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- (71) Applicant (for all designated States except US): UNIVERSITY OF PITTSBURGH - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION [US/US]; 200 Gardner Steel Conference Center, Thackeray, And O' Hara Streets, Pittsburgh, PA 15260 (US).
- (72) Inventor; and  
(71) Applicant : HOLAK, Tad [DE/DE]; Rontgenstr 47, 82152 Martinsried (DE).
- (72) Inventor; and  
(75) Inventor/Applicant (for US only): DOEMLING, Alexander [DE/DE]; 1200 Macon Ave., Pittsburgh, PA 15218 (US).
- (74) Agents: BENT, Stephen, A. et al.; FOLEY & LARDNER LLP, Washington Harbour, 3000 K Street, Nw 6th Floor, Washington, DC 20007-5143 (US).
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(54) Title: NOVEL P53-MDM2/P53-MDM4 ANTAGONISTS TO TREAT PROLIFERATIVE DISEASE

(57) Abstract: High-resolution structural information delineates key interactions between MDM2 or MDM4 and heterocyclic compounds that bind to these proteins. These compounds are potent agonists of the p53-MDM2/p53-MDM4 complex.

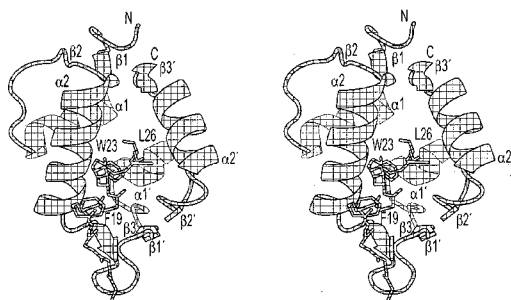


FIG. 1A

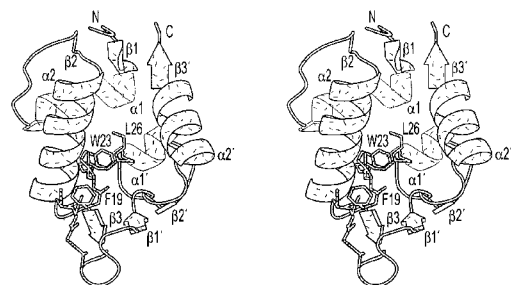


FIG. 1B





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**NOVEL P53-MDM2/P53-MDM4 ANTAGONISTS  
TO TREAT PROLIFERATIVE DISEASE**

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims priority to United States provisional application number 61/308,925, filed February 27, 2010, the entire contents of which are incorporated herein by reference.

**BACKGROUND OF THE INVENTION**

[0002] The tumor suppressor protein p53 acts as a checkpoint in the cell cycle, either preventing or initiating programmed cell death. The occurrence of many human cancers can be linked to impaired nonfunctional p53 protein, with as many as 50% of all cancers being associated with some disruption of the gene that encodes p53. In these cancers, therefore, p53 is most likely inactivated and is unable to initiate programmed cell death.

[0003] Of a variety of biological molecules that are capable of inactivating p53, the oncoprotein MDM2 is believed to be the main negative regulator of this protein. Additionally, MDM2/p53 association has been implicated to play a role in drug resistance that has become a major problem in anti-cancer therapy. To date some classes of compounds have been identified as inhibitors of the MDM2-p53 complex. These are the Nutlin -3 class of compounds, the spiro-oxindoles and compounds that have a benzodiazepinone core and others. Biological studies have shown, however, that compounds within each of these classes are of weak cellular activity with GI<sub>50</sub> values in the 0.9-50 μM range.

[0004] Recently, another protein MDM4 (MDMX), has been identified as a negative regulator of p53. Published PCT WO 2008/119741 (Novartis), discloses a small molecule antagonists of MDM4-p53 complex that contains an imidazole-indole core. Still, the K<sub>i</sub> values for these compounds was in the high micromolar range. Previous work by one of the present inventors has shown, however, that binding of the imidazole-indole class of compounds can be improved by placing appropriate substituent groups. Thus,

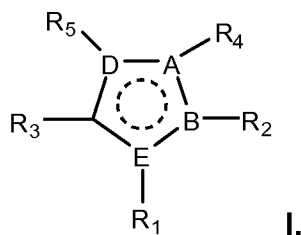
WO 2008/130614 relates nanomolar antagonists of the MDM4-p53 complex that have the imidazole-indole core.


[0005] The present invention provides a new class of molecules that are individual and MDM2-p53 and MDM4-p53 antagonists, as well as methods for synthesizing these compounds and formulations for administering compounds in accordance with the invention to treat cell proliferative disorders.

### SUMMARY OF THE INVENTION

[0006] The present invention relates to novel compounds that are potent agonists of p53-MDM2/p53-MDM4 complexes. The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound according to Formula I their pharmaceutically acceptable salts, solvates, stereoisomers, or tautomers and a pharmaceutically acceptable carrier, as well as to a method for treating a cell proliferative disorder using a compound in accordance with the invention.

[0007] Accordingly, compounds are provided that conform to Formula I.



[0008] For compounds of Formula I,  $R_1$ , is an indole,  $R_2$  and  $R_3$  are different from each other and are phenyl or benzyl. The dashed circle  indicates the presence of one or more optional double bonds and substituent groups  $R_4$  and  $R_5$  are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, and (C<sub>3</sub>-C<sub>14</sub>)aryl.

[0009] A, B, D and E are independently -CR<sub>1</sub>, -CR<sub>2</sub>, -CR<sub>4</sub>, -CR<sub>5</sub>, -N, -O, or -S, provided that when A, D and E are each -N then B is -CR<sub>2</sub>, or when A is -N, B is -NR<sub>2</sub>, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>. Alternatively, when A is -NR<sub>4</sub>, B is N, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>.

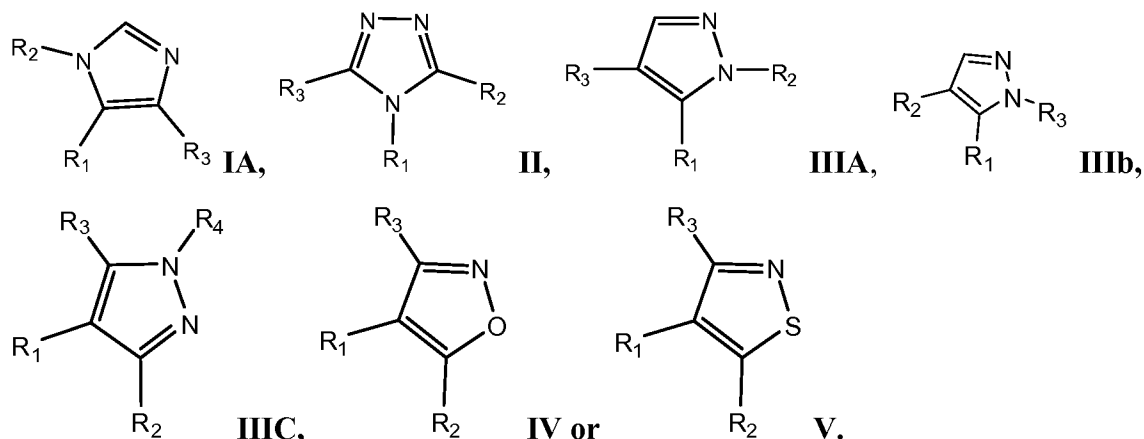
[0010] In another embodiment when A is -N, B is -O, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>, or alternatively, when A is -N, B is -S, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>.

[0011] For Formula 1 compounds any indole, phenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heteroaryl or benzyl groups may be substituted with one or more members selected from the group consisting of halogen, -OH, oxo, -COOR<sup>a</sup>, -C(O)R<sup>a</sup>, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-COOR<sup>a</sup>, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-NR<sup>a</sup>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -C(O)NR<sup>a</sup>R<sup>b</sup>, (C<sub>3</sub>-C<sub>14</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkylene-, -CN, -NO<sub>2</sub>, NR<sup>a</sup>R<sup>b</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S-, (C<sub>3</sub>-C<sub>14</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>14</sub>)heterocycloalkyl, (C<sub>3</sub>-C<sub>14</sub>)aryl, (C<sub>3</sub>-C<sub>14</sub>)heteroaryl, -C(O)NH-(C<sub>1</sub>-C<sub>6</sub>)alkyl, -NHC(O)-(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)haloalkyl, -C(O)-(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl-NR<sup>a</sup>R<sup>b</sup> and (C<sub>1</sub>-C<sub>6</sub>)hydroxyalkyl.

[0012] Substituent groups R<sup>a</sup> and R<sup>b</sup> are independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, hydroxide, (C<sub>1</sub>-C<sub>8</sub>)alkylS(O)<sub>2</sub>-, (C<sub>1</sub>-C<sub>8</sub>)haloalkylS(O)<sub>2</sub>-, (C<sub>1</sub>-C<sub>8</sub>)hydroxyalkylS(O)<sub>2</sub>-, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-COOR<sup>c</sup>, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-COR<sup>c</sup> and optionally substituted (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl or R<sup>a</sup> and R<sup>b</sup> together with the nitrogen atom to which they are bound can form a (C<sub>3</sub>-C<sub>6</sub>)heterocycloalkyl, or a (C<sub>3</sub>-C<sub>6</sub>)heteroaryl.

[0013] Substituent R<sup>c</sup> is selected from the group consisting H, (C<sub>1</sub>-C<sub>8</sub>)alkyl; -NH(OH).

[0014] The present invention also provides compounds that conform to Formula IA, Formula II, Formula IIIA – IIIC, Formula IV, or Formula V, as well as their pharmaceutically acceptable salts, solvates, stereoisomers, and tautomers and pharmaceutical compositions thereof.



#### BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 shows a stereoview of (A) MDM2-p53 complex and (B) MDM4-p53 complex.

**[0016]** Figure 2 shows inhibitors bound to MDM2 and MDM4 proteins. The inhibitors are shown in stick models with carbon atoms colored yellow, nitrogen blue, and oxygen red. Key side-chains of the proteins are labeled. Hydrogen bonds are depicted as yellow dashed lines. **(A)** Compound WW298 binds to MDM4 by filling its Trp23 subpocket with the 6-chloroindole group. The 4-phenyl group is located in the Phe19 and 1-(4-chlorobenzyl) group in the Leu26 pockets, respectively. Two hydrogen bonds to Met53 and His54 are formed. The N,N-dimethylpropylamine part of the WW298 molecule folds over Gly57 and Met61, forming additional hydrophobic protection of the binding cleft. Tyr99 closes the Leu26 subpocket. **(B)** shows an inhibitor in accordance with the invention (WK23), bound to the MDM2 protein. The conformation of WK23 is similar to the conformation of WW298 as shown in Figure 2(A), despite different shapes of the p53 binding sites in MDM2 and MDM4. The His96-Tyr100 region has the most pronounced differences in the shape of the Leu26 pocket, but the position of 1-(4-chlorobenzyl) is not altered in **(A)** and **(B)**. A hydrogen bond is formed between the indole of WK23 and the Leu54 carbonyl oxygen of MDM2. **(C)** The MI-63 inhibitor binds to MDM2 also by nesting the chlorophenyl substructure of the 6-chloroindole into the Trp26 subpocket. The Leu26 subpocket is filled by the 2-fluoro-3-chlorophenyl ring. This ring is located as in WW298 and WK23 (a and b) but its plane is rotated to allow the phenyl substituent atoms to fill the bottom of the MDM2 pocket. The neopentyl fragment fills the Phe19 pocket and is a cause of a substantial induced-fit reshaping of the binding cleft. The Tyr67 side-chain is rotated to form a much steeper wall “closing” the binding region. The whole Tyr67-His73 region acquires a different fold to allow the Tyr67 movement. The compound forms two hydrogen bonds with Leu54 and His96. The ethyl-morpholino part of the compound is not taking part in the binding and is not seen in the electron density.

**[0017]** Figure 3 shows binding of the MDM4 inhibitor (WW298), with respect to the native p53 binding. The inhibitor is shown with yellow carbon atoms. MDM4 bound to the native p53 peptide is presented as a dark blue ribbon plot with most important residues shown in stick model. MDM4 bound to WW298 is similarly shown in light grey-blue. For readability purposes only side-chains of Phe19, Trp23 and Leu26 of p53 are shown (green, labeled in italics). The Trp23 side-chain and the 6-chloroindole part of the inhibitor are bound in a nearly identical position both forming hydrogen bonds with the Met53 carbonyl oxygen. The

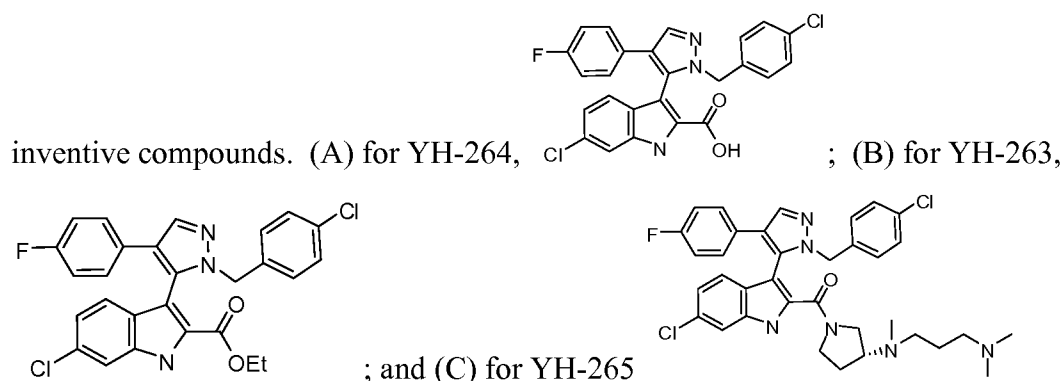
Trp23 subpocket undergoes induced-fit changes to accommodate the larger 6-chloroindole group. Leu56, Leu98, and Leu102 are retracted from the native peptide complex position to make space for an inhibitor. The position of the Tyr99 side-chain is altered but remains in a “closed” orientation. An additional hydrogen bond is formed between the inhibitor and His54.

**[0018]** Figure 4 shows that MDM4-inhibitor WW298 and MDM2 inhibitor WK23 bind in an identical mode. WW298 bound to MDM4 is shown with yellow carbon atoms. For WK23 the carbon atoms are in salmon. MDM2 is shown as a red ribbon plot with important residues shown as stick model. MDM4 is shown similarly in light blue. Important residues are labelled in italics, if different from MDM4, or their numbers given in parentheses, if of the same type as in MDMX. Despite significant structural differences between MDM2 and MDM4, especially in the Pro95-Tyr99 region of MDM4 and the corresponding His96-Tyr100 of MDM2, the ligands are bound in a nearly identical way. Only the position of the chlorophenyl substituent in the Leu26 pocket is shifted between the two structures to adjust to different proteins environment. Clearly, weaker binding of the compounds towards MDM4 compared to MDM2 is caused by the sub-optimal interaction with the Leu26 subpocket.

**[0019]** Figure 5A shows the MDM2 and MDM4 inhibitors used for structural study. WK23 and WW298 differ only by an additional amide moiety attached to the 2-position of the indole ring. MI-63 is a spirooxindole compound. Figure 5B shows binding curves for MDM2 and MDM4 inhibitors based on data from a fluorescence polarization assay. All compounds show much lower affinity for MDM4.

**[0020]** Figure 6 shows the binding to MI-63 to MDM2. Binding of MI-63 causes an induced fit rearrangement that causes changes in the conformation of the protein.

**[0021]** Figure 7 illustrates results of an ex vivo cell growth inhibition study that was carried out against the National Cancer Institute’s (NCI60) panel of cancer cell lines for three of the



## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

### Definitions

[0022] Unless indicated otherwise, the terms and phrases used in this description have the following meanings:

[0023] “Alkyl” refers to a straight or branched chain, saturated hydrocarbon having the indicated number of carbon atoms. For example, (C<sub>1</sub>-C<sub>6</sub>)alkyl is meant to include, but is not limited to methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and neohexyl. An alkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein throughout.

[0024] The term “alkenyl” refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one double bond. Examples of a (C<sub>2</sub>-C<sub>8</sub>)alkenyl group include, but are not limited to, ethylene, propylene, 1-butylene, 2-butylene, isobutylene, *sec*-butylene, 1-pentene, 2-pentene, isopentene, 1-hexene, 2-hexene, 3-hexene, isohexene, 1-heptene, 2-heptene, 3-heptene, isoheptene, 1-octene, 2-octene, 3-octene, 4-octene, and isooctene. An alkenyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0025] The term “alkynyl” refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one triple bond. Examples of a (C<sub>2</sub>-C<sub>8</sub>)alkynyl group include, but are not limited to, acetylene, propyne, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 1-heptyne, 2-heptyne, 3-heptyne, 1-octyne, 2-octyne, 3-octyne and 4-octyne. An alkynyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0026] The term “halogen” and “halo” refers to -F, -Cl, -Br or -I.

[0027] The term “alkoxy” refers to an -O-alkyl group having the indicated number of carbon atoms. For example, a (C<sub>1</sub>-C<sub>6</sub>)alkoxy group includes -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-butyl, -O-*sec*-butyl, -O-*tert*-butyl, -O-pentyl, -O-isopentyl, -O-neopentyl, -O-hexyl, -O-isohexyl, and -O-neohexyl.

[0028] The term “aryl” refers to a 6- to 14-membered monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring system. Examples of an aryl group include phenyl and naphthyl. An aryl group can be unsubstituted or optionally substituted with one or more substituents as described herein throughout.

[0029] “Cycloalkyl” denotes a 3- to 14-membered saturated or unsaturated non-aromatic monocyclic, bicyclic or tricyclic hydrocarbon ring system. Included in this class are cycloalkyl groups which are fused to a benzene ring.

[0030] The term “heteroaryl” refers to an aromatic heterocycle ring of 3 to 14 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including monocyclic, bicyclic, and tricyclic ring systems.

Representative heteroaryls are triazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl, pyrimidyl, azepinyl, oxepinyl, quinoxalinyl and oxazolyl. A heteroaryl group can be unsubstituted or optionally substituted with one or more substituents as described throughout.

[0031] The term “heterocycle” refers to 3- to 14-membered ring systems that are either saturated, unsaturated, or aromatic, and that contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, where the nitrogen and sulfur heteroatoms can be optionally oxidized and the nitrogen heteroatom can be optionally quaternized, including monocyclic, bicyclic, and tricyclic ring systems. The bicyclic and tricyclic ring systems may encompass a heterocycle or heteroaryl fused to a benzene ring. The heterocycle can be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above.

**[0032]** Unless otherwise stated, the term “heterocycloalkyl,” by itself or combined with other terms, represents cyclic versions of “heteroalkyl.” Additionally, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule.

**[0033]** The term “amine or amino” refers to an  $-NR^aR^b$  group wherein  $R^a$  and  $R^b$  each independently refer to a hydrogen,  $(C_1-C_8)$ alkyl, aryl,  $(C_3-C_6)$ heterocycloalkyl, a  $(C_3-C_6)$ heteroaryl and  $(C_1-C_6)$ hydroxyalkyl group. In addition,  $R^a$  and  $R^b$  together with the nitrogen atom to which they are bound can form a  $(C_3-C_6)$ heterocycloalkyl, or a  $(C_3-C_6)$ heteroaryl.

**[0034]** The term “nitrile or cyano” can be used interchangeably and refer to a  $-CN$  group which is bound to a carbon atom of a heteroaryl ring, aryl ring and a heterocycloalkyl ring.

**[0035]** The term “oxo” refers to a  $=O$  atom attached to a saturated or unsaturated  $(C_3-C_8)$  cyclic or a  $(C_1-C_8)$  acyclic moiety. The  $=O$  atom can be attached to a carbon, sulfur, and nitrogen atom that is part of the cyclic or acyclic moiety.

**[0036]** The term “hydroxyalkyl,” refers to an alkyl group having the indicated number of carbon atoms wherein one or more of the alkyl group’s hydrogen atoms is replaced with an  $-OH$  group. Examples of hydroxyalkyl groups include, but are not limited to,  $-CH_2OH$ ,  $-CH_2CH_2OH$ ,  $-CH_2CH_2CH_2OH$ ,  $-CH_2CH_2CH_2CH_2OH$ ,  $-CH_2CH_2CH_2CH_2CH_2OH$ , and branched versions thereof.

**[0037]** The term “haloalkyl,” refers to an alkyl group having the indicated number of carbon atoms wherein one or more hydrogen atoms in the alkyl group is replaced with a halogen atom, which can be the same or different.

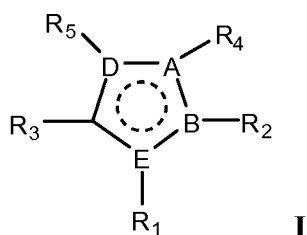
**[0038]** The term “amide” refers to  $C(O)NR^aR^b$  group wherein  $R^a$  and  $R^b$  are independently hydrogen,  $(C_3-C_6)$ heterocycloalkyl, a  $(C_3-C_6)$ heteroaryl  $(C_1-C_6)$ alkyl, or  $R^a$  and  $R^b$  together with the nitrogen atom to which they are bound can form a  $(C_3-C_6)$ heterocycloalkyl, or a  $(C_3-C_6)$ heteroaryl.

**[0039]** The term “sulfonamide” refers to an  $-NR^aS(O)_2R^b$  group where  $R^a$  and  $R^b$  are each independently refer to a hydrogen,  $(C_1-C_8)$ alkyl, aryl, heteroaryl, heterocycloalkyl,  $(C_1-C_8)$ haloalkyl, and  $(C_1-C_6)$ hydroxyalkyl group.

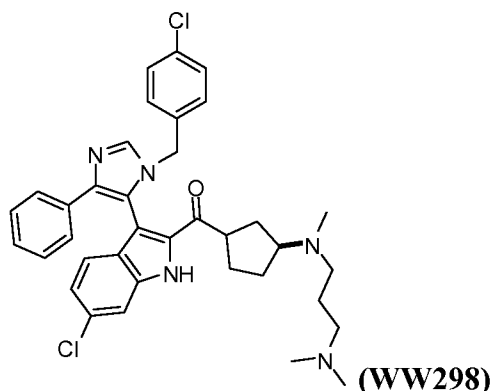
**[0040]**

[0041] The terms “t<sub>R</sub>” and “r.t” are used interchangeably and refer to the run time in a chromatogram. That is, these terms indicate the time interval at which a given compound elutes as identified by a peak in the chromatogram.

[0042] The present invention provides a new class of molecules that are dual antagonists of MDM2/p53 and MDM4/p53 interactions. To design potent dual antagonists of the MDM2/MDM4 proteins the inventors juxtaposed deduced X-ray coordinates for the interaction of p53 with MDM4/MDM2 with X-ray coordinates for two compounds belonging to Formula I.



[0043] Figure 1 shows a stereoview of the p53-MDM2 and p53-MDM4 complexes. Three amino acids from the hydrophobic surface of the p53 peptide, namely Phe19, Trp23 and Leu26 are appropriately placed to enter the hydrophobic pocket of MDM2/MDM4 proteins and are believed to be important for protein-peptide binding interactions. The X-ray data also revealed that the dimensions of the p53 binding pocket (~18 Å), was similar in size to a small organic molecule, thereby illuminating the prospect of designing compounds that could interfere with binding of p53 to MDM2 and MDM4 proteins. Accordingly, the present inventors tested the ability of two structurally close 6-chloroindole-imidazole analogs and a structurally dissimilar spiro-oxindole compound to bind these proteins. Thus, when WW298, an indole-imidazole, was co-crystallized with MDM4 to determine its binding interactions, the deduced X-ray coordinates for this co-crystal revealed that WW298 mimics to some extent the binding interaction of p53 with MDM4 (see Figures 1 and 2).



**[0044]** For example, the 6-chloroindole group interacts with residues in the pocket normally occupied by Trp 23 residue of p53 (Trp23 sub-pocket). Based on the crystallographic coordinates, the  $-NH$  group in the indole ring is within hydrogen bonding distance with the carbonyl of Met53. The crystal structure also provides insights about the position and interactions of the 4-chlorobenzyl and phenyl rings of WW298. As seen in Figures 2A and 3, the 4-chlorobenzyl group is positioned to penetrate the cleft occupied by Leu26 upon binding of p53 (Leu26 sub-pocket), while the phenyl group of WW298 occupies the same pocket as Phe19 of p53 (Phe19 sub-pocket).

