Utilization of so-called 'trigger-linker-effector' chemistry in SMDC design requires the activation of the trigger to initiate the fragmentation of a linker to release an effector (typically an active drug), the biological activity of which is masked in the SMDC form. The modular design of selective SMDCs targeted at tumor-expressing cytochrome P450s such as CYP1B1 require (1) the identification of selective trigger moieties, (2) the use of bio-stable linkers which fragment efficiently following trigger activation (usually by aromatic hydroxylation), and (3) suitable effectors or drugs which do not interfere with the efficiency of the triggering process.

WO 99/40944 describes SMDCs that comprise a drug moiety bound to a carrier framework, the SMDC being described activated as through hydroxylation by CYP1B1 to release the drug moiety.

WO 2010/125350 also describes SMDCs activated as through hydroxylation by CYP1B1 to release a drug moiety.

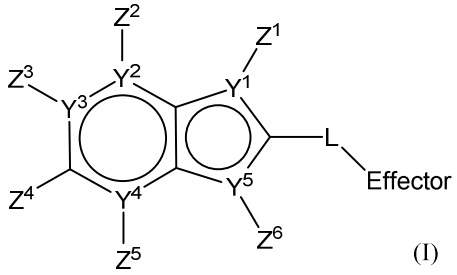
Accordingly, there remains a strong need for novel SMDC's that are useful for patients in need thereof.

**SUMMARY**

The present disclosure provides SMDCs described having novel structural and functional features, wherein these novel features have been developed to fulfill unmet needs of patients in need of these SMDCs.

In particular, the present disclosure provides novel phosphoramidate SMDCs that have both novel structural and novel functional features. The SMDCs disclosed herein are designed to release gemcitabine derivatives at specific cancerous target locations that overexpress cytochrome p450. In another example, the SMDCs disclosed herein are also designed to protect the SMDC gemcitabine derivative moiety against cancer resistance mechanisms by the incorporation of phosphoramidate or phosphorodiamidate structural features as part of the SMDC molecule.

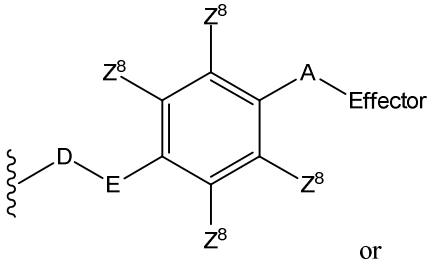
According to a first aspect, the present disclosure refers to a compound of formula (I):



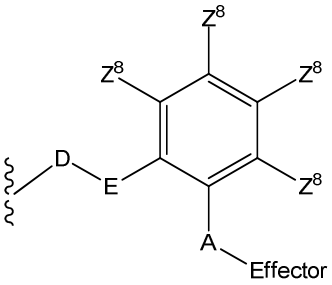

(I)

or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein:

-L- is defined within -L-Effector as: -($C_1$-$C_5$)alkylene-O-C(O)-Effector, -($C_3$-$C_5$)alkenylene-O-Effector,




or




A is -($C_1$-$C_5$)alkylene-O-C(O)-;

E is -O-, -O-C(O)N(H)-, -O-C(S)N(H)- or -S- or -S-C(O)N(H)-;

D is -($C_1$-$C_5$)alkylene- or -($C_3$-$C_5$)alkenylene-;

$Y^1$ is C=C, carbon or nitrogen, wherein if $Y^1$ is nitrogen, $Z^1$ is absent;

Each of $Y^4$ and $Y^5$ is independently carbon or nitrogen, wherein if $Y^3$ is nitrogen, $Z^3$ is absent and if $Y^4$ is nitrogen, $Z^5$ is absent;

$Y^2$ is C or N;

$Y^5$ is an oxygen, carbon, nitrogen or a sulfur atom, wherein $Z^6$ is absent when $Y^5$ is an oxygen, or a sulfur atom;

Each of $Z^1$, and $Z^2$, where present, are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkyloxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkylthioxy, alkenylthioxy, alkynylthioxy, arylthioxy, aralkylthioxy, amino, hydroxy, thio, halo, carboxy, formyl, nitro and cyano, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

$Z^3$, $Z^4$, and $Z^5$ are each independently selected from hydrogen, alkyl, deuterated alkyl, $C_{1\text{-}6}$alkoxy, deuterated $C_{1\text{-}6}$alkoxy, alkenyl, alkynyl, aryl, aralkyl, alkyloxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkylthioxy, alkenylthioxy, alkynylthioxy, arylthioxy, aralkylthioxy, amino, hydroxy, thio, halo, carboxy, formyl, nitro and cyano, wherein each

alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

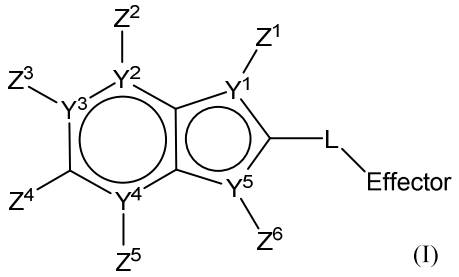
provided that at least one of $Z^1$, $Z^2$ or $Z^4$ is H;

$Z^6$ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl and aralkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

Each $Z^8$ is independently hydrogen, unsubstituted $C_1$-$C_6$ alkyl, substituted $C_1$-$C_6$ alkyl, unsubstituted $C_1$-$C_6$ alkoxy, unsubstituted deuterated $C_1$-$C_6$ alkoxy, substituted $C_1$-$C_6$ alkoxy, and substituted deuterated $C_1$-$C_6$ alkoxy where the substituted alkyl, alkoxy and deuterated alkoxy are substituted with one or more groups selected from amino, mono- or di-substituted amino, cyclic $C_1$-$C_5$ alkylamino, imidazolyl, $C_1$-$C_6$ alkylpiperazinyl, morpholino, thiol, thioether, tetrazole, carboxylic acid, ester, amido, mono- or di-substituted amido, N-connected amide, N-connected sulfonamide, sulfoxy, sulfonate, sulfonyl, sulfoxy, sulfinate, sufinyl, phosphonooxy, phosphate or sulfonamide, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl is optionally substituted with 1-3 halo; and

Effector is part of a (i) phosphoramidate derivative of gemcitabine, (ii) a salt form of a phosphoramidate derivative of gemcitabine, or (iii) a phosphorodiamidate derivative of gemcitabine.

