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(71) Demandeur/Applicant:
VERTEX PHARMACEUTICALS INCORPORATED, US
(72) Inventeurs/Inventors:
FARMER, LUC, US;
PITLIK, JANOS, US;
PERNI, ROBERT, US;
COURTNEY, LAWRENCE, US;
VAN DRIE, JOHN, US
(74) Agent: SMART & BIGGAR

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(54) Title: BRIDGED BICYCLIC SERINE PROTEASE INHIBITORS

(57) **Abrégé/Abstract:**

The present invention relates to peptidomimetic compounds which inhibit serine protease activity, particularly the activity of hepatitis c virus NS3-NS4A protease. As such, they act by interfering with the life cycle of the hepatitis c virus and are also useful as antiviral agents. The compounds of this invention have a bridged bicyclic moiety at the P2 position. The invention further relates to compositions comprising these compounds either for ex vivo use or for administration to a patient suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a patient by administering a composition comprising a compound of this invention.



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(71) Applicant (*for all designated States except US*): **VERTEX PHARMACEUTICALS INCORPORATED** [US/US];
Patent Department, 130 Waverly Street, Cambridge, MA 02139-4242 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **FARMER, Luc** [CA/US]; 19 Howe Lane, Foxborough, MA 02035 (US). **PITLIK, Janos** [HU/US]; 1 Robin Circle, Westborough, MA 01581 (US). **PERNI, Robert** [US/US]; 130 Robert Road, Marlborough, MA 01752 (US). **COURTNEY, Lawrence** [US/US]; 5-5 Kingson Lane, Medway, MA 02051 (US). **VAN DRIE, John** [US/US]; 34 Stinson Road, Andover, MA 01810 (US).

(74) Agents: **DIXON, Lisa** et al.; Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139-4242 (US).

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(54) Title: BRIDGED BICYCLIC SERINE PROTEASE INHIBITORS

(57) Abstract: The present invention relates to peptidomimetic compounds which inhibit serine protease activity, particularly the activity of hepatitis c virus NS3-NS4A protease. As such, they act by interfering with the life cycle of the hepatitis c virus and are also useful as antiviral agents. The compounds of this invention have a bridged bicyclic moiety at the P2 position. The invention further relates to compositions comprising these compounds either for ex vivo use or for administration to a patient suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a patient by administering a composition comprising a compound of this invention.



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BRIDGED BICYCLIC SERINE PROTEASE INHIBITORS5 TECHNICAL FIELD OF THE INVENTION

The present invention relates to peptidomimetic compounds which inhibit serine protease activity, particularly the activity of hepatitis C virus NS3-NS4A protease. As such, they act by interfering with the life
10 cycle of the hepatitis C virus and are also useful as antiviral agents. The compounds of this invention are characterized by a bridged bicyclic moiety at the P2 position. The invention further relates to compositions comprising these compounds either for ex vivo use or for
15 administration to a patient suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a patient by administering a composition comprising a compound of this invention.

BACKGROUND OF THE INVENTION

20 Infection by hepatitis C virus ("HCV") is a compelling human medical problem. HCV is recognized as the causative agent for most cases of non-A, non-B hepatitis, with an estimated human seroprevalence of 3% globally [A. Alberti et al., "Natural History of
25 Hepatitis C," J. Hepatology, 31., (Suppl. 1), pp. 17-24 (1999)]. Nearly four million individuals may be infected in the United States alone [M..J. Alter et al., "The Epidemiology of Viral Hepatitis in the United States, Gastroenterol. Clin. North Am., 23, pp. 437-455 (1994);
30 M. J. Alter "Hepatitis C Virus Infection in the United States," J. Hepatology, 31., (Suppl. 1), pp. 88-91 (1999)].

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Upon first exposure to HCV only about 20% of infected individuals develop acute clinical hepatitis while others appear to resolve the infection spontaneously. In almost 70% of instances, however, the virus establishes a chronic infection that persists for decades [S. Iwarson, "The Natural Course of Chronic Hepatitis," FEMS Microbiology Reviews, 14, pp. 201-204 (1994); D. Lavanchy, "Global Surveillance and Control of Hepatitis C," J. Viral Hepatitis, 6, pp. 35-47 (1999)]. This usually results in recurrent and progressively worsening liver inflammation, which often leads to more severe disease states such as cirrhosis and hepatocellular carcinoma [M.C. Kew, "Hepatitis C and Hepatocellular Carcinoma", FEMS Microbiology Reviews, 14, pp. 211-220 (1994); I. Saito et. al., "Hepatitis C Virus Infection is Associated with the Development of Hepatocellular Carcinoma," Proc. Natl. Acad. Sci. USA, 87, pp. 6547-6549 (1990)]. Unfortunately, there are no broadly effective treatments for the debilitating progression of chronic HCV.

The HCV genome encodes 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, pp. 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, pp. 9524-9528 (1990); A. Takamizawa et. al., "Structure and Organization of the Hepatitis C Virus Genome Isolated From Human Carriers," J. Virol., 65, pp. 1105-1113 (1991)]. The HCV nonstructural (NS) proteins are presumed to provide the essential catalytic machinery for

- 3 -

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, pp. 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, pp. 2832-2843 (1993); A. Grakoui et. al., "Expression and Identification of Hepatitis C Virus Polyprotein Cleavage Products," J. Virol., 67, pp. 1385-1395 (1993); L. Tomei et. al., "NS3 is a serine protease required for processing of hepatitis C virus polyprotein", J. Virol., 67, pp. 4017-4026 (1993)].

The HCV NS protein 3 (NS3) contains a serine protease activity that helps process the majority of the viral enzymes, and is thus considered essential for viral replication and infectivity. It is known that mutations in the yellow fever virus NS3 protease decreases viral infectivity [Chambers, T.J. 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, pp. 8898-8902 (1990)]. 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, pp. 8147-8157 (1994)].

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The HCV NS3 serine protease and its associated cofactor, NS4A, helps process all of the viral enzymes, and is thus considered essential for viral replication. This processing appears to be analogous to that carried
5 out by the human immunodeficiency virus aspartyl protease, which is also involved in viral enzyme processing HIV protease inhibitors, which inhibit viral protein processing are potent antiviral agents in man, indicating that interrupting this stage of the viral life
10 cycle results in therapeutically active agents. Consequently it is an attractive target for drug discovery.

Several potential HCV protease inhibitors have been described in the prior art [PCT publication Nos. WO
15 00/09558, WO 00/09543, WO 99/64442, WO 99/07733, WO 99/07734, WO 99/50230, WO 98/46630, WO 98/17679 and WO 97/43310, United States Patent 5,990,276, M. Llinas-Brunet et al., Bioorg. Med. Chem. Lett., 8, pp. 1713-18 (1998); W. Han et al., Bioorg. Med. Chem. Lett., 10, 711-
20 13 (2000); R. Dunsdon et al., Bioorg. Med. Chem. Lett., 10, pp. 1571-79 (2000); M. Llinas-Brunet et al., Bioorg. Med. Chem. Lett., 10, pp. 2267-70 (2000); and S. LaPlante et al., Bioorg. Med. Chem. Lett., 10, pp. 2271-74 (2000)]. Unfortunately, there are no serine protease
25 inhibitors available currently as anti-HCV agents.

Furthermore, the current understanding of HCV has not led to any other satisfactory anti-HCV agents or treatments. The only established therapy for HCV disease is interferon treatment. However, interferons have
30 significant side effects [M. A. Wlaker et al., "Hepatitis C Virus: An Overview of Current Approaches and Progress," DDT, 4, pp. 518-29 (1999); D. Moradpour et

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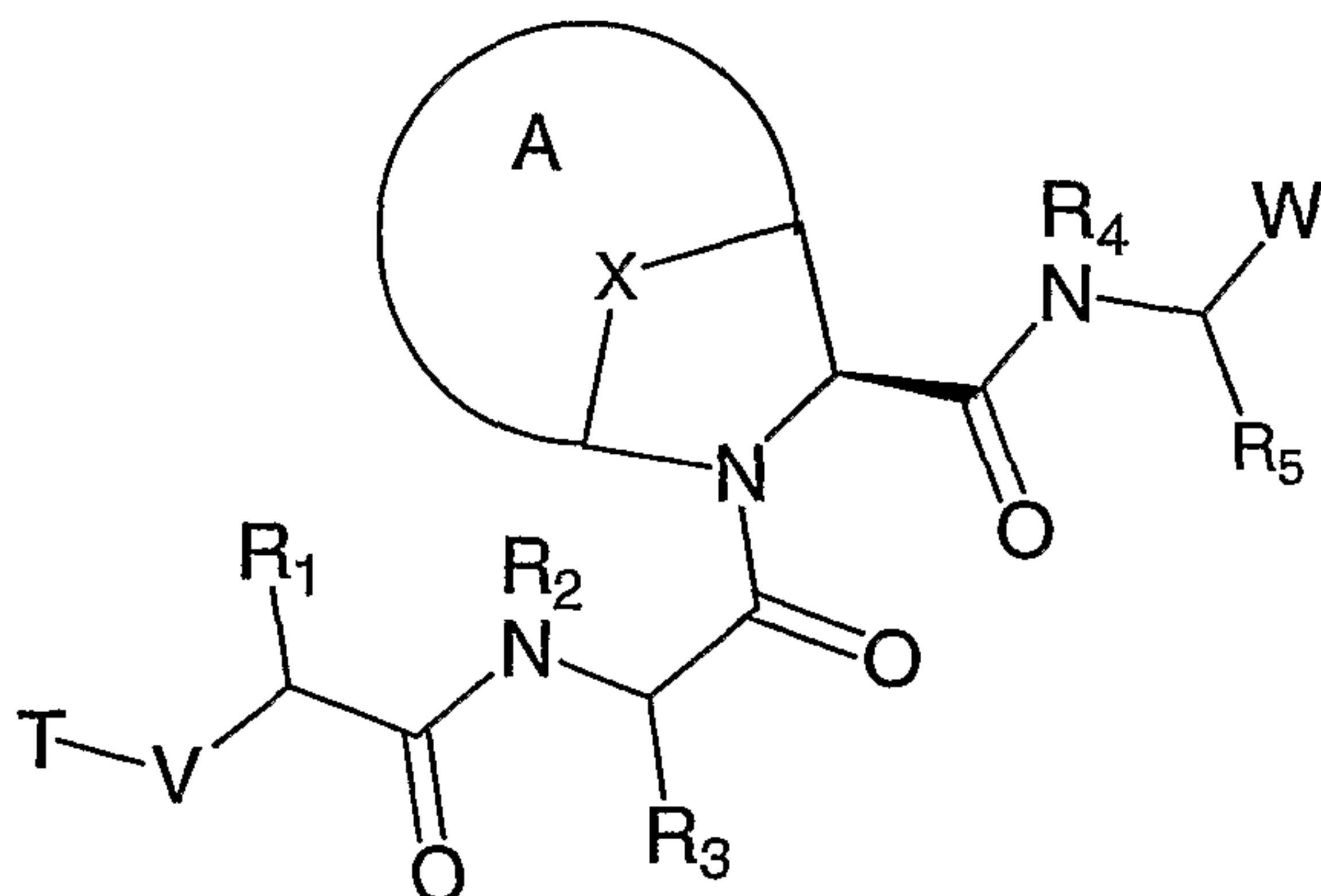
al., "Current and Evolving Therapies for Hepatitis C,"
Eur. J. Gastroenterol. Hepatol., 11, pp. 1199-1202
 (1999); H. L. A. Janssen et al. "Suicide Associated with
 Alfa-Interferon Therapy for Chronic Viral Hepatitis," J.
 5 Hepatol., 21, pp. 241-243 (1994); P.F. Renault et al.,
 "Side Effects of Alpha Interferon," Seminars in Liver
Disease, 9, pp. 273-277. (1989)] and induce long term
 remission in only a fraction (~ 25%) of cases [O.
 Weiland, "Interferon Therapy in Chronic Hepatitis C Virus
 10 Infection" , FEMS Microbiol. Rev., 14, pp. 279-288
 (1994)]. Moreover, the prospects for effective anti-HCV
 vaccines remain uncertain.

Thus, there is a need for more effective anti-
 HCV therapies. Such inhibitors would have therapeutic
 15 potential as protease inhibitors, particularly as serine
 protease inhibitors, and more particularly as HCV NS3
 protease inhibitors. Specifically, such compounds may be
 useful as antiviral agents, particularly as anti-HCV
 agents.

20

SUMMARY OF THE INVENTION

The present invention solves the problem set
 forth above by providing a compound of formula I:



25

(I)

- 6 -

wherein:

A, together with X and the atoms to which X is bound, is a 4- to 7-membered aromatic or non-aromatic ring having up to 4 heteroatoms independently selected from N, NH, O, SO, or SO₂; wherein said ring is optionally fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)heterocyclyl; wherein A has up to 3 substituents selected independently from J;

X is -[CH₂]_o-, -[CJ'J']_o-, -[CH₂]_m-O-, -[CH₂]_m-S(O)₂-, -[CH₂]_m-SO-, -[CH₂]_m-S-, -[CR₂₀R₂₀]_m-NR₂₁-, or -[CR₂₀R₂₀]_m-NJ''-, wherein:

R₂₁ is hydrogen or -C(O)-O-R₂₂;

o is 1 or 2;

R₂₂ is -(C1-C6)alkyl, -(C2-C6)alkenyl, or -(C2-C6)alkynyl;

m is 0 or 1;

J is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

J' is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

J'' is -OR', -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂, wherein each R' is independently:

hydrogen,

-(C1-C12) aliphatic,

-(C3-C10)cycloalkyl or -cycloalkenyl,

-(C1-C12)aliphatic-[(C3-C10)cycloalkyl or -cycloalkenyl],

-(C6-C10)aryl,

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- (C1-C12) aliphatic- (C6-C10) aryl,
- (C3-C10) heterocyclyl,
- (C1-C12) aliphatic- (C6-C10) heterocyclyl,
- (C5-C10) -heteroaryl, or
- 5 - (C1-C12) -aliphatic- (C5-C10) heteroaryl;

R₁ and R₃ are independently:

- (C1-C12) aliphatic,
- (C3-C10) -cycloalkyl or -cycloalkenyl,
- (C1-C12) -aliphatic- [(C3-C10) -cycloalkyl or
- 10 -cycloalkenyl],
- (C6-C10) -aryl,
- (C1-C12) aliphatic- (C6-C10) aryl,
- (C3-C10) -heterocyclyl,
- (C1-C12) aliphatic- (C6-C10) heterocyclyl,
- 15 - (C5-C10) heteroaryl, or
- (C1-C12) aliphatic- (C5-C10) heteroaryl,

wherein each of R₁ and R₃ is independently and optionally substituted with up to 3 substituents independently selected from J;

20 wherein up to 3 aliphatic carbon atoms in R₁ and R₃ may be replaced by a heteroatom selected from O, NH, S, SO, and SO₂ in a chemically stable arrangement;

R₂ and R₄ are independently

- 25 hydrogen,
- (C1-C12) aliphatic,
- (C1-C12) aliphatic- (C3-C10) cycloalkyl, or
- (C1-C12) aliphatic- (C6-C10) aryl,

wherein each of R₂ and R₄ is independently and optionally substituted with up to 3 substituents independently selected from J;

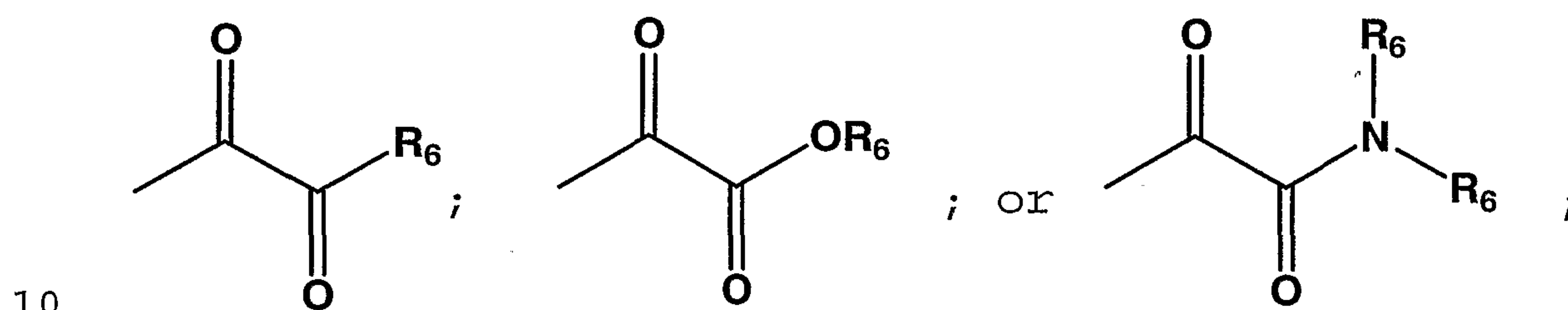
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wherein up to two aliphatic carbon atoms in R_2 and R_4 may be replaced by a heteroatom selected from O, NH, S, SO, and SO_2 ;

R_5 is -(C1-C12)aliphatic, wherein any hydrogen is
 5 optionally replaced with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom of R_5 is optionally substituted with sulfhydryl or hydroxy;

W is: -C(O)OH;



wherein each R_6 is independently:

- hydrogen,
- (C1-C12)aliphatic,
- (C6-C10)aryl,
- 15 -(C6-C10)aryl-(C1-C12)aliphatic,
- (C3-C10)-cycloalkyl or -cycloalkenyl,
- (C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or -cycloalkenyl],
- (C3-C10)heterocyclyl,
- 20 -(C3-C10)heterocyclyl-(C1-C12)aliphatic,
- (C5-C10)heteroaryl, or
- (C1-C12)aliphatic-(C5-C10)heteroaryl, or

two R_6 groups, which are bound to the same nitrogen atom, form together with that nitrogen atom, a
 25 -(C3-C10)heterocyclic ring;

wherein R_6 is optionally substituted with up to 3 J substituents or with a suitable electron withdrawing group;

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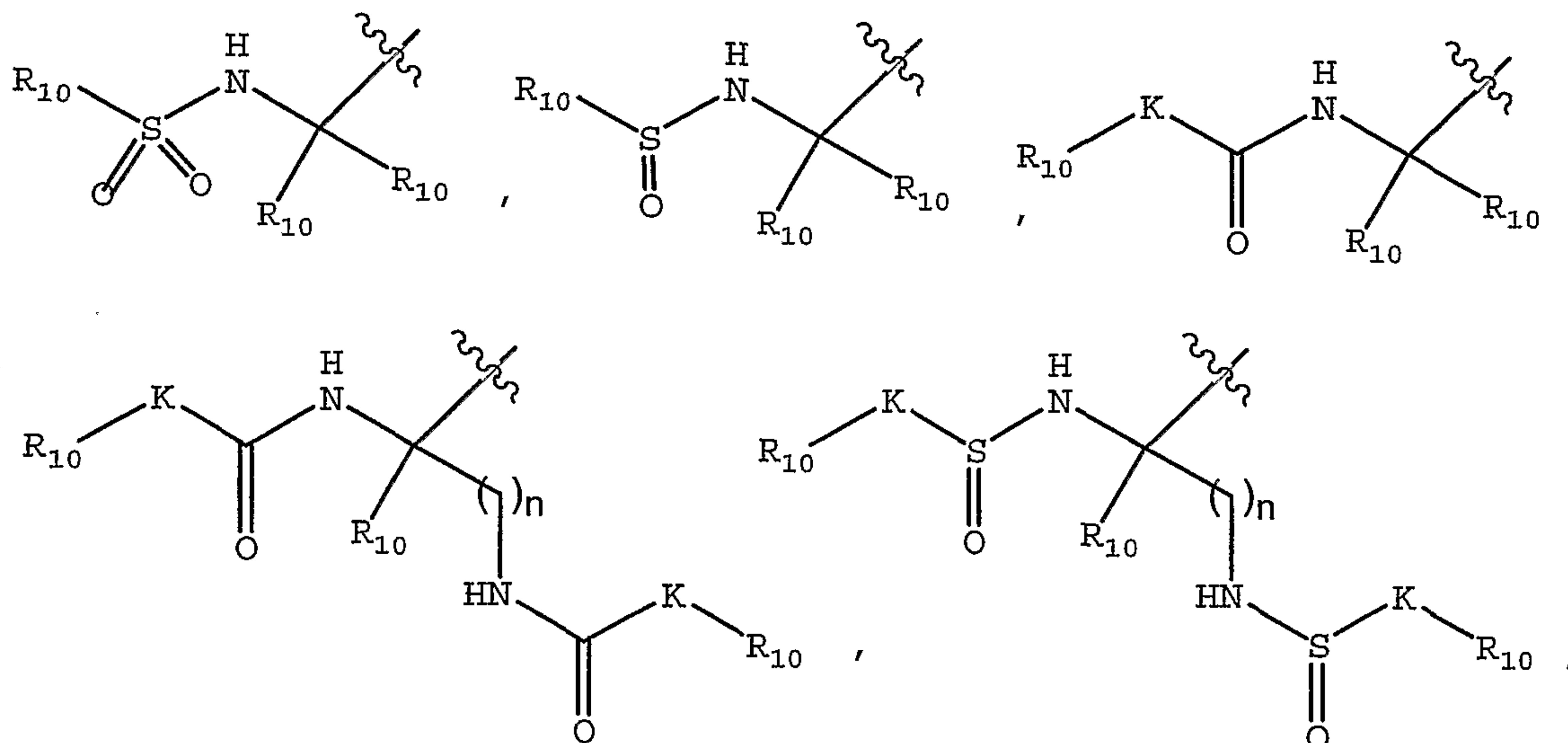
V is $-C(O)N(R_8)-$, $-S(O)N(R_8)-$, $-S(O)_2N(R_8)-$, a bond,
 $-CH(R_8)-$, $-N(R_8)-$, $-O-$, $-O-CH(R_8)-$, $-S-$, $-S-CH(R_8)-$, $-C(O)-$,
 $-C(O)-O-$, $-C(O)-S-$, $-C(O)-CHR_8-$, $-S(O)-$, $-S(O)-CH(R_8)-$,
 $-S(O)-N(R_8)-CHR_8-$, $-S(O)_2-$, $-S(O)_2-CH(R_8)-$, or $-S(O)_2-N(R_8)-$
 5 CHR_8 ;

wherein R_8 is hydrogen or $-(C1-C12)$ aliphatic;

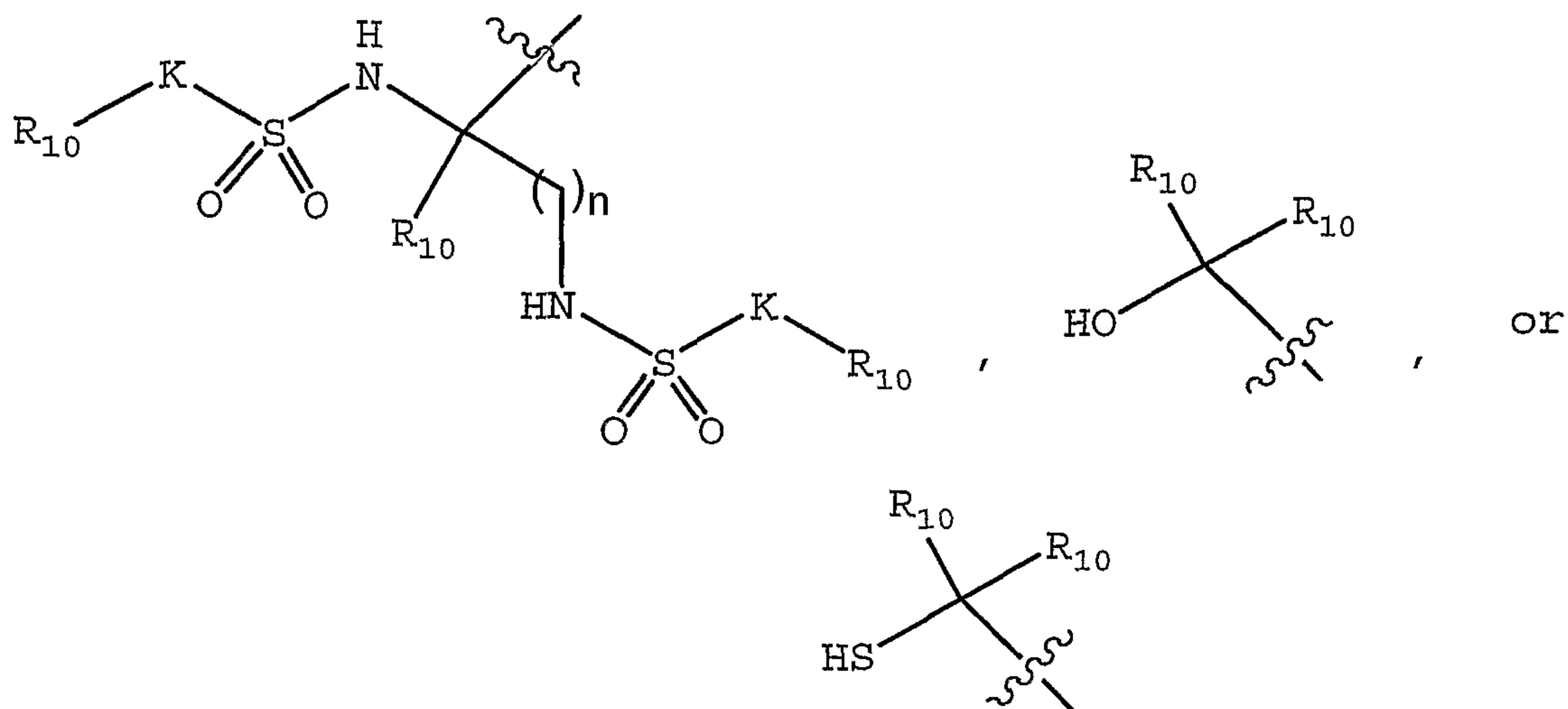
T is:

- (C6-C10) aryl,
- (C1-C12) aliphatic- (C6-C10) aryl,
- 10 - (C3-C10)-cycloalkyl or -cycloalkenyl,
- (C1-C12) aliphatic- [(C3-C10)-cycloalkyl or
 -cycloalkenyl],
- (C3-C10) heterocyclyl,
- (C1-C12) aliphatic- (C3-C10) heterocyclyl,
- 15 - (C5-C10) heteroaryl, or
- (C1-C12) aliphatic- (C5-C10) heteroaryl; or

T is:



- 10 -



wherein:

R_{10} is:

5

hydrogen,

-(C1-C12)aliphatic,

-(C6-C10)aryl,

-(C1-C12)aliphatic-(C6-C10)aryl,

-(C3-C10)-cycloalkyl or -cycloalkenyl,

10

-(C1-C12)aliphatic-[(C3-C10)-cycloalkyl or
-cycloalkenyl],

-(C3-C10)heterocyclyl,

-(C1-C12)aliphatic-(C3-C10)heterocyclyl,

-(C5-C10)heteroaryl, or

15

-(C1-C12)aliphatic-(C5-C10)heteroaryl,

wherein each T is optionally substituted with up to
3 J substituents;

K is a bond, -(C1-C12)aliphatic, -O-, -S-, -NR₉-,
-C(O)-, or -C(O)-NR₉-, wherein R₉ is hydrogen or -(C1-
20 C12)aliphatic;

n is 1-3; and

each R₂₀ is independently hydrogen, -(C1-C6)aliphatic
or -O-((C1-C6)aliphatic); or each R₂₀ is taken together

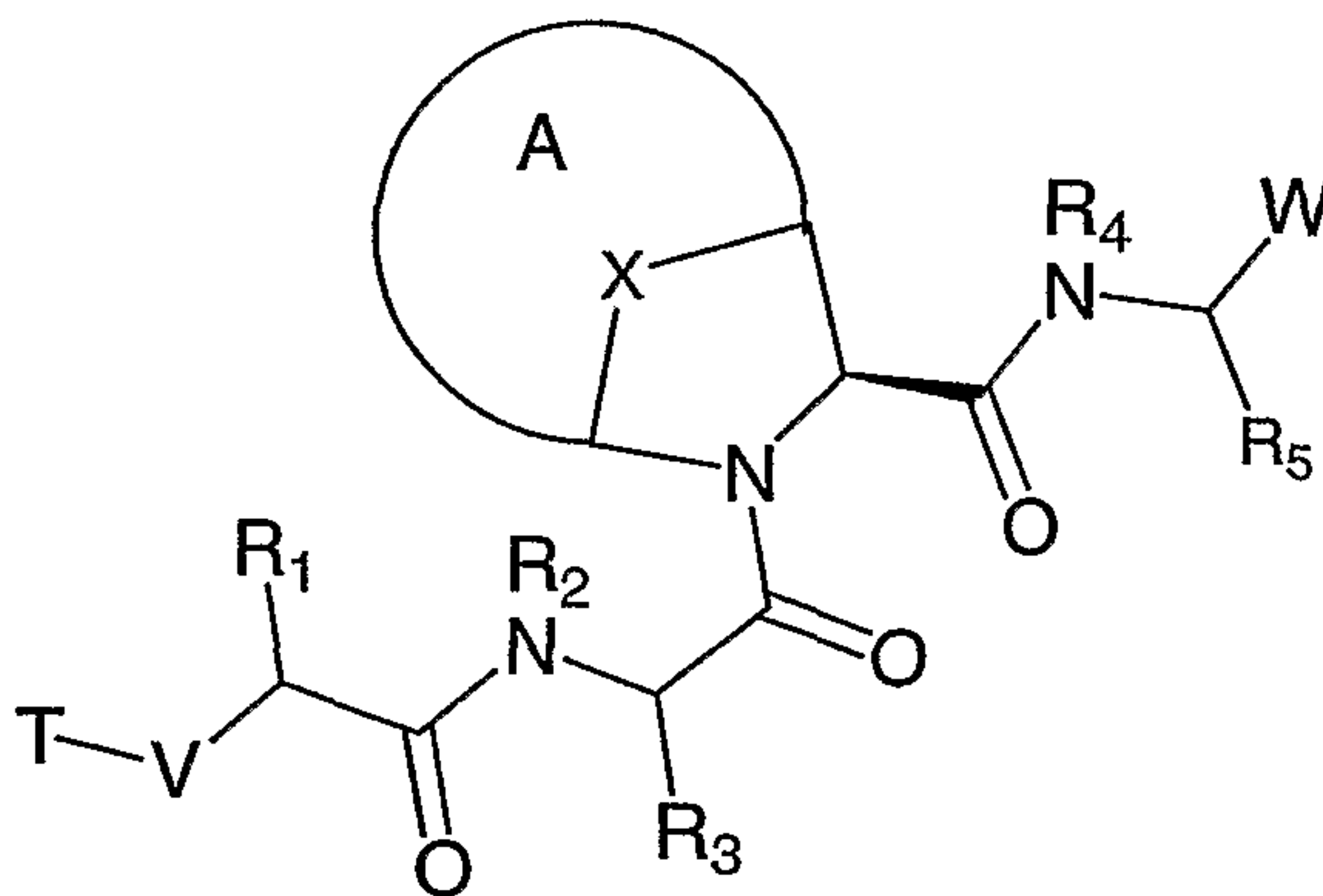
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with the carbon atoms to which they are bound to form a (C3-C6)cycloalkyl.

The invention also relates to compositions that comprise the above compound and the use thereof. Such compositions may be useful to pre-treat invasive devices to be inserted into a patient, to treat biologicals, such as blood, prior to administration to a patient, and for direct administration to a patient. In each case the composition will be used to inhibit HCV replication and to lessen the risk of or the severity of HCV infection.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound of



formula (I):

(I)

wherein:

A, together with X and the atoms to which X is bound, is a 4- to 7-membered aromatic or non-aromatic ring having up to 4 heteroatoms independently selected from N, NH, O, SO, or SO₂; wherein said ring is optionally fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)heterocyclyl; wherein A has up to 3 substituents selected independently from J;

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X is $-\text{[CH}_2\text{]}_o-$, $-\text{[CJ}'\text{J}']_o-$, $-\text{[CH}_2\text{]}_m-\text{O}-$, $-\text{[CH}_2\text{]}_m-\text{S}(\text{O})_2-$,
 $-\text{[CH}_2\text{]}_m-\text{SO}-$, $-\text{[CH}_2\text{]}_m-\text{S}-$, $-\text{[CR}_{20}\text{R}_{20}]_m-\text{NR}_{21}-$, or $-\text{[CR}_{20}\text{R}_{20}]_m-$
 $\text{NJ}''-$, wherein:

R_{21} is hydrogen or $-\text{C}(\text{O})-\text{O}-\text{R}_{22}$;

5 o is 1 or 2;

R_{22} is $-(\text{C1-C6})$ alkyl, $-(\text{C2-C6})$ alkenyl, or
 $-(\text{C2-C6})$ alkynyl;

m is 0 or 1;

J is halogen, $-\text{OR}'$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{R}'$, oxo,
 10 $-\text{OR}'$, $-\text{O-benzyl}$, $-\text{O-phenyl}$, 1,2-methylenedioxy, $-\text{N}(\text{R}')_2$,
 $-\text{SR}'$, $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{C}(\text{O})\text{R}'$, $-\text{COOR}'$, or $-\text{CON}(\text{R}')_2$;

J' is halogen, $-\text{OR}'$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{R}'$, $-\text{OR}'$,
 $-\text{O-benzyl}$, $-\text{O-phenyl}$, 1,2-methylenedioxy, $-\text{N}(\text{R}')_2$, $-\text{SR}'$,
 $-\text{SOR}'$, $-\text{SO}_2\text{R}'$, $-\text{C}(\text{O})\text{R}'$, $-\text{COOR}'$, or $-\text{CON}(\text{R}')_2$;

15 J'' is $-\text{OR}'$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{R}'$, oxo, $-\text{OR}'$, $-\text{O-benzyl}$,
 $-\text{O-phenyl}$, 1,2-methylenedioxy, $-\text{N}(\text{R}')_2$, $-\text{SR}'$, $-\text{SOR}'$,
 $-\text{SO}_2\text{R}'$, $-\text{C}(\text{O})\text{R}'$, $-\text{COOR}'$, or $-\text{CON}(\text{R}')_2$, wherein each R' is
independently:

hydrogen,

20 $-(\text{C1-C12})$ aliphatic,
 $-(\text{C3-C10})$ cycloalkyl or $-\text{cycloalkenyl}$,
 $-(\text{C1-C12})$ aliphatic- $[(\text{C3-C10})$ cycloalkyl or
 $-\text{cycloalkenyl}]$,

$-(\text{C6-C10})$ aryl,
 25 $-(\text{C1-C12})$ aliphatic- (C6-C10) aryl,
 $-(\text{C3-C10})$ heterocyclyl,
 $-(\text{C1-C12})$ aliphatic- (C6-C10) heterocyclyl,
 $-(\text{C5-C10})$ -heteroaryl, or
 $-(\text{C1-C12})$ -aliphatic- (C5-C10) heteroaryl;

30 R_1 and R_3 are independently:

$-(\text{C1-C12})$ aliphatic,
 $-(\text{C3-C10})$ -cycloalkyl or $-\text{cycloalkenyl}$,

- 13 -

- (C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or
-cycloalkenyl],

- (C6-C10)-aryl,

(C1-C12)aliphatic-(C6-C10)aryl,

5 - (C3-C10)-heterocyclyl,

- (C1-C12)aliphatic-(C6-C10)heterocyclyl,

- (C5-C10)heteroaryl, or

- (C1-C12)aliphatic-(C5-C10)heteroaryl,

10 wherein each of R₁ and R₃ is independently and
optionally substituted with up to 3 substituents
independently selected from J;

15 wherein up to 3 aliphatic carbon atoms in R₁ and
R₃ may be replaced by a heteroatom selected from O,
NH, S, SO, and SO₂ in a chemically stable
arrangement;

R₂ and R₄ are independently

hydrogen,

- (C1-C12)aliphatic,

- (C1-C12)aliphatic-(C3-C10)cycloalkyl, or

20 - (C1-C12)aliphatic-(C6-C10)aryl,

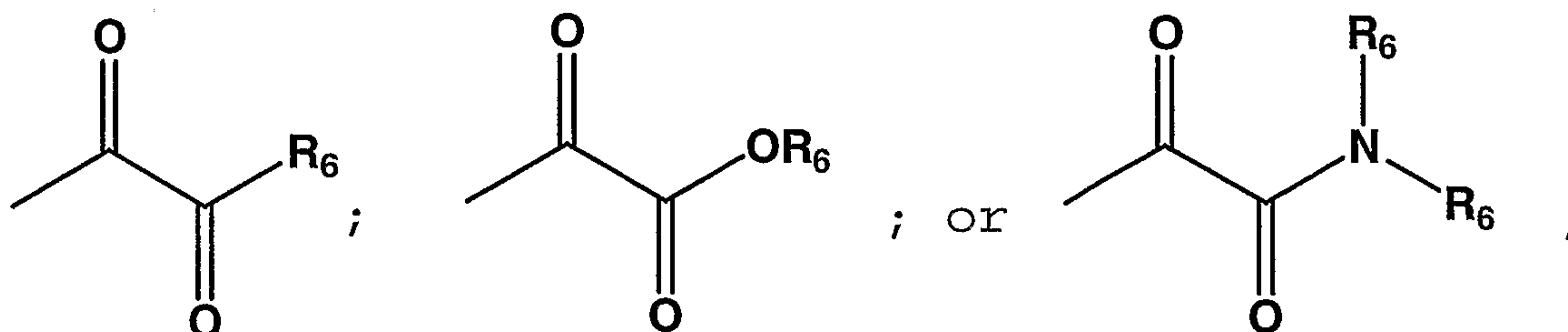
wherein each of R₂ and R₄ is independently and
optionally substituted with up to 3 substituents
independently selected from J;

25 wherein up to two aliphatic carbon atoms in R₂
and R₄ may be replaced by a heteroatom selected from
O, NH, S, SO, and SO₂;

R₅ is - (C1-C12)aliphatic, wherein any hydrogen is
optionally replaced with halogen, and wherein any
hydrogen or halogen atom bound to any terminal carbon
30 atom of R₅ is optionally substituted with sulfhydryl or
hydroxy;

W is: -C(O)OH;

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wherein each R_6 is independently:

hydrogen,

-(C1-C12)aliphatic,

5 -(C6-C10)aryl,

-(C6-C10)aryl-(C1-C12)aliphatic,

-(C3-C10)-cycloalkyl or -cycloalkenyl,

-(C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or
-cycloalkenyl],

10 -(C3-C10)heterocyclyl,

-(C3-C10)heterocyclyl-(C1-C12)aliphatic,

-(C5-C10)heteroaryl, or

-(C1-C12)aliphatic-(C5-C10)heteroaryl, or

15 two R_6 groups, which are bound to the same nitrogen
atom, form together with that nitrogen atom, a

-(C3-C10)heterocyclic ring;

wherein R_6 is optionally substituted with up to 3 J
substituents or with a suitable electron withdrawing
group;

20 V is $-C(O)N(R_8)-$, $-S(O)N(R_8)-$, $-S(O)_2N(R_8)-$, a bond,
-CH(R_8)-, $-N(R_8)-$, $-O-$, $-O-CH(R_8)-$, $-S-$, $-S-CH(R_8)-$, $-C(O)-$,
-C(O)-O-, $-C(O)-S-$, $-C(O)-CH(R_8)-$, $-S(O)-$, $-S(O)-CH(R_8)-$,
-S(O)-N(R_8)-CH(R_8), $-S(O)_2-$, $-S-(O)_2-CH(R_8)-$, or $-S(O)_2-N(R_8)-$
CH(R_8);

