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(54) Title: SUBSTITUTED 6,7-DIHYDROIMIDAZO[1,5-A] pyrimidin-6-ones, their preparation and pharmaceutical compositions  

![Chemical Structure](image)

(57) Abstract  
Platelet activating factor antagonists of formula (I), wherein R^1 is H or C_1-C_4 alkyl optionally substituted by a substituent selected from phenyl, halophenyl, pyrindyl, (C_1-C_4 alkoxy) carbonyl and di-(C_1-C_4 alkyl) amino, or is C_2-C_4 alkyl substituted by hydroxyl or by one or two C_1-C_4 alkoxy groups or is (CH_2)_n CONR^7 R^8 where n is an integer from 1 to 4 and R^7 and R^8 are each independently H or C_1-C_4 alkyl, R^2 is selected from H, OH and C_1-C_4 alkyl, R^3 is selected from halo and C_1-C_4 alkyl, R^4 is methyl, and p is an integer from 0 to 3 and m is an integer from 0 to 3; or a pharmaceutically acceptable salt thereof.
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SUBSTITUTED 6,7-DIHYDROIMIDAZO(1,5,4-EF)(1,5) BENZODIAZEPIN-6-ONES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS

This invention relates to diazepine derivatives which are potent, orally active antagonists of platelet activating factor and as such have clinical utility for treating allergic and inflammatory conditions such as asthma and arthritis respectively.

Platelet activating factor (PAF, 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine) is an ether phospholipid whose structure was first elucidated in 1979. It is produced by, released from and interacts with many pro-inflammatory cells, platelets and the kidney. In addition to potent platelet aggregating activity, PAF exhibits a wide spectrum of biological activities elicited either directly or via the release of other powerful mediators such as thromboxane A₂ or the leukotrienes. In vitro, PAF stimulates the movement and aggregation of neutrophils and the release therefrom of tissue-damaging enzymes and oxygen radicals. These activities contribute to actions of PAF in vivo consistent with it playing a significant role in inflammatory and allergic responses. Thus, intradermal PAF has been shown to induce an inflammatory response, with associated pain, accumulation of inflammatory cells and increased vascular permeability, comparable with the allergic skin reaction following exposure to allergen. Similarly, both the acute bronchoconstriction and chronic inflammatory reactions elicited by allergens in asthma can be mimicked by intratracheal
administration of PAF. Accordingly agents which antagonise the actions of PAF and, consequently also prevent mediator release by PAF, will have clinical utility in the treatment of a variety of allergic and inflammatory conditions such as asthma and arthritis, respectively.

In addition to the above, PAF has been implicated as being involved in a number of other medical conditions. Thus in circulatory shock, which is characterised by systemic hypotension, pulmonary hypertension and increased lung vascular permeability, the symptoms can be mimicked by infusion of PAF. This coupled with evidence showing that circulating PAF levels are increased by endotoxin infusion indicate that PAF is a prime mediator in certain forms of shock. Intravenous infusion of PAF at doses of 20-200 pmol kg\(^{-1}\) min\(^{-1}\) into rats results in the formation of extensive haemorrhagic erosions in the gastric mucosa and thus PAF is the most potent gastric ulcerogen yet described whose endogenous release may underlie or contribute to certain forms of gastric ulceration. Psoriasis is an inflammatory and proliferative disease characterised by skin lesions. PAF is pro-inflammatory and has been isolated from lesioned scale of psoriatic patients indicating PAF has a role in the disease of psoriasis. And finally, increasing evidence supports a potential pathophysiological role for PAF in cardiovascular disease. Thus recent studies in angina patients show PAF is released during atrial pacing and, in pigs, intracoronary injection of PAF induces a prolonged decrease in coronary flow while in guinea pig hearts
it induces regional shunting and ischaemia. PAF has also been shown to initiate thrombus formation in a mesenteric artery preparation both when administered exogenously and when released endogenously. More recently PAF has been shown to play a role in brain ischaemia induced in animal models of stroke.

Thus compounds of the invention, by virtue of their ability to antagonise the actions of PAF, could well be of value in the treatment of any of the above conditions.

In European Patent Application No. 0258033 we disclose a series of 2-substituted 1,4-dihydropyridine derivatives as PAF antagonists. In European Patent Application 0310386 we disclose a further series of dihydropyridine PAF antagonists in which the 2-position substituent may be a 2-methyl-imidazo[4,5-c]-pyrid-1-ylphenyl group.

