Therapeutic Modulators of the Reverse Mode of ATP Synthase

RELATED APPLICATIONS

This application claims the priority benefit of GB application numbers GB1711250.9 (filed 13 July 2017), GB1715756.1 (filed 28 September 2017), GB1715758.7 (filed 28 September 2017), GB1715938.5 (filed 1 October 2017), GB1716492.2 (filed 9 October 2017), GB1800092.7 (filed 4 January 2018), GB1800291.5 (filed 8 January 2018), GB1800581.9 (filed 15 January 2018), GB1801536.2 (filed 30 January 2018), GB1806421.2 (filed 19 April 2018), GB1808331.1 (filed 21 May 2018), GB1809497.9 (filed 8 June 2018), GB1810236.8 (filed 21 June 2018), GB1811188.0 (filed 8 July 2018), and PCT application number PCT/EP2018/051127 (filed 17 January 2017), which claims priority benefit of some aforementioned applications and also further GB application numbers GB1700772.5 (filed 17 January 2017), GB1706046.8 (filed 14 April 2017), GB1707945.0 (filed 17 May 2017), and GB1710198.1 (filed 27 June 2017). The entire teachings of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

This invention discloses compounds that preferentially slow the ATP-hydrolysing mode of ATP synthase, pharmaceutical compositions of these compounds, and methods of use for treating subjects known to have various diseases or disorders including cancer (e.g. diagnosed with), subjects suspected of having various diseases or disorders including cancer or subjects at risk of developing various diseases or disorders including cancer. In a particular embodiment, the subject is a human.

BACKGROUND OF THE INVENTION

ATP synthase

ATP synthase (also known as F_1F_0 ATP synthase, F_0F_1 ATP synthase, F_1F_0-ATPase, F_0F_1-ATPase, F_1F_0 ATP hydrolase) is located at the inner mitochondrial membrane (IM). It can use the proton motive force (pmf) to generate ATP from ADP and Pi [1-3]. ATP synthase is reversible and - depending on its substrate/product concentrations, the pmf and the voltage across inner mitochondrial membrane $\{\Psi_{IM}\}$ - it can work “forwards” (passaging protons, making ATP) or “backwards” (pumping protons, consuming ATP): its “forward” and

"reverse" modes respectively, which may also be termed F_1F_0 ATP synthesis and F_1F_0 ATP hydrolysis respectively.

Inhibitors of ATP synthase

There are drug inhibitors of ATP synthase, reviewed in [4] (herein incorporated in its entirety). Some inhibitors disproportionally/selectively inhibit the reverse mode, as compared to the forward mode, of ATP synthase [4-13]. Macrolides are a class of polyketide. So macrolide F_1F_0 ATP synthase inhibitors are polyketide F_1F_0 ATP synthase inhibitors, and these terms are used interchangeably herein. Polyketide F_1F_0 ATP synthase inhibitors (e.g. oligomycin) inhibit the forward mode, more than the reverse mode, of ATP synthase [11]. Oligomycin is well known in the art as an inhibitor of F_1F_0 ATP synthase, and thence oxidative phosphorylation and aerobic respiration [3]. Human life relies upon aerobic respiration. Indeed, the importance of breathing (O_2 in, CO_2 out) is widely appreciated. Thence the danger of oligomycin is easily apparent.

IF_1 is an endogenous protein, encoded by the ATPIF1 gene, which selectively blocks the reverse mode of ATP synthase [4]. Its activity is pH sensitive and low, but non-zero, at normal matrix pH, and significant upon matrix acidification, caused by collapse of the proton motive force across the mitochondrial inner membrane.

Prior art teaches that compounds of this disclosure are <u>NOT</u> anti-cancer therapeutics

Polyketide F_1F_0 ATP synthase inhibitors (e.g. oligomycin) are poisonous to cancer [14] *and* normal [15] cells. Indeed, intraperitoneal injection of just 1 mg/kg oligomycin kills healthy rats (*n=10*) within 48 hours; LD_{33} = 0.5 mg/kg [15]. Normal cells typically need to use F_1F_0 ATP synthase in its forward mode and so blocking this mode is typically lethal. Thus, polyketide F_1F_0 ATP synthase inhibitors are not suitable as anti-cancer therapeutics: indeed, cytovaricin, ossamycin and peliomycin don't work in xenograft mouse models of cancer (data in [16], oligomycin untested) because a therapeutic window is absent because, to repeat, polyketide F_1F_0 ATP synthase inhibitors are highly poisonous to normal cells, whilst not even being poisonous to all cancer cells: e.g. ineffective against glycolytic cancers exhibiting the Warburg effect [14]. [17] used oligomycin in a xenograft cancer mouse model *but* only by applying oligomycin to the cancer cells *before* they were inoculated into mice, and washing the excess oligomycin off before inoculation into the mice (by culture for 2 days in drug free medium). They did the study like this (atypical, as clear to someone of the art) because

oligomycin toxicity is *not* discriminate for cancer in a mammal. Obviously this experiment has no clinical parallel or utility. The synthesis/structure of some molecules of this disclosure has been disclosed in prior disclosures [P1, P2, P3], wherein these structures are speculated to be anti-cancer medicines merely by analogy to the anti-cancer activity of polyketide F_1F_0 ATP synthase inhibitors in [14]. Indeed, to mirror and use the restriction of [14], these disclosures restrict their suggestion to "cancers having tumor cells that do ***not*** exhibit the Warburg effect" (in claims of [P3], [P1] doesn't claim for any cancer, [P2] cancer claim rejected by USPTO in correspondance on 4/11/2006). [P1, P2, P3] state in the Utility section of their Description, "inhibitors of mitochondrial F_1F_0-ATPase selectively kill metabolically active tumor cells that do not exhibit the Warburg effect i.e., cells that do not maintain a high level of anaerobic carbon metabolism even in the presence of oxygen". So, teaching that their compounds will ***not*** exert anti-cancer activity against cancers that exhibit the Warburg effect i.e. they restrict their suggestion to cancers using oxidative phosphorylation (OXPHOS) and ATP synthase, in its forward mode, to generate ATP. But what undermines this (postulated) approach is that this aerobic profile is what normal cells typically use also, especially on aggregate across an organism: well known to those of the art (evidence: importance of breathing to mammalian life). By this analogy to polyketide F_1F_0 ATP synthase inhibitors, these disclosures speculate these molecules are safe anti-cancer therapeutics. When in fact, by this analogy, they actually teach the opposite. This is clear when [14] isn't considered in isolation, as it shouldn't be, but alongside the rest of the literature e.g. [15], [16] and the knowledge of someone of the art (well known that normal cells need to use F_1F_0 ATP synthase in its forward mode, to generate ATP, and that oligomycin blocks this, and is potently dangerous). So, these prior disclosures [P1, P2, P3] teach someone of the art, that these compounds are, by their chosen analogy to polyketide F_1F_0 ATP synthase inhibitors, *not* suitable for anti-cancer therapy. It isn't sufficient to kill cancer to be an anti-cancer therapeutic. This killing must be selective, leaving normal cells alive. Metabolic poisons such as cyanide or oligomycin do not fit this criterion. By distinction, the present invention discloses *selective* killing of cancer cells, at compound concentrations harmless to normal cells. This couldn't have been anticipated from the prior art. Furthermore, this selective anti-cancer activity is pronounced for cancers that ***do*** exhibit the Warburg effect.

Distinctly, the present disclosure discloses experimental data. Its inventive step is to show that its compounds are safe anti-cancer therapeutics, exactly because of their distinction from polyketide F_1F_0 ATP synthase inhibitors. There is a broad therapeutic margin for the

compounds of this disclosure as a virtue of the distinctive (from oligomycin) way they work, leveraging differences between normal and cancer cells, discovered and disclosed as part of this invention. Indeed, the compounds of this disclosure can kill highly glycolytic cancers exhibiting the Warburg effect. These cancers tend to be the most dangerous, with the worst prognosis (numerous studies find this: representatives: [18-20]).

[P1, P2, P3] do not provide any experimental evidence of any anti-cancer activity, and teach towards treating ischemia. They teach away from the present invention by suggesting, by an analogy in the unpredictable arts, that their compounds exert anti-cancer activity, like oligomycin, by inhibition of F_1F_0 ATP synthesis, wherein oligomycin itself is unsuitable as an anti-cancer drug. [P1, P2, P3] contains millions of compounds. The person of the art would select a subset of these for anti-cancer testing. Teaching of [P1, P2, P3] teaches the person of the art to select compounds that ***maximally*** inhibit F_1F_0 ATP synthesis in the submitochondrial assay they describe. Such compounds would very potently kill cancer *in vitro*, like oligomycin in [14], and so be excitingly entered into subsequent animal studies, wherein a lack of therapeutic margin would become evident (like polyketide F_1F_0 inhibitors in [16]) and no useful cancer drugs would be found, concluding the experimentation. Indeed, none found in subsequent ~16 years, despite long standing need. Whereas, by the present invention, compounds are selected from [P1, P2, P3] for anti-cancer activity by the **inverse**. By selection of compounds that ***minimally*** inhibit F_1F_0 ATP synthesis (as compared to their inhibition of F_1F_0 ATP hydrolysis). Indeed, by experimental evidence herein, the anti-cancer activity of such compounds is evidential. Thus, enabling the person of the art to arrive at working cancer drugs, and having the rationale to arrive at further working cancer drugs e.g. found by a method(s) disclosed herein. These drugs can cause body temperature drop, and can have a very atypical dose-anticancer response profile, which are critical teachings, with compensatory and associated methods, of this invention. These teachings are enabling for rodent trials, and more especially mouse trials (small body, more susceptible to body temperature drop), which is a step that one of the art would use to assess compounds of this invention.

Compounds of the present invention don't just exert anti-cancer activity. They can also affect normal cells, making their metabolism more efficient, which can cause weight gain/reduce weight loss/maintain body weight, all of which combats cachexia. For example, cancer driven cachexia, which is the leading cause of death in cancer patients. By contrast, polyketide F_1F_0

ATP synthase inhibitors are toxic to normal cells, denying them energy, rather than enabling them more energy, by efficiency gain, as molecules of this invention can do.

In short, [P1, P2, P3] teach that F_1F_0 ATP **synthesis** inhibitors only kill oxidative cancers **not** using Warburg metabolism, this invention experimentally shows that F_1F_0 ATP **hydrolysis** inhibitors **do** kill cancers using Warburg metabolism. The former teaching doesn't arrive at therapeutic cancer drugs, the latter does.

[P4] teaches away from the present invention. Its exemplary compound, Bz-423, inhibits the forward and reverse modes of ATP synthase equally or, in other data it discloses, the forward (EC_{50} = 5.5 μM) more than the reverse (EC_{50} = 8.9 μM) mode of ATP synthase. [P4] provides arguments and evidence that Bz-423 slows cellular proliferation, and causes apoptosis, by inhibiting F_1F_0 ATP synthesis and ***not*** by inhibiting F_1F_0 ATP hydrolysis. It extrapolates this feature of Bz-423 to other compounds it discloses (a point the (same) applicant of [P5] stresses often in examination correspondence with the USPTO). For example, in the title of Example 41 in [P4], it is written "Benzodione derivatives inhibit ATP hydrolysis, does not affect cell synthesis properties, and does not affect cell viability", and [P4] goes on to affirm this statement with experimental data, which teaches away from the present invention, wherein compound T5 is "capable of inhibiting ATP hydrolysis, not inhibiting cell synthesis, not affecting cell viability". In [P4], T5 experimental data is included to contrast with that of Bz-423, to show the lack of utility of a specific ATP hydrolysis inhibitor such as T5, as compared to the utility of the exemplary compound, Bz-423, which inhibits ATP synthesis. In this data [P4], Bz-423 inhibits F_1F_0 ATP synthesis and hydrolysis and cellular viability, T5 only inhibits F_1F_0 ATP hydrolysis and *not* cellular viability, = Bz-423 is the exemplary compound and F_1F_0 ATP synthesis inhibition, *not* F_1F_0 ATP hydrolysis inhibition, is experimentally highlighted as the responsible, exemplary mechanism. Bz-423 hyperpolarises Ψ_{IM} and decreases O_2 consumption [21] whilst compounds of the present invention do not, as presented in experimental data of the present disclosure. Example 52 in [P4] states "For ATP synthesis (the relevant enzymatic reaction of the mitochondrial F_1F_0-ATPase in vivo)". Thence indirectly stating that F_1F_0 ATP hydrolysis is irrelevant *in vivo*, which the present invention discloses, with supporting experimental data, is a falsehood. This is a new fundamental biological discovery, which will surprise those of the art. [P4] teaches the use of inhibitors of the forward mode of ATP synthase, which is not

teaching that arrives at the present invention; indeed, it teaches away from the present invention.

Well known to those of the art, biorxiv is a repository for documents that haven't been peer reviewed. In 2015, in a document on biorxiv, the author of this present disclosure suggested the use of F_1F_0 ATP hydrolysis inhibitors as anti-cancer therapeutics [22]. This document was subsequently submitted to peer reviewed journals (elife, BMC Cancer) and was found unworthy of dissemination, let alone pursuit, by those of the art. It demonstrably wasn't considered credible by those of the art. In 2017, a paper was published by others, in a peer-reviewed journal [23], with experimental data showing that inhibiting F_1F_0 ATP hydrolysis assists (!), rather than harms, cancer. With this conclusion reached and emphasised by its authors. This paper is one of many *experimental reports*, published in leading peer reviewed journals, reaching the same conclusion, which directly opposes and teaches away from this author's *suggestion* in a document database well known for unreviewed/unscrutinised manuscripts. Indeed, no journal publication years after a biorxiv submission would be noted very negatively by one of the art.

When selecting a path to pursue from the prior art, in the unpredictable arts, one of the art will always weigh experimental data more heavily than suggestion. Especially wherein experimental data postdates and falsifies/discredits suggestion. Experimental data in the prior art teaches away from the present invention. Indeed, it directly opposes it. Whereas the present invention is of F_1F_0 ATP hydrolysis inhibition conveying anti-cancer therapy, experimental data in [23] shows that F_1F_0 ATP hydrolysis inhibition assists cancer (!), thence increasing its danger. "The ATP synthase complex does not hydrolyze ATP in either IF_1-expressing or IF_1-silenced osteosarcoma cells" [23]. "Even severe hypoxia could not activate the hydrolysis of ATP by the F_1F_0-ATPase complex" [23]. "ATP synthase does not hydrolyze ATP in cancer cells" [23]. Moreover, "in cancer cells IF_1 overexpression fully prevents ATP synthase hydrolytic activity" and "IF_1 is present at higher levels in cancer cells than in untransformed cells" (also observable in gene expression databases, also reported by *many* other investigators in *many* other journal papers, IF_1 overexpression in cancer is a prognostic marker of poor patient outcome, IF_1 knockdown suppresses tumour growth in mice [24]) and "IF_1 overexpression promotes cancer cells survival" [23].

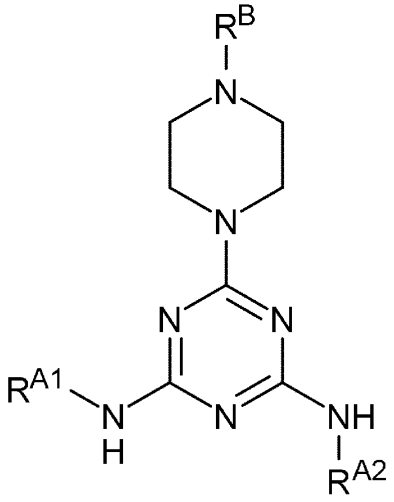
In **Claim 13** of this disclosure, some compounds are excluded from the presented formula by proviso, separating all its enumerations from [P1] and [P4].

Some guidance

All publications, patents and patent applications mentioned or cited in this disclosure are herein incorporated, in entirety, by reference. This disclosure uses IC_{50} and EC_{50} interchangeably, for a process being inhibited or reduced. Chemical structures were drawn using the chemical drawing feature in [25], and if a drawing feature is unknown to the reader they are referred to its documentation, or to explore the software themselves: all clear to those of the art. Hydrogen on structures is typically not shown, present implicitly, but it is shown for some presented structures "On Hetero and Terminal" [25] groups. Herein, the symbol D is used for deuterium (^2H). For compound synthesis schemes herein, starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods or derived by procedures analogous to those described in the literature. Examples and preparations herein describe the manner and process of making and using the invention. It should be understood that there will be other embodiments which fall within the spirit and scope of the invention

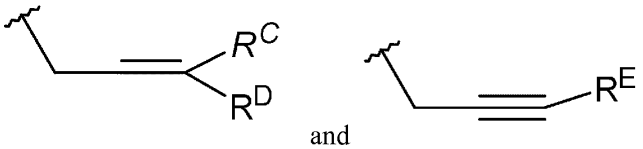
SUMMARY OF THE INVENTION

A first aspect of the invention is a compound, or a composition containing at least one compound, of the following formula:



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, for use in a method of treating, ameliorating, preventing or combating cancer, or for use in a method of treating a disease or disorder selected from (i) cancer that metabolizes much of its glucose and/or glutamine to lactate, for example a cancer exhibiting the Warburg effect and/or a cancer that can be discriminated from surrounding tissue by PET imaging (e.g. ^{18}F-FDG PET); (ii) cachexia or cancer driven cachexia; wherein:

R^{A1} and R^{A2} are each independently selected from the groups



and

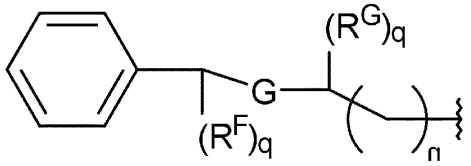
wherein R^C and R^D are each independently selected from hydrogen, deuterium, halogen and alkyl, and wherein R^E is hydrogen, deuterium, or alkyl;

R^B is selected from R^{B1}, hydrogen and deuterium;

wherein R^{B1} is selected from phenyl, benzyl, pyridyl, pyrimidyl and pyrazinyl optionally substituted with one or more substituents R^{B2};

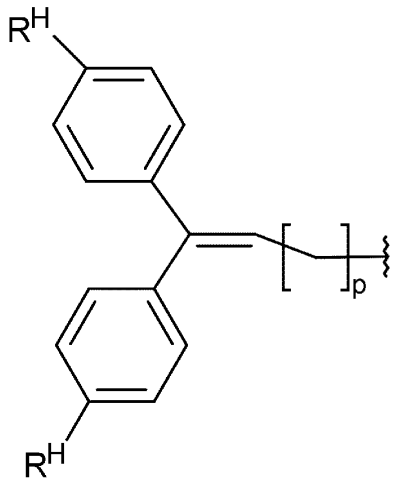
wherein each R^{B2} is independently selected from halogen, alkyl, alkoxy, nitro, amino, methoxy and polyhalogen alkyl;

or R^B is a phenylalkyl of the formula:



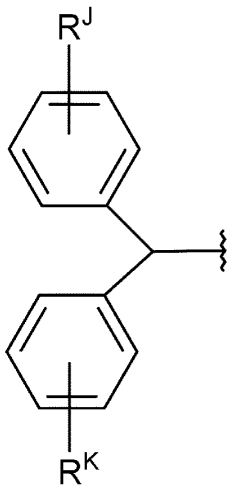
wherein R^F and R^G are hydrogen or alkyl, G is a carbon-carbon double bond or a carbon-carbon single bond, n is 0 or 1 and q is 0 or 1 provided that where q is 0, G is a carbon-carbon double bond and where q is 1, G is a carbon-carbon single bond,

or R^B is a diphenylalkyl of the formula



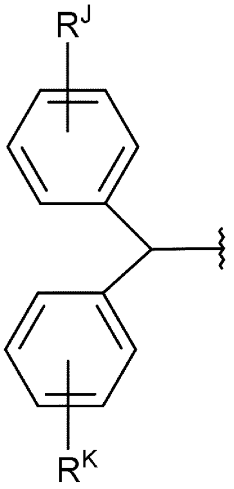
wherein R^H is hydrogen or halogen, and p is 0, 1 or 2;

or R^B is the group

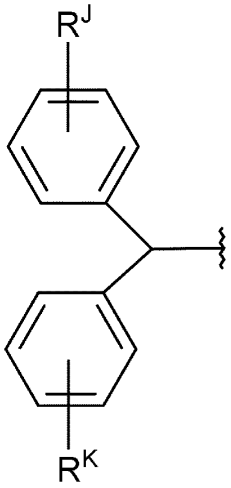


wherein R^J and R^K each independently represent 1-5 optional substituents on each ring, and wherein each R^J and each R^K, when present, is independently selected from halogen, alkyl, alkoxy, nitro, amino, methoxy and polyhalogen alkyl.

In some embodiments, R^B is the group:



In some embodiments, R^B is the group:

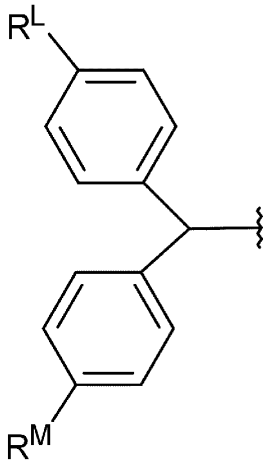


wherein R^J and R^K each independently represent 1 or 2 substituents on each ring, and wherein each R^J and each R^K is independently selected from halogen, alkyl, alkoxy, nitro, amino and polyhalogen alkyl.

In some embodiments, R^J and R^K each independently represent 1 or 2 substituents on each ring, and wherein each R^J and each R^K is independently selected from halogen.

In some embodiments, R^J and R^K each independently represent 1 substituent on each ring, and wherein R^J and R^K are independently selected from halogen.

In some embodiments, R^B is the group:



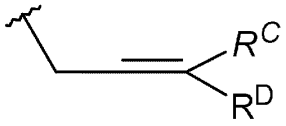
wherein R^L and R^M are each independently selected from halogen, alkyl, alkoxy, nitro, amino and polyhalogen alkyl.

In some embodiments, R^L and R^M are each independently selected from halogen.

In some embodiments, R^L and R^M are the same.

In some embodiments, R^L and R^M are each F.

In some embodiments, R^{A1} and R^{A2} are each independently selected from the group

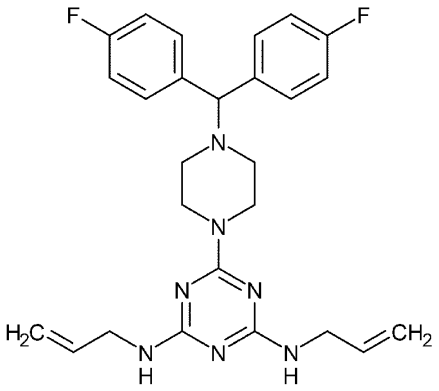


wherein R^C and R^D are each independently selected from hydrogen, deuterium, halogen and alkyl.

In some embodiments, R^{A1} and R^{A2} are the same.

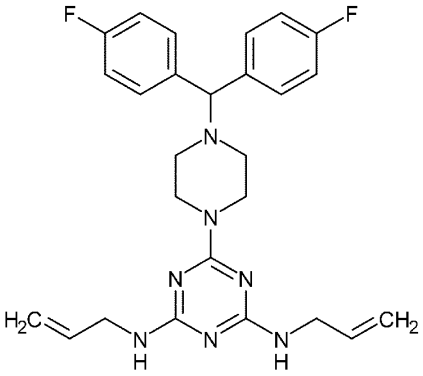
In some embodiments, R^C is hydrogen. In some embodiments, R^D is hydrogen. In some embodiments, R^C and R^D are the same. In some embodiments, R^C and R^D are both hydrogen.

In some embodiments, the compound is:



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof.

In some embodiments, the compound is an isotopologue(s) of:



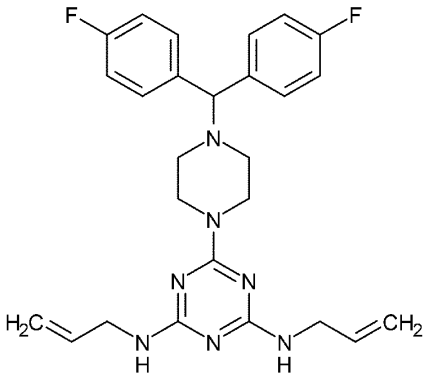
or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof.

Almitrine dimesylate has been used clinically for millions of patient months to treat chronic obstructive pulmonary disease (COPD). However, after being used for decades, it is now only used sporadically. This is because postmarketing surveillance has revealed it doesn't actually treat COPD, thence there is no reward to outweigh its side-effects risk, especially since better/working COPD treatments have emerged. This invention repurposes almitrine for anti-cancer treatment. New experimental data herein shows that almitrine dimesylate exerts strong anti-cancer activity, greater than carboplatin in standardised NCI-60 testing at the National Cancer Institute (NCI, USA). Carboplatin is one of the most used chemotherapies today and is on the World Health Organisation (WHO) list of essential medicines. The potential side-effects of almitrine are mild compared to present chemotherapies, and tend to only occur with

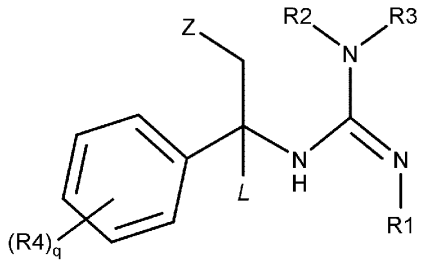
chronic use, yielding the opportunity for a therapeutic window of treatment, which will treat/ameliorate/prevent/combat cancer in a subject.

The compounds described herein, including for example almitrine dimesylate, exert anti-cancer activity because they reduce F_1F_0 ATP hydrolysis in cancer cells. This elucidated mechanism is the core of this invention. Herein is the discovery of a cancer-specific drug target: the reverse mode of ATP synthase. Indeed, new experimental data, disclosed herein, demonstrates that molecules which specifically inhibit F_1F_0 ATP hydrolysis can exert specific anti-cancer activity, at concentrations that do not harm normal cells. Any anti-cancer drug that targets/inhibits F_1F_0 ATP hydrolysis is componentry to this invention. This disclosure discloses numerous anti-cancer drug working examples, many of which are also new compositions of matter, and discloses rationale and methods to find further working examples, which are, in turn, componentry to this invention and encompassed by this disclosure.

Almitrine dimesylate is 6-[4-[bis(4-fluorophenyl)methyl]piperazin-1-yl]-2-N,4-N-bis(prop-2-enyl)-1,3,5-triazine-2,4-diamine methanesulfonic acid, the dimethanesulfonate salt of almitrine. Almitrine has the following structure:



Also described herein for prevention or treatment of cancer in a subject, particularly with cancer exhibiting the Warburg effect, is to use a pharmaceutical composition with an effective amount of one or compounds of the following formula,



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

L is alkyl, or substituted alkyl, or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy, or halogen, or haloalkyl, or haloalkoxy, or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.);

R_1 is hydrogen, cyano, —SO_2R_8, —C(=O)R_9, heteroaryl or thiazolyl;

R_2 is (i) independently hydrogen, alkyl, benzyl, or substituted alkyl, or (ii) taken together with R_3 forms a heterocyclo;

R_3 is (i) independently alkyl, substituted alkyl, alkylthio, aminoalkyl, carbamyl, B_B-aryl, B_B-heterocyclo, B_B-heteroaryl, or B_B-cycloalkyl, or (ii) phenyl optionally substituted with C_{1-4}alkyl, halogen, trifluoromethyl, OCF_3, cyano, nitro, amino, hydroxy, or methoxy, or (iii) independently selected from C_{1-4}alkyl, alkylthio, aminoalkyl, -B_B-aryl, -B_B-heterocyclo, B_B-cycloalkyl, and -B_B-hetaroaryl, optionally having one to three substituents selected from R_{3a}; and/or having fused thereto a five or six membered carbocyclic ring, or (iv) taken together with R_2 forms a heterocyclo optionally substituted with alkyl or substituted alkyl;

B_B is a bond, C_{1-4}alkylene, C_{2-4}alkenylene, substituted C_{1-4}alkylene, substituted C_{2-4}alkenylene, substituted C_{1-4}alkylene-C(=O)NH—, —C(=O)NH—, —C_{1-4}alkylene-C(=O)NH—, —C(=O)NR_{19}—, —C_{1-4}alkylene-C(=O)NR_{19}—, or substituted C_{1-4}alkylene-C(=O)NR_{19}—, —$(CHR_{14})_m$—$(CR_{15}R_{16})_n$— or —$(CHR_{14})_p$—C(=O)NH—;

R_{3a} at each occurrence is selected independently from alkyl, substituted alkyl, halogen, haloalkoxy, cyano, nitro, keto, trifluoromethyl, —$NR_{17}R_{18}$, —SR_{17}, —OR_{17}, —SO_2R_{17a}, —$SO_2NR_{17}R_{18}$, —NR_{17}C(=O)R_{18}, —CO_2R_{17}, —C(=O)R_{17}, cyoloalkyl, aryl, heterocyolo, and heteroaryl, wherein when R_{3a} is cycloalkyl, aryl, heterocyclo or heteroaryl, said cycloalkyl, aryl, heterocyolo and heteroaryl in turn is optionally substituted with alkyl or substituted alkyl;

Z is a heteroaryl, for example an optionally-substituted bicyclic heteroaryl; or

Z is triazolyl optionally substituted with one to two R_7 substituents or imidazolyl optionally substituted with one to two R_7 substituents and/or having fused thereto a benzene ring in turn optionally substituted with one to two R_7 substituents; and

R_7 is alkyl, carbamyl, or substituted alkyl;

R_4 at each occurrence is selected independently of each other R_4 from the group consisting of halogen, trifluoromethyl, OCF_3, alkyl, substituted alkyl, haloalkyl, nitro, cyano, haloalkoxy, OR_{25}, SR_{25}, $NR_{25}R_{26}$, $NR_{25}SO_2R_{27}$, SO_2R_{27}, $SO_2NR_{25}R_{26}$, CO_2R_{26}, $C(=O)R_{26}$, $C(=O)NR_{25}R_{26}$, $OC(=O)R_{25}$, $—OC(=O)NR_{25}R_{26}$, $NR_{25}C(=O)R_{26}$, $NR_{25}CO_2R_{26}$, aryl, heteroaryl, heterocyclo and cycloalkyl;

R_8 is C_{1-4}alkyl or phenyl optionally substituted with alkyl, halogen, haloalkoxy, cyano, nitro, or trifluoromethyl;

R_9 is $—NR_{10}R_{11}$, alkyl, substituted alkyl, alkoxy, alkylthio, cycloalkyl, aryl, heteroaryl, heterocyclo, or $—CO_2R_{12}$, alkyl or phenyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, C_{1-4}alkoxy, haloalkoxy, C_{1-6}alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, NHC(=O)alky, C(=O)alkyl, and/or C_{1-4}alkyl optionally substituted with one to three of trifluoromethyl, hydroxy, cyano, phenyl, pyridinyl; and/or a five or six membered heteroaryl or heterocylo in turn optionally substituted with keto or having a benzene ring fused thereto or

a) C_{1-4}alkyl optionally substituted with one to two of:

i) SR_{13}, OR_{13}, $NR_{13a}R_{13b}$, halogen, trifluoromethyl, CO_2R_{13a}, and $C(=O)NR_{13a}R_{13b}$;

ii) cycloalkyl optionally substituted with one to two of C(=O)H, C_{1-4}acyl, alkenyl, carbamyl, and/or phenyl in turn optionally substituted with halogen;

iii) phenyl or napthyl optionally substituted with one to two of halogen, nitro, amino, alkyl, hydroxy, C_{1-4}alkoxy, or having fused thereto a five or six membered heterocyclo;

iv) pyridinyl, thiophenyl, furanyl, tetrahydrofuranyl, or azepinyl, optionally substituted with alkyl or having fused thereto a five to six membered carbocyclic ring optionally substituted with keto or C_{1-4}alkoxy;

b) 3 to 6 membered cycloalkyl optionally having up to four substituetits selected from alkyl, halogen, cyano, alkenyl, acyl, alkylthio, carbamyl, phenyl in turn optionally substituted with halogen; or having an aryl fused thereto;

c) pheyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, C_{1-4}alkoxy, haloalkoxy, C_{1-4}alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $NHC(=O)$alkyl, $C(=O)$alkyl, and/or C_{1-4}alkyl optionally substituted with one to three of trifluoromethyl, hydroxy, cyano, phenyl, pyridinyl; and/or a five or six membejed heteroaryl or heterocyle in turn optionally substituted with keto or having a benzene ring fused thereto;

d) pyridinyl, thiazolyl, furanyl, thiophenyl, and pyrrolyl optionally substituted with one to two of halogen, alkyl, and phenyl in turn optionally substituted with halogen or trifluoromethyl;

R_{10} and R_{11} are (i) independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, heterocyclo, cycloalkyl, aryl, heteroaryl or C_{1-4}alkyl optionally substituted with one to two of —CO_2alkyl, —$C(=O)NH$(aryl), NH(aryl), cycloalkyl, phenyloxy, phenyl in turn optionally substituted with C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, halogen, amino, nitro, tetrahydrofuranyl, and/or five or six membered heterocyclo, or having a five or six membered heterocyclo fused thereto; pyrrolidinyl optionally substituted with keto; napthyl, anthracenyl, pyridinyl, thiophenyl, furanyl, imidazolyl, benzimidazolyl, or indolyl in turn optionally substituted with C_{1-4}alkyl or C_{1-4}alkoxy; or (ii) taken together form a heteroaryl or heterocyclo selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, tetrahydropyridinyl, and imidazoilidinyl, wherein said heterocyclo formed by R_{10} and R_{11} is optionally substituted with one to two of keto, CO_2H, C_{14}alkoxy, CO_2alkyl, C_{1-4}carbamyl, benzyl; phenyl in turn optionally substituted with alkyl, halogen, or C_{1-4} alkoxy; tetrahydropyridinyl in turn optionally substituted with keto and/or phenyl; alkyl optionally substituted with amino or NHR_{21}wherein R_{21} is alkyl or phenyl optionally substituted with alkyl; and/or has a benzene ring fused thereto in turn optionally substituted with one to two of alkyl, C_{1-4}alkoxy, CO_2alkyl, and/or C_{1-4}carbamyl;

R_{12} and R_{19} are hydrogen or alkyl;

R_{13} is hydrogen or alkyl;

R_{13a} and R_{13b} are selected from hydrogen, alkyl, and aryl;

R_{14}, R_{15} and R_{16} at each occurrence are independently selected from hydrogen, alkyl, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, and phenyl, and/or one of R_{15} and one of R_{16} join together to form a 3 to 6 membered cycloalkyl;

R_{17} and R_{18} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, phenyl, or benzyl wherein the phenyl or benzyl is optionally substituted with alkyl, hydroxy, or hydroxyalkyl;

R_{17a} is alkyl or substituted alkyl;

R_{25} and R_{26} are independently selected from hydrogen, alkyl, or substituted alkyl, or taken together form a heterocyclo or heteroaryl ring;

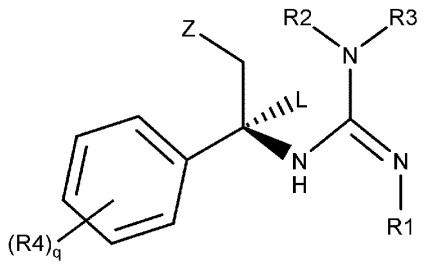
R_{27} is alkyl or substituted alkyl;

q is 0, 1, 2, or 3;

m and n are 0, 1 or 2; and

p is 0, 1, 2, or 3.

In some embodiments, there is an enantiomeric excess of the enantiomer:



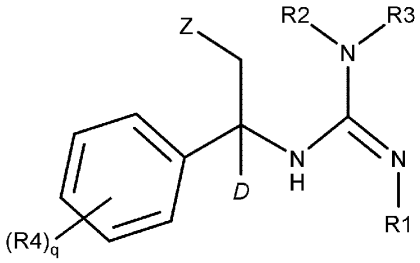
Herein, the terms "S-stereoisomer" and "S-enantiomer" refer to the arrangement of groups around the chiral centre shown in the structure above, regardless of the specific identities of the variables such as Z, L and R_4 within the structure. This chiral configuration is termed *S* by IUPAC designation if Z is nitrogen and L is deuterium for example. But, herein, where *S* is written next to this configuration it is not intended to limit what atoms can be Z or L according to IUPAC stereoisomer naming rules. For example, herein, Z can be carbon (or nitrogen or other atoms as specified herein) even when an *S* is written next to this chiral carbon. However, when R group type aliases, such as Z and L, are not used and all atoms are uniquely specified around a chiral carbon then IUPAC stereoisomer naming is adhered to.

In some embodiments, the *S*-enantiomer of the compound is in enantiomeric excess. In some embodiments, the enantiomeric excess of *S*-enantiomer exceeds 70%.

In some embodiments, L is hydrogen or deuterium.

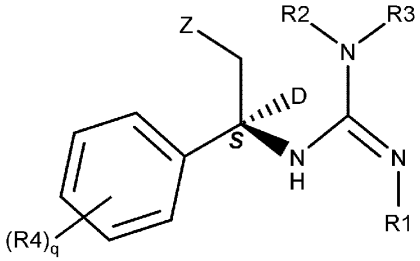
In some embodiments, L is alkyl, or deuterium, or substituted alkyl, or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy, or halogen, or haloalkyl, or haloalkoxy, or any atom or isotope permitted by valence except hydrogen at natural abundance;

In some embodiments, the compound is a compound according to the formula



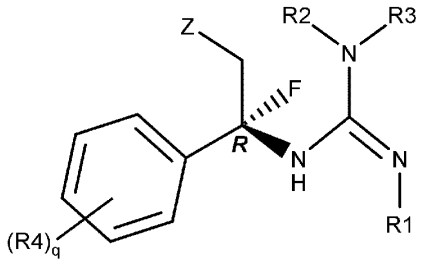
or pharmaceutically-acceptable salts, solvates, hydrates and prodrugs thereof,
wherein D is deuterium (enrichment, for example, exceeding 40% deuterium incorporation at shown position, and optionally at other positions also).

In some embodiments, the compound is a compound according to the formula



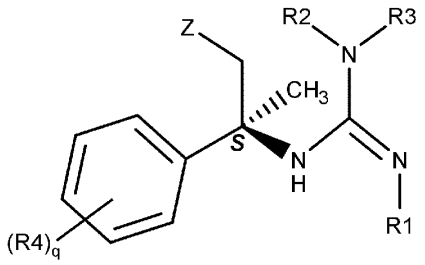
or pharmaceutically-acceptable salts, solvates, hydrates and prodrugs thereof,
wherein D is deuterium (enrichment, for example, exceeding 40% deuterium incorporation at shown position, and optionally at other positions also);
S symbolises the *S* stereoisomer, for example, in enantiomeric excess (ee) exceeding 70%.

In some embodiments, the compound is



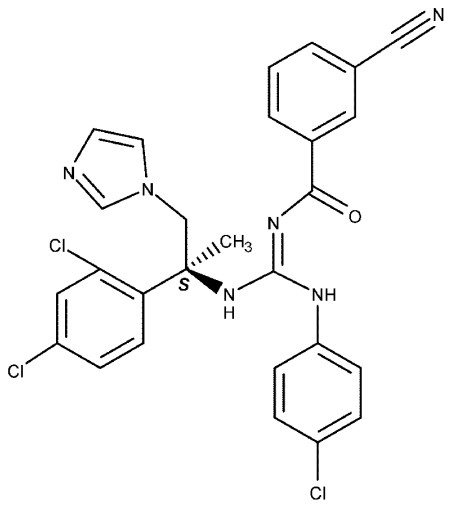
or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof. In some embodiments, the enantiomeric excess (ee) of the *R* stereoisomer exceeds 70%.

In some embodiments, the compound is



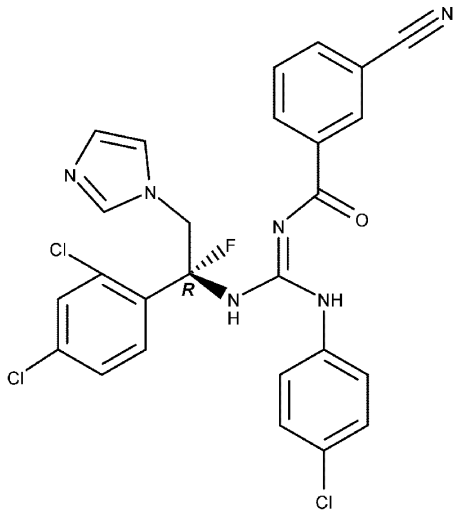
or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof. In some embodiments the enantiomeric excess (ee) of the *S* stereoisomer exceeds 70%.

In some embodiments, the compound is



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof. In some embodiments the enantiomeric excess (ee) of the *S* stereoisomer exceeds 70%.

In some embodiments, the compound is



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof. In some embodiments the enantiomeric excess (ee) of the *R* stereoisomer exceeds 70%.

Figures 1, 2, 3, 4, 5, 6, 7, 8 show anti-cancer activity of carboplatin (10 μM), BTB06584 (10 μM), BTB06584 (100 μM), BMS-199264 (10 μM), BMS-199264 (100 μM), compound 31 (10 μM), almitrine dimesylate (10 μM), compounds 6a and 6b (at 10 and 100 μM), respectively in the NCI one-dose assay. Figure 9 consolidates data from prior figures to show that anti-cancer activity scales with inhibition of F_1F_0 ATP hydrolysis. Figure 10 shows anti-cancer activity of BMS-199264, and Figure 11 shows anti-cancer activity of 6a and 6b, in the NCI five-dose assay. Figure 12 recasts data from Figures 8 & 11. Figure 13 interprets data from Figures 8, 11, and 12. Figure 14 interprets data from Figure 10. Figure 15 presents *in vivo* mouse data for compounds 6a and 6b. Figure 16 presents experimental data on the racemization rate of 6b. Figure 17 discloses that invention compounds can reduce F_1F_0 ATP synthesis by uncoupling the proton motive force, with supporting experimental data.

Compounds of this invention, which reduce F_1F_0 ATP hydrolysis, can also be used to treat/ameliorate/prevent/combat other diseases, disorders and conditions. Compounds of this invention attack cancer characteristics shared with embryonic stem cells, which aren't found

in the adult human body, but are in the blastocyst ~5 days after fertilization. Thus compounds of this invention have utility for preventing unwanted pregnancy, with a later time window than presently available options. Reducing F_1F_0 ATP hydrolysis reduces a futile cycle of ATP synthesis and hydrolysis, used by the body for heat generation (supporting mouse data herein). *If* exogenous heat replaces this reduced endogenous heat (higher room temperature, wearing more clothes, geographical relocation to the tropics etc.), this reduces energy (food) consumption and treats/ameliorates/prevents/combats cachexia, cancer driven cachexia and weight loss, wherein cachexia is the biggest cause of death in cancer patients. Reducing this ATP synthesis/hydrolysis cycle means the oxidative phosphorylation rate is slower, less ROS are produced and the body accumulates less ROS damage per unit time i.e. aging slows. Therefore, F_1F_0 ATP hydrolysis inhibitors of this invention extend lifespan and healthspan, can treat/ameliorate/prevent/combat accelerated aging diseases, progeroid syndromes and the diseases of aging (e.g. Alzheimer's disease, dementia, Parkinson's disease, cancer etc.). It is noteworthy that compounds of this invention both treat and prevent cancer, whereas many present cancer treatments (e.g. radiotherapy) increase subsequent cancer risk. Activated macrophages are distinct from resting macrophages, and other normal adult cells, because the nitric oxide they produce to kill pathogens switches off their use of oxidative phosphorylation and they rely on F_1F_0 ATP hydrolysis to maintain Ψ_{IM}. Compounds of this invention inhibit F_1F_0 ATP hydrolysis and so depolarise Ψ_{IM} in *activated* (not resting) macrophages, which triggers their apoptosis. Compounds of this invention treat/ameliorate/prevent/combat macrophage associated diseases or disorders (e.g. Macrophage Activation Syndrome, HIV hides safely in *activated* macrophages during anti-retroviral therapy {ART} and from here repopulates HIV virus in blood plasma when ART is interrupted or discontinued, virus neuroinvasion via macrophages, thence HIV-associated neurocognitive disorders, Tumour Associated Macrophages (TAMs) are a large component of tumour mass, are an integral drive to cancer pathology, correlate with poor patient prognosis). F_1F_0 ATP hydrolysis inhibitors, by increasing metabolic/bioenergetic efficiency (less heat produced), can cause energy/weight gain in a subject, which has therapeutic, aesthetic, physical/mental performance applications, and commercial applications in livestock and farming. Compounds of this invention reduce F_1F_0 ATP hydrolysis and can reduce body temperature to a value controlled by intersection of compound dosage and ambient temperature (even at maximum effect, compound can't make body fall below, only to, ambient temperature; body temperature controlled by controlling ambient temperature), which can treat/ameliorate/prevent/combat a disease or disorder that causes a higher than normal body

temperature (e.g. fever, infection, sepsis, malignant hyperthermia, neuroleptic malignant syndrome etc.) and a disease or disorder combated (or surgery or medical treatment helped) by hypothermia (e.g. neuroprotection/cardioprotection/tissue protection after a stroke or ischemia, deep hypothermic circulatory arrest for surgery etc.).

An aspect of the invention is a pharmaceutical composition comprising at least one compound as described herein and a pharmaceutically-acceptable carrier or diluent.

An aspect of the invention is a compound or composition as described herein for use in a method of treatment of the human or animal body by therapy.

An aspect of the invention is a compound or composition as described hereinfor use in a method of treating, ameliorating, preventing or combating a disease or disorder selected from

(i) cancer that metabolizes much of its glucose and/or glutamine to lactate, for example a cancer exhibiting the Warburg effect and/or a cancer that can be discriminated from surrounding tissue by PET imaging (e.g. ^{18}F-FDG PET);

(ii) cachexia, cancer driven cachexia or weight loss;

(iii) disease or disorder that causes a higher than normal body temperature such as high environmental temperature, ingesting an uncoupler (e.g. 2,4-dinitrophenol), infection, sepsis, stroke, fever, pyrexia, hyperpyrexia, hyperthermia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, heatstroke, thermoregulatory disorder(s), Kawasaki syndrome, drug or drug withdrawal induced hyperthermia, idiosyncratic drug reaction, fever of unknown or uncertain origin, reaction to incompatible blood product(s), metabolic disorder(s), cancer, injury;

(iv) Tumour Associated Macrophages (TAMs) or any macrophage associated disease or disorder such as Macrophage Activation Syndrome (MAS), HIV, AIDS, HIV-associated neurocognitive disorders (HAND), HIV associated cancers, AIDS-defining cancers, non-AIDS defining cancers;

(v) virus neuroinvasion via macrophages, as used for example by HIV and SARS coronavirus;

(vi) neurocognitive or neurodegenerative diseases/disorders, for example those caused by a virus;

(vii) acute or chronic or systemic inflammation or any inflammatory disease/disorder/syndrome or any autoinflammatory disease/disorder/syndrome or any autoimmune disease/disorder/syndrome;

(viii) low or less than desired metabolic/bioenergetic efficiency in a subject, or low or less than desired physical or mental performance, or low or less than desired body weight;

(ix) disease or disorder treatable by conferring hypothermia in a subject for some medical or other purpose which can include slowing a chemical reaction(s) rate in a subject for therapeutic benefit, preventing/minimizing brain and/or tissue damage, deep hypothermic circulatory arrest for surgery, hypothermia for a surgical purpose, hypothermia for cardiac and/or cardiovascular surgery and/or brain surgery (neurosurgery), Emergency Preservation and Resuscitation (EPR), preserving detached body parts such as limbs and/or organs (for example during organ storage and/or transplant), protective hypothermia, targeted temperature management, therapeutic hypothermia, hypothermia therapy for neonatal encephalopathy, birth asphyxia, haemorrhage, hypovolemia, decompression sickness, burn injury(s) including skin burn, inflammation, allergic reaction, anaphylaxis, tissue/organ rejection, hypoxia, hypoxemia, anoxemia, anoxia, anemia, hypervolemia, altitude sickness, obstructed airway, asthma attack, hypoxia in a body/tissue/organ, hypoglycemia, reperfusion injury (ischemia-reperfusion injury), upon release of a ligature or tourniquet, uraemia, crush syndrome, compartment syndrome, traumatic brain and/or spinal cord injury, major trauma, infection, bacterial and/or viral infection(s) (e.g. meningitis), sepsis, septic shock, ischemic brain/heart/kidney injury, neuroprotection and/or cardioprotection and/or tissue protection during/after a stroke and/or ischemia and/or cardiac arrest and/or resuscitation and/or a period(s) of poor blood flow anywhere in a subject;

(x) poisoning by a toxic amount of a compound(s) in a subject e.g. carbon monoxide/methanol/heavy metal/pesticide poisoning, snake/spider/bee/insect/lizard venom, metabolic poison(s), bacterial toxin(s), endotoxemia or drug/substance overdose e.g. heroin, ethanol, prescription medication(s) or over the counter medication(s);

(xi) accelerated aging disease or progeroid syndrome including Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy, combined xeroderma pigmentosum-Cockayne syndrome, restrictive dermopathy, Wiedemann–Rautenstrauch syndrome, Hutchinson–Gilford progeria syndrome (progeria);

(xii) disease or disorder of ageing (incidence increases with increased age/senescence) and/or a disease/disorder associated with elevated reactive oxygen species including

degenerative diseases, neurodegenerative diseases, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxias, Friedreich's ataxia, dementia, Batten disease, polyglutamine diseases, osteoporosis, atherosclerosis, cardiovascular disease, myocardial infarction, cerebrovascular disease, stroke, heart failure, chronic obstructive pulmonary disease (COPD), hypertension, arthritis, cataracts, type 2 diabetes, andropause, sarcopenia, age-related macular degeneration (AMD), hearing loss, movement disability, cancer;

(xiii) aging, wherein these compounds slow ageing, extend lifespan and healthspan; or

(xiv) skin aging.

Another aspect is a method of treating, ameliorating, preventing or combating any such disease or disorder by administering to a subject in need thereof a therapeutically effective amount of a compound or composition as described herein.

Another aspect is the use of a compound or composition as described herein for the manufacture of a medicament for the treatment, amelioration, prevention or combating of any such disease or disorder.

In some embodiments, the subject is further administered with one or more compounds or compositions approved for human use, optionally for anti-cancer use, by the United States Food and Drug Administration (FDA) and/or European Medicines Agency (EMA), optionally in the same pharmaceutical composition.

In some embodiments, the mg/kg dose administered to the subject is comparable with or larger than the mg/kg dose which would be administered to a subject of smaller bodily size, and optionally the mg/kg dosage administered to adult humans is comparable or greater than the No Observed Adverse Effects Level (NOAEL) mg/kg dosage in mice housed at 22°C.

DETAILED DESCRIPTION OF THE INVENTION

As used herein with reference to the utilities described, the terms “treating” or “treatment” encompass both responsive and prophylaxis measures designed to inhibit or delay the onset of the disease or disorder, or to alleviate, ameliorate, lessen, reduce, modulate or cure the disease or disorder and/or one or more of its symptoms. The terms “subject” and “patient”

refer to organisms to be treated by the compounds/methods of the present invention and can refer to a human or animal.

The invention of this disclosure hinges on the discovery, disclosed herein, that some cancers rely on F_1F_0 ATP hydrolysis, even under normoxia (indeed under hyperoxia: ~21% O_2), during some or all of their cell cycle. Evidence herein: compounds of this disclosure, which specifically inhibit F_1F_0 ATP hydrolysis, slow cancer proliferation at concentrations that they do not harm normal cells.

In some of the most dangerous cancers, refractory to present [chemo/radio] therapies, during some or all of their cell cycle, reactive oxygen species (ROS) decrease [NADPH], because NADPH is consumed in ROS mitigation processes, and this then pulls through increased pentose phosphate pathway (PPP) and glycolytic flux. But such a pivotal increase in glycolytic/PPP flux can only occur because of F_1F_0 ATP hydrolysis, a distinctive feature to these cancers, which stops ATP produced by glycolysis from accumulating and slowing glycolysis by negative feedback inhibition of key glycolytic enzymes. This increased PPP flux maintains [NADPH] and ROS mitigation. In this way, these cancers can maintain a very high ROS mitigation capability, maintain very low intracellular [ROS], and tend to be the most resistant to conventional [chemo/radio] therapies, which work, or often don't work (!), by increasing [ROS]. Compounds of this disclosure undermine this process/resistance. By inhibiting F_1F_0 ATP hydrolysis, they increase the anti-cancer efficacy of any chemical or treatment that increases reactive oxygen species (ROS) in cancer cells. An embodiment of this disclosure is any such co-treatment(s). Indeed, a compound(s) of this disclosure increases the success rate of standard of care [chemo/radio] therapies and permits their use at lower dosing, which reduces their horrendous side-effects. This disclosure encompasses a compound(s) of this invention in co-therapy with chemotherapy, or radiotherapy or any US Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) approved drug(s) or treatment, for example, a drug/treatment approved for cancer therapy. Chemotherapies are well known to those of the art, including, but not limited to, cisplatin, carboplatin, taxol, oxaliplatin etc.

In other embodiments, a compound(s) of this disclosure is used as cancer therapy alone. Indeed, this is a much more cancer-targeted therapeutic approach. The most dangerous cancers use this distinctive metabolism, with ATP synthase distinctively in reverse,

consuming glycolytic ATP, to yield high glycolytic rate, thence abundant glycolytic intermediates for biosynthesis and, crucially, to keep [ROS] low (as prior disclosed), which is necessary to cancer immortality ("limitless replicative potential", a Hallmark of cancer [26]) and thence danger. This distinction is targeted, by compound(s) of this disclosure, without significant damage to normal cells. Normal adult cells normally use a different metabolism, with ATP synthase more in forward mode, and a higher ATP yield from glucose, but at the cost of higher [ROS] and mortality.

This reliance of normal cells upon the forward mode of ATP synthase makes them exquisitely susceptible to oligomycin. The compounds of this disclosure are useful for anti-cancer treatment, unlike oligomycin, because of their distinction from oligomycin, which couldn't have been foreseen without the inventive steps of this disclosure. In normal cells that are actively respiring (known as state 3 respiration [3]), inhibitors of the forward mode of ATP synthase (e.g. oligomycin) cause a state 3 to state 4 transition, hyperpolarize Ψ_{IM}, decrease O_2 consumption and reduce [ATP] (so called "modulators" of the forward mode of ATP synthase, e.g. Bz-423, can also cause one or more of these effects) whilst a specific inhibitor of the reverse mode of ATP synthase does not exert these effects at a working concentration ([12-13], herein incorporated in their entirety). However, at this working concentration, after inhibition of the respiratory chain (e.g. blocked by rotenone, or some other respiratory chain inhibitor, or by a reduced O_2 concentration), a specific inhibitor of the reverse mode of ATP synthase will depolarise Ψ_{IM}. This feature distinguishes a molecule that inhibits the reverse mode of ATP synthase significantly more than it inhibits/modifies the forward mode of ATP synthase, and/or inhibits/modifies ATP synthesis. Such a molecule, put into use as an anti-cancer therapeutic, is an embodiment of this invention. A further embodiment is the process/method of seeking new anti-cancer molecules by assaying whether a candidate molecule can depolarise Ψ_{IM}, when Ψ_{IM} is maintained by F_1F_0 ATP hydrolysis (e.g. when OXPHOS is blocked by a respiratory chain inhibitor or insufficient O_2), but that can't hyperpolarize Ψ_{IM} and/or decrease O_2 consumption, when Ψ_{IM} is maintained by proton pumping by complexes of the respiratory chain. If a candidate molecule meets these requirements, it is an anti-cancer therapeutic, as determined by the invention of this disclosure.

Some cancers intrinsically rely upon ATP synthase in reverse, as revealed by experimental data of this disclosure, and further cancers can have this reliance imposed upon them, to

maintain Ψ_{IM} in the hypoxia of a solid tumour, which also makes them susceptible to drugs of this disclosure. Significant lactate release is correlated with the most dangerous cancers and poor patient outcomes (numerous studies find this: example: [27]). High lactate release indicates high glycolytic rate, which F_1F_0 ATP hydrolysis enables, and which drugs of this disclosure attack. This invention confronts the most deadly cancers by discovering/disclosing a cancer-specific weakness, and the means to selectively attack it.

All the following molecules are – in use as anti-cancer therapeutics - embodiments of this invention: (1) Molecules that inhibit the reverse, and not the forward, mode of ATP synthase, (2) Molecules that inhibit the reverse more than than forward mode of ATP synthase, (3) Molecules that inhibit the reverse mode of ATP synthase, and not its forward mode, but that shuttle protons across the mitochondrial inner membrane, dissipating the pmf as heat (uncoupling [3]), which reduces F_1F_0 ATP synthesis, and in a further embodiment: uncoupling molecules that reduce F_1F_0 ATP hydrolysis more than F_1F_0 ATP synthesis, (4) Molecules that inhibit ATP hydrolysis more than ATP synthesis at the mitochondrial inner membrane, (5) Molecules that have a lower IC_{50} or EC_{50} for F_1F_0 ATP hydrolysis than F_1F_0 ATP synthesis. This invention discloses the process/method of using one or more molecular species, each with one or more of the characteristics in the aforementioned numbered points, as an anti-cancer medicine or treatment. *Some* examples are presented in this disclosure. Any cancer therapy or treatment or drug that leverages, relies upon, utilises or targets that cancers employ ATP synthase in its reverse mode is an embodiment of this disclosure.

MECHANISTIC DISTINCTION FROM POLYKETIDE F_1F_0 ATP SYNTHASE INHIBITORS

The compounds of this invention act by a distinctly different mechanism, upon cancer cells, than oligomycin. Drugs that act against the same molecular target have a similar pattern of activity against the different cancer cell lines of the NCI-60 assay i.e. the smaller, and the larger, of their GI50 values are against the same cell lines (*GI50 is compound concentration that causes 50% growth inhibition of a cell line relative to no-drug control*). The degree of (dis)similarity can be measured using the COMPARE algorithm [28-29], which employs a Pearson correlation coefficient. For example, [30] found that the COMPARE algorithm can successfully group different FDA-approved anti-cancer drugs by their method of action using their NCI-60 GI50 data. Oligomycin A (NSC: 717694 [16]) inhibits F_1F_0 ATP synthase [4, 14] and so do other polyketides: cytovaricin (NSC: 349622 [16]), ossamycin (NSC: 76627

[16]) and peliomycin (NSC: 76455 [16]); indeed, their NCI-60 pattern responses (GI50 values) correlate with that of oligomycin A: 0.896, 0.809 and 0.865 respectively (COMPARE algorithm output, all significant at $p < 0.05$). However, the NCI-60 pattern response (GI50 values) of BMS-199264 is uncorrelated to that of oligomycin A (0.009). As is that of compounds 6b (0.198, not significant at $p < 0.05$) and 6a, which are separated stereoisomers of racemate 19a that both epimerize towards being the 19a racemate during NCI testing, and that have very correlated anti-cancer activity (0.754, $p < 0.00001$). This mechanistic distinction from oligomycin is vital because polyketide F_1F_0 ATP synthase inhibitors are poisonous to normal cells [15], which means they fail in cancer xenograft mouse experiments [16] and are without clinical utility.

Higher HIF-1α (and lower pyruvate kinase {liver isoenzyme}, lower aspartate aminotransferase 2 {mitochondrial} and lower ATP synthase) gene expressions are reported to be a marker of the Warburg effect [14] and correlate (at $p < 0.05$) with insensitivity to the polyketide F_1F_0 ATP synthase inhibitor, cytovaricin (Table 1 of [14]). By contrast, using the same cell lines and gene expression data set used to make Table 1 of [14], BMS-199264 sensitivity (GI_{50}) does not correlate (at $p < 0.05$) with any of these gene expressions. Nor does compound 6b (at $p < 0.05$). And actually higher HIF-1α expression, a marker of the Warburg effect, correlates (0.714, but statistically insignificant at $p < 0.05$) with *higher* sensitivity to BMS-199264 and to 6b (0.332, but statistically insignificant at $p < 0.05$). Figure 5 of [14] presents apoptolidin resistant NCI-60 cell lines, resistant because they utilise the Warburg effect [14], but the majority of these cell lines are *more* sensitive to BMS-19264 than the average, with a lower GI50 value than the average GI50 value (3.9 μM) for BMS-199264.

The lower the bioenergetic cellular index (BEC) of a cancer cell [18], the more it demonstrates the Warburg effect and the more it relies on glycolytic rather than oxidative metabolism. BEC is, by one measure [19], the ratio amount of the β subunit of F1 ATPase (β –F1-ATPase; gene: ATP5B) to that of Glyceraldehyde 3-phosphate dehydrogenase (GAPDH). I calculated BEC for the same cell lines analysed for Table 1 of [14], using the mRNA transcript amounts of ATP5B and GAPDH in each cell line, data sourced from [31-32], and then calculating the ([ATP5B]/[GAPDH] transcript ratio) for each of these cancer cell lines. Using transcript data rather than protein data is a limitation, but [33] report that a protein's cellular amount is generally well correlated (0.76) to its mRNA transcript amount,

at least for cells in the NCI-60 assay, for the protein subset they studied. And furthermore, [14] relied on transcript data, so best comparison with [14] is made using such data. Polyketide F_1F_0 ATP synthase inhibitors don't work well against cancer cells exhibiting the Warburg effect [14] and, indeed, for the cell lines analysed (same ones used as for Table 1 in [14]) there is a significant (at $p < 0.05$) negative Pearson correlation between $\log_{10}$(GI50) and BEC for oligomycin A (-0.9411). So, this correlation shows that the more a cancer uses Warburg metabolism, the less its danger is mitigated by oligomycin A. This significantly reduces the utility of oligomycin A as a cancer medicine because a low BEC score (indicating Warburg metabolism) is characteristic to some of the most dangerous cancers, with the worst patient outcomes [18-20]. By contrast, there is no significant (at $p < 0.05$) Pearson correlation for BMS-199264 and BEC (+0.3639). Or 6b and BEC (0.0298). This means that, distinctly from the polyketide F_1F_0 ATP synthase inhibitors, their anti-cancer action is *not* restricted to those, often less dangerous, cancers that don't utilise Warburg metabolism.

