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(54) Title: ALPHA HELIX MIMETICS AND METHODS FOR USING

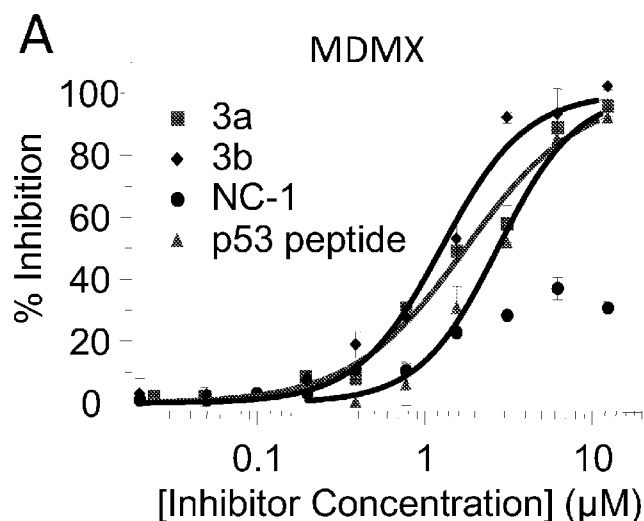


FIG. 2

(57) Abstract: The invention described herein pertains to compounds, such as aminopyrrolopyrimidine carboxamides, that may function as alpha helix mimetics, and various uses therefor. In particular, the invention described herein pertains to treating cancer with optionally substituted aminopyrrolopyrimidine carboxamides.

**Declarations under Rule 4.17:**

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*

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ALPHA HELIX MIMETICS AND METHODS FOR USING

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 USC §119(e) to U.S. Provisional Application Serial No. 61/423,908 filed on December 16, 2010, the entire disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

The invention described herein pertains to compounds, such as aminopyrrolopyrimidine carboxamides, that may function as alpha helix mimetics, and various uses therefor. In particular, the invention described herein pertains to treating cancer with optionally substituted aminopyrrolopyrimidine carboxamides.

BACKGROUND AND SUMMARY OF THE INVENTION

α -Helices represent the most common protein secondary structures and are involved in various protein-protein interactions (PPIs). In many PPIs, short helical peptides play an important role as a recognition motif, where side chains at i, i+3 or i+4, and i+7 positions often become a critical determinant for PPIs. Since α -helix-mediated PPIs are involved in a wide array of cellular signaling pathways, inhibition of these interactions could be promising therapeutic targets. Considerable efforts have been made to develop α -helix-mimicking molecules to disrupt such PPIs. Given that MDMX is overexpressed in many cancers and functions as a major regulator of p53 activity (both independently of and synergistically with MDM2), the development of MDMX inhibitors (either MDMX-specific or dual MDMX/MDM2 inhibitors) is desirable ((a) Toledo et al., Nat. Rev. Cancer 2006, 6, 909. (b) Marine et al., Cell Sci. 2006, 120, 371). For example, foldamer structures of β -peptides and peptoids showed helical structures and effectively disrupted the chosen PPIs. Other important advances in this area are technologies that stabilize peptides in helical conformations. These include miniature proteins, hydrocarbon-stapled peptides, and hydrogen bond surrogate derived α -helical peptides. Peptide- and peptidomimetic-based approaches have been reported. However, without being bound by theory, it is believed herein that non-peptidic molecules have advantages in terms of desirable bioavailability, cell permeability, and inexpensive production cost. Accordingly, there is an unmet need to develop non-peptidic, small molecule α -helix mimetics to disrupt α -helix-mediated protein-protein interactions. Hamilton and co-workers demonstrated that rationally designed terphenyl and similar scaffolds can serve as α -helix mimetics. Additional terphenyl analogs and derivatives have also been reported. However, there are several important issues associated with terphenyl-related structures, such as poor aqueous

solubility, relatively flexible scaffold structure, and long synthetic routes, that may have delayed their wide spread use.

It has been discovered herein that optionally substituted aminopyrrolopyrimidine carboxamides, such as compounds of formulae (II) and (III), are useful in treating diseases that are dependent upon PPIs, such as cancer. Without being bound by theory, it is believed herein that the efficacy of the compounds may be due at least in part to the ability of the compounds described herein to mimic a portion of an alpha helix. Also without being bound by theory, it is further believed that the efficacy of the compounds may be due at least in part to the ability of the compounds described herein to modulate the activity of Mdm2 and/or MdmX (also referred to as Mdm4), such as inhibiting the interaction of Mdm2 and/or MdmX with p53.

Illustratively, the bicyclic ring in the compounds of formulae (II) and (III) provides a planar heterocyclic framework that may provide a pre-organized structure with increased conformational rigidity. Without being bound by theory, and based on an energy-minimization study, it is believed herein that one or more of the three functional groups of this scaffold, such as R^1 , R^2 , and/or R^3 , may mimic the spatial orientation of the side chains of i, i+3 and/or i+4, and i+7 amino acids in an α -helix.

In addition but without being bound by theory, it is believed herein that the pyrrolopyrimidine template may possess favorable physical properties including water solubility and cell permeability. Compounds of formulae (II) and (III), and related compounds described herein may be prepared by solid-phase synthesis, as shown in Scheme 1 (Clark et al., Bioorg. Med. Chem. Lett. 2007, 17, 1250). In addition, since a vast number of structurally diverse primary amines are accessible, and/or commercially available, large combinatorial libraries, such as those described herein, are readily prepared. The compounds of formulae (II) and (III) are useful as α -helix mimetics, and also useful in disrupting the p53-MDMX interaction and/or the p53-MDM2 interaction.

BRIEF DESCRIPTION OF THE DRAWINGS

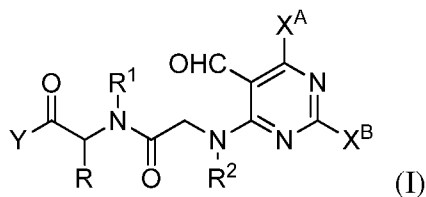
FIG. 1 shows fluorescence polarization (FP) assays to identify small-molecule inhibitors of the p53-MDMX and p53-MDM2 interaction. (A) The saturation curve of Rd-p53 peptide to recombinant MDMX¹⁻¹³⁷ and MDM2¹⁻¹³⁸ proteins. (B) Competitive binding curves of unlabeled p53 peptide (SQETFSDLWKLLPEN-NH₂) and MI-63 to the MDMX and MDM2 proteins. Each data point represents the mean and standard deviation of triplicate experiments.

FIG. 2 shows inhibition curves for Rhodamine-labeled p53 peptide (SQETFSDLWKLLPEN-NH-Rhodamine) binding to human MDMX (amino acids 1-137) (A) and human MDM2 (amino acids 1-138) (B) by fluorescence polarization.

FIG. 3 shows p53 activation by compound 3a. H460 cells with wild type 53 and human lung cancer H1299 cells with deleted p53 are exposed to DMSO, NC-1 (20 μ M), 3a (20 μ M) or MI-63 (20 μ M) for 24 h. Caspase activity is analyzed by Caspase-Glo 3/7 assay kit.

DETAILED DESCRIPTION

In one illustrative embodiment of the invention, compounds of the following formula (I) are described herein



or a pharmaceutically acceptable salt thereof, wherein:

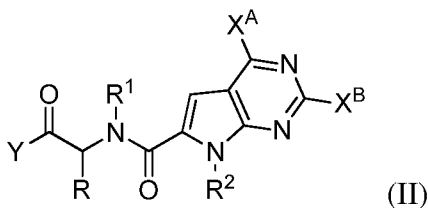
Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R¹ and R² are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; and

X^A and X^B are each independently selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof.

In another embodiment, compounds of the following formula (II) are described herein



or a pharmaceutically acceptable salt thereof, wherein:

Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

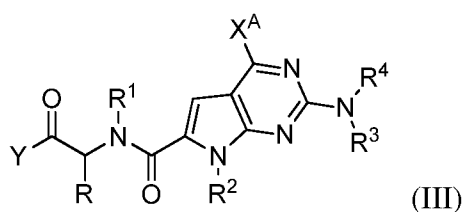
R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R^1 and R^2 are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; and

X^A and X^B are each independently selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof.

In another embodiment, compounds are described wherein X^B is a leaving group, or a precursor thereof. In another embodiment, compounds are described wherein X^B is a leaving group.

In another embodiment, compounds of the following formula (III) are described herein



or a pharmaceutically acceptable salt thereof, wherein:

Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

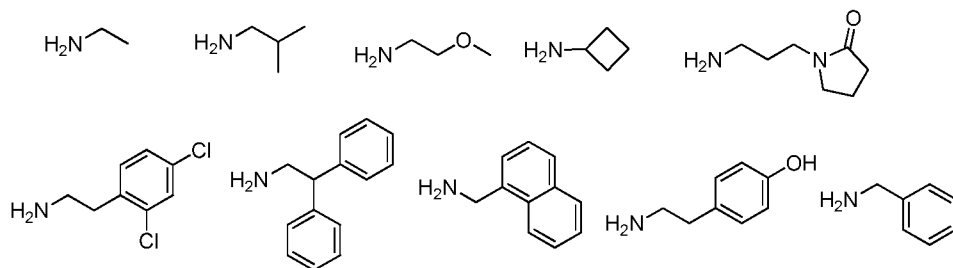
R^1 , R^2 , R^3 , and R^4 are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; or R^3 and R^4 are taken together with the attached nitrogen to form an optionally substituted heterocycle; and

X^A is selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof.

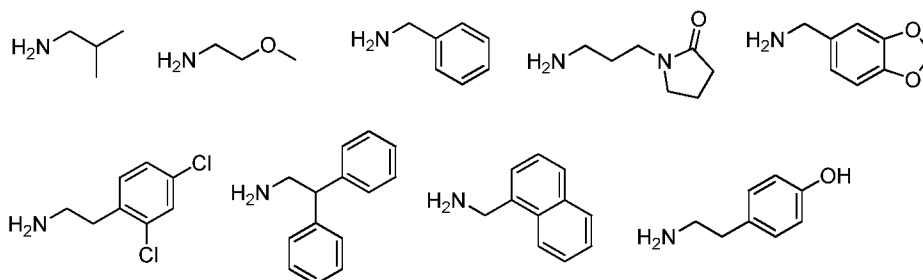
In another embodiment, in any of the compounds described herein, wherein Y is amino or a derivative thereof. In another embodiment, in any of the compounds described herein, wherein Y is amino. In another embodiment, in any of the compounds described herein, wherein R is hydrogen. In another embodiment, in any of the compounds described herein, wherein X^A is a leaving group, or a precursor thereof. In another embodiment, in any of the compounds described herein, wherein X^A is a leaving group. In another embodiment, in any of

the compounds described herein, wherein X^A is amino or a derivative thereof. In another embodiment, in any of the compounds described herein, wherein at least one of R^1 , R^2 , R^3 , and R^4 is a hydrophobic group. In another embodiment, in any of the compounds described herein, wherein at least two of R^1 , R^2 , R^3 , and R^4 are hydrophobic groups. In another embodiment, in any of the compounds described herein, wherein each of R^1 , R^2 , and R^3 is a hydrophobic group. In another embodiment, in any of the compounds described herein, wherein at least one of R^1 , R^2 , R^3 , and R^4 is a side chain of a naturally occurring amino acid. In another embodiment, in any of the compounds described herein, wherein at least two of R^1 , R^2 , R^3 , and R^4 are side chains of naturally occurring amino acids. In another embodiment, in any of the compounds described herein, wherein each of R^1 , R^2 , and R^3 is a side chain of a naturally occurring amino acid. In another embodiment, in any of the compounds described herein, wherein R^1 and R^2 are each independently selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted. In another embodiment, in any of the compounds described herein, wherein R^1 and R^2 are each independently selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted.

In another embodiment, in any of the compounds described herein, wherein R^1 is a radical of one of the formula



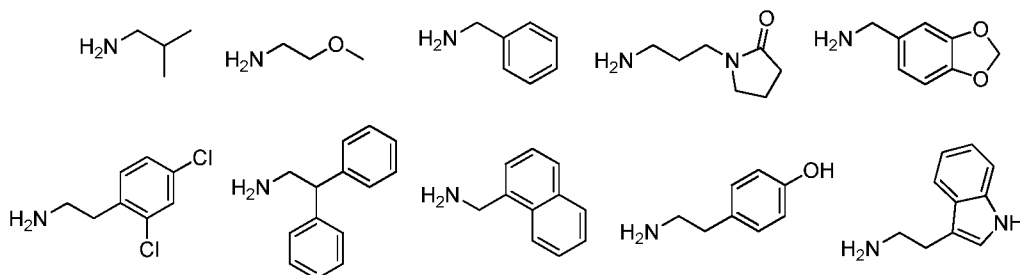
In another embodiment, in any of the compounds described herein, wherein R^2 is a radical of one of the formula



In another embodiment, in any of the compounds described herein, wherein R^3 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted.

In another embodiment, in any of the compounds described herein, wherein R^3 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted.

5 In another embodiment, in any of the compounds described herein, wherein R^3 is a radical of one of the formula



In another embodiment, in any of the compounds described herein, wherein R^4 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted.

10 In another embodiment, in any of the compounds described herein, wherein R^4 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted.

In another embodiment, in any of the compounds described herein, wherein R^4 is H.

15 In another embodiment, in any of the compounds described herein, wherein R^3 and R^4 are taken together with the attached nitrogen to form an optionally substituted heterocycle.

In another embodiment, in any of the compounds described herein, wherein R^3 and R^4 are taken together with the attached nitrogen to form a pyrrolidine, piperidine, morpholine, pyridazine, pyrimidine, pyrazine, or homopyrimidine, each of which is optionally substituted

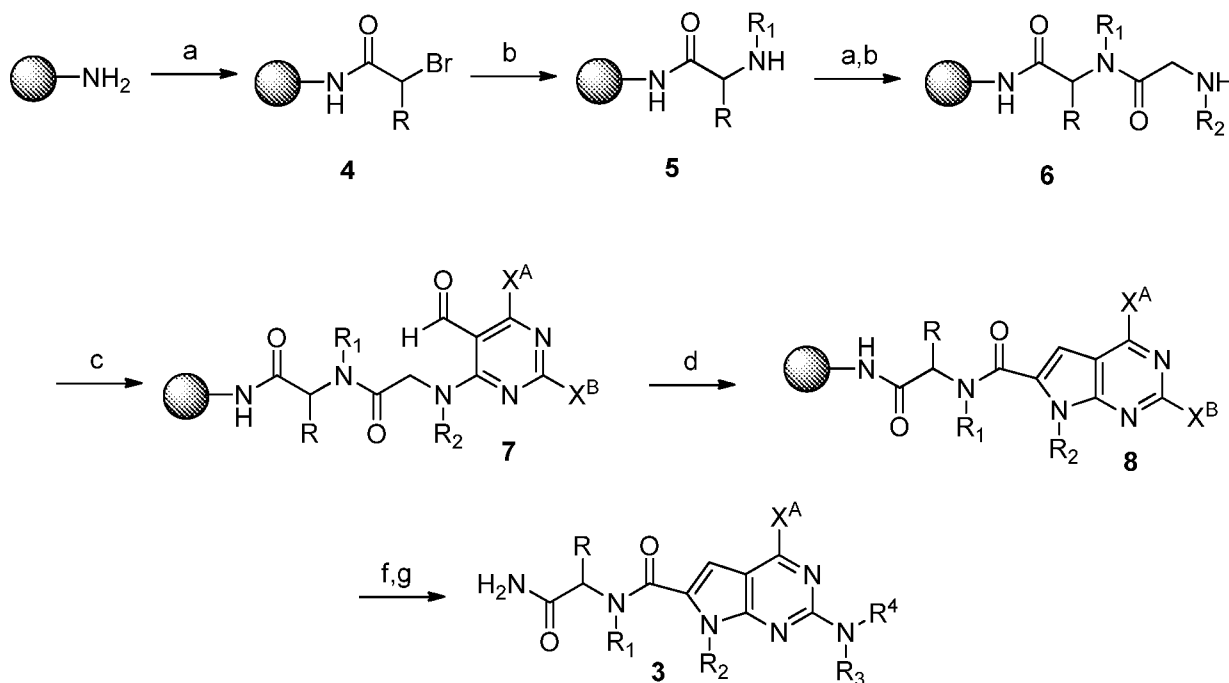
20 In another embodiment, conjugates are described herein, where the conjugate comprises any one of the compounds described herein, a bivalent linker, and a peptide, where the compound and the peptide are each covalently attached to the bivalent linker, and the peptide has at least 50%, greater than 50%, greater than 80%, or greater than 90% sequence
25 homology to an alpha helical portion of one Mdm2 or MdmX.

