



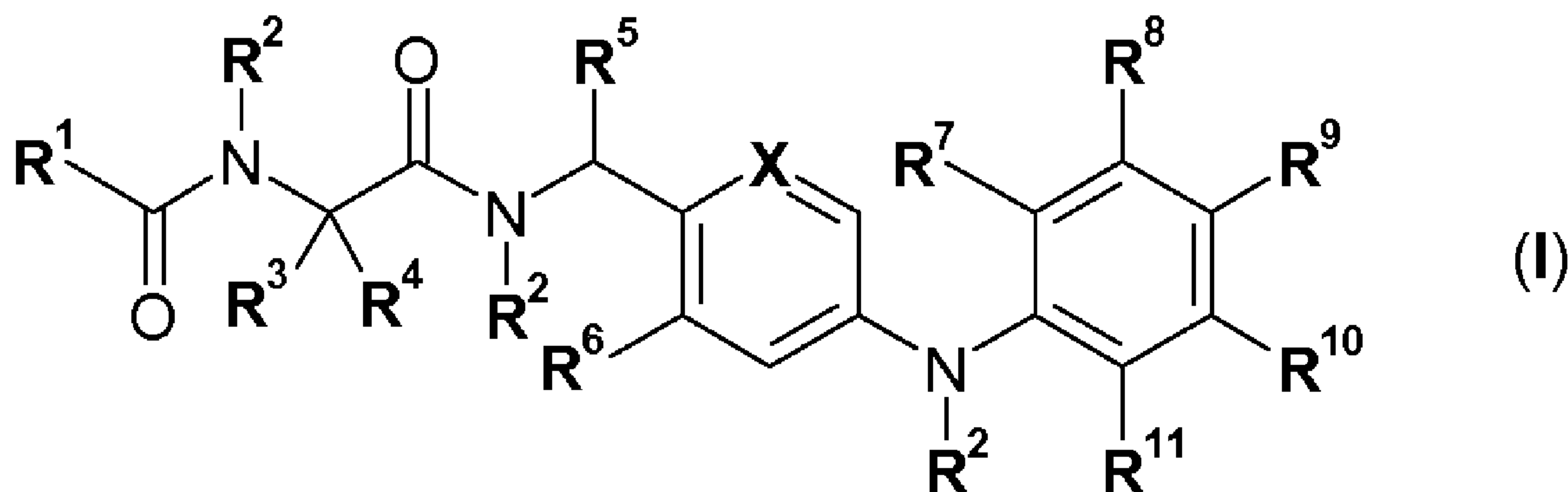
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(54) Titre : COMPOSES EN TANT QU'ANTAGONISTES DE LA BRADYKININE B1

(54) Title: COMPOUNDS AS BRADYKININ B1 ANTAGONISTS



(57) Abrégé/Abstract:

The present invention relates to the compounds of general formula I (see formula I) wherein n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and X are defined as described hereinafter, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases, which have valuable properties, the preparation thereof, the pharmaceutical formulations containing the pharmacologically effective compounds, the preparation thereof and the use thereof.

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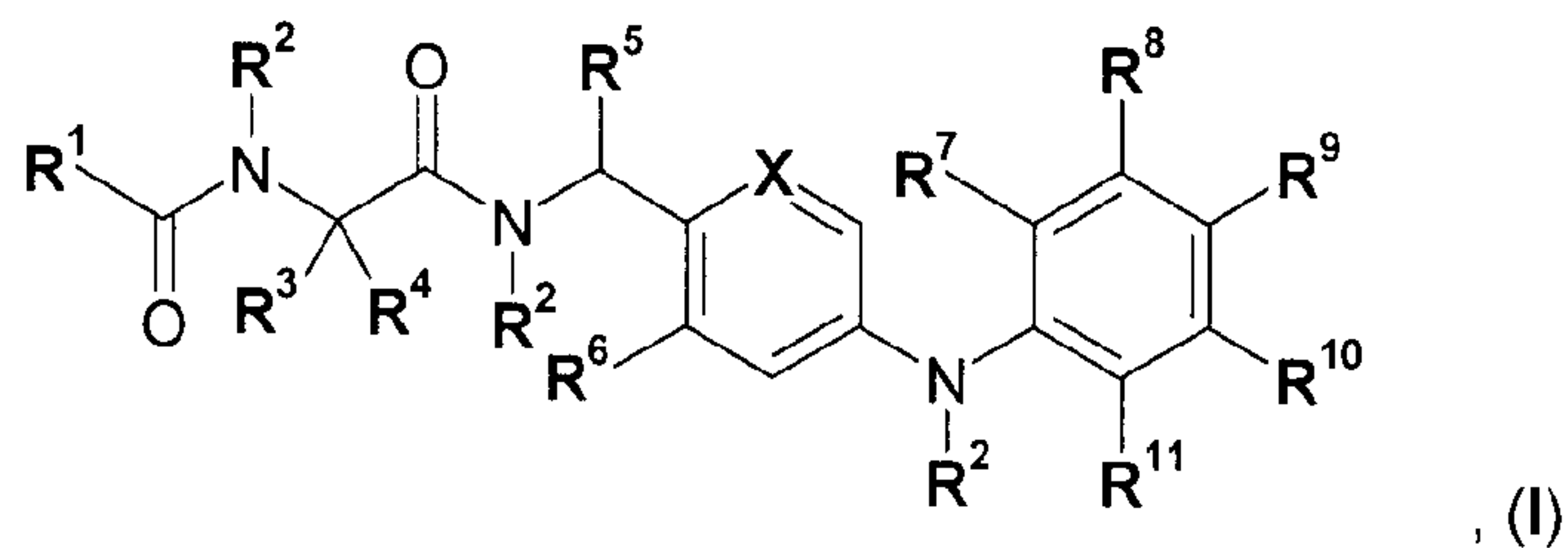
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ABSTRACT

The present invention relates to the compounds of general formula I



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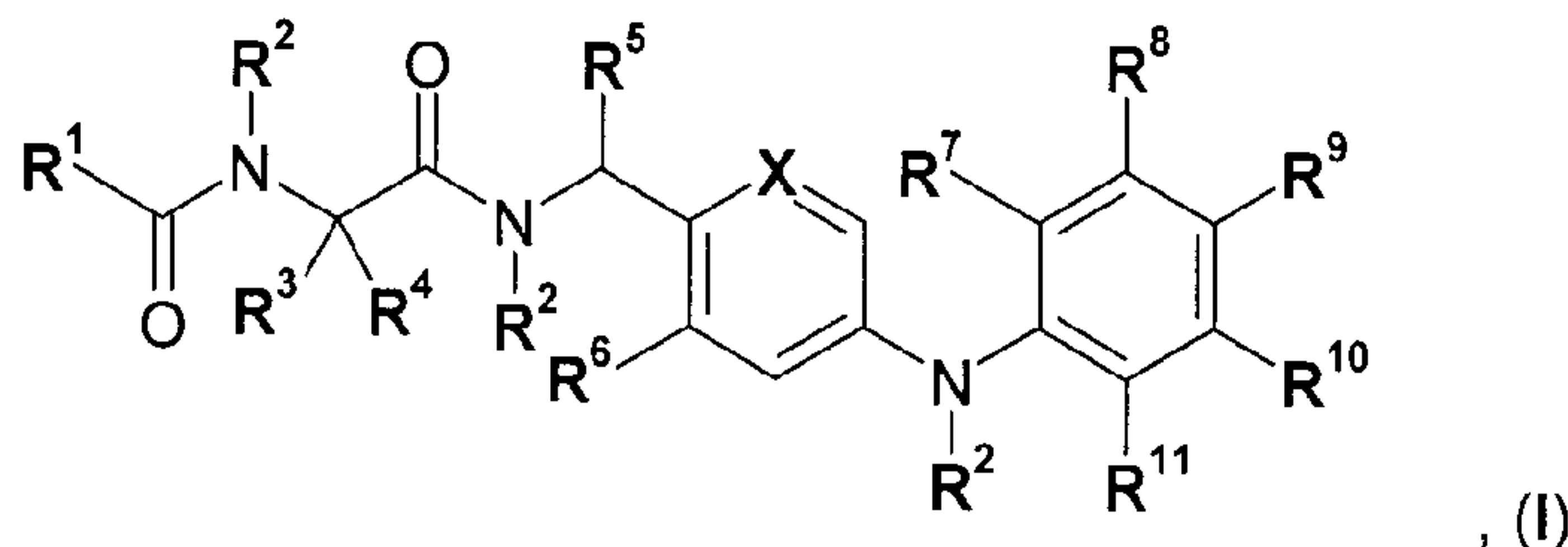
wherein n , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} and X are defined as described hereinafter, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases, which have valuable properties, the preparation thereof, the pharmaceutical
 10 formulations containing the pharmacologically effective compounds, the preparation thereof and the use thereof.

25771-2004

- 1 -

COMPOUNDS AS BRADYKININ B1 ANTAGONISTS

The present invention relates to the compounds of general formula I



wherein n , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} and X are as defined hereinafter, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases, which have valuable properties, the preparation thereof, the pharmaceutical formulations containing the pharmacologically effective compounds, the preparation thereof and the use thereof.

BACKGROUND TO THE INVENTION

TECHNICAL FIELD

The present invention relates to 3-oxo-pyridazine compounds and their use as B1-receptor antagonists, and pharmaceutical formulations containing these compounds.

PRIOR ART

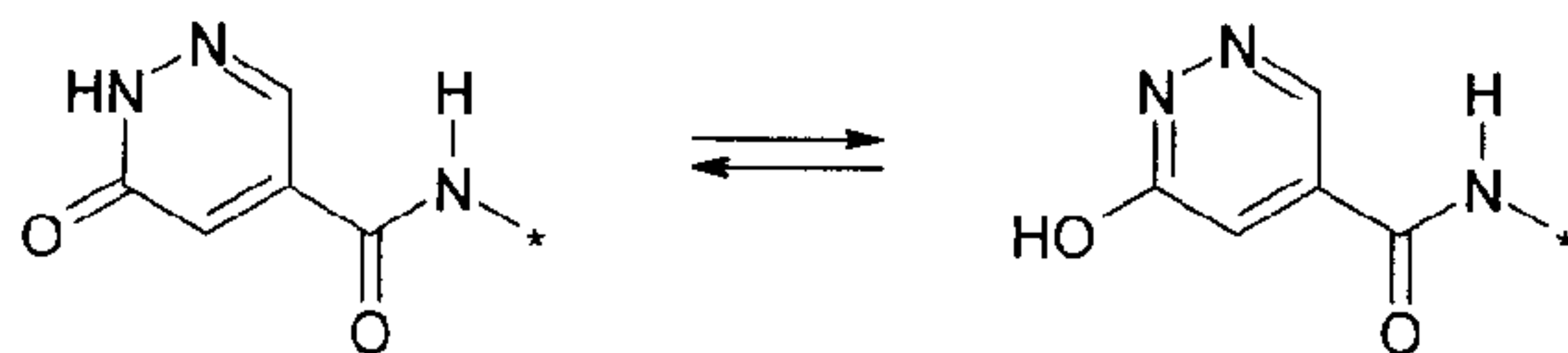
Compounds with a B1-antagonistic activity have already been described in International Patent Application PCT/EP2010/052232 or in the priority application on which it is based.

One aim of the present invention was to provide new compounds which may be suitable in particular as pharmaceutical active substances that can be used for the treatment of diseases at least partly mediated by the B1 receptor, such as pain or inflammation (see "Bradykinin antagonists: new opportunities", Bock M. G. and Longmou J., Carr. Opin. Chem. Biol. 200 Aug; 464: 401-6).

25771-2004

- 2 -

An essential structural feature of the new compounds is the 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid amide group that is present in tautomeric equilibrium with the 6-hydroxy-pyridazine-4-carboxylic acid amide group:



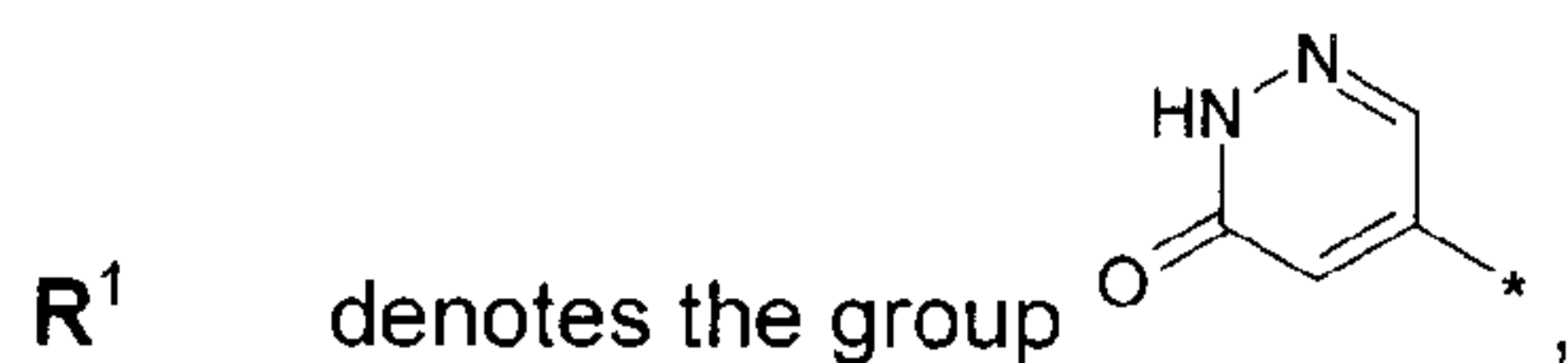
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Compared with the compounds from the prior art, the new substances are characterised in that they exhibit a strong B1-receptor blocking activity and at the same time have improved metabolic stability.

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DETAILED DESCRIPTION OF THE INVENTION

In the above general formula I in one embodiment **1**



15

R^2 denotes H or CH₃,

R^3 and R^4 together with the carbon atom to which they are bound denote a C₃₋₆-cycloalkylene group wherein a -CH₂ unit may be replaced by an oxygen atom,

20

R^5 denotes H or CH₃,

R^6 denotes H, F, Cl or methyl,

25

R^7 denotes H, F, Cl, Br, -CN, C₁₋₄-alkyl, CF₃, CHF₂,

R^8 denotes H,

R^9 denotes F, Cl, Br, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -S-C₁₋₄-alkyl,

25771-2004

- 3 -

R^{10} denotes H,

R^{11} denotes F, Cl, Br, -CN, C_{1-4} -alkyl, CF_3 , CHF_2 , and

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X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

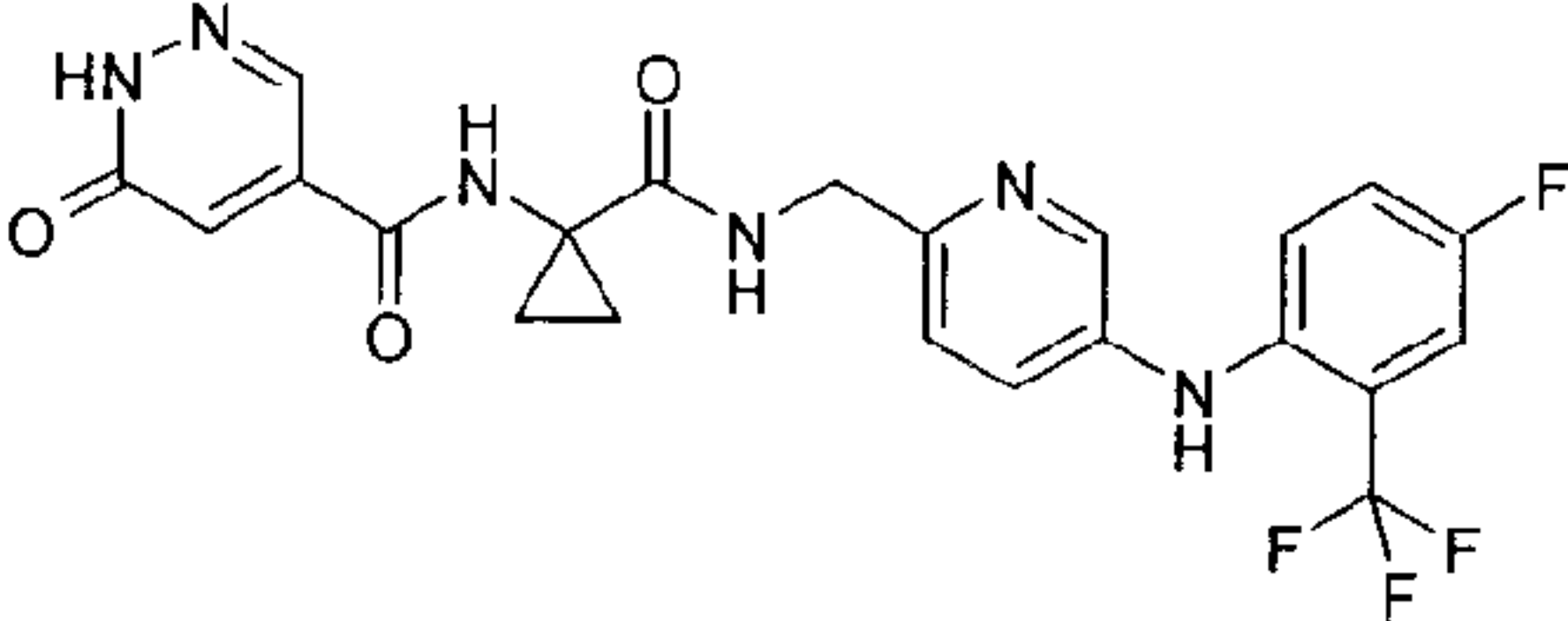
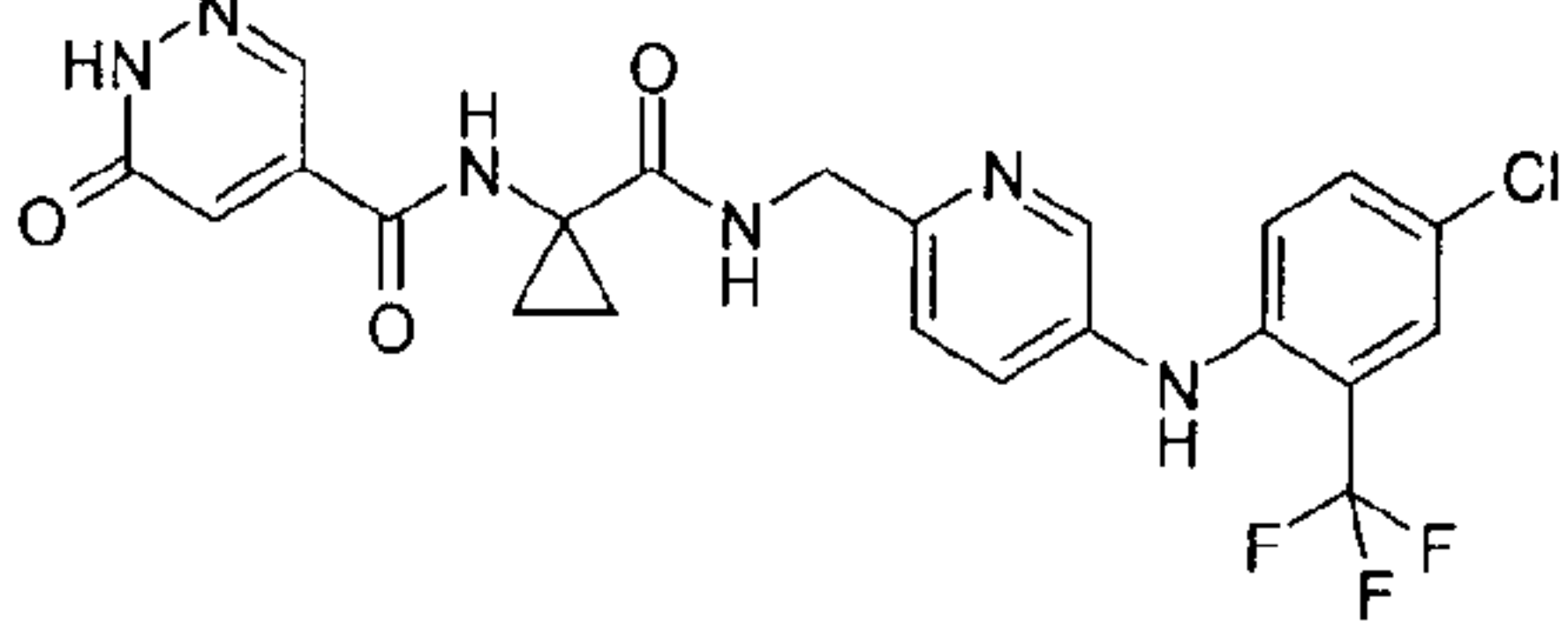
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An embodiment 2 of the present invention comprises the compounds of general formula I, wherein n , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} and X are defined as described hereinbefore in embodiment 1 and