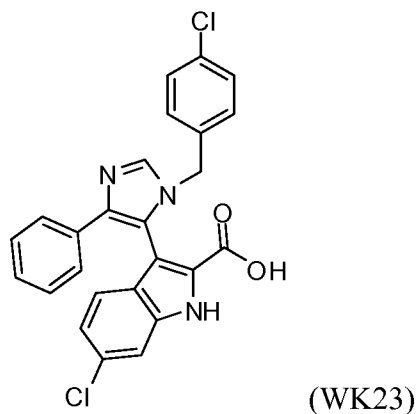
**[0045]** The crystal structure further shows that there are changes in the three dimensional structure of the binding pocket of MDM4 when occupied by WW298, rather than the native ligand p53. For example, the MDM4 binding pocket undergoes an induced fit change to accommodate the bulky hydrophobic chloro group on the indole ring. The presence of chlorine also causes changes in the position of residues more distant from the Trp23 sub-pocket, as well. For example, retraction of the side chain of Leu26 by 0.81 Å as well as topographical changes in the main chains of helices that form the binding pocket are attributed to the occupancy of chlorine in the Trp23 sub-pocket. The 6-chloroindole group of WW298 also causes a shift in the position of the  $\alpha 1$  helix by 0.56 Å near the Met53  $C\alpha$  atom, while the  $\alpha 2'$  helix is displaced by 1.03 Å at Leu98.

**[0046]** Similar changes are seen for other residues in the vicinity of the 4-chlorobenzyl group. To accommodate this bulky hydrophobic group, the  $C\alpha$  of Tyr99 is shifted by 1.27 Å while the phenyl side chain of this residue is pushed outside the binding pocket resulting in a partially open conformation for the binding pocket. See Figure 3.

[0047] These results generally comport with binding of 2FEA a 6-chlorotryptophan peptide as disclosed by Kallen et al., *J. Biol. Chem.* 284: 8812 (2009). One major difference between the orientation of 2FEA and WW298 is that when 2FEA is bound, the side chain of Tyr99 in the MDM4 pocket is flipped outside the pocket which is now forced to adopt an open conformation rather than the partially closed conformation adopted upon binding of WW298. Taken together, these results suggest that the weaker binding potency of WW298 to MDMX when compared to p53, may likely be from energetically unfavorable changes in the position of certain residues in MDM4's pocket.

[0048] The X-ray crystallographic data provided information that can be used, however, to tweak the potency of compounds that are suitable as candidate therapeutics for treating diseases related to improper p53 function, such as cell proliferative diseases.

[0049] To verify that compounds of the imidazole-indole class also are capable of disrupting the p53-MDM2 complex, the present inventors deduced the X-ray crystallographic coordinates of a crystalline complex of MDM2 with WK23.



[0050] As illustrated in Figures 2B and 4, the binding of WK23 to MDM2 is predominantly through hydrophobic interactions and is not significantly different from the binding of p53. The crystallographic data does indicate, however, that Leu54 in the binding pocket is within hydrogen bonding distance from nitrogen of the 6-chloroindole group. Based on the deduced structure it is evident that the bulky chlorine atom penetrates into the pocket, and occupies a position similar to the position of a bromine group in the crystal structure of MDM2 complexed to the known antagonist Nutlin-3.

[0051] In addition to these binding interactions, there are other subtle changes in the position of various residues within the binding pocket when WK23 is present. For example,

for the MDM2-WK23 complex, the 4-chlorobenzyl group occupies the Leu26 pocket and is in greater proximity ( $\sim 2.16$  Å), to Tyr100 than the corresponding C $\gamma$  atom of the native Leu26. The position of the 4-chlorobenzyl group is very similar to the bromophenyl ring of Nutlin-2, with the distance between the Cl and Br atoms of 1.06 Å and the angle between aromatic ring planes of 13°.

**[0052]** Crystallographic data further indicated that binding of WK23 forces the plane of the phenyl ring of Tyr100 to rotate by approximately 75°. The orientation of Tyr100 side chain in MDM2, however, is in a “closed” conformation, similar to the position of this group in the Nutlin-2-MDM2 complex. In general, the Leu26 pocket is filled more completely in the WK23-MDM2 and to a greater depth by the 4-chlorobenzyl substituent than by the aliphatic Leu26 side-chain of p53, with only minor induced-fit changes in the MDM2 structure.

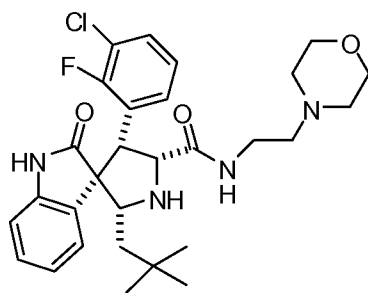
**[0053]** Other changes in the proteins 3-D conformation upon binding WK23 include a flip in the side chain of Met62 which now rests outside the binding pocket as well as changes in the orientation of residues Tyr67 to Gln72 that line the Phe19 sub-pocket.

**[0054]** As seen in Figures 2B and 4, the phenyl group of WK23 is oriented perpendicular to the plane of Phe19 in p53, and fills the aperture to the Phe19 sub-pocket. This is in stark contrast to the orientation of the Phe19 residue of p53, where the phenyl ring penetrates deeper into the binding pocket by approximately 2°Å.

**[0055]** The complex of MDM2 with the MI-63 inhibitor gave crystals with the asymmetric unit that contained three separate MI-63-MDM2 complexes. Despite different crystal contacts and environments, the three complexes show no differences in structures with the exception of changes at the N-terminus, the Tyr100 side-chain (in proximity of it), and the Glu69-Gln71 loop.

**[0056]** Thus, crystallographic data indicate that for the spiro-oxindole analog MI-63, the 6-chloroindole group is located in the Trp23 sub-pocket and is within hydrogen bonding distance to the carbonyl of Leu54. The plane of the indole ring is rotated, however, by 10° when compared to Trp23 of the native ligand p53 or WK23. The 2-fluoro-3-chlorophenyl ring is situated in the Leu26 sub-pocket with the bulky chlorine atom 0.52 Å closer to the  $\alpha 2'$  helix than the phenyl ring in WK23 or Nutlin-2. Similar to WK23, Tyr100 adopts an open conformation, but crystallographic data indicate that the side chain of this residue adopts

different conformations for each molecule present in the asymmetric unit. These results implicate increased flexibility for Tyr100. In contrast to WK23, the neopentyl group of MI-63 occupies the Phe19 sub-pocket. Yet, because the neopentyl group is more flexible and is less bulky, it does not occupy the entire space of this sub-pocket, allowing Tyr67 from the protein to fill up the unoccupied space. This causes the main chain of Tyr67 to rotate by 0.83 Å into the binding pocket. To allow the Tyr67 ring to enter the binding site, the main chain of His73 is retracted by 2.02 Å (at C $\alpha$  position) outward from the binding pocket. Altogether, these changes extensively reshape the Phe19 pocket, forming a “massive” induced fit rearrangement (Figures 2C and 6).



(MI-63)

**[0057]** The pyrrolidine ring of MI-63 extends the hydrophobic interaction with Val93 in a way similar to the imidazole ring of the WK23 inhibitor. The amide group of MI-63 forms a short (2.23 Å) hydrogen bond between its carbonyl oxygen and His96 N $\epsilon$ . This hydrogen bond, although located in a solvent accessible region, is likely to be beneficial to the binding energy. It should be noted that the 6-chloroindole substituent is rigidly tied-up to the pyrrolidine core by a spiro connection, while in compounds WK23 and WW298 there is rotational freedom between the chloroindole and imidazole rings. Because of differences in the shape of the p53 binding cleft of MDM4, the lack of freedom of the 6-chloroindole group may weaken the interactions of MI-63 to MDM4. On the other hand, these reduced degrees of rotational freedom also could contribute the very high affinity of MI-63 to MDM2 by entropy reduction.

**[0058]** The remaining part of the MI-63 molecule, including the morpholine ring and the aliphatic fragment attached to the amide group, is not visible in the electron density map. This indicates high flexibility of this segment of the MI-63 molecule and the lack of any direct interaction with MDM2. Clearly this substituent can be used to improve other drug-required properties such as water solubility, pKa or lipophilicity.

[0059] In summary, MI-63 causes significant ligand-binding induced changes in the shape of the Phe19 pocket. This and the rigid connection between the chloroindole and pyrrolidine rings may well explain its high specificity in binding to MDM2 and a dramatic loss of its potency towards MDMX, as neither the protein nor the ligand seems to be able to undergo necessary structural rearrangements for effective binding to MDMX.

[0060] An unexpected insight from the crystallographic data for the WK23-MDM2 complex is that the imidazole ring of WK23 plays a role in binding. Based on the crystallographic data, strong hydrophobic interactions should exist between the aromatic imidazole ring and the side chain of Val93. The crystallographic data also show that the plane of the imidazole ring is tilted when compared to the plane of the imidazoline in Nutlin-3, which results in the imidazole group to shift by 1.03 Å towards the  $\alpha 2$  helix. Thus, for WK23 these changes in the orientation of imidazole force the 5-membered ring to pucker so that three atoms of the ring are forced to remain in the same plane. As a result, the 4-chlorobenzyl group attached to the ring is pushed into the Leu26 sub-pocket of MDM2.

[0061] Taken together, the data suggest that binding interactions between MDM2 and small heterocyclic scaffolds can be further improved by promoting hydrophobic, hydrogen bonding, and salt bridge interactions between the heterocyclic scaffold and side chains of amino acids surrounding the heterocycle in the binding pocket. Moreover, crystallographic studies implicate an overlap in the binding orientation of indole-imidazole heterocycles to MDM4 and MDM2 proteins. It is evident, therefore, that the 6-chloroindole group is well-suited to bind to the Trp23 sub-pocket present in both proteins. Although, the plane of the chloroindole ring is rotated by  $14.8^\circ$  in MDM4 relative to MDM2, the energy cost for such a rotation is effectively contributed from the gain in binding energy due to the presence of the bulky chlorine on the indole ring. Another difference between the MDM4 and MDM2 proteins appears to be in the Phe19 sub-pocket, particularly at the outer rim of this pocket. As stated above, for effective binding of the inventive compounds there appears to be no need for the phenyl group of the heterocycle to penetrate the Phe19 sub-pocket. Rather, hydrophobic interactions between the phenyl ring and the protein's hydrophobic surface are all that is required for optimal interactions.

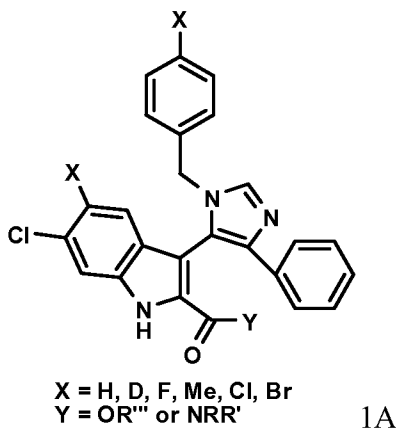
[0062] The significant challenge in developing dual action antagonists is understood to arise from differences in the Leu26 sub-pocket, particularly with respect to the  $\alpha 2'$  helix. X-

ray crystallographic data shows that while Tyr99 forces the MDMX protein to adopt a closed conformation, the position of the equivalent residue, Tyr100 in MDM2 protein can vary depending on the structure of the inhibitor complexed to MDM2. That is, for MDM4-inhibitor complex, Tyr99 forces the protein to adopt a closed conformation, while for MDM2, binding of WK23 does not cause the protein to adopt a closed conformation. Accordingly, candidate dual action antagonists to MDM2-p53 and MDM4-p53 complexes can be developed by optimizing the structure and chemical nature of substituent groups surrounding the heterocyclic core.

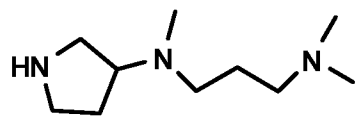
## SYNTHESIS

### 1. *The Imidazole Scaffold*

[0063] In one aspect, therefore, the present invention provides compounds that comport with Formula 1A as well as a method for synthesizing these compounds (Scheme 1).

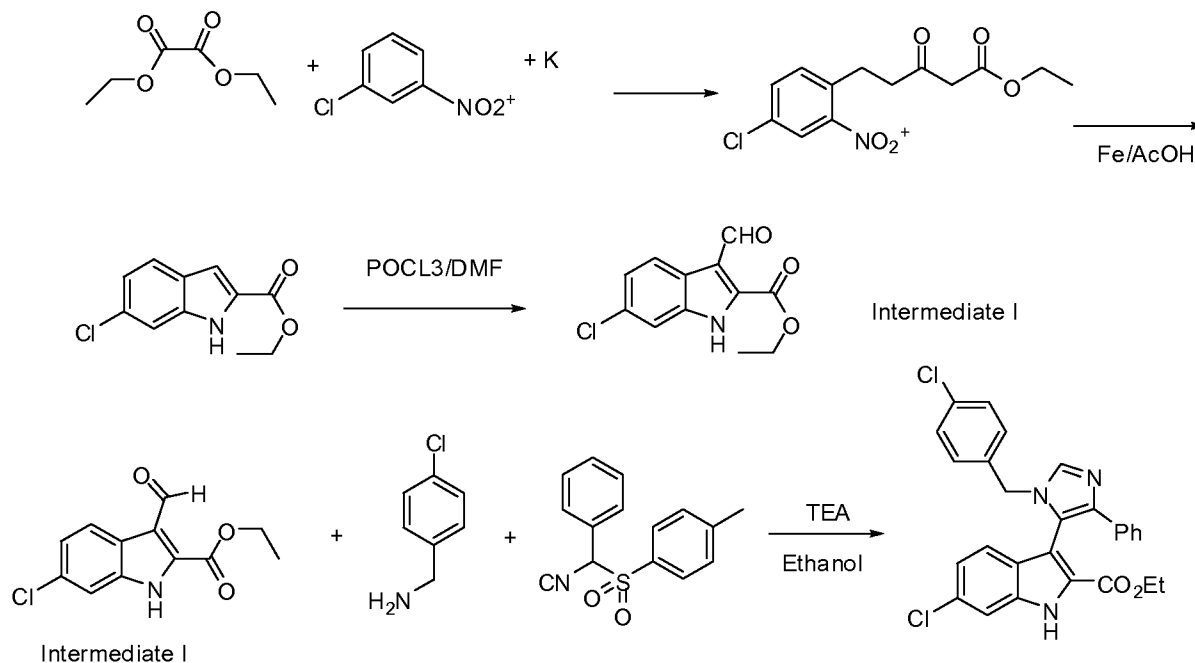


[0064] For Formula 1A compounds, R''' is either a H or a (C<sub>1</sub>-C<sub>6</sub>)alkyl and NRR' is



. Formula 1A compounds can be prepared as shown in Scheme 1.

## Scheme 1

Ethyl 6-chloro-1*H*-indole-2-carboxylate

**[0065]** The first step involves the synthesis of ethyl 6-chloro-1*H*-indole-2-carboxylate as follows. To a mixture of potassium (7.2 g, 185 mmol) in diethyl ether (60 mL) was added ethanol (40 mL) in diethyl ether (100 mL), followed by a solution of diethyl oxalate (27.8 g, 190 mmol) in diethyl ether (100 mL), and finally, a solution of 4-chloro-2-nitrotoluene (27.4 g, 160 mmol) in diethyl ether (40 mL). The reaction mixture was stirred for 15 h and then sonicated for 7 h. The reaction mixture was poured into 1 N HCl (200 mL) at 0°C. Then the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (anhydrous sodium sulfate) and concentrated to afford the intermediate ethyl 3-(4-chloro-2-nitrophenyl)-2-oxopropanoate which was used directly in the next step. <sup>1</sup>H NMR of the crude product indicates that the conversion is about 80 %.

**[0066]** To crude ethyl 3-(4-chloro-2-nitrophenyl)-2-oxopropanoate (ca 130 mmol) in ethanol (260 mL) and glacial acetic acid (260 mL) was added iron powder (74.4 g, 1.33 mol) and the reaction mixture was heated to reflux for 4 h. The mixture was filtered and evaporated. The residue was partitioned between dichloromethane and 1 N HCl. The organic layer was washed with 1 N HCl and brine and dried (anhydrous sodium sulfate). Evaporation of solvent gave the title product as a pale yellow solid 23 g, (65 %) over 2 steps. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 600 MHz): δ 12.02 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.17 (s, 1H),

7.09 (d,  $J = 8.4$  Hz, 1H), 4.34 (t,  $J = 7.2$  Hz, 2H), 1.33 (q,  $J = 7.2$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{d}_6$ -DMSO, 150.92 MHz):  $\delta$  161.0, 137.5, 129.2, 128.3, 125.4, 123.7, 120.7, 111.9, 107.8, 60.6, 14.2 ppm.

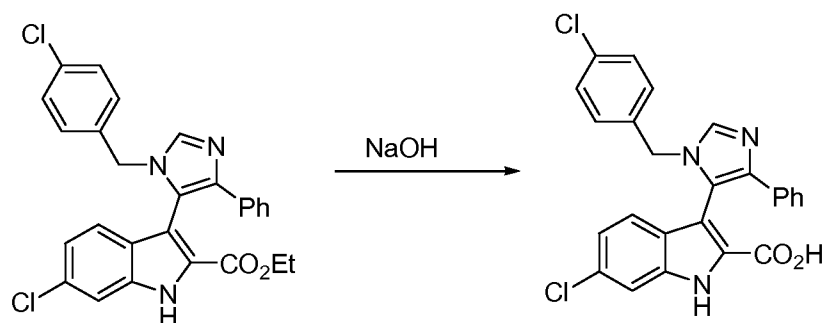
**Ethyl 6-chloro-3-formyl-1*H*-indole-2-carboxylate**

[0067] To a reaction of ethyl 6-chloro-1*H*-indole-2-carboxylate (4.46 g, 20 mmol) and phosphorus oxychloride (3.68 g, 24 mmol) in *N,N*-dimethyl formamide (15 mL), was added in a 100 mL round bottom flask equipped with stir bar. The reaction was heated to 50°C for 30 h. After completion, the reaction mixture is quenched with saturated sodium bicarbonate solution (50 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic phase was washed with brine and dried (anhydrous sodium sulfate). The solvent was evaporated and the crude product was purified by recrystallization (ethyl acetate/hexane) to produce 3.11 g (62 %) title compound as light yellow solid.  $^1\text{H}$  NMR ( $\text{d}_6$ -DMSO, 600 MHz):  $\delta$  12.99 (brs, 1H), 10.63 (s, 1H), 8.26 (d,  $J = 9.0$  Hz, 1H), 7.62 (d,  $J = 1.8$  Hz, 1H), 7.38 (dd,  $J = 9.0, 1.8$  Hz, 1H), 4.51 (q,  $J = 7.2$  Hz, 2H), 1.46 (t,  $J = 7.2$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{d}_6$ -DMSO, 150.92 MHz):  $\delta$  187.4, 159.9, 136.1, 133.5, 130.4, 124.0, 123.9, 123.4, 118.2, 112.6 ppm.

**Ethyl 6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1*H*-imidazol-5-yl)-1*H*-indole-2-carboxylate**

[0068] A 20 mL vial with stir bar was charged with ethyl 6-chloro-3-formyl-1*H*-indole-2-carboxylate (1.00 g, 4.0 mmol), 1-(isocyano(phenyl)methylsulfonyl)-4-methylbenzene (1.10 g, 4.0 mmol), 4-chlorobenzylamine (0.57 g, 4.0 mmol) and triethylamine (0.41 g, 4.0 mmol) in ethanol (10 mL). The reaction was heated to 60 °C for 3 h. Then the solvent was removed in vacuum and the crude product was purified by silica gel chromatography (0-5 % methanol in ethyl acetate) to produce 1.80 g (92 %) of the title compound as the light white solid.  $^1\text{H}$  NMR ( $\text{d}_6$ -DMSO, 600 MHz):  $\delta$  12.41 (s, 1H), 8.13 (s, 1H), 7.55 (s, 1H), 7.40 (d,  $J = 7.2$  Hz, 2H), 7.12-7.19 (m, 4H), 7.09 (t,  $J = 6.6$  Hz, 1H), 7.02 (s, 2H), 6.82 (d,  $J = 8.4$  Hz, 2H), 5.00 (s, 2H), 4.08-4.13 (m, 2H), 1.10 (t,  $J = 7.2$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{d}_6$ -DMSO, 150.92 MHz):  $\delta$  160.2, 138.7, 138.3, 136.5, 136.1, 135.0, 131.7, 129.7, 128.7, 128.0, 127.9, 126.8, 125.8, 125.0, 121.9, 121.4, 119.5, 60.4, 47.5, 13.7 ppm; HRMS ESL-TOF for  $\text{C}_{27}\text{H}_{22}\text{Cl}_2\text{N}_3\text{O}_2$  ( $\text{M}+\text{H}^+$ ) found:  $m/z$ : 490.1090; Calc. Mass: 490.1089.

**6-Chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-imidazol-5-yl)-1H-indole-2-carboxylic acid (WK23)**

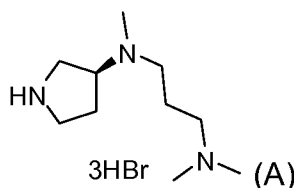


**[0069]** Hydrolysis of ethyl 6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-imidazol-5-yl)-1H-indole-2-carboxylate is carried out as follows. To 900 mg (2 mmol), of the ester is added NaOH solution (2M, 35 mL) in ethanol (35 mL) and the reaction mixture is stirred followed by reflux for 2.5 h. The resulting mixture is poured into a mixture of ice and water. Then 25 mL 4M HCl was added and 3 x extracted with ethyl acetate (a 50 mL). The combined organic phase was washed with brine and dried over sodium sulfate. The solvent was removed in vacuum to produce the title compound, 880 mg (95 %) as light yellow crystals.  $^1\text{H}$  NMR ( $d_6$ -DMSO, 600 MHz):  $\delta$  12.65 (s, 1H), 9.71 (s, 1H), 7.53 (d,  $J = 1.8$  Hz, 1H), 7.40-7.44 (m, 2H), 7.25-7.30 (m, 3H), 7.11 (d,  $J = 8.4$  Hz, 2H), 7.02 (d,  $J = 8.4$  Hz, 1H), 6.95 (dd,  $J = 8.4, 1.2$  Hz, 1H), 6.89 (d,  $J = 8.4$  Hz, 2H), 5.27 (d,  $J = 15.0$  Hz, 1H), 5.17 (d,  $J = 15.0$  Hz, 1H) ppm;  $^{13}\text{C}$  NMR ( $d_6$ -DMSO, 150.92 MHz):  $\delta$  161.2, 136.4, 136.2, 133.2, 132.7, 131.2, 129.8, 129.5, 129.3, 129.0, 128.9, 128.1, 127.2, 126.2, 125.5, 122.1, 121.7, 121.3, 49.5 ppm; HRMS ESL-TOF for  $\text{C}_{25}\text{H}_{18}\text{Cl}_2\text{N}_3\text{O}_2$  ( $\text{M}^+$ ) found:  $m/z$ : 462.0746 ; Calc. Mass: 462.0776.

## 2. The Pyrrolidine Scaffold

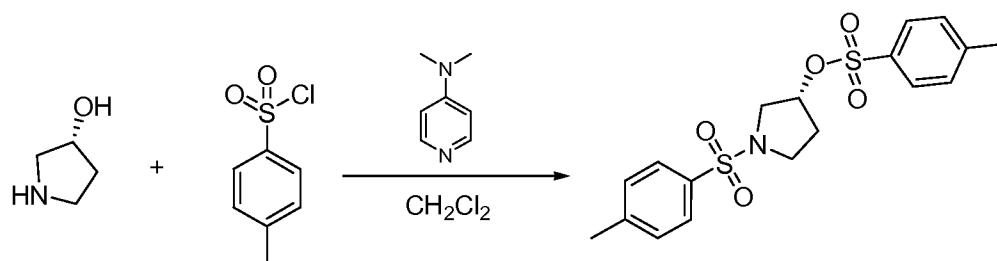
**(S)- $N^1, N^1, N^3$ -trimethyl- $N^3$ -(pyrrolidin-3-yl)propane-1,3-diamine hydrobromide**

**[0070]** The present invention also provides a methodology for generating (S)- $N^1, N^1, N^3$ -trimethyl- $N^3$ -(pyrrolidin-3-yl)propane-1,3-diamine (compound (A)).



[0071] The first step involves the synthesis of (*R*)-1-tosylpyrrolidin-3-yl 4-methylbenzenesulfonate according to the methodology illustrated in Scheme 1A. Thus, 1 g of *R*-Prolinol (11 mmol) is dissolved in 50 mL of dichloromethane, 4.4 g of pyridine (56 mmol) and 122 mg of dimethylaminopyridine (1 mmol) are added at room temperature. The reaction is cooled in an ice bath followed by addition of 5.4 g of toluenesulfonyl chloride (28 mmol).

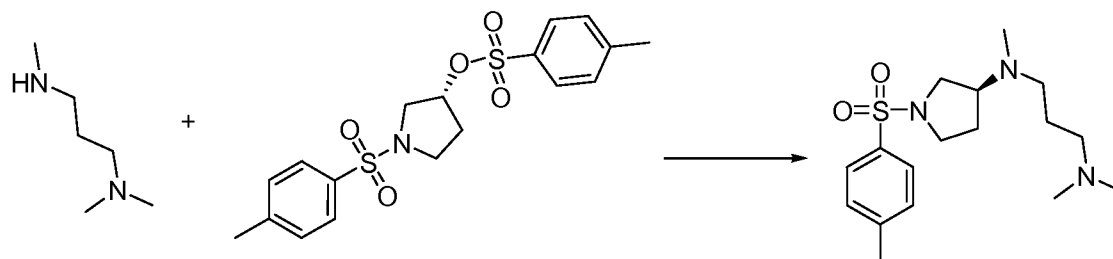
#### Scheme 1A



[0072] Then reaction is allowed to come to room temperature and stirred overnight. It is then filtered and diluted with water (50ml), washed with brine, dried and purified by column chromatography (100% PE to PE:EtOAc=3:1) to give 4 g of product (90% yield).