Molecules of this disclosure undermine cancer by inhibiting the reverse mode of ATP synthase. It is true that polyketide F_1F_0 ATP synthase inhibitors also inhibit this mode, but distinctly, in addition, they also inhibit the forward mode of ATP synthase, indeed more potently [11], and whilst they can exert anti-cancer activity, because this forward mode is vital to many cancers, it is also vital to many normal cells. This makes polyketide F_1F_0 ATP synthase inhibitors unsuitable as clinical molecules. Molecules of this disclosure are therapeutic because of their distinction from, not their similarity to, polyketide F_1F_0 ATP synthase inhibitors.

[14] sum up with "Many cancer cells maintain a high level of anaerobic carbon metabolism even in the presence of oxygen, a phenomenon that is historically known as the Warburg effect. From our results, we conclude that macrolide inhibitors of the mitochondrial F_0F_1-ATP synthase selectively kill metabolically active tumor cells that do not exhibit the Warburg effect". So, [14] find that these macrolides only kill cancers reliant upon OXPHOS, so using F_1F_0-ATP synthase in its forward mode to generate ATP (*which unfortunately is also the metabolic profile of many key types of normal cell*) and thus macrolide inhibition of the forward mode of F_1F_0-ATP synthase is key to this (*unspecific*) anti-cancer activity. By contrast, the molecules of this disclosure exert anti-cancer activity by inhibition of the reverse mode of ATP synthase. BMS-199264 [4, 7, 9, 10, 11], BTB06584 [13], 31 [8] and the stereoisomer 6b (and its racemate, 19a) [5, 6] have been described previously, as molecules

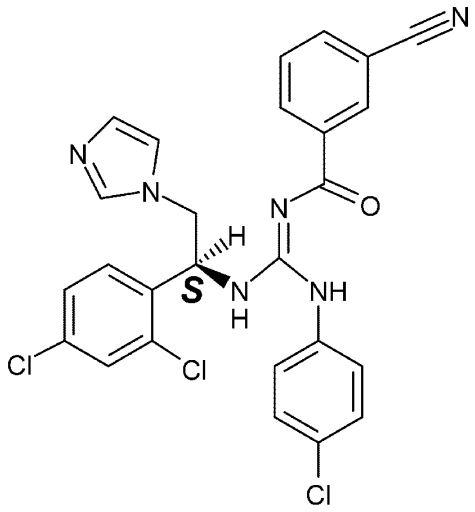
that can inhibit this mode, and this invention discloses their utility as anti-cancer therapeutics, with supporting experimental data, thence identifying new cancer drugs and, more fundamentally/importantly, a new cancer specific drug target: F_1F_0-ATP hydrolysis (**Figure 9**). The opposite stereoisomer to 6b, 6a, also exerts anti-cancer activity (**Figure 8**) because both 6a and 6b racemize towards being the racemate, 19a, during NCI testing. BTB06584 (100 μM) exerts anti-cancer activity (**Figure 3**), despite not inhibiting F_1F_0-ATP synthesis, as a function of inhibiting F_1F_0-ATP hydrolysis (at ≥100 μM), and critically it isn't harmful to normal cells (mouse cortical neurons) at this concentration [13]. Its anti-cancer potency (none at 10 μM, observed at 100 μM; **Figures 2** and **3** respectively) matches its inhibitory potency for F_1F_0-ATP hydrolysis (none at 10 μM, requires ≥100 μM [13]). BMS-199264 (10 μM) exerts anti-cancer activity (**Figure 4**). It doesn't harm normal cells (*ex vivo* rat heart) at this concentration [11]. In NCI five-dose testing [34-35], the mean GI_{50} for BMS-199264 is 3.9 μM (**Figure 10**), which is lower/better than 62% of the 102 FDA approved cancer drugs in [30], their mean GI50 values sourced from Table 1 of [30]: all are directly comparable because they too are sourced from the NCI-60 five-dose assay. Furthermore, in NCI five-dose testing, the mean GI_{50} for 6a and 6b is 0.666 μM and 0.446 μM respectively (**Figure 11**), which, in the 6b case, is lower/better than 77% of 102 FDA approved cancer drugs in [30], including cisplatin (mean GI_{50} = 1.4 μM), which is one of the most used, if not *the* most used, chemotherapies of today, but typically with terrible side-effects. At 10 μM, 6b exerts greater anti-cancer activity than BMS-199264 (**Figure 9**), despite it having less effect on F_1F_0-ATP synthesis, because it inhibits the reverse mode of ATP synthase more potently than BMS-199264. Again, a vindication that the molecules of this disclosure exert anti-cancer activity by inhibiting the reverse mode of ATP synthase, which distinguishes them from the macrolides and, distinctly, makes them usable therapeutically. Indeed, molecules of this disclosure don't appreciably inhibit the forward mode of ATP synthase, in sharp distinction to the macrolides. The compounds that contain a protonable nitrogen atom in their imidazole reduce F_1F_0-ATP synthesis in SMPs because they shuttle protons across the mitochondrial inner membrane, dissipating the proton motive force (uncoupling). **Figure 17** presents structure-activity data for such uncoupling in whole cells, using compounds that are also componentry to this invention as anti-cancer drugs. BMS-199264 (logP = 3.79, *calculated* [25]) uncouples more than 6b (logP =5.97, *calculated* [25]) because its logP is closer to the logP = 3.2 (*calculated*) optimum for uncoupling [36].

19a is a racemate, wherein the *S* stereoisomer, and not the *R* stereoisomer, potently inhibits F_1F_0-ATP hydrolysis [5-6]. I tried to test the anti-cancer activity of the separated stereoisomers. They were successfully separated by superfluid chromatography (SFC). But subsequently underwent racemization during the NCI-60 tests. One stereoisomer sample conveyed slightly better anti-cancer activity than the other, revealing more area under the curve for *S* stereoisomer exposure, and possibly a slight enduing enantiomeric excess (ee) of *S* stereoisomer. Both samples ultimately contained a significant proportion of *S* stereoisomer and both had strong anti-cancer activity (**Figure 8**). The Pearson correlation coefficient (R = 0.8 at 10 μM; R = 0.9437 at 100 μM) for their patterns of anti-cancer activity is significant (at $p < 0.00001$). Racemization of the *S* stereoisomer is slowed by replacing the hydrogen atom on its chiral carbon with a deuterium atom (enrichment) and this is a new composition of matter, which is componentry to this invention, as is the method/process of using it for anti-cancer therapy. With this modification, the enantiomeric excess (ee) of the eutomer endures for longer and so per-unit anti-cancer activity is better, for longer. Analogy by the macrolide inhibitors of [14], which [P1, P2, P3] teaches, would suggest that the *S* and *R* stereoisomers have equal anti-cancer activity, and that this would be weak, because they are both comparably weak reducers of F_1F_0-ATP synthesis (EC_{50} > 100 μM in SMP assays). By contrast, by the invention of this disclosure, the *S* stereoisomer specifically is revealed to be a potent anti-cancer therapeutic.

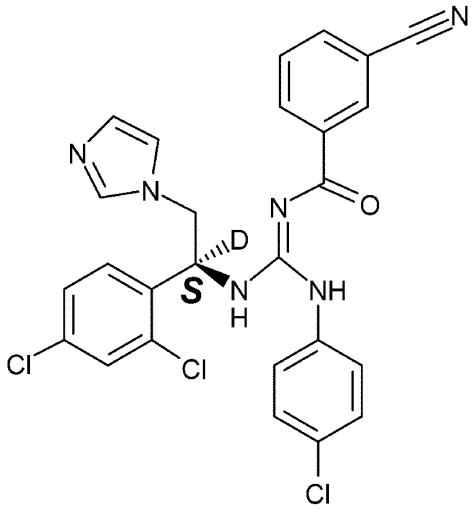
STEREOISOMERISM

For some molecules of this disclosure, one of its stereoisomers has much lower IC_{50} than the other for inhibiting F_1F_0 ATP hydrolysis, and so, by the invention of this disclosure, this is the preferred stereoisomer for anti-cancer use. Indeed, a form with high enantiomeric excess (ee) for this preferred stereoisomer is the preferred embodiment for anti-cancer therapy, e.g. ee = >70%, ee = >95%, >99% more preferred, =100% most preferred. However, ee can be eroded by racemization. This invention discloses an improvement. Embodied by this disclosure are permutations of each of its chiral molecules, wherein the hydrogen attached to each chiral carbon is replaced with a deuterium, wherein the natural abundance of deuterium (0.015%) at this position is enhanced (non-limiting example: >3000 times greater than the natural abundance of deuterium, i.e. a >40% incorporation of deuterium). The deuterium Kinetic Isotope Effect (KIE) [37] slows racemization.

PREFERRED EMBODIMENTS



hydrogen (*H*) at chiral centre



deuterium (*D*) at chiral centre
More preferred

The structure on the left has a low EC_{50} against F_1F_0 ATP hydrolysis (0.018 μM), its [EC_{50} F_1F_0 ATP synthesis/EC_{50} F_1F_0 ATP hydrolysis] ratio > 5,556. In rats, this drug (administered in polyethyleneglycol:water:ethanol, 1:1:1) is orally bioavailable (47%) with good pharmacokinetics (intravenously applied drug half-life in blood = 2.1 hours, C_{max} = 21 μM, volume of distribution = 2.37 l/kg). The deuterated analogue on the right, wherein the hydrogen atom on the chiral carbon is replaced with deuterium, conferring greater stereoisomeric stability because of the kinetic isotope effect (KIE, [37]) is more preferred. The greater the % deuterium enrichment at the chiral carbon (carbon atom number 21) and the greater the enantiomeric excess, the more preferred the embodiment. In other preferred embodiments other atoms or isotopes are in place of hydrogen on the chiral carbon, blocking its racemization, ensuring enduring stereoisomeric excess. For example, fluorine. Or carbon (methyl).

The most valuable innovation of this invention is not a presented structure but a discovered, disclosed principle: the best anti-cancer compound of this invention is a molecule that inhibits F_1F_0 ATP hydrolysis as potently and specifically as possible, whilst it inhibits, by direct binding, the forward mode of the ATP synthase molecule as little as possible: most preferably not at all.

DESTROYING CANCER'S IMMORTALITY, lengthening lives

Unlike normal adult cells, cancer cells are immortal e.g. Hela cancer cells have replicated >>billions of times in laboratories across the world after their originator, the person they killed, Henrietta Lacks, is sadly long since dead. **Figure 13** interprets (particularly) experimental data of **Figures 8, 11, 12**; interpretation expanded upon here. The core: Removing cancer's immortality, rendering it mortal, removes its danger without hurting normal cells, which are mortal anyhow. A hyperpolarised Ψ_{IM} correlates with the most dangerous cancers [38-43]. I argue because this feature/mode is a function of cancer proliferation and thus, the more aggressive/dangerous the cancer, the more time they spend in this operating mode, and thus the more chance it is detected at scale by Ψ_{IM} imaging. In these cancer cells, Ψ_{IM} = around -200 rather than the -140 mV in normal adult cells. ROS cause transient growth arrest to permanent growth arrest, to apoptosis or to necrosis, dependent on the level of ROS [44]. Constitutively activating oxidative phosphorylation (OXPHOS) in cancer cells halts their proliferation [45-46] or pushes them into apoptosis [45-49], via its inherent ROS production [47]. In cancers, a higher glycolytic rate drives greater F_1F_0 ATP hydrolysis, greater pmf and a hyperpolarised Ψ_{IM} (~-200 mV). This reduces the "sink" drive for electrons to enter the respiratory chain (especially when there is high lactate dehydrogenase expression (out)competing for NADH) and so decreases OXPHOS rate, which decreases ROS production, whilst simultaneous aforementioned features of F_1F_0 ATP hydrolysis increase [NADPH] and ROS mitigation. Thus, cancers have decreased ROS production and increased ROS mitigation. The outcome is that cancers have lower [ROS] than normal cells, which is integral to their enduring information fidelity, which permits their "limitless replicative potential" (immortality), which confers their danger. ROS sensing fluorescent probes report higher [ROS] in cancer than normal cells [50], and those of the art typically think cancers do have higher [ROS], but these probes are cationic and accumulate at greater concentrations in cancer cells because of their more hyperpolarised Ψ_{IM} (Nernst; Δ60 mV hyperpolarisation accumulates di-positive probe, like nitroblue tetrazolium, 100 times more). Other ROS sensing cancer studies report extracellular [ROS] [51] and some cancers overexpress NOX enzymes [52-53] at their plasma membrane, which generates greater extracellular [ROS], which reduces intracellular O_2 and [ROS]. High mutation rate inextricably equals higher mutation rate, ultimately too much information lost, thence limited (not limitless) proliferative capability and mortality. Cancers have high mutational load in legacy to a higher mutation rate that excavated their lower [ROS], lower mutation rate, corrupted embryonic stem cell (ES) like phenotype from the genome, and as a legacy of

cancer cells that exited this state by DNA mutation/repair, accrued mutation at higher rate, and mutated back into this state given its genomic proximity. In most cases by a different mutation route than they exited (many DNA mutation routes to a low [ROS] destination). Cancer is an anti-mutator phenotype, preceded and punctuated by mutator epochs, whilst normal adult bodies are in a runaway damage/mutation loop, ageing and ultimately dying. Raise the [ROS] in cancer to that of a normal adult cell and cancer danger attenuates. Indeed, raise [ROS] less than this: cancers have many embryonic stem (ES) cell characteristics [54-57], such as limitless replicative potential and hyperpolarised Ψ_{IM}, and ES cells respond to ROS damage more by apoptosis than repair [57]. In cancer cells, interventional inhibition of F_1F_0 ATP hydrolysis causes Ψ_{IM} depolarisation, more OXPHOS, greater [ROS], which slows cancer cell proliferation, and at greater F_1F_0 ATP hydrolysis inhibition, even more OXPHOS, [ROS], and the cancer cell dies by apoptosis or necrosis. However, once switched into significant OXPHOS, further F_1F_0 ATP hydrolysis inhibition reduces OXPHOS rate, because less ATP needs to be synthesised because less ATP is hydrolysed by F_1F_0 ATP hydrolysis, which reduces [ROS] and anti-cancer action. So, higher doses of an $F1F_0$ ATP hydrolysis inhibitor can have less anti-cancer activity, *seen in experimental data disclosed herein* (**Figures 8, 11, 12**). Normal cells use OXPHOS and they benefit from this slowing of OXPHOS, less [ROS], with slower ageing and increased lifespan. Thus, F_1F_0 ATP hydrolysis inhibitors of this disclosure hurt cancer whilst simultaneously assisting normal cells. They will extend lifespan in subjects with or without cancer, especially useful for a subject(s) with an accelerated aging disease(s) or progeroid syndrome. They will extend healthspan by delaying, and reducing the incidence of, the diseases of ageing (any disease/pathology whose incidence increases with age and/or in which elevated ROS is a contributory factor: numerous such diseases/pathologies known to those of the art) e.g. {non-limiting} Alzheimer's disease, dementia, Parkinson's disease etc.). But with a caveat. This disclosure discloses a new fundamental biological discovery, *supported by disclosed in vivo experimental data* (**Figure 15**): F_1F_0 ATP hydrolysis is not a bug but a feature, necessary for heat production and homeothermy. Thus, inhibiting F_1F_0 ATP hydrolysis in a subject reduces the subject's endogenous heat production, which requires substitution with exogenous heat e.g. higher ambient temperature for the subject e.g. by appropriate geographical (re)location. However, whilst this issue is very serious for smaller animals such as mice (~20 g), it is much less so for rats (~150 g), and even less for humans (~ 62 kg). In a simulation reported in [58], a 30% reduction in metabolic rate in man (70 kg, 170 cm, in 20°C ambient temperature), maintained for 4 hours, only decreases core body temperature by 0.18°C. By contrast, experimental data

in [58] shows that 30% reduction in metabolic rate significantly decreases core body temperature in mice, and less in rats. The flip side of this is that because much more of a small animal's metabolism comprises futile cycling of ATP synthesis and hydrolysis, to generate heat, an F_1F_0 ATP hydrolysis inhibitor can decrease their OXPHOS rate by a greater percentage, which will increase their lifespan by a greater percentage, than for a larger animal. Indeed, F_1F_0 ATP hydrolysis inhibitors of this invention will, if ambient temperature is conducive, increase the lifespan of small animals immensely and an embodiment of this invention is to enter a compound(s) of this invention into a competition to extend a rodent's lifespan, wherein there is a financial prize or other benefit e.g. the Mprize.

F_1F_0 ATP hydrolysis inhibitors of this invention confer greater life extension in an animal than for normal cells in culture because in culture the decrease in electron flow along the respiratory chain decreases ROS production but it also decreases O_2 consumption and this raises pO_2, which increases ROS production, whereas in an animal, their breathing slows to keep tissue pO_2 constant. An invention embodiment is to use an F_1F_0 ATP hydrolysis inhibitor of this invention in co-therapy with a respiratory stimulant (non-limiting e.g. doxapram) to elevate blood and tissue pO_2 to more strongly treat/ameliorate/prevent/combat cancer in a subject. Indeed, relevantly, a compound of this invention – almitrine – increases blood pO_2 in humans.

Eukaryotes must maintain a hyperpolarised Ψ_{IM} or they will undergo apoptosis [59]. In cancers that cannot use OXPHOS because of deficiency(s) in their respiratory chain, or because of hypoxic/anoxic environment (tumours are often hypoxic), F_1F_0 ATP hydrolysis is the only means they can maintain Ψ_{IM}, which an F_1F_0 ATP hydrolysis inhibitor undermines and the subsequent Ψ_{IM} depolarisation triggers cancer apoptosis.

TREATING CACHEXIA

Cancers can utilise aerobic glycolysis (Warburg effect) at one or more stages of their cell cycle. ATP yield from one glucose molecule is 2 ATP by aerobic glycolysis and ~30 ATP by oxidative phosphorylation [1-3]. The former produces 2 molecules of lactate for each glucose consumed, which can be converted, at the cost of 6 ATP, to glucose by the Cori cycle in the liver [1]. Thence, in this case, the overall ATP yield of aerobic glycolysis is -4. *Assuming* equal energy use, and *assuming* the cancer is always rather than disproportionally using aerobic glycolysis, 1 g of cancer uses ~34 times more (potential) energy than 1 g of normal

tissue. However, this is likely an underestimate because cancers typically have higher energy use: cancer uses F_1F_0 ATP hydrolysis, with protons returning to the mitochondrial matrix by UCP2 (overexpressed in many cancers [60-61], to burn glycolytic ATP. This releases glycolytic enzymes from ATP feedback inhibition and permits high glycolytic and PPP rate, producing glycolytic intermediates for biosynthesis and elevated [NADPH] for increased ROS mitigation, thence low [ROS], releasing significant lactate. Elevated blood [lactate] correlates with cancer danger [27]. So, if food intake does not increase upon cancer developing, a growing cancer can deny energy to normal tissues, which atrophies them, which means even more energy is available to the cancer, which grows further and a positive feedback loop (cachexia) ensues which is the leading cause of death in cancer patients. By this invention, F_1F_0 ATP hydrolysis inhibitor(s) switch cancers out of aerobic glycolysis, into OXPHOS, with its associated ROS, ageing, mortality, and break this positive feedback loop, treating/ameliorating/preventing/combating cancer associated cachexia in a subject(s). F_1F_0 ATP hydrolysis inhibitor(s) also assist cachexia sufferers by making normal cells more efficient, thence requiring less glucose, and can treat/ameliorate/prevent/combat non-cancer driven cachexia in a subject(s) too.

Embodied by this invention is a therapeutically effective amount of a compound(s) that reduces F_1F_0 ATP hydrolysis, for example a compound(s) of Formula (I-VI), administered in co-therapy with a therapeutically effective amount of a compound(s) that inhibits UCP2, optionally incorporated in same or different pharmaceutical composition(s), to treat/ameliorate/prevent/combat cancer and/or cachexia in a subject. Genipin and cisplatin are non-limiting examples of compounds that inhibit UCP2, cisplatin acts on additional targets also.

BODY TEMPERATURE

Administered to a subject, F_1F_0-ATP hydrolysis inhibitor(s) conserves ATP, so less ATP needs to be synthesized, therefore respiration rate slows, thence metabolic heat production declines and body temperature can fall towards ambient temperature (if ambient < body temperature). Experimental evidence is disclosed in **Figure 15**. So, when the ambient temperature isn't arduous (not requiring significant energy consuming physiological/behavioural adaptations to maintain body temperature) and dietary intake stays constant, weight gain/maintenance can occur, which can assist cachexia, for example cancer driven cachexia. This is clinically valuable because cachexia is the leading cause of death in

cancer patients. If the ambient temperature is sufficiently close to the required body temperature, then the aforementioned decrease in heat generation is safe, because the body temperature can't fall below the ambient temperature. So, for example, if the ambient temperature is 37 °C, inhibiting F_1F_0-ATP hydrolysis could make body temperature fall to this ambient temperature, but not below it, and this is safe because ~37 °C body temperature is safe. Inhibiting F_1F_0-ATP hydrolysis will reduce, but not abolish, metabolic heat production. So, body metabolism will still contribute to heating the body, just less so, which will shift the thermoneutral and thermal comfort zones (terms well known to those of the art [62], temperatures vary by species, as is well known to those of the art) to higher temperature(s). If the subject is located at a higher temperature to account for this shift, for example at their updated, higher thermoneutral temperature, or make behavioural adaptations (e.g. wearing more clothes), then this shift is harmless. An embodiment of this invention is setting the dosage of a compound(s) that inhibits F_1F_0 ATP hydrolysis with consideration of the ambient temperature, wherein higher dosages are permissible at higher ambient temperatures. The preferred ambient temperature for a dosage permits the subject to be thermoneutral, and/or thermal comfortable, without the metabolic heat (respiration) fraction driven by the F_1F_0 ATP hydrolysis that is lost because of this dosage. This temperature management issue is more important for smaller than larger animals, because surface area scales to mass by a fractional power (e.g. refer Kleiber's law) and so larger animals retain their generated heat better, and so a given percentage drop in (per unit mass) metabolism will cause a smaller drop in body temperature in a bigger animal. The aforementioned weight gain can be of great clinical/health/nutritional value, or aesthetic value (by non-limiting example: bodybuilders), or commercial value when applied to livestock/farm animals or any animal with a commercial value e.g. racing animals, such as horses. This invention encompasses the method/process of using compounds of this disclosure for these applications, or any others wherein weight, nutritional or energetic gain is wanted in an animal or human. An embodiment of this invention is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat cachexia, cancer-associated/driven cachexia, weight loss or a disease or disorder or environmental temperature that causes a higher than normal body temperature (many known to those of the art, only a subset listed here to illustrate and not restrict the invention) which can include, but isn't limited to, ingesting an uncoupler (e.g. 2,4-

dinitrophenol), infection, sepsis, stroke, fever, pyrexia, hyperpyrexia, hyperthermia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, heatstroke, surgery related, infection (non-limiting e.g. roseola, measles, enteroviral infections, parasitic, viral, fungal, Chlamydial, Rickettsial, bacterial, mycobacterial, systemic bacterial, intravascular, HIV associated, nosocomial), pyrogenic infection, thermoregulatory disorder(s), connective tissue disease(s), Kawasaki syndrome, drug overdose, drug induced hyperthermia, alcohol/drug withdrawal, idiosyncratic drug reaction, fever of known (non-limiting e.g. infectious disease(s), inflammation, immunological disease(s), non-infectious inflammatory disease(s) {non-limiting eg. systemic rheumatic and autoimmune diseases, vasculitis, granulomatous diseases, autoinflammatory syndromes}, tissue destruction, reaction to incompatible blood product(s), metabolic disorder(s), inherited metabolic disorder(s), cancer, neoplasm, endogenous or exogenous pyrogen(s), injury, head injury) or unknown or uncertain origin, or to cause greater metabolic/bioenergetic efficiency in the subject, enhancing their physical or mental performance or causing body weight gain, or to confer hypothermia in a subject for some medical or other purpose which can include, but isn't limited to, slowing a chemical reaction(s) rate in a subject for therapeutic benefit, preventing/minimizing brain and/or tissue damage, deep hypothermic circulatory arrest for surgery, hypothermia for a surgical purpose, hypothermia for cardiac and/or cardiovascular surgery and/or brain surgery (neurosurgery), Emergency Preservation and Resuscitation (EPR), preserving detached body parts such as limbs and/or organs (for example during organ storage and/or transplant), protective hypothermia, targeted temperature management, therapeutic hypothermia, hypothermia therapy for neonatal encephalopathy, birth asphyxia, hypoxic-ischemic encephalopathy (HIE), haemorrhage, hypovolemia, decompression sickness, burn injury(s) including skin burn, inflammation, allergic reaction, anaphylaxis, tissue/organ rejection, hypoxia, hypoxemia, anoxemia, anoxia, anemia, hypervolemia, altitude sickness, obstructed airway, asthma attack, hypoxia in a body/tissue/organ, hypoglycemia, reperfusion injury (ischemia-reperfusion injury), upon release of a ligature or tourniquet, uraemia, crush syndrome, compartment syndrome, traumatic brain and/or spinal cord injury, major trauma, infection, bacterial and/or viral infection(s) (non-limiting e.g. meningitis), sepsis, septic shock, ischemic brain/heart/kidney injury, neuroprotection and/or cardioprotection and/or tissue protection during/after a stroke and/or ischemia and/or cardiac arrest and/or resuscitation and/or a period(s) of poor blood flow anywhere in a subject, or to confer hypothermia to treat/ameliorate/prevent/combat a poisoning by a toxic amount of a compound(s) in a subject (non-limiting e.g. carbon monoxide/methanol/heavy metal/pesticide

poisoning, snake/spider/bee/insect/lizard venom, metabolic poison, bacterial toxin(s), endotoxemia, eukaryote produced toxin(s) e.g. (non-limiting) brevetoxin, drug/substance overdose e.g. (non-limiting) heroin, ethanol, a prescription medication(s), an over the counter medication such as paracetamol etc.; hypothermia is protective to toxic insult), or to confer one or more of sedation, anaesthesia, hypoactivity, hibernation, torpor, suspended animation, life extension in a subject. In an embodiment, the amplitude of hypothermia is controlled by setting the ambient temperature, wherein an effective amount of administered F_1F_0 ATP hydrolysis inhibitor reduces subject body temperature to the ambient temperature, and so hypothermic amplitude is controlled by controlling ambient temperature. Another embodiment is that the body temperature that the body falls to, upon administration of an effective amount of F_1F_0 ATP hydrolysis inhibitor, is controlled by controlling feature(s) of electromagnetic radiation upon the subject, for example emergent from a radiation heater(s), optionally controlled by servocontrol, with the set point set at the desired hypothermic body temperature, used as a body heating system alone or in combination with other body warming devices and methods (many possibilites known to those of the art), which are optionally controlled by servocontrol, optionally integrated into the same control loop, optionally used by themselves alone or in combination for this body heating purporse, to "catch" and offset the hypothermic drive, of an effective amount of F_1F_0 ATP hydrolysis inhibitor(s) in the body, at some desired hypothermic body temperature.

Many cancers cause fever in a subject. By the invention of this disclosure, F_1F_0 ATP hydrolysis inhibitors exert anti-cancer activity and can reduce body temperature if [ambient < body temperature]. Thence an embodiment of this invention is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat cancer and cancer associcated fever, especially (but without restriction) one or more of the following cancers, which are well known by those of the art to drive fever in many cases: non Hodgkin lymphoma (NHL), Hodgkin lymphoma, acute leukaemia, kidney cancer (renal cell cancer), liver cancer (hepatocellular carcinoma), bone cancer, adrenal gland tumours such as phaeochromocytomas, tumours in the hypothalamus, solid tumours.

Compounds of this invention, which inhibit F_1F_0 ATP hydrolysis, have utility for making animals and/or humans feel more comfortable in hot weather, climates and geographies. For example, being taken by or administered to people, especially the elderly, during hot summers.

This temperature aspect to compounds of this disclosure isn't relevant to the NCI-60 tests. Because in these studies, the ambient temperature is controlled at 37 °C [35], which is optimal for cells, and so if these drugs make cellular temperature fall to ambient temperature, this is not detrimental. It can be an issue for laboratory animal studies though. Laboratory mice, for example, are typically kept at room temperature (e.g. 20 to 23 °C) which renders them very reliant upon additional metabolic/physiological/behavioural heat production because their thermoneutral zone is much higher, at 30 to 32 °C (can vary depending on strain, size, age, gender etc. [62]). An administered compound(s) of this disclosure, which inhibits F_1F_0 ATP hydrolysis, can add to the cold stress that laboratory mice endure when kept at typical room temperature. An embodiment of this invention is the process/method of keeping laboratory animals at, or close to, their thermoneutral zone when performing animal studies with a compound(s) of this disclosure. For example, keeping mice at 30 to 32 °C. And in a further embodiment, at even higher temperature to compensate for the amount that an administered compound(s) of this disclosure, by inhibiting F_1F_0 ATP hydrolysis, shifts the animal's thermoneutral zone to a zone of higher temperature. The amount shifted will depend on the administered dosage, so in a further embodiment, the ambient temperature is set according to the dosage used. Wherein, for a compound of this disclosure, a higher ambient temperature, within safe limits, can make a greater compound dosage safer.

An embodiment of this invention is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat a medical disease/disorder, wherein the subject is monitored, for example by a healthcare/research professional/worker (doctor, oncologist, nurse, vet, pharmacist, laboratory technician, scientist) or machine/artificial intelligence substitute, for any adverse signs/symptoms/non-normality after compound administration (in an embodiment for 5 minutes, in a further embodiment for 10 minutes, and in a further embodiment for longer) and in a particular embodiment for signs of reduction in body

temperature (methods well known to those of the art, in a particular embodiment the subject's body temperature is monitored) and/or the dosage administered is set, and/or modified (e.g. increased in graduations), by information from this subject wellness/normality/temperature monitoring and/or the subject is located at an ambient temperature (e.g. in a temperature controlled room/enclosure/confine/climate and/or their body temperature is modified/regulated/interdicted by heating effect of electromagnetic radiation e.g. infrared) that maintains their body temperature within safe limits whilst they have an effective amount of compound in their system. An embodiment of this invention is the process/method of considering the ambient temperature in the decision of whether to take or administer a compound(s) of this disclosure, and at what dosage. In an embodiment, a period of medical observation, by a clinical or healthcare professional (e.g. pharmacist), occurs after the subject takes or is administered a compound(s) of this disclosure for the first time, and in a further embodiment when the compound dosage is increased or decreased. In a further embodiment, during this period of medical observation, the subject stays in a location that has medical facilities and/or expertise to treat/combat hypothermia (well known to those of the art), in non-limiting example embodiments this is a hospital or clinic or pharmacy or workplace of healthcare professionals. In an embodiment, during this period of medical observation, the patient stays in a temperature controlled room or area, or at a location where one is available nearby, and if the patient displays signs or symptoms of hypothermia, feels uncomfortable, or their body temperature falls, they can be located in a higher ambient temperature. In an embodiment, while the subject takes or is administered a compound(s) of this invention, or in a monitoring period after it, they stay in a room/confinement/location at a safe ambient temperature for having a compound(s) of this disclosure (non-limiting examples: wherein the ambient temperature is close to the desired body temperature, ~37 °C, or exceeding it within safe limits) and are monitored by observation, and in a further embodiment their body temperature is monitored (methods well known to those of the art), as the controlled room/confinement/location temperature is reduced to a different temperature, in a further embodiment to, at or near, the ambient climatic temperature of that geography at that time, or colder. In a further embodiment, this process/method is iterated until the greatest dosage is found at which the subject has a safe body temperature at, or near, the ambient climatic temperature of that geography at that time or at the ambient temperature(s) at which the subject will spend their time at over their course of compound administration, or that their ambient temperature might fall to at some time over their course of compound administration,

wherein the course of compound administration is the period during which the subject has an effective amount of compound in their body.

Many clinical oncology centres have equipment for body heating, for administrating hyperthermia, for anti-cancer treatment. And other clinical specialities have body heating equipment for heat therapy. An invention embodiment is to administer an effective amount of an F_1F_0 ATP hydrolysis inhibitor(s) to a subject, who is heated by such body heating equipment/apparatus, or other body heating equipment/apparatus. An embodiment of this invention is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat a medical disease/disorder, wherein the subject is warmed by a device(s), for example a medical device(s) (numerous examples known to those of the art e.g. refer [63-64]), to maintain their body temperature within a safe range, optionally locating in an incubator and/or in/under a radiant heater, optionally a scale up of that often used for (especially premature and/or low birth weight) babies (such scale ups, e.g. adult radiant warmer(s), are commercially available, used for example when patients undergo general anaesthesia, which can reduce metabolic rate by 20-30% [63]; teaching of [64] incorporated herein by reference, as applied to adult or infant), and the subject's body temperature is maintained by heating the air to a desired temperature and/or by controlled electromagnetic radiation (e.g. infrared, preferably IR-A, from 0.78 to 1.4 μm), and/or by servo-controlling the body temperature at a desired set-point, most preferably at a body temperature conducive to keeping the subject alive e.g. at or near 37°C and/or at a thermoneutral temperature for the subject (in a further embodiment the desired set-point is set at a lower temperature than a normal body temperature, to induce hypothermia in the subject for a medical purpose). Servocontrol in this context, as well known to those of the art, refers to an electronic feedback system which maintains a constant temperature at the site of a thermistor (or other) probe (for non-limiting example, on the skin over the abdomen) by regulating the heat output of an incubator and/or radiant warmer and/or other body heating device. Componentry to this invention is a servocontrol variant(s) whereby body temperature is recorded by infra-red (and/or other electromagnetic) emission from the body and/or body temperature is increased by infra-red (and/or other electromagnetic) emission towards the body, optionally where temperature detection and heating occurs at different wavelengths, optionally for use for heating a subject

with an effective amount of a compound(s) that inhibits F_1F_0 ATP hydrolysis in their body, optionally a compound(s) of Formula (I-V). An embodiment of this invention is a method in which a subject is administered an effective amount of a compound(s) or pharmaceutical composition(s) that inhibits F_1F_0 ATP hydrolysis, by intravenous injection, wherein the volume injected is heated to be at or close to normal body temperature and/or wherein any method(s), including equipment, used to treat/ameliorate/prevent/combat anaesthetic associated hypothermia (methods are well known to those of the art) is used for a subject administered with a compound(s) that inhibits F_1F_0 ATP hydrolysis, optionally a compound(s) of Formula (I), (II), (III), (IV) or (V). An embodiment of this invention is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat a medical disease/disorder, wherein the subject wears one or more clothes, optionally a hat, to maintain body temperature within safe/comfortable limits as the F_1F_0 ATP hydrolysis inhibitor(s) reduces metabolic heat production. An embodiment of this invention is a method in which a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, is distributed, sold and/or administered with a verbal and/or written communication, optionally in a paper insert/leaflet in a packet(s) containing the compound(s) (optionally called “instructions for use”, and/or “prescribing information” and/or “patient information leaflet”), that this compound(s) can reduce body temperature and, in a further embodiment, communicating that should the subject that has taken or been administered one or more of these compounds feel cold, and/or has a reduction in body temperature, they should do one or more of: wear more clothes, wear warmer clothes, locate in a hotter environment, tell a doctor or pharmacist, go to a hospital. Each of these aforementioned communications is a separate invention embodiment and combinations of these are further embodiments. In a yet further embodiment, communicating that this is a more serious problem in children, optionally communicating that this is because children have a larger surface area to volume ratio than adults, optionally communicating that this problem is especially acute with babies and optionally communicating that this compound(s) should not be administered to babies (in a further embodiment, unless the baby is in a controlled temperature environment such as an infant incubator or radiant warmer). In another embodiment, a method in which a compound(s) of this invention, for example a

compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, is distributed, sold and/or administered with a verbal and/or written communication, optionally in a paper insert/leaflet in a packet(s) containing the compound(s) (optionally called "instructions for use", and/or "prescribing information" and/or "patient information leaflet"), that alcohol shouldn't be consumed in large amounts, and in another embodiment not at all, if the subject is taking or being administered such a compound(s). Optionally communicating because alcohol can corrupt thermoregulation, which can potentially, negatively interact with the thermoregulatory effect(s) of the administered compound(s). Optionally communicating the same caveat/warning/communication in reference to other drug(s) that can disrupt thermoregulation, many of which are known to those of the art (non-limiting examples: phenothiazines {like chlorpromazine etc.}, thioxanthenes etc.), in place of or in addition to the communication relating to alcohol.

BODY HEAT BALANCE EQUATION (1st Law of Thermodynamics)

S = M-W-E-C-K-R;

S = storage of heat in body (=0=heat balance, i.e. no change in body temperature, positive=increased body temperature, negative=decreased body temperature);

M = metabolic heat production (always positive in living organisms);

W = work (positive = useful work accomplished, negative = mechanical work absorbed by body);

E = evaporative heat transfer (positive = transfer to environment);

C = convective heat transfer (positive = transfer to environment);

K = conductive heat transfer (positive = transfer to environment);

R = radiant heat exchange (positive = transfer to environment);

This concept is well known ([65], herein incorporated in entirety) and numerous strategies to keep S=0, as M decreases when an F_1F_0 ATP hydrolysis inhibitor is administered to the subject, will be apparent to those of the art. For (non-limiting) example, if M decreases, use an infra-red lamp to make R negative and substantial enough to offset the decrease in M (thence keep S=0), or increase the air temperature to make C negative and substantially negative to offset the decrease in M (thence keep S=0), or wear clothes to make positive values of one or more of E, C, K, R less positive to offset the decrease in M (thence keep S=0).

TRANSLATING DOSAGE BETWEEN SPECIES

Larger species have lower mass specific basal metabolic rate, because this parameter scales to animal mass by a negative fractional power (e.g. refer Kleiber's law). Thence larger species metabolise drugs slower and so require, and can withstand, a lower mg/kg drug dosage, and this is factored into converting a drug dosage in one species (e.g. mouse) into one of different size (e.g. human), as is well known to those of the art (e.g. refer [66] and the FDA guidelines it refers to). However, by the invention of this disclosure, toxicity of selective F_1F_0 ATP hydrolysis inhibitors scales to animal mass by a negative fractional power and is less in larger animals than predicted by conventional allometric scaling methods used in the art. Because larger animals have a smaller surface area to mass ratio (animal mass is proportional to animal radius^3, animal surface area is proportional to animal radius^2, thence bigger animals have smaller surface area to mass ratio), they retain metabolically generated heat better and thence a given percentage drop in metabolic rate doesn't cause as big a percentage drop in body temperature i.e. they aren't as negatively affected by a drop in metabolic heat production, which F_1F_0 ATP hydrolysis inhibitors cause, which is the defining limit upon their maximally tolerated dosage (MTD), in smaller animals at least, *if* ambient temperature is significantly below optimal body temperature e.g. when ambient temperature = ~22°C.

Mass specific metabolic rate (MR) [62] is, assuming core body temperature stays constant (heat production=heat loss), and that ambient temperature is below the lower critical temperature, which is the lower bound of ambient temperature that an animal is thermoneutral:

$MR = C(Tb-Ta)$;

Tb = body temperature;

Ta = ambient temperature;

C= whole body thermal conductance= heat transfer rate (by all heat transfer mechanisms) from body core to environment for temperature difference of 1°C;

I=insulation=1/C;

$MR = 21.66*M^{-0.25}$;

$C = 4.23*M^{-0.426}$;

where M = body weight (g);

MR and C decrease with increasing M; MR decrease increases drug toxicity; C decrease decreases drug toxicity (for an F_1F_0 ATP hydrolysis inhibitor), let us define a danger quotient

for an F_1F_0 ATP hydrolysis inhibitor: its danger is proportional to C and inversely proportional to MR: danger = C/MR = $(4.23*M^{-0.426})/(21.66*M^{-0.25})$. Using M=20 g for a mouse, and M=62 kg for a human, danger quotient for mouse (=0.12) and human (=0.03). So, *assuming* same ambient temperature for both species, which is *below* the thermoneutral temperature zone of both species, the mg/kg MTD will be ~4 times *more* in humans than in mice, and even greater than this for a human wearing clothes (decreases C). This is far removed from what one of the art would expect: expecting mg/kg MTD in humans to be *less* than in mice: for example, calculating $(21.66*20^{-0.25})/(21.66*62000^{-0.25}) = 20^{-0.25}/62000^{-0.25}$ = ~7.5 times less, or using the more conservative exponent of [66] (and possibly less appropriate, at least for chemotherapeutics: refer FDA guidance cited in [66]) they would calculate $20^{-0.33}/62000^{-0.33}$ = 14.2 times less. Any given mg/kg dose in humans will be metabolised $(20^{-0.25})/(62000^{-0.25})$ = ~7.5 times slower and so because we have ascertained that the maximum permissible mg/kg dose in humans is ~4 times more than in mice: then the potential anti-cancer activity of an F_1F_0 ATP hydrolysis inhibitor is 4*7.5=~30 times higher in a human than a mouse, *at typical room temperature*. So, elucidated by the invention of this disclosure, small animal studies at room temperature (~22°C) will dramatically underestimate the anti-cancer activity possible at room temperature in humans, and severely curtail the therapeutic benefit *if* conventional allometric scaling is used to set the human dose from mice studies. This invention supplies a new method to better translate the dosage of an F_1F_0 ATP hydrolysis inhibitor between species. However, more conventional allometric scaling methods *can* be used [66] *if* the smaller species studies are conducted at an ambient temperature close to optimal homeothermic body temperature, Ta≈Tb, and *especially if* humans will live at this same temperature. Thus, the temperature at which the smaller species study is conducted, and the temperature that the human subjects will reside at, determines the allometric scaling method applied, to find the equivalent human dose, which would not have been apparent to someone of the art without this disclosure. Furthermore, a method as disclosed herein can be used to modulate F_1F_0 ATP hydrolysis inhibitor dosage between individuals of a single species, e.g. humans, of different sizes.

The equations and parameters used in this section illustrate the principles of the invention and are not restrictive. For example, other allometric exponents are contemplated and componentry to this invention. A method of this invention is to compare the MTD (or some other safety metric e.g. NOAEL, LD_{50}, LD_{33} etc.) of an F_1F_0 ATP hydrolysis inhibitor(s) between animal individuals and/or species of different size (e.g. mice, rats, guinea pigs,

rabbits, dogs, primates etc.) to calculate more precisely what the particular allometric scaling relation is, and optionally investigate how this scaling changes with ambient temperature. And then use this relation(s) to calculate/triangulate/estimate a safe starting dose in humans, from prior animal studies. Optionally factoring in what the ambient temperature(s) will be for the humans administered the F_1F_0 ATP hydrolysis inhibitor(s).

ANTI-CANCER DOSAGE

Methods to gauge the anti-cancer activity of a treatment(s) in a subject(s), and/or to gauge the change in anti-cancer activity associated with a change (e.g. dosage change) in treatment(s), are well known to those of the art. They are routinely utilised in pre-clinical studies and clinical practice.

The following methods are very atypical from present dosage methods in the art of chemotherapy, wherein dosage is typically, simply just the maximum dosage that the patient can tolerate. The method of *decreasing* the administered dose of a compound(s) that inhibits F_1F_0 ATP hydrolysis, for (non-limiting) example a compound of Formula (I), in order for it to exert *greater* anti-cancer activity in a subject is an embodiment of this invention.

The anti-cancer activity of a compound(s) of Formula (I) can increase or decrease in proportion to an increase in compound dosage, wherein there is an optimal anti-cancer dosage which is not, as one of the art would expect, at the maximally tolerated dose. Decreasing or increasing (!) the dose away from this optimal dosage decreases anti-cancer activity. Herein is a method to find this optimal dosage in a subject, which is componentry to this invention, as are other methods to find the optimal dosage for a compound(s) of Formula (I), which leverage/utilise the extremely atypical dose vs. anti-cancer activity profile, disclosed herein (**Figures 8, 11, 12**).

If increased dose = increased anti-cancer activity, increase dose further. If increased dose = decreased anti-cancer activity, decrease dose by more than it was increased previously. Make the next increase in dose smaller than prior. Repeat. As this loop is repeated, and the increment increase in dose gets smaller, the person of the art knows that they are increasingly converging upon the optimal dosage. They can choose to exit the loop at any dosage they wish, knowing that the size of the dosage increase increment on loop exit is an indicator of how close they are to the optimal dosage. The smaller the dosage increase increment at loop

exit, the closer that the dosage is to the optimum. The person of the art may choose to do the mirror image of the aforementioned loop and choose decreased, instead of increased, dose increments. There are permutations to these schemes as will be clear to someone of the art, now that this logic has been set out, which are componentry to this invention. To help illustrate (not restrict) the invention the following R [67] programming code is disclosed, wherein the "optimal" parameter symbolises the optimal anti-cancer dosage, and the loop iterates until the administered drug dosage, "dose", equals the optimal. Someone of the art can adjust this code, for example changing parameters and/or mathematical symbols, to explore and understand the invention further. Of course, in reality, the optimal anti-cancer dosage is unknown and is not user specified, as in the code, but the code illustrates a method to find the optimal anti-cancer dosage for a compound of Formula (I), a method componentry to this invention. All parameters are merely illustrative.

```
# R programming code
dose = 1              # first dose to be tried
reset = dose
dt = 600              # step size that dose will be adjusted
res = dt/100000000
# res = an accuracy parameter, larger denominator means more iterations and more accuracy
x = 0
optimum = 60
# optimal anti-cancer dose, unknown in real case, following the logic herein finds it
n = 10
# n = an accuracy parameter, MUST be >1, larger means more iterations and more accuracy
m = n
count = 0             # how many iterations are taken to converge

while (dt > res)
{
dose = dose + dt
if (dose<optimum) {
# Increased dose = Increased anti-cancer activity, so Increase dose further
dose = dose+dt
x=x+1
```

```
}
if (dose>optimum) {      # Increased dose = Decreased anti-cancer activity, so Decrease dose
if (dose<0){
dose=reset
dt = dt/n
}
dose = dose-(dt+(dt/n))
x=x-1
}
if (x==0){dt=dt/m}
# if dose is changed in one direction (increase or decrease) and then subsequently changed in
# opposite direction, decrease step size
if (abs(x)==2){x=0}
count = count + 1
# if (abs(dose-optimum)<1){break}    # not used, but here for interest
}
```

In place of, or after, the aforementioned, or other, method has converged the administered dose to be close to optimum, the dosage can be set randomly, optionally restricted within a range, by some formal/informal random number generator. It need not be perfectly random and can just be the arbitrary choice of a person(s). This formalised/informal random walk is used to find a compound(s) dosage, of Formula (I), with greater anti-cancer activity. It is distinct from conventional methods in its use of dosage reduction (not merely increase) to seek greater anti-cancer activity.

The most optimal dosage, or dosage range, for a compound of Formula (I) is that which causes cancer cell death. This is a narrow dosage range (**Figure 13**). Flanked at lower and higher doses by dosages that exert less anti-cancer activity. An embodiment of this invention is changing the administered dosage of a compound of Formula (I) in a subject until a dosage(s) causes cancer cell death, optionally by apoptosis. Detected, for non-limiting example, by cancer regression rather than merely slowing of cancer growth and/or by apoptosis markers, well known to those of the art (e.g. refer [68]), for example, in the blood.

Using a dosage selection method disclosed herein to find a good anti-cancer dosage for a compound of Formula (I), optionally in a xenograft/syngeneic rodent(s), optionally housing the rodent(s) at an ambient temperature ≥26°C (in further embodiments: ≥28, ≥30, ≥32, ≥34, ≥36°C), is componentry to this invention. As is any housing/rearing of a rodent(s) at an ambient temperature ≥26°C (in further embodiments: ≥28, ≥30, ≥32, ≥34, ≥36°C) whilst administered with a compound(s) of Formula (I), optionally to select the starting dosage(s) for human clinical trial(s).

UNCOUPLING CANCER

The meaning and characteristics of an uncoupler are well known to those of the art e.g. refer [36]. An uncoupler is a molecule that can bind a proton(s) in the mitochondrial intermembrane space (IMS), move across the mitochondrial inner membrane, and release the proton(s) in the mitochondrial matrix, which dissipates the proton motive force (pmf), and that can then return to the IMS, and repeat this sequence iteratively. 2,4 dinitrophenol is an example of an uncoupler. Many other uncouplers are known to those of the art. An invention embodiment is to administrate a therapeutically effective amount of a compound(s) that inhibits F_1F_0 ATP hydrolysis (e.g. a compound(s) of Formula (I), (II), (III), (IV) or (V)), with a therapeutically effective amount of the same or a different compound(s) that uncouples the proton motive force, for use in a method of treatment of the human or animal body by therapy, wherein optionally the F_1F_0 ATP hydrolysis inhibitor(s) and uncoupler(s) are in a single pharmaceutical composition and/or are packaged, and/or distributed, and/or sold together, optionally for the treatment/amelioration/prevention/combat of cancer in a subject(s). As aforementioned, the dosage range that an F_1F_0 ATP hydrolysis inhibitor of Formula (I) kills cancer cells is extremely narrow. This range is broadened by co-administration of an uncoupler(s), which increases OXPHOS rate and [ROS], and reduces the concentration of F_1F_0 ATP hydrolysis inhibitor required. Optionally, an F_1F_0 ATP hydrolysis inhibitor(s) is administered with an aforementioned method(s) to (fractionally) optimise its dosage, before the administration of the uncoupler, which then decreases the dosage of uncoupler required. An F_1F_0 ATP hydrolysis inhibitor(s) decreases metabolic inefficiency and body temperature, an uncoupler(s) increases metabolic inefficiency and body temperature: co-administration, especially optimised co-administration, optionally wherein an optimised amount of each is in a single pharmaceutical composition, can reduce the change in body temperature that each would cause alone; and there is synergy in anti-cancer activity yielded. Componentry to this invention are compounds that inhibit F_1F_0 ATP hydrolysis *and*

that uncouple the proton motive force (pmf) e.g. (non-limiting) BMS-199264. An embodiment of this invention is to administrate, or for the subject to self-administer, a therapeutically effective amount of a compound(s) that inhibits F_1F_0 ATP hydrolysis *and* that uncouples the proton motive force, for use in a method of treatment of the human or animal body by therapy, optionally for the treatment/amelioration/prevention/combat of cancer in a subject(s).

In cancers that cannot use OXPHOS because of deficiency(s) in their respiratory chain, or because of hypoxic environment (tumours are often hypoxic), which thence singly rely upon F_1F_0 ATP hydrolysis to maintain Ψ_{IM}, an uncoupler(s) will erode their Ψ_{IM} and an F_1F_0 ATP hydrolysis inhibitor(s) will block their only means to counter this, their Ψ_{IM} will collapse, triggering their apoptosis. Given the severity of this vulnerability, and the potentiating effect of the two drugs, low drug doses apply. Meanwhile, normal cells will maintain Ψ_{IM} by greater OXPHOS rate.

Also componentry to this invention is the use of a therapeutic amount of uncoupler(s) to treat/ameliorate/prevent/combat cancer in a subject. If Ψ_{IM} depolarises, apoptosis ensues [59]. Aerobic respiration, favoured by normal adult cells, hyperpolarises Ψ_{IM} as it *produces* ATP. Aerobic glycolysis, favoured by many cancers some or all of the time, *consumes* ATP to hyperpolarise Ψ_{IM}. Under the challenge of an uncoupler compound(s), the former is more sustainable than the latter, even more so because of the difference in ATP yields (~30 vs. 2 ATP per glucose), and thence there is a therapeutic margin. In response, some cancers will be able to switch out of aerobic glycolysis, and into aerobic respiration, but its oxidative phosphorylation (OXPHOS) component will increase ROS, bring ageing, mortality and mitigated danger, especially because the uncoupler(s) will drive higher OXPHOS rate. Unlike other chemotherapeutics, uncouplers only interact with protons, not DNA encoded proteins, and so their therapy cannot be resisted by DNA mutation rendered changes in protein structure, which is the basis to present day cancer drug resistance, which kills.

UNCOUPLING IS VIRTUOUS

The imidazole containing compounds of this disclosure inhibit F_1F_0 ATP hydrolysis and uncouple (shuttle protons across the mitochondrial inner membrane (IM), eroding the proton motive force, pmf). The former can exert a specific anti-cancer activity, because it undermines the means some cancers maintain Ψ_{IM} in normoxia (experimentally shown by

data of this disclosure) or in hypoxic tumours, and the compound's uncoupling can also exert specific anti-cancer activity, explained now. The imidazole containing compounds of this disclosure bind ATP synthase at or near the IF_1 binding site. In normal cells they bind ATP synthase at this site and are sequestered from uncoupling, and the ATP they "save" by binding and inhibiting F_1F_0 ATP hydrolysis can (over)compensate for the ATP "lost" to their uncoupling. But some cancers have very high IF_1 expression (numerous studies show this, e.g. refer [23]). And for some cancers, this is to inhibit F_1F_0 ATP hydrolysis, to make their OXPHOS more efficient, which allows them to maintain [ATP] at low [O_2], and thence survive using OXPHOS in hypoxia (their heat generation is less but their temperature is maintained by heat conduction from surrounding tissues). This high IF_1 expression blocks the binding of these compounds to their binding site on ATP synthase, so the compounds aren't sequestered from uncoupling, and this uncoupling increases the O_2 requirement of this cancer which can't be met in the hypoxic microenvironment of its tumour, thence the cancer's intracellular [ATP] can't be maintained and its proliferation is slowed and/or it dies. So, herein, this invention discloses that the uncoupling aspect to the imidazole containing compounds of this disclosure can deliver additional, specific, anti-cancer activity, for example, against those cancers that don't rely upon F_1F_0 ATP hydrolysis. This invention discloses the process/method of using a compound(s) that can inhibit F_1F_0 ATP hydrolysis, and that can shuttle protons across the IM to dissipate the pmf (uncouple), as an anti-cancer therapeutic. Wherein the compound inhibits F_1F_0 ATP hydrolysis by direct interaction with ATP synthase, and reduces F_1F_0 ATP synthesis (primarily) by uncoupling. So, a compound needn't necessarily have a much lower EC_{50} for F_1F_0 ATP hydrolysis than F_1F_0 ATP synthesis, in an SMP assay, to be componentry to this invention as an anti-cancer therapeutic. Indeed, even compounds with a lower EC_{50} for F_1F_0 ATP synthesis than F_1F_0 ATP hydrolysis in an SMP assay can be componentry to this invention, as anti-cancer therapeutics, *provided* they do inhibit F_1F_0 ATP hydrolysis and *provided* their inhibition of F_1F_0 ATP synthesis is (primarily) because of uncoupling rather than inhibiting the forward mode of ATP synthase. Oligomycin, for example, does not fit these requisites. So, this invention discloses the method of using compounds that inhibit F_1F_0 ATP hydrolase, that don't inhibit F_1F_0 ATP synthase, and that uncouple the proton motive force, as anti-cancer therapeutics.

DEUTERATED COMPOUNDS OF THE INVENTION

Deuterium (D or ^2H) is a stable, non-radioactive isotope of hydrogen and has an atomic weight of 2.0144. Hydrogen naturally occurs as a mixture of the isotopes ^1H (hydrogen or

protium), D (^{2}H or deuterium), and T (^{3}H or tritium). Herein, all percentages for the amount of deuterium present are mole percentages. The natural abundance of deuterium is 0.015%. Thence one of the art recognizes that in all chemical structures containing an H atom(s), this H atom(s) actually represents a mixture of H and D in the compound, with about 0.015% being D. Therefore compounds that have a higher level of deuterium incorporation, i.e. compounds enriched to have a greater D incorporation than natural abundance (>0.015%), should be considered unnatural and so distinct from their non-enriched counterparts. A compound is said to be "deuterium enriched" if it has a quantity of deuterium that is greater than in naturally occurring compounds, or synthetic compounds prepared from substrates having the naturally occurring distribution of isotopes. At a lab scale amount (milligram or greater) it can be difficult to achieve 100% deuteration at any one site of a compound. Herein, when 100% deuteration is recited or a deuterium atom is specifically shown in a structure, it is assumed that a small percentage of hydrogen may still be present. Deuterium-enrichment can be achieved either by exchanging compound protons with deuterium or by synthesizing the compound with deuterium enriched starting materials, which are commercially available or can be readily prepared by someone of the art using known methods.

Embodiments of this invention include compounds of Formula (I), (II), (III), (IV), (V) and (VI) with one or more of their hydrogen atoms replaced by deuterium, at a greater frequency than the natural abundance of deuterium (0.015%). For non-limiting example: >3000 times greater than the natural abundance of deuterium (i.e. a >40% incorporation of deuterium at a hydrogen replacement position). Additional examples of the abundance of deuterium at a position in, or positions of, a compound embodiment of this invention include 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 to about 100%. In certain embodiments, the abundance of deuterium at a position in, or positions of, a compound embodiment of this invention is at least 40%. In certain other embodiments, the abundance of deuterium at a position in, or positions of, a compound embodiment of this invention is at least 60%. In futher embodiments, the abundance of deuterium is at least 75%. In yet other embodiments, the abundance of deuterium is at least 90%. It is to be understood that the deuterium-enriched compounds described herein can be combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition.

In the Description and Claims of this disclosure, when a position on a compound structure is designated deuterium (D), or said to have deuterium, or said to be enriched for deuterium, it is because the abundance of deuterium at that position is not at the natural value (0.015%) but greater. Typically, in excess of 40%. The phrase 'enrichment at the chiral centre' herein, for example for a compound of Formula (I), means that the molar amount of deuterium at the chiral centre, as a percentage of the total amount of all hydrogen isotopes at the chiral centre, is greater than 0.015%, especially greater than 1%, preferably greater than 40%, more preferably greater than 45%, and in ascending order of preference, ≥52.5% deuterium enrichment at the chiral centre, ≥60% deuterium enrichment at the chiral centre, ≥67.5% deuterium enrichment at the chiral centre, ≥75% deuterium enrichment at the chiral centre, ≥82.5% deuterium enrichment at the chiral centre, ≥90% deuterium enrichment at the chiral centre, ≥95% deuterium enrichment at the chiral centre, ≥97% deuterium enrichment at the chiral centre, ≥99% deuterium enrichment at the chiral centre, ≥99.5% deuterium enrichment at the chiral centre, 100% deuterium enrichment at the chiral centre. Greater % deuterium enrichment is preferred.

Further possible isotopic variants of the structures of this invention are further embodiments of this invention. An invention embodiment is a compound that inhibits the reverse mode, more than the forward mode, of ATP synthase, which has deuterium in place of hydrogen (at a greater frequency than 0.015% e.g. >40%) at one or more places upon its structure, and/or any other isotopic substitution/enrichment (at a greater than natural frequency e.g. ^{13}C and/or ^{15}N enriched; ^{13}C enrichment {abundance > [natural abundance=1.109%]} at the chiral carbon of compounds of Formula I is especially preferred, especially when, if applicable, its attached hydrogen is enriched for ^{2}H {abundance > [natural abundance=0.015%]; preferred is when ^{13}C enrichment at the chiral carbon >40%, optionally ^{2}H enrichment at the chiral carbon >40% also}).

Molecule synthesis routes described in [5, 6, 7, 8, P1, P2, P3, P4, P5, P6] (including references cited therein, where appropriate, and in their supplementary materials, all herein incorporated in their entirety) - for synthesizing molecules that inhibit F_1F_0 ATP hydrolysis more than F_1F_0 ATP synthesis - are componentry to this disclosure, as synthesis routes for synthesising anti-cancer molecules. In other embodiments of this invention, any given molecule synthesis route described in [5, 6, 7, 8, P1, P2, P3, P4, P5, P6, P7, P8] is used with starting reagents, compounds, solvents and/or intermediates that have deuterium in place of

hydrogen at some position(s). Such compounds are commercially available (e.g. refer C/D/N Isotopes Inc., Pointe-Claire, or CK Isotopes Ltd., Desford, UK, or Cambridge Isotope Laboratories, Tewksbury, MA). Or they can be created in house by invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. For (non-limiting, illustrative) example, a compound can be deprotonated by LiHMDS in tetrahydrofuran (THF) at -78 to -40 °C for 20 minutes, followed by quenching with deuterium oxide (D_2O, "heavy water"), to obtain a deuterated compound [37]. During these steps, a group upon which hydrogen is still desired over deuterium can be Boc protected and this Boc group removed subsequently using trifluoroacetic acid (TFA) treatment at room temperature. At the end, the level of deuterium can be checked by ^1H NMR. The initial deprotonation step isn't absolutely necessary as H/D exchange will occur when a molecule is quenched with D_2O, and this reaction can be catalysed, by acid, base or metal based catalysts such as platinum. If, after D_2O quenching, the level of compound deuteration is insufficient (observed using ^1H NMR) then the compound is quenched with D_2O, or some other deuterium containing solvent, for a longer period of time. Compounds of this disclosure can be synthesised in D_2O, during one or more chemical steps, or a starting compound, intermediate or final molecule of this disclosure can be incubated in D_2O to produce a deuterated version(s). So, deuterium-enriched compounds of this invention can be prepared by substituting a deuterium-enriched reagent or solvent for a non-isotopically labeled reagent or solvent in the synthetic schemes reported in [5, 6, 7, 8, P1, P2, P3, P4, P5, P6, P7, P8].

Non-limiting example embodiments of the invention are deuterated enumerations of Markush Formulas (I), (II), (III), (IV), (V) and (VI). These isotopologues are componentry to the present invention as new compositions of matter, and in non-limiting embodiments are used singly or in combination, optionally in co-therapy with an FDA and/or EMA approved medicine(s) and/or treatment(s), for example a licensed cancer treatment, as anti-cancer therapeutics.

METHODS TO FIND FURTHER COMPOUNDS COMPONENT TO THIS INVENTION

A method to find compounds of this invention, for example to find compounds that slow the proliferation of and/or kill cancer cells, is by screening/seeking compounds that preferentially inhibit the reverse mode of ATP synthase. For example, by separately assaying (in space and/or time) the compounds's effect upon ATP synthesis and ATP hydrolysis by ATP

synthase (in its entirety or, less preferably, a component part of it). Then comparing these assay results. The greater the inhibition of reverse vs. forward mode, the more preferred this compound is for a use of this invention, optionally anti-cancer use. A further method is by screening/seeking compounds that inhibit ATP hydrolysis more than synthesis in submitochondrial particles (SMPs). ATP hydrolysis can be assayed by (non-limiting example) a spectroscopic assay for NADH fluorescence that incubates the SMPs with pyruvate kinase and lactate dehydrogenase enzymes (assay well-known to those of the art). ATP synthesis can be assayed by (non-limiting example) a spectroscopic assay for NADPH fluorescence that incubates the SMPs with hexokinase and glucose-6-phosphate dehydrogenase enzymes (assay well-known to those of the art). These assays are reported in in any one of [5, 7, 8, 11, 12, 13, 70], and/or as referenced therein, all of which are herein incorporated in their entirety. In these SMP assays, the criteria for a candidate anti-cancer compound is a low EC_{50} against ATP hydrolysis (thence anti-cancer activity) and a higher EC_{50} against ATP synthesis (thence safe for normal cells).

