Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2462694 C 2010/08/10

(11)(21) **2 462 694**

(12) **BREVET CANADIEN
CANADIAN PATENT**

(13) **C**

(86) Date de dépôt PCT/PCT Filing Date: 2003/03/17

(87) Date publication PCT/PCT Publication Date: 2003/09/25

(45) Date de délivrance/Issue Date: 2010/08/10

(85) Entrée phase nationale/National Entry: 2004/04/01

(86) N° demande PCT/PCT Application No.: EP 2003/050064

(87) N° publication PCT/PCT Publication No.: 2003/078400

(30) Priorité/Priority: 2002/03/18 (EP02076482.5)

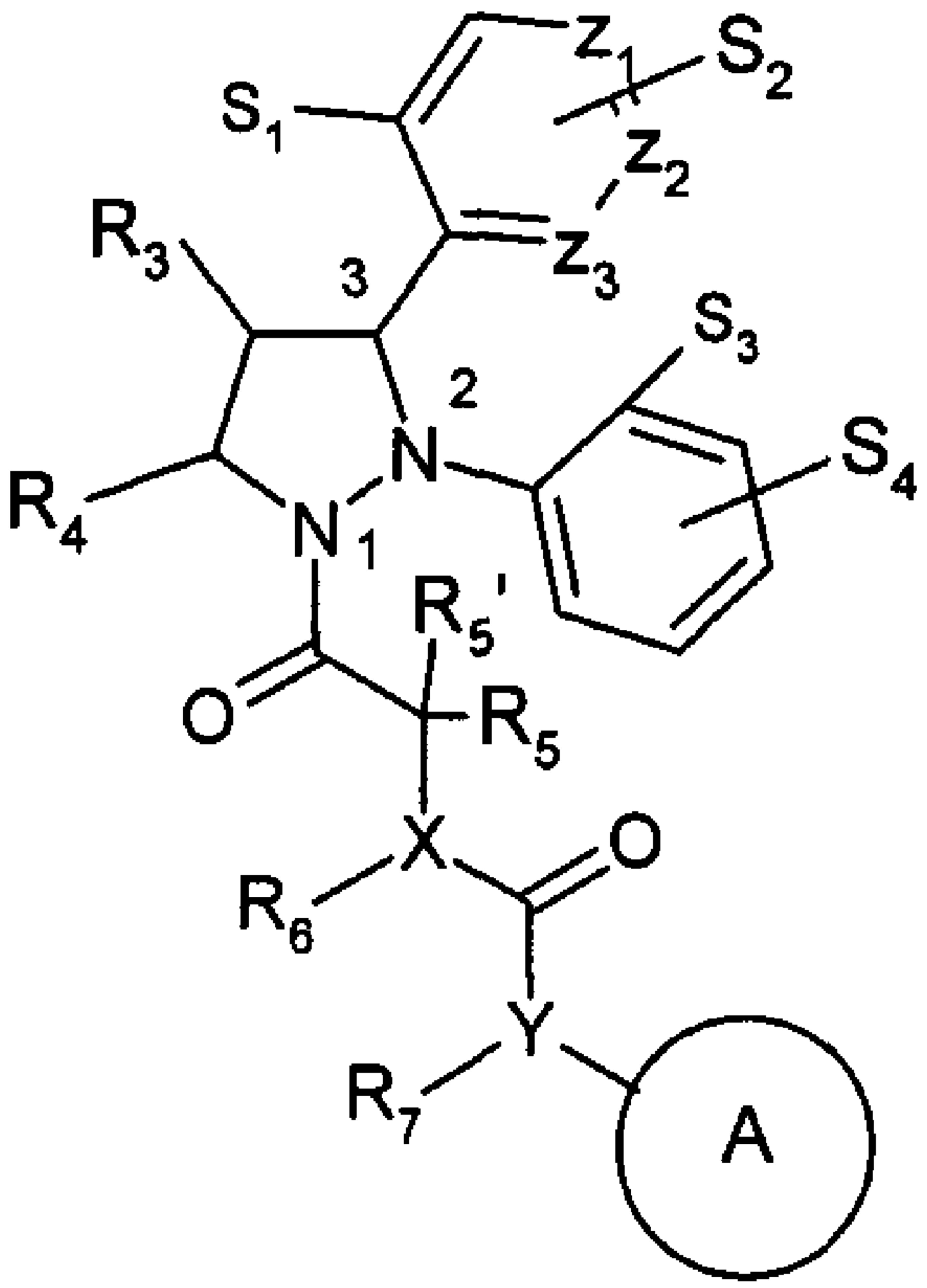
(51) Cl.Int./Int.Cl. *C07D 231/04* (2006.01), *A61K 31/415* (2006.01), *A61P 25/00* (2006.01), *C07D 401/04* (2006.01)

(72) Inventeurs/Inventors:
FEENSTRA, ROELOF W., NL;
LANGE, JOSEPHUS H. M., NL;
PRAS-RAVES, MARIA L., NL;
KRUSE, CORNELIS G., NL;
VAN STUIVENBERG, HERMAN H., NL;
TUINSTRA, TINKA, NL;
KEIZER, HISKIAS G., NL

(73) Propriétaire/Owner:
SOLVAY PHARMACEUTICALS B.V., NL

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : DERIVES DE 2,3-DIARYL-PYRAZOLIDINE ACTIFS DE LA NEUROTENSINE
(54) Title: NEUROTENSIN ACTIVE 2,3-DIARYL-PYRAZOLIDINE DERIVATIVES



(57) Abrégé/Abstract:
The invention relates to a group of novel 2,3 diaryl-pyparazolidine derivatives having formula (1). The symbols used in formula (1) have the meanings given in the specification. The compounds have inhibiting activity on enzymes which degrade the neuropeptide neurotensin and can be used for the treatment of affections and diseases caused by disturbances of the neurotensin mediated transmission.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/078400 A1

(51) International Patent Classification^7: **C07D 231/04**, 401/04, A61P 25/00, A61K 31/415

(21) International Application Number: PCT/EP03/50064

(22) International Filing Date: 17 March 2003 (17.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02076482.5 18 March 2002 (18.03.2002) EP

(71) Applicant *(for all designated States except US)*: **SOLVAY PHARMACEUTICALS B.V.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FEENSTRA, Roelof, W.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **LANGE, Josephus, H., M.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **PRAS-RAVES, Maria, L.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **KRUSE, Cornelis, G.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **VAN STUIVENBERG, Herman, H.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **TUINSTRA, Tinka** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **KEIZER, Hiskias, G.** [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(74) Agent: VERHAGE, Marinus; Octrooibureau Zoan B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

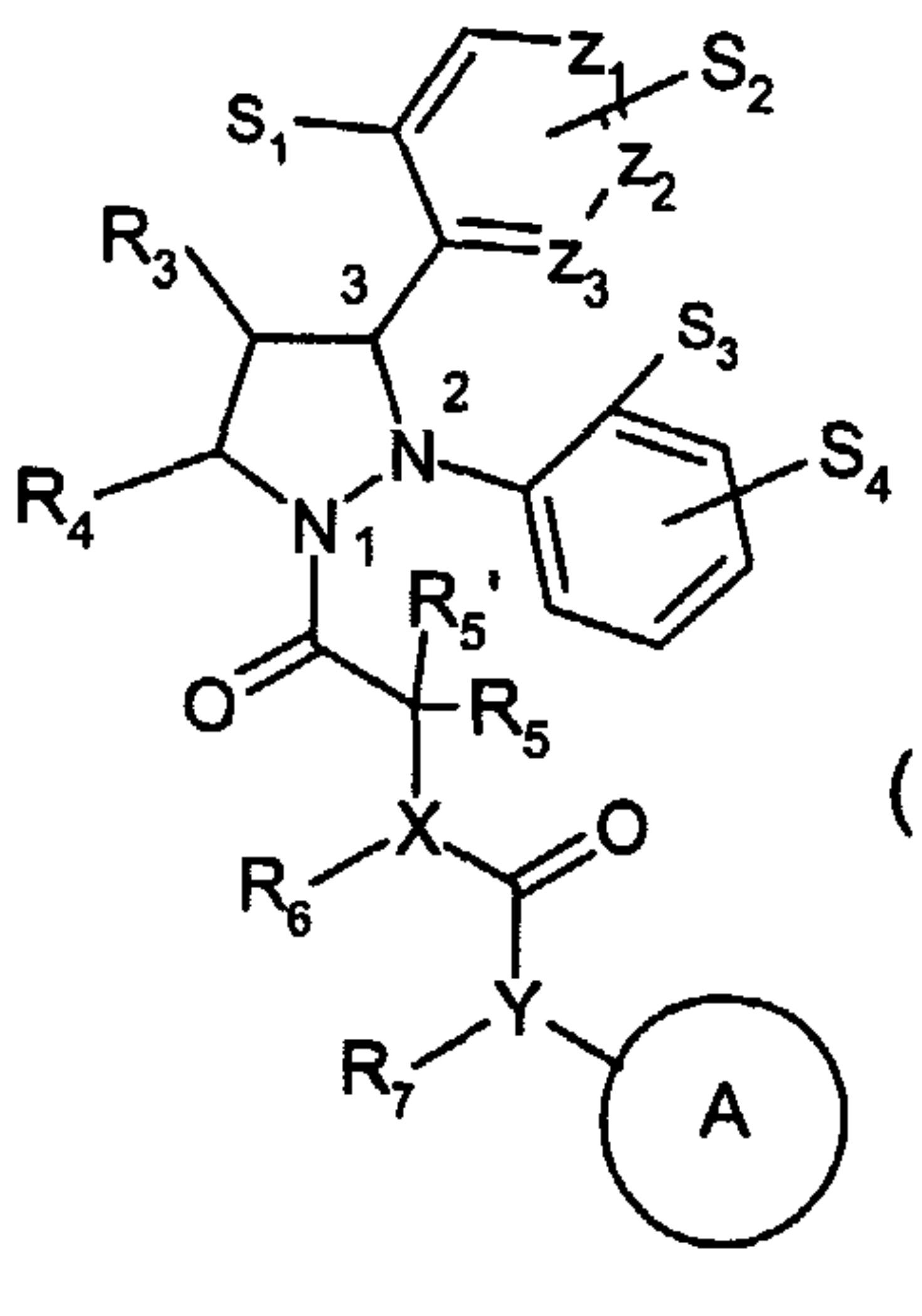
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEUROTENSIN ACTIVE 2,3-DIARYL-PYRAZOLIDINE DERIVATIVES



(1)

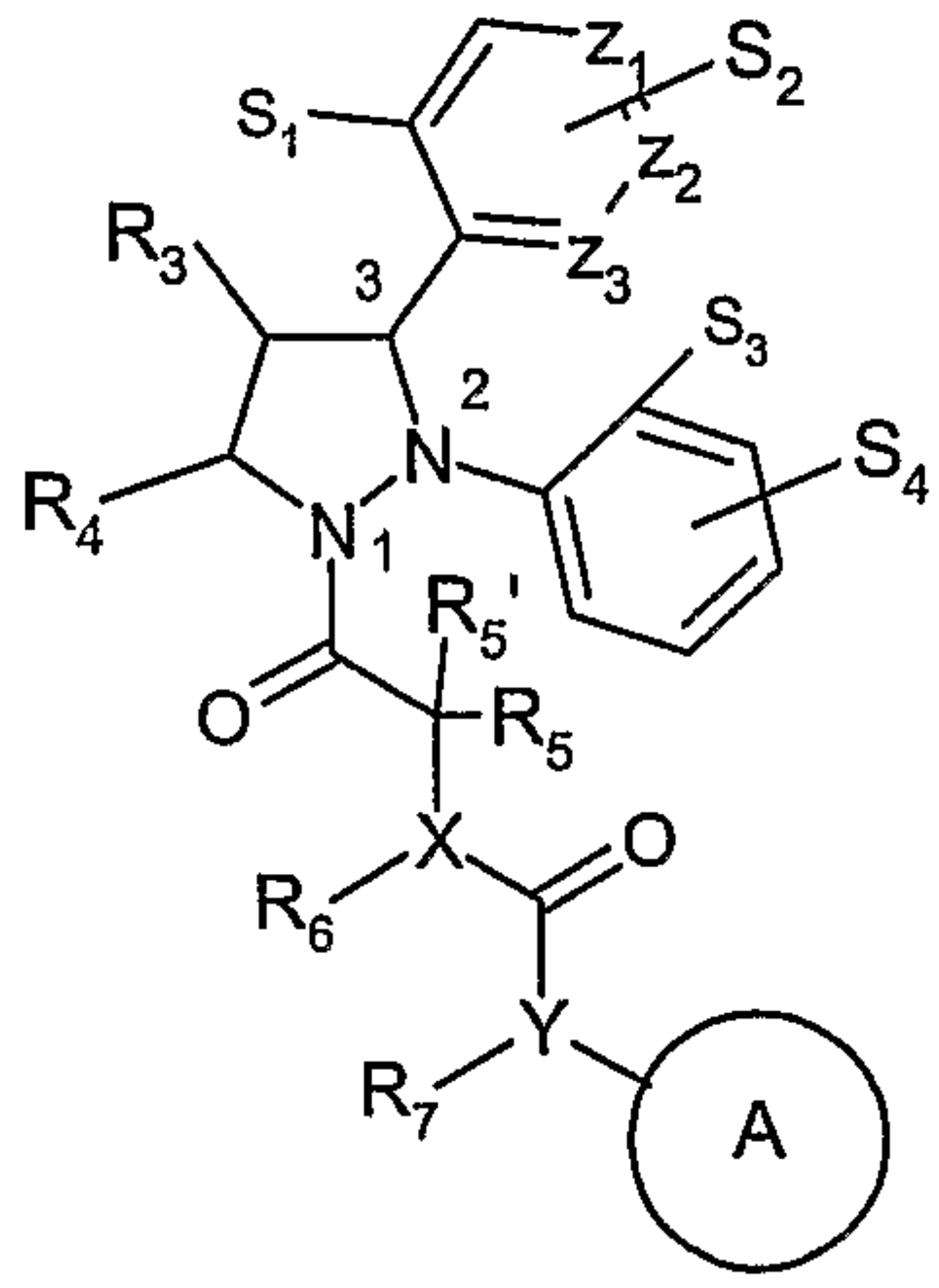
(57) Abstract: The invention relates to a group of novel 2,3 diaryl-pyparazolidine derivatives having formula (1). The symbols used in formula (1) have the meanings given in the specification. The compounds have inhibiting activity on enzymes which degrade the neuropeptide neurotensin and can be used for the treatment of affections and diseases caused by disturbances of the neurotensin mediated transmission.

WO 03/078400 A1

NEUROTENSIN ACTIVE 2,3-DIARYL-PYRAZOLIDINE DERIVATIVES

The invention relates to a group of new 2,3-diaryl-pyrazolidine derivatives having inhibiting activity on enzymes which degrade the neuropeptide neurotensin.

