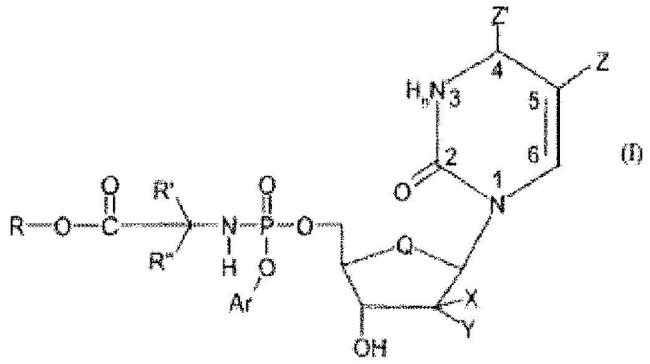
Annex A – Unconditional Amendments

The proposed amendments to EP(UK) 2 955 190 B1 are to paragraphs [0013], [0015], [0017], [0023], [0038], [0044] and [0047] to [0049] of the description and to claims 1 to 15 of the Patent (with deletions shown struck out in red and additions shown underlined) as follows:

Specification:

[0013] According to a first aspect of the present invention there is provided a compound of formula I:



wherein:

R is selected from the group alkyl, aryl and alkylaryl;
R' and R" are, independently, selected from the group H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;
Q is selected from the group -O- and -CH_2-;
X is independently selected from the group ~~H,~~ F, Cl, Br, ~~I, OH~~ and methyl (-CH_3);
Y is F;

Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which ring moieties is carbocyclic or heterocyclic and is optionally substituted;
Z is selected from the group H, alkyl and halogen; and
n is 0 or 1,

wherein

when n is 0, Z' is $-NH_2$ and a double bond exists between position 3 and position 4, and

when n is 1, Z' is =O;

or a pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula I.

~~[0015] Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkylene group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5 to C_7. Where acyclic, the alkyl group is preferably C_1 to C_{16}, more preferably C_1 to C_6.~~

[0017] The ~~alkyl and~~ aryl groups may be substituted or unsubstituted. Where substituted, there will generally be one to three substituents present, preferably one substituent. Substituents may include halogen atoms, by which is meant F, Cl, Br and I atoms, and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyC_{1-6}alkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, C_{1-6}alkylamino, diC_{1-6}alkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, C_{1-6}alkylthiol, sulphonyl and sulphoxide; heterocyclic groups which may themselves be substituted; alkyl groups ~~as defined above, which may~~

themselves be substituted; and aryl groups as defined above, which may themselves be substituted, such as phenyl and substituted phenyl. Substituents on said heterocyclic, alkyl and aryl groups are as defined immediately above.

[0023] Suitably, R is a C_{1-16} primary or secondary alkyl group, a C_{5-7} carbocyclic aryl group or a C_{1-6}alkylC_{5-11}aryl group. More suitably, R is a C_{1-10} alkyl group, a phenyl group or C_{1-3}alkylC_{5-7} aryl group. Preferably R is unsubstituted.

[0038] Preferably, X is independently, selected from the group comprising F, H and OH.

[0044] One, two three or four substituents, which may be the same or different, may be present on Ar and are selected from the group comprising halogen, which may -F, -Cl, -Br or -I; $-NO_2$; $-NH_2$; optionally substituted -C_{1-3}alkyl; optionally substituted -C_{1-3}alkoxy, preferably methoxy ($-OCH_3$); optionally substituted -SC_{1-3}alkyl; -CN; optionally substituted -COC_{1-3}alkyl; and optionally substituted -CO_2C_{1-3}alkyl. The optional substituents are one or more up to six, preferably three, members selected from the group comprising halogen which may be F, Cl, Br and I and NO_2. Preferred substituents on Ar include F, Cl, CF_3, and NO_2.