According to an example, the present disclosure relates to a compound of formula (I):

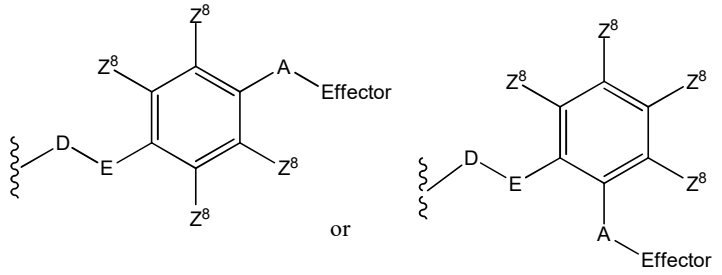



(I)

or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof,

wherein:

-L- is defined within -L-Effector as: -($C_1$-$C_5$)alkylene-O-C(O)-Effector, -($C_3$-$C_5$)alkenylene-O-Effector,




A is -($C_1$-$C_5$)alkylene-O-C(O)-;

E is -O-, -O-C(O)N(H)-, -O-C(S)N(H)- or -S- or -S-C(O)N(H)-;

D is -($C_1$-$C_5$)alkylene- or -($C_3$-$C_5$)alkenylene-;

$Y^1$ is C=C, carbon or nitrogen, wherein if $Y^1$ is nitrogen, $Z^1$ is absent;

Each of $Y^4$ and $Y^5$ is independently carbon or nitrogen, wherein if $Y^3$ is nitrogen, $Z^3$ is absent and if $Y^4$ is nitrogen, $Z^5$ is absent;

$Y^2$ is C or N wherein if $Y^2$ is nitrogen, $Z^2$ is absent;

$Y^5$ is an oxygen, carbon, nitrogen or a sulfur atom, wherein $Z^6$ is absent when $Y^5$ is an oxygen, or a sulfur atom;

Each of $Z^1$, and $Z^2$, where present, are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkyloxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkylthioxy, alkenylthioxy, alkynylthioxy, arylthioxy, aralkylthioxy, amino, hydroxy, thio, halo, carboxy, formyl, nitro and cyano, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

$Z^3$, $Z^4$, and $Z^5$ are each independently selected from hydrogen, alkyl, deuterated alkyl, $C_{1\text{-}6}$alkoxy, deuterated $C_{1\text{-}6}$alkoxy, alkenyl, alkynyl, aryl, aralkyl, alkyloxy, alkenyloxy,

alkynyloxy, aryloxy, aralkyloxy, alkylthioxy, alkenylthioxy, alkynylthioxy, arylthioxy, aralkylthioxy, amino, alkylamino, aralkylamino, arylamino, hydroxy, thio, halo, carboxy, formyl, nitro and cyano, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

provided that at least one of $Z^1$, $Z^2$ or $Z^4$ is H;

$Z^6$ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl and aralkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

Each $Z^8$ is independently hydrogen, unsubstituted $C_1$-$C_6$ alkyl, substituted $C_1$-$C_6$ alkyl, unsubstituted $C_1$-$C_6$ alkoxy, unsubstituted deuterated $C_1$-$C_6$ alkoxy, substituted $C_1$-$C_6$ alkoxy, and substituted deuterated $C_1$-$C_6$ alkoxy where the substituted alkyl, alkoxy and deuterated alkoxy are substituted with one or more groups selected from amino, mono- or di-substituted amino, cyclic $C_1$-$C_5$ alkylamino, imidazolyl, $C_1$-$C_6$ alkylpiperazinyl, morpholino, thiol, thioether, tetrazole, carboxylic acid, ester, amido, mono- or di-substituted amido, N-connected amide, N-connected sulfonamide, sulfoxy, sulfonate, sulfonyl, sulfoxy, sulfinate, sufinyl, phosphonooxy, phosphate or sulfonamide, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl is optionally substituted with 1-3 halo; and

Effector is part of a (i) phosphoramidate derivative of gemcitabine, (ii) a salt form of a phosphoramidate derivative of gemcitabine, or (iii) a phosphorodiamidate derivative of gemcitabine.

Another aspect of the disclosure refers to a composition comprising a compound of the disclosure as described in the specification, together with a pharmaceutically acceptable carrier, or pharmaceutically acceptable salt, ester, amide or solvate of a compound of the disclosure as described in the specification, together with a pharmaceutically acceptable carrier thereof.

Another aspect of the disclosure refers to a compound, or pharmaceutically acceptable salt, ester, amide or solvate, of the disclosure as described in the specification, for use in medicine.

Another example the disclosure relates to a compound of the disclosure as described in the specification, or a pharmaceutically acceptable salt, ester, amide or solvate thereof, for use as a medicament.

Another example of the disclosure relates to a compound of the disclosure as described in the specification, or a pharmaceutically acceptable salt, ester, amide or solvate thereof, for use in a method of treatment or prophylaxis of a proliferative condition. In one aspect, the present disclosure refers to a compound, or pharmaceutically acceptable salt, ester, amide or solvate, of the disclosure as described in the specification, for use in treatment or prophylaxis of a proliferative condition.

Another example of the disclosure relates to method of treatment or prophylaxis comprising adiministering a therapeutically or prophylactically useful amount of a compound of the disclosure as described in the specification to a patient in need thereof.

Another example of the disclosure relates to method of treatment or prophylaxis comprising adiministering a therapeutically or prophylactically useful amount compound of the disclosure as described in the specification to a patient in need thereof, wherein the proliferative condition is a cancer selected from bladder, brain, breast, colon, head and neck, kidney, lung, liver, ovarian, pancreatic, prostate or skin cancer.

Another example of the disclosure relates to a method of treatment or prophylaxis of a proliferative condition, said method comprising administering a therapeutically or

prophylactically useful amount of a compound of the disclosure as described in the specification, or pharmaceutically acceptable salt, ester, amide or solvate thereof, to a subject in need thereof.

Another example of the disclosure relates to the use of a compound of the disclosure as described in the specification, or a pharmaceutically acceptable salt, ester, amide or solvate thereof, for the preparation of medicament for use in a method of treatment or prophylaxis of a proliferative condition. In one aspect, the present disclosure refers to use of a compound, or pharmaceutically acceptable salt, ester, amide or solvate, of the disclosure as described in the specification, for the preparation of a medicament for treatment or prophylaxis of a proliferative condition.

Another example of the disclosure relates to a method of diagnosis of a patient for the presence of tumor cells expressing the CYP1B1 enzyme comprising (a) administering to the patient a specific SMDC disclosed in any of the examples described herein; (b) determining the amount of corresponding hydroxylated metabolite which is subsequently produced; and, (c) correlating the amount with the presence or absence of the tumor cells in the patient. In one aspect, the present disclosure refers to a method of diagnosis of a patient for the presence of tumor cells expressing the CYP1B1 enzyme comprising (a) determining the amount of corresponding hydroxylated metabolite which is produced subsequent to administration of a specific compound of the disclosure as described in the specification; and, (b) correlating the amount with the presence or absence of the tumor cells in the patient.

