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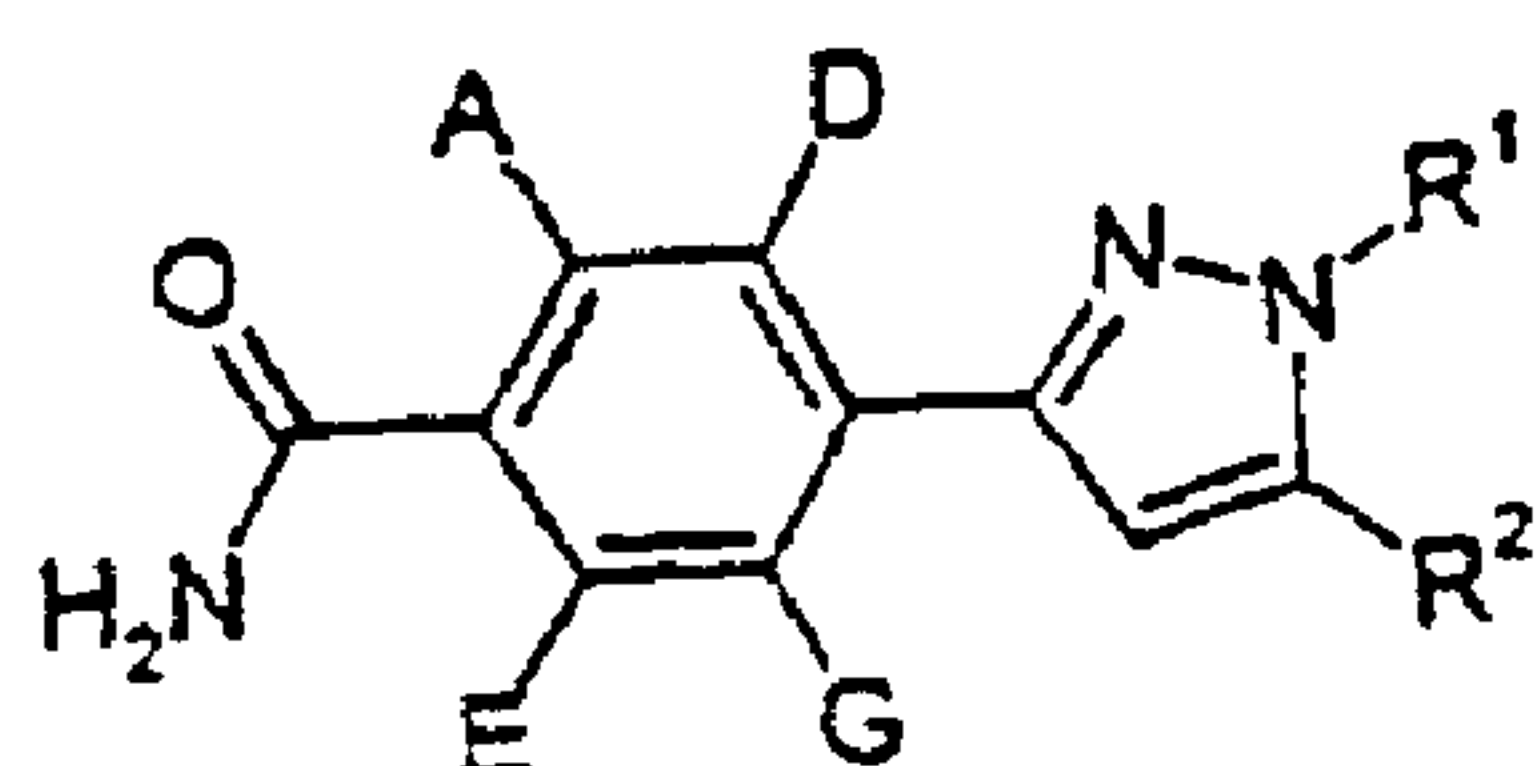
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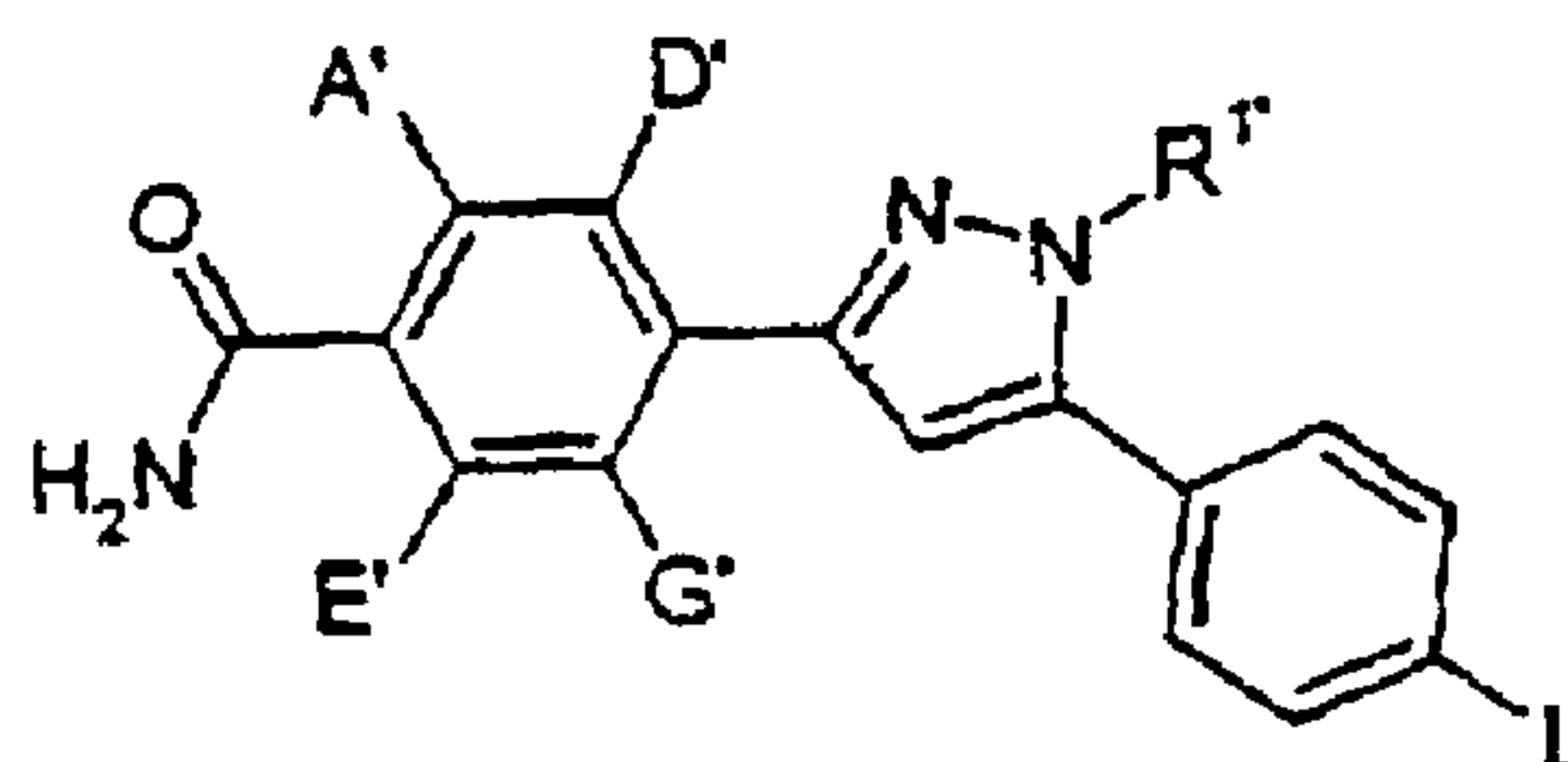
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(54) Titre : UTILISATION D'AMIDES D'ACIDES PYRAZOL-CARBOXYLIQUES

(54) Title: USE OF PYRAZOLE CARBOXAMIDES



(I)



(Ia)

(57) Abrégé/Abstract:

The present invention relates to novel and known pyrazole carboxamides of general formulae (I and Ia), whereby A, A', D, D', E, E', G, G', R¹, R₁, R₂ and L have the meaning as given in the description. The invention also relates to the production of pyrazole carboxamides by means of solid phase chemistry or novel pyrazole carboxamides. The pyrazole carboxamides are used as medicaments, especially (oral) medicaments for the treatment of anaemias. Said carboxamides stimulate the EPO production (erythropoiesis) and can be used with own blood donors.



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Use of pyrazolecarboxamides

A b s t r a c t

The present invention relates to new and known pyrazolecarboxamides of the general formulae (I) and (Ia). Moreover, the preparation of the pyrazolecarboxamides either by means of solid-phase chemistry or by means of the new pyrazolecarboxylic acids is described.

The pyrazolecarboxamides are used as medicaments, in particular as medicaments for the treatment of anaemia.

Use of pyrazole-carboxamides

The present invention relates to the use of pyrazolecarboxamides for preparing medicaments for the prophylaxis and/or treatment of anaemia, to new pyrazole-carboxamides, and to processes for their preparation.

Erythropoietin (EPO) is a glycoprotein having a molecular weight of approximately 34,000 Da. Over 90% of EPO synthesis takes place in the kidney, and the EPO produced there is secreted into the blood. The primary physiological function of EPO is the regulation of erythropoiesis in the bone marrow. EPO stimulates the proliferation and maturation of the erythroid precursor cells there.

The EPO levels in the blood are normally lower; however, if the O₂ content of the blood falls, there is an increase in EPO synthesis and, as a result, also an increase in the EPO levels in the blood. This has the result that haematopoiesis is stimulated and that the haematocrit increases. As a result of this, there is an increase in the O₂ transport capacity in the blood. If the erythrocyte count is sufficient to transport enough O₂, the EPO blood concentration decreases again. An inadequate oxygen supply (hypoxia) can have a number of causes, e.g. heavy blood loss, a relatively long stay at great heights, but also renal insufficiency or bone marrow suppression.

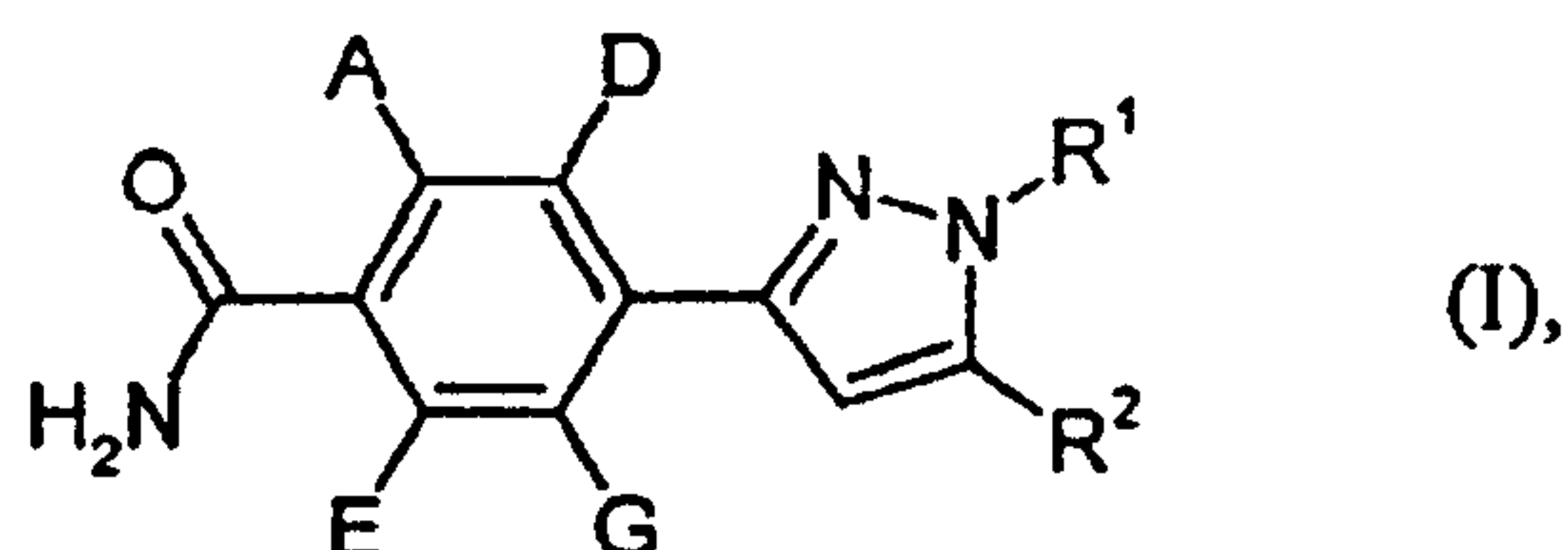
It is known that recombinant human (rh) EPO stimulates erythropoiesis and has thus found use in the therapy of severe anaemia. Furthermore, rh EPO is employed for the proliferation of endogenous blood cells in order to diminish the necessity of foreign blood transfusions.

However, severe side effects which occur on administration of rh EPO are known. These include the genesis and intensification of high blood pressure, the causing of an encephalopathy-like symptomatology up to tonic-clonic spasms and cerebral or myocardial infarct due to thromboses.

Furthermore, rh EPO is not orally available and must therefore be administered i.p., i.v. or subcutaneously, as a result of which the use is restricted to the therapy of severe anaemia.

The publication WO 97/19039 discloses substituted pyrazoles. The synthesis of the pyrazole derivatives is carried out on the solid phase. After cleavage, pyrazolephenyl-carboxamides are obtained. The use as medicaments is not described.

- 5 The present invention relates to the use of pyrazolecarboxamides of the general formula (I)



- 10 in which

A, D, E and G are identical or different and represent hydrogen, halogen, trifluoromethyl, hydroxyl or (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy,

15

R¹ represents hydrogen or (C₁-C₆)-alkyl,

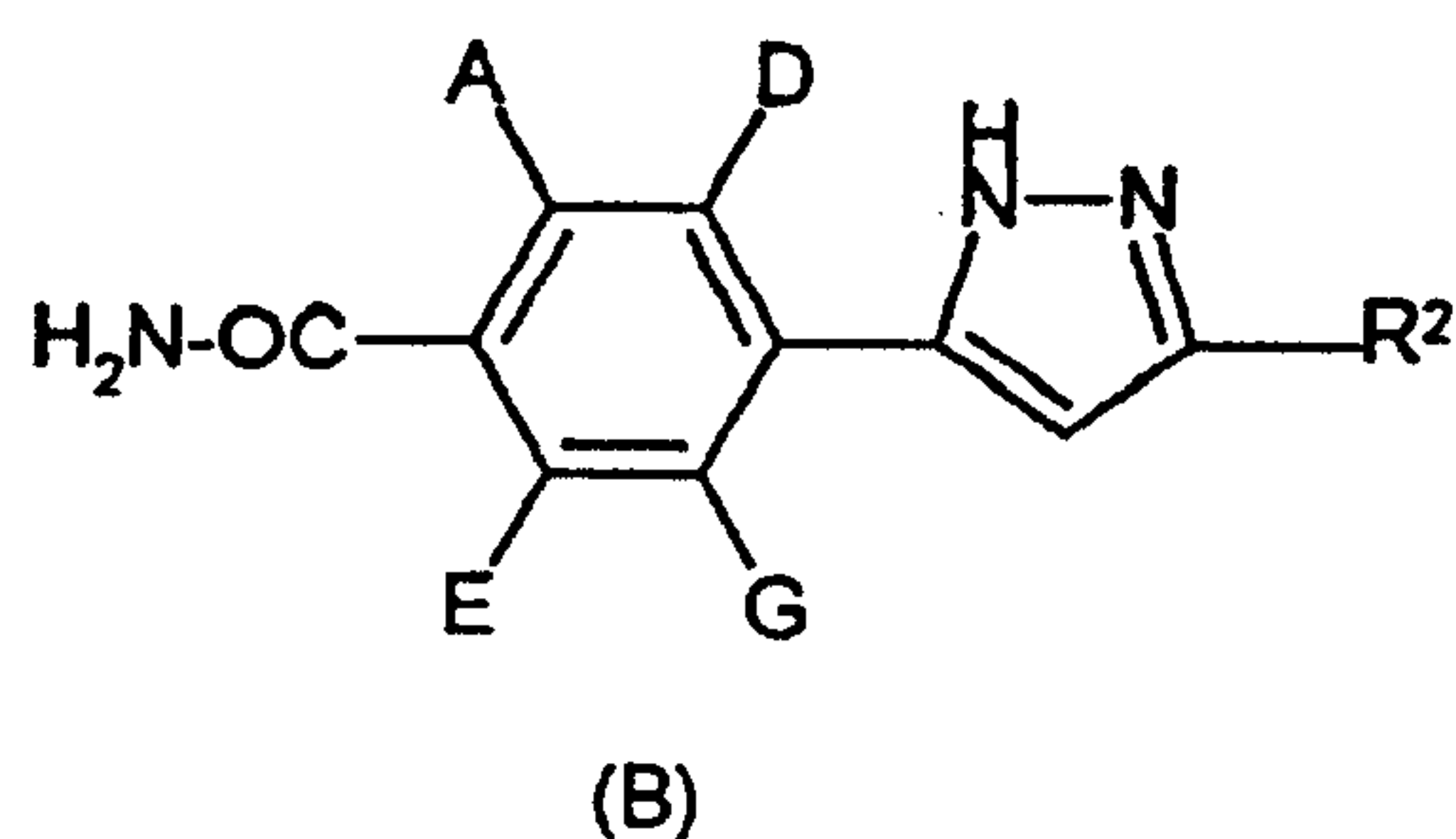
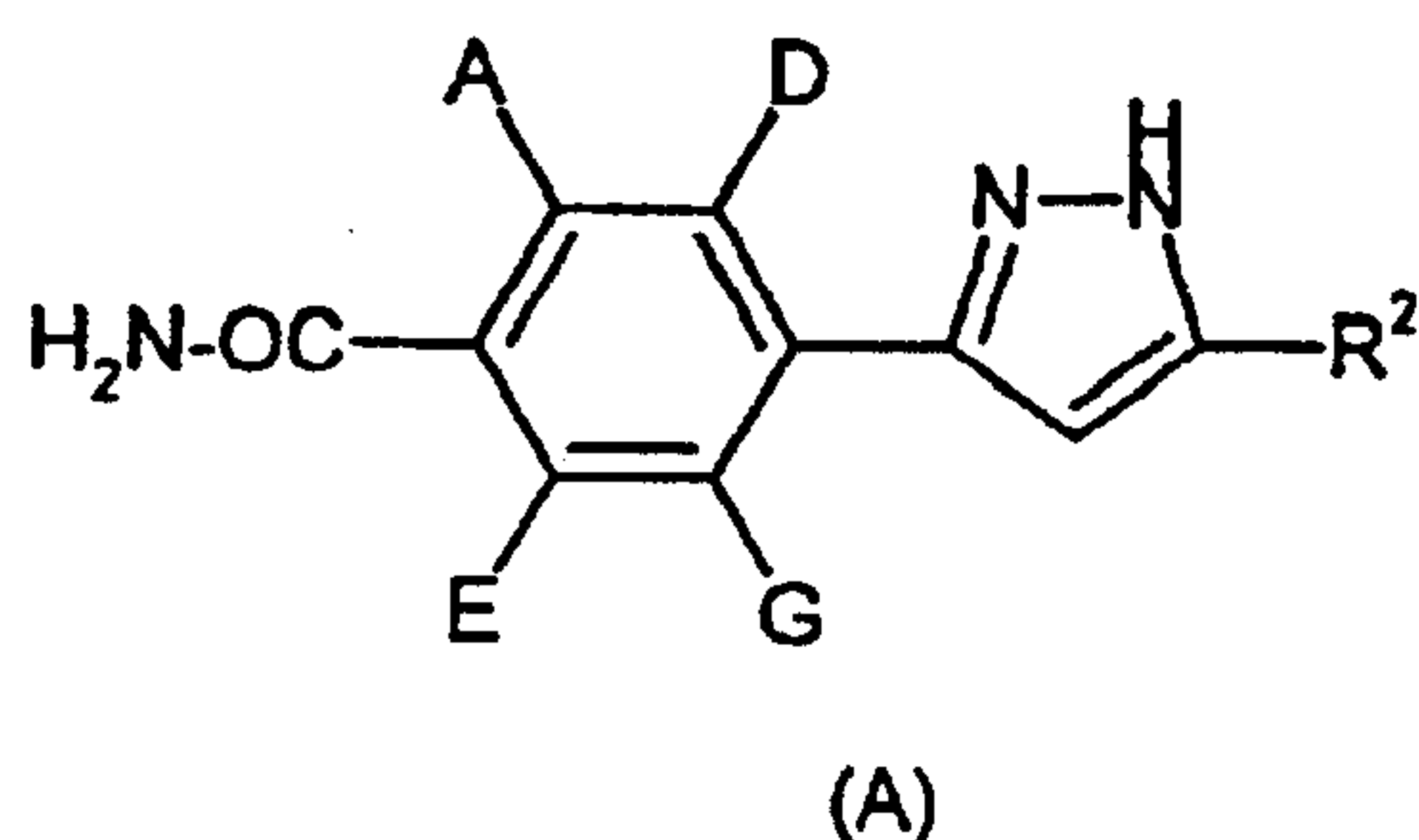
R² represents (C₆-C₁₀)-aryl or a 5- to 6-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the series S, N and/or O, where the abovementioned aromatic ring systems can optionally be substituted up to 3 times in an identical or different manner by halogen, trifluoromethyl, trifluoromethoxy, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy or (C₁-C₆)-alkoxycarbonyl,

20

- 25 and their tautomers and the respective salts,

as medicaments which are suitable for the prophylaxis and/or treatment of disorders, for example of anaemia.

- 30 In the case where R¹ represents hydrogen, tautomers of the formulae



are obtained.

- 5 Depending on the substitution pattern, the compounds can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and their respective mixtures. Like the diastereomers, the racemic forms can be separated into the stereoisomerically uniform constituents
- 10 in a known manner.

Physiologically acceptable salts of the compounds can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid,

15 hydrobromic acid, sulphuric acid, phosphoric acid, methane-sulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

- 20 Salts which can be mentioned are salts with customary bases, such as, for example, alkali metal salts (e.g. sodium or potassium salts), alkaline earth metal salts (e.g. calcium or magnesium salts) or ammonium salts derived from ammonia or organic amines such as, for example, diethylamine, triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine, 1-phenamine
- 25 or methylpiperidine.

(C₆-C₁₀)-Aryl in general represents an aromatic radical having 6 to 10 carbon atoms. Preferred aryl radicals are phenyl and naphthyl.

- 30 (C₁-C₆)-Alkyl represents a straight-chain or branched alkyl radical having 1 to 6 carbon atoms. A straight-chain or branched alkyl radical having 1 to 4 carbon atoms is preferred. Examples which may be mentioned are: methyl, ethyl, n-propyl,

isopropyl, tert-butyl, n-pentyl and n-hexyl. A straight-chain or branched alkyl radical having 1 to 3 carbon atoms is particularly preferred.

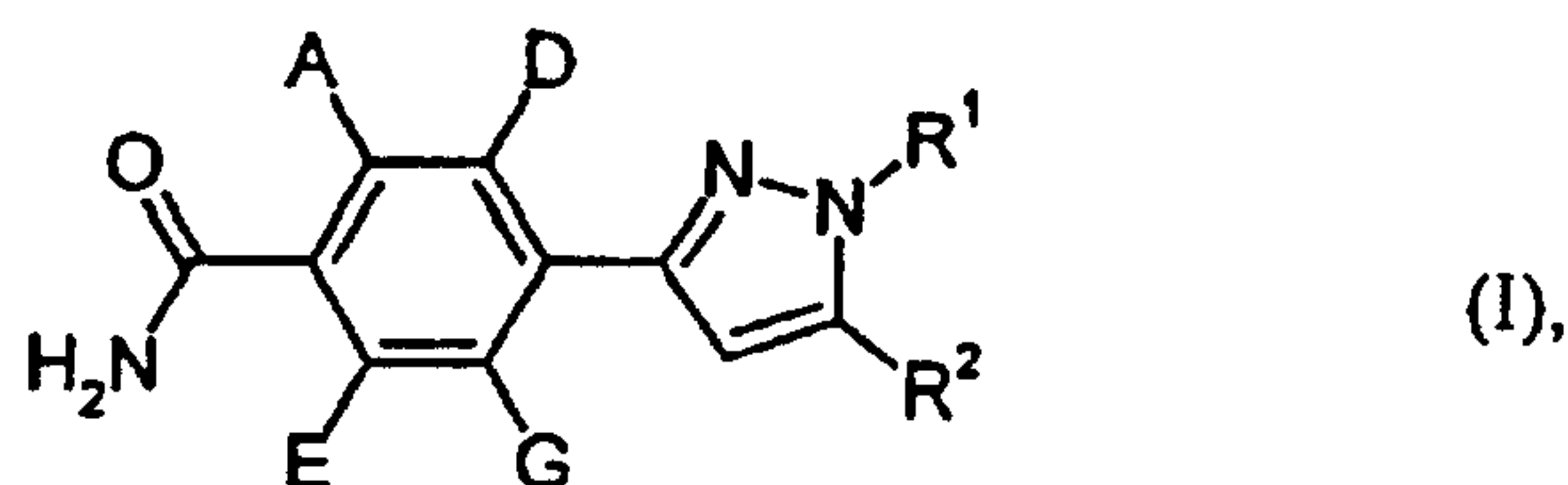
- 5 (C₁-C₆)-Alkoxy represents a straight-chain or branched alkoxy radical having 1 to 6 carbon atoms. A straight-chain or branched alkoxy radical having 1 to 4 carbon atoms is preferred. Examples which may be mentioned are: methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy. A straight-chain or branched alkoxy radical having 1 to 3 carbon atoms is particularly preferred.
- 10 (C₁-C₆)-Alkoxycarbonyl represents a straight-chain or branched alkoxycarbonyl radical having 1 to 6 carbon atoms. A straight-chain or branched alkoxycarbonyl radical having 1 to 4 carbon atoms is preferred. Examples which may be mentioned are: methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and tert-butoxycarbonyl. A straight-chain or branched alkoxycarbonyl radical having 1 to 3 carbon atoms is particularly preferred.
- 15

20 A 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the series S, O and/or N represents, for example, pyridyl, pyrimidyl, pyridazinyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl or imidazolyl. Pyridyl, pyrimidyl, pyridazinyl, furyl and thienyl are preferred.