25 wherein R_8 is hydrogen or -(C1-C12)aliphatic;

T is:

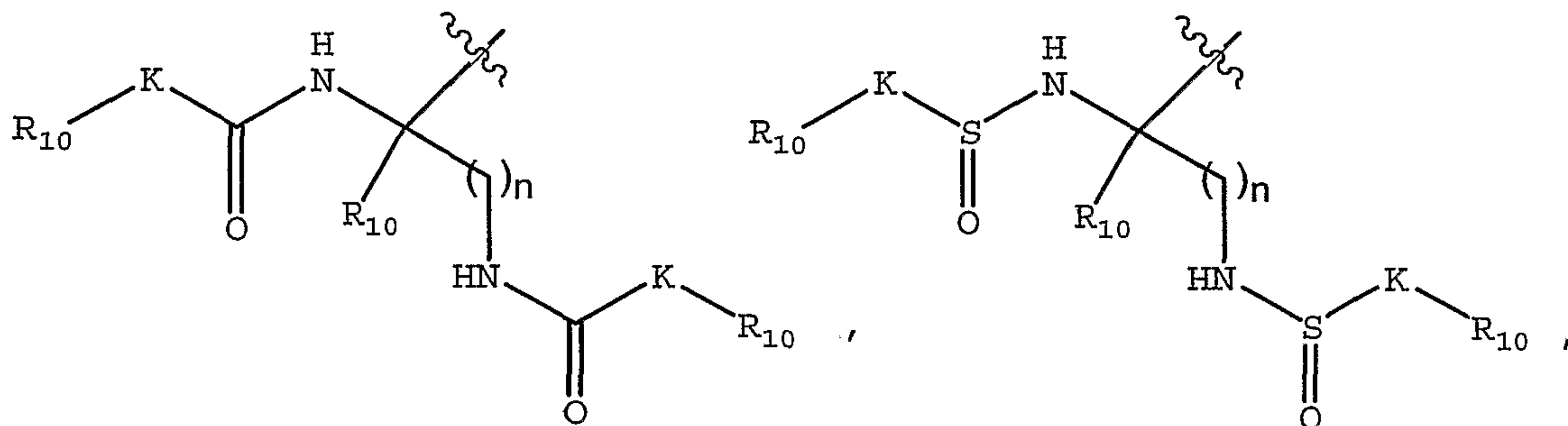
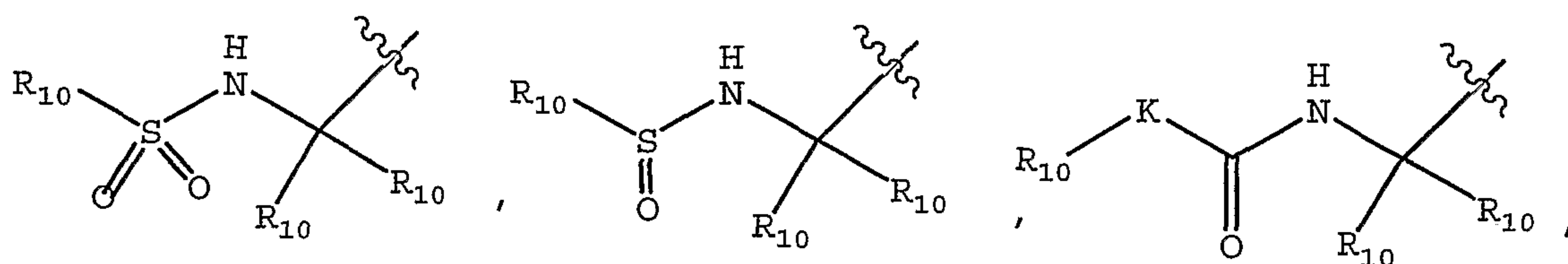
-(C6-C10)aryl,

-(C1-C12)aliphatic-(C6-C10)aryl,

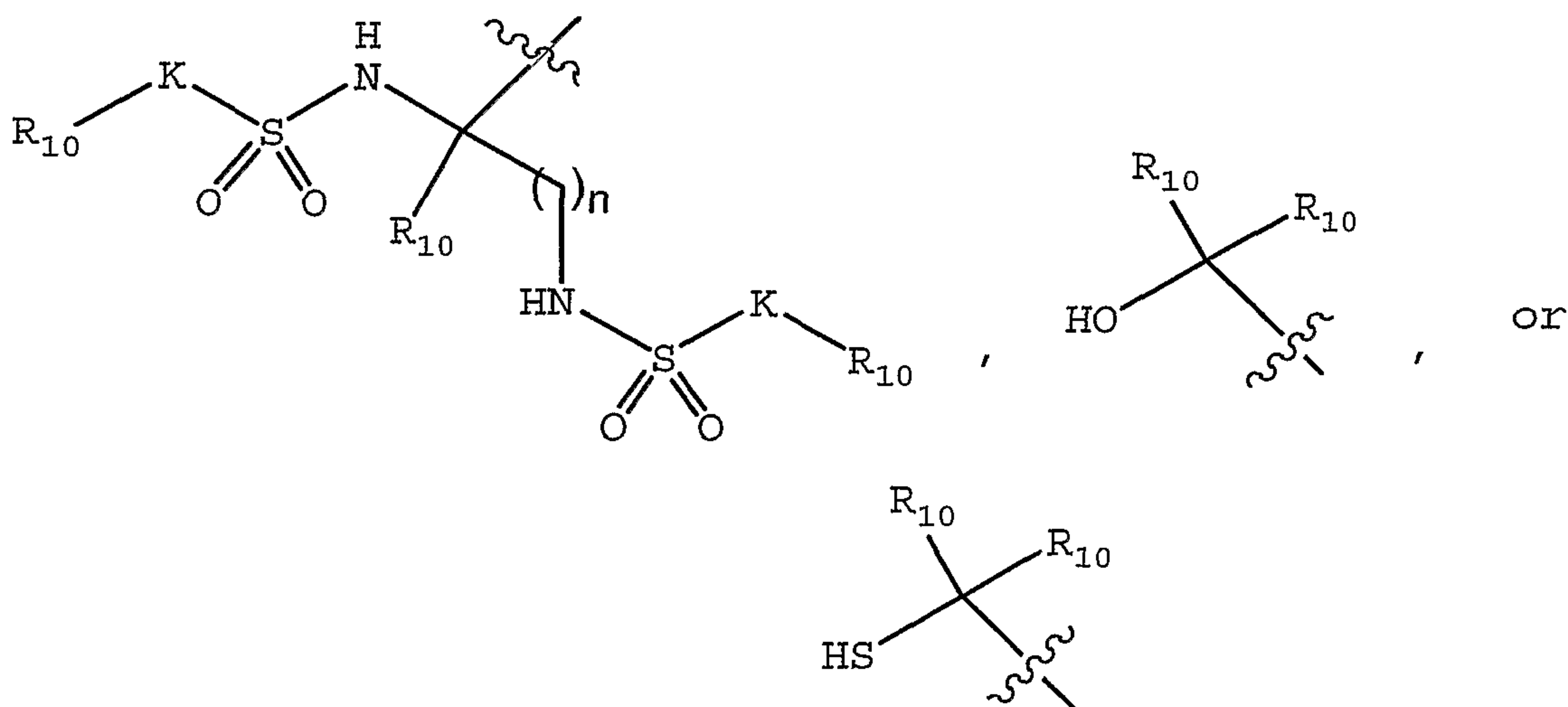
- 15 -

- (C3-C10)-cycloalkyl or -cycloalkenyl,
 - (C1-C12) aliphatic-[(C3-C10)-cycloalkyl or
 -cycloalkenyl],
 - (C3-C10) heterocyclyl,
 5 - (C1-C12) aliphatic-(C3-C10) heterocyclyl,
 - (C5-C10) heteroaryl, or
 - (C1-C12) aliphatic-(C5-C10) heteroaryl; or

T is:



10



wherein:

 R_{10} is:

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hydrogen,
- (C1-C12) aliphatic,
- (C6-C10) aryl,
- (C1-C12) aliphatic- (C6-C10) aryl,
5 - (C3-C10)-cycloalkyl or -cycloalkenyl,
- (C1-C12) aliphatic- [(C3-C10)-cycloalkyl or
-cycloalkenyl],
- (C3-C10) heterocyclyl,
- (C1-C12) aliphatic- (C3-C10) heterocyclyl,
10 - (C5-C10) heteroaryl, or
- (C1-C12) aliphatic- (C5-C10) heteroaryl,
wherein each T is optionally substituted with up to
3 J substituents;
K is a bond, - (C1-C12) aliphatic, -O-, -S-, -NR₉-,
15 -C(O)-, or -C(O)-NR₉-, wherein R₉ is hydrogen or - (C1-
C12) aliphatic;
n is 1-3; and
each R₂₀ is independently hydrogen, - (C1-C6) aliphatic
or -O- ((C1-C6) aliphatic); or each R₂₀ is taken together
20 with the carbon atoms to which they are bound to form a
(C3-C6) cycloalkyl.

DEFINITIONS

The term "aryl" as used herein means a
monocyclic or bicyclic carbocyclic aromatic ring system.
25 Phenyl is an example of a monocyclic aromatic ring
system. Bicyclic aromatic ring systems include systems
wherein both rings are aromatic, e.g., naphthyl, and
systems wherein only one of the two rings is aromatic,
e.g., tetralin.
30 The bond "---" refers to an optionally present
bond.

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The term "heterocyclyl" as used herein means a monocyclic or bicyclic non-aromatic ring system having up to 4, and preferably 1 to 3, heteroatom or heteroatom groups in each ring selected from O, N, NH, S, SO, or SO₂ in a chemically stable arrangement. In a bicyclic non-aromatic ring system embodiment of "heterocyclyl" one or both rings may contain said heteroatom or heteroatom groups.

Heterocyclic rings include 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolane, and benzodithiane.

The term "heteroaryl" as used herein means a monocyclic or bicyclic aromatic ring system having up to 4, and preferably 1 to 3, heteroatom or heteroatom groups in each ring selected from O, N, NH or S in a chemically stable arrangement. In such a bicyclic aromatic ring system embodiment of "heteroaryl":

- one or both rings may be aromatic; and

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- one or both rings may contain said heteroatom or heteroatom groups.

Heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 5 benzimidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-10 thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, purinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-15 quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

20 Each of the above aryl, heterocyclyl or heteroaryl above may contain up to 3 substituents independently selected from halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -C(O)R', -COOR' or -CON(R')₂, 25 wherein R' is independently selected from H, (C1-C6)-alkyl, (C2-C6)-alkenyl or alkynyl.

The term "aliphatic" as used herein means a straight chained or branched alkyl, alkenyl or alkynyl. It is understood that alkenyl or alkynyl embodiments need 30 at least two carbon atoms in the aliphatic chain.

The term "cycloalkyl or cycloalkenyl" refers to a monocyclic or fused or bridged bicyclic carbocyclic

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ring system that is not aromatic. Cycloalkenyl rings have one or more units of unsaturation. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, nornbornyl, adamantyl and decalin-yl.

The phrase "chemically stable arrangement" as used herein refers to a compound structure that renders the compound sufficiently stable to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive condition, for at least a week.

According to a preferred embodiment, ring A together with X and the atoms to which X is bound, has up to 3 heteroatoms independently selected from N, NH, O, SO, and SO₂.

According to a preferred embodiment, ring A together with X and the atoms to which X is bound, is a 3-6 membered carbocyclic non-aromatic or aromatic ring. More preferably, ring A, together with X and the atoms to which X is bound, is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or phenyl. Even more preferably, ring A, together with X and the atoms to which X is bound, is cyclohexyl or cyclopentyl. Most preferably, ring A, together with X and the atoms to which X is bound, is cyclohexyl.

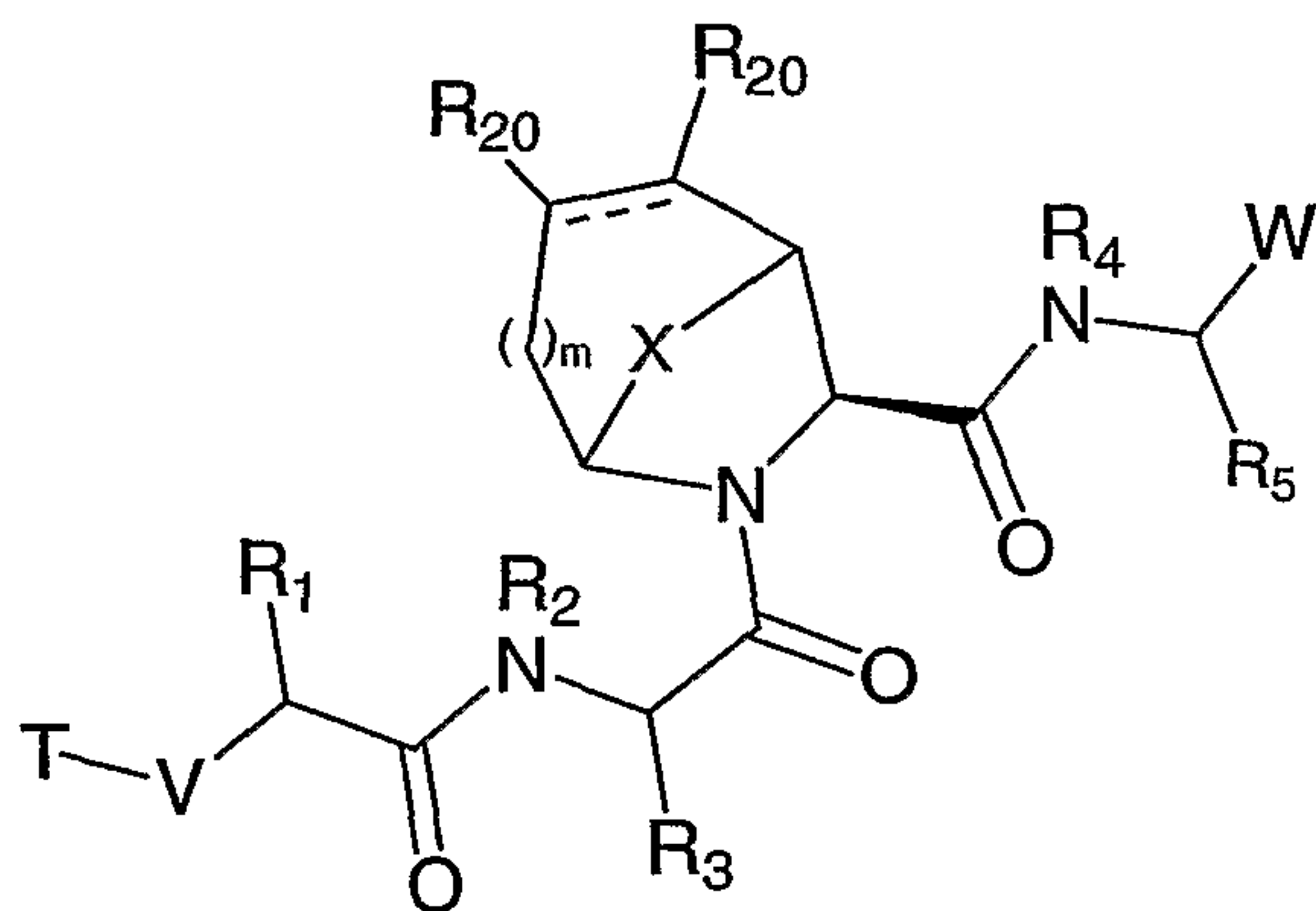
According to another preferred embodiment, ring A, together with X and the atoms to which X is bound, is a 3-6 membered heterocyclic ring. More preferably, ring A together with X and the atoms to which X is bound, is a 5-6 membered heterocyclic ring.

- 20 -

According to another preferred embodiment, ring A together with X and the atoms to which X is bound, is a 5-6 membered heteroaryl ring.

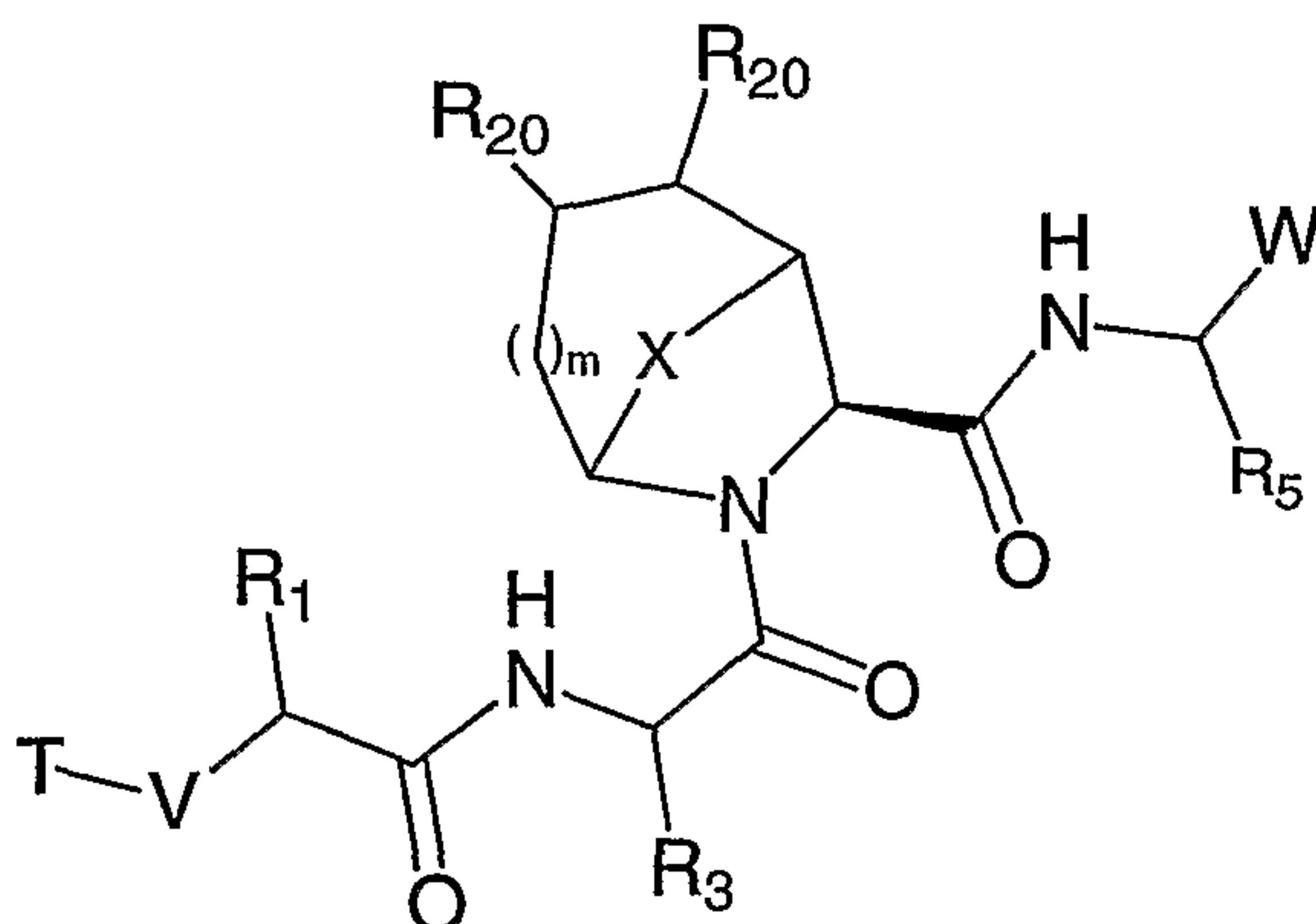
According to yet another preferred embodiment, ring A, together with X and the atoms to which X is bound, is fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)-heterocyclyl. Preferably, ring A together with X and the atoms to which X is bound, is fused to cyclohexyl, cyclopentyl, phenyl or pyridyl.

According to a preferred embodiment, compounds of the present invention have formula (IA):



wherein T, V, R₁, R₂, R₃, R₄, R₅, R₂₀, X, W, and m are as defined herein.

According to another preferred embodiment, compounds of the present invention have formula (IB):



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wherein T, V, R₁, R₃, R₅, R₂₀, X, W and m are as defined herein.

According to a preferred embodiment, V is -NH-.

According to another preferred embodiment, V is
5 -C(O)-.

According to another preferred embodiment, R₅ is C2-C3 alkyl substituted with 1-3 chlorine or fluorine.

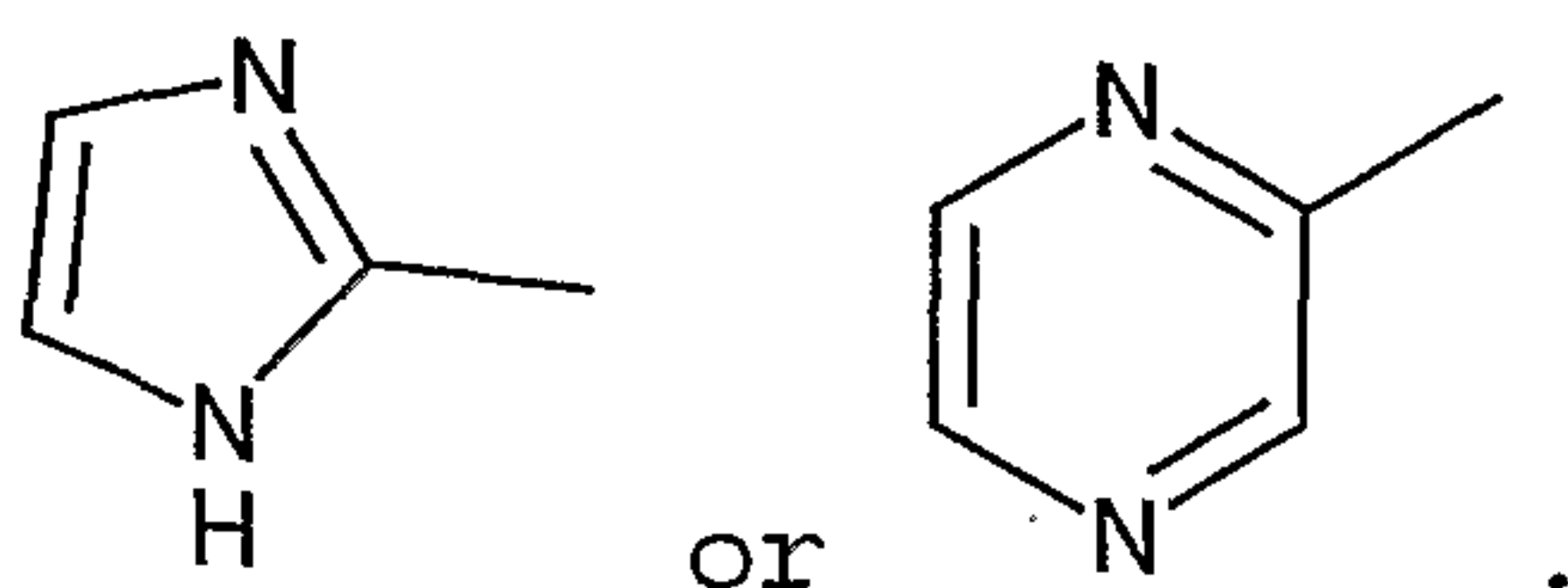
According to yet another preferred embodiment T or R⁶ is a heterocyclyl or heteroaryl, optionally having
10 up to 3 substituents as defined above.

According to yet another preferred embodiment, T is a -(C5-C10)heteroaryl.

According to yet another preferred embodiment, T is selected from 3-1H-benzimidazol-2-one, 3-(1-alkyl)-
15 benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, pyrazolynyl, 1,3-dihydro-imidazol-2-one, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 5-
20 tetrazolyl, pyrazolyl, pyrazinyl or 1,3,5-triazinyl.

Even more preferably, T or R⁷ is 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one,)²-pyrazolynyl, 1,3-dihydro-imidazol-2-one, 2-imidazolyl, 2-pyrrolyl, 2-pyrimidinyl, 5-pyrimidinyl, 5-tetrazolyl or
25 pyrazinyl.

Most preferred is when T or R⁷ is selected from:



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Preferred substituents on T or R⁷ in the above embodiments are halogen, -CF₃, -OCF₃, oxo, -COOR' or -CON(R')₂, wherein R' is as defined above.

In another preferred embodiment of the present invention, R¹ is -CH₂-CH(CH₃)-CH₃, -C(CH₃)₃, -CH(CH₃)₂, -CH(CH₃)-CH₂-CH₃ or cyclohexyl. Most preferably R¹ is cyclohexyl.

According to another preferred embodiment, R₃ is selected from -C(CH₃)₂, -CH(CH₃)₂, -CH(CH₃)-CH₂-CH₃ or cyclohexyl. More preferably, R₃ is selected from -C(CH₃)₃, or -CH(CH₃)₂.

According to yet another preferred embodiment, each R₂ is independently selected from -CH₃ or hydrogen. Even more preferred is when R₂ is hydrogen.

According to another preferred embodiment, R₅ is -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂F, -CH₂CH₂CHF₂, or -CH₂CH₂CF₃. More preferred is when R₅ is -CH₂CH₂CH₂CH₃ or -CH₂CH₂CHF₂. Most preferably R₅ is -CH₂CH₂CH₂CH₃.

According to another preferred embodiment, R₅ is -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂F, -CH₂CHF₂, or -CH₂CF₃. More preferred is when R₅ is -CH₂CH₂CH₃, or -CH₂CHF₂. Most preferably R₅ is -CH₂CH₂CH₃.

According to a preferred embodiment, W is -C(O)-C(O)-R₆. Preferably, R₆ is isopropyl.

According to another preferred embodiment, W is -C(O)-C(O)-OR₆. Preferably, R₆ is hydrogen, (C1-C12)-aliphatic, (C6-C10)-aryl, (C3-C10)-cycloalkyl or -cycloalkenyl, (C3-C10)-heterocyclyl or (C5-C10)heteroaryl. More preferably, R₆ is H or methyl.

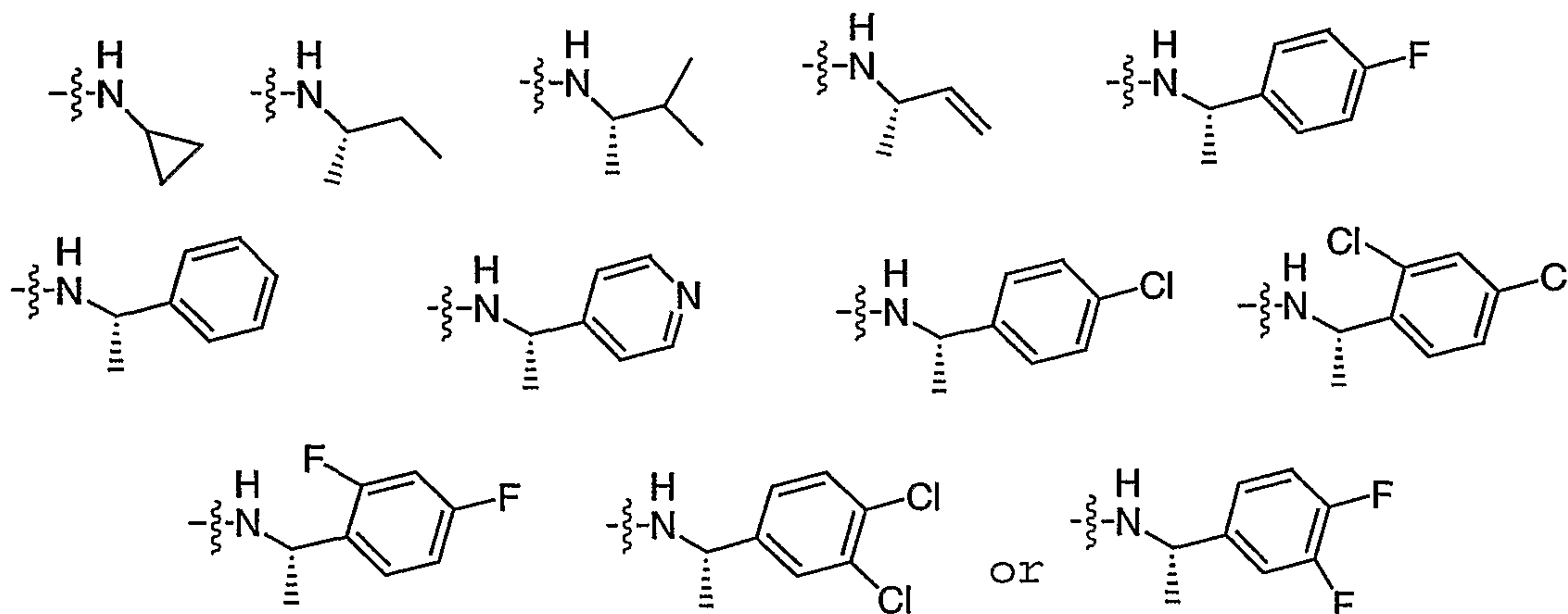
- 23 -

According to another preferred embodiment, W is $-C(O)-C(O)-N(R_6)_2$. Preferably, R_6 is hydrogen, (C3-C10)-cycloalkyl or -cycloalkenyl, or (C3-C10)-heterocyclyl.

In another preferred embodiment of formula I is
 5 where W is $C(O)-C(O)-N(R_6)_2$, the NR_6R_6 portion of the W moiety is $-NH-(C3-C6)$ cycloalkyl, $-NH-CH(CH_3)-(C6-C10)$ aryl or $-NH-CH(CH_3)-(C3-C10)$ heterocyclyl, or $-NH-CH(CH_3)-(C5-C10)$ heteroaryl, wherein said aryl, heterocyclyl, or heteroaryl is optionally substituted with halogen.

10 Alternatively, the NR_6R_6 portion is $-NH-(C3-C6)$ cycloalkyl, $-NH-CH(CH_3)-(C6-C10)$ aryl, or $-NH-CH(CH_3)-(C5-C10)$ heteroaryl, wherein said aryl or said heterocyclyl is optionally substituted with halogen; or
 15 NR_6R_6 is $-NH-(C3-C6)$ cycloalkyl, $-NH-CH(CH_3)-(C6-C10)$ aryl, or $-NH-CH(CH_3)-(C3-C10)$ heterocyclyl, wherein said aryl or said heterocyclyl is optionally substituted with halogen.

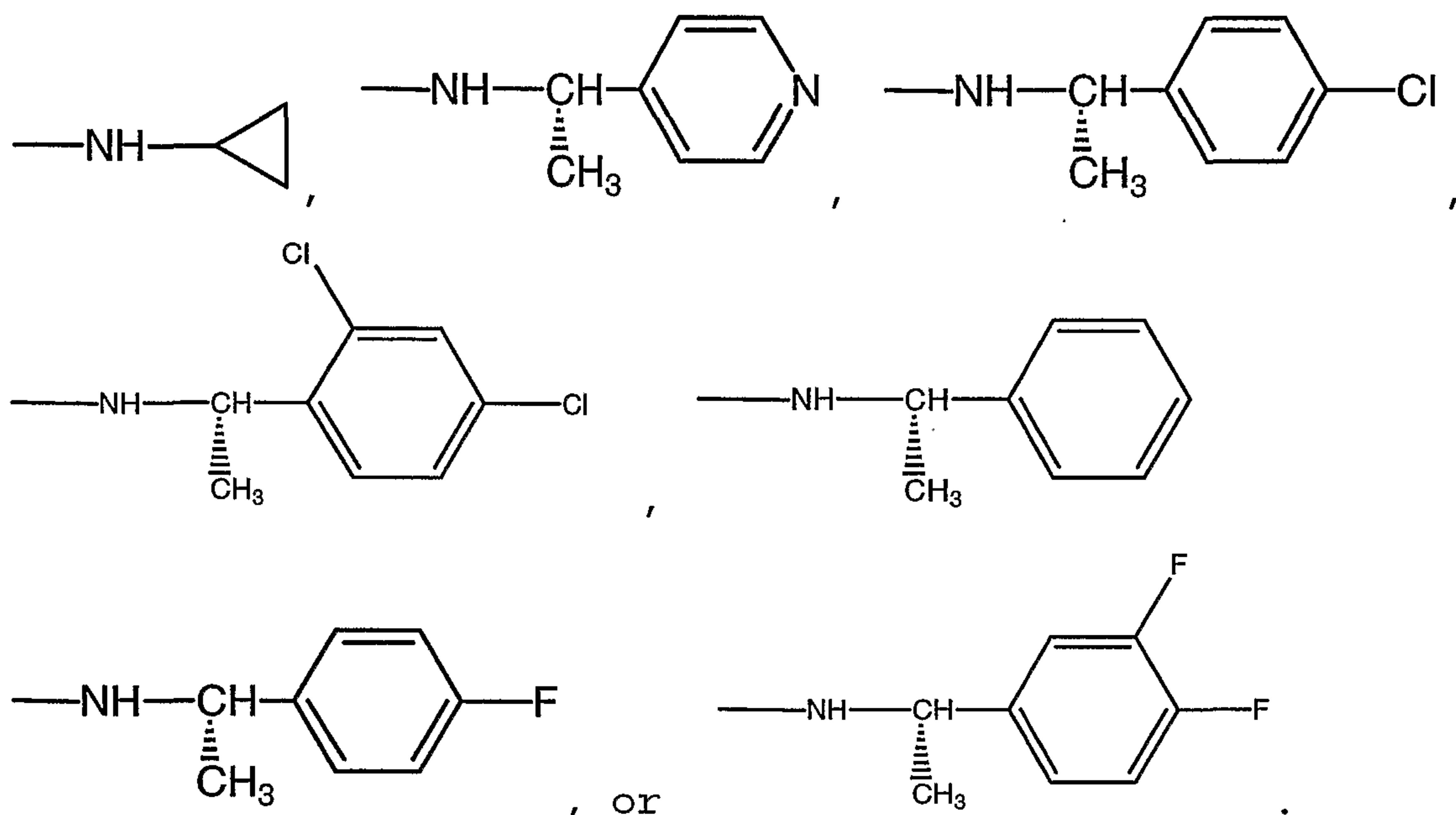
In other preferred embodiment of formula I, NR_6R_6 in W is:



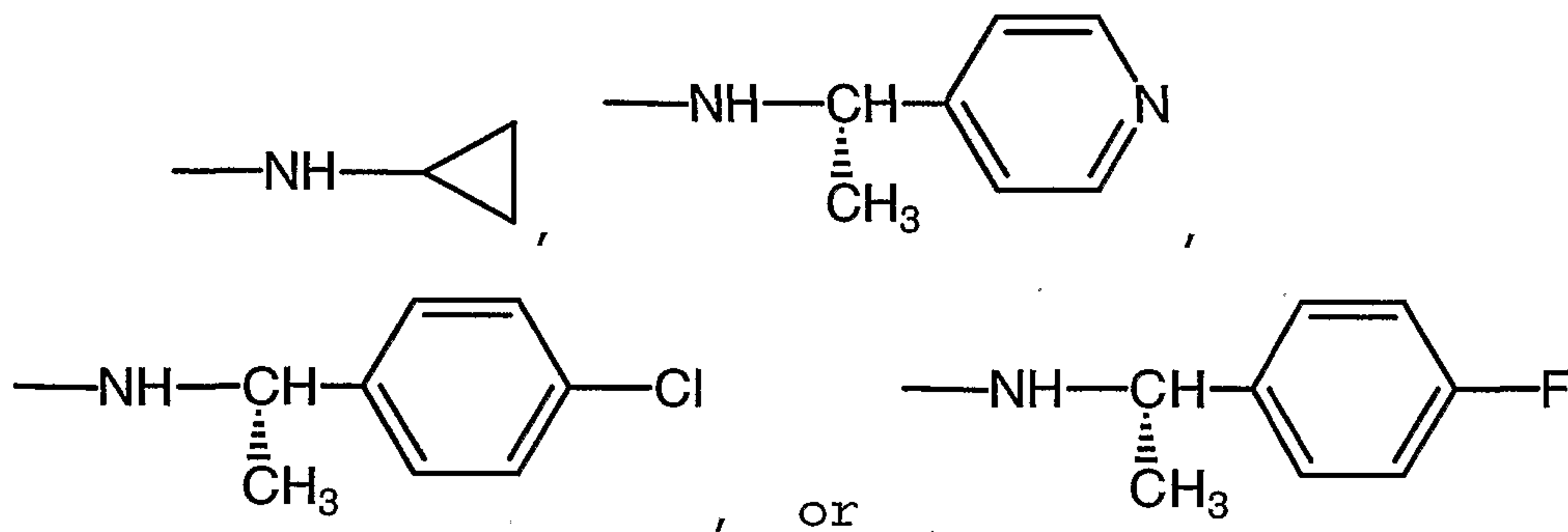
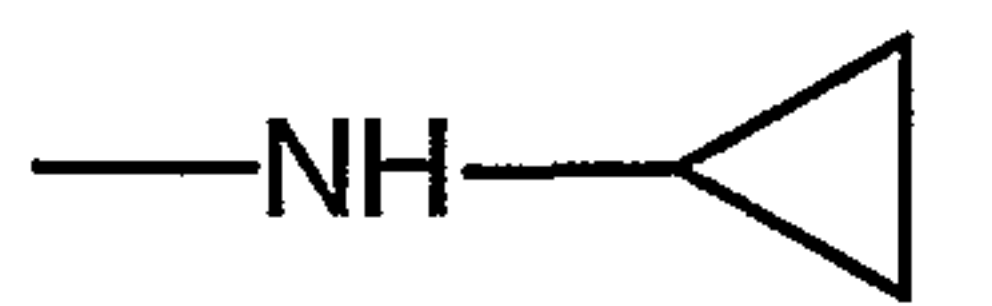
20

More preferably, NR_6R_6 is:

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5

Even more preferably, NR_6R_6 is:Most preferably, NR_6R_6 is:

10

In a preferred embodiment of the present invention, X is $\text{—[CH}_2\text{]}_o\text{—}$, $\text{—[CJ'J']}_o\text{—}$, $\text{—[CH}_2\text{]}_m\text{—O—}$, $\text{—[CH}_2\text{]}_m\text{—S(O)}_2\text{—}$, $\text{—[CH}_2\text{]}_m\text{—SO—}$, $\text{—[CR}_{20}\text{R}_{20}]_m\text{—NR}_{21}\text{—}$, or $\text{—[CR}_{20}\text{R}_{20}]_m\text{—NJ'—}$.

15 In a more preferred embodiment of the present invention, X is $\text{—CR}_{20}\text{R}_{20}\text{—}$; —O— ; —S(O)_2 ; or NR_{21} .

Preferred embodiments of R_{20} are selected from hydrogen, $\text{—C}_1\text{—C}_6\text{—aliphatic}$ and $\text{—O—(C}_1\text{—C}_6\text{—aliphatic)}$; or each R_{20} is taken together with the carbon atoms to which

- 25 -

they are bound to form a (C3-C6)cycloalkyl. Preferably, these aliphatic groups are alkyl groups.

Preferred embodiments of R_{21} are selected from hydrogen and $-C(O)-O-R_{22}$.