$C_{18}H_{21}NO_5S_2$ ,  $^1H$ -NMR ( $CDCl_3$ , 600 MHz):  $\delta$  = 1.98 (1H, m,  $J=3.90$  Hz), 2.02 (1H, t,  $J=1.89$  Hz), 2.45(3H, s), 2.47(3H, s), 3.23 (1H, dt,  $J=6.92, 4.88$  Hz), 3.37 (1H, td,  $J=1.41, 12.4$  Hz), 3.44 (1H, ddd,  $J=3.00, 8.35, 97.2$ Hz), 3.48 (1H, dd,  $J=4.95, 12.27$  Hz), 4.95 (1H, d,  $J=4.74$  Hz), 4.95 (1H, t,  $J=4.98$  Hz), 7.33 (2H, d,  $J=8.16$  Hz), 7.34 (2H, d,  $J=8.52$  Hz), 7.67 (2H, d,  $J=5.29$  Hz), 7.68 (2H, d,  $J=5.10$  Hz).  $^{13}C$ -NMR ( $CDCl_3$ , 150.92 MHz):  $\delta$  = 14.2(EtOAc), 21.1(EtOAc), 21.6, 21.7, 32.2, 45.8, 53.5, 60.4(EtOAc), 79.4, 127.6, 127.7, 129.8, 130.0, 133.2, 133.4, 143.9, 145.2, 171.2(EtOAc).

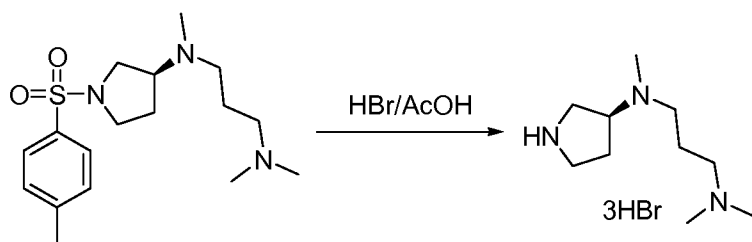
#### Conversion of bis-sulphonate to (*S*)- $N^1, N^1, N^3$ -trimethyl- $N^3$ -(1-tosylpyrrolidin-3-yl) propane-1,3-diamine



[0073] To 1 g of Bisulfonate intermediate (2.5 mmol) is dissolved in 3 ml of *N,N,N'*-trimethylpropane-1,3-diamine in a sealed tube and heated to 90 °C in an oil bath for 12 h. The

mixture was separated by silica column chromatography (100% DCM to DCM/methanol=100:5), to give 700 mg of the target compound (80% yield).  $C_{17}H_{29}N_3O_2S$ ,  $^1H$ -NMR ( $CDCl_3$ , 600 MHz):  $\delta$  = 1.58 (2H, m), 1.66 (1H, m), 2.00 (1H, m), 2.15 (3H, s), 2.20 (6H, s), 2.22 (2H, t,  $J$ =7.44 Hz), 2.32 (1H, m), 2.44 (3H, s), 2.86 (1H, dt,  $J$ =7.15, 7.67 Hz), 2.95 (1H, t,  $J$ =8.85 Hz), 3.19 (1H, dt,  $J$ =7.23, 4.83 Hz), 3.36 (1H, dt,  $J$ =2.95, 4.70 Hz), 3.49 (1H, dd,  $J$ =7.11, 9.33 Hz), 7.33 (2H, d,  $J$ =8.25 Hz), 7.71 (2H, d,  $J$ =8.31 Hz).  $^{13}C$ -NMR ( $CDCl_3$ , 150.92 MHz):  $\delta$  = 21.5, 25.1, 29.3, 39.5, 45.5, 46.8, 51.2, 53.4, 53.6, 57.7, 63.6, 127.6, 129.7, 133.3, 143.5.

**(S)- $N^1, N^1, N^3$ -trimethyl- $N^3$ -(pyrrolidin-3-yl)propane-1,3-diamine hydrobromide salt**



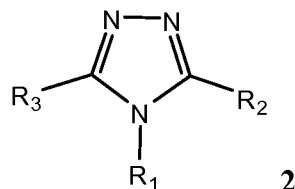
**[0074]** Monosulfonate intermediate (500 mg, 1.47 mmol) is dissolved in a 33% HBr/AcOH (2 ml) solution and heated to reflux for 2.5 h. The reaction is cooled to room temperature. The precipitate is isolated by filtration, washed with ethylacetate and dried to give 450 mg of the target compound (71% yield) as a yellow power which is used in the next step without further purification.

**[0075]**  $C_{10}H_{23}N_3$ ,  $^1H$ -NMR ( $CD_3OD$ , 600 MHz):  $\delta$  = 2.33 (2H, t,  $J$ =7.26 Hz), 2.44 (1H, m), 2.64 (1H, w), 2.98 (3H, s), 3.02 (2H, s), 3.43 (1H, m), 3.67 (1H, m), 3.75 (1H, dd,  $J$ =7.92, 12.66 Hz), 3.89 (1H, dd,  $J$ =8.69, 12.46 Hz), 4.35 (1H, t,  $J$ =7.18 Hz).  $^{13}C$ -NMR ( $CD_3OD$ , 150.92 MHz):  $\delta$  = 63.4, 54.0, 44.5, 42.3, 19.9, 19.5.

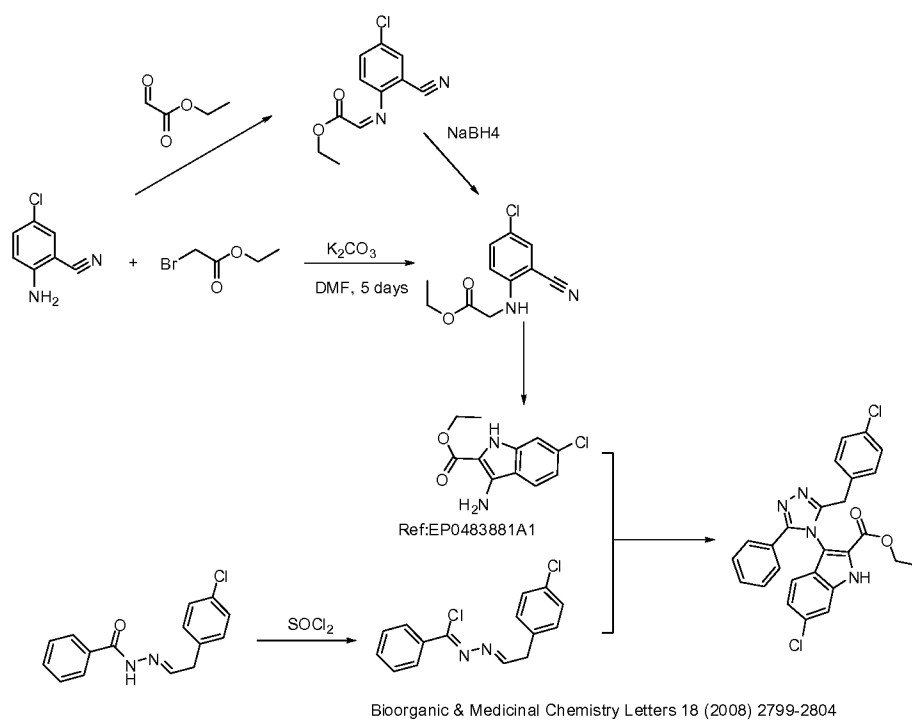
**[0076]** In another aspect, the present invention provides compounds in which the imidazole core is replaced by other 5-membered heterocycles, such as a triazole, a pyrazole, an isoxazole or a thiazole. Inventive compounds belonging to the above classes should mimic the binding geometry of the imidazole analogs. The present invention also provides methods for synthesizing these compounds as well as formulations of the same.

### 3. The Triazole Scaffold

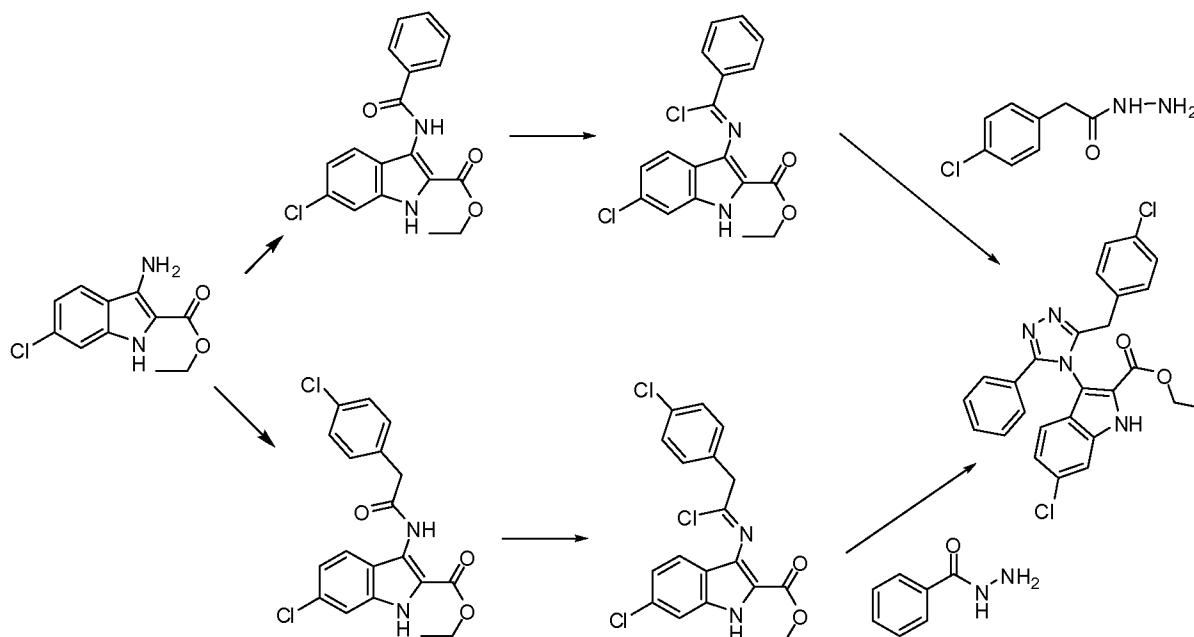
[0077] In one embodiment, therefore, compounds that have a 1,2,4-triazole core and comport with Formula 2 are synthesized as shown in Schemes 2 and 3.



**Scheme 2**



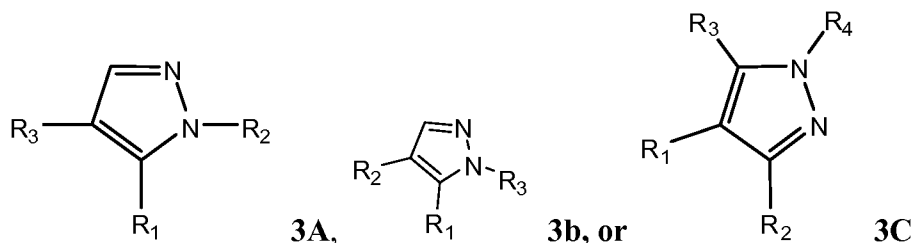
Scheme 3



[0078] According to Scheme 2, therefore, compounds having the triazole core can be synthesized by reacting the appropriately protected indole with 2-(4-chlorophenylethylidene) benzohydrazonoyl chloride. Pursuant to Scheme 3, however, the triazole scaffold is synthesized by reacting an appropriately protected 6-chloroindole with benzohydrazide.

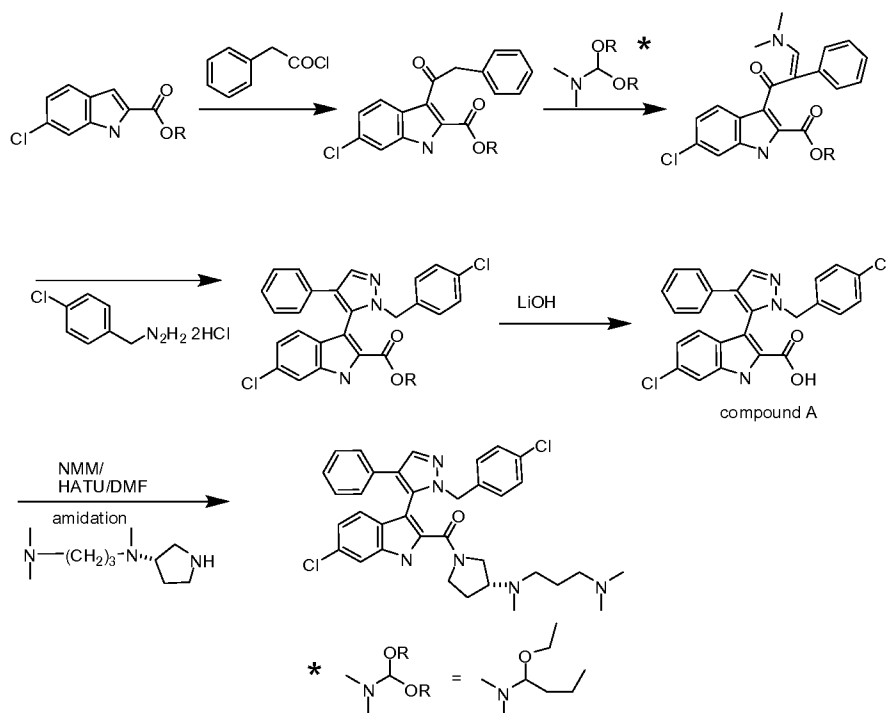
#### 4. The Pyrazole Scaffold

[0079] In another embodiment, the present invention provides synthetic strategies for generating compounds that contain a pyrazole core and comport with Formulae 3A-3C.



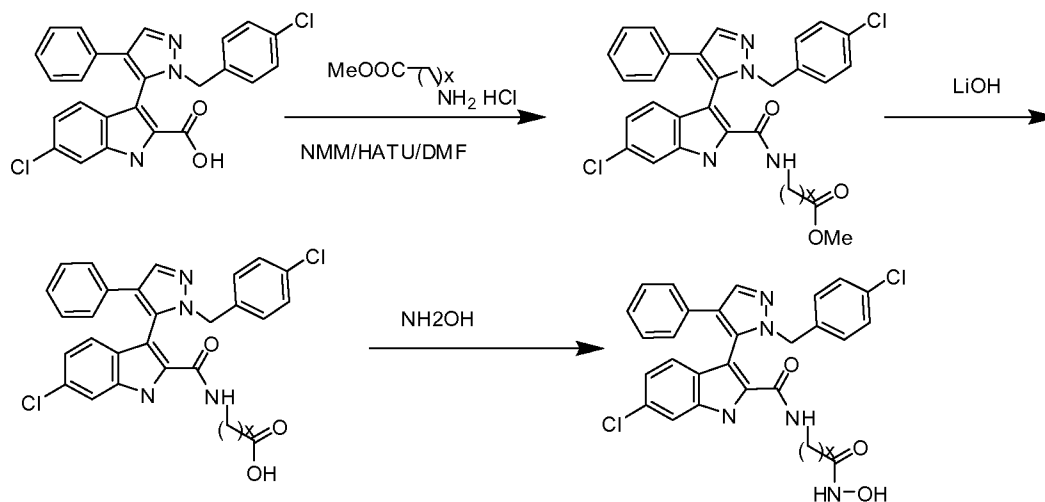
[0080] Scheme 4 show a method for synthesizing compounds in accordance with Formula 3A. Thus, reacting the appropriately protected 6-chloroindole with the acetal of N,N-dimethylformamide results in pyrazole analogs. Alternatively, the inventive compounds are generated by reacting 6-chloroindole with a benzylhydrazide as shown in Scheme 4.

## Scheme 4



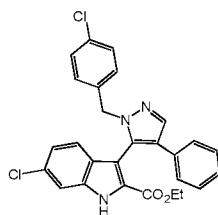
[0081] The present invention further provides a methodology for synthesizing carboxamides of the inventive compounds as shown below in Scheme 4A. Accordingly, amidation of compound (A) with the desired amino alcanoic acid followed by reaction of the product with hydroxylamine gave the desired carboxamide.

## Scheme 4A



[0082] The present invention also provides methodology for synthesizing compounds in accordance with Formulae 3B and 3C, as shown below in Schemes 5 and 6, respectively.



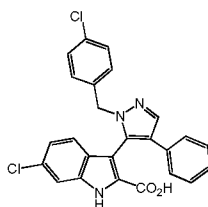


[0086] HPLC/MS:  $t_R = 19.47$  min;  $m/z = 490.1$   $[M+H]^+$ ; HRMS:  $C_{27}H_{22}Cl_2N_3O_2$ , 490.1089 (calcd.), 490.1062 (found).

[0087]  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 9.59 (s, 1H), 7.94 (s, 1H), 7.49 (1H, s), 7.10-7.19 (m, 8H), 6.85 (d, 2H,  $J = 7.8$  Hz), 5.16 (1H, ABd,  $J = 15.6$  Hz), 5.00 (1H, ABd,  $J = 15.0$  Hz), 3.97-4.11 (m, 2H), 1.05 (t, 3H,  $J = 7.2$  Hz).

[0088]  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ): 160.9, 138.0, 136.0, 135.2, 133.5, 132.9, 132.3, 131.4, 128.9, 128.5, 128.4, 126.6, 126.4, 126.2, 123.4, 123.0, 122.2, 112.1, 110.6, 61.4, 53.2, 13.8.

[0089] **6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxylic acid (YH245)**

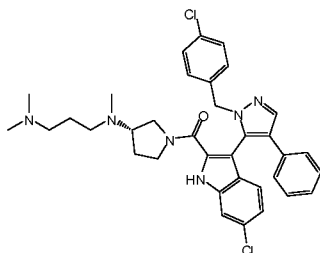


[0090] HPLC/MS:  $t_R = 18.60$  min;  $m/z = 462.1$   $[M+H]^+$ ; HRMS:  $C_{25}H_{17}Cl_2N_3O_2$ , 461.069782 (calcd.), 461.069688 (found).

[0091]  $^1H$  NMR (600 MHz, Acetone): 12.09 (s, 1H), 7.92 (s, 1H), 7.10-7.23 (m, 5H), 6.62-6.88 (m 8H), 5.17-5.28 (m, 2H).

[0092]  $^{13}C$  NMR (150 MHz, Acetone): 171.2, 137.4, 137.0, 134.0, 131.9, 129.4, 129.1, 128.0, 127.7, 126.2, 125.9, 125.2, 121.1, 121.0, 120.1, 112.2, 52.3.

**[0093] (6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-1H-indol-2-yl)((S)-3-((3-(dimethylamino)propyl)(methylamino)pyrrolidin-1-yl)methanone (YH249)**

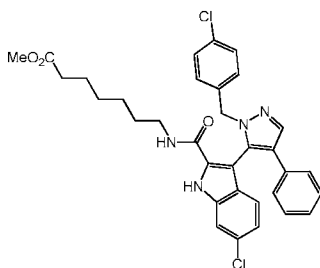


**[0094]** HPLC/MS:  $t_R = 10.73$  min;  $m/z = 629.0$   $[M+H]^+$ .

**[0095]**  $^1H$  NMR (600 MHz, MeOD): 1.28 (m, 1H), 1.76-1.86 (m, 2H), 2.55 (m, 2H), 2.76-78 (m, 6H), 2.84-2.97 (m, 2H), 3.10-3.22 (m, 2H), 3.29 (m, 4H), 3.51 (m, 1H), 3.84 (m, 1H), 5.16 (m, 2H), 6.94 (m, 3H), 7.08-7.21 (m, 6H), 7.51 (m, 1H), 7.95 (m, 1H), 8.14 (s, 1H), 8.74 (br.s, 1H).

**[0096]**  $^{13}C$  NMR (150 MHz, MeOD): 20.1, 33.8, 40.7, 41.6, 42.1, 51.2, 52.1, 53.4, 62.8, 110.3, 119.1, 120.0, 124.1, 124.8, 126.6, 126.9, 127.0, 127.4, 128.3, 129.6, 131.0, 131.6, 133.9, 134.7, 136.1.

**[0097] Methyl 7-(6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)heptanoate (YH250)**

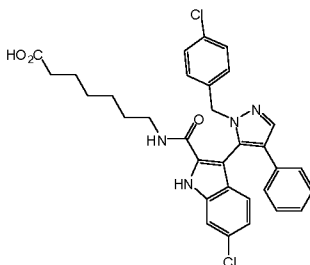


**[0098]** HRMS:  $C_{33}H_{32}N_4O_3Cl_2Na$ , 625.1749 (calcd.), 625.1729 (found).

**[0099]**  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 0.98 (m, 2H), 1.11-1.21 (m, 4H), 1.52-1.55 (m, 2H), 2.27-2.29 (m, 2H), 2.93-3.15 (2H, m), 3.69 (s, 3H), 4.94 (1H, ABd,  $J = 15.0$  Hz), 5.14 (1H, ABd,  $J = 15.0$  Hz), 5.72 (1H, m), 6.87 (m, 2H), 7.13-7.20 (8H, m), 7.59 (s, 1H), 8.03 (s, 1H), 10.88 (br.s, 1H).

[0100]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 8.6, 24.7, 26.3, 28.7, 28.8, 33.9, 39.4, 45.8, 51.5, 53.4, 104.1, 112.7, 121.3, 122.8, 123.6, 126.1, 126.5, 127.1, 128.7, 128.9, 129.3, 129.9, 130.5, 131.3, 131.4, 134.0, 134.5, 135.9, 138.6, 160.3, 174.1.

[0101] **7-(6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)heptanoic acid (YH254)**

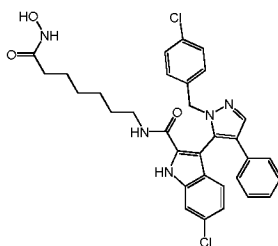


[0102] HPLC/MS:  $t_R = 12.35$  min;  $m/z = 589.2$   $[\text{M}+\text{H}]^+$ ; HRMS:  $\text{C}_{32}\text{H}_{30}\text{N}_4\text{O}_3\text{Cl}_2\text{Na}$ , 611.1593 (calcd.), 611.1566 (found).

[0103]  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 0.85-1.10 (m, 8H), 1.27-1.41 (m, 4H), 2.14 (m, 2H), 2.78-3.03 (m, 2H), 4.88 (1H, ABd,  $J = 14.4$  Hz), 5.02 (1H, ABd,  $J = 13.8$  Hz), 5.68 (s, 1H), 6.78-6.79 (m, 2H), 7.05-7.13 (m, 8H), 7.54 (s, 1H), 7.99 (s, 1H), 11.71 (br.s, 1H).

[0104]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 25.1, 27.8, 28.5, 29.7, 38.1, 53.1, 104.0, 112.7, 121.2, 122.6, 123.4, 126.1, 126.4, 127.0, 128.6, 128.9, 129.2, 129.8, 130.7, 131.1, 131.4, 133.9, 134.5, 136.1, 138.6, 160.6.

[0105] **6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-(7-(hydroxyamino)-7-oxoheptyl)-1H-indole-2-carboxamide (YH256)**

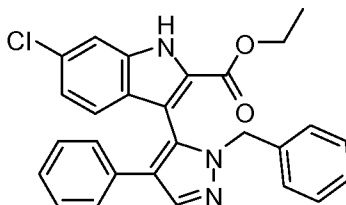


[0106] HRMS:  $\text{C}_{32}\text{H}_{31}\text{N}_5\text{O}_3\text{Cl}_2\text{Na}$ , 626.1702 (calcd.), 626.1694 (found).

[0107]  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 0.88-1.51 (m, 8H), 2.04-2.27 (m, 2H), 3.01-3.05 (m, 2H), 4.94 (1H, ABd,  $J = 16.2$  Hz), 5.08 (1H, ABd,  $J = 15.0$  Hz), 5.73 (s, 1H), 6.81-6.84 (m, 1H), 7.14 (m, 8H), 7.72 (m, 3H), 8.01 (s, 1H).

[0108]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 14.1, 22.7, 28.5, 29.4, 29.7, 31.9, 53.3, 103.9, 112.6, 121.3, 122.8, 123.7, 126.2, 126.4, 127.2, 128.7, 129.0, 129.3, 130.0, 130.8, 131.4, 134.0, 134.4, 138.6.

