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(54) **COMBINATION THERAPY INCLUDING AN MDM2 INHIBITOR AND ONE OR MORE ADDITIONAL PHARMACEUTICALLY ACTIVE AGENTS FOR THE TREATMENT OF CANCERS**

KOMBINATIONSTHERAPIE UMFASSEND EINEN MDM2-HEMMER UND EINEN ODER MEHRERE ZUSÄTZLICHE PHARMAZEUTISCHE WIRKSTOFFE ZUR BEHANDLUNG VON KREBS

POLYTHÉRAPIE RENFERMANT UN INHIBITEUR DE MDM2 ET UN OU PLUSIEURS PRINCIPES PHARMACEUTIQUEMENT ACTIFS SUPPLÉMENTAIRES POUR LE TRAITEMENT DE CANCERS

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Description

FIELD OF THE INVENTION

[0001] The present invention provides 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (in the following also referred to as "Compound A", "AMG 232 " or "2705932") for use in a method for the treatment of acute myelogenous leukemia (AML), said method comprising administering to a patient in need thereof an effective amount of Compound A and decitabine. The present invention further provides Compound A for use in a method for the treatment of AML, said method comprising administering to a patient in need thereof an effective amount of Compound A and cytarabine. The present invention also provides pharmaceutical compositions for use in a method for the treatment of AML, the pharmaceutical compositions comprising Compound A and decitabine or cytarabine, respectively, as well as kits of pharmaceutical compositions for use in the treatment of AML, the kits comprising separate pharmaceutical compositions comprising Compound A and decitabine or cytarabine, respectively.

BACKGROUND OF THE INVENTION

[0002] p53 is a tumor suppressor and transcription factor that responds to cellular stress by activating the transcription of numerous genes involved in cell cycle arrest, apoptosis, senescence, and DNA repair. Unlike normal cells, which have infrequent cause for p53 activation, tumor cells are under constant cellular stress from various insults including hypoxia and pro-apoptotic oncogene activation. Thus, there is a strong selective advantage for inactivation of the p53 pathway in tumors, and it has been proposed that eliminating p53 function may be a prerequisite for tumor survival. In support of this notion, three groups of investigators have used mouse models to demonstrate that absence of p53 function is a continuous requirement for the maintenance of established tumors. When the investigators restored p53 function to tumors with inactivated p53, the tumors regressed.

[0003] p53 is inactivated by mutation and/or loss in 50% of solid tumors and 10% of liquid tumors. Other key members of the p53 pathway are also genetically or epigenetically altered in cancer. MDM2, an oncoprotein, inhibits p53 function, and it is activated by gene amplification at incidence rates that are reported to be as high as 10%. MDM2, in turn, is inhibited by another tumor suppressor, p14ARF. It has been suggested that alterations downstream of p53 may be responsible for at least partially inactivating the p53 pathway in $p53^{WT}$ tumors (p53 wild type). In support of this concept, some $p53^{WT}$ tumors appear to exhibit reduced apoptotic capacity, although their capacity to undergo cell cycle arrest remains intact. One cancer treatment strategy involves the use of small molecules that bind MDM2 and neutralize its interaction with p53. MDM2 inhibits p53 activity by three mechanisms: 1) acting as an E3 ubiquitin ligase to promote p53 degradation; 2) binding to and blocking the p53 transcriptional activation domain; and 3) exporting p53 from the nucleus to the cytoplasm. All three of these mechanisms would be blocked by neutralizing the MDM2-p53 interaction. In particular, this therapeutic strategy could be applied to tumors that are $p53^{WT}$, and studies with small molecule MDM2 inhibitors have yielded promising reductions in tumor growth both *in vitro* and *in vivo.* Further, in patients with p53-inactivated tumors, stabilization of wild type p53 in normal tissues by MDM2 inhibition might allow selective protection of normal tissues from mitotic poisons. As used herein, MDM2 means a human MDM2 protein and p53 means a human p53 protein. It is noted that human MDM2 can also be referred to as HDM2 or hMDM2. Several MDM2 inhibitors are in human clinical trials for the treatment of various cancers.

[0004] The present invention relates to compunds, compositions and kits for use in combination therapy as set out above and defined in the claims. The particular combinations show enhanced anti-cancer activity in certain types of cancers over what is expected when the individual members of the combination therapy are used alone.

SUMMARY OF THE INVENTION

[0005] In one embodiment, the present invention provides 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid (Compound A) for use in a method for the treatment of acute myelogenous leukemia (AML), said method comprising administering to a patient in need thereof an effective amount of Compound A and decitabine. In another embodiment, the present invention provides Compound A for use in a method for the treatment of AML, said method comprising administering to a patient in need thereof an effective amount of Compound A and cytarabine. In further embodiments, the present invention provides pharmaceutical compositions for use in a method for the treatment of AML, the pharmaceutical compositions Compound A and decitabine or cytarabine, respectively. In still further embodiments, the present invention provides kits of pharmaceutical compositions for use in the treatment of AML, the kits comprising separate pharmaceutical compositions comprising Compound A and decitabine or cytarabine, respectively.

[0006] In an embodiment, the AML has a FLT3 ITD mutation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007]

Figure 1 shows data for combinations of AMG 232 and various chemotherapeutic compounds.
Figure 2 shows tumor xenograft data for the combination of AMG 232 and cytarabine in a MOLM13 tumor.
Figure 3 shows tumor xenograft data for the combination of AMG 232 and decitabine in a MOLM13 tumor.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

[0009] The term "therapeutically effective amount" means an amount of a compound, or combination of compounds, that ameliorates, attenuates or eliminates one or more symptom of a particular disease or condition, or prevents or delays the onset of one of more symptom of a particular disease or condition.

[0010] The terms "patient" and "subject" may be used interchangeably and mean animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

[0011] The term "pharmaceutically acceptable" means that the referenced substance, such as a compound, or a salt of the compound, or a formulation containing the compound, or a particular excipient, are suitable for administration to a patient.

[0012] The terms "treating", "treat" or "treatment" and the like include preventative (e.g., prophylactic) and palliative treatment. The term" treating" and the like, in accordance with the present invention, means reducing or eliminating cancers cells in a patient.

[0013] The term "excipient" means any pharmaceutically acceptable additive, carrier, diluent, adjuvant, or other ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration to a patient.

[0014] The phrase "compound(s) of the present invention" includes MDM2 inhibitors and/or the one or more additional pharmaceutically active agents according to the claims.

[0015] An "MDM2 inhibitor" is defined as a compound with a molecular weight less than about 1000 that binds MDM2 as shown with *in vitro* testing or by other means.

[0016] The compounds of the present invention are administered to a patient in a therapeutically effective amount. The compounds can be administered alone or as part of a pharmaceutically acceptable composition or formulation. In addition, the compounds or compositions can be administered all at once, as for example, by a bolus injection, multiple times, such as by a series of tablets, or delivered substantially uniformly over a period of time, as for example, using transdermal delivery. It is also noted that the dose of the compounds can be varied over time.

[0017] As the patient is to receive or is receiving multiple pharmaceutically active compounds, the compounds can be administered simultaneously or sequentially. For example, in the case of tablets, the active compounds may be found in one tablet or in separate tablets, which can be administered at once or sequentially in any order. In addition, it should be recognized that the compositions may be different forms. For example, one or more compounds may be delivered via a tablet, while another is administered via injection or orally as a syrup. All combinations, delivery methods and administration sequences are contemplated.

