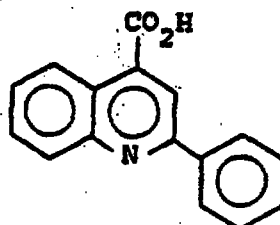


Description

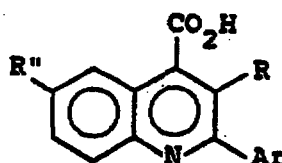
This invention relates to tumor inhibiting pharmaceutical compositions, there use for the manufacture of a medicament for inhibiting the growth of mammalian tumors, and phenylquinolinecarboxylic acids and derivatives thereof useful in such compositions and methods.

Cinchophen, 2-phenyl-4-quinoline carboxylic acid, has been known for many years and has been described as being useful as an antirheumatic and in the treatment of gout. Cinchophen has the formula:



Many cinchophen and cinchoninic acid derivatives have been prepared in investigating the Pfitzinger reaction and for use in color photographic developing.

Buu-Hoi *et al.* [*J. Chem. Soc.*, 386—8 (1953)] report 2-arylcinchoninic acids, prepared by the Pfitzinger reaction, having the formula:

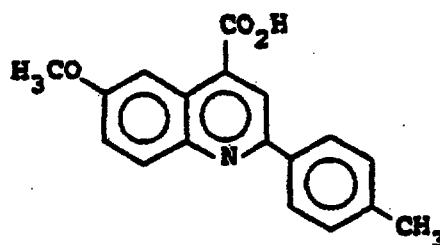


where

R = H, CH₃, C₂H₅ and phenyl;
Ar = fluoro-substituted phenyl; and
R' = H, Br, Cl or CH₃.

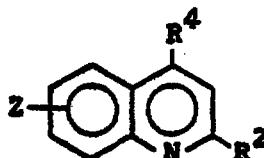
No use for these compounds is described.

Epling *et al.* [*Tet. Lett.*, 23 (38), 3843—3846 (1982)] report



as an intermediate to a new arylmethylsulfonyl chloride convertible to sulfonamides which can be photochemically cleaved.

Starke *et al.* in U.S. Patent 4,009,020, issued February 22, 1977, describe plant growth regulant cinchoninic acid derivatives, including those of the formula:

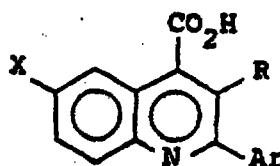


where

Z is H or halogen, preferably H;
R² is, *inter alia*, phenyl and halo-substituted phenyl; and
R⁴ is CN, CO₂H and related esters and amides.

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Buu-Hoi et al. [*J. Org. Chem.*, 18, 1209—1224 (1953)] describe 2-arylcinchoninic acids of the formula:



where

X = H or Br;

R = H, CH₃, C₂H₅ and other groups; and

Ar can be a variety of aromatic groups including 4-biphenyl, 4-alkylphenyl and 4-phenoxyphenyl.

The compounds prepared were part of a program to investigate the toxicity of cinchoninic acids and quinolines, since cinchophen ("Atophan") can produce a degeneration of liver tissue of a possible precancerous nature. Some of the compounds prepared caused degenerative changes in the liver.

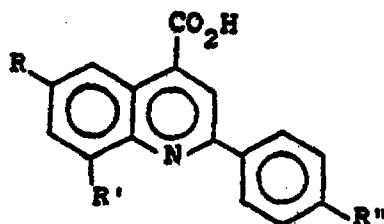
Buu-Hoi et al. [*Rec. trav. Chim.*, 62 713—718 (1943)] report 2-(4-cyclohexylphenyl)cinchoninic acid and 2-(4-biphenyl)cinchoninic acid. Hai et al. [*J. Org. Chem.*, 23, 39—42 (1958)] describe 2-(4-cyclopentylphenyl)cinchoninic acids, including 3-methyl and 3-ethyl derivatives, and 6-bromo and 6-methyl derivatives. Buu-Hoi et al. [*J. Org. Chem.*, 22, 668—671 (1957)] report 2-[4-(4-methoxy-3-chlorophenyl)phenyl]cinchoninic acid and its 3-methyl and 3-ethyl derivatives. Another Buu-Hoi report [*idem.*, 24, 39—41 (1959)] describes the 2-methoxy-3-chlorophenyl isomer.

Yen et al. [*J. Org. Chem.*, 23 1858—1861 (1958)] report 2-phenyl- and 2-(4-fluorophenyl)-6-fluorocinchoninic acids for testing as potential carcinogens.

Steinkopf et al. [*Annalen*, 540, 7—14 (1939); *idem*, 543, 119—128 (1940)] report 2-(5-methyl- and 5-phenyl-2-thienyl)cinchoninic acids. Sy et al. [*J. Chem. Soc.*, 1975—1978 (1954)] report 2-(5-*t*-butyl-2-thienyl)cinchoninic acid and its 3-methyl and 6-bromo derivatives.

Buu-Hoi et al. [*Rec. trav. Chim.*, 72, 774—780 (1953)] report 2-[4-(4-hydroxy- and 4-methoxyphenyl)phenyl]cinchoninic acids and their 3-methyl derivatives.

Boykin et al. [*J. Med. Chem.*, 11, 273—277 (1968)] report cinchoninic acids of the formula:



where

R = H, F, CH₃ or OCH₃;

R' = H, CH₃ or CF₃; and

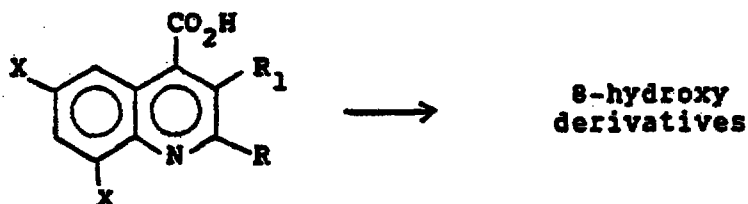
R'' = H, F, Cl, or CH₃ or OCH₃.

Although prepared as part of an antimalarial program, it does not appear that these intermediates were tested for antimalarial activity.

Saggiomo et al. [*J. Org. Chem.*, 11, 277—281 (1968)] report antimalarial quinoline-4-methanols derived from the corresponding acids. The latter include 6,8-dichloro-2-(3-trifluoromethylphenyl)cinchoninic acid and ethyl ester, and 2-(4-chlorophenyl)-6-fluorocinchoninic acid and ethyl ester.

Buu-Hoi et al. [*Rec. trav. Chim.*, 70, 825—832 (1951)] report 2-(4-*n*-propyl-4'-biphenyl)cinchoninic acid and 3-methyl-2-(4-ethyl-4'-biphenyl)cinchoninic acid.

Coles, in U.S. Patent 2,579,420, issued December 18, 1951, describes the conversion of 6,8-dihalocinchoninic acids into 6-halo-8-hydroxycinchoninic acids useful as color formers. Disclosed are compounds of the formula:



8-hydroxy
derivatives

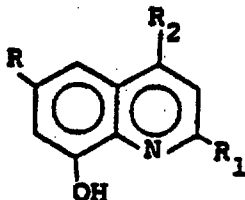
where

X is Cl or Br;

R₁ is, *inter alia*, H or lower alkyl; and

R is, *inter alia*, aryl and heteroaryl, optionally substituted by alkyl, aryl and the like.

Tulagin *et al.*, in U.S. Patent 2,524,741, issued October 3, 1950, describe the use, in color photographic developing, of 8-hydroxyquinolines of the formula:



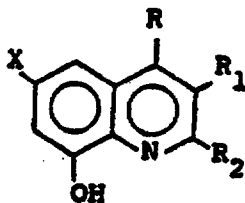
where

R is halogen, NO₂ or SO₃H;

R₁ can be phenyl or phenyl substituted with Cl, CH₃, OCH₃ or NH₂; and

R₂ can be CO₂H.

French Patent 1,040,440 describes compounds similar to Tulagin *et al.*, useful in color photographic chemistry, of the formula:



where

X is halogen;

R is CO₂H, CONH₂ or CONH-alkyl;

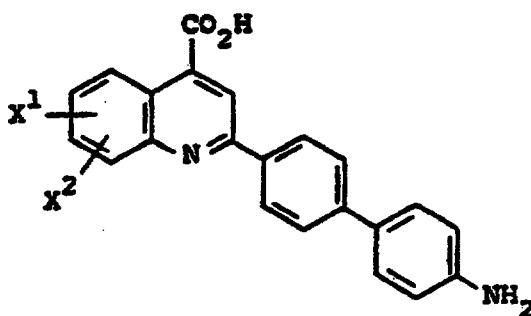
R₁ may be H or lower alkyl; and

R₂ may be aryl or a heterocyclic group.

German Patents 659,496; 668,741; and 668,742 describe 2-phenylcinchoninic acids, containing iodo groups and a free or etherified *p*-hydroxy substituent on the 2-phenyl group. Such compounds are stated to be useful as X-ray contrast agents.

Sakai *et al.*, [Gann, 46, 605—616 (1955)] report that 2-phenyl-4-carboxyquinoline has no tumoricidal effect in *in vitro* tests using NF mouse sarcoma.

United States Patent 2,888,346 issued on May 26, 1959 to Tulagin and Hoffstadt describes compounds of the formula:

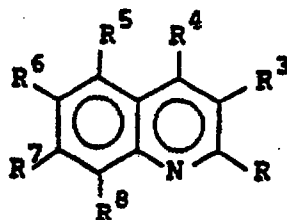


where

X¹ is 6-Cl or X¹ is 6-Cl and X² is 8-Br, and their use to protect organic media from damage from ultraviolet radiation.

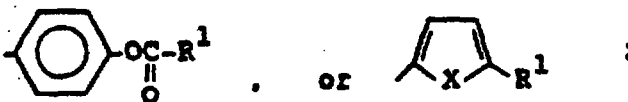
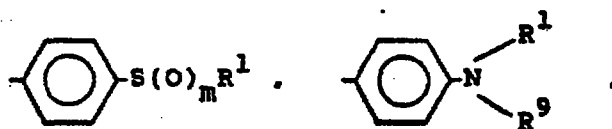
SUMMARY OF THE INVENTION

According to the present invention there is provided an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:



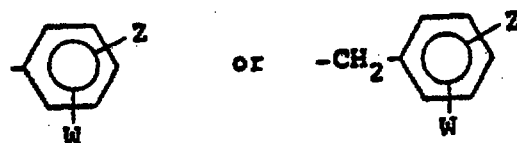
(I)

wherein

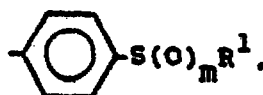


X is O, S(O)_m, NH or CH=N;

R¹ is CH₃CH₂(CH₂)CH, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

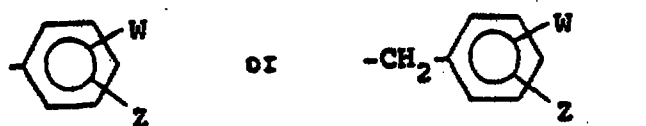


when R is



R¹ can be in addition alkyl of 3—4 carbon atoms;

R² is



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R^5 is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or $(CH_2)_pCOR^{10}$ where p is 1, 2, 3 or 4;

R^4 is CO_2H or CO_2R^{11} ;

R^5 , R^6 , R^7 and R^8 are independently H, F, Cl, Br, I, CH_3 , CF_3 , $S(O)_nR^{12}$ or CH_2CH_3 , at least two of R^5 , R^6 , R^7 , and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R^{10} is OH, OCH_3 , OCH_2CH_3 , NH_2 , $NHCH_3$ or $N(CH_3)_2$;

R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;

R^{12} is alkyl of 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO_2 , alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF_3 or NH_2 ;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

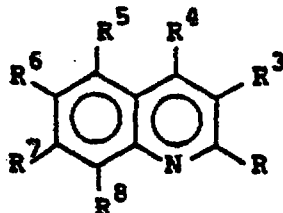
1) R^5 , R^6 and R^7 cannot all be H;

2) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^5 is CH_2CH_3 , or R^7 is Cl, R^1 cannot be cyclohexyl; and

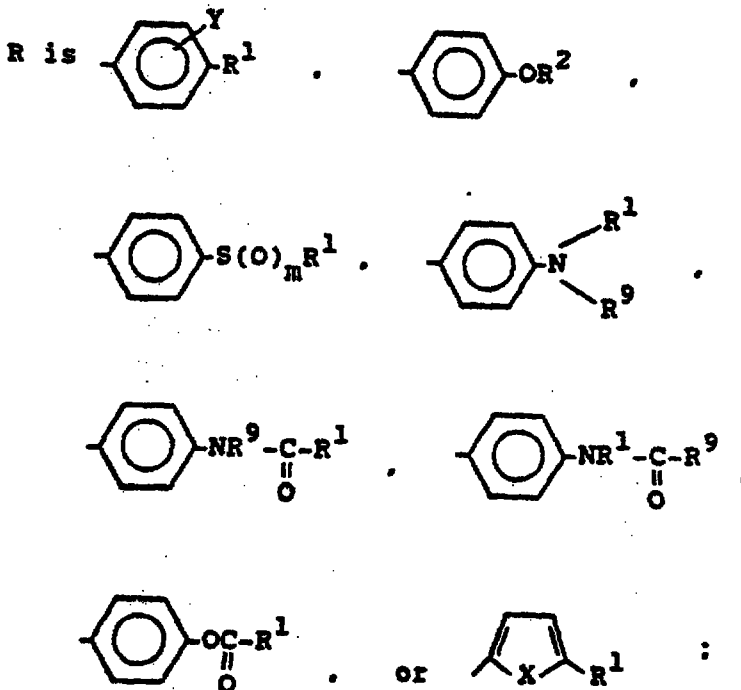
3) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl.

Also provided is their use for the manufacture of medicament for inhibiting the growth of mammalian tumors.

Additionally provided are novel antitumor active phenylquinoline carboxylic acids and derivatives having the formula:

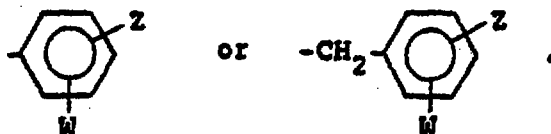


wherein

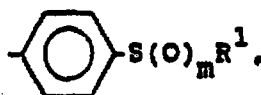


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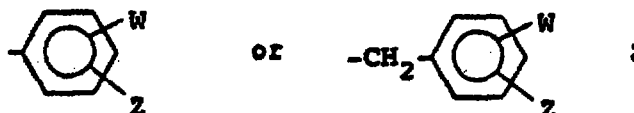
X is O, S(O)_q, NH or CH=N;
 R¹ is CH₃CH₂(CH₃)CH, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms,



when R is



R¹ can be in addition alkyl of 3—4 carbon atoms;
 R² is



R³ is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or (CH₂)_pCOR¹⁰ where p is 1, 2, 3 or 4;

R⁴ is CO₂H or CO₂R¹¹;

R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² or CH₂CH₃, at least two of R⁵, R⁶, R⁷, and R⁸ being H;

R⁹ and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R¹⁰ is OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ or N(CH₃)₂;

R¹¹ is (CH₂)₂₋₄NR⁹R^{9A};

R¹² is alkyl of 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO₂, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF₃ or NH₂;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

1) when R⁴ is CO₂H, R¹ is phenyl or phenoxy, and R⁵, R⁷ and R⁸ are H, R⁶ cannot be Br;

2) R⁵, R⁶ and R⁷ cannot all be H;

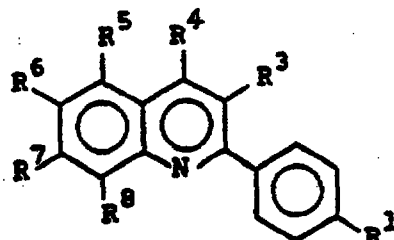
3) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁶ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl;

4) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl; and

5) when R¹ is 4-H₂NC₆H₄ and R³ is H, R⁶ cannot be Cl and R⁸ cannot be Br.

PREFERRED EMBODIMENTS

Preferred antitumor compounds have the formula:



(11)

60 wherein

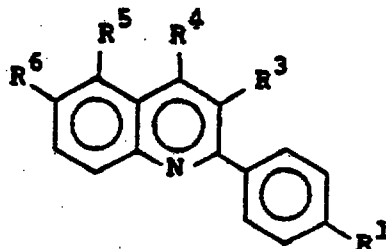
R¹ is cycloalkyl of 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl of 1—5 carbon atoms or CF₃; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R³ is H or alkyl of 1—3 carbon atoms;

R⁴ is CO₂H or a sodium or potassium salt thereof;

R⁵ and R⁶ are independently H, halogen, CH₃ or CF₃; and

R⁷ and R⁸ are independently H or halogen;
or a pharmaceutically suitable salt thereof; with the proviso that:
1) R⁵, R⁶ and R⁷ cannot all be H; and
2) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl.
More preferred antitumor compounds are compounds which have the formula:



(III)

wherein

R¹ is cyclohexyl, phenyl, phenyl substituted with halogen, phenoxy, or phenoxy substituted with halogen;

R³ is H or alkyl of 1—3 carbon atoms;

R⁴ is CO₂H or a sodium or potassium salt thereof; and

R⁵ and R⁶ are independently H, halogen or CF₃, provided that both R⁵ and R⁶ are not H.

Especially preferred are the compounds of Formula III in which:

R¹ is phenyl, phenyl substituted with halogen, phenoxy, or phenoxy substituted with halogen;

R³ is methyl;

R⁵ is H or Cl; and

R⁶ is F or Cl.

Specifically preferred for their antitumor activity are:

(1) 2-(1,1'-Biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

(2) 6-Fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.

(3) 2-(4'-Bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

(4) 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

(5) 2-(1,1'-Biphenyl-4-yl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

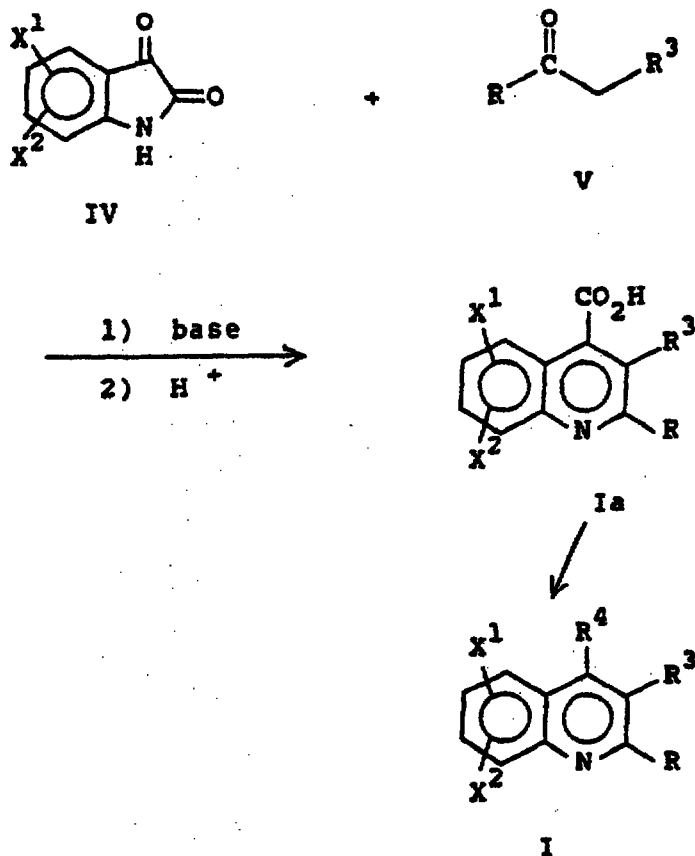
SYNTHESIS

The compounds useful in this invention (Formulae I, II and III) are prepared generally by condensation of an appropriately substituted isatin IV and a ketone V in what is known as the Pfitzinger reaction [Buu-Hoi, N. P.; Royer, R.; Xuong, N. D.; Jucquignon, P.; *J. Org. Chem.*, **18**, 1209 (1953)] to give Ia; then, if desired, further conversion of functional groups on the quinoline provides further compounds of Formula I (Scheme 1). Isatins IV are prepared by the methods described by Papp and references given therein [Papp, F. D.; *Adv. Heterocyclic Chem.*, **18**, 1 (1975)]. The ketones V are prepared by Friedel-Crafts acylation as discussed by House [House, H. O.; *Modern Synthetic Reactions*, 2nd Ed., W. A. Benjamin, 1972, pp. 734ff].

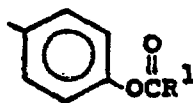
In the following schemes, quinolines bearing up to two unspecified substituents X¹ and X² are depicted. The synthetic disclosure is general for quinolines, including all those within the scope of this invention. When certain values of R⁵, R⁶, R⁷ and R⁸ are desired, as will be apparent to one skilled in the art, a

protected form of the functional group will be carried through the synthesis, to be deprotected to the desired functional group at a later stage.

Scheme 1



Compounds where R^4 is CO_2H are prepared by reacting the appropriate substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with an aqueous solution of a base such as sodium hydroxide, NH_4OH or potassium hydroxide at a temperature in the range of about 25°C to the boiling point of the solvent used. Acidification of the reaction mixture with a mineral acid such as HCl or an organic acid such as acetic acid provides the quinoline carboxylic acid Ia. Compounds in which R is

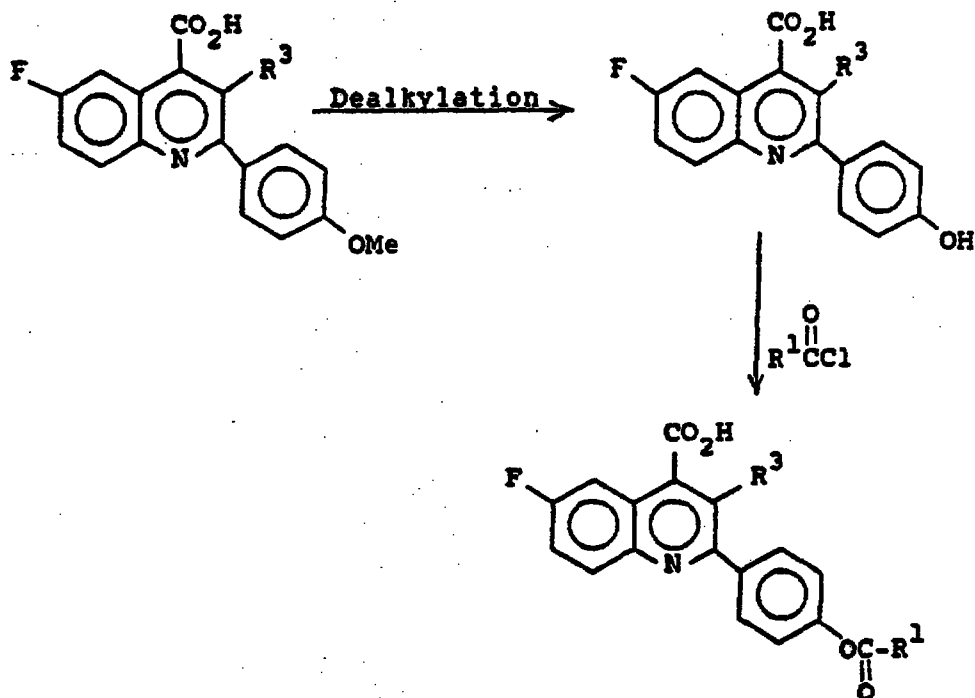


are prepared by acylation of the corresponding hydroxy compound with a carboxylic acid halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent (benzene) at a temperature in the range of about 0°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine.