It has been found that compounds having formula (1)



(1)

wherein,

- S_1 is hydrogen, halogen, hydroxy or alkoxy (1-3C)
- S_2 is hydrogen or halogen
- S_3 is hydrogen, halogen, hydroxy or alkoxy (1-3C)
- S_4 is hydrogen, halogen or alkyl (1-6C) optionally substituted with hydroxy, alkoxy (1-3C), amino, mono- or dialkylamino having 1-3C-atoms in the alkyl group(s), SH or S-alkyl (1-3C)
- X represents nitrogen or carbon
- Y represents nitrogen or oxygen when X is nitrogen, or Y is nitrogen when X is carbon
- R_3 and R_4 are independently of each other hydrogen or alkyl (1-3C)
- R_5 is hydrogen or alkyl (1-6C) which may be substituted with halogen, CN, CF_3, hydroxy, alkoxy (1-3C), sulfonylalkyl (1-3C), amino, mono- or dialkylamino having 1-3C-atoms in the alkyl group(s) when X is carbon or nitrogen, or R_5 represents alkoxy (1-6C), SH or S-alkyl (1-3C) when X is carbon

- R'_5 is hydrogen or alkyl (1-3C)

- R_6 is hydrogen, or alkyl (1-3C)

- R_7 is hydrogen or alkyl (1-3C)

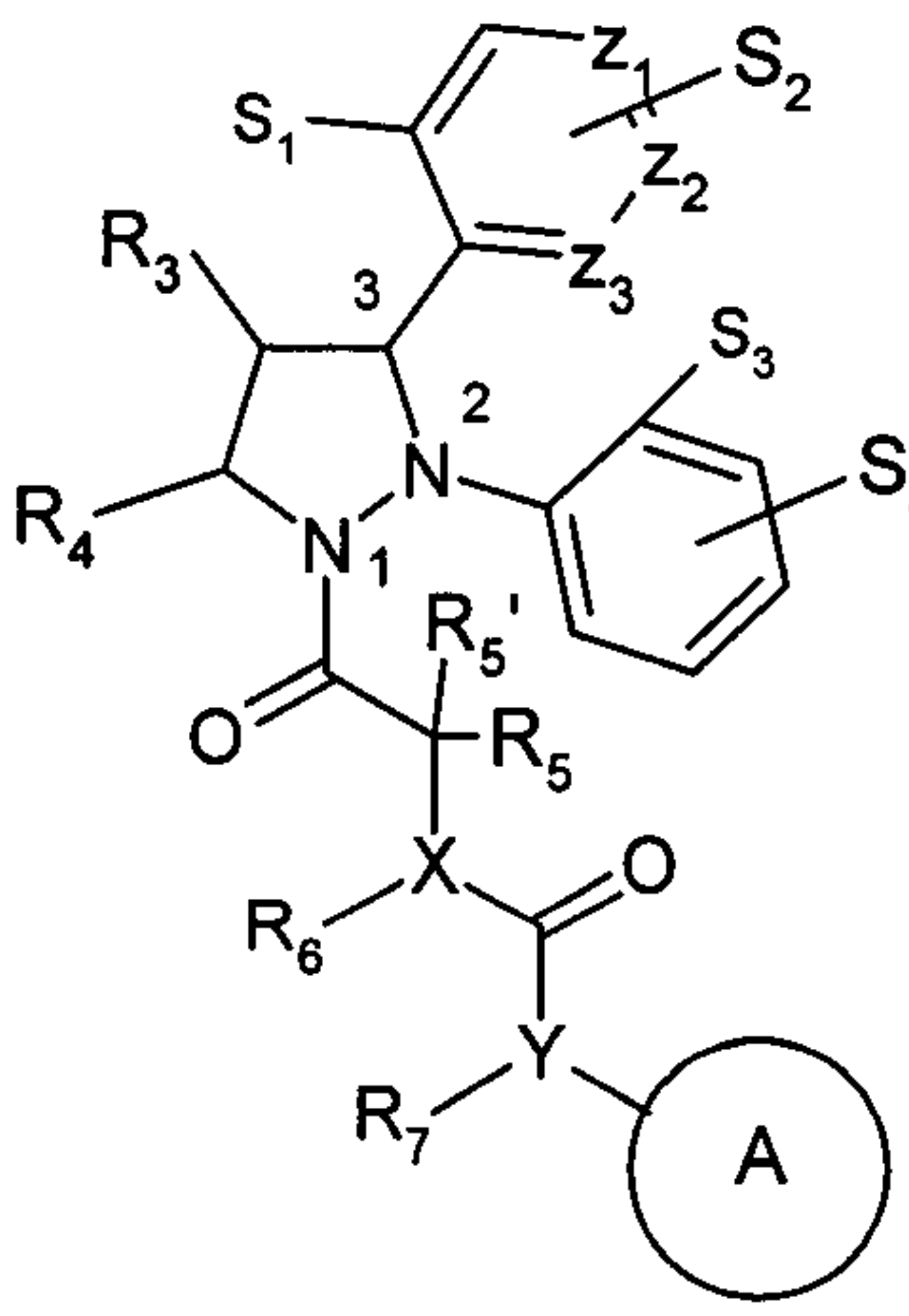
- R_5 and R_6 together or R'_5 and R_6 together can form a 3-7 membered cyclic group which may be substituted with lower alkyl, halogen, CN or CF_3, and $R_5 + R'_5$ together may form a 3-7 membered ring, and

- Z_1, Z_2 and Z_3 represent carbon, or Z_1 is nitrogen and Z_2 and Z_3 are carbon, or Z_1 and Z_3 are carbon and Z_2 is nitrogen, or Z_1 and Z_2 are carbon and Z_3 is nitrogen,

- A is a (poly) cycloalkyl system consisting of 4-10 membered rings which can be substituted with halogen, CF_3, alkyl or alkoxy (1-3C), CN, OH or SH

and salts thereof have neurotensin degrading enzyme inhibiting activity.

According to one aspect of the present invention, there is provided a compound of the formula (1):



wherein,

- S_1 is hydrogen, halogen, hydroxy or alkoxy (1-3C);

- S_2 is hydrogen or halogen;

- S_3 is hydrogen, halogen, hydroxy or alkoxy (1-3C);

- S_4 is hydrogen, halogen or alkyl (1-6C) which is optionally substituted with hydroxy, alkoxy (1-3C), amino, mono- or dialkylamino having 1-3C-atoms in the alkyl group(s), SH or S-alkyl (1-3C);

- R_7 is hydrogen or alkyl (1-3C);

- X is N or CH;

- Y is N or O when X is N, or

Y is N when X is CH, with the understanding that when Y is O, R_7 is absent;

- R_3 and R_4 are independently of each other hydrogen or alkyl (1-3C);

- when X is N, R_5 is hydrogen or alkyl (1-6C) which is optionally substituted with halogen, CN, CF_3, hydroxy, alkoxy (1-3C), sulfonylalkyl (1-3C), amino or mono- or dialkylamino having 1-3 C-atoms in the alkyl group(s);

when X is CH, R_5 is as defined when X is N or R_5 is alkoxy (1-6C), SH or S-alkyl (1-3C);

- R'_5 is hydrogen or alkyl (1-3C);

- R_6 is hydrogen, or alkyl (1-3C); or

- R_5 and R_6 together or R'_5 and R_6 together form a 3-7 membered cyclic group which is optionally substituted with alkyl (1-3C), halogen, CN or CF_3, or R_5 and R'_5 together form a 3-7 membered ring;

- Z_1, Z_2 and Z_3 are carbon, Z_1 is nitrogen and Z_2 and Z_3 are carbon, Z_1 and Z_3 are carbon and Z_2 is nitrogen, or Z_1 and Z_2 are carbon and Z_3 is nitrogen; and

- A is a mono-, di-, tri- or tetracycloalkyl system wherein each cycloalkyl ring in the system has 4 to 10 carbon atoms and is optionally substituted with halogen, CF_3, alkyl (1-3C), alkoxy (1-3C), CN, OH or SH, or a pharmacologically acceptable salt thereof.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (1) as described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or auxiliary substance.

According to still another aspect of the present invention, there is provided a pharmaceutical composition as described herein for treatment of an affection or disease caused by a disturbance of neurotensin mediated transmission.

According to yet another aspect of the present invention, there is provided a pharmaceutical composition as described herein for treatment of psychosis.

According to a further aspect of the present invention, there is provided a pharmaceutical composition as described herein for treatment of Parkinson's disease.

According to yet a further aspect of the present invention, there is provided a pharmaceutical composition as described herein for treatment of depression.

According to still a further aspect of the present invention, there is provided a pharmaceutical composition as described herein for treatment of an anxiety disorder.

More particularly the compounds inhibit the enzymes Thimet oligopeptidase EC 3.4.24.15 and Neurolysine EC 3.4.24.16 which break down the neuropeptide neurotensin.

Due to the inhibition of the neurotensin degrading activity of these enzymes the levels of endogenous neurotensin will rise, causing beneficial effects in the treatment of diseases in which neurotensin levels are disturbed.

The compounds according to the invention are active in inhibiting the abovementioned enzymes in the range of 5.0-8.0 (pIC_{50} values), when tested according to the methods described in Biochem. J. 280 421-426, and Eur. J. Biochem. 202, 269-276.

The compounds according to the invention can be used for the treatment of affections and diseases caused by disturbances of the neurotensin mediated transmission, such as peripheral disturbances like regulation of blood pressure and gastric emptying, neurological disturbances like Parkinson's disease, and central nervous system (CNS) disturbances like anxiety, depression, psychosis and other psychosis disorders.

The compounds having the formula (1) can be obtained according to at least one of the following four methods A, B, C and D. The starting compounds for these four methods are substituted 2,3-diaryl-pyrazolidines having one of the structures indicated in Figure 1:

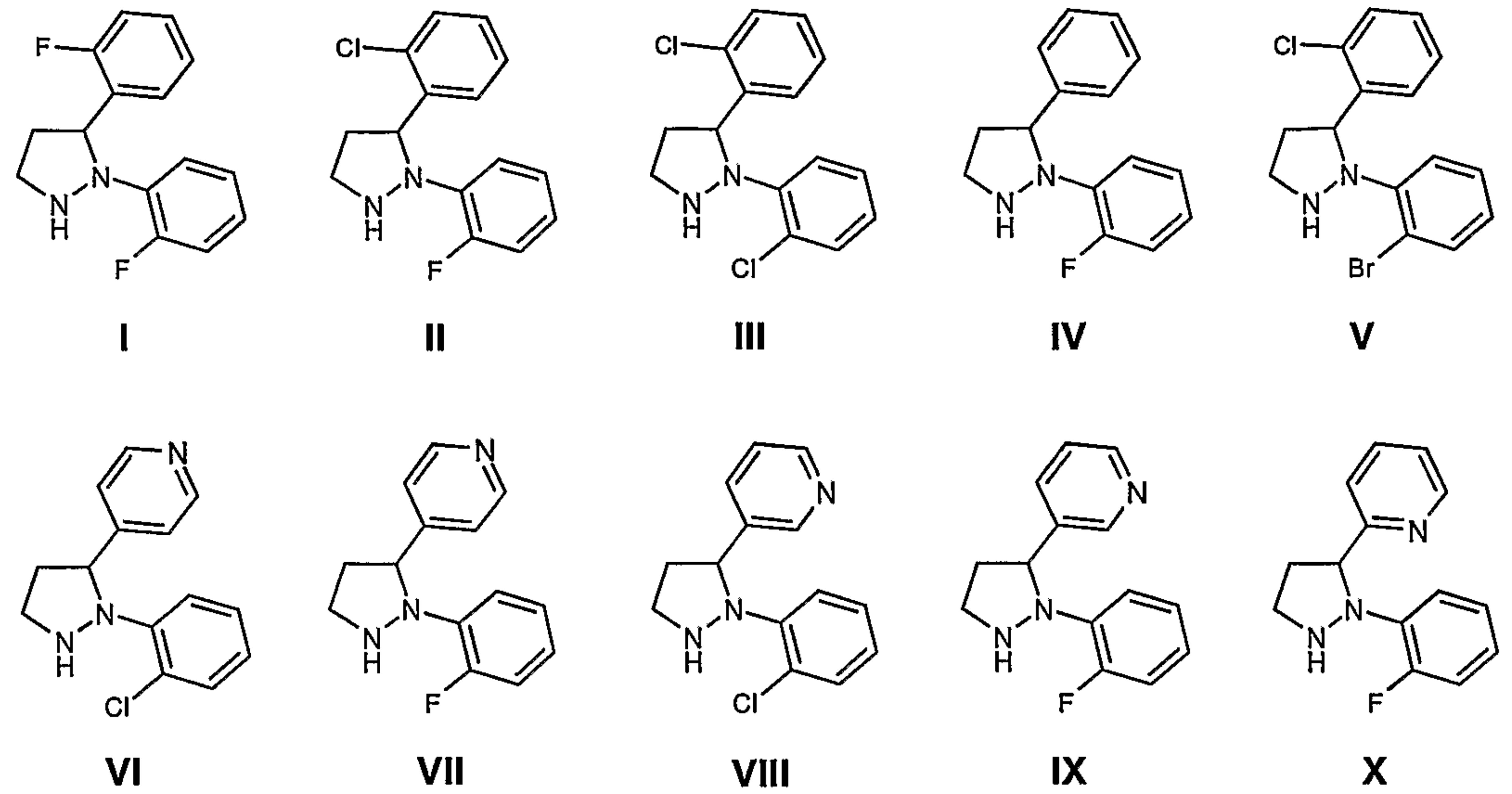


Figure 1

The part R_7-Y-A of the compounds having formula (1) can have the structures of the groups indicated in Figure 2:

