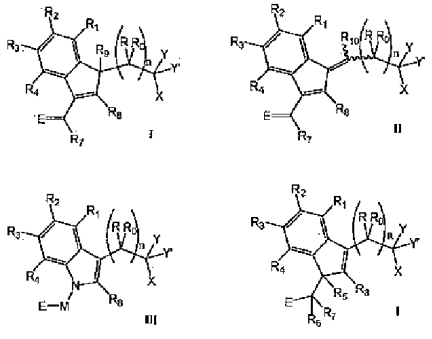
3), that induced non-apoptotic cell death via a mechanism involving oxidative stress (Shaw et al., *Proc. Natl. Acad. Sci. USA, 108*, 8773-8778 (2011)). In contrast to the synthetic lethal approach, a fragment-based screening approach paired with crystallographic studies has been used to identify compounds which irreversibly bind to and inhibit K-Ras in lung tumor cells having the relatively rare G12C ras gene mutation (Ostrem et al., *Nature, 503*, 548-551 (2013)). While compounds of this series potently inhibit Ras through a covalent interaction, the low frequency of this mutation may limit the utility of such compounds. Finally, a new investigational strategy for targeting oncogenic Ras has been described (Zimmerman et al., J. Med. Chem., 57, 5435-5448 (2014)) which involves structure guided design and kinetic analysis of benzimidazole inhibitors targeting the PDEδ prenyl binding site.

**[0018]** WO 97/47303 and WO 2014/047592, U.S. Patent Application Publication Nos. 2003/0009033 and 2003/0194750, U.S. Patents 6,063,818; 6,071,934, 5,965,619; 5,401,774; 6,538,029, 6,121,321, and UK Patent No. GB 1370028 disclose certain anticancer compounds; however, these documents do not disclose that the compounds have any Ras-specific activity, nor any basis for a selective Ras-directed method of use.

**[0019]** The foregoing shows that there exists an unmet need for compounds that are suitable for treating or preventing cancers. There further exists an unmet need for compounds that inhibit Ras-dependent diseases or undesirable conditions.

## BRIEF SUMMARY

**[0020]** The present disclosure provides a compound of formula I:



**[0021]** wherein:

**[0022]** R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl,

**[0033]** or, when $R_5$ and $R_6$ are independently selected from hydrogen or alkyl or $R_5$ and $R_6$ together form a carbon-carbon bond, E is a substituted aryl or heteroaryl, and X is NR'R" wherein R' is hydrogen or hydroxyl and R" is $COR_{11}$, then $R_{11}$ cannot be alkyl, alkoxy or amino;

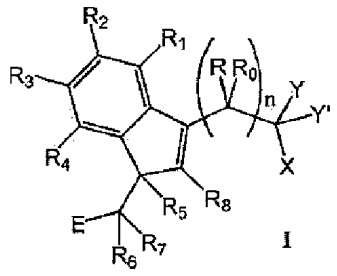
**[0034]** or, when $R_5$, $R_6$, $R_7$ and $R_8$ are independently selected from hydrogen, alkyl and alkoxy, or $R_5$ and $R_6$ form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is hydrogen, alkoxy or alkyl, E is phenyl substituted with at least two hydroxyl groups or at least two alkoxy groups, and Y and Y' together is double-bonded oxygen, then X cannot be substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocycoalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl;

**[0035]** or, when R and $R_0$ are hydrogens, at least one of $R_1$, $R_2$, $R_3$, and $R_4$ is halogen, Y and Y' together is double-bonded oxygen, and X is NR'R", wherein R' is furanylalkyl and R" is selected from hydrogen and $COR_{11}$, wherein $R_{11}$ is selected from hydrogen, amino, alkyl, haloalkyl, alkoxy, alkylmercapto, and aryl, then E cannot be 3,4,5-trimethoxyphenyl;

**[0036]** or, when R' is halophenylalkyl and R" is hydrogen, then E cannot be halophenyl;

**[0037]** or, when n = 0 and Y and Y' together is double-bonded oxygen, then X cannot be alkoxy, aryloxy, arylalkyloxy, or NR'R" wherein R" is hydrogen and R' is alkyl, aryl, or arylalkyl.

**[0037a]** In a first aspect of the present disclosure, there is provided a compound of formula I:




I

wherein:

R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

n is 0, 1 or 2;

$R_1$, $R_2$, $R_3$, and $R_4$ are independently selected from hydrogen, halogen, alkyl, cycloalkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy and sulfonamido;

$R_5$, $R_6$, $R_7$, and $R_8$ are independently selected from hydrogen, alkyl, haloalkyl, and alkoxy; or $R_5$ and $R_6$ together form a carbon-carbon bond;

Y is hydrogen, alkyl, or haloalkyl, and Y' is hydrogen, alkyl, haloalkyl, amino, alkylamino, or alkoxy, or Y and Y' together is double-bonded oxygen or double-bonded sulfur, or Y and Y' together is a double-bonded nitrogen bonded to hydrogen, hydroxyl, alkyl, or haloalkyl;

X is selected from hydrogen, alkyl, haloalkyl, alkoxy, alkylmercapto, and hydroxyl with the proviso that X is not hydroxyl when Y and Y' together is oxygen in a compound of formula I wherein $R_5$ and $R_6$ together is a carbon-carbon bond, or X is NR'R", where R' is independently selected from the group consisting of hydrogen, hydroxyl, alkyl, aryloxy, cyanoalkyl, haloalkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoalkyl, alkylamino, aryl, arylalkyl, arylalkenyl, arylcycloalkyl, arylcycloalkenyl, carbocyclyl, and carbocyclylalkyl where the carbocycle of the carbocyclyl and the carbocyclylalkyl is selected from 7-membered carbocyclic rings containing no double bond, or one, two or three double bonds, 6-membered carbocyclic rings containing no double bond, or one, two or three double bonds, 5-membered carbocyclic rings containing no double bond, or one or two double bonds, 4-membered carbocyclic rings containing no double bond or one double bond and 3-membered carbocyclic rings containing no double bond, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and heterocyclylalkyl is selected from 7-membered heterocyclic rings, 6-membered heterocyclic rings, and 5-membered heterocyclic rings, and the aryl of the aryl, arylalkyl, arylalkylenyl, arylcycloalkyl, or arylcycloalkenyl structure or the carbocyclic or heterocyclic structure is optionally substituted with one or more of halo, alkyl, trifluoromethyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, sulfonamido; R" is selected from hydrogen, alkyl, hydroxyalkyl, alkylamino, dialkylaminoalkyl, cyanoalkyl, haloalkyl, alkylcarbonylalkylcarbonyloxy, pyridyl, and $COR_{11}$, wherein $R_{11}$ is selected from hydrogen, amino, alkyl, haloalkyl, alkoxy, alkylmercapto, and aryl; or R' and R" together form a 5-, 6- or 7-membered, saturated or unsaturated, heterocyclic ring containing at least one nitrogen and optionally oxygen or sulfur, and the heterocyclic ring is optionally substituted with one or more of halo, alkyl, haloalkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, and sulfonamido; and

