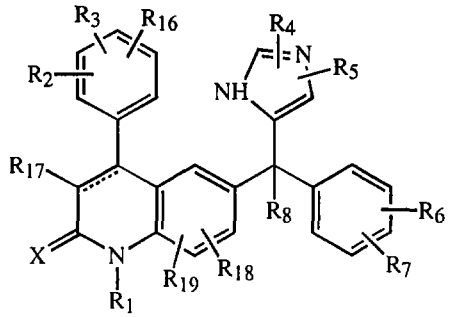
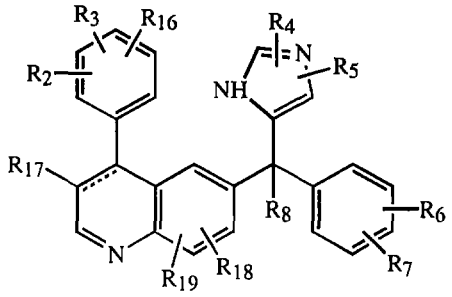
Farnesyl protein transferase inhibitors with *in vivo* radiosensitizing properties

The present invention is concerned with the finding that certain farnesyl protein transferase inhibitors have radiosensitizing properties which makes them useful for preparing a pharmaceutical composition for administration before, during or after irradiation of a tumor for treating cancer *in vivo*.

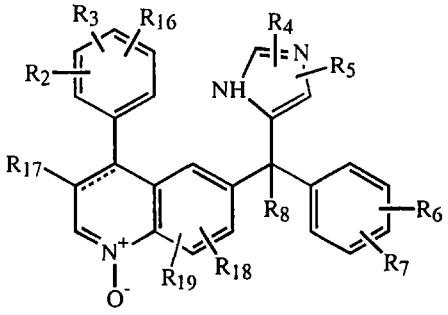
WO-97/21701 describes the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting (imidazoly-5-yl)methyl-2-quinolinone derivatives of formulas (I), (II) and (III), as well as intermediates of formula (II) and (III) that are metabolized *in vivo* to the compounds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



(I)



(II)



(III)

G00002

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)

166166

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^{2}C$_{1-6}$alkyl, Ar^{2}oxy, Ar^{2}C$_{1-6}$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)$_2$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

-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}alkylcarbonylC_{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, hydroxyC_{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;

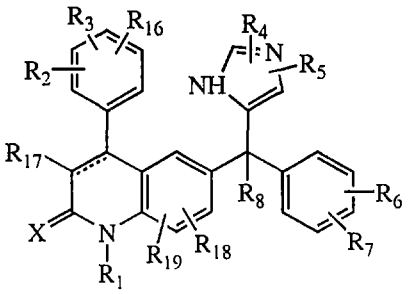
Ar^1 is phenyl or phenyl substituted with C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkyloxy or halo; and

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

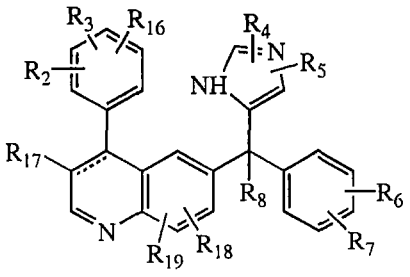
These farnesyl protein transferase inhibitors decrease the growth of tumors *in vivo* by a direct effect on tumor cell growth but also indirectly, *i.e.* by inhibiting angiogenesis (Rak. J. *et al*, Cancer Research, 55, 4575-4580, 1995). Consequently, treatment with these inhibitors suppresses solid tumor growth *in vivo* at least in part by inhibiting angiogenesis. This being the case, one could expect that treatment with these compounds could result in hypoxic tumors, thereby inducing or causing increased radio-resistance.

Unexpectedly, we have now found that that does not happen. On the contrary, it appears that administration of certain farnesyl protein transferase inhibitors as described hereinbefore sensitizes tumor cells *in vivo* to irradiation or ionizing radiation and moreover, resensitizes radioresistant cells. Thus, farnesyl protein transferase inhibitors are useful as *in vivo* radiosensitizing (radiation-sensitizing or radiation-potentiating) agents.

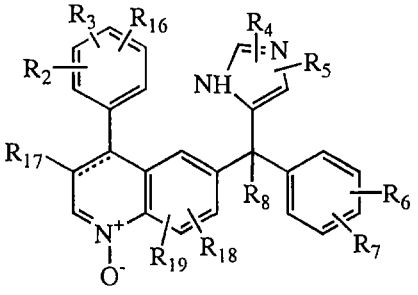
In particular, the present invention is concerned with the use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition having radiosensitizing properties for administration before, during or after irradiation of a tumor for treating cancer *in vivo*, wherein said farnesyl protein transferase inhibitor is an (imidazol-5-yl)methyl-2-quinolinone derivative of formula (I), or a compound of formula (II) or (III) which is metabolized *in vivo* to the compound of formula (I), said compounds being 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}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}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, 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)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, hydroxyC_{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.

