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(54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH ANTI-TUMOR ALKYLATING AGENTS

(57) Abstract: The present invention is concerned with combinations of a farnesyl transferase inhibitor and an anti-tumor alkylating agent for inhibiting the growth of tumor cells and useful in the treatment of cancer.

WO 01/64217 A2

FARNESYL PROTEIN TRANSFERASE
INHIBITOR COMBINATIONS WITH ANTI-TUMOR ALKYLATING AGENTS

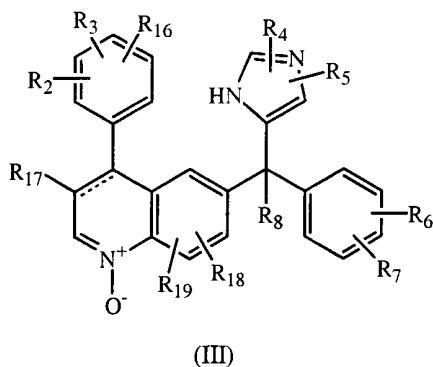
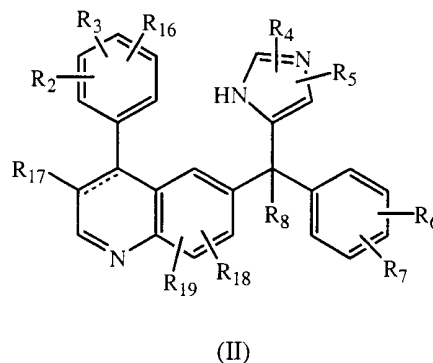
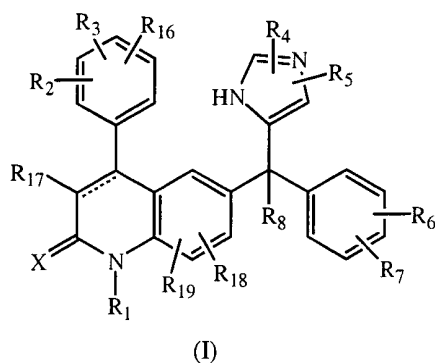
5 The present invention is concerned with combinations of a farnesyl transferase inhibitor and anti-tumor alkylating agents for inhibiting the growth of tumor cells. and useful in the treatment of cancer.

10 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
15 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
20 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
25 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.

30 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 transferase 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
35 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



- 5 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;

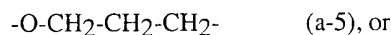
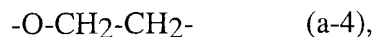
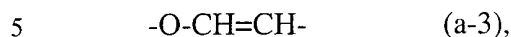
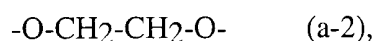
- 10 R^1 is hydrogen, C_{1-12} alkyl, Ar^1 , Ar^2C_{1-6} alkyl, quinolinyl C_{1-6} alkyl, pyridyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, amino C_{1-6} alkyl, or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$, wherein Alk^1 is C_{1-6} alkanediyl,

- 15 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;

- 20 R^2 , R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl, Ar^2 oxy, Ar^2C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_2-6 alkenyl, 4,4-dimethyloxazolyl; or

-3-

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



R^4 and R^5 each independently are hydrogen, halo, Ar^1 , C_{1-6} alkyl, hydroxy C_{1-6} alkyl,

C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl,

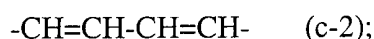
C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl $\text{S(O)}\text{C}_{1-6}$ alkyl or C_{1-6} alkyl $\text{S(O)}_2\text{C}_{1-6}$ alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy,

Ar^2 oxy, 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



R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl,

C_{1-6} alkylcarbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl,

carboxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-

amino C_{1-6} alkyl, imidazolyl, halo C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl,

aminocarbonyl C_{1-6} alkyl, or a radical of formula



wherein R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, Ar^1 , $\text{Ar}^2\text{C}_{1-6}$ alkyl,

C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, or a radical or formula $\text{-Alk}^2\text{-OR}^{13}$

or $\text{-Alk}^2\text{-NR}^{14}\text{R}^{15}$;

R^{11} is hydrogen, C_{1-12} alkyl, Ar^1 or $\text{Ar}^2\text{C}_{1-6}$ alkyl;

R^{12} is hydrogen, C_{1-6} alkyl, C_{1-16} alkylcarbonyl, C_{1-6} alkyloxycarbonyl,

C_{1-6} alkylaminocarbonyl, Ar^1 , $\text{Ar}^2\text{C}_{1-6}$ alkyl, C_{1-6} alkylcarbonyl-

C_{1-6} alkyl, a natural amino acid, Ar^1 carbonyl, $\text{Ar}^2\text{C}_{1-6}$ alkylcarbonyl,

aminocarbonylcarbonyl, C_{1-6} alkyloxy C_{1-6} alkylcarbonyl, hydroxy,

C_{1-6} alkyloxy, aminocarbonyl, di(C_{1-6} alkyl)amino C_{1-6} alkylcarbonyl,

amino, C_{1-6} alkylamino, C_{1-6} alkylcarbonylamino, or a radical or

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

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

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R^{13} is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

R^{14} is hydrogen, C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

R^{15} is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹ or Ar²C₁-6alkyl;

R^{17} is hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxycarbonyl, Ar¹;

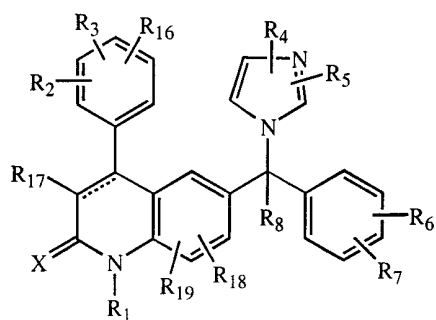
R^{18} is hydrogen, C₁-6alkyl, C₁-6alkyloxy or halo;

R^{19} is hydrogen or C₁-6alkyl;

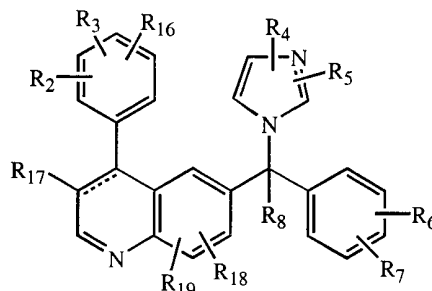
Ar¹ is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo; and

Ar² is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo.

