

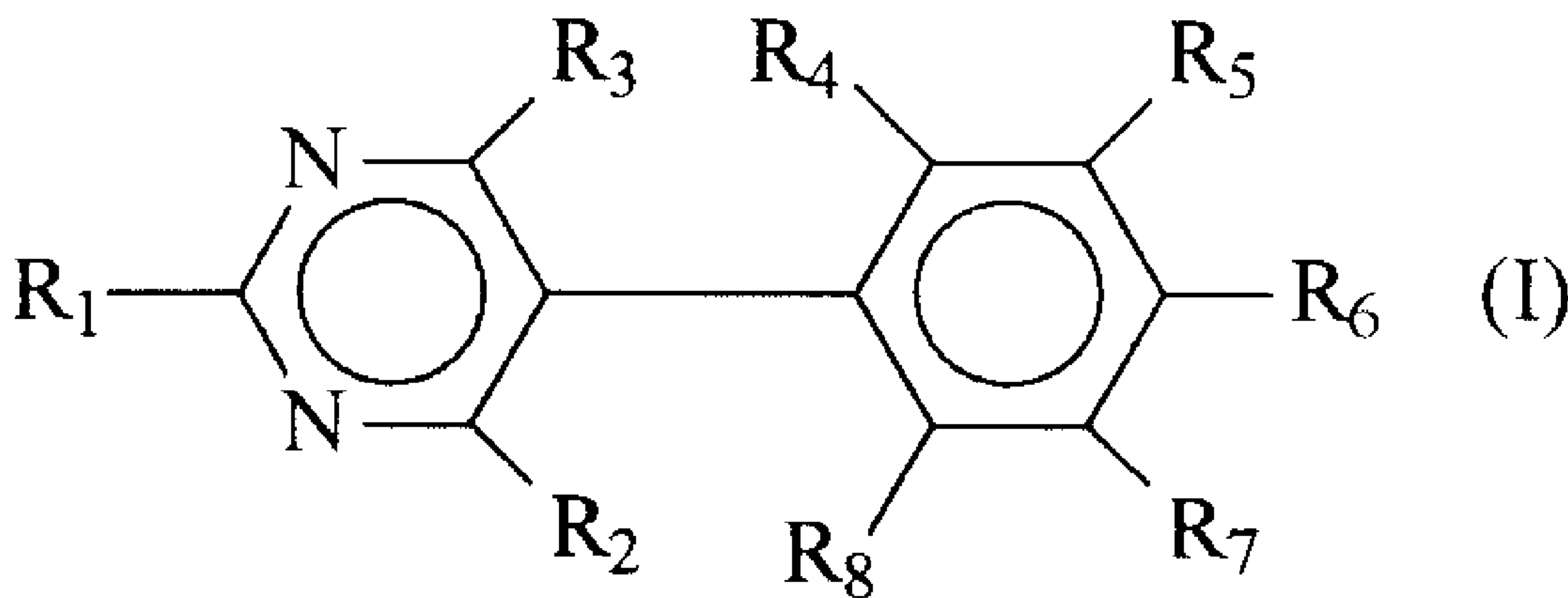


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(54) **COMPOSES PHARMACEUTIQUES AYANT UNE ACTION SUR
LE SNC**

(54) **SUBSTITUTED PHENYLPYRIMIDINES USEFUL IN THE
TREATMENT OF CNS DISORDERS**



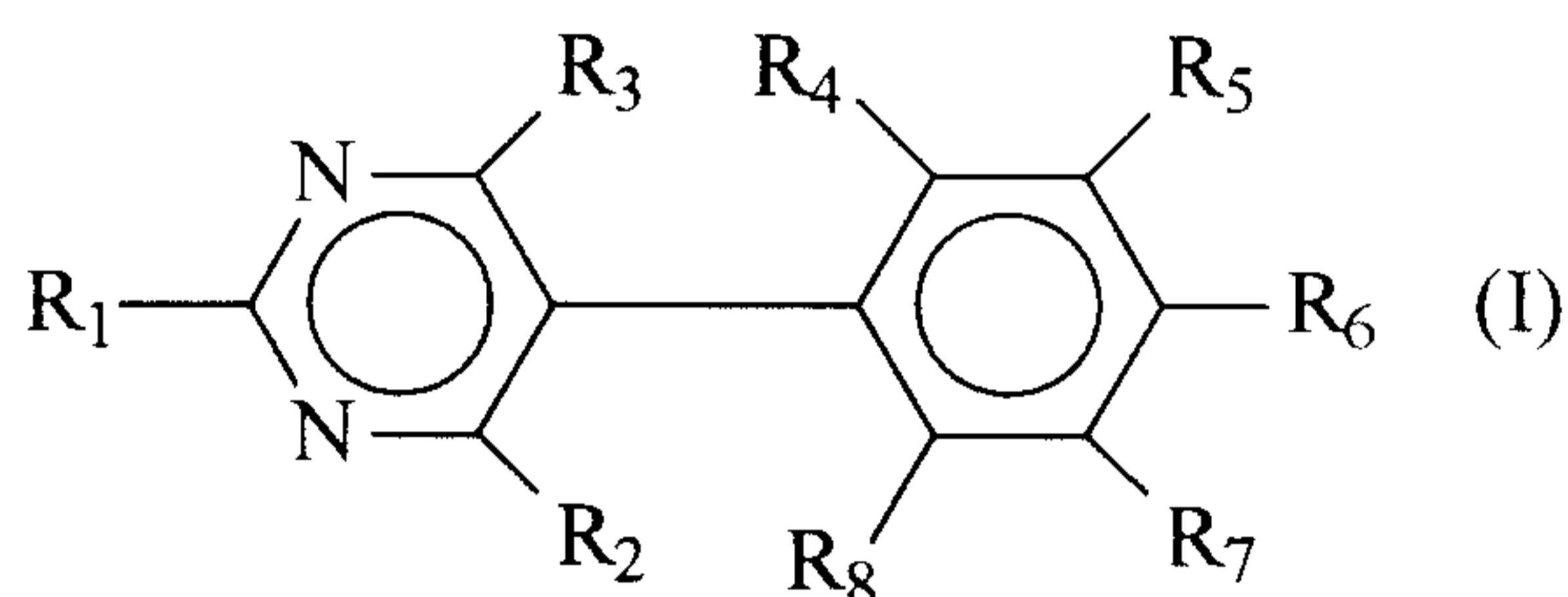
(57) A pyrimidine of formula (I): (see formula I) wherein: R₁ is NH₂, N-(C₁-C₆ alkyl)amino or N,N-di(C₁-C₆ alkyl)amino; R₂ is NH₂; R₃ is trifluoromethyl or CH₂X wherein X is hydroxy, C₁-C₆ alkoxy, phenoxy, benzyloxy or halo; R₄ and R₅ are each halo; and R₆ to R₈ are each hydrogen; or a pharmaceutically acceptable acid addition salt thereof.



ABSTRACT**SUBSTITUTED PHENYLPYRIMIDINES USEFUL IN THE
TREATMENT OF CNS DISORDERS**

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A pyrimidine of formula (I):



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wherein:

R₁ is NH₂, N-(C₁-C₆ alkyl)amino or N,N-di(C₁-C₆ alkyl)amino;R₂ is NH₂;

15

R₃ is trifluoromethyl or CH₂X wherein X is hydroxy, C₁-C₆ alkoxy, phenoxy, benzyloxy or halo;R₄ and R₅ are each halo; andR₆ to R₈ are each hydrogen;

or a pharmaceutically acceptable acid addition salt thereof.

SUBSTITUTED PHENYLPYRIMIDINES USEFUL IN THE
TREATMENT OF CNS DISORDERS

The present invention relates to a class of pyrimidine compounds which are useful in the treatment of central nervous system (CNS) diseases and disorders such as
5 the prevention of cerebral ischaemic damage, to pharmaceutical compositions containing them and to processes of preparing them.

Glutamate is an excitatory amino acid which functions as a neurotransmitter. However, when its
10 extracellular concentration is sufficiently high, glutamate acts as a powerful neurotoxin, capable of killing neurones in the central nervous system, (Rothman & Olney (1986) Prog. Brain. Res., 63, 69). The neurotoxic effect of glutamate has been implicated in a number of central
15 nervous system disorders and disease states including cerebral ischaemic damage, epilepsy and chronic neurodegenerative disorders, such as Alzheimer's disease, motor system disorders, and Huntington's chorea, (Meldrum Clinical Science (1985) 68 113-122). In addition,
20 glutamate has been implicated in other neurological disorders such as manic depression, depression, schizophrenia, high pressure neurological syndrome, chronic pain, trigeminal neuralgia and migraine.

