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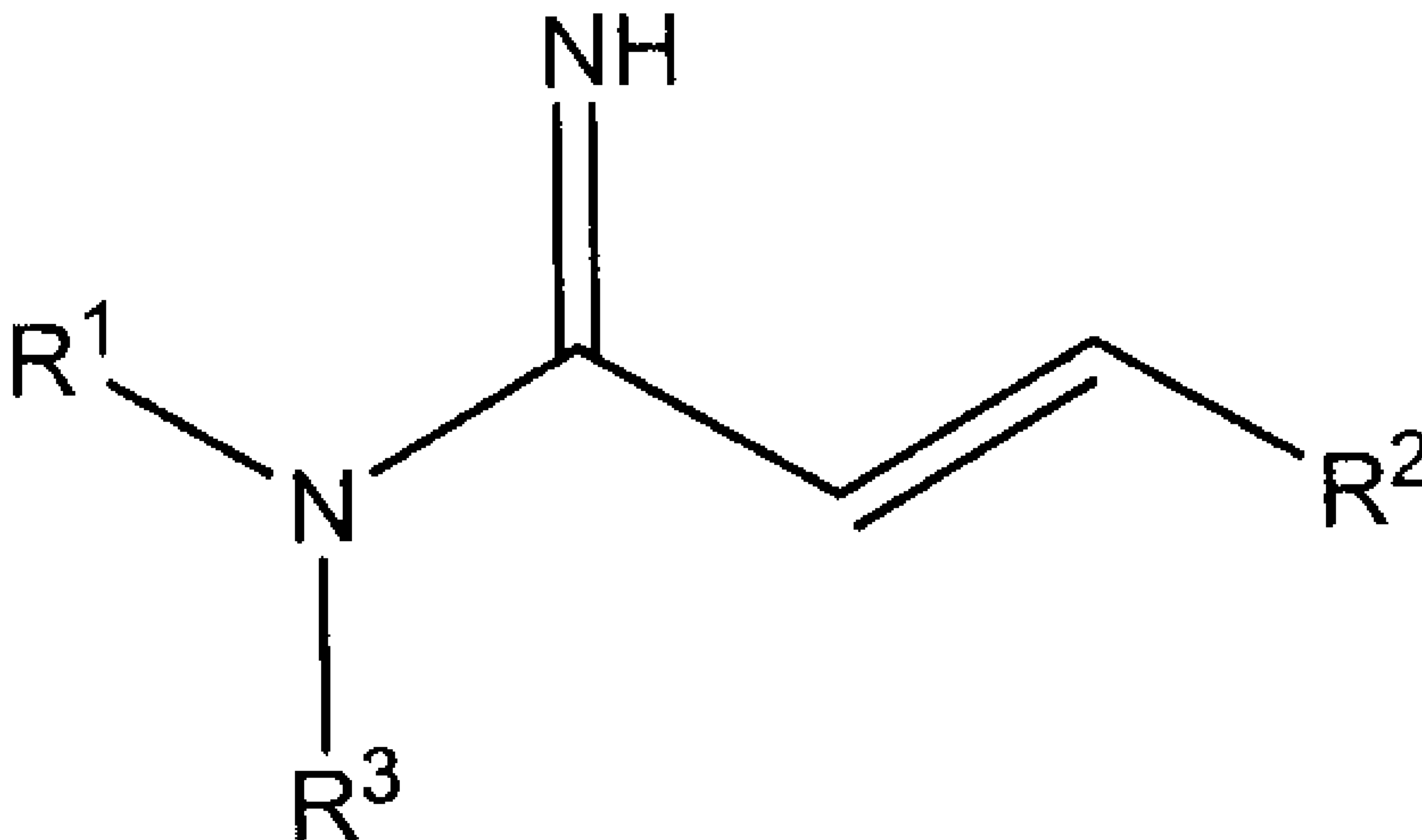
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(54) Titre : DERIVES D'AMIDINE EN TANT QU'ANTAGONISTES SELECTIFS DE RECEPTEURS NMDA

(54) Title: AMIDINE DERIVATIVES AS SELECTIVE ANTAGONISTS OF NMDA RECEPTORS



(I)

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A class of styryl amidine derivatives which are antagonists of the hum NMDA receptor, being selective for those containing the NR2B subunit, are active in the treatment and/or prevention of neurological and neurodegenerative disorders, in particular neuropathic pain and headache, specifically migraine, whils displaying fewer ataxic and related side-effects associated with other classes of NMDA receptor antagonists.

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(54) Title: AMIDINE DERIVATIVES AS SELECTIVE ANTAGONISTS OF NMDA RECEPTORS

(57) Abstract: A class of styryl amidine derivatives which are antagonists of the hum NMDA receptor, being selective for those containing the NR2B subunit, are active in the treatment and/or prevention of neurological and neurodegenerative disorders, in particular neuropathic pain and headache, specifically migraine, whilst displaying fewer ataxic and related side-effects associated with other classes of NMDA receptor antagonists.



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**AMIDINE DERIVATIVES AS SELECTIVE ANTAGONISTS OF
NMDA RECEPTORS**

5 The present invention relates to a class of amidine derivatives and
to their use in the therapy of neurological disorders. In particular, this
invention relates to amidines that are useful as selective antagonists of
NR2B subunit-containing human N-methyl-D-aspartate (NMDA)
receptors. The compounds of the present invention are thus useful for
relieving, treating or preventing neurological and neurodegenerative
10 disorders, including pain (and in particular neuropathic pain and
headache, specifically migraine), epilepsy, stroke, anxiety, cerebral
ischemia, muscular spasms, Alzheimer's Disease, Huntington's Disease
and Parkinson's Disease.

 Glutamate plays a key role in processes related to chronic pain and
15 pain-associated neurotoxicity, largely acting through NMDA receptors.
Much evidence points to the involvement of NMDA receptors in the
development and maintenance of neuropathic pain. NMDA receptor
antagonists, for example ketamine, dextromethorphan and CPP (3-(2-
carboxypiperazin-4-yl)propyl-1-phosphonic acid) have been reported to
20 produce symptomatic relief in a number of neuropathies including
postherpetic neuralgia, central pain caused by spinal cord injury and
phantom limb pain (Kristensen *et al.*, *Pain*, 1992, **51**, 249-253; Eide *et al.*,
Pain, 1995, **61**, 221-228; Knox *et al.*, *Intensive Care*, 1995, **23**, 620-622;
Max *et al.*, *Clin. Neuropharmacol.*, 1995, **18**, 360-368). However, at
25 analgesic doses, psychotomimetic effects that include dizziness, headache,
hallucinations, dysphoria and disturbances of cognitive and motor function
prohibit their widespread use. To exploit NMDA receptor antagonists as
possible treatment options for neuropathic pain, it is necessary to develop
new agents with a reduced side-effect profile.

30 Native NMDA receptors are heterodimers composed of an NMDA
R1 (NR1) subunit and at least one NMDA R2 (NR2) subunit. Receptor

cloning strategies have identified multiple NMDA receptor subunits in the CNS including the NR1 subfamily (with eight isoforms derived from alternative splicing of a single gene) and four NR2 subunits (A, B, C, and D) each encoded by a single gene (for review, see Whiting & Priestley, *Frontiers of Neurobiology* 3, *Amino Acid Neurotransmission*, Portland Press, 1996, 153-176). Functional receptors have different physiological and pharmacological properties and are differentially distributed in the mammalian CNS, demonstrating the functional heterogeneity of NMDA receptors (Ishii *et al.*, *J. Biol. Chem.*, 1993, 268, 2836-2843; Wenzel *et al.*, *NeuroReport*, 1995, 7, 45-48; Laurie *et al.*, *Brain Res. Mol. Brain Res.*, 1997, 51, 23-32).

NR1 is found throughout the brain whereas NR2 subunits show a differential distribution. In particular, whereas NR2C is heavily expressed and NR2A is moderately expressed in the cerebellum, there is negligible expression of NR2B in this structure. Immunocytochemical studies have demonstrated a restricted distribution of the NR2B subunit, with moderate labeling of fibres in laminae I and II of the dorsal horn suggesting a presynaptic location on primary afferent fibres and possible involvement in pain transmission (Boyce *et al.*, *Neuropharmacology*, 1999, 38, 611-623). The patterns of staining observed in the spinal cord, together with the data showing negligible expression of NR2B in the cerebellum, suggest that NR2B antagonists may possess antinociceptive effects, but with a reduced side effect profile in comparison to non-competitive NMDA antagonists or glycine site antagonists.

The NR1/2B selective antagonist CP-101,606 has been reported to possess antinociceptive activity in animal assays of inflammatory hyperalgesia (Taniguchi *et al.*, *Br. J. Pharmacol.*, 1997, 122, 809-812; Sakurada *et al.*, *Pharmacol. Biochem. Behav.*, 1998, 59, 339-345). In an animal assay of inflammatory hyperalgesia (carrageenan-induced mechanical hyperalgesia) the NR1/2B antagonists CP-101,606 and Ro 25-6981 have been shown to possess antinociceptive activity with a

significant separation between analgesic doses and those which induced motor impairment (Boyce *et al.*, *Neuropharmacology*, 1999, **38**, 611-623). NR1/2B antagonists are active in a wide range of animal nociceptive assays, suggesting a clinical utility for other painful conditions in addition to those caused by nerve damage. Moreover, these compounds may have a reduced propensity to elicit the undesirable side-effects (including hallucinations, sedation and ataxia) of ketamine, dextromethorphan and other NMDA ion channel antagonists.

There is a wealth of *in vitro* and animal model data suggesting that changes in the glutamatergic system (receptors, uptake, release) increase neuronal sensitivity to previous physiological stimuli and thereby trigger secondary neuronal damage. The primary pathology underlying the generation of symptoms in Parkinson's disease is degeneration of dopaminergic neurons of the nigrostriatal pathway (Hornykiewicz, *Pharmacol. Rev.*, 1966, **18**, 925-964). Subsequent to loss of striatal dopamine, a series of changes in activity of the basal ganglia circuitry arise, including increased activity in striatal outputs to the lateral segment of the globus pallidus. Overactivity of the striatolateral pallidal pathway is thought to be responsible for the generation of parkinsonian symptoms. It has been demonstrated that selective blockade of NR2B-containing NMDA receptors with the polyamine antagonists ifenprodil and eliprodil cause a significant increase in locomotor activity in a rodent model (Nash *et al.*, *Experimental Neurology*, 1999, **155**, 42-48) and ifenprodil has demonstrated activity in a primate model of Parkinson's disease (Mitchell *et al.*, *Behav. Pharmacol.*, 1995, **6**, 492-507).

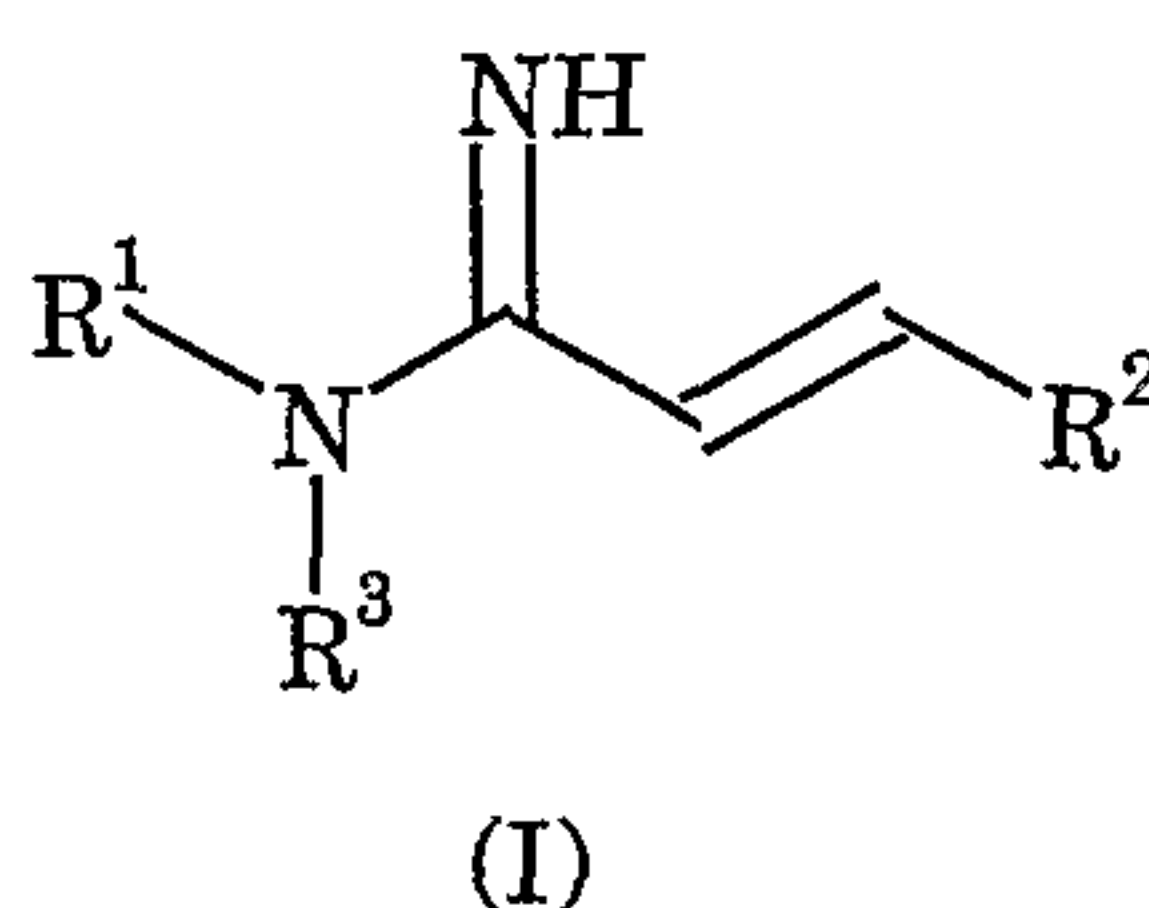
The present invention provides a class of styryl amidine derivatives which are antagonists of the human NMDA receptor, being selective for those containing the NR2B subunit. As such, they will be active in the treatment of neurological and neurodegenerative disorders, especially neuropathic pain, whilst displaying fewer ataxic and related side-effects associated with other classes of NMDA receptor antagonists.

In addition, the compounds in accordance with the present invention may be useful as radioligands in assays for detecting compounds capable of binding to the NR2B subunit of the human NMDA receptor.

Bio. Med. Chem. Lett., 1998, 8, 199 discloses a series of N-(2-phenethyl)cinnamides which were assayed for antagonism at NMDA receptor subtypes, and found to be potent and selective antagonists of the NR1A/2B subtype.

WO 98/37068 is stated to disclose a class of benzoic acid derivatives and related compounds for use in the treatment of arrhythmia.

The present invention provides a compound of formula I, or a pharmaceutically acceptable salt, hydrate or prodrug thereof:



wherein:

R¹ represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted;

R² represents C₃₋₇ cycloalkyl, aryl or heteroaryl, any of which groups may be optionally substituted; and

R³ represents hydrogen or C₁₋₆ alkyl; or

R¹ and R³ are taken together with the intervening nitrogen atom to form an optionally substituted isoquinoline ring.

The groups R¹, R² and R³ may be unsubstituted, or substituted by one or more, suitably one or two, substituents. Examples of optional substituents include C₁₋₆ alkyl, aryl, halogen, halo(C₁₋₆)alkyl, dihalo(C₁₋₆)alkyl, trihalo(C₁₋₆)alkyl, cyano, cyano(C₁₋₆)alkyl, hydroxy, hydroxymethyl, C₁₋₆ alkoxy, halo(C₁₋₆)alkoxy, dihalo(C₁₋₆)alkoxy and

trihalo(C₁₋₆)alkoxy. Representative substituents include C₁₋₆ alkyl, aryl, halogen, trihalo(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy and trihalo(C₁₋₆)alkoxy.

As used herein, the expression "C₁₋₆ alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and
5 hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, 3-methylbutyl and *n*-pentyl. Derived expressions such as "C₁₋₆ alkoxy" are to be construed accordingly. Particular values include methoxy and ethoxy.

Typical C₃₋₇ cycloalkyl groups include cyclopropyl, cyclobutyl,
10 cyclopentyl and cyclohexyl, especially cyclohexyl.

A typical C₃₋₇ cycloalkyl(C₁₋₆)alkyl group is cyclohexylmethyl.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C₁₋₆)alkyl" as used herein includes benzyl,
15 phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl,
20 benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

Suitable heteroaryl(C₁₋₆)alkyl groups include furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, pyrazolylethyl, oxazolylmethyl, isoxazolylmethyl, thiazolylmethyl, isothiazolylmethyl, imidazolylmethyl, benzimidazolylmethyl, oxadiazolylmethyl,
25 thiadiazolylmethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, pyridinylmethyl, pyridinylethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine.

30 For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in

the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound
5 according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic
10 moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope prodrugs of the
15 compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H.
20 Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be
25 understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Suitable values for the substituent R¹ in the compounds according to the invention include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, 3-methylbutyl, *n*-pentyl, cyclobutyl,
30 cyclopentyl, cyclohexyl, cyclohexylmethyl, phenyl, naphthyl, benzyl, phenylethyl, phenylpropyl, pyridinyl, furyl, thienyl, pyrrolyl, indolyl,

triazolyl, furylmethyl, thienylmethyl and pyridinylmethyl, any of which groups may be substituted by one or more substituents. Typical values of R^1 include *n*-butyl, isobutyl, 3-methylbutyl, *n*-pentyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, phenylethyl, phenylpropyl, furylmethyl, thienylmethyl and pyridinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Specific illustrations of particular substituents on the group R^1 include methyl, ethyl, *n*-propyl, phenyl, fluoro, trifluoromethyl, chloro, trichloromethyl, bromo, tribromomethyl, iodo, cyano, cyanomethyl, hydroxy, hydroxymethyl, methoxy, ethoxy and trifluoromethoxy.

More specific illustrations of particular substituents on the group R^1 include methyl, phenyl, fluoro, chloro, bromo, fluoro, iodo, trifluoromethyl, hydroxy, methoxy, ethoxy and trifluoromethoxy.

Representative values of R^1 include *n*-butyl, isobutyl, 3-methylbutyl, *n*-pentyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, methylbenzyl, phenylbenzyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, bromobenzyl, iodobenzyl, trifluoromethylbenzyl, hydroxybenzyl, methoxybenzyl, ethoxybenzyl, trifluoromethoxybenzyl, phenylethyl, phenylpropyl, furylmethyl, thienylmethyl and pyridinylmethyl.

Suitable values for the substituent R^2 in the compounds according to the invention include cyclopentyl, cyclohexyl, phenyl, naphthyl, pyridinyl, furyl, thienyl and pyrrolyl, any of which groups may be optionally substituted by one or more substituents. Typical values of R^2 include cyclohexyl, phenyl and furyl, any of which groups may be optionally substituted by one or more substituents.

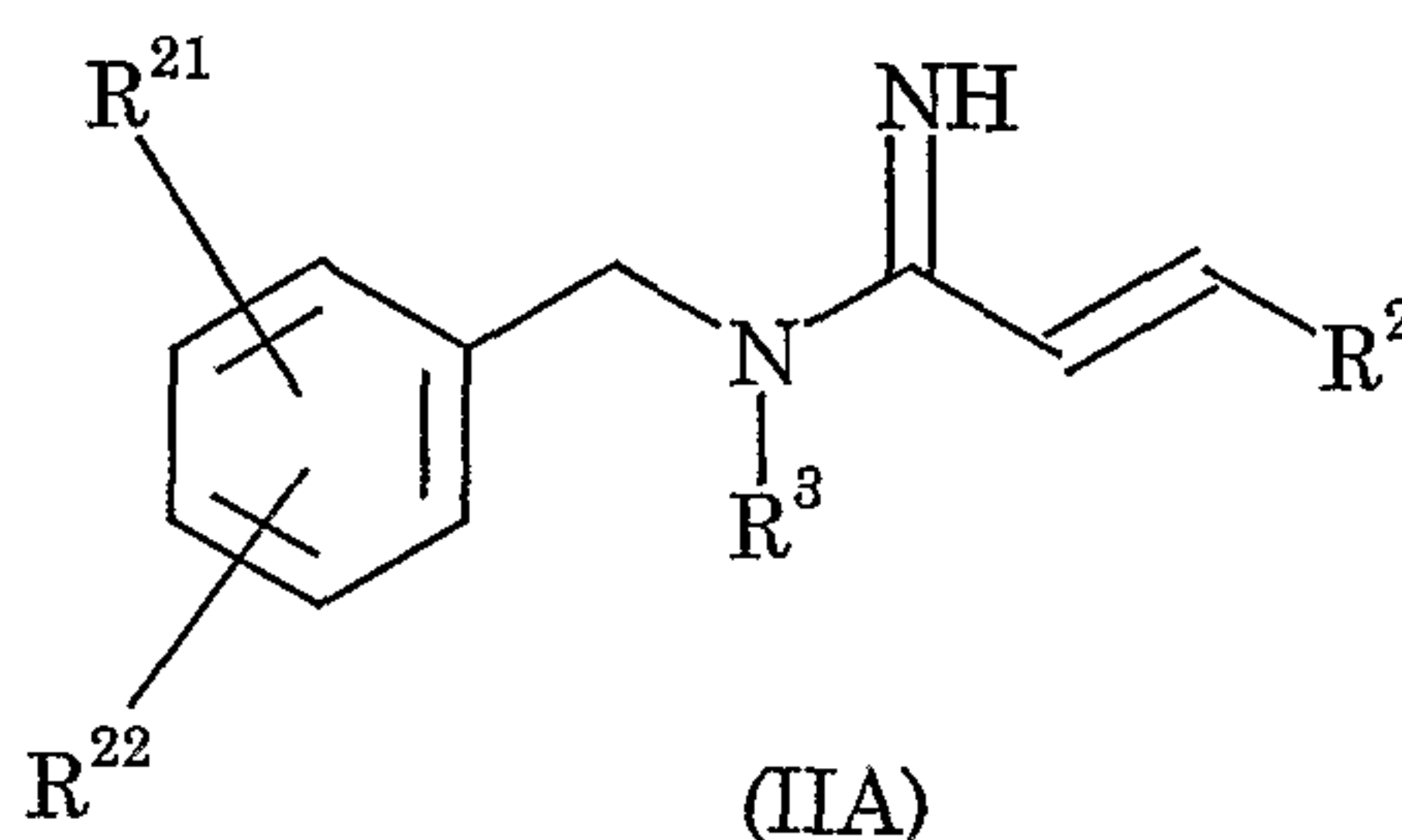
Specific illustrations of particular substituents on the group R^2 include methyl, ethyl, fluoro, chloro, bromo, cyano, hydroxy, methoxy and ethoxy.

More specific illustrations of particular substituents on the group R^2 include fluoro, chloro and methoxy.

Representative values of R^2 include cyclohexyl, phenyl, fluorophenyl, difluorophenyl, chlorophenyl, methoxyphenyl and furyl. Preferred values of R^2 include phenyl, fluorophenyl and difluorophenyl.

