

[0004] Although high-affinity peptide-based inhibitors of MDM2 have been successfully designed in the past (Garcia-Echeverria *et al.*, *Med. Chem.* 43:3205 (2000)), these inhibitors are not suitable therapeutic molecules because of their poor cell permeability and *in vivo* bioavailability. In the last few years, there have been reports of discoveries of potent, non-peptide, small-molecule MDM2 inhibitors. See e.g., U.S. Patent Nos. 7,851,626; 8,088,815; 7,759,383; 7,737,174; and 8,629,141; U.S. Pat. Appl. Nos. 2012/0046306; 2010/0152190; 2011/0112052; 2012/0122947; Int. Pat. Appl. Publ. WO 2011/153509; WO 2013/049250; literature, Vassilev *et al.* *Science* 2004, 303, 844–48; Vu, *et al.* *ACS Med. Chem. Lett.*, 2013, 4 (5), 466–69; Zhang, *et al.* *ACS Med. Chem. Lett.*, 2014, 5 (2), 124–27; Ding *et al.*, *J. Med. Chem.*, 2013, 56 (14), 5979–83; Shu, *et al.* *Org. Process Res. Dev.*, 2013, 17 (2), 247–56; Zhao, *et al.* *J. Med. Chem.*, 2013, 56 (13), 5553–61; Zhao, *et al.* *J. Am. Chem. Soc.*, 2013, 135 (19), 7223–34; Sun *et al.* *J. Med. Chem.*, 2014, 57 (4), 1454–72; Turiso *et al.*, *J. Med. Chem.*, 2013, 56 (10), 4053–70; and Rew *et al.* *J. Med. Chem.*, 2012, 55 (11), 4936–54). Despite these major advances, there is still a need to identify potent, non-peptide MDM2 inhibitors having suitable physiochemical and pharmacological properties that permit use of the inhibitors in therapeutic applications.

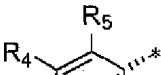
[0005] The present invention provides compounds designed to inhibit MDM2-p53 interactions, and therefore activate the function of p53 and p53-related proteins for therapeutic applications.

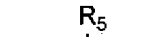
SUMMARY

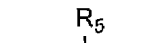
[0006] The present disclosure is directed to inhibitors of MDM2 and MDM2-related proteins, to compositions comprising the inhibitors, and to methods of using the inhibitors in a therapeutic treatment of conditions and diseases wherein inhibition of MDM2 and MDM2-related proteins activity provides a benefit.

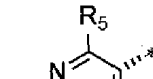
[0007] The present disclosure therefore provides compounds of structural formula (I) that not only demonstrate improvement in their chemical solution stability but also exhibited an unexpected improved anti-tumor activity, including achieving complete tumor regression in an animal model of human osteosarcoma.

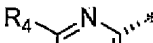
Ar is selected from the group consisting of











and

n is 0, 1, or 2;

R_6 is  ;

R^c and R^d are substituents on one carbon atom of ring B, wherein

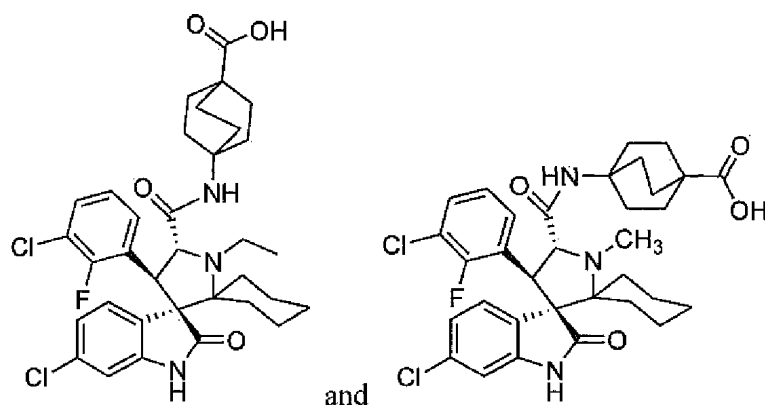
R^e is $-C(=O)OR^a$, $-C(=O)NR^aR^b$, or $-C(=O)NHSO_2CH_3$, or

- 2A -

[0023a] In another aspect, there is provided a compound selected from the group consisting of:



[0023b] In yet another aspect, there is provided a compound selected from the group consisting of



[0023c] In yet another aspect, there is provided the use of a compound as described herein in the manufacture of a medicament for the treatment of a hyperproliferative disease for which a MDM2 inhibitor is indicated.

