TITLE OF THE INVENTION

7-benzyl-4-(2-methylbenzyl)-2,4,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(1H)-one, Salts Thereof and Methods of Using the Same in Combination Therapy

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to, and the benefit of, U.S. Provisional Patent Application Nos. 61/779,828, filed 13 March 2013, now pending; and 61/904,718, filed **15** November 2013, now pending, all of which are incorporated herein by reference in their entireties.

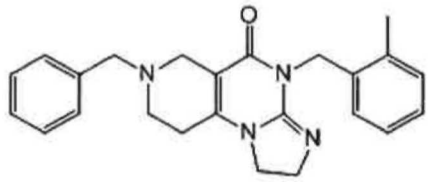
BACKGROUND OF THE INVENTION

[0003] TNF-related apoptosis-inducing ligand (TRAIL; Apo2L) is an endogenous protein that selectively induces apoptosis in cancer cells. TRAIL is a powerful inducer of apoptosis in a wide range of human cancer cell lines via pro-apoptotic death receptor 4 (DR4; TRAIL-R1) and death receptor 5 (DR5; TRAIL-R2) at the cell surface through engagement of the extrinsic or intrinsic apoptotic pathways. TRAIL plays a direct role in tumor suppression during immune surveillance but this anti-tumor mechanism is lost during the disease progression. The ability of TRAIL to initiate apoptosis selectively in cancer cells has led to ongoing clinical trials with administration of recombinant TRAIL and the longer-lived TRAIL-agonist antibodies targeting either of its two pro-apoptotic death receptors.

[0004] Despite its potency, recombinant TRAIL has efficacy-limiting properties such as short serum half-life, stability, cost, and delivery. Delivery of recombinant TRAIL or TRAIL-agonist antibodies to the brain is limited by inability of recombinant TRAIL and TRAIL-agonist antibodies to cross the blood-brain barrier. Accordingly, there is a continuing need for anti-cancer compositions and methods.

BRIEF SUMMARY OF THE INVENTION

[0005] In one aspect, the present invention provides a pharmaceutical composition, comprising a compound (**1**):



Compound (1)

or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition comprises compound (**1**) in the form of a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition comprises compound (**1**) in the form of a pharmaceutically acceptable mono-salt thereof. In one embodiment, the pharmaceutical composition comprises compound (**1**) in the form of a pharmaceutically acceptable di-salt thereof. In one embodiment, the pharmaceutical composition comprises compound (**1**) in the form of a pharmaceutically acceptable salt selected from the group consisting of hydrochloride, hydrobromide, hydrogensulphate, sulfates, phosphates, fumarates, succinates, oxalates and lactates, bisulfates, hydroxyl, tartrate, nitrate, citrate, bitartrate, carbonate, malate, maleate, fumarate sulfonate, methylsulfonate, formate, acetate, and carboxylate. In one embodiment, the pharmaceutical composition comprises compound (**1**) in the form of a pharmaceutically acceptable salt selected from the group consisting of p-toluene-sulfonate, benzenesulfonate, methanesulfonate, oxalate, succinate, tartrate, citrate, fumarate, glucuronate, ascorbate and maleate. In one embodiment, the pharmaceutical composition comprises compound (**1**) in the form of a pharmaceutically acceptable salt selected from the group consisting of ammonium, sodium, potassium, calcium, magnesium, zinc, lithium, and/or with other counter-ions such as methylamino, dimethylamino, diethylamino and triethylamino counter-ions. In one embodiment, the pharmaceutical composition comprises compound (**1**) in the form of a hydrochloride di-salt or hydrobromide di-salt.

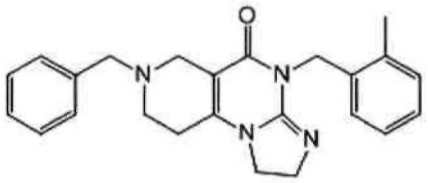
[0006] In one embodiment, the pharmaceutical composition of the present invention includes a pharmaceutically acceptable carrier.