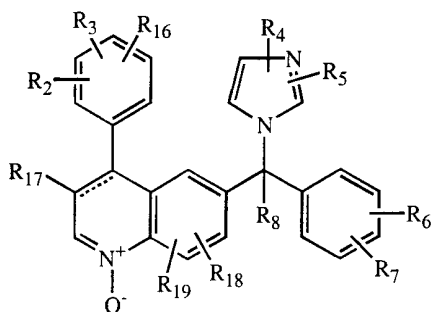
WO-97/16443 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IV), as well as intermediates of formula (V) and (VI) that are metabolized in vivo to the compounds of formula (IV). The compounds of formulas (IV), (V) and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



(IV)



(V)



(VI)

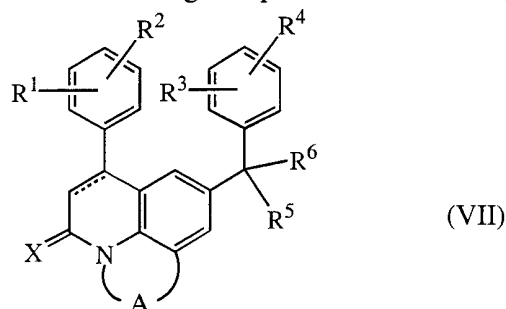
the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

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, quinolinyl C_{1-6} alkyl, pyridyl- C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-amino C_{1-6} alkyl, amino C_{1-6} alkyl,
 or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$,
 5 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, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino-
 10 C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl,
 Ar^2 oxy, 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
 15 $-O-CH_2-O-$ (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
 20 $-CH=CH-CH=CH-$ (a-6);
 R^4 and R^5 each independently are hydrogen, Ar^1 , C_{1-6} alkyl, C_{1-6} alkyloxy C_{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
 25 Ar^2 oxy;
 R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl-
 carbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, hydroxy-
 carbonyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-
 amino C_{1-6} alkyl, halo C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl,
 30 Ar^1 , Ar^2C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkylthio C_{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;
 35 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)



- 5 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;

- 10 -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 |
| 15 -CH ₂ -CH ₂ -O- | (a-5), | -CO-NH- | (a-10); |

wherein optionally one hydrogen atom may be replaced by C₁-4alkyl or Ar¹;

- R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁-6alkyl, trihalomethyl, trihalomethoxy, C₂-6alkenyl, C₁-6alkyloxy, hydroxyC₁-6alkyloxy, C₁-6alkyloxyC₁-6alkyloxy, C₁-6alkyloxycarbonyl, aminoC₁-6alkyloxy, mono- or di(C₁-6alkyl)aminoC₁-6alkyloxy, Ar², Ar²-C₁-6alkyl, Ar²-oxy, Ar²-C₁-6alkyloxy; or when on adjacent positions R¹ and R² taken together may form a bivalent radical of formula

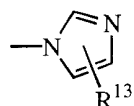
- | | |
|--|-----------|
| -O-CH ₂ -O- | (b-1), |
| -O-CH ₂ -CH ₂ -O- | (b-2), |
| 25 -O-CH=CH- | (b-3), |
| -O-CH ₂ -CH ₂ - | (b-4), |
| -O-CH ₂ -CH ₂ -CH ₂ - | (b-5), or |
| -CH=CH-CH=CH- | (b-6); |

- R³ and R⁴ each independently are hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar³-oxy, C₁-6alkylthio, di(C₁-6alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R³ and R⁴ taken together may form a bivalent radical of formula

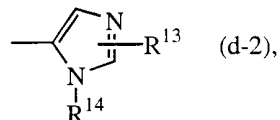
-7-

- O-CH₂-O- (c-1),
 -O-CH₂-CH₂-O- (c-2), or
 -CH=CH-CH=CH- (c-3);

R⁵ is a radical of formula



(d-1),



(d-2),

5

wherein R¹³ is hydrogen, halo, Ar⁴, C₁-6alkyl, hydroxyC₁-6alkyl, C₁-6alkyloxy-C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, amino, C₁-6alkyloxy-carbonyl, C₁-6alkylS(O)C₁-6alkyl or C₁-6alkylS(O)₂C₁-6alkyl;

R¹⁴ is hydrogen, C₁-6alkyl or di(C₁-4alkyl)aminosulfonyl;

- 10 R⁶ is hydrogen, hydroxy, halo, C₁-6alkyl, cyano, haloC₁-6alkyl, hydroxyC₁-6alkyl, cyanoC₁-6alkyl, aminoC₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, C₁-6alkylthioC₁-6alkyl, aminocarbonylC₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, C₁-6alkyloxycarbonyl, mono- or di(C₁-6alkyl)aminoC₁-6alkyl, Ar⁵,
 15 Ar⁵-C₁-6alkyloxyC₁-6alkyl; or a radical of formula

-O-R⁷ (e-1),

-S-R⁷ (e-2),

-N-R⁸R⁹ (e-3),

wherein R⁷ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar⁶, Ar⁶-C₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, or a radical of formula -Alk-OR¹⁰
 20 or -Alk-NR¹¹R¹²;

R⁸ is hydrogen, C₁-6alkyl, Ar⁷ or Ar⁷-C₁-6alkyl;

R⁹ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, C₁-6alkyloxycarbonyl, C₁-6alkylaminocarbonyl, Ar⁸, Ar⁸-C₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, Ar⁸-carbonyl, Ar⁸-C₁-6alkylcarbonyl, aminocarbonyl-carbonyl, C₁-6alkyloxyC₁-6alkylcarbonyl, hydroxy, C₁-6alkyloxy, aminocarbonyl, di(C₁-6alkyl)aminoC₁-6alkylcarbonyl, amino, C₁-6alkylamino, C₁-6alkylcarbonylamino,
 25 or a radical or formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

- 30 wherein Alk is C₁-6alkanediyl;

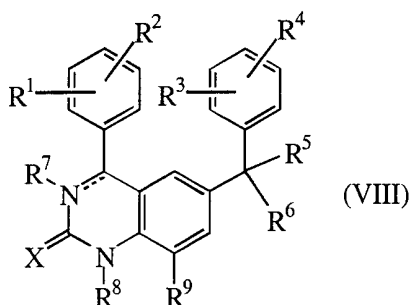
R¹⁰ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxyC₁-6alkyl, Ar⁹ or Ar⁹-C₁-6alkyl;

R¹¹ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹⁰ or Ar¹⁰-C₁-6alkyl;

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R^{12} is hydrogen, C_1 -6alkyl, Ar^{11} or Ar^{11} - C_1 -6alkyl; and
 Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted
 with halo, C_1 -6alkyl, C_1 -6alkyloxy or trifluoromethyl.