[0024] In one example, the present disclosure provides a method of treating a condition or disease by administering a therapeutically effective amount of a compound of structural formula (I) to an individual in need thereof. The disease or condition of interest is treatable by inhibition of MDM2 and MDM-2 related proteins, for example, a cancer or a hyperproliferative disorder.

[0025] The compounds of structural formula (I) inhibit the interaction between p53 or p53-related proteins and MDM2 or MDM2-related proteins. Therefore, in another example, methods are provided to induce senescence, cell cycle arrest, and/or apoptosis in cells containing functional p53 or p53-related proteins comprising contacting the cells with a compound of structural formula (I).

[0026] Still another example is to provide methods of treating, ameliorating, or preventing a hyperproliferative disease, *e.g.*, a cancer, for example, adrenal cortical cancer, advanced cancer, anal cancer, aplastic anemia, bile duct cancer, bladder cancer, bone cancer, bone metastasis, brain/CNS tumors in adults, brain/CNS tumors in children, breast cancer, breast cancer in men, cancer in children, cancer of unknown primary, Castleman disease, cervical cancer, colon/rectum cancer, endometrial cancer, esophagus cancer, Ewing family of tumors, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumor (GIST), gestational trophoblastic disease, Hodgkin disease, Kaposi sarcoma, kidney cancer, laryngeal and hypopharyngeal cancer, leukemia - acute lymphocytic (ALL) in adults, leukemia - acute

myeloid (AML), leukemia - chronic lymphocytic (CLL), leukemia - chronic myeloid (CML), leukemia - chronic myelomonocytic (CMML), leukemia in children, liver cancer, lung cancer - non-small cell, lung cancer - small cell, lung carcinoid tumor, lymphoma of the skin, malignant mesothelioma, multiple myeloma, myelodysplastic syndrome, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-Hodgkin lymphoma in children, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma - adult soft tissue cancer, skin cancer - basal and squamous cell, skin cancer – melanoma, small intestine cancer, stomach cancer, testicular

cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, or Wilms Tumor, in a patient comprising administering to the patient a compound of structural formula (I).

[0027] Another example of the present disclosure is to provide a composition comprising (a) an MDM2 inhibitor of structural formula (I) and (b) an excipient and/or pharmaceutically acceptable carrier.

[0028] Another example of the present disclosure is to utilize a composition comprising a compound of structural formula (I) and a second therapeutically active agent in a method of treating an individual for a disease or condition wherein inhibition of MDM2 and MDM2-related proteins provides a benefit.

[0029] In another example, methods of protecting normal (*e.g.*, non-hyperproliferative) cells in a mammal from the toxic side effects of chemotherapeutic agents and treatments are provided. This method comprises administering to the mammal or therapeutically-effective amount of one or more compound of structural formula (I).

[0030] In another example, the disclosure provides for use of a composition comprising an MDM2 inhibitor of structural formula (I) and an optional second therapeutic agent for the manufacture of a medicament for treating a disease or condition of interest, *e.g.*, a cancer.

[0030a] In yet another aspects, the present invention provides a kit for human pharmaceutical use comprising (a) a container, (b1) a packaged composition comprising a compound as described herein, and, optionally, (b2) a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and (c) a package insert containing directions for use of the composition or compositions.

[0031] Still another example of the present disclosure is to provide a kit for human pharmaceutical use comprising (a) a container, (b1) a packaged composition comprising an MDM2 inhibitor of structural formula (I), and, optionally, (b2) a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and (c) a package insert containing directions for use of the composition or compositions, administered simultaneously or sequentially, in the treatment of the disease or condition.

[0032] An MDM2 inhibitor of structural formula (I) and the second therapeutic agent, e.g., an anticancer agent, can be administered together as a single-unit dose or separately as multi-unit doses, wherein the MDM2 inhibitor of structural formula (I) is administered before the second therapeutic agent or *vice versa*. It is envisioned that one or more dose of an MDM2 inhibitor of structural formula (I) and/or one or more dose of a second therapeutic agent can be administered.