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.

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, pentadecyl 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) and (III) are able to form. The compounds of formulas (I), (II) and (III) 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 formulas (I), (II) and (III) 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 formulas (I), (II) and (III) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of compounds of formulas (I), (II) and (III), 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 formulas (I), (II) and (III) 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 formulas (I), (II) and (III) 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 formulas (I), (II) and (III) 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 formulas (I), (II) and (III)" is meant to include also the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

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}alkylamino 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}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, 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.

Prefered 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, trihalomethoxy, 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}alkyloxy-C_{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-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone;
6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride.monohydrate;
6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone,
6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propyl-phenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and in particular
(+)-(R)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chloro-phenyl)-1-methyl-2(1*H*)-quinolinone (Compound 75 in Table 1 of the Experimental Part); or a pharmaceutically acceptable acid addition salt thereof.

Farnesyl protein transferase inhibitors can be formulated into pharmaceutical compositions as known in the art ; for the compounds of formulas (I), (II) and (III) suitable examples can be found in WO-97/21701. To prepare the aforementioned pharmaceutical compositions, a therapeutically effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with pharmaceutically acceptable carriers, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are, desirably as unitary dosage forms, administered orally, parenterally, percutaneously, rectally or topically for systemic action, which is preferred, or for topical action. In case of oral liquid pharmaceutical preparations, comprising solutions, suspensions, syrups, elixirs and emulsions, any of the usual pharmaceutical media, such as, for example, water, glycols, oils, alcohols and the like, may be employed, whereas in case of oral solid pharmaceutical preparations, comprising powders, pills, capsules and tablets, excipients such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like may be employed. Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms, in which case solid pharmaceutical carriers are obviously employed. In case of injectable pharmaceutical compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, such as semipolair solvents, may be included, for example, to aid solubility. Examples of

carriers for injectable solutions comprise saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of the aforementioned formulas may also be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. For the preparation of injectable suspensions, 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 wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on 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 or as a gel. In case of pharmaceutical compositions for rectal administration, any of the usual excipients may be employed, comprising fat based and water soluble excipients, optionally combined with suitable additives, such as suspending or wetting agents. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, lotions, shampoos, tinctures, pastes, ointments, salves, ovules, powders, inhalations, nose sprays, eye drops and the like. Semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used, but application of said compositions may be, for example, also by aerosol, e.g. with a propellent such as nitrogen, carbon dioxide, a freon, or without a propellent such as a pump spray or drops.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage 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 unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, suppositories, ovules, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Preferably, a therapeutically effective amount of the pharmaceutical composition comprising a farnesyl protein transferase inhibitor is administered orally or parenterally. Said therapeutically effective amount is the amount that effectively

sensitizes a tumor in a host to irradiation. On the basis of the current data, it appears that the pharmaceutical composition comprising (+)-(R)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (compound 75) as the active ingredient can be administered orally in an amount of from 10 up to 1500 mg/m^2 daily, either as a single dose or subdivided into more than one dose, or more particularly in an amount of from 100 to 1000 mg/m^2 daily.

Irradiation means ionizing radiation and in particular gamma radiation, especially that emitted by linear accelerators or by radionuclides that are in common use today. The irradiation of the tumor by radionuclides can be external or internal.

Preferably, the administration of the pharmaceutical composition commences up to one month, in particular up to 10 days or a week, before the irradiation of the tumor. Additionally, it is advantageous to fractionate the irradiation of the tumor and maintain the administration of the pharmaceutical composition in the interval between the first and the last irradiation session.

The amount of farnesyl protein transferase inhibitor, the dose of irradiation and the intermittence of the irradiation doses will depend on a series of parameters such as the type of tumor, its location, the patients' reaction to chemo- or radiotherapy and ultimately is for the physician and radiologists to determine in each individual case.

The present invention also concerns a method of cancer therapy for a host harboring a tumor comprising the steps of

- administering a radiation-sensitizing effective amount of a farnesyl protein transferase inhibitor before, during or after
- administering radiation to said host in the proximity to the tumor.

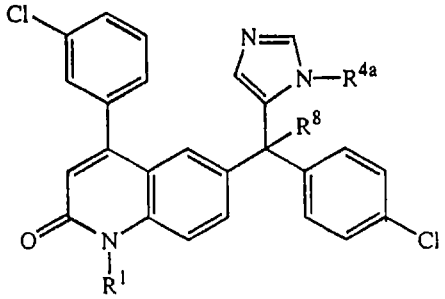
Examples of tumors which may be inhibited, but are not limited to, lung cancer (e.g. adenocarcinoma), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), 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, kidney carninoma, ovary carcinoma, bladder carcinoma and epidermal

carcinoma.

Experimental part

The following tables show the formulas of the compounds of formula (I), their physical data, and references to the examples in WO-97/21701 according to which the compounds in question may be prepared. In the pharmacological example, the radiation sensitizing effect of the compounds of formula (I) is illustrated.

