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(54) **Compounds for treating and/or preventing diseases associated with bone loss**

Verbindungen zur Behandlung und/oder Verhinderung von mit Erkrankungen zusammenhängendem Knochenschwund

Composés utiles pour le traitement et/ou la prévention de maladies liées à la perte osseuse

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DescriptionField of the invention

5 **[0001]** The invention relates to the field of diseases associated with bone loss, and more specifically to a new method for identifying compounds useful for treating and/or preventing diseases associated with bone loss.

Background of the Invention

10 **[0002]** Bone is a dynamic tissue that is continually remodeled throughout life depending on factors such as nutrition and the load the bone must carry. Normal bone formation depends on the delicate balance between new bone addition and old bone resorption. Bone formation is based on the deposition of bone matrix by osteoblasts and bone resorption and more specifically mineralized tissue, chiefly calcium carbonate and calcium phosphate resorption in vertebrates is achieved by osteoclasts. Typically, in a normal adult, about 5-10% of bone is replaced by these processes annually.

15 **[0003]** These osteoclasts are multinucleated cells of up to 400µm related to macrophage and other cells that develop from monocyte cells, which are actively motile cells that migrate along the surface of bone. Like macrophage, osteoclasts are derived from haematopoietic progenitor cells. The bone resorption is initiated when an osteoclast attaches to the surface of mineralized bone, forms a tight "sealing zone" and secretes necessary acids and proteases that initiate the resorption of mineralized tissue from the bone. After a period of several hours to days, the osteoclast detaches from the bone, leaving a pit on the bone surface. Under normal conditions, the pit is a target for osteoblasts, which deposit a material that ultimately becomes new bone.

20 **[0004]** Bone loss can result when the bone resorptive process is dominant over the bone formative process. Diseases associated with bone loss are usually accompanied by increased osteoclast activation. Such diseases include any bone loss resulting notably from an estrogen deficiency after the menopause but not only and comprise osteoporosis, osteopenia due to bone metastases, periarticular erosions in rheumatoid arthritis, primary hyperparathyroidism, hypercalcemia of malignancy, Paget's disease of bone, periodontal disease, immobilization induced osteopenia, and glucocorticoid treatment.

25 **[0005]** As an example, there are currently 20 million people with detectable fractures of the vertebrae due to osteoporosis in the United States. In addition, there are 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12% mortality rate within the first two years, while 30% of the patients require nursing home care after the fracture.

30 **[0006]** Since diseases of bone loss are associated with increased activity of osteoclast, it is important to understand the mechanisms by which osteoclasts are activated in these disease states, and to devise rational and therapeutic means to inhibit or reduce this activation.

35 **[0007]** Thus, the aim of the present invention is to elaborate new screening methods which can be useful for treating and/or preventing bone loss diseases, and to use such compounds to prepare a drug for treating and/or preventing bone loss diseases.

Description of the invention

40 **[0008]** The inventors have presently identified the DOCK5 protein is implicated in sealing zone formation and consequently in bone resorption. Thus, DOCK5 corresponds to a new therapeutic target for treating and/or preventing bone loss diseases. Finally, the inventors have used yeast exchange assay (YEA) for identifying inhibitors of DOCK5, which inhibitors can be useful for treating and/or preventing bone loss diseases.

45 **[0009]** The present description is directed to a method for identifying a compound which inhibits the activation of RAC GTPase, more specifically RAC1/2 GTPase, by DOCK5 protein comprising the steps of:

- coexpressing the DOCK5 and the RAC proteins in a cell, wherein said DOCK5 protein induces the conversion of inactive RAC, which inactive RAC is bound to GDP, to active RAC, which active RAC is bound to GTP,
- 50 - contacting or not said cell with said compound,
- determining the conversion of inactive RAC to active RAC, more specifically the conversion of inactive RAC1/2 to active RAC1/2, in the presence or absence of said compound, and
- 55 - selecting the compound inhibiting the conversion of inactive RAC to active RAC, more specifically the conversion of inactive RAC1/2 to active RAC1/2.

[0010] The selected compound is useful for treating disease associated with bone loss. In fact, the inventors have established that the conversion of inactive RAC to active RAC by DOCK5 is associated with the sealing zone formation.

[0011] In the present description "RAC1/2" means "RAC1 and/or RAC2". In fact, the inhibition of the activation of RAC1 GTPase and/or of RAC2 GTPase give rise to the same kind of results, while both RAC1 and RAC2 are involved in (and thus necessary for) the osteoclast differentiation and resorption functions.

[0012] The present description also relates to a method for identifying a compound which inhibits the activation of RAC1/2 GTPase and which is useful for treating disease associated with bone loss by DOCK5 protein comprising the steps of:

- 10 - coexpressing the DOCK5 and the RAC proteins in a cell, wherein said DOCK5 protein induces the conversion of inactive RAC, which inactive RAC is bound to GDP, to active RAC, which active RAC is bound to GTP.
- contacting or not said cell with said compound,
- 15 - determining the conversion of inactive RAC to active RAC in the presence or absence of said compound,
- selecting the compound inhibiting the conversion of inactive RAC to active RAC since this conversion is associated with the sealing zone formation, and
- 20 - testing the inhibition of bone resorption, corresponding to the testing of mineralised matrix resorption by osteoclasts, by the selected compounds.

[0013] As an example of disease associated with bone loss, one can cite menopause, osteoporosis, osteopenia due to bone metastases, periarticular erosions in rheumatoid arthritis, primary hyperparathyroidism, hypercalcemia of malignancy, Paget's disease of bone, periodontal disease, immobilization induced osteopenia, or in glucocorticoid treatment. Preferably, said disease associated with bone loss is osteoporosis.

[0014] Results from the cellular and bone resorption assay systems used herein are widely accepted in the art as predictive of in vivo effects. As the bone resorption assay uses material that includes bone marrow isolated cells, it is an ex vivo assay. Thus, the showing that the inhibition of RAC activation by DOCK5 inhibits bone resorption in these assays is evidence of the clinical utility of inhibitors of this specific activation for treating osteoporosis. Various scientific publications, such as Carano et al. (1990); Blair & Schlesinger (1992); Schlesinger & Blair (1992); Vaananen et al., 1990; all support the fact that such assays are accepted as being predictive of in vivo activity.

[0015] Methods for determining the conversion of inactive RAC to active RAC are well known from the skilled person. As an example of such methods, one can cite the methods disclosed in the examples and in COTE & VUORI (J. Cell. Sci., vol. 115, p: 4901-4913, 2002).

[0016] The method as described further comprises the step of testing the inhibition of bone resorption by the selected compound.

[0017] This method also includes a further step of comparing the conversion of inactive RAC to active RAC in presence of the tested compound and in the absence of said compound. Said inhibition of bone resorption can be simply tested by method well known from the skilled person, such as the one disclosed in the examples, wherein mineralised matrix resorption by osteoclasts is tested by culturing said osteoclasts on calcium phosphate substrates and mineralised matrix resorption is determined by VON KOSSA staining.

[0018] As used herein, the term "compound" refers to a natural or synthetic compound, such as chemical or peptidic compound.

[0019] Thus, in a first object, the present invention is directed to a compound chosen in the group consisting in:

- 4-[5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutanoic acid;
- 2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamide;
- 50 - 3-(3-chlorophenyl)-7-methyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone;
- 3-[4-(3-bromobenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoic acid;
- 55 - N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-furamide;
- 1-acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazine;

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- 3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2(3H)-furanone;
- 3-[5-(3,4-dichlorophenyl)-2-furyl]acrylic acid;
- 5 - (2-chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-ylidene]methyl]-6-methoxyphenoxy)acetic acid;
- 4-1[4-(diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiadiazole;
- 10 - 4-[4-phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzenediol;
- N-(3,4-dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamide;
- 1-[(2-hydroxyphenyl)carbonothioyl]-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol;
- 15 - 2-methoxyethyl 4-[(4-tert-butylbenzoyl)amino]benzoate;
- N-(2,3-dichlorophenyl)-3-(5-methyl-2-furyl)acrylamide;
- 20 - N-(4-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamide;
- 3-(2-furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-quinazolinone;
- N-(4-ethoxyphenyl)-2-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio]acetamide;
- 25 - 5-(4-nitrobenzylidene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one;
- (3,5-dichlorophenyl)[(phenylsulfonyl)carbonyl]amine;
- 30 - N-(2-bromophenyl)-3-(5-methyl-2-furyl)acrylamide;
- 2-(2-chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamide;
- N-[4-(4-acetyl-1-piperazinyl)phenyl]propanamide;
- 35 - 8-[(dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one;
- 4-tert-butyl-N-[1-[[2-methoxyphenyl]amino]carbonyl]-2-(2-thienyl)vinyl]benzamide;
- 40 - 2-chloro-N-(3-chloro-4-methoxyphenyl)benzamide;
- 2,6-di-tert-butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol;
- 3-benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-quinazolinone;
- 45 - 1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldehyde;
- N-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phenylurea;
- 50 - N-(3,4-dichlorophenyl)-N'-{5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl}urea;
- N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthoxy)acetamide;
- N-[4-(4-acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamide;
- 55 - N-(2-chlorophenyl)-3-(4-fluorophenyl)acrylamide;
- 1-[(dimethyl- λ -4-sulfanylidene)amino]-2-methoxy-4-nitrobenzene;

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- 5-benzylidene-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione;
- 4-ethyl-5,6-dimethyl-2-phenylpyrimidine;
- 5 - 2-(3-chlorobenzylidene)-1H-indene-1,3(2H)-dione;
- 5-{5-[(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)methyl]-2-furyl}-1H-isoindole-1,3(2H)-dione;
- N-(2,5-dimethylphenyl)-3-(4-methoxyphenyl)acrylamide;
- 10 - 2-({2-[(4-nitrophenyl)amino]ethyl}amino)ethanol;
- N-(3-methoxyphenyl)-4-propoxybenzamide;
- 15 - 2-(4-hydroxyphenyl)-3-phenyl-2,3-dihydro-4(1H)-quinazolinone;
- 4-methyl-1-(2-nitrobenzoyl)piperidine;
- 2-hydroxy-N'-[(2-methylphenyl)sulfonyl]benzohydrazide;
- 20 - 4-(1,3-benzothiazol-2-yl)butanoic acid;
- 4-(3-methylbenzylidene)-1-phenyl-3,5-pyrazolidinedione;
- 25 - 4-(2,4-dichlorophenoxy)-N-(2-ethoxyphenyl)butanamide;
- N-(2-methoxyphenyl)-N'-(phenylsulfonyl)benzenecarboximidamide;
- N-[2-(2-chloro-5-iodophenyl)-1,3-benzoxazol-5-yl]-2-methylpropanamide;
- 30 - 5-(4-butoxyphenyl)-3-cyclohexyl-1,2,4-oxadiazole;
- N-(3,4-dichlorophenyl)-N'-4H-1,2,4-triazol-4-yl urea;
- 35 - 6-chloro-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-quinolinone;
- 6-bromo-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-quinolinone; and
- N-(1H-1,2,3-benzotriazol-1-ylmethyl)-4-nitro-1,2,5-oxadiazol-3-amine for use in the treatment and/or the prevention
- 40 of bone loss diseases in a subject in need thereof.

