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CA 2397448 A1 2001/09/07

(21) 2 397 448

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2001/02/26
(87) Date publication PCT/PCT Publication Date: 2001/09/07
(85) Entrée phase nationale/National Entry: 2002/07/12
(86) N° demande PCT/PCT Application No.: EP 2001/002162
(87) N° publication PCT/PCT Publication No.: 2001/064252
(30) Priorité/Priority: 2000/02/29 (00200694.8) EP

(51) Cl.Int.^{7}/Int.Cl.^{7} A61K 45/06, A61P 35/00

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(54) Titre : INHIBITEUR DE FARNESYL PROTEINE TRANSFERASE ASSOCIE A D'AUTRES AGENTS ANTI-CANCEREUX

(54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH FURTHER ANTI-CANCER AGENTS

(57) Abrégé/Abstract:
The present invention is concerned with combinations of a farnesyl transferase inhibitor and two or more further anti-cancer agents for inhibiting the growth of tumor cells and useful in the treatment of cancer.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64252 A3

(51) International Patent Classification[7]: A61K 45/06, A61P 35/00

(21) International Application Number: PCT/EP01/02162

(22) International Filing Date: 26 February 2001 (26.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00200694.8 29 February 2000 (29.02.2000) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
21 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/64252 A3

(54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH FURTHER ANTI-CANCER AGENTS

(57) Abstract: The present invention is concerned with combinations of a farnesyl transferase inhibitor and two or more further anti-cancer agents for inhibiting the growth of tumor cells and useful in the treatment of cancer.

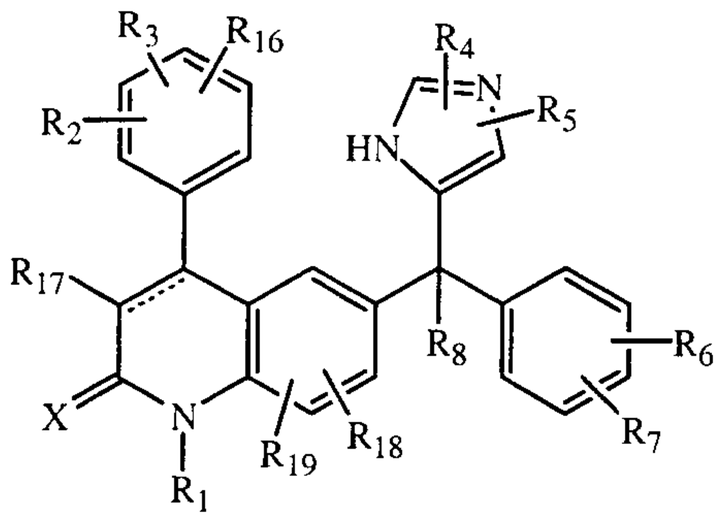
FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH FURTHER ANTI-CANCER AGENTS

The present invention is concerned with combinations of a farnesyl transferase inhibitor and two or more further anti-cancer agents for inhibiting the growth of tumor cells and useful in the treatment of cancer.

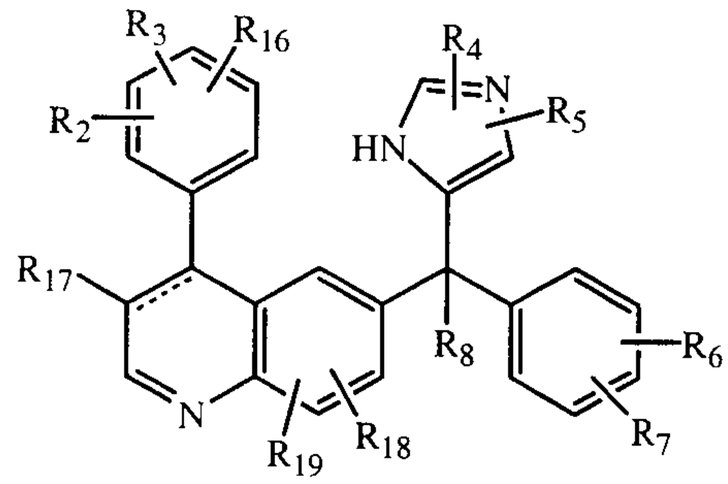
Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer. A particular group of oncogenes is known as ras which have been identified in mammals, birds, insects, mollusks, plants, fungi and yeasts. The family of mammalian ras oncogenes consists of three major members ("isoforms") : H-ras, K-ras and N-ras oncogenes. These ras oncogenes code for highly related proteins generically known as $p21^{ras}$. Once attached to plasma membranes, the mutant or oncogenic forms of $p21^{ras}$ will provide a signal for the transformation and uncontrolled growth of malignant tumor cells. To acquire this transforming potential, the precursor of the $p21^{ras}$ oncoprotein must undergo an enzymatically catalyzed farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Therefore, inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, will prevent the membrane attachment of $p21^{ras}$ and block the aberrant growth of ras-transformed tumors. Hence, it is generally accepted in the art that farnesyl transferase inhibitors can be very useful as anticancer agents for tumors in which ras contributes to transformation.

Since mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50 % of colon and pancreatic carcinomas (Kohl et al., Science, vol 260, 1834 - 1837, 1993), it has been suggested that farnesyl tranferase inhibitors can be very useful against these types of cancer. Following further investigations, it has been found that a farnesyl transferase inhibitor is capable of demonstrating antiproliferative effects in vitro and antitumor effects in vivo in a variety of human tumor cell lines with and without ras gene mutations.

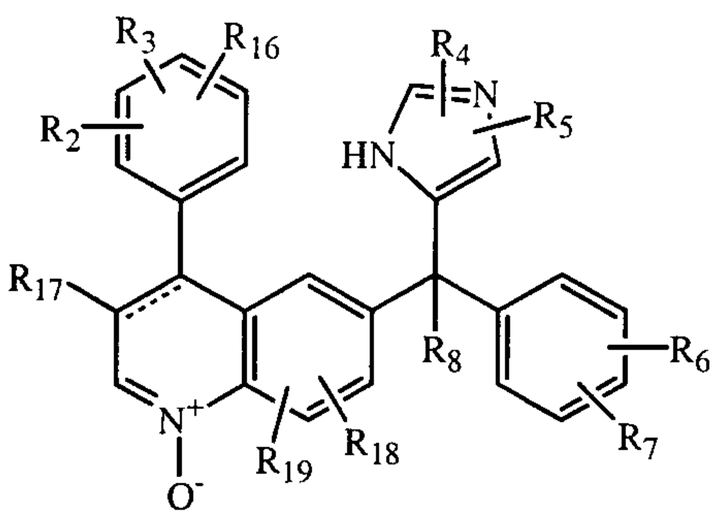
WO-97/21701 describes the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting (imidazoly-5-yl)methyl-2-quinolinone derivatives of formulas (I), (II) and (III), as well as intermediates of formula (II) and (III) that are metabolized in vivo to the compounds of formula (I). The compounds of formulas (I), (II) and (III) are represented by



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9, wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyl-oxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy,

Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or

-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl,

amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

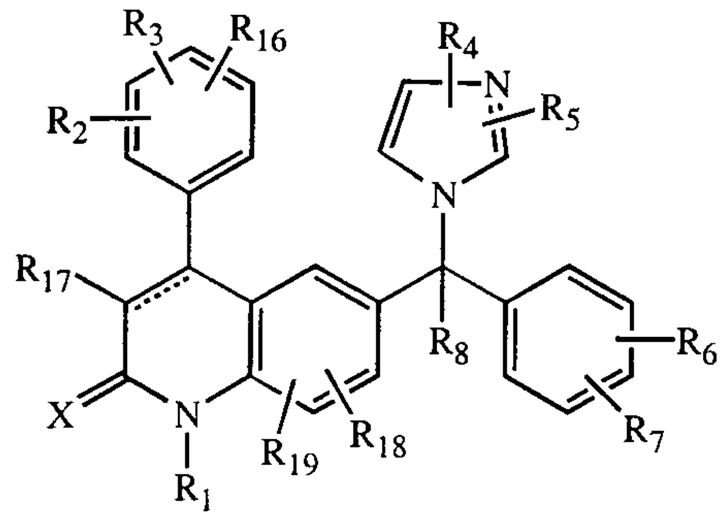
R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{19} is hydrogen or C_{1-6}alkyl;

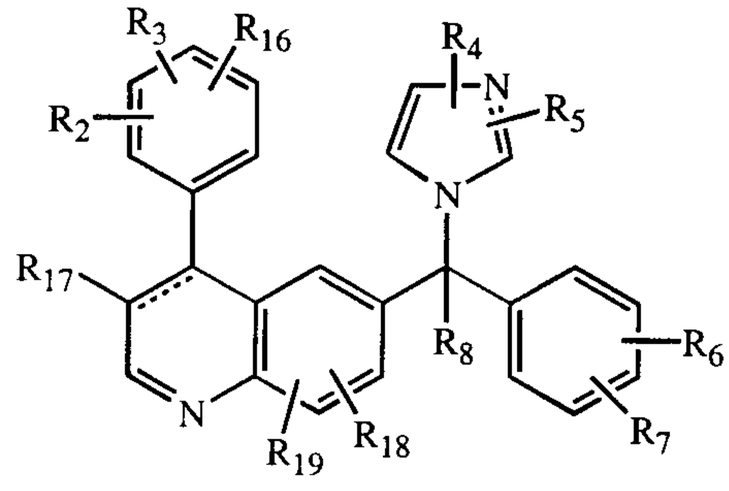
Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

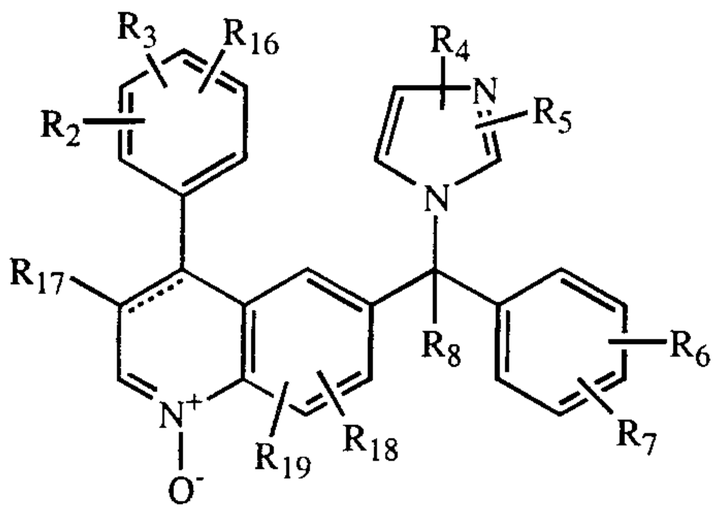
WO-97/16443 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IV), as well as intermediates of formula (V) and (VI) that are metabolized in vivo to the compounds of formula (IV). The compounds of formulas (IV), (V) and (VI) are represented by