[0007] In some embodiments, a pharmaceutical composition in accordance with the present invention includes a second therapeutic agent. In one such embodiment, the second therapeutic agent is an anti-cancer agent. In one embodiment, the anti-cancer agent is a mitotic inhibitor. In one embodiment, the anti-cancer agent is selected from the group consisting of: paclitaxel, docetaxel and a combination thereof. In an alternative embodiment, the second therapeutic agent is an anti-angiogenic agent. In one embodiment, the anti-angiogenic agent is bevacizumab. In one embodiment, the second therapeutic agent is administered as part of combination therapy to

treat a patient. In one embodiment, details for the combination therapy is included in the package insert for compound (**1**).

[0008] In some embodiments, the pharmaceutical composition is formulated for oral administration.

[0009] In another aspect, the present invention provides a method of treatment. In one embodiment, the method of treatment comprises administering to a subject a pharmaceutical composition, the pharmaceutical composition comprising a pharmaceutically effective amount of compound (**1**):



Compound (1)

or a pharmaceutically acceptable salt thereof.

[0010] In one embodiment, the method of treatment comprises administering to the subject a pharmaceutical composition comprising a pharmaceutically effective amount of compound (**1**) or a pharmaceutically acceptable salt thereof. In one embodiment, the method of treatment comprises administering to the subject a pharmaceutical composition comprising a pharmaceutically effective amount of compound (**1**) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

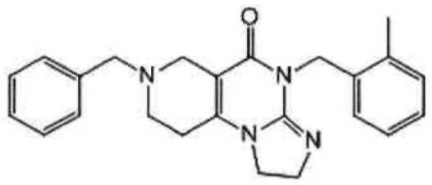
[0011] In some embodiments, the method of treatment comprises further comprising administering an additional therapeutic agent. In one embodiment, the additional therapeutic agent includes an anti-cancer agent. In one embodiment, the additional anti-cancer agent comprises an anti-mitotic agent. In one embodiment, the additional anti-cancer agent comprises paclitaxel, docetaxel, bevacizumab or any combinations thereof.

[0012] In one embodiment, the method of treatment further comprises assaying tumor necrosis factor (TNF)-related apoptosis-inducing ligand in a sample obtained from the subject undergoing treatment. In one embodiment, the TNF-related apoptosis-inducing ligand is assayed in a blood sample obtained from the subject.

[0013] In one embodiment of the method of treatment in accordance with the present invention, the subject undergoing treatment has, or is at risk of having, cancer. In one embodiment, the cancer is selected from the group consisting of colon cancer, breast cancer, glioblastoma multiforme, Mantle cell lymphoma, and colorectal cancer.

[0014] In one embodiment of the method of treatment in accordance with the present invention, the pharmaceutical composition is administered via an oral route of administration. In one embodiment, the pharmaceutical composition is administered via a route of administration selected from the group consisting of: rectal, nasal, pulmonary, epidural, ocular, otic, intra-arterial, intracardiac, intracerebroventricular, intradermal, intravenous, intramuscular, intraperitoneal, intraosseous, intrathecal, intravesical, subcutaneous, topical, transdermal, transmucosal, sublingual, buccal, vaginal, and inhalational routes of administration.

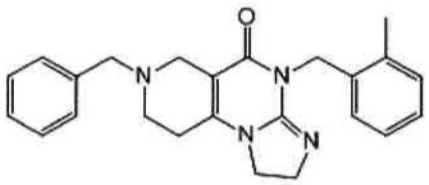
[0015] In one embodiment, the present invention provides a method of treating a subject having, or is at risk of having, brain cancer, the method comprising: administering to the subject a pharmaceutical composition comprising a pharmaceutically effective amount of compound (**1**):



Compound (**1**)

or a pharmaceutically acceptable salt thereof. In one embodiment, the method of treating a subject having, or is at risk of having brain cancer, comprises administering to the subject a pharmaceutical composition comprising a pharmaceutically effective amount of compound (**1**) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0016] In one embodiment, the present invention provides a method of treatment comprising administering to a subject a pharmaceutical composition, the pharmaceutical composition comprising a pharmaceutically effective amount of compound (**1**):



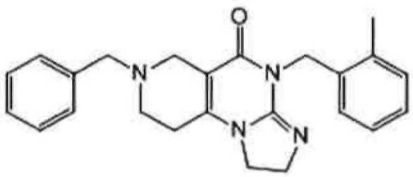
Compound (**1**)

or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[0017] The foregoing summary, as well as the following detailed description of embodiments of the compositions and methods of treatment, will be better understood when read in conjunction with the appended claims. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities described herein.