[0020] More preferably, the compounds are chosen in the group consisting in:

- 4-[5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutanoic acid
- 45 - 2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamide
- 3-(3-chlorophenyl)-7-methyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone
- 50 - 3-[4-(3-bromobenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoic acid
- N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-furamide
- 1-acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazine
- 55 - 3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2(3H)-furanone
- 3-[5-(3,4-dichlorophenyl)-2-furyl]acrylic acid

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- (2-chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-ylidene]methyl]-6-methoxyphenoxy)acetic acid
- 5 - 4-[[4-(diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiadiazole
- 4-[4-phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzenediol
- N-(3,4-dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamide
- 10 - 1-[(2-hydroxyphenyl)carbonothioyl]-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol
- 2-methoxyethyl 4-[(4-tert-butylbenzoyl)amino]benzoate
- N-(2,3-dichlorophenyl)-3-(5-methyl-2-furyl)acrylamide
- 15 - N-(4-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamide
- 3-(2-furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-quinazolinone
- 20 - 2,6-di-tert-butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol
- 3-benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-quinazolinone
- 1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldehyde
- 25 - N-(4-ethoxyphenyl)-2-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio]acetamide
- 5-(4-nitrobenzylidene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one
- 30 - (3,5-dichlorophenyl)[(phenylsulfonyl)carbonyl]amine
- N-(2-bromophenyl)-3-(5-methyl-2-furyl)acrylamide
- 2-(2-chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamide
- 35 - N-[4-(4-acetyl-1-piperazinyl)phenyl]propanamide
- 8-[(dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
- 40 - 4-tert-butyl-N-[1-[[2-methoxyphenyl]amino]carbonyl]-2-(2-thienyl)vinyl]benzamide
- 2-chloro-N-(3-chloro-4-methoxyphenyl)benzamide
- N-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phenylurea
- 45 - N-(3,4-dichlorophenyl)-N'-{5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl}urea
- N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthoxy)acetamide
- 50 - N-[4-(4-acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamide
- N-(2-chlorophenyl)-3-(4-fluorophenyl)acrylamide
- 1-[(dimethyl- λ^4 -sulfanylidene)amino]-2-methoxy-4-nitrobenzene
- 55 - 5-benzylidene-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione; and
- 4-ethyl-5,6-dimethyl-2-phenylpyrimidine.

[0021] As used herein, the expression "DOCK5 protein" refers to a polypeptide comprising at least the DHR2 domain of the protein DOCK5 corresponding to the amino acid 1132 to 1661 of the DOCK5 protein from *Mus musculus* SEQ ID NO:1 and derivatives thereof.

[0022] The present description is also directed to a method for identifying a compound which inhibits the activation of RAC GTPase, more specifically RAC1/2 GTPase, by DOCK5 protein comprising the steps of:

- coexpressing a polypeptide comprising at least the DHR2 domain of the protein DOCK5 and the RAC proteins in a cell, wherein said polypeptide induces the conversion of inactive RAC, which inactive RAC is bound to GDP, to active RAC, which active RAC is bound to GTP,
- contacting or not said cell with said compound,
- determining the conversion of inactive RAC to active RAC, more specifically the conversion of inactive RAC1/2 to active RAC1/2, in the presence or absence of said compound, and
- selecting the compound inhibiting the conversion of inactive RAC to active RAC, more specifically the conversion of inactive RAC1/2 to active RAC1/2.

[0023] The full length Dock5 protein has an aminoterminal SH3 domain, between aminoacids K11 and E68, followed by the DHR1 domain, between aminoacids G440 and E682, and the DHR2 domain between aminoacids M1132 and Y1661 (Figure 3E).

[0024] Preferably, said DOCK5 protein corresponds to SEQ ID NO:1.

[0025] Again preferably, said DOCK5 protein corresponds to SEQ ID NO:4 corresponding to *Homo sapiens* DOCK5 protein.

[0026] As used herein, the expression "RAC protein" refers to SEQ ID NO:2 and derivatives thereof.

[0027] Particularly, said cell is an eukaryotic cell, preferably a yeast cell.

[0028] Advantageously, said method comprises the expression of any protein, capable to interact with the active RAC protein and not with inactive RAC protein. One skilled in the art knows such protein known as a GTPase effector. Particularly, the protein capable to interact with the active RAC protein is chosen in the group comprising PAK1 protein.

[0029] As used herein, the expression "PAK1 protein" refers to the SEQ ID NO:3 and derivatives thereof.

[0030] As used herein, the term "derivatives" refer to a polypeptide having a percentage of identity of at least 80% with amino acid 1132 to 1661 of SEQ ID NO: 1, SEQ ID NO: 2, EQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:9, or orthologs thereof, preferably of at least 90%, as an example of at least 95%, and more preferably of at least 99%.

[0031] As used herein, "percentage of identity" between two amino acids sequences or two nucleic sequences, means the percentage of identical amino-acids or nucleotides, between the two sequences to be compared, obtained with the best alignment of said sequences, this percentage being purely statistical and the differences between these two sequences being randomly spread over the amino acids sequences. As used herein, "best alignment" or "optimal alignment", means the alignment for which the determined percentage of identity (see below) is the highest. Sequences comparison between two sequences are usually realized by comparing these sequences that have been previously align according to the best alignment; this comparison is realized on segments of comparison in order to identify and compared the local regions of similarity. The best sequences alignment to perform comparison can be realized, beside by a manual way, by using the global homology algorithm developed by SMITH and WATERMAN (Ad. App. Math., vol.2, p:482, 1981), by using the local homology algorithm developed by NEDDLEMAN and WUNSCH (J. Mol. Biol., vol.48, p:443, 1970), by using the method of similarities developed by PEARSON and LIPMAN (Proc. Natl. Acd. Sci. USA, vol.85, p:2444, 1988), by using computer softwares using such algorithms (GAP, BESTFIT, BLAST P, BLAST N, FASTA, TFASTA in the Wisconsin Genetics software Package, Genetics Computer Group, 575 Science Dr., Madison, WI USA), by using the MUSCLE multiple alignment algorithms (Edgar, Robert C., Nucleic Acids Research, vol. 32, p:1792, 2004). To get the best local alignment, one can preferably used BLAST software, with the BLOSUM 62 matrix, or the PAM 30 matrix. The identity percentage between two sequences of amino acids two nucleic sequence is determined by comparing these two sequences optimally aligned, the amino acids sequences being able to comprise additions or deletions in respect to the reference sequence in order to get the optimal alignment between these two sequences. The percentage of identity is calculated by determining the number of identical position between these two sequences, and dividing this number by the total number of compared positions, and by multiplying the result obtained by 100 to get the percentage of identity between these two sequences.

[0032] Advantageously, said cell further comprises a reporter gene under the control of a promoter sequence, and said RAC and PAK1 proteins are each fused either with a transactivation domain or with a DNA binding domain specific of said promoter sequence, wherein the interaction of RAC with PAK1 results in the induction of expression of the reporter gene.

[0033] The method corresponds to the Yeast Exchange Assay (YEA) as disclosed in DE TOLEDO et al. (FEBS, vol.480, p:287-292, 200) and International Patent application PCT WO 2005/064007 using the DOCK5 and the RAC protein.

[0034] The term "reporter gene" is well known from the skilled person and can correspond to an auxotrophic marker or to a gene coding for a protein which can be simply detected such as GFP, luciferase or β -gal.

[0035] The determination of the conversion of inactive RAC to active RAC is done by determining the expression of the reporter gene. The inhibition of the expression of the reporter gene corresponding to an inhibition of the conversion of inactive RAC to active RAC.

[0036] The present description also relates to a method for the selection of compounds, which permit to decrease the level of expression of a DOCK5 gene (SEQ ID N°10) in diseases associated with bone loss comprising the step of:

a) contacting a test compound with an host cell expressing a reporter nucleic acid comprising a nucleic acid sequence coding for a reporter placed under the control of a promoter, which promoter comprises all or part of the promoter sequence of DOCK5 gene or a derivative thereof, and

b) measuring the level of expression of the reporter.

[0037] As used herein, the term "derivatives" refer to a nucleic sequence having a percentage of identity of at least 80% with the sequence of DOCK5 promoter, preferably of at least 90%, as an example of at least 95%, and more preferably of at least 99%. The percentage of identity is as defined above.

[0038] By "compound" or "test compound", one should understand compounds of different nature, structure and origin, particularly biological compounds, nuclear factors, cofactors, and the like, chemical, synthetic compounds and the like, which are tested for their capacity of enhancing the level of expression of said gene implicated in antimicrobial defence.

[0039] The concentration of said test compound can be adjusted by the skilled person according to the characteristics of said compound (its toxicity, ability to penetrate cells, etc.), the number of cells, the length of the incubation period, etc. Generally, the cells are exposed to concentrations of test compounds ranging from 1 nM to 1 mM. Of course it is possible to test other concentrations, and also to test simultaneously different test compound concentrations.

[0040] Different adjuvants and/or vectors and/or products facilitating the penetration of the test compounds into the host cell such as liposomes, cationic lipids or polymers can also be used, when necessary.

[0041] By "decreasing the level of expression of a DOCK5 gene", one should understand that the expression level of DOCK5 gene is diminished or inhibited compared to a control level.

[0042] It should be noticed that said expression level of the DOCK5 gene is correlated to the expression level of the reporter gene in the method of the description. In fact, one of skilled in the art can deduce that a test compound can decrease the expression level of the DOCK5 gene from the capacity of said compound to obtain an diminished expression level of the reporter gene in the method of the description.

[0043] In the present description, the control level can be determined, by example, by measuring the expression level of the reporter gene in the absence of the test compound.

[0044] Particularly, the method described herein further comprises a step c) of comparing the level of expression of the reporter gene as measured in step b) with the level of expression of the reporter gene in the absence of said test compound.

[0045] The present description also relates to a method for identifying a compound which inhibits the activation of RAC1/2 GTPase by inhibiting the binding of ELMO1 protein (SEQ ID N°9) to the SH3 domain of DOCK5 comprising the steps of:

a) contacting a test compound with the ELMO1 protein or a derivative thereof;
 b) determining the possible binding of said test compound to the ELMO1 protein or the derivative thereof; and optionally
 c) selecting the compound inhibiting the conversion of inactive RAC1/2 to active RAC1/2.

[0046] As used herein, the expression "ELMO1 protein" refers to SEQ ID N°9 and derivatives thereof. The binding between said ELMO1 protein and the tested compound can be measured by methods well known from one skilled in the art.

If the binding between said ELMO1 protein and said test compound is observed, it can thus be conclude that the compound is an inhibitor of the binding of ELMO1 and the SH3 domain of DOCK5, and that this compound is useful to inhibit the conversion of inactive RAC1/2 to active RAC1/2.

Optionally, said method can include a further step after step b) of contacting a polypeptide comprising at least the SH3 domain of DOCK5 or the derivative thereof with said test compound and ELMO1 protein, and comparing the binding between said ELMO1 protein and said polypeptide in the presence or in the absence of said compound.

[0047] Alternatively, the present description relates to a method for identifying a compound which inhibits the activation of RAC1/2 GTPase by inhibiting the binding of ELMO1 to the SH3 domain of DOCK5 comprising the steps of:

- a) contacting a test compound with the ELMO1 protein or the derivative thereof and a polypeptide comprising at least the SH3 domain of DOCK5 or the derivative thereof;
- b) measuring the binding between said ELMO1 protein and said polypeptide in the presence or in the absence of said compound; and optionally
- c) selecting the compound inhibiting the conversion of inactive RAC1/2 to active RAC1/2.

The binding between said ELMO1 protein and said polypeptide can be measured by methods well known from one skilled in the art. If the binding between said ELMO1 protein and said polypeptide in the presence of the tested compound is lower than the one measured in absence of said compound, it can thus be concluded that the compound is an inhibitor of the binding of ELMO1 to the SH3 domain of DOCK5, and that this compound is useful to inhibit the conversion of inactive RAC1/2 to active RAC1/2.

[0048] Optionally, the compounds as described above are coupled with a bisphosphonate radical. The bisphosphonate radical permits a fast incorporation of the compound after its administration.

[0049] Another object of the present invention is a compound as described above for treating and/or preventing bone loss diseases in a subject in need thereof.

[0050] Therefore, the present invention relates to the use of at least one compound as described above in preparing a drug for treating and/or preventing bone loss disease in a subject in need thereof.

[0051] Another object of the present invention is a pharmaceutical composition comprising at least one compound as described above and, optionally, a pharmaceutically acceptable support for treating and/or preventing bone loss diseases in a subject in need thereof.

[0052] Therefore, the present invention relates to the use of a pharmaceutical composition comprising at least one compound as described above in preparing a drug for treating and/or preventing bone loss diseases in a subject in need thereof.

[0053] As examples of pharmaceutically acceptable supports, the composition can include emulsions, microemulsions, oil in water emulsions, anhydrous lipids and water in oil emulsions or other types of emulsions.

[0054] The inventive composition can further include one or more additives such as diluents, excipients, stabilizers and preservatives. Such additives are well known to those skilled in the art and are described notably in "Ullmann's Encyclopedia of Industrial Chemistry, 6th Ed." (various editors, 1989-1998, Marcel Dekker) and in "Pharmaceutical Dosage Forms and Drug Delivery Systems" (ANSEL et al., 1994, WILLIAMS & WILKINS).