(IV)



(V)



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,

or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9,

wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, amino-C_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, Ar^1, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkyl$S(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy or Ar^2oxy;

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl-carbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy-carbonylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, Ar^1, Ar^2C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl;

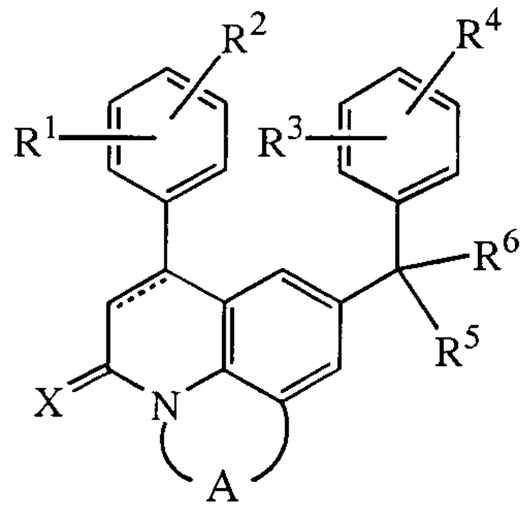
R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{11} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo;

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.

WO-98/40383 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VII)



(VII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

-CH=CH-	(a-1),	$-CH_2-S-$	(a-6),
$-CH_2-CH_2-$	(a-2),	$-CH_2-CH_2-S-$	(a-7),
$-CH_2-CH_2-CH_2-$	(a-3),	-CH=N-	(a-8),
$-CH_2-O-$	(a-4),	-N=N-	(a-9), or
$-CH_2-CH_2-O-$	(a-5),	-CO-NH-	(a-10);

wherein optionally one hydrogen atom may be replaced by C_{1-4}alkyl or Ar^1;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^2, Ar^2-C_{1-6}alkyl, Ar^2-oxy, Ar^2-C_{1-6}alkyloxy; or when on adjacent positions R^1 and R^2 taken together may form a bivalent radical of formula

$-O-CH_2-O-$	(b-1),
$-O-CH_2-CH_2-O-$	(b-2),
-O-CH=CH-	(b-3),
$-O-CH_2-CH_2-$	(b-4),
$-O-CH_2-CH_2-CH_2-$	(b-5), or
-CH=CH-CH=CH-	(b-6);

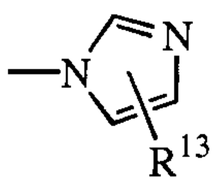
R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^3-oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R^3 and R^4 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1),

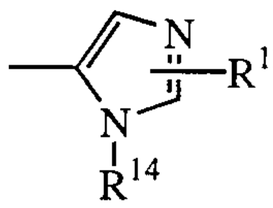
-O-CH_2-CH_2-O- (c-2), or

-CH=CH-CH=CH- (c-3);

R^5 is a radical of formula



(d-1),



(d-2),

wherein R^{13} is hydrogen, halo, Ar^4, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxy-carbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{14} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^5, Ar^5-C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^7 (e-1),

-S-R^7 (e-2),

-N-R^8R^9 (e-3),

wherein R^7 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^6, Ar^6-C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

R^8 is hydrogen, C_{1-6}alkyl, Ar^7 or Ar^7-C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^8, Ar^8-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^8-carbonyl, Ar^8-C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

wherein Alk is C_{1-6}alkanediyl;

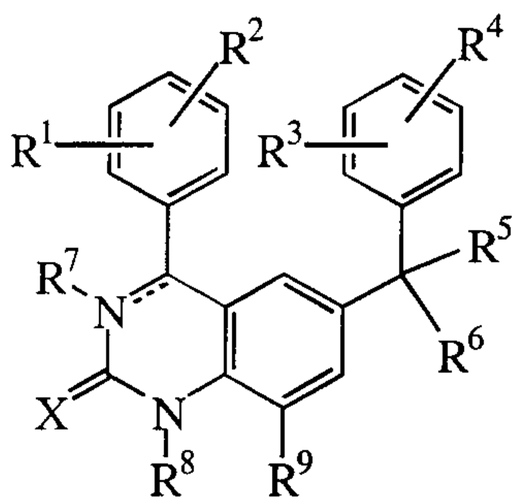
R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, Ar^9 or Ar^9-C_{1-6}alkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^{10} or Ar^{10}-C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, Ar^{11} or Ar^{11}-C_{1-6}alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

WO-98/49157 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VIII)



(VIII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^1C_{1-6}alkyl, Ar^1oxy or Ar^1C_{1-6}alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^{10} (a-1),

-S-R^{10} (a-2),

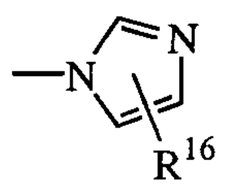
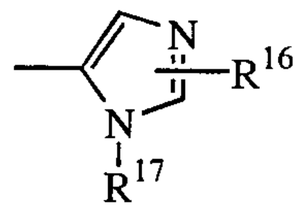
-N-$R^{11}R^{12}$ (a-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^1carbonyl, Ar^1C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino,
or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;
wherein Alk is C_{1-6}alkanediyl;
R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;
R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;
R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^6 is a radical of formula


(b-1),

(b-2),

wherein R^{16} is hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;
R^{17} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^7 is hydrogen or C_{1-6}alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2CH_2 or Het^1CH_2;

R^9 is hydrogen, C_{1-6}alkyl , C_{1-6}alkyloxy or halo; or

R^8 and R^9 taken together to form a bivalent radical of formula

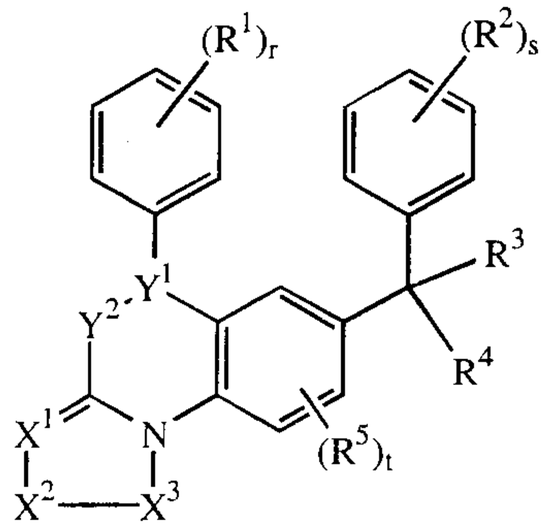
-CH=CH- (c-1),
$-CH_2-CH_2-$ (c-2),
$-CH_2-CH_2-CH_2-$ (c-3),
$-CH_2-O-$ (c-4), or
$-CH_2-CH_2-O-$ (c-5);

Ar^1 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl;

Ar^2 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

Het^1 is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

WO-00/39082 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IX)



(IX)

or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$=X^1-X^2-X^3-$ is a trivalent radical of formula

$=N-CR^6=CR^7-$	(x-1),	$=CR^6-CR^7=CR^8-$	(x-6),
$=N-N=CR^6-$	(x-2),	$=CR^6-N=CR^7-$	(x-7),
$=N-NH-C(=O)-$	(x-3),	$=CR^6-NH-C(=O)-$	(x-8), or
$=N-N=N-$	(x-4),	$=CR^6-N=N-$	(x-9);
$=N-CR^6=N-$	(x-5),		

wherein each R^6, R^7 and R^8 are independently hydrogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkyloxy, aryloxy, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, cyano, amino, thio, C_{1-4}alkylthio, arylthio or aryl;

$>Y^1-Y^2-$ is a trivalent radical of formula

$>CH-CHR^9-$	(y-1),
$>C=N-$	(y-2),
$>CH-NR^9-$	(y-3),or
$>C=CR^9-$	(y-4);

wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxyC_{1-4}alkyl, cyano, carboxyl, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, aryl;

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

each R^1 and R^2 are independently hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, aryl, arylC_{1-6}alkyl, aryloxy or arylC_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminocarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; or

two R^1 or R^2 substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula

-O-CH_2-O-	(a-1),
-O-CH_2-CH_2-O-	(a-2),
-O=CH=CH-	(a-3),
-O-CH_2-CH_2-	(a-4),
-O-CH_2-CH_2- CH_2-	(a-5), or
-CH=CH-CH=CH-	(a-6);

R^3 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonyl, hydroxycarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, aryl, arylC_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

or a radical of formula

-O-R^{10}	(b-1),
-S-R^{10}	(b-2),
-N$R^{11}R^{12}$	(b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl, arylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-N$R^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, aryl, hydroxy, amino, C_{1-6}alkyloxy, C_{1-6}alkylcarbonylC_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC_{1-6}alkylcarbonyl, arylC_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, mono- or di(C_{1-6}alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C_{1-3}alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, or a radical or formula -Alk-OR^{13} or -Alk-N$R^{14}R^{15}$;

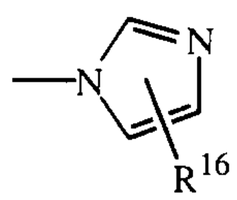
wherein Alk is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

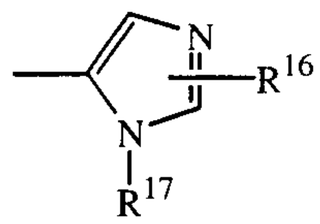
R^{14} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl or arylC_{1-6}alkyl;

R^4 is a radical of formula



(c-1),



(c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, arylC_{1-6}alkyl, trifluoromethyl or di(C_{1-4}alkyl)aminosulfonyl;

R^5 is C_{1-6}alkyl , C_{1-6}alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

Numerous anti-cancer agents have previously been tested and investigated in the clinic in attempts to provide improvements in the treatment of cancers. Examples of such agents are discussed below and it will be noted that these generally suffer from disadvantages in varying degrees relating to their lack of efficacy or toxicity.