Table 1 :



Co. No.	Ex. No.	R^1	R^{4a}	R^8	Physical data
3	B.1	CH_3	CH_3	OH	mp. 233.6°C
4	B.3	CH_3	CH_3	OCH_3	mp. 140-160°C; .$C_2H_2O_4$ .H_2O
5	B.6	CH_3	CH_3	H	mp. 165°C; .$C_2H_2O_4$ .H_2O
6	B.5	CH_3	CH_2CH_3	H	mp. 180°C; .$C_2H_2O_4$ .1/2H_2O
7	B.2	H	CH_3	H	mp. 260°C
8	B.2	H	$(CH_2)_3CH_3$	OH	-
9	B.4	CH_3	$(CH_2)_3CH_3$	OH	mp. 174°C
10	B.3	H	CH_3	$OCH_2COOC_2H_5$	mp. 185°C; .3/2$C_2H_2O_4$
11	B.3	CH_3	CH_3	$O(CH_2)_2N(CH_3)_2$	mp. 120°C
12	B.7	CH_3	CH_3	CH_3	mp. 210°C; .$C_2H_2O_4$
13	B.7	CH_3	CH_3	CH_2CH_3	mp. 196°C; .$C_2H_2O_4$
14	B.13	CH_3	CH_3	NH_2	mp. 220°C
72	B.13	CH_3	CH_3	NH_2	.3/2-(E)-$C_4H_4O_4$
73	B.13	CH_3	CH_3	NH_2	.2HCl
74	B.8b	CH_3	CH_3	NH_2	(A)
75	B.8b	CH_3	CH_3	NH_2	(+)

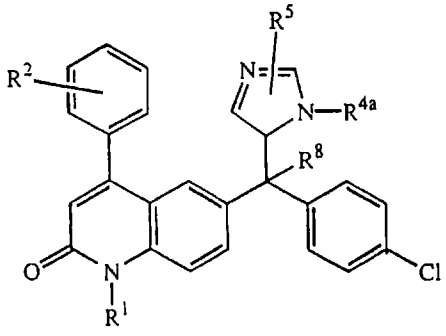
Co. No.	Ex. No.	R^1	R^{4a}	R^8	Physical data
15	B.3	CH_3	CH_3	$O(CH_2)_3OH$	mp. 135°C
16	B.3	CH_3	CH_3	$O(CH_2)_2CH_3$	mp. 180°C; $.C_2H_2O_4.3/2(H_2O)$
17	B.3	CH_3	CH_3	$O(CH_2)_2O\text{-}C_6H_5$	mp. 144°C; $.3/2(C_2H_2O_4)$
18	B.2	H	$CH(CH_3)_2$	OH	-
19	B.4	CH_3	$CH(CH_3)_2$	OH	mp. 254°C
20	B.2	H	$(CH_2)_2OCH_3$	OH	mp. 112°C
21	B.4	CH_3	$(CH_2)_2OCH_3$	OH	mp. 192°C
22	B.3	CH_3	CH_3	$O(CH_2)_2OH$	mp. 198°C
23	B.8a	CH_3	CH_3	OH	mp. 150-200°C; (A); $.C_2H_2O_4$
24	B.8a	CH_3	CH_3	OH	mp. 150-200°C; (B); $.C_2H_2O_4$
25	B.11	CH_3	CH_3	$CH_2\text{-}CN$	mp. 154°C
27	B.2	H	$(CH_2)_3OCH_3$	OH	-
28	B.4	CH_3	$(CH_2)_3OCH_3$	OH	mp. 196°C; $.H_2O$
29	B.3	CH_3	CH_3	$O(CH_2)_3OCH_2CH_3$	mp. 105°C; $.3/2(H_2O)$
31	B.2	H	CH_3	OH	> 260°C
32	B.6	CH_3	$(CH_2)_2OCH_3$	H	mp. 140°C; $.3/2(C_2H_2O_4)$
33	B.6	CH_3	$(CH_2)_3OCH_3$	H	mp. 180°C; .HCl
56	B.12	CH_3	CH_3	$-NHCOCH_3$	$.C_2H_2O_4$
58	B.11	CH_3	CH_3	$-CH_2COOCH_2CH_3$	$.C_2H_2O_4.3/2(H_2O)$
60	B.11	CH_3	CH_3	1-imidazolyl	-
61	B.21	CH_3	CH_3	$-NH\text{-}CH_3$	mp. 164°C
65	B.2	H	$(CH_2)_3SOCH_3$	OH	$.H_2O$
66	B.13	CH_3	CH_3	$-N(CH_3)_2$	$.2C_2H_2O_4.H_2O$ mp. 160°C
67	B.13	CH_3	CH_3	$-NH\text{-}(CH_2)_2OCH_3$	mp. 216°C
68	B.13	CH_3	CH_3	$-NH\text{-}(CH_2)_2\text{-}OH$	-
69	B.7	CH_3	CH_3	$-CH_2Cl$	$.2C_2H_2O_4$ mp. 220°C
70	B.7	CH_3	CH_3	$-CH_2Br$	-
71	*	CH_3	CH_3	$-CH_2OH$	$.2C_2H_2O_4$
76	B.4	$-(CH_2)_2OCH_3$	CH_3	OH	mp. 150°C

