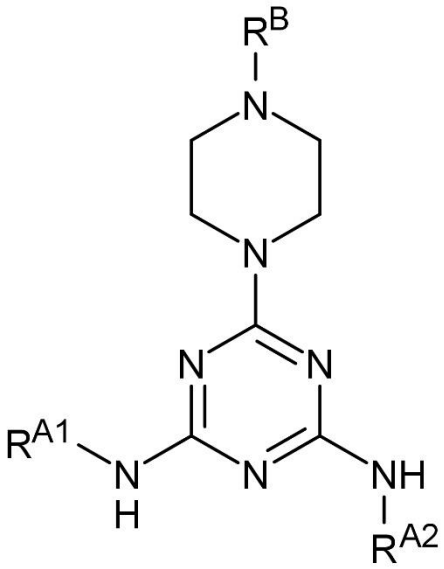
AMENDED CLAIMS (***clean version, using original claim numbers***)

[1] Use of a compound(s), or a composition(s) containing at least one compound (e.g. a pharmaceutical composition also comprising one or more of a pharmaceutically-acceptable carrier(s), additive(s), diluent(s)), of the following formula:



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, in the manufacture of a medicament for the treatment, amelioration, prevention or combat of 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) cancer originating in one of peripheral blood, bone marrow, lung, colon, Central Nervous System (CNS), brain, skin, ovary, kidney, prostate, breast/mammary gland; including metastatic forms of these cancers; cancer found in lymph node/bone/soft tissue/metastatic site(s) and/or found in/causing pleural effusion, ascites; Carcinoma, Adenocarcinoma, Squamous cell carcinoma, Large cell carcinoma, Cystadenocarcinoma, Clear cell carcinoma, Sarcoma, Blastoma, cancer of epithelial/fibroblast/promyeloblast/lymphoblast/T lymphoblast/B lymphocyte cell type, Multi Drug Resistant (MDR) cancer, Anaplastic cancer, Hematopoietic cancer, Acute Lymphoblastic Leukemia (ALL), Childhood/Adult T acute lymphoblastic leukemia, Precursor T-cell acute lymphoblastic leukemia, Acute Myeloid Leukemia (AML), Acute promyelocytic leukemia, Chronic Myeloid Leukemia/Chronic Myelogenous Leukemia

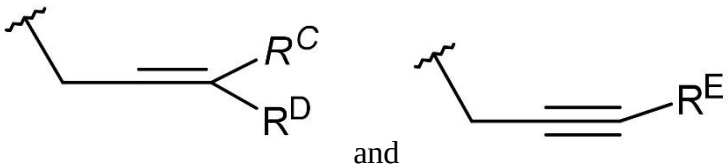
(CML), CML in blast crisis, Cancer with Philadelphia chromosome (BCR-ABL1 positive), Myeloma, Multiple myeloma, Plasma cell myeloma, Plasmacytoma, Lymphoma, Large cell immunoblastic lymphoma, Anaplastic large cell lymphoma, ALK-positive anaplastic large cell lymphoma, ALK positive cancer, Non-Small Cell Lung Cancer (NSCLC), lung carcinoma, lung adenocarcinoma, Minimally invasive lung adenocarcinoma, Non-small cell lung carcinoma, lung squamous cell carcinoma, Mesothelioma, Pleural epithelioid mesothelioma, Pleural mesothelioma, Bronchioalveolar carcinoma, Large cell lung cancer, Large cell lung carcinoma, Colon carcinoma, Colorectal carcinoma, Colon adenocarcinoma, Colorectal adenocarcinoma, Dukes' type C colorectal adenocarcinoma, Dukes' type D colorectal adenocarcinoma, Astrocytoma, Glioblastoma, Gliosarcoma, Glioblastoma multiforme, Melanoma, Malignant melanoma, Cutaneous melanoma, Amelanotic melanoma, Ovarian adenocarcinoma, Ovarian endometrioid adenocarcinoma, Endometrioid carcinoma of ovary, High grade ovarian serous adenocarcinoma, Ovarian serous cystadenocarcinoma, Renal cell carcinoma, Renal cell adenocarcinoma, Papillary renal cell carcinoma, Clear cell renal cell carcinoma, Clear cell renal carcinoma, Multi Drug Resistant (MDR) renal cancer, Prostate carcinoma, Prostate adenocarcinoma, Androgen Receptor negative (AR-) prostate cancer, Breast carcinoma, Breast adenocarcinoma, Ductal carcinoma, Invasive ductal carcinoma, Luminal A breast cancer, Estrogen Receptor positive (ER+) breast cancer, Progesterone Receptor positive (PR+) breast cancer, Hormone Receptor positive (HR+) breast cancer, Hormone responsive breast cancer, Triple Negative Breast Cancer (TNBC), Hormone Receptor negative (HR-) breast cancer, Hormone resistant breast cancer, Estrogen Receptor negative (ER-) breast cancer, Progesterone Receptor negative (PR-) breast cancer, HER2 negative (HER2-) breast cancer;

(iv) cancer that disrupts breathing and/or reduces O_2 delivery to the tissues, for example lung cancer, cancer in the lung, mesothelioma;

(v) chemotherapy and/or radiotherapy resistant/refractory cancer;

(vi) cachexia or cancer driven cachexia; wherein:

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



and

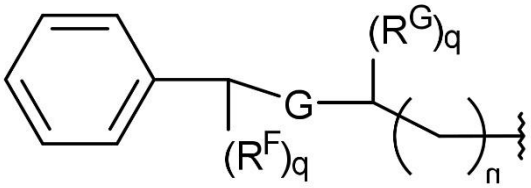
wherein R^C and R^D are each independently selected from hydrogen, deuterium, halogen and alkyl, and wherein R^E is hydrogen, deuterium, or alkyl;

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};

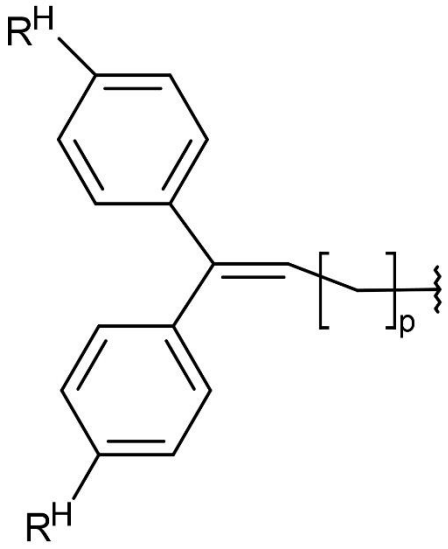
wherein each R^{B2} is independently selected from halogen, alkyl, alkoxy, nitro, amino, methoxy and polyhalogen alkyl;

or R^B is a phenylalkyl of the formula:



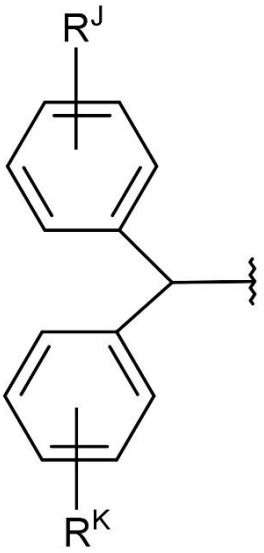
wherein R^F and R^G are hydrogen or alkyl, G is a carbon-carbon double bond or a carbon-carbon single bond, n is 0 or 1 and q is 0 or 1 provided that where q is 0, G is a carbon-carbon double bond and where q is 1, G is a carbon-carbon single bond,

or R^B is a diphenylalkyl of the formula



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

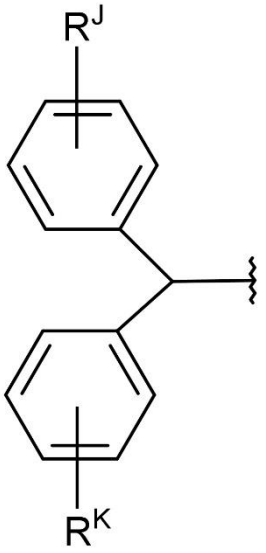
or R^B is the group



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.

