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(54) **Substituted phenylpyrimidine derivatives, useful in the treatment or prevention of CNS disorders**

Substituierte Phenylpyrimidine Derivate, für die Behandlung oder Prevention von ZNS-Erkrankungen

Dérivés de la phénylpyrimidine substituéées, utiles dans le traitement ou la prévention des maladies du système nerveux central

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Description

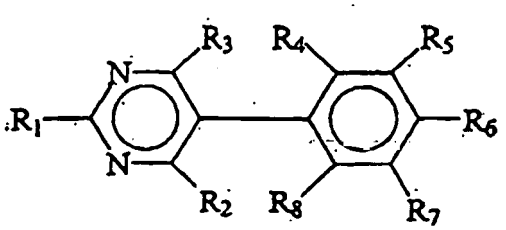
[0001] The present invention relates to .a class of pyrimidine compounds which are useful in the treatment of central nervous system (CNS) diseases and disorders such as the prevention of cerebral ischaemic damage, to pharmaceutical compositions containing them, to their use in; the treatment of such disorders, and to methods of preparing them.

[0002] Glutamate is an excitatory amino acid which functions as a neurotransmitter. However, when its 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 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, glutamate has been implicated in other neurological disorders such as manic depression, depression, schizophrenia, high pressure neurological syndrome, chronic pain, trigeminal neuralgia and migraine.

[0003] In European Patent application No.21121 there 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 1986, A.A.Miller et al New anticonvulsant drugs. Ed. Meldrum and Porter 165-177, 1987).

[0004] The present inventors have now found that a series of substituted pyrimidine compounds, as defined in Formula 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. The pyrimidine compounds of formula I are also inhibitors of aspartate release.

[0005] Thus according to the first aspect of the present invention there is provided a pyrimidine of formula I:



(I)

wherein,
R_1 s N-methylpiperazinyl;
R_2 is amino;
R_3 is selected from trifluoromethyl, hydrogen, methyl, benzyloxymethyl, methoxymethyl and methylthiomethyl;
R_4 is chloro; and
at least one of R_5, R_6 and R_7 is chloro, and the remainder of R_5, R_6 and R_7 are selected from hydrogen and chloro in the case of R_5 and R_7, and from hydrogen, chloro and nitro in the case of R_6, except that R_6 is not hydrogen when R_1 is N-methylpiperazino, R_2 is amino, each of R_3 and R_6 is hydrogen and each of R_4, R_5 and R_7 is chloro;
R_9 is hydrogen;
and pharmaceutically acceptable acid addition salts thereof.

[0006] Certain pyrimidines of Formula (I) are chiral, and it will be appreciated that in these instances, Formula (I) encompasses both the racemic mixture and the individual enantiomers of such compounds.

[0007] R_5, R_6 and R_7 are preferably selected from hydrogen and chloro.

[0008] It is a preferred feature of Formula (I) that at least one of R_5 and R_7 are chloro. In particular, it is preferred that both R_5 and R_7 are chloro. Such compounds are highly potent inhibitors of glutamate release.

[0009] The present invention also provides a subclass of pyrimidines of Formula (I), which whilst being potent inhibitors of glutamate release show only weak (i.e. having an IC_{50} of >20μm) or insignificant inhibitory effects on the enzyme dihydrofolate reductase. Accordingly, in a preferred embodiment of the present invention there are provided pyrimidines of Formula (I) where R_1 to R_8 are hereinbefore defined with the proviso that when
R_7 is chloro, then
R_3 is hydrogen, methyl or methoxymethyl and/or
R_6 is nitro;
or with the proviso that when
R_6 is chloro then

R_4 is chloro, and R_3 is hydrogen, methoxymethyl, methyl or halo.

[0010] Preferred compounds of the present invention are:

2-(4-methylpiperazin-1-yl)-4-amino-5-(2,3,5,-trichlorophenyl)-6-trifluoromethylpyrimidine;
2-(4-methylpiperazin-1-yl)-4-amino-5-(2,3,5-trichlorophenyl)-6-methylpyrimidine;
2-(4-methylpiperazin-1-yl)-4-amino-5-(2,4-dichlorophenyl)pyrimidine; and

pharmaceutically acceptable acid addition salts thereof.

[0011] In a preferred embodiment the present invention also provides a pharmaceutically acceptable acid addition salt of a pyrimidine as described above.

[0012] The compounds of the invention may.be used in the treatment or prophylaxis of acute and chronic disorders of the mammalian central nervous system. The acute condition comprises cerebral ischaemia which may arise from a variety of causes including stroke, cardiac arrest, bypass surgery, neonatal anoxia and hypoglycaemia; also physical injury or trauma of the spinal cord or brain. Chronic neurodegenerative disorders which may be treated include Alzheimer's disease, Huntington's chorea, Olivoponteocerebrellar atrophy and motor system disorders. Other neurological conditions which may be treated with a compound of the invention include depression, manic depression, schizophrenia, chronic pain, epilepsy, trigeminal neuralgia and migraine.

[0013] A compound of the invention can be used in the treatment of a disease or disorder.of the central nervous system of a mammal in which extracellular-glutamate is implicated.

[0014] A mammal predisposed to or having neurotoxic extracellular glutamate levels of the central nervous system can thus be treated.

