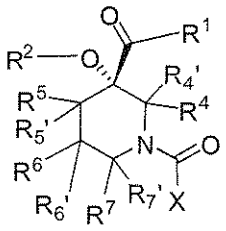
In its many embodiments, the present invention provides novel compounds having HDM2 or MDM2 antagonist activity, methods of preparing such compounds, pharmaceutical compositions comprising one or more of such compounds, methods of preparing pharmaceutical formulations comprising one or more of such compounds, methods of treatment or prevention of one or more diseases associated with HDM2, MDM2, p53, or p53 peptides by administering such compounds or pharmaceutical compositions.

WO2008/005268 (equivalent of US Patent Publication US 2008/0004287 A1) discloses substituted piperidine compounds as HDM2 inhibitors.

Summary ~~of the Invention~~

In its many embodiments, the present ~~invention~~disclosure provides a novel class of substituted piperidine compounds, pharmaceutical compositions comprising one or more said compounds, and methods for using said compounds for treating or preventing a disease associated with the HDM2 protein.

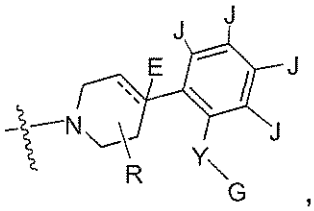
Accordingly, ~~in one aspect~~ the present ~~invention~~disclosure provides a compound of Formula 1



Formula 1

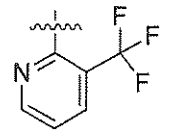
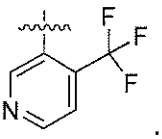
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:

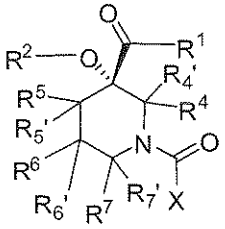


, wherein:

R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, and $R^{7'}$ independently are selected from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl; and

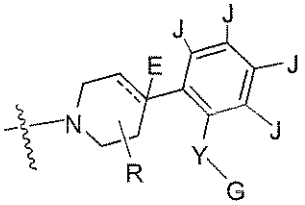
X is  or .

~~In another aspect, t~~The present ~~invention~~disclosure also provides a compound represented by Formula 2 below:



Formula 2

wherein R^1, R^2, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, $R^{7'}$ and X, are selected independently of each other and wherein R^1 is:



wherein E is selected from the group consisting of H, halo, OH, CN, -O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, -C(O)OH, $-C(O)NR^8R^{8'}$, $-(C_1\text{-}C_6)$alkyl-C(O)OH, $-(C_1\text{-}C_6)$alkyl-$C(O)NR^8R^{8'}$, $-(C_2\text{-}C_6)$alkenyl, $-(C_2\text{-}C_6)$alkynyl and heterocyclyl,

J is independently selected from the group consisting of H and halogen,

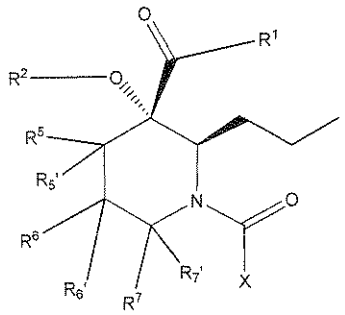
G, Y and R may or may not be present,

wherein when Y is not present, G is not present,

when Y is present it is selected from the group consisting of O,S, NR^8, SO_2, and $CR^8R^{8'}$,

alkylCO_2H, -alkylCO_2alkyl, -alkylCONHalkyl, -alkyl$CONH_2$, -alkylCON(alkyl)$_2$, -alkylCON(alkenyl)$_2$, wherein each of said cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, heteroalkyl, heteroalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of alkyl, heteroalkyl, heteroalkenyl, alkenyl, alkynyl, alkoxyalkoxy, -S-alkyl-S-alkyl, hydroxyalkyl, -alkylSH, hydroxyalkenyl, -alkyl-NH_2, -alkyl-N(alkyl)$_2$, and –alkylNHalkyl.

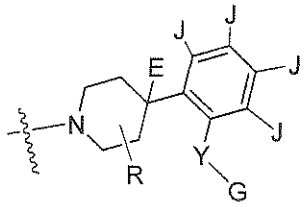
In a first aspect, there is provided a compound of Formula 1A:



Formula 1A

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:



, wherein:

E is present, and is selected from the group consisting of H, halo, OH, CN, -O(C_1-C_6)alkyl, -(C_1-C_6)alkyl, -C(O)OH, -C(O)N$R^8R^{8'}$, -(C_1-C_6)alkyl-C(O)OH, -(C_1-C_6)alkyl-OH, -(C_1-C_6)alkyl-C(O)N$R^8R^{8'}$, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, heterocyclyl, and heteroaryl;

each J independently is selected from the group consisting of H and halogen;

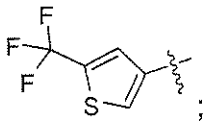
Y and R may or may not be present, when Y is present, it is selected from the group consisting of O, S, NR^8, SO_2, and $CR^8R^{8'}$;

R when present is one or more moieties independently selected from the group consisting of -$(C_1$-$C_6)$alkyl, and –$(CR^8R^{8'})_n$-C(O)OH;

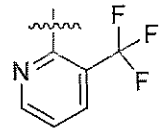
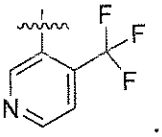
G is present and is selected from the group consisting of–$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, and –$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH;

each R^8 and $R^{8'}$ is independently selected from the group consisting of H, Deuterium (D), and $(C_1$-$C_6)$alkyl; or wherein R^8 and $R^{8'}$ together with the carbon to which each is attached form $(C_3$-$C_8)$cycloalkyl;