5 In yet another preferred embodiment m in X is 0.

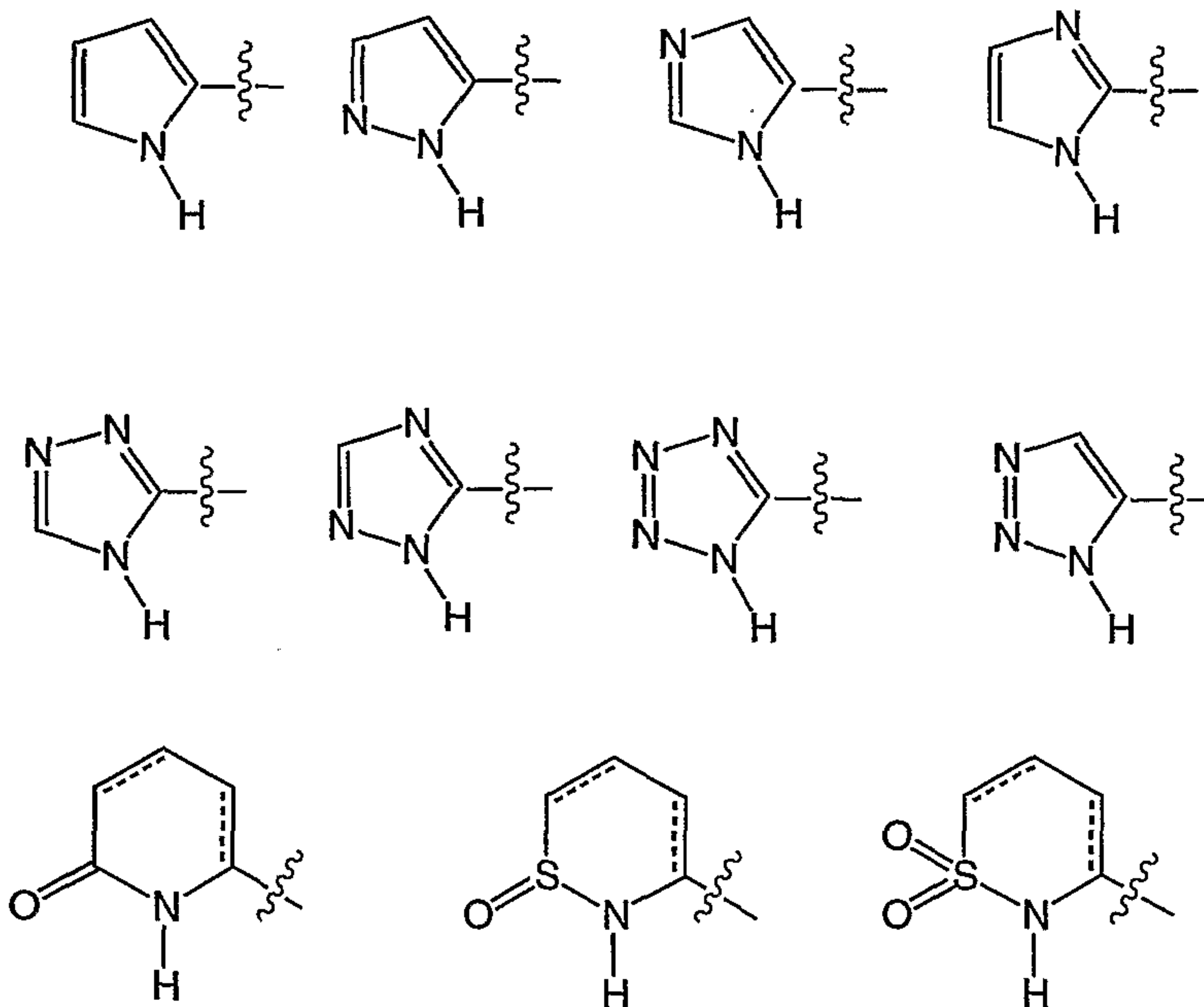
In yet another preferred embodiment, X is $-CH_2-$, $-O-$, $-SO_2-$ or $-NR_{21}-$, wherein R_{21} is hydrogen.

More preferably, X is $-CH_2-$.

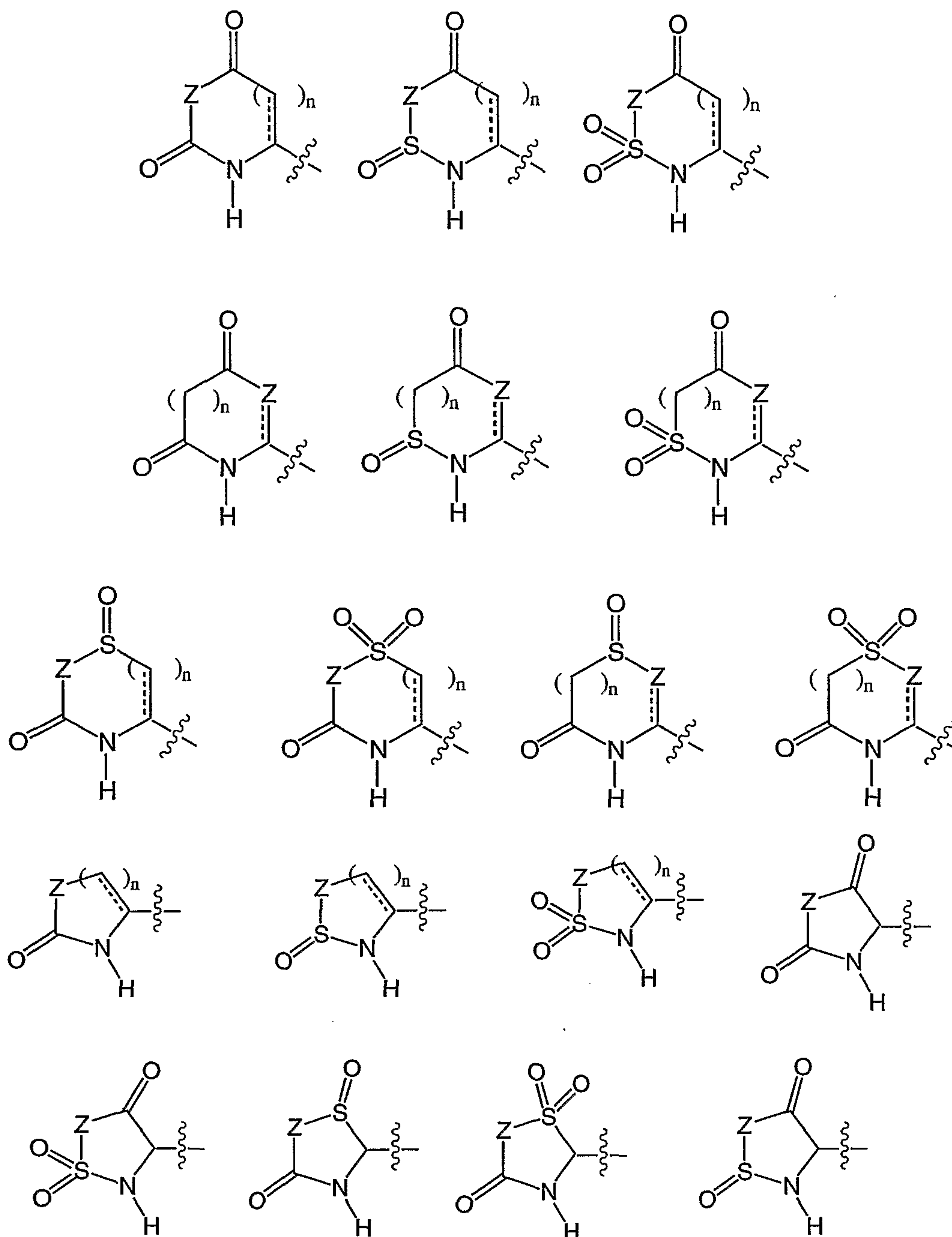
10 Even more preferred is when the bridged bicyclic moiety is fully saturated.

According to another preferred embodiment of this invention, T contains at least one hydrogen bond donor moiety selected from $-NH_2$, $-NH-$, $-OH$, and $-SH$.

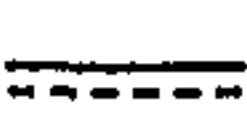
15 In a preferred embodiment, T is:



- 26 -

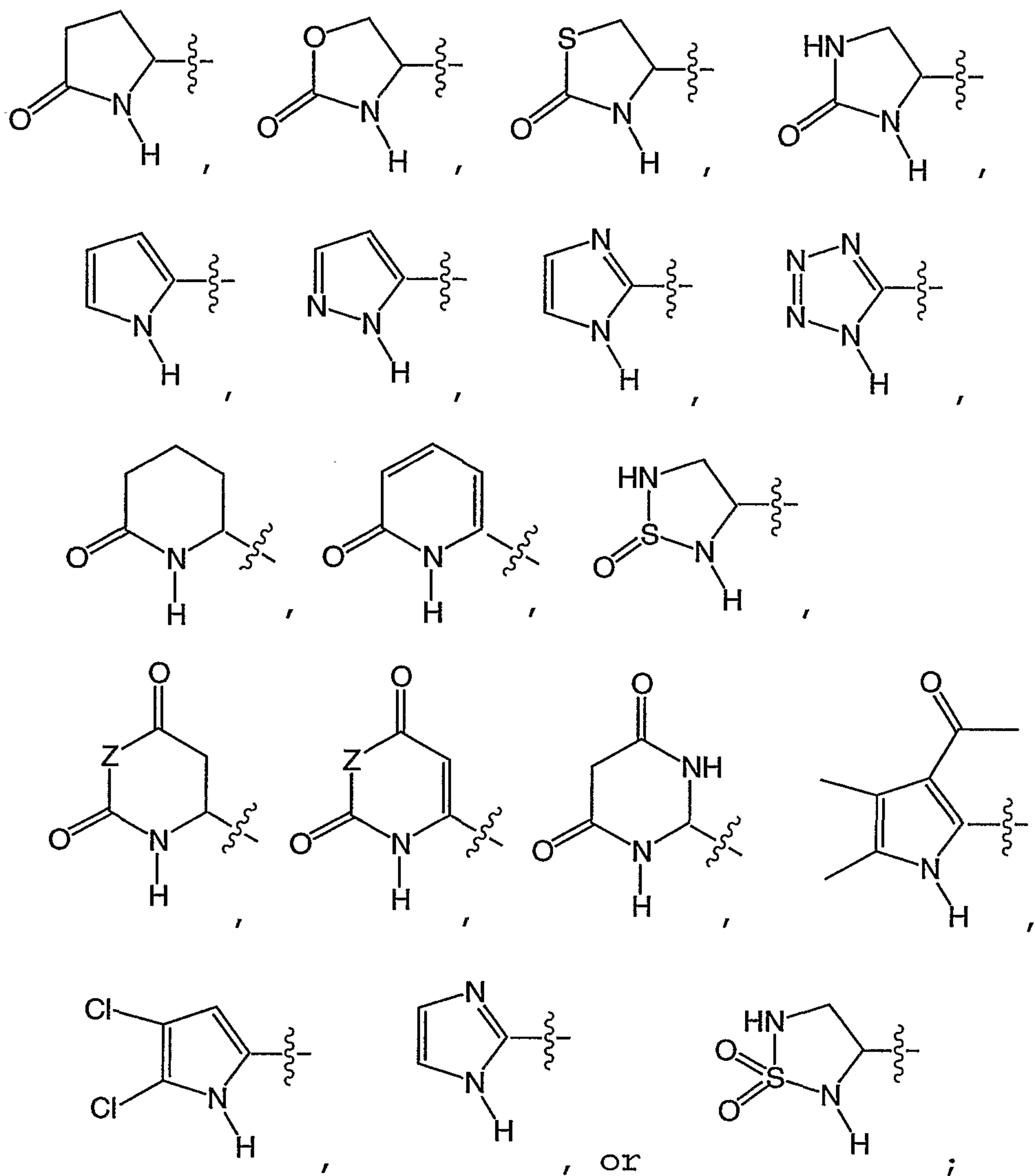


wherein:

- 5 T is optionally substituted with up to 3 J substituents, wherein J is as defined in claim 1;
- Z is independently O, S, NR₁₀, or C(R₁₀)₂;
- n is independently 1 or 2; and
-  is independently a single bond or a double bond.

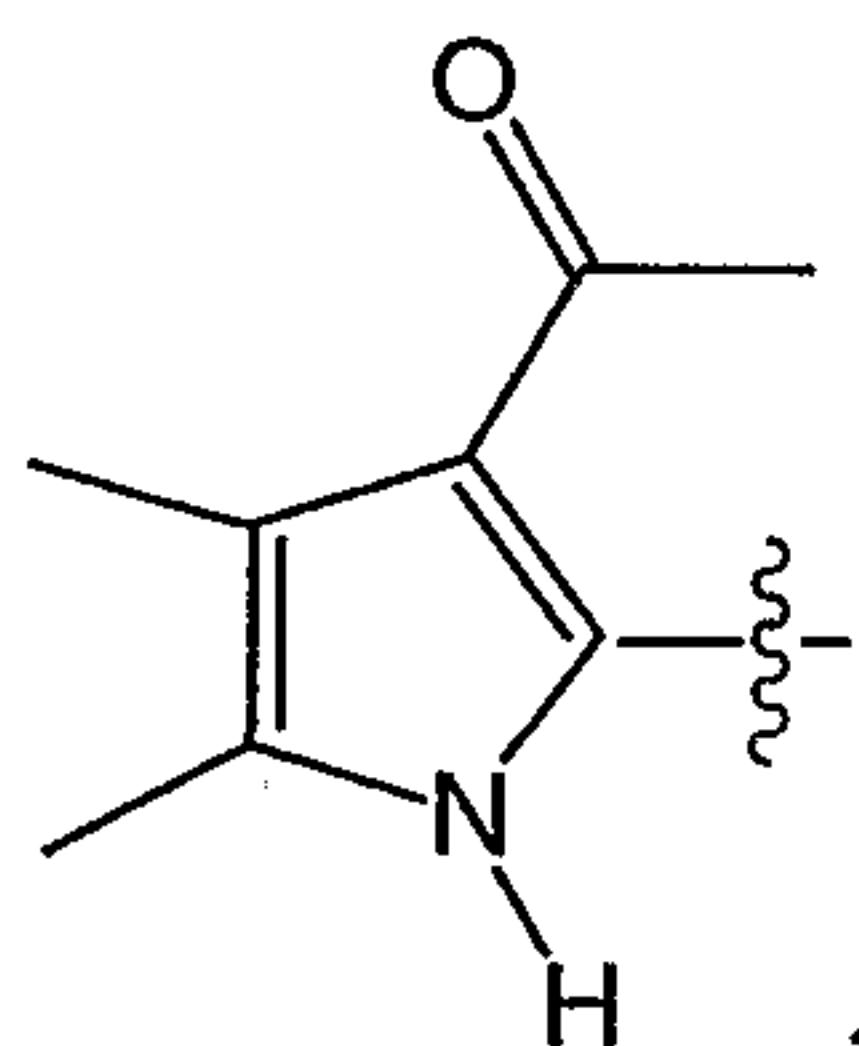
- 27 -

In another preferred embodiment, T is:



wherein Z is as defined above.

More preferably T is



5

According to another preferred embodiment, T is:

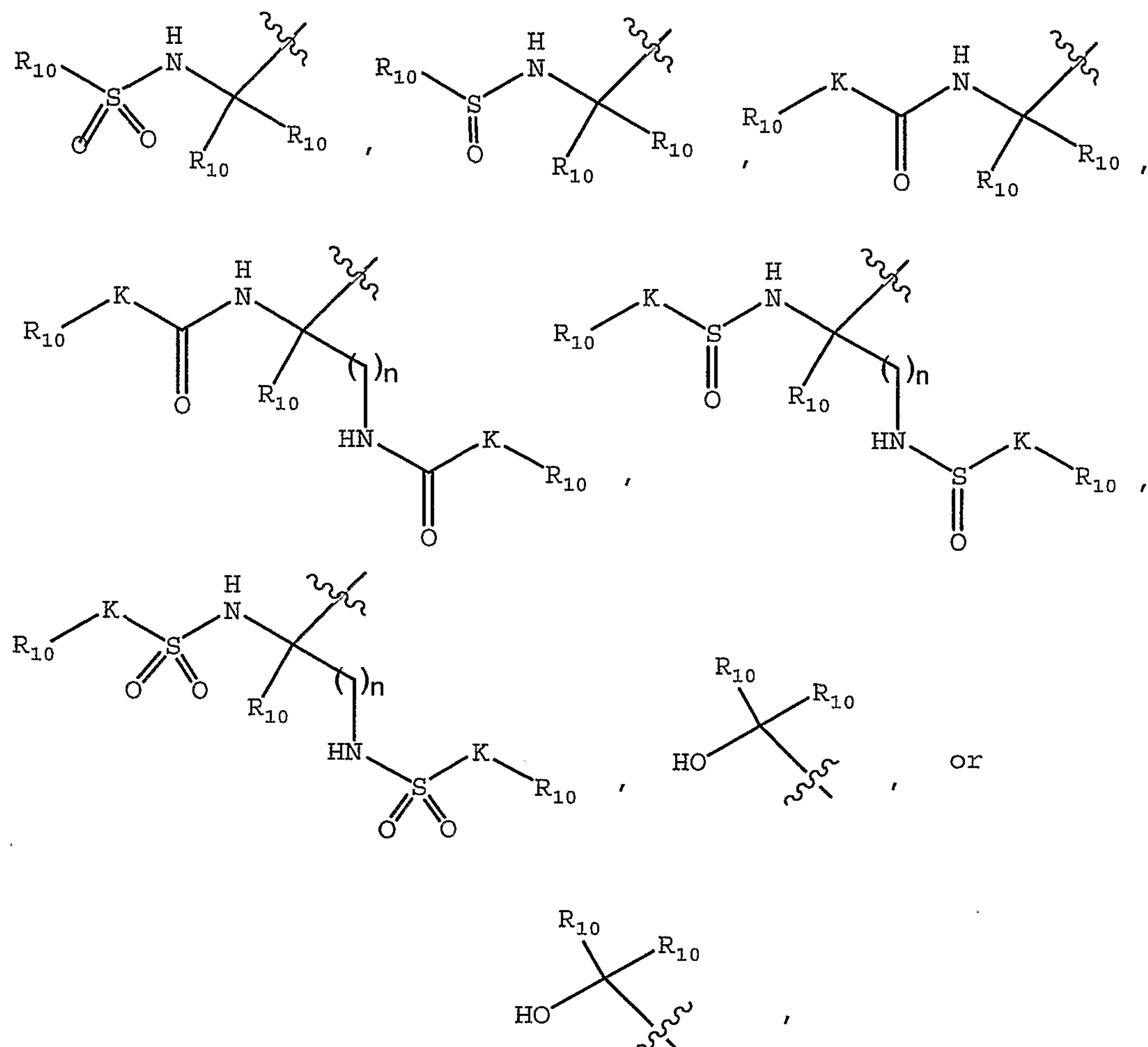
- 28 -

(C6-C10)-aryl,
(C6-C10)-aryl-(C1-C12)aliphatic,
(C3-C10)-cycloalkyl or -cycloalkenyl,
[(C3-C10)-cycloalkyl or -cycloalkenyl]-(C1-C12)-
5 aliphatic,

(C3-C10)-heterocyclyl,
(C3-C10)-heterocyclyl-(C1-C12)-aliphatic,
(C5-C10)heteroaryl, or
(C5-C10)heteroaryl-(C1-C12)-aliphatic,
10 wherein each T is optionally substituted with
up to 3 J substituents.

According to yet another preferred embodiment
of this invention, T:

- 29 -



wherein:

R₁₀ is:

- 5 hydrogen,
 (C1-C12)-aliphatic,
 (C6-C10)-aryl,
 (C6-C10)-aryl-(C1-C12) aliphatic,
 (C3-C10)-cycloalkyl or -cycloalkenyl,
 10 [(C3-C10)-cycloalkyl or -cycloalkenyl]-(C1-
 C12)-aliphatic,
 (C3-C10)-heterocyclyl,
 (C3-C10)-heterocyclyl-(C1-C12)-aliphatic,
 (C5-C10)heteroaryl, or
 15 (C5-C10)heteroaryl-(C1-C12)-aliphatic,

- 30 -

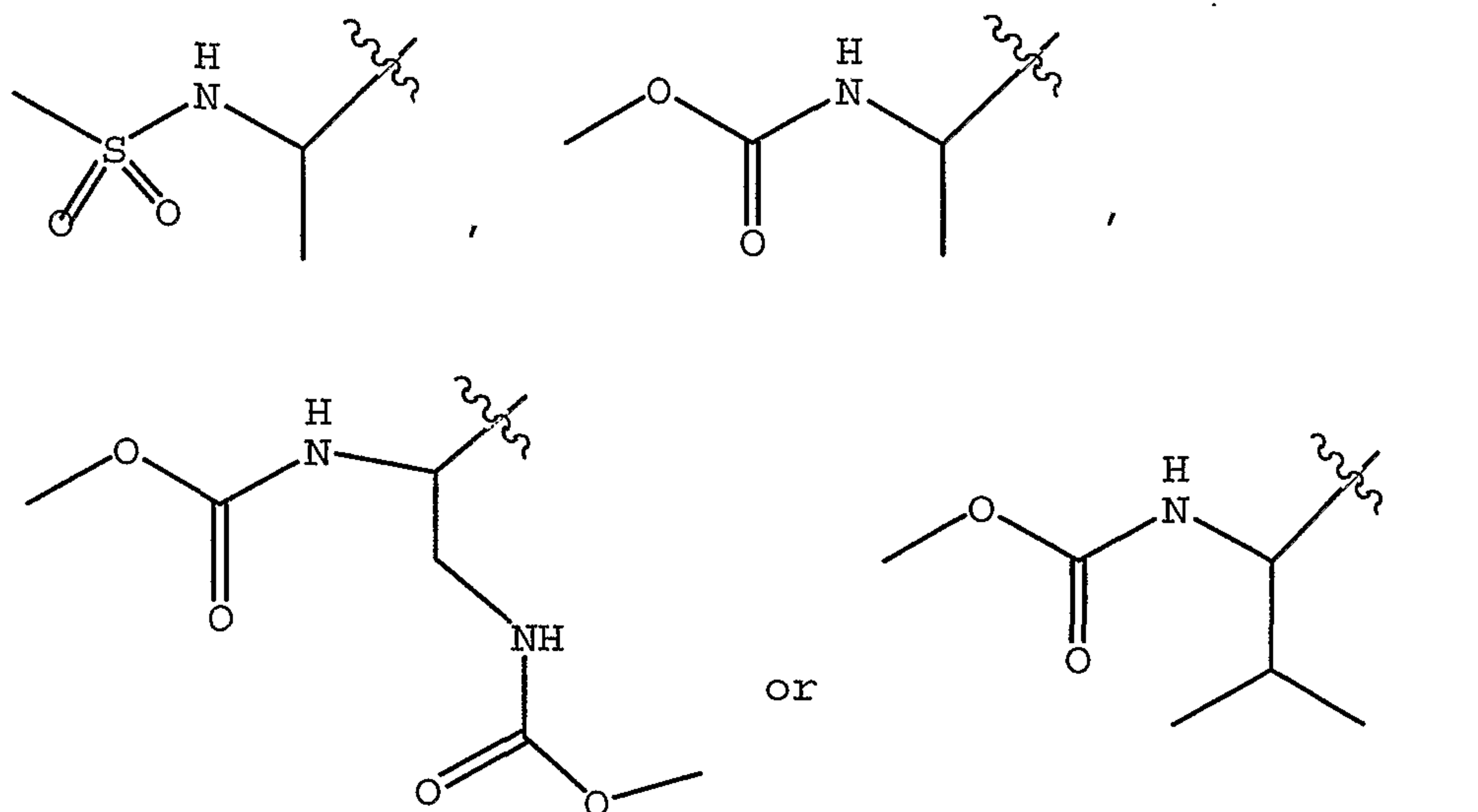
wherein each T is optionally substituted with up to 3 J substituents;

K is a bond, -O-, -S-, -NR₉-, -C(O)-, or -C(O)-NR₉-,
wherein R₉ is hydrogen or C1-C12 aliphatic; and

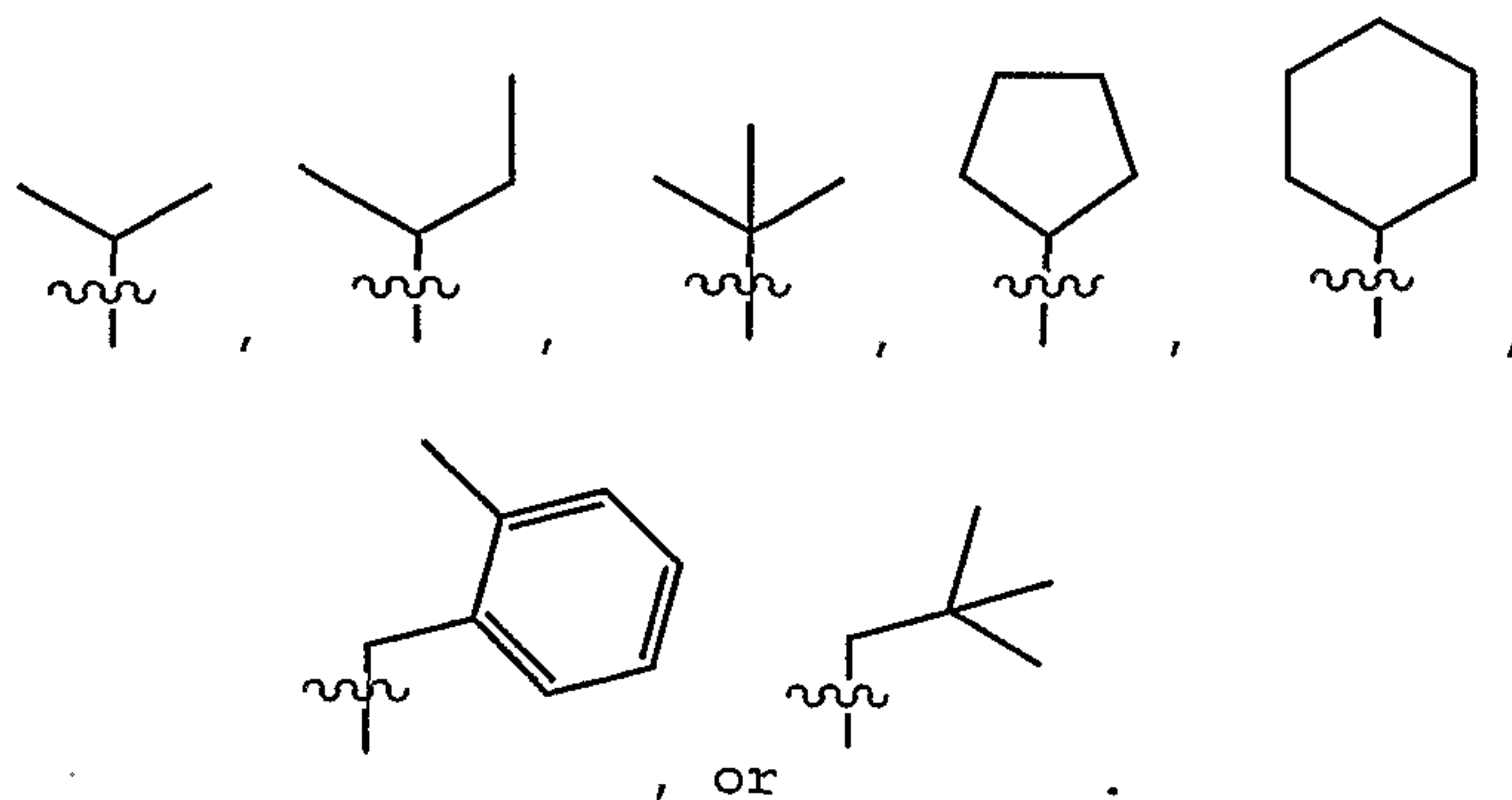
5

n is 1-3.

More preferably, T is:

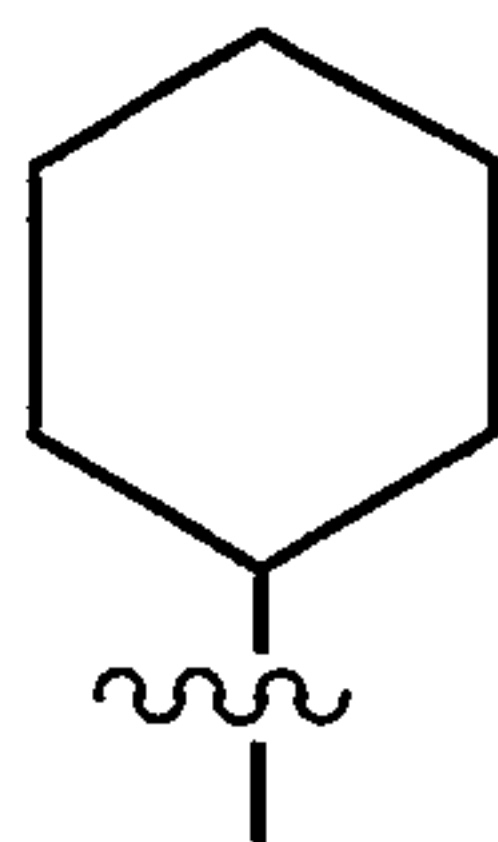


In yet another preferred embodiment, R₁ is:



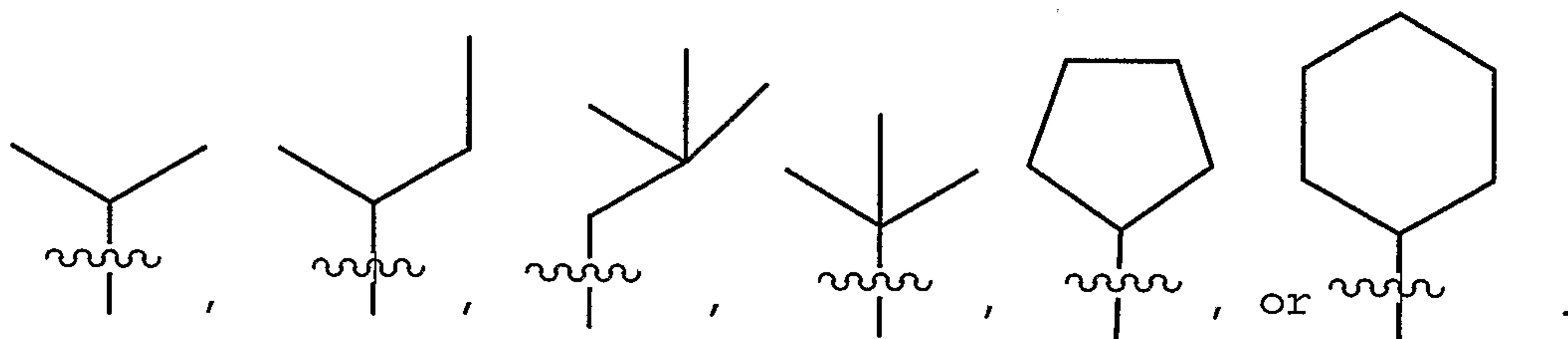
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More preferably, R₁ is:



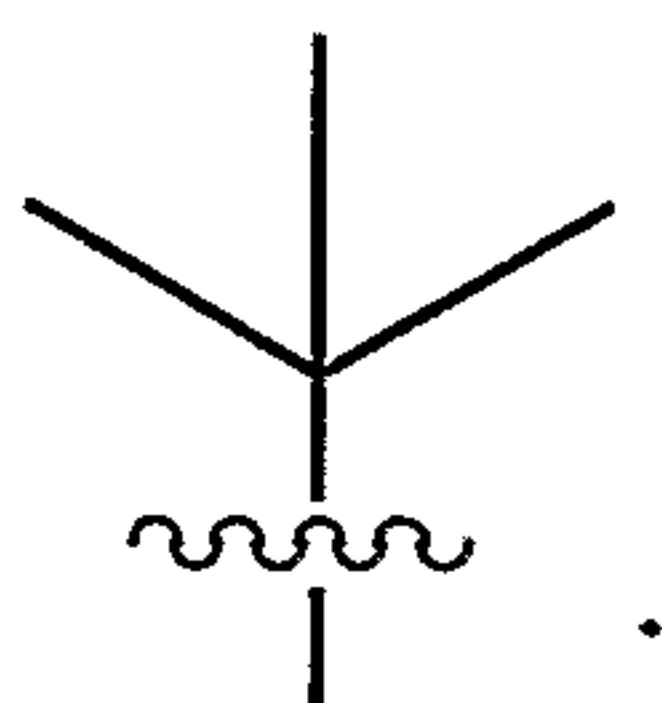
- 31 -

In yet another preferred embodiment, R_3 is:

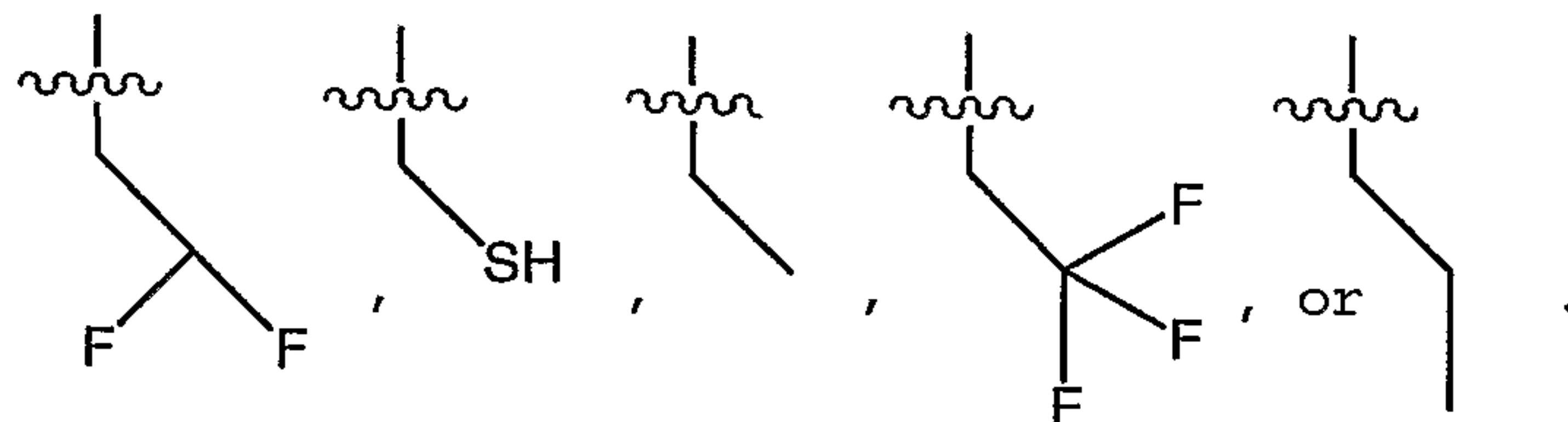


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More preferably, R_3 is:

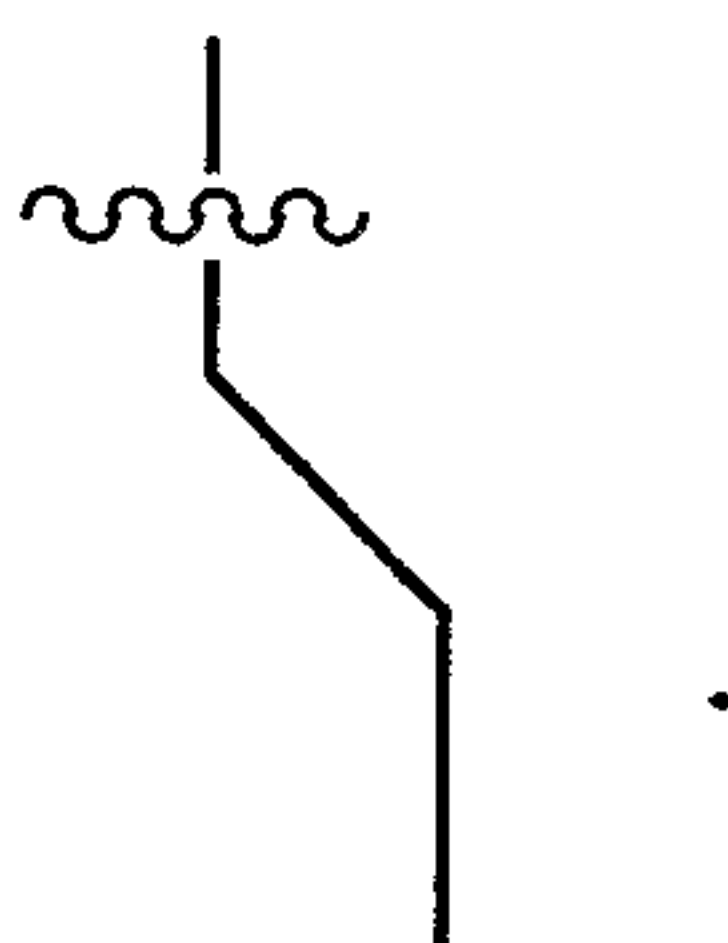


In yet another preferred embodiment, R_5 is:



10

More preferably, R_5 is:



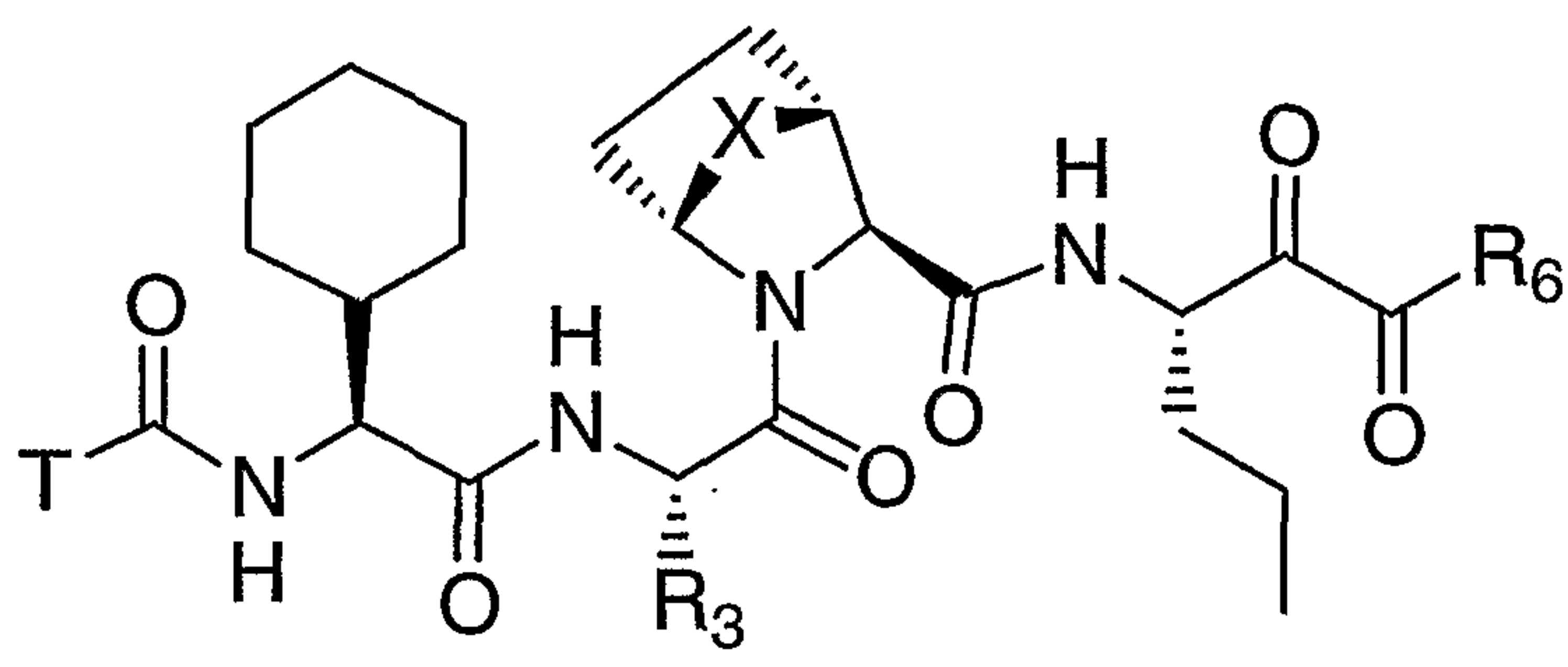
15 In yet another preferred embodiment, R_2 and R_4 are each independently H, methyl, ethyl, or propyl.