[0109] **Ethyl 3-(1-benzyl-4-phenyl-1H-pyrazol-5-yl)-6-chloro-1H-indole-2-carboxylate (YH214)**

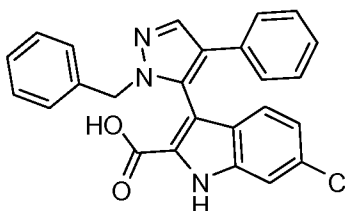


[0110] HPLC/MS:  $t_R = 12.65$  min;  $m/z = 456.3$   $[\text{M}+\text{H}]^+$ ; HRMS:  $\text{C}_{27}\text{H}_{23}\text{ClN}_3\text{O}_2$ , 456.1479 (calcd.), 456.1486 (found).

[0111]  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 9.35 (s, 1H), 7.93 (s, 1H), 7.49 (1H, s), 7.08-7.21 (m, 9H), 6.91 (m, 2H), 5.21 (1H, ABd,  $J = 15.0$  Hz), 5.02 (1H, ABd,  $J = 15.6$  Hz), 3.90-4.07 (m, 2H), 1.02 (t, 3H,  $J = 7.2$  Hz).

[0112]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 13.7, 54.0, 61.3, 110.8, 112.0, 122.3, 123.0, 123.2, 126.1, 126.3, 126.5, 126.7, 127.5, 127.6, 128.3, 128.4, 131.4, 132.2, 133.1, 135.9, 136.7, 137.8, 161.0.

[0113] **3-(1-benzyl-4-phenyl-1H-pyrazol-5-yl)-6-chloro-1H-indole-2-carboxylic acid (YH262)**

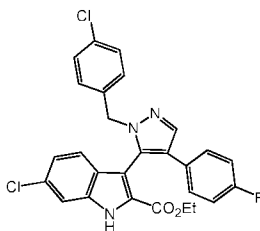


[0114] HPLC/MS:  $t_R = 11.78$  min;  $m/z = 428.1$   $[\text{M}+\text{H}]^+$

[0115]  $^1\text{H}$  NMR (600 MHz, MeOD): 7.89 (s, 1H), 7.42 (1H, s), 7.26-7.27 (m, 2H), 7.01-7.09 (m, 6H), 6.88 (m, 2H), 6.71 (m, 2H), 5.39 (1H, ABd,  $J = 15.6$  Hz), 5.21 (1H, ABd,  $J = 15.6$  Hz).

[0116]  $^{13}\text{C}$  NMR (150 MHz, MeOD): 53.2, 105.7, 111.2, 120.0, 120.9, 121.9, 125.3, 126.2, 126.3, 126.7, 127.0, 127.8, 128.7, 133.4, 134.6, 135.4, 136.6, 137.3, 166.8.

**[0117] Ethyl 6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxylate (YH263)**

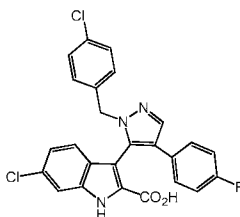


**[0118]** HPLC/MS:  $t_R = 12.59$  min;  $m/z = 508.2$   $[M+H]^+$ ; HRMS:  $C_{27}H_{20}N_3O_2FCl_2$ , 507.091661 (calcd.), 507.092044 (found).

**[0119]**  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 9.35 (s, 1H), 7.89 (s, 1H), 7.52 (s, 1H), 7.09-7.18 (m, 6H), 6.83-6.86 (m, 4H), 5.16 (1H, ABd,  $J = 15.0$  Hz), 5.00 (1H, ABd,  $J = 15.0$  Hz), 4.01-4.16 (m, 2H), 1.08 (t, 3H,  $J = 7.2$  Hz).

**[0120]**  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ): 13.9, 53.3, 61.4, 110.4, 112.1, 115.3, 122.1, 122.5, 123.2, 126.3, 126.6, 127.88, 127.93, 128.4, 128.9, 131.3, 132.5, 133.5, 135.2, 135.9, 137.8, 160.6.

**[0121] 6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxylic acid (YH264)**

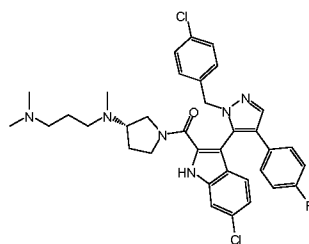


**[0122]** HPLC/MS:  $t_R = 12.21$  min;  $m/z = 480.1$   $[M+H]^+$ .

**[0123]**  $^1H$  NMR (600 MHz, MeOD): 8.57 (s, 1H), 7.88 (s, 1H), 7.43 (s, 1H), 7.27 (m, 2H), 7.04 (m, 2H), 6.69-6.87 (m, 6H), 5.32 (1H, ABd,  $J = 15.6$  Hz), 5.19 (1H, ABd,  $J = 15.6$  Hz).

**[0124]**  $^{13}C$  NMR (150 MHz, MeOD): 52.6, 105.2, 111.4, 114.3, 114.5, 120.2, 120.6, 121.2, 126.2, 127.8, 127.9, 128.0, 128.7, 128.9, 132.6, 134.6, 135.4, 136.0, 136.7, 160.4, 166.6, 169.0.

**[0125] (6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indol-2-yl)((S)-3-((3-(dimethylamino)propyl)(methyl)amino)pyrrolidin-1-yl)methanone (YH265)**

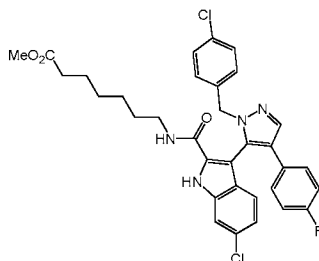


**[0126]** HPLC/MS:  $t_R = 10.23$  min;  $m/z = 647.4$   $[M+H]^+$ ; HRMS:  $C_{35}H_{38}N_6OCl_2F$ , 647.2468 (calcd.), 647.2477 (found).

**[0127]**  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 1.28-1.62 (m, 12H), 1.85-2.07 (m, 6H), 2.14-2.23 (m, 24H), 2.26-2.74 (m, 12H), 2.93-3.75 (m, 12H), 5.07-5.15 (m, 4H), 5.24-5.33 (m, 2H), 6.88-6.98 (m, 16H), 7.00-7.21 (m, 12H), 7.34 (m, 2H), 7.47-7.50 (m, 3H), 7.85-8.04 (m, 1H), 10.64 (br.s, 1H), 10.79 (br.s, 1H).

**[0128]**  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ): 24.6, 25.0, 28.2, 28.5, 29.7, 30.8, 39.2, 39.3, 40.0, 45.4, 45.5, 45.8, 51.3, 52.7, 53.5, 57.3, 57.7, 62.6, 63.8, 105.8, 112.0, 115.6, 115.8, 115.9, 119.7, 121.5, 121.8, 122.3, 125.1, 127.2, 127.7, 128.5, 128.6, 128.7, 129.5, 130.7, 131.1, 132.2, 132.4, 133.5, 134.7, 136.2, 138.2, 138.4, 162.0.

**[0129] Methyl 7-(6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)heptanoate (YH266)**



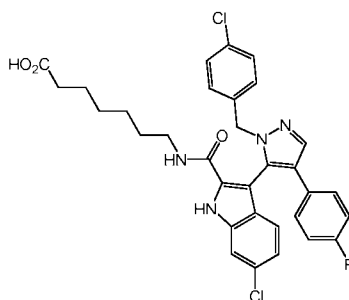
**[0130]** HPLC/MS:  $t_R = 13.07$  min;  $m/z = 621.3$   $[M+H]^+$ ; HRMS:  $C_{33}H_{31}N_4O_3Cl_2FNa$ , 643.1655 (calcd.), 643.1614 (found).

**[0131]**  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 0.99-1.02 (m, 2H), 1.13-1.24 (m, 4H), 1.54-1.57 (m, 2H), 2.29-2.31 (m, 2H), 2.95-3.17 (2H, m), 3.71 (s, 3H), 4.95 (1H, ABd,  $J = 15.0$  Hz), 5.16

(1H, ABd, J = 15.0 Hz), 5.63 (1H, m), 6.87-6.90 (m, 4H), 7.14-7.19 (m, 6H), 7.61 (s, 1H), 8.00 (s, 1H), 10.65 (br.s, 1H).

[0132]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 24.7, 26.3, 28.7, 28.8, 33.9, 38.6, 39.4, 51.6, 53.5, 103.8, 112.6, 115.9, 116.0, 121.2, 122.7, 122.9, 126.5, 127.7, 127.8, 128.7, 129.3, 129.9, 130.3, 131.5, 134.1, 134.4, 135.8, 138.4, 160.1, 174.1.

[0133] 7-(6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)heptanoic acid (YH267)

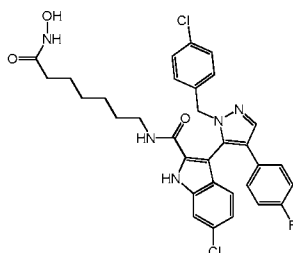


[0134] HPLC/MS:  $t_R$  = 12.29 min;  $m/z$  = 607.1  $[\text{M}+\text{H}]^+$ ; HRMS:  $\text{C}_{32}\text{H}_{29}\text{N}_4\text{O}_3\text{Cl}_2\text{FNa}$ , 629.1498 (calcd.), 629.1552 (found).

[0135]  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 0.92-1.28 (m, 8H), 1.57-1.60 (m, 2H), 2.35 (m, 2H), 2.92-3.14 (m, 2H), 4.94 (1H, ABd, J = 15.0 Hz), 5.15 (1H, ABd, J = 15.0 Hz), 5.66 (s, 1H), 6.86-6.89 (m, 4H), 7.14-7.33 (m, 6H), 7.62 (s, 1H), 8.01 (s, 1H), 10.95 (br.s, 1H).

[0136]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 24.6, 26.1, 28.5, 28.7, 33.8, 38.6, 39.3, 53.5, 103.9, 112.8, 115.9, 116.0, 121.1, 122.8, 122.9, 126.4, 127.7, 127.9, 128.7, 129.3, 129.7, 131.5, 134.1, 134.4, 135.9, 138.4, 160.3, 177.9.

[0137] 6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-N-(7-(hydroxyamino)-7-oxoheptyl)-1H-indole-2-carboxamide (YH268)

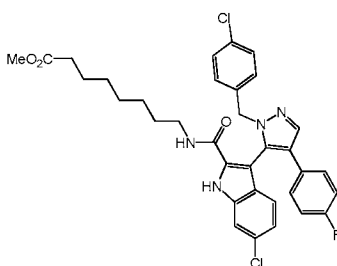


[0138] HRMS:  $\text{C}_{32}\text{H}_{30}\text{N}_5\text{O}_3\text{Cl}_2\text{FNa}$ , 644.1607 (calcd.), 644.1568 (found).

[0139]  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 0.89-1.46 (m, 8H), 2.00 (m, 2H), 2.83-2.86 (m, 2H), 3.05-3.10 (m, 2H), 4.92-5.03 (m, 2H), 5.69 (s, 1H), 6.80-6.88 (m, 4H), 7.08-7.16 (m, 6H), 7.58 (s, 1H), 7.96 (s, 1H).

[0140]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 14.1, 22.7, 28.5, 29.4, 29.7, 31.9, 33.9, 36.5, 53.2, 56.0, 103.9, 115.8, 115.9, 121.1, 122.6, 123.0, 126.3, 127.8, 128.6, 128.7, 129.3, 130.7, 133.9, 134.5, 138.5, 160.6, 160.9.

[0141] **Methyl 8-(6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)octanoate (YH271)**

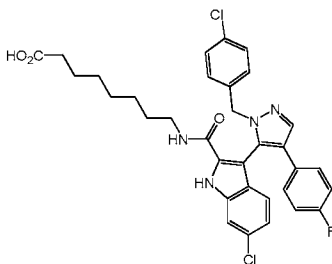


[0142] HPLC/MS:  $t_R = 13.18$  min;  $m/z = 635.3$   $[\text{M}+\text{H}]^+$ ; HRMS:  $\text{C}_{34}\text{H}_{33}\text{Cl}_2\text{FN}_4\text{O}_3\text{Na}$ , 657.1811 (calcd.), 657.1833 (found).

[0143]  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 0.99-1.01 (m, 2H), 1.13-1.27 (m, 6H), 1.59-1.63 (m, 2H), 2.31-2.33 (m, 2H), 2.98-3.17 (m, 2H), 3.70 (s, 3H), 4.94 (1H, ABd,  $J = 15.0$  Hz), 5.15 (1H, ABd,  $J = 14.4$  Hz), 5.67 (m, 1H), 6.86-6.88 (m, 4H), 7.14-7.19 (m, 6H), 7.61 (s, 1H), 8.00 (s, 1H).

[0144]  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 24.8, 26.4, 28.8, 28.9, 34.0, 38.6, 39.5, 51.5, 53.4, 103.8, 112.8, 115.8, 116.0, 121.1, 122.7, 122.8, 126.4, 127.6, 127.7, 127.8, 128.7, 129.3, 129.9, 130.4, 131.4, 134.1, 134.5, 136.0, 138.4, 160.3, 161.0, 162.6, 174.2.

[0145] **8-(6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)octanoic acid (YH272)**

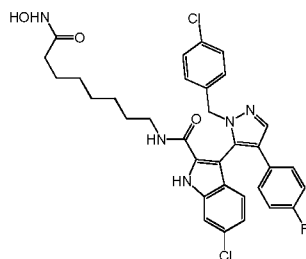


[0146] HPLC/MS:  $t_R = 12.35$  min;  $m/z = 621.2$   $[M+H]^+$ ; HRMS:  $C_{33}H_{31}Cl_2FN_4O_3Na$ , 643.1655 (calcd.), 643.1678 (found).

[0147]  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 0.92-0.98 (m, 2H), 1.08-1.28 (m, 6H), 1.60-1.64 (m, 2H), 1.87-1.89 (m, 2H), 2.36-2.39 (m, 2H), 2.88-3.12 (m, 2H), 3.78 (m, 1H), 4.92 (1H, ABd,  $J = 15.0$  Hz), 5.14 (1H, ABd,  $J = 15.0$  Hz), 5.67 (m, 1H), 6.84-6.88 (m, 4H), 7.12-7.17 (m, 6H), 7.61 (s, 1H), 8.00 (s, 1H), 11.19 (br.s, 1H).

[0148]  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ): 24.8, 25.6, 26.0, 28.4, 28.6, 38.6, 39.3, 53.4, 68.0, 103.9, 112.8, 115.9, 116.0, 121.1, 122.8, 122.9, 126.3, 127.4, 127.7, 127.8, 128.7, 129.3, 129.7, 130.5, 131.5, 134.1, 134.4, 136.0, 138.4, 160.4, 161.0, 162.7.

[0149] **6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamide (YH273)**

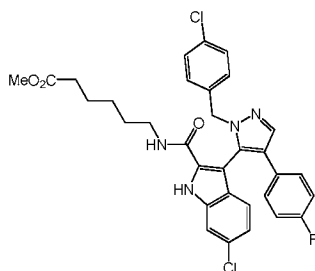


[0150] HPLC/MS:  $t_R = 12.31$  min;  $m/z = 621.3$   $[M+H]^+$ ; HRMS:  $C_{33}H_{32}Cl_2FN_5O_3Na$ , 658.1764 (calcd.), 658.1772 (found).

[0151]  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 0.81-1.44 (m, 8H), 2.02-2.14 (m, 2H), 2.83-2.86 (m, 2H), 2.80-3.03 (m, 2H), 4.89-5.07 (m, 2H), 5.94 (s, 1H), 6.74-6.79 (m, 3H), 7.03-7.18 (m, 8H), 7.53 (s, 1H), 7.94 (s, 1H).

[0152]  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ): 25.9, 26.0, 28.5, 28.8, 29.1, 29.7, 39.1, 39.2, 53.2, 104.2, 112.7, 115.8, 121.1, 122.4, 126.3, 127.8, 128.59, 128.61, 129.18, 129.23, 130.1, 131.1, 133.8, 134.6, 136.3, 138.3, 160.5, 160.8.

[0153] **Methyl 6-(6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)hexanoate (YH275)**

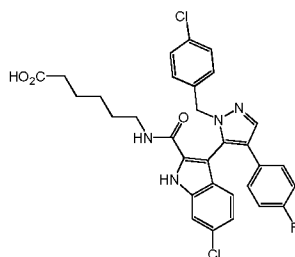


**[0154]** HPLC/MS:  $t_R = 12.73$  min;  $m/z = 607.2$   $[M+H]^+$ ; HRMS:  $C_{32}H_{29}Cl_2FN_4O_3Na$ , 629.1498 (calcd.), 629.1500 (found).

**[0155]**  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 1.01-1.05 (m, 2H), 1.14-1.20 (m, 2H), 1.51-1.55 (m, 2H), 2.24-2.26 (m, 2H), 2.96-3.18 (m, 2H), 3.71 (s, 3H), 4.94 (1H, ABd,  $J = 15.0$  Hz), 5.16 (1H, ABd,  $J = 15.0$  Hz), 5.67 (m, 1H), 6.87-6.90 (m, 4H), 7.14-7.19 (m, 6H), 7.61 (s, 1H), 8.01 (s, 1H), 10.87 (br.s, 1H).

**[0156]**  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ): 24.5, 26.1, 28.7, 33.8, 39.3, 51.7, 53.5, 103.8, 112.7, 115.9, 116.1, 121.2, 122.7, 122.9, 126.4, 127.49, 127.51, 127.7, 127.8, 128.7, 129.3, 129.8, 130.3, 131.5, 134.1, 134.4, 135.9, 138.4, 160.2, 161.0, 162.6, 173.9.

**[0157]** **6-(6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)hexanoic acid (YH276)**

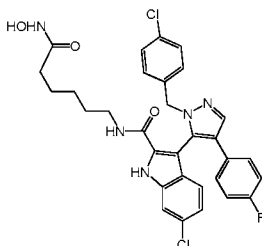


**[0158]** HPLC/MS:  $t_R$  (run time) = 11.98 min;  $m/z = 593.3$   $[M+H]^+$ .

**[0159]**  $^1H$  NMR (600 MHz,  $CDCl_3$ ): 1.01-1.05 (m, 2H), 1.13-1.19 (m, 2H), 1.55-1.59 (m, 2H), 2.31 (m, 2H), 2.96-3.14 (m, 2H), 4.95 (1H, ABd,  $J = 15.0$  Hz), 5.16 (1H, ABd,  $J = 15.0$  Hz), 5.67 (m, 1H), 6.84-6.89 (m, 4H), 7.13-7.18 (m, 6H), 7.62 (s, 1H), 8.02 (s, 1H), 11.09 (s, 1H).

**[0160]**  $^{13}C$  NMR (150 MHz,  $CDCl_3$ ): 24.4, 25.9, 28.7, 29.7, 39.1, 53.5, 68.0, 103.9, 112.8, 115.9, 116.1, 121.1, 123.0, 126.3, 127.8, 128.7, 129.3, 129.6, 131.5, 134.1, 134.3, 136.0, 138.5, 160.4, 161.1, 162.7.

**[0161] 6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-N-(6-hydroxyamino)-6-oxohexyl)-1H-indole-2-carboxamide (YH277)**

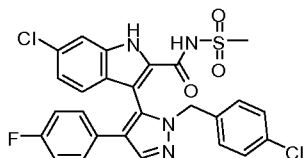


**[0162]** HPLC/MS:  $t_R = 11.98$  min;  $m/z = 608.2$   $[M+H]^+$ .

**[0163]**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 0.99-1.02 (m, 4H), 1.20-1.25 (m, 2H), 2.00-2.07 (m, 2H), 2.70-3.02 (m, 2H), 4.88 (1H, ABd,  $J = 13.8$  Hz), 4.97 (1H, ABd,  $J = 13.8$  Hz), 5.70 (m, 1H), 6.68-6.76 (m, 4H), 6.99-7.06 (m, 6H), 7.50 (s, 1H), 7.93 (s, 1H).

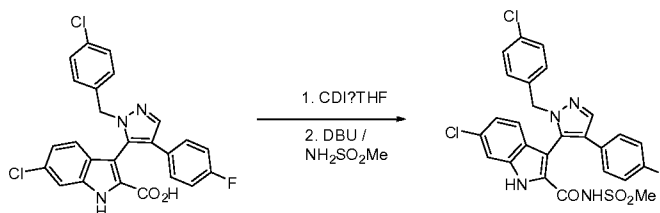
**[0164]**  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ): 19.2, 22.7, 25.5, 28.8, 29.7, 53.1, 103.8, 112.7, 115.6, 115.8, 121.1, 122.4, 122.6, 126.3, 127.8, 128.6, 129.2, 129.8, 131.2, 133.8, 134.5, 136.3, 138.5, 160.8.

**[0165] 6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-N-(methylsulfonyl)-1H-indole-2-carboxamide (YH392)**



**[0166]** The mixture of 6-chloro-3-(1-(4-chlorobenzyl)-4-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxylic acid (YH264, 0.05 mmol, 24 mg) and CDI (0.1 mmol, 16 mg) in 1 mL of dry THF was stirring under 50 °C for 2 hours. The mixture was cooled to ambient temperature and the sulphonamide (0.1 mmol, 9.5 mg) was added. The reaction mixture was stirred for 10 min and diazabicyclo[5.4.0]undec-7-en (DBU) (0.1 mmol, 15  $\mu\text{L}$ ) was added. After stirring at room temperature overnight, the residue was purified by silica gel chromatography (EtOAc/methanol, 5/1) to give the product as yellow solids (12 mg, 43% yield).

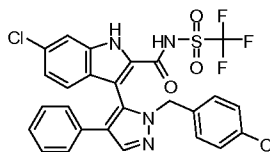
[0167] Schematically the reaction is depicted as follows:



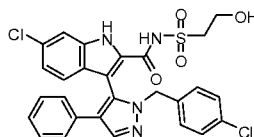
[0168] HPLC/MS:  $t_R = 14.03$  min;  $m/z = 556.6$   $[M+H]^+$ .

[0169] Carboxamides of the following pyrazole derivatives were synthesized using an analogous synthetic route

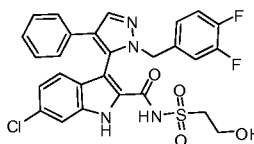
[0170] **6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-((trifluoromethyl)sulfonyl)-1H-indole-2-carboxamide:**



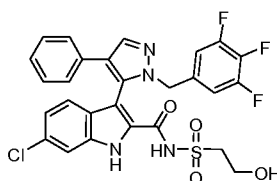
[0171] **6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-((2-hydroxyethyl)sulfonyl)-1H-indole-2-carboxamide:**



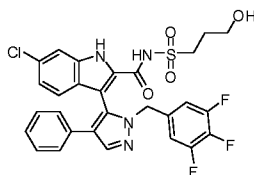
[0172] **6-chloro-3-(1-(3,4-difluorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-((2-hydroxyethyl)sulfonyl)-1H-indole-2-carboxamide:**



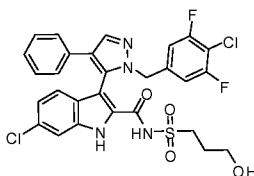
[0173] **6-chloro-N-((2-hydroxyethyl)sulfonyl)-3-(4-phenyl-1-(3,4,5-trifluorobenzyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamide:**



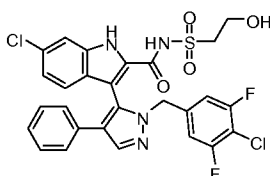
[0174] 6-chloro-N-((3-hydroxypropyl)sulfonyl)-3-(4-phenyl-1-(3,4,5-trifluorobenzyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamide:



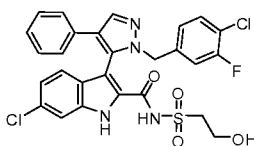
[0175] 6-chloro-3-(1-(4-chloro-3,5-difluorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-((3-hydroxypropyl)sulfonyl)-1H-indole-2-carboxamide:



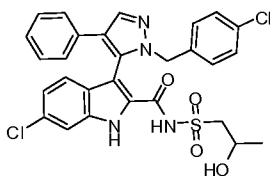
[0176] 6-chloro-3-(1-(4-chloro-3,5-difluorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-((2-hydroxyethyl)sulfonyl)-1H-indole-2-carboxamide:



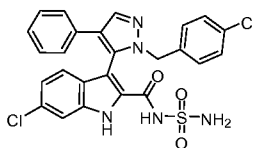
[0177] 6-chloro-3-(1-(4-chloro-3-fluorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-((2-hydroxyethyl)sulfonyl)-1H-indole-2-carboxamide:



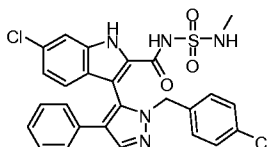
[0178] 6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-((2-hydroxypropyl)sulfonyl)-1H-indole-2-carboxamide:



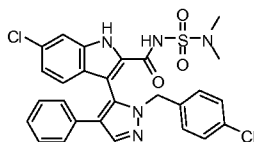
[0179] 6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-sulfamoyl-1H-indole-2-carboxamide:



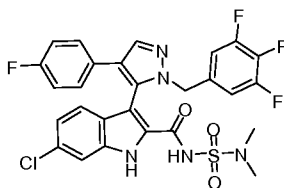
[0180] 6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-(N-methylsulfamoyl)-1H-indole-2-carboxamide:



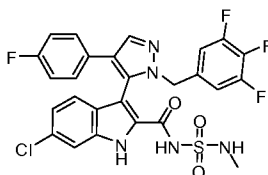
[0181] 6-chloro-3-(1-(4-chlorobenzyl)-4-phenyl-1H-pyrazol-5-yl)-N-(N,N-dimethylsulfamoyl)-1H-indole-2-carboxamide:



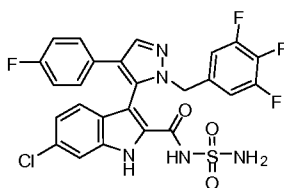
[0182] 6-chloro-N-(N,N-dimethylsulfamoyl)-3-(4-(4-fluorophenyl)-1-(3,4,5-trifluorobenzyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamide:



[0183] 6-chloro-3-(4-(4-fluorophenyl)-1-(3,4,5-trifluorobenzyl)-1H-pyrazol-5-yl)-N-(N-methylsulfamoyl)-1H-indole-2-carboxamide:



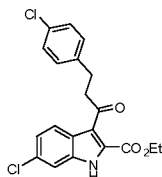
**[0184] 6-chloro-3-(4-(4-fluorophenyl)-1-(3,4,5-trifluorobenzyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamide:**



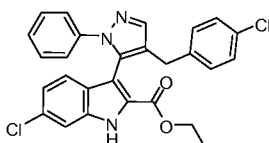
**[0185] Ethyl 6-chloro-3-(3-(4-chlorophenyl)propanoyl)-1H-indole-2-carboxylate(WW482)**

**[0186]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.41 (3H, t,  $J$ =7.14 Hz), 3.07 (2H, t,  $J$ =7.62 Hz), 3.43 (2H, t,  $J$ =7.62 Hz), 4.44 (2H, q,  $J$ =7.05 Hz), 7.18 (2H, d,  $J$ =8.31 Hz), 7.22 (1H, d,  $J$ =1.68 Hz), 7.24 (2H, d,  $J$ =8.34 Hz), 7.43 (1H, d,  $J$ =1.62 Hz), 7.88 (1H, d,  $J$ =8.69 Hz), 9.05 (1H, w).

