TITLE OF THE INVENTION

EXATECAN-DERIVED TOPOISOMERASE-1 INHIBITORS PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF

BACKGROUND OF THE INVENTION

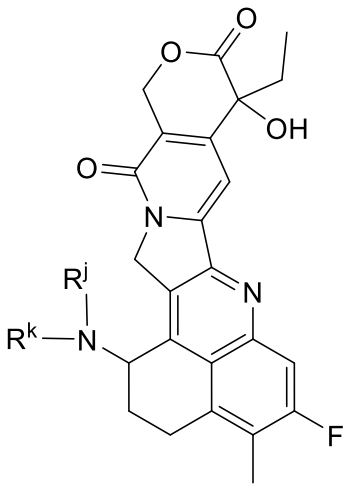
[0001] The present disclosure relates to topoisomerase-1 inhibitors derived from the exatecan scaffold, which can be used for oncologic therapies. The topoisomerase-1 inhibitors are cytotoxic chemotherapeutic derivatives with a camptothecin core. Documents reporting the use of the camptothecin derivative, exatecan (chemical name: (1S, 9S)-l-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4- methyl-lH,12H-benzo[de]pyrano[3',4,:6,7]imidazo[l,2-b] quinoline-10,13(9H,15H)-dione) are disclosed in WO2014057687, US11103593, US9808537, US7091186, US 2010/0062008, WO2015057699, Clinical Cancer Research (2016) 22 (20): 5097-5108, and *Cancer Sci* (2016) 107: 1039-1046. See also WO2022068878, WO2017062271, CN113816969, CN112125915, and US20210353764.

SUMMARY

[0002] The compounds of this disclosure represent a class of topoisomerase-1 inhibitors derived from the exatecan scaffold. Specifically, the compounds are described as alcohol and amine containing exatecan amides, and analogs therein. The compounds are cytotoxic and can be applied as chemotherapeutic drugs in oncologic settings, for example as an anti-tumor agent. The compounds are potent, novel in structure, active across multiple cancer cell lines.

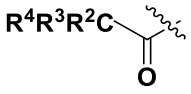
[0003] For each of the following examples, any variable not explicitly defined in the example is as defined in Formula (I). In each of the examples described herein, each variable is selected independently of the other unless otherwise noted.

[0004] In one example, the present disclosure provides alcohol and amine containing exatecan derivatives, and pharmaceutically acceptable salts, solvates, or steroisomer thereof, comprising a structure of formula I:



I

wherein:

R^k is selected from hydrogen, -C_{1-6} alkyl, $(CH_2)_nC(O)NHC_{1-6}$ alkyl, $(CH_2)_nC_{6-10}$ aryl and  , said alkyl and aryl optionally substituted with 1 to 3 groups of hydroxyl, -C_{1-6} alkylOH, and said alkyl optionally substituted with 1 to 10 groups of halogen;

R^j represents hydrogen or C_{1-6} alkyl, said alkyl optionally substituted with 1 to 10 halogen;

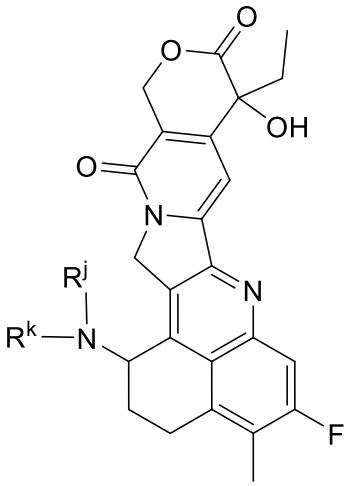
R^2 and R^3 are independently selected from hydrogen, -C_{1-6} alkyl, OH, -C_{1-6} alkylOH, halogen, -C_{1-9}haloalkyl, -$(CH_2)_nNH_2$, -NHC_{1-6}alkyl, -$N(C_{1-6}$ alkyl$)_2$, -C_{3-6} cycloalkyl, -$(CH_2)_nC_{6-10}$aryl,and -(CH_2)nOC_{1-6}alkyl, that R^2 and R^3 are not both halogen at the same time;

R^4 is selected from C_{1-6} alkyl, OH, –C_{1-6} alkylOH, -CH(OH)C_{1-6} alkyl, -C_{1-9}haloalkyl, halogen, -C_{3-6}cycloalkyl, -$(CH_2)_nOC_{1-3}$alkyl, -$(CH_2)_nOC_{1-9}$haloalkyl, -$CR^xR^yC_{1-6}$ alkylOH, -$(CH_2)_nNH_2$, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, and -$NHC(O)C_{1-6}$alkylNH_2;

R^x and R^y represent C_{1-3} alkylene that combine to form a C_{3-6}cycloalkyl, or spirocycloalkyl;

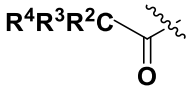
each n independently represents 0, 1, 2, or 3.