More preferably, R_2 and R_4 are each H.

According to a preferred embodiment, V is $-C(O)-NR_8-$. More preferably, V is $-C(O)-NH-$.

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More preferably, the compound of this invention has the structure and stereochemistry depicted below in formula II:



wherein R_3 and R_6 represent the most preferred embodiments set forth above.

Any of the preferred embodiments recited above may be combined to produce a preferred embodiment of this invention.

10

The compounds of this invention may be synthesized by standard chemical schemes well-known in the art. Such schemes are set forth below, but other equivalent schemes, which will be readily apparent to the ordinary skilled organic chemist, may alternatively be used to synthesize various portions of the molecule. For example, compounds of formula I, wherein W is $C(O)OH$ or $C(O)C(O)R_6$ may be prepared according to the methods depicted in schemes 11 and/or 12. More specific synthesis schemes for individual compounds within applicants' invention are set forth in the examples.

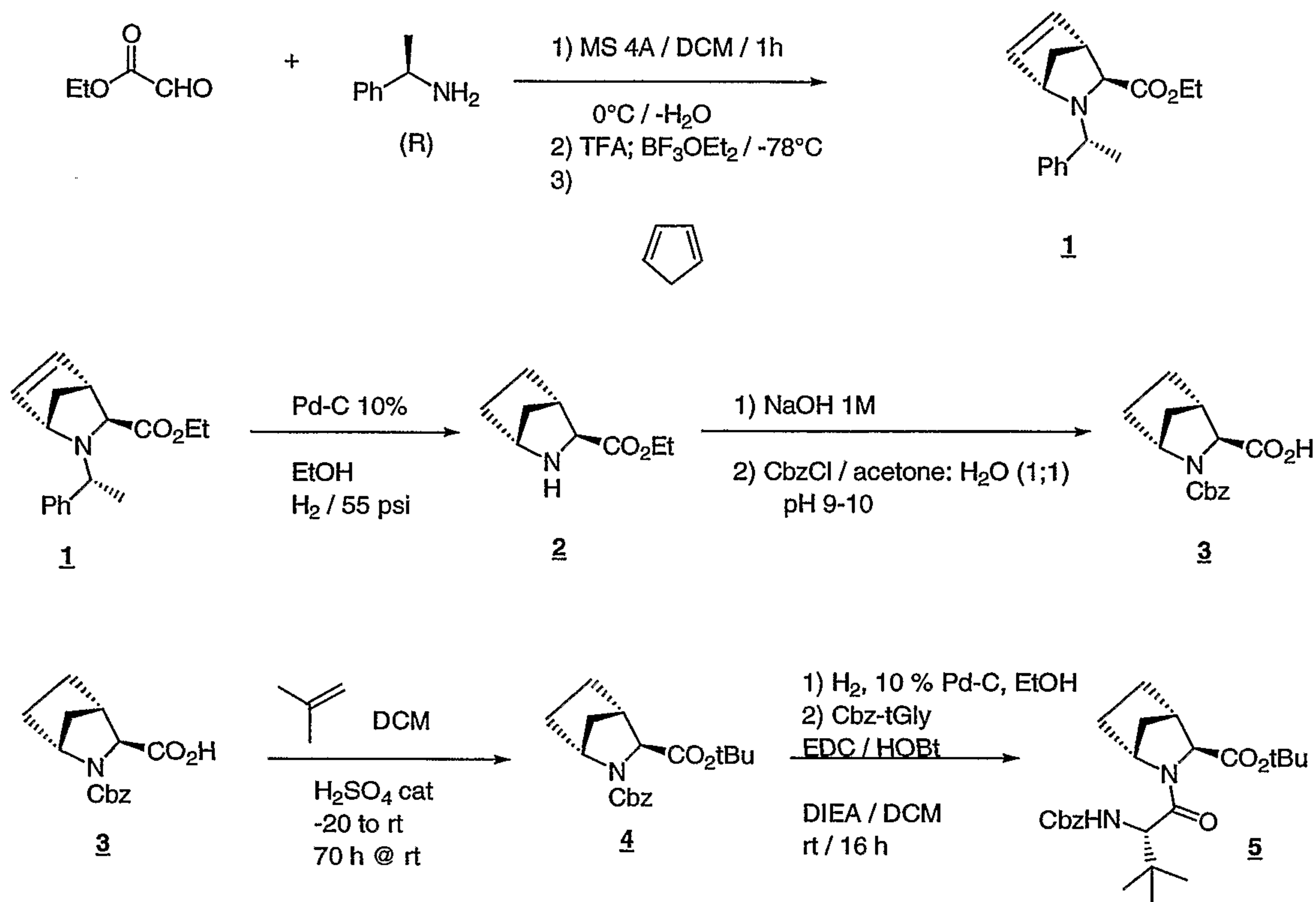
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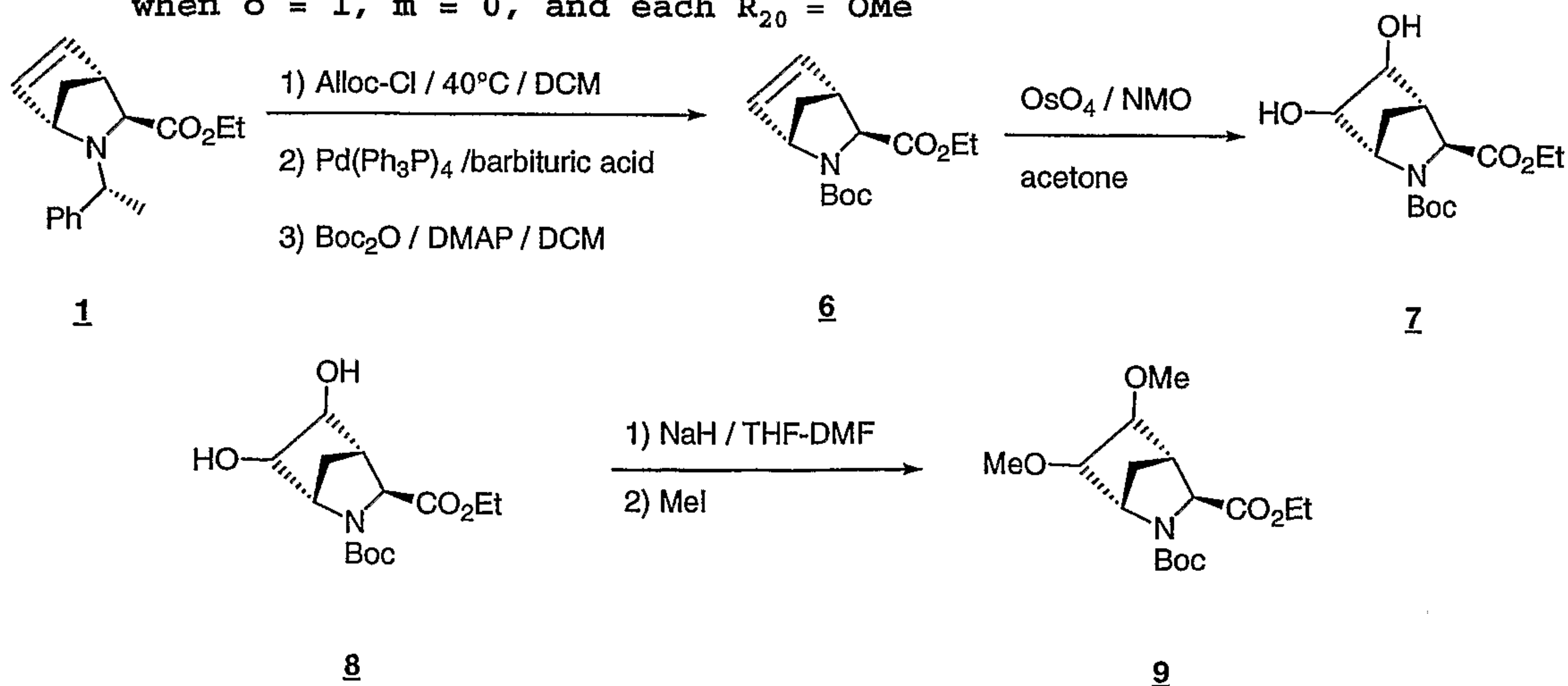
Scheme 1.

Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $o = 1$, $m = 0$, each $R_{20} = H$, and $R_3 = t\text{-Bu}$



Scheme 2.

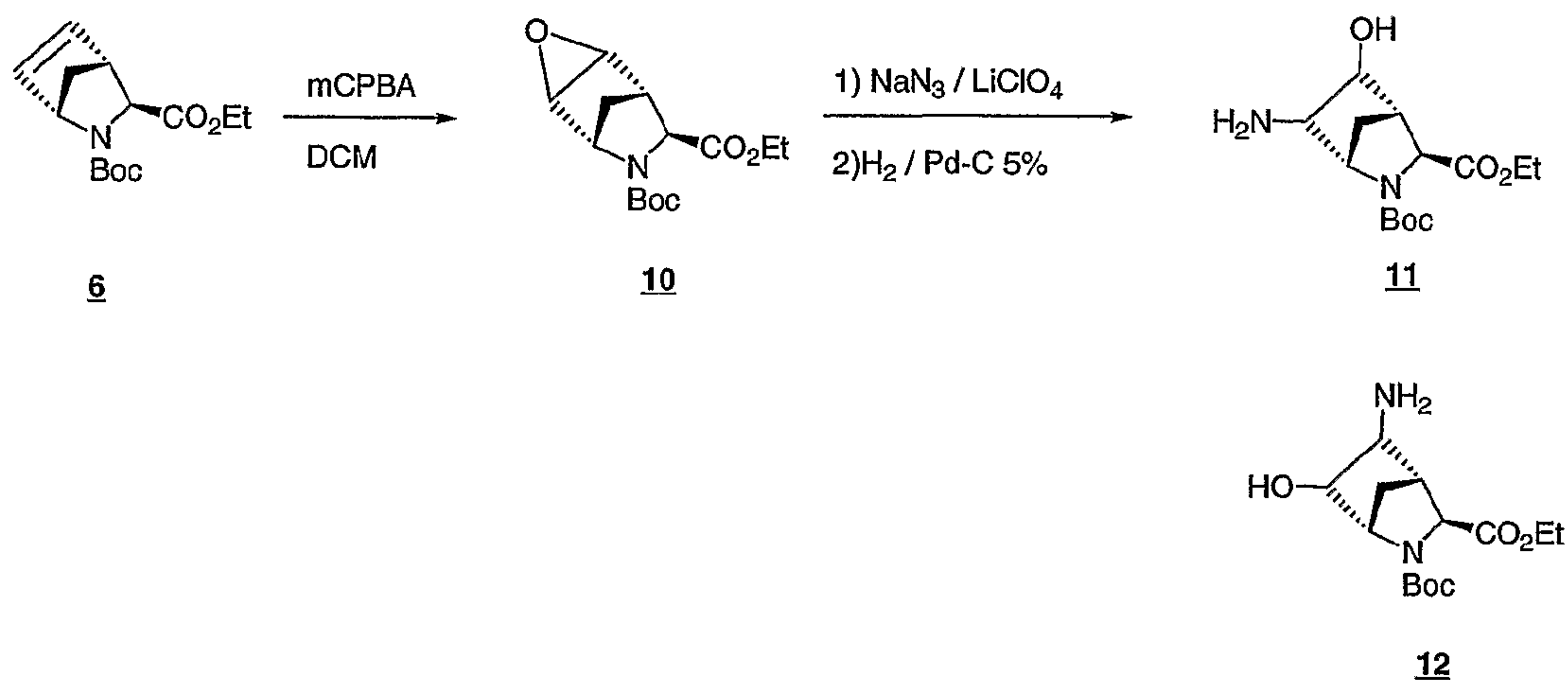
Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $o = 1$, $m = 0$, and each $R_{20} = \text{OMe}$



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Scheme 3.

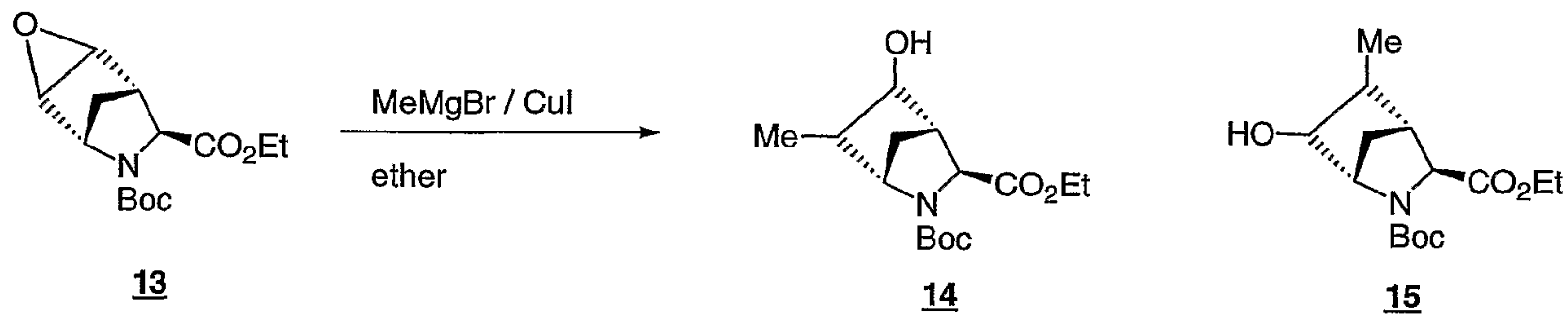
Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $o = 1$, $m = 0$, and one $R_{20} = \text{NH}_2$ and the other $R_{20} = \text{OH}$



Scheme 4.

Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
acid

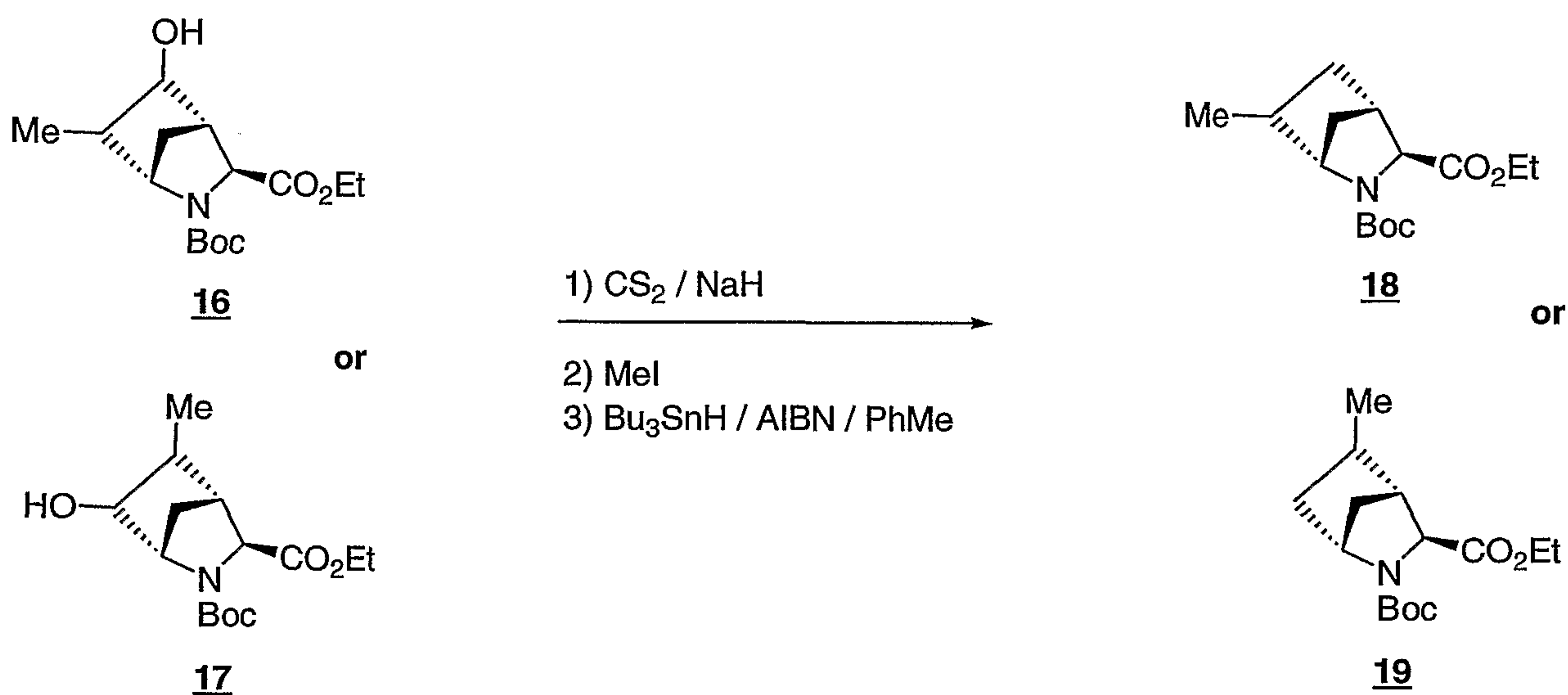
when $o = 1$, $m = 0$, and one $R_{20} = \text{Me}$ and the other $R_{20} = \text{OH}$



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Scheme 5.

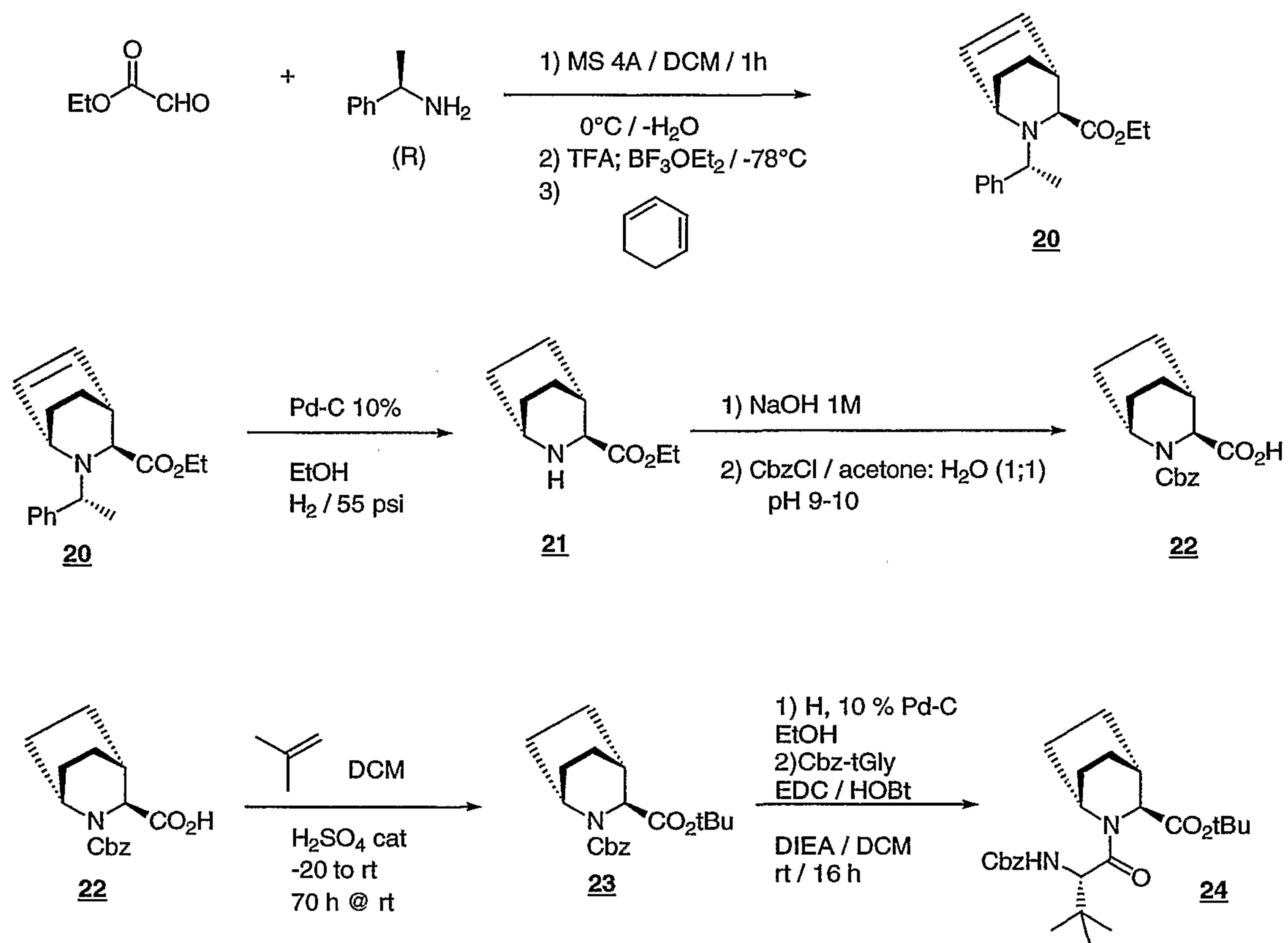
Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $o = 1$, $m = 0$, and one $R_{20} = \text{Me}$ and the other $R_{20} = \text{H}$



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Scheme 6.

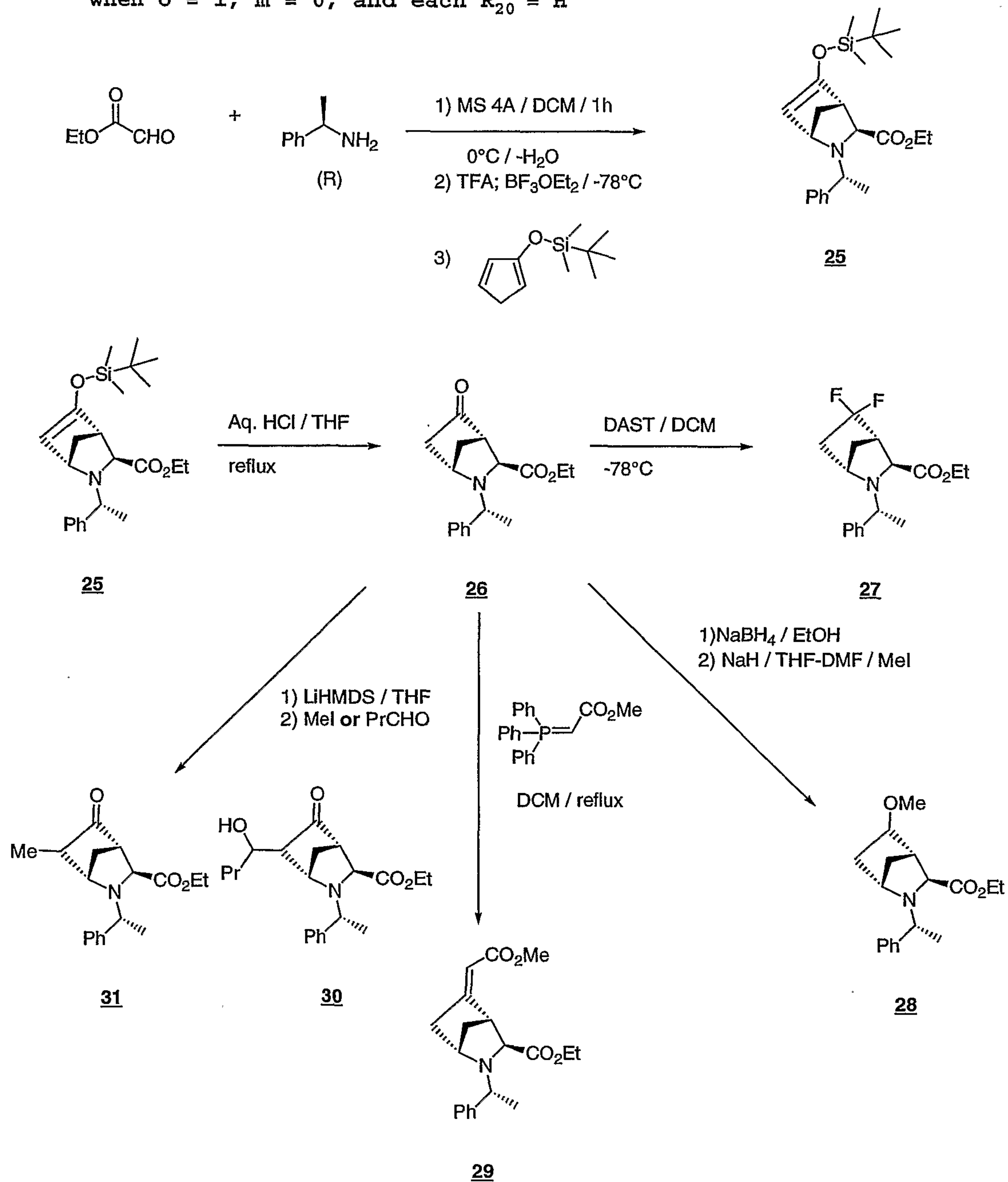
Synthesis of the Azabicyclo[2.2.2] octane-3-carboxylic acid
when $o = 2$, $m = 0$, each $R_{20} = H$, and $R_3 = t\text{-Bu}$



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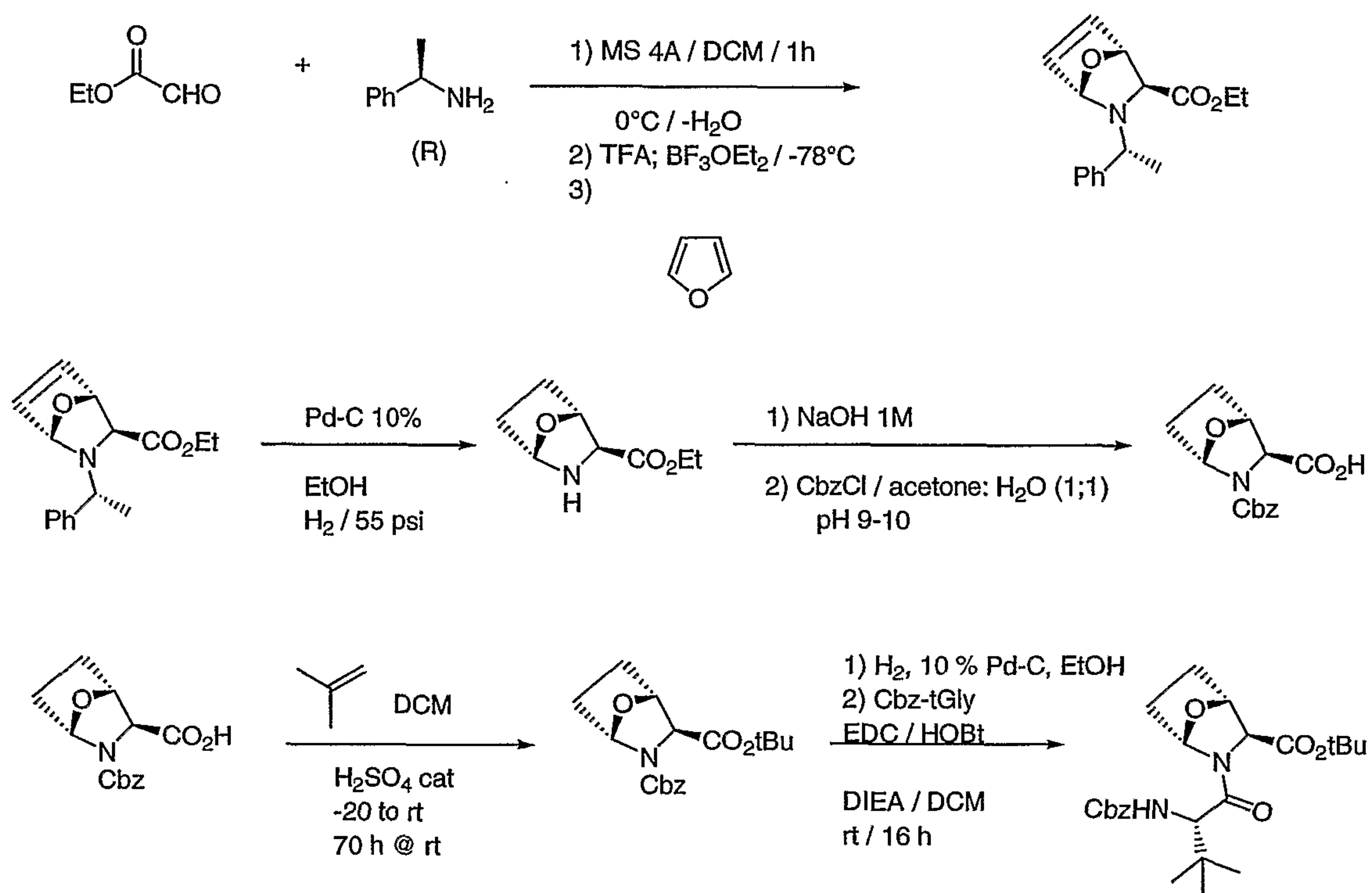
Scheme 7.

Synthesis of the Azabicyclo[2.2.1] heptane-3-carboxylic acid
when $o = 1$, $m = 0$, and each $R_{20} = H$



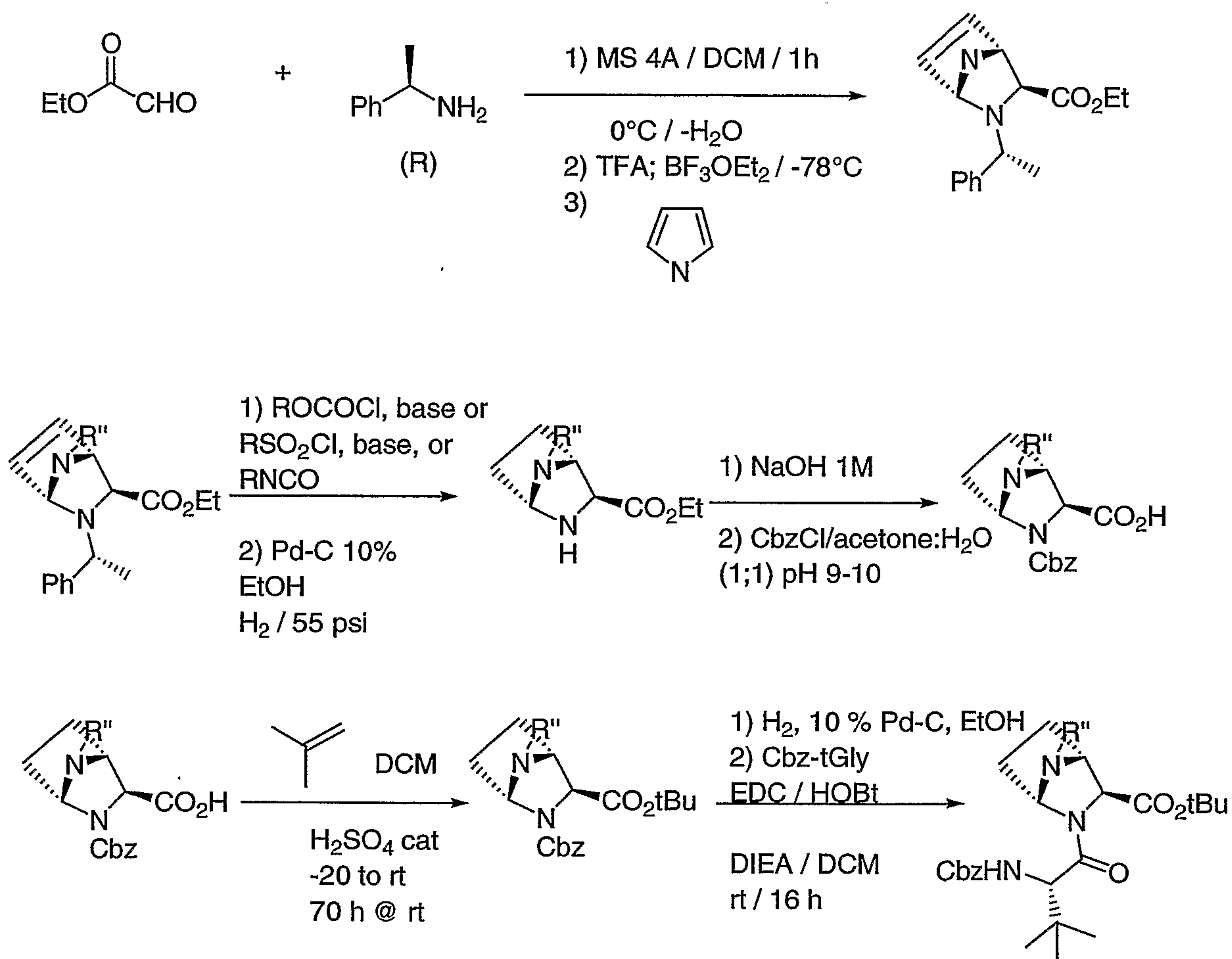
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Scheme 8.
Synthesis of Scaffolds when X is O



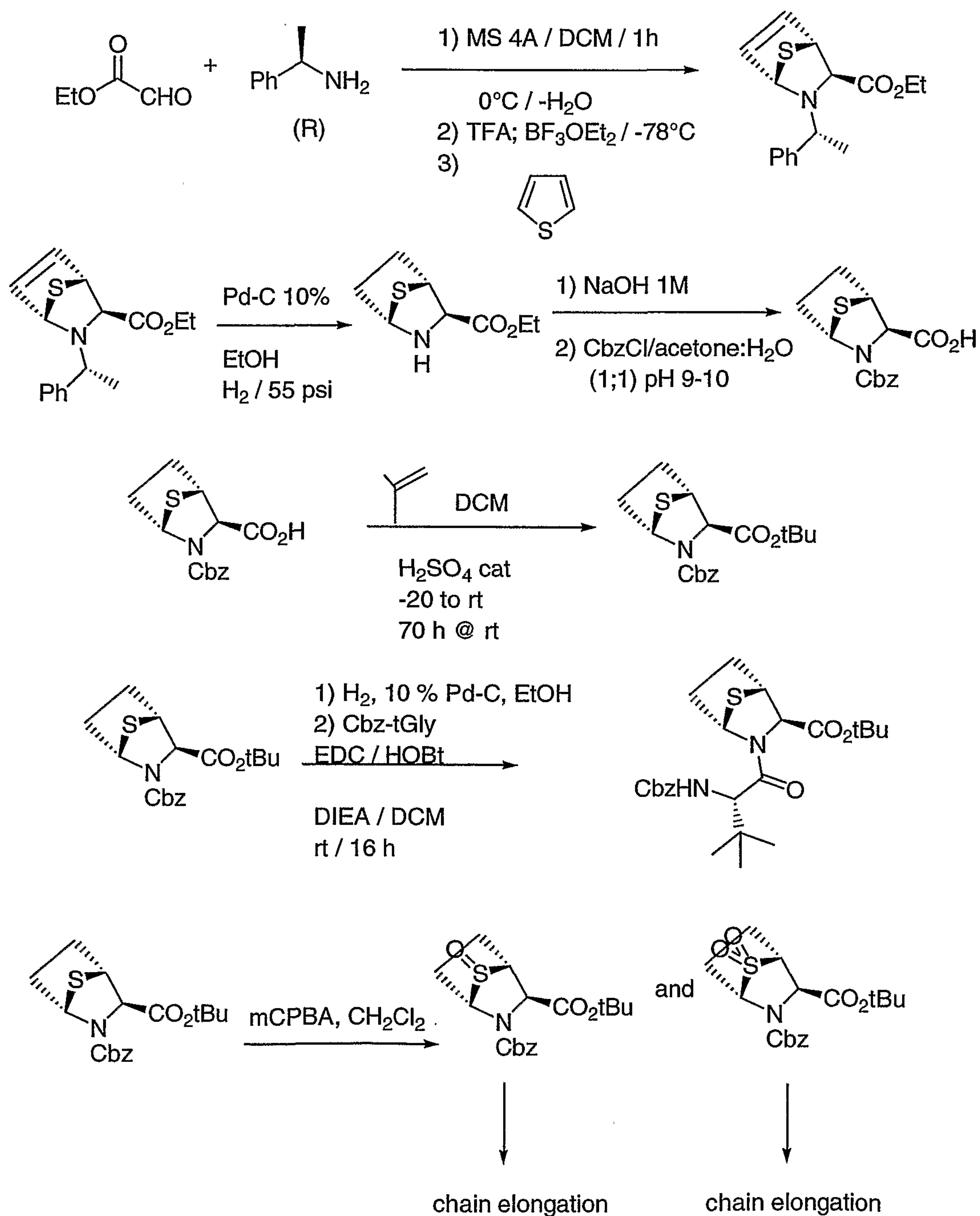
- 39 -

Scheme 9.

Synthesis of Scaffolds when X is NR₂₁ or NJwherein R'' is R₂₁ or J''

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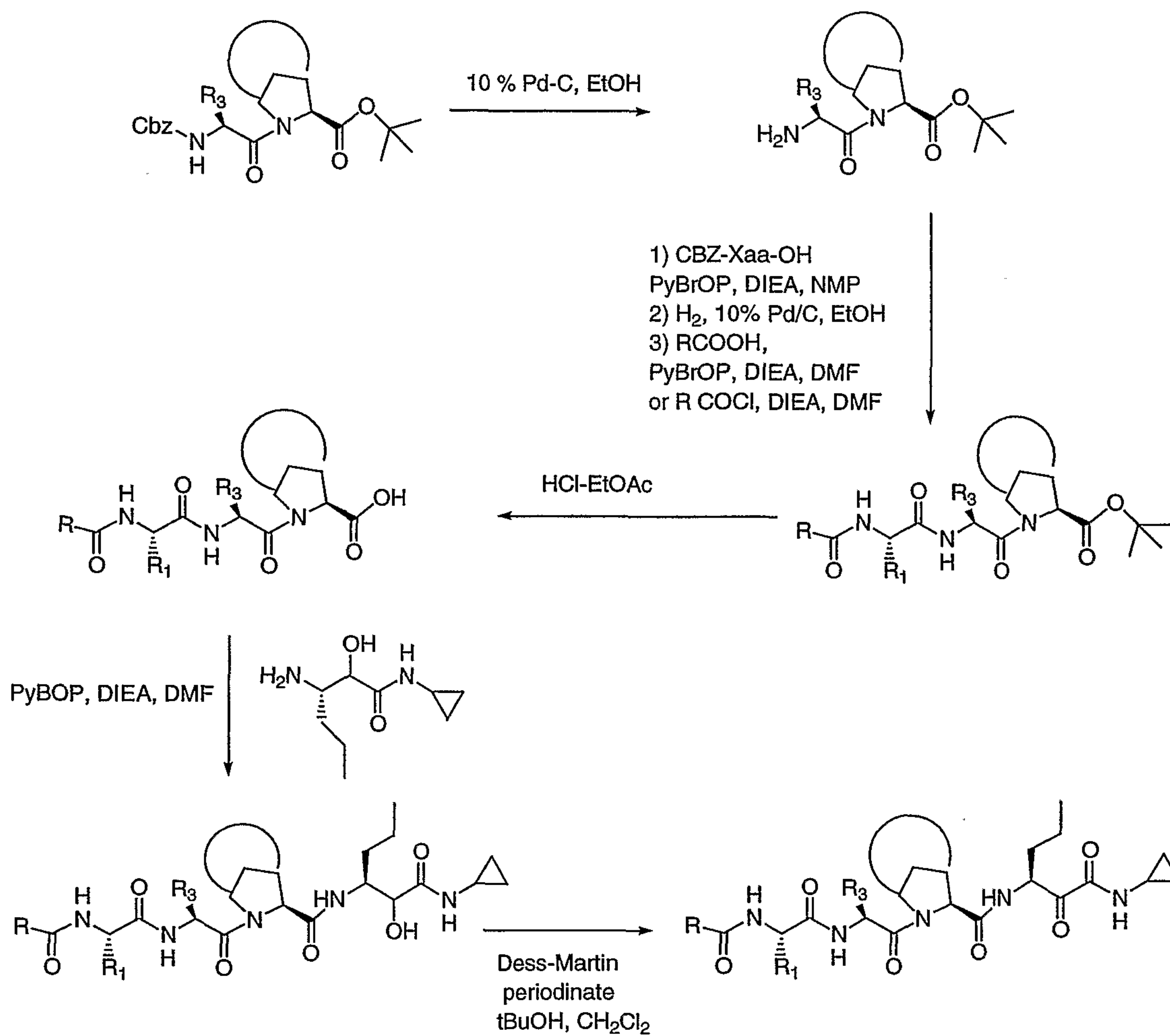
Scheme 10.

