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(71) Applicant (for all designated States except US): YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Hi Tech Park, Edmond J Safra Campus, Givat Ram, P.O. Box 39135, 91390 Jerusalem (IL).

(71) Applicant and
(72) Inventors: SLAVIN, Shimon [IL/IL]; 21 Oren Street, Ein Kerem, 95744 Jerusalem (IL). GAZIT, Aviv [IL/IL]; 14 Nof Arim Street, 96190 Jerusalem (IL).

(74) Agents: LUZZATTO, Kfir et al.; LUZZATTO & LUZZATTO, Box 5352, 84152 Beersheba (IL).


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(54) Title: EXTENSION OF LIFESPAN WITH DRUGS

(57) Abstract: New compounds, inhibiting protein tyrosine kinases (PTKs) or steroid-related enzymes (SREs), which affect apoptosis in malignant tissues, and can be used in the preparation of medicaments for treating various disorders, and for elongating the lifespan of a subject while sustaining that subject in good health. Further, a method and antiaging compositions are provided for extending the lifespan.
EXTENSION OF LIFESPAN WITH DRUGS

Field of the Invention
The present invention is directed towards drugs which affect protein tyrosine kinases (PTKs) or steroid-related enzymes (SREs). More particularly the present invention relates to inhibiting PTKs and SREs activity, and to treating disorders related to PTKs or SREs activity in a subject. Specifically, the present invention is directed, inter alia, to encouraging apoptosis in malignant tissue, inhibiting apoptosis in non-malignant or healthy tissue, and elongating the lifespan of a subject while sustaining that subject in good health condition.

Background
The dream of healthy longevity and even immortality had obsessed humans for eons. Gilgamesh in the Sumerian epos, Methuselah in the bible, Taoist Chinese philosophy, and alchemists in their search for elixir of life are just few examples in the long search to stop or reverse the cruel march of time, aging and death.

In 1900, a newborn child in Western Europe could look forward to an average life expectancy of only 49 years. Infectious diseases were the major causes of death, killing most people before they reached an age when aging sets in. Three-quarters of a century later, life expectancy had risen to 73 years and "organic" diseases, including all the diseases of aging, had replaced infectious diseases as the major cause of death. Today, the life expectancy has risen to 80 for women (74 for men), and coping with an aging population has become a major economic and social challenge.

While the lifespan expectation and the mean lifespan rose dramatically in the last century, the maximal lifespan (about 120 years) had not changed.
Finding cure for devastating and life-limiting diseases such as Alzheimer, heart conditions, cancer, and diabetes, will ease the aging process. It may also increase the mean lifespan by 15 years, but will have no influence on the human lifespan record.

Aging research had dramatically advanced within the last decade. Single gene mutations were found to be sufficient for increasing the mean and maximum lifespan values in *Saccharomyces cerevisiae* yeast, *Caenorhabditis elegans* nematode, *Drosophila melanogaster* fly, and mice, by up to 20-500%.

Aging research mainly deals with understanding the mechanism of aging, with little or no practical clinical use so far. Many of the genes involved in the aging process, also play crucial roles in early developmental stages in life. Therefore, gene manipulation of these genes may have very serious and unpredictable effects on health, and cannot be considered an option for clinical use in the foreseeable future, even if social, religious and political hurdles can be overcome.

Regenerative medicine using embryonic or adult stem cells for rejuvenation of aging tissues seems to be a promising approach. But, the usage of such method for extending the lifespan, confronts huge scientific and legal obstacles. Approved life-extending drugs do not have legal limitations, and therefore, could be used when desired.

The search for drugs with lifespan extending effects *per se*, in contrast to drugs used for the treatment of different medical conditions, which improve patients' illness and consequently result in an lifespan increase, has just begun. For example, administration of 10 mM phenyl butyric acid (PBA) to *D. melanogaster*, resulted in a 35% life extension increment
[Kang, H-L., et al. (2002) PNAS 99: 838]. The mechanism by which PBA contributes to the lifespan elongation is still unclear since it dramatically altered the expression of numerous genes, affecting many physiological pathways.


The following relates to the aging and small molecule inhibitors of crucially important enzymes, PTKs (protein kinases), and SREs (steroid related enzymes).

IGF-1 and aging

The insulin-like growth factors (IGFs) are polypeptides with high sequence similarity to insulin. They can trigger cellular responses such as mitogenesis in cell culture. IGF-2 is thought to be a primary growth factor required for early development while IGF-1 expression is seen in life later.

IGF-2 is primarily fetal in action and it is also essential for development and function of organs such as the brain, liver and kidney.

Insulin-like growth factor 1 (IGF-1) is mainly secreted by the liver as a result of stimulation by growth hormone (hGH). Almost every cell in the human body is affected by IGF-1, especially cells in muscle, cartilage, bone, liver, kidney, nerves, skin, and lungs. In addition to the insulin-like effects, IGF-1 can also regulate cell growth and development, especially in nerve cells, as well as cellular DNA synthesis. IGF-1 and its receptor play a key role in normal growth and development [Dupont, J. and Holzenberger, M. (2003) Birth Defects Res. 69: 257].

While crucial in early life, overexpression of IGF axis seems to lead to a shorter lifespan in the aging organism. Reduction of IGF level expression in aging humans may thus be an attempt by the body to minimize this effect.

The hypothalamic activity of the GH-IGF network declines with age. An increased cardiovascular mortality in adults with GH deficiency can be found. Aging is accompanied by a progressive decline in circulating IGF-1, suggesting a continuing diminution of the GH-IGF axis throughout aging. Moreover, some studies suggest that GH might play an important role in lipid metabolism in healthy elderly subjects [Ceda G.P. et al., (1998) J. Clin. Endocrinol. Metab. 83:499].

It has been demonstrated that aging is in part regulated by genes. E.g., the lifespan of *Caenorhabditis elegans* worm can be increased by more than 200 percent through genetic engineering. Mutations that result in loss or decrease of function of insulin-like signaling in worms, flies and mice are associated with extended lifespan. Among the 60 single gene mutations known to extend the lifespan in nematode, fly and mice, mutations in the growth hormone-IGF-1, [Longo, V.D. and Finch, C.E. (2003) Science 299: 1342; Liang, H. et al., (2003) Exper. Gerontology 38:1353; Hamet, P. and Tremblay, J. (2003) Metabolism 52: 5], phosphatidyl inositol 3 kinase (PIK3), AKT kinase (a serine/threonine
kinase, also called protein kinase B (PKB) and FOXO (Forkhead transcription factor family) axis genes, had been the most extensively studied.


Forkhead transcription factors belonging to the FOXO subfamily are negatively regulated by protein kinase B (PKB) in response to signaling by
insulin and insulin-like growth factor in *C. elegans* and mammals. Loss-of-function mutations in *daf-16* (*C. elegans* only FOXO transcription factor) completely suppress the dauer-constitutive and longevity phenotypes associated with reduced function of insulin-signaling components.


Inhibition of IGF-1 receptor and closely related insulin receptor, by dominant negative mutants, antisense oligonucleotides, and peptides is well established. Dissimilarly, only few small chemical compounds molecules capable of inhibiting IGF-1 receptor or related receptors are known [De Meytes, P. and Whittaker, J. (2002) Nature Reviews Drug Discovery 1: 769; and Surmacz, E. (2003) Oncogene 22: 6589].

To date only three classes of sub-micromolar, small organic molecule inhibitors have been described:


US 20040121407A1 publication relates to treatments and compositions that putatively alter the lifespan regulation and cellular responses to diseases and disorders by antagonizing the GH/IGF-1 axis. This patent application offers theoretical discussion and speculative future uses of the GH/IGF-1 regulation, and does not exemplify neither proves the claimed use of any of the compounds described therein, in any living animal or even cells.

In the present application, some novel as well as known chemical compounds, which are capable of inhibiting IGF-1 axis component functions are described, and proof for the efficacy in the lifespan extension of flies and nematodes is further exemplified.

**Inhibitors of SREs and aging**

Vast amount of research and publications on the biological role of sex steroids during development, middle life and aging exists. The relation of these hormones to aging rate and lifespan extension is unknown and will most probably will turn out to be complex. In aging mammals serum hormone levels of, e.g., growth hormone (GH), IGF-1, dehydroepiandrosteron (DHEA), sex steroids testosterone, and estradiol (E) decrease dramatically. The decrease in these hormones levels may be an important factor in the rise of life shortening diseases which account for 70% of all deaths, such as diabetes mellitus and obesity, myocardial infarction caused by atherosclerosis, dementia, and cancer. However, attempts to extend the lifespan by affecting said levels have not been done. *C. elegans* nematode and flies cannot synthesize sterols de novo, getting their supply of cholesterol from food, but they have an elaborate
enzymatic machinery to modify sterols (ecdysone and related sterols are used in fly, see e.g. Kurzchal J. and Ward S.: Nature Cell Biology (2003) 8:684). In nematodes, the mutants in daf-9 and daf-12, encoding cytochrome hydroxylase enzyme and nuclear hormone receptor respectively, were found to prolong the lifespan. A mutation involved in the biosynthesis of ecdysone caused 45% increase in the lifespan in flies [Simon A. et al: Science (2003) 299:1407]. In the last decade several potent aromatase inhibitors have been developed [e.g., Johnston S. and Dowsett M.: Nature Reviews Cancer (2003) 3:821]. Aromatase is a microsomal cytochrome P450 enzyme (CYP19 gene) that catalyzes the aromatization of ring A of androgen steroids to estrogen. Aromatase inhibitors are in clinical use for breast cancer treatment, and since they proved to be better than long established tamoxifene (an estradiol receptor inhibitor), they were recently approved by the FDA as first line treatment. Aromatase inhibitors were given for long periods of time (up to 4 years) with no serious adverse effects on bone metabolism, plasma lipids, and cardiovascular system. It is an object of this invention to provide pharmaceutical compositions for extending the lifespan of a subject comprising SREs, such as, e.g., aromatase inhibitors or estradiol receptor inhibitors.

In the present application, known chemical compounds, which are capable of inhibiting SREs are provided for the lifespan extension, and their efficacy for flies and nematodes is exemplified.

**Objectives**

PTKs and SREs are of fundamental importance for the biological regulation and signal transduction; and specifically IGF-1, aromatase, or estradiol receptor are found to affect nearly all aspects of cellular activities. It is therefore an object of the present invention to provide some
known as well as novel compounds which are capable of inhibiting PTKs or SREs, such as IGF-1 inhibitors, estradiol receptor inhibitors, or aromatase inhibitors, that may be used for treating disorders associated with PTKs or SREs. Further, it is an object of the present invention to provide pharmaceutical compositions comprising such compounds as the active components and methods for their preparation. Still another object of the present invention is to provide for methods of treating disorders associated with PTKs or SREs. Particularly, the compounds of the present invention are intended for elongating the lifespan in a subject.