According to the present invention, there are provided compounds of formula (I):

![Chemical Structure](image)
wherein $R^1$ is either H or $C_1-C_4$ alkyl optionally substituted by a substituent selected from phenyl, halophenyl, pyridyl, ($C_1-C_4$ alkoxy) carbonyl and di-($C_1-C_4$ alkyl) amino, or $C_2-C_4$ alkyl substituted by hydroxyl or by one or two $C_1-C_4$ alkoxy groups or is $(CH_2)_n CONR^7 R^8$ where $n$ is an integer from 1 to 4 and $R^7$ and $R^8$ are each independently H or $C_1-C_4$ alkyl, and $R^2$ is selected from H, OH and $C_1-C_4$ alkyl; $R^3$ is selected from halo or $C_1-C_4$ alkyl; $R^4$ is methyl; $p$ is 0-3 and $m$ is 0-3; and their pharmaceutically acceptable salts.

Examples of $R^1$ are H, CH$_3$ and ethoxycarbonylmethyl. $R^2$ may be selected from H, OH and CH$_3$. Particularly preferred compounds are 7-methyl-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-6,7-dihydroimidazo[1,5-ef][1,5]benzodiazepin-6-one, in which $R^1$ is CH$_3$ and $R^2$ is H and $m$ and $p$ are 0; and 4-[4-(2-methylimidazo-[4,5-c]pyrid-1-yl)phenyl]-7-ethoxycarbonylmethyl-6,7-dihydroimidazo[1,5-ef][1,5] benzodiazepin-6-one, in which $R^1$ is ethoxycarbonyl methyl and $R^2$ is H and $m$ and $p$ are 0.

When $R^2$ is OH formula (I) may alternatively be written as formula (Ia), these forms of the compound being tautomeric.
Such compounds and their salts may exist as one tautomer or as a mixture of tautomers, which may generally be separated by physical means such as fractional crystallisation or chromatography. The invention includes all tautomers whether separated or not.

When at least one of $R^1$, $R^2$ or $R^3$ comprises a branched alkyl or alkoxy group having 4 carbon atoms the compound may contain a chiral centre and exist as a pair of isomers which may be separated by conventional means. The invention includes all such enantiomers, whether separated or not.

The pharmaceutically acceptable salts of the compounds of formula (I) are those formed from acids which form non-toxic addition salts, for example the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate, methane-sulphonate and dimethane-sulphonate, benzenesulphonate and p-toluencesulphonate.

When $R^1$ is H and $R^2$ is H or $C_1$-$C_4$ alkyl the compounds of formula (I) may be made by the following method.
In this method 6-amino-4-[(4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl][1,5]benzodiazepin-4-one (see Preparation), or the derivative thereof containing the appropriate substituents $R^3$ and $R^4$ (compound II) reacts with an orthoester of the appropriate carboxylic acid in the presence of that acid and compound (I) may be isolated by conventional means.

The compound (I) in which $R^2$ is OH may be made from compound (II) by reaction of the latter with trichloromethyl chloroformate in 1,2-dichloroethane as a solvent.

Compounds of formula (I) in which $R^1$ is optionally substituted alkyl may be prepared from the corresponding compounds in which $R^1$ is H by reaction of the latter with compound $R^1$-X when X is chloro, bromo or iodo. The reaction is generally conducted in the presence of a base such as sodium hydride.

The activity of the compounds of the invention is shown by their ability to inhibit the platelet aggregating activity of PAF in vitro. Testing is performed as follows:

Blood samples are taken from either rabbit or man into 0.1 vol disodium ethylenediamine tetraacetic acid buffer and the samples centrifuged for 15 minutes to obtain platelet rich plasma. The plasma is further centrifuged to give a platelet pellet which is washed with a buffer solution (4 mM KH$_2$PO$_4$, 6mM Na$_2$HPO$_4$, 100 mM NaCl, 0.1% glucose and 0.1% bovine serum albumin, pH 7.25) and finally resuspended in buffer solution to a concentration of $2 \times 10^8$ platelets/ml. A sample (0.5 ml) is pre-incubated for two minutes at 37°C in a Paton aggregometer with stirring, either with vehicle alone, or with vehicle containing the particular compound
under test. PAF is added at a sufficient concentration to give a maximum aggregating response in the absence of test compound (10^{-8} to 10^{-9} molar), and the platelet aggregation is measured by following the increase in light transmission of the solution. The experiment is repeated in the presence of test compound at a range of concentrations and the concentration of compound required to reduce the response to 50% of its maximum value is recorded as the \text{IC}_{50} value.

