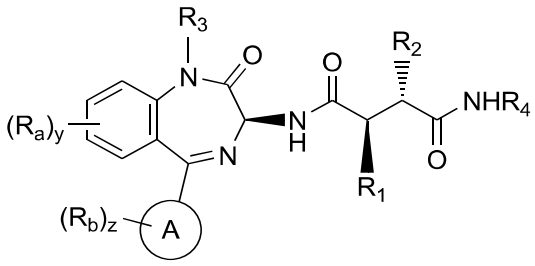
SUMMARY

[005] The present disclosure provides a composition comprising one or more B-cell maturation antigen (BCMA)-targeting immuno-therapeutics and one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

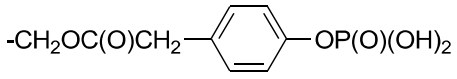
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

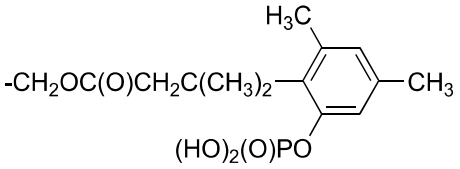
R_4 is H or R_y;

R_x

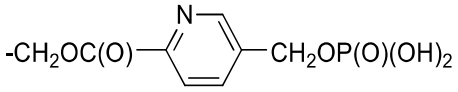
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$,

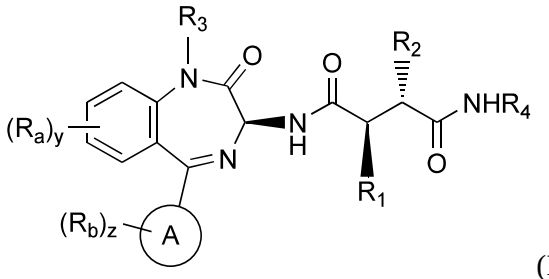
cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is 1 or 2.

[006] The present disclosure also provides a method of treating, suppressing or inhibiting a B-cell maturation antigen (BCMA)-related disorder or a disease associated with BCMA expression in a subject comprising the step of administering to said subject a first composition comprising one or more BCMA-targeting immuno-therapeutics and a second composition comprising one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

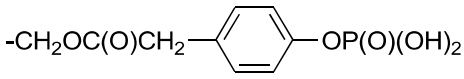
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

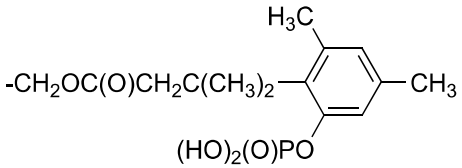
R_4 is H or R_y;

R_x

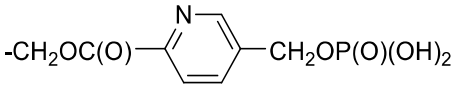
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$,

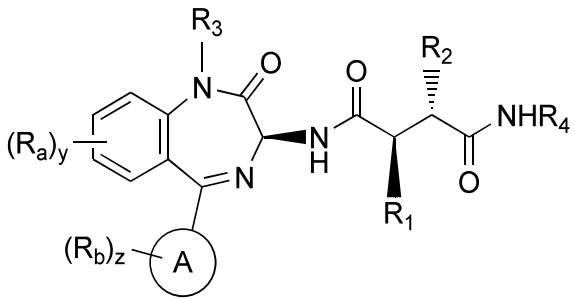
cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is 1 or 2.

[007] The present disclosure also provides a method of treating, suppressing or inhibiting a proliferative disease in a subject comprising the step of administering to said subject a first composition comprising one or more B-cell maturation antigen (BCMA)-targeting immuno-therapeutics and a second composition comprising one or more compounds represented by the structure of Formula (I):



and/or at least one salt thereof, wherein:

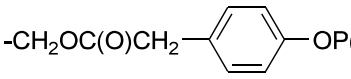
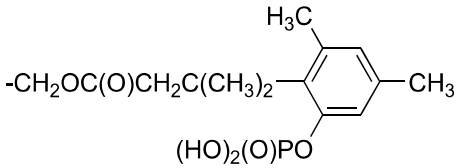
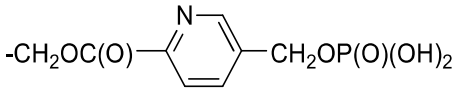
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, , , or ;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$,

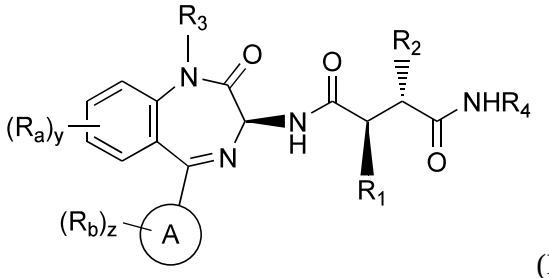
cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is 1 or 2.

[008] The present disclosure also provides a method of improving the efficacy of an anti-B-cell maturation antigen (BCMA) therapy in a subject comprising the step of administering to said subject a first composition comprising one or more BCMA-targeting immuno-therapeutics and a second composition comprising one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

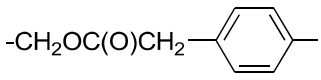
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

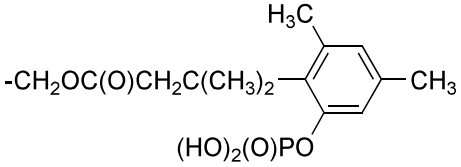
R_4 is H or R_y;

R_x

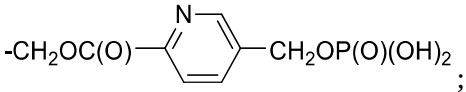
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OH_3$, or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

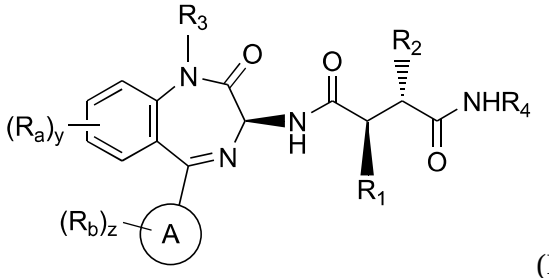
each R_a is independently F, Cl, -CN, $-OCH_3$, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is 1 or 2.