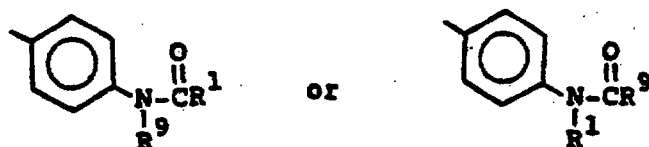
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The aforementioned hydroxy compound is prepared from an ether by a dealkylation reaction using BBr_3 or $(\text{CH}_3)_3\text{SiH}$ in an inert solvent such as dimethylformamide, methylene chloride, or chloroform at a temperature in the range of about 0°C to the boiling point of the solvent used (Scheme 2).

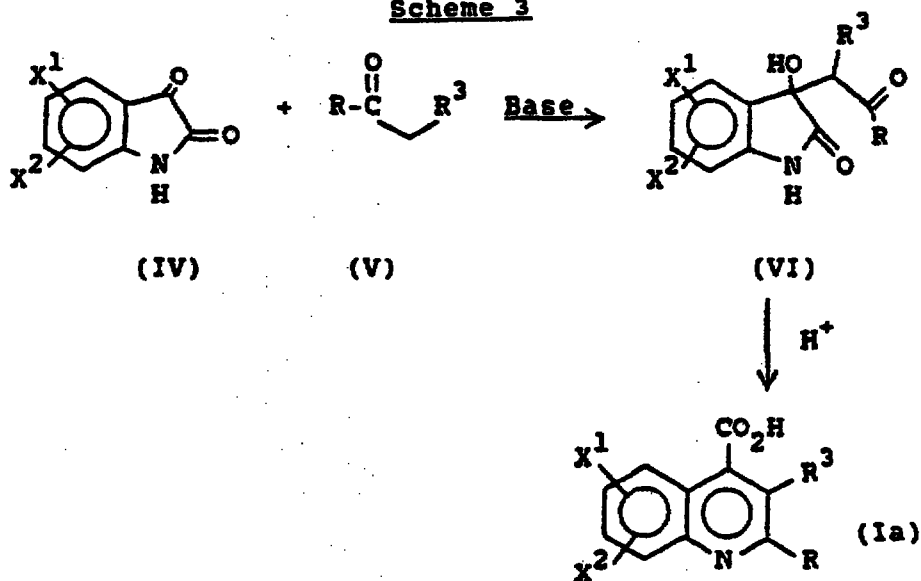
Scheme 2



In Scheme 3, quinolines bearing up to two unspecified substituents X^1 and X^2 are depicted. The synthetic disclosure is general for quinolines, including all those within the scope of this invention. This method is preferred over the Pfitzinger procedure for certain substituents on the isatin (IV) such as $\text{X}^1 = 4\text{-Cl}$, or when W, Y or Z are NO_2 , or when R is



Scheme 3

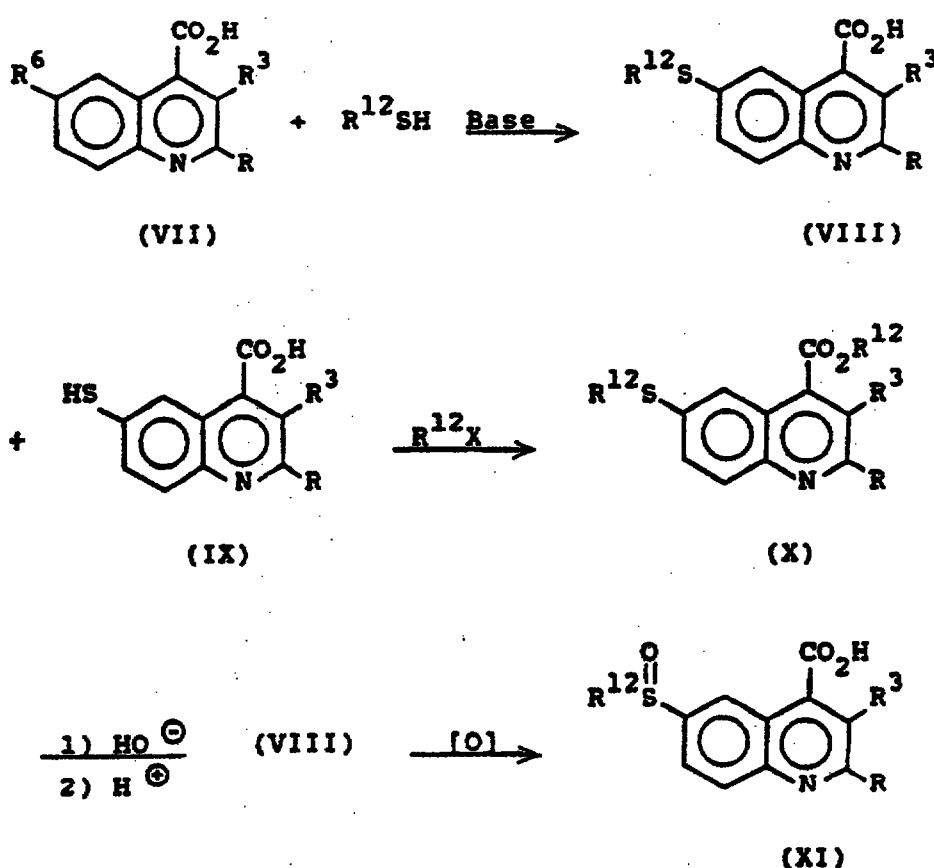


The compounds Ia of Scheme 3 are prepared by reacting the appropriate substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as diethylamine or triethylamine at a temperature of 25° to 50°C for 2 to 48 hours. Recrystallization of the product (VI) from a solvent is possible although decomposition often occurs. The product (VI) is dissolved in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as hydrochloric acid and heated to a temperature of 50°C to the reflux temperature of the mixture of 2 to 48 hours to provide the quinoline carboxylic acid (Ia).

Quinolonecarboxylic acids such as (VIII) where R^6 is $R^{12}S(O)_n$ are best prepared by reacting the appropriately substituted quinolinecarboxylic acid (VII) where R^6 is F with an appropriate thiolate $R^{12}S^-$ such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to the reflux temperature of the solvent for 2 to 8 hours (Scheme 4).

It may be necessary, depending upon the reaction conditions chosen, to alkylate the thiol (IX) generated during the reaction by reacting the crude reaction product in an appropriate solvent such as acetone with an alkyl halide $R^{12}X$ such as methyl iodide with or without a base such as potassium carbonate at a temperature of 25°C to the reflux temperature of the solvent for 2 to 24 hours. This gives the corresponding ester (X) which is hydrolyzed by reacting in an appropriate solvent such as ethanol with water and a base such as potassium hydroxide at reflux for 12 to 24 hours to give, after acidification of the reaction mixture with a mineral acid such as HCl, the quinolinecarboxylic acid (VIII). (VIII) can be converted to the corresponding sulfoxide by reacting (VIII) in an appropriate solvent such as ethyl acetate with an oxidizing reagent such as *m*-chloroperoxybenzoic acid at -20° to 25°C for 6 to 24 hours.

Scheme 4

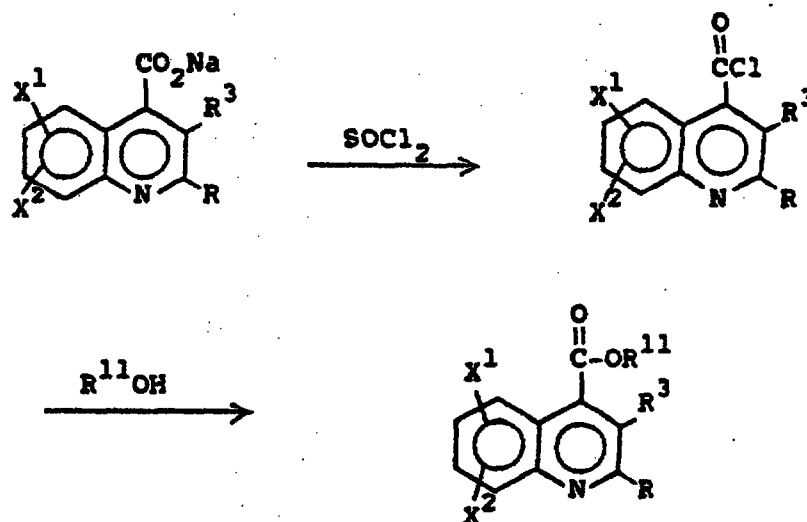


A salt of the carboxylic acid is prepared by dissolving the acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-2-butanol or lysine at a temperature in the range of about 0°C to the boiling point of the solvent used. A salt of an amino group is prepared by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl.

A metal salt of a compound of Formula I (e.g., $R^4 = CO_2Na$) can be converted to a corresponding ester in two steps. Conversion of the salt to an acid halide is carried out first by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as a hydrocarbon (benzene) at a temperature in the range of about 25°C to the boiling point of the solvent used. This reaction is followed by the addition of an alcohol,

$R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature in the range of $10^{\circ}C$ to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylaminopyridine to provide the ester (Scheme 5).

Scheme 5



The invention can be further understood by the following examples in which parts and percentages are by weight unless otherwise indicated; all temperatures are in degrees Centigrade.

Example 1

2-(4-Cyclohexylphenyl)-6-fluoro-3-methylquinoline-4-carboxylic acid

5-Fluoroisatin (100 g, 0.61 mole) and 4-cyclohexylpropiophenone (131 g, 0.61 mole) were suspended in 1100 ml of ethanol and stirred mechanically as a solution of 219 g (5.5 mole) of KOH in 550 ml of water was added dropwise. After the addition was complete, the mixture was heated at reflux for 12 hours, cooled, and the ethanol evaporated under reduced pressure. The resulting solid was dissolved in water and washed with ethyl ether. The aqueous layer was acidified with HCl. The resulting precipitate was filtered and dried. Recrystallization from dimethylformamide and water gave 117 g of 2-(4-cyclohexylphenyl)-6-fluoro-3-methylquinoline-4-carboxylic acid, m.p. $316-323^{\circ}$.

Example 2

2-(4-Biphenyl)-6-fluoro-3-methylquinoline-4-carboxylic acid

4-Phenylpropiophenone (18.9 g, 0.09 mole) and 5-fluoroisatin (20 g, 0.09 mole) were suspended in 360 ml of ethanol and stirred mechanically as a solution of 35.2 g of KOH in 100 ml water was added dropwise over 15 minutes. The reaction mixture was heated at reflux for 12 hours, cooled, and the ethanol evaporated under reduced pressure. The resulting yellow solid was dissolved in water and washed with ethyl ether. The aqueous layer was cooled to 5° and acidified with glacial acetic acid. The resulting yellow precipitate was filtered and dried. Recrystallization from 200 ml of dimethylformamide and 25 ml water provided 13.8 g of 2-(4-biphenyl)-6-fluoro-3-methylquinoline-4-carboxylic acid as a white solid, m.p. $303-306^{\circ}(d)$.

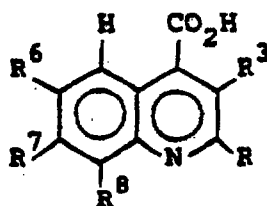
Example 28

2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid

5-Fluoroisatin (72.6 g, 0.44 mole) and 4-(2-fluorophenyl) propiophenone (100 g, 0.44 mole) were suspended in 720 ml of ethanol and stirred mechanically as a solution of KOH (147.8 g, 2.64 mole) in 300 ml of water was added dropwise over 15 minutes. The reaction mixture was heated at reflux for 12 hours, cooled, and the ethanol evaporated under reduced pressure. The resulting solid was dissolved in water and washed with ethyl ether. The aqueous layer was cooled to 5° and acidified with glacial acetic acid. The resulting precipitate was filtered, washed 2 times with 300 ml of ethyl ether and dried. Recrystallization from dimethylformamide and water gave 84 g of a white 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, m.p. $315-317^{\circ}$.

The compounds of Examples 1, 2 and 28, other compounds which have been prepared using the procedures described for the compounds of Examples 1, 2 and 28, and other compounds which may be prepared by such procedures, are listed in Table 1.

Table 1



Ex.	R	R ³	R ⁶	R ⁷	R ⁸	m.p. (°C)
1	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	F	H	H	316-323
2	4-C ₆ H ₅ C ₆ H ₄	CH ₃	F	H	H	303-306(d)
3	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	Cl	H	H	320-322(d)
4	4-c-C ₆ H ₁₁ C ₆ H ₄	H	Cl	H	H	264-265
5	4-c-C ₆ H ₁₁ C ₆ H ₄	H	F	H	H	280-284
6	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	CH ₃	H	H	308-312(d)
7	4-n-C ₁₀ H ₂₁ C ₆ H ₄	CH ₃	F	H	H	256-261
8	4-n-C ₆ H ₁₃ C ₆ H ₄	CH ₃	F	H	H	278-285
9	4-CH ₃ CH ₂ (CH ₃)CHC ₆ H ₄	CH ₃	F	H	H	290-297
10	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃ CH ₂	F	H	H	295-297
11	4-C ₆ H ₅ OC ₆ H ₄	CH ₃	F	H	H	318-320(d)
12	4-(4-BrC ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	318-323(d)
13	4-(CH ₃) ₂ CHSC ₆ H ₄	CH ₃	F	H	H	280-283
14	4-C ₆ H ₅ C ₆ H ₄	CH ₃	CH ₃	H	H	327-329(d)
15	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃ CH ₂	CH ₃	H	H	290(d)
16	4-C ₆ H ₅ CH ₂ OC ₆ H ₄	CH ₃	F	H	H	297-302
17	4-CH ₃ CH ₂ (CH ₃)CHC ₆ H ₄	CH ₃ CH ₂	F	H	H	286-291
18	4-C ₆ H ₅ C ₆ H ₄	CH ₃ CH ₂	F	H	H	274-279(d)
19	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	H	H	302-305
20	4-C ₆ H ₅ OC ₆ H ₄	CH ₃	Cl	H	H	296-301
21	4-C ₆ H ₅ SC ₆ H ₄	CH ₃	Cl	H	H	313-316
22	4-C ₆ H ₅ CH ₂ C ₆ H ₄	CH ₃	Cl	H	H	265-275
23	4-(4-FC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	H	H	319-323
24	4-(4-CH ₃ OC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	H	H	310-314
25	4-(CH ₃) ₂ CHS(O)C ₆ H ₄	CH ₃	F	H	H	

Table 1 (continued)

Ex.	R	R ³	R ⁶	R ⁷	R ⁸	m.p.(°C)
26	4-C ₆ H ₅ CH ₂ SC ₆ H ₄	CH ₃	F	H	H	281-287
27	4-(4-BrC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	H	H	319-324(d)
28	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	315-317
29	4-(4-ClC ₆ H ₄ O)C ₆ H ₄	CH ₃	F	H	H	299-303
30	4-(4-CH ₃ C ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	317-319
31	4-(4-FC ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	310-314
32	4-(4-CF ₃ C ₆ H ₄)C ₆ H ₄	CH ₃ O	F	H	H	
33	4-C ₆ H ₅ C ₆ H ₄	H	F	H	H	272-278
34	4-C ₆ H ₅ S(O)C ₆ H ₄	CH ₃	F	H	H	239-247
35	4-(4-FC ₆ H ₄ O)C ₆ H ₄	CH ₃	F	H	H	291-297
36	4-(3,4-Cl ₂ C ₆ H ₃)C ₆ H ₄	CH ₃	F	H	H	315-319
37	4-C ₆ H ₅ C ₆ H ₄	CH ₃ O	F	H	H	219-223
38	4-(3-Cl,4-CH ₃ C ₆ H ₃)C ₆ H ₄	CH ₃	F	H	H	316-324
39	4-(3,4-(CH ₃) ₂ C ₆ H ₃)C ₆ H ₄	CH ₃	F	H	H	321-324
40	4-(4-(CH ₃ CH ₂)C ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	309-315
41	4-(3-(CH ₃ CH ₂)C ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	
42	4-C ₆ H ₅ -3-pyridyl	CH ₃	F	H	H	
43	4-C ₆ H ₅ -2-furanyl	CH ₃	F	H	H	
44	4-C ₆ H ₅ -2-thienyl	CH ₃	F	H	H	345-350
45	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	Br	H	H	325-330
46	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	Br	H	Br	275-280
47	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	Cl	H	
48	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	CF ₃	H	H	320-325
49	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	Cl	H	315-320
50	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	H	Cl	H	315-318
51	4-C ₆ H ₅ C ₆ H ₄	CH ₃	CH ₃ CH ₂	H	H	295-300
52	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Br	H	H	313-314
53	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	Br	H	H	273-278
54	4-(4-FC ₆ H ₄)C ₆ H ₄	CH ₃	F	Cl	H	
55	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃	H	324-328
56	4-C ₆ H ₅ C ₆ H ₄	CH ₃	CF ₃	H	H	320-323
57	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	CF ₃	H	H	294-298

Table 1 (continued)

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Ex.	R	R ³	R ⁶	R ⁷	R ⁸	m.p. (°C)
58	4-C ₆ H ₅ C ₆ H ₄	CH ₃	CH ₃	Cl	H	333-336
59	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	CH ₃	Cl	H	314-318
60	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Br	H	Br	270-273
61	4-C ₆ H ₅ C ₆ H ₄	CH ₃	F	Cl	H	327-332
62	4-C-C ₃ H ₅ C ₆ H ₄	CH ₃	F	H	H	
63	4-C-C ₅ H ₉ C ₆ H ₄	CH ₃	F	H	H	
64	4-(C ₆ H ₅ (CH ₃)N)C ₆ H ₄	CH ₃	F	H	H	
65	4-(C ₆ H ₅ CONH)C ₆ H ₄	CH ₃	F	H	H	
66	4-(C ₆ H ₅ CO ₂)C ₆ H ₄	CH ₃	F	H	H	
67	5-C ₆ H ₅ -2-imidazolyl	CH ₃	F	H	H	
68	(4-C ₆ H ₅ , 2-CH ₃)C ₆ H ₃	CH ₃	F	H	H	316-320°
69	4-(2-FC ₆ H ₄), 3-FC ₆ H ₃	CH ₃	F	H	H	
70	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	H	H	
71	4-C ₆ H ₅ C ₆ H ₄	CH ₃	I	H	H	325-327
72	4-(4-CF ₃ C ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	
73	4-(3-FC ₆ H ₄)C ₆ H ₄	CH ₃	F	H	H	305-310
74	4-(2,4-F ₂ C ₆ H ₃)C ₆ H ₄	CH ₃	F	H	H	325-328
75	4-(4-FC ₆ H ₄ O)C ₆ H ₄	H	F	H	H	310-315

C-C₆H₁₁ = cyclohexylC-C₅H₉ = cyclopentylC-C₃H₅ = cyclopropyl

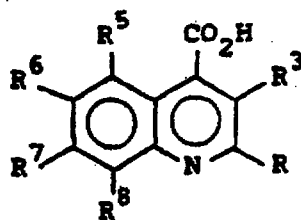
Example 76

2-(4-Biphenyl)-3-methyl-6-methylthio-4-quinoline carboxylic acid

The compound of Example 2, 2-(4-biphenyl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, (7.2 g, 0.02 mole) and potassium methylmercaptide (6 g) were dissolved in 100 ml of dimethylformamide and warmed at 130° for 3 hours. The mixture was cooled and the solvent evaporated under reduced pressure. The residue was dissolved in 250 ml of H₂O, filtered and the filtrate acidified to pH 2. The yellow precipitate was filtered and dried. A portion of the yellow precipitate (1.8 g, 0.005 mole) was suspended in acetone containing 5 ml of methyl iodide and 4 g of potassium carbonate and was heated to reflux for 24 hours. The reaction mixture was filtered and evaporated at reduced pressure. The residue was dissolved in ethyl ether, washed with H₂O, dried with sodium sulfate and evaporated at reduced pressure to give a solid. The solid obtained in this manner from several batches (6 g) was combined and dissolved in 70 ml of ethanol and 30 ml of H₂O containing 10 g of potassium hydroxide. The mixture was heated at reflux for 12 hours. The mixture was cooled, evaporated at reduced pressure, dissolved in 300 ml of H₂O and washed with ethyl ether. The aqueous solution was acidified to pH 2 with HCl and the precipitate collected, washed with water and hot ethanol to give 4.9 g of 2-(4-Biphenyl)-3-methyl-6-methylthio-4-quinolinecarboxylic acid, m.p. 316-318°(d).

The compound of Example 76 and other compounds which can be prepared using this procedure are listed in Table 2.

Table 2



Ex.	R	R ³	R ⁵	R ⁶	R ⁷	R ⁸	m.p. (°C)
76	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃ S	H	H	316-318(d)
77	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃ S(O)	H	H	
78	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	CH ₃ S	H	H	
79	4-(4-CH ₃ C ₆ H ₄)C ₆ H ₄	CH ₃	H	CH ₃ S	H	H	

Example 81

2-(4-Biphenyl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid

4-Chloro-5-fluoroisatin (4 g, 0.02 mole), diethylamine (1.46 g, 0.02 mole) and 4-phenylpropiophenone (4.4 g, 0.021 mole) were suspended in 100 ml of ethanol and stirred for 12 hours. The precipitate was filtered, washed with cold ethanol and dried to give 2.1 g of crude adduct (m.p. 202-206°).

This was dissolved in 75 ml of tetrahydrofuran and 30 ml of concentrated HCl. The resulting solution was refluxed for 24 hours, cooled and diluted with H₂O. The tetrahydrofuran was evaporated under reduced pressure. The precipitate was filtered, washed with ether and boiled with methanol to give 0.90 g of 2-(4-biphenyl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid as a crystalline solid, m.p. 300-305°.