E is a substituted or unsubstituted, saturated or unsaturated, 7- membered, 6-membered, 5-membered, 4-membered or 3-membered carbocyclic or heterocyclic ring; or

a pharmaceutically acceptable salt thereof or a prodrug thereof;

with the proviso that when E is a substituted aryl or heteroaryl, then no substituent on the aryl or heteroaryl ring can be alkylsulfinyl or alkylsulfonyl, and no substituent on the aryl ring can be alkylmercapto, nor *p*-halo when R' is dialkylaminoalkyl;

or, when $R_5$ and $R_6$ together is a carbon-carbon bond, R" is hydrogen and R' is a substituted arylalkyl, then E cannot be a substituted or unsubstituted heterocyclic ring selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, imidazolyl, triazinyl, thiophenyl, furanyl, thiazolyl, pyrazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, azinyl, tratrazolyl, pyridazinyl, and pyrrolyl;

or, when n is 1 or 2, $R_5$ and $R_6$ together form a carbon-carbon bond, Y and Y' are hydrogens or Y and Y' together is oxygen, and E is a substituted phenyl, then X cannot be hydrogen, alkyl, haloalkyl, alkylmercapto or NR'R" wherein R' is hydrogen, hydroxyl or alkyl, and R" is hydrogen, alkyl or haloalkyl;

or, when $R_5$ and $R_6$ are independently selected from hydrogen or alkyl or $R_5$ and $R_6$ together form a carbon-carbon bond, E is a substituted aryl or heteroaryl, and X is NR'R" wherein R' is hydrogen or hydroxyl and R" is $COR_{11}$, then $R_{11}$ cannot be alkyl, alkoxy or amino;

or, when $R_5$, $R_6$, $R_7$ and $R_8$ are independently selected from hydrogen, alkyl and alkoxy, or $R_5$ and $R_6$ form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is hydrogen, alkoxy or alkyl, E is phenyl substituted with at least two hydroxyl groups or at least two alkoxy groups, and Y and Y' together is double-bonded oxygen, then X cannot be substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocyclylalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl;

or, when R and $R_0$ are hydrogens, at least one of $R_1$, $R_2$, $R_3$, and $R_4$ is halogen, Y and Y' together is double-bonded oxygen, and X is NR'R", wherein R' is furanylalkyl and R" is selected from hydrogen and $COR_{11}$, wherein $R_{11}$ is selected from hydrogen, amino, alkyl, haloalkyl, alkoxy, alkylmercapto, and aryl, then E cannot be 3,4,5-trimethoxyphenyl;

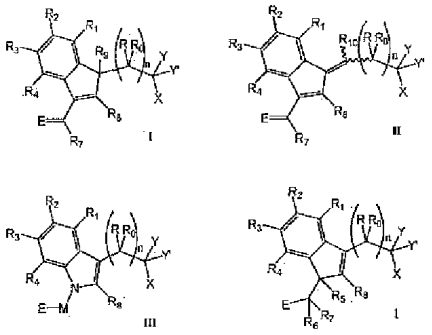
or, when R' is halophenylalkyl and R" is hydrogen, then E cannot be halophenyl;

or, when n = 0 and Y and Y' together is double-bonded oxygen, then X cannot be alkoxy, aryloxy, arylalkyloxy, or NR'R" wherein R" is hydrogen and R' is alkyl, aryl, or arylalkyl.

**[0038]** In an embodiment, when R and $R_0$ are hydrogen, n is 1, three of $R_1$, $R_2$, $R_3$, and $R_4$ are hydrogens and one is halogen, alkyl, or alkoxy or two of $R_1$, $R_2$, $R_3$ and $R_4$ are hydrogens and two are alkoxy, $R_5$ and $R_6$ together form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is alkyl, Y and Y' together is oxygen, X is NR'R" wherein R" is hydrogen, and R' is a substituted aryl, then E cannot be a substituted aryl. For example, when R and $R_0$ are hydrogen, n is 1, three of $R_1$, $R_2$, $R_3$, and $R_4$ are hydrogens and one is halogen, alkyl, or alkoxy or two of $R_1$, $R_2$, $R_3$ and $R_4$ are hydrogens and two are alkoxy, $R_5$ and $R_6$ together form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is alkyl, Y and Y' together is oxygen, X is NR'R" wherein R" is

hydrogen, R' is an aryl substituted with any of halo, alkoxy, amino, alkylamino, dialkylamino and sulfonamido, then E cannot be a substituted aryl wherein two substituents are identically selected from hydroxyl and alkoxy.

**[0039]** The present disclosure additionally provides a compound of formula I:



**[0040]** wherein:

**[0041]** R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

**[0042]** n is 0, 1 or 2;

**[0043]** $R_1$, $R_2$, $R_3$, and $R_4$ are independently selected from hydrogen, halogen, alkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl,

aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy and sulfamido, or any two of $R_1$, $R_2$, $R_3$ and $R_4$ form an alkylenedioxy group;

**[0044]** $R_5$, $R_6$, $R_7$ and $R_8$ are independently selected from hydrogen, alkyl and alkoxy, or $R_5$ and $R_6$ form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is hydrogen, alkoxy or alkyl,

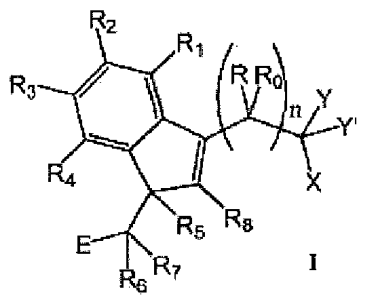
**[0045]** E is phenyl substituted with at least two hydroxyl groups or at least two alkoxy groups, and at least one substituted or unsubstituted group selected from phosphonooxy, phosphonoalkyloxy, formyloxy, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy and heterocyclylalkylcarbonyloxy;

**[0046]** Y and Y' together is double-bonded oxygen;

**[0047]** X is substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocyclylalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl;

**[0048]** or a pharmaceutically acceptable salt thereof.

**[0048a]** In a second aspect of the present disclosure, there is provided a compound of formula I:




I

wherein:

R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

n is 0, 1 or 2;

$R_1$, $R_2$, $R_3$, and $R_4$ are independently selected from hydrogen, halogen, alkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, hydroxyalkyl, aldehydo, amino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy and sulfonamido;

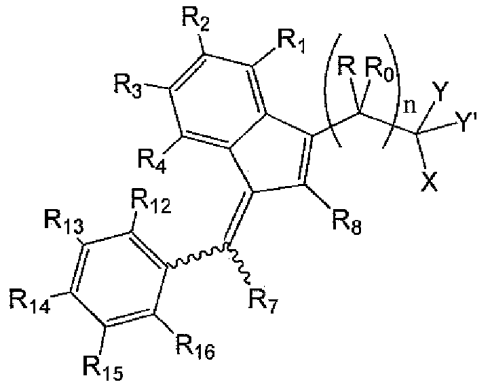
$R_5$, $R_6$, $R_7$ and $R_8$ are independently selected from hydrogen, alkyl, and alkoxy, or $R_5$ and $R_6$ form a carbon-carbon bond, $R_7$ is hydrogen, and $R_8$ is hydrogen, alkoxy or alkyl;

E is phenyl substituted with at least two hydroxyl groups or at least two alkoxy groups, and at least one substituted or unsubstituted group selected from phosphonooxy, phosphonoalkyloxy, formyloxy, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy and heterocyclylalkylcarbonyloxy;

Y and Y' together is double-bonded oxygen;

X is substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocycoalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl;
or, a pharmaceutically acceptable salt thereof.

**[0049]** The present disclosure further provides a compound of formula (II):

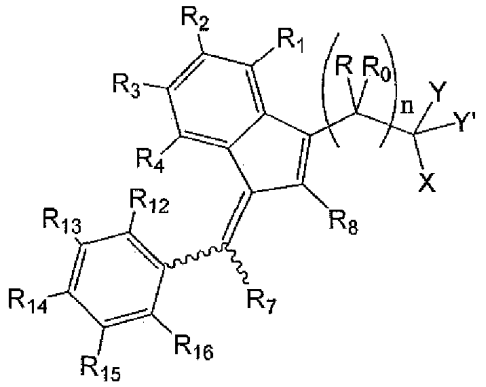



(II),

**[0050]** wherein:

alkylcarbonylalkylcarbonyloxy, and pyridinyl. For example, when $R_7$ is hydrogen and $R_8$ is selected from hydrogen, alkyl and alkoxy, at least two of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are identically selected from hydroxyl or alkyl, Y and Y' together is oxygen and R" is hydrogen, then R' cannot be phenylalkyl.

**[0067]** The present disclosure also provides a compound of formula (II):



(II),

**[0068]** wherein:

**[0069]** R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

**[0070]** n is 0, 1 or 2;

**[0071]** Y is hydrogen, alkyl, or haloalkyl, and Y' is hydrogen, alkyl, haloalkyl, amino, alkylamino, or alkoxy, or Y and Y' together is double-bonded oxygen or double-bonded sulfur, or Y and Y' together is a double-bonded nitrogen bonded to hydrogen, hydroxyl, alkyl, or haloalkyl;

dioxolanyl, dithiolanyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dithiazolyl, and tetrazolyl, then $R_7$ and $R_8$ are independently selected from hydrogen, alkyl, haloalkyl and alkoxy.