Synthesis of Scaffolds when X is SO or SO₂

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Scheme 11.

Synthesis of Compounds of Formula I when W is $C(O)C(O)N(R_6)_2$ - Method A



wherein RC(O)NH- corresponds to T-V-

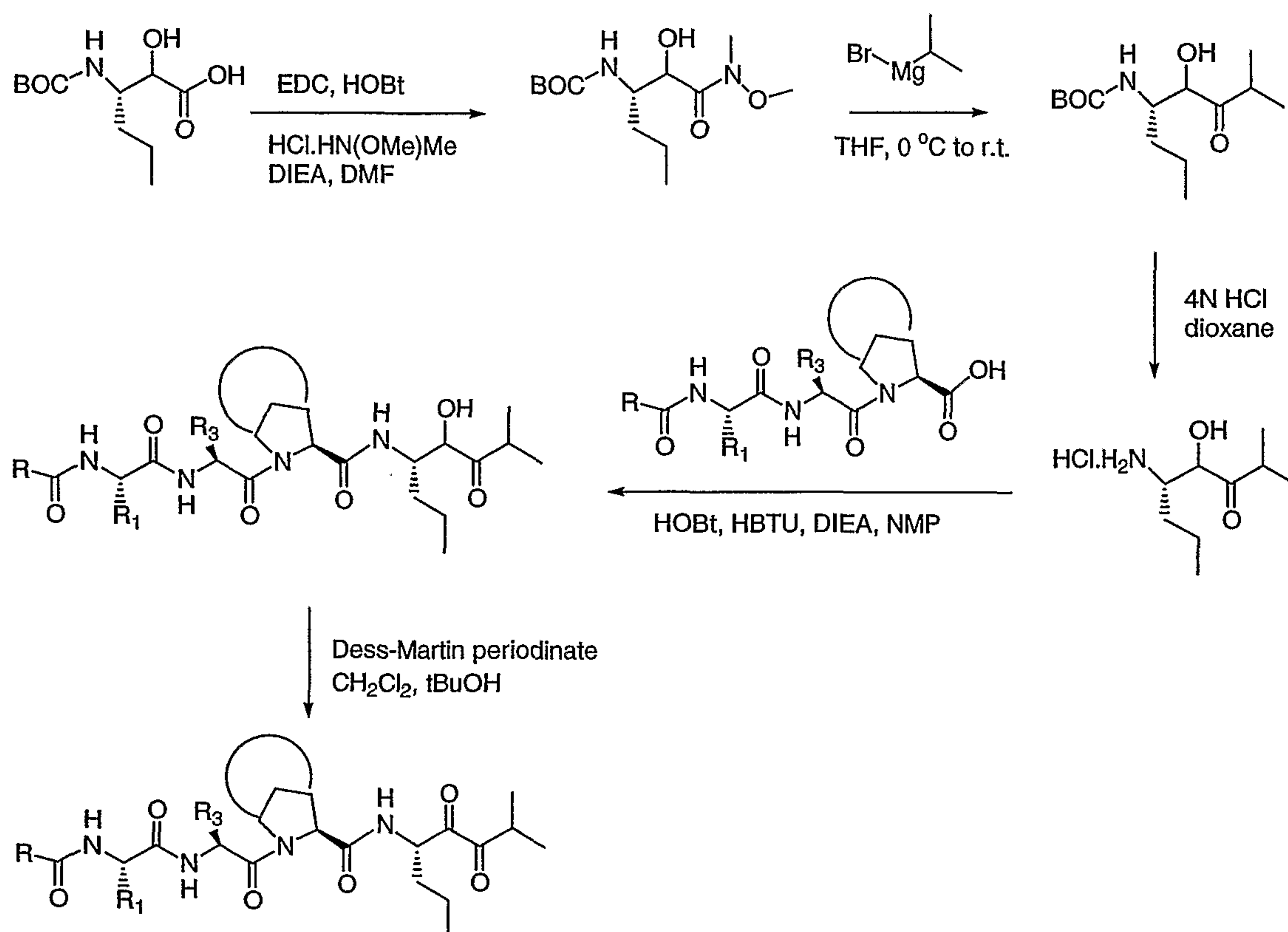


wherein RC(O)NH- corresponds to T-V-

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Scheme 13.

Synthesis of Compounds of Formula I when W is $C(O)C(O)R_6$ -
Method A

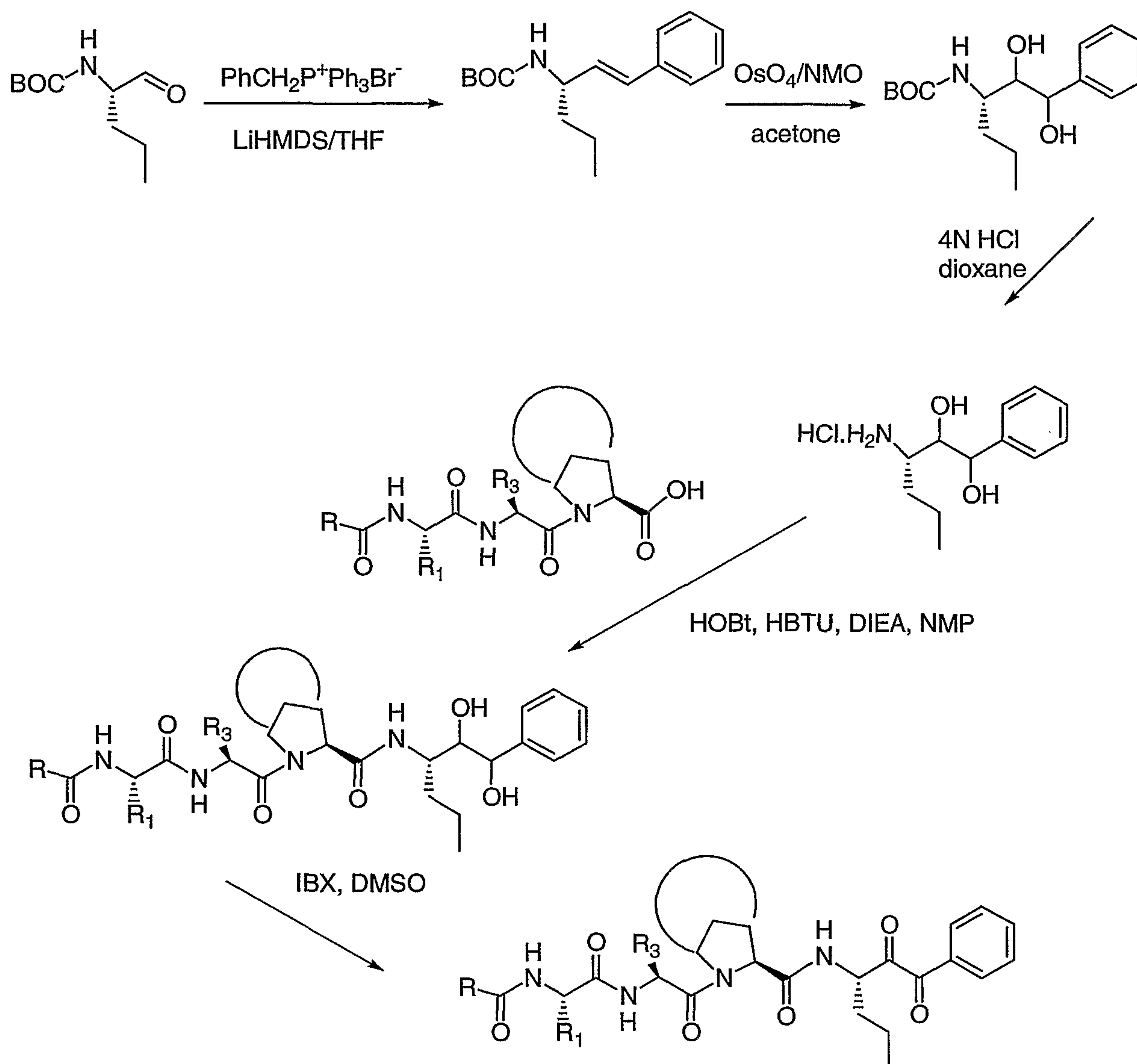


wherein RC(O)NH- corresponds to T-V-

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Scheme 14.

Synthesis of Compounds of Formula I when W is $C(O)C(O)R_6$ - Method B



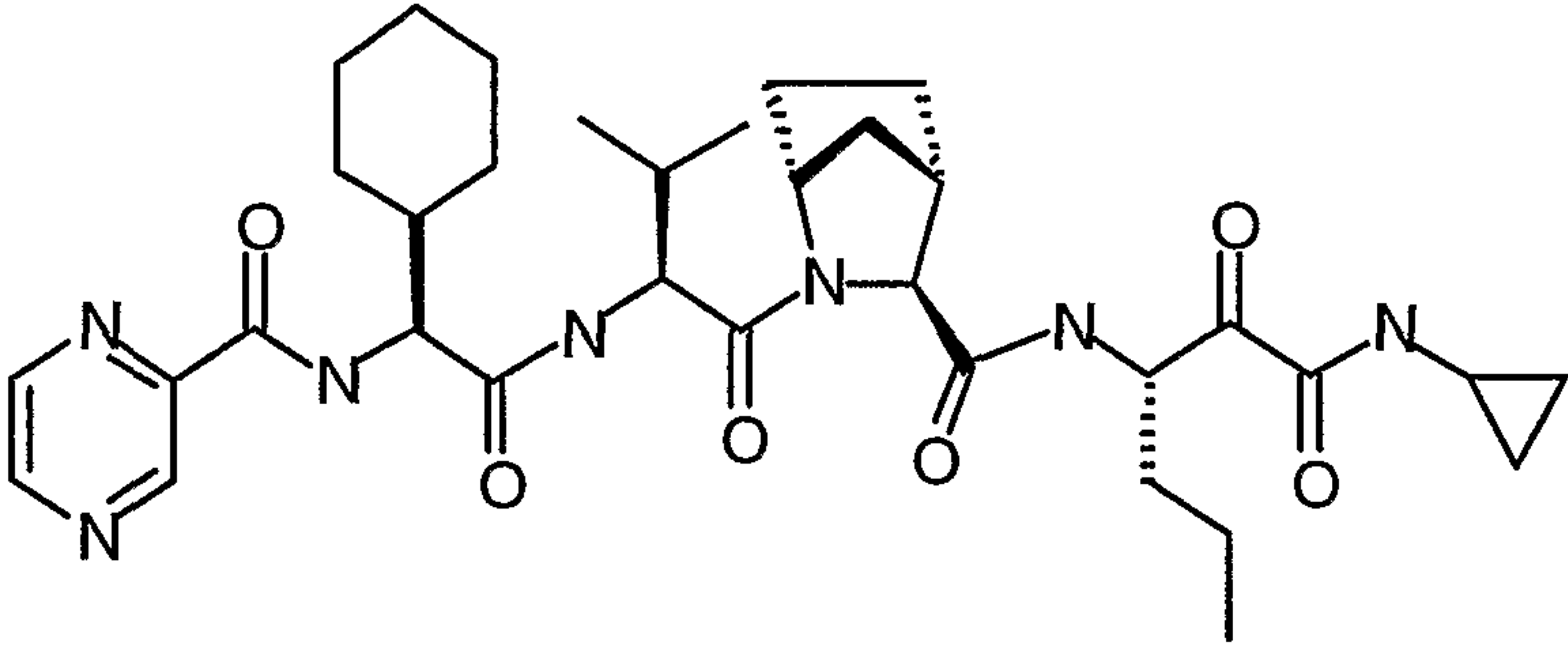
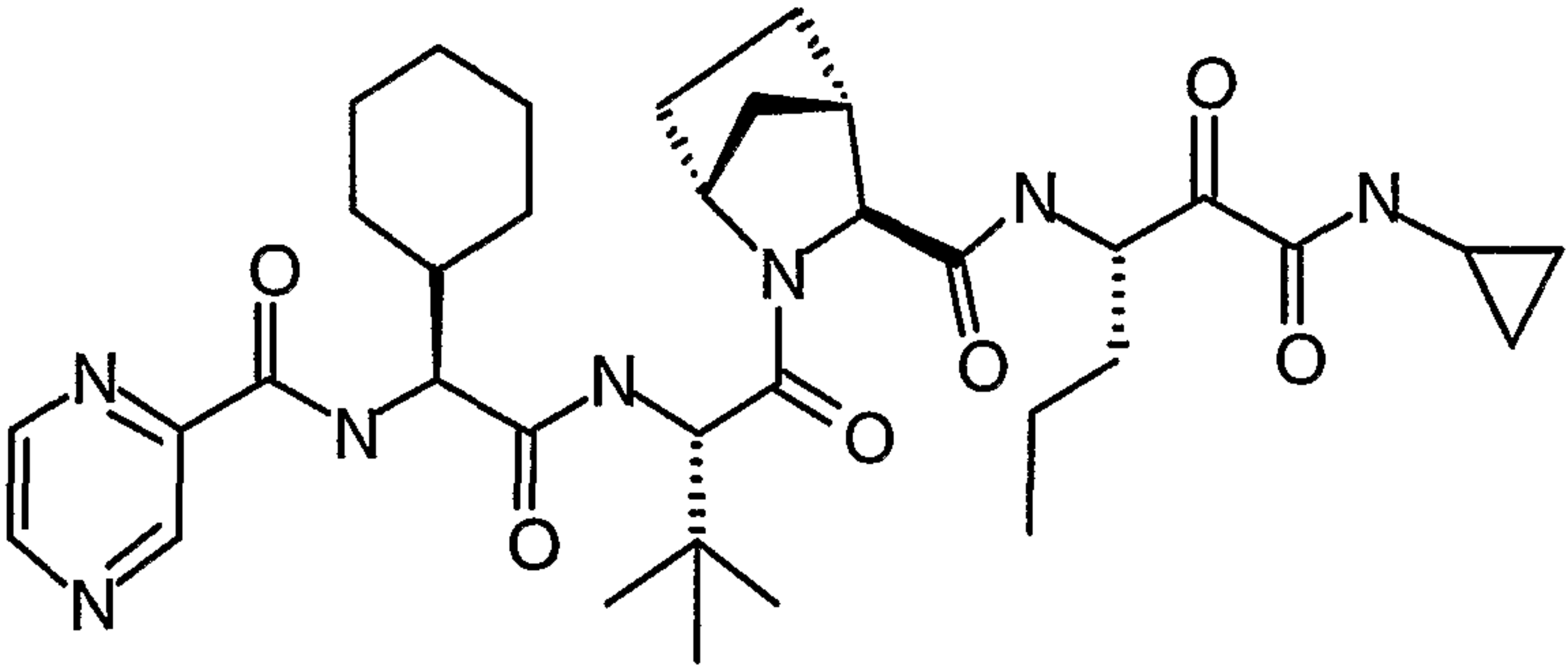
wherein $RC(O)NH-$ corresponds to T-V-

As set forth above, the compounds of this invention are capable of inhibiting the activity of HCV NS3-NS4A protease. In order to quantitate the activity of the compounds of this

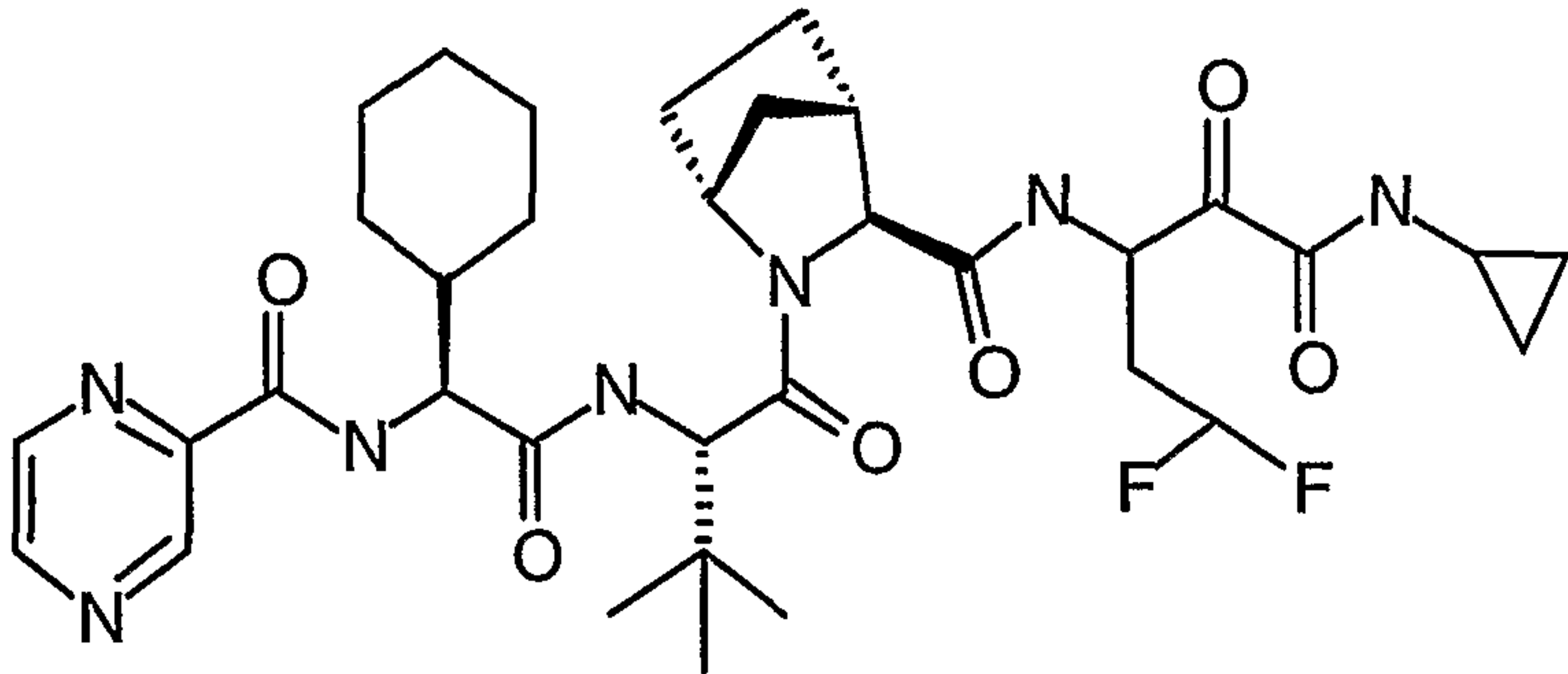
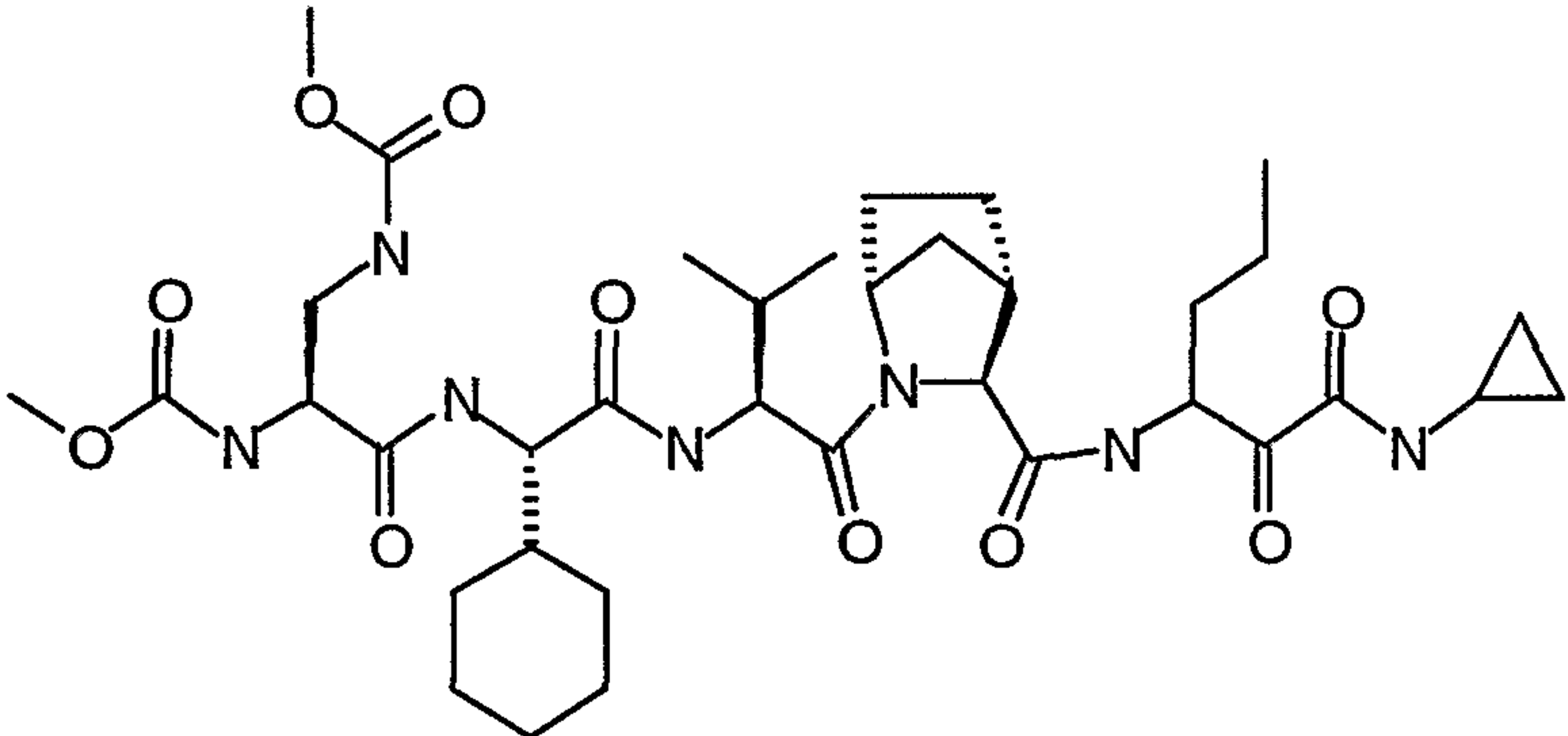
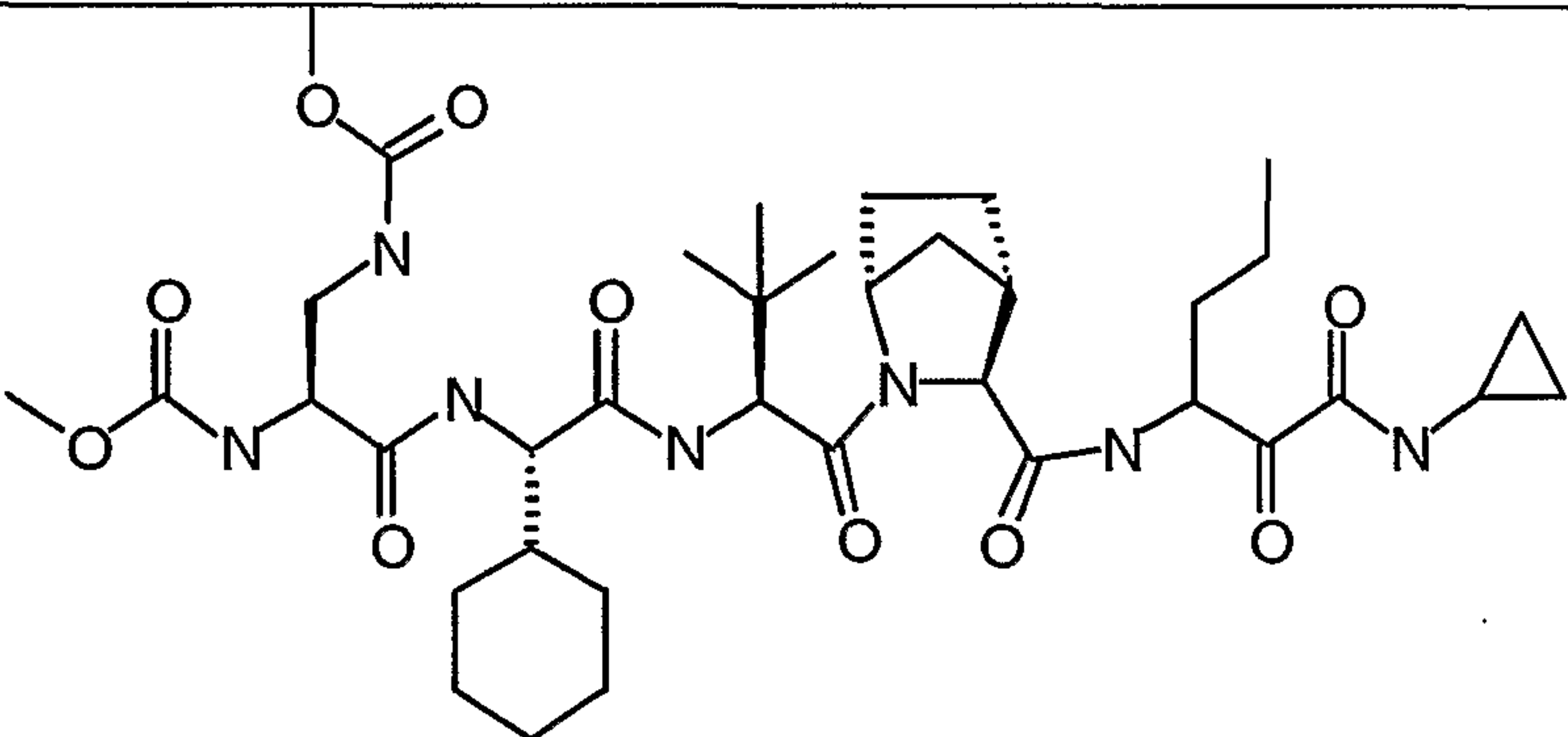
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invention, cells containing HCV replicon were incubated with the compounds of this invention, and a Taqman Real Time PCR assay was conducted to determine the percentage inhibition of HCV RNA level and the IC50 were calculated therefrom. The result are shown below in Table 1:

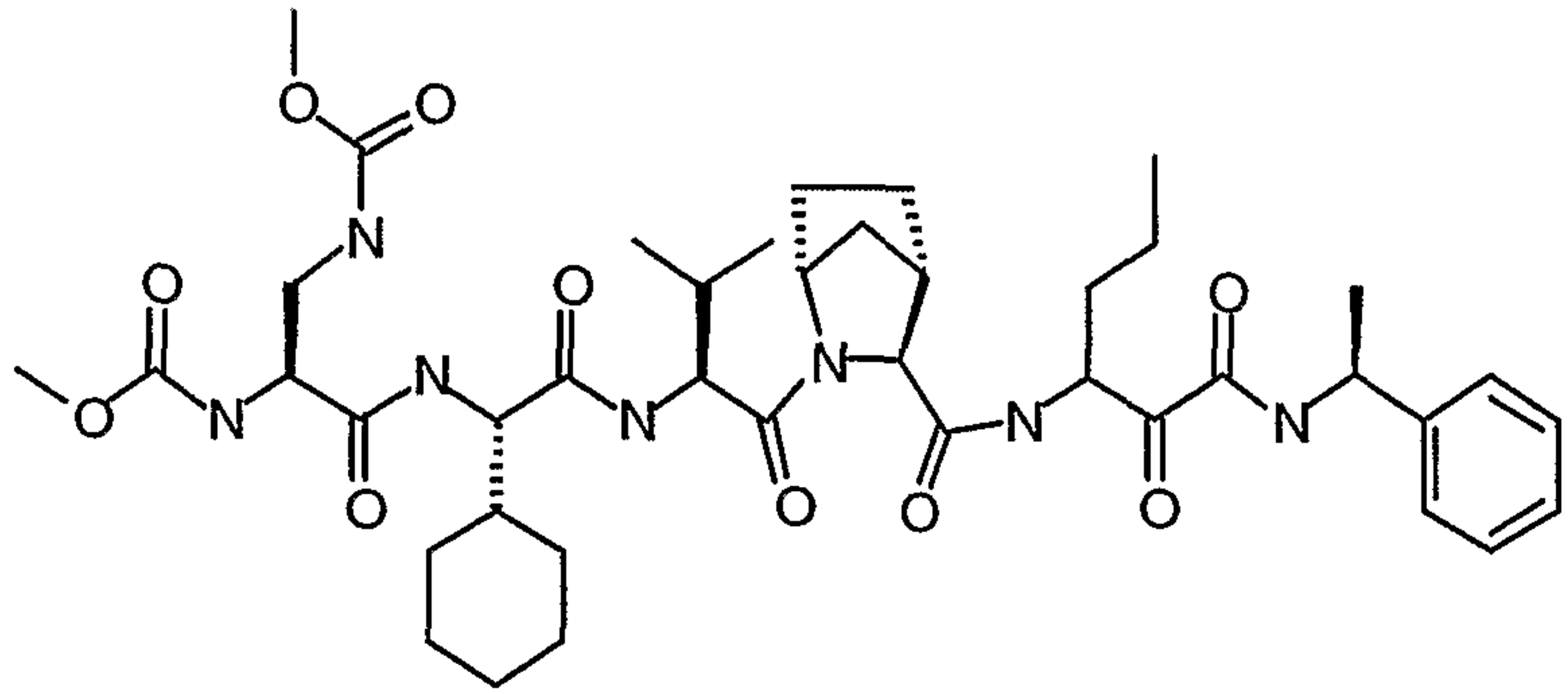
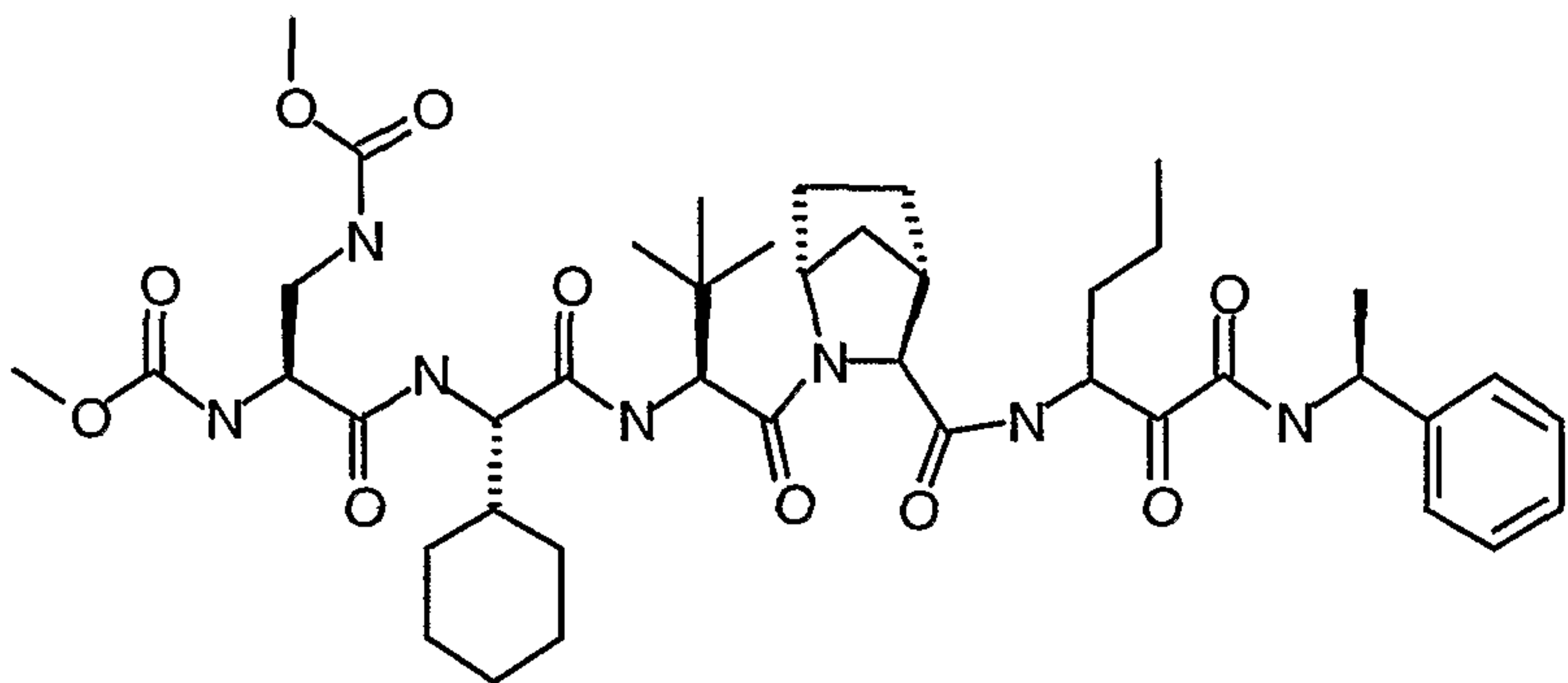
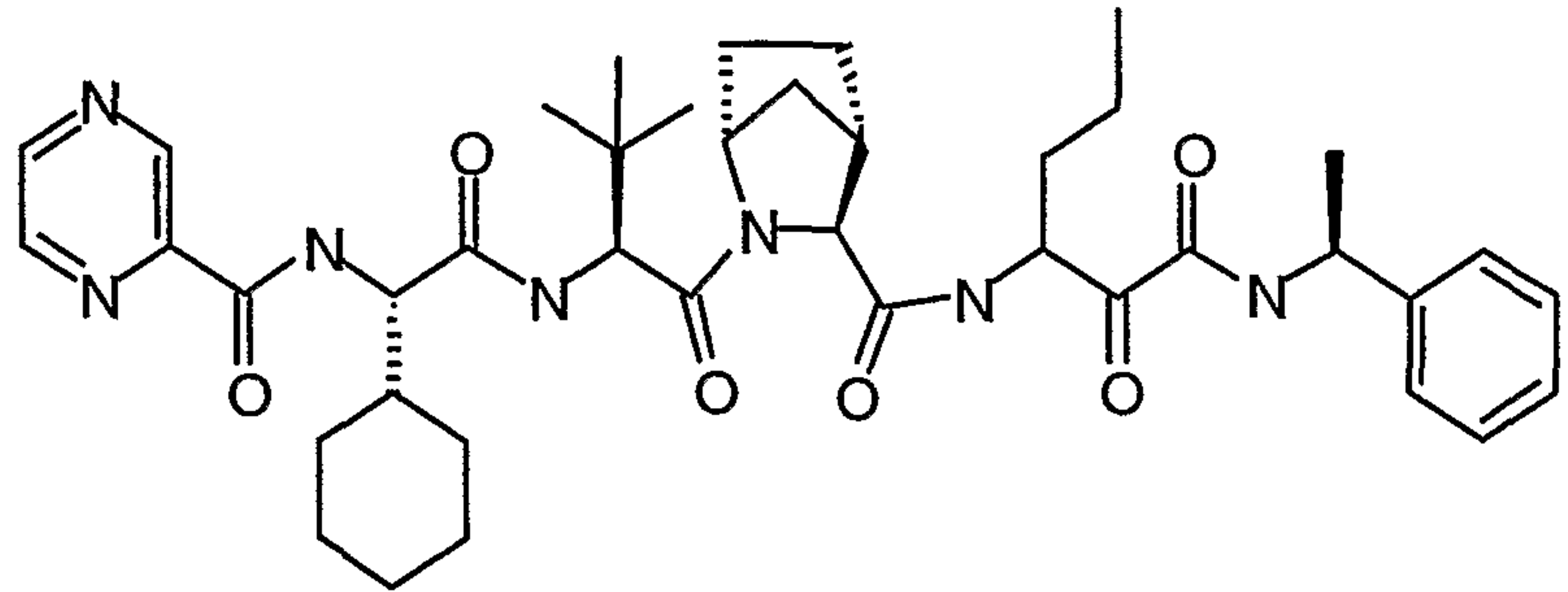
TABLE 1