A 5- to 6-membered aromatic benzo-fused heterocycle having up to 3 heteroatoms from the series S, O and/or N represents, for example, benzothiophene, indole, quinoline or benzofuran. Benzothiophene and quinoline are preferred.

25

Compounds preferably used are those of the general formula (I)



in which

30

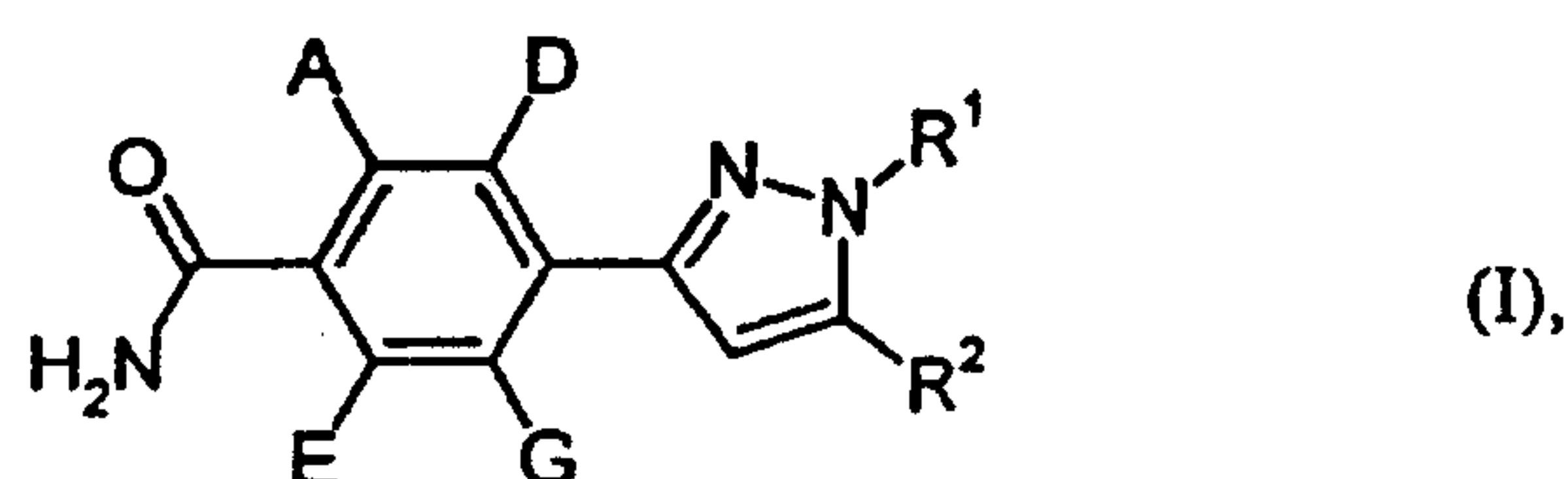
A, D, E and G are identical or different and represent hydrogen, fluorine, chlorine, bromine or trifluoromethyl,

R¹ represents hydrogen or methyl,

- 5 R^2 represents phenyl, furyl, thienyl, benzothiophenyl or pyridyl, where the abovementioned aromatic ring systems can optionally be substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, (C_1-C_4) -alkyl or (C_1-C_4) -alkoxy or (C_1-C_4) -alkoxycarbonyl

and their tautomers and the respective salts.

- 10 Compounds particularly preferably used are those of the general formula (I)



in which

15

A, D, E and G represent hydrogen and

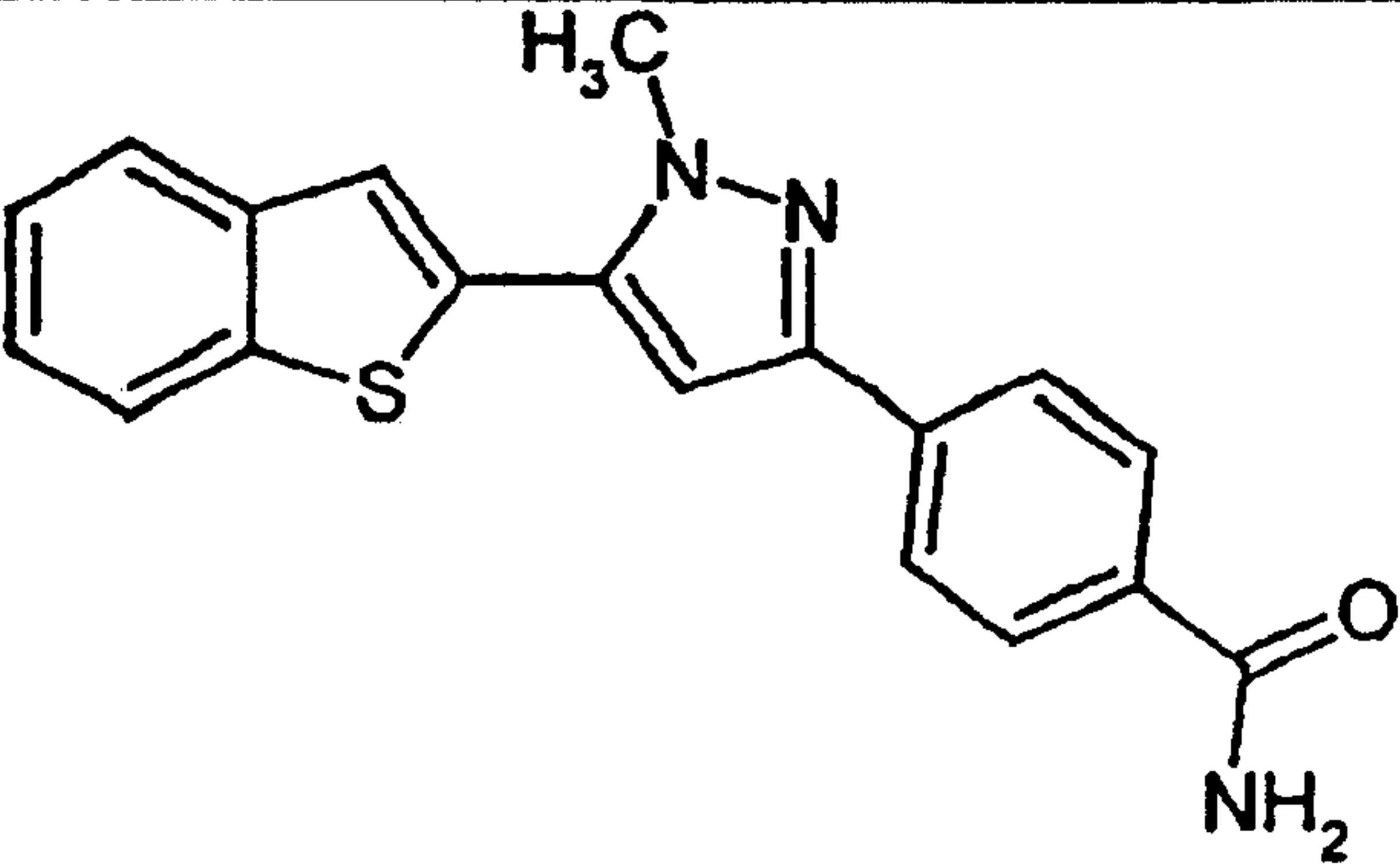
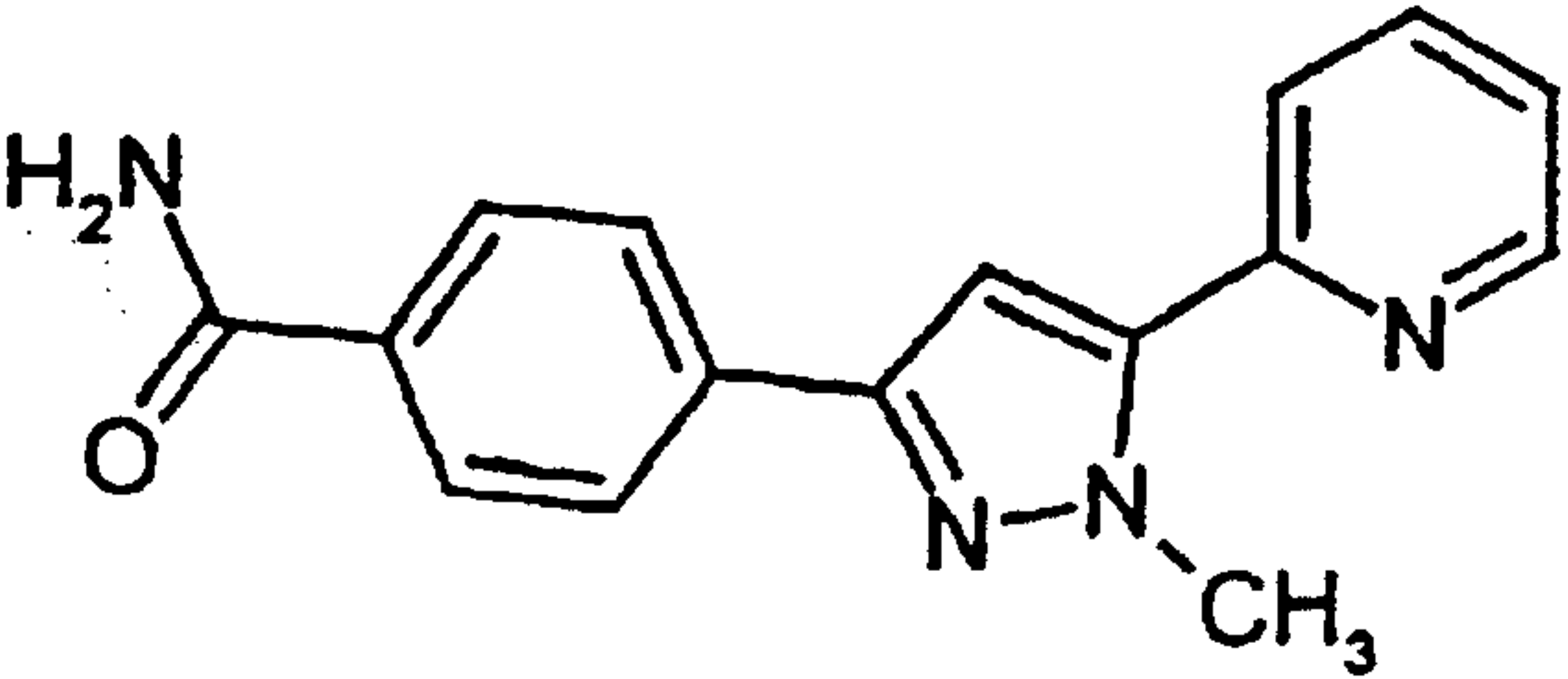
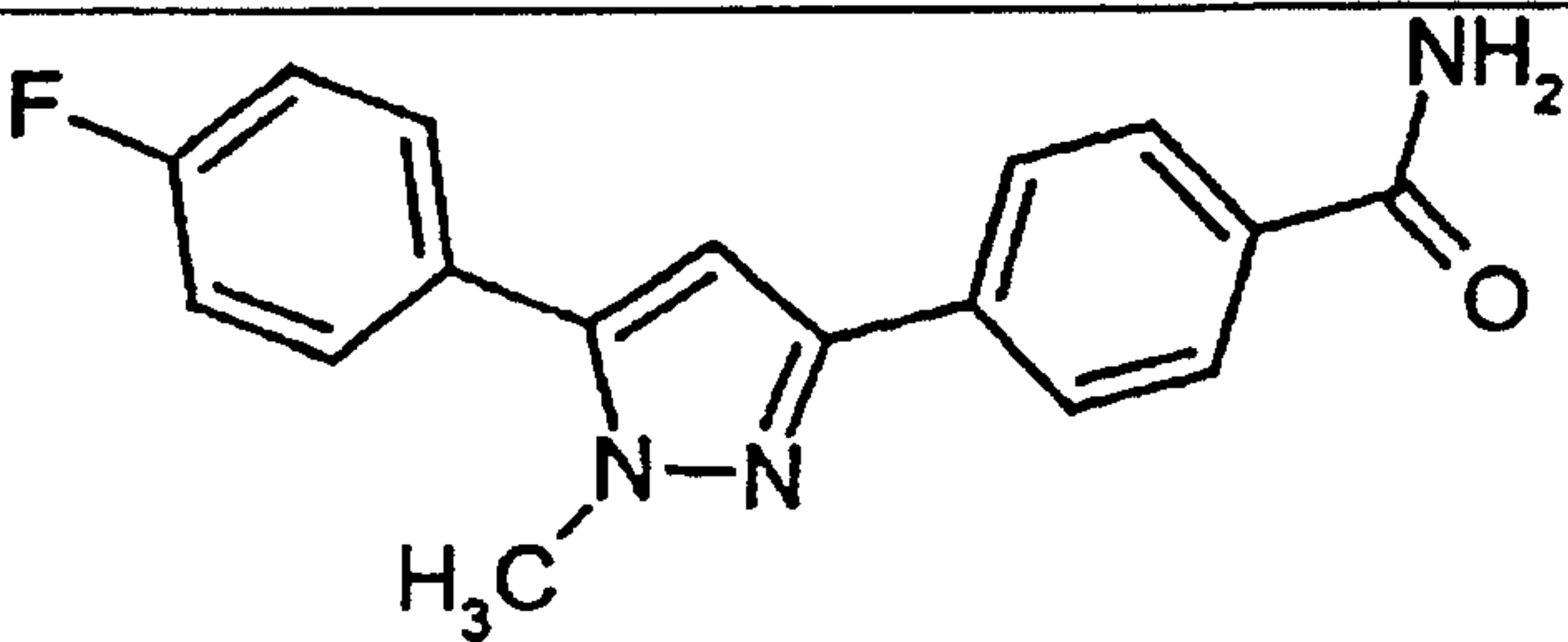
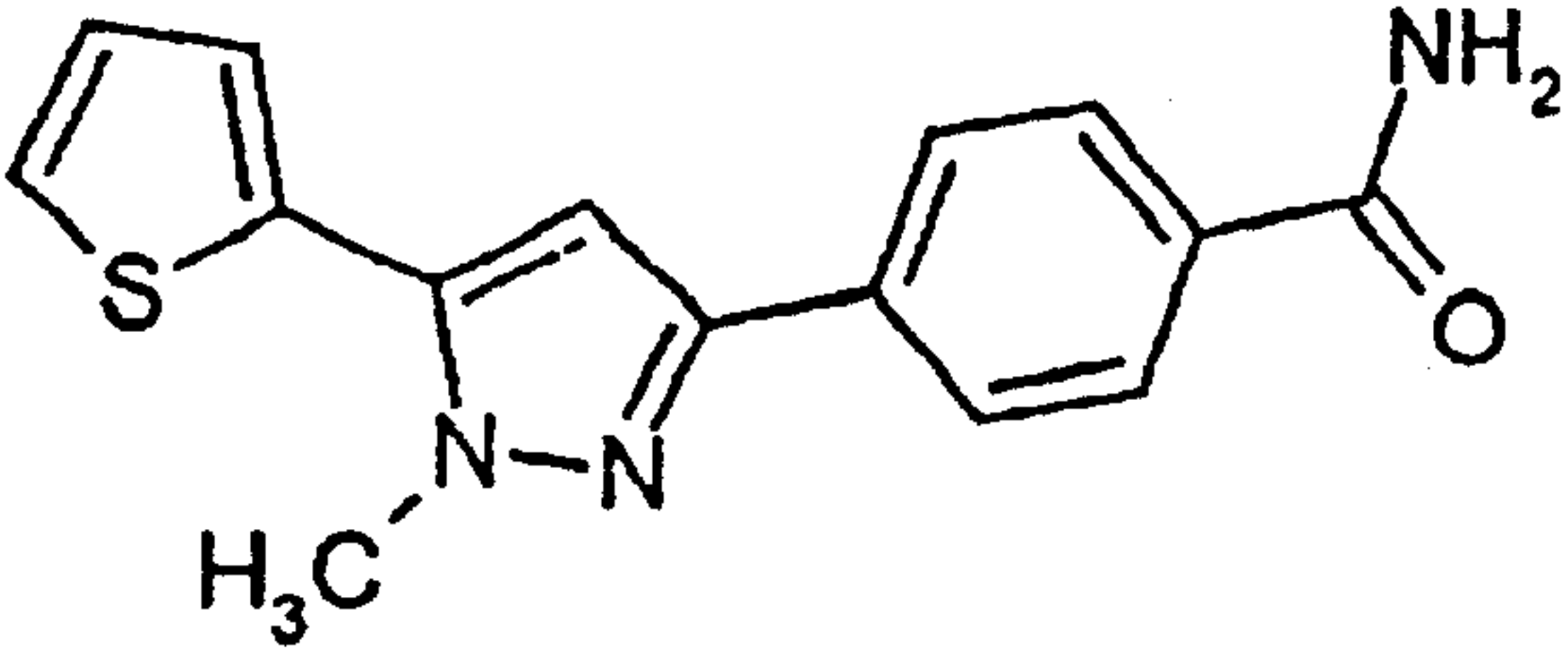
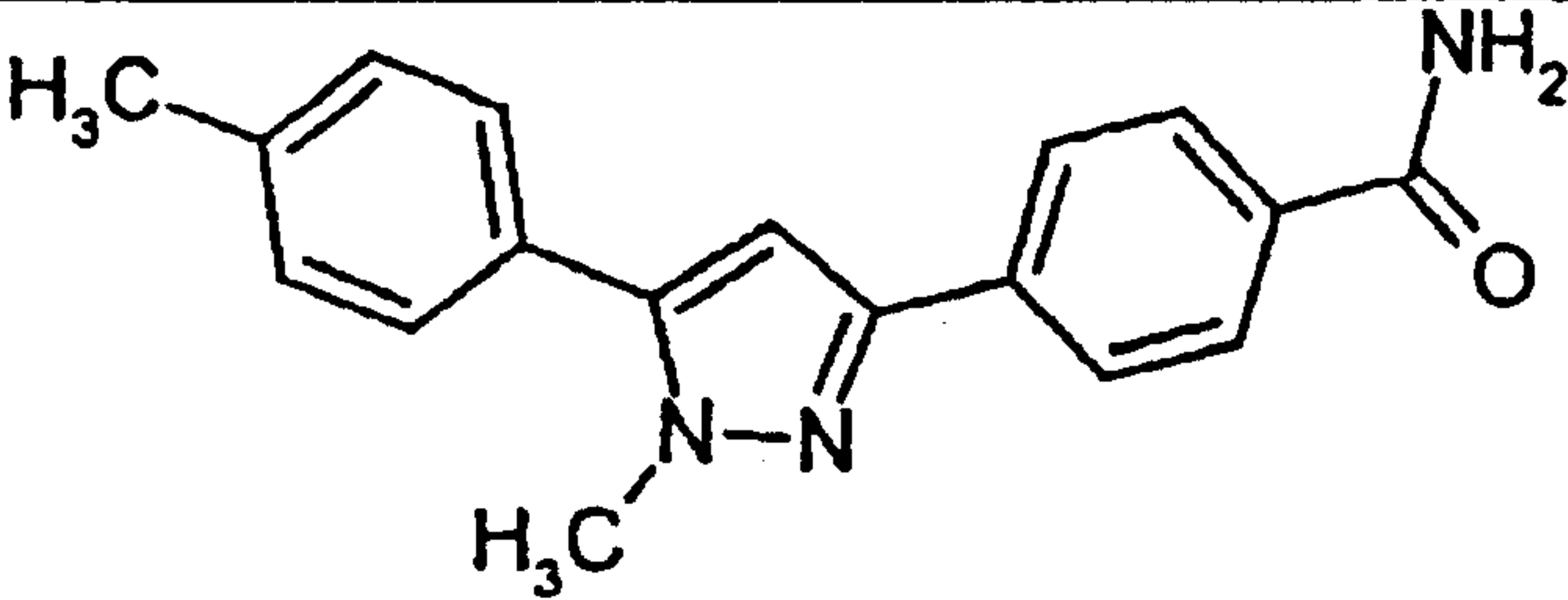
R^1 represents hydrogen or methyl and

- 20 R^2 represents phenyl, benzothiophenyl or pyridyl, where the abovementioned aromatic ring systems can optionally be substituted by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, methyl or methoxy.

and their tautomers and their salts.

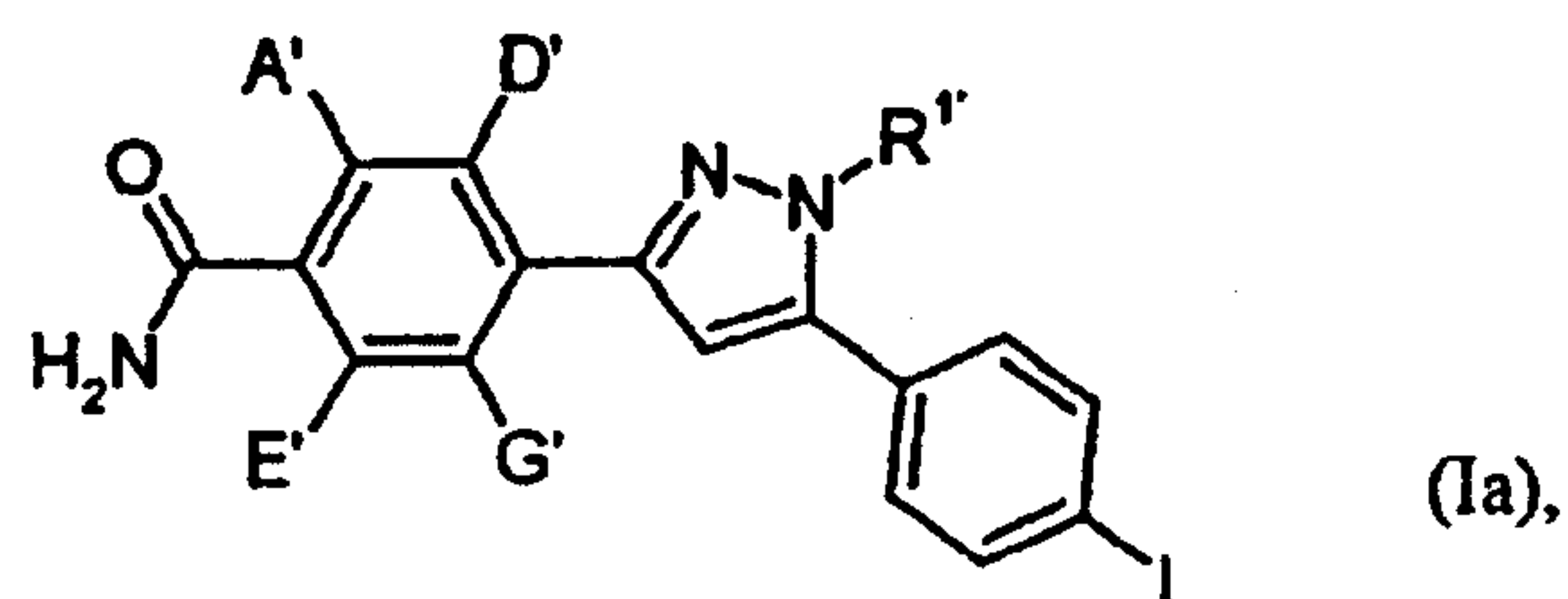
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Very particularly preferably used compounds are those shown in the following table:

Structures






and their salts.