Co. No.	Ex. No.	R^1	R^{4a}	R^8	Physical data
77	*	CH_3	CH_3	$-CH_2OCH_3$	$.2C_2H_2O_4$ mp.166°C
78	B.13	CH_3	CH_3	$-NH-OCH_3$	mp. 170°C
79	B.20	CH_3	CH_3	$-NH-CONH_2$	$.2H_2O$
80	**	CH_3	CH_3	$-CH_2CONH_2$	-
81	B.13	CH_3	CH_3	-NH-OH	-
82	B.13	CH_3	CH_3	$-NH(CH_2)_2N(CH_3)_2$	-
83	B.4	$(CH_2)_2N(CH_3)_2$	CH_3	OH	$.3/2C_2H_2O_4$ $.3/2H_2O$ mp. 200 °C
84	*	CH_3	CH_3	$-CH_2N(CH_3)_2$	$.C_2H_2O_4$ mp. 210°C
85	B.4	CH_3	CH_3	$-N(CH_3)_2$	-
86	B.4	CH_3	CH_3	$NHCOCH_2N(CH_3)_2$	-
87	B.4	CH_3	CH_3	$-NH(CH_2)_9CH_3$	-
88	B.4	CH_3	CH_3	$-NH(CH_2)_2NH_2$	-
89	B.20	CH_3	CH_3	$-NHCOCH_2OCH_3$	.HCl mp. 220°C
90	B.6	CH_3	CH_3	H	-
91	B.20	CH_3	CH_3	$-NHCOCH_2C_6H_5$	$.C_2H_2O_4.H_2O$ mp. 170°C
92	B.20	CH_3	CH_3	$-NHCOC_6H_5$	mp. 242°C
93	B.20	CH_3	CH_3	$-NHCOCONH_2$	$.C_2H_2O_4.H_2O$ mp. 186°C
94	B.13	CH_3	CH_3	$-NHC_6H_5$	mp. 165°C

* : prepared by functional-group transformation of compound 70

** : prepared by functional-group transformation of compound 25

Table 2:



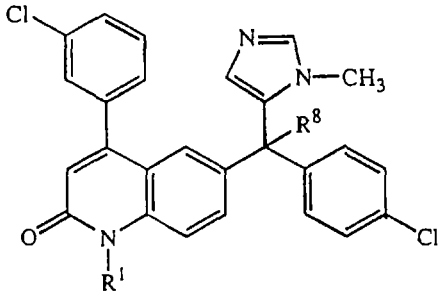
Co. No.	Ex. No.	R^1	R^2	R^{4a}	R^5	R^8	Physical data
1	B.1	CH_3	H	CH_3	H	OH	mp. >250°C
2	B.5	CH_3	H	CH_3	H	H	mp. 100-110°C
26	B.1	CH_3	3-Cl	CH_3	2-CH_3	OH	mp. 200°C
30	B.6	CH_3	3-Cl	CH_3	2-CH_3	H	mp. 120-140°C; .3/2($C_2H_2O_4$).H_2O
34	B.1	CH_3	3-O-CH_2-CH_3	CH_3	H	OH	mp. 190°C
35	B.6	CH_3	3-O-CH_2-CH_3	CH_3	H	H	mp. 160-180°C; .HCl.H_2O
36	B.1	CH_3	3-O-CH_3	CH_3	H	OH	mp. 210°C
37	B.1	CH_3	3-O-(CH_2)$_2$-CH_3	CH_3	H	OH	mp. 150-160°C
38	B.1	CH_3	3-O-(CH_2)$_3$-CH_3	CH_3	H	OH	mp. 150-160°C
49	B.1	CH_3	4-O-CH_2-CH_3	CH_3	H	OH	mp. 184.2°C
50	B.1	CH_3	3-O-CH-(CH_3)$_2$	CH_3	H	OH	mp. 147.1°C
51	B.6	CH_3	3-O-(CH_2)$_3$-CH_3	CH_3	H	H	mp. 164.2°C; .3/2($C_2H_2O_4$)
52	B.6	CH_3	3-O-(CH_2)$_2$-CH_3	CH_3	H	H	.3/2($C_2H_2O_4$)
53	B.6	CH_3	3-O-CH-(CH_3)$_2$	CH_3	H	H	mp. 133.9°C; .$C_2H_2O_4$.H_2O
54	B.14	CH_3	3-OH	CH_3	H	OH	-
64	B.10	CH_3	3-OH	CH_3	H	OH	.HCl.H_2O
55	B.6	CH_3	3-OH	CH_3	H	H	mp. >250°C
57	B.1	CH_3	2-OCH_2CH_3	CH_3	H	OH	-
59	B.13	CH_3	3-OCH_2CH_3	CH_3	H	NH_2	-
95	B.8a	CH_3	3-OCH_2CH_3	CH_3	H	NH_2	(A)
96	B.8a	CH_3	3-OCH_2CH_3	CH_3	H	NH_2	(B)
62	B.15	CH_3	3-O(CH_2)$_2$N(CH_3)$_2$	CH_3	H	OH	-
63	B.11	CH_3	3-O(CH_2)$_2$-OH	CH_3	H	OH	-
97	B.1	CH_3	3-CH_2CH_3	CH_3	H	OH	-
98	B.13	CH_3	3-CH_2CH_3	CH_3	H	NH_2	mp. 240°C
99	B.1	CH_3	3-(CH_2)$_2$$CH_3$	CH_3	H	OH	-
100	B.13	CH_3	3-(CH_2)$_2$$CH_3$	CH_3	H	NH_2	-
101	*	CH_3	3-O-(CH_2)$_2$OCH_3	CH_3	H	OH	.3/2(C_2.H_2O_4) mp. 193°C
102	B.1	CH_3	3-CH_3	CH_3	H	OH	mp. >250°C
103	B.13	CH_3	3-CH_3	CH_3	H	NH_2	-
104	B.1	CH_3	3-Br	CH_3	H	OH	-
105	B.13	CH_3	3-Br	CH_3	H	NH_2	-