**Summary of the Invention**

The present invention relates to the use of protein tyrosine kinases (PTKs) inhibitors of formula (Ia) or (Ib), and steroid-related enzymes (SREs) inhibitors, such as aromatases inhibitors, in the preparation of a pharmaceutical composition for extending the lifespan of a subject, wherein said subject is particularly a mammal, most preferably a human. Said steroid-related enzyme may be an aromatase, such as letrozole, anastrozole, fadrozole and vorozole, or estradiol receptor inhibitor selected from fulvestrant, tamoxifene and raloxifene, or a compound selected from AGS 308 and AGS 333, and said formulae have the structures:

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\[ \text{(Ia)} \]

\[ \text{(Ib)} \]
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formula (Ia)  
formula (Ib)
wherein, \( R_1 \) is H, OH, halogen, wherein the halogen may be F, Cl, Br, or I, nitro, CN, aldehyde, substituted ketone, COOH, trifluoromethyl, amide, substituted or unsubstituted alkyl, particularly isopropyl, or t-butyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkyloxy, preferably methoxy, haloalkyl or haloaryl comprising at least one substituent selected from F, Cl, Br, or I, arloxy, preferably phenoxy, alkylamino, alkylamido, arylamino, arylamido:

\( R_2 \) is H, OH, alkyl, preferably t-butyl or isopropyl, aryl, arylalkyl, alkylaryl, alkyloxy, preferably methoxy, alkylthio, wherein the sulfur may replace any of the carbon atoms of the alkylthio, or arylthio, arylalkylthio, arylthioalkyl, particularly arylthiomethyl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazolinyl, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxazolidonyl, isoxazolidonyl, pyrazolinyl, pyrazolidinyl, piperidyl, piperazine, morpholinyl, preferably the heteroaryl is one of pyrrolyl, thiophenyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, furyl, furazanyl, isobenzofuranyl, pyranyl, chromenyl, xanthanyl, phenoxyxanthiinyl, indolyl, isoindolyl, indolizinyl, isoindolylzynyl, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl:

\( R_3 \) is CN, amide, nitrileamido, aminothiol, amino, alkyl, alkenyl, alkynyl, alkylamino, alkylamido, alkyleneamino, alkyleneamido, particularly dicyanoethylene amino, wherein the alkyl, alkenyl, or alkynyl moieties in the above substituents may be substituted or unsubstituted, substituted or unsubstituted aryl, arylcarbonyl, arylalkylcarbonyl, arylalkylcarbonyl, arylamido, particularly phenylamido, arylalkylamido, particularly phenylmethylamido, or phenylethlamido, arylalkyleneamido, arylamino,
arylalkylamino, arylalkylenamino arylsulfonyl, particularly phenylsulfonyl, arylalkylenesulfonyl, arylalkylenenitrileamidoalkylamido, particularly phenylenenitrileamidopropylamido, wherein the aryl moiety in any of the aryl containing substituents may be phenyl optionally substituted, preferably at positions 3, 4, and 5, with at least one substituent selected from halogen, alkyl, haloalkyl, hydroxy, alkylxy, arlyoxy, alkylaryloxy and arylalkyloxy, preferably with at least one of bromide, t-butyl, trifluoromethyl, hydroxy, and methoxy, particularly, 4-trifluoromethylpheny lamido, 4,5-dimethoxyphenylethylamido, 3-bromide-4-hydroxy-5-t-butyl-phenylenenitrileamidopropylamido, most preferably \( R_3 \) is arylecarbonyl where the aryl is substituted with hydroxy at positions 3, and 4 or at positions 3, 4, and 5.

\( R_4 \) is H, aryl, arylalkyl, alkylaryl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazoliny1, imidazolidinyl, pyrroliny1, pyrrolidinyl, oxazoliny1, isoxazoliny1, oxazolidinyl, oxazolidony1, isoxazolidony1, pyrazoliny1, pyrazolidinyl, piperidyl, piperazine, morpholiny1, preferably the heteroaryl is one of pyrroly1, thienyl, thiazolyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, fury1, furazany1, isobenzozofurany1, pyranyl, chromenyl, xanthenyl, phenoxyxantheny1, indolyl, isoindolyl, indoliziny1, isoindoly1, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyraziny1, pyrimidiny1, pyridaziny1, or \( R_4 \) forms a fused phenylpyrrolidone ring with the main aromatic ring; and

Het is a 5 or 6-membered hetero ring, preferably said ring selected from imidazoline, imidazolidine, carbostyryl, pyrrole, pyrroline, pyrrolidine, thiophene, thiazole, isothiazole, furan, furazan, oxazole, isoxazole, oxazolidine, isoxazolidone, pyrazole, pyrazoline, pyrazolidine, pyridine,
pyrazine, pyrimidine, pyridazine, piperidyl, piperazinyl, morpholinyl, particularly Het is either one of oxazolidone, cyclic urea, and pyrrolidone, and pharmaceutically acceptable salts thereof.

In one aspect, the present invention provides use of a compound, or a mixture of compounds, inhibiting a SRE or a PTK, in the preparation of a pharmaceutical composition for extending the lifespan of a subject, wherein said compound is selected from the group consisting of compounds of formula (Ia), compounds of formula (Ib), aromatase inhibitors, estradiol receptor inhibitors, and antilipolytic compounds AGS 308 and AGS 333.

In another aspect, the present invention provides a method of elongating the lifespan of a subject, particularly a mammal, most preferably a human, comprising administering to said subject an effective amount of a compound, or a mixture of compounds, inhibiting a SRE or a PTK, selected from the group consisting of compounds of formula (Ia), compounds of formula (Ib), aromatase inhibitors, estradiol receptor inhibitors, and antilipolytic compounds AGS 308 and AGS 333 as an active ingredient, and optionally further comprising a carrier, diluent, excipient and/or additive.

The invention further provides a subclass of compounds of formulae (Ia) and (Ib), novel compounds of formulae (IIa) and (IIb):

![Formula (IIa)](image1)

![Formula (IIb)](image2)
where the substituents R₁, R₂, R₃, R₄, R₅, and Het are as defined for formulae (Ia) and (Ib) with the exclusion of the following combinations:

R₁ is hydroxy, R₂ is hydrogen, R₃ is cyano, and R₄ forms a fused phenyl pyrroolidone with the main aromatic ring;

R₁ is hydroxy, R₂ is hydrogen, R₃ is 3,4-dihydroxybenzoyl, and R₄ is hydrogen;

R₁ is bromide, R₂ is t-butyl, R₃ is cyano, and R₄ is hydrogen; or

Het is oxazolidone, R₂ and R₄ are hydrogen, and R₃ is phenylmethylamido, or 3,4-dihydroxybenzoyl.

In one preferred embodiment, the present invention provides use of compounds of formulae (Ia), and (Ib) in the preparation of pharmaceutical composition for extending the lifespan in a subject, particularly mammalian, most preferably human.

In another preferred embodiment, the present invention provides use of compounds of formulae (IIa), and (IIb) in the preparation of pharmaceutical composition for extending the lifespan in a subject, particularly mammalian, most preferably human.

In still another preferred embodiment, the present invention provides use of aromatase inhibitors in the preparation of pharmaceutical composition for extending the lifespan in a subject, particularly mammalian, most preferably human.

In a further preferred embodiment, the present invention provides use of estradiol receptor inhibitors in the preparation of pharmaceutical composition for extending the lifespan in a subject, particularly mammalian, most preferably human.
In another aspect, the present invention provides pharmaceutically acceptable compositions comprising a SRE inhibitor or a PTK inhibitor selected from compounds of formula (Ia) or (Ib), aromatase inhibitors, and estradiol receptor inhibitors, or mixtures thereof optionally further comprising a carrier, diluent, excipient and/or additive.

In one aspect the present invention provides a method of elongating the lifespan of a mammalian, preferably human subject, the method comprising the step of administering to that subject an effective amount of at least one compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising that compound.

In one particular aspect the present invention provides a method for preventing and/or delaying the appearance of age-dependent and/or age-related disorders in a mammalian, preferably human subject, comprising the step of administering to that subject an effective amount of at least one compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising that compound.

In another particular aspect the present invention provides an anti-aging method for a mammalian, preferably human subject, comprising the step of administering to that subject an effective amount of at least one compound of formula (Ia), or (Ib), or formula (IIa), or (IIb), or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the same.

In a further aspect the present invention provides a method of elongating the lifespan of a mammalian, preferably human subject, the method
comprising the step of administering to that subject an effective amount of at least one compound selected from compounds of formula (IIa) or (IIb), aromatase inhibitors, and estradiol receptor inhibitors, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising that compound.

In a further particular aspect the present invention provides a method for preventing and/or delaying the appearance of age-dependent and/or age-related disorders in a mammalian, preferably human subject, comprising the step of administering to that subject an effective amount of at least one compound selected from compounds of formula (IIa) or (IIb), aromatase inhibitors, and estradiol receptor inhibitors, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising that compound.

In a preferred embodiment the administration of any of the compounds of formula (Ia) or (Ib) or (IIa) or (IIb), or pharmaceutical compositions comprising the same, delays aging symptoms and/or slows the aging process. Particularly, the subject is a mammalian subject afflicted with a premature aging disorder, the subject being the most preferably a human.

In another preferred embodiment the present invention provides pharmaceutically acceptable glucose amine salt of a compound of formula (Ia) or (Ib), where that salt being preferably a combination, particularly at 1:1 ratio, of N- methyl glucose amine and the compound AG 1024, designated AGS 250.

In another aspect the present invention provides a method for the manufacture of compounds as defined in formulae (IIa) and (IIb), where this method comprises the following steps: a) mixing together a derivative
of a hydroxy-benzaldehyde, a derivative of acetonitrile, and L-alanine in a solvent; b) refluxing; c) evaporating; and d) triturating.

In one particular embodiment the present invention provides a method for the manufacture of the compound AGS 250, which comprises the steps of: a) mixing together AGS 200 and N-methyl glucose amine; b) refluxing; c) evaporating; and d) triturating. Preferably, the solvent is ethanol in the manufacture of any of the novel compounds of the present invention, and the trituration is preferably carried-out in hexane, or in acetone-hexane mixture.

In still another aspect the present invention provides a pharmaceutical composition comprising a compound of formula (IIa) or (IIb), or mixtures thereof for the treatment of protein tyrosine kinase family (PTKs)-associated disorders in a mammalian subject in need.

In one particular embodiment the PTK is selected from the platelet-derived growth factor (PDGF), the epidermal growth factor (EGF), the insulin growth factor (IGF), and, preferably, the insulin-like growth factor-I (IGF-1) receptor.

In one particular aspect the PTK associated disorder is selected from (a) proliferative diseases, in particular sarcomas, carcinomas, lymphomas or melanomas; (b) fibrotic conditions, including pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy; (c) metabolic diseases, in particular diabetes; (d) other PTK-associated disorders such as arthritis, rheumatoid arthritis, psoriasis, neurodegenerative diseases; and (e) other abnormal conditions for example, transplant rejection, wound healing or inflammation.
In one particular embodiment the disorder comprises a malignant disorder selected from sarcomas, melanomas, lymphomas and carcinomas.

In one aspect the present invention provides a method for the treatment and/or prevention of PTK-associated disorders in a mammalian subject in need, comprising the step of administering to that subject a therapeutically effective amount of at least one of the compounds of formula (IIa), or (IIb), or a therapeutically effective amount of a pharmaceutical composition comprising that compound, wherein the PTK associated disorder particularly includes PDGF, EGF, IGF and preferably IGF-1 receptor related diseases.

In a particular aspect the disorder is selected from (a) proliferative diseases, in particular sarcomas, carcinomas, lymphomas or melanomas; (b) fibrotic conditions, including pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy; (c) metabolic diseases, in particular diabetes; (d) other disorders such as arthritis, rheumatoid arthritis, psoriasis, neurodegenerative diseases; and (e) other abnormal conditions for example, transplant rejection, wound healing or inflammation.

**Brief description of the drawings**

The above and other characteristics and advantages of the invention will be more readily apparent through the following examples, and with reference to the appended drawings, wherein:

Fig. 1. shows the lifespan extension in nematodes; the graph demonstrates the positive effect of compounds AGS-199 and AGS-250 of the present invention on the extension of lifespan in *C. elegans*;

Fig. 2. shows the lifespan extension in fruit flies; the graph demonstrates the positive effect of compounds AGS-200 and AGS-250 of the
present invention on the extension of lifespan in *D. melanogaster*; and
Fig. 3. shows the lifespan extension in nematodes; the graph demonstrates the positive effect of an aromatase inhibitor, arimidex at 50 μM, on the extension of the lifespan in *C. elegans*.

**Detailed Description of the Invention**

It is well known that PTKs and SREs belong among prominent factors in the biological regulation and signal transduction; and such proteins as IGF-1, aromatase, or estradiol receptor affect all aspects of cellular activities, being involved in processes that may run in parallel, or may enhance or cancel each other, in an unpredictable entanglement of regulation cascades. It is therefore surprising that inhibitors of IGF-1, aromatase inhibitors, and estradiol receptor inhibitors have now been found by us to extend the lifespan of worms or flies.