[0033] In one example, an MDM2 inhibitor of structural formula (I) and a second therapeutic agent are administered simultaneously. In related embodiments, an MDM2 inhibitor of structural formula (I) and a second therapeutic agent are administered from a single composition or from separate compositions. In a further embodiment, the MDM2 inhibitor of structural formula (I) and second therapeutic agent are administered sequentially. An MDM2 inhibitor of structural formula (I), as used in the present disclosure, can be administered in an amount of about 0.005 to about 500 milligrams per dose, about 0.05 to about 250 milligrams per dose, or about 0.5 to about 100 milligrams per dose.

[0034] These and other embodiments and features of the present invention will become apparent from the following detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF DRAWINGS

[0035] Figure 1A contains a graph of % purity vs. time (days) for compounds AA-MI-061, Cpd No. 2, Cpd No. 7, and Cpd No. 8 in 1:1 CH₃CN/H₂O.

[0036] Figure 1B contains a graph of % purity vs. time (days) for compounds AA-MI-061, Cpd No. 2, Cpd No. 7, and Cpd No. 8 in 1:1 MeOH/H₂O.

[0037] Figure 1C contain graphs of % purity vs. time (days) for compounds AA-MI-061, Cpd No. 2, Cpd No. 7, and Cpd No. 8 in cell culture media.

[0038] Figure 2A contains a graph of mean tumor volume (mm³) vs. time (days) showing the efficacy of various tested compounds for tumor regression in the SJSA-1 xenograft model.

[0039] Figure 2B contains a graph of mean tumor volume (mm³) vs. time (days) showing the efficacy of various tested compounds for tumor regression in the SJSA-1 xenograft model.

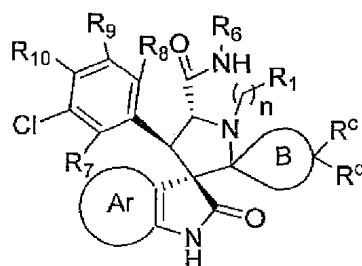
[0040] Figure 3 contains a graph of mean tumor volume (mm³) vs. time (days) showing the efficacy of various doses and dose schedules of Cpd No. 8 for tumor regression in the SJSA-1 xenograft model.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

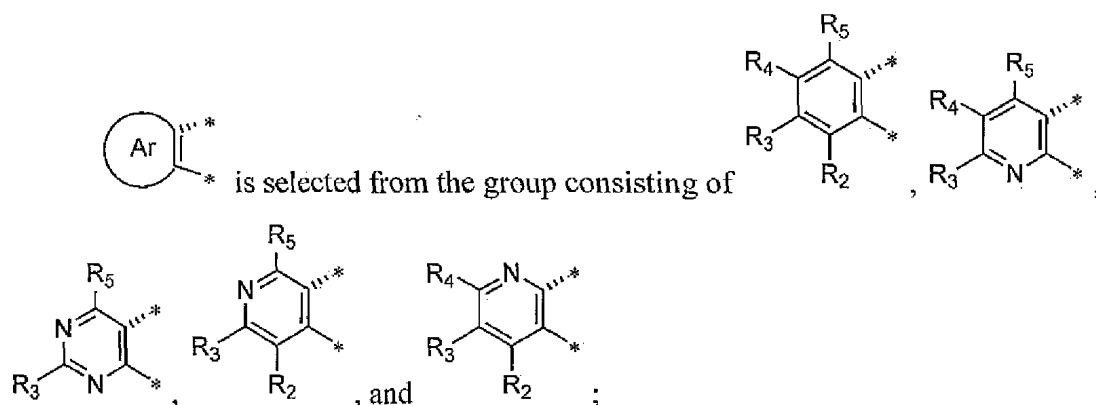
[0041] Spiro-oxindole-based antagonists are a class of inhibitors of the p53-MDM2 interaction and are described in U.S. Patent Nos. 7,759,383, 7,737,174, and 8,629,141. Some spiro-oxindole MDM2 inhibitors quickly converted, in protic solution, from one diastereomer to three other diastereomers (Zhao, et al. J Am Chem Soc. 2013, 135(19):7223-34). Efforts were made to