In the chemotherapeutic treatment of cancers, cisplatin (cis-diaminedichloroplatinum (II)) has been used successfully for many years in the treatment of various human solid malignant tumors for example testicular cancer, ovarian cancer and cancers of the head and neck, bladder, oesophagus and lung. More recently, other diamino –platinum complexes for example carboplatin have also shown efficacy as chemotherapeutic agents in the treatment of various human solid malignanttumors, carboplatin being approved for the treatment of ovarian cancer. Although cisplatin and other platinum coordination compounds have been widely used as chemotherapeutic agents in humans, they are not therapeutically effective in all patients or against all types of tumors. Moreover, such compounds need to be administered at relatively high dosage levels which can lead to

toxicity problems such as kidney damage. Also, and especially with cisplatin, the compounds cause nausea and vomiting in patients to a varying extent.

The taxane compounds are a class of compounds having the taxane ring system and related to or derived from extracts from certain species of yew (Taxus) trees. These compounds have been found to have activity against tumor cell growth and certain compounds in this class have been used in the clinic for the treatment of various cancers. Thus, for example, paclitaxel is a diterpene isolated from the bark of the the yew tree, Taxus brevifolia, and can be produced by partial synthesis from 10-acetylbacctin, a precursor obtained from yew needles and twigs or by total synthesis, see Holton et al, J. Am. Chem. Soc. 116; 1597-1601 (1994) and Nicholau et al, Nature 367:630 (1994). Paclitaxel has shown neoplastic activity and more recently it has been established that its antitumor activity is due to the promotion of microtubule polymerisation, Kumar N. J., Biol. Chem. 256: 1035-1041 (1981); Rowinsky et al, J. Natl. Cancer Inst. 82: 1247-1259 (1990); and Schiff et al, Nature 277:655-667 (1979). Paclitaxel has now demonstrated efficacy in several human tumors in clinical trials, McGuire et al , Ann. Int. Med. 111: 273-279 (1989); Holmes et al, J. Natl. Cancer Inst. 83: 1797-1805 (1991); Kohn et al J. Natl. Cancer Inst. 86: 18-24 (1994); and Kohn et al , American Society for Clinical Oncology, 12 (1993). Paclitaxel has for example been used for the treatment of ovarian cancer and also breast cancer. Another taxane compound which has been used in the clinic is docetaxel which has been shown to have particular efficacy in the treatment of advanced breast cancer. Docetaxel has shown a better solubility in excipient systems than paclitaxel, therefore increasing the ease with which it can be handled and used in pharmaceutical compositions.

The class of camptothecin compounds are related to or derived from the parent camptothecin compound which is a water-insoluble alkaloid derived from the Chinese tree Camptothecin acuminata and the Indian tree Nothapodytes foetida. Camptothecin has a potent inhibitory activity against biosynthesis of DNA and has shown high activity against tumor cell growth in various experimental systems. Its clinical use in anti-cancer therapy is however limited significantly by its high toxicity, and various analogues have been developed in attempts to reduce the toxicity of camptothecin while retaining the potency of its anti-tumor effect. Example of such analogues include irinotecan and topotecan.These compounds have been found to be specific inhibitors of DNA topoisomerase I. Topoisomerases are enzymes that are capable of altering DNA topology in eukaryotic cells. They are critical for important cellular functions and cell proliferation. There are two classes of topoisomerases in eukaryotic cells, namely type I and type II. Topoisomerase I is a monomeric enzyme of approximately 100,000 molecular weight.

The enzyme binds to DNA and introduces a transient single-strand break, unwinds the double helix (or allows it to unwind) and subsequently reseals the break before dissociating from the DNA strand. Irinotecan, namely 7-ethyl-10-(4-(1-piperidino)-1-piperidino)carbonyloxy-(20S)-camptothecin, and its hydrochloride, also known as CPT 11, have been found to have improved potency and reduced toxicity and with superior water-solubility. Irinotecan has been found to have clinical efficacy in the treatment of various cancers especially colorectal cancer. Another important camptothecin compound is topotecan, namely (S)-9-dimethylaminomethyl-10-hydroxy-camptothecin which, in clinical trials has shown efficacy against several solid tumors, particularly ovarian cancer and non-small cell lung carcinoma.

Anti-tumor vinca alkaloids are related to or derived from extracts of the periwinkle plant (Vinca rosea). Among these compounds, vinblastine and vincristine are important clinical agents for the treatment of leukaemias, lymphomas and testicular cancer, and vinorelbine has activity against lung cancer and breast cancer. However these compounds each suffer from toxicological effects, for example vinblastine causes leukopenia which reaches a nadir in 7 to 10 days following drug administration, after which recovery ensues within 7 days, while vincristine demonstrates some neurological toxicity for example numbness and trembling of the extremities, loss of deep tendon reflexes and weakness of distal limb musculature. Vinorelbine has some toxicity in the form of granulocytopenia but with only modest thrombocytopenia and less neurotoxicity than other vinca alkaloids.

Anti-tumor nucleoside derivatives have been used for many years for the treatment of various cancers. Among the oldest and most widely used of these derivatives is 5-fluorouracil (5-FU) which has been been used to treat a number of cancers such as colorectal, breast, hepatic and head and neck tumors. In order to enhance the cytotoxic effect of 5-FU, leucovorin (5-formyltetrahydrofolate) has been used with the drug to modulate levels of thymidylate synthase which are critical to ensure that malignant cells are sensitive to the effect of 5-FU. However, various factors limit the use of 5-FU, for example tumor resistance, toxicities, including gastrointestinal and haematological effects, and the need for intravenous administration. Various approaches have been taken to overcome these disadvantages including proposals to overcome the poor bioavailability of 5-FU and also to increase the therapeutic index of 5-FU, either by reducing systemic toxicity or by increasing the amount of active drug reaching the tumor. One such compound which provides improved therapeutic advantage over 5-FU is capecitabine, which has the chemical name [1-(5-deoxy-beta-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxopyrimidin-4-yl]-carbamic acid, pentyl ester. Capecitabine is a pro-drug of 5-FU which is well absorbed after oral dosing and

delivers pharmacologically-active concentrations of 5-FU to tumors, with little systemic exposure to the active drug. As well as offering potentially superior activity to 5-FU, it can also be used for oral therapy with prolonged administration. Another anti-tumor nucleoside derivative is gemcitabine which has the chemical name 2'-deoxy-2',2'-difluoro-cytidine, and which has been used in the treatment of various cancers including non-small cell lung cancer and pancreatic cancer.

Alkylating agents used in chemotherapy encompass a diverse group of chemicals that have the common feature that they have the capacity to contribute, under physiological conditions, alkyl groups to biologically vital macromolecules such as DNA. With most of the more important agents such as the nitrogen mustards and the nitrosoureas the active alkylating moieties are generated in vivo after complex degradative reactions, some of which are enzymatic. The most important pharmacological actions of the alkylating agents are those that disturb the fundamental mechanisms concerned with cell proliferation in particular DNA synthesis and cell division. The capacity of alkylating agents to interfere with DNA function and integrity in rapidly proliferating tissues provides the basis for their therapeutic applications and for many of their toxic properties. Alkylating agents as a class have therefore been investigated for their anti-tumor activity and certain of these compounds have been widely used in anti-cancer therapy although they tend to have in common a propensity to cause dose-limiting toxicity to bone marrow elements and to a lesser extent the intestinal mucosa.

Among the alkylating agents, the nitrogen mustards represent an important group of anti-tumor compounds which are characterised by the presence of a bis-(2-chloroethyl) grouping and include cyclophosphamide, which has the chemical name 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide, and chlorambucil, which has the chemical name 4-[bis(2-chloroethyl)amino]benzenebutoic acid. Cyclophosphamide has a broad spectrum of clinical activity and is used as a component of many effective drug combinations for malignant lymphomas, Hodgkin's disease, Burkitt's lymphoma and in adjuvant therapy for treating breast cancer. Chlorambucil has been used for treating chronic leukocytic leukaemia and malignant lymphomas including lymphosarcoma.

Another important class of alkylating agents are the nitrosoureas which are characterised by the capacity to undergo spontaneous non-enzymatic degradation with the formation of the 2-chloroethyl carbonium ion from CNU compounds. Examples of such nitrosourea compounds include carmustine (BCNU) which has the chemical name 1,3-bis(2-chloroethyl)-1-nitrosourea, and lomustine (CCNU) which has the chemical

name 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea. Carmustine and lomustine have an important therapeutic role in the treatment of brain tumors and gastrointestinal neoplasms although these compounds cause profound, cumulative myelosuppression that restricts their therapeutic value.

Anthracycline derivatives are important anti-tumor agents and comprise antibiotics obtained from the fungus Strep. peuticus var. caesius and their derivatives, characterised by having a tetracycline ring structure with an unusual sugar, daunosamine, attached by a glycosidic linkage. Among these compounds, the most widely used include daunorubicin, which has the chemical name 7-(3-amino-2,3,6-trideoxy-L-lyxohexosyloxy)-9-acetyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-4-methoxy-5,12-naphthacenequinone, doxorubicin, which has the chemical name 10-[(3-amino-2,3,6-trideoxy-alphaL-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-5,12-naphthacenedione, and idarubicin, which has the chemical name 9-acetyl-7-[(3-amino-2,3,6-trideoxy-alphaL-lyxohexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-5,12-naphthacenedione. Daunorubicin and idarubicin have been used primarily for the treatment of acute leukaemias whereas doxorubicin displays broader activity against human neoplasms, including a variety of solid tumors particularly breast cancer. However, anthracycline derivatives generally display a serious cardiomyopathy at higher doses, which limits the doses at which these compounds can be administered.