Another example of the disclosure relates to a method of (1) identifying the presence of a tumor in a patient; and (2) treating the patient, identified as needing the treatment, by administering a therapeutically or prophylactically useful amount of a compound of the disclosure as described in the specification, or pharmaceutically acceptable salt, ester, amide or solvate thereof. In one aspect, the present disclosure refers to use of a therapeutically or prophylactically useful amount of a compound of the disclosure as described in the specification, or pharmaceutically acceptable salt, ester, amide or solvate thereof, for the preparation of a medicament for treating the patient, the use comprising (1) identifying the presence of a tumor in a patient; and (2) treating the patient, identified as needing the treatment.

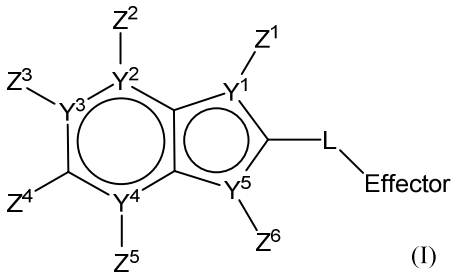
Further aspects and example of the disclosure will follow from the discussion that follows below.

## BRIEF DESCRIPTION OF THE FIGURES

Fig. 1a shows a mechanism for CYP1B1-induced 3-hydroxylation of (5,7-di(methoxy)benzofuran-2-yl)methyl (1-((2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate (I) followed by spontaneous release of the cytotoxic Effector molecule by 1,4 elimination.

What is claimed is:

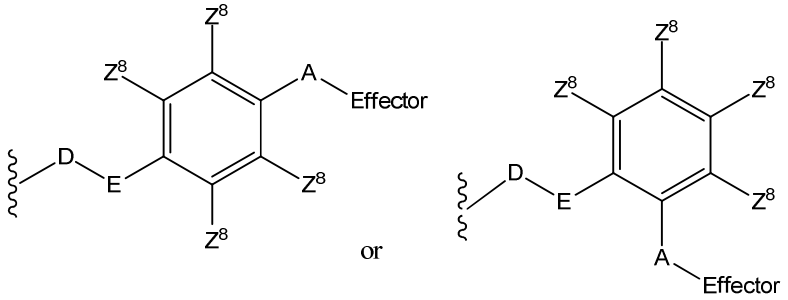
1. A compound of formula (I):




(I)

or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein:

-L- is defined within -L-Effector as: -($C_1$-$C_5$)alkylene-O-C(O)-Effector, -($C_3$-$C_5$)alkenylene-O-Effector,




A is -($C_1$-$C_5$)alkylene-O-C(O)-;

E is -O-, -O-C(O)N(H)-, -O-C(S)N(H)- or -S- or -S-C(O)N(H)-;

D is -($C_1$-$C_5$)alkylene- or -($C_3$-$C_5$)alkenylene-;

$Y^1$ is C=C, carbon or nitrogen, wherein if $Y^1$ is nitrogen, $Z^1$ is absent;

Each of $Y^4$ and $Y^5$ is independently carbon or nitrogen, wherein if $Y^3$ is nitrogen, $Z^3$ is absent and if $Y^4$ is nitrogen, $Z^5$ is absent;

$Y^2$ is C or N;

$Y^5$ is an oxygen, carbon, nitrogen or a sulfur atom, wherein $Z^6$ is absent when $Y^5$ is an oxygen, or a sulfur atom;

Each of $Z^1$, and $Z^2$, where present, are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkyloxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkylthioxy, alkenylthioxy, alkynylthioxy, arylthioxy, aralkylthioxy, amino, hydroxy, thio, halo,

carboxy, formyl, nitro and cyano, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

$Z^3$, $Z^4$, and $Z^5$ are each independently selected from hydrogen, alkyl, deuterated alkyl, $C_{1-6}$alkoxy, deuterated $C_{1-6}$alkoxy, alkenyl, alkynyl, aryl, aralkyl, alkyloxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkylthioxy, alkenylthioxy, alkynylthioxy, arylthioxy, aralkylthioxy, amino, hydroxy, thio, halo, carboxy, formyl, nitro and cyano, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

provided that at least one of $Z^1$, $Z^2$ or $Z^4$ is H;

$Z^6$ is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl and aralkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl moiety is independently optionally substituted with 1-3 halo;

Each $Z^8$ is independently hydrogen, unsubstituted $C_1$-$C_6$ alkyl, substituted $C_1$-$C_6$ alkyl, unsubstituted $C_1$-$C_6$ alkoxy, unsubstituted deuterated $C_1$-$C_6$ alkoxy, substituted $C_1$-$C_6$ alkoxy, and substituted deuterated $C_1$-$C_6$ alkoxy where the substituted alkyl, alkoxy and deuterated alkoxy are substituted with one or more groups selected from amino, mono- or di-substituted amino, cyclic $C_1$-$C_5$ alkylamino, imidazolyl, $C_1$-$C_6$ alkylpiperazinyl, morpholino, thiol, thioether, tetrazole, carboxylic acid, ester, amido, mono- or di-substituted amido, N-connected amide, N-connected sulfonamide, sulfoxy, sulfonate, sulfonyl, sulfoxy, sulfinate, sufinyl, phosphonooxy, phosphate or sulfonamide, wherein each alkyl, alkenyl, alkynyl, alkoxy, and aryl is optionally substituted with 1-3 halo; and

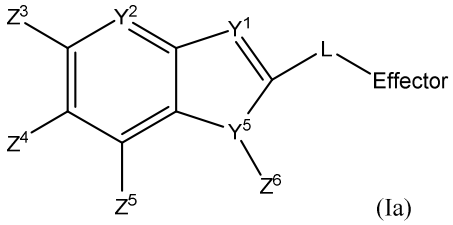
Effector is part of a (i) phosphoramidate derivative of gemcitabine, (ii) a salt form of a phosphoramidate derivative of gemcitabine, or (iii) a phosphorodiamidate derivative of gemcitabine.

2. The compound, of claim 1, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein $Y^3$ and $Y^4$ are each carbon.

3. The compound according to any of the above claims, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein $Z^3$, $Z^4$ and $Z^5$ are each selected from halo, unsubstituted $C_1$-$C_3$ alkyl, substituted $C_1$-$C_3$ alkyl, unsubstituted $C_1$-$C_3$ alkoxy, substituted $C_1$-$C_3$ alkoxy, unsubstituted deuterated $C_1$-$C_3$ alkoxy, or substituted $C_1$-$C_3$ alkoxy, wherein each alkyl and alkoxy moiety can be independently substituted with 1-3 halo.