[0018] The compounds of the present invention can be used to treat acute myelogenous leukemia (AML). The methods of treating AML comprise administering to a patient in need thereof a therapeutically effective amount of the compounds, or pharmaceutically acceptable salts of any of the compounds.

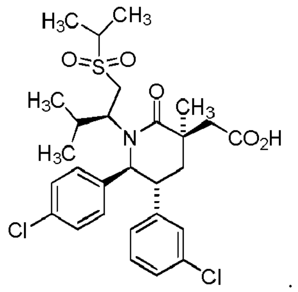
[0019] The compounds of the present invention may be designated as follows in the application and figures.

Compound A	AMG 232
Compound 12	cytarabine

[0020] The MDM2 inhibitors of the present invention, i.e. Compound A, is in published PCT application WO2011/153,509. This compound is also referred to as AMG 232 (Example 362) having the structure and name shown below.

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxo-piperidin-3-yl)acetic acid

[0021]

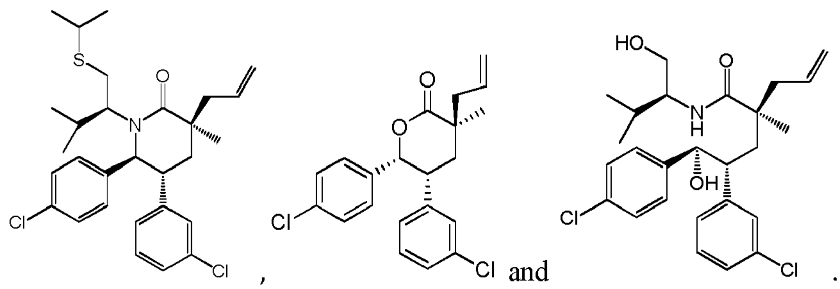


[0022] A particular synthesis of AMG 232 is set forth in U.S. provisional patent application number 61/833,196, filed June 10, 2013.

Procedures to Make Certain Intermediates and Starting Materials

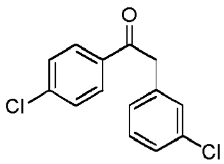
Method for making

[0023]



Step A. 2-(3-Chlorophenyl)-1-(4-chlorophenyl)ethanone

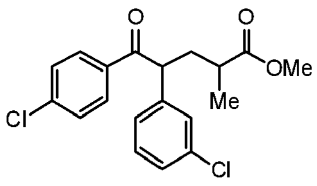
[0024]



[0025] Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 117 mL) was slowly added to a -78°C solution of 2-(3-chlorophenyl) acetic acid (10 g, 58.6 mmol) in tetrahydrofuran (58 mL) over 1 hour. After stirring at -78°C for 40 minutes, a solution of methyl 4-chlorobenzoate (10 g, 58.6 mmol) in tetrahydrofuran (35 mL) was added over a period of 10 minutes. The reaction was stirred at -78°C for 3 hours then allowed to warm to 25°C. After two hours at 25 °C, the reaction was quenched with saturated aqueous ammonium chloride solution, and most of the tetrahydrofuran was removed under reduced pressure. The residue was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and the filtrate was concentrated. The product was recrystallized from ether/pentane to provide the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.05 (m, 2H), 7.62 (m, 2H), 7.33 (m, 3H), 7.21 (br d, J = 7.3 Hz, 1H), 4.45 (s, 2H). MS (ESI) = 265.1 [M + H]$^+$.

Step B: Methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-5-oxopentanoate

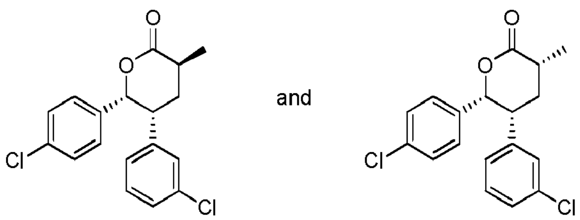
[0026]



[0027] Methyl methacrylate (12.65 mL, 119 mmol) was added to a solution of 2-(3-chlorophenyl)-1-(4-chlorophenyl)ethanone (30 g, 113 mmol) in tetrahydrofuran (283 mL). Potassium tert-butoxide (1.27 g, 11.3 mmol) was then added and the reaction was stirred at room temperature for 2 days. The solvent was removed under a vacuum and replaced with 300 mL of ethyl acetate. The organic phase was washed with brine (50 mL), water (3 x 50 mL), and brine (50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated under a vacuum to afford methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-5-oxopentanoate as an approximately 1:1 mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.87 (m, 2H), 7.38 (m, 2H), 7.27-7.14 (series of m, 4H), 4.61 (m, 1H), 3.69 (s, 1.5H), 3.60 (s, 1.5 H), 2.45 (m, 1H), 2.34 (m, 1H), 2.10 (ddd, *J*= 13.9, 9.4, 5.5 Hz, 0.5H), 1.96 (ddd, *J*= 13.7, 9.0, 4.3 Hz, 0.5H), 1.22 (d, J = 7.0 Hz, 1.5H), 1.16 (d, *J*= 7.0, 1.5 H). MS (ESI) = 387.0 $[M+23]^+$.

Step C: (3S,5R,6R)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2H-pyran-2-one and (3R,5R,6R)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2H-pyran-2-one

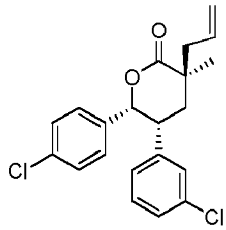
[0028]



[0029] Methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-5-oxopentanoate (40 g, 104.0 mmol) was dissolved in 200 mL of anhydrous toluene and concentrated under a vacuum. The residue was placed under high vacuum for 2 hours before use. The compound was split into 2 x 20 g batches and processed as follows: methyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-2-methyl-5-oxopentanoate (20 g, 52.0 mmol) in anhydrous 2-propanol (104 mL) was treated with potassium *tert*-butoxide (2.33 g, 20.8 mmol) in a 250 mL glass hydrogenation vessel. R.uCl_2(*S*-xylbinap)(*S*-DAIPEN) (0.191 g, 0.156 mmol, Strem Chemicals, Inc., Newburyport, MA) in 3.8 mL of toluene was added. After 1.5 hours, the vessel was pressurized to 50 psi (344.7 kPa) and purged with hydrogen five times and allowed to stir at room temperature. The reaction was recharged with additional hydrogen as needed. After 3 days, the reactions were combined and partitioned between 50% saturated ammonium chloride solution and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered, and concentrated.