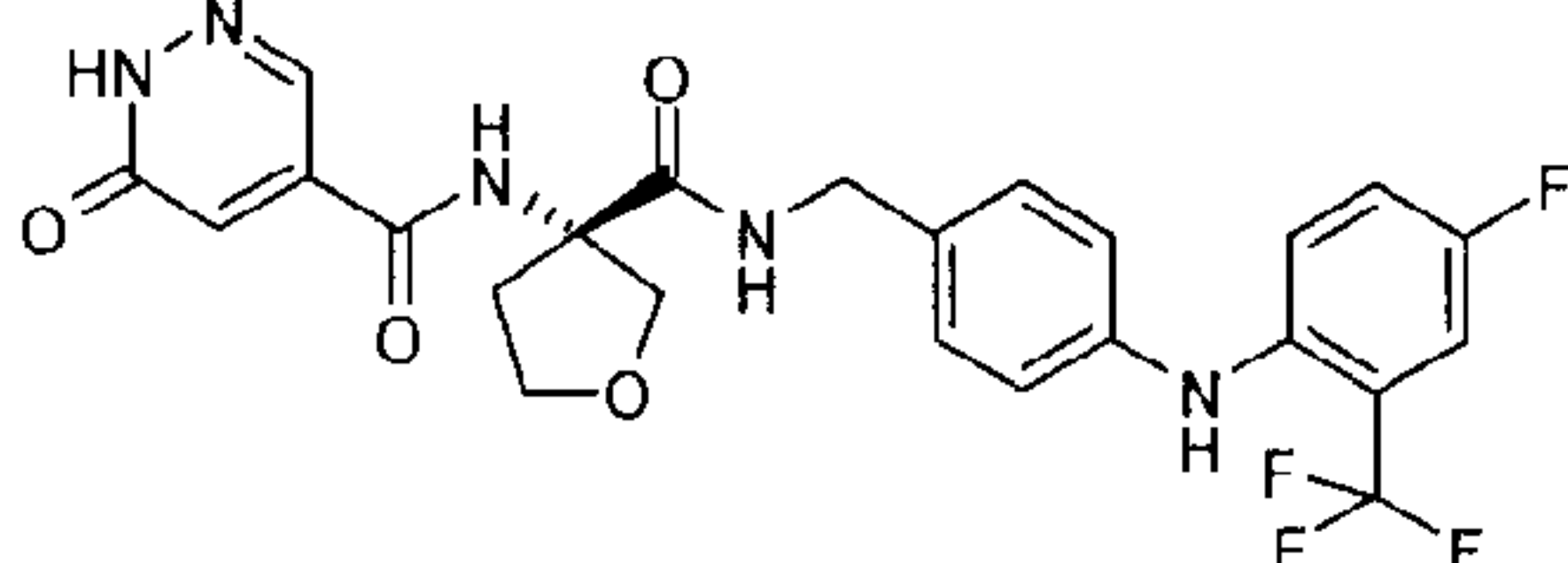
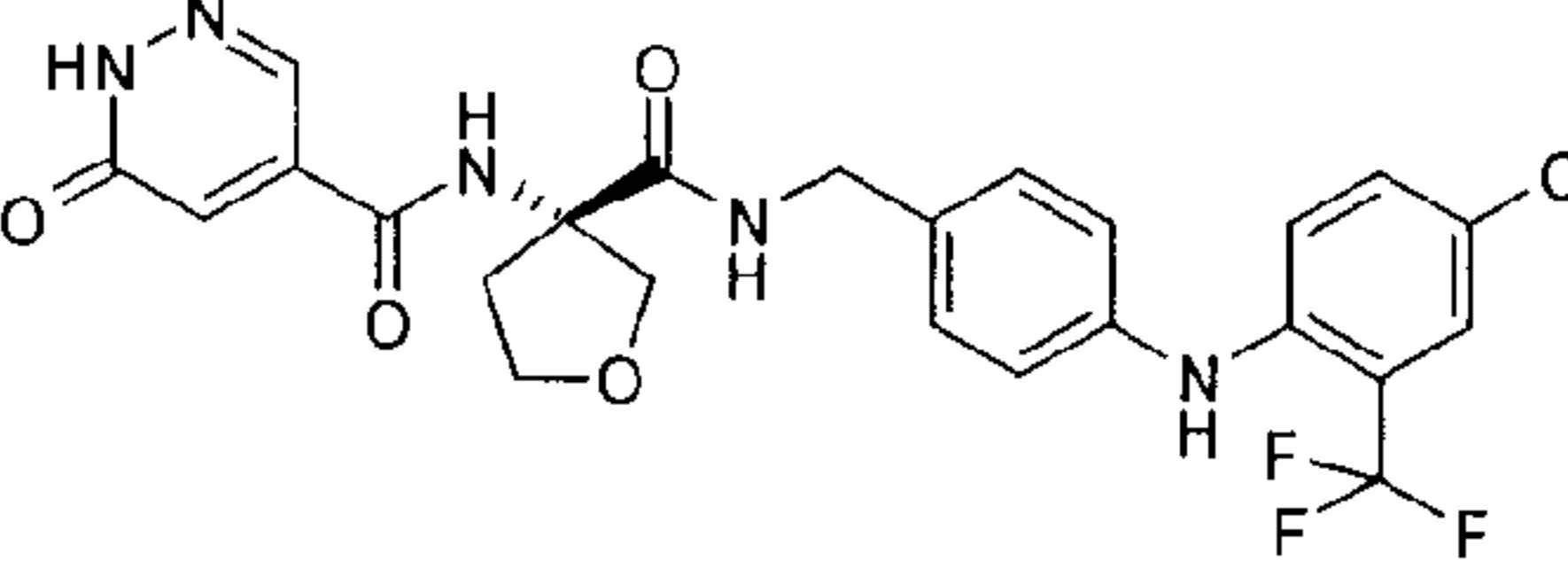
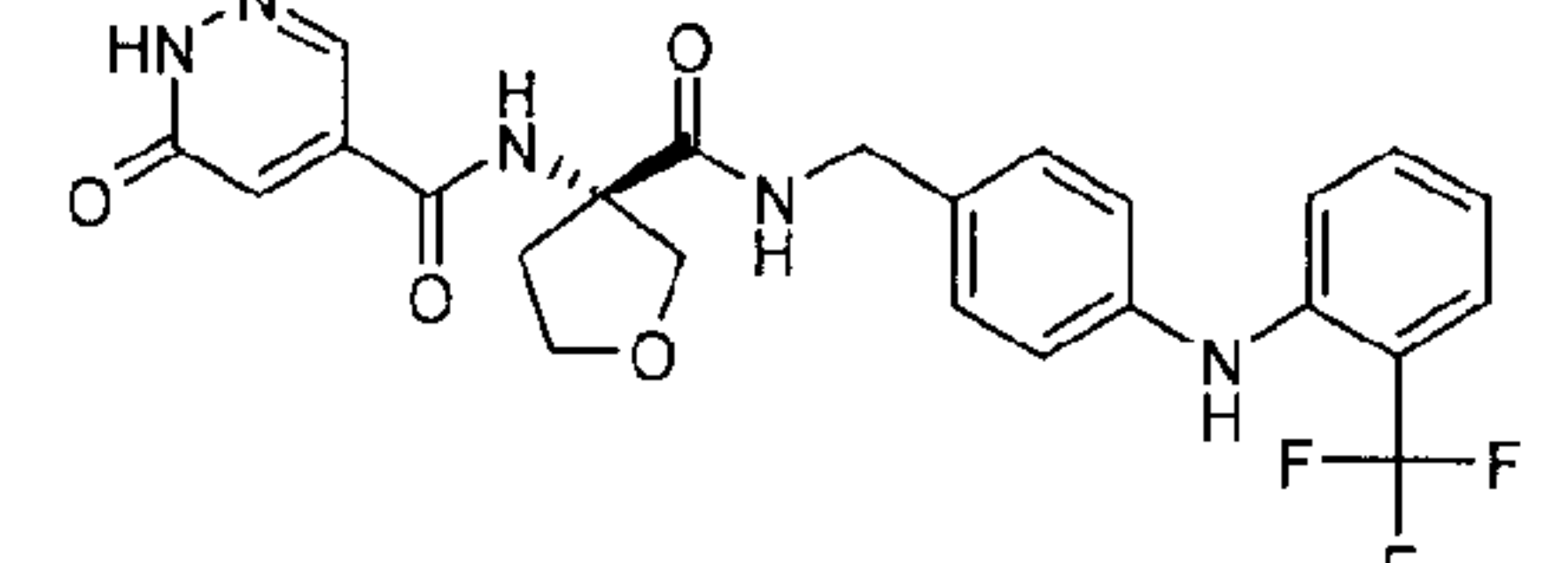
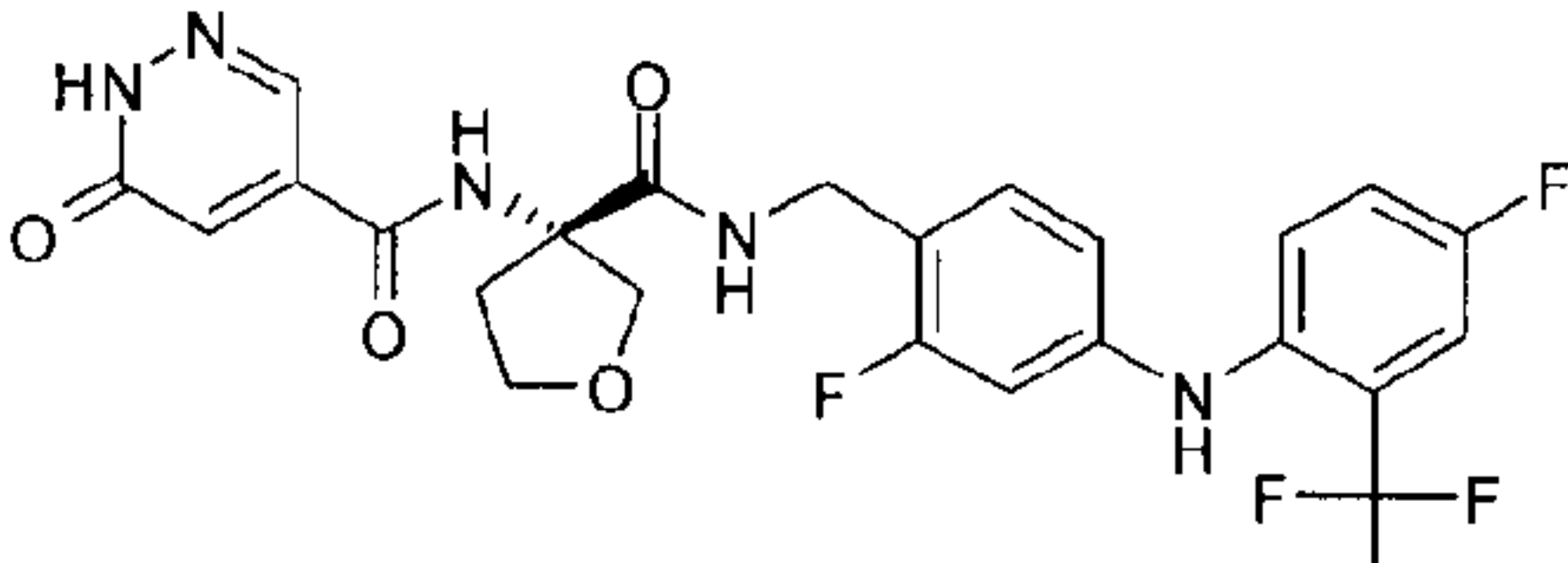
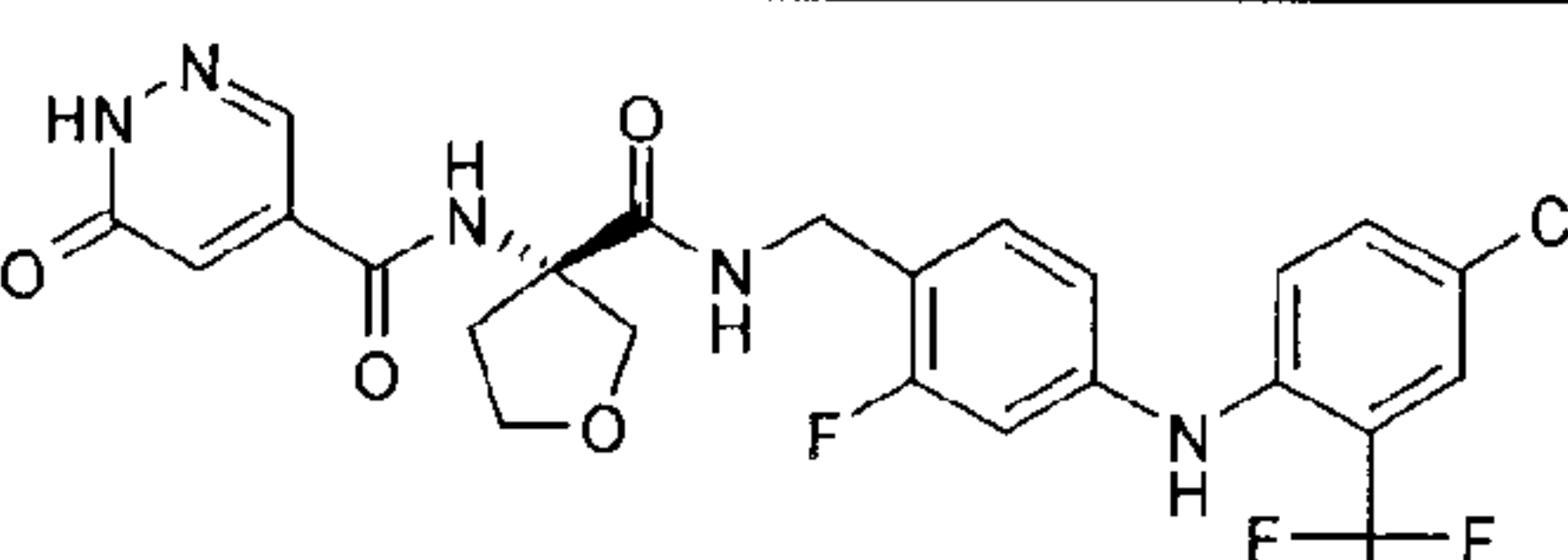
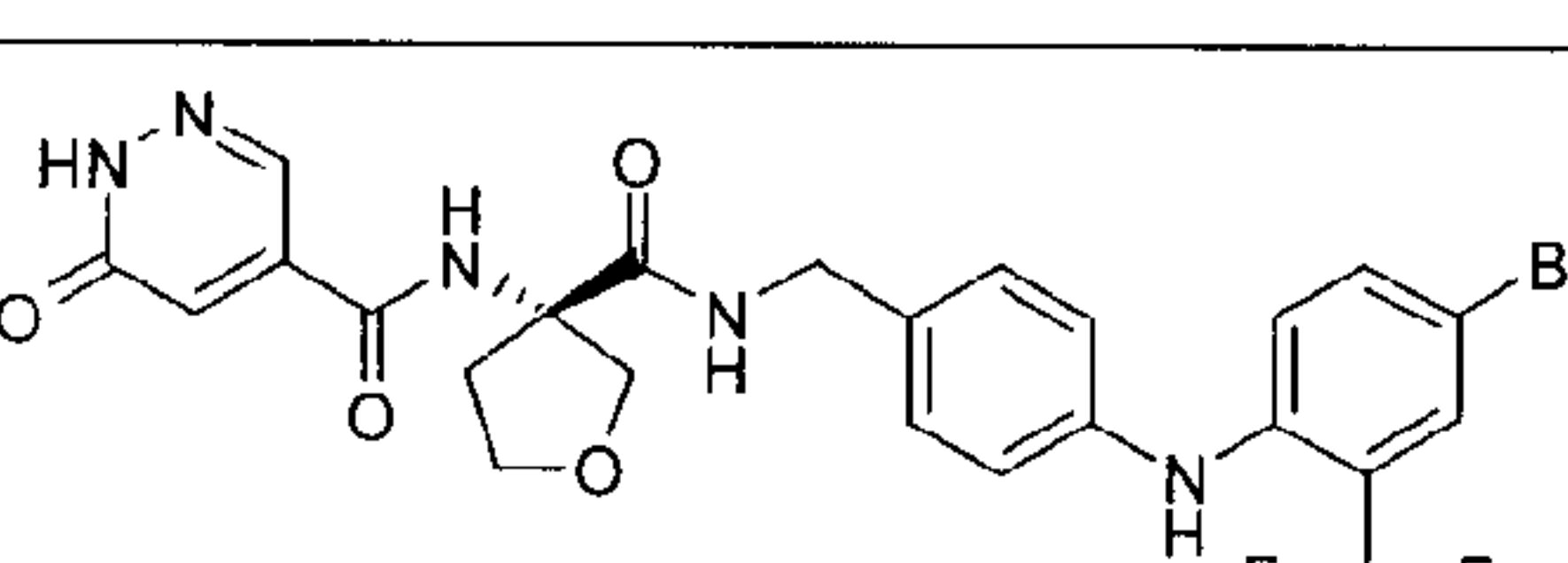
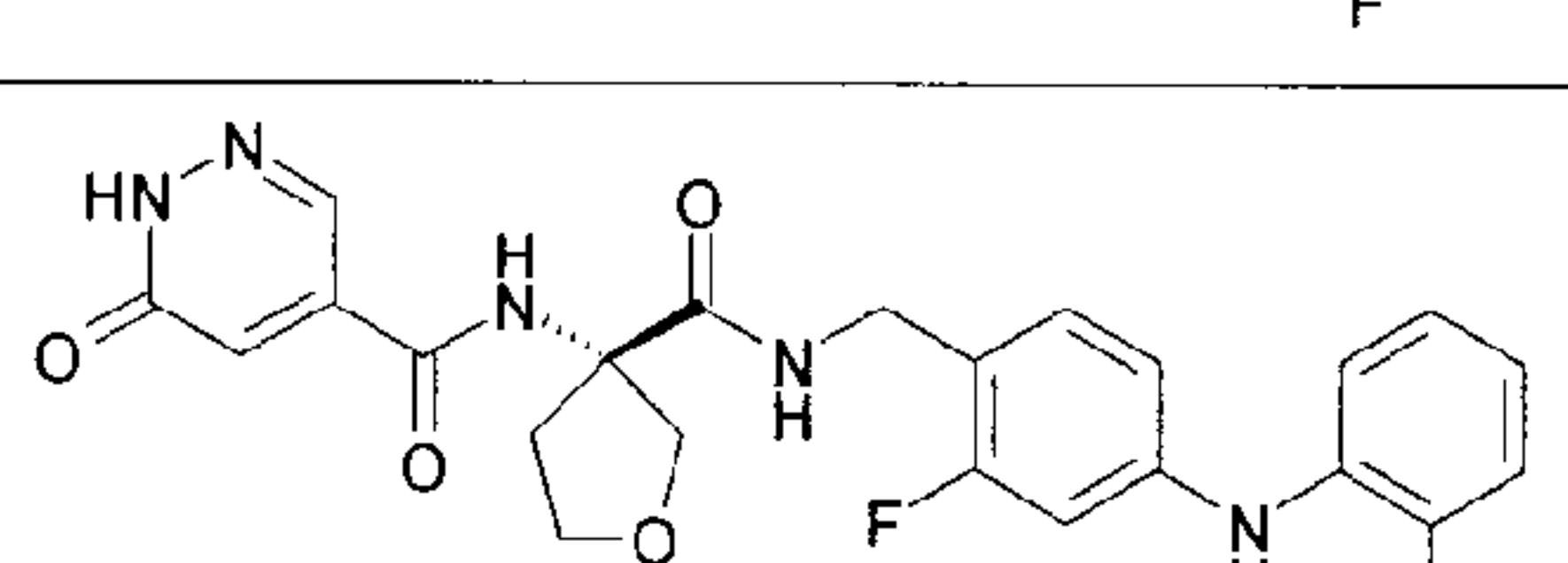
15 R^2 denotes H,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

20 The following are mentioned for example as most particularly preferred compounds of the above general formula I:

No.	Structure
(1)	
(2)	

25771-2004

No.	Structure
(3)	
(4)	
(5)	
(6)	
(7)	
(8)	
(9)	

25771-2004

- 5 -

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

In another aspect of the invention, a pharmaceutical formulation comprising a compound as described herein and one or more inert carriers and/or diluents is provided.

TERMS AND DEFINITIONS USED

Unless otherwise stated, all the substituents are independent of one another. If for example there are a plurality of C₁₋₄-alkyl groups as substituents in one group, in the case of three substituents C₁₋₄-alkyl, one may represent methyl, one *n*-propyl and one *tert*-butyl.

Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. If present, an asterisk (*) in the structural formula of the substituent is to be understood as being the linking point to the rest of the molecule.

Also included in the subject matter of this invention are the compounds according to the invention, including the salts thereof, in which one or more hydrogen atoms, for example one, two, three, four or five hydrogen atoms, are replaced by deuterium.

By the term "C₁₋₄-alkyl" (including those that are part of other groups) are meant alkyl groups with 1 to 4 carbon atoms. Examples include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. The abbreviations Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc. may optionally also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl and butyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl.

Moreover the definitions mentioned previously also include those groups wherein each methylene group may be substituted by up to two and each methyl group may be substituted by up to three fluorine atoms.

25771-2004

- 6 -

By the term "C₃₋₆-cycloalkyl" (including those that are part of other groups) are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples include: cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

5

If they contain suitable basic functions, for example amino groups, compounds of general formula I may be converted, particularly for pharmaceutical use, into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of inorganic acids for this purpose include hydrobromic acid, phosphoric acid, nitric acid, hydrochloric acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or

10 *p*-toluenesulphonic acid, while organic acids that may be used include malic acid, succinic acid, acetic acid, fumaric acid, maleic acid, mandelic acid, lactic acid, tartaric acid or citric acid.

15

In addition, the compounds of general formula I, if they contain suitable carboxylic acid functions, may be converted into the physiologically acceptable salts thereof with inorganic or organic bases, particularly for pharmaceutical applications. Examples of inorganic bases include alkali or alkaline earth metal hydroxides, e.g. sodium hydroxide or potassium hydroxide, or carbonates, ammonia, zinc or ammonium hydroxides; examples of organic

20 amines include diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine or dicyclohexylamine.

The compounds according to the invention may be present as racemates, provided that they have only one chiral element, but may also be obtained as pure enantiomers, i.e. In the (*R*) or (*S*) form.

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However, the application also includes the individual diastereomeric pairs of antipodes or mixtures thereof, which are obtained if there is more than one chiral element in the compounds of general formula I, as well as the individual optically active enantiomers of

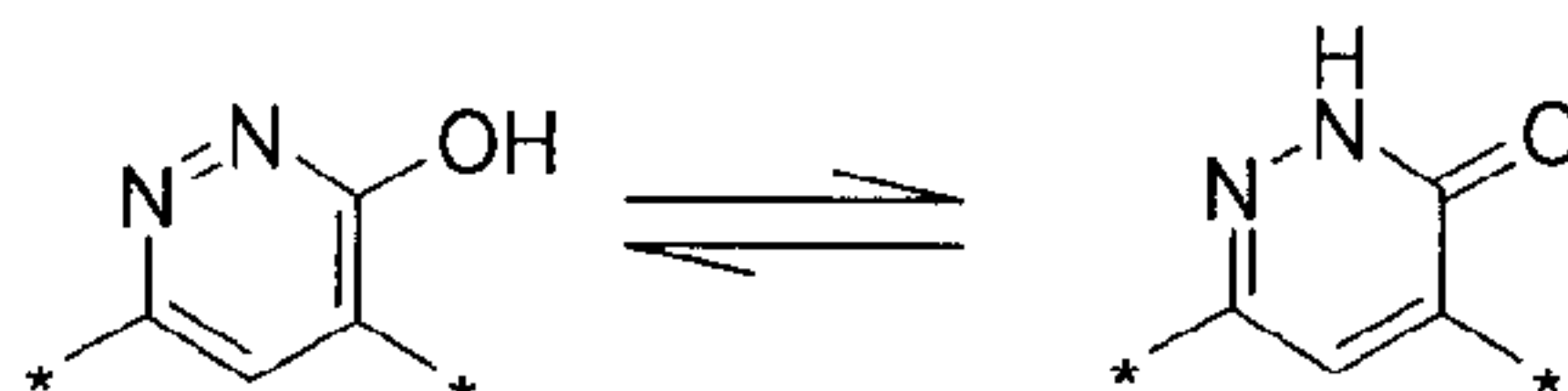
30 which the above-mentioned racemates are made up.

Compounds with a carbon double bond may be present in both the E and Z form.

25771-2004

- 7 -

If a compound is present in different tautomeric forms, the compound prepared is not limited to one tautomeric form but includes all the tautomeric forms. This also applies particularly to nitrogen-containing heteroaryls:



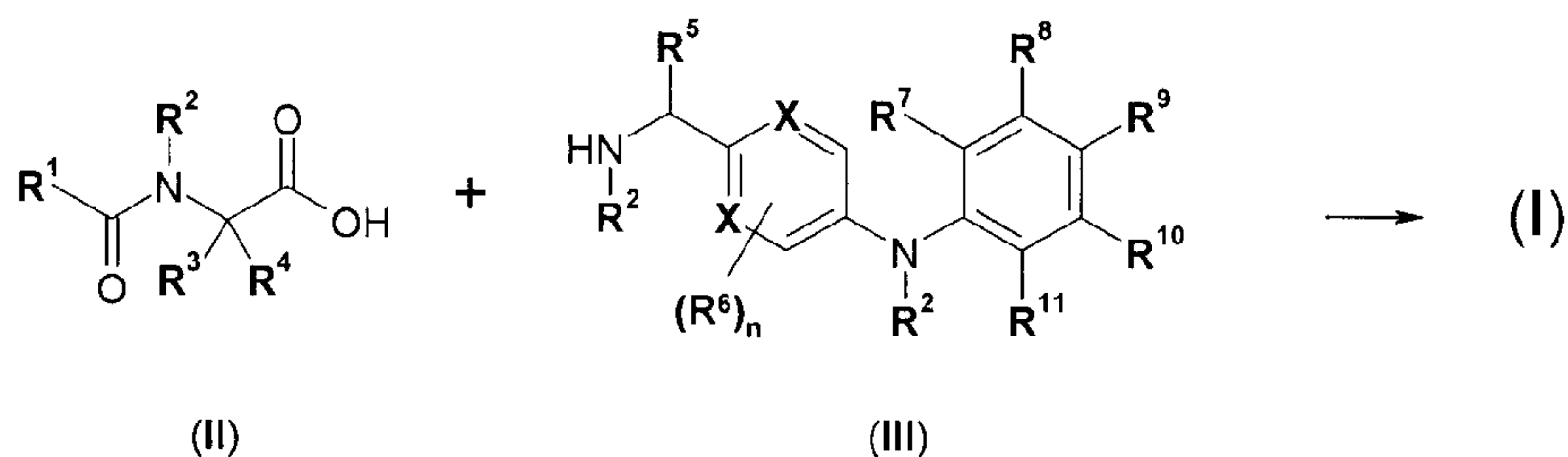
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PREPARATION METHODS

According to the invention the compounds of general formula I are obtained by methods known per se, for example by the following methods:

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(A) amide coupling:



15

The linking of carboxylic acids of general formula II as shown, wherein all the groups are as hereinbefore defined, with amines of general formula III, wherein all the groups are as hereinbefore defined, to form carboxylic acid amides of general formula I wherein all the groups are as hereinbefore defined, may be carried out by conventional methods of amide formation.

20

The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)-N,N'-N'-

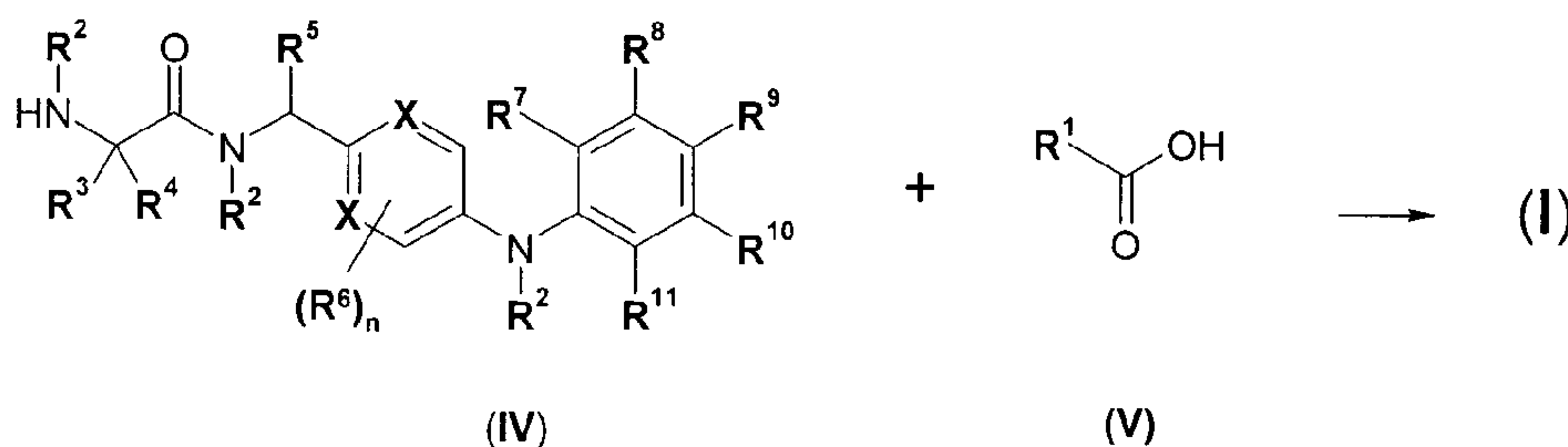
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25771-2004

- 8 -

tetramethyluronium hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1H-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP). By adding 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOOBt) the reaction speed can be increased. The couplings are normally carried out with equimolar amounts of the coupling components as well as the coupling reagent in solvents such as dichloromethane, tetrahydrofuran (THF), acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMA), N-methylpyrrolidone (NMP) or mixtures. If necessary, an auxiliary base such as diisopropylethylamine (DIPEA, Hünig base) is additionally used.

B) Amide coupling:



An alternative method of preparing compounds of general formula I consists in linking carboxylic acids of general formula V, wherein all the groups are as hereinbefore defined, with amines of general formula IV, wherein all the groups are as hereinbefore defined.

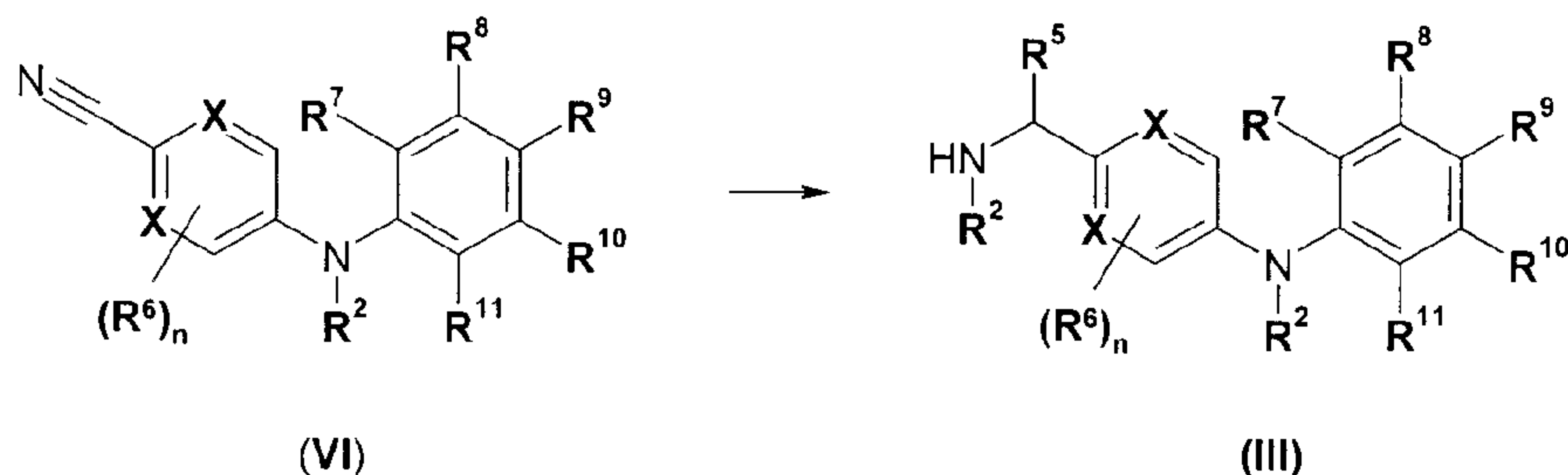
The compounds of general formula V are either commercially obtainable or may be prepared by methods known from the literature

It is also possible to convert the carboxylic acids of general formula V into carboxylic acid chlorides and then react these with amines of general formula IV. Carboxylic acid chlorides are synthesised by methods known from the literature (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, vol. E5/1).

25771-2004

- 9 -

(C) Reduction of the nitrile group:



The reduction of a nitrile of general formula **VI** to an amine of general formula **III**, wherein the group **R²** at the amine nitrogen denotes hydrogen and all the other groups are as hereinbefore defined, may be carried out under standard conditions of catalytic hydrogenolysis with a catalyst such as Raney nickel, for example, in a solvent such as ammoniacal methanol or ethanol or with a reducing agent such as lithium aluminium hydride or sodium borohydride in a solvent such as tetrahydrofuran, optionally in the presence of a Lewis acid such as aluminium chloride.

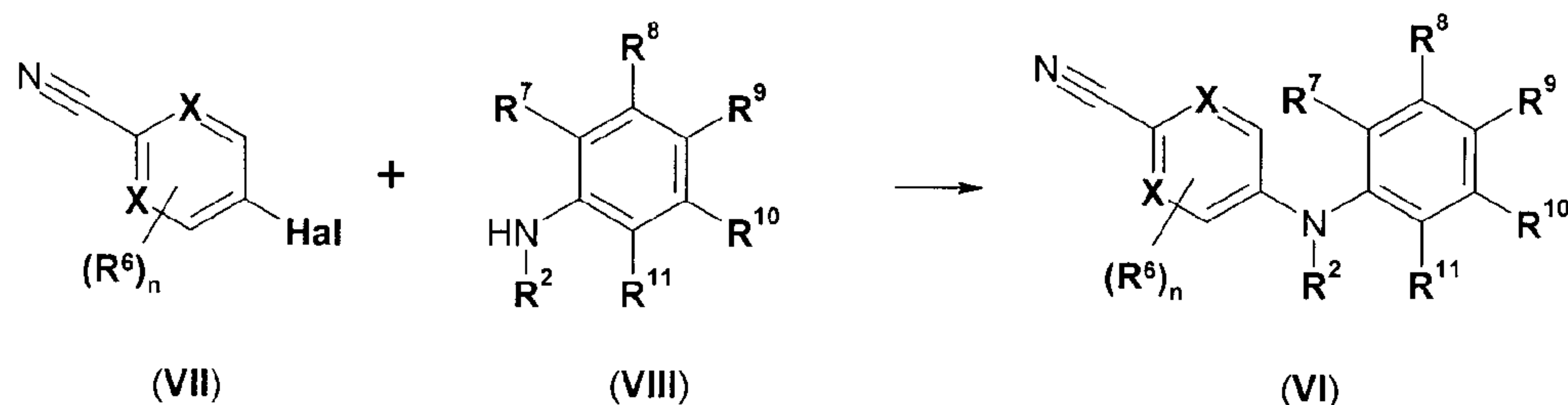
Compounds of general formula **III**, wherein the group **R²** at the amine nitrogen denotes not hydrogen but an alkyl group, for example, may also be prepared from compounds of general formula **VI**. Thus, for example, the reaction of a nitrile of general formula **VI** with an alkyl Grignard reagent produces ketones which can be converted by reductive amination into the compounds of general formula **III**. The reductive amination is carried out using known methods, for example with a reducing agent such as sodium triacetoxyborohydride, sodium borohydride or sodium cyanoborohydride, conveniently in a solvent such as tetrahydrofuran or dichloromethane optionally substituted by the addition of acetic acid.

Alternatively the ketones obtained may also be converted into oximes. The subsequent reduction of the oximes then yields compounds of general formula **III**.

(D) nucleophilic aromatic substitution or transition-metal-catalysed coupling:

25771-2004

- 10 -



The reaction of an aniline of general formula **VIII**, wherein all the groups are as hereinbefore defined, with a nitrile of general formula **VII**, wherein **X**, **R₆** and **n** are as hereinbefore defined, and **Hal** denotes a fluorine, chlorine or bromine atom, is carried out using known methods, for example in a solvent such as tetrahydrofuran, dimethylformamide or dimethylsulphoxide and conveniently in the presence of a base such as triethylamine, sodium hydroxide solution or potassium carbonate at a temperature of 20°C to 160°C. If the aniline of general formula **VIII** is liquid, the reaction may also be carried out without a solvent and additional base.

An alternative method of preparing compounds of general formula **VI** is the palladium-catalysed reaction of a nitrile of general formula **VII**, wherein **Hal** denotes bromine or chlorine, with an aniline of general formula **VIII**. Reaction conditions for this reaction, which is also known as a Buchwald-Hartwig reaction, are known from the literature.

Description of the method of binding the cynoBK1-receptor

CHO cells that express the cynomolgus BK1-receptor are cultivated in "HAM'S F-12 Medium". The medium is removed from confluent cultures, the cells are washed with PBS buffer, scraped off or detached using Versene and isolated by centrifuging. Then the cells are homogenised in suspension, the homogenate is centrifuged and resuspended. After the protein content has been determined 200 µl of the homogenate (50 to 250 µg protein/assay) are incubated for 60-180 minutes at ambient temperature with 0.5 to 5.0 nM kallidine (DesArg10,Leu9), [3,4-Prolyl-3,43H(N)] and increasing concentrations of the test substance in a total volume of 250 µl. The incubation is stopped by rapid filtration through GF/B glass fibre filters that have been pre-treated with polyethyleneimine (0.3%). The radioactivity bound to the protein is measured with a TopCount NXT. The radioactivity bound in the

25771-2004

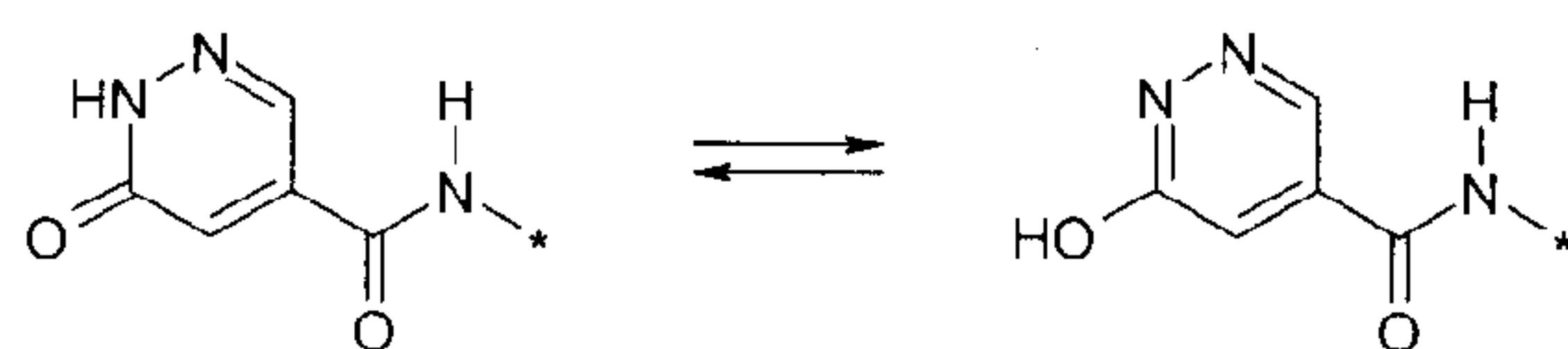
- 11 -

presence of 1.0 μM kallidine (DesArg10) is defined as non-specific binding. The concentration binding curve may be analysed using computer-aided non-linear curve fitting to determine the corresponding K_i value for the test substance.