In accordance with the above said, the present invention is directed towards the use of compounds of formula (Ia) or (Ib) in the preparation of a pharmaceutical composition for extending the lifespan of a subject,

![Diagram](image-url)
wherein, $R_1$ is $H$, OH, halogen, wherein the halogen may be F, Cl, Br, or I, nitro, CN, aldehyde, substituted ketone, COOH, trifluoromethyl, amide, substituted or unsubstituted alkyl, particularly isopropyl, or t-butyl, alkenyl, alkynyl, aryl, arylalkyl, alkyaryl, alkylxoy, preferably methoxy, haloalkyl or haloaryl comprising at least one substituent selected from F, Cl, Br, or I, aryloxoy, preferably phenoxy, alkylamino, alkylamido, arylamino, arylamido;

$R_2$ is $H$, OH, alkyl, preferably t-butyl or isopropyl, aryl, arylalkyl, alkylarylation, alkylxoy, preferably methoxy, alkylthio, wherein the sulfur may replace any of the carbon atoms of the alkylthio, or arythio, arylalkylthio, arylthioalkyl, particularly arylthiomethyl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazolinyl, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxazolidonyl, isoxazolidonyl, pyrazolinyl, pyrazolidinyl, piperidyl, piperazine, morpholinyl, preferably the heteroaryl is one of pyrrolyl, thieryl, thiazolyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, furyl, furazanyl, isobenzozofuranyl, pyranyl, chromenyl, xanthenyl, phenoxyxanthiinyl, indolyl, isoindolyl, indolizinyl, isoindolylzinyln, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl;

$R_3$ is CN, amide, nitrileamido, aminothiol, amino, alkyl, alkenyl, alkynyl, alkylamino, alkylamido, alkyleneamino, alkyleneamido, particularly dicyanoethylene amino, wherein the alkyl, alkenyl, or alkynyl moieties in the above substituents may be substituted or unsubstituted, substituted or unsubstituted aryl, arylcarbonyl, arylalkylcarbonyl, arylalkylene carbonyl, arylamido, particularly phenylamido, arylalkylamido, particularly phenylmethylamido, or phenylethylamido, arylalkyleneamido, arylamino,
arylalkylamino, arylalkyleneamino arylsulfonyl, particularly phenylsulfonyl, arylalkylenesulfonfyl, arylalkylenenitrileamidoalkylamido, particularly phenylenenitrileamidopropylamido, wherein the aryl moiety in any of the aryl containing substituents may be phenyl optionally substituted, preferably at positions 3, 4, and 5, with at least one substituent selected from halogen, alkyl, haloalkyl, hydroxy, alkoxy, arlyoxy, alkylaryloxy and arylalkyloxy, preferably with at least one of bromide, t-butyl, trifluoromethyl, hydroxy, and methoxy, particularly, 4-trifluoromethylphenylamido, 4,5-dimethoxyphenylethylamido, 3-bromide-4-hydroxy-5-t-butyl-phenylenenitrileamidopropylamido, most preferably R₃ is arylcarbonyl where the aryl is substituted with hydroxy at positions 3, and 4 or at positions 3, 4, and 5.

R₄ is H, aryl, arylalkyl, alkylaryl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazolinyl, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxazolidonyl, isoxazolidonyl, pyrazolinyl, pyrazolidinyl, piperidyl, piperazine, morpholinyl, preferably the heteroaryl is one of pyrrolyl, thienyl, thiazolyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, furyl, furazanyl, isobenznorfuranyl, pyranyl, chromenyl, xanthenyl, phenoxyxanthiinyl, indolyl, isoindolyl, indolizinyl, isoindolizinyl, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or R₄ forms a fused phenylpyrrolidone ring with the main aromatic ring; and

Het is a 5 or 6-membered hetero ring, preferably said ring selected from imidazoline, imidazolidine, carbostyryl, pyrrole, pyrroline, pyrrolidine, thiophene, thiazole, isothiazole, furan, furazan, oxazole, isoxazole, oxazolidine, isoxazolidone, pyrazole, pyrazoline, pyrazolidine, pyridine,
pyrazine, pyrimidine, pyridazine, piperidyl, piperazinyl, morpholinyl, particularly Het is either one of oxazolidone, cyclic urea, and pyrrolidone, and pharmaceutically acceptable salts thereof.

The use of the term "alkyl" throughout the specification and in the claims essentially refers to a saturated aliphatic hydrocarbon chain, straight or branched, that may contain between 1-20 carbon atoms, inclusive, preferably between 1-10 carbon atoms, and most preferably between 1-4 carbon atoms. A substituted alkyl chain refers to an alkyl as defined herein above substituted with groups such as, but not limited to, cycloalkyl, substituted or unsubstituted aryl, heteroaryl, alkylhalide, haloaryl, alkylthio, arylthio, halogen, alkylamido, alkylamino, hydroxy, alkoxy, aryloxy, nitro, and sulfonamido.

The use of the term "aryl" throughout the specification in the claims essentially refers to at least one carbocyclic system having conjugated carbon-carbon double bonds, wherein when the aryl contains more than one ring then the rings are fused. Non-limitative examples of aryl moieties are phenyl, naphthyl, and anthracyl. Substituted aryl is therefore an aryl as defined hereinabove, bearing substituents selected from, but not limited to, substituted or unsubstituted alkyl, cycloalkyl, halogen, alkylhalide, alkylamido, alkylamino, alkylthio, hydroxy, alkoxy, nitro.

The use of the term "heteroaryl" refers to any of the aryl rings defined hereinabove, where at least one of the carbon atoms of those rings may be substituted with an atom of a different element. Preferably this element is at least one of oxygen, nitrogen, and sulfur.

The use of the term "heterocycloalkyl" refers to a monocyclic or fused carbon atom chain which is in either saturated state or which has pi non-
conjugated bonds, and where at least one of the carbon atoms of the ring is substituted with an atom of a different element. Preferably, this element is at least one of oxygen, nitrogen, and sulfur.

In one aspect the invention provides a pharmaceutical preparation comprising at least one compound of formula (Ia) or (Ib) as the active component and may further comprise pharmaceutically acceptable carriers, diluents, vehicles, excipients and/or additives. Said carriers, diluents, vehicles, excipients, or additives facilitate the consumption of the active component(s), are compatible with the latter, and do not carry any negative or inhibitory effect on the active component(s) performance and/or no side or negative effects on the recipient of the pharmaceutical preparation. In other embodiments the pharmaceutical preparation of the invention may further comprise additional pharmaceutically active agents.

In another aspect the invention provides a pharmaceutical preparation comprising at least one aromatase inhibitor. Although using potent aromatase inhibitors in generally healthy aging population might be expected to involve risks, our results show that the balance of potentially positive and negative effects of the inhibitors tipped to the positive direction, and led to an increase of the lifespan in worms, for example arimidex increased the mean lifespan of worms in some experiments by 27%.

Arimidex and fomara are reversible synthetic aromatase inhibitors while formestane and exemestane, analogs of androstenedione, are irreversible inhibitors.
Our aim was to provide drugs based on SREs inhibitors that would decelerate aging and extend the lifespan, similarly to inhibitors of IGF-1 in the GH-Insulin-IGF-1 axis. Aromatase inhibitors in the estrogen pathway were tested. The pharmacologic intervention was done on adult organisms to minimize development effects on the lifespan determination. The lifespan extension was achieved, and also encouraging was the leveling of the survival curve. From day 14 to 19, well after the reproduction period, very few deaths occurred while in the same time period in the control cohort 78% died.

The lifespan was characterized by mean, median and maximal lifespan, and the extension was calculated relative to control + DMSO.

Arimidex increased the lifespan in worms, as measured by the mentioned three parameters, by 27%, 64% and 20%, respectively. Antilipolytic compounds AGS 308 and AGS 333 also showed surprising effects on the lifespan extension; the former increasing the lifespan parameters by 36%, 33% and 22%, and the latter by 20%, 19% and 21% respectively.

Thus the present invention is also directed to the use of SREs inhibitors, such as aromatase inhibitors, in the preparation of a pharmaceutical composition for extending the lifespan of a subject.

In a preferred embodiment, the pharmaceutical preparation of the invention comprises at least one aromatase inhibitor as the active
component, and may further comprise pharmaceutically acceptable carriers, diluents, vehicles, excipients and/or additives. Said carriers, diluents, vehicles, excipients, or additives facilitate the consumption of the active component(s), are compatible with the latter, and do not carry any negative or inhibitory effect on the active component(s) performance and/or no side or negative effects on the recipient of the pharmaceutical preparation. In other embodiments the pharmaceutical preparation of the invention may further comprise additional pharmaceutically active agents.

The pharmaceutical formulation of the invention is intended to be used in the elongation of the lifespan of a subject, wherein said subject is particularly a mammal, and most preferably a human. While formulations include those suitable for topical, oral, rectal, nasal; preferred formulations are intended for parenteral administration, including intramuscular, intravenous, intradermal and subcutaneous administration.

The pharmaceutical formulation of the invention, used in the elongation of the lifespan of a subject, particularly a mammal, and most preferably a human, may comprise, in a preferred embodiment of the invention, a pharmaceutically acceptable known compound, e.g. antineoplastic or entiestrogen, such as triazole derivatives letrozole and anastrozole, imidazole derivative fadrozole, pyrazole derivative AGS 308, antiestrogens fulvestrant or raloxifene, etc.

In a preferred embodiment, pharmaceutical compositions comprising at least one aromatase inhibitor as the active component, are intended to be used for the treatment of aromatase activity related diseases, disorders, or conditions in a subject in need, particularly a mammal, and most preferably a human.
Another aspect of the invention relates to a method of elongating the lifespan of a subject, particularly a mammal, most preferably a human, comprising administering to said subject an effective amount of an aromatase inhibitor or estradiol receptor inhibitor, specifically any one of fadrozole, letrozole, anastrozole, 3,5-dimethylpyrazole, and raloxifene, or mixtures thereof, or pharmaceutically acceptable salts thereof. As shown by the experiments, administration of such compounds to nematodes resulted in elongation of their lifespan.

In accordance with the above formula (Ia) or (Ib), in one preferred embodiment the present invention is directed to the use of the following compounds:
In a broader embodiment, said pharmaceutical composition may comprise any of the compounds AG 336, AG 2262, AG 2263, AG 538 (AGS 199) and AG 1024 (AGS 200) or mixtures thereof.

In accordance with the above description, the present invention is directed towards selected compounds of formulae (Ia) and (Ib) of the present invention which form a subclass of novel compounds:
wherein \( R_1, R_2, \) and \( R_3, R_4 \) and Het are as defined above for formulae (Ia) and (Ib), with the exclusion of the following combinations:

- \( R_1 \) is hydroxy, \( R_2 \) is hydrogen, \( R_3 \) is cyano, and \( R_4 \) forms a fused phenyl pyrroolidone hetero ring with the main aromatic ring; or
- \( R_1 \) is hydroxy, \( R_2 \) is hydrogen, \( R_3 \) is 3,4-dihydroxybenzoyl, and \( R_4 \) is hydrogen; or
- \( R_1 \) is bromide, \( R_2 \) is \( t \)-butyl, \( R_3 \) is cyano, and \( R_4 \) is hydrogen; or
- Het is oxazolidone, \( R_2 \) and \( R_4 \) are hydrogen, and \( R_3 \) is phenylmethylamido, or 3,4-dihydroxybenzoyl;
- and to pharmaceutically acceptable salts thereof.

In preferred embodiments, the present invention is directed to the following compounds of formulae (IIa) and (IIb):

\[
\text{AGS 192}
\]
AGS 320

AGS 321

AGS 322

AGS 323
In still another preferred embodiment the present invention is directed to a pharmaceutically acceptable glucose amine salt of a compound of formula (Ia) designated AGS 250, wherein said salt is preferably a combination, particularly at 1:1 ratio, of N-methyl glucose amine and the compound AGS 200 (AG 1024).

\[
\begin{align*}
&\text{C}_{14}\text{H}_{13}\text{BrN}_{2}\text{O} & \text{C}_{7}\text{H}_{15}\text{NO}_{5} \\
&\text{M.W. : 305.17 g/mol} & \text{M.W. : 193.20 g/mol} \\
\end{align*}
\]

AGS 200 (AG 1024)  \quad \text{N-methyl D-glucose amine}

AGS 250 · 1:1 salt of AGS 200 and N-methyl-D-glucose amine  \quad \text{M.W. 498 g/mol}

In another embodiment, the invention relates to a method for the manufacture of a compound of formula (IIa) or (IIb). Said method comprises the steps of: (a) mixing together a derivative of a hydroxy-benzaldehyde, a derivative of acetonitrile, and beta-alanine in a solvent; b) refluxing; c) evaporating; and d) triturating, as described in Examples 1 to 4. In a preferred embodiment, said solvent is ethanol and the evaporation and trituration processes are carried out in hexane.