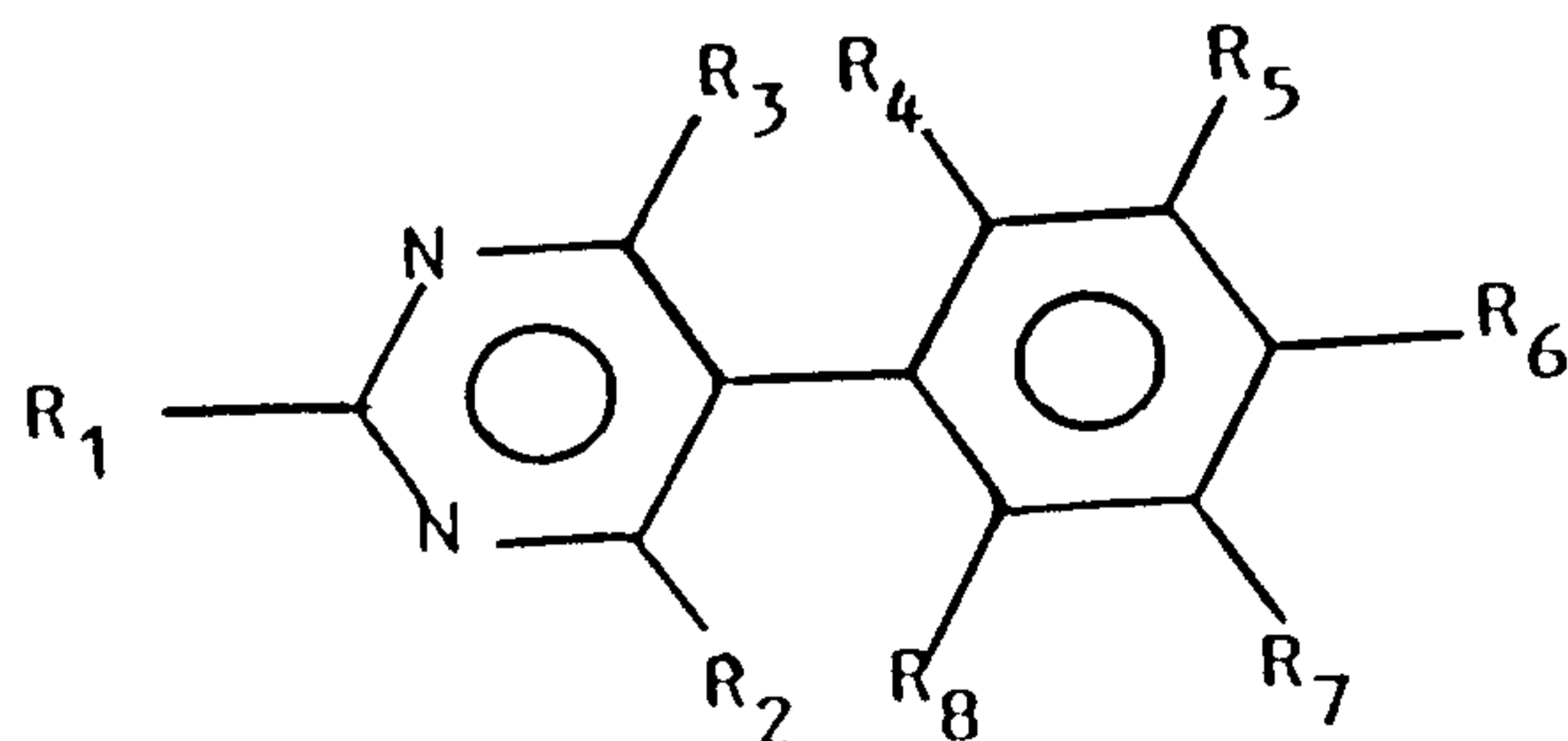
In European Patent application No. 21121 there
25 is disclosed a group of 3,5-diamino-6-(substituted phenyl)-1,2,4-triazines which are active in the treatment of CNS disorders, for example in the treatment of epilepsy. One

compound described in that application, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine), has been shown to inhibit the release of the excitatory amino acids, glutamate and aspartate, (Leach et al *Epilepsia* 27, 490-497
5 1986, A.A. Miller et al *New anticonvulsant drugs*. Ed. Meldrum and Porter 165-177, 1987).

Certain phenylpyrimidines are known in the art as having antimalarial activity. See for example *Brit. J. Pharmacol.* 6, 185-200 (1951; *JACS*, 73, 3763-70, (1951).
10 Other phenylpyrimidines are known from *Chem. Biol. Pteridines*, 463-468, (1982) and *Pharmacotherap.* Budesinsky, p. 129-141, (1963), ed. Oldrich Hanc.

The present inventors have found that a series of substituted pyrimidine compounds, as defined in formula
15 I, are potent inhibitors of glutamate release; these compounds are useful in the treatment of the above mentioned disorders and disease states of the central nervous system in which glutamate release is implicated. The pyrimidine compounds of formula I are also inhibitors
20 of aspartate release.

Thus in a first aspect of the present invention there is provided a pyrimidine of formula I:



25

I

wherein:

R₁ is selected from the group consisting of NH₂, N-(C₁-C₆ alkyl)amino and N,N-di(C₁-C₆ alkyl)amino;

R₂ is NH₂;

5 R₃ is trifluoromethyl or CH₂X wherein X is selected from the group consisting of hydroxy, C₁-C₆ alkoxy, phenoxy, benzyloxy and halo;

R₄ and R₅ are each halo; and

R₆ to R₈ are each hydrogen;

10 and pharmaceutically acceptable acid addition salts thereof.

Certain compounds of formula I are chiral, and it will be appreciated that in these instances, formula I encompasses both the racemic mixture and the individual
15 enantiomers of such compounds.

In the present invention,

R₁ is preferably amino,

R₃ is preferably methoxymethyl, trifluoromethyl, benzyloxymethyl or phenoxyethyl. Alternatively, R₃ may be
20 fluoromethyl.

R₄ is preferably chloro and R₅ is preferably chloro.

Preferably the alkyl moieties contain from 1 to 4 carbon atoms.

In formula I, advantageously R₃ trifluoromethyl or
25 methoxymethyl.

The compounds of formula I, whilst being potent inhibitors of glutamate release show only weak (i.e. having

an IC_{50} of $>20\mu m$) or insignificant inhibitory effects on the enzyme dihydrofolate reductase.

Compounds of formula I may be used in the treatment or prophylaxis of acute and chronic disorders of the mammalian central nervous system in which glutamate release is implicated. The acute condition comprises cerebral ischaemia which may arise from a variety of causes including stroke, cardiac arrest, bypass surgery, neonatal anoxia and hypoglycaemia; and also physical injury or trauma of the spinal cord or brain. Chronic neurodegenerative disorders which may be treated include Alzheimer's disease, Huntingdon's chorea, olivopontocerebellar atrophy and motor system disorders. Other neurological conditions which may be treated with a compound of formula I include depression, manic depression, schizophrenia, chronic pain, epilepsy, trigeminal neuralgia and migraine.

Treatment or prevention of a CNS disorder or disease of a mammal, including man, in which glutamate release is implicated may therefore be achieved by administration to the mammal of a non-toxic effective amount of a compound of formula I or a pharmaceutically acceptable acid addition salt thereof.

In particular, a mammal predisposed to or having neurotoxic extracellular glutamate levels of the central nervous system may be treated by administration to the mammal of a non-toxic effective amount of a compound of formula I or a pharmaceutically acceptable acid addition salt thereof.

Preferred novel compounds of the present invention include the following, the numbers referring to the Examples hereinafter appearing:-

10 Example No.

1. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-trifluoromethylpyrimidine

2. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-methoxymethylpyrimidine

15 3.3 2,4-Diamino-5-(2,3-dichlorophenyl)-6-hydroxymethylpyrimidine

3.4 2,4-Diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine

20 4. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-phenoxy-methylpyrimidine

or a pharmaceutically acceptable acid addition salt thereof.

Suitable pharmaceutically acceptable acid addition salts of the compounds of formula I include those formed with both organic or inorganic acids. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, *p*-toluenesulphonic, benzenesulphonic and isethionic acids. These salts can be

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made by reacting the compound as the free base with the appropriate acid.

While it is possible for the compounds of formula I to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. The formulations of the present invention comprise a novel compound of formula I, as above defined, or a pharmaceutically acceptable acid addition salt thereof together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula I or a pharmaceutically acceptable acid addition salt thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with

liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the Formula I which is effective at such dosage or as a multiple of the same, for instance, units containing 5mg to 500mg, usually around 10mg to 250mg.

The compounds of the Formula I are preferably used to treat CNS disorders or diseases by oral administration or injection (intraparenteral or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Thus for example when treating a patient with epilepsy the dose range is likely to be significantly lower than when treating a patient after stroke to