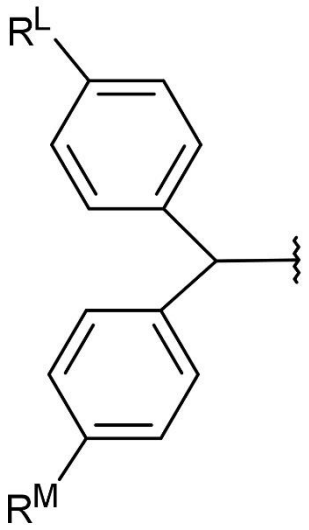
[2] Use of a compound or composition in the manufacture of a medicament according to **Claim 1**, wherein one or more of the following applies:

R^B is the group:



;

R^B is the group:



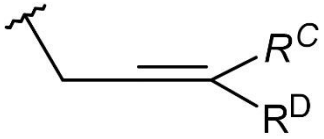
wherein R^L and R^M are each independently selected from halogen, alkyl, alkoxy, nitro, amino and polyhalogen alkyl;

R^L and R^M are each independently selected from halogen;

R^L and R^M are the same;

R^L and R^M are each F;

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



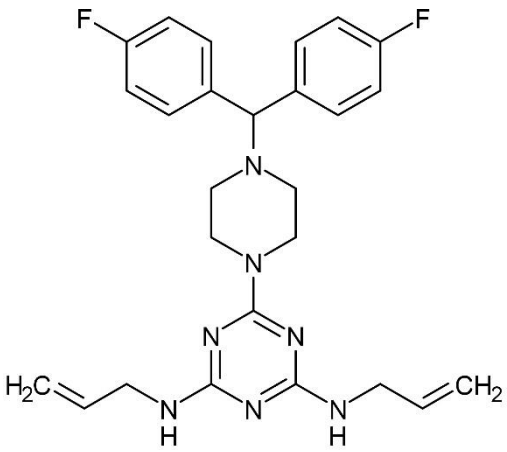
wherein R^C and R^D are each independently selected from hydrogen, deuterium, halogen and alkyl;

R^{A1} and R^{A2} are the same;

R^C is hydrogen;

R^D is hydrogen.

[11] Use of a compound or composition in the manufacture of a medicament according to **Claim 1**, wherein the compound is:



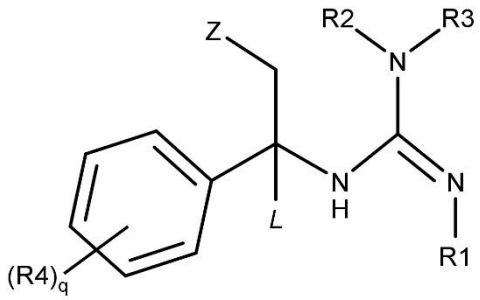
or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof or an isotopologue(s) or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof;

preferably almitrine dimesylate;

optionally for oral administration to a subject;

optionally for topical/local administration to a subject (e.g. to a cancer/tumour).

[13] A compound having the formula,



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a stereoisomer 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 (including any accompanying hydrogens by valence e.g. (non-limiting) OH, NH_2, SH, SiH_3, PH_2 etc.) except hydrogen at natural abundance;

R_1 is hydrogen, cyano, —SO_2R_8, —C(═O)R_9, or heteroaryl (such as 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-heteroaryl, 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, $C_{1\text{-}4}$alkylene, $C_{2\text{-}4}$alkenylene, substituted $C_{1\text{-}4}$alkylene, substituted $C_{2\text{-}4}$alkenylene, substituted $C_{1\text{-}4}$alkylene-C(=O)NH—, —C(=O)NH—, —$C_{1\text{-}4}$alkylene-C(=O)NH—, —C(=O)NR_{19}—, —$C_{1\text{-}4}$alkylene-C(=O)NR_{19}—, or substituted $C_{1\text{-}4}$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}, —$C(=O)R_{17}$, cycloalkyl, aryl, heterocyclo, and heteroaryl, wherein when R_{3a} is cycloalkyl, aryl, heterocyclo or heteroaryl, said cycloalkyl, aryl, heterocyclo 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 $C_{1\text{-}4}$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, $C_{1\text{-}4}$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)alky, 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 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 substituents selected from alkyl, halogen, cyano, alkenyl, acyl, alkylthio, carbamyl, phenyl in turn optionally substituted with halogen; or having an aryl fused thereto;

c) phenyl 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 membered heteroaryl or heterocyclo 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_{1-4}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;

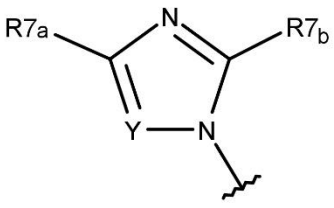
R_{27} is alkyl or substituted alkyl;

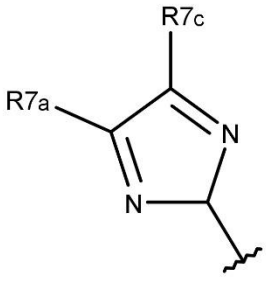
q is 0, 1, 2, or 3;

m and n are 0, 1 or 2; and

p is 0, 1, 2, or 3.

[17] A compound according to **Claim 13**, 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~~heteroaryl;

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;

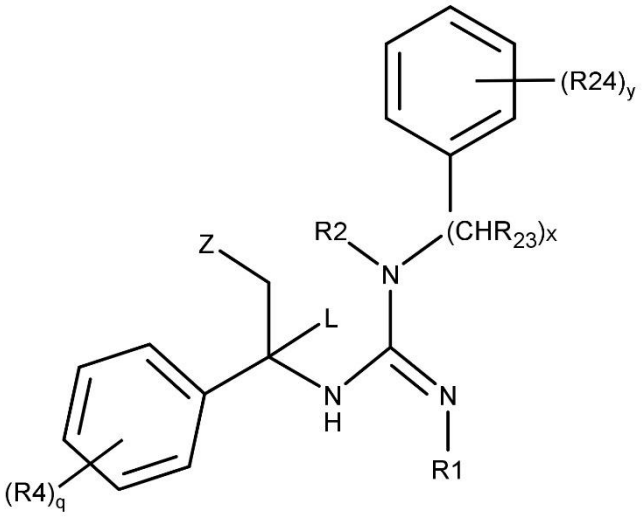
R_{22} is hydrogen or alkyl;

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 carbamyl$C_{1\text{-}4}$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.

[21] A pharmaceutical composition comprising at least one compound (or pharmaceutically acceptable salt thereof) as defined in **Claim 13** and at least one of a pharmaceutically-acceptable carrier(s), additive(s), diluent(s);
optionally wherein the pharmaceutical composition confers modified/controlled/extended/sustained/prolonged/slowed release of the compound(s) when administered to a subject,
optionally such that its constituent compound(s) amount/dose causes a smaller maximal drop, or no drop, in the subject's body temperature (but wherein the duration of the subject's body temperature drop might be extended, all be it at less amplitude: i.e. possibly less in amplitude and more in duration) than if this same/equivalent compound(s) amount/dose was administered to the subject alone or in an uncontrolled release pharmaceutical composition;
optionally wherein the pharmaceutical composition confers temperature controlled release of the compound(s) when administered to a subject,
optionally wherein the pharmaceutical composition only/preferentially releases compound(s) when subject body (or part(s) thereof) temperature is normal (e.g. within normal/typical/physiological limits range for the subject) and/or higher than normal,
optionally wherein it is higher because of exogenous heating of the subject's entire body (e.g. in a device for conferring heat/hyperthermia therapy e.g. as sometimes used clinically for anti-cancer therapy) or body part(s), wherein a body part(s) where drug release is desired, e.g. in a cancer/tumor, is exogenously heated by a method(s) of the art,
optionally wherein it is higher because of fever,
optionally wherein it is higher at a pathologically elevated temperature;
optionally wherein the pharmaceutical composition only/preferentially releases compound(s) when subject body (or part(s) thereof) temperature is normal (e.g. within normal/typical/physiological limits range for the subject) and/or higher than normal, such that