Example 86

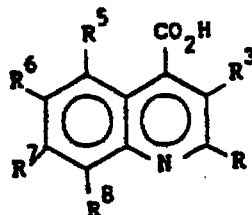
6-Fluoro-3-methyl-2-(4-nitrophenoxyphenyl)-4-quinolinecarboxylic acid

5-Fluoroisatin (2.0 g, 0.0104 mole), diethylamine (0.77 g, 0.0105 mole) and 4-(4-nitrophenoxy)propiophenone (2.82 g, 0.0104 mole) were suspended in 100 ml of ethanol and stirred at 25° for 12 hours. The precipitate was filtered, washed with toluene and air dried to give 3.0 g of crude adduct.

The crude product obtained from two of the above preparations (5.0 g, 0.0108 mole) was combined in 180 ml of tetrahydrofuran and 40 ml of concentrated HCl. The resulting solution was refluxed for 12 hours, cooled and the solvent was evaporated under reduced pressure. The solid residue was washed with ethyl ether and dried to give 4.37 g of 6-fluoro-3-methyl-2-(4-nitrophenoxyphenyl)-4-quinolinecarboxylic acid as a white solid, m.p. 335-337°.

The compounds of Examples 81 and 86, other compounds which have been prepared using the procedures for the compounds of Examples 81 and 86, and other compounds which may be prepared by such procedures, are listed in Table 3.

Table 3



Ex.	R	R ³	R ⁵	R ⁶	R ⁷	R ⁸	m.p. (°C)
80	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	H	H	H	295-296 (d)
81	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	F	H	H	305-308 (d)
82	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	H	Cl	H	301-305 (d)
83	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	CH ₃	H	H	295-298 (d)
84	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	F	H	H	300-305
85	4-(4-CH ₃ C ₆ H ₄)C ₆ H ₄	CH ₃	Cl	F	H	H	293-296
86	4-(4-NO ₂ C ₆ H ₄ O)C ₆ H ₄	CH ₃	H	F	H	H	335-337
87	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	H	F	H	307-311 (d)
88	4-(4-CF ₃ C ₆ H ₄)C ₆ H ₄	CH ₃ CH ₂	Cl	F	H	H	
89	4-(3-Cl,4-CH ₃ C ₆ H ₃)C ₆ H ₄	CH ₃	Cl	F	H	H	
90	4-(3-Cl,4-CH ₃ C ₆ H ₃)C ₆ H ₄	CH ₃	Cl	H	H	H	

Example 91

Sodium 2-(4-Cyclohexylphenyl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 1 (10.0 g, 0.0275 mole) was suspended in 400 ml of ethanol and treated with 1N NaOH (27.5 ml, 0.0275 mole). The mixture was stirred until the solution was clear; the ethanol and water were evaporated at reduced pressure to give 9.95 g of the sodium salt as a white solid, m.p. 350°(d).

Example 92

Sodium 2-(4-Biphenyl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 2 (3.57 g, 0.01 mole) was dissolved in 500 ml of ethanol and treated with 1N NaOH (10 ml), and heated at reflux for 30 minutes. The ethanol and water were evaporated at reduced pressure to give 3.6 g of the sodium salt as a pale tan solid, m.p. >360°.

Example 118

Sodium 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 28 (37.5 g, 0.10 mole) was suspended in 1,000 ml of ethanol and treated with 1N NaOH (100 ml, 0.10 mole). The mixture was warmed and stirred until clear; the ethanol and water were evaporated at reduced pressure to give 39.6 g of the white solid sodium 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methylquinoline-4-carboxylate, m.p. >360°.

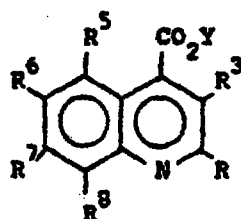
Example 164

Sodium 2-(4-Biphenyl)-5-chloro-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Example 81 (7.85 g, 0.02 mole) was suspended in 150 ml of water and treated with 1N NaOH (19.9 ml, 0.0199 mole), and 150 ml of ethanol was added. The mixture was stirred until the solution was clear and filtered to remove any insoluble material. The ethanol and water were removed at reduced pressure to give 8.1 g of the white solid sodium salt, m.p. >360°.

The compounds of Examples 91, 92, 118 and 164, other compounds which have been prepared by the procedures given above, and other compounds which can be prepared using such procedures are listed in Table 4.

Table 4



Ex.	R	R ³	R ⁵	R ⁶	R ⁷	R ⁸	Y	m.p. (°C)
91	4-C-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	F	H	H	Na	350(d)
92	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	F	H	H	Na	>360
93	4-C-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	Cl	H	H	Na	>350
94	4-C-C ₆ H ₁₁ C ₆ H ₄	H	H	Cl	H	H	Na	>350
95	4-C-C ₆ H ₁₁ C ₆ H ₄	H	H	F	H	H	Na	>350
96	4-C-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	CH ₃	H	H	Na	342-351
97	4-n-C ₁₀ H ₂₁ C ₆ H ₄	CH ₃	H	F	H	H	Na	332-335
98	4-n-C ₆ H ₁₃ C ₆ H ₄	CH ₃	H	F	H	H	Na	
99	4-CH ₃ CH ₂ (CH ₃)CHC ₆ H ₄	CH ₃	H	F	H	H	Na	340-345
100	4-C-C ₆ H ₁₁ C ₆ H ₄	CH ₃ CH ₂	H	F	H	H	Na	>350
101	4-C ₆ H ₅ OC ₆ H ₄	CH ₃	H	F	H	H	Na	>350
102	4-(4-BrC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	Na	>350
103	4-(CH ₃) ₂ CHSC ₆ H ₄	CH ₃	H	F	H	H	Na	339-343
104	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃	H	H	Na	>350
105	4-C-C ₆ H ₁₁ C ₆ H ₄	CH ₃ CH ₂	H	CH ₃	H	H	Na	>350
106	4-C ₆ H ₅ CH ₂ OC ₆ H ₄	CH ₃	H	F	H	H	Na	>350
107	4-CH ₃ CH ₂ (CH ₃)CHC ₆ H ₄	CH ₃ CH ₂	H	F	H	H	Na	302-306
108	4-C ₆ H ₅ C ₆ H ₄	CH ₃ CH ₂	H	F	H	H	Na	>350
109	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	Cl	H	H	Na	>350
110	4-C ₆ H ₅ OC ₆ H ₄	CH ₃	H	Cl	H	H	Na	170-175
111	4-C ₆ H ₅ SC ₆ H ₄	CH ₃	H	Cl	H	H	Na	319-324
112	4-C ₆ H ₅ CH ₂ C ₆ H ₄	CH ₃	H	Cl	H	H	Na	305-315
113	4-(4-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	Cl	H	H	Na	>350
114	4-(4-CH ₃ OC ₆ H ₄)C ₆ H ₄	CH ₃	H	Cl	H	H	Na	>360
115	4-(CH ₃) ₂ CHS(O)C ₆ H ₄	CH ₃	H	F	H	H	Na	

Table 4 (continued)

Ex.	R	R ³	R ⁵	R ⁶	R ⁷	R ⁸	Y	m.p. (°C)
116	4-C ₆ H ₅ CH ₂ SC ₆ H ₄	CH ₃	H	F	H	H	Na	
117	4-(4-BrC ₆ H ₄)C ₆ H ₄	CH ₃	H	Cl	H	H	Na	>360
118	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	Na	>360
119	4-(4-ClC ₆ H ₄ O)C ₆ H ₄	CH ₃	H	F	H	H	Na	>350
120	4-(4-CH ₃ C ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	Na	>350
121	4-(4-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	Na	>360
122	4-(4-CF ₃ C ₆ H ₄)C ₆ H ₄	CH ₃ O	H	F	H	H	Na	
123	4-C ₆ H ₅ C ₆ H ₄	H	H	F	H	H	Na	>360
124	4-C ₆ H ₅ S(O)C ₆ H ₄	CH ₃	H	F	H	H	Na	251-260
125	4-(4-FC ₆ H ₄ O)C ₆ H ₄	CH ₃	H	F	H	H	Na	
126	4-(3,4-Cl ₂ C ₆ H ₃)C ₆ H ₄	CH ₃	H	F	H	H	Na	338-351
127	4-C ₆ H ₅ C ₆ H ₄	CH ₃ O	H	F	H	H	Na	345-349
128	4-(3-Cl,4-CH ₃ C ₆ H ₃)C ₆ H ₄	CH ₃	H	F	H	H	Na	>360
129	4-(3,4-(CH ₃) ₂ C ₆ H ₃)C ₆ H ₄	CH ₃	H	F	H	H	Na	>350
130	4-(4-(CH ₃ CH ₂)C ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	Na	>360
131	4-(3-(CH ₃ CH ₂)C ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	Na	
132	4-C ₆ H ₅ -3-pyridyl	CH ₃	H	F	H	H	Na	
133	4-C ₆ H ₅ -2-furanyl	CH ₃	H	F	H	H	Na	
134	4-C ₆ H ₅ -2-thienyl	CH ₃	H	F	H	H	Na	>360
135	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	Br	H	H	Na	>360
136	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	Br	H	Br	Na	298-300(d)
137	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	Cl	Cl	H	Na	
138	4-c-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	CF ₃	H	H	Na	
139	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	H	Cl	H	Na	>360
140	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	H	H	Cl	H	Na	
141	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃ CH ₂	H	H	Na	>360
142	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	Br	H	H	Na	>360
143	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	H	Br	H	H	Na	228
144	4-(4-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	Cl	H	Na	
145	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	H	CH ₃	H	Na	>350
146	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CF ₃	H	H	Na	>360
147	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	H	CF ₃	H	H	Na	338-342

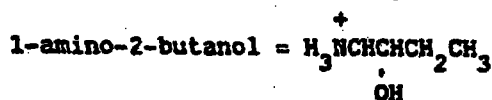
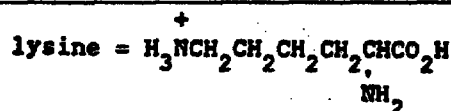
Table 4 continued

Ex.	R	R ³	R ⁵	R ⁶	R ⁷	R ⁸	Y	m.p. (°C)
148	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃	Cl	H	Na	>360
149	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	H	CH ₃	Cl	H	Na	318-320
150	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	Br	H	Br	Na	340-345
151	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	F	Cl	H	Na	>360
152	4-C-C ₃ H ₅ C ₆ H ₄	CH ₃	H	F	H	H	Na	
153	4-C-C ₅ H ₉ C ₆ H ₄	CH ₃	H	F	H	H	Na	
154	4-(C ₆ H ₅ (CH ₃)N)C ₆ H ₄	CH ₃	H	F	H	H	Na	
155	4-(C ₆ H ₅ CONH)C ₆ H ₄	CH ₃	H	F	H	H	Na	
156	4-(C ₆ H ₅ CO ₂)C ₆ H ₄	CH ₃	H	F	H	H	Na	
157	4-C ₆ H ₅ -2-imidazolyl	CH ₃	H	F	H	H	Na	
158	4-C ₆ H ₅ , 2-CH ₃ C ₆ H ₃	CH ₃	H	F	H	H	Na	>360
159	4-(2-FC ₆ H ₄), 3-FC ₆ H ₃	CH ₃	H	F	H	H	Na	
160	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	Cl	H	H	Na	
161	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃ S	H	H	Na	>350
162	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	CH ₃ S(O)	H	H	Na	
163	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	H	H	H	Na	>360
164	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	F	H	H	Na	>360
165	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	H	Cl	H	Na	>350
166	4-C ₆ H ₅ C ₆ H ₄	CH ₃	Cl	CH ₃	H	H	Na	>340
167	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	F	H	H	Na	330-335(d)
168	4-(4-CH ₃ C ₆ H ₄)C ₆ H ₄	CH ₃	Cl	F	H	H	Na	>345
169	4-C-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	F	H	H	K	350-360(d)
170	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	F	H	H	K	>350
171	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	Cl	H	H	K	>350
172	4-(C ₆ H ₅ O)C ₆ H ₄	CH ₃	H	Cl	H	H	K	164-171
173	4-(C ₆ H ₅ S)C ₆ H ₄	CH ₃	H	Cl	H	H	K	310-325
174	4-(4-BrC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	K	370
175	4-(4-BrC ₆ H ₄)C ₆ H ₄	CH ₃	H	Cl	H	H	K	>360
176	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	K	339-346
177	4-(4-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	K	270-275

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Table 4 continued

Ex.	R	R ³	R ⁵	R ⁶	R ⁷	R ⁸	Y	m.p. (°C)
178	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	F	H	H	lysine	222-231
179	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	F	H	H	1-amino-2-butanol	128-134
180	4-n-C ₆ H ₁₃ C ₆ H ₄	CH ₃	H	F	H	H	lysine	205-212
181	4-C-C ₆ H ₁₁ C ₆ H ₄	CH ₃	H	F	H	H	lysine	226-231
182	4-C ₆ H ₅ C ₆ H ₄	H	H	F	H	H	K	326-329
183	4-(4-BrC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	lysine	253-258
184	4-(4-NO ₂ C ₆ H ₄ O)C ₆ H ₄	CH ₃	H	F	H	H	Na	>360
185	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	I	H	H	Na	>360
186	4-C ₆ H ₅ C ₆ H ₄	CH ₃	H	H	F	H	Na	360
187	4-(4-FC ₆ H ₄ O)C ₆ H ₄	H	H	F	H	H	Na	
188	4-(2,4-F ₂ C ₆ H ₃)C ₆ H ₄	CH ₃	H	F	H	H	Na	
189	4-(2-FC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	F	H	H	Na	330-335(d)
190	4-(3-FC ₆ H ₄)C ₆ H ₄	CH ₃	H	H	H	H	Na	>360
191	4-(4-HOC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	Na	>360



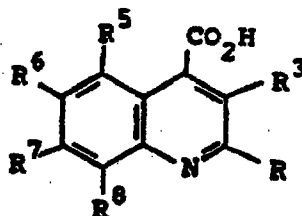
Example 192

6-Chloro-2-(4'-hydroxy-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid.

The compound of Example 24 (4.0 g, 0.01 mole) was added in portions to a solution of borontribromide (5.7 ml, 0.06 mole) in 90 ml of chloroform at 25° under nitrogen. This maroon suspension was stirred for 1 hour then poured onto wet ice. The resulting yellow precipitate was filtered, washed with chloroform and air dried. The solid was dissolved in 1N NaOH, washed with chloroform and then acidified with glacial acetic acid to give a yellow precipitate which was filtered and air dried to give 4.2 g of the yellow solid 6-chloro-2-(4'-hydroxy-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid, m.p. >360°.

The compound of Example 192 and other compounds which can be prepared using such procedures are listed in Table 5.

Table 5



Ex.	R	R ³	R ⁵	R ⁶	R ⁷	R ⁸	m.p. (°C)
192	4-(4-HOC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	>360
193	4-(4-HOC ₆ H ₄)C ₆ H ₄	CH ₃	H	F	H	H	
194	4-(4-HOC ₆ H ₄)C ₆ H ₄	CH ₃	Cl	F	H	H	

Utility

Results of the various biological tests described below establish that the compounds of this invention have the property of inhibiting not only the growth of transplanted mouse tumors but also the growth of human tumors implanted in mice.

The efficacy of the compounds of this invention against the transplanted mouse tumors was evaluated in test systems currently in use at the National Cancer Institute for the detection and assessment of anticancer activity. Most clinically effective drugs exhibit activity in these tests and the tests have a good record of predicting clinical efficacy [Goldin, A., Venditti, J. M. MacDonald, J. S., Muggia, F. M., Henney, J. E. and V. T. Devita, Jr., *Europ. J. Cancer*, 17, 129—142, (1981); Venditti, J. M., *Seminars in Oncology*, 8 (4) (1981); Goldin, A. and J. M. Venditti, in *Recent Results in Cancer Research*, 70, S. K. Carter and Y. Sakurai, Eds., Springer-Verlag, Berlin/Heidelberg, 1980].

Melanotic Melanoma B16 Test

The animals used were B₆C₃F₁ mice, all of one sex, weighing a minimum of 18 g for males and 17 g for females and all within a 4 g weight range at the start of the test. The test group comprised 9 or 10 mice. The tumor was implanted in each of the test mice by the subcutaneous injection of 0.5 ml of a tumor homogenate prepared by homogenizing a 1 g portion of melanotic melanoma in 10 ml of cold physiological saline. The test compounds suspended in hydroxypropylcellulose were administered intraperitoneally at various doses once daily for nine consecutive days starting on day one relative to the day of tumor inoculation (day 0). The control mice received injections of hydroxypropylcellulose vehicle only. The mice were weighed and survivors were recorded on a regular basis for 60 days. The median survival times and the ratio of the median survival times for treated (T) to control (C) mice were calculated. The median survival time of the nontreated tumored mice ranged from 15 to 17 days. Drug effectiveness was assessed on the basis of the survival time. Results were expressed as a percentage of the control survival time (Survival Time T/C × 100%). The criterion for effectiveness was determined by: T/C × 100 ≥ 125 percent.

Results with the compound of Example 1 and cis-platin, a drug used clinically, are shown in Table 6. The data indicate that the compound of Example 1 is effective against the B16 melanoma in mice.

Table 6**Melanotic Melanoma B16 Test**

<u>Compound</u>	<u>Dose (mg/kg)</u>	<u>T/C × 100 (percent) 2 Tests</u>
Example 1	400	131. 179
	200	145. 150
	100	145. 155
	50	148. 138
	25	127. 125
Cisplatin	2	212. 136
	1	- . 175

Lymphoid Leukemia L1210

The animals used in this test were CD₂F₁ mice, all males weighing a minimum of 18 g and all within a 4 g weight range at the start of the test. The test group group consisted of six mice. The tumor was implanted in each of the test mice by the intraperitoneal injection of 0.1 ml of diluted ascitic fluid containing 10⁵ cells drawn from a mouse with L1210 leukemia. The test compounds were suspended in hydroxypropylcellulose or saline with Tween® 80 surfactant or dissolved in saline and injected intraperitoneal, at various doses, once daily for nine consecutive days starting on day one relative to the day of tumor inoculation (day 0). The control mice received injections of saline or hydroxypropylcellulose vehicle only. The mice were weighed and survivors were recorded on a regular basis for 30 days. The median survival time and the ratio of the median survival time for treated (T) and control (C) mice was calculated. The median survival time of the non-treated tumored mice ranged from 8—9 days. Drug effectiveness was assessed on the basis of the survival time. Results were expressed as a percentage of the control survival time (Median Survival Time T/C × 100%). The criterion for effectiveness was determined by: T/C × 100 ≥ 125 percent.

Results of tests with compounds of this invention are shown in Table 7. The data indicate that the compounds of the invention are effective against the L1210 leukemia in mice.

Human Colon Tumor Test *in vitro*

The compounds of this invention were also tested for their ability to inhibit the growth of human colon carcinoma cells *in vitro*. Compounds effective in inhibiting the growth of these cells also show activity in inhibiting the L1210 leukemia in mice.

- 5 The human colon carcinoma cells, designated HCT-15, were derived from a specimen of an adenocarcinoma of human colon removed during surgery. The cells were grown in Roswell Park Medical Institute (RPMI) Medium 1640 supplemented with 10% heat inactivated fetal calf serum, penicillin (100 units/ml), streptomycin (100 µg/ml), gentamicin (20 µg/ml), fungizone (25 µg/ml), 0.075 percent sodium bicarbonate, 10 µM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid and 10 µM N-
- 10 tris(hydroxymethyl)methylglycine. To determine the potency of the test compounds in inhibiting the growth of the cells, the procedure was as follows: on day 0, replicate 35 mm tissue culture dishes were each inoculated with 1.5×10^5 HCT-15 cells in 2 ml supplemented RPMI Medium 1640. On day 1 cells from sample dishes were harvested using trypsin (0.25%) treatment and counted with a hemocytometer to determine the number of cells per dish at the time of the addition of the compounds. Compounds of this
- 15 invention were added in varying concentrations to other cultures. On day 4, treated and control cultures were harvested by trypsin treatment and the number of cells was determined. The number of doublings for the control cells was determined from the cell numbers on days 1 and 4. The ID_{50} , the concentration of compound required to inhibit by 50 percent the number of doublings, was then calculated from the dose-response curve in which cell numbers were plotted on log-log paper against compound concentrations in
- 20 micrograms per ml. Results of tests with compounds of this invention and with reference drugs used clinically are shown in Table 7. They show that the compounds are active in inhibiting the growth of the human colon tumor cells.