5 Test results of the cynoBK1-receptor binding assay:

Example No.	K_i [nM]
(1)	3.5
(2)	5.1
(3)	12
(4)	27
(5)	11
(6)	3.2
(7)	30
(8)	37
(9)	6.6

10 An essential structural feature of the new compounds is the 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid amide group which is contained in all the compounds according to the invention and is in tautomeric equilibrium with the 6-hydroxy-pyridazine-4-carboxylic acid amide group:



15 Compared with the compounds from the prior art the new substances are characterised in that they exhibit a very strong B1-receptor blocking activity and at the same time have much better metabolic stability. The metabolic stability can be measured by determining the decomposition in human hepatocytes and using the rate of decomposition to calculate the clearance, which in turn is expressed as a percentage of the human hepatic blood flow (%Qh). A substance with a high metabolic clearance (e.g. >70%Qh) will presumably exhibit

25771-2004

- 12 -

a shorter duration of activity in the human body than a substance that is metabolically more stable and thus has a lower clearance (e.g. <30%Qh). Thus, in the interests of achieving a long duration of activity it is highly advantageous if the active substance has a high metabolic stability (low clearance). Surprisingly the new substances exhibit a low clearance in human

5 hepatocytes, as is apparent from the following Table:

Example No.	K _i [nM]	Clearance [%Qh]
(1)	3.5	1
(3)	12	7
(5)	11	22
(6)	3.2	6

Description of method for determining metabolic clearance in human hepatocytes

10 The metabolic breakdown of the test substance is determined in a hepatocyte suspension. Cryopreserved primary human hepatocytes are incubated in a suitable incubation medium (e.g. Dulbecco's modified eagle medium, DMEM) which contains 5% human serum. After 30 minutes' pre-incubation in the incubator (37°C, 10% carbon dioxide) 5 µL of the test compound (80 µM, prepared from a 2 mM stock solution in dimethylsulphoxide and diluted

15 1:25 with incubation medium) are added to 395 µL of hepatocyte suspension (cell density in the range from 0.25 - 1 million cells/mL, typically 1 million cells/mL; final concentration of the test compound 1µM). The cells are incubated for 6 hours in an incubator with an orbital agitator. At times 0, 0.5, 1, 2, 4 and 6 h, 25 µL of the medium are removed in each case. The medium removed is mixed with an excess of acetonitrile and centrifuged for 5 minutes.

20 The supernatant is removed, evaporated to dryness under nitrogen and taken up in a mixture of 25% methanol and 0.1% formic acid. The reduction in the concentration of the test substance in the incubation medium is determined by coupling liquid chromatography with electrospray mass spectrometry. The linear phase of the decrease in the concentration of the test substance in the medium is used for the calculation. The intrinsic clearance is calculated

25 as follows: $CL_{\text{INTRINSIC}} = \text{dose} / AUC = (C_0/CD) / (AUD + clast/k) \times 1000/60$. C₀: initial concentration in the incubation [µM], CD: cell density of the vital cells [10e6cells/mL], AUD:

25771-2004

- 13 -

area under the curve [$\mu\text{M} \times \text{h}$], clast: concentration of the last data point [μM], k: increase in the regression lines for the reduction in the test substance [h^{-1}]. The intrinsic in vitro clearance calculated is now converted into the intrinsic in vivo clearance:

CL_INTRINSIC_INVIVO [$\text{ml}/\text{min}/\text{kg}$] = (CL_INTRINSIC [$\mu\text{L}/\text{min}/10^6\text{cells}$] x hepatocellularity
5 [10⁶ cells/g liver] x liver factor [g/kg body weight]) / 1000

and the estimated human clearance is calculated using the well-stirred model:

CL [$\text{ml}/\text{min}/\text{kg}$] = CL_INTRINSIC_INVIVO [$\text{ml}/\text{min}/\text{kg}$] x hepatic blood flow [$\text{ml}/\text{min}/\text{kg}$] /
(CL_INTRINSIC_INVIVO [$\text{ml}/\text{min}/\text{kg}$] + hepatic blood flow [$\text{ml}/\text{min}/\text{kg}$]).

The following parameters are used for the calculation: hepatocellularity, human: 120x10⁶
10 cells / g liver; liver factor, human: 25.7 g liver / kg body weight; hepatic blood flow, human:
21 ml/(min x kg).

EXPERIMENTAL SECTION

15 Generally, there are mass spectra and ¹H NMR spectra for the compounds that have been prepared. The ratios given for the eluants are in volume units of the solvents in question. For ammonia, the given volume units are based on a concentrated solution of ammonia in water.

20 Unless indicated otherwise, the acid, base and salt solutions used for working up the reaction solutions are aqueous systems having the stated concentrations.

For chromatographic purification, silica gel from Millipore (MATREXTM, 35 to 70 μm) or Alox
25 (E. Merck, Darmstadt, Alumina 90 standardized, 63 to 200 μm , article No. 1.01097.9050) is used.

In the descriptions of the experiments, the following abbreviations are used:

30 TLC thin layer chromatograph
DMSO dimethylsulphoxide
RP reverse phase

25771-2004

R_t retention time
tert tertiary
TBTU 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate
THF tetrahydrofuran

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The following analytical HPLC methods were used:

Method 1: Column: Interchim Strategy C18, 5 µM, 4.6 x 50 mm
Detection: 220 – 320 nm
Eluant A: water / 0.1% acetic acid
Eluant B: acetonitrile
Gradient:

10

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	3.0
0.3	95.0	5.0	3.0
2.0	2.0	98.0	3.0
2.4	2.0	98.0	3.0
2.45	95.0	5.0	3.0
2.8	95.0	5.0	3.0

15

Method 2: Column: Merck Cromolith Flash RP18e, 4.6 x 25 mm
Eluant A: water / 0.1% formic acid
Eluant B: acetonitrile / 0.1% formic acid
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.6
2.7	10.0	90.0	1.6
3.0	10.0	90.0	1.6
3.3	90.0	10.0	1.6

25771-2004

- 15 -

Method 3: Column: YMC-Pack ODS-AQ, 3 µM, 4.6 x 75 mm
 Eluant A: water / 0.15% formic acid
 Eluant B: acetonitrile
 Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.0	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.5	90.0	10.0	1.6

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Method 4: Column: Zorbax Stable Bond C18, 1.8 µM, 3 x 30 mm
 Eluant A: water / 0.15% formic acid
 Eluant B: acetonitrile
 Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
1.0	10.0	90.0	1.6
2.5	10.0	90.0	1.6
2.75	95.0	5.0	1.6

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25771-2004

- 16 -

5 Method 5: Column: Sunfire C18, 3.5 μ M, 4.6 x 50 mm
 Detection: 180 – 820 nm
 Eluant A: water / 0.1% trifluoroacetic acid
 Eluant B: acetonitrile / 0.1% trifluoroacetic acid
 Temperature: 40°C
 Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	0.0	100.0	1.5
2.5	0.0	100.0	1.5
2.6	95.0	5.0	1.5

10 Method 6: Column: Sunfire C18, 3.5 μ M, 4.6 x 50 mm
 Detection: 180 – 820 nm
 Eluant A: water / 0.1% trifluoroacetic acid
 Eluant B: acetonitrile / 0.1% trifluoroacetic acid
 Temperature: 40°C
 Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	0.0	100.0	1.5
3.0	0.0	100.0	1.5
3.4	95.0	5.0	1.5

15 Method 7: Column: YMC-Pack ODS-AQ, 3 μ M, 4.6 x 75 mm
 Eluant A: water / 0.15% formic acid
 Eluant B: acetonitrile
 Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
4.5	10.0	90.0	1.6

25771-2004

- 17 -

time in min	%A	%B	flow rate in mL/min
5.0	10.0	90.0	1.6
5.50	90.0	10.0	1.6

Method 8: Column: Zorbax Stable Bond C18, 1.8 μ M, 3 x 30 mm
 Eluant A: water / 0.15% formic acid
 Eluant B: acetonitrile
 Gradient:

5

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.00	50.0	50.0	1.6
2.25	10.0	90.0	1.6
2.50	10.0	90.0	1.6
2.75	95.0	5.0	1.6

Method 9: Column: Zorbax Stable Bond C18, 1.8 μ M, 3 x 30 mm
 Eluant A: water / 0.15% formic acid
 Eluant B: acetonitrile
 Gradient:

10

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.25	10.0	90.0	1.6
2.50	10.0	90.0	1.6
2.75	95.0	5.0	1.6

Method 10: Column: Zorbax Stable Bond C18, 3.5 μ M, 4.6 x 75 mm
 Eluant A: water / 0.15% formic acid
 Eluant B: acetonitrile
 Gradient:

15

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6

25771-2004

- 18 -

time in min	%A	%B	flow rate in mL/min
4.5	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.50	90.0	10.0	1.6

Method 11: Column: X Terra C18, 3.5 μ M, 4.6 x 50 mm

Detection: 180 – 820 nm

Eluant A: water / 0.1% trifluoroacetic acid

Eluant B: acetonitrile / 0.1% trifluoroacetic acid

Temperature: 40°C

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	0.0	100.0	1.5
3.0	0.0	100.0	1.5
3.4	95.0	5.0	1.5

Method 12: Column: Merck Cromolith Flash RP18e, 4.6 x 25 mm

Eluant A: water / 0.1% formic acid

Eluant B: acetonitrile / 0.1% formic acid

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.6
2.7	10.0	90.0	1.6
3.0	10.0	90.0	1.6
3.3	95.0	5.0	1.6

Method 13: Column: Merck Cromolith SpeedROD RP-18e, 4.6 x 50 mm

Eluant A: water / 0.1% formic acid

Eluant B: acetonitrile / 0.1% formic acid

Gradient:

25771-2004

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.5
4.5	10.0	90.0	1.5
5.0	10.0	90.0	1.5
5.5	95.0	5.0	1.5

Method 14: Column: Zorbax Stable Bond C18, 3.5 µM, 4.6 x 75 mm
Eluant A: water / 0.15% formic acid
Eluant B: acetonitrile
Gradient:

5

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.0	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.5	90.0	10.0	1.6

The following preparative methods were used for the reversed-phase chromatography:

Method 1: Column: Atlantis C18, 5 µM, 100 x 30 mm
Detection: 210 – 500 nm
Eluant A: water / 0.1% trifluoroacetic acid
Eluant B: acetonitrile
Gradient:

10

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	5
0.5	95.0	5.0	50
8.0	5.0	95.0	50
9.0	5.0	95.0	50
9.5	95.0	5.0	50
10.0	95.0	5.0	50
10.1	95.0	5.0	5

25771-2004

- 20 -

Method 2: Column: Varian Pursuit 5 µM, 50 x 200 mm
 Eluant A: water / 0.1% trifluoroacetic acid
 Eluant B: acetonitrile / 0.1% trifluoroacetic acid
 Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	180
1.15	95.0	5.0	180
12.4	2.0	98.0	180
14.0	2.0	98.0	180
15.3	95.0	5.0	180
15.3	95.0	5.5	180

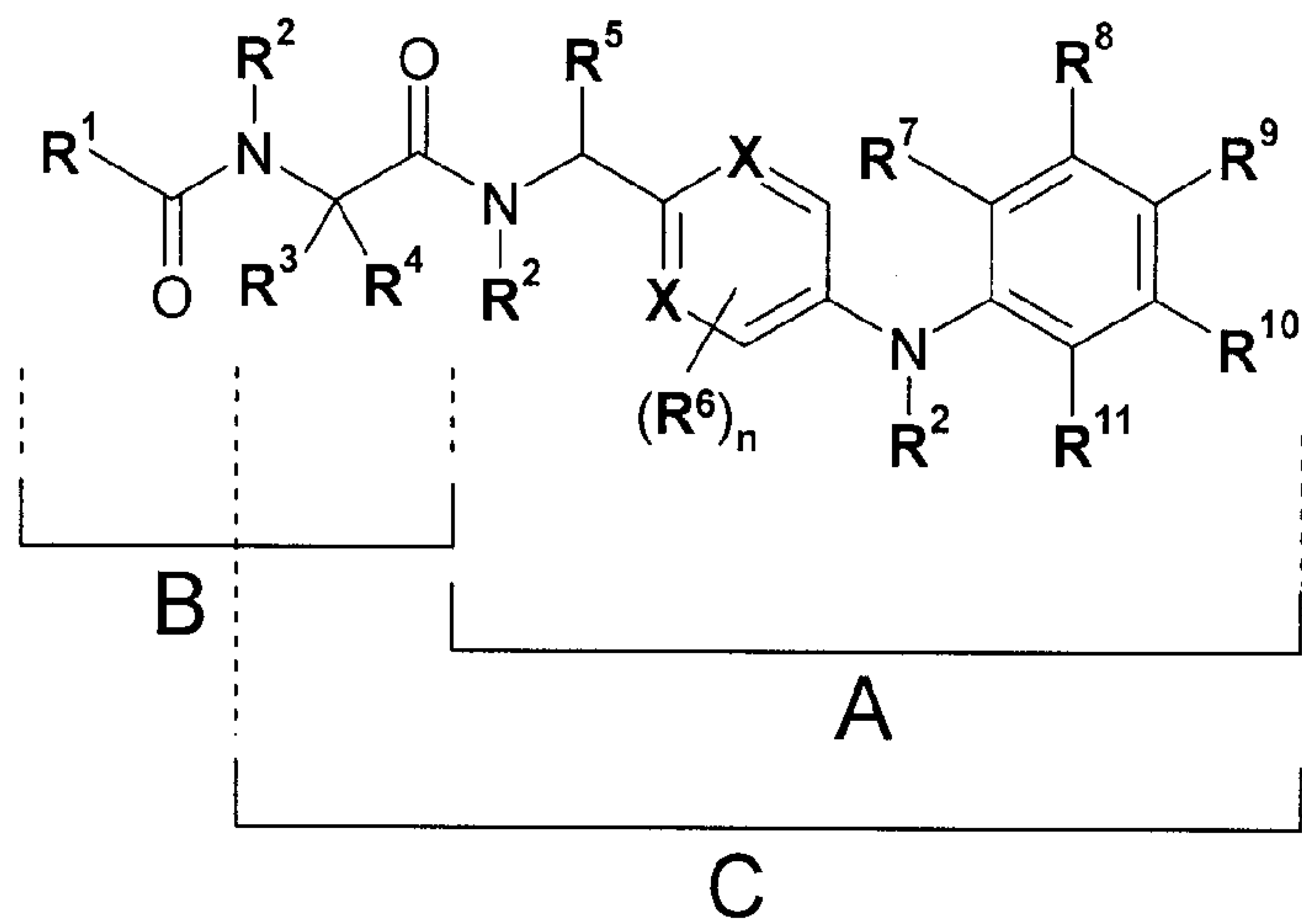
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Method 3: Column: YMC-Pack ODS-AQ 5 µM, 30 x 100 mm
 Eluant A: water / 0.15% formic acid
 Eluant B: acetonitrile
 Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	50
2.0	95.0	5.0	50
6.0	10.0	90.0	50
12.0	10.0	90.0	50
13	90.0	10.0	50

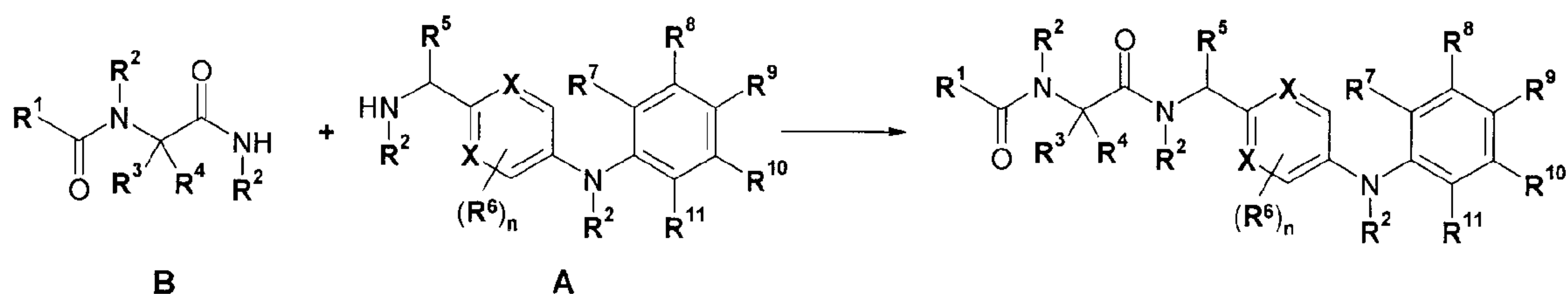
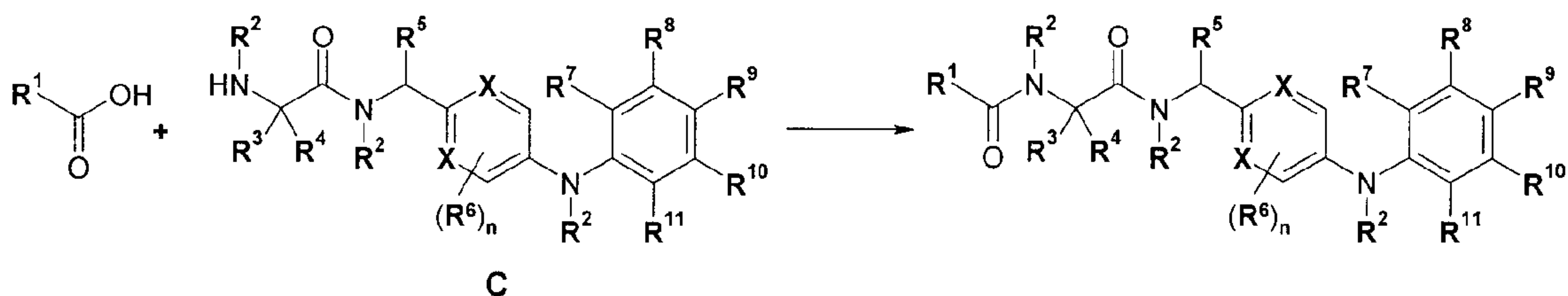
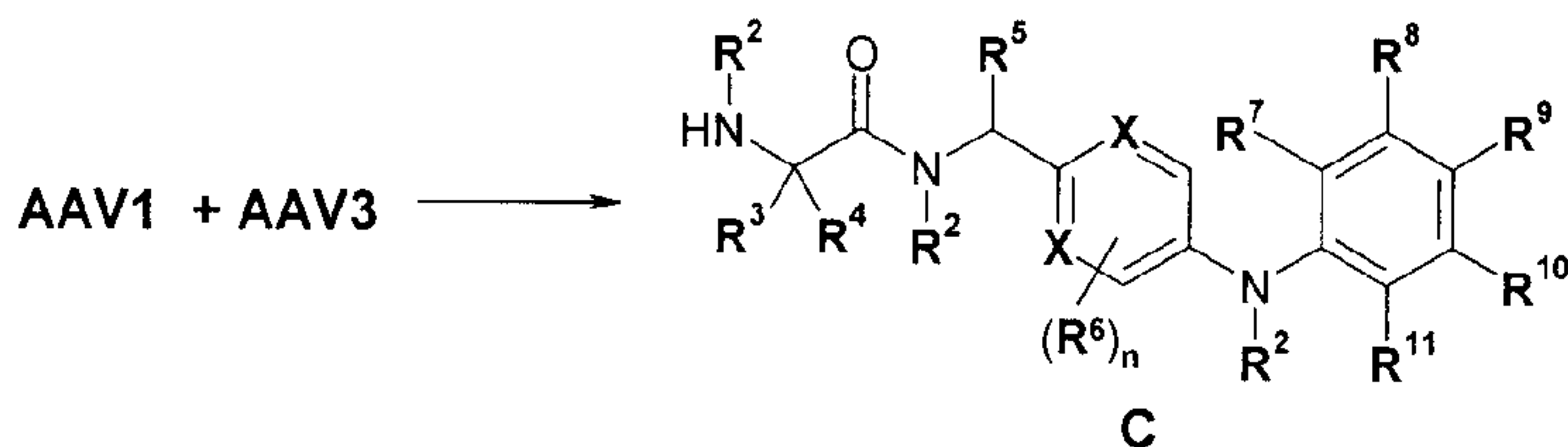
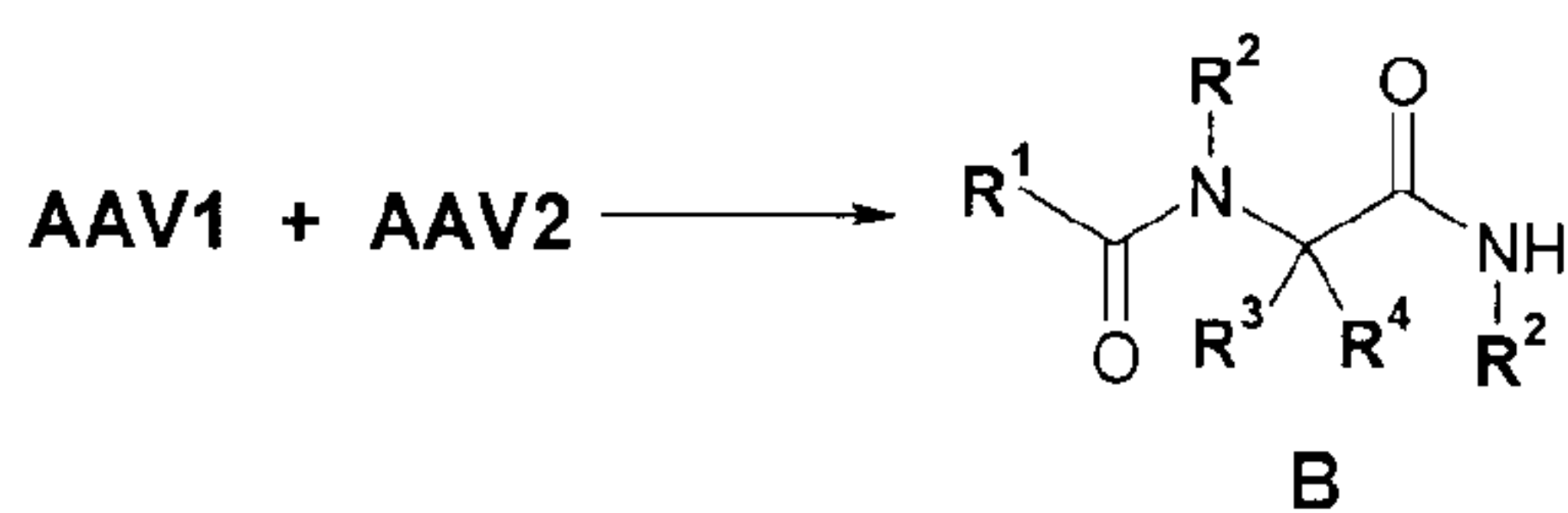
10

The compounds of general formula I may be prepared from the following intermediates **A**, **B** and **C**:



25771-2004

- 22 -

**AAV 1: amide coupling**

A solution of the carboxylic acid component (1 mol-equivalent), triethylamine (2.5 mol-equivalents) and TBTU (1.1 mol-equivalents) in THF was stirred for 30 minutes at ambient temperature. Then the amine component (1.1 mol-equivalent as hydrochloride) was added and stirring was continued overnight. Then the mixture was evaporated down, mixed with water, made alkaline with dilute potassium carbonate solution and extracted with ethyl acetate. The product was isolated and purified by column chromatography (either silica gel or reversed phase chromatography).

AAV 2: Ester hydrolysis

2N sodium hydroxide solution (2 mol-equivalents) was added to a solution of the ester (1 mol-equivalent) in methanol and the mixture was stirred for 1 to 5 hours at ambient

25771-2004

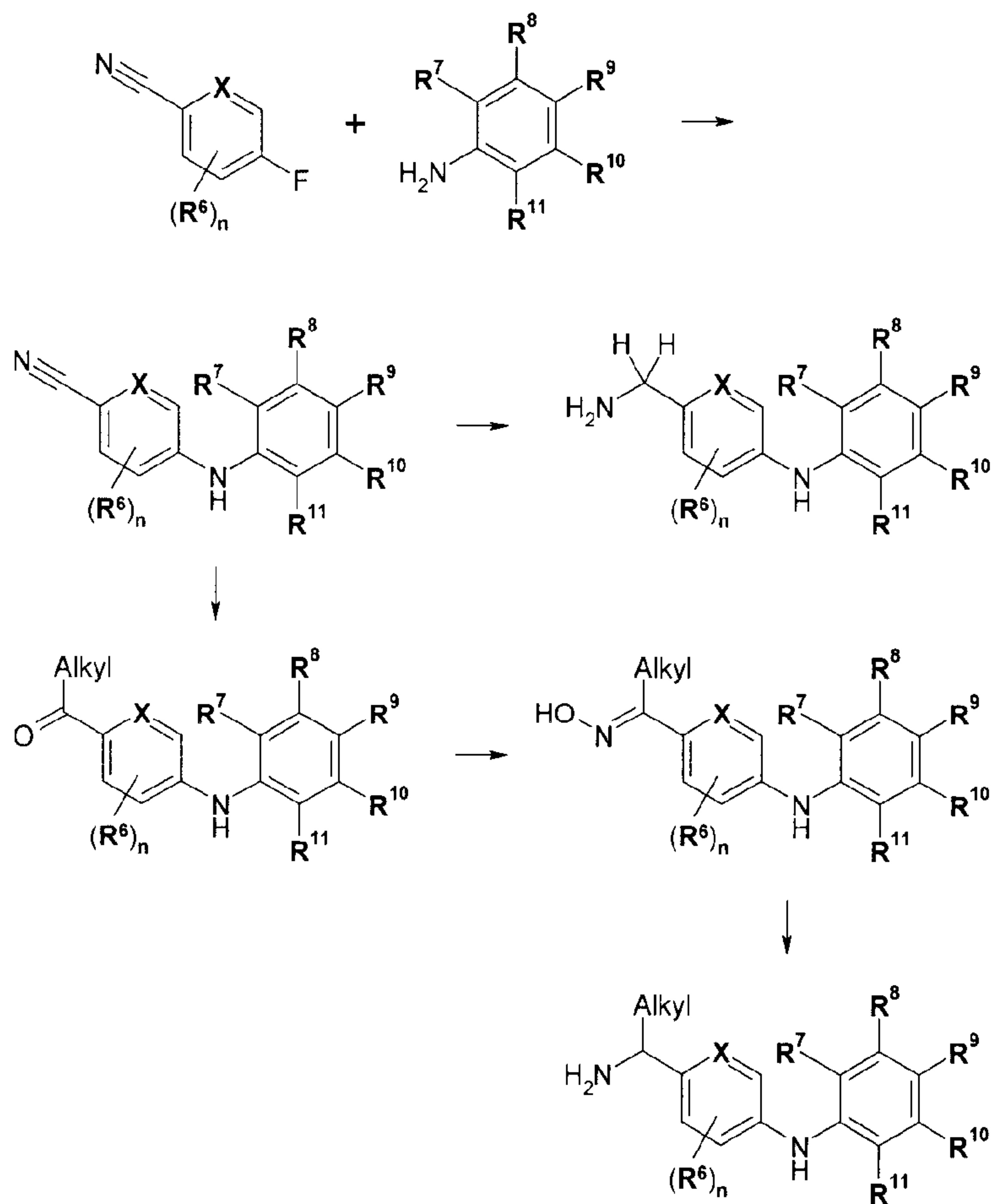
- 23 -

temperature. Then it was acidified with acetic acid and the mixture was evaporated to dryness in vacuo. The crude product thus obtained was purified in the normal way by column chromatography on silica gel.

5 **AAV 3:** Cleaving the *tert*-butoxycarbonyl protective group

A solution of the *tert*-butoxycarbonyl-amino compound (1 mol-equivalent) in dichloromethane was combined with trifluoroacetic acid (3 to 10 mol-equivalents) and stirred at ambient temperature until the protective group had been cleaved completely. The reaction mixture was then evaporated to dryness and the crude product thus obtained was purified by
10 chromatography.

AAV 4: Preparation of the intermediate A



25771-2004

- 24 -

A solution of the aniline component (1 mol-equivalent) and a strong base such as e.g. potassium-*tert*-butoxide (1 mol-equivalent) in DMSO was stirred for one hour at ambient temperature, then combined with the 4-fluoro-benzonitrile component (1 mol-equivalent) and stirred overnight at approx. 80°C. For working up the mixture was filtered through Alox and
5 evaporated to dryness in vacuo.

The nitrile group of the diphenylamine intermediate product thus obtained was then reduced to the aminomethyl group with the addition of Raney nickel at 55°C and 3 bar excess hydrogen pressure and the product obtained was purified by chromatography.

In order to prepare the intermediate **A** with an alpha-alkylbenzyl group (e.g. A1, A4, A5) the
10 nitrile derivative (1 mol-equivalent) was dissolved in diethyl ether and at 0 to 5°C it was added with stirring to a solution of alkylmagnesium bromide (4 mol-equivalents) in diethyl ether and then stirred for another 30 minutes approx. The reaction mixture was then stirred into 1M hydrochloric acid at -5°C and the alkylketone thus obtained was isolated and purified by chromatography in the usual way.