when the composition is administered to the subject it releases compound(s), which reduces subject body (or part(s) thereof) temperature, such that less/no compound(s) is then released per unit time and so the reduction in subject body (or part(s) thereof) temperature is slowed/abated and/or subject body (or part(s) thereof) temperature rises, if it rises enough then more compound(s) is released per unit time, and the loop iterates again one or more times such that subject body (or part(s) thereof) temperature drop is less in amplitude than if this same/equivalent compound(s) amount/dose was administered to the subject alone or in an uncontrolled release pharmaceutical composition;

optionally wherein the pharmaceutical composition comprises/includes one or more of biocompatible thermosensitive polymer (optionally with polysaccharide(s) to modulate the drug encapsulation and release efficiency), which undergoes a volume change at a temperature exceeding its phase/volume transition temperature, which releases the compound(s), preferably wherein the volume change is reversible if the temperature subsequently falls below the phase/volume transition temperature, preferably wherein the phase/volume transition temperature is tuned/set (optionally by tuning copolymerization conditions and by varying the content of repeating units in the copolymer) to be at normal subject body temperature or at a higher temperature, for example at a pathologically elevated body temperature, and/or at a tumor temperature and/or at an exogenously heated body/body part(s) temperature;

optionally wherein the pharmaceutical composition confers a trigger, wherein the trigger is one or more exogenously controlled stimuli (e.g. selected from temperature, ultrasonic, electronic etc.), controlled release of the compound(s) when administered to a subject;

optionally wherein the pharmaceutical composition confers a trigger, wherein the trigger is one or more cancer associated stimuli, controlled release of the compound(s) when administered to a subject;

optionally wherein the pharmaceutical composition confers pH controlled release of the compound(s) when administered to a subject, optionally only/preferentially releasing compound(s) when in an acidic environment, wherein extracellular acidity is a hallmark of cancers using Warburg metabolism;

optionally wherein the pharmaceutical composition confers dual temperature and pH controlled release of the compound(s) when administered to a subject,

optionally only/preferentially releasing compound(s) when the composition is in a body area hotter than normal subject body temperature *and* in an acidic environment;

optionally wherein the pharmaceutical composition comprises/includes one or more of temperature responsive nanoparticle, thermosensitive hydrogels/nanogel, liposome, temperature sensitive liposome, heat-activated liposome (lysolipid thermally sensitive liposome) as used in Thermadox® (optionally used with exogenous heating by one or more of radiofrequency thermal ablation {RFA}, microwave hyperthermia, or high-intensity focused ultrasound {HIFU}), thermosensitive micelle, polymeric micelle, core shell structure, core shell microgel particle, thermoresponsive composite film, smart three dimensionally ordered porous material, thermosensitive microcontainer, nanoscale delivery vehicle;

optionally wherein the pharmaceutical composition is distributed/sold/administered with a verbal/written communication (optionally in a paper insert/leaflet in a packet(s) containing the composition(s) {optionally called "instructions for use", and/or "prescribing information" and/or "patient information leaflet"}) that its administration to a subject can cause their body temperature to drop [optionally informing that this is especially the case if a large/excess (e.g. more than the recommended) dose(s) is administered, optionally informing that this is especially the case if the subject is a child/baby (optionally informing that it is unsuitable for children and/or babies {optionally with the caveat that it can be administered to them if they are in a temperature controlled environment e.g. infant incubator/radiant warmer})] and optionally with one or more instructions to carry out should this body temperature drop happen to the subject (e.g. the subject should wear more clothes, wear warmer clothes, locate in a hotter environment, tell a doctor or pharmacist, go to a hospital) and/or optionally informing that the subject should/must minimize/stop alcohol intake (and/or other drug(s) intake that can affect thermoregulation such as a phenothiazine {like chlorpromazine etc.}, thioxanthenes etc.) for a period if this pharmaceutical composition is administered to the subject;

optionally wherein the pharmaceutical composition also comprises/includes one or more of an uncoupler (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), optionally wherein the body temperature reduction drive in a subject that administration of the pharmaceutical composition causes, because of its componentry F_1F_0 ATP hydrolysis inhibitor(s) {**a compound(s)/composition(s) according to one or more parent claims to this dependent claim**}, is completely/partially cancelled/offset by the body temperature increase drive caused by a componentry uncoupler(s) in the same pharmaceutical composition, such that the

subject's body temperature change is smaller in absolute value (optionally zero) than if either the amount of F_1F_0 ATP hydrolysis inhibitor(s) or uncoupler(s) was administered alone and/or in the pharmaceutical composition without the other component, optionally wherein a componentry F_1F_0 ATP hydrolysis inhibitor compound is also an uncoupler {**a compound(s)/composition(s) according to one or more parent claims to this dependent claim**}, optionally wherein these two opposite subject body temperature modifying aspects of the same compound completely or partially cancel such that the subject's body temperature is not much changed, if at all, by administration of this pharmaceutical composition, optionally wherein a combination of F_1F_0 ATP hydrolysis inhibitor(s) and uncoupler(s) compounds in the same pharmaceutical composition exerts greater anti-cancer activity when administered to a subject than if the same amount of either was administered without the other in the pharmaceutical composition, optionally wherein the combination amount of an F_1F_0 ATP hydrolysis inhibitor(s) and uncoupler(s) compounds in the same pharmaceutical composition is synergistic for anti-cancer activity;

optionally wherein the pharmaceutical composition also comprises/includes one or more of a compound(s) that inhibits UCP2 (e.g. genipin and/or cisplatin);

optionally wherein the pharmaceutical composition also comprises/includes one or more of a cyclodextrin(s);

optionally wherein the pharmaceutical composition is distributed/sold/administered with a verbal/written communication (optionally in a paper insert/leaflet in a packet(s) containing the composition(s) {optionally called "instructions for use", and/or "prescribing information" and/or "patient information leaflet"}) that it should not be administered to a female subject who is pregnant (optionally delimiting this to early pregnancy, optionally to the first two months or first month or first 3 weeks or first 2 weeks or first week or for a number of days that is less than the number of days in 2 months) and/or who is trying/wants to get pregnant over the period of administration and/or that it should not be administered within the early days and/or weeks of a subject's pregnancy and/or in the early days (e,g. up to one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 days later) and/or weeks after having (optionally unprotected) sex with the intention/want (at the time and/or retrospectively) of getting pregnant;

optionally wherein more than one of the optional embodiments of this claim apply;

or a pharmaceutical composition comprising at least one compound (or pharmaceutically acceptable salt thereof) for the manufacture of a medicament according to **Claim 27**, optionally with at least one compound (or pharmaceutically acceptable salt thereof) as

defined in **Claim 13**, and at least one of a pharmaceutically-acceptable carrier(s), additive(s), diluent(s), wherein one or more of the aforementioned optional embodiments of this claim apply to this pharmaceutical composition.

[**22]** A compound(s) according to **Claim 13**, or a pharmaceutical composition(s) according to **Claim 21**, for use in therapy. A compound(s) according to **Claim 13**, or a pharmaceutical composition(s) according to **Claim 21**, for use as a medicament.