**[0187]**  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 14.2, 29.9, 45.2, 62.2, 111.5, 121.6, 123.8, 123.8, 125.3, 126.4, 128.5, 129.8, 131.7, 132.4, 135.1, 139.7, 160.2.



**[0188] Ethyl 6-chloro-3-(4-(4-chlorobenzyl)-1-(phenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxylate (WW509)**

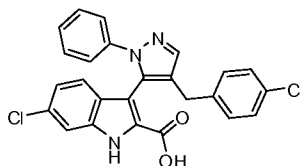


**[0189]** HRMS (ESI-TOF)  $m/z$  (calc.): 489.1011, (found)  $[\text{M}+\text{H}]^+$ : 490.1134.

**[0190]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.11 (3H, t,  $J$ =7.14 Hz), 3.61 (1H, d,  $J$ =15.86 Hz), 3.71 (1H, d,  $J$ =15.90 Hz), 4.01 (1H, m), 4.10 (1H, m), 6.89 (2H, d,  $J$ =8.31 Hz), 7.10 (2H, d,  $J$ =8.34 Hz), 7.14 (2H, m), 7.18 (3H, m), 7.35 (1H, d,  $J$ =8.69 Hz), 7.45 (1H, m), 7.68 (1H, d,  $J$ =2.27 Hz), 9.10 (1H, w).

**[0191]**  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 14.0, 29.8, 61.3, 110.9, 112.0, 121.9, 122.1, 122.9, 123.2, 126.3, 126.5, 126.8, 128.1, 128.6, 129.6, 131.6, 132.2, 139.1, 140.2, 140.3.

**[0192] 6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxylic acid (WW512)**

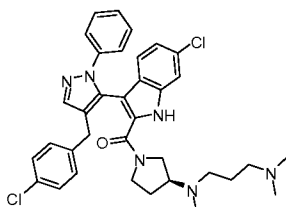


**[0193]** HRMS (ESI-TOF)  $m/z$  (calc.): 461.0698, (found)  $[M+H]^+$ : 462.0795; HPLC-MS  $r_t$ : 12.28,  $m/z$   $[M+H]^+$ : 462.3.

**[0194]**  $^1H$ -NMR (MeOD, 600 MHz):  $\delta$  = 3.70 (2H, dd,  $J$ =15.81, 31.36 Hz), 6.96 (2H, d,  $J$ =8.31 Hz), 7.07 (3H, m), 7.20 (5H, m), 7.47 (1H, t,  $J$ =1.8Hz), 7.66 (1H, d,  $J$ =2.44 Hz).

**[0195]**  $^{13}C$ -NMR (CDCl<sub>3</sub>, 150.92 MHz):  $\delta$  = 29.3, 109.5, 111.9, 121.2, 121.5, 121.9, 124.0, 126.2, 127.1, 127.5, 127.7, 128.2, 129.6, 130.9, 131.2, 134.0, 136.3, 139.3, 139.7, 140.0, 161.7.

**[0196] (6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1H-indol-2-yl)((S)-3-(3-(dimethylamino)propyl)(methylamino)pyrrolidin-1-yl)methanone (WW536)**



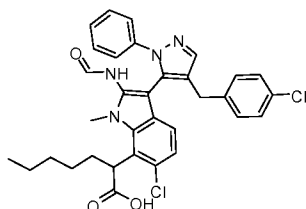
**[0197]** HRMS (ESI-TOF)  $m/z$  (calc.): 628.2484, (found)  $[M+H]^+$ : 629.2556; HPLC-MS  $r_t$ : 15.63,  $m/z$   $[M+H]^+$ : 629.2.

**[0198]**  $^1H$ -NMR (CD<sub>3</sub>OD, 600 MHz):  $\delta$  = 0.80 (1H, m), 1.21 (1H, m), 1.60-1.70 (1H, m), 1.75-1.90 (2H, m), 2.00-2.10 (2H, m), 2.24-2.30 (3H, m), 2.31-2.5 (2H, m), 2.61-2.99 (10H, m), 3.09-3.20 (3H, m), 3.36-3.7 (3H, m), 3.87-3.90 (2H, m), 6.89-7.35 (10H, m), 7.35-7.52 (2H, m), 7.60-7.72 (1H, m), 7.94-8.06 (1H, m).

**[0199]**  $^{13}C$ -NMR (CD<sub>3</sub>OD, 150.92 MHz):  $\delta$  = 13.1, 19.5, 19.7, 20.1, 21.0, 21.1, 21.2, 27.2, 28.2, 28.9, 29.0, 29.1, 29.4, 30.3, 35.6, 37.5, 38.0, 38.3, 38.4, 42.2, 42.2, 50.3, 52.1, 52.3, 56.7, 56.8, 60.1, 62.3, 63.4, 63.6, 105.9, 106.0, 111.7, 111.8, 120.9, 121.0, 121.2, 121.5, 123.0, 124.1, 124.1, 125.1, 126.3, 127.5, 127.7, 128.0, 128.1, 128.4, 128.7, 128.8, 129.5,

129.6, 129.8, 129.8, 129.9, 130.0, 131.0, 131.4, 132.8, 133.6, 133.7, 136.1, 137.6, 139.2, 139.5, 140.5, 140.9, 144.0, 161.4, 163.3, 163.5, 171.6.

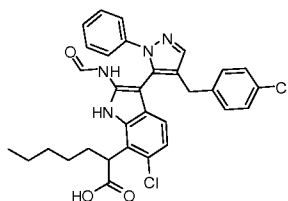
**[0200] Methyl 7-(6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1-phenyl-1H-indole-2-carboxamido)heptanoate (WW535)**



**[0201]** HRMS (ESI-TOF)  $m/z$  (calc.): 602.1851, (found)  $[M+Na]^+$ : 625.1753.

**[0202]**  $^1H$ -NMR ( $CDCl_3$ , 600 MHz):  $\delta$  = 1.14 (0.6H, s), 1.32 (5.1H, d,  $J=39.67$  Hz), 1.61 (3.3H, d,  $J=27.13$  Hz), 2.30 (2.2H, d,  $J=7.32$  Hz), 2.81 (1.2H, d,  $J=6.80$  Hz), 2.89 (1.0H, d,  $J=6.72$  Hz), 2.99 (3.0H, s), 3.12 (0.4H, s), 3.19 (0.7H, s), 3.67 (3.1H, s), 5.53 (0.7H, d,  $J=5.29$  Hz), 5.76 (0.3H, s), 6.89 (1.8H, t,  $J=7.18$  Hz), 7.13 (7.3H, d,  $J=45.70$  Hz), 7.48 (0.6H, s), 7.81 (0.5H, s), 8.03 (0.2H, s), 10.63 (0.5H, s).

**[0203] 7-(6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1-phenyl-1H-indole-2-carboxamido)heptanoic acid (WW540)**



**[0204]** HRMS (ESI-TOF)  $m/z$  (calc.): 588.1695, (found)  $[M+Na]^+$ : 611.1650;

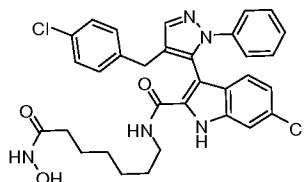
**[0205]** HPLC-MS run time (r.t): 18.14,  $m/z$   $[M+H]^+$ : 589.2.

**[0206]**  $^1H$ -NMR ( $CD_3OD$ , 600 MHz):  $\delta$  = 0.90 (2H, m), 1.14 (6H, m), 1.67(2H, m), 2.04 (2H, m), 3.08 (1H, m), 3.21 (1H, m), 3.62 (1H, d,  $J=15$ Hz), 3.72 (1H, d,  $J=15$ Hz), 5.54 (1H, s), 6.90(2H, d,  $J=8.4$  Hz), 7.11(2H, d,  $J=8.4$  Hz), 7.14-7.19(4H, m), 7.51(1H, s), 7.84(1H, s), 10.53(1H, s).

**[0207]**  $^{13}C$ -NMR ( $CD_3OD$ , 150.92 MHz):  $\delta$  = 24.3, 24.8, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 33.7, 33.9, 39.4, 103.1, 104.6, 112.5, 114.5, 117.8, 121.2, 122.7, 123.0, 123.6,

126.6, 127.6, 128.6, 129.0, 129.6, 129.7, 131.2, 131.6, 132.1, 135.6, 138.5, 139.3, 141.0, 160.6, 178.0.

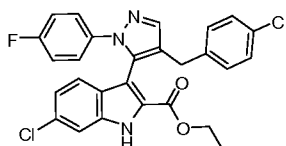
**[0208] 6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-N-(7-(hydroxyamino)-7-oxoheptyl)-1H-indole-2-carboxamide (WW538)**



**[0209]** HRMS (ESI-TOF)  $m/z$  (calc.): 603.1804, (found)  $[M+H]^+$ :

**[0210]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 0.89 (1H, s), 0.99 (2H, s), 1.24 (5H, m), 1.55 (3H, s), 2.01 (2H, s), 2.98 (1H, s), 3.28 (1H, s), 3.60 (1H, d,  $J=15.30$  Hz), 3.70 (1H, d,  $J=15.24$  Hz), 5.55 (1H, s), 6.88 (2H, d,  $J=7.86$  Hz), 7.08 (2H, d,  $J=8.40$  Hz), 7.13 (2H, d,  $J=7.20$  Hz), 7.18 (2H, s), 7.47 (1H, s), 7.83 (1H, s).

**[0211] Ethyl 6-chloro-3-(4-(4-chlorobenzyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxylate (WW515)**

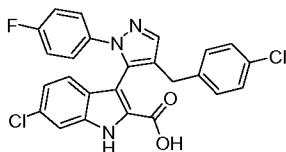


**[0212]** HRMS (ESI-TOF)  $m/z$  (calc.): 507.0917, (found)  $[M+H]^+$ : 508.1045.

**[0213]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.13 (3H, t,  $J=7.14$  Hz), 3.60 (1H, d,  $J=15.86$  Hz), 3.70 (1H, d,  $J=15.84$  Hz), 4.05 (1H, m), 4.12 (1H, m), 6.87 (1H, t,  $J=8.49$  Hz), 6.88 (2H, d,  $J=8.22$  Hz), 7.10 (2H, d,  $J=8.69$  Hz), 7.16 (3H, m), 7.32 (1H, d,  $J=8.69$  Hz), 7.45 (1H, d,  $J=1.51$  Hz), 7.67 (1H, s), 9.33 (1H, s).

**[0214]**  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 14.0, 29.8, 61.3, 110.7, 112.1, 115.4, 115.6, 121.9, 122.0, 123.0, 125.0, 125.0, 126.3, 126.4, 128.2, 129.6, 131.7, 132.3, 132.4, 135.8, 136.3, 139.0, 140.4, 160.4, 160.5, 162.0.

**[0215] 6-chloro-3-(4-(4-chlorobenzyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxylic acid (WW519)**

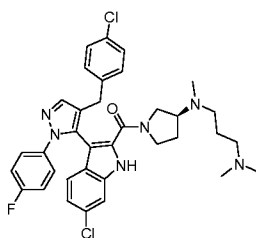


**[0216]** HRMS (ESI-TOF)  $m/z$  (calc.): 479.0604, (found)  $[M+H]^+$ : 629.2556; HPLC-MS r.t: 12.23,  $m/z$   $[M+H]^+$ : 480.1.

**[0217]**  $^1\text{H-NMR}$  (MeOD, 600 MHz):  $\delta$  = 3.70 (2H, dd,  $J=15.78, 33.85$  Hz), 6.95 (2H, d,  $J=8.22$  Hz), 6.98 (1H, d,  $J=8.52$  Hz), 7.06-7.08 (3H, m), 7.19-7.22 (3H, m), 7.48 (1H, d,  $J=1.13$  Hz), 7.66 (1H, s).

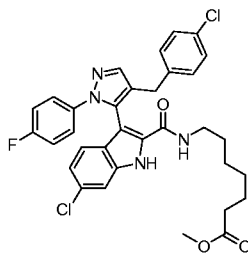
**[0218]**  $^{13}\text{C-NMR}$  (MeOH, 150.92 MHz):  $\delta$  = 29.2, 111.9, 114.9, 115.0, 121.2, 121.6, 121.9, 126.1, 126.1, 126.2, 127.7, 129.6, 130.9, 131.2, 134.2, 136.3, 139.3, 139.8, 152.4, 152.5, 160.8, 161.7, 162.4.

**[0219] (6-chloro-3-(4-(4-chlorobenzyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indol-2-yl)((S)-3-((3-(dimethylamino)propyl)(methyl)amino)pyrrolidin-1-yl)methanone (WW529)**



**[0220]** HRMS (ESI-TOF)  $m/z$  (calc.): 646.239, (found)  $[M+H]^+$ : 629.2556; HPLC-MS r\_t: 9.95,  $m/z$   $[M+H]^+$ : 647.3.

**[0221] Methyl 7-(6-chloro-3-(4-(4-chlorobenzyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)heptanoate (WW543)**

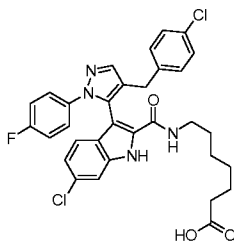


[0222] HRMS (ESI-TOF) m/z (calc.): 620.1757, (found)  $[M+H]^+$ : 643.1620;

[0223]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.17 (2H, m), 1.29 (4.0H, m), 1.61 (2H, m,  $J=7.65$  Hz), 2.31 (2H, t,  $J=7.37$  Hz), 3.15 (1H, td,  $J=6.48, 19.89$  Hz), 3.25 (1H, td,  $J=6.77, 20.45$  Hz), 3.62 (1H, d,  $J=15.49$  Hz), 3.69 (3H, s), 3.71 (1H, d,  $J=15.42$  Hz), 5.54 (1H, t,  $J=5.67$  Hz), 6.86 (2H, t,  $J=8.69$  Hz), 6.89 (2H, d,  $J=8.28$  Hz), 7.11 (1H, d,  $J=8.31$  Hz), 7.13 (1H, s), 7.17 (2H, dd,  $J=4.41, 8.67$  Hz), 7.51 (1H, s), 7.81 (1H, s).

[0224]  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 14.2, 21.1, 24.7, 26.4, 28.7, 29.1, 29.8, 33.9, 39.6, 51.5, 60.4, 104.2, 112.5, 115.9, 116.0, 121.1, 122.7, 123.6, 124.7, 124.8, 126.6, 128.6, 129.6, 129.8, 131.2, 131.7, 132.2, 135.6, 135.6, 135.7, 138.4, 141.0, 160.4, 160.6, 162.3, 171.2, 174.0.

[0225] **7-(6-chloro-3-(4-(4-chlorobenzyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)heptanoic acid (WW544)**

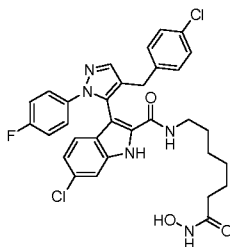


[0226] HRMS (ESI-TOF) m/z (calc.): 606.1601, (found)  $[M+H]^+$ : 605.1530; HPLC-MS r.t: 12.35, m/z  $[M+H]^+$ : 607.3.

[0227]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.11 (2H, m), 1.27 (3H, m), 1.59 (2H, w), 2.37 (2H, w), 2.82 (1H, s), 3.10 (1H, w), 3.20 (1H, w), 3.60 (1H, d,  $J=15.18$  Hz), 3.69 (1H, d,  $J=15.18$  Hz), 5.55 (1H, s), 6.86 (4H, m), 7.12 (5H, m), 7.51 (1H, w), 7.81 (1H, s).

[0228]  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 26.0, 28.3, 28.9, 29.8, 38.6, 39.2, 104.3, 112.6, 115.9, 116.0, 121.0, 122.7, 123.6, 124.8, 124.8, 126.4, 128.6, 129.6, 129.7, 131.3, 131.8, 132.1, 135.5, 135.9, 138.4, 141.0, 160.6, 162.3.

**[0229] 6-chloro-3-(4-(4-chlorobenzyl)-1-(4-fluorophenyl)-1H-pyrazol-5-yl)-N-(7-(hydroxyamino)-7-oxoheptyl)-1H-indole-2-carboxamide (WW558)**

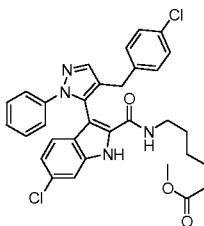


**[0230]** HRMS (ESI-TOF)  $m/z$  (calc.): 621.1710, (found)  $[M+H]^+$ : 622.1808; HPLC-MS r.t: 11.85,  $m/z$   $[M+H]^+$ : 622.3.

**[0231]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.02 (2H, m), 1.27 (5H, m), 1.58 (2H, m), 2.07 (2H, m), 3.01 (1H, m), 3.26 (1H, m), 3.60 (1H, d,  $J=15.18$  Hz), 3.71 (1H, d,  $J=15.24$  Hz), 5.53 (1H, s), 6.87 (3H, m), 7.13 (5H, s), 7.51 (1H, m), 7.82 (1H, s).

**[0232]**  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 28.7, 29.8, 104.2, 111.0, 112.6, 116.0, 116.1, 118.3, 121.0, 122.2, 122.8, 123.6, 125.0, 126.4, 128.6, 129.6, 131.3, 132.1, 132.2, 135.3, 136.6, 138.3, 140.9, 152.1, 160.5.

**[0233] Methyl 8-(6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)octanoate (WW582)**



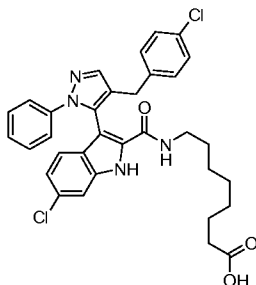
**[0234]** HRMS (ESI-TOF)  $m/z$  (calc.): 616.2008.

**[0235]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.14 (12H, m), 1.30 (6H, s), 1.47 (1H, m), 1.63 (1H, m), 1.73 (1H, m), 2.33 (2H, t,  $J=7.50$  Hz), 3.14 (1H, m), 3.24 (1H, m), 3.63 (1H, d,  $J=15.11$  Hz), 3.70 (3H, s), 3.71 (1H, m), 5.56 (1H, t,  $J=5.48$  Hz), 6.91 (1H, d,  $J=8.31$  Hz), 7.11 (1H, d,  $J=8.58$  Hz), 7.14 (2H, d,  $J=7.98$  Hz), 7.18 (4H, d,  $J=15.90$  Hz), 7.50 (1H, s), 7.83 (1H, s).

**[0236]**  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 24.8, 24.9, 26.5, 27.0, 28.9, 29.0, 29.1, 29.2, 29.9, 34.0, 34.1, 39.6, 40.3, 51.5, 104.5, 112.5, 121.2, 122.6, 123.0, 123.6, 126.6, 127.6,

128.6, 128.7, 129.0, 129.6, 129.8, 129.9, 131.1, 131.6, 132.1, 135.7, 138.5, 139.4,  
141.0, 160.5, 174.2.

**[0237] 8-(6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)octanoic acid (WW587)**

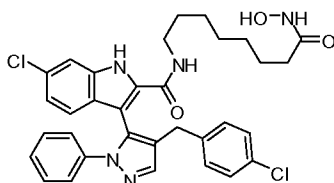


**[0238]** HRMS (ESI-TOF)  $m/z$  (calc.): 602.1851, (found)  $[M+K]^+$ : 641.1529.

**[0239]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.11 (2H, m), 1.28 (9H, m), 1.65 (1H, m), 2.37 (2H, t,  $J=7.37$  Hz), 3.09 (1H, td,  $J=6.55, 20.13$  Hz), 3.20 (1H, td,  $J=6.58, 20.07$  Hz), 3.62 (1H, d,  $J=15.49$  Hz), 3.72 (1H, d,  $J=15.36$  Hz), 5.54 (1H, t,  $J=5.67$  Hz), 6.89 (2H, d,  $J=8.31$  Hz), 7.12 (1H, d,  $J=8.31$  Hz), 7.14 (2H, d,  $J=8.28$  Hz), 7.18 (5H, m), 7.51 (1H, s), 7.84 (1H, s).

**[0240]**  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150.92 MHz):  $\delta$  = 24.6, 26.3, 28.7, 28.8, 29.0, 29.8, 33.8, 39.5, 104.6, 112.5, 121.2, 122.7, 123.0, 123.6, 126.6, 127.6, 128.6, 129.0, 129.6, 129.7, 131.2, 131.6, 132.1, 135.6, 138.5, 139.3, 141.0, 160.5, 177.9.

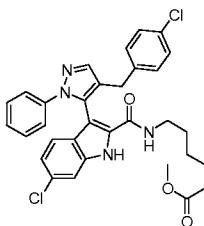
**[0241] 6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-N-(8-(hydroxyamino)-8-oxooctyl)-1H-indole-2-carboxamide (WW588)**



**[0242]** HRMS (ESI-TOF)  $m/z$  (calc.): 617.1960.

**[0243]**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 0.96 (1H, m), 1.00 (2H, m), 1.23 (7H, m), 1.53 (7H, m), 2.08 (2H, m), 2.21 (2H, m), 3.04 (1H, s), 3.18 (1H, s), 3.36 (1H, m), 3.59 (1H, d,  $J=18.60$  Hz), 3.68 (1H, d,  $J=16.86$  Hz), 5.59 (1H, s), 6.87 (1H, m), 7.15 (6H, m), 7.46 (1H, s), 7.77-7.82 (1H, m).

**[0244] Methyl 6-(6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)hexanoate (WW582)**

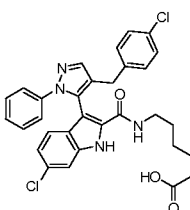


**[0245]** HPLC-MS  $r_t$ : 12.73,  $m/z$   $[M+H]^+$ : 589.2.

**[0246]**  $^1H$ -NMR ( $CDCl_3$ , 600 MHz):  $\delta$  = 1.17 (2H, m), 1.32 (2H, m), 1.61 (2H, m), 1.68 (2H, s), 2.30 (2H, t,  $J=7.49$  Hz), 3.12 (1H, td,  $J=6.57, 20.10$  Hz), 3.24 (1H, td,  $J=6.66, 20.29$  Hz), 3.63 (1H, d,  $J=15.42$  Hz), 3.70 (3H, s), 3.72 (1H, d,  $J=15.42$  Hz), 5.53 (1H, t,  $J=5.67$  Hz), 6.90 (2H, d,  $J=8.31$  Hz), 7.11-7.13 (1H, m), 7.13 (2H, d,  $J=1.74$  Hz), 7.15 (5H, m), 7.49 (1H, d,  $J=1.51$  Hz), 7.82 (1H, s), 10.44 (1H, s).

