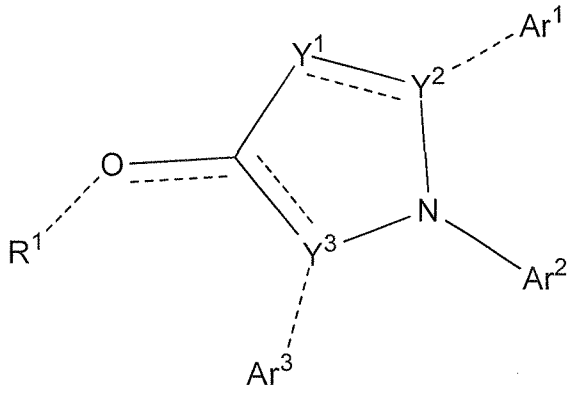
compound MI-2, an irreversible MALT1 protease inhibitor, was identified as a lead compound with nanomolar activity in cell-based assays and selective activity against ABC-DLBCLs. Importantly we show that MALT1 inhibitors kill ABC-DLBCLs *in vitro* and *in vivo*, are non-toxic to animals and also suppress primary human non GCB-DLBCL specimens. Hence we demonstrate that MALT1 is a bona fide therapeutic target, and provide a lead compound that forms the basis of a new class of therapeutic agents for B-cell lymphomas.

The disclosure provides~~, in one embodiment,~~ a method of modulating MALT1, comprising contacting MALT1 with an effective amount or concentration of a compound of formula (I)



(I)

wherein

a dashed bond indicates that a bond can be present or absent;

when a double bond is present between Y^1 and Y^2, Y^1 is N or CR, Y^2 is C, and Ar^1 is present; when a single bond is present between Y^1 and Y^2, Y^1 is CR_2, Y^2 is O or S, and Ar^1 is absent, and each independently selected R is H or (C1-C6)alkyl;

R^1 is alkyl, alkoxyalkyl, or arylalkyl, wherein any alkyl, alkoxyalkyl, or arylalkyl, can be mono- or independently multi-substituted with halo or (C1-C6)alkoxy, provided that when a double bond is present between the oxygen atom and the ring comprising Y^3, R^1 is absent and Ar^3 is present, and when a single bond is present between the oxygen atom and the ring, R^1 is present, a double bond between Y^3 and the carbon atom bearing the oxygen atom is present, and Ar^3 is absent;

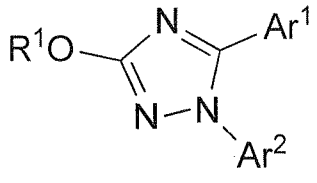
Ar^1 is phenyl substituted with 1-3 J^1 groups; J^1 is halo or (C1-C6)alkoxy;

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula $-N(R)C(O)-R^2$ and R^2 is alkyl, aryl, or arylamino, wherein any alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups;

Ar^3 is phenyl substituted with 1-3 J^3 groups; J^3 is halo or (C1-C6)alkoxy;

or any salt, hydrate, tautomer, or stereoisomer thereof.

The disclosure further provides, in one aspect, an ex vivo method of modulating MALT1, comprising contacting MALT1 with an effective amount or concentration of a compound of formula (IA)



(IA)

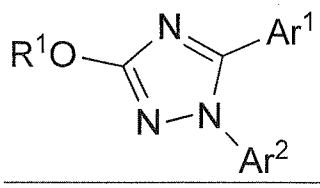
wherein

R^1 is alkyl, alkoxyalkyl, or arylalkyl, wherein any alkyl, alkoxyalkyl, or arylalkyl, can be mono- or independently multi-substituted with halo or (C1-C6)alkoxy, Ar^1 is phenyl substituted with 1-3 J^1 groups; J^1 is halo or (C1-C6)alkoxy;

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula $-N(R)C(O)-R^2$ and R^2 is alkyl, aryl, or arylamino, wherein any alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

or any salt, hydrate, tautomer, or stereoisomer thereof.