[0055] As used in the present application, the term "subject" refers to a mammal such as a rodent, cat, dog, primate or human, preferably said subject is a human.

[0056] The present description relates to a therapeutic method for treating a subject and/or preventing bone loss diseases, comprising the administration of a therapeutically effective quantity of a pharmaceutical composition as described above.

[0057] A "therapeutically effective quantity" means a quantity that inhibits or reduces the osteoclasts activation. Those skilled in the art will be able to determine said therapeutically effective quantity based on their general knowledge and on the methods described in the examples.

[0058] The compounds can be administered by any mode of administration such as, for example, by intramuscular, intravenous or oral route, etc.

[0059] The inventive compounds preferably will be administered at a concentration chosen by those skilled in the art according to the state of advancement of the disease and the targeting mode used, the age and the weight of the subject. Preferably, the compound will be administered at a concentration of between 5 and 200 μ M, preferably at a concentration comprised between 10 and 100 μ M.

[0060] In the following, the invention is described in more detail with reference to amino acid sequences, nucleic acid sequences and the examples. Yet, no limitation of the invention is intended by the details of the examples.

EXAMPLES

1) Dock 5 mRNA expression

[0061] The expression of Dock5 was established in different mouse tissue. For this, DNaseI-treated total RNA was extracted using the High pure RNA isolation kit (ROCHE DIAGNOSTICS). To generate cDNA, RNA was primed with 10-mer random primers and reverse transcription catalysed using SUPERScript II reverse transcriptase (INVITROGEN). Quantitative PCR was performed with a Light Cycler (ROCHE DIAGNOSTICS) or a Mx3000p PCR system (STRATAGENE) using the PLATINIUM Tag DNA polymerase (INVITROGEN) and SYBR GREEN I (BIOWITAKKER)

as in described in COELHO et al. (Proc. Natl. Acad. Sci. U.S.A., vol.102, p:1 1917-11922, 2005) with the primers Dock5-Up (TGGTGACACAGGGACAGTGG, SEQ ID NO:5) and Dock5-Do (CACCCCACTAGCAGTGG, SEQ ID NO: 6) for Dock5, and Gapdh-Up (ACAGTCCATGCCATCACTGCC, SEQ ID NO: 7) and Gapdh-Do (GCCTGCTTACCACCT-TCTT, SEQ ID NO: 8) for Gapdh as a control.

[0062] The specificity was assessed by purification and sequencing of the PCR product. All real-time PCR measures to quantify cDNA were done in triplicate, and the 95% confidence limits of the ratios to Gapdh were determined by Student's *t*-test. The figure 1A and B show the expression of Dock5 in different mouse tissues. In figure 1A, said expression has been normalised according to Dock5 osteoclasts' expression (i.e., Dock5 osteoclasts' expression corresponding to 100% level).

[0063] The analysed tissues of figure 1A are as follow: Muscle 1 (M1), Muscle 2 (M2), heart (H), mammary gland at 10.5 days of embryo's development (GM 10.5), mammary gland at 13.5 days of embryo's development (GM 13.5), mammary gland at 15.5 days of embryo's development (GM 15.5), mammary gland at 18.5 days of embryo's development (GM 18.5), mammary gland of juvenile mouse (GM j), mammary gland at lactation (GM l), brain (Br), kidney (Kd), uterus (Ut), liver (Lv), macrophage (Mac), Testis 1 (T1), Testis 2 (T2), spleen (Sp), colon (Co), bone marrow (Bm), placenta at 13.5 days of embryo's development (PI 13.5), placenta at 15.5 days of embryo's development (GM 15.5), and osteoclasts (Os).

[0064] Furthermore, total RNA of bone marrow macrophages (ND), induced for osteoclastic differentiation (OC) or dendritic cell differentiation (DC) and from mesenchymal stem cells (MSC J0) induced for osteoblastic differentiation (MSC J4) were extracted and level of Dock5 mRNA relative to Gapdh mRNA was determined by RT-PCR.

[0065] The results of figure 1B show that Dock5 mRNA is not expressed in dendritic cells and osteoblasts.

[0066] The results show that Dock5 is predominantly expressed in osteoclasts, but an important expression of Dock5 is also found in placenta (i.e., nearly 50%) and testis. The expression of Dock5 is reduced in bone marrow, colon, spleen and testis compared to osteoclasts (i.e., nearly 20%), whereas its expression in the other tested tissues is fewer (i.e., nearly 10%). Thus, the results established that the expression of Dock5 is very specific from the osteoclasts.

2) obtaining of DOCK5 polyclonal antibody

[0067] A rabbit polyclonal antibody was raised to a mouse DOCK5 C-terminus peptide corresponding to amino acids 1658-1869 from mouse DOCK5 and purified by immunoaffinity. In fact, the amino acids sequences significantly differ between the different members of the subgroup DOCK-A.

[0068] Osteoclastogenesis was induced by RANKL-stimulation in purified mouse bone marrow macrophages were purified and in RAW264.7 cell line as described in BRAZIER *et al.* (abovementioned, 2006), which cells were maintained in culture. At 0, 3 or 5 days of stimulation, the cells were subjected to SDS-PAGE and blotted on polyvinyl difluoride membrane (MILLIPORE IMMOBILON-P pore size 0.45 μ m). After transfer, the membrane was incubated in TBS-T (Tris buffered saline containing 0.1% TWEEN) with 2% skim milk at room temperature for 30 min and then with rabbit antisera diluted 1:1000 in TBS-T overnight at 4°C. The bound antibodies were detected by peroxidase labelled anti-rabbit immunoglobulin chemoluminescence system (AMERSHAM) and LAS-1000 image analyser (FUJI FILM). As a control, the membrane was further incubated with GAPDH antibodies, the bound antibodies being detected as previously.

[0069] The Figure 2A and B show the expression of DOCK5 and GAPDH proteins in purified mouse bone marrow macrophages at 0, 3 and 5 days from the RANKL-stimulated osteoclastogenesis.

[0070] The results established that a protein of 215 kDa was induced during RANKL-stimulated osteoclastogenesis of purified mouse bone marrow macrophages (figure 2) and of RAW264.7 cell line (data not shown). This size is compatible with the size of the DOCK5 protein deduced from its mRNA.

[0071] Furthermore, total proteins were extracted from mouse tissues and subjected to western blot with antibodies against Dock5 and against tubulin for normalization.

[0072] The analysed tissues of figure 2C are as follow Ey: Eye, Sp: Spleen, St: Stomach, Te: Testis, P1: Placenta, Lu: Lung, Br: Brain, He: Heart, Li: Liver, Ki: Kidney; Mu: Muscle.

[0073] The results of figure 2A confirm that Dock 5 is predominantly expressed in osteoclasts, testis and placenta.

3) DOCK5 polyclonal antibody specificity

[0074] ShRNA target sequences were selected in mouse *Dock5* open reading frames, and the 65-mer sense and antisense strands of DNA oligonucleotides were designed according to the CLONTECH BIOINFORMATICS DATA server and are described in BRAZIER *et al.* (abovementioned, 2006). The oligonucleotide was then synthesised by INVITROGEN annealed and cloned in pSINREN-RETROQ vector containing a puromycin resistance selection marker according to the manufacturer's instructions (CLONTECH). The pSIREN-RETROQ-Luc vector (CLONTECH) targeting firefly luciferase was used as a control. Retrovirus packaging was done by co-transfection of pSIREN-RETROQ vectors, the Friend MLV-based Gag-Pol expression vector pC57GP (LASSAUX et al., J. Virol., vol.79, p:6560-6564, 2005), and

the VSV-G envelope glycoprotein expression vector pCSIG (BATTINI et al., Proc. Natl. Acad. Sci., vol.96, p:1385-1390, 1999) into 293T cells using Jet PI (QBIAGEN) according to manufacturer's instructions. Viral supernatants were harvested 3 days after transfection and filtered through a 0.45 μ m pore size filter.

5 [0075] For infections, RAW264.7 cells were plated at $2 \cdot 10^5$ cells per 6-cm dish. The next day, the medium was replaced for 4h with 1.5 ml of viral supernatant and 0.5 ml of growth medium containing 8 μ g/ml polybrene. Cells were left to recover in growth medium for 24 h, and infected cells were selected by addition of puromycin (3 μ g/ml) for another 24h. Infected RAW264.7 were scrapped and reseeded in growth medium at $5 \cdot 10^4$ cells/well of a 6-well plate for RANKL-stimulated osteoclastogenesis as described in BRAZIER *et al.* (abovementioned, 2006).

10 [0076] Then, the detection of the DOCK5 protein was realized with the rabbit polyclonal anti-DOCK5 as described previously.

[0077] The Figure 2A shows the expression of DOCK5 and GAPDH proteins in RAW264.7 cell lines infected with retrovirus coding for either small hairpin RNA directed against firefly luciferase (shLuc) or dock5 (shDock5) at 0, 3 and 5 days from the RANKL-stimulated osteoclastogenesis.

15 [0078] As described previously, the results established that a protein of 215 kDa was induced during RANKL-stimulated osteoclastogenesis of RAW264.7 cell line infected with a retrovirus coding for a small hairpin RNA directed against firefly luciferase. For RAW264.7 cell line infected with a retrovirus coding for a small hairpin RNA directed against Dock5, no protein of 215 kDa was detected during RANKL-stimulated osteoclastogenesis. Finally, the results confirmed that the protein DOCK5, such as its corresponding RNA, is induced during osteoclastogenesis, and that the obtained rabbit polyclonal anti-DOCK5 antibody is specific of the DOCK5 protein.

20 4) Dock5 mediates Rac activation *in vivo*

[0079] We therefore examined whether the DOCK5 protein, and more specifically its DHR2 domain, could activate small GTPases of the Rho-family-i.e., RAC1/2 and cdc42-.

25 [0080] To this end a GFP protein fused to the DHR2 domain of DOCK5 (see Figure 3A) was generated.

[0081] *In vivo* GTP loading of Rac and cdc42 was analysed as previously described in COTE & VUORI (J. Cell. Sci., vol.115, p: 4901-4913, 2002).

30 [0082] Briefly, 293-T cells were transfected in six-wells plates with a vector coding for the GFP fusion protein comprising the DHR2 domain of DOCK5 (DHR2) or with a vector coding for GFP (GFP). 48 hours after transfection, cells were lysed in MLB buffer (25mM HEPES, pH 7.5, 150 mM NaCl, 1% NP-40, 10 mM MgCl₂, 1 mM EDTA and 10% glycerol). The clarified lysates were incubated for 30 minutes with the GST-PAK-PBD fusion protein bound to Glutathione sepharose. The beads were washed extensively with MLB buffer and the bound GTP-loaded Rac and cdc-42 were detected by immunoblotting. Equal amount of input lysate were analysed by immunoblotting to verify the expression levels of Rac, cdc42, GFP-DHR2 and GFP proteins. GST-PAK-PBD was expressed and purified for these experiments as described previously in ABASSI & VUORI (EMBO J., vol.21, p:4571-4582, 2002).

35 [0083] The figure 3B shows the expression levels of Rac, cdc42, GFP-DHR2 and GFP proteins in total cell lysates (total) and the protein detected after GTP-trapping.

40 [0084] The results show that the expression of the DHR2 domain in 293-T cells induces the activation of endogeneous Rac but has no effect on cdc42 (figure 3B). Finally, the results established that the DHR2 domain of DOCK5 is able to activate the Rac GTPase, whereas it has no effect on cdc42.

5) ELMO1 binds to the SH3 domain of DOCK5

45 [0085] 293-T cells were cotransfected as described previously with a vector coding for the ELMO1 protein or deleted from the C-terminus (Δ T625) - (GUMIENNY et al., Cell, vol.107, p:27-41, 2001) and a vector coding GFP fusion proteins comprising the Full length DOCK5 protein (FL), the DHR2 domain, the DOCK5 protein sequence deleted from (i) the amino acids 1 to 559 of its N-terminus extremity (Δ Nter), including the SH3 domain and half of the DHR1 domain, or the DOCK5 protein sequence deleted from (ii) the amino acids 1 to 82 comprising the SH3 domain (Δ SH3) (see figure 3 E).