[0030] The crude product (predominantly, (4*R*,5*R*)-isopropyl 4-(3-chlorophenyl)-5-(4-chlorophenyl)-5-hydroxy-2-methylpentanoate) was dissolved in tetrahydrofuran (450 mL) and methanol (150 mL). Lithium hydroxide (1.4 M, 149 mL, 208 mmol) was added, and the solution was stirred at room temperature for 24 hours. The mixture was concentrated under a vacuum and the residue was redissolved in ethyl acetate. Aqueous IN hydrochloric acid was added with stirring until the aqueous layer had a pH of about 1. The layers were separated and the organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated. The material was dissolved in 200 mL of anhydrous toluene and treated with pyridinium p-toluenesulfonate (PPTS, 0.784 g, 3.12 mmol). The reaction was heated to reflux under Dean-Stark conditions until the seco-acid was consumed (about 2 hours). The reaction was cooled to room temperature and washed with saturated sodium bicarbonate (50 mL) and brine (50 mL). The solution was dried over sodium sulfate, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (120 g column; eluting with 100% dichloromethane). The title compounds were obtained as a white solid with an approximate 94:6 enantiomeric ratio and a 7:3 mixture of methyl diastereomers. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.22-6.98 (series of m, 5H), 6.91 (dt, *J* = 7.4, 1.2 Hz, 0.3H), 6.81 (m, 2H), 6.73 *(dt, J*= 7.6, 1.4 Hz, 0.7H), 5.76 (d, *J* = 4.1 Hz, 0.3 H), 5.69 (d, *J* = 4.7 Hz, 0.7H), 3.67 (dt, *J* = 6.6, 4.3 Hz, 0.3H), 3.55 (td, *J* = 7.8, 4.7 Hz, 0.7 H), 2.96 (d of quintets, *J* = 13.5, 6.7 Hz, 0.7 H), 2.81

(m, 0.3 H), 2.56 (dt, J = 14.3, 8.0 Hz, 0.7 H), 2.32 (dt, J = 13.69, 7.0 Hz, 0.3 H), 2.06 (ddd, J = 13.7, 8.4, 4.1, 0.3 H), 1.85 (ddd, J = 14.1, 12.5, 7.4, 0.7 H), 1.42 (d, J = 7.0 Hz, 0.9 H), 1.41 (d, J = 6.7 Hz, 2.1H). MS (ESI) = 357.0 [M + 23] $^+$. $[\alpha]_D$ (22 °C, c = 1.0, CH_2Cl_2) = -31.9°; m.p. 98-99 °C. Step D. (3*S*,5*R*,6*R*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2*H*-pyran-2-one

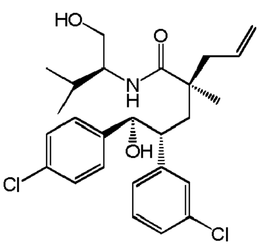


[0031] A solution of (3*S*,5*R*,6*R*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2*H*-pyran-2-one and (3*R*,5*S*,6*S*)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2*H*-pyran-2-one (4.5 g, 13.4 mmol) and allyl bromide (3.48 mL, 40.3 mmol) in tetrahydrofuran (22 mL) at -35 °C (acetonitrile/dry ice bath) was treated with a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 17.45 mL, 17.45 mmol). The reaction was allowed to warm to -5 °C over 1 hour and then was quenched with 50% saturated ammonium chloride. The reaction was diluted with 100 mL of ethyl acetate and the layers were separated.

[0032] The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated under a vacuum to afford the title compound as a white solid upon standing under a vacuum. Chiral SFC (92% CO_2, 8% methanol (20 mM ammonia), 5 mL/min, Phenomenex Lux-2 column (Phenomenex, Torrance, CA), 100 bar (10,000 kPa), 40°C, 5 minute method) was used to determine that the compound had an enantiomeric ratio of 96:4. (Major enantiomer: title compound, retention time = 2.45 minutes, 96%; minor enantiomer (structure not shown, retention time = 2.12 min, 4%). The title compound was recrystallized by adding to heptane (4.7 g slurried in 40 mL) at reflux and 1.5 mL of toluene was added dropwise to solubilize. The solution was cooled to 0 °C. The white solid was filtered and rinsed with 20 mL of cold heptanes to afford a white powder. Chiral SFC (92% CO_2, 8% methanol, Phenomenex Lux-2 column, same method as above) indicated an enantiomeric ratio of 99.2:0.8. (major enantiomer, 2.45 min, 99.2%; minor enantiomer: 2.12 min, 0.8%). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.24 (ddd, J= 8.0, 2.0, 1.2 Hz, 1H), 7.20-7.15 (series of m, 3H), 6.91 (t, J= 2.0 Hz, 1H), 6.78 (br d, J= 7.6 Hz, 1H), 6.60 (m, 2H), 5.84 (ddt, J= 17.6, 10.2, 7.4 Hz, 1H), 5.70 (d, J= 5.3 Hz, 1H), 5.21-5.13 (series of m, 2H), 3.82 (dt, J= 11.7, 4.5 Hz, 1H), 2.62 (ABX J_{AB} = 13.7 Hz, J_{AX} = 7.6 Hz, 1H), 2.53 (ABX, J_{AB} = 13.9 Hz, J_{Bx} = 7.2 Hz, 1H). 1.99 (dd, J= 14.1, 11.9 Hz, 1H), 1.92 (ddd, J = 13.9, 3.9, 1.2 Hz, ^{1}H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 175.9, 140.2, 134.5, 134.3, 134.0, 132.2, 129.8, 128.6, 128.0, 127.9, 127.8, 126.4, 119.9, 83.9, 44.5, 42.4, 40.7, 31.8, 26.1. MS (ESI) = 375.2 [M + H]$^+$. IR = 1730 cm^{-1}. $[\alpha]_D$ (24°C, c = 1.0, CH_2Cl_2) = -191°.m.p. 111-114 °C.

Step E. (*S*)-2-((2*R*,3*R*)-2-(3-Chlorophenyl)-3-(4-chlorophenyl)-3-hydroxypropyl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methylpent-4-enamide

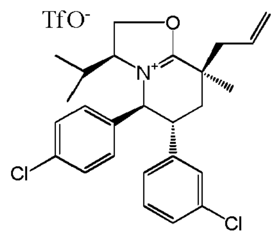
[0033]



[0034] (3*S*,5*R*,6*R*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-3-methyltetrahydro-2*H*-pyran-2-one (113 g, 300.0 mmol) was combined with (*S*)-2-amino-3-methyllbutan-1-ol (93 g, 900.0 mmol) and the suspension was heated at 100 °C for 5 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (1000 mL) and washed with IN hydrochloric acid (2X), water, and brine. The organic layer was dried over magnesium sulfate and concentrated under a vacuum to give the title compound as white solid which was used in next step without further purification.

Step F. (3*S*,5*S*,6*R*,8*S*)-8-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-isopropyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridin-4-ium trifluoromethanesulfonate

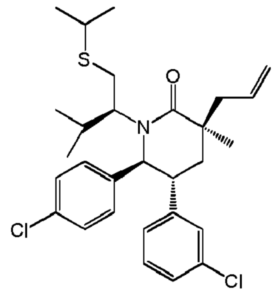
[0035]



[0036] Trifluoromethanesulfonic anhydride (57 mL, 339 mmol) was added dropwise over 60 minutes via addition funnel to a solution of (*S*)-2-((2*R*,3*R*)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-3-hydroxypropyl)-N-((*S*)-1-hydroxy-3-methylbutan-2-yl)-2-methylpent-4-enamide (73.7 g, 154 mmol) and 2,6-dimethylpyridine (78 mL, 678 mmol) in dichloromethane (700 mL) at -50 °C. The reaction mixture was stirred at -50 °C for one additional hour and concentrated under a vacuum to provide the title compound as a reddish solid which was used in next step without further purification.

Step G. (3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylthio)-3-methylbutan-2-yl)-3-methylpiperidin-2-one

[0037]



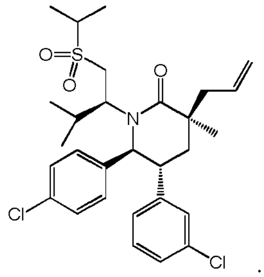
[0038] (3*S*,5*S*,6*R*,8*S)*-8-Allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-isopropyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridin-4-ium trifluoromethanesulfonate (736 mg, 1.242 mmol) was weighed into an oven dried 50 mL pear-bottom flask and dissolved in 20 mL dry toluene. The toluene was removed under a vacuum to remove trace water in the solid. The process was repeated twice, and the resulting residue was dried under a strong vacuum.