The activity of the compounds of formula (I) is also demonstrated \textit{in vivo} by their ability to protect mice from the lethal effect of an injection of PAF. A mixture of PAF (50 \mu g/kg) and DL-propranolol (5 mg/kg) in 0.9% w/v sodium chloride is injected (0.2 ml) via a tail vein into mice. The compounds under test are either injected into the tail vein immediately prior to the PAF/propranolol injection or administered orally by gavage two hours earlier. The compounds are tested at several doses in groups of 5 mice and the dose which reduces mortality to 50% is recorded as the \text{PD}_{50} value.

For therapeutic use the compounds of the formula (I) will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents.
They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For administration to man in the curative or prophylactic treatment of allergic bronchial conditions and arthritis, oral dosages of the compounds will generally be in the range of from 2-1000 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 1 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration would typically be within the range 1 to 10 mg per single dose as required. For the treatment of allergic and bronchial hyper-reactive conditions, inhalation via a nebuliser or aerosol may be the preferred route of drug administration. Dose levels by this route would be within the range 0.1 to 50 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.
Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compound of the formula (I) or a pharmaceutically acceptable salt thereof, for use in medicine, in particular in the treatment of allergic and inflammatory conditions in a human being.

The preparation of the compounds of the invention is further illustrated by the following Examples.
EXAMPLE 1

4-[(4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-6,7-dihydroimidazo[1,5,4-ef]-[1,5]-benzodiazepin-6-one

\[
\text{HC(OEt)₃} \rightarrow \text{HCO₂H}
\]

9-Amino-4-[(4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-[1,5]benzodiazepin-4-one (0.765g, 2mmol) was suspended in triethylorthoformate (10ml, 60mmol) and formic acid (3ml, 8mmol) added to give a clear solution which was stirred at room temperature for two hours and under reflux for one hour.

On cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and aqueous sodium hydrogen carbonate such that the aqueous phase had pH 8. The organic extract was washed with water, dried over magnesium sulphate and the drying agent filtered off.
Pre-adsorption silica (Kieselgel 60, 70-230 mesh, 1g) was added to the filtrate which was concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (Kieselgel 60, 230-400 mesh) eluting with 5% diethylamine in ethyl acetate.

Product-containing fractions were combined, concentrated under reduced pressure and the residue triturated with methanol to give the title compound (25mg, 3%). M.Pt. > 300°C.

Analysis %:

Found

C₂₃H₁₆N₆O. 3/4 H₂O requires

C, 68.05; H, 4.34; N, 20.70
EXAMPLE 2

2-Methyl-4-[4-{2-methylimidazo-[4,5-c]pyrid-1-yl}phenyl]-6,7-dihydroimidazo[1,5,4-ef][1,5]benzodiazepin-6-one

This compound was prepared by the method of Example 1 substituting triethylorthoacetate and acetic acid for triethylorthoformate and formic acid respectively, to yield the title compound, (90mg, 26%)

M.Pt. > 300°C

Analysis %:-

Found

C₂₄H₁₈N₂O. 1/2 H₂O requires

C, 69.37; H, 4.43; N, 19.87

C, 69.38; H, 4.61; N, 20.23
EXAMPEL 3

2-Hydroxy-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-
6,7-dihydroimidazo[1,5,4-ef][1,5]benzodiazepin-6-one

Trichloromethylchloroformate (0.1g, 0.5mmol) was added to a
stirred suspension of 9-amino-4-[4-(2-methylimidazo[4,5-c]-
pyrid-1-yl)phenyl][1,5]benzodiazepin-4-one (0.1g, 0.26mmol) in
anhydrous 1,2-dichloroethane (5ml) under a nitrogen atmosphere and
the reaction mixture stirred under reflux for 16 hours.