The disclosure further provides, in another aspect, an ex vivo method of modulating MALT1, comprising contacting MALT1 with an effective amount or concentration of a compound of formula (IA)



(IA)

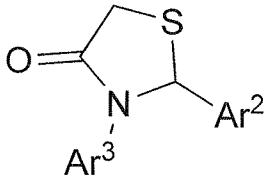
wherein

R^1 is alkyl, alkoxyalkyl, or arylalkyl, wherein any alkyl, alkoxyalkyl, or arylalkyl, can be mono- or independently multi-substituted with halo or (C1-C6)alkoxy, Ar^1 is phenyl substituted with 1-3 J^1 groups; J^1 is halo or (C1-C6)alkoxy;

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is C_{1-4}alkyl, aryl, or arylamino, wherein any C_{1-4} alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

or any salt, hydrate, tautomer, or stereoisomer thereof.

The disclosure further provides, in another aspect, an ex vivo method of modulating MALT1, comprising contacting MALT1 with an effective amount or concentration of a compound of formula (IB)



(IB),

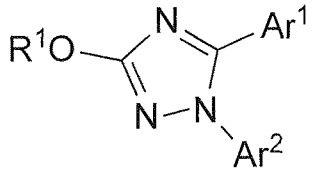
wherein

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is alkyl, aryl, or arylamino, wherein any alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

Ar^3 is phenyl substituted with 1-3 J^3 groups; J^3 is halo or (C1-C6)alkoxy; or any salt, hydrate, tautomer, or stereoisomer thereof.

The disclosure further provides, in various embodiments, a method of treating or preventing cancer comprising administering to a patient an effective dose of a compound of formula (I) as defined above. More specifically, the cancer can be a lymphoma, such as a diffuse large B-cell lymphoma (DLBCL).

The disclosure further provides, in another aspect, a compound of formula (IA) for use in treating or preventing cancer, wherein said compound of formula (IA) is:



(IA)

wherein

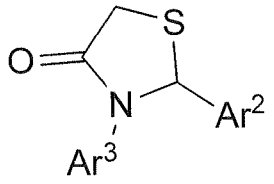
R^1 is alkyl, alkoxyalkyl, or arylalkyl, wherein any alkyl, alkoxyalkyl, or arylalkyl, can be mono- or independently multi-substituted with halo or (C1-C6)alkoxy,

Ar^1 is phenyl substituted with 1-3 J^1 groups; J^1 is halo or (C1-C6)alkoxy;

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is C_{1-4}alkyl, aryl, or arylamino, wherein any C_{1-4}alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

or any salt, hydrate, tautomer, or stereoisomer thereof.

The disclosure further provides, in another aspect, a compound of formula (IB) for use in treating or preventing cancer, wherein said compound of formula (IB) is:



(IB),

wherein

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is alkyl, aryl, or arylamino, wherein any alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

Ar^3 is phenyl substituted with 1-3 J^3 groups; J^3 is halo or (C1-C6)alkoxy;

or any salt, hydrate, tautomer, or stereoisomer thereof.

The disclosure further provides, in ~~another aspect~~various embodiments, a method of identifying a small molecule modulator of MALT1, comprising contacting a recombinant form of MALT1 (340-789) fused with a leucine zipper dimerization motif (LZ-MALT1) and a candidate modulator compound, using the MALT1 substrate peptide LRSR linked to the fluorogen AMC (7-amino-4-methylcoumarin), such that cleavage of the Ac-LRSR-AMC substrate by MALT1 results in release of AMC and a fluorescent signal, wherein a decrease in the cleavage of the Ac-LRSR-AMC substrate by the recombinant form of MALT1 in the presence of the candidate modulator indicates that the candidate modulator is a small molecule modulator of MALT1.

The disclosure further provides, in another aspect, use of a compound as disclosed above for the manufacture of a medicament for the treatment of cancer, wherein the cancer is lymphoma.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A depicts two perspective views of the structure of a recombinant form of MALT1 (340-789) fused with a leucine zipper dimerization motif (LZ-MALT1), which promotes its dimerization and activation.

Figure 1B is a graphic representation of the results by which 324 candidate compounds were selected from a compound library for validation in a concentration response assay using LZ-MALT1

Figure 1C is a graphic representation of the results by which nineteen compounds were selected for further validation based on their biochemical activity (IC_{50} <20 μM).