5 The invention moreover relates to new substances of the general formula (Ia)



in which

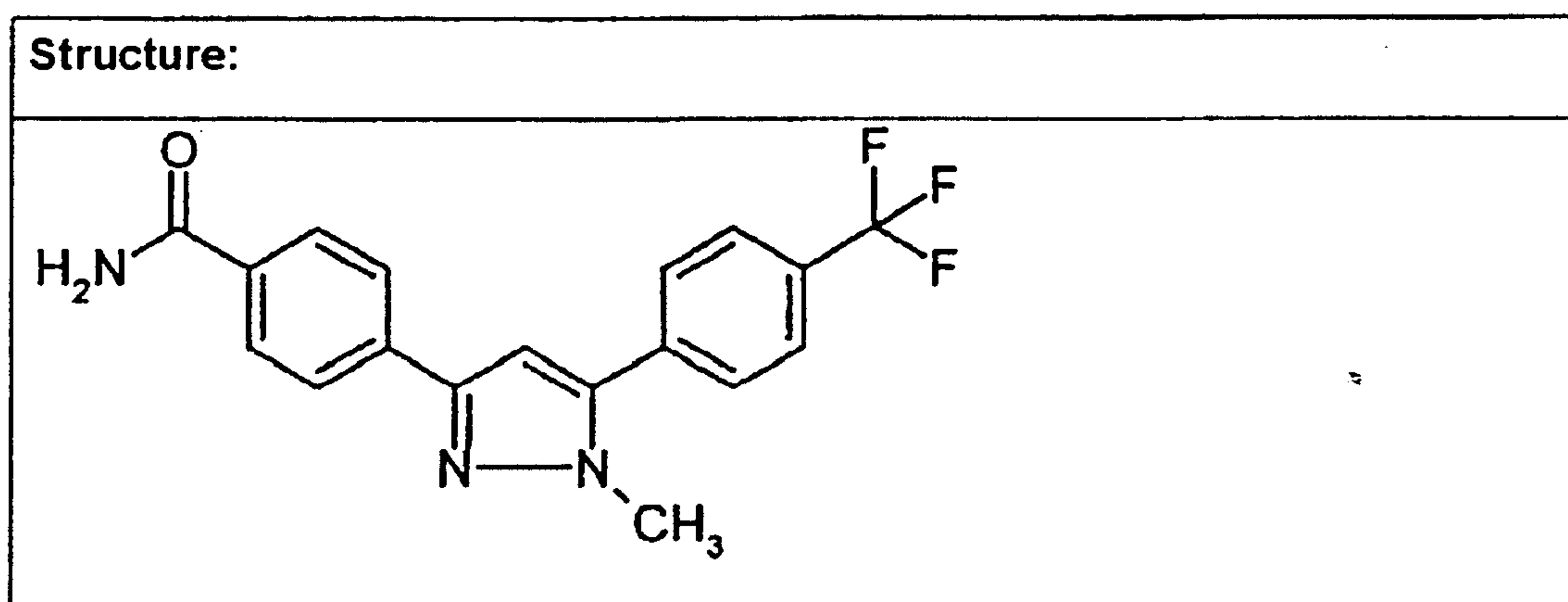
5 A', D', E', G' and R¹ have the meaning of A, D, E, G and R¹ indicated above

and

10 L represents CF₃ or OCF₃ (i.e. in other words L = R² where R² = para-C₆H₄-CF₃ or para-C₆H₄-OCF₃),

and their tautomers and respective salts.

15 A very particularly preferred compound according to the invention is that of the following structure:

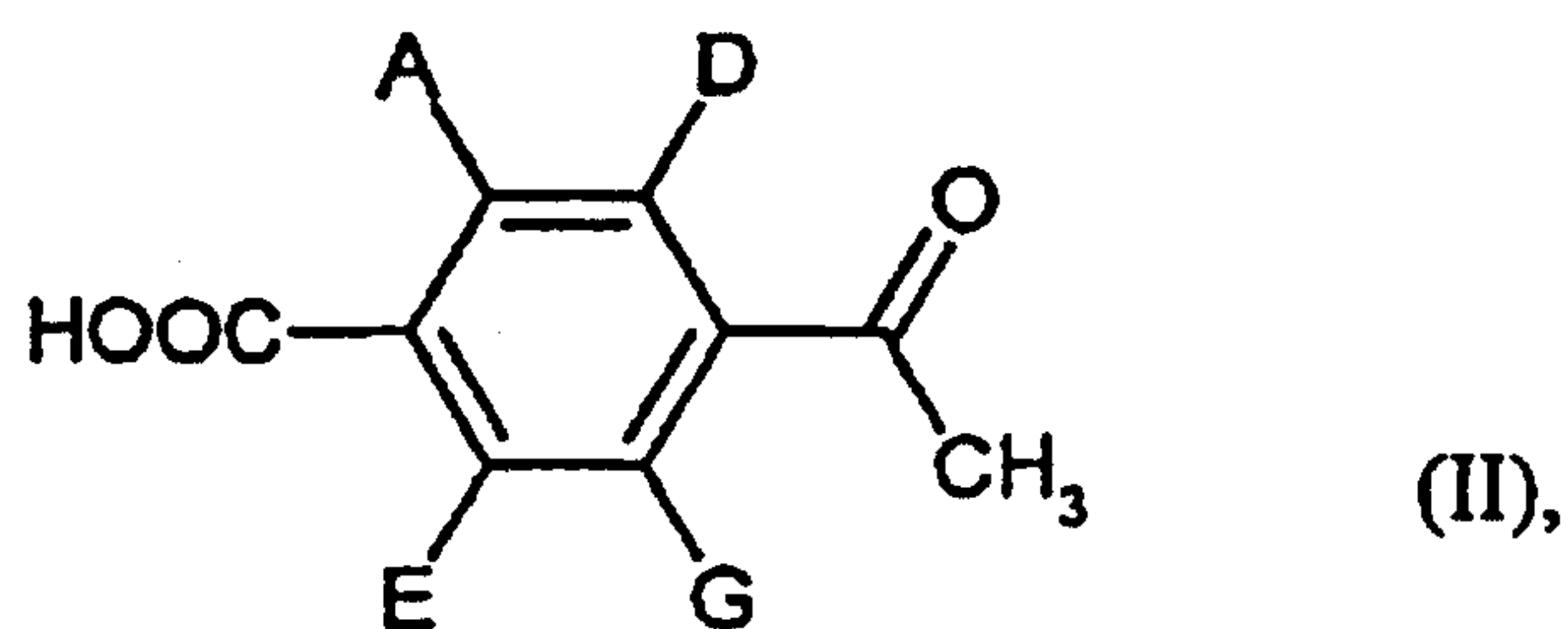


and its salts.

20

Moreover, processes for the preparation of the compounds of the general formula (I) and the new substances of the general formula (Ia) have been found, which are characterized in that

25 [A] compounds of the general formula (II)



in which

5 A, D, E and G have the meaning indicated above,

are coupled to an amino-functionalized resin and then reacted with compounds of the general formula (III)

$$10 \qquad \text{R}^3\text{OOC-R}^3 \qquad \text{(III),}$$

in which

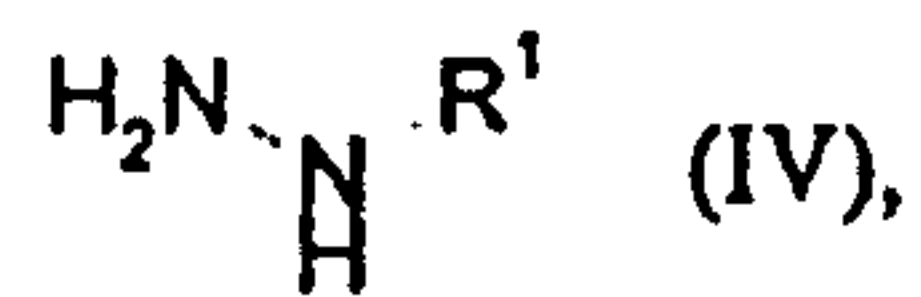
R^2 has the meaning indicated above

15

and

R^3 represents a (C₁-C₄)-alkyl radical,

20 on the solid phase and then reacted with compounds of the general formula (IV)



in which

25

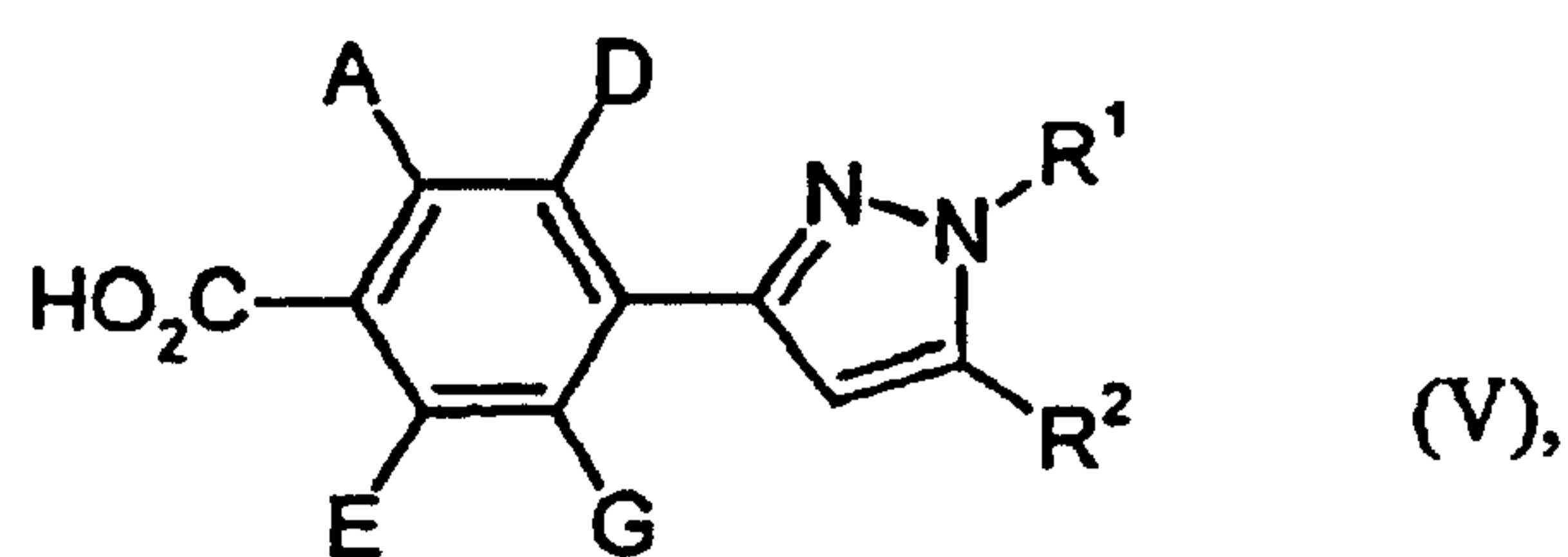
R^1 has the meaning indicated above,

the compounds are then cleaved from the resin and, if appropriate (i.e. for $R^1 \neq H$), separated into the isomers,

30

or

[B] pyrazolecarboxylic acids of the general formula (V)



5 in which

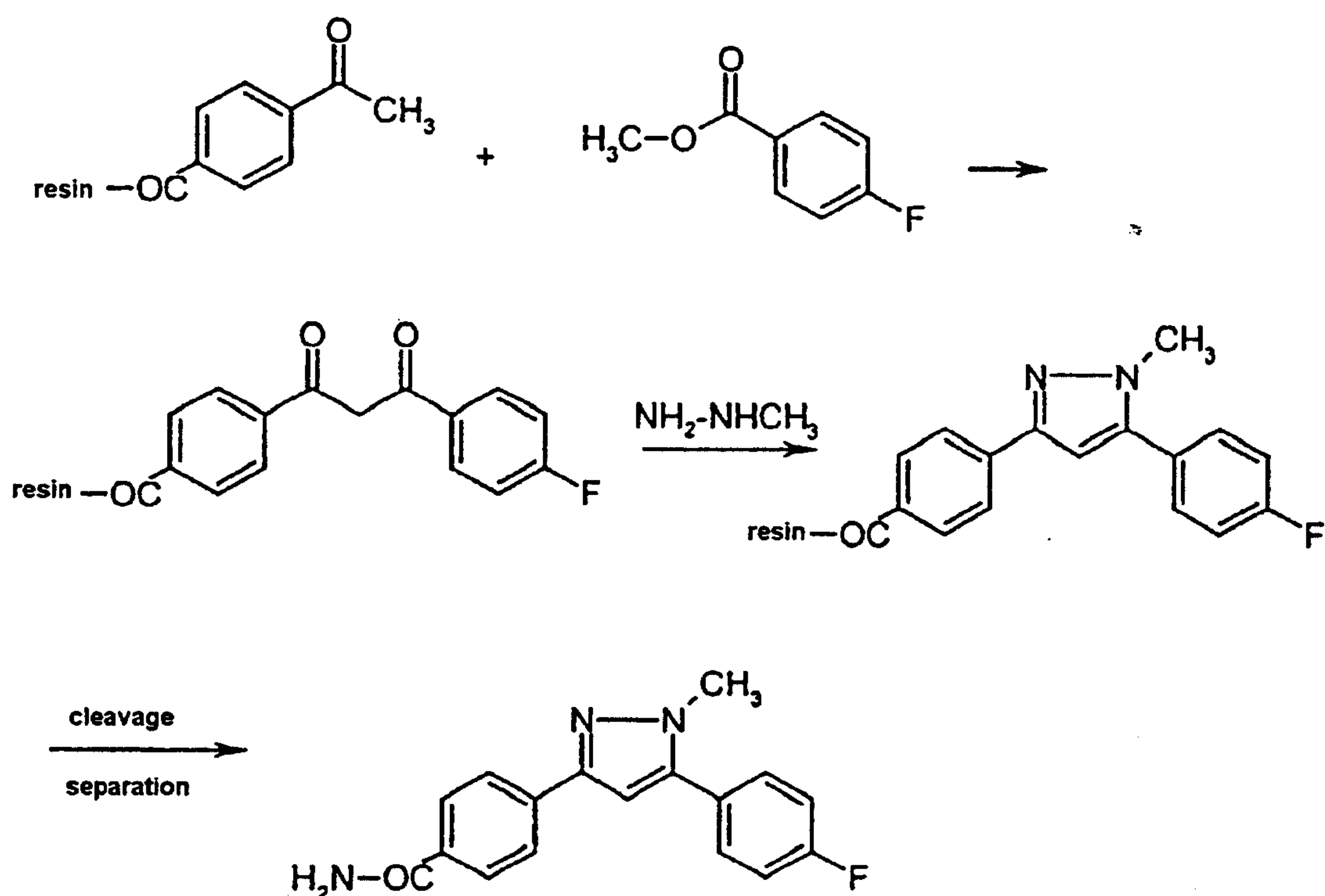
R^1 , R^2 , A, D, E and G have the meaning indicated above,

10 are reacted with ammonia, if appropriate in the presence of a dehydrating agent or via an activated carboxylic acid derivative (e.g. carboxylic acid halide, anhydride or imidazolide).

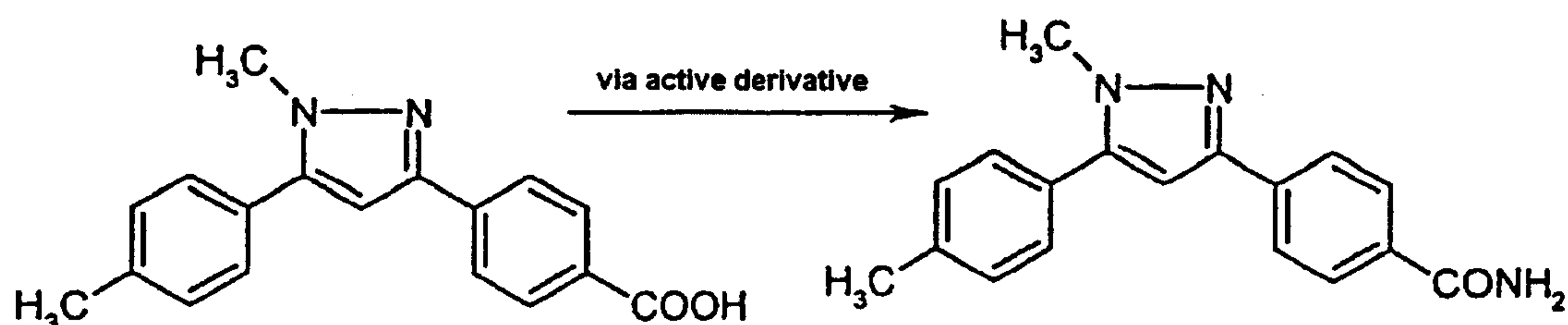
The processes can be illustrated by way of example by the following reaction schemes:

15

Process [A]:



Process [B]:



Suitable solvents here for the processes described beforehand are inert organic solvents which do not change under the reaction conditions. These include
5 halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane or cyclohexane, dimethylformamide, dimethylacetamide, acetonitrile or DMSO and ethers such as, for example, diethyl ether, dioxane or tetrahydrofuran.
10 It is also possible to employ mixtures of the solvents. Dimethylformamide and dichloromethane are particularly preferred.

The reactions described beforehand are in general carried out in a temperature range from -78°C up to reflux temperature, preferably from 0°C to the boiling point of the
15 solvent used.

The reactions described beforehand can be carried out at normal pressure, elevated pressure or at reduced pressure (e.g. from 0.5 to 5 bar). In general, the reaction is carried out at normal pressure.

20

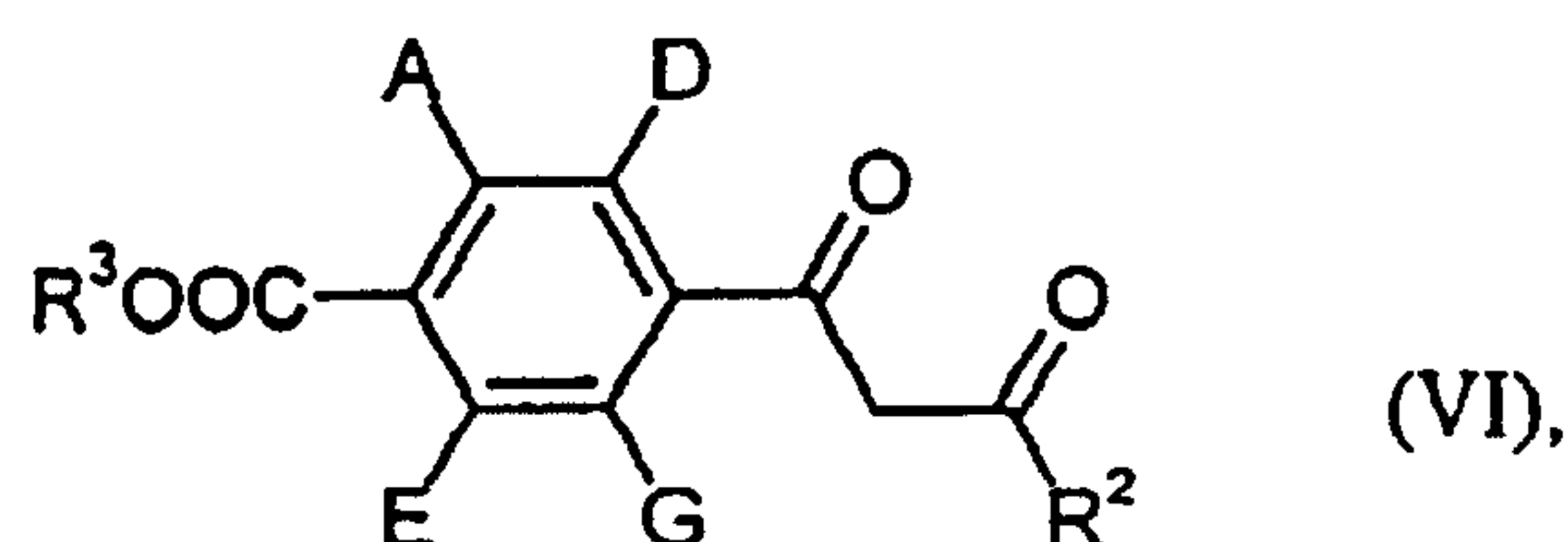
Suitable dehydrating reagents for process [B] are carbodiimides such as, for example, diiso-propylcarbodiimide, dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride or carbonyl compounds such as carbonyldiimidazole or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulphonate or propanephosphonic anhydride or isobutyl chloroformate or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate or diphenyl phosphoramidate or methanesulphonyl chloride, if appropriate in the presence of bases such as triethylamine or N-ethylmorpholine or N-methylpiperidine or dicyclohexylcarbodiimide and N-hydroxysuccinimide. Carbonyldiimidazole (CDI)
25 is preferred.
30

As the solid phase, the customary amino-functionalized polystyrenes are employed. Amino-functionalized polystyrene/polyethylene copolymers which are modified with a polyethylene glycol chain are preferred. So-called SAM resins (abbreviation for standard amide resin) and RAM resins (abbreviation for Rink amide resin) are particularly preferred. Examples of amino-functionalized resins which can be used according to the invention are Tentagel SAM (S 30022) and Tentagel R RAM (R 28 023), both from Rapp Polymere GmbH.

The compounds of the general formulae (II), (III) and (IV) are known per se.