[0004a] In one aspect, there is provided a compound having a structural Formula I, or a pharmaceutically acceptable salt or solvate thereof:



I

wherein:

R^k is selected from hydrogen, -C_{1-6} alkyl, $(CH_2)_nC(O)NHC_{1-6}$ alkyl, $(CH_2)_nC_{6-10}$ aryl and , said alkyl and aryl optionally substituted with 1 to 3 groups of hydroxyl, -C_{1-6} alkylOH, said alkyl further optionally substituted with 1 to 10 groups of halogen;

R^j represents hydrogen or C_{1-6} alkyl, said alkyl optionally substituted with 1 to 10 halogen;

R^2 and R^3 are independently selected from hydrogen, -C_{1-6} alkyl, OH, -C_{1-6} alkylOH, halogen, -C_{1-9}haloalkyl, -$(CH_2)_nNH_2$, -NHC_{1-6}alkyl, -$N(C_{1-6}$ alkyl$)_2$, -C_{3-6} cycloalkyl, -$(CH_2)_nC_{6-10}$aryl,and -(CH_2)nOC_{1-6}alkyl, provided that R^2 and R^3 are not both halogen at the same time;

R^4 is selected from C_{1-6} alkyl, OH, –C_{1-6} alkylOH, -$CH(OH)C_{1-6}$ alkyl, -C_{1-9}haloalkyl, halogen, -C_{3-6}cycloalkyl, -$(CH_2)_nOC_{1-3}$alkyl, -$(CH_2)_nOC_{1-9}$haloalkyl, -$CR^xR^yC_{1-6}$ alkylOH, -$(CH_2)_nNH_2$, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, and -$NHC(O)C_{1-6}$alkylNH_2;

wherein any hydrogen atom in an alkyl of R^2, R^3 and/or R^4 is not deuterated,

R^x and R^y represent C_{1-3} alkylene that combine to form a C_{3-6}cycloalkyl, or spirocycloalkyl;

each n independently represents 0, 1, 2, or 3;
provided that:

R^j and R^k, or R^2 and R^3 are not hydrogen at the same time;

R^j is not C_{1-6} alkyl when R^k is $(CH_2)_n$phenyl;

R^k is not C_{1-6} alkyl when R^j is hydrogen;

when one of R^2 and R^3 is hydrogen the other is not C_{1-6} alkyl; and

at least one of R^2 and R^3 is hydrogen.

[0005] An example of the disclosure is realized when R^j is hydrogen.

[0006] Another example of the disclosure is realized when R^j is C_{1-6} alkyl, said alkyl optionally substituted with 1 to 5 groups of halogen. A sub-example of this example of the

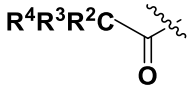
disclosure is realized when R^j is C_{1-6} alkyl substituted with 1 to 4 halogen.

[0007] An example of this disclosure is realized when R^k is hydrogen.

[0008] Another example of this disclosure is realized when R^k is -C_{1-6} alkyl, said alkyl optionally substituted to 1 to 10 halogen, or 1 to 3 groups selected from hydroxyl and -C_{1-6} alkylOH.

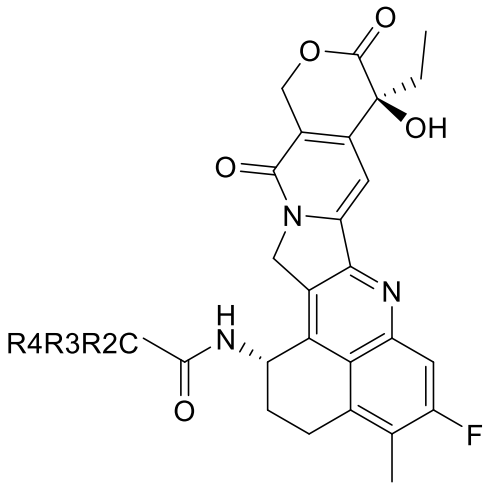
[0009] Another example of this disclosure is realized when R^k is $(CH_2)_nC(O)NHC_{1-6}$ alkyl, said alkyl optionally substituted to 1 to 10 halogen, or 1 to 3 groups selected from hydroxyl, and -C_{1-6} alkylOH.

[0010] Another example of this disclosure is realized when R^k is $(CH_2)_nC_{6-10}$ aryl, said aryl optinally substituted with 1 to 3 groups selected from hydroxyl, and -C_{1-6} alkylOH.

[0011] Another example of this disclosure is realized when R^k is 

, wherein R^2, R^3 and R^4 are as described herein.

[0012] An example of this disclosure is realized by Formula I', or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof represented by structural formula:



I'.