[23] A compound(s) according to **Claim 13**, or a pharmaceutical composition(s) according to **Claim 21,** for use in the treatment of 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) and/or a cancer that uses more glucose than surrounding normal tissue and/or a glycolytic cancer and/or a non-oxidative cancer and/or a cancer that favours glycolytic rather than oxidative metabolism (wherein this correlates with cancer danger and poor prognosis and so dangerous cancers with poor prognosis are hereby contemplated) and/or a cancer releasing a lot of lactate (e.g. causing elevated blood lactate in the subject) and/or a cancer residing in extracellular acidity and/or a cancer with a low bioenergetic cellular index (BEC) value/score and/or a cancer using aerobic glycolysis and/or a cancer residing in hypoxia (e.g. hypoxic tumour, e.g. solid tumour) and/or a cancer that is predominantly/disproportionally utilizing ATP synthase in its "reverse" ATP consuming, instead of its "forward" ATP producing, mode and/or a cancer that's proliferation/viability/danger is reduced by administering a compound that selectively/preferentially inhibits/reduces F_1F_0 ATP hydrolysis, wherein the compound inhibits/reduces F_1F_0 ATP synthesis much less (e.g. >1000 fold less, e.g. >5000 fold less), minimally or not at all and/or a cancer that has a relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) hyperpolarized membrane potential across its mitochondrial inner membrane and/or a cancer that has relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) low intracellular Reactive Oxygen Species (ROS) concentration and/or a cancer with relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) less susceptibility to a polyketide F_1F_0 ATP synthase inhibitor (e.g. Oligomycin A) because its metabolism is more glycolytic and less oxidative (e.g. wherein the cancer demonstrates the Warburg effect) and/or a cancer with high HIF-1α

gene expression (which incidentally tends to correlate with less susceptibility to a polyketide F_1F_0 ATP synthase inhibitor);

(iii) cancer originating in one of peripheral blood, bone marrow, lung, colon, Central Nervous System (CNS), brain, skin, ovary, kidney, prostate, breast/mammary gland; including metastatic forms of these cancers; cancer found in lymph node/bone/soft tissue/metastatic site(s) and/or found in/causing pleural effusion, ascites; Carcinoma, Adenocarcinoma, Squamous cell carcinoma, Large cell carcinoma, Cystadenocarcinoma, Clear cell carcinoma, Sarcoma, Blastoma, cancer of epithelial/fibroblast/promyeloblast/lymphoblast/T lymphoblast/B lymphocyte cell type, Multi Drug Resistant (MDR) cancer, Anaplastic cancer, Hematopoietic cancer, Acute Lymphoblastic Leukemia (ALL), Childhood/Adult T acute lymphoblastic leukemia, Precursor T-cell acute lymphoblastic leukemia, Acute Myeloid Leukemia (AML), Acute promyelocytic leukemia, Chronic Myeloid Leukemia/Chronic Myelogenous Leukemia (CML), CML in blast crisis, Cancer with Philadelphia chromosome (BCR-ABL1 positive), Myeloma, Multiple myeloma, Plasma cell myeloma, Plasmacytoma, Lymphoma, Large cell immunoblastic lymphoma, Anaplastic large cell lymphoma, ALK-positive anaplastic large cell lymphoma, ALK positive cancer, Non-Small Cell Lung Cancer (NSCLC), lung carcinoma, lung adenocarcinoma, Minimally invasive lung adenocarcinoma, Non-small cell lung carcinoma, lung squamous cell carcinoma, Mesothelioma, Pleural epithelioid mesothelioma, Pleural mesothelioma, Bronchioalveolar carcinoma, Large cell lung cancer, Large cell lung carcinoma, Colon carcinoma, Colorectal carcinoma, Colon adenocarcinoma, Colorectal adenocarcinoma, Dukes' type C colorectal adenocarcinoma, Dukes' type D colorectal adenocarcinoma, Astrocytoma, Glioblastoma, Gliosarcoma, Glioblastoma multiforme, Melanoma, Malignant melanoma, Cutaneous melanoma, Amelanotic melanoma, Ovarian adenocarcinoma, Ovarian endometrioid adenocarcinoma, Endometrioid carcinoma of ovary, High grade ovarian serous adenocarcinoma, Ovarian serous cystadenocarcinoma, Renal cell carcinoma, Renal cell adenocarcinoma, Papillary renal cell carcinoma, Clear cell renal cell carcinoma, Clear cell renal carcinoma, Multi Drug Resistant (MDR) renal cancer, Prostate carcinoma, Prostate adenocarcinoma, Androgen Receptor negative (AR-) prostate cancer, Breast carcinoma, Breast adenocarcinoma, Ductal carcinoma, Invasive ductal carcinoma, Luminal A breast cancer, Estrogen Receptor positive (ER+) breast cancer, Progesterone Receptor positive (PR+) breast cancer, Hormone Receptor positive (HR+) breast cancer, Hormone responsive breast cancer, Triple Negative Breast Cancer (TNBC), Hormone Receptor negative (HR-) breast cancer, Hormone resistant breast cancer, Estrogen

Receptor negative (ER-) breast cancer, Progesterone Receptor negative (PR-) breast cancer, HER2 negative (HER2-) breast cancer;

(iv) cancer that causes/drives fever, for example, Non Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL), acute leukaemia, kidney cancer (renal cell cancer), liver cancer (hepatocellular carcinoma), bone cancer, adrenal gland tumour (such as phaeochromocytoma), tumour in the hypothalamus, solid tumour;

(v) HIV associated cancer: AIDS-defining cancer (e.g. Kaposi Sarcoma (KS), Non-Hodgkin Lymphoma (NHL), cervical cancer), Non-AIDS Defining Cancer (NADC, type of cancer more likely to occur in people who are infected with HIV than in people who are not infected);

(vi) cancer that causes/drives cachexia;

(vii) cancer in a child/adolescent, childhood/pediatric cancer;

(viii) chemotherapy and/or radiotherapy resistant/refractory cancer;

(ix) cancer occurring/associated with inflammation and/or with Tumour Associated Macrophages (TAMs);

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

(xi) 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, head injury, connective tissue disease(s), alcohol/drug withdrawal, drug overdose, fever of known origin (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, inherited metabolic disorder(s), endogenous or exogenous pyrogen(s), pyrogenic infection, infection (non-limiting e.g. roseola, measles, enteroviral infections, parasitic, viral, fungal, Chlamydial, Rickettsial, bacterial, mycobacterial, systemic bacterial, intravascular, HIV associated, nosocomial), surgery related;

(xii) normal or higher than normal body temperature and feeling hot, optionally uncomfortably hot (e.g. because of sweating more than desired/comfortable e.g. because the subject's body is overly exerted to stop/slow body temperature rising e.g. because the body's

physiological cooling mechanisms are being heavily utilized), because of high environmental temperature (e.g. because of hot/tropical climate e.g. because of summer season);

(xiii) 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;

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

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

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

(xvii) 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;

(xviii) 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, to confer one or more of sedation,

anaesthesia, hypoactivity, hibernation, torpor, suspended animation, life extension in a subject;

(xix) 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);

(xx) 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);

(xxi) disease or disorder of aging (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;

(xxii) aging, wherein these compounds slow aging, extend lifespan and healthspan; ~~or~~

(xxiii) skin aging;

(xxiv) 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

(xxv) inflammatory/autoinflammatory/autoimmune disease/disorder/syndrome 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

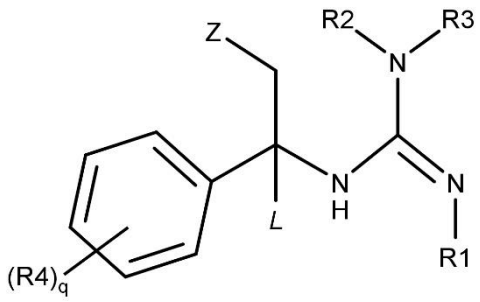
syndrome (HIDS), cryopyrin associated periodic syndrome (CAPS), Blau syndrome, Majeed syndrome, deficiency of interleukin-1 receptor antagonist (DIRA), mevalonate kinase deficiency, pyogenic-arthritis-pyoderma gangrenosum and acne syndrome (PAPA), periodic fever aphthous stomatitis pharyngitis adenitis (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.

[24] Use of a compound(s)/composition(s) in the manufacture of a medicament according to **Claim 1** or **Claim 27**, or a compound(s)/composition(s) for use according to **Claim 23**, wherein the subject is further administered with one or more treatments or compounds or compositions approved for human use, optionally for anti-cancer use (permits their use at lower dosing, which reduces their horrendous side-effects; renders chemotherapy and/or radiotherapy resistant cancers sensitive to chemotherapy and/or radiotherapy), optionally for HIV or AIDs treatment (e.g. with anti-retroviral therapy {ART} or combination anti-retroviral therapy {cART}), by the United States Food and Drug Administration (FDA)

and/or European Medicines Agency (EMA), optionally in the same pharmaceutical composition.