**[0084]** In an embodiment, when R and $R_0$ are hydrogen, n is 1, three of $R_1$, $R_2$, $R_3$, and $R_4$ are hydrogens and one is halogen, alkyl, or alkoxy or two of $R_1$, $R_2$, $R_3$ and $R_4$ are hydrogens and two are alkoxy, $R_5$ and $R_6$ together form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is alkyl, Y and Y' together is oxygen, X is NR'R" wherein R" is hydrogen, and R' is a substituted aryl, then each of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ must be hydrogen. For example, when R and $R_0$ are hydrogen, n is 1, three of $R_1$, $R_2$, $R_3$, and $R_4$ are hydrogens and one is halogen, alkyl, or alkoxy or two of $R_1$, $R_2$, $R_3$ and $R_4$ are hydrogens and two are alkoxy, $R_5$ and $R_6$ together form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is alkyl, Y and Y' together is oxygen, X is NR'R" wherein R" is hydrogen, and R' is an aryl substituted with any of halo, alkoxy, amino, alkylamino, dialkylamino and sulfonamido, then no two of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ can be identically selected from hydroxyl and alkoxy;

**[0085]** or, when $R_7$ is hydrogen, $R_8$ is hydrogen, alkoxy or alkyl, least two of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are identically selected from hydroxyl or alkoxy, and Y and Y' together is double-bonded oxygen, then X cannot be substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocycoalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl. For example, when $R_7$ is hydrogen and $R_8$ is selected from hydrogen, alkyl and alkoxy, at least two of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are identically selected from hydroxyl or alkyl, Y and Y' together is oxygen and R" is hydrogen, then R' cannot be phenylalkyl.

**[0086]** The compounds of the present disclosure are suitable for treating or preventing cancer.

**[0087]** The present disclosure further provides a pharmaceutical composition comprising a compound described above and a pharmaceutically acceptable carrier.

**[0087a]** In a third aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of the first aspect or second aspect, a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

**[0088]** The present disclosure further provides a method of therapeutically or prophylactically treating a human or nonhuman mammalian patient with cancer comprising administering to said patient an anticancer effective amount of at least one compound of formula I or II, a pharmaceutically acceptable salt or prodrug thereof, either alone or in combination with at least one therapeutic agent which is not a compound of the present disclosure, or a pharmaceutically acceptable salt or prodrug thereof, for example, an anticancer drug or radiation.

**[0089]** In an embodiment, the present disclosure provides a method of therapeutically or prophylactically treating a human or nonhuman mammalian patient with a disease or condition treatable by the inhibition of one or more neoplastic or cancerous process, which method comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of at least one neoplastic or cancerous inhibitory compound of formula I or II, as described above, or a pharmaceutically acceptable salt or prodrug thereof, either alone or in combination with at least one therapeutic agent which is not a compound of formula I or II as described above, or a pharmaceutically acceptable salt or prodrug thereof, for example an anticancer drug or radiation.

**[0089a]** In a fourth aspect of the present disclosure, there is provided a use of at least one compound of the first aspect or second aspect, a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for therapeutically or prophylactically treating a human or nonhuman mammalian patient with cancer, wherein said medicament is to be administered to said patient either alone or in combination with at least one therapeutic agent which is not a compound of the first aspect or second aspect, or pharmaceutically acceptable salt or prodrug thereof.

**[0089b]** In a fifth aspect of the present disclosure, there is provided a use of at least one neoplastic or cancerous inhibitory compound of the first aspect or second aspect or a compound selected from **(001)**, **(002)**, **(006)**-**(008)**, **(012)**-**(014)**, **(016)**-**(022)**, **(026)**, **(029)**-**(033)**, **(063)**, **(065)**-**(067)**, **(069)**, **(095)**-**(100)**, **(130)**-**(135)**, **(138)**, **(139)**, **(141)**, **(143)**, **(144)**, **(145)**, **(151)**, **(152)**, **(154)**, **(155)**, **(214)**, **(300)**-**(309)**, **(311)**-**(336)**, **(338)**-**(353)**, **(355)**, **(202)**,

(203), (401), (404), (410), (412), (413), (415), (416), (420), (423), (425)-(428), (430), (431), (433), (434), and (436), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for therapeutically or prophylactically treating a human or nonhuman mammalian patient with a disease or condition treatable by the inhibition of one or more neoplastic or cancerous process, wherein said medicament is to be administered to said patient either alone or in combination withat least one therapeutic agent which is not a compound of the first aspect or second aspect or a compound selected from (001), (002), (006)-(008), (012)-(014), (016)-(022), (026), (029)-(033), (063), (065)-(067), (069), (095)-(100), (130)-(135), (138), (139), (141), (143), (144), (145), (151), (152), (154), (155), (214), (300)-(309), (311)-(336), (338)-(353), (355), (202), (203), (401), (404), (410), (412), (413), (415), (416), (420), (423), (425)-(428), (430), (431), (433), (434), and (436), or a pharmaceutically acceptable salt or prodrug thereof.

**[0089c]** In a sixth aspect of the present disclosure, there is provided a compound of the first aspect or second aspect, a pharmaceutically acceptable salt or prodrug thereof, or the pharmaceutical composition of the third aspect, for use in the treatment or prophylaxis of a human or nonhuman mammalian patient with cancer.

**[0089d]** In a seventh aspect of the present disclosure, there is provided a compound of the first aspect or second aspect or a compound selected from (001), (002), (006)-(008), (012)-(014), (016)-(022), (026), (029)-(033), (063), (065)-(067), (069), (095)-(100), (130)-(135), (138), (139), (141), (143), (144), (145), (151), (152), (154), (155), (214), (300)-(309), (311)-(336), (338)-(353), (355), (202), (203), (401), (404), (410), (412), (413), (415), (416), (420), (423), (425)-(428), (430), (431), (433), (434), and (436), or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment ot prophylaxis of a disease or condition treatable by the inhibition of one or more neoplastic or cancerous process in a human or nonhuman mammalian patient, either alone or in combination with at least one therapeutic agent which is not a compound of the first aspect or second aspect or a compound selected from (001), (002), (006)-(008), (012)-(014), (016)-(022), (026), (029)-(033), (063), (065)-(067), (069), (095)-(100), (130)-(135), (138), (139), (141), (143), (144), (145), (151), (152), (154), (155), (214), (300)-(309), (311)-(336), (338)-(353), (355), (202), (203), (401), (404), (410), (412), (413), (415), (416), (420), (423), (425)-(428), (430), (431), (433), (434), and (436), or a pharmaceutically acceptable salt or prodrug thereof.

## BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

**[0090]** FIG. 1 depicts the chemical structures of sulindac and certain derivatives thereof reportedly having anticancer activity.

**[0091]** FIG. 2 depicts the chemical structures of certain other sulindac derivatives reported to inhibit Ras.

**[0092]** FIG. 3 shows chemical structures of selective Ras-inhibitory compounds identified by synthetic lethal screening.

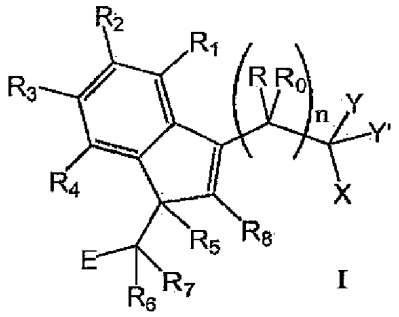
**[0093]** FIG. 4 depicts the results of a Ras Binding Domain (RBD) pulldown assay paired with Western blot showing the relative levels of Ras activation in a panel of colorectal cancer cell lines.

**[0094]** FIG. 5A reveals a correlation between sensitivity of tumor cells to compound **006** and Ras activation status of the cells as determined by Western blot analysis.

**[0095]** FIG. 5B reveals a correlation between sensitivity of tumor cells to compound **007** and Ras activation status of the cells as determined by Western blot analysis.

