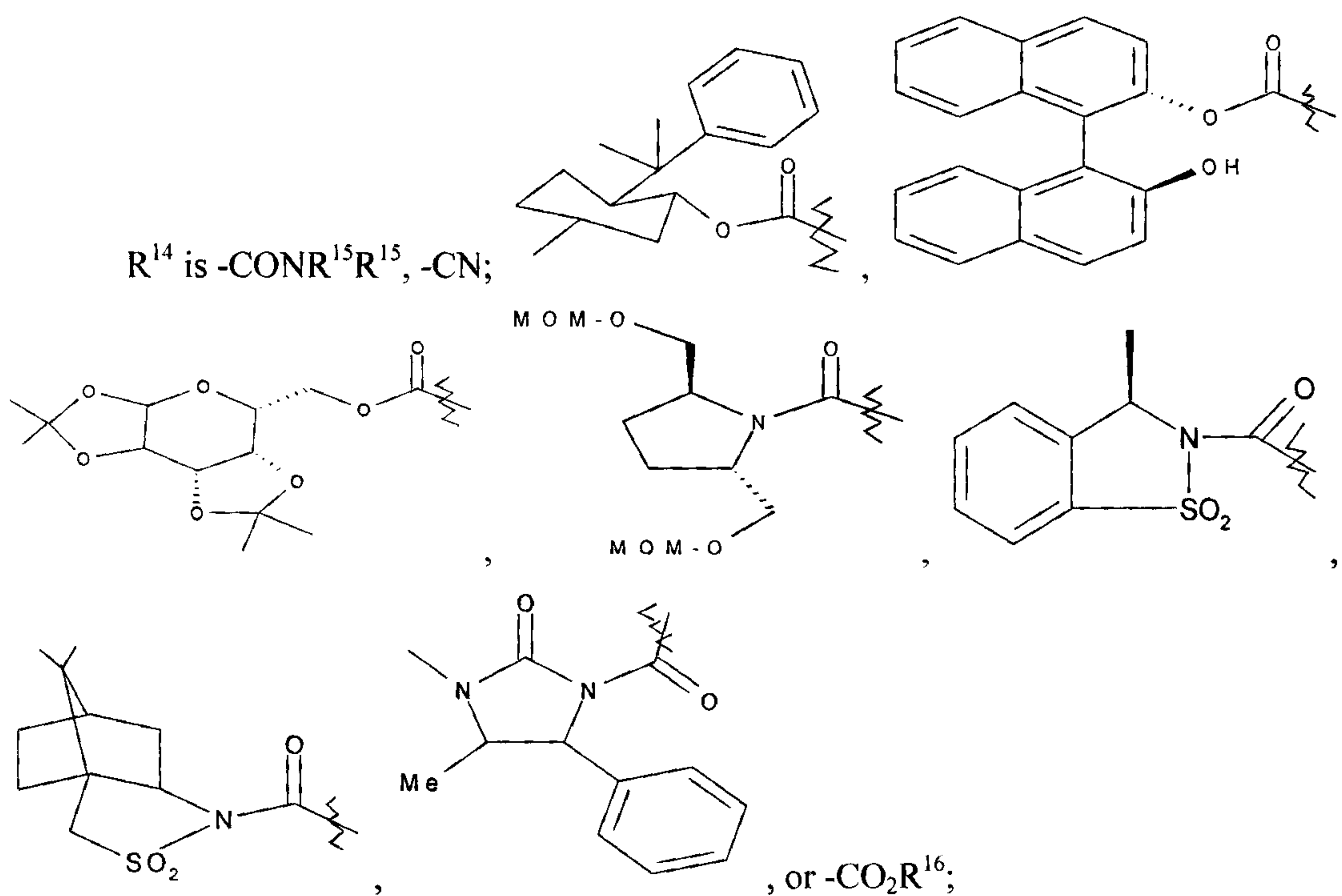
15 one or more ring group substituents;

an iminic glycinimide derivative adduct is



5

R^{14} is $-\text{CONR}^{15}R^{15}$, $-\text{CN}$;

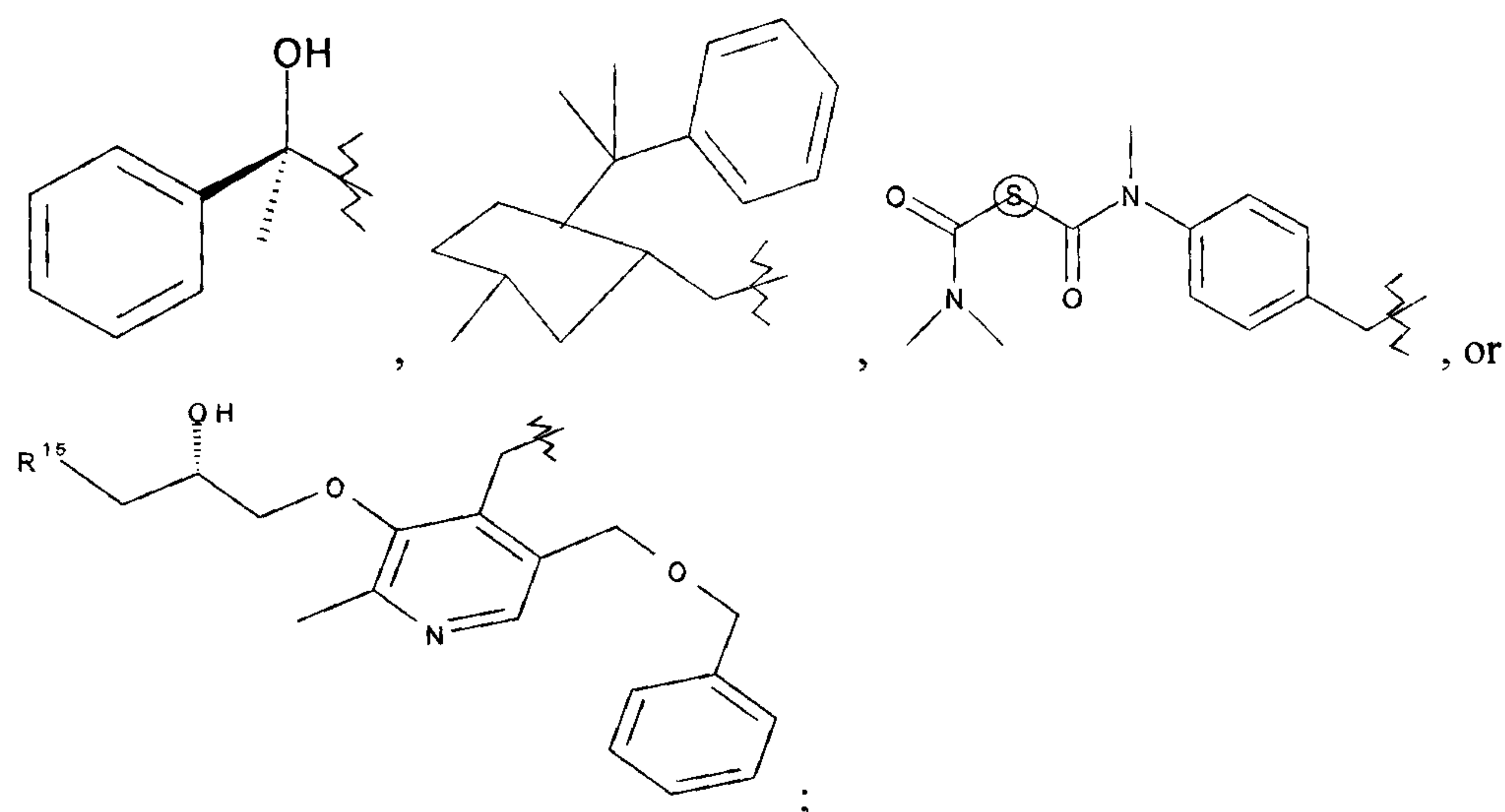


10

R¹⁶ is an acid protecting group, optionally substituted aryl, or optionally substituted aliphatic group;

R¹⁷ is optionally substituted aryl, optionally substituted aliphatic group,

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R¹⁸ is hydrogen, alkyl, or alkylthio; or optionally substituted aryl;

wherein;

5 (S) is a solid phase

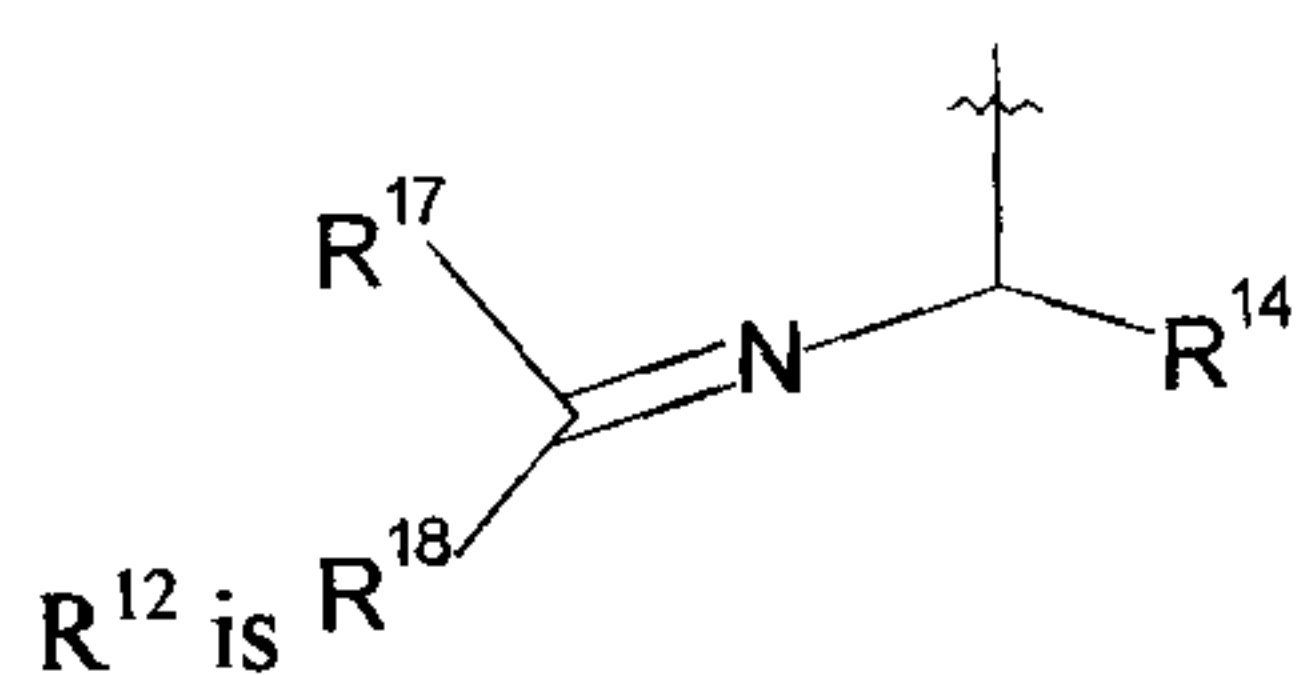
ring group substituents mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y¹Y²N-, Y¹Y²NC(O)-, Y¹Y²NC(O)O, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, wherein Y¹, Y² and Y³ are independently hydrogen, alkyl, aryl or heteroaryl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, and the other of Y¹ and Y² is as defined previously, or for where the substituent is Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl or when the ring system is saturated or partially saturated, the ring group substituents further include, methylene (H₂C=), oxo (O=) and thioxo (S=); and

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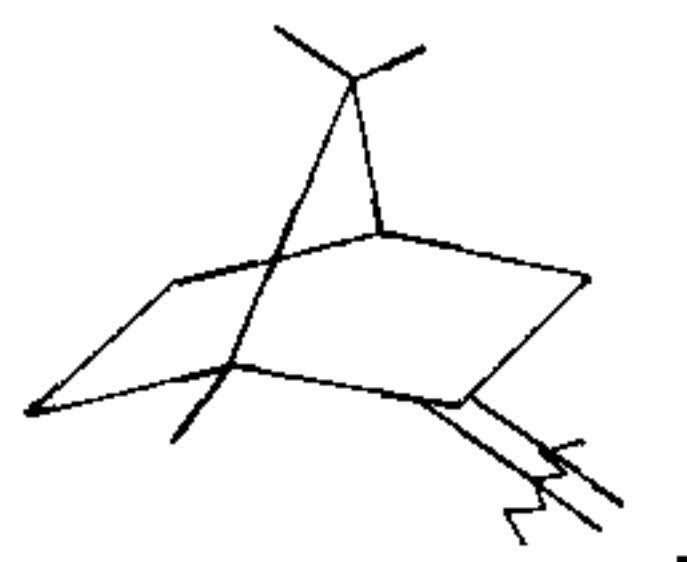
aliphatic group substituents means aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH, -C(O)-CH₂OH, -C(O)-CH₂SH, -C(O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulphonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H₂C=), oxo (O=), thioxo (S=), Y¹Y²N-, Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³-, Y¹Y²NSO₂-, or Y³SO₂NY¹- wherein Y¹ and Y² are independently hydrogen, alkyl, aryl or heteroaryl, and Y³ is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y¹Y²N-, then one of Y¹ and Y² may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxy carbonyl, cyclyloxy carbonyl, aryloxy carbonyl or heteroaryloxy carbonyl, and the other of Y¹ and Y² is as defined previously, or for where the substituent is Y¹Y²NC(O)-, Y¹Y²NC(O)O-, Y¹Y²NC(O)NY³- or Y¹Y²NSO₂-, Y¹ and Y² may also be taken together with the N atom through which Y¹ and Y² are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl; and

cyclyl means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

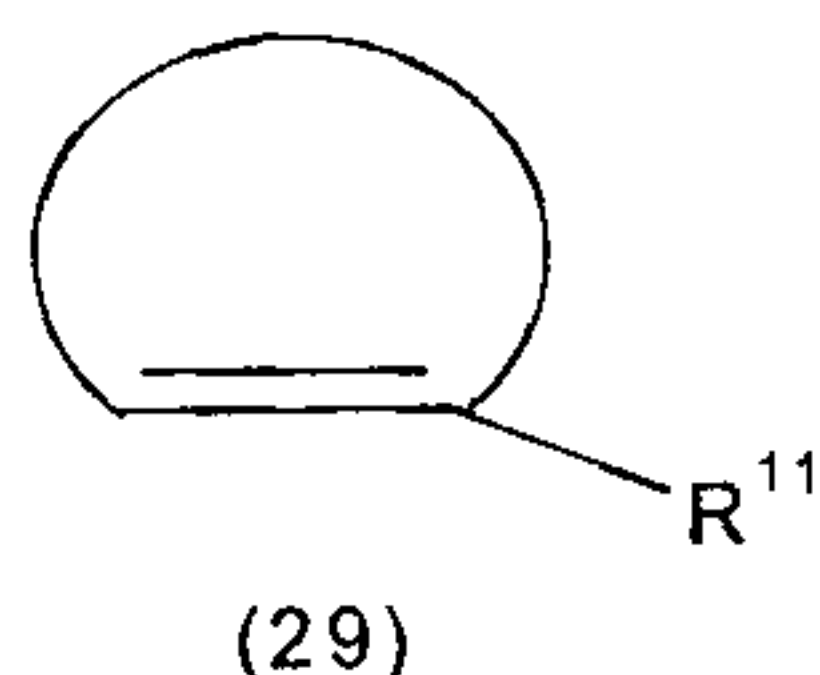
49. A process according to claim 47 or 48 wherein:



R¹⁷ and R¹⁸ taken together with the carbon to which R¹⁷ and R¹⁸ are attached are



50. A process according to claim 47 further comprising the step wherein the compound of formula 24 is prepared by effecting a Michael addition with an iminic glycinimide compound on a compound of formula 29