[27] Optionally with a compound(s)/composition(s) for use according to **Claim 23**, use of at least one compound, or a composition(s) containing at least one compound (e.g. a pharmaceutical composition also comprising one or more of a pharmaceutically-acceptable carrier(s), additive(s), diluent(s)), according to the formula:



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, or a stereoisomer or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, in the manufacture of a medicament for 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) and/or a cancer that uses more glucose than surrounding normal tissue and/or a glycolytic cancer and/or a non-oxidative cancer and/or a cancer that favours glycolytic rather than oxidative metabolism (wherein this correlates with cancer danger and poor prognosis and so dangerous cancers with poor prognosis are hereby contemplated) and/or a cancer releasing a lot of lactate (e.g. causing elevated blood lactate in the subject) and/or a cancer residing in extracellular acidity and/or a cancer with a low bioenergetic cellular index (BEC) value/score and/or a cancer using aerobic glycolysis and/or a cancer residing in hypoxia (e.g. hypoxic tumour, e.g. solid tumour) and/or a cancer that is predominantly/disproportionally utilizing ATP synthase in its "reverse" ATP consuming, instead of its "forward" ATP producing, mode and/or a cancer that's proliferation/viability/danger is reduced by administering a compound that selectively/preferentially inhibits/reduces F_1F_0 ATP hydrolysis, wherein the compound inhibits/reduces F_1F_0 ATP synthesis much less (e.g. >1000 fold less, e.g. >5000 fold less), minimally or not at all and/or a cancer that has a relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) hyperpolarized membrane potential across its

mitochondrial inner membrane and/or a cancer that has relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) low intracellular Reactive Oxygen Species (ROS) concentration and/or a cancer with relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) less susceptibility to a polyketide F_1F_0 ATP synthase inhibitor (e.g. Oligomycin A) because its metabolism is more glycolytic and less oxidative (e.g. wherein the cancer demonstrates the Warburg effect) and/or a cancer with high HIF-1α gene expression (which incidentally tends to correlate with less susceptibility to a polyketide F_1F_0 ATP synthase inhibitor);

(ii) cancer originating in one of peripheral blood, bone marrow, lung, colon, Central Nervous System (CNS), brain, skin, ovary, kidney, prostate, breast/mammary gland; including metastatic forms of these cancers; cancer found in lymph node/bone/soft tissue/metastatic site(s) and/or found in/causing pleural effusion, ascites; Carcinoma, Adenocarcinoma, Squamous cell carcinoma, Large cell carcinoma, Cystadenocarcinoma, Clear cell carcinoma, Sarcoma, Blastoma, cancer of epithelial/fibroblast/promyeloblast/lymphoblast/T lymphoblast/B lymphocyte cell type, Multi Drug Resistant (MDR) cancer, Anaplastic cancer, Hematopoietic cancer, Acute Lymphoblastic Leukemia (ALL), Childhood/Adult T acute lymphoblastic leukemia, Precursor T-cell acute lymphoblastic leukemia, Acute Myeloid Leukemia (AML), Acute promyelocytic leukemia, Chronic Myeloid Leukemia/Chronic Myelogenous Leukemia (CML), CML in blast crisis, Cancer with Philadelphia chromosome (BCR-ABL1 positive), Myeloma, Multiple myeloma, Plasma cell myeloma, Plasmacytoma, Lymphoma, Large cell immunoblastic lymphoma, Anaplastic large cell lymphoma, ALK-positive anaplastic large cell lymphoma, ALK positive cancer, Non-Small Cell Lung Cancer (NSCLC), lung carcinoma, lung adenocarcinoma, Minimally invasive lung adenocarcinoma, Non-small cell lung carcinoma, lung squamous cell carcinoma, Mesothelioma, Pleural epithelioid mesothelioma, Pleural mesothelioma, Bronchioalveolar carcinoma, Large cell lung cancer, Large cell lung carcinoma, Colon carcinoma, Colorectal carcinoma, Colon adenocarcinoma, Colorectal adenocarcinoma, Dukes' type C colorectal adenocarcinoma, Dukes' type D colorectal adenocarcinoma, Astrocytoma, Glioblastoma, Gliosarcoma, Glioblastoma multiforme, Melanoma, Malignant melanoma, Cutaneous melanoma, Amelanotic melanoma, Ovarian adenocarcinoma, Ovarian endometrioid adenocarcinoma, Endometrioid carcinoma of ovary, High grade ovarian serous adenocarcinoma, Ovarian serous cystadenocarcinoma, Renal cell carcinoma, Renal cell adenocarcinoma, Papillary renal cell carcinoma, Clear cell renal cell carcinoma, Clear cell renal carcinoma, Multi Drug Resistant (MDR) renal cancer,

Prostate carcinoma, Prostate adenocarcinoma, Androgen Receptor negative (AR-) prostate cancer, Breast carcinoma, Breast adenocarcinoma, Ductal carcinoma, Invasive ductal carcinoma, Luminal A breast cancer, Estrogen Receptor positive (ER+) breast cancer, Progesterone Receptor positive (PR+) breast cancer, Hormone Receptor positive (HR+) breast cancer, Hormone responsive breast cancer, Triple Negative Breast Cancer (TNBC), Hormone Receptor negative (HR-) breast cancer, Hormone resistant breast cancer, Estrogen Receptor negative (ER-) breast cancer, Progesterone Receptor negative (PR-) breast cancer, HER2 negative (HER2-) breast cancer;

(iii) cancer that causes/drives fever, for example, Non Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL), acute leukaemia, kidney cancer (renal cell cancer), liver cancer (hepatocellular carcinoma), bone cancer, adrenal gland tumour (such as phaeochromocytoma), tumour in the hypothalamus, solid tumour;

(iv) HIV associated cancer: AIDS-defining cancer (e.g. Kaposi Sarcoma (KS), Non-Hodgkin Lymphoma (NHL), cervical cancer), Non-AIDS Defining Cancer (NADC, type of cancer more likely to occur in people who are infected with HIV than in people who are not infected);

(v) cancer that causes/drives cachexia;

(vi) cancer in a child/adolescent, childhood/pediatric cancer;

(vii) chemotherapy and/or radiotherapy resistant/refractory cancer;

(viii) cancer occurring/associated with inflammation and/or with Tumour Associated Macrophages (TAMs);

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

(x) 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, head injury, connective tissue disease(s), alcohol/drug withdrawal, drug overdose, fever of known origin (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, inherited metabolic disorder(s), endogenous or exogenous pyrogen(s), pyrogenic infection, infection

(non-limiting e.g. roseola, measles, enteroviral infections, parasitic, viral, fungal, Chlamydial, Rickettsial, bacterial, mycobacterial, systemic bacterial, intravascular, HIV associated, nosocomial), surgery related;

(xi) normal or higher than normal body temperature and feeling hot, optionally uncomfortably hot (e.g. because of sweating more than desired/comfortable e.g. because the subject's body is overly exerted to stop/slow body temperature rising e.g. because the body's physiological cooling mechanisms are being heavily utilized), because of high environmental temperature (e.g. because of hot/tropical climate e.g. because of summer season);

(xii) 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;

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

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

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

(xvi) 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;

(xvii) 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, to confer one or more of sedation, anaesthesia, hypoactivity, hibernation, torpor, suspended animation, life extension in a subject;

(xviii) 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);

(xix) 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);

(xx) disease or disorder of aging (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;

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

(xxii) skin aging; or

(xxiii) inflammatory/autoinflammatory/autoimmune disease/disorder/syndrome 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;

wherein

L is hydrogen;