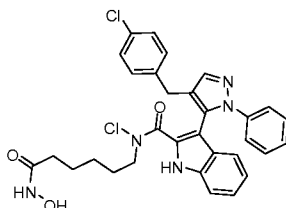
**[0247]**  $^{13}C$ -NMR ( $CDCl_3$ , 150.92 MHz):  $\delta$  = 24.5, 26.2, 29.0, 29.9, 33.8, 39.4, 51.6, 104.6, 112.4, 121.3, 122.6, 122.9, 123.6, 126.7, 127.6, 128.6, 129.0, 129.6, 129.8, 131.2, 131.5, 132.1, 135.6, 138.5, 139.4, 141.0, 160.4, 173.9.

**[0248] 6-(6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamido)hexanoic acid (WW585)**



**[0249]** HPLC-MS  $r_t$ : 12.39,  $m/z$   $[M+K]^+$ : 603.2.

**[0250] 6-chloro-3-(4-(4-chlorobenzyl)-1-phenyl-1H-pyrazol-5-yl)-N-(6-(hydroxyamino)-6-oxohexyl)-1H-indole-2-carboxamide (WW590)**

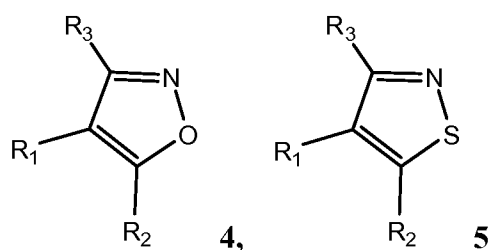


**[0251]** HPLC-MS  $r_t$ : 11.86,  $m/z$   $[M+H]^+$ : 590.3.

[0252]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 0.89-0.97 (2H, d, m), 1.28 (3H, s), 1.73 (7H, m), 3.13 (1H, m), 3.36 (1H, m), 3.65 (1H, m), 5.57 (1H, s), 6.87 (1H, s), 7.15 (3H, m), 7.46 (1H, s), 7.88 (1H, s).

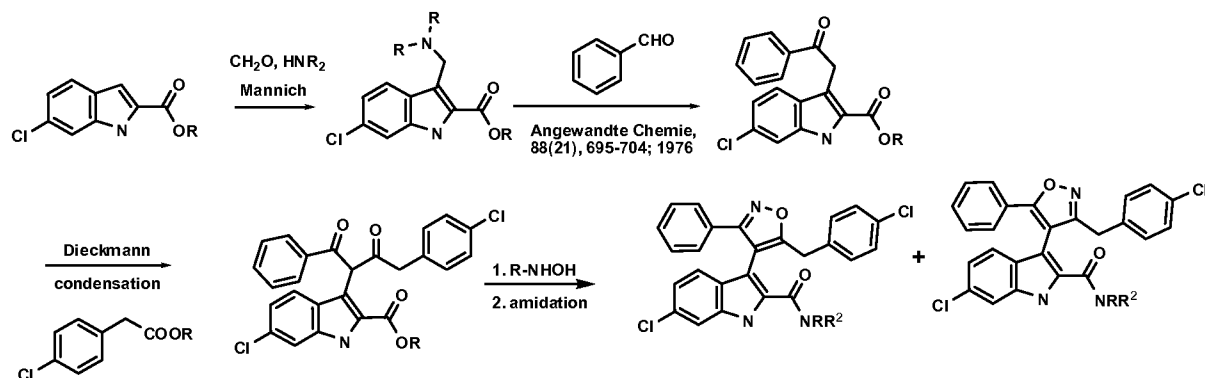
### 5. The Isoxazole and Isothiazole Scaffolds

[0253] In another aspect of this invention, are provided methods for generating inventive compounds that have an isoxazole core (Formula 4), or a isothiazole core (Formula 5).



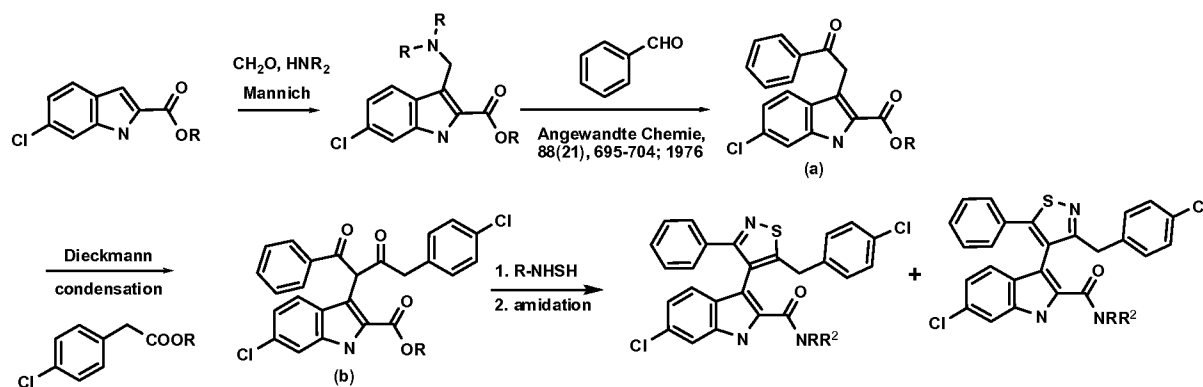
[0254] Synthesis of compounds that comport to Formula 4 will be achieved as illustrated in Scheme 7.

#### Scheme 7



[0255] Thus, reaction of the indole with aldehyde followed by Dieckmann condensation of (a) with a benzyl ester results in the  $\alpha,\beta$ -diketone (b), which is allowed to react with a hydroxylamine to give the corresponding isoxazole. The isothiazoles are obtained in a similar manner by reacting (b) with a thiohydroxylamine as shown in Scheme 8.

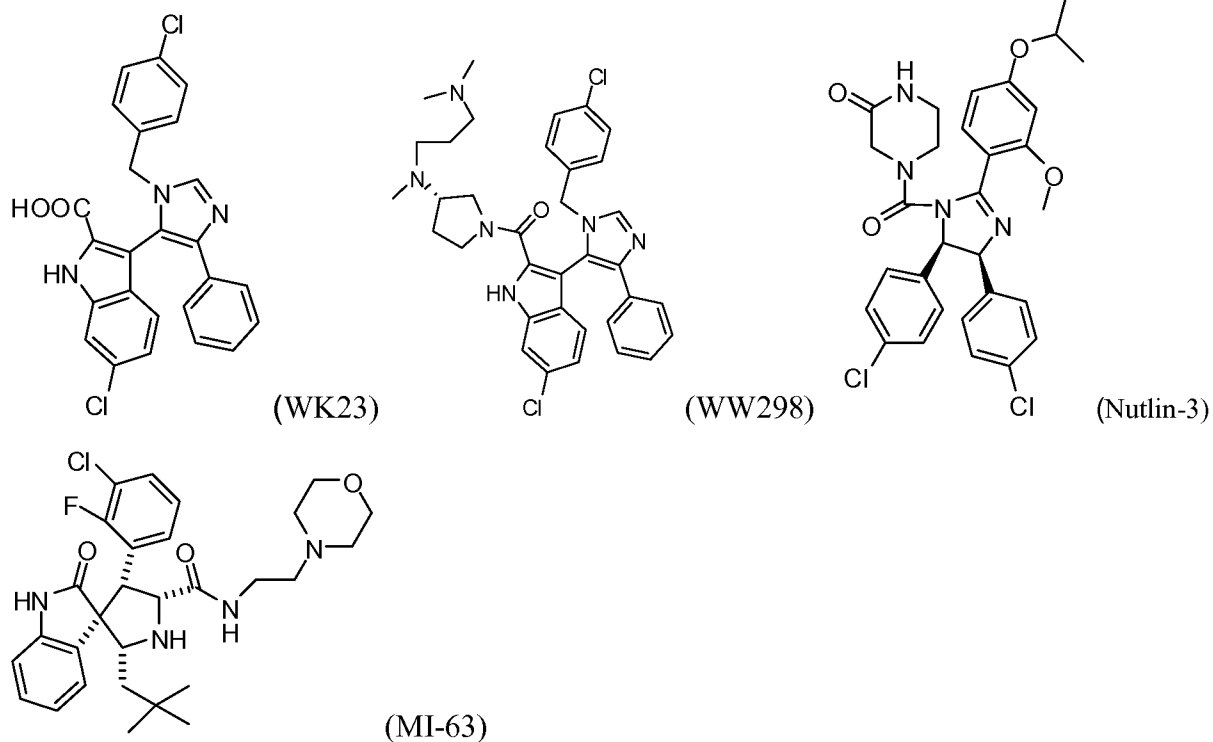
## Scheme 8



## BIOLOGICAL ACTIVITY OF INVENTIVE COMPOUNDS

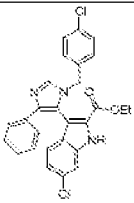
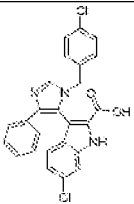
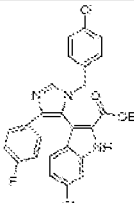
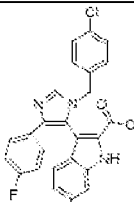
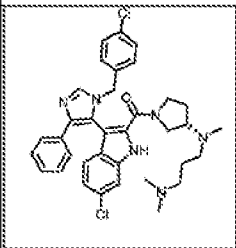
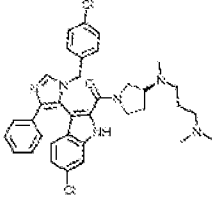
*a. Protein Inhibition Studies*

[0256] Inventive compounds are potent antagonists of the p53/MDM2 and p53/MDM4 complex based on fluorescent polarization analysis, AIDA NMR and HSQC NMR analysis. Figure 5 compares the binding curve for an inventive compound that belongs to the imidazole-indole class (WK23), to the binding curves of known antagonists, namely, WW298, Nutlin-3 and a spiro-oxindole compound (MI-63). The structures for compounds used in this study are as follows:



**[0257]** As illustrated in this figure, the inventive compound WK23 had weaker binding affinity to MDM2 when compared to the affinity of other known antagonists, and yet WK23 showed greater affinity for MDM4 than Nutlin-3 and had a similar affinity for MDM4 as WW298. Table 1 provides protein inhibition data for additional compounds that belong to the imidazole-indole class, while Table 2 presents data from protein inhibition studies for a representative group of the pyrazolo-indole-class compounds.

**Table 1:** Fluorescence polarization binding assay. Measured binding constants of MDM2 and MDMX ligands.

		MDM2		MDMX	
		Ki[ $\mu$ M]			Ki[ $\mu$ M]
WK21		n.i.			n.a.
WK23		0.916			36
WK29B		n.a.			n.a.
WK211A		0.3			n.a.
WK297		0.2			Low interaction (ca.50)
WK298		0.109			11

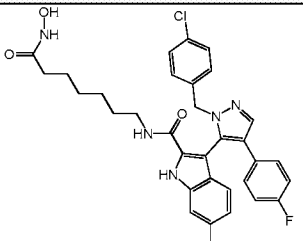
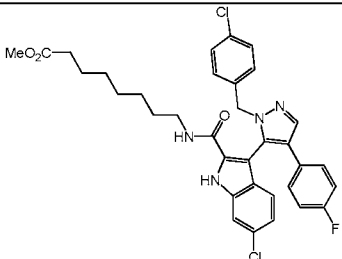
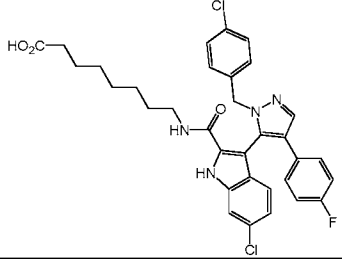
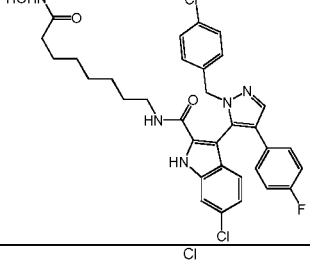
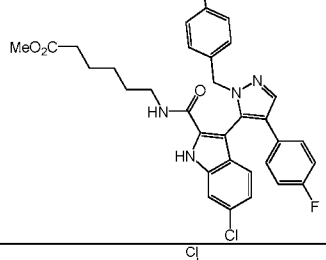
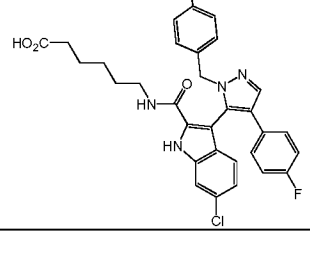
n.i. no interaction.

n.a. could not be measured because of the high fluorescence of the compound.

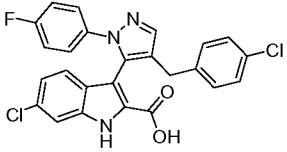
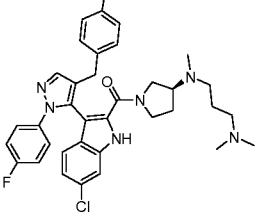
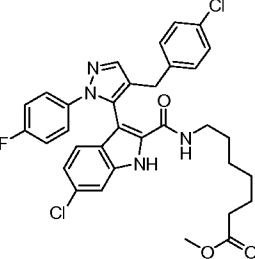
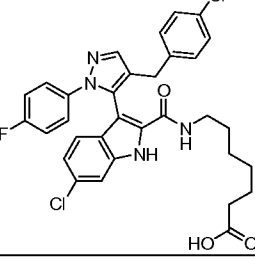
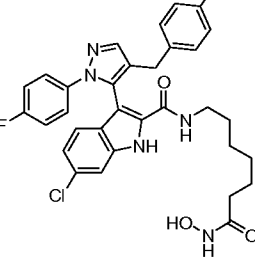
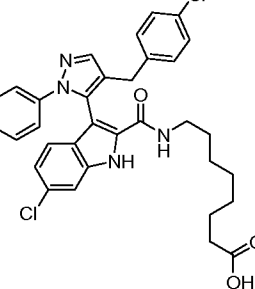
Table 2

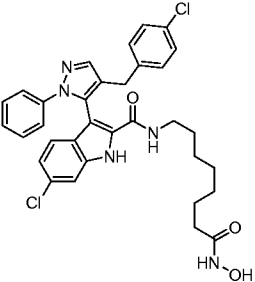
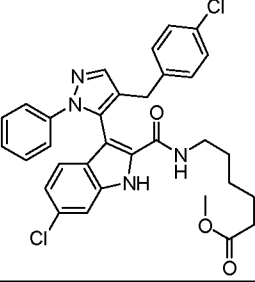
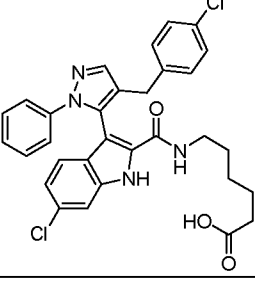
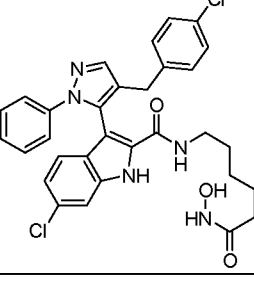
Compound	MW	Structure	Ki(MDM2/P5) [ $\mu$ M]	Ki (MDMX/P4) [ $\mu$ M]
YH262	427.10875		1.4	12
YH215	490.38054		30	<60
YH245	462.32738		0.3	10
YH249	629.62182		3.4	<60
YH250	603.53818		<60	<60
YH254	589.5116		0.4	15

Compound	MW	Structure	Ki(MDM2/P5) [ $\mu$ M]	Ki (MDMX/P4) [ $\mu$ M]
YH256	604.52624		1.2	<60
YH263	507.09166		Low solubility	<60
YH264	479.06036		0.1	23
YH265	646.23899		0.02	fluorescent
YH266	620.17572		Low solubility	<60
YH267	606.16007		0.6	45

Compound	MW	Structure	Ki(MDM2/P5) [ $\mu$ M]	Ki (MDMX/P4) [ $\mu$ M]
YH268	621.17097		1.3	35
YH271	634.19137		> 55	<60
YH272	620.17572		1.2	<60
YH273	635.18662		2	<60
YH275	606.16007		20	<60
YH276	592.14442		0.9	<60

Compound	MW	Structure	Ki(MDM2/P5) [ $\mu$ M]	Ki (MDMX/P4) [ $\mu$ M]
YH277	607.15532		0.8	<60
WW509	490.381		50	15
WW512	462.327		0.4	10
WW536	629.622		0.7	>50
WW535	603.538		<60	<60
WW540	604.5262		0.23	9.8
WW538	589.512		1	29

Compound	MW	Structure	Ki(MDM2/P5) [ $\mu$ M]	Ki (MDMX/P4) [ $\mu$ M]
WW519	480.318		0.2	19
WW529	647.612		2	<60
WW543	621.529		c.a. 50	20
WW544	607.502		1.4	26
WW558	622.517		4	23
WW587	603.5382		2.7	>30

Compound	MW	Structure	Ki(MDM2/P5) [ $\mu$ M]	Ki (MDMX/P4) [ $\mu$ M]
WW588	618.5528		2	>30
WW582	589.5116		> 50	> 30
WW585	575.485		2.6	<60
WW590	590.4997		2.7	30

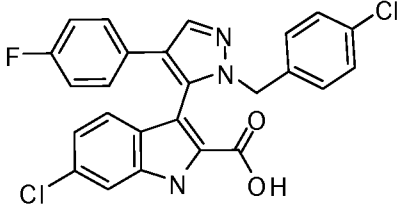
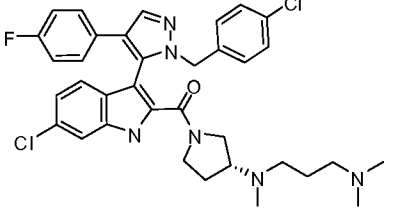
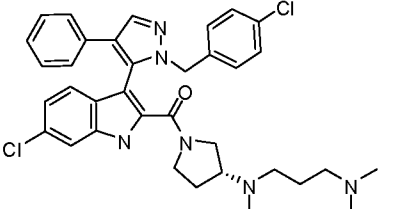
**[0258]** As illustrated in Table 1 above, compounds in accordance with the present invention have affinity for both MDM2 and MDM4 proteins. Accordingly, the inventive compounds are dual action antagonists and are candidate therapeutics for treating cell proliferative disorders such as cancer.

**[0259]** Exemplary inventive compounds also were tested for their ability to disrupt p53-hMDM2 protein-protein interaction, using a fluorescent based biosensor assay described, for example, by Dudgeon *et al.*, *J. Biomol. Screen.* 15: 766-82 (2010), and by Dudgeon *et al.*, *Assay and Drug Development Technologies* 8: 437-58 (2010). Briefly, U2OS cells are co-

infected with adenovirus constructs expressing a p53-monomeric TagGFP protein having a nuclear localization sequence (NLS) and a hDM2-monomeric Tag RFP cytoplasm-nucleus shuttling protein interaction partner having a NLS and a nuclear export sequence (NES). Initially, the hDM2 protein component binds to the p53 component and both proteins are localized in the nucleolus. Treatment of cells using an inventive compound disrupts the p53-hDM2 protein-protein interaction, which results in an export and redistribution of the unbound hDM2-RFP component in the cellular cytoplasm. The disruption of the hDM2-p53 biosensor interaction is determined via a molecular translocation image analysis algorithm that measures the difference in the average fluorescent intensity associated with hDM2-RFP component in the cytoplasm and nuclear compartments. See Dudgeon *et al.*, *J. Biomol. Screen.* 15: 766-82 (2010), and Dudgeon *et al.*, *Assay and Drug Development Technologies* 8: 437-58 (2010).

[0260] As shown in Table 3 below, the inventive compounds were potent disrupters of cellular protein-protein interactions with potencies in the low micromolar range.

**Table 3**

ID No.	Structure	Potency $\mu\text{M}$ (Biosensor Assay)	Solubility* (mg/ml)
YH264		13	1.5
YH265		1.8	0.5
WW536		9	0.5

[0261] Alternatively, the NMR-based technique “Antagonist Induced Dissociation Assay (AIDA-NMR),” can be used to study an antagonist’s ability to disrupt a protein-protein interaction. See Bista et al., *JACS*, Vol. 131, pp7500-7501, (2009). An advantage to using AIDA to study disruption of protein-protein interactions is that this NMR based method provides unambiguous information on whether the antagonist activity of a compound is strong enough to dissociate a protein-protein complex and whether dissociation is through precipitation, denaturation or release of a protein in its functional folded state. AIDA has revealed that compounds in accordance with the present invention are potent disrupters of MDM2- or MDMX-p53 protein complexes and are thus suitable as therapeutics directed to the treatment of cell proliferative disorders.

[0262] Accordingly, the present invention provides a method for treating cell proliferative disorders using an agent that is selected from a compound comporting with Formula 1, its salt, prodrug, solvate, stereoisomer, or tautomer or by using a pharmaceutically acceptable formulation of such agent with a pharmaceutically acceptable carrier.

*b. NCI60 Cancer Cell Screening*

[0263] Compounds in accordance with this invention were tested for their ability to arrest the growth of cancer cells in culture. Specifically, exemplary compounds were submitted to the National Institute of Cancer for inclusion into their screening assay encompassing a variety of different cancer cell lines. See Figures 7A-7C. Briefly, a single 10  $\mu$ M dose of the test compound dissolved in a suitable solvent is added to each well of a tissue culture plate containing the desired cancer cells plated at a known cell density in a tissue culture plate.

[0264] After incubation for a fixed period of time the cell density and viability is determined for each well of the tissue culture plate. The percent inhibition by a representative compound of this invention for each cancer cell line included in the screen is graphically represented in Figures 7A-7C. The data illustrate that the inventive compounds do arrest the growth of various cancer cells in culture, with compound YH265 exhibiting the most potency against colon, melanoma, and CNS cancer cells.

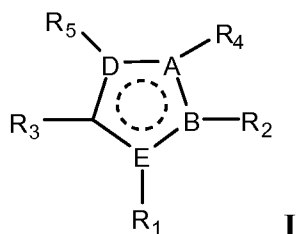
## PHARMACEUTICALLY ACCEPTABLE FORMULATIONS

[0265] Despite evidence suggesting that the regulatory role of the p53 tumor suppressor protein is compromised in many cancer cells by sequestration to its negative regulators, MDM2 and MDMX, there are no known anticancer therapies that target the disruption of MDM2-p53 or MDMX-p53 protein-protein interactions. In some embodiments, compounds of the invention and their pharmaceutically acceptable formulations provide a novel method for treating cancer. Pharmaceutically acceptable formulations in accordance with the present invention are manufactured using the inventive compounds, its prodrug or a pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer and a pharmaceutically acceptable carrier. For Formula I compounds, the polar amino and sulfonamide groups can promote hydrophilic interactions, such as hydrogen bonding with conventional aqueous carrier solvents, such as saline. Inventive compounds that do not readily dissolve in an aqueous medium, however, can be formulated by adding to the aqueous medium, pharmaceutically acceptable hydrophobic solvents, such as poly-alkylene glycol gelatin, gum arabic, lactose, starch, petroleum jelly and vegetable oil. By the same token, aqueous carriers can be used to formulate the hydrophilic Formulae III compounds. Accordingly, several Formula I compounds showed good aqueous solubility in pH 7.0, phosphate buffer. See Table 3. Additional excipients, such as flavoring agents, preservatives, stabilizers, emulsifying agents, buffers and the like may be added in accordance with accepted practices of pharmaceutical compounding.

[0266] A formulation of a compound of this invention can be administered intravenously, intraperitoneally, orally, buccally, or by parenteral administration. The compounds can be formulated, alone or together with other known antineoplastic agents, in suitable unit dosage formulations that may contain conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles, as described above, which are appropriate for each route of administration. The invention also contemplates administration of the compounds of the invention in a depot formulation, in which the active ingredient is released over a defined time period.