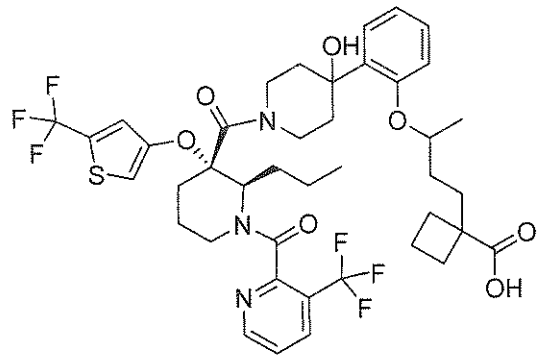
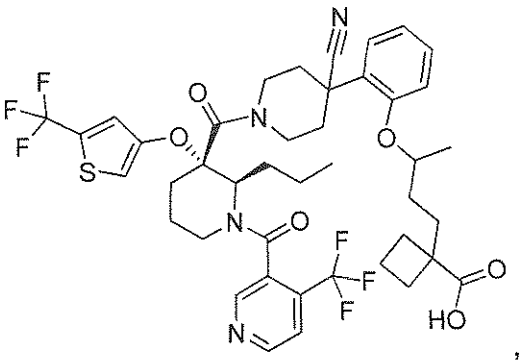
each n independently is 0-10; provided that when n is 0, any oxygen, nitrogen or sulfur atom of Y is not directly linked to any oxygen, nitrogen, sulfur or phosphorus atom of G;

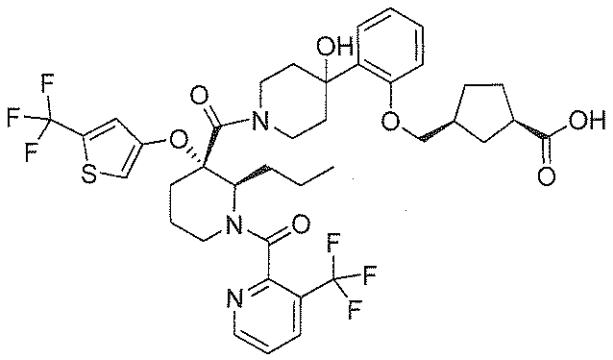
R^2 is ;

R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, and $R^{7'}$ independently are selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl; and

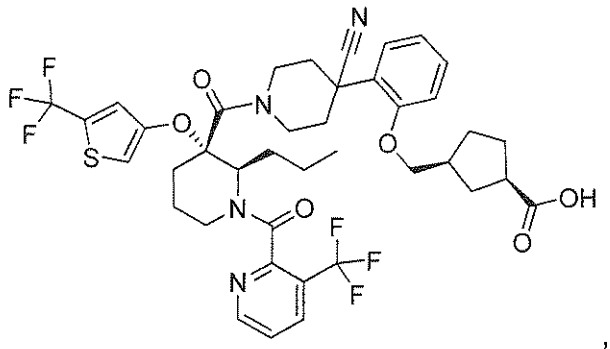
X is  or .

In a second aspect, there is provided a compound selected from the group consisting of:

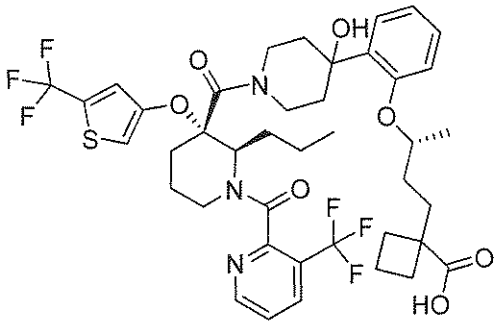
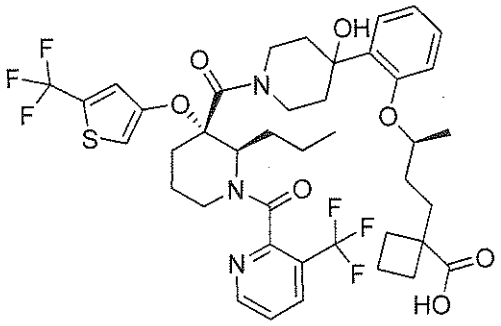
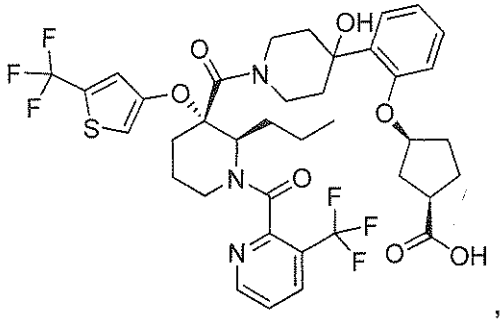
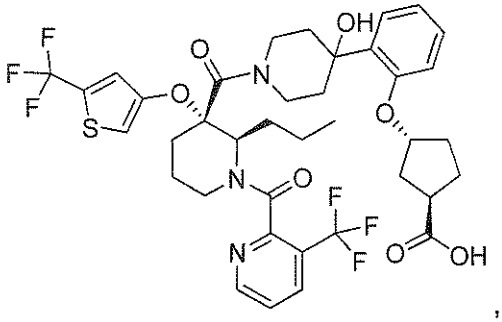
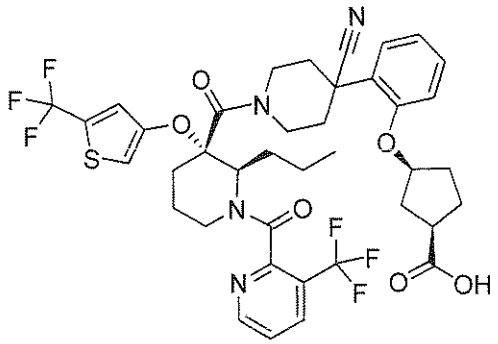
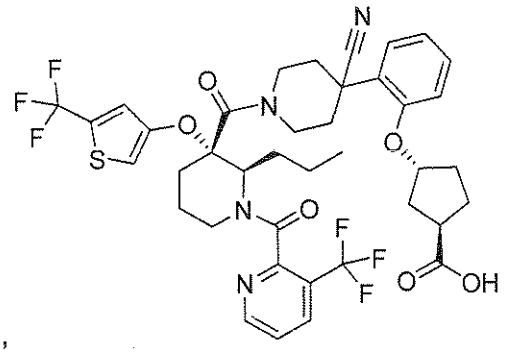
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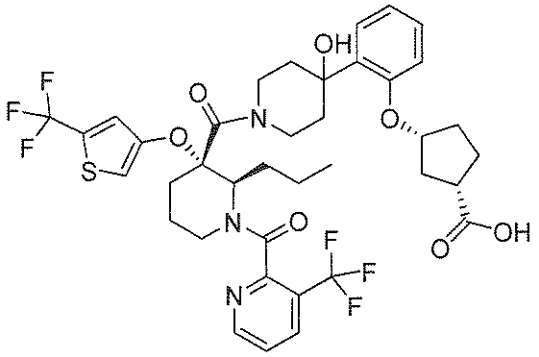
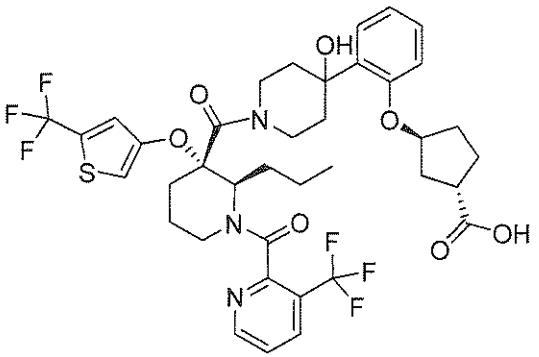
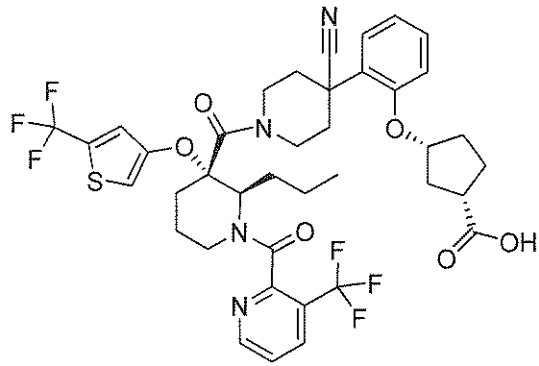
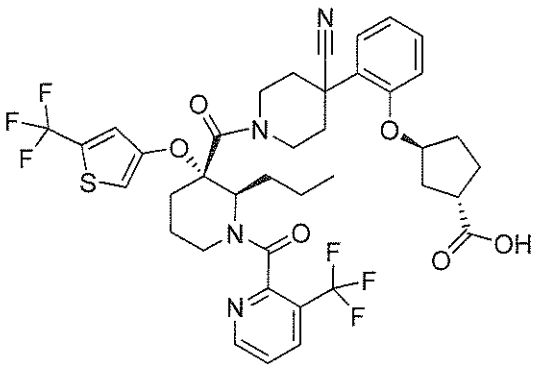
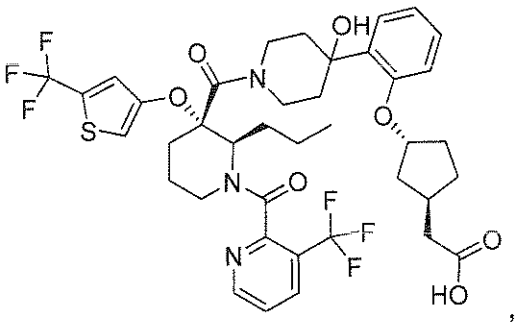
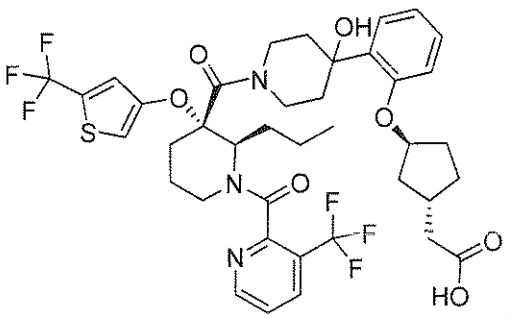
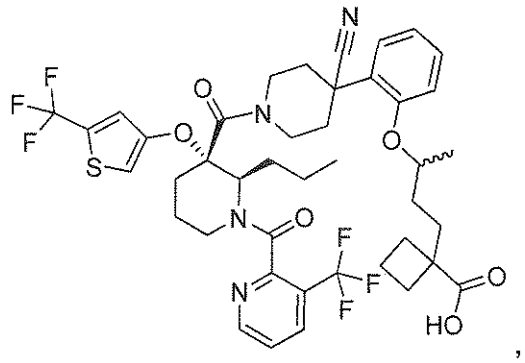
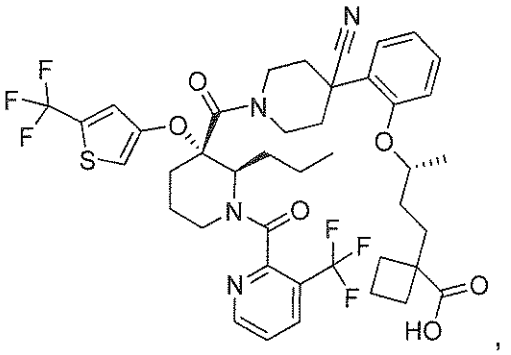