CANCER TYPES PARTICULARLY TARGETED BY THIS INVENTION

Leukemia cancer cell line examples in **Figure 8** show that Compound 6b can inhibit cancer proliferation strongly at 10 μM and then nearly not at all at 100 μM. As disclosed earlier, lower [6b] switches cancer cells into greater OXPHOS use/rate, exerting anti-cancer activity, but higher [6b] decreases OXPHOS rate, exerting less anti-cancer activity. Extrapolating this data, even greater [6b] may assist cancer and increase its proliferation rate. And if a cancer has appropriate adaptations and is using OXPHOS greatly in the first place, without 6b administration, then 6b administration may only ever help and never hinder that cancer. Compound 6b, and other F_1F_0 ATP hydrolysis inhibiting compounds of this invention, are best administered to cancers showing signs of glycolytic rather than oxidative metabolism. For example, those that show up, at least before treatment by this invention, in positron emission tomography (PET) imaging using fluorine-18 (^{18}F) fluorodeoxyglucose (FDG), ^{18}F-FDG PET [71].

Particularly vulnerable to compounds of this invention: cancers that exhibit the Warburg effect (i.e. that produce ATP primarily by glycolysis, rather than oxidative phosphorylation, even in abundant O_2), highly glycolytic cancers (which metabolize glucose and/or glutamine to lactate rather than metabolizing one or both fully with the use of oxidative phosphorylation) and cancers that reside in hypoxia, which forces them to produce ATP

primarily by glycolysis. As explained in a preceding section, the imidazole containing molecules of this disclosure, with their uncoupling capability, can also attack cancers that reside in hypoxia, which use high IF_1 expression to enable oxidative phosphorylation at low $[O_2]$. Many cancers reside in hypoxia as tumours are often hypoxic.

So, if a cancer is highly glycolytic, either because of the Warburg effect (inherent glycolytic metabolism, regardless of $[O_2]$) or because of residing in hypoxia (imposed glycolytic metabolism, because of low $[O_2]$), or uses oxidative metabolism but resides in hypoxia (survival enabled by high IF_1 expression), it will be treated/ameliorated/prevented/combated by a compound of this invention. How to identify such cancers?

Cancers exhibiting the Warburg effect, or that have an imposed (by low $[O_2]$) glycolytic metabolism, are those that show up in positron emission tomography (PET) imaging using ^{18}F-FDG PET, optionally integrated with computed tomography (CT) [71]. FDG is a glucose analogue and glycolytic cancers take up more FDG than their surrounding tissue because glycolysis is an inefficient metabolism of glucose (yielding only ~2 ATP per glucose compared to ~30 ATP per glucose yielded by aerobic respiration [1-2]) and so they must uptake more glucose to obtain even the equivalent energy yield to nearby normal cells, which are using oxidative metabolism, as most normal cells do. So, if a cancer presents in this FDG-PET diagnostic (higher glucose uptake than surround), it is susceptible to a compound of this invention. Highly glycolytic cancers also release much lactate. So, if a patient has a high blood lactate level, noticeably above the normal non-pathological range, as clear to someone of the art, then their cancer is susceptible to a compound of this invention. Higher lactate levels in and around the cancer or tumour (than surrounding tissue) can also be detected using imaging technologies, for example ^{1}H Magnetic Resonance Spectroscopy (^{1}H-MRS) or chemical exchange saturation transfer magnetic resonance imaging (CEST MRI) [72], or other imaging modalities and methods of the art. So, if a cancer presents (higher [lactate] than surround) in a lactate imaging diagnostic it is susceptible to a compound of this invention. Cancer release of lactic acid acidifies its extracellular space and this acidification can be detected by imaging modalities, well known to those of the art e.g. [73-74], and if a cancer can be discriminated from its surrounding tissue by this method then it is susceptible to a compound of this invention. An oxygen-sensitive chemical probe can be used to obtain 3D maps of tissue pO2 [75], and if a cancer is shown to reside in notable hypoxia then it is susceptible to a compound of this disclosure, because it is either glycolytic or likely using

high IF_1 expression to enable oxidative metabolism, both of which make it susceptible to a compound of this invention. Imaging technologies can be integrated to improve signal to noise e.g. [75] integrate pO_2 and lactate imaging. Such integration can give added information: for example, a cancer producing much lactate in a high pO_2 environment is exhibiting the Warburg effect because it is heavily utilising glycolytic metabolism in abundant O_2. Cancer gene expression markers and indicators of the Warburg effect, well known to those of the art e.g. [18-20], specify that a cancer is susceptible to a compound of this invention, wherein the cancer's genetic material can be retrieved by biopsy, surgery, cancer cells or parts circulating in the bloodstream or some other method of the art.

If a cancer uses oxidative phosphorylation (OXPHOS) rather than glycolytic metabolism, and it does not already improve its OXPHOS efficiency by high IF_1 gene expression (which many cancers do e.g. refer [23]) then a compound of this invention, by preferentially inhibiting F_1F_0 ATP hydrolysis, will confer this efficiency gain and actually assist, rather than harm, this cancer. How to identify these cancers? A cancer's IF_1 gene expression, and particularly its gene expression ratio of IF_1 to a core ATP synthase sub-unit (e.g. ATP6), is informative. More so if compared to the corresponding gene expressions in a normal cell of its host tissue, so detecting difference from normal. If a cancer uses oxidative, rather than glycolytic, metabolism and does not have an appreciably higher IF_1 (or IF_1/ATP6 ratio) gene expression than its corresponding normal tissue then it isn't prudent to use a compound of this invention for cancer therapy. More simply, it is best to use a compound(s) of this invention against highly glycolytic cancers and some (non-limiting) imaging methods have been described herein to identify these.

This invention discloses a method of using a compound(s) that preferentially inhibits the ATP-hydrolysing mode of ATP synthase, for example a compound(s) of Formula (I), (II), (III), (IV) or (V), or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat a cancer that preferentially uses glycolytic rather than oxidative metabolism, for example a cancer exhibiting the Warburg effect, and discloses methods to identify these cancers. Identification methods specified are to illustrate the invention and not to limit its scope: this invention encompasses all methods to identify glycolytic cancers, in order to identify cancers most amenable to treatment by a compound(s) of this invention.

So, innovatively and usefully, compounds of this disclosure are selected for anti-cancer therapy by metabolic feature of the cancer, which belie how the cancer survives and proliferates, and its weaknesses, weaknesses that compounds of this disclosure attack, rather than the typical, often too arbitrary, often unhelpful, allocation by tissue type, which is the present standard in the art. A diversity of cancers, from different tissues, will be susceptible to compounds of this invention, especially the most dangerous: glycolytic cancers, with high lactate efflux, often have the worst prognosis [18-20, 27]. Experimental data of this disclosure shows that compounds of this invention are effective against many cancers.

Compounds of the present invention treat tumour growth, treat metastasis, treat metastatic cancer, treat non-metastatic cancer, treat tumour implantation, are useful as an adjunct to chemo-/radio- therapy, treat cancers including, but not limited to, Chondrosarcoma, Ewing's sarcoma, Malignant fibrous histiocytoma of bone/osteosarcoma, Osteosarcoma, Rhabdomyosarcoma, Heart cancer, brain cancer, Astrocytoma, Brainstem glioma, Pilocytic astrocytoma, ependymoma, primitive neuroectodermal tumor, Cerebellar astrocytoma, Cerebral astrocytoma, malignant glioma, Medulloblastoma, Neuroblastoma, Oligodendroglioma, Pineal astrocytoma, Pituitary adenoma, Visual pathway and hypothalamic glioma, Breast cancer, Invasive lobular carcinoma, Tubular carcinoma, Invasive cribriform carcinoma, Medullary carcinoma, Male breast cancer, Phyllodes tumor, Inflammatory Breast Cancer, Adrenocortical carcinoma, Islet cell carcinoma, Multiple endocrine neoplasia syndrome, Parathyroid cancer, Pheochromocytoma, Thyroid cancer, Merkel cell carcinoma, intraocular melanoma, retinoblastoma, Anal cancer, Appendix cancer, cholangiocarcinoma, Carcinoid tumor, Colon cancer, Extrahepatic bile duct cancer, Gallbladder cancer, Gastric (stomach) cancer, Gastrointestinal carcinoid tumor, Gastrointestinal stromal tumor (GIST), Hepatocellular cancer, Pancreatic cancer, Rectal cancer, Bladder cancer, Cervical cancer, Endometrial cancer, Extragonadal germ cell tumor, Ovarian cancer, Ovarian epithelial cancer (surface epithelial-stromal tumor), Ovarian germ cell tumor, Penile cancer, Renal cell carcinoma, Renal pelvis and ureter, transitional cell cancer, Prostate cancer, Testicular cancer, Gestational trophoblastic tumor, Ureter and renal pelvis, transitional cell cancer, Urethral cancer, Uterine sarcoma, Vaginal cancer, Vulvar cancer, Wilms tumor, Esophageal cancer, Head and neck cancer, Nasopharyngeal carcinoma, Oral cancer, Oropharyngeal cancer, Paranasal sinus and nasal cavity cancer, Pharyngeal cancer, Salivary gland cancer, Hypopharyngeal cancer, Acute biphenotypic leukemia, Acute eosinophilic leukemia, Acute lymphoblastic leukemia, Acute myeloid leukemia, Acute

myeloid dendritic cell leukemia, AIDS-related lymphoma, Anaplastic large cell lymphoma, Angioimmunoblastic T-cell lymphoma, B-cell prolymphocytic leukemia, Burkitt's lymphoma, Chronic lymphocytic leukemia, Chronic myelogenous leukemia, Cutaneous T-cell lymphoma, Diffuse large B-cell lymphoma, Follicular lymphoma, Hairy cell leukemia, Hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, Hairy cell leukemia, Intravascular large B-cell lymphoma, Large granular lymphocytic leukemia, Lymphoplasmacytic lymphoma, Lymphomatoid granulomatosis, Mantle cell lymphoma, Marginal zone B-cell lymphoma, Mast cell leukemia, Mediastinal large B cell lymphoma, Multiple myeloma/plasma cell neoplasm, Myelodysplastic syndromes, Mucosa-associated lymphoid tissue lymphoma, Mycosis fungoides, Nodal marginal zone B cell lymphoma, Non-Hodgkin lymphoma, Precursor B lymphoblastic leukemia, Primary central nervous system lymphoma, Primary cutaneous follicular lymphoma, Primary cutaneous immunocytoma, Primary effusion lymphoma, Plasmablastic lymphoma, Sézary syndrome, Splenic marginal zone lymphoma, T-cell prolymphocytic leukemia, Basal-cell carcinoma, Melanoma, Skin cancer (non-melanoma), Bronchial adenomas/carcinoids, Small cell lung cancer, Mesothelioma, Non-small cell lung cancer, Pleuropulmonary blastoma, Laryngeal cancer, Thymoma and thymic carcinoma, AIDS-related cancers, Kaposi sarcoma, Epithelioid hemangioendothelioma (EHE), Desmoplastic small round cell tumor, Liposarcoma. The compounds of the present invention treat cancers including, but not limited to, those that originate in the Testis, Cerebral cortex, Skin, Fallopian tube, Parathyroid gland, Small intestine, large intestine, Kidney, Skeletal muscle, Duodenun, Spleen, Epididymis, Bone marrow, Lymph node, Adrenal gland, Esophagus, Thyroid gland, Heart muscle, Tonsil, Lung, Prostate, Rectum, Anus, Adipose tissue, Colon, Stomach, Cervix, Gallbladder, Seminal vesicle, Breast, Ovary, Endometrium, Smooth muscle, Salivary gland, Pancreas, Urinary bladder, blood, brain, gum, head, liver, nasopharynx, neck, tongue, uterus.

CANCER IMAGING

An F_1F_0 ATP hydrolysis inhibitor compound(s) of this invention, for example a compound(s) of Formula (I), (II), (III), (IV) or (V), has greater binding affinity for ATP synthase operating in reverse than forwards. Thence such a compound(s) disproportionally accumulates in cancer cells because, as disclosed herein, cancers disproportionally utilise ATP synthase in reverse, as compared to normal cells. Thus, when the compound(s) is labelled, for example by ^{11}C or some other radionuclide incorporation, it can be used for cancer imaging, for example by positron emission tomography (PET). Example embodiments are one or more of

^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{124}I incorporated into a compound of this invention at a greater than natural abundance, most preferably incorporated at their corresponding position(s) in the compound(s) e.g. ^{11}C in place of ^{12}C, ^{13}N in place of ^{14}N, ^{124}I at halogen designated position(s) etc. All radionuclide substitutions of corresponding atoms in Formula (I-V) are contemplated and componentry to the present invention, as is their use for anti-cancer imaging and/or therapy. Alternative embodiments include iodine incorporated at a position(s) designated halogen in one or more compounds of Formula (I-V), and this compound(s) is then used for iodinated x-ray contrast imaging of cancer. Alternatively ^{123}I is incorporated at halogen position(s) of one or more compounds of Formula (I-V), and this compound(s) is used to image cancer using single photon emission computed tomography (SPECT). If a cancer shows up (above background tissue) in one or more of these imaging modalities, it is a good signal that this cancer will be responsive to a compound of this invention for anti-cancer therapy.

Given this asymmetric accumulation of compounds of Formula (I-V) into cancer cells, radionuclides incorporated into one or more of these compound(s) can disproportionally damage cancer, and thence be used for radiotherapy. To illustrate, tritium at greater than natural abundance at one or more places on a compound(s) of this invention, wherein this compound(s) is used for anti-cancer therapy. Alternatively, or in addition, ^{125}I and/or ^{131}I incorporated, optionally at a position(s) designated halogen in Formula (I-V). Optionally, radionuclide imaging is performed prior to radionuclide therapy (radiotherapy) with compounds of this invention.

A boronated compound(s) of this invention, for example a compound(s) of Formula (I), (II), (III), (IV) or (V), substituted at one or more positions with ^{10}B, for use in neutron capture therapy, optionally for an anti-cancer use, is componentry to the present invention, as is a method wherein ^{157}Gd is used in place of ^{10}B.

AGING

An invention embodiment is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat an accelerated aging disease or progeroid syndrome

including, but not limited to, Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy, combined xeroderma pigmentosum-Cockayne syndrome, restrictive dermopathy, Wiedemann–Rautenstrauch syndrome, Hutchinson–Gilford progeria syndrome (progeria) and/or to treat/ameliorate/prevent/combat an aging associated disease or disease/disorder of aging (incidence increases with increased age/senescence) and/or a disease/disorder associated with reactive oxygen species (ROS, e.g. elevated [ROS]) including, but not limited to, degenerative diseases, neurodegenerative diseases, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxias, Friedreich's ataxia, dementia, hereditary spastic paraplegia, Batten disease, polyglutamine diseases, osteoporosis, atherosclerosis, cardiovascular disease, myocardial infarction, cerebrovascular disease, stroke, heart failure, chronic obstructive pulmonary disease (COPD), hypertension, arthritis, cataracts, type 2 diabetes, andropause, sarcopenia, age-related macular degeneration (AMD), hearing loss, movement disability, cancer etc. Not only does an F_1F_0 ATP hydrolysis inhibitor compound of this invention treat/ameliorate/combat cancer in a subject, it also prevents cancer in a subject, which is distinct from many other cancer treatments (e.g. radiotherapy) which are a drive to further cancer, and so compounds of this invention are especially preferred for cancer treatment in children, who have enough lifespan left for secondary cancers, as a result of radiotherapy for example [76], to be a very severe concern.

ANTI-AGING SKIN CREAM

F_1F_0 ATP hydrolysis inhibitor compounds of this invention slow aging but can reduce body temperature. An invention embodiment is to target an F_1F_0 ATP hydrolysis inhibitor compound(s) to a part/area of the body where slower aging is desired, optionally for aesthetic/cosmetic or medical/therapeutic desire or need. This body part or area will have slower aging and lesser heat production, but heat transfer from surrounding body areas will maintain the temperature of this body part/area at an acceptable value. So, the temperature issue is mitigated and slower aging endures in that body part/area. An invention embodiment is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat skin aging, optionally administered to the skin, optionally by skin and/or subcutaneous injection,

optionally as a skin cream, optionally to the face. In another embodiment, administered to the scalp and/or hair, optionally in a hair treatment, optionally in a shampoo, to treat/ameliorate/prevent/combat hair follicle and hair aging/loss/greying. All means of applying a compound(s) of this invention to the skin, and/or scalp and/or hair are contemplated by, and componentry to, this invention.

BRAIN AGING

Neurodegenerative diseases have an ageing component to their etiology [77] as their onset is a function of age (oxidative stress [77]). Indeed, all these diseases (prototypical examples include Parkinson's disease, dementia, Alzheimer's disease, amyotrophic lateral sclerosis {ALS}, Huntington's disease, Friedreich's ataxia, hereditary spastic paraplegia) can be thought of as the brain ageing faster and dying before the rest of the body (adult brain mass decreases with age [78]). In our rapidly greying societies these diseases are a demographic time bomb. Indeed, beyond immeasurable personal suffering, they stand to decimate whole economies (healthcare spending becomes unsustainable percentage of GDP, already ~30% in the USA). For example, nearly half of Americans, over 85, have dementia, which in time is an age that an increasing proportion of the population will surpass, it has no cure and can be completely debilitating, which strains families and communities [78]. Thus, any treatment that can slow brain ageing, to make brain function last as long as the rest of the body, will greatly assist in matching "healthspan" to lifespan, which is arguably the Holy Grail in modern medicine.

An invention embodiment is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat brain aging and neurodegenerative disease(s). Optionally wherein the compound(s) is disproportionally delivered to the brain or central nervous system (CNS), or to specific brain/CNS area(s) or cell type(s), by administration route, strategy or targeting. Illustratively, not restrictively, brain targeting had been shown with exogenous dopamine [79-80]. Preferred brain structures/cells/neurons to target are those whose failure drives a neurodegenerative disease e.g. dopamine neurons in the pars compacta (in the substantia nigra). There are few of them, only 7,200 in rat [81], and in humans their number decline by aging at 5-10% per decade [82], which is a predisposing drive to Parkinson's

disease (PD). An invention embodiment is a method in which a subject takes or is administered an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V) or another compound that selectively inhibits F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, to treat/ameliorate/prevent/combat Parkinson's disease, optionally wherein the compound(s) is disproportionally administered to dopamine neurons in the substantia nigra. If a compound of this invention decreases their heat generation, heat transfer from neighbouring brain and/or body regions will substitute this heat.

SURGERY

An embodiment of this invention is a method in which a subject takes or is administered and/or has a plasma blood level of an effective amount of a compound(s) of this invention, for example a compound of Formula (I), (II), (III), (IV), (V) or (VI) or another compound that selectively reduces F_1F_0 ATP hydrolysis, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, and the subject is administered an analgesic(s) and/or an anti-nausea medication(s) and/or an anxiolytic and/or antidepressant and/or a local and/or a general anaesthetic (examples well known to those of the art), and/or optionally another drug commonly used in surgery, such as an anti-anxiety/sedative drug used before general anaesthesia or after surgery (examples are well known to those of the art), optionally to treat/ameliorate/prevent/combat cancer, optionally wherein the subject undergoes surgery to remove a tumour(s).

EMERGENCY CONTRACEPTIVES

Adult bodies don't contain embryonic stem (ES) cells. ES cells are in the inner cell mass of the blastocyst, which forms ~5 days post-fertilization, and exist temporarily because they soon differentiate into other cell types, without ES cell characteristics. So, a compound(s) that specifically kills ES cells will have utility as an emergency contraceptive, taken after unprotected sex for example, with a later window of effectiveness than present emergency contraceptives. Furthermore, it will have utility as a contraceptive, which can be administered instead of, or in combination with, another contraceptive(s) such as the combined oral contraceptive pill, wherein this term and the range of compositions it can refer to are well known to those of the art.

Cancer cell metabolism is similar to that of ES cells. Both can proliferate rapidly, forever (without limit, immortal). They share gene expression fingerprints [54]. ES cells also have a hyperpolarised Ψ_{IM} [55], employ aerobic glycolysis some or all of the time [56] and tend to respond to ROS damage by apoptosis rather than repair [57].

F_1F_0 ATP hydrolysis inhibitors have anti-cancer activity, as disclosed by this invention, and, also by this invention, anti-ES cell activity. An embodiment of this invention is a compound(s) that inhibits F_1F_0 ATP hydrolysis, for example a compound(s) of Formula I-V, administered or self-administered to a subject, for use in preventing/ending their pregnancy/conception, optionally co-administered (optionally in a pharmaceutical composition) with another compound(s) or combination of compounds with this use, many of which are known to those of the art .e.g. progestin, antiprogestin, estrogen etc. This use could be after unprotected sex for example. In another embodiment, this use is restricted to the time during which ES cells exist in embryogenesis, which is early.

An embodiment of this invention is an F_1F_0 ATP hydrolysis inhibitor(s) in use as an anti-cancer medicine, or some other therapeutic use in a subject, wherein the compound(s) is distributed, sold and/or administered with a verbal and/or written warning, optionally in a paper insert in a packet containing the compound(s), that it should not be administered to a woman in the early days and/or weeks of pregnancy and/or in a woman trying to get pregnant.

COMPOUNDS OF THIS INVENTION ARE ANTI-INFLAMMATORIES

An embodiment of this invention is a method of using a therapeutically effective amount of at least one compound of this disclosure, which inhibits F_1F_0 ATP hydrolysis, as an immunosuppressant and/or anti-inflammatory therapeutic. This therapeutic opportunity exists because if Ψ_{IM} collapses in a cell, apoptosis ensues [59], and *activated* macrophages, unlike *resting* macrophages, singly use and thence completely rely upon ATP synthase in its reverse mode, hydrolysing ATP, to maintain Ψ_{IM} [83]. This is because activated macrophages produce nitric oxide (NO), which switches down/off their OXPHOS (NO increases the Km of Complex IV for O_2). Compounds of the present invention inhibit F_1F_0 ATP hydrolysis and *selectively* collapse Ψ_{IM} in *activated* macrophages, *selectively* killing them (optionally administered in co-therapy with an uncoupler(s), to erode Ψ_{IM} as the F_1F_0 ATP hydrolysis

inhibitor(s) blocks the only means *activated* macrophages can counter this erosion; thence Ψ_{IM} collapses at lower dose of F_1F_0 ATP hydrolysis inhibitor). Thus a therapeutically effective amount of at least one compound of this invention, an F_1F_0 ATP hydrolysis inhibitor, for example a compound of Formula (I), (II), (III), (IV) or (V) or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof (optionally in co-therapy with an uncoupler(s), optionally administered in the same pharmaceutical composition and/or administered/packaged/sold together, optionally the same compound is both an F_1F_0 ATP hydrolysis *and* uncoupler e.g. BMS-199264), attenuate the activated macrophage component to inflammation, and its pathologies, and treats/ameliorates/prevents/combats any disease or disorder associated with the undesirable activation or activity of macrophages, and/or any other NO producing cells of the innate immune system (e.g. monocyte-derived inflammatory dendritic cells), and/or immune or inflammation diseases/disorders/pathologies including, but not limited to, acute inflammation, chronic inflammation, systemic inflammation, inflammation because of infection or foreign bodies or injury or chemical or toxin or drug or stress or frostbite or burn or ionising radiation, inflammatory diseases/disorders/syndromes, Macrophage Activation Syndrome (MAS), autoinflammatory diseases/disorders/syndromes, age-related chronic inflammatory diseases ("inflammaging"), autoimmune diseases/disorders/syndromes, diseases/disorders of the innate immune system, sore throat, sore throat associated with cold or flu or fever, high-intensity exercise associated inflammation, ulcerative colitis, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), rheumatoid arthritis, osteoarthritis, psoriatic arthritis, atopic dermatitis, allergic airway inflammation, asthma, inflammation associated depression, exercise-induced acute inflammation, atherosclerosis, allergy, hay fever, anaphylaxis, inflammatory myopathies, drug-induced inflammation, systemic inflammatory response syndrome, sepsis-related multiple organ dysfunction/multiple organ failure, microbial infection, acute brain/lung/hepatic/renal injuries, acne vulgaris, celiac disease, celiac sprue, chronic prostatitis, colitis, diverticulitis, glomerulonephritis, hidradenitis suppurativa, hypersensitivities, interstitial cystitis, Mast Cell Activation Syndrome, mastocytosis, otitis, pelvic inflammatory disease (PID), reperfusion injury, rheumatic fever, rhinitis, sarcoidosis, transplant rejection, parasitosis, eosinophilia, type III hypersensitivity, ischaemia, chronic peptic ulcer, tuberculosis, Crohn's disease, hepatitis, chronic active hepatitis, immune hepatitis, ankylosing spondylitis, diverticulitis, fibromyalgia, systemic lupus erythematous (SLE), Alzheimer's disease, Parkinson's disease, neurodegenerative disease, cardiovascular disease, chronic obstructive pulmonary disease,

bronchitis, acute bronchitis, appendicitis, acute appendicitis, bursitis, colitis, cystitis, dermatitis, encephalitis, gingivitis, meningitis, infective meningitis, myelitis, nephritis, neuritis, periodontitis, chronic periodontitis, phlebitis, prostatitis, RSD/CRPS, rhinitis, sinusitis, chronic sinusitis, tendonitis, testiculitis, tonsillitis, urethritis, vasculitis, respiratory bronchiolitis–associated interstitial lung disease and desquamative interstitial pneumonia, interstitial lung disease, Löfgren syndrome, Heerfordt syndrome, monocytosis, liver fibrosis, steatohepatitis, nonalcoholic steatohepatitis, silicosis, histiocytoses, Langerhans' cell histiocytosis, haemophagocytic lymphohistiocytosis, pulmonary langerhans cell histiocytosis, obesity, type II diabetes, gout, pseudogout, organ transplant rejection, epidermal hyperplasia, chronic fatigue syndrome, graft versus host disease (GVHD), lymphadenopathy.

In clinical utility, the anti-inflammatory activity of compounds of this invention juxtaposes well with their aforementioned ability to reduce body temperature.

The anti-inflammatory action by compounds of this invention has an anti-cancer action. Because it reduces the number of Tumour Associated Macrophages (TAMs) [84]. These can constitute a large component of tumour mass and their presence is often associated with poor patient prognosis because they can drive cancer pathology. Indeed, inflammation is now considered one of the hallmarks of cancer [85]. The anti-inflammatory action, and thence anti-cancer action, of these compounds synergises with their direct anti-cancer activities disclosed herein.

Macrophages can be subverted by pathogens, which hide inside them in safety from the immune system. Non-limiting examples of such pathogens are HIV (causes HIV/AIDS; HIV virus can lay latent in macrophages during antiretroviral therapy, wherein HIV virus becomes undetectable in blood, and then repopulate the virus in blood when antiretroviral therapy is interrupted or discontinued; HIV can replicate in macrophages [86-87]), *Mycobacterium tuberculosis* (causes tuberculosis), *Leishmania* parasite (causes Leishmaniasis), Chikungunya virus (causes Chikungunya), *Legionella pneumophila* (causes Legionnaires' disease), adenovirus (causes pink eye), *T. whipplei* (causes Whipple's Disease) and *Brucella spp.* (causes brucellosis). So, by exerting anti-macrophage activity, compounds of this disclosure can treat/ameliorate/prevent/combat such disorders and diseases. Because the compounds of this invention are selective for activated macrophages, an option is to activate macrophages before the compound administration, by administering to the patient an effective amount of a

compound, protein, antibody or some other entity, e.g. pathogen, attenuated pathogen or pathogen component that activates macrophages. Some examples (non-limiting) of factors that can activate macrophages are cytokines such as interferon-gamma (IFN-gamma) and/or tumour necrosis factor (TNF), and/or IL-4, and/or IL-13, and/or IL-10, and/or IL-2, and/or IL-12, and/or IL-6, and/or IL-18 and/or chemokines (CCL3, CCL4, CCL5) and/or a bacterial endotoxin such as lipopolysaccharide (LPS), or a commercially available agent for macrophage activation in biological research (e.g. CAS 61512-20-7) or an antibody targeting a receptor on the macrophage cell surface or on the surface of a different cell type, which then activates a macrophage by mechanism. Macrophage activating antibodies are well known to those of the art.

An embodiment of this invention is the use of an effective amount of at least one compound of this invention, which inhibits F_1F_0 ATP hydrolysis, to treat/ameliorate/prevent/combat HIV infection, optionally with an effective amount of a compound, protein, antibody, pathogen or pathogen component that activates macrophages (isn't absolutely necessary because HIV activates macrophages [88-89], which drives the chronic inflammation pathology component to HIV infection) optionally in co-therapy with, or after, anti-retroviral therapy (ART) or combination anti-retroviral therapy (cART). Even after prolonged cART, which drives plasma HIV down to undetectable levels, HIV-1 DNA and RNA is detectable in macrophages: they are an HIV reservoir that remains extant, even during cART, and that the virus can spread from during any interruption or termination of cART [87]: thence the vital importance of the methods and compounds herein. Furthermore, these compounds treat/ameliorate/prevent/combat HIV-associated chronic inflammation.

Macrophages mediate HIV virus neuroinvasion (and neuroinvasion by other viruses also e.g. SARS coronavirus) and compounds of this invention oppose this and treat/ameliorate/prevent/combat HIV-associated neurocognitive disorders (HAND) (and neurocognitive and neurodegenerative diseases/disorders caused by other viruses also e.g. SARS coronavirus). The anti-HIV and anti-cancer activity of the compounds of this invention synergise to treat/ameliorate/prevent/combat HIV associated cancers: AIDS-defining cancers (Kaposi sarcoma, aggressive B-cell non-Hodgkin lymphoma, cervical cancer.) and non-AIDS defining cancers. This disclosure encompasses a compound(s) of this invention in co-therapy with any Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) approved drug(s) or treatment for HIV or AIDS. Examples include, but aren't limited to,

abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, disoproxil fumarate (tenofovir DF, TDF), zidovudine (azidothymidine, AZT, ZDV), atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir, enfuvirtide, maraviroc, dolutegravir, elvitegravir, raltegravir, cobicistat.

Non-limiting examples of autoinflammatory diseases/disorders/syndromes that the compounds of this invention treat/ameliorate/prevent/combat include, but aren't limited to, recurrent fever syndromes, which can be hereditary or acquired, characterized by recurrent fever associated with rash, serositis, lymphadenopathy and musculoskeletal involvement. Examples include familial mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), Hyperimmunoglobulinemia D with recurrent fever syndrome (HIDS), cryopyrin associated periodic syndrome (CAPS), Blau syndrome, Majeed syndrome, deficiency of interleukin-1 receptor antagonist (DIRA), mevalonate kinase deficiency, pyogenic-arthritis-pyoderma gangrenosum and acne syndrome (PAPA), periodic fever aphthous stomatitis pharyngitis adenitis (PFAPA) syndrome, Behcet's disease, Still's disease, Crohn's disease, Schnitzler's syndrome, Sweet's syndrome, NLRP12-associated autoinflammatory disorders, deficiency of interleukin-1 receptor antagonist (DIRA), pyoderma gangrenosum, cystic acne, aseptic arthritis, periodic Fever Associated with mevalonate kinase deficiency (hyperimmunoglobulin D Syndrome), Pyogenic Arthritis Pyoderma Gangrenosum Acne (PAPA) syndrome, Periodic Fever Aphthous Stomatitis, Pharyngitis and Adenopathy (PFAPA) syndrome, Adult-Onset Still's Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Chronic Recurrent Multifocal Osteomyelitis (CRMO), Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) syndrome, Cryopyrin associated Periodic Syndrome (CAPS), Familial cold auto inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), Familial cold urticarial, Neonatal onset multisystemic inflammatory disorder (NOMID), hereditary Periodic Fever Syndromes, Periodic Fever Syndromes, systemic autoinflammatory diseases.

Non-limiting examples of autoimmune diseases/disorders/syndromes that the compounds of this invention treat/ameliorate/prevent/combat include, but aren't limited to, Addison's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune pancreatitis,

autoimmune retinopathy, autoimmune urticaria, axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss, Cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, coxsackie myocarditis, CREST syndrome, Berger's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, immune hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (Type 1 diabetes), juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR) PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage-Turner syndrome, Pemphigus, peripheral neuropathy, perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's

arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)), idiopathic thrombocytopenia purpura, splenomegaly.

SLOW RELEASE FORMULATIONS

An invention embodiment is to administer to a subject a therapeutic amount of at least one compound of this invention, for example a compound of Formula (I), (II), (III), (IV) or (V), in a formulation/dosage selected from modified release, extended release, long acting release, sustained release, prolonged release, controlled release, slow release or similar, as clear to someone of the art, for use in a method of treatment of the human or animal body by therapy. Such a formulation exposes the subject body to the compound(s) over a longer period of time than if the compound was applied alone. This is useful because it delivers good area under the curve for the compound, which for example exerts anti-cancer activity in the subject, without an abrupt large body temperature drop. Any body temperature drop is less in amplitude, more in duration, which is safer. Methods to make such formulations for a compound are well known to those of the art. To illustrate with some non-limiting examples: compound is administered in an excipient/tablet/pill which takes time to dissolve/degrade/disintegrate because it is, for example, poorly soluble. Furthermore, enteric coating, acrylics (e.g. chitin), liposomes, drug-polymer conjugate(s), microencapsulation (coating an active pharmaceutical ingredient around an inert core and layering it with insoluble substances to form a microsphere), dissolution systems (rate release is dependent on dissolution of an excipient; 2 categories: reservoir, matrix), diffusion systems (rate release is dependent on rate that drug dissolves through a barrier, usually a type of polymer; 2 categories: reservoir, matrix), osmotic systems, ion exchange resins, matrix systems (sub-categories: hydrophobic matrices, lipid matrices, hydrophilic matrices, biodegradable matrices, mineral matrices), stimuli induced release (e.g. temperature, ultrasonic, electronic etc.) and other encapsulation technologies known to those of the art.

An invention embodiment is using a dosage regime of F_1F_0 ATP hydrolysis inhibitor that doesn't cause a significant temperature drop in a human. Optionally spreading the daily therapeutic dose over multiple pills per day so that any body temperature drop is lowered in amplitude, lengthened in duration, which is safer.

ALBUMIN AS SLOW RELEASE ASSIST

Compound 31 of this invention is a 1,4-benzodiazepine, which is a compound class known to bind albumin in blood extensively. For example, 99% of diazepam is protein bound in the blood, wherein the overwhelming majority of this protein is albumin. Albumin can bind many things non-specifically but it has high affinity binding sites with higher affinity binding to certain substances [90], for example, 1,4-benzodiazepines. Indeed, albumin has two specific high affinity binding sites, one of which is called the "benzodiazepine site", also called Site II, the diazepam site or the indole-BDZ site, which can bind a range of benzodiazepines, and so possibly Compound 31 also. Compound 31 binding albumin in blood will buffer, slow and prolong Compound 31 exposure to the tissues, which will buffer, reduce the amplitude, slow and prolong Compound 31 effect on body temperature. In the anti-cancer data of this disclosure, Compound 31 (**Figure 6**) outperformed the FDA approved, widely used, chemotherapeutic carboplatin (**Figure 1**). However, it underperformed by comparison to its EC_{50} F_1F_0 ATP hydrolysis (**Figure 9**) and its sequestration by binding albumin in the 5% fetal bovine serum (FBS) added to RPMI 1640 medium used in NCI-60 testing [35] might be contributory to this underperformance (in addition to Compound 31 interaction with CYP2C9, as cited in **Figure 9** and legend). Reducing FBS amount to 2% and assaying if Compound 31 exerts greater anti-cancer activity vs. no drug control (also with FBS reduced to 2%) would reveal this. N.B. carboplatin does not bind albumin with any great affinity, indeed, its protein (i.e. mainly albumin) binding in blood is very low.

TEMPERATURE CONTROLLED RELEASE

An invention embodiment is a temperature-sensitive pharmaceutical composition/vehicle that only releases a compound of this invention, for example a compound of Formula (I), (II), (III), (IV), (V) or other F_1F_0 ATP hydrolysis inhibitor(s), when the body is at normal body temperature or higher. The latter is reached if the subject has a fever for example. Many cancers cause fever. Such a temperature-sensitive delivery composition/vehicle, releasing drug(s) at normal body temperature (37°C) for example, can effect a safety feedback loop because as F_1F_0 ATP hydrolysis inhibitor is released, body temperature falls, thence less drug is released, body temperature can thence recover, further compound is released, and this loop iterates, implementing extended release and minimising the perturbation to body temperature from optimal. For non-limiting example, a F_1F_0 ATP hydrolysis inhibitor(s) is loaded into a

structure incorporating biocompatible thermo-sensitive polymer which shrinks at a temperature exceeding its phase/volume transition temperature, releasing the compound. This volumetric change is reversible. Should the temperature subsequently fall below the phase/volume transition temperature the structure expands and compound release doesn't occur [91]. In some embodiments the phase/volume transition temperature is tuned to be at normal body temperature, in other embodiments, at a pathologically elevated body temperature(s). Biocompatible thermosensitive polymers can be used to prepare temperature-responsive hydrogels/nanogels and thence nanoparticles, optionally with polysaccharides to modulate the drug encapsulation and release efficiency, which have a phase transition temperature, above which they release the "cargo" compound(s). Transition temperature can be readily tuned by the copolymerization conditions and by varying the content of repeating units in the copolymer. Non-limiting options for making temperature sensitive vehicles for compounds of this invention include thermosensitive hydrogels/nanogels, temperature sensitive liposomes [92-94] (these have been used in clinical trials e.g. ThermoDox), thermosensitive micelles, polymeric micelles, core shell structures, core–shell microgel particles, thermoresponsive composite films, smart three dimensionally ordered porous materials, thermosensitive microcontainers, nanoscale drug delivery vehicles.

Also contemplated and componentry to this invention is a compound(s) of this invention administered/released by a pharmaceutical composition/vehicle triggered by temperature in parallel with one or more other stimuli e.g. pH, and/or a pharmaceutical composition/vehicle that disproportionally delivers a compound(s) of this invention to cancer as compared to normal tissue(s) in a subject (numerous strategies available to those of the art e.g. refer [95]). For example, by the pharmaceutical composition/vehicle release being triggered by one or more cancer associated stimuli e.g. acidic pH, or one or more externally applied stimuli to the cancer/tumour e.g. heat.

DESCRIPTION OF THE DRAWINGS

For purposes of clarity, not every component is labelled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention.

Figures 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12: Experimental evidence: molecules that specifically inhibit the reverse mode of ATP synthase: specifically exert anti-cancer activity: representative, non-limiting examples.

Figures 1, 2, 3, 4, 5, 6, 7, 8 show results from the NCI-60 one-dose *in vitro* assay [34-35] at the Developmental Therapeutics Program (DTP), at the National Cancer Institute (NCI, Bethesda, MD, USA). Its protocol is well known to those of the art, and it tests the effect, if any, of a test compound on the growth/survivability of a cancer cell line as compared to the no compound control. When this protocol was first developed, a compound was tested against 60 cancer cell lines, hence the name NCI-60, but more recently this has been reduced to 59 cell lines, and there is some variation over time in the cancer cell lines making up this 59 (and sometimes it drifts from being 59 also). However, a constant is that there is always representative cell lines from leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate and kidney. In a one-dose NCI compound test report, NCI report a number for each cell line, which they call "Growth Percent", which is its growth relative to the no-compound control, and relative to the time zero number of cells. This reported parameter allows detection of both growth inhibition (values between 0 and 100) and lethality (values less than 0). For example, an NCI "Growth Percent" value of 100 means no growth inhibition. Value of 40 means 60% growth inhibition. Value of 0 means no net growth over the course of the experiment. Value of -40 means 60% lethality. Value of -100 means all cells are dead. I don't present NCI one-dose data in this original format. Instead, if the NCI "Growth Percent" value for a cell is positive, it is manipulated: [100 minus this original NCI-60 "Growth Percent" data point], to yield the percentage "Growth Inhibition". If the original NCI "Growth Percent" value for a cell is negative, it is made positive to be the percentage of original cancer cells (at time zero) killed: "Percentage Killed" {and in these cases, of course, all growth has been inhibited, so percentage "Growth Inhibition" is then specified to be 100% for this cancer cell line}. In my one-dose figures, "Growth Inhibition" (0-100%) is presented on the x-axis and, if applicable, "Percentage Killed" (0-100%) further along on the x-axis. The latter is applicable when there is not just cancer growth inhibition but a reduction in the number of cancer cells from the start time i.e. when the compound is not merely slowing cancer growth, but is actively reducing the number of cancer cells from the starting number. In cases where there is only growth inhibition, only "Growth inhibition" is presented on the x-axis. In all cases, the greater the percentage number on the x-axis, for a given cancer cell

line named on the y-axis, the greater the anti-cancer activity of this compound against this cancer cell line.

NCI-60 tests are performed at a controlled temperature of 37 °C [35].

To perform the anti-cancer testing reported: BMS-199264 hydrochloride was purchased from Sigma-Aldrich. BTB06584 was purchased from AdooQ Bioscience, Irvine, CA, USA. Compounds 19a (separated into 6a and 6b stereoisomers) and 31 were synthesized by reaction schemes disclosed herein. Almitrine dimesylate was purchased from Ak Scientific, Palo Alto, CA, USA. Tested compounds are available from NCI by NSC number which are: BTB06584 (NSC: 794220), BMS-199264 HCl (NSC: 795767), almitrine dimesylate (NSC: 800450), 6b (NSC: 801828), 6a (NSC: 801827), 31 (NSC: 802605).

Figure 1: Anti-cancer activity of carboplatin in National Cancer Institute (NCI) one-dose (10 μM) assay. Data retrieved from NCI Developmental Therapeutics Program (DTP) screening database [32], database entry NSC: 241240. To retrieve this data, input NSC at https://dtp.cancer.gov/dtpstandard/dwindex/index.jsp. DTP database contains anti-cancer performance (or more typically lack thereof) for >800,000 compounds in the exact same experimental protocol. New entries become publically searchable after 3 years delay (to give time for compound submitters to secure IP protection, should they wish, before public disclosure by this database). This figure presents the anti-cancer performance of an FDA licensed cancer drug, carboplatin, one of the most used cancer drugs today, which is on the World Health Organisation (WHO) list of most Essential medicines, in exactly the same experimental protocol used for the novel cancer drugs of this disclosure, presented in later figures. This figure inclusion enables a direct like-for-like comparison between the new cancer drugs, disclosed by this disclosure, with a cancer drug in present, widespread clinical use.

Figure 2: No anti-cancer activity of BTB06584 at 10 μM (NCI one-dose assay).

Figure 3: Anti-cancer activity of BTB06584 at 100 μM (NCI one-dose assay).

Figure 4: Anti-cancer activity of BMS-199264 hydrochloride at 10 μM (NCI one-dose assay).

Figure 5: Anti-cancer activity of BMS-199264 hydrochloride at 100 μM (NCI one-dose assay).

Figure 6: Anti-cancer activity of compound 31 at 10 μM (NCI one-dose assay).

Figure 7: Anti-cancer activity of almitrine dimesylate at 10 μM (NCI one-dose assay).

Figure 8: (**8A**) A racemic mixture, or racemate, has equal amounts of the *S* and *R* enantiomers of a chiral molecule. Structure 19a is a racemate and (*R*/*S*) symbolises the chiral carbon as *R* or *S*. Structure 6a is its *R* stereoisomer, structure 6b is its *S* stereoisomer. The EC_{50} F_1F_0 ATP hydrolase of the racemate (19a, 0.033 μM) is approximately half as potent as that of the isolated S stereoisomer (6b, 0.018 μM) because it contains half as much of the *S* stereoisomer per unit mass, because it also contains R stereoisomer (EC_{50} F_1F_0 ATP hydrolase > 100 μM) in a 50:50 ratio. Superfluid chromatography (SFC) was used to separate 19a into its component *R* and *S* stereoisomers, which don't and do potently inhibit F_1F_0 ATP hydrolase respectively (EC_{50} values from SMPs in [5-6]), and two samples of opposite >97% enantiomeric excess (ee) was achieved: termed 6a and 6b respectively. These were independently tested in NCI one-dose (10 μM) testing: their results are shown in Figures (**8B**) and (**8C**) respectively. The anti-cancer activity of 6a and 6b was similar (Pearson correlation: $R = 0.8$, significant at $p < 0.00001$). This is because during the 48 hours of NCI one-dose testing, they underwent racemization and their ee eroded. Such that both samples ultimately contained a significant proportion of *S* stereoisomer and both exerted anti-cancer activity by inhibiting F_1F_0 ATP hydrolysis. Racemization is not instantaneous and so one sample, 6b, conferred greater/longer *S* stereoisomer exposure to the cancer cells than the other sample, 6a. Racemization isn't necessarily complete at testing end. These features explain why the 6b origin (>97% ee 6b at start) sample has greater anti-cancer activity than the 6a origin (>97% ee 6a at start) sample: 66% vs. 57% mean cancer growth inhibition, across all 59 cancer cell lines, respectively. During, and more certainly by end, of NCI one-dose testing, 6a and 6b have $97\% > ee \geq 50\%$ i.e. they are a racemate or scalemate. Although the fidelity of the (distinction between) 6a and 6b samples erodes during NCI testing, as they each converge (by epimerization) upon being 19a, I still use the 6a and 6b terms at times in this disclosure to refer to these samples during NCI testing. In addition, given that during NCI testing 6a → 19a, and 6b → 19a, I use the terms 6a, 6b and 19a interchangeably at other times during this disclosure. Racemization reduces, and increases, the anti-cancer activity of 6b and 6a respectively. (**8D**) 6b exerts greater anti-cancer activity than 6a. 6b is the *S* stereoisomer, 6a the *R* stereoisomer. However, also contemplated by, and componentry to, the present invention is if samples labelled 6b and 6a are the *R* and *S* stereoisomers respectively. (**8E**) and (**8F**) are the anti-cancer activities of 6a and 6b respectively in the NCI one-dose (100 μM) assay. In this assay, median cancer growth inhibition for both 6a and 6b >79%. With some and same cancer cell lines, for both 6a or 6b, anti-cancer activity is much less at 100

μM than 10 μM. Pearson correlation coefficient between 6a and 6b anti-cancer activity at 100 μM = 0.9437 ($p < 0.00001$).

Figure 9: Anti-cancer potency (mean % decrease in cancer growth, as compared to no compound control, in NCI-60 one-dose testing) scales with inhibition of (EC_{50}) F_1F_0 ATP hydrolase, across diverse chemical structures. EC_{50} values against ATP synthase, for BMS-199264 (N.B. EC_{50} is for pure BMS-199264, not BMS-199264 HCl), 19a, 6a, 6b and 31 are from sub-mitochondrial (SMP) studies in [5-8], BTB06584 potency information (is not an EC_{50}) is from a whole cell study [13]. Compound 31 EC_{50} for CYP2C9 is from [8].

6b and 6a anti-cancer activities are similar because of their epimerization in biological systems, which erodes their enantiomeric excess (ee) during NCI testing, making them converge upon being the racemate, 19a. Thus, during NCI testing, 6b EC_{50} F_1F_0 ATP hydrolase is not constant but in the range 0.033 μM ≥ EC_{50} F_1F_0 ATP hydrolase ≤ 0.018 μM because EC_{50} F_1F_0 ATP hydrolase → 0.033 μM as 6b → 19a, as racemization proceeds. Similarly, 6a EC_{50} F_1F_0 ATP hydrolase → 0.033 μM as 6a → 19a.

Mean % cancer growth inhibition for BMS-199264 at 100 μM is >100% because for most cancer cell lines tested it doesn't just cause 100% cancer growth inhibition but, in addition, causes cancer regression, wherein the number of cancer cells at experiment end is less than at experiment start. BMS-199264 predominantly exerts anti-cancer activity at 10 μM by inhibiting F_1F_0 ATP hydrolase, and at 100 μM, by reducing F_1F_0 ATP synthesis.

31 has less anti-cancer activity than its EC_{50} F_1F_0 ATP hydrolase value would predict because it is broken down by cytochrome P450 enzyme: CYP2C9, which it inhibits competitively (31 being consumed in the process). Average log2 transcript intensity of CYP2C9, across all NCI-60 cell lines, is 3.539 [31-32]. Average log2 transcript intensity of ATP5A1, the alpha subunit of F_1 ATP synthase, across all NCI-60 lines, is 9.871 [31-32]. There are 3 alpha subunits per ATP synthase [1]. So, on average, approximately, there is a comparable amount of CYP2C9 and ATP synthase in an NCI-60 cancer cell line: 3.539:(9.871/3=3.29) ≈ 1. If we equate EC_{50} as some measure of binding affinity then compound 31 has a greater affinity for binding ATP synthase in its reverse mode (EC_{50} = 0.022 μM) than for binding CYP2C9 (EC_{50} = 2 μM) (these EC_{50} values come from different assays, thence this comparison isn't very robust). However, ATP synthase does not always operate in reverse, it likely has different operating propensities at different stages of the cell cycle, and compound 31 EC_{50}

F_1F_0 ATP synthesis is > 30 μM. Thus, CYP2C9 can meaningfully reduce compound 31 inhibition of F_1F_0 ATP hydrolase, and thence its anti-cancer activity. Especially because CYP2C9, a cytochrome P450 enzyme, does not merely bind and sequester compound 31, but metabolises and inactivates compound 31 at a rate set by its kcat for compound 31. Compound 31 as substrate for an enzyme(s) of the cytochrome P450 enzyme, whilst itself having anti-cancer activity, means it can add to the anti-cancer action, for example potentiate the anti-cancer action, of other anti-cancer therapeutics which are also broken down by this system e.g. idarubicin.

At 10 μM, 6b (and 6a) exerts more anti-cancer activity than BMS-199264, despite having less effect on F_1F_0-ATP synthesis, because it inhibits F_1F_0-ATP hydrolysis more potently.

Figure 10: Anti-cancer activity of BMS-199264 hydrochloride. Results are from the NCI-60 five-dose *in vitro* assay [34-35] at the Developmental Therapeutics Program (DTP), at the National Cancer Institute (NCI, Bethesda, MD, USA). In this assay, which is well known to those of the art, a compound is tested, *in vitro*, against 59 different cancer cell lines, sourced from 9 different tissue types, across 5 different concentrations. 9 graphs in 9 sub-figures are presented (labelled **10A** to **10I**), one for each of the 9 tissue types. These graphs are as outputted by the NCI but changed from colour to black and white. On the y-axis of each is the aforementioned "Growth Percent" parameter used by NCI, which is growth relative to the no-compound control, and relative to the time zero number of cells. This parameter allows detection of both growth inhibition (values between 0 and 100) and lethality (values less than 0). GI50 is the compound concentration that causes 50% growth inhibition of a cell line relative to the no-compound control. Each cancer cell line has a GI50 value and the "mean GI50" of all 59 cell lines can be calculated: this mean GI50 for BMS-199264 hydrochloride is 3.9 μM.

Figure 11: Anti-cancer activity of 6a and 6b in NCI-60 five-dose *in vitro* assay [34-35]. Mean GI50 for 6b is 0.446 μM. Mean GI50 for 6a is 0.666 μM.

Figure 12. Greater anti-cancer activity occurs with greater anti-cancer drug concentration. This is what someone of the art would expect. However, compounds 6a and 6b can, upon *some* (and overwhelmingly *same*) cancer cell lines, exert less anti-cancer activity at 100 μM than 10 μM in the NCI one-dose assay (Figures **12A** and **12B**) and can, upon *some* (and overwhelmingly *same*) cancer cell lines, exert less anti-cancer activity at 10 μM than 1 μM in the NCI five-dose assay (Figure **12C**). In 12A and 12B, most inhibited cancer cell lines at 10 μM are least inhibited at 100 μM. Next most inhibited cancer cell lines at 10 μM undergo cell

death at 100 μM. Least inhibited cancer cell lines at 10 μM are more inhibited at 100 μM. Thus, to interpret, as one increases compound concentration, there are 3 zones passed, with their boundaries different for different cancer cell lines: (1) increased compound concentration increases anti-cancer activity, (2) compound causes cancer cell death, (3) increased compound concentration decreases anti-cancer activity. The anti-cancer activity of compounds 6a and 6b is highly correlated, which verifies the voracity of this data. 6b, as compared to 6a, is the stronger acting sample in NCI one-dose assay and, because it has the lower mean GI50, in the NCI five-dose assay also, wherein 6b has more cancer cell lines with *less* activity at 10 μM than 1 μM. Interpretation: 6a, and 6b, [compound] increase/decrease driven increase/decrease in anti-cancer activity is by action on same target. Data in Figures 12A and 12B is from data in Figure 8. Data in Figure 12C is from data in Figure 11.

Figure 13. This diagram is an interpretation of experimental data in Figures 8, 11 and 12. It does not itself present real data. (**13A**) In Figure 11, increasing concentration of 6a or 6b (both symbolised as 19a in the present figure) slows cancer proliferation, until a concentration of maximum slowing, after which further increase in compound concentration decreases cancer growth inhibition. The present diagram incorporates Figure 11 data with an additional observation from Figure 8, wherein high 6a and 6b doses decrease the cell number of *some* cancer cell lines, which I suggest is due to apoptosis. This observation is incorporated by a narrow dosage range that causes cancer cell death, the boundaries of which varies by cancer cell line, and it's narrowness explains why cancer cell killing is not observed for most cancer cell lines in the broadly separated doses of NCI five-dose testing. The diagram shows that increasing compound concentration increasingly blocks F_1F_0 ATP hydrolysis in cancer cells, which increasingly increases their OXPHOS rate, and thence reactive oxygen species [ROS]. Elevated [ROS] slows proliferation by ROS checkpoint blockade and atrophies DNA information fidelity, which reduces the number of possible cell divisions from limitless to a value increasingly convergent upon the Hayflick limit [96] of normal cells. At the inverted peak, the OXPHOS rate is so great, and [ROS] so elevated, apoptosis is triggered (by comparison, normal cells use this OXPHOS rate routinely). However, as compound concentration is increased beyond this point, greater F_1F_0 ATP hydrolysis inhibition makes OXPHOS more efficient (less ATP needs to be made because less ATP is hydrolysed), which reduces the OXPHOS rate and [ROS], and anti-cancer activity is less. (**13B**) Upper panel shows same diagram as (A), relating to a cancer cell, above an equivalent diagram for a normal cell, with equivalent x-axis. It shows that there are concentrations of an F_1F_0 ATP hydrolysis inhibitor(s) that harm cancer and help normal cells.

Cancers have, and need, lower intracellular [ROS] than normal cells. There are concentrations of F_1F_0 ATP hydrolysis inhibitor(s) that simultaneously raise [ROS] in cancer cells and decrease [ROS] in normal cells. In normal cells, greater F_1F_0 ATP hydrolysis inhibition makes OXPHOS more efficient (less ATP needs to be made because less ATP is hydrolysed), which reduces the OXPHOS rate and [ROS] and increases normal cell lifespan. F_1F_0 ATP hydrolysis inhibitor(s) conferred OXPHOS efficiency gain comes from, and so its maximum is dictated by, proportion of OXPHOS produced ATP hydrolysed by F_1F_0 ATP hydrolysis, which is high, and so lifespan (and healthspan) extension significant, especially if it reduces [ROS] sufficiently to reduce DNA mutation rate below DNA repair rate. Especially, if this [ROS] is sufficient to keep cells differentiated, maintaining tissue and organ function.

Figure 14. This diagram is an interpretation of experimental data in Figure 10. It does not itself present real data. BMS-199264 is distinct from compound 6b because, in addition to inhibiting F_1F_0 ATP hydrolysis, it can also significantly reduce F_1F_0 ATP synthesis at NCI tested concentrations. Background: BMS-199264 EC_{50} F_1F_0 ATP hydrolysis = 0.48 μM, EC_{50} F_1F_0 ATP synthesis = 18 μM. **(14A)** Cancer cell. At lower [BMS-199264], anti-cancer activity is predominantly by inhibition of F_1F_0 ATP hydrolysis in cancer cells, which increases their OXPHOS rate, and thence reactive oxygen species [ROS]. Elevated [ROS] slows proliferation by ROS checkpoint blockade and atrophies DNA information fidelity, which reduces the number of possible cell divisions from limitless to a value, at increasing [BMS-199264], increasingly convergent upon the Hayflick limit [96] of normal cells. At higher [BMS-199264], anti-cancer activity is additionally by reduction of F_1F_0 ATP synthesis, principally by BMS-199264 conferred uncoupling of the proton motive force (refer **Figure 17**), which increases cancer OXPHOS rate and intracellular [ROS]. So much that apoptosis ensues. (**14B**) Upper panel shows same diagram as (A), relating to a cancer cell, above equivalent diagram for a normal cell, with equivalent x-axis. It shows that lower [BMS-199264], which inhibits F_1F_0 ATP hydrolysis, harms cancer and helps normal cells. Thus, there is a therapeutic window. However, higher [BMS-199264], which significantly reduces F_1F_0 ATP synthesis, harms both cancer and normal cells. Greater [ROS] sensitivity of cancer, running an embryonic stem (ES) cell type phenotype, shown in relative positioning of plots upon equivalent x-axis.

Figure 15. *In vivo* study of compounds 6a and 6b, conducted at 22°C room temperature. METHODOLOGY: 4 mice were used and in the presented table "Day" refers to the number of days since the 1st drug/vehicle dose on Day 1. Some experimental details: intravenous (IV)

administration (tail vein), dosing volume = 10 µl/g, solution (not suspension), sterilised (0.22 µm filter) vortexed vehicle= 12.5% solutol, 12.5% ethanol, 75% water, IV solutions freshly prepared before injection except on days 22 and 39 when solutions prepared on previous dosing days were used (sub-optimal), Female *Mus Musculus* C57BL/6 strain, 6-8 weeks old at study start, mice sourced from Shanghai Lingchang Bio-Technology Co. Ltd, mice were observed/quarantined for a few days after arrival and before dosing, ad libitum Co^{60} irradiation sterilized dry granule food & reverse osmosis autoclaved water, corn cob bedding, polysulfone individually ventilated cage (IVC, containing up to 5 animals): 325 mm x 210 mm x 180 mm, 12 hour light/dark cycle, 40-70% humidity, 20-26°C room temperature, StudyDirector™ software (Studylog Systems, Inc. CA, USA) used to allocate/randomize control/treatment groups, animals marked by ear coding (notch), care and use of animals in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), when recording rectal temperature: care was taken to ensure constant depth of probe insertion across different recordings, time was afforded for rectal probe temperature to equilibrate with rectal temperature, and time was afforded between recordings for probe temperature to reset.

RESULTS: **Figures (15A)** and **(15B)**: For each animal, the 1st rectal temperature recording is typically of an atypically high body temperature, which is associated with the stress of being handled, which a mouse becomes habituated to during the course of the experiment. This handling effect has been reported in other rectal thermistor studies of rodents e.g. [97-98]. **Mouse 3** rectal temperature was <30°C by 45 minutes after 20 mg/kg IV injection of **6b**, it died ~210 minutes after this IV injection, whilst drinking water, "choked on water" was reported observation, water temperature was at room temperature (RT) = ~22°C (so ingestion reduces body temperature, if it isn't already at RT). **Mouse 4** rectal temperature was <30°C by 45 minutes after 40 mg/kg IV injection of **6b**, survived >6 hours, found dead the next day, did not survive the night. After IV of 6b: Mouse 3 and 4 exhibited hypoactivity and tachypnea, both signs of hypothermia [99], coinciding with their rectal temperature drop (<30°C). **Mouse 2** exhibited hypoactivity but recovered after 30 minutes, matching its recovery of rectal temperature. With 6b IV administration, there is a dose-dependent drop in rectal temperature.

Before 6b dosing experiments, **Mouse 1, 2 and 3** had all survived IV injections of **6a**. 6a doesn't potently reduce rectal temperature like 6b: the dose-dependent rectal temperature

reduction (with hypoactivity reported over same timescale that rectal temperature is reduced) that 6a can cause is because of *in vivo* epimerization of 6a to 6b. Similarly, when 6b is the administered compound, *in vivo* epimerization of 6b to 6a reduces the effective dose of 6b and chemical modifications to the 6b compound structure to prevent or slow this epimerization are componentry to this invention: for example, a non-limiting example embodiment is to replace the hydrogen on the chiral carbon of 6b with deuterium. >40 mg/kg doses of 6a weren't trialled because I ran out of 6a compound. Indeed, I only had enough 6a to dose 2 of the 3 test mice with 40 mg/kg.

Vehicle control can cause a drop in rectal temperature because of its 12.5% ethanol content: 12.5% of 10 ul/g solution administered = 1.25 ul/g ethanol = 0.000989226 g/g = 0.99 g/kg = 1 g/kg ethanol (IV). 1.9 g/kg ethanol (intraperitoneal injection, IP) reduced rat body temperature by 1.6°C (in 24.5 to 25°C ambient temperature; raising temperature of IP injected ethanol solution to 37°C didn't have major impact) [100]. Ideally, future studies should not use ethanol as a vehicle component. The problem is not its hypOthermia, which is safely mitigated by a higher ambient temperature [100]. But because at just a slightly higher ambient temperature than this, ethanol can cause hypERthermia [100]. And the ambient temperature that safely mitigates ethanol driven hypothermia, without causing ethanol driven hyperthermia, varies with the ethanol dose [100]. This [ethanol dose/ambient temperature/hypothermia/hyperthermia/safe rectal temperature] matrix can be mapped by experimentation, and indeed there is much in the literature already e.g. non-limiting examples: [100-106], to guide the best use of ethanol as a vehicle component in future studies. However, this experimentation can be avoided: alternative vehicle options, which are not a potent drug in and of themselves, as ethanol is, are well known to those of the art, e.g. see [107-108]: one or more of these can be employed as an alternative. When ethanol as vehicle is used, the fraction of rectal temperature drop accountable to the test drug can be calculated by subtracting any rectal temperature drop observed just with the ethanol containing vehicle control (assumes that ethanol and drug induced rectal temperature drops are additive and not potentiating). Drug induced rectal temperature reductions in this study, when they occur, are dose-dependent and well in excess of any rectal temperature drop observed when only ethanol containing vehicle control is injected.