In another embodiment, methods are described herein for treating a disease in a patient that is responsive to the disruption or antagonism of one or more alpha helical-based protein-protein interactions. The methods include the step of administering to the patient a
30 therapeutically effective amount of one or more compounds described herein, and/or one or

more compositions thereof, or a combination thereof. In another embodiment, the method is useful for treating a disease that is responsive to disruption or antagonism of the protein-protein interaction between Mdm2 and p53, MdmX and p53, or a combination thereof. In another embodiment, the method is useful for treating cancer.

5 In another embodiment, processes for preparing optionally substituted aminopyrrolopyrimidine carboxamides are described. The processes include one or more steps illustrated in Schemes 1 and 2

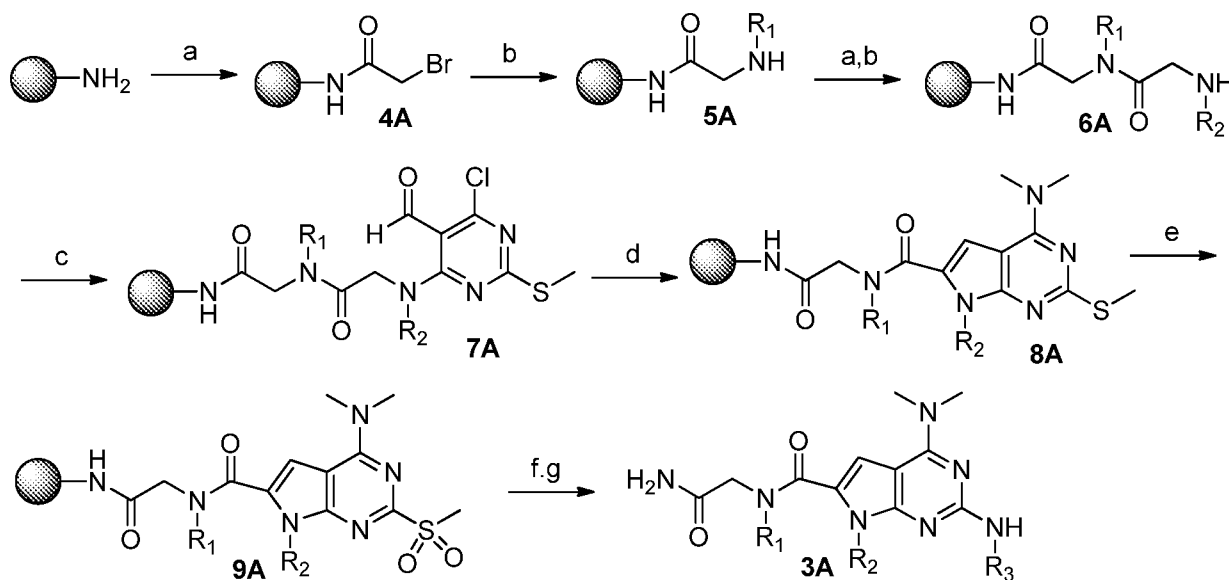
Scheme 1. Solid-phase synthesis.



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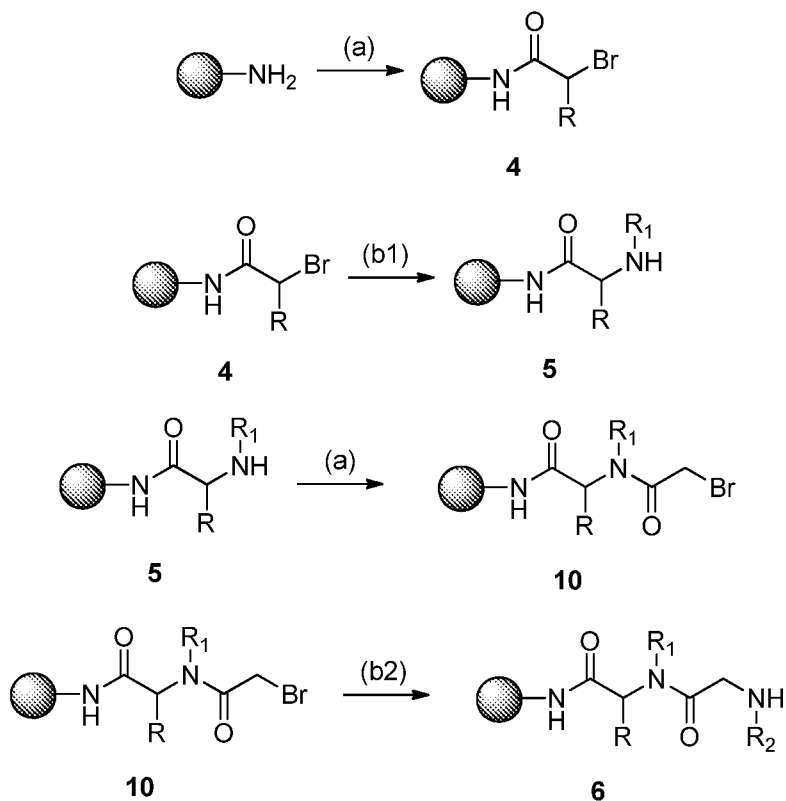
Reagents and conditions: (a) $\text{BrCH(R)CO}_2\text{H}$, DIC, DMF, rt; (b) R^1NH_2 , or R^2NH_2 , DMF, rt; (c) X^{A} , X^{B} substituted 4-chloropyrimidine-5-carbaldehyde, DIEA/DMF, rt; (d) DBU/DMF-MeOH, 90°C ; (f) R_3NH_2 , DIEA/NMP, 170°C ; (g) TFA/DCM, rt.

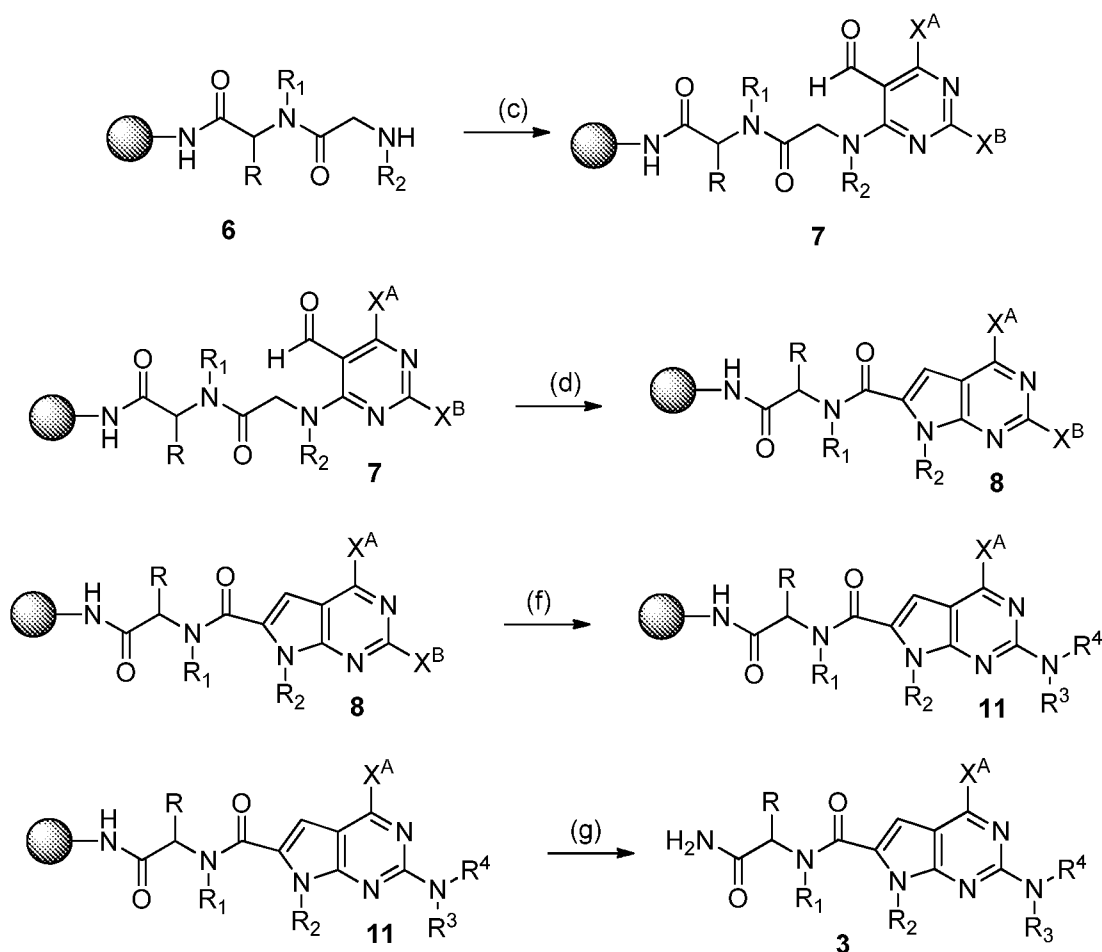
Scheme 2. Solid-phase synthesis.



Reagents and conditions: (a) BrCH₂CO₂H, DIC, DMF, rt; (b) RNH₂, DMF, rt; (c) 4,6-dichloro-2-(methylthio)pyrimidine-5-carbaldehyde, DIEA/DMF, rt; (d) DBU/DMF-MeOH, 90°C; (e) mCPBA, NaHCO₃, DCM, rt; (f) R₃NH₂, DIEA/NMP, 170°C; (g) TFA/DCM, rt.

In another embodiment, process for preparing the compounds of formula (III) are described, where the processes include one or more of the following steps:





- 5 wherein (a) represents addition of $\text{BrCH(R)CO}_2\text{H}$; (b1) represent addition of R^1NH_2 ; (b2) represents addition of R^2NH_2 ; (c) represents addition of X^A , X^B substituted 4-chloropyrimidine-5-carbaldehyde; (d) represents cyclization under using a base; (f) represents addition of R^3NH_2 ; and (g) represent cleavage of the resin using an acid; and where X^A , X^B , R , R^1 , R^2 , R^3 , and R^4 are as defined for any of the compounds described herein, or any subgenera
- 10 of the compounds described herein.

The process includes peptoid synthesis conditions to introduce two functionalities (R_1 and R_2). This sub-monomer route includes bromoacetylation of amine group on Rink amide MBHA resin, followed by displacement of the bromide with primary amines (Figliozzi et al., Methods Enzymol. 1996, 267, 437). After repeating the same procedure, the resulting dimeric peptoids 6 are then coupled with 4,6-dichloro-2-(methylthio)pyrimidine-5-carbaldehyde to afford aldehydes 7 in nearly quantitative yield for 5 steps. Treatment of the aldehydes 7 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF and MeOH provides pyrrolopyrimidines 8 through concomitant cyclization and dimethylamination (Agarwal et al., Syn. Commun. 2004, 34, 2925). The thioether group is oxidized by m-chloroperbenzoic acid (mCPBA) to give a sulfone, which is subsequently substituted with various amines. The resin-

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bound tri-substituted bicyclic product of formula (III) is cleaved with trifluoroacetic acid (TFA). Crude products are analyzed for purity and identity by LC-MS. A series of compounds of formula (III) are synthesized employing a variety of different amines. Synthesis with most tested amines result in above 80% purity of the final products of formula (III) as determined by LC-MS, which is sufficiently pure for biological testing without further purification.

The most common by-product (< 5%) in the synthesis has been observed to be the corresponding 4-methoxy-substituted product (instead of the N,N-dimethylamino group) obtained during the cyclization step.

It is to be understood that the forgoing processes may be adapted using conventional modifications to prepare the compounds described herein by, for example, the selection of alternative activated carboxylic acids other than bromo acetic acid, alternative amines, alternative substituted pyrimidine carboxaldehydes, and the like.

In another embodiment, the compounds described herein are useful for modulating protein-protein interactions, including various alpha-helix mediated protein-protein interactions, such as BCL2 family proteins.

Described herein are novel pyrrolopyrimidine-based scaffolds that are non-peptidic, small molecule α -helix mimetics for disrupting α -helix-mediated protein-protein interactions. It has been discovered that the scaffolds have increased conformational rigidity. Also described herein are processes for preparing the scaffolds using a facile solid phase synthetic route. It is to be understood that the process may be used in divergent syntheses, such as to prepare libraries. Also described herein are cell permeable, inhibitors of MDMX. Also described herein are cell permeable, inhibitors of MDM2. Also described herein are cell permeable, dual MDMX/MDM2 inhibitors. The cell permeable, dual MDMX/MDM2 inhibitors may be assayed using a fluorescence polarization-based assay. Without being bound by theory, it is believed herein that the results of the assay described herein support that the compounds described herein may act as α -helix mimetics.

In another embodiment, pyrrolopyrimidine-based alpha helix mimetic scaffolds, including optionally substituted aminopyrrolopyrimidine carboxamides, are described herein. In another embodiment, pyrrolopyrimidine-based alpha helix mimetic scaffolds are described herein that mimic one or more of i, i+3, i+4, and/or i+7 residues of alpha helices.

It is to be appreciated that the compounds described herein may be advantageous to other α -helix mimetics, such as terphenyl-related compounds, due to their increased conformational rigidity, improved aqueous solubility, excellent cell permeability, and ease of synthesis.

In addition, various genera and subgenera of each of Y, R, R¹, R², R³, X^A, and X^B of formulae (I), (II), and (III), are described herein. It is to be understood that all possible combinations of the various genera and subgenera of each of Y, R, R¹, R², R³, X^A, and X^B described herein represent additional illustrative embodiments of compounds of the invention described herein. It is to be further understood that each of those additional illustrative
5 embodiments of compounds may be used in any of the compositions, methods, and/or uses described herein.

In another embodiment, processes for preparing pyrrolopyrimidine-based alpha helix mimetic scaffolds are described herein. In one aspect, the processes include solid-phase
10 synthesis.

In another embodiment, methods for treating cancer in a patient are described herein. In one aspect, the methods include the step of administering to the patient a therapeutically effective amount of one or more compounds described herein, and/or administering a therapeutically effective amount of one or more pharmaceutical compositions
15 including one or more compounds described herein.

In another embodiment, methods for treating cancer in a patient are described herein, where the cancer is responsive to the modulation, such as the inhibition, of Mdm2 and related biological processes. In another embodiment, methods for treating cancer in a patient are described herein, where the cancer is responsive to the modulation, such as the inhibition, of
20 MdmX and related biological processes. In another embodiment, methods for treating cancer in a patient are described herein, where the cancer is responsive to the modulation, such as the inhibition, of both Mdm2 and MdmX and related biological processes.