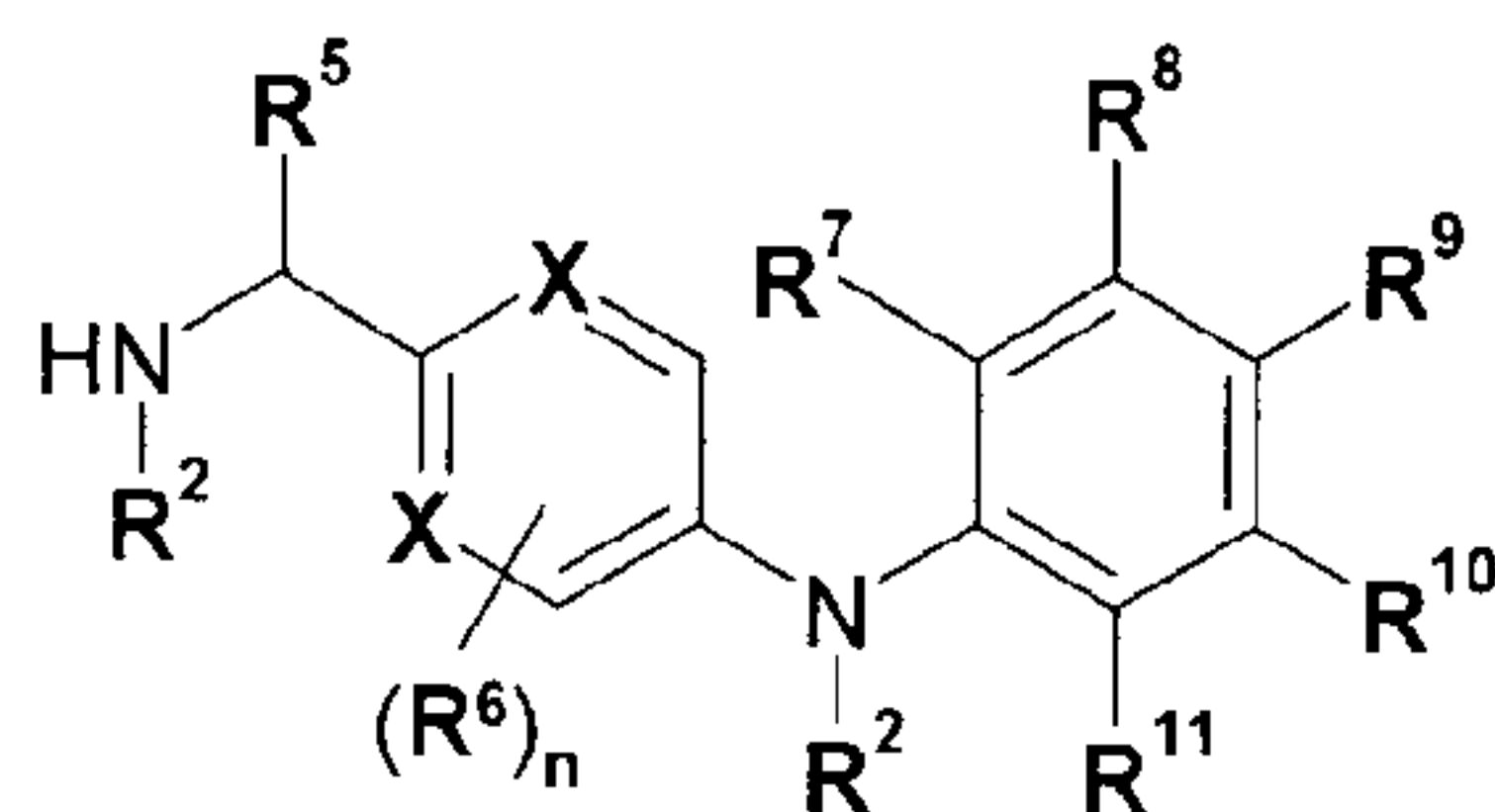
15 A solution of the ketone thus obtained (1 mol-equivalent) in acetonitrile was combined with triethylamine (2 mol-equivalents) and hydroxylamine-hydrochloride (1.3 mol-equivalents) and refluxed for 4 hours. Then water was added and the mixture was extracted with dichloromethane. The resulting oxime was isolated from the organic phase and purified by conventional methods.

20 A solution of the oxime (1 mol-equivalent) in methanol was combined with methanolic hydrochloric acid (6.6 mol-equivalents). After the addition of zinc powder (1.4 mol-equivalents) the mixture was refluxed for 3 hours with stirring. After cooling the mixture was combined with water and extracted with dichloromethane. If necessary, the amine thus obtained was purified by chromatography.

25 Another possible way of reducing the oxime to the corresponding amine is by catalytic hydrogenation. For this, the oxime was hydrogenated in methanolic ammonia solution after the addition of Raney nickel at 50°C and at an excess hydrogen pressure of 50 psi until the uptake of hydrogen had ended. If necessary, the amine thus obtained was purified by chromatography.

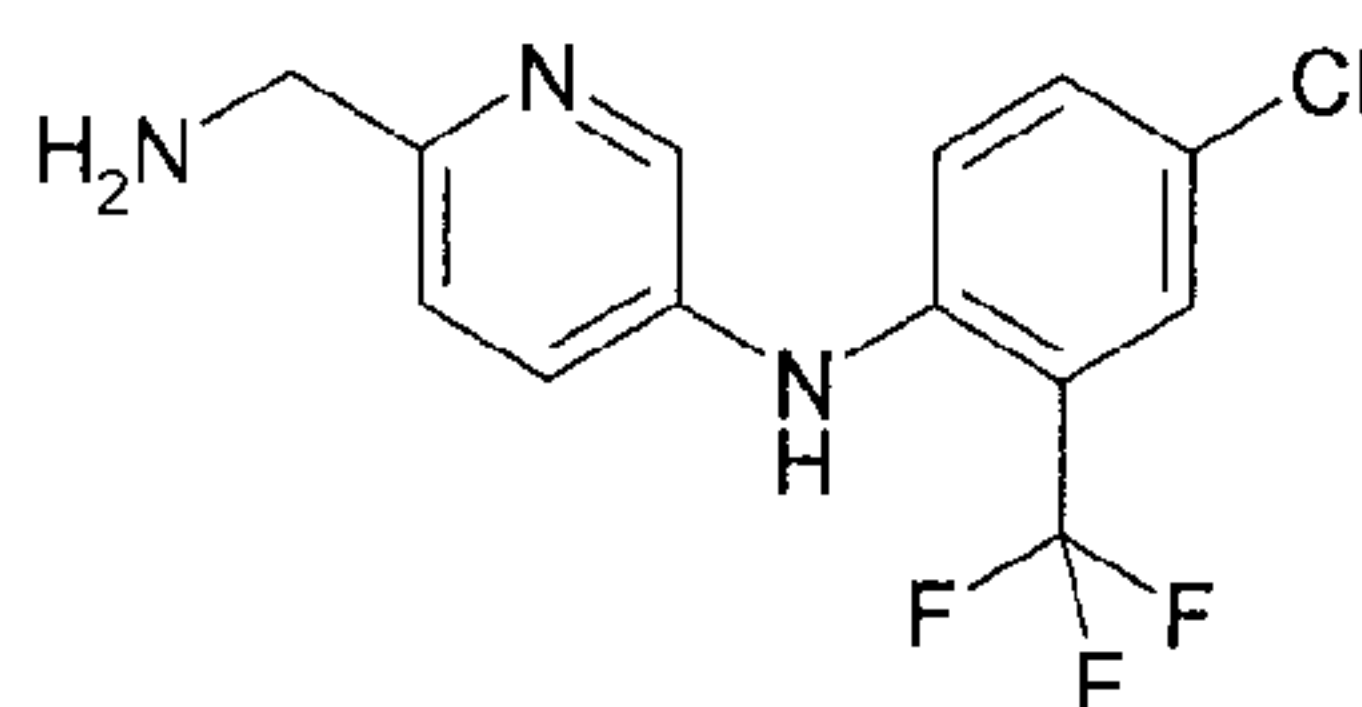
25771-2004

- 25 -

Preparation of the Intermediates A

The following intermediates A1 to A31 were prepared according to general working method
 5 AAV4:

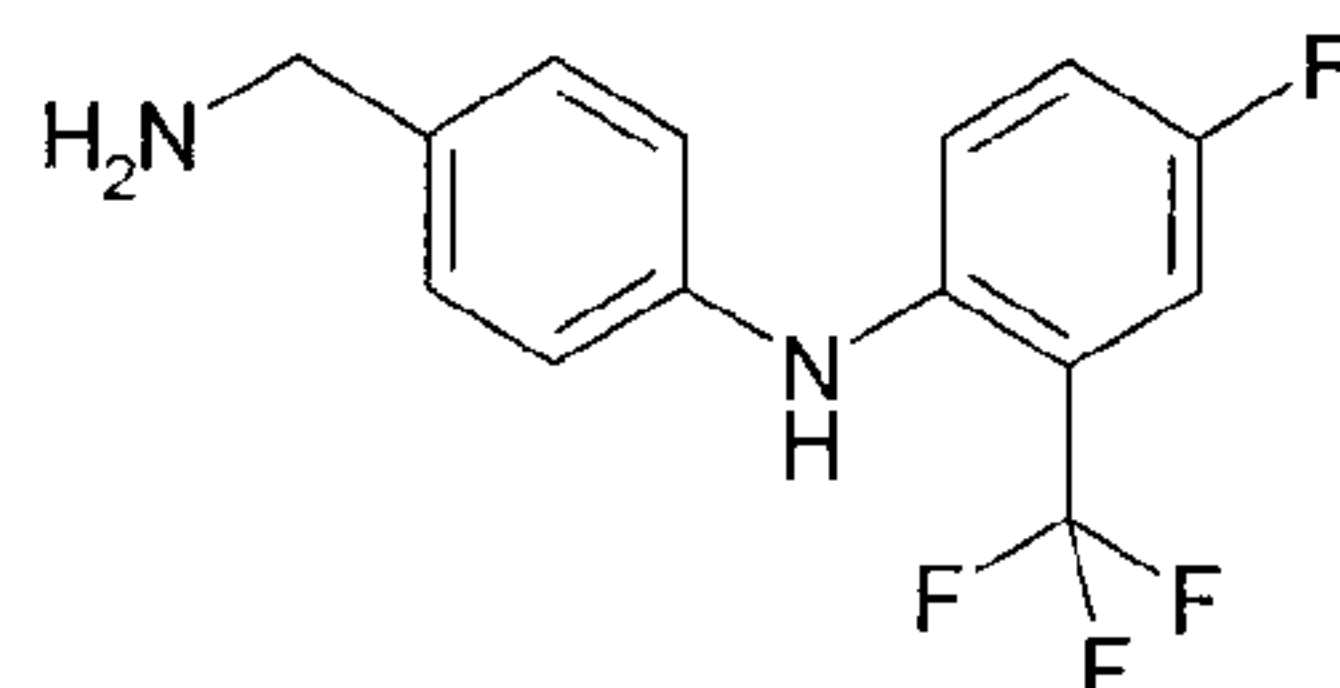
intermediate A1: (6-aminomethyl-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



HPLC: $R_t = 1.74$ minutes (method 13)

10 Mass spectrum (ESI): $[M+H]^+ = 302$

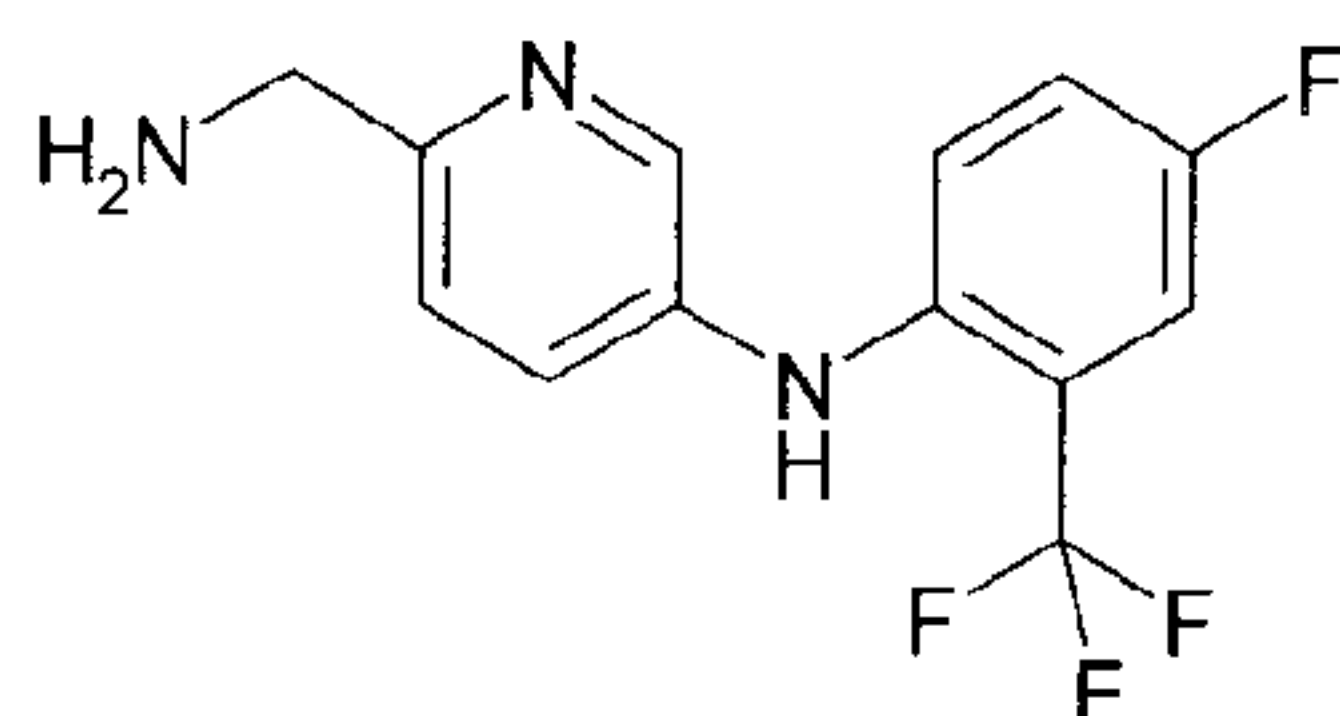
intermediate A2: (4-aminomethyl-phenyl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine



Mass spectrum (ESI): $[M+H]^+ = 285$

15 thin layer chromatogram (silica gel, $\text{CH}_2\text{Cl}_2/\text{ethanol}$ 19:1): $R_f = 0.16$

intermediate A3: (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-
 amine

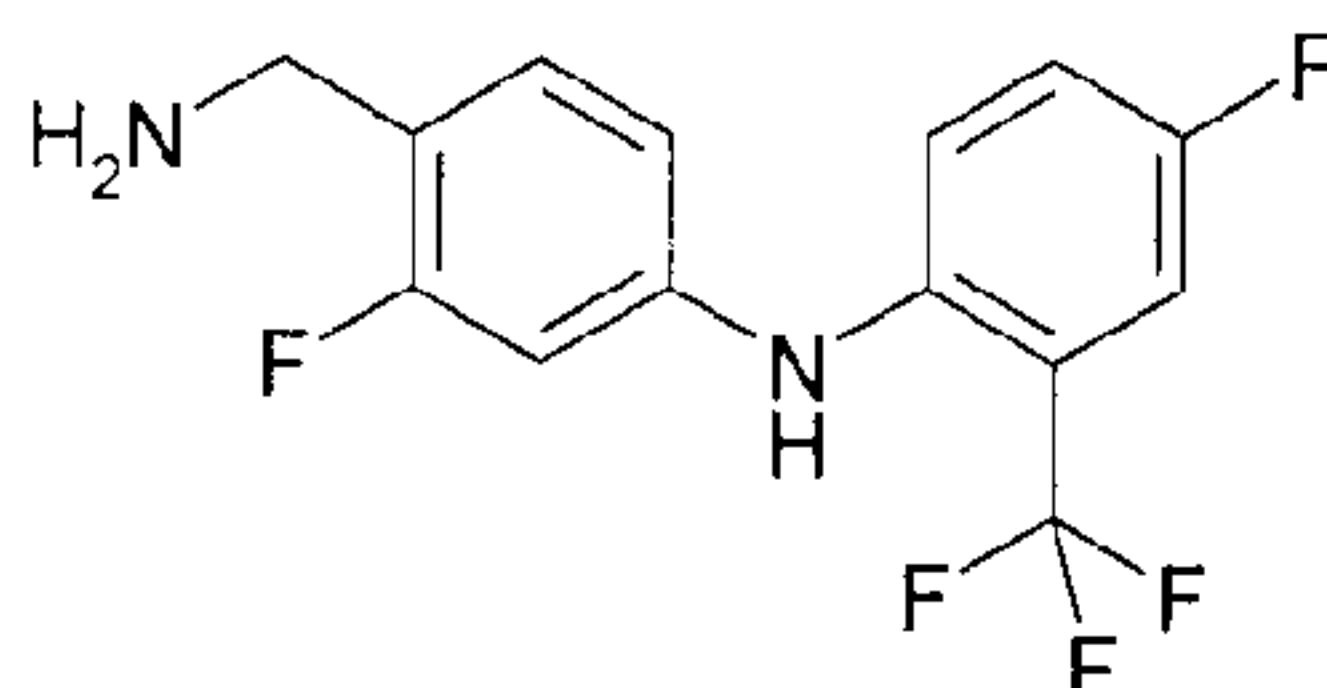


25771-2004

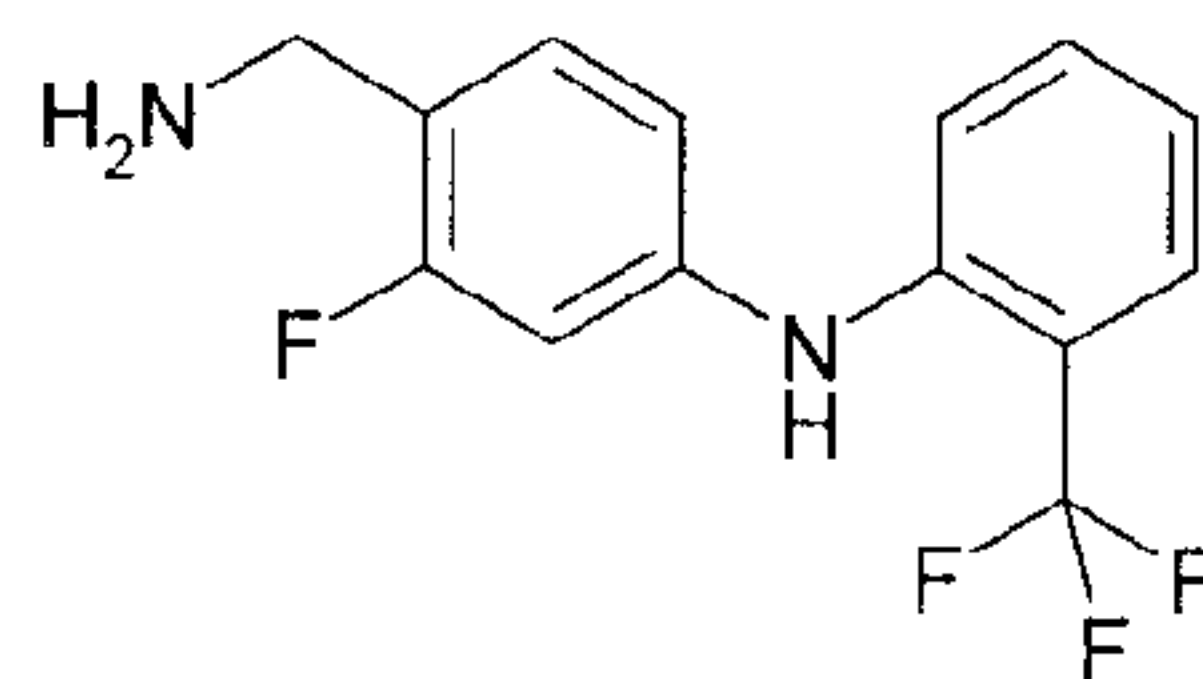
- 26 -

HPLC: $R_t = 2.06$ minutes (method 3)Mass spectrum (ESI): $[M+H]^+ = 286$; $[M-H]^- = 284$

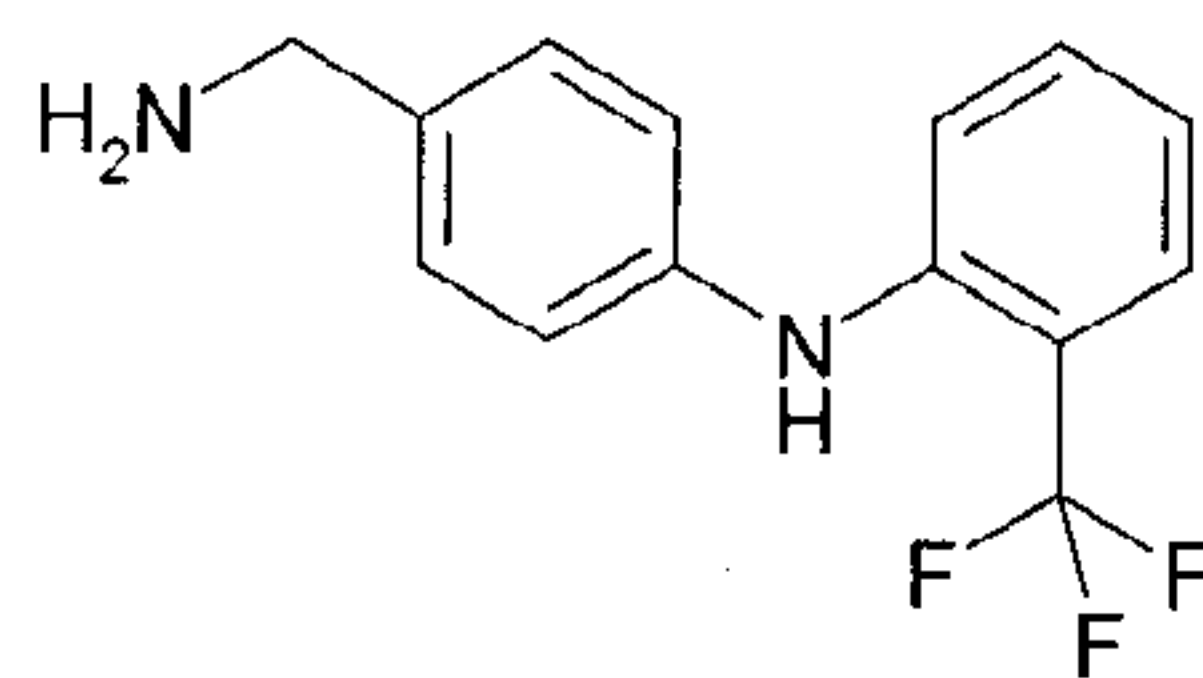
5 intermediate A4: (4-aminomethyl-3-fluoro-phenyl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

Mass spectrum (ESI): $[M+H]^+ = 303$ thin layer chromatogram (silica gel, CH_2Cl_2 /ethanol 19:1): $R_f = 0.08$

10 intermediate A5: (4-aminomethyl-3-fluoro-phenyl)-(2-trifluoromethyl-phenyl)-amine

Mass spectrum (ESI): $[M-H]^- = 283$ thin layer chromatogram (silica gel, CH_2Cl_2 /ethanol 19:1): $R_f = 0.09$

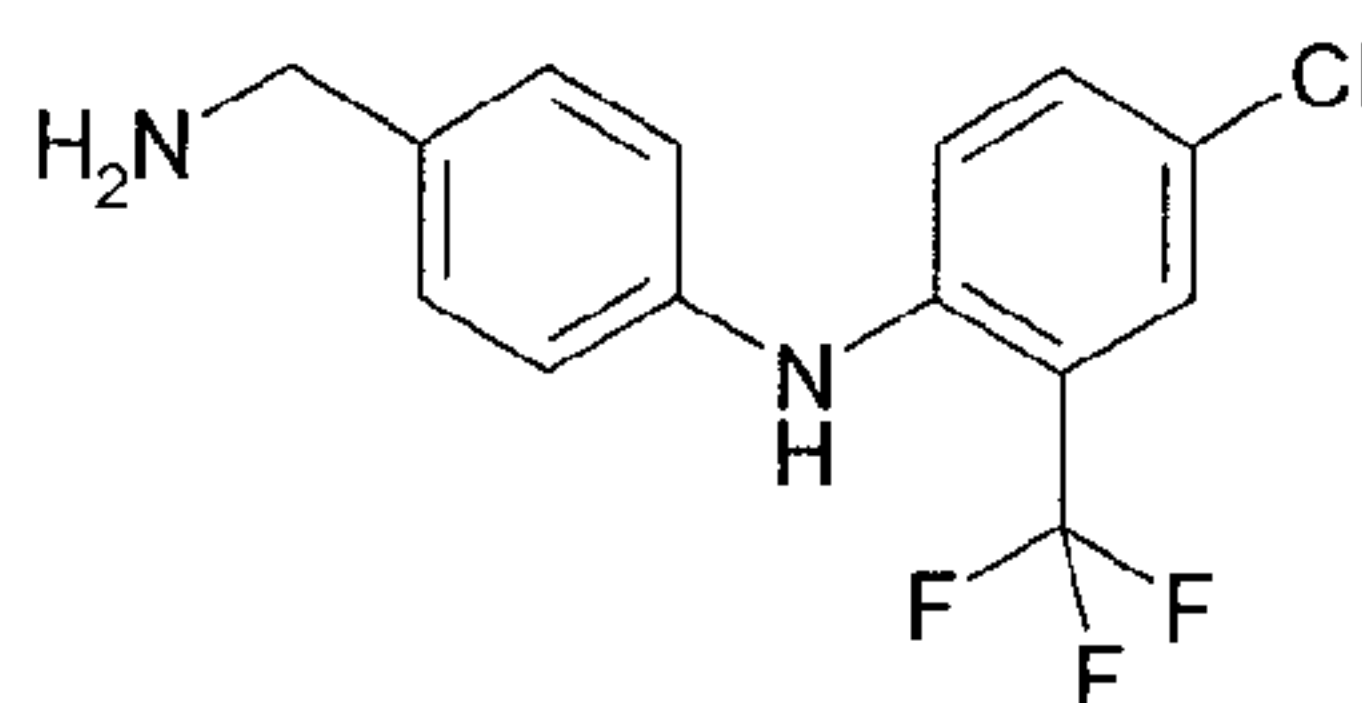
15 intermediate A6: (4-aminomethyl-phenyl)-(2-trifluoromethyl-phenyl)-amine

HPLC: $R_t = 1.36$ minutes (method 1)Mass spectrum (ESI): $[M+H-NH_3]^+ = 250$

20 intermediate A7: (4-aminomethyl-phenyl)-(4-chloro-2-trifluoromethyl-phenyl)-amine

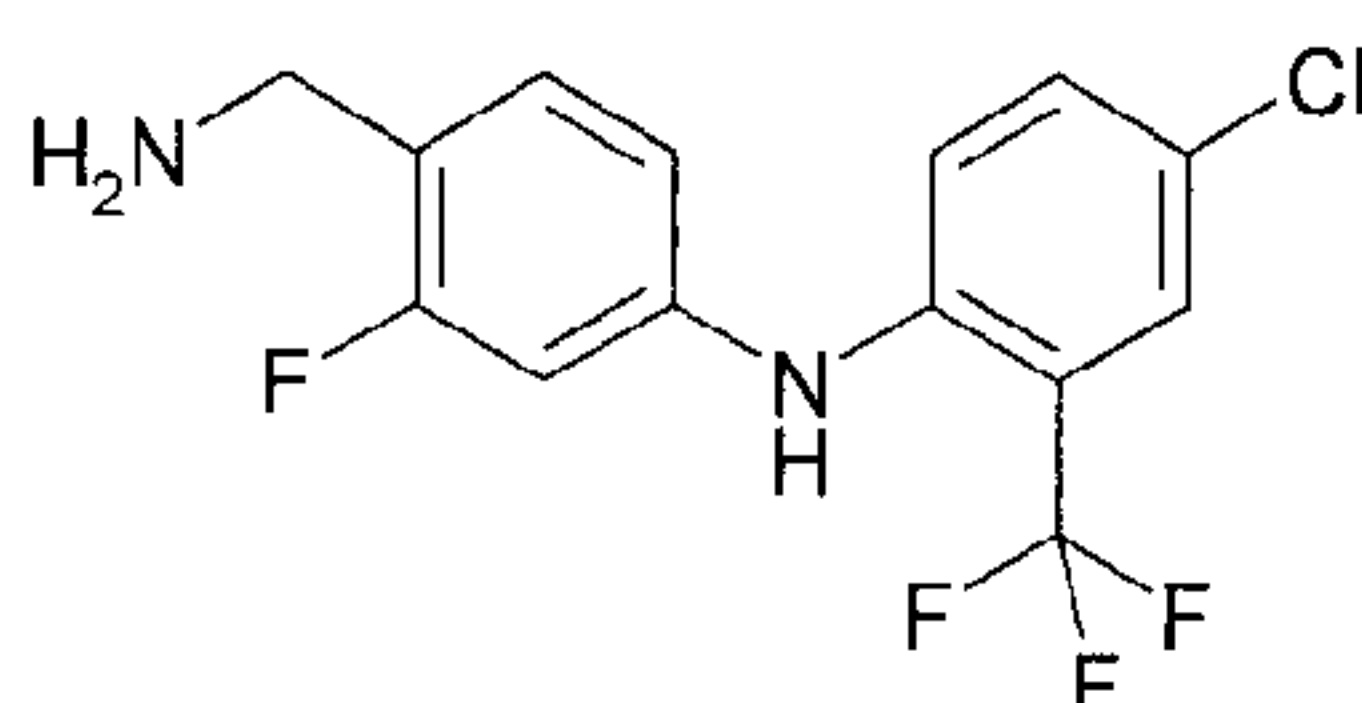
25771-2004

- 27 -



Mass spectrum (ESI): $[M+H-NH_3]^+ = 284/286$

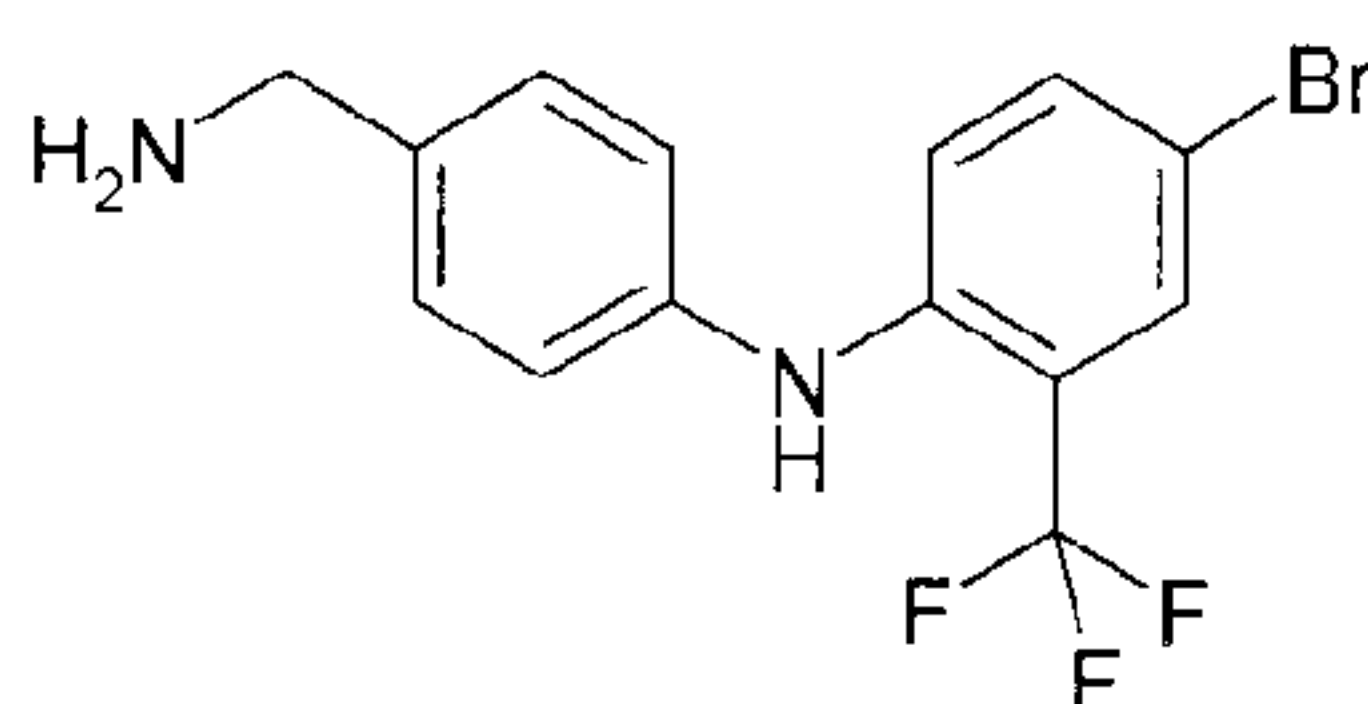
intermediate A8: (4-aminomethyl-3-fluoro-phenyl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