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



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

- 10 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 -6alkyl,
 trihalomethyl, trihalomethoxy, C_2 -6alkenyl, C_1 -6alkyloxy, hydroxy C_1 -6alkyloxy,
 C_1 -6alkyloxy C_1 -6alkyloxy, C_1 -6alkyloxycarbonyl, amino C_1 -6alkyloxy, mono- or
 15 di(C_1 -6alkyl)amino C_1 -6alkyloxy, Ar^1 , Ar^1 - C_1 -6alkyl, Ar^1 -oxy or
 Ar^1 - C_1 -6alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_1 -6alkyl, C_1 -6alkyloxy,
 Ar^1 -oxy, C_1 -6alkylthio, di(C_1 -6alkyl)amino, trihalomethyl or trihalomethoxy;

- R^5 is hydrogen, halo, C_1 -6alkyl, cyano, halo C_1 -6alkyl, hydroxy C_1 -6alkyl,
 20 cyano C_1 -6alkyl, amino C_1 -6alkyl, C_1 -6alkyloxy C_1 -6alkyl,
 C_1 -6alkylthio C_1 -6alkyl, aminocarbonyl C_1 -6alkyl,
 C_1 -6alkyloxycarbonyl C_1 -6alkyl, C_1 -6alkylcarbonyl- C_1 -6alkyl,
 C_1 -6alkyloxycarbonyl, mono- or di(C_1 -6alkyl)amino C_1 -6alkyl, Ar^1 ,
 Ar^1 - C_1 -6alkyloxy C_1 -6alkyl; or a radical of formula

25 $-O-R^{10}$ (a-1),

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

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

wherein R^{10} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^1 , Ar^1 - C_1 -6alkyl,
 C_1 -6alkyloxycarbonyl C_1 -6alkyl, or a radical of formula $-Alk-OR^{13}$
 or $-Alk-NR^{14}R^{15}$;

30

R^{11} is hydrogen, C_1 -6alkyl, Ar^1 or Ar^1 - C_1 -6alkyl;

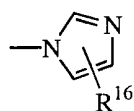
R¹² is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, C₁-6alkyloxycarbonyl, C₁-6alkylaminocarbonyl, Ar¹, Ar¹C₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, Ar¹carbonyl, Ar¹C₁-6alkylcarbonyl, aminocarbonyl-carbonyl, C₁-6alkyloxyC₁-6alkylcarbonyl, hydroxy, C₁-6alkyloxy, aminocarbonyl, di(C₁-6alkyl)aminoC₁-6alkylcarbonyl, amino, C₁-6alkylamino, C₁-6alkylcarbonylamino, or a radical or formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵; wherein Alk is C₁-6alkanediyl;

R¹³ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

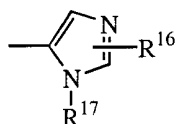
R¹⁴ is hydrogen, C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

R¹⁵ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹ or Ar¹C₁-6alkyl;

R⁶ is a radical of formula



(b-1),



(b-2),

wherein R¹⁶ is hydrogen, halo, Ar¹, C₁-6alkyl, hydroxyC₁-6alkyl, C₁-6alkyloxy-C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, amino, C₁-6alkyloxycarbonyl, C₁-6alkylthioC₁-6alkyl, C₁-6alkylS(O)C₁-6alkyl or C₁-6alkylS(O)₂C₁-6alkyl;

R¹⁷ is hydrogen, C₁-6alkyl or di(C₁-4alkyl)aminosulfonyl;

R⁷ is hydrogen or C₁-6alkyl provided that the dotted line does not represent a bond;

R⁸ is hydrogen, C₁-6alkyl or Ar²CH₂ or Het¹CH₂;

R⁹ is hydrogen, C₁-6alkyl, C₁-6alkyloxy or halo; or

R⁸ and R⁹ taken together to form a bivalent radical of formula

-CH=CH- (c-1),

-CH₂-CH₂- (c-2),

-CH₂-CH₂-CH₂- (c-3),

-CH₂-O- (c-4), or

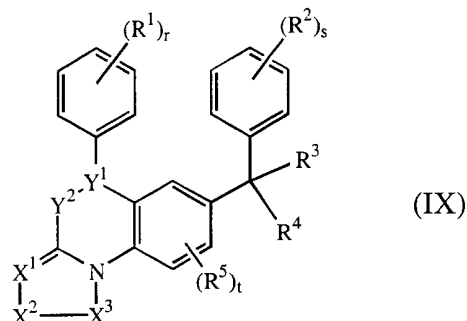
-CH₂-CH₂-O- (c-5);

Ar¹ is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl;

Ar² is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl; and

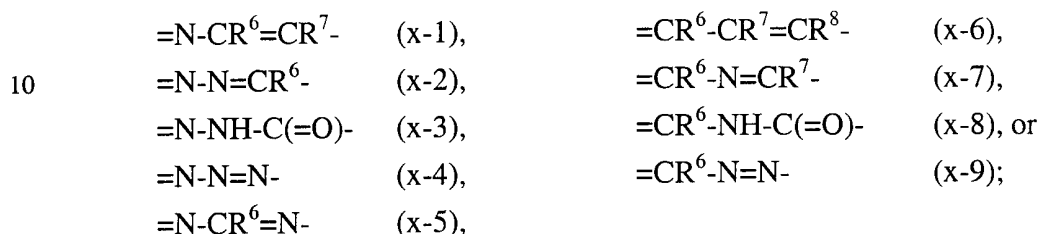
Het¹ is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl.

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



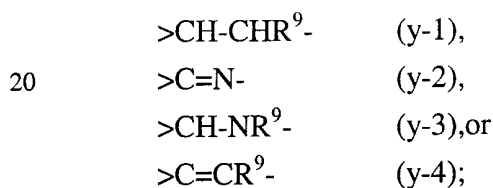
or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

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



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, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, cyano, amino, thio, C_{1-4} alkylthio, arylthio or aryl;

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



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

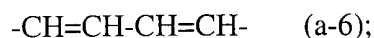
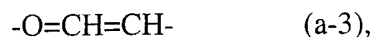
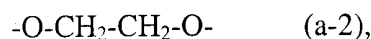
r and s are each independently 0, 1, 2, 3, 4 or 5;

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, hydroxy C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkyloxy C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, amino C_{1-6} alkyloxy, mono- or

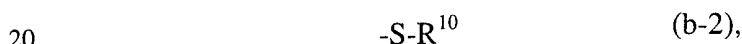
di(C₁₋₆alkyl)amino, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, aryl, arylC₁₋₆alkyl, aryloxy or arylC₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, aminocarbonyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminocarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl; or

- 5 two R¹ or R² substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula



- R³ is hydrogen, halo, C₁₋₆alkyl, cyano, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, aryl, arylC₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

or a radical of formula



wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, aryl, arylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical of formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

- 25 R¹¹ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

- R¹² is hydrogen, C₁₋₆alkyl, aryl, hydroxy, amino, C₁₋₆alkyloxy, C₁₋₆alkylcarbonylC₁₋₆alkyl, arylC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC₁₋₆alkylcarbonyl, arylC₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, mono- or di(C₁₋₆alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C₁₋₃alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, or a radical or formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

- 35 wherein Alk is C₁₋₆alkanediyl;

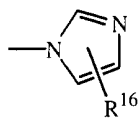
R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxyC₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

R¹⁴ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

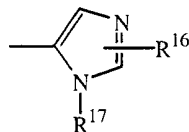
-12-

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

5 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} alkylthio C_{1-6} alkyl,

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

10 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, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{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} alkyloxy C_{1-6} alkyl, aryl C_{1-6} alkyl, trifluoromethyl or di(C_{1-4} alkyl)aminosulfonyl;

15 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.