[009] The present disclosure also provides a method of decreasing B-cell maturation antigen (BCMA) shedding from a cancer cell in a subject comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

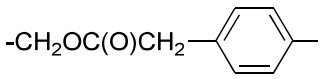
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

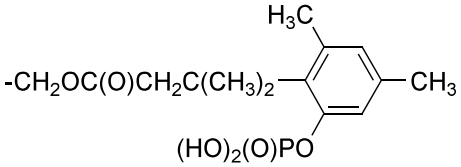
R_4 is H or R_y;

R_x

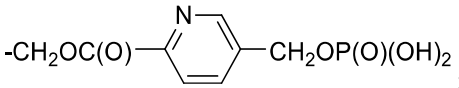
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$,

or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$,

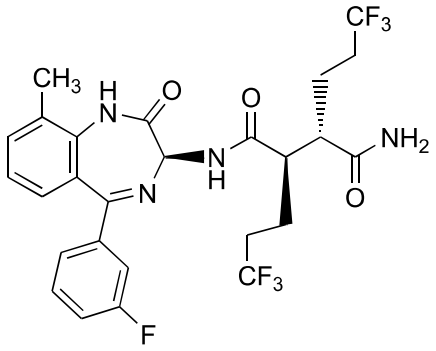
cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

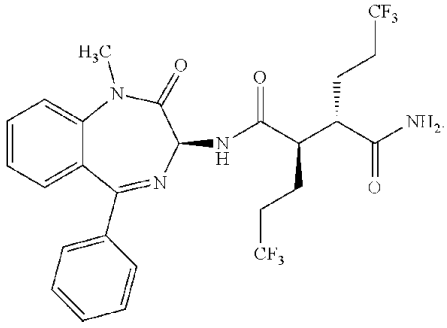
z is 1 or 2.

[0009a] In one aspect, provided herein is a composition comprising one or more B-cell maturation antigen (BCMA)-targeting immuno-therapeutics wherein said BCMA-targeting immunotherapeutic comprises chimeric antigen receptor T (CAR-T) cells, a bispecific antibody, an antibody-drug conjugate, a tri-specific antibody, a trifunctional antibody, a chemically-linked Fab, or a bi-specific T-cell engager (BiTE) and one or more compounds represented by the structure of formula (22):



(22)

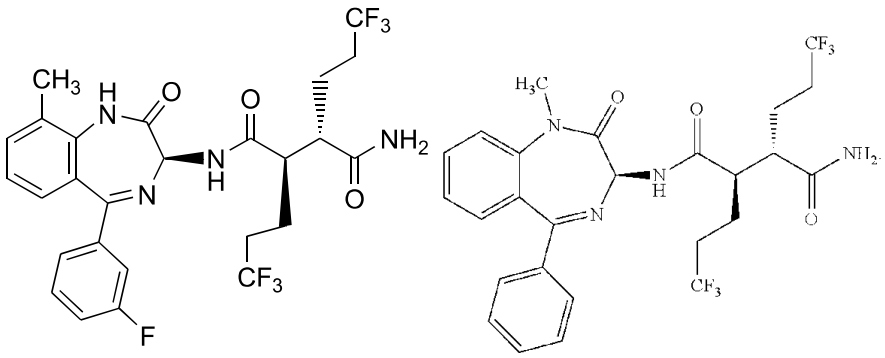
or by the structure of formula (1):



(1),

and/or at least one salt thereof

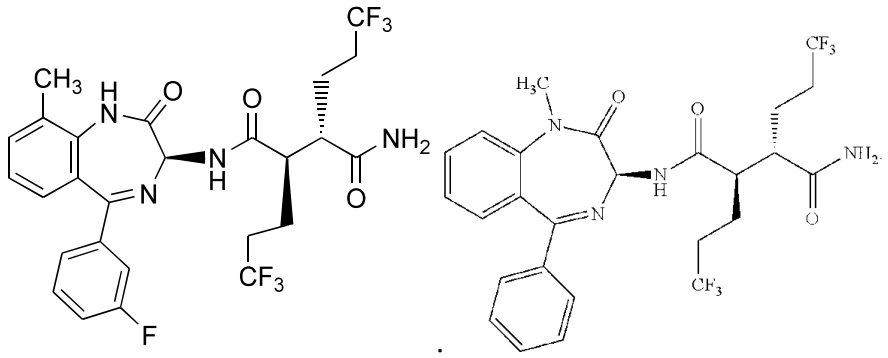
[0009b] In another aspect, provided herein is use of a first composition comprising one or more BCMA-targeting immuno-therapeutics in the manufacture of a first medicament and a second composition comprising one or more compounds represented by the structure formula (1) or formula (22):



and/or at least one salt thereof in the manufacture of a second medicament,

wherein the first and second medicaments are to be used in combination therapy for treating, suppressing, or inhibiting a B-cell maturation antigen (BCMA)-related disorder or a disease associated with BCMA expression in a subject, wherein said BCMA-related disorder or disease associated with BCMA expression comprises multiple myeloma or lymphoma

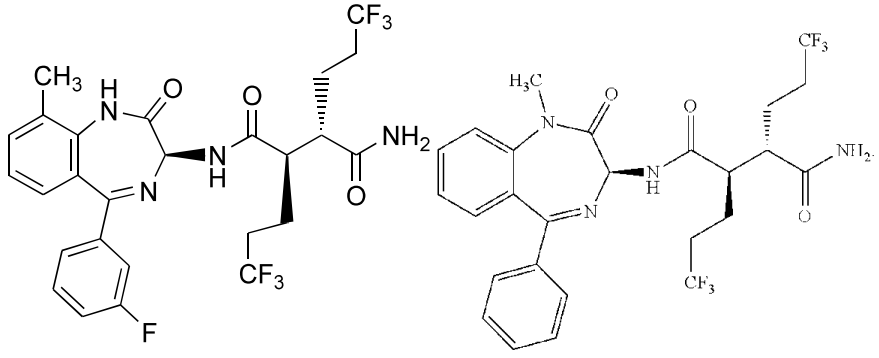
[0009c] In another aspect, provided herein is use of a composition comprising one or more compounds represented by the structure of formula (1) or formula (22):



in the manufacture of a medicament for improving the efficacy of one or more BCMA-targeting immuno-therapeutics,

wherein said BCMA-targeting immunotherapeutic comprises chimeric antigen receptor T (CAR-T) cells, a bispecific antibody, an antibody-drug conjugate, a tri-specific antibody, a trifunctional antibody, a chemically-linked Fab, or a bi-specific T-cell engager (BiTE).

[0009d] In another aspect, provided herein is use of a composition comprising one or more compounds represented by the structure of formula (1) or formula (22):



in the manufacture of a medicament for decreasing B-cell maturation antigen (BCMA) shedding from a BCMA-expressing cell in a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[0011] **Figure 1. Levels of cell-bound BCMA on multiple myeloma (MM) cells incubated with γ-secretase inhibitors (GSIs)**. U266 cells (MM cell line) were incubated with 0.3nM, 0.5nM, 1nM or 3nM of GSI (Compound 1, Compound 22, LY3039478 or PF3084014) for 24 hours, and BCMA levels were measured by flow cytometry.