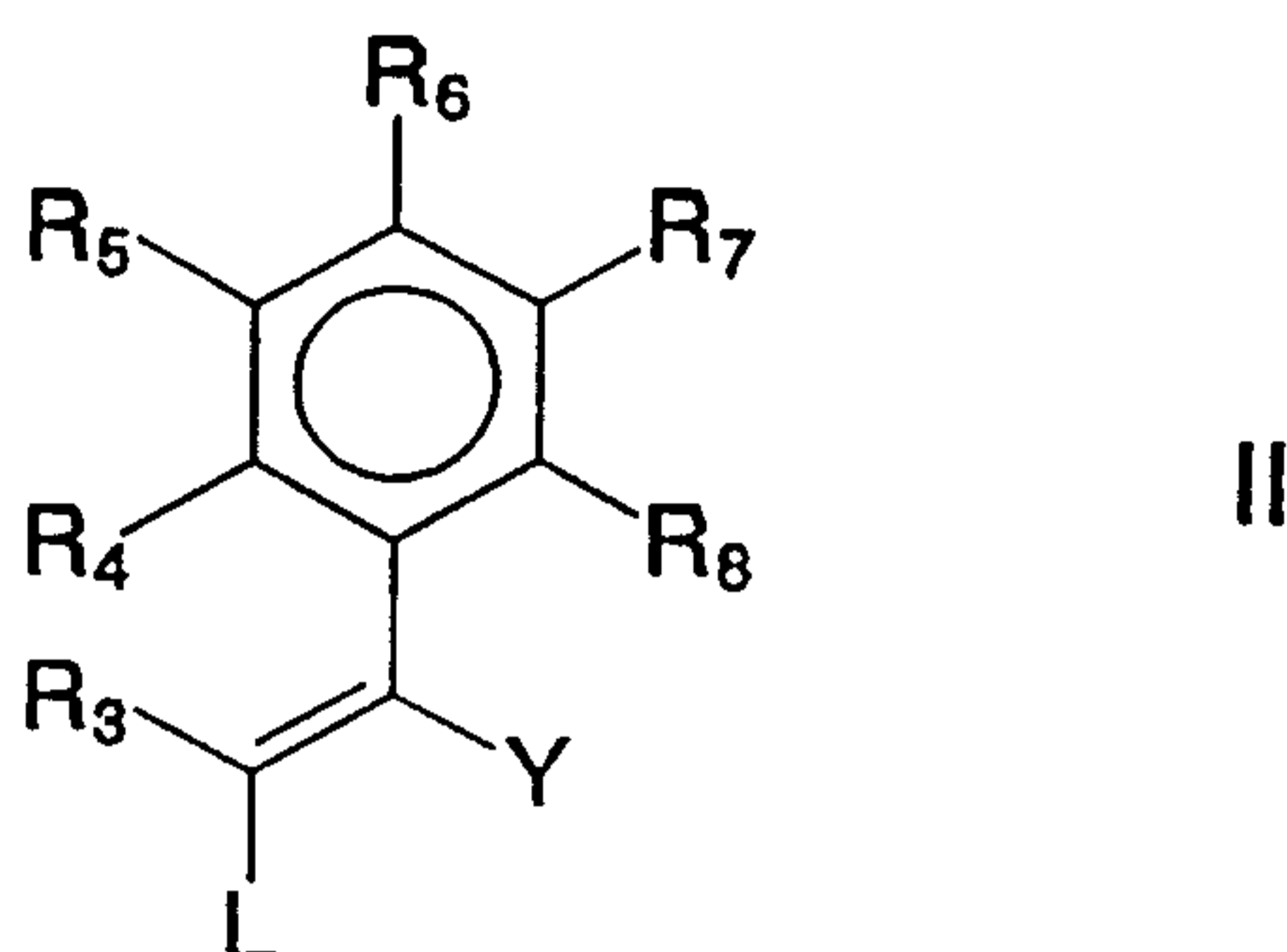
alleviate cerebral ischaemic damage. Also the route of administration is likely to vary depending on the condition and its severity.

The compounds of the formula I may be administered orally or via injection at a dose of from 0.1 to 30 mg/kg per day. The dose range for adult humans is generally from 8 to 2,400 mg/day and preferably 35 to 1,050 mg/day. As certain compounds of the formula I are long acting, it may be advantageous to administer an initial dose of 70 to 2,400 mg on the first day and then a lower dose of 20 to 1,200 mg on subsequent days.

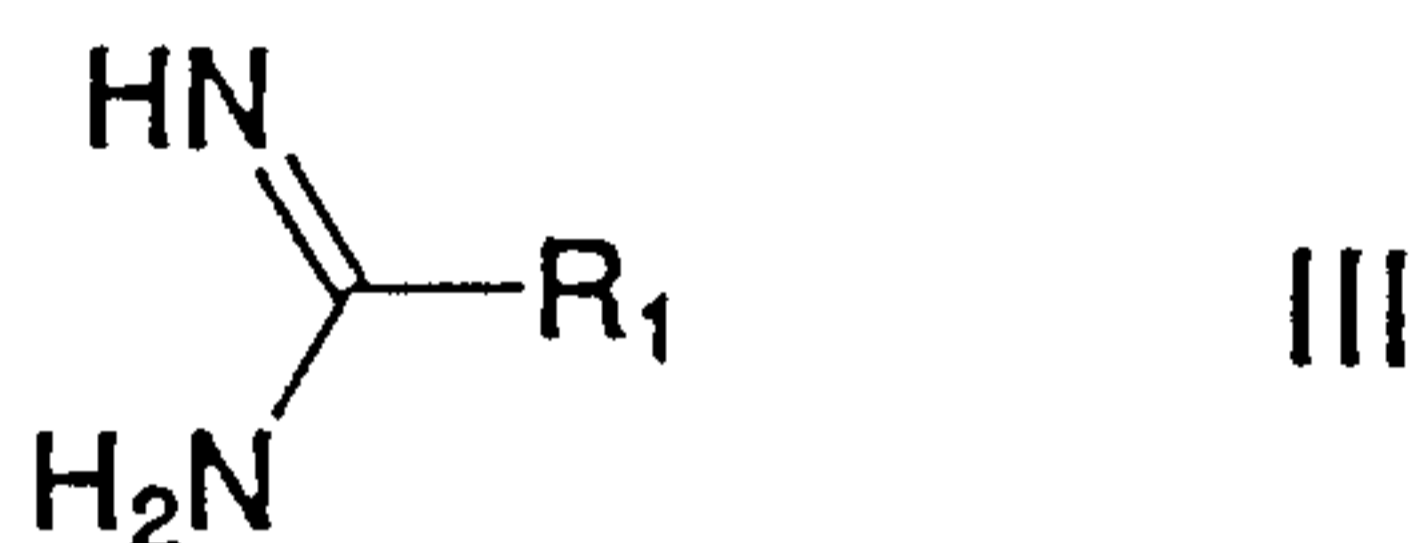
Long acting compounds are advantageous in the clinic because they are easier to manage. In the chronic situation, they may be administered without infusion and there is the minimum of direct, medical intervention; also in acute conditions, patient compliance is encouraged by minimising daily dosing. Conversely, short acting compounds permit the clinician to control the pharmacological effect of the compound with great precision, since such compounds will be cleared from the central nervous system rapidly.

Compounds of the present invention may be made in any manner known to make analogous compounds known in the art (eg. JACS vol 73 (1951) 3763-70).

A pyrimidine of formula I or a pharmaceutically acceptable acid addition salt thereof, may be prepared by a process which comprises reacting a compound of formula II:



wherein R_3 to R_8 are as defined above, L is a leaving group and Y is cyano, with a compound of formula III:



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wherein R_1 is as defined above; isolating the pyrimidine of formula I thus obtained as the free base or as a pharmaceutically acceptable acid addition salt thereof; and optionally converting the said base into a pharmaceutically acceptable acid addition salt thereof or into another pyrimidine of formula I or a pharmaceutically acceptable acid addition salt thereof.

Where in the product of the above process R_3 is a group CH_2OR where R is alkyl, this product may be converted to CH_2X by reaction with HX ($X = \text{halo}$) in, for example acetic acid. This may be further converted to fluoromethyl by treatment with for example cesium fluoride (CsF). Alternatively, the group CH_2OR can be dealkylated to give the corresponding alcohol, for example with Me_3SiI , and this further converted to fluoromethyl with

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diethylaminosulphur trifluoride (DAST). For example:

(a) a compound of the formula II, wherein R_3 is CH_2OR in which R is C_1-C_6 alkyl, is reacted with a compound of the formula III to give a pyrimidine of the formula I
5 wherein R_3 is a said CH_2OR group;

(b) the thus obtained pyrimidine is isolated and dealkylated to give another pyrimidine of the formula I wherein R_3 is CH_2OH ; and

(c) the thus obtained pyrimidine is reacted with
10 diethylaminosulphur trifluoride to give a pyrimidine of the formula I wherein R_3 is fluoromethyl.

It will be appreciated that other interconversions may be effected as required by those skilled in the art using standard methodologies.

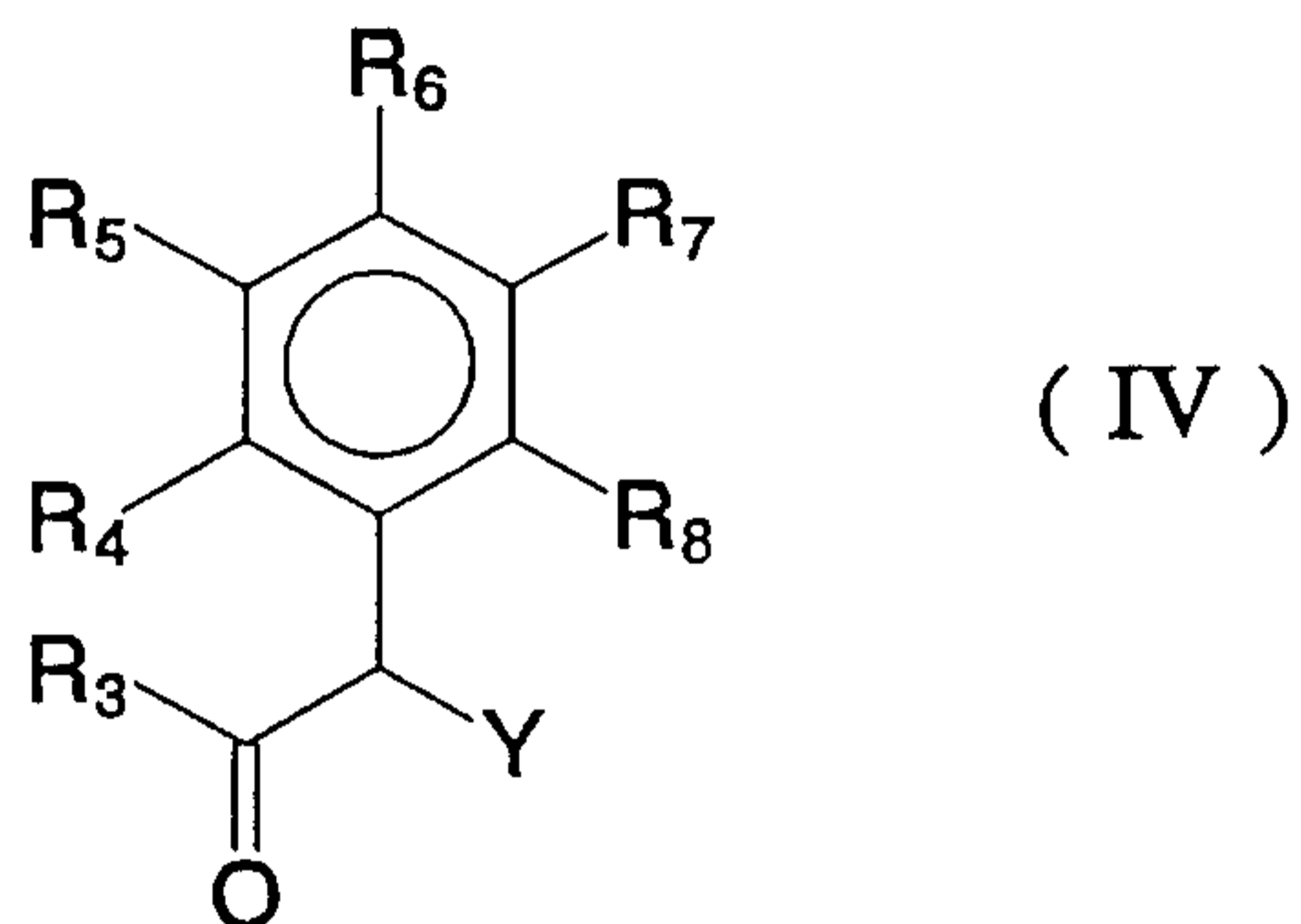
15 Examples of suitable leaving groups (L) include C_{1-4} alkoxy, halo, anilino, morpholino, C_{1-4} alkylamino, benzylamino or alkylthio.