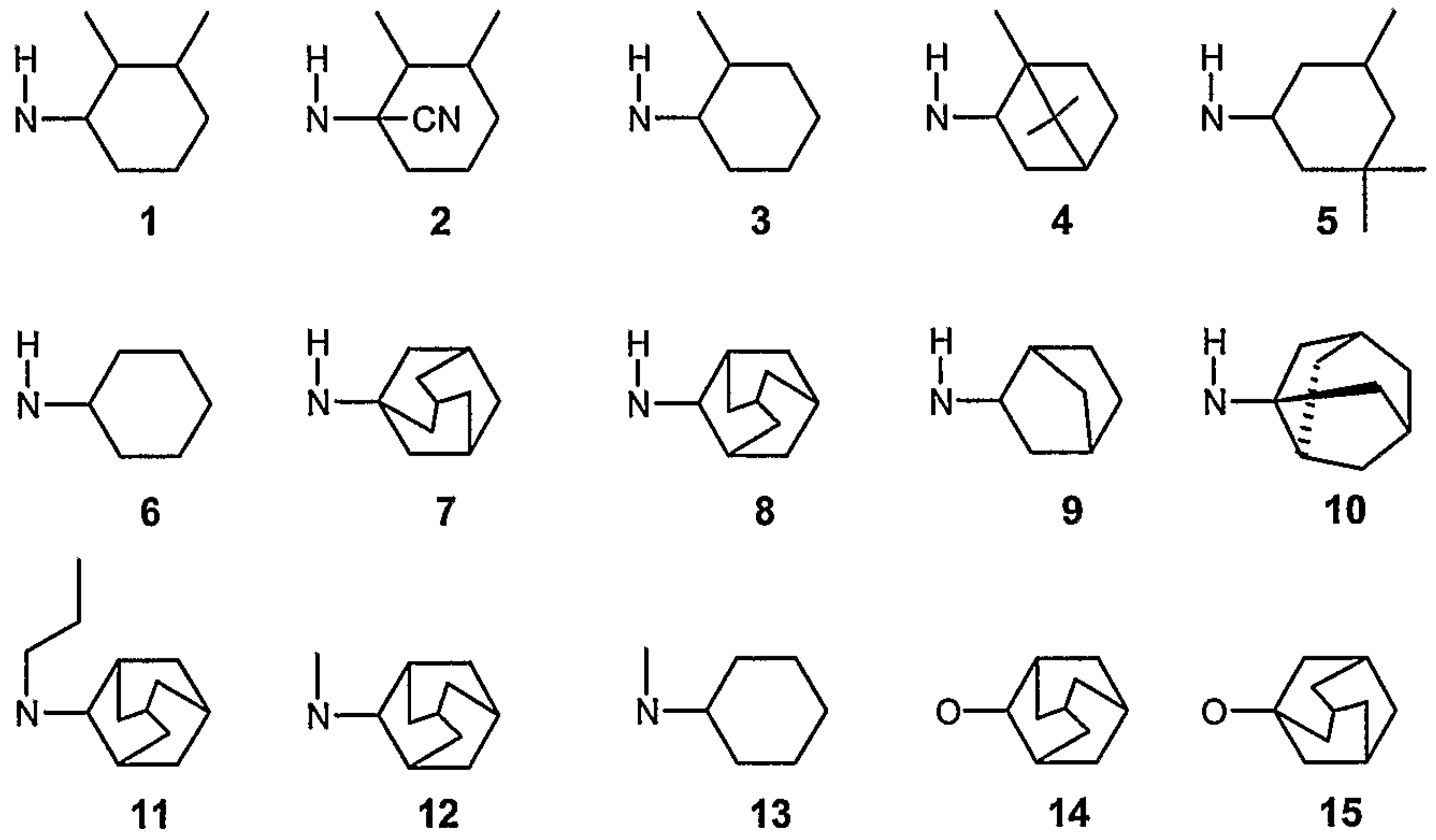
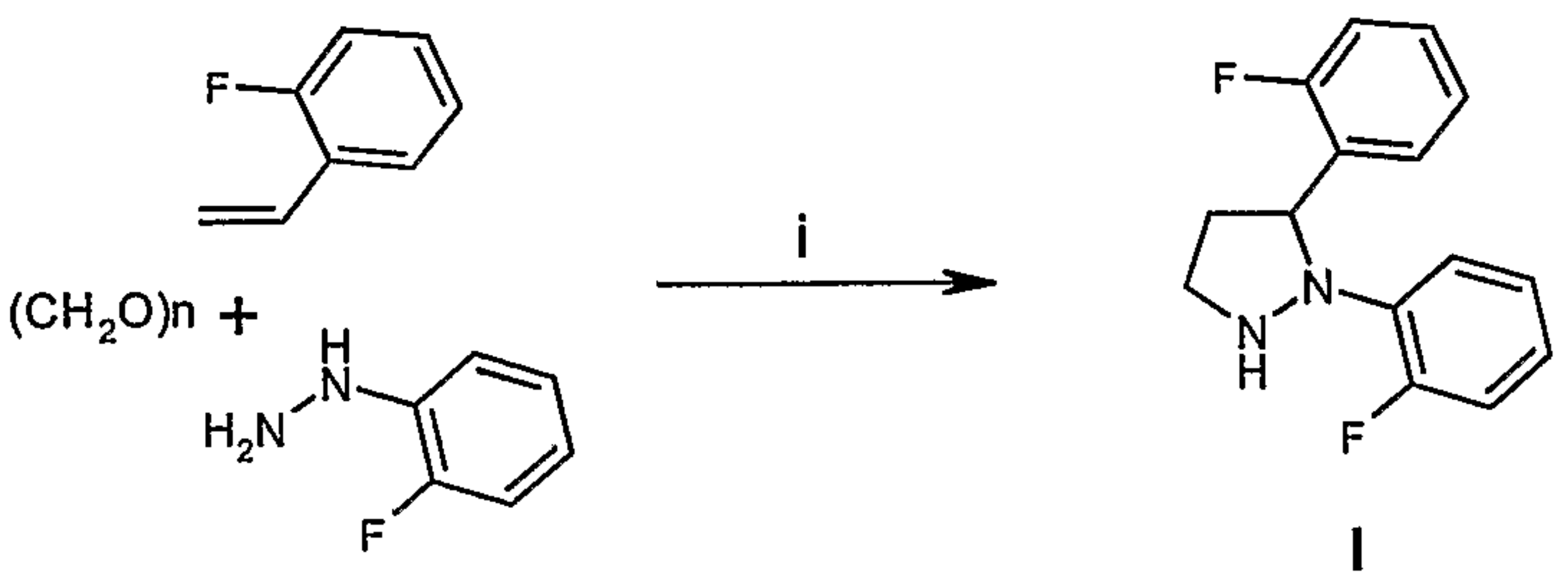


Figure 2

The starting pyrazolidine derivatives of Figure 1 can be obtained according to the method of Scheme 1:

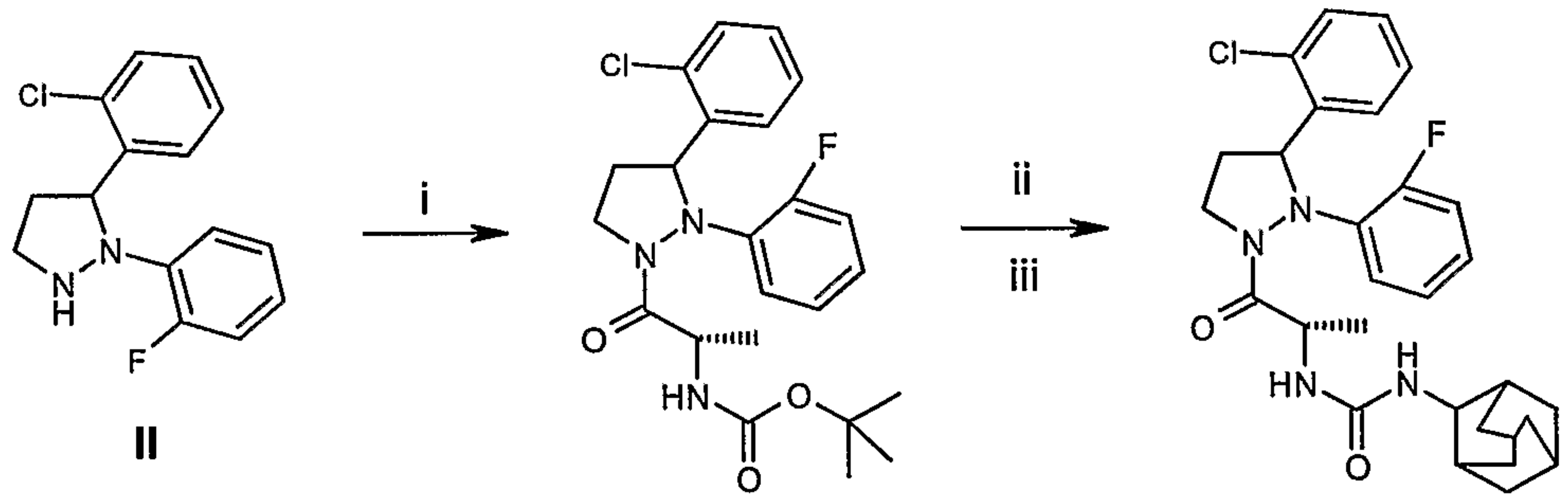


Scheme 1

as elucidated in Example 5

Method A:

The compounds mentioned the compounds mentioned in table A, can be synthesized according to the synthesis of compound **A23/A24**. After step i two diastereomers evolve which, after step iii has been performed, can be separated by column chromatography into enantiomeric pure diastereomers **A23** and **A24**. See scheme A.1.

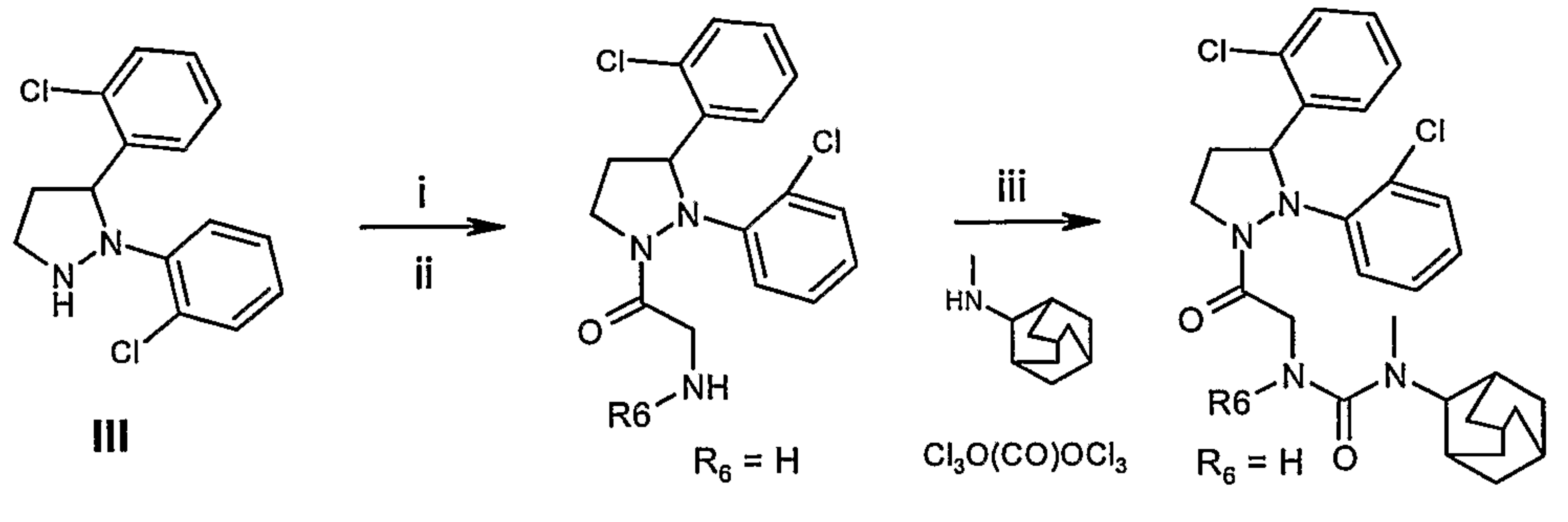


A23+A24

Scheme A.1

Method B:

The compounds mentioned in Table B can be obtained according to the synthesis indicated in Scheme B.1.



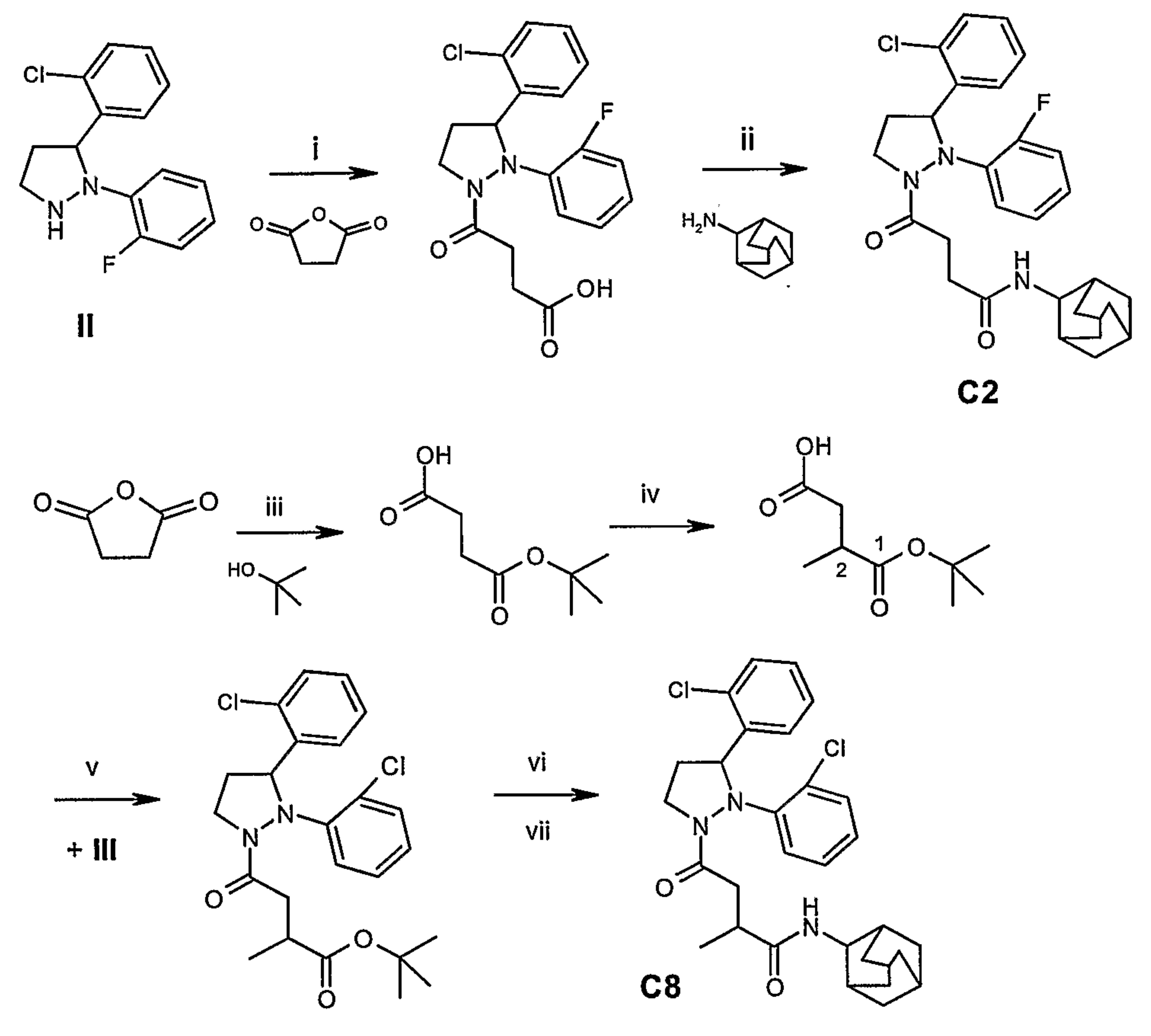
B2

Scheme B.1

Reaction step i and ii of Scheme B.1 are indentical to the procedures described in Scheme A.1, step i and step ii respectively.