WHAT IS CLAIMED:

1. A compound having the structural formula:



wherein

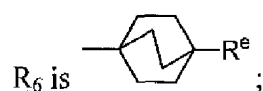


B is a C₄₋₇ carbocyclic ring;

R₁ is H, substituted or unsubstituted C₁₋₄alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, OR^a, or NR^aR^b;

n is 0, 1, or 2;

R₂, R₃, R₄, R₅, R₇, R₈, R₉, and R₁₀, independently, are selected from the group consisting of H, F, Cl, CH₃, and CF₃;



R^a is hydrogen or substituted or unsubstituted C₁₋₄alkyl;

R^b is hydrogen or substituted or unsubstituted C₁₋₄alkyl;

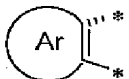
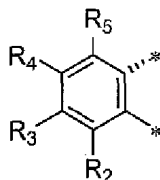
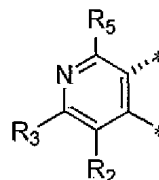
R^c and R^d are substituents on one carbon atom of ring B, wherein

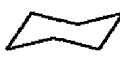
R^c is H, C_{1-3} alkyl, C_{1-3} alkyleneOR^a, OR^a, or halo;

R^d is H, C_{1-3} alkyl, C_{1-3} alkyleneOR^a, OR^a, or halo; and

R^e is $-C(=O)OR^a$, $-C(=O)NR^aR^b$, or $-C(=O)NHSO_2CH_3$, or

a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein  is  or .

3. The compound of claim 1 or 2, wherein B is  or .

4. The compound of any preceding claim, where n is 0 or 1.

5. The compound of claim 4, wherein R_1 is H or CH_3 .

6. The compound of any preceding claim, wherein $-(CH_2)_n-R_1$ is H, CH_3 , or CH_2CH_3 .

7. The compound of any preceding claim, wherein R_2 is H.

8. The compound of any preceding claim, wherein R_3 is halo.

9. The compound of claim 8, wherein R_3 is chloro.

10. The compound of any preceding claim, wherein R_4 is H.

11. The compound of any preceding claim, wherein R_5 is H.

12. The compound of any preceding claim, wherein R_4 and R_5 are H.

13. The compound of any preceding claim, wherein R_7 is halo.

14. The compound of claim 13, wherein R_7 is fluoro.

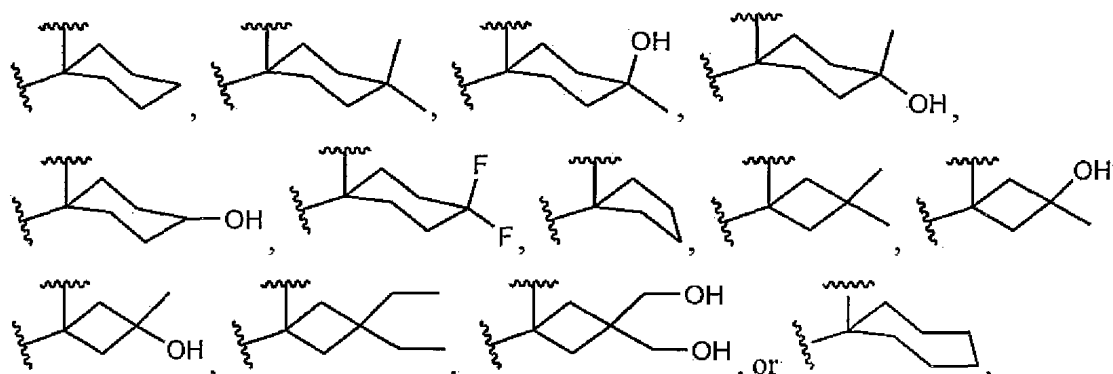
15. The compound of any preceding claim, wherein each of R_8 , R_9 , and R_{10} is H.