The presented data shows that inhibiting the reverse mode of ATP synthase reduces body temperature. 6b potently inhibits the reverse mode of ATP synthase (IC_{50} = 0.018 μM [5-6]),

6a does not (IC_{50} > 100 μM [5-6]). 6b potently reduces rectal temperature, 6a does not (it does to a minor degree, which is evidence for *in vivo* epimerization of 6a to 6b, on a faster timescale than 6a clearance). A significant reduction in body temperature is lethal. Thence the maximal tolerated dose (MTD) of 6b, at room temperature = ~22°C, is lower than the MTD of 6a. Body temperature cannot fall below ambient temperature and so the MTD of 6b is increased by ensuring ambient temperature is closer to the normal mouse body temperature, which ensures that mouse body temperature is maintained at an acceptable value. This brings greater alignment between the MTD of 6a and 6b, which in the case of 6a is very safe: LD_{50} >40 mg/kg (IV). This is safer than the FDA approved anti-depressants clomipramine HCl and imipramine HCl: LD_{50} {mouse, IV} of 22 mg/kg and LD_{50} {mouse, IV} of 27 mg/kg respectively (Register of Toxic Effects of Chemical Substances, RTECS). Some patients take these drugs daily, safely, for years.

Non-limiting example embodiments to maintain mice, or some other animal, including humans, at a life permissive body temperature, whilst having a compound of this disclosure in their body, include locating them in a temperature-controlled room or confinement. For example, in small animal experiments, a plant growth or egg incubator or similar type device. An embodiment is to administer a compound of this disclosure to an animal(s), including human(s), in a hot country, geography or climate e.g. Dubai or somewhere else in the Middle East, more preferably during summer when it has high daytime *and* night temperatures. There are many methods in the literature to keep rodents at elevated temperature, easing the cold stress they feel at typical room temperatures [62]: e.g. partially submerging water proof mouse cages into fish tanks, in use as water baths, heated by thermostatic electric fish tank heaters [111], or by heating cages with chemical reaction hand warmers [109-110]. Such methods, or any method with equivalent intention, when employed with an animal(s)/human(s) with a compound of this invention in its body, is componentry to this invention. Adaptive heating can be employed, which adjusts the heating element output (e.g. an infrared lamp, or any other heating element(s)) in response to the measured body temperature (e.g. by rectal temperature probe or by thermal imaging, or any other body temperature recording device(s)), to maintain a life-permissive body temperature, when a compound of this invention is in the body. With a compound of this disclosure, the need for (and amplitude of) ambient temperature intervention is more important for smaller than larger animals e.g. more so for a mouse (~20 g) than a rat (~150 g). If an experimenter has to work with a compound of this disclosure at typical room temperature (20-25°C) then the test

species, and individual(s), chosen should be as large as possible. All methods of maintaining body temperature within a temperature range that permits life, whilst having a compound of this invention in the body, are componentry to this invention. For (non-limiting) example, wearing clothes.

Figure (15C): diagram, prediction, **not** real experimental data.

Figure 16. The enantiomeric excess (ee) of 6a and 6b is stable in presented ee stability experiments. By contrast, as disclosed elsewhere herein, 6a and 6b significantly epimerize within 48 hours in a biological system (NCI-60 testing). This ee instability in biological media is an unexpected result. This finding is componentry to the invention of this disclosure, as are any modifications to the structure of 6a or 6b to slow their ee erosion due to epimerization/racemization. The ee instability is unexpected because it runs contrary to theory. The 2nd order rate constant (k_{gb}) for general-base catalysed racemization can be predicted for 6a and 6b by theory from [112] (and its supplementary information, all incorporated by reference). Joined to the stereogenic carbon of 6a and 6b there is a phenyl group, alkyl and a guanidine group: $\sum\Delta\Delta G(R_1,R_2,R_3) = -19.9 +2.8 -19.1 = -36.2$ kcal/mol. The value for the guanidine group (19.1) is not from [112] but from one of its authors, Dr. Andrew Leach, by personal communication, who sourced it by quantum mechanical calculation with the Gaussian 03 software package. The cross-conjugation correction [112] was not applied in this case because Dr. Leach wrote "I would not expect guanidine to be a conjugating group". $\log(k_{gb}) = -0.11 * \sum\Delta\Delta G(R_1,R_2,R_3) - 9.81$, $\therefore K_{gb} = 0.00000148593\ M^{-1}s^{-1}$. This is not particularly fast. Racemization might occur faster for 6a and 6b in cells than predicted by theory because their high lipophibicity concentrates them in biological membranes. 6a logP = 5.97, calculated from 6a structure using [25]. This means 6a accumulates ~1,000,000 times more in model-lipid octanol than water, which means 6a disproportionally accumulates in biological membranes, which drives it to high concentration, which permits significant intermolecular racemization. The protonable nitrogen atom of the 6a imidazole group pulls a proton off the stereogenic carbon of another 6a molecule, leaving a planar carboanion, and when a proton reattaches to this carbon there is an equal probability of it doing so from either side, and so there is a 50% chance that the stereochemistry changes. Thence, racemization proceeds at a faster rate than predicted by methodology of [112], the present state of the art in racemization theory/prediction. The same process can apply to 6b. Deuterium in place of hydrogen on the stereogenic carbon of 6b decreases the rate of this racemization, because a carbon-deuterium bond is stronger than a

carbon-hydrogen bond (kinetic istope effect, KIE) and this isotopologue of 6b is componentry to this invention. The difference in % cáncer growth inhibition between 6a and 6b for each cell line at 10 μM drug dose (in NCI-60 one-dose testing) correlates with the difference in % cáncer growth inhibition between 6a and 6b for each cell line at 1 μM drug dose (in NCI-60 five-dose testing). Pearson correlation coefficient, R = 0.7919, p-value < 0.00001, significant at $p < 0.05$. This shows that there are cellular factors, which can vary between different cáncer cell lines, determining the rate of 6a and/or 6b racemization. For example, this could be membrane volume and/or the level of expression of a racemase/epimerase enzyme(s), and/or an enzyme(s) that converts the drug into a form that can undergo enzyme-catalysed epimerisation. In NCI-60 one-dose testing at 10 μM, across cell lines tested, there is a positive correlation between % cancer growth inhibition of 6b and the product [(% cancer growth inhibition due to 6b) – (% cancer growth inhibition due to 6a)]. Pearson correlation coefficient, R = 0.4167, p = 0.000927, significant at $p < 0.05$. Thus, when the anti-cancer performance of 6a is further behind the anti-cancer performance of 6b, anti-cancer performance of 6b is better. This suggests that for 6a to have greater anti-cancer activity, 6b needs to have less anti-cancer activity. Conversely, for 6b to have greater anti-cancer activity, 6a needs to have less anti-cancer activity. This is because what gives 6a its anti-cancer activity, racemization, takes away anti-cancer activity from 6b. Thus, in cancer cell lines that enable faster epimerization of 6a and 6b, there is greater 6a vs. 6b anti-cancer activity. This explains why, for NCI-60 one-dose (10 μM) assay, across the cell lines, there is a negative correlation (although not significant) between % cancer growth inhibition of 6a and the product [(% cancer growth inhibition due to 6b) – (% cancer growth inhibition due to 6a)]. Pearson correlation coefficient, R = -0.2136, but not significant at $p < 0.05$. The same phenomenon (6a and 6b compete for anti-cancer activity, because what gives to 6a, racemization, takes away from 6b) is observed in NCI60 five-dose data at 1 μM. Across cell lines tested, there is a positive correlation between % cancer growth inhibition of 6b and the product [(% cancer growth inhibition due to 6b) – (% cancer growth inhibition due to 6a)]. Pearson correlation coefficient, R = 0.3125, p = 0.017949, significant at $p < 0.05$. There is a negative correlation between % cancer growth inhibition of 6a and the product [(% cancer growth inhibition due to 6b) – (% cancer growth inhibition due to 6a)]. Pearson correlation coefficient, R = -0.4211, p = 0.00111, significant at $p < 0.05$.

Figure 17: Mechanistic distinction from oligomycin enables therapeutic utility. Drawn molecules of this figure (**17A**) have an imidazole group, with a protonable nitrogen atom that can shuttle protons across the mitochondrial inner membrane (IM), dissipating the proton

motive force (pmf, uncoupling). This figure presents experimental data (**17B**) using the HL-1 cardiac muscle cell line (cancer derived, but now very cardiac differentiated e.g. spontaneously contracts and beats like heart cells). Refer to the "Benchmark Drugs" first, which produce cellular effects well known to those of the art [3]. Oligomycin here refers to Oligomycin B. Oligomycin binds ATP synthase and blocks its forward, proton passing, ATP synthesizing, mode. This means less protons pass through ATP synthase, less pmf consumed per unit time, pmf increases, Ψ_{IM} hyperpolarizes, electron flow along the respiratory chain slows, and O_2 consumption is decreased. Carbonilcyanide p-triflouromethoxyphenylhydrazone (FCCP) is an uncoupler that shuttles protons across the IM, dissipates pmf (as heat), pmf decreases, Ψ_{IM} depolarizes, electron flow along the respiratory chain speeds, and O_2 consumption is increased. Distinct from oligomycin, three molecules of this figure increase, rather than decrease, O_2 consumption, which signifies their mechanistic distinction from oligomycin: they reduce ATP synthesis more by uncoupling than any inhibition of forward mode ATP synthase. They all contain a protonable nitrogen atom, with a basic pKa value conducive to uncoupling i.e. a pKa value reasonably close to {pH of mitochondrial intermembrane space + pH of mitochondrial matrix)/2}. Although for VG025, its most conducive pKa is on its main ring rather than its imidazole. In a NADPH-linked sub-mitochondrial (SMP) assay of ATP synthesis, these molecules would decrease ATP production because they dissipate pmf as heat, and so there is less pmf available for ATP production. In interpretation, this uncoupling could be incorrectly attributed to inhibition of the forward mode of ATP synthase and so the full mechanistic distinction of these molecules from oligomycin could be missed. This has been the case with other imidazole containing compounds of this disclosure. Also with a protonable nitrogen in their imidazole, also with a pKa conducive to uncoupling, and wherein their inhibition of F_1F_0 ATP synthesis in the NADPH-linked SMP assay has been attributed to inhibiting the forward mode of ATP synthase [5-8]. But wherein their uncoupling is likely to be the more predominant factor (extrapolated from data of this figure) and wherein they do not inhibit the forward mode of ATP synthase much, if at all, in stark distinction to oligomycin. Uncoupling capability, which decreases with increased logP (refer next paragraph), explains why different molecules of the present figure exert different effects on O_2 consumption. The high logP value of VG019 means its uncoupling is minimal and its effect on O_2 consumption is zero (rounded) at a concentration (100 μM) it inhibits the reverse mode of ATP synthase, in stark distinction to oligomycin (3 μM), which dramatically decreases O_2 consumption (-40%), because, distinctly, it potently inhibits the forward mode of ATP synthase.

LogP = ~3.2 is the optimal compromise for best passing a membrane: its hydrophobic core (selecting for high logP) and hydrophilic boundary layer (selecting for low logP) ([36], herein incorporated in its entirety). The imidazole containing molecules presented in this figure, and in this disclosure's drawings more generally, have logP > 3.2 and present increased logP = decreased uncoupling. The uncoupling capability/liability of a molecule actually hinges on its intersection of pKa(s) and logP [36] but for the molecules in this disclosure's drawings, wherein the imidazole pKa values are, generally, all within a fairly narrow range, the more primary determinant to each molecule's uncoupling rate, relative to the others, is the molecule's logP value relative to the others.

The drawn molecules of this figure *do* inhibit the reverse mode of ATP synthase. When a respiratory chain inhibitor blocks electron flow, Ψ_{IM} is maintained, not by proton pumping by the respiratory complexes, but by proton pumping by ATP synthase i.e. the reverse mode of ATP synthase. In the presented data, when the respiratory chain is blocked, the presented molecules depolarise Ψ_{IM} because they block the reverse mode of ATP synthase. They do not affect Ψ_{IM} by these means when the respiratory chain is operational. Because Ψ_{IM} is not set/maintained by the reverse mode of ATP synthase in this case. Although the molecules with stronger uncoupling capability, they can shuttle more protons across the IM (dissipate more pmf) than the respiratory chain can increase its rate to replace, and they do depolarise Ψ_{IM}. When the respiratory chain is blocked, a stronger uncoupler in this figure depolarises Ψ_{IM} more. Because not only does it inhibit the generator of Ψ_{IM} (reverse mode ATP synthase), it simultaneously erodes Ψ_{IM} (uncoupling).

Oligomycin does inhibit the reverse mode of ATP synthase. But distinctly it inhibits its forward mode more [11]. So, using oligomycin, there is *no* margin to inhibit the reverse mode (anti-cancer), without adversely affecting cells using OXPHOS i.e. most normal cells. Contrast this with molecule VG019 of this figure, for example, which can inhibit the reverse mode of ATP synthase, and yet – in observed distinction to oligomycin – does not affect cells using OXPHOS: it does not change their O_2 consumption or Ψ_{IM} (at 100 μM). This grants it, in distinction to oligomycin, anti-cancer selectivity. Other molecules of this disclosure have even greater cancer selectivity. For example, a preferred embodiment (refer disclosure section: "Preferred Embodiments") inhibits F_1F_0 ATP hydrolysis >5,556 times more than F_1F_0 ATP synthesis, in NADH-linked and NADPH-linked SMP assays [5-6], whilst

oligomycin – inversely - inhibits F_1F_0 ATP hydrolysis less than F_1F_0 ATP synthesis in such assays [11].

Computational calculations of logP and pKa were made using [25]. The data presented in this Figure is from [12] (herein incorporated in entirety), but the analysis/(re)interpretation is novel. As is the process/method of using these molecules as anti-cancer therapeutics, which is componentry to this invention. The imidazole of the drawn molecules is 4-yl. Permutations, with 5-yl instead, are also disclosed by this invention as anti-cancer therapeutics.

EXAMPLE EMBODIMENTS OF THE INVENTION

The Drawings present embodiments of the invention. Further examples are enumerations of Markush Formulas (I), (II), (III), (IV), (V) and (VI), presented henceforth. Note: none of these formulae share Markush symbols, which can be, for example, symbols of the type: R_x, wherein x is an integer, well known to those of the art. They each have their own, as specified for each, in their own sections of this disclosure.

In this disclosure, the term "Formula [X]" is used when a statement is true for Formula (I), (II), (III), (IV), (V) and (VI), and all are being referred to independently. A compound of Formula [X] is a compound of Formula (I), or Formula (II), or Formula (III), or Formula (IV), or Formula (V), or Formula (VI), or any compound presented in this disclosure's Drawings.

This invention is described using these example embodiments but it isn't limited to these. These merely illustrate the invention. Compounds of other structures, which are identified as therapeutic inhibitors by the rationale and methods of the present invention, are also encompassed by the present invention.

Encompassed by this invention are methods of treating a subject suffering from a medical disease or disorder by administering an effective amount of at least one compound of Formula (I), (II), (III), (IV), (V) or (VI) or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a pharmaceutical composition(s) comprising one or compounds of Formula (I), (II), (III), (IV), (V) or (VI), for use in a method of treatment of the human or animal body by therapy, particularly for use in a method of treating, ameliorating, preventing or combating a disease or disorder selected from

(i) cancer;

(ii) cancer that metabolizes much of its glucose and/or glutamine to lactate, for example a cancer exhibiting the Warburg effect and/or a cancer that can be discriminated from surrounding tissue by PET imaging (e.g. ^{18}F-FDG PET);

(iii) cachexia, cancer driven cachexia or weight loss;

(iv) disease or disorder that causes a higher than normal body temperature such as high environmental temperature, ingesting an uncoupler (e.g. 2,4-dinitrophenol), infection, sepsis, stroke, fever, pyrexia, hyperpyrexia, hyperthermia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, heatstroke, thermoregulatory disorder(s), Kawasaki syndrome, drug or drug withdrawal induced hyperthermia, idiosyncratic drug reaction, fever of unknown or uncertain origin, reaction to incompatible blood product(s), metabolic disorder(s), cancer, injury;

(v) Tumour Associated Macrophages (TAMs) or any macrophage associated disease or disorder such as Macrophage Activation Syndrome (MAS), HIV, AIDS, HIV-associated neurocognitive disorders (HAND), HIV associated cancers, AIDS-defining cancers, non-AIDS defining cancers;

(vi) virus neuroinvasion via macrophages, as used for example by HIV and SARS coronavirus;

(vii) neurocognitive or neurodegenerative diseases/disorders, for example those caused by a virus;

(viii) acute or chronic or systemic inflammation or any inflammatory disease/disorder/syndrome or any autoinflammatory disease/disorder/syndrome or any autoimmune disease/disorder/syndrome;

(ix) low or less than desired metabolic/bioenergetic efficiency in a subject, or low or less than desired physical or mental performance, or low or less than desired body weight;

(x) diseases or disorders treatable by conferring hypothermia in a subject for some medical or other purpose which can include slowing a chemical reaction(s) rate in a subject for therapeutic benefit, preventing/minimizing brain and/or tissue damage, deep hypothermic circulatory arrest for surgery, hypothermia for a surgical purpose, hypothermia for cardiac and/or cardiovascular surgery and/or brain surgery (neurosurgery), Emergency Preservation and Resuscitation (EPR), preserving detached body parts such as limbs and/or organs (for example during organ storage and/or transplant), protective hypothermia, targeted temperature management, therapeutic hypothermia, hypothermia therapy for neonatal encephalopathy, birth asphyxia, haemorrhage, hypovolemia, decompression sickness, burn

injury(s) including skin burn, inflammation, allergic reaction, anaphylaxis, tissue/organ rejection, hypoxia, hypoxemia, anoxemia, anoxia, anemia, hypervolemia, altitude sickness, obstructed airway, asthma attack, hypoxia in a body/tissue/organ, hypoglycemia, reperfusion injury (ischemia-reperfusion injury), upon release of a ligature or tourniquet, uraemia, crush syndrome, compartment syndrome, traumatic brain and/or spinal cord injury, major trauma, infection, bacterial and/or viral infection(s) (e.g. meningitis), sepsis, septic shock, ischemic brain/heart/kidney injury, neuroprotection and/or cardioprotection and/or tissue protection during/after a stroke and/or ischemia and/or cardiac arrest and/or resuscitation and/or a period(s) of poor blood flow anywhere in a subject;

(xi) poisoning by a toxic amount of a compound(s) in a subject e.g. carbon monoxide/methanol/heavy metal/pesticide poisoning, snake/spider/bee/insect/lizard venom, metabolic poison(s), bacterial toxin(s), endotoxemia or drug/substance overdose e.g. heroin, ethanol, prescription medication(s) or over the counter medication(s);

(xii) accelerated aging disease or progeroid syndrome including Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy, combined xeroderma pigmentosum-Cockayne syndrome, restrictive dermopathy, Wiedemann–Rautenstrauch syndrome, Hutchinson–Gilford progeria syndrome (progeria);

(xiii) disease or disorder of ageing (incidence increases with increased age/senescence) and/or a disease/disorder associated with elevated reactive oxygen species including degenerative diseases, neurodegenerative diseases, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxias, Friedreich's ataxia, dementia, Batten disease, polyglutamine diseases, osteoporosis, atherosclerosis, cardiovascular disease, myocardial infarction, cerebrovascular disease, stroke, heart failure, chronic obstructive pulmonary disease (COPD), hypertension, arthritis, cataracts, type 2 diabetes, andropause, sarcopenia, age-related macular degeneration (AMD), hearing loss, movement disability, cancer;

(xiv) aging, wherein these compounds slow ageing, extend lifespan and healthspan;

(xv) skin aging;

(xvi) cardiovascular diseases and conditions associated with ischemia and associated conditions including, without limitation, ischemia-reperfusion injury, myocardial ischemia, ischemic heart disease, chronic stable angina pectoris, myocardial infarction, congestive heart failure, an acute coronary syndrome, muscle cell damage, necrosis, cardiac arrhythmias, non-Q wave MI, unstable angina, high blood pressure, coronary artery disease, ischemic hypoxia,

cyanosis, gangrene, acute limb ischemia, stroke, ischemic stroke, brain ischemia, vascular dementia, transient ischemic attack (TIA), ischemic colitis, mesenteric ischemia, angina pectoris, ischemic heart disease, ischemic neuropathy, hypoxic-ischemic encephalopathy, cerebral hypoxia, brain hypoxia, ischemia resulting from vascular occlusion, cerebral infarction, stroke and related cerebral vascular diseases (including cerebrovascular accident and transient ischemic attack), muscle cell damage, necrosis; or

(xvii) acute inflammation, chronic inflammation, systemic inflammation, inflammation because of infection or foreign bodies or injury or chemical or toxin or drug or stress or frostbite or burn or ionising radiation, inflammatory diseases/disorders/syndromes, Macrophage Activation Syndrome (MAS), autoinflammatory diseases/disorders/syndromes, age-related chronic inflammatory diseases ("inflammaging"), autoimmune diseases/disorders/syndromes, diseases/disorders of the innate immune system, sore throat, sore throat associated with cold or flu or fever, high-intensity exercise associated inflammation, ulcerative colitis, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), rheumatoid arthritis, osteoarthritis, psoriatic arthritis, atopic dermatitis, allergic airway inflammation, asthma, inflammation associated depression, exercise-induced acute inflammation, atherosclerosis, allergy, hay fever, anaphylaxis, inflammatory myopathies, drug-induced inflammation, systemic inflammatory response syndrome, sepsis-related multiple organ dysfunction/multiple organ failure, microbial infection, acute brain/lung/hepatic/renal injuries, acne vulgaris, celiac disease, celiac sprue, chronic prostatitis, colitis, diverticulitis, glomerulonephritis, hidradenitis suppurativa, hypersensitivities, interstitial cystitis, Mast Cell Activation Syndrome, mastocytosis, otitis, pelvic inflammatory disease (PID), reperfusion injury, rheumatic fever, rhinitis, sarcoidosis, transplant rejection, parasitosis, eosinophilia, type III hypersensitivity, ischaemia, chronic peptic ulcer, tuberculosis, Crohn's disease, hepatitis, chronic active hepatitis, immune hepatitis, ankylosing spondylitis, diverticulitis, fibromyalgia, systemic lupus erythematous (SLE), Alzheimer's disease, Parkinson's disease, neurodegenerative disease, cardiovascular disease, chronic obstructive pulmonary disease, bronchitis, acute bronchitis, appendicitis, acute appendicitis, bursitis, colitis, cystitis, dermatitis, encephalitis, gingivitis, meningitis, infective meningitis, myelitis, nephritis, neuritis, periodontitis, chronic periodontitis, phlebitis, prostatitis, RSD/CRPS, rhinitis, sinusitis, chronic sinusitis, tendonitis, testiculitis, tonsillitis, urethritis, vasculitis, respiratory bronchiolitis–associated interstitial lung disease and desquamative interstitial pneumonia, interstitial lung disease, Löfgren syndrome, Heerfordt syndrome, monocytosis, liver fibrosis, steatohepatitis, nonalcoholic steatohepatitis,

silicosis, histiocytoses, Langerhans' cell histiocytosis, haemophagocytic lymphohistiocytosis, pulmonary langerhans cell histiocytosis, obesity, type II diabetes, gout, pseudogout, organ transplant rejection, epidermal hyperplasia, chronic fatigue syndrome, graft versus host disease (GVHD), lymphadenopathy, familial mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), Hyperimmunoglobulinemia D with recurrent fever syndrome (HIDS), cryopyrin associated periodic syndrome (CAPS), Blau syndrome, Majeed syndrome, deficiency of interleukin-1 receptor antagonist (DIRA), mevalonate kinase deficiency, pyogenic-arthritis-pyoderma gangrenosum and acne syndrome (PAPA), periodic fever aphthous stomatitis pharyngitis adenitis (PFAPA) syndrome, Behcet's disease, Still's disease, Crohn's disease, Schnitzler's syndrome, Sweet's syndrome, NLRP12-associated autoinflammatory disorders, deficiency of interleukin-1 receptor antagonist (DIRA), pyoderma gangrenosum, cystic acne, aseptic arthritis, periodic Fever Associated with mevalonate kinase deficiency (hyperimmunoglobulin D Syndrome), Pyogenic Arthritis Pyoderma Gangrenosum Acne (PAPA) syndrome, Periodic Fever Aphthous Stomatitis, Pharyngitis and Adenopathy (PFAPA) syndrome, Adult-Onset Still's Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Chronic Recurrent Multifocal Osteomyelitis (CRMO), Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) syndrome, Cryopyrin associated Periodic Syndrome (CAPS), Familial cold auto inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), Familial cold urticarial, Neonatal onset multisystemic inflammatory disorder (NOMID), hereditary Periodic Fever Syndromes, Periodic Fever Syndromes, systemic autoinflammatory diseases, Addison's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss, Cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, coxsackie myocarditis, CREST syndrome, Berger's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant

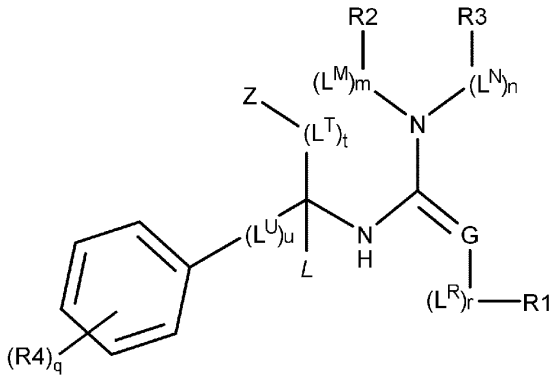
cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, immune hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (Type 1 diabetes), juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR) PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage-Turner syndrome, Pemphigus, peripheral neuropathy, perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)), idiopathic thrombocytopenia purpura, splenomegaly.

EXAMPLE (I)

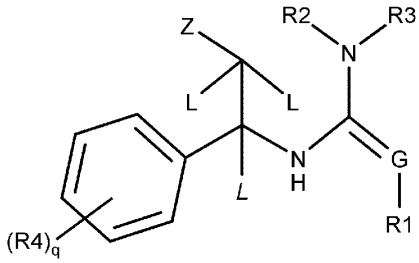
Summary of Formula (I)

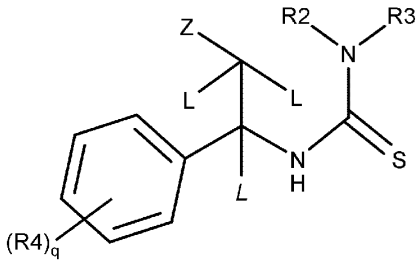
This invention embodiment relates to compounds having the following formula:

Formula (I)

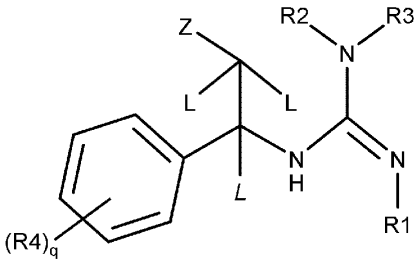


including





or



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

L^M, L^N, L^U, L^T and L^R are each independently selected from a single bond or CR^V_2, wherein each R^V is independently selected from hydrogen, alkyl, or substituted alkyl (non-limiting examples: CF_3, CCl_3), or deuterated alkyl (non-limiting example: CD_3), or aminoalkyl, or thioalkyl, or alkoxy, or halogen, or haloalkyl, or haloalkoxy;

m, n, u, t, and r are each independently selected from 0, 1, 2, 3 and 4;

L is independently at each point of its use alkyl, or substituted alkyl (non-limiting examples: CF_3, CCl_3), or deuterated alkyl (non-limiting example: CD_3), or aminoalkyl, or thioalkyl, or alkoxy, or halogen, or haloalkyl, or haloalkoxy or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.);

R_1 is R_{extra}, hydrogen, cyano, —SO_2R_8, —C(=O)R_9, or heteroaryl;

R_{extra} is selected from L (defined earlier), alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkylene, substituted alkylene, alkynyl, substituted alkynyl, alkoxy, thioalkyl, aminoalkyl, carbamyl, sulfonyl, sulfonamide, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, haloalkyl, haloalkoxy, alkoxyalkyl, morpholinylalkyl, aryl, arylalkyl, heterocyclo, heteroaryl, (heterocyclo)alkyl, acyl, alkoxycarbonyl, substituted amino;

R_2 is (i) independently hydrogen, L (defined earlier), alkyl, or substituted alkyl, or (ii) taken together with R_3 forms a heterocyclo;

R_3 is (i) independently alkyl, substituted alkyl, L, alkylthio, aminoalkyl, carbamyl, B_B-aryl, B_B-heterocyclo, B_B-heteroaryl, or B_B-cycloalkyl, or (ii) taken together with R_2 forms a heterocyclo;

Z is heteroaryl;

B_B is a bond, C_{1-4}alkylene, C_{2-4}alkenylene, substituted C_{1-4}alkylene, substituted C_{2-4}alkenylene, —C(=O)NR_{19}—, —C_{1-4}alkylene-C(=O)NR_{19}—, or substituted C_{1-4}alkylene-C(=O)NR_{19}—;

R_4 at each occurrence is selected independently of each other R_4 from the group consisting of halogen, alkyl, haloalkyl, nitro, cyano, haloalkoxy, OR_{25}, SR_{25}, $NR_{25}R_{26}$, $NR_{25}SO_2R_{27}$, SO_2R_{27}, $SO_2NR_{25}R_{26}$, CO_2R_{26}, C(=O)R_{26}, C(=)$NR_{25}R_{26}$, OC(=O)R_{25}, —OC(=O)$NR_{25}R_{26}$, NR_{25}C(=O)R_{26}, $NR_{25}CO_2R_{26}$, aryl, heteroaryl, heterocyclo and cycloalkyl;

R_8 is alkyl, substituted alkyl, aryl, or heteroaryl;

R_9 is —$NR_{10}R_{11}$, alkyl, substituted alkyl, alkoxy, alkylthio, cycloalkyl, aryl, heteroaryl, heterocycle, or —CO_2R_{12};

R_{10} and R_{11}, are (i) independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, heterocyclo, cycloalkyl, aryl, and heteroaryl; or (ii) taken together form a hetero cyclo or heteroaryl;

R_{12} and R_{19} are hydrogen or alkyl;

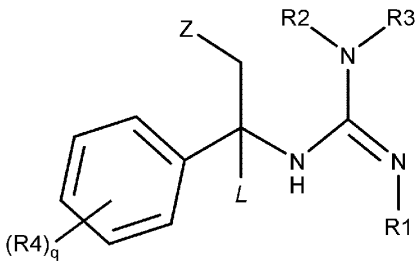
R_{25} and R_{26} are independently selected from hydrogen, alkyl, or substituted alkyl, or taken together form a heterocyclo or heteroaryl ring;

R_{27} is alkyl or substituted alkyl, and

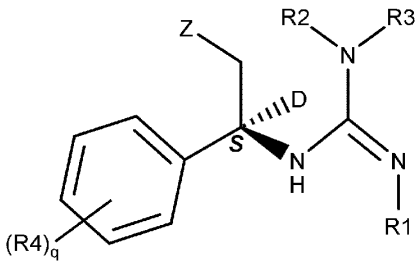
q is 0, 1, 2, or 3.

Preferred compounds of Formula (I)

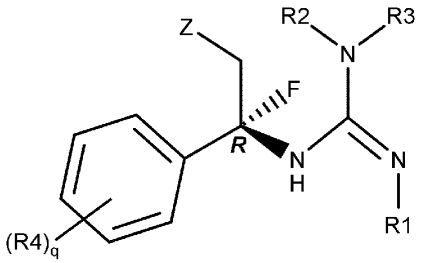
Preferred methods are to use, and preferred compounds are, compounds with the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



and even more preferred methods are to use, and preferred compounds are, compounds with the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



other preferred methods are to use, and preferred compounds are, compounds with the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



in which, in the preceding three structures shown:

L is hydrogen, or methyl, or CF_3, or CD_3, or deuterium (D);

D is deuterium (enrichment, for example, exceeding 40% deuterium incorporation at shown position, and optionally at other positions also);

S symbolises the *S* stereoisomer, for example, in enantiomeric excess (ee) exceeding 70%;

R symbolises the *R* stereoisomer, for example, in enantiomeric excess (ee) exceeding 70% (following IUPAC naming rules the chiral carbon of the fluorine (F) analogue is labelled *R* rather than *S*, but note that the arrangement of which bond is up, bold wedge, and down, dashed, around the stereogenic carbon is the same as the preceeding structures labelled *S* at their chiral carbon, it is this molecule arrangement that is salient, and that is disclosed, rather than a mere label in a naming convention. This clarification won't be repeated at every place to which it applies in this disclosure, at every point at which there is an F in place of an H on the chiral carbon, or any other higher order of priority atom (by IUPAC rules), e.g. (non-limiting) any other halogen, because this clarification here itself is likely superfluous: all this is very clear to someone of the art. So, when there is said to be an enantiomeric excess (ee) in this disclosure in relation to this example embodiment, Formula (I), it applies to this molecular configuration, this arrangement of solid/dashed wedges, about the chiral carbon, whether this be *S* or *R* by IUPAC naming rules);

Z is triazolyl optionally substituted with one to two R_7 or imidazolyl optionally substituted with one to two R_7 and/or having fused thereto a benzene ring in turn optionally substituted with one to two R7;

R_1 is cyano or $-C(=O)R_9$;

R_2 is hydrogen, alkyl, or benzyl;

R_3 is aryl or arylalkyl optionally substituted with alkyl, halogen, trifluoromethyl, OCF_3, cyano, nitro, amino, hydroxy, or methoxy;

R_4 is halogen, alkyl, trifluoromethyl, or OCF_3;

R_7 is alkyl, carbamyl or carbamylC_{1-4}alkyl;

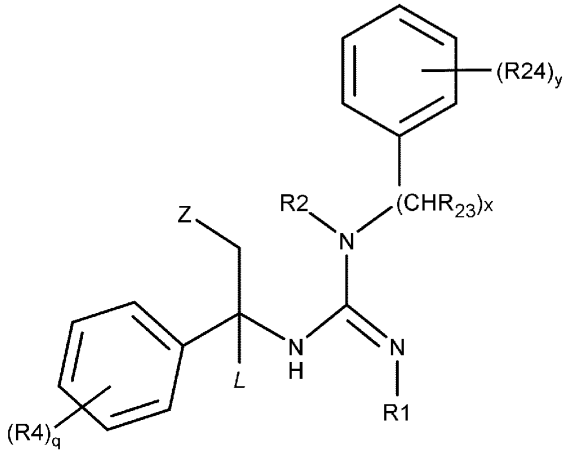
R_9 is —$NR_{10}R_{11}$, alkyl, substituted alkyl, alkoxy, alkylthio, cycloalkyl, aryl, heteroaryl, heterocycle, or —CO_2R_{12};

R_{10} and R_{11} are (i) independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, heterocyclo, cycloalkyl, aryl, and heteroaryl; or (ii) taken together form a heterocyclo or heteroaryl;

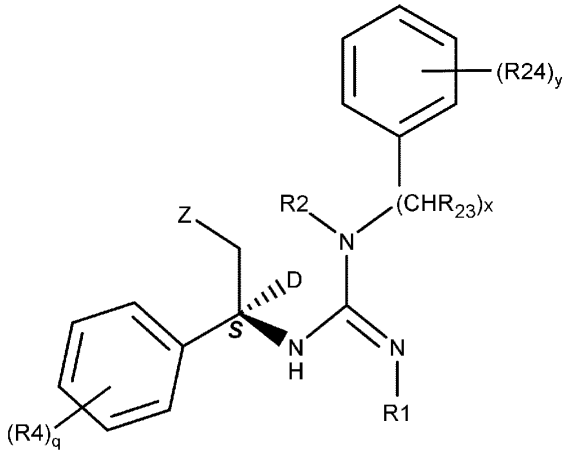
R_{12} is hydrogen or alkyl; and

q is 0, 1, 2, or 3.

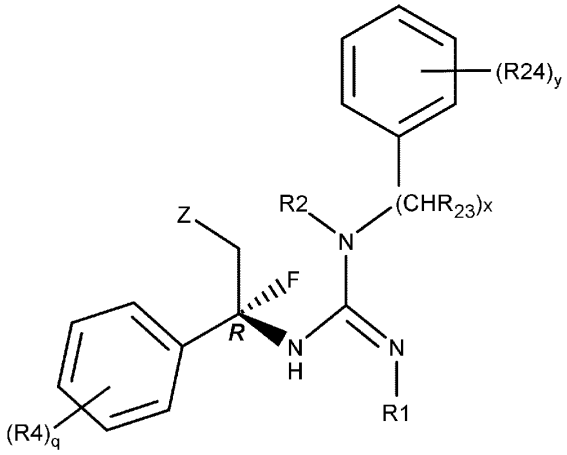
Further preferred are compounds having the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



and even more preferred are compounds having the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,

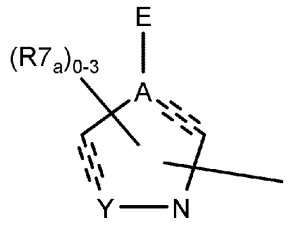


other preferred compounds are those with the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,

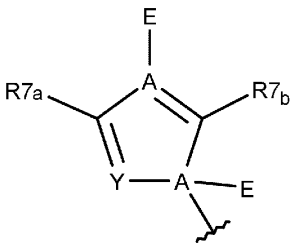
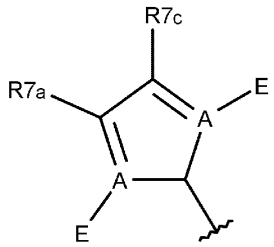


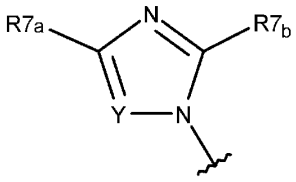
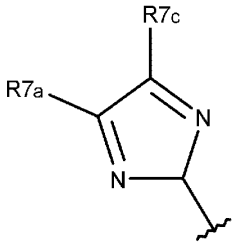
in which, for the preceding three structures shown:

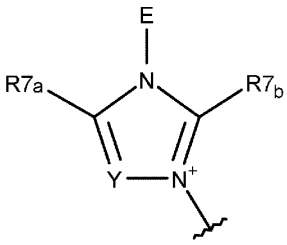
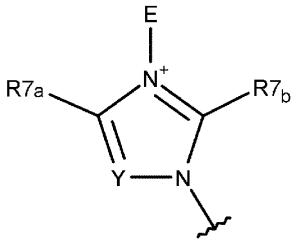
z is



and more preferably

z is  or 

or  or 

or  or 

L is hydrogen, or methyl, or CF_3, or CD_3, or deuterium (D);

D is deuterium (enrichment, for example, exceeding 40% deuterium incorporation at shown position, and optionally at other positions also);

S symbolises the *S* stereoisomer, for example, in enantiomeric excess (ee) exceeding 70%;

A is nitrogen (N), or N^+, or carbon;

E is absent, or alkyl, or substituted alkyl, or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.), for example hydrogen, deuterium or fluorine;

Y is N, CH or CR_{7c};

R_1 is cyano or —C(=O)R_9;

R_2 is hydrogen or $C_{1\text{-}4}$alkyl;

R_4 is halogen, $C_{1\text{-}4}$alkyl, trifluoromethyl; or OCF_3;

R_{7a}, R_{7b}, and R_{7c} are independently E (defined earlier), hydrogen, alkyl, carbamyl or carbamyl$C_{1\text{-}4}$alkyl, or R_{7a} and R_{7c} join to form an optionally substituted fused phenyl ring;

R_9 is —$NR_{10}R_{11}$, alkyl, substituted alkyl, alkoxy, alkylthio, cycloalkyl, aryl, heteroaryl, heterocycle, or —CO_2R_{12};

R_{10} and R_{11} are (i) independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, heterocyclo, cycloalkyl, aryl, and heteroaryl; or (ii) taken together form a heterocyclo or heteroaryl;

R_{12} is hydrogen or alkyl;

R_{23} is hydrogen, alkyl, hydroxyalkyl, or phenyl;

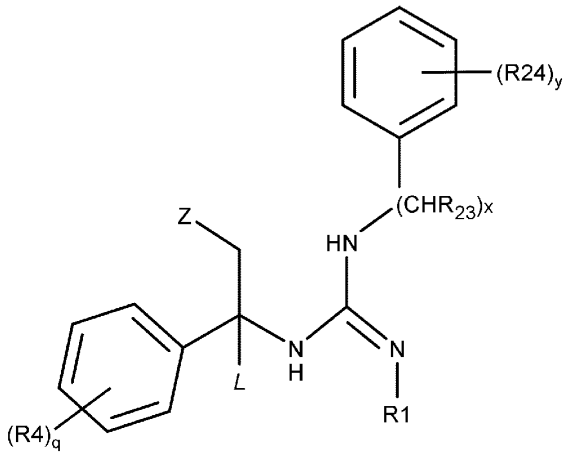
R_{24} is alkyl, halogen, trifluoromethyl, cyano, halogen, hydroxy, OCF_3, methoxy, phenyloxy, benzyloxy, cyano, or acyl, or two R_{24} groups join to form a fused cycloalkyl or benzene ring;

q is 1 or 2;

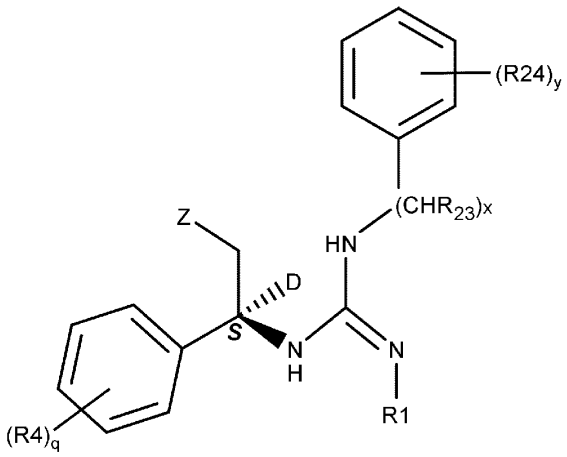
x is 0, 1, or 2; and

y is 0, 1, 2, or 3.

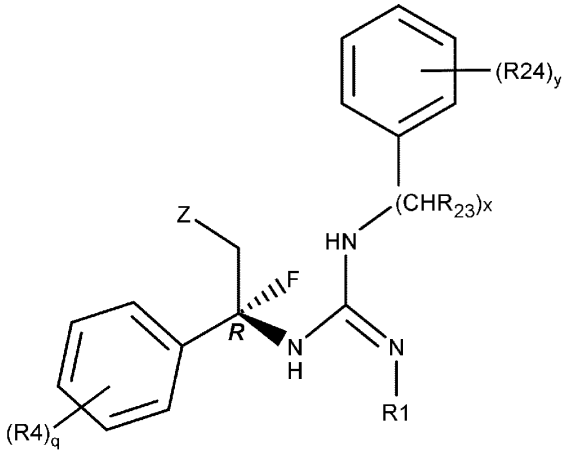
More preferred are compounds having the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



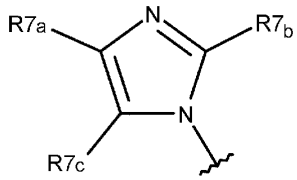
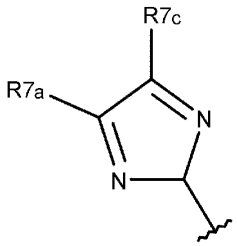
and even more preferred are compounds having the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,

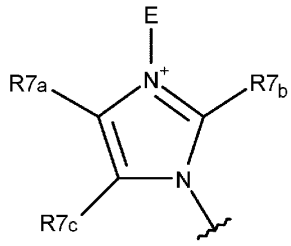
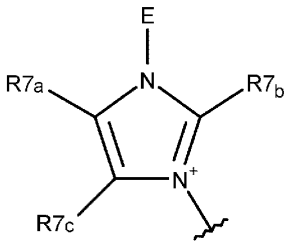


other preferred compounds are those with the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



in which, for the preceding three structures shown:

z is  or 

or  or 

L is hydrogen, or methyl or deuterium;

D is deuterium (enrichment, for example, exceeding 40% deuterium incorporation at shown position, and optionally at other positions also);

S symbolises the *S* stereoisomer, for example, in enantiomeric excess (ee) exceeding 70%;

R_1 is cyano or —C(=O)R_9;

R_4 is halogen, C_{1-4}alkyl, trifluoromethyl, or OCF_3;

R_{7c} is hydrogen or R_7 and R_{7c} join to form a fused benzene ring optionally substituted with C_{1-4}alkyl or —$(CH_2)_{1-2}$—NHC(=O)C_{1-4}alkyl,

R_{7b} is hydrogen, C_{1-4}alkyl, or —$(CH_2)_{1-2}$—NHC(=O)C_{1-4}alkyl;

R_9 is a) —$NR_{10}R_{11}$

b) C_{1-8}alkyl optionally substituted with one to two of:

i) SR_{13}, OR_{13}, $NR_{13a}R_{13b}$, halogen, trifluoromethyl, CO_2R_{13a}, and C(=O)$NR_{13a}R_{13b}$;

ii) cycloalkyl optionally substituted with one to two of C(=O)H, C_{1-4}acyl, alkenyl, carbamyl, and/or phenyl in turn optionally substituted with halogen;

iii) phenyl or napthyl optionally substituted with one to two of halogen, nitro, amino, alkyl, hydroxy, C_{1-4}alkoxy, or having fused thereto a five or six membered heterocyclo;

iv) pyridinyl, thiophenyl, furanyl, tetrahydrofuranyl, or azepinyl, optionally substituted with alkyl or having fused thereto a five to six membered carbocyclic ring optionally substituted with keto or C_{1-4}alkoxy;

c) C_{1-4}alkoxy;

d) C_{1-4}alkylthio;

e) CO_2alkyl;

f) 3 to 6 membered cycloalkyl optionally having up to four substituents selected from alkyl, halogen, cyano, alkenyl, acyl, alkylthio, carbamyl, and/or phenyl in turn optionally substituted with halogen; or having an aryl fused thereto;

g) phenyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, C_{1-4}alkoxy, haloalkoxy, C_{1-6}alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino, NH(C_{1-4}alkyl), N(C_{1-4}alkyl)$_2$, NHC(=O)alkyl, C(=O)alkyl, and/or C_{1-4} alkyl in turn optionally substituted with one to three of trifluoromethyl; hydroxy, cyano, phenyl, pyridinyl; and/or a five or six membered heteroaryl or heterocyle in turn optionally substituted with keto or having a benzene ring fused thereto;

h) pyridinyl, thiazolyl, furanyl, thiophenyl, and pyrrolyl optionally substituted with one to two of halogen, alkyl, and phenyl in turn optionally substituted with halogen or trifluoromethyl;

R_{10} is hydrogen, alkyl, or alkoxy;

R_{11} is alkyl, substituted alkyl, alkoxy, heterocyclo, cycloalkyl, aryl, or heteroaryl;

or R_{10} and R_{11}, taken together form a heterocyclo or heteroaryl;

R_{23} is hydrogen, alkyl, hydroxyalkyl, or phenyl;

R_{24} is alkyl, halogen, trifluoromethyl, cyano, halogen, hydroxy, OCF_3, methoxy, phenyloxy, benzyloxy, cyano, or acyl, or two R_{24} groups join to form a fused cycloalkyl or benzene ring;

q is 0, 1, or 2;

x is 0 or 1; and

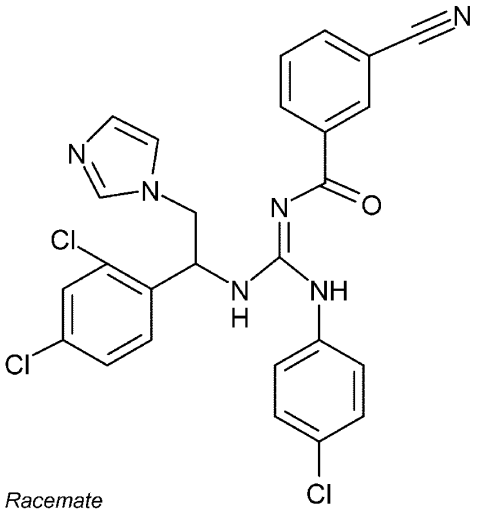
y is 0, 1, or 2.

Most preferred are compounds as immediately defined above wherein, R_1 is cyano or —C(=O)R_9; R_9 is optionally substituted phenyl or phenyl C_{1-4}alkyl; x is 0 or 1; and q and y are 1 or 2. For this preferred structure, its *S* stereoisomer is preferred. And further preferred is for its L group to be deuterium.

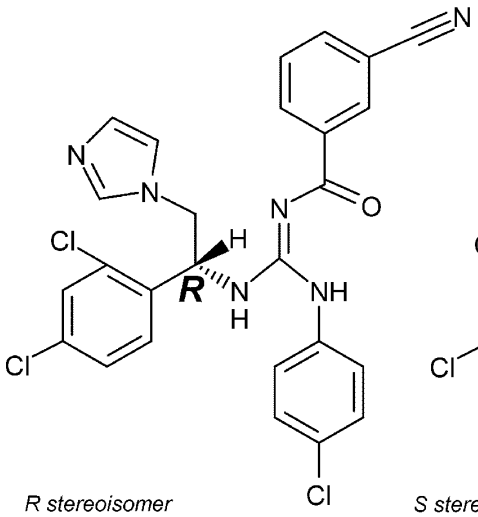
Example embodiments of Formula (I)

Compounds from [5-6], selected as specific anti-cancer therapeutics by the invention of this disclosure, selected because they inhibit the reverse, more than the forward, mode of ATP synthase. EC_{50} and IC_{50} used interchangeably. EC_{50} values for F_1F_0 ATP hydrolysis, and F_1F_0 ATP synthesis, in NADH-linked and NADPH-linked sub-mitochondrial (SMP) assays respectively, sourced from [5-6], are presented. [5-6] refer to these EC_{50} values as IC_{50} values

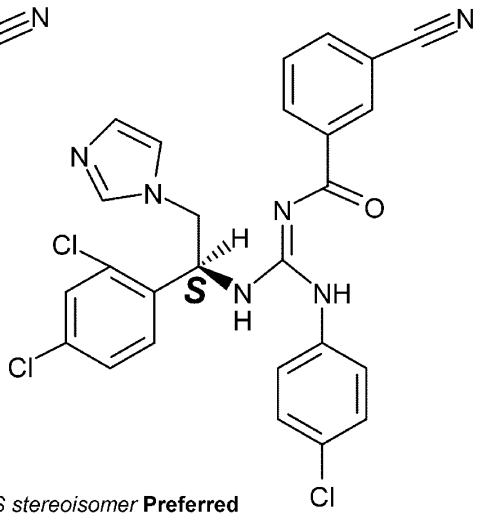
for inhibiting F_1F_0 ATP hydrolase (reverse mode) and F_1F_0 ATP synthase (forward mode). However, this in incorrect. Because, as identified by the invention of this disclosure, explained herein, although these molecules inhibit F_1F_0 ATP hydrolase, their reducing of F_1F_0 ATP synthesis is not (predominantly) because of inhibiting F_1F_0 ATP synthase, but by uncoupling. More preferred molecules of this invention have a low EC_{50} for F_1F_0 ATP hydrolysis, and a higher EC_{50} for F_1F_0 ATP synthesis, and their ratio difference is large.



Racemate
EC_{50} F_1F_0 ATP hydrolase = 0.033 ± 0.02 (μM)
EC_{50} F_1F_0 ATP synthesis > 100 (μM)
EC_{50} Ratio >3,030



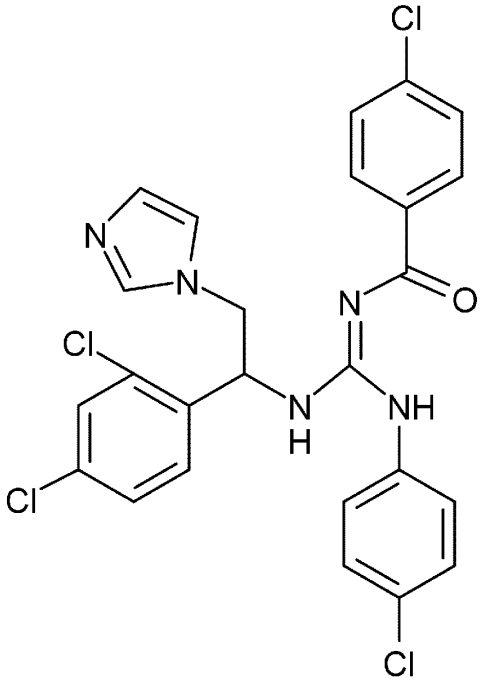
R stereoisomer
EC_{50} F_1F_0 ATP hydrolase > 100 (μM)
EC_{50} F_1F_0 ATP synthesis > 100 (μM)



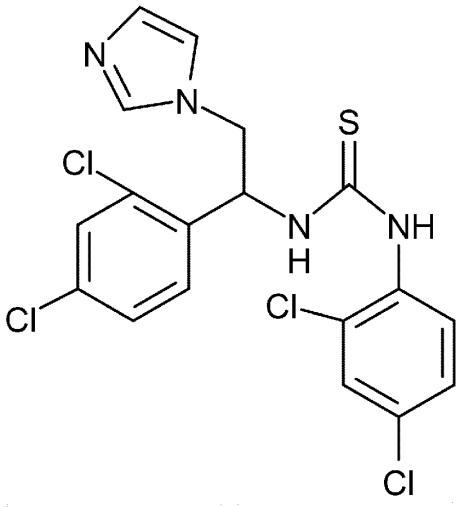
S stereoisomer **Preferred**
EC_{50} F_1F_0 ATP hydrolase = 0.018 ± 0.016 (μM)
EC_{50} F_1F_0 ATP synthesis > 100 (μM)
EC_{50} Ratio >5,556
In rat: orally bioavailable (47%), i.v. half-life (2.1 hours), C_{max} = 21 μM, volume of distribution V_{SS} = 2.37 L/kg

Further example embodiments of Formula (I), with SMP data, reinterpreted (as aforementioned, these molecules don't significantly inhibit F_1F_0 ATP synthase but do reduce F_1F_0 ATP synthesis by uncoupling), from [5],

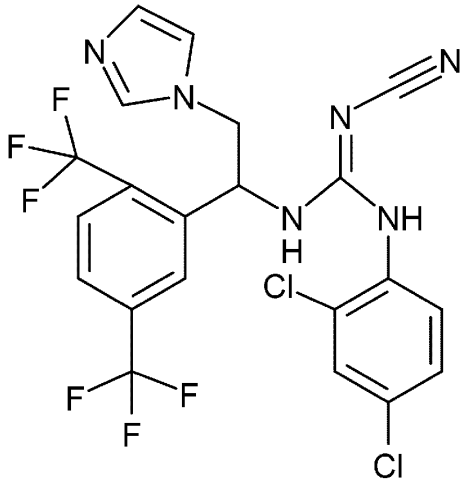
5



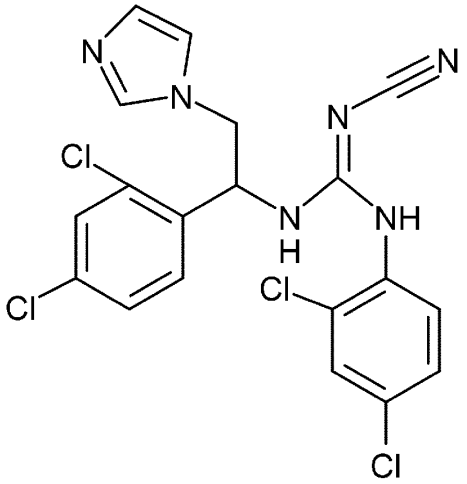
EC_{50} F_1F_0 ATP hydrolase = 0.082 ± 0.03 (μM)
EC_{50} F_1F_0 ATP synthesis > 100 (μM)
EC_{50} Ratio >1,220



EC_{50} F_1F_0 ATP hydrolase = 2.41 (μM)
EC_{50} F_1F_0 ATP synthesis > 100 (μM)
EC_{50} Ratio >41.5



EC_{50} F_1F_0 ATP hydrolase = 0.71 ± 0.34 (µM)
EC_{50} F_1F_0 ATP synthesis > 100 (µM)
EC_{50} Ratio >141

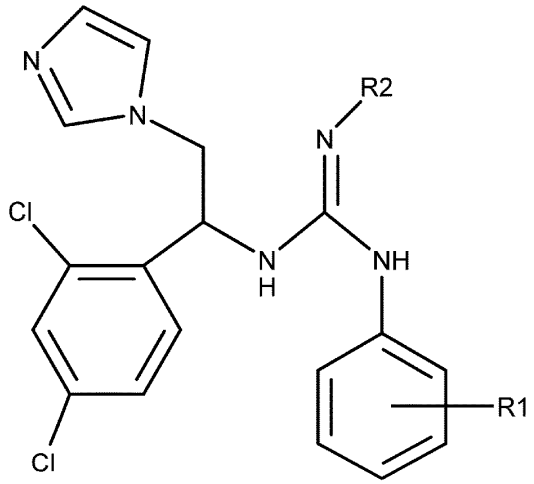


EC_{50} F_1F_0 ATP hydrolase = 0.60 ± 0.16 (µM)
EC_{50} F_1F_0 ATP synthesis > 100 (µM)
EC_{50} Ratio >167

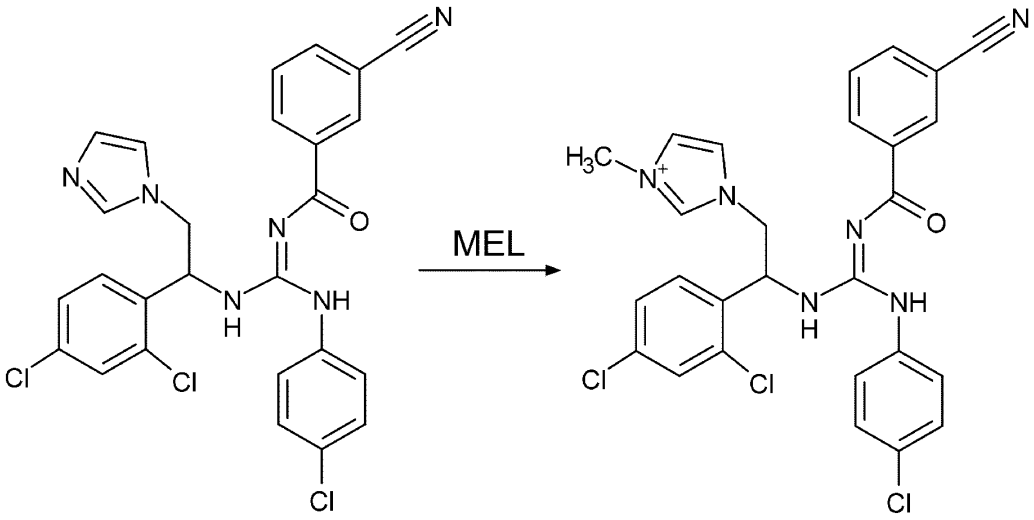
Further examples [5]:

For all: **EC_{50} F_1F_0 ATP synthesis > 100 µM**

R1	**R2**	**EC_{50} F_1F_0 ATP hydrolase (µM)**
4-Cl	CN	8.8
2-Cl	CN	2.23
2,3-Cl_2	CN	2.49 ± 0.72
3-CL	CN	9.17
4-Cl	C(=O)4-CN-Ph	0.28
4-Cl	C(=O)Et	2.27



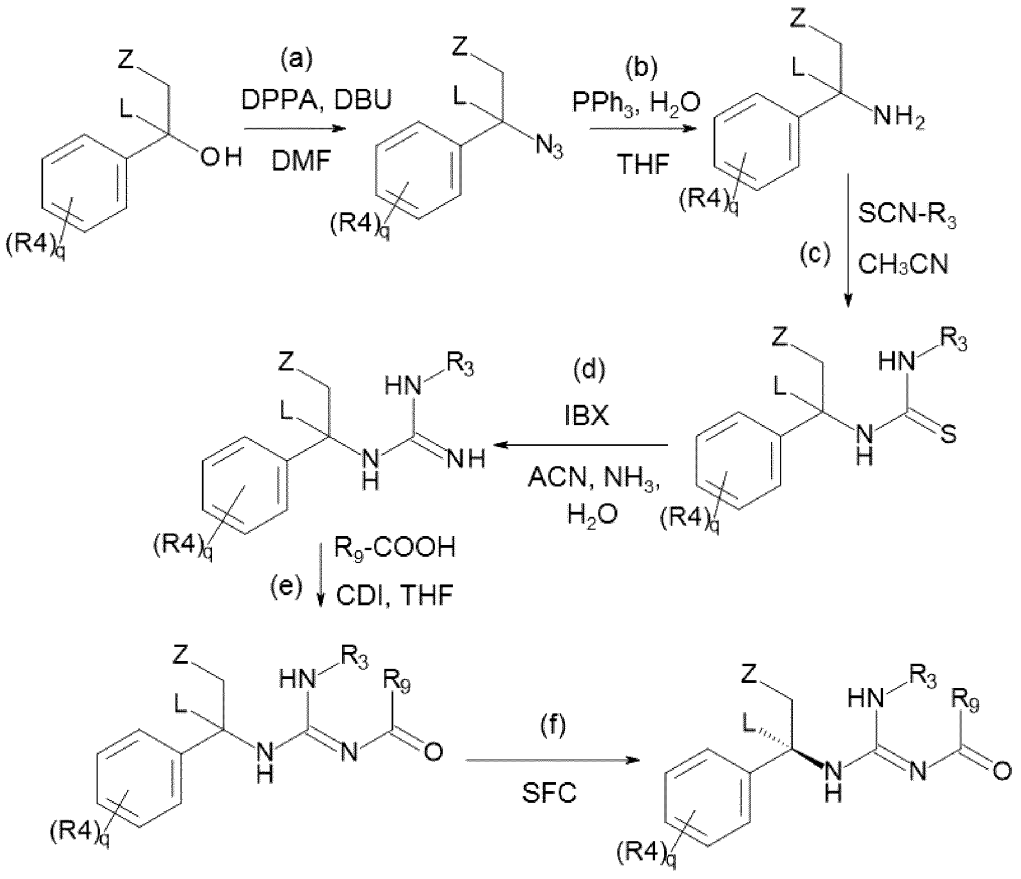
Further example, with synthesis step, effectively without a protonable element in its imidazole, which diminishes the molecule's ability to uncouple the proton motive force:


N
N
N
O
N
H
NH
Cl
Cl
Cl
MEL
H3C
N+
N
N
O
N
H
NH
Cl
Cl
Cl
N

GENERAL COMPOUND SYNTHESIS

A general synthetic route applicable to some compounds of the invention is set out in *Scheme 1* below.