In another embodiment, pharmaceutical compositions containing one or more of the compounds are also described herein. In one aspect, the compositions include a
25 therapeutically effective amount of the one or more compounds for treating a patient with cancer. It is to be understood that the compositions may include other component and/or ingredients, including, but not limited to, other therapeutically active compounds, and/or one or more carriers, diluents, excipients, and the like. In another embodiment, methods for using the compounds and pharmaceutical compositions for treating patients with cancer are also
30 described herein. In one aspect, the methods include the step of administering one or more of the compounds and/or compositions described herein to a patient with cancer. In another aspect, the methods include administering a therapeutically effective amount of the one or more compounds and/or compositions described herein for treating patients with cancer. In another embodiment, uses of the compounds and compositions in the manufacture of a medicament for
35 treating patients with cancer are also described herein. In one aspect, the medicaments include

a therapeutically effective amount of the one or more compounds and/or compositions for treating a patient with cancer.

It is appreciated herein that the compounds described herein may be used alone or in combination with other compounds useful for treating cancer, including those compounds that may be therapeutically effective by the same or different modes of action. In addition, it is appreciated herein that the compounds described herein may be used in combination with other compounds that are administered to treat other symptoms of cancer, such as compounds administered to treat pain, and the like.

In each of the foregoing and following embodiments, it is to be understood that the formulae include and represent not only all pharmaceutically acceptable salts of the compounds, but also include any and all hydrates and/or solvates of the compound formulae. It is appreciated that certain functional groups, such as the hydroxy, amino, and like groups form complexes and/or coordination compounds with water and/or various solvents, in the various physical forms of the compounds. Accordingly, the above formulae are to be understood to include and represent those various hydrates and/or solvates. In each of the foregoing and following embodiments, it is also to be understood that the formulae include and represent each possible isomer, such as stereoisomers and geometric isomers, both individually and in any and all possible mixtures. In each of the foregoing and following embodiments, it is also to be understood that the formulae include and represent any and all crystalline forms, partially crystalline forms, and non crystalline and/or amorphous forms of the compounds.

As used herein, the term “aminopyrrolopyrimidine carboxamides” generally refers to the compounds described herein and analogs and derivatives thereof. It is also to be understood that in each of the foregoing, any corresponding pharmaceutically acceptable salt is also included in the illustrative embodiments described herein.

Illustrative derivatives include, but are not limited to, both those compounds that may be synthetically prepared from the compounds described herein, as well as those compounds that may be prepared in a similar way as those described herein, but differing in the selection of starting materials. For example, described herein are compounds of formulae (I), (II), and (III) that include various functional groups on aromatic rings, such as R^3 . It is to be understood that derivatives of those compounds also include the compounds having for example different functional groups on those aromatic rings than those explicitly set forth in the definition of formulae (I), (II), and (III). In addition, it is to be understood that derivatives of those compounds also include the compounds having those same or different functional groups at different positions on the aromatic ring. Similarly, derivatives include parallel variations of other functional groups on the compounds described herein, such as R^1 , and the like.

It is to be understood that such derivatives may include prodrugs of the compounds described herein, compounds described herein that include one or more protection or protecting groups, including compounds that are used in the preparation of other compounds described herein.

5 In addition, as used herein the term aminopyrrolopyrimidine carboxamides also refers to prodrug derivatives of the compounds described herein, and including prodrugs of the various analogs and derivatives thereof. In addition, as used herein, the term aminopyrrolopyrimidine carboxamides refers to both the amorphous as well as any and all morphological forms of each of the compounds described herein. In addition, as used herein,
10 the term aminopyrrolopyrimidine carboxamides refers to any and all hydrates, or other solvates, of the compounds described herein.

It is to be understood that each of the foregoing embodiments may be combined in chemically relevant ways to generate subsets of the embodiments described herein. Accordingly, it is to be further understood that all such subsets are also illustrative
15 embodiments of the invention described herein.

The compounds described herein may contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. It is to be understood that in one embodiment, the invention described herein is not limited to any particular stereochemical requirement, and that the compounds, and compositions, methods, uses, and medicaments that
20 include them may be optically pure, or may be any of a variety of stereoisomeric mixtures, including racemic and other mixtures of enantiomers, other mixtures of diastereomers, and the like. It is also to be understood that such mixtures of stereoisomers may include a single stereochemical configuration at one or more chiral centers, while including mixtures of stereochemical configuration at one or more other chiral centers.

25 Similarly, the compounds described herein may include geometric centers, such as cis, trans, E, and Z double bonds. It is to be understood that in another embodiment, the invention described herein is not limited to any particular geometric isomer requirement, and that the compounds, and compositions, methods, uses, and medicaments that include them may be pure, or may be any of a variety of geometric isomer mixtures. It is also to be understood
30 that such mixtures of geometric isomers may include a single configuration at one or more double bonds, while including mixtures of geometry at one or more other double bonds.

As used herein, the term "alkyl" includes a chain of carbon atoms, which is optionally branched. As used herein, the term "alkenyl" and "alkynyl" includes a chain of carbon atoms, which is optionally branched, and includes at least one double bond or triple
35 bond, respectively. It is to be understood that alkynyl may also include one or more double

bonds. It is to be further understood that in certain embodiments, alkyl is advantageously of limited length, including C₁-C₂₄, C₁-C₁₂, C₁-C₈, C₁-C₆, and C₁-C₄. It is to be further understood that in certain embodiments alkenyl and/or alkynyl may each be advantageously of limited length, including C₂-C₂₄, C₂-C₁₂, C₂-C₈, C₂-C₆, and C₂-C₄. It is appreciated herein that shorter alkyl, alkenyl, and/or alkynyl groups may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior. Illustrative alkyl groups are, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, heptyl, octyl and the like.

As used herein, the term "cycloalkyl" includes a chain of carbon atoms, which is optionally branched, where at least a portion of the chain is cyclic. It is to be understood that cycloalkylalkyl is a subset of cycloalkyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkyl include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 2-methylcyclopropyl, cyclopentyleth-2-yl, adamantyl, and the like. As used herein, the term "cycloalkenyl" includes a chain of carbon atoms, which is optionally branched, and includes at least one double bond, where at least a portion of the chain is cyclic. It is to be understood that the one or more double bonds may be in the cyclic portion of cycloalkenyl and/or the non-cyclic portion of cycloalkenyl. It is to be understood that cycloalkenylalkyl and cycloalkylalkenyl are each subsets of cycloalkenyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkenyl include, but are not limited to, cyclopentenyl, cyclohexylethen-2-yl, cycloheptenylpropenyl, and the like. It is to be further understood that chain forming cycloalkyl and/or cycloalkenyl is advantageously of limited length, including C₃-C₂₄, C₃-C₁₂, C₃-C₈, C₃-C₆, and C₅-C₆. It is appreciated herein that shorter alkyl and/or alkenyl chains forming cycloalkyl and/or cycloalkenyl, respectively, may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior.

As used herein, the term "heteroalkyl" includes a chain of atoms that includes both carbon and at least one heteroatom, and is optionally branched. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain variations, illustrative heteroatoms also include phosphorus, and selenium. As used herein, the term "cycloheteroalkyl" including heterocyclyl and heterocycle, includes a chain of atoms that includes both carbon and at least one heteroatom, such as heteroalkyl, and is optionally branched, where at least a portion of the chain is cyclic. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain variations, illustrative heteroatoms also include phosphorus, and selenium. Illustrative cycloheteroalkyl include, but are not limited to, tetrahydrofuryl, pyrrolidinyl, tetrahydropyranlyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl, quinuclidinyl, and the like.

As used herein, the term “aryl” includes monocyclic and polycyclic aromatic carbocyclic groups, each of which may be optionally substituted. Illustrative aromatic carbocyclic groups described herein include, but are not limited to, phenyl, naphthyl, and the like. As used herein, the term “heteroaryl” includes aromatic heterocyclic groups, each of which may be optionally substituted. Illustrative aromatic heterocyclic groups include, but are not limited to, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, quinolinyl, quinazolinyl, quinoxalinyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzisoxazolyl, benzisothiazolyl, and the like.

As used herein, the term “amino” includes the group NH_2 , alkylamino, and dialkylamino, where the two alkyl groups in dialkylamino may be the same or different, i.e. alkylalkylamino. Illustratively, amino includes methylamino, ethylamino, dimethylamino, methylethylamino, and the like. In addition, it is to be understood that when amino modifies or is modified by another term, such as aminoalkyl, or acylamino, the above variations of the term amino are included therein. Illustratively, aminoalkyl includes H_2N -alkyl, methylaminoalkyl, ethylaminoalkyl, dimethylaminoalkyl, methylethylaminoalkyl, and the like. Illustratively, acylamino includes acylmethylamino, acylethylamino, and the like.

As used herein, the term “amino and derivatives thereof” includes amino as described herein, and alkylamino, alkenylamino, alkynylamino, heteroalkylamino, heteroalkenylamino, heteroalkynylamino, cycloalkylamino, cycloalkenylamino, cycloheteroalkylamino, cycloheteroalkenylamino, arylamino, arylalkylamino, arylalkenylamino, arylalkynylamino, heteroarylamino, heteroarylalkylamino, heteroarylalkenylamino, heteroarylalkynylamino, acylamino, and the like, each of which is optionally substituted. The term “amino derivative” also includes urea, carbamate, and the like.

As used herein, the term “hydroxy and derivatives thereof” includes OH, and alkyloxy, alkenyloxy, alkynyloxy, heteroalkyloxy, heteroalkenyloxy, heteroalkynyloxy, cycloalkyloxy, cycloalkenyloxy, cycloheteroalkyloxy, cycloheteroalkenyloxy, aryloxy, arylalkyloxy, arylalkenyloxy, arylalkynyloxy, heteroaryloxy, heteroarylalkyloxy, heteroarylalkenyloxy, heteroarylalkynyloxy, acyloxy, and the like, each of which is optionally substituted. The term “hydroxy derivative” also includes carbamate, and the like.

As used herein, the term “thio and derivatives thereof” includes SH, and alkylthio, alkenylthio, alkynylthio, heteroalkylthio, heteroalkenylthio, heteroalkynylthio, cycloalkylthio, cycloalkenylthio, cycloheteroalkylthio, cycloheteroalkenylthio, arylthio, arylalkylthio, arylalkenylthio, arylalkynylthio, heteroarylthio, heteroarylalkylthio,

heteroarylalkenylthio, heteroarylalkynylthio, acylthio, and the like, each of which is optionally substituted. The term "thio derivative" also includes thiocarbamate, and the like.

As used herein, the term "carboxylate and derivatives thereof" includes the group CO₂H and salts thereof, and esters and amides thereof, and CN.

5 As used herein, the term "sulfinyl or a derivative thereof" includes SO₂H and salts thereof, and esters and amides thereof.

As used herein, the term "sulfonyl or a derivative thereof" includes SO₃H and salts thereof, and esters and amides thereof.

10 The term "optionally substituted" as used herein includes the replacement of hydrogen atoms with other functional groups on the radical that is optionally substituted. Such other functional groups illustratively include, but are not limited to, amino, hydroxy, halo, thiol, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxy, thiol, alkyl, haloalkyl, 15 heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is optionally substituted.

As used herein, the terms "optionally substituted aryl" and "optionally substituted heteroaryl" include the replacement of hydrogen atoms with other functional groups on the aryl or heteroaryl that is optionally substituted. Such other functional groups 20 illustratively include, but are not limited to, amino, hydroxy, halo, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxy, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is 25 optionally substituted.

Illustrative substituents include, but are not limited to, a radical $-(CH_2)_xZ^X$, where x is an integer from 0-6 and Z^X is selected from halogen, hydroxy, alkanoyloxy, including C₁-C₆ alkanoyloxy, optionally substituted aroyloxy, alkyl, including C₁-C₆ alkyl, alkoxy, including C₁-C₆ alkoxy, cycloalkyl, including C₃-C₈ cycloalkyl, cycloalkoxy, including 30 C₃-C₈ cycloalkoxy, alkenyl, including C₂-C₆ alkenyl, alkynyl, including C₂-C₆ alkynyl, haloalkyl, including C₁-C₆ haloalkyl, haloalkoxy, including C₁-C₆ haloalkoxy, halocycloalkyl, including C₃-C₈ halocycloalkyl, halocycloalkoxy, including C₃-C₈ halocycloalkoxy, amino, C₁-C₆ alkylamino, (C₁-C₆ alkyl)(C₁-C₆ alkyl)amino, alkylcarbonylamino, N-(C₁-C₆ alkyl)alkylcarbonylamino, aminoalkyl, C₁-C₆ alkylaminoalkyl, (C₁-C₆ alkyl)(C₁-C₆ alkyl)aminoalkyl, alkylcarbonylaminoalkyl, N-(C₁-C₆ alkyl)alkylcarbonylaminoalkyl, cyano, 35

and nitro; or Z^X is selected from $-CO_2R^4$ and $-CONR^5R^6$, where R^4 , R^5 , and R^6 are each independently selected in each occurrence from hydrogen, C_1 - C_6 alkyl, aryl- C_1 - C_6 alkyl, and heteroaryl- C_1 - C_6 alkyl.

The term "prodrug" as used herein generally refers to any compound that when administered to a biological system generates a biologically active compound as a result of one or more spontaneous chemical reaction(s), enzyme-catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination thereof. In vivo, the prodrug is typically acted upon by an enzyme (such as esterases, amidases, phosphatases, and the like), simple biological chemistry, or other process in vivo to liberate or regenerate the more pharmacologically active drug. This activation may occur through the action of an endogenous host enzyme or a non-endogenous enzyme that is administered to the host preceding, following, or during administration of the prodrug. Additional details of prodrug use are described in U.S. Pat. No. 5,627,165; and Pathalk et al., *Enzymic protecting group techniques in organic synthesis*, Stereosel. Biocatal. 775-797 (2000). It is appreciated that the prodrug is advantageously converted to the original drug as soon as the goal, such as targeted delivery, safety, stability, and the like is achieved, followed by the subsequent rapid elimination of the released remains of the group forming the prodrug.

Prodrugs may be prepared from the compounds described herein by attaching groups that ultimately cleave in vivo to one or more functional groups present on the compound, such as $-OH$ -, $-SH$ -, $-CO_2H$ -, $-NR_2$. Illustrative prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxy, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. Illustrative esters, also referred to as active esters, include but are not limited to 1-indanyl, N-oxy succinimide; acyloxyalkyl groups such as acetoxymethyl, pivaloyloxymethyl, β -acetoxylethyl, β -pivaloyloxylethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, (1-aminoethyl)carbonyloxymethyl, and the like; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, α -ethoxycarbonyloxylethyl, β -ethoxycarbonyloxylethyl, and the like; dialkylaminoalkyl groups, including di-lower alkylamino alkyl groups, such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl, diethylaminoethyl, and the like; 2-(alkoxycarbonyl)-2-alkenyl groups such as 2-(isobutoxycarbonyl) pent-2-enyl, 2-(ethoxycarbonyl)but-2-enyl, and the like; and lactone groups such as phthalidyl, dimethoxyphthalidyl, and the like.