**WHAT IS CLAIMED IS:**


1. A compound according to formula I



wherein:

$R_1$ , is an indole;

$R_2$  and  $R_3$  are different from each other and are phenyl or benzyl;

 indicates the presence of one or more optional double bonds;

$R_4$  and  $R_5$  are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>8</sub>)alkyl, and (C<sub>3</sub>-C<sub>14</sub>)aryl;

$R^a$  and  $R^b$  are independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, hydroxide, (C<sub>1</sub>-C<sub>8</sub>)alkylS(O)<sub>2</sub>-, (C<sub>1</sub>-C<sub>8</sub>)haloalkylS(O)<sub>2</sub>-, (C<sub>1</sub>-C<sub>8</sub>)hydroxyalkylS(O)<sub>2</sub>-, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-COOR<sup>c</sup>, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-COR<sup>c</sup> and optionally substituted (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl;

wherein

$R^a$  and  $R^b$  together with the nitrogen atom to which they are bound can form a (C<sub>3</sub>-C<sub>6</sub>)heterocycloalkyl, or a (C<sub>3</sub>-C<sub>6</sub>)heteroaryl;

$R^c$  is selected from the group consisting H, (C<sub>1</sub>-C<sub>8</sub>)alkyl; -NH(OH); and

A, B, D and E are independently -CR<sub>1</sub>, -CR<sub>2</sub>, -CR<sub>4</sub>, -CR<sub>5</sub>, -N, -O, or -S, provided that

when A, D and E are each -N then B is -CR<sub>2</sub>,

when A is -N, B is -NR<sub>2</sub>, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>, and

when A is -NR<sub>4</sub>, B is N, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>,

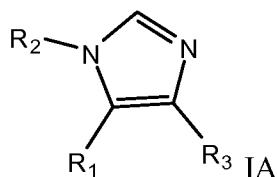
when in A is -N, B is -O, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>, and

when A is -N, B is -S, and D is -CR<sub>5</sub> then E is -CR<sub>1</sub>,

and wherein

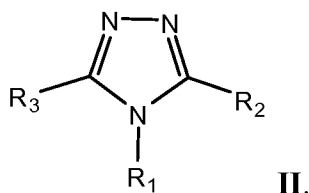
the aforementioned indole, phenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heterocycloalkyl, (C<sub>3</sub>-C<sub>6</sub>)heteroaryl or benzyl groups may be substituted with one or more members selected from the group consisting of halogen, -OH, oxo, -COOR<sup>a</sup>, -C(O)R<sup>a</sup>, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-COOR<sup>a</sup>, -(C<sub>1</sub>-C<sub>8</sub>)alkyl-NR<sup>a</sup>R<sup>b</sup>, S(O)<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -C(O)NR<sup>a</sup>R<sup>b</sup>, (C<sub>3</sub>-C<sub>14</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkylene-, -CN, -NO<sub>2</sub>, NR<sup>a</sup>R<sup>b</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkyl-S-, (C<sub>3</sub>-C<sub>14</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>14</sub>)heterocycloalkyl, (C<sub>3</sub>-C<sub>14</sub>)aryl, (C<sub>3</sub>-C<sub>14</sub>)heteroaryl, -C(O)NH-(C<sub>1</sub>-C<sub>6</sub>)alkyl, -NHC(O)-(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)haloalkyl, -C(O)-(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl-NR<sup>a</sup>R<sup>b</sup> and (C<sub>1</sub>-C<sub>6</sub>)hydroxyalkyl.

2. The compound according to claim 1, wherein said compound is a substituted imidazole represented by Formula IA

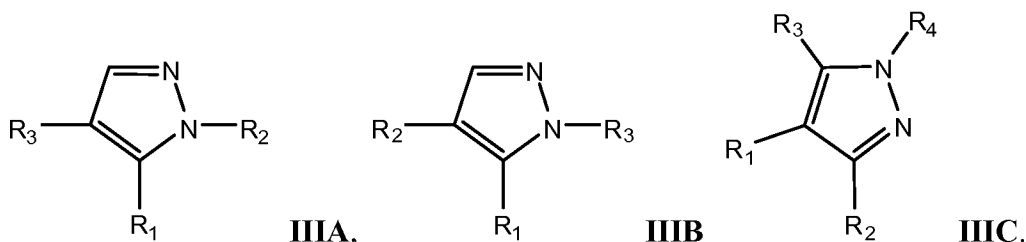


3. The compound according to claim 2, wherein R<sub>1</sub> is 6-chloroindole, R<sub>2</sub> is 4-chlorobenzyl and R<sub>3</sub> is phenyl.

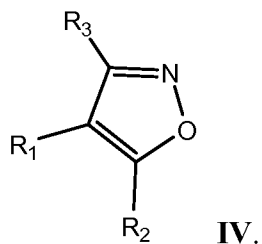
4. The compound according to claim 1, wherein said compound is a substituted triazole represented by Formula II



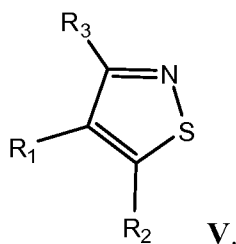
5. The compound according to claim 1, wherein said compound is a substituted pyrazole represented by Formulae IIIA, IIIB or IIIC



6. The compound according to claim 1, wherein said compound is a substituted isoxazole represented by Formulae IV

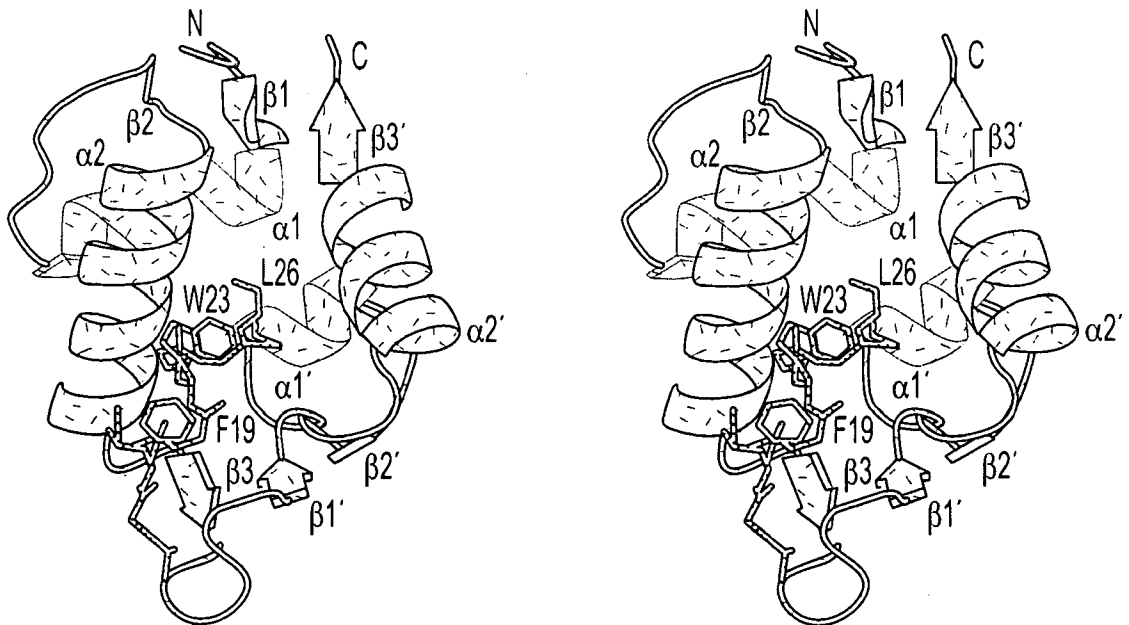
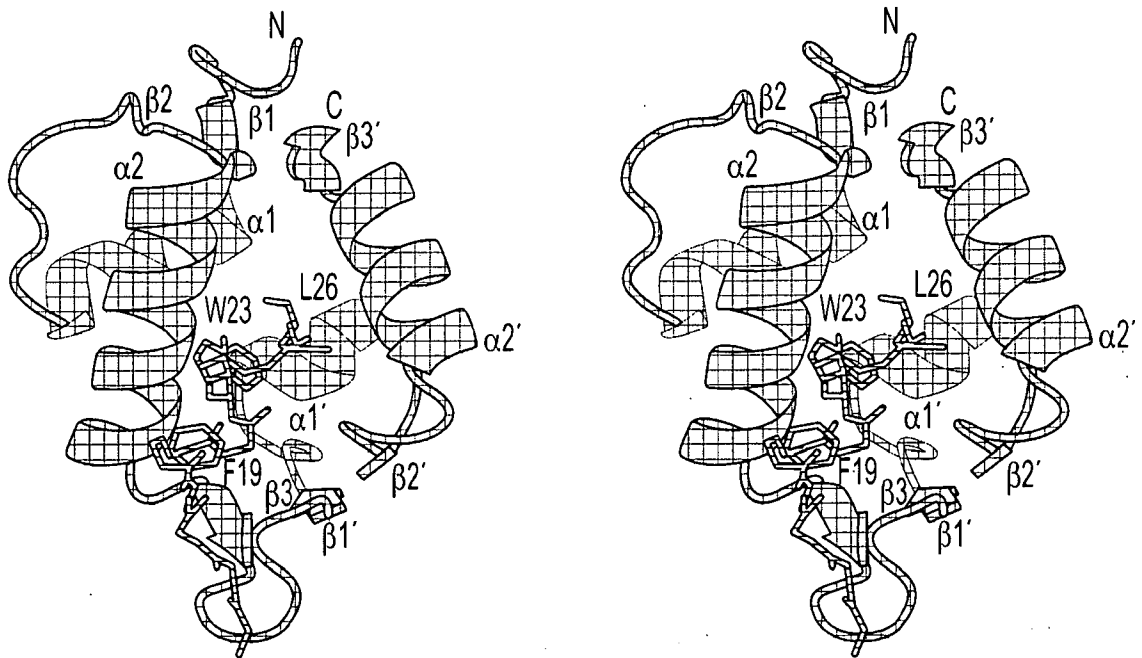


7. The compound according to claim 1, wherein said compound is a substituted isothiazole represented by Formulae V



8. A pharmaceutical composition that comprises (A) a therapeutically effective amount of at least one compound according to any of claims 1 to 7 and (B) a pharmaceutically acceptable carrier therefor.

9. A method for treating a cell proliferative disorder, comprising contacting a cell with at least one compound according to any of claims 1 to 7.



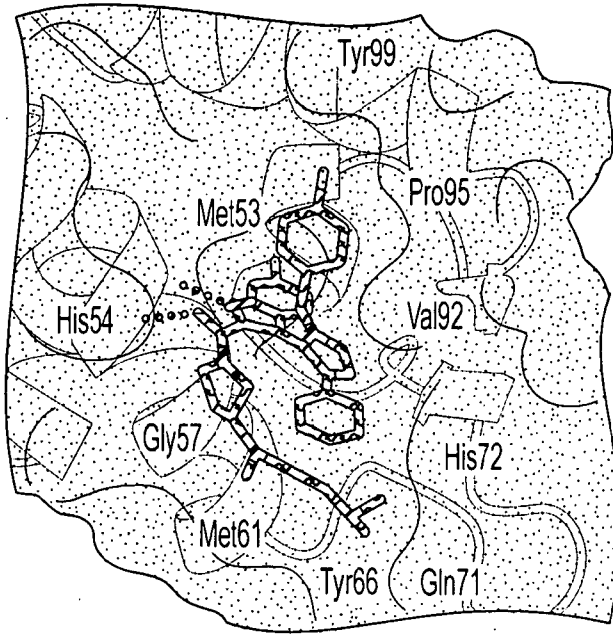


FIG. 2A

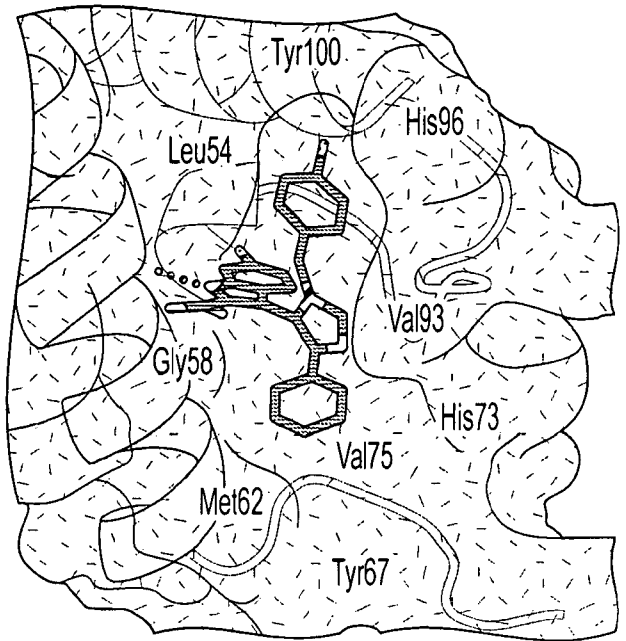


FIG. 2B

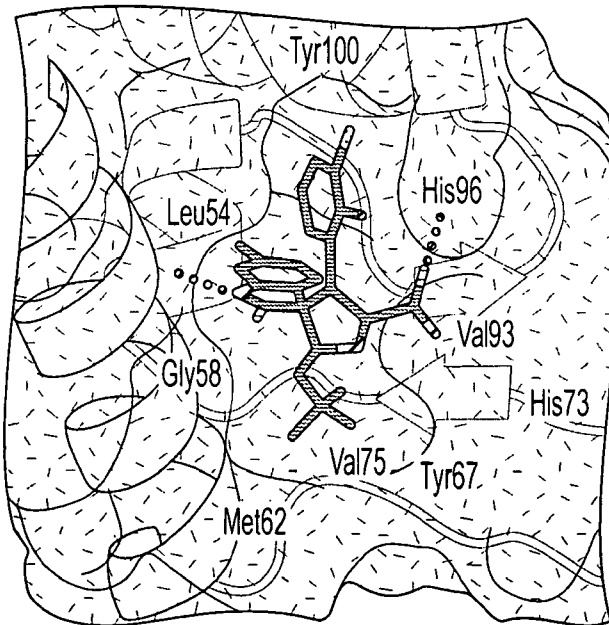


FIG. 2C

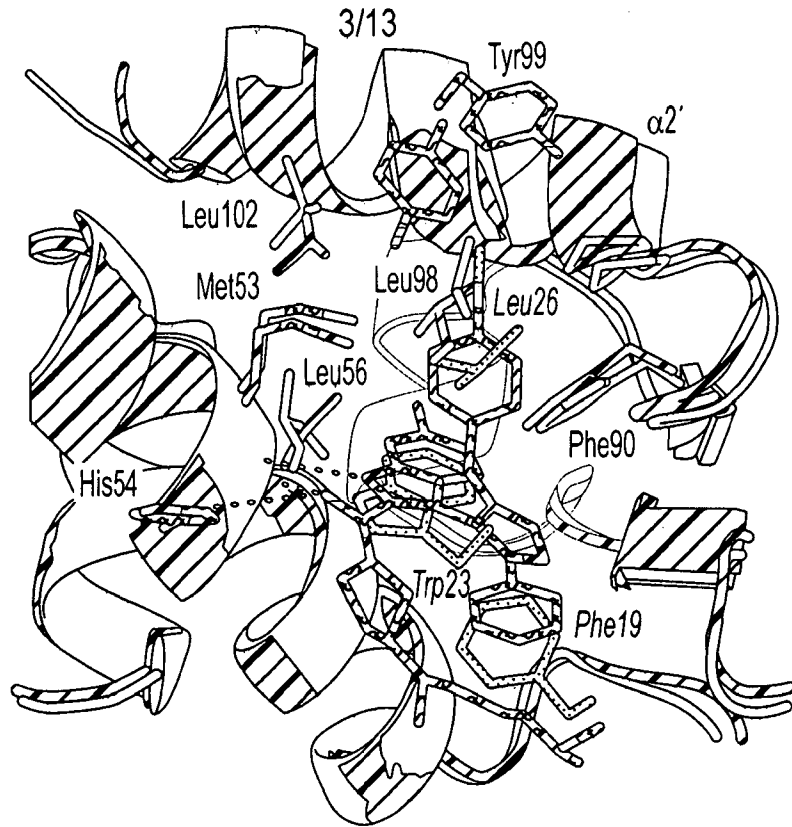


FIG. 3

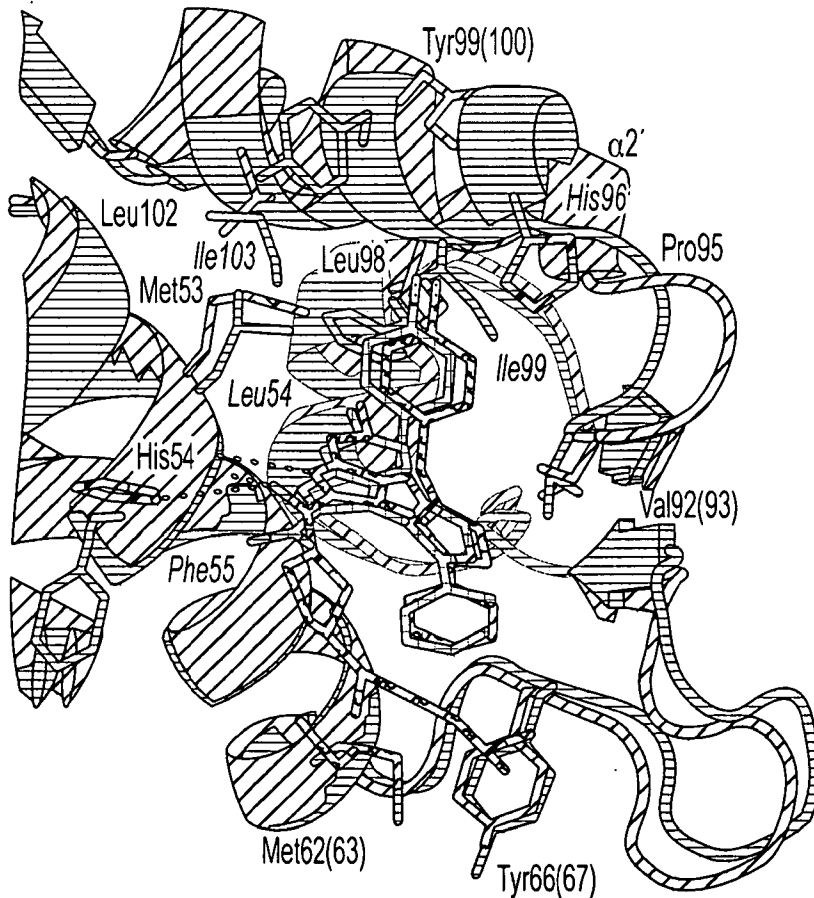


FIG. 4

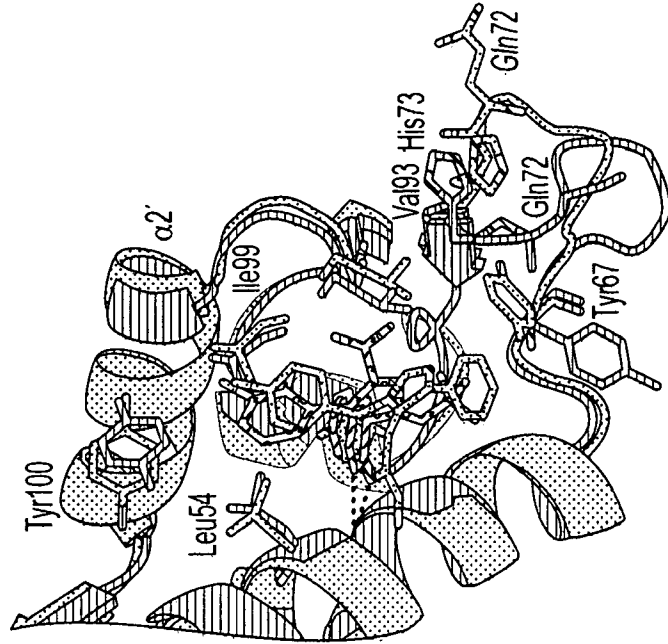


FIG. 6

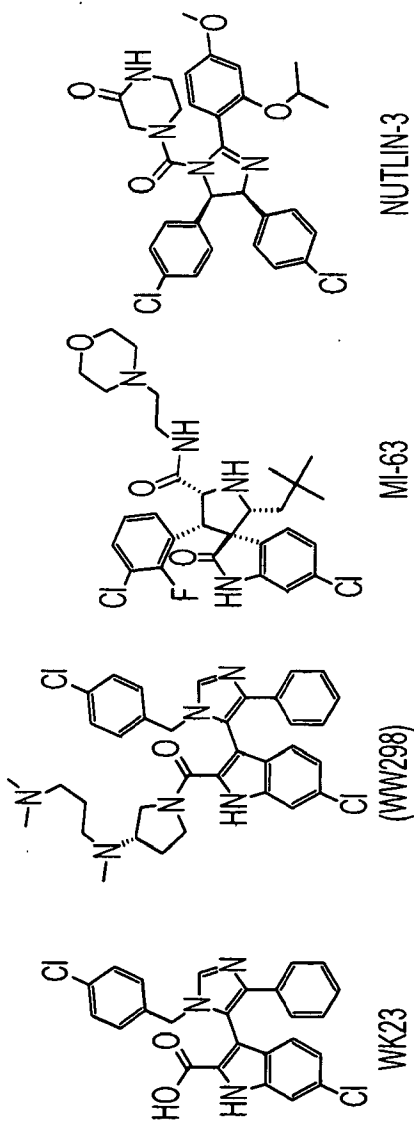


FIG. 5A

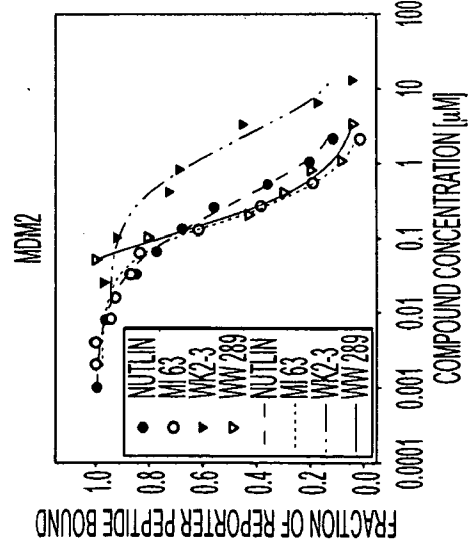
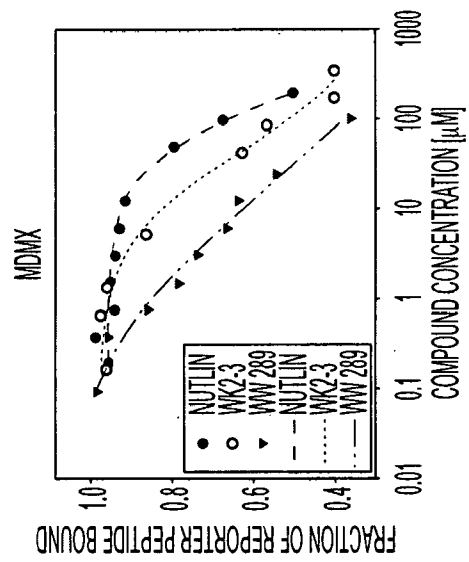
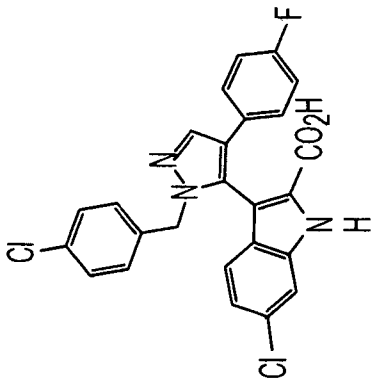


FIG. 5B

5/13



0.1 uM (Mdm2)  
23 uM (Mdm4)

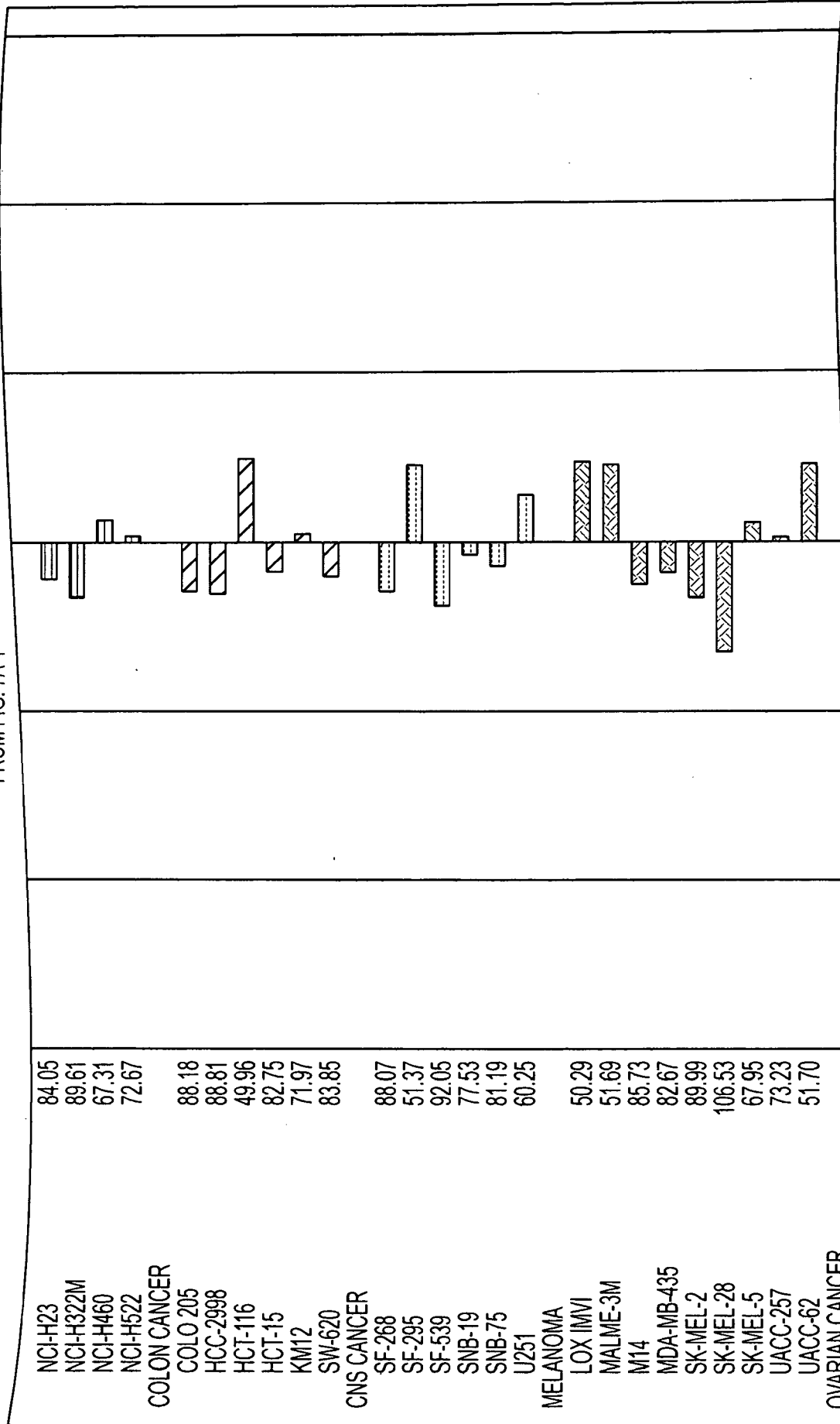
DEVELOPMENTAL THERAPEUTICS PROGRAM ONE DOSE MEAN GRAPH		NSC: D-754938 / 1	CONC: 1.00E-5 MOLAR	TEST DATE: DEC 06, 2010
		EXPERIMENT ID: 10120569		
PANEL/CELL LINE	GROWTH PERCENT	MEAN GROWTH PERCENT-GROWTH PERCENT		
LEUKEMIA		[Bar chart showing growth percent for leukemia cell lines]		
CCR6-CEM	-22.48			
HL-60(TB)	-2.51			
K-562	54.39			
RPMI-8226	34.94			
SR	26.06			
NON-SMALL CELL LUNG CANCER		[Bar chart showing growth percent for non-small cell lung cancer cell lines]		
A549/ATCC	86.59			
EKVX	54.10			
HOP-62	80.06			
NCI-H226	78.60			