Preferably the reaction of the compounds of formulae II and III is carried out in a non-aqueous solvent, for
20 example an alkanol, eg. ethanol at elevated temperatures (eg. between 50 to 110°C) in a base, preferably an alkanoxide, preferably under reflux using sodium ethoxide as the base.

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Compounds of formula II may be made by methods known in the art (JACS, 1951, 73, 3763-3770) for example by the reaction of a compound of formula IV:

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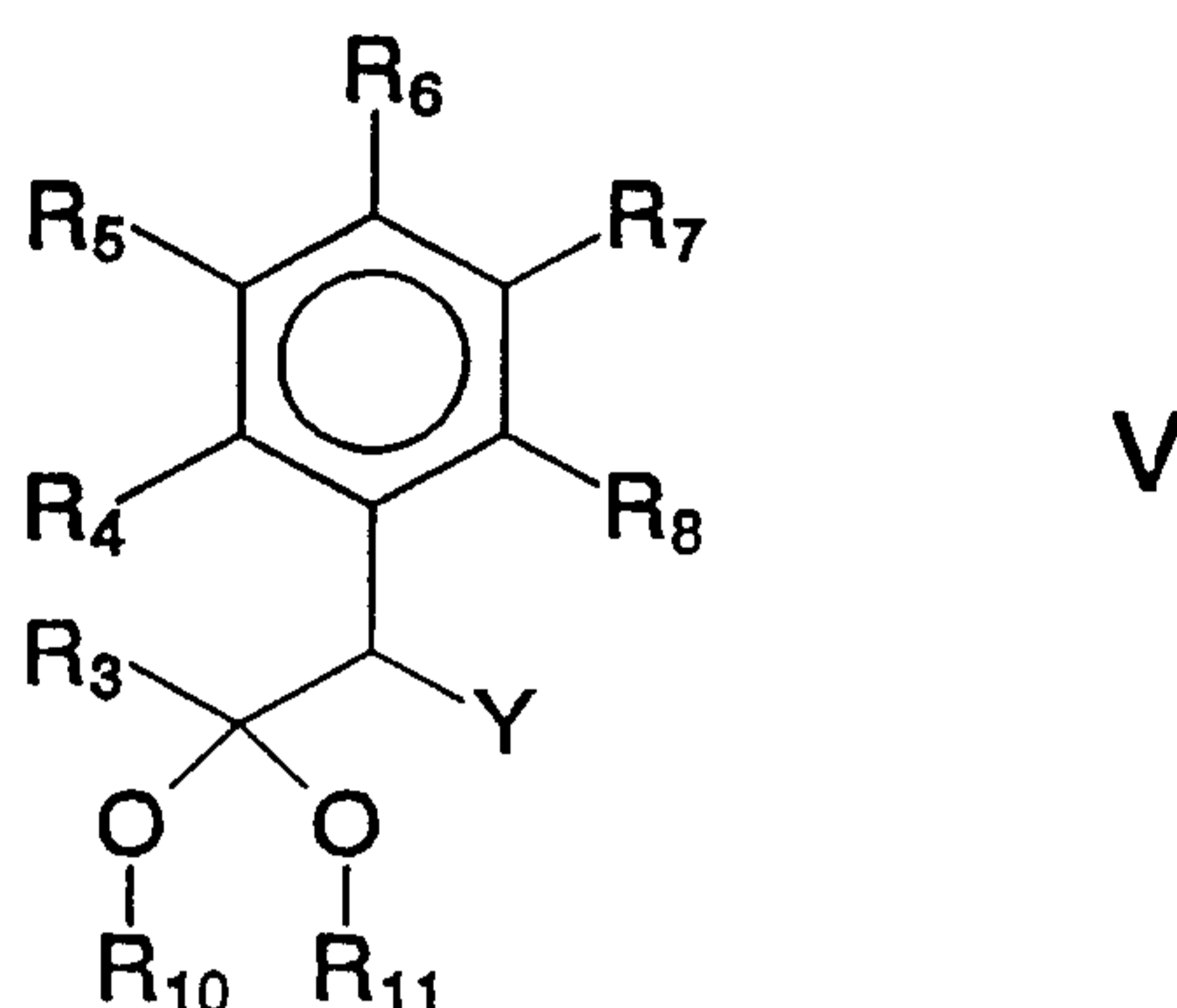


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wherein Y is cyano with diazomethane or with alkylorthoesters (JACS 1952, 74, 1310-1313), or by condensation with an amine. The compounds of formula IV can be made by methods known in the art (JACS, 1951, 73, 3763-70).

A pyrimidine of formula I may alternatively be prepared by a process which comprises reacting a compound of formula V:

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10 wherein R_3 to R_8 and Y are as defined above and R_{10} and R_{11} are both alkyl or together form a group $-(C(R)_2)_n-$ wherein R is hydrogen or alkyl and n is an integer of 2 to 4, with a compound of formula III as defined above.

15 Most preferably R_1 is amino. Preferably the reaction is carried out in a non-aqueous solvent, eg. ethanol, under reflux using sodium ethoxide as the base.

In the Examples of the invention set forth below, the chemical and other abbreviations used are standard in the art and have these meanings:-

	DMF	:	dimethylformamide
20	Et ₂ O	:	diethyl ether
	NaOEt	:	sodium ethoxide
	EtOH	:	ethanol
	AcOH	:	acetic acid
	MeOH	:	methanol
25	DMSO	:	dimethylsulphoxide
	DME	:	dimethoxyethane
	Et ₃ N	:	triethylamine

Example 1Synthesis of 2,4-Diamino-5-(2,3-dichlorophenyl)-6-trifluoromethyl pyrimidine1. Preparation of 2,3-dichlorobenzyl alcohol

To a solution of 2,3-dichlorobenzaldehyde (Aldrich, 50gms) in alcohol (800mL) at room temperature was added NaBH_4 (8.54gms) and the resulting mixture stirred for 1.5 hours. The reaction was quenched with water and the solvent evaporated in vacuo before partitioning the residue between CHCl_3 and saturated NaHCO_3 solution. The organic phase was washed with brine, dried over MgSO_4 , filtered and the solvent evaporated in vacuo to leave a white solid, 48.38gms, mp. 87-87.5°C.

2. Preparation of 2,3-dichlorobenzyl bromide

To a solution of the alcohol in benzene (500ml) under N_2 was added PBr_3 (167.8gms), and the mixture stirred at $55-60^\circ C$ for 3.5 hours. After cooling, the mixture was poured onto crushed ice (2L) and the benzene layer separated. The aqueous phase was washed with benzene (x3) and the combined benzene extracts washed with saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, filtered and the solvent evaporated to leave a brownish liquid which solidified on standing. 37.53gms, mp. $31-32^\circ C$.

3. Preparation of 2,3-dichlorophenylacetonitrile

The bromide was suspended in DMSO (155ml)/ water(105ml) at $0^\circ C$ and KCN (20.24gms) added in portions. After stirring at $30-35^\circ C$ for 2 hours, the suspension was diluted with water and extracted with Et_2O . The combined ether extracts were washed with water, dried over $MgSO_4$, filtered and the solvent evaporated in vacuo to leave a white solid, 27.52gms, mp. $64-67^\circ C$.

4. Preparation of 2-(2,3-dichlorophenyl)-4,4,4-trifluoro-3-oxo-butynitrile

To a solution of $NaOEt$ (from 1.48gms Na) in $EtOH$ (25ml) at room temperature under N_2 was added the nitrile (10.0gms) followed by ethyl trifluoroacetate (9.3gms) and the mixture stirred at reflux for 5 hours. After cooling, the solvent was removed in vacuo and the residue dissolved in water. The aqueous phase was washed with Et_2O (discarded), acidified with H_2SO_4 and extracted with Et_2O . The combined Et_2O extracts were washed with water, dried over $MgSO_4$, filtered and the solvent evaporated in vacuo to leave an oil. This was triturated with petroleum ether, and the solid filtered off and dried. 9.56gms, mp. $74-75^\circ C$.