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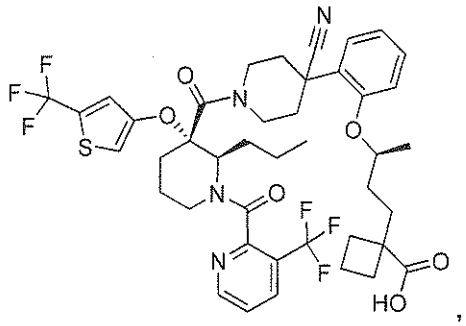
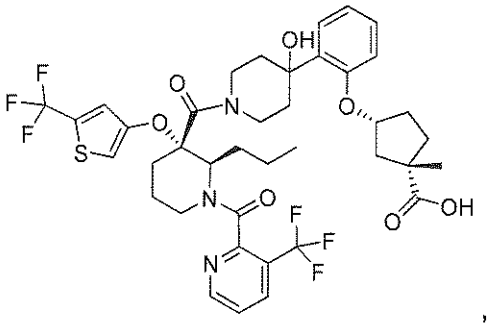
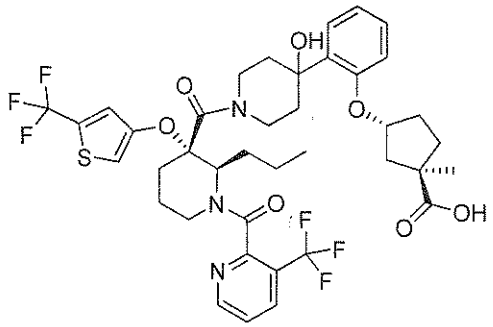
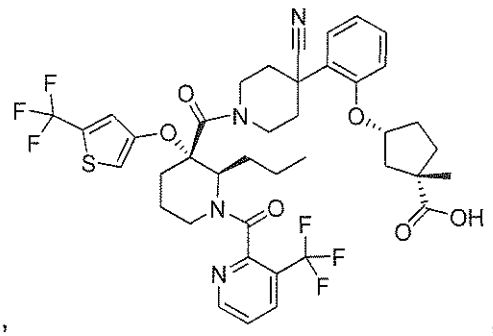
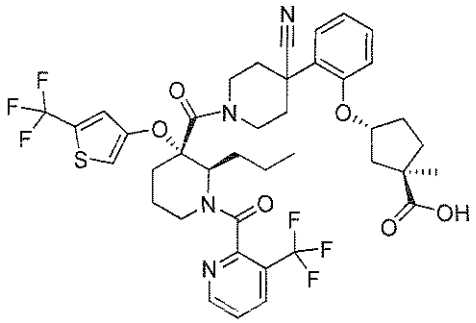
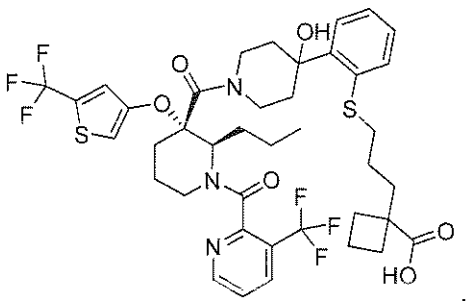
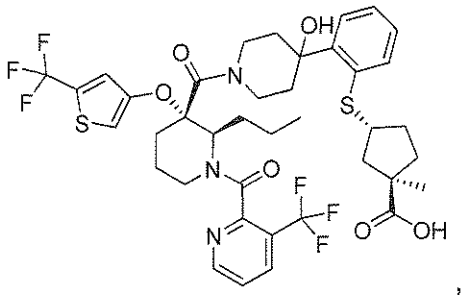
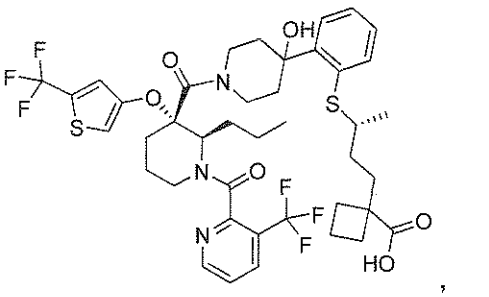
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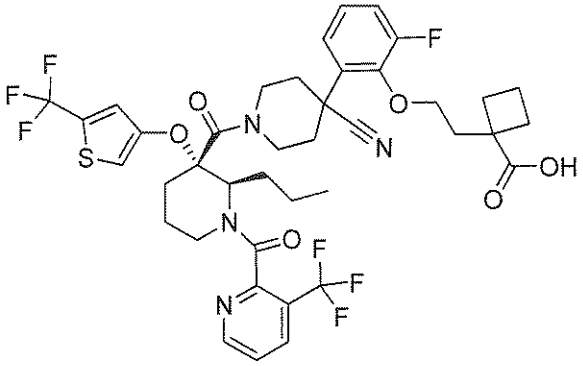