Scheme 1



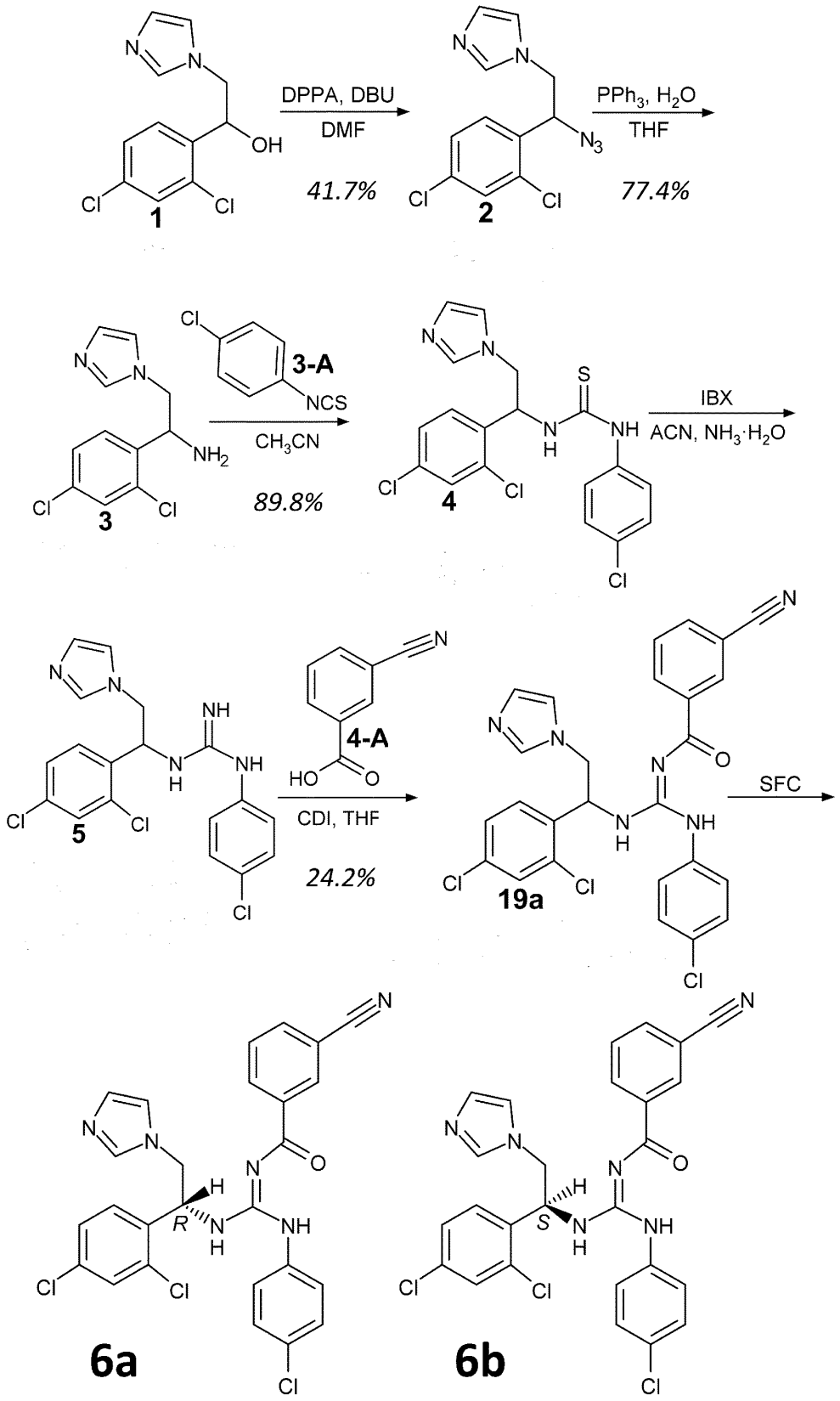
The person skilled in the art is able to make modifications to this general synthetic route, based on the common general knowledge, the chemical reaction literature, and/or the content of prior art disclosures cited herein, in order to synthesise compounds of the invention where necessary.

SPECIFIC COMPOUND SYNTHESIS

Racemate 19a [5] was synthesised by the following synthesis route, *Scheme 2*, and separated into component stereoisomers using superfluid chromatography (SFC). Starting reagents for this synthesis were sourced commercially using the LabNetwork (www.labnetwork.com), which is a website that permits one to search for chemical suppliers for inputted

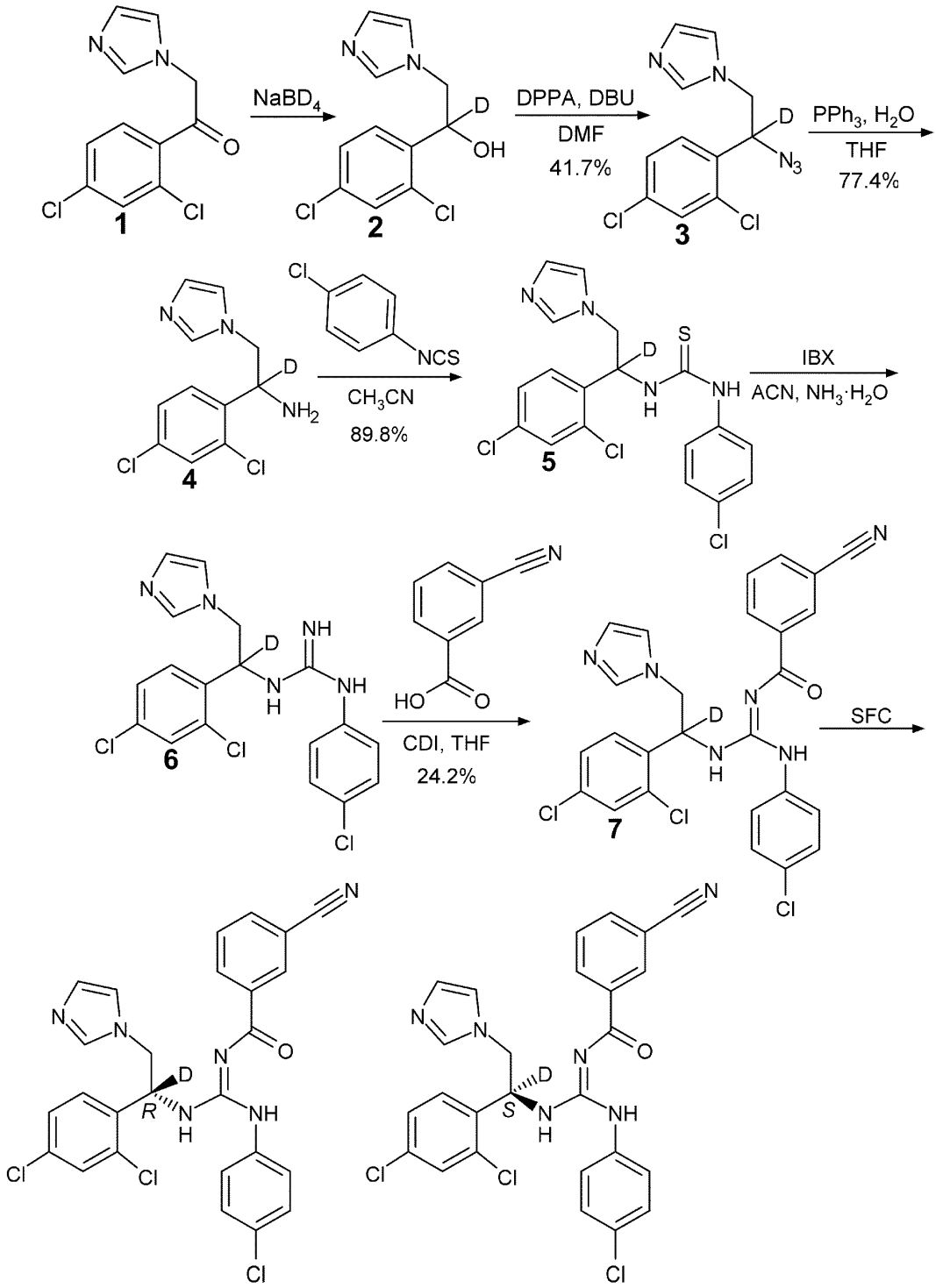
structures/chemical names e.g. there are numerous suppliers listed on LabNetwork for the starting compound, Compound 1.

Scheme 2


DPPA, DBU
DMF
41.7%
PPh3, H2O
THF
77.4%
1
2
3-A
NCS
CH3CN
89.8%
3
4
IBX
ACN, NH3·H2O
4-A
CDI, THF
24.2%
5
19a
SFC
6a
6b

The reaction scheme below, *Scheme 3*, is modified from that presented above, in order to produce a deuterated analogue, with deuterium in place of hydrogen on the chiral carbon. The scheme is provided for the purpose of illustrating the invention, and should not be regarded in any manner as limiting the scope or the spirit of the invention. This illustrating, not limiting, feature applies to all the compound synthesis schemes of this disclosure. The starting compound in the scheme below, Compound 1, is available from multiple suppliers listed on LabNetwork (e.g. Manchester Organics Ltd., UK).

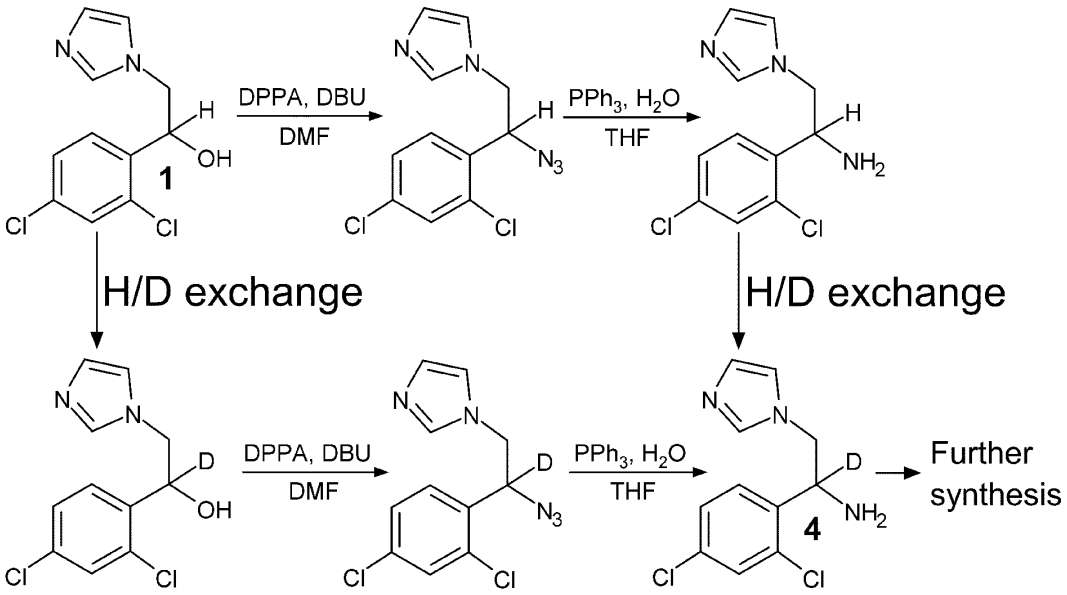
Scheme 3



Compound 4 in *Scheme 3* is of the form of Compound 1, the starting compound, in the molecule synthesis embodiments of [P1] (presented in its "Process of Preparation" section), BUT with the exception that is deuterated on its chiral carbon. This deuterated form can be

substituted into the synthesis schemes described in [P1] to produce deuterated molecules, with deuterium on their chiral carbon, which are componentry to the present invention, and in a non-limiting embodiment, one of more of these new compositions of matter are used as anti-cancer medicines. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods. Further methods to synthesize Compound 4, of *Scheme 3* above, are given below in *Scheme 4*.

Scheme 4



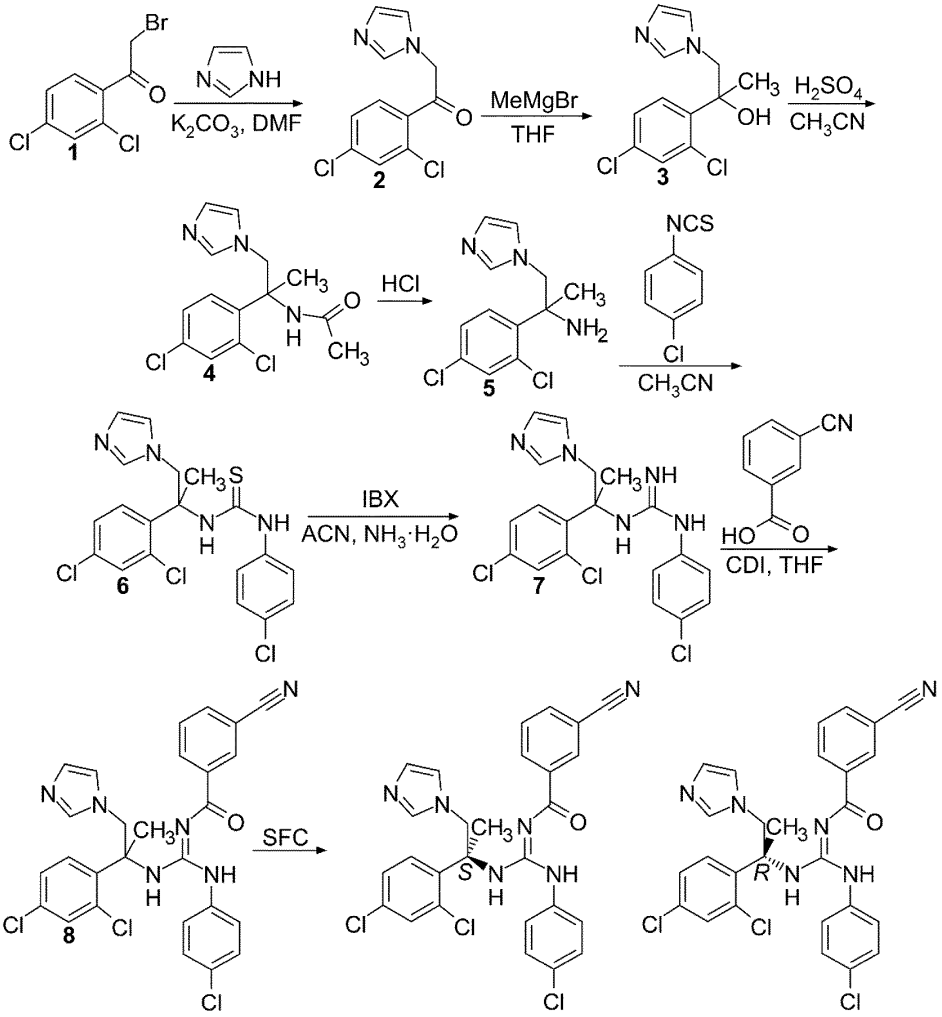
Compound 1 in *Scheme 4* is available from multiple suppliers listed on LabNetwork (e.g. Apollo Scientific Ltd., Stockport, UK). Conducting *Scheme 4*, the aim is to obtain a higher degree of deuterium incorporation on the chiral carbon than natural abundance: for Compound 4 ultimately, and for Compound 1 first if the lower arm of the synthesis route is used. In both cases, the greater the deuterium incorporation, the better. Deuterium incorporation at other positions of each molecule is permissible and within the scope of the invention, as is elevated deuterium incorporation only at the chiral carbon. Reactions described in [L, H, G, K, M, J1, J2, J3, I, F, S] deuterate (herein defined as replace hydrogen with deuterium) the α-carbon to a secondary alcohol and so the chiral carbon of Compound 1. Reactions described in [A, B, P, E1, E2, F] deuterate the α-carbon to primary amines, thence

can deuterate the chiral carbon of Compound 4. Reactions described in [N] deuterate sp3 carbons, thence can deuterate the chiral carbon of Compounds 1 and 4. Reactions described in [O1, O2] can deuterate the β-carbon to phenyl groups and so can deuterate the chiral carbon of Compounds 1 and 4. Reactions described in [R1, R2, Q1, Q2] can deuterate widely, upon aromatic and alkyl molecular components, and thence can deuterate the chiral carbon of Compounds 1 and 4. Reactions described in [D] deuterate the β-carbon to tertiary amines, thence can deuterate the chiral carbon of Compounds 1 and 4. The teaching of [D] is especially preferred for use in the present context. Whichever option(s) is chosen, solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. The level of deuteration can be modulated by modulating the reaction time: greater deuterium incorporation by longer reaction time. One can do multiple cycles of one or more of these reactions until the desired level of deuterium incorporation occurs, monitored by ^{1}H and/or ^{2}H NMR (e.g. deuterium incorporation quantified by decrease of ^{1}H NMR integral intensity at specified position(s) compared to starting material) and/or mass spectrometry. Some of the reactions cited herein use commercially available catalysts e.g. 10% Pd/C catalyst [O1, O2, Q1, R1, R2], and/or Pt/C catalyst [R1, R2, Q1, Q2], or shvo catalyst [D], or $RuCl_2(P(Ph)_3)_3$ (CAS no: 15529-49-4) [A], or 5% Ru/C catalyst [K], or Ru-macho catalyst [G, M], all available from Sigma-Aldrich. Others teach, or cite literature teaching, how to prepare the catalyst to use. The aforementioned list of synthesis options, to make Compound 4 in *Scheme 4*, is not exhaustive. A person skilled in the art will know how to find further options. For example using computational tools, including artificial intelligence (AI, non-limiting e.g. [AI1, AI2, AI3]), to search the chemical reaction literature/databases, e.g. (non-limiting) the Reaxys or CAS databases, and their own skill in the art to find, plan and prioritise synthesis routes. 2-(1H-imidazol-1-yl)-1-phenylethanamine is commercially available on LabNetwork and can be deuterated at its chiral carbon (and optionally at other positions also) by one or more of the aforementioned methods disclosed herein for deuterating the chiral carbon of 1-(2,4-dichlorophenyl)-2-(imidazol-1-yl)ethanamine. Before or after deuteration, its phenyl group can be (non-limiting) alkylated, halogenated, or CF_3 added (non-limiting example: at the IUPAC 2,5 positions), at desired position(s) by methods well known to those of the art. Then it can be a starting compound in the synthesis schemes of [P1] and used to produce deuterated compositions of matter that are componentry to this invention, which in non-limiting embodiments, are used singly or in a combination in anti-cancer therapy, in an animal or human. Alternatively, the final products, rather than starting materials, of the synthesis schemes of [P1] can be deuterated, to produce

deuterated compositions of matter that are componentry to this invention, which in non-limiting embodiments, are used singly or in a combination in anti-cancer therapy, in an animal or human. Reactions described in [A, B, E1, E2, F] can deuterate the α-carbon to secondary amines, and thence the chiral carbon of Compound 19a, in *Scheme 2* presented previously, and the chiral carbon of other molecules with the scaffold of [P1], as presented in the abstract of [P1]. These compounds can also be deuterated at their chiral carbon, and in further embodiments at further or other position(s), by reactions described in [N], which deuterate sp3 carbons. And/or by reactions described in [O1, O2], which can deuterate the β-carbon to phenyl groups. And/or by reactions described in [R1, R2, Q1, Q2], which deuterate aromatic and alkyl molecular components. And/or by reactions described in [D], which can deuterate the β-carbon to tertiary amines. Some of these reactions are stereoretentive [F, N, E1, E2] and thus can be used, optionally, *after* stereoisomer enrichment. Others are not, e.g. [Q1, Q2], and so should be used *before* any enantiomeric excess (ee) enrichment step. All patents and papers cited by the present disclosure, and their supplementary materials, are herein incorporated by reference, and are componentry, to the present disclosure.

The reaction scheme below, *Scheme 5*, differs from *Scheme 2* in order to produce methylated analogues, with methyl in place of hydrogen on the chiral carbon.

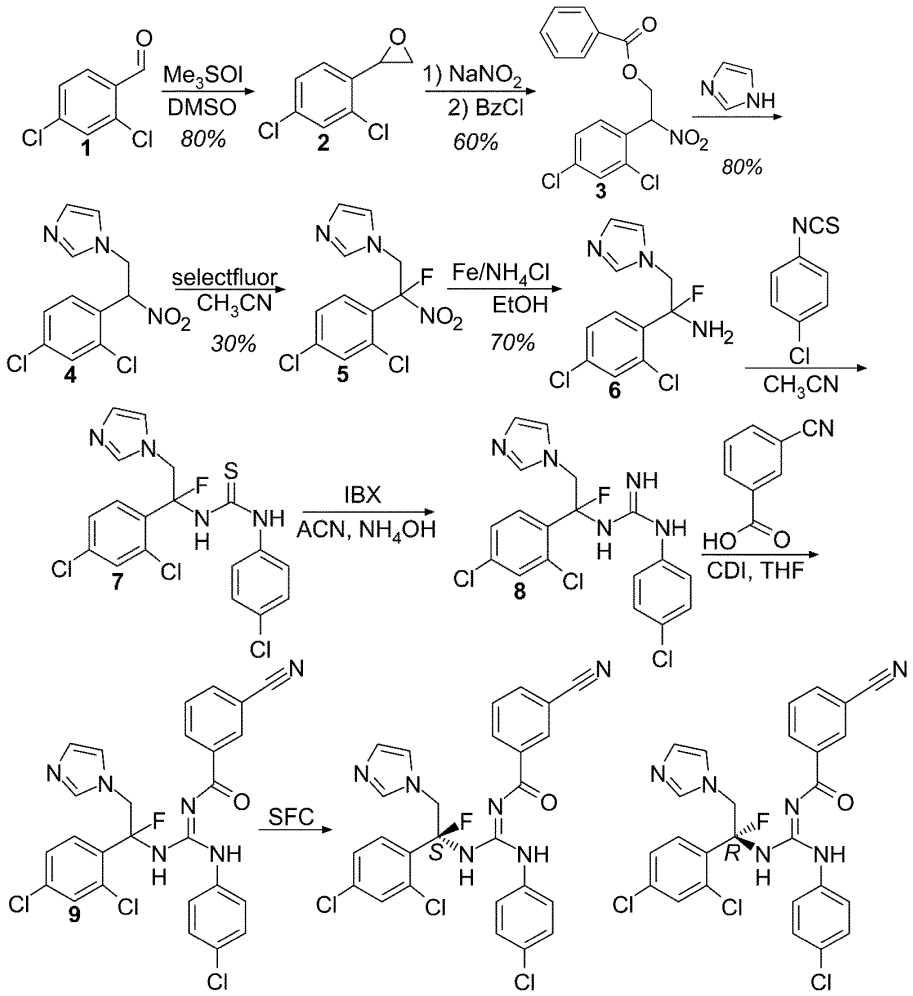
Scheme 5



Compound 5 in *Scheme 5* is of the form of Compound 1, the starting compound, in the molecule synthesis embodiments of [P1] (presented in its "Process of Preparation" section), BUT with the exception that is methylated on its chiral carbon. This methylated form can be substituted into the synthesis schemes described in [P1] to produce methylated molecules, with methyl on their chiral carbon, that are componentry to the present invention, and in a non-limiting embodiment, one of more of these new compositions of matter are used as anti-cancer medicines. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods.

The reaction scheme below, *Scheme 6*, differs from *Scheme 2* in order to produce fluorinated analogues, with fluorine in place of hydrogen on the chiral carbon.

Scheme 6



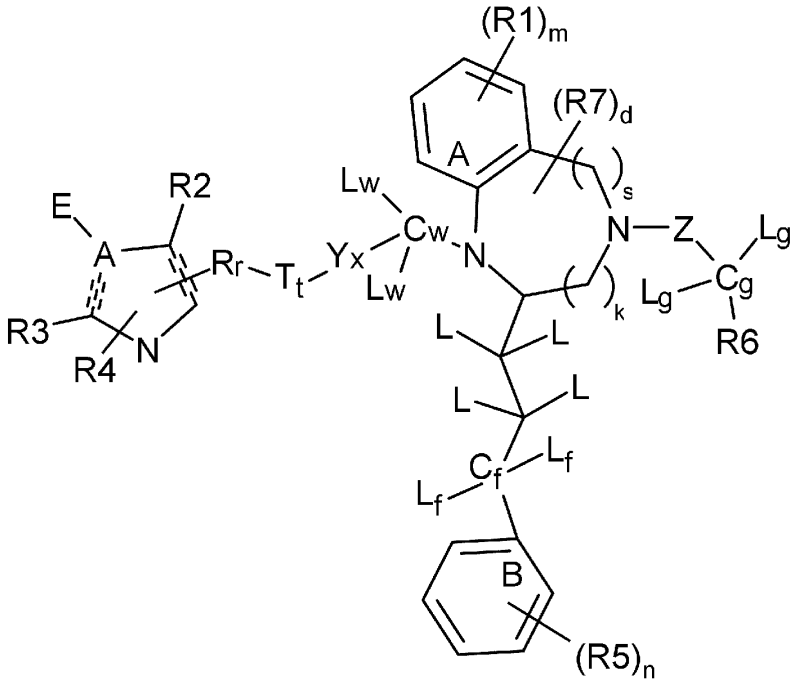
Compound 6 in *Scheme 6* is of the form of Compound 1, the starting compound, in the molecule synthesis embodiments of [P1] (presented in its "Process of Preparation" section), BUT with the exception that is fluorinated on its chiral carbon. This fluorinated form can be substituted into the synthesis schemes described in [P1] to produce fluorinated molecules, with fluorine on their chiral carbon, that are componentry to the present invention, and in a non-limiting embodiment, one of more of these new compositions of matter are used as anti-cancer medicines. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods.

EXAMPLE (II)

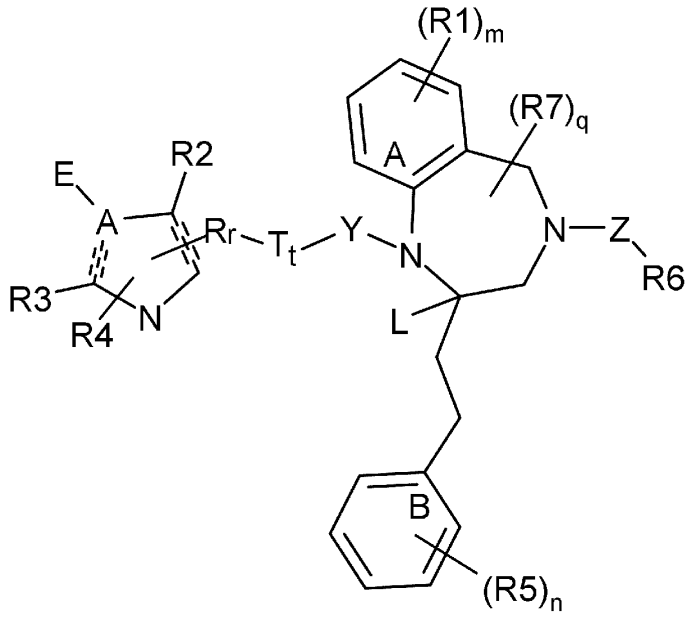
Summary of Formula (II)

This invention embodiment relates to compounds having the formula:

Formula (II)



including



or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, wherein:

L is independently at each point of use alkyl, or substituted alkyl, or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy, or halogen, or haloalkyl, or haloalkoxy, or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.), for example hydrogen, or deuterium, or fluorine;

A is nitrogen (N), or N^+, or carbon;

E is absent, or alkyl, or substituted alkyl, or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.), for example hydrogen, or deuterium or fluorine;

C is carbon;

x, w, f, g are independently selected to be 0, 1, 2 or 3;

d is a selected integer between 0 and 7;

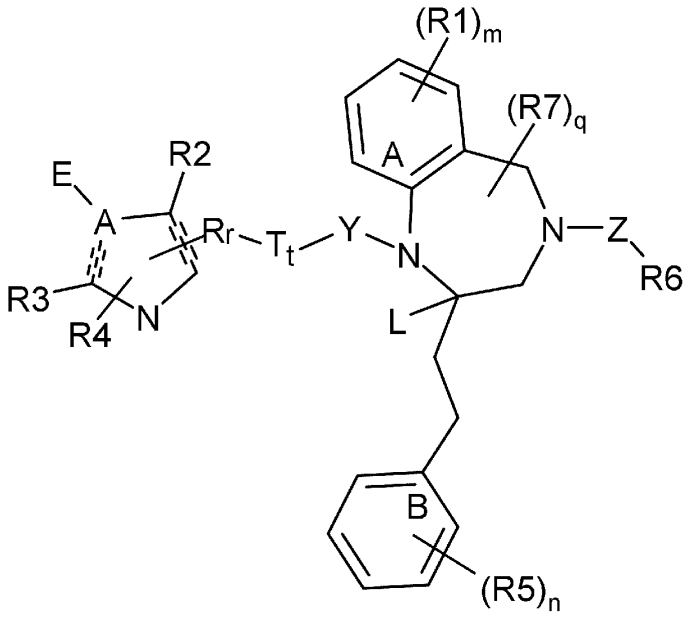
k and s are independently selected to be 1, 2, or 3;

The 5-sided ring structure is attached by any one of its available ring atoms, and none, one or two of its bonds can be a double bond, for example at locations shown by the “single or double bond” symbol;

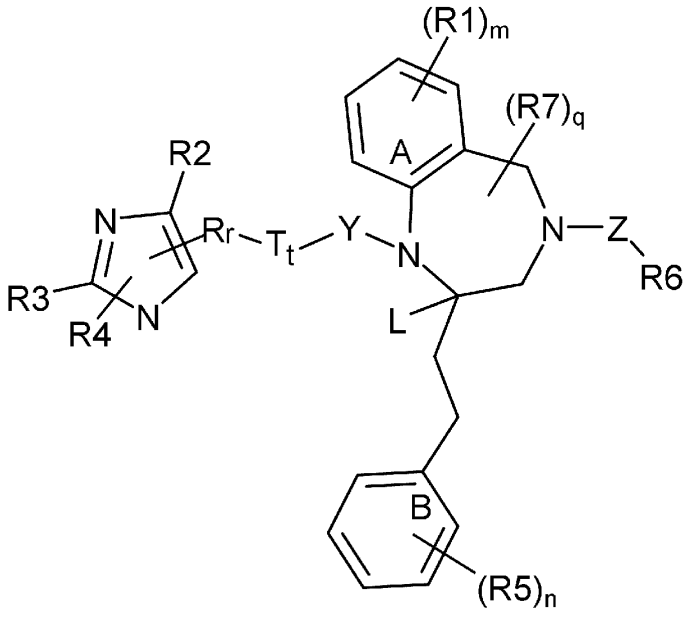
R_1 and R_5 are attached to any available carbon atom of phenyl rings A and B, respectively, and at each occurrence are independently selected from hydrogen, deuterium, alkyl, substituted alkyl, trifluoromethoxy, halogen, cyano, nitro, OR_8, NR_8R_9, $C(=O)R_8$, CO_2R_8, $C(=O)NR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$,
$S(O)_oR_9$, $NR_8SO_2R_9$, $SO_2NR_8R_9$, cycloalkyl, heterocycle, aryl, and heteroaryl, and/or two of R_1 and/or two of R_5 join together to form a fused benzo ring;
R_2, R_3 and R_4 are independently selected from E (defined earlier), hydrogen, or deuterium, or alkyl, or deuterated alkyl, and substituted alkyl, or one of R_2, R_3 and R_4 is a bond to R, T or Y and the other of R_2, R_3 and R_4 are independently selected from hydrogen, alkyl, and substituted alkyl;
Z and Y are independently selected from C(=O),—CO_2—, —SO_2—, —CH_2—, —$CH_2C(=O)$—, and —C(=O)C(=O)—, or Z may be absent;
R and T are selected from —CH_2—, —C(=O)—, and —$CH[(CH_2)_p(Q)]$—, wherein Q is $NR_{10}R_{11}$, OR_{10} or CN;
R_6 is selected from thienyl, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, heterocyclo, heteroaryl and aryl optionally substituted with a lower aliphatic group or one or more functional groups selected independently from the group consisting of –NH_2, -OH, phenyl, halogen, (C_1-C_4)alkoxy or -$NHCOCH_3$;
R_7 is selected from L (defined earlier), hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aminoalkyl, halogen, cyano, nitro, keto (=0), hydroxy, alkoxy, alkylthio, C(=O)H, acyl, CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamidyl, cycloalkyl, heterocycle, aryl, and heteroaryl;
R_8 and R_9 are independently selected from hydrogen, alkyl, substituted alkyl, C_{2-4} alkenyl optionally substituted, cycloalkyl, heterocycle, aryl, and heteroaryl, or R_8 and R_9 taken together to form a heterocycle or heteroaryl, except R_9 is not hydrogen when attached to a sulfonyl group as in SO_2R_9;
R_{10} and R_{11} are independently selected from hydrogen, alkyl, and substituted alkyl;
m and n are independently selected from 0, 1, 2 and 3
o, p and q are independently 0, 1 or 2; and
r and t are 0 or 1.

Preferred compounds of Formula (II)

Preferred methods are to use, and preferred compounds are, compounds with the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



including



wherein:

L is hydrogen, or deuterium, or methyl, or fluorine;

A is nitrogen (N), or N^+, or carbon;

E is absent, or alkyl, or substituted alkyl, or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.), for example hydrogen or deuterium;

R_1 and R_5 are attached to any available carbon atom of phenyl ring A and phenyl ring B, respectively, and at each occurrence are independently selected from hydrogen, deuterium, alkyl, aralkyl, aminoalkyl, halogen, cyano, nitro, hydroxy, alkoxy, trifluoromethoxy, alkylthio, NH_2, NH(alkyl), $N(alkyl)_2$, C(=O)H, acyl, CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide,

cycloalkyl, heterocycle, aryl, and heteroaryl, and/or two of R_1 and/or two of R_5 join together to form a fused benzo ring;

R_2, R_3 and R_4 are independently selected from hydrogen and alkyl;

Z is —CO_2—, —SO_2—, or is absent;

Y, R and T are selected from —CH_2— and —C(=O) —,

R_6 is selected from:

C_{1-4}alkyl or C_{1-4}alkenyl optionally substituted with up to three of halogen, aryl and CO_2C_{1-6}alkyl;

phenyl optionally substituted with up to three R_{12} and/or having fused thereto a benzo-ring or a five to six membered heteroaryl;

heteroaryl selected from thiophenyl, imidazolyl, pyrazolyl, and isoxazolyl wherein said heteroaryl is optionally substituted with up to two R_{12},

R_7 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aminoalkyl, halogen, cyano, nitro, keto (=0), hydroxy, alkoxy, alkylthio, C(=O)H, acyl, CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide, cycloalkyl, heterocycle, aryl, and heteroaryl;

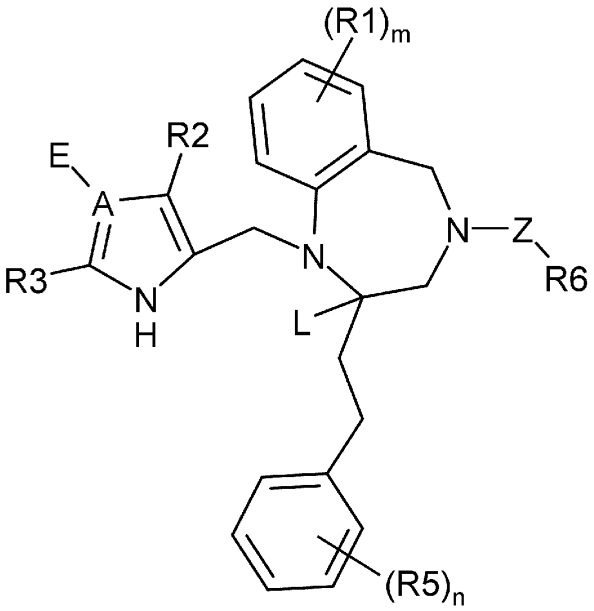
R_{12} at each occurrence is independently selected from each other R_{12} from the group consisting of C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, alkoxy, NHC(=O)alkyl, —CO_2alkyl, —SO_2phenyl, aryl, five to six membered monocyclic heteroaryl, and phenyloxy or benzyloxy in turn optionally substituted with halogen, hydroxyl, C_{1-4}alkyl, and/or O(C_{1-4}alkyl);

m and n are independently selected from 0, 1, 2 or 3; and

q is 0, 1 or 2; and

r and t are 0 or 1.

More preferred are compounds having the following formula, or pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof,



wherein

R_1 and R_5 are attached to any available carbon atom of phenyl ring A and phenyl ring B, respectively, and at each occurrence are independently selected from alkyl, halogen, cyano, hydroxy, alkoxy, NH_2, NH(alkyl), $N(alkyl)_2$, C(=O)H, acyl, CO_2H, alkoxycarbonyl, and/or two of R_1 and/or two of R_5 join together to form a fused benzo ring;

R_2, R_3 and R_4 are independently selected from hydrogen and lower alkyl;

Z is $—CO_2—$, $—SO_2—$, or is absent;

R_6 is selected from:

C_{1-4}alkyl or C_{1-4}alkenyl optionally substituted with up to three of halogen, aryl and CO_2C_{1-6}alkyl;

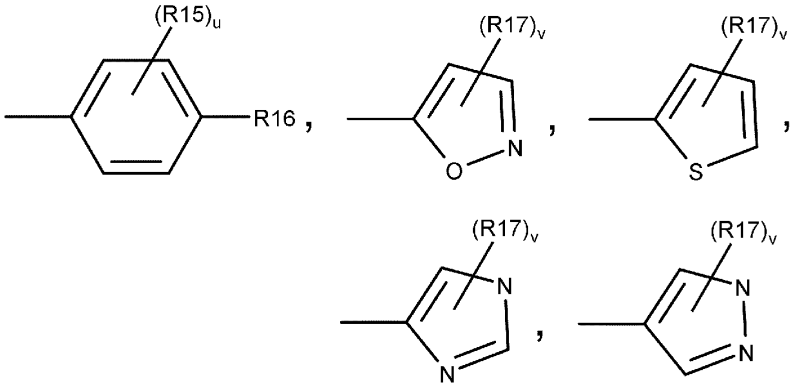
phenyl optionally substituted with up to three R_{12} and/or having fused thereto a benzo ring or a five to six membered heteroaryl;

heteroaryl selected from thiophenyl, imidazolyl, pyrazolyl, and isoxazolyl, wherein said heteroaryl is optionally substituted with up to two R_{12},

R_{12} at each occurrence is independently selected from each other R_{12} from the group consisting of C_{1-6} alkyl, halogen, nitro, cyano, hydroxy, alkoxy, NHC(=O)alkyl, $—CO_2$alkyl, $—SO_2$phenyl, aryl, five to six membered monocyclic heteroaryl, and phenyloxy or benzyloxy in turn optionally substituted with halogen, hydroxyl, C_{1-4} alkyl, and/or $O(C_{1-4}$ alkyl); and

m and n are independently selected from 0, 1, or 2.

Even more preferred are compounds as immediately defined above wherein R_6 is selected from C_{1-4}alkyl, trifluoromethyl, benzyl, C_{2-3}alkenyl substituted with phenyl,



wherein:

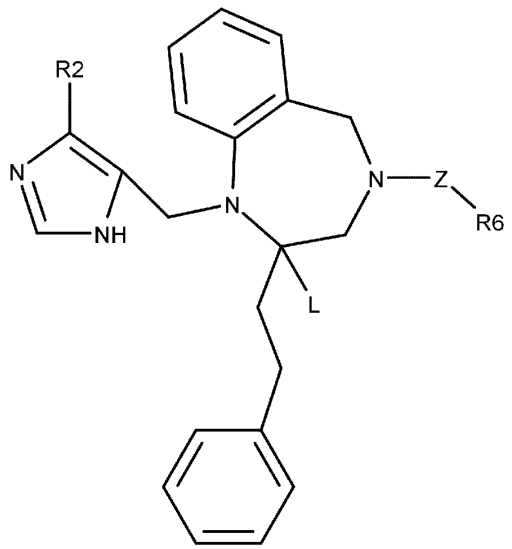
R_{15} is halogen, alkyl, nitro, cyano, hydroxy, alkoxy, NHC(=O)alkyl, and/or two R_{15} groups are taken together to form a fused benzo ring or a five to six membered heteroaryl;

R_{16} is selected from hydrogen, deuterium, halogen, alkyl, nitro, cyano, hydroxy, alkoxy, NHC(=O)alkyl, and phenyloxy or benzyloxy in turn optionally substituted with 1 to 3 of hydrogen, deuterium, halogen, cyano, and C_{1-4}alkoxy;

R_{17} is selected from alkyl, alkoxy, CO_2C_{1-6}alkyl, and SO_2phenyl;

and u and v are independently 0, 1 or 2.

Most preferred compounds of Formula (II) are those having the formula:



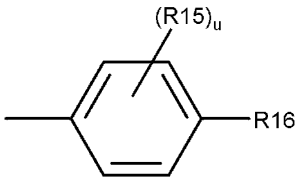
wherein

L is deuterium;

R_2 is hydrogen or CH_3;

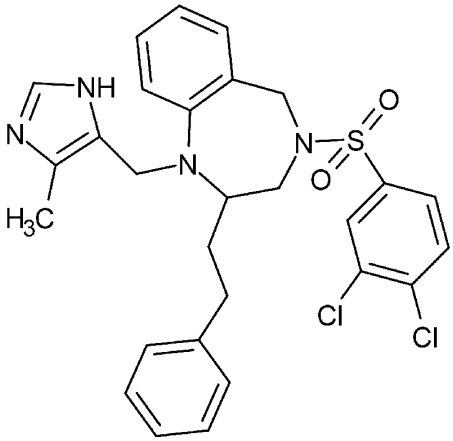
Z is —CO_2—, —SO_2—, or is absent; and

R_6 is selected from the groups recited immediately above, most preferably

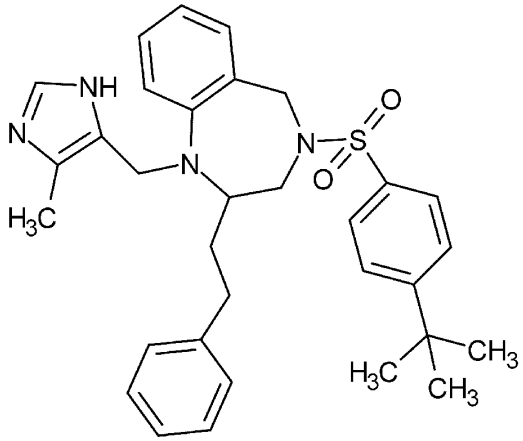


Example embodiments of Formula (II)

Compounds from [8, 12], selected as specific anti-cancer therapeutics by the invention of this disclosure, selected because they inhibit the reverse, more than the forward, mode of ATP synthase. EC_{50} and IC_{50} used interchangeably. EC_{50} values for F_1F_0 ATP hydrolysis, and F_1F_0 ATP synthesis, in NADH-linked and NADPH-linked sub-mitochondrial (SMP) assays respectively, sourced from [8], are presented. [8] refer to these EC_{50} values as IC_{50} values for inhibiting F_1F_0 ATP hydrolase (reverse mode) and F_1F_0 ATP synthase (forward mode). However, this in incorrect. Because, as identified by the invention of this disclosure, explained herein, although these molecules inhibit F_1F_0 ATP hydrolase, their reducing of F_1F_0 ATP synthesis is not (predominantly) because of inhibiting F_1F_0 ATP synthase, but by uncoupling.



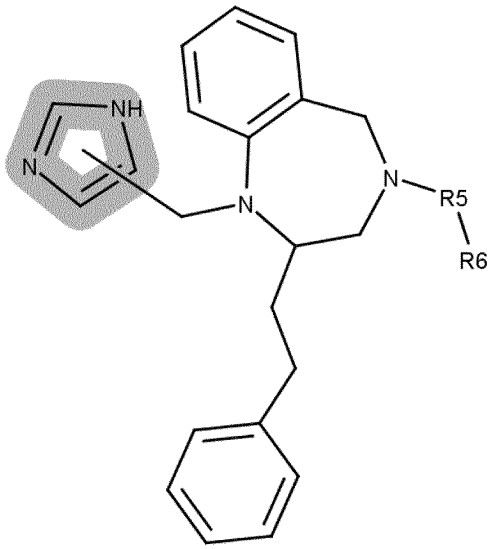
EC_{50} F_1F_0 ATP hydrolase = 0.022 (μM)
EC_{50} F_1F_0 ATP synthesis > 30 (μM)
EC_{50} Ratio >1,364



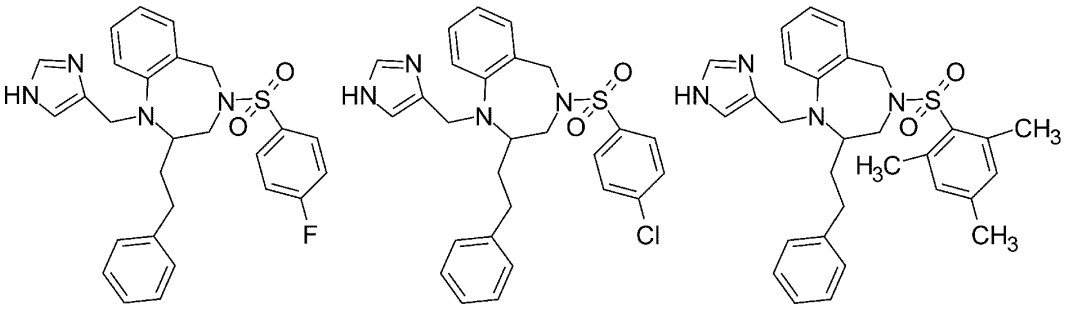
EC_{50} F_1F_0 ATP hydrolase = 0.077 (μM)
EC_{50} F_1F_0 ATP synthesis > 30 (μM)
EC_{50} Ratio >390

For all compounds: **EC_{50} F_1F_0 ATP synthesis > 30 μM**

R6	R5	Imidazole	EC_{50} F_1F_0 ATP hydrolase (μM)
4-F-Ph	SO_2	5-yl	0.221
Ph	SO_2	5-yl	0.282
4-OH-Ph	SO_2	5-yl	0.667
4-OMe-Ph	SO_2	5-yl	0.077
2,5-di-Cl-Ph	SO_2	5-yl	0.158
4-(AcNH)-Ph	SO_2	5-yl	2.981
4-CN-Ph	SO_2	5-yl	0.255
2-Cl-4-CN-Ph	SO_2	5-yl	0.939
3-NO_2-Ph	SO_2	5-yl	0.423
Naphth-1-yl	SO_2	5-yl	0.338
Thiophen-2-yl	SO_2	5-yl	0.636
Benzofurazan-7-yl	SO_2	5-yl	1.777
Quinolin-8-yl	SO_2	5-yl	2.935
Bn	SO_2	5-yl	2.405
CF_3	SO_2	5-yl	0.077
4-*t*-Bu-Ph	SO_2	5-yl	0.008
4-*t*-Bu-Ph	CH_2	5-yl	2.138
4-*t*-Bu-Ph	CH_2	4-Me-5-yl	2.352
4-*t*-Bu-Ph	SO_2	2-yl	>10
4-F-Ph	SO_2	2-Me-5-yl	9.623
4-F-Ph	SO_2	4-Me-5-yl	0.151

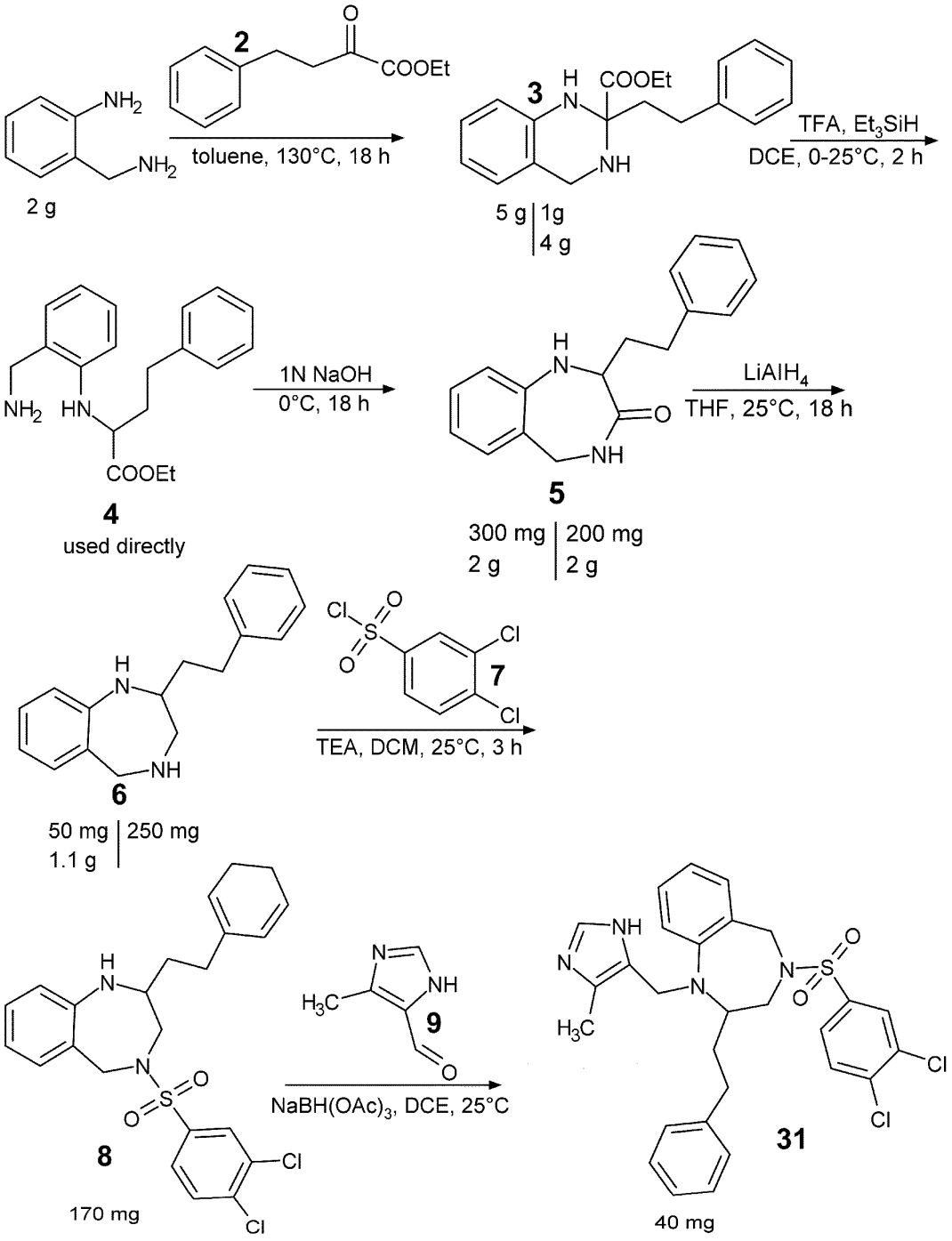


Further examples [12],



Scheme IIa is route used for synthesizing Compound 31 [8], starting reagents were sourced commercially using the LabNetwork (www.labnetwork.com).

Scheme IIa



Compound 31, in *Scheme IIa*, can be deuterated at its chiral carbon, and in further embodiments at further or other position(s), by reactions described in [N], which deuterate sp3 carbons. And/or by reactions described in [R1, R2, Q1, Q2], which deuterate aromatic and alkyl molecular components. And/or by reactions described in [D], which deuterate α and

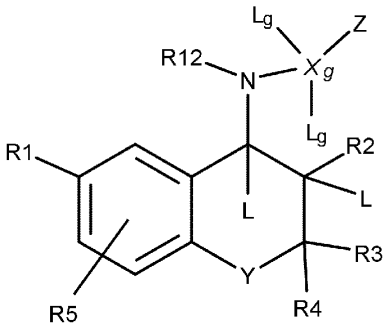
β-carbons to tertiary amines. And/or by reactions described in [F, E1, E2, Ex1], which deuterate α carbons to tertiary amines. Alternatively, to produce a Compound 31 isotopologue, deuterated on its chiral carbon, and in further embodiments at further or other position(s), an intermediate in Compound 31 synthesis, presented in *Scheme IIa*, can be deuterated. For (non-limiting) example, Compound 6 in *Scheme IIa* can be deuterated by reactions described in [A, B, E1, E2, F], which can deuterate the α-carbon to secondary amines. And/or by reactions described in [N], which deuterate sp3 carbons. And/or by reactions described in [R1, R2, Q1, Q2], which deuterate aromatic and alkyl molecular components. A deuterated Compound 6 can be inputted into synthesis schemes of [P2], in place of Compound 10 in Scheme III in the "Process of Preparation" section of [P2], to make deuterated isotopologues with the scaffold of [P2]. These are componentry to the present invention as new compositions of matter, and in non-limiting embodiments are used singly or in combination, optionally in co-therapy with an FDA and/or EMA approved medicine(s) and/or treatment(s), for example a licensed cancer treatment, as anti-cancer therapeutics. Throughout this disclosure, deuteration methods conveyed are illustrative rather than limiting. All stereoisomers of all the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form.

EXAMPLE (III)

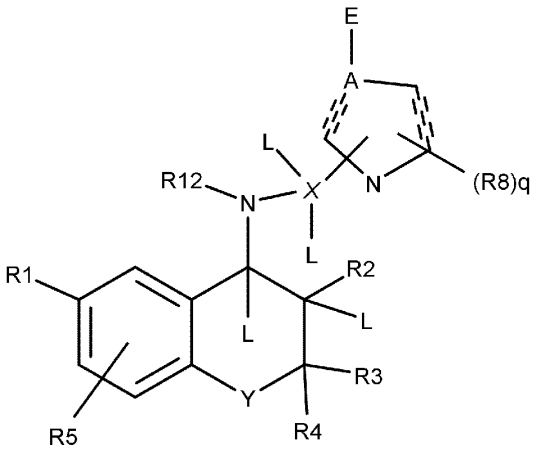
Summary of Formula (III)

This invention embodiment relates to compounds having the following formula:

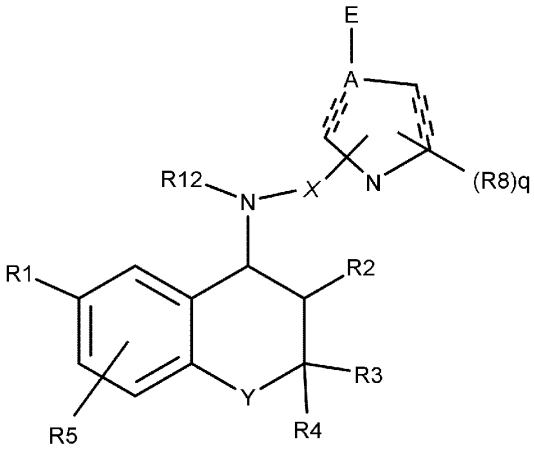
Formula (III)



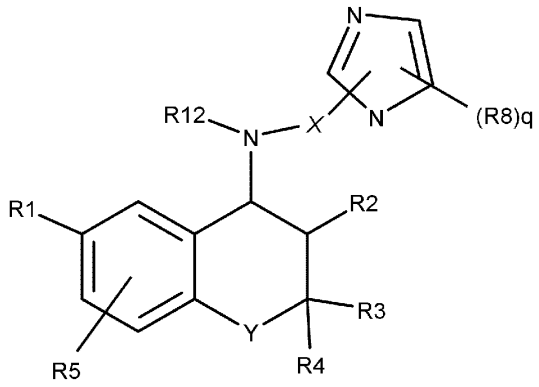
including



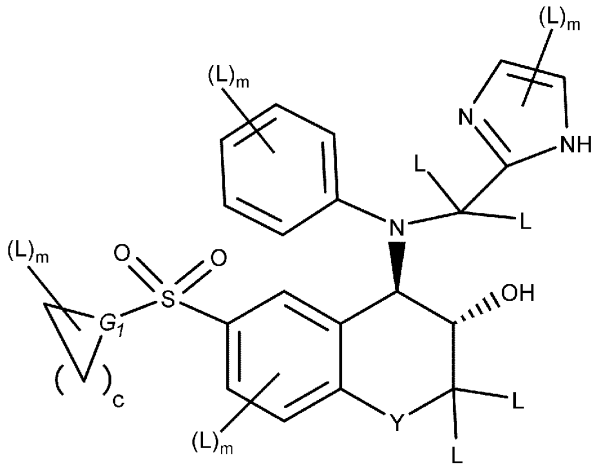
including



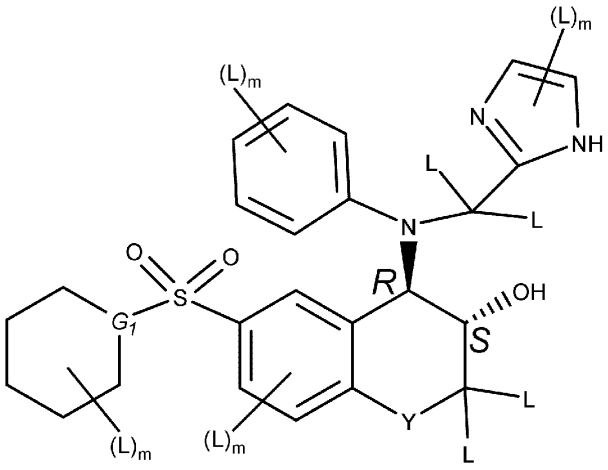
including



including



including



5

or their enantiomers, diastereomers, pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, wherein:

Optionally, one or more places have deuterium in place of hydrogen, at an artificially high level of deuterium incorporation, in excess of the naturally occuring abundance;

Optionally, one or more places have fluorine, or other halogen, or methyl, or alkyl, or substituted alkyl, in place of hydrogen;

Z is heteroaryl;

g is selected from 0, 1, 2, 3, 4;

L is independently at each point of its use hydrogen, alkyl, or substituted alkyl (non-limiting example: CF_3), or deuterated alkyl (non-limiting example: CD_3), or aminoalkyl, or thioalkyl, or alkoxy, or halogen, or haloalkyl, or haloalkoxy or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.);

G_1 is N or C;

c is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9;

m is independently at each point of use selected from 0, 1, 2, 3, 4, 5, 6, as valence permits;

R2 is hydrogen, L (defined earlier), hydroxy, or —OC(O)R14;

R14 is hydrogen, alkyl, haloalkyl, aryl, arylalkyl, cycloalkyl or (cycloalkyl)alkyl;

R3 and R4 are each independently hydrogen, or L (defined earlier), or CF_3, or chlorine or other halogen, or alkyl, or substituted alkyl, or deuterated alkyl, or arylalkyl, or R3 and R4 taken together with the carbon atom to which they are attached form a 3- to 7-membered carbocyclic ring;

R5 is independently at each point of use hydrogen, L (defined earlier), alkyl, halogen, heterocyclo, nitrile, haloalkyl or aryl;

R12 is selected from hydrogen, aryl, heteroaryl, heterocyclo;

X is alkyl;

Y is a single bond, —CH2—, —C(O)—, —O—, —S— or —N(R14) —;

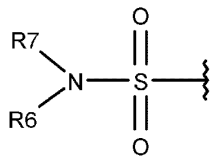
A is nitrogen (N), or N^+, or carbon;

E is absent, or alkyl, or substituted alkyl (non-limiting example: CF_3), or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.), for example hydrogen, or deuterium, or fluorine;

R8 is independently selected at each point of use from E (defined earlier), hydrogen, alkyl, halogen, carbamyl, carbamylC_{1-4}alkyl, substituted alkyl or two R8 groups join to form an optionally substituted fused phenyl ring;
q is 0, 1, 2, 3 or 4.

R1 is selected from L (defined earlier), hydrogen, deuterium, CN, SO_2-piperidine, SO_2-piperidine substituted with 0-10 of R5, R9, cyano, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkylene, substituted alkylene, alkynyl, substituted alkynyl, alkoxy, thioalkyl, aminoalkyl, carbamyl, sulfonyl, sulfonamide, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, haloalkyl, haloalkoxy, alkoxyalkyl, morpholinylalkyl, aryl, arylalkyl, heterocyclo, heteroaryl, (heterocyclo)alkyl, acyl, alkoxycarbonyl, substituted amino;
Most preferably R1 is smaller than 300 Daltons;

R9 is



;

R6 and R7 are independently hydrogen, L (defined earlier), R1 (provided R1 is not R9), alkyl, cycloalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, hydroxyalkyl substituted with a carboxylic ester or carboxylic acid, alkoxyalkyl, thioalkyl, (cycloalkyl)alkyl, morpholinylalkyl, heterocyclo or (heterocyclo)alkyl; or R6 and R7 taken together with the nitrogen atom to which they are attached form a 5- to 7-membered mono or bicyclic ring including fused rings such as
l-pyrrolidinyl, l-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 4-thiamorpholine dioxide, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl; or 1-piperazinyl, l-pyrrolidinyl, 1-piperidinyl or 1-azepinyl substituted with one or more L (defined earlier), alkyl, alkoxy, alkylthio, halo, trifluoromethyl, hydroxy, aryl, arylalkyl, —COOR14 or —CO-substituted amino;
or R5 and R6 taken together with the atoms to which they are attached form a 5- to 7-membered ring optionally substituted with aryl;

Encompassed by this invention are methods of administering a therapeutically effective amount of any compound(s) of [P6], or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, optionally in a pharmaceutical composition(s), optionally in co-therapy with another anti-cancer treatment(s), to treat/ameliorate/prevent/combat cancer in a subject. Especially preferred for this use are compounds of [P6] with 3*S*, 4*R* stereochemistry.