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Table 7

<u>Example</u> <u>No.</u>	<u>L1210 Leukemia</u> <u>(dose in mg/kg) %T/C</u>	<u>in vitro HCT-15</u> <u>ID50 µg/ml</u>
1	(200) 189	0.05
2	(50) 186	0.10
3	(400) 207	0.50
4	(200) 128	0.48
5	(400) 141	0.02
6	(400) 162	0.24
7	(200) 136	2.30
8	(400) 147	0.40
9	(200) 127	0.07
10	(200) 163	0.03
11	(25) 176	0.19
12	(50) 261	1.00
13	(400) 129	0.24
14	(50) 195	0.38
15	(200) 158	0.28
16	(400) 190	1.00
17	(400) 136	0.65
18	(100) 185	<0.50
19	(25) 234	<0.50
20	(200) 211	<0.50
21	(200) 160	<5.0 and >0.5
22	(100) 135	<5.0 and >0.5
23	(25) 159	<5.0 and >0.5
24	(400) 154	0.28
26	(300) 136	<0.50
27	(50) 155	NT
28	(18) 174	<0.50
29	(18) 194	<0.50
30	(300) 291	<0.50
31	(37.5) 218	<0.50

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Table 7 continued

<u>Example</u> <u>No.</u>	<u>L1210 Leukemia</u> <u>(dose in mg/kg) %T/C</u>	<u>in vitro HCT-15</u> <u>ID50 µg/ml</u>
32	(175) 153	<5.0 and >0.5
33	(200) 170	<0.50
34	(400) 170	NT
35	(150) 204	NT
36	(75) 185	NT
37	(50) 155	NT
38	NT	>1
39	NT	<0.1
40	NT	>1
45	(400) 160	0.13
46	NT	0.42
47	NT	3.20
48	NT	0.10
49	(200) 174	>5.00
50	(100) 131	>5.00
51	(75) 173	<0.50
52	(75) 189	<0.50
53	(75) 136	<0.50
54	(300) 125	<0.50
55	(150) 156	<5.0 and >0.5
56	(75) 176	<0.50
57	(150) 197	<0.50
58	(150) 141	>0.50
59	(300) 152	>5.00
60	(300) 192	<0.50
61	(75) 160	NT
68	NT	<1 and >0.1
71	NT	<1.0 and >0.1
73	NT	<0.1
74	(50) 104	NT

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Table 7 continued

<u>Example</u> <u>No.</u>	<u>L1210 Leukemia</u> <u>(dose in mg/kg) XT/C</u>	<u>in vitro HCT-15</u> <u>ID50 µg/ml</u>
75	(150) 145	NT
76	NT	<1.0 and >0.1
80	(25) 128	<0.50
81	(25) 191	<0.50
82	NT	>1.00
83	NT	>1.00
84	NT	<0.1
85	NT	<1 and >0.1
86	(175) 153	<5.0 and >0.50
87	(100) 146	<0.50
91	(100) 103 + (40) 140*	0.04
92	(50) 180, 176, 172	0.03
93	(50) 101*	0.06, 0.04
94	(100) 107*	0.65
95	(100) 108*	0.04
96	(37.5) 97*	<0.50
97	(25) 110*	0.14
99	(50) 101*	0.07, 0.34
100	(50) 103*	0.028, 0.24
101	(50) 154, 161	0.41
102	(12.5) 164	1.0, 1.9
103	(200) 108*	0.17
104	(100) 137, 164	0.22
105	(12.5) 108*	0.33
106	(25) 107*	1.20
107	(25) 116*	0.09
108	(100) 166	0.10
109	(100) 172	<0.50
110	(25) 135	<0.50
111	(25) 125, 135	<0.50

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Table 7 continued

<u>Example</u> <u>No.</u>	<u>L1210 Leukemia</u> <u>(dose in mg/kg) &T/C</u>	<u>in vitro HCT-15</u> <u>ID50 µg/ml</u>
112	(25) 128	<0.50
113	(25) 166, 166	<5.0 and >0.5
114	(50) 121*	1.30
116	(75) 102*	<0.50
117	(25) 163, 175	<5.0 and >0.5
118	(25) 179, 195	0.017
119	(18) 170	<0.50
120	(100) 132	<0.50
121	(18) 175	<0.50
122	(175) 153	<5.0 and >0.5
123	(21.9) 145	<0.50
124	(360) 184	NT
125	(150) 150	NT
126	(37.5) 150	NT
127	(50) 193	NT
128	NT	>1
129	NT	<0.1
134	(100) 110*	<1 and >0.1
135	(400) 160	0.13, 0.55
136	(25) 103*	>0.50
137	(50) 107*	>5.00
139	(100) 146	<5.00
141	(75) 139	<0.50
142	(37.5) 169	<0.50
143	(37.5) 132	<0.50
144	(37.5) 123*	<0.50
145	(75) 132	<0.50
146	(37.5) 164	<0.50
147	(18) 132	<0.50
148	(37.5) 102*	>5.00

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Table 7 continued

<u>Example</u> <u>No.</u>	<u>L1210 Leukemia</u> <u>(dose in mg/kg) &T/C</u>	<u>in vitro HCT-15</u> <u>ID50 ug/ml</u>
149	(75) 107*	>5.00
150	(37.5) 105*	<0.50
151	(75) 144	<5.0 and >0.5
158	NT	<1 and >0.1
161	(100) 148	>1.00
163	(43.8) 180	<0.50
164	(22.5) 234	<0.50
165	NT	>1.00
166	NT	<1.0 and >0.1
167	(12.5) 197	<0.1
169	NT	0.04
170	(25) 188	0.10
171	(100) 164	<0.50
172	(100) 151	<0.50
173	(25) 122	<0.50
174	(12.5) 156, 159	<5 and >0.5
175	(12.5), 156, 159	<5.0 and >0.5
176	(37) 175	<0.50, 0.41
177	(37.5) 172	<0.50
178	(75) 172	<0.50
179	(37.5) 166	<0.50
180	(18) 101*	<0.50
181	(37.5) 108*	<0.50
182	(46) 168	<0.50
183	(22.5) 208	<5.0 and >0.5
184	(175) 153	<5.0 and >0.5
185	(50) 175	<1.0 and >0.1
186	(45) 123	<0.50
187	(75) 131	<0.50
188	(12.5) 187	<0.01

Table 7 continued

5	Example	L1210 Leukemia	in vitro HCT-15
	No.	(dose in mg/kg) %T/C	ID50 µg/ml
10	189	(12.5) 197	<0.1.
	192	(200) 166	>1
	Adriamycin	NT	0.01
15	Cisplatin	NT	0.66
	5-Fluorouracil	NT	0.27

20 * Dosing Q3DX9 instead of Q1DX9
 = Compounds dosed at non-optimal Q1DX9
 instead of Q3DX9, should be active if
 25 dosed Q3DX9.
 NT = not tested

30 The compounds of Examples 1 and 91 were also tested for effectiveness against a human colon tumor
 implanted in athymic mice. These mice are immunodeficient and thus do not reject implanted tumors of
 human origin.

Human Colon Tumor HCT—15

35 The animals used were Swiss NU/NU athymic mice, weighing 20—22 g each at the start of the test. The
 test group consisted of twelve mice, seven males and five females. The HCT—15 tumor cell line, derived
 from a patient with adenocarcinoma of the colon, was maintained in culture. The tumor was implanted in
 each of the test mice by the subcutaneous injection in the flank region of 0.2 ml of physiological saline
 containing 10^7 HCT—15 cultured cells. Tumors appeared within 72 hours and treatment started one week
 after tumor inoculation.

40 Test compounds, suspended in methocel (0.5% in water) or dissolved in water, were injected intra-
 peritoneally once daily for five consecutive days starting on day seven relative to the day of tumor
 inoculation (day 0). The body weight and the size of the tumor were determined daily. Tumor size was
 determined by two-dimensional caliper measurements. Tumor weight was estimated from the formula:

$$45 \quad \frac{1 \times w^2}{2}$$

50 = mg tumor weight in which 1 = length and w = width of the tumor in mm. The net tumor weight was
 determined by subtracting from the actual tumor weight at the time of evaluation the initial estimated
 tumor weight at the time treatment was started (day 7). Drug effectiveness was assessed on the basis of
 inhibition of the gain in net tumor weight in the treated (T) compared to that of the control (C) mice. Percent
 tumor growth inhibition was calculated by the formula:

$$55 \quad \text{Percent tumor growth inhibition} = 1 - \frac{\text{net tumor weight:Treated}}{\text{net tumor weight:Control}} \times 100\%$$

60 Results of a test are shown in Table 8. The data indicate that the compounds of this invention inhibited
 the growth of the HCT—15 human colon tumor in mice. 5-Fluorouracil used as a reference drug was toxic at
 the 40 mg/kg dose and ineffective at the 20 mg/kg dose. 5-Fluorouracil is sometimes used in the treatment
 65 of colon tumors in man but is not consistently effective.

Table 8

Human Colon Tumor HCT-15 In Mice

<u>Compound</u>	<u>Dose mg/kg</u>	<u>Day 7*</u>		<u>Day 21</u>	
		<u>Average Tumor Weight (mg)</u>	<u>Average Tumor Weight (mg)</u>	<u>Net Tumor Weight gain (mg)</u>	<u>Tumor Growth Inhibition (Percent)</u>
Methocel Control	0	56.2	349.9	293.7	0
Example 1	200	56.8	156.3	99.4	66.2
	100	56.6	212.9	156.3	46.8
	50	56.3	252.9	196.6	33.1
Example 91	40	56.8	256.9	200.1	32.0
	20	56.2	245.1	188.9	35.7
	10	56.8	322.8	266.0	10.0
5-Fluorouracil	40		Toxic		
	20	56.7	421.7	365	0

*Day treatment was started.

In summary, tests have shown that the compounds of this invention have antitumor activity against transplanted mouse tumors including the L1210 lymphoid leukemia and the B16 melanotic melanoma, in mice. The compounds are also active against the human colon tumor HCT-15 in tissue culture or xenografted in athymic mice.

Dosage Forms

The antitumor compounds (active ingredients) of this invention can be administered to inhibit tumors by any means that produces contact of the active ingredient with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals; either as individual therapeutic active ingredients or in a combination of therapeutic active ingredients. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be a tumor-inhibiting amount of active ingredient and will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular active ingredient, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be about 5 to 400 milligrams per kilogram of body weight. Ordinarily 10 to 200, and preferably 10 to 50 milligrams per kilogram per day given in divided doses 2 to 4 times a day or in sustained release form is effective to obtain desired results.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5—95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions, it can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate and stearic acid. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar

coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffers substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 175 milligrams of lactose, 24 milligrams of talc, and 6 milligrams magnesium stearate.

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

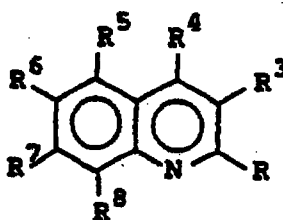
A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P, and 0.025 milliliters of vanillin.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:



(I)



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coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

5 In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffers substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used
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30 Injectable

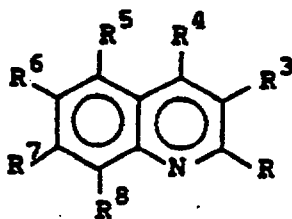
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35 Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P, and 0.025 milliliters of vanillin.

40 **Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE**

1. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:



(I)



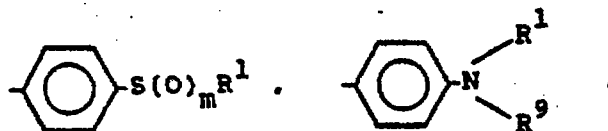
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wherein

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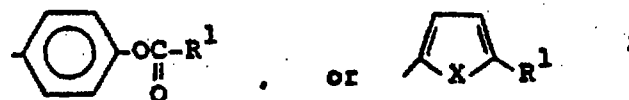


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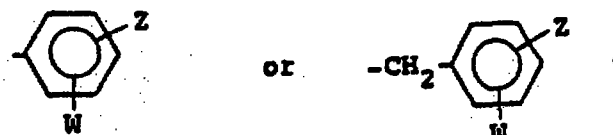
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30

X is O, S(O)_n, NH or CH=N;
R¹ is CH₃CH₂(CH₃)CH, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

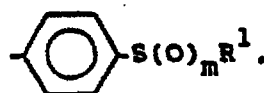
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when R is

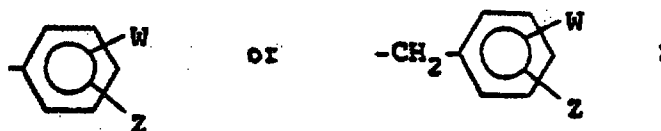
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R¹ can be in addition alkyl of 3—4 carbon atoms;

50

R² is



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R³ is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or (CH₂)_pCOR¹⁰ where p is 1, 2, 3 or 4;

R⁴ is CO₂H or CO₂R¹¹;

60

R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² or CH₂CH₃, at least two of R⁵, R⁶, R⁷ and R⁸ being H;

R⁹ and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R¹⁰ is OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ or N(CH₃)₂;

R¹¹ is (CH₂)₂₋₄NR^{9A};

65

R¹² is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;



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W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO₂, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF₃ or NH₂;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

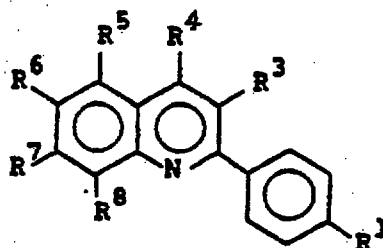
or a pharmaceutically suitable salt thereof; with the following provisos:

1) R⁵, R⁶ and R⁷ cannot all be H;

2) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁶ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl; and

3) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl.

2. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:



(II)

wherein

R¹ is cycloalkyl of 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl of 1—5 carbon atoms or CF₃; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R² is H or alkyl of 1—3 carbon atoms;

R³ is CO₂H or a sodium or potassium salt thereof;

R⁴ and R⁵ are independently H, halogen, CH₃ or CF₃; and

R⁶ and R⁸ are independently H or halogen;

or a pharmaceutically suitable salt thereof; provided that R⁵, R⁶ and R⁷ cannot all be H and that when R¹ is cyclohexyl and R³ is H, R⁶ must all be Cl or F, but R⁶ and R⁸ cannot both be Cl.

3. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 21.

4. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 22.

5. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 23.

6. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 24.

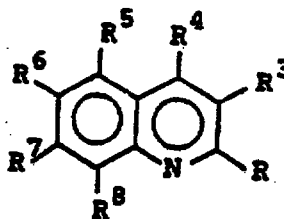
7. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 25.

8. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 26.

9. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 27.

10. An antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 28.

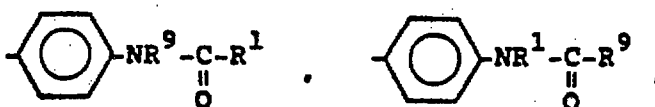
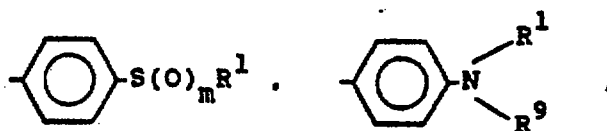
11. Use of at least one compound having the formula:



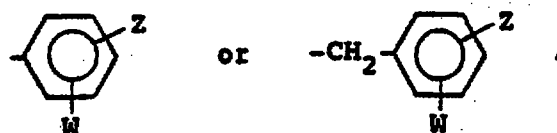
(I)



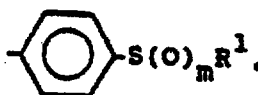
wherein



30 X is O, S(O)_n, NH or CH=N;
R¹ is CH₃CH₂(CH₂)CH, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

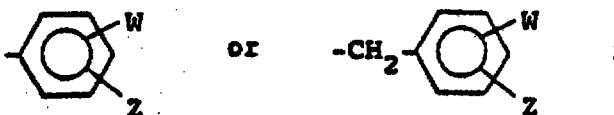


40 when R is



R¹ can be in addition alkyl of 3—4 carbon atoms;

50 R² is



55 R³ is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or (CH₂)_pCOR¹⁰ where p is 1, 2, 3 or 4;

R⁴ is CO₂H or CO₂R¹¹;

60 R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² or CH₂CH₃, at least two of R⁵, R⁶, R⁷ and R⁸ being H;

R⁹ and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R¹⁰ is OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ or N(CH₃)₂;

R¹¹ is (CH₂)₂₋₄NR⁹R^{9A};

65 R¹² is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

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W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO₂, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF₃ or NH₂;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

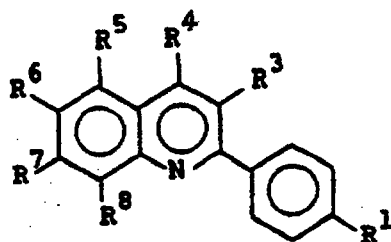
or a pharmaceutically suitable salt thereof; with the following provisos:

1) R⁵, R⁶ and R⁷ cannot all be H;

2) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁶ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl; and

3) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

12. Use of at least one compound having the formula:



(II)

wherein

R¹ is cycloalkyl or 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl of 1—5 carbon atoms or CF₃; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R³ is H or alkyl of 1—3 carbon atoms;

R⁴ is CO₂H or a sodium or potassium salt thereof;

R⁵ and R⁶ are independently H, halogen, CH₃ or CF₃; and

R⁷ and R⁸ are independently H or halogen;

or a pharmaceutically suitable salt thereof; provided that R⁵, R⁶ and R⁷ cannot all be H and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

13. Use of at least one compound of Claim 21, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

14. Use of at least one compound of Claim 22, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

15. Use of at least one compound of Claim 23, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

16. Use of at least one compound of Claim 24, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

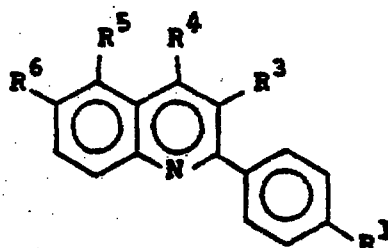
17. Use of at least one compound of Claim 25, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

18. Use of at least one compound of Claim 26, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

19. Use of at least one compound of Claim 27, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

20. Use of at least one compound of Claim 28, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

21. A compound having the formula:



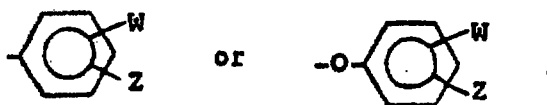
(III)



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wherein

R¹ is cycloalkyl of 3—7 carbon atoms,



10 R³ is H or alkyl of 1—3 carbon atoms;

R⁴ is CO₂H or a sodium or potassium salt thereof;

R⁵ and R⁶ are independently H, halogen or CF₃ provided that both R⁵ and R⁶ are not hydrogen; and

W and Z are independently H, halogen, alkyl of 1—5 carbon atoms or CF₃;

15 provided that when R¹ is phenyl or phenoxy, and R⁵ is H, then R⁶ cannot be Br; and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F.

22. A compound of Claim 21 wherein:

R¹ is phenyl, phenyl substituted with at least one halogen, phenoxy, or phenoxy substituted with at least one halogen;

R³ is methyl;

20 R⁵ is H or Cl; and

R⁶ is F or Cl.

23. The compound of Claim 21 which is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

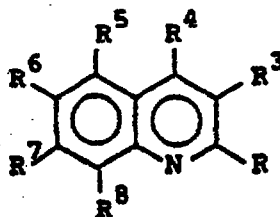
24. The compound of Claim 21 which is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.

25. The compound of Claim 21 which is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

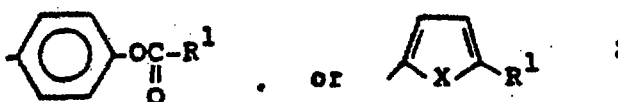
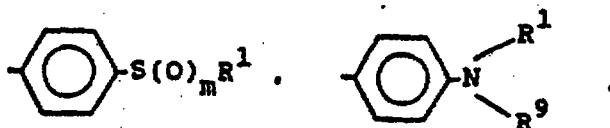
26. The compound of Claim 21 which is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

27. The compound of Claim 21 which is 2-(1,1'-biphenyl-4-yl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

28. A compound having the formula:



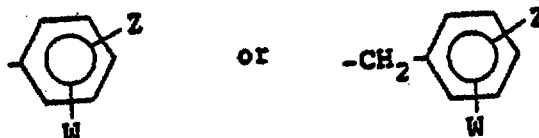
wherein



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X is O, S(O)_n, NH or CH=N;
R¹ is CH₃CH₂(CH₂)₃CH, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

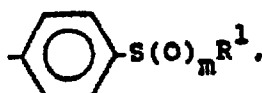
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when R is

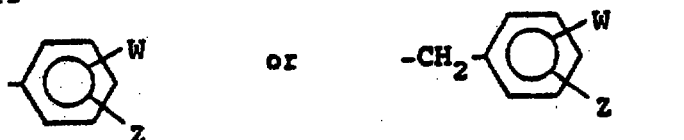
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R¹ can be in addition alkyl of 3—4 carbon atoms;

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R² is



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R³ is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or (CH₂)_pCOR¹⁰ where p is 1, 2, 3 or 4;

30

R⁴ is CO₂H or CO₂R¹¹;
R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² or CH₂CH₃, at least two of R⁵, R⁶, R⁷ and R⁸ being H;

R⁹ and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R¹⁰ is OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ or N(CH₃)₂;

35

R¹¹ is (CH₂)₂₋₄NR⁹R^{9A};

R¹² is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO₂, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF₃ or NH₂;

m is 0 or 1;

n is 0 or 1; and

40

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

1) when R⁴ is CO₂H, R¹ is phenyl or phenoxy, and R⁵, R⁷ and R⁸ are H, R⁶ cannot be Br;

2) R⁵, R⁶ and R⁷ cannot all be H;

3) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁶ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl;

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4) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁵ and R⁸ cannot both be Cl;

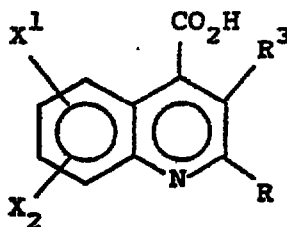
5) when R¹ is 4—H₂NC₆H₄ and R³ is H, R⁶ cannot be Cl and R⁸ cannot be Br;

6) when R¹ is alkyl of 6 carbons and Y is H, then R⁴ cannot be CO₂H, R⁵, R⁷ and R⁸ cannot be H, and R⁶ cannot be H, Cl, Br, I or CH₃.