16. The compound of any preceding claim, wherein R^a and R^b, individually, are H, CH₃, or CH₂CH₃.

17. The compound of any preceding claim, wherein R^c and R^d, individually, are H, halo, OH, CH₃, CH₂CH₃, or CH₂OH.

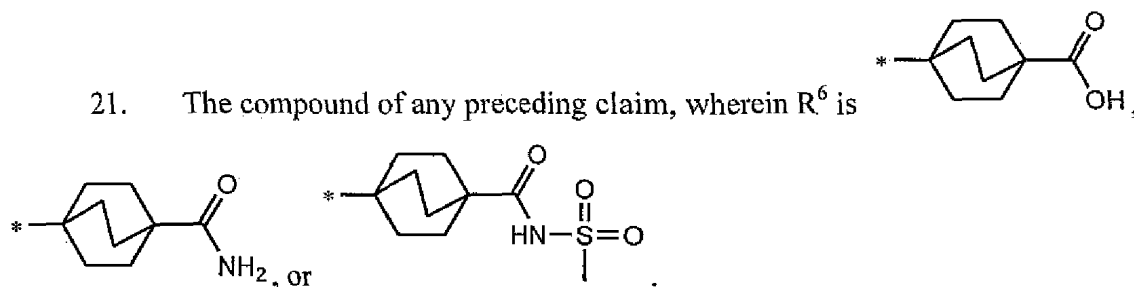
18. The compound of any preceding claim, wherein R^c and R^d are F and F, H and H, OH and CH₃, OH and H, CH₃ and CH₃, CH₃ and OH, H and OH, CH₂CH₃ and CH₂CH₃, or CH₂OH and CH₂OH.