[0013] An example of this disclosure is realized when no hydrogen atom in an alkyl containing substituent of R^2, R^3 and R^4 is deuterated.

[0014] Another example of this disclosure is realized when at least one hydrogen atom in an alkyl containing substituent of R^2, R^3 and R^4 is deuterated.

[0015] Another example of this disclosure is realized when n is 0. Another example of this disclosure is realized when n is 1. Another example of this disclosure is realized when n is 2. Still another example of this disclosure is realized when n is 3.

[0016] Another example of this disclosure is realized when R^x and R^y combine with the atoms to which they are attached to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

[0017] Another example of this disclosure is realized when R^2 is selected from hydrogen, C_{1-6} alkyl, CH_2OC_{1-6}alkyl, -$(CH_2)_nOH$, -CH_2F, -CHF_2, -CF_3, -(CH_2)phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)nNH_2$, -$NHCH_3$, and -$N(CH_3)_2$. A sub-example of this example of the disclosure is realized when R^2 is selected from hydrogen, C_{1-6} alkyl, CH_2OCH_3, -OH, -CH_2OH, -CH_2F, -CHF_2, -CF_3, and -NH_2. Another sub-example of this example of the disclosure is realized when R^2 is hydrogen. Another sub-example of this example of the disclosure is realized when R^2 is C_{1-6} alkyl selected from -CH_3, -CH_2CH_3, and -$CH_2CH(CH_3)_2$. Another sub-example of this example of the disclosure is realized when R^2 is $(CH_2)_nOCH_3$. Another sub-example of this example of the disclosure is realized when R^2 is -OH or -CH_2OH. Another sub-example of this example of the disclosure is realized when R^2 is -CH_2F, -CHF_2, or -CF_3. Still another sub-example of this example of the disclosure is realized when R^2 is NH_2. Another sub-example of this example of the disclosure is realized when any hydrogen atom in an alkyl containing substituent of R^2 is not deuterated.

[0018] Another example of this disclosure is realized when R^3 is selected from hydrogen, C_{1-6} alkyl, CH_2OC_{1-6}alkyl, -$(CH_2)_nOH$, -CH_2F, -CHF_2, -CF_3, -(CH_2)phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)nNH_2$, -$NHCH_3$, and -$N(CH_3)_2$. A sub-example of this example of the disclosure is realized when R^3 is selected from hydrogen, C_{1-6} alkyl, CH_2OCH_3, -OH, -CH_2OH, -CH_2F, -CHF_2, -CF_3, and -NH_2. Another sub-example of this example of the disclosure is realized when R^3 is hydrogen. Another sub-example of this example of the disclosure is realized when R^3 is C_{1-6} alkyl selected from -CH_3, -CH_2CH_3, and -$CH_2CH(CH_3)_2$. Another sub-example of this example of the disclosure is realized when R^3 is -CH_2OCH_3. Another sub-example of this example of the disclosure is realized when R^3 is -OH or -CH_2OH. Another sub-example of this example of the disclosure is realized when R^3 is -CH_2F, -CHF_2, or -CF_3. Still another sub-example of this example of the disclosure is realized when R^3 is NH_2. Another sub-example of this example of the disclosure is realized when any hydrogen atom in an alkyl containing substituent of R^3 is not deuterated.

[0019] Another example of this disclosure is realized when both R^2 and R^3 are hydrogen.

[0020] Still another example of the disclosure is realized when at least one of R^2 and R^3 is -OH, or $-(CH_2)_nOH$ where n is not 0. An example of this disclosure is realized when one of R^2 and R^3 is -OH or $-(CH_2)_nOH$, where n is not 0. Another example of this disclosure is realized when one

of R^2 and R^3 is -OH and the other is not. Yet another example of this disclosure is realized when one of R^2 and R^3 is -OH and the other is selected from hydrogen and $C_{1\text{-}6}$alkyl. Still another example of this disclosure is realized when one of R^2 and R^3 is $-CH_2OH$ and the other is not. Yet another example of this disclosure is realized when one of R^2 and R^3 is $-CH_2OH$ and the other is selected from hydrogen and $C_{1\text{-}6}$alkyl. Still another example of this disclosure is realized when one or the other of R^2 and R^3 contains a $C_{1\text{-}6}$alkyl and no hydrogen in said alkyl is deuterated.