Methanol (5ml) was added to give a clear solution, followed
by pre-adsorption silica (Kieselgel 60, 70-230 mesh, 1g) and the
solution evaporated to dryness under reduced pressure. The
residue was purified by flash chromatography (Kieselgel 60,
230-400 mesh) eluting with 25% methanol in ethyl acetate.
Product-containing fractions were combined, evaporated to dryness under reduced pressure and the residue triturated with methanol to give the hygroscopic title compound (55mg, 50%). M.Pt. > 300°C

Analysis %:-

Found C, 64.52; H, 3.99; N, 19.3

C_{23}H_{16}N_{2}O_{2}.H_{2}O requires C, 64.78; H, 4.25; N, 19.7
EXAMPLE 4

4-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-7-ethoxycarbonylmethyl-6,7-dihydroimidazo[1,5,4-ef][1,5]benzodiazepin-6-one

Sodium hydride (60% dispersion in mineral oil, 60mg, 1.5mmol) was added to a stirred suspension of the title product from Example 1 (0.51g, 1.3mmol) in anhydrous dimethylformamide (10ml) under nitrogen. After being stirred under reflux for 1 hour, the reaction mixture was cooled to room temperature, whereupon ethyl bromoacetate (0.166ml, 1.5mmol) was added and the solution stirred for an additional 36 hours at room temperature.
The dimethylformamide was evaporated off under reduced pressure. The residue was diluted with water, hydrochloric acid (2M) added to give pH1, followed by sodium hydrogen carbonate to give pH8 and product extracted with ethyl acetate. The organic extract was washed three times with water, dried over magnesium sulphate and the drying agent filtered off. Pre-adsorption silica (Kieselgel 60, 70-230 mesh, 2g) was added to the filtrate which was evaporated to dryness under reduced pressure.

The residue was purified by flash chromatography (Kieselgel 60, 230-400 mesh) eluting with 2% methanol in chloroform. Product containing fractions were combined, evaporated to dryness under reduced pressure and the residue triturated with ether to give the yellow title compound (30mg, 5%).

M.Pt. 237°-239°C

Analysis%:-

Found

C₂₇H₂₂N₆O₃·3/4 H₂O requires

C, 66.08; H, 4.65; N, 16.91
C, 65.91; H, 4.81; N, 17.08
EXAMPLE 5

7-Methyl-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-6,7-dihydroimidazo[1,5,4-ef][1,5]benzodiazepin-6-one

The procedure of Example 4 was followed, using methyl iodide instead of ethyl bromoacetate, to yield the title compound, (30mg, 13%). M.Pt. 320°-323°C

Analysis%:-

Found
C₂₄H₂₈N₄O₂. 1/2 H₂O requires
C, 69.32; H, 4.50; N, 20.25
C, 69.38; H, 4.61; N, 20.23
PREPARATION

6-Amino-2,3-dihydro-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1H-[1,5]benzodiazepin-2-one

(a) 2,3-Dihydro-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-6-nitro-1H-[1,5]benzodiazepin-2-one
A mixture of 3-nitro-1,2-phenylenediamine (5g, 33mmol) and ethyl 4'-[(2-methylimidazo[4,5-c]-pyrid-1-yl)benzoylacetate (9.7g, 10mmol) in 100 ml of toluene was heated at reflux for 16 hours. After cooling, the red/orange precipitate (12g) was filtered and washed with ether.

This material was used directly without further purification in Step (b) below, m.p. 200°C (broad).

$^1$H-NMR (300MHz, DMSO-d6) 2.52 (3H, s), 4.30 (2H, s), 6.68 (1H, s), 7.27 (1H, d, J 5 Hz), 7.82 and 8.29 (each 2H, d, J 8 Hz), 8.33 (1H, d, J 5 Hz), 8.92 (1H, s) and 9.70 (1H brs).

Ethyl 4'-(2-methylimidazo[4,5-c]-pyrid-1-yl)benzoylacetate may be prepared as described in European Patent Application No. 0310386A.

(b) A solution of the product from Step (a) (10.3g, 25mmol), and stannous chloride dihydrate (28g, 125mmol) in 2M HCl (20ml), ethanol (40ml) and water (75ml) was heated at reflux for 20 minutes, then stood at ambient temperature overnight (16 hours). Precipitated solids were filtered off, then the filtrate was adjusted to pH 6 by addition of saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried (magnesium sulphate) and evaporated to a solid (3g).
Two crude batches, obtained as described above, were chromatographed on silica gel, eluting using a gradient of 2-10% of diethylamine in ethyl acetate to afford the title compound as a yellow solid (3.7g, 20%), m.p. 259-263°C.