Co. No.	Ex. No.	R^1	R^2	R^{4a}	R^5	R^8	Physical data
106	B.1	CH_3	3-O-CF_3	CH_3	H	OH	-
107	B.13	CH_3	3-O-CF_3	CH_3	H	NH_2	mp. 168°C
108	B.1	CH_3	3-C_6H_5	CH_3	H	OH	-
109	B.13	CH_3	3-C_6H_5	CH_3	H	NH_2	-
110	B.1	CH_3	3-F	CH_3	H	OH	-
111	B.13	CH_3	3-F	CH_3	H	NH_2	mp. >250°C
112	B.1	CH_3	3-(E)-CH=CH-CH_3	CH_3	H	OH	mp. >250°C
113	B.2	H	3-Cl	CH_3	3-Cl	OH	-
114	B.4	CH_3	3-Cl	CH_3	3-Cl	OH	-
115	B.1	CH_3	3-Cl	H	3-CH_3	OH	-
116	B.4	CH_3	3-Cl	CH_3	3-CH_3	OH	-
117	**	CH_3	3-CN	CH_3	H	OH	-
160	B.1	CH_3	3-CF_3	CH_3	H	OH	-

* : prepared by functional-group transformation of compound 54

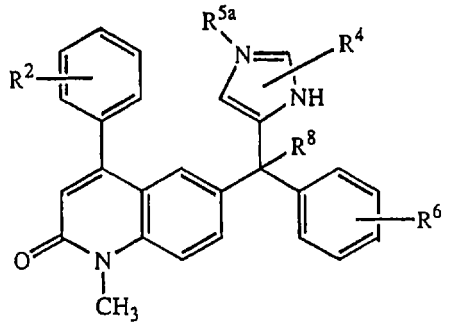
** : prepared by functional-group transformation of compound 104

Table 3 :



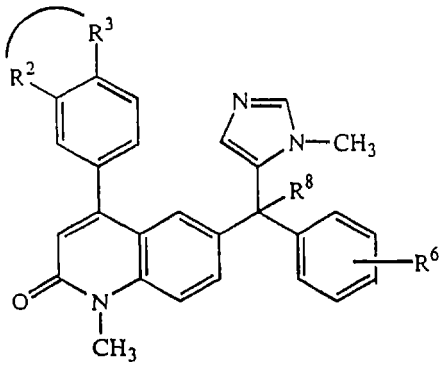
Co. No.	Ex. No.	R^1	R^8	Physical data
39	B.4	$CH_2CONHCH(COOCH_3)(CH_2CH(CH_3)_2)$	H	mp. 240°C (S)
40	B.4	CH_2-2-quinolinyl	H	mp. 240°C; .2 HCl
41	B.4	$CH_2CONHCH(COOCH_3)(CH_2CH(CH_3)_2)$	OH	mp. > 260°C (S)

Table 4 :