Preferred compounds of Formula (III)

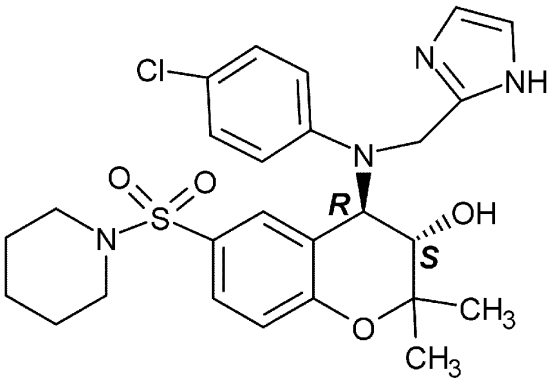
Preferred methods are to use, and preferred compounds are, compounds of Formula (III), their enantiomers, diastereomers, pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, in which:

Z is triazolyl optionally substituted with one to two R8 or imidazolyl optionally substituted with one to two R8 and/or having fused thereto a benzene ring in turn optionally substituted with one to two R8;
Y is oxygen;
R2 is hydroxyl;
R3 and R4 are methyl or chlorine;
R1 is R9;
G_1 is nitrogen;
R6 and R7 are alkyl; or R6 and R7 taken together with the nitrogen atom to which they are attached (G_1 = N) form a 6-membered ring;
X is alkyl;
R12 is aryl or heterocyclo;
A is N;
E is absent, or deuterium, or hydrogen;
R5 and R8 are hydrogen;
Stereochemistry is 3*S*, 4*R*;

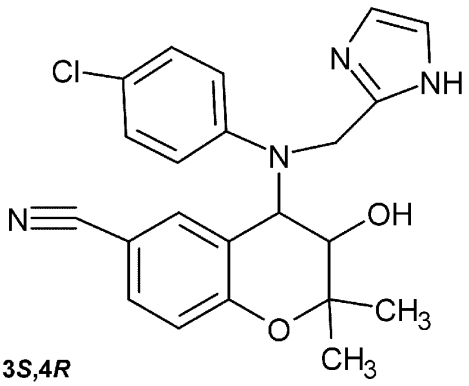
Example embodiments of Formula (III)

Immediately below, compounds from [7], selected as specific anti-cancer therapeutics by the invention of this disclosure. EC_{50} values for F_1F_0 ATP hydrolysis, and F_1F_0 ATP synthesis, in NADH-linked and NADPH-linked sub-mitochondrial (SMP) assays respectively. [7] refers to these EC_{50} values as IC_{50} values for inhibiting F_1F_0 ATP hydrolase (reverse mode) and F_1F_0 ATP synthase (forward mode). However, this in incorrect. Because, as identified by the

invention of this disclosure, explained herein, although these molecules inhibit F_1F_0 ATP hydrolase, their reducing of F_1F_0 ATP synthesis is not (predominantly) because of inhibiting F_1F_0 ATP synthase, but by uncoupling. The structure on the left is BMS-199264. It does not harm *ex vivo* rat heart at a concentration (10 μM [11]) that it exerts anti-cancer activity (discovery of this disclosure).



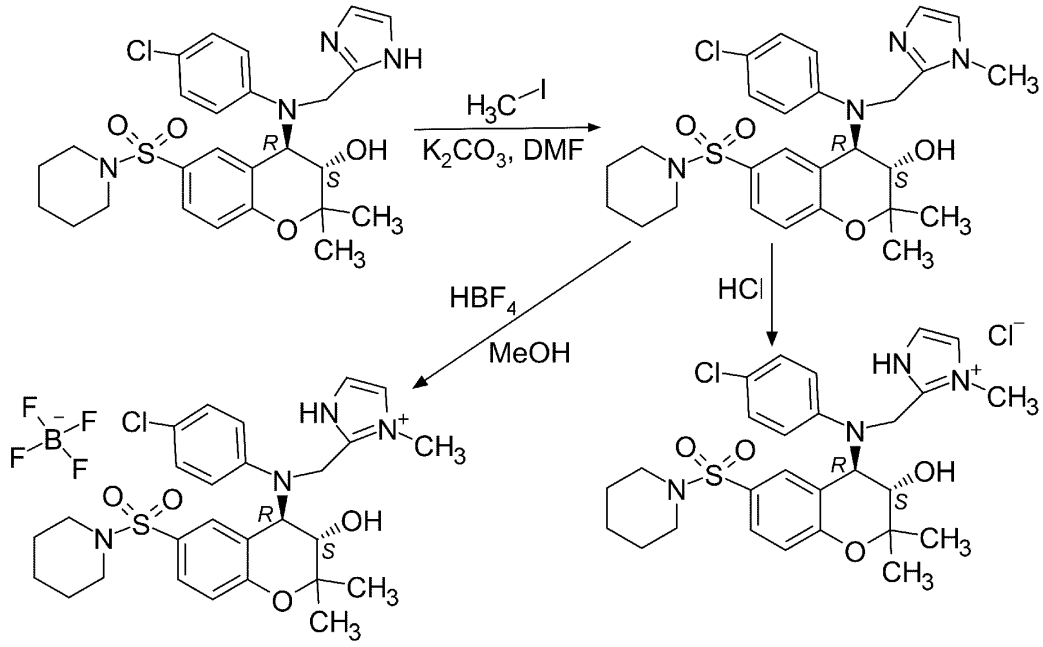
EC_{50} F_1F_0 ATP hydrolase = 0.48 ± 0.23 (μM)
EC_{50} F_1F_0 ATP synthesis = 18 ± 9.5 (μM)
EC_{50} Ratio = 38
10 μM doesn't harm *ex vivo* rat heart



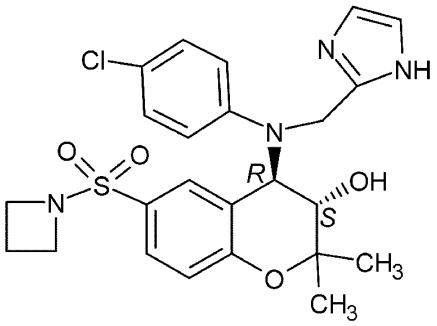
3*S*,4*R*
EC_{50} F_1F_0 ATP hydrolase = 0.24 ± 0.13 (μM)
EC_{50} F_1F_0 ATP synthesis = 3.8 ± 2.1 (μM)
3*R*,4*S*
EC_{50} F_1F_0 ATP hydrolase = 0.48 ± 0.23 (μM)
EC_{50} F_1F_0 ATP synthesis = 4 ± 0.45 (μM)

For the following example embodiment, with synthesis scheme (as 2 possible salts shown, *Scheme IIIa*), the starting material is BMS-199264, which is available commercially. For example from Sigma-Aldrich, a chemical and reagents vender well known to those of the art.

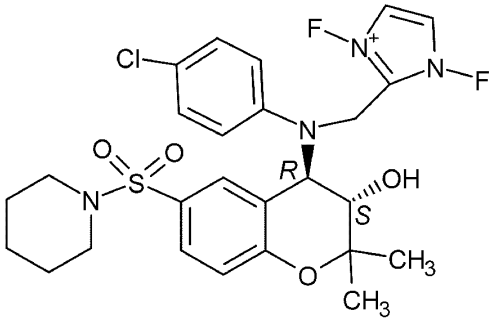
Scheme IIIa



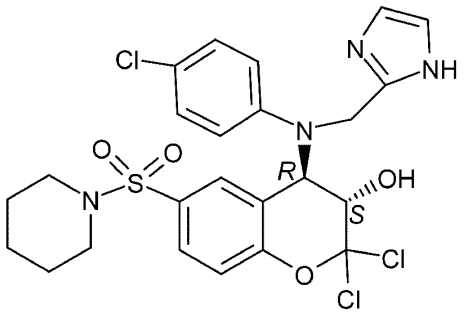
Further example embodiment:



The following example embodiment does not uncouple the proton motive force (pmf) because its imidazole group, unlike BMS-199264, for example, does not have a protonable element.



The following example embodiment (logP=3.79, calculated from structure [31]) uncouples the proton motive force (pmf) less than BMS-199264 (logP=4.35, calculated from structure [31]) because its logP is further removed from the logP=~3,2 optimum for uncoupling [32].

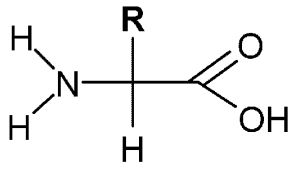


BMS-199264, and/or its analogues, can be deuterated by reactions described in [R1, R2, Q1, Q2], which deuterate aromatic and alkyl molecular components. Furthermore, there is a great wealth of reactions available to deuterate their aromatic rings, and those skilled in the art will know these. For (non-limiting) example, refer [Ex2]. Carbon 1 of BMS-199264, a chiral centre, can be deuterated by reactions described in [D, F, E1, E2, Ex1], which deuterate α carbons to tertiary amines, and/or by reactions described in [N], which deuterate sp3 carbons, and/or by reactions described in [I, M, G, H], which deuterate α and β-carbons to an OH group. Carbon 6 of BMS-199264, a chiral centre, can be deuterated by reactions described in [L, H, G, A, K, M, J1, J2, J3, I, F, S], which deuterate the α-carbon to an OH group, and/or by reactions described in [D], which deuterate α and β-carbons to tertiary amines, and/or by reactions described in [N], which deuterate sp3 carbons. The scaffold of [P6] is presented in its abstract. Deuterated isotopologues of this [P6] scaffold, for (non-limiting) example deuterated BMS-199264, are componentry to the present invention as new compositions of matter, and in non-limiting embodiments are used singly or in combination, optionally in co-therapy with an FDA and/or EMA approved medicine(s) and/or treatment(s), for example a licensed cancer treatment, as anti-cancer therapeutics.

EXAMPLE (IV)

Background

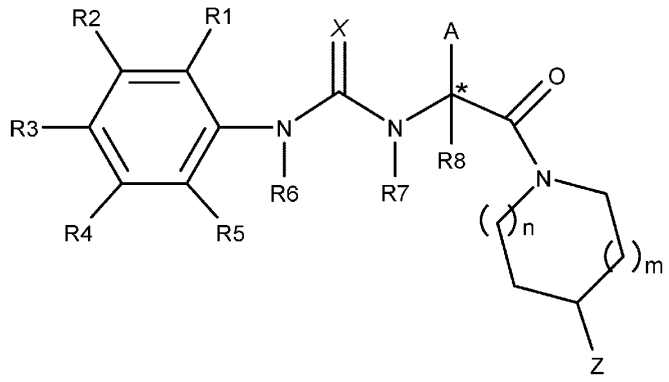
Well known to those of the art: amino acids have the following structure, wherein the R group is different in different amino acids.



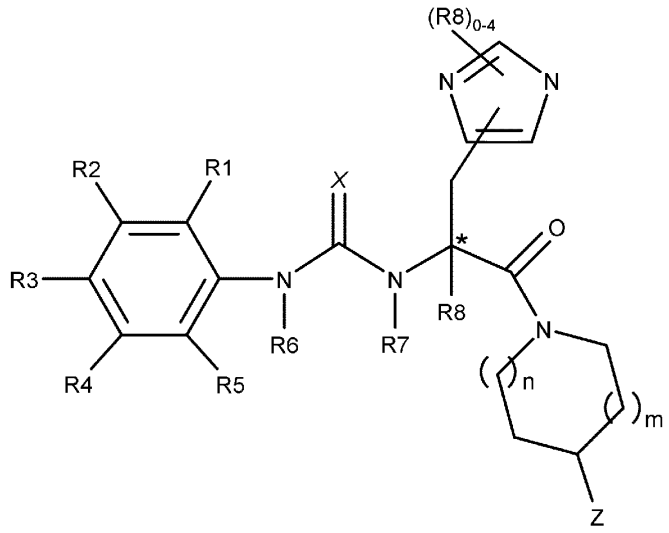
Summary of Formula (IV)

This invention embodiment relates to compounds having the following formula:

Formula (IV)



including



or their enantiomers, diastereomers, pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, wherein:

X is selected from O or S;

A is selected from hydrogen, deuterium, alkyl, substituted alkyl, cycloalkyl, heterocycle, aryl, heteroaryl, aminoalkyl, thioalkyl, alkoxy and an R group of a proteogenic amino acid, or other amino acid synthesized or used by a living system (non-limiting example of such a system: a human), which is optionally isotopically enriched, and/or substituted by alkyl, substituted alkyl, deuterated alkyl, halogen, cycloalkyl, heterocycle, aryl, heteroaryl, aminoalkyl, thioalkyl, alkoxy, haloalkyl, haloalkoxy, or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.);

n and m are 0, 1, or 2;

R_1 through R_5 are independently selected from hydrogen, halogen, NO_2, CN, $C_{1\text{-}8}$alkyl, substituted $C_{1\text{-}8}$alkyl, $C_{3\text{-}8}$cycloalkyl, aryl, heterocyclo, heteroaryl, OR_9, SR_9, COR_{11}, CO_2R_{11}, $CONR_9R_{10}$ or NR_9R_{10};

R_6 and R_7 are independently hydrogen, alkyl or substituted alkyl;

R_8 is hydrogen, deuterium, $C_{1\text{-}8}$alkyl, substituted $C_{1\text{-}8}$alkyl, deuterated $C_{1\text{-}8}$alkyl, aryl, heterocyclo, heteroaryl, aminoalkyl, thioalkyl, alkoxy, halogen, haloalkyl, haloalkoxy, or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.);

Z is hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heterocyclo, heteroaryl, COR_{11}, CO_2R_{11}, SO_2R_{11}, $S(O)R_{11}$ or $CONR_9R_{10}$;

R_9 and R_{10} are independently hydrogen, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{3-10}cycloalkyl, aryl, heterocyclo, heteroaryl, COR_{13}, SO_2R_{13} or $S(O)R_{13}$; and

R_{11}, R_{12} and R_{13} are independently hydrogen, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{3-10}cycloalkyl, aryl, heterocyclo or heteroaryl;

wherein each occurrence of R_9-R_{13} is chosen independently.

Preferred compounds of Formula (IV)

Preferred methods are to use, and preferred compounds are, compounds of Formula (IV), their enantiomers, diastereomers, pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, in which:

R_2, R_3 and R_4 are all hydrogen; and/or

R_6 and R_7 are both hydrogen; and/or

n and m are both 1; and/or

R_1 and R_5 are both C_{1-8} alkyl, preferably both R_1 and R_5 are isopropyl groups.

Other preferred methods use, and preferred compounds are, compounds of Formula (IV), their enantiomers, diastereomers, pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, in which:

Z is C_{1-8}alkyl, C_{2-8}alkenyl, C_{1-8}haloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl —COR_{11}, —CO_2R_{11}, —SO_2R_{11}, —$S(O)R_{11}$ or —$CONR_9R_{10}$; especially preferable is benzyl, —$C(O)_2H$ or —$C(O)_2C_{1-8}$alkyl;

R_9 is hydrogen;

R_{10} is C_{1-8}alkyl or C_{3-10}cycloalkyl; aryl or arylalkyl; and

R_{11} is hydrogen, C_{1-8}alkyl, C_{3-10}cycloalkyl, C_{3-10}heterocycloalkyl, C_{3-10}aryl or C_{3-10} arylalkyl.

Other preferred methods use, and preferred compounds are, compounds of Formula (IV), their enantiomers, diastereomers, pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, in which:

A is hydrogen, deuterium, $C_{1\text{-}8}$alkyl, heteroaryl, aryl, or alkyl substituted with heterocyclo, aryl, OH, SH, ST^1, —C(O), H, T^3-NT^5T^6, -T^8-$C(O)_tT^9$-NT^5T^6 or T^3-$N(T^2)T^4NT^5T^6$,

T^1 is alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alkyl;

T^2 and T^3 are each independently a single bond, -T^8-$S(O)_t$-T^9-, -T^8-C(O)-T^9-, -T^{18}-C(S)-T^9-, -T^8-S-T^9-, -T^8-O—C(O)-T^9-, -T^8-$C(O)_tT^9$-, -T^8-$C(=NT^{10})$-T^9- or –T^8-C(O) —C(O)-T^9-;

T^5, T^6, T^7, T^8 and T^9 are independently hydrogen, alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alky, each group optionally substituted where valence allows by one to three groups selected from halo, cyano, nitro, OH, oxo, —SH, alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocylco)alkyl, heteroaryl or (heteroaryl)alkyl, —OT^{11}, —ST^{11}, —$C(O)_tH$, —$C(O)_tT^{11}$, —O—C(O)T^{11}, $T^8C(O)_tN(T^{12})T^{11}$, —SO_3H, —$S(O)_tT^{11}$, $S(O)_tN(T^{12})T^{11}$, —T^{13}-$NT^{11}T^{12}$, -T^{13}—$N(T^{12})$-T^4-$NT^{11}T^{22}$, -T^{13}-$N(T^{11})$-T^{12}-T^{11} and -T^{13}-$N(T^{18})$-T^{14}-H; or

T^8 and T^9 are each independently a single bond, alkylene, alkenylene or alkynylene;

T^{11} is alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alkyl;

T^{12} is halo, cyano, nitro, OH, oxo, —SH, alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alkyl, —$C(O)_tH$ or —SO_3H;

T^{13} and T^{14} are each independently a single bond, —$S(O)_t$—, —C(O)—, —C(S)—, —O—, —S—, —O—C(O)—, —$C(O)_t$—, —$C(=NT^{13})$— or —C(O)—C(O)—;

wherein each occurrence of T^1-T^{14} is chosen independently; and

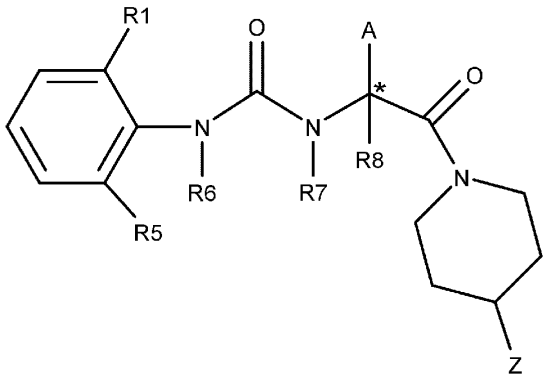
t is 1 or 2.

Preferred compounds of the foregoing section are those in which A is hydrogen, deuterium, $C_{1\text{-}8}$alkyl, hydroxyalkyl, heterocycloalkyl, heteroaryl alkyl, aryl, arylalkyl, or alkyl substituted with a group selected from SH, ST^4, —$C(O)_tH$, T^6-NT^8T^9, -T^{11}-$C(O)_tT^{12}$-NT^8T^9 and T^6-$N(T^5)T^7NT^8T^9$.

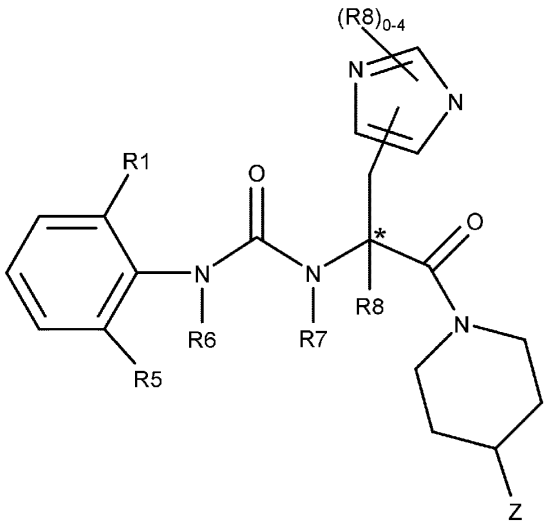
More preferred are those compounds in which A is hydrogen, deuterium, methyl, —$CH_2(CH_3)_2$, —$(CH_2)_2(CH_3)_2$, —$CH(CH_3)CH_2(CH_3)$, —$(CH_2)OH$, hydroxyethyl, —$(CH_2)_2SCH_3$, —CH_2SH, phenyl, —CH_2(phenyl), —CH_2(p-hydroxyphenyl), —CH_2(indole), —$(CH_2)C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —$(CH_2)_2C(O)OH$, —$CH_2C(O)OH$, —$(CH_2)_4NH_2$, —$(CH_2)_3(=NH)CNH_2$, or —CH_2(imidazole). Especially preferred A groups are —$CH(CH_3)CH_2(CH_3)$, phenyl, phenyl alkyl or —CH_2(2-indole).

Alternatively preferred methods use, and preferred compounds are, compounds of Formula (IVb), their enantiomers, diastereomers, pharmaceutically-acceptable salts, solvates, hydrates or prodrugs thereof, in which:

Formula (IVb)



including



wherein:

A is hydrogen, deuterium, C_{1-8}alkyl, heteroaryl, aryl, or alkyl substituted with heterocyclo, aryl, OH, SH, ST^1, —$C(O)_tH$, T^3-NT^5T^6, -T^8-$C(O)_tT^9$-NT^5T^6 or T^3-$N(T^2)T^4NT^5T^6$;

R^1 and R^5 are independently C_{1-8}alkyl optionally substituted where valence allows;

R^6 and R^7 are independently hydrogen or C_{1-8}alkyl;

R^8 is hydrogen, halogen, deuterium, C_{1-8}alkyl or substituted C_{1-8}alkyl;

Z is hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{1-8}haloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl —COR^{11}, —CO_2R^{11}, —SO_2R^{11}, —$S(O)R^{11}$ or —$CONR^9R^{10}$;

R^9 is hydrogen,

R^{10} is C_{1-8}alkyl or C_{3-10}cycloalkyl; aryl or arylalkyl;

R^{11} is hydrogen, C_{1-8}alkyl, C_{3-10}cycloalkyl, C_{3-10}heterocycloalkyl, C_{3-10}aryl or C_{3-10}arylalkyl.

T^1 is alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alkyl;

T^2 and T^3 are each independently a single bond, -T^8-$S(O)_t$-T^9-, -T^8-$C(O)$-T^9-, -T^{18}-$C(S)$-T^9-, -T^8-O-T^9-, -T^8-S-T^9-, -T^8-O—$C(O)$-T^9-, -T^8-$C(O)_tT^9$-, -T^8-$C(=NT^{10})$-T^9- or -T^8-$C(O)$—$C(O)$-T^9-;

T^5, T^6, T^7, T^8 and T^9 are independently hydrogen, alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alky, each group optionally substituted where valence allows by one to three groups selected from halo, cyano,

nitro, OH, oxo, —SH, alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocylco)alkyl, heteroaryl or (heteroaryl)alkyl, —OT^{11}, —ST^{11}, —$C(O)_tH$, —$C(O)_tT^{11}$, —O—$C(O)T^{11}$, $T^8C(O)_tN(T^{12})T^{11}$, —SO_3H, —$S(O)_tT^{11}$, $S(O)_tN(T^{12})T^{11}$, -T^{13}-$NT^{11}T^{12}$, -T^{13}-$N(T^{12})$-T^4-$NT^{11}T^{22}$, -T^{13}-$N(T^{11})$-T^{12}-T^{11} and -T^{13}-$N(T^{18})$-T^{14}-H; or

T^8 and T^9 are each independently a single bond, alkylene, alkenylene or alkynylene;

T^{11} is alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alkyl;

T^{12} is halo, cyano, nitro, OH, oxo, —SH, alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocylco)alkyl, heteroaryl or (heteroaryl)alkyl, —$C(O)_tH$ or —SO_3H;

T^{13} and T^{14} are each independently a single bond, —$S(O)_t$—, —C(O)—, —C(S)—, —O—, —S—, —O—C(O)—, —$C(O)_t$—, —$C(=NT^{13})$- or —C(O)—C(O)—; and

t is 1 or 2.

More preferred methods/compounds use/are:

A is hydrogen, deuterium, methyl, —$CH_2(CH_3)_2$, —$(CH_2)_2(CH_3)_2$, —$CH(CH_3)CH_2(CH_3)$, —$(CH_2)OH$, hydroxyethyl, —$(CH_2)_2SCH_3$, —CH_2SH, phenyl, —CH_2(phenyl), —CH_2(p-hydroxyphenyl), —CH_2(indole), —$(CH_2)C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —$(CH_2)_2C(O)OH$, —$CH_2C(O)OH$, —$(CH_2)_4NH_2$, —$(CH_2)_3(=NH)CNH_2$ or —CH_2(imidazole).

Especially preferred methods/compounds use/are:

A is —$CH(CH_3)CH_2(CH_3)$, phenyl, CH_2(phenyl) or —CH_2(2-indole).

Also, especially preferred methods/compounds use/are:

R^8 is hydrogen and the configuration about the carbon marked with the * is *S*, provided A is not H. Also preferred: R^8 is deuterium and the configuration about the carbon marked with the * is *S*, provided A is not H or deuterium.

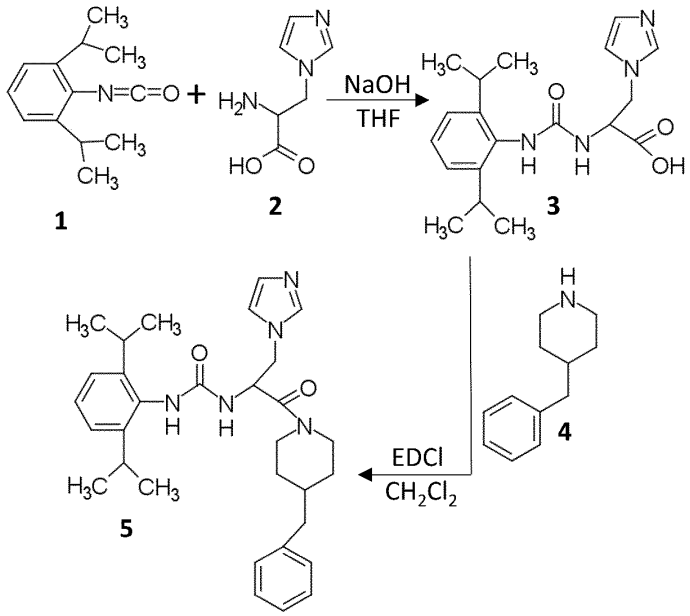
Other preferred methods/compounds use/are:

R^1 and R^5 are both isopropyl; and/or $R^6R^7$and R^9 are all hydrogen; and/or Z is CH_2(phenyl), —$C(O)_2H$ or —$C(O)_2C_{1\text{-}8}$alkyl.

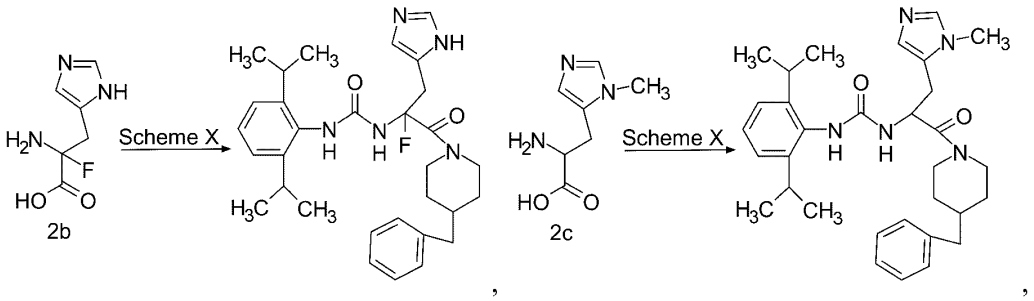
Example embodiments of Formula (IV)

In the following scheme, *Scheme X*, all reactants are commercially available e.g. Compound 2 is available from Oxchem Corporation, IL, USA.

Scheme X

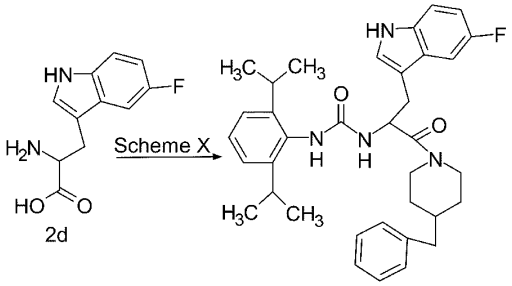


Using *Scheme X*, above, with different amino acids as the Compound 2 input, gives different Compound 5 products (all reactants are commercially available e.g. Compound 2b is available from Aurora Fine Chemicals LLC, San Diego, USA, Compound 2c and 2d from Sigma-Aldrich).

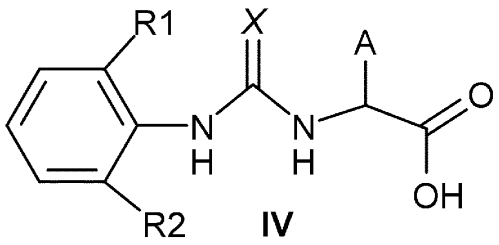


,

,



Following is Structure IV, from Scheme I, in the "Process of Preparation" section of [P3], symbol definitions are as in [P3]. Scheme I in [P3] is a more general form of *Scheme X* above.



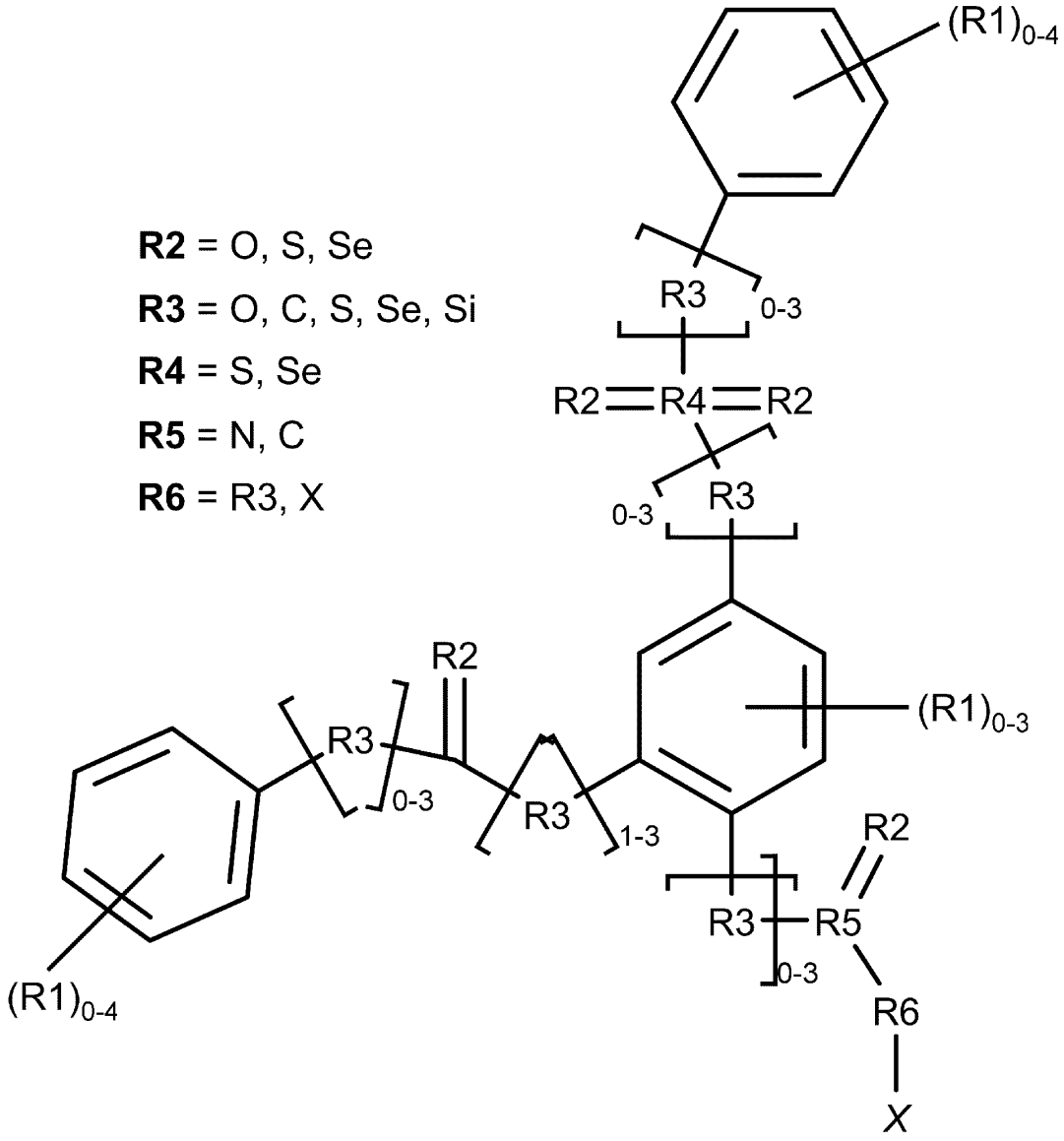
IV

This Structure IV can be deuterated, as can final compounds of the scaffold of [P3] (scaffold presented in its abstract), at its chiral carbon, and in further embodiments at further or other position(s), by reactions described in [A, B, E1, E2, F], which can deuterate the α-carbon to secondary amines. And/or by reactions described in [Ex3], which can deuterate the α-carbon to a carbonyl, using pyrrolidine (available from Sigma-Aldrich) as catalyst, and/or by reactions described in [Ex4], which deuterate ketones. And/or by reactions described in [N], which deuterate sp3 carbons. And/or by reactions described in [R1, R2, Q1, Q2], which deuterate aromatic and alkyl molecular components. Deuterated Compound IV structure(s) can be inputted into the synthesis Scheme I of [P3], in place of an undeuterated Compound IV form compound(s), to make deuterated isotopologue(s) with the scaffold of [P3], its scaffold is shown in its abstract. Alternatively, to achieve this aim, a compound(s) of Structure III form in Scheme I of [P3] can be deuterated at its chiral carbon, and in further embodiments at further or other position(s), by reactions described in [A, B, P, E1, E2, F], which deuterate the α-carbon to primary amines. And/or by a methodology used to deuterate amino acids, of which many are known to those of the art (non-limiting e.g. [AA1-AA6, B]), because Structure III (of [P3]) is of the amino acid form. Indeed, deuterated (and/or other isotopically enriched e.g. ^{13}C and/or ^{15}N) amino acids can be sourced commercially, e.g. (non-limiting) from Sigma-Aldrich or Cambridge Isotope Laboratories Inc., and used in Scheme I of [P3] to produce isotopically enriched compound embodiments of the present invention. For (illustrative, non-limiting) example, Cambridge Isotope Laboratories Inc. sell histidine enriched (97-99%) for ^{13}C, ^{15}N, ^{2}H at the respective positions of C, N and H in histidine (item number: CDNLM-6806-PK). Sigma-aldrich sell this also (item number: 750158 ALDRICH). Deuterated (and other isotopically enriched) compound embodiments of the scaffold of [P3] (scaffold presented in its abstract), most preferably deuterated at their

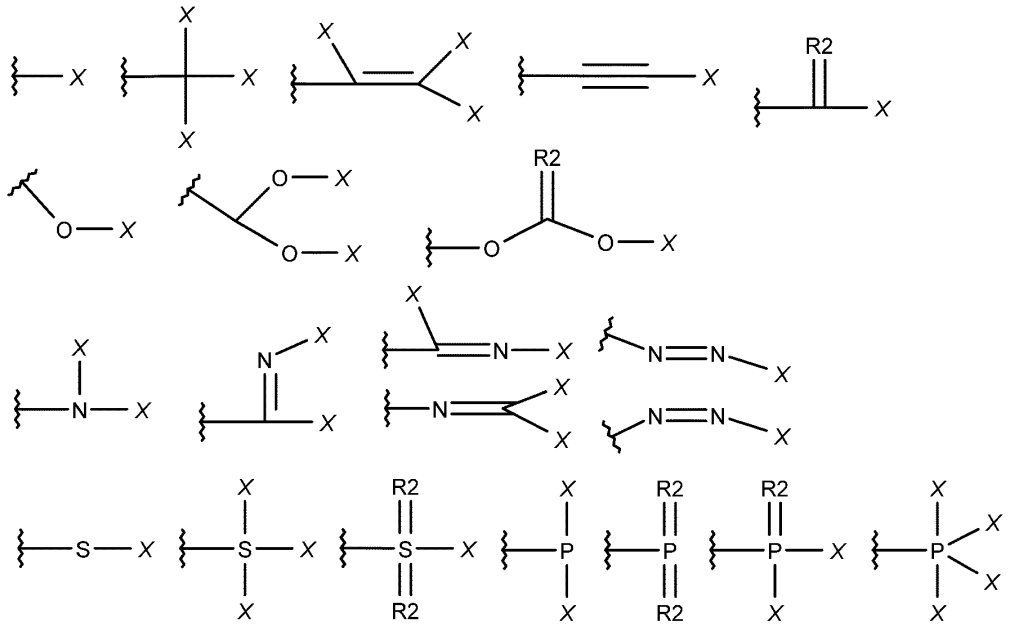
chiral carbon (which in an embodiment is ^{13}C at enriched, non-natural abundance, e.g. {non-limiting} >70% ^{13}C incorporation), are componentry to the present invention as new compositions of matter. And in non-limiting embodiments, these are used singly or in combination, optionally in co-therapy with an FDA and/or EMA approved medicine(s) and/or treatment(s), for example a licensed cancer treatment, as anti-cancer therapeutics.

EXAMPLE (V)

Formula (V)



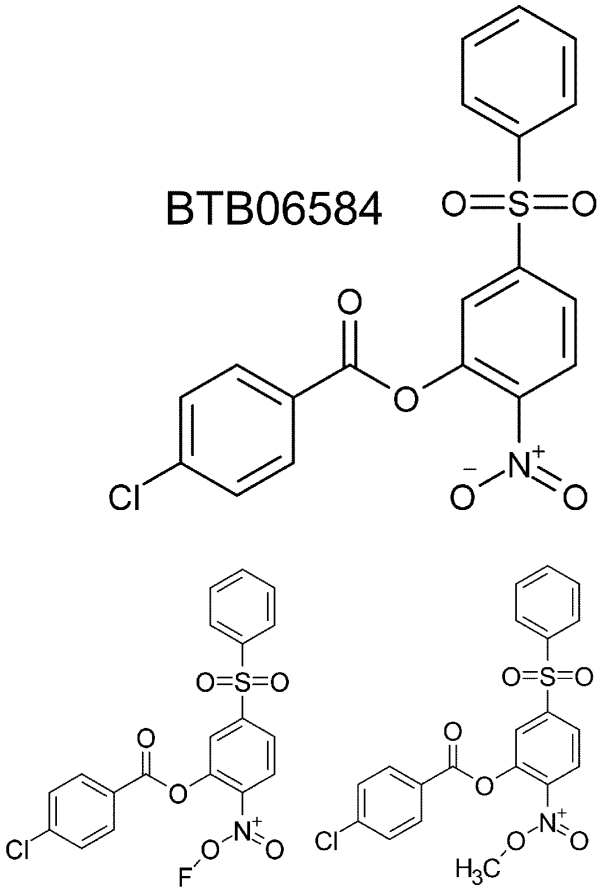
R1 =



X = absent, H, Deuterium, OH (hydroxyl), SH (thiol), =0 (keto), CN (cyano), halogen, CH_3 (methyl), methoxy (OCH_3), trifluoromethyl, OCF_3, NH_2 (amino), NOOH (nitro), =N-OH, COOH (carboxyl), COH (formyl), N=O (nitroso), O-N=O (nitrosooxy), alkyl(C_{1-4}), alkoxy(C_{1-4}), haloalkyl(C_{1-4}), alkylthio(C_{1-4}), hydroxyalkyl(C_{1-4}), aminoalkyl(C_{1-4}), cycloalkyl (C_{1-4}), haloalkoxy(C_{1-4}), alkenyl(C_{1-4}), alkynyl(C_{1-4}), alkoxycarbonyl(C_{1-4}), substituted alkyl(C_{1-4}) {which is an alkyl with between 1 and 4 carbons and one or more independent substituents of X}

Molecular permutations of BTB06584. Enumerations of this Markush structure, and their pharmaceutically-acceptable salts, solvates, hydrates and prodrugs thereof, are disclosed as anti-cancer molecules: the process/method of their use as anti-cancer molecules is disclosed by this invention. As valence permits: R1 is selected from the options of R1 (independently in each case of R1), X is selected from the options of X (independently in each case of X), R2 is selected from the options of R2 (independently in each case of R2), R3 is selected from the options of R3 (independently in each case of R3), R4 is selected from the options of R4 (independently in each case of R4). In other embodiments one or more phenyl groups has one or more of its double bonds replaced with a single bond. In other embodiments, one or more phenyl groups is replaced with cyclohexane, each with the same possible substitutions as the phenyl it replaces. Hydrogen atoms aren't shown in this figure, but in further embodiments one or more hydrogen atoms is replaced with deuterium. In further embodiments: any possible isotopic substitution at one or more places.

Example embodiments of Formula (V)



BTB06584, and/or its analogues, can be deuterated by reactions described in [R1, R2, Q1, Q2], which deuterate aromatic and alkyl molecular components. Furthermore, there is a great wealth of reactions available to deuterate their aromatic rings, and those skilled in the art will know these. For (non-limiting) example, refer [Ex2]. Deuterated isotopologues of Formula (V), for (non-limiting) example deuterated BTB06584, are componentry to the present invention as new compositions of matter, and in non-limiting embodiments are used singly or in combination, optionally in co-therapy with an FDA and/or EMA approved medicine(s) and/or treatment(s), for example a licensed cancer treatment, as anti-cancer therapeutics.

EXAMPLE (VI)

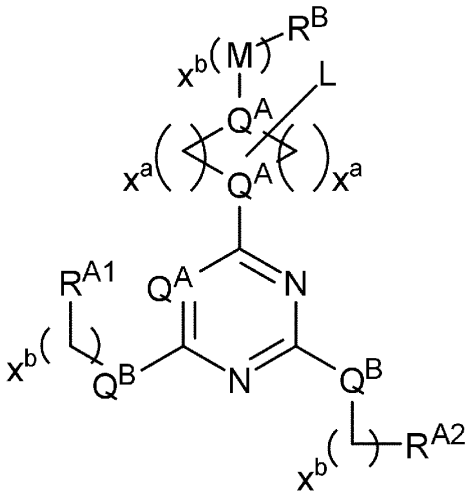
Encompassed by this embodiment are methods of treating a subject suffering from cancer by administering an effective amount of at least one compound of Formula (VI) or a

pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a pharmaceutical composition(s) comprising one or compounds of Formula (VI).

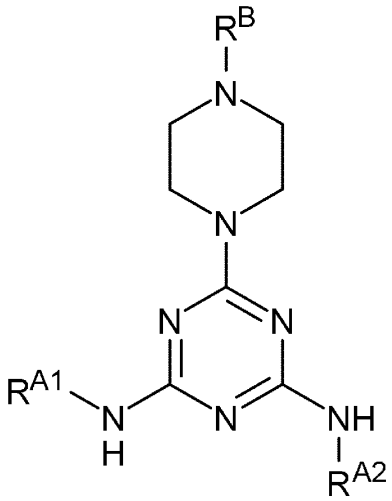
Summary of Formula (VI)

This invention embodiment relates to compounds having the following formula:

Formula (VI)



including



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

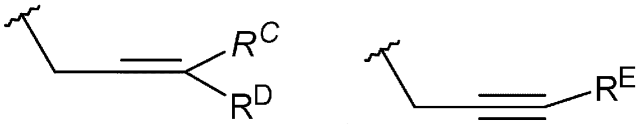
each Q^A is independently selected from N and CH;

each Q^B is independently selected from NH and CH_2;

M is independently selected from O, NH and CH_2;

x^a is independently at each point of use selected from 1, 2, 3, 4, or 5; x^b is independently at each point of use selected from 0, 1, 2, 3, 4, or 5; L represents 0-5 optional substituents on the ring independently selected from alkyl, substituted alkyl, deuterated alkyl, aminoalkyl, thioalkyl, alkoxy, halogen, haloalkyl, haloalkoxy, or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.);

R^{A1} and R^{A2} are each independently selected from the groups



and

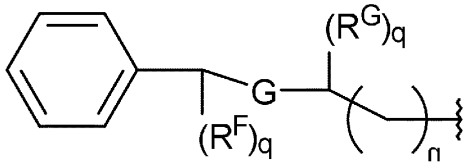
wherein R^C and R^D are each independently selected from hydrogen, deuterium, halogen and alkyl, and wherein R^E is hydrogen, deuterium, or alkyl;

R^B is selected from R^{B1}, hydrogen and deuterium;

wherein R^{B1} is selected from phenyl, benzyl, heteroaryl, pyridyl, pyrimidyl and pyrazinyl optionally substituted with one or more substituents R^{B2};

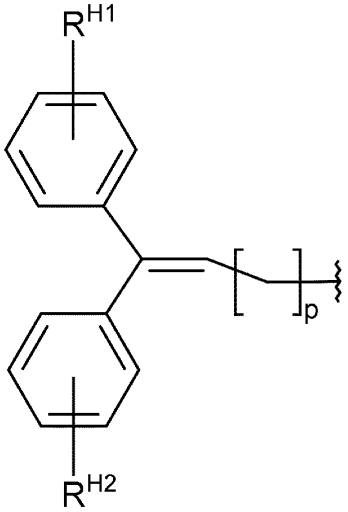
wherein each R^{B2} is independently selected from halogen, alkyl, alkoxy, nitro, amino, methoxy and polyhalogen alkyl;

or R^B is a phenylalkyl of the formula:



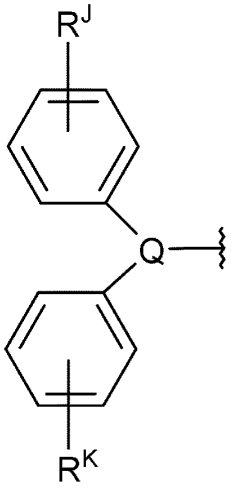
wherein R^F and R^G are hydrogen or alkyl, G is a carbon-carbon double bond or a carbon-carbon single bond, n is 0 or 1 and q is 0 or 1 provided that where q is 0, G is a carbon-carbon double bond and where q is 1, G is a carbon-carbon single bond,

or R^B is a diphenylalkyl of the formula



wherein R^{H1} and R^{H2} each independently represent 1-5 optional substituents on each ring, and wherein each R^{H1} and R^{H2}, when present, is independently selected at each point of use from hydrogen, L (defined earlier) or halogen, and p is 0, 1 or 2;

or R^B is the group



Wherein Q is CH or N, R^J and R^K each independently represent 1-5 optional substituents on each ring, and wherein each R^J and each R^K, when present, is independently selected from L (defined earlier), halogen, alkyl, alkoxy, nitro, amino and polyhalogen alkyl.

In some embodiments, when one or both of R^J and R^K is alkoxy, this alkoxy group may be methoxy.

It is to be understood that in the compounds of general Formula (VI), wherein R^{A1} and/or R^{A2} are alkenyl moieties having different substituents at the position R^C and R^D, that compound may exist in *cis* or *trans* isomeric forms both of which are considered to be within the scope of the present invention. All isotopic forms of Formula (VI) are within the scope of the present invention.

Preferred embodiments of Formula (VI)

For Formula (VI), the symbols R^C and R^D as defined in subgroups R^{A1} and R^{A2}, may be hydrogen, halogen (suitably fluorine, chlorine or bromine), alkyl, suitably "lower alkyl" (herein now defined) having from 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert butyl, pentyl and the like, most preferably methyl;
and the moiety R^E may be hydrogen, or lower alkyl having from 1 to 5 carbon atoms such as methyl, ethyl, propyl, butyl, or pentyl, most suitably methyl.

The subgroup R^B may be hydrogen; phenyl; or substituted phenyl. The substituted phenyl group may include one or more of the preferred substituents in any of the available positions for substitution, however, mono substitution in the 4-position of the phenyl nucleus is especially preferred. Suitable substituents for the phenyl nucleus include halogen, preferably fluorine, chlorine or bromine; lower alkyl, lower alkoxy, and poly halogen lower alkyl (i.e. substituted alkyl) wherein the alkyl moiety contains from 1 to 5 carbon atoms, especially preferred however are methyl, methoxy, and trifluoromethyl; and nitro and amino.

Where the subgroup R^B represents substituted pyridyl, substituted pyrimidyl, or substituted pyrazinyl, the substituting group may be located on one or more of the available carbon atoms in the nucleus, and may be the same or different. Preferred among the substituting groups are lower alkyl or lower alkoxy having from 1 to 5 carbon atoms such as methyl, ethyl, butyl or penty; or methoxy, propoxy, butoxy or pentoxy.

Where the moiety R^B represents substituted benzyl, the benzyl moiety may be substituted in one or more of the available positions on the phenyl nucleus thereof. Among the preferred substituents are halogen (suitably fluorine, chlorine or bromine), lower alkoxy having from 1 to 5 carbon atoms, especially preferred is methoxy and most preferred being di- and tri-methoxy; or alkylenedioxy suitably lower alkylenedioxy such as methylenedioxy,

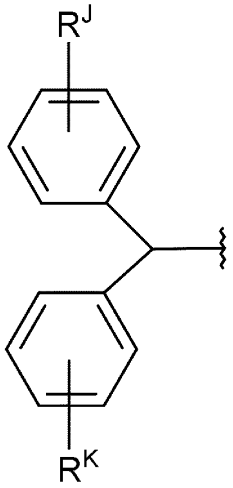
ethylenedioxy, propylenedioxy and the like, most suitably, the alkylenedioxy moiety is attached across the 3- and 4-positions of the phenyl nucleus, although the bridging of other carbon atoms in the phenyl nucleus is to be considered within the scope of the present invention.

The moieties R^F and R^G may be hydrogen, or lower alkyl of 1 to 5 carbon atoms, most preferred however being methyl.

The groups R^{H1} and R^{H2} may be independently hydrogen, or halogen suitably fluorine, chlorine or bromine.

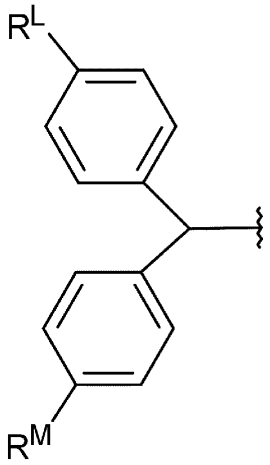
Preferred embodiments of Formula (VI) include wherein R^C and R^D are methyl, R^E is methyl and R^B is selected from chlorophenyl, methylphenyl, methoxyphenyl, trifluorophenyl, chlorophenyl, dimethoxybenzyl, trimethoxybenzyl, methylenedioxybenzyl and ethylenedioxybenzyl.

In some embodiments R^B is the group



.

In some embodiments, R^B is the group



wherein R^L and R^M are each independently selected from halogen, alkyl, alkoxy, nitro, amino and polyhalogen alkyl.

Synthesis of structures of Formula (VI)

Synthesis routes for example embodiments of Formula (VI) are in [P7], which is herein incorporated in entirety by reference. One or more chemical enumerations/structures from [P7], in use as an anti-cancer therapeutic, is componentry to the present invention. Indeed, encompassed by this embodiment are methods of treating a subject suffering from cancer by administering an effective amount of at least one compound from [P7] or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a pharmaceutical composition(s) comprising one or compounds from [P7].

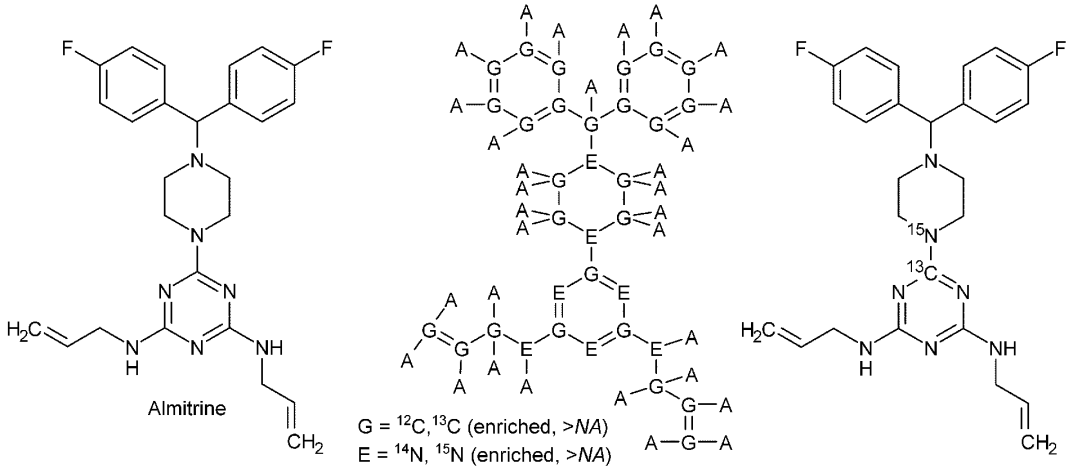
Example embodiments of Formula (VI)

Invention embodiments include compounds of Formula (VI), whether a decoupler or not, and any compound(s) of any formula, which has decoupling activity (changes F_1F_0 ATP synthase stoichiometry), in use for anti-cancer therapy.

Decoupler drugs as anti-cancer medicines

Enumerations of Formulas I-V exert anti-cancer activity by inhibiting, and so reducing, F_1F_0 ATP hydrolysis. The present embodiment also exerts anti-cancer activity by reducing F_1F_0 ATP hydrolysis. However, not by inhibition of F_1F_0 ATP hydrolysis, but by making F_1F_0 ATP hydrolysis more efficient! Such that less ATP is hydrolysed per unit proton motive force (pmf) generated i.e. F_1F_0 ATP hydrolysis is reduced. The shared feature of these

embodiments is that cancer function is impaired, and cancer danger reduced, by reducing F_1F_0 ATP hydrolysis in cancer cells. The present embodiment relates to and discloses the method/use of a "decoupler" drug(s) as an anti-cancer therapeutic e.g. (non-limiting) almitrine, which is a compound of Formula (VI). Disclosed experimental data shows that almitrine exerts anti-cancer activity (**Figure 7**).



Decoupler drugs modify the H^+/ATP stoichiometry of ATP synthase, so modifying the ATP/O ratio, without significantly changing Ψ_{IM} [113-116]. Such drugs symmetrically modify the forward and reverse modes of ATP synthase: they make the forward mode *less* efficient (less ATP synthesized per protons passed) and the reverse mode *more* efficient (more protons pumped per ATP hydrolysed). In other words, they reduce the (fractional) ATP yield/cost of a proton passing through ATP synthase energetically "downhill"/"uphill", in relation to the direction of the proton motive force (pmf). In isolated mitochondria, the almitrine conferred decrease in F_1F_0 ATP synthesis and hydrolysis is maximal at ~60%, no matter how great the almitrine concentration [114]. Almitrine can double the stoichiometry: double the number of protons required/pumped for/by ATP synthesis/hydrolysis. Almitrine reduces the amount of ATP that F_1F_0 ATP synthase synthesizes, but it also reduces the amount of ATP that F_1F_0 ATP synthase hydrolyses, which is normally, without almitrine, significant. Indeed, this disclosure discloses a new fundamental biological discovery, with supporting *in vivo* experimental data (**Figure 15**): F_1F_0 ATP hydrolysis isn't a bug but a feature, substantial and essential to heat generation and homeothermy. Almitrine reduces ATP synthesis and hydrolysis and these aspects largely offset and intracellular [ATP] remains

within survivable limits. Almitrine reduces inefficiency (heat generation) but simultaneously increases inefficiency (heat generation). Making the forward mode of ATP synthase less efficient might be bad for normal cells, as it might be for cancer cells that use OXPHOS, but this decoupler action disproportionally affects cells with a higher respiratory rate [114], which could disproportionally affect cancer cells. Although decouplers make the reverse mode of ATP synthase *more* efficient, this action still exerts anti-cancer activity on cancers using ATP synthase in reverse. Because these cancers use this mode *for* its inefficiency: to consume ATP, to permit high glycolytic and PPP flux, to enable high [NADPH] and low [ROS]. So, slowing/reducing this F_1F_0 ATP hydrolysis exerts anti-cancer activity. The same cancer can be disrupted by *both* almitrine actions, upon the forward *and* reverse modes of ATP synthase, at different stages of the cell cycle.

In normal cells, almitrine decreases ATP synthesis, but decreases ATP hydrolysis also, and so [ATP] is maintained. In cancer cells residing in hypoxia, thence forced to survive with a lower OXPHOS rate, which already rely upon high IF_1 expression (many cancers overexpress IF_1 [23-24]) to block ATP hydrolysis and buoy [ATP], almitrine conferred decrease in ATP synthesis strikes them disproportionally.

Comparing **Figure 1** and **7**, one observes that in standardized NCI one-dose testing [16-17], almitrine dismesylate (10 μM) exerts <u>*greater*</u> anti-cancer activity than carboplatin (10 μM), which is an FDA approved chemotherapeutic, one of the most used chemotherapies today, and is on the World Health Organisation (WHO) list of essential medicines. Furthermore, almitrine dismesylate is <u>*less*</u> toxic to normal cells than carboplatin. In mice, intraperitoneal injection (IP) LD_{50} (dosage at which 50% of test mice die) = 118 mg/kg for carboplatin [117] and = 370 mg/kg for almitrine dismesylate [118].

In humans, 200 mg per day of oral almitrine dimesylate has been trialled for sleep apnea, which is a drive to snoring [119]. In humans, oral almitrine dimesylate has been used for decades, totalling millions of patient months of almitrine administration, for chronic obstructive pulmonary disease (COPD), often at 200 mg oral almitrine dimesylate per day [120, 121]. A single 200 mg oral almitrine dimesylate dose (70% orally bioavailable) renders a mean *cmax* plasma concentration of 286 ng/ml = 0.6 μM [121]. Because almitrine volume of distribution (V_D) = 17 l/kg [121], and human volume = ~1 l/kg [122], corresponding almitrine tissue concentration (*assuming* uniform) = (0.6*17) = ~10 μM, which is an

almitrine concentration that exerts anti-cancer activity in NCI testing (**Figure 7**). Almitrine has a long lifetime in the body and 24 hours after 200 mg oral almitrine dimesylate, plasma [almitrine] is still ~50 ng/ml [121] which will compound with the next daily 200 mg almitrine dimesylate dose and drive almitrine tissue concentrations >10 μM. A different human study [123] recorded mean *cmax* plasma concentration, post a single 150 mg oral almitrine dimesylate dose, to be 379 ng/ml, and an even higher volume of distribution for almitrine. In clinical use for COPD, a plasma concentration of 300 ng/ml almitrine is the directive [120], which corresponds to an anti-cancer tissue concentration (~10 μM) of almitrine. Non-limiting anti-cancer embodiments of this invention are almitrine dosages/formulations/compositions/salts/patterns of administration (e.g. sequential administration scheme) already used in humans (for example, as reported in the literature). Furthermore, higher or lower almitrine doses for anti-cancer therapy, optionally administered intravenously and/or with layoff periods (no drug administered), are further embodiments of this invention. An invention embodiment is a method of trialling almitrine as an anti-cancer drug in human cancer patients without first performing Phase I trials with almitrine or first trialling almitrine in healthy human subjects.

Almitrine acts upon BK potassium channels in chemoreceptors, within the caratoid bodies, and acts as a respiratory stimulant, which increases blood and tissue oxygenation, decreasing their [CO_2] [125, 126]. This respiratory stimulation should exert an additional anti-cancer effect *in vivo* because increasing [O_2] in blood and tissues increases their [ROS], especially in combination with ROS inducing [chemo/radio] therapies (permitting their use at lower doses, reducing their side effects). This synergises with the almitrine conferred reduction in F_1F_0 ATP hydrolysis in cancer cells, which corrupts the system cancers use to maintain low intracellular [ROS] at key stage(s) of the cell cycle, which is paramount to their "limitless replicative potential" (Hallmark of cancer [26]) and thence danger. Almitrine will be especially valuable against cancers (e.g. lung, breast) that can disrupt breathing and/or reduce O_2 delivery to tissues. Embodiments of this invention are to use almitrine, or any other drug(s) that modifies ATP synthase stoichiometry (a decoupler), as an anti-cancer medicine, optionally in co-therapy with one or more FDA and/or EMA approved drug(s), e.g. a cancer drug(s), and/or in co-therapy with any other compound(s) embodiments of the present invention e.g. a compound(s) of Formula (I-V) herein. Almitrine dimesylate is also known as almitrine bismesylate or almitrine dimethanesulfonate. All pharmaceutical salts of almitrine

are contemplated as anti-cancer therapeutics, as is almitrine in complex with another drug(s) e.g. almitrine-raubasine.

When used *chronically*, almitrine can have side effects [120]. A 30 year national pharmacovigilance survey in France, representing several million patient months of almitrine treatment [124], showed that upon multi-year use (mean onset of adverse reactions = 11 months), *some* patients receiving oral almitrine exhibited weight loss (795 cases) and peripheral neuropathy (2,304 cases) [120]. Although these side effects didn't present in all patients and only in a minority of cases that they did present were they categorised as serious (<10%) [120]. Almitrine has never been FDA approved. Almitrine has now been withdrawn from use in France, Portugal and Poland, where it was previously approved to treat chronic obstructive pulmonary disease (COPD). This withdrawal was because of the aforementioned two side effects and because alternative treatments emerged and because "available efficacy data, including data which became available since the initial marketing authorisation, showed only very limited clinical efficacy of almitrine in its approved indications" [120]. Although almitrine *does* increase arterial pO2, this does *not* translate to significant clinical benefit for COPD sufferers [120].

Almitrine's anti-cancer activity was unknown prior to this disclosure, despite almitrine being around since the early 1970s. Its anti-cancer activity is unexpected to a person of the art. Especially because another respiratory stimulant, doxapram, has been publically shown by others to have no anti-cancer activity in the same one-dose (10 μM) NCI-60 test in which, disclosed herein, almitrine dimesylate (10 μM) exerts anti-cancer activity. *Doxapram in NCI-60 (10 μM) testing: mean % cancer growth inhibition = -3.7% (median = -2.3%) i.e. negative numbers show cancer growth promotion (!) rather inhibition, as compared to no drug control, NSC: 760347 in* [16]. Thence, the discovery of almitrine conferred anticancer activity, disclosed herein, is unforeseen by a person of the art, novel and componentry to the invention of this disclosure. The risk-reward axis for almitrine is sufficient for an anti-cancer drug. Especially when used acutely, because most of almitrine's side-effects only occur with chronic use. *Acute* almitrine use for cancer treatment has a different risk-reward axis than *chronic* almitrine use for COPD treatment (for which it is ineffective [120]), especially because almitrine's side-effects are mostly associated with chronic use, and because cancer can be an immediately life-threatening disease for too many patients, with too few life-saving

options. Indeed, the merit of anti-cancer treatment merits the risk of higher almitrine dosages than 200 mg per day.