[0039] A solution of sodium isopropyl sulfide was prepared by adding potassium 2-methylpropan-2-olate (3.0 mL, 3.00 mmol, 1 M solution in tetrahydrofuran) to a solution of propane-2-thiol (331 mg, 4.35 mmol) in 8 mL dimethylformamide that had been prepared under nitrogen and cooled to 0 °C. The sulfide solution was allowed to stir at room temperature for five minutes and was cooled to 0°C. The dry (3*S*,5*S*,6*R*,8*S*)-8-allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-isopropyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridin-4-ium trifluoromethanesulfonate (736 mg, 1.242 mmol) was dissolved in dimethylformamide (8 mL total) and transferred (3 transfers total) via syringe to the sulfide solution over the course of 5 minutes. After 5 minutes, the ice bath was removed and the pale orange solution was allowed to warm to room temperature.

[0040] After stirring overnight, the mixture was partitioned between ethyl acetate and saturated ammonium chloride solution. The aqueous phase was saturated in sodium chloride and back-extracted three times. The combined organics were washed twice with saturated sodium bicarbonate, twice with brine, dried over sodium sulfate, filtered, and concentrated under a vacuum to provide a residue that was purified by silica gel column chromatography (80 g column, gradient elution of 0% to 50 % ethyl acetate in hexanes).

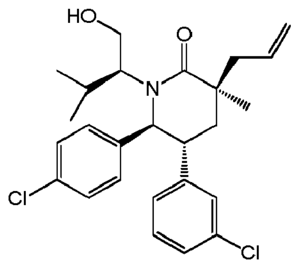
Method for making

[0041]



Step A. (3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-hydroxy-3-methylbutan-2-yl)-3-methylpiperidin-2-one

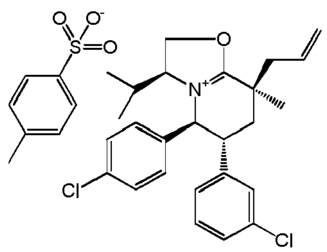
[0042]



[0043] Lithium hydroxide hydrate (64.6 g, 1540 mmol) was added portionwise, over a 5 minute period, to a solution of (3*S*,5*S*,6*R*,8*S*)-8-al[yl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-isopropyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*α*]pyridin-4-ium trifluoromethanesulfonate (Step F above) dissolved in tetrahydrofuran (500ml) and water (300 ml). The reaction mixture was stirred at room temperature for 1 hour and concentrated under a vacuum. The residue was dissolved in ethyl acetate (ca. 1.3 L) and the layers were separated. The organic layer was washed with IN hydrochloric acid (ice cooled, with enough hydrochloric acid to protonate and remove any remaining 2,6-dimethylpyridine (300 mL x 2)), water and brine. The solvent was removed under a vacuum to give a residue which was purified by silica gel column chromatography (1500 g column, gradient elution of 0% to 50% ethyl acetate in hexanes. The product was also crystallized from cyclohexane.

Step B. (3*S*,5*S*,6*R*,8*S*)-8-Allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-isopropyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*α*]pyridin-4-ium 4-methylbenzenesulfonate

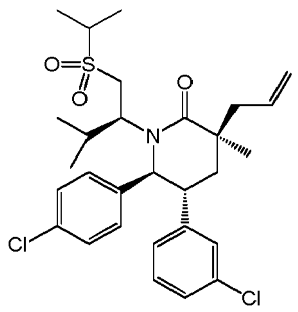
[0044]



[0045] (3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-hydroxy-3-methylbutan-2-yl)-3-methylpiperidin-2-one (49.77 g, 98 mmol) was transferred to a 1000 mL flask containing 4-methylbenzenesulfonic acid hydrate (19.27 g, 101 mmol) and a stirring bar. The reactants were suspended in toluene (230 mL). The flask was equipped with a Dean Stark trap and reflux condenser, and the stirred mixture was heated at reflux in a preheated bath. After 1 hour, the solvent was carefully removed under a vacuum and the resulting residue was further dried under high vacuum. The title compound was taken to the next step without purification.

Step C. (3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methylpiperidin-2-one

[0046]

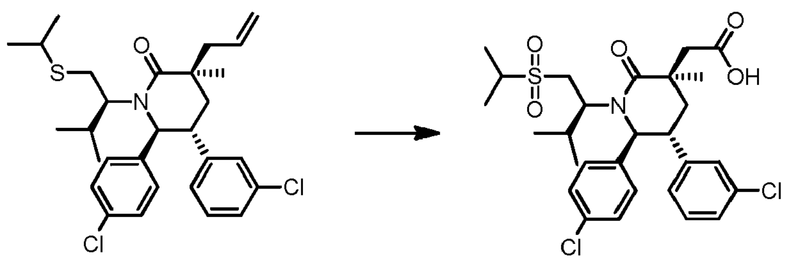


[0047] (3*S*,5*S*,6*R*,8*S*)-8-Allyl-6-(3-chlorophenyl)-5-(4-chlorophenyl)-3-isopropyl-8-methyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridin-4-ium 4-methylbenzenesulfonate, dry, powdered potassium carbonate (26.9 g, 195 mmol) and propane-2-thiol (14ml, 150 mmol) were added along with 200 mL freshly sparged dimethylformamide. The mixture was heated under argon at 50°C. After about 21 hours, a solution of *meta*-chloroperbenzoic acid (68.2 g, 77% pure by weight, in 100 mL dimethylformamide) was transferred to a dropping funnel and rapidly added to the stirred reaction mixture while the flask was immersed in an ice bath. After 5 minutes, the resulting yellow solution was allowed to warm to room temperature. After 10 minutes, additional *meta*-chloroperbenzoic acid (12 g, 77% wt %) was added as a solid and the mixture was stirred at room temperature. Upon completion, the mixture was poured into ethyl acetate and washed with 1 M sodium hydroxide (500 mL) that had been poured into ice. The aqueous phase was back-extracted three times and washed with additional 1 M NaOH ((500 mL, also poured into ice). The aqueous layer was washed once with ethyl acetate and the organics were combined. Sodium thiosulfate (1 M in water, 250 mL) was added to the organics in a large Erlenmeyer flask, and the mixture was stirred for twenty minutes. The organic phase was washed again with sodium thiosulfate (1 M in water, 250 mL) and the mixture was allowed to stand over the weekend. The organics were concentrated to ca. 500 mL, then sequentially washed with 10% aqueous citric acid, 1 M sodium hydroxide, and brine. The organics were dried over sodium sulfate, filtered, and concentrated to give the crude product. The residue was purified by flash column chromatography (1.5 kg silica gel column, gradient elution of 0% to 50% ethyl acetate in hexanes) to give the title compound as a white solid.