20 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

25 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-

30 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.

35 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.

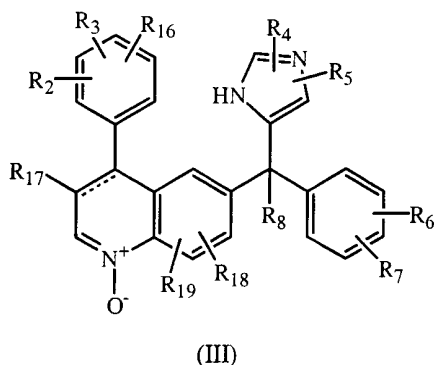
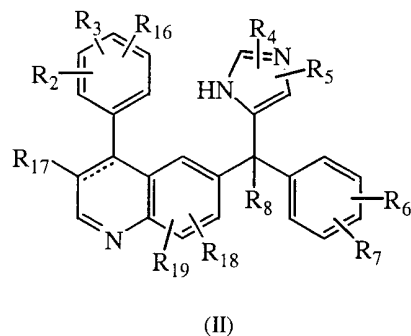
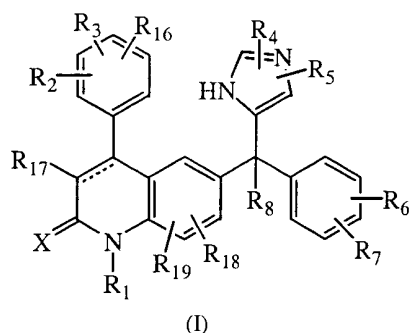
Another important class of alkylating agents are the nitrosoureas which are characterised by the capacity to undergo spontaneous non-enzymatic degradation with the formation of the 2-chloroethyl carbonium ion from CNU compounds. Examples of such nitrosourea compounds include carmustine (BCNU) which has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

There is therefore a need to increase the inhibitory efficacy of the nitrogen mustard and nitrosourea alkylating agents against tumor growth and also to provide a means for the use of lower dosages of such 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 nitrogen mustard or nitrosourea alkylating agent and a farnesyl transferase inhibitor of the type described above 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 nitrogen mustard or nitrosourea alkylating agent and 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):

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

5 the dotted line represents an optional bond;

X is oxygen or sulfur;

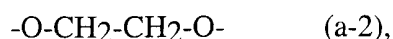
R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinylC₁₋₆alkyl, pyridyl-C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)-aminoC₁₋₆alkyl, aminoC₁₋₆alkyl,

10 or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹, wherein Alk¹ is C₁₋₆alkanediyl,

R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

15 R², R³ and R¹⁶ each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, aminoC₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar²C₁₋₆alkyl, Ar²oxy, Ar²C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, 4,4-dimethyloxazolyl; or

20 when on adjacent positions R² and R³ taken together may form a bivalent radical of formula



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

-O-CH₂-CH₂- (a-4),-O-CH₂-CH₂-CH₂- (a-5), or

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

5 R⁴ and R⁵ each independently are hydrogen, halo, Ar¹, C₁-6alkyl, hydroxyC₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, amino, hydroxycarbonyl, C₁-6alkyloxycarbonyl, C₁-6alkylS(O)C₁-6alkyl or C₁-6alkylS(O)₂C₁-6alkyl;

R⁶ and R⁷ each independently are hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar²oxy, trihalomethyl, C₁-6alkylthio, di(C₁-6alkyl)amino, or

10 when on adjacent positions R⁶ and R⁷ taken together may form a bivalent radical of formula

-O-CH₂-O- (c-1), or

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

15 R⁸ is hydrogen, C₁-6alkyl, cyano, hydroxycarbonyl, C₁-6alkyloxycarbonyl, C₁-6alkyl-carbonylC₁-6alkyl, cyanoC₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, carboxy-C₁-6alkyl, hydroxyC₁-6alkyl, aminoC₁-6alkyl, mono- or di(C₁-6alkyl)amino-C₁-6alkyl, imidazolyl, haloC₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, aminocarbonyl-C₁-6alkyl, or a radical of formula

-O-R¹⁰ (b-1),20 -S-R¹⁰ (b-2),-N-R¹¹R¹² (b-3),

wherein R¹⁰ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹, Ar²C₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

25 R¹¹ is hydrogen, C₁-12alkyl, Ar¹ or Ar²C₁-6alkyl;

R¹² is hydrogen, C₁-6alkyl, C₁-16alkylcarbonyl, C₁-6alkyloxycarbonyl, C₁-6alkylaminocarbonyl, Ar¹, Ar²C₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, a natural amino acid, Ar¹carbonyl, Ar²C₁-6alkylcarbonyl, aminocarbonylcarbonyl, C₁-6alkyloxyC₁-6alkylcarbonyl, hydroxy, C₁-6alkyloxy, aminocarbonyl, di(C₁-6alkyl)aminoC₁-6alkylcarbonyl, amino, C₁-6alkylamino, C₁-6alkylcarbonylamino, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

30 wherein Alk² is C₁-6alkanediyl;

R¹³ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

35

R¹⁴ is hydrogen, C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

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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;

5 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.

10

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.

15

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, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{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.

20

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.

25

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.

30

Another group of interesting compounds are those compounds of formula (I) wherein R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{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.

35

Still another group of interesting compounds are those compounds of formula (I) wherein R^3 is hydrogen or halo; and R^2 is halo, C₁-6alkyl, C₂-6alkenyl, C₁-6alkyloxy, trihalomethoxy or hydroxyC₁-6alkyloxy.

- 5 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).

- 10 A still further group of interesting compounds are those compounds of formula (I) wherein R^5 is hydrogen and R^4 is hydrogen or C₁-6alkyl.

Yet another group of interesting compounds are those compounds of formula (I) wherein R^7 is hydrogen; and R^6 is C₁-6alkyl or halo, preferably chloro, especially 4-chloro.

- 15 A particular group of compounds are those compounds of formula (I) wherein R^8 is hydrogen, hydroxy, haloC₁-6alkyl, hydroxyC₁-6alkyl, cyanoC₁-6alkyl, C₁-6alkyloxy-carbonylC₁-6alkyl, imidazolyl, or a radical of formula $-NR^{11}R^{12}$ wherein R^{11} is hydrogen or C₁-12alkyl and R^{12} is hydrogen, C₁-6alkyl, C₁-6alkyloxy, hydroxy, C₁-6alkyloxyC₁-6alkylcarbonyl, or a radical of formula $-Alk^2-OR^{13}$ wherein R^{13} is hydrogen or C₁-6alkyl.