Suitable values of R^3 include hydrogen and methyl, preferably hydrogen.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and pharmaceutically acceptable salts, hydrates or prodrugs thereof:



wherein R^2 and R^3 are as defined above;

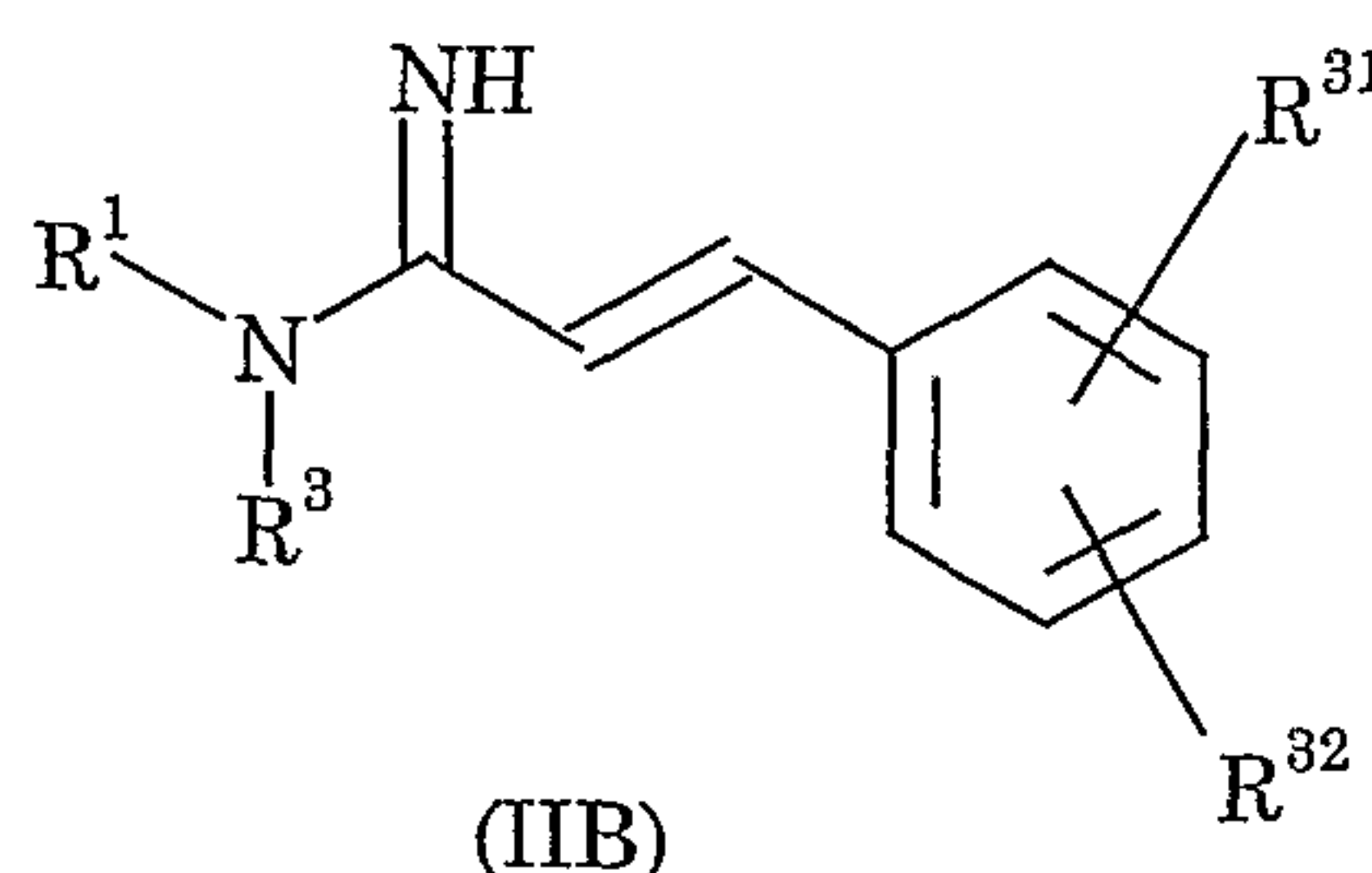
R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6})alkoxy; and

R^{22} represents hydrogen or halogen.

Particular values of R^{21} include hydrogen, methyl, phenyl, fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, methoxy, ethoxy and trifluoromethoxy.

Suitably, R^{22} represents hydrogen or chloro, especially hydrogen.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and pharmaceutically acceptable salts, hydrates or prodrugs thereof:



wherein R^1 and R^3 are as defined above;

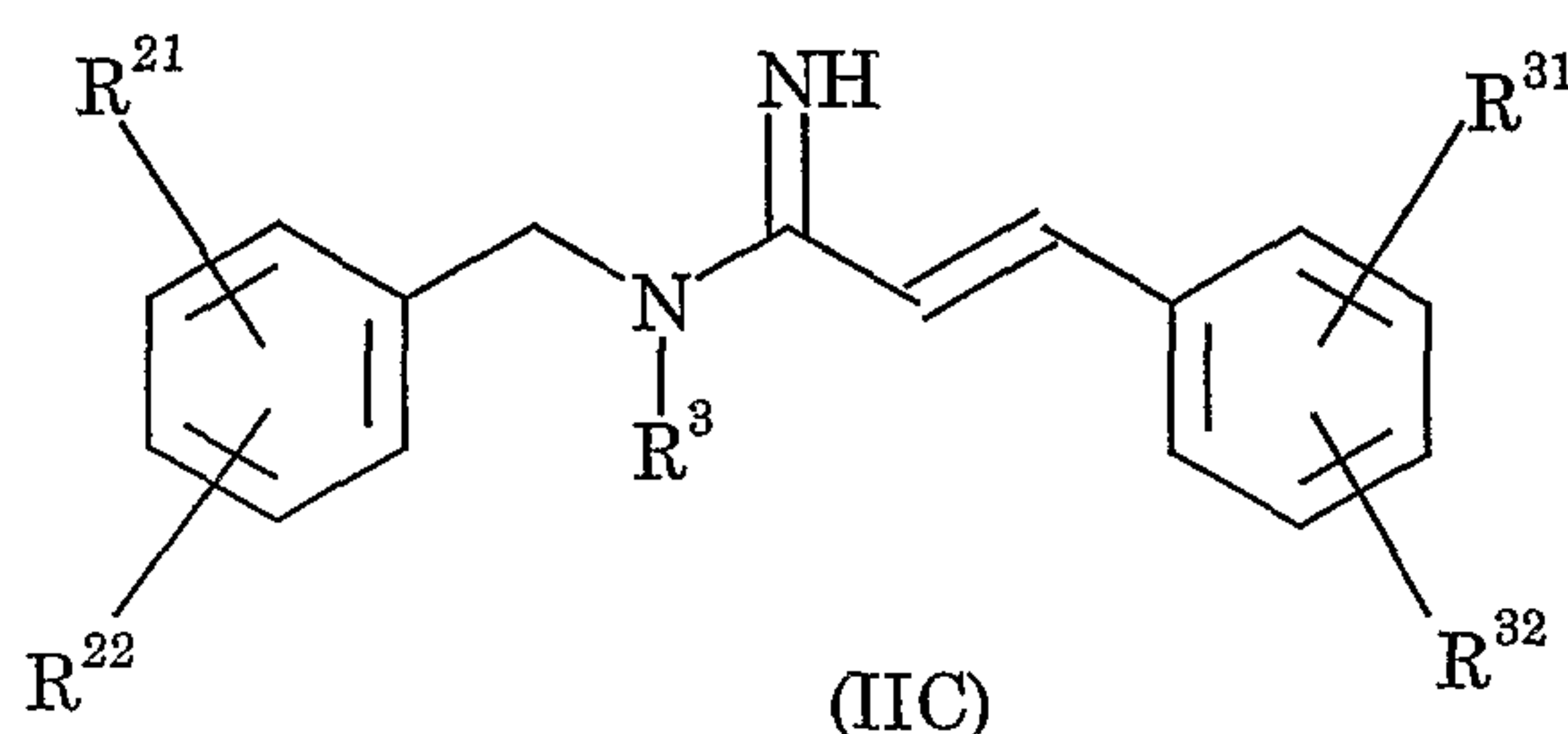
R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy; and

R^{32} represents hydrogen or halogen.

5 Particular values of R^{31} include hydrogen, fluoro, chloro and methoxy, especially fluoro.

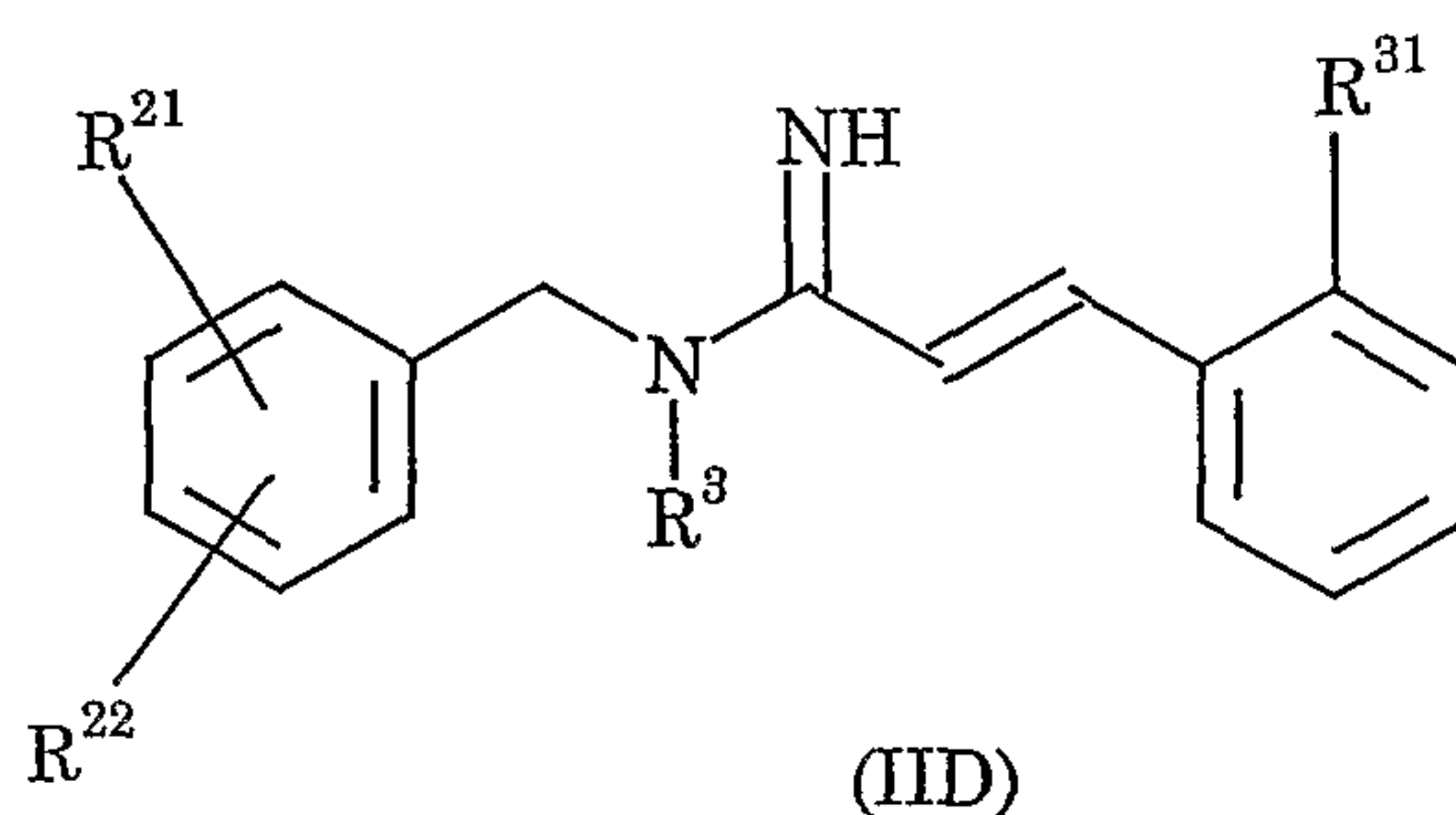
Suitably, R^{32} represents hydrogen or fluoro, especially hydrogen.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and pharmaceutically
10 acceptable salts, hydrates or prodrugs thereof:



wherein R^3 , R^{21} , R^{22} , R^{31} and R^{32} are as defined above.

15 Another sub-class of compounds according to the invention is represented by the compounds of formula IID, and pharmaceutically acceptable salts, hydrates or prodrugs thereof:



20

wherein R^3 , R^{21} , R^{22} and R^{31} are as defined above.

Specific compounds within the scope of the present invention include:

- (*E*)-N-(3-iodobenzyl)cinnamamide;
(*E*)-N-(benzyl)cinnamamide;
(*E*)-N-(4-chlorobenzyl)cinnamamide;
(*E*)-N-(2-chlorobenzyl)cinnamamide;
5 (*E*)-N-(3-chlorobenzyl)cinnamamide;
(*E*)-N-(4-fluorobenzyl)cinnamamide;
(*E*)-N-(4-trifluoromethylbenzyl)cinnamamide;
(*E*)-N-(4-methoxybenzyl)cinnamamide;
(*E*)-N-(4-methylbenzyl)cinnamamide;
10 (*E*)-N-(3-methylbenzyl)cinnamamide;
(*E*)-N-(2-methylbenzyl)cinnamamide;
(*E*)-N-(3,4-dichlorobenzyl)cinnamamide;
(*E*)-N-(2-phenylethyl)cinnamamide;
(*E*)-N-(*R*)- α -methylbenzylcinnamamide;
15 (*E*)-N-(*S*)- α -methylbenzylcinnamamide;
(*E*)-N-(3-trifluoromethylbenzyl)cinnamamide;
(*E*)-N-(3,5-dichlorobenzyl)cinnamamide;
(*E*)-N-(2-methoxybenzyl)cinnamamide;
(*E*)-N-(3-methoxybenzyl)cinnamamide;
20 (*E*)-N-(2-trifluoromethylbenzyl)cinnamamide;
(*E*)-N-(2,5-dichlorobenzyl)cinnamamide;
(*E*)-N-(3-bromobenzyl)cinnamamide;
(*E*)-N-(4-pyridylmethyl)cinnamamide;
(*E*)-N-methyl-N-benzylcinnamamide;
25 (*E*)-N-(2,3-dichlorobenzyl)cinnamamide;
(*E*)-N-(cyclohexylmethyl)cinnamamide;
(*E*)-N-(isobutyl)cinnamamide;
(*E*)-N-(*n*-butyl)cinnamamide;
(*E*)-N-(2-trifluoromethoxybenzyl)cinnamamide;
30 (*E*)-N-(3-thienylmethyl)cinnamamide;
(*E*)-N-(2-bromobenzyl)cinnamamide;

- (*E*)-N-(2-ethoxybenzyl)cinnamamide;
- (*E*)-N-(2-phenylbenzyl)cinnamamide;
- (*E*)-N-(2-furylmethyl)cinnamamide;
- (*E*)-N-(cyclohexyl)cinnamamide;
- 5 (*E*)-N-(3-methyl-1-butyl)cinnamamide;
- (*E*)-2-(3-phenyl-1-imino-2-propenyl)-1,2,3,4-tetrahydroisoquinoline;
- (*E*)-N-(*n*-pentyl)cinnamamide;
- (*E*)-N-(3-phenyl-1-propyl)cinnamamide;
- (*E*)-N-(2-hydroxybenzyl)cinnamamide;
- 10 (*E*)-N-phenylcinnamamide;
- (*E*)-N-benzyl-2-chlorocinnamamide;
- (*E*)-N-benzyl-3-chlorocinnamamide;
- (*E*)-N-benzyl-4-chlorocinnamamide;
- (*E*)-N-benzyl-4-fluorocinnamamide;
- 15 (*E*)-N-benzyl-4-methoxycinnamamide;
- (*E*)-N-benzyl-3-methoxycinnamamide;
- (*E*)-N-benzyl-2-methoxycinnamamide;
- (*E*)-N-benzyl-3,4-difluorocinnamamide;
- (*E*)-N-benzyl-3-cyclohexaneacrylamide;
- 20 and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

The compounds of formula I, and the pharmaceutically acceptable salts, hydrates and prodrugs thereof, are useful for the relief of neurological and neurodegenerative disorders, including pain (and in particular neuropathic pain and headache, specifically migraine), epilepsy, stroke, anxiety, cerebral ischemia, muscular spasms, Alzheimer's Disease, Huntington's Disease and Parkinson's Disease.

For the treatment of any of these neurological and neurodegenerative diseases, a compound of formula I is administered in an amount that is effective to treat or prevent the said disease or condition.

30 The compound may be administered orally, topically, parenterally, by inhalation spray or rectally, in dosages containing conventional non-toxic

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pharmaceutically acceptable diluents, adjuvants and vehicles. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intradermal, epidural, and intrasternal injection or infusion techniques.

5 The therapeutic dose of the compound of formula I will vary with the nature or severity of the condition to be treated, the particular compound selected, its route of administration and other factors. It will also vary according to the age, weight and response of the individual patient. A representative dose ranges from about 0.001 mg/kg per day to about 100 mg/kg per day.

10 In another aspect, the present invention provides use of the compound of formula I, or a pharmaceutically acceptable salt or hydrate thereof, for the manufacture of a medicament for treatment and/or prevention of neurological and/or neurodegenerative disorders.

There is also provided a compound of formula IIA, or a pharmaceutically acceptable salt or hydrate thereof, for use in medical therapy.

15 In a still further aspect of the invention, there is provided the compound of formula I, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment and/or prevention of neurological and/or neurodegenerative disorders.

In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, hydrate or prodrug thereof in combination with a pharmaceutically acceptable carrier. Optionally other therapeutic ingredients may be included as well. Examples of dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments and aerosols.

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In particular, the invention provides such a pharmaceutical composition for use in the treatment and/or prevention of neurological and/or neurodegenerative disorders.

5 The compositions may be presented in multiple dosage containers or in unit dosage form and prepared by methods well-known in the art of pharmacy.

The compounds of formula I can be combined as the active ingredient with the pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form desired. In preparing oral dosage forms, any of the usual pharmaceutical media
10 may be employed, such as, for example, water, alcohols, oils, flavouring agents, preservatives and colouring agents in the case of oral liquid preparations such as, for example, suspensions, elixirs and solutions; or starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders and disintegrating agents in the case of oral solid preparations such as, for example,
15 powders, capsules and tablets. Solid oral

preparations are preferred over liquid preparations. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Examples of suitable dosage units typically range from about 0.01 mg to about 1.0 g of the active ingredient.

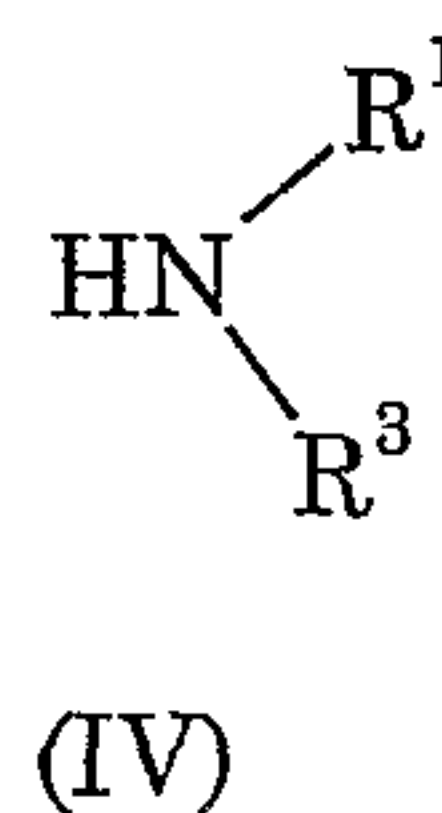
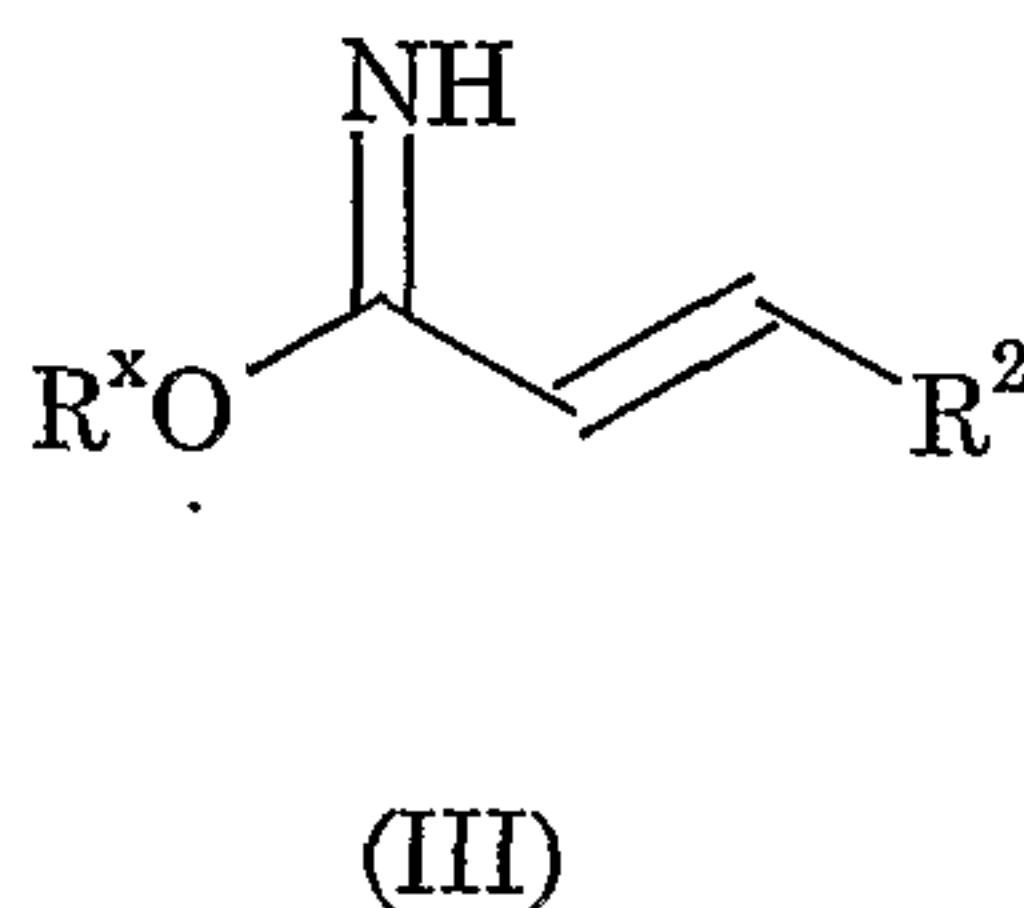
5 The diseases or conditions described herein may be effectively treated by the administration of from about 0.01 to about 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

10 The active ingredient may be combined with the carrier materials to produce the dosage form. For example, a formulation intended for oral administration to humans may contain from about 0.5 mg to about 5 g of the compound, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage units will generally contain between from about
15 1 mg to about 1000 mg of active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg.

It will be understood that the specific dose level for any particular patient depends upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration,
20 rate of excretion, drug combination and the severity of the particular disease or condition undergoing therapy.

The compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:

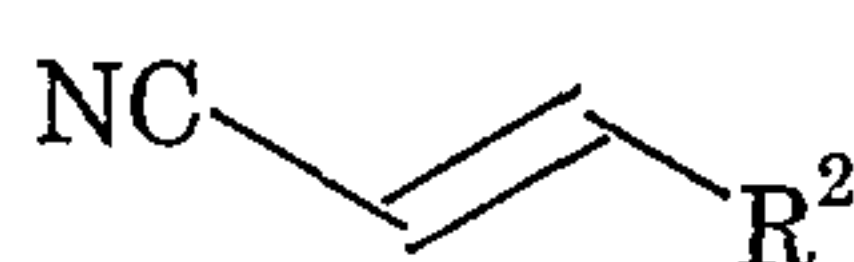
25



wherein R^1 , R^2 and R^3 are as defined above, and R^x represents C_{1-6} alkyl, preferably methyl or ethyl.

The reaction between compounds III and IV is conveniently effected by stirring the reactants in a suitable solvent, typically methanol.