[0015] Certain substituted phenylpyrimidines of the present invention are known in the art as having antimalarial activity. See for example Brit.J.Pharmacol. 6, 185-200 (1951); JACS, 73, 3763-70, (1951). Other phenylpyrimidines are know from Chem.Biol. Ptderidines, 463-468, (1982) and Pharmacotherap.Budesinsky, p.129-141, (1963), ed. Oldrich Hanc.

[0016] Nonetheless, compounds of the present invention are novel and accordingly the present invention provides a pyrimidine of Formula (I) or an acid addition salt thereof wherein R_1 to R_9 are as hereindefined.

[0017] Preferred novel compounds of the present invention include the following, the numbers referring to the Examples hereinafter appearing:-

Example No.

[0018]

1. 4-Amino-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)-6-trifluoromethylpyrimidine
2. 4-Amino-6-methyl-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)pyrimidine
3. 2-N-methylpiperazinyl-4-amino-5-(2,4-dichlorophenyl)pyrimidine

or an acid-addition salt thereof.

[0019] Suitable acid addition salts of the compounds of Formula I include those formed with both organic or inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. These salts can be made by reacting the compound as the free base with the appropriate acid.

[0020] 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 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.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

[0026] 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.

[0027] Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

[0028] 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.

[0029] 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.

[0030] 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.

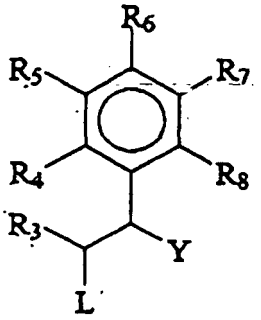
[0031] The compounds of the Formula (I) may be administered orally or via injection at a dose of from 0.1 to 30mg/kg per day. The dose range for adult humans is generally from 8 to 2,400 mg/day and preferably 35 to 1,050 mg/day. As certain compounds of the Formula (I) are long acting, it may be advantageous to administer an.initial dose of 70 to 2,400 mg the first day then a lower dose of 20 to 1,200 mg on subsequent days.

[0032] An example of such a long acting compounds is 4-amino-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)-6-trifluoromethylpyrimidine.

[0033] Long acting compounds in the clinic are advantageous 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.

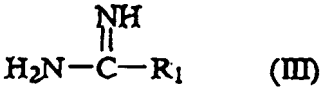
Compounds of the present invention may be made in any manner known to make analogous compounds known in the art (eg. JACS vol 73 (1951) 3763-70).

[0034] The present invention also provides a process for the preparation of a compound of formula (I) or an acid addition salt thereof, which comprises the reaction of a compound of formula (II):



(II)

wherein R_3 to R_8 are as hereinbefore defined, L is a leaving group, and Y is cyano with a compound or salt thereof of formula (III) :



(III)

wherein R_1 is as hereindefined; isolating the compound of Formula (I) as the free base or as a pharmaceutically acceptable acid addition salt thereof; and optionally converting the base into a pharmaceutically acceptable acid addition salt thereof or into another pyrimidine of Formula (I) or an acid addition salt thereof.

[0035] If it is required to make a compound of Formula (I) in which one of R_6 is nitro, this can be made from the corresponding compound of Formula (I) where R_6 is hydrogen by utilising standard nitration conditions, e.g. sulphuric acid and potassium nitrate, and then further converted by standard reduction means to the corresponding amino compound, e.g utilising PtO_2, AcoH, H_2.

[0036] It will be appreciated that amino or halo compounds can be further converted to R_4 to R_8 as herewithin defined by standard interconversion, for example, via the diazonium salts. When R_3 is alkyl this may be converted into perhaloalkyl, or a halogenated,alkyl moiety by reaction with the appropriate halogen or N-halo succinimide (NXS) in a suitable solvent such as acetic acid.

[0037] Where in the product of the above process R_3 is a group CH_2OR where R is alkyl or arylalkyl this product may be converted to CH_2X by reaction with HX (X = halo) in, for example acetic acid, and this further converted to the corresponding cyano compound, for example by treatment with sodium cyanide and DMF, or 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 diethylaminosulphur trifluoride (DAST).

[0038] Where R_3 contains an alkylthio moiety, this can be oxidised to the corresponding sulphoxide and sulphone using for example MCPBA (metachlorperbenzoic acid).

[0039] It will be appreciated that other interconversions may be effected as required by those skilled in the art using standard methodologies.

[0040] Example of suitable leaving groups (L) include C_{1-4} alkoxy, halo, anilino, morpholino, C_{1-4} alkylamino, benzylamino, or alkylthio.

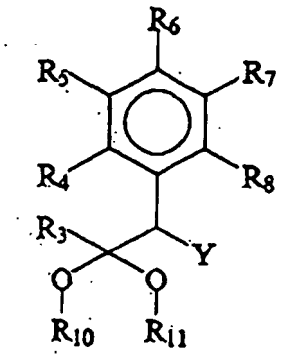
[0041] Advantageously, R_1 is N-methylpiperazinyl. Preferably L is C_1-C_4 alkoxy.

[0042] Preferably the reaction of the compound of Formula (I) and (II) is carried out in a non-aqueous solvent, for example an alkanol, e.g. ethanol at elevated temperatures (e.g. between 50 to 110°C) in base, preferably an akanoxide, preferably under reflux using sodium ethoxide as the base.