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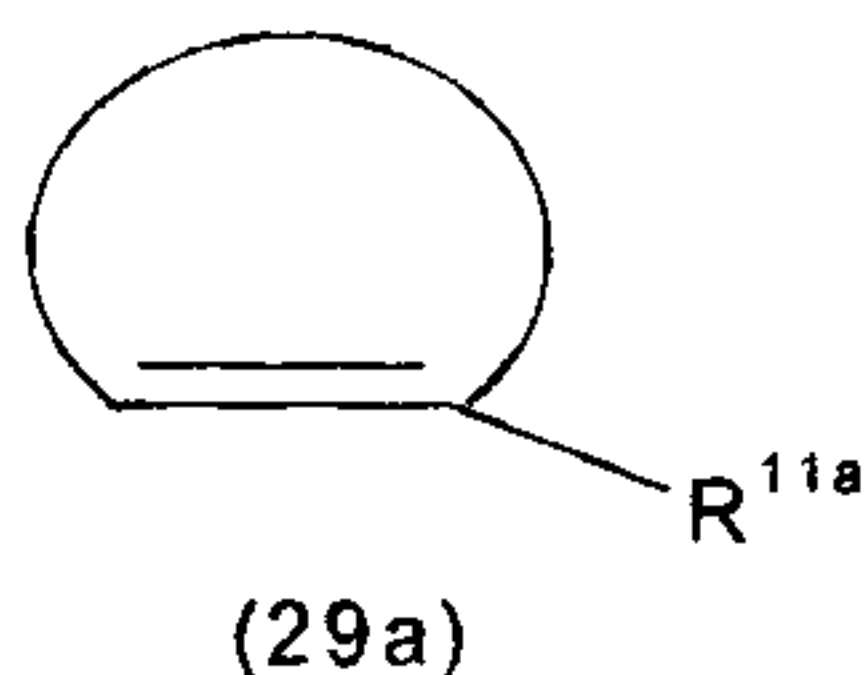
wherein:



is optionally substituted cycloalkenyl or optionally substituted fused arylcycloalkenyl;

wherein:

5 the compound of formula 29 may be prepared by esterifying a compound of formula 29a

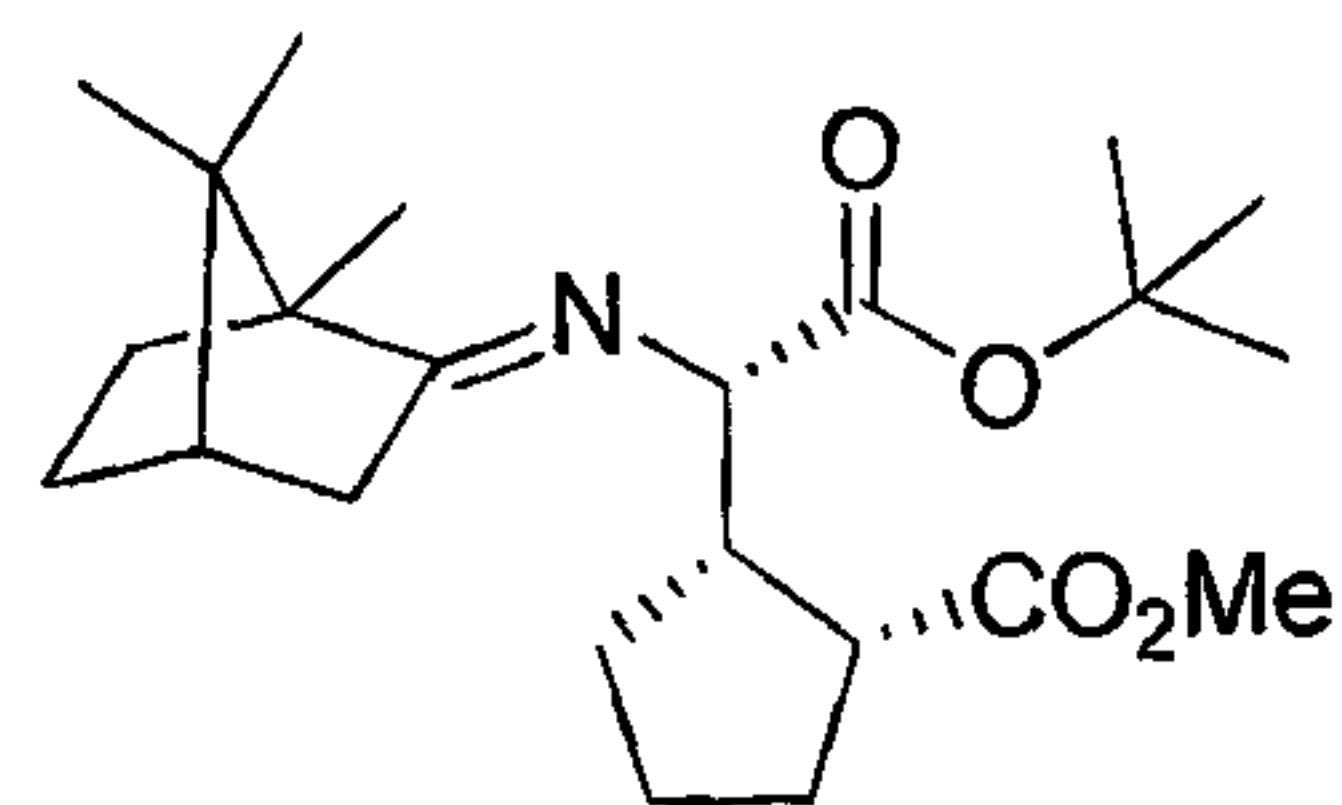


wherein:

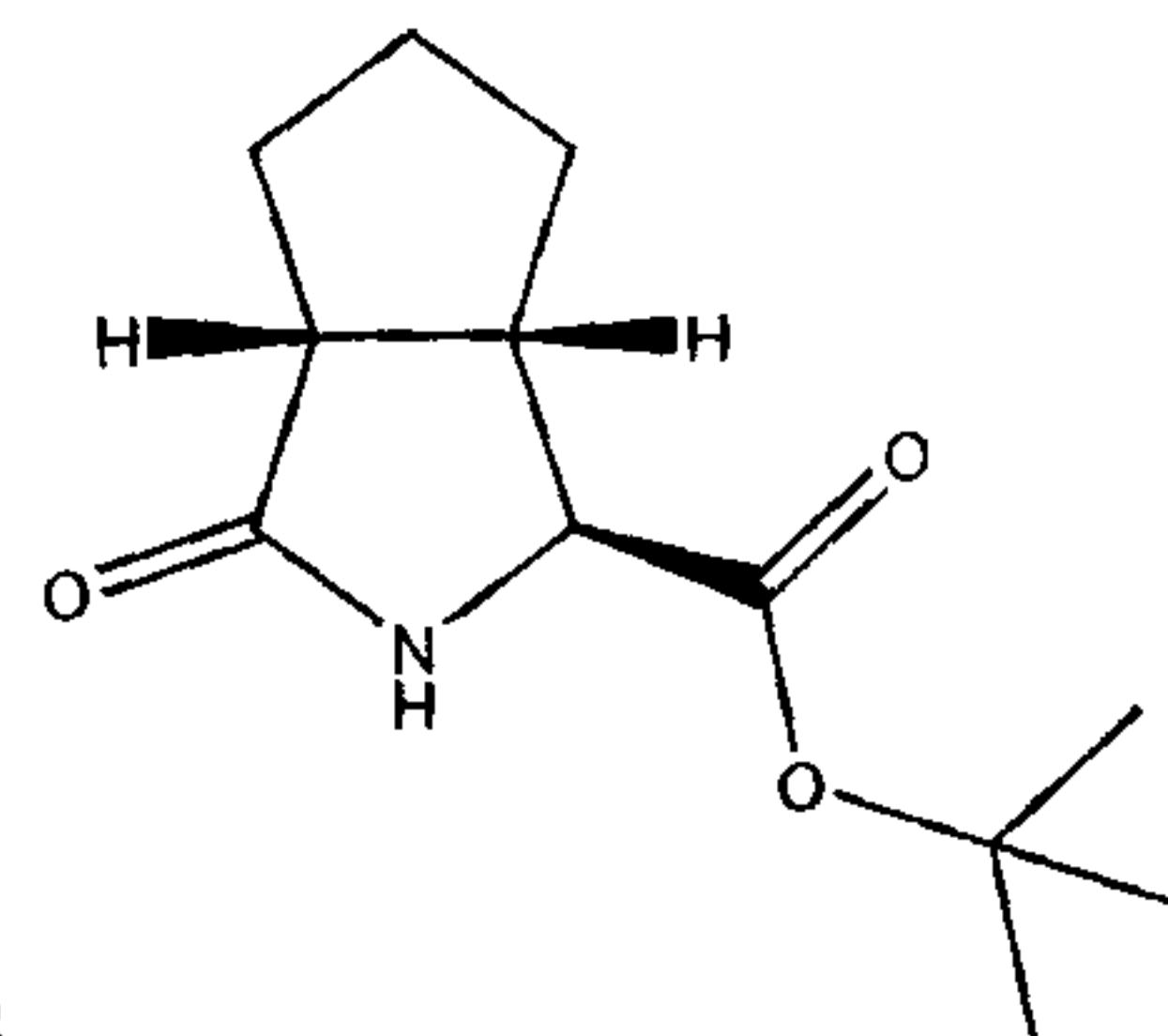
R^{11a} is $-CHO$, $-COR^{15}$, $-C\equiv N$, or $-CONR^{15}R^{15}$.

51. The process of claim 50 wherein the process is carried out at a temperature between $0^{\circ}C$ and—
10 $78^{\circ}C$.
52. The process of claim 51 wherein the process is carried out at $-60^{\circ}C$.
53. The process of claim 52 wherein the process is catalyzed by a chiral phase transfer catalyst.
54. The process of claim 52 wherein the process is catalyzed by a nonchiral phase transfer catalyst.
- 15 55. The process of any one of claims 50 to 54 wherein the protecting group is BOC.
56. The process of claim 55 wherein the iminic glycinimide is (N-diphenylmethylene)-glycine tert-butyl ester.
57. The process of claim 55 wherein the compound of formula 29 is 1-carboxy-1-cyclopentene methyl ester.
- 20 58. The process of claim 47 wherein R^{13} is lower alkyl.
59. The process of claim 58 wherein R^{13} is methyl.
60. The process of claim 47 wherein R^{14} is CO_2R^{16} .
61. The process of claim 60 wherein R^{16} is C_1-C_4 alkyl.
62. The process of claim 61 wherein R^{16} is t-butyl.
- 25 63. The process of claim 47 wherein p^O is benzyloxycarbonyl.

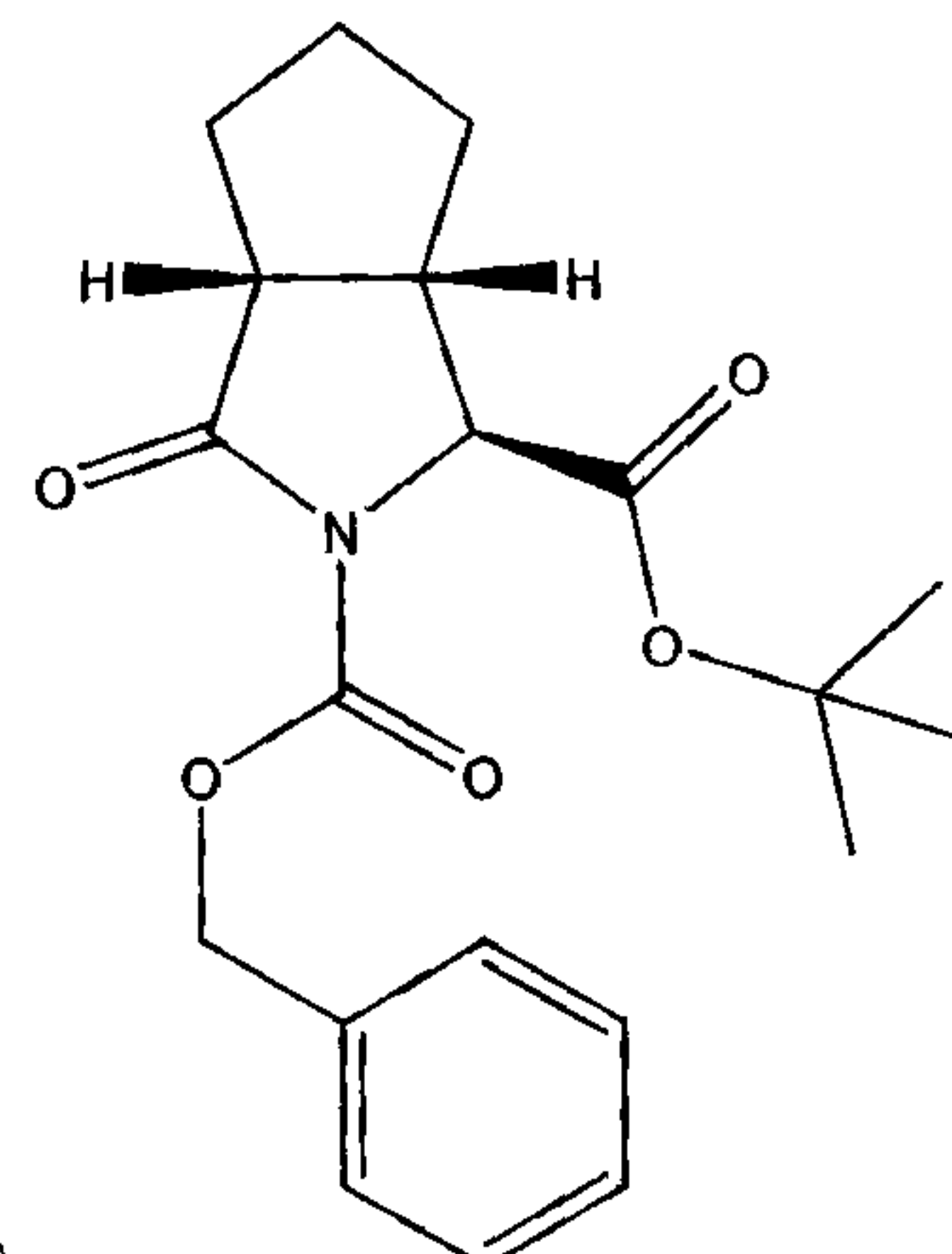
64. The process of claim 47 wherein the compound of formula 24 is