[0012] **Figure 2A. Levels of soluble BCMA in cell media after incubation of multiple myeloma (MM) cells with Compound 22.** U266 cells (MM cell line) were incubated with 0.3nM, 1nM, 3nM and 10nM of Compound 22 for 24 hours, and levels of soluble BCMA were measured by ELISA.

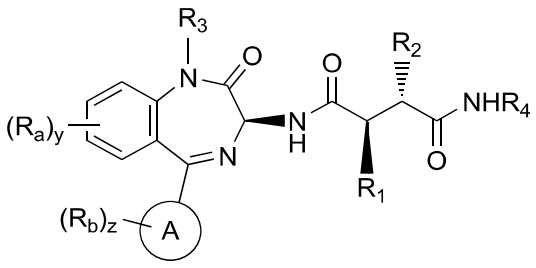
[0013] **Figure 2B. Levels of soluble BCMA in cell media after incubation of multiple myeloma (MM) cells with LY3039478.** U266 cells (MM cell line) were incubated with 0.3nM, 1nM, 3nM and 10nM of LY3039478 for 24 hours, and levels of soluble BCMA were measured by ELISA.

[0014] **Figure 2C. Levels of soluble BCMA in cell media after incubation of multiple myeloma (MM) cells with Compound 1.** U266 cells (MM cell line) were incubated with 0.3nM, 1nM, 3nM and 10nM of Compound 1 for 24 hours, and levels of soluble BCMA were measured by ELISA.

[0015] **Figure 2D. Levels of soluble BCMA in cell media after incubation of multiple myeloma (MM) cells with PF3084014.** U266 cells (MM cell line) were incubated with 0.3nM, 1nM, 3nM and 10nM of PF3084014 for 24 hours, and BCMA levels were measured by ELISA.

[0016] **Figure 3. Levels of soluble BCMA in cell media after incubation of multiple myeloma (MM) cells with γ-secretase inhibitors (GSIs)**. U266 cells (MM cell line) were incubated with 0.3nM, 1nM, 3nM and 10nM of GSI (Compound 1, Compound 22, LY3039478 or PF3084014) for 24 hours, and BCMA levels were measured by ELISA.

[0017] **Figure 4A. Levels of BCMA in Lymphoma Cell Lines after treatment with the γ-secretase inhibitor (GSI), Compound 1.** Cells from five different lymphoma cell lines (SP49 (MCL with Notch4 GOF); Toledo (DLBCL); RC (Double Hit DLBCL – MYC, BCL2); SUDHL-4 (DLBCL); and SUDHL-6



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

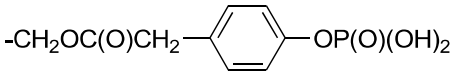
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

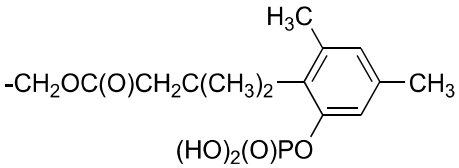
R_4 is H or R_y;

R_x

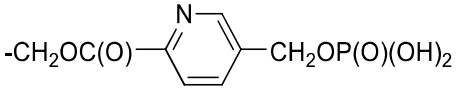
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$, or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$,

cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

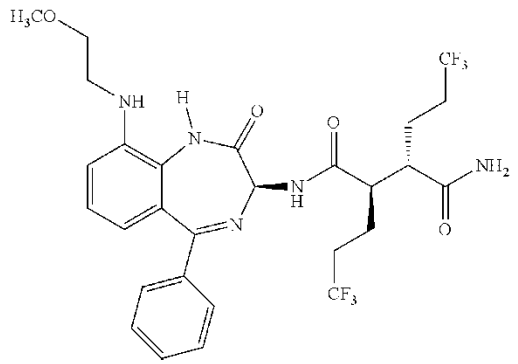
y is zero, 1 or 2; and

z is zero, 1, or 2.

[0025] In one embodiment, the present invention provides compositions comprising compounds as described herein formulated at a dose of 4 mg. In one embodiment, the present invention provides compositions comprising compounds as described herein formulated for intravenous administration.

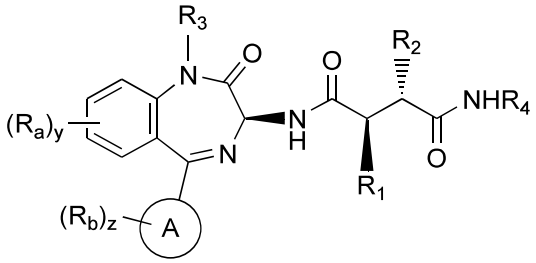
[0026] In one embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (II):

(21)



.

[0039] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$;

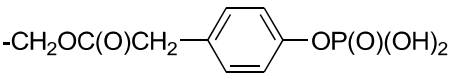
R_2 is $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

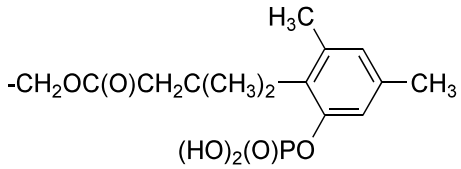
R_4 is H or R_y;

R_x

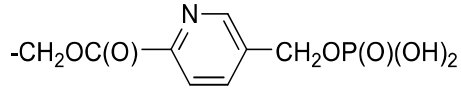
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$, or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently Cl, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, and/or -O(cyclopropyl);

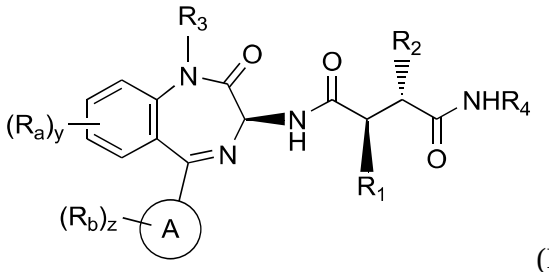
each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

z is 1 or 2.

benzodiazepin-1-yl)methyl L-alaninate (55); S-(((2S,3R)-6,6,6-trifluoro-3-(((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)carbamoyl)-2-(3,3,3-trifluoropropyl)hexanoyl)amino)-L-cysteine (56); *tert*-butyl S-(((2S,3R)-6,6,6-trifluoro-3-(((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)carbamoyl)-2-(3,3,3-trifluoropropyl)hexanoyl)amino)-L-cysteinate (57); methyl S-(((2S,3R)-6,6,6-trifluoro-3-(((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)carbamoyl)-2-(3,3,3-trifluoropropyl) hexanoyl)amino)-L-cysteinate (58); ((3S)-3-(((2R,3S)-3-carbamoyl-6,6,6-trifluoro-2-(3,3,3-trifluoropropyl)hexanoyl)amino)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)methyl (4-(phosphonooxy)phenyl)acetate (59); and ((3S)-3-(((2R,3S)-3-carbamoyl-6,6,6-trifluoro-2-(3,3,3-trifluoropropyl)hexanoyl)amino)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)methyl L-valyl-L-valinate (60); and salts thereof.