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29. A process for preparing compounds of Claim 28 characterized by reacting a quinoline carboxylic acid of the formula:

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by (a) when R is OH; acylating the hydroxy with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate R¹²S such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of this solvent, or (c) dissolving the

65

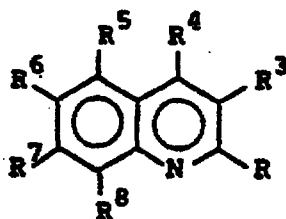
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quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as SOCl₂ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, R¹¹OH, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

30. A process for preparing the compounds of Claim 28 consisting essentially of (1) reacting an appropriately substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as dimethylamine or triethylamine at a temperature of 25°C to 50°C for 2 to 48 hours, (2) dissolving the resulting intermediate (VI) in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as HCl and heating from 50°C to reflux temperature of the solvent mixture for 2 to 48 hours, and optionally the above quinoline carboxylic acid from (2) is further reacted by (a) acylating the corresponding hydroxy, where R is OH, with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate R¹²S such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of the solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as SOCl₂ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, R¹¹OH, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

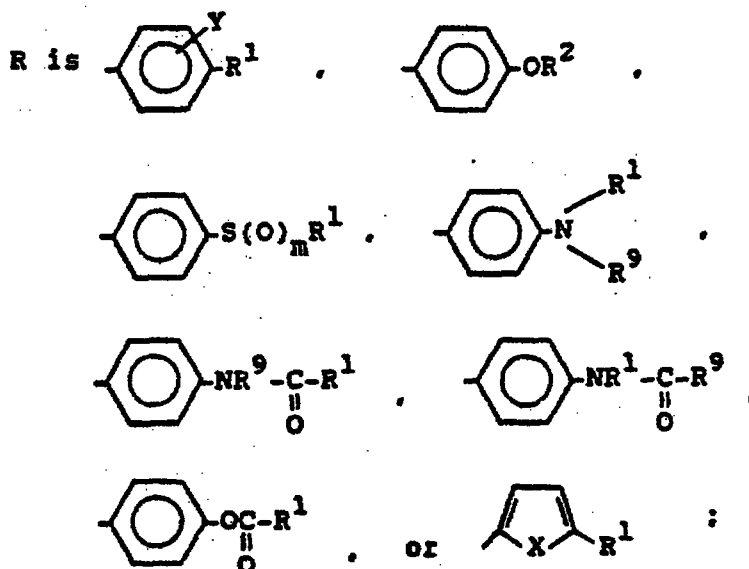
Claims for the Contracting State: AT

1. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound having the formula:



(I)

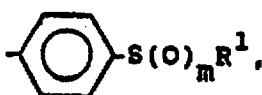
wherein



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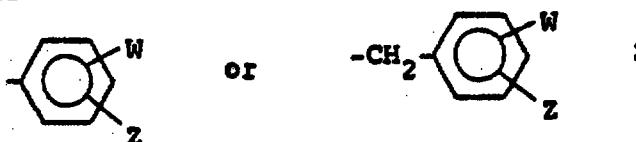


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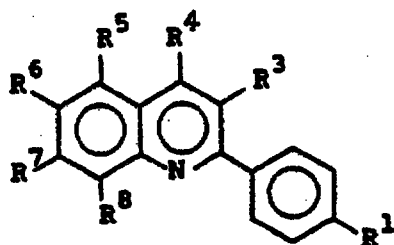
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R^7 and R^8 are independently H or halogen;
or a pharmaceutically suitable salt thereof; provided that R^5 , R^6 and R^7 cannot all be H and that when R^1 is cyclohexyl and R^3 is H, R^6 must all be Cl or F, but R^6 and R^8 cannot both be Cl, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

3. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 21, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

4. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 22, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

5. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 23, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

6. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 24, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

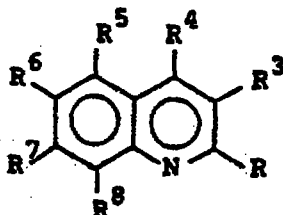
7. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 25, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

8. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 26, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

9. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 27, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

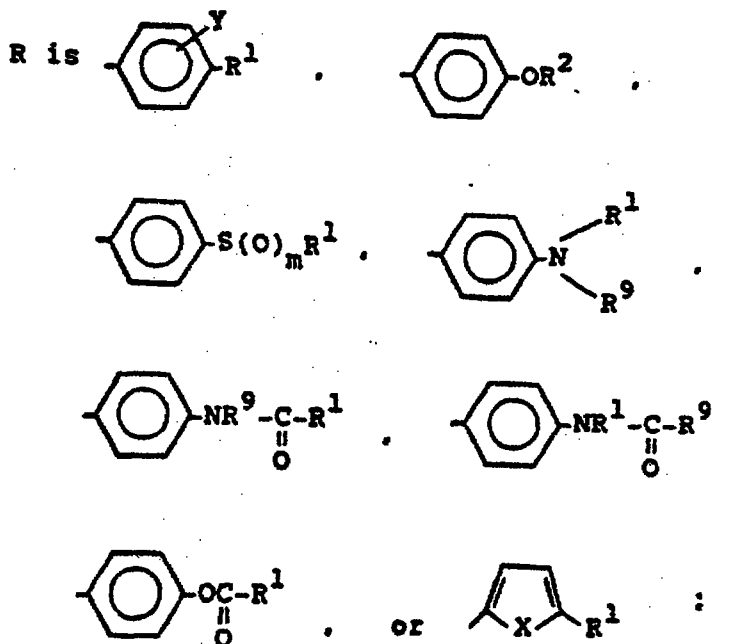
10. Process for preparing an antitumor pharmaceutical composition consisting of a suitable pharmaceutical carrier and at least one compound of Claim 28, which comprises mixing at least one compound and a suitable pharmaceutical carrier.

11. Use of at least one compound having the formula:



(I)

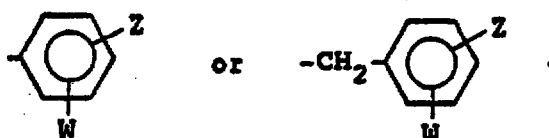
wherein



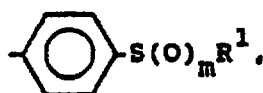


X is O, S(O)_n, NH or CH=N;

R¹ is CH₃CH₂(CH₂)₃CH, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.

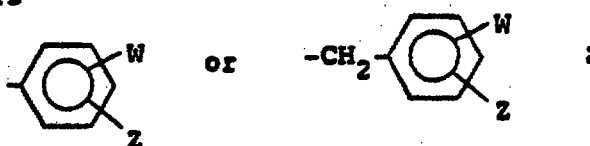


when R is



R¹ can be in addition alkyl of 3—4 carbon atoms;

R² is



R³ is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or (CH₂)_pCOR¹⁰ where p is 1, 2, 3 or 4;

R⁴ is CO₂H or CO₂R¹¹;

R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² or CH₂CH₃, at least two of R⁵, R⁶, R⁷ and R⁸ being H;

R⁹ and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R¹⁰ is OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ or N(CH₃)₂;

R¹¹ is (CH₂)₂₋₄NR⁹R^{9A};

R¹² is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO₂, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF₃ or NH₂;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

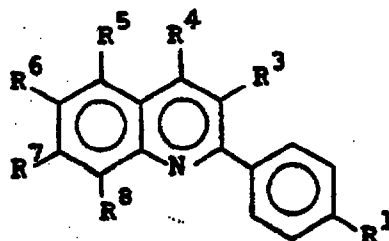
or a pharmaceutically suitable salt thereof; with the following provisos:

1) R⁵, R⁶ and R⁷ cannot all be H;

2) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁵ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl; and

3) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

12. Use of at least one compound having the formula:



(II)

wherein

R¹ is cycloalkyl or 3—7 carbon atoms; phenyl; phenyl substituted with one halogen, alkyl or 1—5 carbon atoms or CF₃; phenoxy; or phenoxy substituted with one halogen or alkyl of 1—5 carbon atoms;

R³ is H or alkyl of 1—3 carbon atoms;

R⁴ is CO₂H or a sodium or potassium salt thereof;

R⁵ and R⁶ are independently H, halogen, CH₃ or CF₃; and

R⁷ and R⁸ are independently H or halogen;

or a pharmaceutically suitable salt thereof; provided that R⁵, R⁶ and R⁷ cannot all be H and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

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13. Use of at least one compound of Claim 21, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

14. Use of at least one compound of Claim 22, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

5 15. Use of at least one compound of Claim 23, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

16. Use of at least one compound of Claim 24, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

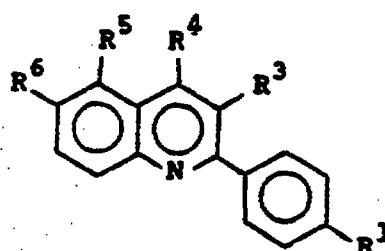
10 17. Use of at least one compound of Claim 25, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

18. Use of at least one compound of Claim 26, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

19. Use of at least one compound of Claim 27, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

15 20. Use of at least one compound of Claim 28, in a tumor-inhibiting amount for the manufacture of a medicament for inhibiting the growth of mammalian tumors.

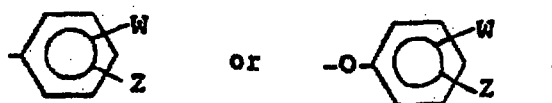
21. A process for preparing a compound having the formula:



(III)

wherein

30 R¹ is cycloalkyl of 3—7 carbon atoms,



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R³ is H or alkyl of 1—3 carbon atoms;

R⁴ is CO₂H or a sodium or potassium salt thereof;

R⁵ and R⁶ are independently H, halogen or CF₃, provided that both R⁵ and R⁶ are not hydrogen; and

W and Z are independently H, halogen, alkyl of 1—5 carbon atoms or CF₃;

40 provided that when R¹ is phenyl or phenoxy, and R⁵ is H, then R⁶ cannot be Br; and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, which comprises (1) reacting an appropriately substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as diethylamine or triethylamine at a temperature of 25°C to 50°C for 2 to 48 hours, (2) dissolving the resulting intermediate (VI) in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as HCl and heating from 50°C to reflux temperature of the solvent mixture for 2 to 48 hours, and optionally the above quinoline carboxylic acid from (2) is further reacted by (a) acylating the corresponding hydroxy, where R is OH, with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate R¹²S such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of the solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as SOCl₂ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, R¹¹OH, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

60 22. A process of Claim 21 wherein:

R¹ is phenyl, phenyl substituted with at least one halogen, phenoxy, or phenoxy substituted with at least one halogen;

R³ is methyl;

R⁵ is H or Cl; and

65 R⁶ is F or Cl.

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23. The process of Claim 21 wherein the compound prepared is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

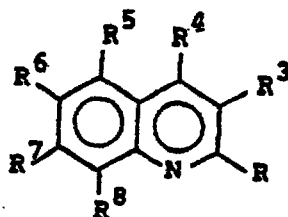
24. The process of Claim 21 wherein the compound prepared is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.

25. The process of Claim 21 wherein the compound prepared is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

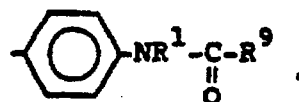
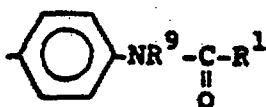
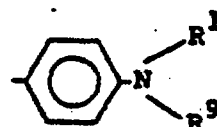
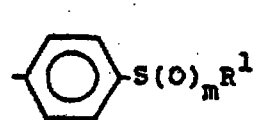
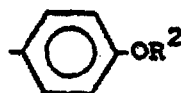
26. The process of Claim 21 wherein the compound prepared is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

27. The process of Claim 21 wherein the compound prepared is 2-(1,1'-biphenyl-4-yl)-5-chloro-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

28. Process for preparing a compound having the formula:

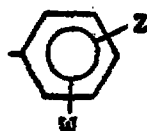


wherein

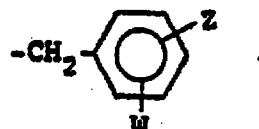


X is O, S(O)_m, NH or CH=N;

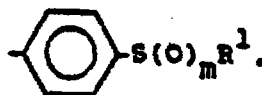
R¹ is CH₂CH₂(CH₂)CH, alkyl of 5—12 carbon atoms, alkenyl of 5—12 carbon atoms, cycloalkyl of 3—7 carbon atoms, cycloalkylalkyl of 5—12 carbon atoms, cycloalkenyl of 5—7 carbon atoms.



or



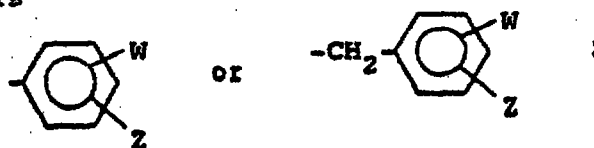
when R is



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R¹ can be in addition alkyl of 3—4 carbon atoms;

R² is



R³ is H, alkoxy of 1—3 carbon atoms, alkylthio of 1—3 carbon atoms or alkyl of 1—3 carbon atoms optionally substituted with one or more of F, Cl, Br or (CH₂)_pCOR¹⁰ where p is 1, 2, 3 or 4;

R⁴ is CO₂H or CO₂R¹¹;

R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² or CH₂CH₃, at least two of R⁵, R⁶, R⁷ and R⁸ being H;

R⁹ and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;

R¹⁰ is OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ or N(CH₃)₂;

R¹¹ is (CH₂)₂₋₄NR⁹R^{9A};

R¹² is alkyl or 1—5 carbon atoms optionally substituted with one or more of F, Cl and Br;

W, Y and Z are independently H, F, Cl, Br, alkyl of 1—5 carbon atoms, NO₂, alkoxy of 1—5 carbon atoms, alkylthio of 1—5 carbon atoms, OH, CF₃ or NH₂;

m is 0 or 1;

n is 0 or 1; and

q is 0, 1 or 2;

or a pharmaceutically suitable salt thereof; with the following provisos:

1) when R⁴ is CO₂H, R¹ is phenyl or phenoxy, and R⁵, R⁷ and R⁸ are H, R⁶ cannot be Br;

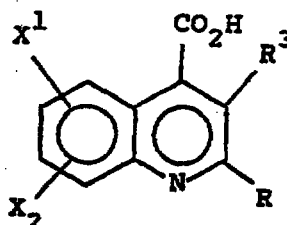
2) R⁵, R⁶ and R⁷ cannot all be H;

3) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁶ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl;

4) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl;

5) when R¹ is 4—H₂NC₆H₄ and R³ is H, R⁶ cannot be Cl and R⁸ cannot be Br;

6) when R¹ is alkyl of 6 carbons and Y is H, then R⁴ cannot be CO₂H, R⁵, R⁷ and R⁸ cannot be H, and R⁶ cannot be H, Cl, Br, I or CH₃, characterized by reacting a quinoline carboxylic acid of the formula:



by (a) when R is OH; acylating the hydroxy with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate R¹²S such as MeSK in a solvent such as dimethylformamide at a temperature of 50°C to reflux of this solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of 0°C to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl; or (d) treating the salt, (c), by treatment with a reagent such as SOCl₂ or oxalyl chloride in an inert solvent such as benzene at a temperature of 25°C to the boiling point of the solvent used to form an acid halide and then adding an alcohol, R¹¹OH, in a solvent such as tetrahydrofuran at a temperature of 10°C to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

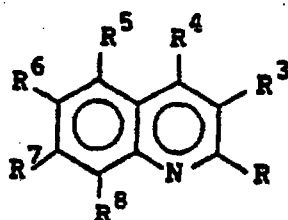
29. A process for preparing the compounds of Claim 28 consisting essentially of (1) reacting an appropriately substituted isatin (IV) with a substituted ketone (V) in a solvent such as ethanol with a base such as dimethylamine or triethylamine at a temperature of 25°C to 50°C for 2 to 48 hours, (2) dissolving the resulting intermediate (VI) in an appropriate solvent such as tetrahydrofuran containing 25—50% by volume of a mineral acid such as HCl and heating from 50°C to reflux temperature of the solvent mixture for 2 to 48 hours, and optionally the above quinoline carboxylic acid from (2) is further reacted by (a) acylating the corresponding hydroxy, where R is OH, with a carboxylic halide such as benzoyl chloride in an inert solvent such as chloroform or a hydrocarbon solvent such as benzene at a temperature from 0°C to the

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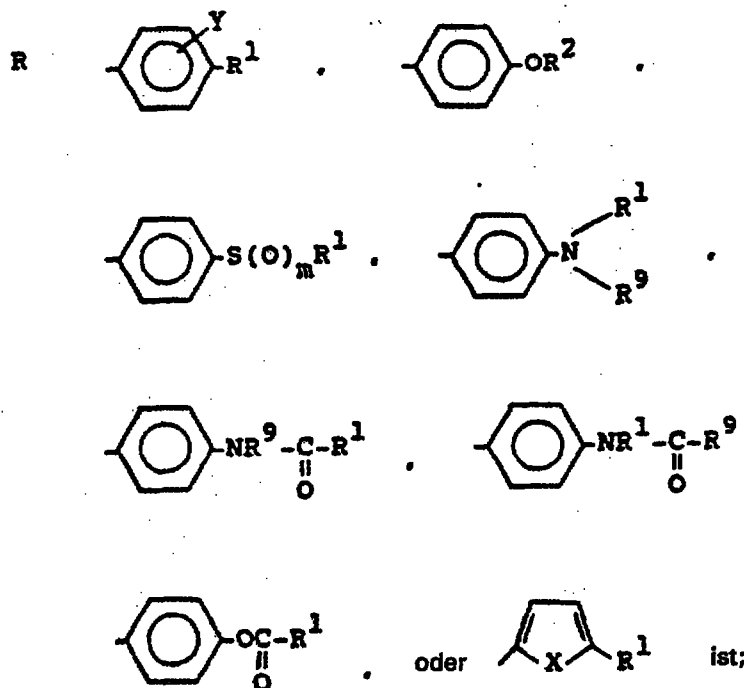
boiling point of the solvent, optionally in the presence of a base such as pyridine, or (b) reacting the appropriately substituted quinoline carboxylic acid with an appropriate thiolate $R^{12}S$ such as $MeSK$ in a solvent such as dimethylformamide at a temperature of $50^{\circ}C$ to reflux of the solvent, or (c) dissolving the quinoline carboxylic acid in a protic solvent such as ethanol, and then treating with a metal oxide or hydroxide such as sodium or potassium oxide or hydroxide or an amine such as 1-amino-butanol or lysine at a temperature of $0^{\circ}C$ to the boiling point of the solvent used and optionally preparing a salt of an amine group by dissolving the amine in a solvent such as ethyl ether and adding a mineral acid such as HCl ; or (d) treating the salt, (c), by treatment with a reagent such as $SOCl_2$ or oxalyl chloride in an inert solvent such as benzene at a temperature of $25^{\circ}C$ to the boiling point of the solvent used to form an acid halide and then adding an alcohol, $R^{11}OH$, in a solvent such as tetrahydrofuran at a temperature of $10^{\circ}C$ to the boiling point of the solvent used, optionally in the presence of a base such as pyridine, triethylamine, or 4-dimethylamine pyridine.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

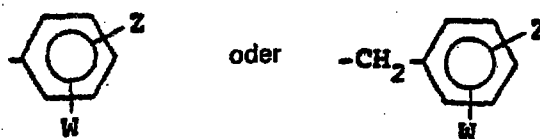
1. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel



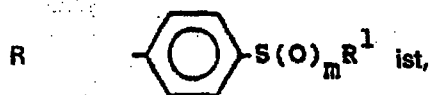
worin



X O, $S(O)_2$, NH oder $CH=N$ ist;
 R^1 $CH_3CH_2(CH_2)_nCH_3$, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

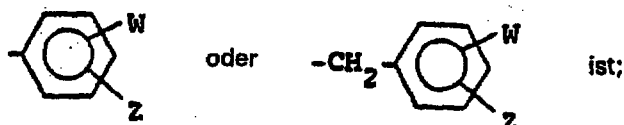


ist, wenn



kann R¹ zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R²



R³ H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder (CH₂)_pCOR¹⁰, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R⁴ CO₂H oder CO₂R¹¹ ist;

R⁵, R⁶, R⁷ und R⁸ unabhängig voneinander H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² oder CH₂CH₃ sind, wobei wenigstens zwei von R⁵, R⁶, R⁷ und R⁸ H sind;

R⁹ und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R¹⁰ OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ oder N(CH₃)₂ ist;

R¹¹ (CH₂)₂₋₄NR⁹R^{9A} ist;

R¹² Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO₂, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF₃ oder NH₂ sind;

m 0 oder 1 ist;

n 0 oder 1 ist; und

q 0, 1 oder 2 ist;

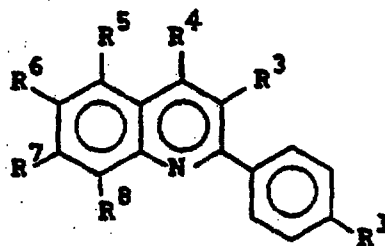
oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) R⁵, R⁶ und R⁷ nicht alle H sein können;

2) wenn R⁴ CO₂CH₂CH₂N(CH₃)₂ ist, R⁶ CH₂CH₃ ist oder R⁷ Cl ist, R¹ nicht Cyclohexyl sein kann; und

3) wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können.

2. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel



(II)

worin

R¹ Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF₃ substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

R³ H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R⁴ CO₂H oder dessen Natrium- oder Kaliumsalz ist;

R⁵ und R⁶ unabhängig voneinander H, Halogen, CH₃ oder CF₃ sind; und

R⁷ und R⁸ unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz derselben;

vorausgesetzt, daß R⁵, R⁶ und R⁷ nicht alle H sein können und daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können.

3. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 21.

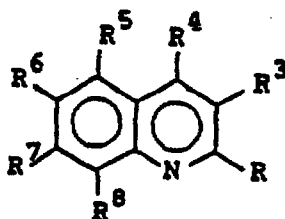
4. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 22.

5. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 23.



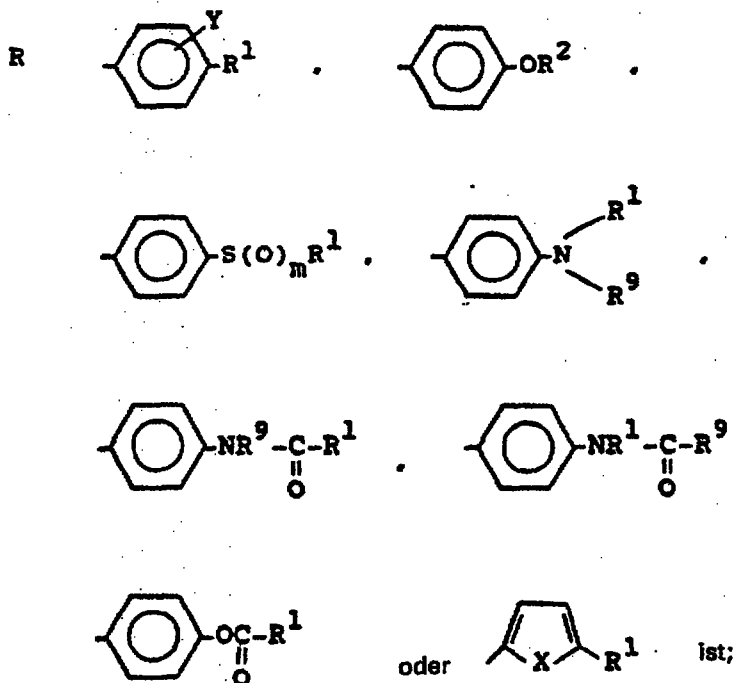
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6. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 24.
7. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 25.
8. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 26.
9. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 27.
10. Pharmazeutische Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 28.
11. Verwendung wenigstens einer Verbindung der Formel



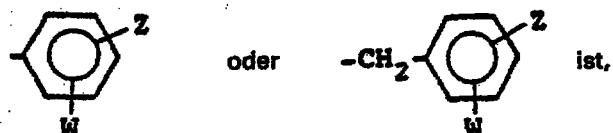
(I)

worin

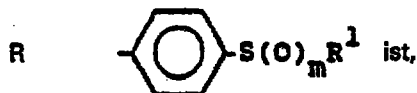


X O, S(O)_m, NH oder CH=N ist;

R¹ CH₃CH₂(CH₃)CH, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,



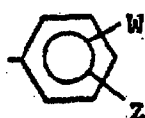
wenn



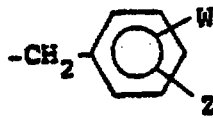
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kann R¹ zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R²



oder



ist;

R³ H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder (CH₂)_pCOR¹⁰, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R⁴ CO₂H oder CO₂R¹¹ ist;

R⁵, R⁶, R⁷ und R⁸ unabhängig voneinander H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² oder CH₂CH₃ sind, wobei wenigstens zwei von R⁵, R⁶, R⁷ und R⁸ H sind;

R⁹ und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R¹⁰ OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ oder N(CH₃)₂ ist;

R¹¹ (CH₂)₂₋₄NR^{9A} ist;

R¹² Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO₂, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF₃ oder NH₂ sind;

m 0 oder 1 ist;

n 0 oder 1 ist; und

q 0, 1 oder 2 ist;

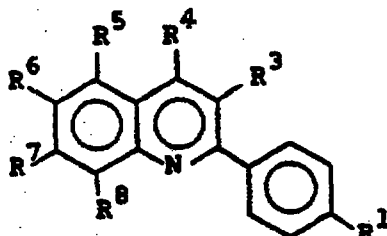
oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) R⁵, R⁶ und R⁷ nicht alle H sein können;

2) wenn R⁴ CO₂CH₂CH₂N(CH₃)₂ ist, R⁵ CH₂CH₃ ist oder R⁷ Cl ist, R¹ nicht Cyclohexyl sein kann; und

3) wenn R¹ Cyclohexyl ist und R³ H ist, R⁵ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können, in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

12. Verwendung wenigstens einer Verbindung der Formel



(II)

worin

R¹ Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF₃ substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

R³ H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R⁴ CO₂H oder dessen Natrium- oder Kaliumsalz ist;

R⁵ und R⁶ unabhängig voneinander H, Halogen, CH₃ oder CF₃ sind; und

R⁷ und R⁸ unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz derselben; vorausgesetzt, daß R⁵, R⁶ und R⁷ nicht alle H sein können und daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁵ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können, in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

13. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 21 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

14. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 22 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

15. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 23 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

16. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 24 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

17. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 25 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

18. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 26 in einer tumor-

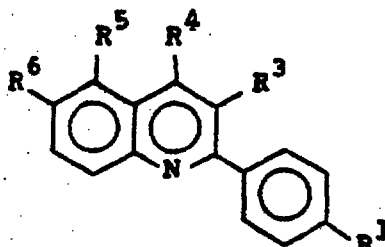
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inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

19. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 27 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

20. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 28 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.