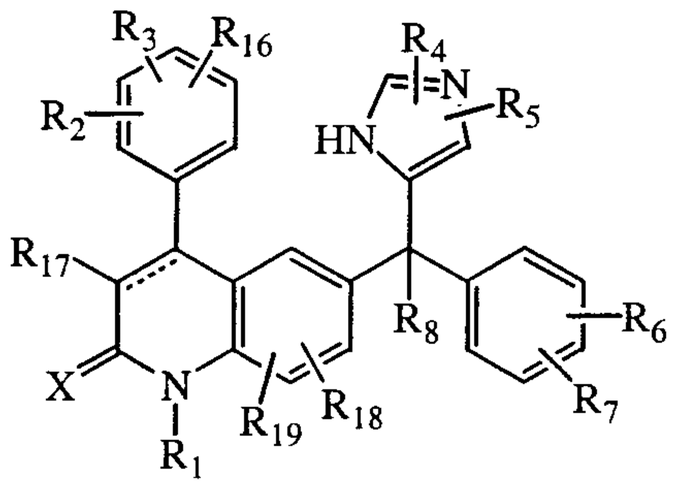
Amplification of the human epidermal growth factor receptor 2 protein (HER 2) in primary breast carcinomas has been shown to correlate with a poor clinical prognosis for certain patients. Trastuzumab is a highly purified recombinant DNA-derived humanized monoclonal IgG1 kappa antibody that binds with high affiniity and specificity to the extracellular domain of the HER2 receptor. In vitro and in vivo preclinical studies have shown that administration of trastuzumab alone or in combination with paclitaxel or carboplatin significantly inhibits the growth of breast tumor-derived cell lines that over-express the HER2 gene product. In a clinical studies trastuzumab has been shown to have clinical activity in the treatment of breast cancer. The most common adverse effects attributed to trastuzumab in clinical studies were fever and chills, pain, asthenia, nausea, vomiting, increased cough, diarrhea, headache, dyspnea, infection, rhinitis, and insomnia. Trastuzumab has been approved in the USA as single agent for the treatment of patients who have metastatic breast cancer involving over-expression of the HER2 protein and who have received one or more chemotherapy regimes; in combination with paclitaxel, it has also been approved for the treatment of such patients who have not received chemotherapy.

Podophyllotoxin, which is extracted from the mandrake plant, is the parent compound from which two glycosides have been developed which show significant therapeutic activity in several human neoplasms, including pediatric leukemia, small cell carcinomas of the lung, testicular tumors, Hodgkin's disease, and large cell lymphomas. These derivatives are referred to as etoposide (VP-16) which has the chemical name 4^1-demethylepipodophyllotoxin-9-[4,6-O-(R)-ethylidene-beta-D-glucopyranoside] and teniposide (VM-26) which has the chemical name 4^1-demethylepipodophyllotoxin-9-[4,6-O-(R)-thenylidene-beta-D-glucopyranoside]. These compounds have a similar mechanism of action which involves the induction of DNA strand breaks by an interaction with DNA topoisomerase II or the formation of free radicals. Both etoposide and teniposide, however, suffer from certain toxic side-effects especially myelosuppression.

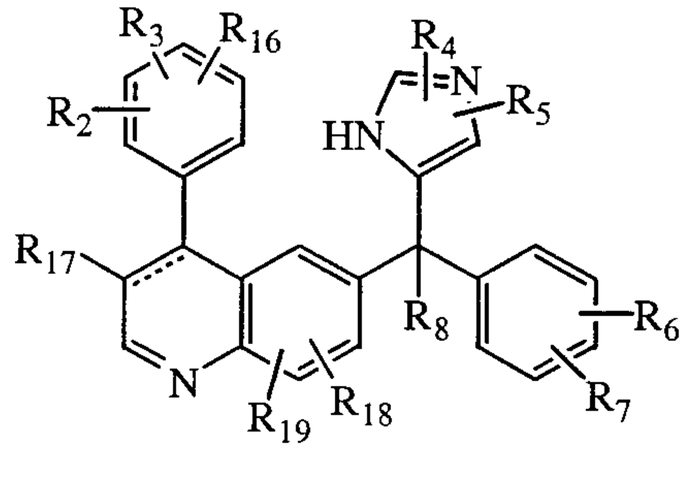
There is therefore a need to increase the inhibitory efficacy of such agents against tumor growth and also to provide a means for the use of lower dosages of the agents to reduce the potential of adverse toxic side effects to the patient.

It is an object of the invention to provide a therapeutic combination of a farnesyl transferase inhibitor of the type described above together with two or more further anti-cancer agents,which has an advantageous inhibitory effect against tumor cell growth, in comparison with the respective effects shown by the individual components of the combination.

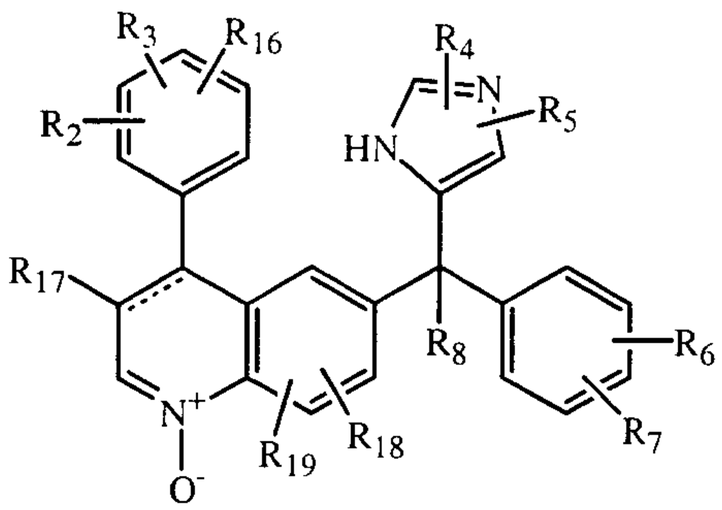
According to the invention therefore we provide a combination of a farnesyl transferase inhibitor of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) above, in particular a compound of formula (I), (II) or (III):



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,
or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9,
wherein Alk^1 is C_{1-6}alkanediyl,
R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or
when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),
-O-CH_2-CH_2-O- (a-2),
-O-CH=CH- (a-3),
-O-CH_2-CH_2- (a-4),
-O-CH_2-CH_2-CH_2- (a-5), or
-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl , C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS$(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or

-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxy-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)amino-C_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonyl-C_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino,

or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{19} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and two or more further anti-cancer agents.

The above described combinations are hereinafter referred to as combinations according to the invention. These combinations may provide a synergistic effect whereby they demonstrate an advantageous therapeutic effect which is greater than that which would have been expected from the effects of the individual components of the combinations.

In Formulas (I), (II) and (III), R^4 or R^5 may also be bound to one of the nitrogen atoms in the imidazole ring. In that case the hydrogen on the nitrogen is replaced by R^4 or R^5 and the meaning of R^4 and R^5 when bound to the nitrogen is limited to hydrogen, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl, C_{1-6}alkylS(O)$_2C_{1-6}$alkyl.

Preferably the substituent R^{18} is situated on the 5 or 7 position of the quinolinone moiety and substituent R^{19} is situated on the 8 position when R^{18} is on the 7-position.

Interesting compounds are these compounds of formula (I) wherein X is oxygen.

Also interesting compounds are these compounds of formula (I) wherein the dotted line represents a bond, so as to form a double bond.

Another group of interesting compounds are those compounds of formula (I) wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, wherein Alk^1 is methylene and R^9 is C_{1-8}alkyl-amino substituted with C_{1-6}alkyloxycarbonyl.

Still another group of interesting compounds are those compounds of formula (I) wherein R^3 is hydrogen or halo; and R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalomethoxy or hydroxyC_{1-6}alkyloxy.

A further group of interesting compounds are those compounds of formula (I) wherein R^2 and R^3 are on adjacent positions and taken together to form a bivalent radical of formula (a-1), (a-2) or (a-3).

A still further group of interesting compounds are those compounds of formula (I) wherein R^5 is hydrogen and R^4 is hydrogen or C_{1-6}alkyl.

Yet another group of interesting compounds are those compounds of formula (I) wherein R^7 is hydrogen; and R^6 is C_{1-6}alkyl or halo, preferably chloro, especially 4-chloro.

A particular group of compounds are those compounds of formula (I) wherein R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxy-carbonylC_{1-6}alkyl, imidazolyl, or a radical of formula $-NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, or a radical of formula $-Alk^2-OR^{13}$ wherein R^{13} is hydrogen or C_{1-6}alkyl.

Preferred compounds are those compounds wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or a radical of formula $-Alk^1-C(=O)-R^9$, wherein Alk^1 is methylene and R^9 is C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl; R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalo-methoxy, hydroxyC_{1-6}alkyloxy or Ar^1; R^3 is hydrogen; R^4 is methyl bound to the nitrogen in 3-position of the imidazole; R^5 is hydrogen; R^6 is chloro; R^7 is hydrogen; R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula $-NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, or a radical of formula $-Alk^2-OR^{13}$ wherein R^{13} is C_{1-6}alkyl; R^{17} is hydrogen and R^{18} is hydrogen.

Most preferred compounds are
4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-2(1H)-quinolinone,
6-[amino(4-chlorophenyl)-1-methyl-1H-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone;
6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone;
6-[(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone monohydrochloride.monohydrate;
6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone,
6-amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1H)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and

(+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone (Compound 75 in Table 1 of the Experimental part of WO-97/21701) ; or a pharmaceutically acceptable acid addition salt thereof. The latter compound is especially preferred.

Further preferred embodiments of the present invention include compounds of formula (IX) wherein one or more of the following restrictions apply:

- $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9) wherein each R^6 independently is hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, amino or aryl and R^7 is hydrogen;
- $>Y^1-Y^2-$ is a trivalent radical of formula (y-1), (y-2), (y-3), or (y-4) wherein each R^9 independently is hydrogen, halo, carboxyl, C_{1-4}alkyl or C_{1-4}alkyloxycarbonyl;
- r is 0, 1 or 2;
- s is 0 or 1;
- t is 0;
- R^1 is halo, C_{1-6}alkyl or two R^1 substituents ortho to one another on the phenyl ring may independently form together a bivalent radical of formula (a-1);
- R^2 is halo;
- R^3 is halo or a radical of formula (b-1) or (b-3) wherein
  R^{10} is hydrogen or a radical of formula -Alk-OR^{13}.
  R^{11} is hydrogen;
  R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy or mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl;
  Alk is C_{1-6}alkanediyl and R^{13} is hydrogen;
- R^4 is a radical of formula (c-1) or (c-2) wherein
  R^{16} is hydrogen, halo or mono- or di(C_{1-4}alkyl)amino;
  R^{17} is hydrogen or C_{1-6}alkyl;
- aryl is phenyl.