[0044] In another embodiment, the present invention provides compositions comprising compounds represented by the structure of Formula (I):



(I)

and/or at least one salt thereof, wherein:

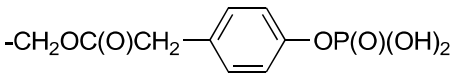
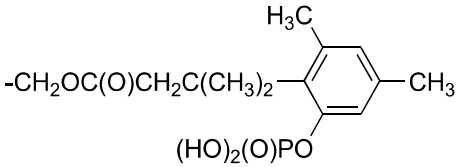
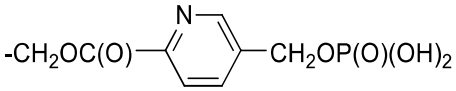
R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

R_4 is H or R_y;

R_x

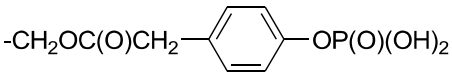
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$, , , or ;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$, or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

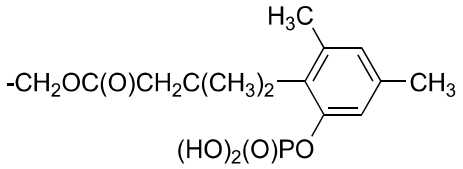
Ring A is phenyl or pyridinyl;

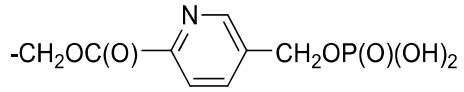
each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

O)CH(NH$_2$)CH(CH$_3$)$_2$, 

,



, or 

;

R_y is: -SCH$_2$CH(NH$_2$)C(O)OH, -SCH$_2$CH(NH$_2$)C(O)OCH$_3$, or -SCH$_2$CH(NH$_2$)C(O)OC(CH$_3$)$_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH$_3$, C$_{1-3}$ alkyl, -CH$_2$OH, -CF$_3$, cyclopropyl, -OCH$_3$, -O(cyclopropyl) and/or -NHCH$_2$CH$_2$OCH$_3$;

each R_b is independently F, Cl, -CH$_3$, -CH$_2$OH, -CF$_3$, cyclopropyl, and/or -OCH$_3$;

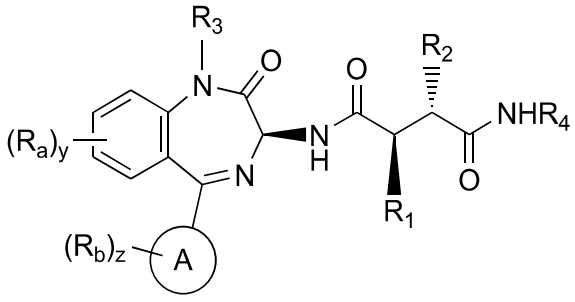
y is zero, 1 or 2; and

z is zero, 1, or 2.

[0078] In another embodiment, z is 1 or 2.

[0079] In one embodiment, the BCMA-targeting immunotherapeutic comprises an antibody drug conjugate, bispecific antibody, tri-specific antibody, trifunctional antibody, chemically linked Fab or a bi-specific T-cell engager (BiTE).

[0080] In another embodiment, the present invention also provides a method as described herein comprising the step of administering to a subject a first composition comprising one or more B-cell maturation antigen (BCMA)-targeting immuno-therapeutics, a second composition comprising one or more immunotherapeutic compounds, and a third composition comprising one or more compounds represented by the structure of Formula (I):



and/or at least one salt thereof, wherein:

R_1 is -CH$_2$CF$_3$ or -CH$_2$CH$_2$CF$_3$;

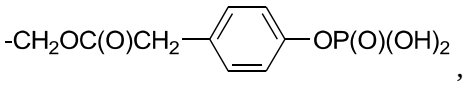
R_2 is -CH$_2$CF$_3$, -CH$_2$CH$_2$CF$_3$, or -CH$_2$CH$_2$CH$_2$CF$_3$;

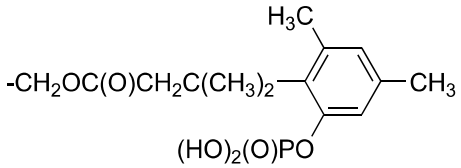
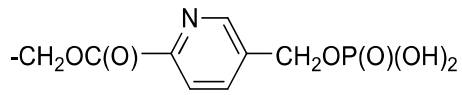
R_3 is H, -CH$_3$ or Rx;

R_4 is H or R_y;

R_x

is: -CH$_2$OC(O)CH(CH$_3$)NH$_2$, -CH$_2$OC(O)CH(NH$_2$)CH(CH$_3$)$_2$, -CH$_2$OC(O)CH((CH(CH$_3$)$_2$)NHC(

O)CH(NH$_2$)CH(CH$_3$)$_2$,  ,

 , or  ;

R_y is: -SCH$_2$CH(NH$_2$)C(O)OH, -SCH$_2$CH(NH$_2$)C(O)OCH$_3$, or -SCH$_2$CH(NH$_2$)C(O)OC(CH$_3$)$_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH$_3$, C$_{1-3}$ alkyl, -CH$_2$OH, -CF$_3$, cyclopropyl, -OCH$_3$, -O(cyclopropyl) and/or -NHCH$_2$CH$_2$OCH$_3$;

each R_b is independently F, Cl, -CH$_3$, -CH$_2$OH, -CF$_3$, cyclopropyl, and/or -OCH$_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.

[0081] In another embodiment, z is 1 or 2.

Targeting antigens

[0082] In one embodiment, the CAR or TCR binds to an epitope of an antigen via an antibody or an antibody fragment that is directed to the antigen. In another embodiment, the antibody is a monoclonal antibody. In another embodiment, the antibody is a polyclonal antibody. In another embodiment, the antibody fragment is a single-chain variable fragment (scFv).