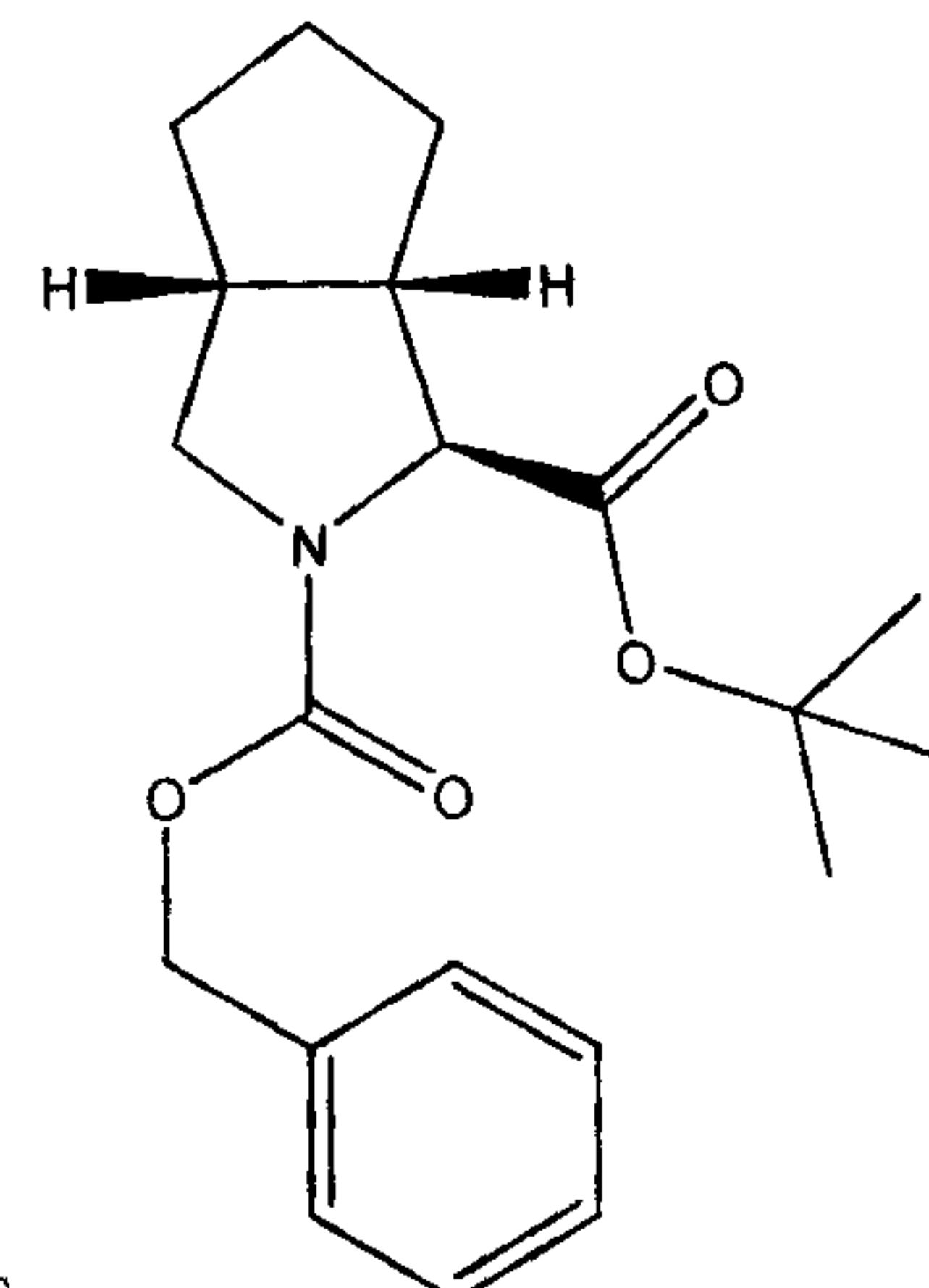
- 333 -



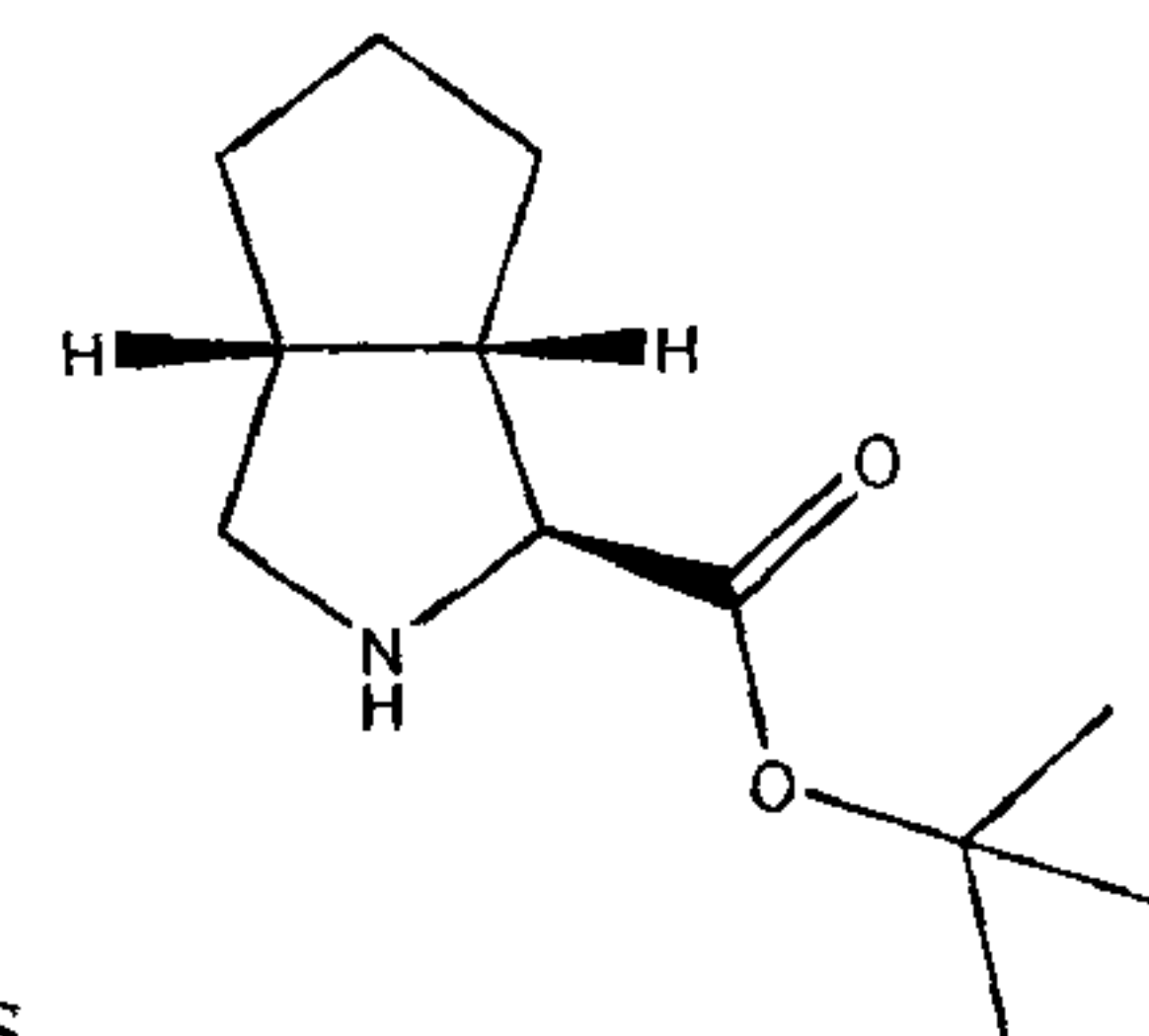
65. The process of claim 47 wherein the compound of formula 25 is



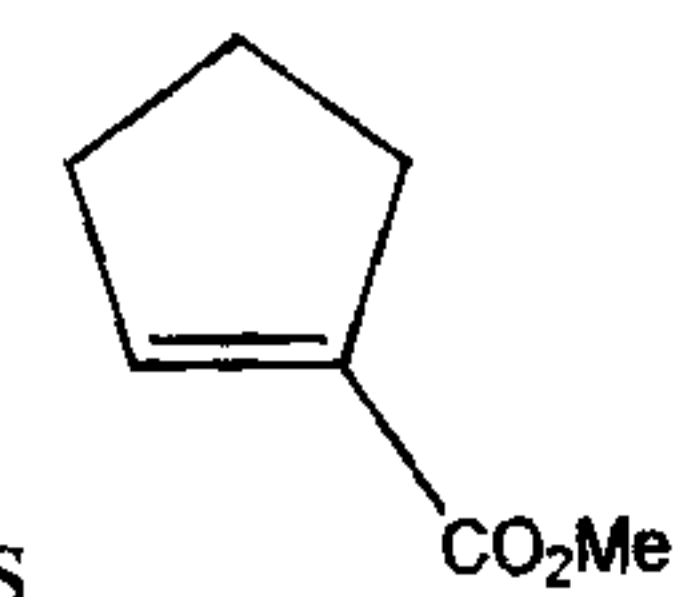
66. The process of claim 47 wherein the compound of formula 26 is



67. The process of claim 47 wherein the compound of formula 27 is

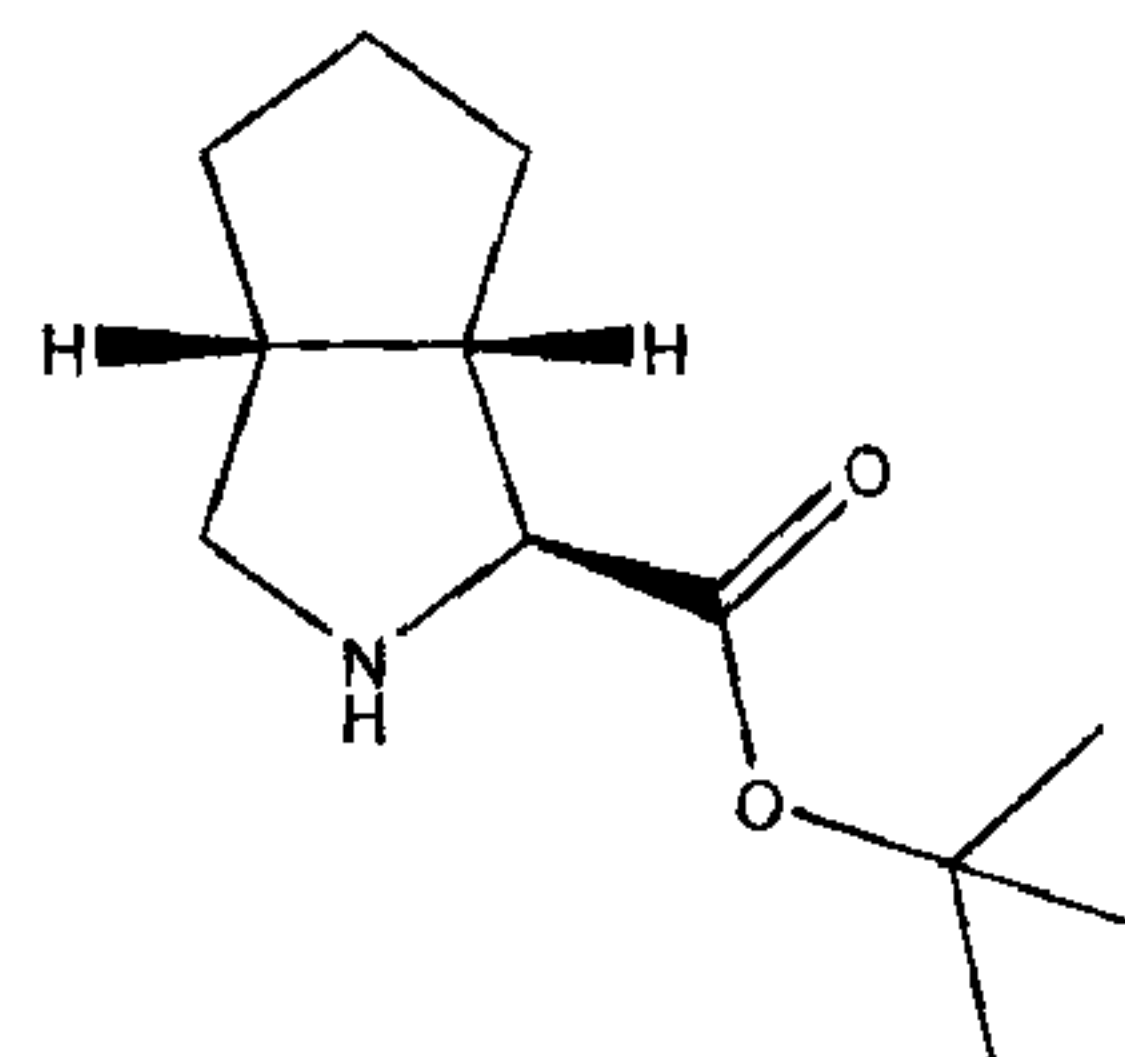


68. The process of claim 47 wherein the compound of formula 28 is

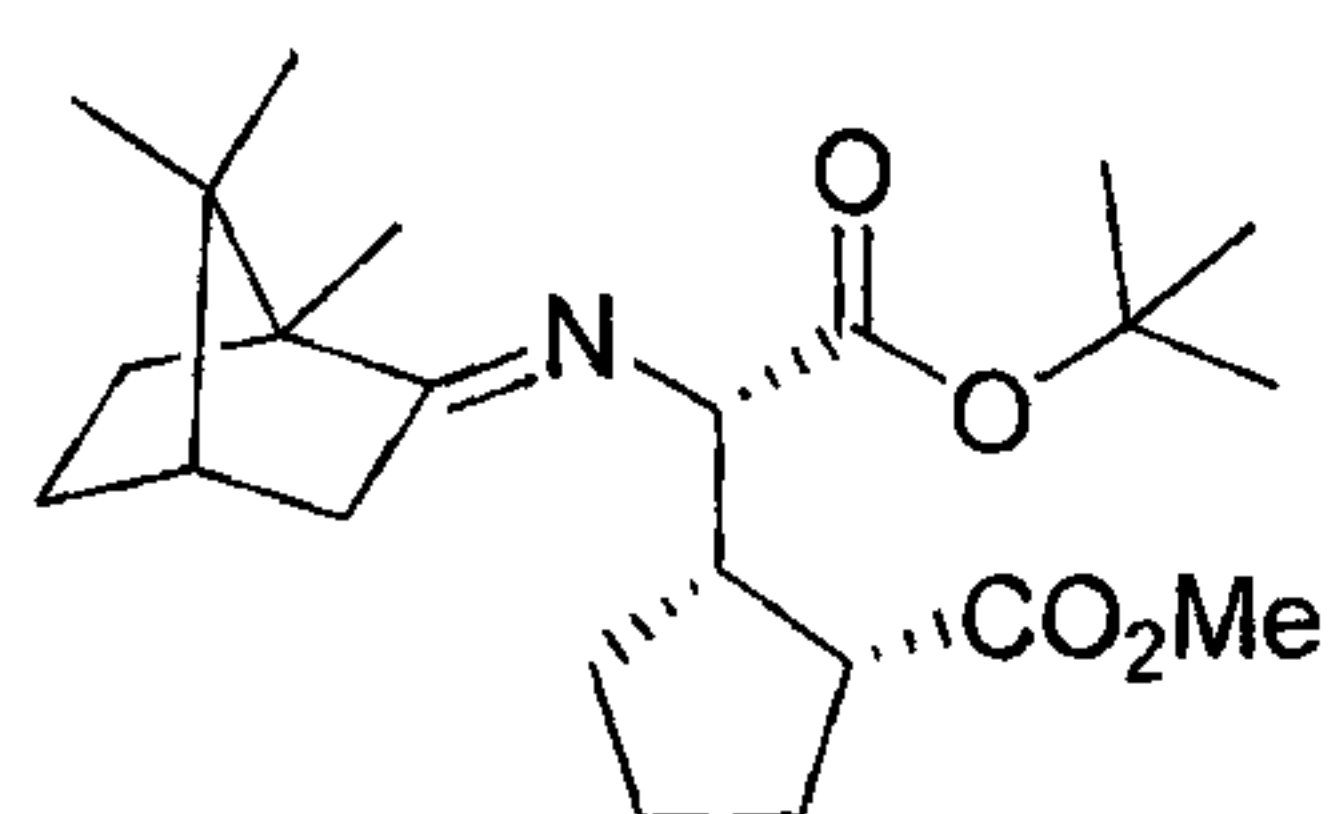


- 5 69. The process of claim 50 wherein the compound of formula 29 is

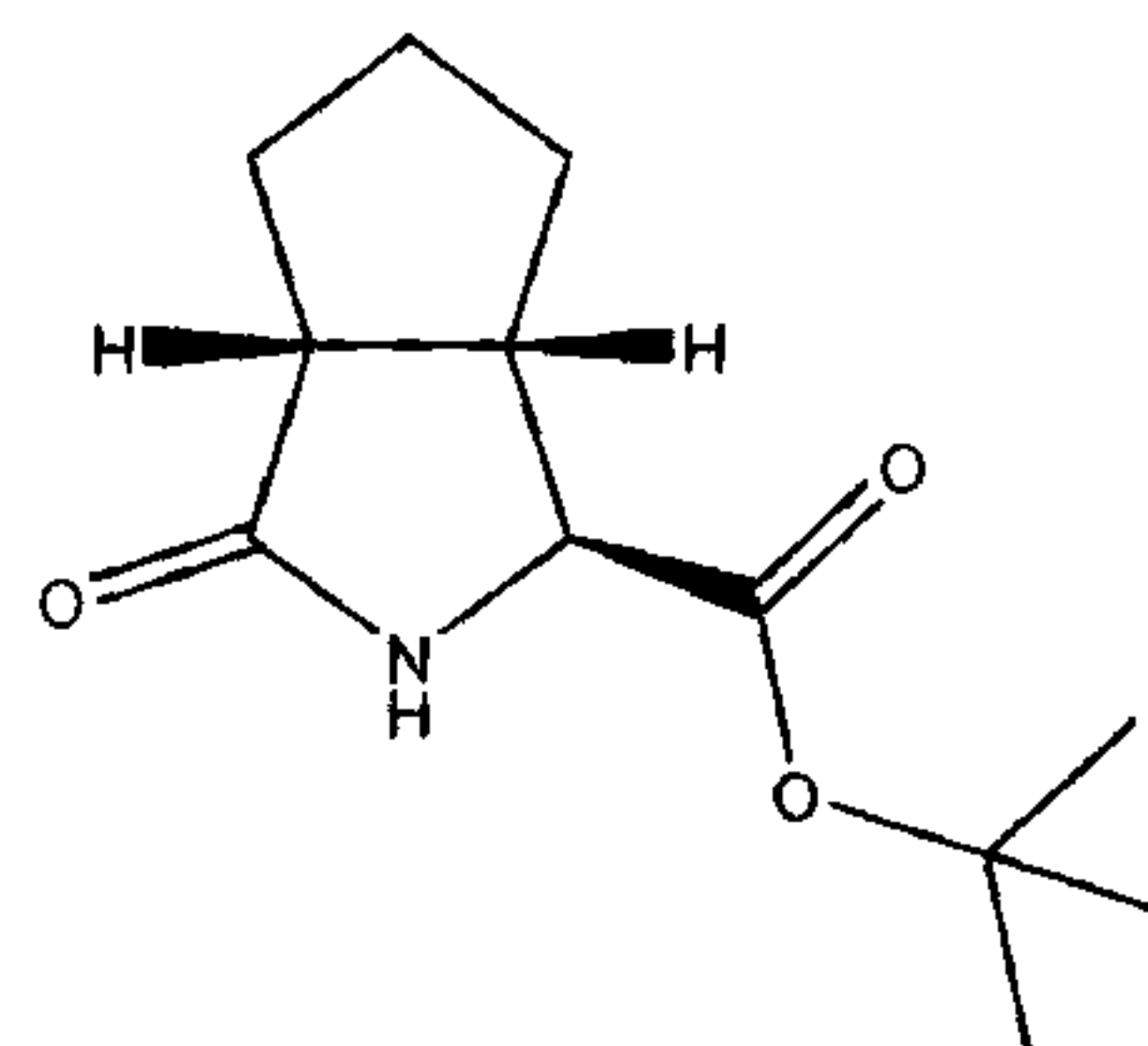
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70. The process of claim 47 for preparing the compound comprising the steps of:

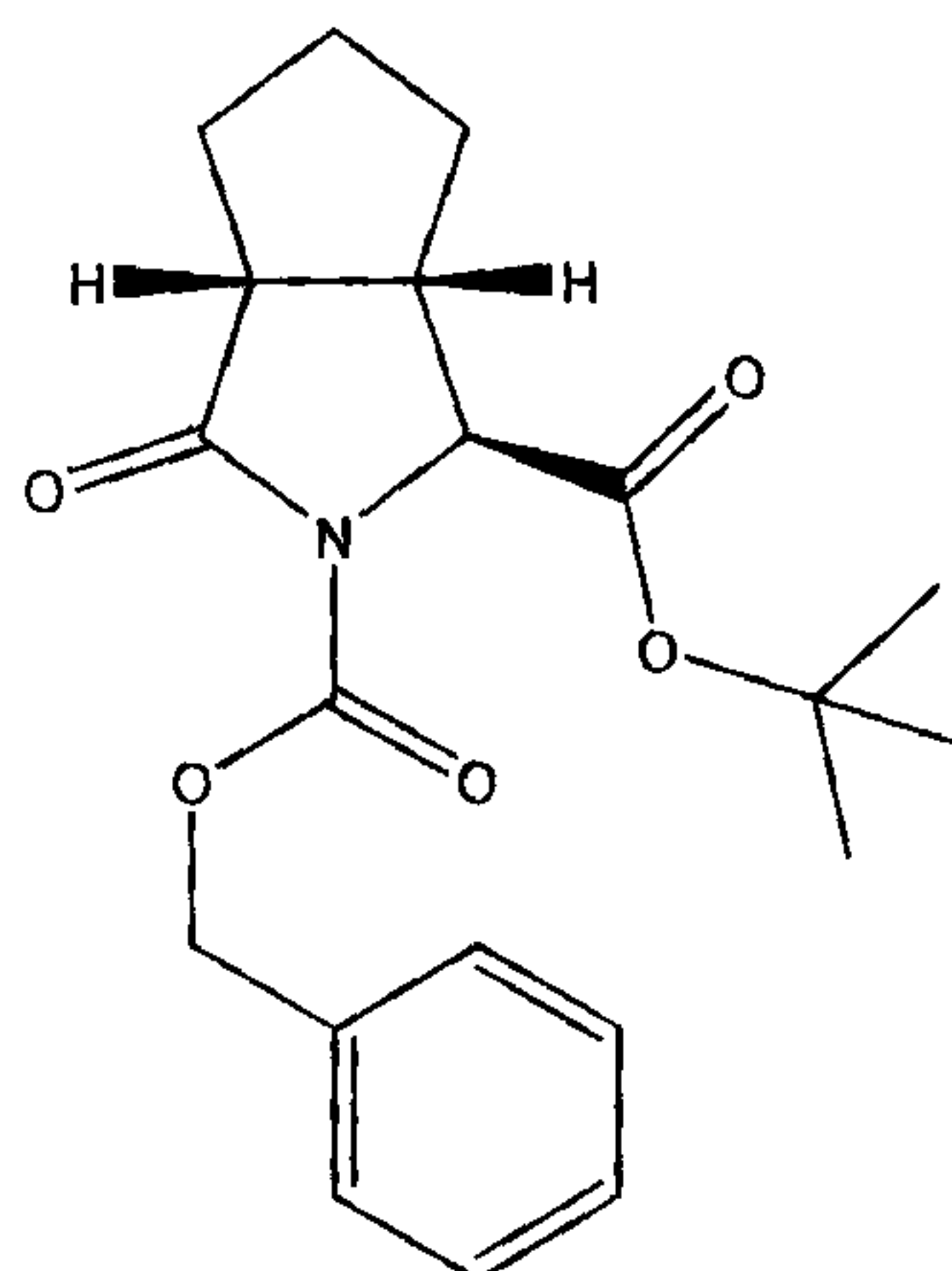
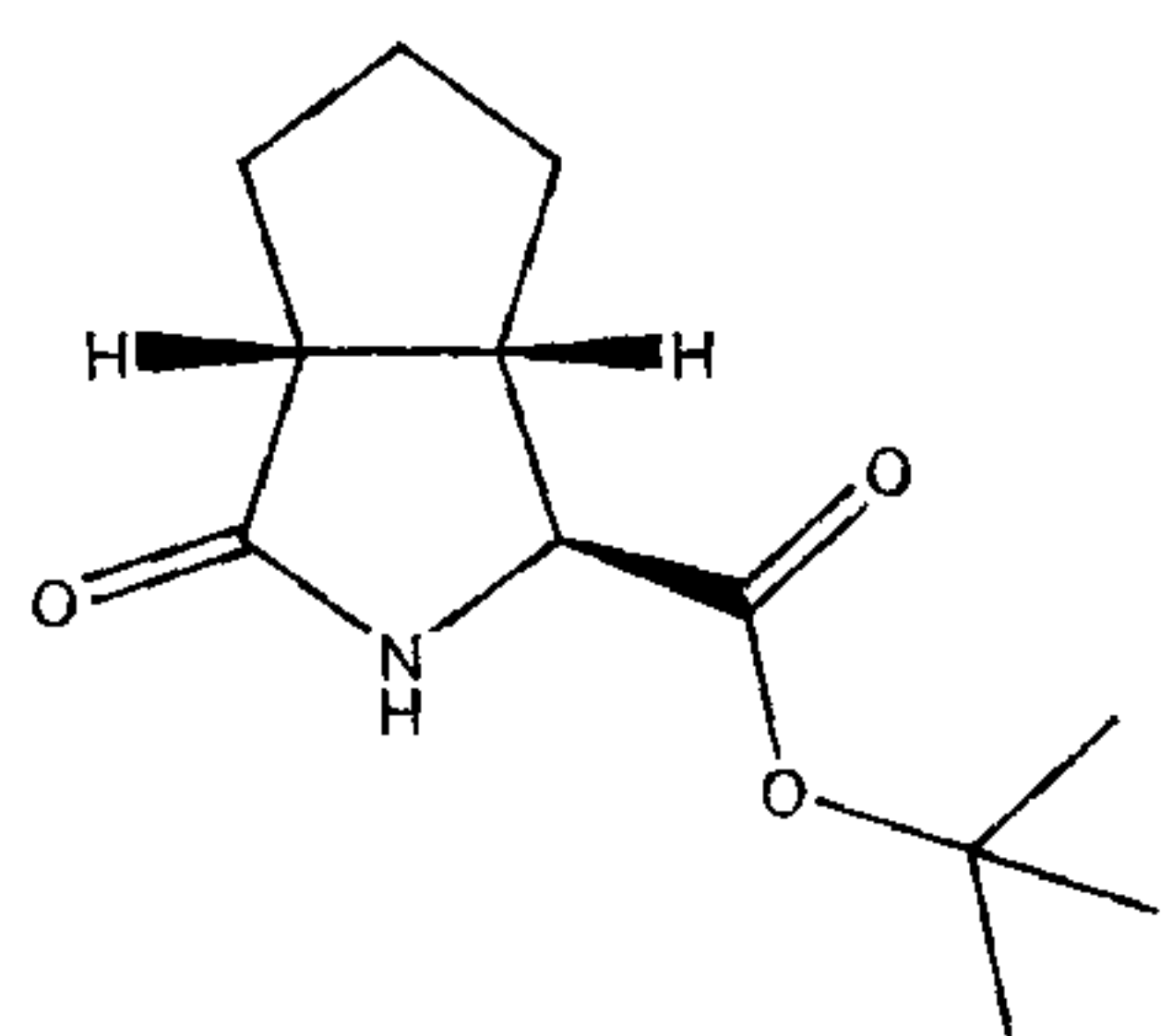


(a) cleaving and cyclizing the compound



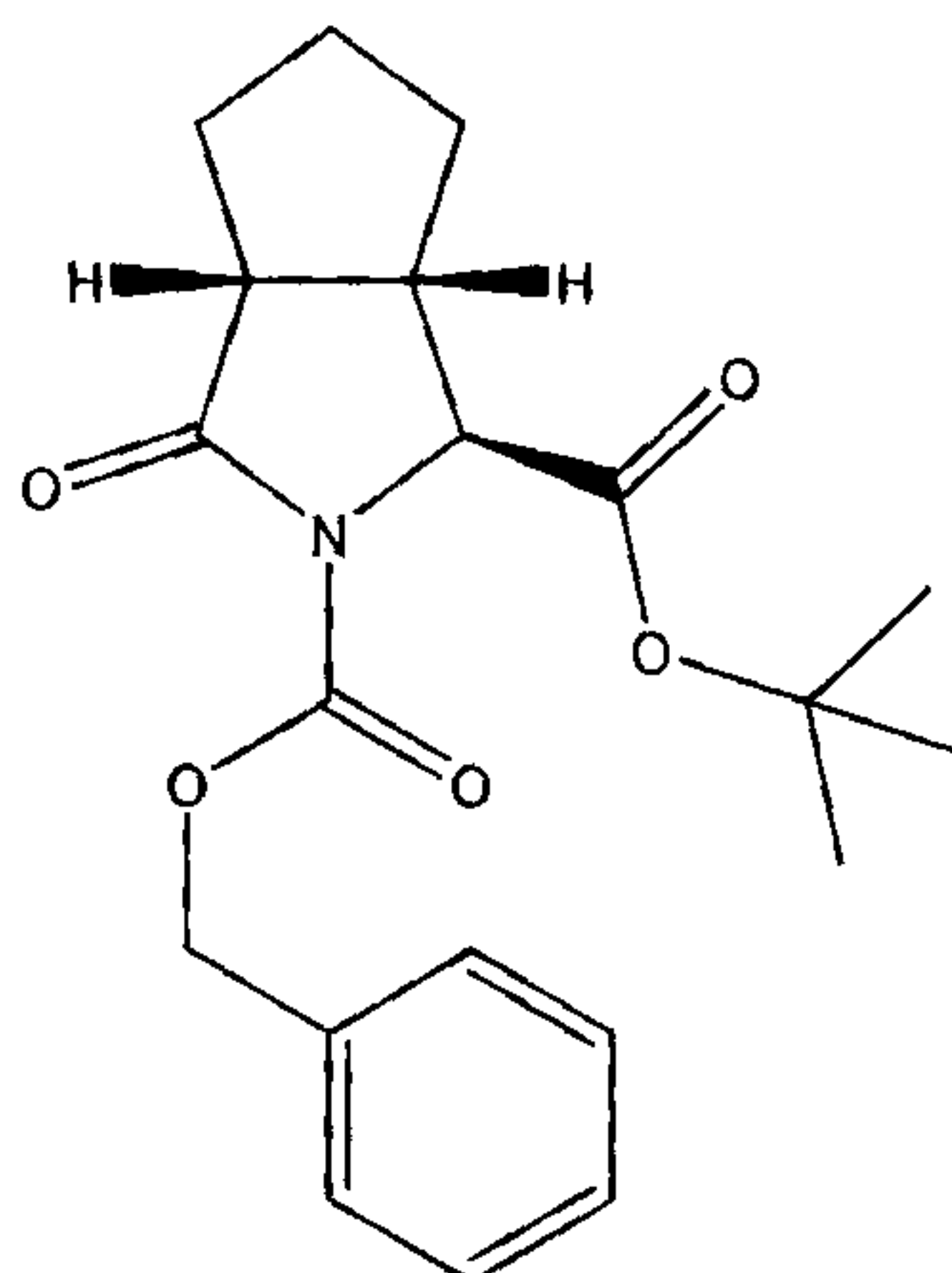
5 under cleaving and cyclizing conditions to form the compound