5 The intermediates of formula III may be prepared by reacting a compound of formula V with a compound of formula VI:



(V)

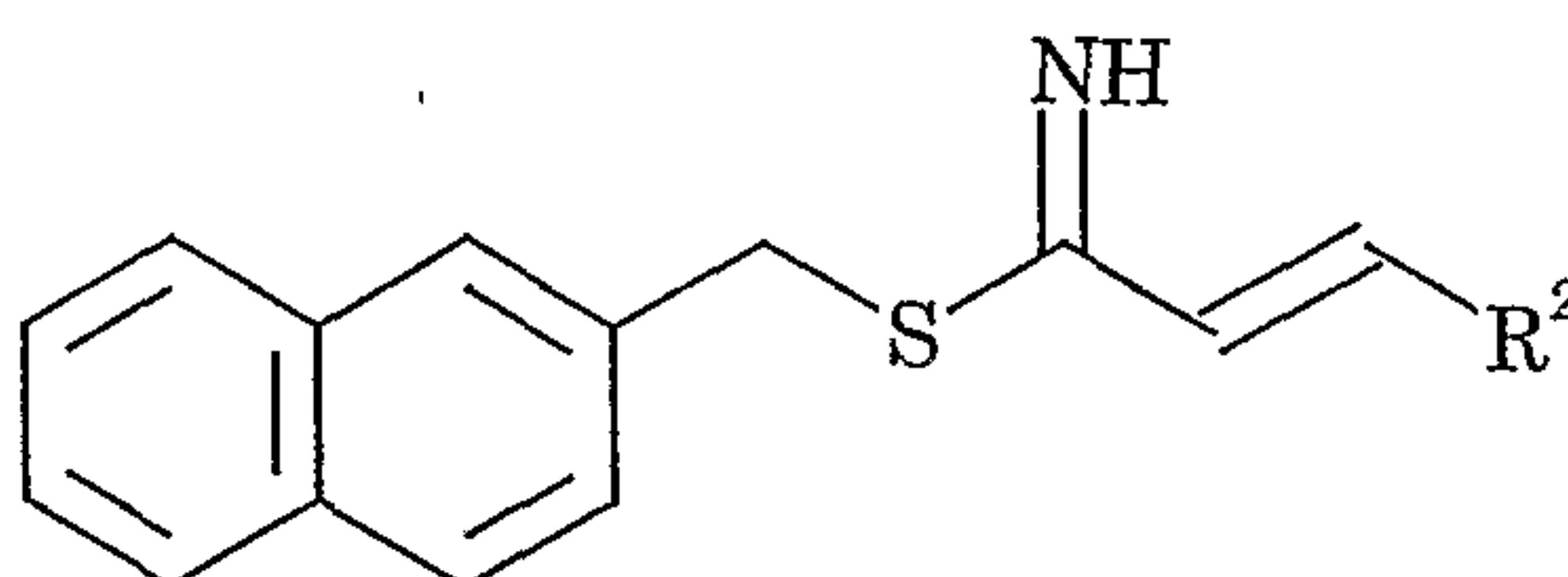


(VI)

10 wherein R^2 and R^x are as defined above.

The reaction between the compounds of formula V and VI is conveniently effected by stirring the reactants in the presence of hydrogen chloride, in a suitable solvent, typically ether.

15 In another procedure, the compounds of formula I as described above may be prepared by a process which comprises reacting a compound of formula IV as defined above with a compound of formula VII:

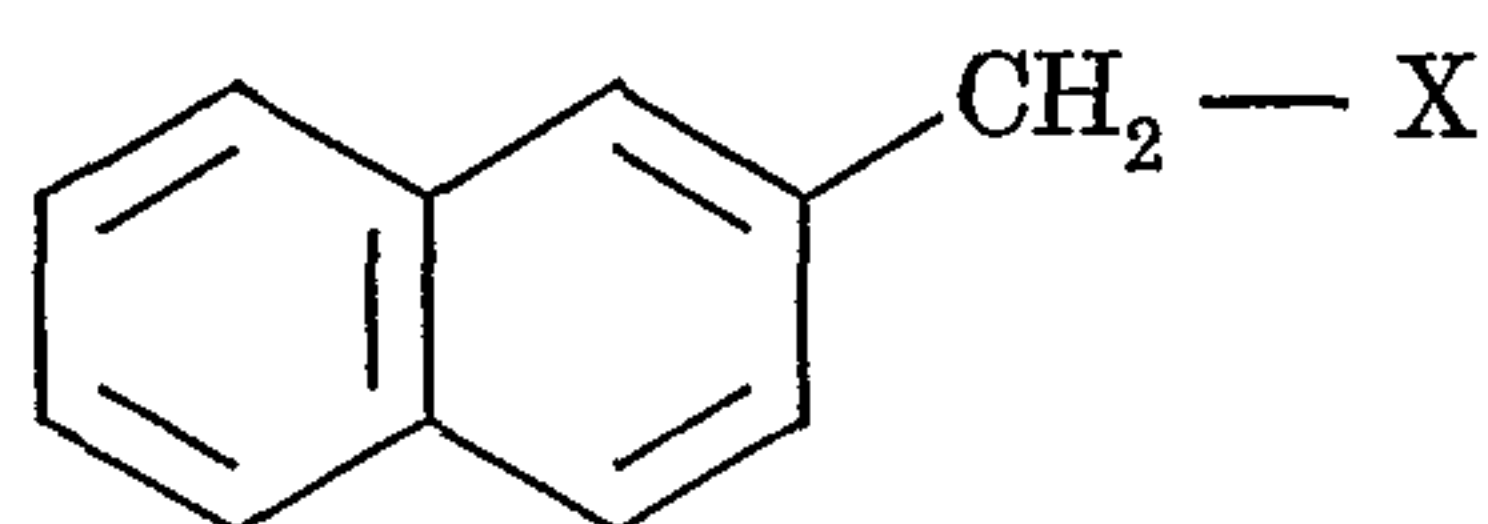


(VII)

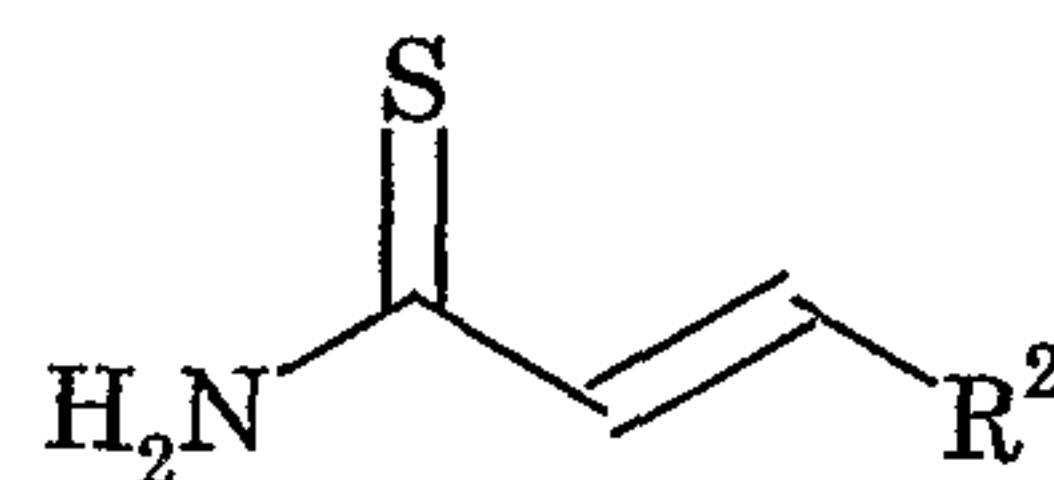
20 wherein R^2 is as defined above.

The reaction between compounds IV and VII is conveniently effected by stirring the reactants in a suitable solvent, typically chloroform or ethanol, at room temperature.

25 The intermediates of formula VII above may be prepared by reacting a compound of formula VIII with a compound of formula IX:



(VIII)

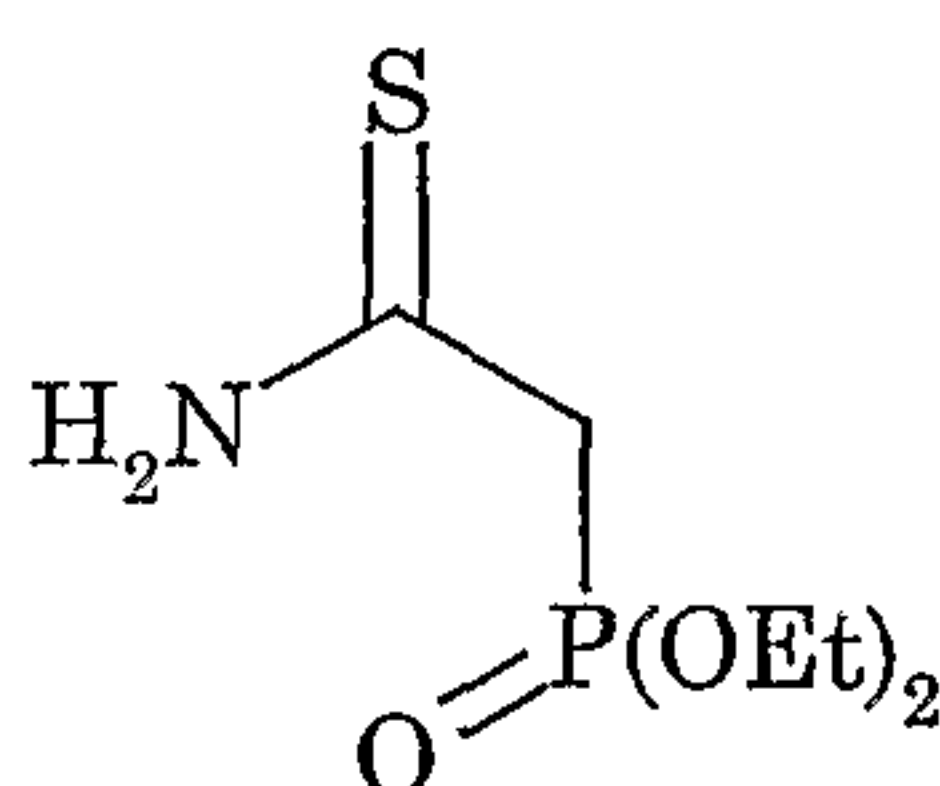


(IX)

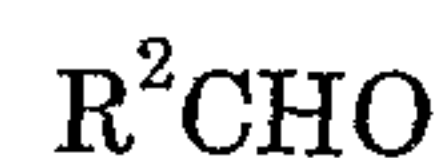
wherein R^2 is as defined above, and X represents a halogen atom, e.g.
5 bromo.

The reaction between compounds VIII and IX is conveniently effected by refluxing the reactants in a suitable solvent, typically chloroform.

The intermediates of formula IX above may be prepared by
10 reacting the compound of formula X with a compound of formula XI:



(X)



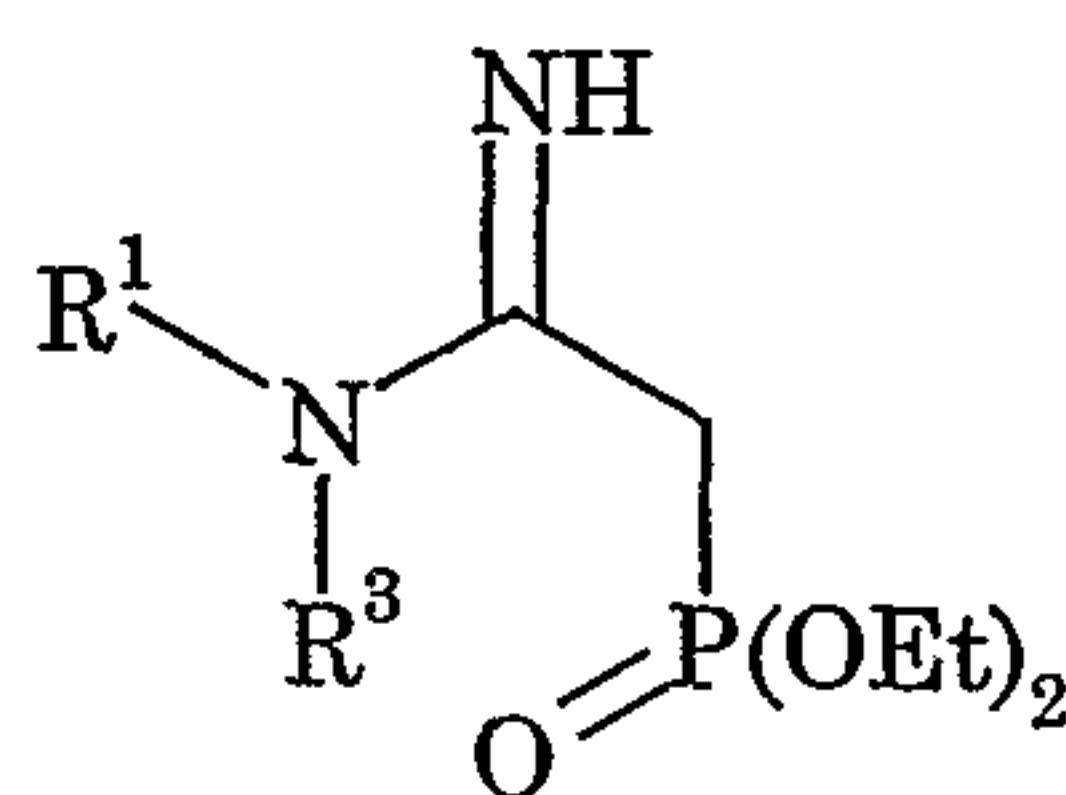
(XI)

wherein R^2 is as defined above.

15 The reaction between compounds X and XI is conveniently effected by treating compound X with a strong base, e.g. sodium hydride, in the presence of a suitable solvent, typically THF, then adding compound XI and stirring the reaction mixture at a temperature between 0°C and room temperature.

20 In a further procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula XI as defined above with a compound of formula XII:

- 16 -

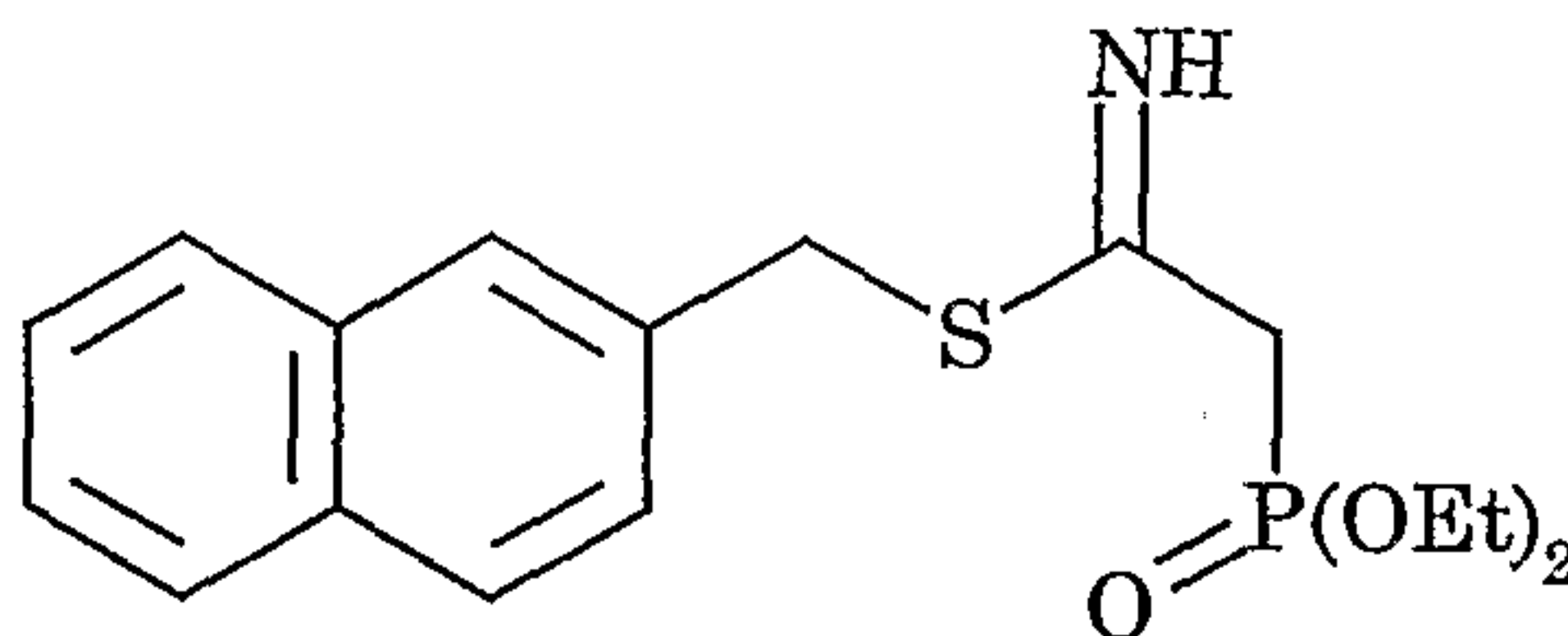


(XII)

wherein R^1 and R^3 are as defined above.

The reaction between compounds XI and XII is conveniently effected under basic conditions. For example, the reactants may be stirred with sodium hydroxide at room temperature in a suitable solvent, e.g. dichloromethane, typically in the presence of tetra-*n*-butylammonium bromide; or the reactants may be heated with potassium carbonate at reflux in a suitable solvent, typically tetrahydrofuran.

The intermediates of formula XII above may be prepared by reacting a compound of formula IV as defined above with a compound of formula XIII:



(XIII)

under conditions analogous to those described above for the reaction between compounds IV and VII.

The intermediates of formula XIII above may be prepared by reacting a compound of formula VIII with a compound of formula X, under conditions analogous to those described above for the reaction between compounds VIII and IX.

Where they are not commercially available, the starting materials of formula IV, V, VI, VIII, X and XI may be prepared by methods

analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography or crystallisation. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-*d*-tartaric acid and/or (+)-di-*p*-toluoyl-*l*-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The following assays are used to demonstrate biological activity and utility for the compounds of formula I.

[³H]-Ifenprodil binding to recombinant human NR1a/NR2B receptors

5 Ifenprodil is an NMDA receptor antagonist which acts through a distinct modulatory site from those of glutamate, glycine and MK-801 (dizocilpine) and is selective for NR2B-containing receptors (Grimwood *et al.*, *J. Neurochem.*, 1996, **66**, 2589-2595). [³H]-Ifenprodil binding to cell membranes expressing recombinant human NR1a/NR2B receptors is
10 determined essentially as described by Grimwood *et al.*, *NeuroReport*, 1999, **10**, 461-465.

The compounds of the accompanying Examples were tested in the above assay, and all were found to demonstrate a 50% inhibition of [³H]-ifenprodil binding at a concentration of 5 μ M or less.

15

Functional Ca⁺⁺ antagonism assay-FLIPR

Human NR1a/2B receptor transfected cells are plated in a 96-well format and grown for one day in normal growth media (Dulbeccos MEM with Na pyruvate). NR1a/2B expression in these cells is induced by the
20 addition of dexamethasone in the presence of ketamine for 16-24 hours. After receptor induction cells are washed with assay buffer (Hanks balanced salt solution (HBSS-Mg free) containing 20 mM HEPES, 0.1% BSA, 2 mM CaCl₂ and 250 μ M probenecid). Each 96 well cell plate is loaded with the Ca⁺⁺ sensitive dye Fluo-3 (Molecular Probes, Inc.) in assay
25 buffer. The cells are then washed with assay buffer leaving them in 100 μ l buffer. Test compounds in solution are pipetted by FLIPR (Fluorometric Imaging Plate Reader, Molecular Dynamics) for 2 min pretreatment. During this time the fluorescence intensity is recorded (excitation at 488 nm and emission at 530 nm). The glutamate/glycine 50 μ l agonist solution
30 (final concentration 1 μ M/1 μ M) is then added by FLIPR into each well already containing 150 μ l of buffer (containing the test compound or

vehicle) and the fluorescence is continuously monitored for 10 min. Fluorescence values in the presence of an antagonist are compared to those for the agonist alone.

Of those compounds of the accompanying Examples which were tested in this assay, all were found to possess an EC₅₀ value of 10 µM or less.

Carrageenan-induced mechanical hyperalgesia in rats

The ability of test compounds to reverse carrageenan induced hyperalgesia can be determined using the method described by Boyce *et al.*, *Neuropharmacology*, 1994, **33**, 1609-1611.

EXAMPLE 1

(E)-N-(3-Iodobenzyl)cinnamamide hydrochloride

3-Iodobenzylamine (85µl, 0.64mmol) was added to a solution of (E)-ethyl cinnamimidate hydrochloride (112.9mg, 0.571mmol) [prepared by the method of E.C. Roberts and Y.F. Shealy, *J. Het. Chem.* **1974**, *11*, 547] in methanol (1ml) and the mixture stirred at room temperature overnight (18 hours). The mixture was diluted with diethyl ether (3ml), the crystalline product collected under suction, washed with methanol-diethyl ether (1:3) then diethyl ether and dried *in vacuo* to give the title product as a white solid (173mg, 76%); δ_H (360MHz, DMSO-d₆) 4.60 (2H, d, J 5.2Hz, ArCH₂N), 6.89 (1H, d, J 16.5Hz, CH=CHPh), 7.22 (1H, t, J 7.8Hz, ArH), 7.46 (1H, d, J 7.8Hz, ArH), 7.50 (3H, m, ArH), 7.60 (2H, m, ArH), 7.73 (1H, d, J 7.9Hz, ArH), 7.83 (1H, s, ArH), 7.92 (1H, d, J 16.5Hz, CH=CHPh), 9.03 (1H, br s, NH), 9.52 (1H, br s, NH), 10.26 (1H, br s, NH); m/z (ES⁺) 363 ([M+H]⁺).

The following Examples were prepared in an analogous process to the one described above:

EXAMPLE 2**(E)-N-(Benzyl)cinnamamidine hydrochloride**

5 (Found: C, 70.35; H, 6.16; N, 10.30. C₁₆H₁₇ClN₂ requires C, 70.45; H, 6.28; N, 10.27%); δ_{H} (360MHz, DMSO-d₆) 4.64 (2H, s, PhCH₂N), 6.93 (1H, d, J 16.5Hz, CH=CHPh), 7.37 (1H, m, ArH), 7.42 (4H, m, ArH), 7.49 (3H, m, ArH), 7.60 (2H, m, ArH), 7.96 (1H, d, J 16.5Hz, CH=CHPh), 9.04 (1H, br s, NH), 9.54 (1H, br s, NH), 10.31 (1H, br s, NH); m/z (ES⁺) 237
10 ([M+H]⁺).

EXAMPLE 3**(E)-N-(4-Chlorobenzyl)cinnamamidine hydrochloride**

15 δ_{H} (360MHz, DMSO-d₆) 4.63 (2H, s, ArCH₂N), 6.90 (1H, d, J 16.4Hz, CH=CHPh), 7.48 (7H, m, ArH), 7.60 (2H, m, ArH), 7.93 (1H, d, J 16.4Hz, CH=CHPh), 9.04 (1H, br s, NH), 9.53 (1H, br s, NH), 10.30 (1H, br s, NH); m/z (ES⁺) 271/273 ([M+H]⁺).

20

EXAMPLE 4**(E)-N-(2-Chlorobenzyl)cinnamamidine hydrochloride**

δ_{H} (360MHz, DMSO-d₆) 4.68 (2H, s, ArCH₂N), 6.91 (1H, d, J 16.5Hz, CH=CHPh), 7.42-7.62 (9H, m, ArH), 7.94 (1H, d, J 16.5Hz, CH=CHPh),
25 9.08 (1H, br s, NH), 9.58 (1H, br s, NH), 10.10 (1H, br s, NH); m/z (ES⁺) 271/273 ([M+H]⁺).

EXAMPLE 5

30 **(E)-N-(3-Chlorobenzyl)cinnamamidine hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 4.65 (2H, s, PhCH_2N), 6.91(1H, d, J 16.5Hz, CH=CHPh), 7.47 (7H, m, ArH), 7.60 (2H, m, ArH), 7.95 (1H, d, J 16.5Hz, CH=CHPh), 9.07 (1H, br s, NH), 9.55(1H, br s, NH), 10.35 (1H, br s, NH); m/z (ES^+) 271/273 ($[\text{M}+\text{H}]^+$).

5

EXAMPLE 6

(E)-N-(4-Fluorobenzyl)cinnamamidine hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.61 (2H, s, ArCH_2N), 6.89 (1H, d, J 16.4Hz, CH=CHPh), 7.26 (2H, m, ArH), 7.50 (5H, m, ArH), 7.59 (2H, m, ArH), 7.92 (1H, d, J 16.5Hz, CH=CHPh), 9.03 (1H, br s, NH), 9.51 (1H, br s, NH), 10.26 (1H, br s, NH); m/z (ES^+) 255 ($[\text{M}+\text{H}]^+$).

10

EXAMPLE 7

15

(E)-N-(4-Trifluoromethylbenzyl)cinnamamidine hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.75 (2H, s, ArCH_2N), 6.91 (1H, d, J 16.5Hz, CH=CHPh), 7.51 (3H, m, ArH), 7.63 (4H, m, ArH), 7.80 (2H, m, ArH), 7.94 (1H, d, J 16.5Hz, CH=CHPh); m/z (ES^+) 305 ($[\text{M}+\text{H}]^+$).