[0083] Appropriate target antigens for CAR T-cell therapies should be uniformly expressed on the malignancy to be treated and should not be expressed on normal essential cells. B-cell maturation antigen (BCMA) is such an appropriate target antigen. BCMA is a member of the tumor necrosis factor superfamily. Among hematologic cells, BCMA is only expressed by some B cells, normal plasma cells, and malignant plasma cells; BCMA is not expressed by hematopoietic stem cells. BCMA is uniformly expressed by the malignant plasma cells of many cases of multiple myeloma (MM) and that BCMA is not expressed by normal essential nonhematopoietic tissues. Thus, in one embodiment, the CAR-T target antigen is BCMA.

[0084] BCMA targeting methods that may be used in combination with one or more compounds represented by the structure of Formula (I) as described herein are known in the art and include BCMA-directed CAR-T, antibody drug conjugate, bispecific antibody, and tri-specific antibody.

[0085] BCMA CAR-T cells are known in the art and are described in, for example, WO2016090320A1, which is incorporated herein by reference in its entirety. In another embodiment, BCMA CAR-T cells from Novartis in collaboration with University of Pennsylvania (in one embodiment, CAR-T BCMA cells, in another embodiment, MTV273, in another embodiment, MCM998), Unicar-Therapy Biomedicine (in one embodiment, CD19 and BCMA-specific CAR-T cells), Bluebird & Celgene (in one embodiment, Bb2121, in another embodiment, Bb21217, in another embodiment, JCARH123), Gilead/Kite (in one embodiment, KITE-

drug. In one embodiment, the alkylating drug comprises Procarbazine (MATULANE®), Dacarbazine (DTIC), Altretamine (HEXALEN®), or a combination thereof.

[00131] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with an antimetabolite. In one embodiment, the antimetabolite comprises an antifolic acid compound (Methotrexate), an amino acid antagonists (Azaserine), or a combination thereof.

[00132] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with a purine antagonist. In one embodiment, the purine antagonist comprises Mercaptopurine (6-MP), Thioguanine (6-TG), Fludarabine Phosphate, Cladribine (LEUSTATIN®), Pentostatin (NIPENT™), or a combination thereof.

[00133] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with a pyrimidine antagonist. In one embodiment, the pyrimidine antagonist comprises Fluorouracil (5-FU), Cytarabine (ARA-C), Azacitidine, or a combination thereof.

[00134] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with a plant alkaloid. In one embodiment, the pyrimidine antagonist comprises Vinblastine (VELBAN®), Vincristine (ONCOVIN®), Etoposide (VP-16, VEPE-SID®), Teniposide (VUMON®), Topotecan (HYCAMTIN®), Irinotecan (CAMPTOSAR®), Paclitaxel (TAXOL®), Docetaxel (TAXOTERE®), or a combination thereof.

[00135] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with FOLFIRI, wherein in one embodiment FOLFIRI comprises folinic acid (leucovorin), fluorouracil (5-FU) and irinotecan (CAMPTOSAR®). In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with folinic acid (leucovorin), fluorouracil (5-FU), irinotecan (CAMPTOSAR®), or a combination thereof.

[00136] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with an antibiotic. In one embodiment, the antibiotic comprises Anthracyclines, Doxorubicin (ADRIAMYCIN, RUBEX, DOXIL®), Daunorubicin (DAUNOXOME®), Dactinomycin (COSMEGEN®), Idarubincin (IDAMYCIN®), Plicamycin (MITHRAMYCIN®), Mitomycin (MUTAMYCIN®), Bleomycin (BLENOXANE®), or a combination thereof.

[00137] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with an immunotherapeutic. In one embodiment, the immunotherapeutic comprises a monoclonal antibody. In one embodiment, the monoclonal antibody comprises an anti-PD-1 antibody, which in one embodiment comprises nivolumab.

[00138] In another embodiment, the monoclonal antibody comprises alemtuzumab (CAMPATH®), trastuzumab (HERCEPTIN®), Bevacizumab (AVASTIN®), Cetuximab (ERBITUX®), or a combination thereof. In another embodiment, the monocolonal antibody comprises a radiolabeled antibody, which, in one embodiment, comprises britumomab, tiuxetan (ZEVALIN®), or a combination thereof. In another embodiment, the monocolonal antibody comprises a chemolabeled antibody, which in one embodiment comprises Brentuximab vedotin (ADCETRIS®), Ado-trastuzumab emtansine (KADCYLA®, also called TDM-1), denileukin diftitox (ONTAK®), or a combination thereof. In another embodiment, the monocolonal antibody comprises a bispecific antibody, which in one embodiment, comprises blinatumomab (BLINCYTO®).

[00139] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with a hormonal agent. In one embodiment, the hormonal agent comprises Tamoxifen (NOLVADEX®), Flutamide (EULEXIN®), Gonadotropin-Releasing Hormone Agonists, (Leuprolide and Goserelin (ZOLADEX®)), Aromatase Inhibitors, Aminoglutethimide, Anastrozole (ARIMIDEX®), or a combination thereof.

[00140] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with Amsacrine, Hydroxyurea (Hydrea), Asparaginase (EL-SPAR®), Mitoxantrone (NOVANTRONE®), Mitotane, Retinoic Acid Derivatives, Bone Marrow Growth Factors, Amifostine, or a combination thereof.

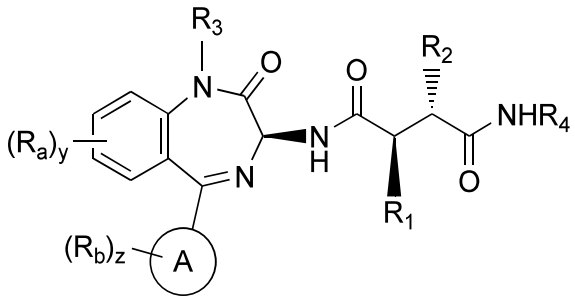
[00141] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with an agent that inhibits one or more cancer stem cell pathways. In one embodiment, such agent comprises an inhibitor of Hedgehog, WNT, BMP, or a combination thereof.

[00142] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with any one or more of the following: REVLIMID® (lenalidomide), AVASTIN® (Bevacizumab), HERCEPTIN® (trastuzumab), RITUXAN® (rituximab), OPDIVO® (nivolumab), GLEEVEC® (imatinib mesylate), IMBRUVICA® (ibrutinib), VELCADE® (bortezomib), ZYTIGA® (abiraterone acetate), XTANDI® (enzalutamide), ALIMTA® (Pemetrexed), GARDASIL®, IBRANCE® (palbociclib), PERJETA® (pertuzumab), TASIGNA® (nilotinib), XGEVA® (Denosumab), AFINITOR® (everolimus), JAKAFI® (ruxolitinib), TARCEVA® (erlotinib), KEYTRUDA® (pembrolizumab), SUTENT® (sunitinib malate)|, YERVOY® (ipilimumab), NEXAVAR® (sorafenib), ZOLADEX (goserelin acetate), ERBITUX®, DARZALEX® (daratumumab), XELODA® (capecitabine), GAZYVA® (obinutuzumab), VENCLEXTA® (venetoclax), and TECENTRIQ® (atezolizumab).