50 [0086] 48 hours after transfection, cells were lysed in MLB buffer (25mM HEPES, pH 7.5, 150 mM NaCl, 1% NP-40, 10 mM MgCl₂, 1 mM EDTA and 10% glycerol). The clarified lysates were immunoprecipitated with anti-GFP antibody and the bound ELMO1 protein was detected by immunoblotting. Equal amount of input lysate were analysed by immunoblotting to verify the expression levels of ELMO1 protein.

55 [0087] The figure 3C and 3F show the expression levels of ELMO1 protein in total cell lysates (total) and after immunoprecipitation with anti-GFOP antibody (IP GFP), in cells cotransfeted with a vector coding for ELMO1 protein and full length DOCK5 (FL), the DHR2 domain (DHR2), DOCK5 deleted from its SH3 domain (Δ SH3) or from its N-term domain (Δ Nter).

[0088] The results show that deletion if Dock5 SH3 domain or coexpression of full lengh ELMO1 with full length Dock5 greatly increased its exchange activity on Rac thus establishing that the N-term domain of DOCK5, and more specifically

its SH3 domain, is necessary for the binding of ELMO1 to DOCK5 (Figure 3C). Figure 3F shows that Dock5 N-terminal domain binds Elmo1 C-terminus.

6) The SH3 domain of DOCK5 inhibits Rac activation *in vivo*

[0089] *In vivo* GTP loading of Rac was determined as previously in the presence of different domains of the DOCK5 protein and, eventually, the simultaneous presence of the ELMO1 protein.

[0090] The figure 3D shows the expression levels of Rac in total cell lysates (total) and the RAC-GTP protein detected after GTP trapping in the cells transfected with a vector coding for the GFP protein (GFP), for the DHR2 domain of DOCK5 (DHR2), for the DOCK5 protein deleted from its SH3 domain (Δ SH3), for the DOCK protein (FL), eventually cotransfected with a vector coding for the ELMO1 protein (FL+Elmo1).

[0091] The results show as previously that the expression of the DHR2 domain is able to activate the Rac GTPase and that the SH3 domain inhibits this activation (Figure 3D). In fact, the deletion of the SH3 domain results in the activation of the Rac GTPase by the deleted DOCK5 protein. Finally, the binding of ELMO1 to the SH3 domain results in the activation of the Rac GTPase.

7) DOCK5 is a major activator of Rac in osteoclasts.

[0092] RAW264.7 cell lines stimulated with RANKL were infected as described previously with a retrovirus coding for either small hairpin RNA directed against firefly luciferase (shLuc) or dock5 (shDock5).

[0093] Furthermore, the levels of active Rac in TCL from Dock5^{+/+} and Dock5^{-/-} osteoclasts were determined. Dock5^{-/-} mice were obtained by gene trap (Laurin et al. 2008) to generate Dock5 deficient osteoclasts.

[0094] The *in vivo* GTP loading of Rac was determined as disclosed previously.

[0095] The figure 4 shows the average of three independent experiments with active Rac levels set to 1 in control shLuc and Dock5^{+/+} osteoclasts. Error bars : SD.

[0096] The figure 4A show the expression levels of Rac in total cell lysates (total Rac) and the RAC-GTP protein detected after GTP trapping in the cells infected with a retrovirus coding for either small hairpin RNA directed against firefly luciferase (shLuc) or dock5 (shDock5).

[0097] The figure 4B shows that Dock5^{-/-} osteoclasts have reduced active Rac levels compared to the control level of Dock5^{+/+} osteoclasts.

[0098] The results established that the inhibition of DOCK5 expression results in a decrease of the levels of active RAC (i.e., 40%) in osteoclasts expressing Dock5 shRNAs and osteoclasts derived from Dock5 KO BMMs as compared to controls. Thus, DOCK5 is an essential exchange factor of RAC in osteoclasts.

8) DOCK5 is necessary for mineralised matrix resorption

[0099] RAW264.7 cell lines were infected as described previously with a retrovirus coding for either small hairpin RNA directed against firefly luciferase (shLuc) or dock5 (shDock5), and then osteoclastogenesis was stimulated with RANKL. The obtained cells were then cultured on calcium phosphate substrates to induce the formation of the actin ring. After 48 hours, cells were fixed and stained for actin using rhodamine-labeled Phalloidin to reveal the sealing zone (figure 5).

[0100] The figure 6 shows the polymerisation of actin in RAW264.7 cell lines stimulated with RANKL which have been infected with a retrovirus coding for either small hairpin RNA directed against firefly luciferase (shLuc) or dock5 (shDock5) and the mineralised matrix resorption in the presence of said osteoclasts.

[0101] The results show that in the osteoclasts, the DOCK5 protein is associated with the podosome and with the sealing zone (data not shown). The osteoclasts wherein DOCK5 expression was inhibited show a default of contraction and of sealing zone formation. The measure of mineralised matrix resorption surface by VON KOSSA staining shows a strong decrease of the resorption by osteoclasts wherein DOCK5 expression was decreased.

9) Confirmation by osteoclasts from Dock5^{-/-} mice

[0102] BMMs (bone marrow macrophages) isolated from Dock5^{+/+} and Dock5^{-/-} mice were differentiated into osteoclasts in the presence of 100 ng/ml RANKL and 10 ng/ml M-CSF. TCL (total cell extracts) were prepared at days 0, 3 and 4 and subjected to western blot with antibodies against Dock5 and β -gal and against tubulin for normalization.

[0103] Osteoclasts derived from Dock5^{-/-} BMMs express Dock5 truncated after aminoacid 1115, between DHR1 and DHR2 domains, and fused to a β -geo cassette (Figure 7A).

[0104] Furthermore, the differentiated osteoclasts were fixed and stained with TRAP and Hoeschst at day 5 to determine the number of MNCs (multinucleated cells). Figure 7B (average and SD from four independent experiments **: significant difference, p<0.01, Mann & Whitney test) shows that the efficiency of TRAP positive MNCs formation was reduced in

Dock^{-/-} BMMs as compared to Dock^{+/+} and osteoclasts were smaller.

[0105] Furthermore, in order to show that osteoclasts differentiated from Dock^{5-/-} BMMs can't assemble a sealing zone, they were seeded on calcium-phosphate substrate to induce the formation of the actin ring. After 48 hours, cells were fixed and stained for actin using rhodamine-labeled Phalloidin (green) to reveal the sealing zone and with Hoeschst dye to stain nuclei (blue) (data not shown). It was observed that on calcium-phosphate substrates, sealing zone assembly and resorption was defective in Dock^{5-/-} osteoclasts.

[0106] Finally, to demonstrate that Dock^{5-/-} osteoclasts can't form resorption pit, derived from Dock^{5-/-} BMMs were differentiated on bone sliced for 5 days, fixed and observed by scanning electron microscopy.

The results show that when seeded on bone slices, Dock^{5-/-} osteoclasts did not form resorption pits.

Moreover, in order to show that Dock^{5-/-} osteoclasts are defective for bone resorption, the levels of collagen degradation peptide (CTX) were determined in the medium of Dock^{5+/+} and Dock^{5-/-} osteoclasts after 5 days of differentiation and bone slices were stained. Figure 7C shows average and SD of three osteoclast-seeded wells from one experiment, representative of three independent experiments.

The measurement of collagen telopeptide (CTX) confirmed that the resorbing activity of Dock^{5-/-} osteoclasts was defective (Figure 7C).

10) Suppression of Dock5 impairs RAC activation in osteoclasts.

[0107] The levels of osteoclastic markers in wild type and Dock5 deficient osteoclasts derived from BMM of Dock^{5+/+} or Dock^{5-/-} animals or from control and Dock5 shRNA expressing RAW264.7 cells. Total RNA was prepared from Dock^{5+/+} and Dock^{5-/-} BMMs grown for 5 days in the presence of M-CSF only (black bars) or in the presence of RANKL and M-CSF to obtain osteoclasts (white bars). The levels of indicated gene mRNAs relative to Gapdh mRNA were determined by RT-PCR.

[0108] The results of figure 8A show that the expression of osteoclast differentiation markers is normal in osteoclasts differentiated from Dock^{5-/-} BMMs. This indicated osteoclast maturation was not affected and suggested Dock5 deficiency did not impair the capacity of osteoclasts to respond to M-CSF and RANKL in vitro.

[0109] Moreover, the ability of Dock^{5-/-} preosteoclasts to respond to M-CSF and RANKL was not the result of a compensatory increase in Dock1 or Dock2 expression as their mRNA levels were identical as in Dock^{5+/+} (Figure 8B).

[0110] Preosteoclasts prepared from Dock^{5+/+} and Dock^{5-/-} BMMs were stimulated with M-CSF or RANKL for the indicated amount of time. The levels of ERK, p38 and Akt phosphorylation in TCL were determined by western blot.

[0111] The results show that M-CSF-driven phosphorylation ERK and p38MAP kinase (Figure 8C) and RANKL-driven phosphorylation of Akt (Figure 8D) were unaffected in Dock^{5-/-} preosteoclasts as compared to controls.

[0112] Finally, these results established that DOCK5 is a new therapeutic target for limiting bone loss in menopause, osteoporosis, osteopenia due to bone metastases, periarticular erosions in rheumatoid arthritis, primary hyperparathyroidism, hypercalcemia of malignancy, Paget's disease of bone, periodontal disease, immobilization induced osteopenia, or in glucocorticoid treatment. Because of the specific osteoclasts DOCK5 expression, the targeting of DOCK5 may limit side effects such as the ones observed with drugs for treating bone loss.

11) Identification of DOCK5 inhibitor

[0113] In order to identify DOCK5 inhibitors, which inhibitors can be useful for treating bone loss associated disease, we use the Yeast Exchange Assay (YEA) as disclosed in DE TOLEDO et al. (FEBS, vol.480, p:287-292, 200) and International Patent application PCT WO 2005/064007.

[0114] Briefly, we transform a yeast strain TAT7 (Mata, trp1, his3, leu2, ura3, ade2, LYS:: (LexAop)4-HIS3, URA3:: (LexAop)8-lacZ) provided by J. CAMONIS) with vectors expressing the DHR2 domain of DOCK5 fused to a myc-tag (SEQ ID NO: ...), the wild type Rac GTPase fused to LexA and its effector PAK fused to the transactivation domain of GAL4.

[0115] In the obtained transformed yeast, the expression of the DHR2 domain of DOCK5 induces the activation of Rac, which activated Rac interacts with its effector PAK resulting in the expression of reporter genes β -Gal and His3 (see Figure 6).

[0116] In order to modify yeast cell membrane permeability, a mutation in the Erg6 gene has been introduced as disclosed in BLANGY et al. (Biol. Cell., vol.98(9), p:511-22, 2006). This mutation of the Erg6 gene increases the entry of the screened compounds in the yeast cells, and thus enables to limit the concentration of the screened compounds.

[0117] For screening DOCK5 inhibitors, which can be useful for treating bone loss diseases, the transformed yeast is contacted with several chemical or peptidic molecules, and the chemical or peptidic molecules inhibiting the expression of reporter genes β -Gal and His3 are selected for further testing in the bone loss model disclosed in 8 and then in bone loss diseases models.

[0118] The yeast strain TAT7 was used to identify DOCK5 inhibitors. The strain was seeded, in a 96-well culture plate in a selective medium devoid of histidine or in a non selective medium where histidine is added. 2560 compounds were

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screened to select the ones which inhibit the growth of the strains in a selective medium without having effect on the growth in a non selective medium. DMSO was used as a control.

[0119] The compounds were tested at a concentration of 200 μ M in presence of 1% DMSO. The growth of the yeasts was measured by optical density at 600 nm at t= 2 hours, 15 hours, 20 hours and 24 hours after seeding. The inhibiting compounds were defined as follows:

- At time n, the growth derivative Cr (medium) = (OD600Tn-OD600T2)/Tn-T2 in test medium (-HIS) and in toxic medium (+HIS).
- At each time and for each plate, the Cr (-HIS) and Cr (+HIS) medium control was calculated on the control.
- the ratio R(compound)= Cr (-HIS) and Cr(+HIS) and R was calculated for each plate
- the inhibition rate was determined by dividing by the control ratio I(compound)= R(compound)/R(control) *
- the selected compounds are those showing a ratio I(compound) < 0.9 at each time.