5

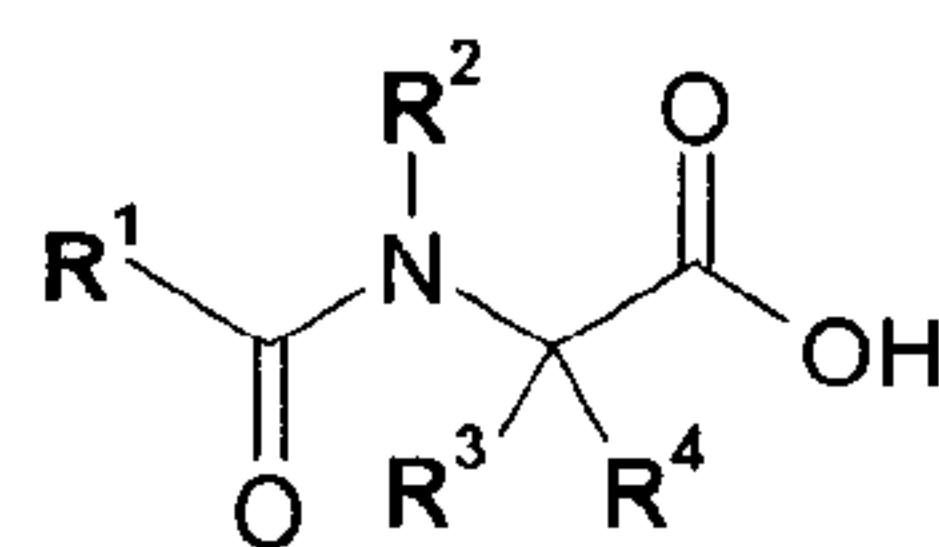
HPLC: $R_t = 1.83$ minutes (method 2)

intermediate A9: (4-aminomethyl-phenyl)-(4-bromo-2-trifluoromethyl-phenyl)-amine



10 HPLC: $R_t = 1.81$ minutes (method 2)

Preparation of the Intermediates B



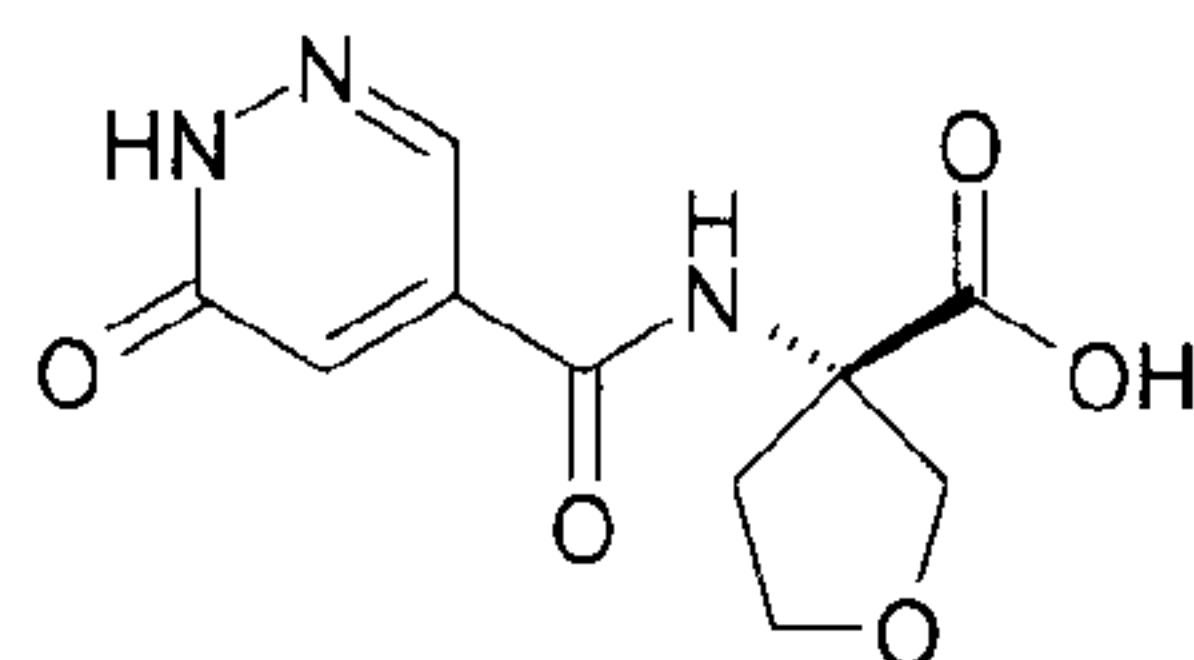
15 The following Intermediate B1 was prepared by amide coupling according to general working method AAV1 and subsequent ester saponification according to general working method AAV2:

intermediate B1: (S)-3-[(6-oxo-1,6-dihydro-pyridazine-4-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid

20

25771-2004

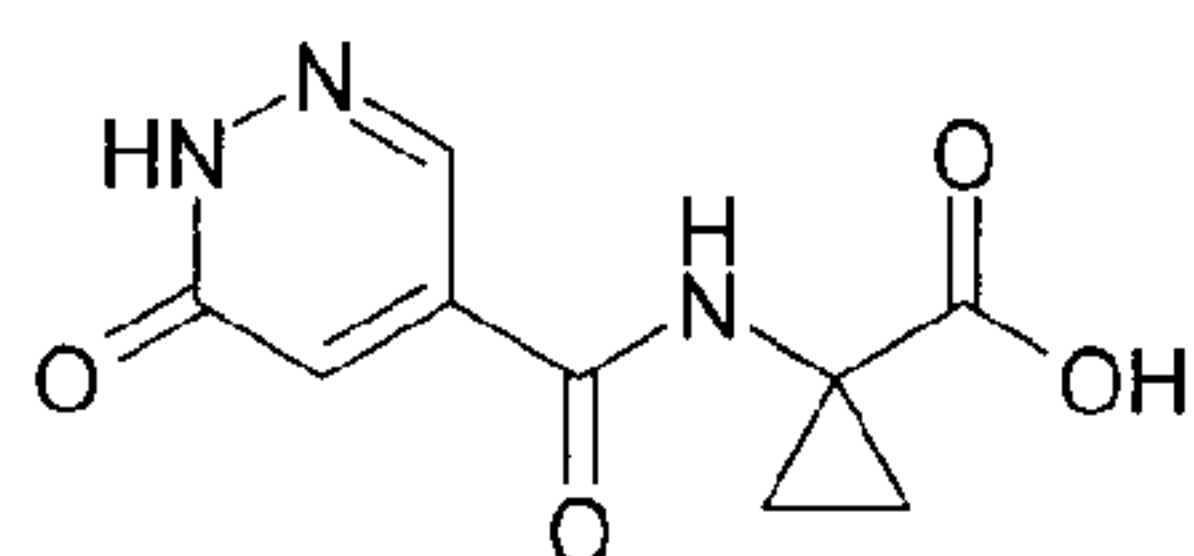
- 28 -

HPLC: $R_t = 0.33$ minutes (method 2)Mass spectrum (ESI): $[M+H]^+ = 254$

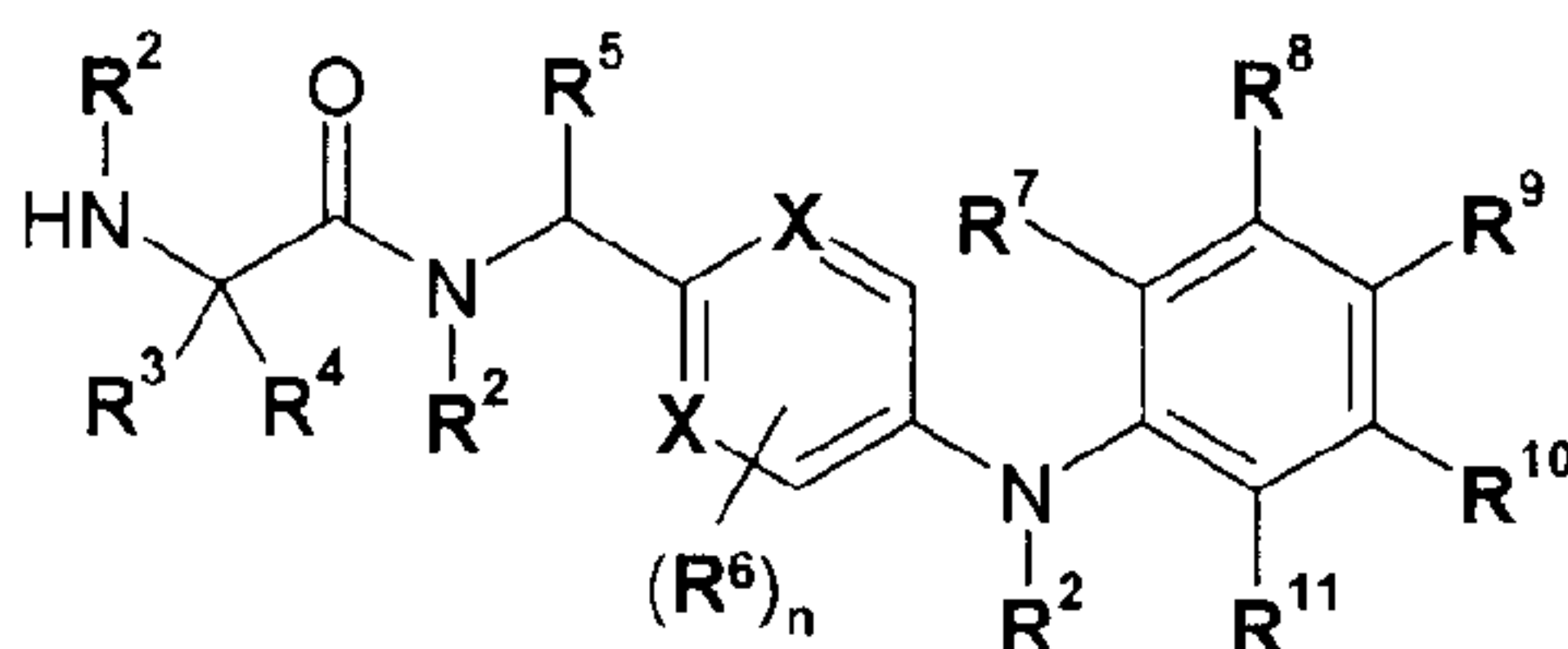
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The following Intermediate B2 may be prepared analogously:

intermediate B2: 1-[(6-oxo-1,6-dihydro-pyridazine-4-carbonyl)-amino]-
cyclopropanecarboxylic acid



10

Preparation of the Intermediates C

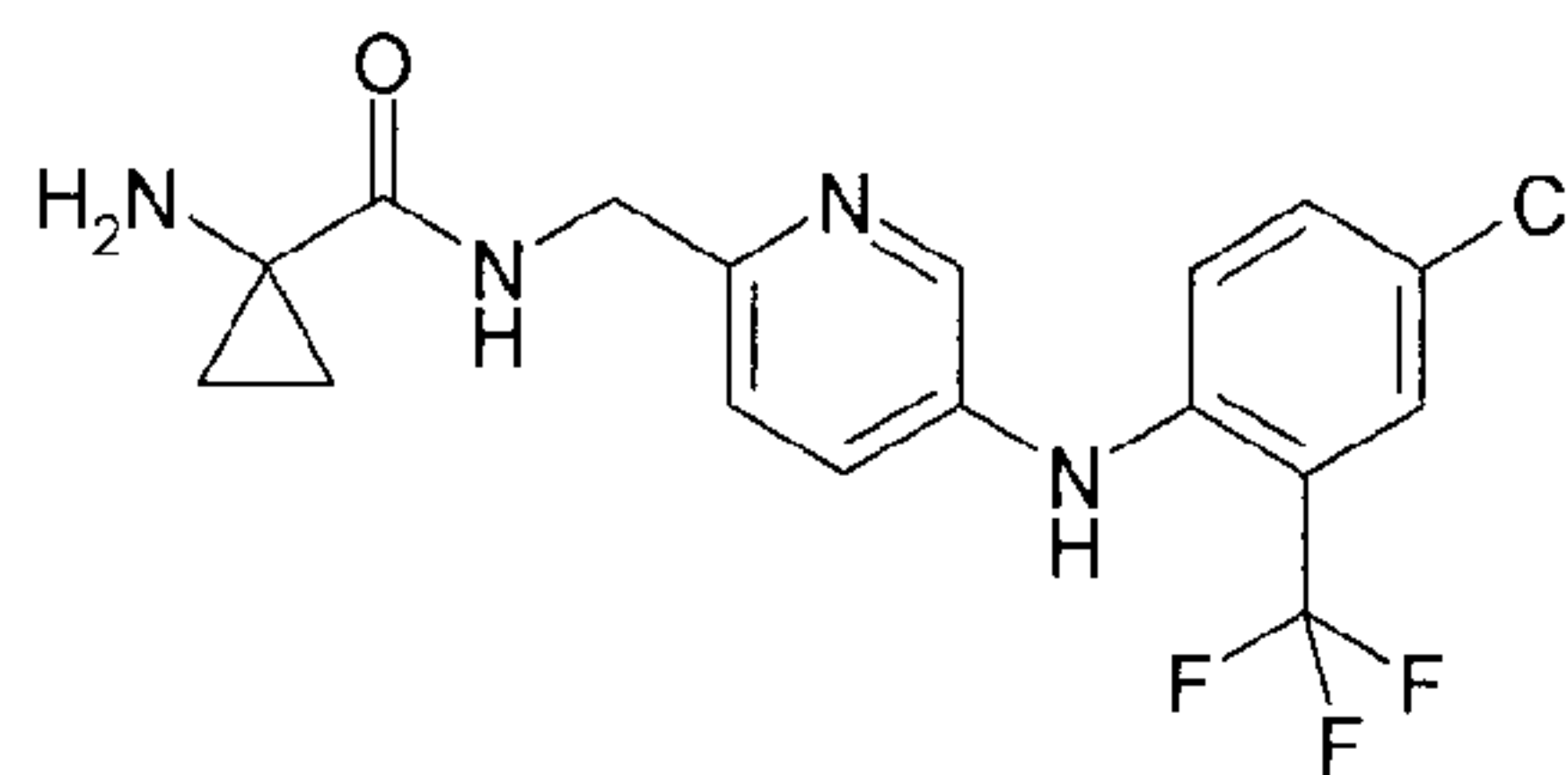
15 The following Intermediates C1 to C6 were prepared by amide coupling according to general working method AAV1 and subsequent cleaving of the *tert*-butoxycarbonyl-protective group according to general working method AAV3:

intermediate C1: 1-amino-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

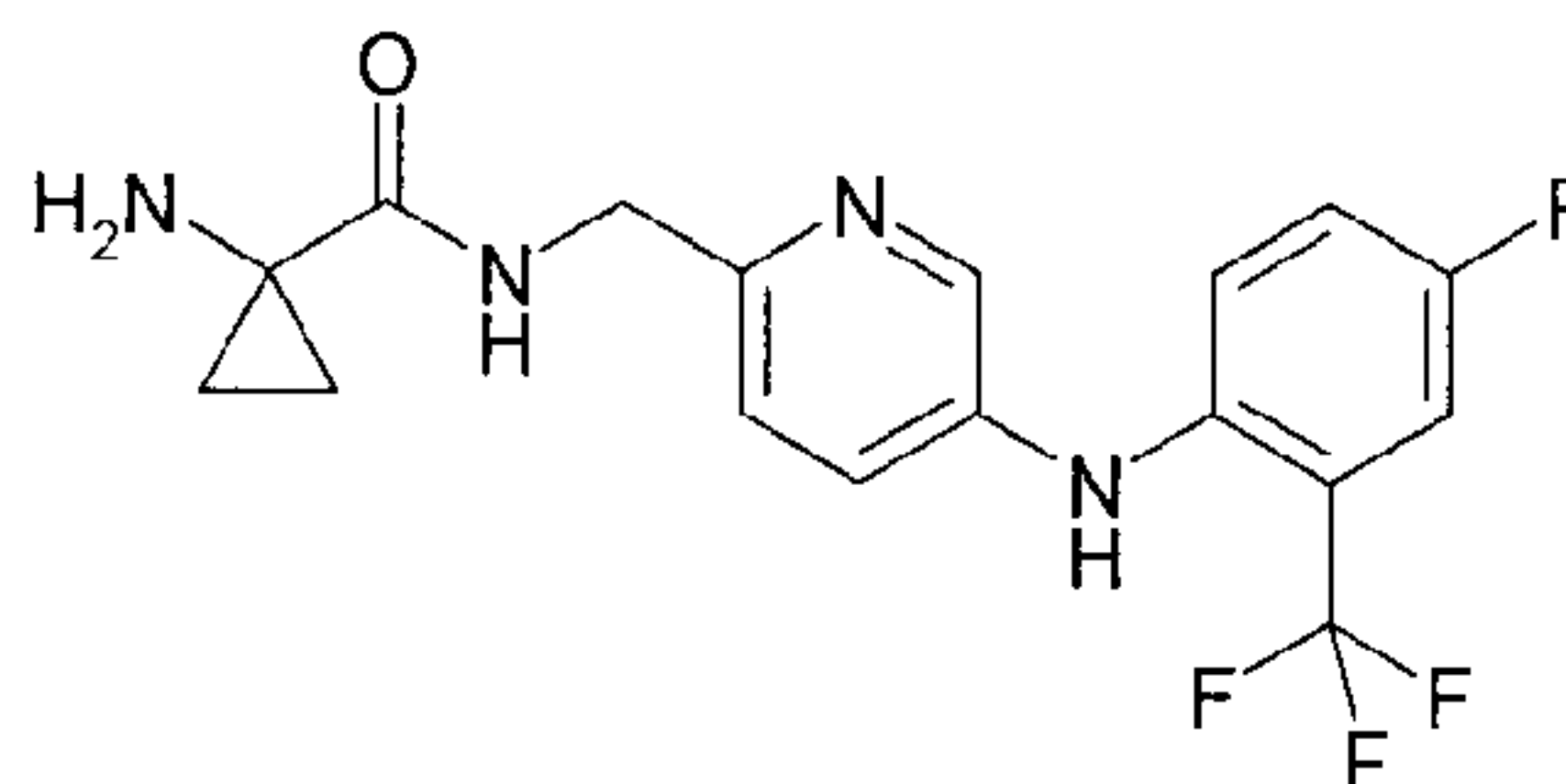
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25771-2004

- 29 -

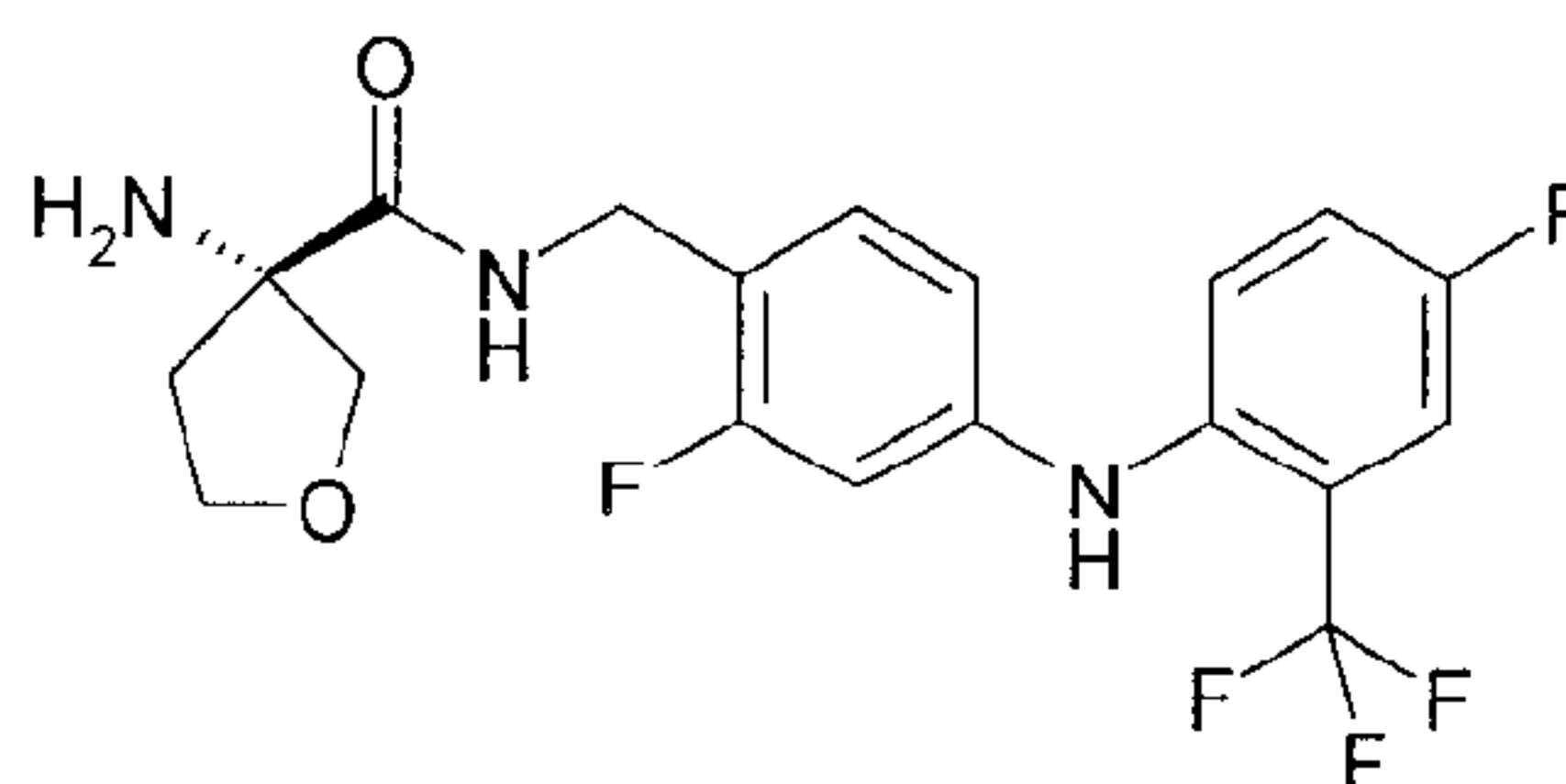
HPLC: $R_t = 1.55$ minutes (method 13)Mass spectrum (ESI): $[M-H]^- = 383$

- 5 intermediate C2: 1-amino-cyclopropanecarboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

HPLC: $R_t = 2.33$ minutes (method 7)Mass spectrum (ESI): $[M+H]^+ = 369$; $[M-H]^- = 367$

10

- intermediate C3: (S)-3-amino-tetrahydrofuran-3-carboxylic acid-2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide

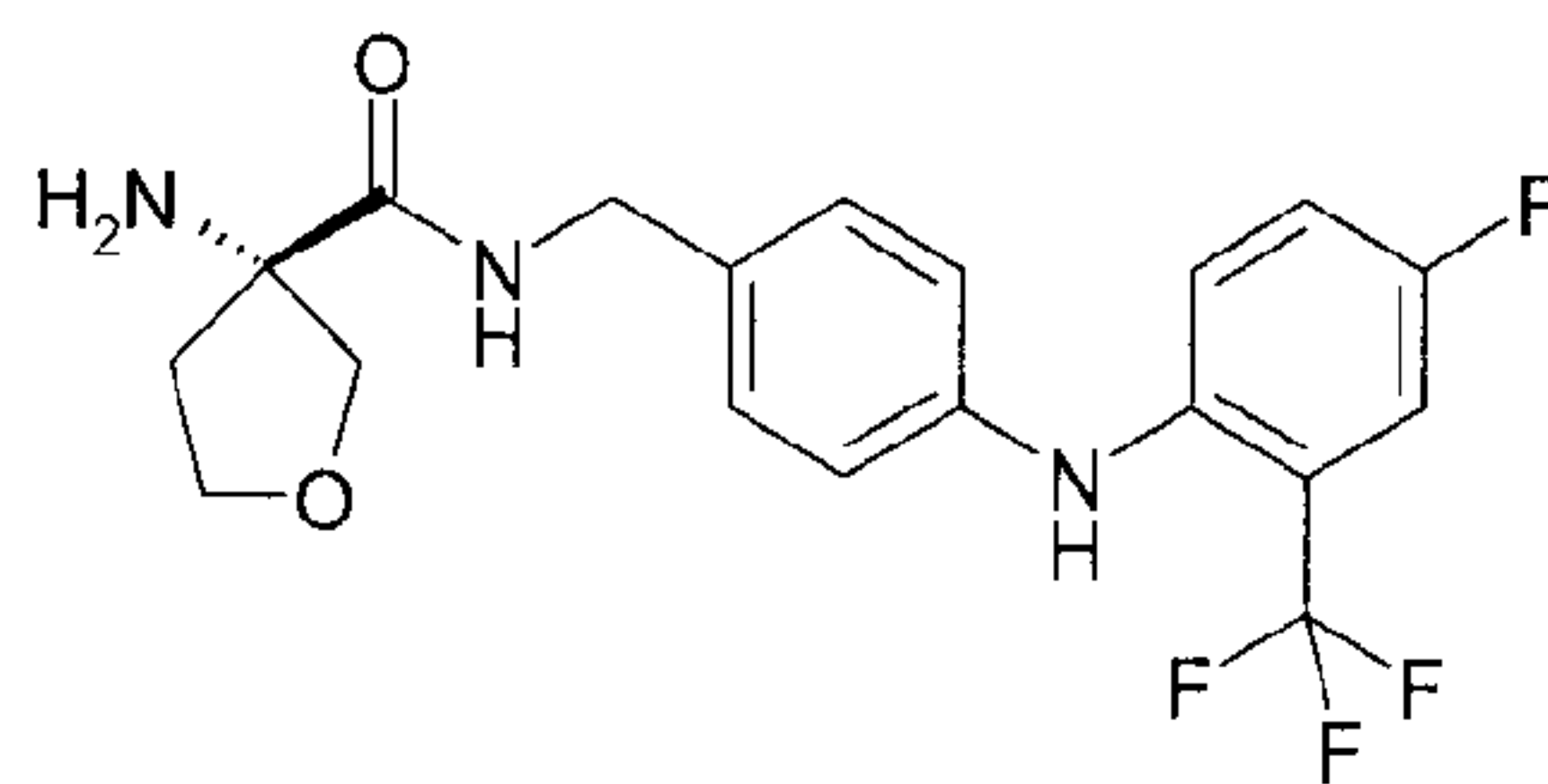
Mass spectrum (ESI): $[M+H]^+ = 416$

15

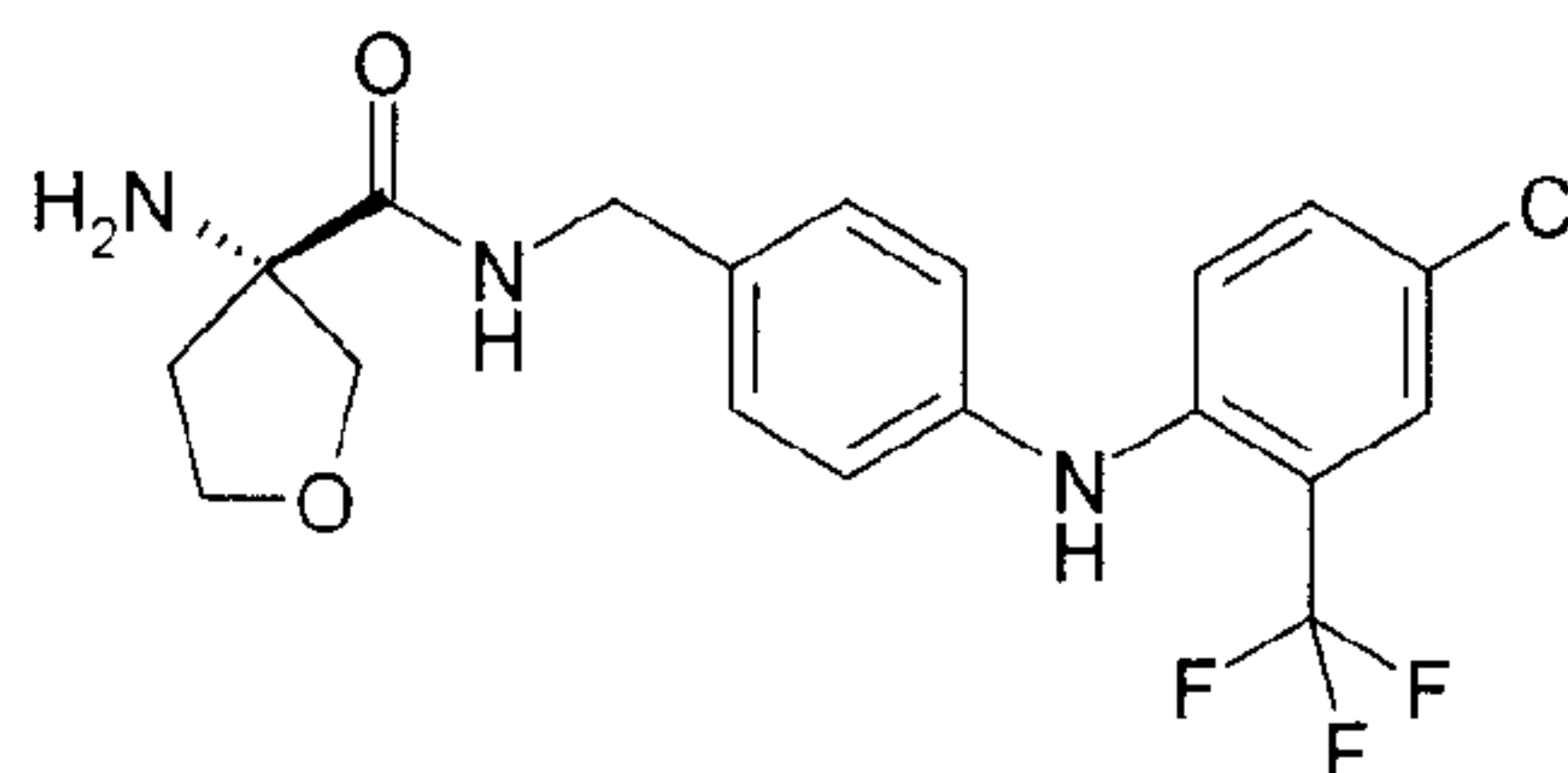
- intermediate C4: (S)-3-amino-tetrahydrofuran-3-carboxylic acid-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide