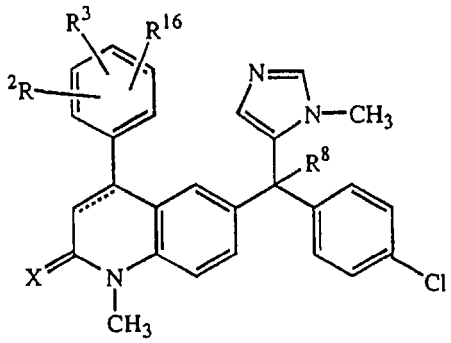
Co. No.	Ex. No.	R^2	R^4	R^{5a}	R^6	R^8	Physical data
42	B.6	H	H	H	4-Cl	H	mp. 170°C; $.C_2H_2O_4 .1/2\ H_2O$
43	B.10	H	H	H	4-Cl	OH	mp. 180°C; $.H_2O$
44	B.5	H	H	CH_3	4-Cl	H	mp. 152°C
45	B.6	3-Cl	H	H	4-Cl	H	mp. 175°C; $.C_2H_2O_4$
46	B.5	3-Cl	H	CH_2CH_3	4-Cl	H	mp. 132°C; $.C_2H_2O_4$
47	B.5	3-Cl	H	CH_3	4-Cl	H	mp. 115°C; $.3/2\ C_2H_2O_4$
48	B.9	3-Cl	H	CH_3	4-Cl	OH	mp. 230°C
118	B.4	3-Cl	3-CH_3	CH_3	4-Cl	OH	mp. 222°C

Table 5 :



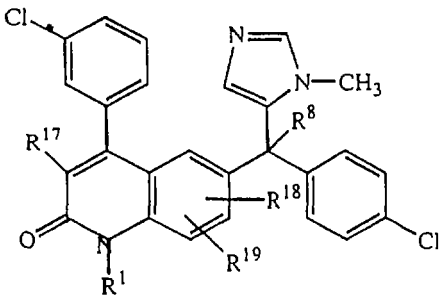
Co. No.	Ex. No.	$-R^2-R^3-$	R^6	R^8
119	B.1	$-O-CH_2-O-$	4-Cl	OH
120	B.13	$-O-CH_2-O-$	4-Cl	NH_2
121	B.1	$-O-CH_2-CH_2-O-$	4-Cl	OH
122	B.13	$-O-CH_2-CH_2-O-$	4-Cl	NH_2
123	B.1	-O-CH=CH-	4-Cl	OH

Table 6 :



Co. No.	Ex. No.	X	.....	R^2	R^3	R^{16}	R^8	Physical data
124	B.1	O	double	3-OCH_3	4-OCH_3	5-OCH_3	OH	mp. 230°C
125	B.13	O	double	3-OCH_3	4-OCH_3	5-OCH_3	NH_2	mp. 218°C .$C_2H_2O_4$
126	B.1	O	single	3-Cl	H	H	OH	mp. 160°C
127	B.1	O	single	3-Cl	H	H	OH	-
128	B.16	S	double	3-Cl	H	H	H	-

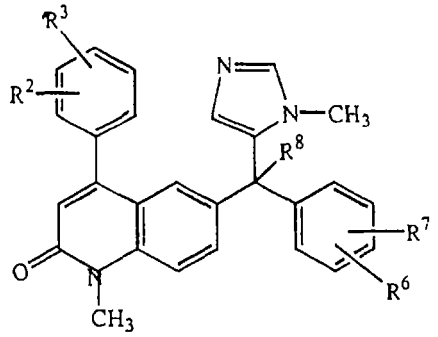
Table 7 :



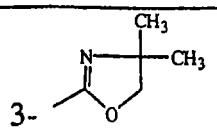
Co. No.	Ex. No.	R^1	R^{17}	R^{18}	R^{19}	R^8	Physical data
129	B.17	H	CN	H	H	H	-
130	B.4	CH_3	CN	H	H	H	mp. 202°C
131	B.17	H	CN	H	H	OH	-
132	B.4	CH_3	CN	H	H	OH	-
133	B.17	H	CN	H	H	$-CH_2CN$	-
134	B.4	CH_3	CN	H	H	$-CH_2CN$	mp. 138°C
135	B.18	H	CH_3	H	H	OH	-
136	B.4	CH_3	CH_3	H	H	OH	-
137	B.13	CH_3	CH_3	H	H	NH_2	mp. >250°C
138	B.18	H	C_6H_5	H	H	H	-

Co. No.	Ex. No.	R^1	R^{17}	R^{18}	R^{19}	R^8	Physical data
139	B.4	CH_3	C_6H_5	H	H	H	.3/2($C_2H_2O_4$) mp. 180°C
140	B.18	H	C_6H_5	H	H	OH	-
141	B.4	CH_3	C_6H_5	H	H	OH	-
142	B.13	CH_3	C_6H_5	H	H	NH_2	-
143	B.13	CH_3	Cl	H	H	NH_2	-
144	B.17	H	$-COOCH_2CH_3$	H	H	OH	-
145	B.4	CH_3	$-COOCH_2CH_3$	H	H	OH	-
146	B.1	CH_3	H	8-CH_3	H	OH	-
147	B.13	CH_3	H	8-CH_3	H	NH_2	.H_2O
148	B.1	CH_3	H	7-Cl	H	OH	-
149	B.1	CH_3	H	7-CH_3	H	OH	-
150	B.1	CH_3	H	5-CH_3	H	OH	-
151	B.1	CH_3	H	8-OCH_3	H	OH	-
161	B.1	CH_3	H	7-CH_3	8-CH_3	OH	mp. 255°C