The compounds of the formula (V) are new and can be prepared, for example, by

[C] reacting compounds of the general formula (VI)



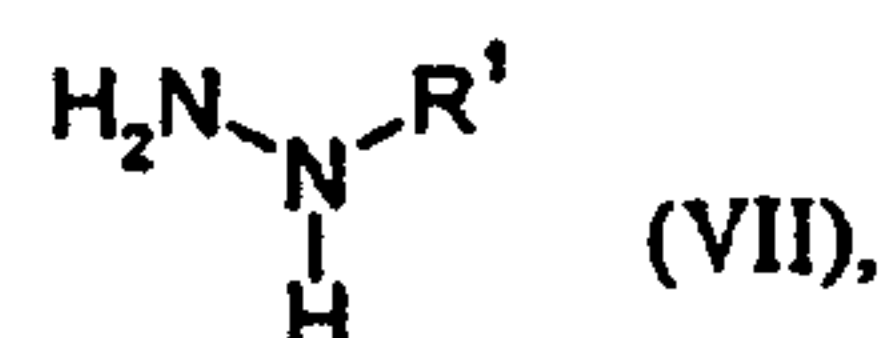
in which

A, D, E, G and R₂ have the meaning indicated above

and

R³ represents a (C₁-C₄)-alkyl radical,

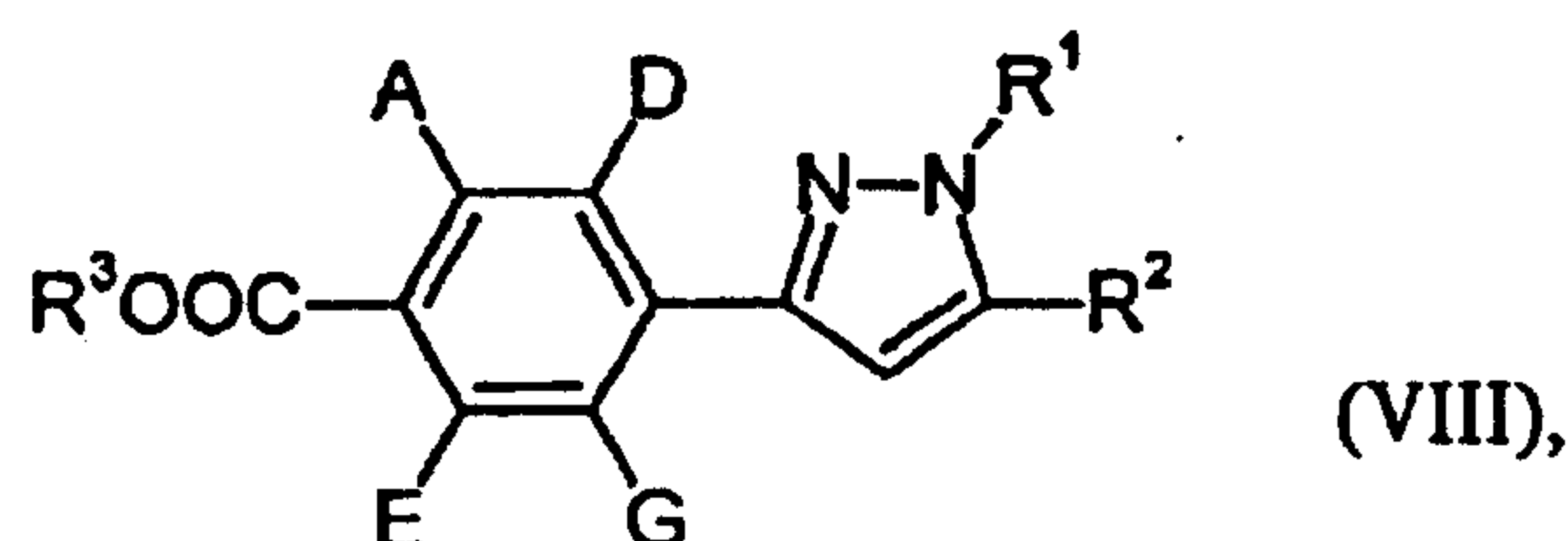
with compounds of the general formula (VII)



in which

R¹ has the meaning indicated above,

in inert solvents and separating the resulting esters of the general formula (VIII)



5 in which

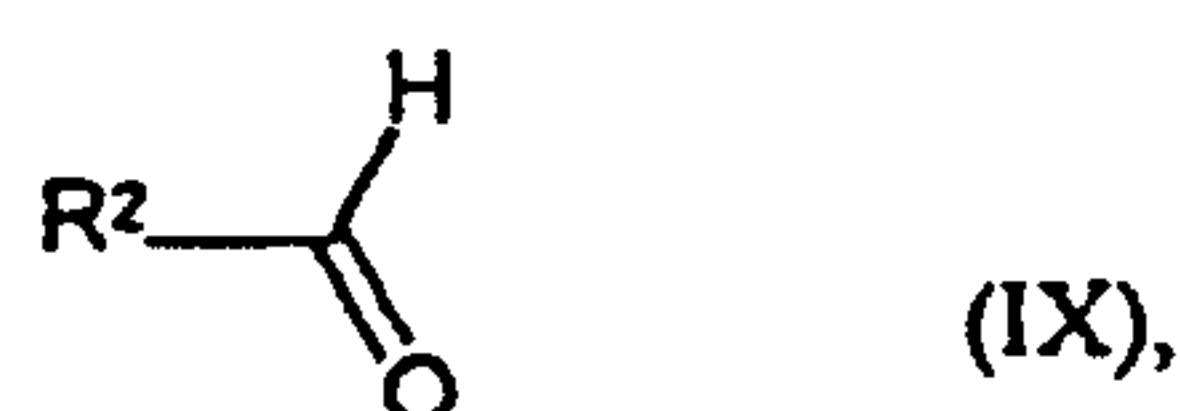
A, D, E, G, R¹, R² and R³ have the meaning indicated above,

10 in the case in which R¹ represents a (C₁-C₆)-alkyl radical, into the isomers and hydrolysing them to give carboxylic acids of the general formula (V),

and in the case in which R¹ represents H, first preparing isomeric mixtures where R¹ ≠ H by N-alkylation, which are separated by suitable separation methods into compounds of the formula (V) where R¹ represents (C₁-C₆)-alkyl, which are then
15 hydrolysed,

or

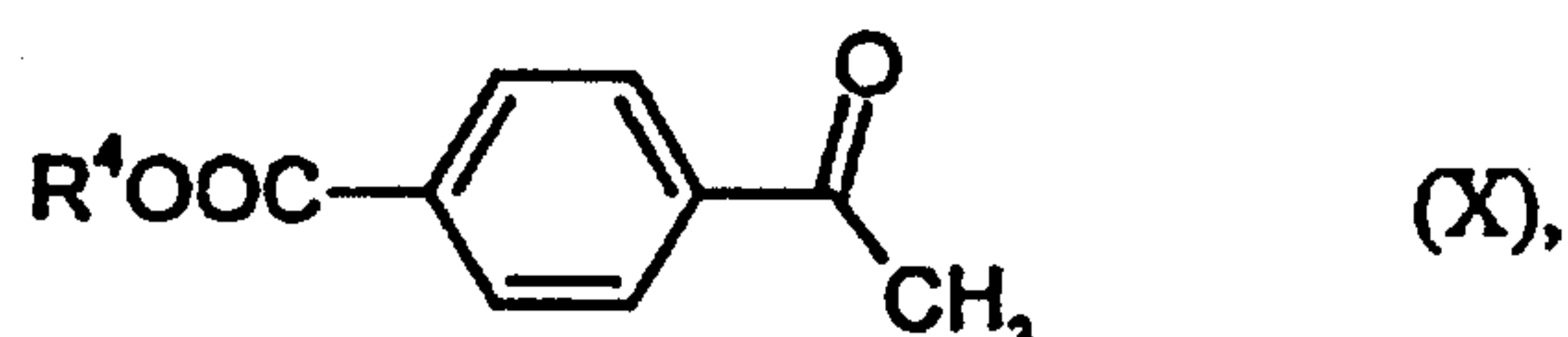
20 [D] in the case in which R¹ represents methyl, reacting aldehydes of the formula (IX)



in which

25 R² has the meaning indicated above,

with acetophenones of the general formula (X)



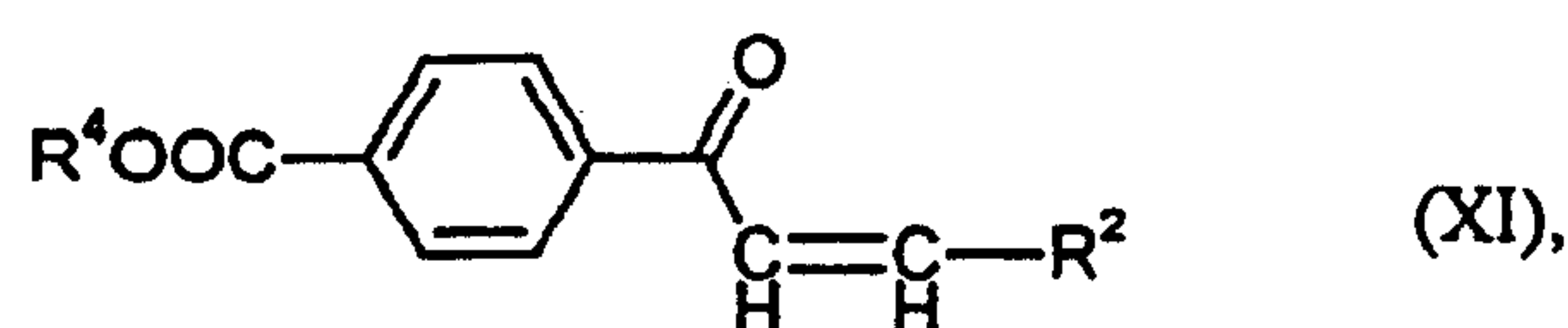
30

in which

R^4 represents a (C_1-C_4) -alkyl chain,

5 if appropriate in the presence of a catalyst,

and reacting the resulting compounds of the formula (XI)

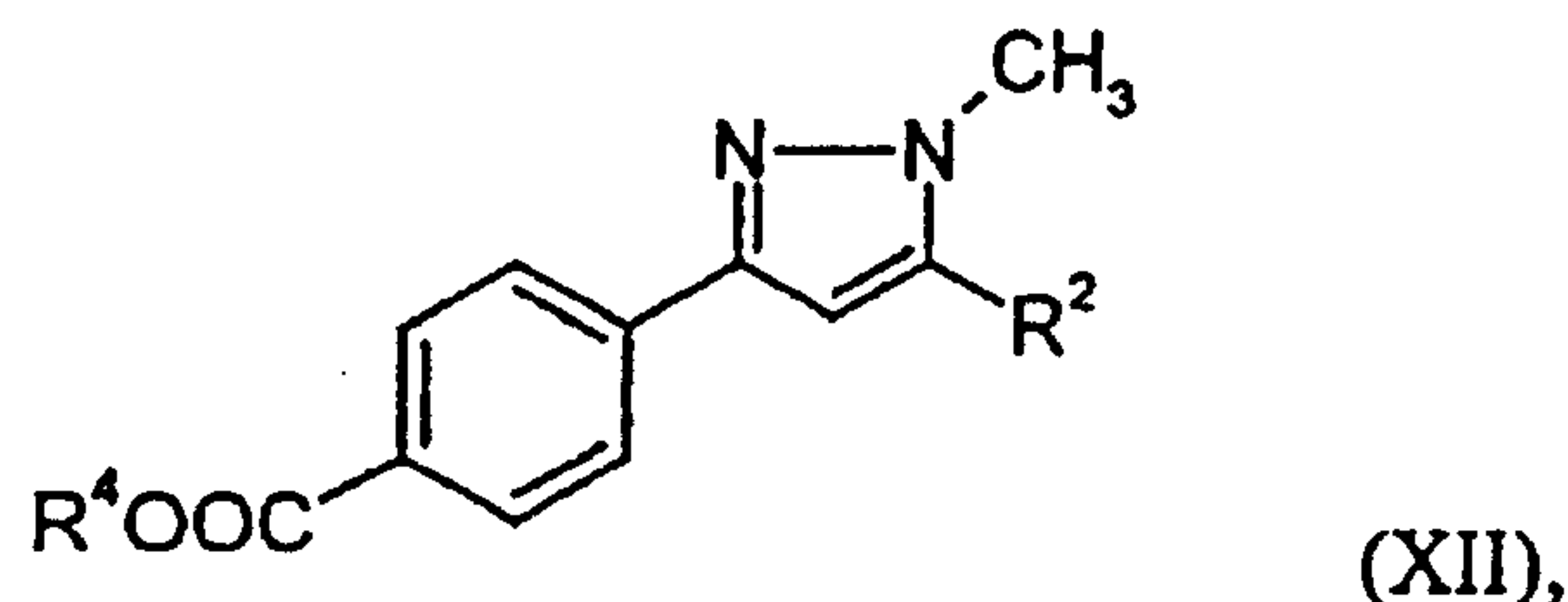


10 in which

R^2 and R^4 have the meaning indicated above,

with methylhydrazine to give compounds of the formula (XII)

15



in which

20 R^2 and R^4 have the meaning indicated above,

from which, by hydrolysis as described above, the compounds of the formula (V) where R^1 = methyl are obtained.

25 Suitable solvents here for processes [C] and [D] are inert organic solvents which do not change under the reaction conditions. These include halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane or cyclohexane,
30 dimethylformamide, tetrahydrofuran, acetonitrile or alcohols such as methanol,

ethanol, 2-propanol or DMSO. It is also possible to employ mixtures of the solvents. Ethanol and DMSO are particularly preferred.

5 For the reaction of the aldehyde with the acetophenones described under [A], possible catalysts are the customary acidic and basic catalysts, preferably acid (e.g. para-toluenesulphonyl chloride).

10 The reactions described beforehand are in general carried out in a temperature range from -78°C up to reflux temperature, preferably from 0°C up to the boiling point of the solvent used.

The reactions described beforehand can be carried out at normal pressure, elevated pressure or at reduced pressure (e.g. from 0.5 to 5 bar). In general, the reaction is carried out at normal pressure.

15 The carboxylic acid esters are hydrolysed according to customary methods, by treating the esters with customary bases or acids in inert solvents, where, in the case of basic hydrolysis, the initially resulting salts can be converted into the free carboxylic acids by treating with acid.

20 Suitable bases for the hydrolysis are the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example, sodium hydroxide, lithium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium carbonate or potassium carbonate or sodium hydrogencarbonate. Sodium hydroxide or lithium hydroxide is particularly preferably employed.

25 Suitable solvents for the hydrolysis are water or the organic solvents customary for hydrolysis. These preferably include alcohols such as methanol, ethanol, propanol, isopropanol or butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide or dimethyl sulphoxide. Alcohols such as methanol, ethanol, propanol or isopropanol are particularly preferably used. It is also possible to employ mixtures of the solvents mentioned. Water/tetrahydrofuran or water/ethanol is preferred.

35 The hydrolysis is in general carried out in a temperature range from 0°C to +100°C, preferably from 0°C to +80°C.

In general, the hydrolysis is carried out at normal pressure. However, it is also possible to work at reduced pressure or at elevated pressure (e.g. from 0.5 to 5 bar).

- 5 When carrying out the hydrolysis, the base or the acid is in general employed in an amount from 1 to 3 mol, preferably from 1 to 2.5 mol, based on 1 mol of the ester. Molar amounts of the reactants are particularly preferably used.

10 The compounds of the general formulae (VI) and (XI) are known per se or can be prepared by customary methods [cf. Erne, D. et al., *Helv. Chim. Acta* 62(1979), 994-1006; Hasegawa, E. et al., *J. Org. Chem.* 56 (1991), 1631-1635; Watanabe, Kenichi et al., *Bull. Chem. Soc. Jpn.* 55 (1988) 3208-3211].

15 The compounds of the general formulae (VII), (VIII), (IX), (X) and (XII) are new in some cases or are known and can be prepared as described above.

20 The compounds of the general formula (I) used according to the invention and the new substances of the general formula (Ia) show an unforeseeable, useful spectrum of pharmacological action and are therefore suitable for the treatment and prophylaxis of disorders.

25 They can preferably be employed in medicaments for the treatment and prophylaxis of anaemia, such as, for example, in anaemia of prematurely born infants, anaemia in chronic renal insufficiency, anaemia after chemotherapy and anaemia in HIV patients, and thus also for the treatment of severe anaemia.

30 In the case of completely intact endogenous EPO production too, an additional stimulation of erythropoiesis can be induced by the administration of the compounds according to the invention, which can be utilized, in particular, in autologous blood donors.

35 All customary administration forms are suitable for the administration of the compounds according to the invention and compounds used according to the invention. Preferably, administration is carried out orally, transdermally or parenterally. Oral administration, in which there is a further advantage compared with the therapy of anaemia with rh EPO known from the prior art, is very particularly preferred.

The compounds according to the invention act, in particular, as erythropoietin sensitizers.

- 5 Compounds which are able to influence the action of the EPO present in the body so efficiently that erythropoiesis is increased, in particular so that the oxygen supply is improved are described as erythropoietin sensitizers. They are surprisingly orally active, as a result of which therapeutic use with exclusion or reduction of the known side effects is significantly improved and simultaneously simplified.

10

- The present invention thus also relates to the use of EPO sensitizers for the stimulation of erythropoiesis, in particular for the prophylaxis and/or treatment of anaemia, preferably severe anaemia such as, for example, anaemia of prematurely born infants, anaemia in chronic renal insufficiency, anaemia after chemotherapy or
15 alternatively anaemia in HIV patients. In addition, the addition of EPO sensitizers in the case of completely intact endogenous EPO production is also suitable for the additional stimulation of erythropoiesis, which can be utilized, in particular, in autologous blood donors.

- 20 The oral administration of these so-called EPO sensitizers for the purposes mentioned previously is particularly preferred.

- The compounds according to the invention thus make possible efficient stimulation of erythropoiesis and consequently prophylaxis or therapy of anaemia, which
25 additionally intervenes before the stage in which the conventional treatment methods using EPO commence, since the compounds according to the invention allow the endogenous EPO to be effectively influenced, as a result of which the direct administration of EPO with the disadvantages associated therewith can be avoided.

- 30 The present invention thus further relates to medicaments and pharmaceutical compositions which contain at least one compound of the general formula (I) together with one or more pharmacologically acceptable excipients or carriers, and their use for the stimulation of erythropoiesis, in particular for purposes of the prophylaxis and/or treatment of anaemia, such as, for example, anaemia of
35 prematurely born infants, anaemia in chronic renal insufficiency, anaemia after chemotherapy or anaemia in HIV patients.

Test description (in vitro)

Cell proliferation of human erythroid precursor cells

- 5 20 ml of heparinized blood were diluted with 20 ml of PBS and centrifuged for 20 min ($220 \times g$). The supernatant was discarded, and the cells were resuspended in 30 ml of PBS and pipetted onto 17 ml of Ficoll Paque ($d = 1.077 \text{ g/ml}$, Pharmacia) in a 50 ml tube. The samples were centrifuged at $800 \times g$ for 20 min. The mononuclear cells on the boundary layer were transferred to a new centrifuge tube, diluted with a
10 3-fold volume of PBS and centrifuged at $300 \times g$ for 5 min.

The CD34-positive cells from this cell fraction were isolated by means of a commercial purification process (CD34 Multisort Kit from Miltenyi).

- 15 CD34-positive cells (6000-10,000 cells/ml) were resuspended in stem cell medium (0.9% methylcellulose, 30% calf serum, 1% albumin (bovine), $100 \mu\text{M}$ 2-mercaptoethanol and 2 mM L-glutamine) from StemCell Technologies Inc. 10 mU/ml of human erythropoietin, 10 ng/ml of human IL-3 and 0-10 μM test substance were added. 500 μl /well (24-well plates) were cultured at 37°C in 5% CO_2 ,
20 95% air for 14 days.

- Cultures were diluted with 20ml of 0.9% w/v NaCl solution, centrifuged at $600 \times g$ for 15 min and resuspended in 200 μl of 0.9% w/v NaCl. For the determination of the number of erythroid cells, 50 μl of the cell suspension were pipetted into 10 μl of
25 benzidine dyeing solution (20 μg of benzidine in 500 μl of DMSO, 30 μl of H_2O_2 and 60 μl of conc. acetic acid). The number of blue cells was counted microscopically.

Test description of mouse haematocrit

- 30 Normal mice were treated with test substances for a number of days. The administration was carried out intraperitoneally, subcutaneously or orally. Preferred solvents are solutol/DMSO/sucrose/NaCl solution or glycofurol.

- From day 0 (before the first administration) up to about 3 days after the last
35 administration, about 70 μl of blood are repeatedly taken by puncture of the retroorbital venous plexus using a haematocrit capillary. The samples are centrifuged and the haematocrit is determined by manual reading. The primary parameter is the

haematocrit increase compared with the starting value of the treated animals in comparison with the alteration of the haematocrit in the placebo control (two times standardized value).

- 5 The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, non-toxic, pharmaceutically suitable carriers or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of approximately 0.5 to 90% by
10 weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds using solvents and/or carriers, if appropriate using emulsifiers and/or dispersants,
15 where, for example, if water is used as a diluent organic solvents can optionally be used as auxiliary solvents.

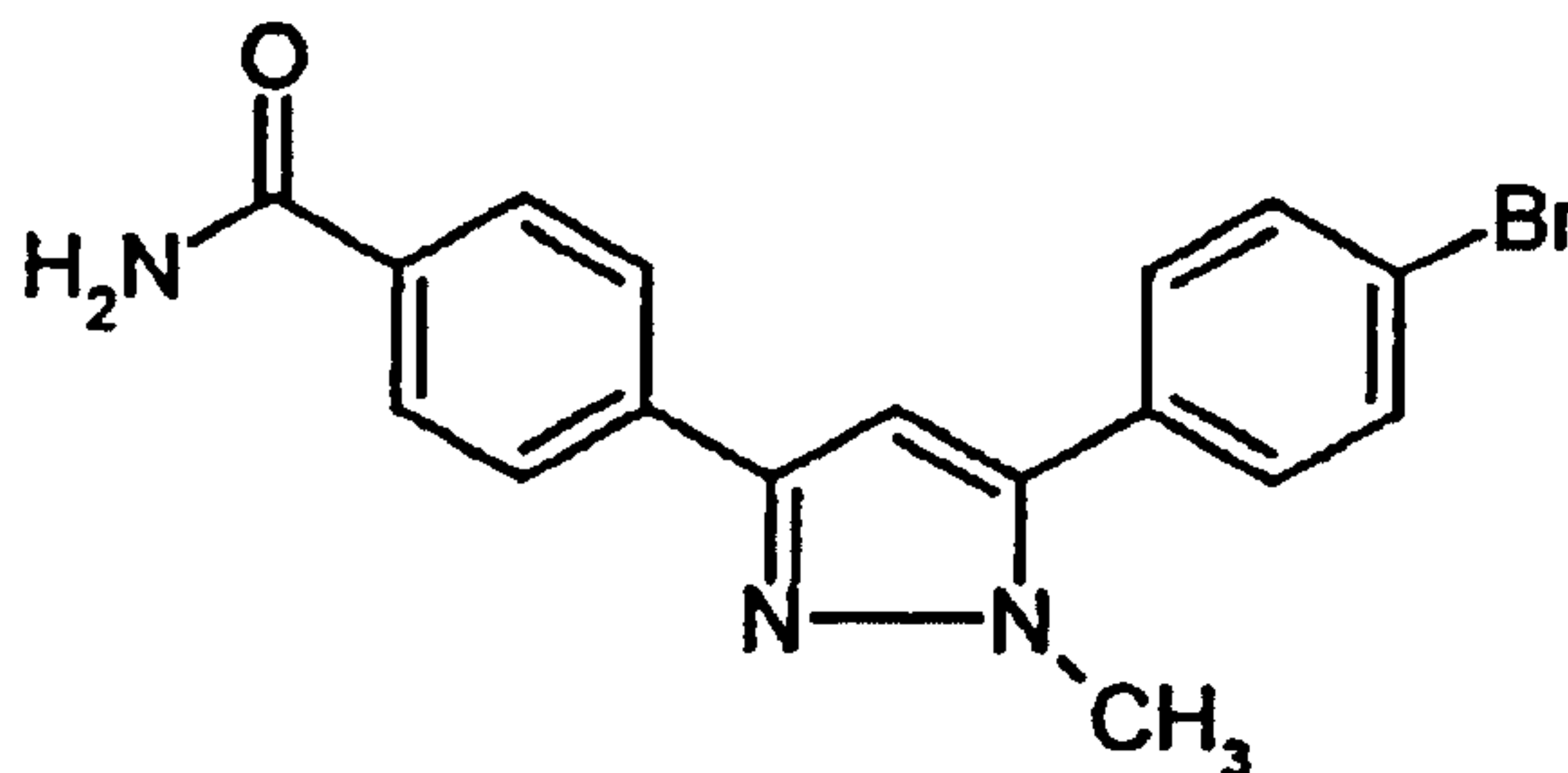
Administration is carried out in a customary manner, preferably orally, transdermally or parenterally, in particular perlingually or intravenously.
20

In general, it has proved advantageous in the case of intravenous administration to administer amounts of approximately 0.01 to 10 mg/kg, preferably approximately 0.1 to 10 mg/kg, of body weight to achieve effective results.

- 25 In spite of this, if appropriate it may be necessary to depart from the amounts mentioned, namely depending on the body weight or on the type of administration route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be adequate to manage with less than the abovementioned
30 minimum amount, while in other cases the upper limit mentioned has to be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into a number of individual doses over the course of the day.

Preparation Examples**Example 1**

5 3-(4-Aminocarbonylphenyl)-5-(4-bromophenyl)-1-methyl-pyrazole



10 Tentagel SAM resin (100 mg, loading 0.22 mmol/g) is suspended in dimethylformamide (10 ml), treated with acetophenone-4-carboxylic acid (144 mg, 0.88 mmol), TBTU (TBTU = o-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate) (282 mg, 0.88 mmol) and DIEA (DIEA - diisopropylethylamide) (16 mg, 0.12 mmol) and is shaken overnight at room temperature. The liquid phase is then filtered off with suction and the resin is washed with dimethylformamide, methanol, methylene chloride and diethyl ether (two times 5 ml each).

15

20 For the Claisen condensation, the resin (100 mg, 0.21 mmol) is suspended in dimethylacetamide (10 ml) under argon, treated with methyl 4-bromo-benzoate (812 mg, 3.78 mmol) and shaken at room temperature for 10 min. NaH (disp. in mineral oil, 60% strength, 96.6 mg, 2.52 mmol) is then added and the mixture is shaken at 90°C for 1 h. The liquid phase is then filtered off with suction and the resin is washed with dimethylformamide, methanol, methylene chloride and diethyl ether (two times 5 ml each).

25 For the condensation, the resin (100 mg, 0.2 mmol) is suspended in dimethylacetamide and treated with 2 ml of a 1.5 M solution of methylhydrazine in dimethylacetamide. The mixture is stirred at 70°C for 48 h. The liquid phase is then filtered off with suction and the resin is washed with dimethylformamide, methanol, methylene chloride and diethyl ether (two times 5 ml each).