[00143] In another embodiment, the present invention provides a composition comprising one or more compounds represented by the structure of Formula (I) as described herein in combination with any one or more of the following: abemaciclib, epacadostat, apalutamide, Carfilzomib, Crizotinib (PF-02341066), GDC-0449 (vismodegib), ONCOVEX$^{GM\text{-}CSF}$, PLX4032 (RG7204), Ponatinib, SGN-35 (brentuximab vedotin), Tivozanib (AV-951), T-DM1 (Trastuzumab-DM1), and XL184 (cabozantinib).

[00144] Accordingly, the compositions of the present invention may be administered in combination with other anti-cancer treatments useful in the treatment of cancer or other proliferative diseases. The invention herein further comprises use of the compositions of the present invention in preparing medicaments for the treatment of cancer, and/or it comprises the packaging of the compositions of the present invention together

or more B-cell maturation antigen (BCMA)-targeting immuno-therapeutics and a second composition comprising one or more compounds represented by the structure of Formula (I):



and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

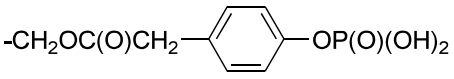
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

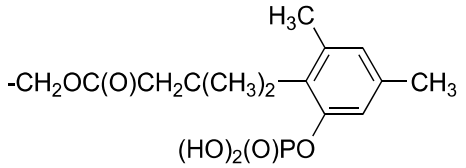
R_4 is H or R_y;

R_x

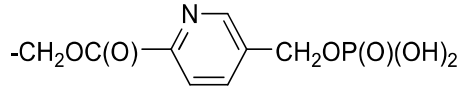
is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC(O)CH(NH_2)CH(CH_3)_2$,



,



, or



;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$, or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

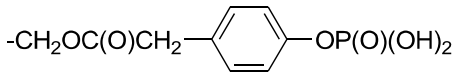
y is zero, 1 or 2; and

z is zero, 1, or 2.

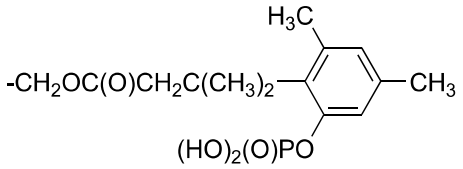
[00191] In another embodiment, z is 1 or 2.

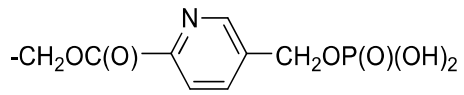
[00192] In one embodiment, the BCMA-related disorder comprises a proliferative disease. In another embodiment, the BCMA-related disorder comprises multiple myeloma, acute myelomonocytic leukemia (AMML) with eosinophilia, T cell lymphoma, acute monocytic leukemia, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or a combination thereof.

[00193] In another embodiment, the present invention provides the use of the described compounds or compositions for treating, suppressing or inhibiting a proliferative disease in a subject. In another embodiment,

O)CH(NH$_2$)CH(CH$_3$)$_2$, 

,



, or 

;

R_y is: -SCH$_2$CH(NH$_2$)C(O)OH, -SCH$_2$CH(NH$_2$)C(O)OCH$_3$, or -SCH$_2$CH(NH$_2$)C(O)OC(CH$_3$)$_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH$_3$, C$_{1\text{-}3}$ alkyl, -CH$_2$OH, -CF$_3$, cyclopropyl, -OCH$_3$, -O(cyclopropyl) and/or -NHCH$_2$CH$_2$OCH$_3$;

each R_b is independently F, Cl, -CH$_3$, -CH$_2$OH, -CF$_3$, cyclopropyl, and/or -OCH$_3$;

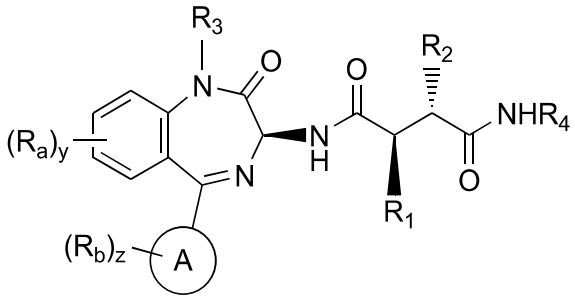
y is zero, 1 or 2; and

z is zero, 1, or 2.

[00195] In another embodiment, z is 1 or 2.

[00196] In one embodiment, the present invention provides the use of the described compounds or compositions for improving the efficacy of an anti-B-cell maturation antigen (BCMA) therapy in a subject.

[00197] In another embodiment, the present invention also provides a method of improving the efficacy of an anti-B-cell maturation antigen (BCMA) therapy in a subject comprising the step of administering to said subject a first composition comprising one or more B-cell maturation antigen (BCMA)-targeting immuno-therapeutics and a second composition comprising one or more compounds represented by the structure of Formula (I):



and/or at least one salt thereof, wherein:

R_1 is -CH$_2$CF$_3$ or -CH$_2$CH$_2$CF$_3$;

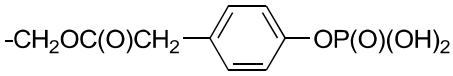
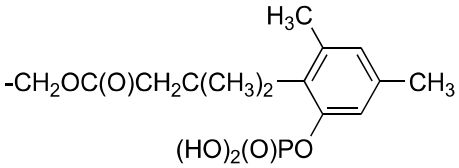
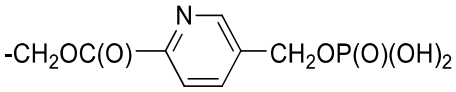
R_2 is -CH$_2$CF$_3$, -CH$_2$CH$_2$CF$_3$, or -CH$_2$CH$_2$CH$_2$CF$_3$;

R_3 is H, -CH$_3$ or Rx;

R_4 is H or R_y;

R_x

is: -CH$_2$OC(O)CH(CH$_3$)NH$_2$, -CH$_2$OC(O)CH(NH$_2$)CH(CH$_3$)$_2$, -CH$_2$OC(O)CH((CH(CH$_3$)$_2$)NHC(O)CH(N

$H_2)CH(CH_3)_2$, , , or ;