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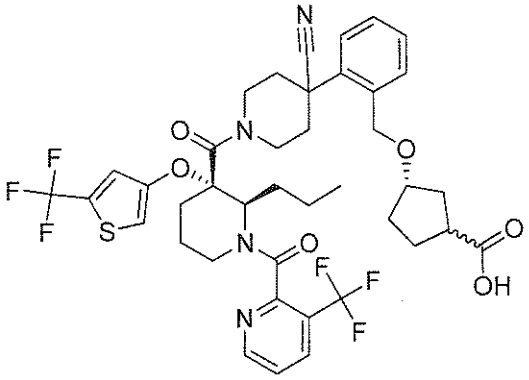

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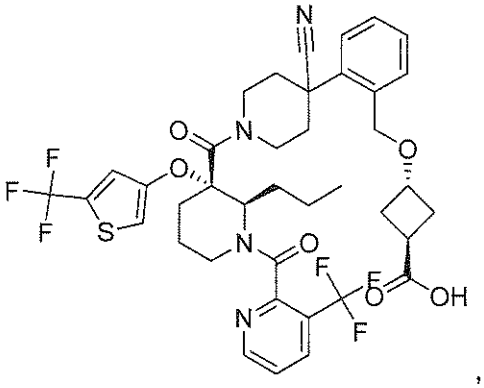

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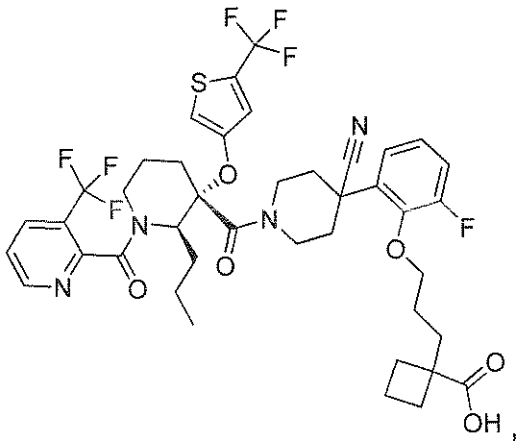
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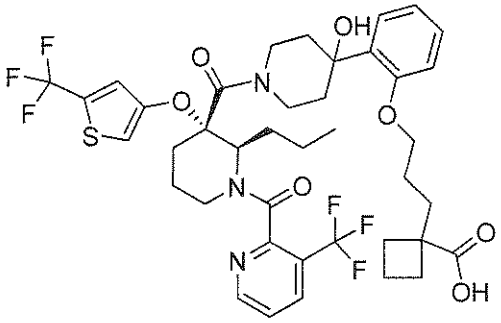
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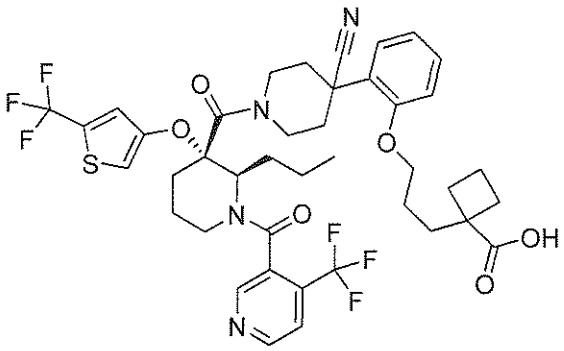


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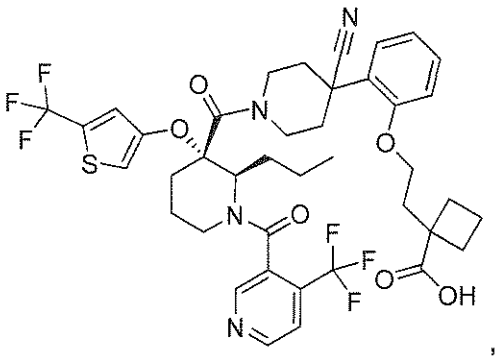


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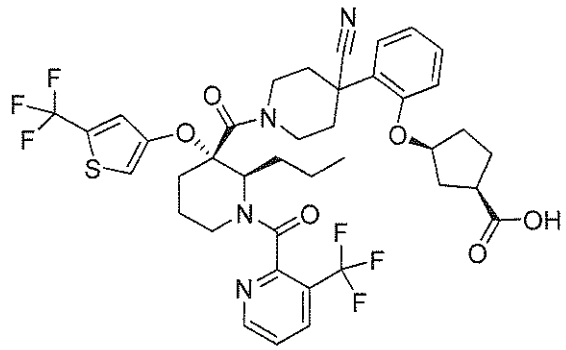