In a further aspect, the invention relates to pharmaceutical preparations comprising as active ingredient at least one compound of formula (IIa) or
(IIb), and optionally further comprising a carrier, diluent, vehicle, excipient and/or additive.

In another aspect, the present invention is directed to the use of at least one compound of the compounds of formula (IIa) or (IIb), preferably any of the said compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323 in the manufacture of a pharmaceutical composition.

In still another preferred embodiment the present invention is directed to the use of a salt of compound AG 1024 (AGS 200), particularly the novel N'-methyl glucose amine salt (designated AG 250, and synthesized according to Example 5 in the preparation of a pharmaceutical composition. This pharmaceutical preparation is particularly intended to be used in the elongation of the lifespan of a subject.

In one particular case synthesis of the salt designated AGS 250, comprises the steps of: a) mixing together AGS 200 and N'-methyl glucose amine; b) refluxing; c) evaporating; and d) triturating.

As used herein "pharmacologically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic composition is contemplated.

A carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient.
Pharmaceutical preparations comprising the active component(s) with one or more acceptable carriers may be provided in either solid, liquid, sol-gel, aerosol, spread, cream, lotion, ointment spray, suspension, drops, solution, or powder form, and administration may therefore take the various corresponding oral, gastrointestinal, rectal, subcutaneous, parenteral, nasal, respiratory, or topical routes. Oral administration may be followed by adsorption of the active components through the sidewalls of different sections of the alimentary tract, whereas by subcutaneous or parenteral administration is meant, *inter alia*, subdermally, intravenously, arterially, or intramuscularly. Topical administration of the active component(s), or corresponding pharmaceutical preparations may take place through any exposed surface of the recipient's organs, and the nasal or respiratory routes may be implemented with the use of a suitable inhalator dispenser device, the active component(s) being accompanied with a dense pharmaceutically acceptable propellant.

While formulations include those suitable for topical, oral, rectal, nasal, preferred formulations are intended for parenteral administration, including intramuscular, intravenous, intradermal and subcutaneous administration.

The pharmaceutical forms suitable for injection use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid
polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

In particular, the pharmaceutical preparations for the lifespan extension of the present invention may be administered in the form of solid tablets, a gelatin capsules or elixirs.

The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the art of pharmacy. It is understood by the skilled artisan, that the preferred dosage would be individualized to the patient following good laboratory practice and standard medical practice.

The terms "pharmaceutical composition" and "pharmaceutical preparation" have the same meaning and are similarly used.

In a preferred embodiment, pharmaceutical compositions comprising at least one of the compounds of formula (IIa) or (IIb) as the active component(s), are intended to be used for the treatment of PTKs activity related diseases, disorders, or conditions in a subject in need, particularly a mammal, and most preferably a human.

In a specific embodiment, said compound of formula (IIa) or (IIb) is any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, AGS 323, and mixtures thereof.
In a particular embodiment, said PTK associated disorder or condition is related to the platelet-derived growth factor (PDGF), the epidermal growth factor (EGF), the insulin growth factor (IGF), and particularly the insulin-like growth factor-1 (IGF-1) receptor activities.

The term "growth factor" relates to a complex family of polypeptide hormones or biological factors that are produced by the body to control growth, division and maturation of blood cells by the bone marrow. They regulate the division and proliferation of cells and influence the growth rate of some cancers. Perturbation of growth factor production or of the response to growth factor is important in neoplastic transformation.

The Insulin like Growth Factor (IGF) is of particular importance in the present invention. IGF factors I and II are polypeptides with considerable sequence similarity to insulin.

Insulin-like growth factor-1 (IGF-1) is a mitogen and an important mediator of the growth hormone effect. IGF-1 also acts as potent survival factor in numerous cell lines exposed to environmental stresses, primary through activation of the AKT signal pathway.

In a different embodiment, the pharmaceutical compositions comprising compound (IIa) or (IIb) as active agent may be used for the treatment of protein tyrosine kinase family (PTKs) associated disorders selected from (a) proliferative diseases, in particular sarcomas, carcinomas, lymphomas or melanomas; (b) fibrotic conditions, including pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy; (c) metabolic diseases, for instance diabetes; (d) other disorders such as arthritis, rheumatoid arthritis, psoriasis,
neurodegenerative diseases; and (e) other abnormal conditions for example, transplant rejection, wound healing or inflammation.

The terms "associated disorder" and "related disorder" are used similarly throughout the present description and they relate to disorders associated with a malfunction of PTK or SRE or a receptor related to them.

A "disorder" is a condition in which there is a disturbance of normal functioning. A "disease" is any abnormal condition of the body or mind that causes discomfort, dysfunction, or distress to the person affected or those in contact with the person. Sometimes the term is used broadly to include injuries, disabilities, syndromes, symptoms, deviant behaviors, and atypical variations of structure and function, while in other contexts these may be considered distinguishable categories.

Disease, disorder, condition and illness, are equally used herein, and they refer, but do not limit to: neoplastic or proliferative disorders, non-neoplastic disorders, neurological disorders, metabolic disorders, skeletal muscle disorders, diseases caused by protein misfolding or protein aggregation, cardiovascular disorder, dermatological disorder, fibrotic conditions, inflammatory disorders, geriatric disorder, age related and/or associated disorders.

As mentioned above, a "neoplastic or proliferative disorder" is a disease or disorder characterized by cells that have the capacity for autonomous growth or replication; an abnormal state or condition characterized by proliferative cell growth.

A "neurological disorder" is a disease or disorder characterized by an abnormality or malfunction of neuronal cells or neuronal support cells.
The disorder can affect the central and/or peripheral nervous system. Exemplary neurological diseases include: neuropathies, skeletal muscle atrophy and neurodegenerative diseases. Exemplary neurodegenerative diseases include: Alzheimer's, Amyotrophic lateral sclerosis (ALS) and Parkinson's disease.

A "cardiovascular disorder" is a disease or disorder characterized by an abnormality or malfunction of the cardiovascular system. Exemplary cardiovascular diseases include: cardiac dysrhythmias, chronic congestive heart failure, ischemic stroke, coronary artery disease and cardiomyopathy.

A "metabolic disorder" is a disease or disorder characterized by an abnormality or malfunction of metabolism. One category of metabolic disorders are disorders of glucose or insulin metabolism.

A "dermatological disorder" is a disease or disorder characterized by an abnormality or malfunction of the skin and/or its appearance.

Examples of diseases caused by protein misfolding or protein aggregation include among others: Parkinson's disease, prion diseases, familial amyloid polyneuropathy, tauopathies, polyglutamine aggregation disorders, Fragil-X syndrome, myotonic dystrophy and Alzheimer's disease.

The compounds of formula (IIa) or (IIb), particularly the compounds specifically disclosed above, are effective in treating disorders, diseases, and conditions related with PTKs activity in a subject, particularly a mammal, most preferably a human in need of such treatment. Therefore the present invention is directed to the use of compounds of formula (IIa)
or (IIb) in the treatment of diseases, disorders, and conditions, related with PTKs activity, by administering an effective amount of at least one compound of the compounds of formula (IIa) or (IIb) to a subject, particularly a mammal, most preferably a human, in need of such treatment. Particularly the present invention is directed to the compounds designated AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323, for use in the treatment of diseases, disorders, and conditions, related with PTKs activity, by administering an effective amount of at least one compound of the compounds of formula (IIa) or (IIb) to a subject, particularly a mammal, most preferably a human, in need of such treatment.

PTKs signal pathways include a series of extracellular and intracellular signaling components that have a downstream target, for example a transcription factor. The IGF-1 axis, includes the IGF-1 receptor and intracellular signaling components including PI(3) kinase, PTEN phosphatase, PI(3,4)P₂, 14-3-3 protein and PI(3,4,5)P₃ phosphatidylinositol kinases, AKT serine/threonine kinase (e.g. AKT-1, 2, or 3) or a Forkhead transcription factor (e.g. FOXO·1, 3 or 4).

Insulin-like growth factor 1 (IGF-1) activates upstream kinases, important for the survival of various cell types. This enzyme, called phosphoinositide 3-kinase (PI3-K), triggers the activation of AKT. The PI3-K/AKT pathway is involved in many biological processes, including both the programmed death of cells, or apoptosis, and its prevention.

IGF-1 axis members play important roles in many different biological processes such as cell death and survival, insulin metabolism, cytoprotective response, radiation resistance, promotion of neuronal
survival and inhibition of neurodegeneration, may prevent cancers and also be involved in metastases of breast and colon cancer cells.

The present invention is also directed to the use of compounds of formula (IIa) or (IIb) in the treatment of malignant disorders such as sarcomas, melanomas, lymphomas or carcinomas, by administering an effective amount of at least one compound of formula (IIa) or (IIb) to a subject, particularly a mammal, most preferably a human subject in need of such treatment. Particularly the present invention is directed to the compounds designated AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323, for use in the treatment malignant disorders, by administering an effective amount of at least one compound of formula (IIa) or (IIb) to a mammalian subject in need, most preferably a human.

An additional aspect of the present invention is directed to the use of compounds of formula (IIa) or (IIb), preferably any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, AGS 323 and mixtures thereof, or pharmaceutical preparation comprising them, for elongating the lifespan of a mammal subject, particularly a human.

The term "Lifespan" used herein, relates to: a lifetime; the average or maximum length of time an organism can be expected to survive or last.

"Maximum lifespan" corresponds to the age at which the survival curves touch the age-axis (0%); it represents the age at which the oldest known member of the species has died. (In animal studies, maximum lifespan is typically taken to be the mean lifespan of the most long-lived 10%).
"Mean lifespan" or average lifespan, corresponds to the age at which the horizontal line for 50% survival intersects the survival curve. Mean lifespan varies with susceptibility to disease, accident and homicide/suicide, whereas maximum lifespan is determined by "rate of aging".

In aging research, maximum lifespan is regarded as a proxy for aging. Chemicals, calorie restriction with adequate nutrition, or other interventions which increase maximum lifespan are said to have slowed the aging process.

The vast variation in the lifespan across individuals is determined by both genetic and environmental effects.

"Life extension" consists of attempts to extend life beyond the maximum natural lifespan. So far none has been proven successful in humans.

In a preferred embodiment, the present invention provides a method for the prevention and treatment of diseases, disorders, and conditions related with PTKs activity in a subject, particularly a mammal, most preferably a human, in need of such treatment by administering to that subject an effective amount of at least one compound of the compounds of formula (IIa) or (IIb), specifically any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323 disclosed hereinabove, or of a pharmaceutical preparation comprising one of said compounds as the active component(s).

"Treatment" refers to therapeutic treatment. Those in need of treatment are mammal subjects suffering from any PTK activity related disorder, or SRE activity related disorder. By "patient" or "subject in need" is meant
any mammal for which administration of any of the compounds of the invention or any pharmaceutical composition comprising any of said compounds or mixes thereof, is desired in order to overcome or slow down such infliction.

To provide a "preventive treatment" or "prophylactic treatment" is acting in a protective manner; to defend against or prevent something, especially a condition or disease.

The term "effective amount" or "sufficient amount" means an amount necessary to achieve a selected result. The "effective treatment amount" is determined by the severity of the disease in conjunction with the preventive or therapeutic objectives, the route of administration and the patient's general condition (age, sex, weight and other considerations known to the attending physician).

"Mammal" for purposes of treatment refers to any animal classified as a mammal including, human, research animals, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal is human.

Diseases, disorders, and conditions, related with PTKs activity, for which the compounds of formula (IIa) or (IIb) are effective in treating or preventing are proliferative, fibrotic, metabolic disorders, and other abnormal conditions.

