(51) International Patent Classification 6:
C07D 239/34, A61K 31/505

(11) International Publication Number: WO 95/25096

(21) International Application Number: PCT/KR95/00021

(22) International Filing Date: 15 March 1995 (15.03.95)

(30) Priority Data:
1994/5089 15 March 1994 (15.03.94) KR


(72) Inventors; and


(54) Title: BENZOYLUREA DERIVATIVES AND ANTIQUEPLASTIC COMPOSITIONS CONTAINING THEM

(57) Abstract

The present invention concerns benzoylurea derivatives represented by formula (I), wherein R and R1 are the same or different, and each represents hydrogen; one or more halogen atoms selected from the group consisting of fluorine, chlorine and bromine; straight or branch chained alkoxy group having 1 to 6 carbon atoms; haloalkyl group or nitro group; R2 represents hydrogen; straight or branch chained alkyl group having 1 to 6 carbon atoms; W, X and Y are the same or different, and each represents hydrogen; one or more halogen atoms selected from the group consisting of fluorine, chlorine and bromine; straight or branch chained alkyl group having 1 to 6 carbon atoms; straight or branch chained haloalkyl group having 1 to 6 carbon atoms; or phenyl group, optionally substituted with halogen, alkyl group having 1 to 6 carbon atoms or haloalkyl group; and Z represents oxygen or sulfur atom, and pharmaceutically acceptable salts thereof.
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BENZOYLUREA DERIVATIVES AND ANTINEOPLASTIC COMPOSITIONS CONTAINING THEM

FIELD OF THE INVENTION

The present invention relates to novel benzoylurea derivatives and antineoplastic compositions containing the derivatives as the active ingredients.

BACKGROUND OF THE INVENTION

Benzoylphenylurea compounds are well known as insecticides which inhibit the chitin synthesis of insects, and some of them are commercially available. For example, chlorfluazuron is commercially available and HO-221 exhibited antineoplastic activity acting as a strong inhibitor of DNA polymerase α [USP 4,727,077; JP 142,160; EP 178,572, EP 226,104, EP 335,408]. But extremely poor solubility of HO-221 in water severely restricted the possibility of practical application in the medicinal use. Thus the effort has been focused to synthesis of derivatives with higher physiological activity and better solubility.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to novel benzoylurea derivatives, pharmaceutically acceptable salts thereof and antineoplastic compositions containing the derivatives or the salts thereof as an active ingredient. Additional features and advantages of the invention will be set forth in the description which follows, and some parts will be apparent from the description or may be learned from the practice of the invention. The advantages of the invention will be realized and attained by the compounds and processes particularly pointed out in the written description and claims.

To achieve these and other advantages and in accordance with the purpose of the invention, as embodied and broadly described, the invention provides novel benzoylurea derivatives, which have antineoplastic activity, and the pharmaceutical
uses of these derivatives. It is to be understood that both the foregoing general
description and the following detailed description are examplary and explanatory and
are intended to provide further explanation of the invention as claimed.

5 DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns benzoylurea derivatives represented by the
following formula (I);

![Chemical Structure]

wherein

R and R² are the same or different, and each represents hydrogen; one or more
halogen atoms selected from the group consisting of flourine, chlorine and
bromine; straight or branch chained alkoxy group having 1 to 6 carbon atoms;
haloalkyl group or nitro group,

R¹ represents hydrogen; straight or branch chained alkyl group having 1 to 6 carbon
atoms,

W, X and Y are the same or different, and each represents hydrogen; one or more
halogen atoms selected from the group consisting of flourine, chlorine and
bromine; straight or branch chained alkyl group having 1 to 6 carbon atoms;
straight or branch chained haloalkyl group having 1 to 6 carbon atoms; or phenyl
group, optionally substituted with halogen, alkyl group having 1 to 6 carbon
atoms or haloalkyl group,and

Z represents oxygen or sulfur atom. And pharmaceutically acceptable salts
thereof.

The preparation of the benzoylurea derivatives can be accomplished in several
ways depending on the Z of formula (I).
Benzoylurea derivatives represented by the following formula (I-a), wherein \( Z \) is an oxygen atom, can be prepared in two ways, both using benzamide of formula (II) and aniline derivative of formula (IV) respectively.

The first method as the most general method can be represented by Eq. A.

The benzamide of formula (II) is converted to substituted benzoyl isocyanate of formula (III) by reaction with oxalyl chloride or phosgene and then reacted with aniline derivatives of formula (IV) to give benzoylurea derivatives of formula (I-a) where \( R_1 \) is hydrogen atom.

Eq. A

\[
\begin{align*}
\text{Oxalyl chloride} & \quad \text{or phosgene} \\
\text{(II)} & \quad \text{(III)} \\
\end{align*}
\]

wherein \( R, R_1, R_2, X, Y \) and \( W \) are as defined above.

The solvents which can be used in the above process for preparing formula (III) include benzene, toluene, xylene, chlorobenzene, 1,2-dichloroethane, methylene chloride, ethyl acetate and tetrahydrofuran and the reaction can be terminated when hydrogen chloride is no longer produced.

To afford compound (I-a) where \( R_1 \) is hydrogen atom, benzoyl isocyanate of formula (III) is reacted with aniline derivatives of formula (IV). Wherein benzene, toluene, xylene, chlorobenzene, 1,2-dichloroethane, methylene chloride, ethyl acetate, diethyl ether or tetrahydrofuran can be used as a solvent in the above process, and the reaction can be terminated when the added aniline derivative is all consumed. This can be easily monitored by various methods, e.g. thin layer chromatography.
The products obtained in the above process can be isolated and purified by chromatography or recrystallization, as well-known in the prior art. As shown in the examples, the reaction mixture can be filtered to afford solid which can be recrystallized. The filtrate can be freed from solvent by evaporation or distillation and the residue can be recrystallized or chromatographed to afford the desired benzoylurea derivatives represented by formula (I-a) wherein R₁ is hydrogen atom. The identification of the compounds can be accomplished by nmr, ir and/or mass spectrometry.