25771-2004

- 30 -

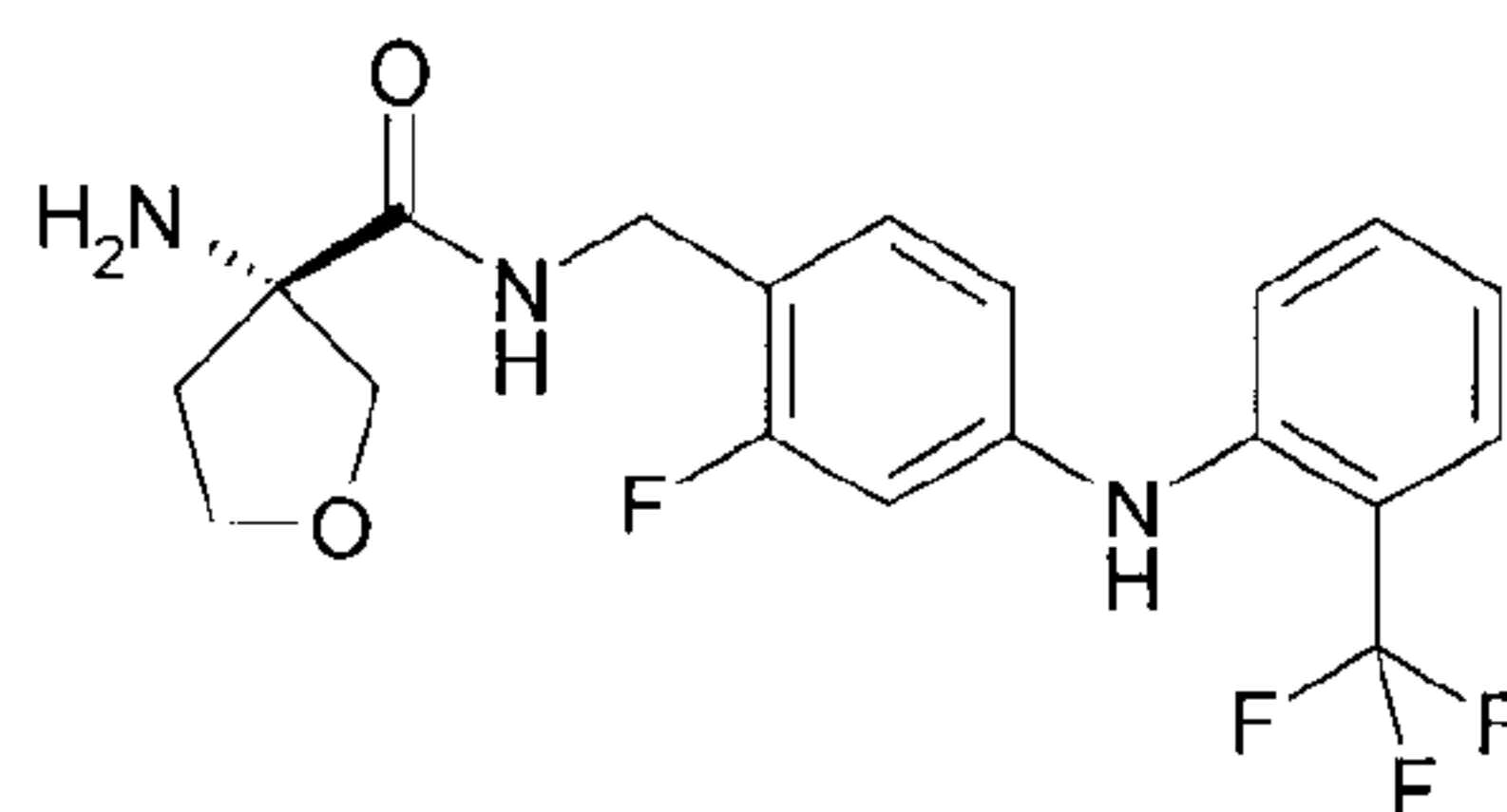
HPLC: $R_t = 1.99$ minutes (method 2)Mass spectrum (ESI): $[M+H]^+ = 398$

- 5 intermediate C5: (S)-3-amino-tetrahydrofuran-3-carboxylic acid-4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylamide

HPLC: $R_t = 2.41$ minutes (method 2)

10

- intermediate C6: (S)-3-amino-tetrahydrofuran-3-carboxylic acid 2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylamide

Mass spectrum (ESI): $[M+H]^+ = 398$

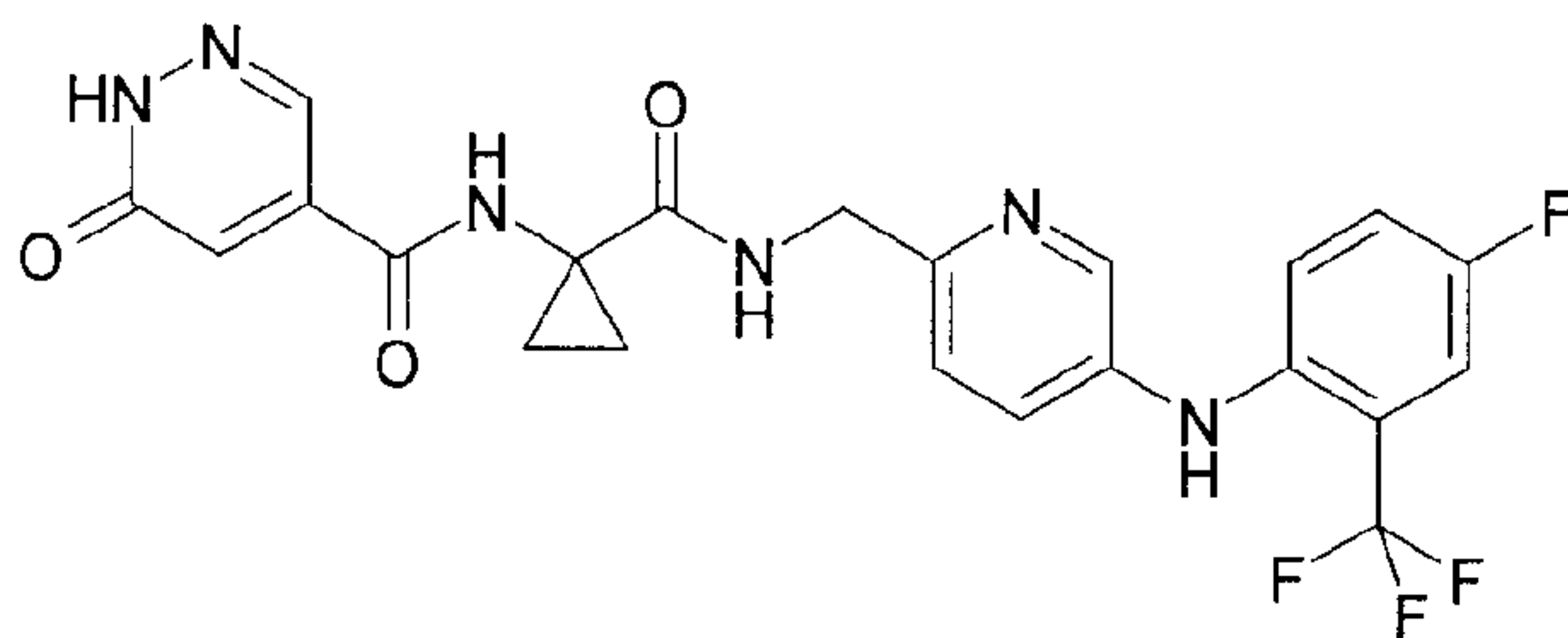
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Preparation of the End Compounds:

25771-2004

- 31 -

Example 1: 6-oxo-5,6-dihydro-pyridazine-4-carboxylic acid-(1-{{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl})-amide

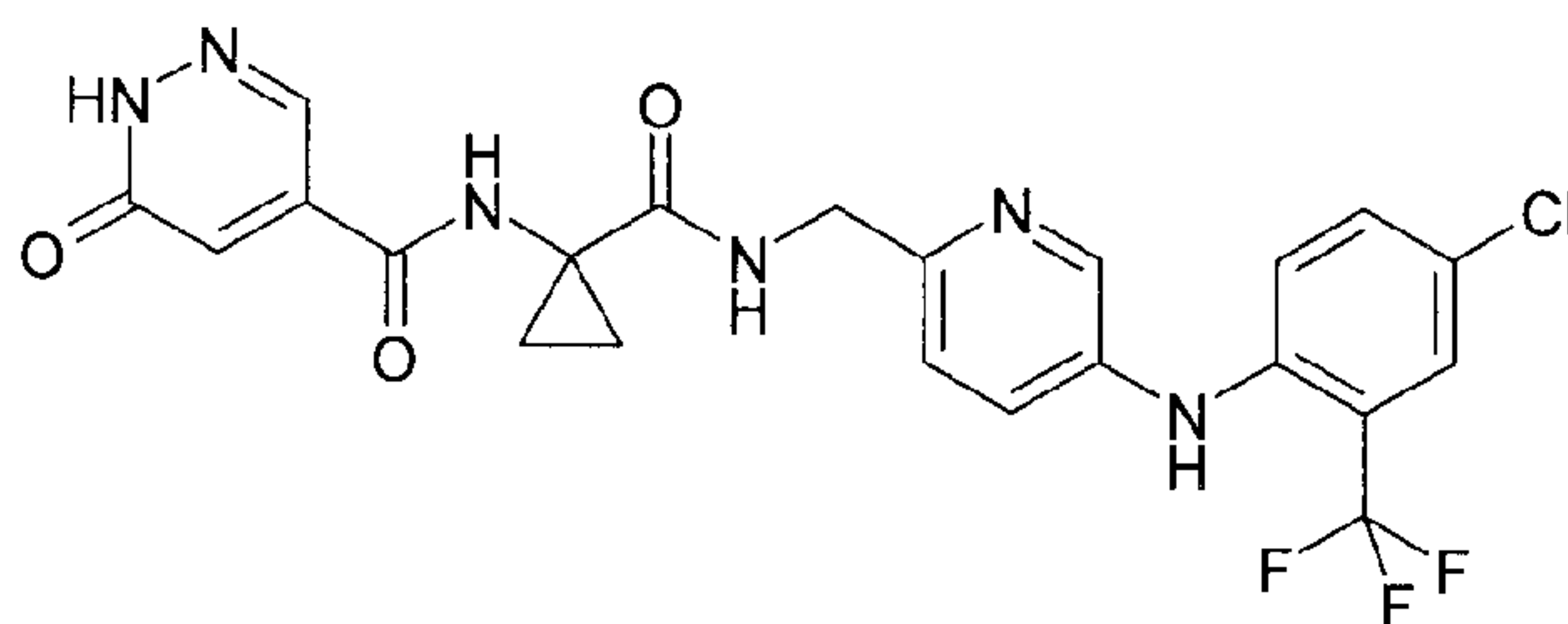


- 5 Prepared from intermediate C2 and 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid according to AAV1.

$C_{22}H_{18}F_4N_6O_3$ (490.42)

$R_t = 2.80$ minutes (method 7)

- 10 Example 2: 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-(1-{{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl})-amide



- 15 Prepared from intermediate C1 and 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid according to AAV1.

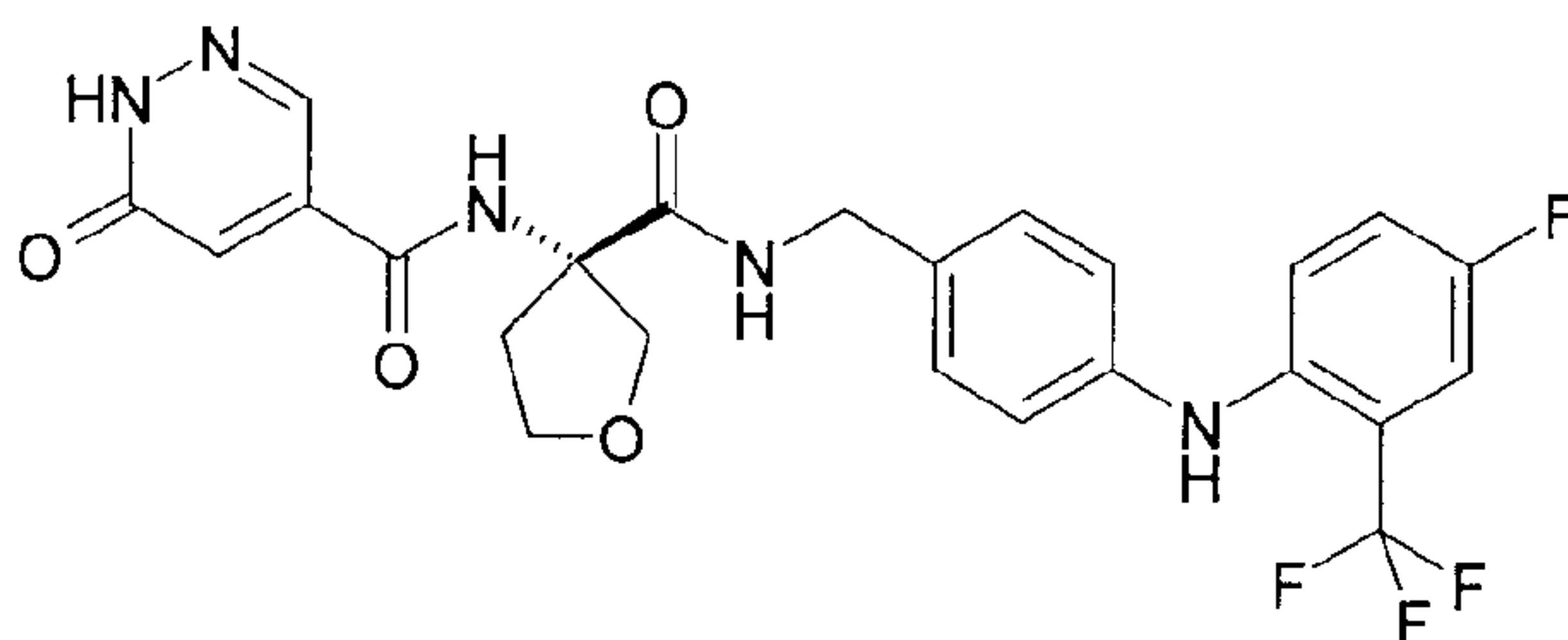
$C_{22}H_{18}ClF_3N_6O_3$ (506.87)

$R_t = 2.13$ minutes (method 2)

- 20 Example 3: (S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

25771-2004

- 32 -

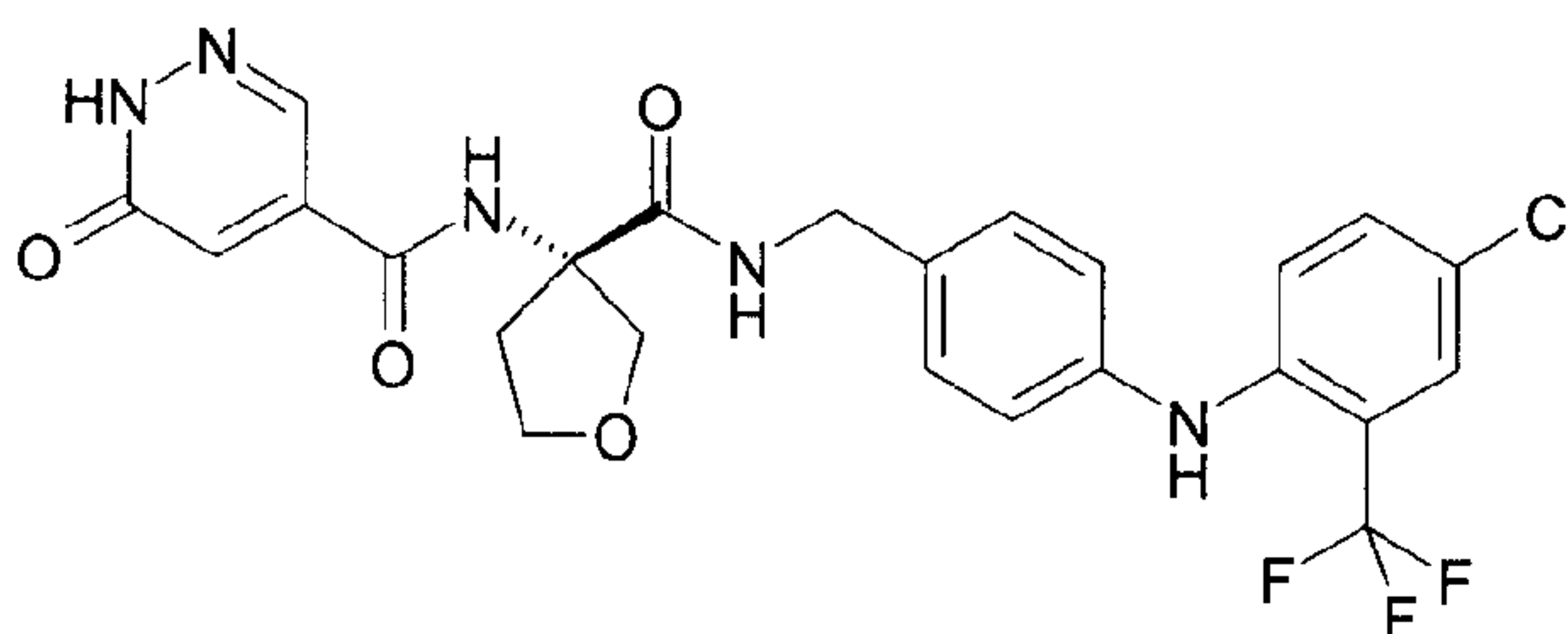


Prepared from intermediate C4 and 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid according to AAV1.

$C_{24}H_{21}F_4N_5O_4$ (519.45)

5 $R_t = 2.39$ minutes (method 2)

Example 4: (S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



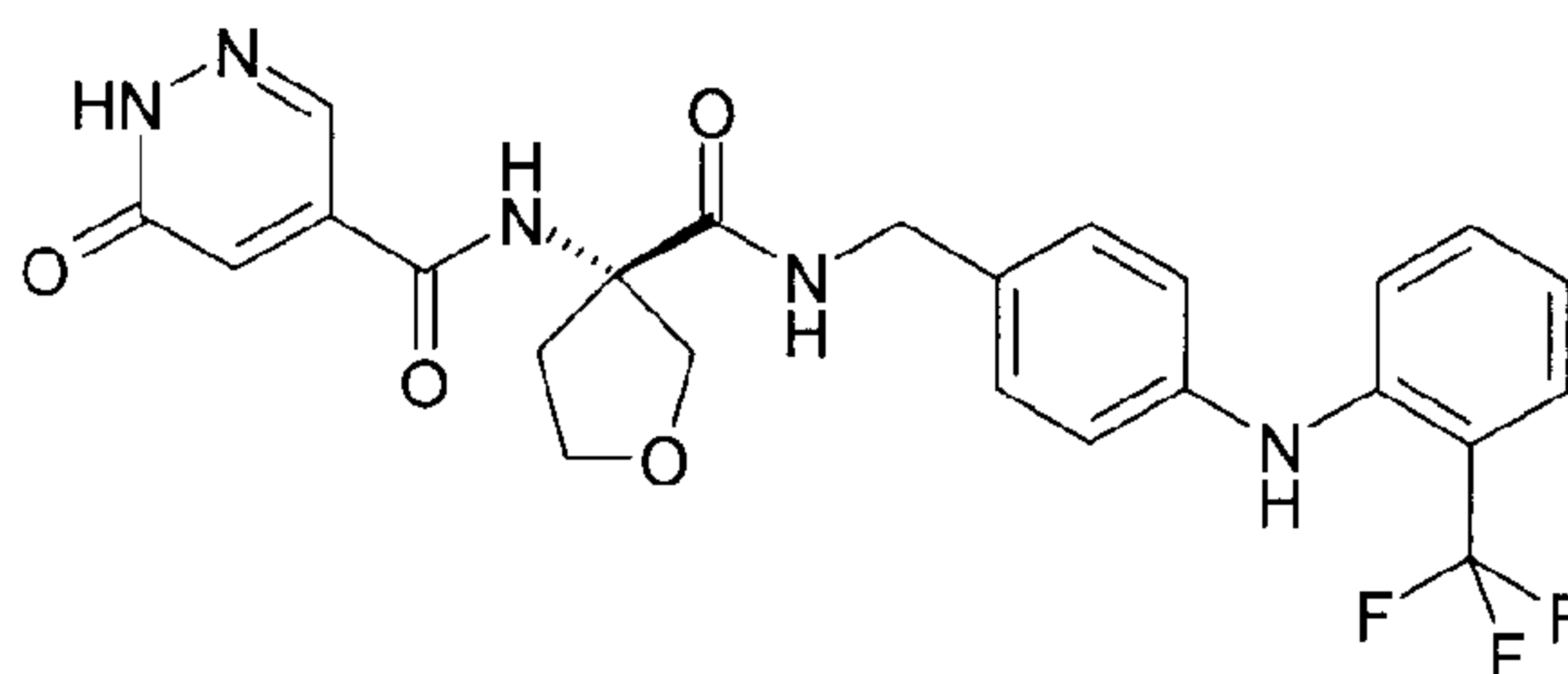
10 Prepared from intermediates A7 and B1 according to AAV1.

$C_{24}H_{21}ClF_3N_5O_4$ (535.91)

$R_t = 2.28$ minutes (method 2)

Example 5: (S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

15



Prepared from intermediates A6 and B1 according to AAV1.

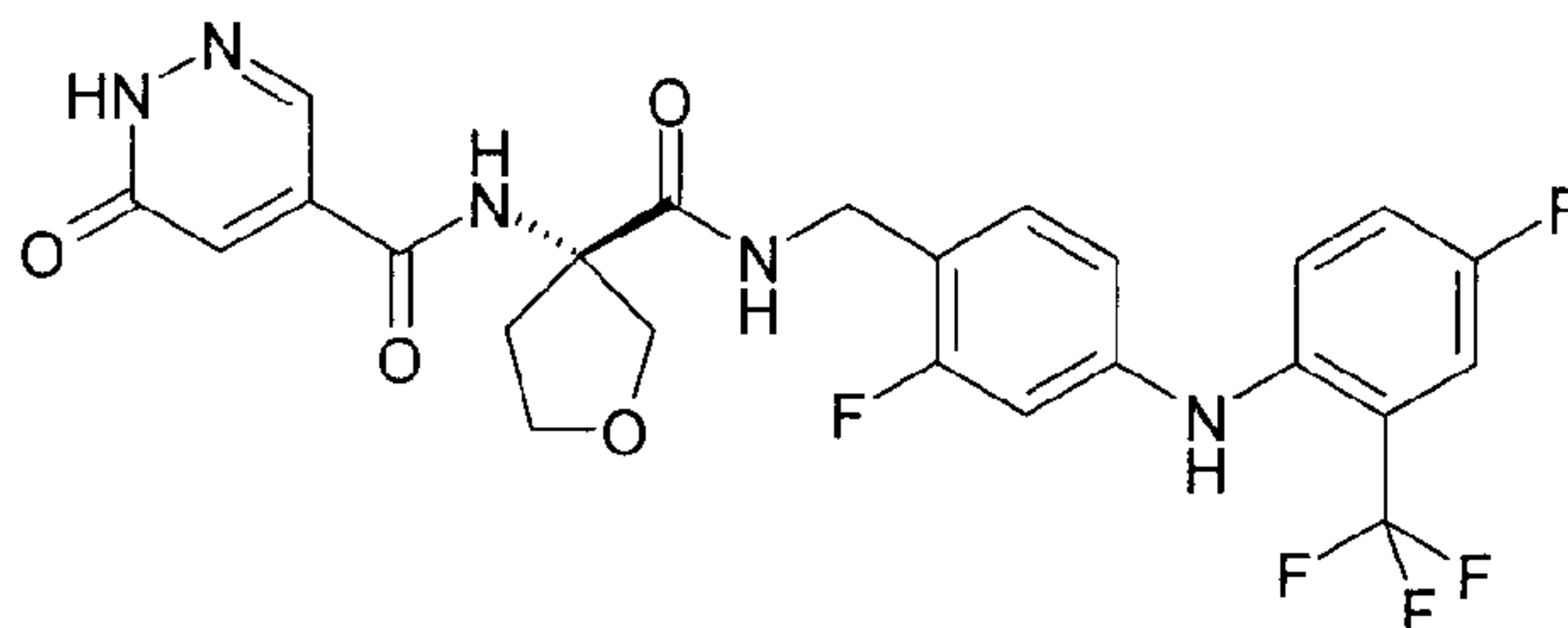
$C_{24}H_{22}F_3N_5O_4$ (501.46)

25771-2004

- 33 -

 $R_t = 2.09$ minutes (method 2)

Example 6: (S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

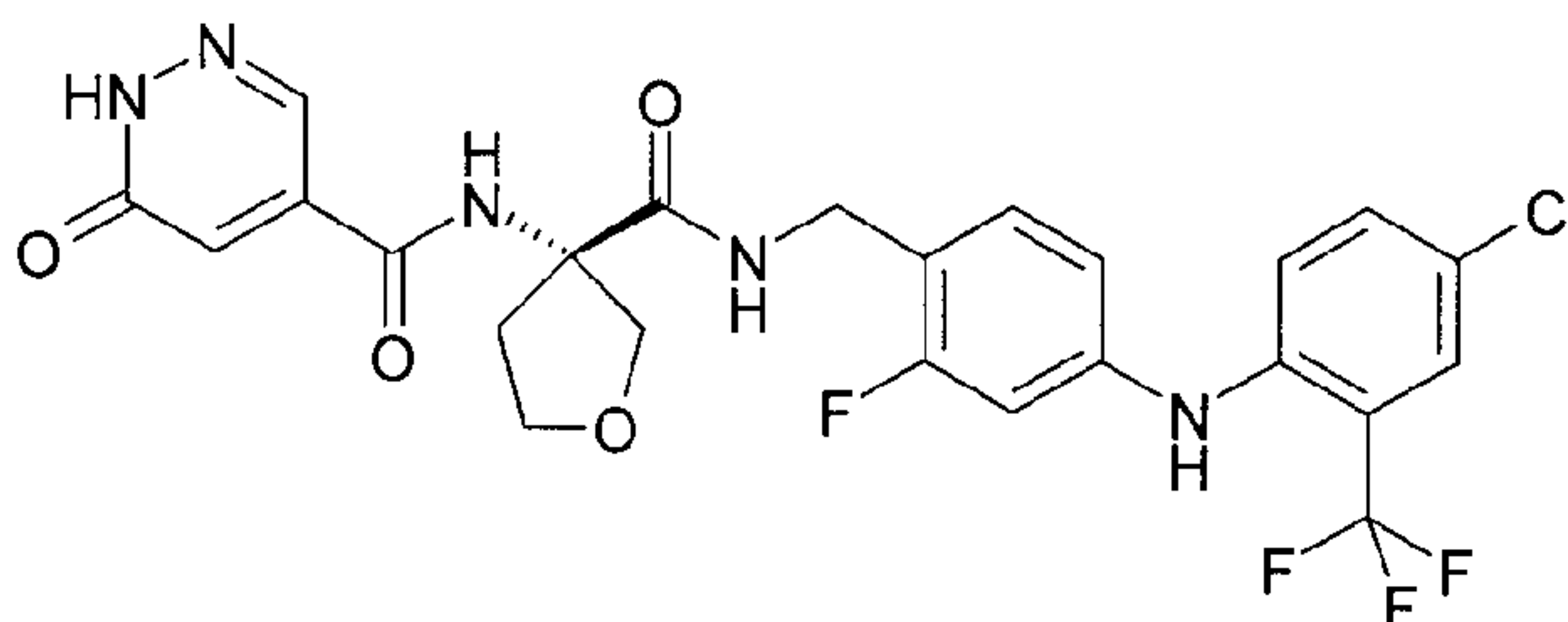


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Prepared from intermediates A4 and B1 according to AAV1.