20

EXAMPLE 8

(E)-N-(4-Methoxybenzyl)cinnamamidine hydrochloride

δ_{H} (360MHz, DMSO- d_6) 3.76 (3H, s, OCH_3), 4.54 (2H, s, ArCH_2N), 6.88 (1H, d, J 16.5Hz, CH=CHPh), 6.98 (2H, m, ArH), 7.37 (2H, m, ArH), 7.49 (3H, m, ArH), 7.59 (2H, m, ArH), 7.92 (1H, d, J 16.5Hz, CH=CHPh); m/z (ES^+) 267($[\text{M}+\text{H}]^+$).

25

EXAMPLE 9

30

(E)-N-(4-Methylbenzyl)cinnamamidine hydrochloride

δ_{H} (360MHz, DMSO- d_6) 2.31 (3H, s, ArCH₃), 4.57 (2H, s, ArCH₂N), 6.91(1H, d, J 16.5Hz, CH=CHPh), 7.22 (2H, m, ArH), 7.35 (2H, m, ArH), 7.50 (3H, m, ArH), 7.59 (2H, m, ArH), 7.94 (1H, d, J 16.5Hz, CH=CHPh), 8.99 (1H, br s, NH), 9.51 (1H, br s, NH), 10.24 (1H, br s, NH); m/z (ES⁺) 251([M+H]⁺).

EXAMPLE 10

(E)-N-(3-Methylbenzyl)cinnamamide hydrochloride

δ_{H} (360MHz, DMSO- d_6) 2.33 (3H, s, ArCH₃), 4.58 (2H, s, ArCH₂N), 6.91(1H, d, J 16.4Hz, CH=CHPh), 7.15-7.32 (4H, m, ArH), 7.49 (3H, m, ArH), 7.60 (2H, m, ArH), 7.91(1H, d, J 16.5Hz, CH=CHPh); m/z (ES⁺) 251([M+H]⁺).

EXAMPLE 11

(E)-N-(2-Methylbenzyl)cinnamamide hydrochloride

δ_{H} (360MHz, DMSO- d_6) 2.33 (3H, s, ArCH₃), 4.60 (2H, s, ArCH₂N), 6.99 (1H, d, J 16.5Hz, CH=CHPh), 7.26 (4H, m, ArH), 7.50 (3H, m, ArH), 7.60 (2H, m, ArH), 8.00 (1H, d, J 16.5Hz, CH=CHPh); m/z (ES⁺) 251([M+H]⁺).

EXAMPLE 12

(E)-N-(3,4-Dichlorobenzyl)cinnamamide hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.66 (2H, s, ArCH₂N), 6.94 (1H, d, J 16.5Hz, CH=CHPh), 7.47 (4H, m, ArH), 7.60 (2H, m, ArH), 7.69 (1H, m, ArH), 7.77 (1H, m, ArH), 7.98 (1H, d, J 16.5Hz, CH=CHPh), 9.14 (1H, br s, NH), 9.61 (1H, br s, NH), 10.48 (1H, br s, NH); m/z (ES⁺) 305/307([M+H]⁺).

EXAMPLE 13**(E)-N-(2-Phenylethyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 2.95 (2H, t, $\text{NCH}_2\text{CH}_2\text{Ph}$), 3.61 (2H, t, $\text{NCH}_2\text{CH}_2\text{Ph}$), 6.86 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.34 (5H, m, ArH), 7.50 (3H, m, ArH), 7.58 (2H, m, ArH), 7.86 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 8.85 (1H, br s, NH), 9.37 (1H, br s, NH), 9.94 (1H, br s, NH); m/z (ES^+) 251($[\text{M}+\text{H}]^+$).

EXAMPLE 14**(E)-N-(R)- α -Methylbenzylcinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 1.57 (3H, d, J 6.7Hz, $\text{NCH}(\text{CH}_3)\text{Ph}$), 5.11 (1H, m, $\text{NCH}(\text{CH}_3)\text{Ph}$), 6.96 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.31-7.49 (8H, m, ArH), 7.61 (2H, m, ArH), 7.91 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$); m/z (ES^+) 251($[\text{M}+\text{H}]^+$).

EXAMPLE 15**(E)-N-(S)- α -Methylbenzylcinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 1.57 (3H, d, J 6.7Hz, $\text{NCH}(\text{CH}_3)\text{Ph}$), 5.17 (1H, m, $\text{NCH}(\text{CH}_3)\text{Ph}$), 7.05 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.30-7.52 (8H, m, ArH), 7.60 (2H, m, ArH), 7.99 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$); m/z (ES^+) 251($[\text{M}+\text{H}]^+$).

EXAMPLE 16**(E)-N-(3-Trifluoromethylbenzyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 4.75 (2H, s, ArCH_2N), 6.93 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.50 (3H, m, ArH), 7.59-7.77 (5H, m, ArH), 7.85 (1H, m, ArH),

7.97 (1H, d, J 16.5Hz, CH=CHPh), 9.13 (1H, br s, NH), 9.60 (1H, br s, NH), 10.43 (1H, br s, NH); m/z (ES⁺) 305 ([M+H]⁺).

EXAMPLE 17

5

(E)-N-(3,5-Dichlorobenzyl)cinnamamide hydrochloride

δ_H (360MHz, DMSO-d₆) 4.67 (2H, s, ArCH₂N), 6.92 (1H, d, J 16.5Hz, CH=CHPh), 7.50 (3H, m, ArH), 7.55 (2H, m, ArH), 7.60 (3H, m, ArH), 7.96 (1H, d, J 16.5Hz, CH=CHPh), 9.13 (1H, br s, NH), 9.60 (1H, br s, NH), 10.44 (1H, br s, NH); m/z (ES⁺) 305/307([M+H]⁺).

10

EXAMPLE 18

(E)-N-(2-Methoxybenzyl)cinnamamide hydrochloride

δ_H (360MHz, DMSO-d₆) 3.85 (3H, s, ArOCH₃), 4.54 (2H, s, ArCH₂N), 6.92 (1H, d, J 16.5Hz, CH=CHPh), 6.99 (1H, m, ArH), 7.09 (1H, d, ArH), 7.31-7.39 (2H, m, ArH), 7.49 (3H, m, ArH), 7.59 (2H, m, ArH), 7.94 (1H, d, J 16.5Hz, CH=CHPh), 8.91 (1H, br s, NH), 9.53 (1H, br s, NH), 9.96 (1H, br s, NH); m/z (ES⁺) 267([M+H]⁺).

20

EXAMPLE 19

(E)-N-(3-Methoxybenzyl)cinnamamide hydrochloride

δ_H (360MHz, DMSO-d₆) 3.77 (3H, s, ArOCH₃), 4.59 (2H, d; ArCH₂N), 6.91-7.04 (4H, m, ArH, CH=CHPh), 7.33 (1H, m, ArH), 7.49 (3H, m, ArH), 7.59 (2H, m, ArH), 7.96 (1H, d, J 16.5Hz, CH=CHPh), 9.03 (1H, br s, NH), 9.54 (1H, br s, NH), 10.33. (1H, br s, NH); m/z (ES⁺) 267([M+H]⁺).

25

EXAMPLE 20

30

(E)-N-(2-Trifluoromethylbenzyl)cinnamamide hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.77 (2H, s, ArCH_2N), 6.93 (1H, d, J 16.5Hz, CH=CHPh), 7.50 (3H, m, ArH), 7.62 (4H, m, ArH), 7.77 (1H, m, ArH), 7.84 (1H, m, ArH), 7.96 (1H, d, J 16.5Hz, CH=CHPh), 9.18 (1H, br s, NH), 9.68 (1H, br s, NH), 10.12 (1H, br s, NH); m/z (ES^+) 305 ($[\text{M}+\text{H}]^+$).

5

EXAMPLE 21

(E)-N-(2,5-Dichlorobenzyl)cinnamamidinium hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.68 (2H, s, ArCH_2N), 6.98 (1H, d, J 16.1Hz, CH=CHPh), 7.50-7.59 (8H, m, ArH), 8.01 (1H, d, J 16.6Hz, CH=CHPh); m/z (ES^+) 305/307($[\text{M}+\text{H}]^+$).

10

EXAMPLE 22

(E)-N-(3-Bromobenzyl)cinnamamidinium hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.64 (2H, d, ArCH_2N), 6.92 (1H, d, J 16.5Hz, CH=CHPh), 7.28-7.67 (9H, m, ArH), 7.96 (1H, d, J 16.5Hz, CH=CHPh), 9.08 (1H, br s, NH), 9.57 (1H, br s, NH), 10.38 (1H, br s, NH); m/z (ES^+) 315/317 ($[\text{M}+\text{H}]^+$).

15

20

EXAMPLE 23

(E)-N-(4-Pyridylmethyl)cinnamamidinium hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.99 (2H, d, ArCH_2N), 7.03 (1H, d, J 16.4Hz, CH=CHPh), 7.52 (3H, m, ArH), 7.62 (2H, m, ArH), 7.95 (2H, m, ArH), 8.08 (1H, d, J 16.4Hz, CH=CHPh), 8.88 (2H, d, ArH), 9.38 (1H, br s, NH), 9.78 (1H, br s, NH), 10.86 (1H, br s, NH); m/z (ES^+) 238 ($[\text{M}+\text{H}]^+$).

25

EXAMPLE 24

30

(E)-N-Methyl-N-benzylcinnamamidinium hydrochloride

δ_{H} (400MHz, DMSO- d_6 , 340K) 3.11 (3H, s, NCH_3), 4.93 (2H, s, ArCH_2N), 7.17 (1H, d, J 16.0 Hz, $\text{CH}=\text{CHPh}$), 7.32-7.48 (8H, m, ArH), 7.61-7.72 (3H, m, ArH, $\text{CH}=\text{CHPh}$); m/z (ES^+) 251 ($[\text{M}+\text{H}]^+$).

5

EXAMPLE 25**(E)-N-(2,3-Dichlorobenzyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 4.72 (2H, s, ArCH_2N), 6.97 (1H, d, J 16.4Hz, $\text{CH}=\text{CHPh}$), 7.44 (2H, m, ArH), 7.50 (3H, m, ArH), 7.61 (2H, m, ArH), 7.68 (1H, m, ArH), 8.00 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 9.67 (3H, br s, 3 x NH); m/z (ES^+) 305/307($[\text{M}+\text{H}]^+$).

10

EXAMPLE 26**(E)-N-(Cyclohexylmethyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 0.95-1.02 (2H, m), 1.18-1.24 (3H, m), 1.65-1.79 (6H, m), 3.20 (2H, t, CH_2N), 6.92 (1H, d, J 16.4Hz, $\text{CH}=\text{CHPh}$), 7.49 (3H, m, ArH), 7.59 (2H, m, ArH), 7.88 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 8.76 (1H, br s, NH), 9.32 (1H, br s, NH), 9.83 (1H, br s, NH); m/z (ES^+) 243($[\text{M}+\text{H}]^+$).

20

EXAMPLE 27**(E)-N-(Isobutyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 0.95 (6H, m), 1.95 (1H, m), 3.18 (2H, d, CH_2N), 6.98 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.49 (3H, m, ArH), 7.59 (2H, m, ArH), 7.92 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$); m/z (ES^+) 203($[\text{M}+\text{H}]^+$).

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EXAMPLE 28

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(E)-N-(n-Butyl)cinnamamide hydrochloride

δ_{H} (360MHz, DMSO- d_6) 0.92 (3H, m), 1.39 (2H, m), 1.59 (2H, m), 3.32 (2H, s, CH_2N), 6.90 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.49 (3H, m, ArH), 7.58 (2H, m, ArH), 7.89 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 8.76 (1H, br s, NH), 9.34 (1H, br s, NH), 9.88 (1H, br s, NH); m/z (ES^+) 203($[\text{M}+\text{H}]^+$).

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EXAMPLE 29

(E)-N-(2-Trifluoromethoxybenzyl)cinnamamidinium hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.69 (2H, d, ArCH_2N), 6.91 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.45-7.62 (9H, m, ArH), 7.94 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 9.14 (1H, br s, NH), 9.63 (1H, br s, NH), 10.11 (1H, br s, NH); m/z (ES^+) 321 ($[\text{M}+\text{H}]^+$).

10

EXAMPLE 30

(E)-N-(3-Thienylmethyl)cinnamamidinium hydrochloride

δ_{H} (360MHz, DMSO- d_6) 4.83 (2H, d, ArCH_2N), 6.84 (1H, d, J 16.4Hz, $\text{CH}=\text{CHPh}$), 7.07 (2H, m, ArH), 7.23 (2H, m, ArH), 7.56 (4H, m, ArH), 7.87 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 9.48 (1H, br s, NH), 9.50 (1H, br s, NH), 10.22 (1H, br s, NH); m/z (ES^+) 243 ($[\text{M}+\text{H}]^+$).

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EXAMPLE 31

(E)-N-(2-Bromobenzyl)cinnamamidinium hydrochloride

δ_{H} (250MHz, DMSO- d_6) 4.64 (2H, s, ArCH_2N), 6.90 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.36 (1H, m, ArH), 7.49 (5H, m, ArH), 7.60 (2H, m, ArH), 7.74 (1H, d, J 10.9Hz, ArH), 7.92 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$); m/z (ES^+) 315/317 ($[\text{M}+\text{H}]^+$).

25

30

EXAMPLE 32**(E)-N-(2-Ethoxybenzyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 1.35 (3H, t, CH_2CH_3), 4.09 (2H, q, CH_2CH_3),
5 4.54 (2H, s, ArCH_2N), 6.87 (1H, d, J 16.4Hz, $\text{CH}=\text{CHPh}$), 6.98 (1H, dt,
ArH), 7.07 (1H, d, ArH), 7.33 (2H, m, ArH), 7.49 (3H, m, ArH), 7.58 (2H,
m, ArH), 7.88 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 8.83 (1H, br s, NH), 9.42 (1H,
br s, NH), 9.82 (1H, br s, NH); m/z (ES^+) 281 ($[\text{M}+\text{H}]^+$).

10

EXAMPLE 33**(E)-N-(2-Phenylbenzyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 4.47 (2H, s, ArCH_2N), 6.79 (1H, d, J 16.4Hz,
 $\text{CH}=\text{CHPh}$), 7.34-7.46 (12H, m, ArH), 7.58 (2H, m, ArH), 7.77 (1H, d, J
15 16.4Hz, $\text{CH}=\text{CHPh}$), 8.80 (1H, br s, NH), 9.26 (1H, br s, NH), 9.83 (1H, br
s, NH); m/z (ES^+) 313 ($[\text{M}+\text{H}]^+$).

EXAMPLE 34**(E)-N-(2-Furylmethyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 4.64 (2H, s, ArCH_2N), 6.49 (1H, m, ArH),
6.55 (1H, m, ArH), 6.80 (1H, d, J 16.4Hz, $\text{CH}=\text{CHPh}$), 7.50 (2H, m, ArH),
7.59 (2H, m, ArH), 7.73 (1H, m, ArH), 7.83 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$);
m/z (ES^+) 226 ($[\text{M}+\text{H}]^+$).

25

EXAMPLE 35**(E)-N-(Cyclohexyl)cinnamamide hydrochloride**

δ_{H} (360MHz, DMSO- d_6) 1.19 (1H, m, AlkH), 1.33 (4H, m, AlkH),
30 1.61 (1H, m, AlkH), 1.75 (2H, m, AlkH), 1.91 (2H, m, AlkH), 3.65 (1H, m,
AlkH), 6.84 (1H, d, J 16.5Hz, $\text{CH}=\text{CHPh}$), 7.50 (3H, m, ArH), 7.58 (2H, m,

ArH), 7.83 (1H, d, J 16.5Hz, CH=CHPh), 8.69 (1H, br s, NH), 9.21 (1H, br s, NH), 9.49 (1H, br s, NH); m/z (ES⁺) 229 ([M+H]⁺).

EXAMPLE 36

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(E)-N-(3-Methyl-1-butyl)cinnamamidine hydrochloride

δ_H (360MHz, MeOH-d₄) 1.00 (6H, m, AlkH), 1.62 (1H, m, AlkH), 3.39 (2H, t, AlkH), 3.83 (2H, s, AlkH), 6.70 (1H, d, J 16.5Hz, CH=CHPh), 7.47 (2H, m, ArH), 7.54 (1H, m, ArH), 7.62 (2H, m, ArH), 7.70 (2H, d, J 16.4Hz, CH=CHPh); m/z (ES⁺) 217 ([M+H]⁺).

10

EXAMPLE 37

(E)-2-(3-Phenyl-1-imino-2-propenyl)-1,2,3,4-tetrahydroisoquinoline

δ_H (400MHz, DMSO-d₆, 333K) 3.01 (2H, m, AlkH), 3.70 (2H, br s, AlkH), 4.75 (2H, br s, AlkH), 7.20 (1H, d, J 16.1Hz, CH=CHPh), 7.23-7.29 (4H, m, ArH), 7.50 (3H, m, ArH), 7.62 (1H, d, J 16.1Hz, CH=CHPh), 7.76 (2H, m, ArH), 8.98 (3H, br s, 3 x NH); m/z (ES⁺) 263 ([M+H]⁺).

15

20

EXAMPLE 38

(E)-N-(n-Pentyl)cinnamamidine hydrochloride

δ_H (360MHz, DMSO-d₆) 0.90 (3H, t, J 7.1Hz, CH₃), 1.33 (4H, m, AlkH), 1.61 (2H, m, AlkH), 6.85 (1H, d, J 16.5Hz, CH=CHPh), 7.49 (3H, m, ArH), 7.59 (2H, m, ArH), 7.83 (1H, d, J 16.5Hz, CH=CHPh), 8.70 (1H, br s, NH), 9.30 (1H, br s, NH), 9.80 (1H, br s, NH); m/z (ES⁺) 217 ([M+H]⁺).

25

EXAMPLE 39

30 (E)-N-(3-Phenyl-1-propyl)cinnamamidine hydrogen oxalate

δ_{H} (360MHz, DMSO- d_6) 1.92 (2H, m, AlkH), 2.69 (2H, m, AlkH), 3.33 (2H, m, AlkH), 6.79 (1H, d, J 16.4Hz, CH=CHPh), 7.26 (5H, m, ArH), 7.50 (3H, m, ArH), 7.60 (2H, m, ArH), 7.76 (1H, d, J 16.6Hz, CH=CHPh), 8.65 (1H, br s, NH), 9.21 (1H, br s, NH), 9.67 (1H, br s, NH); m/z (ES⁺) 265 ([M+H]⁺).

EXAMPLE 40

(E)-N-(2-Hydroxybenzyl)cinnamamidine

2-Hydroxybenzylamine (276.4mg, 2.24mmol) and sodium methoxide (123.2mg, 2.28mmol) were added to a solution of (E)-ethyl cinnamimidate hydrochloride (482.3mg, 2.28mmol) [prepared by the method of E.C. Roberts and Y.F. Shealy, *J. Het. Chem.* **1974**, *11*, 547] in methanol (10ml) and the mixture stirred at room temperature for 6.5 hours. The reaction mixture was then poured into water (50ml) and extracted with dichloromethane (50ml then 2 x 25ml). The combined extracts were dried (MgSO₄) and concentrated to a small volume. Methanol was added and the precipitate collected under suction, washed with methanol and dried *in vacuo* to give the title compound as a buff solid (90.2mg, 16%); δ_{H} (360MHz, DMSO- d_6) 4.25 (2H, s, ArCH₂N), 6.61 (1H, d, J 16.5Hz, CH=CHPh), 6.67 (2H, m, ArH), 7.08 (2H, m, ArH), 7.31-7.43 (4H, m, ArH and CH=CHPh), 7.51 (2H, m, ArH); m/z (ES⁺) 253 ([M+H]⁺).

EXAMPLE 41

(E)-N-Phenylcinnamamidine hydrochloride

Step 1: (E)-S-(2-Naphthylmethyl)thiocinnamimidate hydrobromide

2-Bromomethylnaphthalene (371.2mg, 1.68mmol) was added to a suspension of thiocinnamamide (273.1mg, 1.67mmol) [prepared by the method of I.T. Barnish, C.W.G. Fishwick, D.R. Hill and C. Szantay, Jr., *Tetrahedron*, **1989**, *45*, 6771] in chloroform (5ml). The mixture was heated

at reflux for 1.5 hours, allowed to cool and diluted with diethyl ether (5ml). The crystallised solid was collected under suction, washed with 50% chloroform in diethyl ether then diethyl ether and dried *in vacuo* to give the title compound as a pale yellow solid (436.6mg, 68%); δ_{H} (360MHz, CDCl₃) 5.11 (2H, s, ArCH₂S), 7.41-7.55 (6H, m, ArH), 7.66 (2H, m, ArH), 7.76 (1H, d, J 16.2Hz, CH=CHPh), 7.83-7.88 (3H, m, ArH), 7.96 (1H, d, J 16.2Hz, CH=CHPh), 8.02 (1H, s, ArH), 11.47 (1H, br s, NH), 12.28 (1H, br s, NH); m/z (ES⁺) 304 ([M+H]⁺), 141 (100%).

10 Step 2: (E)-N-Phenylcinnamamide hydrochloride

Aniline (51 μ l, 0.56mmol) was added to a solution of (E)-S-(2-naphthylmethyl)-thiocinnamimide hydrobromide (216.1mg, 0.56mmol) in chloroform (4ml) and the mixture stirred at room temperature for 30 minutes. The reaction mixture was concentrated *in vacuo*, treated with saturated aqueous sodium hydrogen carbonate solution (20ml) and extracted with dichloromethane (2 x 10ml). The combined extracts were dried (MgSO₄), concentrated and the residue purified by flash chromatography eluting with dichloromethane-methanol-ammonia (180:8:1). The purified product free base (50.2mg) was dissolved in dichloromethane and treated with 1M HCl in diethyl ether (0.29ml). The mixture was evaporated and the residue recrystallised from methanol-diethyl ether to give the title compound (38.0mg, 26%); δ_{H} (360MHz, DMSO-d₆) 7.04 (1H, d, J 16.1Hz, CH=CHPh), 7.41-7.47 (3H, m, ArH), 7.52-7.59 (5H, m, ArH), 7.65 (2H, m, ArH), 8.06 (1H, d, J 16.1Hz, CH=CHPh), 8.72 (1H, br s, NH), 9.67 (1H, br s, NH), 11.73 (1H, br s, NH); m/z (ES⁺) 223 ([M+H]⁺).

EXAMPLE 42

30 (E)-N-Benzyl-2-chlorocinnamamide hydrochloride

Step 1: 2-(Diethylphosphono)-S-(2-naphthylmethyl)thioacetimidate hydrobromide

2-Bromomethylnaphthalene (5.23g, 23.7mmol) was added to a solution of diethyl (2-amino-2-thioxoethyl)phosphonate (5.00g, 23.7mmol) in chloroform (50ml). The mixture was heated at reflux for 1.5 hours, allowed to cool and concentrated *in vacuo*. The residue was triturated with acetone and the resulting white solid collected under suction to give the title compound (7.84g, 77%); δ_{H} (360MHz, DMSO- d_6) 1.22 (6H, t, 7.0Hz, 2 x OCH_2CH_3) 3.81 (2H, d, J 22Hz, CH_2P), 4.09 (4H, m, 2 x OCH_2CH_3), 4.85 (2H, s, ArCH_2S), 7.56 (3H, m, ArH), 7.89-7.98 (3H, m, ArH), 8.04 (1H, s, ArH); m/z (ES^+) 352 ($[\text{M}+\text{H}]^+$).

Step 2: N-Benzyl-2-(diethylphosphono)acetamidine hydrobromide

Benzylamine (0.54ml, 4.95mmol) was added to a suspension of 2-(diethylphosphono)-S-(2-naphthylmethyl)thioacetimidate hydrobromide (2.1187g, 4.90mmol) in ethanol (10ml). The mixture was stirred at room temperature for 2 hours, then warmed and diluted with diethyl ether to cloud point. It was allowed to cool to give a crystalline solid, which was collected under suction, washed with 10% ethanol in diethyl ether then diethyl ether and dried *in vacuo* to afford the title compound (0.8520g, 48%); δ_{H} (360MHz, DMSO- d_6) 1.24 (6H, t, 7.0Hz, 2 x OCH_2CH_3) 3.22 (2H, d, J 22Hz, CH_2P), 4.09 (4H, m, 2 x OCH_2CH_3), 4.53 (2H, s, ArCH_2N), 7.40 (5H, m, ArH), 9.04 (1H, v br s, NH), 9.24 (1H, v br s, NH), 9.94 (1H, v br s, NH); m/z (ES^+) 285 ($[\text{M}+\text{H}]^+$).