Method C:

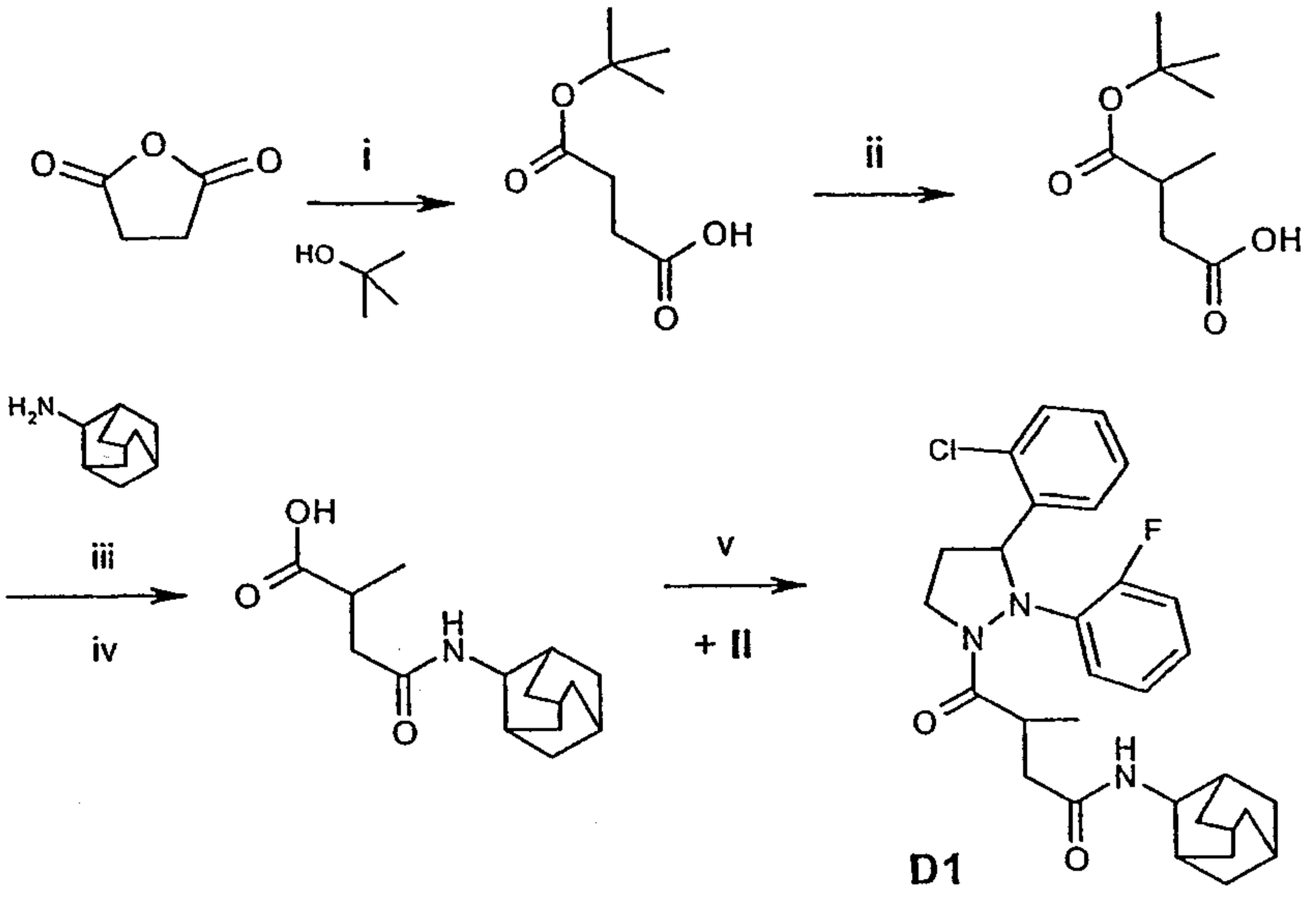
The compounds mentioned in Table C can be prepared according to the synthesis of compounds **C2** and **C8** as depicted in Scheme C.1:



Scheme C.1

Method D:

The compounds mentioned in Table D can be obtained according to the synthesis of compound D1 as indicated in Scheme D.1:



Scheme D.1

Reaction step i and ii of Scheme D.1 are identical to the procedures described in Scheme C.1 reaction steps iii and iv respectively.

Brief Description of the Drawings

Appendix 1 is a Nuclear Magnetic Resonance (NMR) spectrum for compound A1 listed in Table A of Example 1.

Appendix 2 is a NMR spectrum for compound A2 listed in Table A of Example 1.

Appendix 3 is a NMR spectrum for compound A3 listed in Table A of Example 1.

Appendix 4 is a NMR spectrum for compound A18 listed in Table A of Example 1.

Appendix 5 is a NMR spectrum for compound A22 listed in Table A of Example 1.

Appendix 6 is a NMR spectrum for compound A29 listed in Table A of Example 1.

The preparation of the compounds having formula (1) and of a number of intermediates according to methods A-D will now be described in detail in the following Examples.

Example 1

Step i (scheme A.1):

To a stirred 50 ml of dry acetonitril at room temperature and under a nitrogen atmosphere, were added: 4 g (14.5 mmol) of **II**, 2.7 g (14.3 mmol) of N-Boc-L-Alanine and 3.8 g (18.4 mmol of DCC (dicyclohexylcarbodiimide). A precipitate formed directly. Stirring was continued for one night. Thin layer chromatography of the reaction mixture displays an 8-like double spot containing the two possible diastereomers. The precipitate was removed by filtration. To the filtrate about 20 g of silica was added and concentrated *in vacuo.* The resulting powder was put on top of a dry column (SiO_2) after which elution was performed (eluent: CH_2Cl_2/MeOH 98/2). The part of the column containing the two diastereomers was collected and taken into MeOH. The latter suspension was filtered, the residue washed one more time with MeOH. The combined MeOH fractions were concentrated *in vacuo* and the resulting residue taken into CH_2Cl_2 after which it was dried on $MgSO_4$. Removal of the drying agent by filtration and solvent by evaporation *in vacuo*, ca. 5 g (80%) of crude product was isolated.

Step ii (scheme A.1):

While stirring, the 5 g (ca. 10 mmol) resulting from step i, were dissolved in 100 ml of a solution consisting of trifluoroacetic acid/CH_2Cl_2/H_2O 70/25/5. Stirring was continued for 2 hours. Subsequently the reaction mixture was concentrated *in vacuo*, the resulting residu was taken into CH_2Cl_2. The latter solution was treated with a saturated K_2CO_3 (aq) solution, and washed with water and brine and eventually dried on $MgSO_4$.

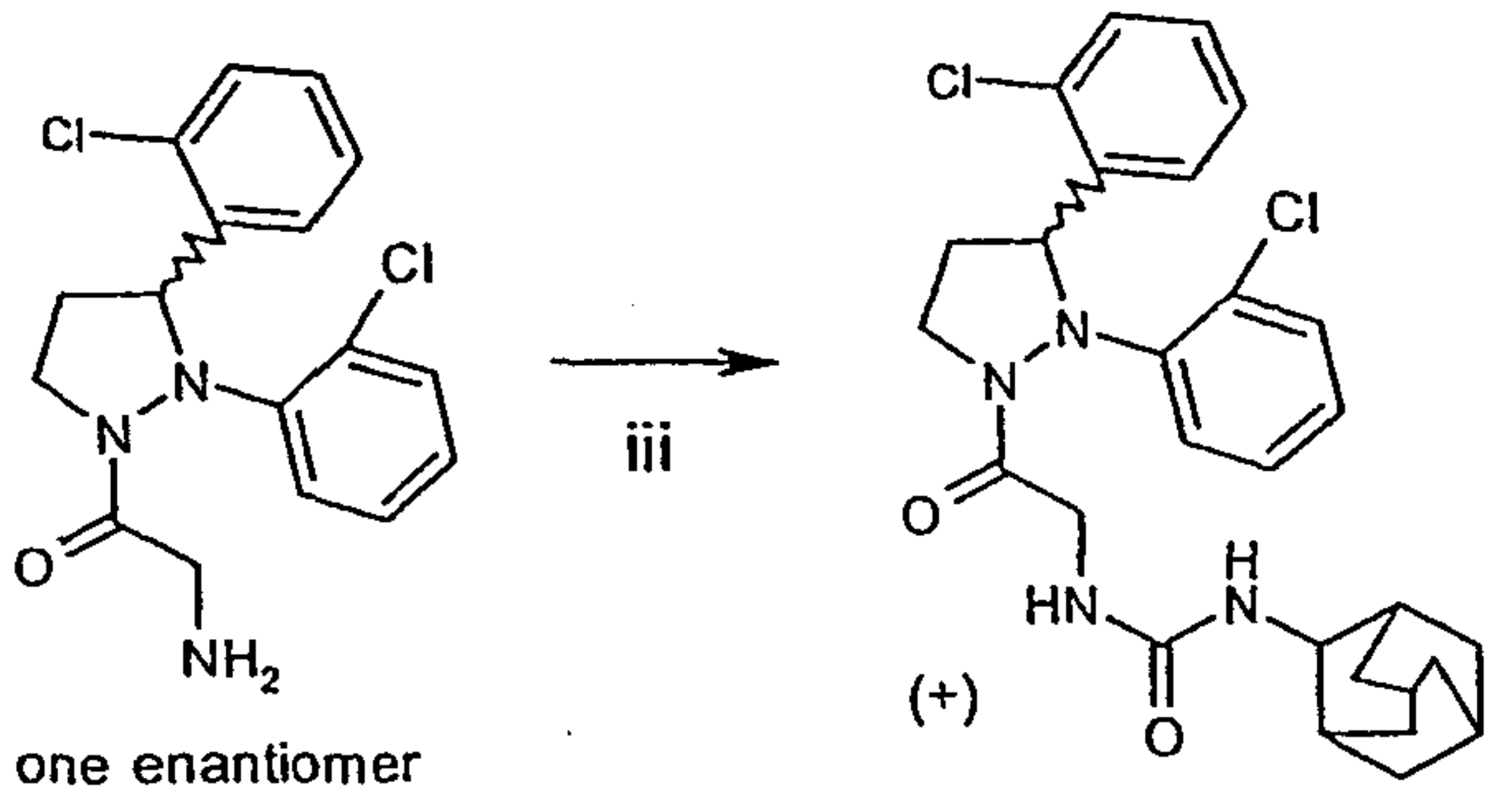
After removal of the drying agent by filtration and the solvent by evapotation *in vacuo*, 4 g (ca. 100%) of the crude amine was isolated.

Step iii (scheme A.1):

At room temperature and under a nitrogen atmosphere, 0.50 g (1.44 mmol) of the crude amine of step ii was suspended in 10 ml of acetonitril while stirring. Subsequently, 0.26 g (1.44 mmol) of 2-adamantylisocyanate was added. The reaction was continued for 2 hours. To the reaction mixture about 2 g of silica was added and concentrated *in vacuo*. The resulting powder was put on top of a dry column (SiO_2) after which elution was performed (eluent: EtOAc/petroleum ether 1/1). The parts of the column containing the diastereomers were collected separately, and taken into MeOH. The resulting two suspensions were separately filtered, each of the the two residues washed with MeOH one time. For each diastereomer the corresponding MeOH fractions were combined and concentrated *in vacuo* after which each residue was taken into CH_2Cl_2 after which the two solutions were dried on $MgSO_4$. After removal of the drying agent and the solvent *in vacuo*, two solids, each containing one diastereomer, were obtained: 0.16 g of **A23** (21%), melting point 140-3 °C, and 0.22 g of **A24** (29%) melting point 145-8 °C.

Note:

Compound **A12** has been prepared enantiomerically pure. The intermediate after step ii (scheme A.1), was separated into its enantiomers after which step iii (scheme A.2) was performed. The (+)- enantiomer of **A12** was the eutomer.



A12

Scheme A.2

The separation into the enantiomers of the intermediate after step ii (scheme A.1) was accomplished by using a Chiralcel™ CD column (25x5 cm^2, 20μ, eluent: hexane/ethanol 4/1).

The compounds of Table A have been prepared in the same manner:

Table A						
R_3, R_4, R_6, R_7, S_2, S_4 = H						
X, Y = N						
Compound	pyrazolidine	R_5	R_5'	YR_7A	remark	melting point
A1	I	H	H	1		see app. 1
A2	II	H	H	1		see app. 2
A3	II	H	H	2		see app. 3
A4	III	H	H	3		153-5
A5	III	H	H	4		>220
A6	II	H	H	5		185-8
A7	II	H	H	4		120-5
A8	II	H	H	6		130-3
A9	III	H	H	6		195-8
A10	IV	H	H	7		241-2
A11	III	H	H	7		>280
A12	III	H	H	8	[α] +94	164-5
A13	II	H	H	8		135-40
A14	II	H	H	9		105-10
A15	III	H	H	8		168-71
A16	I	H	H	7		208-210
A17	II	H	H	7		115-120
A18	V	H	H	7		see app. 4
A19	I	H	H	8		140-5
A20	III	Me	H	8	diastereomers	125-145
A21	III	Me	H	8		132-150
A22	I	H	H	10		see app. 5
A23	II	Me	H	8	diastereomers	140-3
A24	II	Me	H	8		145-8
A25	II	Et	H	8	diastereomers	145-8
A26	II	Et	H	8		155-8
A27	II	nBut	H	8		122-5
A28	II	iBut	H	8		122-5
A29	II	H	H	10		see app. 6
A30	VI	H	H	8		221-3
A31	X	H	H	8		208-210
A32	VIII	H	H	8		145-165
A33	II	nPr	H	8		110-130

Six of the examples (*compounds A1, 2, 3, 18, 22 and 29*) were found to be amorphous: no reliable, reproducible melting points could be determined. Instead Nuclear Magnetic Resonance (NMR) spectra are supplied. Those spectra are reproduced as appendices 1-6, set out in the drawings.

Example 2

Step iii (scheme B.1):

0.20 g (0.67 mmol) of triphosgene was dissolved in 10 ml of dry dichloromethane. To the latter mixture a solution of 0.70 g (2.0 mmol) of the pyrazolidine derivative and 0.42 ml (2.4 mmol) di-isopropylethylamine was added in a period of 45 minutes. The reaction mixture was stirred continuously. Subsequently, a solution containing 0.33 g (2.0 mmol) of methyl-2-adamantyl amine and 0.42 ml (2.4 mmol) of di-isopropylethylamine in 5 ml of dry dichloromethane, was added to the reaction mixture in 5 minutes. The reaction mixture was allowed to react for one night after which the solvent was evaporated *in vacuo*. The residue was taken into ethylacetate and the latter solution treated with 5% aqueous $NaHCO_3$ and brine respectively. The organic layer was separated and dried on $MgSO_4$. Filtration of the drying agent and removal of the solvent *in vacuo* yielded an oil which was subjected to flash column chromatography (SiO_2, eluent: CH_2Cl_2/MeOH 99/1). Collection of the product containing fractions and subsequent removal of the eluent *in vacuo* gave an oil which crystallized upon stirring in di-isopropylether. Filtration and drying in the air gave 0.69 g (64%) of solid **B2** (m.p.: 184-6 °C).

Note: The applied methyl-2-adamantyl amine can easily be prepared by standard reductive amination procedures starting from 2-adamantanon and methylamine hydrochloride while using $NaBH(OAc)_3$ as the reductive agent.