R_y is: $-SCH_2CH(NH_2)C(O)OH$, $-SCH_2CH(NH_2)C(O)OCH_3$, or $-SCH_2CH(NH_2)C(O)OC(CH_3)_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, $-OCH_3$, C_{1-3} alkyl, $-CH_2OH$, $-CF_3$, cyclopropyl, $-OCH_3$, -O(cyclopropyl) and/or $-NHCH_2CH_2OCH_3$;

each R_b is independently F, Cl, $-CH_3$, $-CH_2OH$, $-CF_3$, cyclopropyl, and/or $-OCH_3$;

y is zero, 1 or 2; and

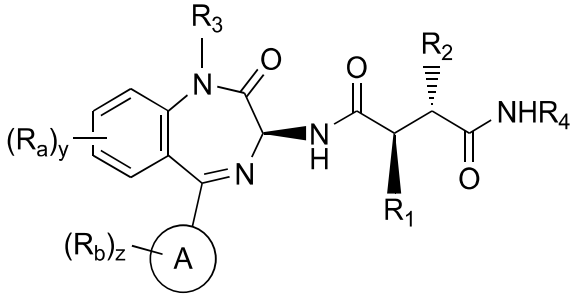
z is zero, 1, or 2.

[00198] In another embodiment, z is 1 or 2.

[00199] In one embodiment, the anti-B-cell maturation antigen (BCMA) therapy comprises an anti-cancer therapy.

[00200] In one embodiment, the present invention provides the use of the described compound or compositions for decreasing B-cell maturation antigen (BCMA) shedding from a cancer cell in a subject.

[00201] In another embodiment, the present invention also provides a method of decreasing B-cell maturation antigen (BCMA) shedding from a cancer cell in a subject comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I):



and/or at least one salt thereof, wherein:

R_1 is $-CH_2CF_3$ or $-CH_2CH_2CF_3$;

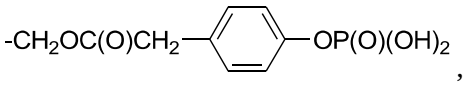
R_2 is $-CH_2CF_3$, $-CH_2CH_2CF_3$, or $-CH_2CH_2CH_2CF_3$;

R_3 is H, $-CH_3$ or Rx;

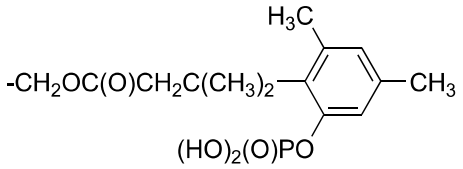
R_4 is H or R_y;

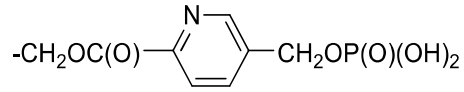
R_x

is: $-CH_2OC(O)CH(CH_3)NH_2$, $-CH_2OC(O)CH(NH_2)CH(CH_3)_2$, $-CH_2OC(O)CH((CH(CH_3)_2)NHC($

O)CH(NH$_2$)CH(CH$_3$)$_2$, 

,



, or 

;

R_y is: -SCH$_2$CH(NH$_2$)C(O)OH, -SCH$_2$CH(NH$_2$)C(O)OCH$_3$, or -SCH$_2$CH(NH$_2$)C(O)OC(CH$_3$)$_3$;

Ring A is phenyl or pyridinyl;

each R_a is independently F, Cl, -CN, -OCH$_3$, C$_{1-3}$ alkyl, -CH$_2$OH, -CF$_3$, cyclopropyl, -OCH$_3$, -O(cyclopropyl) and/or -NHCH$_2$CH$_2$OCH$_3$;

each R_b is independently F, Cl, -CH$_3$, -CH$_2$OH, -CF$_3$, cyclopropyl, and/or -OCH$_3$;

y is zero, 1 or 2; and

z is zero, 1, or 2.

[00202] In another embodiment, z is 1 or 2.

[00203] In another embodiment, the present invention also provides a method of decreasing B-cell maturation antigen (BCMA) shedding from a cell in a subject comprising the step of administering to said subject a composition comprising one or more compounds represented by the structure of Formula (I) as described herein. In one embodiment, the cell comprises a late memory B cell committed to plasma cell (PC) differentiation or a PC. In another embodiment, the cell comprises a multiple myeloma cell.

[00204] In one embodiment, the present invention provides the use of a therapeutically acceptable amount of one or more compounds or compositions as described herein for treating, suppressing or inhibiting a proliferative disease in a subject. In another embodiment, the present invention provides the use of a therapeutically effective amount of one or more compounds or compositions as described herein for treating, suppressing or inhibiting a proliferative disease in a subject. In another embodiment, the present invention provides the use of a synergistically effective amount of one or more compounds or compositions as described herein for treating, suppressing or inhibiting a proliferative disease in a subject. In another embodiment, the present invention provides the use of a synergistically therapeutically effective amount of one or more compounds or compositions as described herein for treating, suppressing or inhibiting a proliferative disease in a subject.

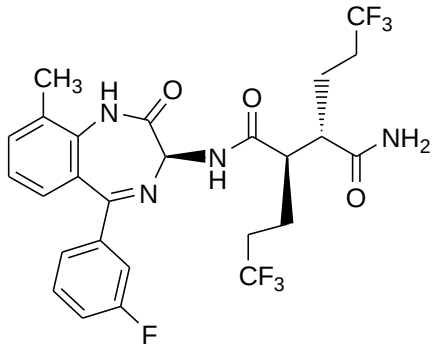
[00205] In one embodiment, the proliferative disease comprises a Desmoid tumor.

[00206] In one embodiment, the proliferative disease comprises a pre-cancerous condition or a benign proliferative disorder.