4. The compound according to any of the above claims, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein $Z^3$, $Z^4$ and $Z^5$ are each selected from bromo, chloro, fluro, methyl, deuterated methyl optionally substituted with 1-3 halo, methoxy optionally substituted with 1-3 halo, or deuterated methoxy.

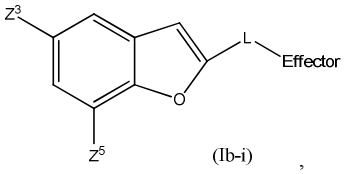
5. The compound according to any of the above claims having formula (Ia):



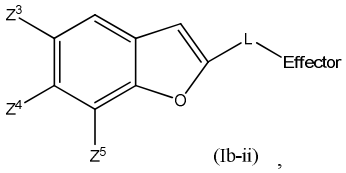
(Ia) .

or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein L, $Y^1$, $Y^2$, $Y^5$, $Z^3$, $Z^4$ , $Z^5$, and $Z^6$ are each as defined in any one of claims 1-4, and Effector is part of a (i) a phosphoric acid derivative of gemcitabine, or (ii) a salt form of a phosphoric acid derivative of gemcitabine.

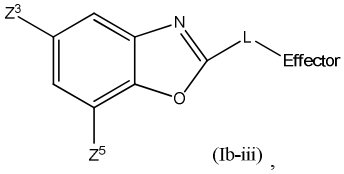
6. The compound according to any of the above claims having formulae (Ib-i), (Ib-ii), (Ib-iii), (Ib-iv), (Ib-v), (Ib-vi), (Ib-vii), (Ib-viii), (Ib-ix), (Ib-x), (Ib-xi), (Ib-xii), (Ib-xiii), (Ib-xiv), (Ib-xv), (Ib-xvi), (Ib-xvii), or (Ib-xviii):



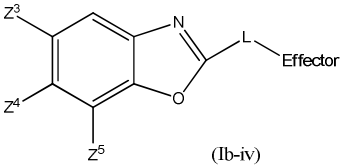
(Ib-i) ,



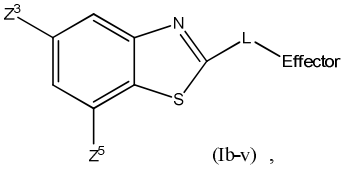
(Ib-ii) ,



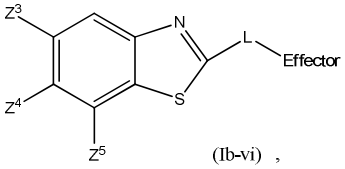
(Ib-iii) ,



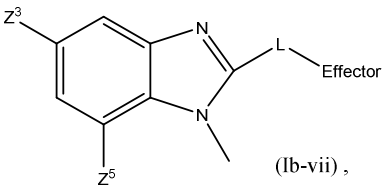
(Ib-iv) ,



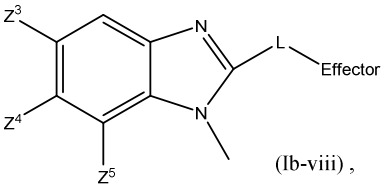
(Ib-v) ,



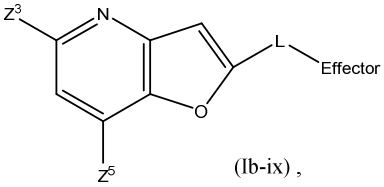
(Ib-vi) ,



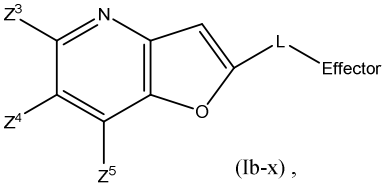

(Ib-vii) ,



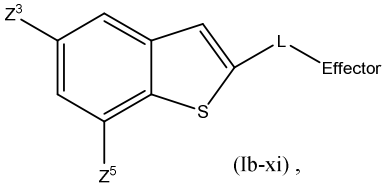

(Ib-viii) ,



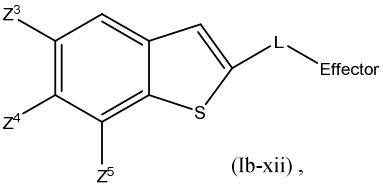

(Ib-ix) ,



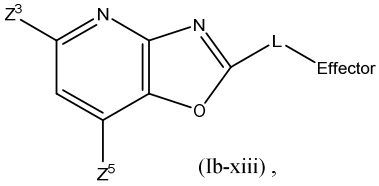

(Ib-x) ,



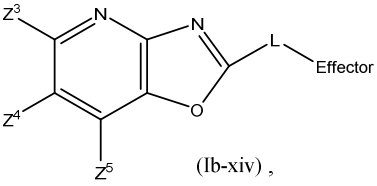

(Ib-xi) ,



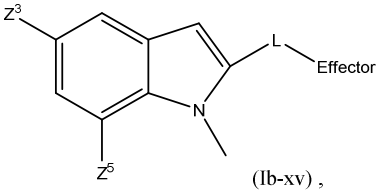

(Ib-xii) ,



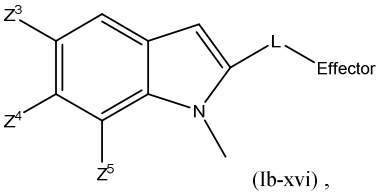

(Ib-xiii) ,



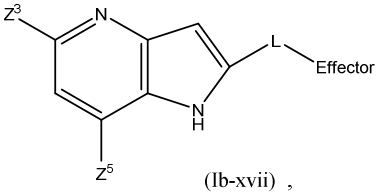

(Ib-xiv) ,



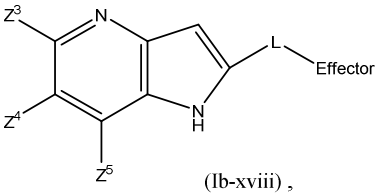

(Ib-xv) ,




(Ib-xvi) ,




(Ib-xvii) ,



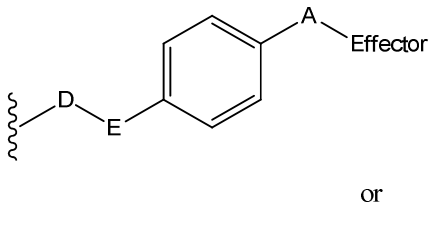

(Ib-xviii) ,

or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer of any of the above formulae, wherein:

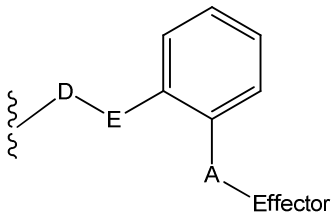
$Z^3$ and $Z^5$ are each independently halo, methyl optionally substituted with 1-3 halo, methoxy optionally substituted with 1-3 halo or deuterated methoxy;