[0043] Compounds of Formula (II) may be made by methods known in the art (JACS supra) for example by the method of JACS, 1952, 74, 1310-1313.

[0044] In Formula (III) when R^1 is methyl piperazinyl these can be made by standard methods, for example by reaction of a known compound of Formula (III) where R^1 is N-methylpiperazine. This reaction preferably takes place at room temperature in water.

[0045] Further provided by the present invention is a process for the preparation of a pyrimidine of Formula (I) which process comprises reacting a compound of Formula (V):



(V)

wherein R_3 to R_8 and Y are as hereinbefore defined and R_{10} and R_{11} are both alkyl or together form a group $-(CR_2)_n-$ where R is hydrogen or alkyl, and n is an integer of from 2 to 4, with a compound of Formula (III) as defined above.

[0046] Preferably the reaction is carried out in a non-aqueous solvent, e.g. ethanol, under reflux using sodium ethoxide as the base.

[0047] Still further provided by the present invention is a pharmaceutical formulation comprising a pyrimidine of Formula (I) as defined above or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carriers therefor.

[0048] Preferably said a pharmaceutical formulation is suitable for oral administration and comprises a pyrimidine of Formula (I)as defined above or a pharmaceutically acceptable acid addition salt thereof and one or more carriers therefor.

[0049] More preferably the present invention provides capsules or tablets suitable for oral administration, each containing a predetermined amount of a pyrimidine of Formula (I) as defined above or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carriers therefor.

[0050] The present invention further provides a pharmaceutical formulation suitable for parenteral administration comprising a pyrimidine of Formula (I) as defined above or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carriers therefor.

[0051] Preferably said pharmaceutical formulation suitable for parenteral administration is presented in unit-dose containers and comprises a pyrimidine of Formula (I) as defined above or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carriers therefor.

[0052] Compounds of Formula (I) may also be prepared from the corresponding dihydropyrimidine by utilising standard dehydrogenation conditions, (e.g. JCS, 1956, 1019).

[0053] Such dihydropyrimidines can be prepared by the reaction of a compound of Formula (II) where R_3 to R_8 are as defined and L is hydrogen with a compound of Formula (III).

[0054] In the Examples of the invention set forth below, the chemical and other abbreviations used are standard in the art and have these meanings:-

$NaBH_4$: sodium borohydride

$CHCl_3$: chloroform

$NaHCO_3$: sodium bicarbonate

$MgSO_4$: magnesium sulphate

PBr_3 : phosphorus tribromide

DMF : dimethylformamide

KCN : potassium cyanide

Et_2O : diethyl ether

NaOEt : sodium ethoxide

EtOH : ethanol

H_2O_4 : sulphuric acid

AcOH : acetic acid

MeOH : methanol

N_2 : nitrogen

HCl : hydrochloric acid

NaOH : sodium hydroxide

SiO_2 : silica

DMSO : dimethylsulphoxide

Na : sodium

DME : dimethoxyethane

MeI : methyl iodide (iodomethane)

EtOAc : ethyl acetate

CH_2Cl_2 : dichloromethane

Et_3N : triethylamine

$MeNH_2$: methylamine

NH_4OH : ammonium hydroxide

$SOCl_2$: thionyl chloride

THF : tetrahydrofuran

NaH : sodium hydride

CCl_4 : carbon tetrachloride

DHFR : dihydrofolate reductase

PtO_2 : platinum oxide (Adams' catalyst)

NXS : N-halo succinimide

X_2 : halogen

TFAA : trifluoroacetic anhydri de

CsF : cesium fluoride

Me_3SiI : trimethylsilyliodide

DAST : diethylaminosulphur trifluoride

MCPBA : metachloroperbenzoic acid

AIBN : α,α'-azoisobutyronitrile (2,2'-azobis(2-methylpropionitrile)

Example 1

Preparation of 4-Amino-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)-6-trifluoromethylpyrimidine

1. Preparation of N-methylpiperazinoformamidine hydriodide

[0055] Thiourea (10.8g) was dissolved in acetone (250ml) at 50°C. Iodomethane (10ml) was added and the reaction was stirred at 50°C for 4 hours. After cooling, the solution was diluted with ether (1 litre) and the methiodide salt was filtered, washed with ether and dried in vacuo, 29.2g, 113-115°C. The methiodide salt (5g) was dissolved in water, (30ml) and N-methylpiperazine was added. The solution was stirred, with nitrogen bubbled through, at room temperature for 24 hours. The solution was concentrated in vacuo. The residue was slurried with ethanol, filtered and dried in vacuo, 4.98g, m.pt.230-242°C.

2. Preparation of 2,3,5-trichlorobenzylalcohol

[0056] To a solution of 2,3,5-trichlorobenzaldehyde (Aldrich, 50gms) in ethanol (1.0L) at room temperature was added $NaBH_4$ (7.00gms) and the resulting mixture stirred for 3.5 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. 43.00gms, mp. 90-93°C.

3. Preparation of 2,3,5-trichlorobenzyl bromide

[0057] To a solution of the alcohol in benzene (400ml) under N_2 was added PBr_3 (126.58gms), and the mixture stirred at 55-60°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. 40-42°C.