The second method for the preparation of benzoylurea derivative (I-a) can be represented by Eq. B. The aniline derivative of formula (IV) is converted to an isocyanate of formula (V) using phosgene, and then reacted with substituted benzamide of formula (II) to give benzoylurea derivatives of formula (I-a) wherein R₁ is a hydrogen atom.

\[
\text{Eq. B.}
\]

\[
\begin{align*}
\text{(IV)} & \quad \text{phosgene} \quad \text{(V)} \\
\text{(II)} & \quad \text{(I-a), } R^1 = H
\end{align*}
\]

wherein R, R₁, R₂, X, Y and W are as defined above.

In the above preparation, ethyl acetate, tetrahydrofuran, benzene, toluene, chlorobenzene, xylene, 1,2-dichloroethane or methylene chloride can be used as a solvent. The monitoring of the reaction and identification of the products can be accomplished as the first method.

Also benzoylurea derivative of the following formula (I-b), wherein Z is a sulfur atom, can be prepared in three ways.
The first method as the most general method can be represented by Eq. C. Reaction of substituted benzoyl chloride derivative of formula (VI) with potassium thiocyanate affords benzoyl isothiocyanate of formula (VII) and then reaction with aniline derivative of formula (IV) gives benzoylurea derivative of formula (I-b) wherein \( R^1 \) is hydrogen atom.

**Eq. C.**

\[
\begin{align*}
\text{Ar}^2 \text{C}=\text{Cl} & \quad \text{potassium thiocyanate} \quad \text{Ar}^1 \text{C}=\text{N}=\text{C}=\text{S} \\
(\text{VI}) & \quad (\text{VII})
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 \text{Ar}^2 \text{O} & \quad \text{W} \text{X} \text{Y} \\
\text{R}^2 & \quad \text{R}^1 \text{R}^3 \text{R}^4 \text{R}^5
\end{align*}
\]

(IV) \quad (I-b), \quad R^1 = H

wherein \( R, R^1, R^2, X, Y \) and \( W \) are as defined above.

The process to obtain compound (VII) from compound (VI) in the above Eq. C is a known process by the prior art and the process is performed with compound (VI) and potassium thiocyanate in a mixture of organic solvent and water. The organic solvent include methylene chloride, benzene, toluene, xylene, chlorobenzene or 1,2-dichlorethane with various phase transfer catalyst including ammonium salts, e.g. benzyltriethylammonium chloride. The reaction is terminated when the starting material of formula (VI) is all consumed and can be easily monitored by thin layer chromatography or gas chromatography.

The desired compound (I-b) where \( R^1 \) is hydrogen atom is obtained by the reaction of benzoyl isothiocyanate of formula (VII) with aniline derivative of formula (IV). Wherein toluene, xylene, chlorobenzene, 1,2-dichlorehane, methylene chloride, ethyl acetate, diethyl ether or tetrahydrofuran can be used as the solvent. The reaction is terminated when the aniline derivative of formula (IV) is all consumed and can be easily monitored by thin layer chromatography or gas chromatography.
The products obtained in the above process can be isolated and purified by the methods known in the prior art. The reaction mixture can be filtered to afford solid which can be recrystallized. The filtrate can be freed from solvent by evaporation or distillation and the residue can be recrystallized or chromatographed to afford the desired benzoylurea derivatives of formula (I-b) \((R^1 = H)\). The identification of the compounds can be accomplished by nmr, ir and/or mass spectrometry.

The second method for the preparation of benzoylurea derivative (I-b) can be represented by Eq. D. The substituted benzamide of formula (II) is converted to benzoyl isothiocyanate of formula (VII) by treatment with thiophosgene, and then to desired benzoylurea derivative I-b \((R^1 = H)\) by addition of aniline derivative of formula (IV).

**Eq. D.**

\[
\begin{align*}
\text{O} & \quad \text{Thiophosgene} & \quad \text{O} \\
\text{C-NH}_2 & \quad \rightarrow & \quad \text{C-N=S} \\
\text{(II)} & \quad & \quad \text{(VII)}
\end{align*}
\]

wherein \(R, R^1, R^2, X, Y,\) and \(W\) are as defined above.

In the preparation of compound (VII) from compound (II), benzene, toluene, xylene, chlorobenzene, 1,2-dichloroethane, methylene chloride, ethyl acetate or tetrahydrofuran can be used as the solvent and the reaction can be terminated when evolution of hydrogen chloride is ceased.

The preparation of benzoylurea derivative (I-b) \((R^1 = H)\) from compound (VII) can be accomplished as described for the above Eq. C, and termination of the reaction and identification of the product can also be accomplished as described for the above Eq. C.
The third method for the preparation of benzoylurea derivative (I-b) can be represented by Eq. E. The substituted aniline derivative of formula (IV) is converted to isothiocyanate of formula (VIII) by treatment with thiophosgene, and then to desired benzoylurea derivative (I-b) (R¹ = H) by addition of substituted benzamide derivative of formula (II).