[0018] In another aspect, the present invention provides a method of treatment, which comprises administering to a subject in need of such treatment a combination of a first therapeutic agent including the following compound (1) and a second therapeutic agent, the method comprising:

(i) administering to the subject the first therapeutic agent including compound (1):



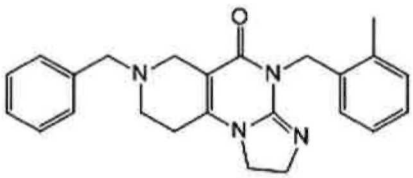
compound (1)

or a pharmaceutically acceptable salt thereof;

(ii) waiting until a predetermined waiting time has elapsed after the time of administration of the first therapeutic agent to the subject; and (iii) administering the second therapeutic agent to the subject, wherein the predetermined waiting time is chosen so as to obtain a delayed therapeutic effect of the first therapeutic agent without an increased risk or with a reduced risk of possible combined toxic effects of the first and second therapeutic agents.

[0019] In another aspect, the present invention provides a method of treatment, which comprises administering to a subject in need of such treatment a combination of a first therapeutic agent and a second therapeutic agent, the method comprising:

(i) administering to the subject the first therapeutic agent including compound (1):



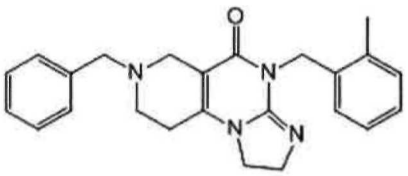
compound (1)

or a pharmaceutically acceptable salt thereof;

(ii) monitoring level of compound (1) or a pharmaceutically acceptable salt thereof or a metabolite thereof in the subject using pharmacokinetic profiling; and

(iii) administering the second therapeutic agent conditional on the level of the first therapeutic agent in the subject.

[0020] In another aspect, the present invention provides a method of treatment, which comprises administering to a subject in need of such treatment a combination of a first therapeutic agent and a second therapeutic agent, the method comprising:
(i) administering to the subject the first therapeutic agent including compound (1):

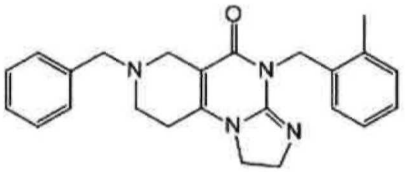


compound (1)

or a pharmaceutically acceptable salt thereof; and

(iii) administering the second therapeutic agent conditional on the expected half life of exemplary compound (1) of about 3 hours to about 8 hours in the subject undergoing treatment. In some embodiments, the expected half life of exemplary compound (1) is from about 3 hours to about 24 hours in the subject undergoing treatment.

[0021] In another aspect, the present invention provides a method of treatment, which comprises administering to a subject in need of such treatment a combination of a first therapeutic agent and a second therapeutic agent, the method comprising:
(i) administering to the subject the first therapeutic agent including compound (1):



compound (1)

or a pharmaceutically acceptable salt thereof; and

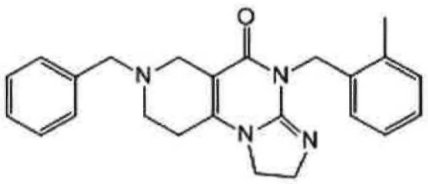
(iii) administering the second therapeutic agent conditional on adverse events from the first therapeutic agent have resolved or are resolving. In some embodiments, adverse events from the first therapeutic agent are related to the blood levels of the the first therapeutic agent or metabolites thereof in the subject undergoing treatment.

[0022] In another aspect, the present invention provides a kit for monitoring of compound (1) or a pharmaceutically acceptable salt thereof or a metabolite thereof in an individual treated with compound (1) or a pharmaceutically acceptable salt thereof or a metabolite thereof using pharmacokinetic profiling, the kit comprising a plurality of point-of-care device or a point of use device capable of quantitating the drug in the at least two samples or matrices suitable for

[0028] The singular terms "a," "an," and "the" are not intended to be limiting and include plural referents unless explicitly state or the context clearly indicates otherwise.