Therefore in one preferred embodiment the compounds of formula (IIa) or (IIb) of the present invention, specifically any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323 disclosed above, are directed
towards the treatment of proliferative disorders, diseases, and conditions selected from solid tumors, soft tissue tumors, hematopoietic cancers and metastatic cancers. Examples of the different forms of cancer are: sarcomas, adenocarcinomas, lymphomas and carcinomas affecting lungs, breast, gastrointestinal (colon, rectal, small intestine), liver, genitourinary tract (renal, bladder, urothelial cells), pharynx, prostate and ovary. Other proliferative disorders may include papillomas, blastoglioma, Kaposi's sarcoma, melanoma, squamous cell carcinoma, astrocytoma, thyroid cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, leukemia, lymphoma, Hodgkin's disease, Burkitt's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, angiogenesis, restenosis, in-stent restenosis and vascular graft restenosis.

In another embodiment of the present invention the compounds of formula (Ia) or (Ib), specifically any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323 disclosed above, are directed towards the treatment of fibrotic disorders, diseases, and conditions selected from pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, thrombic microangiopathy syndromes and transplant rejection.

In still another embodiment of the present invention, the compounds of formula (Ia) or (Ib), specifically any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323 disclosed above, are directed towards the treatment of conditions selected from metabolic disorders, inflammation, neurodegenerative diseases, psoriasis, diabetes, and wound healing.
Another aspect of the invention relates to a method of elongating the lifespan of a subject, particularly a mammal, most preferably a human, comprising administering to said subject an effective amount of any of the compounds of formula (Ia) or (Ib), specifically any of the compounds AG 336, AG 2262, AG 2263, AG 538, AG 1024, mixtures thereof, pharmaceutically acceptable salts or a pharmaceutical preparation comprising at least one of such compounds. As demonstrated in the Examples, administration of compounds of formula (Ia) or (Ib) to nematodes and flies resulted in elongation of their lifespan.

In a particular embodiment the present invention provides a method of elongating the lifespan of a subject, particularly a mammal, most preferably a human, by administering to that subject an effective amount of at least one compound of the compounds of formula (IIa) or (IIb), specifically any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323.

In another embodiment, the present invention provides a method of elongating the lifespan of a subject, particularly a mammal, most preferably a human, by administering to that subject a pharmaceutical preparation comprising an effective amount of at least one compound selected from the group consisting of a compound having formula (Ia), a compound having formula (Ib), a compound having formula (IIa), a compound having formula (IIb), an aromatase inhibitor, an estradiol receptor inhibitor, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising any of said compounds. In still another embodiment, the present invention provides a method of elongating the lifespan of a subject, particularly a mammal, most preferably a human, by administering to that subject a
pharmaceutical preparation comprising an effective amount of at least one compound selected from the group consisting of a AG 336, AG 2262, AG 2263, AG 538, AG 1024, AGS 192, AGS 195, AGS 206, AGS 244, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, AGS 323, letrozole, anastrozole, formestane, exemestane, fulvestrant, raloxifene, tamoxifene, AGS 308, and AGS 333, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising any of said compounds.

An effective amount of the composition of the invention, useful for the lifespan elongation, will be an amount sufficient to prolong the lifespan beyond expectancy. For example, an effective amount of the composition of the invention will confer longevity by extending the mean and maximum lifespan values of a certain population treated with said compositions by delaying the appearance of aging symptoms.

The terms "life extension", "life expansion" and "longevity" are used in the invention as analogues.

Animal lifespans are not the same as humans'. The relatively long lifespan of humans is partially explained in molecular terms by the low level of free radical production, the low level of fatty acid unsaturation and the high level of DNA repair enzymes in human cells.

In a preferred embodiment, the method of the invention is intended to prevent and/or delay the appearance of age dependent disorders in a mammalian subject, most preferably a human, by administering to that subject an effective amount of at least one compound selected from the group consisting of formula (Ia), formula (Ib), AG 336, AG 2262, AG 2263, AG 538, AG 1024, formula (IIa), formula (IIb), AGS 192, AGS 195, AGS
206, AGS 244, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, AGS 323, letrozole, anastrozole, formestane, exemestane, fulvestrant, raloxifene, tamoxifene, AGS 308, and AGS 333, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising any of said compounds.

"Age-dependent" means definitely occurring with age, age eventually causes the disease. Eye cataracts, eye macular degeneration, osteoporosis, osteoarthritis, vulvovaginal atrophy (women), nodular prostate hyperplasia (men), senile emphysema, wrinkled skin, poor vision (presbyopia), brain cell loss, weak immune system (monoclonal gammopathy) are examples of age dependent disorders.

The invention is directed to a method of preventing and/or delaying the appearance of age related disorders in a mammalian subject, preferably human. In a preferred embodiment, the method comprises the step of administering to said subject an effective amount of at least one compound selected from the group consisting of a compound having formula (Ia), a compound having formula (Ib), a compound having formula (IIa), a compound having formula (IIb), and an aromatase inhibitor, estradiol receptor inhibitor, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising any of said compounds. In another preferred embodiment, the method of the invention comprises the step of administering to said subject an effective amount of at least one compound selected from the group consisting of a AG 336, AG 2262, AG 2263, AG 538, AG 1024, AGS 192, AGS 195, AGS 206, AGS 244, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, AGS 323, letrozole, anastrozole, formestane, exemestane, fulvestrant, raloxifene, tamoxifene, AGS 308, and AGS 333, or a pharmaceutically acceptable salt.
thereof, or an effective amount of a pharmaceutical composition comprising any of said compounds.

"Age-related" means increasing in prevalence with age, age just raises its prevalence. Atherosclerosis (stroke, heart attack, etc.) temporal arteritis, myelodysplastic syndrome, chronic lymphocytic leukemia, plasma cell myeloma, ("multiple" myeloma), hypertension, type II diabetes, Alzheimer's disease (controversy), idiopathic Parkinson's disease, prostate cancer, skin cancer, breast cancer, colon cancer, "atrophic gastritis" (stomach cancer precursor), calcific aortic stenosis, Paget's disease of bone, glaucoma, iatrogenic disease and polypharmacy ("vulnerability to infections") are some examples of age related disorders.

The invention is also related to an anti-aging method for treating a mammalian subject, preferably a human, comprising the step of administering to said subject an effective amount of at least one compound of formula (Ia) or (Ib) or formula (IIa) or (IIb) or a pharmaceutically acceptable salt or a pharmaceutical composition comprising an effective amount of any compound of the invention.

In a preferred embodiment, said compounds are specifically selected from the groups AG 336, AG 2262, AG 2263, AG 538 or AG 1024; and AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, or AGS 323.

"Aging" is the progressive loss of physiological functions that increases the probability of death; the organic process of growing older and showing the effects of increasing age.
"Anti-aging" are strategies, programs, and supplements that reduce, prevent, and reverse the decline of physiological functions and age-related dysfunction, disorders, and diseases.

Aging changes are frequently associated with an increase in likelihood of mortality, but this is not necessarily the case. For example, graying of hair is a symptom of aging, but graying does not increase likelihood of mortality. Aging changes which are not associated with a specific disease, but which are associated with a generalized increase in mortality would qualify as "biomarkers" of aging and would distinguish "biological age" from "chronological age". Biomarkers would be better predictors of the increased likelihood of mortality (independent of specific disease) than the passage of time (chronological age).

In a specific embodiment, the anti-aging method is intended to delay aging symptoms or slow the aging process.

"Aging symptoms" are changes that typically occur with age. These age changes include: loss of hearing ability, decline in the ability to taste salt and bitter, reduction of the thymus, increased levels of antibodies, some form of arthritis, teeth loss, twice higher insulin requirements to achieve the glucose uptake of the young, reduced sensitivity to growth factors and hormones due to fewer receptors and dysfunctional post-receptor pathways, decline in body weight, increase in body fat, decline in muscle strength, decline in reaction time, drop in degree of saturation of fats in the brains of old animals, diminution of the sleeping time and quality sleep, presbyopia (reduced ability to focus on close-up objects), physical disability (defined as the inability to use public transportation) and appearance of various pathological conditions.
Thus, the invention is also directed to a method for delaying aging symptoms in a mammalian subject, preferably a human, afflicted with a premature aging disorder by employing the compounds of the invention, namely compounds of formula (Ia) or (Ib) and of formula (IIa) or (IIb).

There are several diseases that cause rapid aging. The relation to normal aging is not yet fully understood but many phenotypes and features of aging appear at earlier chronological age in these diseases. Examples of such diseases include Classic progeria (Hutchinson-Gilford syndrome), Werner's syndrome, Ataxia-telangiectasia (“fragile chromosome syndrome”), Leprechaunism (an insulin receptor mutation disease), Rothmund's syndrome (mental retardation, skin pigment blotches, osteoporosis, and cataracts) and Progeroid syndrome (early signs but long life).

The invention is also directed to the treatment of such disorders by employing any of the compounds of formula (Ia) or (Ib) and formula (IIa) or (IIb). Said compounds are selected from the groups AG 336, AG 2262, AG 2263, AG 538 or AG 1024; and AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322 or AGS 323; respectively.

As used in the specifications and the appended claims and in accordance with long-standing patent Law practice, the singular forms “a” “an” and “the” generally mean “at least one”, “one or more”, and other plural references unless the context clearly dictates otherwise. Thus, for example “a cell”, “a peptide” and “a nucleic acid” include mixture of cells, one or more peptides and a plurality of nucleic acids of the type described.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of
a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The contents of all publications quoted to herein are fully incorporated by reference.

The following examples are representative of techniques employed by the inventors in carrying out aspects of the present invention. It should be appreciated that while these techniques are exemplary of preferred embodiments for the practice of the invention, those of skill in the art, in light of the present disclosure, will recognize that numerous modifications can be made without departing from the spirit and intended scope of the invention.

Examples

Preparations
The following examples illustrate in a non-limitative way the methods of preparation of several of the novel compounds, grouped under the definition of formulae (IIa) and (IIb), the products are identified by NMR and Mass Spectrometry (MS) methods.

Example 1 – Preparation of AGS 320
250 mg, 1 mM, 3-bromo 4-hydroxy 5-tert. butyl benzaldehyde, 190 mg, 1.05 mM, phenyl sulphonyl acetonitrile, and 20 mg β-alanine in 20 ml ethanol
were refluxed for 4 hours. Evaporation and trituration with hexane gave 402 mg, 95% yield, lemon yellow solid, m.p. 186°C.
NMR CDCl₃ 8.07(1H,s,vinyl), 8.05(2H,m), 7.98(1H,d,J=2.2 Hz), 7.90(1H,d,J=2.2 Hz), 7.65(3H,m), 1.48 (9H,s).
MS m/e 422, 420(M⁺,40%), 421, 419(M⁺,70%), 406, 404(M⁺ CH₃,82), 380, 378(M⁺ O-HCN,13), 367, 365(M⁺-6,8%), 250, 248(M⁺ PhSO₂⁻,2 CH₃,60), 185, 183(35).

Example 2 – Preparation of AGS 321
154 mg, 0.6 mM, 3-bromo 4-hydroxy 5-tert.butyl benzaldehyde, 143 mg, 0.63 mM, 2-cyano-N-(4-trifluoromethyl)-phenyl-acetamide and 10 mg β-alanine in 20 ml ethanol were refluxed for 3 hours. Cooling and filtering gave 274 mg, 97% yield, lemon yellow solid, m.p. 225°C.
NMR CDCl₃ 8.30(1H,s,vinyl), 8.05(1H,d,J=2.2 Hz), 7.96(1H,d,J=2.2 Hz), 7.77, 7.65(4H,AB, JAB=8.3 Hz), 1.45(9H,s).
MS m/e 471,469(M⁺,35%), 468,466(M⁺,70%), 453,451(M⁺ CH₃,40), 308, 306(M⁺-NHAr,82), 250, 250(M⁺-NHAr⁺56,20%), 212(25), 57(100).