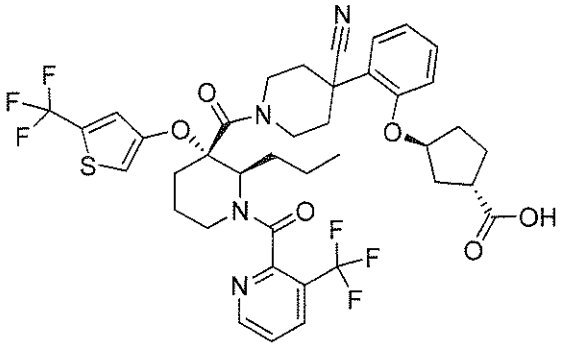
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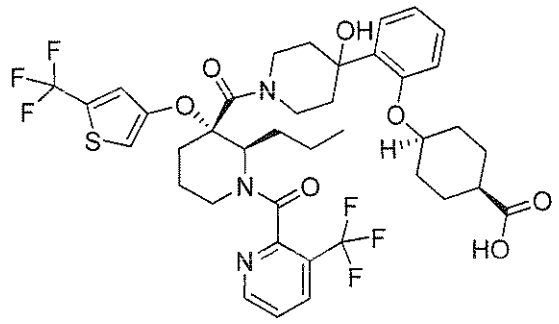
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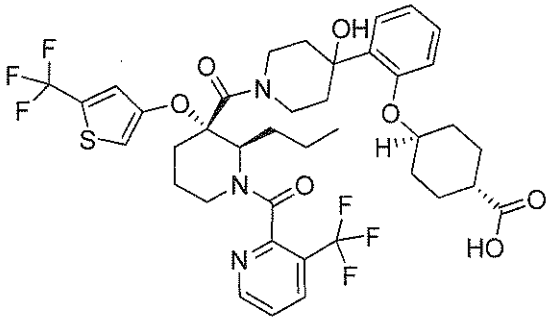
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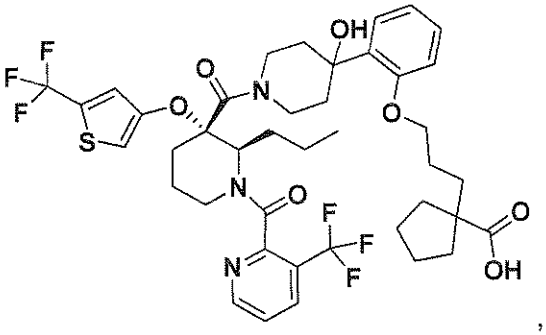
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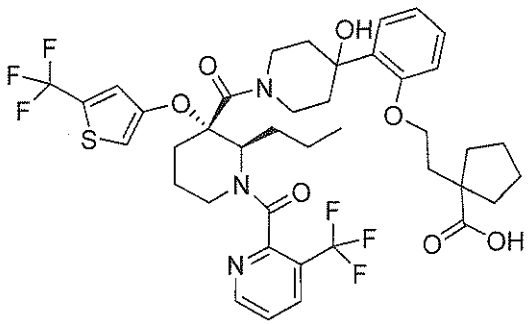
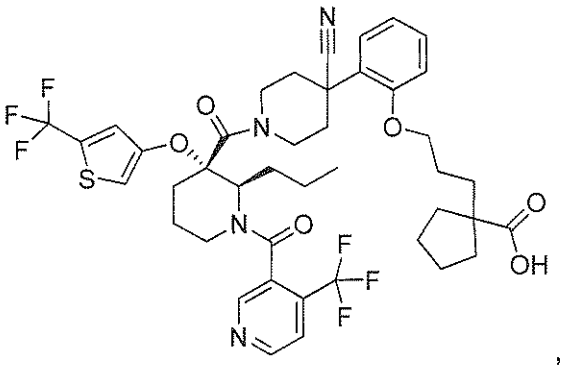
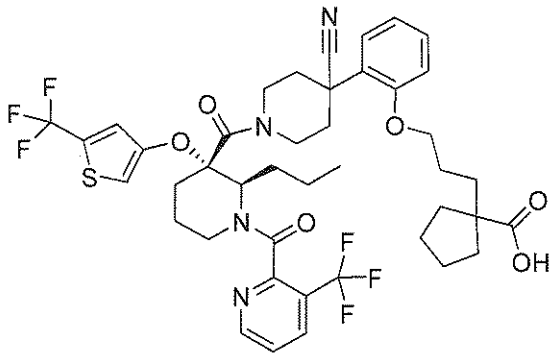
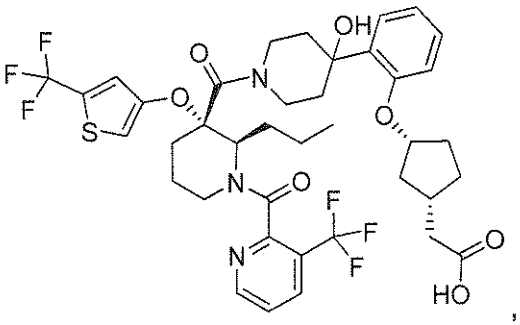
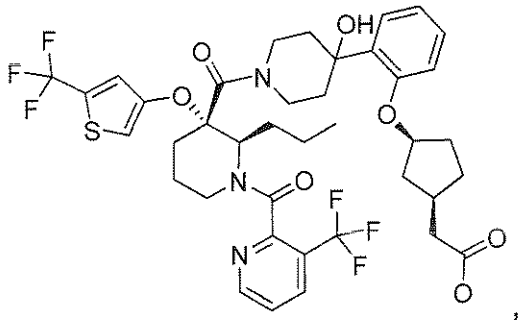
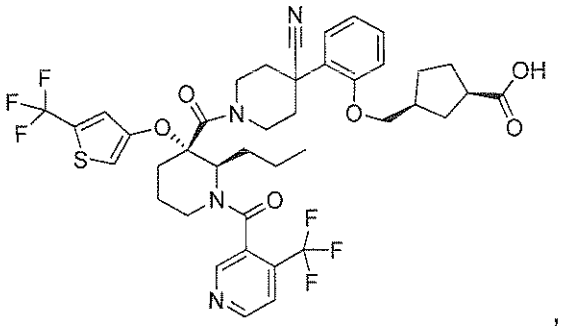
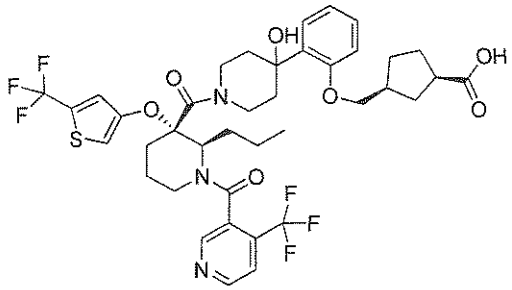
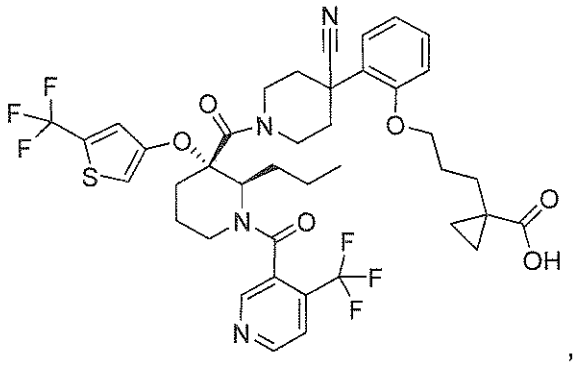
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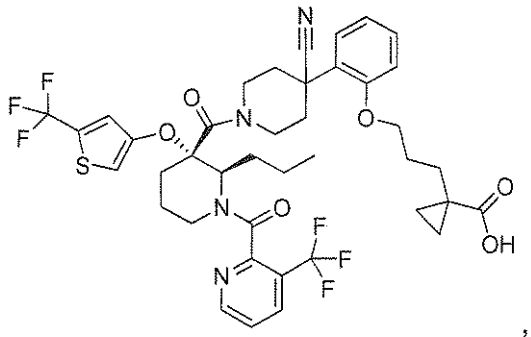
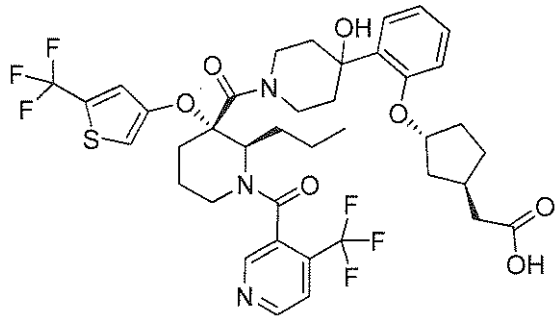
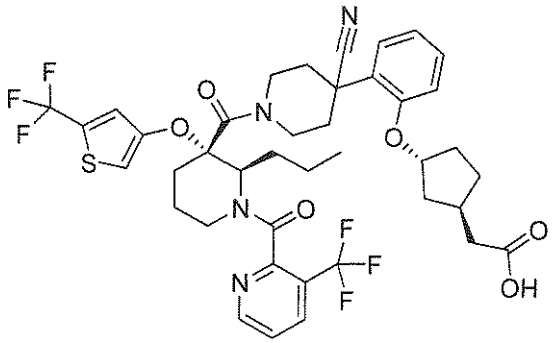
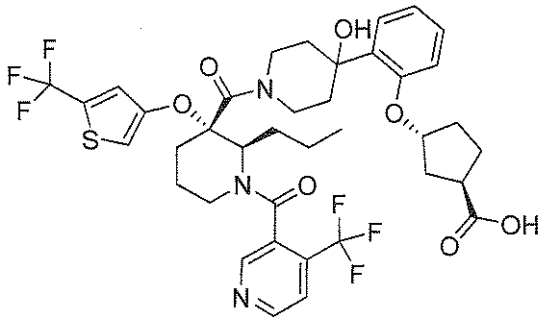
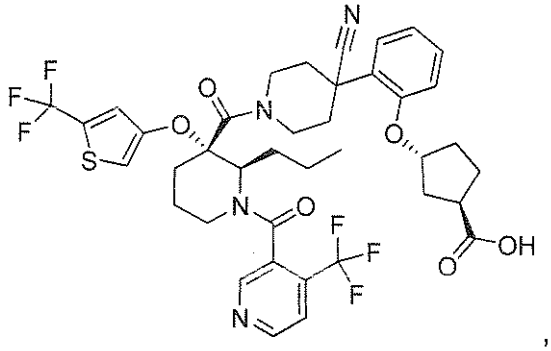
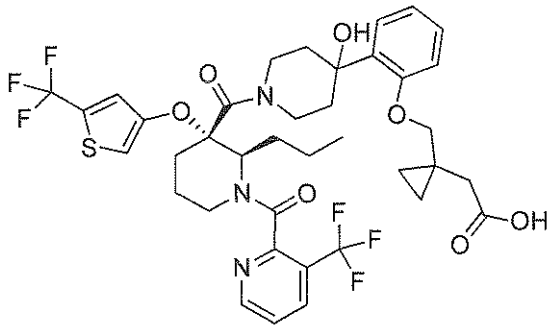