TO FIG. 7A-2

FIG. 7A-1

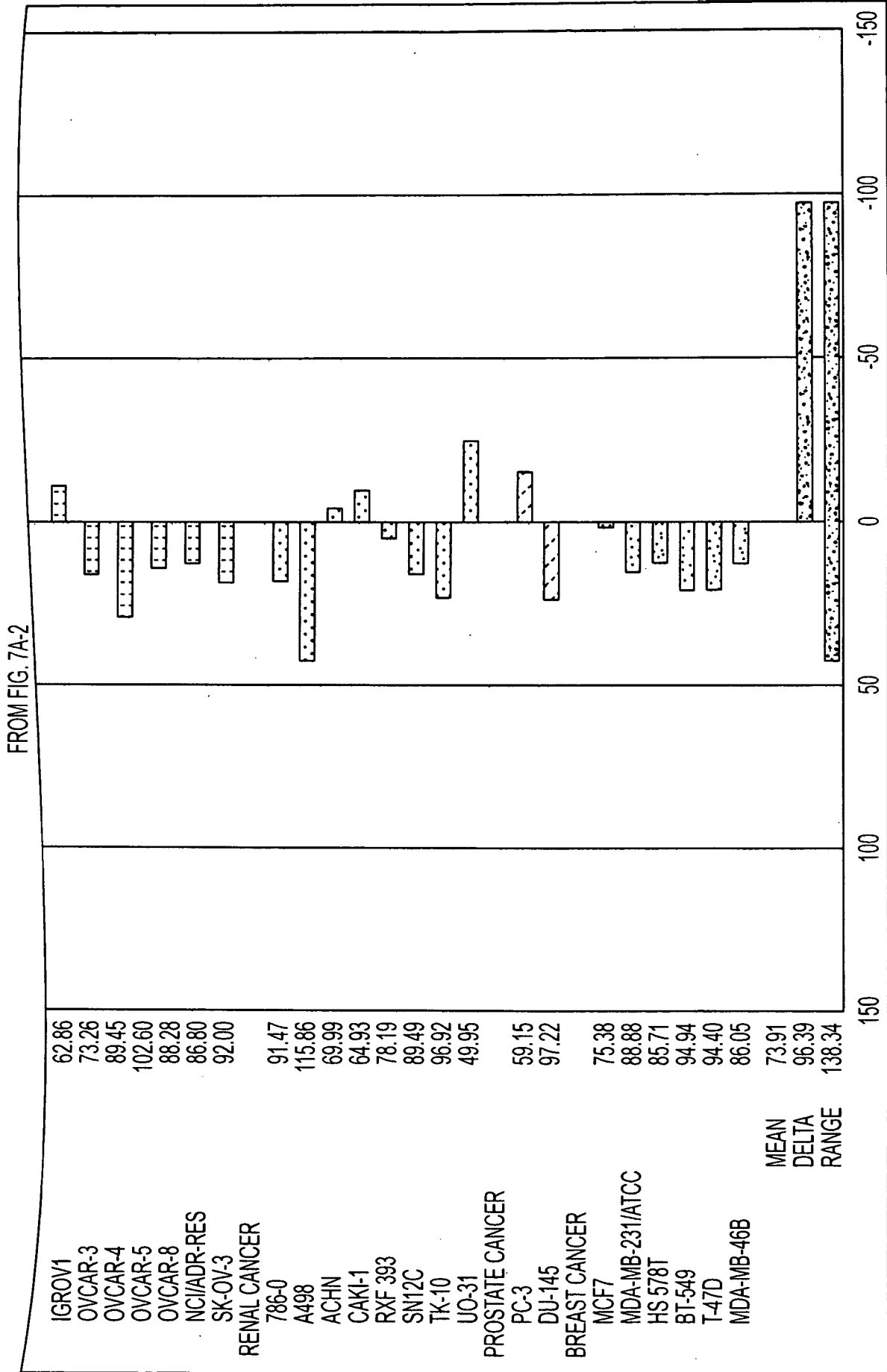
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FROM FIG. 7A-1

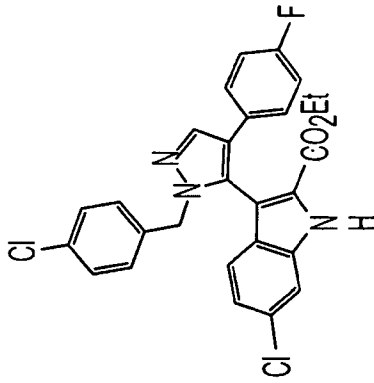


TO FIG. 7A-3

FIG. 7A-2



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**YH263**

N.A. (Mdm2)

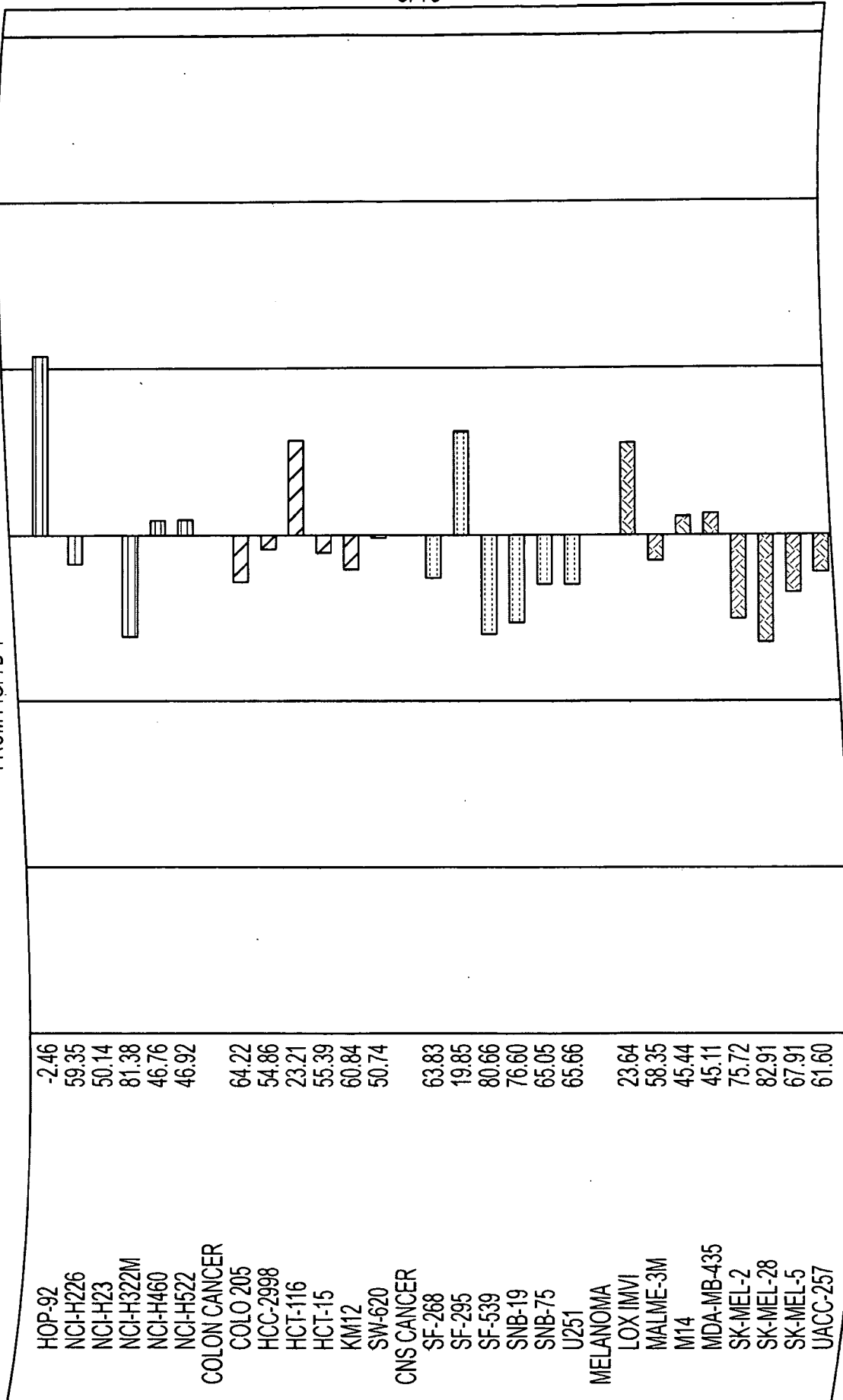
DEVELOPMENTAL THERAPEUTICS PROGRAM ONE DOSE MEAN GRAPH		NSC: D-754937 / 1	CONC: 1.00E-5 MOLAR	TEST DATE: DEC 06, 2010
		EXPERIMENT ID: 10120S69		
PANEL/CELL LINE	GROWTH PERCENT	MEAN GROWTH PERCENT-GROWTH PERCENT		
LEUKEMIA		[Bar chart showing growth percent for leukemia cell lines]		
CCR5-CEM	-50.78			
HL-60(TB)	13.08			
K-562	34.00			
MOLT-4	38.45			
RPMI-8226	30.86			
SR	49.55			
NON-SMALL CELL LUNG CANCER		[Bar chart showing growth percent for non-small cell lung cancer cell lines]		
A549/ATCC	56.17			
EKVX	42.55			
HOP-62	65.47			

TO FIG. 7B-2

**FIG. 7B-1**

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FROM FIG. 7B-1



TO FIG. 7B-3

FIG. 7B-2

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FROM FIG. 7B-2

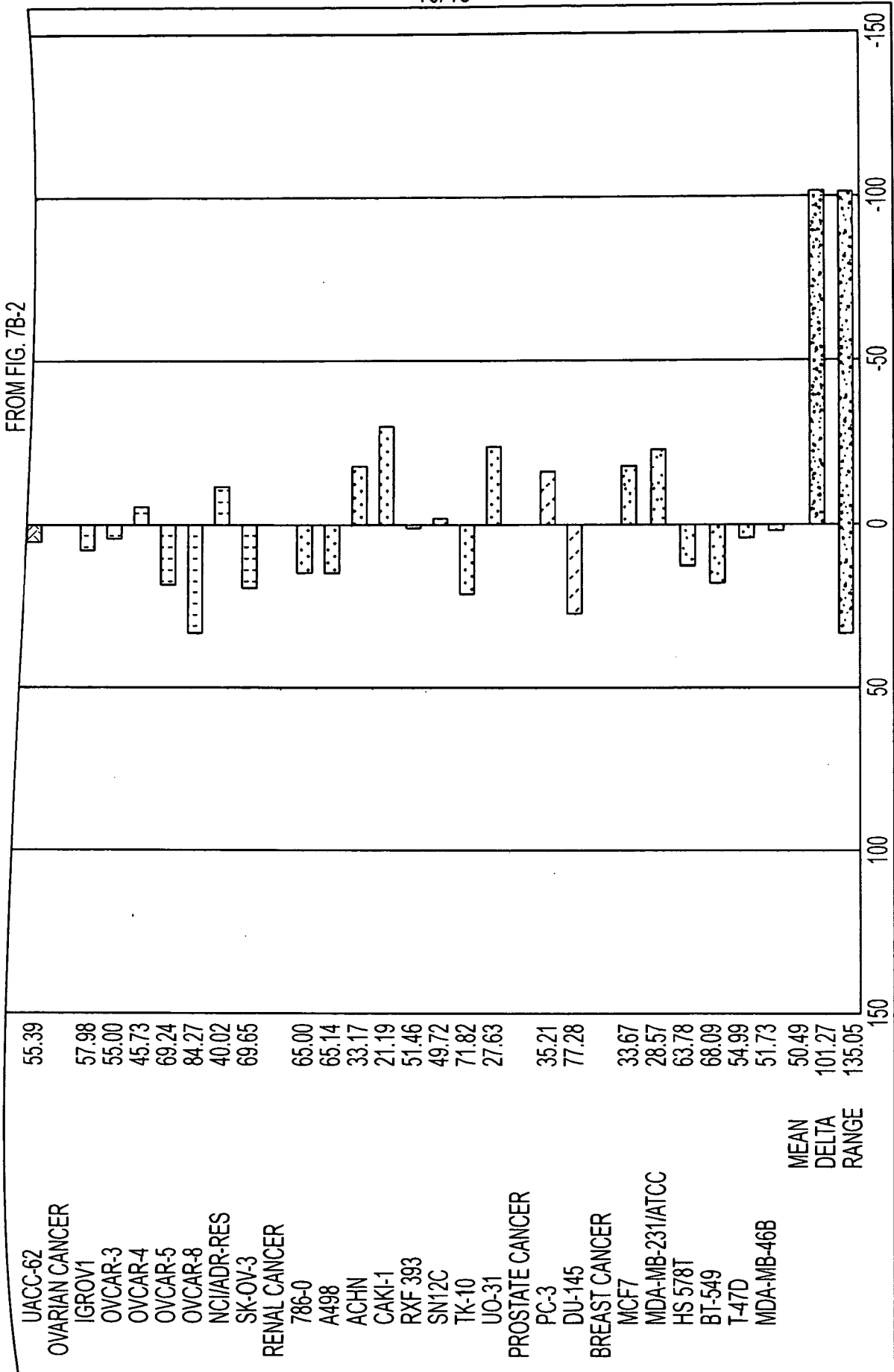
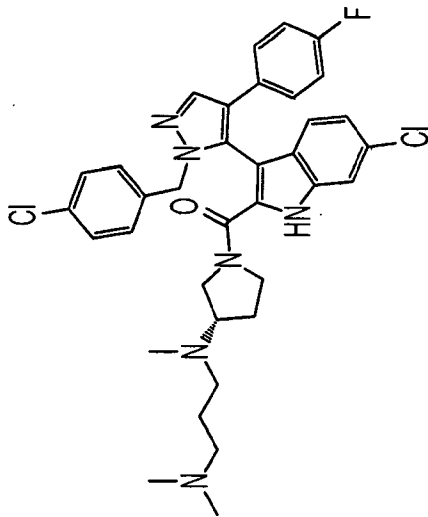


FIG. 7B-3

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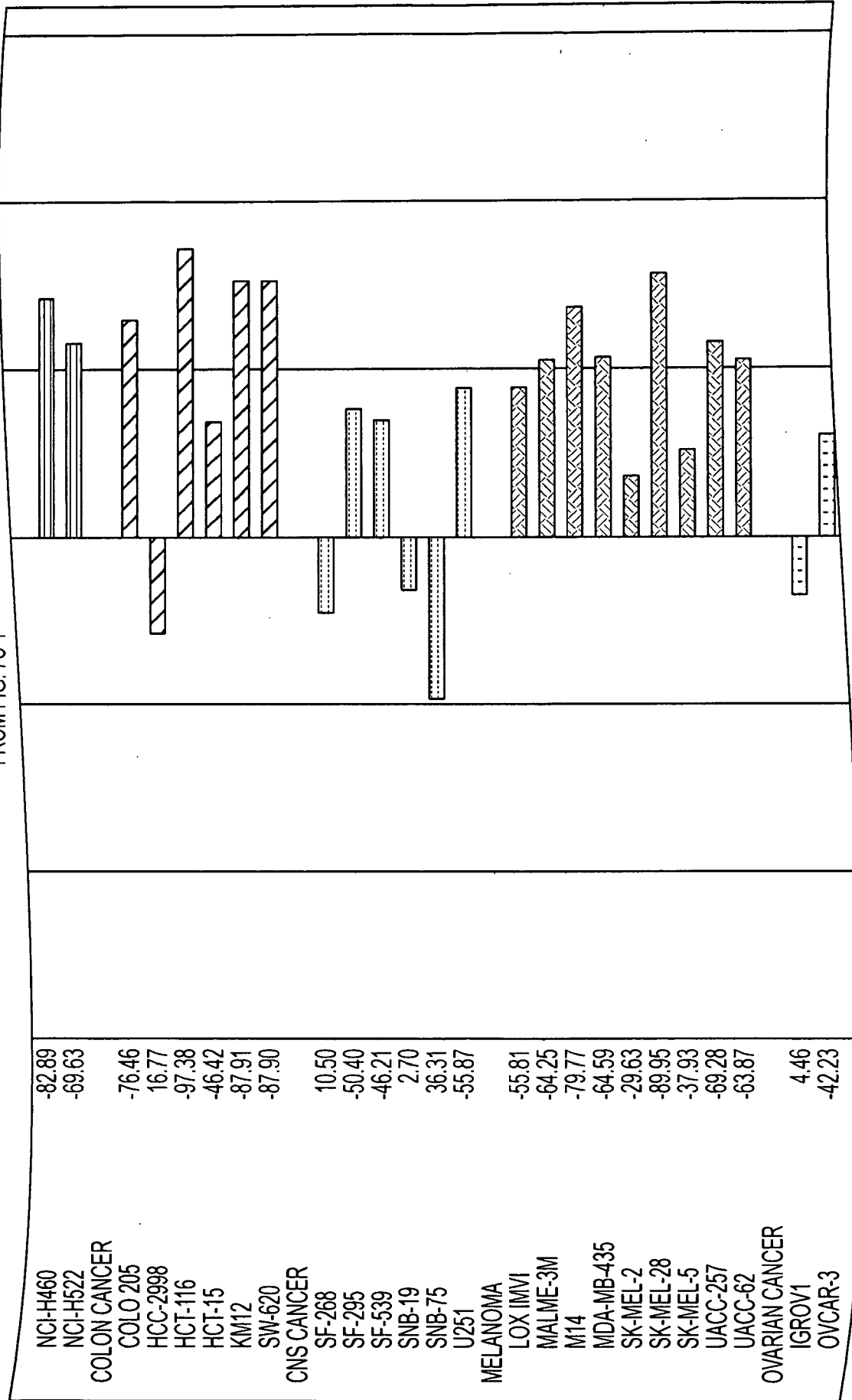
**YH265** 0.02  $\mu$ M (Mdm2)

DEVELOPMENTAL THERAPEUTICS PROGRAM ONE DOSE MEAN GRAPH		NSC: D-754939 / 1	CONC: 1.00E-5 MOLAR	TEST DATE: DEC 06, 2010
		EXPERIMENT ID: 10120S69		
PANEL/CELL LINE	GROWTH PERCENT	MEAN GROWTH PERCENT-GROWTH PERCENT		
<b>LEUKEMIA</b>				
CCRF-CEM	-17.30	[Bar chart showing growth percent for CCRF-CEM]		
RPMI-8226	-40.94	[Bar chart showing growth percent for RPMI-8226]		
<b>NON-SMALL CELL LUNG CANCER</b>				
A549/ATCC	37.52	[Bar chart showing growth percent for A549/ATCC]		
EKVX	35.42	[Bar chart showing growth percent for EKVX]		
HOP-62	-31.87	[Bar chart showing growth percent for HOP-62]		
HOP-92	-10.12	[Bar chart showing growth percent for HOP-92]		
NCI-H226	52.91	[Bar chart showing growth percent for NCI-H226]		
NCI-H23	42.86	[Bar chart showing growth percent for NCI-H23]		
NCI-H322M	32.96	[Bar chart showing growth percent for NCI-H322M]		

TO FIG. 7C-2

**FIG. 7C-1**

FROM FIG. 7C-1



TO FIG. 7C-2

FIG. 7C-2

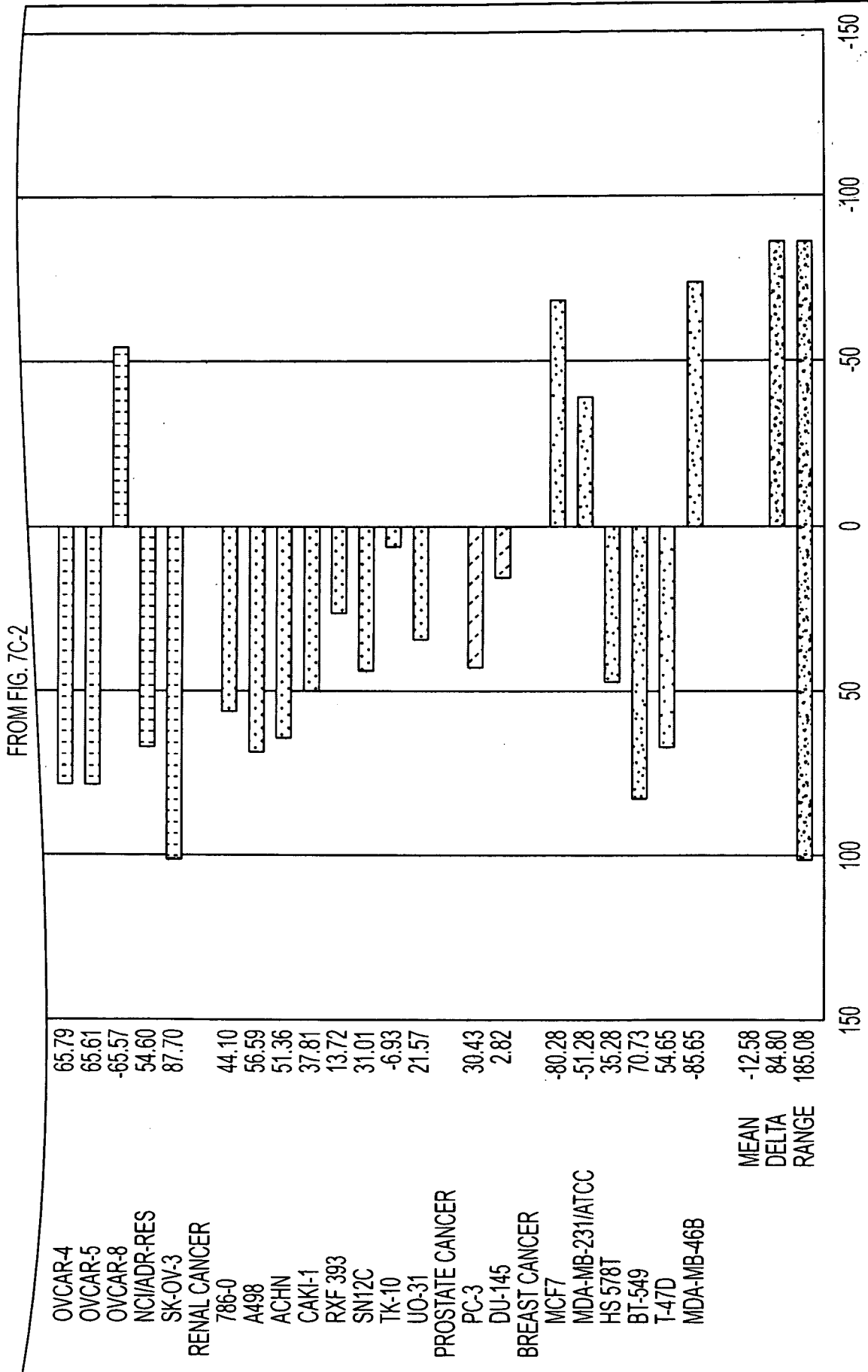


FIG. 7C-3