Table 8 :



Co. No.	Ex. No.	R^2	R^3	R^6	R^7	R^8	Physical data
152	B.1	3-OCH_2CH_3	H	4-OCH_2CH_3	H	OH	.3/2($C_2H_2O_4$)
153	B.1	3-Cl	H	H	H	OH	-
154	B.1	3-Cl	H	4-CH_3	H	OH	-
155	B.1	3-Cl	H	4-OCH_3	H	OH	-
156	B.1	3-Cl	H	4-CF_3	H	OH	-
157	B.1	3-Cl	H	2-Cl	4-Cl	OH	-
158	B.1	3-Cl	5-Cl	4-Cl	H	OH	-

Co. No.	Ex. No.	R^2	R^3	R^6	R^7	R^8	Physical data
159	B.1		H	4-Cl	H	OH	-
162	B.1	3-Cl	H	4-S-CH_3	H	OH	mp. 169°C .$C_2H_2O_4$.H_2O; mp.decomposes > 172°C
163	B.1	3-Cl	H	4-$N(CH_3)_2$	H	OH	
164	B.1	3-Cl	H	-CH=CH-CH=CH- *		OH	.$C_2H_2O_4$

* : R^6 and R^7 taken together to form a bivalent radical between positions 3 and 4 on the phenyl moiety

Pharmacological example 1

Male athymic nude mice weighing approximately 22 to 25 g were inoculated subcutaneously in the inguinal region with 1 x 10^6 of LoVo human colon tumor cells (LoVo cells) on day 0. After three weeks to allow tumors to become established (diameter approximately 0.5 to 1 cm), treatment was started with solvent or compound 75 via the oral route, and either with or without a single shot irradiation on day 32. Parameters for activity were tumor growth rate and weight of the tumors at day 42.

Compound 75 was dissolved in water and acidified with 1 N HCl solution to pH 2.5 and administered orally (po) as 0.1 ml of compound solution per 10 g mouse body weight twice daily (bid). The dose administered was either 50 or 100 mg compound per kg bodyweight ; treatment either preceded irradiation (days 22-32), followed irradiation (days 32-42) or continued throughout the duration of the experiment (days 22-42).

Irradiation treatment consisted of a single dose of radiation on day 32 with a dose of 7 Gy that stabilized tumor growth in untreated animals, *i.e.* a dose that stopped the increase in tumor volume, but did not cause any reduction in its size either.

The following table (Table 9) shows each of the arms that were evaluated in the experiment. In each arm of the experiment 16 animals were included. The column 'tumor (g)' contains the median of the tumor weight of the animals sacrificed at day 42 of the experiment. Figures 1 and 2 represent the observed data in graphical form.

Figure 1 shows the distribution of the tumor weights (g) of the test animals receiving 50 mpk of test compound (po, bid).

Figure 2 shows the distribution of the tumor weights (g) of the test animals receiving 100 mpk of test compound (po, bid).

The gray box in the figures depicts the 25-75 percentiles, the solid black line therein represents the median, the lines extending from the gray box depict the 10-90 percentiles and the black dots represent the outliers. The Roman mumbers correspond to the groups of test animals as identified in Table 9.

From a statistical analysis of the data it follows that treatment with compound 75 (both 50 and 100 mpk) potentiates the effect of irradiation, more in particular that pretreatment with compound 75 (both 50 and 100 mpk) and irradiation reduces tumor weight in a statistically significant manner (when compared to irradiation alone).

Table 9

Group	Compound 75	treatment schedule	Irradiation	tumor (g)
I	solvent	day 22-42	none	0.475
II	50 mpk	day 22-42	none	0.255
III	50 mpk	day 22-32	none	0.273
IV	50 mpk	day 32-42	none	0.295
V	100 mpk	day 22-42	none	0.205
VI	100 mpk	day 22-32	none	0.234
VII	100 mpk	day 32-42	none	0.277
VIII	50 mpk	day 22-42	7 Gy	0.207
IX	50 mpk	day 22-32	7 Gy	0.156 (p = 0.03)*
X	50 mpk	day 32-42	7 Gy	0.259
XI	100 mpk	day 22-42	7 Gy	0.164 (p = 0.0317)*
XII	100 mpk	day 22-32	7 Gy	0.141 (p = 0.0022)*
XIII	100 mpk	day 32-42	7 Gy	0.214
XIV	Solvent	day 22-42	7 Gy	0.256

* Mann-Whitney U test vs Group XIV (radiotherapy only)

Example 2

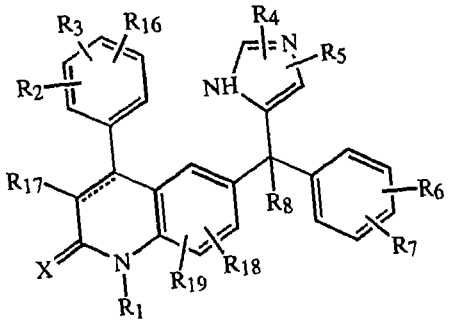
Radioresistant human glioma cell lines (SF763, U87, U251) were treated with compound 75, 48 h prior to irradiation (2 Gy). The dose administered was 0.4 nM for U251 and 2 nM for SF763 and U87.