[0021] Another example of the disclosure is realized when at least one of R^2 and R^3 is $-(CH_2)_nNH_2$, $-NHCH_3$, or $-N(CH_3)_2$. An example of the disclosure is realized when at least one of R^2 and R^3 is $(CH_2)_nNH_2$. Still another example is realized when one of R^2 and R^3 is NH_2 and the other is not. Yet another example of this disclosure is realized when one of R^2 and R^3 is NH_2 and the other is selected from hydrogen, CH_2phenyl and $C_{1\text{-}6}$alkyl. Another example is realized when one of R^2 and R^3 is CH_2NH_2 and the other is not. Yet another example of this disclosure is realized when one of R^2 and R^3 is CH_2NH_2 and the other is selected from hydrogen, CH_2phenyl and $C_{1\text{-}6}$alkyl. Still another example of this disclosure is realized when one or the other of R^2 and R^3 contains $C_{1\text{-}6}$alkyl and no hydrogen in said alkyl is deuterated.

[0022] Another example of the disclosure is realized when R^4 is selected from $C_{1\text{-}6}$ alkyl, $-C_{1\text{-}6}$ alkylOH, OH, $-CH(OH)C_{1\text{-}6}$ alkyl, $-(CH_2)_nOC_{1\text{-}3}$alkyl, $-C_{3\text{-}6}$cycloalkyl, $-C_{1\text{-}9}$haloalkyl, $-(CH_2)_nOC_{1\text{-}9}$haloalkyl, halogen, $-CR^xR^yC_{1\text{-}6}$ alkylOH, $-(CH_2)_nNH_2$, $-NHC_{1\text{-}6}$ alkyl, $-N(C_{1\text{-}6}$ alkyl$)_2$, and $-NHC(O)C_{1\text{-}6}$alkylNH_2. An example of the disclosure is realized when R^4 is selected from $C_{1\text{-}6}$ alkyl, $-(CH_2)_nOH$, $-CH(CH_3)OH$, $-CH_2F$, $-CHF_2$, $-CF_3$, fluorine, $(CH_2)nOCHF_2$, cyclopropyl, $-(CH_2)_nNH_2$, -spirocyclopropylCH_2OH, and $-NHC(O)CH(CH_3)NH_2$. Another example of this disclosure is realized when R^4 is selected from CH_3, $-(CH_2)_nOH$ or $-CH(CH_3)OH$. Another example of the disclosure is realized when R^4 is $-CH_3$. Another example of the disclosure is realized when R^4 is $-(CH_2)_nOH$. Another example of the disclosure is realized when R^4 is $-(CH_2)_2OH$ or $-CH_2OH$. Another example of the disclosure is realized when R^4 is $-(CH_2)_2OH$. Another example of the disclosure is realized when R^4 is $-CH_2OH$. Another example of the disclosure is realized when R^4 is $-CH(CH_3)OH$. Another example of the disclosure is realized when R^4 is $-CH_2F$, $-CHF_2$, or $-CF_3$. Another example of the disclosure is realized when R^4 is $-(CH_2)_nNH_2$. Another example of the disclosure is realized when R^4 is NH_2. Another example of the disclosure is realized when R^4 is $NHC(O)CH(CH_3)NH_2$. Another example of the disclosure is realized when R^4 is $-CR^xR^yC_{1\text{-}6}$ alkylOH, wherein R^x and R^y are

alkylene substituents that combine to form cyclopropyl or spirocyclopropyl. Another example of the disclosure is realized when R^4 is -spirocyclopropylCH_2OH. Another example of the disclosure is realized when R^4 is –(CH_2)n$OCHF_2$ or CHF_2. Still another example of this disclosure is realized when R^4 contains an C_{1-6}alkyl and no hydrogen in said alkyl is deuterated.

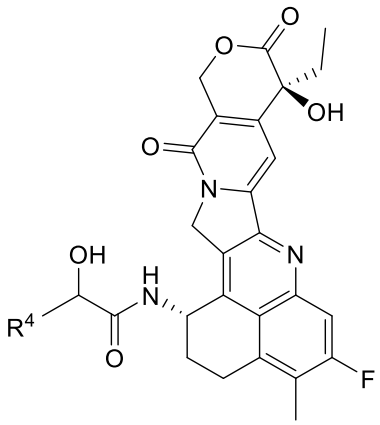
[0023] Another example of the disclosure is realized when one of R^2 and R^3 is -OH or -$(CH_2)_n$OH, where n is not 0, and R^4 is selected from C_{1-6} alkyl, –C_{1-6} alkylOH, -$(CH_2)_n$$OC_{1-3}$alkyl, -CH(OH)$C_{1-6}$ alkyl, -C_{3-6}cycloalkyl, -C_{1-9}haloalkyl, -$(CH_2)_n$$OC_{1-9}$haloalkyl, halogen, -$CR^xR^yC_{1-6}$ alkylOH, -$(CH_2)_nNH_2$, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, and -NHC(O)C_{1-6}alkylNH_2. Yet another example of this disclosure is realized when one of R^2 and R^3 is -OH or -CH_2OH, the other is selected from hydrogen and C_{1-6}alkyl and R^4 is selected from CH_3, -$(CH_2)_n$OH, -$CH(CH_3)OH$, -CH_2F, -CHF_2, -CF_3, fluorine, (CH_2)n$OCHF_2$, cyclopropyl, -$(CH_2)_nNH_2$, and -spirocyclopropylCH_2OH, -NHC(O)$CH(CH_3)NH_2$. An example of the disclosure is realized when one of R^2 and R^3 is -OH or -$(CH_2)_n$OH, where n is not 0, the other is selected from hydrogen and C_{1-6}alkyl and R^4 is selected from CH_3, –$(CH_2)_2$OH, -CH_2OH, -$CH(CH_3)OH$, -CH_2F, -CHF_2, -CF_3, fluorine, and -$(CH_2)_nNH_2$. Another example of the disclosure is realized when one of R^2 and R^3 is -OH or -$(CH_2)_n$OH where n is not 0, the other is selected from hydrogen and C_{1-6}alkyl and R^4 is selected from CH_3, –$(CH_2)_2$OH, -CH_2OH, and -$(CH_2)_nNH_2$. An example of this disclosure is realized when n is 0, 1, or 2. Still another example of this disclosure is realized when R^2, R^3 and/or R^4 contains an C_{1-6}alkyl and no hydrogen in said alkyl is deuterated.