Further illustrative prodrugs contain a chemical moiety, such as an amide or phosphorus group functioning to increase solubility and/or stability of the compounds described

herein. Further illustrative prodrugs for amino groups include, but are not limited to, (C₃-C₂₀)alkanoyl; halo-(C₃-C₂₀)alkanoyl; (C₃-C₂₀)alkenoyl; (C₄-C₇)cycloalkanoyl; (C₃-C₆)-cycloalkyl(C₂-C₁₆)alkanoyl; optionally substituted aroyl, such as unsubstituted aroyl or aroyl substituted by 1 to 3 substituents selected from the group consisting of halogen, cyano, trifluoromethanesulphonyloxy, (C₁-C₃)alkyl and (C₁-C₃)alkoxy, each of which is optionally further substituted with one or more of 1 to 3 halogen atoms; optionally substituted aryl(C₂-C₁₆)alkanoyl and optionally substituted heteroaryl(C₂-C₁₆)alkanoyl, such as the aryl or heteroaryl radical being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of halogen, (C₁-C₃)alkyl and (C₁-C₃)alkoxy, each of which is optionally further substituted with 1 to 3 halogen atoms; and optionally substituted heteroarylalkanoyl having one to three heteroatoms selected from O, S and N in the heteroaryl moiety and 2 to 10 carbon atoms in the alkanoyl moiety, such as the heteroaryl radical being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of halogen, cyano, trifluoromethanesulphonyloxy, (C₁-C₃)alkyl, and (C₁-C₃)alkoxy, each of which is optionally further substituted with 1 to 3 halogen atoms. The groups illustrated are exemplary, not exhaustive, and may be prepared by conventional processes.

It is understood that the prodrugs themselves may not possess significant biological activity, but instead undergo one or more spontaneous chemical reaction(s), enzyme-catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination thereof after administration in vivo to produce the compound described herein that is biologically active or is a precursor of the biologically active compound. However, it is appreciated that in some cases, the prodrug is biologically active. It is also appreciated that prodrugs may often serve to improve drug efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, and the like. Prodrugs also refer to derivatives of the compounds described herein that include groups that simply mask undesirable drug properties or improve drug delivery. For example, one or more compounds described herein may exhibit an undesirable property that is advantageously blocked or minimized may become pharmacological, pharmaceutical, or pharmacokinetic barriers in clinical drug application, such as low oral drug absorption, lack of site specificity, chemical instability, toxicity, and poor patient acceptance (bad taste, odor, pain at injection site, and the like), and others. It is appreciated herein that a prodrug, or other strategy using reversible derivatives, can be useful in the optimization of the clinical application of a drug.

The term "therapeutically effective amount" as used herein, refers to that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical

doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. In one aspect, the therapeutically effective amount is that which may treat or alleviate the disease or symptoms of the disease at a reasonable benefit/risk ratio applicable to any medical treatment. However, it is to be understood that the total daily usage of the compounds and compositions described herein may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known to the researcher, veterinarian, medical doctor or other clinician of ordinary skill.

It is also appreciated that the therapeutically effective amount, whether referring to monotherapy or combination therapy, is advantageously selected with reference to any toxicity, or other undesirable side effect, that might occur during administration of one or more of the compounds described herein. Further, it is appreciated that the co-therapies described herein may allow for the administration of lower doses of compounds that show such toxicity, or other undesirable side effect, where those lower doses are below thresholds of toxicity or lower in the therapeutic window than would otherwise be administered in the absence of a cotherapy.

As used herein, the term "composition" generally refers to any product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. It is to be understood that the compositions described herein may be prepared from isolated compounds described herein or from salts, solutions, hydrates, solvates, and other forms of the compounds described herein. It is also to be understood that the compositions may be prepared from various amorphous, non-amorphous, partially crystalline, crystalline, and/or other morphological forms of the compounds described herein. It is also to be understood that the compositions may be prepared from various hydrates and/or solvates of the compounds described herein. Accordingly, such pharmaceutical compositions that recite compounds described herein are to be understood to include each of, or any combination of, the various morphological forms and/or solvate or hydrate forms of the compounds described herein. Illustratively, compositions may include one or more carriers, diluents, and/or excipients. The compounds described herein, or compositions containing them, may be formulated in a

therapeutically effective amount in any conventional dosage forms appropriate for the methods described herein. The compounds described herein, or compositions containing them, including such formulations, may be administered by a wide variety of conventional routes for the methods described herein, and in a wide variety of dosage formats, utilizing known procedures (see generally, Remington: The Science and Practice of Pharmacy, (21st ed., 2005)).

The term “administering” as used herein includes all means of introducing the compounds and compositions described herein to the patient, including, but are not limited to, oral (po), intravenous (iv), intramuscular (im), subcutaneous (sc), transdermal, inhalation, buccal, ocular, sublingual, vaginal, rectal, and the like. The compounds and compositions described herein may be administered in unit dosage forms and/or formulations containing conventional nontoxic pharmaceutically-acceptable carriers, adjuvants, and vehicles.

Illustrative routes of oral administration include tablets, capsules, elixirs, syrups, and the like.

Illustrative routes for parenteral administration include intravenous, intraarterial, intraperitoneal, epidural, intraurethral, intrasternal, intramuscular and subcutaneous, as well as any other art recognized route of parenteral administration.

The dosage of each compound of the claimed combinations depends on several factors, including: the administration method, the condition to be treated, the severity of the condition, whether the condition is to be treated or prevented, and the age, weight, and health of the person to be treated. Additionally, pharmacogenomic (the effect of genotype on the pharmacokinetic, pharmacodynamic or efficacy profile of a therapeutic) information about a particular patient may affect the dosage used.

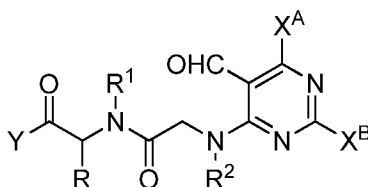
In addition to the foregoing illustrative dosages and dosing protocols, it is to be understood that an effective amount of any one or a mixture of the compounds described herein can be readily determined by the attending diagnostician or physician by the use of known techniques and/or by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician or physician, including, but not limited to the species of mammal, including human, its size, age, and general health, the specific disease or disorder involved, the degree of or involvement or the severity of the disease or disorder, the response of the individual patient, the particular compound administered, the mode of administration, the bioavailability characteristics of the preparation administered, the dose regimen selected, the use of concomitant medication, and other relevant circumstances.

In making the pharmaceutical compositions of the compounds described herein, a therapeutically effective amount of one or more compounds in any of the various forms

described herein may be mixed with one or more excipients, diluted by one or more excipients, or enclosed within such a carrier which can be in the form of a capsule, sachet, paper, or other container. Excipients may serve as a diluent, and can be solid, semi-solid, or liquid materials, which act as a vehicle, carrier or medium for the active ingredient. Thus, the formulation compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. The compositions may contain anywhere from about 0.1% to about 99.9% active ingredients, depending upon the selected dose and dosage form.

Additional illustrative embodiments of the invention are described by the following numbered clauses:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

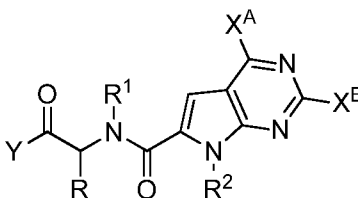
Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R¹ and R² are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; and

X^A and X^B are each independently selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof;

2. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

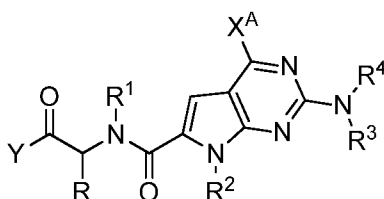
R^1 and R^2 are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; and

X^A and X^B are each independently selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol an derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof;

3. The compound of clause 1 or 2 wherein X^B is a leaving group, or a precursor thereof;

4. The compound of clause 1 or 2 wherein X^B is a leaving group;

5. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R^1 , R^2 , R^3 , and R^4 are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; or R^3 and R^4 are taken together with the attached nitrogen to form an optionally substituted heterocycle; and

X^A is selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol an derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof;

6. The compound of any one of the preceding clauses wherein Y is amino or a derivative thereof;

7. The compound of any one of the preceding clauses wherein Y is amino;
 8. The compound of any one of the preceding clauses wherein R is hydrogen;

9. The compound of any one of the preceding clauses wherein X^A is a leaving group, or a precursor thereof;

10. The compound of any one of the preceding clauses wherein X^A is a leaving group;

11. The compound of any one of the preceding clauses wherein X^A is amino or a derivative thereof;

12. The compound of any one of the preceding clauses wherein at least one of R¹, R², R³, and R⁴ is a hydrophobic group;

13. The compound of any one of the preceding clauses wherein at least two of R¹, R², R³, and R⁴ are hydrophobic groups;

14. The compound of any one of the preceding clauses wherein each of R¹, R², and R³ is a hydrophobic group;

15. The compound of any one of the preceding clauses wherein at least one of R¹, R², R³, and R⁴ is a side chain of a naturally occurring amino acid;

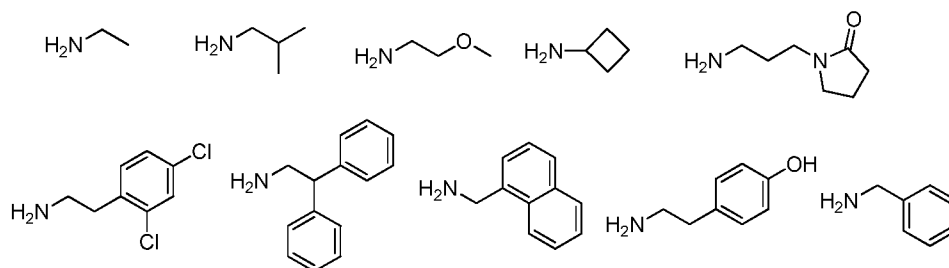
16. The compound of any one of the preceding clauses wherein at least two of R¹, R², R³, and R⁴ are side chains of naturally occurring amino acids;

17. The compound of any one of the preceding clauses wherein each of R¹, R², and R³ is a side chain of a naturally occurring amino acid;

18. The compound of any one of the preceding clauses wherein R¹ and R² are each independently selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted;

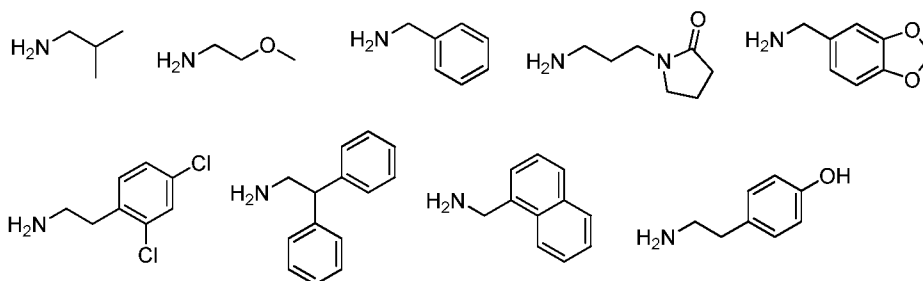
19. The compound of any one of the preceding clauses wherein R¹ and R² are each independently selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted;

20. The compound of any one of the preceding clauses wherein R¹ is a radical of one of the formula



;

21. The compound of any one of the preceding clauses wherein R^2 is a radical of one of the formula

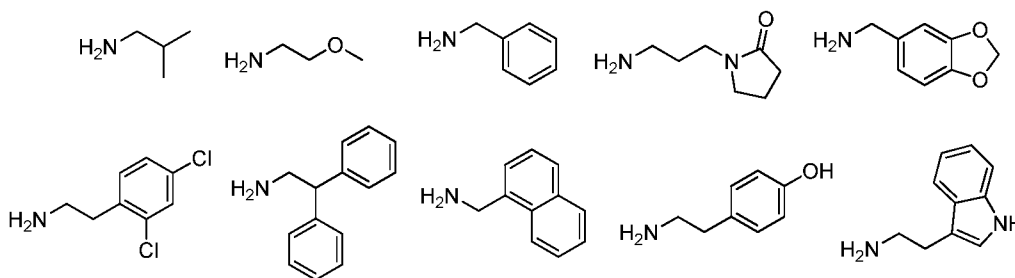


;

22. The compound of any one of the preceding clauses wherein R^3 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted;

23. The compound of any one of the preceding clauses wherein R^3 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted;

24. The compound of any one of the preceding clauses wherein R^3 is a radical of one of the formula



;

25. The compound of any one of the preceding clauses wherein R^4 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted;

26. The compound of any one of the preceding clauses wherein R^4 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted;

27. The compound of any one of the preceding clauses wherein R^4 is H;

28. The compound of any one of the preceding clauses wherein R^3 and R^4 are taken together with the attached nitrogen to form an optionally substituted heterocycle;

29. The compound of any one of the preceding clauses wherein R^3 and R^4 are taken together with the attached nitrogen to form a pyrrolidine, piperidine, morpholine, pyridazine, pyrimidine, pyrazine, or homopyrimidine, each of which is optionally substituted

30. A conjugate comprising a compound of any one of the preceding clauses, a bivalent linker, and a peptide, where the compound and the peptide are each covalently attached to the bivalent linker, and the peptide has at least 50%, greater than 50%, greater than 80%, or greater than 90% sequence homology to an alpha helical portion of one Mdm2 or MdmX;

31. A pharmaceutical composition comprising one or more compounds of any one of the preceding clauses;

32. The composition of the preceding clause further comprising one or more carriers, diluents, or excipients, or a combination thereof;

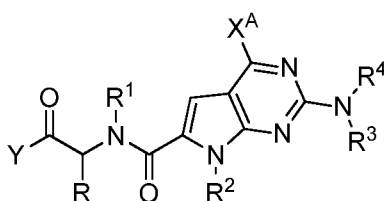
33. A method for treating a disease in a patient, comprising the step of administering to the patient a therapeutically effective amount of one or more compounds and/or one or more compositions of any one of the preceding clauses; where the disease is responsive to the disruption or antagonism of one or more alpha helical-based protein-protein interactions;

34. The method of clause 33 wherein the protein-protein interaction is between Mdm2 and p53, MdmX and p53, or a combination thereof;

35. The method of clause 33 wherein the disease is cancer;

36. A method for treating cancer in a patient, the method comprising the step of administering to the patient a therapeutically effective amount of one or more compounds and/or one or more compositions of any one of the preceding clauses;