5. Preparation of 2-(2,3-dichlorophenyl)-4,4,4-trifluoro-3-methoxybut-2-enonitrile
To a solution of the trifluoromethyl ketone in Et₂O (90ml) at room temperature was added diazomethane (from 19.35gms Diazald) in Et₂O (180ml), and the resulting mixture left to stand at room temperature overnight. Excess diazomethane was then removed in vacuo into AcOH, and the residue was dissolved in Et₂O, dried over MgSO₄, filtered and the solvent evaporated in vacuo to leave a brownish solid, 6.44gms.
6. Preparation of 2,4-Diamino-5-(2,3-dichlorophenyl)-6-trifluoromethylpyrimidine
To a solution of the above enol ether in ethanol (37ml) was added guanidine hydrochloride (1.92gms) followed by a solution of NaOEt (from 540mgs of Na) in EtOH (90ml), and the resulting mixture stirred at reflux for 3 hours. After cooling, the suspension was filtered, and the filtrate evaporated to dryness in vacuo. Chromatography on silica gel eluting with CHCl₃ to 2% MeOH-CHCl₃ gave the desired product which was triturated with Et₂O and dried in vacuo, 673mg, m.pt. 218-9°C.
7. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-trifluoromethylpyrimidine methanesulphonate
To a suspension of the free base (100mg) in ethanol was added methanesulphonic acid (30mg) and the resulting clear solution stirred at room temperature for 2 hours. The solution was evaporated to dryness, and the resulting solid triturated with ether, filtered, and dried in vacuo, 107mg, m.pt. 253-256°C.
8. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-trifluoromethylpyrimidine hydrochloride
To a solution of the free base (150mg) in methanol was added ethereal hydrogen chloride. After stirring, the solvent was evaporated to dryness and the resulting solid triturated with ether, filtered, and dried in vacuo, 160mg, m.pt. 233-236°C.

Example 2Synthesis of 2,4-Diamino-5-(2,3-dichlorophenyl)-6-methoxymethyl pyrimidine1. Preparation of 2-(2,3-dichlorophenyl)-4-methoxy-3-oxo-butyronitrile

To a stirred refluxing solution of NaOEt (from 1.38gms Na) in EtOH (25ml) was added a mixture of ethyl methoxyacetate (8.85gms) and 2,3-dichlorophenylacetonitrile (Example 1.3) (9.3g) dissolved in DME (20ml) during 5 minutes. After 5 hours a precipitate had appeared (sodium salt of product). The mixture was cooled and filtered, the filtrate evaporated to dryness in vacuo and the residue partitioned between ether and water (the ether phase was discarded). The aqueous residue was acidified with 2N H₂SO₄ and extracted with ether (2x). The combined Et₂O extracts were washed with water, dried over MgSO₄, filtered and evaporated in vacuo to give a yellow solid (a). The sodium salt (above) was dissolved in water and the solution extracted with ether and discarded. The aqueous solution was acidified with 2N H₂SO₄ and extracted with ether. The ether extract was washed with water, dried over MgSO₄, filtered and evaporated in vacuo to give a white solid (b).

The above products (a) and (b) were combined to give a yield of 10.4gms which was used without further purification. Single spot by TLC (19:1 CH₂Cl₂: MeOH) Rf 0.35.

2. Preparation of 2-(2,3-dichlorophenyl)-3,4-dimethoxybut-2-enonitrile

To a stirred solution of the above nitrile (9.4gms) in ether was added in portions diazomethane (0.4 - 0.45M) in ether. Initially vigorous frothing occurred and after further addition no immediate reaction was produced. The mixture was left stirring at room temperature for 3 hours and evaporated in vacuo, into AcOH to give the enol ether.

3. Preparation of 2,4-Diamino-5-(2,3-dichlorophenyl)-6-methoxymethylpyrimidine

To a solution of NaOEt (from 0.92gms Na) in EtOH (40ml) was added guanidine hydrochloride (3.44gms). A solution of the enol ether (above) in EtOH (30ml) was added and the mixture refluxed for ca. 3 hours. After cooling, the solvent was evaporated off in vacuo and the residue treated with 5N NaOH (ca. 50ml). The red solid was filtered off, dissolved in AcOH (ca. 20ml), diluted with water (40ml), treated with charcoal, and filtered. The filtrate (yellow solution) was made alkaline with 2N NaOH, and the white precipitate filtered off, dried and recrystallised from EtOH, 4.39gms, mp. 237-240°C.

Example 3

Preparation of 2,4-Diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine

1. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-(diethoxymethyl)pyrimidine

To a stirred refluxing solution of NaOEt (from 1.38g sodium) in ethanol (25ml) was added over 5 minutes a mixture of ethyl diethoxyacetate (13.21g; 75mmol) and (Example 1.3) 2,3-dichlorophenylacetonitrile (9.3g; 50mmol) in dry dimethoxyethane (20ml). After 4 hours cooled and evaporated in vacuo. The residue was partitioned between water (100ml) and ether (100ml), the ether phase discarded and the aqueous residue acidified with

1N H_2SO_4 . Extraction with CH_2Cl_2 gave the acyl acetonitrile (13.47g), which was used without further purification.

To a stirred solution of the above acyl acetonitrile in ether (100ml), cooled on ice was added in portions a solution of diazomethane (ca. 3g) in ether. After 2 hours the solution was evaporated in vacuo to give the desired enol ether as an oil, which was used without further purification.

To a solution of NaOEt (from 1.4g sodium) in ethanol (50ml) was added guanidine hydrochloride (4.8g; 50mmol). A solution of the above enol ether in ethanol (20ml) was added and the mixture refluxed for 4 hours cooled, and concentrated in vacuo to ca. 30ml and diluted with water to give a dark purple solid which was filtered, dissolved in CH_2Cl_2 , washed with water, dried over $MgSO_4$ and evaporated in vacuo. The residue was triturated with ethanol (50ml) and filtered to give the desired product (8.4g) which was used without further purification. (mp. 214-217°C).

2. 2,4-Diamino-5-(2,3-dichlorophenyl)pyrimidine-6-carboxaldehyde

A mixture of the above acetal (7g) and 0.4M HCl (150ml) was refluxed with stirring for 1 hour, cooled on ice and neutralised with 2M NaOH. The mixture was filtered, washed with water and dried in air to give the desired product (6.2g), which was used without further purification.

3. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-hydroxymethylpyrimidine

To a stirred solution of the above aldehyde (2.8g; 10mmol) in a mixture of dimethoxyethane (15ml) and ethanol (15ml) was added in portions sodium borohydride (110mg; 3mmol). After 30 minutes the solution was treated with water (50ml) and a few drops of acetic acid added to destroy excess borohydride. Extracted with dichloromethane (2 x 50ml), washed with water and the extract was then dried over $MgSO_4$. Evaporation of the solvent in vacuo gave a pink solid, which was triturated with ether, filtered and dried

(1.6g). Recrystallisation from methanol (50ml) gave the desired product as fine colourless crystals. 0.65g, m.p. 173-6°C.

4. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine

To a stirred suspension of 2,4-diamino-5-(2,3-dichlorophenyl)-6-hydroxymethylpyrimidine (185mg; 1mmol) in dry dichloromethane (25ml), under nitrogen at -70°C, was added dropwise diethylaminosulphur trifluoride (263µl; 2mmol). The mixture was allowed to warm to 0°C and kept at this temperature for 4 hours. After cooling to -70°C the mixture was quenched with aqueous sodium bicarbonate, extracted with dichloromethane (2 x 50ml), washed with saturated brine and dried (MgSO₄). Concentration gave a colourless gum (0.2g). Chromatography on silica gel, eluting with 0.01:1:19 Et₃N:MeOH:CH₂Cl₂ gave the desired product which was triturated with CCl₄ and dried in vacuo. 111mg, mp. 224-6°C.

Example 4

2,4-Diamino-5-(2,3-dichlorophenyl)-6-phenoxyethylpyrimidine

To a stirred solution of NaOEt (from 1.38g sodium), in ethanol (70ml) at reflux, was added over 10 minutes a mixture of 2,3-dichlorophenyl-acetonitrile (9.3g) and ethyl phenoxyacetate (13.5g) in dry dimethoxyethane (50ml). After stirring at reflux for 3 hours the mixture was cooled, filtered and the solvents evaporated in vacuo. The residue was dissolved in water, washed with ether (discarded), acidified with 2N hydrochloric acid and extracted with dichloromethane. The combined extracts were washed with brine, dried (MgSO₄) and evaporated in vacuo to leave a tan coloured solid (8g), which was used without further purification.