**Eq. E.**

\[
\begin{align*}
\text{NH}_2 & \quad \text{W} \quad X \\
\text{R}^2 & \quad \text{Y} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{C=N} \\
\text{R} & \quad \text{W} \\
\text{Y} & \quad \text{X} \\
\text{R} & \quad \text{NH}_2
\end{align*}
\]

**(IV)**

\[
\begin{align*}
\text{S=C=N} & \quad \text{W} \\
\text{R} & \quad \text{X} \\
\text{Y} & \quad \text{N} \\
\text{R} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{Y} \\
\text{W} & \quad \text{X}
\end{align*}
\]

**(VIII)**

wherein R, R¹, R², X, Y and W are as defined above.

In the preparation of compound (VIII) from compound (IV) by treatment with thiophosgene, ethyl acetate, tetrahydrofuran, benzene, toluene, chlorobenzene, xylene, 1,2-dichloroethane or methylene chloride can be used as the solvent and the reaction can be terminated when evolution of hydrogen chloride is ceased.

In the reaction of isothiocyanate (VIII) with benzamide (II) toluene, xylene, chlorobenzene or ethyl acetate can be used as the solvent and the reaction can be terminated when compound (VIII) is all consumed.

The preparation of benzoylurea derivative (I-b) (R¹ = H) from compound (VII) can be accomplished as described for the above Eq. C, and termination of the reaction and identification of the product can also be accomplished as described for the above Eq. C.

The benzoylurea derivatives (I) (R₁ = H) prepared by the methods described in Eqs. A, B, C, D and E can be converted to benzoylurea derivatives (I) (R¹ = alkyl group) by reaction with various alkylating agents in the presence of base. The
solvents which can be used in the reaction include acetonitrile, N, N-dimethylformamide and dimethyl sulfoxide, and the bases which can be used include hydroxides or carbonates of alkaline metals and alkaline earth metals, and also tertiary amines.

The end of the reaction is when all the benzoylurea derivatives (I) \((R^1 = H)\) is consumed which can be easily monitored by thin layer chromatography or gas chromatography.

The representative examples of benzoylurea derivatives of formula (I) are given in the Table 1 and these do not restrict the scope of the present invention.
$$\text{R}^2 \text{O} \text{-NH-} \text{R}^1 \text{O} \text{-W} \text{-Y} \text{-X} \text{N} \text{-Z} \text{R}$$

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The preparation of aniline derivatives of the formula (IV) used as the starting material in the preparation of the desired benzoyleurea derivatives of formula (I) is given below by Eq. F. The hydroxypyrazole derivatives of formula (IX) are reacted with halonitrobenzene derivatives of formula (X) to afford a novel derivatives of formula (XI). The pyrazoleoxy derivatives thus obtained was reduced to afford the aniniline derivatives of formula (IV).

\[
\begin{align*}
  \text{Eq. F} \\
  \text{(IX)} \xrightarrow{\text{O}_2\text{N}^-} \text{(XI)} \\
\end{align*}
\]

25

\[
\begin{align*}
  \text{Hydrogenation} \xrightarrow{\text{NH}_2^-} \\
  \text{(IV)}
\end{align*}
\]

wherein R, R¹, R², X, Y and W are as defined above.

In the reaction of hydroxypyrazole (IX) and halonitrobenzene (X), the solvent can be chosen among N,N-dimethylformamide, dimethylsulfoxide, acetonitrile, tetrahydrofuran, etc.. The bases which can be used include hydroxides, bicarbonates and carbonates of alkali metals and alkaline earth metals and tertiary amines. The
progress of the reaction can be easily monitored by thin layer chromatography, gas chromatography, etc..

The reduction of nitrobenzene (XI) to aniline derivatives (IV) can be accomplished by catalytic hydrogenation using nickel or palladium catalyst, or by acid and metals (iron, zinc, etc.). The solvents which can be used include water, or preferably primary alcohols, e.g., methanol or ethanol. The progress of the reaction can be easily monitored by thin layer chromatography, gas chromatography, etc.. The recovery of the product can be accomplished by filtration and removal of the solvent followed by recrystallization or chromatography. The identification of the product can be accomplished by NMR, IR, mass spectrometry, etc..

The aniline derivatives (IV) prepared according to Eq. F can be classified into three classes depending on substitution pattern of oxygen on pyrazoles.

\[
\begin{align*}
\text{NH}_2 & \text{O} \quad \text{NH}_2 & \text{O} \\
R & \text{Y} & R & \text{Y} \\
W & X & W & X
\end{align*}
\]

(IV-a)

(IV-b)

(IV-c)

The compounds (IV-a) have been prepared from 5-hydroxy pyrazole derivatives (IX) wherein the hydroxy group is on 5-position by the prior art (Korean Patent No.75,599).

The compounds (IV-b) and (IV-c) are novel compound in accordance with the present invention can be prepared from pyrazole derivatives (IX) wherein the hydroxy group is on 3- and 4-positions, respectively. Also pyrazole derivatives (IX) can be easily prepared by the prior arts (J. Heterocyclic Chem. 1993, 30, 49 and J. Heterocyclic Chem. 1991, 28, 1971, respectively).

The representative examples of nitrobenzene derivatives of formula (XI) and aniline derivatives of formula (IV) are given in the Table 2 and Table 3, respectively. And these do not restrict the scope of the present invention.
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<td>5-CF₃</td>
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</table>
The following examples are sample of practical synthesis and the scope of the present invention is not restricted by them.