Applying compound 75 to the cells dramatically reduced the surviving of the cells after irradiation : for SF763 and U87, a decrease of surviving fraction of about 55 % was demonstrated, whereas for U251, the decrease was 25 %.

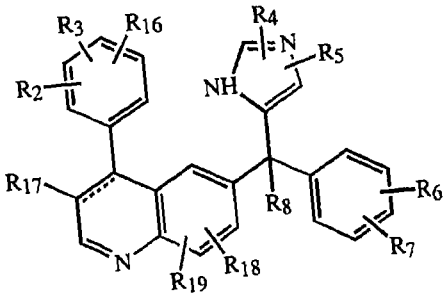
These results demonstrate that treatment with compound 75 resensitizes radioresistant cells to irradiation.

Claims

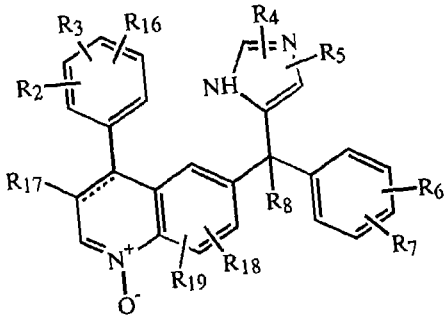
1. Use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition having radiosensitizing properties for administration before, during or after irradiation of a tumor for treating cancer *in vivo*, wherein the said farnesyl protein transferase inhibitor is a compound of formula (I), or a compound of formula (II) or (III) which is metabolized *in vivo* to a compound of formula (I), said compounds being represented by



(I)



(II)



(III)

a stereoisomeric form thereof, a pharmaceutically acceptable acid or base addition salt thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C1-12alkyl, Ar^1, Ar^2C1-6alkyl, quinolinylC1-6alkyl, pyridyl-C1-6alkyl, hydroxyC1-6alkyl, C1-6alkyloxyC1-6alkyl, mono- or di(C1-6alkyl)-aminoC1-6alkyl, aminoC1-6alkyl,

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 C1-6alkanediyl,

R^9 is hydroxy, C1-6alkyl, C1-6alkyloxy, amino, C1-8alkylamino or C1-8alkylamino substituted with C1-6alkyloxycarbonyl;

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, Ar2oxy, 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, hydroxy-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, 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, 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}alkylcarbonylC_{1-6}alkyl, a natural amino acid, Ar^1carbonyl, Ar^2C_{1-6}alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6}alkyloxy-C_{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 of 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, hydroxyC_{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.

2. The use of claim 1 wherein said farnesyl protein transferase inhibitor is a compound of formula (I) and wherein X is oxygen.

3. The use of claim 1 wherein said farnesyl protein transferase inhibitor is a compound of formula (I) and wherein the dotted line represents a bond.

4. The use of claim 1 wherein said farnesyl protein transferase inhibitor is a compound of formula (I) and 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)aminoC_{1-6}alkyl.

5. The use of claim 1 wherein said farnesyl protein transferase inhibitor is a compound of formula (I) 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.

6. The use of claim 1 wherein said farnesyl protein transferase inhibitor is a compound of formula (I) and 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.

7. The use of claim 1 wherein the compound is
4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)-methyl]-1-methyl-2(1*H*)-quinolinone, 6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxy-phenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride.monohydrate;
6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxy-phenyl)-1-methyl-2(1*H*)-quinolinone, and
6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salts thereof.

8. The use of claim 1 wherein the compound is
(+)-(R)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone; or a pharmaceutically acceptable acid addition salt thereof.

9. The use of any one of the preceding claims wherein a therapeutically effective amount of the pharmaceutical composition is administered orally, parenterally, rectally or topically.

10. The use of claim 9 wherein the pharmaceutical composition is administered orally in an amount of from 10 to 1500 mg/m^2 daily, either as a single dose or subdivided into more than one dose.

11. The use of claim 1 wherein the irradiation is ionizing irradiation.

12. The use of claim 1 wherein the irradiation of the tumor is external or internal.

13. The use of claim 1 wherein the administration of the pharmaceutical composition commences up to one month before the irradiation of the tumor.

5

14. The use of claim 1 wherein the irradiation of the tumor is fractionated and the administration of the pharmaceutical composition is maintained in the interval between the first and the last irradiation session.