Step 3: (E)-N-Benzyl-2-chlorocinnamamidine hydrochloride

A rapidly stirred mixture of N-benzyl-2-(diethylphosphono)acetamidine hydrobromide (196.0mg, 0.537mmol), 2-chlorobenzaldehyde (63 μl , 0.56mmol) and potassium carbonate (324.2mg, 2.35mmol) in tetrahydrofuran (10ml) was heated at reflux for 6 hours. The reaction mixture was poured into water (50ml) and extracted with

dichloromethane (2 x 25ml). The combined extracts were dried (MgSO₄) and concentrated, then the residue was dissolved in methanol and treated with 1M HCl in diethyl ether (0.6ml). The mixture was evaporated and the resulting solid recrystallised twice from methanol-diethyl ether to afford the title compound (57.5mg, 35%); δ_{H} (360MHz, DMSO-d₆) 4.65 (2H, br s, PhCH₂N), 6.96 (1H, d, J 16.4Hz, CH=CHAr), 7.38 (1H, m, ArH), 7.43 (4H, m, ArH), 7.47-7.53 (2H, m, ArH), 7.59 (1H, m, ArH), 7.78 (1H, m, ArH), 8.09 (1H, d, J 16.4Hz, CH=CHAr), 9.10 (1H, br s, NH), 9.64 (1H, br s, NH), 10.36 (1H, br s, NH); m/z (ES⁺) 271/273 ([M+H]⁺).

The following Examples were prepared in an analogous process to the one described above:

EXAMPLE 43

(E)-N-Benzyl-3-chlorocinnamamide hydrochloride

δ_{H} (360MHz, DMSO-d₆) 4.63 (2H, d, J 4.4Hz, PhCH₂NH), 6.97 (1H, d, J 16.4Hz, CH=CHAr), 7.35-7.43 (5H, m, ArH), 7.55 (3H, m, ArH), 7.65 (1H, s, ArH), 7.89 (1H, d, J 16.4Hz, CH=CHAr), 9.08 (1H, br s, NH), 9.55 (1H, br s, NH), 10.27 (1H, br s, NH); m/z (ES⁺) 271/273 ([M+H]⁺).

EXAMPLE 44

(E)-N-Benzyl-4-chlorocinnamamide hydrochloride

δ_{H} (400MHz, DMSO-d₆) 4.61 (2H, d, J 5.8Hz, PhCH₂NH), 6.86 (1H, d, J 16.4Hz, CH=CHAr), 7.33-7.45 (5H, m, ArH), 7.56-7.63 (4H, m, ArH), 7.85 (1H, d, J 16.4Hz, CH=CHAr), 8.98 (1H, br s, NH), 9.44 (1H, br s, NH), 10.16 (1H, br s, NH); m/z (ES⁺) 271/273 ([M+H]⁺).

EXAMPLE 45**(E)-N-Benzyl-4-fluorocinnamamide hydrochloride**

5 δ_H (360MHz, DMSO- d_6) 4.61 (2H, d, J 5.9Hz, $ArCH_2N$), 6.80 (1H, d, J 16.4Hz, $CH=CHAr$), 7.40 (7H, m, ArH), 7.67 (2H, m, ArH), 7.86 (1H, d, J 16.5Hz, $CH=CHAr$), 9.40 (1H, br s, NH), 9.97 (1H, br s, NH), 10.1 (1H, br s, NH); m/z (ES⁺) 255 ([M+H]⁺).

EXAMPLE 46

10

(E)-N-Benzyl-4-methoxycinnamamide hydrochloride

15 δ_H (360MHz, DMSO- d_6) 3.83 (3H, s, $ArOCH_3$), 4.60 (2H, d, J 5.9Hz, $ArCH_2N$), 6.69 (1H, d, J 16.3Hz, $CH=CHAr$), 7.06 (2H, d, J 8.8Hz, ArH), 7.41 (5H, m, ArH), 7.56 (2H, d, J 8.8Hz, ArH), 7.82 (1H, d, J 16.4Hz, $CH=CHAr$); m/z (ES⁺) 267 ([M+H]⁺).

EXAMPLE 47**(E)-N-Benzyl-3-methoxycinnamamide hydrochloride**

20 δ_H (360MHz, DMSO- d_6) 3.81 (3H, s, $ArOCH_3$), 4.61 (2H, s, $ArCH_2N$), 6.88 (1H, d, J 16.5Hz, $CH=CHAr$), 7.41 (5H, m, ArH), 7.07 (1H, m, ArH), 7.16 (2H, m, ArH), 7.40 (6H, m ArH), 7.83 (1H, d, J 16.4Hz, $CH=CHAr$); m/z (ES⁺) 267 ([M+H]⁺).

25

EXAMPLE 48**(E)-N-Benzyl-2-methoxycinnamamide hydrochloride**

30 δ_H (360MHz, DMSO- d_6) 3.90 (3H, s, $ArOCH_3$), 4.60 (2H, d, J 5.9Hz, $ArCH_2N$), 6.95 (1H, d, J 16.6Hz, $CH=CHAr$), 7.41 (5H, m, ArH), 7.06 (1H, t, J 7.4Hz, ArH), 7.16 (1H, d, J 8.3Hz, ArH), 7.45 (6H, m ArH), 7.98 (1H, d,

J 16.6Hz, CH=CHAr), 9.9 (1H, br s, NH), 9.40 (1H, br s, NH), 10.10 (1H, br s, NH); m/z (ES⁺) 267 ([M+H]⁺).

EXAMPLE 49

5

(E)-N-Benzyl-3,4-difluorocinnamidine hydrochloride

δ_H (360MHz, DMSO-d₆) 4.62 (2H, s, ArCH₂N), 6.87 (1H, d, J 16.4Hz, CH=CHAr), 7.35-7.48 (6H, m, ArH), 7.57 (1H, m, ArH), 7.71 (1H, m, ArH), 7.82 (1H, d, J 16.4Hz, CH=CHAr), 9.03 (1H, br s NH), 9.49 (1H, br s, NH), 10.22 (1H, br s, NH); m/z (ES⁺) 272 ([M+H]⁺).

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EXAMPLE 50

(E)-N-Benzyl-3-cyclohexaneacrylamidine hydrochloride

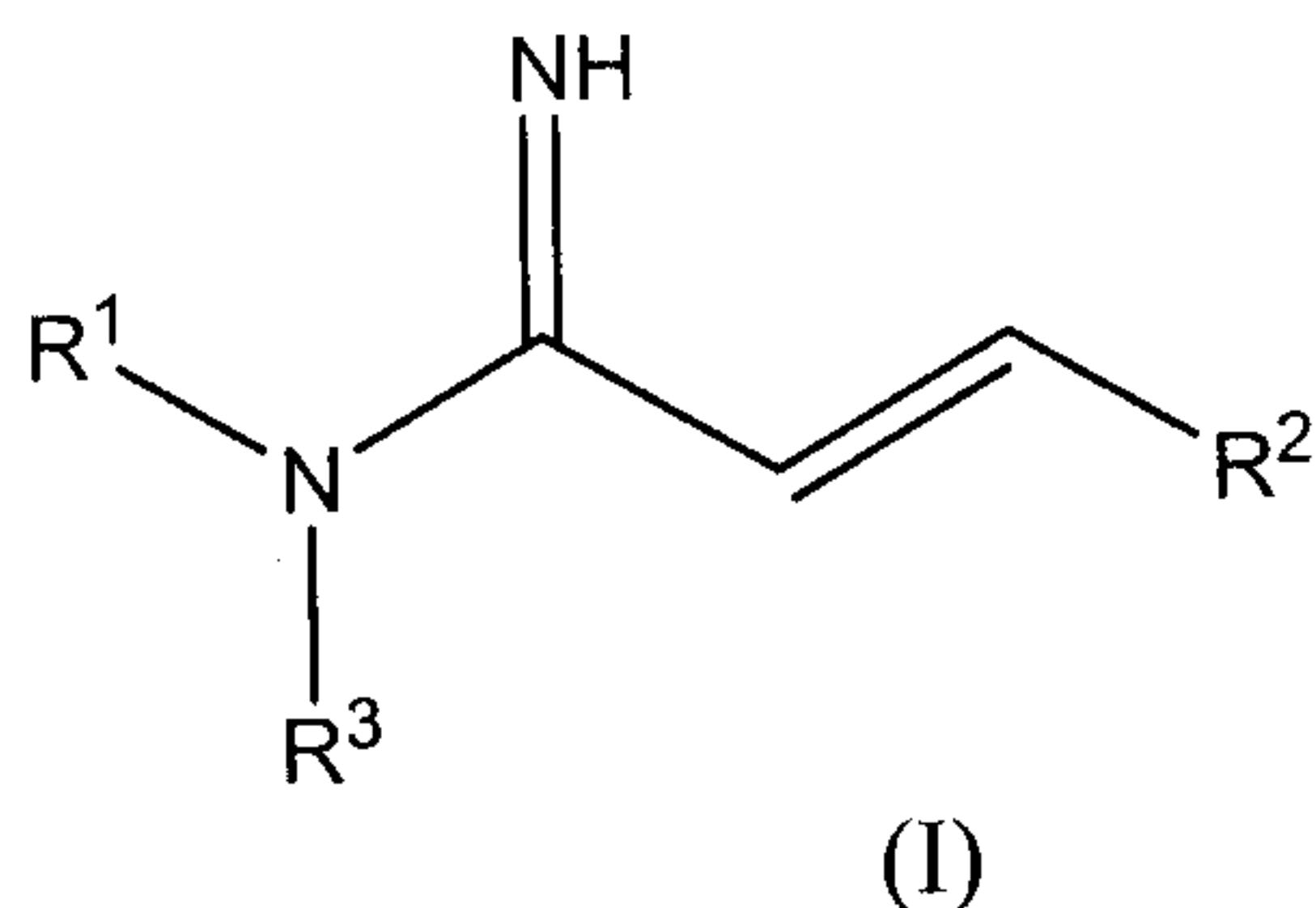
δ_H (360MHz, DMSO-d₆) 1.07-1.35 (5H, m, AlkH), 1.62-1.74 (5H, m, AlkH), 2.19-2.26 (1H, m, AlkH), 4.53 (2H, s, ArCH₂N), 1.91 (2H, m, AlkH), 6.06 (1H, dd, J 16.2Hz, 1.1Hz, CH=CHc-Hex), 7.04 (1H, dd, J 16.2Hz, 6.6Hz, CH=CHc-Hex), 7.33-7.46 (5H, m, ArH), 9.00 (1H, br s, NH), 9.21 (1H, br s, NH), 10.00 (1H, br s, NH); m/z (ES⁺) 243 ([M+H]⁺).

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CLAIMS:

1. Use of a compound of formula I, or a pharmaceutically acceptable salt or hydrate thereof:



wherein:

R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^2 represents cyclopentyl, cyclohexyl, phenyl, naphthyl, pyridinyl, furyl, thienyl or pyrrolyl, any of which groups may be optionally substituted; and

R^3 represents hydrogen or C_{1-6} alkyl which optionally is substituted; or

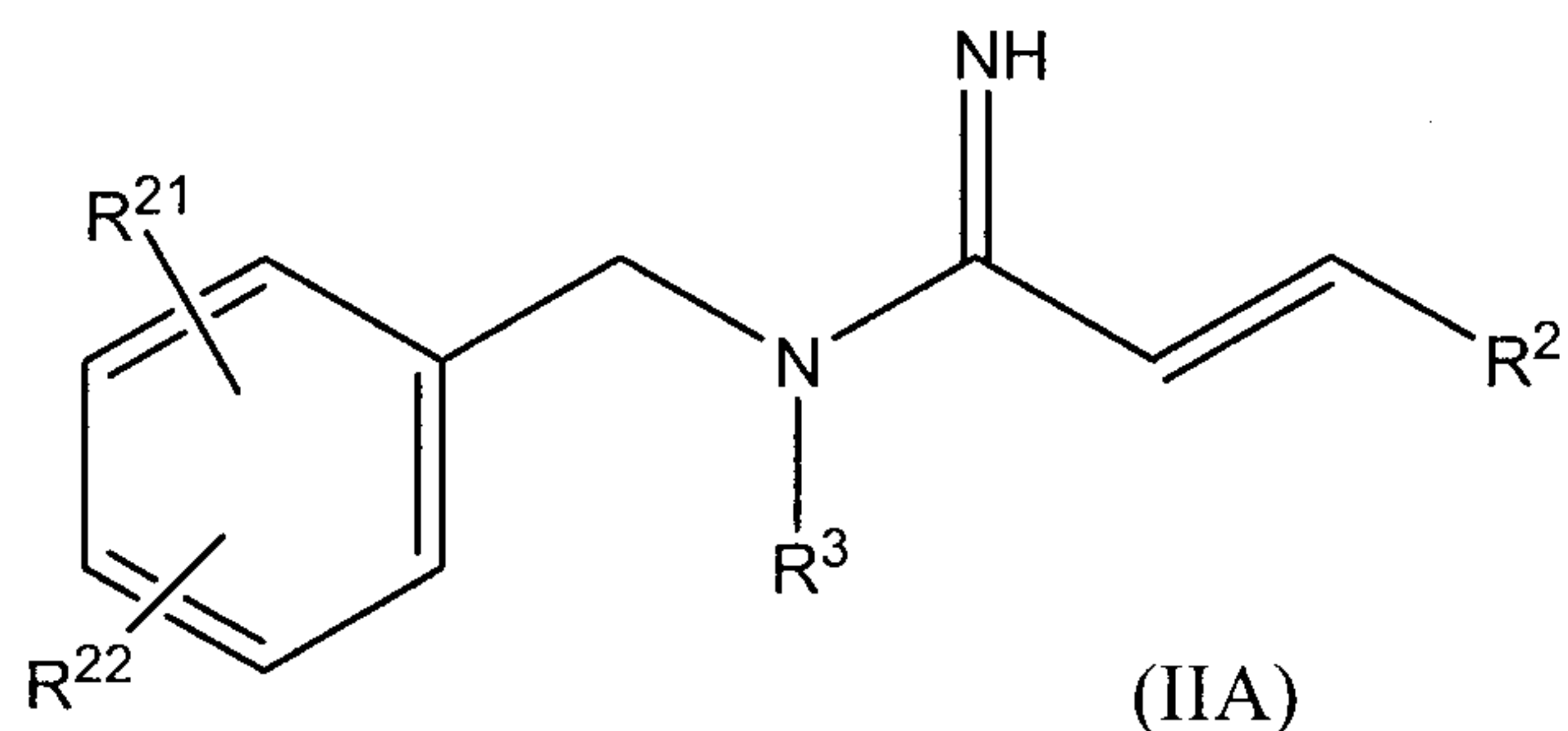
R^1 and R^3 are taken together with the intervening nitrogen atom to form an optionally substituted isoquinoline ring;

wherein the optional substituents on R^1 , R^2 and R^3 are one or two groups independently selected from C_{1-6} alkyl, aryl, halogen, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, trihalo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, (C_{1-6})alkoxy, halo(C_{1-6})alkoxy, dihalo(C_{1-6})alkoxy and trihalo(C_{1-6})alkoxy;

for the manufacture of a medicament for treatment and/or prevention of neurological and/or neurodegenerative disorders.

2. The use as claimed in claim 1, wherein the compound is represented by formula IIA, or a pharmaceutically acceptable salt or hydrate thereof:

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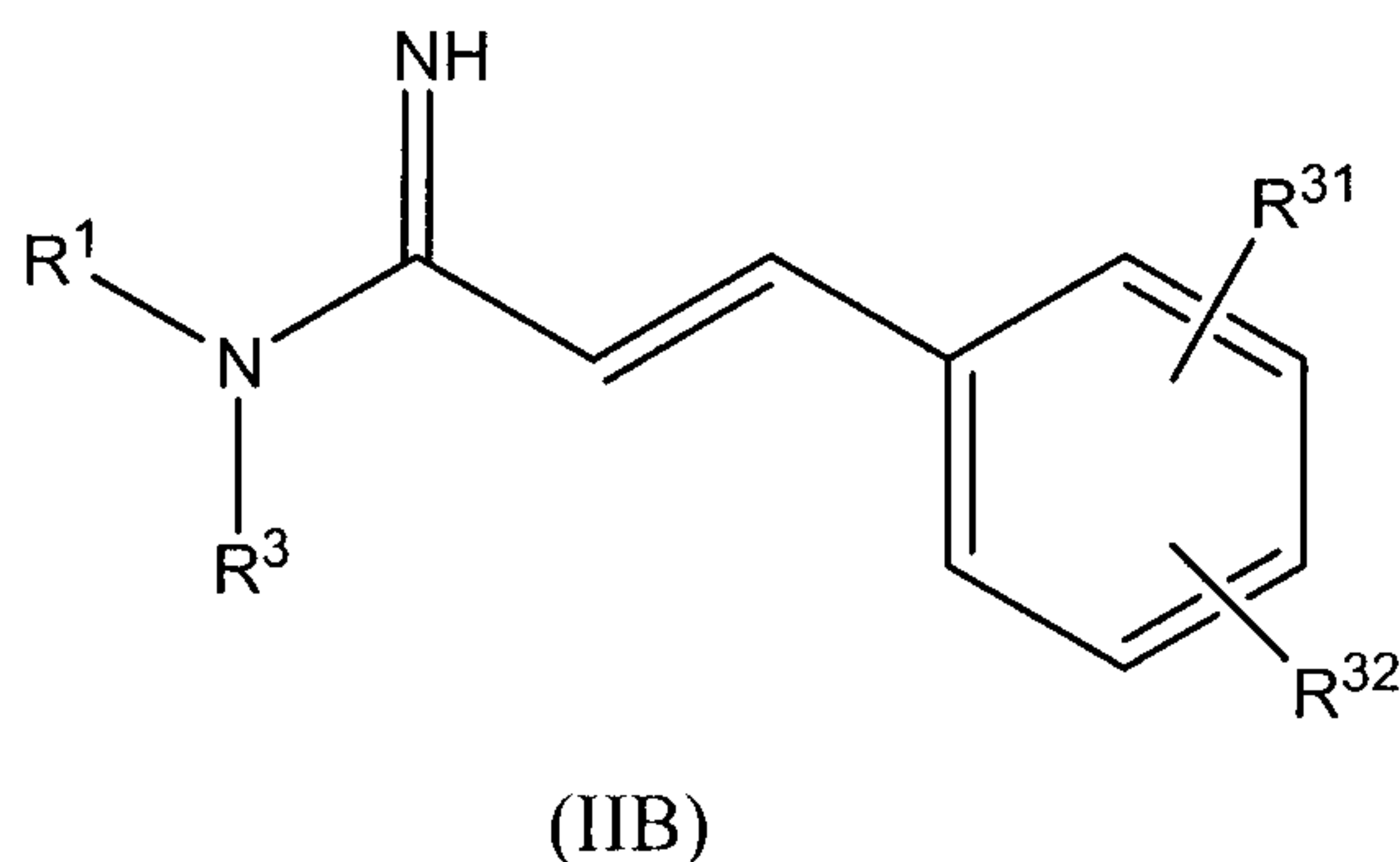


wherein R^2 and R^3 are as defined in claim 1;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy; and

R^{22} represents hydrogen or halogen.

3. The use as claimed in claim 1, wherein the compound is represented by formula IIB, or a pharmaceutically acceptable salt or hydrate thereof:



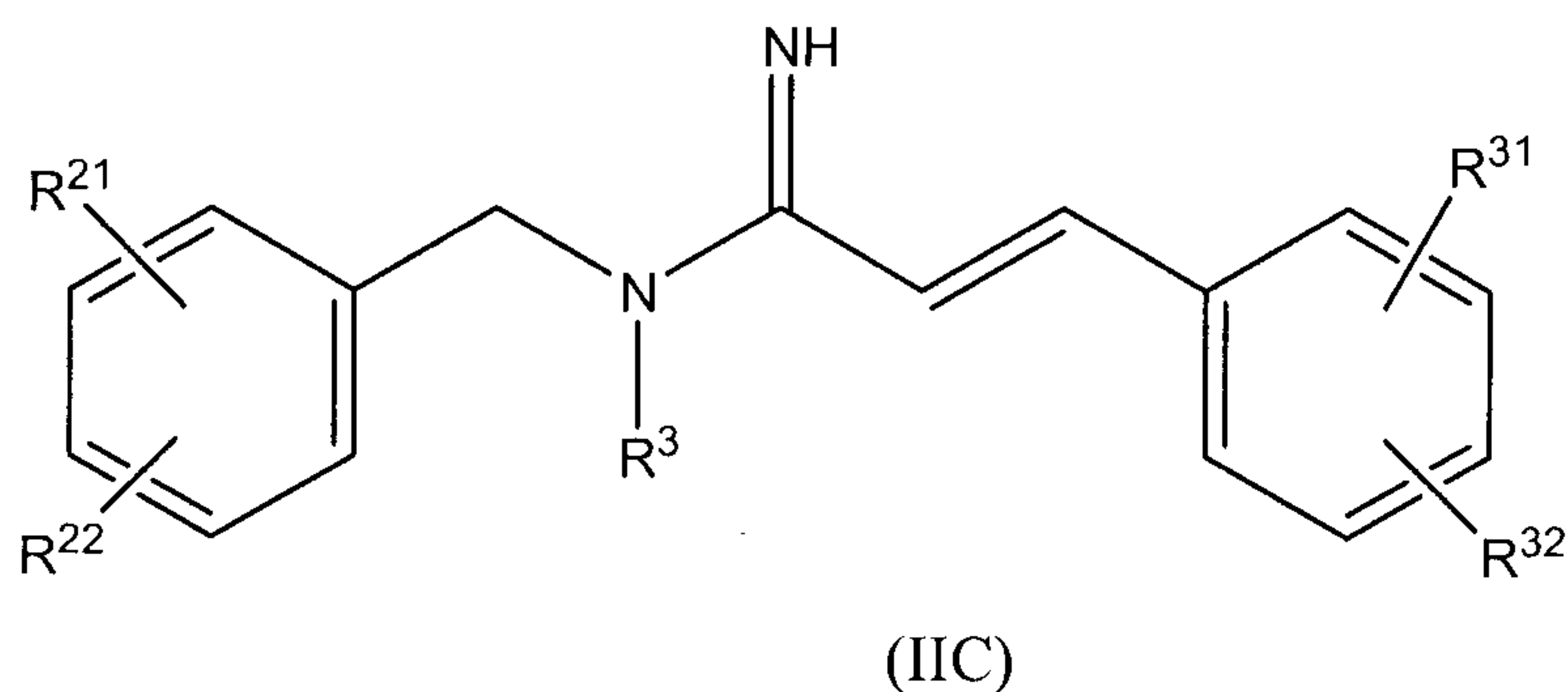
wherein R^1 and R^3 are as defined in claim 1;

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy; and

R^{32} represents hydrogen or halogen.