(b) protecting the nitrogen of the lactam moiety in the compound

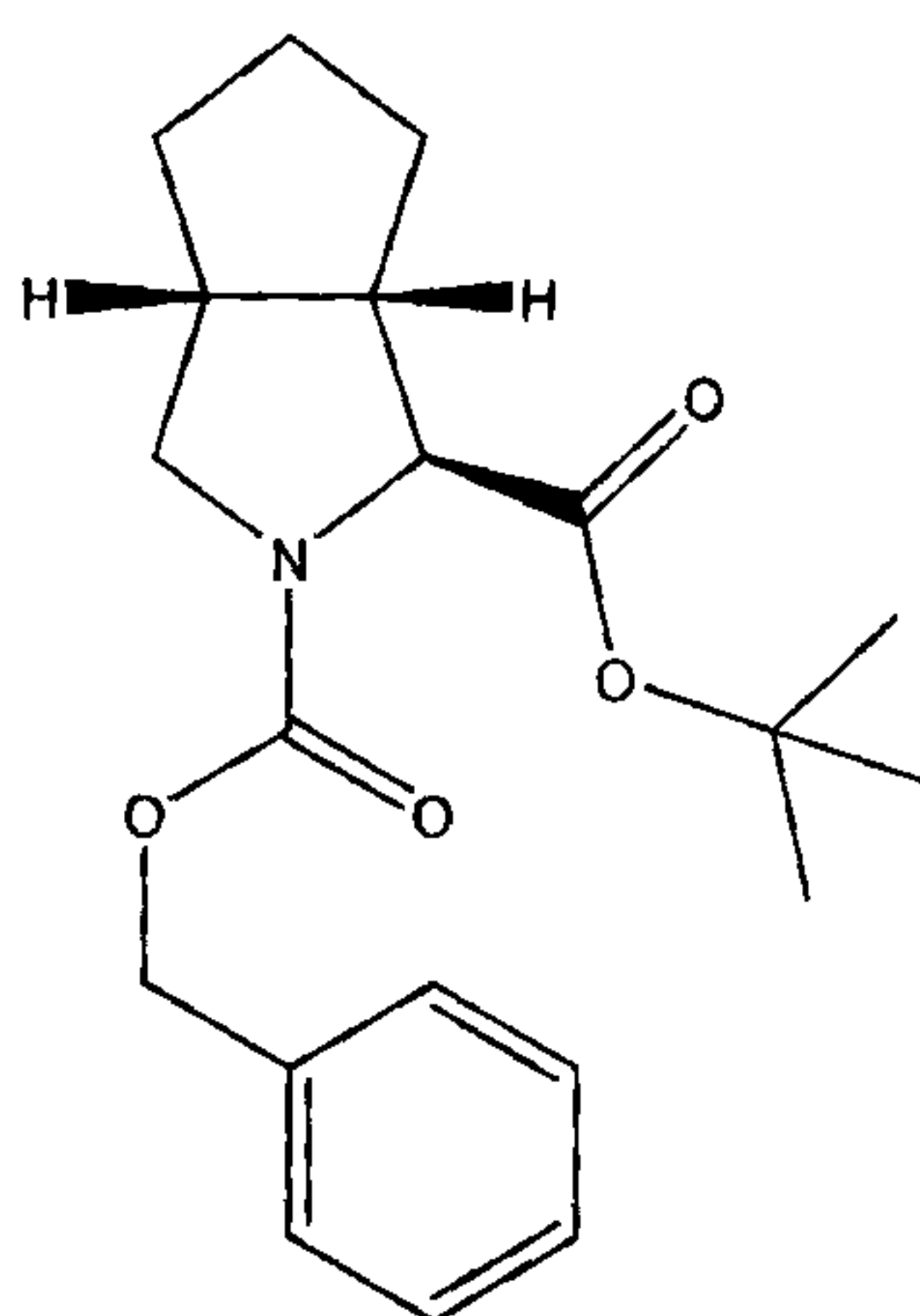


with benzyloxycarbonyl to form the compound

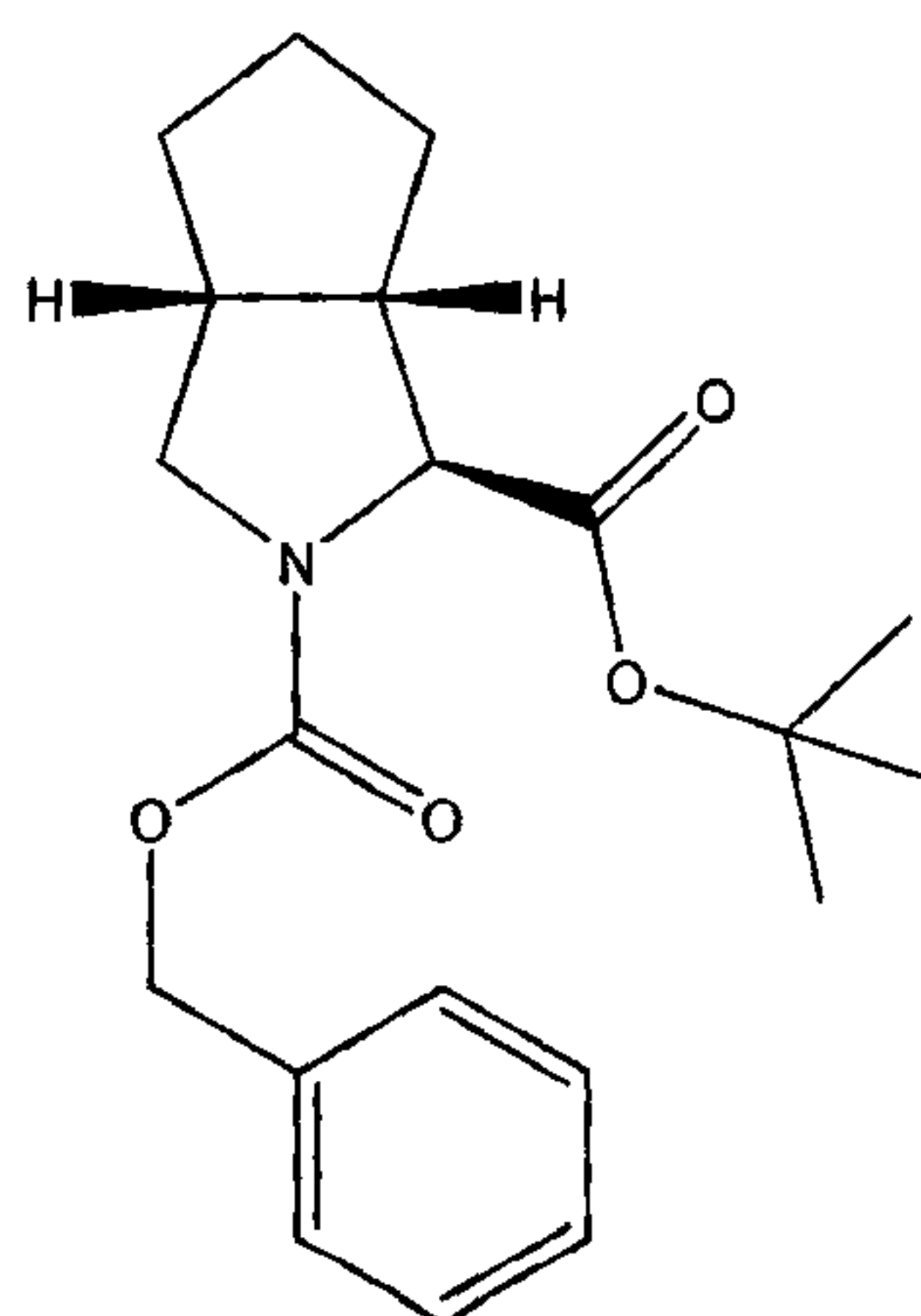
- 335 -



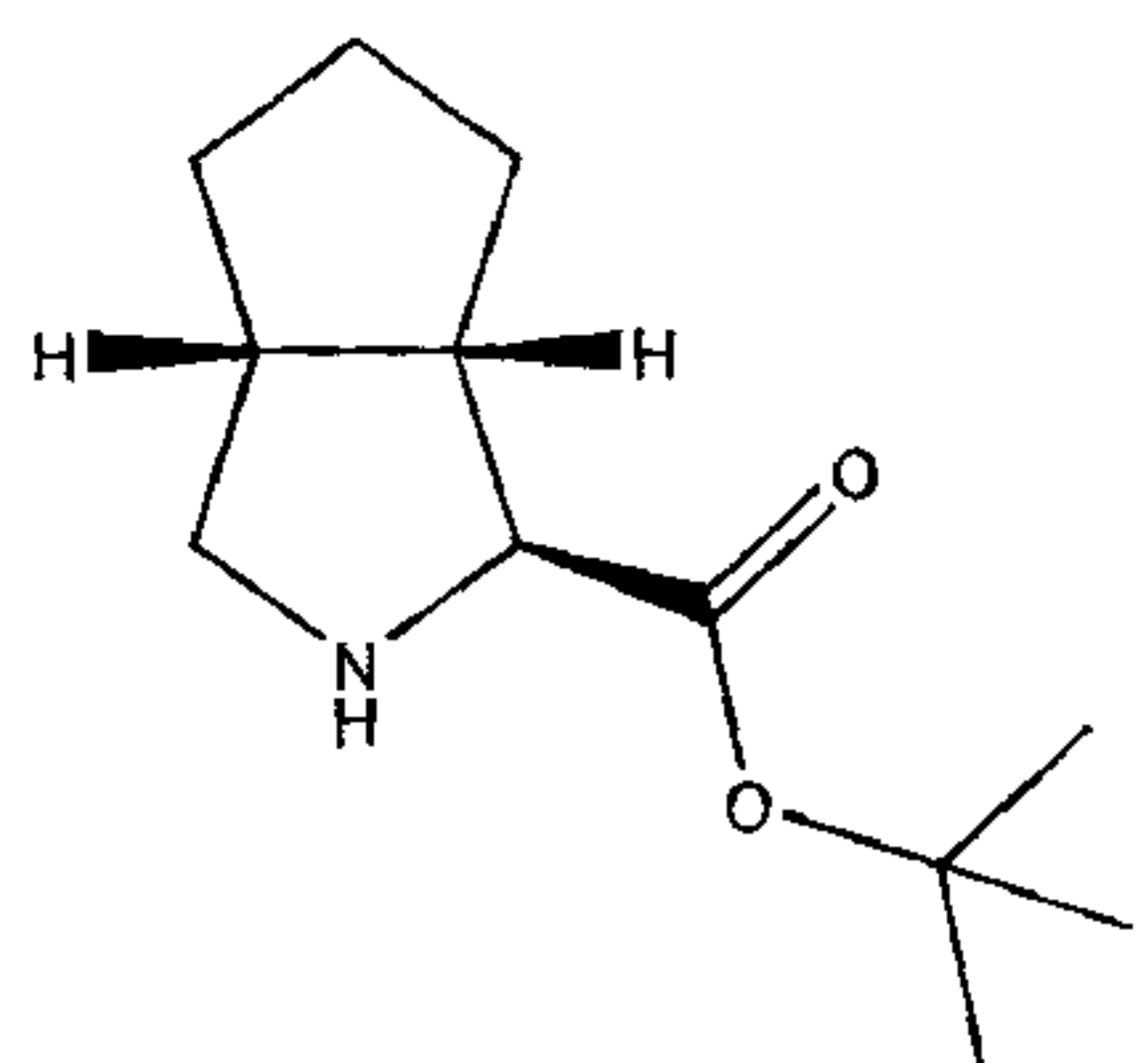
(c) reducing the compound under reducing conditions to



form the compound ; and



(d) deprotecting the compound under deprotecting conditions



to form the compound

5 71. The compound as claimed in any one of claims 2, 22, 31, or 48, wherein a ring system in the definition of cyclyl is 5 to 6 ring atoms.

Figure 1.

Combination treatment with Interferon alpha-2B and Compound CU

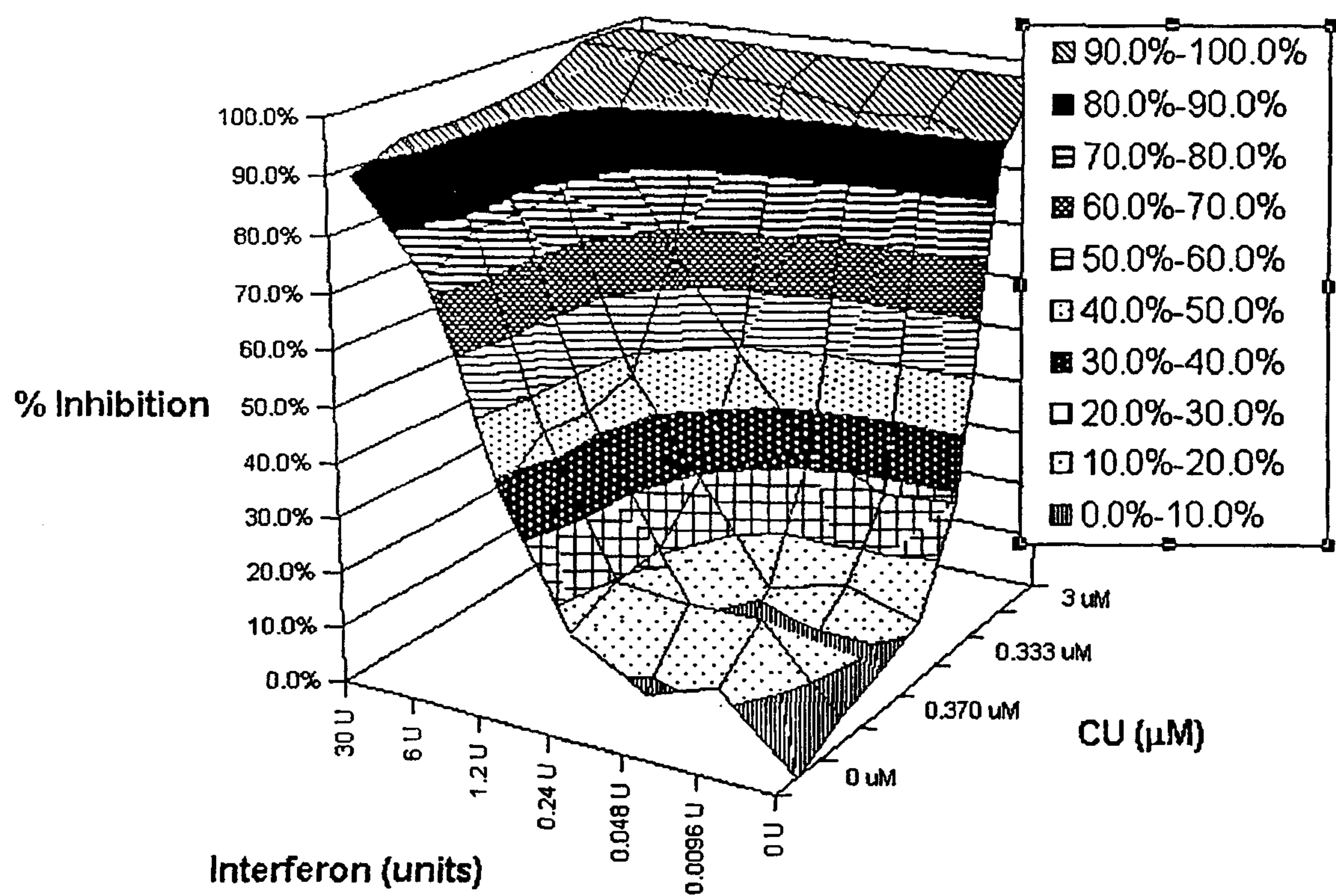


Fig 2.

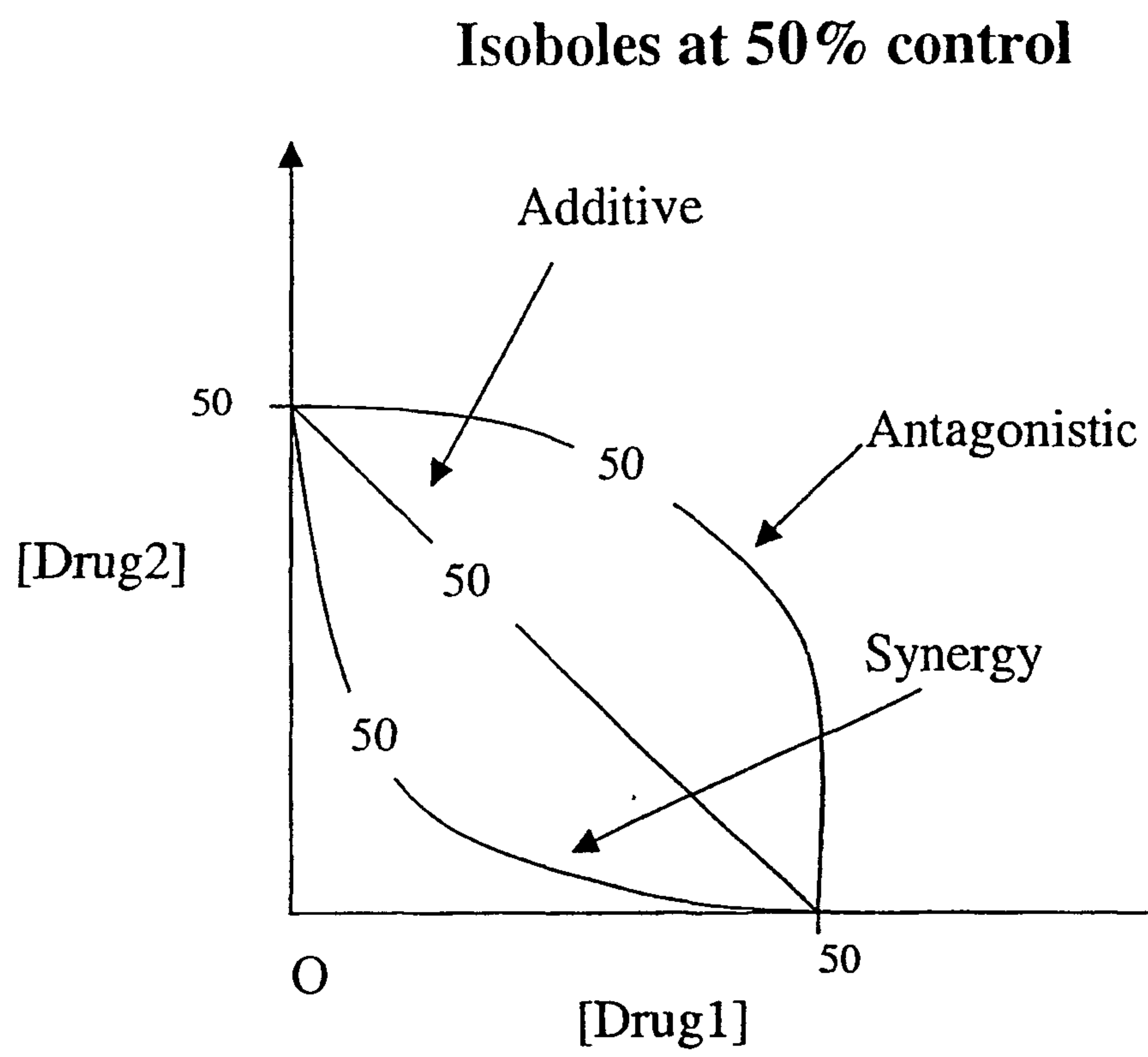


Fig. 3.