CLAIM(S):

1. A compound of formula I:




I

wherein:

R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

n is 0, 1 or 2;

$R_1$, $R_2$, $R_3$, and $R_4$ are independently selected from hydrogen, halogen, alkyl, cycloalkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy,

heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy and sulfonamido;

$R_5$, $R_6$, $R_7$, and $R_8$ are independently selected from hydrogen, alkyl, haloalkyl, and alkoxy; or $R_5$ and $R_6$ together form a carbon-carbon bond;

Y is hydrogen, alkyl, or haloalkyl, and Y' is hydrogen, alkyl, haloalkyl, amino, alkylamino, or alkoxy, or Y and Y' together is double-bonded oxygen or double-bonded sulfur, or Y and Y' together is a double-bonded nitrogen bonded to hydrogen, hydroxyl, alkyl, or haloalkyl;

X is selected from hydrogen, alkyl, haloalkyl, alkoxy, alkylmercapto, and hydroxyl with the proviso that X is not hydroxyl when Y and Y' together is oxygen in a compound of formula I wherein $R_5$ and $R_6$ together is a carbon-carbon bond, or X is NR'R", where R' is independently selected from the group consisting of hydrogen, hydroxyl, alkyl, aryloxy, cyanoalkyl, haloalkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoalkyl, alkylamino, aryl, arylalkyl, arylalkenyl, arylcycloalkyl, arylcycloalkenyl, carbocyclyl, and carbocyclylalkyl where the carbocycle of the carbocyclyl and the carbocyclylalkyl is selected from 7-membered carbocyclic rings containing no double bond, or one, two or three double bonds, 6-membered carbocyclic rings containing no double bond, or one, two or three double bonds, 5-membered carbocyclic rings containing no double bond, or one or two double bonds, 4-membered carbocyclic rings containing no double bond or one double bond and 3-membered carbocyclic rings containing no double bond, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and heterocyclylalkyl is selected from 7-membered heterocyclic rings, 6-membered heterocyclic rings, and 5-membered heterocyclic rings, and the aryl of the aryl, arylalkyl, arylalkylenyl, arylcycloalkyl, or arylcycloalkenyl structure or the carbocyclic or heterocyclic structure is optionally substituted with one or more of halo, alkyl, trifluoromethyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, sulfonamido; R" is selected from hydrogen, alkyl, hydroxyalkyl, alkylamino, dialkylaminoalkyl, cyanoalkyl, haloalkyl, alkylcarbonylalkylcarbonyloxy, pyridyl, and $COR_{11}$, wherein $R_{11}$ is selected from hydrogen, amino, alkyl, haloalkyl, alkoxy, alkylmercapto, and aryl; or R' and R" together form a 5-, 6- or 7-membered, saturated or unsaturated, heterocyclic ring containing at least one nitrogen and optionally oxygen or sulfur, and the heterocyclic ring is optionally substituted with one or more of halo, alkyl, haloalkyl, hydroxyl, alkoxy, amino, alkylamino,

dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, and sulfonamido; and

E is a substituted or unsubstituted, saturated or unsaturated, 7- membered, 6-membered, 5-membered, 4-membered or 3-membered carbocyclic or heterocyclic ring; or

a pharmaceutically acceptable salt thereof or a prodrug thereof;

with the proviso that when E is a substituted aryl or heteroaryl, then no substituent on the aryl or heteroaryl ring can be alkylsulfinyl or alkylsulfonyl, and no substituent on the aryl ring can be alkylmercapto, nor *p*-halo when R' is dialkylaminoalkyl;

or, when $R_5$ and $R_6$ together is a carbon-carbon bond, R" is hydrogen and R' is a substituted arylalkyl, then E cannot be a substituted or unsubstituted heterocyclic ring selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, imidazolyl, triazinyl, thiophenyl, furanyl, thiazolyl, pyrazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, azinyl, tratrazolyl, pyridazinyl, and pyrrolyl;

or, when n is 1 or 2, $R_5$ and $R_6$ together form a carbon-carbon bond, Y and Y' are hydrogens or Y and Y' together is oxygen, and E is a substituted phenyl, then X cannot be hydrogen, alkyl, haloalkyl, alkylmercapto or NR'R" wherein R' is hydrogen, hydroxyl or alkyl, and R" is hydrogen, alkyl or haloalkyl;

or, when $R_5$ and $R_6$ are independently selected from hydrogen or alkyl or $R_5$ and $R_6$ together form a carbon-carbon bond, E is a substituted aryl or heteroaryl, and X is NR'R" wherein R' is hydrogen or hydroxyl and R" is $COR_{11}$, then $R_{11}$ cannot be alkyl, alkoxy or amino;

or, when $R_5$, $R_6$, $R_7$ and $R_8$ are independently selected from hydrogen, alkyl and alkoxy, or $R_5$ and $R_6$ form a carbon-carbon bond, $R_7$ is hydrogen, $R_8$ is hydrogen, alkoxy or alkyl, E is phenyl substituted with at least two hydroxyl groups or at least two alkoxy groups, and Y and Y' together is double-bonded oxygen, then X cannot be substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocyclylalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from

hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl;

or, when R and $R_0$ are hydrogens, at least one of $R_1$, $R_2$, $R_3$, and $R_4$ is halogen, Y and Y' together is double-bonded oxygen, and X is NR'R", wherein R' is furanylalkyl and R" is selected from hydrogen and $COR_{11}$, wherein $R_{11}$ is selected from hydrogen, amino, alkyl, haloalkyl, alkoxy, alkylmercapto, and aryl, then E cannot be 3,4,5-trimethoxyphenyl;

or, when R' is halophenylalkyl and R" is hydrogen, then E cannot be halophenyl;

or, when n = 0 and Y and Y' together is double-bonded oxygen, then X cannot be alkoxy, aryloxy, arylalkyloxy, or NR'R" wherein R" is hydrogen and R' is alkyl, aryl, or arylalkyl.

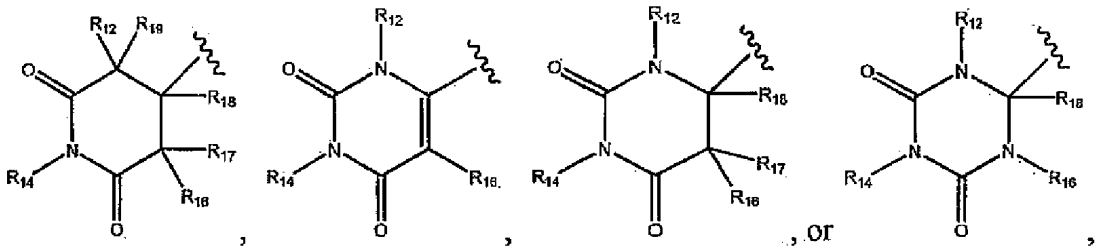
2. The compound, salt, or prodrug of claim 1, wherein in R', the 7-membered heterocyclic ring is selected from azepanyl, oxazepanyl, thiazepanyl, azepinyl, oxepinyl, thiepanyl, homopiperazinyl, diazepinyl and thiazepinyl, the 6-membered heterocyclic ring is selected from piperidinyl, oxanyl, thianyl, pyridinyl, pyranyl, thiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, diazinyl, oxazinyl, thiazinyl, dioxinyl, dithiinyl, trioxanyl, trithianyl, triazinyl and tetrazinyl, and the 5-membered heterocyclic ring is selected from pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiaphenyl, pyrrolyl, furanyl, thiophenyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dithiazolyl and tetrazolyl.

3. The compound, salt, or prodrug of claim 1 or 2, wherein E is a carbocyclic or heterocyclic ring, optionally substituted with one or more substituents selected from hydroxyl, carboxyl, halogen, alkyl, haloalkyl, cyano, cyanoalkyl, nitro, oxo, alkoxy, formyloxy, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, hydroxyalkyl, aldehydo, mercapto, alkylmercapto, azido, and substituted or unsubstituted groups selected from alkylsulfonyl, alkylsulfinyl, alkylsulfinyloxy, alkylsulfonyloxy, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy, carbamate, carbamido,

alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, sulfonamido, and alkylenedioxy spanning two substituent positions.

