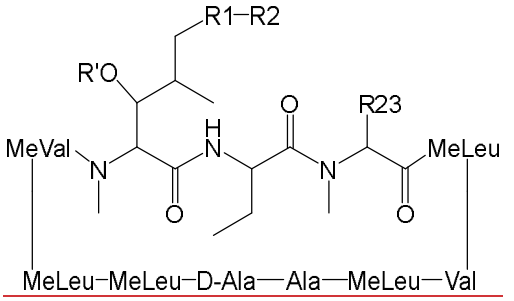
amsacrine, anastrozole, asparaginase, bcg, beta-hydroxy beta-methylbutyrate, bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carfilzomib, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, delanzomib, dienestrol, diethylstilbestrol, disulfiram, docetaxel, doxorubicin, epigallocatechin-3-gallate, epirubicin, epoxomicin, estradiol, estramnustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, ixazomib, marizomib, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oprozomib, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, vinorelbine, or a combination thereof.

[0027] In some embodiments, the one or more cancer therapies comprise surgery, chemotherapy, radiotherapy, immunotherapy, or a combination thereof

[0027a] Disclosed herein is a use of a composition comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, in the manufacture of a medicament for treating a proliferative disease, for alleviating one or more symptoms of a proliferative disease, for preventing or delaying the onset of one or more symptoms of a proliferative disease, or for preventing a proliferative disease, in a subject, wherein the proliferative disease is cancer,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

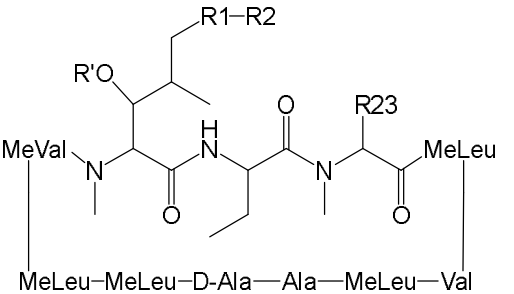
xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

[0027b] Disclosed herein is a pharmaceutical composition, comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, for use in preventing or treating a proliferative disease, or alleviating one or more symptoms of a proliferative disease, or preventing or delaying the onset of one or more symptoms of a proliferative disease, or preventing or delaying the onset of a proliferative disease,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

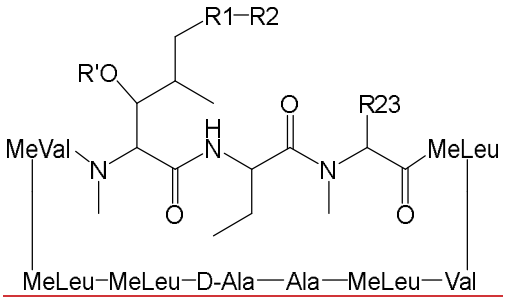
xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

[0027c] Disclosed herein is a use of a composition comprising a cyclosporine analogue of Formula L, or a pharmaceutically acceptable salt, solvate, stereoisomer thereof, in the manufacture of a medicament for sensitizing cancer cells to anti-cancer agents or therapies, wherein the cancer cells comprise cells of liver cancer, thereby sensitizing the cancer cells to one or more anticancer agents, one or more cancer therapies, or both,



Formula L

wherein:

a. R' is H or acetyl;

b. R1 is a saturated or unsaturated straight or branched aliphatic carbon chain from 2 to 15 carbon atoms in length;

c. R2 is selected from the group consisting of:

i. H;

ii. an unsubstituted, N–substituted, or N,N-disubstituted amide;

iii. a N-substituted or unsubstituted acyl protected amine;

iv. a N-substituted or unsubstituted amine;

v. a carboxylic acid;

vi. a nitrile;

vii. an ester;

viii. a ketone;

ix. a hydroxy, dihydroxy, trihydroxy, or polyhydroxy alkyl; and

x. a substituted or unsubstituted aryl;

xi. a saturated or unsaturated. straight or branched aliphatic chain optionally containing a substituent selected from the group consisting of a hydrogen, a ketone, a hydroxyl, a nitrile, a carboxylic acid, an ester, a 1,3-dioxolane, a halogen, and an oxo;

xii. an aromatic group containing a substituent selected from the group consisting of a halogen, an ester, and a nitro; and

xiii. a combination of the saturated or unsaturated, straight or branched aliphatic chain of (xi) and the aromatic group of (xii); and

d. R23 is a saturated or unsaturated straight chain or branched optionally substituted aliphatic carbon chain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] **FIGS. 1A-C** are plots showing antifibrotic activity of CRV431 in human precision cut liver slices (PCLS).

[0029] **FIGS. 2A-B** are PCA plots showing the distribution of the sample and donor for comparison of TGFb/PDGF + CRV431 vs TGFb/PDGF + Vehicle by group.

[0030] **FIG. 2C** is a MA plot, and **FIGS. 3A-B** are heatmap, generated for comparison of TGFb/PDGF + CRV431 vs TGFb/PDGF + Vehicle by group.

[0031] **FIG. 4** is a volcano plot showing significant differently expressed genes identified in the comparison of TGFb/PDGF + CRV431 vs TGFb/PDGF + Vehicle by group.

[0032] **FIGS. 5A-B** are venn diagrams showing significant gene overlapping between all three donors.

[0033] **FIGS. 6A-B** are PCA plots showing the distribution of the sample and donor for comparison of Nonstimulated + CRV431 vs Nonstimulated + Vehicle by group.

[0034] **FIG. 6C** is a MA plot, and **FIGS. 7A-B** are heatmap generated for comparison of Nonstimulated + CRV431 vs Nonstimulated + Vehicle by group.

[0035] **FIG. 8** is a volcano plot showing significant differently expressed genes identified in the comparison of Nonstimulated + CRV431 vs Nonstimulated + Vehicle by group.