[0120] Results are shown in table 2.

[0121] 55 compounds were thus selected as inhibiting the activation of RAC1/2 by Dock5.

12) Toxicity test on osteoclast precursors.

[0122] The selected compounds were then tested for their toxicity on osteoclast precursors. Since these cells do not express Dock5, a Dock5 inhibitor should not affect their growth. RAW264.7 cells used as osteoclasts inhibitors were allowed to grow for 72 hours with 10 to 100 μ M of compound. The growth of the cells was compared to control cells which were grown with 0.5% DMSO.

[0123] The results are presented in table 2. The optimal concentration was the determined for the compounds which were not toxic (the concentration which does not affect the growth of the cells).

13) Toxicity test on differentiated osteoclasts.

[0124] The compounds were tested for their toxicity on differentiated osteoclasts at the concentration determined above. RAW264.7 cells differentiated in osteoclasts were allowed to grow for 72 hours in presence of the tested compounds. The tartrate-resistant acid phosphatase (TRAP) was then revealed in osteoclasts by coloration (SUDA et al., 1997). This osteoclasts specific labeling permits to visualize the cell morphology. The cell morphology was then compared to control cells which were allowed to grow in presence of 0.5% DMSO. The compounds were then classified in 3 categories:

- compounds which induce the death of all the osteoclasts after 72 hours (-)
- compounds which induce morphological anomalies and/or death of part of the osteoclasts (+/-)
- Compounds which do not induce visible modifications of the osteoclasts.

[0125] The results are shown in table 2.

14) Resorption inhibition test

[0126] The identified compounds were used at the same concentration as defined above on osteoclasts seeded on mineralised matrix resorption surface of calcium phosphate (Osteologic Biocoat Clontech Reference 354609) during 72 hours. Then the mineralised matrix was coloured with silver nitrate in order to show the resorbed areas. The compounds were classified in 3 categories:

- Compounds that totally prevent resorption in 72 hours (-)
- Compounds that induce an attenuated resorption compared to the control (+/-)
- Compounds that do not visibly modify the osteoclasts resorption activity compared to the control. (+)

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[0127] The compounds of the resorption categories (+/-) and (-) represent new inhibitors of the bone resorption. They were used at a concentration of 10 to 100 μ M.

[0128] To confirm the results, the compounds were then tested *in vivo* in a mouse which presents osteoporose.

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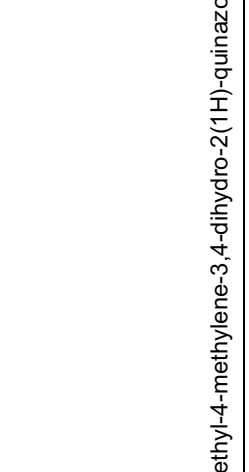
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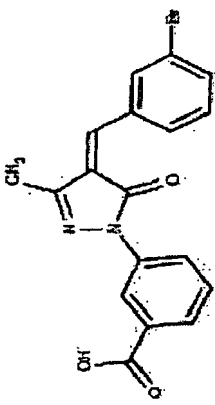
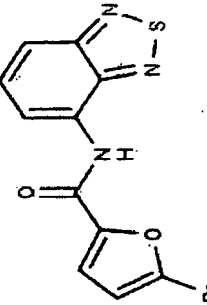
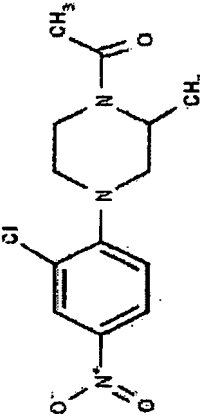
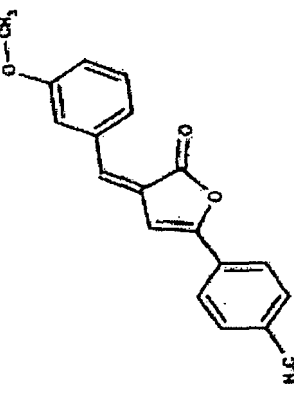
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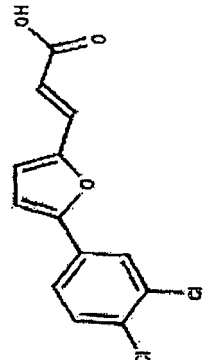
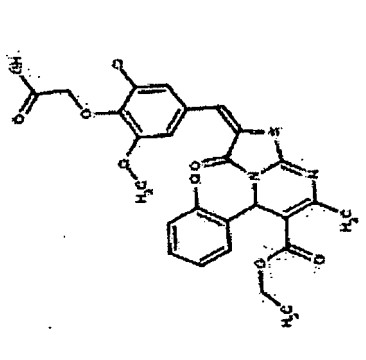
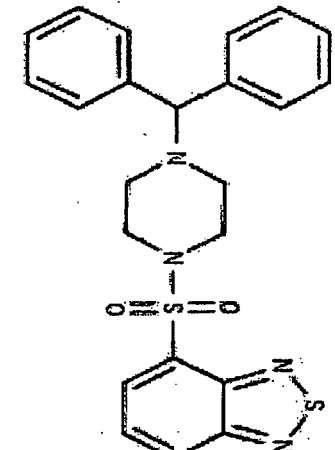
Table 1: compound identified by the screening method of the present invention

Structure	Mol Weight	Mol Formula	Mol Name	compound n°
	446,3	C19 H16 Br N3 O5	4-[5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutanoic acid	4
	368,7	C13 H12 Cl3 N O3 S	2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamide	5
	284,7	C16 H13 Cl N2 O	3-(3-chlorophenyl)-7-methyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone	11

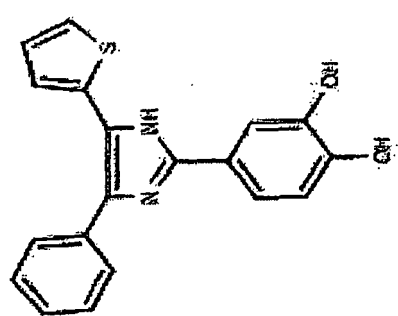
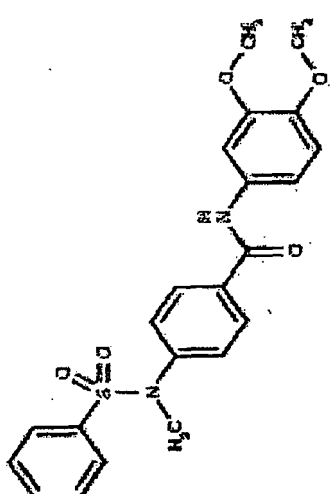
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
18	3-[4-(3-bromobenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoic acid	C18 H13 Br N2 O3	385,2	
20	N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-furamide	C11 H6 Br N3 O2 S	324,2	
22	1-acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazine	C13 H16 Cl N3 O3	297,7	
23	3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2(3H)-furanone	C19 H16 O3	292,3	

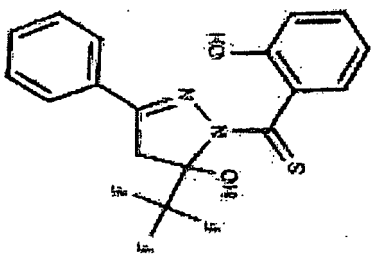
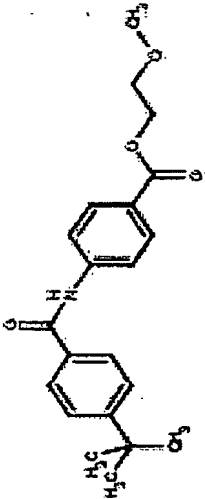
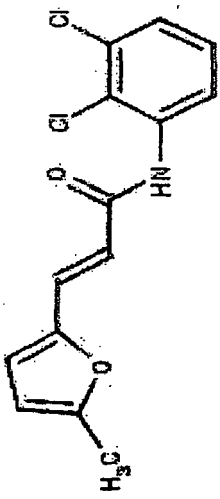
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
24	3-[5-(3,4-dichlorophenyl)-2-furyl]acrylic acid	C13 H8 Cl2 O3	283,1	
25	(2-chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-ylidene]methyl]-6-methoxyphenoxy)acetic acid	C26 H22 Cl2 N2 O7 S	577,4	
26	4-[[4-(diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiazole	C23 H22 N4 O2 S2	450,6	

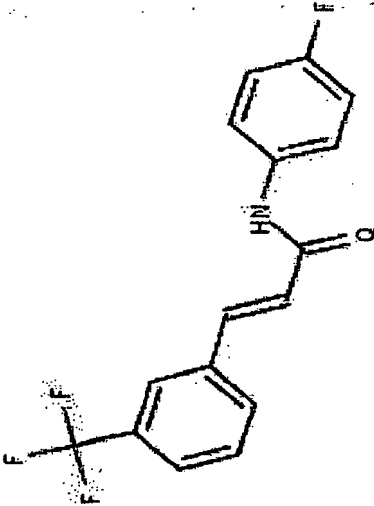
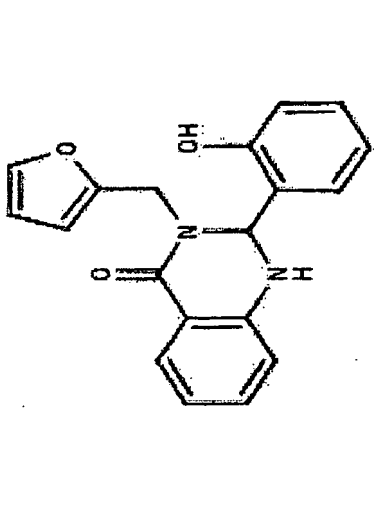

(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
34	4-[4-phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzenediol	C19 H14 N2 O2 S	334,4	
37	N-(3,4-dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamide	C22 H22 N2 O5 S	426,5	

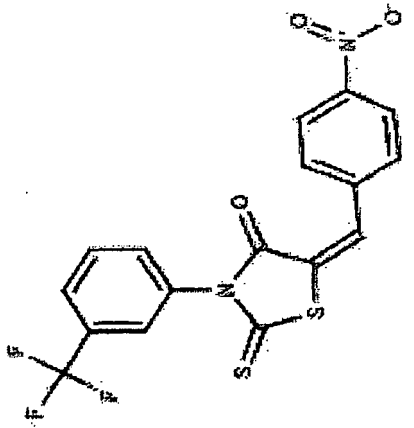
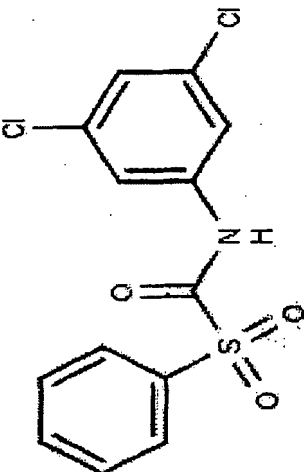
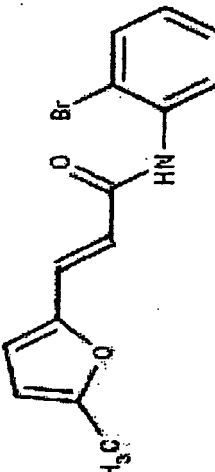
(continued)

5	10	15	20	25	30	35	40	45	50	55
compound n°	Mol Name	Mol Formula	Mol Weight	Structure						
42	1-[(2-hydroxyphenyl)carbonothioyl]-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol	C17 H13 F3 N2 O2 S	366,4							
44	2-methoxyethyl 4-[(4-tert-butylbenzoyl)amino]benzoate	C21 H25 N O4	355,4							
47	N-(2,3-dichlorophenyl)-3-(5-methyl-2-furyl)acrylamide	C14 H11 Cl2 N O2	296,2							