Synthesis of Compound AMG 232 (Alternative 1)

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

[0048]



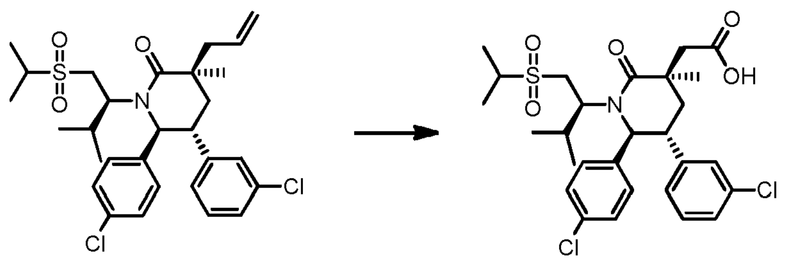
[0049] Ruthenium(III) chloride trihydrate (22 mg, 0.084 mmol) and sodium periodate (1.12 g, 5.24 mmol) were added to a mixture of (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylthio)-3-methylbutan-2-yl)-3-methylpiperidin-2-one (390 mg, 0.752 mmol) in acetonitrile (4.0 mL), carbon tetrachloride (4.0 mL),and water (6.0 mL). The resulting dark brown mixture was vigorously stirred at ambient temperature overnight. The mixture was filtered through a pad of diatomaceous earth, washing with ethyl acetate. The filtrate was partitioned between 2 M HCl and ethyl acetate. The aqueous phase was back-extracted twice with ethyl acetate, and the combined organics were washed with brine, dried over sodium sulfate, filtered, and concentrated under a vacuum to a residue that was purified by flash chromatography (40 g silica gel column, gradient elution of 0% to 15% isopropanol in hexanes). Fractions containing the desired product were combined, stripped of solvent, redissolved in minimal ACN/water, frozen, and lyophilized to give a white powder.

[0050] Subsequently, a mixture of (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylthio)-3-methylbutan-2-yl)-3-methylpiperidin-2-one (388 mg, 0.748 mmol), ruthenium(III) chloride trihydrate (19.56 mg, 0.075 mmol), and sodium periodate (1.15 g, 5.38 mmol) in acetonitrile (4 mL), carbon tetrachloride (4.00mL), and water (4.00 mL) was vigorously stirred at ambient temperature. After four hours, the mixture was filtered through a pad of diatomaceous earth, and the filtrate was partitioned between ethyl acetate and 2 M HCl. The aqueous phase was back-extracted twice with ethyl acetate, and the combined organics were washed with brine, dried over sodium sulfate, filtered, and concentrated under a vacuum to a residue. The residue was purified by flash chromatography (40 g silica gel column, gradient elution of 0% to 15% isopropanol in hexanes). Fractions containing the product were concentrated and combined with the solid obtained in the prior experiment. The combined material was dissolved in minimal acetonitrile/water, frozen, and lyophilized overnight to give a white solid.

Synthesis of AMG 232 (Alternative 2)

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

[0051]



[0052] Sodium periodate (2.85 g, 13.32 mmol) and ruthenium(III) chloride trihydrate (0.049 g, 0.189 mmol) were added to a mixture of (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methylpiperidin-2-one (1.73 g, 3.14 mmol) in acetonitrile (18 mL), carbon tetrachloride (18 mL), and water (27 mL). The mixture was stirred vigorously at room temperature for 25 hours. The mixture was diluted with 2M HCl and filtered through a pad of diatomaceous earth and rinsed with ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated under a vacuum. The material was purified twice by flash chromatography (120g silica gel, gradient elution of 0% to 20% isopropanol in hexanes; 120 g column, gradient elution of 0% to 15% gradient isopropanol in hexanes). It was purified once more by flash chromatography (220 g silica gel; gradient elution 0% to 20% isopropanol in hexanes, 45 minutes) using a method in which the purest fractions were concentrated and set aside and mixed fractions were pooled and resubjected to the chromatography.

[0053] Subsequently, a mixture of (3*S*,5*R*,6*S*)-3-allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methylpiperidin-2-one (4.1 g, 7.45 mmol), ruthenium(III) chloride trihydrate (0.120 g, 0.459 mmol), and sodium periodate (6.73 g, 31.5 mmol) in acetonitrile (40 mL), carbon tetrachloride (40 mL), and water (60 mL) was vigorously stirred at ambient temperature for 23 hours. The reaction was diluted by addition of 2 M aqueous HCl and filtered through a diatomaceous earth pad, washing with copious ethyl acetate. Most of the organics were removed under a vacuum. The crude product was extracted into ethyl acetate, washed with brine, dried over sodium sulfate, filtered, and concentrated to a residue that was purified twice by flash chromatography (330 g silica gel column, gradient elution of 0% to 20% isopropanol in hexanes; 330 g silica gel column, gradient elution of 0% to 20% isopropanol in hexanes) to give an off-white foam. The material was purified by flash chromatography three additional times (220 g silica gel column; gradient elution 0% to 20% isopropanol in hexanes, 45 minutes) using a method in which the purest fractions were concentrated and set aside and mixed fractions were pooled and resubjected to the chromatography.

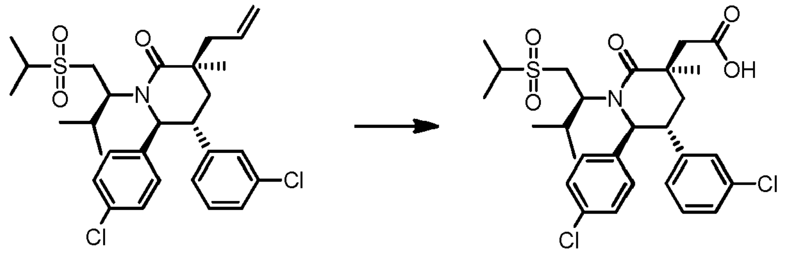
[0054] Mixed fractions from both experiments were combined and purified by flash chromatography twice more (220 g silica gel column; gradient elution 0% to 20% isopropanol in hexanes, 45 minutes), and again the pure fractions were set aside.

[0055] All of the pure fractions were combined, concentrated under a vacuum, dissolved in minimal acetonitrile/water and lyophilized.

Synthesis of AMG 232 (Alternative 3)

2-((3*R*,5*R*,6*S*)-5-(3-Chlorophenyl)-6-(4-chlorophenyl)-1-((*S*)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxo-piperidin-3-yl)acetic acid

[0056]



[0057] (3*S*,5*R*,6*S*)-3-Allyl-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methylpiperidin-2-one (5.05 g, 9.17 mmol) was weighed into a 500 mL round bottom flask containing a large stir bar and 2.04 g sodium periodate (2.04 g). The mixture was diluted with carbon tetrachloride (52 mL), acetonitrile, (52 mL) and water (78 mL). The flask was immersed in a room temperature water bath and the internal temperature was monitored with a digital thermocouple.

[0058] Ruthenium chloride hydrate (approximately 50 mg) was added in a single portion. The internal temperature rose to 22 °C, then ice was added to the bath to cool the mixture. Additional ruthenium chloride hydrate (25 mg) was added 3 minutes later. After stirring for a total of thirty minutes, Three portions of sodium periodate (2.08 g, 2.07 g and 2.08 g) were slowly added on 15 minute intervals. The temperature was kept below 19 °C, and ice was quickly added to the bath if the internal temperature began to rise. The mixture was stirred at ambient temperature overnight. The mixture was filtered through a pad of diatomaceous earth and the filter cake was washed copiously with ethyl acetate. The filtrate was concentrated under a vacuum and partitioned between 2 M HCl (100 mL) and ethyl acetate (200 mL).

[0059] Two rounds of flash column chromatography (330 g silica gel, then 220 g silica gel, gradient elution of 0% to 20% isopropanol in hexanes) provided the title compound. A portion of this material was lyophilized from acetonitrile and water. The less pure fractions were repurified by two additional rounds of flash column chromatography (220 g then 330 g silica gel columns, gradient elution of 0% to 20% isopropanol in hexanes). The most pure fractions from both runs were combined, concentrated under a vacuum and lyophilized from acetonitrile and water to give the title compound.

[0060] The invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: Compound A, and a second pharmaceutical compound that is either decitabine or cytarabine. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes and bags. Typically, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician or veterinarian.