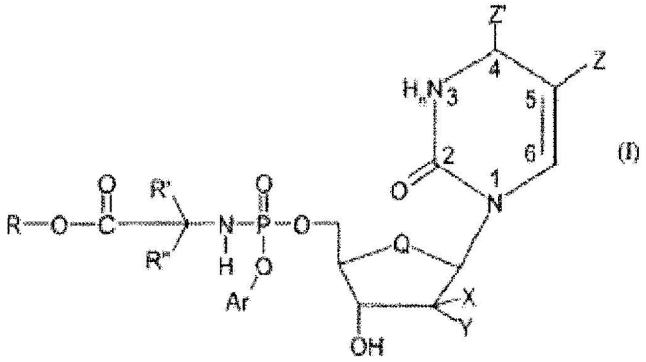
[0047] Suitably, Z is selected from the group comprising H, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-6} alkenyl, substituted C_{1-6} alkenyl, C_{1-6} alkynyl, substituted C_{1-6} alkynyl and halogen, where halogen is F, Cl, Br or I. Substituents that may be present on the alkenyl or alkynyl moiety are selected from the group comprising F, Cl, Br, I, and -CO_2Me. One, two or three substituents may be present. The alkenyl and alkynyl groups may contain one or more sites of unsaturation.

[0048] ~~Where Z is substituted alkenyl or alkynyl, the substituent is preferably on the terminal C atom.~~

[0049] Preferably Z is selected from the group comprising H, F and ~~optionally substituted~~ C_{1-6}alkyl particularly Me ($-CH_3$)~~, optionally substituted C_{1-6}alkenyl and optionally substituted C_{1-6}alkynyl, the optional substituents being as recited immediately above~~.

Claims:

1. A chemical compound having formula I:



(I)

wherein:

R is selected from the group alkyl, aryl and alkylaryl;

R' and R" are independently selected from the group H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;

Q is selected from the group -O- and $-CH_2-$;

X is independently selected from the group ~~H,~~ F, Cl, Br, ~~I, OH~~ and methyl ($-CH_3$);

Y is F;

Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which said ring moieties is carbocyclic or heterocyclic and is optionally substituted;

Z is selected from the group H, alkyl and halogen; and

n is 0 or 1,

wherein when n is 0, Z' is -NH_2 and a double bond exists between position 3 and position 4,

and

when n is 1, Z' is =O;

or a pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula I.

~~2. A compound according to claim 1 wherein R is selected from the group a C_{1-6} primary or secondary alkyl group, a C_{5-7} carbocyclic aryl group or a C_{1-6}alkylC_{5-7} aryl group; optionally wherein R is selected from the group methyl (-CH_3), ethyl (-C_2H_5) and benzyl (-$CH_2C_6H_5$); further optionally wherein R is benzyl.~~

~~3. A compound according to claim 1 or claim 2 wherein Ar is an optionally substituted C_6 monocyclic aromatic ring moiety, ie is optionally substituted phenyl; optionally wherein Ar is selected from the group -C_6H_5, *p*CF_3C6H_4-, *p*FC_6H_4-, *p*$NO_2C_6H_4$-, *p*ClC_6H_4- and *o*ClC_6H_4-.~~

~~4. A compound according to any one of the preceding claims wherein R' and R" are, independently, selected from the group H, C_{1-6} primary, secondary and tertiary alkyl, C_{1-3}alkylC_{5-7} aryl, or, when together they form an alkylene chain, they provide, together with the C atom to which they are attached, a C_{3-8} carbocyclic aliphatic ring.~~

~~5. A compound according to claim 4 wherein R' and R" are, independently, selected from the group H, methyl, benzyl and -$CH_2CH(CH_3)_2$, or, R' and R" together with the C atom to which they are attached, provide a C_{5-6} ring.~~

~~6. A compound according to claim 5 wherein R' and R" are each methyl.~~

~~7. A compound according to claim 5 wherein one of R' and R" is H and one of R' and R" is methyl.~~

~~8. A compound according to claim 5 wherein the carbocyclic ring is a pentyl ring.~~

~~9. A compound according to any one of the preceding claims wherein R' and R" correspond to the side chains of a naturally occurring amino acid.~~