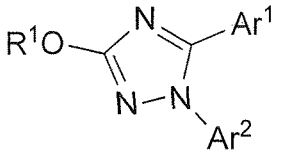
Figure 1D shows the chemical structure of compound MI-2.

Figure 1E shows a photograph of a Western blot of gel electrophoresis results demonstrating that MI-2 caused a dose-dependent decrease in MALT1-mediated cleavage, noted by an increase in the uncleaved CYLD protein and a

CLAIMS

What is claimed is:

1. An ex vivo method of modulating MALT1, comprising contacting MALT1 with an effective amount or concentration of a compound of formula (IA)



(IA)

wherein

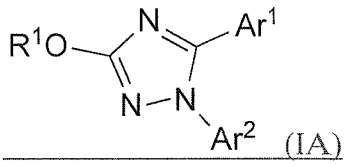
R^1 is alkyl, alkoxyalkyl, or arylalkyl, wherein any alkyl, alkoxyalkyl, or arylalkyl, can be mono- or independently multi-substituted with halo or (C1-C6)alkoxy,

Ar^1 is phenyl substituted with 1-3 J^1 groups; J^1 is halo or (C1-C6)alkoxy;

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is alkyl, aryl, or arylamino, wherein any alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

or any salt, hydrate, tautomer, or stereoisomer thereof.

2. An ex vivo method of modulating MALT1, comprising contacting MALT1 with an effective amount or concentration of a compound of formula (IA)



(IA)

wherein

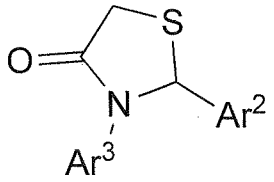
R^1 is alkyl, alkoxyalkyl, or arylalkyl, wherein any alkyl, alkoxyalkyl, or arylalkyl, can be mono- or independently multi-substituted with halo or (C1-C6)alkoxy,

Ar^1 is phenyl substituted with 1-3 J^1 groups; J^1 is halo or (C1-C6)alkoxy;

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is C_{1-4}alkyl, aryl, or arylamino, wherein any C_{1-4}alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

or any salt, hydrate, tautomer, or stereoisomer thereof.

~~2~~3. An ex vivo method of modulating MALT1, comprising contacting MALT1 with an effective amount or concentration of a compound of formula (IB)



(IB),

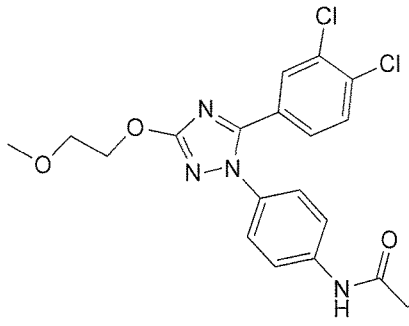
wherein

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is alkyl, aryl, or arylamino, wherein any alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

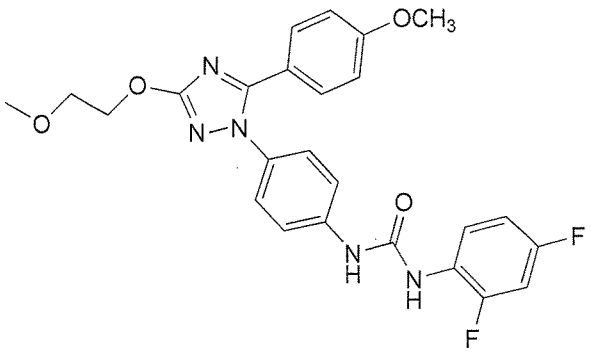
Ar^3 is phenyl substituted with 1-3 J^3 groups; J^3 is halo or (C1-C6)alkoxy;

or any salt, hydrate, tautomer, or stereoisomer thereof.

34. The method of claim 1 or claim 2 wherein the compound is any of



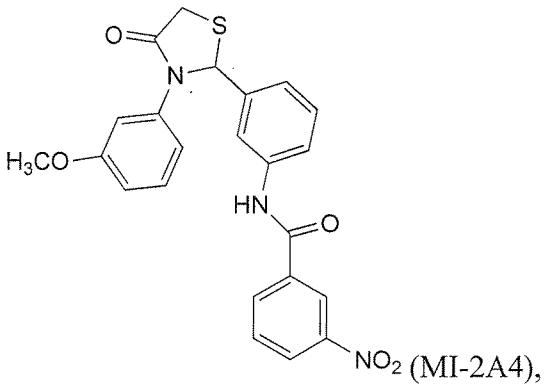
(MI-2)



(MI-2A5),

or any salt, hydrate, tautomer, or stereoisomer thereof.