4. The use as claimed in any one of claims 1 to 3, wherein the compound is represented by formula IIC, or a pharmaceutically acceptable salt or hydrate thereof:

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wherein

R^3 is as defined in claim 1;

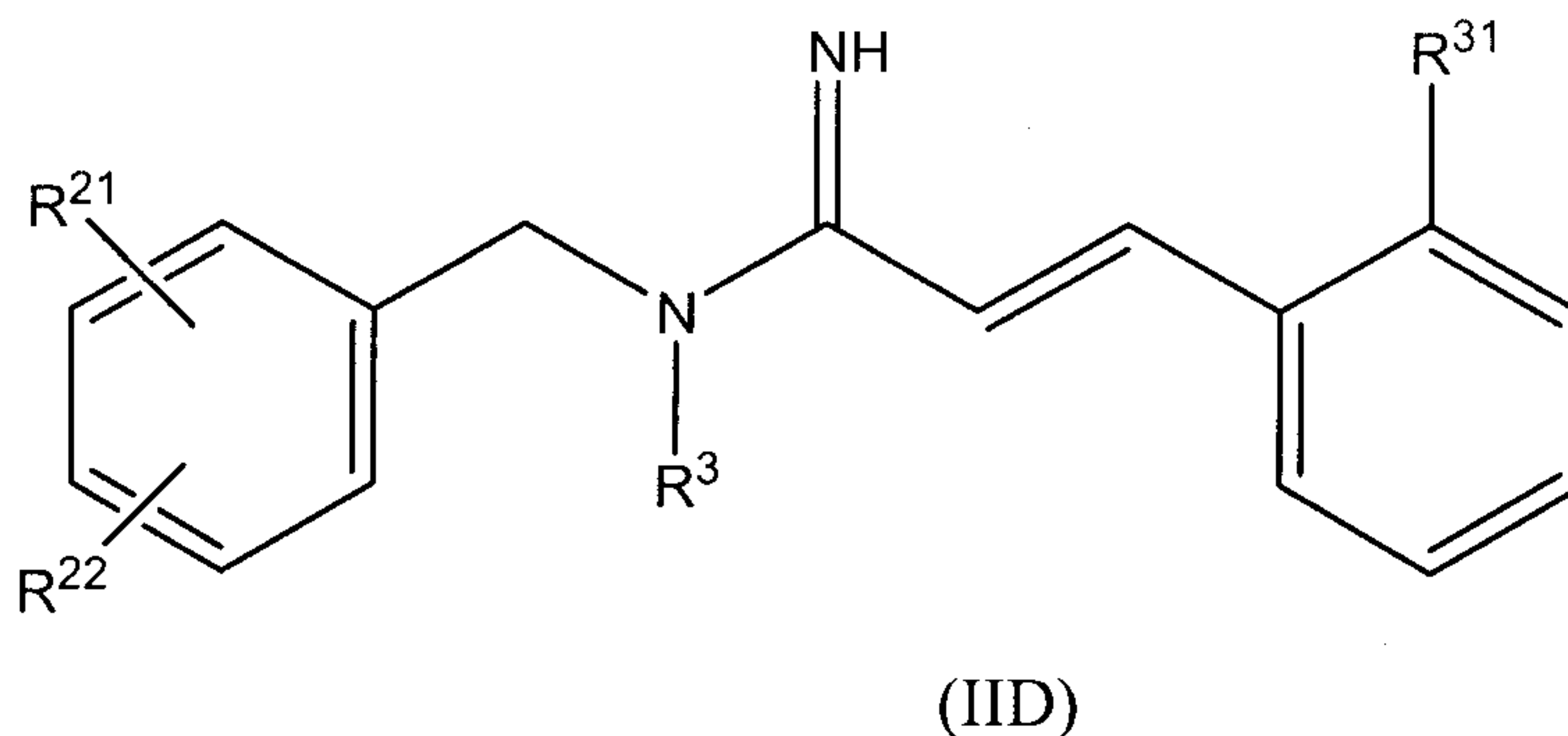
R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

R^{22} represents hydrogen or halogen;

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy; and

R^{32} represents hydrogen or halogen.

5. The use as claimed in claim 4, wherein the compound is represented by formula IID, or a pharmaceutically acceptable salt or hydrate thereof:



wherein R^3 is as defined in claim 4;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

R^{22} represents hydrogen or halogen; and

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy.

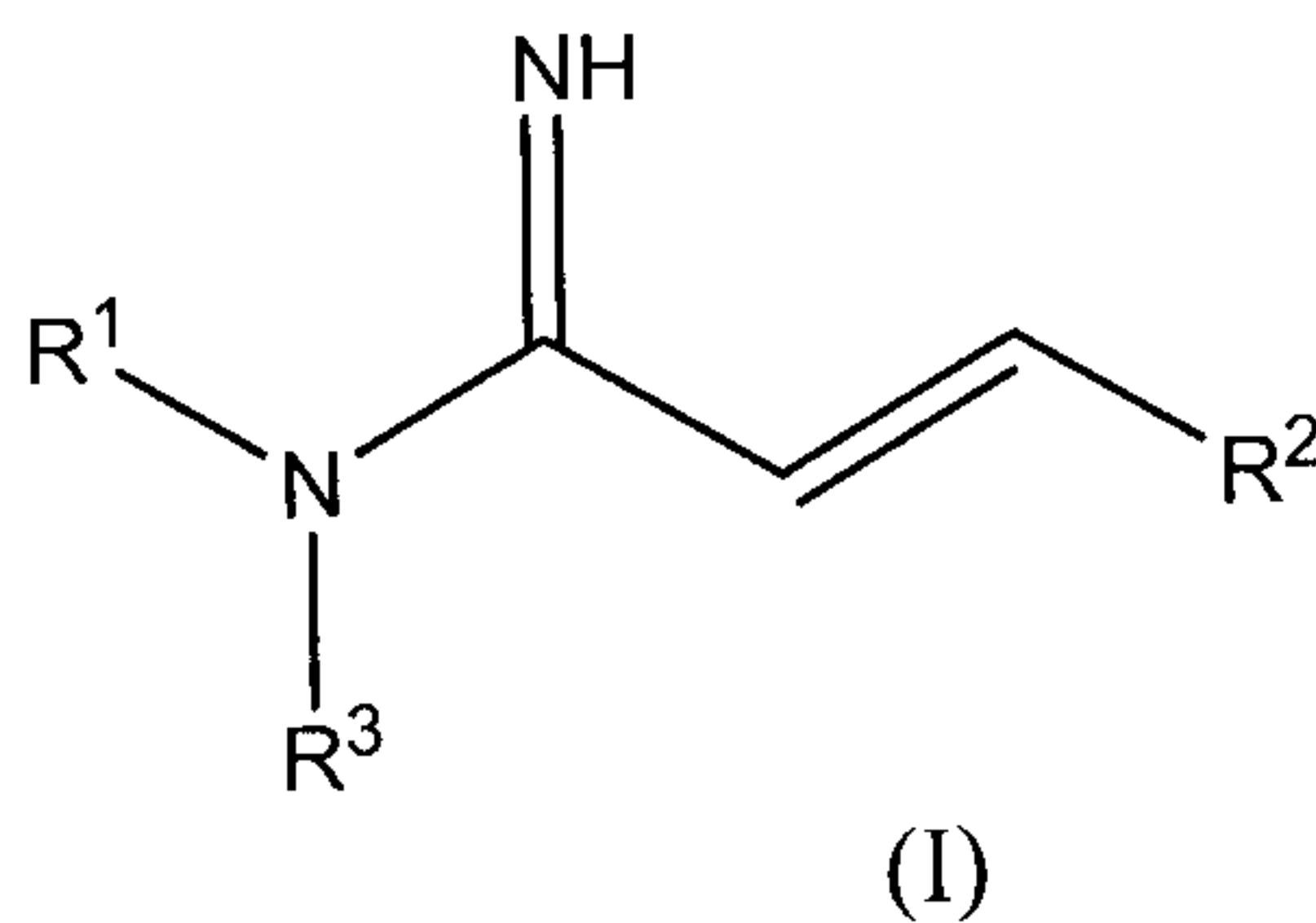
6. The use according to claim 1, wherein the compound is selected from:
(E)-N-(3-iodobenzyl)cinnamamidine;

(E)-N-(benzyl)cinnamamide;
(E)-N-(4-chlorobenzyl)cinnamamide;
(E)-N-(2-chlorobenzyl)cinnamamide;
(E)-N-(3-chlorobenzyl)cinnamamide;
(E)-N-(4-fluorobenzyl)cinnamamide;
(E)-N-(4-trifluoromethylbenzyl)cinnamamide;
(E)-N-(4-methoxybenzyl)cinnamamide;
(E)-N-(4-methylbenzyl)cinnamamide;
(E)-N-(3-methylbenzyl)cinnamamide;
(E)-N-(2-methylbenzyl)cinnamamide;
(E)-N-(3,4-dichlorobenzyl)cinnamamide;
(E)-N-(2-phenylethyl)cinnamamide;
(E)-N-(R)- α -methylbenzylcinnamamide;
(E)-N-(S)- α -methylbenzylcinnamamide;
(E)-N-(3-trifluoromethylbenzyl)cinnamamide;
(E)-N-(3,5-dichlorobenzyl)cinnamamide;
(E)-N-(2-methoxybenzyl)cinnamamide;
(E)-N-(3-methoxybenzyl)cinnamamide;
(E)-N-(2-trifluoromethylbenzyl)cinnamamide;
(E)-N-(2,5-dichlorobenzyl)cinnamamide;
(E)-N-(3-bromobenzyl)cinnamamide;
(E)-N-(4-pyridylmethyl)cinnamamide;
(E)-N-methyl-N-benzylcinnamamide;
(E)-N-(2,3-dichlorobenzyl)cinnamamide;
(E)-N-(cyclohexylmethyl)cinnamamide;
(E)-N-(isobutyl)cinnamamide;
(E)-N-(n-butyl)cinnamamide;
(E)-N-(2-trifluoromethoxybenzyl)cinnamamide;
(E)-N-(3-thienylmethyl)cinnamamide;
(E)-N-(2-bromobenzyl)cinnamamide;
(E)-N-(2-ethoxybenzyl)cinnamamide;
(E)-N-(2-phenylbenzyl)cinnamamide;
(E)-N-(2-furylmethyl)cinnamamide;
(E)-N-(cyclohexyl)cinnamamide;

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(E)-N-(3-methyl-1-butyl)cinnamamidine;
 (E)-2-(3-phenyl-1-imino-2-propenyl)-1,2,3,4-tetrahydroisoquinoline;
 (E)-N-(n-pentyl)cinnamamidine;
 (E)-N-(3-phenyl-1-propyl)cinnamamidine;
 (E)-N-(2-hydroxybenzyl)cinnamamidine;
 (E)-N-phenylcinnamamidine;
 (E)-N-benzyl-2-chlorocinnamamidine;
 (E)-N-benzyl-3-chlorocinnamamidine;
 (E)-N-benzyl-4-chlorocinnamamidine;
 (E)-N-benzyl-4-fluorocinnamamidine;
 (E)-N-benzyl-4-methoxycinnamamidine;
 (E)-N-benzyl-3-methoxycinnamamidine;
 (E)-N-benzyl-2-methoxycinnamamidine;
 (E)-N-benzyl-3,4-difluorocinnamamidine;
 (E)-N-benzyl-3-cyclohexaneacrylamidine; and
 pharmaceutically acceptable salts and hydrates thereof.

7. A pharmaceutical composition for use in the treatment and/or prevention of neurological and/or neurodegenerative disorders, comprising a compound of formula I, or a pharmaceutically acceptable salt or hydrate thereof:



wherein:

R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^2 represents cyclopentyl, cyclohexyl, phenyl, naphthyl, pyridinyl, furyl, thienyl or pyrrolyl, any of which groups may be optionally substituted; and

R^3 represents hydrogen or C_{1-6} alkyl which optionally is substituted; or

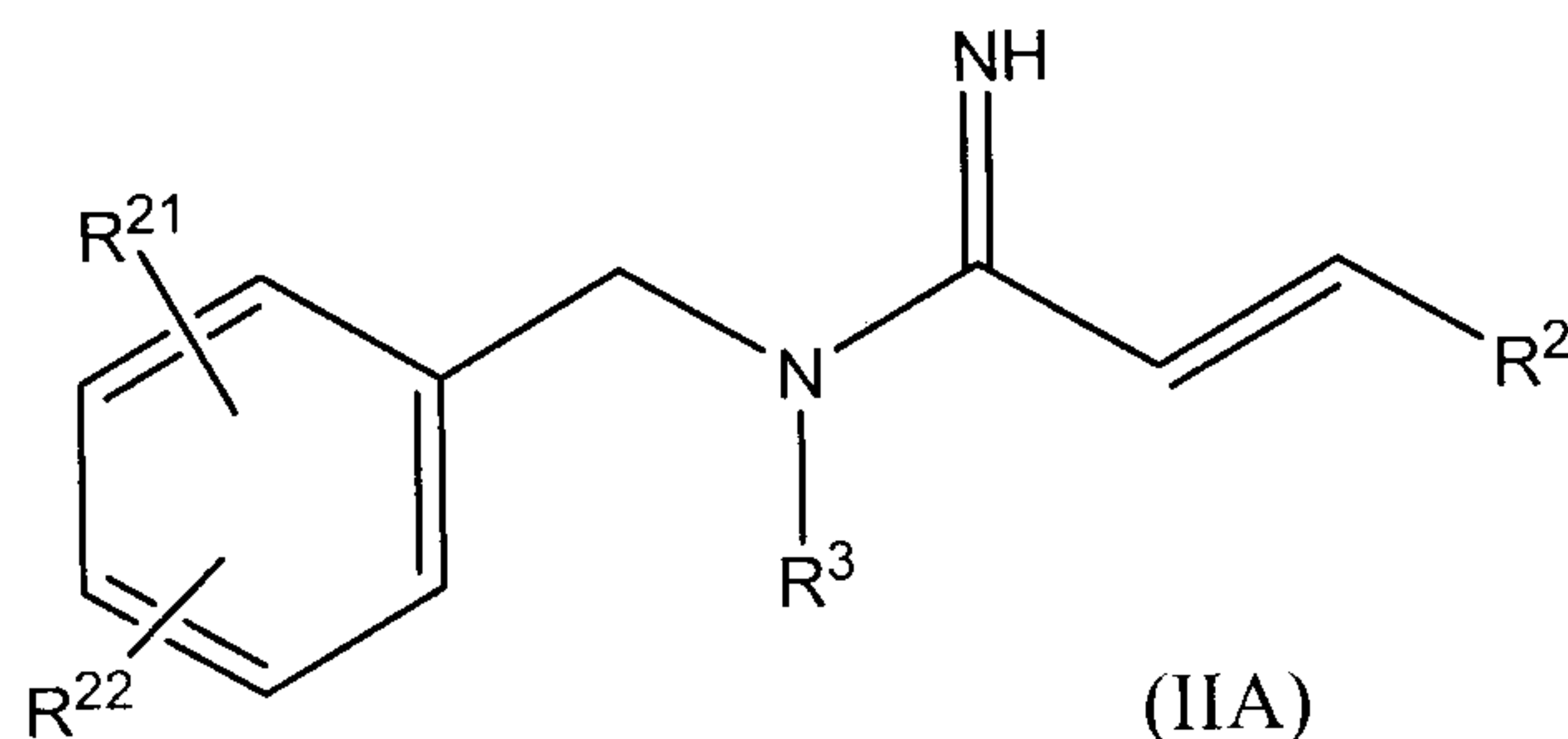
- 41 -

R^1 and R^3 are taken together with the intervening nitrogen atom to form an optionally substituted isoquinoline ring;

wherein the optional substituents on R^1 , R^2 and R^3 are one or two groups independently selected from C_{1-6} alkyl, aryl, halogen, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, trihalo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, (C_{1-6})alkoxy, halo(C_{1-6})alkoxy, dihalo(C_{1-6})alkoxy and trihalo(C_{1-6})alkoxy;

in combination with a pharmaceutically acceptable carrier.

8. The pharmaceutical composition as claimed in claim 7, wherein the compound is represented by formula IIA, or a pharmaceutically acceptable salt or hydrate thereof:



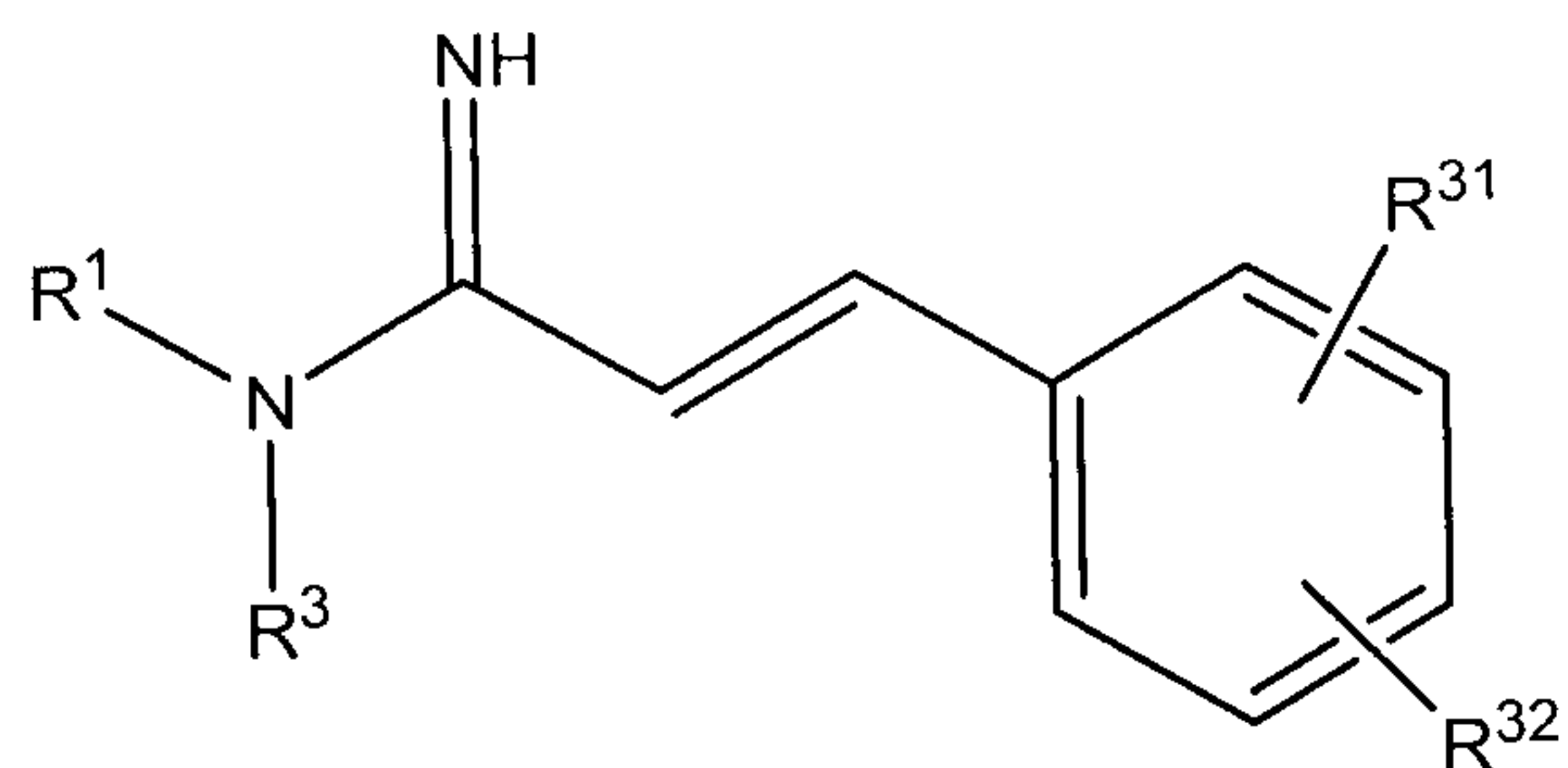
wherein R^2 and R^3 are as defined in claim 7;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy; and

R^{22} represents hydrogen or halogen.

9. The pharmaceutical composition as claimed in claim 7, wherein the compound is represented by formula IIB, or a pharmaceutically acceptable salt or hydrate thereof:

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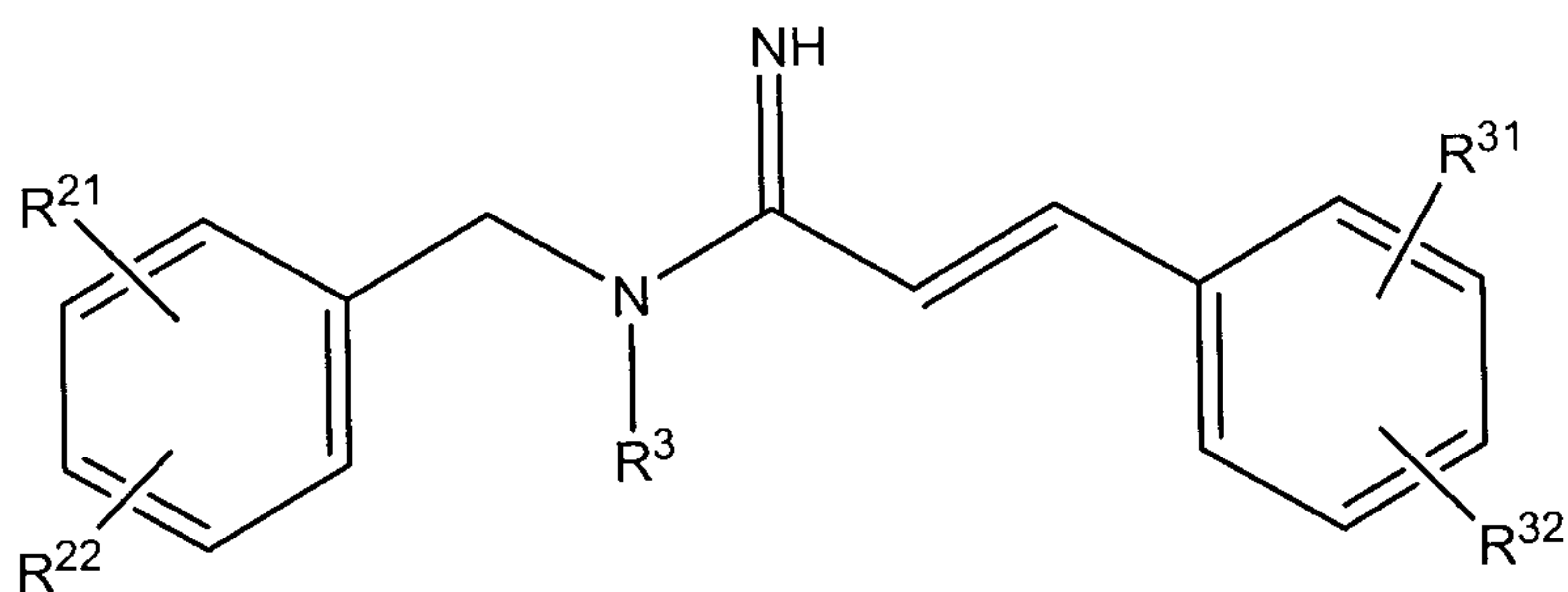
(IIB)

wherein R^1 and R^3 are as defined in claim 7;

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy; and

R^{32} represents hydrogen or halogen.

10. The pharmaceutical composition as claimed in any one of claims 7 to 9, wherein the compound is represented by formula IIC, or a pharmaceutically acceptable salt or hydrate thereof:



(IIC)

wherein

R^3 is as defined in claim 7;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

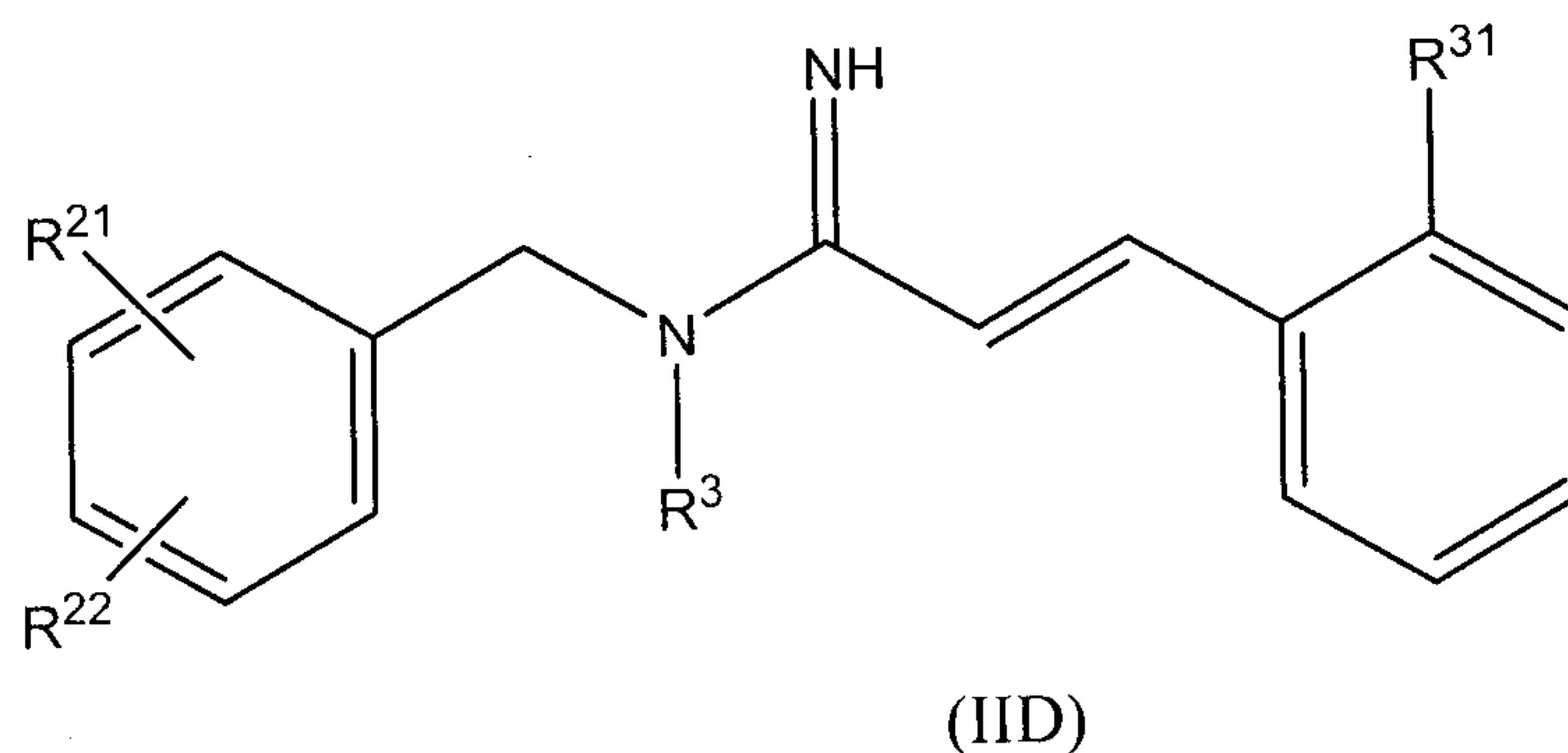
R^{22} represents hydrogen or halogen;

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy; and

R^{32} represents hydrogen or halogen.