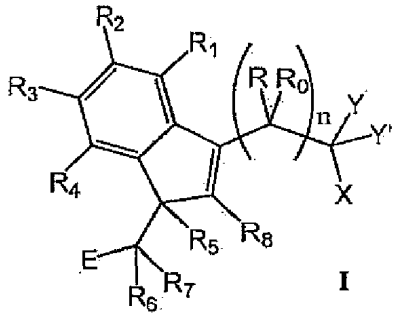
4. The compound of any one of claims 1-3, prodrug, or a salt thereof, wherein E is selected from cycloheptanyl, cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclohexanyl, cyclohexenyl, cyclohexadienyl, phenyl, cyclopentanyl, cyclopentenyl, cyclopentadienyl, cyclopropanyl, cyclobutanyl, azepanyl, oxazepanyl, thiazepanyl, azepinyl, oxepinyl, thiepanyl, homopiperazinyl, diazepinyl, thiazepinyl, piperidinyl, oxanyl, thianyl, pyridinyl, pyranyl, thiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, diazinyl, oxazinyl, thiazinyl, dioxinyl, dithiinyl, trioxanyl, trithianyl, triazinyl, tetrazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiaphenyl, pyrrolyl, furanyl, thiophenyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dithiazolyl, and tetrazolyl, each of which is substituted or unsubstituted.

5. The compound, prodrug, or salt of claim 4, wherein E is:



wherein $R_{12}$, $R_{14}$, $R_{16}$, $R_{17}$, $R_{18}$ and $R_{19}$ are independently selected from hydrogen, hydroxyl, carboxyl, halogen, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, hydroxyalkyl, aldehydo, mercapto, alkylmercapto, azido, cyano, cyanoalkyl, nitro, and substituted or unsubstituted groups selected from alkylsulfonyl, alkylsulfinyl, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy, and sulfonamido.

6. A compound of formula I:



I

wherein:

R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

n is 0, 1 or 2;

$R_1$, $R_2$, $R_3$, and $R_4$ are independently selected from hydrogen, halogen, alkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, hydroxyalkyl, aldehydo, amino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy and sulfonamido;

$R_5$, $R_6$, $R_7$ and $R_8$ are independently selected from hydrogen, alkyl, and alkoxy, or $R_5$ and $R_6$ form a carbon-carbon bond, $R_7$ is hydrogen, and $R_8$ is hydrogen, alkoxy or alkyl;

E is phenyl substituted with at least two hydroxyl groups or at least two alkoxy groups, and at least one substituted or unsubstituted group selected from phosphonooxy, phosphonoalkyloxy, formyloxy, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy and heterocyclylalkylcarbonyloxy;

Y and Y' together is double-bonded oxygen;

X is substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocycoalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl;

or, a pharmaceutically acceptable salt thereof.

7. The compound of claim 6, wherein R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, alkoxy, alkylamino and amino; n is 0, 1 or 2;

at least one of $R_1$, $R_2$, $R_3$ and $R_4$ is hydrogen and three of $R_1$, $R_2$, $R_3$ and $R_4$ are independently selected from hydrogen, hydroxyl, halogen, alkoxy, alkyl and alkylmercapto;

$R_5$ and $R_6$ together form a carbon-carbon bond, $R_7$ is hydrogen and $R_8$ is selected from hydrogen, alkyl and alkoxy;

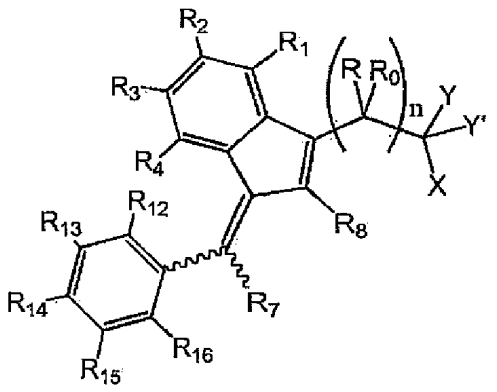
E is phenyl substituted with at least two hydroxyl groups or at least two alkoxy groups, and at least one substituted or unsubstituted group selected from phosphonooxy, phosphonoalkyloxy, formyloxy, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy and heterocyclylalkylcarbonyloxy;

Y and Y' together is double-bonded oxygen;

X is substituted alkoxy or NR'R", where R' is selected from hydrogen, alkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, phenyl, indanyl, carbocycoalkyl wherein the carbocycle is 3-membered, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and the heterocyclylalkyl is selected from pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, and N-morpholino, and wherein any of the cyclic structures of the R' is unsubstituted or substituted with one or more of halo, haloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino, and sulfonamido; and R" is selected from hydrogen, alkyl, alkylamino, cyanoalkyl, haloalkyl, hydroxyalkyl, dialkylaminoalkyl, alkylcarbonylalkylcarbonyloxy, and pyridinyl;

or, a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, which is of formula (II):



(II),

wherein:

R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or

R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

n is 0, 1 or 2;

Y is hydrogen, alkyl, or haloalkyl, and Y' is hydrogen, alkyl, haloalkyl, amino, alkylamino, or alkoxy, or Y and Y' together is double-bonded oxygen or double-bonded sulfur, or Y and Y' together is a double-bonded nitrogen bonded to hydrogen, hydroxyl, alkyl, or haloalkyl;

$R_1$, $R_2$, $R_3$, $R_4$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, and $R_{16}$ are independently selected from hydrogen, halogen, alkyl, cycloalkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, hydroxyalkyl, aldehydo, amino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy and sulfonamido, or any two of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ form an alkylenedioxy group;

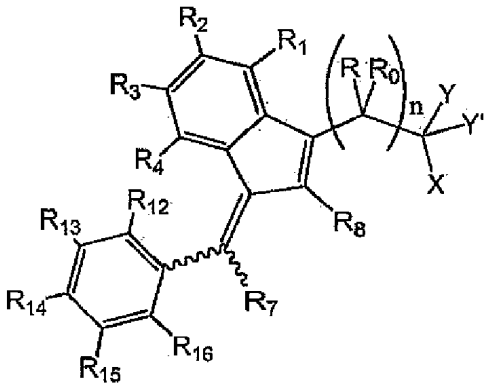
$R_7$ and $R_8$ are independently selected from hydrogen, alkyl, haloalkyl, and alkoxy;

X is selected from hydrogen, alkyl, haloalkyl, alkoxy, alkylmercapto, and hydroxyl with the proviso that X is not hydroxyl when Y and Y' together is oxygen, or X is NR'R", where R' is selected from the group consisting of hydrogen, hydroxyl, alkyl, aryloxy, cyanoalkyl, haloalkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, arylalkenyl, arylcycloalkyl, arylcycloalkenyl, aryl, carbocyclyl, and carbocyclylalkyl where the carbocycle of the carbocyclyl and the carbocyclylalkyl is selected from 7-membered carbocyclic rings containing no double bond, or one, two or three double bonds, 6-membered carbocyclic rings containing no double bond, or one, two, or three double bonds, 5-membered carbocyclic rings containing no double bond, or one or two double bonds, 4-membered carbocyclic rings containing no double bond or one double bond and 3-membered carbocyclic rings containing no double bond, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and heterocyclylalkyl is selected from 7-membered heterocyclic rings, 6-membered heterocyclic rings, and 5-membered heterocyclic rings, and the aryl of the aryl, arylalkyl, arylalkylenyl, arylcycloalkyl, or arylcycloalkenyl structure or the carbocyclic or heterocyclic structure is optionally substituted with one or more of halo, alkyl,

trifluoromethyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, and sulfonamido; and R" is selected from hydrogen, alkyl, hydroxyalkyl, aminoalkyl, dialkylaminoalkyl, cyanoalkyl, haloalkyl, alkylcarbonylalkylcarbonyloxy, pyridyl, and $COR_{11}$ wherein $R_{11}$ is selected from hydrogen, amino, alkyl, haloalkyl, alkoxy, alkylmercapto, and aryl; or R' and R" together form a 5-, 6- or 7-membered, saturated or unsaturated, heterocyclic ring containing at least one nitrogen, and optionally oxygen and/or sulfur, and the heterocyclic ring is optionally substituted with one or more of halo, alkyl, haloalkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, and sulfonamido; or

a pharmaceutically acceptable salt thereof or a prodrug thereof.