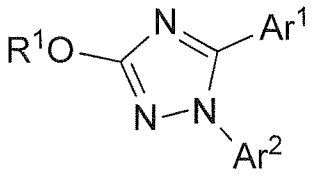
45. The method of claim ~~2~~ 3 wherein the compound is



(MI-2A4),

or any salt, hydrate, tautomer, or stereoisomer thereof.

~~5~~6. A compound of formula (IA) for use in treating or preventing cancer, wherein said compound of formula (IA) is:



(IA)

wherein

R^1 is alkyl, alkoxyalkyl, or arylalkyl, wherein any alkyl, alkoxyalkyl, or arylalkyl, can be mono- or independently multi-substituted with halo or (C1-

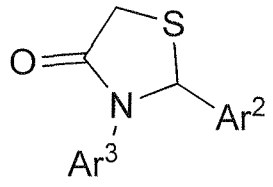
C6)alkoxy,

Ar^1 is phenyl substituted with 1-3 J^1 groups; J^1 is halo or (C1-C6)alkoxy;

Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is C_{1-4}alkyl, aryl, or arylamino, wherein any C_{1-4}alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

or any salt, hydrate, tautomer, or stereoisomer thereof.

~~67~~. A compound of formula (IB) for use in treating or preventing cancer, wherein said compound of formula (IB) is:



(IB),

wherein

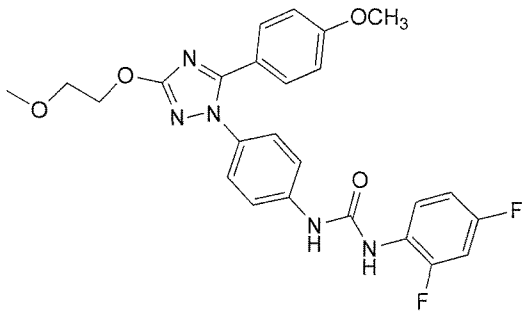
Ar^2 is phenyl substituted with 1-3 J^2 groups; J^2 is a group of formula -N(R)C(O)-R^2 and R^2 is alkyl, aryl, or arylamino, wherein any alkyl, aryl, or arylamino is substituted with 0-2 halo, nitro, or (C1-C6)alkoxy groups; and each independently selected R is H or (C1-C6)alkyl;

Ar^3 is phenyl substituted with 1-3 J^3 groups; J^3 is halo or (C1-C6)alkoxy;

or any salt, hydrate, tautomer, or stereoisomer thereof.

~~78~~. The compound of claim ~~56~~, wherein the compound is any of

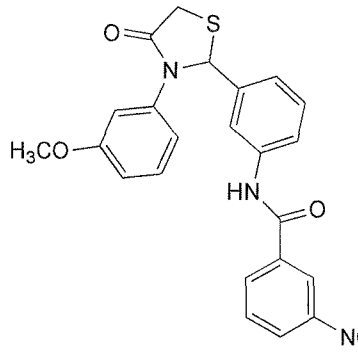
, or



(MI-2A5),

or any salt, hydrate, tautomer, or stereoisomer thereof.

~~8~~9. The compound of claim ~~6~~7, wherein the compound is any of



(MI-2A4),

or any salt, hydrate, tautomer, or stereoisomer thereof.

~~9. The compound of claim 5 or 6, wherein the cancer is a lymphoma.~~

~~10. The compound of claim 9, wherein the lymphoma is a diffuse large B-cell lymphoma.~~

~~11~~10. Use of a compound of any one of claims ~~5~~6-~~8~~ 9 for the manufacture of a medicament for the treatment of cancer, wherein the cancer is lymphoma.

~~12. The use of claim 11 wherein the cancer is lymphoma.~~

~~13~~11. The use of claim ~~12~~ 10, wherein the lymphoma is a diffuse large B-cell lymphoma.