$Z^4$, when present, is halo, methyl optionally substituted with 1-3 halo, methoxy optionally substituted with 1-3 halo or deuterated methoxy;

-L-Effector is: -($C_1$-$C_3$)alkylene-O-C(O)-Effector,




or



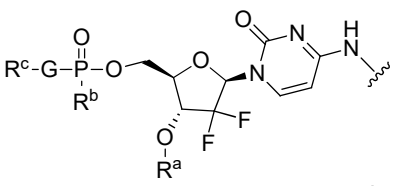

D is -($C_1$-$C_3$)alkylene-;

E is -O-, -O-C(O)N(H)-, -O-C(S)N(H)-, -S- or -S-C(O)N(H)-;

A is -($C_1$-$C_3$)alkylene-O-C(O)-; and

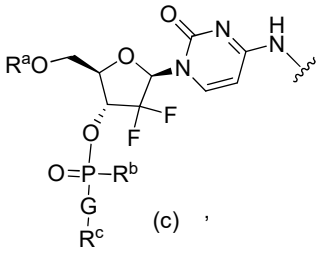
Effector is part of a (i) phosphoramidate derivative of gemcitabine, (ii) a salt form of a phosphoramidate derivative of gemcitabine or (iii) a phosphordiamidate derivative of gemcitabine.

7. The compound according to any of the above claims, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein the -Effector is of formulae (b), (c), (d) or (e):

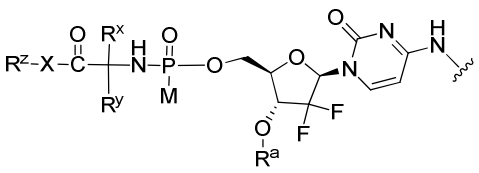


(b)

,

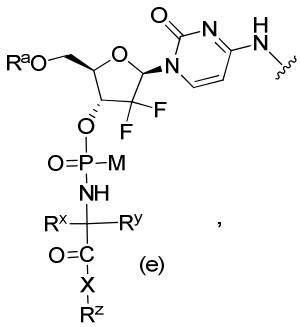


(c) ,



(d)

or



(e) ,

wherein:

G is -N(H)- or -O-;

M is -OH, -O-aryl, -O-($C_1$-$C_5$)alkyl-heterocycloalkyl, -$O^-$ Na+, -$O^-$ $Et_3NH^+$, -$O^-$ $K^+$ or -$O^-$ $NH_4^+$.

$M^2$ is -$O^-$ Na+, -$O^-$ $Et_3NH^+$, -$O^-$ $K^+$, -$O^-$ $NH_4^+$ or N-C($R^xR^y$)C(O)X$R^z$

X is -O- or -N($R^d$)-

$R^a$ is H;

$R^b$ is -O-$R^{b'}$ when G is -N(H)-, wherein $R^{b'}$ is aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkyl, cycloalkyl, alkoxyalkyl, acyloxyalkyl, alkylthioalkyl, alkylthiocarbonylalkyl, -alkyl-C(=O)-O-$R^d$, -alkyl-O-C(=O)-$R^d$, or -alkyl-C($R^e$)$R^f$, wherein any of the alkyl, heteroaryl or aryl portions of $R^b$ can be substituted with halo, alkyl, or alkoxy;

or $R^b$ is $M^2$ when G is -O-;

$R^c$ is aryl, -C(O)-aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkyl, cycloalkyl, alkoxyalkyl, acyloxyalkyl, alkylthioalkyl, alkylthiocarbonylalkyl, -alkyl-C(=O)-O-$R^d$, -alkyl-O-C(=O)-$R^d$, or -alkyl-C($R^e$)$R^f$, wherein any of the alkyl, heteroaryl or aryl portions of $R^c$ can be substituted with halo, alkyl, or alkoxy, wherein any of the alkyl, heteroaryl or aryl portions of $R^c$ can be substituted with halo, alkyl, or alkoxy;

$R^d$ is H or alkyl;

$R^e$ is -alkylthio-($C_1$-$C_{25}$)alkyl or -alkyloxy-($C_1$-$C_{25}$)alkyl;

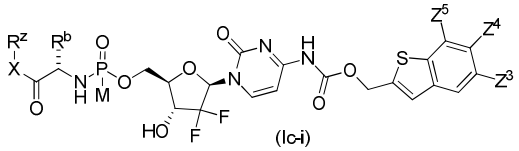
$R^f$ is -alkylthio-($C_1$-$C_{25}$)alkyl or -alkyloxy-($C_1$-$C_{25}$)alkyl;

$R^x$ and $R^y$ are each independently H, or alkyl optionally substituted with heterocycloalkyl, or alxoxyaryl, or $R^x$ and $R^y$, together with the carbon atom to which they are attached, form a cycloalkyl, aryl, or heteroaryl group; and

$R^z$ is -($C_1$-$C_6$)alkyl optionally substituted with heterocycloalkyl or aryl.

8. The compound according to any of the above claims, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein the linker region (L) is -$C(H)_2$-O-C(O)-.

9. The compound according to claim 1 having formulae(Ic-i), (Ic-ii), (Ic-iii), (Ic-iv), (Ic-v), (Ic-vi), (Ic-vii), (Ic-viii), (Ic-ix), (Ic-x), (Ic-xi), (Ic-xii), (Ic-xiii), (Ic-xiv), (Ic-xv), (Ic-xvi), (Ic-xvii), (Ic-xviii), (Ic-xix), or (Ic-xx):



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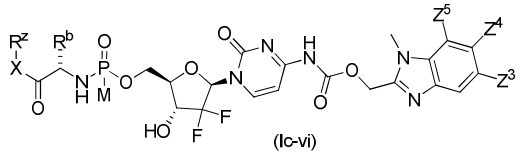
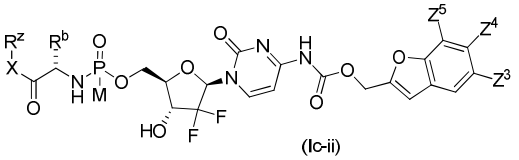
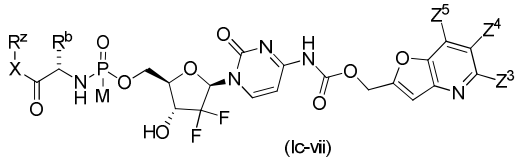