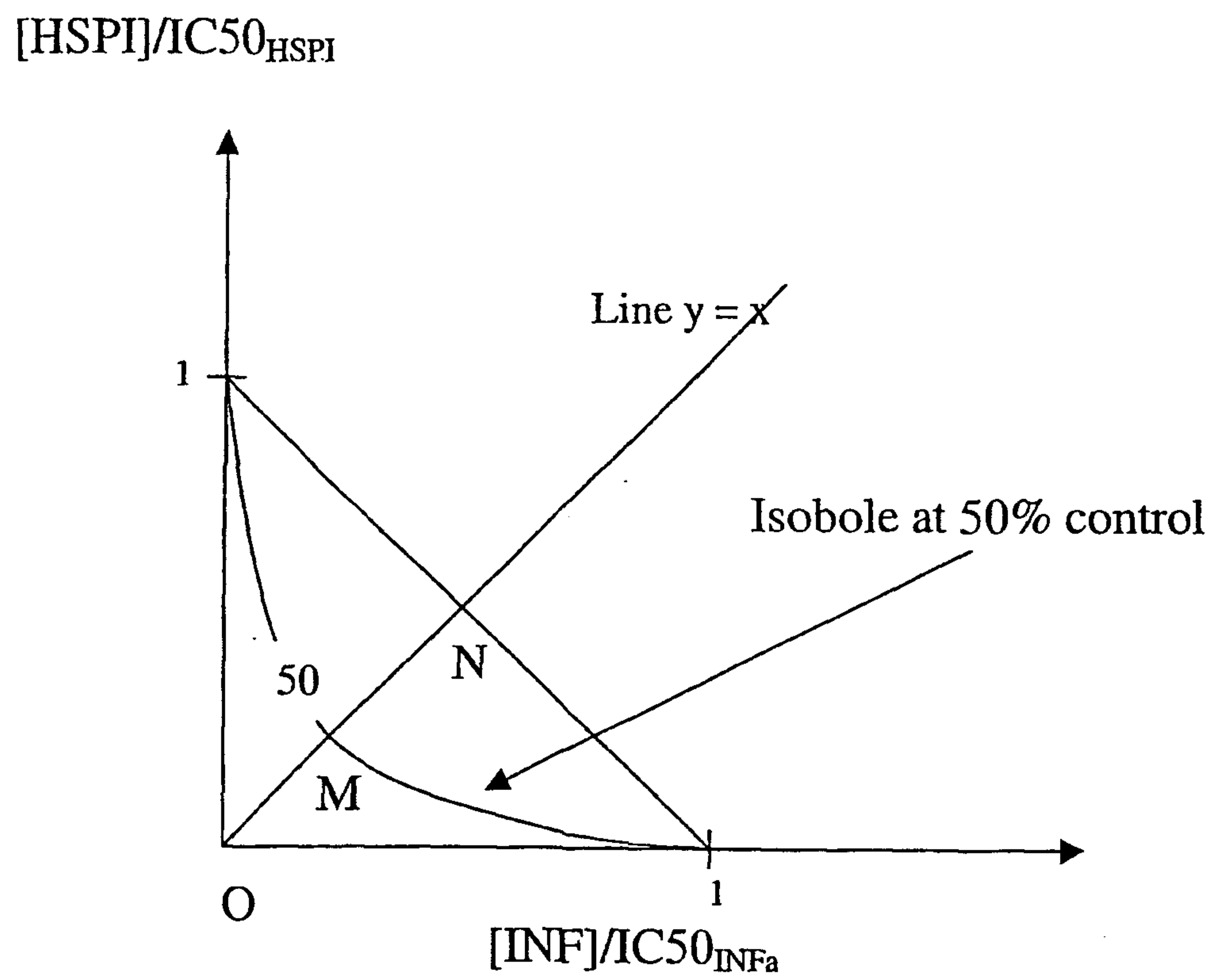


Fig. 4.

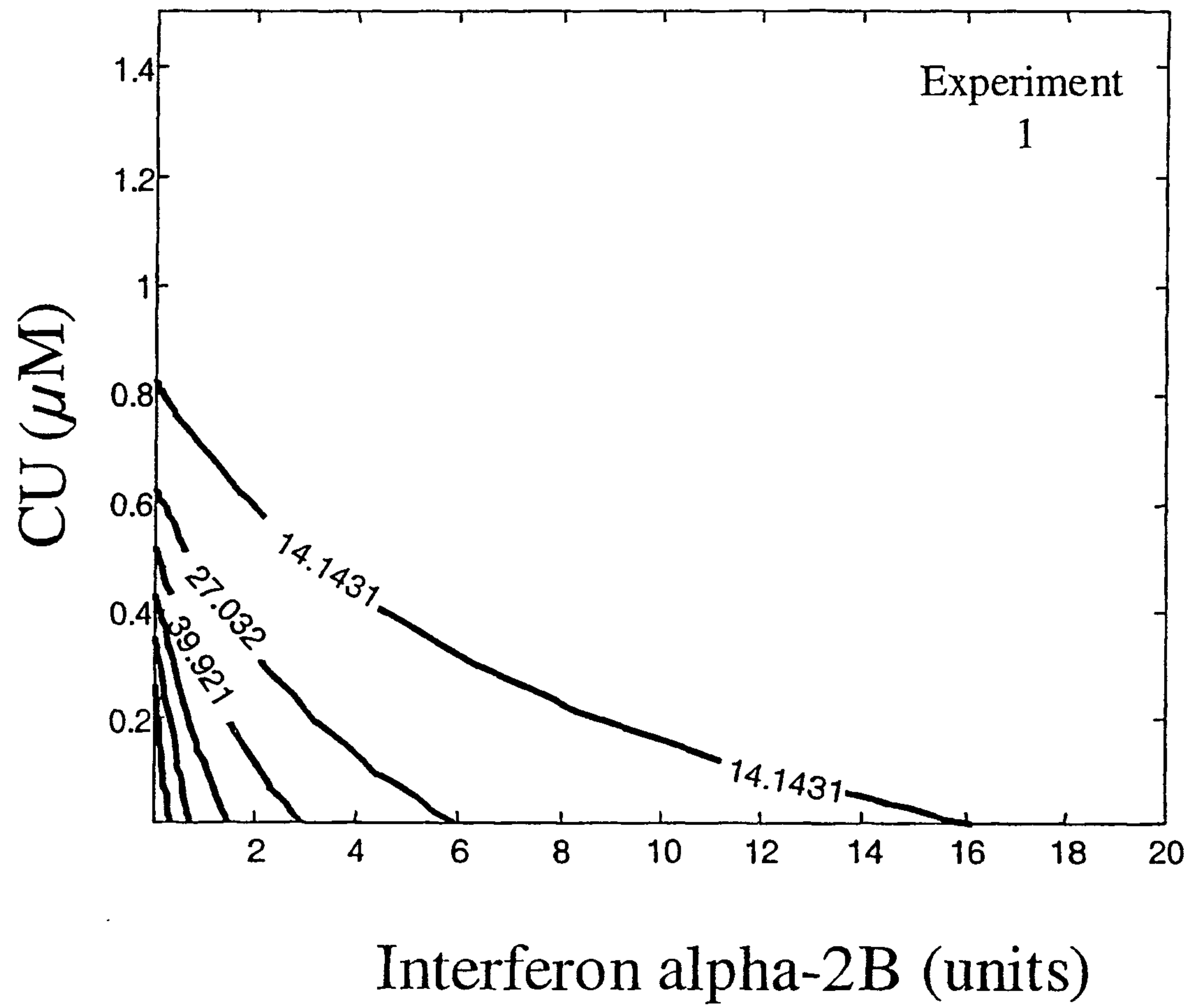


Fig. 5

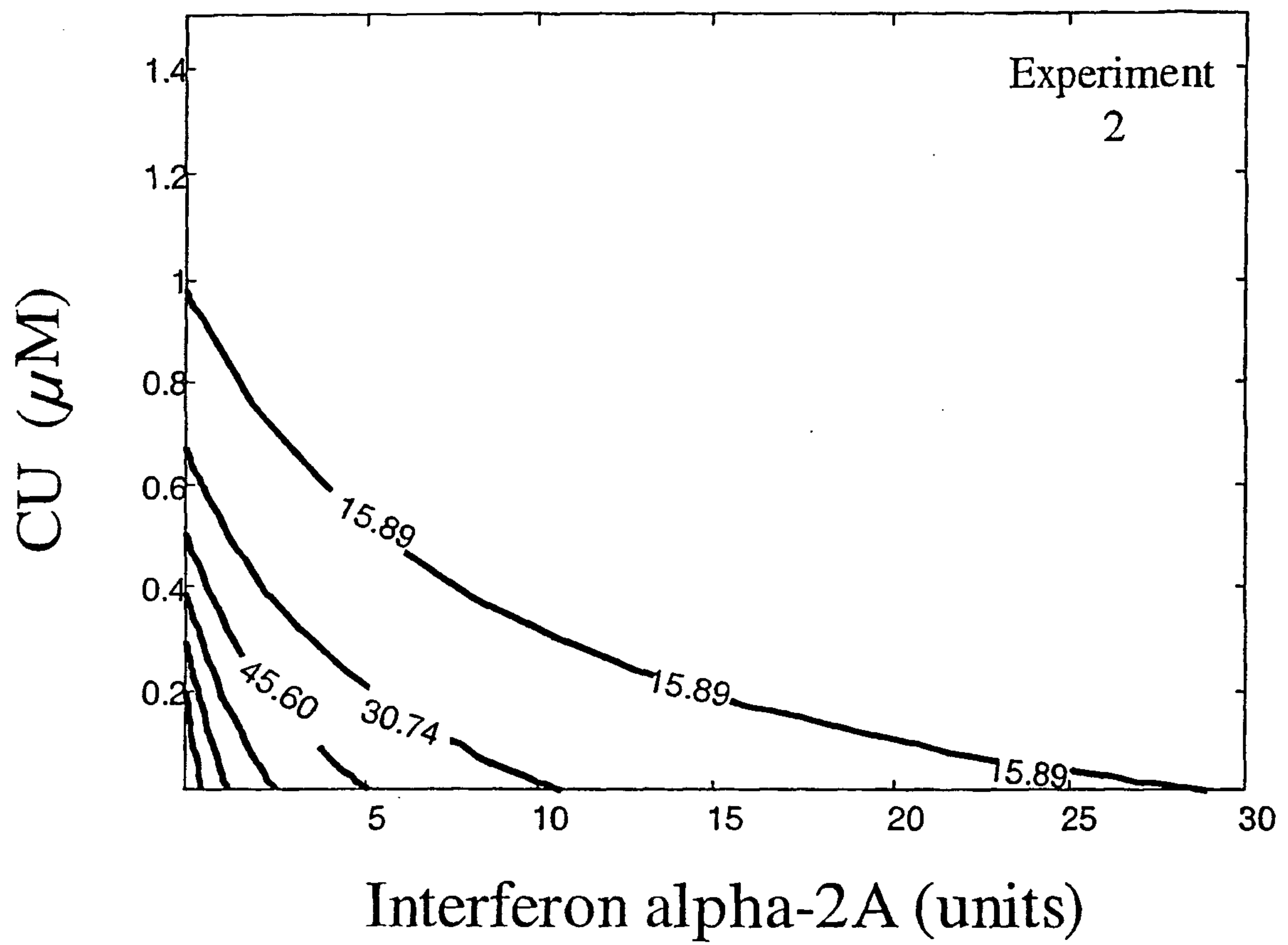
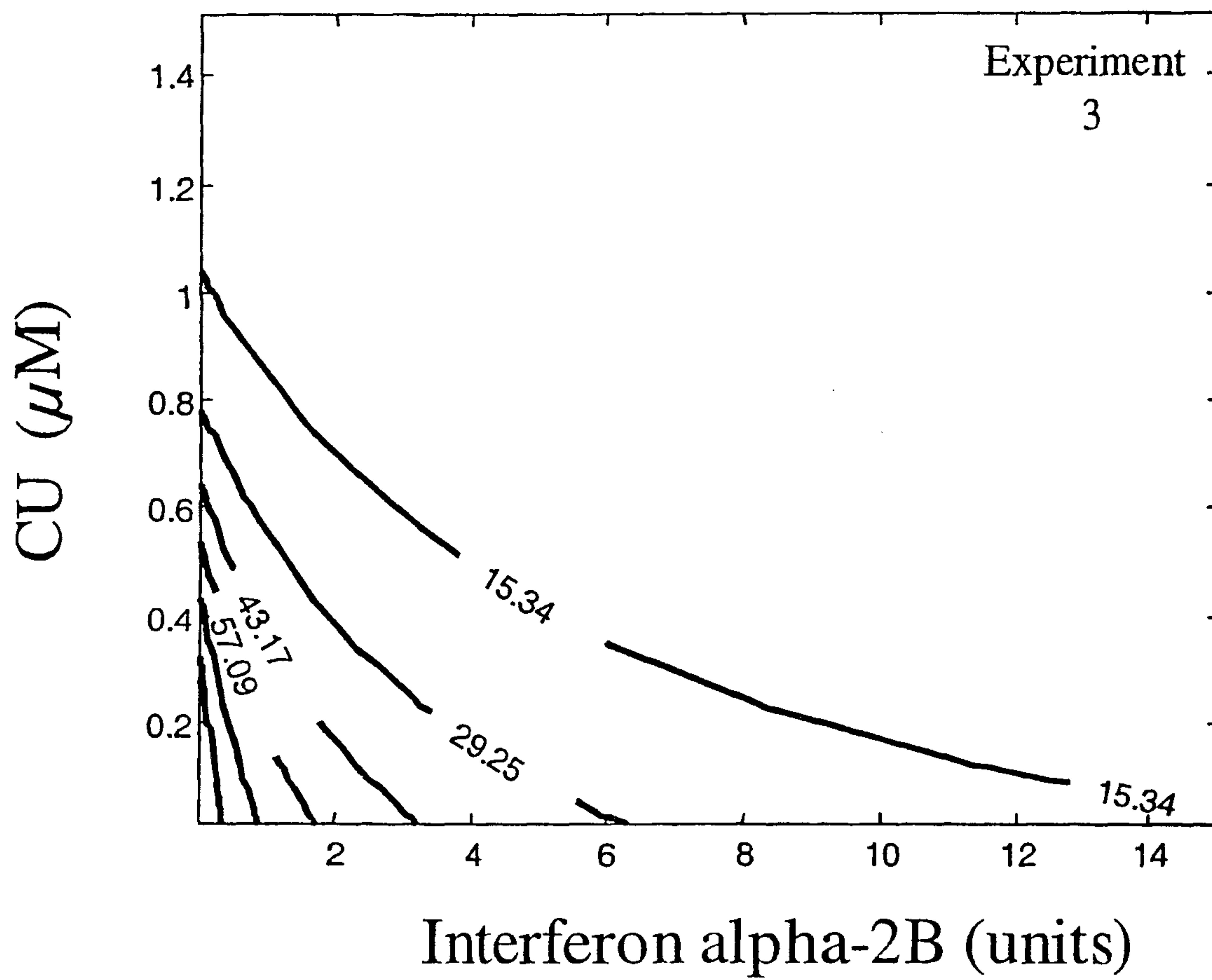