37. A process for preparing a compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

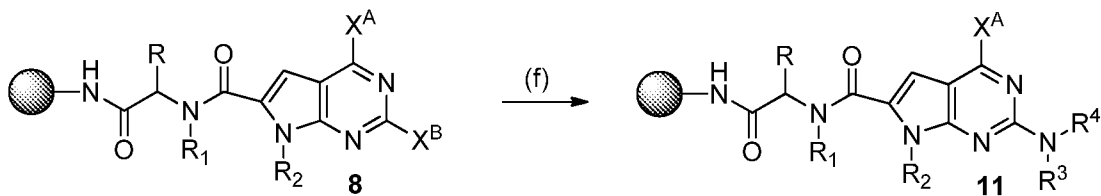
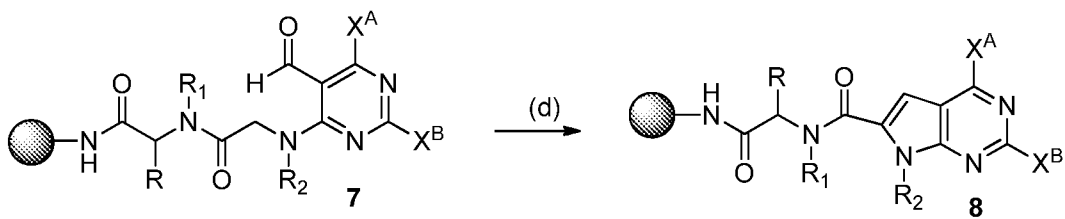
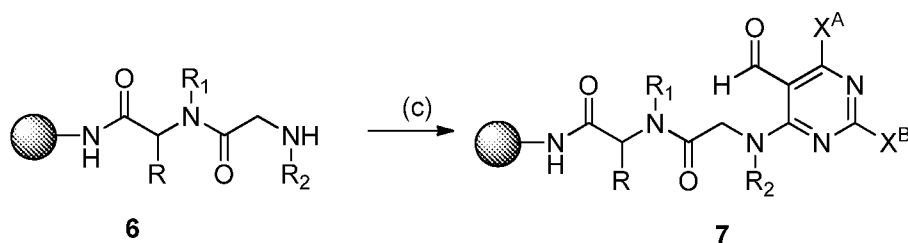
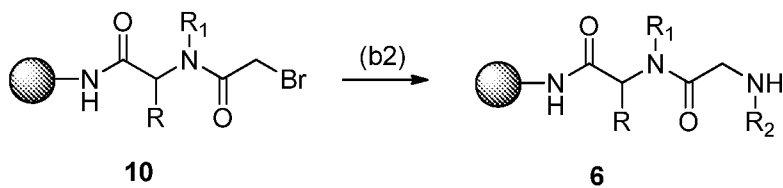
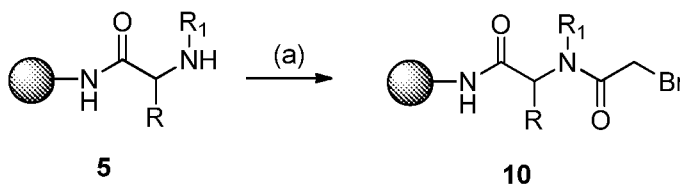
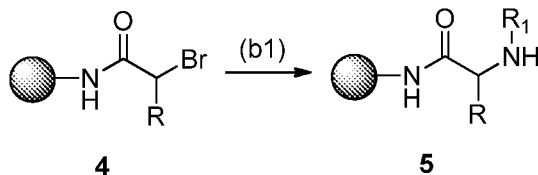
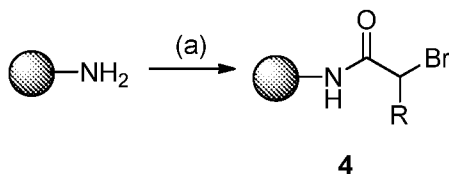
Y is hydroxy or a derivative thereof, or amino or a derivative thereof;

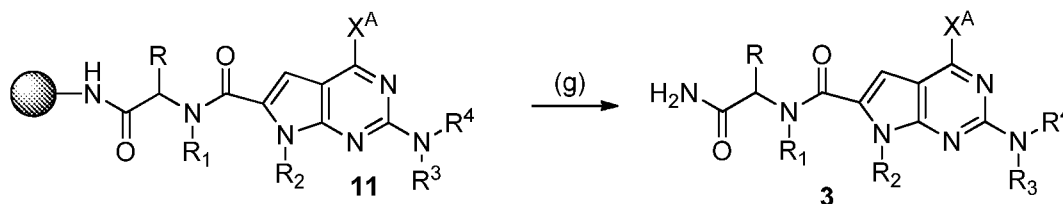
R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R¹, R², R³, and R⁴ are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; or R³ and R⁴ are taken together with the attached nitrogen to form an optionally substituted heterocycle; and

X^A is selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof;

the process comprising one or more of the following steps:





wherein (a) represents addition of $\text{BrCH(R)CO}_2\text{H}$; (b1) represents addition of R^1NH_2 ; (b2) represents addition of R^2NH_2 ; (c) represents addition of X^{A} , X^{B} substituted 4-chloropyrimidine-5-carbaldehyde; (d) represents cyclization in the presence of a base; (f) represents addition of R^3NH_2 ; and (g) represents cleavage of the resin in the presence of an acid; and wherein X^{A} , X^{B} , R, R^1 , R^2 , R^3 , and R^4 are as defined in any of the preceding clauses, or as defined herein.

The effective use of the compounds, compositions, and methods described herein for treating or ameliorating one or more effects of a cancer using one or more compounds described herein may be based upon animal models, such as murine, canine, porcine, and non-human primate animal models of disease.

The following examples further illustrate specific embodiments of the invention; however, the following illustrative examples should not be interpreted in any way to limit the invention.

EXAMPLES

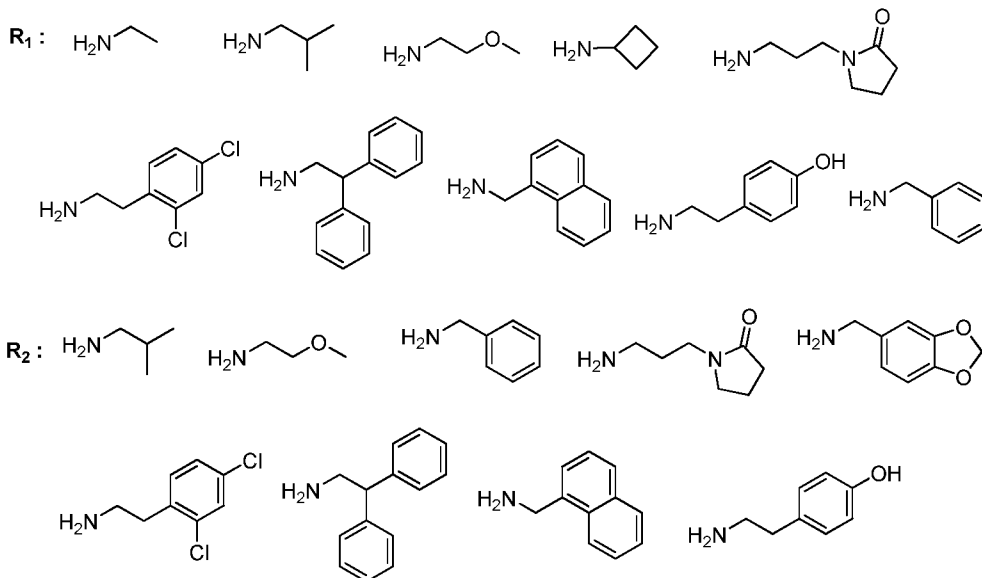
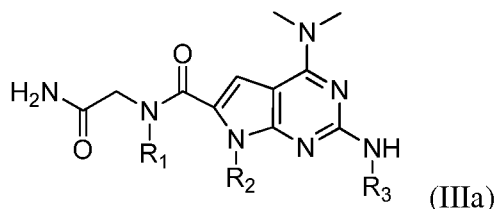
EXAMPLE. Materials and General Methods. Unless otherwise noted, all chemicals and reagents were purchased from commercial suppliers (Sigma-Aldrich and Acros) and used without further purification. Rink amide MBHA resin (0.69 mmol/g) was purchased from Novabiochem. LC/MS characterization was performed on an Agilent 1200 LC/MS system (Agilent Technology) with a C18 reversed-phase column (Agilent Technology, 5 μM , 4.6 mm x 125 mm). A gradient elution of 100% A in 4 min followed by 90% B in 20 min was used at flow rate of 1 mL/min (solvent A: H_2O , 0.1% TFA; B: acetonitrile, 0.1% TFA). Preparative HPLC purification was performed on an Agilent 1120 Compact LC system (Agilent Technology) with a C18 reversed-phase column (Agilent Technology, 5 μM , 25 mm x 125 mm) using a linear gradient from 10% B to 100% B by changing solvent composition over 40 minutes. Peptoid synthesis under microwave conditions was performed in a 1000 W Whirlpool microwave oven (model MT4155SPT) with 10% power. Thermal reactions were carried out in a heating mantle filled with sea sand using 4 ml glass vials (Fisher Scientific).

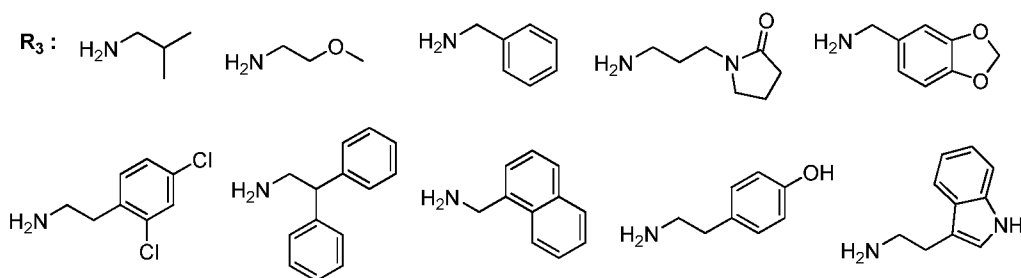
EXAMPLE. General Procedure for Synthesis. Rink amide MBHA resin (100 mg, 56 μmol) was swelled with dimethylformamide (DMF) (2 mL) in a 5 mL fritted syringe for

2 h. The Fmoc protecting group on the resin was removed by treating with 20 % piperidine in DMF (2 x 10 min). To the resin, two peptoid residues were added by a standard submonomer route using a microwave-assisted protocol. At the end of the reaction, the reaction mixture was drained and the resins were washed with DMF (3x), CH₂Cl₂ (2x), MeOH (2x), and DMF (3x).

The resin was treated with 4,6-dichloro-2-methylthio-5-formylaldehyde (5 equiv.) and triethylamine (TEA) (5 equiv.) in tetrahydrofuran (THF) at room temperature overnight. The reaction mixture was drained and washed with DMF (3×), CH₂Cl₂ (2×), MeOH (2×), and DMF (3×). For cyclization and dimethylamination, the resins were reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (20 equiv.) in DMF (2 mL) and MeOH (1 mL) at 90°C overnight. After thorough washing, the sulfide group was oxidized into a sulfone by treating with m-chloroperoxybenzoic acid (mCPBA) (10 equiv.) and NaHCO₃ (15 equiv.) in THF (2 mL)/H₂O (400 μL) at room temperature overnight. The resin was thoroughly washed with DMF (3×), CH₂Cl₂ (2×), MeOH (2×), and DMF (3×). The resulting sulfone group was replaced with various amines (Scheme 3) by treating with an amine (20 equiv.) and N,N-diisopropylethylamine (DIEA) (100 equiv.) in N-methyl-2-pyrrolidone (NMP) at 170°C overnight. After thorough washing with DMF (3×), CH₂Cl₂ (2×), MeOH (2×), and CH₂Cl₂ (5×), the products were cleaved from the resin using a cleavage cocktail (95% trifluoroacetic acid (TFA), 2.5% triisopropylsilane, and 2.5% water) for 2 hrs at room temperature.

Scheme 3. Amines used in the synthesis of 900 member library of compounds of formula (IIIa).



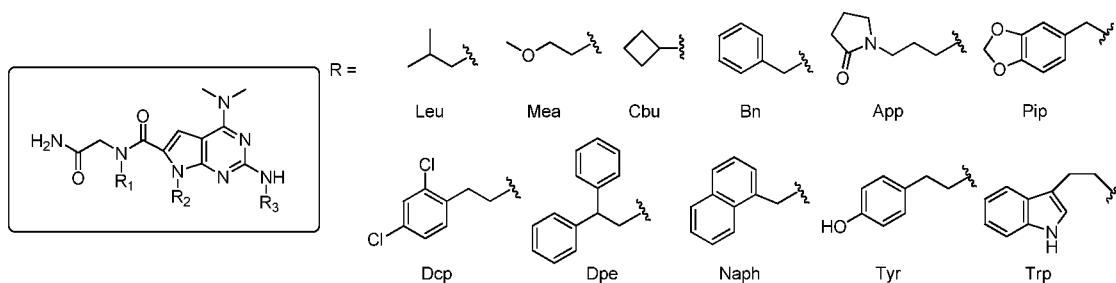


EXAMPLE. Library Synthesis. A library of compounds of formula (III) was synthesized manually in a parallel fashion. After Fmoc deprotection, NH₂ group of Rink amide MBHA resin (5 g) was bromoacetylated in a 250mL peptide synthesis vessel (Chemglass Life Sciences) to provide compound 4 (Scheme 1). After thorough washing, the resin was split into 10 fritted syringe reactors in equal quantities (~500 mg of resin in each reactor). The resin in each reactor was then treated with 10 different primary amines shown in Scheme 3 to introduce R₁ group (giving 10 different monomeric peptoids 5 in Scheme 1). The peptoids 5 in 10 individual reactors were bromoacetylated, respectively. After that, the beads in each reactor were split into 9 reactors to couple with 9 different primary amines (R₂) shown in Scheme 3. As a result, 90 different dimeric peptoids 6 were obtained (~55 mg of resin in each reactor). After thorough washing, dimeric peptoids 6 in each reactor were transformed into sulfone compounds 9 by three steps, following the aforementioned procedure (Scheme 1). The resin was split into 10 reaction vials in equal quantities (~5 mg of resin in each reactor). The 900 sulfone compounds in each reactor were then coupled with desired amines shown in Scheme 3 to provide final products 3. After cleavage with a cleavage cocktail (95% TFA, 2.5% triisopropylsilane, and 2.5% water), the crude product were dried by evaporating with a stream of nitrogen and dissolved in DMSO to make a ~10 mM stock solution.

It is to be understood that the amines for each of R¹, R², and R³ shown in Scheme 3 were each used to prepare the library in a 10x9x10 matrix of combinations. Without being bound by theory, it is believed herein that primary amines containing hydrophobic groups (aromatic or aliphatic, including those shown in Scheme 3 may mimic the side chains of the three amino acids of p53 (Phe, Trp, and Leu).

A group of 90 compounds (10% of the library) was randomly chosen from the library, and their purity and identity were characterized by LC-MS. As shown in the following table, the average purity of the crude final products was 83%. The compounds in the entire library were assayed without further purification.

Purity of the 90 illustrative compounds selected randomly.