Intravenous delivery of 459±155 mg almitrine, infused within 24 hours, caused *reversible* lactic acidosis and hepatic dysfunction in 30% of 25 patients [127]. The other 70% of patients had no ill effects, and unaltered plasma [lactate]. The side-affected minority correlated with an impaired liver function parameter, increased plasma [bilirubin], *prior* to almitrine administration. Thus, this side-affected cohort is largely predictable. Most side-affected were women, but not all women were affected (N.B. women can have a smaller liver relative to body size e.g. refer [128]). The liver converts lactate to glucose by the Cori cycle [1] and an impaired/overwhelmed liver cannot process the elevated plasma lactate that almitrine administration can cause [115], which renders lactate acidosis. An embodiment of this invention is to select a cancer patient's almitrine dosage dependent upon their liver function. That is, in a further (non-limiting) embodiment, assessed by measuring plasma [bilirubin]. For non-limiting example: if (plasma [bilirubin] > 17 μM) {the patient should not be administered high almitrine dosage(s)}. Patients with better liver function are at less risk of almitrine driven lactic acidosis [127] and can endure higher almitrine dosages. Another embodiment is to record plasma [lactate], and/or a liver function assay chemical(s) (non-limiting e.g. bilirubin), whilst a cancer patient is administered with almitrine, or a course of almitrine administrations, and to lower the administered almitrine dosage/frequency if these plasma concentrations become abnormal. An invention embodiment is to use almitrine, *and* a drug(s)/treatment(s) treating/mitigating lactic acidosis, in anti-cancer therapy. Another embodiment is almitrine for anti-cancer therapy, given with a dosage adjustment dependent upon initial body weight, before treatment, and optionally reducing the dosage if significant weight loss occurs. Almitrine in co-therapy with a high(er) calorie diet, as an anti-cancer treatment, is another embodiment. Almitrine in co-therapy with a drug to treat or mitigate peripheral neuropathy (e.g. {non-limiting} gabapentin, duloxetine, pregabalin etc.), as an anti-cancer treatment, is an embodiment of this invention. An embodiment is to use almitrine for anti-cancer therapy and to monitor the almitrine recipient, or for the almitrine recipient to self-monitor, for weight loss and/or signs of neuropathy, and/or odd neurological sensations, especially in the body periphery e.g. the limbs. An embodiment is to use almitrine for anti-cancer therapy under medical supervision. Wherein, in animal or human, almitrine dosage, frequency, route and duration of administration is directed/recommended, and/or almitrine is administered, by a medically qualified professional(s) e.g. a doctor or vet or nurse or

pharmacist. In an embodiment, an oncologist or other cancer specialist or a medically qualified professional that has undergone additional training and/or qualification and/or residency in oncology beyond a degree in human and/or veterinary medicine. And optionally wherein one or more of the dosage, frequency, route and duration of almitrine administration is modulated in the light of cancer progression/regression/stasis during the course of almitrine administration.

Mechanistic studies in animals [129-130] have identified that it might not be almitrine itself that causes almitrine associated neuropathy but instead difluorobenzhydrylpiperadine (DFBP), which is the major almitrine metabolite formed in humans. DFBP also causes weight loss in [129] and so DFBP could also be the basis to almitrine associated weight loss (reported in [120]), or this could just be a function of altered feeding behaviour as a function of the DFBP generated neuropathy. To render DFBP from almitrine, the bond between almitrine's nitrogen, at atom number 11, and carbon, at atom number 9, must be broken. An embodiment of this invention is almitrine isotopically enriched (greater than natural abundance, e.g. {non-limiting} >70%) for ^{15}N at Atom Number 11, and/or isotopically enriched for ^{13}C at Atom Number 9, which will make this bond stronger by the kinetic isotope effect (KIE), which will reduce the rate of DFBP formation, and reduce neuropathy (Atom Numbers as labelled by [25]). Kinetic isotope effect (KIE) is the change in the rate of a chemical reaction when one (or more) of the atoms in the reactants is replaced with its isotope. Heavier isotopes form stronger bonds that require higher energy to break them, which ultimately slows down the chemical reaction rate. Other atom(s) of almitrine enriched (greater than natural abundance, e.g. {non-limiting} >70%) with their heavier, stable respective isotope(s) (e.g. {non-limiting} ^{2}H replacements of ^{1}H) is also componentry to the present invention. As is one or more hydrogen atom(s) upon almitrine, or an aforementioned almitrine isotopologue, replaced by fluorine (or other halogen), especially near the N11-C9 bond that breaks to release DFBP, preferably upon the piperazine ring. The use of one or more of the new compositions of matter of this disclosure, to treat a condition for which almitrine has been used in humans, for (non-limiting) example, chronic obstructive pulmonary disease (COPD), is componentry to this invention. As is their use as an anti-cancer treatment.

Following reactions are illustrative, not restrictive: almitrine could be deuterated, upon its piperazine ring and/or other loci, by reactions described in [N], which deuterate sp3 carbons.

And/or by reactions described in [R1, R2, Q1, Q2] which deuterate widely, upon aromatic and alkyl molecular components. And/or by reactions described in [O1, O2], which deuterate α- and β-carbons to phenyl groups. And/or by reactions described in [D], which deuterate α- and β-carbons to tertiary amines. And/or by reactions described in [F, E1, E2, Ex1], which deuterate α-carbons to tertiary amines. And/or by reactions described in [A, B, E1, E2, F], which deuterate α-carbons to secondary amines. Whichever option(s) is chosen, solvents, temperatures, pressures, and other reaction conditions can be selected by one of ordinary skill in the art. Deuteration can be modulated by modulating reaction time: greater deuterium incorporation by longer reaction time. One can do multiple cycles of one or more of these reactions until the desired level of deuterium incorporation occurs, monitored by ^{1}H and/or ^{2}H NMR and/or mass spectrometry.

Encompassed by this invention are methods of administering an effective amount of almitrine (and/or one or more of its metabolites), or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a pharmaceutical composition(s) comprising almitrine (and/or one or more of its metabolites), optionally in co-therapy with another anti-cancer treatment(s), to treat/ameliorate/prevent/combat cancer in a subject. Encompassed by this invention are methods of administering an effective amount of GAL021 [125-126] and/or any compound(s) of [P8], or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a pharmaceutical composition(s) comprising GAL021 [125-126] and/or any compound(s) of [P8], optionally in co-therapy with another anti-cancer treatment(s), to treat/ameliorate/prevent/combat cancer in a subject. Encompassed by this invention are methods of administering an effective amount of a (e.g. chemoreceptor) respiratory stimulant(s), or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a pharmaceutical composition(s) comprising a respiratory stimulant(s), optionally in co-therapy with another anti-cancer treatment(s), to treat/ameliorate/prevent/combat cancer in a subject. Encompassed by this invention are methods of administering an effective amount of a compound(s) that increases pO2 in the subject's blood, or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a pharmaceutical composition(s) comprising a compound(s) that increases pO2 in the subject's blood, optionally in co-therapy with another anti-cancer treatment(s), to treat/ameliorate/prevent/combat cancer in the subject.

A method of treating, ameliorating, preventing or combating cancer in a subject wherein the method comprises the subject taking, or being administered, a therapeutically effective

amount of almitrine and/or other compound(s) of Formula VI (and/or a pharmaceutical composition(s) containing a therapeutically effective amount of almitrine and/or other compound(s) of Formula VI herein). Almitrine and/or other compound(s) of Formula VI, (and/or a pharmaceutical composition(s) containing almitrine and/or other compound(s) of Formula VI) for use in the treatment/amelioration/prevention/combat of cancer in a subject. The use of almitrine, and/or other compound(s) of Formula VI, in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of cancer, optionally in a ready-to-use drug form, optionally in a package together with instructions for its anti-cancer use. Almitrine, and/or other compound(s) of Formula VI, for use in a method for the treatment/amelioration/prevention/combat of cancer and/or ischemia and/or stroke (reduces ATP hydrolysis and maintains intracellular [ATP] when O_2 and glucose is in short supply because of a vascular occlusion or similar) in a subject.

Definitions used to specify Formulas (I), (II), (III), (IV), (V) and (VI)

The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 21 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two, three, or four substituents selected from the group consisting of halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=0), OR_a, SR_a, NR_aR_b, NR_aSO_2, $NR_aSO_2R_c$, SO_2R_c, $SO_2NR_aR_b$, CO_2R_a, $C(=O)R_a$, $C(=O)NR_aR_b$, $OC(=O)R_a$, —$OC(=O)NR_aR_b$, $NR_aC(=O)R_b$, $NR_aCO_2R_b$, =N—OH, =N—O-alkyl, aryl, heteroaryl, heterocyclo and cycloalkyl, wherein R_a and R_b are selected from hydrogen, alkyl, alkenyl, cycloalkyl, heterocyclo, aryl, and heteroaryl, and R_c is selected from hydrogen, alkyl, cycloalkyl, heterocyclo aryl and heteroaryl. When a substituted alkyl includes an aryl, heterocyclo, heteroaryl, or cycloalkyl substituent, said ringed systems are as defined below and thus may in turn have zero to four substituents (preferably 0-2 substituents), also as defined below. When either R_a, R_b or R_c is an alkyl, said alkyl may optionally be substituted with 1-2 of halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=0), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl),

$N(alkyl)_2$, $NHSO_2$, $NHSO_2(alkyl)$, $SO_2(alkyl)$, SO_2NH_2, $SO_2NH(alkyl)$, CO_2H, $CO_2(alkyl)$, C(=O)H, C(=O)alkyl, $C(=O)NH_2$, C(=O)NH(alkyl), $C(=O)N(alkyl)_2$, OC(=O)alkyl, —$OC(=O)NH_2$,—OC(=O)NH(alkyl), NHC(=O)alkyl, and/or $NHCO_2(alkyl)$.

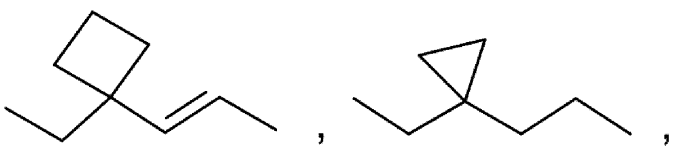
"Alkyl" when used in conjunction with another group such as in arylalkyl refers to a substituted alkyl in which at least one of the substituents is the specifically named group. For example, the term arylalkyl includes benzyl, or any other straight or branched chain alkyl having at least one aryl group attached at any point of the alkyl chain. As a further example, the term carbamylalkyl includes the group —$(CH2)_n$—NH—C(=O)alkyl, Wherein n is 1 to 12.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 21 carbon atoms and at least one double bond. Alkenyl groups of 2 to 6 carbon atoms and having one double bond are most preferred.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 21 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred.

The term "alkylene" refers to bivalent straight or branched chain hydrocarbon groups having 1 to 21 carbon atoms, preferably 1 to 8 carbon atoms, e.g., $\{—CH_2—\}_n$, Wherein n is 1 to 12, preferably 1—8. Lower alkylene groups, that is, alkylene groups of 1 to 4 carbon atoms, are most preferred. The terms "alkenylene" and "alkynylene" refer to bivalent radicals of alkenyl and alknyl groups, respectively, as defined above.

When reference is made to a substituted alkylene, alkenylene, or alkynylene group, these groups are substituted with one to four substituents as defined above for alkyl groups. A substituted alkylene, alkenylene, or alkynylene may have a ringed substituent attached in a spiro fashion as in



and so forth.

The term "alkoxy" refers to an alkyl or substituted alkyl group as defined above having one, two or three oxygen atoms (—O—) in the alkyl chain. For example, the term "alkoxy" includes the groups —O—C_{1-12}alkyl, —C_{1-6}alkylene-O—C_{1-6}alkyl, —C_{1-4}alkylene-O-phenyl, and so forth.

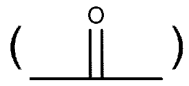
The term "thioalkyl" or "alkylthio" refers to an alkyl or substituted alkyl group as defined above having one or more sulphur (—S—) atoms in the alkyl chain. For example, the term "thioalkyl" or "alkylthio" includes the groups —$(CH_2)_n$—S—CH_2aryl, —$(CH_2)_n$—S—aryl, etc. etc.

The term "aminoalkyl" or "alkylamino" refers to an alkyl or substituted alkyl group as defined above having one or more nitrogen (—NR'—) atoms in the alkyl chain. For example, the term "aminoalkyl" includes the groups —NR'—C_{1-12}alkyl and —CH_2—NR'-aryl, etc. (where R' is hydrogen, alkyl or substituted alkyl as defined above.) "Amino" refers to the group —NH_2.

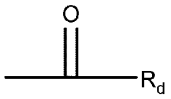
When a subscript is used as in C_{1-8}alkyl, the subscript refers to the number of carbon atoms the group may contain. Zero when used in a subscript denotes a bond, e.g., C_{0-4} alkyl refers to a bond or an alkyl of 1 to 4 carbon atoms. When used with alkoxy, thioalkyl or aminoalkyl, a subscript refers to the number of carbon atoms that the group may contain in addition to heteroatoms. Thus, for example, monovalent. C_{1-2}aminoalkyl includes the groups —CH_2—NH_2, —NH—CH_3, —$(CH_2)_2$—NH_2, —NH—CH_2—CH_3, —CH_2—NH_2—CH_3, and —N—$(CH_3)_2$. A lower aminoalkyl comprises an aminoalkyl having one to four carbon atoms.

The alkoxy, thioalkyl, or aminoalkyl groups may be monovalent or bivalent. By "monovalent" it is meant that the group has a valency (i.e., power to combine with another group), of one, and by "bivalent" it is meant that the group has a valency of two. For example, a monovalent alkoxy includes groups such as —O—C_{1-12}alkyl, —C_{1-6}alkylene—O—C_{1-6}alkyl, etc., whereas a bivalent alkoxy includes groups such as —O—C_{1-2}alkylene-, —C_{1-6}alkylene-O—C_{1-6}alkylene-, etc.

The term "acyl" refers to a carbonyl

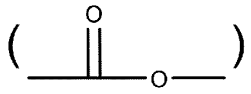


linked to an organic group i.e.

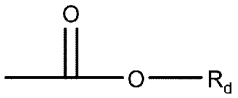


wherein R_d may be selected from alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, heterocyclo, cycloalkyl, or heteroaryl, as defined herein.

The term "alkoxycarbonyl" refers to a group having a carboxy or ester group



linked to an organic radical, i.e.,



Wherein R_d is as defined above for acyl.

The term "carbamyl" refers to a functional group in which a nitrogen atom is directly bonded to a carbonyl, i.e., as in —$NR_eC(=O)R_f$ or —$C(=O)NR_eR_f$, wherein R_e and R_f can be hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, cycloalkyl, aryl, heterocyclo, or heteroaryl, or they may join to form a ring.

The term "sulfonyl" refers to a sulphoxide group (i.e.,—$S(O)_{1-2}$) linked to an organic radical R_c, as defined above.

The term "sulfonamide" or "sulfonamido" refers to the group —$S(O)_2NR_eR_f$, wherein R_e and R_f are as defined above. Preferably when one of R_e and R_f is optionally substituted heteroaryl or heterocycle (as defined below), the other of R_e and R_f is hydrogen or alkyl.

The term "cycloalkyl" refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. The term "cycloalkyl" includes such rings having zero to four substituents (preferably 0-2 substituents), selected from the group consisting of halogen, alkyl, substituted alkyl (e.g., trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, keto, OR_d, SR_d NR_dR_e NR_cSO_2, $NR_cSO_2R_e$, C(=O)H, acyl, —CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide, —$OC(=O)R_d$, =N—OH, =N—O-alkyl, aryl, heteroaryl, heterocyclo, a 4 to 7 membered carbocyclic ring, and a five or six membered ketal, e.g., 1,3-dioxolane or 1,3-dioxane, wherein R_c, R_d and R_e are defined as above. The term "cycloalkyl" also includes such rings having a phenyl ring fused thereto or having a carbon-carbon bridge of 3 to 4 carbon atoms. Additionally, when a cycloalkyl is substituted with a further ring, i.e., aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclo, heterocycloalkyl, cycloalkylalkyl, or a further cycloalkyl ring, such ring in turn may be substituted with one to two of C_{0-4}alkyl optionally substituted with halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=0), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl), $N(alkyl)_2$, $NHSO_2$, $NHSO_2$(alkyl), SO_2(alkyl), SO_2NH_2, SO_2NH(alkyl), CO_2H, CO_2(alkyl), C(=O)H, C(=O)alkyl, $C(=O)NH_2$, C(=O)NH(alkyl), $C(=O)N(alkyl)_2$, OC(=O)alkyl, —$OC(=O)NH_2$, —OC(=O)NH(alkyl), NHC(=O)alkyl, and $NHCO_2$(alkyl).

The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

The term "aryl" refers to phenyl, biphenyl, l-naphthyl, 2-naphthyl, and anthracenyl, with phenyl being preferred. The term "aryl" includes such rings having zero to four substituents (preferably 0—2 substituents), selected from the group consisting of halo, alkyl, substituted alkyl (e.g., trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, OR_d, SR_d, NR_dR_e, NR_dSO_2, $NR_dSO_2R_c$, C(=O)H, acyl, —CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide, —$OC(=O)R_d$, heteroaryl, heterocyclo, cycloalkyl, phenyl, benzyl, napthyl, including phenylethyl, phenyloxy, and phenylthio, wherein R_c, R_d and R_e are defined as above. Additionally, two substituents attached to an aryl, particularly a phenyl group, may

join to form a further ring such as a fused or spiro-ring, e.g., cyclopentyl or cyclohexyl or fused heterocycle or heteroaryl. When an aryl is substituted with a further ring, such ring in turn may be substituted with one to two of C_{0-4}alkyl optionally substituted with halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=0), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl), N(alkyl)2, $NHSO_2$, $NHSO_2$(alkyl), SO_2(alkyl), SO_2NH_2, SO_2NH(alkyl), CO_2H, CO_2(alkyl), C(=O)H, C(=O)alkyl, C(=O)NH_2, C(=O)NH(alkyl), C(=O)N(alkyl)$_2$, OC(=O)alkyl, —OC(=O)NH_2, —OC(=O)NH(alkyl), NHC(=O)alkyl, and $NHCO_2$(alkyl).

The term "heterocyclo" refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups, in which at least one of the rings has at least one heteroatom selected from O, S and N. Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may contain zero to four substituents (preferably 0-2 substituents), selected from the group consisting of halo, alkyl, substituted alkyl (e.g., trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, keto, OR_d, SR_d, NR_dR_e, NR_dSO_2, $NR_dSO_2R_c$, SO_2R_d, C(=O)H, acyl, —CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide, —OC(=O)R_d, =N—OH, =N—O-alkyl, aryl, heteroaryl, cycloalkyl, a five or six membered ketal, e.g., 1,3-dioxolane or 1,3-dioxane, or a monocyclic 4 to 7 membered non aromatic ring having one to four heteroatoms, wherein R_c, R_d and R_e are defined as above. The term "heterocyclo" also includes such rings having a phenyl ring fused thereto or having a carbon-carbon bridge of 3 to 4 carbon atoms. Additionally, when a heterocyclo is substituted with a further ring, i.e., aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or a further heterocyclo ring, such ring in turn may be substituted with one to two of C_{0-4}alkyl optionally substituted with halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=0), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl), N(alkyl)$_2$, $NHSO_2$, $NHSO_2$(alkyl), SO_2(alkyl),

SO_2NH_2, SO_2NH(alkyl), CO_2H, CO_2(alkyl), C(=O)H, C(=O)alkyl, $C(=O)NH_2$, C(=O)NH(alkyl), $C(=O)N(alkyl)_2$, OC(=O)alkyl, —$OC(=O)NH_2$, —OC(=O)NH (alkyl), NHC(=O)alkyl, and $NHCO_2$(alkyl).

Exemplary monocyclic groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5 to 7 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom selected from O, S and N in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero to four substituents (preferably 0-2 substituents), selected from the group consisting of halo, alkyl, substituted alkyl (e.g., trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, OR_d, SR_d, NR_dR_e, NR_dSO_2, $NR_dSO_2R_c$, SO_2R_d, C(=O)H, acyl, —CO_2H, alkoxycarbonyl, carbamyl, sulfonyl, sulfonamide, —$OC(=O)R_d$, heterocyclo, cycloalkyl, aryl, or a monocyclic 4 to 7 membered aromatic ring having one to four heteroatoms, including phenylethyl, phenyloxy, and phenylthio, wherein R_c, R_d and R_e are defined as above. Additionally, when a heteroaryl is substituted with a further ring, i.e., aryl, arylalkyl, heterocyclo, heterocycloalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, or a further heteroaryl ring, such ring in turn may be substituted with one to two of C_{0-4} alkyl optionally substituted with halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=0), OH, O(alkyl), phenyloxy, benzyloxy, SH, S(alkyl), NH_2, NH(alkyl), $N(alkyl)_2$, $NHSO_2$,

$NHSO_2(alkyl)_n$, $SO_2(alkyl)$, SO_2NH_2, $SO_2NH(alkyl)$, CO_2H, $CO_2(alkyl)$, C(=O)H, C(=O)alkyl, $C(=O)NH_2$, C(=O)NH(alkyl), $C(=O)N(alkyl)_2$, OC(=O)alkyl,—$OC(=O)NH_2$, —OC(=O)NH(alkyl), NHC(=O)alkyl, and $NHCO_2(alkyl)$.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl

(i.e.),

thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyridinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

When the term “unsaturated” is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

The phrase “optionally substituted” is intended to include substituted or unsubstituted possibilities. Accordingly, the phrase “each group of which may be optionally substituted means that each group includes both substituted and unsubstituted groups.

The use of the phrase “Where valence allows” means that the groups may be substituted only to the degree and nature allowed by valency of the group. This is commonly understood by those of skill in the art. For example, a hydrogen substituent cannot be further substituted nor can a phenyl group be directly substituted by an oxo group due to limits on valency.

The term "substituted amino" refers to a group of the formula $-NZ^2Z^3$ wherein Z^2 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, (cycloalkyl)alkyl, morpholinylalkyl, heterocyclo or (heterocyclo)alkyl and Z^3 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl, (cycloalkyl)alkyl or hydroxyalkyl further substituted with a carboxylic ester or carboxylic acid, with the proviso that when Z^2 is hydrogen, then Z^3 is other than hydrogen; or Z^2 and Z^3 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl; or 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

The term "heterocyclo" or "hetero" also includes such monocyclic and bicyclic rings wherein an available carbon atom is substituted with a $(C_1\text{-}C_4)$-alkyl, aryl, $(C_1\text{-}C_4)$-alkylthio, $(C_1\text{-}C_4)$-alkoxy, halo, nitro, keto, cyano, hydroxy, azo, thiazo, amino, -NH-$(C_1\text{-}C_4)$-alkyl, -N($(C_1\text{-}C_4)$-alkyl)$_2$, $-CF_3$, (aminoester)alkyl, carboxylic acid, carboxylic ester, $-OCHF_2$ or $(C_1\text{-}C_4)$-alkoxy further substituted with a carboxylic acid or such monocyclic and bicyclic rings wherein two or three available carbons have substituents selected from methyl, methoxy, methylthio, halo, $-CF_3$, nitro, hydroxy, amino and $-OCHF_2$.

Stereoisomers

All stereoisomers of Formula [X], such as those, for example, which may exist due to asymmetric carbons, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms, are contemplated and within the scope of this invention. Individual stereoisomers of the compounds of this invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other or other selected, stereoisomers. The chiral centers of the present invention can have the *S* or *R* configuration as defined by the IUPAC 1974 Recommendations.

For the molecules presented in this invention's Description and Drawings: the present invention contemplates all polymorphs, metabolites, isotopologues, geometric/conformational isomers, rotamers, atropisomers, stereoisomers, optically active forms, tautomers, keto-enol tautomers, cis- and trans- isomers, *E* and *Z* isomers, *R*- and *S*-enantiomers, diastereomers, isomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, other mixtures thereof and isotopic variants (e.g. deuterium in place of hydrogen in some or

all places upon the molecule{s}) as falling within the scope of the invention. All such isomers, as well as mixtures thereof, are intended to be included in this invention. As well as analogues and pharmaceutically/physiologically acceptable salts/ethers/esters/solvates/hydrates/chelates/complexes/metal complexes/mixtures/prodrugs/particles/radionuclides/derivatives/carriers/crystalline forms/liposomes thereof. Unless indicated otherwise, chemical structures and graphical representations of compounds herein encompass all stereoisomers. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers. The present invention is not limited to any particular mechanism, nor to any understanding of the action of the agents being administered.

The invention also embraces isotopically labelled compounds of the invention which are identical to those recited herein, except 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, phosphorus, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Salts, solvates, prodrugs

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.

The compounds of Formula [X] form salts which are also within the scope of this invention. Reference to a compound of the Formula [X] herein is understood to include reference to salts thereof, unless otherwise indicated.

As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (e.g., acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of ordinary skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and

bases. For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable). However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation, isolation or purification of a pharmaceutically acceptable compound.

The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of Formula [X] contains both a basic moiety, such as, but not limited to an amine or a pyridine or imidazole ring, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

Salts of the compounds of the Formula [X] may be formed, for example, by reacting a compound of the Formula [X] with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of Formula [X] which contain a basic moiety, such as, but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihalo acetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methane-sulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

The compounds of Formula [X] which contain an acidic moiety, such as, but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines [formed with N,N-bis(dehydro-abietyl)ethylenediamine], N-methyl D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e. g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

Compounds of the Formula [X], and salts thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

In addition, compounds of the Formulas [X] may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (i.e., a compound of Formula [X]) is a prodrug within the scope and spirit of the invention.

For example, pro-drug compounds of the Formulas [X] may be carboxylate ester moieties. A carboxylate ester may be conveniently formed by esterifying any of the carboxylic acid functionalities found on the disclosed ring structure(s).

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985), and *Methods in Enzymology*, Vol. 42, p. 309—396, edited by K. Widder, et. al. (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113—191 (1991);

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, p. 1—38 (1992);

d) H. Bundgaard, et al., *Journal of Pharmaceutical Sciences*, Vol. 77, p. 285 (1988); and
e) N. Kakeya, et. al., *Chem Phar Bull*, Vol. 32, p. 692 (1984).

It should further be understood that solvates (e.g., hydrates) of the compounds of Formula [X] are also within the scope of the present invention. Methods of solvation are generally known in the art.

Chelates, metal complexes, mixtures, radio-nuclides and liposomes of Formula [X] are within the scope of this invention.

Dosage

As used herein, the term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route.

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art. The specific dose level and frequency of dosage for any particular subject may vary and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

An exemplary effective amount of compounds of Formula [X] may be within the dosage range of about 0.001 to about 300 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses. But more exactly it depends upon the compound used, the condition and its advancement/severity, the route of administration, type of dosing (e.g. pulse or consistent etc.), what other treatments are undertaken alongside or previously (e.g. chemotherapeutics, surgery, radiotherapy etc.), the age, sex, condition, previous/other diseases of the patient, pharmacokinetics of compound in that patient, response to treatment and exceptions to this dosage range may be contemplated by the present invention, and they might be changed during treatment to find

the optimum. Optimal dosages to be administered to a subject may be determined by those skilled in the art. When the compounds described herein are co-administered with another agent, the effective amount may be less than when the agent is used alone.

Pharmaceutical composition

As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo*. Disclosed is a pharmaceutical composition of a therapeutically effective amount of a compound(s) of Formula [X] or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, additives and/or diluents.

As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (e.g., such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see e.g., Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, Pa. [1975].

Administration

The compounds of Formula [X] may be administered by any means suitable for the condition to be treated. For example: oral, parenteral, enteral, infusion, injection, sub-lingual, topical, rectal, transdermal, intramuscular and inhalation. The compound may be delivered orally, such as in the form of tablets, capsules, granules, microgranules, pellets, soft-gels, powders, or liquid formulations including syrups, liquids, solutions, elixirs, suspensions, emulsions or magmas; sublingually; bucally; transdermally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystal line cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavouring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may be orally delivered by sublingual and/or buccal administration, e.g., with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (e.g., GANTREZ®); and agents to control release such as polyacrylic copolymer (e.g., CARBOPOL 934®). Lubricants, glidants, flavours, colouring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

Co-administration

As used herein, the term "co-administration" refers to the administration of at least two agent(s) (e.g., a compound of the present invention) or therapies to a subject. In some embodiments, the co-administration of two or more agents/therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents/therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents/therapies are co-administered, the respective agents/therapies are administered at lower dosages than appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents/therapies lowers the requisite dosage of a known potentially harmful (e.g., toxic) agent(s).

PATENTS, OR PATENT APPLICATIONS, CITED

[P1] Atwal KS, Grover GJ, Ding CZ, Stein PD, Lloyd J, Ahmad S, Hamann LG, Green D, Ferrara FN, inventors; Bristol-Myers Squibb Co., assignee. (1-phenyl-2-heteoaryl) ethyl-guanidine compounds as inhibitors of mitochondrial F1F0 ATP hydrolase. United States patent US 6,916,813. 2005 Jul 12.

[P2] Ding C, Hamann L, Stein P, Pudzianowski A, inventors; Ding Charles Z., Hamann Lawrence G., Stein Philip D., Pudzianowski Andrew T., assignee. Benzodiazepine inhibitors of mitochondial F1F0 ATP hydrolase and methods of inhibiting F1F0 ATP hydrolase. United States patent application US 10/461,736. 2003 Jun 13.

[P3] Hamann LG, Pudzianowski AT, inventors; Bristol-Myers Squibb Company, assignee. N-substituted phenylurea inhibitors of mitochondrial F1F0 ATP hydrolase. United States patent US 6,846,836. 2005 Jan 25.

[P4] Glick GD, inventor; University of Michigan, assignee. Methods and compositions for treating diseases and conditions associated with mitochondrial function. United States patent application US 11/726,219. 2009 Nov 5.

[P5] Glick G, inventor; University of Michigan, assignee. Methods and compositions for treating diseases and conditions associated with mitochondrial function. United States patent application US 11/110,228. 2005 Dec 8.

[P6] Ding CZ, Atwal KS, inventors; Bristol-Myers Squibb Company, assignee. Sulfonamido substituted benzopyran derivatives. United States patent US 5,869,478. 1999 Feb 9.

[P7] Regnier G, Canevari R, Laubie M, inventors; En Nom Collectif Science Union, Medicale Rech France, assignee. S-triazine compounds. United States patent US 3,647,794. 1972 Mar 7.

[P8] Dax SL, Woodward R, Peng S, inventors; Galleon Pharmaceuticals Inc, assignee. Compounds as respiratory stimulants for treatment of breathing control disorders or diseases. United States patent US 9,351,972. 2016 May 31.

NON-PATENT REFERENCES

[1] Stryer L, Berg JM, Tymoczko JL (2002) Biochemistry, 4th Ed. New York, NY: WH Freeman.

[2] Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P (1994) Molecular Biology Of The Cell, 3rd Ed. New York, NY: Garland Publishing.

[3] Nicholls DG, Ferguson S (2013) Bioenergetics. Academic Press.

[4] Hong S, Pedersen PL (2008) ATP synthase and the actions of inhibitors utilized to study its roles in human health, disease, and other scientific areas. Microbiology and Molecular Biology Reviews 72(4):590-641.

[5] Atwal KS, Ahmad S, Ding CZ, Stein PD, Lloyd J, Hamann LG, Green DW, Ferrara FN, Wang P, Rogers WL, Doweyko LM, Miller AV, Bisaha SN, Schmidt JB, Li L, Yost KJ, Lan HJ, Madsen CS (2004) N-[1-Aryl-2-(1-imidazolo)ethyl]-guanidine derivatives as potent inhibitors of the bovine mitochondrial F_1F_0 ATP hydrolase. Bioorg. Med. Chem. Lett. 141027-1030.

[6] Bisaha SN, Malley MF, Pudzianowski A, Monshizadegan H, Wang P, Madsen CS, Gougoutas JZ, Stein PD (2005) A switch in enantiomer preference between mitochondrial F 1 F 0-ATPase chemotypes. Bioorganic & medicinal chemistry letters 15(11):2749-51.

[7] Atwal KS, Wang P, Rogers WL, Sleph P, Monshizadegan H, Ferrara FN, Traeger S, Green DW, Grover GJ (2004) Small molecule mitochondrial F_1F_0 ATPase hydrolase inhibitors as cardioprotective agents. Identification of 4-(N-arylimidazole)-substituted benzopyran derivatives as selective hydrolase inhibitors. J. Med. Chem. 471081-1084. **INCLUDING** this paper's supplementary material.

[8] Hamann LG, Ding CZ, Miller AV, Madsen CS, Wang P, Stein PD, Pudzianowski AT, Green DW, Monshizadegan H, Atwal KS (2004) Benzodiazepine-based selective inhibitors of mitochondrial F_1F_0 ATP hydrolase. Bioorg. Med. Chem. Lett. 141031-1034.

[9] Grover GJ, Marone PA, Koetzner L, Seto-Young D (2008) Energetic signalling in the control of mitochondrial F 1 F 0 ATP synthase activity in health and disease. The international journal of biochemistry & cell biology 40(12):2698-2701.

[10] Grover GJ, Malm J (2008) Pharmacological Profile of the Selective Mitochondrial F1F0 ATP Hydrolase Inhibitor BMS-199264 in Myocardial Ischemia. Cardiovascular therapeutics 26(4):287-296.

[11] Grover GJ, Atwal KS, Sleph PG, Wang FL, Monshizadegan H, Monticello T, Green DW (2004) Excessive ATP hydrolysis in ischemic myocardium by mitochondrial F1F0-ATPase: effect of selective pharmacological inhibition of mitochondrial ATPase hydrolase activity. American Journal of Physiology-Heart and Circulatory Physiology 287(4):H1747-H1755.

[12] Ivanes F (2013) New mechanisms of protection of cardiomyocytes from ischemia/reperfusion injury (Doctoral dissertation, Université Claude Bernard-Lyon I).

[13] Ivanes F, Faccenda D, Gatliff J, Ahmed AA, Cocco S, Cheng CHK, ... & Campanella M (2014) The compound BTB06584 is an IF1-dependent selective inhibitor of the mitochondrial F1Fo-ATPase. British journal of pharmacology 171(18):4193-4206.

[14] Salomon AR, Voehringer DW, Herzenberg LA, Khosla C (2000) Understanding and exploiting the mechanistic basis for selectivity of polyketide inhibitors of F0F1-ATPase. Proceedings of the National Academy of Sciences. 97(26):14766-71.

[15] Kramar R, Hohenegger M, Srour AN, Khanakah G. Oligomycin toxicity in intact rats. Inflammation Research. 1984 Dec 1;15(5):660-3.

[16] National Cancer Institute (NCI) Developmental Therapeutics Program (DTP) Screening Data Database https://dtp.cancer.gov/dtpstandard/dwindex/index.jsp. Accessed on 29/06/17

[17] Gao C, Shen Y, Jin F, Miao Y, Qiu X (2016) Cancer stem cells in small cell lung cancer cell line H446: higher dependency on oxidative phosphorylation and mitochondrial substrate-level phosphorylation than non-stem cancer cells. PloS one. 11(5):e0154576.

[18] Cuezva JM, Krajewska M, de Heredia ML, Krajewski S, Santamaría G, Kim H, Zapata JM, Marusawa H, Chamorro M, Reed JC (2002) The bioenergetic signature of cancer. Cancer research. 62(22):6674-81.

[19] Aldea M, Clofent J, De Arenas CN, Chamorro M, Velasco M, Berrendero JR, Navarro C, Cuezva JM (2011) Reverse phase protein microarrays quantify and validate the bioenergetic signature as biomarker in colorectal cancer. Cancer letters. 311(2):210-8.

[20] Hjerpe E, Brage SE, Carlson J, Stolt MF, Schedvins K, Johansson H, Shoshan M, Åvall-Lundqvist E (2013) Metabolic markers GAPDH, PKM2, ATP5B and BEC-index in advanced serous ovarian cancer. BMC clinical pathology. 13(1):30.

[21] Johnson KM, Chen X, Boitano A, Swenson L, Opipari Jr AW, Glick GD (2005) Identification and validation of the mitochondrial F1F0-ATPase as the molecular target of the immunomodulatory benzodiazepine Bz-423. Chemistry & biology. 12(4):485-96.

[22] Forrest MD (2015) Why cancer cells have a more hyperpolarised mitochondrial membrane potential and emergent prospects for therapy. bioRxiv. 025197.

[23] Sgarbi G, Barbato S, Costanzini A, Solaini G, Baracca A. The role of the ATPase inhibitor factor 1 (IF1) in cancer cells adaptation to hypoxia and anoxia. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 2018 Feb 1;1859(2):99-109.(epublished 31 Oct 2017)

[24] Yin T, Lu L, Xiong Z, Wei S, Cui D (2015) ATPase inhibitory factor 1 is a prognostic marker and contributes to proliferation and invasion of human gastric cancer cells. Biomedicine & Pharmacotherapy. 70:90-6.

[25] Marvin cheminformatics suite (version 16.3.21; academic license; ChemAxon Kft., Budapest, Hungary; www.chemaxon.com)

[26] Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell. 100(1):57-70.

[27] Walenta S, Wetterling M, Lehrke M, Schwickert G, Sundfør K, Rofstad EK, Mueller-Klieser W (2000) High lactate levels predict likelihood of metastases, tumor recurrence, and restricted patient survival in human cervical cancers. Cancer research. 60(4):916-21.

[28] Paull KD, Shoemaker RH, Hodes L, Monks A, Scudiero DA, Rubinstein L, Plowman J, Boyd MR (1989) Display and analysis of patterns of differential activity of drugs against human tumor cell lines: development of mean graph and COMPARE algorithm. JNCI: Journal of the National Cancer Institute. 81(14):1088-92.

[29] https://dtp.cancer.gov/databases_tools/compare.htm. Accessed on 29/06/17

[30] Holbeck SL, Collins JM, Doroshow JH (2010) Analysis of Food and Drug Administration–approved anticancer agents in the NCI60 panel of human tumor cell lines. Molecular cancer therapeutics. 9(5):1451-60.

[31] Reinhold WC, Sunshine M, Liu H, Varma S, Kohn KW, Morris J, Doroshow J, Pommier Y (2012) CellMiner: a web-based suite of genomic and pharmacologic tools to explore transcript and drug patterns in the NCI-60 cell line set. Cancer research. 72(14):3499-511.

[32] https://discover.nci.nih.gov/cellminer/home.do. Accessed on 29/06/17

[33] Gholami AM, Hahne H, Wu Z, Auer FJ, Meng C, Wilhelm M, Kuster B (2013) Global proteome analysis of the NCI-60 cell line panel. Cell reports. 4(3):609-20.

[34] Shoemaker RH (2006) The NCI60 human tumour cell line anticancer drug screen. Nature Rev Cancer 6:813-23.

[35] NCI-60 Screening Methodology. Details of both the one-dose and five-dose assays. https://dtp.cancer.gov/discovery_development/nci-60/methodology.htm (accessed on 25th June, 2017).

[36] Martineau LC (2012) Simple thermodynamic model of unassisted proton shuttle uncoupling and prediction of activity from calculated speciation, lipophilicity, and molecular geometry. Journal of theoretical biology. 303:33-61.

[37] Jacques V, Czarnik AW, Judge TM, Van der Ploeg LH, DeWitt SH (2015) Differentiation of antiinflammatory and antitumorigenic properties of stabilized enantiomers of thalidomide analogs. Proceedings of the National Academy of Sciences. 112(12):E1471-9.

[38] Houston MA, Augenlicht LH, Heerdt BG (2011) Stable differences in intrinsic mitochondrial membrane potential of tumor cell subpopulations reflect phenotypic heterogeneity. International journal of cell biology 2011.

[39] Heerdt BG, Houston MA, Augenlicht LH (2005) The intrinsic mitochondrial membrane potential of colonic carcinoma cells is linked to the probability of tumor progression. Cancer Res 65:9861–9867.

[40] Heerdt BG, Houston MA, Augenlicht LH. Growth properties of colonic tumor cells are a function of the intrinsic mitochondrial membrane potential. Cancer Res 2006;66(3):1591–6.

[41] Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, Lee CT, Lopaschuk GD, Puttagunta L, Bonnet S, Harry G. A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer cell. 2007 Jan 31;11(1):37-51.

[42] Ye XQ, Wang GH, Huang GJ, Bian XW, Qian GS, Yu SC. Heterogeneity of mitochondrial membrane potential: a novel tool to isolate and identify cancer stem cells from a tumor mass?. Stem Cell Reviews and Reports. 2011 Mar 1;7(1):153-60.

[43] Lee DG, Choi BK, Kim YH, Oh HS, Park SH, Bae YS, Kwon BS. The repopulating cancer cells in melanoma are characterized by increased mitochondrial membrane potential. Cancer Letters. 2016 Nov 28;382(2):186-94.

[44] Boonstra J, Post JA (2004) Molecular events associated with reactive oxygen species and cell cycle progression in mammalian cells. Gene. 337:1-3.

[45] Fantin VR, St-Pierre J, Leder P (2006) Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer cell 9(6):425-434.

[46] Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, Wei R, ... & Cantley LC (2008) The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature 452(7184):230-233.

[47] Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C et al. (2007) A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer cell 11(1):37-51.

[48] Wadhwa R, Sugihara T, Yoshida A, Nomura H, Reddel RR, et al. (2000) Selective toxicity of MKT-077 to cancer cells is mediated by its binding to the hsp70 family protein mot-2 and reactivation of p53 function. Cancer Res 60:6818–6821.

[49] Schulz TJ, Thierbach R, Voigt A, et al (2006) Induction of oxidative metabolism by mitochondrial frataxin inhibits cancer growth: Otto Warburg revisited. J Biol Chem 281:977-81.

[50] Devi GS, Prasad MH, Saraswathi I, Raghu D, Rao DN, Reddy PP (2000) Free radicals antioxidant enzymes and lipid peroxidation in different types of leukemias. Clin Chim Acta 293:53–62

[51] Szatrowski, T. P., & Nathan, C. F. (1991). Production of large amounts of hydrogen peroxide by human tumor cells. Cancer research, 51(3), 794-798.

[52] Lu W, Hu Y, Chen G, Chen Z, Zhang H, Wang F, Feng L, Pelicano H, Wang H, Keating MJ, Liu J (2012) Novel role of NOX in supporting aerobic glycolysis in cancer cells with mitochondrial dysfunction and as a potential target for cancer therapy. PLoS biology. 10(5):e1001326.

[53] Block K, Gorin Y. Aiding and abetting roles of NOX oxidases in cellular transformation. Nature Reviews Cancer. 2012 Sep 1;12(9):627-37.

[54] Ben-Porath I, Thomson MW, Carey VJ, Ge R, Bell GW, Regev A, Weinberg RA (2008) An embryonic stem cell–like gene expression signature in poorly differentiated aggressive human tumors. Nature genetics. 40(5):499.

[55] Chung S, Dzeja PP, Faustino RS, Perez-Terzic C, Behfar A, Terzic A (2007) Mitochondrial oxidative metabolism is required for the cardiac differentiation of stem cells. Nat Clin Pract Cardiovasc Med 4: S60 – S67.

[56] Teslaa T, Teitell MA (2014) Pluripotent stem cell energy metabolism: an update. The EMBO journal e201490446.

[57] Hong Y, Stambrook PJ (2004) Restoration of an absent G1 arrest and protection from apoptosis in embryonic stem cells after ionizing radiation. PNAS 101(40):14443-14448.

[58] Gordon CJ (1991) Toxic-induced hypothermia and hypometabolism: Do they increase uncertainty in the extrapolation of toxicological data from experimental animals to humans? Neuroscience & Biobehavioral Reviews. 15(1):95-8.

[59] Zamzami N, Kroemer G (2001) The mitochondrion in apoptosis: how Pandora's box opens. Nat. Rev. Mol. Cell Biol. 2:67–71

[60] Donadelli M, Dando I, Dalla Pozza E, Palmieri M (2015) Mitochondrial uncoupling protein 2 and pancreatic cancer: A new potential target therapy. World journal of gastroenterology: WJG 21(11):3232.

[61] Ayyasamy V, Owens KM, Desouki MM, Liang P, Bakin A, Thangaraj K, et al. (2011) Cellular Model of Warburg Effect Identifies Tumor Promoting Function of UCP2 in Breast Cancer and Its Suppression by Genipin. PLoS ONE 6(9):e24792. doi:10.1371/journal.pone.0024792.

[62] Gordon CJ (2012) Thermal physiology of laboratory mice: Defining thermoneutrality. Journal of Thermal Biology. 37(8):654-85.

[63] Bindu B, Bindra A, Rath G (2017) Temperature management under general anesthesia: Compulsion or option. Journal of anaesthesiology, clinical pharmacology. 33(3):306.

[64] Bell EF (1983) Infant incubators and radiant warmers. Early human development. 8(3-4):351-75.

[65] Parsons K (2014) Human thermal environments: the effects of hot, moderate, and cold environments on human health, comfort, and performance. CRC press.

[66] Nair AB, Jacob S (2016) A simple practice guide for dose conversion between animals and human. Journal of basic and clinical pharmacy. 7(2):27.

[67] R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/

[68] Ward TH, Cummings J, Dean E, Greystoke A, Hou JM, Backen A, Ranson M, Dive C (2008) Biomarkers of apoptosis. British journal of cancer. 99(6):841.

[69] Yin T, Lu L, Xiong Z, Wei S, Cui D (2015) ATPase inhibitory factor 1 is a prognostic marker and contributes to proliferation and invasion of human gastric cancer cells. Biomedicine & Pharmacotherapy. 70:90-6.

[70] Zheng J, Ramirez VD (2000) Inhibition of mitochondrial proton F0F1-ATPase/ATP synthase by polyphenolic phytochemicals. British journal of pharmacology. 130(5):1115-23.

[71] Zhu A, Lee D, Shim H. Metabolic positron emission tomography imaging in cancer detection and therapy response (2011) In Seminars in oncology (Vol. 38, No. 1, pp. 55-69). WB Saunders.

[72] Zhang L, Martins AF, Mai Y, Zhao P, Funk AM, Clavijo Jordan MV, Zhang S, Chen W, Wu Y, Sherry AD. Imaging Extracellular Lactate In Vitro and In Vivo Using CEST MRI and a Paramagnetic Shift Reagent (2017) Chemistry-A European Journal. 23(8):1752-6.

[73] Chen LQ, Pagel MD (2015) Evaluating pH in the Extracellular Tumor Microenvironment Using CEST MRI and Other Imaging Methods. Advances in radiology.

[74] Anderson M, Moshnikova A, Engelman DM, Reshetnyak YK, Andreev OA (2016) Probe for the measurement of cell surface pH in vivo and ex vivo. Proceedings of the National Academy of Sciences. 201608247.

[75] Manzoor AA, Schroeder T, Dewhirst MW (2008) One-stop-shop tumor imaging: buy hypoxia, get lactate free. The Journal of clinical investigation. 118(5):1616.

[76] Ng J, Shuryak I (2015) Minimizing second cancer risk following radiotherapy: current perspectives. Cancer management and research. 7:1.

[77] Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 443(7113):787-95

[78] Umphred DA, Lazaro RT, Roller M, Burton G, editors Neurological rehabilitation. Elsevier Health Sciences; 2013 Aug 7

[79] Kang YS, Jung HJ, Oh JS, Song DY (2016) Use of PEGylated Immunoliposomes to Deliver Dopamine Across the Blood–Brain Barrier in a Rat Model of Parkinson's Disease. CNS Neuroscience & Therapeutics. 22(10):817-23.

[80] Di Gioia S, Trapani A, Mandracchia D, De Giglio E, Cometa S, Mangini V, Arnesano F, Belgiovine G, Castellani S, Pace L, Lavecchia MA (2015) Intranasal delivery of dopamine to the striatum using glycol chitosan/sulfobutylether-β-cyclodextrin based nanoparticles. European Journal of Pharmaceutics and Biopharmaceutics. 94:180-93.

[81] Oorschot DE. Total number of neurons in the neostriatal, pallidal, subthalamic, and substantia nigral nuclei of the rat basal ganglia: a stereological study using the cavalieri and optical disector methods. J Comp Neurol. 1996;366:580–599.

[82] Naoi M, Maruyama W (1999) Cell death of dopamine neurons in aging and Parkinson's disease. Mechanisms of ageing and development. 111(2):175-88

[83] Garedew A, Henderson SO, Moncada S (2010) Activated macrophages utilize glycolytic ATP to maintain mitochondrial membrane potential and prevent apoptotic cell death. Cell Death & Differentiation. 17(10):1540-50.

[84] Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P (2017) Tumour-associated macrophages as treatment targets in oncology. Nature reviews Clinical oncology.

[85] Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 30(7):1073-81.

[86] Honeycutt JB, Wahl A, Baker C, Spagnuolo RA, Foster J, Zakharova O, Wietgrefe S, Caro-Vegas C, Madden V, Sharpe G, Haase AT (2016) Macrophages sustain HIV replication in vivo independently of T cells. The Journal of clinical investigation. 126(4):1353.

[87] Araínga M, Edagwa B, Mosley RL, Poluektova LY, Gorantla S, Gendelman HE. A mature macrophage is a principal HIV-1 cellular reservoir in humanized mice after treatment with long acting antiretroviral therapy (2017) Retrovirology. 14(1):17.

[88] Appelberg KS, Wallet MA, Taylor JP, Cash MN, Sleasman JW, Goodenow MM. HIV-1 Infection Primes Macrophages through STAT Signaling to Promote Enhanced Inflammation and Viral Replication (2017) AIDS Research and Human Retroviruses.

[89] Burdo TH, Lentz MR, Autissier P, Krishnan A, Halpern E, Letendre S, Rosenberg ES, Ellis RJ, Williams KC (2011) Soluble CD163 made by monocyte/macrophages is a novel marker of HIV activity in early and chronic infection prior to and after anti-retroviral therapy. Journal of Infectious Diseases. 204(1):154-63.

[90] Yamasaki K, Chuang VT, Maruyama T, Otagiri M (2013) Albumin–drug interaction and its clinical implication. Biochimica et Biophysica Acta (BBA)-General Subjects. 1830(12):5435-43.

[91] Karimi M, Sahandi Zangabad P, Ghasemi A, Amiri M, Bahrami M, Malekzad H, Ghahramanzadeh Asl H, Mahdieh Z, Bozorgomid M, Ghasemi A, Rahmani Taji Boyuk MR (2016) Temperature-responsive smart nanocarriers for delivery of therapeutic agents: applications and recent advances. ACS applied materials & interfaces. 8(33):21107-33.

[92] Ta T, Porter TM (2013) Thermosensitive liposomes for localized delivery and triggered release of chemotherapy. Journal of controlled release. 169(1-2):112-25.

[93] Zangabad PS, Mirkiani S, Shahsavari S, Masoudi B, Masroor M, Hamed H, Jafari Z, Taghipour YD, Hashemi H, Karimi M, Hamblin MR (2017) Stimulus-responsive liposomes as smart nanoplatforms for drug delivery applications. Nanotechnology reviews.

[94] Kneidl B, Peller M, Winter G, Lindner LH, Hossann M (2014) Thermosensitive liposomal drug delivery systems: state of the art review. International journal of nanomedicine. 9:4387.

[95] Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y (2014) Engineered nanoparticles for drug delivery in cancer therapy. Angewandte Chemie International Edition. 53(46):12320-64.

[96] Hayflick L (1965) The limited in vitro lifetime of human diploid cell strains. Experimental cell research. 37(3):614-36.

[97] Cabanac A, Briese E (1992) Handling elevates the colonic temperature of mice. Physiology & behavior. 51(1):95-8.

[98] Michel C, Cabanac M (1999) Opposite effects of gentle handling on body temperature and body weight in rats. Physiology & behavior. 67(4):617-22.

[99] McCullough L, Arora S (2004) Diagnosis and treatment of hypothermia. American family physician. 70(12):2325-32.

[100] Freund G (1973) Hypothermia after acute ethanol and benzyl alcohol administration. Life sciences. 13(4):345-9.

[101] Lomax P, Bajorek JG, Chesarek WA, Chaffee RR (1980) Ethanol-induced hypothermia in the rat. Pharmacology. 21(4):288-94.

[102] Myers RD (1981) Alcohol's effect on body temperature: hypothermia, hyperthermia or poikilothermia? Brain research bulletin. 7(2):209-20.

[103] Kalant H, Le AD (1983) Effects of ethanol on thermoregulation. Pharmacology & therapeutics. 23(3):313-64.

[104] Malcolm RD, Alkana RL (1983) Temperature dependence of ethanol lethality in mice. Journal of Pharmacy and Pharmacology. 35(5):306-11.

[105] Briese E, Hernandez L (1996) Ethanol anapyrexia in rats. Pharmacology Biochemistry and Behavior. 54(2):399-402.

[106] Lomax P, Bajorek JG, Bajorek TA, Chaffee RR (1981) Thermoregulatory mechanisms and ethanol hypothermia. European journal of pharmacology. 71(4):483-7.

[107] Gad SC, Spainhour CB, Shoemake C, Pallman DR, Stricker-Krongrad A, Downing PA, Seals RE, Eagle LA, Polhamus K, Daly J (2016) Tolerable levels of nonclinical vehicles and formulations used in studies by multiple routes in multiple species with notes on methods to improve utility. International journal of toxicology 2:95-178.

[108] Gad SC, Cassidy CD, Aubert N, Spainhour B, Robbe H (2006) Nonclinical vehicle use in studies by multiple routes in multiple species. International journal of toxicology. 25(6):499-521.

[109] Gordon CJ, Puckett ET, Repasky ES, Johnstone AF (2017) A Device that Allows Rodents to Behaviorally Thermoregulate when Housed in Vivariums. Journal of the American Association for Laboratory Animal Science. 56(2):173-6.

[110] Boily P (2009) Role of voluntary motor activity on menthol-induced hyperthermia in mice. Journal of Thermal Biology. 34(8):420-5.

[111] Gaskill BN, Rohr SA, Pajor EA, Lucas JR, Garner JP (2009) Some like it hot: mouse temperature preferences in laboratory housing. Applied Animal Behaviour Science. 116(2):279-85.

[112] Ballard A, Ahmad HO, Narduolo S, Rosa L, Chand N, Cosgrove DA, Varkonyi P, Asaad N, Tomasi S, Buurma NJ, Leach AG (2018) Quantitative Prediction of Rate Constants for Aqueous Racemization To Avoid Pointless Stereoselective Syntheses. Angewandte Chemie. 130(4):994-7.

[A] Takahashi M, Oshima K, Matsubara S (2005) Ruthenium catalyzed deuterium labelling of a-carbon in primary alcohol and primary/secondary amine in D2O. Chemistry letters. 34(2):192-3.

[B] Chatterjee B, Krishnakumar V, Gunanathan C (2016) Selective a-Deuteration of Amines and Amino Acids Using D2O. Organic letters. 18(22):5892-5.

[C] Michelotti A, Rodrigues F, Roche M (2017) Development and Scale-Up of Stereoretentive a-Deuteration of Amines. Organic Process Research & Development. 21(11):1741-4.

[D] Neubert L, Michalik D, Ba¨hn S, Imm S, Neumann H, Atzrodt J, Derdau V, Holla W, Beller M (2012) Ruthenium-catalyzed selective a, ß-deuteration of bioactive amines. Journal of the American Chemical Society. 12;134(29):12239-44.

[E1] Taglang C, Martínez-Prieto LM, del Rosal I, Maron L, Poteau R, Philippot K, Chaudret B, Perato S, Sam Lone A, Puente C, Dugave C (2015) Enantiospecific C? H Activation Using Ruthenium Nanocatalysts. Angewandte Chemie International Edition. 54(36):10474-7.

[E2] Pieters G, Taglang C, Bonnefille E, Gutmann T, Puente C, Berthet JC, Dugave C, Chaudret B, Rousseau B (2014) Regioselective and stereospecific deuteration of bioactive aza compounds by the use of ruthenium nanoparticles. Angewandte Chemie International Edition. 53(1):230-4.

[F] Bhatia S, Spahlinger G, Boukhumseen N, Boll Q, Li Z, Jackson JE (2016) Stereoretentive H/D Exchange via an Electroactivated Heterogeneous Catalyst at sp3 C–H Sites Bearing Amines or Alcohols. European Journal of Organic Chemistry. 24:4230-5.

[G] Chatterjee B, Gunanathan C (2015) Ruthenium Catalyzed Selective a-and a, ß-Deuteration of Alcohols Using D2O. Organic letters. 17(19):4794-7.

[H] Khaskin E, Milstein D (2013) Simple and Efficient Catalytic Reaction for the Selective Deuteration of Alcohols. ACS Catalysis. 3(3):448-52.

[I] Bai W, Lee KH, Tse SK, Chan KW, Lin Z, Jia G (2015) Ruthenium-catalyzed deuteration of alcohols with deuterium oxide. Organometallics. 34(15):3686-98.

[J1] Breno KL, Tyler DR (2001) C- H Bond Activation in Aqueous Solution: A Linear Free Energy Relationship Investigation of the Rate-Limiting Step in the H/D Exchange of Alcohols Catalyzed by a Molybdocene. Organometallics. 20(18):3864-8.

[J2] Balzarek C, Weakley TJ, Tyler DR (2000) C- H Bond Activation in Aqueous Solution: Kinetics and Mechanism of H/D Exchange in Alcohols Catalyzed by Molybdocenes. Journal of the American Chemical Society. 122(39):9427-34.

[J3] Balzarek C, Tyler DR (1999) Intra-and Intermolecular H/D Exchange in Aqueous Solution Catalyzed by Molybdocenes. Angewandte Chemie International Edition. 38(16):2406-8.

[K] Maegawa T, Fujiwara Y, Inagaki Y, Monguchi Y, Sajiki H (2008) A convenient and effective method for the regioselective deuteration of alcohols. Advanced Synthesis & Catalysis. 350(14-15):2215-8.

[L] Bossi G, Putignano E, Rigo P, Baratta W (2011) Pincer Ru and Os complexes as efficient catalysts for racemization and deuteration of alcohols. Dalton Transactions. 40(35):8986-95.

[M] Zhang L, Nguyen DH, Raffa G, Desset S, Paul S, Dumeignil F, Gauvin RM (2016) Efficient deuterium labelling of alcohols in deuterated water catalyzed by ruthenium pincer complexes. Catalysis Communications. 84:67-70.

[N] Palmer WN, Chirik PJ (2017) Cobalt-Catalyzed Stereoretentive Hydrogen Isotope Exchange of C (sp3)–H Bonds. ACS Catalysis. 7(9):5674-8.

[O1] Sajiki H, Aoki F, Esaki H, Maegawa T, Hirota K (2004) Efficient C- H/C- D Exchange Reaction on the Alkyl Side Chain of Aromatic Compounds Using Heterogeneous Pd/C in D2O. Organic letters. 6(9):1485-7.

[O2] Esaki H, Aoki F, Umemura M, Kato M, Maegawa T, Monguchi Y, Sajiki H (2007) Efficient H/D Exchange Reactions of Alkyl-Substituted Benzene Derivatives by Means of the Pd/C–H2–D2O System. Chemistry-A European Journal. 13(14):4052-63.

[P] Hale LV, Szymczak NK (2016) Stereoretentive deuteration of a-chiral amines with D2O. Journal of the American Chemical Society. 138(41):13489-92.

[Q1] Derdau V, Atzrodt J (2006) CH/CD exchange reactions of aromatic compounds in D2O with NaBD4-activated catalysts. Synlett. (12):1918-22.

[Q2] Derdau V, Atzrodt J, Zimmermann J, Kroll C, Brückner F (2009) Hydrogen–Deuterium Exchange Reactions of Aromatic Compounds and Heterocycles by NaBD4-Activated Rhodium, Platinum and Palladium Catalysts. Chemistry-a European Journal. 15(40):10397-404.

[R1] Ito N, Watahiki T, Maesawa T, Maegawa T, Sajiki H (2008) HD exchange reaction taking advantage of the synergistic effect of heterogeneous palladium and platinum mixed catalyst. Synthesis. 09:1467-78.

[R2] Maegawa T, Ito N, Oono K, Monguchi Y, Sajiki H (2009) Bimetallic Palladium-Platinum-on-Carbon-Catalyzed HD Exchange Reaction: Synergistic Effect on Multiple Deuterium Incorporation. Synthesis. (16):2674-8.

[S] Kar S, Goeppert A, Sen R, Kothandaraman J, Prakash GS (2018) Regioselective deuteration of alcohols in D2O catalysed by homogeneous manganese and iron pincer complexes. Green Chemistry.

[AI1] Segler MH, Preuss M, Waller MP (2018) Planning chemical syntheses with deep neural networks and symbolic AI. Nature. 555(7698):604.

[AI2] Klucznik T, Mikulak-Klucznik B, McCormack MP, Lima H, Szymkuć S, Bhowmick M, Molga K, Zhou Y, Rickershauser L, Gajewska EP, Toutchkine A (2018) Efficient syntheses of diverse, medicinally relevant targets planned by computer and executed in the laboratory. Chem. 4(3):522-32.

[AI3] Segler MH, Preuss M, Waller MP. Learning to Plan Chemical Syntheses (2017) arXiv preprint arXiv:1708.04202.

[Ex1] Loh YY, Nagao K, Hoover AJ, Hesk D, Rivera NR, Colletti SL, Davies IW, MacMillan DW (2017) Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. Science. eaap9674.

[Ex2] Yu RP, Hesk D, Rivera N, Pelczer I, Chirik PJ (2016) Iron-catalysed tritiation of pharmaceuticals. Nature. 529(7585):195.

[Ex3] Zhan M, Zhang T, Huang H, Xie Y, Chen Y (2014) A simple method for α-position deuterated carbonyl compounds with pyrrolidine as catalyst. Journal of Labelled Compounds and Radiopharmaceuticals. 57(8):533-9.

[Ex4] Fodor-Csorba K, Galli G, Holly S, Gács-Baitz E (2002) Microwave-assisted deuterium exchange reactions for the preparation of reactive intermediates. Tetrahedron letters. 43(21):3789-92.

[AA1] Takeda R, Abe H, Shibata N, Moriwaki H, Izawa K, Soloshonok VA (2017) Asymmetric synthesis of α-deuterated α-amino acids. Organic & biomolecular chemistry. 15(33):6978-83.