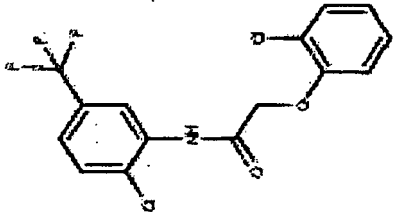
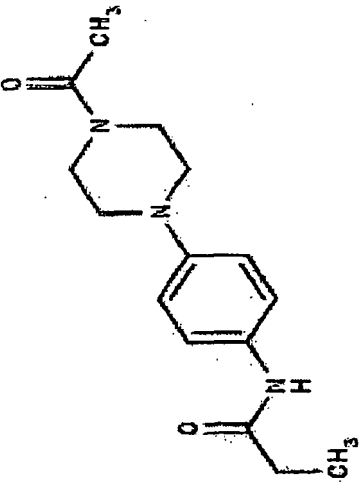
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
54	N-(4-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamide	C ₁₆ H ₁₁ F ₄ N O	309,3	
55	3-(2-furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-quinazolinone	C ₁₉ H ₁₆ N ₂ O ₃	320,3	
3	N-(4-ethoxyphenyl)-2-[(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thioacetamide	C ₁₉ H ₁₉ N ₃ O ₄ S	385,4	

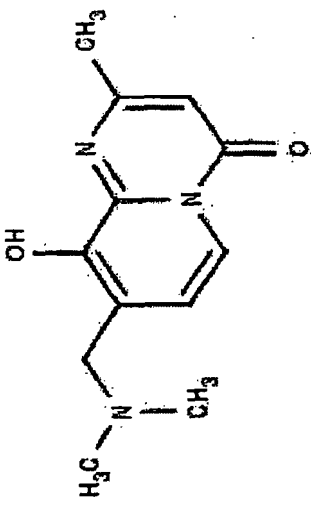
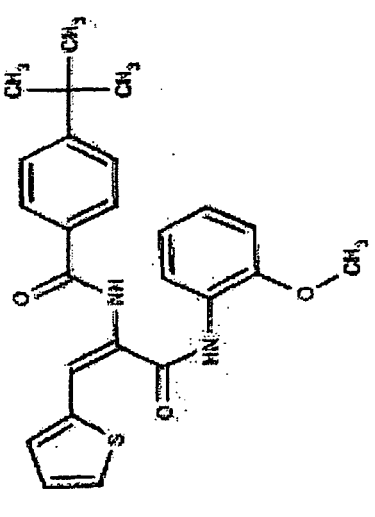
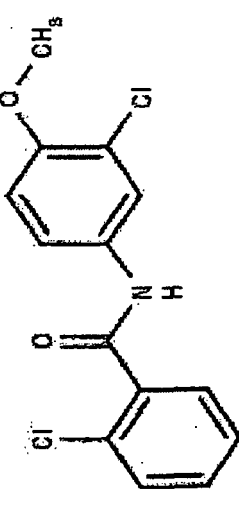
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
16	5-(4-nitrobenzylidene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one	C17 H9 F3 N2 O3 S2	410,4	
21	(3,5-dichlorophenyl)[(phenylsulfonyl)carbonyl]amine	C13 H9 Cl2 N O3 S	330,2	
6	N-(2-bromophenyl)-3-(5-methyl-2-furyl)acrylamide	C14 H12 Br N O2	306,2	

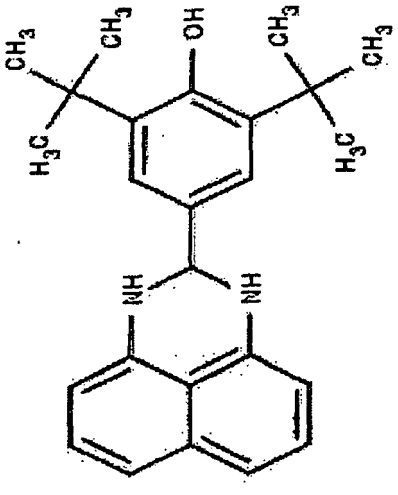
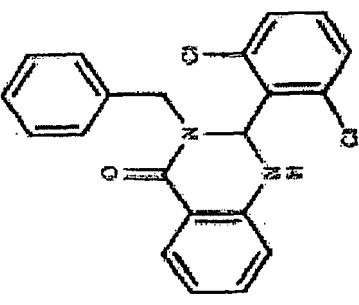
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
12	2-(2-chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	C15 H10 Cl2 F3 N O2	364,1	
13	N-[4-(4-acetyl-1-piperazinyl)phenyl]propanamide	C15 H21 N3 O2	275,3	

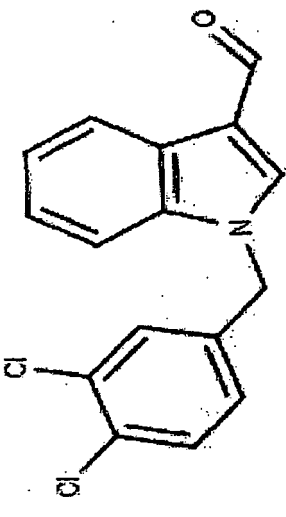
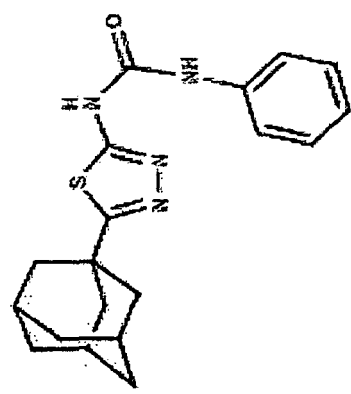
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
14	8-[(dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	C ₁₂ H ₁₅ N ₃ O ₂	233,3	
46	4-tert-butyl-N-[1-[(2-methoxyphenyl)amino]carbonyl]-2-(2-thienyl)vinyl]benzamide	C ₂₅ H ₂₆ N ₂ O ₃ S	434,6	
51	2-chloro-N-(3-chloro-4-methoxyphenyl)benzamide	C ₁₄ H ₁₁ Cl ₂ N O ₂	296,2	

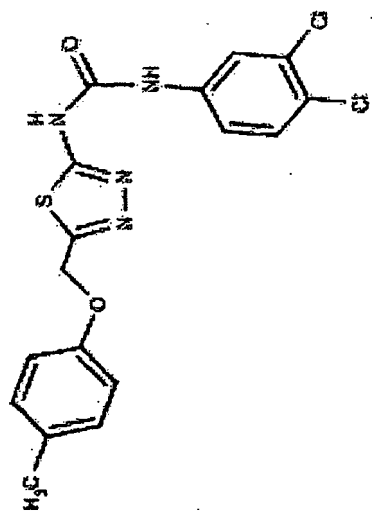
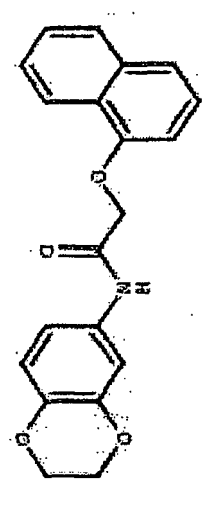
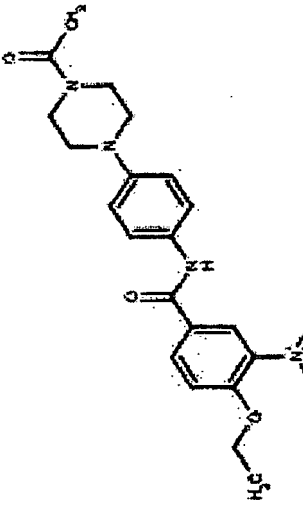
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
30	2,6-di-tert-butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol	C ₂₅ H ₃₀ N ₂ O	374,5	
33	3-benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-quinazolinone	C ₂₁ H ₁₆ Cl ₂ N ₂ O	383,3	

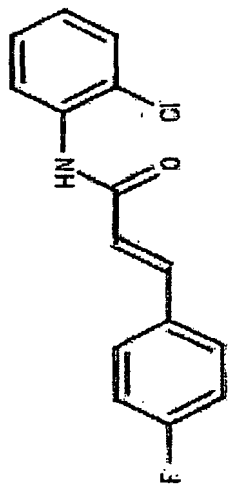
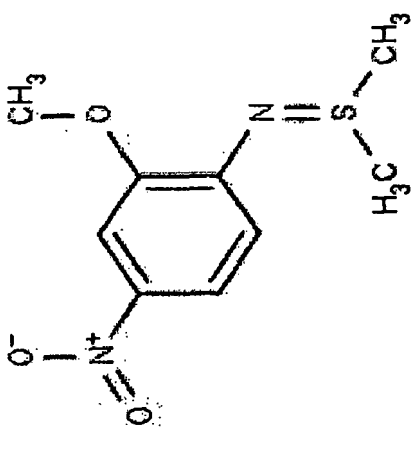
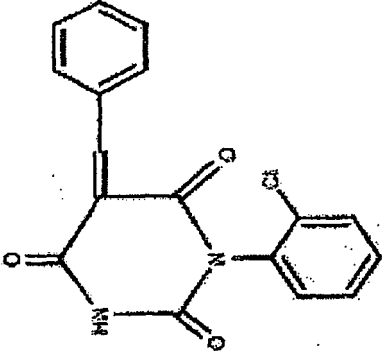
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
35	1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldehyde	C ₁₆ H ₁₁ Cl ₂ N O	304,2	
49	N-[5-(1-adamanty)-1,3,4-thiadiazol-2-yl]-N'-phenylurea	C ₁₉ H ₂₂ N ₄ O S	354,5	

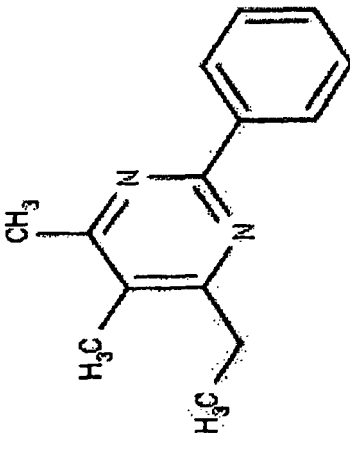
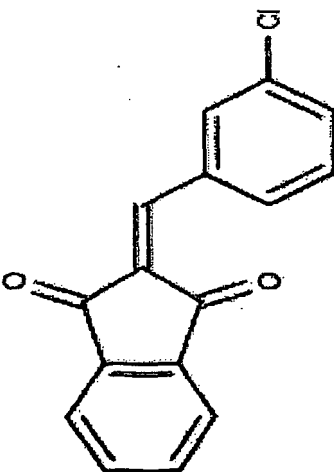
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
53	N-(3,4-dichlorophenyl)-N'-{5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl}urea	C17 H14 Cl2 N4 O2 S	409,3	
10	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthyl)oxyacetamide	C20 H17 N O4	335,4	
27	N-[4-(4-acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamide	C21 H24 N4 O5	412,4	

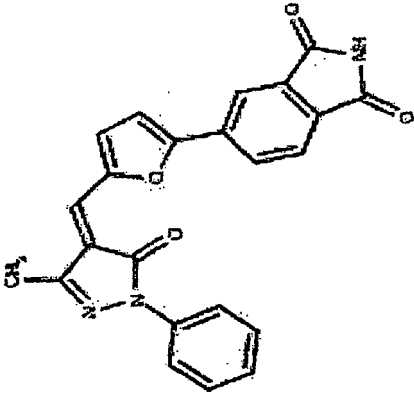
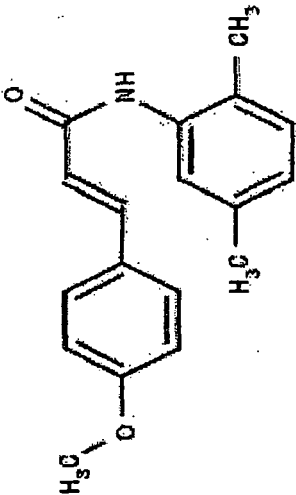
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
40	N-(2-chlorophenyl)-3-(4-fluorophenyl)acrylamide	C ₁₅ H ₁₁ Cl F N O	275,7	
43	1-[(dimethyl-lambda~4~-sulfanylidene)amino]-2-methoxy-4-nitrobenzene	C ₉ H ₁₂ N ₂ O ₃ S	228,3	
48	5-benzylidene-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione	C ₁₇ H ₁₁ Cl N ₂ O ₃	326,7	