11. The pharmaceutical composition as claimed in claim 10, wherein the compound is represented by formula IID, or a pharmaceutically acceptable salt or hydrate thereof:

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wherein R^3 is as defined in claim 10;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

R^{22} represents hydrogen or halogen; and

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy.

12. The pharmaceutical composition according to claim 7, wherein the compound is selected from:

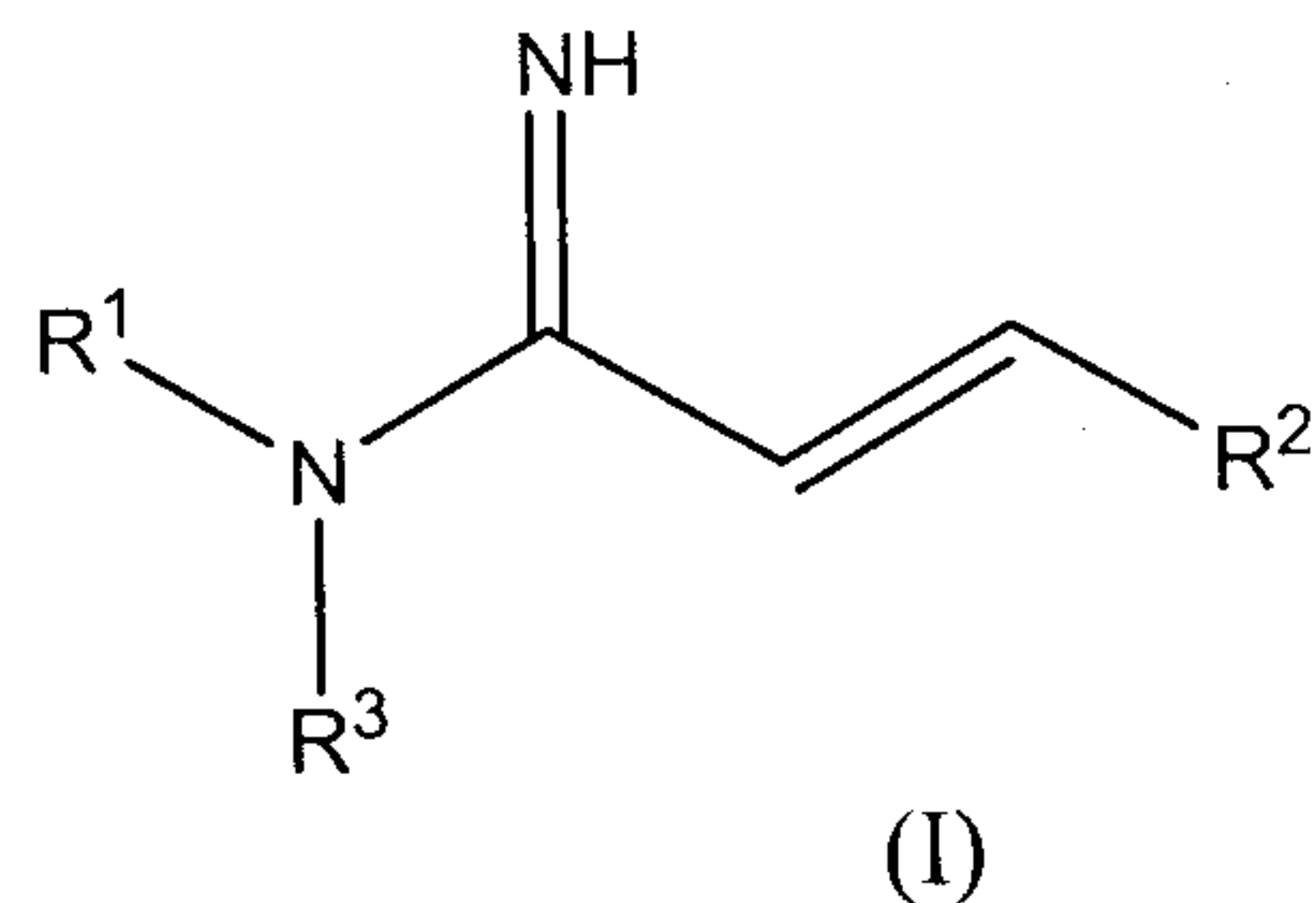
- (E)-N-(3-iodobenzyl)cinnamamide;
- (E)-N-(benzyl)cinnamamide;
- (E)-N-(4-chlorobenzyl)cinnamamide;
- (E)-N-(2-chlorobenzyl)cinnamamide;
- (E)-N-(3-chlorobenzyl)cinnamamide;
- (E)-N-(4-fluorobenzyl)cinnamamide;
- (E)-N-(4-trifluoromethylbenzyl)cinnamamide;
- (E)-N-(4-methoxybenzyl)cinnamamide;
- (E)-N-(4-methylbenzyl)cinnamamide;
- (E)-N-(3-methylbenzyl)cinnamamide;
- (E)-N-(2-methylbenzyl)cinnamamide;
- (E)-N-(3,4-dichlorobenzyl)cinnamamide;
- (E)-N-(2-phenylethyl)cinnamamide;
- (E)-N-(R)- α -methylbenzylcinnamamide;
- (E)-N-(S)- α -methylbenzylcinnamamide;
- (E)-N-(3-trifluoromethylbenzyl)cinnamamide;
- (E)-N-(3,5-dichlorobenzyl)cinnamamide;
- (E)-N-(2-methoxybenzyl)cinnamamide;

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(E)-N-(3-methoxybenzyl)cinnamamidine;
(E)-N-(2-trifluoromethylbenzyl)cinnamamidine;
(E)-N-(2,5-dichlorobenzyl)cinnamamidine;
(E)-N-(3-bromobenzyl)cinnamamidine;
(E)-N-(4-pyridylmethyl)cinnamamidine;
(E)-N-methyl-N-benzylcinnamamidine;
(E)-N-(2,3-dichlorobenzyl)cinnamamidine;
(E)-N-(cyclohexylmethyl)cinnamamidine;
(E)-N-(isobutyl)cinnamamidine;
(E)-N-(n-butyl)cinnamamidine;
(E)-N-(2-trifluoromethoxybenzyl)cinnamamidine;
(E)-N-(3-thienylmethyl)cinnamamidine;
(E)-N-(2-bromobenzyl)cinnamamidine;
(E)-N-(2-ethoxybenzyl)cinnamamidine;
(E)-N-(2-phenylbenzyl)cinnamamidine;
(E)-N-(2-furylmethyl)cinnamamidine;
(E)-N-(cyclohexyl)cinnamamidine;
(E)-N-(3-methyl-1-butyl)cinnamamidine;
(E)-2-(3-phenyl-1-imino-2-propenyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-N-(n-pentyl)cinnamamidine;
(E)-N-(3-phenyl-1-propyl)cinnamamidine;
(E)-N-(2-hydroxybenzyl)cinnamamidine;
(E)-N-phenylcinnamamidine;
(E)-N-benzyl-2-chlorocinnamamidine;
(E)-N-benzyl-3-chlorocinnamamidine;
(E)-N-benzyl-4-chlorocinnamamidine;
(E)-N-benzyl-4-fluorocinnamamidine;
(E)-N-benzyl-4-methoxycinnamamidine;
(E)-N-benzyl-3-methoxycinnamamidine;
(E)-N-benzyl-2-methoxycinnamamidine;
(E)-N-benzyl-3,4-difluorocinnamamidine;
(E)-N-benzyl-3-cyclohexaneacrylamidine; and
pharmaceutically acceptable salts and hydrates thereof.

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13. A compound of formula I, or a pharmaceutically acceptable salt or hydrate thereof:



wherein:

R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^2 represents cyclopentyl, cyclohexyl, phenyl, naphthyl, pyridinyl, furyl, thienyl or pyrrolyl, any of which groups may be optionally substituted; and

R^3 represents hydrogen or C_{1-6} alkyl which optionally is substituted; or

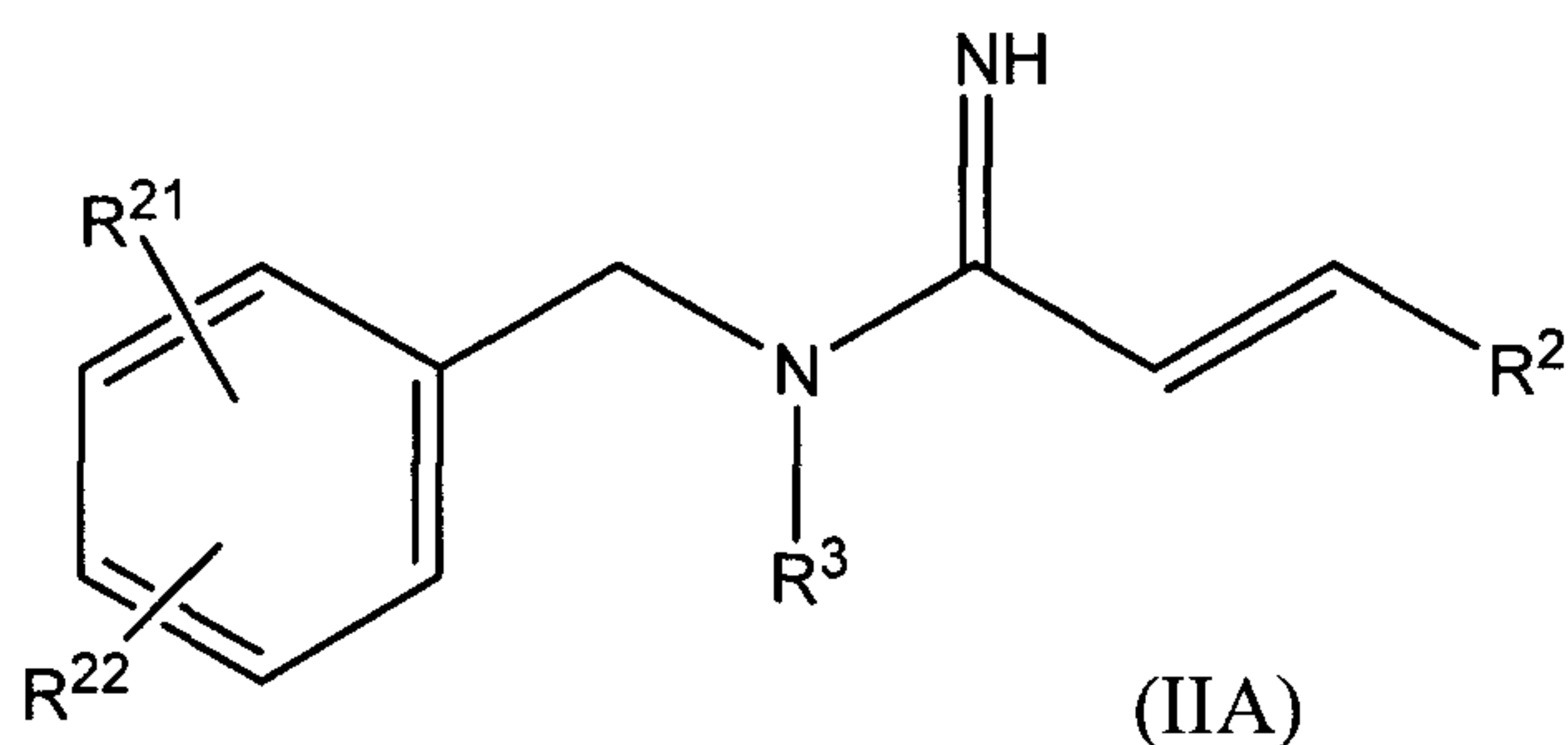
R^1 and R^3 are taken together with the intervening nitrogen atom to form an optionally substituted isoquinoline ring;

wherein the optional substituents on R^1 , R^2 and R^3 are one or two groups independently selected from C_{1-6} alkyl, aryl, halogen, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, trihalo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, (C_{1-6})alkoxy, halo(C_{1-6})alkoxy, dihalo(C_{1-6})alkoxy and trihalo(C_{1-6})alkoxy;

for use in treatment or prevention of a neurological disorder or a neurodegenerative disorder.

14. The compound as claimed in claim 13, wherein the compound is represented by formula IIA, or a pharmaceutically acceptable salt or hydrate thereof:

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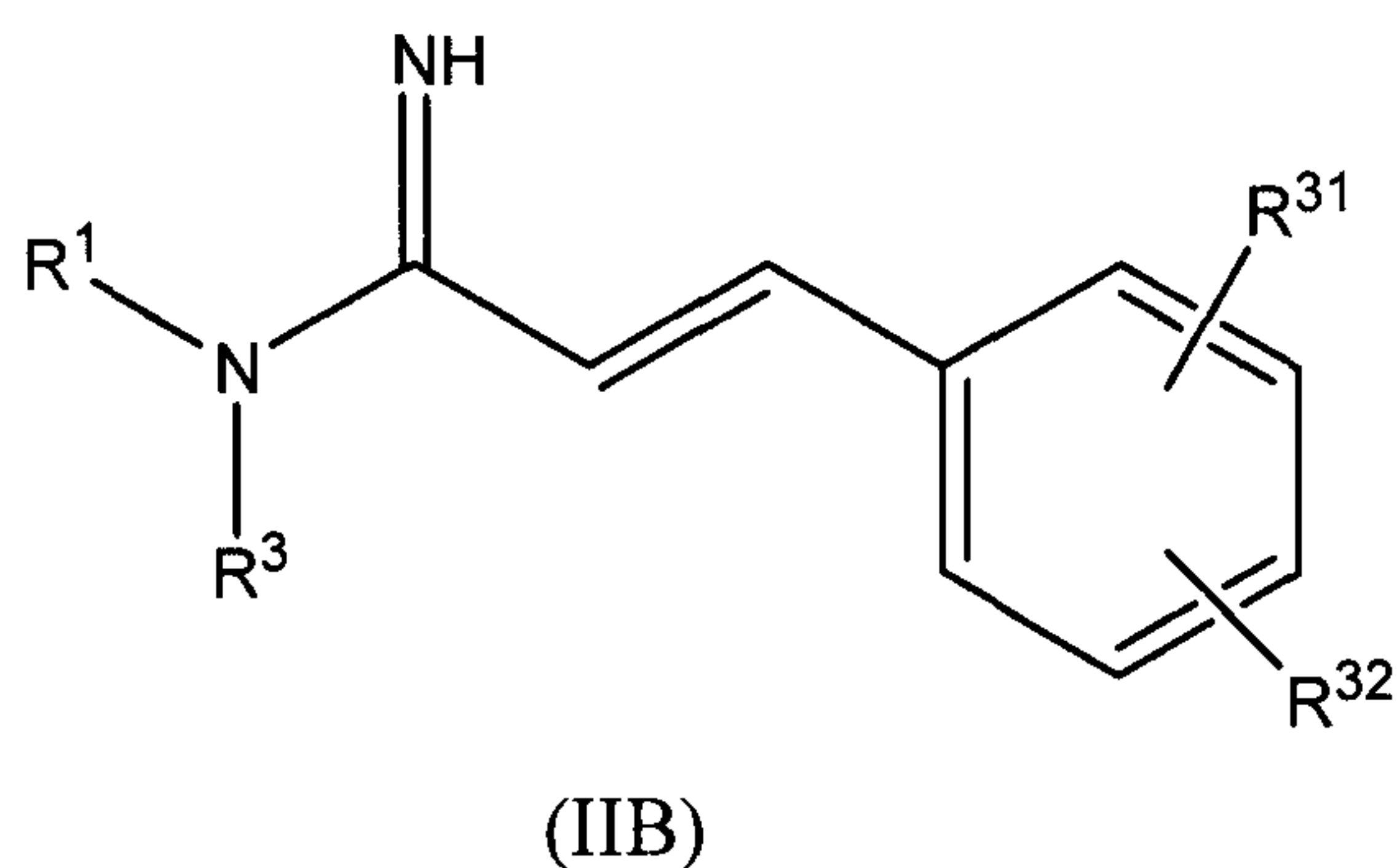


wherein R^2 and R^3 are as defined in claim 13;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy; and

R^{22} represents hydrogen or halogen.

15. The compound as claimed in claim 13, wherein the compound is represented by formula IIB, or a pharmaceutically acceptable salt or hydrate thereof:



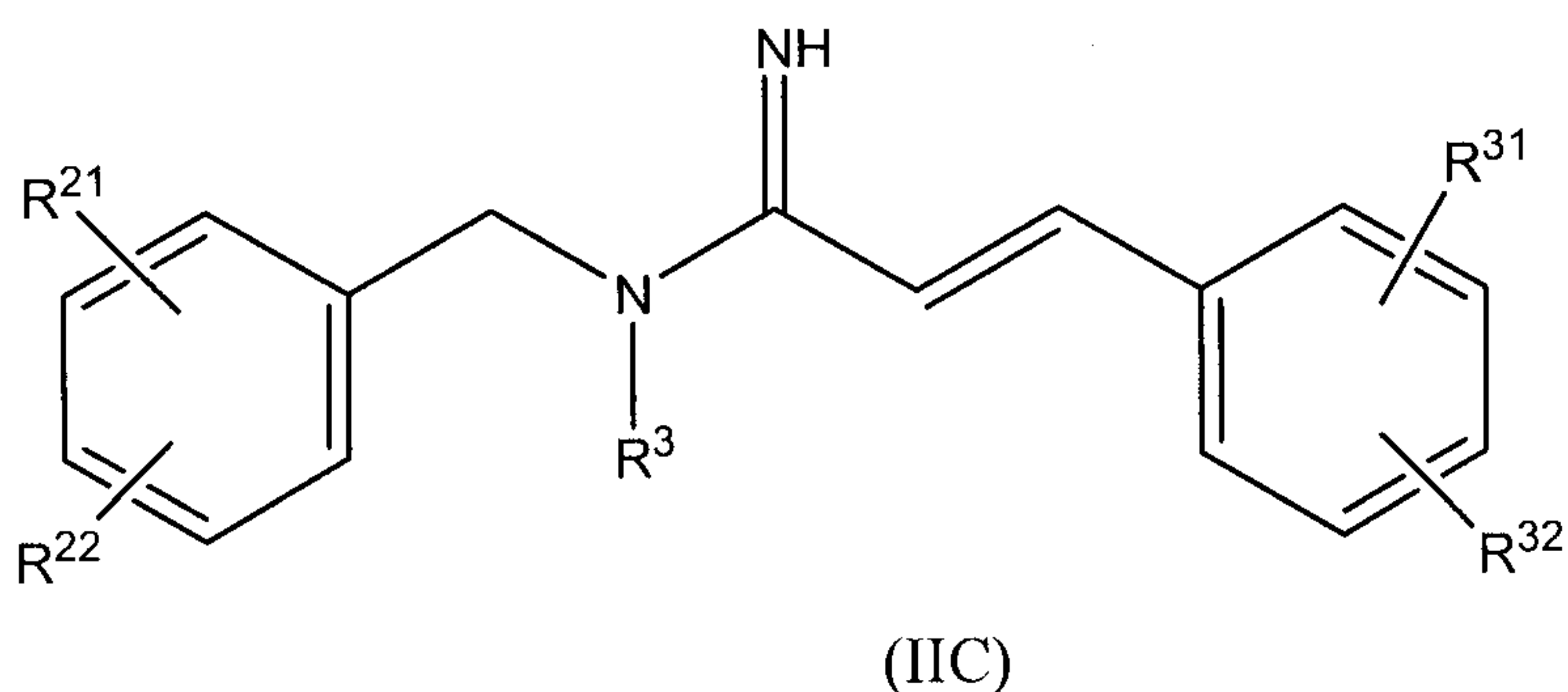
wherein R^1 and R^3 are as defined in claim 13;

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy; and

R^{32} represents hydrogen or halogen.

16. The compound as claimed in any one of claims 13 to 15, wherein the compound is represented by formula IIC, or a pharmaceutically acceptable salt or hydrate thereof:

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wherein

R^3 is as defined in claim 13;

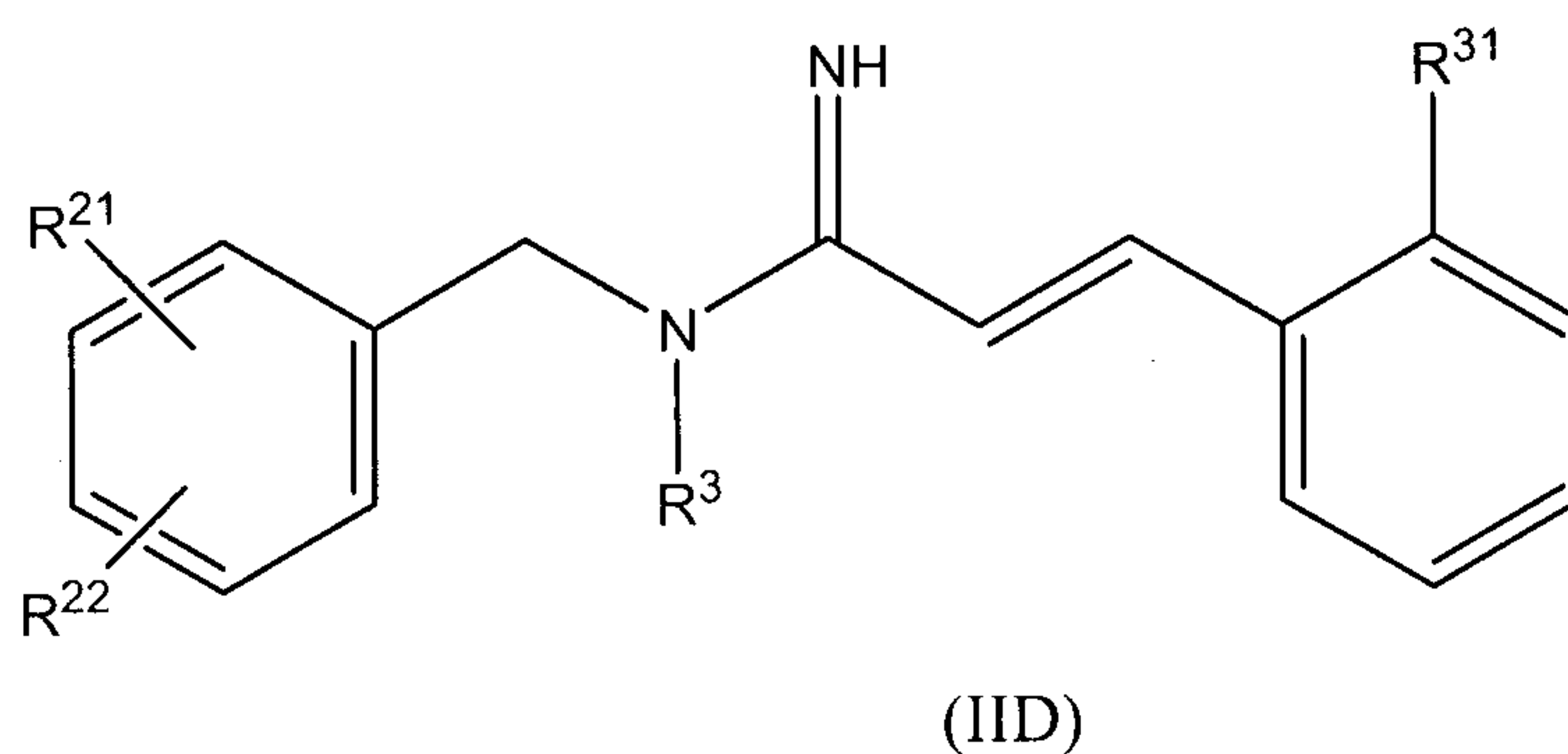
R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

R^{22} represents hydrogen or halogen;

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy; and

R^{32} represents hydrogen or halogen.