To a suspension of the crude acyl acetonitrile (8g) in ether (150ml) was added in portions an excess of a solution of diazomethane in ether. After stirring for 1 hour at room temperature the solution was

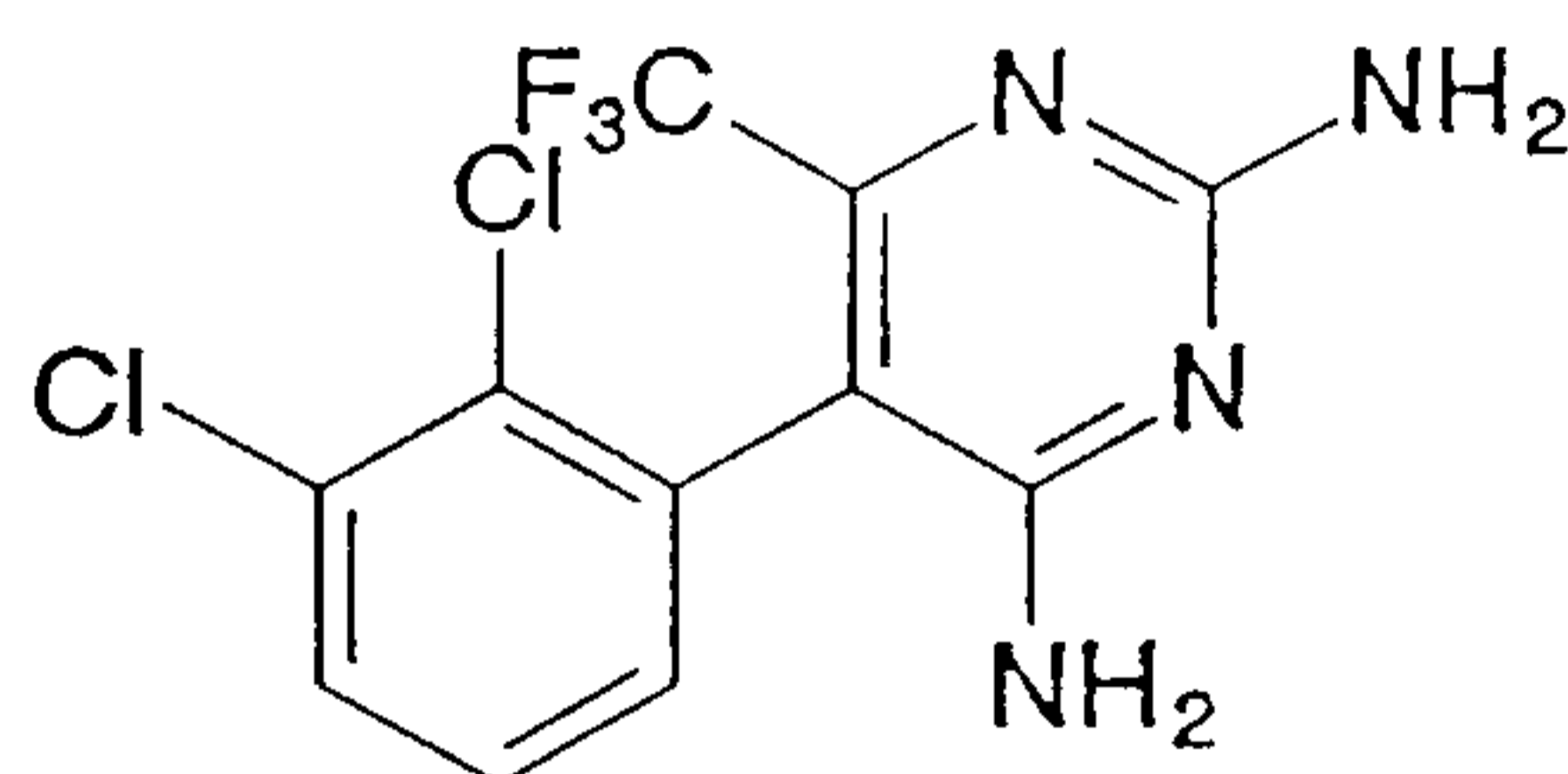
concentrated in vacuo to give the enol ether, which was used without further purification.

To a solution of sodium ethoxide (from 0.63g sodium) in ethanol (25ml) at room temperature was added guanidine hydrochloride (2.39g). After 15 minutes a solution of the above enol ether in ethanol (25ml) was added and the mixture stirred at reflux for 4 hours. After cooling the solvent was evaporated in vacuo. The residue was suspended in 2N NaOH (75ml), filtered, washed with water, dried in air and recrystallised from ethanol to give the desired product as a colourless solid. 3.82g, mp. 211-213°C.

Preferred among the compounds of formula I are the pyrimidines of the foregoing Examples 1 and 2 together with pharmaceutically acceptable acid addition salts thereof. These bases have the following respective two-dimensional structures:

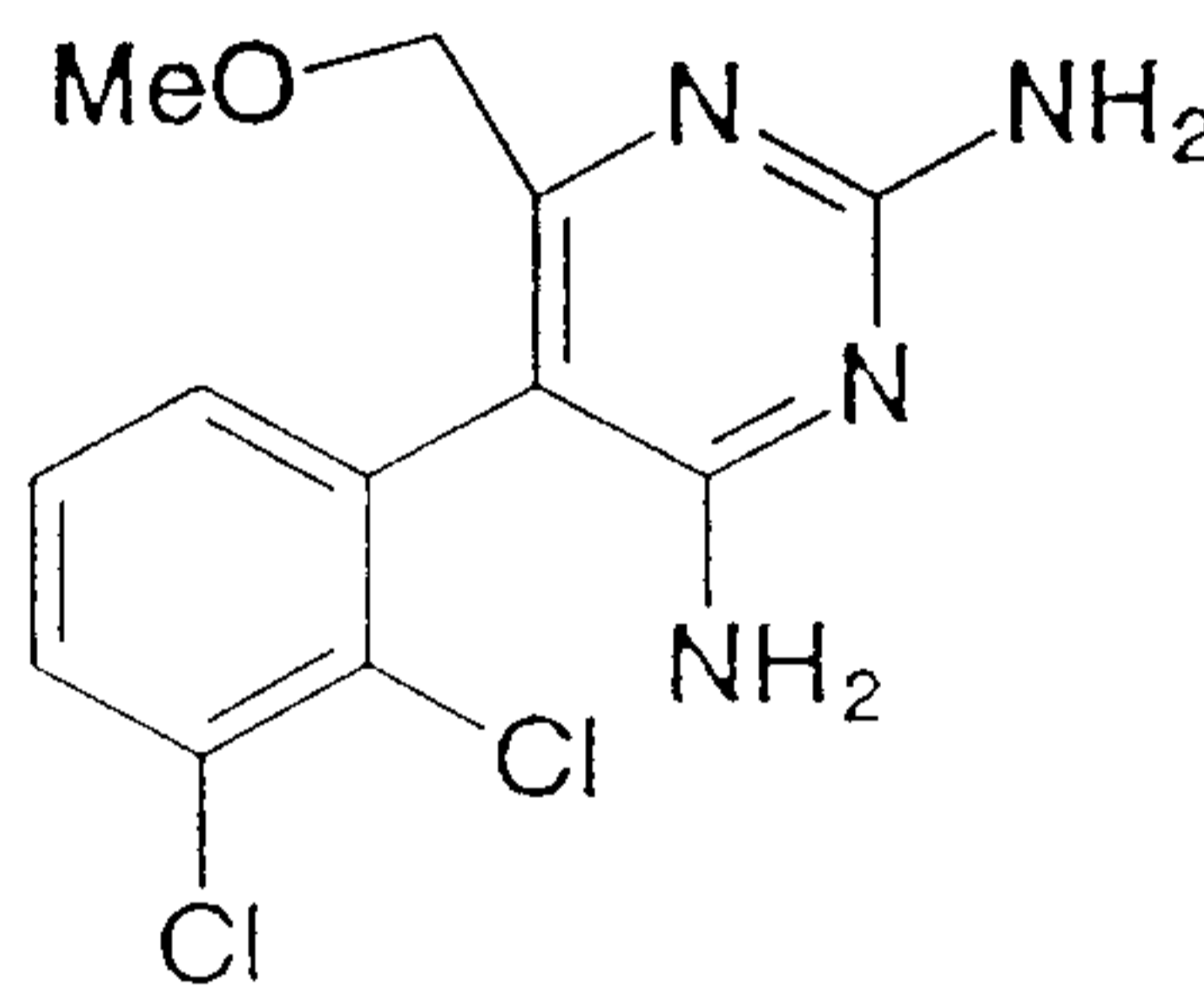
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Example 1



10

Example 2



15

TABLE OF ¹H NMR DATA (δ)

20

EXAMPLE NO.	SOLVENT	ASSIGNMENT
1	DMSO-d ₆	6.10 (s, 2H), 6.45 (s, 2H), 7.15 (d, 1H), 7.30 (t, 1H), 7.55 (d, 1H)
2	DMSO-d ₆	3.04 (s, 3H, -OMe), 3.76 (d, 1H, J12Hz, -CH ₂ OMe), 3.85 (d, 1H, J12Hz, -OCH ₂ OMe), 5.84 (br.s, 2H, -NH ₂), 6.05 (br.s, 2H-NH ₂), 7.22 (dd, 1H, J7.5, 1.5Hz, 6'- H), 7.38 (dd, 1H, J7.5Hz, 5'-H) 7.6 (dd, 1H, J7.5, 1.5Hz, 4'-H)

3	DMSO-d ₆	4.75 (2xddd, 2H, J47, 15Hz, -CH ₂ F), 5.95 (br.s, 2H, -NH ₂), 6.15 (br.s, 2H, -NH ₂), 7.25 (dd, 1H, J7.5, 1.0Hz, 6' -H), 7.39 (dd, 1H, J7.5Hz), 7.64 (dd, 1H, J7.5, 1.0Hz)
4	DMSO-d ₆	4.43 (d, 1H, J11Hz), 4.53 (d, 1H, J11Hz), 5.95 (br.s, 2H), 6.12 (br.s, 2H), 6.7 (m, 2H), 6.85 (dd, 1H, J7Hz), 7.10-7.40 (m, 4H), 7.55 (dd, 1H, J7, 1.0Hz)

In the foregoing, the signals have been abbreviated as follows:

s = singlet; d = doublet; dd = doublet of doublets;
t = triplet; m = multiplet; br.s = broad singlet.