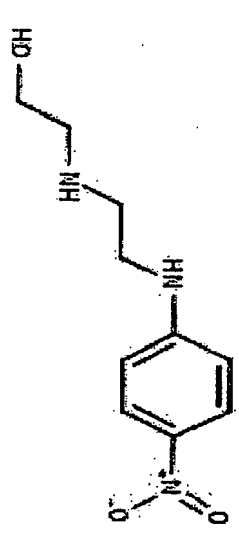
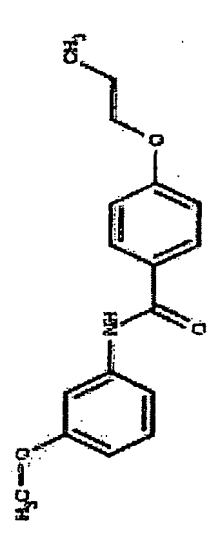
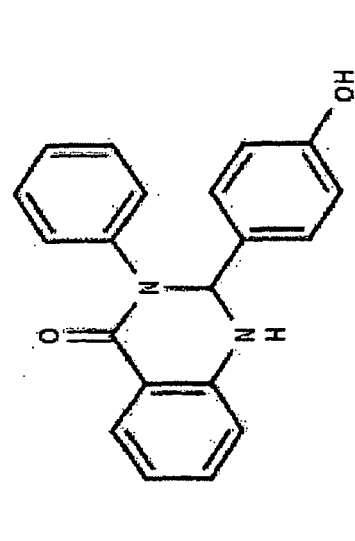
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
50	4-ethyl-5,6-dimethyl-2-phenylpyrimidine	C ₁₄ H ₁₆ N ₂	212,3	 <p>The structure shows a pyrimidine ring with a phenyl group at position 2, an ethyl group at position 4, and methyl groups at positions 5 and 6.</p>
1	2-(3-chlorobenzylidene)-1H-indene-1,3(2H)-dione	C ₁₆ H ₉ Cl O ₂	268,7	 <p>The structure shows an indene-1,3-dione core with a 3-chlorobenzylidene group attached to the 2-position.</p>

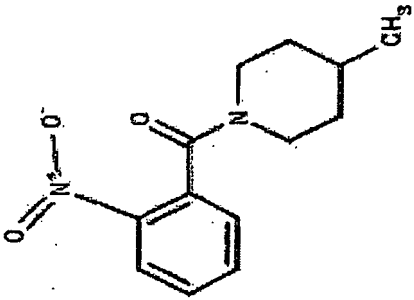
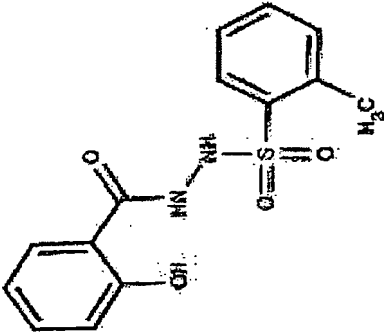
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
7	5-[5-[(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)methyl]-2-furyl]-1H-indole-1,3(2H)-dione	C23 H15 N3 O4	397,4	
8	N-(2,5-dimethylphenyl)-3-(4-methoxyphenyl)acrylamide	C18 H19 N O2	281,4	

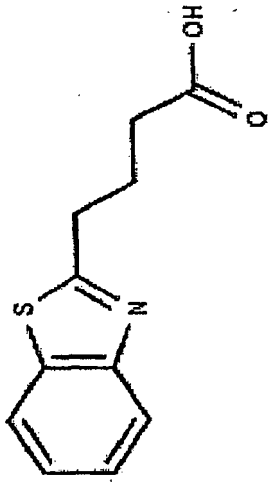
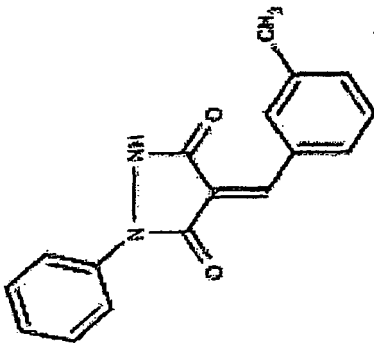
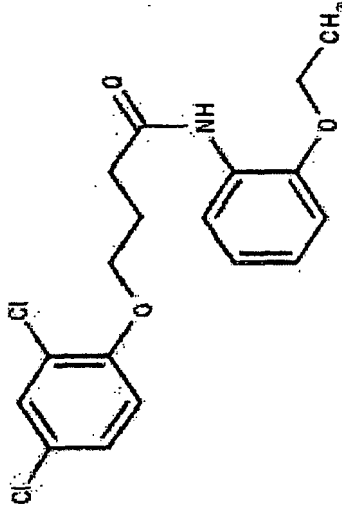
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compound n°	Mol Name	Mol Formula	Mol Weight	Structure
15	2-({2-[(4-nitrophenyl)amino]ethyl}amino)ethanol	C10 H15 N3 O3	225,2	
17	N-(3-methoxyphenyl)-4-propoxybenzamide	C17 H19 N O3	285,3	
19	2-(4-hydroxyphenyl)-3-phenyl-2,3-dihydro-4(1H)-quinazolinone	C20 H16 N2 O2	316,4	

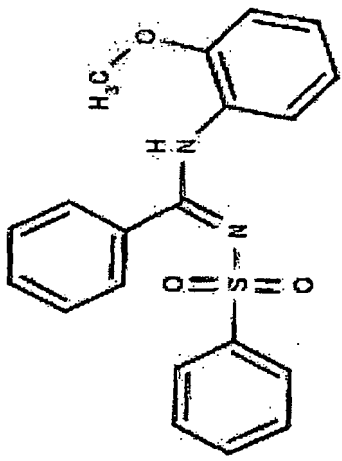
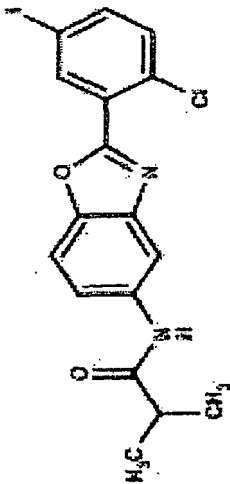
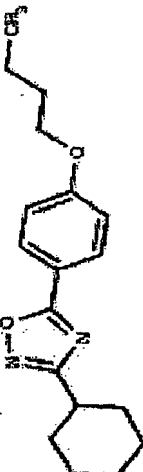
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
28	4-methyl-1-(2-nitrobenzoyl)piperidine	C13 H16 N2 O3	248,3	
31	2-hydroxy-N'-[(2-methylphenyl)sulfonyl]benzohydrazide	C14 H14 N2 O4 S	306,3	

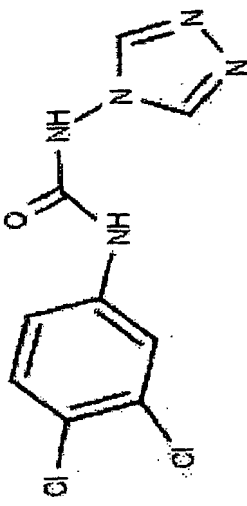
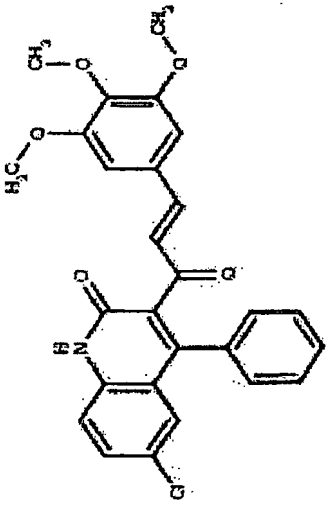
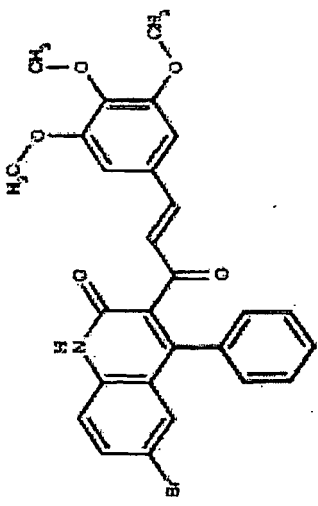
(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
39	4-(1,3-benzothiazol-2-yl)butanoic acid	C11 H11 N O2 S	221,3	
41	4-(3-methylbenzylidene)-1-phenyl-3,5-pyrazolidinedione	C17 H14 N2 O2	278,3	
2	4-(2,4-dichlorophenoxy)-N-(2-ethoxyphenyl)butanamide	C18 H19 Cl2 N O3	368,3	

(continued)

5	10	15	20	25	30	35	40	45	50	55
compound n°	Mol Name	Mol Formula	Mol Weight	Structure						
9	N-(2-methoxyphenyl)-N'-(phenylsulfonyl)benzenecarboximidamide	C20 H18 N2 O3 S	366,4							
32	N-[2-(2-chloro-5-iodophenyl)-1,3-benzoxazol-5-yl]-2-methylpropanamide	C17 H14 Cl I N2 O2	440,7							
38	5-(4-butoxyphenyl)-3-cyclohexyl-1,2,4-oxadiazole	C18 H24 N2 O2	300,4							

(continued)

compound n°	Mol Name	Mol Formula	Mol Weight	Structure
52	N-(3,4-dichlorophenyl)-N'-4H-1,2,4-triazol-4-ylurea	C9 H7 Cl2 N5 O	272,1	
29	6-chloro-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-quinolinone	C27 H22 Cl N O5	475,9	
36	6-bromo-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-quinolinone	C27 H22 Br N O5	520,4	

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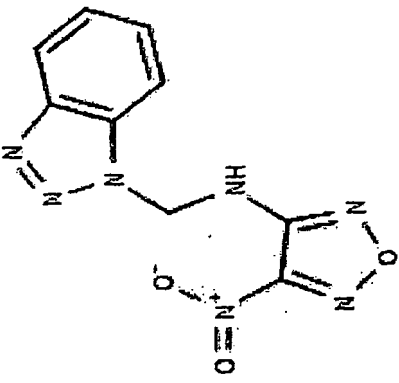
compound n°	Mol Name	Mol Formula	Mol Weight	Structure
45	N-(1H-1,2,3-benzotriazol-1-ylmethyl)-4-nitro-1,2,5-oxadiazol-3-amine	C9H7N7 O3	261,2	

Table 2

	Mol Name	Compound N°	Concentration μM	Survival at 72 hours	Resorption
5	4-[5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutanoic acid	4	100 μM	-	-
10	2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamide	5	100 μM	-	-
	3-(3-chlorophenyl)-7-methyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone	11	100 μM	-	-
15	3-[4-(3-bromobenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoic acid	18	100 μM	-	-
	N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-fyamide	20	100 μM	-	-
	1-acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazine	22	100 μM	-	-
20	3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2(3H)-furanone	23	100 μM	-	-
	3-[5-(3,4-dichlorophenyl)-2-furyl]acrylic acid	24	100 μM	-	-
25	(2-chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-ylidene]methyl]-6-methoxyphenoxy)acetic acid	25	25 μM	-	-
	4-[[4-(diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiadiazole	26	100 μM	-	-
30	4-[4-phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzenediol	34	10 μM	-	-
	N-(3,4-dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamide	37	50 μM	-	-
35	1-[(2-hydroxyphenyl)carbonothioyl]-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol	42	25 μM	-	-
	2-methoxyethyl 4-[(4-tert-butylbenzoyl)amino]benzoate	44	10 μM	-	-
	N-(2,3-dichlorophenyl)-3-(5-methyl-2-furyl)acrylamide	47	100 μM	-	-
40	N-(4-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamide	54	50 μM	-	-
	3-(2-furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-quinazolinone	55	100 μM	-	-
45	2,6-di-tert-butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol	30	100 μM	-	+/-
	3-benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-quinazolinone	33	100 μM	-	+/-
50	1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldehyde	35	50 μM	-	+/-
	N-(4-ethoxyphenyl)-2-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio]acetamide	3	100 μM	+/-	-
55	5-(4-nitrobenzylidene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one	16	100 μM	+/-	-
	(3,5-dichlorophenyl)[(phenylsulfonyl)carbonyl]amine	21	50 μM	+/-	-
	N-(2-bromophenyl)-3-(5-methyl-2-furyl)acrylamide	6	25 μM	+	-

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(continued)