R_1 is hydrogen, cyano, —SO_2R_8, —C(═O)R_9, or heteroaryl (such as 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-heteroaryl, 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}, —$C(=O)R_{17}$, cycloalkyl, aryl, heterocyclo, and heteroaryl, wherein when R_{3a} is cycloalkyl, aryl, heterocyclo or heteroaryl, said cycloalkyl, aryl, heterocyclo 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 $C_{1\text{-}4}$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, $C_{1\text{-}4}$alkoxy, haloalkoxy, $C_{1\text{-}6}$alkyl, CO_2alkyl, SO_2alkyl, SO_2NH_2, amino, $NH(C_{1\text{-}4}alkyl)$, $N(C_{1\text{-}4}alkyl)_2$, $NHC(=O)$alky, $C(=O)$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~~heterocyclo in turn optionally substituted with keto or having a benzene ring fused thereto or

a) $C_{1\text{-}4}$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 $C(=O)H$, $C_{1\text{-}4}$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, $C_{1\text{-}4}$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 substituents selected from alkyl, halogen, cyano, alkenyl, acyl, alkylthio, carbamyl, phenyl in turn optionally substituted with halogen; or having an aryl fused thereto;

c) phenyl 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 membered heteroaryl or heterocyclo 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_{1-4}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, 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 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;

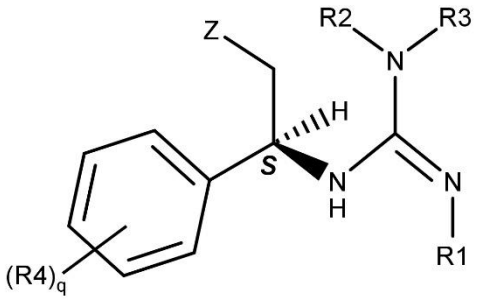
R_{27} is alkyl or substituted alkyl;

q is 0, 1, 2, or 3;

m and n are 0, 1 or 2; and

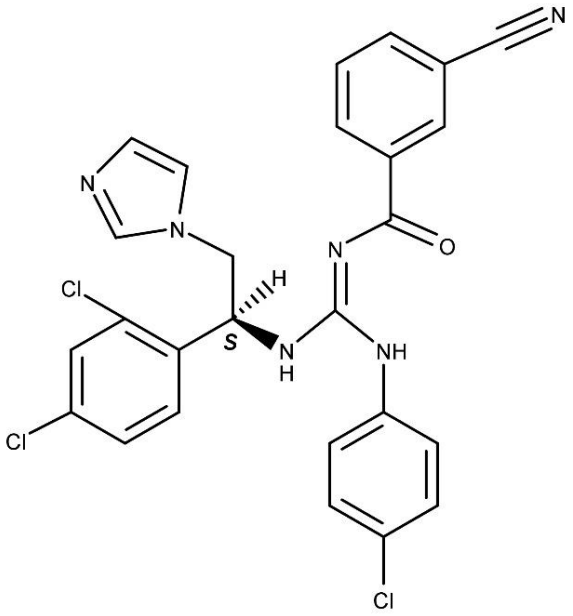
p is 0, 1, 2, or 3.

[29] Use of a compound in the manufacture of a medicament according to **Claim 27** of the formula



or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof,
optionally wherein there is an enantiomeric excess (ee) of the *S* stereisomer,
preferably that exceeds 70%,
and more preferably that exceeds 90%.

[31] Use of a compound in the manufacture of a medicament according to **Claim 27**, having the structure



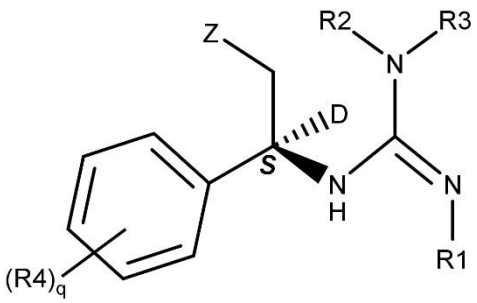
or a pharmaceutically-acceptable salt, solvate, hydrate or prodrug thereof, wherein:

the enantiomeric excess (ee) of the *S* stereoisomer exceeds 70%,

and more preferably exceeds 90%.

[32] Use of a compound(s)/composition(s) in the manufacture of a medicament according to **Claim 27**, or a compound(s)/composition(s) for use according to **Claim 23**, wherein comparable or larger mg/kg doses are used in, or administered to, larger animals/subjects, which is very distinct from most drugs, 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.

[34] A compound according to **Claim 13**, of the formula,



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

D is deuterium (enrichment, for example, exceeding 40% deuterium incorporation at position shown [optionally at other H positions also]. The greater the deuterium enrichment at the position shown [chiral carbon], the more preferred); and

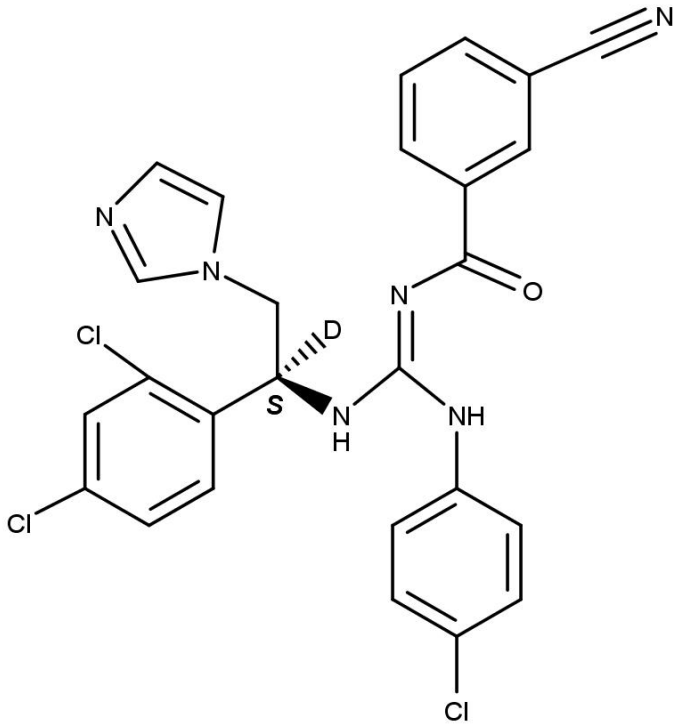
optionally there is an enantiomeric excess (ee) of the *S* stereoisomer,

preferably exceeding 70%,

and more preferably exceeding 90%;

alternatively there is tritium instead of (or in addition to) deuterium enrichment at the chiral carbon [optionally at other H positions also].

[35] A compound according to **Claim 34**, having the structure:



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

there is deuterium (D) enrichment at the chiral centre (optionally at other H positions also), the greater the deuterium enrichment at this position, the more preferred,

optionally wherein deuterium incorporation at the chiral centre exceeds 40%; and

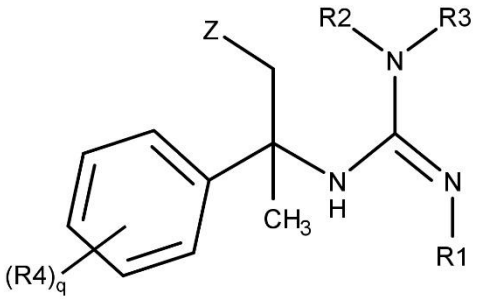
optionally there is an enantiomeric excess (ee) of the *S* stereoisomer,

preferably exceeding 70%,

and more preferably exceeding 90%;

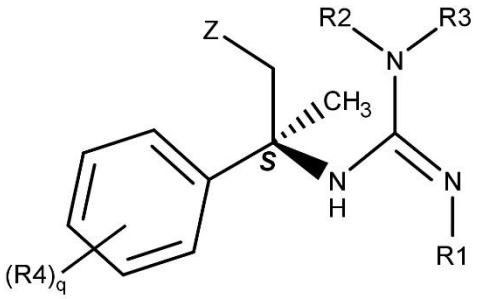
alternatively there is tritium instead of (or in addition to) deuterium enrichment at the chiral carbon [optionally at other H positions also].