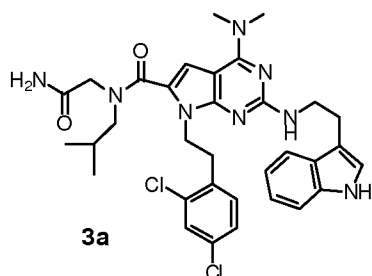


Example	R ₁	R ₂	R ₃	Purity (%)	Calculated Mass (M)	Found Mass (M+H)
3-3	Dcp	Naph	Leu	89.6	645.24	646.00
3-4	Dcp	Dpe	Mea	89.4	687.25	688.00
3-5	Naph	Dcp	Bn	81.9	679.23	680.00
3-6	Mea	Bn	App	84.4	550.30	551.20
3-7	Leu	Mea	Dcp	70.4	563.22	564.20
3-8	Pip	Leu	Dpe	62.1	647.32	648.20
3-9	Bn	Pip	Naph	67.5	641.26	642.00
3-10	App	Bn	Tyr	92.9	612.32	613.00
3-11	Leu	Bn	Trp	70.2	566.31	567.20
3-12	Leu	Bn	Leu	82.6	479.30	480.20
3-13	Tyr	Leu	Mea	89.0	511.29	512.20
3-14	Dpe	Bn	Bn	87.2	637.32	638.20
3-15	Mea	Bn	App	89.5	550.30	551.20
3-16	Dcp	Dpe	Pip	64.9	763.24	764.00
3-17	Mea	Mea	Dcp	90.4	565.20	566.00
3-18	Leu	Bn	Dpe	74.5	603.33	604.20
3-19	Naph	Dcp	Naph	74.0	729.24	730.00
3-20	Dpe	Dpe	Tyr	92.2	757.38	758.00
3-21	Bn	Tyr	Trp	80.4	630.30	631.00
3-22	Naph	Bn	Leu	86.2	563.30	564.00
3-23	Bn	Dcp	Mea	96.0	597.19	598.00
3-24	App	Pip	Bn	82.6	626.30	627.00
3-25	App	Dcp	App	96.6	699.28	700.00
3-26	Dcp	Cbu	Dcp	91.0	675.13	676.00
3-27	Bn	Pip	Dpe	88.4	681.30	682.00
3-28	App	Pip	Naph	68.7	676.31	677.00
3-29	Tyr	App	Tyr	93.1	642.33	643.20
3-30	Mea	Bn	Trp	88.6	568.29	569.20
3-31	Dcp	App	Leu	81.0	630.26	631.00
3-32	Mea	Naph	Mea	94.3	533.28	534.00

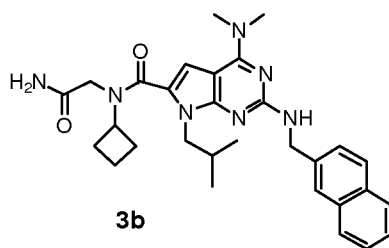
Example	R ₁	R ₂	R ₃	Purity (%)	Calculated Mass (M)	Found Mass (M+H)
3-33	Dcp	Leu	Bn	79.8	595.23	596.00
3-34	Cbu	Tyr	App	81.8	576.31	577.00
3-35	Dcp	Dcp	Dcp	86.1	793.08	793.80
3-36	Naph	Leu	Dpe	64.8	653.34	654.00
3-37	Bn	App	Naph	83.3	632.32	633.20
3-38	Dcp	App	Tyr	87.6	694.25	695.00
3-39	App	Mea	Leu	84.8	516.32	517.20
3-40	Mea	Naph	Mea	94.1	533.28	534.20
3-41	Leu	Leu	Bn	88.6	479.31	480.00
3-42	Dpe	Dpe	App	77.8	762.40	763.20
3-43	Naph	Naph	Dcp	89.9	729.24	730.00
3-44	Leu	Dcp	Dpe	67.6	685.27	686.00
3-45	Naph	App	Tyr	80.5	662.34	663.00
3-46	Dcp	Pip	Trp	66.7	726.22	727.00
3-47	App	Bn	Leu	82.9	548.32	549.00
3-48	Dpe	Tyr	Mea	83.4	635.32	636.00
3-49	Bn	Naph	Bn	86.8	597.29	598.00
3-50	Dpe	Pip	App	76.6	716.33	717.20
3-51	Naph	Dcp	Dcp	91.2	761.16	762.00
3-52	Cbu	Bn	Dpe	81.6	601.31	602.00
3-53	Bn	App	Naph	81.6	632.32	633.00
3-54	Dpe	Tyr	Tyr	93.7	697.34	698.00
3-55	Dpe	Mea	Trp	89.9	658.34	659.00
3-56	Naph	Tyr	Leu	88.4	593.31	594.20
3-57	App	Tyr	Mea	91.1	580.31	581.00
3-58	Leu	Naph	Bn	80.5	563.31	564.20
3-59	Dpe	Bn	App	83.1	632.32	673.20
3-60	Leu	Naph	Dcp	74.2	645.24	646.00
3-61	Dpe	Mea	Dpe	75.1	695.36	696.00
3-62	Bn	Naph	Tyr	85.6	627.30	628.00
3-63	Leu	Leu	Leu	80.5	445.32	446.00
3-64	Dpe	App	Mea	93.3	640.35	641.20
3-65	Pip	Naph	Bn	88.8	641.28	642.00
3-66	Tyr	Bn	App	84.1	612.31	613.20
3-67	Tyr	Cbu	Dcp	82.3	623.21	624.00
3-68	Naph	Dpe	Dpe	75.2	777.38	778.00
3-69	Dpe	Bn	Naph	70.7	687.33	688.20
3-70	Cbu	Pip	Tyr	92.9	585.26	586.00

Example	R ₁	R ₂	R ₃	Purity (%)	Calculated Mass (M)	Found Mass (M+H)
3-71	Naph	Pip	Leu	88.7	607.29	608.00
3-72	Tyr	Tyr	Mea	87.9	575.28	576.00
3-73	Pip	Dcp	Bn	87.9	673.20	674.00
3-74	Tyr	Naph	App	67.3	662.33	663.00
3-75	Bn	Dpe	Dcp	69.1	719.25	720.00
3-76	Naph	Bn	Dpe	89.2	687.33	688.00
3-77	Bn	Naph	Tyr	85.5	627.30	628.00
3-78	Dpe	Bn	Trp	75.0	690.34	691.20
3-79	Dpe	Naph	Leu	83.4	653.35	654.20
3-80	Mea	Mea	Mea	94.1	451.26	452.20
3-81	Naph	Dcp	Bn	84.7	679.22	680.00
3-82	Leu	Bn	App	87.2	548.32	549.20
3-83	Mea	Bn	Tyr	88.9	545.28	546.00
3-84	Bn	Naph	Trp	88.2	650.31	651.00
3-85	Dcp	Naph	Leu	85.9	645.24	646.00
3-86	Cbu	Mea	Mea	92.8	447.25	448.00
3-87	Leu	Bn	Bn	69.3	513.29	514.20
3-88	Dpe	Dcp	App	68.3	754.29	755.00
3-89	Bn	Dpe	Dcp	86.7	719.25	720.00
3-90	App	Leu	Dpe	68.2	638.37	639.20
3-91	Dcp	Naph	Naph	75.5	729.24	730.00
3-92	Dpe	App	Tyr	93.6	702.37	703.00

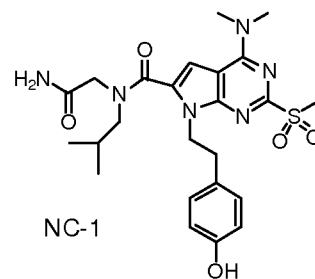
EXAMPLE. Resynthesis. Compounds 3-1 (3a), 3-2 (3b), and 9-1 (NC-1) were resynthesized on 100 mg of MBHA resin, following the general procedure as described above. After cleavage reaction, the crude compounds were purified by HPLC. The overall isolated yields of 3a, 3b, and NC-1 were 26%, 40%, and 42%, respectively. Solubility of 3-1 (3a) and 3-2 (3b) in water and phosphate buffer saline (pH 7.4) were >150 µg/ml, which is reportedly above that necessary for desirable water solubility (100 µg/ml) for favorable oral absorption of drugs (15. Muller, C. E. Chem. Biodiv. 2009, 6, 2071).

**3a**

Exact Mass: 648.25

**3b**

Exact Mass: 527.30



NC-1

Exact Mass: 516.22

EXAMPLE. The library compounds was assayed at ~40 μM concentration for the ability to displace a Rhodamine-labeled 15-mer p53 peptide from MDMX protein by a fluorescence polarization (FP) assay (FIG. 1). The binding affinities of the compounds described herein are assayed using the same FP-based competitive assays. A 15-mer peptide derived from p53 and a known MDM2 inhibitor, MI-63, are used as controls (Ding et al., J. Med. Chem. 2006, 49, 3432). As shown in FIG. 2(A), compounds 3-1 and 3-2 (also referred to herein as 3a and 3b, respectively) each effectively inhibited the p53-MDMX binding with K_i of 0.62 μM and 0.45 μM , respectively, which are comparable with that of a 15-mer p53 peptide ($K_i = 0.8 \mu\text{M}$). The compounds also inhibited the p53-MDM2 interaction with K_i of 0.62 μM and 0.84 μM , respectively, similar to the binding affinities for MDMX (FIG. 2). These results support that the compounds described herein may act as dual inhibitors of MDMX-p53 and MDM2-p53 interactions.

K_i values of inhibitors. K_i $\pm$ SD (μM)

Example	MDMX	MDM2
3-1 (3a)	0.62 $\pm$ 0.12	0.62 $\pm$ 0.04
3-2 (3b)	0.45 $\pm$ 0.18	0.84 $\pm$ 0.74
p53 peptide (a)	0.8 $\pm$ 0.2	1.7 $\pm$ 0.1
MI-63	16.7 $\pm$ 6.8	0.42 $\pm$ 0.32

(a) Unlabeled 15-mer p53 peptide (SQETFSDLWKLLPEN).

EXAMPLE. The cellular activity of the compounds described herein is assayed. Without being bound by theory, it is believed herein that the compounds may be cell permeable. H460 cells were treated with DMSO, designated concentration of compound 3b and 10 μM NC-1 for 12 h and harvested for a Western blot analysis. The effect of the compounds on cellular levels of p53 and the cyclin-dependent kinase inhibitor p21, a major transcriptional target of p53, is examined. Human lung cancer H460 cells expressing wild type p53 are incubated with 3-1 (3a), 3-2 (3b), DMSO (untreated control), or 9-1 (also referred to herein as NC-1), and cell

lysates are analyzed by Western blot to monitor p53 and p21 levels. Treatment with 3a and 3b leads to an increase of p53 and p21 levels in a dose-dependent manner, whereas DMSO and 9-1 (NC-1) do not. These results support that the compounds described herein are cell-permeable, and/or able to induce p53 level and activity in cells.

5 EXAMPLE. Activation of p53 by the MDMX/MDM2 inhibitors results in cell cycle arrest and apoptosis. The ability of the compounds described herein to induce apoptosis is examined by monitoring the effect of 3a on caspase activity. H460 cells with wild type p53 and human lung cancer H1299 cells with deleted p53 are exposed to DMSO, 9-1 (NC-1), 3-1 (3a), or MI-63 (a positive control) for 24 hours, and caspase activity is measured by a commercially
10 available Caspase-Glo 3/7 assay kit (Promega).. As shown in FIG. 3, compounds 3a and MI-63 induced caspase 3/7 activity (about 3- and 5-fold, respectively) in H460 cells, while they had no effect on H1299 cells. This result supports that 3a triggers apoptosis through a p53-dependent pathway by binding to MDMX/MDM2 and inhibiting their function toward p53.

 EXAMPLE. Computational Structure Optimization, Docking, and
15 Visualization. The geometry-optimized structure of an illustrative compound of formula (III) was obtained as follows. First, the compounds initial conformations were generated by the molecular mechanics simulation software CHARMM (Frisch et al., Gaussian, Inc: Pittsburgh, PA, 2003) with force field parameters obtained by Antechamber (Brooks et al., J. Comput. Chem. 2009, 30, 1545) using the AM1-BCC charge models and general AMBER force field
20 (Wang et al., J. Mol. Graph. Model. 2006, 25, 247260). The generated conformations were grouped into two conformations based on the structural similarity. A representative conformation which has functional groups facing the same direction was selected, and was subjected to geometry optimization at the HF/6-31G* level using Gaussian 03 software (Wang et al., J. Comput. Chem. 2004, 25, 1157). The molecular visualization software PyMol
25 (DeLano, 2002. The PyMOL Molecular Graphics System. Palo Alto, CA, USA) was used. MDMX is visualized with its molecular surface with surface charge distribution: red for negatively-charged residues and blue for positively-charged residues. Since the p53-MDMX complex (PDB entry: 2Z5S) is already known, instead of performing de novo docking of the compound onto MDMX, the rigid-body fitting of the geometry-optimized structure of the
30 compound was performed to maximize the overlap between the functional groups of the compound and the side chains of the functionally important residues (F19, W23, and L26) in the p53 peptide using PyMol.

 EXAMPLE. Plasmid Constructs and Protein Production. The gene encoding p53-binding domain of human MDMX (a.a. 1-137) or human MDM2 (a.a. 1-138) was
35 amplified by polymerase chain reaction (PCR) and cloned into the pGEX-4T1 plasmid. The

recombinant GST fusion proteins were expressed in BL21 (DE3) E. coli cells and purified by a 5-ml GSTrap HP column (GE Life Sciences) according to the manufacturer's instructions. Purified GST-tagged MDMX protein was used in the compound primary screening. For the dose-dependent assays, the GST-tags of MDMX and MDM2 were cleaved by thrombin, and
5 purified through benzamidine FF and GSTrap HP columns. Proteins were concentrated by ultrafiltration (Millipore-Amicon ultra) and dialyzed against phosphate buffered saline (PBS) (pH 7.5) containing 2 mM phenylmethanesulfonylfluoride (PMSF), 10% glycerol and 1mM dithiothreitol (DTT).

EXAMPLE. The efficacy of the scaffolds as α -helix mimetics described herein is
10 assessed by monitoring the ability to disrupt the p53-MDM2, p53-MDM4, and/or p53-MDMX interaction. MDM2 and its homolog MDMX bind to the tumor suppressor p53 and regulate its stability and activity. It has been reported that the interactions are mediated mainly by three residues (Phe19, Trp23, and Leu26) of p53 and the hydrophobic pocket in MDMX and MDM2 (see, generally, (a) Pazgier et al., Proc. Natl. Acad. Sci. USA. 2009, 106, 4665. (b) Phan et al.,
15 J. Biol. Chem. 2010, 285, 2174; 9. Czarna et al., Cell Cycle 2009, 8, 1176). Despite the similarity in the p53 recognition surface of MDMX and MDM2, few MDMX inhibitors have been reported, whereas a number of MDM2 inhibitors have been reported (10. (a) Murray et al., Biopolymers 2007, 88, 657. (b) Dömling, Curr. Opin. Chem. Biol. 2008, 12, 281. (c) Shangary et al., Annu. Rev. Pharmacol. Toxicol. 2009, 49, 223). It has also been reported that those
20 inhibitors targeting MDM2 showed significantly less affinity to MDMX, and there is only one report of MDMX-specific small molecule inhibitor (11. Laurie et al., Nature 2006, 444, 61 ; 12. Reed et al., J. Biol. Chem. 2010, 285, 10786).

EXAMPLE. Fluorescence Polarization Assays. A previously established fluorescence polarization (FP) assays (Ding et al., J. Am. Chem. Soc. 2005, 127, 10130; Reed et al., J. Biol. Chem. 2010, 285, 10786) was adapted to monitor the displacement of a Rhodamine-labeled p53 peptide (Rd-p53 peptide) from MDMX or MDM2 by the compounds described
25 herein or by unlabeled p53 peptide. The p53 peptide (SQETFSDLWKLLPEN-NH₂) and N-terminally labeled Rhodamine p53 peptide (SQETFSDLWKLLPEN-NH-Rhodamine) were synthesized by the Antagene Inc. The p53 peptide binds to MDMX with $K_D \approx 0.9 \mu\text{M}$ and to MDM2 with $K_D \approx 0.4 \mu\text{M}$ (FIG. 1(A)). K_D values were calculated as described previously (Chai et al., BMC. Biochem. 2009, 10, 32). The specificity of this assay was confirmed by the competitive displacement of the unlabeled p53 peptide and the specific MDM2 inhibitor MI-63 (Shangary et al., Proc. Natl. Acad. Sci. USA. 2008, 105, 3933.) using assay conditions as
30 described below (FIG. 1(B)). All FP assays were performed in 384-well black plates (Nalge

Nunc International). For liquid transfer, Precision Microplate Pipetting System (BioTek Instruments, Inc.) was used.

EXAMPLE. For inhibition studies, in each well of the microtiter plates, 40 μ l solution containing 1.5 μ M of MDM2 or MDMX and 75 nM of the Rd-p53 peptide in 1 $\times$ PBS (pH 7.5) with 0.01% Triton was combined with 20 μ l of each library compound (final concentration of 40 μ M and 2% DMSO). Following incubation at 23°C for 30 min, the fluorescence signals (excitation at 531 nm and emission at 595 nm) were monitored using a SpectraMax M5^e (Molecular Devices). Positive controls (100% inhibition) contained Rd-p53 peptide only, and negative controls contained Rd-p53 peptide and MDMX or MDM2 proteins.