30 For the cleavage, the resin (100 mg) is treated with 2 ml of a 1:1 (v:v) mixture of methylene chloride and trifluoroacetic acid and shaken at room temperature for 1 h. The liquid phase is separated off, the solid phase is washed with methylene chloride

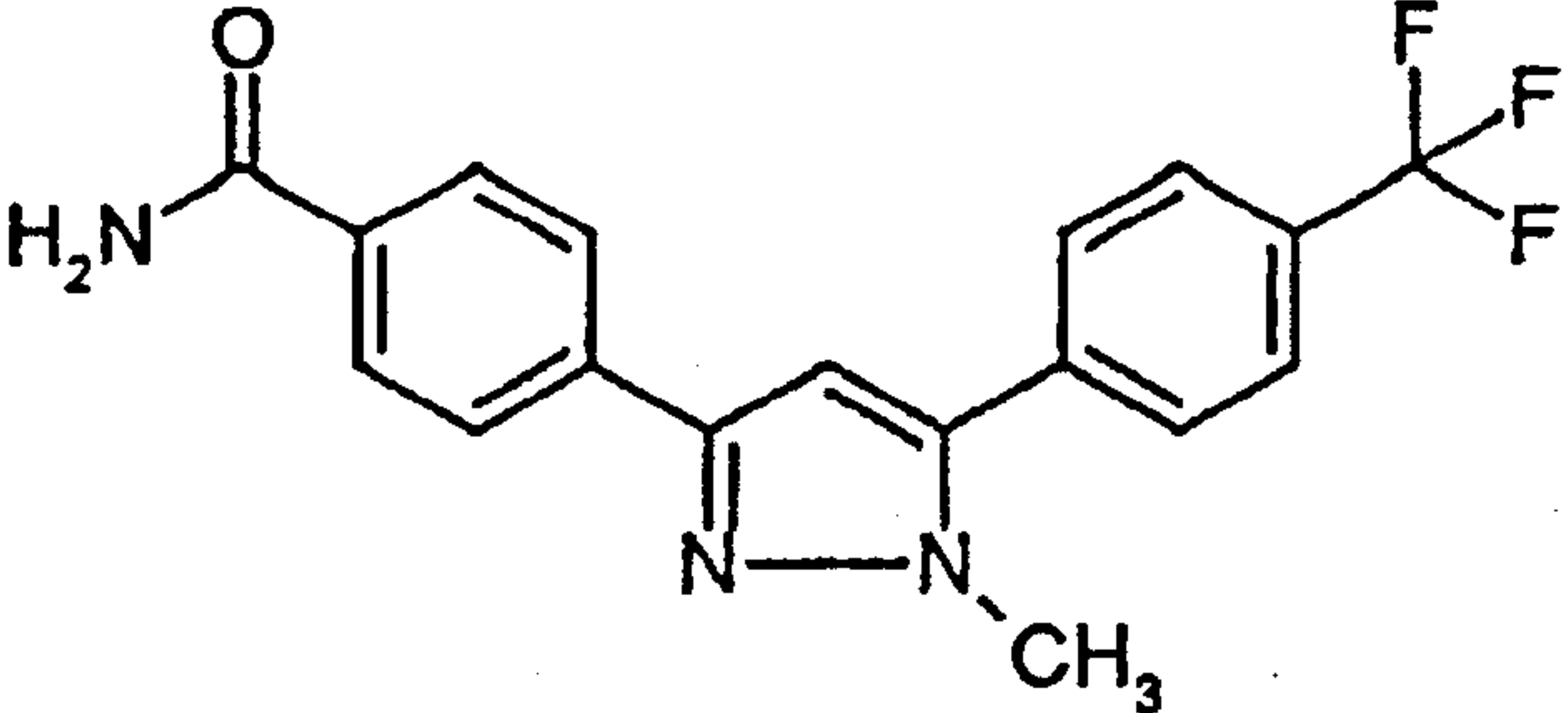
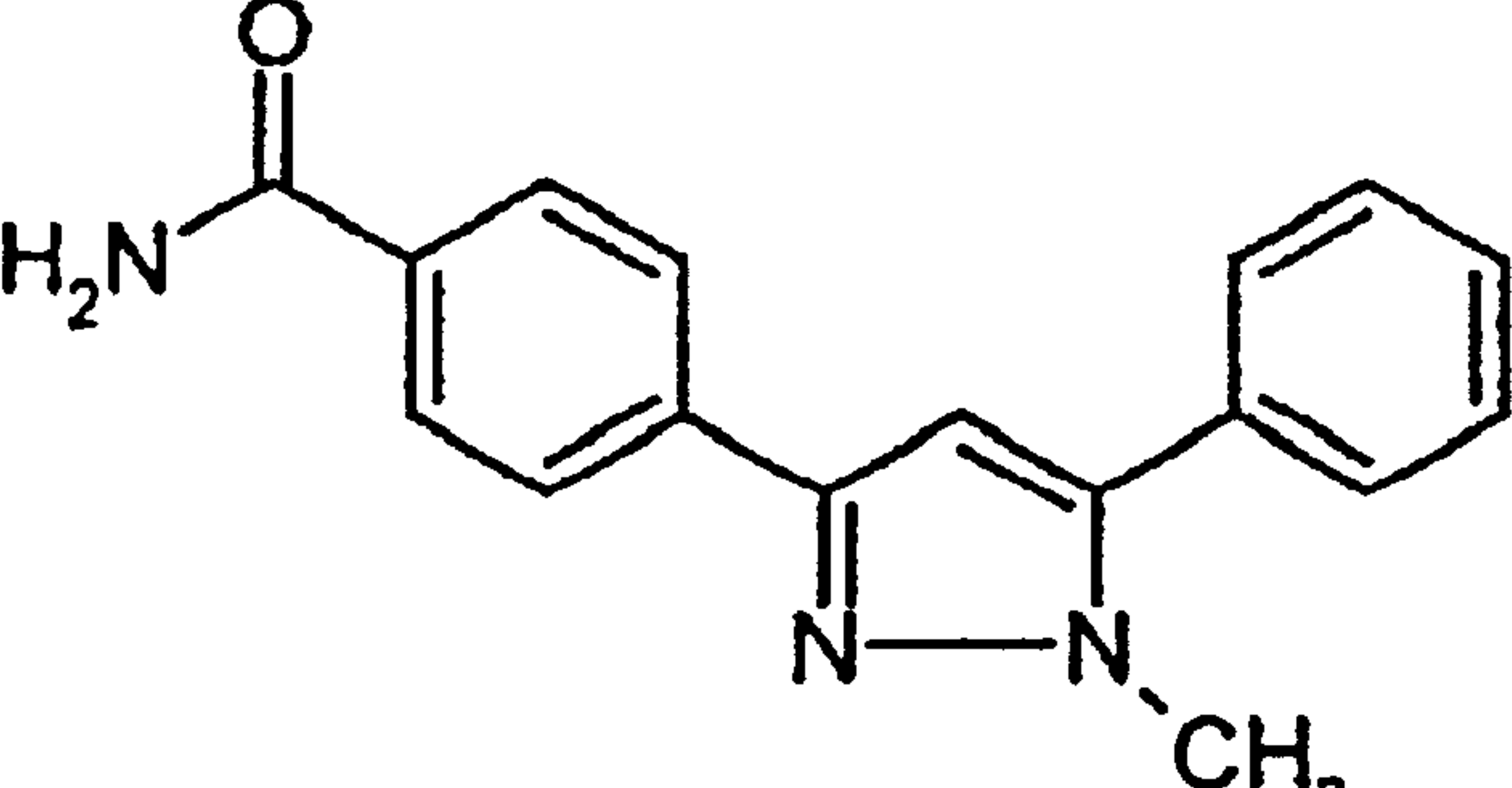
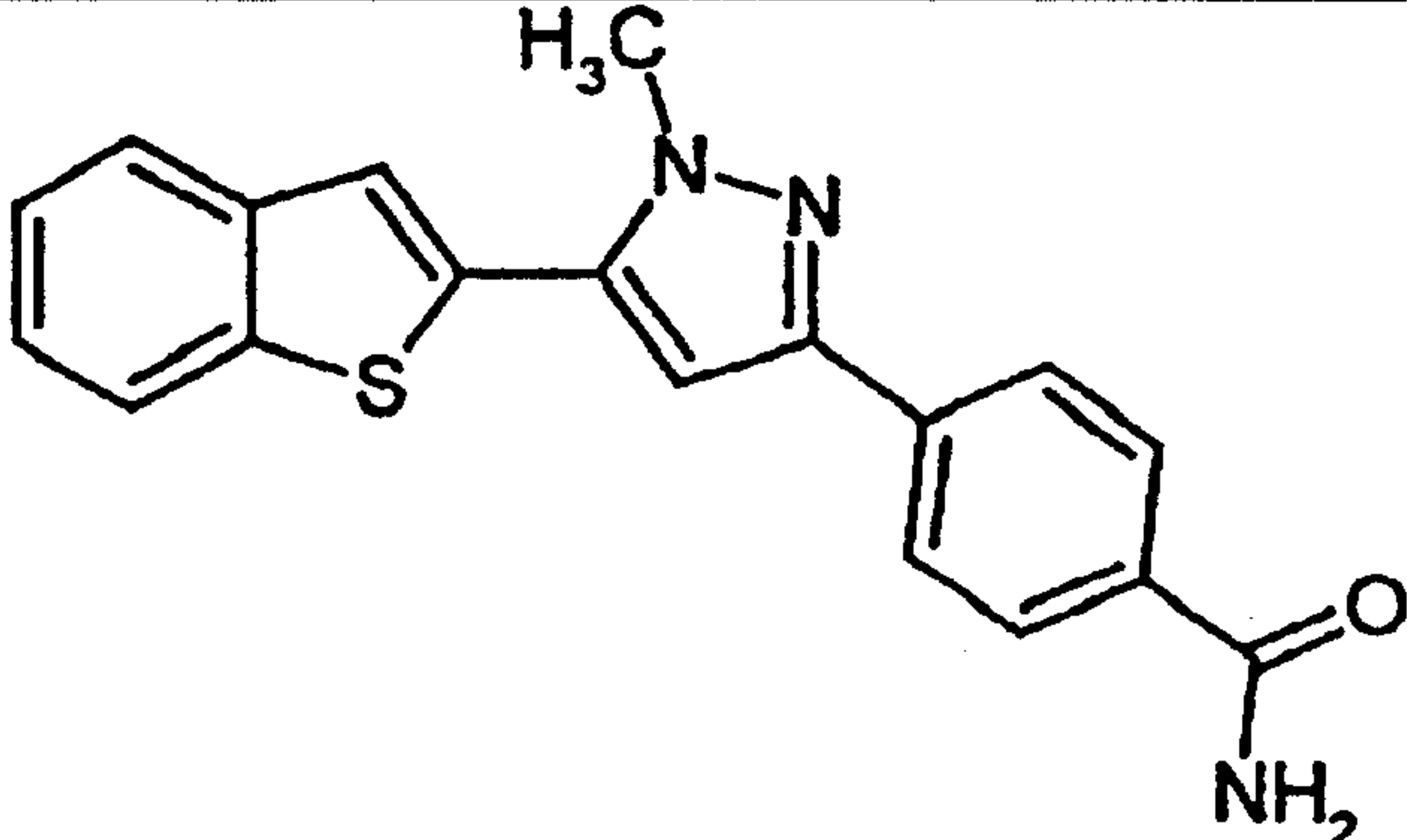
and the combined liquid phases are evaporated. The product precipitates as a regioisomer mixture in a yield of 4 mg, and the desired isomer is separated by means of preparative HPLC.

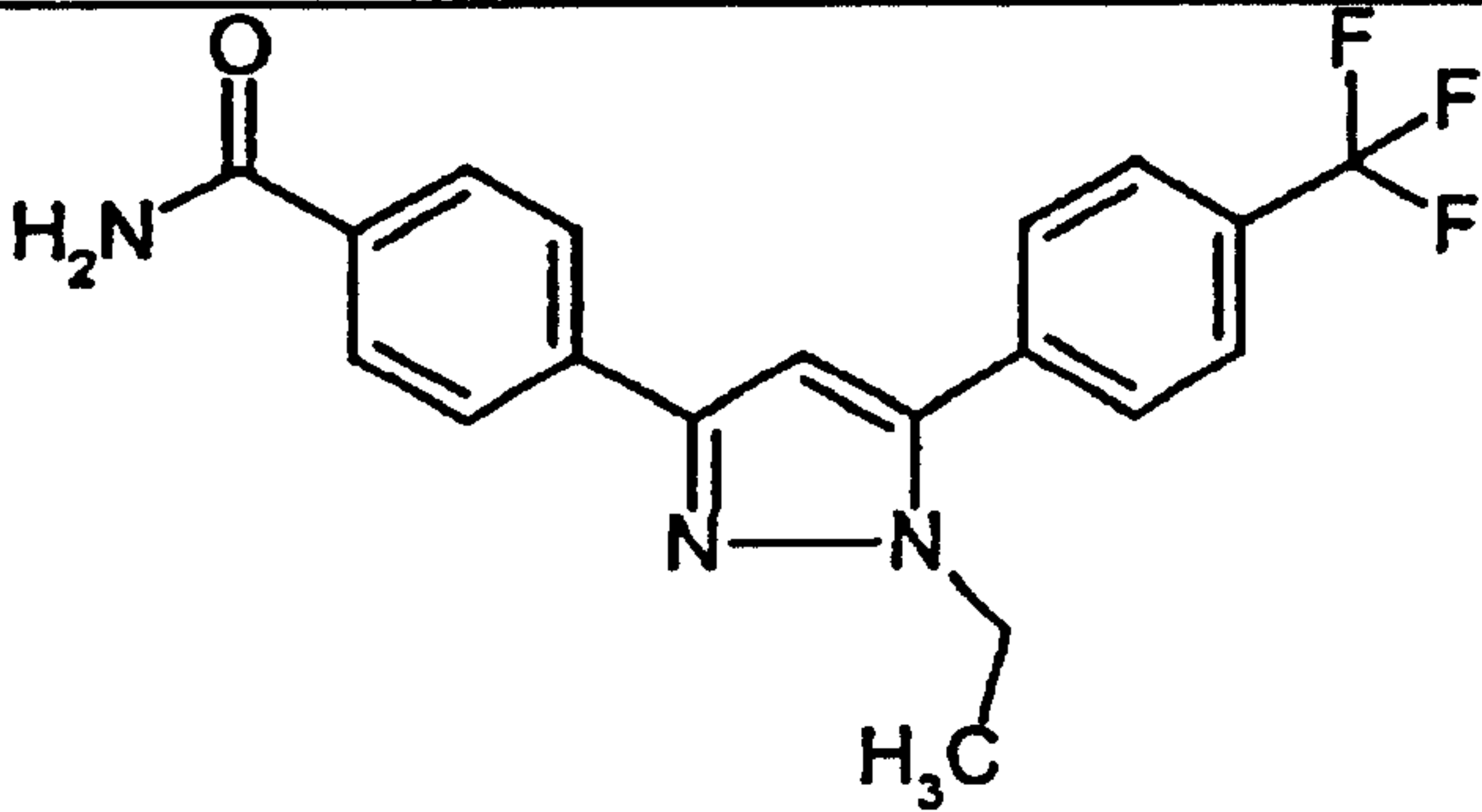
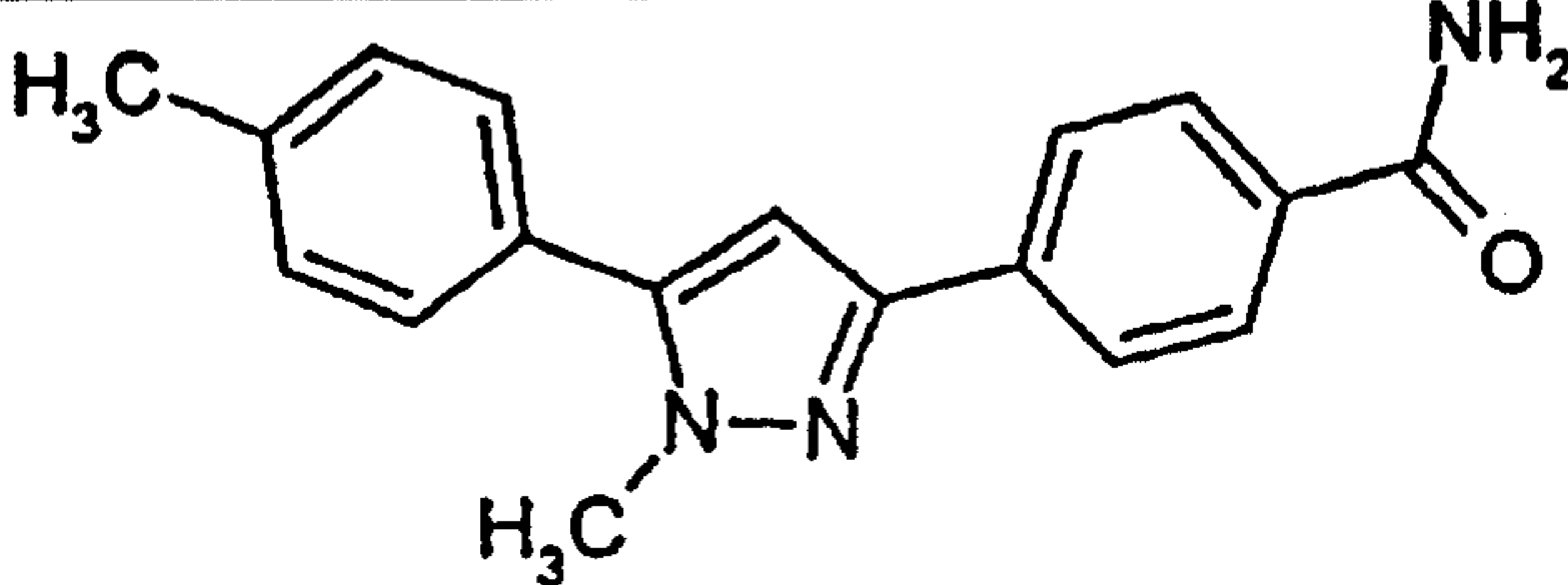
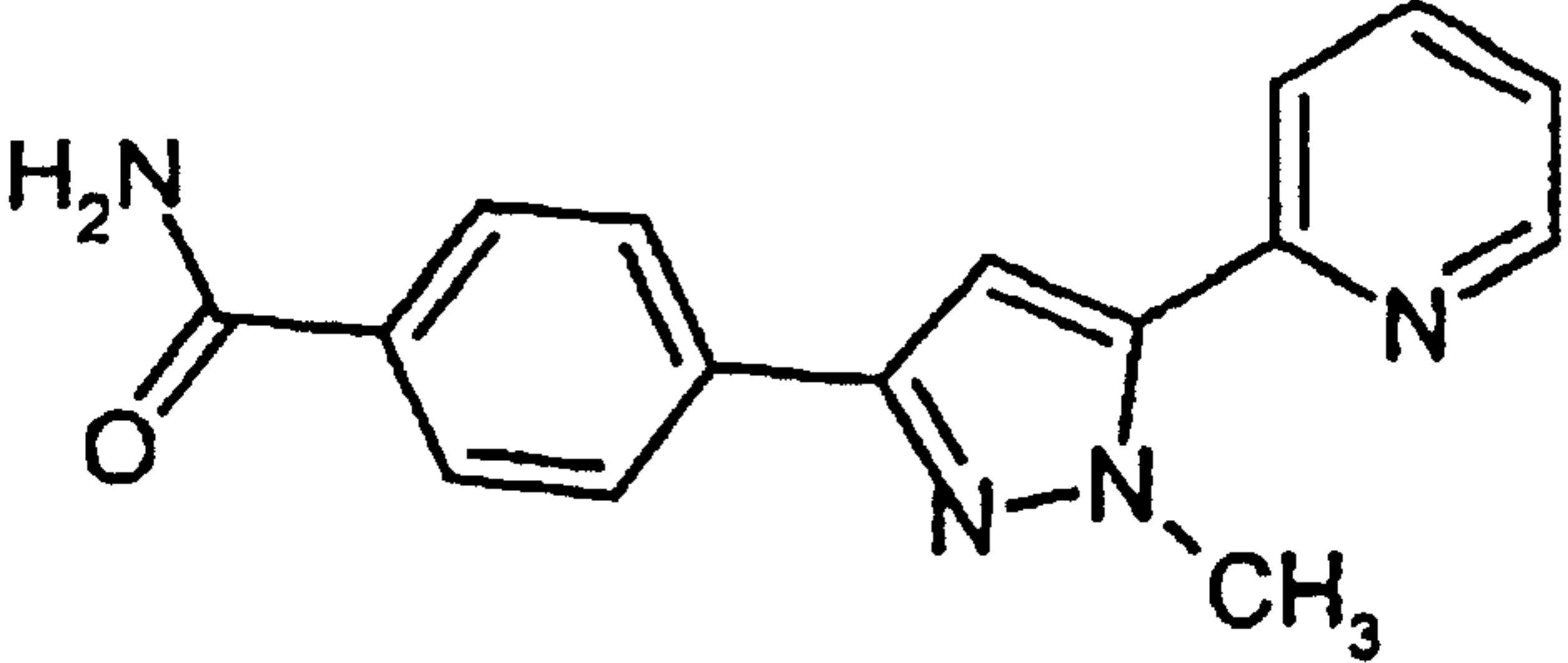
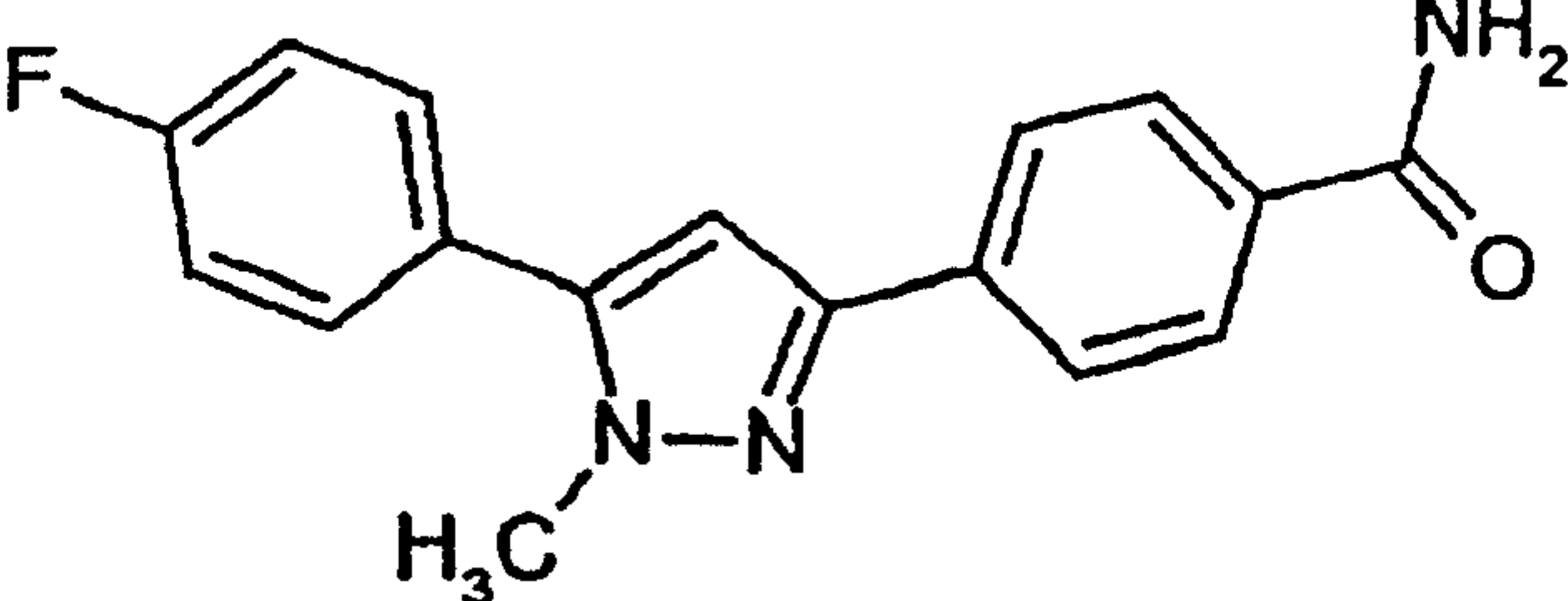
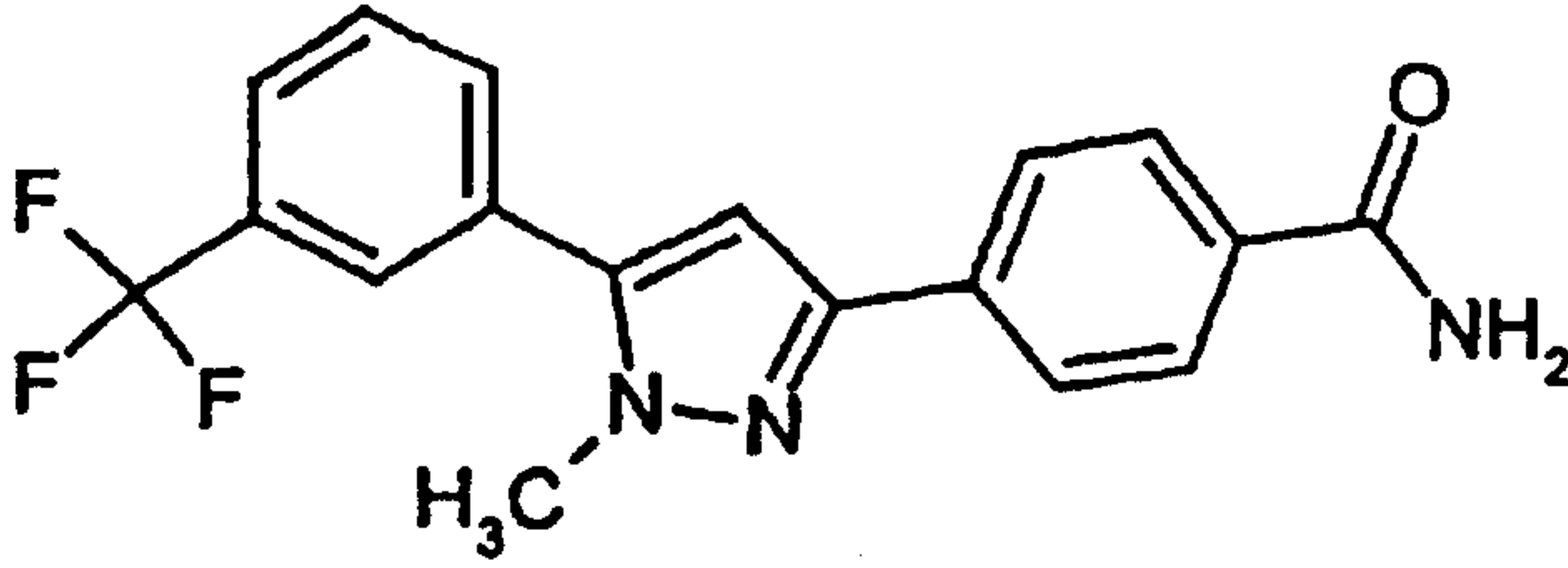
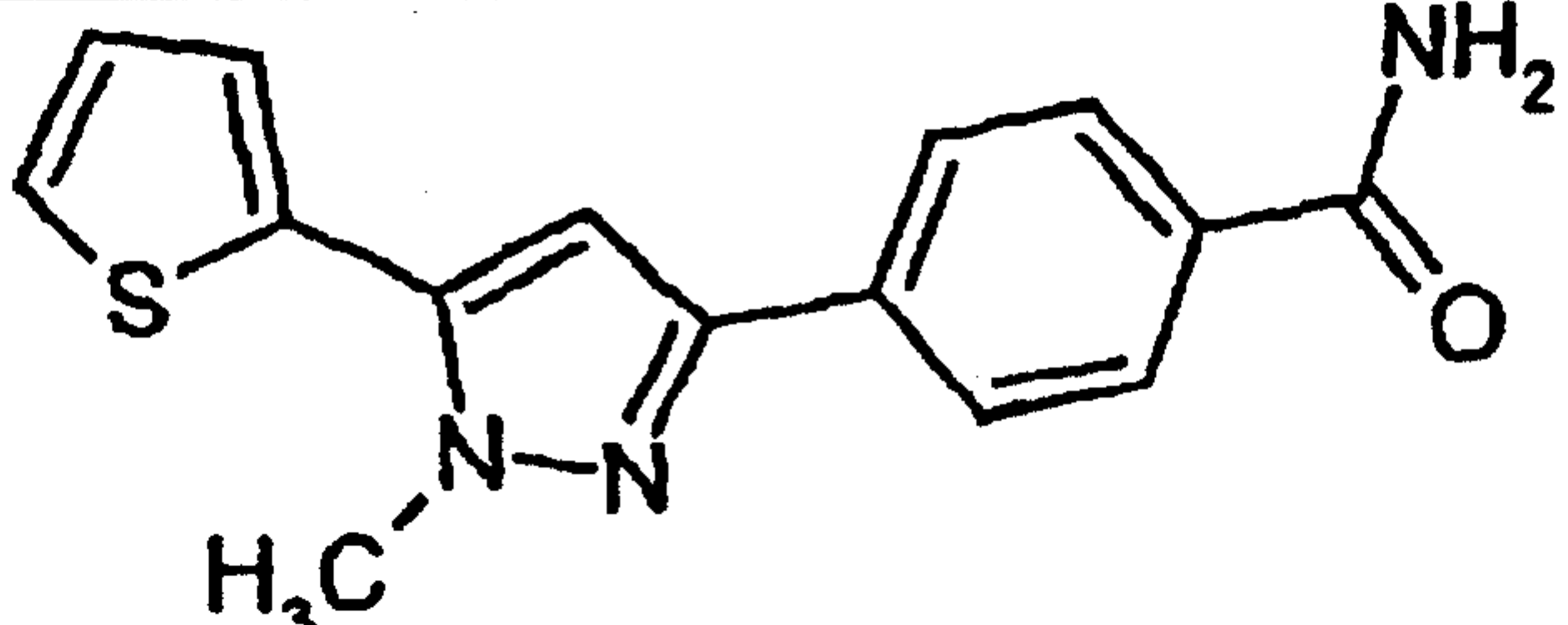
- 5 HPLC: 3.33 and 3.39 min, eluent: aq. 0.05% TFA (A), 0.05% TFA in acetonitrile (B); LiChrospher 100 RP-18; temp. 40°C; flow = 2.5 ml/min; gradient: t=0 min: 90%A, 10%B; t=5 min: 10%A, 90%B; t=7 min: 10%A, 90%B; t=7.05 min: 90%A, 10%B; t=8 min: 90%A, 10%B.