4. Preparation of 2,3,5-trichlorophenylacetonitrile

[0058] The bromide was suspended in DMF (130ml)/ water (86.67ml) at 0°C and KCN(12.99gms) added in portions. After stirring at 30-35° for 3 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. Chromatography on silica gel eluting with hexane to 20% ether-hexane gave the desired product as a white solid, 18.52gms, mp. 60-62°C.

5. Preparation of 2-(2,3,5-trichlorophenyl)-4,4,4-trifluoro-3-oxobutyronitrile

[0059] To a solution of NaOEt (from 1.04gms Na) in EtOH (60ml) at room temperature under N_2 was added the nitrile (8.40gms) followed by ethyl trifluoroacetate (6.57gms) 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_2O_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. The solid was azeotroped with toluene (x5), 4.89gms, mp. 160-163°C.

6. Preparation of 2-(2,3,5-trichlorophenyl)-4,4,4-trifluoro-3-methoxybut-2-enonitrile

[0060] To a solution of the trifluoromethyl ketone in Et_2O (39.62ml) at room temperature was added diazomethane (from 8.55gms Diazald) in Et_2O (79.62ml), 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 Et_2O, dried over $MgSO_4$, filtered and the solvent evaporated in vacuo to leave a brownish oil, 5.20gms.

7. Preparation of 4-Amino-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)-6-trifluoromethylpyrimidine

[0061] To a solution of NaOEt (from 0.144g of Na) in EtOH (12.5ml) was added N-methylpiperazinoformamidine hydriodide (1.39g). After stirring for 10 minutes at room temperature a solution of the above intermediate (0.85g) in EtOH

(2.5ml) was added and the resulting mixture was stirred at reflux for 4.5 hours After cooling, the suspension was filtered, and the filtrate was evaporated to dryness in vacuo. Chromatography on silica gel, eluting with $CHCl_3$ -4% MeOH/$CHCl_3$, gave the desired product which was triturated with petroleum ether (b.p. 40-60°C) and dried in vacuo. 0.56g, m.pt 127-129°C.

8. 4-Amino-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)-6-trifluoromethylpyrimidine methanesulphonate

[0062] The phenyl pyrimidine base (9.6g) was dissolved in absolute ethanol, cooled at 0°C, and methanesulphonic acid (2.14g, 1.62ml) was added. After stirring at room temperature for 2 hours, the solution was evaporated to dryness and the residue triturated with Et_2O, filtered and dried in vacuo to leave a beige coloured solid. This was dissolved in water (500mls) and freeze-dried to leave 10.7g as a tan coloured solid. The methanesulphonate salt could be further purified by triturating with ^tBuOH (30ml), filtering, dissolving in water and again freeze drying to leave the title product as a off-white solid. 8.33g mp. 145-7°C.

Example 2

Synthesis of 4-Amino-6-methyl-2-(4-methylpiperazin-1-yl)-5-(2,3,5-trichlorophenyl)pyrimidine

[0063] To a solution of NaOEt (from 0.16g of sodium) in ethanol (15ml) was added N-methylpiperazinoformamidine hydriodide (1.6g). After stirring for 10 minutes the enol ether of Example 6.2 (0.82g) in ethanol (5ml) was added and the mixture was stirred at reflux for 5 hours. The mixture was left standing at room temperature overnight and then filtered. The filtrate was concentrated and the residue was purified by chromatography on SiO_2 gel, eluting with $CHCl_3$ to 4% MeOH/$CHCl_3$ to give the desired product, 0.31g, mp. 156-159°C.

Example 3

2-(4-methylpiperazin-1-yl)-4-amino-5-(2,4-dichlorophenyl)pyrimidine

[0064] A) A solution of 55.7g (0.4equiv) of S-methylisothiourea sulphate in 280ml of water was prepared and gently heated on a steam bath with stirring. Then 40g (0.4mol) of N-methyl-piperazine was slowly dripped into the solution while sweeping the flask out with nitrogen. The evolved gases were collected in several portions of a solution of 132g of mercuric chloride in 400ml of ethanol, which caused evolved methylmercaptan to be precipitated as methylmercuric chloride. After the addition of the N-methylpiperazine was complete, the reaction was continued until no more methylmercuric chloride precipitated. The reaction mixture was then concentrated in vacuo and chilled which caused the N-methyl-N'-amidinopiperazine sulphate to crystallise; 50.79g was collected.
B). A mixture of 76.3g (0.356 mol) of α-formyl-2,4-dichlorophenyl-acetonitrile, 63.7g of isoamyl alcohol, 0.36g of p-toluenesulphonic acid, 895 ml of toluene, and 10 drops of concentrated sulphuric acid were heated under reflux for 20 hours in the presence of a Dean and Stark trap to remove water formed in the reaction. Then an equal portion of i-amyl alcohol and a few drops of sulphuric acid were added, and the reaction was heated for another 20 hours, until the theoretical amount of water had been collected. The solution was cooled.
C) An 8.2g portion of sodium was dissolved in 500ml of absolute ethanol, and 50g of N-methyl-N'-amidinopiperazine sulphate was added. The mixture was allowed to stir for 10 minutes. This was then added to solution B. The mixture was refluxed with stirring for 6 hours, allowed to stand overnight and the solvent removed in vacuo. The residue was then extracted with dilute hydrochloric acid, which dissolved most of it. The solution was extracted three times with ether, followed by neutralization of the aqueous fraction, which precipitated a gum which solidified upon standing overnight; weight 30g. This was crystallised repeatedly from 50% ethanol with the aid of decolourising charcoal. Very slow cooling was required in order for crystals to be formed; mp. 137°C.