Example 3 – Preparation of AGS 322
150 mg, 0.58 mM, 3-bromo 4-hydroxy 5-tert.butyl benzaldehyde, 150 mg, 0.6 mM, 2-cyano-N-[2-(3,4-dimethoxyphenyl)-ethyl]-acetamide, and 10 mg β-alanine in 20 ml ethanol were refluxed for 4 hours. Evaporation and chromatography gave 174 mg, 61% yield, lemon yellow solid, m.p. 74°C.
NMR CDCl₃ 8.25(1H,s,vinyl), 7.96(1H,d,J=2.1 Hz), 7.90(1H,d,J=2.1 Hz), 6.84(3H,m), 3.89, 3.87(6H,2 s, OCH₃), 3.66(2H,q,J=7.0 Hz), 2.86(2H,t,J=7.0 Hz), 1.42(9H,s).
MS m/e 489, 487(M⁺,12%), 488, 486(M⁺,35%), 473, 471(M⁺ CH₃,4), 308, 306(M⁺-NHAr,8), 165(100), 157(55).
Example 4 – Preparation of AGS 323
170 mg, 0.56 mM, 3-iodo 4-hydroxy 5-tert.butyl benzaldehyde, 145 mg, 0.58 mM, 2-cyano-N-[2-(3,4-dimethoxyphenyl)-ethyl]-acetamide, and 10 mg β-alanine in 20 ml ethanol were refluxed for 4 hours. Evaporation and chromatography gave 117 mg, 39% yield, lemon yellow solid, m.p. 67°C.
NMR CDCl₃: δ 8.14(1H,s,vinyl), 8.10(1H,d,J=2.0 Hz), 7.95(1H,d,J=2.0 Hz), 6.84(3H,m), 3.89, 3.87(6H,2 s, OCH₃), 3.60(2H,q,J=7.0 Hz), 2.83(2H,t,J=7.0 Hz), 1.42(9H,s).
MS m/e: 534(M⁺,24%),499(M⁺-CH₃,28),354(M⁺-NHaR,5), 298(M⁺-NHaR⁺-56,7%), 254(298-CH₃-OH,6), 164(100), 151(55).

Example 5 – Preparation of AGS 250
610 mg, 2 mM, AGS 200 and 400 mg, 2 mM, N-methyl glucose amine in 30 ml ethanol were heated at reflux 5 minutes. The clear orange solution was evaporated, triturated with acetone-hexane and filtered to give 930 mg, 93% yield, orange-red solid.

Assays
The following assays demonstrate in a non-limitative way the positive life-extending effect of the compounds of the present invention in several organisms. It will be appreciated that such illustrations of the inhibitory effect of the compounds of the present invention on PTKs activity, particularly that of IGF-1 receptor kinase, may be further broadened and implemented to other species, particularly mammals, and most preferably humans.

Example 6 – Nematodes
C. elegans nematodes were grown at 25°C on agar and fed E. coli, in 20x3 cohorts. The inhibitors were added after L4 stage of the larvae. Nematodes were transferred and fresh inhibitor added every 3 days. Three criteria
were used to measure the lifespan extension, with mean lifespan considered the most important.

a. Mean lifespan - sum of all days lived divided by number of nematodes
b. Maximum lifespan - day when the last survivor died.
c. Median lifespan - day when half the nematodes were alive.

Lifespan extension was calculated relative to the control+DMSO group.

Table 1 and Figure 1 demonstrate the significant life-extension effect experienced after the administration of some of the compounds of the present invention in identical concentrations. Total sum of days, and mean as well as the maximal lifespan were all increased, although more extensively for some compounds than others, and particularly for AGS 199.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Control +DMSO</th>
<th>AGS 199 50 μM</th>
<th>AGS 200 50 μM</th>
<th>AGS 250 50 μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of days live</td>
<td>646</td>
<td>633</td>
<td>1016</td>
<td>669</td>
<td>828</td>
</tr>
<tr>
<td>Mean lifespan</td>
<td>10.8</td>
<td>10.6</td>
<td>16.9</td>
<td>11.1</td>
<td>13.8</td>
</tr>
<tr>
<td>Extension</td>
<td>---</td>
<td>---</td>
<td>60%</td>
<td>6%</td>
<td>31%</td>
</tr>
<tr>
<td>Median lifespan</td>
<td>11</td>
<td>11</td>
<td>17</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Extension</td>
<td>---</td>
<td>---</td>
<td>55%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Maximal lifespan</td>
<td>20</td>
<td>18</td>
<td>27</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Extension</td>
<td>---</td>
<td>---</td>
<td>50%</td>
<td>16%</td>
<td>28%</td>
</tr>
</tbody>
</table>

**Example 7 - Flies**

*D. melanogaster* flies were grown at 29°C, in 20x3 cohorts. Flies were transferred and fresh inhibitor added every 3 days. Three criteria were
used to measure the lifespan extension, with mean lifespan considered the most important.

a. Mean lifespan - sum of all days lived divided by number of flies.
b. Maximum lifespan - day the last survivor died.
c. Median lifespan - day half the flies were alive.

In this particular assay every compound effect was examined at different concentrations, i.e. 50 ?M, 100 ?M, and 200 ?M, and compared to the control group. The results for AGS 250 are presented in Table 2, the results for AGS 250 and AGS 200 in Figure 2.

<table>
<thead>
<tr>
<th></th>
<th>Control n=56</th>
<th>50 ?M n=56</th>
<th>100 ?M n=58</th>
<th>200 ?M n=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of days live</td>
<td>865</td>
<td>1211</td>
<td>1428</td>
<td>1430</td>
</tr>
<tr>
<td>Mean lifespan</td>
<td>15.4</td>
<td>21.6</td>
<td>24.6</td>
<td>23.5</td>
</tr>
<tr>
<td>Extension</td>
<td>---</td>
<td>40%</td>
<td>60%</td>
<td>53%</td>
</tr>
<tr>
<td>Median lifespan</td>
<td>18</td>
<td>24.5</td>
<td>26.5</td>
<td>25.5</td>
</tr>
<tr>
<td>Extension</td>
<td>----</td>
<td>36%</td>
<td>47%</td>
<td>42%</td>
</tr>
<tr>
<td>Maximal lifespan</td>
<td>21</td>
<td>28</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Extension</td>
<td>----</td>
<td>33%</td>
<td>33%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Here again evidence for the elongation of lifespan is demonstrated in every parameter, achieving best results at 100 ?M for mean, and median lifespan increase by 60%, 47%, respectively, and maximal lifespan increase by 38%, at a concentration of 200 ?M. It is also clear from the above disclosed data that the life extension effect reaches a plateau in the concentration range of 100-200 ?M.
In a second experiment the mean lifespan was 26% (50 ?M), 27% (100 ?M) and 37% (200 ?M). No difference was observed between male and female flies.

The same experiments were carried out for several other compounds, and the results are detailed as follows:

**AGS 199**

The optimal concentration (in 1% DMSO) was 50-100 ?M which gave 17-20% mean lifespan extension (900 ?M gave only 2% extension).

**AGS 200**

The optimal concentration (in 1% DMSO) was 50-100 ?M which gave 26-27% mean lifespan extension (500 ?M shortened mean lifespan by 55% and 900 ?M was toxic).

Attention should be paid to the highest concentration showing positive effects, since once passing a certain value which is compound-specific, the reversal shortening lifespan effect may be undesirably achieved.

**Example 8 - Mice**

BALB/c mice and C57Bl/6 mice, 3 mice for each experiment group were injected 5 days a week for a period of 6 weeks with AGS 199 (25 mg/Kg), AGS 200 (12.5 mg/Kg) and AGS 250 (25 mg/Kg). Glucose level was tested twice a week. Glucose level was normal (80 vs. 90-100 normally) and no signs of diabetes developed. Administration of 25 mg/Kg of AGS 200 and 50 mg/Kg of AGS 250 were toxic to the mice (died within 24 hours).

**Example 9**

The effect of SRE inhibitors on the lifespan of worms was checked.
60 worms cohorts were used for each experiment, checking the effect of an aromatase inhibitor, arimidex, on the life span. Lifespan extension was calculated relative to control + DMSO. Mean, median and maximal lifespan were calculated. Results for various arimidex concentrations are summarized in Table 3.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Control (DMSO)</th>
<th>arimidex 25 ?M</th>
<th>arimidex 50 ?M</th>
<th>arimidex 100 ?M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of days live</td>
<td>690</td>
<td>679</td>
<td>639</td>
<td>862</td>
<td>520</td>
</tr>
<tr>
<td>Mean lifespan</td>
<td>11.5</td>
<td>11.3</td>
<td>10.7</td>
<td>14.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Extension</td>
<td>...</td>
<td>...</td>
<td>-5 %</td>
<td>27%</td>
<td>-23%</td>
</tr>
<tr>
<td>Median lifespan</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Extension</td>
<td>...</td>
<td>...</td>
<td>9%</td>
<td>64%</td>
<td>-10%</td>
</tr>
<tr>
<td>Maximal lifespan</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Extension</td>
<td>...</td>
<td>...</td>
<td>-5%</td>
<td>20%</td>
<td>-20%</td>
</tr>
</tbody>
</table>

A second experiment with 50 ?M arimidex gave 29%, 65% and 21% extension for mean, median and maximal lifespan, respectively. Figure 3 shows the survival curve with 50 ?M arimidex.

Tamoxifene at 50 ?M gave 11%, 26% and 14% extension of mean, median and maximal lifespan, respectively.
**Example 10**

The results for AGS 308 are summarized in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Control (DMSO)</th>
<th>AGS 308 50 ?M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sum of days live</strong></td>
<td>690</td>
<td>725</td>
<td>984</td>
</tr>
<tr>
<td><strong>Mean lifespan</strong></td>
<td>11.5</td>
<td>12.1</td>
<td>16.4</td>
</tr>
<tr>
<td><strong>Extension</strong></td>
<td>...</td>
<td>...</td>
<td>36 %</td>
</tr>
<tr>
<td><strong>Median lifespan</strong></td>
<td>12</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td><strong>Extension</strong></td>
<td>...</td>
<td>...</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Maximal lifespan</strong></td>
<td>17</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td><strong>Extension</strong></td>
<td>...</td>
<td>...</td>
<td>22%</td>
</tr>
</tbody>
</table>

The lifespan extension was calculated relative to control+DMSO. 60 worms cohorts were used for each experiment.

An experiment with 50 ?M AGS 333 gave 20%,19% and 21% extension for mean, median and maximal lifespan, respectively.
1. A compound of the formula (IIa) or (IIb):

![Diagram of chemical structures](image)

(formula (IIa))

(formula (IIb))

wherein

- **R₁** can be H, OH, halogen (wherein the halogen may be F, Cl, Br, or I), nitro, CN, aldehyde, substituted ketone, COOH, trifluoromethyl, amide, substituted or unsubstituted alkyl, particularly isopropyl, or t-butyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkxyox, preferably methoxy, haloalkyl or haloaryl comprising at least one substituent selected from F, Cl, Br, or I, aryloxoy, preferably phenoxy, alkylamino, alkylamido, aroylamino, aroylamido;

- **R₂** can be H, OH, alkyl, preferably t-butyl or isopropyl, aryl, arylalkyl, alkylaryl, alkxyox, preferably methoxy, alkylthio, wherein the sulfur may replace any of the carbon atoms of the alkylthio, or arylthio, arylalkylthio, arythioalkyl, particularly arylthiomethyl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazolinyl, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazoliny, isoxazoliny, oxazolidinyl, oxazolidony, isoxazolidonyl, pyrazolinyl, pyrazolidinyl, piperidyl, piperazine, morpholinyl, preferably the heteroaryl
is one of pyrrolyl, thienyl, thiazolyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, furyl, furazanyl, isobenzofuranyl, pyranyl, chromenyl, xantheny1, phenoxyxanthiinyl, indolyl, isoindolyl, indolizinyl, isoindolyziny1, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl;