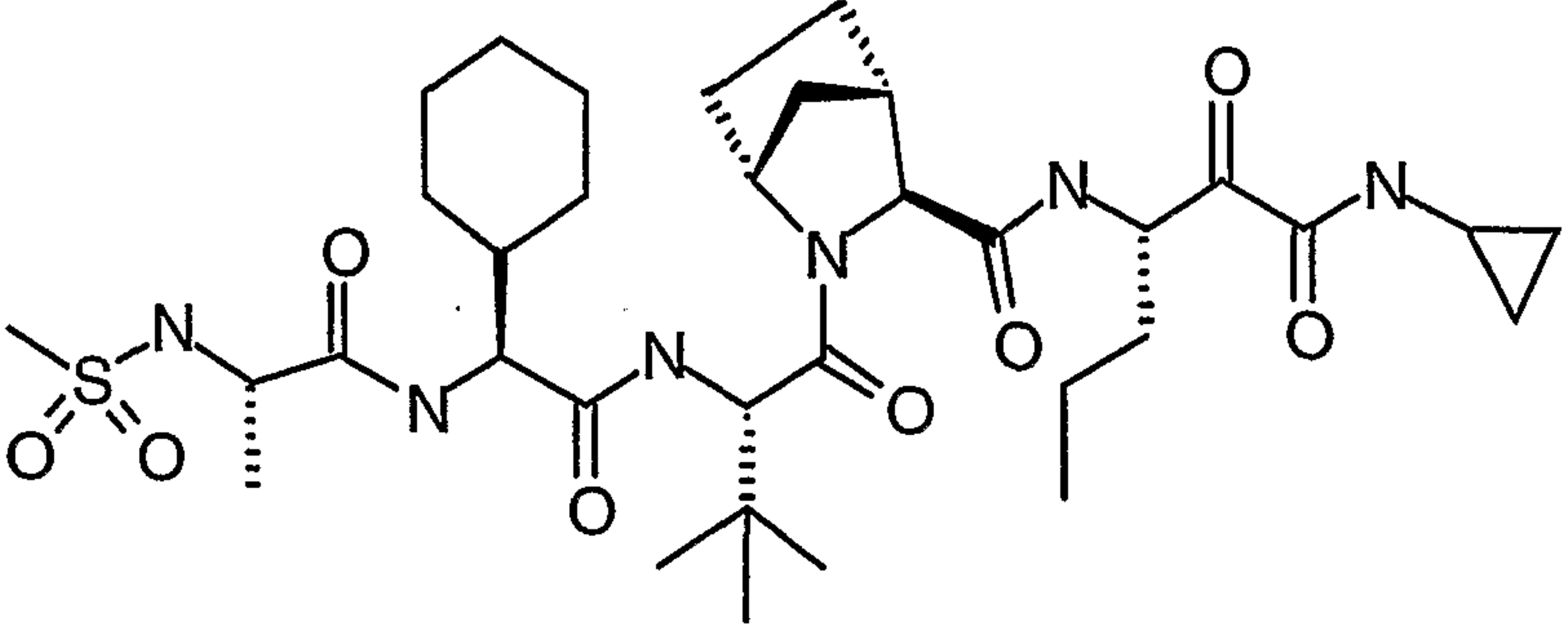
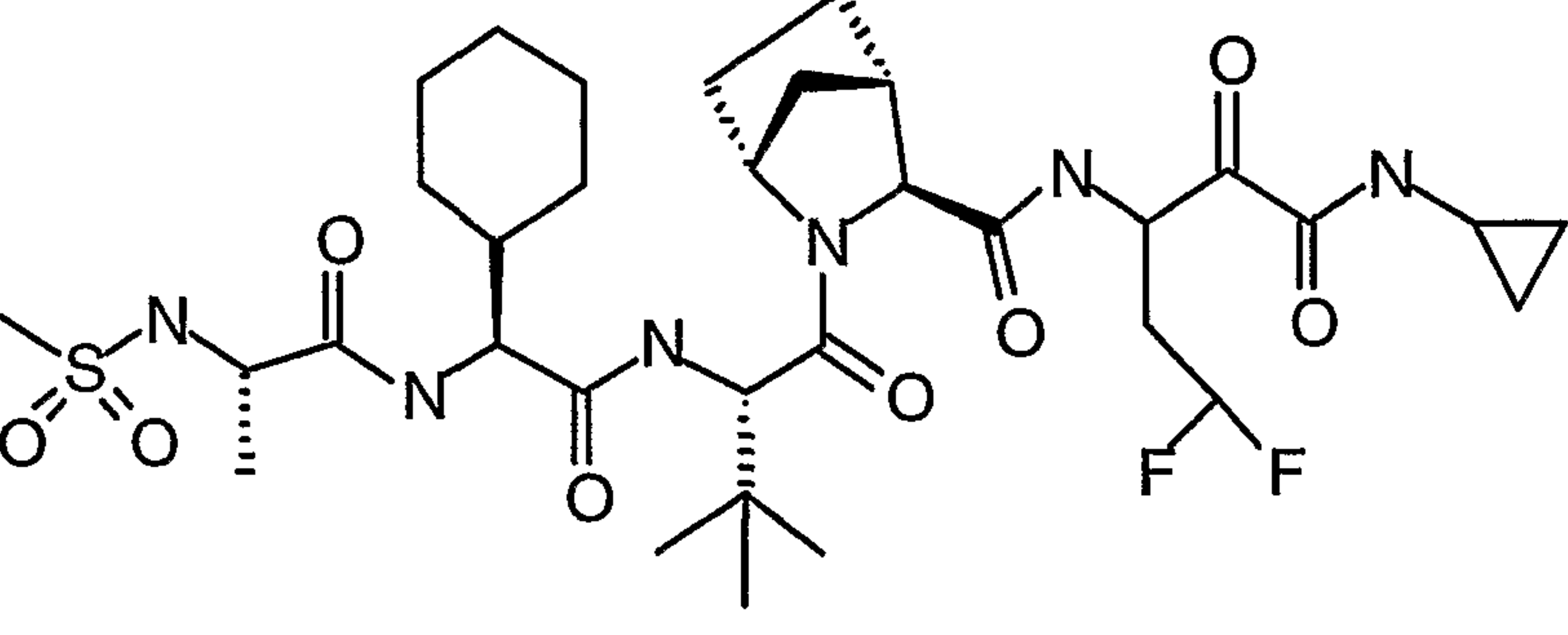
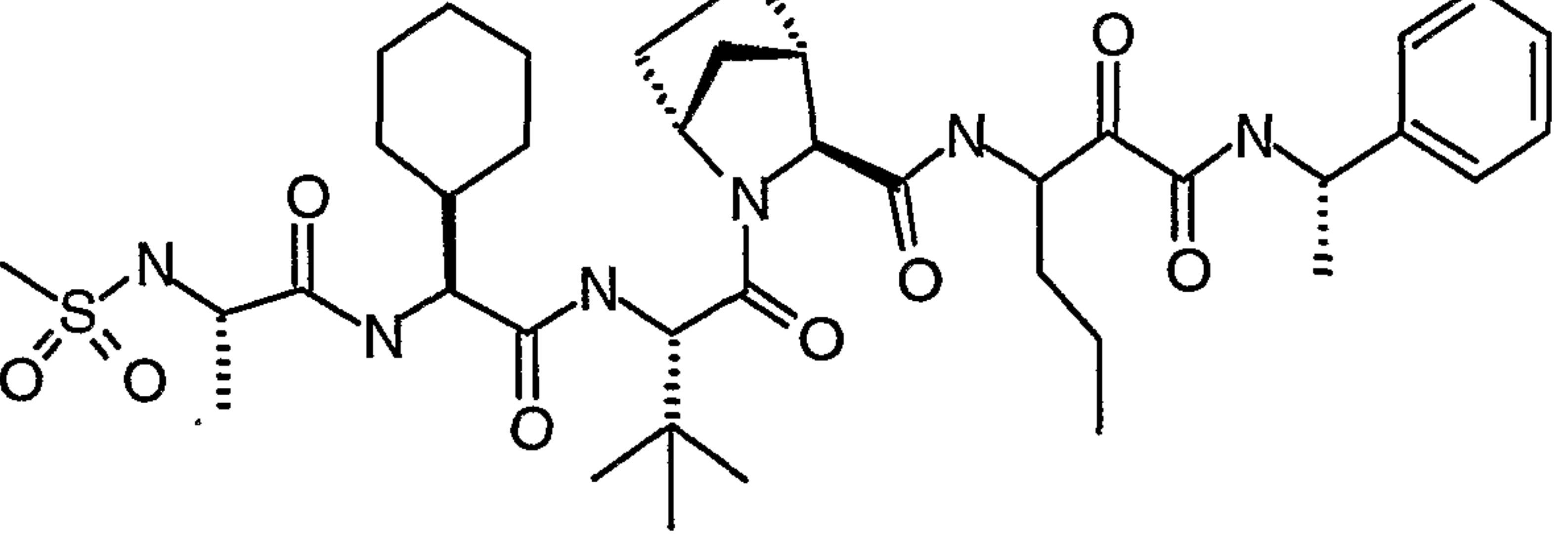
Cmpd No.	Structure	Ki (nM)	IC50 (nM)
1		220	>1000
2		90	886

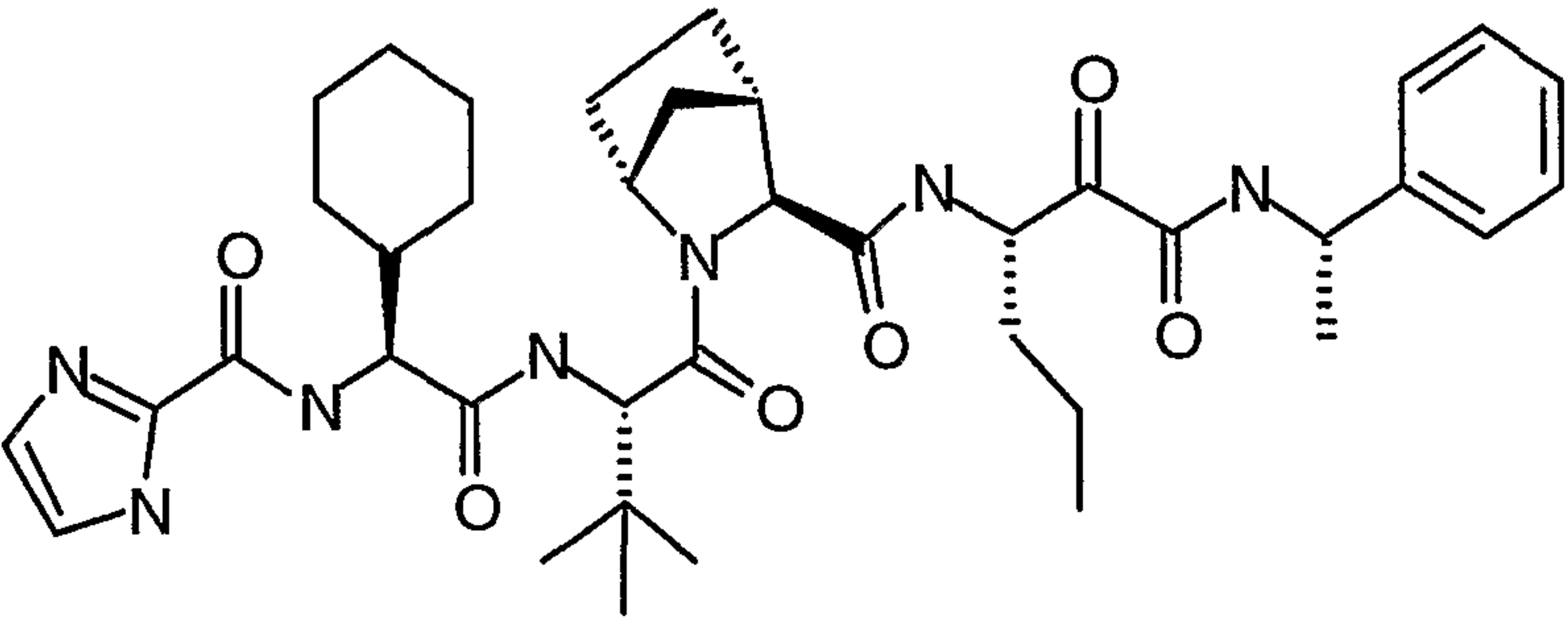
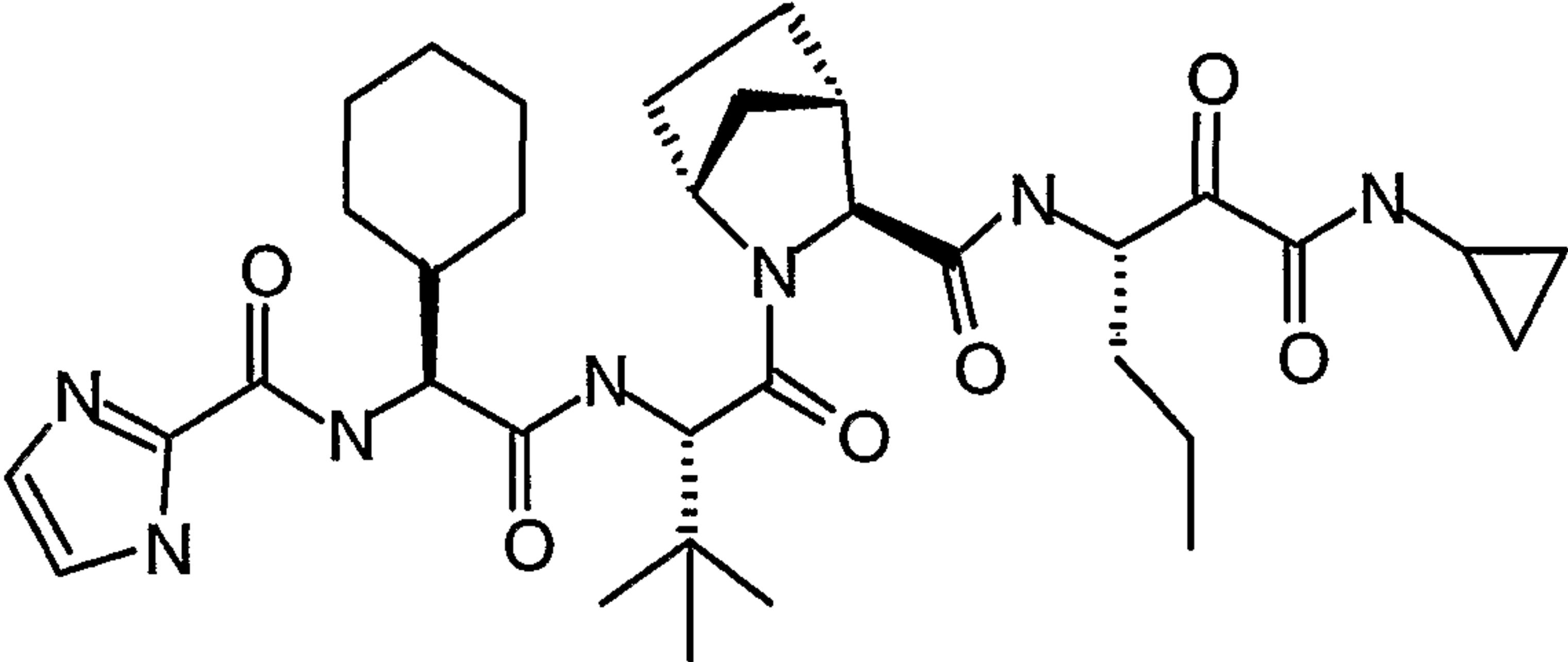
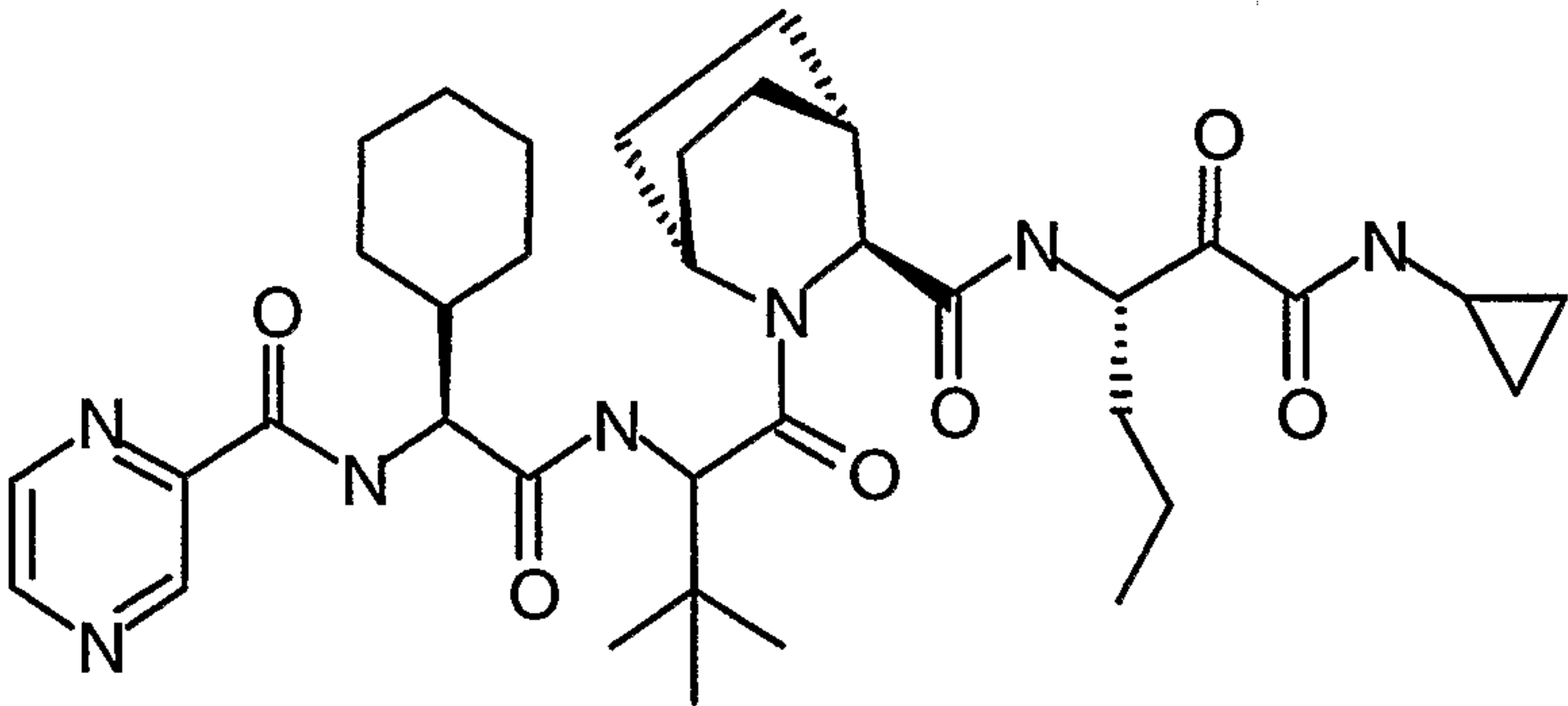
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3		63	632
4		95	>10000
5		39	1410

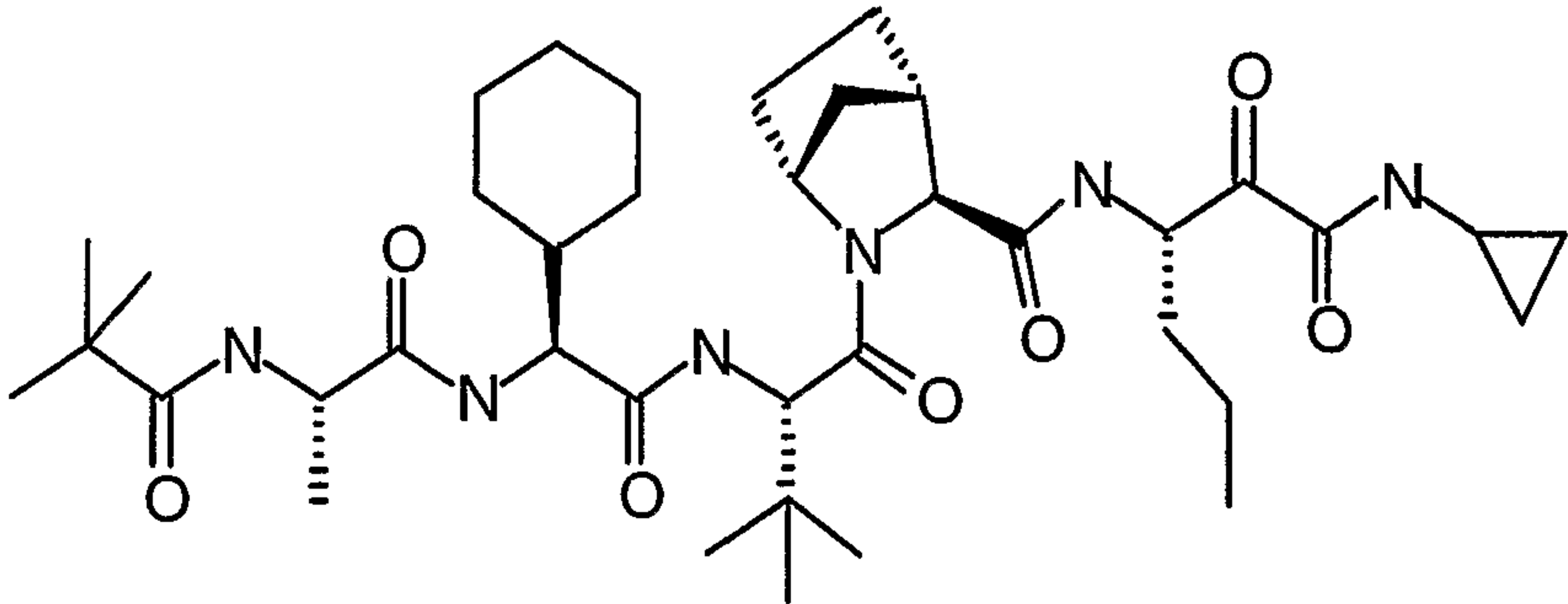
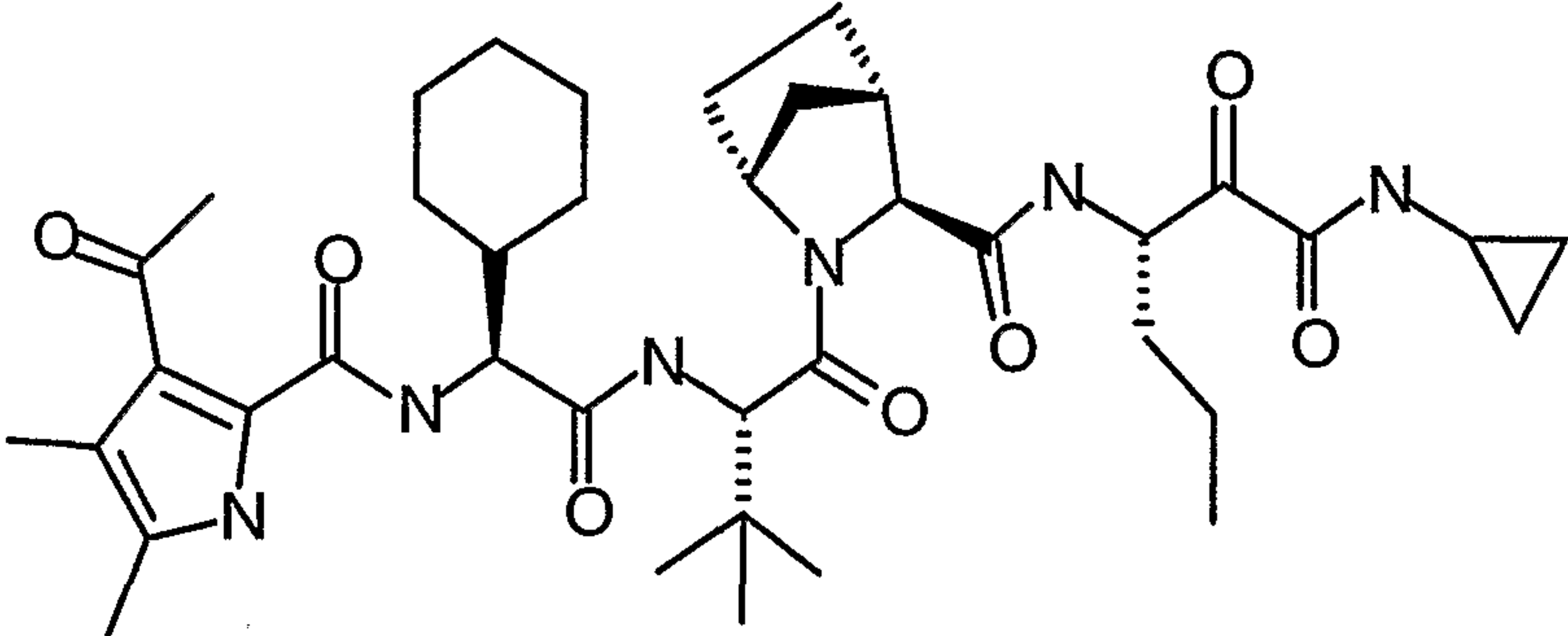
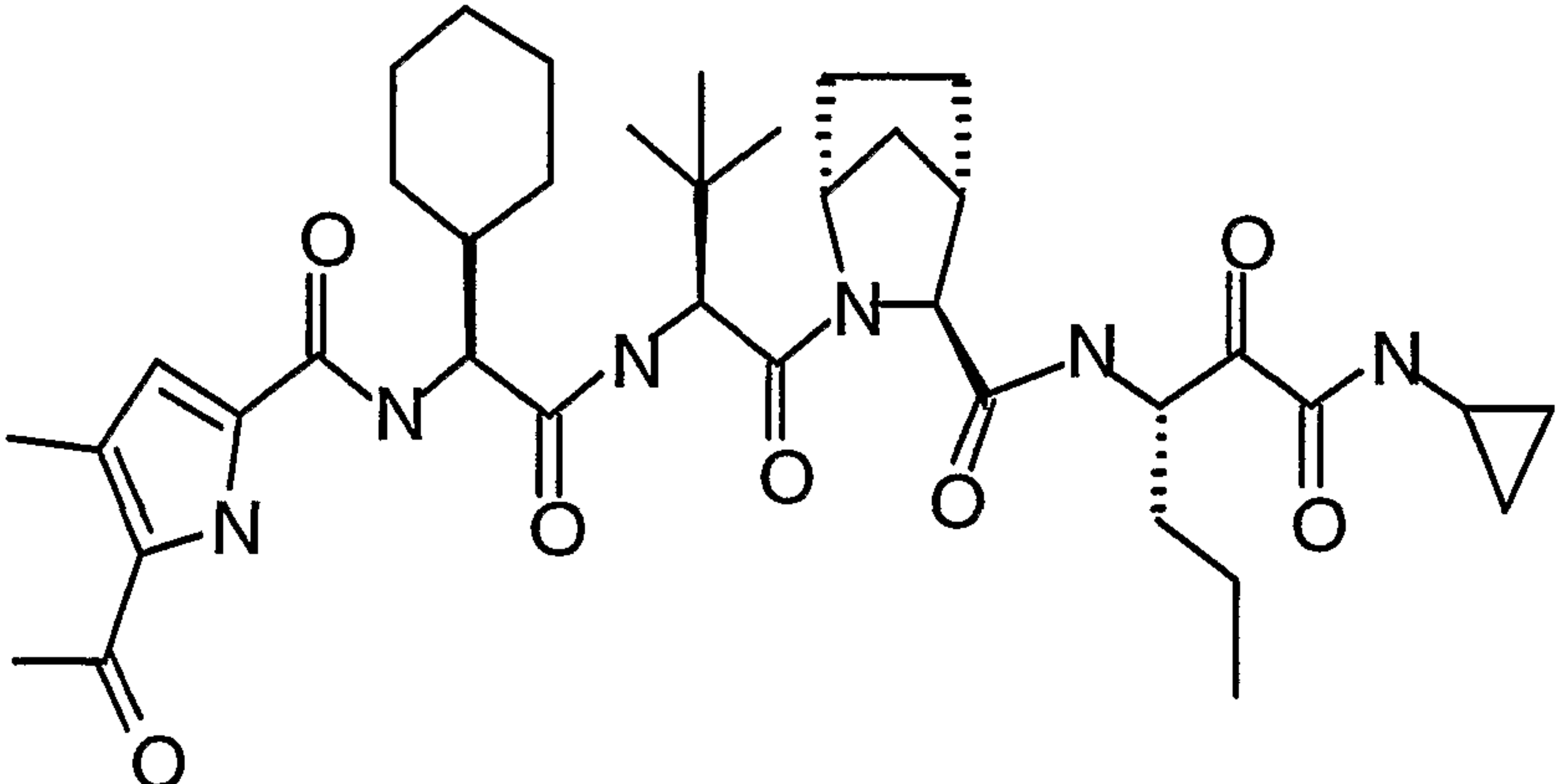
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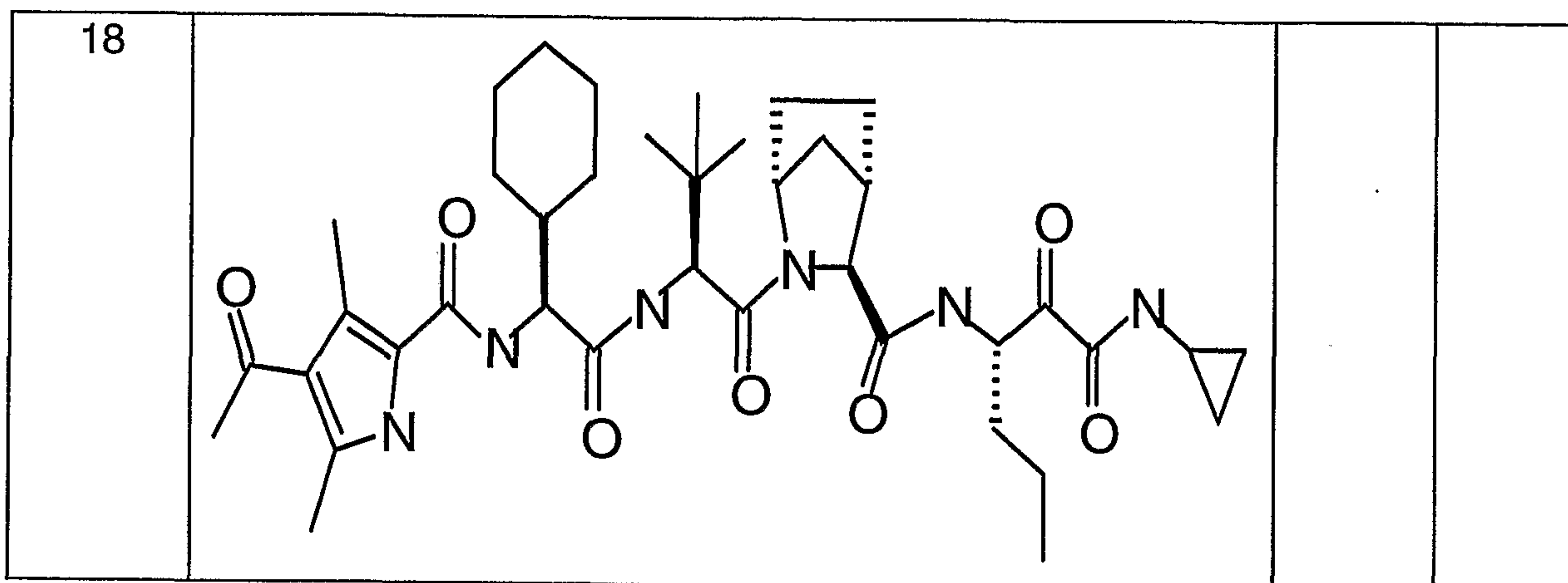
6		96	2650
7		49	449
8		110	679

9		55	4310
10		28	10000
11		50	1230

12		68	412
13		42	251
14		125	1240

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15		66	1295
16		54	<100
17			



Another embodiment of this invention provides a composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof in an amount effective to decrease the viral load in a sample or in a patient, wherein said virus encodes a serine protease necessary for the viral life cycle, and a pharmaceutically acceptable carrier.

If pharmaceutically acceptable salts of the compounds of this invention are utilized in these compositions, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentane-propionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate,

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succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, 5 salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, 10 such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and 15 phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance 20 selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow 25 administration by injection, alter metabolism and alter rate of excretion.

Pharmaceutically acceptable carriers that may be used in these compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, 30 lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of

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saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

10 According to a preferred embodiment, the compositions of this invention are formulated for pharmaceutical administration to a mammal, preferably a human being.

Such pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and

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solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any
5 bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil,
10 especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable
15 dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other
20 dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to,
25 capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule
30 form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with

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emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These may be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract may be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical

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compositions may be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Most preferred are pharmaceutical compositions formulated for oral administration.

In a related embodiment, the compositions of this invention additionally comprise another anti-viral agent, preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as α -, β -, and γ -interferons and pegylated

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derivatized interferon- α compounds; other anti-viral agents, such as ribavirin and amantadine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in
5 the HCV life cycle, including helicase and polymerase inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., VX-497 and other IMPDH inhibitors disclosed in United States Patent 5,807,876, mycophenolic acid and
10 derivatives thereof); or combinations of any of the above.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if
15 necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may,
20 however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the
25 activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of
30 active ingredients will also depend upon the particular described compound and the presence or absence and the

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nature of the additional anti-viral agent in the composition.

According to another embodiment, the invention provides a method for treating a patient infected with a virus characterized by a virally encoded serine protease that is necessary for the life cycle of the virus by administering to said patient a pharmaceutically acceptable composition of this invention. Preferably, the methods of this invention are used to treat a patient suffering from a HCV infection. Such treatment may completely eradicate the viral infection or reduce the severity thereof.. More preferably, the patient is a human being.

In an alternate embodiment, the methods of this invention additionally comprise the step of administering to said patient an anti-viral agent preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as α -, β -, and γ -interferons and pegylated derivatized interferon- α compounds; other anti-viral agents, such as ribavirin and amantadine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase and polymerase inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., VX-497 and other IMPDH inhibitors disclosed in United States Patent 5,807,876, mycophenolic acid and derivatives thereof); or combinations of any of the above.

Such additional agent may be administered to said patient as part of a single dosage form comprising

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both a compound of this invention and an additional anti-viral agent. Alternatively the additional agent may be administered separately from the compound of this invention, as part of a multiple dosage form, wherein
5 said additional agent is administered prior to, together with or following a composition comprising a compound of this invention.

In yet another embodiment the present invention provides a method of pre-treating a biological substance
10 intended for administration to a patient comprising the step of contacting said biological substance with a pharmaceutically acceptable composition comprising a compound of this invention. Such biological substances include, but are not limited to, blood and components
15 thereof such as plasma, platelets, subpopulations of blood cells and the like; organs such as kidney, liver, heart, lung, etc; sperm and ova; bone marrow and components thereof, and other fluids to be infused into a patient such as saline, dextrose, etc.

20 According to another embodiment the invention provides methods of treating materials that may potentially come into contact with a virus characterized by a virally encoded serine protease necessary for its life cycle. This method comprises the step of contacting
25 said material with a compound according to the invention. Such materials include, but are not limited to, surgical instruments and garments; laboratory instruments and garments; blood collection apparatuses and materials; and invasive devices, such as shunts, stents, etc.

30 In another embodiment, the compounds of this invention may be used as laboratory tools to aid in the isolation of a virally encoded serine protease. This

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method comprises the steps of providing a compound of this invention attached to a solid support; contacting said solid support with a sample containing a viral serine protease under conditions that cause said protease to bind to said solid support; and eluting said serine protease from said solid support. Preferably, the viral serine protease isolated by this method is HCV NS3-NS4A protease.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Example 1

Ethyl (1S,3S,4R) -2- [(1R) -1-phenylethyl] -2-azabicyclo [2.2.1] hept-5-ene-3-carboxylate (1) (example for $n = 0$, $m = 0$; each $R_{20} = H$) see Scheme 1

(R)-Methylbenzylamine (15 mL; .118 mol; 1.05 eq) was added to a stirred 0°C solution of for example, ethyl glyoxylate 50% in toluene (23 mL; .112 mol; 1.0 eq) in 600 mL of anhydrous DCM containing 27 g of 4A molecular sieve. The reaction mixture was stirred at 0°C for 1 h. then it was lowered to -78°C. The 3 following reagents were sequentially added with 5 min. in between each addition:

TFA (9.08 mL; .118 mmol; 1.05 eq), boron trifluoride etherate (14.93 mL; .118 mol; 1.05 eq) and, for example, cyclopentadiene (16.37 mL; .146 mol; 1.3 eq). The reaction mixture was stirred at -78°C for 5 h before it was allowed to warm to rt. The molecular sieves were separated and the reaction mixture was carefully washed with saturated aqueous sodium hydrogen carbonate (250 mL), brine (250 mL), and dried with magnesium sulfate.

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Concentration and purification by flash chromatography (Hexanes: EtOAc:TEA (89:10:1) afforded (in order of elution) 2.3 g (7.%) of minor endo-isomer and 23.5 g (78%) of the major exo-isomer 1. The compound was characterized using NMR.

Example 2

Ethyl(1S,3S,4R)-2-azabicyclo[2.2.1]heptane-3-carboxylate (2) (example for o = 1, m = 0; each R₂₀ = H)

The aza Diels-Alder adduct 1 (23.5 g; 0.086 mol) was dissolved in 200 mL of absolute ethanol, and, for example, Pd-C 10% (600 mg) was added. The mixture was stirred at rt under hydrogen (55 psi) for 16 h. Filtration through a pad of celite (or nylon/carbon filter combination) and concentration yielded 14.2 g of 2 (97%) as a pale yellow oil which was used directly for the next step. The compound was characterized using NMR.

Example 3

(1S,3S,4R)-2-Benzoylazabicyclo[2.2.1]heptane-3-carboxylic acid 3 (example for o = 1, m = 0, each R₂₀ = H)

Amino ester 2 (3.45 g; 0.0204 mol; 1.0 eq) was added a mixture of, for example, 1N NaOH (71 mL; .143 mol; 3.5 eq) and 71 mL of water and stirred at rt for 4 h (TLC monitoring w/ mixture of EtOAc and 5% TEA). When the saponification is complete, 100 mL of acetone was added and the temperature was lowered to 0°C. Benzyl chloroformate (3.5 mL; 0.0244 mol; 1.2 eq) in 40 mL of acetone was slowly added and the reaction mixture was allowed to stir at rt for 16 h with maintaining the pH to roughly 9 to 10 with 1N NaOH. The acetone was removed and 200 mL of water was added. The aqueous phase was washed with ether (3X 200 mL) and the aqueous phase acidified to pH 2-3 with 2N HCl. Extraction of the product with (3X

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250 mL) of EtOAc, drying (Na_2SO_4) and concentration *in vacuo* provided 3.85 g (70%) of amino acid 3. The compound was used directly for the next step. The compound was characterized using NMR.

5

Example 4

tert-Butyl(1*S*,3*S*,4*R*)-2-Benzoylazabicyclo[2.2.1]heptane-3-carboxylate (4) (example for $o = 1$, $m = 0$, each $R_{20} = \text{H}$)

In a sealed tube, 140 μL of concentrated sulfuric acid was added to a solution of acid 3 (3.86g; 0.014 mol) in 30 mL
10 of DCM. The solution was brought to -20°C and saturated with isobutylene, causing a volume increase of 14 mL. After 70 h at rt, the cap was remove to release the pressure and the solution was added to 25 mL of water containing sodium carbonate sufficient to neutralize all
15 acid. The compound 4 was used directly for the next step without further purification. The compound was characterized using NMR.

Removal of the Cbz group with hydrogenation under 1 atm of hydrogen using Pd-C10% in ethanol gave, after 5 h, the
20 desired aminoester intermediate in quantitative yield. The crude compound was coupled to *tert*-butylglycine shown in the next step.

Example 5

tert-Butyl glycine coupling to product 5 (example for $o =$
25 1 , $m = 0$, each $R_{20} = \text{H}$, $R_3 = t\text{-Bu}$)

To a solution of Cbz-*tert*-butyl glycine (3.33 g; 0.0126 mol; 1.0 eq) in 20 mL of DCM at 0°C was added, for example, EDC (2.89 g; 0.015 mol; 1.2 eq), HOBt (2.5 g; 0.0163 mol; 1.3 eq) and DIEA (6.57 mL; 0.038 mol; 3.0 eq).
30 The resulting mixture was stirred at 0°C for 15 min. after which, the above amino ester was slowly added in 10 mL of DCM. The resulting reaction mixture was stirred at rt for

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16 h. Concentrated to a residue that was redissolved in EtOAc. Successive washes with 0.5N HCL, satd' aqueous NaHCO₃ and brine gave after drying (Na₂SO₄) and concentration *in vacuo* the desired product which was
5 subjected to flash chromatography (20% EtOAc/ 80% hexanes) to provide pure 5. The compound was characterized using NMR. The rest of the synthesis was done using standard amino acid coupling which were reported in previous patent.

10

Example 6

Ethyl (1S,3S,4R)-2-[(1R)-1-phenylethyl]-2-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (1) (example for o = 1, m = 0; each R₂₀ = H) see Scheme 2

15

The preparation of the azabicyclo[2.2.2]oct-5-ene was achieved using the same experimental as above with the procedural change that 1,3-cyclohexadiene was used instead of cyclopentadiene. The rest of the synthesis was done using standard amino acid coupling which have been reported.