[0024] Another example of the disclosure is realized when one of R^2 and R^3 is one of R^2 and R^3 is -$(CH_2)_nNH_2$, -$NHCH_3$, or -N$(CH_3)_2$ and the other is selected from hydrogen, CH_2phenyl and C_{1-6}alkyl and R^4 is selected from C_{1-6} alkyl, –C_{1-6} alkylOH, -CH(OH)C_{1-6} alkyl, -$(CH_2)_n$$OC_{1-3}$alkyl, -$C_{3-6}$cycloalkyl, -$C_{1-9}$haloalkyl, -$(CH_2)_n$$OC_{1-9}$haloalkyl, halogen, -$CR^xR^yC_{1-6}$ alkylOH, -$(CH_2)_nNH_2$, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, and -NHC(O)C_{1-6}alkylNH_2. Yet another example of this disclosure is realized when one of R^2 and R^3 is $(CH_2)_nNH_2$, -$NHCH_3$, or -N$(CH_3)_2$ and the other is selected from hydrogen, CH_2phenyl and C_{1-6}alkyl and R^4 is selected from CH_3, -$(CH_2)_n$OH, -$CH(CH_3)OH$, -CH_2F, -CHF_2, -CF_3, fluorine, (CH_2)n$OCHF_2$, cyclopropyl, -$(CH_2)_nNH_2$, and -spirocyclopropylCH_2OH, -NHC(O)$CH(CH_3)NH_2$. An example of the disclosure is realized when one of R^2 and R^3 is $(CH_2)_nNH_2$, -$NHCH_3$, or -N$(CH_3)_2$ and the other is selected from hydrogen, CH_2phenyl and C_{1-6}alkyl and R^4 is selected from CH_3, -$(CH_2)_n$OH, -$CH(CH_3)OH$, -CH_2F, -CHF_2, -CF_3, fluorine, and -$(CH_2)_nNH_2$. Another example

of the disclosure is realized when one of R^2 and R^3 is$(CH_2)_nNH_2$, -$NHCH_3$, or -$N(CH_3)_2$ and the other is selected from hydrogen, CH_2phenyl and C_{1-6}alkyl and R^4 is selected from -$(CH_2)_n$OH, or -$(CH_2)_nNH_2$. An example of this disclosure is realized when R^4 is -$(CH_2)_2$OH. Another example of this disclosure is realized when R^4 is CH_2OH. Another example of this disclosure is realized when R^4 is $(CH_2)_nNH_2$. Still another example of this disclosure is realized when R^2, R^3 and/or R^4 contains an C_{1-6}alkyl and no hydrogen in said alkyl is deuterated.

[0025] Another example of this disclosure is realized when both R^2 and R^3 are hydrogen and R^4 is selected from CH_3, -$(CH_2)_n$OH, -$CH(CH_3)OH$, -CH_2F, -CHF_2, -CF_3, fluorine, (CH_2)n$OCHF_2$, cyclopropyl, -$(CH_2)_nNH_2$, and -spirocyclopropylCH_2OH, -$NHC(O)CH(CH_3)NH_2$.