The compounds of Table B have been prepared in the same manner:

Table B							
R_3, R_4, R_5, $R_{5'}$, S_2, S_4 = H							
Compound	pyrazolidine	X	Y	R_6	R_7	YR_7A	melting point
B1	III	N	N	H	nPr	11	132-4
B2	III	N	N	H	Me	12	184-6
B3	III	N	N	Me	H	4	222-4
B4	III	N	N	H	Me	13	140-2
B5	III	N	O	H	▨	14	110-2
B6	II	N	O	H	▨	15	142-4
B7	II	N	O	H	▨	14	135-8
B8	I	N	O	H	▨	14	141-3
B9	I	N	O	H	▨	15	151-4

Note: The needed intermediate after step ii (scheme B.1) in the case of **B3** (R_6 = Me), can be prepared analogously to steps i en ii in scheme A.1.

Example 3

Step i (scheme C.1):

16 g (160 mmol) of succinic anhydride were dissolved in dry diethyl ether. Subsequently, 44 g (160 mmol) of **II**, dissolved in diethyl ether were added dropwise to the stirred succinic anhydride solution. After the addition was complete, the reaction mixture was brought to reflux temperature which was continued for one night. A precipitate had formed which was filtered, the residu was washed two times with diethyl ether. Drying on the air afforded 45.6 g (75%) of the desired intermediate.

Step ii (scheme C.1):

Under a nitrogen atmosphere, 4.5 g (12 mmol) of the intermediate of step i and 7.9 g (61 mmol, 5.1 eq.) of diisopropylethylamine were dissolved in 50 ml of dry CH_2Cl_2, the resulting stirred solution was brought to 4 °C. Subsequently, 0.90 g (7.0 mmol) of 1-hydroxy-7-aza-benztriazole, and 4.20 g (15 mmol) of 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate were added. Then 2.19 g (15 mmol) of 2-amino-adamantane was added to the reaction mixture which was allowed to react for one hour at room temperature.

To the reaction mixture about 4 g of silica was added and concentrated *in vacuo*. The resulting powder was put on top of a dry column (SiO_2) after which elution was performed (eluent: EtOAc/petroleum ether 1/1). The part of the column containing the product was collected, and taken into MeOH. The resulting suspension was filtered, the residue washed with MeOH one time. The MeOH fractions were combined and concentrated *in vacuo* after which the residue was taken into CH_2Cl_2 and the resulting solution was dried on $MgSO_4$. After removal of the drying agent and the solvent *in vacuo*, a solid was obtained: 2.0 g of **C2** (32%), melting point 192-5 °C.

Step iii (scheme C.1):

While stirring and under a nitrogen atmosphere, 6.0 g (60 mmol) of succinic anhydride was suspended in 35 ml of toluene. Subsequently, 2.07 g (18 mmol) N-hydroxy-succinimide, 0.73 g (6 mmol) of 4-dimethylaminopyridine, 13.3 g (18 mmol) of dry *tert.* butanol and 1.82 g (18 mmol) of triethylamine were added. The reaction mixture was brought to reflux temperature and allowed to react for one night. The reaction mixture was cooled, after which EtOAc was added. The resulting solution was treated respectively with 10% citric acid (aq) and brine, after which the organic fraction was dried on $MgSO_4$. Removal of the drying agent and solvent by evaporation *in vacuo* yielded a brown oil. Crystallization from diethylether/hexane gave 4.4 g (42%) of the desired monoester.

Step iv (scheme C.1):

This reaction was carried out according to the procedure described in *Synthesis* (2000) p1369-71. The mono tert.butyl ester of succinic acid was methylated in the 2-position by reaction with lithium diisopropyl amide and methyliodide in tetrahydrofuran at –78 °C. The isolated yield of the 2-methyl-succinic acid mono *tert.*butyl ester amounted to 60%.

Step v (scheme C.1):

While stirring, 1.8 g (9.8 mmol) of 2-methyl-succinic acid mono *tert.*butyl ester (step iv) was dissolved in 45 ml of dry CH_2Cl_2 after which the solution was brought to 4 °C. To the latter solution, 0.9 g (6.4 mmol) of 1-hydroxy-7-aza-benztriazole, and 4.0 g (15 mmol) of 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate were added. Subsequent addition of **III** 4.1 g (14 mmol) did not give a raise in temperature, the reaction was allowed to proceed for a night at room temperature. Ca. 3 g of silicagel (SiO2) were added to the reaction mixture after which it was concentrated *in vacuo*. The resulting powder was put on top of a dry column (SiO_2) after which elution was performed (eluent: EtOAc/petroleum ether 1/4). The part of the column containing the product was collected and taken into MeOH. The latter suspension was filtered, the residu washed one more time with MeOH. The combined MeOH fractions were concentrated *in vacuo* and the resulting residu taken into CH_2Cl_2 after which it was dried on $MgSO_4$. Removal of the drying agent by filtration and solvent by evaporation *in vacuo*, 3 g (66%) of the desired intermediate was isolated.

Step vi (scheme C.1):

Hydrolysis of the *tert.* butyl ester of the intermediate of step v was accomplished as follows; 3 g (6.4 mmol) of the *tert.* butyl ester was dissolved in 30 ml of dry CH_2Cl_2 after which 10 ml of trifluoroacetic acid was added dropwise. After two hours the reaction was complete, the reactionmixture was concentrated *in vacuo* after which the residu dissolved in a little diethylether, was put on top of a short column (dry SiO_2) and eluted with diethylether. The product containing eluate was concentrated *in vacuo*, the residue was stirred for a night in petroleum ether. Crystals were collected by filtration, after drying on the air 2.1 g (80%) were obtained of the desired intermediate.

Step vii (scheme C.1):

Under a nitrogen atmosphere, 2.17 g (5.3 mmol) of the intermediate of step vi and 4.7 ml (27 mmol, 5.1 eq.) of diisopropylethylamine were dissolved in 25 ml of dry CH_2Cl_2, the resulting stirred solution was brought to 4 °C. Subsequently, 0.42 g (3.1 mmol) of 1-hydroxy-7-aza-benztriazole, and 1.85 g (6.6 mmol) of 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate were added. Then 1.0 g (6.6 mmol) of 2-amino-adamantane was added to the reaction mixture which was allowed to react for one hour at room temperature.

To the reaction mixture about 4 g of silica was added and concentrated *in vacuo*. The resulting powder was put on top of a dry column (SiO_2) after which elution was performed (eluent: EtOAc/petroleum ether 1/2). The parts of the column containing the diastereomic racemates were collected separately, and taken into MeOH. The resulting two suspensions were separately filtered, each of the the two residues washed with MeOH one time. For each diastereomic racemate the corresponding MeOH fractions were combined and concentrated *in vacuo* after which each residue was taken into CH_2Cl_2 after which the two solutions were dried on $MgSO_4$. After removal of the drying agent and the solvent *in vacuo*, two solids, each containing one of the possible diastereomeric racemates, were obtained: 1.08 g of **C8** (37%), the active racemate, melting point 238-40 °C, and 1.09 g (37%) of the other, pharmacologically inactive racemate (37%) melting point 125-30 °C. (not in table C).

The compounds of Table C have been obtained in a similar manner:

Table C					
R_3, R_4, R_5, R_5', S_2, S_4 = H					
X = C, Y = N					
Compound	pyrazolidine	R_6	R_7	YR_7A	melting point
C1	III	H	H	8	210-2
C2	II	H	H	8	90-4
C3	II	H	H	7	230-2
C4	I	H	H	8	160-4
C5	I	H	H	7	198-202
C6	VII	H	H	7	208-210
C7	VII	H	H	8	215-7
C8	III	Me	H	8	238-240
C9	IX	H	H	8	147-150

Example 4

Step iii (scheme D.1):

Under a nitrogen atmosphere, 0.92 g (4.9 mmol) of the intermediate of step ii and 4.4 ml (25 mmol, 5.1 eq.) of diisopropylethylamine were dissolved in 15 ml of dry CH_2Cl_2, the resulting stirred solution was brought to 4 °C. Subsequently, 0.45 g (3.3 mmol) of 1-hydroxy-7-aza-benztriazole, and 2.1 g (7.5 mmol) of 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate were added. Then 1.08 g (7.2 mmol) of 2-amino-adamantane was added to the reaction mixture which was allowed to react for one hour at room temperature. This reaction mixture was used for the following step iv.

Step iv (scheme D.1):

To the stirred reaction mixture of step iii, 45 ml of dry CH_2Cl_2 were added, and 11 ml (143 mmol) of trifluoroacetic acid as well. Stirring was continued for 24 hours.
The reactionmixture was concentrated *in vacuo* after which the residu was dissolved in a little diethylether, was put on top of a short column (dry SiO_2) and eluted with diethylether. The product containing eluate was concentrated *in vacuo*, affording 0.87 g (67%, 2 steps) of the desired acid intermediate.

Step v (scheme D.1):

While stirring, 0.87 g (3.28 mmol) of methyl-succinic acid mono amide (step iv) was dissolved in 15 ml of dry CH_2Cl_2 after which the solution was brought to 4 °C. To the latter solution, 0.3 g (2.2 mmol) of 1-hydroxy-7-aza-benztriazole, and 1.40 g (5.0 mmol) of 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate were added. Subsequent addition of **II** 1.33 g (4.80 mmol) did not give a raise in temperature, the reaction was allowed to proceed for a night at room temperature. Ca. 3 g of silicagel (SiO_2) were added to the reaction mixture after which it was concentrated *in vacuo*. The resulting powder was put on top of a dry column (SiO_2) after which elution was performed (eluent: EtOAc/petroleum ether 1/1).
The parts of the column containing the diastereomeric racemates were collected separately, and taken into MeOH. The resulting two suspensions were separately filtered, each of the the two residues washed with MeOH one time. For each diastereomeric racemate the corresponding MeOH fractions were combined and concentrated *in vacuo* after which each residue was taken into CH_2Cl_2 after which the two solutions were dried on $MgSO_4$. After removal of the drying agent and the solvent *in vacuo*, two solids, each containing one of the possible diastereomeric racemates, were obtained: 0.31 g (18%) of the inactive racemate (not in table D), melting behavior: melting 90-5°C, solidifies at 130 °C, remelting 160-5 °C, and 0.40 g (23%) of the active racemate **D1**, melting behavior: melting 80-2 °C, solidifies at 100 °C, remelting at 125-8 °C.

The compounds indicated in Table D have been prepared in a similar manner:

Table D						
R_3, R_4, R_5', S_2, S_4 = H						
X = C, Y = N						
Compound	pyrazolidine	R_5	R_6	YR_7A	remark	melting point
D1	II	Me	H	8		80-2/125-8
D2	II	nBut	H	8	diastereomers	80-1/150-5
D3	II	nBut	H	8		210-2
D4	II	iBut	H	8		155-8
D5	II	Et	H	8	diastereomers	90-2/125-8
D6	II	Et	H	8		90-2/155-7

Example 5

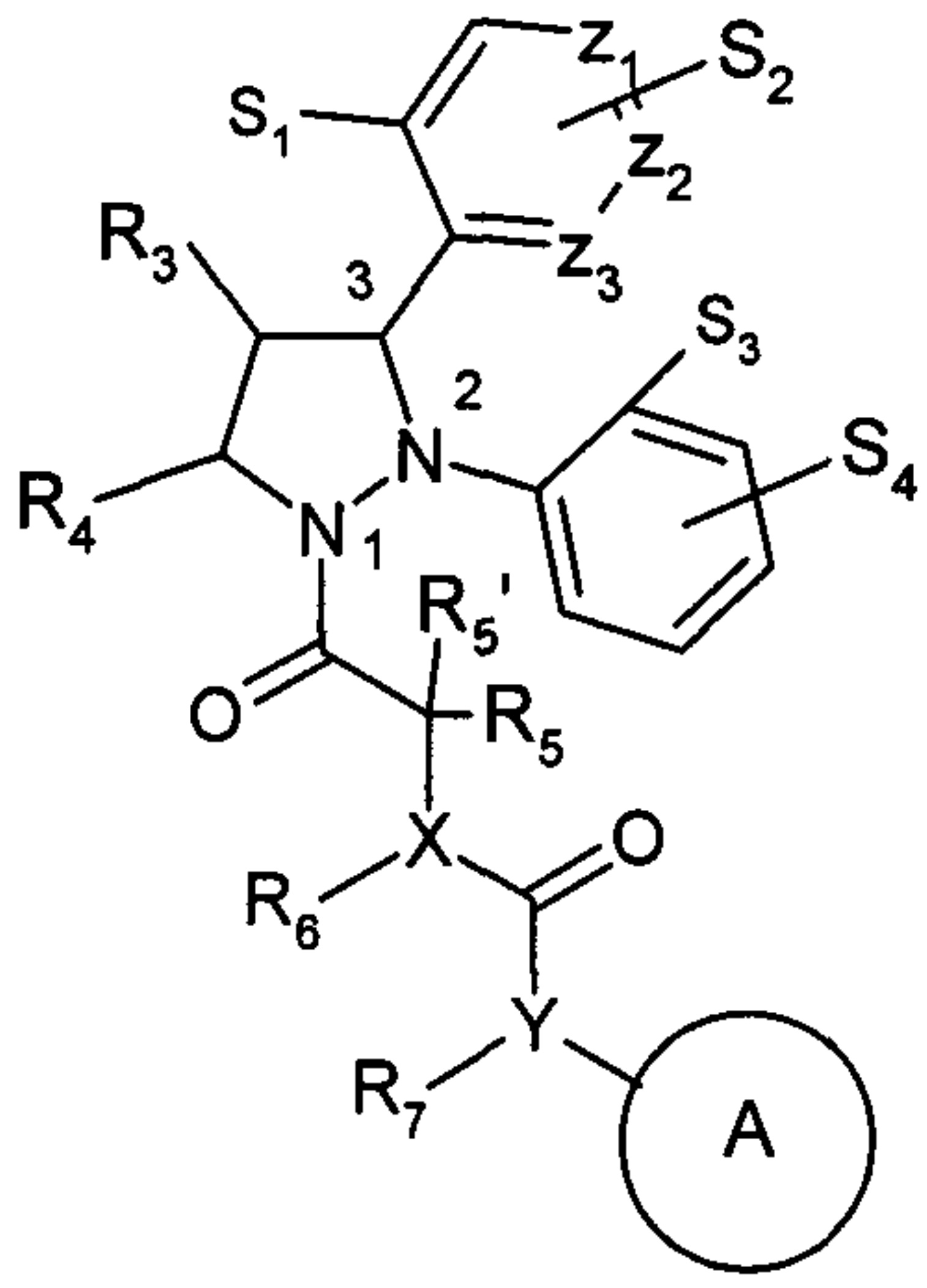
The 2,3-diaryl-pyrazolidines I to X used as starting materials in the above Examples 1 to 4 have been prepared as follows:

Step i (scheme 1):

A mixture of 16.9 ml of acetic acid and 2.3 ml of water was cooled (ice/water) after which 6.8 ml of concentrated sulfuric acid was carefully added. To the cooled solution, while vigorously stirring and under a nitrogen atmosphere, 13.3 g (82 mmol) of 2-fluorophenyl hydrazine was added in portions. To the latter solution, a mixture consisting of 10.0 g (82 mmol) of 2-fluorostyrene and 2.46 g (82 mmol) of paraformaldehyde, was added portionwise while keeping the temperature below 25 °C. The reaction may accumulate for some time. Vigorously stirring was continued for one night at room temperature. While cooling, 50 ml of water were added, after which extraction took place with diethyl ether (2x). The remaining aqueous fraction was made basic with 50% NaOH (aq) and subsequently extracted with diethyl ether (2x). The latter ethereal fraction was washed with water (3x) and brine (1x), and eventually dried on $MgSO_4$. Filtration of the drying agent and removal of the solvent *in vacuo*, yielded 16 g (75%) of a crude siruppy oil. The oil was not purified and should be stored under a nitrogen atmosphere at –20 °C to prevent oxidation of the pyrrolidine nucleus.