A particular group of compounds consists of those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, $C_{(1-4)}$alkyl or forms a bivalent radical of formula (a-1), R^2 is halo or C_{1-4}alkyl, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2), R^6 is hydrogen, C_{1-4}alkyl or phenyl, R^7 is hydrogen, R^9 is hydrogen or C_{1-4}alkyl, R^{10} is hydrogen or -Alk-OR^{13}, R^{11} is hydrogen and R^{12} is hydrogen or C_{1-6}alkylcarbonyl and R^{13} is hydrogen;

Preferred compounds are those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, preferably chloro and most preferably 3-chloro, R^2 is halo, preferably 4-chloro or 4-fluoro, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2), R^6 is hydrogen, R^7 is hydrogen, R^9 is hydrogen, R^{10} is hydrogen, R^{11} is hydrogen and R^{12} is hydrogen;

Other preferred compounds are those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-2), (x-3) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most preferably 3-chloro or R^1 is C_{1-4}alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4}alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.

The most preferred compounds of formula (IX) are
7-[(4-fluorophenyl)(1H-imidazol-1-yl)methyl]-5-phenylimidazo[1,2-a]quinoline;
α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)-5-phenylimidazo[1,2-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)-imidazo[1,2-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)imidazo[1,2-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-1-methyl-α-(1-methyl-1H-imidazol-5-yl)-1,2,4-triazolo[4,3-a]quinoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-4,5-dihydro-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanol;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine;
5-(3-chlorophenyl)-α-(4-chlorophenyl)-N-hydroxy-α-(1-methyl-1H-imidazol-5-yl)tetrahydro[1,5-a]quinoline-7-methanamine;

α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)-5-(3-methylphenyl)tetrazolo[1,5-a]quinoline-7-methanamine; the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof.

5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine, especially the (-) enantiomer, and its pharmaceutically acceptable acid addition salts are especially preferred.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C_{1-6}alkyl defines straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl and the like; C_{1-8}alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C_{1-6}alkyl as well as the higher homologues thereof containing 7 or 8 carbon atoms such as, for example heptyl or octyl; C_{1-12}alkyl again encompasses C_{1-8}alkyl and the higher homologues thereof containing 9 to 12 carbon atoms, such as, for example, nonyl, decyl, undecyl, dodecyl; C_{1-16}alkyl again encompasses C_{1-12}alkyl and the higher homologues thereof containing 13 to 16 carbon atoms, such as, for example, tridecyl, tetradecyl, pentedecyl and hexadecyl; C_{2-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; C_{1-6}alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof. The term "C(=O)" refers to a carbonyl group, "S(O)" refers to a sulfoxide and "$S(O)_2$" to a sulfon. The term "natural amino acid" refers to a natural amino acid that is bound via a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of the amino acid and the amino group of the remainder of the molecule. Examples of natural amino acids are glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylanaline, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine.

The pharmaceutically acceptable acid or base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. The compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have basic properties can be converted in their

pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

The compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The terms acid or base addition salt also comprise the hydrates and the solvent addition forms which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may also exist in their tautomeric forms. Such forms although not explicitly indicated

in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX)" is meant to include also the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

The further anti-cancer agents are preferably selected from those described above, namely platinum coordination compounds, taxane compounds, camptothecin compounds, anti-tumor vinca alkaloids, anti-tumor nucleoside derivatives, nitrogen mustard or nitrosourea alkylating agents, anti-tumor anthracycline derivatives, trastzumab and anti-tumor podophyllotoxin derivatives.

The term " platinum coordination compound" is used herein to denote any tumor cell growth inhibiting platinum coordination compound which provides platinum in the form of an ion. Preferred platinum coordination compounds include cisplatin, carboplatin, chloro(diethylenetriamine)-platinum (II) chloride; dichloro(ethylenediamine)-platinum (II); diamine(1,1-cyclobutanedicarboxylato)-platinum (II) (carboplatin); spiroplatin; iproplatin; diamine(2-ethylmalonato)-platinum (II); (1,2-diaminocyclohexane)malonatoplatinum (II); (4-carboxyphthalo)(1,2-diaminocyclohexane)platinum (II); (1,2-diaminocyclohexane)-(isocitrato)platinum (II); (1,2-diaminocyclohexane)-cis-(pyruvato)platinum (II); and (1,2-diaminocyclohexane)-oxalato-platinum (II); ormaplatin and tetraplatin.

Cisplatin is the most preferred platinum coordination compound. Cisplatin is commercially available for example under the trade name Platinol from Bristol Myers Squibb Corporation as a powder for constitution with water, sterile saline or other suitable vehicle. Other platinum coordination compounds and their pharmaceutical compositions are commercially available and/or can be prepared by conventional techniques.

The taxane compound used in the combinations according to the invention is preferably paclitaxel or docetaxel referred to above. Paclitaxel is available commercially for example under the trade name Taxol from Bristol Myers Squibb and docetaxel is available commercially under the trade name Taxotere from Rhone-Poulenc Rorer. Both compounds and other taxane compounds may be prepared in conventional manner for example as described in EP 253738, EP 253739 and WO 92/09589 or by processes analogous thereto.

Preferred camptothecin compounds for use in accordance with the invention include irinotecan and topotecan referred to above. Irinotecan is commercially available for example from Rhone-Poulenc Rorer under the trade name Campto and may be prepared for example as descibed in European patent specification No. 137145 or by processes analogous thereto. Topotecan is commercially available for example from SmithKline Beecham under the trade name Hycamtin and and may be prepared for example as descibed in European patent specification No. 321122 or by processes analogous thereto. Other camptothecin compounds may be prepared in conventional manner for example by processes analogous to those described above for irinotecan and topotecan.

Preferred anti-tumor vinca alkaloids for use in accordance with the invention include vinblastine, vincristine and vinorelbine referred to above. Vinblastine is commercially available for example as the sulphate salt for injection from Eli Lilly and Co under the trade name Velban, and may be prepared for example as described in German patent specification No. 2124023 or by processes analogous thereto. Vincristine is commercially available for example as the sulphate salt for injection from Eli Lilly and Co under the trade name Oncovin and may be prepared for example as described in the above German patent specification No. 2124023 or by processes analogous thereto. Vinorelbine is commercially available for example as the tartrate salt for injection from Glaxo Wellcome under the trade name Navelbine and may be prepared for example as described in U.S. patent specification No. 4307100, or by processes analogous thereto Other anti-tumor vinca alkaloids may be prepared in conventional manner for example by processes analogous to those described above for vinoblastine, vincristine and vinorelbine.

Preferred anti-tumor nucleoside derivatives for use in accordance with the invention include 5-fluorouracil, gemcitabine and capecitabine referred to above. 5- Fluorouracil is widely available commercially, and may be prepared for example as described in US Patent No. 2802005. Gemcitabine is commercially available for example from Eli Lilly under the trade name Gemzar and may be prepared for example as described in European patent specification No. 122707 or by processes analogous thereto. Capecitabine is commercially available for example from Hoffman-La Roche under under the trade name Xeloda and may be prepared for example as described in European patent specification No. 698611 or by processes analogous thereto. Other anti-tumor nucleoside derivatives may be prepared in conventional manner for

example by processes analogous to those described above for capecitabine and gemcitabine.

Preferred nitrogen mustard compounds for use in accordance with the invention include cyclophosphamide and chlorambucil referred to above. Cyclophosphamide is commercially available for example from Bristol-Myers Squibb under the trade name Cytoxan and may be prepared for example as described in U.K. patent specification No. 1235022 or by processes analogous thereto. Chlorambucil is commercially available for example from Glaxo Wellcome under the trade name Leukeran and may be prepared for example as described in U.S. patent specification No. 3046301, or by processes analogous thereto. Preferred nitrosourea compounds for use in accordance with the invention include carmustine and lomustine referred to above. Carmustine is commercially available for example from Bristol-Myers Squibb under the trade name BiCNU and may be prepared for example as described in European patent specification No. 902015, or by processes analogous thereto. Lomustine is commercially available for example from Bristol-Myers Squibb under the trade name CeeNU and may be prepared for example as described in U.S. patent specification No. 4377687, or by processes analogous thereto.

Preferred anti-tumor anthracycline derivatives for use in accordance with the invention include daunorubicin, doxorubicin and idarubicin referred to above. Daunorubicin is commercially available for example as the hydrochloride salt from Bedford Laboratories under the trade name Cerubidine, and may be prepared for example as described in U.S. patent specification No. 4020270, or by processes analogous thereto. Doxorubicin is commercially available for example as the hydrochloride salt from Astra, and may be prepared for example as described in U.S. patent specification No. 3803124 or by processes analogous thereto. Idarubicin is commercially available for example as the hydrochloride salt from Pharmacia & Upjohn under the trade name Idamycin, and may be prepared for example as described in U.S patent specification No. 4046878 or by processes analogous thereto Other anti-tumor anthracycline derivatives may be prepared in conventional manner for example by processes analogous to those described above for daunorubicin, doxorubicin and idarubicin.

Trastzumab is commercially available from Genentech under the trade name Herceptin and may be obtained as described in U.S. Patent specification No. 5821337 or PCT patent specifications WO 94/04679 and WO 92/22653.

Preferred anti-tumor anti-tumor podophyllotoxin derivatives for use in accordance with the invention include etoposide and teniposide referred to above. Etoposide is commercially available for example from Bristol-Myers Squibb under the trade name VePesid, and may be prepared for example as described in European patent specification No. 111058, or by processes analogous thereto. Teniposide is commercially available for example from Bristol-Myers Squibb under the trade name Vumon and may be prepared for example as described in PCT patent specification No. WO 93/02094, or by processes analogous thereto. Other anti-tumor podophyllotoxin derivatives may be prepared in conventional manner for example by processes analogous to those described above for etoposide and teniposide.