I. COMPOSITIONS

[0029] In one aspect, the present invention provides a pharmaceutical composition, comprising a compound (1):

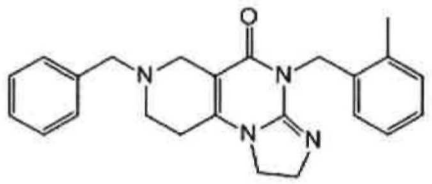


Compound (1)

or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition comprises compound (1) or a pharmaceutically acceptable mono-salt thereof. In one embodiment, the pharmaceutical composition comprises compound (1) or a pharmaceutically acceptable di-salt thereof. In one embodiment, the pharmaceutical composition comprises compound (1) or a pharmaceutically acceptable mono- or multi-salt (e.g., di – salt or tri-salt, where it is understood that througout this disclosure a di-salt encompasses a multi-salt or tri-salt) thereof selected from the group consisting of hydrochloride, hydrobromide, hydrogensulphate, sulfates, phosphates, fumarates, succinates, oxalates and lactates, bisulfates, hydroxyl, tartrate, nitrate, citrate, bitartrate, carbonate, malate, maleate, fumarate sulfonate, methylsulfonate, formate, and carboxylate. In one embodiment, the pharmaceutical composition comprises compound (1) or a pharmaceutically acceptable salt thereof selected from the group consisting of p-toluene-sulfonate, benzenesulfonate, methanesulfonate, oxalate, succinate, tartrate, citrate, fumarate and maleate. In one embodiment, the pharmaceutical composition comprises compound (1) or a pharmaceutically acceptable salt selected from the group consisting of ammonium, sodium, potassium, calcium, magnesium, zinc, lithium, and/or with counter-ions such as methylamino, dimethylamino, diethylamino and triethylamino counter-ions. In one embodiment, the pharmaceutical composition comprises compound (1), a hydrochloride di-salt thereof (e.g., di-hydrochloride salt) or a hydrobromide di-salt thereof (e.g., di-hydrobromide salt).

[0030] In one embodiment, a pharmaceutical composition in accordance with the present invention includes a di-salt (e.g., a di-hydrochloride salt) of compound (1).

[0031] Salts (e.g., di-salts or tri-salts) of compound (1) can be prepared from compound (1):



Compound (1)

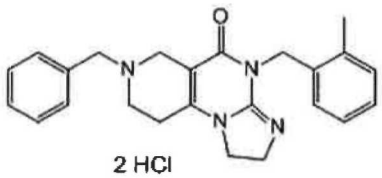
, which can be obtained commercially or synthesized using standard chemical synthetic methodology known to one of ordinary skill in the art.

[0032] In one embodiment, the pharmaceutical composition in accordance with the present invention includes at least one pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers, included, but are not limited to, those found in Handbook of Pharmaceutical Excipients, 7th Edition, edited by Raymond C. Rowe et al., American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and earlier editions.

[0033] Exemplary pharmaceutically acceptable carriers, methods for making pharmaceutical compositions and various dosage forms, as well as modes of administration are well-known in the art, for example as detailed in Pharmaceutical Dosage Forms: Tablets, edited by Larry L. Augsburger and Stephen W. Hoag., London: Informa Healthcare, 2008; and in L. V. Allen, Jr. et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Ed., Philadelphia, Pa.: Lippincott, Williams & Wilkins, 2004; A. R. Gennaro, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, 21st ed., 2005, particularly chapter 89; and J. G. Hardman et al., Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill Professional, 10th ed., 2001.

[0034] In some embodiments, the pharmaceutical composition of the present invention is formulated as intravenous formulation. In one embodiment, the intravenous formulation comprises compound (1) or a pharmaceutically acceptable salt of compound (1) dissolved in a solvent. In one embodiment, the solvent comprises water. In one such embodiment, the intravenous formulation comprises compound (1) or a pharmaceutically acceptable salt of compound (1) dissolved in water at a concentration of 25 mg/ml. In some embodiments, the intravenous formulation includes a higher or a lower concentration of compound (1) or a pharmaceutically acceptable salt thereof. In one embodiment, the intravenous formulation includes compound (1) or a pharmaceutically acceptable salt thereof in a concentration of from about 5 mg/ml to about 100 mg/ml. In one embodiment, the intravenous formulation includes compound (1) or a pharmaceutically acceptable salt thereof in a concentration of about 50

sequentially. The second therapeutic agent can be any suitable therapeutic agent, including any of the pharmaceutically active agents disclosed in in this application. In one embodiment, the pharmaceutically accetable salt of compound (**1**) includes a di-hydrochloride salt having the structure of compound (2):



Compound (2)

[0072]

[0073] It is understood that compound (2), or an alternative di-salt thereof apparent from the teaching of this disclosure, can be substitued for a compound (**1**) in any of the compositions or dosing regimens described hererin.