The Z' factor, indicating the quality of a FP assay, was calculated based on the following

equation: $Z' factor = 1 - \frac{3 \times (SD_+ + SD_-)}{|\mu_+ - \mu_-|}$, where μ_+ and μ_- represent the means of the positive

and negative control signals, respectively, and SD_+ and SD_- are standard deviations of the mean values for the positive and negative controls, respectively (Arai, T.; Yatabe, M.; Furui, M.; Akatsuka, H.; Uehata, M.; Kamiyama, T. Anal. Biochem. 2010-2011). The FP assay achieved a

Z'-factor of 0.8, based on negative (containing Rd-p53 peptide with MDMX or MDM2 proteins) and positive (containing Rd-p53 peptide only) controls (16 data points per positive and negative controls). The primary screen of a 900-compound library yielded 7 putative hits that inhibited the p53-MDMX by at least 50%. By subsequent dose-dependent experiments of these compounds, two compounds, denoted 3-1 (3a) and 3-2 (3b), were chosen for further studies. Inhibitory activity was calculated as the mean value of negative controls minus the average sample value divided by the mean value of negative controls minus the mean value of positive controls, multiplied by 100. Dose-dependent experiments were carried out using the same conditions as above. IC₅₀ values were determined by the Hill equation using Igor4.01 (Lake Oswego, Oregon, USA). Ki values were calculated by a conventional web-based computer program developed for FP-based binding assays (see, e.g., http://sw16.im.med.umich.edu/software/calc_ki/) (Ding et al., J. Med. Chem. 2006, 49, 3432). The primary screen experiments were performed in duplicate and the dose response experiments were performed in triplicate.

EXAMPLE. Cell Culture and Western Blot. H460 cells were seeded in 6-well plates and grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum (FBS), 100 U per mL penicillin, and 100 U per mL streptomycin. Compounds 3a, 3b, and NC-1 were dissolved in DMSO and diluted directly into the medium to the indicated concentrations; 0.1% DMSO was used as a control. After incubation with the compounds for 12 h, cells were harvested and lysed in 50 mM Tris-HCl pH 8.0, 150 mM NaCl, 5 mM EDTA,

0.5% NP-40 supplemented with 2 mM DTT and 1 mM PMSF. An equal amount of protein samples (50 µg) was subjected to SDS-PAGE and transferred to a PVDF membrane (PALL Life Science). The membranes with transferred proteins were blocked with 1×TBST containing 5% non-fat, dried milk for 1h at room temperature, and then incubated with anti-p53 (mouse monoclonal, DO-1, Santa Cruz), anti-p21 (rabbit polyclonal, M19, Santa Cruz), or anti-β-actin antibodies (Sigma) followed by a secondary antibody labeled with horseradish peroxidase (Pierce). The blots were developed by an enhanced chemiluminescence detection kit (Thermo Scientific), and signals were visualized by Omega 12iC Molecular Image System (UltraLUM).

EXAMPLE. Caspase Assays. H460 and H1299 cells were plated at 4×10^3 cells/well in white-walled 96-well plates, cultured for 24 hrs in DMEM with 10% FBS, and treated with 3a (20 µM), NC-1 (20 µM), MI-63 (20 µM), and DMSO for another 24 hrs. The caspase 3/7 activity was measured using Caspase-Glo 3/7 Assay kit (Promega) according to the manufacturer's instructions. Briefly, 100 µl of caspase-Glo substrate reagent was added into each well containing 100 µl cell culture media and luciferase activity was determined at room temperature using FlexStation II³⁸⁴ (Molecular devices) after 40 min.

The following publications, and all other publications cited herein are incorporated herein in their entirety by reference.

1. (a) Davis et al., Chem. Soc. Rev. 2007, 36, 326. (b) Hershberger et al., J. Curr. Top. Med. Chem. 2007, 7, 928. (c) Wilson, J. Chem. Soc. Rev. 2009, 38, 3289. (d) Jochim et al., Mol. Biosyst. 2009, 5, 924. (e) Cummings et al., Curr. Opin. Chem. Biol. 2010, 14, 341. (c) Walensky et al., Science 2004, 305, 1466. (d) Fasan et al., Angew. Chem. Int. Ed. 2004, 43, 2109. (e) Wang et al., Angew. Chem. Int. Ed. 2005, 44, 6525. (f) Hara et al., J. Am. Chem. Soc. 2006, 128, 1995. (g) Sadowsky et al., J. Am. Chem. Soc. 2007, 129, 139. (h) Bautista et al., J. Am. Chem. Soc. 2010, 132, 2904.

2. (a) Lu et al., J. Comb. Chem. 2006, 8, 315. (b) Volonterio et al., Org. Lett. 2007, 9, 3733. (c) Maity et al., Org. Lett. 2008, 10, 1473. (d) Plante et al., J. Chem. Commun. 2009, 5091. (e) Shaginian et al., J. Am. Chem. Soc. 2009, 131, 5564. (f) Marimganti et al., Org. Lett. 2009, 11, 4418. (g) Tosovska et al., Org. Lett. 2010, 12, 1588. (h) Bourne et al., Chemistry, 2010, 16, 8439.

3. Yin et al., H.; Lee, G. I.; Sedey, K. A.; Rodriguez, J. M.; Wang, H. G.; Sebt, S. M.; Hamilton, A. D. J. Am. Chem. Soc. 2005, 127, 5463.

4. Welsch et al., Curr. Opin. Chem. Biol. 2010, 14, 347.

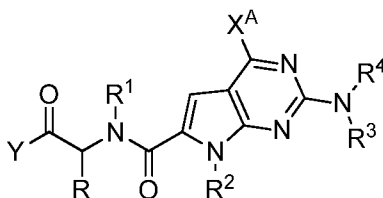
5. Michel et al., J. Am. Chem. Soc. 2009, 131, 6356.

6. Hayashi et al., Bioorg. Med. Chem. 2009, 17, 7884

7. Olivos et al., Org. Lett. 2002, 4, 4057.

WHAT IS CLAIMED IS:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R¹, R², R³, and R⁴ are each independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; or R³ and R⁴ are taken together with the attached nitrogen to form an optionally substituted heterocycle; and

X^A is selected from the group consisting of H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof.

2. The compound of claim 1 wherein Y is amino or a derivative thereof.
3. The compound of claim 1 wherein Y is amino.
4. The compound of claim 1 wherein R is hydrogen.
5. The compound of claim 1 wherein X^A is a leaving group, or a precursor thereof.
6. The compound of claim 1 wherein X^A is a leaving group.
7. The compound of claim 1 wherein X^A is amino or a derivative thereof.
8. The compound of any one of claims 1 to 7 wherein at least one of R¹, R², R³, and R⁴ is a hydrophobic group.
9. The compound of any one of claims 1 to 7 wherein at least two of R¹, R², R³, and R⁴ are hydrophobic groups.
10. The compound of any one of claims 1 to 7 wherein each of R¹, R², and R³ is a hydrophobic group.

11. The compound of any one of claims 1 to 7 wherein at least one of R^1 , R^2 , R^3 , and R^4 is a side chain of a naturally occurring amino acid.

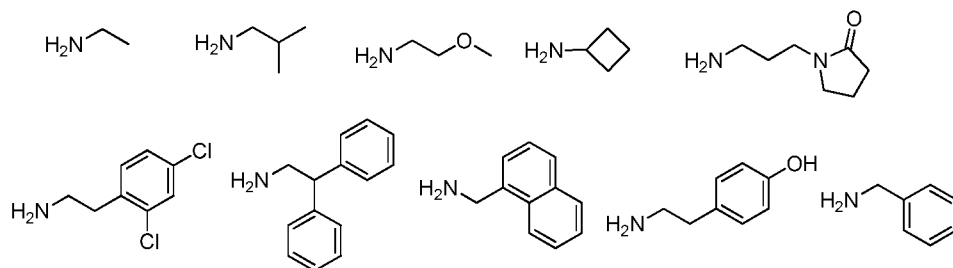
12. The compound of any one of claims 1 to 7 wherein at least two of R^1 , R^2 , R^3 , and R^4 are side chains of naturally occurring amino acids.

13. The compound of any one of claims 1 to 7 wherein each of R^1 , R^2 , and R^3 is a side chain of a naturally occurring amino acid.

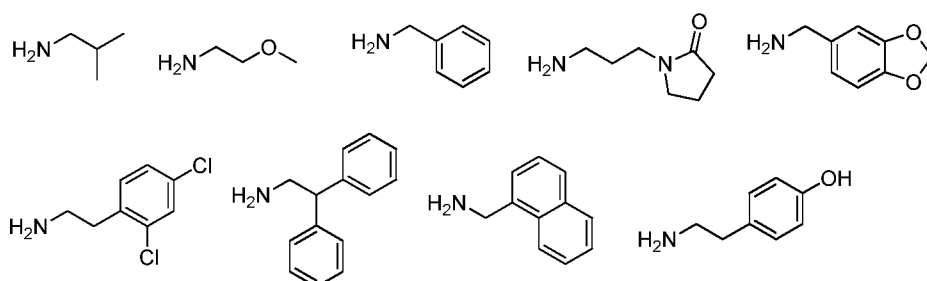
14. The compound of any one of claims 1 to 7 wherein R^1 and R^2 are each independently selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted.

15. The compound of any one of claims 1 to 7 wherein R^1 and R^2 are each independently selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted.

16. The compound of any one of claims 1 to 7 wherein R^1 is a radical of one of the formula



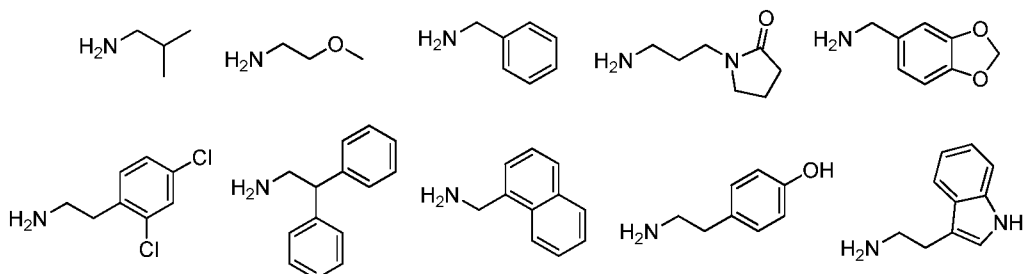
17. The compound of any one of claims 1 to 7 wherein R^2 is a radical of one of the formula



18. The compound of any one of claims 1 to 7 wherein R^3 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted.

19. The compound of any one of claims 1 to 7 wherein R^3 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted.

20. The compound of any one of claims 1 to 7 wherein R^3 is a radical of one of the formula



21. The compound of any one of claims 1 to 7 wherein R^4 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted.

22. The compound of any one of claims 1 to 7 wherein R^4 is selected from alkyl, cycloalkyl, heteroalkyl, heterocyclyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted.

23. The compound of any one of claims 1 to 7 wherein R^4 is H.

24. The compound of any one of claims 1 to 7 wherein R^3 and R^4 are taken together with the attached nitrogen to form an optionally substituted heterocycle.

25. The compound of any one of claims 1 to 7 wherein R^3 and R^4 are taken together with the attached nitrogen to form a pyrrolidine, piperidine, morpholine, pyridazine, pyrimidine, pyrazine, or homopyrimidine, each of which is optionally substituted.

26. A conjugate comprising a compound of any one of claims 1 to 7, a bivalent linker, and a peptide, where the compound and the peptide are each covalently attached to the bivalent linker, and the peptide has at least 50% sequence homology to an alpha helical portion of one Mdm2 or MdmX.

27. A pharmaceutical composition comprising one or more compounds of any one of claims 1 to 7.

28. The composition of claim 27 further comprising one or more carriers, diluents, or excipients, or a combination thereof.

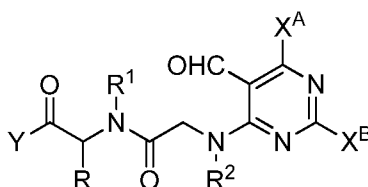
29. A method for treating a disease in a patient, comprising the step of administering to the patient a therapeutically effective amount of one or more compounds of any one of claims 1 to 7, or one or more compositions of the one or more compounds of any one of claims 1 to 7, or a combination thereof, where the one or more compositions further comprise one or more carriers, diluents, or excipients, or a combination thereof; and where the disease is responsive to the disruption or antagonism of one or more alpha helical-based protein-protein interactions.

30. The method of claim 29 wherein the protein-protein interaction is between Mdm2 and p53, MdmX and p53, or a combination thereof.

31. The method of claim 29 wherein the disease is cancer.

32. A method for treating cancer in a patient, the method comprising the step of administering to the patient a therapeutically effective amount of one or more compounds of any one of claims 1 to 7, or one or more compositions of the one or more compounds of any one of claims 1 to 7, or a combination thereof, where the one or more compositions further comprise one or more carriers, diluents, or excipients, or a combination thereof.

33. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

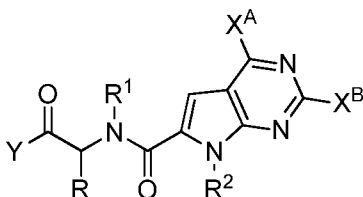
Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R¹ and R² are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; and

X^A and X^B are each independently selected from the group consisting of H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof.

34. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Y is hydroxy or a derivative thereof, or amino or a derivative thereof, or a hydroxy or amino prodrug;

R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

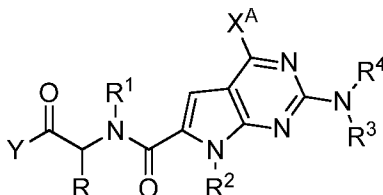
R^1 and R^2 are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; and

X^A and X^B are each independently selected from the group consisting of H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof.