9. The compound of claim 1, which is of formula (II):




(II),

wherein:

R and $R_0$ are independently selected from hydrogen, hydroxyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cyano, cyanoalkyl, halogen, azido, alkoxy, haloalkyl and a substituted or unsubstituted group selected from aminocarbonyl, aminocarbonylalkyl, aminosulfonyl, aminosulfonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, amino, alkylamino, dialkylamino, aminocarbonylalkylamino, and carbocyclylamino, carbocyclylalkylamino, heterocyclylamino and heterocyclylalkylamino wherein the ring structures are saturated or unsaturated; or R and $R_0$ together is double-bonded oxygen or double-bonded sulfur, or R and $R_0$ together is a double-bonded nitrogen bonded to one of hydrogen, hydroxyl, alkyl, or haloalkyl, or R and $R_0$ together is a double-bonded carbon bonded to two substituents independently selected

from hydrogen, hydroxyl, alkyl and haloalkyl, or $R_0$ is nitrogen which is part of a substituted or unsubstituted, saturated or unsaturated, 3-, 4-, 5-, 6- or 7- membered heterocyclic ring; or R and $R_0$ together is a substituted or unsubstituted, saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered heterocyclic ring;

n is 0, 1 or 2;

Y is hydrogen, alkyl, or haloalkyl, and Y' is hydrogen, alkyl, haloalkyl, amino, alkylamino, or alkoxy, or Y and Y' together is double-bonded oxygen or double-bonded sulfur, or Y and Y' together is a double-bonded nitrogen bonded to hydrogen, hydroxyl, alkyl, or haloalkyl;

$R_1$, $R_2$, $R_3$, $R_4$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are independently selected from hydrogen, halogen, alkyl, cycloalkyl, haloalkyl, hydroxyl, carboxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, alkylmercapto, cyano, cyanoalkyl, nitro, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, alkoxycarbonyl, alkylaminocarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkyloxy, aminocarbonyloxyalkyloxy, arylcarbonyloxy, arylalkylcarbonyloxy, aryloxycarbonyloxy, heterocyclylcarbonyloxy, heterocyclylalkylcarbonyloxy, phosphonooxy, phosphonoalkyloxy, and sulfonamido, or any two of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ form an alkylenedioxy group;

$R_7$ and $R_8$ are independently selected from hydrogen, alkyl, haloalkyl, and alkoxy;

X is selected from hydrogen, alkyl, haloalkyl, alkoxy, alkylmercapto, and hydroxyl with the proviso that X is not hydroxyl when Y and Y' together is oxygen, or X is NR'R", where R' is selected from the group consisting of hydrogen, hydroxyl, alkyl, aryloxy, cyanoalkyl, haloalkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, polyhydroxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, aminoalkyl, arylalkyl, arylalkenyl, arylcycloalkyl, arylcycloalkenyl, aryl, carbocyclyl, and carbocyclylalkyl where the carbocycle of the carbocyclyl and the carbocyclylalkyl is selected from 7-membered carbocyclic rings containing no double bond, or one, two or three double bonds, 6-membered carbocyclic rings containing no double bond, or one, two or three double bonds, 5-membered carbocyclic rings containing no double bond, or one or two double bonds, 4-membered carbocyclic rings containing no double bond or one double bond and 3-membered carbocyclic rings containing no double bond, heterocyclyl, and heterocyclylalkyl, where the heterocycle of the heterocyclyl and heterocyclylalkyl is selected from 7-membered heterocyclic rings, 6-

membered heterocyclic rings, and 5-membered heterocyclic rings, and the aryl of the aryl, arylalkyl, arylalkylenyl, arylcycloalkyl, or arylcycloalkenyl structure or the carbocyclic or heterocyclic structure is optionally substituted with one or more of halo, alkyl, trifluoromethyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, and sulfonamido; and R" is selected from hydrogen, hydroxyalkyl, aminoalkyl, dialkylaminoalkyl, cyanoalkyl, haloalkyl, alkylcarbonylalkylcarbonyloxy, pyridyl, and $COR_{11}$ wherein $R_{11}$ is selected from hydrogen, amino, alkyl, haloalkyl, alkylmercapto, and aryl; or R' and R" together form a 5-, 6- or 7-membered, saturated or unsaturated, heterocyclic ring containing at least one nitrogen, and optionally oxygen and/or sulfur, and the heterocyclic ring is optionally substituted with one or more of halo, alkyl, haloalkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, carboxamido, aldehydo, cyano, oxo, alkylcarbonyloxy, and sulfonamido; or

a pharmaceutically acceptable salt thereof or a prodrug thereof.

10. The compound, prodrug, or salt of claim 9, wherein X is NR'R" where R' is selected from alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl selected from the group consisting of phenylalkyl, indanyl, heterocyclyl, and heterocyclylalkyl, where the heterocycle is selected from furanyl, pyrrolyl, thiophenyl, and imidazolyl, and the cyclic structure of heterocyclyl and heterocyclylalkyl is optionally substituted with one or more of halo, alkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, dialkylamino, mercapto, alkylmercapto, and carboxamido; R" is selected from hydrogen, alkyl, cyanoalkyl, and dialkylaminoalkyl, or R' and R" together form a 5, 6, or 7-member heterocyclic ring, saturated or unsaturated, substituted or unsubstituted, that contains at least one nitrogen and optionally oxygen.

11. The compound, prodrug, or salt of claim 10, wherein X is NR'R" where R' is selected from alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, heterocyclyl, and heterocyclylalkyl where the heterocycle is selected from furanyl, pyrrolyl, and thiophenyl, and the cyclic structure of heterocyclyl and heterocyclylalkyl is optionally substituted with one or more of halo, alkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, and dialkylamino; R" is selected from hydrogen, alkyl, and dialkylaminoalkyl, or R' and R"

together form a 5, 6, or 7-member heterocyclic ring, saturated or unsaturated, substituted or unsubstituted, that contains at least one nitrogen and optionally oxygen.

12. The compound, prodrug, or salt of claim 11, wherein X is NR'R" where R' is selected from dialkylaminoalkyl, arylalkyl, heterocyclyl, and heterocyclylalkyl where the heterocycle is selected from furanyl and pyrrolyl, and the cyclic structure is optionally substituted with one or more of halo, alkyl, haloalkyl, alkoxy, alkylamino and dialkylamino; and R" is selected from hydrogen, alkyl, haloalkyl or dialkylaminoalkyl.

13. The compound, prodrug, or salt of claim 12, wherein X is NR'R" where R' is benzyl, or a heterocyclyl or heterocyclylalkyl selected from 2-furfuryl, 2-pyrrolylmethyl, and (1-methyl-1H-pyrrol-2-yl)methyl; and R" is hydrogen.

14. The compound, prodrug, or salt of claim 13, wherein X is NR'R" where R' is heterocyclyl or heterocyclylalkyl selected from 2-furfuryl, (1H-pyrrol-2-yl)methyl, and (1-methyl-1H-pyrrol-2-yl)methyl; and R" is hydrogen.

15. The compound, prodrug, or salt of any one of claims 8-14, wherein R and $R_0$ are independently selected from hydrogen and hydroxyl, and $R_1$, $R_2$, $R_3$ and $R_4$ are independently selected from halogen, alkoxy, alkyl and haloalkyl; n is 1; $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are independently selected from hydrogen, halogen, alkyl, haloalkyl, hydroxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, and sulfonamido; or any two of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ form an alkylenedioxy group.

16. The compound, prodrug, or salt of claim 15, wherein $R_1$, $R_2$, $R_3$ and $R_4$ are independently selected from halogen, alkoxy, alkyl and haloalkyl; three of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are independently selected from hydrogen, halogen, alkyl, haloalkyl, hydroxyl, alkoxy, formyloxy, alkylcarbonyloxy, hydroxyalkyl, aldehydo, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, mercapto, azido, and substituted or unsubstituted groups selected from alkylsulfinyloxy, alkylsulfonyloxy, carbamate, carbamido, and sulfonamido, and one of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ is independently selected from hydroxyl, hydroxyalkyl, amino, alkylamino, dialkylamino, and mercapto.

17. The compound, prodrug, or salt of claim 16, wherein three of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are independently selected from halogen, alkyl, haloalkyl, alkoxy, amino, alkylamino, aminoalkyl, alkylaminoalkyl, dialkylamino, and mercapto, and one of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ is independently selected from hydroxyl, hydroxyalkyl, aldehydo, amino, alkylamino, dialkylamino, and mercapto; and $R_8$ is methyl.