[0026] Another example of the disclosure of Formula I and Formula I' is represented by structural Formula II:

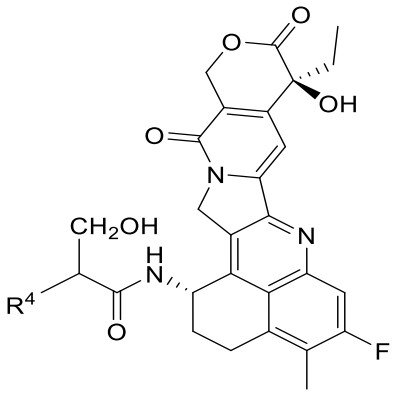


II

or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 is as described herein. A sub-example of the disclosure of Formula II is realized when R^4 is selected from -CH_3, -OH, -CH_2OH, -$(CH_2)_2$OH, -$CH(CH_3)OH$, $(CH_2)_2OCHF_2$, -$C(CH_3)_2CH_2OH$, -CH_2F, -CHF_2, -CF_3, fluorine, and -$(CH_2)_nNH_2$. A sub-example of the disclosure of Formula II is realized when R^4 is –CH_3. A sub-example of the disclosure of Formula II is realized when R^4 is -OH. A sub-example of the disclosure of Formula II is realized when R^4 is -CH_2OH, or -$(CH_2)_2$OH. A sub-example of the disclosure of Formula II is realized when R^4 is -$CH(CH_3)OH$. Another sub-example of the disclosure of Formula II is realized when R^4 is $(CH_2)_2OCHF_2$. Another sub-example of the disclosure of Formula II is realized when R^4 is -$C(CH_3)_2CH_2OH$. Another sub-example of the disclosure of Formula II is realized when R^4 is -CH_2F, -CHF_2, or -CF_3. A sub-example of the disclosure of Formula II is realized when R^4 is fluorine. A sub-example of the disclosure of Formula II is realized when R^4 is -$(CH_2)_nNH_2$. Another

sub-example of the disclosure of Formula II is realized when R^4 contains an $C_{1\text{-}6}$alkyl and no hydrogen in said alkyl is deuterated.

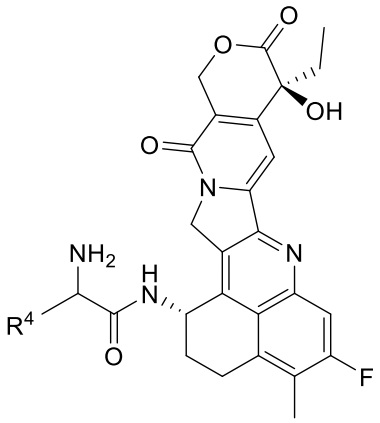
[0027] Another example of the disclosure of Formula I and Formula I' is represented by structural Formula III:



III

or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 is as described herein. A sub-example of the disclosure of Formula III is realized when R^4 is selected from CH_3, $-CH_2OH$, $-(CH_2)_2OH$, $-CH(CH_3)OH$, $(CH_2)_2OCHF_2$, $-C(CH_3)_2CH_2OH$, halogen, $-CH_2F$, $-CHF_2$, -OH, $-CF_3$, and $-(CH_2)_nNH_2$. A sub-example of the disclosure of Formula III is realized when R^4 is $–CH_3$. A sub-example of the disclosure of Formula II is realized when R^4 is -OH. A sub-example of the disclosure of Formula III is realized when R^4 is $--CH_2OH$, or $-(CH_2)_2OH$. A sub-example of the disclosure of Formula III is realized when R^4 is $-CH(CH_3)OH$. Another sub-example of the disclosure of Formula III is realized when R^4 is $(CH_2)_2OCHF_2$. Another sub-example of the disclosure of Formula III is realized when R^4 is $-C(CH_3)_2CH_2OH$. Another sub-example of the disclosure of Formula III is realized when R^4 is $-CH_2F$, $-CHF_2$, or $-CF_3$. Another sub-example of the disclosure of Formula III is realized when R^4 is fluorine. A sub-example of the disclosure of Formula III is realized when R^4 is $-(CH_2)_nNH_2$. Another sub-example of the disclosure of Formula III is realized when R^4 contains an $C_{1\text{-}6}$alkyl and no hydrogen in said alkyl is deuterated.

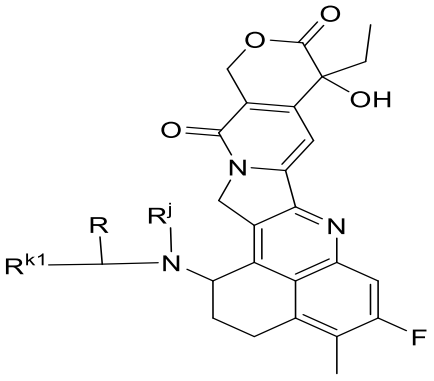
[0028] Another example of the disclosure of Formula I and Formula I' is represented by structural Formula IV:



IV

or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 is as described herein. A sub-example of the disclosure of Formula IV is realized when R^4 is OH, $-CH_2F$, $-CHF_2$, $-CF_3$, fluorine, or $(CH_2)_nNH_2$.