Anal. Calcd for $C_{15}H_{17}Cl_2N_5$;			
	C, 53.27;	H, 5.07;	N, 20.71;
Found	C, 53.58;	H, 5.14:	N, 20.40.

[0065] Preferred among the compounds of formula (I) is the pyrimidine of the foregoing Example 1, together with salts (in particular, pharmaceutically acceptable salts) thereof; this base has the following two-dimensional structure.

Example 1

[0066]

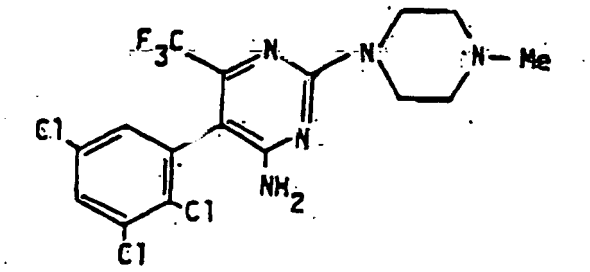


TABLE OF ^{1}H NMR DATA (δ)		
Example No.	**Solvent**	**Assignment**
1	$CDCl_3$	7.56(d,1H), 7.18(d,1H), 4.65-4.50 (br.s,2H), 3.88(t, 4H), 2.5(t,4H), 2.36(s,3H)
2	$CDCl_3$	7,51(d,1H), 7.17(d,1H), 4.40-4.22 (br.s,2H), 3.82 (t,4H), 2.48(t, 4H) , 2.34(s,3H), 2.0(s, 3H)

[0067] In the foregoing, the signals have been abbreviated as follows:
s=singlet; d=doublet; dd=doublet of doúblets; t=triplet; q=quadruplet; m=multiplet; br.s=broad singlet; br.t=broad triplet.

Pharmacological Activity

Inhibition of Glutamate release and Inhibition of Rat Liver (DHFR)

[0068] 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 DHFR activity was a modification of that set out in Biochemical Pharmacology Vol.20 pp 561-574, 1971.
[0069] The results are given in Table 1, the IC_{50} being the concentration of compound to cause 50% inhibition of (a) veratrine-evoked release of glutamate and (b) of DHFR enzyme activity.

TABLE 1

Compound of Example No.	**IC_{50} (μM) Glutamate Release (P95 limits)**	**IC_{50} (μM) Rat Liver DNFR (P95 limits)**
1	1.18 (0.50-2.60)	>100
2	4.80 (2.30-10.20)	>100.00
3	ca. 10.00	>100.00

Toxicological Example

[0070] The compound of Example 1 has been administered intravenously to groups of six male and six female Wistar rats once daily at dose levels of upto 15mg/kg/day. The no observsed effect dose was 2.5mg/kg/day.

Pharmacutical Formulation Example

[0071]

Tablet:

INGREDIENT		
A	Compound of Example 1	150 mg)
	Lactose	200 mg)
	Maize Starch	50 mg)
	Polyvinylpyrrolidone	4 mg)
	Magnesium Stearate	4 mg)
) = contents per tablet.		

[0072] The drug was mixed with the lactose and starch and granulated with a solution of the polyvinylpyrrolidone in water. The resultant granules were dried, mixed with magnesium stearate and compressed to give tablets.

B: INJECTION (I)

[0073] The salt of the compound of Formula I was dissolved in sterile water for injection.

INTRAVENOUS INJECTION FORMULATION (II)

[0074]

Active ingredient	0.20g
Sterile, pyrogen-free phosphate buffer (pH9.0) to	10ml

[0075] The compound of Example I as a salt is dissolved in most of the phosphate buffer at 35-40°C, then made up to volume and filtered through a sterile micropore filter into sterile 10ml glass vials (Type 1) which are sealed with sterile closures and overseals.
In the following Examples, the active compound maybe any compound of formula (I) or pharmaceutically acceptable salt thereof.

C: Capsule formulations

Capsule Formulation A

[0076] Formulation A may be prepared by admixing the ingredients and filling two-part hard gelatin capsules with the resulting mixture.

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

Capsule Formulation B

[0077]

		mg/capsule
(a)	Active ingredient	250
(b)	Macrogel 4000 8P	350
		600

[0078] Capsules may be prepared by melting the Macrogel 4000 BP, dispersing the active ingredient in the melt, and filling two-part hard gelatin capsules therewith.

Capsule Formulation B (Controlled release capsule)

[0079]

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

[0080] 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

[0081]

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

[0082] 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

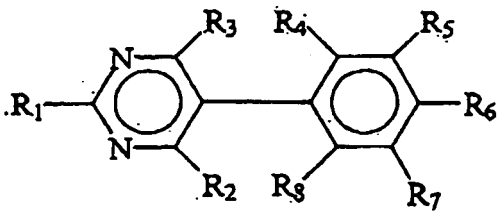
[0083]

	mg/suppository
Active ingredient (63μm)*	250
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	1770
	2020
* The active ingredient is used as a powder wherein at least 90% of the particles are of 63μm diameter or less.	

[0084] One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200μm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaming Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250μm 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.