 $C_{24}H_{20}F_5N_5O_4$ (537.44) $R_t = 2.15$ minutes (method 2)

10 **Example 7:** (S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-2-fluoro-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



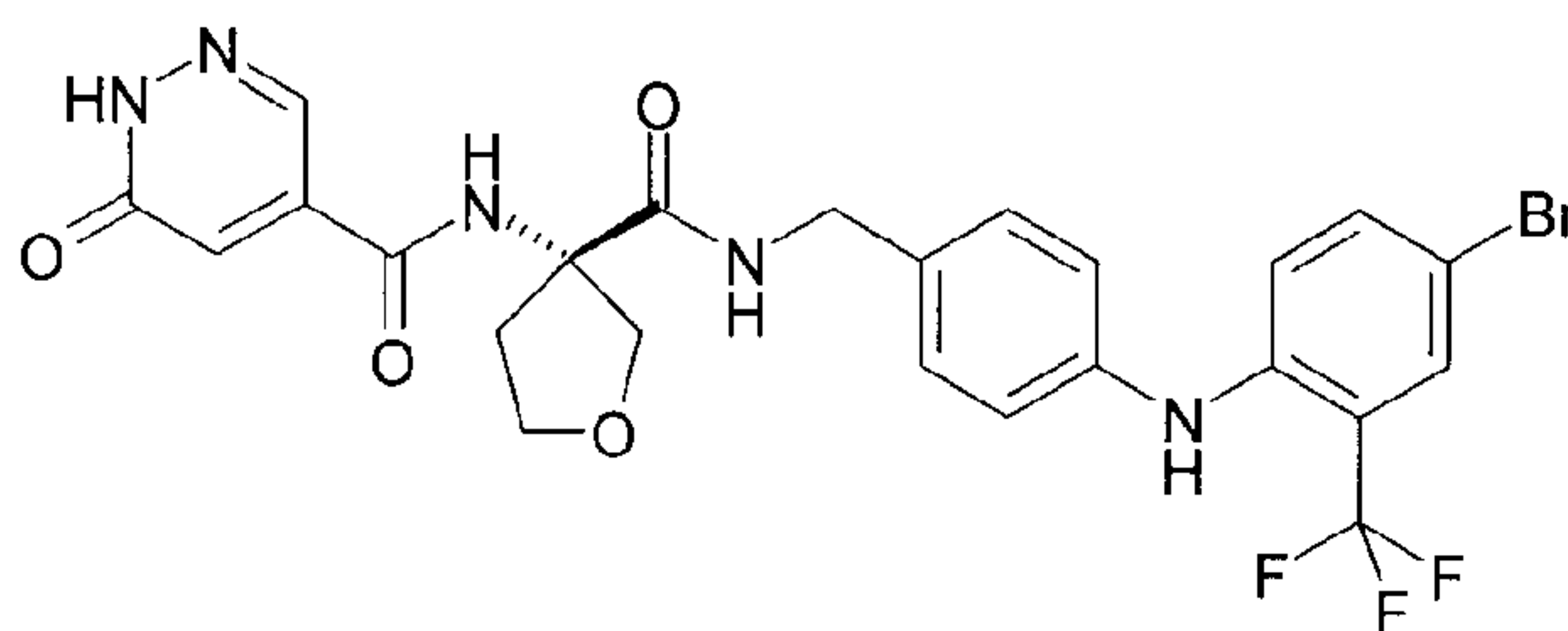
Prepared from intermediates A8 and B1 according to AAV1.

15 $C_{24}H_{20}ClF_4N_5O_4$ (553.90) $R_t = 2.31$ minutes (method 2)

Example 8: (S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-bromo-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

25771-2004

- 34 -



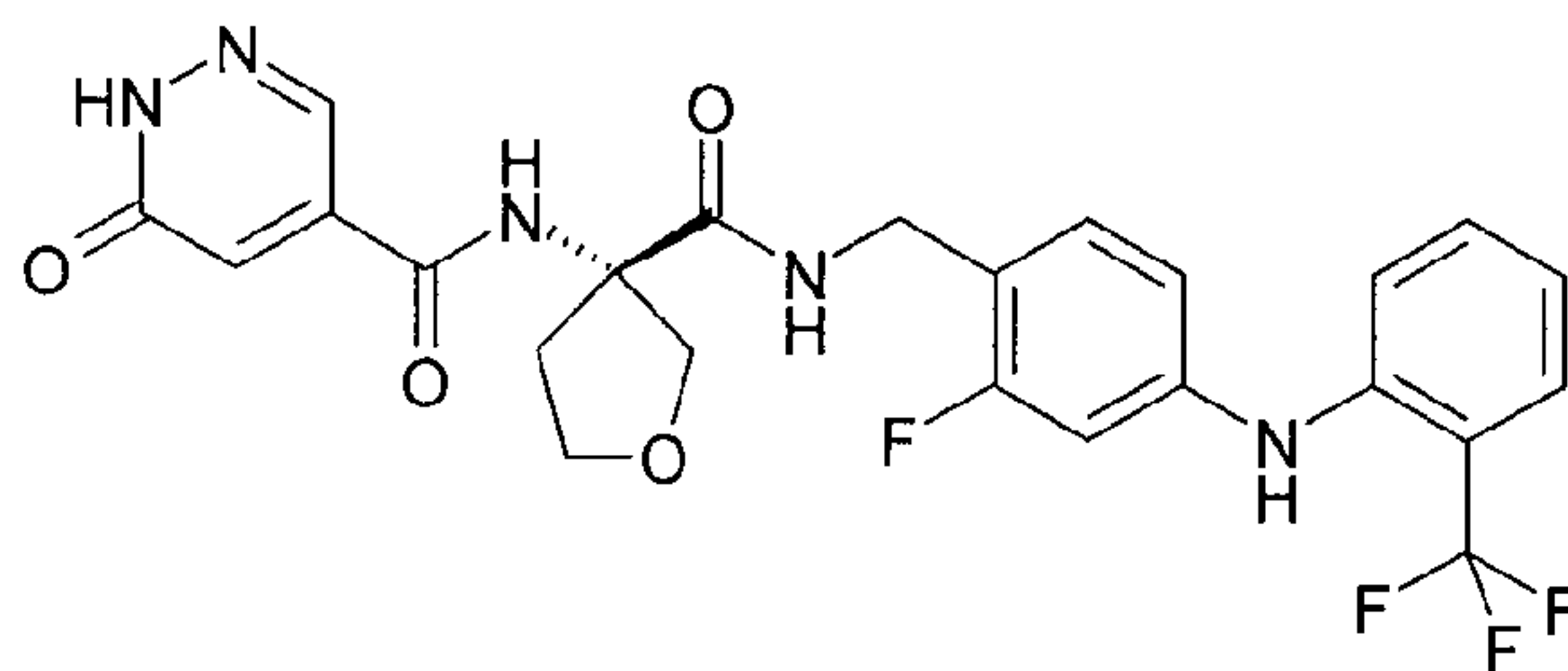
Prepared from intermediates A9 and B1 according to AAV1.

$C_{24}H_{21}BrF_3N_5O_4$ (580.35)

$R_t = 2.32$ minutes (method 2)

5

Example 9: (S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid {3-[2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-amide



Prepared from intermediates A5 and B1 according to AAV1.

10 $C_{24}H_{21}F_4N_5O_4$ (519.45)

$R_t = 1.35$ minutes (method 7)

mass spectroscopy (ESI): $[M+H]^+ = 520$

$[M-H]^- = 518$

15 The following Examples describe pharmaceutical formulations which contain as active substance any desired compound of general formula I, without restricting the scope of the present invention thereto:

25771-2004

- 35 -

Example IDry ampoule with 75 mg of active compound per 10 ml

5 Composition:

Active compound	75.0 mg
Mannitol	500 mg
Water for injection	ad 10.0 ml

10

Production:

Active compound and mannitol are dissolved in water. The charged ampoules are freeze dried. Water for injection is used to dissolve to give the solution ready for use.

15 Example IITablet with 50 mg of active compound

Composition:

20	(1) Active compound	50.0 mg
	(2) Lactose	98.0 mg
	(3) Maize starch	50.0 mg
	(4) Polyvinylpyrrolidone	15.0 mg
	(5) Magnesium stearate	<u>2.0 mg</u>
25		215.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, biplanar with a bevel on both sides and dividing groove on one side.

30

Diameter of the tablets: 9 mm.

25771-2004

- 36 -

Example IIITablet with 350 mg of active compound

5 Composition:

(1) Active compound	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
10 (5) Magnesium stearate	<u>4.0 mg</u>
	600.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, biplanar with a bevel on both
15 sides and dividing groove on one side.

Diameter of the tablets: 12 mm.

Example IVCapsule with 50 mg of active compound

20 Composition:

(1) Active compound	50.0 mg
(2) Maize starch dried	58.0 mg
(3) Lactose powdered	50.0 mg
25 (4) Magnesium stearate	<u>2.0 mg</u>
	160.0 mg

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

30

This powder mixture is packed into hard gelatine two-piece capsules of size 3 in a capsule-filling machine.

25771-2004

- 37 -

Example VCapsules with 350 mg of active compound

Composition:

5	(1) Active compound	350.0 mg
	(2) Maize starch dried	46.0 mg
	(3) Lactose powdered	30.0 mg
	(4) Magnesium stearate	<u>4.0 mg</u>
		430.0 mg

10

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous stirring.

15 This powder mixture is packed into hard gelatine two-piece capsules of size 0 in a capsule-filling machine.

Example VI20 Suppositories with 100 mg of active compound

1 suppository comprises:

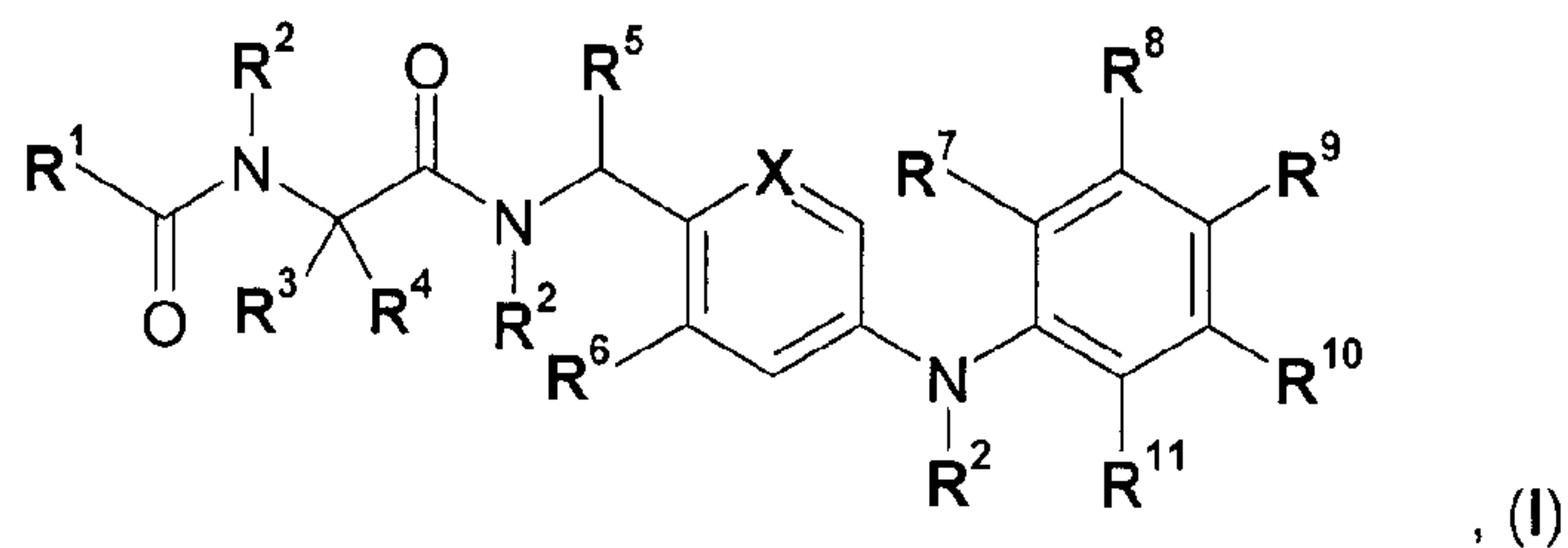
	Active compound	100.0 mg
	Polyethylene glycol (M.W. 1500)	600.0 mg
	Polyethylene glycol (M.W. 6000)	460.0 mg
25	Polyethylene sorbitan monostearate	<u>840.0 mg</u>
		2000.0 mg

25771-2004

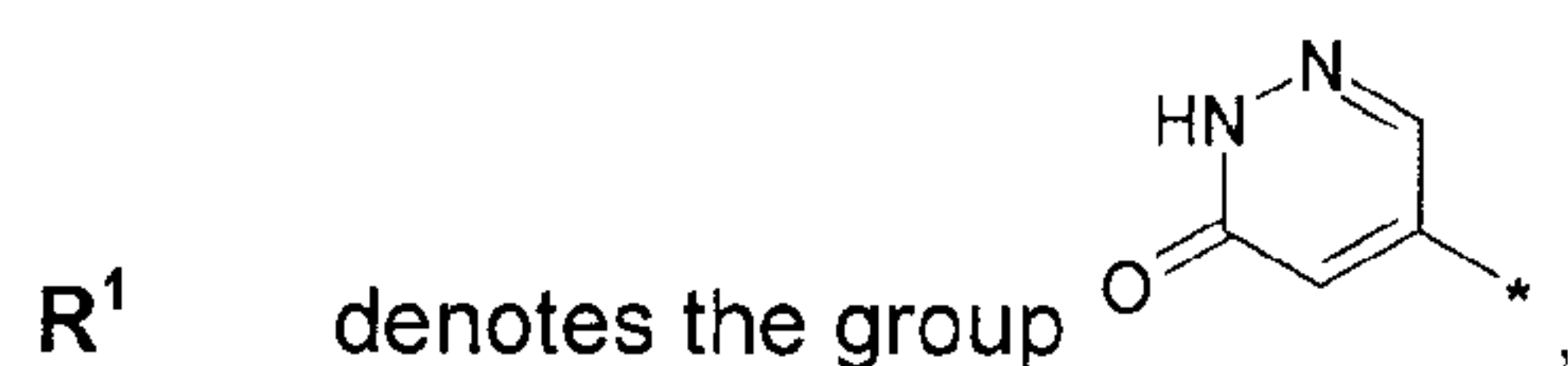
- 38 -

CLAIMS:

1. Compounds of general formula I



5 wherein



R^2 denotes H or CH_3 ,

10

R^3 and R^4 together with the carbon atom to which they are bound denote a C_{3-6} -cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

R^5 denotes H or CH_3 ,

15

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, $-CN$, C_{1-4} -alkyl, CF_3 , CHF_2 ,

20

R^8 denotes H,

R^9 denotes F, Cl, Br, C_{1-4} -alkyl, $-O-C_{1-4}$ -alkyl, $-S-C_{1-4}$ -alkyl,

R^{10} denotes H,

25

R^{11} denotes F, Cl, Br, $-CN$, C_{1-4} -alkyl, CF_3 , CHF_2 , and

25771-2004

- 39 -

X denotes CH or N,

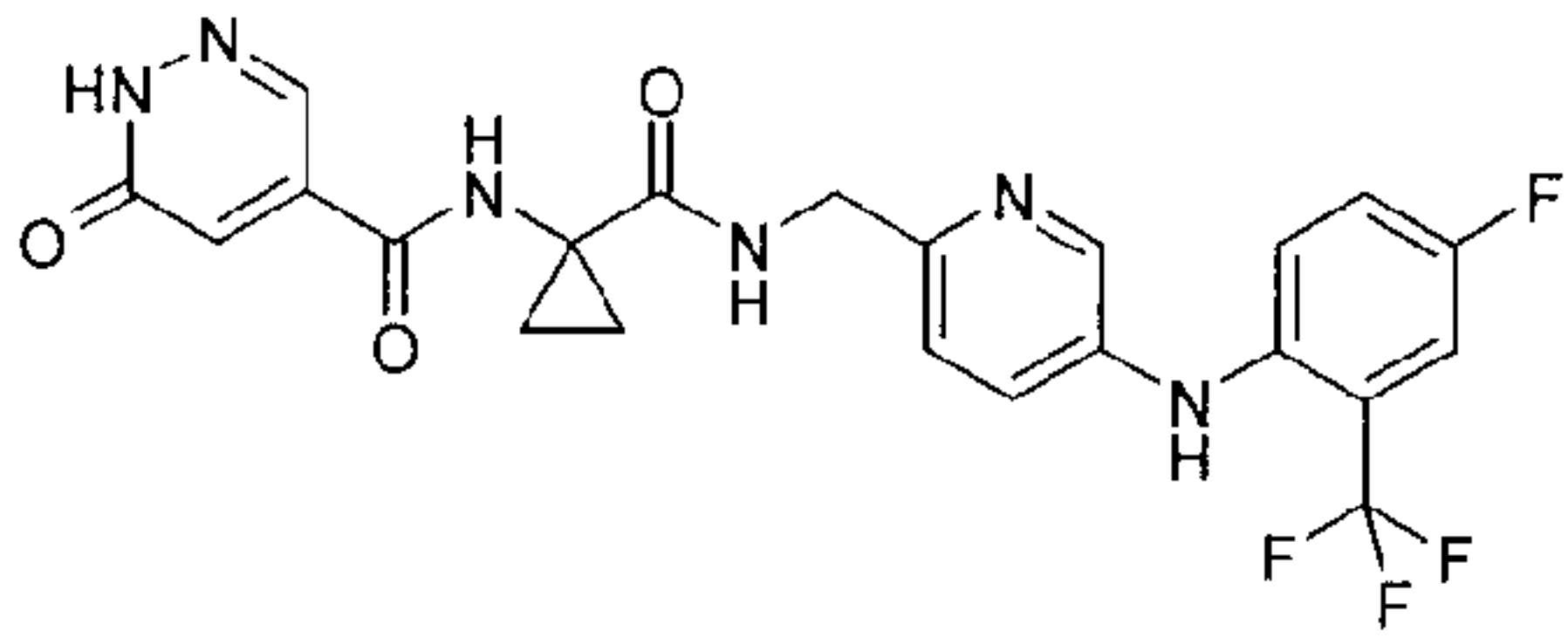
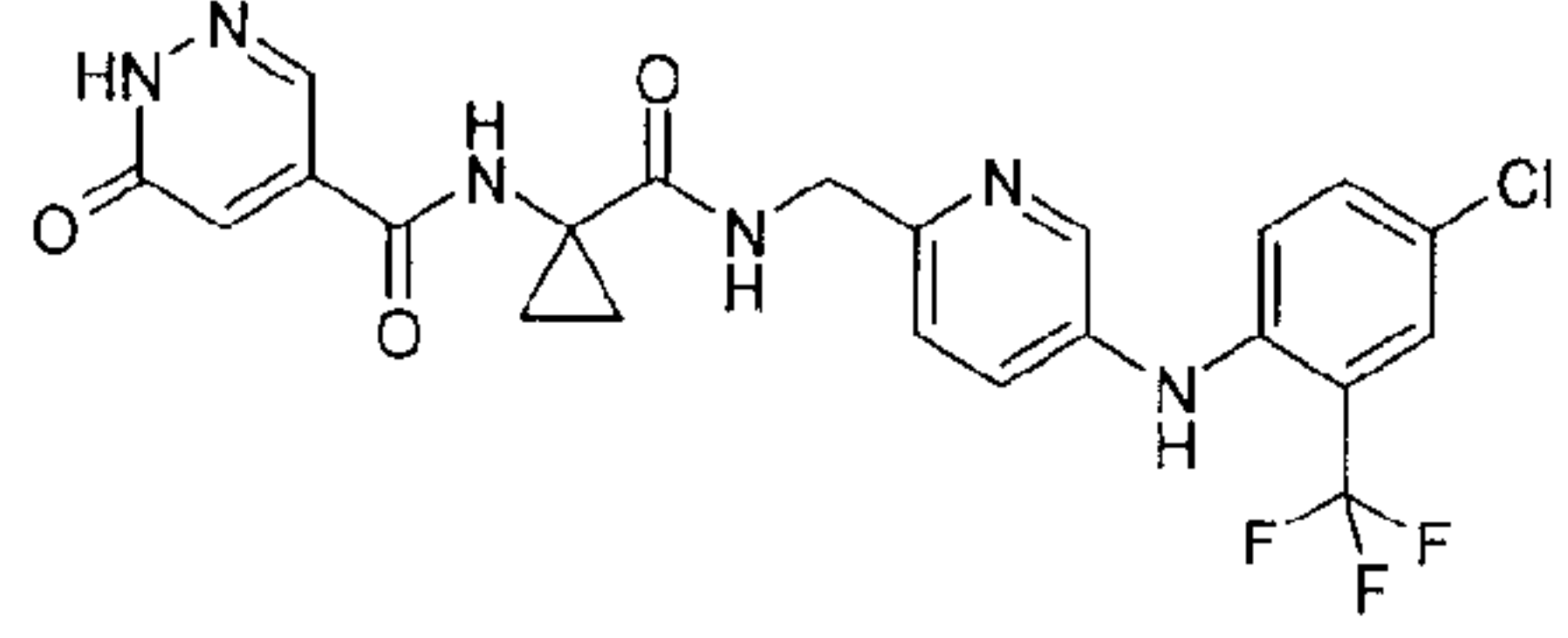
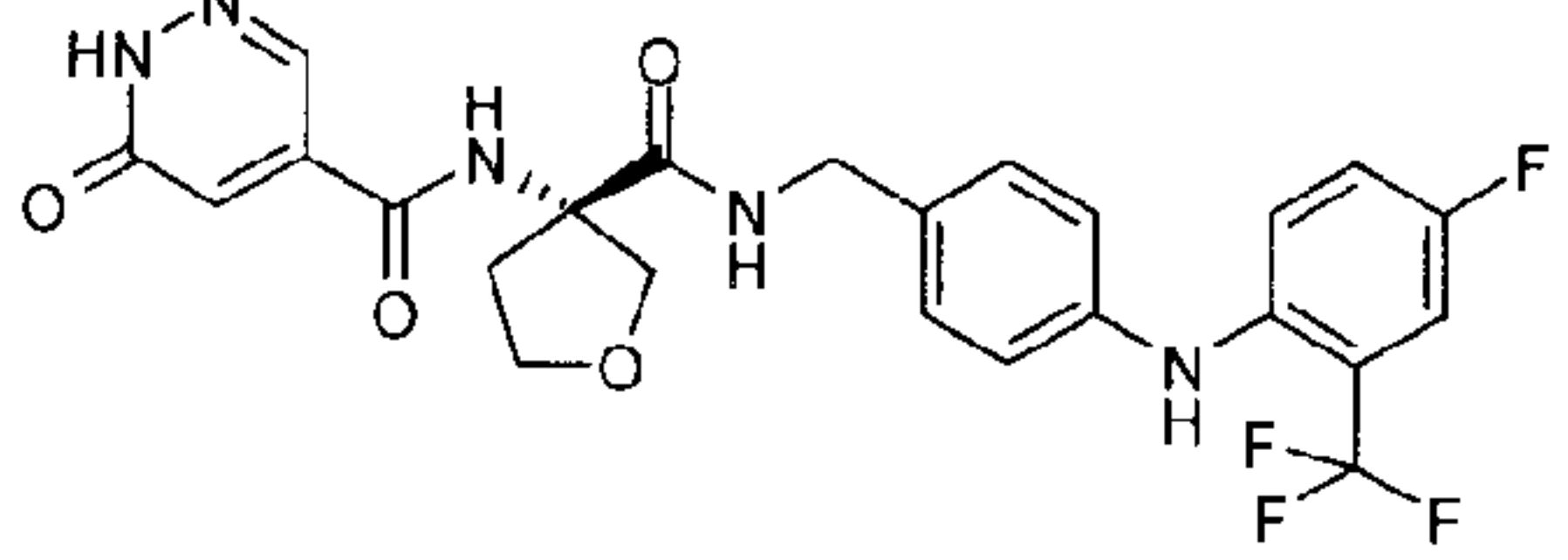
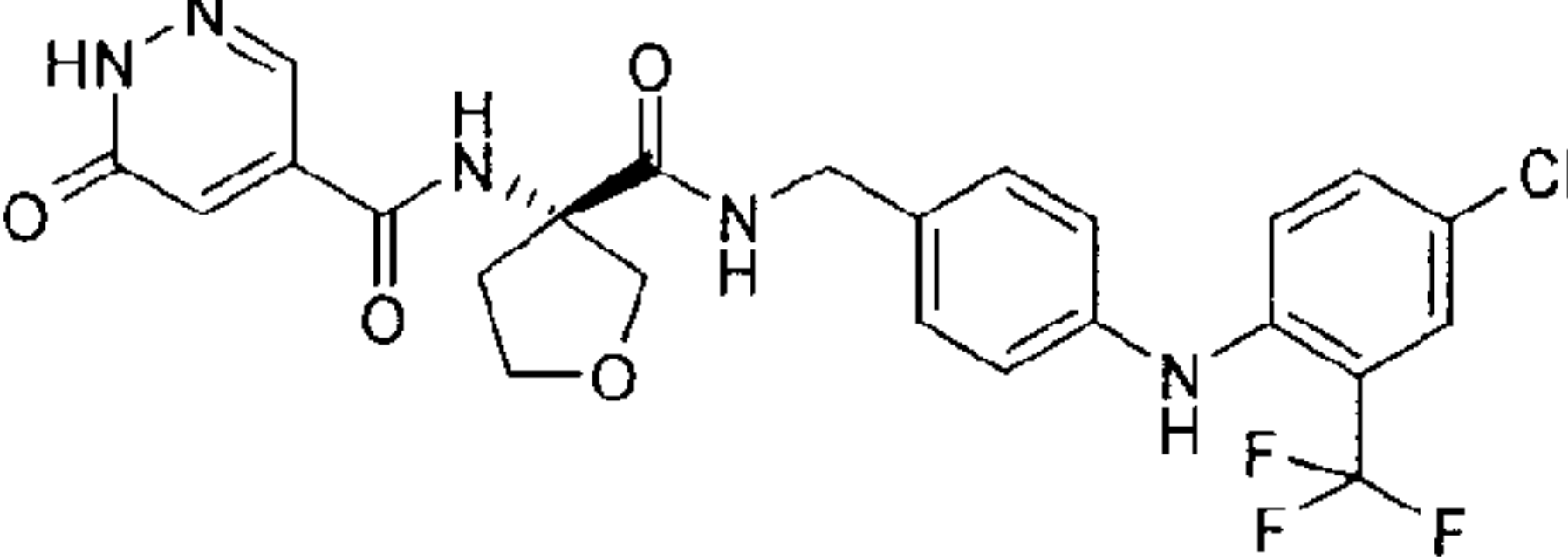
the enantiomers, the diastereomers, the mixtures and the salts thereof.