[0029] Another example of the disclosure of Formula I and Formula I' is represented by structural Formula V:



V

or a pharmaceutically acceptable salt or solvate thereof, wherein R^j is as described herein. A sub-example of the disclosure of Formula V is realized when R^j is C_{1-6} alkyl, said alkyl optionally substituted with 1 to 10 groups of halogen.

[0030] Another example of Formula V is realized when R is hydrogen or $-C_{1-6}$ alkyl.

[0031] Another example of Formula V is realized when R^{k1} is $-C_{1-6}$ alkyl, said alkyl optionally substituted to 1 to 10 halogen, and/or 1 to 3 groups selected from hydroxyl and $-C_{1-6}$ alkylOH. A sub-example of the disclosure is realized when R^{k1} is $-C_{1-6}$ alkyl, said alkyl substituted with 1 to 3 groups selected from hydroxyl and $-C_{1-6}$ alkylOH, and/or 1 to 10 halogen.

[0032] Another example of this disclosure is realized when R^{k1} is $(CH_2)_nC(O)NHC_{1-6}$ alkyl, said alkyl optionally substituted to 1 to 10 halogen and/or 1 to 3 groups selected from hydroxyl, and -C_{1-6} alkylOH.

[0033] Another example of this disclosure is realized when R^{k1} is $(CH_2)_nC_{6-10}$ aryl, said aryl optionally substituted with 1 to 3 groups selected from hydroxyl, and -C_{1-6} alkylOH.

[0033a] In another aspect, there is provided a compound, or a pharmaceutically acceptable salt or solvate thereof which is:

N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,4-dihydroxybutanamide;

(*R*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,4-dihydroxybutanamide;

N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,4-dihydroxybutanamide;

(S)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,4-dihydroxybutanamide;

N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,4-dihydroxy-3,3-dimethylbutanamide;

(*R*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,4-dihydroxy-3,3-dimethylbutanamide;

(*S*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,4-dihydroxy-3,3-dimethylbutanamide;

N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,3-dihydroxy-2-methylpropanamide;

N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,3-dihydroxy-2-methylpropanamide;

N-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,3-dihydroxy-2-methylpropanamide;

N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,3-dihydroxy-2-methylpropanamide;

N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,3-dihydroxy-2-methylpropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluoro-3-hydroxybutanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluoro-3-hydroxybutanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluoro-3-hydroxybutanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluoro-3-hydroxybutanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluoro-3-hydroxypropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluoro-3-hydroxypropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-(hydroxymethyl)propenamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-(hydroxymethyl)propenamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-(hydroxymethyl)propenamide;

N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-(hydroxymethyl)propenamide;

1-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3,3-difluoro-2-methyl-1-oxopropan-2-aminium;

1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3,3-difluoro-2-methyl-1-oxopropan-2-aminium;

1-((-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3,3-difluoro-2-methyl-1-oxopropan-2-aminium;

1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3,3-difluoro-2-methyl-1-oxopropan-2-aminium;

3-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-1,1,1-trifluoro-3-oxopropan-2-aminium;

3-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-1,1,1-trifluoro-3-oxopropan-2-aminium;

((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-1,1,1-trifluoro-3-oxopropan-2-aminium;

(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-1,1,1-trifluoro-3-oxopropan-2-aminium;

2-amino-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-methylpropanamide;

2-amino-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-methylpropanamide;

2-amino-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-methylpropanamide;
2-amino-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoro-2-methylpropanamide;
2-amino-2-benzyl-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoropropanamide;
2-amino-2-benzyl-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoropropanamide;
2-amino-2-benzyl-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoropropanamide;
2-amino-2-benzyl-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3,3,3-trifluoropropanamide;
2-amino-2-cyclopropyl-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)propenamide;
2-amino-2-cyclopropyl-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)propenamide;
4-(difluoromethoxy)-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-hydroxybutanamide;
(*R*)-4-(difluoromethoxy)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-hydroxybutanamide;
2-cyclopropyl-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;
2-cyclopropyl-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;

2-cyclopropyl-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;
2-cyclopropyl-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2,2-dimethylpropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2,2-dimethylpropanamide;
(*S*)-*N*-(-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxybutanamide;
(*S*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxybutanamide;
N-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxybutanamide;
(*R*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxybutanamide;
N-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;
1-(2,3-dihydroxypropanamido)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-7-ium hexafluorophosphate (V);
(1*S*,9*S*)-1-((*S*)-2,3-dihydroxypropanamido)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-7-ium hexafluorophosphate (V);
1-(2,3-dihydroxypropanamido)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-7-ium hexafluorophosphate (V);
(1*S*,9*S*)-1-((*R*)-2,3-dihydroxypropanamido)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-7-ium hexafluorophosphate (V);