**EXAMPLE 1.**

**N-[[[3,5-Dichloro-4-(1-methyl-3-trifluoromethyl-5-pyrazolyl)oxyphenyl]amino]carbonyl]-2-nitrobenzamide**

2-Nitrobenzamide (0.3 g, 1.8 mmol) in 8 mL of 1,2-dichloroethane was treated with oxayl chloride (0.23 g, 1.8 mmol) for 20 h at 100 °C followed by addition of 3,5-dichloro-4-O-(1-methyl-3-trifluoromethyl-5-pyrazolyl)aniline (0.59 g, 1.8 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1 : 5) to afford the desired compound in a 70% yield (0.654 g) as a solid.

m.p. : 225 °C

$^1$H NMR (acetone-$d_6$) : δ 3.9 (s, 3H), 5.8 (s, 1H), 7.8 - 8.3 (m, 6H), 10.5 (s, 1H), 10.7 (s, 1H).

**EXAMPLE 2.**

**N-[[[3,5-Dichloro-4-(1-t-butyl-3-trifluoromethyl-5-pyrazolyl)oxyphenyl]amino]carbonyl]-2-nitrobenzamide**

2-Nitrobenzamide (0.3 g, 1.8 mmol) in 8 mL of 1,2-dichloroethane was treated with oxayl chloride (0.23 g, 1.8 mmol) for 20 h at 100 °C followed by addition of 3,5-dichloro-4-(1-t-butyl-3-trifluoromethyl-5-pyrazolyl)oxyaniline (0.66 g, 1.8 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:5) to afford the desired compound in a 65% yield (0.657 g) as a solid.

m.p. : 228 - 229 °C

$^1$H NMR (acetone-$d_6$) : δ 1.8 (s, 9H), 5.8 (s, 1H), 7.8 - 8.3 (m, 6H), 10.5 (s, 1H), 10.7 (s, 1H).

**EXAMPLE 3**
N-[[3-Chloro-4-(1-methyl-3-trifluoromethyl-5-pyrazoyl)oxyphenyl] amino]carbonyl]-2-nitrobenzamide

2-Nitrobenzamide (0.1 g, 0.6 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.07 g, 0.6 mmol) for 20 h at 100 °C followed by addition of 3-chloro-4-(1-methyl-3-trifluoromethyl-5-pyrazoyl)oxyaniline (0.17 g, 0.6 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 64 % yield (0.185 g) as a solid.

m.p. : 205 °C

$^1$H NMR (acetone- $d_6$) : δ 3.9 (s, 3H), 5.9 (s, 1H), 7.4 - 8.3 (m, 7H), 10.4 (s, 1H), 10.6 (s, 1H).

EXAMPLE 4

N-[[3-Chloro-4-(1-t-butyl-3-trifluoromethyl-5-pyrazoyl)oxyphenyl] amino]carbonyl]-2-nitrobenzamide

2-Nitrobenzamide (0.1 g, 0.6 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.07g, 0.6 mmol) for 20 h at 100 °C followed by addition of 3-chloro-4-(1-t-butyl-3-trifluoromethyl-5-pyrazoyl)oxyaniline (0.2 g, 0.6 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 66 % yield (0.208 g) as a solid.

m.p. : 195 - 197 °C

$^1$H NMR (acetone- $d_6$) : δ 1.8 (s, 9H), 5.9 (s, 1H), 7.4 - 8.3 (m, 7H), 10.4 (s, 1H), 10.6 (s, 1H).

EXAMPLE 5

N-[[3-Trifluoromethyl-4-(1-phenyl-3-trifluoromethyl-5-pyrazoyl) oxyphenyl] aminocarbonyl]-2-nitrobenzamide

2-Nitrobenzamide (0.1 g, 0.6 mmol) in 8 mL of 1,2-dichloroethane was treated
with oxalyl chloride (0.07 g, 0.6 mmol) for 20 h at 100 °C followed by addition of 3-trifluoromethyl-4-(1-phenyl-3-trifluoromethyl-5-pyrazoyloxyaniline (0.23 g, 0.6 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate: hexane = 1:4) to afford the desired compound in a 62% yield (0.215 g) as a solid.

m.p.: 153 - 154 °C

$^1$H NMR (acetone-$d_6$): δ 6.3 (s, 1H), 7.4 - 8.3 (m, 12H), 10.4 (s, 1H), 10.7 (s, 1H).

**EXAMPLE 6**

$N\-[[2,5\text{-Dichloro}\-4\-(1\text{-methyl}\-3\text{-trifluoromethyl}\-5\text{-pyrazoyloxyphenyl}]\text{aminocarboxyl}]-2\text{-nitrobenzamide}$

2-Nitrobenzamide (0.1 g, 0.6 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.07 g, 0.6 mmol) for 20 h at 100 °C followed by addition of 2,5-dichloro-4-(1-methyl-3-trifluoromethyl-5-pyrazoyloxyaniline (0.19 g, 0.6 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate: hexane = 1:4) to afford the desired compound in a 70% yield (0.217 g) as a solid.

m.p.: 208 - 209 °C

$^1$H NMR (acetone-$d_6$): δ 3.9 (s, 3H), 6.1 (s, 1H), 7.7 - 8.7 (m, 6H), 10.6 (s, 1H), 11.2 (s, 1H).

**EXAMPLE 7**

$N\-[[3\text{-Chloro}\-4\-(1\text{-phenyl}\-3\text{-trifluoromethyl}\-5\text{-pyrazoyloxyphenyl}]\text{aminocarboxyl}]-2\text{-nitrobenzamide}$

2-Nitrobenzamide (0.1 g, 0.6 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.07 g, 0.6 mmol) for 20 h at 100 °C followed by addition of 3-chloro-4-(1-phenyl-3-trifluoromethyl-5-pyrazoyloxyaniline (0.21 g, 0.6 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel,
ethyl acetate : hexane = 1:3) to afford the desired compound in a 74% yield (0.185 g) as a solid.

m.p.: 212 - 214 °C

^1H NMR (acetone-\textit{d}_6): \delta 6.1 (s, 1H), 7.5 - 8.3 (m, 12H), 10.4 (s, 1H), 10.6 (s, 1H).