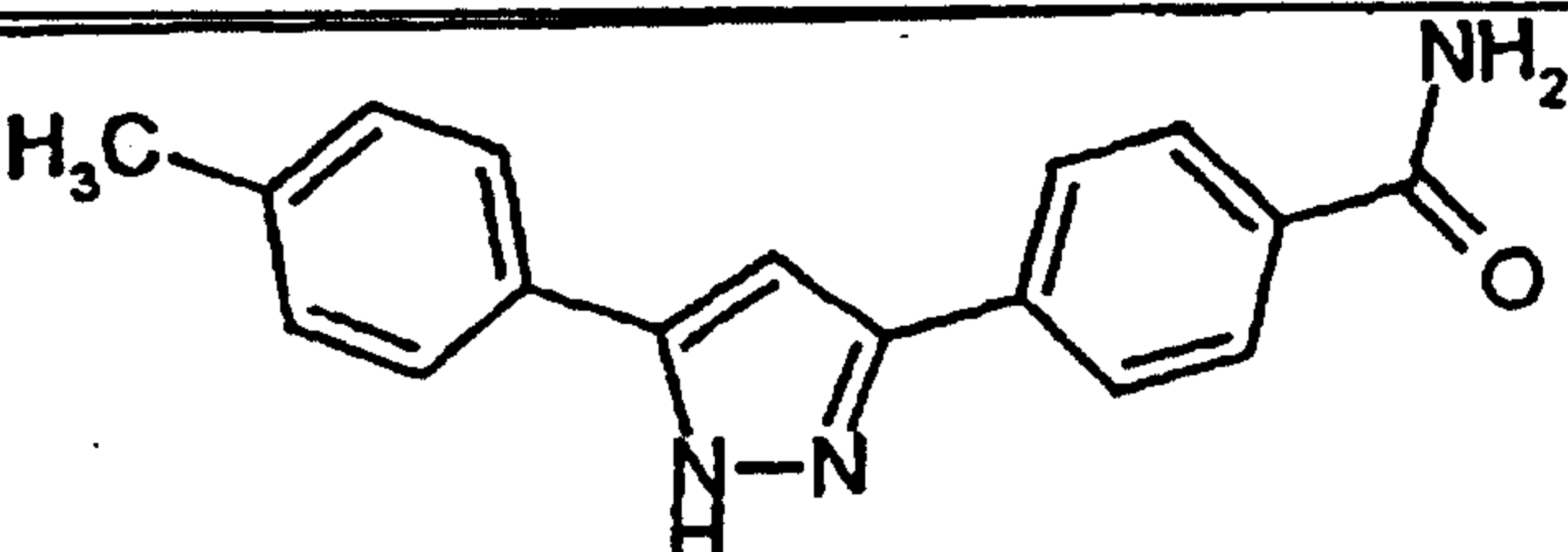
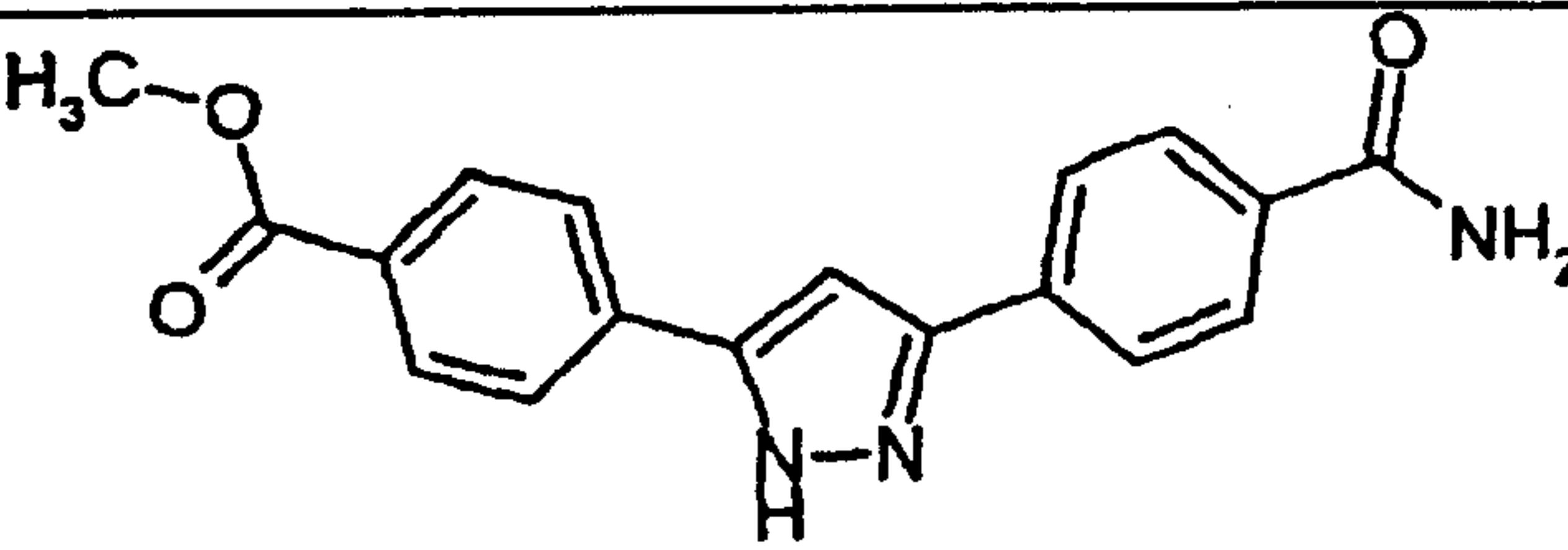
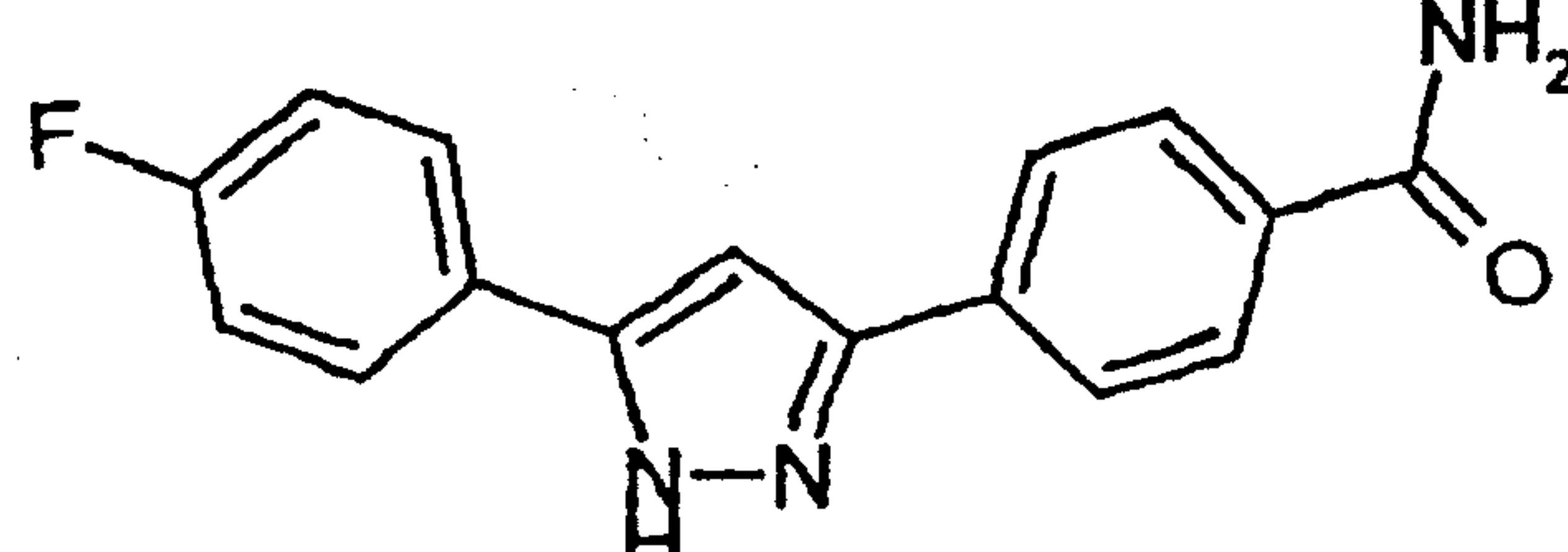
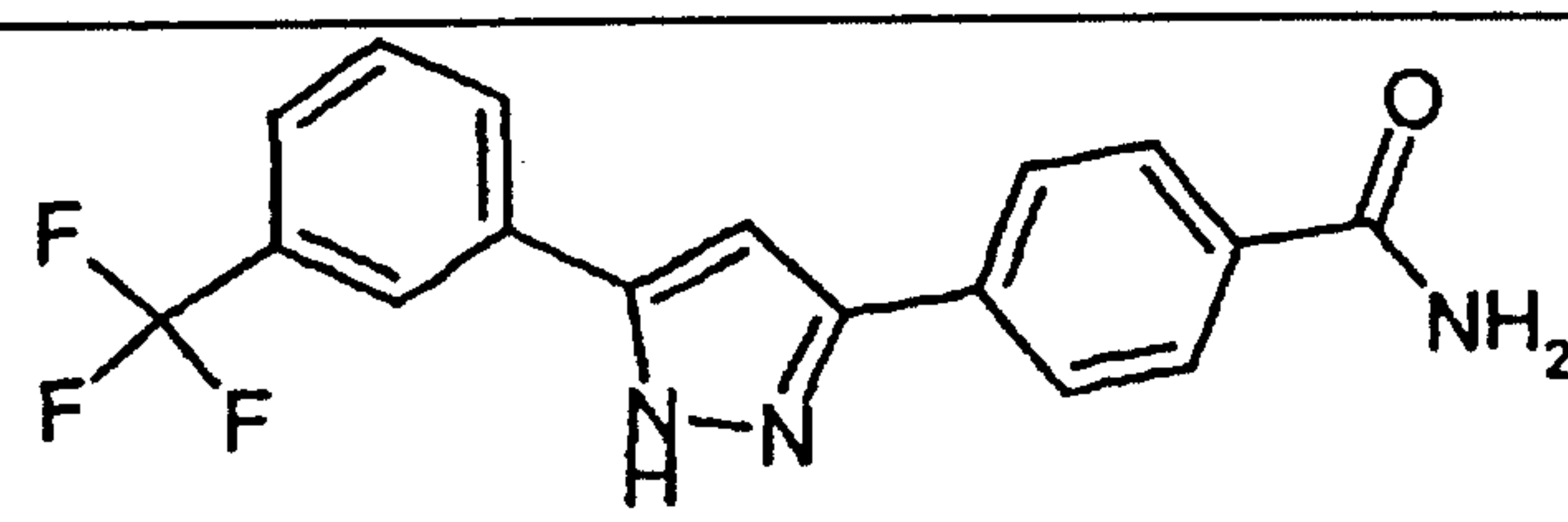
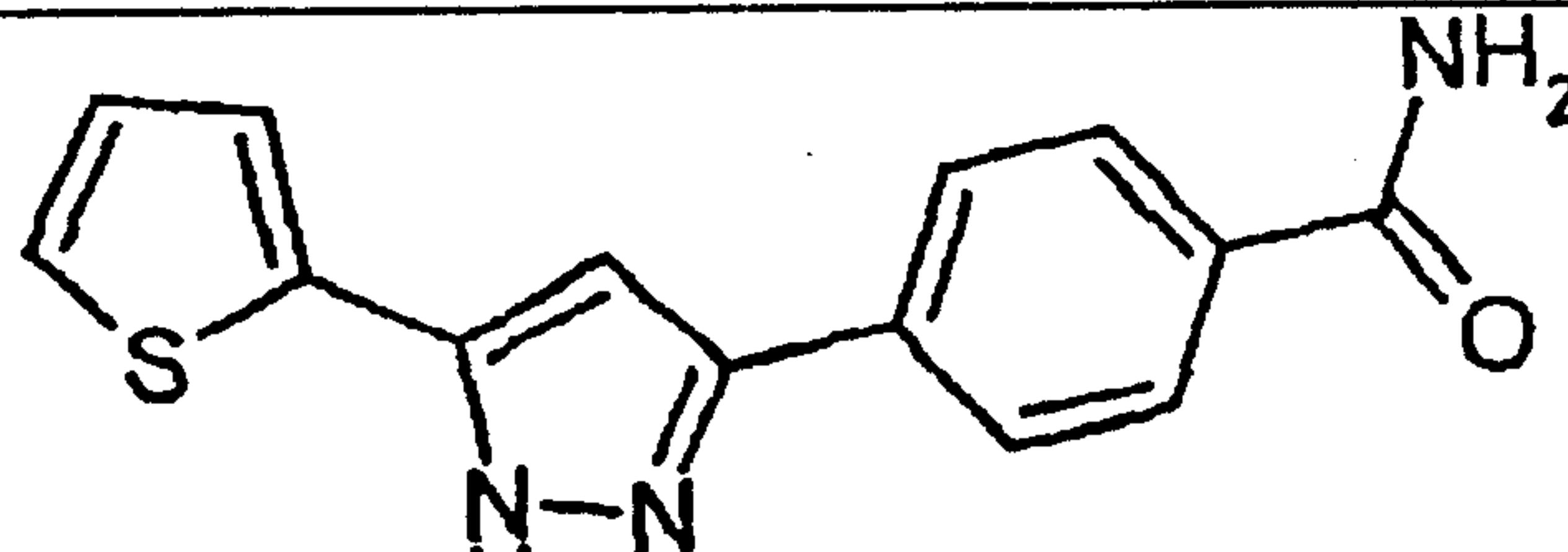
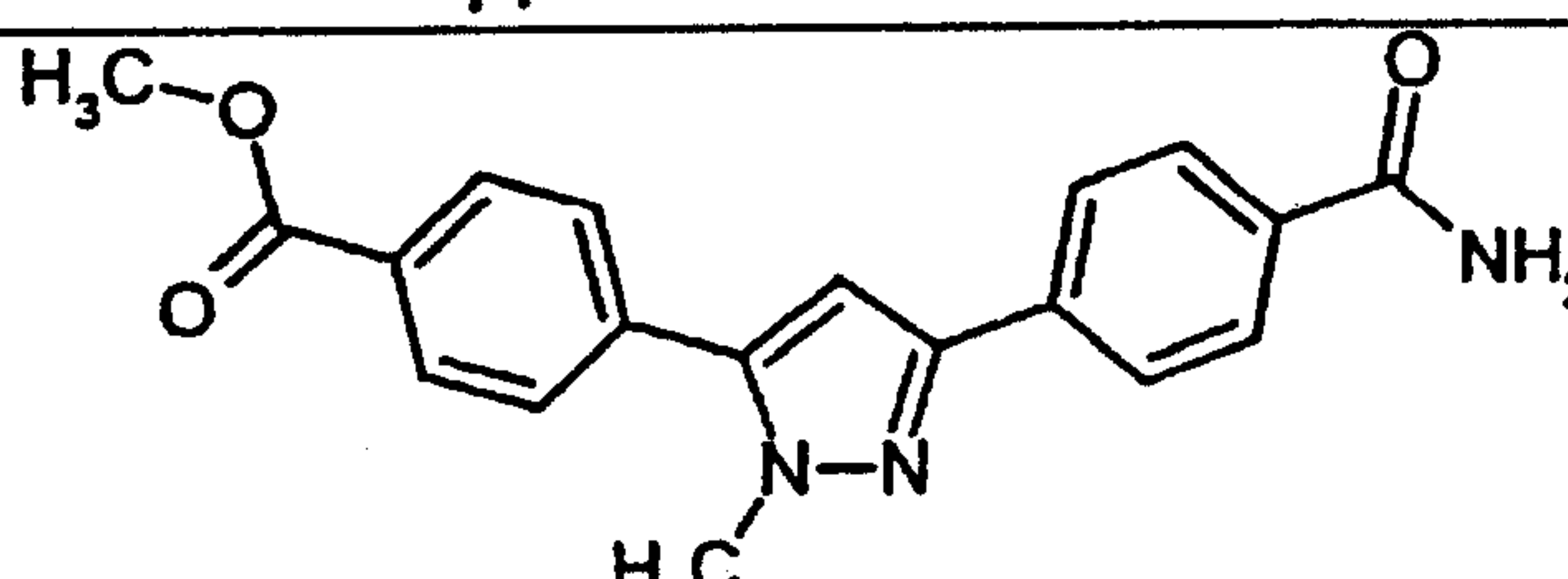
MS ES+: 356 found

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The examples shown in the following table are prepared in analogy to the procedure of Example 1.

Ex. No.	Structure	MW	R _t /method*
2		345.33	3.42 min [B]
3		277.33	4.93 min [C]
4		333.41	4.64 min [D]

Ex. No.	Structure	MW	R _t / method*
5		359.35	3.66 min [B]
6		291.36	3.88 min [A]
7		278.32	2.4 and 3.07 min [A]
8		295.32	3.81 min [A]
9		345.33	4.16 min [A]
10		283.35	3.66 min [A]

Ex. No.	Structure	MW	R _t / method*
11		277.33	3.68 min [A]
12		321.34	3.51 min [A]
13		281.29	3.58 min [A]
14		331.30	3.96 min [A]
15		269.33	3.40 min [A]
16		335.37	3.73 min [A]

Method [A]: HPLC: eluent: aq. 0.05% TFA (A), 0.05% TFA in acetonitrile (B); Symmetry C18; temp. 40°C; gradient: t=0 min: 10%A, 90%B, flow: 0.5 ml/min; t=4 min: 90%A, 10%B, flow: 0.5 ml; t=6 min: 90%A, 10%B, flow: 0.5 ml/min; 5 t=6.1 min: 10%A, 90%B, flow: 1.0 ml/min; t=7.5 min: 10%A, 90%B, flow: 0.5 ml/min

Method [B]: HPLC: eluent: aq. 0.05% TFA (A), 0.05% TFA in acetonitrile (B); LiChrospher 100 RP-18; temp. 40°C; flow = 2.5 ml/min; gradient: t=0 min: 90%A, 10%B; t=5 min: 10%A, 90%B; t=7 min: 10%A, 90%B; t=7.05 min: 90%A, 10%B; t=8 min: 90%A, 10%B.

5

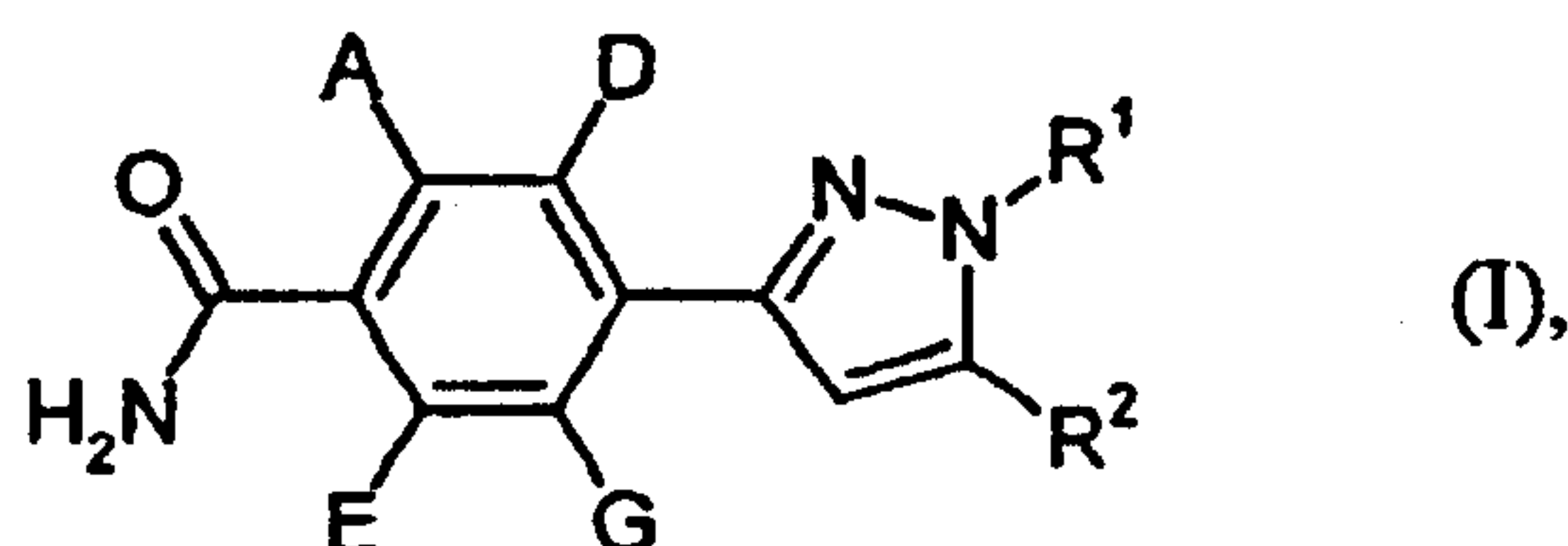
Method [C]: HPLC: eluent: aq. 0.05% TFA (A), 0.05% TFA in acetonitrile (B); LiChrospher 100 RP-18; temp. 40°C; flow = 1.5 ml/min; gradient: t=0 min: 100%A, 0%B; t=8 min: 0%A, 100%B; t=9 min: 0%A, 100%B; t=9.10 min: 100%A, 0%B; t=10 min: 100%A, 0%B.