Claims

1. A pyrimidine of formula (I):



(I)

wherein,
R_1 is N-methyl-piperazino;
R_2 is amino;
R_3 hydrogen,
methyl,
trifluoromethyl,
benzylozymethyl,
methoxymethyl or
methyl-thiomethyl;
R_4 is chloro;
at least one of R_5, R_6 and R_7 is chloro, and the remainder of R_5, R_6 and R_7 are selected from hydrogen and chloro in the case of R_5 and R_7, and from hydrogen, chloro and nitro in the case of R_6 except that R_6 is not hydrogen when R_1 is N-methylpiperazino, R_3 is hydrogen and each of R_5 and R_7 is chloro;
R_8 is hydrogen;
and pharmaceutically acceptable acid addition salts thereof.

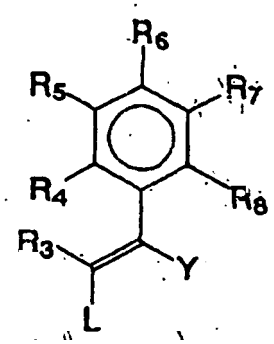
2. A compound according to claim 1, wherein R_5, R_6 and R_7 are selected from hydrogen and chloro.

3. A compound according to any one of the preceding claims wherein one or both of R_5 and R_7 are chloro.

4. 2-(4-Methylpiperazin-1-yl)-4-amino-5-(2,3,5-trichlorophenyl)-6-trifluoromethylpyrimidine;
2-(4-Methylpiperazin-1-yl)-4-amino-5-(2,3,5-trichlorophenyl)-6-methylpyrimidine;
2-(4-Methylpiperazin-1-yl)-4-amino-5-(2,4-dichlorophenyl)pyrimidine; and
pharmaceutically acceptable acid addition salts thereof.

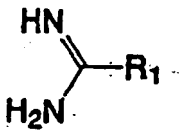
5. A pharmaceutically acceptable acid addition salt of a pyrimidine as claimed in any one of claims 1 to 4.

6. 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 comprises reacting a compound of formula (II):



(II)

wherein R_3 to R_4 are as defined in claim 1, L is a leaving group and Y is cyano, with a compound of formula (III) :

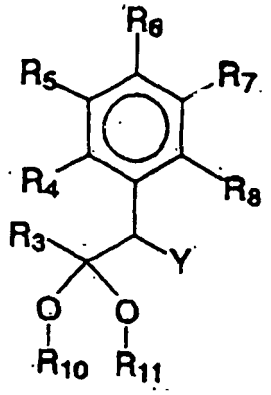


(III)

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

7. A process according to claim 6, wherein L is C_1-C_4 alkoxy.

8. A process for the preparation of a pyrimidine of formula (I) as defined in claim 1, which process comprises reacting a compound of formula (V):



(V)

wherein R_3 to R_8 are as defined in claim 1, Y is as defined in claim 6 and 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, with a compound of formula (III) as defined in claim 6.

9. A pharmaceutical formulation comprising a pyrimidine of formula (I) as claimed in any one of claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carrier therefor.

10. A pharmaceutical formulation suitable for oral administration comprising a pyrimidine of formula (I) as claimed in any one of claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carrier therefor.

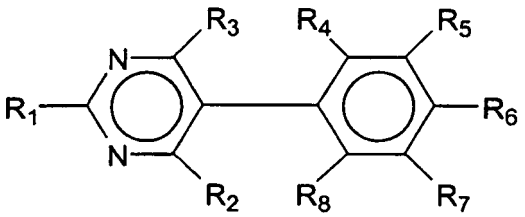
11. Capsules or tablets suitable for oral administration, each containing a predetermined amount of a pyrimidine of formula (I) as claimed in any one of claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carrier therefor:

12. A pharmaceutical formulation suitable for parenteral administration comprising a pyrimidine of formula (I) as claimed in any one of claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carrier therefor.

13. A pharmaceutical formulation suitable for parenteral administration, which formulation is presented in unit-dose containers and comprises a pyrimidine of formula (I) as claimed in any one of claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof and one or more acceptable carrier therefor.

Patentansprüche

1. Pyrimidin der Formel (I) :



(I)

worin
R_1 N-Methylpiperazino ist;
R_2 Amino ist;
R_3 Wasserstoff, Methyl, Trifluormethyl, Benzyloxymethyl, Methoxymethyl oder Methylthiomethyl ist;
R_4 Chlor ist;
wenigstens ein Vertreter aus R_5, R_6, und R_7 Chlor ist und der Rest aus R_5, R_6 und R_7 aus Wasserstoff und Chlor im Falle von R_5 und R_7 und aus Wasserstoff, Chlor und Nitro im Falle von R_6 ausgewählt ist, außer dass R_6 nicht Wasserstoff ist, wenn R_1 N-Methylpiperazino ist, R_3 Wasserstoff ist und R_5 und R_7 jeweils Chlor sind;
R_8 Wasserstoff ist;
und pharmazeutisch akzeptable Säureadditionssalze davon.

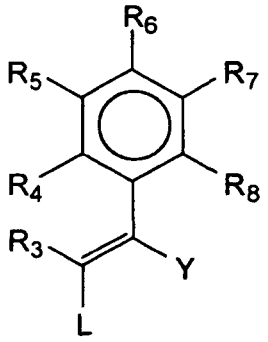
2. Verbindung gemäß Anspruch 1, worin R_5, R_6 und R_7 aus Wasserstoff und Chlor ausgewählt sind.