R₃ is CN, amide, nitrileamido, aminothiol, amino, alkyl, alkenyl, alkynyl, alkylamino, alkylamido, alkyleneamino, alkyleneamido, particularly dicyanoethylene amino, wherein the alkyl, alkenyl, or alkynyl moieties in the above substituents may be substituted or unsubstituted, substituted or unsubstituted aryl, arylcarbonyl, aryalkylcarbonyl, aryalkylenecarbonyl, arylamido, particularly phenylamido, arylalkylamido, particularly phenylmethylamido, or phenylethylamido, aryalkyleneamido, arylamino, aryalkylamino, aryalkyleneamino arylsulfonyl, particularly phenylsulfonyl, aryalkylenesulfonyl, aryalkylenenitrileamidoalkylamido, particularly phenylalkylenenitrileamidoalkylamido, wherein the aryl moiety in any of the aryl containing substituents may be phenyl optionally substituted, preferably at positions 3, 4, and 5, with at least one substituent selected from halogen, alkyl, haloalkyl, hydroxy, alkoxy, arlyoxy, alkylaryloxy and aryalkyloxy, preferably with at least one of bromide, t-butyl, trifluoromethyl, hydroxy, and methoxy, particularly, 4^-trifluoroethylphenylamido, 4,5-dimethoxyphenylethylamido, 3-bromide-4^-hydroxy-5^-t^-butyl-phenylalkylenenitrileamidoalkylamido, most preferably R₃ is arylcarbonyl where the aryl is substituted with hydroxy at positions 3, and 4 or at positions 3, 4, and 5;

R₄ is H, aryl, aryalkyl, alkylaryl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazoliny1, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazoliny1, isoxazoliny1, oxazolidinyl, oxazolidon1, isoxazolidon1, pyrazoliny1, pyrazolidinyl, piperidyl, piperazine, morpholiny1, preferably the heteroaryl is one of
pyrrolyl, thienyl, thiazolyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, furyl, furazanyl, isobenzozofuranyl, pyranyl, chromenyl, xanthanyl, phenoxyxanthiinyl, indolyl, isoindolyl, indolizinyln, isoindolizinyln, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or R₄ forms a fused phenylpyrrolidone ring with the main aromatic ring; and
Het is a 5 or 6-membered hetero ring, preferably said ring selected from imidazoline, imidazolidine, carbostyril, pyrrole, pyrrolone, pyrrolidine, thiophene, thiazole, isothiazole, furan, furazan, oxazole, isoxazole, oxazolidine, isoxazolidine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrazine, pyrimidine, pyridazine, piperidyl, piperazinyl, morpholinyl, particularly Het is either one of oxazolidone, cyclic urea, and pyrrolidone; and pharmaceutically acceptable salts thereof;
with the exclusion of the following combinations:
R₁ is hydroxy, R₂ is hydrogen, R₃ is cyano, and R₄ forms a fused phenyl pyrrolidone with the main aromatic ring;
R₁ is hydroxy, R₂ is hydrogen, R₃ is 3,4-dihydroxybenzoyl, and R₄ is hydrogen;
R₁ is bromide, R₂ is t-butyl, R₃ is cyano, and R₄ is hydrogen; and
Het is oxazolidone, R₂ and R₄ are hydrogen, and R₃ is phenylmethylamido or 3,4-dihydroxybenzoyl.

2. A compound according to claim 1, wherein said compound may be any of the compounds AGS 192, AGS 195, AGS 206, AGS 244, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, AGS 323.

3. Use of a compound that inhibits SRE or PTK in the preparation of a pharmaceutical composition for extending the lifespan of a subject, wherein said compound is selected from the group consisting of aromatase
inhibitors, estradiol receptor inhibitors, and a compound of formula (Ia) or (Ib):

![Chemical structures](image)

wherein,

R₁ is H, OH, halogen, wherein the halogen may be F, Cl, Br, or I, nitro, CN, aldehyde, substituted ketone, COOH, trifluoromethyl, amide, substituted or unsubstituted alkyl, particularly isopropyl, or t-butyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkoxy, preferably methoxy, haloalkyl or haloaryl comprising at least one substituent selected from F, Cl, Br, or I, aryloxy, preferably phenoxy, alkylamino, alkylamido, arylamino, arylamido;

R₂ is H, OH, alkyl, preferably t-butyl or isopropyl, aryl, arylalkyl, alkylaryl, alkoxy, preferably methoxy, alkylthio, wherein the sulfur may replace any of the carbon atoms of the alkylthio, or arylthio, arylalkylthio, arythioalkyl, particularly arylthiomethyl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazolinyl, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazoliny, isoxazoliny, oxazolidinyl, oxazolidony, isoxazolidony, pyrazolinyl, pyrazolidinyl, piperidynl, piperazine, morpholiny, preferably the heteroaryl is one of pyrrolyl, thienyl, thiazolyl, benzothienyl, naphthothienyl, purinyl,
isothiazolyl, furyl, furazanyl, isobenzozofuranyl, pyranyl, chromenyl, xanthenyl, phenoxyxanthiinyln, indolyl, isoindolyl, indolizinyln, isoindolzylnyl, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyln;

\( R_3 \) is CN, amide, nitrideamido, aminothiol, amino, alkyl, alkenyl, alkynyl, alkylamino, alkylamido, alkyleneamino, alkyleneamido, particularly dicyanoethylene amino, wherein the alkyl, alkenyl, or alkynyl moieties in the above substituents may be substituted or unsubstituted, substituted or unsubstituted aryl, arylcarbonyl, arylalkylcarbonyl, arylalkylenearbonyl, arylamido, particularly phenylamido, arylalklamido, particularly phenylmethylamido, or phenylethylamido, arylalkyleneamido, arylamino, arylalkylamino, arylalkyleneamino arylsulfonyl, particularly phenylsulfonyl, arylalkylene sulfonyl, arylalkylenenitrileamidoalkylamido, particularly phenylenenitrileamidopropylamido, wherein the aryl moiety in any of the aryl containing substituents may be phenyl optionally substituted, preferably at positions 3, 4, and 5, with at least one substituent selected from halogen, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, alkylaryloxy and arylalkyloxy, preferably with at least one of bromide, t-butyln, trifluoromethyl, hydroxy, and methoxy, particularly, 4-trifluoromethylphenylamido, 4,5-dimethoxyphenylethlamido, 3-bromide-4-hydroxy-5-t-butylnphenylenenitrileamidopropylamido, most preferably \( R_3 \) is arylcarbonyl where the aryl is substituted with hydroxy at positions 3, and 4 or at positions 3, 4, and 5:

\( R_4 \) is H, aryl, arylalkyl, alkylaryl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, hetroarylalkyl, alkylheteroaryl, preferably the heterocycloalkyl is one of cyclic urea, imidazolinyln, imidazolidinyln, pyrrolinyl, pyrrolidinyl, oxazolinyln, isoxazolinyln, oxazolidinyln, oxazolidonyln, isoxazolidonyln, pyrazolinyln, pyrazolidinyl, piperidyl, piperazine, morpholinyln, preferably the heteroaryl is one of pyrrolyn, thienyl, thiazolyl, benzothienyl, napthothienyl, purinyl,
isothiazolyl, furyl, furazanyl, isobenzofuranyl, pyranyl, chromenyl, xanthenyl, phenoxyxanthiinyl, indolyl, isoindolyl, indolizinyln, isoindolizinyln, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or R₄ forms a fused phenylpyrrolidone ring with the main aromatic ring; and
Het is a 5 or 6-membered hetero ring, preferably said ring selected from imidazoline, imidazolidine, carbostyril, pyrrole, pyrroline, pyrrolidine, thiophene, thiazole, isothiazole, furan, furazan, oxazole, isoxazole, oxazolidine, isoxazolidone, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrazine, pyrimidine, pyridazine, piperidyl, piperazinyl, morpholinyl, particularly Het is either one of oxazolidone, cyclic urea, and pyrrolidone, and pharmaceutically acceptable salts thereof; and wherein said subject is particularly a mammal, most preferably a human; said composition optionally further comprising a carrier, diluent, excipient and/or additive.

4. Use according to claim 3, wherein said compound that inhibits SRE is an aromatase inhibitor.

5. Use according to claim 3, wherein said compound that inhibits SRE is an estradiol receptor inhibitor.

6. The use of a compound of formula (Ia) or (Ib) as defined in claim 3, wherein said compound is selected from AG 336, AG 2262, AG 2263, AG 538, AG 1024, and mixtures thereof.

7. A method of elongating the lifespan of a subject, particularly a mammal, most preferably a human, comprising administering to said subject an effective amount of a compound inhibiting SRE or PTK, wherein said compound is selected from the group consisting of aromatase
inhibitor, estradiol receptor inhibitor, and a compound of formula (Ia) or (Ib):

\[ \text{formula (Ia)} \]
\[ \text{formula (Ib)} \]

wherein,

- $R_1$ is H, OH, halogen, wherein the halogen may be F, Cl, Br, or I, nitro, CN, aldehyde, substituted ketone, COOH, trifluoromethyl, amide, substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkyloxy, preferably methoxy, haloalkyl or haloaryl comprising at least one substituent selected from F, Cl, Br, or I, aryloxy, preferably phenoxy, alkylamino, alkylamido, arylamino, arylamido;
- $R_2$ is H, OH, alkyl, preferably t-butyl or isopropyl, aryl, arylalkyl, alkylaryl, alkylxy, preferably methoxy, alkylthio, wherein the sulfur may replace any of the carbon atoms of the alkylthio, or arylthio, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably said heterocycloalkyl in any of the substituents comprising it is one of cyclic urea, imidazolinyl, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, oxazolidinyl, oxazolidonyl, isoxazolidonyl, pyrazolinyl, pyrazolidinyl, piperidyl, piperazine, morpholinyl, preferably said in any of the substituents comprising it heteroaryl is one of pyrrolyl, thienyl, thiazolyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, furyl, furazanyl, isobenzoxofuranyl, pyranyl, chromenyl, xanthrenyl, phenoxyxanthiinyl,
indolyl, isoindolyl, indolizinyln, isoindolyzinyln, benzothienyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl;
R₃ is CN, amide, nitrileamido, amidosulfide, amino, alkyl, alkenyl, alkynyl, alkylamino, alkylamido, alkyleneamino, particularly dicyanoethylene amino, alkyleneamido wherein the alkyl, alkenyl, or alkynyl moieties in the above substituents may be substituted or unsubstituted, substituted or unsubstituted aryl, arylcarbonyl, arylalkylcarbonyl, arylalkylenecarbonyl, arylamido, arylalkylenamido, arylamino, arylalkylenamino arylsulfonyl, arylalkylenesulfonyl, arylalkylennitrileamidoalkylamido, particularly phenylenenitrileamidopropylamido, wherein the aryl moiety in any of the aryl containing substituents may be phenyl optionally substituted, preferably at positions 3, 4, and 5, with at least one substituent selected from halogen, alkyl, haloalkyl, hydroxy, alkoxy, arloxy, alkylaryloxy and arylalkyloxy, preferably with at least one of bromide, t-butyl, trifluoromethyl, hydroxy, and methoxy, most preferably R₃ is aryl carbonyl where the aryl is substituted with hydroxy at positions 3, and 4 or at positions 3, 4, and 5;
R₄ is H, aryl, arylalkyl, alkylaryl, heterocycloalkyl, alkylheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, alkylheteroaryl, preferably said heterocycloalkyl in any of the substituents comprising it is one of cyclic urea, imidazolinyl, imidazolidinyl, pyrrolinyl, pyrrolidinyl, oxazolinyl, isoaxazolinyl, oxazolidinyl, oxazolidonyl, isoaxazolidonyl, pyrazolyl, pyrazolidinyl, piperidyl, piperazine, morpholinyl, preferably said heteroaryl in any of the substituents comprising it is one of pyrrolyl, thienyl, thiazolyl, benzothienyl, naphthothienyl, purinyl, isothiazolyl, furyl, furazanyl, isobenzonzoafuranyl, pyranyl, chromenyl, xanthendyl, phenoxyxanthiinyl, indolyl, isoindolyl, indolizinyln, isoindolyzinyln, benzothienyl, oxazolyl, isoaxazolyl, pyrazolyl, pyridyl, pyrazinyl,
pyrimidinyl, pyrazinyl, or R₄ forms a fused phenylpyrrolidone ring with
the main aromatic ring; and
Het is a 5 or 6-membered hetero ring, preferably said ring selected from
imidazoline, imidazolidine, carbostyryl, pyrrole, pyrroline, pyrrolidine,
thiophene, thiazole, isothiazole, furan, furazan, oxazole, isoxazole,
oxazolidine, isoxazolidone, pyrazole, pyrazoline, pyrazolidine, pyridine,
pyrazine, pyrimidine, pyridazine, piperidyl, piperaizinyl, morpholinyl,
particularly Het is either one of oxazolidone, cyclic urea, and pyrrolidone;
and pharmaceutically acceptable salts thereof.