**EXAMPLE 8**

\textit{N}-(\textit{[3,5-Dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyphenyl] amino} carbonyl)-2-nitrobenzamide

2-Nitrobenzamide (0.1 g, 0.6 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.07 g, 0.6 mmol) for 20 h at 100 °C followed by addition of 3,5-dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.19 g, 0.6 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 73% yield (0.227 g) as a solid.

m.p.: 253 °C

^1H NMR (acetone-\textit{d}_6): \delta 3.8 (s, 3H), 7.3 (s, 1H), 7.8 - 8.3 (m, 7H), 10.4 (s, 1H), 10.6 (s, 1H).

**EXAMPLE 9**

\textit{N}-(\textit{[3-Chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyphenyl] amino} carbonyl)-2-nitrobenzamide

2-Nitrobenzamide (0.1 g, 0.6 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.07 g, 0.6 mmol) for 20 h at 100 °C followed by addition of 3-chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.17 g, 0.6 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 71% yield (0.205 g) as a solid.

m.p.: 201 °C

^1H NMR (acetone-\textit{d}_6): \delta 3.9 (s, 3H), 7.1 - 8.3 (m, 8H), 10.4 (s, 1H), 10.5 (s, 1H).
EXAMPLE 10

N-[[3-Chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazolyl)oxyphenyl]amino]carbonyl]-2,6-difluorobenzamide

2,6-Difluorobenzamide (0.16 g, 1.03 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.13 g, 1.03 mmol) for 20 h at 100 °C followed by addition of 3-chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazolyl)oxyanilino (0.3 g, 1.03 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1: 3) to afford the desired compound in a 71% yield (0.34 g) as a solid.

m.p. : 195 °C

$^1$H NMR (acetone-$d_6$) : δ 4.0 (s, 3H), 6.8 - 8.1 (m, 7H), 10.7 (s, 1H), 10.8 (s, 1H).

EXAMPLE 11

N-[[3,5-Dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazolyl)oxyphenyl]amino]carbonyl]-2,6-difluorobenzamide

2,6-Difluorobenzamide (0.16 g, 1.03 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.13 g, 1.03 mmol) for 20 h at 100 °C followed by addition of 3,5-dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazolyl)oxyanilino (0.33 g, 1.03 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was recrystallized (ethyl acetate+hexane) to afford the desired compound in a 68% yield (0.355 g) as a solid.

m.p. : 212 - 214 °C

$^1$H NMR (acetone-$d_6$) : δ 3.9 (s, 3H), 6.9 - 7.9 (m, 6H), 10.3 (s, 1H), 10.6 (s, 1H).

EXAMPLE 12

N-[[3,5-Dichloro-4-(1-methyl-5-trifluoromethyl-3-pyrazolyl)oxyphenyl]amino]carbonyl]-2,6-difluorobenzamide

2,6-Difluorobenzamide (0.12 g, 0.76 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.09 g, 0.76 mmol) for 20 h at 100 °C followed by
addition of 3,5-dichloro-4-(1-methyl-5-trifluoromethyl-3-pyrazoyl)oxyaniline (0.25 g, 0.76 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was recrystallized (ethyl acetate + hexane) to afford the desired compound in a 71 % yield (0.276 g) as a solid.

m.p. : 224 °C

$^1$H NMR (acetone - $d_6$) : $\delta$ 3.9 (s, 3H), 6.1 (s, 1H), 7.0 - 7.5 (m, 5H), 10.0 (s, 1H), 10.7 (s, 1H).

EXAMPLE 13

$N$-[[3-Chloro-4-(1-methyl-5-trifluoromethyl-3-pyrazoyl)oxyphenyl]amino]carbonyl]-2,6-difluorobenzamide

2,6-Difluorobenzamide (0.25 g, 1.59 mmol) in 8 mL of 1,2-dichloroethane was treated with oxalyl chloride (0.20 g, 1.59 mmol) for 20 h at 100 °C followed by addition of 3-chloro-4-(1-methyl-5-trifluoromethyl-3-pyrazoyl)oxyaniline (0.46 g, 1.59 mmol) after cooling and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was recrystallized (ethyl acetate + hexane) to afford the desired compound in a 69 % yield (0.52 g) as a solid.

m.p. : 155 - 157 °C

$^1$H NMR (acetone - $d_6$) : $\delta$ 3.8 (s, 3H), 6.1 (s, 1H), 6.9 - 7.8 (m, 5H), 10.1 (s, 1H), 10.5 (s, 1H).

EXAMPLE 14

$N$-[[3-Chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyphenyl]amino]thiocyoxymethyl]-2,6-difluorobenzamide

2,6-Difluorobenzoyl isothiocyanate (0.14 g, 0.70 mmol) in 5 mL of methylene chloride was treated with 3-chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.20 g, 0.70 mmol) for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1: 3) to afford the desired compound in a 73 % yield (0.25 g).
as a solid.

m.p. : 166 °C

\(^1\)H NMR (acetone-\(d_6\)) : δ 3.9 (s, 3H), 7.2 - 8.2 (m, 7H), 11.1 (s, 1H), 13.0 (s, 1H).