Generally combinations according to the invention comprise the above-defined farnesyl transferase inhibitor and two further anti-cancer agents.

Examples of preferred combinations according to the invention include combinations in which the above-defined farnesyl transferase inhibitor is employed in conjunction with two further anti-cancer agents preferably selected from platinum coordination compounds, for example cisplatin and carboplatin, and anti-tumor nucleoside derivatives, for example gemcitabine and capecitabine; combinations in which the two further further anti-cancer agents are cisplatin and gemcitabine are especially preferred.

Other preferred combinations according to the invention include those in which the two further anti-cancer agents are preferably selected from platinum coordination compounds, for example cisplatin and carboplatin, and taxane compounds for example paclitaxel or docetaxel; combinations in which the two further anti-cancer agents are carboplatin and paclitaxel are especially preferred.

Other preferred combinations according to the invention include those in which the two further anti-cancer agents are preferably selected from taxane compounds, for example paclitaxel or docetaxel, and anti-tumor nucleoside derivatives, for example gemcitabine and capecitabine; combinations in which the two further anti-cancer agents are paclitaxel and gemcitabine are especially preferred.

Other preferred combinations according to the invention include those in which the two further anti-cancer agents are preferably selected from camptothecin compounds, for example irinotecan or topotecan, and anti-tumor nucleoside derivatives, for example gemcitabine and capecitabine; combinations in which the two further anti-cancer agents are irinotecan and capecitabine are especially preferred.

The present invention also relates to combinations according to the invention for use in medical therapy for example for inhibiting the growth of tumor cells.

The present invention also relates to the use of combinations according to the invention for the preparation of a pharmaceutical composition for inhibiting the growth of tumor cells.

The present invention also relates to a method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination according to the invention.

This invention further provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a combination according to the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g. loss of contact inhibition). This includes the abnormal growth of : (1) tumor cells (tumors) expressing an activated ras oncogene; (2) tumor cells in which the ras protein is activated as a result of oncogenic mutation of another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant ras activation occurs. Furthermore, it has been suggested in literature that ras oncogenes not only contribute to the growth of of tumors in vivo by a direct effect on tumor cell growth but also indirectly, i.e. by facilitating tumor-induced angiogenesis (Rak. J. et al, Cancer Research, 55, 4575-4580, 1995). Hence, pharmacologically targetting mutant ras oncogenes could conceivably suppress solid tumor growth in vivo, in part, by inhibiting tumor-induced angiogenesis.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of a combination according to the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated ras oncogene by the administration of an effective amount of combination according to the present invention. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of

mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carninoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

This invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein ras proteins are aberrantly activated as a result of oncogenic mutation in genes, i.e. the ras gene itself is not activated by mutation to an oncogenic form, with said inhibition being accomplished by the administration of an effective amount of a combination according to the invention, to a subject in need of such a treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which ras is activated due to mutation or overexpression of tyrosine kinase oncogenes may be inhibited by the combinations according to the invention.

The farnesyl transferase inhibitor and the two or more further anti-cancer agents may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the respective compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular farnesyl transferase inhibitor and further anti-cancer agents being administered, their route of administration, the particular tumor being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The farnesyl transferase inhibitor is advantageously administered in an effective amount of from 0.0001 mg/kg to 100 mg/kg body weight, and in particular from 0.001 mg/kg to 10 mg/kg body weight. More particularly, for an adult patient, the dosage is conveniently in the range of 50 to 500mg bid, advantageously 100 to 400 mg bid and particularly 300mg bid.

The platinum coordination compound is advantageously administered in a dosage of 1 to 500mg per square meter (mg/m^2) of body surface area, for example 50 to 400 mg/m^2, particularly for cisplatin in a dosage of about 75 mg/m^2 and for carboplatin in about 300mg/m^2 per course of treatment. These dosages may be administered for example

once, twice or more per course of treatment, which may be repeated for example every 7, 14,21 or 28 days.

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2, particularly for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2, particularly for irinotecan in a dosage of about 200 to 350 mg/m^2 and for topotecan in about 1 to 2 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7,14,21 or 28 days.

The anti-tumor vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2 , for vincristine in a dosage of about 1 to 2 mg/m^2 , and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7,14, 21 or 28 days.

The anti-tumor nucleoside derivative is advantageously administered in a dosage of 200 to 2000 mg per square meter (mg/m^2) of body surface area, for example 700 to1500 mg/m^2, particularly for 5-FU in a dosage of 200 to 500mg/m^2, and for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to 1500 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

The nitrogen mustard or nitrosourea alkylating agent is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2, particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2 , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, and for carmustine in a dosage of about 150-200 mg/m^2 , per course of treatment. These dosages may be

administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

The anti-tumor anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2, particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2 , for daunorubicin in a dosage of about 25 to 45mg/m^2 , and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7,14,21 or 28 days.

Trastuzumab is advantageously administered in a dosage of 1 to 5mg per square meter (mg/m^2) of body surface area, particularly 2 to 4mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

The anti-tumor podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250mg/m^2, particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7,14,21 or 28 days.

It is especially preferred to administer the farnesyl tranferase inhibitor at a dosage of 100 or 200mg bid for 7, 14, 21 or 28 days with a dosage of the further anti-cancer agents in the ranges indicated above.

In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the farnesyl transferase inhibitor and the further anti-cancer agents may be formulated into various pharmaceutical forms for administration purposes. The components may formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing both components. Farnesyl protein transferase inhibitors can be prepared and formulated into pharmaceutical compositions by methods known in the art and in particular according to the methods described in the published patent specifications mentioned herein and incorporated by reference; for the compounds of formulae (I), (II) and (III) suitable examples can be found in WO-97/21701. Compounds of formulae (IV), (V), and (VI) can be prepared and formulated using methods described in WO 97/16443, compounds

of formulae (VII) and (VIII) according to methods described in WO 98/40383 and WO 98/49157 and compounds of formula (IX) according to methods described in WO 00/39082 respectively.

The present invention therefore also relates to a pharmaceutical composition comprising a farnesyl tranferase inhibitor of formula (I) and two or more further anti-cancer agents, together with one or more pharmaceutical carriers. To prepare pharmaceutical compositions for use in accordance with the invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity

of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

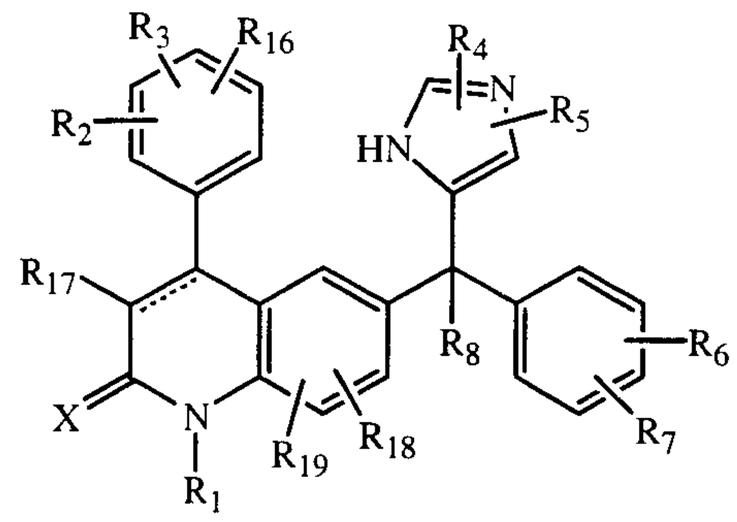
It may be appropriate to administer the required dose of each component of the combination as two, three, four or more sub-doses at appropriate intervals throughout the course of treatment Said sub-doses may be formulated as unit dosage forms, for example, in each case containing independently 0.01 to 500 mg, for example 0.1 to 200 mg and in particular 1 to 100mg of each active ingredient per unit dosage form.

Experimental Testing of Combinations for Inhibition of Tumor Growth

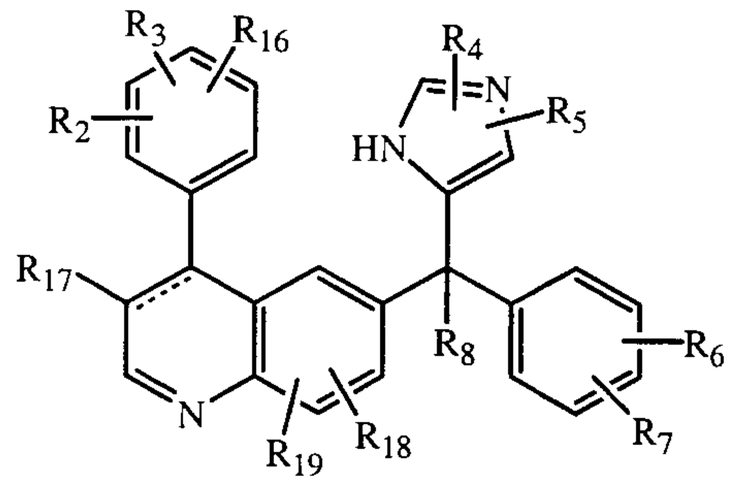
The combinations according to the invention may be tested for their efficacy in inhibiting tumor growth using conventional assays described in the literature for example the HTB177 lung carcinoma described by Liu M et al, Cancer Research, Vol. 58, No.21, 1 November 1998, pages 4947-4956, and the anti-mitotic assay described by Moasser M et al, Proc. Natl. Acad. Sci. USA, Vol. 95, pages 1369-1374, February 1998. Other *in vitro* and *in vivo* models for determining ant-tumor effects of combinations and possible synergy of the combinations according to the invention are described in WO 98/54966 and WO 98/32114. Clinical models for determining the efficacy and possible synergism for combination therapy in the clinic are generally described in Cancer: Principles and Practice of Oncology, Fifth Edition, edited by Vincent T DeVita, Jr., Samuel Hellman, Steven A. Rosenberg, Lippincott-Raven, Philadelphia, 1997, especially Chapter 17, pages 342-346.