[0061] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0062] It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, . etc ... Second Week, Monday, Tuesday,... " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a compound of the present invention can consist of one tablet or capsule, while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this and aid in correct administration of the active agents.

[0063] In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered microchip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

[0064] The compounds of the present invention and other pharmaceutically active compounds, if desired, can be administered to a patient either orally, rectally, parenterally, (for example, intravenously, intramuscularly, or subcutaneously) intracisternally, intravaginally, intraperitoneally, intravesically, locally (for example, powders, ointments or drops), or as a buccal or nasal spray. All methods that are used by those skilled in the art to administer a pharmaceutically active agent are contemplated.

[0065] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0066] These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Microorganism contamination can be prevented by adding various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0067] Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (a) solution retarders, as for example, paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, and tablets, the dosage forms may also comprise buffering agents.

[0068] Solid compositions of a similar type may also be used as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

[0069] Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compound can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0070] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame seed oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0071] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. Suspensions, in addition to the active compound, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

[0072] Compositions for rectal administration are preferable suppositories, which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary room temperature, but liquid at body temperature, and therefore, melt in the rectum or vaginal cavity and release the active component.

[0073] Dosage forms for topical administration of the compound of the present invention include ointments, powders, sprays and inhalants. The active compound or compounds are admixed under sterile condition with a physiologically acceptable carrier, and any preservatives, buffers, or propellants that may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0074] The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 3,000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram body weight is typically sufficient. The specific dosage and dosage range that can be used depends on a number of factors, including the requirements of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered. A particular dosage of a compound of the present invention is the FDA approved dosage, if the compound has been approved.

[0075] The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water (hydrate), ethanol, and the like. The present invention contemplates and encompasses both the solvated and unsolvated forms.

[0076] It is also possible that the compounds of the present invention may exist in different tautomeric forms. All tautomers of the compound of the present invention are contemplated.. Also, for example, all keto-enol or imine-enamine forms of the compounds are included in this invention.

[0077] Those skilled in the art will recognize that the compound names and structures contained herein may be based on a particular tautomer of a compound. While the name or structure for only a particular tautomer may be used, it is intended that all tautomers are encompassed by the present invention, unless stated otherwise.

[0078] It is also intended that the present invention encompass compounds that are synthesized *in vitro* using laboratory techniques, such as those well known to synthetic chemists; or synthesized using *in vivo* techniques, such as through metabolism, fermentation, digestion, and the like. It is also contemplated that the compounds of the present invention may be synthesized using a combination *of in vitro* and *in vivo* techniques.

[0079] The present invention also includes isotopically-labelled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{16}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl. In one aspect, the present invention relates to compounds wherein one or more hydrogen atom is replaced with deuterium (^{2}H) atoms.

[0080] The compounds of the present invention that contains the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of this invention can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0081] The compounds of the present invention may exist in various solid states including crystalline states and as an amorphous state. The different crystalline states, also called polymorphs, and the amorphous states of the present compounds are contemplated as part of this invention.

[0082] In synthesizing the compounds of the present invention, it may be desirable to use certain leaving groups. The term "leaving groups" ("LG") generally refer to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH_3), N-hydroxysuccinimide, N-hydroxybenzotriazole, and the like. Examples of nucleophiles include, but are not limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

[0083] The examples presented below illustrate specific embodiments of the present invention. These examples are meant to be representative and are not intended to limit the scope of the claims in any manner

[0084] The following abbreviations may be used herein:

932 or 2705932	AMG 232
ADD	additivity
AML	acute myelogenous leukemia
ATP	adenosine triphosphate

(continued)

Cispl	cisplatin
CML	chronic myelogenous leukemia
CPT-11	irinotecan
DIC	drug in capsules
DLBCL	diffuse large B-cell lymphoma
Dox	doxorubicin
GBM	glioblastoma
HPβCD	hydroxypropyl beta cyclodextrin
HPMC	hydroxypropyl methylcellulose
MDS	myelodysplastic syndrome
mpk	milligrams per kilogram
NHL	non-Hodgkin's lymphoma
NMR	nuclear magnetic resonance
NSCLC	non-small cell lung cancer
PBS	phosphate buffered saline
PCT	patent cooperation treaty
RTK	receptor tyrosine kinase
TGI	tumor growth inhibition
Tx begins	treatment begins

Cell Culture Reagents

Tween® 80	polyoxyethylene (20) sorbitan monooleate (Uniqema Americas, Inc., Wilmington, DE)
Pluronic® F68	polyoxyethylene-polyoxypropylene block copolymer (BASF Corp., Mount Olive, NJ)

EXAMPLES

In Vivo Tumor Xenograft Combination Studies

[0085] *In vivo* tumor xenograft studies were conducted following these general procedures:
Tumor cells (Table 1) were cultured, harvested and implanted subcutaneously into the right flank of female athymic nude mice. When tumors reached about 200mm^3, mice were randomized into treatment groups (n=10/group) and treatment was initiated (on days indicated on graphs). Compound names, dosing frequency, and routes of administration are listed in Table 2. Tumor sizes and body weights were measured 2 to 3 times per week. Tumor volume was measured by digital calipers, calculated as L x W x H and expressed in mm^3. Statistical significance of observed differences between growth curves was evaluated by repeated measures analysis of covariance (RMANOVA) of the log transformed tumor volume data with Dunnett adjusted multiple comparisons comparing the control group to the treatment groups. For combination studies, RMANOVA was run with the combination group compared one to one with each single agent treatment group.

[0086] BD Matrigel™ Basement Membrane Matrix is a solubilized basement membrane preparation extracted from the Engelbreth-Holm-Swarm (EHS) mouse sarcoma (BD Biosciences, San Jose, CA)

[0087] All studies were measured in a blinded manner.

Table 1:

Cell Line	**Tumor Type**	**Cells/mo use**	**Source #**	**Matrigel (cells: matrigel)**
RKO	Colon	5×10^6	(ATCC) CRL-2577	1:1

(continued)

Cell Line	Tumor Type	Cells/mo use	Source #	Matrigel (cells: matrigel)
SJSA-1	Osteosarcoma	5×10^6	(ATCC) CRL-2098	2:1
HCT116	Colorectal	2×10^6	(ATCC) CCL-247	2:1
A375sq2	Melanoma	5×10^6	See Reference above	2:1
NCI-H460	Non-small cell lung	5×10^6	(ATCC) HTB-177	no
U87	Glioblastoma	5×10^6	(ATCC) HTB-14	no
Molm13	Acute myelogenous leukemia	2.5×10^6	(DSMZ) AC-554	1:1

Table 2:

Treatment	Route	Frequency
AMG 232	PO	QD
1009089 (MEK)*	PO	QD
Cisplatin*	IP	1x/wk
CPT-11*	IP	1x/wk
Doxorubicin*	IV	1x/wk
2112819 (BRAF)*	PO	QD
RG7112 (MDM2)*	PO	QD
2520765 (PI3K)*	PO	QD
Cytarabine	IP	5 days on, 2 days off
Decitabine	IP	3x/wk
*Reference - not part of the claimed subject matter Definition of abbreviations: PO: oral gavage IP: intraperitoneal IV: intravenous QD: once per day Wk: week		

In vivo combination studies conducted:

[0088]

1. AMG 232 + MEK (RKO)*,
2. AMG 232 + BRAF (RKO)*
3. AMG 232 + cisplatin (H460)*
4. AMG 232 + cisplatin (HCT-116)*
5. AMG 232 + doxorubicin (SJSA-1)*
6. AMG 232 + irinotecan (HCT116)*
7. AMG 232 + MEK (A375sq2)*
8. AMG 232 + BRAF (A375sq2)*
9. AMG 232 + BRAF+ PI3K (RKO, triple combination)*
10. AMG 232 + doxorubicin (Molm-13)*
11. AMG 232 + MEK (Molm-13)*
12. AMG 232 + cytarabine (Molm-13)
13. AMG 232 + decitabine (Molm-13)
14. AMG 232 + sorafenib (Molm-13)*

[0089] The results of the *in vivo* tumor xenograft combination studies are shown in Figure 2 and 3.
. The data obtained and summarized in the Figures indicates that the claimed combinations of AMG 232 with decitabine or cytarabine, respectively, show enhanced activity against AML over what is expected when the individual members of the combination therapy are used alone.