[36] A compound according to **Claim 13**, of the formula,



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

optionally wherein there is an enantiomeric excess (ee) of the *S* stereoisomer

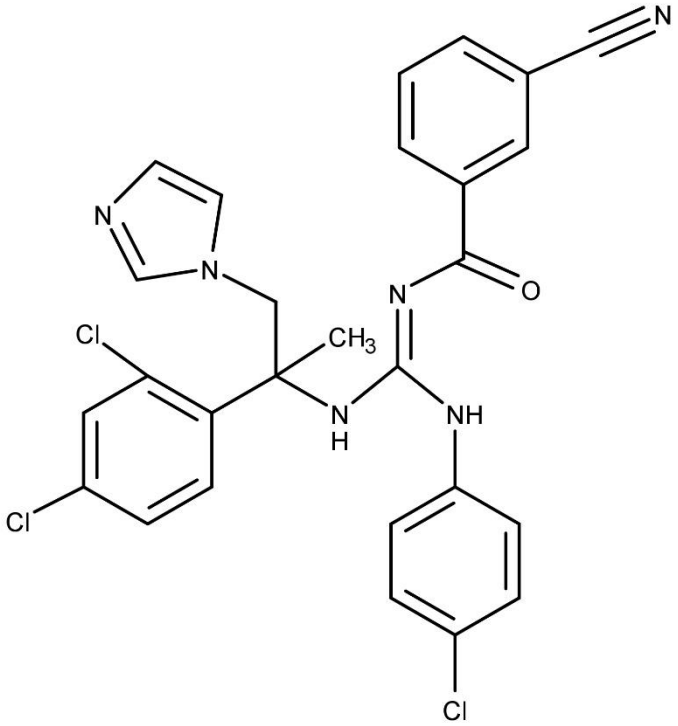


optionally exceeding 70%;

optionally wherein there is an enantiomeric excess (ee) of the *R* stereoisomer instead,

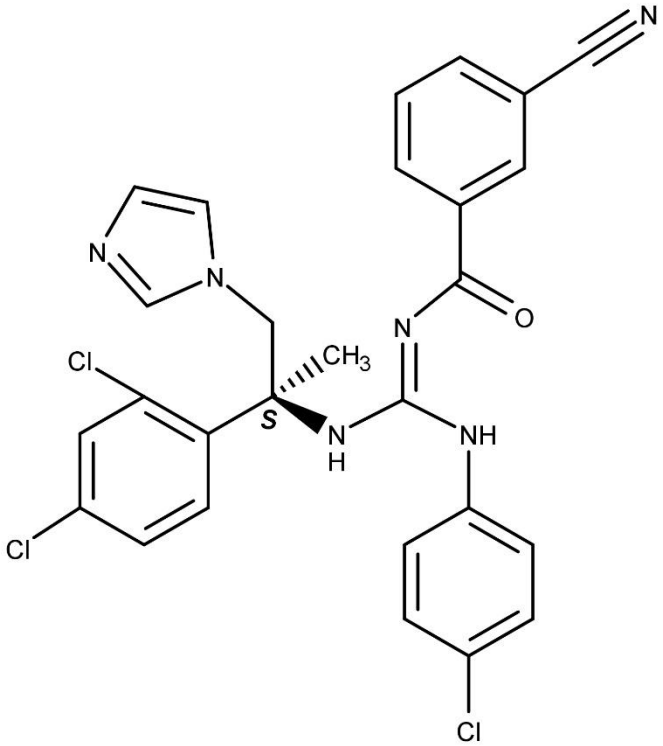
optionally exceeding 70%.

[37] A compound according to **Claim 36**, having the structure:



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

optionally wherein there is an enantiomeric excess (ee) of the *S* stereoisomer



optionally exceeding 70%;

optionally wherein there is an enantiomeric excess (ee) of the *R* stereoisomer instead, optionally exceeding 70%.

[38] Use of a compound(s)/composition(s) in the manufacture of a medicament according to **Claim 27**, and/or a compound(s)/composition(s) for use according to **Claim 23**, wherein an effective amount of compound(s)/composition(s) is administered to the subject topically/locally, wherein the reduction in metabolic heat generation at the administered body region(s) is substituted by heat transfer from other regions (e.g. by blood flow) of the subject's body, wherein this method delivers compound(s)/composition(s) conferred treatment to the administered body region(s) whilst the body temperature reduction side-effect of the compound(s)/composition(s) is mitigated/beaten, optionally wherein the administered body region(s) is one or more of the Central Nervous System/brain (or part(s)/cell type(s) thereof e.g. some or all dopamine neurons in the substantia nigra) and/or skin (or part(s) thereof) and/or hair (or part(s) thereof) and/or a tumor/cancer (or part(s) thereof),
and/or wherein an effective amount of compound(s)/composition(s) is administered to the subject systemically,
and/or optionally the subject is monitored/observed/watched (optionally by a healthcare worker such as doctor, nurse, vet, pharmacist, paramedic) after compound(s)/composition(s) administration for any adverse sign(s)/symptom(s)/abnormality,
and/or optionally the subject is located in an ambient temperature exceeding 30°C and/or optionally the subject wears one or more items of clothing and/or optionally wherein the subject's body temperature is monitored (continuously or at regular/irregular time intervals),
and/or optionally wherein the greater the ambient temperature the subject is in, the greater the dose administered,
and/or optionally wherein the subject moves to a different geography/space with a higher ambient temperature for compound(s)/composition(s) administration,
and/or optionally wherein the daily dose is spread over multiple doses per day so that any compound(s)/composition(s) driven body temperature drop in the subject is lowered in amplitude and lengthened in duration (which is safer),
and/or optionally the subject is monitored, for example by a healthcare professional(s) and/or machine substitute(s), for sign(s) of reduction in body temperature and/or the subject is located at an ambient temperature that maintains their body temperature within safe limits whilst they have an effective amount of compound(s)/composition(s) in their system and/or the subject wears (and/or is covered by) insulating material(s), e.g. clothing/clothes (and/or bedding/blanket(s)), and/or is in a heated/insulated space (e.g. for conferring

heat/hyperthermia therapy e.g. as used for cancer therapy) and/or hot climate, optionally exceeding one or more of 24°C, 25°C, 26°C, 27°C, 28°C, 29°C, 30°C, 31°C, 32°C, 33°C, 34°C, 35°C, 36°C, 37°C, 38°C, 39°C, 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, optionally at or around 37°C, wherein a higher (e.g. in the thirties/forties °C), but safe, ambient temperature (and/or greater bodily insulation, for example by clothing/clothes and/or bedding/blanket(s)) can permit a greater compound(s)/composition(s) dose(s) to be safely administered, wherein a preferred ambient temperature is the thermoneutral temperature for the subject with the amount of bodily insulation they have, e.g. the amount of clothing they are wearing, if any, and the amount of the compound(s)/composition(s) in their system;

alternatively wherein the compound(s)/composition(s) is administered to the subject to deliberately reduce their body temperature, optionally to a desired/specified/controlled temperature, wherein the amplitude of hypothermia conferred in the subject by the compound(s)/composition(s) administration is controlled by setting the ambient temperature, wherein a sufficient amount of administered compound(s)/composition(s) reduces subject body temperature to slightly higher than their ambient temperature, such that hypothermic amplitude is controlled by controlling ambient temperature;

alternatively wherein the compound(s)/composition(s) is administered to the subject to deliberately reduce their body temperature to a desired/specified/controlled temperature, wherein a sufficient amount of administered compound(s)/composition(s) reduces subject body temperature to a temperature that it cannot fall below because the subject is heated by incident electromagnetic radiation (optionally the intensity of which is controlled by servocontrol, with the set point set at the desired hypothermic body temperature, optionally from a radiation heater), which "catches" and offsets the hypothermic drive of an administered compound(s)/composition(s), at a desired/specified hypothermic body temperature.