20

Example 7

Cells containing hepatitis C virus (HCV) replicon were maintained in DMEM containing 10% fetal bovine serum (FBS), 0.25 mg per ml of G418, with appropriate supplements (media A).

25

On day 1, replicon cell monolayer was treated with a trypsin:EDTA mixture, removed, and then dilutedh media A into a final concentration of 100,000 cells per ml wit. 10,000 cells in 100 ul are plated into each well of a 96-well tissue culture plate, and culture overnight
30 in a tissue culture incubator at 37°C.

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On day 2, compounds (in 100% DMSO) were serially diluted into DMEM containing 2% FBS, 0.5% DMSO, with appropriate supplements (media B). The final concentration of DMSO was maintained at 0.5% throughout the dilution series.

The media on the replicon cell monolayer was removed, and then media B containing various concentrations of compounds was added. Media B without any compound was added to other wells as no compound controls.

Cells were incubated with compound or 0.5% DMSO in media B for 48 hours in a tissue culture incubator at 37°C.

At the end of the 48-hour incubation, the media was removed, and the replicon cell monolayer was washed once with PBS and stored at -80°C prior to RNA extraction.

Culture plates with treated replicon cell monolayers were thawed, and a fixed amount of another RNA virus, such as Bovine Viral Diarrhea Virus (BVDV) was added to cells in each well. RNA extraction reagents (such as reagents from RNeasy kits) were added to the cells immediately to avoid degradation of RNA. Total RNA was extracted according the instruction of manufacturer with modification to improve extraction efficiency and consistency. Finally, total cellular RNA, including HCV replicon RNA, was eluted and stored at -80°C until further processing.

A Taqman real-time RT-PCR quantification assay was set up with two sets of specific primers and probe. One was for HCV and the other was for BVDV. Total RNA

- 65 -

extractants from treated HCV replicon cells were added to the PCR reactions for quantification of both HCV and BVDV RNA in the same PCR well. Experimental failure was flagged and rejected based on the level of BVDV RNA in each well. The level of HCV RNA in each well was calculated according to a standard curve that is run in the same PCR plate. The percentage of inhibition or decrease of HCV RNA level due to compound treatment was calculated using the DMSO or no compound control as 0% of inhibition. The IC₅₀ (concentration at which 50% inhibition of HCV RNA level is observed) was calculated from the titration curve of any given compound.

The IC₅₀ values inhibitory activity of some of the compounds of the present invention is shown in Table 1 above.

Example 8

The K_i determinations were performed as follows. The K_i values for some compounds of the present invention are recited above in Table 1.

HPLC Microbore method for separation of 5AB substrate and products Substrate

NH₂-Glu-Asp-Val-Val-(alpha)Abu-Cys-Ser-Met-Ser-Tyr-COOH

Stock solution of 20 mM 5AB was made in DMSO w/ 0.2M DTT.

This was stored in aliquots at -20 C.

Buffer: 50 mM HEPES, pH 7.8; 20% glycerol; 100 mM NaCl

Total assay volume was 200 µL

	X1 (µL)	Conc. in assay
Buffer	155	see above
5 mM KK4A	1	25 µM

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1 M DTT	1	5 mM
DMSO or inhibitor	3	1.5% v/v
0.25 μ M tNS3	20	25 nM
200 μ M 5AB (initiate)	20	20 μ M

The buffer was combined with KK4A, DTT, and tNS3; 177 μ L of this solution was distributed each into wells of 96 well plate and incubated at 30 °C for ~5-10 min.

5 3 μ L of appropriate concentration of test compound dissolved in DMSO (DMSO only for control) was added to each well and incubate at 30 °C for 15 min.

Reaction was initiated by addition of 20 μ L of 200 μ M 5AB substrate (20 μ M concentration is equivalent or slightly
10 lower than the K_m for 5AB) and incubated for 20 min at 30 °C. The reaction was terminated by addition of 50 μ L of 10% TFA 200 μ L aliquots were transferred to HPLC vials The SMSY product was isolated from substrate and KK4A by the method which follows.

15

Microbore separation method

Instrumentation:

Hewlett Packard 1100

Degasser G1322A

20 Binary pump G1312A

Autosampler G1313A

Column thermostated chamber G1316A

Diode array detector G1315A

Column: Phenomenex Jupiter; 5 micron C18; 300 angstroms;

25 150x2 mm; P/O 00F-4053-B0

Column thermostat: 40 °C

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Injection volume: 100 µL

Solvent A = HPLC grade water + 0.1% TFA

Solvent B = HPLC grade acetonitrile + 0.1% TFA

Time (min)	%B	Flow (ml/min)	Max press.
0	5	0.2	400
12	60	0.2	400
13	100	0.2	400
16	100	0.2	400
17	5	0.2	400

5

Stop time: 17 min

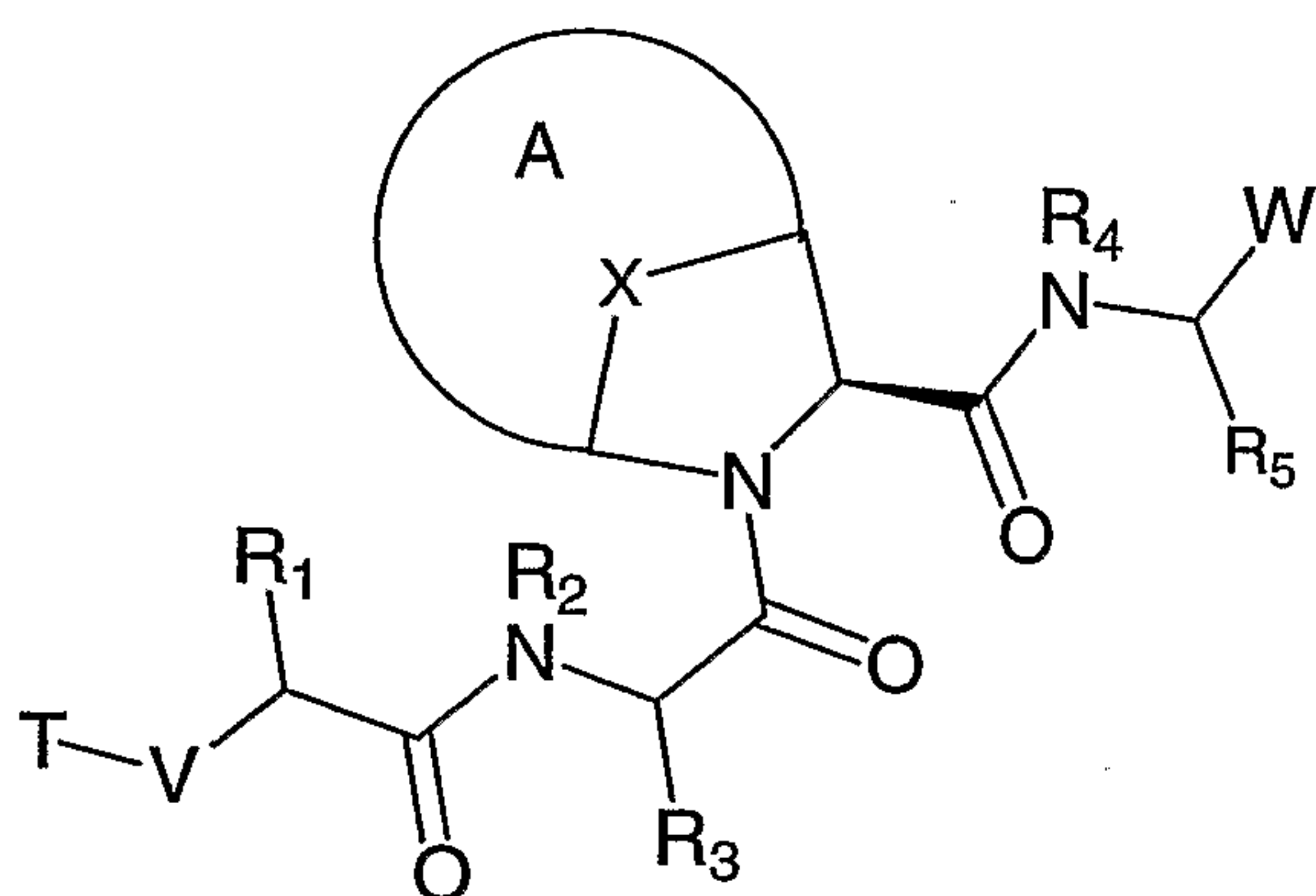
Post-run time: 10 min

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CLAIMS

What is claimed is:

- 5 1. A compound of the formula (I):



(I)

10 wherein:

A, together with X and the atoms to which X is bound, is a 4- to 7-membered aromatic or non-aromatic ring having up to 4 heteroatoms independently selected from N, NH, O, SO, or SO₂; wherein said ring is optionally
 15 fused to a (C6-C10)aryl, (C5-C10)heteroaryl, (C3-C10)cycloalkyl or (C3-C10)heterocyclyl; wherein A has up to 3 substituents selected independently from J;

X is -[CH₂]_o-, -[CJ'J']_o-, -[CH₂]_m-O-, -[CH₂]_m-S(O)₂-,
 -[CH₂]_m-SO-, -[CH₂]_m-S-, -[CR₂₀R₂₀]_m-NR₂₁-, or -[CR₂₀R₂₀]_m-
 20 NJ''-, wherein:

R₂₁ is hydrogen or -C(O)-O-R₂₂;

o is 1 or 2;

R₂₂ is -(C1-C6)alkyl, -(C2-C6)alkenyl, or
 -(C2-C6)alkynyl;

25 m is 0 or 1;

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J is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

J' is halogen, -OR', -NO₂, -CF₃, -OCF₃, -R', -OR',
 5 -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂;

J'' is -OR', -CF₃, -OCF₃, -R', oxo, -OR', -O-benzyl, -O-phenyl, 1,2-methylenedioxy, -N(R')₂, -SR', -SOR', -SO₂R', -C(O)R', -COOR', or -CON(R')₂, wherein each R' is
 10 independently:

hydrogen,
 -(C1-C12) aliphatic,
 -(C3-C10)cycloalkyl or -cycloalkenyl,
 -(C1-C12)aliphatic-[(C3-C10)cycloalkyl or
 15 -cycloalkenyl],
 -(C6-C10)aryl,
 -(C1-C12)aliphatic-(C6-C10)aryl,
 -(C3-C10)heterocyclyl,
 -(C1-C12)aliphatic-(C6-C10)heterocyclyl,
 20 -(C5-C10)-heteroaryl, or
 -(C1-C12)-aliphatic-(C5-C10)heteroaryl;

R₁ and R₃ are independently:

-(C1-C12)aliphatic,
 -(C3-C10)-cycloalkyl or -cycloalkenyl,
 25 -(C1-C12)-aliphatic-[(C3-C10)-cycloalkyl or -cycloalkenyl],
 -(C6-C10)-aryl,
 (C1-C12)aliphatic-(C6-C10)aryl,
 -(C3-C10)-heterocyclyl,
 30 -(C1-C12)aliphatic-(C6-C10)heterocyclyl,
 -(C5-C10)heteroaryl, or
 -(C1-C12)aliphatic-(C5-C10)heteroaryl,

- 70 -

wherein each of R_1 and R_3 is independently and optionally substituted with up to 3 substituents independently selected from J;

wherein up to 3 aliphatic carbon atoms in R_1 and R_3 may be replaced by a heteroatom selected from O, NH, S, SO, and SO₂ in a chemically stable arrangement;

R_2 and R_4 are independently

hydrogen,

-(C1-C12)aliphatic,

-(C1-C12)aliphatic-(C3-C10)cycloalkyl, or

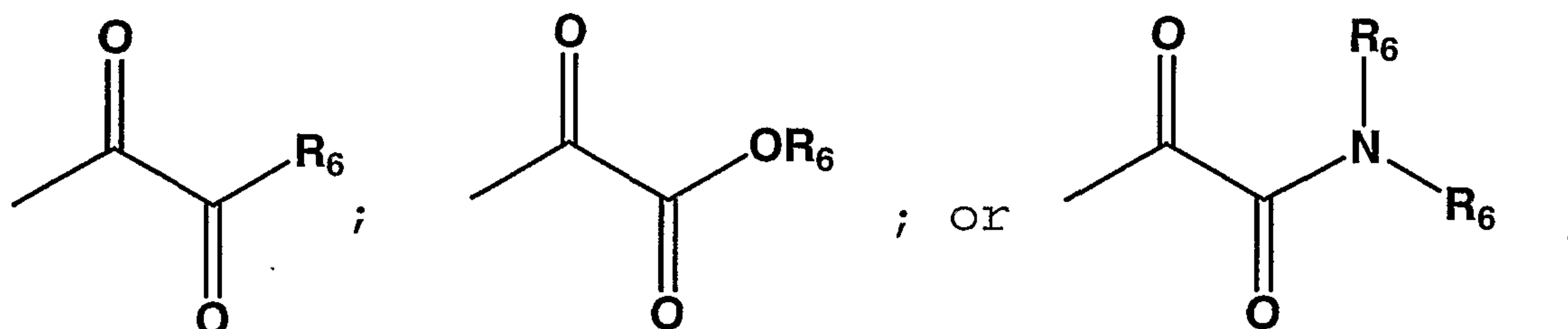
-(C1-C12)aliphatic-(C6-C10)aryl,

wherein each of R_2 and R_4 is independently and optionally substituted with up to 3 substituents independently selected from J;

wherein up to two aliphatic carbon atoms in R_2 and R_4 may be replaced by a heteroatom selected from O, NH, S, SO, and SO₂;

R_5 is -(C1-C12)aliphatic, wherein any hydrogen is optionally replaced with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom of R_5 is optionally substituted with sulfhydryl or hydroxy;

W is: -C(O)OH;



wherein each R_6 is independently:

hydrogen,

-(C1-C12)aliphatic,

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- (C6-C10) aryl,
 - (C6-C10) aryl- (C1-C12) aliphatic,
 - (C3-C10) -cycloalkyl or -cycloalkenyl,
 - (C1-C12) -aliphatic- [(C3-C10) -cycloalkyl or
 5 -cycloalkenyl],

- (C3-C10) heterocyclyl,
 - (C3-C10) heterocyclyl- (C1-C12) aliphatic,
 - (C5-C10) heteroaryl, or
 - (C1-C12) aliphatic- (C5-C10) heteroaryl, or
 10 two R₆ groups, which are bound to the same nitrogen
 atom, form together with that nitrogen atom, a
 - (C3-C10) heterocyclic ring;

wherein R₆ is optionally substituted with up to 3 J
 substituents or with a suitable electron withdrawing
 15 group;

V is -C(O)N(R₈)-, -S(O)N(R₈)-, -S(O)₂N(R₈)-, a bond,
 -CH(R₈)-, -N(R₈)-, -O-, -O-CH(R₈)-, -S-, -S-CH(R₈), -C(O)-,
 -C(O)-O-, -C(O)-S-, -C(O)-CHR₈-, -S(O)-, -S(O)-CH(R₈),
 -S(O)-N(R₈)-CHR₈-, -S(O)₂-, -S-(O)₂-CH(R₈)-, or -S(O)₂-N(R₈)-
 20 CHR₈;

wherein R₈ is hydrogen or - (C1-C12) aliphatic;

T is:

- (C6-C10) aryl,
 - (C1-C12) aliphatic- (C6-C10) aryl,
 25 - (C3-C10) -cycloalkyl or -cycloalkenyl,
 - (C1-C12) aliphatic- [(C3-C10) -cycloalkyl or
 -cycloalkenyl],
 - (C3-C10) heterocyclyl,
 - (C1-C12) aliphatic- (C3-C10) heterocyclyl,
 30 - (C5-C10) heteroaryl, or
 - (C1-C12) aliphatic- (C5-C10) heteroaryl; or

T is:

[illegible]

- (C3-C10)heterocyclyl,

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-(C1-C12)aliphatic-(C3-C10)heterocyclyl,

-(C5-C10)heteroaryl, or

-(C1-C12)aliphatic-(C5-C10)heteroaryl,

wherein each T is optionally substituted with up to

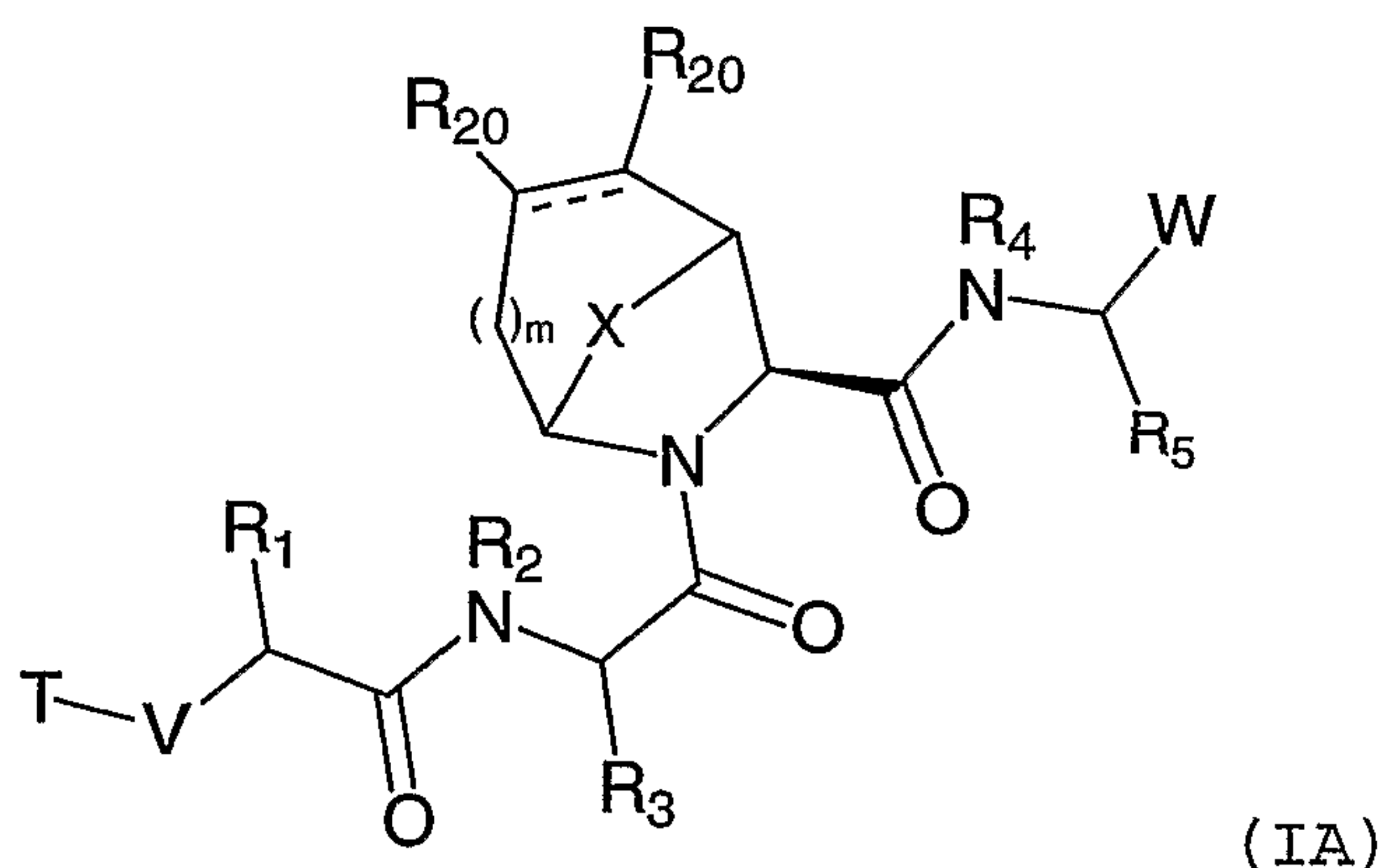
5 3 J substituents;

K is a bond, -(C1-C12)aliphatic, -O-, -S-, -NR₉-,
-C(O)-, or -C(O)-NR₉-, wherein R₉ is hydrogen or -(C1-
C12)aliphatic;

n is 1-3; and

10 each R₂₀ is independently hydrogen, -(C1-C6)aliphatic
or -O-((C1-C6)aliphatic); or each R₂₀ is taken together
with the carbon atoms to which they are bound to form a
(C3-C6)cycloalkyl.

15 2. The compound according to claim 1, wherein
the compound of formula (I):



wherein the variables are as defined

20 above.

3. The compound according to claim 1 or
claim 2, wherein:

X is -[CH₂]_o-, -[CH₂]_m-O-, -[CH₂]_m-S(O)₂, or -[CR₂₀R₂₀]_m-
25 NR₂₁; wherein:

- 74 -

R_{21} is hydrogen or $-C(O)-O-R_{22}$;

o is 1 or 2;

R_{22} is $-(C1-C6)alkyl$, $-(C2-C6)alkenyl$, or
 $-(C2-C6)alkynyl$;

5 m is 0 or 1;

R_5 is $-(C2-C7)alkyl$ optionally substituted with
 halogen;

each R_{20} is independently hydrogen, $-(C1-C6)alkyl$ or
 $-O-((C1-C6)alkyl)$; or each R_{20} is taken together with the
 10 carbon atoms to which they are bound to form a $(C3-$
 $C6)cycloalkyl$;

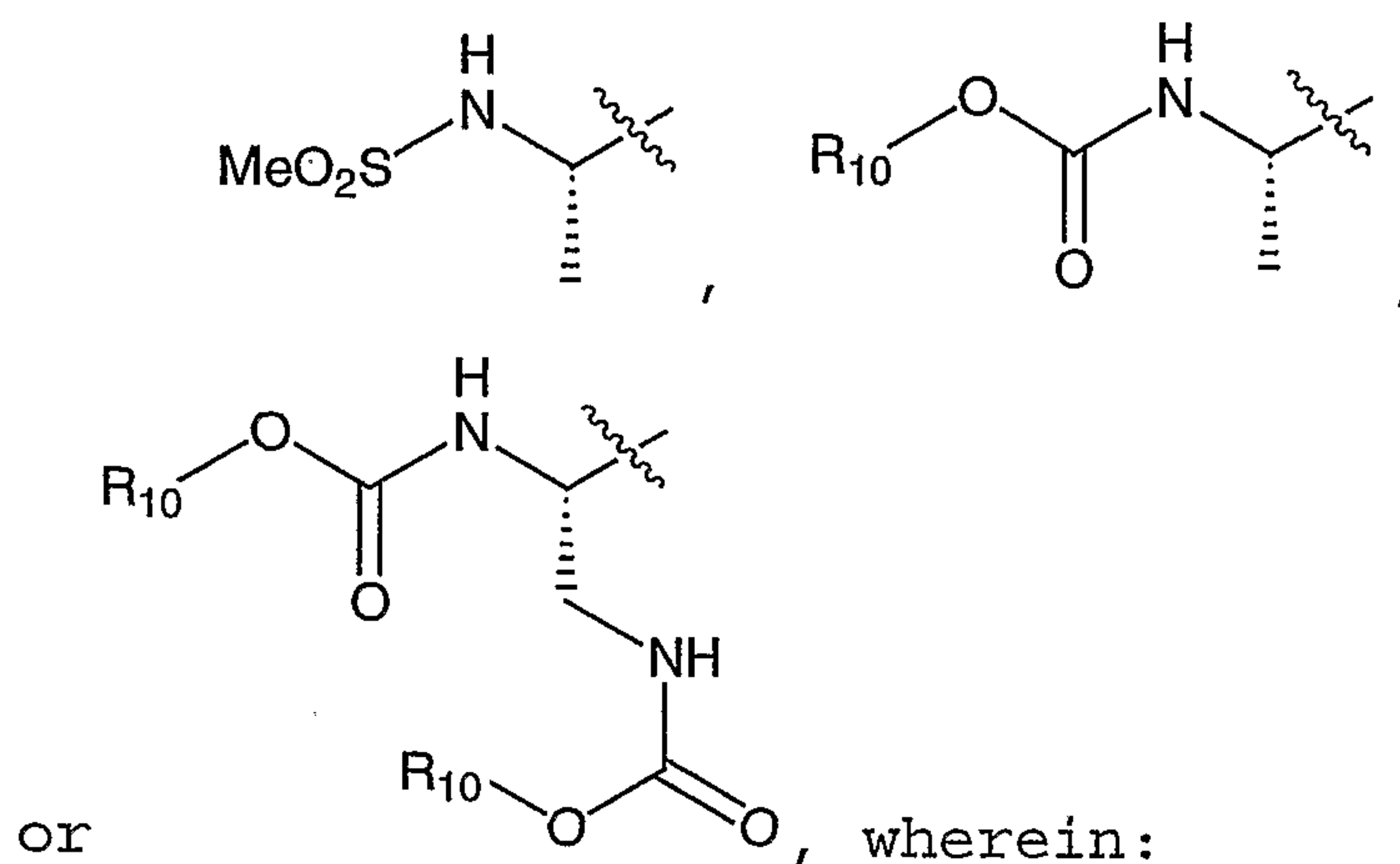
R_3 and R_1 are independently $-(C1-C10)alkyl$,
 $-(C3-C7)cycloalkyl$, or $-((C1-C6)alkyl)-((C3-$
 $C7)cycloalkyl)$;

15 V is a bond, $-CH(R_8)-$, $-N(R_8)-$, $-O-$, $-O-CH(R_8)-$, $-S-$,
 $-S-CH(R_8)-$, $-C(O)-$, $-C(O)-O-$, $-C(O)-S-$, $-C(O)-CH(R_8)-$,
 $-C(O)N(R_8)-$, $-S(O)-$, $-S(O)-CH(R_8)-$, $-S(O)N(R_8)-$,
 $-S(O)-N(R_8)-CH(R_8)-$, $-S(O)_2-$, $-S-(O)_2-CH(R_8)-$, $-S(O)_2N(R_8)-$, or
 $-S(O)_2-N(R_8)-CH(R_8)-$;

20 wherein R_8 is hydrogen or $-(C1-C3)alkyl$;

T is $-(C6-C10)aryl$, $-(C5-C10)heteroaryl$,
 $-(C3-C6)cycloalkyl$, $-(C3-C10)heterocyclyl$, $-(C1-C6)alkyl-$
 $(C6-C10)aryl$, $-(C1-C6)alkyl-(C5-C10)heteroaryl$,
 $-(C1-C6)alkyl-(C3-C6)cycloalkyl$, $-(C1-C6)alkyl-$
 25 $(C3-C10)heterocyclyl$, $-(C2-C6)alkenyl-(C6-C10)aryl$,
 $-(C2-C6)alkenyl-(C5-C10)heteroaryl$, $-(C2-C6)alkenyl-$
 $(C3-C6)cycloalkyl$, $-(C2-C6)alkenyl-(C3-C10)heterocyclyl$,

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R_{10} is -(C1-C4)alkyl; and

W is -C(O)OH or -C(O)-C(O)- R_6 , wherein:

5 R_6 is -(C1-C6)alkyl, -(C6-C10)aryl,
 -(C3-C6)cycloalkyl, -(C5-C10)heteroaryl,
 -(C3-C10)heterocyclyl, or

W is -C(O)-C(O)NR₆R₆, wherein:

10 NR₆R₆ is -NH-((C1-C6)alkyl),
 -NH-((C3-C6)cycloalkyl), -NH-CH(CH₃)-aryl, -NH-CH(CH₃)-
 (C5-C10)heteroaryl or -NH-CH(CH₃)-(C3-C10)heterocyclyl,
 wherein said aryl, heteroaryl, or heterocyclyl is
 optionally substituted with a suitable electron
 withdrawing group.

15

4. The compound according to claim 3, wherein
 V is -NH-.

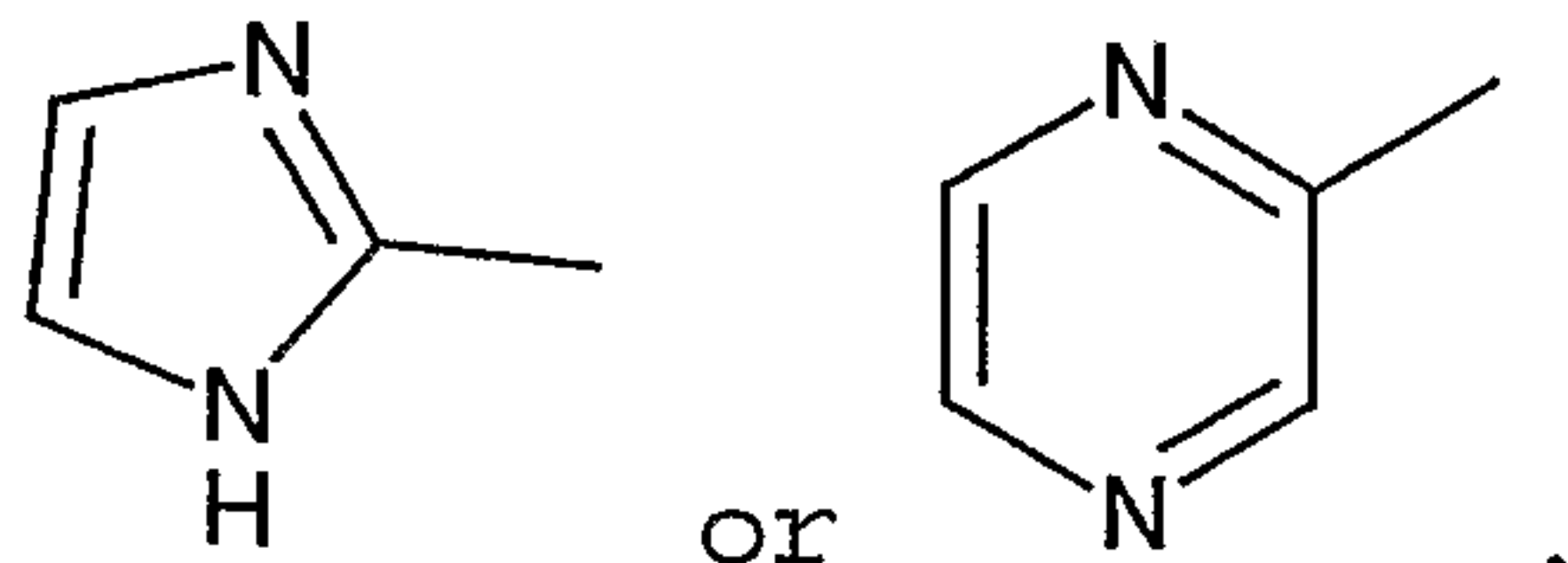
5. The compound according to claim 3, wherein
 20 V is -C(O)-.

6. The compound according to claim 3,
 wherein T is a -(C5-C10)heteroaryl.

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7. The compound according to claim 6, wherein

T is:



5 8. The compound according to claim 3, wherein
 R_1 is $-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)_2$,
 $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_3$, or cyclohexyl.

9. The compound according to claim 8, wherein
 10 R_1 is cyclohexyl.

10. The compound according to claim 3, wherein
 R_3 is $-\text{C}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_3$, or cyclohexyl.

15 11. The compound according to claim 10,
 wherein R_3 is $-\text{C}(\text{CH}_3)_3$ or $-\text{CH}(\text{CH}_3)_2$.

12. The compound according to claim 3, wherein
 each R_{20} is independently $-\text{CH}_3$ or hydrogen.

20

13. The compound according to claim 12,
 wherein each R_{20} is hydrogen.

14. The compound according to claim 3, wherein
 25 R_5 is $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{CH}_2\text{CHF}_2$, or
 $-\text{CH}_2\text{CH}_2\text{CF}_3$.

15. The compound according to claim 14,

- 77 -

wherein R_5 is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ or $-\text{CH}_2\text{CH}_2\text{CHF}_2$.

16. The compound according to claim 15,
wherein R_5 is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$.

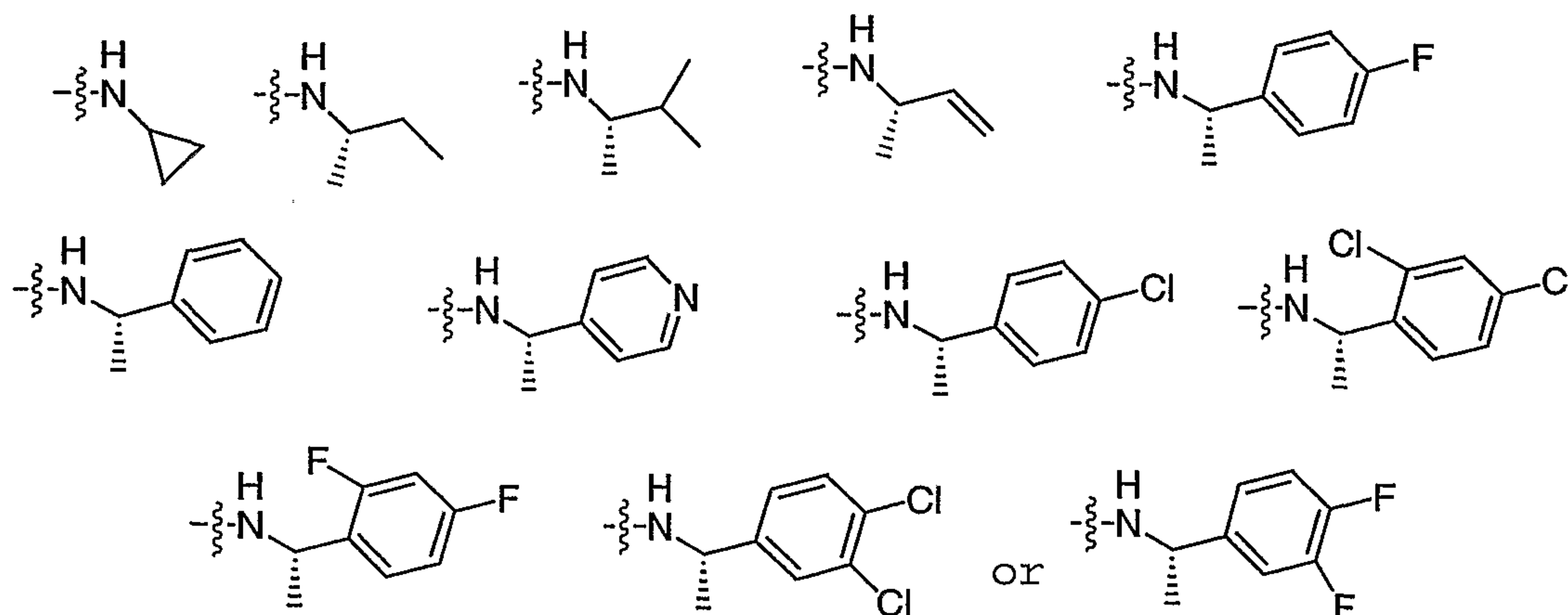
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17. The compound according to claim 3, wherein
W is $\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_6$.

18. The compound according to claim 3, wherein
10 W is $\text{C}(\text{O})-\text{C}(\text{O})\text{NR}_6\text{R}_6$ and NR_6R_6 is $-\text{NH}-(\text{C}3-\text{C}6)\text{cycloalkyl}$,
 $-\text{NH}-\text{CH}(\text{CH}_3)-(\text{C}6-\text{C}10)\text{aryl}$, $-\text{NH}-\text{CH}(\text{CH}_3)-(\text{C}3-$
 $\text{C}10)\text{heterocyclyl}$, or $-\text{NH}-\text{CH}(\text{CH}_3)-(\text{C}5-\text{C}10)\text{heteroaryl}$,
wherein said aryl, heterocyclyl, or heteroaryl is
optionally substituted with halogen.