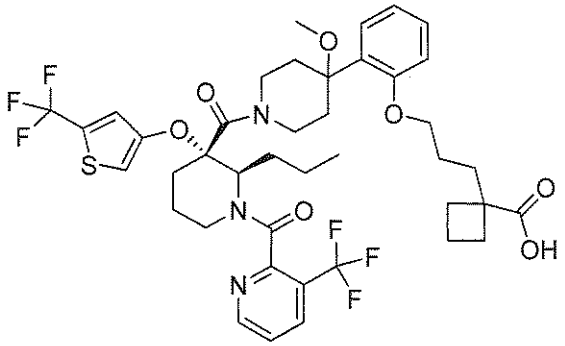
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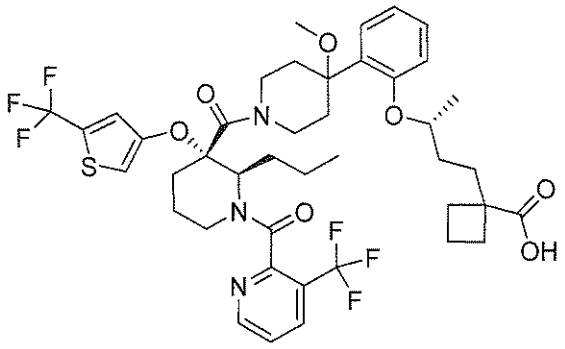
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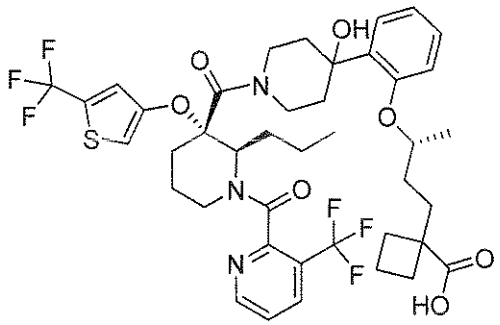
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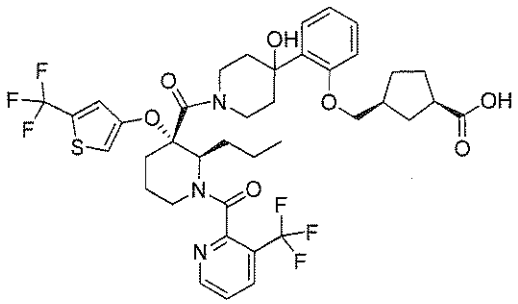
or a pharmaceutically acceptable salt thereof.