Claims

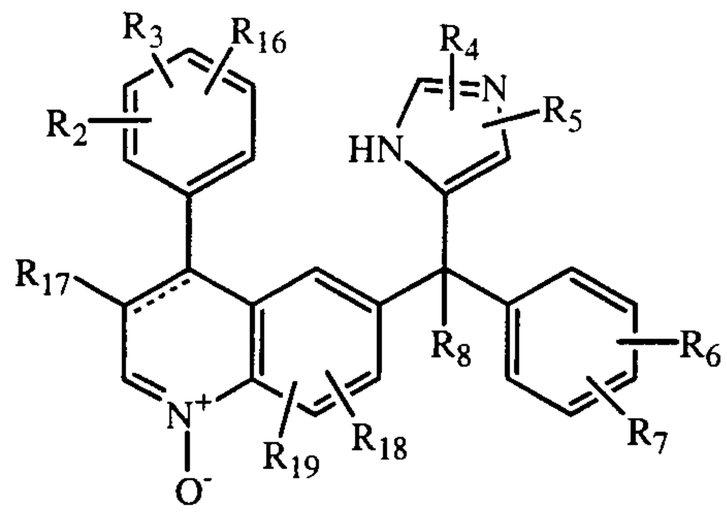
1. A combination of a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) below:



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aminoC_{1-6}alkyl, or a radical of formula -Alk^1-C(=O)-R^9, -Alk^1-S(O)-R^9 or -Alk^1-$S(O)_2$-R^9, wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2, R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^2oxy, trihalomethyl, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, or

when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

-O-CH_2-O- (c-1), or

-CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, imidazolyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, or a radical of formula

-O-R^{10} (b-1),

-S-R^{10} (b-2),

-N-$R^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-12}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-16}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^2C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino, or a radical or formula -Alk^2-OR^{13} or -Alk^2-$NR^{14}R^{15}$;

wherein Alk^2 is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^2C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^2C_{1-6}alkyl;

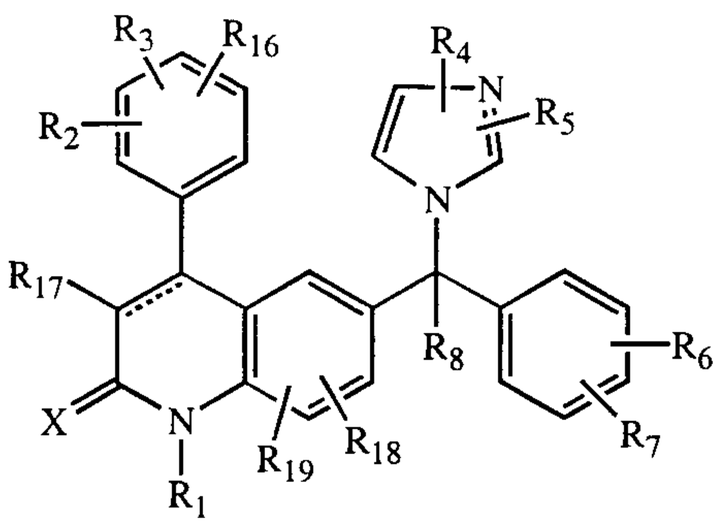
R^{17} is hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, Ar^1;

R^{18} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

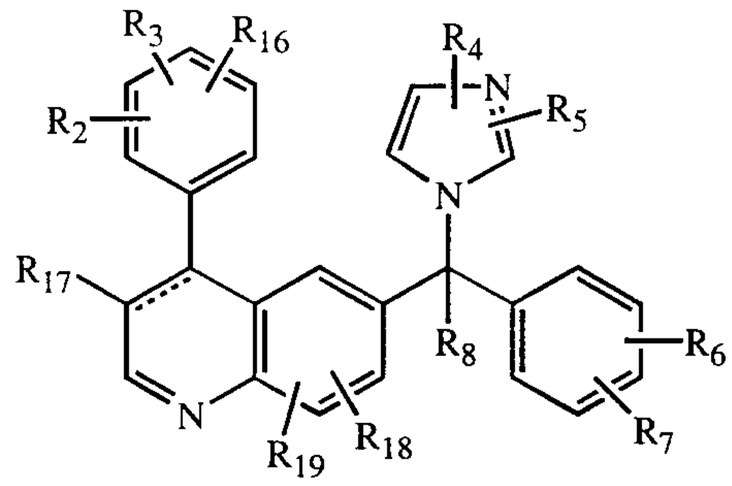
R^{19} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.



(IV)



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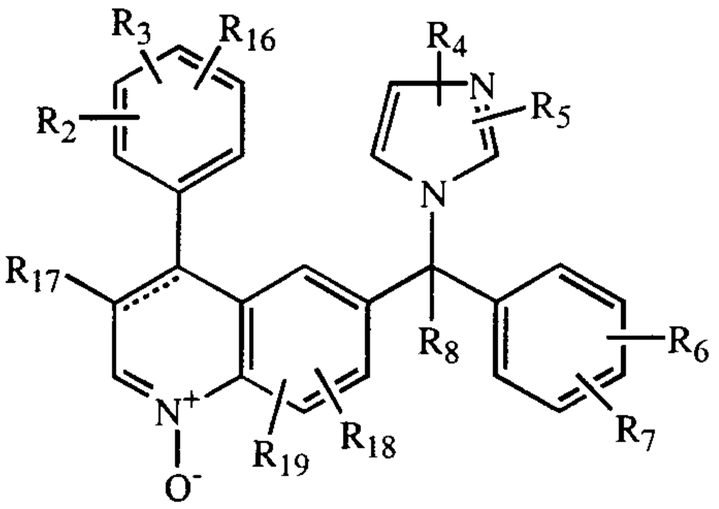


(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12}alkyl, Ar^1, Ar^2C_{1-6}alkyl, quinolinylC_{1-6}alkyl, pyridyl-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, aminoC_{1-6}alkyl,

or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$,

wherein Alk^1 is C_{1-6}alkanediyl,

R^9 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, C_{1-8}alkylamino or C_{1-8}alkylamino substituted with C_{1-6}alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, amino-C_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^2C_{1-6}alkyl, Ar^2oxy, Ar^2C_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2-O- (a-2),

-O-CH=CH- (a-3),

-O-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2- (a-5), or

-CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, Ar^1, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS$(O)_2C_{1-6}$alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy or Ar^2oxy;

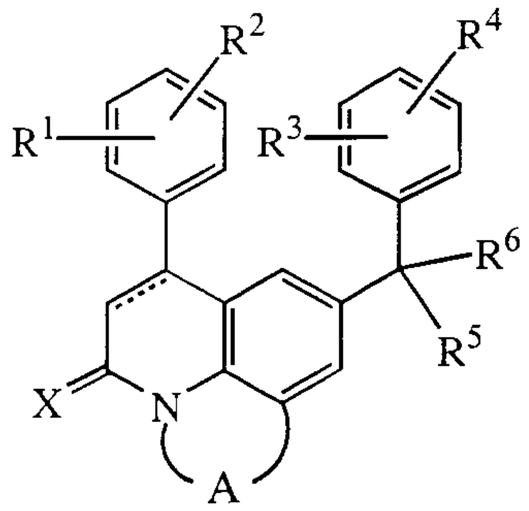
R^8 is hydrogen, C_{1-6}alkyl, cyano, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl-carbonylC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy-carbonylC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, Ar^1, Ar^2C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl;

R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or halo;

R^{11} is hydrogen or C_{1-6}alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo;

Ar^2 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo.



(VII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

-CH=CH-	(a-1),	$-CH_2-S-$	(a-6),
$-CH_2-CH_2-$	(a-2),	$-CH_2-CH_2-S-$	(a-7),
$-CH_2-CH_2-CH_2-$	(a-3),	-CH=N-	(a-8),
$-CH_2-O-$	(a-4),	-N=N-	(a-9), or
$-CH_2-CH_2-O-$	(a-5),	-CO-NH-	(a-10);

wherein optionally one hydrogen atom may be replaced by C_{1-4}alkyl or Ar^1;

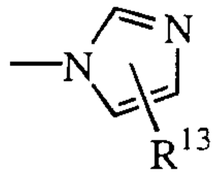
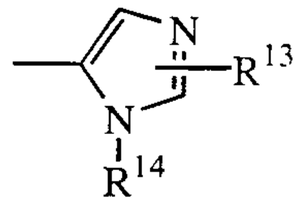
R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^2, Ar^2-C_{1-6}alkyl, Ar^2-oxy, Ar^2-C_{1-6}alkyloxy; or when on adjacent positions R^1 and R^2 taken together may form a bivalent radical of formula

$-O-CH_2-O-$	(b-1),
$-O-CH_2-CH_2-O-$	(b-2),
-O-CH=CH-	(b-3),
$-O-CH_2-CH_2-$	(b-4),
$-O-CH_2-CH_2-CH_2-$	(b-5), or
-CH=CH-CH=CH-	(b-6);

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^3-oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R^3 and R^4 taken together may form a bivalent radical of formula

$-O-CH_2-O-$	(c-1),
$-O-CH_2-CH_2-O-$	(c-2), or
-CH=CH-CH=CH-	(c-3);

R^5 is a radical of formula


(d-1),

(d-2),

wherein R^{13} is hydrogen, halo, Ar^4, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxy-carbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{14} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^5, Ar^5-C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^7 (e-1),

-S-R^7 (e-2),

-N-R^8R^9 (e-3),

wherein R^7 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^6, Ar^6-C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

R^8 is hydrogen, C_{1-6}alkyl, Ar^7 or Ar^7-C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^8, Ar^8-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^8-carbonyl, Ar^8-C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino,

or a radical or formula -Alk-OR^{10} or -Alk-$NR^{11}R^{12}$;

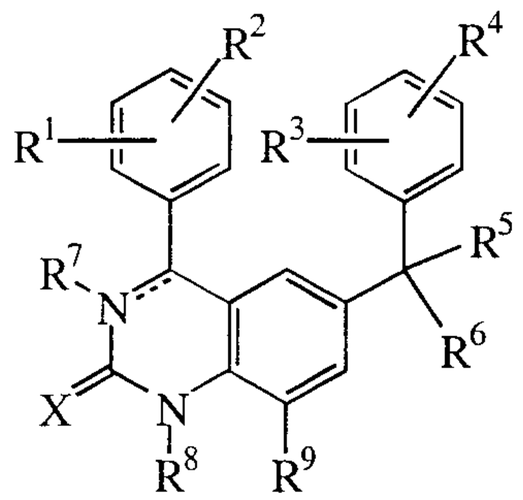
wherein Alk is C_{1-6}alkanediyl;

R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, Ar^9 or Ar^9-C_{1-6}alkyl;

R^{11} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^{10} or Ar^{10}-C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, Ar^{11} or Ar^{11}-C_{1-6}alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.