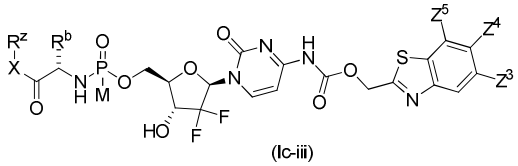
(Ic-vi),



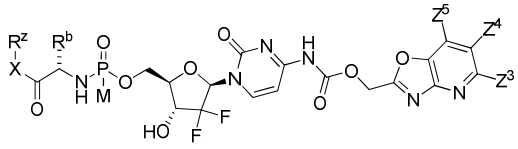
(Ic-ii),



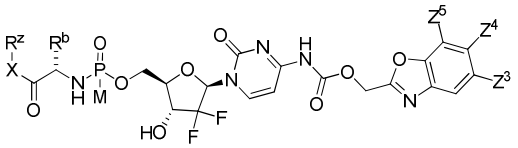
(Ic-vii),



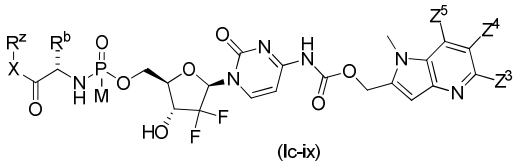
(Ic-iii),



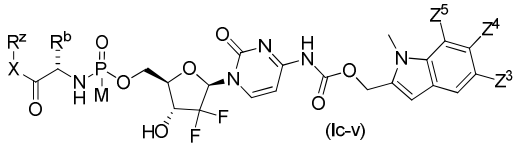
(Ic-viii),



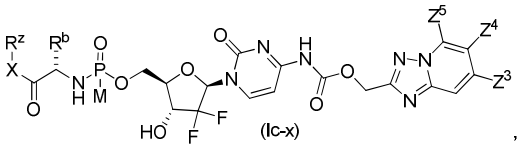
(Ic-iv),



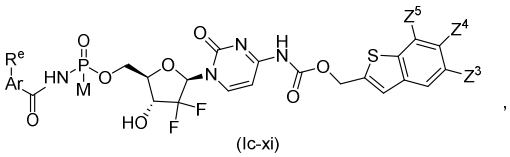
(Ic-ix),



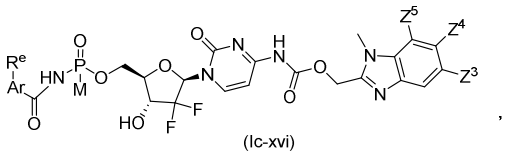
(Ic-v),



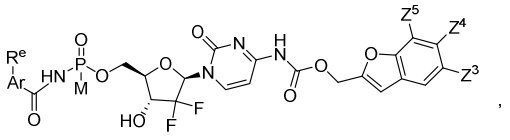
(Ic-x),



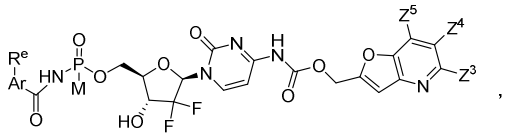
(Ic-xi)



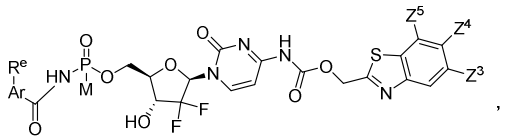
(Ic-xvi)



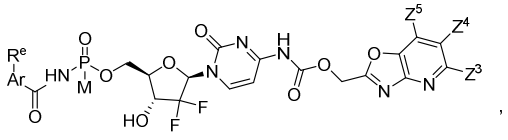
(Ic-xii)



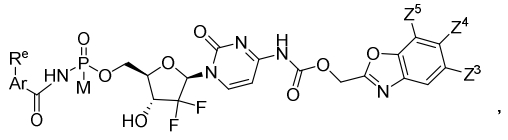
(Ic-xvii)



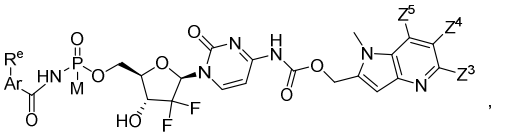
(Ic-xiii)



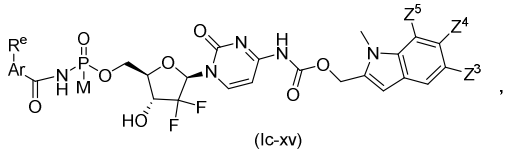
(Ic-xviii)



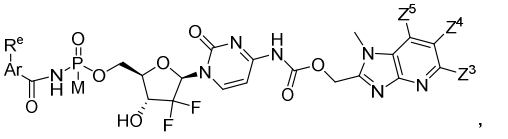
(Ic-xiv)



(Ic-xix)



(Ic-xv)



(Ic-xx)

or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer of anyof the above formulae, wherein:

$Z^3$, $Z^4$, and $Z^5$ are each independently methyl optionally substituted with 1-3 halo, halo, methoxy optionally substituted with 1-3 halo or deuterated methoxy;

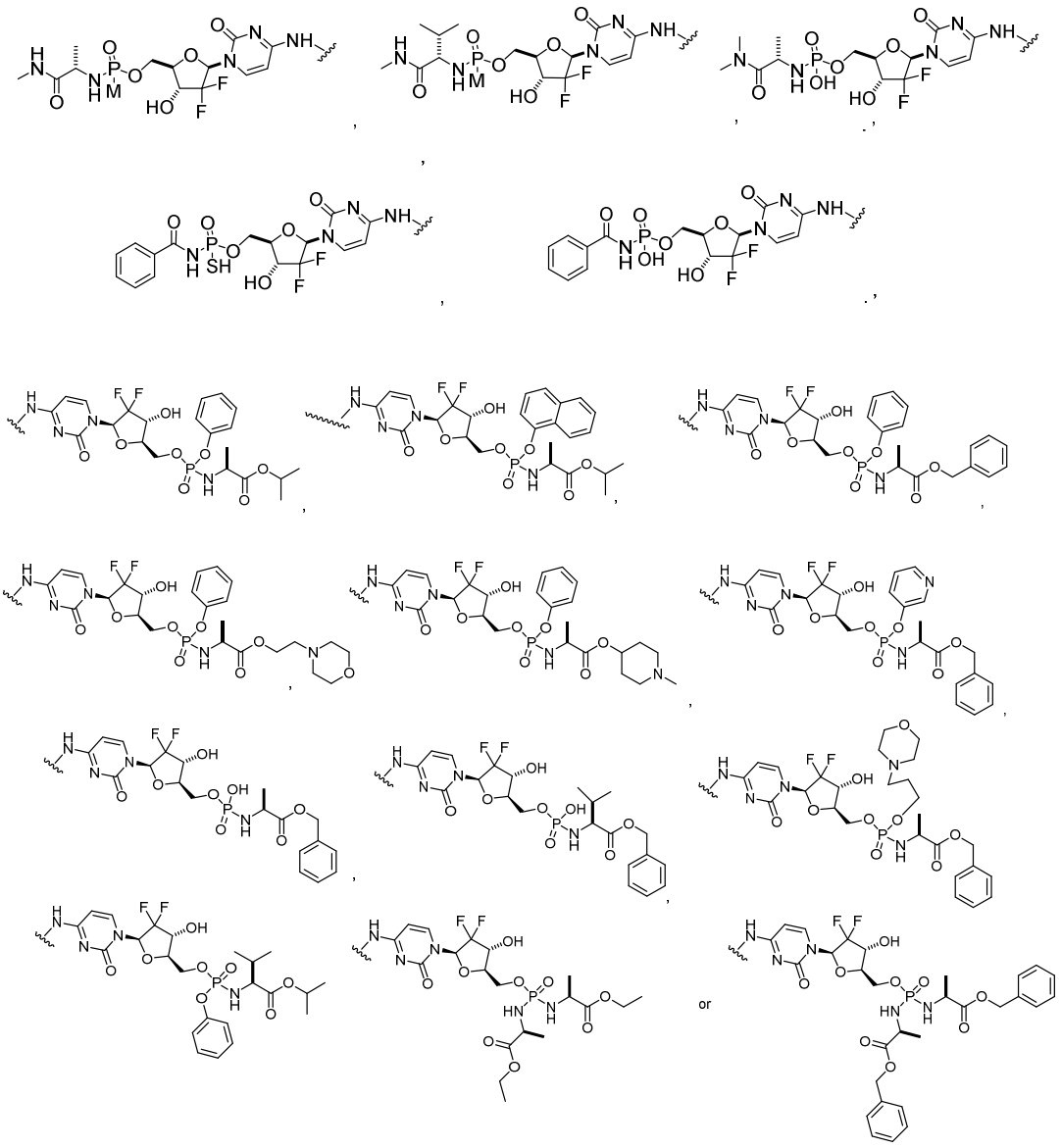
$R^b$ is -($C_1$-$C_5$)alkyl optionally substituted with heterocycloalkyl, or alxoxyaryl;