Fig. 6

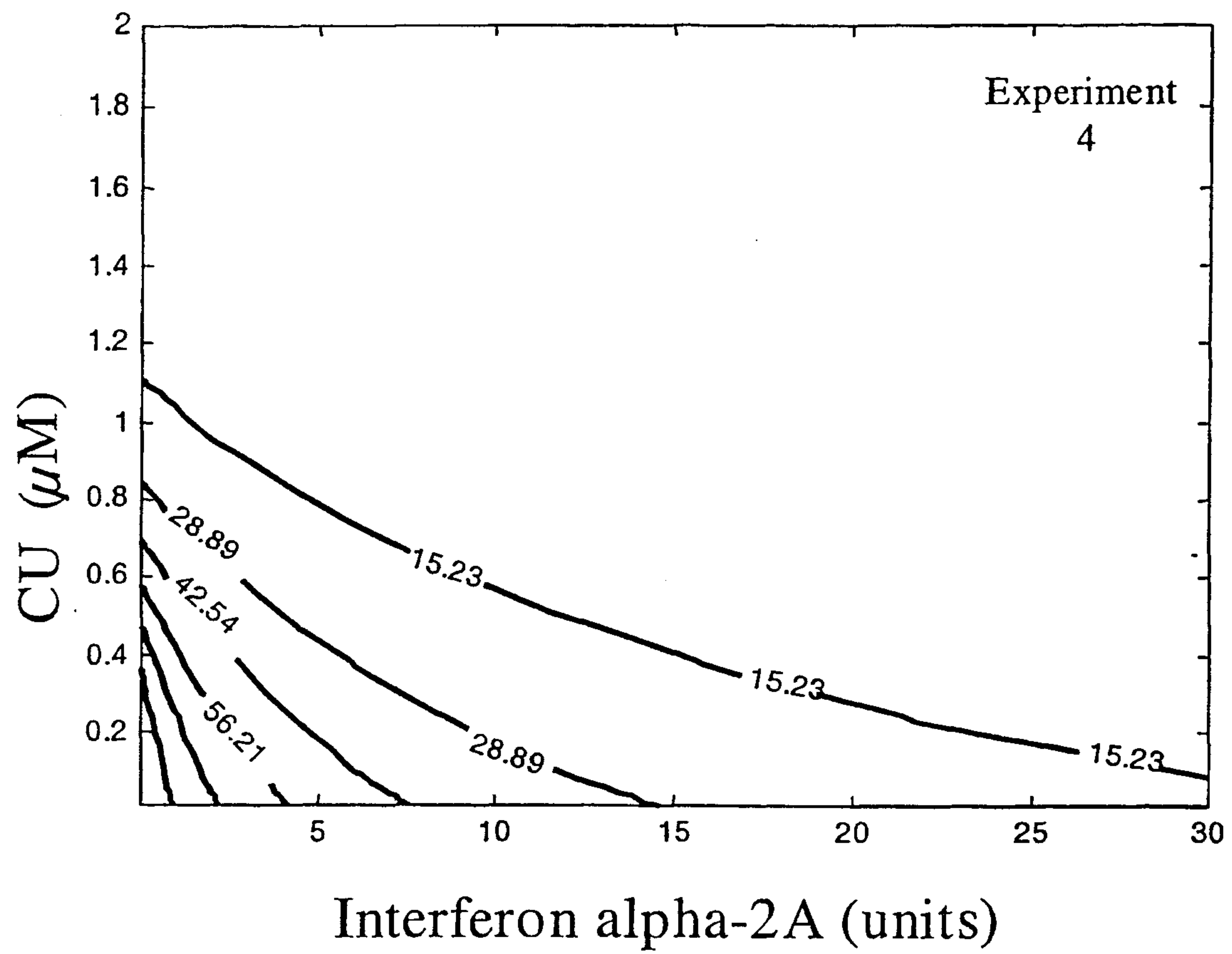


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Fig. 7



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Fig. 8.

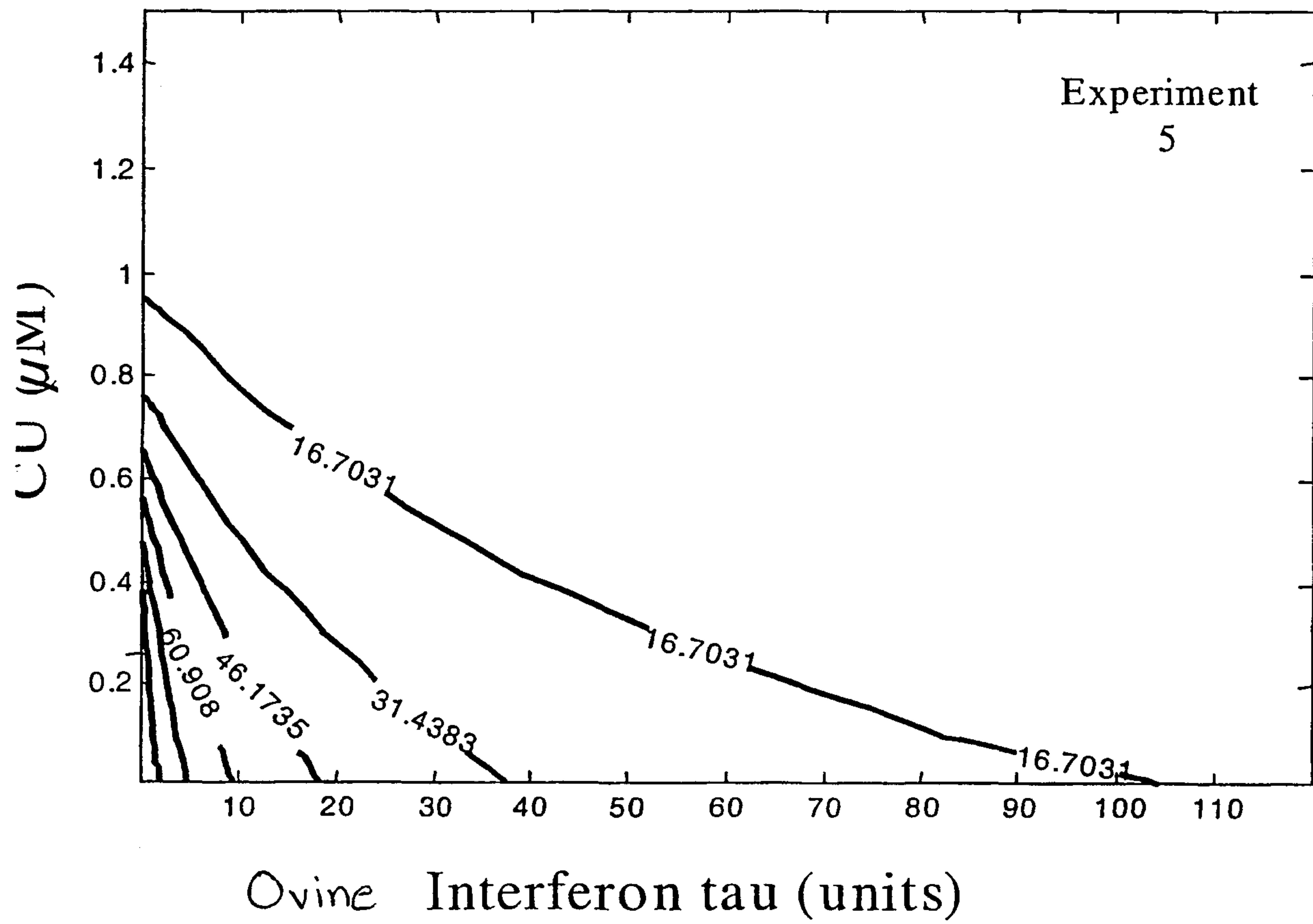


Fig 9.

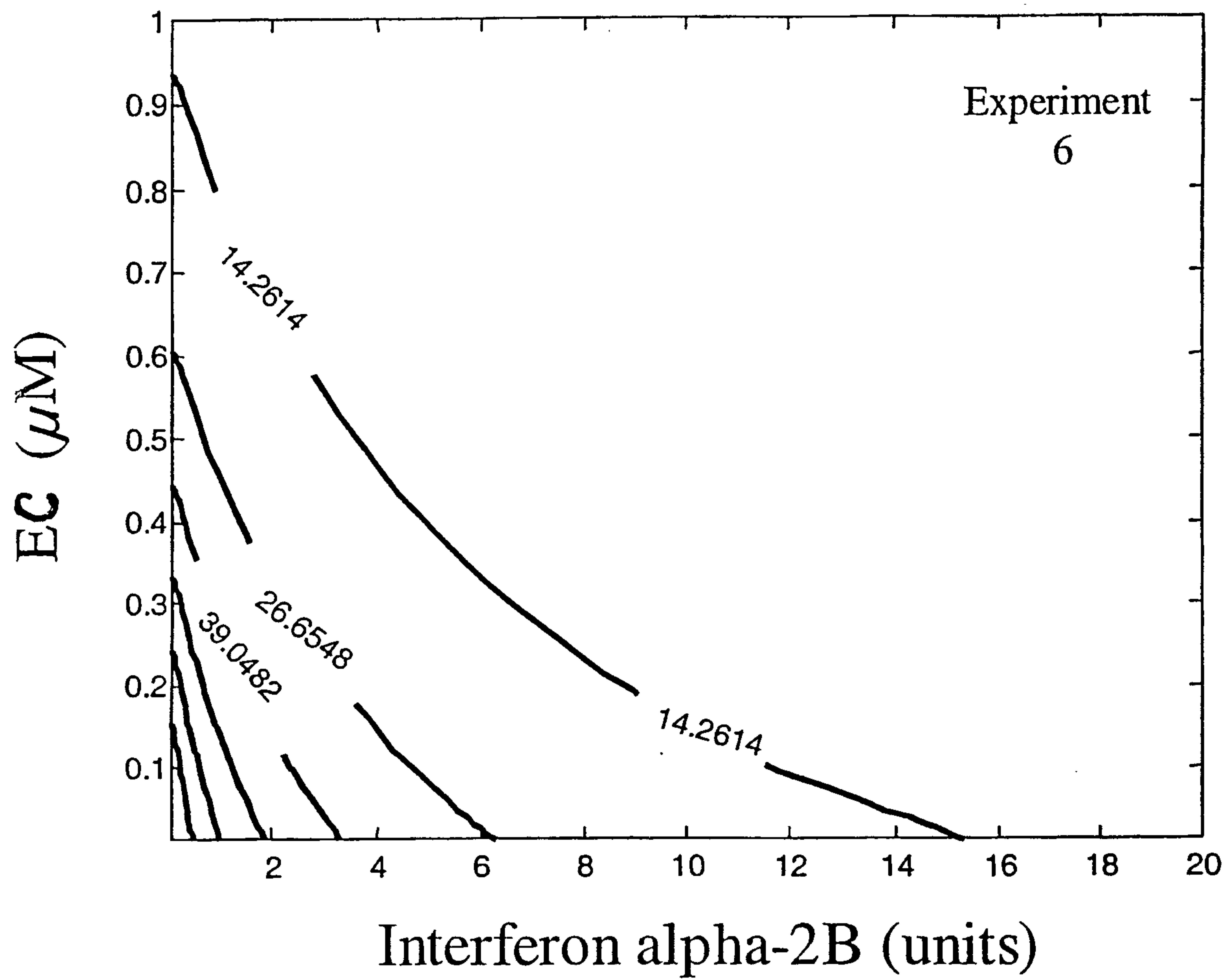
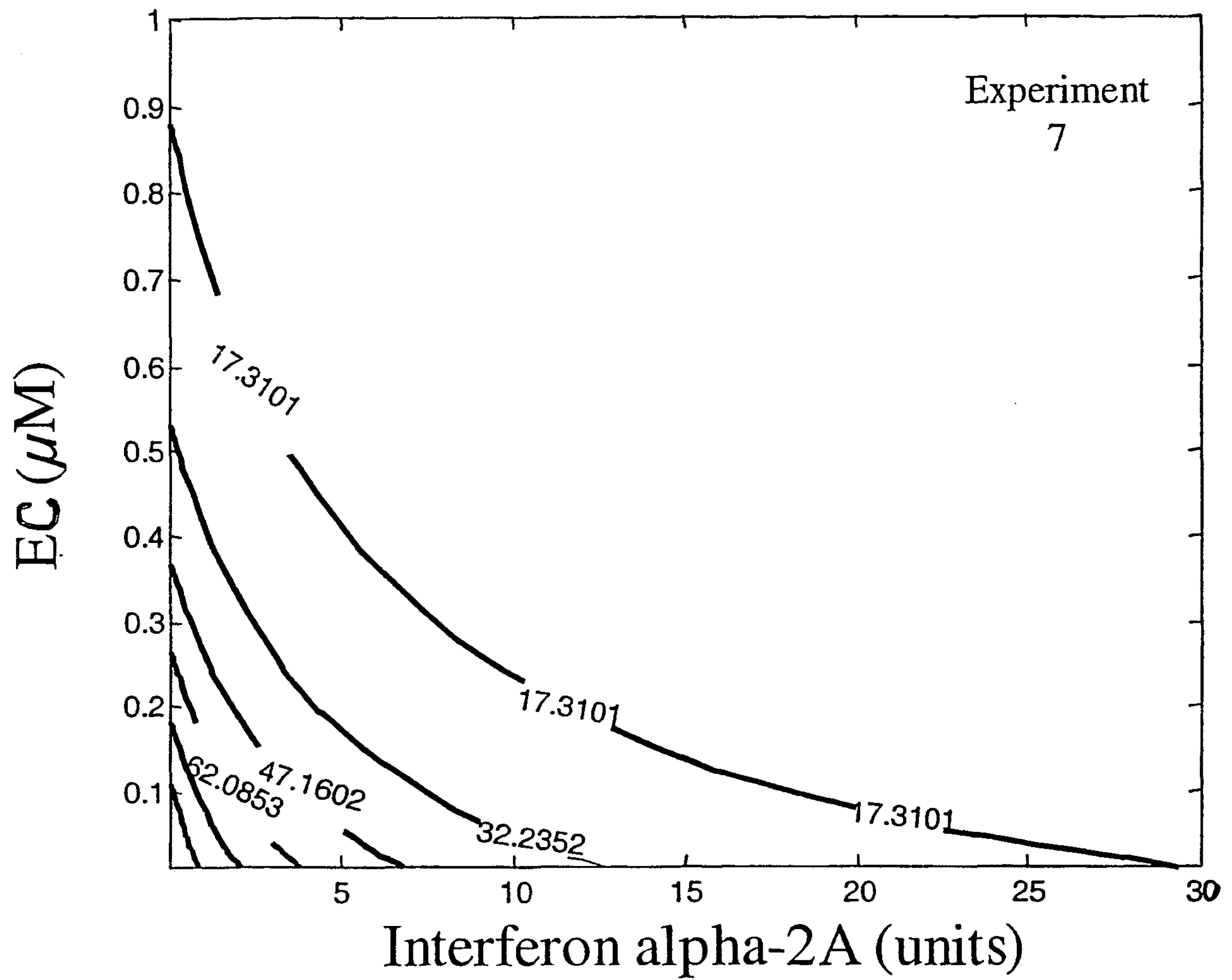


Fig. 10.



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Fig 11.

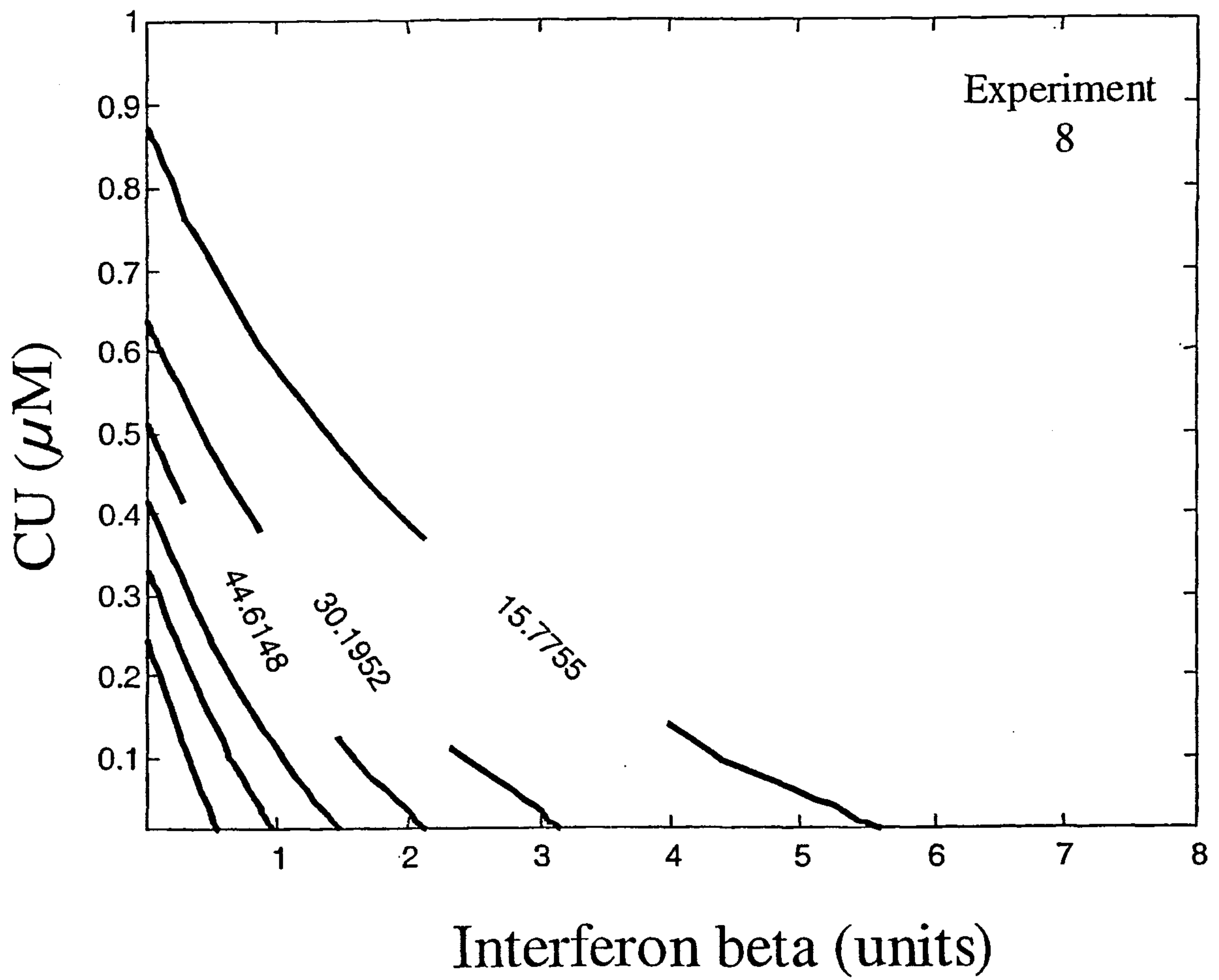


Fig. 12.