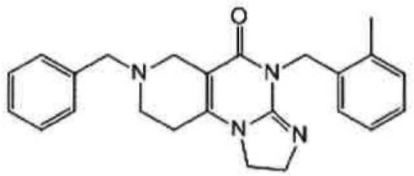
[0074] In some embodiments, the method of treatment comprises administering to a subject in need of such treatment, a pharmaceutically effective amount of compound (**1**) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0075] In some embodiments, the method of treatment of the present invention comprises administering a synergistic pharmaceutical combination, either simultaneously or sequentially, to a subject in need of such treatment, wherein the synergistic pharmaceutical combination comprising (i) a first therapeutic agent comprising compound (**1**) or a pharmaceutically acceptable salt thereof; and (ii) a second therapeutic agent. In one embodiment, the method of treatment comprises administering to a subject in need of such treatment, either simultaneously or sequentially, therapeutically synergistic effective amounts of a first therapeutic agent comprising compound (**1**) or a pharmaceutically acceptable salt thereof in combination with a second therapeutic agent. In one embodiment, the method of treatment comprises administering to a subject in need of such treatment an effective amount of a first therapeutic agent comprising compound (**1**) or a pharmaceutically acceptable salt thereof in combination with an effective amount of a second therapeutic agent, wherein the combination provides a synergistic effect in the in vivo treatment of cancer sensitive to the combination, and wherein the first therapeutic agent and the second therapeutic agent are administered either simultaneously or sequentially. In one embodiment, the method of treatment comprises administering to a subject in need of such treatment an effective amount of a first therapeutic agent comprising compound (**1**) or a pharmaceutically acceptable salt thereof in combination

cycle of once weekly, once every two weeks, once every three weeks, once every four weeks or combinations thereof.

[00107] In an aspect, the present invention provides a method of treatment, which comprises administering to a subject in need of such treatment a combination of a first therapeutic agent including the following compound (**1**) and a second therapeutic agent, the method comprising:

(i) administering to the subject the first therapeutic agent including compound (**1**):



compound (**1**)

or a pharmaceutically acceptable salt (e.g., a di-salt or tri-salt) thereof;

(ii) waiting until a predetermined waiting time has elapsed after the time of administration of the first therapeutic agent to the subject; and / or until adverse events are resolved or resolving; and

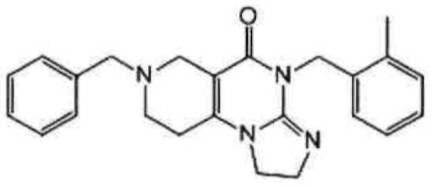
(iii) administering the second therapeutic agent to the subject, wherein the predetermined waiting time is chosen so as to obtain a delayed therapeutic effect of the first therapeutic agent without an increased risk of possible combined toxic effects of the first and second therapeutic agents. In some embodiments of the method of treatment, the predetermined waiting time is determined based on the clearance rate of compound (**1**) or the pharmaceutically acceptable salt thereof. In some embodiments of the method of treatment, the predetermined waiting time is determined by a quantitative assessment of renal function and parameters of renal. In some embodiments of the method of treatment, the predetermined waiting time is determined by an assays for the determination of renal function, wherein the assay is selected from the group consisting of serum level of compound (**1**) or the pharmaceutically acceptable salt thereof; compound (**1**) or the pharmaceutically acceptable salt thereof clearance rate; 24-hour urinary clearance of compound (**1**) or the pharmaceutically acceptable salt thereof or a metabolite thereof.