10

Method [D]: HPLC: eluent: aq. 0.05% TFA (A), 0.05% TFA in acetonitrile (B); Vydac TPB 10 C18; temp. 40°C; flow = 4 ml/min; gradient: t=0.5 min: 90%A, 10%B; t=6.2 min: 10%A, 90%B; t=7 min: 10%A, 90%B; t=7.05 min: 90%A, 10%B; t=7.5 min: 90%A, 10%B.

Patent Claims

1. Use of pyrazolecarboxamides of the general formula (I)



in which

A, D, E and G are identical or different and represent hydrogen, halogen, trifluoromethyl, hydroxyl or (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy,

R¹ represents hydrogen or (C₁-C₆)-alkyl,

R² represents (C₆-C₁₀)-aryl or a 5- to 6-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the series S, N and/or O, the abovementioned aromatic ring systems optionally being substituted up to 3 times in an identical or different manner by halogen, trifluoromethyl, trifluoromethoxy, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy or (C₁-C₆)-alkoxycarbonyl,

and their tautomers and the respective salts

for preparing medicaments for the prophylaxis and/or treatment of disorders, in particular anaemia.

2. Use according to Claim 1, where in the general formula (I)

A, D, E and G are identical or different and represent hydrogen, fluorine, chlorine, bromine or trifluoromethyl,

R¹ represents hydrogen or methyl,

R² represents phenyl, furyl, thienyl, benzothiophenyl or pyridyl, where the abovementioned aromatic ring systems can optionally be

substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy or (C₁-C₄)-alkoxycarbonyl.

- 5 3. Use according to Claim 1, where in the general formula (I)

A, D, E and G represent hydrogen and

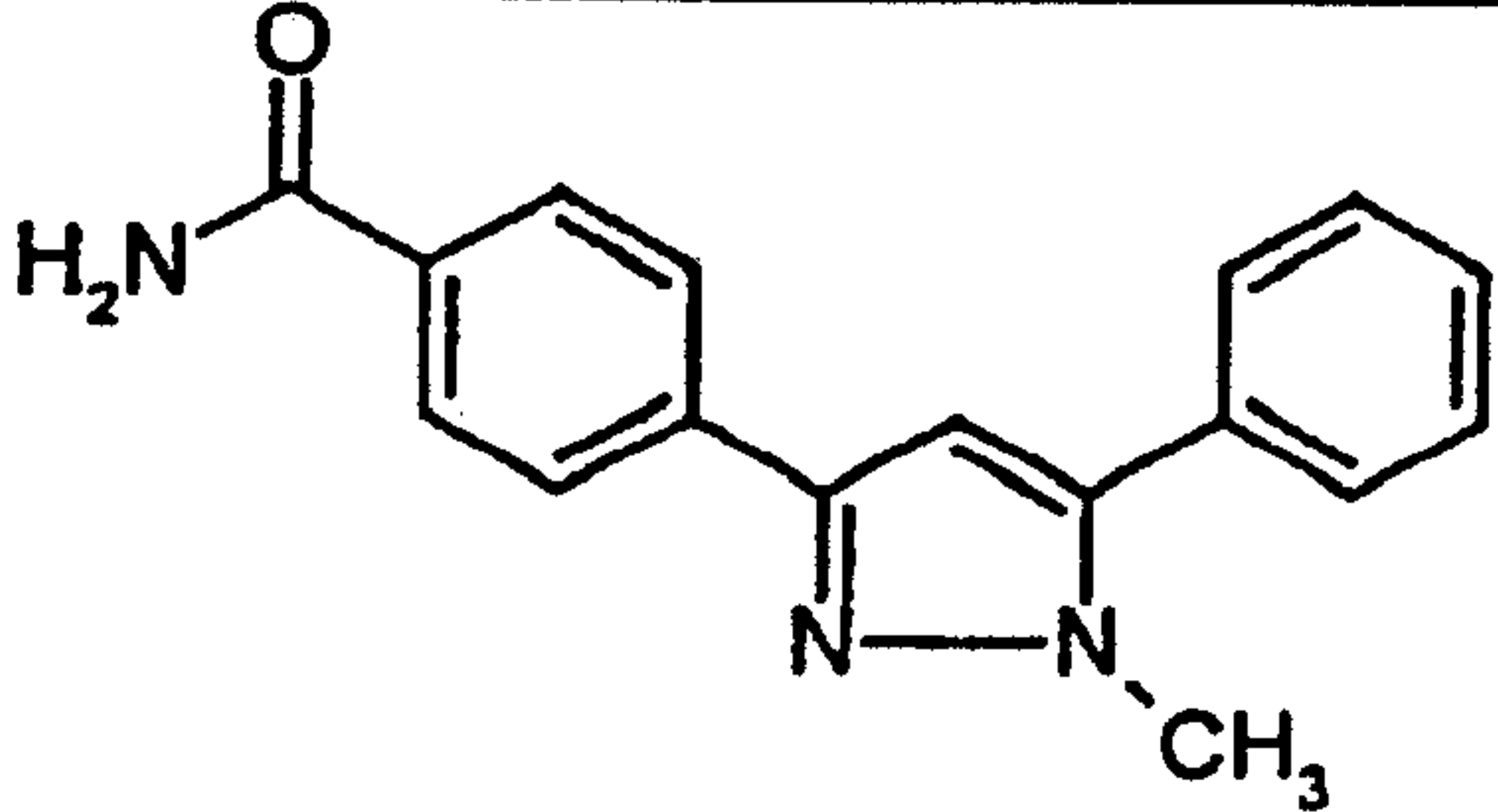
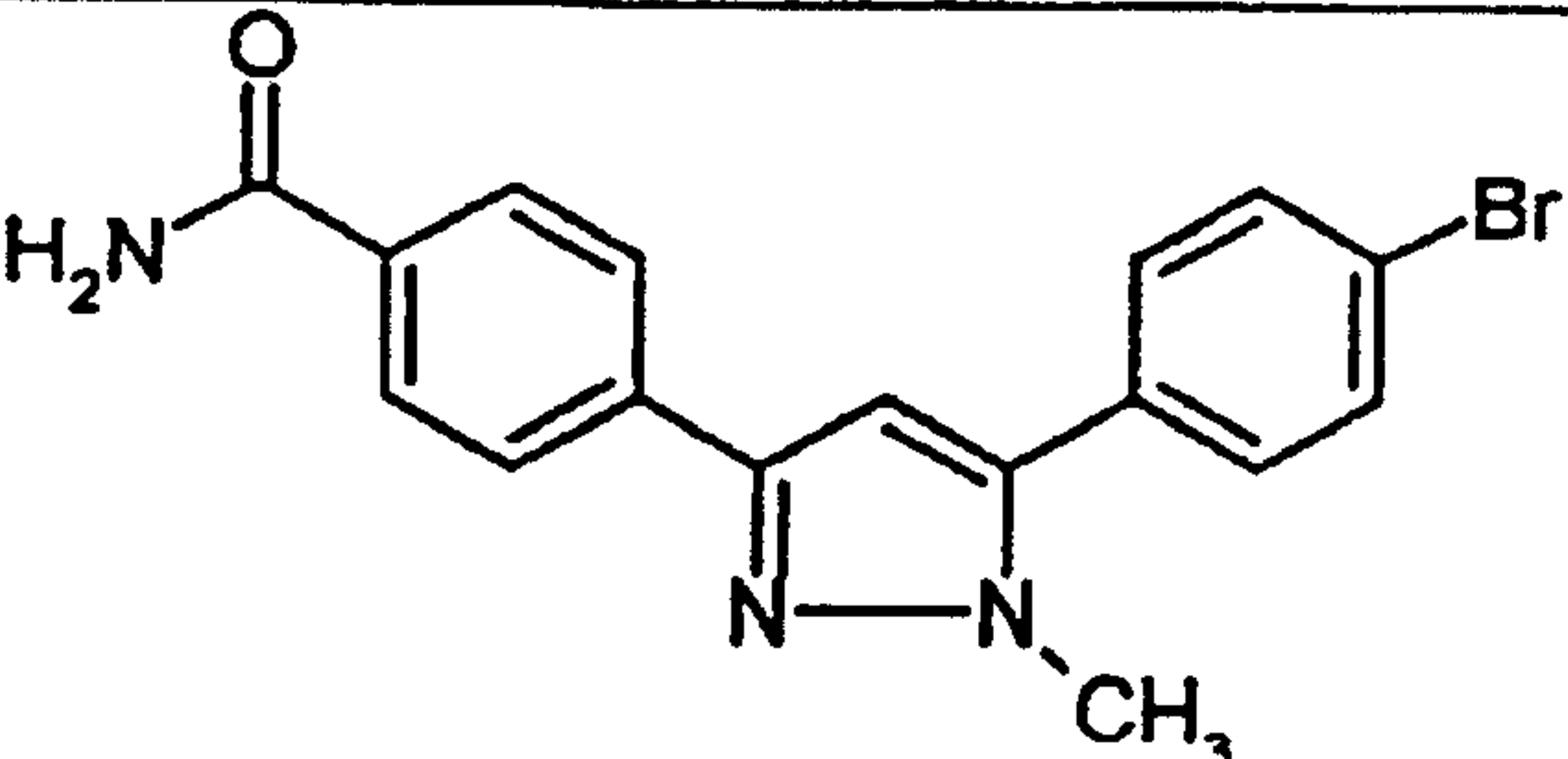
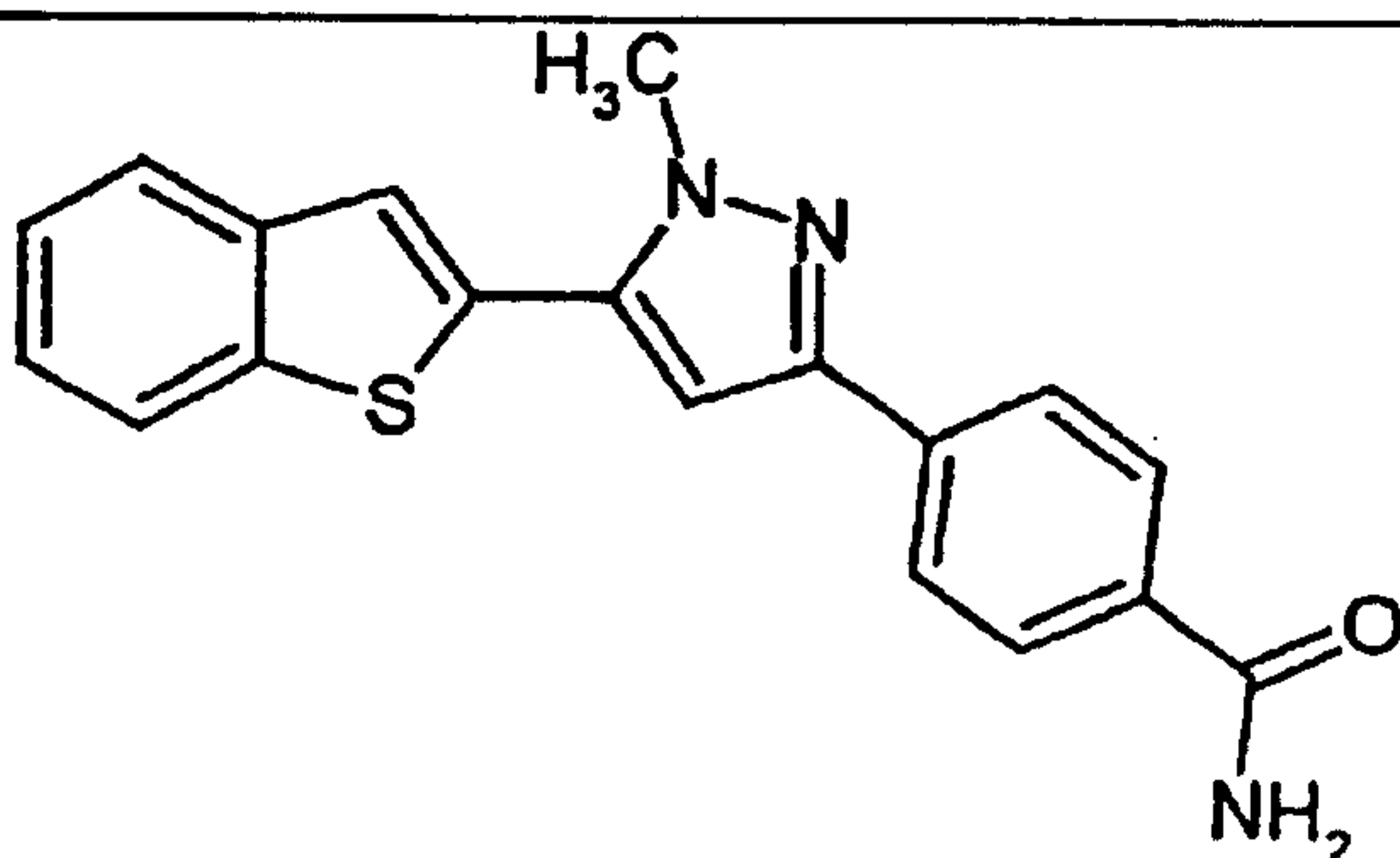
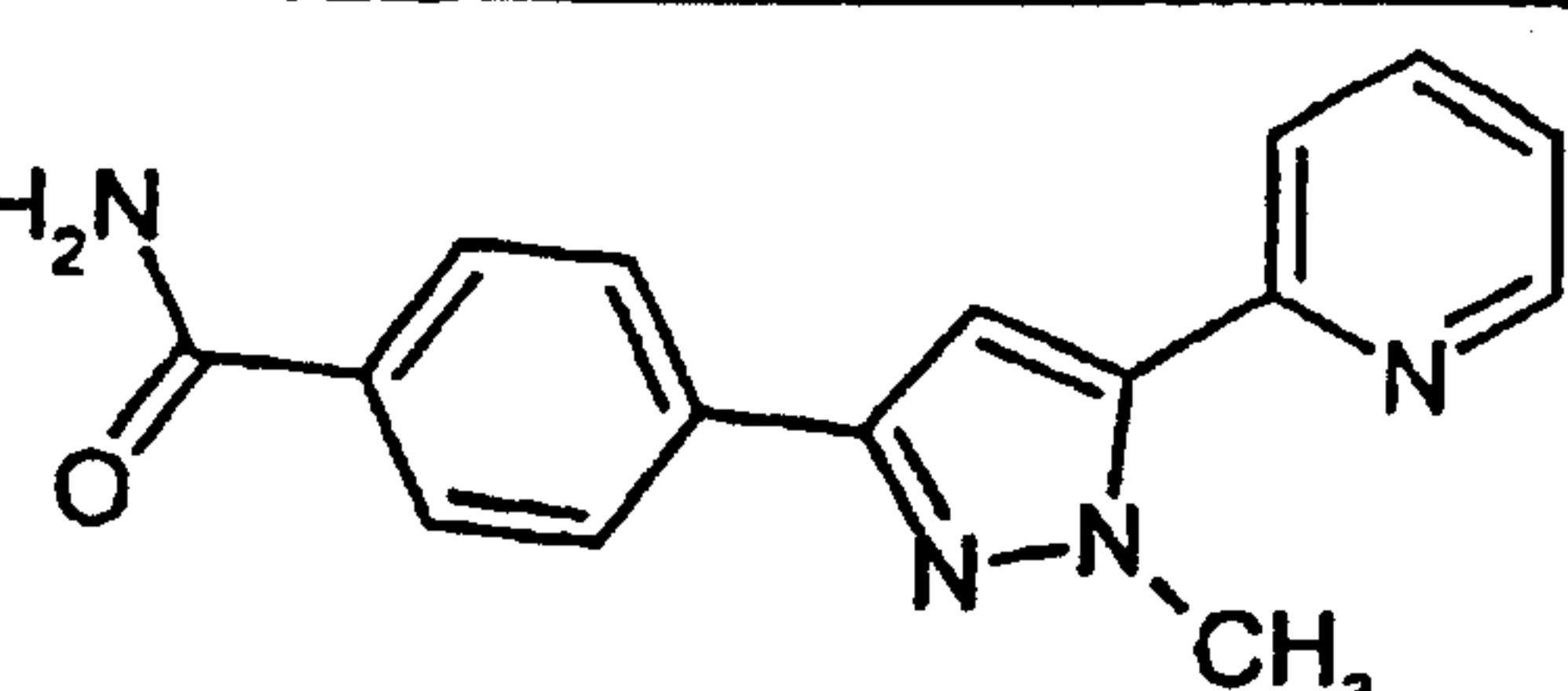
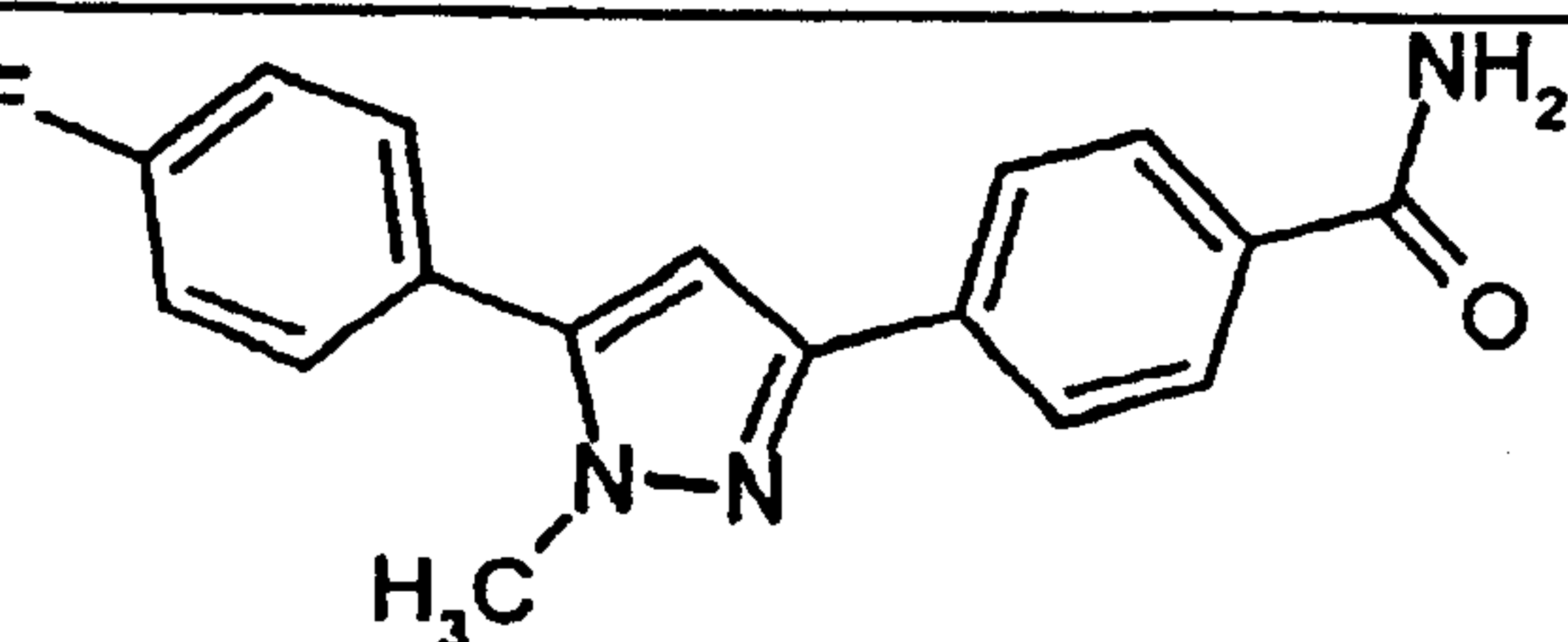
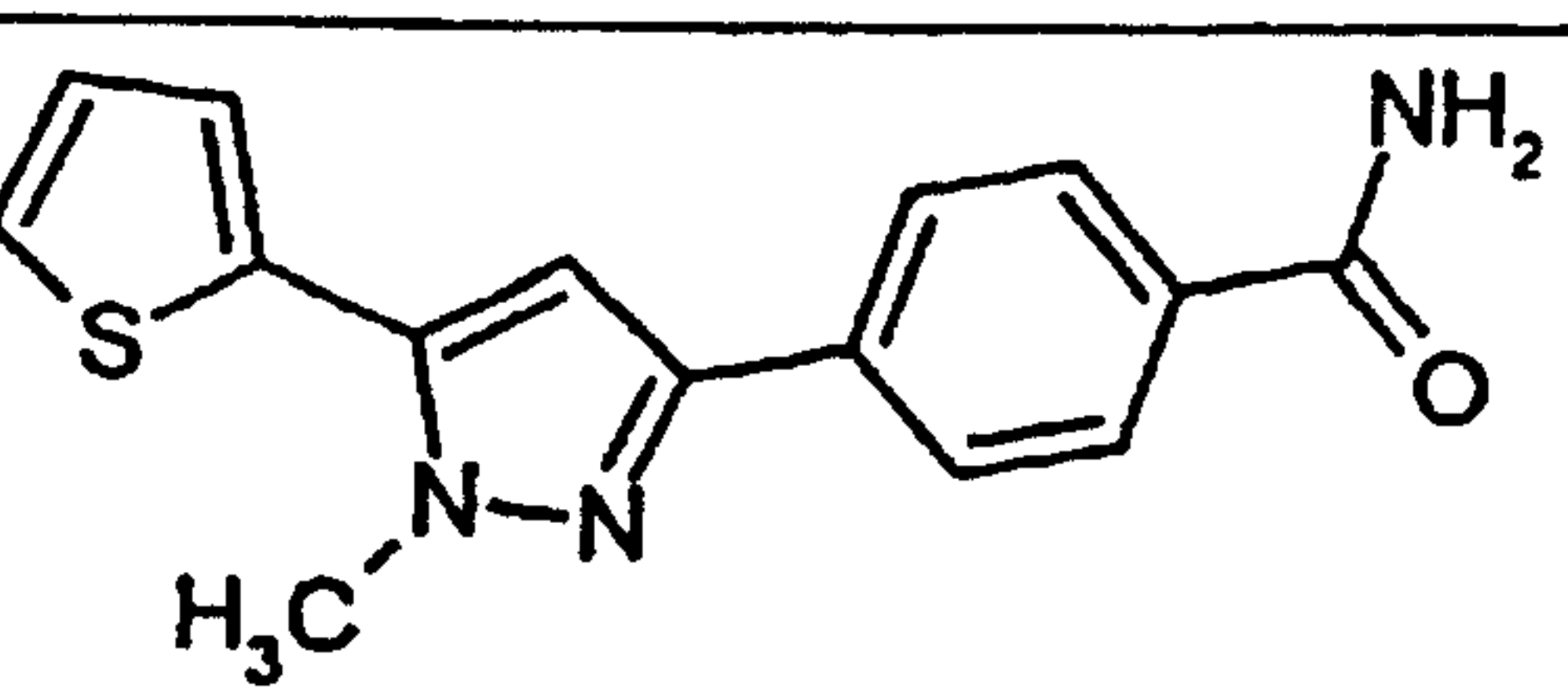
R¹ represents hydrogen or methyl and

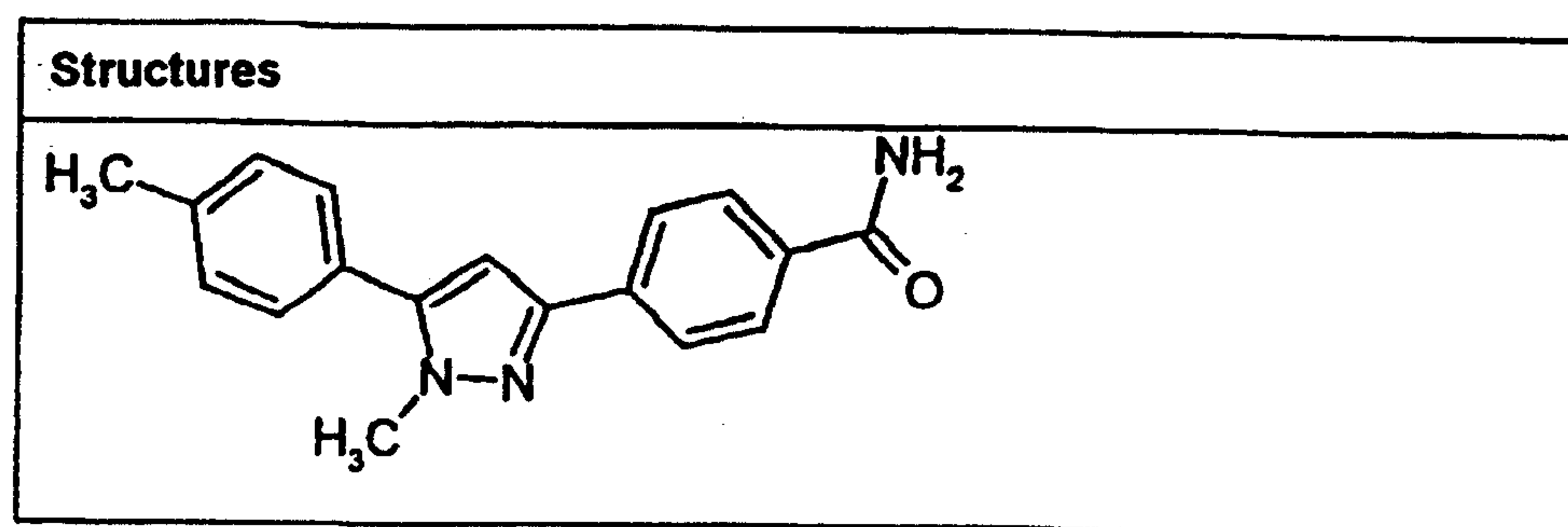
10

R² represents phenyl, thienyl, benzothiophenyl or pyridyl, where the abovementioned aromatic ring systems can optionally be substituted by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, methyl or methoxy.