~~10. A compound according to any one of the preceding claims wherein Z is selected from the group H, C_{1-6}alkyl, substituted C_{1-6}alkyl, C_{1-6}alkenyl, substituted C_{1-6} alkenyl, C_{1-6}alkynyl, and halogen.~~

~~11. A compound according to any one of the preceding claims wherein Q is O.~~

~~12. A compound according to any one of claims 1 to 11 wherein when n is 0, each of X and Y is F.~~

~~13~~2. A compound according to ~~any one of~~ claim~~s~~ 1 ~~to 12~~, for use in a method of treatment, preferably in the prophylaxis or treatment of cancer.

~~14~~3. A pharmaceutical composition comprising a compound according to ~~any one of~~ claim~~s~~ 1 ~~to 12~~, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

~~15~~4. A method of preparing a pharmaceutical composition comprising the step of combining a compound according to ~~any one of~~ claim~~s~~ 1 ~~to 12~~, with a pharmaceutically acceptable excipient, carrier or diluent.

Annex B – Conditional Amendments

The proposed amendments to EP(UK) 2 955 190 B1 are to paragraphs [0013], [0015], [0017], [0023], [0038], [0044] and [0047] to [0049] of the description and to claims 1 to 15 of the Patent (with deletions shown struck out in red and additions shown underlined) as follows:

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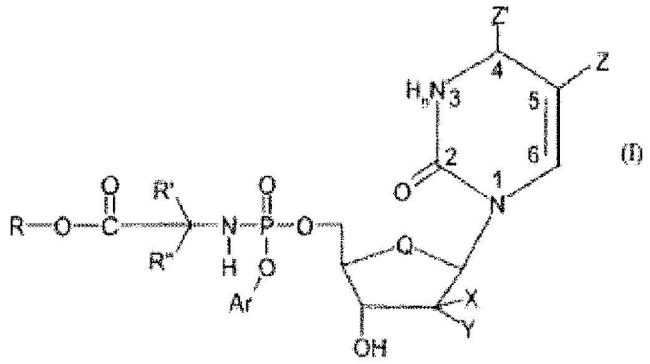

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when n is 0, Z' is -NH_2 and a double bond exists between position 3 and position 4, and

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themselves be substituted; and aryl groups as defined above, which may themselves be substituted, such as phenyl and substituted phenyl. Substituents on said heterocyclic, alkyl and aryl groups are as defined immediately above.

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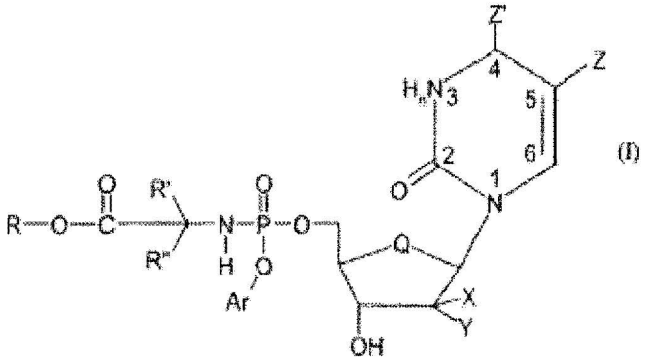

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~~9. A compound according to any one of the preceding claims wherein R' and R" correspond to the side chains of a naturally occurring amino acid.~~

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~~12. A compound according to any one of claims 1 to 11 wherein when n is 0, each of X and Y is F.~~

~~13~~2. A compound according to ~~any one of~~ claim~~s~~ 1 ~~to 12~~, for use in a method of treatment, preferably in the prophylaxis or treatment of cancer.

~~14~~3. A pharmaceutical composition comprising a compound according to ~~any one of~~ claim~~s~~ 1 ~~to 12~~, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

~~15~~4. A method of preparing a pharmaceutical composition comprising the step of combining a compound according to ~~any one of~~ claim~~s~~ 1 ~~to 12~~, with a pharmaceutically acceptable excipient, carrier or diluent.