[00108] In one embodiment of the method of treatment, the predetermined waiting time substantially equals to the time required for systemic clearance of compound (**1**) or a pharmaceutically acceptable salt thereof from the body of the subject. In one embodiment of the method of treatment, the predetermined waiting time substantially equals to the time

from about 1165 ng/dl to about 1500 ng/dl, from about 1175 ng/dl to about 1500 ng/dl, from about 1185 ng/dl to about 1500 ng/dl, from about 1195 ng/dl to about 1500 ng/dl, from about 1205 ng/dl to about 1500 ng/dl, from about 1215 ng/dl to about 1500 ng/dl, from about 1225 ng/dl to about 1500 ng/dl, from about 1235 ng/dl to about 1500 ng/dl, from about 1245 ng/dl to about 1500 ng/dl, from about 1255 ng/dl to about 1500 ng/dl, from about 1265 ng/dl to about 1500 ng/dl, from about 1275 ng/dl to about 1500 ng/dl, from about 1285 ng/dl to about 1500 ng/dl, from about 1295 ng/dl to about 1500 ng/dl, from about 1305 ng/dl to about 1500 ng/dl, from about 1315 ng/dl to about 1500 ng/dl, from about 1325 ng/dl to about 1500 ng/dl, from about 1335 ng/dl to about 1500 ng/dl, from about 1345 ng/dl to about 1500 ng/dl, from about 1355 ng/dl to about 1500 ng/dl, from about 1365 ng/dl to about 1500 ng/dl, from about 1375 ng/dl to about 1500 ng/dl, from about 1385 ng/dl to about 1500 ng/dl, from about 1395 ng/dl to about 1500 ng/dl, from about 1405 ng/dl to about 1500 ng/dl, from about 1415 ng/dl to about 1500 ng/dl, from about 1425 ng/dl to about 1500 ng/dl, from about 1435 ng/dl to about 1500 ng/dl, from about 1445 ng/dl to about 1500 ng/dl, from about 1455 ng/dl to about 1500 ng/dl, from about 1465 ng/dl to about 1500 ng/dl, from about 1475 ng/dl to about 1500 ng/dl, from about 1485 ng/dl to about 1500 ng/dl, from about 1495 ng/dl to about 1500 ng/dl, and from about 1500 ng/dl to about 1500 ng/dl.

[00116] In another aspect, the present invention provides a method of treatment, or use of the composition to treat a disease state, which comprises administering to a subject in need of such treatment a combination of a first therapeutic agent and a second therapeutic agent, the method comprising:

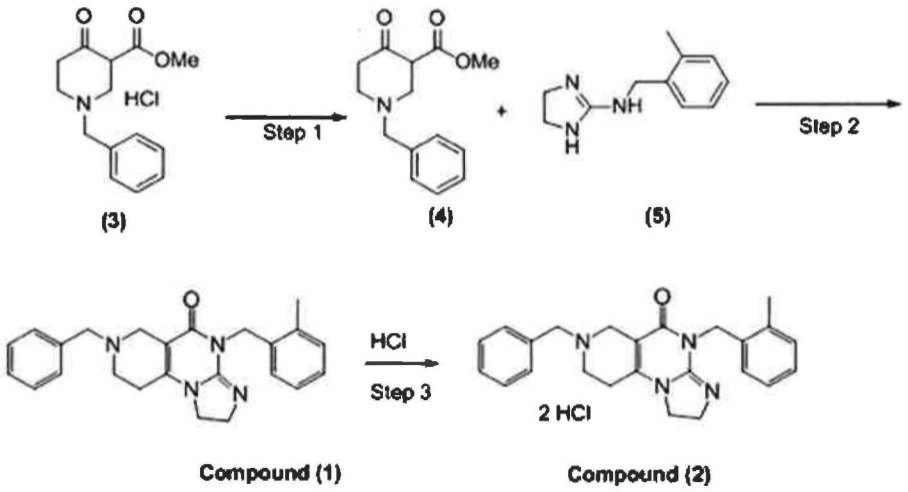
(i) administering to the subject the first therapeutic agent including compound (**1**):



compound (**1**)

or a pharmaceutically acceptable salt thereof;

(ii) monitoring level of compound (**1**) or a pharmaceutically acceptable salt thereof or a metabolite thereof in the subject using pharmacokinetic profiling; and