21. Verbindung der Formel



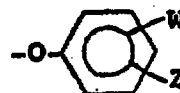
(III)

worin

R¹ Cycloalkyl mit 3—7 Kohlenstoff-Atomen,



oder



ist;

R³ H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R⁴ CO₂H oder dessen Natrium- oder Kaliumsalz ist;

R⁵ und R⁶ unabhängig voneinander H, Halogen oder CF₃ sind, vorausgesetzt, daß R⁵ und R⁶ nicht beide Wasserstoff sind; und W und Z unabhängig voneinander H, Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF₃ sind;

vorausgesetzt, daß, wenn R¹ Phenyl oder Phenoxy ist und R⁵ H ist, R⁶ nicht Br sein kann, und daß, wenn R¹ Cyclohexyl und R⁵ H ist, R⁶ Cl oder F sein muß.

22. Verbindung des Anspruchs 21, worin

R¹ Phenyl, mit wenigstens einem Halogen substituiertes Phenyl, Phenoxy oder mit wenigstens einem Halogen substituiertes Phenoxy ist;

R³ Methyl ist;

R⁵ H oder Cl ist; und

R⁶ F oder Cl ist.

23. Verbindung des Anspruchs 21, welche 2-(1,1'-Biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

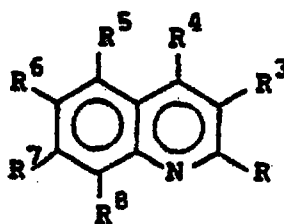
24. Verbindung des Anspruchs 21, welche 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

25. Verbindung des Anspruchs 21, welche 2-(4'-Brom-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

26. Verbindung des Anspruchs 21, welche 2-(2'-Fluor-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

27. Verbindung des Anspruchs 21, welche 2-(1,1'-Biphenyl-4-yl)-5-chlor-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

28. Verbindung der Formel



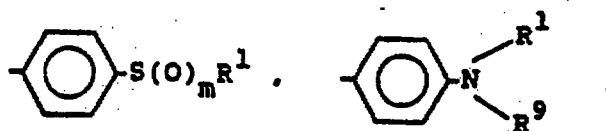
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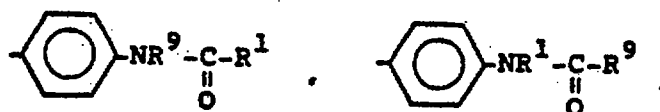


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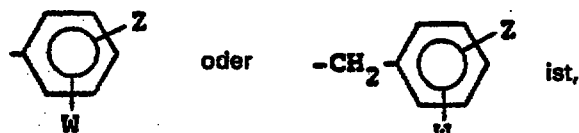
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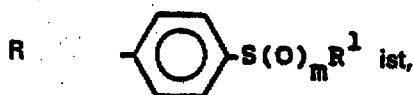
X O, S(O)_q, NH oder CH=N ist;
R¹ CH₃CH₂(CH₃)CH, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

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wenn

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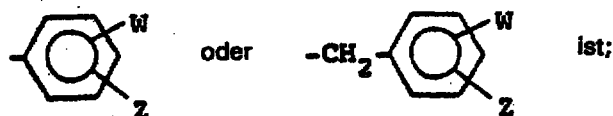


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kann R¹ zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R²

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R³ H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder (CH₂)_pCOR¹⁰, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R⁴ CO₂H oder CO₂R¹¹ ist;

R⁵, R⁶, R⁷ und R⁸ unabhängig voneinander H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² oder CH₂CH₃ sind, wobei wenigstens zwei von R⁵, R⁶, R⁷ und R⁸ H sind;

R⁹ und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R¹⁰ OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ oder N(CH₃)₂ ist;

R¹¹ (CH₂)₂₋₄NR⁹R^{9A} ist;

R¹² Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und

Br substituiert ist;



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W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO₂, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF₃ oder NH₂ sind;

m 0 oder 1 ist;

n oder 1 ist; und

q 0, 1 oder 2 ist;

oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) wenn R⁴ CO₂H ist, R¹ Phenyl oder Phenoxy ist und R⁵, R⁷ und R⁸ H sind, R⁶ nicht Br sein kann;

2) R⁶, R⁸ und R⁷ nicht alle H sein können;

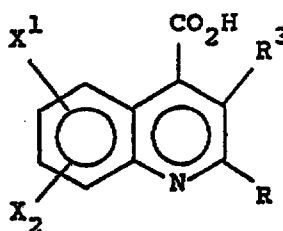
3) wenn R⁴ CO₂CH₂CH₂N(CH₃)₂ ist, R⁶ CH₂CH₃ ist oder R⁷ Cl ist, R¹ nicht Cyclohexyl sein kann;

4) wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können;

5) wenn R¹ 4-H₂NC₆H₄ und R³ H ist, R⁶ nicht Cl sein kann und R⁸ nicht Br sein kann;

6) wenn R¹ Alkyl mit 6 Kohlenstoffatomen ist und Y H ist, R⁴ nicht CO₂H sein kann, R⁵, R⁷ und R⁸ nicht H sein können und R⁶ nicht H, Cl, Br, I oder CH₃ sein kann.

29. Verfahren zur Herstellung von Verbindungen des Anspruchs 28 gekennzeichnet durch Umsetzung einer Chinolincarbonsäure der Formel



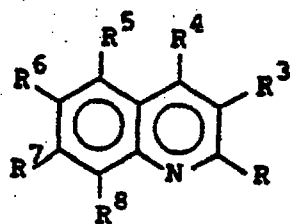
durch (a), wenn R OH ist, Acylierung der Hydroxygruppe mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, oder (b) Umsetzung der geeignet substituierten Chinolincarbonsäure mit einem geeigneten Thiolat R¹²S wie MeSK in einem Lösungsmittel wie Dimethylformamide bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels, oder (c) Lösen der Chinolincarbonsäure in einem protischen Lösungsmittel wie Ethanol und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kalium-oxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellung eines Salzes einer Aminogruppe durch Lösen desamins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes (c), durch Behandlung mit einem Reagenz wie SOCl₂ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, R¹¹OH, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamin oder 4-Dimethylaminopyridin.

30. Verfahren zur Herstellung der Verbindungen von Anspruch 28, im wesentlichen bestehend aus (1) Umsetzung eines geeignet substituierten Isatins (IV) mit einem substituierten Keton (V) in einem Lösungsmittel wie Ethanol mit einer Base wie Diethylamin oder Triethylamin bei einer Temperatur von 25°C bis 50°C für 2 bis 48 Stunden, (2) Lösen der entstandenen Zwischenstufe (VI) in einem geeigneten Lösungsmittel wie Tetrahydrofuran, welches 25—50 Vol.-% einer Mineralsäure wie HCl enthält, und 2 bis 48 Stunden Erhitzen auf 50°C bis zur Rückflußtemperatur des Lösungsmittelgemischs, und wahlweise wird die voranstehende Chinolincarbonsäure aus (2) weiter umgesetzt durch (a) Acylierung der entsprechenden Hydroxygruppe, in der R OH ist, mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittels, wahlweise in der Gegenwart einer Base wie Pyridin, oder (b) durch Umsetzung der geeignet substituierten Chinolincarbonsäure mit einem geeigneten Thiolat R¹²S wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels oder (c) durch Lösen der Chinolincarbonsäure in einem protischen Lösungsmittel wie Ethanol, und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellen eines Salzes einer Aminogruppe durch Lösen desamins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes, (c) durch Behandlung mit einem Reagenz wie SOCl₂ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, R¹¹OH, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamine oder 4-Dimethylaminopyridin.

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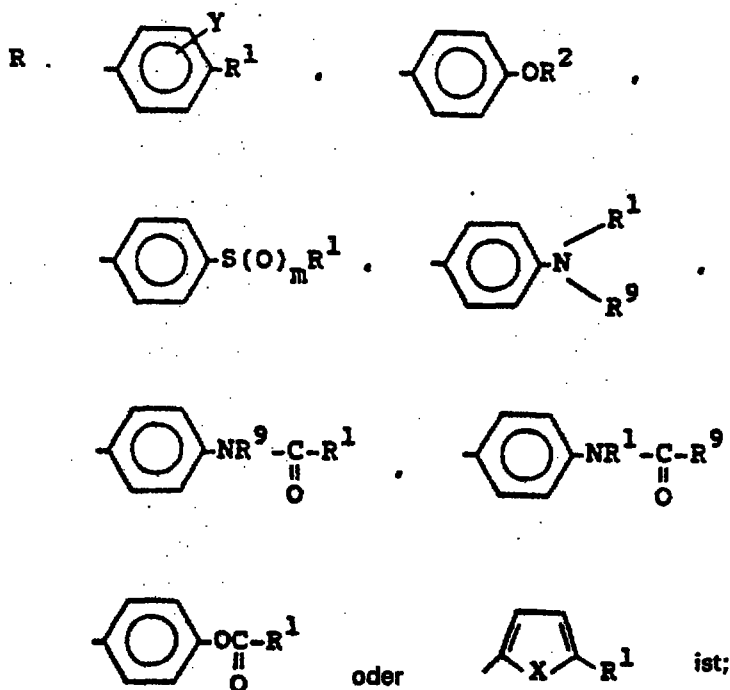
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel

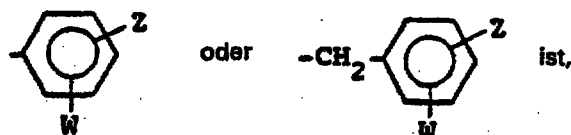


(I)

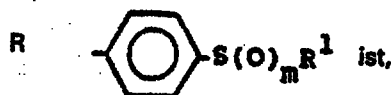
worin



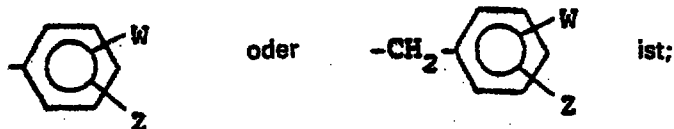
X O, S(O)_m, NH oder CH=N ist;
R¹ CH₃CH₂(CH₂)CH, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,



wenn



kann R¹ zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;





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R³ H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder (CH₂)_pCOR¹⁰, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R⁴ CO₂H oder CO₂R¹¹ ist;

R⁵, R⁶, R⁷ und R⁸ unabhängig voneinander H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² oder CH₂CH₃ sind, wobei wenigstens zwei von R⁵, R⁶, R⁷ und R⁸ H sind;

R⁹ und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R¹⁰ OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ oder N(CH₃)₂ ist;

R¹¹ (CH₂)₂₋₄NR^{9A} ist;

R¹² Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO₂, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF₃ oder NH₂ sind;

m 0 oder 1 ist;

n oder 1 ist; und

q 0, 1 oder 2 ist;

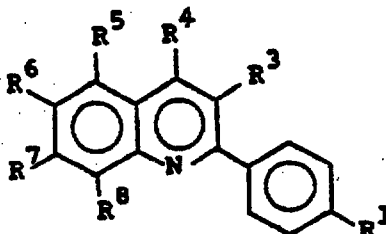
oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) R⁵, R⁶ und R⁷ nicht alle H sein können;

2) wenn R⁴ CO₂CH₂CH₂N(CH₃)₂ ist, R⁶ CH₂CH₃ ist oder R⁷ Cl ist, R¹ nicht Cyclohexyl sein kann; und

3) wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

2. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung der Formel



(II)

worin

R¹ Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF₃ substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

R³ H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R⁴ CO₂H oder dessen Natrium- oder Kaliumsalz ist;

R⁵ und R⁶ unabhängig voneinander H, Halogen, CH₃ oder CF₃ sind; und

R⁷ und R⁸ unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz derselben;

vorausgesetzt, daß R⁵, R⁶ und R⁷ nicht alle H sein können und daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

3. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 21, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

4. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 22, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

5. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 23, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

6. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 24, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

7. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 25, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

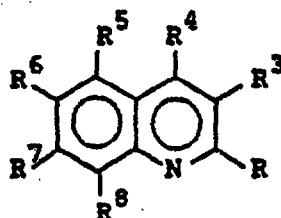
8. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 26, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

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9. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 27, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

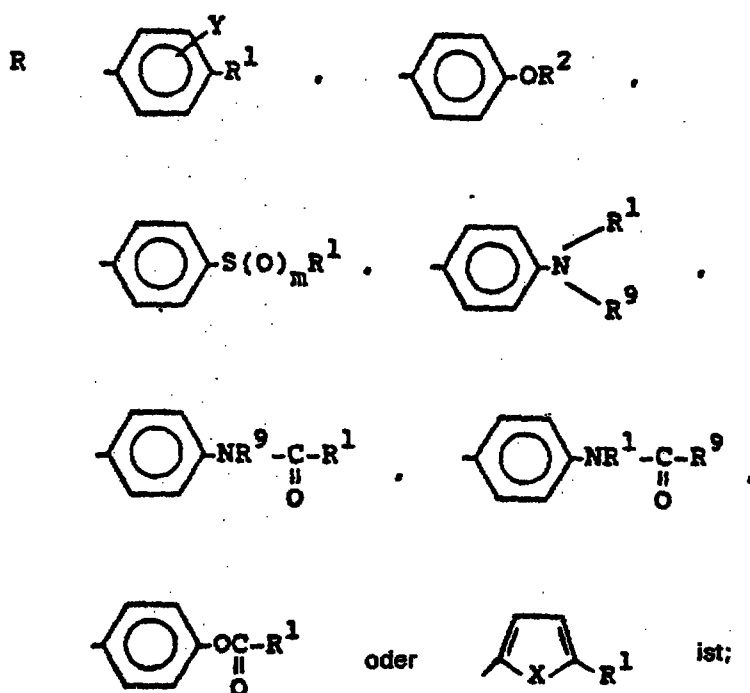
10. Verfahren zur Herstellung einer pharmazeutischen Anti-Tumor-Zusammensetzung bestehend aus einem geeigneten pharmazeutischen Träger und wenigstens einer Verbindung des Anspruchs 28, umfassend das Vermischen mindestens einer Verbindung mit einem geeigneten Träger.

11. Verwendung wenigstens einer Verbindung der Formel

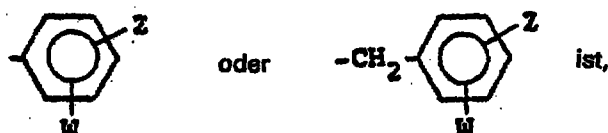


(I)

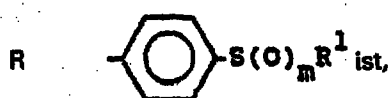
worin



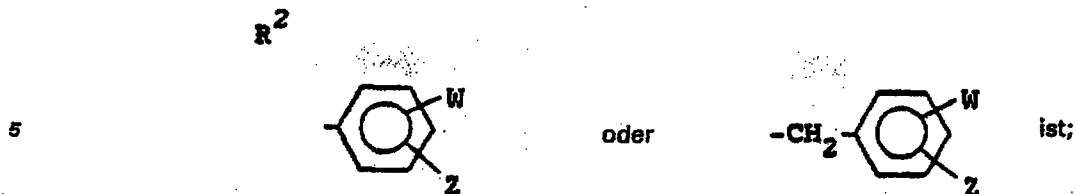
X O, S(O)_m, NH oder CH=N ist;
R¹ CH₂CH₂(CH₃)CH, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,



wenn

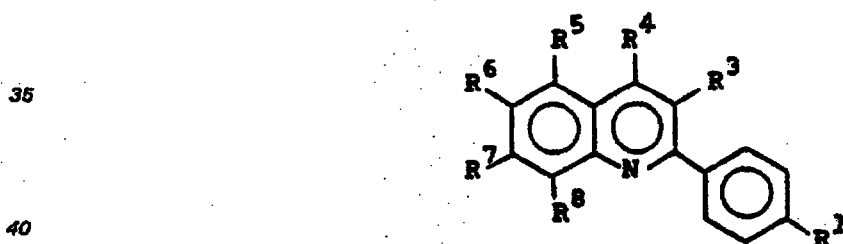


kann R¹ zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;



- 10 R^3 H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder $(CH_2)_pCOR^{10}$, worin p 1, 2, 3 oder 4 ist, substituiert ist;
 R^4 CO_2H oder CO_2R^{11} ist;
 R^5 , R^6 , R^7 und R^8 unabhängig voneinander H, F, Cl, Br, I, CH_3 , CF_3 , $S(O)_nR^{12}$ oder CH_2CH_3 sind, wobei wenigstens zwei von R^5 , R^6 , R^7 und R^8 H sind;
15 R^9 und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;
 R^{10} OH, OCH_3 , OCH_2CH_3 , NH_2 , $NHCH_3$ oder $N(CH_3)_2$ ist;
 R^{11} $(CH_2)_{2-4}NR^{9A}$ ist;
 R^{12} Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;
20 W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO_2 , Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF_3 oder NH_2 sind;
m 0 oder 1 ist;
n oder 1 ist; und
q 0, 1 oder 2 ist;
25 oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:
1) R^5 , R^6 und R^7 nicht alle H sein können;
2) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, R^8 CH_2CH_3 ist oder R^7 Cl ist, R^1 nicht Cyclohexyl sein kann; und
3) wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können,
in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von
30 Säugertumoren.

12. Verwendung wenigstens einer Verbindung der Formel



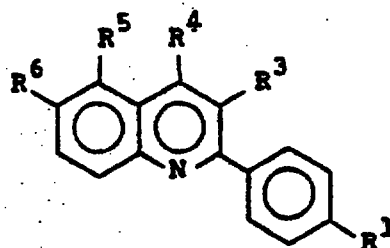
(II)

worin

- R^1 Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Phenyl, mit einem Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF_3 substituiertes Phenyl, Phenoxy, oder mit einem Halogen oder Alkyl mit 1—5 Kohlenstoff-Atomen substituiertes Phenoxy ist;
45 R^3 H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;
 R^4 CO_2H oder dessen Natrium- oder Kaliumsalz ist;
 R^5 und R^6 unabhängig voneinander H, Halogen, CH_3 oder CF_3 sind; und
 R^7 und R^8 unabhängig voneinander H oder Halogen sind; oder ein pharmazeutisch geeignetes Salz
50 derselben; vorausgesetzt, daß R^5 , R^6 und R^7 nicht alle H sein können und daß, wenn R^1 Cyclohexyl ist und R^3 H ist, R^6 Cl oder F sein muß, aber R^6 und R^8 nicht beide Cl sein können, in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
13. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 21 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
55 14. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 22 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
15. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 23 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
16. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 24 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
60 17. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 25 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
18. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 26 in einer tumor-inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
65 19. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 27 in einer tumor-

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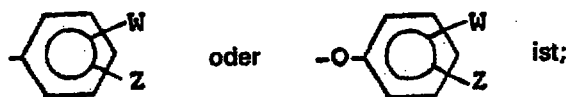
inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
20. Verwendung wenigstens einer Verbindung der Formel des Anspruchs 28 in einer tumor-
inhibierenden Menge zur Herstellung eines Medikaments zur Wachstumsinhibierung von Säugertumoren.
21. Verbindung zur Herstellung einer Verbindung der Formel



(III)

15 worin

R¹ Cycloalkyl mit 3—7 Kohlenstoff-Atomen,



ist;

R³ H oder Alkyl mit 1—3 Kohlenstoff-Atomen ist;

R⁴ CO₂H oder dessen Natrium- oder Kaliumsalz ist;

R⁵ und R⁶ unabhängig voneinander H, Halogen oder CF₃ sind, vorausgesetzt, daß R⁵ und R⁶ nicht beide Wasserstoff sind; und W und Z unabhängig voneinander H, Halogen, Alkyl mit 1—5 Kohlenstoff-Atomen oder CF₃ sind;

vorausgesetzt, daß, wenn R¹ Phenyl oder Phenoxy ist und R⁵ H ist, R⁶ nicht Br sein kann, und daß, wenn R¹ Cyclohexyl und R³ H ist, R⁶ Cl oder F sein muß, umfassend

(1) Umsetzung eines geeignet substituierten Isatins (IV) mit einem substituierten Keton (V) in einem Lösungsmittel wie Ethanol mit einer Base wie Diethylamin oder Triethylamin bei einer Temperatur von 25°C bis 50°C für 2 bis 48 Stunden, (2) Lösen der entstandenen Zwischenstufe (VI) in einem geeigneten Lösungsmittel wie Tetrahydrofuran, welches 25—50 Vol.-% einer Mineralsäure wie HCl enthält, und 2 bis 48 Stunden Erhitzen auf 50°C bis zur Rückflußtemperatur des Lösungsmittelgemischs, und wahlweise wird die voranstehende Chinolincarbonensäure aus (2) weiter umgesetzt durch (a) Acylierung der entsprechenden Hydroxygruppe, in der R OH ist, mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittel, wahlweise in der Gegenwart einer Base wie Pyridin, oder (b) durch Umsetzung der geeignet substituierten Chinolincarbonensäure mit einem geeigneten Thiolat R¹²S wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels oder (c) durch Lösen der Chinolincarbonensäure in einem protischen Lösungsmittel wie Ethanol, und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellen eines Salzes einer Aminogruppe durch Lösen desamins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes, (c) durch Behandlung mit einem Reagenz wie SOCl₂ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, R¹¹OH, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamine oder 4-Dimethylaminopyridin.