[AA2] O'Reilly E, Balducci D, Paradisi F (2010) A stereoselective synthesis of α-deuterium-labelled (S)-α-amino acids. Amino acids. 39(3):849-58.

[AA3] Johns RB, Whelan DJ (1966) Synthesis of α-deuterated amino acids. Australian Journal of Chemistry. 19(11):2143-7.

[AA4] Mosin O, Ignatov I, Skladnev D, Shvets V (2015) The Biosynthesis of Deuterium Labeled Amino Acids Using a Strain of Facultative Methylotrophic Bacterium Brevibacterium Methylicum 5662 With RuMP Cycle of Carbon Assimilation. European Journal of Molecular Biotechnology. (1):37-52.

[AA5] Blomquist AT, Cedergren RJ, Hiscock BF, Tripp SL, Harpp DN (1966) Synthesis of highly deuterated amino acids. Proceedings of the National Academy of Sciences. 55(3):453-6.

[AA6] Thanassi JW (1971) General procedure for the preparation of deuterated and tritiated amino acids by incorporation of solvent isotope during synthesis. The Journal of organic chemistry. 36(20):3019-21.

[113] Rigoulet M, Ouhabi R, Leverve X, Putod-Paramelle F, Guérin B (1989) Almitrine, a new kind of energy-transduction inhibitor acting on mitochondrial ATP synthase. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 975(3):325-9.

[114] Rigoulet M, Fraisse L, Ouhabi R, Guérin B, Fontaine E, Leverve X (1990) Flux-dependent increase in the stoichiometry of charge translocation by mitochondrial ATPase/ATP synthase induced by almitrine. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1018(1):91-7.

[115] Leverve XM, Fontaine E, Putod-Paramelle F, Rigoulet M (1994) Decrease in cytosolic ATP/ADP ratio and activation of pyruvate kinase after in vitro addition of almitrine in hepatocytes isolated from fasted rats. The FEBS Journal. 224(3):967-74.

[116] Rigoulet M (1990) Control processes in oxidative phosphorylation: kinetic constraints and stoichiometry. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1018(2-3):185-9.

[117] Cayman chemical Safety data sheet for carboplatin. https://www.caymanchem.com/msdss/13112m.pdf (accessed on 9/10/17)

[118] Guidechem Safety data sheet for almitrine dimesylate. http://www.guidechem.com/msds/29608-49-9.html (accessed on 9/10/17)

[119] Mangin P, Krieger J, Kurtz D. Effect of oral almitrine on the sleep apnea syndrome. Revue francaise des maladies respiratoires. 1983;11(6):899-906.

[120] European Medicines Agency (23rd May 2013) Assessment report for almitrine-containing medicinal products for oral use. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Almitrine/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500144134.pdf (accessed on 12/07/17)

[121] Stavchansky S, Doluisio JT, Macleod CM, Szalkowski MB, Bachand RT, Heilman R, Sebree TB, Geary RS (1989) Single oral dose proportionality pharmacokinetics of almitrine bismesylate in humans. Biopharmaceutics & drug disposition. 10(3):229-37.

[122] http://bionumbers.hms.harvard.edu/bionumber.aspx?id=109718 (accessed on 20/06/18)

[123] Bury T, Jeannot JP, Ansquer JC, Radermecker M (1989) Dose-response and pharmacokinetic study with almitrine bismesylate after single oral administrations in COPD patients. European Respiratory Journal. 2(1):49-55.

[124] Oral almitrine to be withdrawn by EU Member States (29th May 2013) http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Almitrine/Position_provided_by_CMDh/WC500143802.pdf (accessed on 20/06/2018)

[125] Cotten JF (2014) The latest pharmacologic ventilator. Anesthesiology: The Journal of the American Society of Anesthesiologists. 121(3):442-4.

[126] Golder FJ, Hewitt MM, McLeod JF (2013) Respiratory stimulant drugs in the post-operative setting. Respiratory physiology & neurobiology. 189(2):395-402.

[127] B'chir A, Mebazaa A, Losser MR, Romieu M, Payen D (1998) Intravenous almitrine bismesylate reversibly induces lactic acidosis and hepatic dysfunction in patients with acute lung injury. Anesthesiology: The Journal of the American Society of Anesthesiologists. 89(4):823-30.

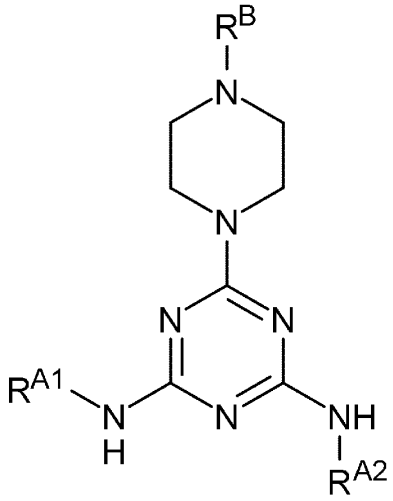
[128] Chan SC, Liu CL, Lo CM, Lam BK, Lee EW, Wong Y, Fan ST (2006) Estimating liver weight of adults by body weight and gender. World journal of gastroenterology. 12(14):2217.

[129] Yamanaka Y, Shimada T, Mochizuki R, Suzuki Y, Takenouchi K, Takeda T, Uno H, Izawa Y, Fujiwara K (1997) Neuronal and muscular inclusions in rats with hindlimb dysfunction after treating with difluorobenzhydrylpiperadine. Toxicologic pathology. 25(2):150-7.

[130] Yamanaka Y, Sakamoto E, Sakuma Y, Uno H, Koyama T, Izawa Y, Fujiwara K (1995) Lipidosis of the dorsal root ganglia in rats treated with an almitrine metabolite. Archives of toxicology. 69(6):391.

Claims

[1] A compound, or a composition containing at least one compound, of the following formula:

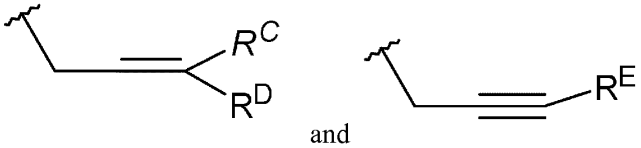


or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, for use in a method of treating, ameliorating, preventing or combating cancer, or for use in a method of treating a disease or disorder selected from

(i) cancer that metabolizes much of its glucose and/or glutamine to lactate, for example a cancer exhibiting the Warburg effect and/or a cancer that can be discriminated from surrounding tissue by PET imaging (e.g. ^{18}F-FDG PET);

(ii) cachexia or cancer driven cachexia; wherein:

R^{A1} and R^{A2} are each independently selected from the groups



and

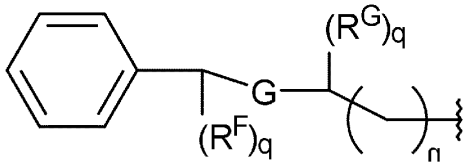
wherein R^C and R^D are each independently selected from hydrogen, deuterium, halogen and alkyl, and wherein R^E is hydrogen, deuterium, or alkyl;

R^B is selected from R^{B1}, hydrogen and deuterium;

wherein R^{B1} is selected from phenyl, benzyl, pyridyl, pyrimidyl and pyrazinyl optionally substituted with one or more substituents R^{B2};

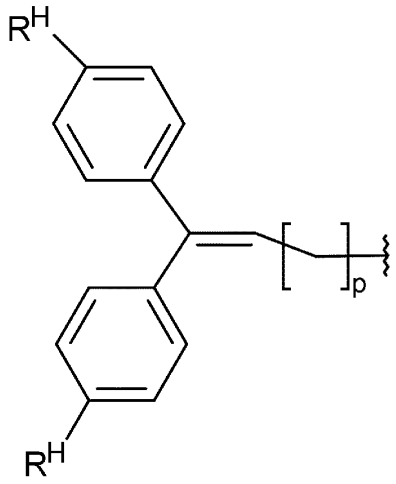
wherein each R^{B2} is independently selected from halogen, alkyl, alkoxy, nitro, amino, methoxy and polyhalogen alkyl;

or R^B is a phenylalkyl of the formula:



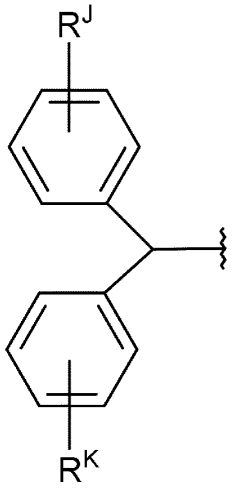
wherein R^F and R^G are hydrogen or alkyl, G is a carbon-carbon double bond or a carbon-carbon single bond, n is 0 or 1 and q is 0 or 1 provided that where q is 0, G is a carbon-carbon double bond and where q is 1, G is a carbon-carbon single bond,

or R^B is a diphenylalkyl of the formula



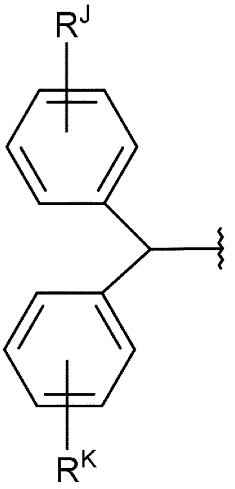
wherein R^H is hydrogen or halogen, and p is 0, 1 or 2;

or R^B is the group

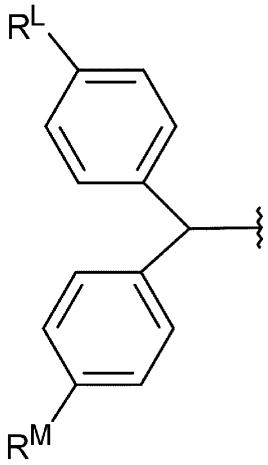


wherein R^J and R^K each independently represent 1-5 optional substituents on each ring, and wherein each R^J and each R^K, when present, is independently selected from halogen, alkyl, alkoxy, nitro, amino and polyhalogen alkyl.

[2] A compound or composition for use according to **Claim 1**, wherein R^B is the group:



[3] A compound or composition for use according to **Claim 2**, wherein R^B is the group:



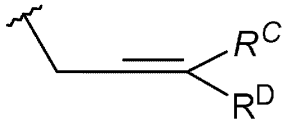
wherein R^L and R^M are each independently selected from halogen, alkyl, alkoxy, nitro, amino and polyhalogen alkyl.

[4] A compound or composition for use according to **Claim 3**, wherein R^L and R^M are each independently selected from halogen.

[5] A compound or composition for use according to **Claim 3** or **4**, wherein R^L and R^M are the same.

[6] A compound or composition for use according to **Claim 3**, wherein R^L and R^M are each F.

[7] A compound or composition for use according to any one of **Claims 1** to **6**, wherein R^{A1} and R^{A2} are each independently selected from the group



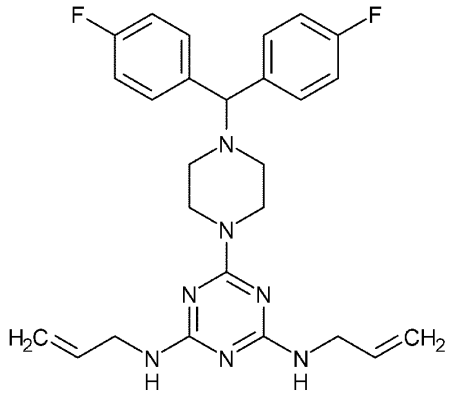
wherein R^C and R^D are each independently selected from hydrogen, deuterium, halogen and alkyl.

[8] A compound or composition for use according to **Claim 7**, wherein R^{A1} and R^{A2} are the same.

[9] A compound or composition for use according to **Claim 7** or **8**, wherein R^C is hydrogen.

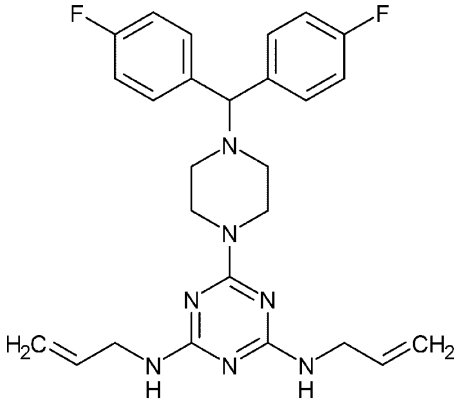
[10] A compound or composition for use according to any one of **Claims 7** to **9**, wherein R^D is hydrogen.

[11] A compound or composition for use according to **Claim 1**, wherein the compound is:



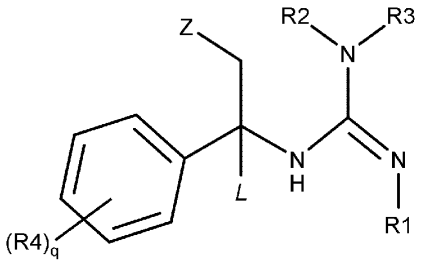
or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof.

[12] A compound or composition for use according to **Claim 1**, wherein the compound is an isotopologue(s) of:



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof.

[13] A compound having the formula,



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

L is alkyl, or deuterium, or substituted alkyl, or deuterated alkyl, or aminoalkyl, or thioalkyl, or alkoxy, or halogen, or haloalkyl, or haloalkoxy, or any atom or isotope permitted by valence except hydrogen at natural abundance;

R_1 is hydrogen, cyano, —SO_2R_8, —C(=O)R_9, heteroaryl or thiazolyl;

R_2 is (i) independently hydrogen, alkyl, benzyl, or substituted alkyl, or (ii) taken together with R_3 forms a heterocyclo;

R_3 is (i) independently alkyl, substituted alkyl, alkylthio, aminoalkyl, carbamyl, B_B-aryl, B_B-heterocyclo, B_B-heteroaryl, or B_B-cycloalkyl, or (ii) phenyl optionally substituted with C_{1-4}alkyl, halogen, trifluoromethyl, OCF_3, cyano, nitro, amino, hydroxy, or methoxy, or (iii) independently selected from C_{1-4}alkyl, alkylthio, aminoalkyl, -B_B-aryl, -B_B-heterocyclo, B_B-cycloalkyl, and -B_B-hetaroaryl, optionally having one to three substituents selected from R_{3a}; and/or having fused thereto a five or six membered carbocyclic ring, or (iv) taken together with R_2 forms a heterocyclo optionally substituted with alkyl or substituted alkyl;

B_B is a bond, C_{1-4}alkylene, C_{2-4}alkenylene, substituted C_{1-4}alkylene, substituted C_{2-4}alkenylene, substituted C_{1-4}alkylene-C(=O)NH—, —C(=O)NH—, —C_{1-4}alkylene-C(=O)NH—, —C(=O)NR_{19}—, —C_{1-4}alkylene-C(=O)NR_{19}—, or substituted C_{1-4}alkylene-C(=O)NR_{19}—, —$(CHR_{14})_m$—$(CR_{15}R_{16})_n$— or —$(CHR_{14})_p$—C(=O)NH—;

R_{3a} at each occurrence is selected independently from alkyl, substituted alkyl, halogen, haloalkoxy, cyano, nitro, keto, trifluoromethyl, —$NR_{17}R_{18}$, —SR_{17}, —OR_{17}, —SO_2R_{17a}, —$SO_2NR_{17}R_{18}$, —NR_{17}C(=O)R_{18}, —CO_2R_{17}, —C(=O)R_{17}, cyoloalkyl, aryl, heterocyolo, and heteroaryl, wherein when R_{3a} is cycloalkyl, aryl, heterocyclo or heteroaryl, said cycloalkyl, aryl, heterocyolo and heteroaryl in turn is optionally substituted with alkyl or substituted alkyl;

Z is a heteroaryl, for example an optionally-substituted bicyclic heteroaryl; or

Z is triazolyl optionally substituted with one to two R_7 substituents or imidazolyl optionally substituted with one to two R_7 substituents and/or having fused thereto a benzene ring in turn optionally substituted with one to two R_7 substituents; and

R_7 is alkyl, carbamyl, or substituted alkyl;

R_4 at each occurrence is selected independently of each other R_4 from the group consisting of halogen, trifluoromethyl, OCF_3, alkyl, substituted alkyl, haloalkyl, nitro, cyano, haloalkoxy, OR_{25}, SR_{25}, $NR_{25}R_{26}$, $NR_{25}SO_2R_{27}$, SO_2R_{27}, $SO_2NR_{25}R_{26}$, CO_2R_{26}, $C(=O)R_{26}$, $C(=O)NR_{25}R_{26}$, $OC(=O)R_{25}$, $—OC(=O)NR_{25}R_{26}$, $NR_{25}C(=O)R_{26}$, $NR_{25}CO_2R_{26}$, aryl, heteroaryl, heterocyclo and cycloalkyl;

R_8 is C_{1-4}alkyl or phenyl optionally substituted with alkyl, halogen, haloalkoxy, cyano, nitro, or trifluoromethyl;

R_9 is $—NR_{10}R_{11}$, alkyl, substituted alkyl, alkoxy, alkylthio, cycloalkyl, aryl, heteroaryl, heterocyclo, or $—CO_2R_{12}$, alkyl or phenyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, C_{1-4}alkoxy, haloalkoxy, C_{1-6}alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, NHC(=O)alky, C(=O)alkyl, and/or C_{1-4}alkyl optionally substituted with one to three of trifluoromethyl, hydroxy, cyano, phenyl, pyridinyl; and/or a five or six membered heteroaryl or heterocylo in turn optionally substituted with keto or having a benzene ring fused thereto or

a) C_{1-4}alkyl optionally substituted with one to two of:

i) SR_{13}, OR_{13}, $NR_{13a}R_{13b}$, halogen, trifluoromethyl, CO_2R_{13a}, and $C(=O)NR_{13a}R_{13b}$;

ii) cycloalkyl optionally substituted with one to two of C(=O)H, C_{1-4}acyl, alkenyl, carbamyl, and/or phenyl in turn optionally substituted with halogen;

iii) phenyl or napthyl optionally substituted with one to two of halogen, nitro, amino, alkyl, hydroxy, C_{1-4}alkoxy, or having fused thereto a five or six membered heterocyclo;

iv) pyridinyl, thiophenyl, furanyl, tetrahydrofuranyl, or azepinyl, optionally substituted with alkyl or having fused thereto a five to six membered carbocyclic ring optionally substituted with keto or C_{1-4}alkoxy;

b) 3 to 6 membered cycloalkyl optionally having up to four substituetits selected from alkyl, halogen, cyano, alkenyl, acyl, alkylthio, carbamyl, phenyl in turn optionally substituted with halogen; or having an aryl fused thereto;

c) pheyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, C_{1-4}alkoxy, haloalkoxy, C_{1-4}alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, NHC(=O)alkyl, C(=O)alkyl, and/or C_{1-4}alkyl optionally substituted with one to three of trifluoromethyl, hydroxy, cyano, phenyl, pyridinyl; and/or a five or six

membejed heteroaryl or heterocyle in turn optionally substituted with keto or having a benzene ring fused thereto;

d) pyridinyl, thiazolyl, furanyl, thiophenyl, and pyrrolyl optionally substituted with one to two of halogen, alkyl, and phenyl in turn optionally substituted with halogen or trifluoromethyl;

R_{10} and R_{11} are (i) independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, heterocyclo, cycloalkyl, aryl, heteroaryl or C_{1-4}alkyl optionally substituted with one to two of —CO_2alkyl, —C(=O)NH(aryl), NH(aryl), cycloalkyl, phenyloxy, phenyl in turn optionally substituted with C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, halogen, amino, nitro, tetrahydrofuranyl, and/or five or six membered heterocyclo, or having a five or six membered heterocyclo fused thereto; pyrrolidinyl optionally substituted with keto; napthyl, anthracenyl, pyridinyl, thiophenyl, furanyl, imidazolyl, benzimidazolyl, or indolyl in turn optionally substituted with C_{1-4}alkyl or C_{1-4}alkoxy; or (ii) taken together form a heteroaryl or heterocyclo selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, tetrahydropyridinyl, and imidazoilidinyl, wherein said heterocyclo formed by R_{10} and R_{11} is optionally substituted with one to two of keto, CO_2H, C_{14}alkoxy, CO_2alkyl, C_{1-4}carbamyl, benzyl; phenyl in turn optionally substituted with alkyl, halogen, or C_{1-4} alkoxy; tetrahydropyridinyl in turn optionally substituted with keto and/or phenyl; alkyl optionally substituted with amino or NHR_{21}wherein R_{21} is alkyl or phenyl optionally substituted with alkyl; and/or has a benzene ring fused thereto in turn optionally substituted with one to two of alkyl, C_{1-4}alkoxy, CO_2alkyl, and/or C_{1-4}carbamyl;

R_{12} and R_{19} are hydrogen or alkyl;

R_{13} is hydrogen or alkyl;

R_{13a} and R_{13b} are selected from hydrogen, alkyl, and aryl;

R_{14}, R_{15} and R_{16} at each occurrence are independently selected from hydrogen, alkyl, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, and phenyl, and/or one of R_{15} and one of R_{16} join together to form a 3 to 6 membered cycloalkyl;

R_{17} and R_{18} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, phenyl, or benzyl wherein the phenyl or benzyl is optionally substituted with alkyl, hydroxy, or hydroxyalkyl;

R_{17a} is alkyl or substituted alkyl;

R_{25} and R_{26} are independently selected from hydrogen, alkyl, or substituted alkyl, or taken together form a heterocyclo or heteroaryl ring;

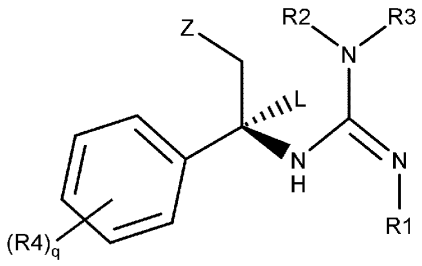
R_{27} is alkyl or substituted alkyl;

q is 0, 1, 2, or 3;

m and n are 0, 1 or 2; and

p is 0, 1, 2, or 3.

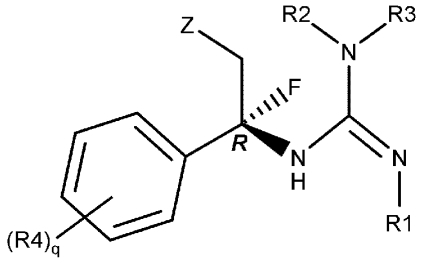
[14] A compound according to **Claim 13**, of the formula,



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

there is an enantiomeric excess (ee) of the particular stereoisomer shown in the formula.

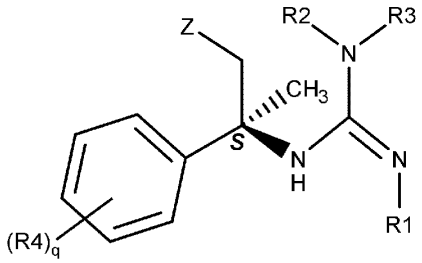
[15] A compound according to **Claim 13**, of the formula,



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

the enantiomeric excess (ee) of the *R* stereoisomer exceeds 70%;

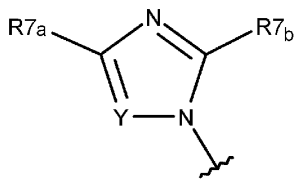
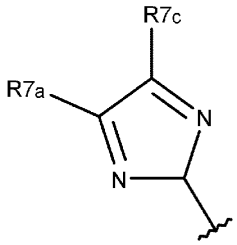
[16] A compound according to **Claim 13**, of the formula,



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

the enantiomeric excess (ee) of the *S* stereoisomer exceeds 70%;

[17] A compound according to any one of **Claims 13 to 16**, wherein,

z is  or 

Y is CH, N or CR_{7c};

R_1 is cyano, $—SO_2R_8$, $—C(=O)R_9$, or heteroaryl;

R_2 is (i) independently hydrogen, alkyl, or substituted alkyl, or (ii) taken together with R_3 forms a heterocyclo;

R_3 is (i) independently selected from

(a) alkyl optionally substituted with one to two of hydroxy and alkoxy;

(b) alkylthio or aminoalkyl optionally substituted with hydroxy or alkoxy;

(c) -A_1-aryl, wherein the aryl is optionally substituted with up to four substituents selected from alkyl, substituted alkyl, halogen, haloalkoxy, cyano, nitro, $—NR_{17}R_{18}$, $—SR_{17}$, $—OR_{17}$, $—SO_2R_{17a}$, $—SO_2NR_{17}R_{18}$, $—NR_{17}C(=O)R_{18}$, $—CO_2R_{17}$, $—C(=O)R_{17}$, cycloalkyl, aryl, heterocyclo, and heteroaryl, and/or has fused thereto a five or six membered cycloalkyl ring;

(d) -A_2-heteroaryl wherein the heteroaryl is a five or six membered monocyclic ring having 1 to 3 heteroatoms selected from N, O, and S, or an eight or nine membered bicyclic ringed system having at least one aromatic ring and 1 to 4 heteroatoms selected from N, O, and S in at least one of the rings, said heteroaryl being optionally substituted with halogen. alkyl, alkoxycarbonyl, sulfonamide, nitro, cyano, trifluoromethyl, alkylthio, alkoxy, keto, —C(=O)H, acyl, benzyloxy, hydroxy, hydroxyalkyl, or phenyl optionally substituted with alkyl or substituted alkyl;

(e) -A_2-heterocyclo wherein the heterocyclo is optionally substituted with one to two groups selected from alkyl, keto, hydroxy, hydroxyalkyl, —C(=O)H, acyl, CO_2H, alkoxycarbonyl, phenyl, and/or benzyl, and/or has a bridged carbon—carbon chain or fused benzene ring joined thereto;

(f) -A_2-cycloalkyl wherein the cycloalkyl is optionally substituted with one to two groups selected from alkyl, keto, —C(=O)H, acyl, CO_2H, alkoxycarbonyl, and/or benzyl, and/or has a bridged carbon—carbon chain or fused benzene ring joined thereto; or

(ii) taken together with R_2 forms a heterocyclo;

R_4 at each occurrence is selected independently of each other R_4 from the group consisting of halogen, alkyl, haloalkyl, cyano, and haloalkoxy;

R_{7a}, R_{7b} and R_{7c} are independently selected from hydrogen, alkyl, carbamyl, or carbamylalkyl, or R_{7a} and R_{7c} join to form an aryl or heteoraryl;

R_8 is alkyl, arylalkyl, or aryl;

R_9 is —$NR_{10}R_{11}$, alkyl, substituted alkyl, alkoxy, alkylthio, cycloalkyl, aryl, heteroaryl, heterocyclo, CO_2R_{12}, or phenyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, $C_{1\text{-}4}$alkoxy, haloalkoxy, $C_{1\text{-}6}$alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino, NH($C_{1\text{-}4}$alkyl), N($C_{1\text{-}4}$alkyl)$_2$, NHC(=O)alkyl, C(=O)alkyl, and/or $C_{1\text{-}4}$alkyl optionally substituted with one to three of trifluoromethyl, hydroxy, cyano, phenyl, pyridinyl; and/or a five or six membered heteroaryl or heterocyclo in turn optionally substituted with keto or having a benzene ring fused thereto;

R_{10} is independently hydrogen, alkyl, or alkoxy; and

R_{11} is independently hydrogen, alkyl, substituted alkyl, alkoxy heterocyclo cycloalkyl, aryl, or heteroaryl; or

R_{10} and R_{11} taken together form a heterocyclo or heteroaryl optionally substituted with alkyl, keto, CO_2H, alkoxycarbonyl, hydroxy, alkoxy, alkyl, carbamyl, aryl, or substituted alkyl, wherein when the R_{10} and R_{11} group comprises a phenyl ring, said phenyl ring is optionally substituted with one to two of alkyl, halogen, and alkoxy;

R_{12} is hydrogen or alkyl;

A_1 is —$(CHR_{14})_m$—V—$(CR_{15}R_{16})_n$— or —$(CHR_{14})_p$—(C=O)NH—;

A_2 is —$(CHR_{14})_m$—V—$(CR_{15}R_{16})_n$;

V is a bond, S, or —NR_{22}—;

R_{14}, R_{15} and R_{16} at each occurrence are independently selected from hydrogen, alkyl, hydroxy, hydroxy$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxy, and phenyl, and/or one of R_{15} and one of R_{16} join together to form a three to six membered cycloalkyl;

R_{17} and R_{18} are independently selected from hydrogen, alkyl, phenyl, and benzyl, wherein the phenyl and benzyl is optionally substituted with alkyl, hydroxy, or hydroxyalkyl;

R_{17a} is alkyl or substituted alkyl;

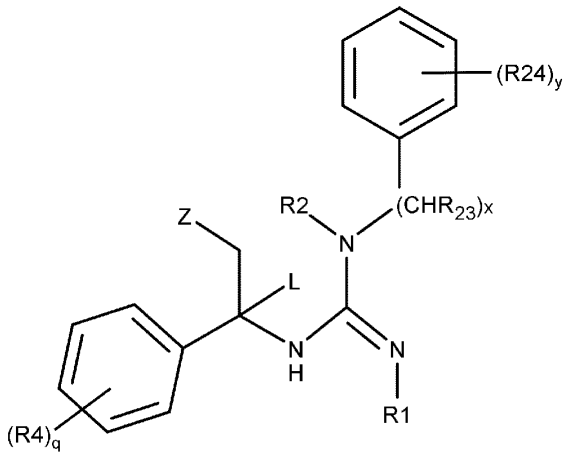
R_{22} is hydrogen or alkyl;

m and n are 0, 1, 2, or 3;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, or 3.

[18] A compound according to **Claim 17** having the formula,



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

R_{7a}, R_{7b} and R_{7c} are independently selected from hydrogen, alkyl, carbamyl or carbamylC_{1-4}alkyl, or R_{7a} and R_{7c} join to form a fused phenyl ring;

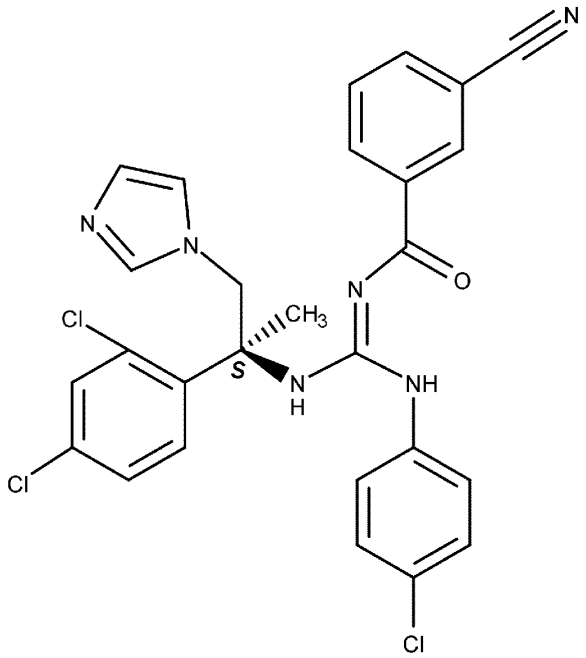
R_{23} is selected from hydrogen, alkyl, hydroxyalkyl, or phenyl;

R_{24} is selected from alkyl, halogen, trifluoromethyl, cyano, halogen, hydroxy, OCF_3, methoxy, phenyloxy, benzyloxy, cyano, acyl, or two R_{24} groups join to form a fused cycloalkyl or benzene ring; and

x is 0, 1, or 2; and

y is 0, 1, 2, or 3.

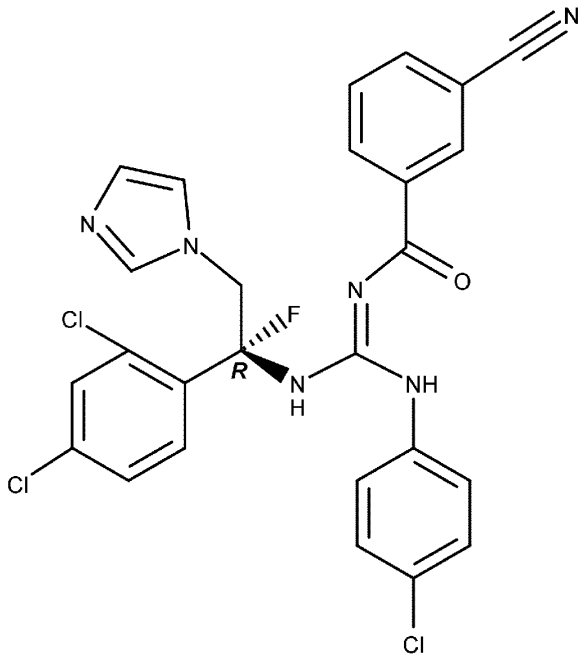
[19] A compound having the structure



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

the enantiomeric excess (ee) of the *S* stereoisomer exceeds 70%.

[20] A compound having the structure



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

the enantiomeric excess (ee) of the *R* stereoisomer exceeds 70%.

[21] A pharmaceutical composition comprising at least one compound as defined in any one of **Claims 13 to 20** and a pharmaceutically-acceptable carrier or diluent.

[22] A compound according to any one of **Claims 13 to 20**, or a pharmaceutical composition according to **Claim 21**, for use in a method of treatment of the human or animal body by therapy.

[23] A compound according to any one of **claims 13 to 20**, or a pharmaceutical composition according to **Claim 21,** for use in a method of treating, ameliorating, preventing or combating a disease or disorder selected from

(i) cancer that metabolizes much of its glucose and/or glutamine to lactate, for example a cancer exhibiting the Warburg effect and/or a cancer that can be discriminated from surrounding tissue by PET imaging (e.g. ^{18}F-FDG PET);

(ii) cachexia, cancer driven cachexia or weight loss;

(iii) disease or disorder that causes a higher than normal body temperature such as high environmental temperature, ingesting an uncoupler (e.g. 2,4-dinitrophenol), infection, sepsis, stroke, fever, pyrexia, hyperpyrexia, hyperthermia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, heatstroke, thermoregulatory disorder(s), Kawasaki syndrome, drug or drug withdrawal induced hyperthermia, idiosyncratic drug reaction, fever of unknown or uncertain origin, reaction to incompatible blood product(s), metabolic disorder(s), cancer, injury;

(iv) Tumour Associated Macrophages (TAMs) or any macrophage associated disease or disorder such as Macrophage Activation Syndrome (MAS), HIV, AIDS, HIV-associated neurocognitive disorders (HAND), HIV associated cancers, AIDS-defining cancers, non-AIDS defining cancers;

(v) virus neuroinvasion via macrophages, as used for example by HIV and SARS coronavirus;

(vi) neurocognitive or neurodegenerative diseases/disorders, for example those caused by a virus;

(vii) acute or chronic or systemic inflammation or any inflammatory disease/disorder/syndrome or any autoinflammatory disease/disorder/syndrome or any autoimmune disease/disorder/syndrome;

(viii) low or less than desired metabolic/bioenergetic efficiency in a subject, or low or less than desired physical or mental performance, or low or less than desired body weight;

(ix) disease or disorder treatable by conferring hypothermia in a subject for some medical or other purpose which can include slowing a chemical reaction(s) rate in a subject for therapeutic benefit, preventing/minimizing brain and/or tissue damage, deep hypothermic circulatory arrest for surgery, hypothermia for a surgical purpose, hypothermia for cardiac and/or cardiovascular surgery and/or brain surgery (neurosurgery), Emergency Preservation and Resuscitation (EPR), preserving detached body parts such as limbs and/or organs (for example during organ storage and/or transplant), protective hypothermia, targeted temperature management, therapeutic hypothermia, hypothermia therapy for neonatal encephalopathy, birth asphyxia, haemorrhage, hypovolemia, decompression sickness, burn injury(s) including skin burn, inflammation, allergic reaction, anaphylaxis, tissue/organ rejection, hypoxia, hypoxemia, anoxemia, anoxia, anemia, hypervolemia, altitude sickness, obstructed airway, asthma attack, hypoxia in a body/tissue/organ, hypoglycemia, reperfusion injury (ischemia-reperfusion injury), upon release of a ligature or tourniquet, uraemia, crush syndrome, compartment syndrome, traumatic brain and/or spinal cord injury, major trauma, infection, bacterial and/or viral infection(s) (e.g. meningitis), sepsis, septic shock, ischemic brain/heart/kidney injury, neuroprotection and/or cardioprotection and/or tissue protection during/after a stroke and/or ischemia and/or cardiac arrest and/or resuscitation and/or a period(s) of poor blood flow anywhere in a subject;

(x) poisoning by a toxic amount of a compound(s) in a subject e.g. carbon monoxide/methanol/heavy metal/pesticide poisoning, snake/spider/bee/insect/lizard venom, metabolic poison(s), bacterial toxin(s), endotoxemia or drug/substance overdose e.g. heroin, ethanol, prescription medication(s) or over the counter medication(s);

(xi) accelerated aging disease or progeroid syndrome including Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy, combined xeroderma pigmentosum-Cockayne syndrome, restrictive dermopathy, Wiedemann–Rautenstrauch syndrome, Hutchinson–Gilford progeria syndrome (progeria);

(xii) disease or disorder of ageing (incidence increases with increased age/senescence) and/or a disease/disorder associated with elevated reactive oxygen species including

degenerative diseases, neurodegenerative diseases, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxias, Friedreich's ataxia, dementia, Batten disease, polyglutamine diseases, osteoporosis, atherosclerosis, cardiovascular disease, myocardial infarction, cerebrovascular disease, stroke, heart failure, chronic obstructive pulmonary disease (COPD), hypertension, arthritis, cataracts, type 2 diabetes, andropause, sarcopenia, age-related macular degeneration (AMD), hearing loss, movement disability, cancer;

(xiii) aging, wherein these compounds slow ageing, extend lifespan and healthspan; or

(xiv) skin aging.

[24] A compound or composition for use according to any one of **Claims 1 to 12** or **Claim 23**, wherein the subject is further administered with one or more compounds or compositions approved for human use, optionally for anti-cancer use, by the United States Food and Drug Administration (FDA) and/or European Medicines Agency (EMA), optionally in the same pharmaceutical composition.

[25] A compound for use according to **Claim 23**, wherein the mg/kg dose administered to the subject is comparable with or larger than the mg/kg dose which would be administered to a subject of smaller bodily size, and optionally the mg/kg dosage administered to adult humans is comparable or greater than the No Observed Adverse Effects Level (NOAEL) mg/kg dosage in mice housed at 22°C.

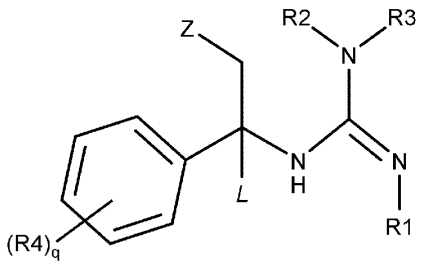
[26] A compound for use according to **Claim 23** wherein the inflammatory/autoinflammatory/autoimmune disease/disorder/syndrome is selected from acute inflammation, chronic inflammation, systemic inflammation, inflammation because of infection or foreign bodies or injury or chemical or toxin or drug or stress or frostbite or burn or ionising radiation, inflammatory diseases/disorders/syndromes, Macrophage Activation Syndrome (MAS), autoinflammatory diseases/disorders/syndromes, age-related chronic inflammatory diseases ("inflammaging"), autoimmune diseases/disorders/syndromes, diseases/disorders of the innate immune system, sore throat, sore throat associated with cold or flu or fever, high-intensity exercise associated inflammation, ulcerative colitis, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), rheumatoid arthritis, osteoarthritis, psoriatic arthritis, atopic dermatitis, allergic airway inflammation, asthma, inflammation associated depression, exercise-induced acute inflammation, atherosclerosis,

allergy, hay fever, anaphylaxis, inflammatory myopathies, drug-induced inflammation, systemic inflammatory response syndrome, sepsis-related multiple organ dysfunction/multiple organ failure, microbial infection, acute brain/lung/hepatic/renal injuries, acne vulgaris, celiac disease, celiac sprue, chronic prostatitis, colitis, diverticulitis, glomerulonephritis, hidradenitis suppurativa, hypersensitivities, interstitial cystitis, Mast Cell Activation Syndrome, mastocytosis, otitis, pelvic inflammatory disease (PID), reperfusion injury, rheumatic fever, rhinitis, sarcoidosis, transplant rejection, parasitosis, eosinophilia, type III hypersensitivity, ischaemia, chronic peptic ulcer, tuberculosis, Crohn's disease, hepatitis, chronic active hepatitis, immune hepatitis, ankylosing spondylitis, diverticulitis, fibromyalgia, systemic lupus erythematous (SLE), Alzheimer's disease, Parkinson's disease, neurodegenerative disease, cardiovascular disease, chronic obstructive pulmonary disease, bronchitis, acute bronchitis, appendicitis, acute appendicitis, bursitis, colitis, cystitis, dermatitis, encephalitis, gingivitis, meningitis, infective meningitis, myelitis, nephritis, neuritis, periodontitis, chronic periodontitis, phlebitis, prostatitis, RSD/CRPS, rhinitis, sinusitis, chronic sinusitis, tendonitis, testiculitis, tonsillitis, urethritis, vasculitis, respiratory bronchiolitis–associated interstitial lung disease and desquamative interstitial pneumonia, interstitial lung disease, Löfgren syndrome, Heerfordt syndrome, monocytosis, liver fibrosis, steatohepatitis, nonalcoholic steatohepatitis, silicosis, histiocytoses, Langerhans' cell histiocytosis, haemophagocytic lymphohistiocytosis, pulmonary langerhans cell histiocytosis, obesity, type II diabetes, gout, pseudogout, organ transplant rejection, epidermal hyperplasia, chronic fatigue syndrome, graft versus host disease (GVHD), lymphadenopathy, familial mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), Hyperimmunoglobulinemia D with recurrent fever syndrome (HIDS), cryopyrin associated periodic syndrome (CAPS), Blau syndrome, Majeed syndrome, deficiency of interleukin-1 receptor antagonist (DIRA), mevalonate kinase deficiency, pyogenic-arthritis-pyoderma gangrenosum and acne syndrome (PAPA), periodic fever aphthous stomatitis pharyngitis adenitis (PFAPA) syndrome, Behcet’s disease, Still’s disease, Crohn’s disease, Schnitzler’s syndrome, Sweet’s syndrome, NLRP12-associated autoinflammatory disorders, deficiency of interleukin-1 receptor antagonist (DIRA), pyoderma gangrenosum, cystic acne, aseptic arthritis, periodic Fever Associated with mevalonate kinase deficiency (hyperimmunoglobulin D Syndrome), Pyogenic Arthritis Pyoderma Gangrenosum Acne (PAPA) syndrome, Periodic Fever Aphthous Stomatitis, Pharyngitis and Adenopathy (PFAPA) syndrome, Adult-Onset Still’s Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Chronic Recurrent Multifocal Osteomyelitis (CRMO), Synovitis Acne

Pustulosis Hyperostosis Osteitis (SAPHO) syndrome, Cryopyrin associated Periodic Syndrome (CAPS), Familial cold auto inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), Familial cold urticarial, Neonatal onset multisystemic inflammatory disorder (NOMID), hereditary Periodic Fever Syndromes, Periodic Fever Syndromes, systemic autoinflammatory diseases, Addison's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss, Cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, coxsackie myocarditis, CREST syndrome, Berger's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, immune hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (Type 1 diabetes), juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR) PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage-Turner syndrome, Pemphigus, peripheral neuropathy, perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis

nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)), idiopathic thrombocytopenia purpura, splenomegaly.

[27] A compound according to the formula:



for use in the prevention or treatment of a disease or disorder selected from:

(i) cancer that metabolizes much of its glucose and/or glutamine to lactate, for example a cancer exhibiting the Warburg effect and/or a cancer that can be discriminated from surrounding tissue by PET imaging (e.g. ^{18}F-FDG PET);

(ii) cachexia, cancer driven cachexia or weight loss;

(iii) disease or disorder that causes a higher than normal body temperature such as high environmental temperature, ingesting an uncoupler (e.g. 2,4-dinitrophenol), infection, sepsis, stroke, fever, pyrexia, hyperpyrexia, hyperthermia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, heatstroke, thermoregulatory disorder(s), Kawasaki syndrome, drug or drug withdrawal induced hyperthermia, idiosyncratic drug reaction, fever of unknown or uncertain origin, reaction to incompatible blood product(s), metabolic disorder(s), cancer, injury;

(iv) Tumour Associated Macrophages (TAMs) or any macrophage associated disease or disorder such as Macrophage Activation Syndrome (MAS), AIDS, HIV-associated neurocognitive disorders (HAND), HIV associated cancers, AIDS-defining cancers or non-AIDS defining cancers;

(v) virus neuroinvasion via macrophages, as used for example by HIV and SARS coronavirus;

(vi) neurocognitive or neurodegenerative diseases/disorders, for example those caused by a virus;

(vii) acute or chronic or systemic inflammation or any inflammatory disease/disorder/syndrome or any autoinflammatory disease/disorder/syndrome or any autoimmune disease/disorder/syndrome;

(viii) low or less than desired metabolic/bioenergetic efficiency in a subject, or low or less than desired physical or mental performance, or low or less than desired body weight;

(ix) disease or disorder treatable by conferring hypothermia in a subject for some medical or other purpose which can include slowing a chemical reaction(s) rate in a subject for therapeutic benefit, preventing/minimizing brain and/or tissue damage, deep hypothermic circulatory arrest for surgery, hypothermia for a surgical purpose, hypothermia for cardiac and/or cardiovascular surgery and/or brain surgery (neurosurgery), Emergency Preservation and Resuscitation (EPR), preserving detached body parts such as limbs and/or organs (for example during organ storage and/or transplant), protective hypothermia, targeted temperature management, therapeutic hypothermia, hypothermia therapy for neonatal encephalopathy, birth asphyxia, haemorrhage, hypovolemia, decompression sickness, burn injury(s) including skin burn, inflammation, allergic reaction, anaphylaxis, tissue/organ rejection, hypoxia, hypoxemia, anoxemia, anoxia, anemia, hypervolemia, altitude sickness, obstructed airway, asthma attack, hypoxia in a body/tissue/organ, hypoglycemia, reperfusion injury (ischemia-reperfusion injury), upon release of a ligature or tourniquet, uraemia, crush syndrome, compartment syndrome, traumatic brain and/or spinal cord injury, major trauma, infection, bacterial and/or viral infection(s) (e.g. meningitis), sepsis, septic shock, ischemic brain/heart/kidney injury, neuroprotection and/or cardioprotection and/or tissue protection during/after a stroke and/or ischemia and/or cardiac arrest and/or resuscitation and/or a period(s) of poor blood flow anywhere in a subject;

(x) poisoning by a toxic amount of a compound(s) in a subject e.g. carbon monoxide/methanol/heavy metal/pesticide poisoning, snake/spider/bee/insect/lizard venom,

metabolic poison(s), bacterial toxin(s), endotoxemia or drug/substance overdose e.g. heroin, ethanol, prescription medication(s) or over the counter medication(s);

(xi) accelerated aging disease or progeroid syndrome including Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy, combined xeroderma pigmentosum-Cockayne syndrome, restrictive dermopathy, Wiedemann–Rautenstrauch syndrome, Hutchinson–Gilford progeria syndrome (progeria);

(xii) disease or disorder of ageing (incidence increases with increased age/senescence) and/or a disease/disorder associated with elevated reactive oxygen species including degenerative diseases, neurodegenerative diseases, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxias, Friedreich's ataxia, dementia, Batten disease, polyglutamine diseases, osteoporosis, atherosclerosis, cardiovascular disease, myocardial infarction, cerebrovascular disease, stroke, heart failure, chronic obstructive pulmonary disease (COPD), hypertension, arthritis, cataracts, type 2 diabetes, andropause, sarcopenia, age-related macular degeneration (AMD), hearing loss, movement disability, cancer;

(xiii) aging, wherein these compounds slow ageing, extend lifespan and healthspan; or

(xiv) skin aging;

wherein

L is selected from alkyl, substituted alkyl, deuterated alkyl, aminoalkyl, thioalkyl, alkoxy, halogen, haloalkyl, haloalkoxy, or any atom or isotope permitted by valence (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.);

R_1 is hydrogen, cyano, —SO_2R_8, —C(=O)R_9, heteroaryl or thiazolyl;

R_2 is (i) independently hydrogen, alkyl, benzyl, or substituted alkyl, or (ii) taken together with R_3 forms a heterocyclo;

R_3 is (i) independently alkyl, substituted alkyl, alkylthio, aminoalkyl, carbamyl, B_B-aryl, B_B-heterocyclo, B_B-heteroaryl, or B_B-cycloalkyl, or (ii) phenyl optionally substituted with $C_{1\text{-}4}$alkyl, halogen, trifluoromethyl, OCF_3, cyano, nitro, amino, hydroxy, or methoxy, or (iii) independently selected from $C_{1\text{-}4}$alkyl, alkylthio, aminoalkyl, -B_B-aryl, -B_B-heterocyclo, B_B-cycloalkyl, and -B_B-hetaroaryl, optionally having one to three substituents selected from R_{3a}; and/or having fused thereto a five or six membered carbocyclic ring, or (iv) taken together with R_2 forms a heterocyclo optionally substituted with alkyl or substituted alkyl;

B_B is a bond, C_{1-4}alkylene, C_{2-4}alkenylene, substituted C_{1-4}alkylene, substituted C_{2-4}alkenylene, substituted C_{1-4}alkylene-C(=O)NH—, —C(=O)NH—, —C_{1-4}alkylene-C(=O)NH—, —C(=O)NR_{19}—, —C_{1-4}alkylene-C(=O)NR_{19}—, or substituted C_{1-4}alkylene-C(=O)NR_{19}—, —$(CHR_{14})_m$—$(CR_{15}R_{16})_n$— or —$(CHR_{14})_p$—C(=O)NH—;

R_{3a} at each occurrence is selected independently from alkyl, substituted alkyl, halogen, haloalkoxy, cyano, nitro, keto, trifluoromethyl, —$NR_{17}R_{18}$, —SR_{17}, —OR_{17}, —SO_2R_{17a}, —$SO_2NR_{17}R_{18}$, —$NR_{17}C(=O)R_{18}$, —CO_2R_{17}, —C(=O)R_{17}, cyoloalkyl, aryl, heterocyolo, and heteroaryl, wherein when R_{3a} is cycloalkyl, aryl, heterocyclo or heteroaryl, said cycloalkyl, aryl, heterocyolo and heteroaryl in turn is optionally substituted with alkyl or substituted alkyl;

Z is a heteroaryl, for example an optionally-substituted bicyclic heteroaryl; or

Z is triazolyl optionally substituted with one to two R_7 substituents or imidazolyl optionally substituted with one to two R_7 substituents and/or having fused thereto a benzene ring in turn optionally substituted with one to two R_7 substituents; and

R_7 is alkyl, carbamyl, or substituted alkyl;

R_4 at each occurrence is selected independently of each other R_4 from the group consisting of halogen, trifluoromethyl, OCF_3, alkyl, substituted alkyl, haloalkyl, nitro, cyano, haloalkoxy, OR_{25}, SR_{25}, $NR_{25}R_{26}$, $NR_{25}SO_2R_{27}$, SO_2R_{27}, $SO_2NR_{25}R_{26}$, CO_2R_{26}, C(=O)R_{26}, C(=O)$NR_{25}R_{26}$, OC(=O)R_{25}, —OC(=O)$NR_{25}R_{26}$, NR_{25}C(=O)R_{26}, $NR_{25}CO_2R_{26}$, aryl, heteroaryl, heterocyclo and cycloalkyl;

R_8 is C_{1-4}alkyl or phenyl optionally substituted with alkyl, halogen, haloalkoxy, cyano, nitro, or trifluoromethyl;

R_9 is —$NR_{10}R_{11}$, alkyl, substituted alkyl, alkoxy, alkylthio, cycloalkyl, aryl, heteroaryl, heterocyclo, or —CO_2R_{12}, alkyl or phenyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, C_{1-4}alkoxy, haloalkoxy, C_{1-6}alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino, NH(C_{1-4}alkyl), N(C_{1-4}alkyl)$_2$, NHC(=O)alky, C(=O)alkyl, and/or C_{1-4}alkyl optionally substituted with one to three of trifluoromethyl, hydroxy, cyano, phenyl, pyridinyl; and/or a five or six membered heteroaryl or heterocylo in turn optionally substituted with keto or having a benzene ring fused thereto or

a) C_{1-4}alkyl optionally substituted with one to two of:

i) SR_{13}, OR_{13}, $NR_{13a}R_{13b}$, halogen, trifluoromethyl, CO_2R_{13a}, and C(=O)$NR_{13a}R_{13b}$;

ii) cycloalkyl optionally substituted with one to two of C(=O)H, C_{1-4}acyl, alkenyl, carbamyl, and/or phenyl in turn optionally substituted with halogen;

iii) phenyl or napthyl optionally substituted with one to two of halogen, nitro, amino, alkyl, hydroxy, C_{1-4}alkoxy, or having fused thereto a five or six membered heterocyclo;
iv) pyridinyl, thiophenyl, furanyl, tetrahydrofuranyl, or azepinyl, optionally substituted with alkyl or having fused thereto a five to six membered carbocyclic ring optionally substituted with keto or C_{1-4}alkoxy;
b) 3 to 6 membered cycloalkyl optionally having up to four substituetits selected from alkyl, halogen, cyano, alkenyl, acyl, alkylthio, carbamyl, phenyl in turn optionally substituted with halogen; or having an aryl fused thereto;
c) pheyl optionally substituted with one to four of halogen, cyano, trifluoromethyl, nitro, hydroxy, C_{1-4}alkoxy, haloalkoxy, C_{1-4}alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino NH(C_{1-4}alkyl), N(C_{1-4}alkyl)$_2$, NHC(=O)alkyl, C(=O)alkyl, and/or C_{1-4}alkyl optionally substituted with one to three of trifluoromethyl, hydroxy, cyano, phenyl, pyridinyl; and/or a five or six membejed heteroaryl or heterocyle in turn optionally substituted with keto or having a benzene ring fused thereto;
d) pyridinyl, thiazolyl, furanyl, thiophenyl, and pyrrolyl optionally substituted with one to two of halogen, alkyl, and phenyl in turn optionally substituted with halogen or trifluoromethyl;

R_{10} and R_{11} are (i) independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, heterocyclo, cycloalkyl, aryl, heteroaryl or C_{1-4}alkyl optionally substituted with one to two of —CO_2alkyl, —C(=O)NH(aryl), NH(aryl), cycloalkyl, phenyloxy, phenyl in turn optionally substituted with C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, halogen, amino, nitro, tetrahydrofuranyl, and/or five or six membered heterocyclo, or having a five or six membered heterocyclo fused thereto; pyrrolidinyl optionally substituted with keto; napthyl, anthracenyl, pyridinyl, thiophenyl, furanyl, imidazolyl, benzimidazolyl, or indolyl in turn optionally substituted with C_{1-4}alkyl or C_{1-4}alkoxy; or
(ii) taken together form a heteroaryl or heterocyclo selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl, tetrahydropyridinyl, and imidazoilidinyl, wherein said heterocyclo formed by R_{10} and R_{11} is optionally substituted with one to two of keto, CO_2H, C_{14}alkoxy, CO_2alkyl, C_{1-4}carbamyl, benzyl; phenyl in turn optionally substituted with alkyl, halogen, or C_{1-4} alkoxy; tetrahydropyridinyl in turn optionally substituted with keto and/or phenyl; alkyl optionally substituted with amino or NHR_{21}wherein R_{21} is alkyl or phenyl optionally substituted with alkyl; and/or has a benzene ring fused thereto in turn optionally substituted with one to two of alkyl, C_{1-4}alkoxy, CO_2alkyl, and/or C_{1-4}carbamyl;

R_{12} and R_{19} are hydrogen or alkyl;

R_{13} is hydrogen or alkyl;

R_{13a} and R_{13b} are selected from hydrogen, alkyl, and aryl;

R_{14}, R_{15} and R_{16} at each occurrence are independently selected from hydrogen, alkyl, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, and phenyl, and/or one of R_{15} and one of R_{16} join together to form a 3 to 6 membered cycloalkyl;

R_{17} and R_{18} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, phenyl, or benzyl wherein the phenyl or benzyl is optionally substituted with alkyl, hydroxy, or hydroxyalkyl;

R_{17a} is alkyl or substituted alkyl;

R_{25} and R_{26} are independently selected from hydrogen, alkyl, or substituted alkyl, or taken together form a heterocyclo or heteroaryl ring;

R_{27} is alkyl or substituted alkyl;

q is 0, 1, 2, or 3;

m and n are 0, 1 or 2; and

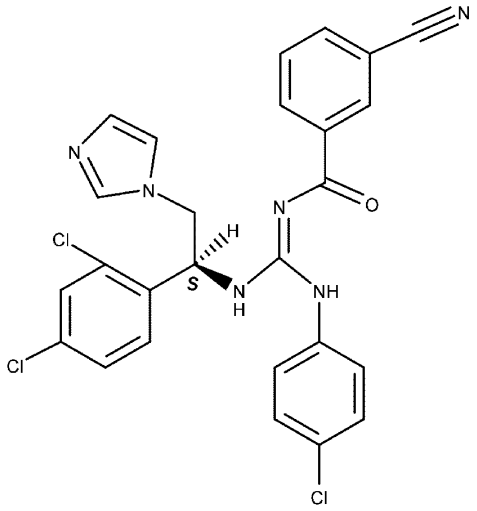
p is 0, 1, 2, or 3.

[28] A compound for use according to **Claim 27**, wherein L is hydrogen.

[29] A compound for use according to **Claim 27 or 28**, wherein the *S*-enantiomer is in enantiomeric excess.

[30] A compound for use according to **Claim 29**, wherein the enantiomeric excess of *S*-enantiomer exceeds 70%.

[31] A compound for use according to **Claim 27**, having the structure



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

the enantiomeric excess (ee) of the *S* stereoisomer exceeds 70%.

[32] A compound for use according to any one of **Claims 27 to 31**, wherein comparable or larger mg/kg doses are used in larger animals, which is very distinct from most drugs, and the mg/kg dosage administered to adult humans is comparable or greater than the No Observed Adverse Effects Level (NOAEL) mg/kg dosage in mice housed at 22°C.

[33] A compound that reduces F_1F_0 ATP hydrolysis in a subject, for use in treating, ameliorating, preventing or combating a disease or disorder selected from:

(i) cachexia, cancer driven cachexia or weight loss;

(ii) disease or disorder that causes a higher than normal body temperature such as high environmental temperature, ingesting an uncoupler (e.g. 2,4-dinitrophenol), infection, sepsis, stroke, fever, pyrexia, hyperpyrexia, hyperthermia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, heatstroke, thermoregulatory disorder(s), Kawasaki syndrome, drug or drug withdrawal induced hyperthermia, idiosyncratic drug reaction, fever of unknown or uncertain origin, reaction to incompatible blood product(s), metabolic disorder(s), cancer, injury;

(iii) Tumour Associated Macrophages (TAMs) or any macrophage associated disease or disorder such as Macrophage Activation Syndrome (MAS), AIDS, HIV-associated neurocognitive disorders (HAND), HIV associated cancers, AIDS-defining cancers or non-AIDS defining cancers;

(iv) virus neuroinvasion via macrophages, as used for example by HIV and SARS coronavirus;

(v) neurocognitive or neurodegenerative diseases/disorders, for example those caused by a virus;

(vi) low or less than desired metabolic/bioenergetic efficiency in a subject, or low or less than desired physical or mental performance, or low or less than desired body weight;

(vii) to confer hypothermia in a subject for some medical or other purpose which can include slowing a chemical reaction(s) rate in a subject for therapeutic benefit, preventing/minimizing brain and/or tissue damage, deep hypothermic circulatory arrest for surgery, hypothermia for a surgical purpose, hypothermia for cardiac and/or cardiovascular surgery and/or brain surgery (neurosurgery), Emergency Preservation and Resuscitation (EPR), preserving detached body parts such as limbs and/or organs (for example during organ storage and/or transplant), protective hypothermia, targeted temperature management, therapeutic hypothermia, hypothermia therapy for neonatal encephalopathy, birth asphyxia, haemorrhage, hypovolemia, decompression sickness, burn injury(s) including skin burn, inflammation, allergic reaction, anaphylaxis, tissue/organ rejection, hypoxia, hypoxemia, anoxemia, anoxia, anemia, hypervolemia, altitude sickness, obstructed airway, asthma attack, hypoxia in a body/tissue/organ, hypoglycemia, reperfusion injury (ischemia-reperfusion injury), upon release of a ligature or tourniquet, uraemia, crush syndrome, compartment syndrome, traumatic brain and/or spinal cord injury, major trauma, infection, bacterial and/or viral infection(s) (e.g. meningitis), sepsis, septic shock, ischemic brain/heart/kidney injury, neuroprotection and/or cardioprotection and/or tissue protection during/after a stroke and/or ischemia and/or cardiac arrest and/or resuscitation and/or a period(s) of poor blood flow anywhere in a subject;

(viii) to confer hypothermia to treat/ameliorate/prevent/combat a poisoning by a toxic amount of a compound(s) in a subject e.g. carbon monoxide/methanol/heavy metal/pesticide poisoning, snake/spider/bee/insect/lizard venom, metabolic poison(s), bacterial toxin(s), endotoxemia or drug/substance overdose e.g. heroin, ethanol, prescription medication(s) or over the counter medication(s);

(ix) accelerated aging disease or progeroid syndrome including Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy, combined xeroderma pigmentosum-Cockayne syndrome, restrictive dermopathy, Wiedemann–Rautenstrauch syndrome, Hutchinson–Gilford progeria syndrome (progeria);

(x) disease or disorder of ageing (incidence increases with increased age/senescence) and/or a disease/disorder associated with elevated reactive oxygen species including degenerative diseases, neurodegenerative diseases, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxias, Friedreich's ataxia, dementia, Batten disease, polyglutamine diseases, osteoporosis, atherosclerosis, cardiovascular disease, myocardial infarction, cerebrovascular disease, stroke, heart failure, chronic obstructive pulmonary disease (COPD), hypertension, arthritis, cataracts, type 2 diabetes, andropause, sarcopenia, age-related macular degeneration (AMD), hearing loss, movement disability, cancer;

(xi) aging, wherein these compounds slow ageing, extend lifespan and healthspan; or

(xii) skin aging.