Claims

1. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid for use in a method for the treatment of acute myelogenous leukemia, said method comprising administering to a patient in need thereof an effective amount of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and decitabine.

2. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid for use in a method for the treatment of acute myelogenous leukemia, said method comprising administering to a patient in need thereof an effective amount of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and cytarabine.

3. 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid for use in a method for the treatment of acute myelogenous leukemia according to claim 1 or 2, wherein the acute myelogenous leukemia has a FLT3-ITD mutation.

4. A pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and decitabine for use in a method for the treatment of acute myelogenous leukemia.

5. A pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and cytarabine for use in a method for the treatment of acute myelogenous leukemia.

6. A kit of pharmaceutical compositions for use in a method of treatment of acute myelogenous leukemia, said kit comprising separate pharmaceutical compositions, one of the pharmaceutical compositions comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and the other pharmaceutical composition comprising decitabine.

7. A kit of pharmaceutical compositions for use in a method of treatment of acute myelogenous leukemia, said kit comprising separate pharmaceutical compositions, one of the pharmaceutical compositions comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and the other pharmaceutical composition comprising cytarabine.

Patentansprüche

1. 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsaure zur Verwendung in einem Verfahren zur Behandlung von akuter myeloischer Leukämie, wobei das Verfahren die Verabreichung einer wirksamen Menge von 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsaure und Decitabin an einen Patienten, der dessen Bedarf, umfasst.

2. 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsaure zur Verwendung in einem Verfahren zur Behandlung von akuter myeloischer Leukämie, wobei das Verfahren die Verabreichung einer wirksamen Menge von 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsäure und Cytarabin an einen Patienten, der dessen Bedarf, umfasst.

3. 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsäure zur Verwendung in einem Verfahren zur Behandlung von akuter myeloischer Leukämie gemäß Anspruch 1 oder 2, worin die akute myeloische Leukämie eine FLT3-ITD-Mutation aufweist.

4. Pharmazeutische Zusammensetzung, umfassend 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsäure und Decitabin zur Verwendung in einem Verfahren zur Behandlung von akuter myeloischer Leukämie.

5. Pharmazeutische Zusammensetzung, umfassend 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsäure und Cytarabin zur Verwendung in einem Verfahren zur Behandlung von akuter myeloischer Leukämie.

6. Kit von pharmazeutischen Zusammensetzungen zur Verwendung in einem Verfahren zur Behandlung von akuter myeloischer Leukämie, wobei das Kit separate pharmazeutische Zusammensetzungen umfasst, worin eine der pharmazeutischen Zusammensetzungen 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsäure umfasst und die andere pharmazeutische Zusammensetzung Decitabin umfasst.

7. Kit von pharmazeutischen Zusammensetzungen zur Verwendung in einem Verfahren zur Behandlung von akuter myeloischer Leukämie, wobei das Kit separate pharmazeutische Zusammensetzungen umfasst, worin eine der pharmazeutischen Zusammensetzungen 2-((3R,5R,6S)-5-(3-Chlorphenyl)-6-(4-chlorphenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)essigsäure umfasst und die andere pharmazeutische Zusammensetzung Cytarabin umfasst.

Revendications

1. Acide 2-((3R,5R,65)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-((S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique destiné à être utilisé dans un procédé de traitement de la leucémie aiguë myéloblastique, ledit procédé comprenant l'administration à un patient en ayant besoin d'une quantité efficace d'acide 2-((3R,5R,6S)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-((S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique et de décitabine.

2. Acide 2-((3R,5R,65)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-((S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique destiné à être utilisé dans un procédé de traitement de la leucémie aiguë myéloblastique, ledit procédé comprenant l'administration à un patient en ayant besoin d'une quantité efficace d'acide 2-((3R,5R,6S)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-((S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique et de cytarabine.

3. Acide 2-((3R,5R,6S)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-((S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique destiné à être utilisé dans un procédé de traitement de la leucémie aiguë myéloblastique selon la revendication 1 ou 2, dans lequel la leucémie aiguë myéloblastique présente une mutation FLT3-ITD.

4. Composition pharmaceutique comprenant l'acide 2-((3R,5R,6S)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-(S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique et de la décitabine destinée à être utilisée dans un procédé de traitement de la leucémie aiguë myéloblastique.

5. Composition pharmaceutique comprenant l'acide 2-((3R,5R,6S)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-(S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique et de la cytarabine destinée à être utilisée dans un procédé de traitement de la leucémie aiguë myéloblastique.

6. Kit de compositions pharmaceutiques destiné à être utilisé dans un procédé de traitement de la leucémie aiguë myéloblastique, ledit kit comprenant des compositions pharmaceutiques distinctes, l'une des compositions pharmaceutiques comprenant l'acide 2-((3R,5R,6S)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-((S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique et l'autre composition pharmaceutique comprenant de la décitabine.

7. Kit de compositions pharmaceutiques destiné à être utilisé dans un procédé de traitement de la leucémie aiguë myéloblastique, ledit kit comprenant des compositions pharmaceutiques distinctes, l'une des compositions pharmaceutiques comprenant l'acide 2-((3R,5R,6S)-5-(3-chlorophényl)-6-(4-chlorophényl)-1-((S)-1-(isopropylsulfonyl)-3-méthylbutan-2-yl)-3-méthyl-2-oxopipéridin-3-yl)acétique et l'autre composition pharmaceutique comprenant de la cytarabine.