In a third aspect, there is provided a compound that is



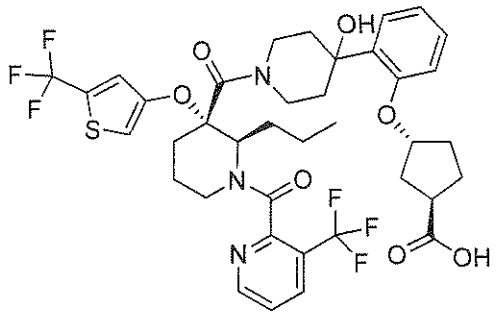
or a pharmaceutically acceptable salt thereof.

In a fourth aspect, there is provided a compound that is



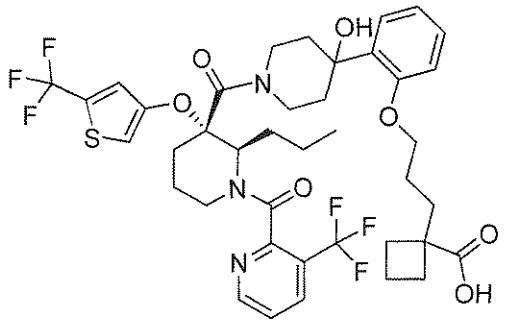
or a pharmaceutically acceptable salt thereof.

In a fifth aspect, there is provided a compound that is



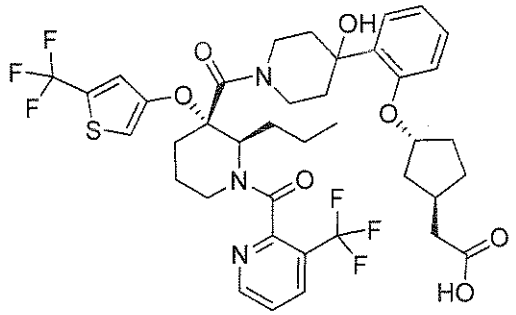
or a pharmaceutically acceptable salt thereof.

In a sixth aspect, there is provided a compound that is



or a pharmaceutically acceptable salt thereof.

In a seventh aspect, there is provided a compound that is



or a pharmaceutically acceptable salt thereof.

In an eighth aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of at least one compound as defined above or a pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier.

In a ninth aspect, there is provided the use of a compound as defined above for the preparation of a medicament for the treatment of cancer selected from the group consisting of colorectal, bladder, breast, colon, rectum, endometrium, kidney, liver, lung, head and neck, esophagus, gall bladder, cervix, pancreas, prostrate, larynx, ovaries, stomach, uterus, Non-Hodgkin's lymphoma, sarcoma, osteosarcoma, liposarcoma, thyroid cancer, hematopoietic tumors of the lymphoid lineage, hematopoetic tumors of myeloid lineage, myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, skin cancer, mesothelioma, seminoma, teratocarcinoma, xenoderoma pigmentosum, keratoctanthoma, glioblastoma, acute myeloid leukemia, acute lymphoblastic leukemia, thyroid follicular cancer and Kaposi's sarcoma.

In the assay for HDM2 inhibitory activity (fluorescence polarization assay) [Zhang et al., J. Analytical Biochemistry 331: 138-146 (2004)] the compounds of the present invention exhibit FP IC_{50}, values of less than 0.5 μM. Also, the cytochrome P450 3A4 enzyme inhibition studies of the compounds of the present invention indicate that these compounds have an IC_{50} CYP3A4 (pre and co incubation) of more than 1 μM. The compounds of the present invention by themselves or in combination with one or more other suitable agents disclosed later in this application can be useful as HDM2 or MDM2 inhibitors and can be useful in the treatment and prevention of proliferative diseases such as cancers.

Such treatment or prevention can be done with the inventive compound as well as with pharmaceutical compositions or formulations comprising the compound.

Detailed description of the invention

In one embodiment, the present invention provides compounds illustrated as Formula 1, as described above, or pharmaceutically acceptable salts, solvates, esters, or prodrugs thereof, wherein the various moieties are as described above.