(VIII)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, Ar^1, Ar^1C_{1-6}alkyl, Ar^1oxy or Ar^1C_{1-6}alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, Ar^1oxy, C_{1-6}alkylthio, di(C_{1-6}alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyloxyC_{1-6}alkyl; or a radical of formula

-O-R^{10} (a-1),

-S-R^{10} (a-2),

-N-$R^{11}R^{12}$ (a-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminocarbonyl, Ar^1, Ar^1C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, Ar^1carbonyl, Ar^1C_{1-6}alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, C_{1-6}alkyloxy, aminocarbonyl, di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, C_{1-6}alkylcarbonylamino,

or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

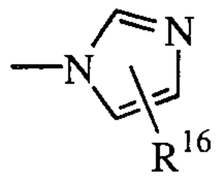
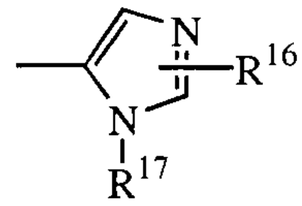
wherein Alk is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxy-C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, Ar^1 or Ar^1C_{1-6}alkyl;

R^6 is a radical of formula

 (b-1),  (b-2),

wherein R^{16} is hydrogen, halo, Ar^1, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl or di(C_{1-4}alkyl)aminosulfonyl;

R^7 is hydrogen or C_{1-6}alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2CH_2 or Het^1CH_2;

R^9 is hydrogen, C_{1-6}alkyl , C_{1-6}alkyloxy or halo; or

R^8 and R^9 taken together to form a bivalent radical of formula

-CH=CH- (c-1),

$-CH_2-CH_2-$ (c-2),

$-CH_2-CH_2-CH_2-$ (c-3),

$-CH_2-O-$ (c-4), or

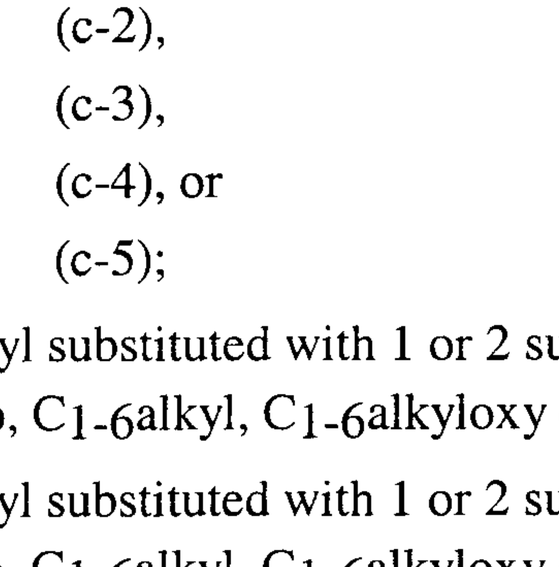
$-CH_2-CH_2-O-$ (c-5);

Ar^1 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl;

Ar^2 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

Het^1 is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl

and

 (IX)

or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$=X^1-X^2-X^3-$ is a trivalent radical of formula

$=N-CR^6=CR^7-$	(x-1),	$=CR^6-CR^7=CR^8-$	(x-6),
$=N-N=CR^6-$	(x-2),	$=CR^6-N=CR^7-$	(x-7),
$=N-NH-C(=O)-$	(x-3),	$=CR^6-NH-C(=O)-$	(x-8), or
$=N-N=N-$	(x-4),	$=CR^6-N=N-$	(x-9);
$=N-CR^6=N-$	(x-5),		

wherein each R^6, R^7 and R^8 are independently hydrogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkyloxy, aryloxy, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, cyano, amino, thio, C_{1-4}alkylthio, arylthio or aryl;

$>Y^1-Y^2-$ is a trivalent radical of formula

$>CH-CHR^9-$	(y-1),		
$>C=N-$	(y-2),		
$>CH-NR^9-$	(y-3),or		
$>C=CR^9-$	(y-4);		

wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxyC_{1-4}alkyl, cyano, carboxyl, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyloxycarbonyl, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, aryl;

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

each R^1 and R^2 are independently hydroxy, halo, cyano, C_{1-6}alkyl, trihalomethyl, trihalomethoxy, C_{2-6}alkenyl, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aminoC_{1-6}alkyloxy, mono- or di(C_{1-6}alkyl)amino, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy, aryl, arylC_{1-6}alkyl, aryloxy or arylC_{1-6}alkyloxy, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, aminoC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminocarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl; or

two R^1 or R^2 substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula

$-O-CH_2-O-$	(a-1),	
$-O-CH_2-CH_2-O-$	(a-2),	
$-O=CH=CH-$	(a-3),	
$-O-CH_2-CH_2-$	(a-4),	
$-O-CH_2-CH_2-CH_2-$	(a-5), or	
$-CH=CH-CH=CH-$	(a-6);	

R^3 is hydrogen, halo, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonyl, hydroxycarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, aryl, arylC_{1-6}alkyloxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

or a radical of formula

$-O-R^{10}$ (b-1),

$-S-R^{10}$ (b-2),

$-NR^{11}R^{12}$ (b-3),

wherein R^{10} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl, arylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, or a radical of formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{12} is hydrogen, C_{1-6}alkyl, aryl, hydroxy, amino, C_{1-6}alkyloxy, C_{1-6}alkylcarbonylC_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC_{1-6}alkylcarbonyl, arylC_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, mono- or di(C_{1-6}alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C_{1-3}alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkylcarbonyl, or a radical or formula -Alk-OR^{13} or -Alk-$NR^{14}R^{15}$;

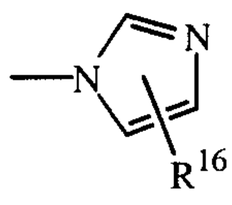
wherein Alk is C_{1-6}alkanediyl;

R^{13} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

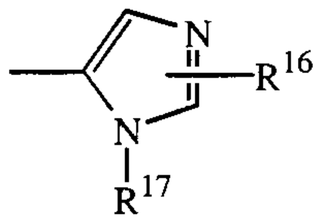
R^{14} is hydrogen, C_{1-6}alkyl, aryl or arylC_{1-6}alkyl;

R^{15} is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, aryl or arylC_{1-6}alkyl;

R^4 is a radical of formula



(c-1),



(c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthioC_{1-6}alkyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2C_{1-6}$alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl,

C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylS(O)C_{1-6}alkyl or C_{1-6}alkylS(O)$_2$$C_{1-6}$alkyl;

R^{17} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, arylC_{1-6}alkyl, trifluoromethyl or di(C_{1-4}alkyl)aminosulfonyl;

R^5 is C_{1-6}alkyl , C_{1-6}alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl: and two or more further anti-cancer agents.

2. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein X is oxygen and the dotted line represents a bond.

3. A combination as claimed in claim 1 or claim 2 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl or mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl and wherein R^3 is hydrogen and R^2 is halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkyloxy, trihalomethoxy or hydroxyC_{1-6}alkyloxy.

4. A combination as claimed in any of the preceding claims wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^8 is hydrogen, hydroxy, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, imidazolyl, or a radical of formula -$NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12}alkyl and R^{12} is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, hydroxy, or a radical of formula -Alk^2-OR^{13} wherein R^{13} is hydrogen or C_{1-6}alkyl.

5. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is selected from:

4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)-methyl]-1-methyl-2(1H)-quinolinone,

6-[amino(4-chlorophenyl)-1-methyl-1H-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone;

6-[(4-chlorophenyl)hydroxy(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxy-phenyl)-1-methyl-2(1H)-quinolinone;

6-[(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone monohydrochloride.monohydrate;

6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1H)-quinolinone, and 6-amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1H)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salts thereof.

6. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone; or a pharmaceutically acceptable acid addition salt thereof.

7 A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-2), (x-3) or (x-4), >Y1-Y2 is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most preferably 3-chloro or R^1 is C_{1-4}alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4}alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.

8. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is 5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine or a pharmaceutically acceptable acid addition salt thereof.

9. A combination as claimed in any of the preceding claims in which the two or more further anti-cancer agents are independently selected from platinum coordination compounds, taxane compounds, camptothecin compounds, anti-tumour vinca alkaloids, anti-tumor nucleoside derivatives, nitrogen mustard or nitrosourea alkylating agents, anti-tumor anthracycline derivatives, trastzumab and anti-tumor podophyllotoxin derivatives.

10. A combination as claimed in claim 9 in which platinum coordination compounds is cisplatin or carboplatin.

11. A combination as claimed in claim 9 in which the taxane compound is paclitaxel or docetaxel.

12. A combination as claimed in claim 9 in which the anti-tumor vinca alkaloid is vinblastine, vincristine or vinorelbine.

13. A combination as claimed in claim 9 in which the anti-tumor nucleoside derivative is 5-fluorouracil, gemcitabine or capecitabine.

14. A combination as claimed in claim 9 in which the nitrogen mustard or nitrosourea alkylating agent is cyclophosphamide, chlorambucil, carmustine or lomustine.

15. A combination as claimed in claim 9 in which the anti-tumor anthracycline derivative is daunorubicin, doxorubicin or idarubicin.

16. A combination as claimed in claim 9 in which the anti-tumor podophyllotoxin derivative is etoposide and teniposide.

17. A combination as claimed in any of the preceding claims in the form of a pharmaceutical composition comprising a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) (as defined in claim 1) and two or more further anti-cancer agents, together with one or more pharmaceutical carriers.

18. A combination as claimed in any of the preceding claims for use in medical therapy.

19. A combination as claimed in claim 18 for inhibiting the growth of tumor cells.

20. Use of a combination as claimed in any of claims 1 to 19 in the manufacture of a pharmaceutical composition for inhibiting the growth of tumor cells.

21. A method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination as claimed in any of claims 1 to 19.