- 5 2. Compounds of general formula I according to claim 1, wherein R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , n and **X** are defined as in claim 1 and

R^2 denotes H,

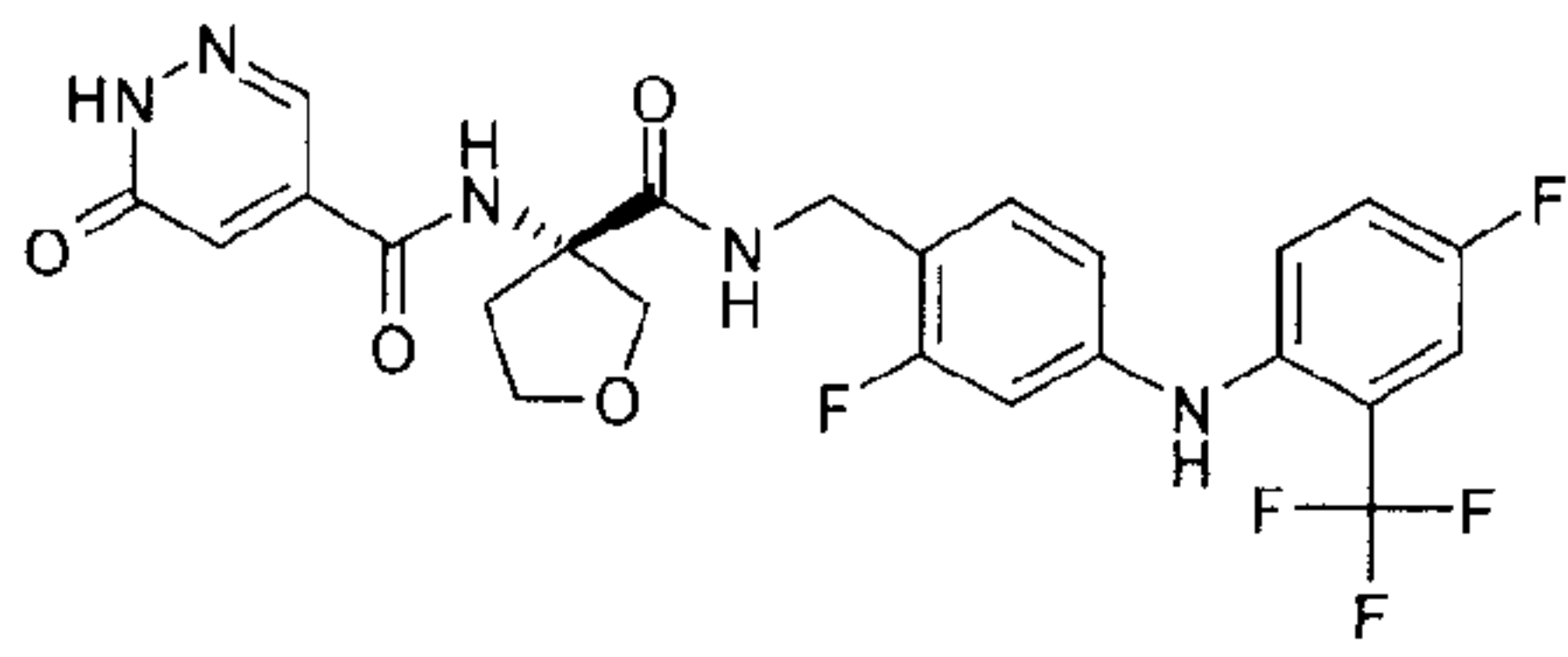
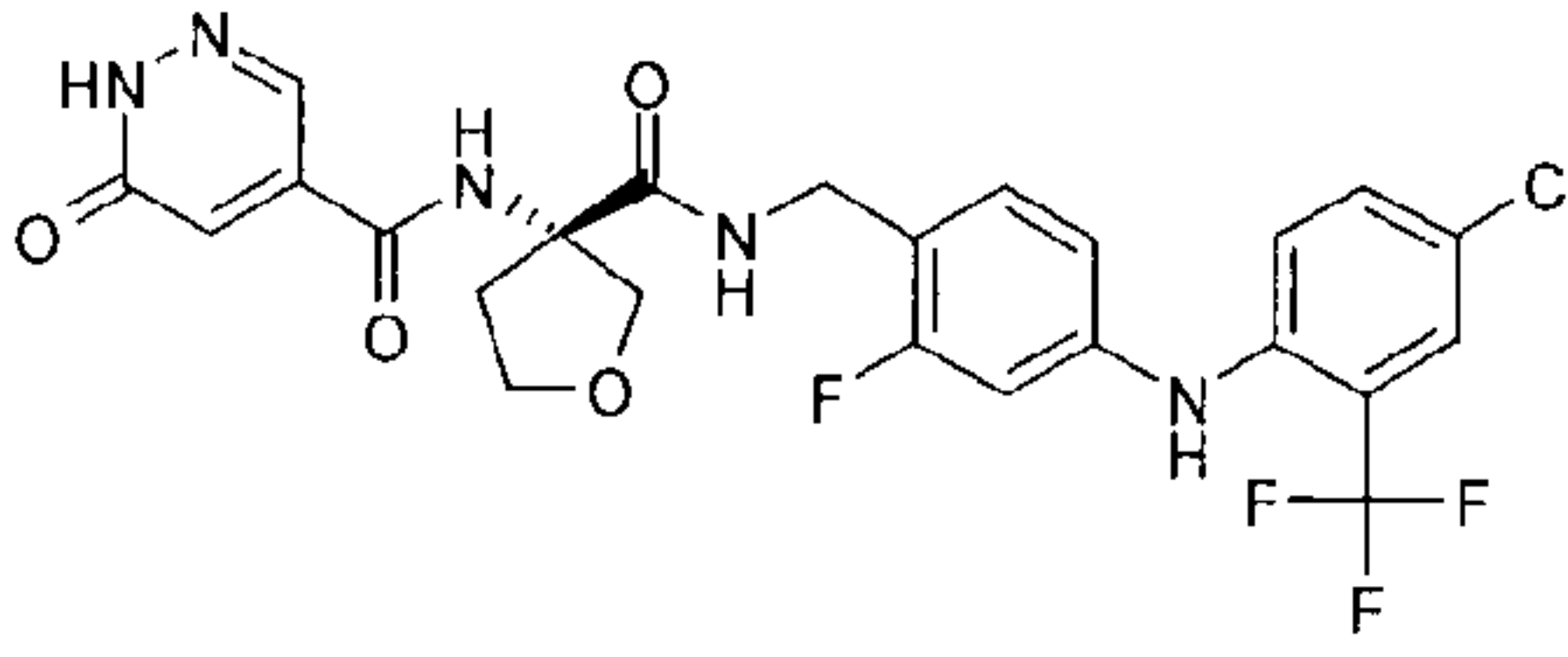
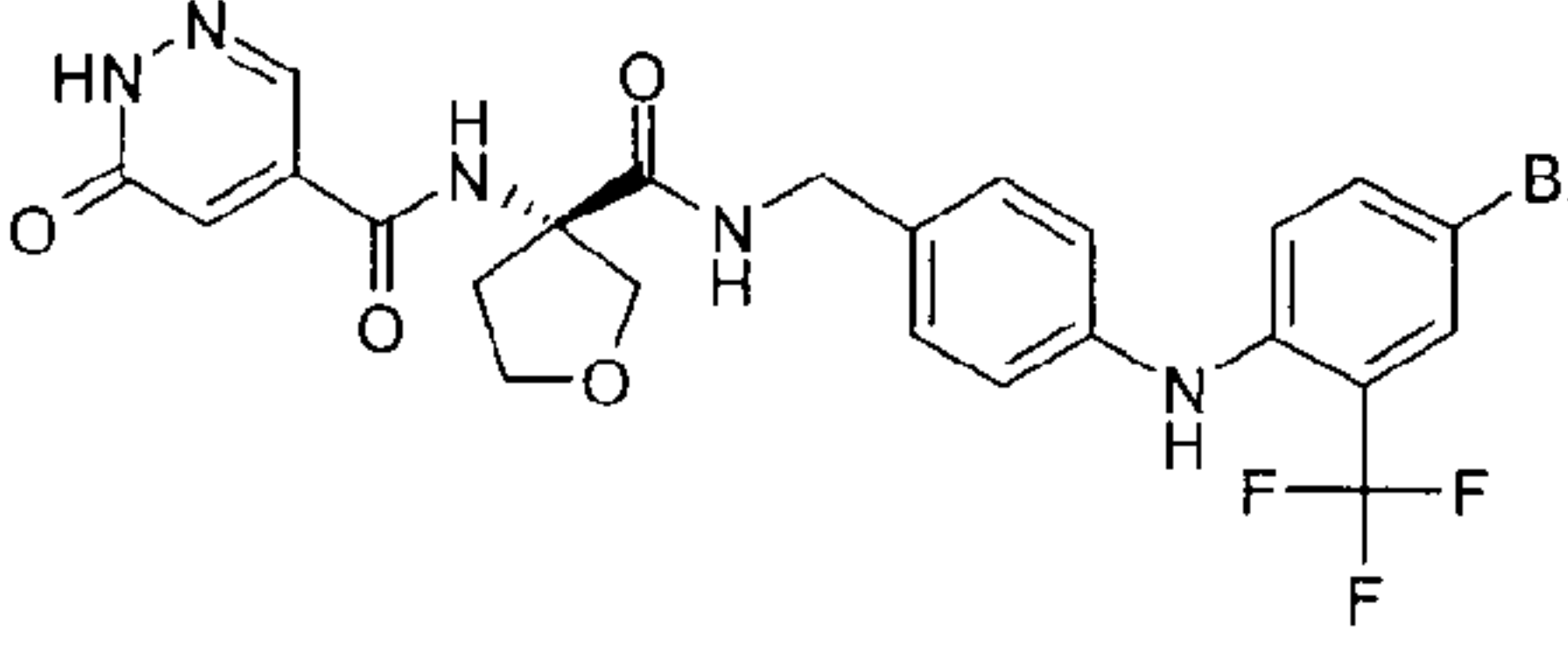
- 10 the enantiomers, the diastereomers, the mixtures and the salts thereof.

3. The following compound of general formula I according to claim 1:

No.	Structure
(1)	
(2)	
(3)	
(4)	

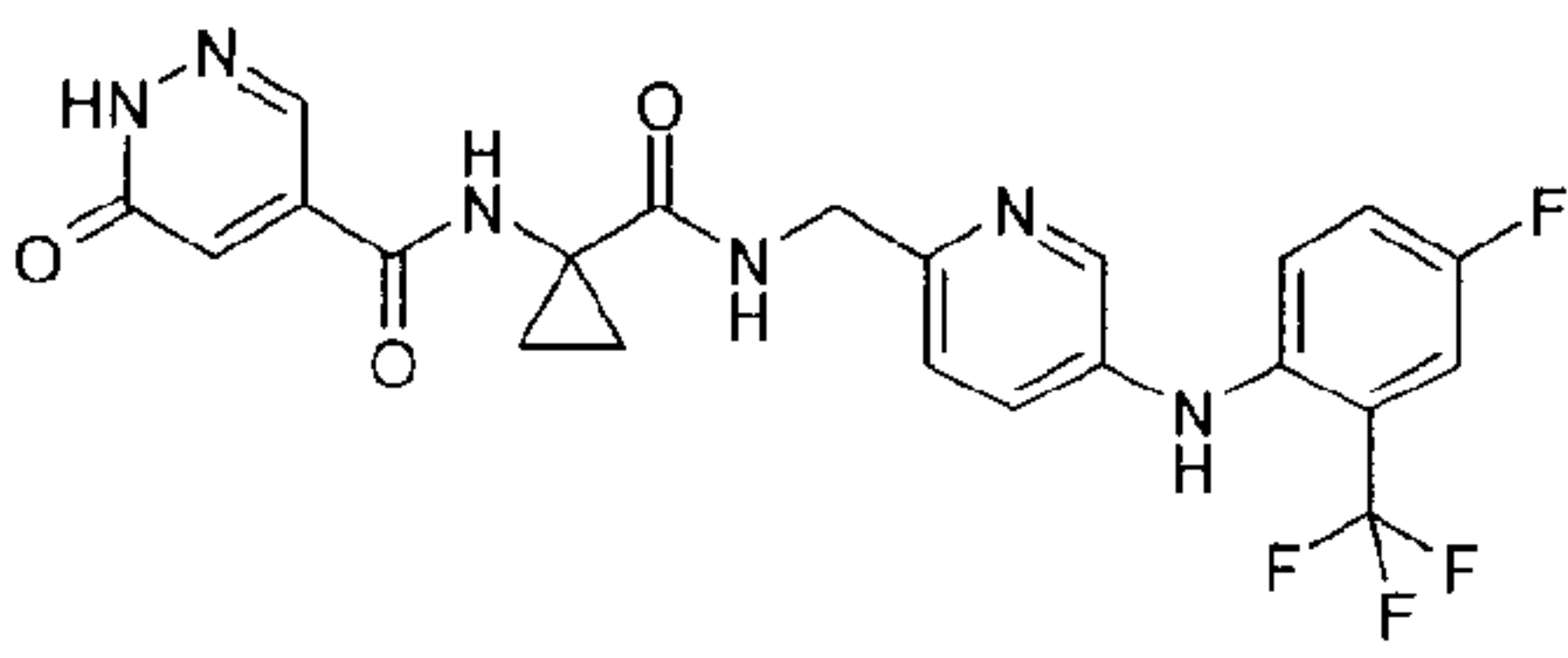
25771-2004

- 40 -

No.	Structure
(6)	
(7)	
(8)	

or

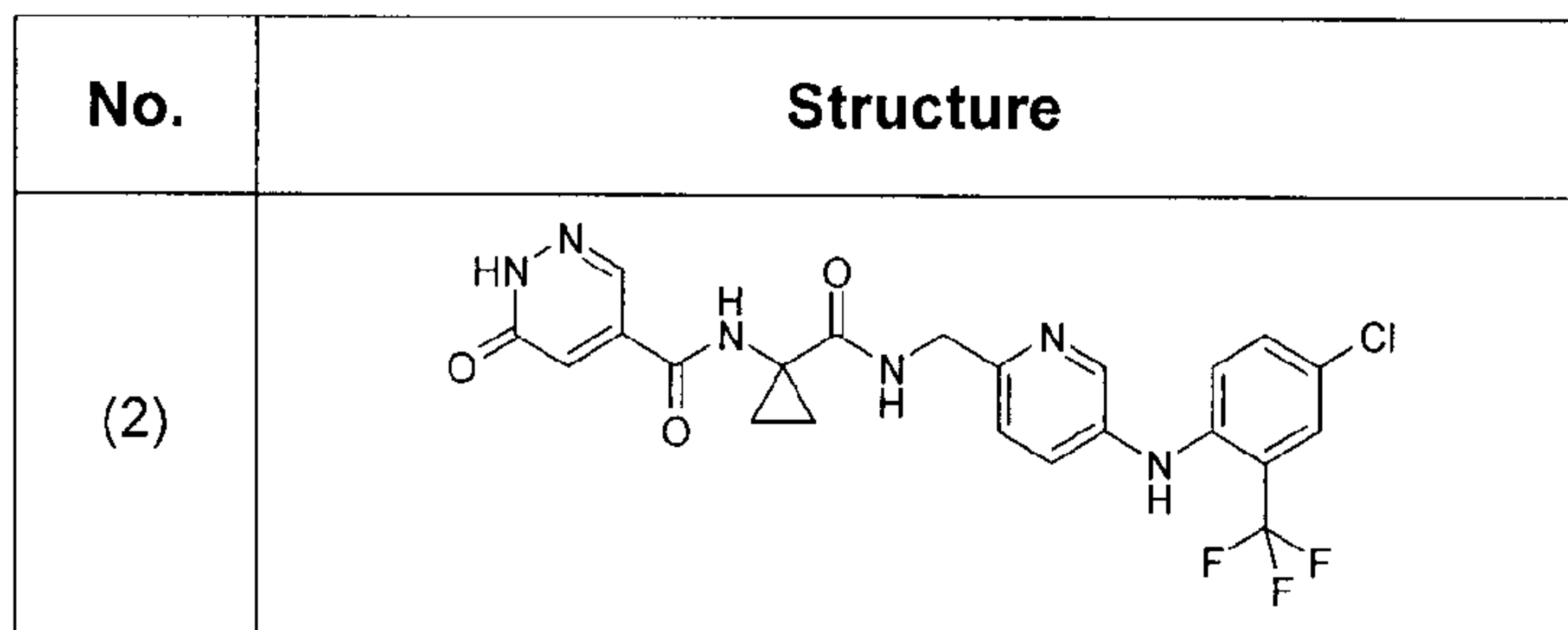
4. The compound:

No.	Structure
(1)	

25771-2004

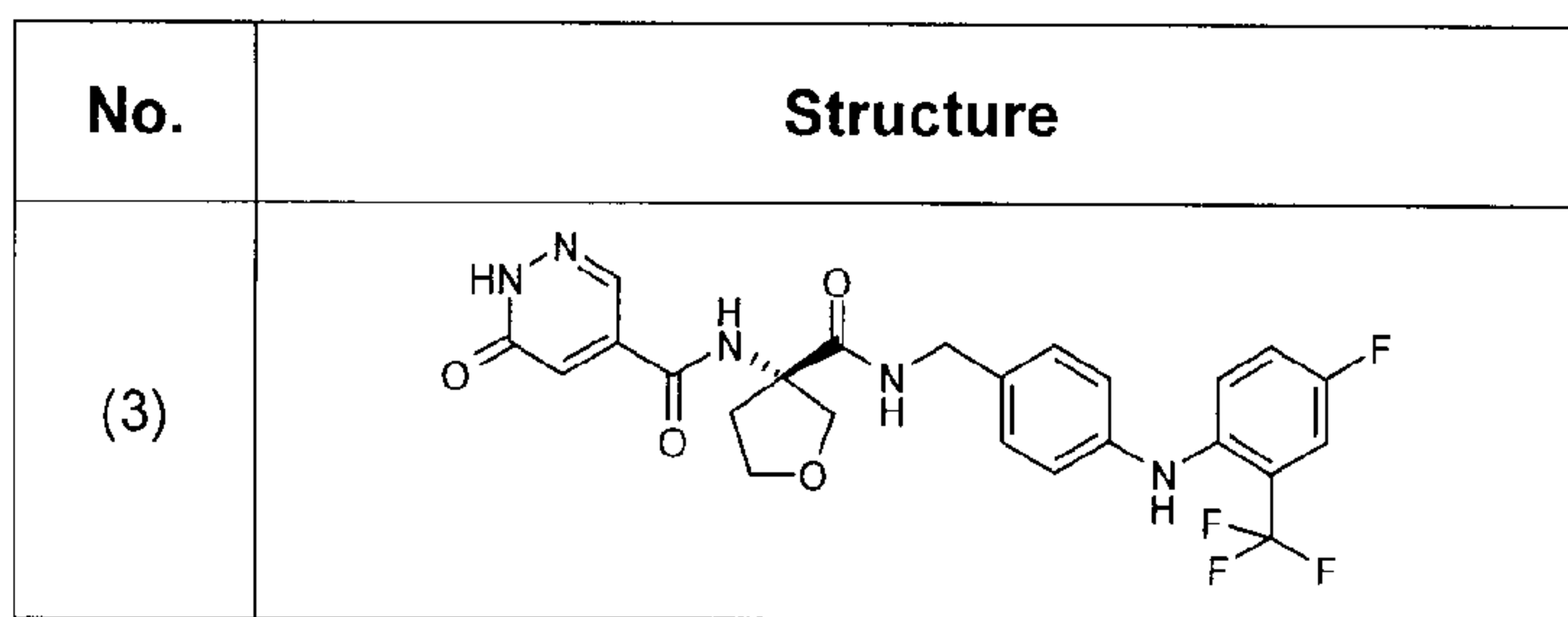
- 41 -

5. The compound:

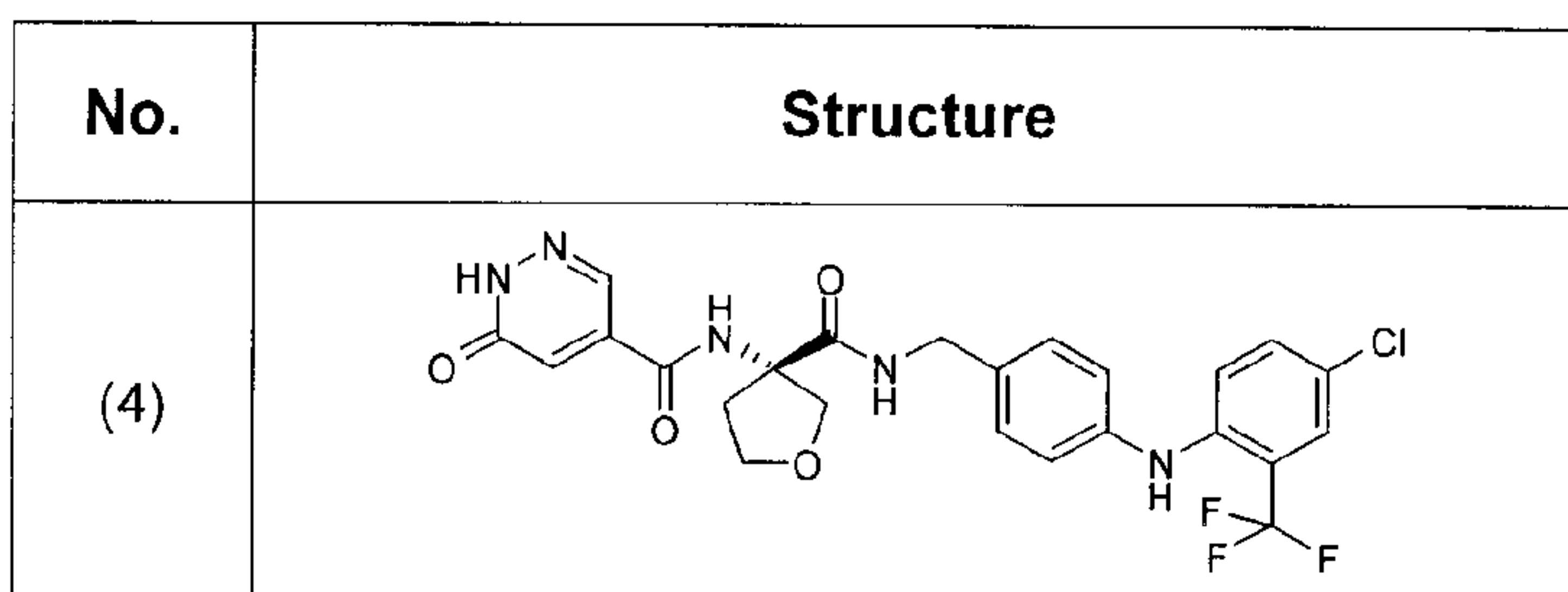


6. The compound:

5



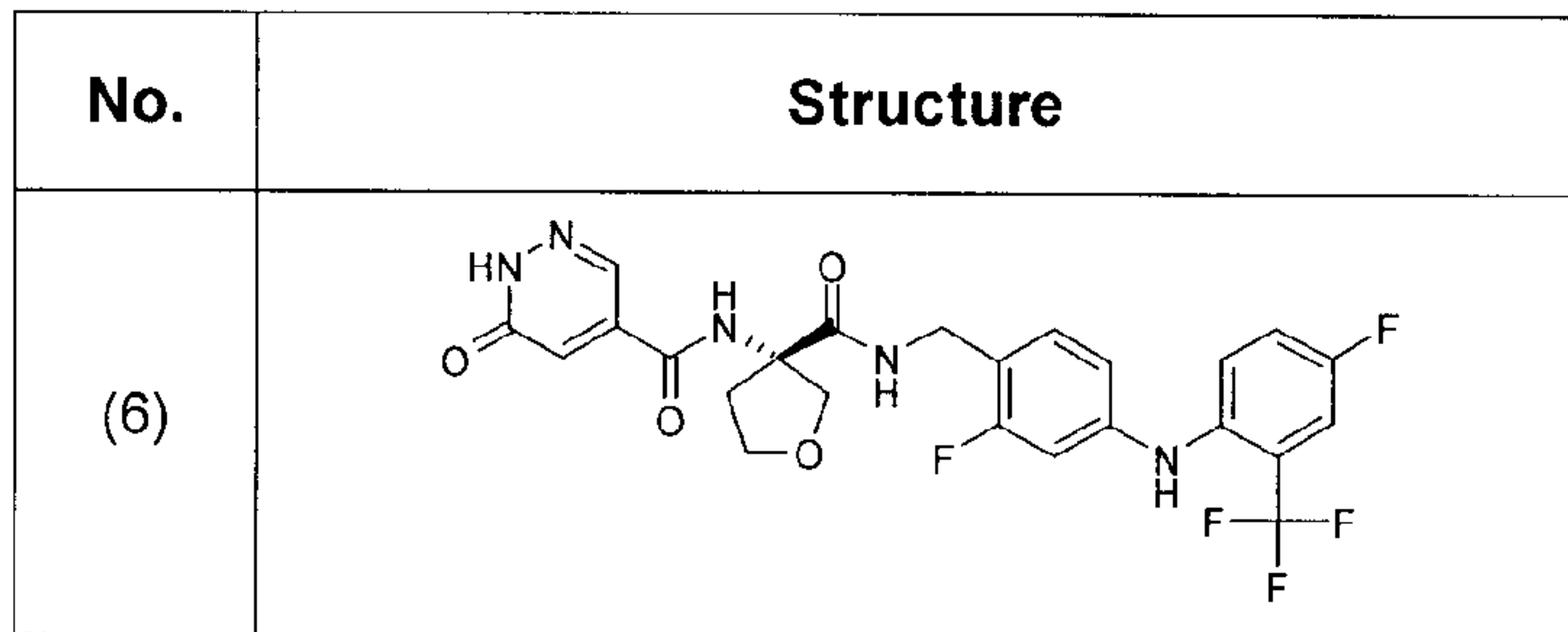
7. The compound:



25771-2004

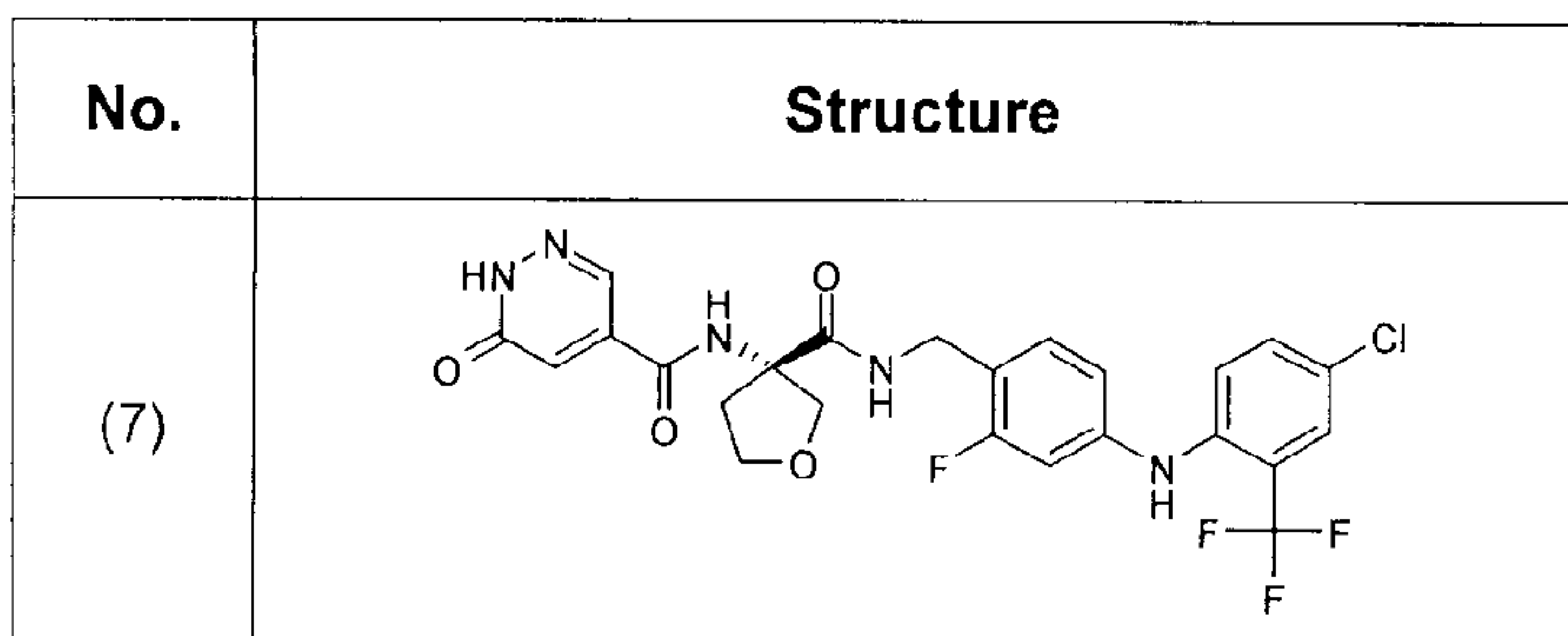
- 42 -

8. The compound:

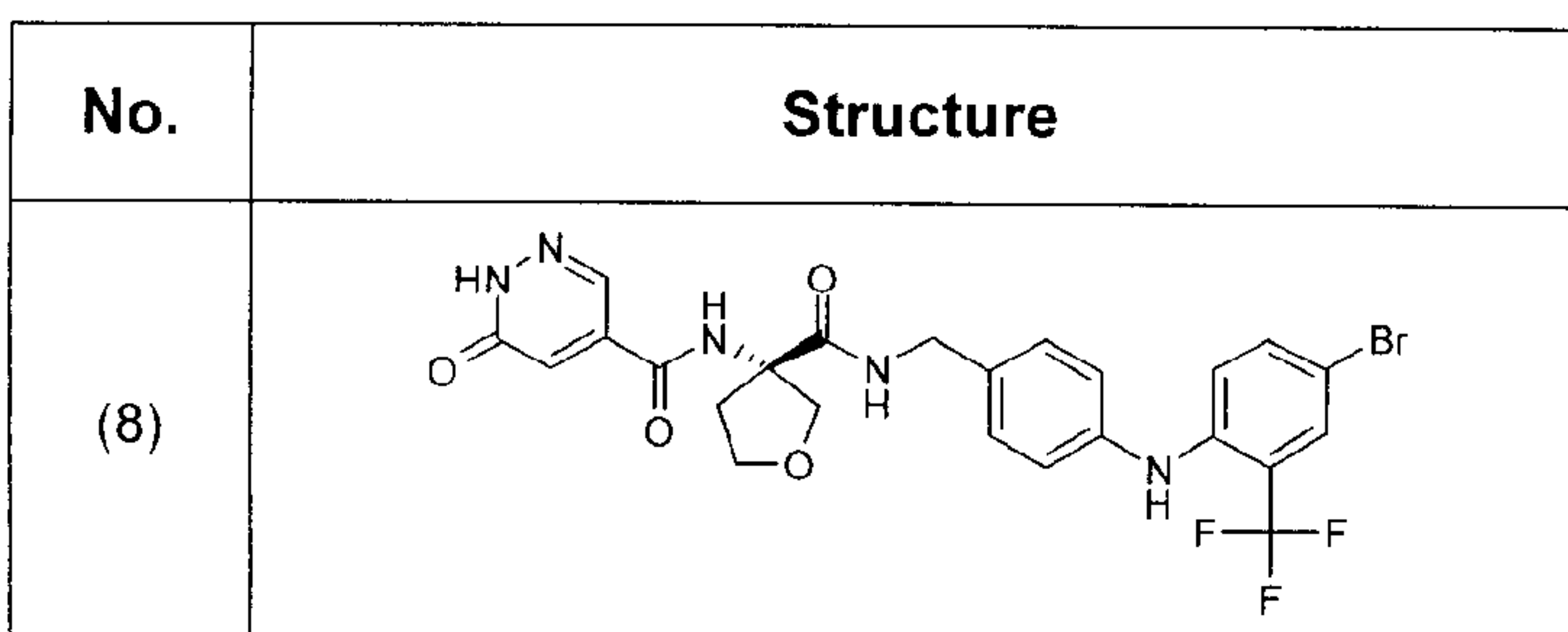


9. The compound:

5



10. The compound:



- 10 11. Physiologically acceptable salt of a compound as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 with an inorganic or organic acid or base.

25771-2004

- 43 -

12. Pharmaceutical formulation comprising a compound as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 or a physiologically acceptable salt according to claim 11 together with one or more inert carriers and/or diluents.
- 5 13. Use of a compound as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 as a bradykinin B1 antagonist.