3. Verbindung gemäß einem der vorhergehenden Ansprüche, worin eines oder beide aus R_5 und R_7 Chlor sind.

4. 2-(4-Methylpiperazin-1-yl)-4-amino-5-(2,3,5-trichlorphenyl)-6-trifluormethylpyrimidin; 2-(4-Methylpiperazin-1-yl)-4-amino-5-(2,3,5-trichlorphenyl)-6-methylpyrimidin; 2-(4-Methylpiperazin-1-yl)-4-amino-5-(2,4-dichlorphenyl)pyrimidin; und pharmazeutisch akzeptable Säureadditionssalze davon.

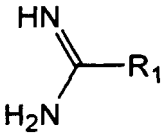
5. Pharmazeutisch akzeptables Säureadditionssalz eines Pyrimidins gemäß einem der Ansprüche 1 bis 4.

6. Verfahren zur Herstellung eines Pyrimidins der Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch akzeptablen Säureadditionssalzes davon, wobei das Verfahren das Umsetzen einer Verbindung der Formel (II):



(II)

worin R_3 bis R_8 wie in Anspruch 1 definiert sind, L eine Abgangsgruppe ist und Y Cyano ist, mit einer Verbindung der Formel (III):

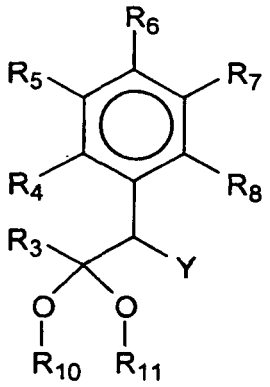


(III)

worin R_1 wie in Anspruch 1 definiert ist, oder einem Salz davon; Isolieren des resultierenden Pyrimidins der Formel (I) als freie Base oder als pharmazeutisch akzeptables Säureadditionssalz davon; und gegebenenfalls Umwandeln der Base zu einem pharmazeutisch akzeptablen Säureadditionssalz davon oder zu einem anderen Pyrimidin der Formel (I) oder einem pharmazeutisch akzeptablen Säureadditionssalz davon umfasst.

7. Verfahren gemäß Anspruch 6, worin L C_{1-4}-Alkoxy ist.

8. Verfahren zur Herstellung eines Pyrimidins der Formel (I) gemäß Anspruch 1, wobei das Verfahren das Umsetzen einer Verbindung der Formel (V):



(V)

worin R_3 bis R_8 wie in Anspruch 1 definiert sind, Y wie in Anspruch 6 definiert ist und R_{10} und R_{11} beide Alkyl sind oder zusammen eine Gruppe $-(C(R)_2)_n-$ bilden, worin R Wasserstoff oder Alkyl ist und n eine ganze Zahl von 2 bis 4 ist, mit einer Verbindung der Formel (III) wie in Anspruch 6 definiert umfasst.

9. Pharmazeutische Formulierung, die ein Pyrimidin der Formel (I) gemäß einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Säureadditionssalz davon und einen oder mehrere akzeptable Träger dafür umfasst.

10. Pharmazeutische Formulierung, die zur oralen Verabreichung geeignet ist, umfassend ein Pyrimidin der Formel (I) gemäß einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Säureadditionssalz davon und einen oder mehrere akzeptable Träger dafür.

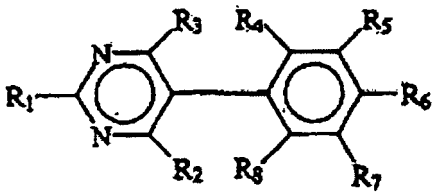
11. Kapseln oder Tabletten, die zur oralen Verabreichung geeignet sind, wobei jede eine vorher festgelegte Menge eines Pyrimidins der Formel (I) gemäß einem der Ansprüche 1 bis 4 oder eines pharmazeutisch akzeptablen Säureadditionssalzes davon und einen oder mehrere akzeptable Träger dafür enthält.

12. Pharmazeutische Formulierung, die zur parenteralen Verabreichung geeignet ist, umfassend ein Pyrimidin der Formel (I) gemäß einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Säureadditionssalz davon und einen oder mehrere akzeptable Träger dafür.

13. Pharmazeutische Formulierung, die zur parenteralen Verabreichung geeignet ist, wobei die Formulierung in Einheitsdosisbehältern angeboten wird und ein Pyrimidin der Formel (I) gemäß einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Säureadditionssalz davon und einen oder mehrere akzeptable Träger dafür umfasst.

Revendications

1. Pyrimidine de formule (I) :



(I)

dans laquelle,
R_1 est un N-méthyl-pipérazino ;
R_2 est un amino ;
R_3 est un atome d'hydrogène,
un groupe méthyle,
trifluorométhyle,
benzyloxyméthyle,
méthoxyméthyle ou
méthylthiométhyle ;
R_4 est un chloro ;
au moins l'un de R_5, R_6 et R_7 est un chloro, et le reste de R_5, R_6 et R_7 sont choisis parmi un atome d'hydrogène et un chloro dans le cas de R_5 et R_7, et parmi un atome d'hydrogène, un chloro et un nitro dans le cas de R_6 excepté que R_6 n'est pas un atome d'hydrogène lorsque R_1 est un N-méthyl-pipérazino, R_3 est un atome d'hydrogène, et chacun de R_5 et R_7 est un chloro ;
R_9 est un atome d'hydrogène ;
et les sels d'addition acide pharmaceutiquement acceptables de celle-ci.