**EXAMPLE 15**

\(N\)-[[3,5-Dichloro-4-\((1\text{-methyl-3-trifluoromethyl-4-pyrazoyl)}\text{oxyphenyl}\)] amino]thioxymethyl]-2,6-difluorobenzamide

2,6-Difluorobenzoyl isothiocyanate (0.14 g, 0.70 mmol) in 5 mL of methylene chloride was treated with 3,5-dichloro-4-\((1\text{-methyl-3-trifluoromethyl-4-pyrazoyl)}\text{oxyaniline (0.23 g, 0.70 mmol)} for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1: 3) to afford the desired compound in a 74 % yield (0.27 g) as a solid.

m.p. : 158 °C

\(^1\)H NMR (acetone-\(d_6\)) : δ 3.9 (s, 3H), 7.2 - 8.2 (m, 7H), 11.2 (s, 1H), 13.0 (s, 1H).

**EXAMPLE 16**

\(N\)-[[3-Chloro-4-\((1\text{-phenyl-3-trifluoromethyl-4-pyrazoyl)}\text{oxyphenyl}\)] amino]thioxymethyl]-2,6-difluorobenzamide

2,6-Difluorobenzoyl isothiocyanate (0.1 g, 0.50 mmol) in 5 mL of methylene chloride was treated with 3-chloro-4-\((1\text{-phenyl-3-trifluoromethyl-4-pyrazoyl)}\text{oxyaniline (0.17 g, 0.50 mmol)} for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1: 3) to afford the desired compound in a 79 % yield (0.218 g) as a solid.

m.p. : 140 -142 °C

\(^1\)H NMR (acetone-\(d_6\)) : δ 7.1 - 8.6 (m, 12H), 11.0 (s, 1H), 11.1 (s, 1H).

**EXAMPLE 17**

\(N\)-[[3,5-Dichloro-4-\((1\text{-phenyl-3-trifluoromethyl-4-pyrazoyl)}\text{oxyphenyl}\)] amino]thioxymethyl]-2,6-difluorobenzamide

2,6-Difluorobenzoyl isothiocyanate (0.1 g, 0.50 mmol) in 5 mL of methylene
chloride was treated with 3,5-dichloro-4-(1-phenyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.19 g, 0.50 mmol) for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 74% yield (0.217 g) as a solid.

m.p.: 156 °C

^1^H NMR (acetone-^d_6): δ 7.2 - 8.2 (m, 11H), 11.2 (s, 1H), 13.0 (s, 1H).

EXAMPLE 18

N-[[3-Chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyphenyl]amino]thioxymethyl]-2-nitrobenzamide

2-Nitrobenzoyl isothiocyanate (0.1 g, 0.47 mmol) in 5 mL of acetone was treated with 3-chloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.13 g, 0.47 mmol) for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 80% yield (0.19 g) as a solid.

m.p.: 188 °C

^1^H NMR (acetone-^d_6): δ 3.9 (s, 3H), 7.0 - 8.2 (m, 8H), 11.1 (s, 1H), 12.5 (s, 1H).

EXAMPLE 19

N-[[3,5-Dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyphenyl]amino]thioxymethyl]-2-nitrobenzamide

2-Nitrobenzoyl isothiocyanate (0.1 g, 0.47 mmol) in 5 mL of acetone was treated with 3,5-dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.15 g, 0.47 mmol) for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 83% yield (0.21 g) as a solid.

m.p.: 219 - 220 °C

^1^H NMR (acetone-^d_6): δ 3.9 (s, 3H), 7.3 (s, 1H), 7.7 - 8.7 (m, 6H), 11.2 (s, 1H), 12.8 (s, 1H).

EXAMPLE 20
2-Nitrobenzoyl isothiocyanate (0.06 g, 0.28 mmol) in 5 mL of acetone was treated with 3-chloro-4-(1-phenyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.1 g, 0.28 mmol) for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 80 % yield (0.127 g) as a solid. M.p. : 200 - 202 °C

\[ ^1\text{H} \text{NMR (acetone-}d_6\text{)} : \delta 7.2 - 8.6 \text{ (m, 13H), 11.1 (s, 1H), 12.4 (s, 1H).} \]

**EXAMPLE 21**

2-Nitrobenzoyl isothiocyanate (0.05 g, 0.26 mmol) in 5 mL of acetone was treated with 3,5-dichloro-4-(1-phenyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline (0.1 g, 0.26 mmol) for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to afford the desired compound in a 82 % yield (0.126 g) as a solid. M.p. : 198 - 200 °C

\[ ^1\text{H} \text{NMR (acetone-}d_6\text{)} : \delta 7.2 - 8.3 \text{ (m, 12H), 11.2 (s, 1H), 12.6 (s, 1H).} \]

**EXAMPLE 22**

2-Nitrobenzoyl isothiocyanate (0.1 g, 0.47 mmol) in 5 mL of acetone was treated with 3,5-dichloro-4-(1-methyl-5-trifluoromethyl-3-pyrazoyl)oxyaniline (0.15 g, 0.47 mmol) for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, ethyl acetate : hexane = 1:4) to afford the desired compound in a 78 % yield (0.198 g) as a solid. M.p. : 199 - 200 °C

\[ ^1\text{H} \text{NMR (acetone-}d_6\text{)} : \delta 3.9 \text{ (s, 3H), 6.2 (s, 1H), 7.6 - 8.2 \text{ (m, 6H), 11.1 (s, 1H), 12.5} \]
EXAMPLE 23

3,5-Dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxy-1-nitrobenzene

A solution of 1-methyl-3-trifluoromethyl-4-hydroxypyrrole (1 g, 6.02 mmol),
3,4,5-trichloro-1-nitrobenzene (1.36 g, 6.02 mmol), and potassium carbonate (1.24 g,
9.03 mmol) in 8 mL of dimethylformamide was stirred at 90 °C for 3 h. The
reaction mixture was poured into water and extracted with ethyl acetate. The organic
layer was washed with water and saturated brine, dried over MgSO₄ and evaporated.
The residue was purified by washing with hexane to give the desired compound in a
83 % yield (1.8 g) as a solid.
m.p. : 163 - 164 °C

¹H NMR (CDCl₃) : δ 3.9 (s, 3H), 7.0 (s, 1H), 8.2 (s, 2H).