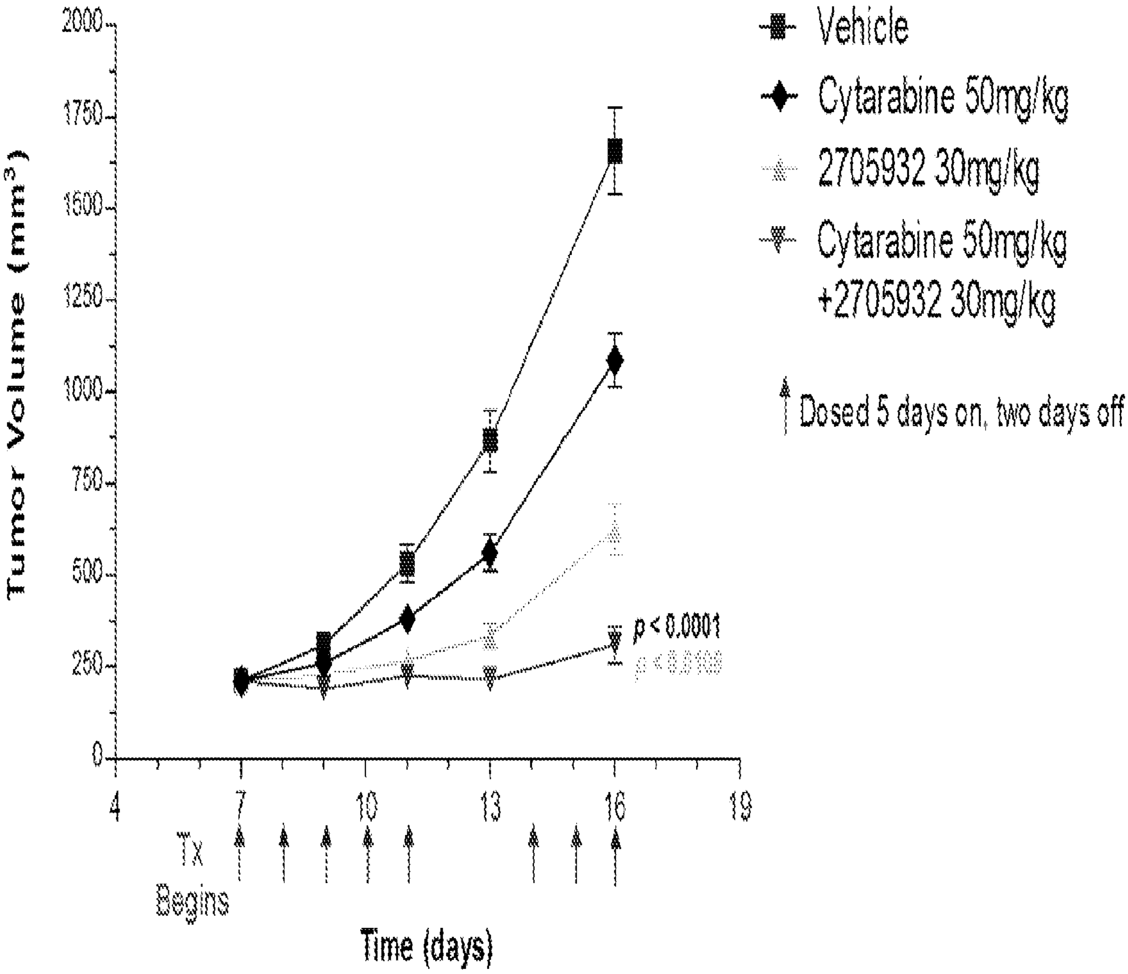
Figure 1

AMG 232 – Chemotherapeutic Combinations

		MCF7 (Breast)	RKO (Colon)	KS-1 (GBM)	A427 (NSCLC)	SJSA-1 (Sarcoma)	SW982 (Sarcoma)	MKN45 (Stomach)	NCI-SNU-1 (Stomach)	EOL-1 (AML)	MOLM-13 (AML)	HT-29 (Colon) TP53	PC-3 (Prostate) TP53
Platinums	AMG 232 x Cisplatin				0.70							0.19	0.48
	AMG 232 x Oxaliplatin		8.85									0.08	0.18
Topoisomerase II	AMG 232 x Doxorubicin	4.63								4.37	9.63	1.14	2.14
	AMG 232 x Etoposide					2.16	9.05	2.86	1.88			1.92	0.52
Topoisomerase I	AMG 232 x Irinotecan		1.69									0.95	0.67
DNA Alkylation	AMG 232 x Temozolomide			2.61								0.04	0.18
Nucleoside Analogs	AMG 232 x Cytarabine									6.90	8.70	0.56	1.33
	AMG 232 x Decitabine									12.49	13.57	0.07	0.86

Figure 2

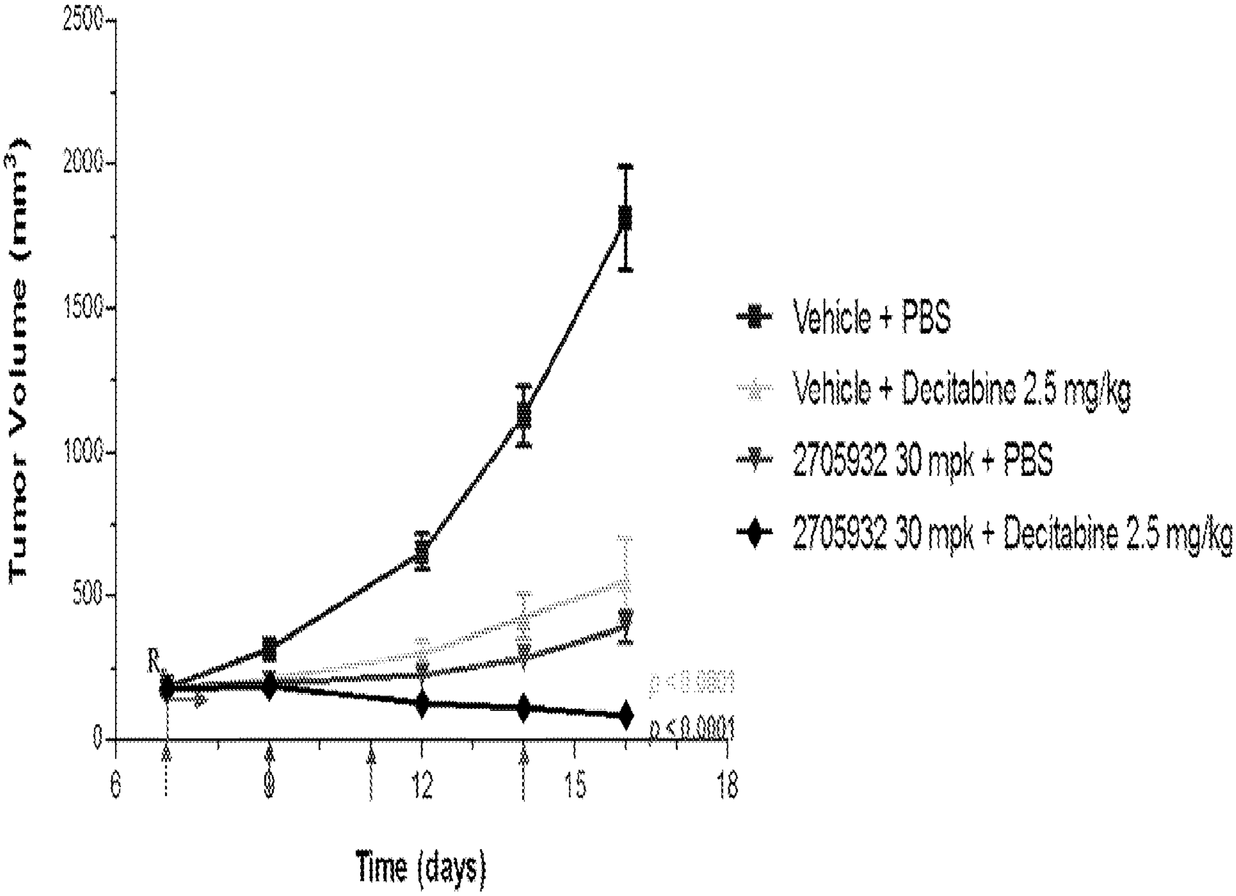
MDM2 Inhibitor and Cytarabine in Molm13 Tumors



Vehicle: 15% HPβCD, 1% Pluronic F68, pH 9.4 and Saline

Figure 3

MDM2 Inhibitor and Decitabine in Molm13 Tumors



Vehicle (2705932): 15% HPßCD, 1% Pluronic F68, pH 9.4

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2011153509 A **[0020]**
- US 61833196 **[0022]**