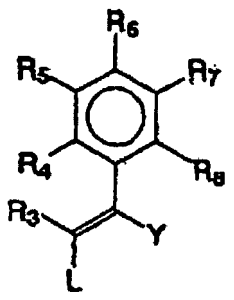
2. Composé selon la revendication 1, dans lequel R_5, R_6 et R_7 sont choisis parmi un atome d'hydrogène et un chloro.

3. Composé selon l'une quelconque des revendications précédentes, dans lequel un ou les deux de R_5 et R_7 sont un chloro.

4. 2-(4-Méthylpipérazin-1-yl)-4-amino-5-(2,3,5-trichlorophényl)-6-trifluorométhylpyrimidine ;
2-(4-méthylpipérazin-1-yl)-4-amino-5-(2,3,5-trichlorophényl)-6-méthylpyrimidine ;
2-(4-méthylpipérazin-1-yl)-4-amino-5-(2,4-dichlorophényl)pyrimidine ; et les sels d'addition acide pharmaceutiquement acceptables de celles-ci.

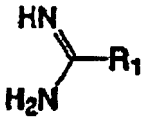
5. Sel d'addition acide pharmaceutiquement acceptable d'une pyrimidine selon l'une quelconque des revendications 1 à 4.

6. Procédé de préparation d'une pyrimidine de formule (I) telle que définie dans la revendication 1 ou un sel d'addition acide pharmaceutiquement acceptable de celle-ci, lequel procédé comprend la réaction d'un composé de formule (II) :



(II)

dans laquelle R_3 à R_8 sont tels que définis dans la revendication 1, L est un groupe partant et Y est un cyano, avec un composé de formule (III) :

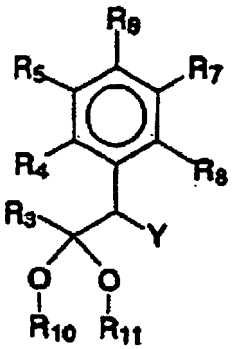


(III)

dans laquelle R_1 est tel que défini dans la revendication 1, ou un sel de celui-ci ; l'isolement de la pyrimidine résultante de formule (I) sous forme de base libre ou sous forme de sel d'addition acide pharmaceutiquement acceptable de celle-ci ; et facultativement la conversion de la base en un sel d'addition acide pharmaceutiquement acceptable de celle-ci ou en une autre pyrimidine de formule (I) ou un sel d'addition acide pharmaceutiquement acceptable de celle-ci.

7. Procédé selon la revendication 6, dans lequel L est un groupe alcoxy en C_1 à C_4.

8. Procédé de préparation d'une pyrimidine de formule (I) tel que défini dans la revendication 1, lequel procédé comprend la réaction d'un composé de formule (V) :



(V)

dans laquelle R_3 à R_8 sont tels que définis dans la revendication 1, Y est tel que défini dans la revendication 6 et R_{10} et R_{11} sont tous deux un groupe alkyle ou conjointement forment un groupe $-(C(R)_2)_n-$ où R est un atome d'hydrogène ou un groupe alkyle et n est un entier de 2 à 4, avec un composé de formule (III) tel que défini dans la revendication 6.

9. Formulation pharmaceutique comprenant une pyrimidine de formule (I) tel que revendiquée dans l'une quelconque des revendications 1 à 4 ou un sel d'addition acide pharmaceutiquement acceptable de celle-ci et un ou plusieurs véhicule(s) acceptable(s) pour celle-ci.

10. Formulation pharmaceutique appropriée pour une administration orale, comprenant une pyrimidine de formule (I) tel que revendiquée dans l'une quelconque des revendications 1 à 4 ou un sel d'addition acide pharmaceutiquement acceptable de celle-ci et un ou plusieurs véhicule(s) acceptable(s) pour celle-ci.

11. Capsules ou comprimés appropriés pour une administration orale, chacun contenant une quantité prédéterminée d'une pyrimidine de formule (I) tel que revendiquée dans l'une quelconque des revendications 1 à 4 ou un sel d'addition acide pharmaceutiquement acceptable de celle-ci et un ou plusieurs véhicule(s) acceptable(s) pour celle-ci.

12. Formulation pharmaceutique appropriée pour une administration parentérale, comprenant une pyrimidine de formule (I) tel que revendiquée dans l'une quelconque des revendications 1 à 4 ou un sel d'addition acide pharmaceutiquement acceptable de celle-ci et un ou plusieurs véhicule(s) acceptable(s) pour celle-ci.

13. Formulation pharmaceutique appropriée pour une administration parentérale, laquelle formulation est présentée dans des conteneurs de dose unitaire et comprend une pyrimidine de formule (I) tel que revendiquée dans l'une quelconque des revendications 1 à 4 ou un sel d'addition acide pharmaceutiquement acceptable de celle-ci et un ou plusieurs véhicule(s) acceptable(s) pour celle-ci.

REFERENCES CITED IN THE DESCRIPTION

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