- Preferred compounds are those compounds wherein R^1 is hydrogen, C₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, di(C₁-6alkyl)aminoC₁-6alkyl, or a radical of formula $-Alk^1-C(=O)-R^9$, wherein Alk^1 is methylene and R^9 is C₁-8alkylamino substituted with C₁-6alkyloxycarbonyl; R^2 is halo, C₁-6alkyl, C₂-6alkenyl, C₁-6alkyloxy, trihalomethoxy, hydroxyC₁-6alkyloxy or Ar¹; 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, haloC₁-6alkyl, hydroxyC₁-6alkyl, cyanoC₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, imidazolyl, or a radical of formula $-NR^{11}R^{12}$ wherein R^{11} is hydrogen or C₁-12alkyl and R^{12} is hydrogen, C₁-6alkyl, C₁-6alkyloxy, C₁-6alkyloxyC₁-6alkylcarbonyl, or a radical of formula $-Alk^2-OR^{13}$ wherein R^{13} is C₁-6alkyl; R^{17} is hydrogen and R^{18} is hydrogen.

- 35 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;
 5 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-propyl-phenyl)-2(1H)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and
 10 (+)-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
 15 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
 20 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;
- 25 • 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;
- 30 • 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)amino C_{1-6} alkylcarbonyl;
- 35 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 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)-
- 10 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.
- 15 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

20 and iodo; C₁₋₆alkyl 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; C₁₋₈alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C₁₋₆alkyl as well as the higher homologues thereof containing 7 or 8 carbon atoms such as, for example heptyl or

25 octyl; C₁₋₁₂alkyl again encompasses C₁₋₈alkyl and the higher homologues thereof containing 9 to 12 carbon atoms, such as, for example, nonyl, decyl, undecyl, dodecyl; C₁₋₁₆alkyl again encompasses C₁₋₁₂alkyl and the higher homologues thereof containing 13 to 16 carbon atoms, such as, for example, tridecyl, tetradecyl, pentadecyl and hexadecyl; C₂₋₆alkenyl defines straight and branched chain hydrocarbon radicals

30 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; C₁₋₆alkanediyl 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,

35 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, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine.

5

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

35

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.

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 UK 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. 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.

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.

5 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;
10 (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 tumors *in vivo* by a direct effect on tumor cell growth but also indirectly, *i.e.* by facilitating tumor-induced angiogenesis
15 (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.
20 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
25 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
30 (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 carcinoma,
35 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 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

5 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 nitrogen mustard or nitrosourea alkylating agent and the farnesyl transferase

10 inhibitor may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two 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

15 regimes for each component of the combination will depend on the particular nitrogen mustard or nitrosourea alkylating agent and farnesyl transferase inhibitor 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

20 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

25 conveniently in the range of 50 to 500mg bid, advantageously 100 to 400 mg bid and particularly 300mg bid.

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

30 120 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, for carmustine in a dosage of about 150 to 200 mg/m^2 , and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment. These dosages may be administered for example once,

35 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 transferase inhibitor at a dosage of 100 or 200mg bid for 7, 14, 21 or 28 days with a dosage of the nitrogen mustard or nitrosourea alkylating agent in the ranges indicated above.

5 In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the nitrogen mustard or nitrosourea alkylating agent and the farnesyl transferase inhibitor may be formulated into various pharmaceutical forms for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition
10 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
15 (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.

20 The present invention therefore also relates to a pharmaceutical composition comprising a nitrogen mustard or nitrosourea alkylating agent and a farnesyl transferase inhibitor of formula (I) 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
25 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
30 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,
35 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
5 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
10 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
15 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
20 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
25 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.

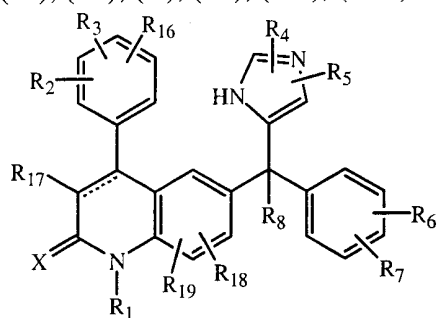
Experimental Testing of Combinations for Inhibition of Tumor Growth

30 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
35 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

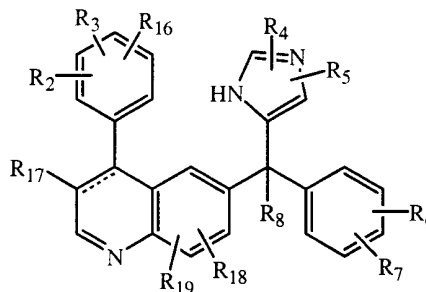
described in Cancer: Principles and Practice of Oncology, Fifth Edition, edited by Vincent T DeVita, Jr., Samuel Hellman, Steven A. Rosenberg, Lippincott-Raven, Philadelphia, 1997, especially Chapter 17, pages 342-346.

Claims

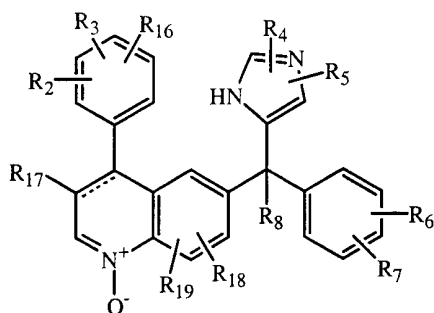
1. A combination of a nitrogen mustard or nitrosourea alkylating agent
and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II),
5 (III), (IV), (V), (VI), (VII), (VIII) and (IX) below:



(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;

10 X is oxygen or sulfur;

R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinylC₁₋₆alkyl,

pyridylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or

di(C₁₋₆alkyl)aminoC₁₋₆alkyl, aminoC₁₋₆alkyl,

or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹,

15 wherein Alk¹ is C₁₋₆alkanediyl,

R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or

C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

R², R³ and R¹⁶ each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl,

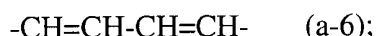
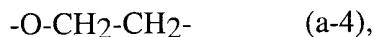
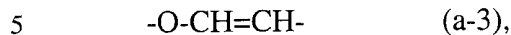
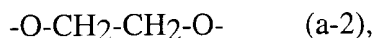
C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, aminoC₁₋₆alkyl-

20 oxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar²C₁₋₆alkyl, Ar²oxy,

Ar²C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, trihalomethyl,

trihalomethoxy, C₂₋₆alkenyl, 4,4-dimethyloxazolyl; or

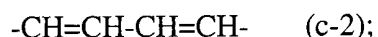
when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula



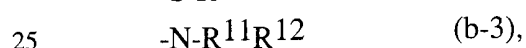
R^4 and R^5 each independently are hydrogen, halo, Ar^1 , $\text{C}_1\text{-6alkyl}$, hydroxy $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkyloxyC}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkyloxy}$, $\text{C}_1\text{-6alkylthio}$, amino, hydroxycarbonyl, $\text{C}_1\text{-6alkyloxycarbonyl}$, $\text{C}_1\text{-6alkylS(O)C}_1\text{-6alkyl}$ or $\text{C}_1\text{-6alkylS(O)}_2\text{C}_1\text{-6alkyl}$;

R^6 and R^7 each independently are hydrogen, halo, cyano, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkyloxy}$, Ar^2oxy , trihalomethyl, $\text{C}_1\text{-6alkylthio}$, di($\text{C}_1\text{-6alkyl}$)amino, or

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



R^8 is hydrogen, $\text{C}_1\text{-6alkyl}$, cyano, hydroxycarbonyl, $\text{C}_1\text{-6alkyloxycarbonyl}$, $\text{C}_1\text{-6alkylcarbonylC}_1\text{-6alkyl}$, cyano $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkyloxycarbonylC}_1\text{-6alkyl}$, carboxy $\text{C}_1\text{-6alkyl}$, hydroxy $\text{C}_1\text{-6alkyl}$, amino $\text{C}_1\text{-6alkyl}$, mono- or di($\text{C}_1\text{-6alkyl}$)-amino $\text{C}_1\text{-6alkyl}$, imidazolyl, halo $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkyloxyC}_1\text{-6alkyl}$, aminocarbonyl $\text{C}_1\text{-6alkyl}$, or a radical of formula



wherein R^{10} is hydrogen, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkylcarbonyl}$, Ar^1 , $\text{Ar}^2\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkyloxycarbonylC}_1\text{-6alkyl}$, or a radical or formula $\text{-Alk}^2\text{-OR}^{13}$ or $\text{-Alk}^2\text{-NR}^{14}\text{R}^{15}$;

R^{11} is hydrogen, $\text{C}_1\text{-12alkyl}$, Ar^1 or $\text{Ar}^2\text{C}_1\text{-6alkyl}$;

R^{12} is hydrogen, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-16alkylcarbonyl}$, $\text{C}_1\text{-6alkyloxycarbonyl}$, $\text{C}_1\text{-6alkylaminocarbonyl}$, Ar^1 , $\text{Ar}^2\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkylcarbonylC}_1\text{-6alkyl}$, a natural amino acid, $\text{Ar}^1\text{carbonyl}$, $\text{Ar}^2\text{C}_1\text{-6alkylcarbonyl}$, aminocarbonylcarbonyl, $\text{C}_1\text{-6alkyloxyC}_1\text{-6alkylcarbonyl}$, hydroxy, $\text{C}_1\text{-6alkyloxy}$, aminocarbonyl, di($\text{C}_1\text{-6alkyl}$)amino $\text{C}_1\text{-6alkylcarbonyl}$, amino, $\text{C}_1\text{-6alkylamino}$, $\text{C}_1\text{-6alkylcarbonylamino}$, or a radical or formula $\text{-Alk}^2\text{-OR}^{13}$ or $\text{-Alk}^2\text{-NR}^{14}\text{R}^{15}$;

wherein Alk^2 is $\text{C}_1\text{-6alkanediyl}$;

-30-

R¹³ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

R¹⁴ is hydrogen, C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

R¹⁵ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹ or Ar²C₁-6alkyl;

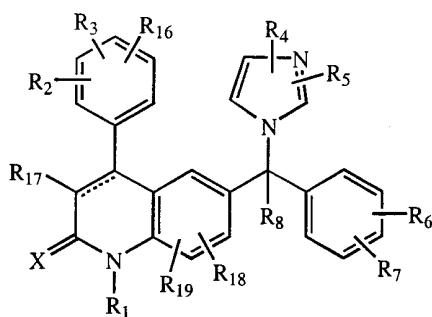
R¹⁷ is hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxycarbonyl, Ar¹;

R¹⁸ is hydrogen, C₁-6alkyl, C₁-6alkyloxy or halo;

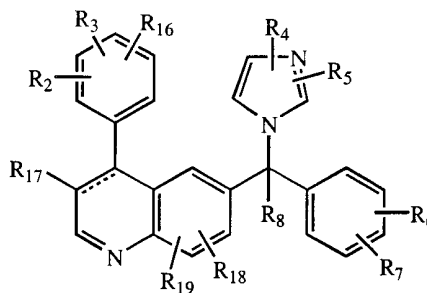
R¹⁹ is hydrogen or C₁-6alkyl;

Ar¹ is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo; and

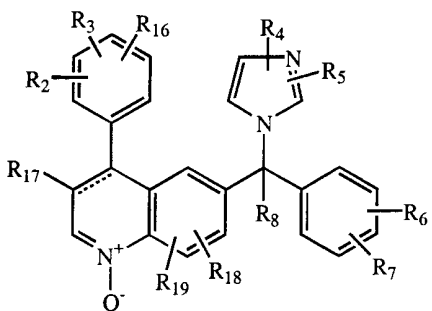
Ar² is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo.



(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;

R¹ is hydrogen, C₁-12alkyl, Ar¹, Ar²C₁-6alkyl, quinoliny-C₁-6alkyl, pyridyl-C₁-6alkyl, hydroxy-C₁-6alkyl, C₁-6alkyloxy-C₁-6alkyl, mono- or di(C₁-6alkyl)-amino-C₁-6alkyl, amino-C₁-6alkyl, or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹,

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, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino- C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , $\text{Ar}^2\text{C}_{1-6}$ alkyl, Ar^2oxy , $\text{Ar}^2\text{C}_{1-6}$ 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-CH₂-O- (a-1),

-O-CH₂-CH₂-O- (a-2),

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

-O-CH₂-CH₂- (a-4),

-O-CH₂-CH₂-CH₂- (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} alkyloxy C_{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)₂ C_{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 ;

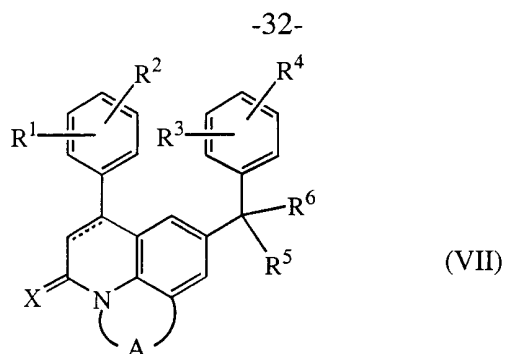
R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl-carbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, hydroxy-carbonyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-amino C_{1-6} alkyl, halo C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, Ar^1 , $\text{Ar}^2\text{C}_{1-6}$ alkyloxy C_{1-6} alkyl, C_{1-6} alkylthio C_{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.