19. The compound of any claim 1 through 16, wherein R^c and R^d taken together with ring B form:

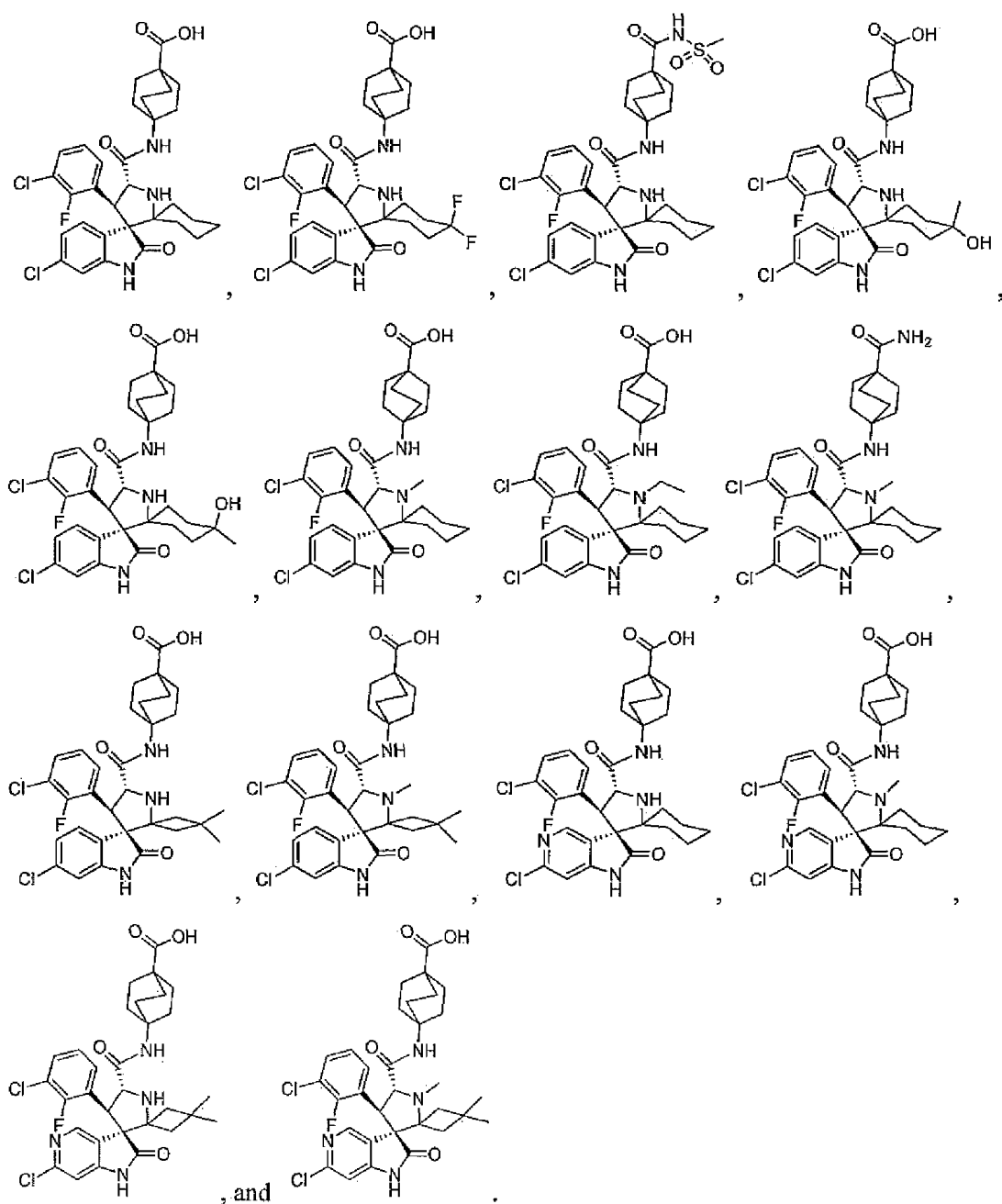


20. The compound of any preceding claim, wherein R^e is -C(=O)OH, -C(=O)NH₂, or -C(=O)NHSO₂CH₃.

21. The compound of any preceding claim, wherein R⁶ is

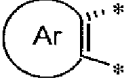
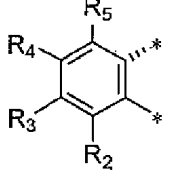
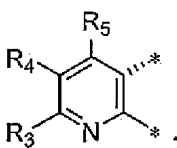


22. A compound selected from the group consisting of:



23. A composition comprising (a) a compound of claim 1, and (b) an excipient and/or pharmaceutically acceptable carrier.

24. The composition of claim 23 further comprising a chemotherapeutic agent useful in the treatment of a hyperproliferative disease.

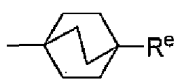
25. The compound of claim 1, wherein  is  or .

B is  or ;

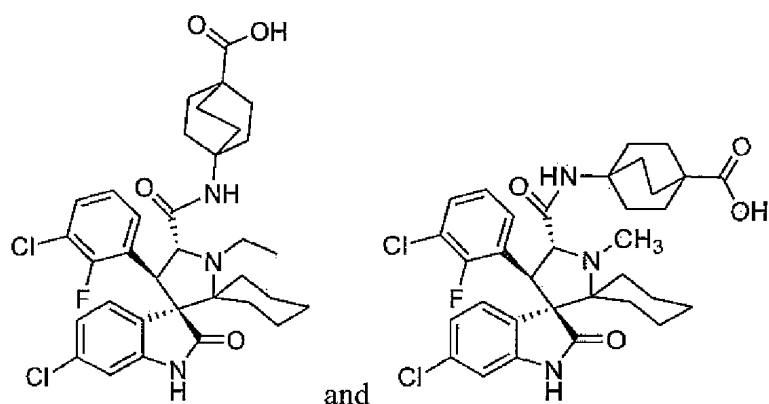
$-(CH_2)_n-R_1$ is H, CH_3 , or CH_2CH_3 ;

$R_2, R_3, R_4, R_5, R_8, R_9$, and R_{10} , independently, are selected from the group consisting of H, F, Cl, and CH_3 ;

R_7 is F; and

R_6 is .

26. A compound selected from the group consisting of



27. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament for the treatment of a hyperproliferative disease for which a MDM2 inhibitor is indicated.

28. The use of claim 27 wherein the hyperproliferative disease is a cancer.

29. The use of claim 27 further comprising a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition, wherein the disease is a cancer and the second therapeutic agent is one or more of a chemotherapeutic agent, and radiation.

30. A kit for human pharmaceutical use comprising (a) a container, (b1) a packaged composition comprising a compound as claimed in any one of claims 1 to 26, and, optionally, (b2) a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and (c) a package insert containing directions for use of the composition or compositions.