8. A method according to claim 7, wherein said compound is selected
from AG 336, AG 2262, AG 2263, AG 538, AG 1024, and mixtures thereof.

9. A compound according to claim 4, wherein said aromatase inhibitor
is selected from letrozole, anastrozole, formestane, and exemestane.

10. A compound according to claim 5, wherein said estradiol receptor
inhibitor is selected from fulvestrant, raloxifene, and tamoxifene.

11. A pharmaceutically acceptable glucose amine salt of a compound of
formula (Ia) or (Ib), said salt being preferably a combination, particularly
at 1:1 ratio, of N-methyl glucose amine and the compound AG 1024,
designated AGS 250.

12. A method for the manufacture of a compound as defined in any of
claims 1 or 2, said method comprising the steps of:
   a) mixing together a derivative of a hydroxy-benzaldehyde, a
derivative of acetonitrile, and L-alanine in a solvent;
   b) refluxing;
   c) evaporating; and
d) triturating.

13. A method for the manufacture of compound AGS 250 of claim 11, said method comprising the step of:
a) mixing together AGS 200 and N-methyl glucose amine;
b) refluxing;
c) evaporating; and
d) triturating;

14. The method of claim 12 or 13, wherein said solvent is ethanol.

15. The method of claim 12 to 13, wherein the evaporation and trituration are carried out in hexane, or acetone-hexane mixture.

16. A pharmaceutical composition comprising any of the compounds defined in claims 1, 2, or 9, or mixtures thereof, optionally further comprising a carrier, diluent, excipient and/or additive.

17. The pharmaceutical composition of claim 16, wherein said pharmaceutical composition comprises as active ingredient at least one compound selected from AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, and AGS 323.

18. The pharmaceutical composition of claim 16 or 17, for the treatment of protein tyrosine kinase family (PTKs)-associated disorders in a mammalian subject in need.

19. The pharmaceutical composition of claim 18, wherein said PTK is selected from the platelet-derived growth factor (PDGF), the epidermal
growth factor (EGF), the insulin growth factor (IGF), and, preferably, the insulin-like growth factor-I (IGF-1) receptor.

20. The pharmaceutical composition of claim 18, wherein said disorder is selected from (a) proliferative diseases, in particular sarcomas, carcinomas, lymphomas or melanomas; (b) fibrotic conditions, including pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy; (c) metabolic diseases, in particular diabetes; (d) other PTK-associated disorders such as arthritis, rheumatoid arthritis, psoriasis, neurodegenerative diseases; and (e) other abnormal conditions for example, transplant rejection, wound healing or inflammation.

21. The pharmaceutical composition of any of claims 16 to 19, for use in the treatment of malignant disorders in a mammalian subject in need, wherein said disorders are sarcomas, melanomas, lymphomas or carcinomas.

22. The pharmaceutical composition of claim 16 or 17, for extending the lifespan of a mammalian subject, preferably a human subject.

23. A pharmaceutical composition for extending the lifespan of a mammalian subject, preferably a human subject, comprising as an active ingredient a compound selected from AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 308, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322, AGS 323, AGS 333, AG 336, AG 2262, AG 2263, AG 538, AG 1024, letrozole, anastrozole, formestane, exemestane, fulvestrant, raloxifene, and tamoxifene.

24. A method for the treatment and/ or prevention of PTK-associated disorders in a mammalian subject in need, comprising the step of
administering to said subject a therapeutically effective amount of at least one of the compounds as defined in any of claims 1, 2, and 9, or a therapeutically effective amount of a pharmaceutical composition comprising said compound, wherein said PTK-associated disorder particularly includes PDGF, EGF, IGF and preferably IGF-1 receptor related diseases.

25. The method of claim 24, wherein said disorder is selected from (a) proliferative diseases, in particular sarcomas, carcinomas, lymphomas or melanomas; (b) fibrotic conditions, including pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy; (c) metabolic diseases, in particular diabetes; (d) other disorders such as arthritis, rheumatoid arthritis, psoriasis, neurodegenerative diseases; and (e) other abnormal conditions for example, transplant rejection, wound healing or inflammation.

26. The method of any one of claims 24 and 25, wherein said mammalian subject is human.

27. A method of elongating the lifespan of a mammalian, preferably human subject, comprising the step of administering to said subject an effective amount of at least one compound that inhibits SRE or PTK selected from the group consisting of aromatase inhibitors, estradiol receptor inhibitors, and compounds of formula (IIa) or (IIb).

28. A method according to claim 27, comprising the step of administering to said subject an effective amount of at least one compound of formula (IIa) or (IIb) or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising said compound.
29. The method of claim 28, wherein said compound is selected from AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322 and AGS 323.

30. A method for preventing and/or delaying the appearance of age-dependent and/or age-related disorders in a mammalian, preferably human subject, comprising the step of administering to said subject an effective amount of at least one compound of formula (Ia) or (Ib) or formula (IIa) or (IIb) or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising said compound.

31. The method of claim 30, wherein said compound is selected from the groups AG 336, AG 2262, AG 2263, AG 538 or AG 1024; and AGS 192, AGS 195, AGS 206, AGS 244, AGS 250, AGS 317, AGS 318, AGS 319, AGS 320, AGS 321, AGS 322 and AGS 323.

32. An anti-aging method for a mammalian, preferably human subject, comprising the step of administering to said subject an effective amount of at least one compound of formula (Ia) or (Ib) or formula (IIa) or (IIb) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the same.

33. The method of claim 32, wherein administration of any of said compounds or pharmaceutical compositions delays aging symptoms and/or slows the aging process.

34. The method of claim 32, wherein said subject is a mammalian subject afflicted with a premature aging disorder.
35. Use of an aromatase inhibitor according to claim 4 in the preparation of a pharmaceutical composition for extending the lifespan of a subject, wherein said subject is particularly a mammal, most preferably a human.

36. A method of elongating the lifespan of a subject according to claim 27, comprising administering to said subject an effective amount of an aromatase inhibitor.

37. A pharmaceutical composition for extending life span, comprising an aromatase inhibitor as an active ingredient, and optionally further comprising a carrier, diluent, excipient and/or additive.

38. Use of an estradiol receptor inhibitor according to claim 3 in the preparation of a pharmaceutical composition for extending the lifespan of a subject, wherein said subject is particularly a mammal, most preferably a human.

39. A method of elongating the lifespan of a subject according to claim 27, comprising administering to said subject an effective amount of an estradiol receptor inhibitor.

40. A pharmaceutical composition for extending life span, comprising an estradiol receptor inhibitor as an active ingredient, and optionally further comprising a carrier, diluent, excipient and/or additive.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/277 C07C255/40 C07C255/41 C07C255/42 C07C317/46
C07C327/44 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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X Further documents are listed in the continuation of Box C.

X See patent family annex.

* Special categories of cited documents:
*"A" document defining the general state of the art which is not considered to be of particular relevance.
*"E" earlier document but published on or after the international filing date.
*"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).
*"O" document referring to an oral disclosure, use, exhibition or other means.
*"P" document published prior to the international filing date but later than the priority date claimed.

*"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
*"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.
*"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
*"A" document member of the same patent family.

Date of the actual completion of the international search
5 July 2006

Date of mailing of the international search report
17/07/2006

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epi nl, Fax (+31-70) 340-3018

Authorized officer
Cooper, S
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<td>GAZIT A ET AL: &quot;TYRPHOSTINS. 2. HETEROCYCLIC AND -SUBSTITUTED BENZYLIDENEMALONONITRILE TYRPHOSTINS AS POTENT INHIBITORS OF EGF RECEPTOR AND ERBB2/NEU TYROSINE KINASES&quot; JOURNAL OF MEDICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 6, 1 June 1991 (1991-06-01), pages 1896-1907, XP000472938 ISSN: 0022-2623 Compound 7 in table I; compounds 16,18 and 21 in table II; table III</td>
<td>1,7-10, 12-16, 18-28, 30-34</td>
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<td>claim 25; examples 70,75,77,79,81,83,85-87,89,90,92,93</td>
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<td>WO 03/066608 A (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW; GAZIT, AVIV; LEVITZ) 14 August 2003 (2003-08-14) paragraphs [0017] - [0025]; claims 1-57; figures 1-4; table 1</td>
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<td>WO 2005/016333 A (ST. BONIFACE GENERAL HOSPITAL; ZAHRAKDA, PETER) 24 February 2005 (2005-02-24) the whole document</td>
<td>7,8,27, 28,30-34</td>
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<td>GALIA BLUM ET AL: &quot;Development of New Insulin-like Growth Factor-1 Receptor Kinase Inhibitors Using Catechol Mimics&quot; THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 42, 2003, pages 40442-40454, XP002388066 Schemes 1,2, and 5; compounds AG538, #4,#10,#23,#29,#28 in table 1</td>
<td>1,7,8, 12-17, 19-28, 30-34</td>
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<td>WO 95/24190 A (SUGEN, INC; YISSUM RESEARCH DEVELOPMENT COMPANY)&lt;br&gt;14 September 1995 (1995-09-14)&lt;br&gt;Compounds&lt;br&gt;M9,M10,M12,M14-M16,M19-M23,M28,M30,M31,M33&lt;br&gt;,M35 in table 1; claims&lt;br&gt;5-23,30,31,33-39,41</td>
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<td>GAZIT A ET AL: &quot;TYRPHOSTINS I: SYNTHESIS AND BIOLOGICAL ACTIVITY OF PROTEIN TYROSINE KINASE INHIBITORS&quot;&lt;br&gt;JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US,&lt;br&gt;vol. 32, no. 19, 1989, pages 2344-2352,&lt;br&gt;XP002048362&lt;br&gt;ISSN: 0022-2623&lt;br&gt;Table I, serial numbers 8-10,14-19,23-25;&lt;br&gt;Table III, serial numbers&lt;br&gt;39,40,45,46,48-53</td>
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<td>WO 96/40629 A (SUGEN, INC)&lt;br&gt;19 December 1996 (1996-12-19)&lt;br&gt;Compounds 731,735,736,739-741,744,748 on pages 4-6; the examples; claims 1,15-17</td>
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Form PCT/IBA/210 (continuation of second sheet) (April 2005)

page 3 of 5
INTERNATIONAL SEARCH REPORT

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>Compounds TYR 1, 2, 5, 6, 13, 14, 12, 20, 25, 27, 32 in Figure 1; claim 15</td>
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<td>1, 7, 12-16, 18-22, 24-28, 30, 32-34</td>
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<td>X</td>
<td>GAZIT A ET AL: &quot;TYRPHOSTINS. 6. DIMERIC BENZYLIDENEMALONONITRILE TYRPHOSTINS: POTENT INHIBITORS OF EGF RECEPTOR TYROSINE KINASE IN VITRO&quot; JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 39, no. 25, 6 December 1996 (1996-12-06), pages 4905-4911, XP002050462 ISSN: 0022-2623 Scheme 1; chart 1; compounds 1-11, 13, 16, 17, 20 in table 1; compound 21 in table 2</td>
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<td>&amp; SYNTHESIS, vol. 11, 1983, pages 917–918,</td>
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<td>&amp; J. HETEROCYCL. CHEM., vol. 27, no. 3, 1990, pages 647–660,</td>
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<td>&amp; J. CHEM. SOC., vol. 119, 1953, page 121,</td>
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<td>WO 2005/002672 A (PRESIDENT AND FELLOWS OF HARVARD COLLEGE; BIOMOL INTERNATIONAL L.P; SI) 13 January 2005 (2005-01-13) Page 3, lines 7–24; page 92, line 27 to page 93, line 7; page 134, lines 4–9; examples 6,14,15</td>
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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 7-10, 24-34, 36 and 39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant’s protest.

[ ] No protest accompanied the payment of additional search fees.

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