18. The compound, prodrug, or salt of claim 8, wherein $R_2$ is selected from halogen, alkoxy and alkylmercapto, $R_1$ and $R_3$ are hydrogen; and three of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ are independently selected from hydrogen, halogen, alkyl, haloalkyl, alkoxy, alkylamino, alkylaminoalkyl, and dialkylamino, and one of $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ is independently selected from hydroxyl, hydroxyalkyl, amino, alkylamino, dialkylamino, and mercapto.

19. The compound, prodrug, or salt of claim 18, wherein $R_2$ is selected from halogen and alkoxy, and $R_1$ and $R_3$ are hydrogen.

20. The compound, prodrug, or salt of claim 19, wherein $R_2$ is selected from fluoro and methoxy.

21. The compound of claim 1 or 6, which is selected from:

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethylbenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide **(001)**,

(Z)-2-(5-fluoro-1-(4-formoxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide **(002)**,

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide **(006)**,

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide **(007)**,

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5,6-dimethoxy-2-methyl-1H-inden-3-yl)acetamide **(008)**,

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**012**),

(Z)-2-(1-(3-bromo-4-hydroxy-5-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**013**),

(Z)-2-(1-(3-chloro-4-hydroxy-5-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**014**),

(Z)-2-(1-(3-fluoro-4-hydroxy-5-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**016**),

(Z)-2-(5-fluoro-1-((7-hydroxybenzo[d][1,3]dioxol-5-yl)methylene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**017**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)acetamide (**018**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**019**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(3-hydroxy-4-methoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**020**),

(Z)-2-(5-fluoro-1-(4-(hydroxymethyl)-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**021**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**022**),

(Z)-N-(2-(dimethylamino)ethyl)-2-(5-fluoro-1-(furan-2-ylmethylene)-2-methyl-1H-inden-3-yl)acetamide (**026**),

(Z)-2-(5-fluoro-1-(4-mesyloxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**029**),

(Z)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide (**030**),

(Z)-2-(5-fluoro-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide (**031**),

(Z)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpiperidin-3-yl)acetamide (**032**), and

(Z)-2-(5-fluoro-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpiperidin-3-yl)acetamide (**033**),

(Z)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(5-methylpyridin-3-yl)acetamide (**063**),

(Z)-2-(1-(4-aminocarbonyl-3,5-dimethoxybenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**065**),

(Z)-methyl 2,6-dimethoxy-4-((5-methoxy-2-methyl-3-(2-((1-methylpyrrolidin-3-yl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)benzoate (**066**),

(Z)-2-(1-(3,5-dimethoxy-4-sulfamoylbenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide (**067**),

(Z)-2-(1-(3,5-dimethoxy-4-ureidobenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)-N-((4-methylpyridin-3-yl)methyl)acetamide (**069**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-ethoxycarbonyl-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**095**),

(Z)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**096**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)acetamide (**097**),

(Z)-2-(1-(3,5-dimethoxy-4-sulfamoylbenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)-N-((6-methylpyridin-2-yl)methyl)acetamide (**098**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (**099**),

(Z)-2-(5-fluoro-1-(4-mercapto-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**100**),

(Z)-2-(1-((6-(dimethylamino)pyridin-3-yl)methylene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**130**),

(Z)-2-(1-((2-(dimethylamino)pyrimidin-5-yl)methylene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**131**),

(Z)-N-(2-(dimethylamino)ethyl)-2-(5-fluoro-1-(furan-2-ylmethylene)-2-methyl-1H-inden-3-yl)acetamide (**132**),

(Z)-N-(2-(dimethylamino)ethyl)-2-(5-methoxy-2-methyl-1-(pyridin-4-ylmethylene)-1H-inden-3-yl)acetamide (**133**),

(Z)-N-(2-(dimethylamino)ethyl)-2-(1-((2-(dimethylamino)pyrimidin-5-yl)methylene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**134**),

(Z)-N-(furan-2-ylmethyl)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-methylacetamide (**135**),

(Z)-2-(1-(4-(dimethylamino)benzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(2-(dimethylamino)ethyl)-N-methylacetamide (**138**),

(R,Z)-1-(3-(dimethylamino)pyrrolidin-1-yl)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)ethanone hydrochloride (**139**),

(S,Z)-1-(3-(dimethylamino)pyrrolidin-1-yl)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)ethanone hydrochloride (**141**),

(Z)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-1-(4-methylpiperazin-1-yl)ethanone hydrochloride (**143**),

(R,Z)-2-(2,5-dimethyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-1-(3-(dimethylamino)pyrrolidin-1-yl)ethanone hydrochloride (**144**),

(S,Z)-2-(5,6-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide hydrochloride (**145**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-phenoxyacetamide (**151**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-N-(trifluoromethyl)acetamide (**152**),

(Z)-2-(5-cyano-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**154**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-5-(trifluoromethyl)-1H-inden-3-yl)acetamide (**155**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (**214**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate (**300**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (**301**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate (**302**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (**303**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate (**304**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate (**305**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate (**306**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate **(307)**,

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate **(308)**,

(Z)-(4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate **(309)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate **(311)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate **(312)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate **(313)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate **(314)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate **(315)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(316)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate **(317)**,

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate **(318)**,

(Z)-(4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate **(319)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate **(320)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate **(321)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate **(322)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate **(323)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate **(324)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate **(325)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(326)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate **(327)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate **(328)**,

(Z)-(4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate **(329)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate **(330)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate **(331)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate **(332)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate **(333)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate **(334)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate **(335)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(336)**,

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate **(338)**,

(Z)-(4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate **(339)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate **(340)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate **(341)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate **(342)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate **(343)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate **(344)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (1-methylpiperidin-4-yl)carbamate **(345)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(346)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate **(347)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate **(348)**,

(Z)-(4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenoxy)methyl dihydrogen phosphate **(349)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-(phenylamino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate **(350)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-(phenylamino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(351)**,

(Z)-4-((5-fluoro-3-(2-((3-methoxyphenyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate **(352)**,

(Z)-4-((5-fluoro-3-(2-((3-methoxyphenyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(353)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-2-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (4-nitrophenyl) carbonate **(354)**,

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-2-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate **(355)**,

(Z)-2-(benzylamino)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**202**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-2-((pyridin-4-ylmethyl)amino)acetamide (**203**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-2-(1H-imidazol-1-yl)acetamide (**401**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-2-((furan-2-ylmethyl)amino)acetamide (**404**),

(Z)-2-(cyclopropylamino)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (410),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)-2-(pyrrolidin-1-yl)acetamide (**412**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)-2-((pyridin-3-ylmethyl)amino)acetamide (**413**),

(Z)-2-(dimethylamino)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-phenylacetamide (**415**),

(Z)-2-azido-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-phenylacetamide (**416**),

(Z)-2-(ethylamino)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide (**420**),

(Z)-2-(((1H-imidazol-2-yl)methyl)amino)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(pyridin-3-ylmethyl)acetamide (**423**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-2-((1-methylpyrrolidin-3-yl)amino)-N-(pyridin-3-ylmethyl)acetamide (**425**),

(Z)-N-benzyl-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-2-((oxazol-2-ylmethyl)amino)acetamide (**426**),

(Z)-N-benzyl-2-(cyclopropylamino)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)acetamide (**427**),

(Z)-N-benzyl-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-2-((pyridin-3-ylmethyl)amino)acetamide (**428**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-2-((1-methylpyrrolidin-3-yl)amino)acetamide (**430**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)-2-((oxazol-2-ylmethyl)amino)acetamide (**431**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-2-((1-methylpiperidin-4-yl)amino)-N-(pyridin-2-ylmethyl)acetamide (**433**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(pyridin-2-ylmethyl)-2-((pyridin-3-ylmethyl)amino)acetamide (**434**),

(Z)-2-cyano-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**436**),

or the corresponding Z- or E-isomer thereof, prodrug, or salt thereof.