CLAIMS:

1. A compound of the formula (1):



wherein,

- S_1 is hydrogen, halogen, hydroxy or alkoxy (1-3C);

- S_2 is hydrogen or halogen;

- S_3 is hydrogen, halogen, hydroxy or alkoxy (1-3C);

- S_4 is hydrogen, halogen or alkyl (1-6C) which is optionally substituted with hydroxy, alkoxy (1-3C), amino, mono- or dialkylamino having 1-3C-atoms in the alkyl group(s), SH or S-alkyl (1-3C);

- R_7 is hydrogen or alkyl (1-3C);

- X is N or CH;

- Y is N or O when X is N, or

Y is N when X is CH, with the understanding that when Y is O, R_7 is absent;

- R_3 and R_4 are independently of each other hydrogen or alkyl (1-3C);

- when X is N, R_5 is hydrogen or alkyl (1-6C) which is optionally substituted with halogen, CN, CF_3, hydroxy, alkoxy (1-3C), sulfonylalkyl (1-3C), amino or mono- or dialkylamino having 1-3 C-atoms in the alkyl group(s);

when X is CH, R_5 is as defined when X is N or R_5 is alkoxy (1-6C), SH or S-alkyl (1-3C);

- R'_5 is hydrogen or alkyl (1-3C);

- R_6 is hydrogen, or alkyl (1-3C); or

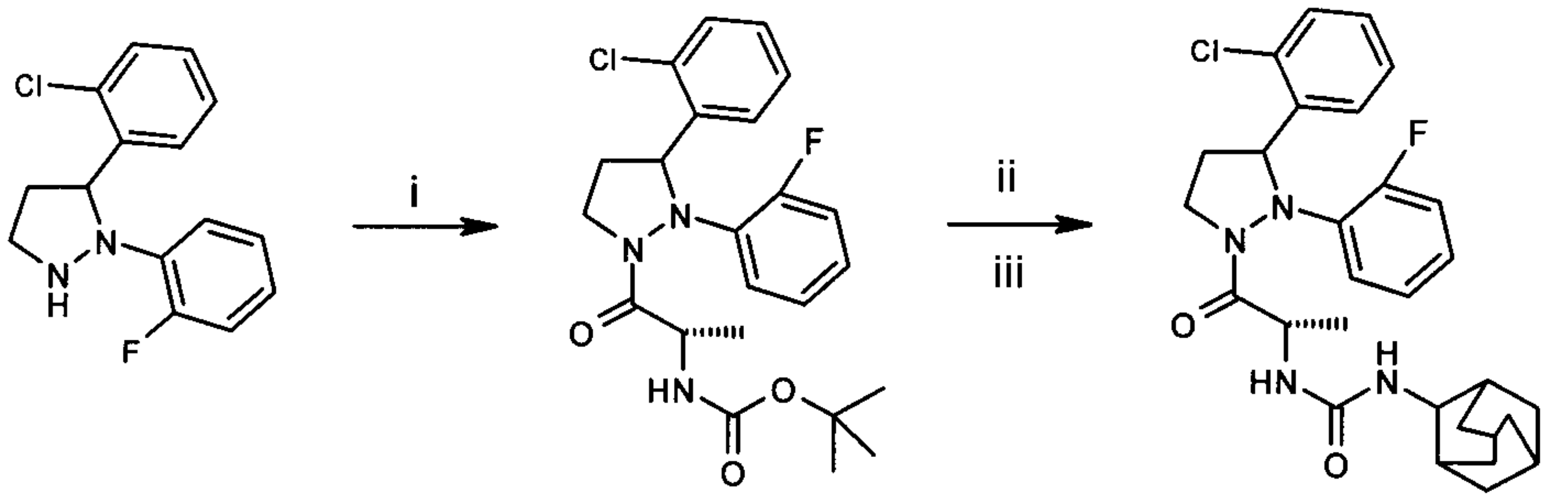
- R_5 and R_6 together or R'_5 and R_6 together form a 3-7 membered cyclic group which is optionally substituted with alkyl (1-3C), halogen, CN or CF_3, or R_5 and R'_5 together form a 3-7 membered ring;

- Z_1, Z_2 and Z_3 are carbon, Z_1 is nitrogen and Z_2 and Z_3 are carbon, Z_1 and Z_3 are carbon and Z_2 is nitrogen, or Z_1 and Z_2 are carbon and Z_3 is nitrogen; and

- A is a mono-, di-, tri- or tetracycloalkyl system wherein each cycloalkyl ring in the system has 4 to 10 carbon atoms and is optionally substituted with halogen, CF_3, alkyl (1-3C), alkoxy (1-3C), CN, OH or SH, or a pharmacologically acceptable salt thereof.

2. A process for preparation of a compound of formula (1) as defined in claim 1, wherein the compound is prepared according to one of the methods set out in the following schemes:

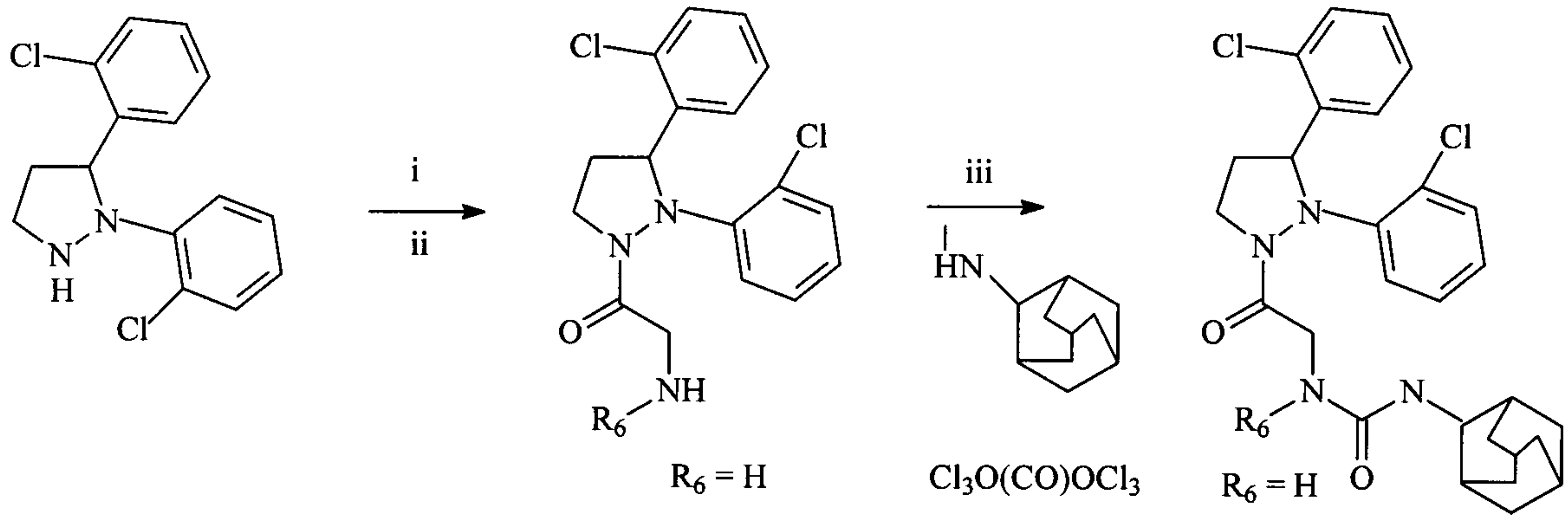
a)



Scheme A

wherein after step i two diastereomers evolve which, after step iii has been performed, are optionally separated by column chromatography into enantiomeric pure diastereomers using a Chiralcel™ CD column having the following properties: 25x5 cm^2, 20µ, and eluent: hexane/ethanol 4/1;

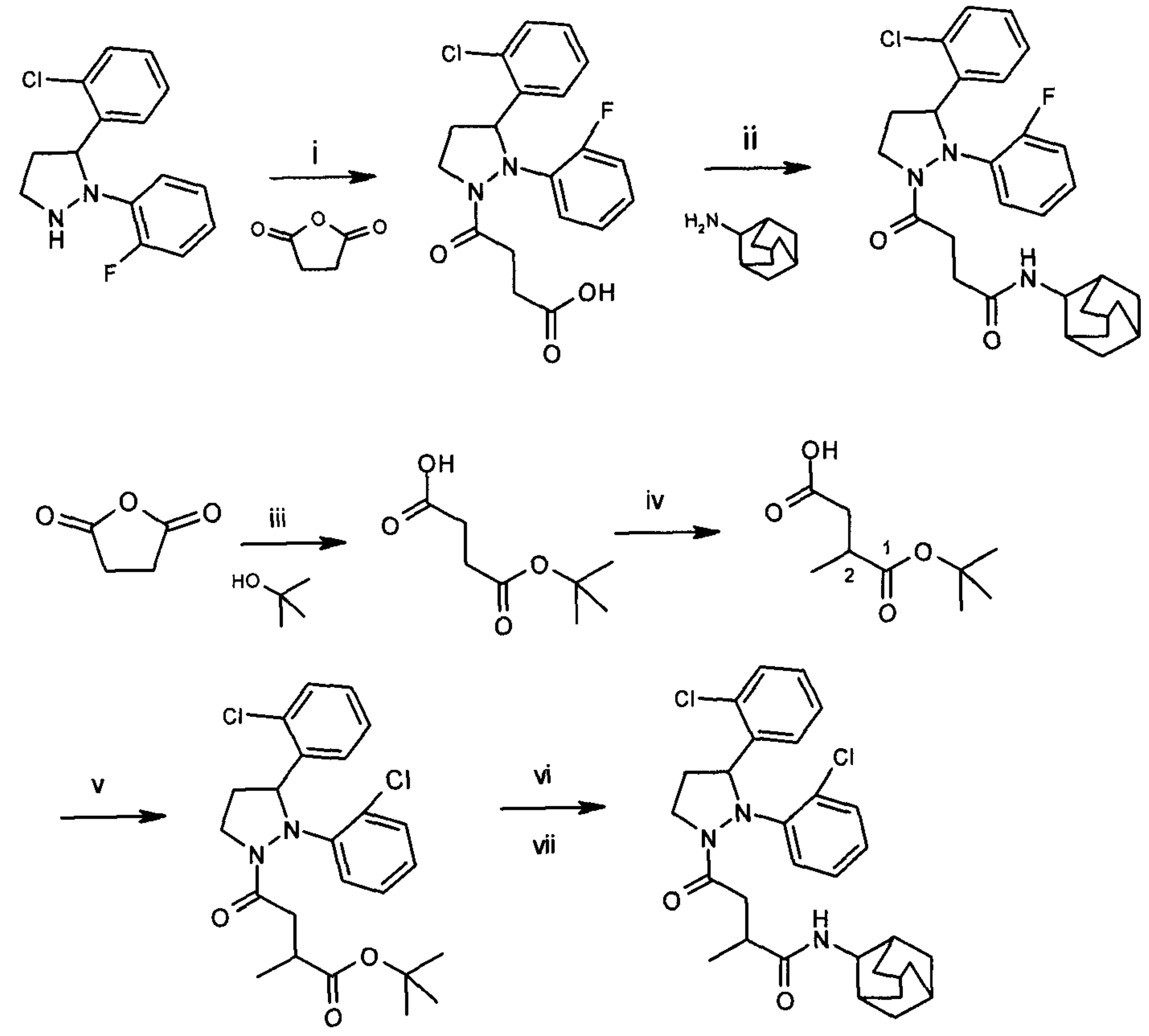
b)



Scheme B

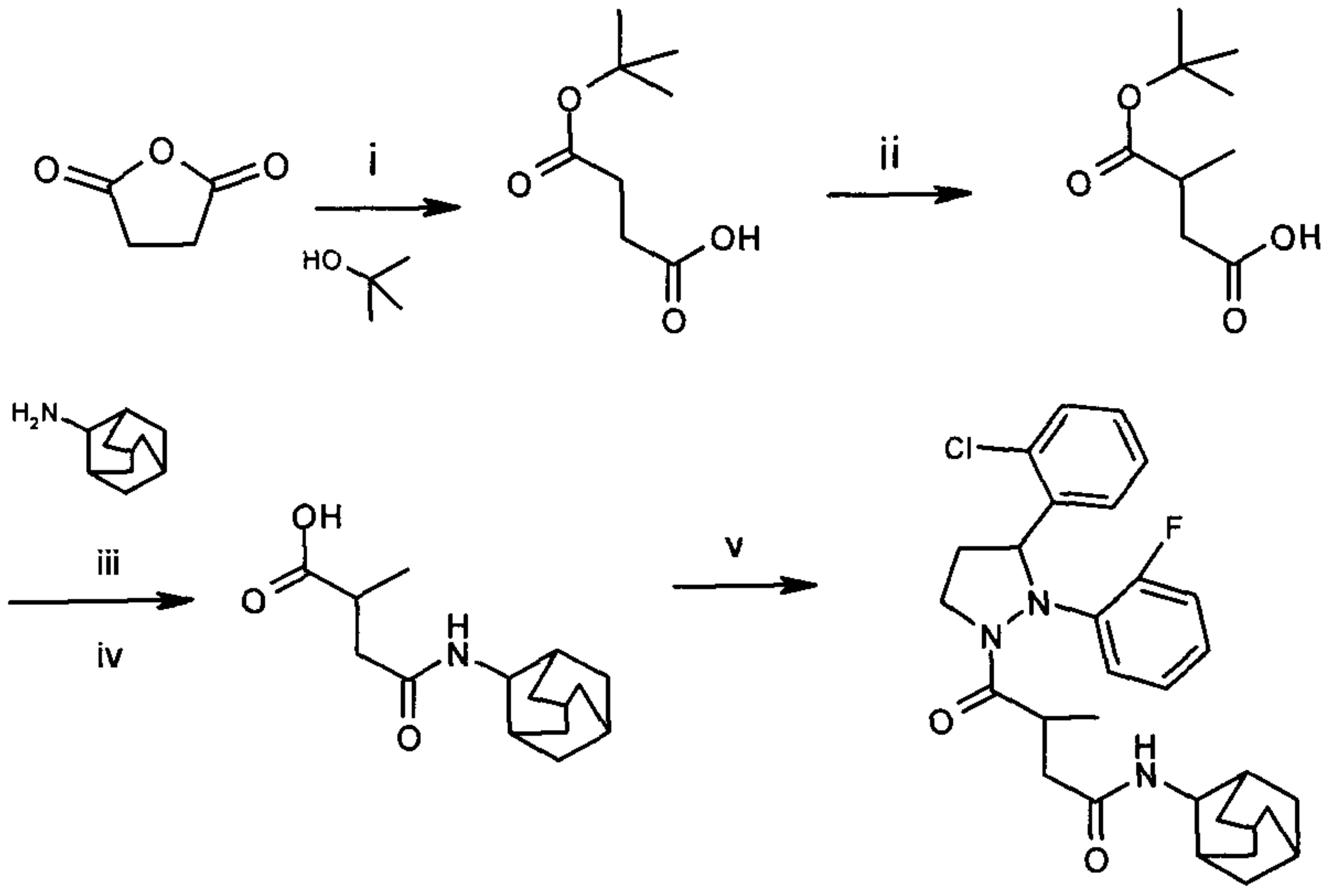
wherein the reaction steps i and ii are as defined in scheme A;

c)



Scheme C ; and

d)



Scheme D

wherein the reaction steps i and ii are as defined in steps iii and iv in scheme C, respectively.