$R^e$ is H, halo, alkyl, -($C_1$-$C_5$)alkyl or -($C_1$-$C_5$)alkoxy;

$R^z$ is -($C_1$-$C_5$)alkyl optionally substituted with heterocycloalkyl or aryl; and

M is -OH, -O-aryl, -O-($C_1$-$C_5$)alkyl-heterocycloalkyl, $-O^-$ Na+, $-O^-$ $Et_3NH^+$, $-O^-$ $K^+$ or $-O^-$ $NH_4^+$.

10. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein -Effector has one of the following structures:



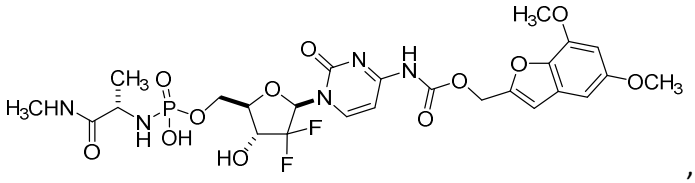
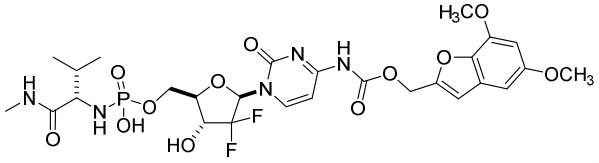
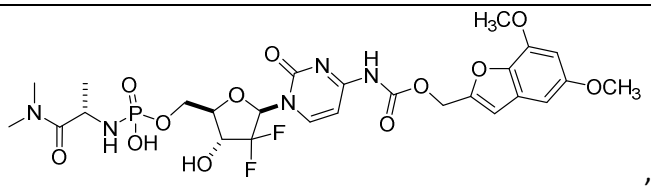
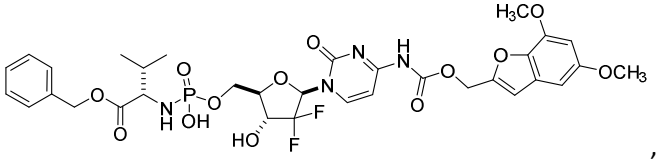
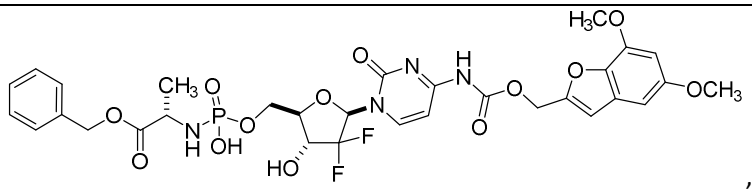
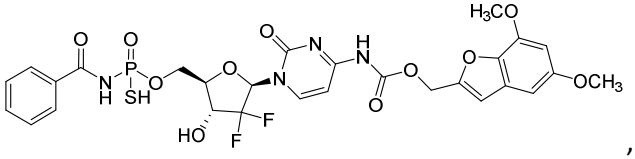
wherein M is -O-($C_1$-$C_3$)alkyl -N-morpholino, -Oaryl, -$O^-$ Na+, -$O^-$ $Et_3NH^+$, -$O^-$ $K^+$ or -$O^-$ $NH_4^+$.