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

the dotted line represents an optional bond;

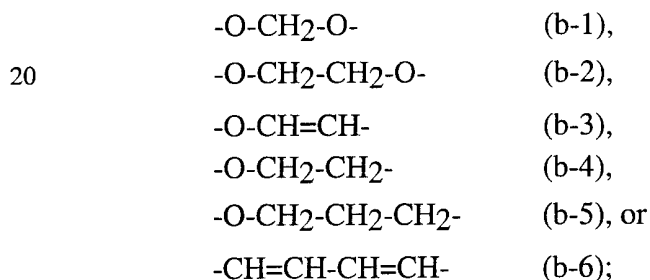
5 X is oxygen or sulfur;

-A- is a bivalent radical of formula

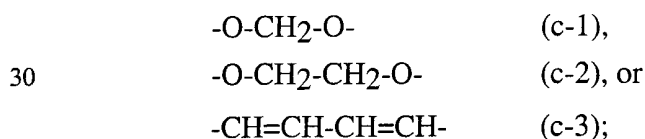


wherein optionally one hydrogen atom may be replaced by C₁-4alkyl or Ar¹;

R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁-6alkyl, trihalomethyl, trihalomethoxy, C₂-6alkenyl, C₁-6alkyloxy, hydroxyC₁-6alkyloxy, C₁-6alkyloxyC₁-6alkyloxy, C₁-6alkyloxycarbonyl, aminoC₁-6alkyloxy, mono- or
 15 di(C₁-6alkyl)aminoC₁-6alkyloxy, Ar², Ar²-C₁-6alkyl, Ar²-oxy, Ar²-C₁-6alkyloxy; or when on adjacent positions R¹ and R² taken together may form a bivalent radical of formula

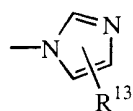


25 R³ and R⁴ each independently are hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar³-oxy, C₁-6alkylthio, di(C₁-6alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R³ and R⁴ taken together may form a bivalent radical of formula

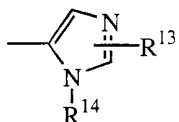


R⁵ is a radical of formula

-33-



(d-1),



(d-2),

wherein R^{13} is hydrogen, halo, Ar^4 , C_1 -6alkyl, hydroxy C_1 -6alkyl, C_1 -6alkyloxy- C_1 -6alkyl, C_1 -6alkyloxy, C_1 -6alkylthio, amino, C_1 -6alkyloxy-carbonyl, C_1 -6alkylS(O) C_1 -6alkyl or C_1 -6alkylS(O) $_2$ C_1 -6alkyl;

5 R^{14} is hydrogen, C_1 -6alkyl or di(C_1 -4alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_1 -6alkyl, cyano, halo C_1 -6alkyl, hydroxy C_1 -6alkyl, cyano C_1 -6alkyl, amino C_1 -6alkyl, C_1 -6alkyloxy C_1 -6alkyl, C_1 -6alkylthio C_1 -6alkyl, aminocarbonyl C_1 -6alkyl, C_1 -6alkyloxycarbonyl C_1 -6alkyl, C_1 -6alkylcarbonyl- C_1 -6alkyl, C_1 -6alkyloxycarbonyl, mono- or di(C_1 -6alkyl)amino C_1 -6alkyl, Ar^5 , Ar^5 - C_1 -6alkyloxy C_1 -6alkyl; or a radical of formula

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

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

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

15 wherein R^7 is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^6 , Ar^6 - C_1 -6alkyl, C_1 -6alkyloxycarbonyl C_1 -6alkyl, or a radical of formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

R^8 is hydrogen, C_1 -6alkyl, Ar^7 or Ar^7 - C_1 -6alkyl;

20 R^9 is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, C_1 -6alkyloxycarbonyl, C_1 -6alkylaminocarbonyl, Ar^8 , Ar^8 - C_1 -6alkyl, C_1 -6alkylcarbonyl- C_1 -6alkyl, Ar^8 -carbonyl, Ar^8 - C_1 -6alkylcarbonyl, aminocarbonyl-carbonyl, C_1 -6alkyloxy C_1 -6alkylcarbonyl, hydroxy, C_1 -6alkyloxy, aminocarbonyl, di(C_1 -6alkyl)amino C_1 -6alkylcarbonyl, amino, C_1 -6alkylamino, C_1 -6alkylcarbonylamino, or a radical or formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

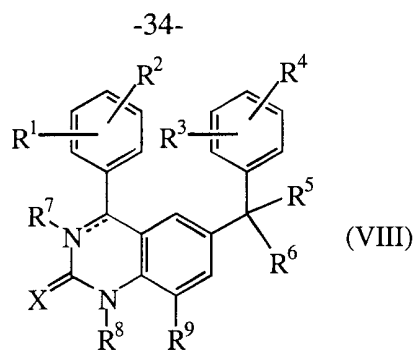
25 wherein Alk is C_1 -6alkanediyl;

R^{10} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, hydroxy C_1 -6alkyl, Ar^9 or Ar^9 - C_1 -6alkyl;

30 R^{11} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^{10} or Ar^{10} - C_1 -6alkyl;

R^{12} is hydrogen, C_1 -6alkyl, Ar^{11} or Ar^{11} - C_1 -6alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_1 -6alkyl, C_1 -6alkyloxy or trifluoromethyl.



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

the dotted line represents an optional bond;

5 X is oxygen or sulfur;

R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁-6alkyl, trihalomethyl, trihalomethoxy, C₂-6alkenyl, C₁-6alkyloxy, hydroxyC₁-6alkyloxy, C₁-6alkyloxyC₁-6alkyloxy, C₁-6alkyloxycarbonyl, aminoC₁-6alkyloxy, mono- or di(C₁-6alkyl)aminoC₁-6alkyloxy, Ar¹, Ar¹C₁-6alkyl, Ar¹oxy or

10 Ar¹C₁-6alkyloxy;

R³ and R⁴ each independently are hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar¹oxy, C₁-6alkylthio, di(C₁-6alkyl)amino, trihalomethyl or trihalomethoxy;

R⁵ is hydrogen, halo, C₁-6alkyl, cyano, haloC₁-6alkyl, hydroxyC₁-6alkyl, cyanoC₁-6alkyl, aminoC₁-6alkyl, C₁-6alkyloxyC₁-6alkyl,

15 C₁-6alkylthioC₁-6alkyl, aminocarbonylC₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, C₁-6alkyloxycarbonyl, mono- or di(C₁-6alkyl)aminoC₁-6alkyl, Ar¹, Ar¹C₁-6alkyloxyC₁-6alkyl; or a radical of formula