Pharmacological Activity

10 Inhibition of Glutamate release and Inhibition of Rat Liver DHFR

Compounds of formula I were tested for their effect on veratrine-evoked release of glutamate from rat brain slices according to the protocol described in *Epilepsia* 27(5): 490-497, 1986. The protocol for testing for inhibition of dihydrofolate reductase (DHFR) activity was a modification of that set out in *Biochemical Pharmacology* Vol. 20 pp 561-574, 1971.

The results are given in Table 1, the IC₅₀ being the concentration of compound to cause 50% inhibition of (a) veratrine-evoked release of glutamate and (b) DHFR enzyme activity.

TABLE 1

Compound of Example No.	IC ₅₀ (μM) Glutamate Release (P95 limits)	IC ₅₀ (μM) Rat Liver DHFR
5 1	3.1 (2.1-4.6)	>100.00
2	3.2 (1.7-6.1)	>100
3	<10.00	<u>ca.</u> 100
4	2.6 (0.80-8.50)	>100.00

10

Pharmaceutical Formulation ExamplesA: Injection

15 The salt of the compound of formula I was dissolved in sterile water for injection.

In the following Examples, the active compound may be any compound of formula I or pharmaceutically acceptable
20 salt thereof.

B: Capsule formulationsCapsule Formulation A

Formulation A may be prepared by admixing the
25 ingredients and filling two-part hard gelatin capsules with the resulting mixture.

	<u>mg/capsule</u>
(a) Active ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
5 (d) Magnesium Stearate	2
	<hr/>
	420

Capsule Formulation B

	<u>mg/capsule</u>
(a) Active ingredient	250
10 (b) Macrogel 4000 BP (Trade Mark)	350
	<hr/>
	600

Capsules may be prepared by melting the Macrogel 4000 BP (Trade Mark), dispersing the active ingredient in the melt, and filling two-part hard gelatin capsules therewith.

Capsule Formulation B (Controlled release capsule)

	<u>mg/capsule</u>
(a) Active ingredient	250
20 (b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Ethyl Cellulose	13
	<hr/>
	513

25 The controlled-release capsule formulation may be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with ethyl cellulose (d) as a controlled-release membrane and filled into two-part hard gelatin capsules.

Syrup formulation

	Active ingredient	0.2500 g
	Sorbitol Solution	1.5000 g
	Glycerol	1.0000 g
5	Sodium Benzoate	0.0050 g
	Flavour	0.0125ml
	Purified Water q.s. to	5.0 ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

Suppository formulation

15		<u>mg/suppository</u>
	Active ingredient (63 μ m)*	250
	Hard Fat, BP (Witepsol H15 (Trade Mark) - Dynamit Nobel)	1770
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		2020

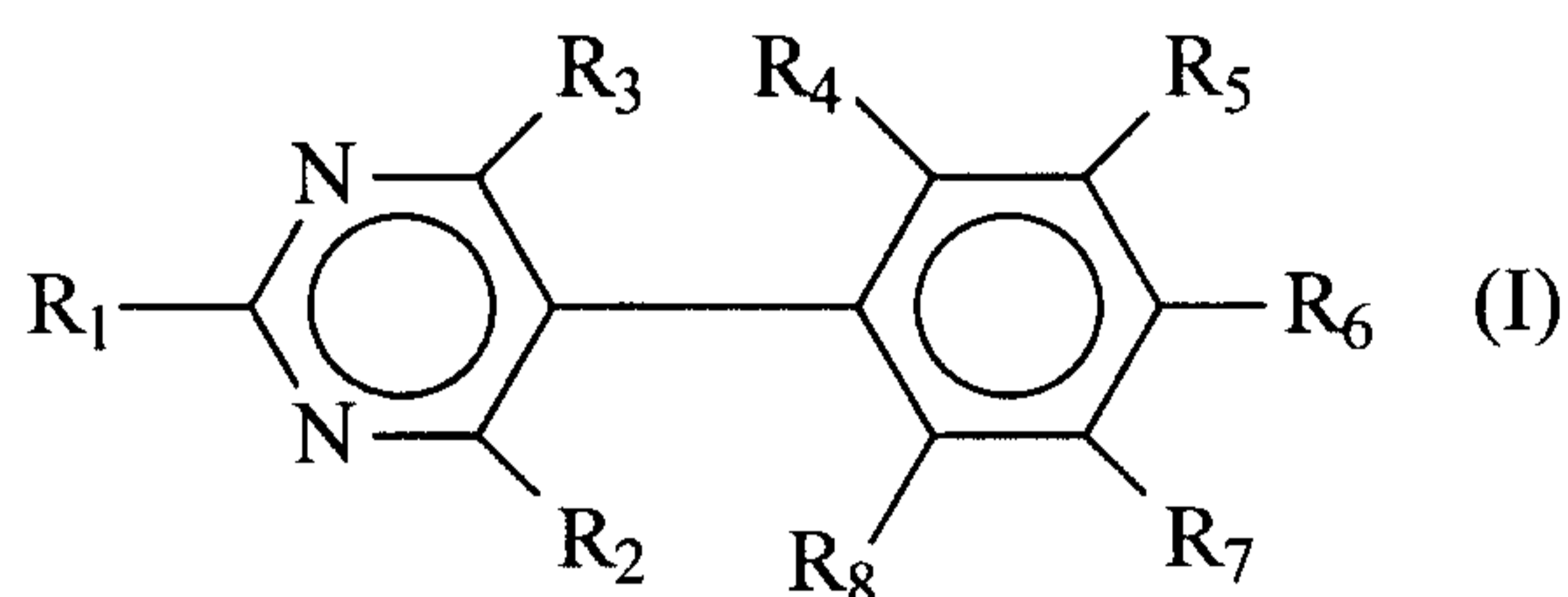
* The active ingredient is used as a powder wherein at least 90% of the particles are of 63 μ m diameter or less.

One-fifth of the Witepsol H15 (Trade Mark) is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 μ m sieve and added to the molten base with mixing, using a Silverson (Trade Mark) fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 (Trade Mark) is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250 μ m stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

The embodiments of the invention, in which an exclusive privilege or property is claimed, are defined as follows:

1. A pyrimidine of formula (I):

5



wherein:

R_1 is NH_2 , N -(C_1 - C_6 alkyl)amino or N,N -di(C_1 - C_6 alkyl)amino;

10 R_2 is NH_2 ;

R_3 is trifluoromethyl or CH_2X wherein X is hydroxy, C_1 - C_6 alkoxy, phenoxy, benzyloxy or halo;

R_4 and R_5 are each halo; and

R_6 to R_8 are each hydrogen;

15 or a pharmaceutically acceptable acid addition salt thereof.

2. A pyrimidine or salt according to claim 1, wherein R_3 is fluoromethyl.

3. A pyrimidine or salt according to claim 1 or 2, wherein R_4 and R_5 are each chloro.

20 4. A compound according claim 1, wherein R_1 is NH_2 , N -ethylamino or N,N -dimethylamino; R_3 is selected from trifluoromethyl, benzyloxymethyl and methoxymethyl; and R_4 and R_5 are each chloro.