[39] A method of identifying a compound(s) to treat/ameliorate/prevent/combat a disease/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) and/or a cancer that uses more glucose than surrounding normal tissue and/or a glycolytic cancer and/or a non-oxidative

cancer and/or a cancer that favours glycolytic rather than oxidative metabolism (wherein this correlates with cancer danger and poor prognosis and so dangerous cancers with poor prognosis are hereby contemplated) and/or a cancer releasing a lot of lactate (e.g. causing elevated blood lactate in the subject) and/or a cancer residing in extracellular acidity and/or a cancer with a low bioenergetic cellular index (BEC) value/score and/or a cancer using aerobic glycolysis and/or a cancer residing in hypoxia (e.g. hypoxic tumour, e.g. solid tumour) and/or a cancer that is predominantly/disproportionally utilizing ATP synthase in its "reverse" ATP consuming, instead of its "forward" ATP producing, mode and/or a cancer that's proliferation/viability/danger is reduced by administering a compound that selectively/preferentially inhibits/reduces F_1F_0 ATP hydrolysis, wherein the compound inhibits/reduces F_1F_0 ATP synthesis much less (e.g. >1000 fold less, e.g. >5000 fold less), minimally or not at all and/or a cancer that has a relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) hyperpolarized membrane potential across its mitochondrial inner membrane and/or a cancer that has relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) low intracellular Reactive Oxygen Species (ROS) concentration and/or a cancer with relatively (e.g. as compared to normal cells of the tissue from which the cancer derives) less susceptibility to a polyketide F_1F_0 ATP synthase inhibitor (e.g. Oligomycin A) because its metabolism is more glycolytic and less oxidative (e.g. wherein the cancer demonstrates the Warburg effect) and/or a cancer with high HIF-1α gene expression (which incidentally tends to correlate with less susceptibility to a polyketide F_1F_0 ATP synthase inhibitor);

(iii) cancer originating in one of peripheral blood, bone marrow, lung, colon, Central Nervous System (CNS), brain, skin, ovary, kidney, prostate, breast/mammary gland; including metastatic forms of these cancers; cancer found in lymph node/bone/soft tissue/metastatic site(s) and/or found in/causing pleural effusion, ascites; Carcinoma, Adenocarcinoma, Squamous cell carcinoma, Large cell carcinoma, Cystadenocarcinoma, Clear cell carcinoma, Sarcoma, Blastoma, cancer of epithelial/fibroblast/promyeloblast/lymphoblast/T lymphoblast/B lymphocyte cell type, Multi Drug Resistant (MDR) cancer, Anaplastic cancer, Hematopoietic cancer, Acute Lymphoblastic Leukemia (ALL), Childhood/Adult T acute lymphoblastic leukemia, Precursor T-cell acute lymphoblastic leukemia, Acute Myeloid Leukemia (AML), Acute promyelocytic leukemia, Chronic Myeloid Leukemia/Chronic Myelogenous Leukemia (CML), CML in blast crisis, Cancer with Philadelphia chromosome (BCR-ABL1 positive), Myeloma, Multiple myeloma, Plasma cell myeloma, Plasmacytoma, Lymphoma, Large cell

immunoblastic lymphoma, Anaplastic large cell lymphoma, ALK-positive anaplastic large cell lymphoma, ALK positive cancer, Non-Small Cell Lung Cancer (NSCLC), lung carcinoma, lung adenocarcinoma, Minimally invasive lung adenocarcinoma, Non-small cell lung carcinoma, lung squamous cell carcinoma, Mesothelioma, Pleural epithelioid mesothelioma, Pleural mesothelioma, Bronchioalveolar carcinoma, Large cell lung cancer, Large cell lung carcinoma, Colon carcinoma, Colorectal carcinoma, Colon adenocarcinoma, Colorectal adenocarcinoma, Dukes' type C colorectal adenocarcinoma, Dukes' type D colorectal adenocarcinoma, Astrocytoma, Glioblastoma, Gliosarcoma, Glioblastoma multiforme, Melanoma, Malignant melanoma, Cutaneous melanoma, Amelanotic melanoma, Ovarian adenocarcinoma, Ovarian endometrioid adenocarcinoma, Endometrioid carcinoma of ovary, High grade ovarian serous adenocarcinoma, Ovarian serous cystadenocarcinoma, Renal cell carcinoma, Renal cell adenocarcinoma, Papillary renal cell carcinoma, Clear cell renal cell carcinoma, Clear cell renal carcinoma, Multi Drug Resistant (MDR) renal cancer, Prostate carcinoma, Prostate adenocarcinoma, Androgen Receptor negative (AR-) prostate cancer, Breast carcinoma, Breast adenocarcinoma, Ductal carcinoma, Invasive ductal carcinoma, Luminal A breast cancer, Estrogen Receptor positive (ER+) breast cancer, Progesterone Receptor positive (PR+) breast cancer, Hormone Receptor positive (HR+) breast cancer, Hormone responsive breast cancer, Triple Negative Breast Cancer (TNBC), Hormone Receptor negative (HR-) breast cancer, Hormone resistant breast cancer, Estrogen Receptor negative (ER-) breast cancer, Progesterone Receptor negative (PR-) breast cancer, HER2 negative (HER2-) breast cancer;

(iv) cancer that causes/drives fever, for example, Non Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL), acute leukaemia, kidney cancer (renal cell cancer), liver cancer (hepatocellular carcinoma), bone cancer, adrenal gland tumour (such as phaeochromocytoma), tumour in the hypothalamus, solid tumour;

(v) HIV associated cancer: AIDS-defining cancer (e.g. Kaposi Sarcoma (KS), Non-Hodgkin Lymphoma (NHL), cervical cancer), Non-AIDS Defining Cancer (NADC, type of cancer more likely to occur in people who are infected with HIV than in people who are not infected);

(vi) cancer that causes/drives cachexia;

(vii) cancer in a child/adolescent, childhood/pediatric cancer;

(viii) chemotherapy and/or radiotherapy resistant/refractory cancer;

(ix) cancer occurring/associated with inflammation and/or with Tumour Associated Macrophages (TAMs);

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

(xi) 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, head injury, connective tissue disease(s), alcohol/drug withdrawal, drug overdose, fever of known origin (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, inherited metabolic disorder(s), endogenous or exogenous pyrogen(s), pyrogenic infection, infection (non-limiting e.g. roseola, measles, enteroviral infections, parasitic, viral, fungal, Chlamydial, Rickettsial, bacterial, mycobacterial, systemic bacterial, intravascular, HIV associated, nosocomial), surgery related;

(xii) normal or higher than normal body temperature and feeling hot, optionally uncomfortably hot (e.g. because of sweating more than desired/comfortable e.g. because the subject's body is overly exerted to stop/slow body temperature rising e.g. because the body's physiological cooling mechanisms are being heavily utilized), because of high environmental temperature (e.g. because of hot/tropical climate e.g. because of summer season);

(xiii) 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;

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

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

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

(xvii) 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;

(xviii) 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, to confer one or more of sedation, anaesthesia, hypoactivity, hibernation, torpor, suspended animation, life extension in a subject;

(xix) 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);

(xx) 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);

(xxi) disease or disorder of aging (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;

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

(xxiii) skin aging; or

(xxiv) inflammatory/autoinflammatory/autoimmune disease/disorder/syndrome 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;

comprising:

independently assaying a compound's effect upon ATP synthesis and ATP hydrolysis by ATP synthase; preferably *in vitro*; preferably in sub-mitochondrial particles (SMPs); wherein a

desired/sought compound inhibits/reduces ATP hydrolysis more than it inhibits/reduces ATP synthesis (by ATP synthase), wherein greater disparity is more preferred; optimally where there is a sizeable differential between a compound's EC_{50} F_1F_0 ATP synthesis and a smaller valued EC_{50} F_1F_0 ATP hydrolysis, for example (in order of increasing preference) one or more of >10, >100, >1000, >5000, >10000 times difference; wherein one or more compounds according to **Claim 13**, and/or compound(s) in the manufacture of a medicament according to **Claim 27**, are independently tested in this assay, screening/selecting for a compound(s) that inhibits/reduces ATP hydrolysis more than it inhibits/reduces ATP synthesis (by ATP synthase), wherein one or more compounds with this characteristic are selected; preferably wherein these selected compounds are ranked according to which have the greatest differential between their EC_{50} F_1F_0 ATP synthesis and their smaller valued EC_{50} F_1F_0 ATP hydrolysis, wherein one or more of the most highly ranked are selected for further optional step(s) of this claim;

optionally wherein one or more compounds selected by the aforementioned step is combined with at least one of a pharmaceutically-acceptable carrier(s), additive(s), diluent(s) to produce/manufacture a pharmaceutical composition(s);

optional use of this selected compound(s)/composition(s) in the manufacture of a medicament to treat/ameliorate/prevent/combat a disease or disorder aforementioned in this present claim.