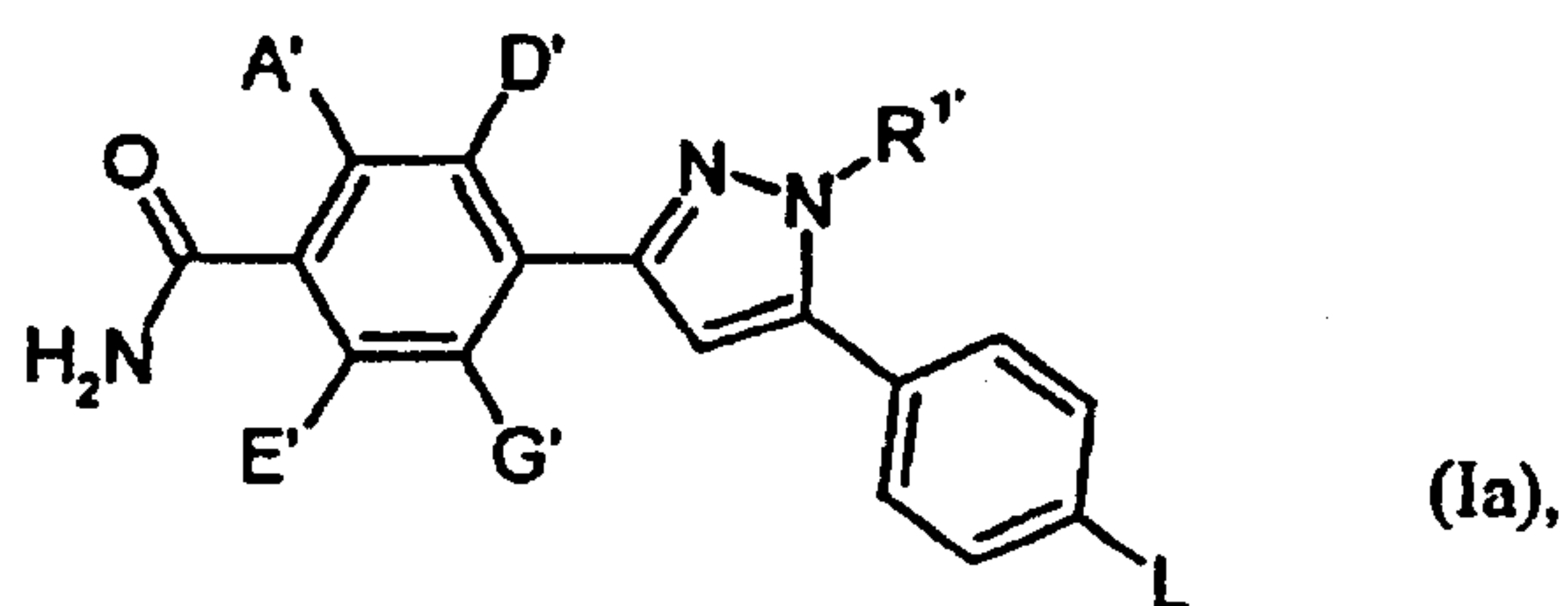
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4. Use of pyrazolecarboxamides according to Claim 1, where the compounds of the general formula (I) have the following structures:

Structures









5. Pyrazolecarboxamides of the general formula (Ia)



5 in which

A', D', E', G' and R¹ have the meaning of A, D, E, G and R¹ indicated above

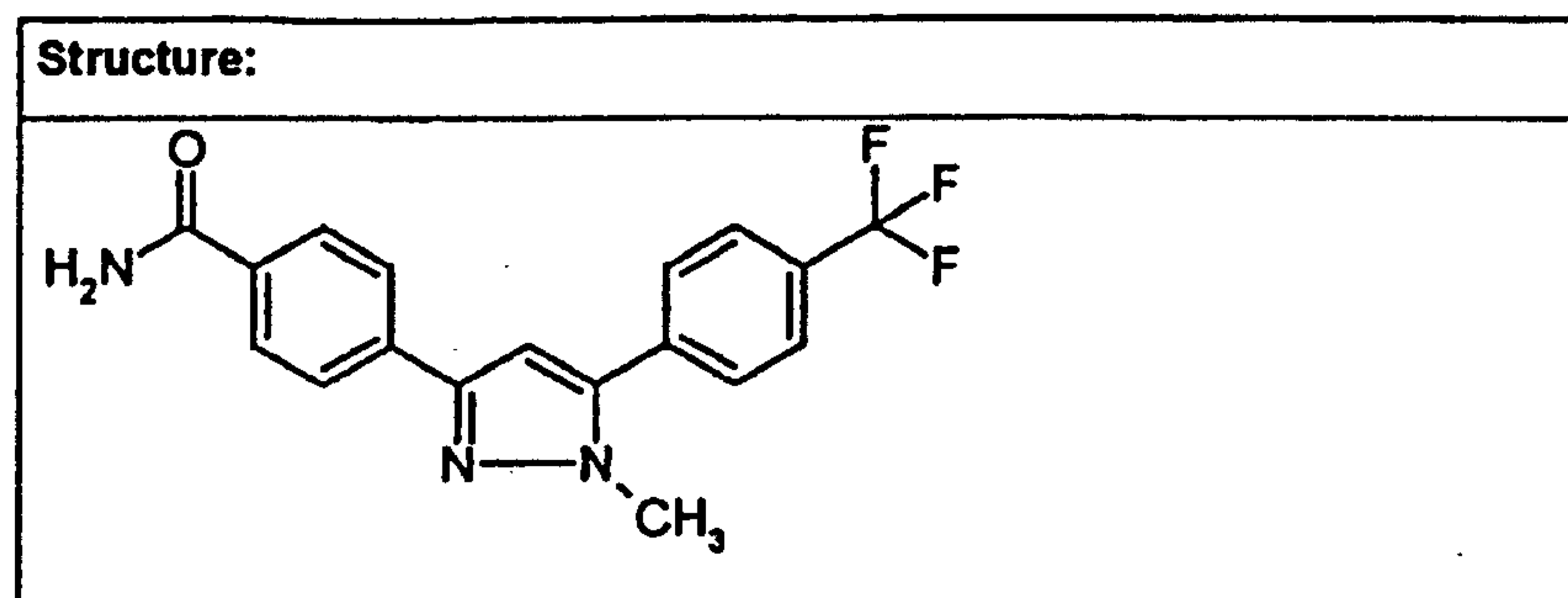
and

10

L represents CF₃ or OCF₃.

6. Pyrazolecarboxamide of the general formula (Ia) according to Claim 5 having the following structure:

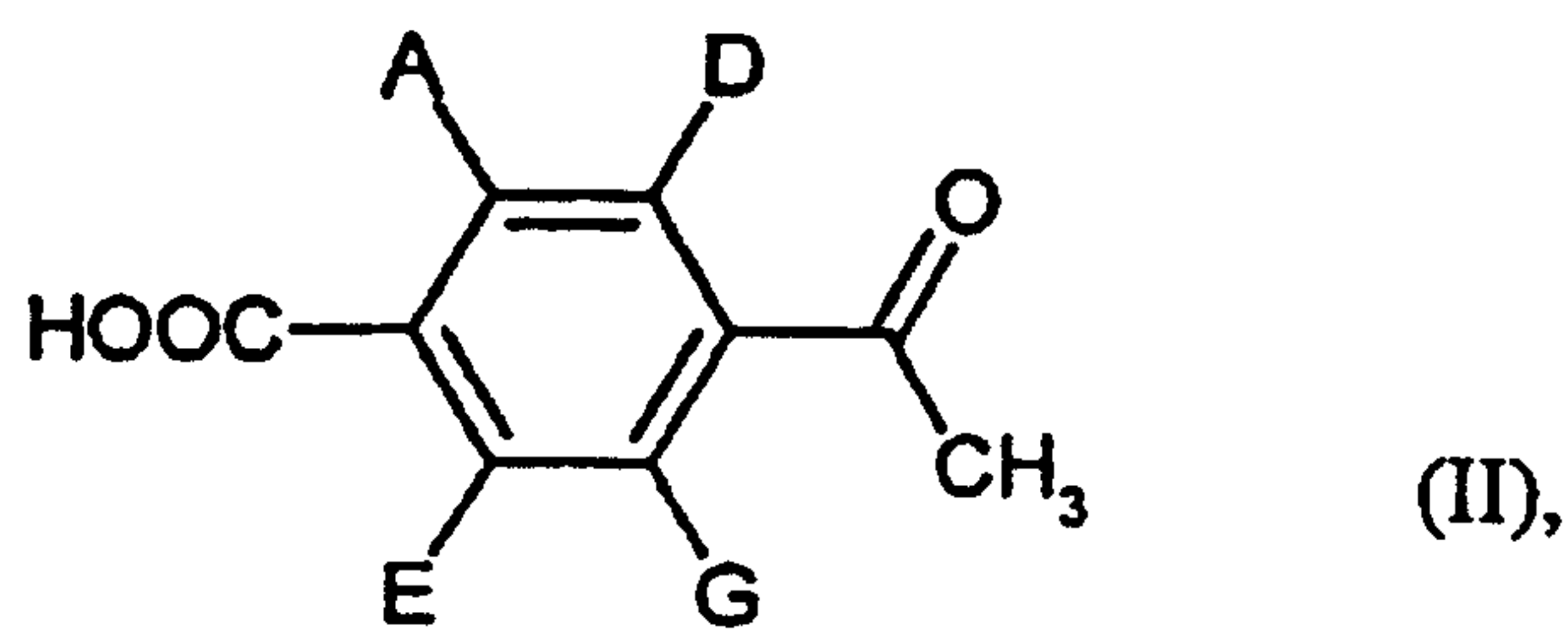
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7. Process for the preparation of pyrazolecarboxamides of the general formula (I) according to Claims 5 to 6, characterized in that

20

[A] compounds of the general formula (II)



in which

5 A, D, E and G have the meaning indicated above,

are coupled to an amino-functionalized resin and then reacted with compounds of the general formula (III)

$$10 \qquad \text{R}^3\text{OOC-R}^3 \qquad \text{(III),}$$

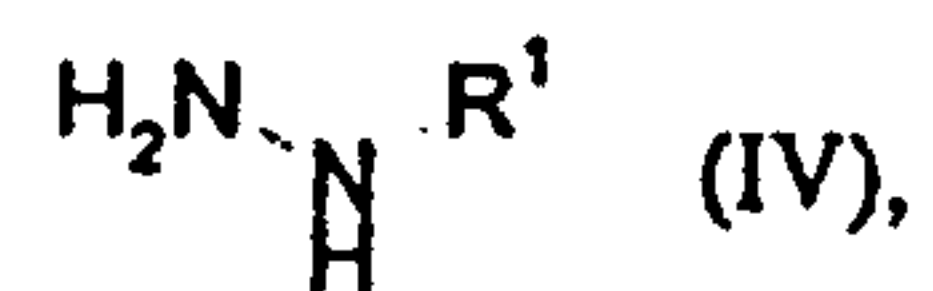
in which

R^2 has the meaning indicated above

15 and

R^3 represents a (C₁-C₄)-alkyl radical,

20 on the solid phase and then reacted with compounds of the general formula (IV)



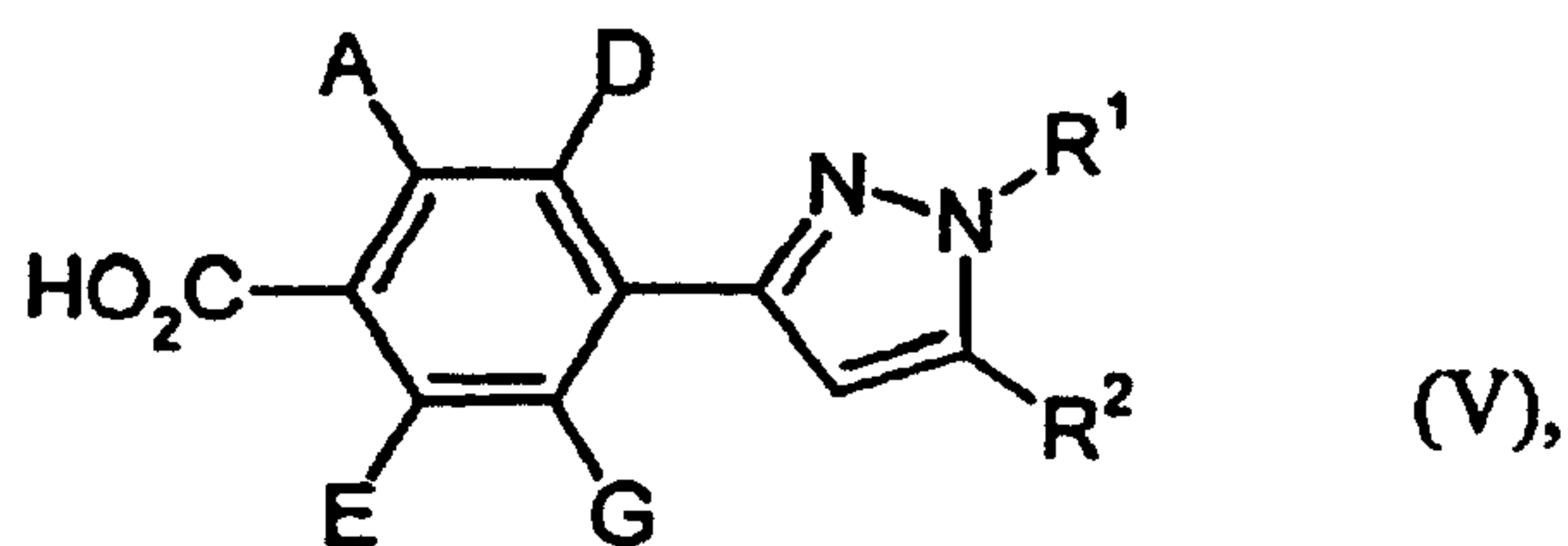
25 in which

R^1 has the meaning indicated above,

30 the compounds are then cleaved from the resin and, if appropriate (namely for $R^1 \neq H$), separated into the isomers,

or

[B] pyrazolecarboxylic acids of the general formula (V)



5 in which

R^1 , R^2 , A, D, E and G have the meaning indicated above,

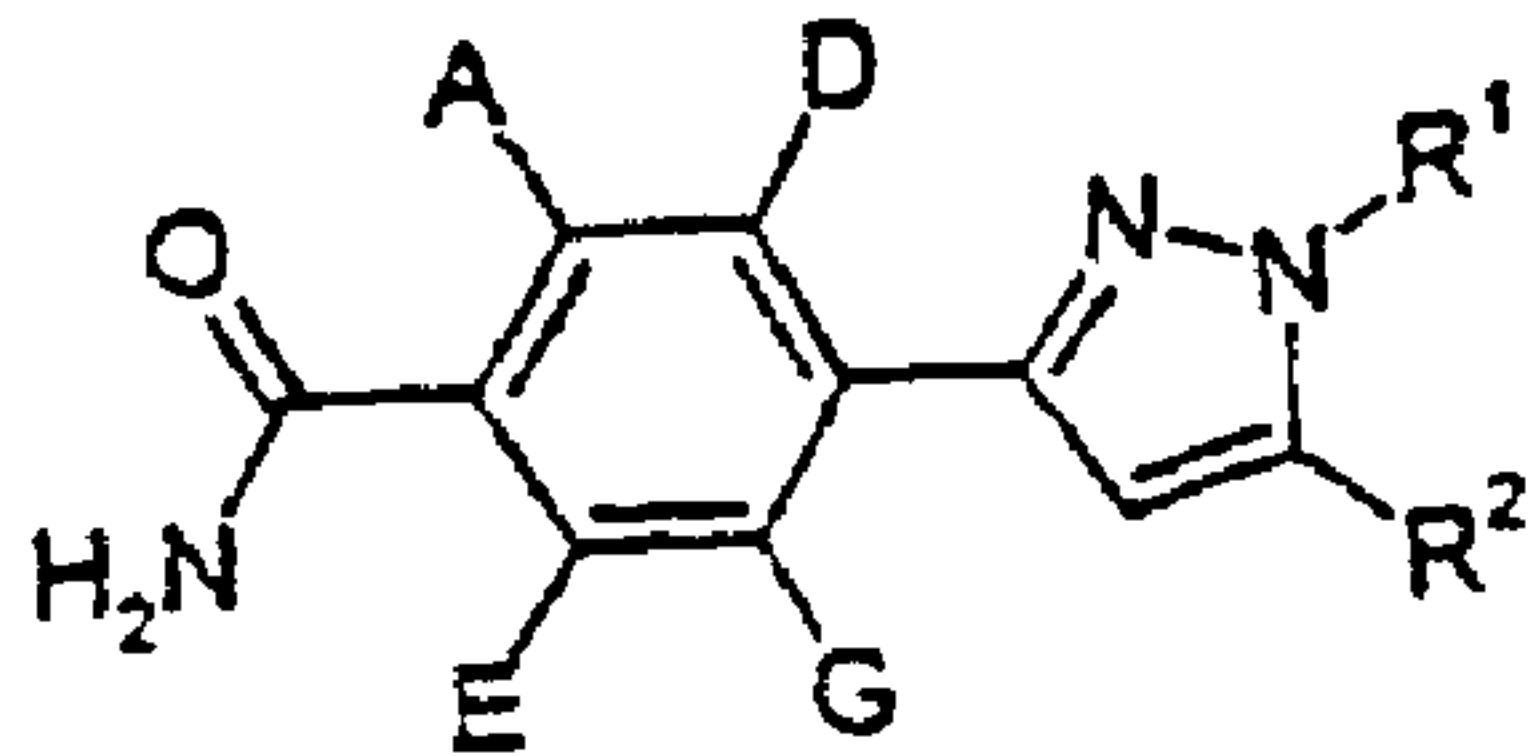
10 are reacted with ammonia, if appropriate in the presence of a dehydrating agent or via an activated carboxylic acid derivative.

8. Medicament comprising at least one pyrazolecarboxamide according to Claims 1 to 6 and pharmacologically acceptable formulating agents.
- 15 9. Medicament according to Claims 1 to 6 for the prophylaxis and/or treatment of anaemia.
10. Medicament according to Claims 1 to 6 for the treatment of anaemia of prematurely born infants, anaemia in chronic renal insufficiency, anaemia
20 after chemotherapy and anaemia in HIV patients.
11. Medicament according to Claim 8 for stimulating the erythropoiesis of autologous blood donors.
- 25 12. Pyrazolecarboxamides according to Claims 5 and 6 for the treatment and prophylaxis of disorders.
13. Use of erythropoietin sensitizers for producing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of anaemia.
30
14. Use according to Claim 13 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of anaemia of prematurely

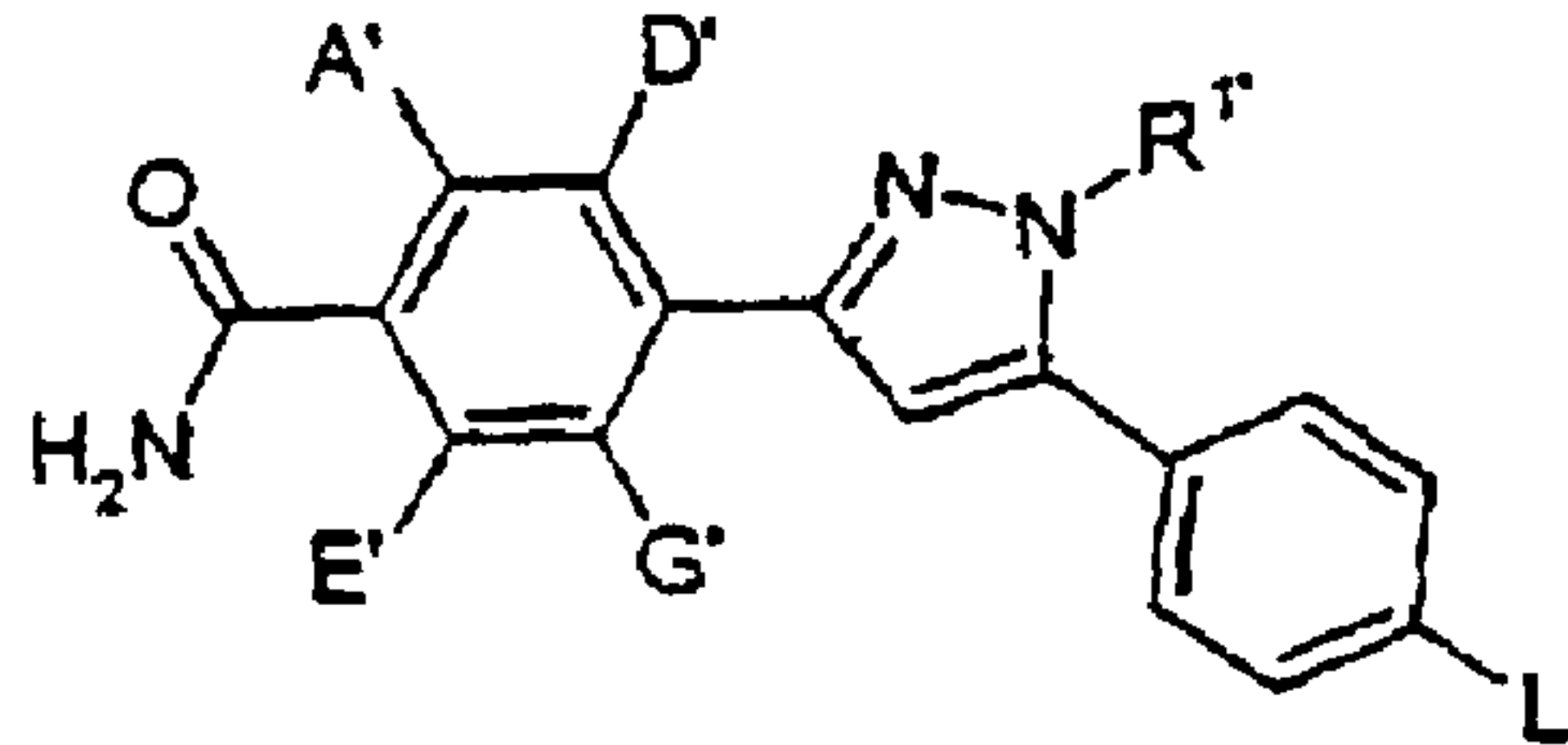
born infants, anaemia in chronic renal insufficiency, anaemia after chemotherapy and anaemia in HIV patients.

- 5 15. Use of erythropoietin sensitizers for producing medicaments or pharmaceutical compositions for stimulating the erythropoiesis of autologous blood donors.
16. Use according to one of Claims 13 to 15, characterized in that the erythropoietin sensitizers are administered orally.

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(I)



(Ia)