22. The compound, Z- or E-isomer, prodrug, or salt of claim 21, wherein the compound is selected from:

(Z)-2-(5-fluoro-1-(4-formoxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**002**),

(Z)-N-(furan-2-ylmethyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**006**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**007**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)acetamide (**018**),

(Z)-2-(5-fluoro-1-(4-hydroxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-((1-methyl-1H-pyrrol-2-yl)methyl)acetamide (**019**),

(Z)-N-((1H-pyrrol-2-yl)methyl)-2-(1-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methoxy-2-methyl-1H-inden-3-yl)acetamide (**022**),

(Z)-2-(5-fluoro-1-(4-mesyloxy-3,5-dimethoxybenzylidene)-2-methyl-1H-inden-3-yl)-N-(furan-2-ylmethyl)acetamide (**029**),

(Z)-2-(5-methoxy-2-methyl-1-(3,4,5-trimethoxybenzylidene)-1H-inden-3-yl)-N-(1-methylpyrrolidin-3-yl)acetamide (**030**),

(Z)-4-((3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-5-methoxy-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (**301**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl nicotinate (**311**),

(Z)-4-((5-fluoro-3-(2-((furan-2-ylmethyl)amino)-2-oxoethyl)-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl dihydrogen phosphate (**318**),

(Z)-4-((5-fluoro-2-methyl-3-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl 4-methylpiperazine-1-carboxylate (**326**),

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl benzoate (**330**),

(Z)-4-((3-(2-(benzylamino)-2-oxoethyl)-5-fluoro-2-methyl-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl morpholine-4-carboxylate (**334**), and

(Z)-4-((5-fluoro-2-methyl-3-(2-(((1-methyl-1H-pyrrol-2-yl)methyl)amino)-2-oxoethyl)-1H-inden-1-ylidene)methyl)-2,6-dimethoxyphenyl (2-(dimethylamino)ethyl)carbamate (**343**).

23. A pharmaceutical composition comprising a compound of any one of claims 1-22, a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23, further including at least one therapeutic agent which is not a compound of formula I or II, a pharmaceutically acceptable salt or prodrug thereof.

25. Use of at least one compound of any one of claims 1-22, a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for therapeutically or prophylactically treating a human or nonhuman mammalian patient with cancer, wherein said medicament is to be administered to said patienteither alone or in combination with at least one therapeutic agent which is not a compound of claims 1-22, or pharmaceutically acceptable salt or prodrug thereof.

26. The use of claim 25, wherein the cancer is selected from pancreatic cancer, lung cancer, colorectal cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, head and neck cancer, endocrine cancer, uterine cancer, breast cancer, sarcoma cancer, gastric cancer, hepatic cancer, esophageal cancer, central nervous system cancer, brain cancer, hepatic cancer, germline cancer, lymphoma, and leukemia.

27. The use of claim 26, wherein the cancer is selected from pancreatic cancer, colorectal cancer, and lung cancer.

28. The use of any one of claims 25-27, wherein the cancer is drug-resistant or radiation-resistant.

29. Use of at least one neoplastic or cancerous inhibitory compound of any one of claims 1-22 or a compound selected from (**001**), (**002**), (**006**)-(**008**), (**012**)-(**014**), (**016**)-(**022**), (**026**), (**029**)-(**033**), (**063**), (**065**)-(**067**), (**069**), (**095**)-(**100**), (**130**)-(**135**), (**138**), (**139**), (**141**), (**143**), (**144**), (**145**), (**151**), (**152**), (**154**), (**155**), (**214**), (**300**)-(**309**), (**311**)-(**336**), (**338**)-(**353**), (**355**), (**202**), (**203**), (**401**), (**404**), (**410**), (**412**), (**413**), (**415**), (**416**), (**420**), (**423**), (**425**)-(**428**), (**430**), (**431**), (**433**), (**434**), and (**436**), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for therapeutically or prophylactically treating a human or nonhuman mammalian patient with a disease or condition treatable by the inhibition of one or more neoplastic or cancerous process, wherein said medicament is to be administered to said patient either alone or in combination withat least one therapeutic agent which is not a compound of any one of claims 1-20 or a compound selected from (**001**), (**002**), (**006**)-(**008**), (**012**)-(**014**), (**016**)-(**022**), (**026**), (**029**)-

**(033)**, **(063)**, **(065)**-**(067)**, **(069)**, **(095)**-**(100)**, **(130)**-**(135)**, **(138)**, **(139)**, **(141)**, **(143)**, **(144)**, **(145)**, **(151)**, **(152)**, **(154)**, **(155)**, **(214)**, **(300)**-**(309)**, **(311)**-**(336)**, **(338)**-**(353)**, **(355)**, **(202)**, **(203)**, **(401)**, **(404)**, **(410)**, **(412)**, **(413)**, **(415)**, **(416)**, **(420)**, **(423)**, **(425)**-**(428)**, **(430)**, **(431)**, **(433)**, **(434)**, and **(436)**, or a pharmaceutically acceptable salt or prodrug thereof.

30. The use of claim 29, wherein the neoplastic or cancerous process is selected from growth, proliferation, survival, metastasis, drug resistance and radiation resistance of a tumor cell.

31. The use of claim 25 or 29, wherein the at least one therapeutic agent, which is not a compound of any one of claims 1-22, is selected from an antitumor drug or radiation.

32. A compound of any one of claims 1-22, a pharmaceutically acceptable salt or prodrug thereof, or the pharmaceutical composition of claim 23, for use in the treatment or prophylaxis of a human or nonhuman mammalian patient with cancer.

33. The compound, pharmaceutically acceptable salt or prodrug for use according to claim 32, wherein the cancer is selected from pancreatic cancer, lung cancer, colorectal cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, head and neck cancer, endocrine cancer, uterine cancer, breast cancer, sarcoma cancer, gastric cancer, hepatic cancer, esophageal cancer, central nervous system cancer, brain cancer, hepatic cancer, germline cancer, lymphoma, and leukemia.

34. The compound, pharmaceutically acceptable salt or prodrug for use according to claim 33, wherein the cancer is selected from pancreatic cancer, colorectal cancer, and lung cancer.

35. The compound, pharmaceutically acceptable salt or prodrug for use according to any one of claims 32-34, wherein the cancer is drug-resistant or radiation-resistant.

36. A compound of any one of claims 1-22 or a compound selected from **(001)**, **(002)**, **(006)**-**(008)**, **(012)**-**(014)**, **(016)**-**(022)**, **(026)**, **(029)**-**(033)**, **(063)**, **(065)**-**(067)**, **(069)**, **(095)**-**(100)**, **(130)**-**(135)**, **(138)**, **(139)**, **(141)**, **(143)**, **(144)**, **(145)**, **(151)**, **(152)**, **(154)**, **(155)**, **(214)**, **(300)**-**(309)**, **(311)**-**(336)**, **(338)**-**(353)**, **(355)**, **(202)**, **(203)**, **(401)**, **(404)**, **(410)**, **(412)**, **(413)**, **(415)**, **(416)**, **(420)**, **(423)**, **(425)**-**(428)**, **(430)**, **(431)**, **(433)**, **(434)**, and **(436)**, or a

pharmaceutically acceptable salt or prodrug thereof, for use in the treatment ot prophylaxis of a disease or condition treatable by the inhibition of one or more neoplastic or cancerous process in a human or nonhuman mammalian patient, either alone or in combination with at least one therapeutic agent which is not a compound of any one of claims 1-20 or a compound selected from **(001)**, **(002)**, **(006)-(008)**, **(012)-(014)**, **(016)-(022)**, **(026)**, **(029)-(033)**, **(063)**, **(065)-(067)**, **(069)**, **(095)-(100)**, **(130)-(135)**, **(138)**, **(139)**, **(141)**, **(143)**, **(144)**, **(145)**, **(151)**, **(152)**, **(154)**, **(155)**, **(214)**, **(300)-(309)**, **(311)-(336)**, **(338)-(353)**, **(355)**, **(202)**, **(203)**, **(401)**, **(404)**, **(410)**, **(412)**, **(413)**, **(415)**, **(416)**, **(420)**, **(423)**, **(425)-(428)**, **(430)**, **(431)**, **(433)**, **(434)**, and **(436)**, or a pharmaceutically acceptable salt or prodrug thereof.

37. The compound or a pharmaceutically acceptable salt or prodrug thereof for use according to claim 36, wherein the neoplastic or cancerous process is selected from growth, proliferation, survival, metastasis, drug resistance and radiation resistance of a tumor cell.