22. Verfahren des Anspruchs 21, worin

R¹ Phenyl, mit wenigstens einem Halogen substituiertes Phenyl, Phenoxy oder mit wenigstens einem Halogen substituiertes Phenoxy ist;

R³ Methyl ist;

R⁵ H oder Cl ist; und

R⁶ F oder Cl ist.

23. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(1,1'-Biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonensäure, -Natrium- oder -Kalium-Salz ist.

24. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolincarbonensäure, -Natrium- oder -Kalium-Salz ist.

25. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(4'-Brom-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonensäure, -Natrium- oder -Kalium-Salz ist.

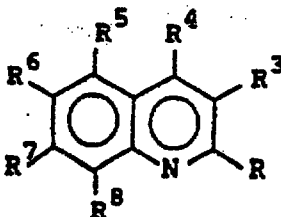
26. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(2'-Fluor-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonensäure, -Natrium- oder -Kalium-Salz ist.



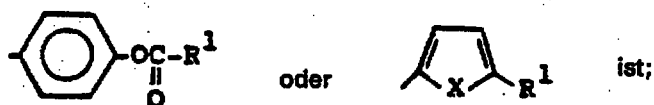
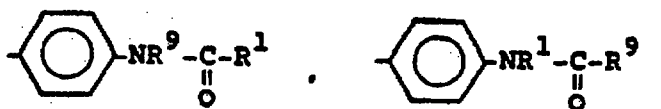
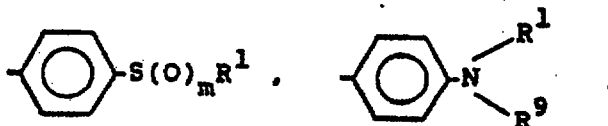
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27. Verfahren des Anspruchs 21, worin die hergestellte Verbindung 2-(1,1'-Biphenyl-4-yl)-5-chlor-6-fluor-3-methyl-4-chinolincarbonsäure, -Natrium- oder -Kalium-Salz ist.

28. Verfahren zur Herstellung einer Verbindung der Formel

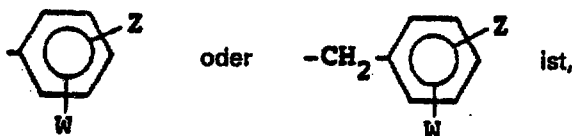


worin

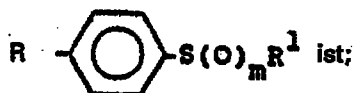


X O, S(O)_m, NH oder CH=N ist;

R¹ CH₃CH₂(CH₃)CH, Alkyl mit 5—12 Kohlenstoff-Atomen, Alkenyl mit 5—12 Kohlenstoff-Atomen, Cycloalkyl mit 3—7 Kohlenstoff-Atomen, Cycloalkylalkyl mit 5—12 Kohlenstoff-Atomen, Cycloalkenyl mit 5—7 Kohlenstoff-Atomen,

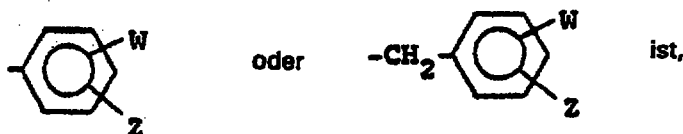


wenn



kann R¹ zusätzlich Alkyl mit 3—4 Kohlenstoff-Atomen sein;

R²





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R³ H, Alkoxy mit 1—3 Kohlenstoff-Atomen, Alkylthio mit 1—3 Kohlenstoff-Atomen oder Alkyl mit 1—3 Kohlenstoff-Atomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl, Br oder (CH₂)_pCOR¹⁰, worin p 1, 2, 3 oder 4 ist, substituiert ist;

R⁴ CO₂H oder CO₂R¹¹ ist;

R⁵, R⁶, R⁷ und R⁸ unabhängig voneinander H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² oder CH₂CH₃ sind, wobei wenigstens zwei von R⁵, R⁶, R⁷ und R⁸ H sind;

R⁹ und R^{9A} unabhängig voneinander H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

R¹⁰ OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ oder N(CH₃)₂ ist;

R¹¹ (CH₂)₂₋₄NR⁹R^{9A} ist;

R¹² Alkyl mit 1—5 Kohlenstoffatomen ist, welches gegebenenfalls mit einem oder mehreren F, Cl und Br substituiert ist;

W, Y und Z unabhängig voneinander H, F, Cl, Br, Alkyl mit 1—5 Kohlenstoff-Atomen, NO₂, Alkoxy mit 1—5 Kohlenstoff-Atomen, Alkylthio mit 1—5 Kohlenstoff-Atomen, OH, CF₃ oder NH₂ sind;

m 0 oder 1 ist;

n 0 oder 1 ist; und

q 0, 1 oder 2 ist;

oder einem pharmazeutisch geeigneten Salz derselben; vorausgesetzt, daß:

1) wenn R⁴ CO₂H ist, R¹ Phenyl oder Phenoxy ist und R⁵, R⁷ und R⁸ H sind, R⁶ nicht Br sein kann;

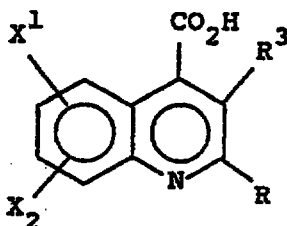
2) R⁵, R⁶ und R⁷ nicht alle H sein können;

3) wenn R⁴ CO₂CH₂CH₂N(CH₃)₂ ist, R⁶ CH₂CH₃ ist oder R⁷ Cl ist, R¹ nicht Cyclohexyl sein kann;

4) wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können;

5) wenn R¹ 4-H₂NC₆H₄ und R³ H ist, R⁶ nicht Cl sein kann und R⁸ nicht Br sein kann;

6) wenn R¹ Alkyl mit 6 Kohlenstoffatomen ist und Y H ist, R⁴ nicht C O₂H sein kann, R⁵, R⁷ und R⁸ nicht H sein können und R⁶ nicht H, Cl, Br, I oder CH₃ sein kann gekennzeichnet durch Umsetzung einer Chinolincarbonensäure der Formel



durch (a), wenn R OH ist, Acylierung der Hydroxygruppe mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittels, wahlweise in Gegenwart einer Base wie pyridin, oder (b) Umsetzung der geeignet substituierten Chinolincarbonensäure mit einem geeigneten Thiolat R¹²S wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels, oder (c) Lösen der Chinolincarbonensäure in einem protischen Lösungsmittel wie Ethanol und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellung eines Salzes einer Aminogruppe durch Lösen desamins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes (c), durch Behandlung mit einem Reagenz wie SOCl₂ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, R¹¹OH, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamin oder 4-Dimethyliminopyridin.

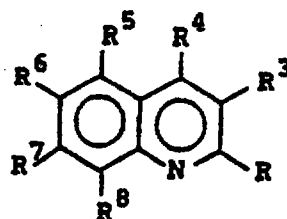
29. Verfahren zur Herstellung der Verbindungen des Anspruch 28, im wesentlichen bestehend aus (1) Umsetzung eines geeignet substituierten Isatins (IV) mit einem substituierten Keton (V) in einem Lösungsmittel wie Ethanol mit einer Base wie Diethylamin oder Triethylamin bei einer Temperatur von 25°C bis 50°C für 2 bis 48 Stunden, (2) Lösen der entstandenen Zwischenstufe (VI) in einem geeigneten Lösungsmittel wie Tetrahydrofuran, welches 25—50 Vol.-% einer Mineralsäure wie HCl enthält, und 2 bis 48 Stunden Erhitzen auf 50°C bis zur Rückflußtemperatur des Lösungsmittelgemisches, und wahlweise wird die voranstehende Chinolincarbonensäure (2) weiter umgesetzt durch (a) Acylierung der entsprechenden Hydroxygruppe, in der R OH ist, mit einem Carboxylhalogenid wie Benzoylchlorid in einem inerten Lösungsmittel wie Chloroform oder einem Kohlenwasserstoff-Lösungsmittel wie Benzol bei einer Temperatur von 0°C bis zum Siedepunkt des Lösungsmittels, wahlweise in der Gegenwart einer Base wie pyridin, oder (b) durch Umsetzung der geeignet substituierten Chinolincarbonensäure mit einem geeigneten Thiolat R¹²S wie MeSK in einem Lösungsmittel wie Dimethylformamid bei einer Temperatur von 50°C bis zum Rückfluß des Lösungsmittels oder (c) durch Lösen der Chinolincarbonensäure in einem protischen

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Lösungsmittel wie Ethanol, und dann Behandeln mit einem Metalloxid oder -hydroxid wie Natrium- oder Kaliumoxid oder -hydroxid oder einem Amin wie 1-Aminobutanol oder Lysin bei einer Temperatur von 0°C bis zum Siedepunkt des verwendeten Lösungsmittels und wahlweise Herstellen eines Salzes einer Aminogruppe durch Lösen desamins in einem Lösungsmittel wie Ethylether und Zugabe einer Mineralsäure wie HCl, oder (d) Behandeln des Salzes, (c) durch Behandlung mit einem Reagenz wie SOCl₂ oder Oxalylchlorid in einem inerten Lösungsmittel wie Benzol bei einer Temperatur von 25°C bis zum Siedepunkt des verwendeten Lösungsmittels unter Bildung eines Säurehalogenids und dann Zugabe eines Alkohols, R¹¹OH, in einem Lösungsmittel wie Tetrahydrofuran bei einer Temperatur von 10°C bis zum Siedepunkt des verwendeten Lösungsmittels, wahlweise in Gegenwart einer Base wie Pyridin, Triethylamin oder 4-Dimethylaminopyridin.

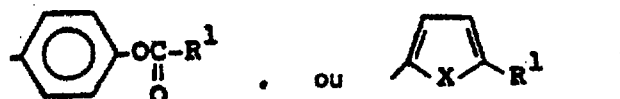
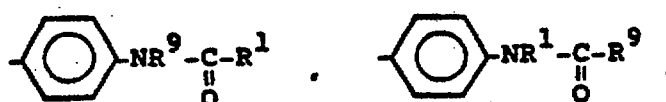
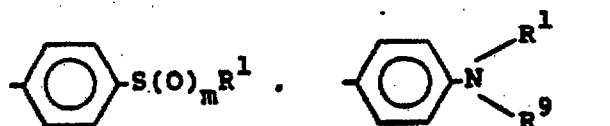
Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:



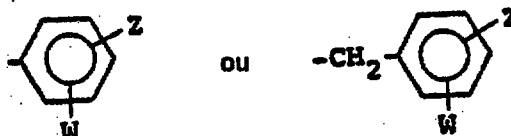
(I)

dans laquelle

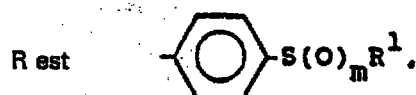


X est O, S(O)_q, NH ou CH=N;

R¹ est un groupe CH₃CH₂(CH₂)CH, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

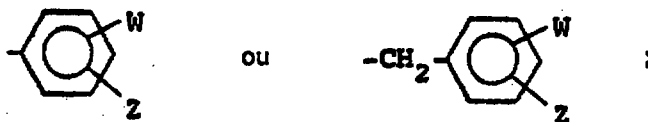


lorsque



R¹ peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R² est



R³ est H, un groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou (CH₂)_pCOR¹⁰ où p est 1, 2, 3 ou 4;

R⁴ est CO₂H ou CO₂R¹¹;

R⁵, R⁶, R⁷ et R⁸ sont indépendamment H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² ou CH₂CH₃, au moins deux de R⁵, R⁶, R⁷ et R⁸ étant H;

R⁹ et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R¹⁰ est OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ ou N(CH₃)₂;

R¹¹ est (CH₂)₂₋₄NR⁹R^{9A};

R¹² est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO₂, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF₃ ou NH₂;

m est 0 ou 1;

n est 0 ou 1; et

q est 0, 1 ou 2;

ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

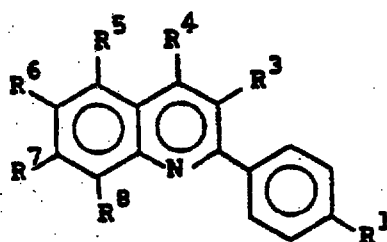
1) R⁵, R⁶ et R⁷ ne peuvent pas tous être H;

2) si R⁴ est CO₂CH₂CH₂N(CH₃)₂, R⁵ est CH₂CH₃ ou R⁷ est Cl, R¹ ne peut pas être un groupe cyclohexyle;

et

3) si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁶ et R⁸ ne peuvent pas être tous deux Cl.

2. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:



(II)

dans laquelle

R¹ est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF₃; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle 1 à 5 atomes de carbone;

R³ est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R⁴ est CO₂H ou son sel de sodium ou de potassium;

R⁵ et R⁶ sont indépendamment H, un halogène, CH₃ ou CF₃; et

R⁷ et R⁸ sont indépendamment H ou un halogène

ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R⁵, R⁶ et R⁷ ne peuvent pas tous être H et que si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁶ et R⁸ peuvent pas être tous deux Cl.

3. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 21.

4. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 22.

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5. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 23.

6. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 24.

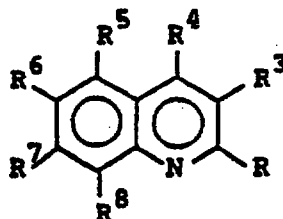
7. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 25.

8. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 26.

9. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 27.

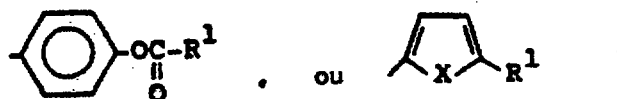
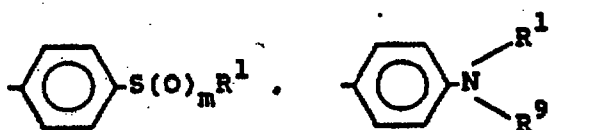
10. Une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 28.

11. Utilisation d'au moins un composé répondant à la formule:



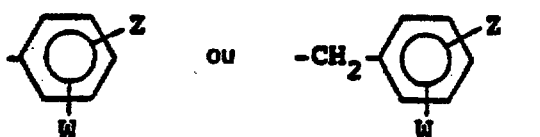
(I)

dans laquelle

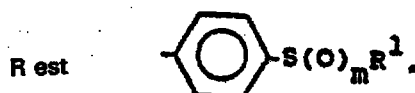


X est O, S(O)_m, NH ou CH=N;

R¹ est un groupe CH₃CH₂(CH₂)CH, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,



lorsque

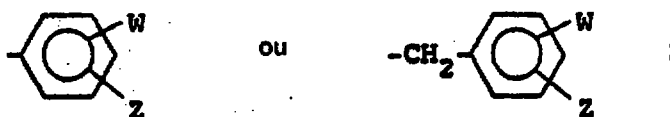




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R¹ peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R² est



10 R³ est H, un groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou (CH₂)_pCOR¹⁰ où p est 1, 2, 3 ou 4;

R⁴ est CO₂H ou CO₂R¹¹;

R⁵, R⁶, R⁷ et R⁸ sont indépendamment H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² ou CH₂CH₃, au moins deux de R⁵, R⁶, R⁷ et R⁸ étant H;

R⁹ et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R¹⁰ est OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ ou N(CH₃)₂;

R¹¹ est (CH₂)₂₋₄NR⁹R^{9A};

20 R¹² est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO₂, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF₃ ou NH₂;

m est 0 ou 1;

n est 0 ou 1; et

25 q est 0, 1 ou 2;

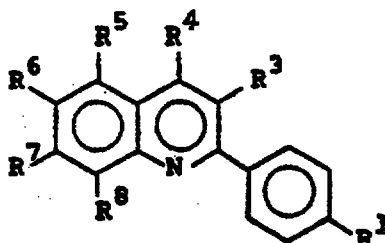
ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) R⁵, R⁶ et R⁷ ne peuvent pas tous être H;

2) si R⁴ est CO₂CH₂CH₂N(CH₃)₂, R⁵ est CH₂CH₃ ou R⁷ est Cl, R¹ ne peut pas être un groupe cyclohexyle; et

30 3) si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁶ et R⁸ ne peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

12. Utilisation d'au moins un composé répondant à la formule:



(II)

dans laquelle

45 R¹ est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF₃; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle 1 à 5 atomes de carbone;

R³ est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R⁴ est CO₂H ou son sel de sodium ou de potassium;

50 R⁵ et R⁶ sont indépendamment H, un halogène, CH₃ ou CF₃; et

R⁷ et R⁸ sont indépendamment H ou un halogène

ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R⁵, R⁶ et R⁷ ne peuvent pas tous être H et que si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁶ et R⁸ peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

55 13. Utilisation d'au moins un composé de la revendication 21, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

14. Utilisation d'au moins un composé de la revendication 22, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

60 15. Utilisation d'au moins un composé de la revendication 23, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

16. Utilisation d'au moins un composé de la revendication 24, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

65 17. Utilisation d'au moins un composé de la revendication 25, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

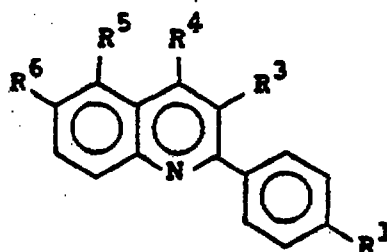
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18. Utilisation d'au moins un composé de la revendication 26, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

19. Utilisation d'au moins un composé de la revendication 27, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

20. Utilisation d'au moins un composé de la revendication 28, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

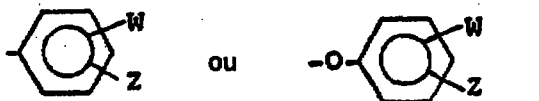
21. Un composé répondant à la formule:



(III)

dans laquelle

R¹ est un groupe cycloalkyle de 3 à 7 atomes de carbone,



R³ est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R⁴ est CO₂H ou son sel de sodium ou de potassium;

R⁵ et R⁶ sont indépendamment H, un halogène ou CF₃, avec la condition que R⁵ et R⁶ ne soient pas tous deux de l'hydrogène; et

W et Z sont indépendamment H, un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF₃; avec la condition que si R¹ est un groupe phényle ou phénoxy et R⁵ est H, alors R⁶ ne peut pas être Br; et que si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F.

22. Un composé de la revendication 21, dans lequel:

R¹ est un groupe phényle, phényle substitué par au moins un halogène ou groupe phénoxy, ou phénoxy substitué par au moins un halogène;

R³ est un groupe méthyle;

R⁶ est H ou Cl; et

R⁶ est F ou Cl.

23. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

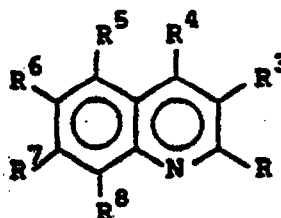
24. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 6 - fluoro - 3 - méthyl - 2 - (4 - phénoxyphényl) - 4 - quinoléine-carboxylique.

25. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (4' - bromo - 1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

26. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (2' - fluoro - 1,1' - diphényl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

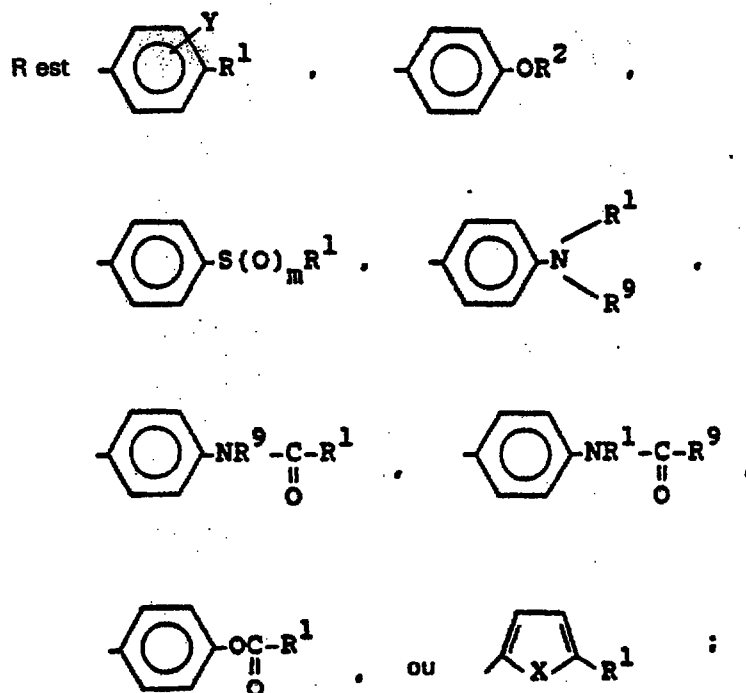
27. Le composé de la revendication 21, qui est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphényl - 4 - yl) - 5 - chloro - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

28. Un composé répondant à la formule:



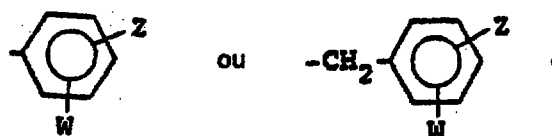
dans laquelle

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X est O, S(O)ₘ, NH ou CH=N;

R¹ est un groupe CH₃CH₂(CH₂)ₙCH, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,

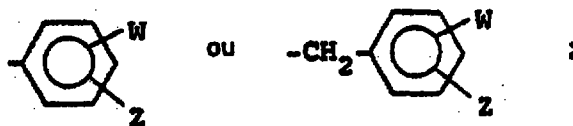


lorsque



R¹ peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R² est



R³ est H, une groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou (CH₂)ₚCOR¹⁰ où p est 1, 2, 3 ou 4;

R⁴ est CO₂H ou CO₂R¹¹;

R⁵, R⁶, R⁷ et R⁸ sont indépendamment H, F, Cl, Br, I, CH₃, CF₃, S(O)ₘR¹² ou CH₂CH₃, au moins deux de R⁵, R⁶, R⁷ et R⁸ étant H;

R⁹ et R¹⁰ sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R¹¹ est OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ ou N(CH₃)₂;

R¹² est (CH₂)₂-₄NR⁹R¹⁰;

R¹³ est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO₂, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF₃ ou NH₂;

m est 0 ou 1;



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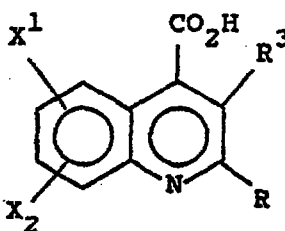
n est 0 ou 1; et

q est 0, 1 ou 2;

ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

- 1) si R^4 est CO_2H , R^1 est un groupe phényle ou phénoxy et R^6 , R^7 et R^8 sont H, R^6 ne peut pas être Br;
- 2) R^5 , R^6 et R^7 ne peuvent pas tous être H;
- 3) si R^4 est $\text{CO}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, R^6 est CH_2CH_3 , ou R^7 est Cl, R^1 ne peut pas être un groupe cyclohexyle;
- 4) si R^1 est un groupe cyclohexyle et R^3 est H, R^6 doit être Cl ou F, mais R^5 et R^8 ne peuvent pas être tous deux Cl;
- 5) si R^1 est $4\text{-H}_2\text{NC}_6\text{H}_4$ et R^3 est H, R^6 ne peut pas être Cl et R^8 ne peut pas être Br;
- 6) si R^1 est un groupe alkyle de 6 atomes de carbone et Y est H, alors R^4 ne peut pas être CO_2H , R^5 , R^7 et R^8 ne peuvent pas être H, et R^6 ne peut pas être H, Cl, Br, I ou CH_3 .