Scheme 1

[00125] In one embodiment, the process for making dihydrochloride salt of compound (**1**) commences with the intermediary compound of (3), also known as N-Benzyl-3-carbomethoxy-4-piperidone hydrochloride, which is commercially available. In one embodiment, the synthetic process includes neutralizing the intermediary compound of (3) with a base (Step 1) to produce the compound of (4), a free base. In one embodiment, the synthetic process includes neutralizing the intermediary compound of (3) with an inorganic base to produce the compound of (4). In one embodiment, the synthetic process includes neutralizing the intermediary compound of (3) with an organic base to produce the compound of (4). In one embodiment, the intermediary compound of (3) is neutralized in the presence of an alcohol. In one such embodiment, the intermediary compound of (3) is neutralized in the presence of n-butanol. In one embodiment, the intermediary compound of (3) is neutralized in the presence of at least one organic solvent. In one such embodiment, the intermediary compound of (3) is neutralized in the presence of n-butanol and/or ethyl acetate. In one embodiment, the intermediary compound of (3) is neutralized in the presence of a base and at least one organic solvent. In one such embodiment, the intermediary compound of (3) is neutralized in the presence of NaHCO3 and n-butanol. In one embodiment, the intermediary compound of (3) is neutralized in the presence of n-butanol and triethyl amine (Et3N).

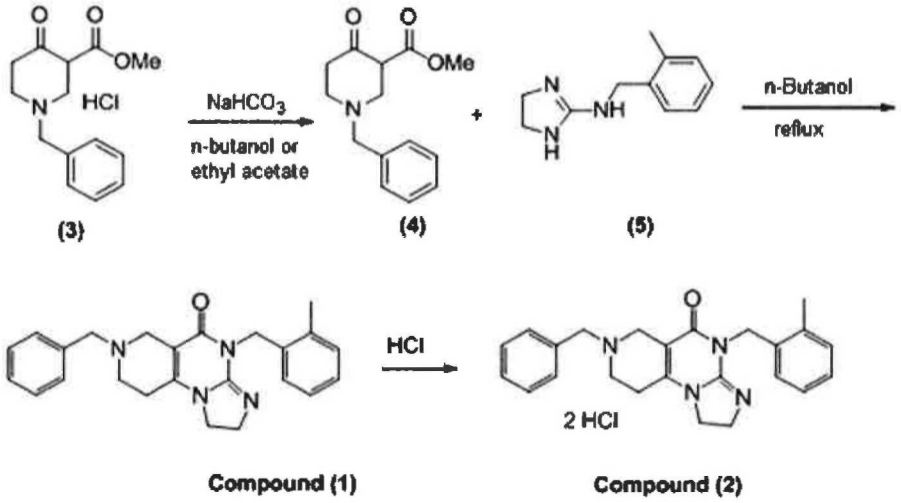
[00126] In one embodiment, the synthetic process includes reacting the compound of (4) with the compound of (5) (Step 2) to produce intermediary compound of (**1**). In one embodiment, the reaction in Step 2 includes heating the compound of (4) with the compound of (5). In one embodiment, the reaction in Step 2 includes refluxing heating the compound of (4) and the compound of (5) in the presence of a solvent. In one embodiment, the reaction in Step 2

includes use of Dean-stark trap to remove water and/or methanol (MeOH) formed in the reaction.

[00127] In one embodiment, the synthetic process includes forming a dihydrochloride salt of the compound of (**1**) (Step 3). In one embodiment, the reaction in Step 3 includes treating compound of (**1**) with HCl in dioxane. In one embodiment, the reaction in Step 3 includes treating compound (3) with 4N HCl in dioxane.

[00128] In one embodiment, the synthetic process optionally includes recrystallization of the di-salt of compound (**1**).

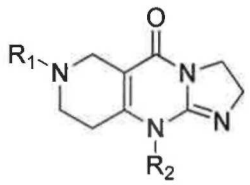
[00129] In one preferred embodiment, the synthetic process for the preparation of the di-hydrochloride salt of compound (**1**) is as illustrated in the following Scheme 2.



Scheme 2

VIII. DERIVATIVES AND ANALOGS OF AND SALTS OF COMPOUND (1) AND RELATED COMPOUNDS

[00130] In one aspect, the present invention provides analogs and related salts of compound (**1**) and processes of making the same. In one embodiment, the compounds related to compound (**1**) have the structure of compound (10):



(10)

[00131] , wherein R_1 and R_2 independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, carboxyl, haloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aralkyl, hydroxyalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, alkanoyl,