35. The compound of claim 33 or 34 wherein X^B is a leaving group, or a precursor thereof.

36. The compound of claim 33 or 34 wherein X^B is a leaving group.

37. A process for preparing a compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

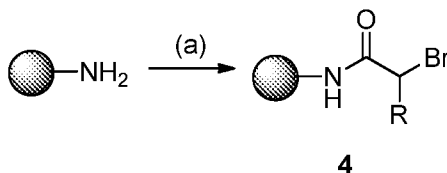
Y is hydroxy or a derivative thereof, or amino or a derivative thereof;

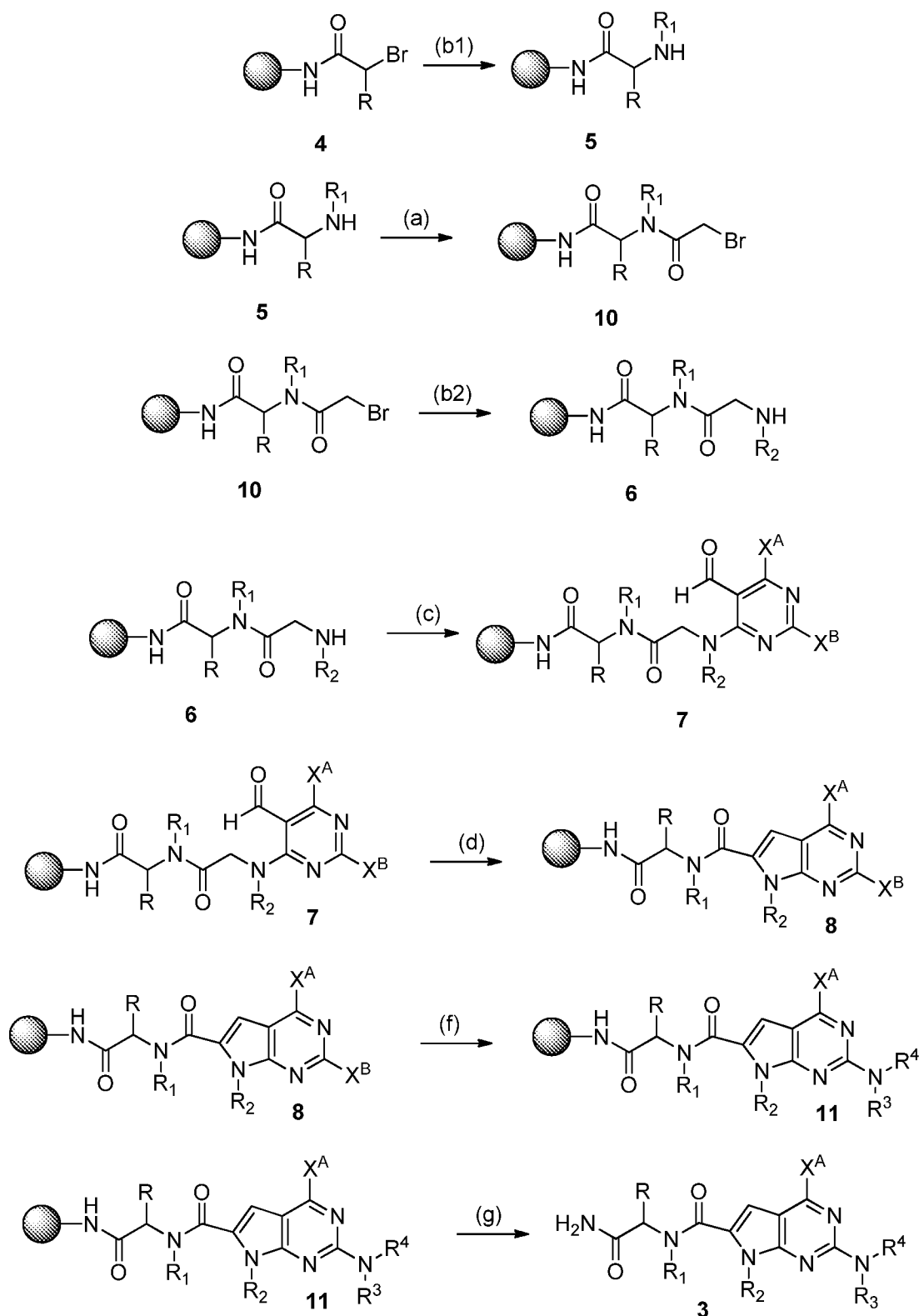
R is hydrogen, or carboxylate or a derivative thereof, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted;

R^1 , R^2 , R^3 , and R^4 are each independently selected from alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heteroalkyl, heterocyclyl, heteroalkenyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted; or R^3 and R^4 are taken together with the attached nitrogen to form an optionally substituted heterocycle; and

X^A is selected from H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof;

the process comprising one or more of the following steps:





wherein (a) represents addition of $\text{BrCH(R)CO}_2\text{H}$; (b1) represents addition of R^1NH_2 ; (b2) represents addition of R^2NH_2 ; (c) represents addition of X^A , X^B substituted 4-chloropyrimidine-5-carbaldehyde; (d) represents cyclization in the presence of a base; (f) represents addition of R^3NH_2 ; and (g) represents cleavage of the resin in the presence of an acid; and

wherein X^A , R, R^1 , R^2 , R^3 , and R^4 are as defined in any one of claims 1 to 7; and X^B is selected from the group consisting of H, halo, hydroxy and derivatives thereof, amino and derivatives thereof, thiol and derivatives thereof, sulfinyl and derivatives thereof, and sulfonyl and derivatives thereof.

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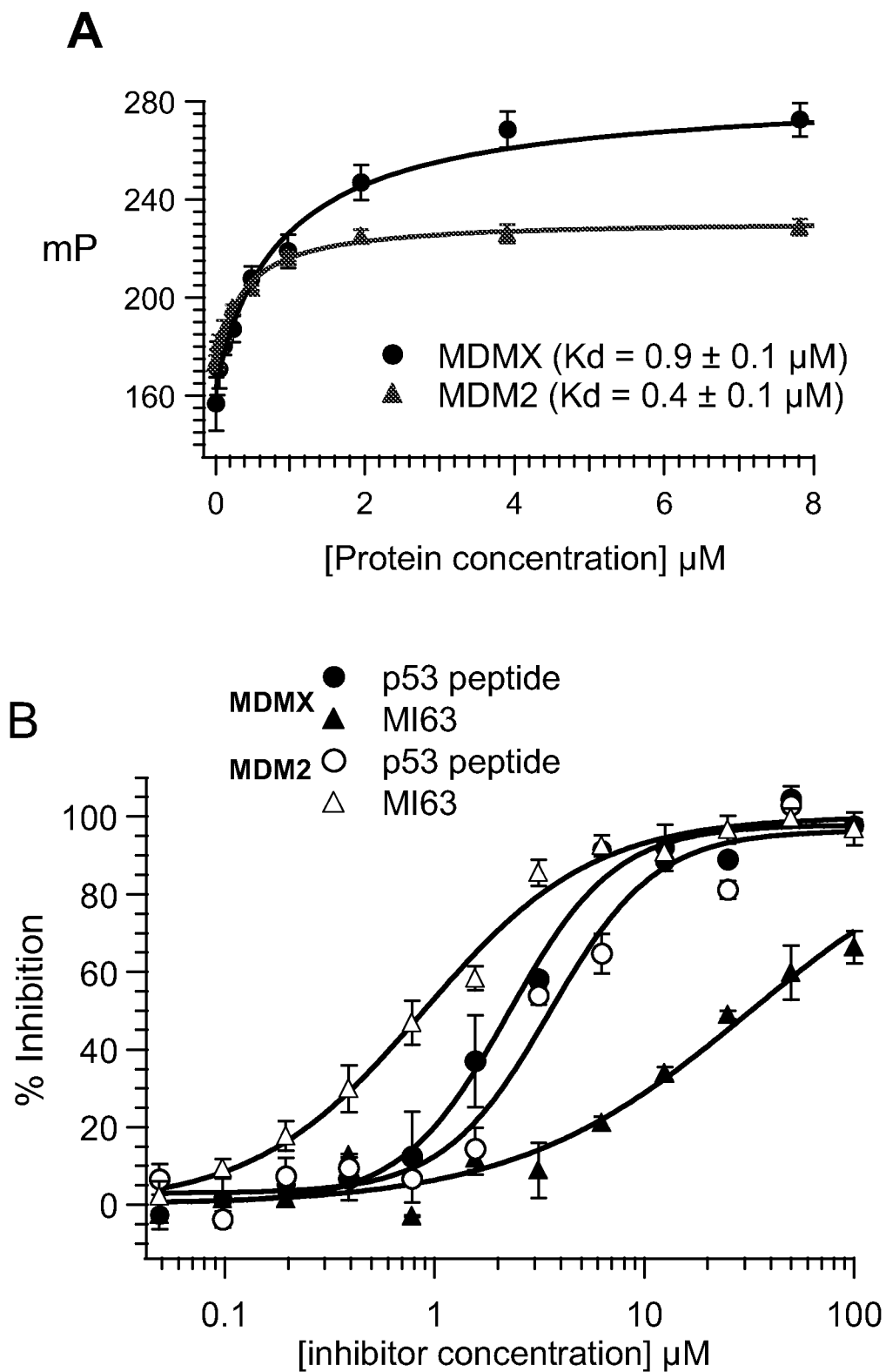


FIG. 1

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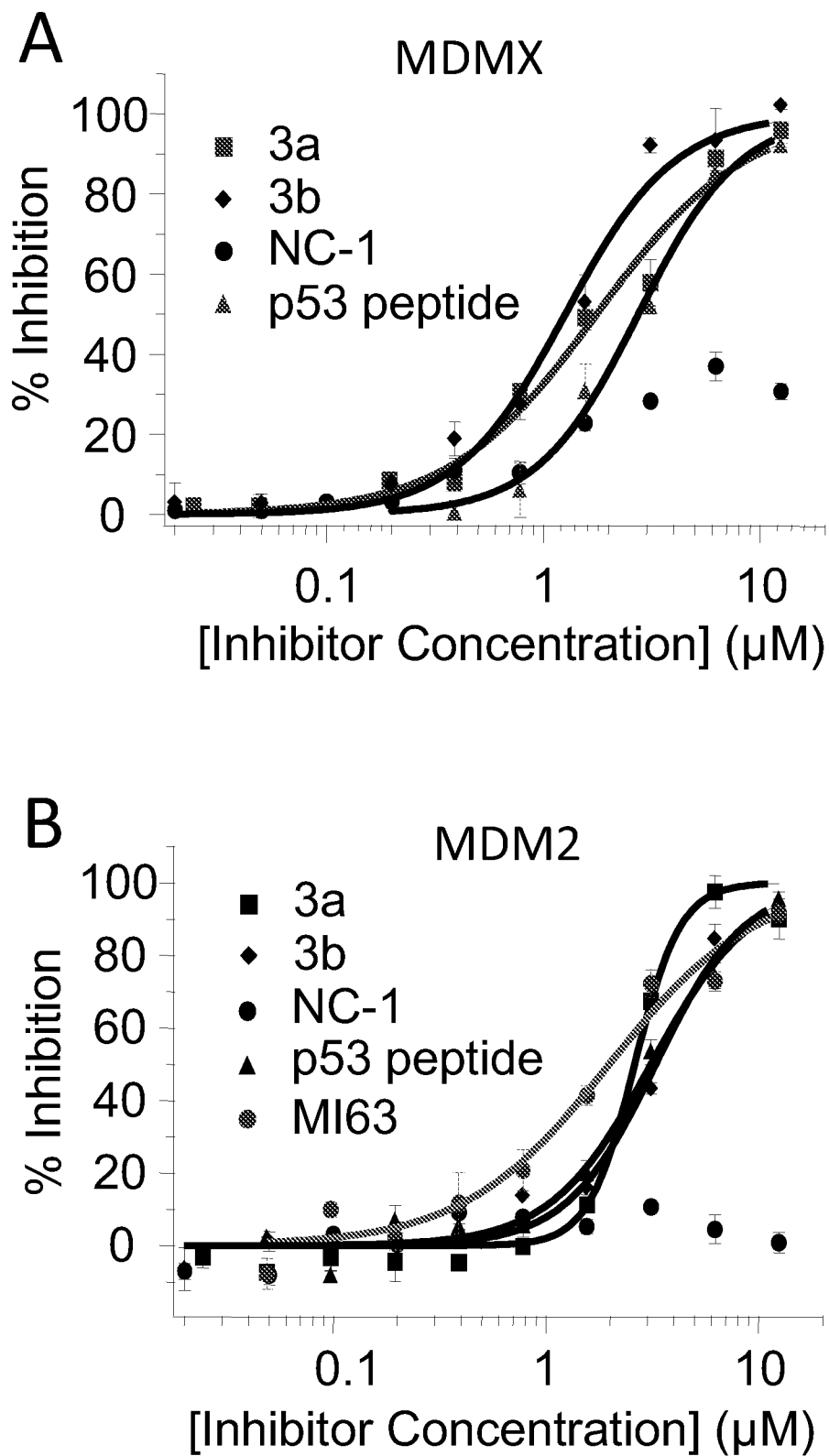


FIG. 2

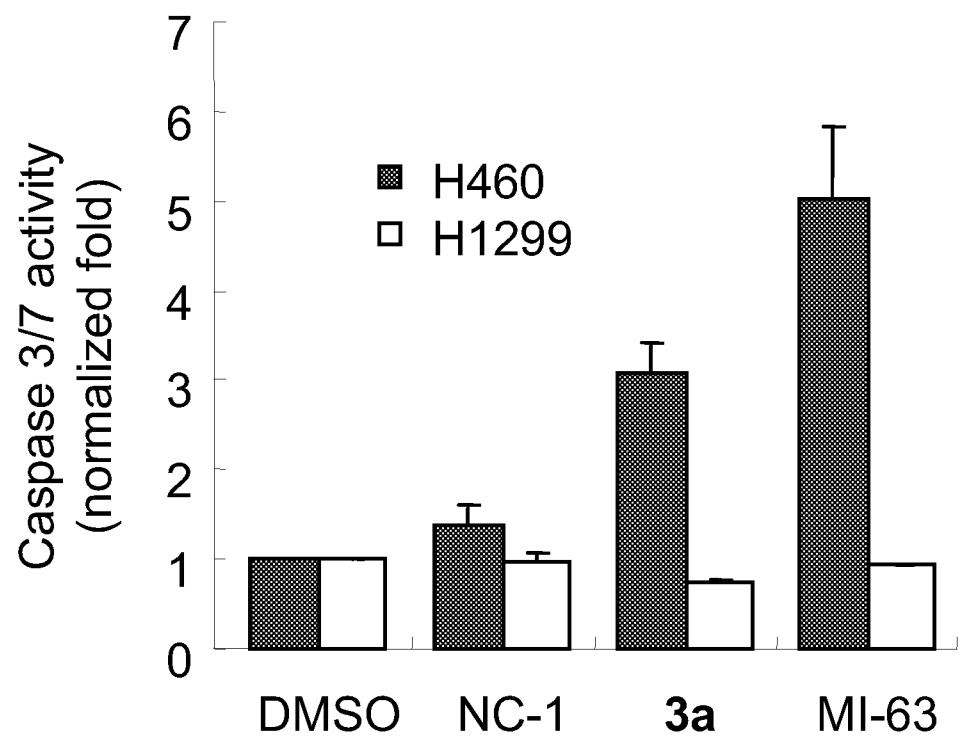


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/65518

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/90; A61K 31/519; C07D 487/00 (2012.01)

USPC - 514/265.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A01N 43/90; A61K 31/519; C07D 487/00 (2012.01)

USPC: 514/265.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC: 544/280 (text search) Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar

pyrrolo\$pyrimidine, pyrimidine, alpha-helix, mimetic, mimic, protein-protein interaction, inhibit\$, Mdmx, Mdm2, p53

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/028434 A2 (KASIBHATLA et al.) 31 March 2005 (31.03.2005) pg 5, ln 16 to pg 6, ln 16; pg 15, ln 27-30; pg 16, ln 20-30; pg 22, ln 3-20 This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	1-37
Y	WO 2010/128685 A1 (ODAGAMI et al.) 11 November 2010 (11.11.2010) pg 31, ln 10 to pg 32, ln 34; pg 40, ln 37 to pg 41, ln 7; pg 41, ln 20-24; pg 72, ln 9 to pg 73, ln 1; pg 75, ln 2-34; pg 76, ln 36 to pg 77, ln 10; pg 77, ln 18 to pg 78, ln 3	1-37
Y	SHAGINIAN et al. Design, Synthesis, and Evaluation of an α -Helix Mimetic Library Targeting Protein-Protein Interactions, J Am Chem Soc. 2009 April 22; Vol 131(15): pp 5564-5572. Entire document, especially, abstract; pg 2, para 4 to pg 3, para 3; pg 7, para 2; pg 13-21, Fig 3-Fig 10.	26
Y	US 2010/0222255 A1 (KIRSHENBAUM et al.) 02 September 2010 (02.09.2010) para [0308]-[0315]	37
X, P	LEE et al. Novel Pyrrolopyrimidine-Based α -Helix Mimetics: Cell-Permeable Inhibitors of Protein-Protein Interactions, J Am Chem Soc. 2011 February 2; Vol.133(4): pp 6767-679. Entire document	1-37

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

08 April 2012 (08.04.2012)

Date of mailing of the international search report

25 APR 2012

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