EXAMPLE 24

3-Chloro-4-(1-methyl-5-trifluoromethyl-3-pyrazoyl)oxy-1-nitrobenzene

A solution of 1-methyl-5-trifluoromethyl-3-hydroxypyrrole (3 g, 18.1
mmol), 3,4-dichloro-1-nitrobenzene (3.47 g, 18.1 mmol), and potassium carbonate
(3.74 g, 27.1 mmol) in 10 mL of dimethylformamide was stirred at 90 °C for 4 h.
The reaction mixture was poured into water and extracted with ethyl acetate. The
organic layer was washed with water and saturated brine, dried over MgSO₄ and
evaporated. The residue was chromatographed (silica gel, ethyl acetate : hexane = 1:
9) to give the desired compound in a 91 % yield (5.3 g) as an oil.

¹H NMR (CDCl₃) : δ 3.9 (s, 3H), 6.2 (s, 1H), 7.3 (d, 1H), 8.0 - 8.3 (m, 2H).

EXAMPLE 25

3,5-Dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxyaniline

A solution of 3,5-dichloro-4-(1-methyl-3-trifluoromethyl-4-pyrazoyl)oxy-1-nitrobenzene (1 g, 2.81 mmol) and raney nickel (0.05 g) in methanol (30 ml) was
stirred under hydrogen gas at 90 °C for 4 h. The raney nickel was removed by
filtration, and the solvent was evaporated. The residue was chromatographed (silica
gel, ethyl acetate : hexane = 1:5) to give the desired compound in a 89% yield (0.82 g) as a solid.
mp : 136 - 138 °C

$^1$H NMR (acetone-$d_6$) : δ 3.9 (s, 3H), 5.2 (s, 2H), 6.9 (s, 2H), 7.2 (s, 1H).

**EXAMPLE 26**

3-Chloro-4-(1-methyl-5-trifluoromethyl-3-pyrazoyl)oxyaniline

A solution of 3-chloro-4-(1-methyl-5-trifluoromethyl-3-pyrazoyl) oxynitrobenzene (1 g, 3.11 mmol) and raney nickel (0.05 g) in methanol (30 ml) was stirred under hydrogen gas at 90 °C for 4 h. The raney nickel was removed by filtration, and the solvent was evaporated. The residue was chromatographed (silica gel, ethyl acetate : hexane = 1:3) to give the desired compound in a 97% yield (0.88 g) as a solid.
mp : 65 - 67 °C

$^1$H NMR (CDCl$_3$) : δ 3.7 (s, 2H), 3.8 (s, 3H), 6.0 (s, 1H), 6.4 - 7.1 (m, 3H).

The antineoplastic activity of the benzoyleurea derivatives of the present invention, exhibiting excellent in vitro towards human cancer cell lines, were determined as shown in the following procedures A and B.

A. Culture of Cancer Cell Lines

The human tumor cell lines of A-549 (lung carcinoma), SK-OV-3 (adeno carcinoma, ovary malignant ascites), SK-MEL-2 (malignant melanoma, metastasis to skin of thigh), XF 498 (central nerve system tumor) and HCT 15 (colon adenocarcinoma) were used. They were obtained from the National Cancer Institute (NCI) of USA and culture at Korea Research Institute of Chemical Technology. The cell culture was done with RPMI 1460 media, fortified with 5% bovine fetal serum in an incubator at 37 °C under 5% CO$_2$ atmosphere. The transfer of cell lines were once in three to four days, and detachment of cells from culture flask was accomplished by 0.25% trypsin and 3 mM trans-1,2-diaminocyclohexane-$N,N,N,N$-tetraacetic acid in phosphate buffered saline.

B. Determination of Anti-tumor Activity
Sulforhodamine B (SRB) assay method, developed to determine in vitro anti-tumor activity at NCI of USA in 1989, was used in the test. The cells in culture were detached and inoculated to 96-well microplate (Falcon Co.) so that the number of cells for each well is the following: $5 \times 10^3$ (A 549, HCT 15), $1 \times 10^4$ (SK-MEL-2, XF 498), $2 \times 10^4$ (SK-OV-3). The inoculated cells were incubated in an CO$_2$ incubator for 24 h and the culture media was removed by aspirator and 100 µl of culture media containing test compounds was added to the wells. The dose of the test compounds were in log scale. Six concentrations of the test compounds and three wells for each concentration were used. Dimethylsulfoxide was used to dissolve the test compounds when necessary and the solutions were filtered through 0.22 µm filter to maintain sterility before use. The microplate was further incubated for 48 h. After incubation, the culture media was removed and the cells were fastened by the addition of 100 µl of 10 % trichloroacetic acid and standing for 1 h at 4 ºC. Then the plate was washed with water five to six times and dried at room temperature. The cells were dyed for 30 min by addition of 100 µl of 0.4 % SRB in 1 % acetic acid to each well, and washed five to six times with 1 % acetic acid to remove SRB not bound to the cells. The plate was again dried at room temperature followed by addition of 100 µl of unbuffered 10mM Trisma base solution. The SRB was extracted by using titer plate shaker for 10 min and the absorbancy at 520 nm was measured with microplate reader. To determine the anti-tumor activity of the test compounds toward tumor cells, $T_z$ (number of cells before the addition of the test compounds), $C$ (number of cells after 48 h incubation without test compounds), and $T$ (number of cells after 48 h incubation with test compounds) were determined. The anti-tumor activity was determined by the following equation (1) or (2).
If \[ T_{z} > T, \quad \frac{(T-T_{z})}{(C-T_{z})} \times 100 \] (1)

If \[ T_{z} < T, \quad \frac{(T-T_{z})}{(T_{z})} \times 100 \] (2)

The values thus obtained were applied to Lotus program using data regression to give \( ED_{50} \), the concentration where the test compounds inhibit the growth of the tumor cells.