29. Un procédé pour préparer des composés de la revendication 28, caractérisé en ce qu'on fait réagir un acide quinoléine-carboxylique de la formule:



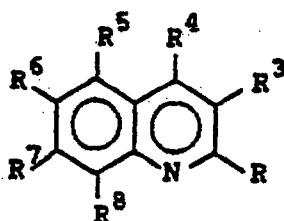
(a) lorsque R est OH, en acylant le groupe hydroxyle avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène, à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate $R^{12}\text{S}$ approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et le point de reflux de solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, et en traitant ensuite avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium ou une amine telle que le 1-amino-butanol ou la lysine à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que SOCl_2 ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, $R^{11}\text{OH}$, dans un solvant tel que le tétrahydrofur à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

30. Un procédé pour préparer les composés de la revendication 28, consistant essentiellement (1) à faire réagir une isatine convenablement substituée (IV) avec une cétone substituée (V) dans un solvant tel que l'éthanol avec une base telle que la diéthylamine ou la triéthylamine à une température de 25°C à 50°C pendant 2 à 48 heures, (2) à dissoudre le composé intermédiaire (VI) résultant dans un solvant approprié tel que le tétrahydrofur contenant 25 à 50% en volume d'un acide minéral tel que HCl et chauffer entre 50°C et la température de reflux du mélange dissolvant pendant 2 à 48 heures, et, facultativement, à faire réagir encore l'acide quinoléine-carboxylique venant de (2) ci-dessus (a) en acylant le groupe hydroxyle correspondant, lorsque R est OH, avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate $R^{12}\text{S}$ approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et la température de reflux du solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, puis en traitant avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium, ou une amine telle que le 1-amino-butanol ou la lysine, à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que SOCl_2 ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, $R^{11}\text{OH}$, dans un solvant tel que le tétrahydrofur à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

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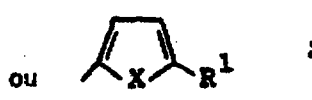
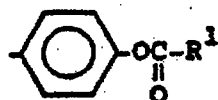
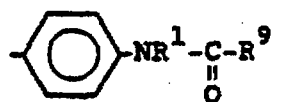
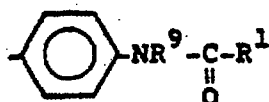
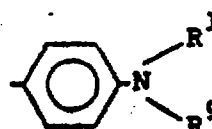
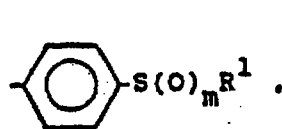
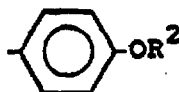
Revendications pour l'Etat contractant: AT

1. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:



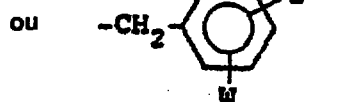
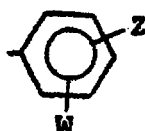
(I)

dans laquelle



X est O, S(O)_q, NH ou CH=N;

R¹ est un groupe CH₃CH₂(CH₂)CH, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,



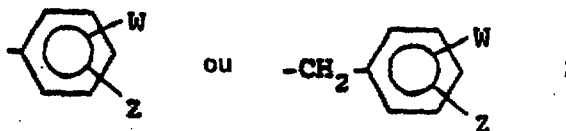
lorsque



R¹ peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;



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R² est

10 R³ est H, un groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou (CH₂)_pCOR¹⁰ où p est 1, 2, 3 ou 4;

R⁴ est CO₂H ou CO₂R¹¹;

R⁵, R⁶, R⁷ et R⁸ sont indépendamment H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² ou CH₂CH₃, au moins deux de R⁵, R⁶, R⁷ et R⁸ étant H;

15 R⁹ et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R¹⁰ est OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ ou N(CH₃)₂;

R¹¹ est (CH₂)₂₋₄NR⁹R^{9A};

R¹² est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

20 W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO₂, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF₃ ou NH₂;

m est 0 ou 1;

n est 0 ou 1; et

q est 0, 1 ou 2;

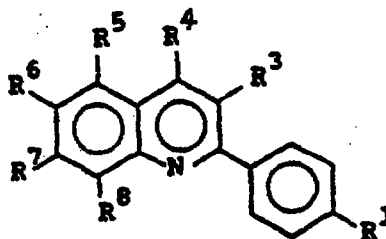
25 ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) R⁵, R⁶ et R⁷ ne peuvent pas tous être H;

2) si R⁴ est CO₂CH₂CH₂N(CH₃)₂, R⁶ est CH₂CH₃ ou R⁷ est Cl, R¹ ne peut pas être un groupe cyclohexyle; et

3) si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁶ et R⁸ ne peuvent pas être tous deux Cl, qui consiste à mélanger au moins un composé avec un support pharmaceutique approprié.

30 2. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé répondant à la formule:



40 dans laquelle

R¹ est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF₃; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle de 1 à 5 atomes de carbone;

45 R³ est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R⁴ est CO₂H ou son sel de sodium ou de potassium;

R⁵ et R⁶ sont indépendamment H, un halogène, CH₃ ou CF₃; et

R⁷ et R⁸ sont indépendamment H ou un halogène

50 ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R⁵, R⁶ et R⁷ ne peuvent pas tous être H et que si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁶ et R⁸ peuvent pas être tous deux Cl, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

55 3. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 21, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

4. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 22, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

60 5. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 23, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

65 6. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 24, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.



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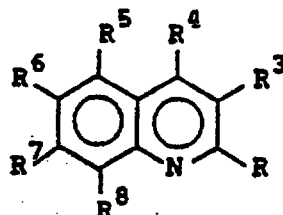
7. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 25, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

8. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 26, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

9. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 27, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

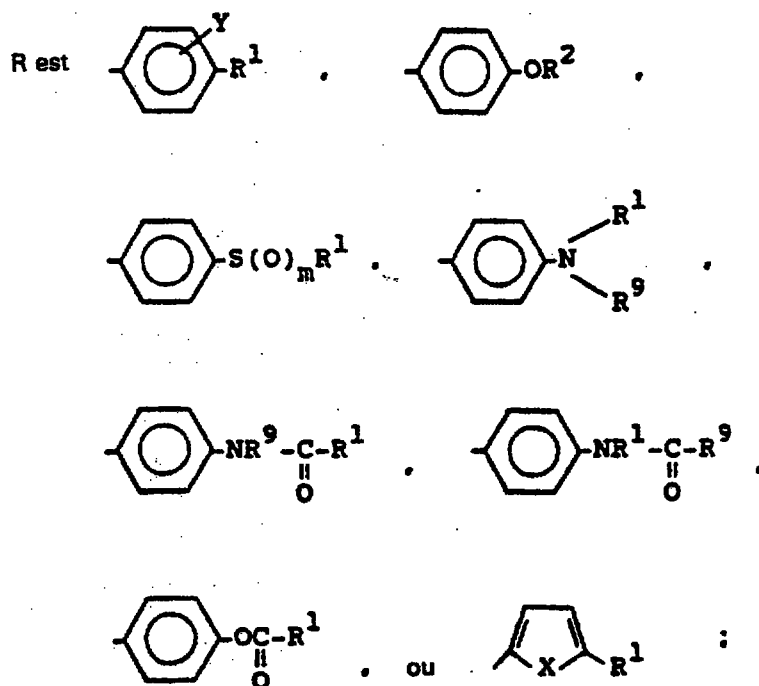
10. Procédé pour préparer une composition pharmaceutique antitumorale constituée d'un support ou véhicule pharmaceutique approprié et d'au moins un composé de la revendication 28, qui consiste à mélanger au moins un composé et un support ou véhicule pharmaceutique approprié.

11. Utilisation d'au moins un composé répondant à la formule:



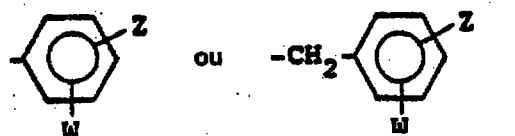
(I)

dans laquelle



X est O, S(O)_n, NH ou CH=N;

R¹ est un groupe CH₃CH₂(CH₂)_nCH, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,



lorsque

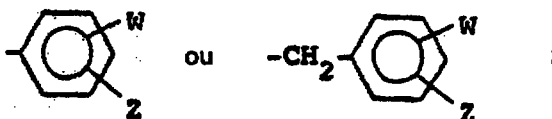


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R¹ peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R² est

5



10 R³ est H, une groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou (CH₂)_pCOR¹⁰ où p est 1, 2, 3 ou 4;

R⁴ est CO₂H ou CO₂R¹¹;

15 R⁵, R⁶, R⁷ et R⁸ sont indépendamment H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² ou CH₂CH₃, au moins deux de R⁵, R⁶, R⁷ et R⁸ étant H;

R⁹ et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R¹⁰ est OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ ou N(CH₃)₂;

R¹¹ est (CH₂)₂₋₄NR⁹R^{9A};

20 R¹² est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO₂, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF₃ ou NH₂;

m est 0 ou 1;

n est 0 ou 1; et

25 q est 0, 1 ou 2;

ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

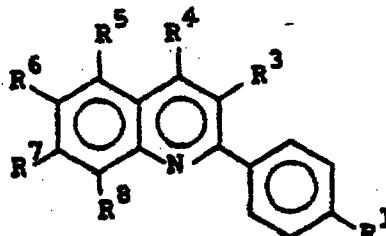
1) R⁵, R⁶ et R⁷ ne peuvent pas tous être H;

2) si R⁴ est CO₂CH₂CH₂N(CH₃)₂, R⁹ est CH₂CH₃ ou R⁷ est Cl, R¹ ne peut pas être un groupe cyclohexyle; et

3) si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁵ et R⁸ ne peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

12. Utilisation d'au moins un composé répondant à la formule:

35



(II)

40

dans laquelle

45 R¹ est un groupe cycloalkyle de 3 à 7 atomes de carbone; phényle; phényle substitué par un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF₃; phénoxy; ou phénoxy substitué par un halogène ou un groupe alkyle 1 à 5 atomes de carbone;

R³ est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R⁴ est CO₂H ou son sel de sodium ou de potassium;

50 R⁵ et R⁶ sont indépendamment H, un halogène, CH₃ ou CF₃; et

R⁷ et R⁸ sont indépendamment H ou un halogène

ou un sel pharmaceutiquement acceptable de ce composé; avec la condition que R⁵, R⁶ et R⁷ ne peuvent pas tous être H et que si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁵ et R⁸ peuvent pas être tous deux Cl, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

55 13. Utilisation d'au moins un composé de la revendication 21, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

14. Utilisation d'au moins un composé de la revendication 22, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

60 15. Utilisation d'au moins un composé de la revendication 23, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

16. Utilisation d'au moins un composé de la revendication 24, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

65 17. Utilisation d'au moins un composé de la revendication 25, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

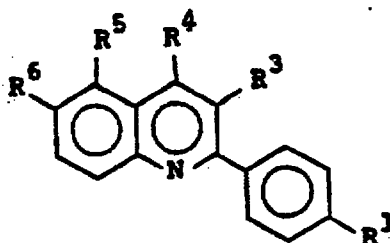
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18. Utilisation d'au moins un composé de la revendication 26, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

19. Utilisation d'au moins un composé de la revendication 27, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

20. Utilisation d'au moins un composé de la revendication 28, en une quantité inhibitrice de tumeur pour la fabrication d'un médicament destiné à inhiber la croissance de tumeurs mammaires.

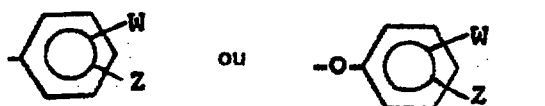
21. Un procédé pour préparer un composé répondant à la formule:



(III)

dans laquelle

R¹ est un groupe cycloalkyle de 3 à 7 atomes de carbone,



R³ est H ou un groupe alkyle de 1 à 3 atomes de carbone;

R⁴ est CO₂H ou son sel de sodium ou de potassium;

R⁵ et R⁶ sont indépendamment H, un halogène ou CF₃, avec la condition que R⁵ et R⁶ ne soient pas tous deux de l'hydrogène; et

W et Z sont indépendamment H, un halogène, un groupe alkyle de 1 à 5 atomes de carbone ou CF₃; avec la condition que si R¹ est un groupe phényle ou phénoxy et R⁵ est H, alors R⁶ ne peut pas être Br; et que si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, qui consiste (1) à faire réagir une isatine convenablement substituée (IV) avec une cétone substituée (V) dans un solvant tel que l'éthanol avec une base telle que la diéthylamine ou la triéthylamine à une température de 25°C à 50°C pendant 2 à 48 heures, (2) à dissoudre le composé intermédiaire (VI) résultant dans un solvant approprié tel que le tétrahydrofurane contenant 25 à 50% en volume d'un acide minéral tel que HCl et chauffer entre 50°C et la température de reflux du mélange dissolvant pendant 2 à 48 heures, et, facultativement, à faire réagir encore l'acide quinoléine-carboxylique venant de (2) ci-dessus (a) en acylant le groupe hydroxyle correspondant, lorsque R est OH, avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate R¹²S approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et la température de reflux du solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, puis en traitant avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium, ou une amine telle que le 1-aminobutanol ou la lysine, à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que SOCl₂ ou le chlorure d'oxalyde dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, R¹¹OH, dans un solvant tel que le tétrahydrofurane à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

22. Un procédé de la revendication 21, dans lequel:

R¹ est un groupe phényle, phényle substitués par au moins un halogène ou groupe phénoxy, ou phénoxy substitué par au moins un halogène;

R³ est un groupe méthyle;

R⁵ est H ou Cl; et

R⁶ est F ou Cl.

23. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphenyl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

24. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 6 - fluoro - 3 - méthyl - 2 - (4 - phénoxyphényl) - 4 - quinoléine-carboxylique.

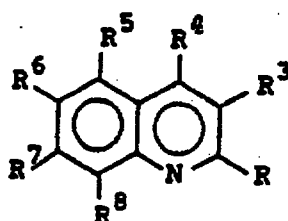
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25. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (4' - bromo - 1,1' - diphenyl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

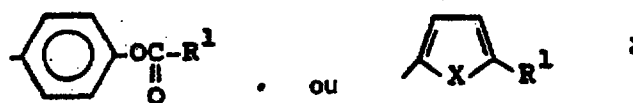
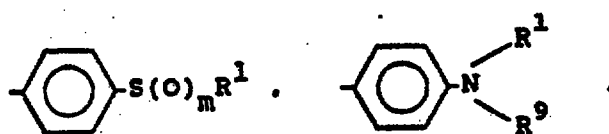
26. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (2' - fluoro - 1,1' - diphenyl - 4 - yl) - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

27. Le procédé de la revendication 21, dans lequel le composé préparé est le sel de sodium ou de potassium de l'acide 2 - (1,1' - diphenyl - 4 - yl) - 5 - chloro - 6 - fluoro - 3 - méthyl - 4 - quinoléine-carboxylique.

28. Procédé pour préparer un composé répondant à la formule:

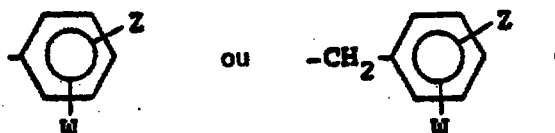


dans laquelle



X est O, S(O)_m, NH ou CH=N;

R¹ est un groupe CH₂CH₂(CH₂)_nCH, alkyle de 5 à 12 atomes de carbone, alcényle de 5 à 12 atomes de carbone, cycloalkyle de 3 à 7 atomes de carbone, cycloalkylalkyle de 5 à 12 atomes de carbone, cycloalcényle de 5 à 7 atomes de carbone,



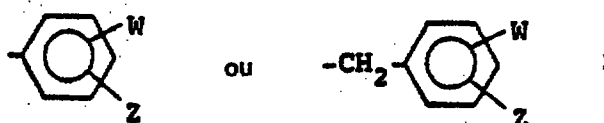
lorsque



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R¹ peut être, de plus, un groupe alkyle de 3 ou 4 atomes de carbone;

R² est



10 R³ est H, un groupe alcoxy de 1 à 3 atomes de carbone, alkylthio de 1 à 3 atomes de carbone ou alkyle de 1 à 3 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl, Br ou (CH₂)_pCOR¹⁰ où p est 1, 2, 3 ou 4;

R⁴ est CO₂H ou CO₂R¹¹;

15 R⁵, R⁶, R⁷ et R⁸ sont indépendamment H, F, Cl, Br, I, CH₃, CF₃, S(O)_nR¹² ou CH₂CH₃, au moins deux de R⁵, R⁶, R⁷ et R⁸ étant H;

R⁹ et R^{9A} sont indépendamment H ou un groupe alkyle de 1 à 3 atomes de carbone;

R¹⁰ est OH, OCH₃, OCH₂CH₃, NH₂, NHCH₃ ou N(CH₃)₂;

R¹¹ est (CH₂)₂₋₄NR⁹R^{9A};

20 R¹² est un groupe alkyle de 1 à 5 atomes de carbone facultativement substitué par un ou plusieurs de F, Cl et Br;

W, Y et Z sont indépendamment H, F, Cl, Br, un groupe alkyle de 1 à 5 atomes de carbone, NO₂, alcoxy de 1 à 5 atomes de carbone, alkylthio de 1 à 5 atomes de carbone, OH, CF₃ ou NH₂;

m est 0 ou 1;

25 n est 0 ou 1; et

q est 0, 1 ou 2;

ou un sel pharmaceutiquement acceptable de ce composé; avec les conditions suivantes:

1) si R⁴ est CO₂H, R¹ est un groupe phényle ou phénoxy et R⁵, R⁷ et R⁸ sont H, R⁶ ne peut pas être Br;

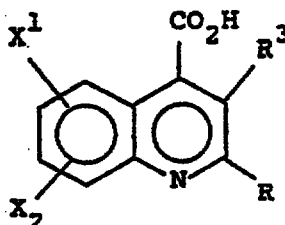
2) R⁵, R⁶ et R⁷ ne peuvent pas tous être H;

30 3) si R⁴ est CO₂CH₂CH₂N(CH₃)₂, R⁶ est CH₂CH₃ ou R⁷ est Cl, R¹ ne peut pas être un groupe cyclohexyle;

4) si R¹ est un groupe cyclohexyle et R³ est H, R⁶ doit être Cl ou F, mais R⁵ et R⁸ ne peuvent pas être tous deux Cl;

5) si R¹ est 4-H₂NC₆H₄ et R³ est H, R⁶ ne peut pas être Cl et R⁸ ne peut pas être Br;

6) si R¹ est un groupe alkyle de 6 atomes de carbone et Y est H, alors R⁴ ne peut pas être CO₂H, R⁵, R⁷ et R⁸ ne peuvent pas être H, et R⁶ ne peut pas être H, Cl, Br, I ou CH₃, caractérisé en ce qu'on fait réagir un acide quinoléine-carboxylique de la formule:



(a) lorsque R est OH, en acylant le groupe hydroxyle avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène, à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un thiolate R¹²S approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et le point de reflux de solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, et en traitant ensuite avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium ou une amine telle que le 1-amino-butanol ou la lysine à une température comprise entre 0°C et le point d'ébullition du solvant employé et en préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que SOCl₂ ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en ajoutant un alcool, R¹¹OH, dans un solvant tel que le tétrahydrofurane à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

29. Un procédé pour préparer les composés de la revendication 28, consistant essentiellement (1) à faire réagir une isatine convenablement substituée (IV) avec une cétone substituée (V) dans un solvant tel



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que l'éthanol avec une base telle que la diéthylamine ou la triéthylamine à une température de 25°C à 50°C pendant 2 à 48 heures, (2) à dissoudre le composé intermédiaire (VI) résultant dans un solvant approprié tel que le tétrahydrofurane contenant 25 à 50% en volume d'un acide minéral tel que HCl et chauffer entre 50°C et la température de reflux du mélange dissolvant pendant 2 à 48 heures, et, facultativement, à faire
5 réagir encore l'acide quinoléine-carboxylique venant de (2) ci-dessus (a) en acylant le groupe hydroxyle correspondant, lorsque R est OH, avec un halogénure carboxylique tel que le chlorure de benzoyle dans un solvant inerte tel que le chloroforme ou un solvant hydrocarboné tel que le benzène à une température comprise entre 0°C et le point d'ébullition du solvant, facultativement en présence d'une base telle que la pyridine, ou (b) en faisant réagir l'acide quinoléine-carboxylique convenablement substitué avec un
10 thiolate R¹²S approprié tel que MeSK dans un solvant tel que le diméthylformamide à une température comprise entre 50°C et la température de reflux du solvant, ou (c) en dissolvant l'acide quinoléine-carboxylique dans un solvant protique tel que l'éthanol, puis en traitant avec un oxyde ou hydroxyde de métal tel que l'oxyde ou l'hydroxyde de sodium ou de potassium, ou un amine telle que le 1-aminobutanol ou la lysine, à une température comprise entre 0°C et le point d'ébullition du solvant employé et en
15 préparant facultativement un sel d'un groupe amino en dissolvant l'amine dans un solvant tel que l'éther d'éthyle et en ajoutant un acide minéral tel que HCl; ou (d) en traitant le sel, (c), par traitement avec un réactif tel que SOCl₂ ou le chlorure d'oxalyle dans un solvant inerte tel que le benzène à une température comprise entre 25°C et le point d'ébullition du solvant employé pour former un halogénure d'acide, puis en
20 ajoutant un alcool, R¹¹OH, dans un solvant tel que le tétrahydrofurane à une température comprise entre 10°C et le point d'ébullition du solvant employé, facultativement en présence d'une base telle que la pyridine, la triéthylamine ou la 4-diméthylaminopyridine.

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