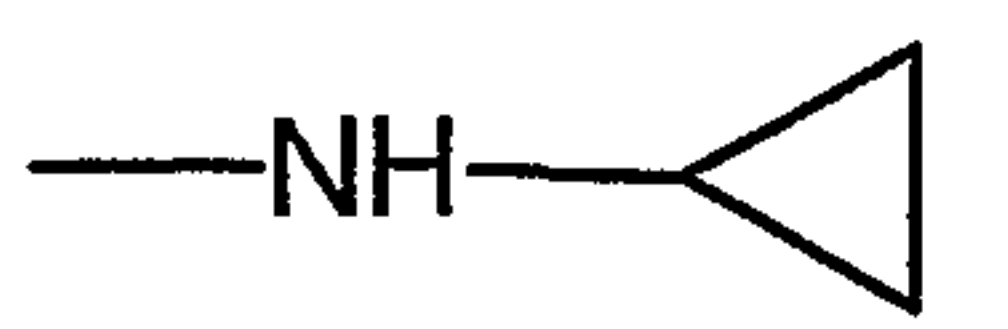
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19. The compound according to claim 18,
wherein NR_6R_6 is:



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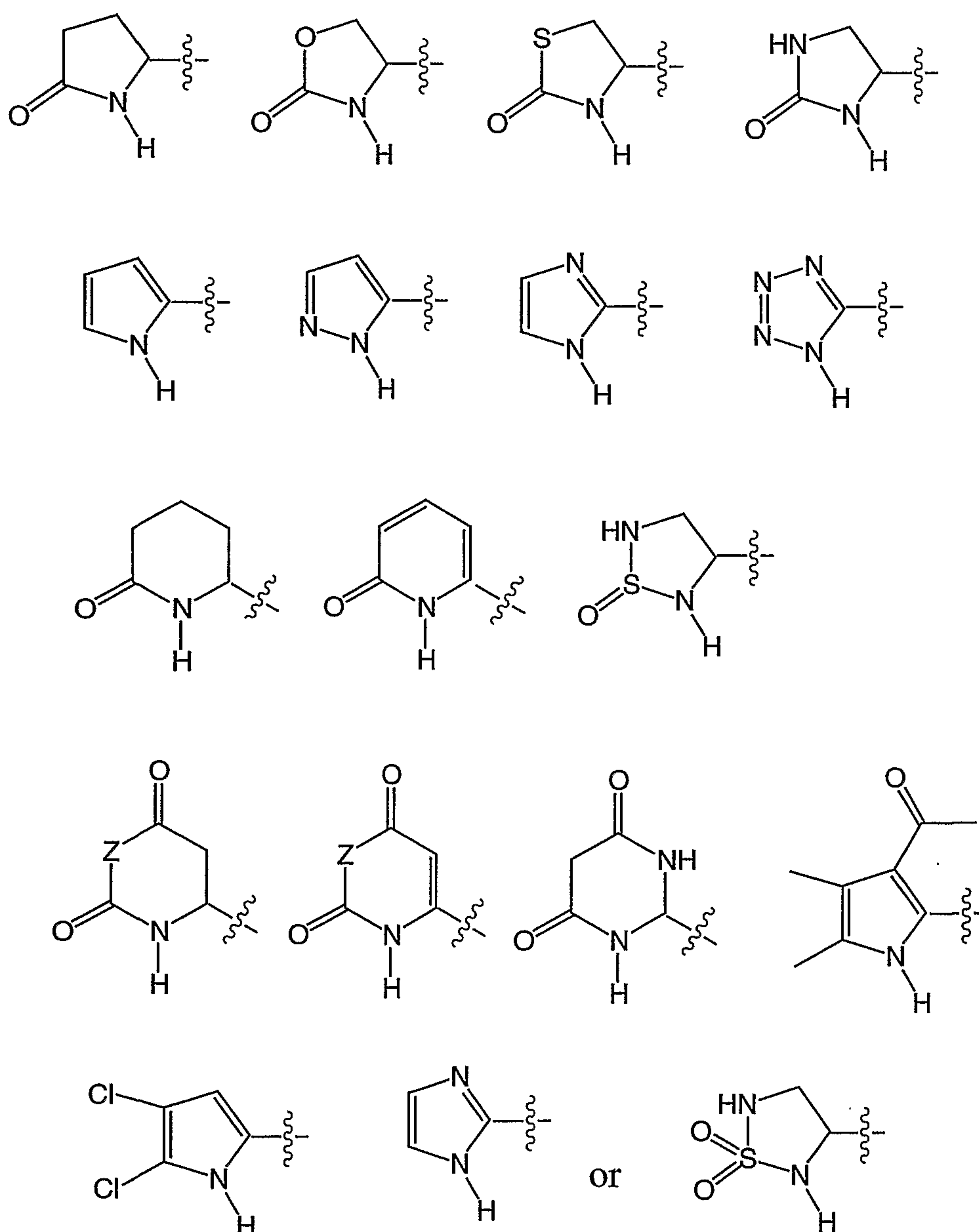
20. The compound according to claim 19,
wherein NR_6R_6 is:



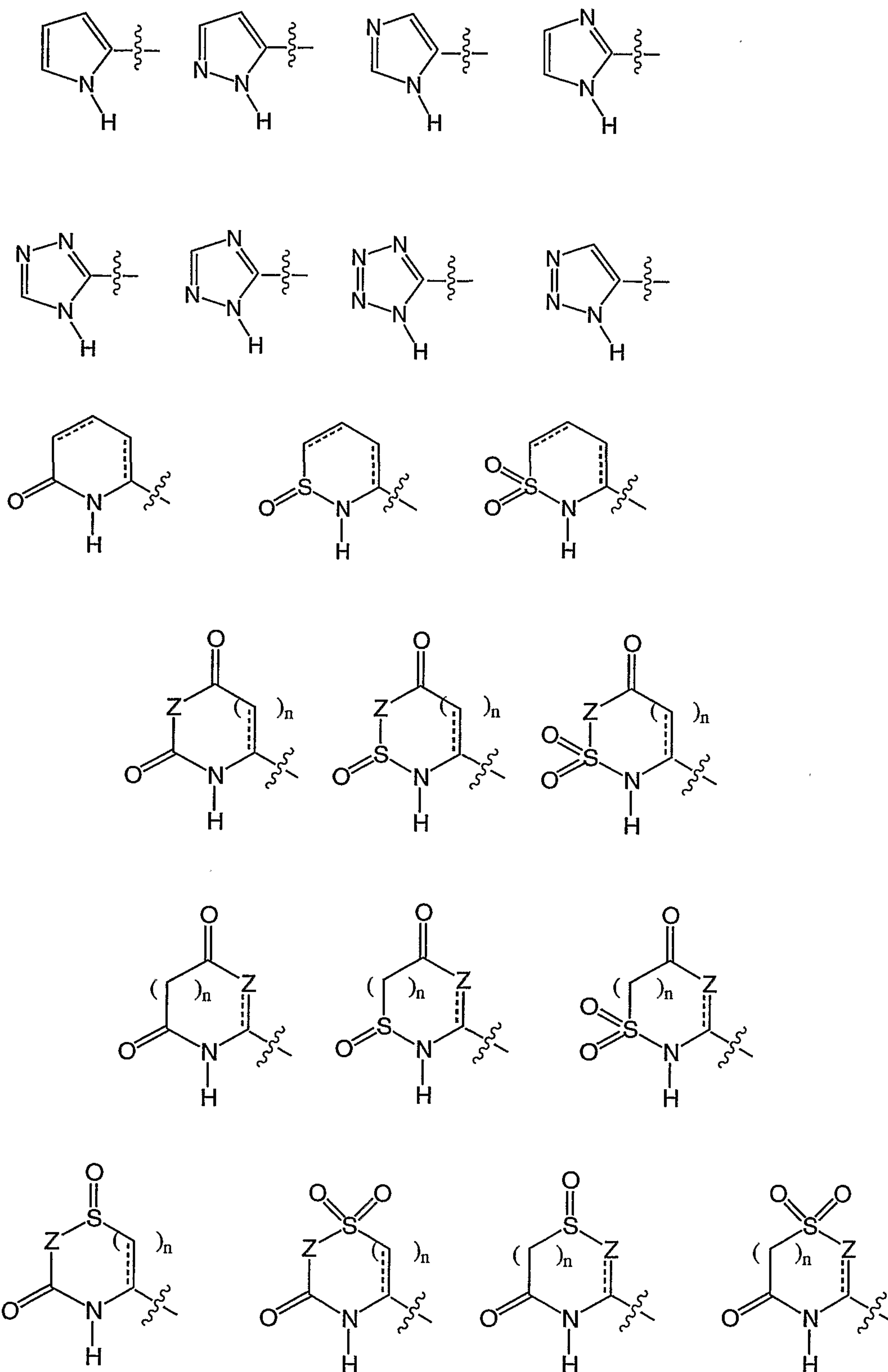
- 78 -

21. The compound according to claim 1 or claim 2, wherein T contains at least one hydrogen bond donor moiety selected from $-NH_2$, $-NH-$, $-OH$, and $-SH$.

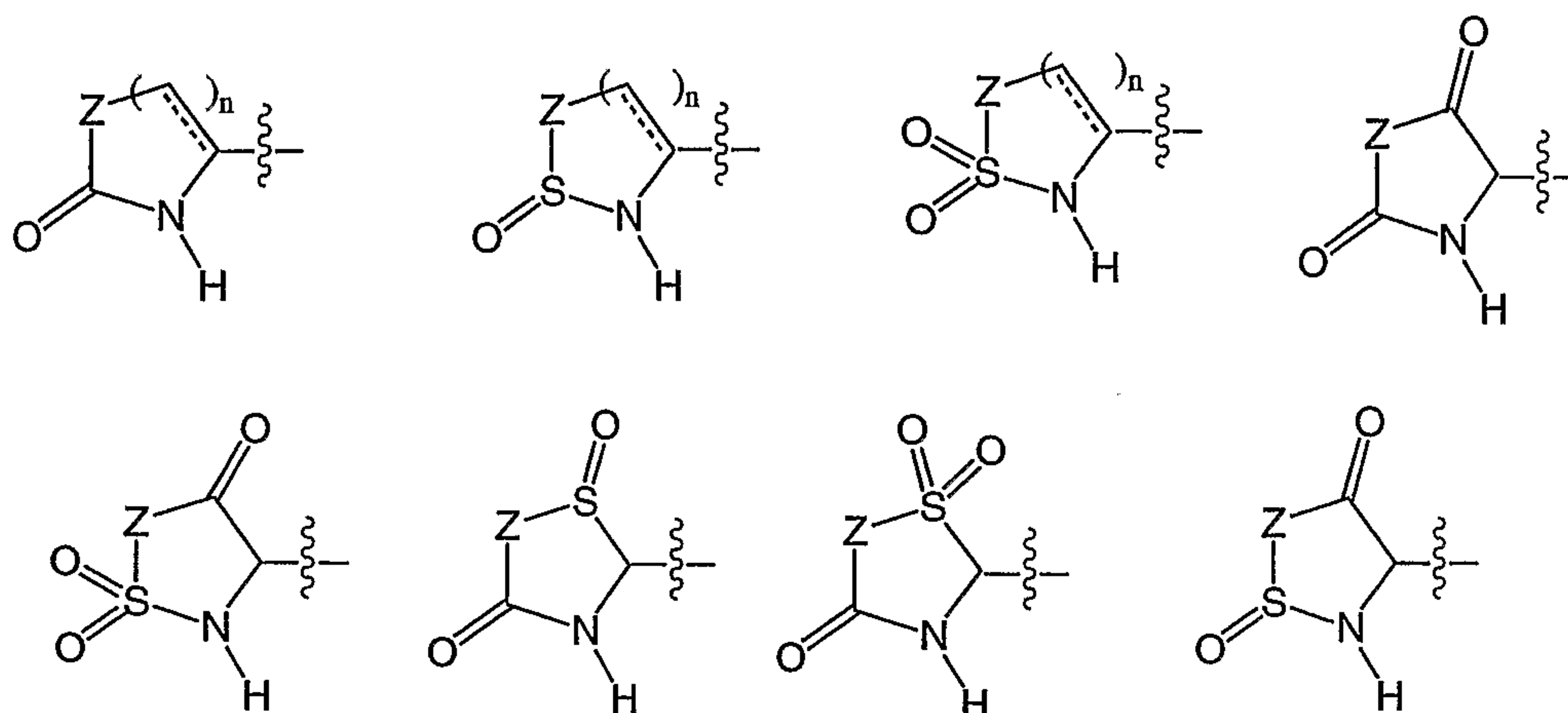
5 22. The compound according to claim 21, wherein T is:



- 79 -



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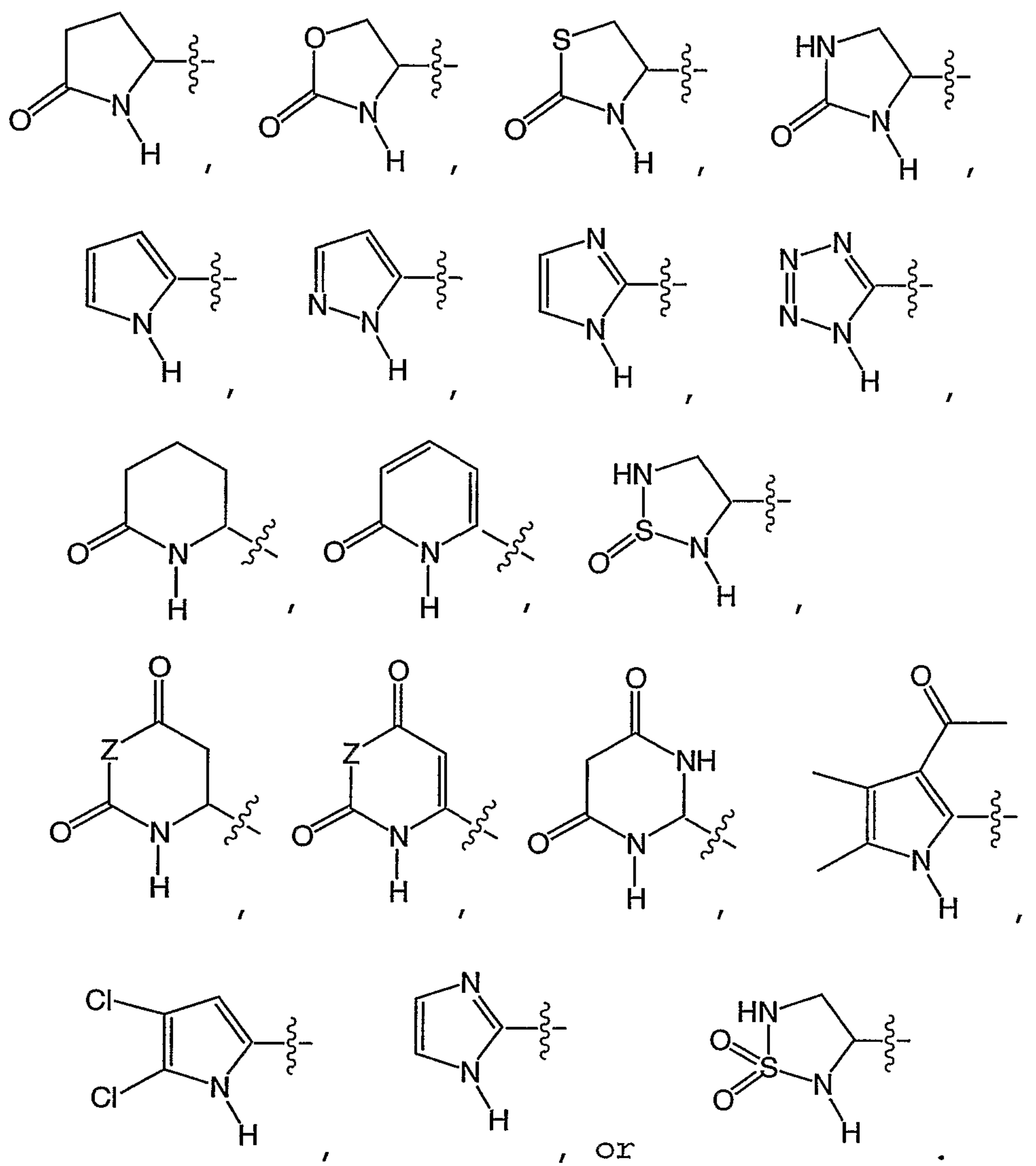


wherein:

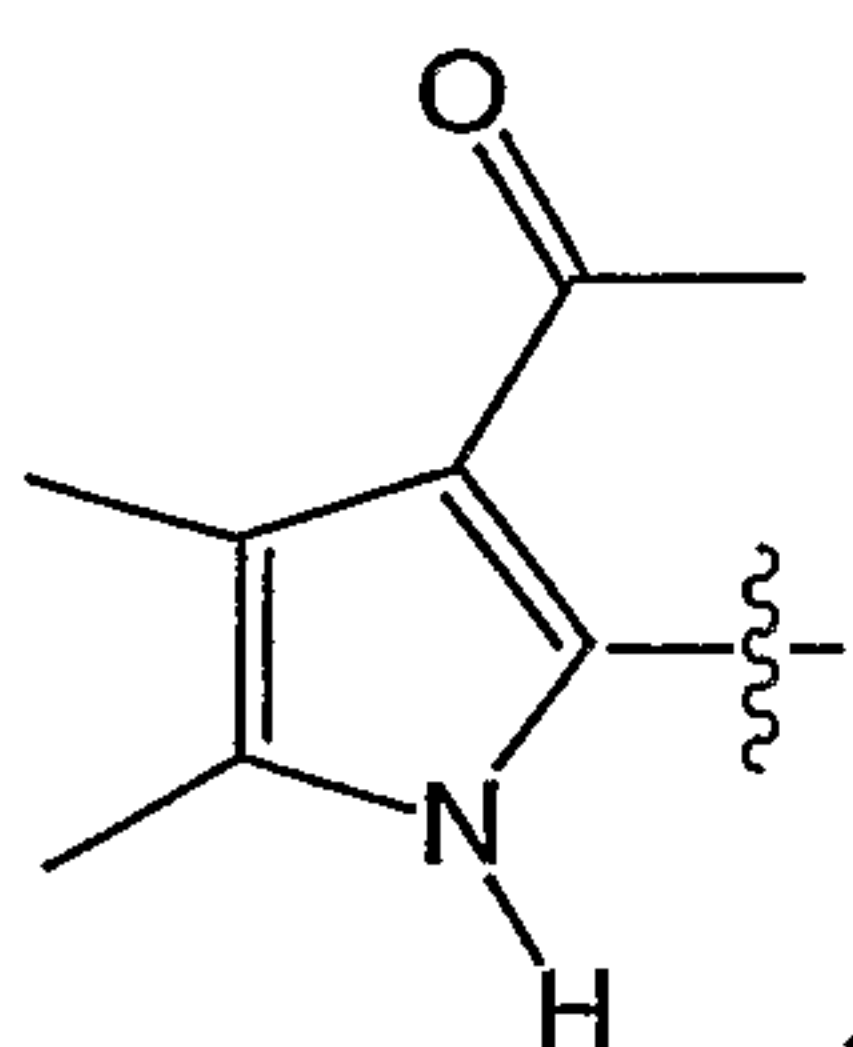
- T is optionally substituted with up to 3 J
 5 substituents, wherein J is as defined in claim 1;
 Z is independently O, S, NR₁₀, or C(R₁₀)₂;
 n is independently 1 or 2; and
 ----- is independently a single bond or a double bond.

- 10 23. The compound according to claim 22, wherein T
 is:

- 81 -



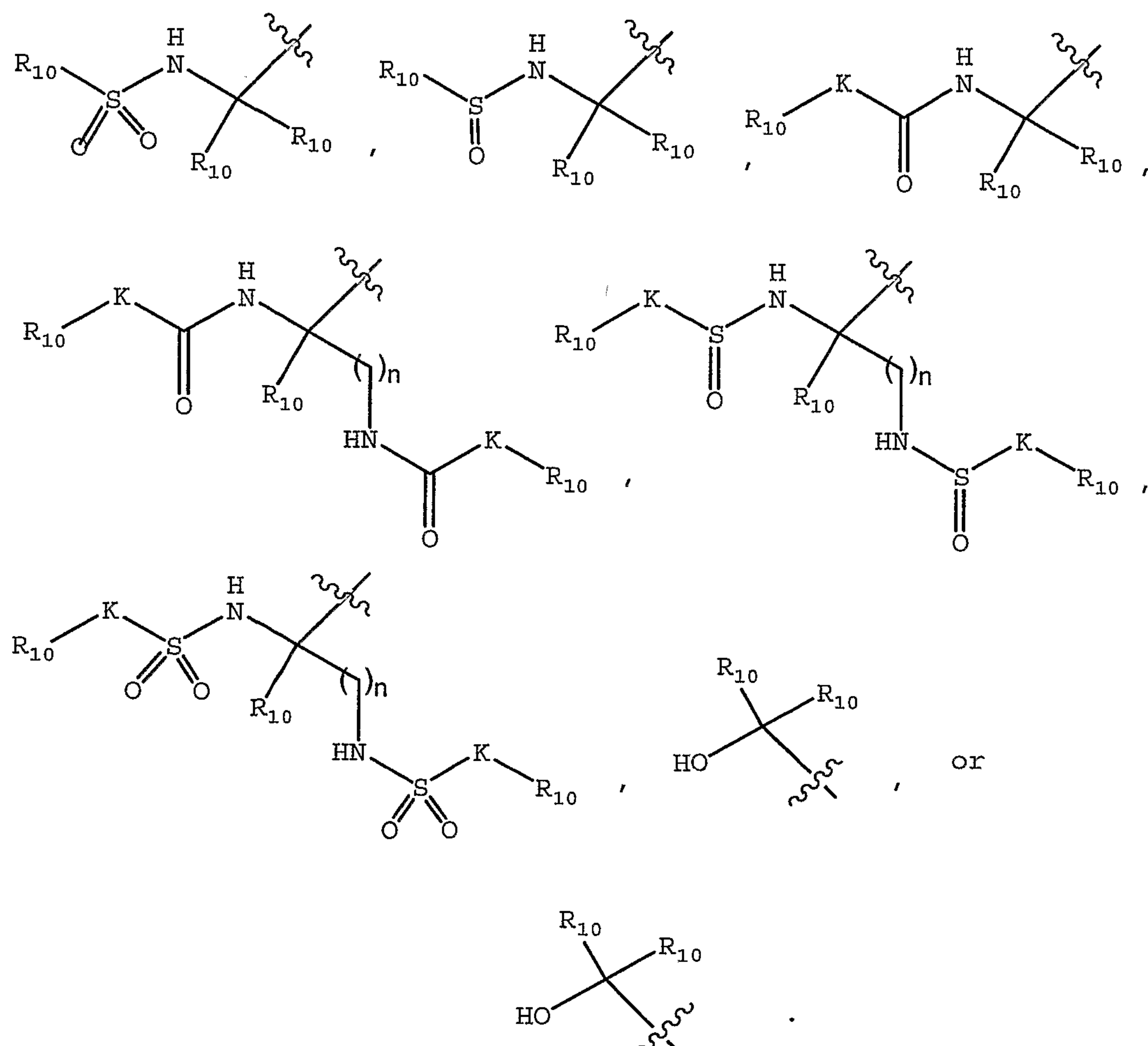
24. The compound according to claim 23,
wherein T is



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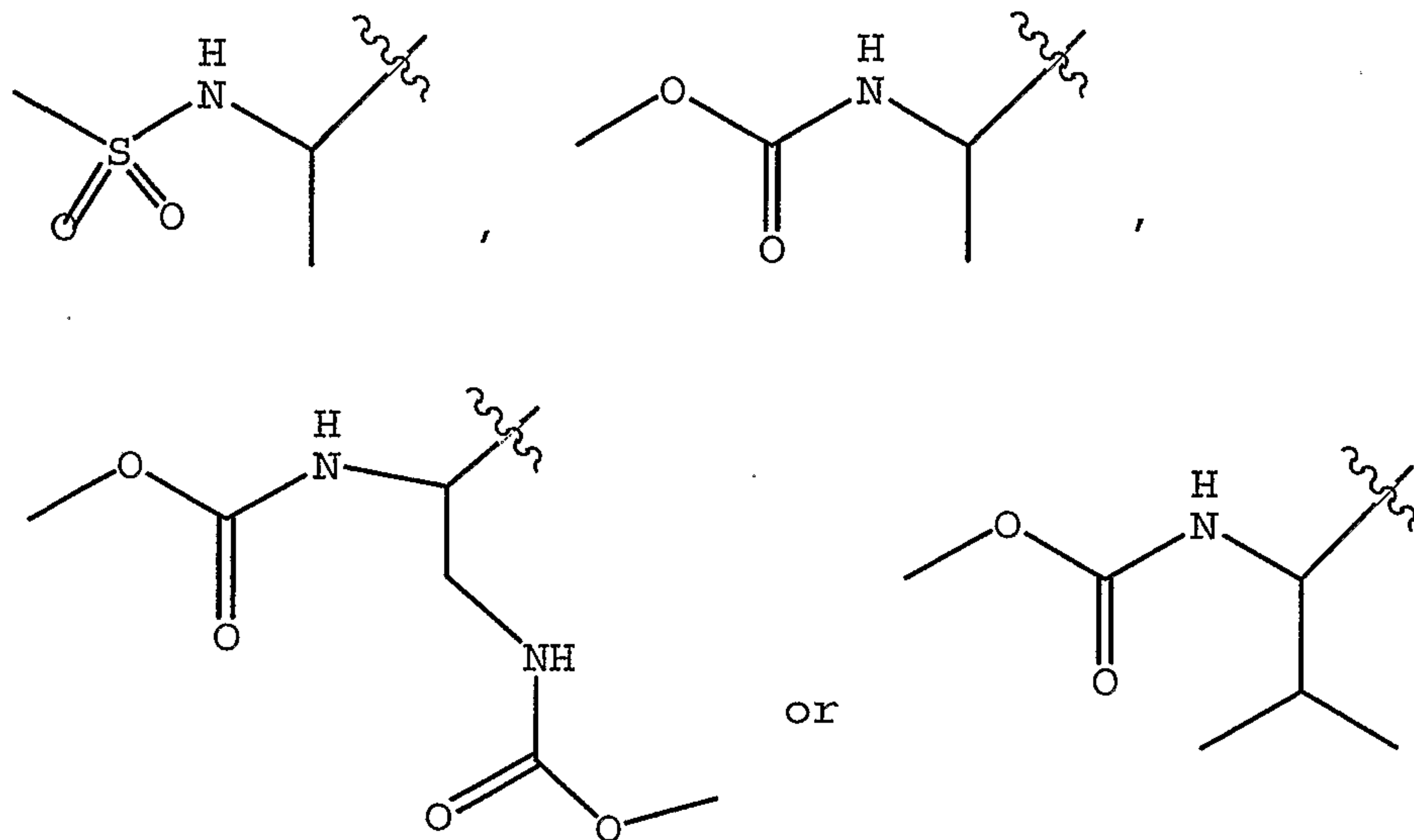
25. The compound according to claim 21,
wherein T is:

- 82 -

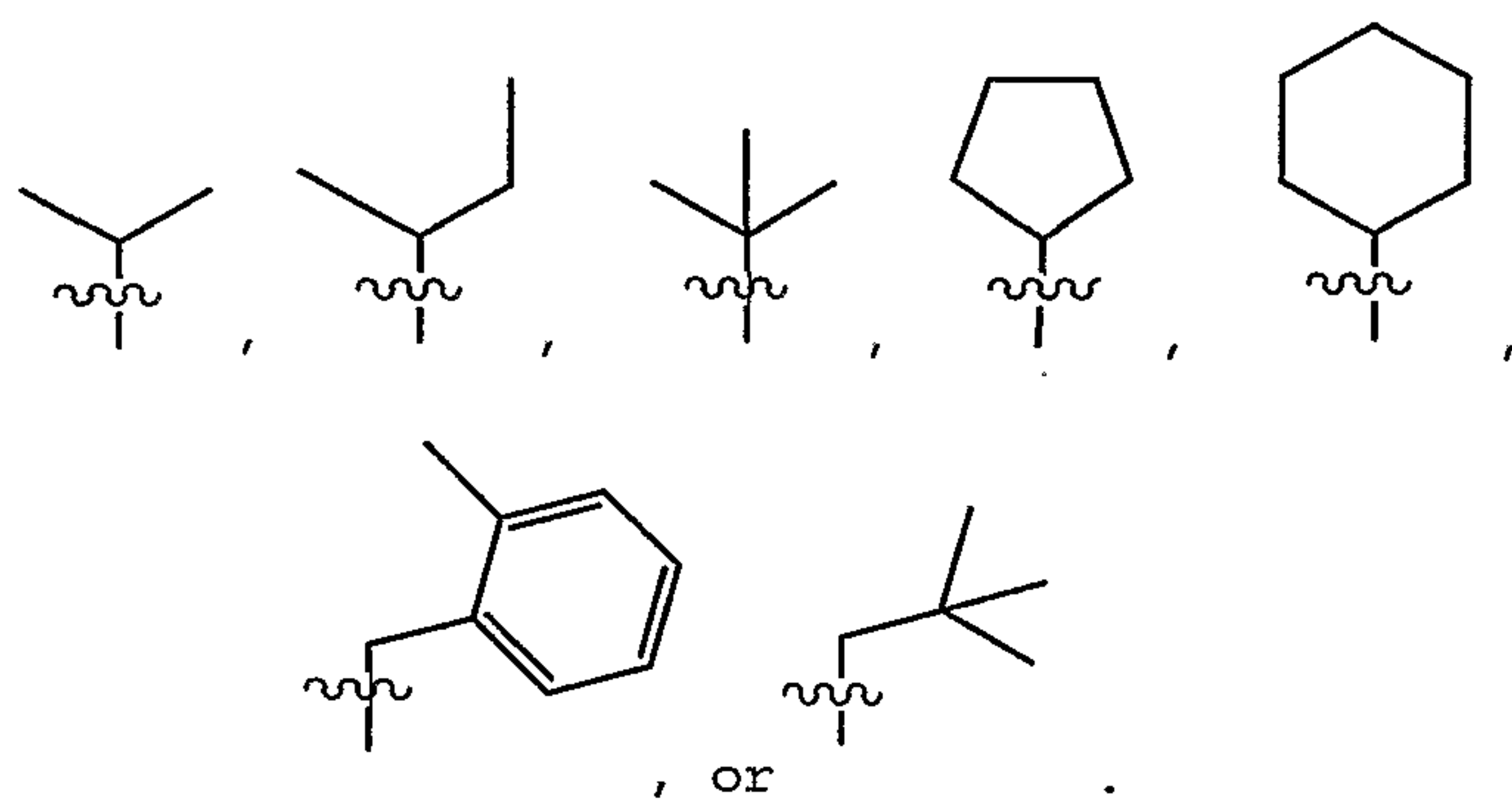


- 5 26. The compound according to claim 25,
wherein T is:

- 83 -

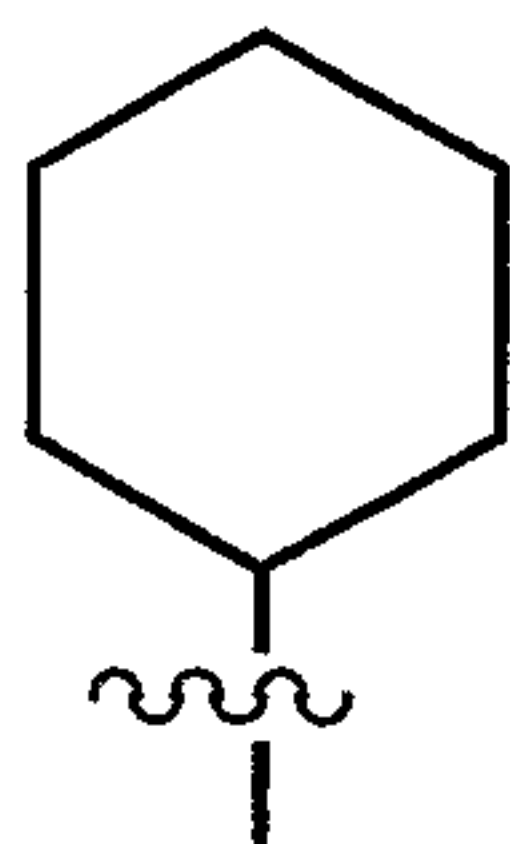


27. The compound according to claim 1 or claim 2, wherein R_1 is:



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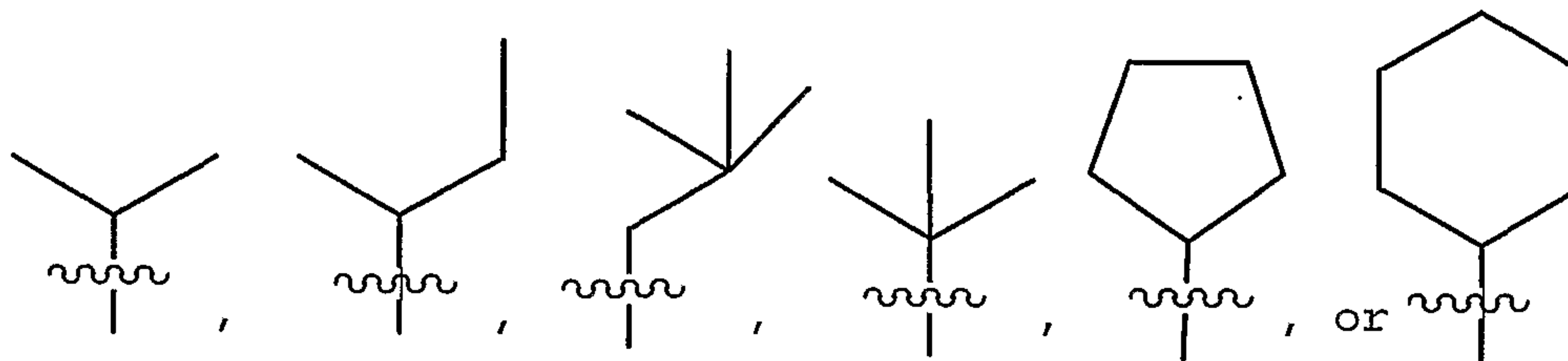
28. The compound according to claim 27, wherein R_1 is:



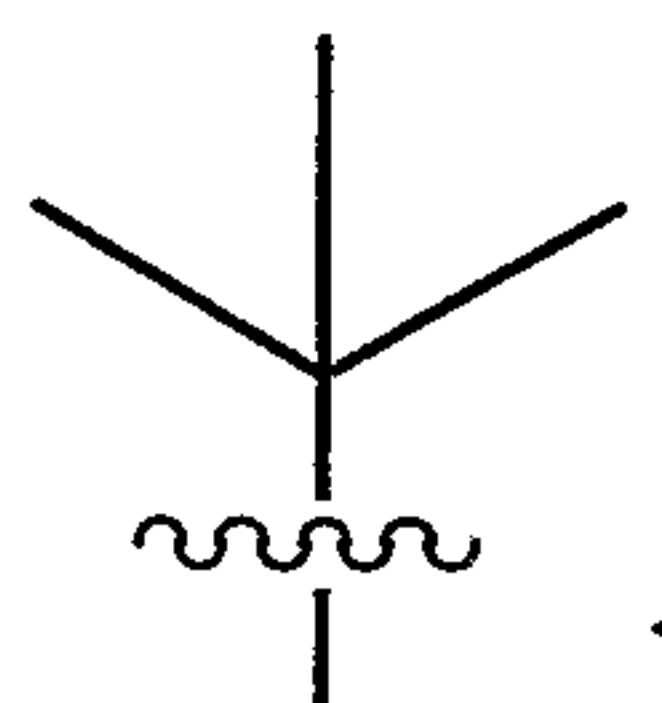
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29. The compound according to claim 1 or claim 2, wherein R_3 is:

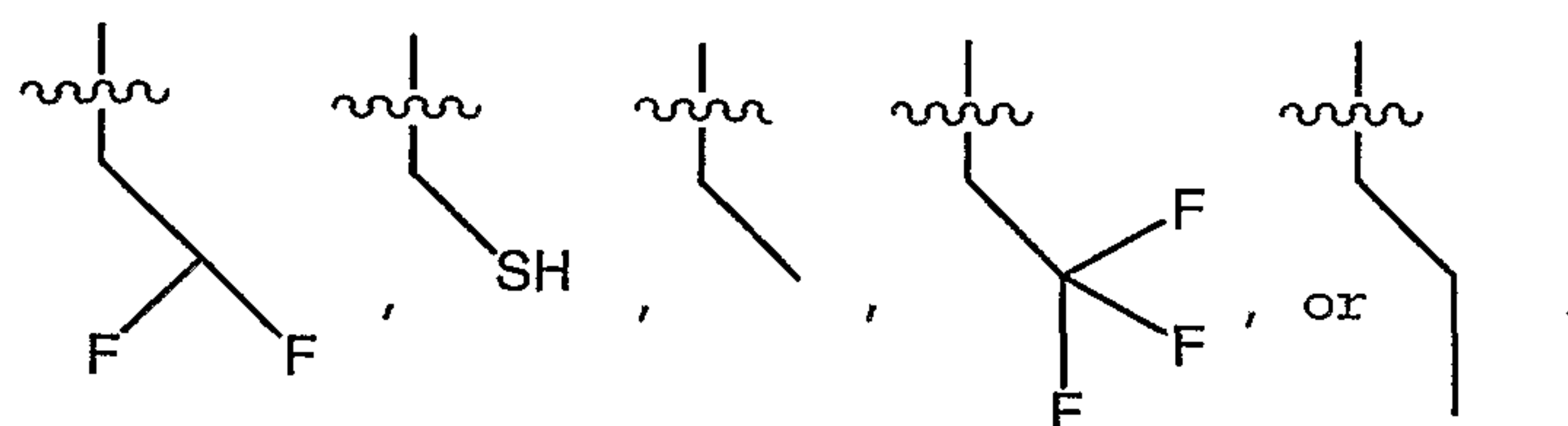
- 84 -



30. The compound according to claim 29,
 5 wherein R_3 is:

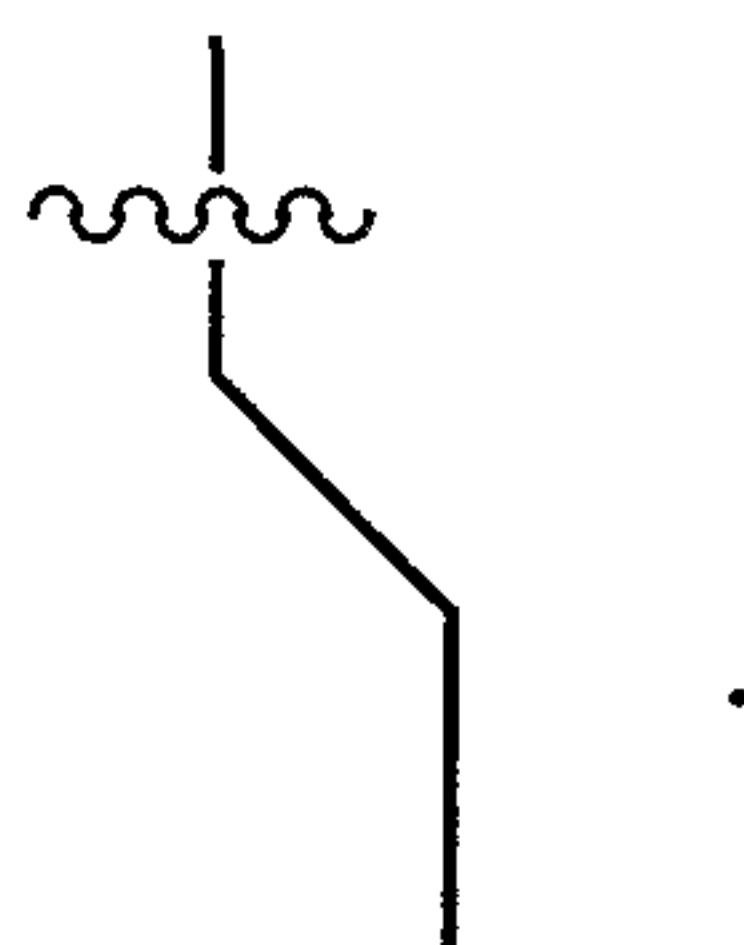


31. The compound according to claim 1 or
 claim 2, wherein R_5 is:



10

32. The compound according to claim 31,
 wherein R_5 is:



15

33. The compound according to claim 1 or
 claim 2, wherein R_2 and R_4 are each independently H,
 methyl, ethyl, or propyl.

- 85 -

34. The compound according to claim 33,
wherein R_2 and R_4 are each H.

35. The compound according to claim 1 or 2,
5 wherein X is $-\text{[CH}_2\text{]}_o-$, $-\text{[CJ'J']}_o-$, $-\text{[CH}_2\text{]}_m\text{-O-}$, $-\text{[CH}_2\text{]}_m\text{-S(O)}_2-$, $-\text{[CH}_2\text{]}_m\text{-SO-}$, $-\text{[CR}_{20}\text{R}_{20}\text{]}_m\text{-NR}_{21}-$, or $-\text{[CR}_{20}\text{R}_{20}\text{]}_m\text{-NJ''-}$.

36. A composition comprising a compound
according to any one of claims 1-35 or a pharmaceutically
10 acceptable salt, derivative or prodrug thereof in an
amount effective to inhibit a serine protease; and a
acceptable carrier, adjuvant or vehicle.

37. The composition according to claim 36,
wherein said composition is formulated for administration
15 to a patient.

38. The composition according to claim 37,
wherein said composition comprises an additional agent
selected from an immunomodulatory agent; an antiviral
20 agent; a second inhibitor of HCV protease; an inhibitor
of another target in the HCV life cycle; or combinations
thereof.

39. The composition according to claim 38,
25 wherein said immunomodulatory agent is α -, β -, or γ -
interferon; the antiviral agent is ribavarin or
amantadine; or the inhibitor of another target in the HCV
life cycle is an inhibitor of HCV helicase, polymerase,
or metalloprotease.

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40. A method of inhibiting the activity of a serine protease comprising the step of contacting said serine protease with a compound according to any one of claims 1-35.

5 41. The method according to claim 40, wherein said protease is an HCV NS3 protease.

42. A method of treating an HCV infection in a patient comprising the step of administering to said patient a composition according to claim 37 or claim 38.

10 43. The method according to claim 42, comprising the additional step of administering to said patient an additional agent selected from an immunomodulatory agent; an antiviral agent; a second inhibitor of HCV protease; an inhibitor of another target
15 in the HCV life cycle; or combinations thereof; wherein said additional agent is administered to said patient as part of said composition according to claim 37 or as a separate dosage form.

20 44. The method according to claim 43, wherein said immunomodulatory agent is α -, β -, or γ -interferon; said antiviral agent is ribavirin or amantadine; or said inhibitor of another target in the HCV life cycle is an inhibitor of HCV helicase, polymerase, or metalloprotease.

25 45. A method of eliminating or reducing HCV contamination of a biological sample or medical or laboratory equipment, comprising the step of contacting

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said biological sample or medical or laboratory equipment with a composition according to claim 36.

46. The method according to claim 45, wherein said sample or equipment is selected from blood, body
5 fluids other than blood, biological tissue, a surgical instrument, a surgical garment, a laboratory instrument, a laboratory garment, a blood or other bodily fluid collection apparatus; a blood or other bodily fluid storage material.