Some of the result of the above in vitro tests are compared to Cisplatin (Sigma Tau Co, Italy) and given in the following Table 4.

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<tr>
<th>Compound No.</th>
<th>( ED_{50} (\mu g / ml) )</th>
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<td>A-549</td>
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<tr>
<td>Cisplatin*</td>
<td>0.7754</td>
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* Italy, Sigmatau

The result shows the benzoylurea derivatives containing pyrazoles of the present invention have excellent activities toward human tumor cell lines compared to...
well-known Cisplatin.
WHAT IS CLAIMED IS:

1. A compound of formula (I), useful as anti-tumor agents:

   \[ \text{structure image} \quad (I) \]

   wherein

   R and R\(^2\) are the same or different, and each represents hydrogen; one or more halogen atoms selected from the group consisting of fluorine, chlorine and bromine; straight or branch chained alkoxy group having 1 to 6 carbon atoms; haloalkyl group or nitro group,

   R\(^1\) represents hydrogen; straight or branch chained alkyl group having 1 to 6 carbon atoms,

   W, X and Y are the same or different, and each represents hydrogen; one or more halogen atoms selected from the group consisting of fluorine, chlorine and bromine; straight or branch chained alkyl group having 1 to 6 carbon atoms; straight or branch chained haloalkyl group having 1 to 6 carbon atoms; or phenyl group, optionally substituted with halogen, alkyl group having 1 to 6 carbon atoms or haloalkyl group, and

   Z represents oxygen or sulfur atom. And pharmaceutically acceptable salts thereof.

2. The compound according to claim 1, wherein

   R and R\(^2\) are the same or different, and each represents hydrogen; one or more halogen atoms selected from the group consisting of fluorine and chlorine; haloalkyl group; or nitro group,

   R\(^1\) represents hydrogen; straight or branch chained alkyl group having 1 to 6
carbon atoms,

W, X and Y are the same or different, and each represents hydrogen; one or more halogen atoms selected from the group consisting of fluorine, chlorine and bromine; straight or branch chained alkyl group having 1 to 6 carbon atoms; straight or branch chained haloalkyl group having 1 to 6 carbon atoms; or phenyl group,

Z represents oxygen or sulfur atom, and pharmaceutically acceptable salts thereof.

3. The compound according to claim 1, wherein

R represents 2-nitro or 2,6-dichloro

R² represents hydrogen; one or more halogen atoms selected from the group consisting of fluorine, chlorine and bromine; or trifluoromethyl group,

R¹ represents hydrogen,

X represents methyl, t-butyl or phenyl group,

W represents hydrogen,

Y represents methyl or trifluoromethyl group,

Z represents oxygen or sulfur atom, and pharmaceutically acceptable salts thereof.

4. A compound of formula (IV-b) useful as starting materials for synthesis of a compound (I) as claimed in claim 1.

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} & \quad \text{W} \\
\text{R}^2 & \quad \text{N} & \quad \text{Y} \\
\text{X} & \quad & \\
\end{align*}
\]

(IVb)

wherein R², X, Y and W are as defined in claim 1.

5. The compound according to claim 4, wherein

R² represents hydrogen; one or more halogen atoms selected from the group
consisting of flourine, chlorine and bromine; or trifluoromethyl group,
X represents methyl, t-butyl or phenyl group,
W represents hydrogen,
Y represents methyl or trifluoromethyl group,

6. A compound of formula (IV-c) useful as starting materials for synthesis of a compound (I) as claimed in claim 1.

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} \\
R^2 & \quad W \\
& \quad N \\
& \quad N \\
& \quad X
\end{align*}
\]

( IV-c )

wherein \( R_2, X, Y, \) and \( W \) are as defined in claim 1.

7. The compound according to claim 6, wherein
\( R_2 \) represents hydrogen; one or more halogen atoms selected from the group consisting of flourine, chlorine and bromine; or trifluoromethyl group,
X represents methyl, t-butyl or phenyl group,
W represents hydrogen,
Y represents methyl or trifluoromethyl group,
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC\textsuperscript{6}: C 07 D 239/34; A 61 K 31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC\textsuperscript{6}: C 07 D 239/34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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| A        | EP 0 545 441 A1 (ISHIRA SANGYO KAISHA, LTD.)
09 June 1993 (09.06.93), claims 1-4, 6-9. | 1-6                  |
| A        | EP 0 413 977 A2 (ISHIRA SANGYO KAISHA, LTD.)
27 February 1991 (27.02.91); claims 1-7, 11. | 1-6                  |
| A        | EP 0 262 560 A2 (ISHIRA SANGYO KAISHA, LTD.)
06 April 1988 (06.04.88), claims 1, 2. | 1-6                  |

Further documents are listed in the continuation of Box C.

See patent family annex.

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  "P" document published prior to the international filing date but later than the priority date claimed

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- Document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- Document member of the same patent family

Date of the actual completion of the international search
29 May 1995 (29.05.95)

Date of mailing of the international search report
14 June 1995 (14.06.95)

Name and mailing address of the ISA/AT
AUSTRIAN PATENT OFFICE
Kohlmarkt 8-10
A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer
Brus e.h.
Telephone No. 1/5337058/32

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