-O-R¹⁰ (a-1),

20 -S-R¹⁰ (a-2),

-N-R¹¹R¹² (a-3),

wherein R¹⁰ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹, Ar¹C₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, or a radical of formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

25 R¹¹ is hydrogen, C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

R¹² is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, C₁-6alkyloxycarbonyl, C₁-6alkylaminocarbonyl, Ar¹, Ar¹C₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, Ar¹carbonyl, Ar¹C₁-6alkylcarbonyl, aminocarbonyl-carbonyl, C₁-6alkyloxyC₁-6alkylcarbonyl, hydroxy, C₁-6alkyloxy, aminocarbonyl, di(C₁-6alkyl)aminoC₁-6alkylcarbonyl, amino,

30

-35-

C₁-6alkylamino, C₁-6alkylcarbonylamino,
or a radical or formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;
wherein Alk is C₁-6alkanediyl;

R¹³ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-

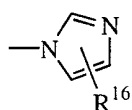
5

C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

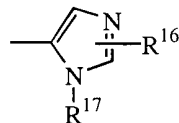
R¹⁴ is hydrogen, C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

R¹⁵ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹ or
Ar¹C₁-6alkyl;

R⁶ is a radical of formula



(b-1),



(b-2),

10

wherein R¹⁶ is hydrogen, halo, Ar¹, C₁-6alkyl, hydroxyC₁-6alkyl, C₁-6alkyloxy-
C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, amino,
C₁-6alkyloxycarbonyl, C₁-6alkylthioC₁-6alkyl,
C₁-6alkylS(O)C₁-6alkyl or C₁-6alkylS(O)₂C₁-6alkyl;

15

R¹⁷ is hydrogen, C₁-6alkyl or di(C₁-4alkyl)aminosulfonyl;

R⁷ is hydrogen or C₁-6alkyl provided that the dotted line does not represent a bond;

R⁸ is hydrogen, C₁-6alkyl or Ar²CH₂ or Het¹CH₂;

R⁹ is hydrogen, C₁-6alkyl, C₁-6alkyloxy or halo; or

R⁸ and R⁹ taken together to form a bivalent radical of formula

20

-CH=CH- (c-1),

-CH₂-CH₂- (c-2),

-CH₂-CH₂-CH₂- (c-3),

-CH₂-O- (c-4), or

-CH₂-CH₂-O- (c-5);

25

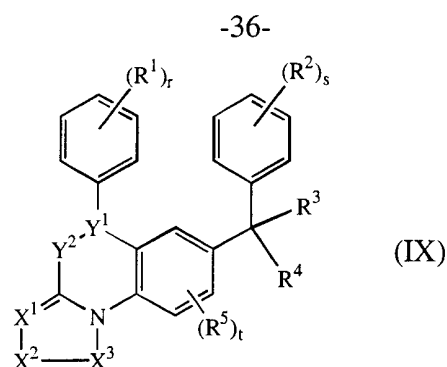
Ar¹ is phenyl; or phenyl substituted with 1 or 2 substituents each independently
selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl;

Ar² is phenyl; or phenyl substituted with 1 or 2 substituents each independently
selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl; and

30

Het¹ is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently
selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl

and



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

- 5 $=N-CR^6=CR^7-$ (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),

- 10 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, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, cyano, amino, thio, C_{1-4} alkylthio, arylthio or aryl;

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

- 15 $>CH-CHR^9-$ (y-1),
 $>C=N-$ (y-2),
 $>CH-NR^9-$ (y-3), or
 $>C=CR^9-$ (y-4);

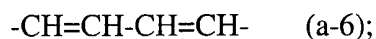
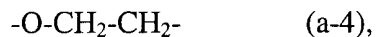
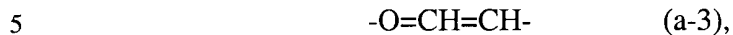
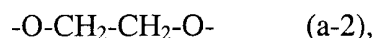
- 20 wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxy C_{1-4} alkyl, cyano, carboxyl, C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, mono- or di(C_{1-4} alkyl)amino, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, aryl;

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

t is 0, 1, 2 or 3;

- 25 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, hydroxy C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkyloxy C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, aryl, aryl C_{1-6} alkyl, aryloxy or aryl C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl,
 aminocarbonyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)aminocarbonyl, mono- or
 di(C_{1-6} alkyl)amino C_{1-6} alkyl; or
- 30

two R¹ or R² substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula



R³ is hydrogen, halo, C₁₋₆alkyl, cyano, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, aryl, arylC₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl; or a radical of formula



wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, aryl, arylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical of formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

R¹¹ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

R¹² is hydrogen, C₁₋₆alkyl, aryl, hydroxy, amino, C₁₋₆alkyloxy, C₁₋₆alkylcarbonylC₁₋₆alkyl, arylC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC₁₋₆alkylcarbonyl, arylC₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, mono- or di(C₁₋₆alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C₁₋₃alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, or a radical or formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

wherein Alk is C₁₋₆alkanediyl;

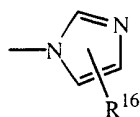
R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxyC₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

R¹⁴ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

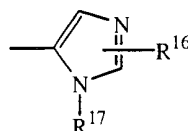
R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, aryl or arylC₁₋₆alkyl;

R⁴ is a radical of formula

-38-



(c-1),



(c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{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} alkylthio C_{1-6} alkyl,

5 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, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or

10 C_{1-6} alkylS(O) $_2$ C_{1-6} alkyl;

R^{17} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aryl C_{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

15 independently selected from halo, C_{1-6} alkyl, C_{1-6} alkyloxy or trifluoromethyl.

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.

20

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} alkyloxy C_{1-6} alkyl or mono- or di(C_{1-6} alkyl)amino C_{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 hydroxy C_{1-6} alkyloxy.

25

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, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, cyano C_{1-6} alkyl,

30 C_{1-6} alkyloxycarbonyl C_{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} alkyloxy C_{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,
 5 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-
 10 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
 15 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
 20 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), $>Y^1-Y^2$ is a trivalent radical of formula (y-2), (y-3) or
 25 (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.
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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.
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9. A combination as claimed in any of the preceding claims in which the nitrogen mustard or nitrosourea alkylating agent is cyclophosphamide, chlorambucil, carmustine or lomustine.

10. A combination as claimed in any of the preceding claims in the form of a pharmaceutical composition comprising a nitrogen mustard or nitrosourea alkylating agent and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) (as defined in claim 1) together with one or more pharmaceutical carriers.
11. A combination as claimed in any of the preceding claims for use in medical therapy.
12. A combination as claimed in claim 11 for inhibiting the growth of tumor cells.
13. Use of a combination as claimed in any of claims 1 to 12 in the manufacture of a pharmaceutical composition for inhibiting the growth of tumor cells.
14. 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 12.