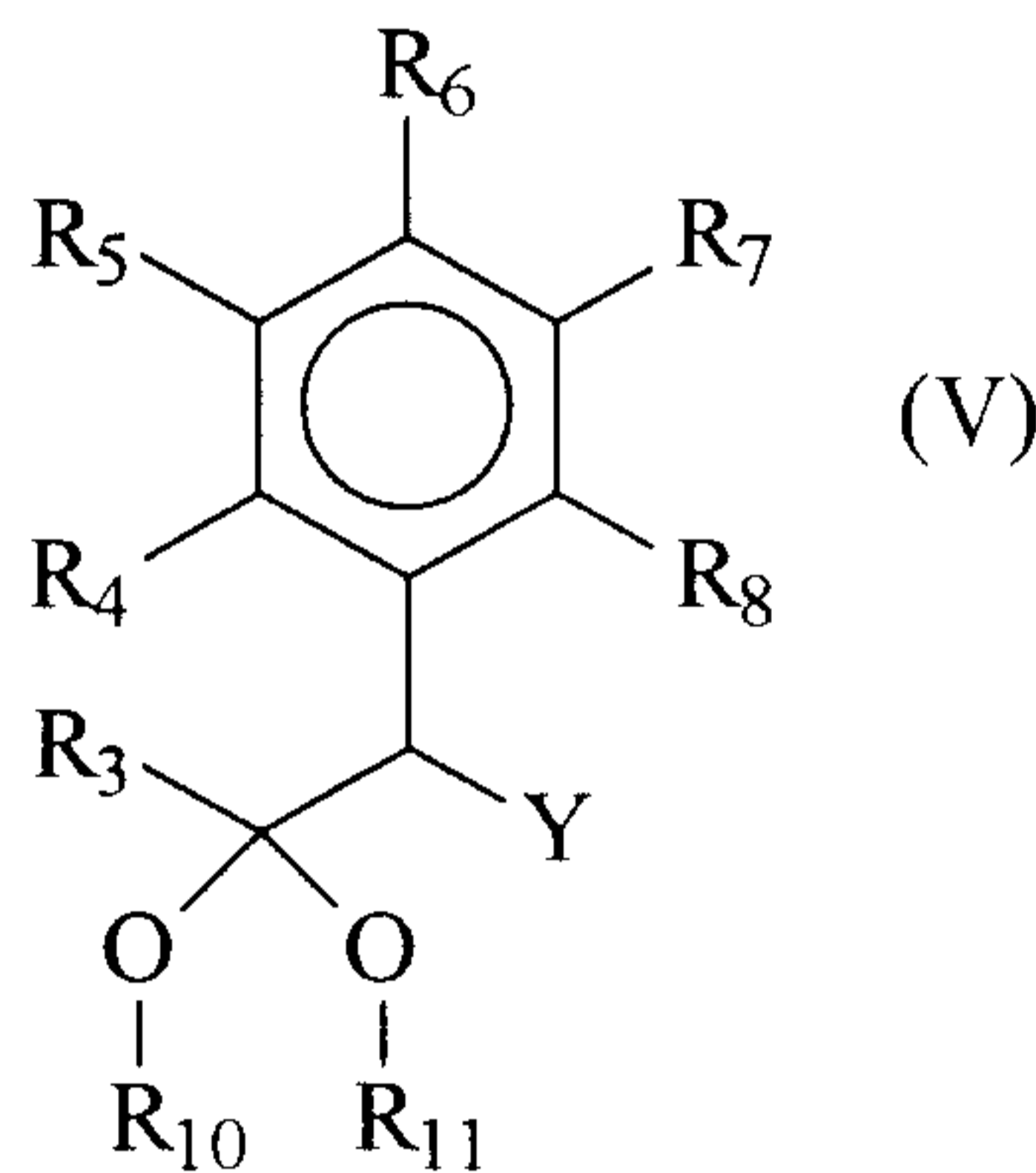
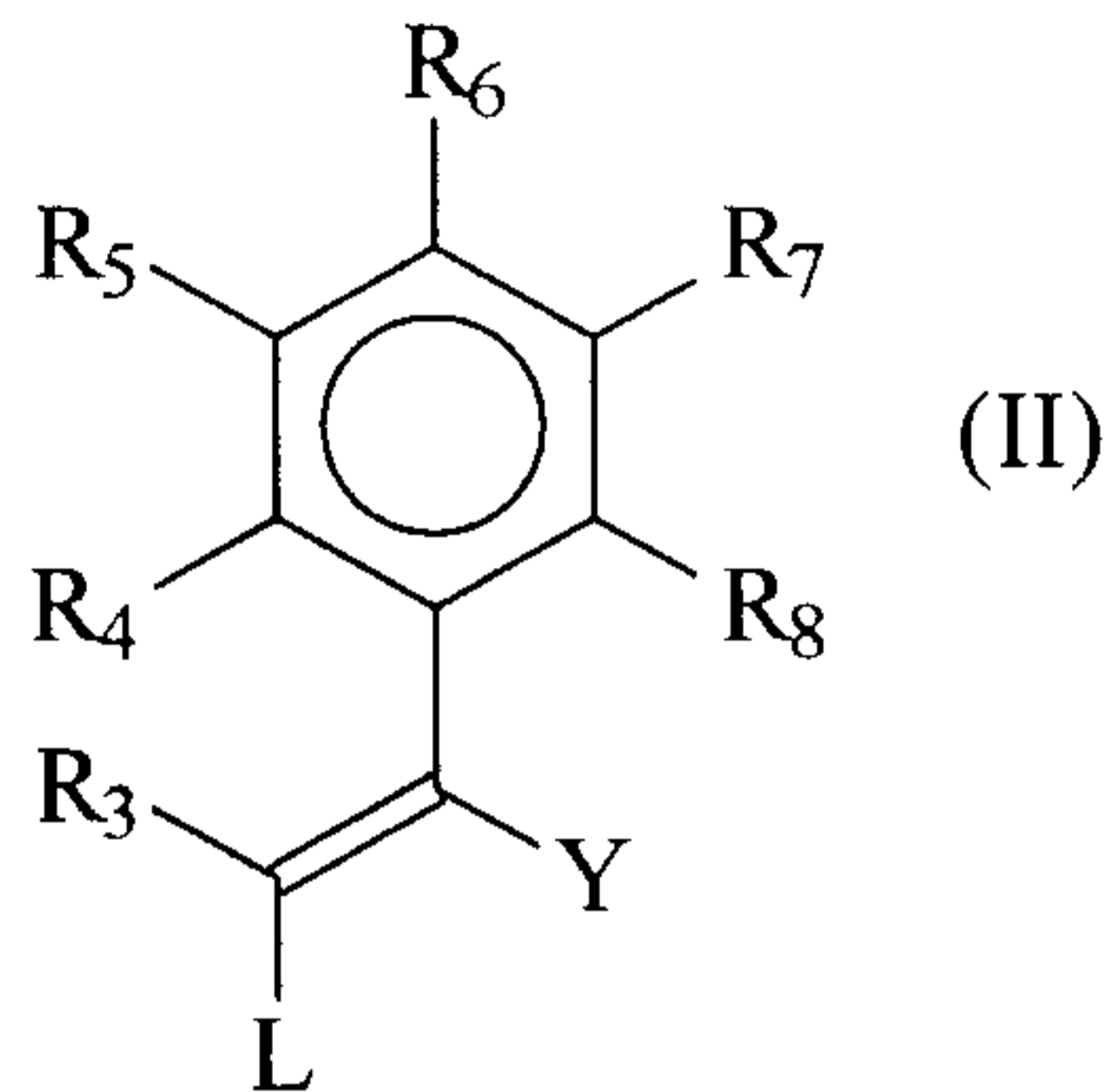
25 5. A pyrimidine of formula (I), according to claim 1, selected from 2,4-diamino-5-(2,3-dichlorophenyl)-6-trifluoromethylpyrimidine; 2,4-diamino-5-(2,3-dichlorophenyl)-6-methoxymethylpyrimidine; 2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine; 2,4-diamino-5-(2,3-dichlorophenyl)-6-phenoxyethylpyrimidine; 2,4-diamino-5-(2,3-dichlorophenyl)-6-hydroxymethylpyrimidine; and pharmaceutically acceptable acid addition salts thereof.

30 6. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine or a pharmaceutically acceptable acid addition salt thereof.

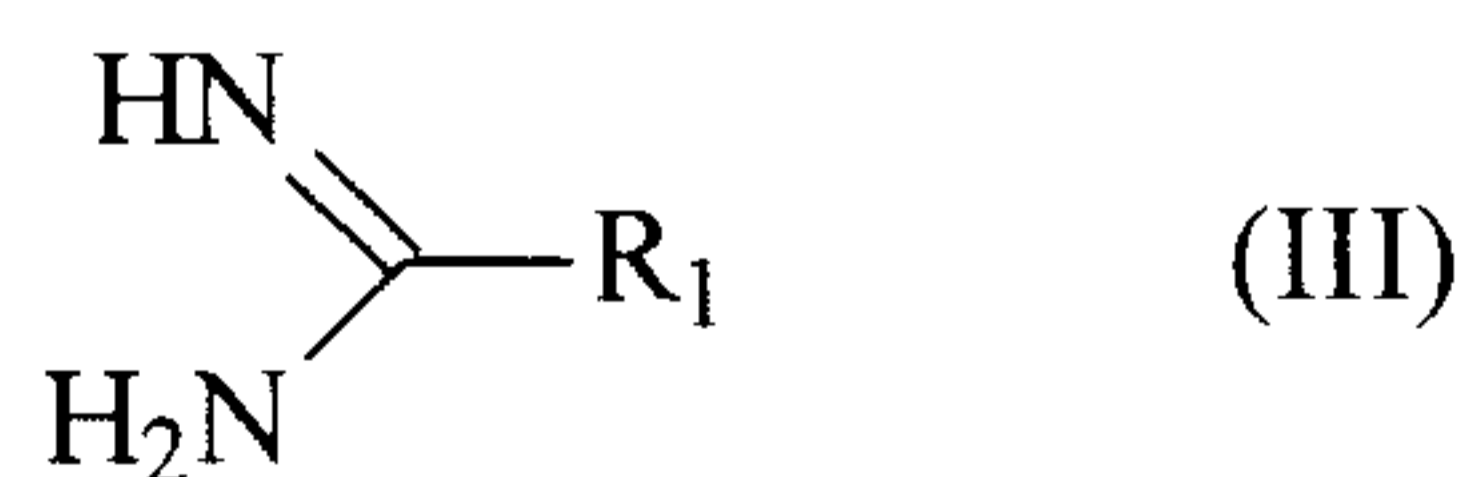
7. 2,4-Diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine.

8. A pharmaceutically acceptable acid addition salt of 2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine.

9. A process for the preparation of a pyrimidine of formula (I) as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, which process
5 comprises reacting a compound of formula (II) or (V):



wherein R_3 to R_8 are as defined in claim 1, R_{10} and R_{11} are both alkyl or together form a group $-(C(R)_2)_n-$ where R is hydrogen or alkyl and n is an integer from 2 to 4, L is a leaving group and Y is cyano, with a compound of formula (III):



25 wherein R_1 is as defined in claim 1, isolating the resulting pyrimidine of formula (I) as the free base or as a pharmaceutically acceptable acid addition salt thereof; and, when desired, converting the base into a pharmaceutically acceptable acid addition salt thereof or into another pyrimidine of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

10. A pharmaceutical composition adapted for administration to mammals for the purpose of inhibiting glutamate release, and comprising a pyrimidine or salt as defined in any one of claims 1 to 8, and a pharmaceutically acceptable adjuvant.

11. A pyrimidine or salt of any one of claims 1 to 8, for use in the treatment of central nervous system diseases and disorders.

12. Use of a pyrimidine or salt of any one of claims 1 to 8, as a glutamate release inhibitor.

13. Use of a pyrimidine or salt of any one of claims 1 to 8, in the manufacture of a medicament for the treatment of central nervous system diseases and disorders.

14. A glutamate release inhibitor pharmaceutical composition comprising an acceptable glutamate release inhibiting amount of a pyrimidine or salt of any one of claims 1 to 8, in association with a pharmaceutically acceptable carrier.

15. A pyrimidine salt as defined in claim 1.