3. A pharmaceutical composition comprising a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or auxiliary substance.

4. A pharmaceutical composition according to claim 3 for treatment of an affection or disease caused by a disturbance of neurotensin mediated transmission.

5. A pharmaceutical composition according to claim 3 for treatment of psychosis.

6. A pharmaceutical composition according to claim 3 for treatment of Parkinson's disease.

7. A pharmaceutical composition according to claim 3 for treatment of depression.

8. A pharmaceutical composition according to claim 3 for treatment of an anxiety disorder.

9. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof in preparation of a pharmaceutical composition for treatment of an affection or disease caused by a disturbance of neurotensin mediated transmission.

10. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof in preparation of a pharmaceutical composition for treatment of psychosis.

11. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof in preparation of a pharmaceutical composition for treatment of Parkinson's disease.

12. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof in preparation of a pharmaceutical composition for treatment of depression.

13. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof in preparation of a pharmaceutical composition for treatment of an anxiety disorder.

14. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of an affection or disease caused by a disturbance of neurotensin mediated transmission.

15. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of psychosis.

16. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of Parkinson's disease.

17. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of depression.

18. Use of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of an anxiety disorder.

19. A compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of an affection or disease caused by a disturbance of neurotensin mediated transmission.

20. A compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of psychosis.

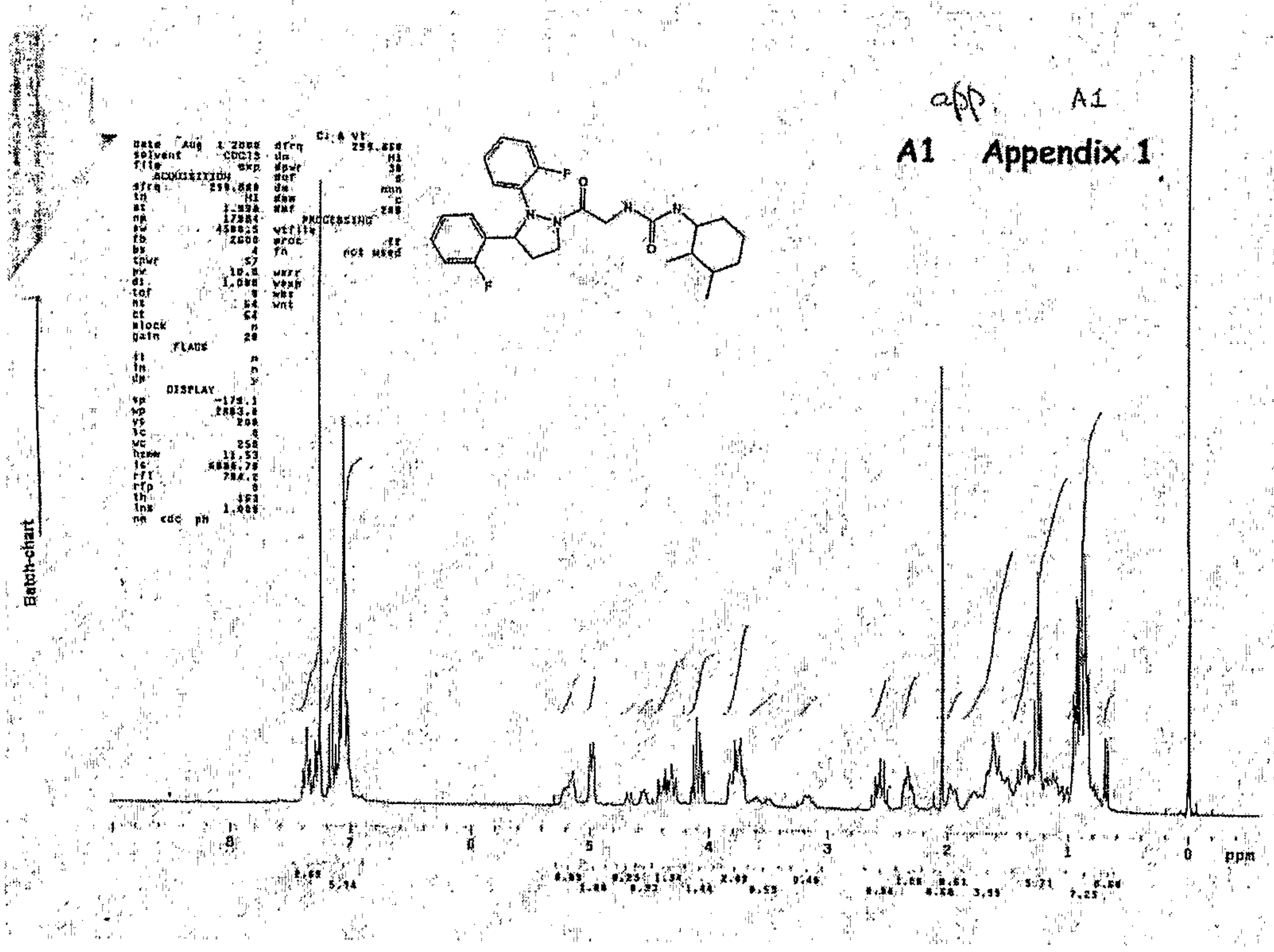
21. A compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of Parkinson's disease.

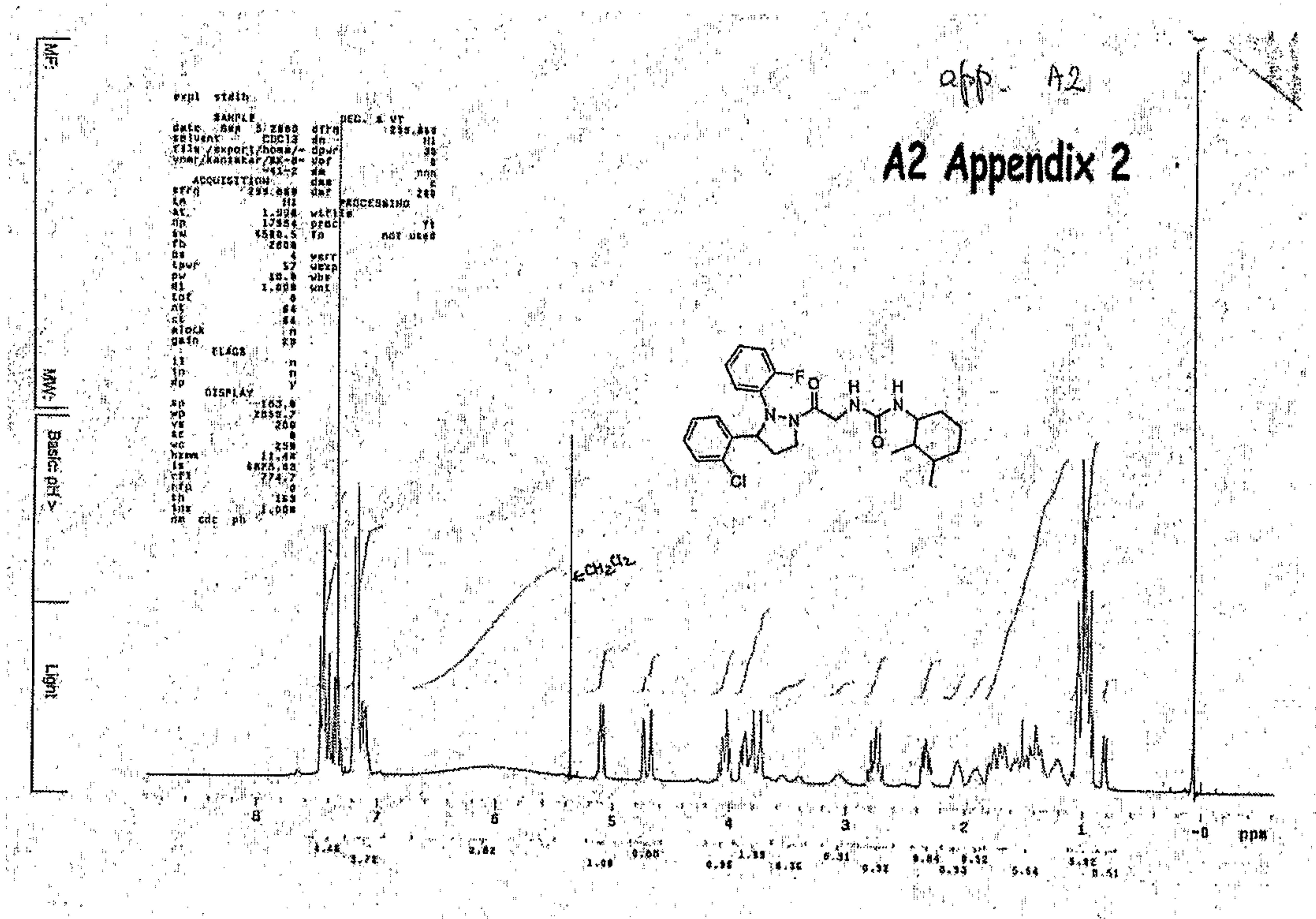
22. A compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of depression.

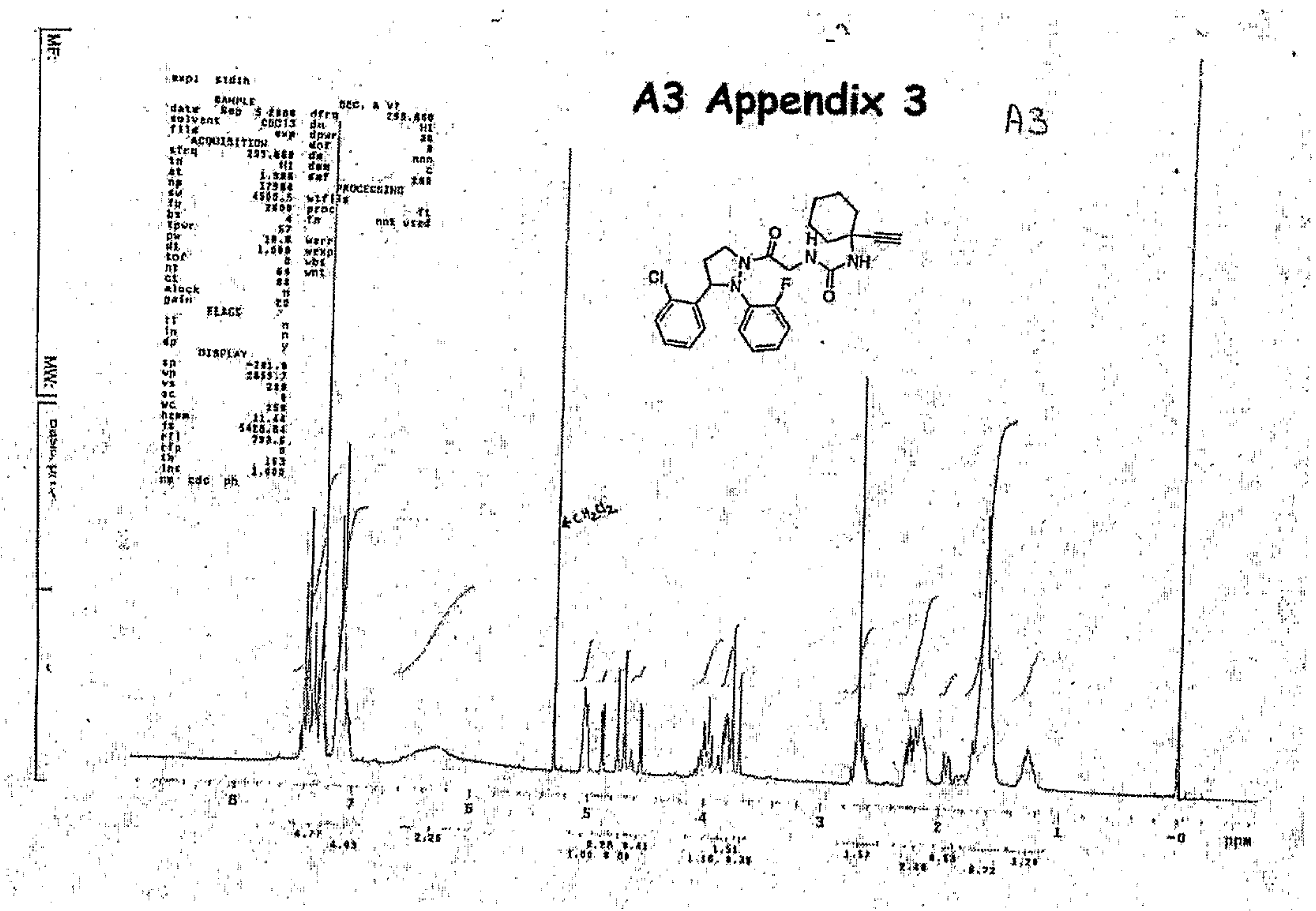
23. A compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof for treatment of an anxiety disorder.