N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-hydroxy-2-(1-(hydroxymethyl)cyclopropyl)acetamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-hydroxy-2-(1-(hydroxymethyl)cyclopropyl)acetamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2-methoxybutanamide;
(*R*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2-methoxybutanamide;
(*S*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2-methoxybutanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2-methylpropanamide;
(*S*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2-methylpropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2-methylpropanamide;
(*R*)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxy-2-methylpropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxypropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxypropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxypropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxypropanamide;

N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxy-2-methylpropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxy-2-methylpropanamide;
(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-1-((2-hydroxypropyl)amino)-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxy-2-methylpropanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-fluoro-3-hydroxy-2-methylpropanamide;
N-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2,2-dimethylbutanamide;
N-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2,2-dimethylbutanamide;
2-(difluoromethyl)-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2-methylbutanamide;
2-(difluoromethyl)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2-methylbutanamide;
2-(difluoromethyl)-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2-methylbutanamide;
2-(difluoromethyl)-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-4-hydroxy-2-methylbutanamide;
2-amino-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-methylpropanamide;

2-amino-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2-methylpropanamide;
1-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-4-methyl-1-oxopentan-2-aminium;
1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-4-methyl-1-oxopentan-2-aminium;
3-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-2-hydroxy-3-oxopropan-1-aminium;
(*R*)-3-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-2-hydroxy-3-oxopropan-1-aminium;
3-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-2-hydroxy-3-oxopropan-1-aminium;
(*S*)-3-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-2-hydroxy-3-oxopropan-1-aminium;
2-amino-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;
(*S*)-2-amino-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-3-hydroxypropanamide;
1-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3-hydroxy-1-oxopropan-2-aminium;
(*R*)-1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3-hydroxy-1-oxopropan-2-aminium;

1-((1-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3,3-difluoro-2-methyl-1-oxopropan-2-yl)amino)-1-oxopropan-2-aminium;

(2*R*)-1-((1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3,3-difluoro-2-methyl-1-oxopropan-2-yl)amino)-1-oxopropan-2-aminium;

(2*S*)-1-((1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3,3-difluoro-2-methyl-1-oxopropan-2-yl)amino)-1-oxopropan-2-aminium;

1-((9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3-methoxy-2-methyl-1-oxopropan-2-aminium;

1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3-methoxy-2-methyl-1-oxopropan-2-aminium;

1-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-3-methoxy-2-methyl-1-oxopropan-2-aminium;

4-amino-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluorobutanamide;

4-amino-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)-2,2-difluorobutanamide;

2,3-diamino-*N*-(9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)propanamide;

(*S*)-2,3-diamino-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)propanamide;

(*R*)-2,3-diamino-*N*-((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)propanamide;

(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-1-((2-hydroxyethyl)amino)-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;

(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-1-((3-hydroxypropyl)amino)-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;

(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-1-((1-hydroxypropan-2-yl)amino)-4-methyl-1,2,3,9,12,15-

hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;
(1*S*,9*S*)-1-((3,3-difluoro-2-hydroxypropyl)amino)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;
2-(((1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl)amino)-N-isopropylacetamide;
(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-1-((2-(hydroxymethyl)benzyl)amino)-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;
(1*S*,9*S*)-1-((2,2-difluoropropyl)amino)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;
(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-1-((2,2,3,3-tetrafluoropropyl)amino)-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione;
(1*S*,9*S*)-1-((1,1-difluoropropan-2-yl)amino)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione; or
(1S,9S)-1-((2,2-difluoroethyl)(methyl)amino)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-1,2,3,9,12,15-hexahydro-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione.

[0034] An example of this disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, I', II, III, IV, V or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable carrier(s), diluent(s) or excipients(s). In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[0035] Another example of the disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, I', II, III, IV, or V as described herein, or a tautomer, mesomere, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carrier(s), diluent(s) or excipient(s).

[0036] Another example of the disclosure relates to a compound of Formula I, I', II, III, IV, or V as described herein, or a tautomer, mesomere, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof for use as a drug or drug component.

[0037] Another example of the disclosure relates to a compound of Formula I, I', II, III, IV, or V as described herein, or a tautomer, mesomere, racemate, enantiomer, diastereomer thereof, or mixture thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition in the preparation of a medicament for treating or preventing a tumor.

[0037a] In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt or solvate thereof, or of the pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment or prevention of cancers or tumors.

[0037b] In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt or solvate thereof, or of the pharmaceutical composition as defined herein, for use in therapy.

[0038] In another example, the compounds of the disclosure include those identified herein as Examples in the tables below, and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0039] The compounds of the disclosure may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this disclosure. Unless a specific stereochemistry is indicated, the present disclosure