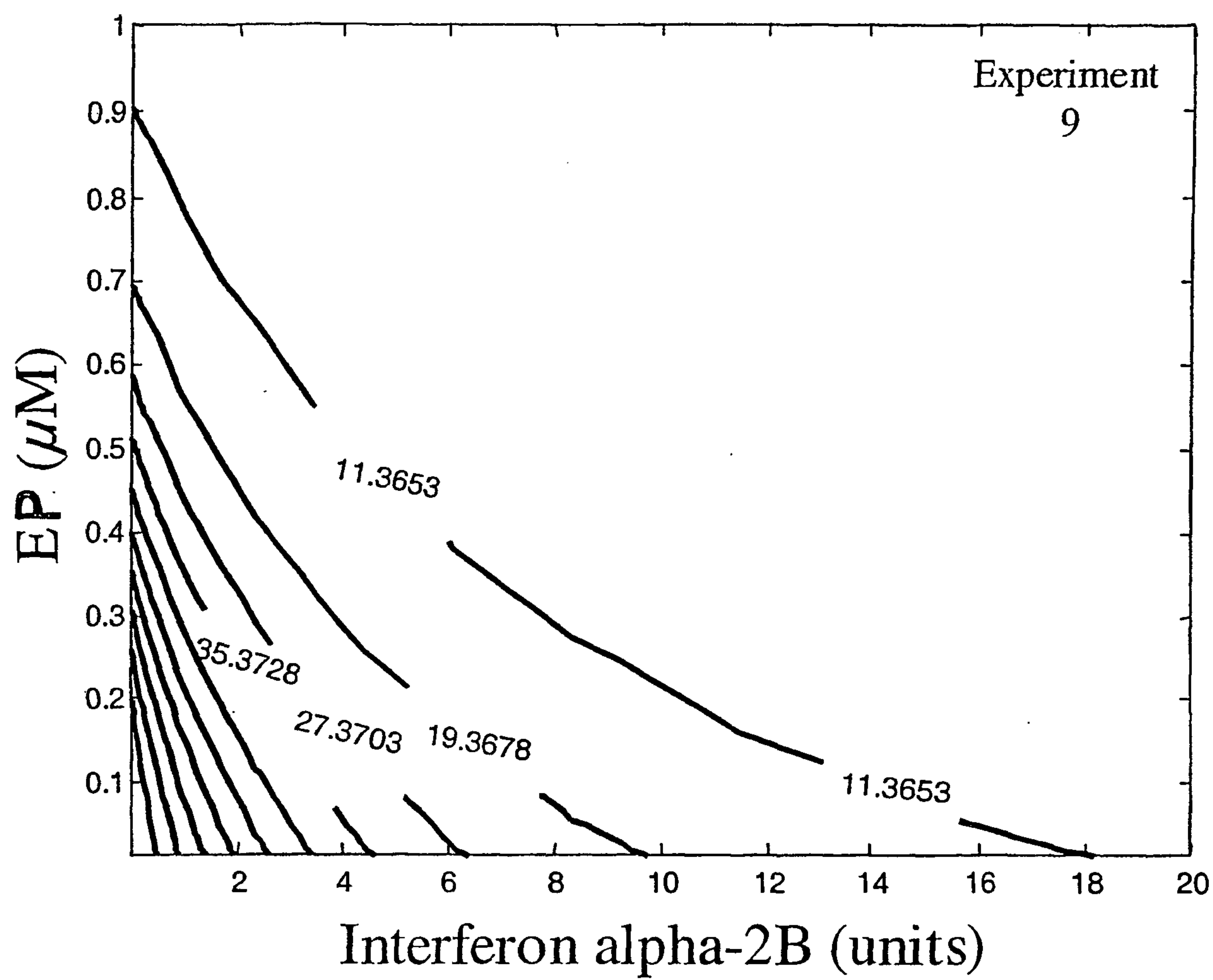
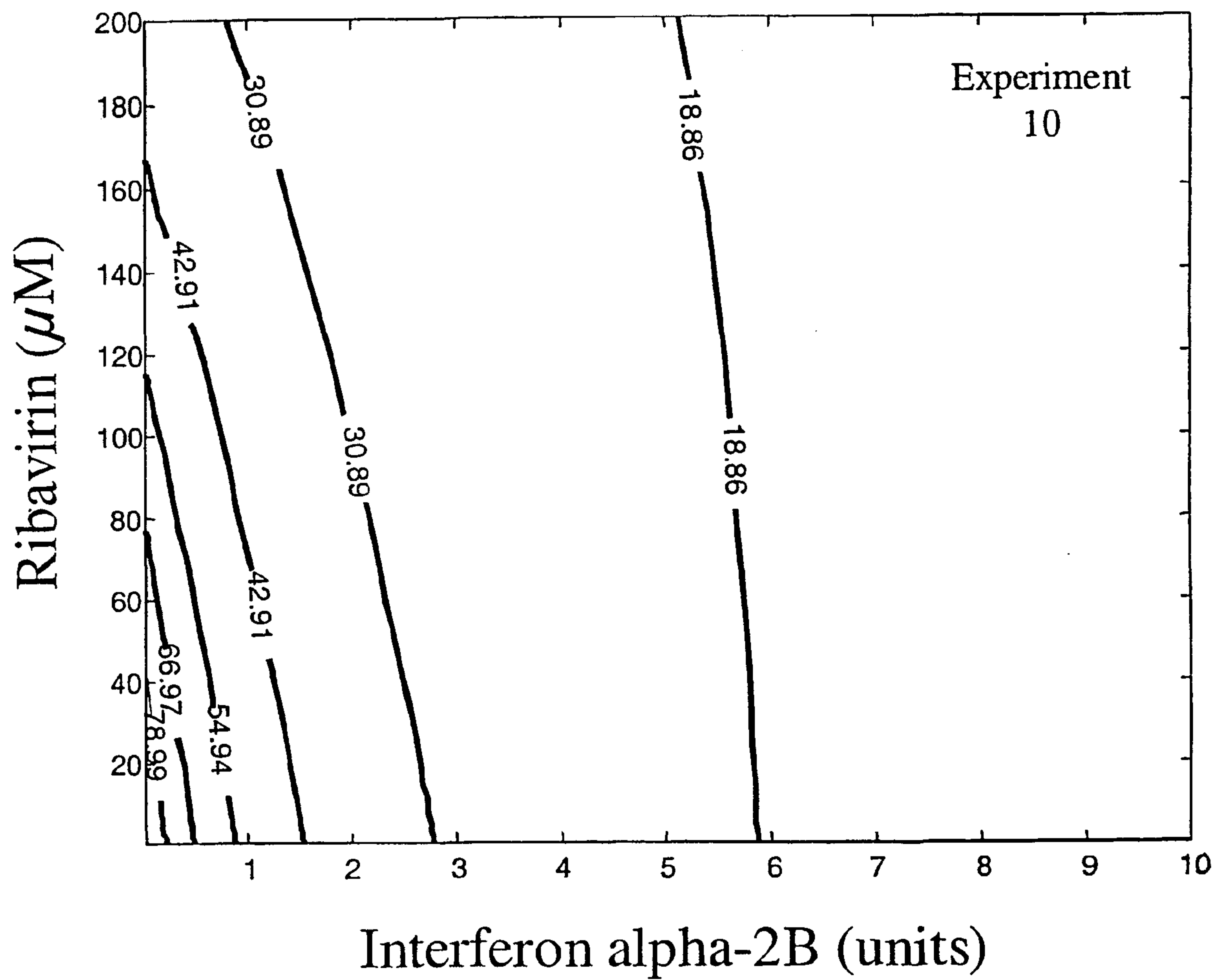


Fig 13.



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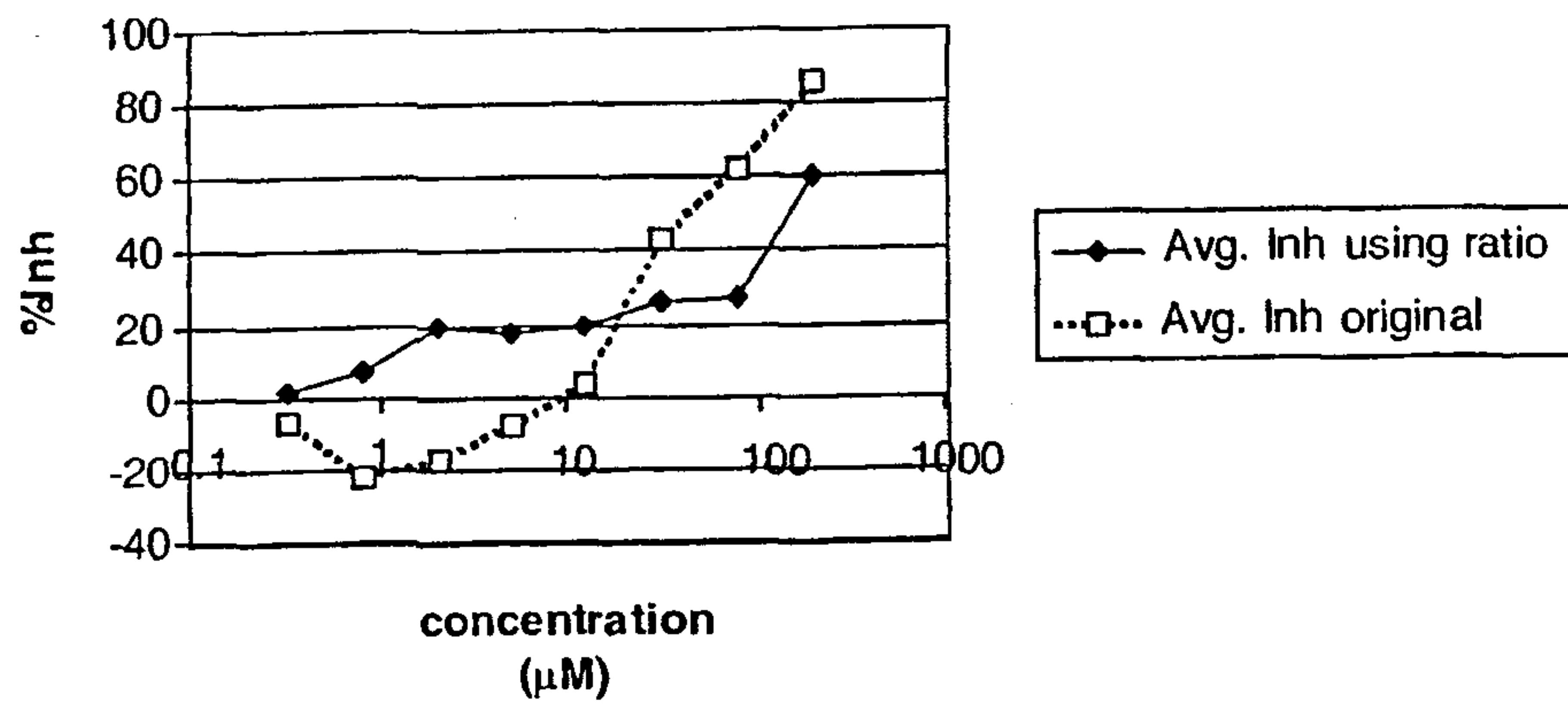
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Fig. 14

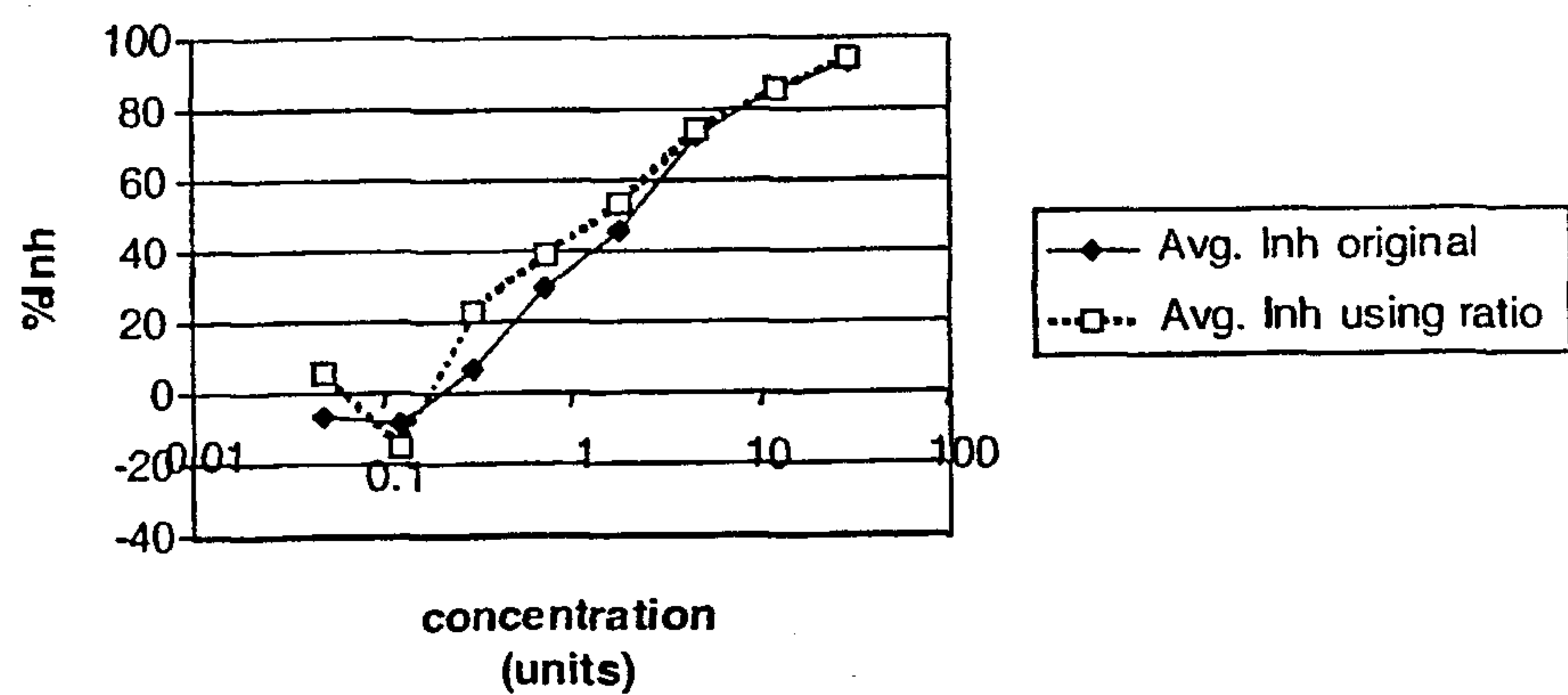
A

Ribavirin Alone



B

Interferon alpha-2B Alone



Combination treatment with Interferon alpha-2B and Compound CU