Analysis %:-

\[ C_{22}H_{18}N_6 \cdot 0.1/2 H_2O \text{ requires: } C, 67.51; H, 4.89; N, 21.47% \]

\[ C, 67.63; H, 4.86; N, 21.56% \]
1. A compound of formula (I):

![Chemical Structure](image)

wherein $R^1$ is H or $C_1$-$C_4$ alkyl optionally substituted by a substituent selected from phenyl, halophenyl, pyridyl, ($C_1$-$C_4$ alkoxy) carbonyl and di-($C_1$-$C_4$ alkyl) amino, or is $C_2$-$C_4$ alkyl substituted by hydroxyl or by one or two $C_1$-$C_4$ alkoxy groups or is $(CH_2)_n CONR^7R^8$ where $n$ is an integer from 1 to 4 and $R^7$ and $R^8$ are each independently H or $C_1$-$C_4$ alkyl,

$R^2$ is selected from H, OH and $C_1$-$C_4$ alkyl,

$R^3$ is selected from halo and $C_1$-$C_4$ alkyl,

$R^4$ is methyl,

and $p$ is an integer from 0 to 3 and $m$ is an integer from 0 to 3;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, in which $R^1$ is H, CH$_3$ or ethoxycarbonylmethyl.

3. A compound according to claim 1 or 2, in which $R^2$ is H, OH or CH$_3$. 
4. 7-Methyl-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-6,7-dihyrimidazo[1,5,4-ef][1,5]benzodiazepin-6-one.

5. 4-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-7-ethoxycarbonylmethyl-6,7-dihyrimidazo[1,5,4-ef][1,5]benzodiazepin-6-one.

6. A composition comprising a compound according to any preceding claim and a pharmaceutical carrier or excipient.

7. A compound according to any one of claims 1 to 5 for use in medicine.

8. Use of a compound according to any one of claims 1 to 5 for making a medicament for antagonising platelet activating factor.


![Chemical Structure](image)

wherein $R^1$ is H or $C_1-C_4$ alkyl optionally substituted by a substituent selected from phenyl, halophenyl, pyridyl, $(C_1-C_4)$ alkoxy) carbonyl and di-$(C_1-C_4$ alkyl) amino, or is $C_2-C_4$ alkyl substituted by hydroxyl or by one or two $C_1-C_4$ alkoxy groups or is $(CH_2)_n CONR^7R^8$ where $n$ is an integer from 1 to 4 and $R^7$ and $R^8$ are each independently H or $C_1-C_4$ alkyl,
R² is selected from H, OH and C₁₋₄ alkyl,
R³ is selected from halo and C₁₋₄ alkyl,
R⁴ is methyl,
and p is an integer from 0 to 3 and m is an integer from 0 to 3;
or a pharmaceutically acceptable salt thereof which comprises allowing a compound of formula (II):

\[
\begin{align*}
\text{II} & \quad \text{(II)} \\
\end{align*}
\]

wherein R³, R⁴, p and m are as defined for formula (I), to react either with an acid of formula R²CO₂H and an orthoester thereof, where R² is as defined for formula (I), or with trichloroethyl chloroformate, if necessary allowing the product to react with a compound of formula R¹X wherein R¹ is an optionally substituted alkyl group as defined for formula (I) and X is Cl, Br or I,
and if necessary forming a salt of the product.
### INTERNATIONAL SEARCH REPORT

#### I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

| Int.Cl. | 5 C07D519/00; A61K31/55; //C07D519/00, 487:00, 471:00 |

#### II. FIELDS SEARCHED

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<td>C07D ; A61K</td>
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Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched:

#### III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
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<td>A</td>
<td>EP,A,0 310 386 (PFIZER) 5 April 1989 cited in the application see claims 1,16</td>
<td>1,8</td>
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<td>A</td>
<td>EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA. vol. 13, no. 1, 1978, CHATENAY-MALABRY FR pages 53 - 59; P. GENESTE ET AL.: 'Recherches en série de l'imidazo-(4,5,1-jk)- benzodiazépine- 1,4 et de l'imidazo-(1,5,4- ef)- benzodiazépine- 1,5' * see page 54, compounds 3a-e *</td>
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<td>P,A</td>
<td>EP,A,0 389 189 (PFIZER) 26 September 1990 see claims 1,10</td>
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#### IV. CERTIFICATION

- **Date of the Actual Completion of the International Search:** 14 NOVEMBER 1991
- **Date of Mailing of this International Search Report:** 2 2. 11, 91
- **International Searching Authority:** EUROPEAN PATENT OFFICE
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