17. The compound as claimed in claim 16, wherein the compound is represented by formula IID, or a pharmaceutically acceptable salt or hydrate thereof:



wherein R^3 is as defined in claim 16;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

R^{22} represents hydrogen or halogen; and

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy.

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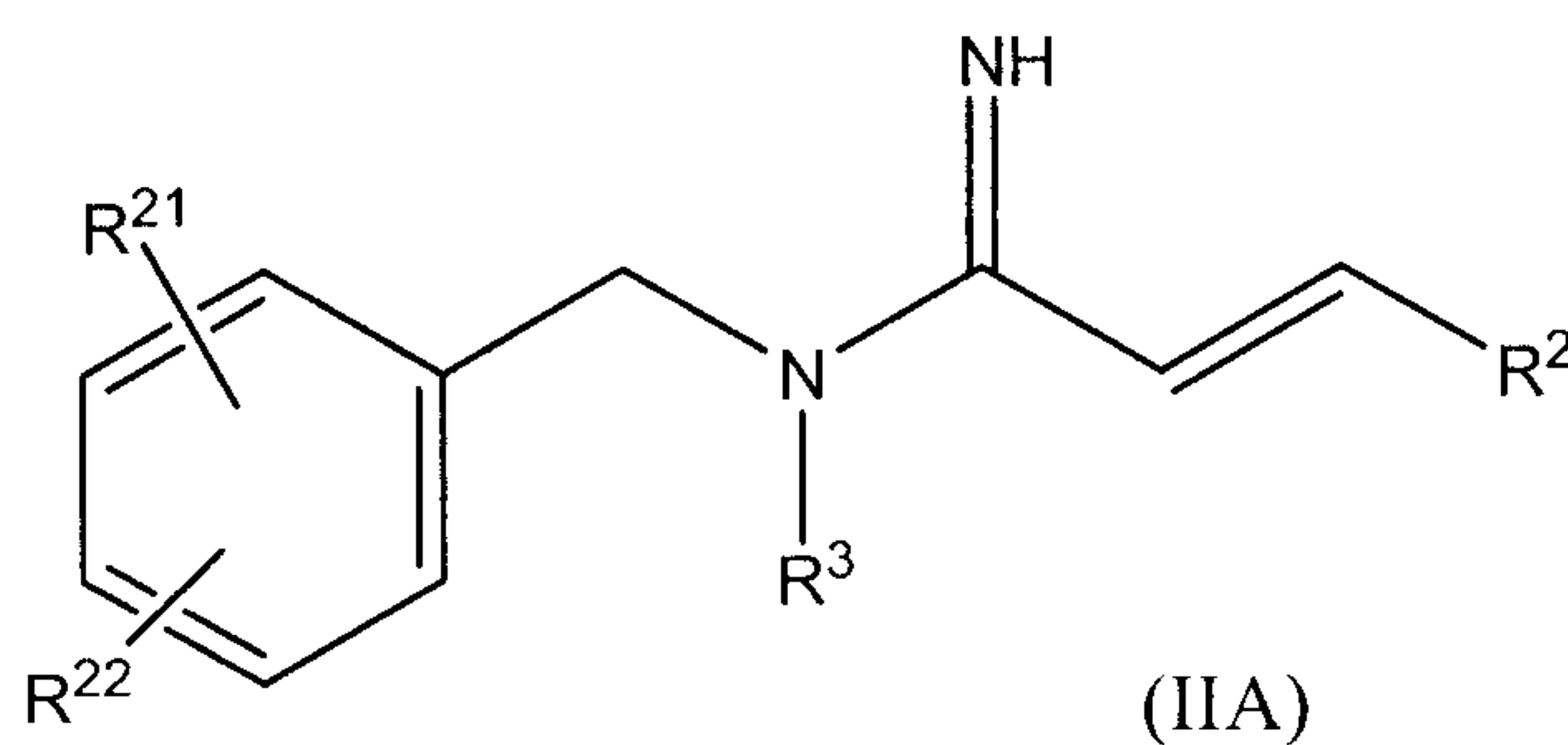
18. The compound according to claim 13, wherein the compound is selected from:

(E)-N-(3-iodobenzyl)cinnamamide;
(E)-N-(benzyl)cinnamamide;
(E)-N-(4-chlorobenzyl)cinnamamide;
(E)-N-(2-chlorobenzyl)cinnamamide;
(E)-N-(3-chlorobenzyl)cinnamamide;
(E)-N-(4-fluorobenzyl)cinnamamide;
(E)-N-(4-trifluoromethylbenzyl)cinnamamide;
(E)-N-(4-methoxybenzyl)cinnamamide;
(E)-N-(4-methylbenzyl)cinnamamide;
(E)-N-(3-methylbenzyl)cinnamamide;
(E)-N-(2-methylbenzyl)cinnamamide;
(E)-N-(3,4-dichlorobenzyl)cinnamamide;
(E)-N-(2-phenylethyl)cinnamamide;
(E)-N-(R)- α -methylbenzylcinnamamide;
(E)-N-(S)- α -methylbenzylcinnamamide;
(E)-N-(3-trifluoromethylbenzyl)cinnamamide;
(E)-N-(3,5-dichlorobenzyl)cinnamamide;
(E)-N-(2-methoxybenzyl)cinnamamide;
(E)-N-(3-methoxybenzyl)cinnamamide;
(E)-N-(2-trifluoromethylbenzyl)cinnamamide;
(E)-N-(2,5-dichlorobenzyl)cinnamamide;
(E)-N-(3-bromobenzyl)cinnamamide;
(E)-N-(4-pyridylmethyl)cinnamamide;
(E)-N-methyl-N-benzylcinnamamide;
(E)-N-(2,3-dichlorobenzyl)cinnamamide;
(E)-N-(cyclohexylmethyl)cinnamamide;
(E)-N-(isobutyl)cinnamamide;
(E)-N-(n-butyl)cinnamamide;
(E)-N-(2-trifluoromethoxybenzyl)cinnamamide;
(E)-N-(3-thienylmethyl)cinnamamide;
(E)-N-(2-bromobenzyl)cinnamamide;
(E)-N-(2-ethoxybenzyl)cinnamamide;

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(E)-N-(2-phenylbenzyl)cinnamamide;
 (E)-N-(2-furylmethyl)cinnamamide;
 (E)-N-(cyclohexyl)cinnamamide;
 (E)-N-(3-methyl-1-butyl)cinnamamide;
 (E)-2-(3-phenyl-1-imino-2-propenyl)-1,2,3,4-tetrahydroisoquinoline;
 (E)-N-(n-pentyl)cinnamamide;
 (E)-N-(3-phenyl-1-propyl)cinnamamide;
 (E)-N-(2-hydroxybenzyl)cinnamamide;
 (E)-N-phenylcinnamamide;
 (E)-N-benzyl-2-chlorocinnamamide;
 (E)-N-benzyl-3-chlorocinnamamide;
 (E)-N-benzyl-4-chlorocinnamamide;
 (E)-N-benzyl-4-fluorocinnamamide;
 (E)-N-benzyl-4-methoxycinnamamide;
 (E)-N-benzyl-3-methoxycinnamamide;
 (E)-N-benzyl-2-methoxycinnamamide;
 (E)-N-benzyl-3,4-difluorocinnamamide;
 (E)-N-benzyl-3-cyclohexanecarboxamide; and
 pharmaceutically acceptable salts and hydrates thereof.

19. A compound represented by formula IIA, or a pharmaceutically acceptable salt or hydrate thereof:



wherein

R^2 represents cyclopentyl, cyclohexyl, phenyl, naphthyl, pyridinyl, furyl, thienyl or pyrrolyl, any of which groups may be optionally substituted;

R^3 represents hydrogen or C_{1-6} alkyl which optionally is substituted;

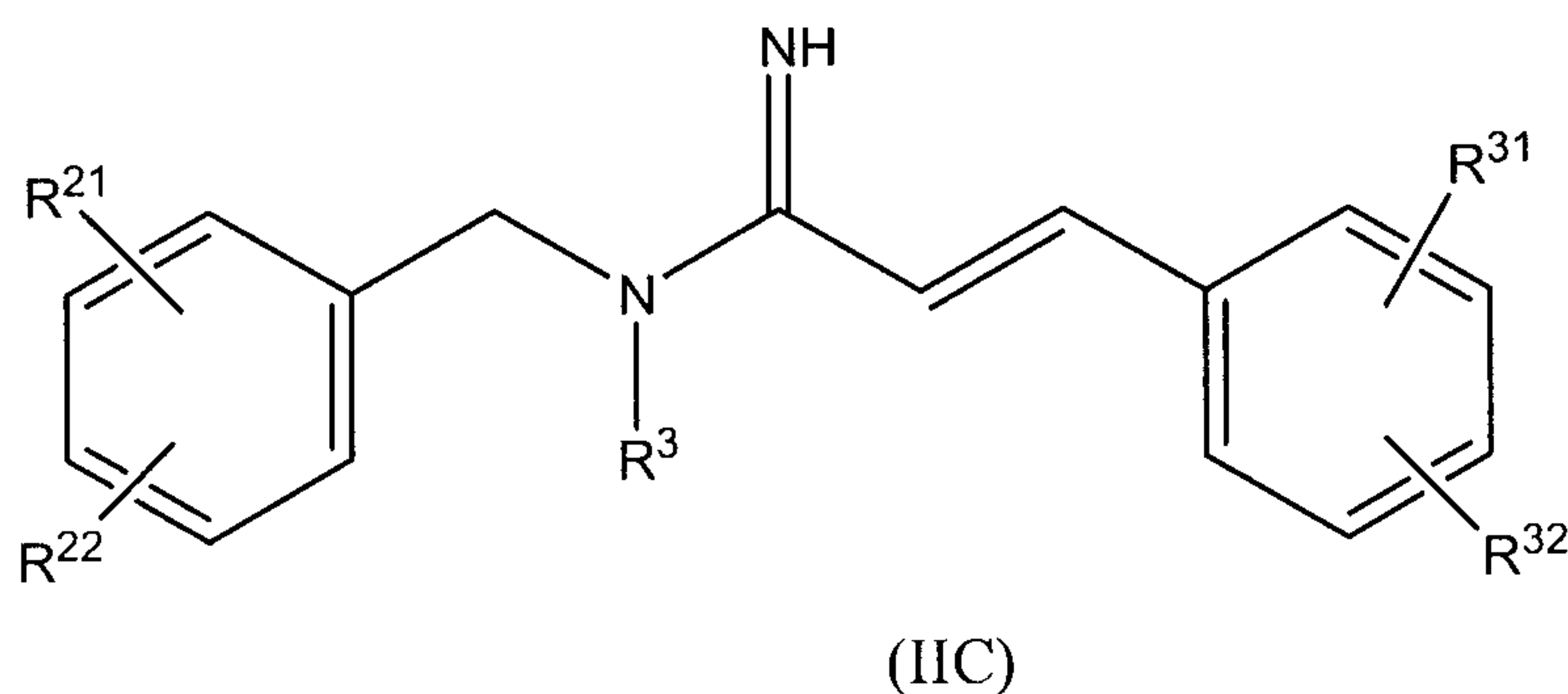
- 50 -

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy; and

R^{22} represents hydrogen or halogen;

wherein the optional substituents on R^2 and R^3 are one or two groups independently selected from C_{1-6} alkyl, aryl, halogen, halo(C_{1-6})alkyl, dihalo(C_{1-6})alkyl, trihalo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, (C_{1-6})alkoxy, halo(C_{1-6})alkoxy, dihalo(C_{1-6})alkoxy and trihalo(C_{1-6})alkoxy.

20. The compound claimed in claim 19, wherein the compound is represented by formula IIC, or a pharmaceutically acceptable salt or hydrate thereof:



wherein

R^3 is as defined in claim 19;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

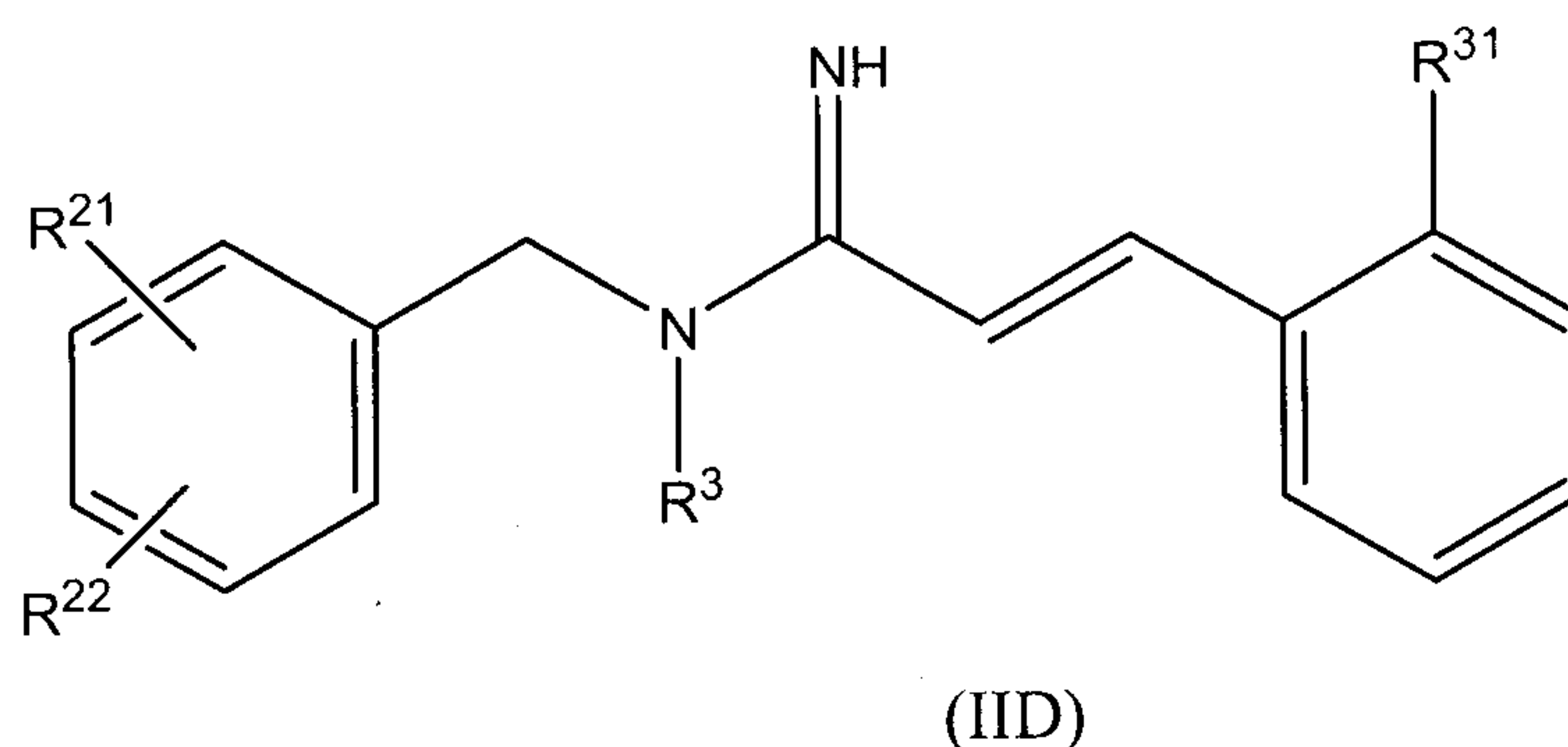
R^{22} represents hydrogen or halogen;

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy ; and

R^{32} represents hydrogen or halogen.

21. The compound as claimed in claim 20, wherein the compound is represented by formula IID, or a pharmaceutically acceptable salt or hydrate thereof:

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wherein R^3 is as defined in claim 20;

R^{21} represents hydrogen, C_{1-6} alkyl, aryl, halogen, trihalo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy or trihalo(C_{1-6} alkyl)alkoxy;

R^{22} represents hydrogen or halogen; and

R^{31} represents hydrogen, C_{1-6} alkyl, halogen or C_{1-6} alkoxy.

22. The compound according to claim 20, selected from:

- (E)-N-(3-iodobenzyl)cinnamamide;
- (E)-N-(benzyl)cinnamamide;
- (E)-N-(4-chlorobenzyl)cinnamamide;
- (E)-N-(2-chlorobenzyl)cinnamamide;
- (E)-N-(3-chlorobenzyl)cinnamamide;
- (E)-N-(4-fluorobenzyl)cinnamamide;
- (E)-N-(4-trifluoromethylbenzyl)cinnamamide;
- (E)-N-(4-methoxybenzyl)cinnamamide;
- (E)-N-(4-methylbenzyl)cinnamamide;
- (E)-N-(3-methylbenzyl)cinnamamide;
- (E)-N-(2-methylbenzyl)cinnamamide;
- (E)-N-(3,4-dichlorobenzyl)cinnamamide;
- (E)-N-(2-phenylethyl)cinnamamide;
- (E)-N-(R)- α -methylbenzylcinnamamide;
- (E)-N-(S)- α -methylbenzylcinnamamide;
- (E)-N-(3-trifluoromethylbenzyl)cinnamamide;
- (E)-N-(3,5-dichlorobenzyl)cinnamamide;
- (E)-N-(2-methoxybenzyl)cinnamamide;
- (E)-N-(3-methoxybenzyl)cinnamamide;
- (E)-N-(2-trifluoromethylbenzyl)cinnamamide;

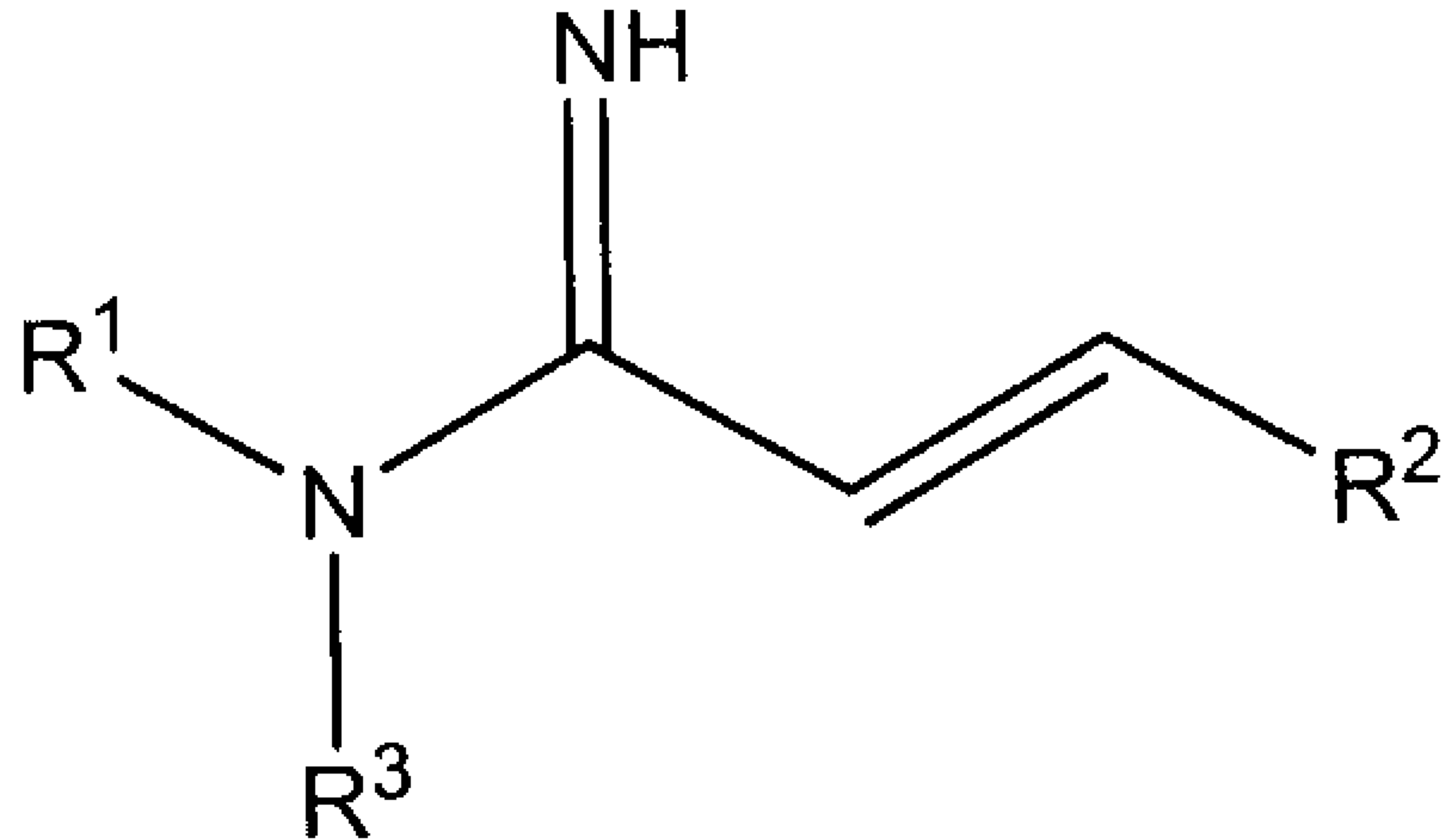
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(E)-N-(2,5-dichlorobenzyl)cinnamamide;
(E)-N-(3-bromobenzyl)cinnamamide;
(E)-N-(4-pyridylmethyl)cinnamamide;
(E)-N-methyl-N-benzylcinnamamide;
(E)-N-(2,3-dichlorobenzyl)cinnamamide;
(E)-N-(cyclohexylmethyl)cinnamamide;
(E)-N-(isobutyl)cinnamamide;
(E)-N-(n-butyl)cinnamamide;
(E)-N-(2-trifluoromethoxybenzyl)cinnamamide;
(E)-N-(3-thienylmethyl)cinnamamide;
(E)-N-(2-bromobenzyl)cinnamamide;
(E)-N-(2-ethoxybenzyl)cinnamamide;
(E)-N-(2-phenylbenzyl)cinnamamide;
(E)-N-(2-furylmethyl)cinnamamide;
(E)-N-(cyclohexyl)cinnamamide;
(E)-N-(3-methyl-1-butyl)cinnamamide;
(E)-2-(3-phenyl-1-imino-2-propenyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-N-(n-pentyl)cinnamamide;
(E)-N-(3-phenyl-1-propyl)cinnamamide;
(E)-N-(2-hydroxybenzyl)cinnamamide;
(E)-N-phenylcinnamamide;
(E)-N-benzyl-2-chlorocinnamamide;
(E)-N-benzyl-3-chlorocinnamamide;
(E)-N-benzyl-4-chlorocinnamamide;
(E)-N-benzyl-4-fluorocinnamamide;
(E)-N-benzyl-4-methoxycinnamamide;
(E)-N-benzyl-3-methoxycinnamamide;
(E)-N-benzyl-2-methoxycinnamamide;
(E)-N-benzyl-3,4-difluorocinnamamide;
(E)-N-benzyl-3-cyclohexanecarboxamide; and
pharmaceutically acceptable salts and hydrates thereof.

23. A pharmaceutical composition comprising the compound of formula IIA as defined in any one of claims 20 to 22, or a pharmaceutically acceptable salt or hydrate or thereof, in combination with a pharmaceutically acceptable carrier.

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24. The compound of formula IIA as defined in any one of claims 20 to 22, or a pharmaceutically acceptable salt or hydrate or thereof, for use in therapy.
25. Use of the compound of formula IIA as defined in any one of claims 20 to 22, or a pharmaceutically acceptable salt or hydrate or thereof, for the manufacture of a medicament for the treatment and/or prevention of neurological and neurodegenerative disorders.



(I)