[00207] In one embodiment, the term "pre-cancerous" or, alternatively, “pre-malignant” as used herein interchangeably refers to diseases, syndromes or other conditions associated with an increased risk of cancer. Pre-cancer conditions in the context of the present invention include, but are not limited to: breast calcifications, vaginal intra-epithelial neoplasia, Barrett's esophagus, atrophic gastritis, dyskeratosis congenital, sideropenic

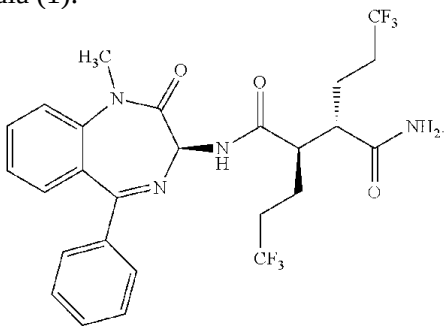
CLAIMS

1. A composition comprising one or more B-cell maturation antigen (BCMA)-targeting immuno-therapeutics wherein said BCMA-targeting immunotherapeutic comprises chimeric antigen receptor T (CAR-T) cells, a bispecific antibody, an antibody-drug conjugate, a tri-specific antibody, a trifunctional antibody, a chemically-linked Fab, or a bi-specific T-cell engager (BiTE) and one or more compounds represented by the structure of formula (22):



(22)

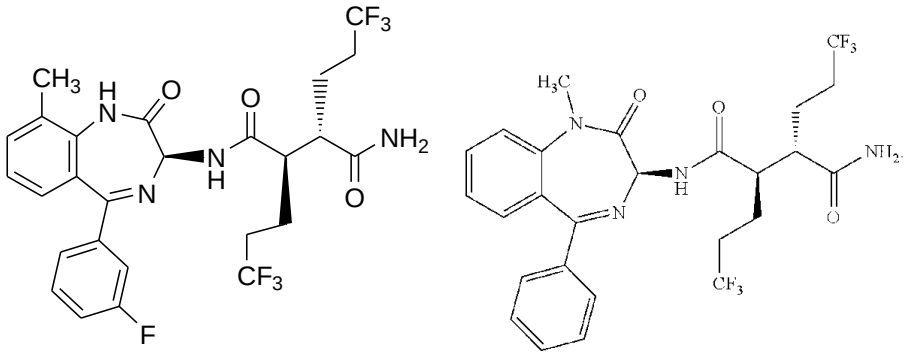
or by the structure of formula (1):



(1),

and/or at least one salt thereof.

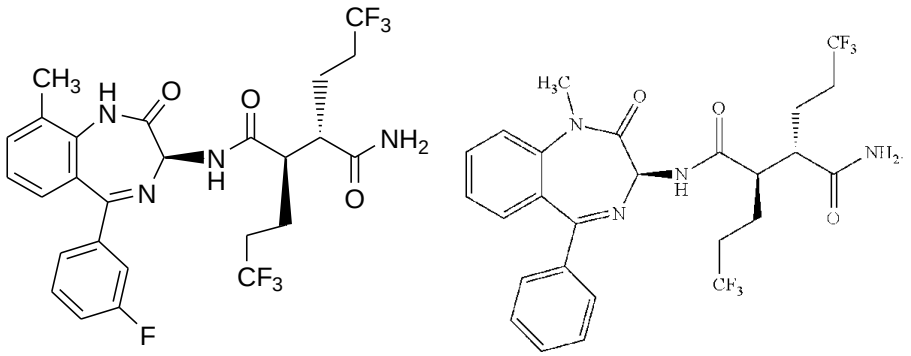
2. Use of a first composition comprising one or more BCMA-targeting immuno-therapeutics in the manufacture of a first medicament and a second composition comprising one or more compounds represented by the structure of formula (1) or formula (22):



and/or at least one salt thereof in the manufacture of a second medicament,

wherein the first and second medicaments are to be used in combination therapy for treating, suppressing, or inhibiting a B-cell maturation antigen (BCMA)-related disorder or a disease associated with BCMA expression in a subject, wherein said BCMA-related disorder or disease associated with BCMA expression comprises multiple myeloma or lymphoma.

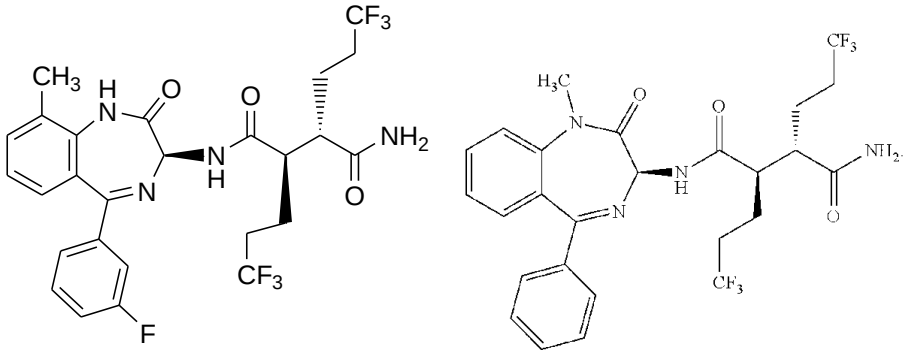
3. The use according to claim 2, wherein said lymphoma comprises mantle cell lymphoma (MCL) or diffuse large B cell lymphoma (DLBCL).
4. The use according to any of claims 2-3, wherein said one or more compounds represented by the structure of formula (1) or formula (22) are to be administered at a dose of 1.2 mg, 2.4 mg, 4 mg, 6 mg, or 8.4 mg per administration twice a week.
5. The use according to any of claims 2-4, wherein any of said first or second compositions is to be administered intravenously.
6. The use according to any of claims 2-4, wherein any of said first or second compositions is to be administered orally.
7. Use of a composition comprising one or more compounds represented by the structure of formula (1) or formula (22):



in the manufacture of a medicament for improving the efficacy of one or more BCMA-targeting immuno-therapeutics,

wherein said BCMA-targeting immunotherapeutic comprises chimeric antigen receptor T (CAR-T) cells, a bispecific antibody, an antibody-drug conjugate, a tri-specific antibody, a trifunctional antibody, a chemically-linked Fab, or a bi-specific T-cell engager (BiTE).

8. Use of a composition comprising one or more compounds represented by the structure of formula (1) or formula (22):



in the manufacture of a medicament for decreasing B-cell maturation antigen (BCMA) shedding from a BCMA-expressing cell in a subject.

9. The use according to claim 8, wherein said cell is a cancer cell.
10. The use according to claim 9, wherein said cancer is multiple myeloma.
11. The use according to claim 9, wherein said cancer is leukemia.
12. The use according to claim 11, wherein said leukemia comprises T-cell acute lymphoblastic leukemia (T-ALL).
13. The use according to claim 9, wherein said cancer is lymphoma.
14. The use according to claim 13, wherein said lymphoma comprises mantle cell lymphoma (MCL) or diffuse large B cell lymphoma (DLBCL).
15. The use according to claim 9, wherein said cancer is a solid tumor.
16. The use according to any of claims 2-3, wherein said one or more compounds represented by the structure of formula (1) or formula (22) are to be administered at a dose of 1.2 mg, 2.4 mg, 4 mg, 6 mg, or 8.4 mg per administration twice a week.
17. The use according to any of claims 2-4, wherein any of said first or second compositions is to be administered intravenously
18. The use according to any of claims 2-4, wherein any of said first or second compositions is to be administered orally.