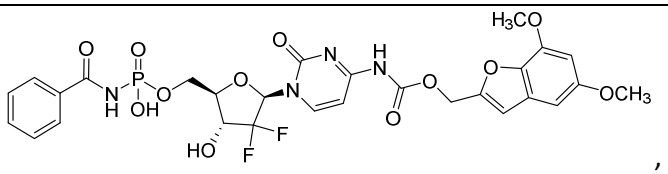
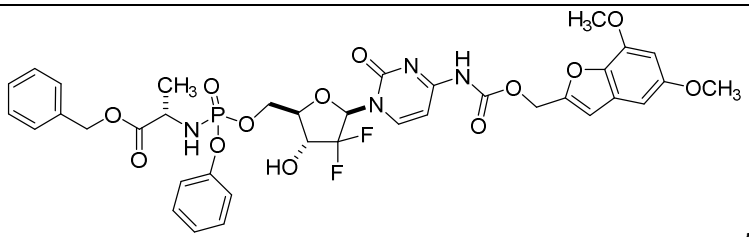
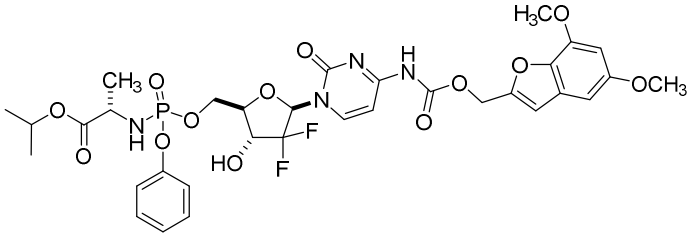
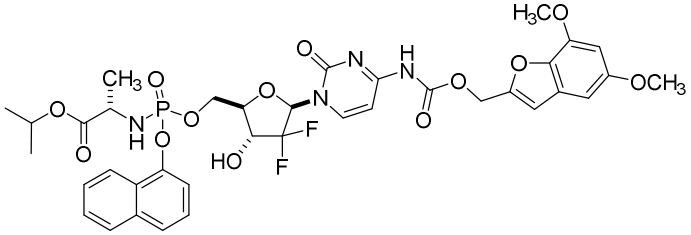
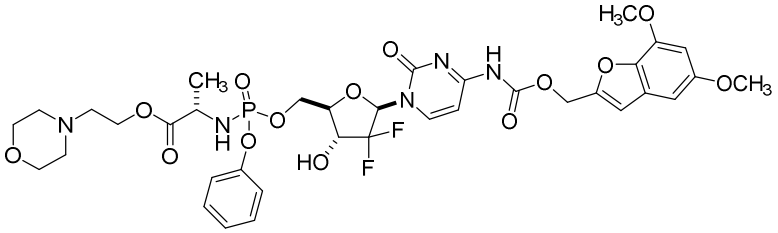
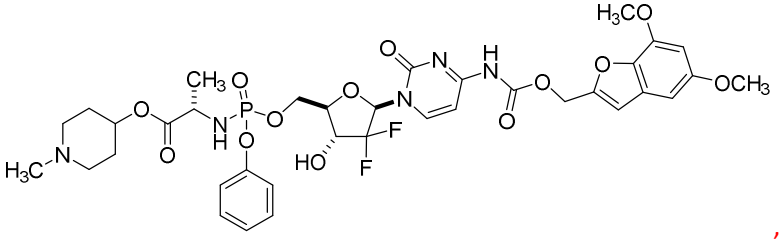
11. The compound according claim 10, wherein M is -O-$(CH_2)_3$-N-morpholino, -Oaryl, -$O^-$ Na+, -$O^-$ $Et_3NH^+$, -$O^-$ $K^+$ or -$O^-$ $NH_4^+$.

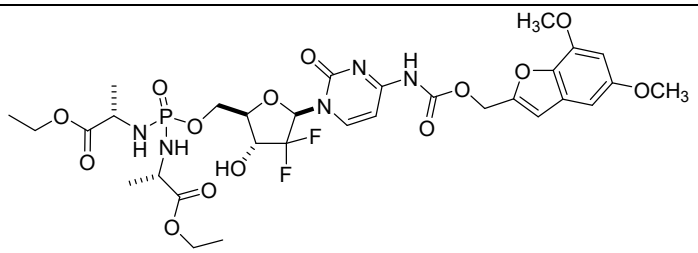
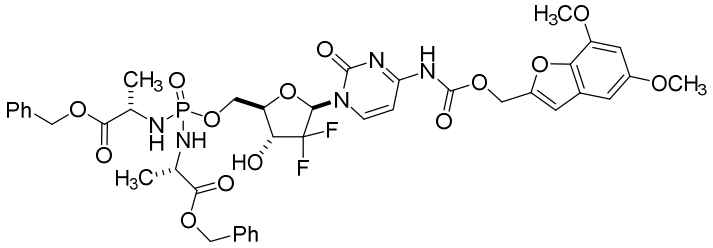
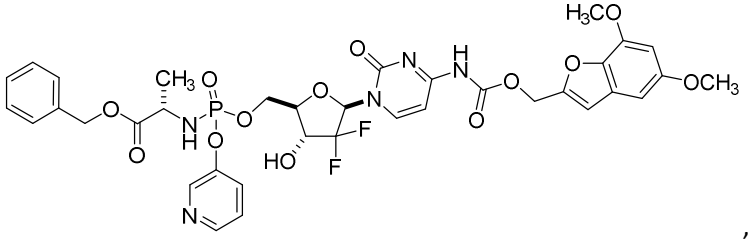
12. The compound according to any of the above claims, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein $Z^3$, $Z^5$ and $Z^4$, when present, are each methoxy optionally substituted with 1-3 halo or deuterated methoxy.

13. The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer thereof, wherein $Z^3$ and $Z^5$ are each independently bromo or fluoro, and $Z^4$, when present, is methoxy optionally substituted with 1-3 halo, or deuterated methoxy.

14. The compound according to claim 1 having one of the following structures:

| **Compound #** | **Structure** |
|---|---|
| 1 |  , |
| 2 |  , |
| 3 |  , |
| 4 |  , |
| 5 |  , |
| 6 |  , |

| | |
|---|---|
| 7 |  , |
| 8 |  , |
| 9 |  , |
| 10 |  , |
| 11 |  , |
| 12 |  , |

| | |
|---|---|
| 13 |  |
| 14 |  |
| 15 |  , |

or a pharmaceutically acceptable salt, ester, amide, solvate, or stereoisomer of any one of compounds 1-15.

15. A composition comprising a compound according to any of the above claims, together with a pharmaceutically acceptable carrier, or pharmaceutically acceptable salt, ester, amide or solvate of a compound according to any of the above claims, together with a pharmaceutically acceptable carrier thereof.

16. A compound, or pharmaceutically acceptable salt, ester, amide or solvate, as defined in any one of claims 1 to 14, for use in medicine.

17. A compound, or pharmaceutically acceptable salt, ester, amide or solvate, as defined in any one of claims 1 to 14, for use in treatment or prophylaxis of a proliferative condition.

18. The compound, or pharmaceutically acceptable salt, ester, amide or solvate, for use in the treatment or prophylaxis of claim 17, wherein the proliferative condition is a cancer selected from bladder, brain, breast, colon, head and neck, kidney, lung, liver, ovarian, pancreatic, prostate or skin cancer.

19. Use of a compound, or pharmaceutically acceptable salt, ester, amide or solvate, as defined in any one of claims 1 to 14, for the preparation of a medicament for treatment or prophylaxis of a proliferative condition.

20. A method of diagnosis of a patient for the presence of tumor cells expressing the CYP1B1 enzyme comprising (a) determining the amount of corresponding hydroxylated metabolite which is produced subsequent to administration of a specific compound according to any of claims 1-14; and, (b) correlating the amount with the presence or absence of the tumor cells in the patient.

21. Use of a therapeutically or prophylactically useful amount of a compound according to any of claims 1-14, or pharmaceutically acceptable salt, ester, amide or solvate thereof, for the preparation of a medicament for treating the patient, the use comprising (1) identifying the presence of a tumor in a patient; and (2) treating the patient, identified as needing the treatment.