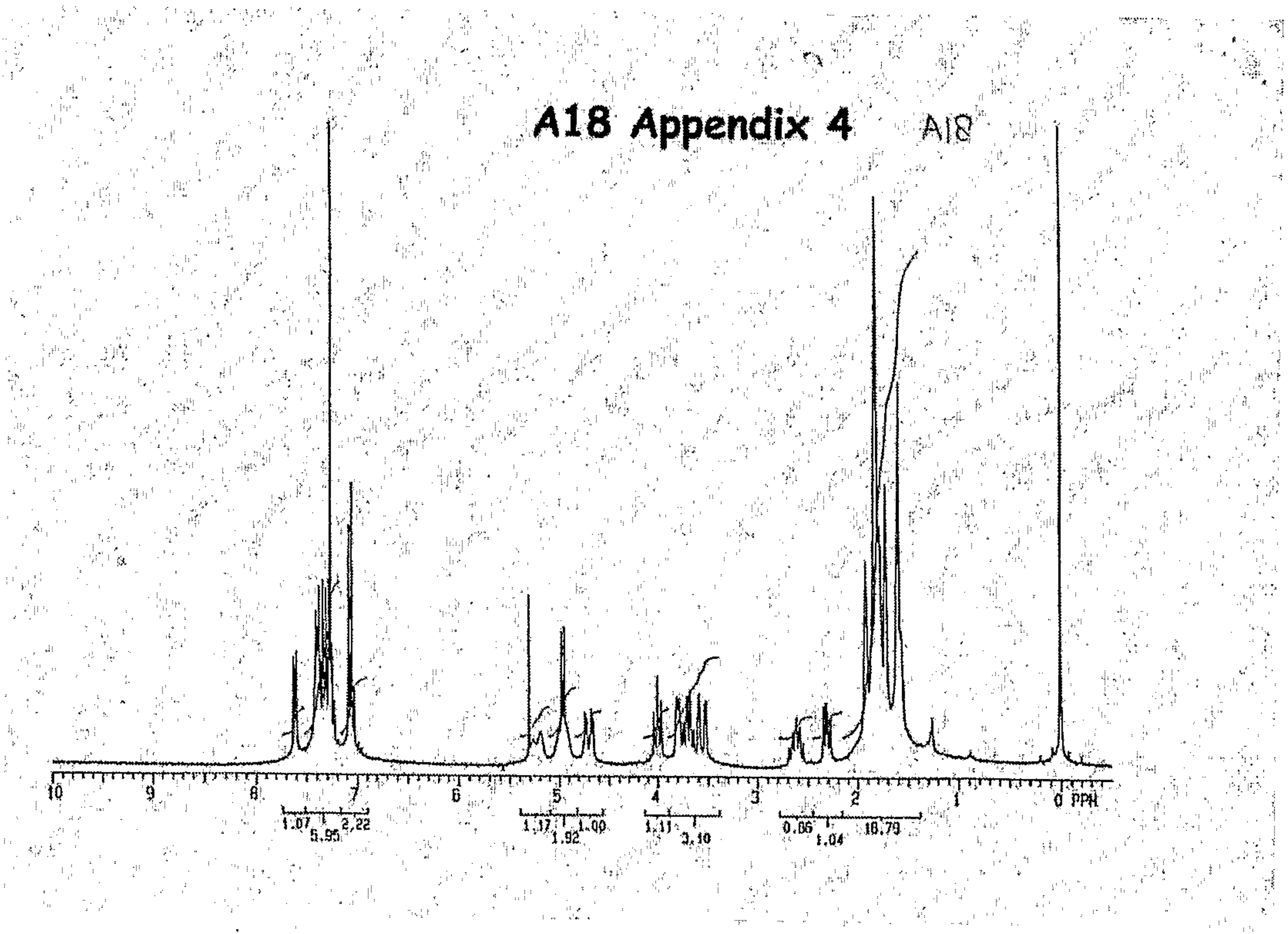
FETHERSTONHAUGH & CO.
OTTAWA, CANADA

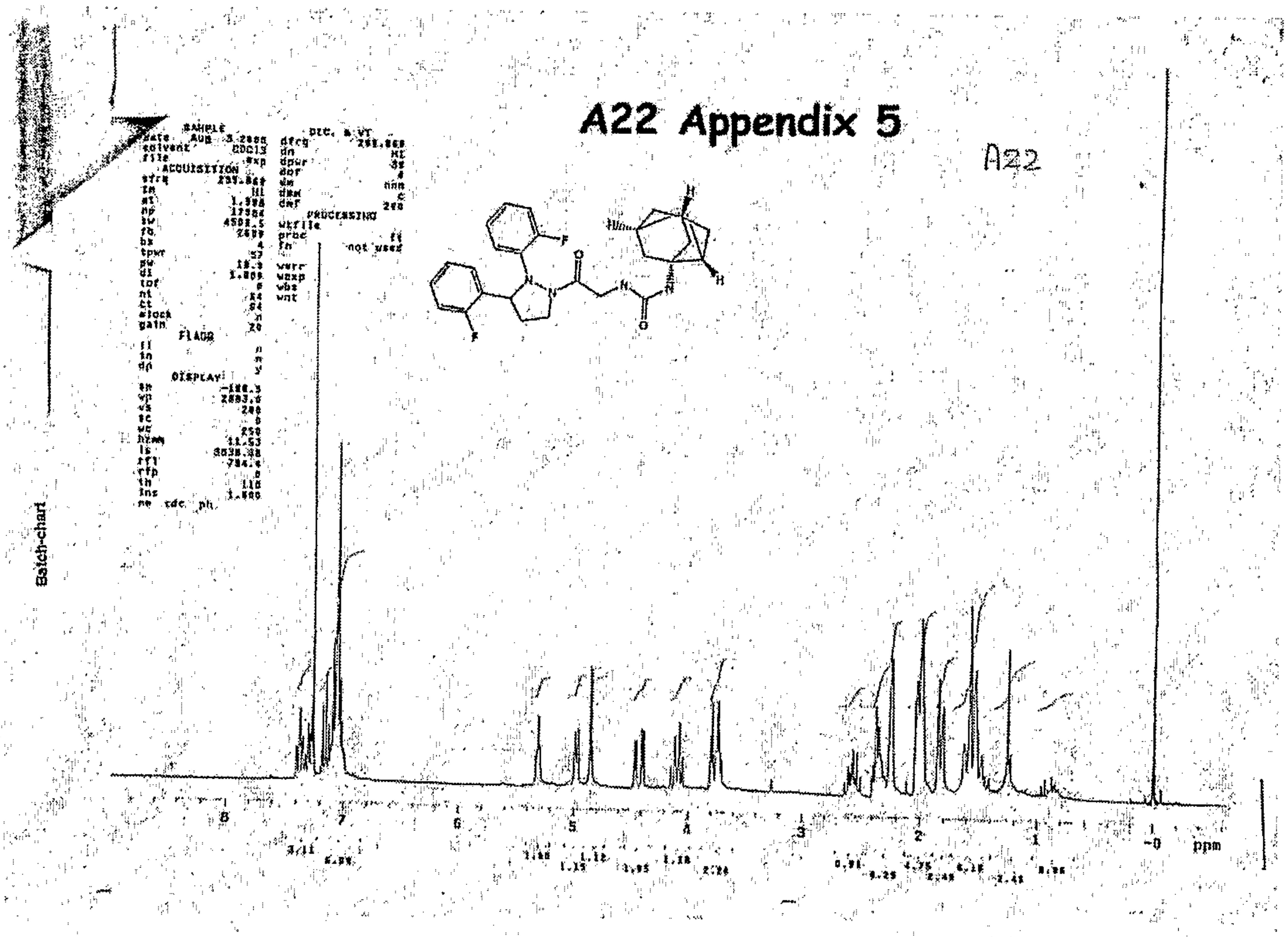
PATENT AGENTS

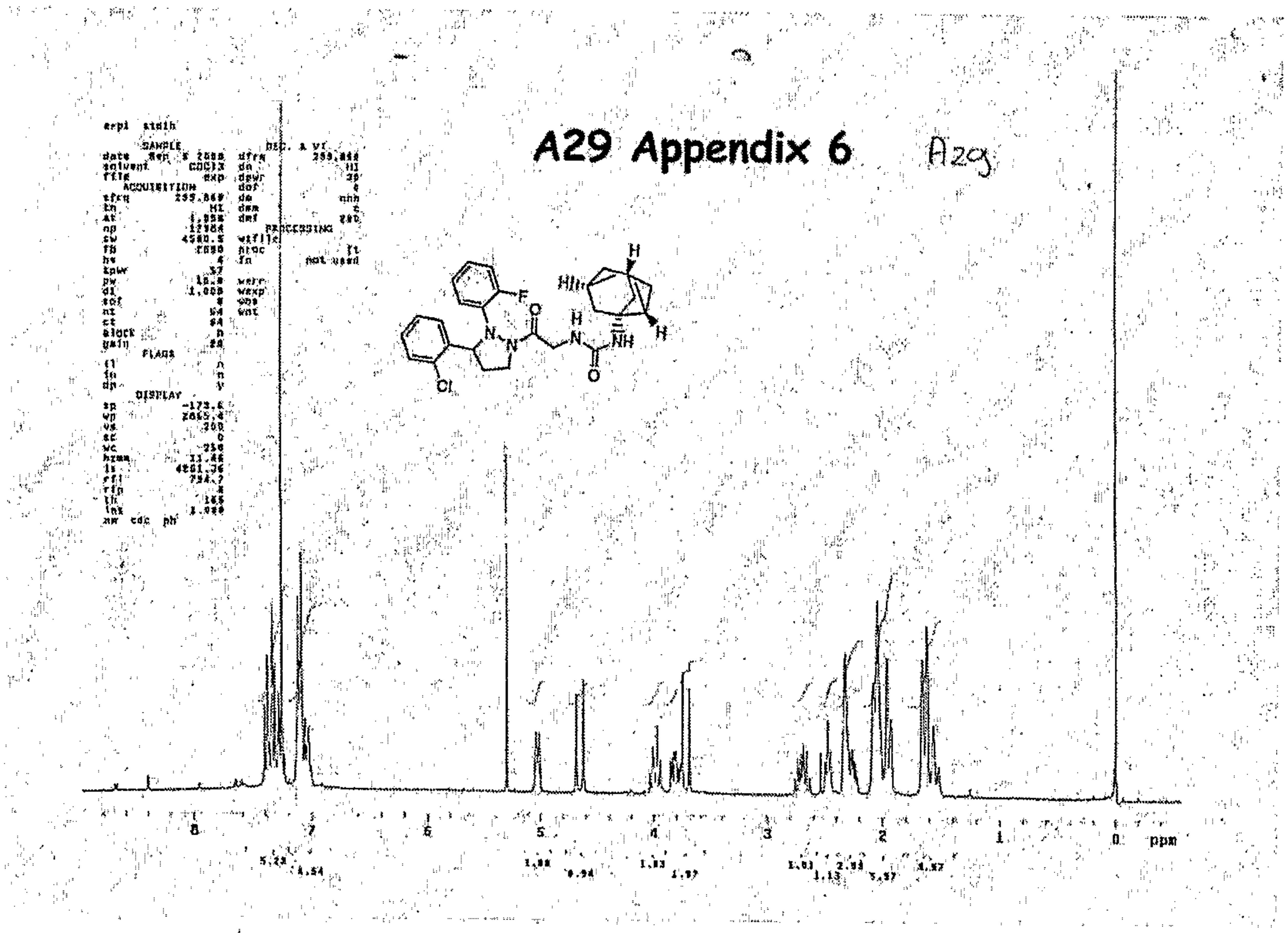

app. A1
A1 Appendix 1
Batch-chart
F
F
N
N
O
O
N
8
7
6
5
4
3
2
1
0
ppm

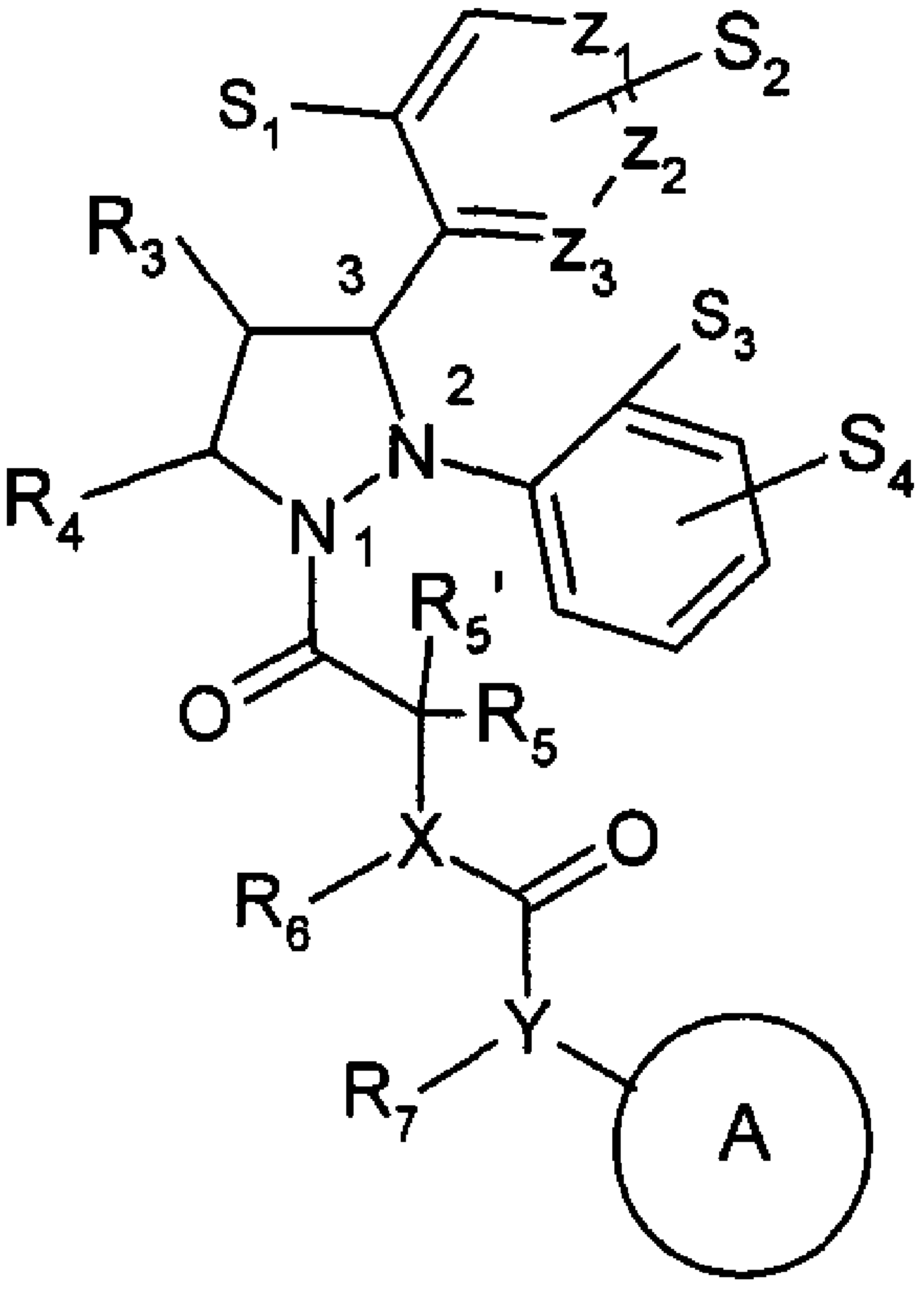

app. A2
A2 Appendix 2
MF:
MW:
Basic pH >
Light
F
Cl
N
N
O
O
H
N
H
N
CH2Cl2
8
7
6
5
4
3
2
1
0
ppm


A3 Appendix 3
A3
MF:
MW:
Cl
N
O
H
N
NH
O
F
CH2Cl2
8
7
6
5
4
3
2
1
0
ppm
4.77
4.03
2.25
1.00
8.28
9.41
1.51
1.36
1.57
2.40
0.53
8.72
1.20


A18 Appendix 4
A18
10
9
8
7
6
5
4
3
2
1
0 PPM
1.07
5.95
2.22
1.17
1.92
1.00
1.11
3.10
0.86
1.04
18.79


A22 Appendix 5
A22
Batch-chart
8
7
6
5
4
3
2
1
0
ppm


A29 Appendix 6
A29
Cl
8
7
6
5
4
3
2
1
0
ppm


S1
Z1
S2
Z2
Z3
R3
3
S3
2
N
S4
R4
N1
R5'
O
R5
X
O
R6
Y
R7
A