	Mol Name	Compound N°	Concentration μ M	Survival at 72 hours	Resorption
5	2-(2-chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	12	100 μ M	+	-
	N-[4-(4-acetyl-1-piperazinyl)phenyl]propanamide	13	50 μ M	+	-
10	8-[(dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	14	100 μ M	+	-
	4-tert-butyl-N-[1-[(2-methoxyphenyl)amino]carbonyl]-2-(2-thienyl)vinyl]benzamide	46	100 μ M	+	-
15	2-chloro-N-(3-chloro-4-methoxyphenyl)benzamide	51	50 μ M	+	-
	N-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phenylurea	49	50 μ M	+/-	+/-
	N-(3,4-dichlorophenyl)-N'-{5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl} urea	53	100 μ M	+/-	+/-
20	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthoxy)acetamide	10	50 μ M	+	+/-
	N-[4-(4-acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamide	27	100 μ M	+	+/-
25	N-(2-chlorophenyl)-3-(4-fluorophenyl)acrylamide	40	100 μ M	+	+/-
	1-[(dimethyl-lambda~4~-sulfanylidene)amino]-2-methoxy-4-nitrobenzene	43	100 μ M	+	+/-
30	5-benzylidene-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione	48	100 μ M	+	+/-
	4-ethyl-5,6-dimethyl-2-phenylpyrimidine	50	100 μ M	+	+/-

SEQUENCE LISTING

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[0129]

<110> CNRS BLANGY, ANNE

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<120> NEW METHOD FOR IDENTIFYING COMPOUNDS USEFUL FOR TREATING AND/OR PREVENTING DISEASE - ASSOCIATED BONE LOSS

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<151> 2008-08-18

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<170> PatentIn version 3.5

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10 Asp Thr Val His Ile Leu Glu Met Tyr Glu Gly Trp Tyr Arg Gly Tyr
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15 Ala Leu Gln Asn Arg Ser Lys Lys Gly Ile Phe Pro Glu Thr Tyr Ile
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His Leu Lys Glu Ala Thr Val Glu Asp Gly Gly Gln His Glu Thr Val
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25 Glu Trp Ala Val Ile Trp Arg Lys Leu Tyr Val Asn Asn Lys Val Thr
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Leu Phe Arg Gln Leu Gln Gln Met Thr Tyr Ser Leu Ile Glu Trp Arg
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35 Lys Lys Lys Val Thr Ala Lys Ile Asp His Gly Asn Arg Met Leu Gly
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 Glu Thr Ser Thr Val Ala Leu Phe Arg Ala His Glu Val Ala Ser Lys
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 Arg Ile Glu Glu Lys Ile Gln Glu Glu Lys Ser Ile Leu Gln Asn Leu
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 Asp Leu Arg Gly Gln Ala Ile Phe Ser Thr Val His Thr Tyr Gly Leu
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 Tyr Val Asn Phe Lys Asn Phe Val Cys Asn Ile Gly Glu Asp Ala Glu
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 Met Glu Thr Tyr Ile Arg Gln Arg Gln Leu Ile Met Ser Pro Leu Ile
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 Thr Ser His Val Ile Gly Glu Asn Glu Pro Leu Thr Ser Val Leu Asn
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 Lys Val Ile Ala Ala Lys Glu Val Asn His Lys Gly Gln Gly Leu Trp
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 Val Ser Leu Lys Leu Leu Pro Gly Asp Leu Thr Gln Val Gln Lys Asn
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5 Phe Pro Glu Ile Ile Leu Pro Gly Asp Val Arg Asn Asp Ile Tyr Val
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60 Phe Thr Pro Ser Lys Asp Ser Thr Lys Asp Ser Phe Gln Ile Ala Thr
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65 Leu Ile Cys Ser Thr Lys Leu Thr Gln Asn Val Asp Leu Leu Gly Leu
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70 Leu Asn Trp Arg Ser Asn Ser Gln Asn Ile Lys His Asn Leu Lys Lys
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75 Leu Met Glu Val Asp Gly Gly Glu Ile Val Lys Phe Leu Gln Asp Thr
660 665 670

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Leu Asp Ala Leu Phe Asn Ile Met Met Glu Met Ser Asp Asn Glu Thr
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5 Tyr Asp Phe Leu Val Phe Asp Ala Leu Val Phe Ile Ile Ser Leu Ile
690 695 700

10 Gly Asp Ile Lys Phe Gln His Phe Asn Pro Val Leu Glu Thr Tyr Ile
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Tyr Lys His Phe Ser Ala Thr Leu Ala His Val Lys Leu Ser Lys Val
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15 Leu Asn Phe Tyr Val Ala Asn Ala Glu Asp Pro Ser Lys Thr Glu Leu
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20 Leu Phe Ala Ala Leu Lys Ala Leu Lys Tyr Leu Phe Arg Phe Ile Ile
755 760 765

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Asp Glu Phe Asn Asp Ser Ile Arg Gln Leu Phe Leu Ala Phe Asn Thr
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 1160 1165 1170

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10	Leu	Leu	Asp	Tyr	Arg	Thr	Ile	Ile	Ile	His	Asp	Glu	Ser	Lys	Glu
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15	Asn	Arg	Met	Ser	Cys	Thr	Val	Asn	Val	Leu	Asn	Phe	Tyr	Lys	Asp
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20	Lys	Lys	Arg	Glu	Asp	Ile	Tyr	Ile	Arg	Tyr	Leu	Tyr	Lys	Leu	Arg
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30	Leu	Leu	Leu	His	Ala	Glu	Leu	Leu	Gln	Trp	Ser	Asp	Lys	Pro	Cys
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35	Val	Pro	His	Leu	Leu	Gln	Arg	Asp	Ser	Tyr	Tyr	Val	Tyr	Thr	Gln
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Ile Glu Thr Met Glu Leu Thr Asn Glu Arg Val Ser Asn Cys Val
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Ser Asn Tyr Glu Lys Ala Phe Phe Thr Glu Lys Tyr Leu Gln Glu
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Glu Lys Leu Thr Glu Gln Leu Lys Pro Leu His Ala Arg Leu Ser
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50 Ser Cys Phe Arg Glu Leu Lys Glu Lys Val Glu Lys Leu Tyr Gly
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55 Val Ile Thr Leu Pro Pro Ser Met Thr Glu Arg Lys Pro Ser Arg
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Ala Gly Ser Met Val Leu Pro Tyr Ile Leu Ser Ser Thr Leu Arg
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5 Arg Leu Ser Val Thr Ser Val Ala Ser Ser Val Ile Ser Thr Ser
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Arg Val Glu Asp Leu Pro Pro Lys Glu Asp Ser Glu Asn Arg Ile
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20 Ser Lys Phe Lys Arg Lys Asp Trp Asn Leu Ser Lys Ser Gln Val
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Lys Thr Gln Arg Pro Lys Ser Leu Gln Leu Val Asp Ser Arg Leu
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Lys Pro Val Asn Leu Gly Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr
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Cys Phe Ser Leu Val Ser Pro Ala Ser Phe Glu Asn Val Arg Ala Lys
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Trp Tyr Pro Glu Val Arg His His Cys Pro Asn Thr Pro Ile Ile Leu
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15 Asn Lys Lys Lys Glu Lys Glu Arg Pro Glu Ile Ser Leu Pro Ser Asp
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Val Ile His Arg Asp Ile Lys Ser Asp Asn Ile Leu Leu Gly Met Asp
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Thr Pro Glu Leu Gln Asn Pro Glu Lys Leu Ser Ala Ile Phe Arg Asp
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Lys Lys Lys Val Thr Ala Lys Ile Asp His Gly Asn Arg Met Leu Gly
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 260 265 270
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 Lys Leu Asn Asn Leu Gln Ala Val Phe Thr Asp Leu Ser Ser Met Asp
 275 280 285
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 Leu Ile Arg Pro Arg Val Ser Leu Val Cys Gln Ile Val Arg Val Gly
 290 295 300
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 His Met Glu Leu Lys Glu Gly Lys Lys His Thr Cys Gly Leu Arg Arg
 305 310 315 320
 40
 Pro Phe Gly Val Ala Val Met Asp Ile Thr Asp Ile Ile His Gly Lys
 325 330 335
 45
 Val Asp Asp Glu Glu Lys Gln His Phe Ile Pro Phe Gln Gln Ile Ala
 340 345 350
 50
 Met Glu Thr Tyr Ile Arg Gln Arg Gln Leu Ile Met Ser Pro Leu Ile
 355 360 365
 55
 Thr Ser His Val Ile Gly Glu Asn Glu Pro Leu Thr Ser Val Leu Asn
 370 375 380
 60
 Lys Val Ile Ala Ala Lys Glu Val Asn His Lys Gly Gln Gly Leu Trp
 385 390 395 400
 65
 Val Ser Leu Lys Leu Leu Pro Gly Asp Leu Thr Gln Val Gln Lys Asn
 405 410 415
 70
 Phe Ser His Leu Val Asp Arg Ser Thr Ala Ile Ala Arg Lys Met Gly
 420 425 430
 75
 Phe Pro Glu Ile Ile Leu Pro Gly Asp Val Arg Asn Asp Ile Tyr Val
 435 440 445

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Thr Leu Ile His Gly Glu Phe Asp Lys Gly Lys Lys Lys Thr Pro Lys
 450 455 460

5

Asn Val Glu Val Thr Met Ser Val His Asp Glu Glu Gly Lys Leu Leu
 465 470 475 480

10

Glu Lys Ala Ile His Pro Gly Ala Gly Tyr Glu Gly Ile Ser Glu Tyr
 485 490 495

15

Lys Ser Val Val Tyr Tyr Gln Val Lys Gln Pro Cys Trp Tyr Glu Thr
 500 505 510

20

Val Lys Val Ser Ile Ala Ile Glu Glu Val Thr Arg Cys His Ile Arg
 515 520 525

25

Phe Thr Phe Arg His Arg Ser Ser Gln Glu Thr Arg Asp Lys Ser Glu
 530 535 540

30

Arg Ala Phe Gly Val Ala Phe Val Lys Leu Met Asn Pro Asp Gly Thr
 545 550 555 560

35

Thr Leu Gln Asp Gly Arg His Asp Leu Val Val Tyr Lys Gly Asp Asn
 565 570 575

40

Lys Lys Met Glu Asp Ala Lys Phe Tyr Leu Thr Leu Pro Gly Thr Lys
 580 585 590

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Met Glu Met Glu Glu Lys Glu Leu Gln Ala Ser Lys Asn Leu Val Thr
 595 600 605

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Phe Thr Pro Ser Lys Asp Ser Thr Lys Asp Ser Phe Gln Ile Ala Thr
 610 615 620

55

Leu Ile Cys Ser Thr Lys Leu Thr Gln Asn Val Asp Leu Leu Gly Leu
 625 630 635 640

60

Leu Asn Trp Arg Ser Asn Ser Gln Asn Ile Lys His Asn Leu Lys Lys
 645 650 655

65

Leu Met Glu Val Asp Gly Gly Glu Ile Val Lys Phe Leu Gln Asp Thr
 660 665 670

70

Leu Asp Ala Leu Phe Asn Ile Met Met Glu Met Ser Asp Ser Glu Thr
 675 680 685

75

Tyr Asp Phe Leu Val Phe Asp Ala Leu Val Phe Ile Ile Ser Leu Ile
 690 695 700

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	Gly	Asp	Ile	Lys	Phe	Gln	His	Phe	Asn	Pro	Val	Leu	Glu	Thr	Tyr	Ile
	705					710					715					720
5	Tyr	Lys	His	Phe	Ser	Ala	Thr	Leu	Ala	Tyr	Val	Lys	Leu	Ser	Lys	Val
					725					730					735	
10	Leu	Asn	Phe	Tyr	Val	Ala	Asn	Ala	Asp	Asp	Ser	Ser	Lys	Thr	Glu	Leu
			740						745					750		
15	Leu	Phe	Ala	Ala	Leu	Lys	Ala	Leu	Lys	Tyr	Leu	Phe	Arg	Phe	Ile	Ile
			755					760					765			
20	Gln	Ser	Arg	Val	Leu	Tyr	Leu	Arg	Phe	Tyr	Gly	Gln	Ser	Lys	Asp	Gly
		770					775					780				
25	Asp	Glu	Phe	Asn	Asn	Ser	Ile	Arg	Gln	Leu	Phe	Leu	Ala	Phe	Asn	Met
	785					790					795					800
30	Leu	Met	Asp	Arg	Pro	Leu	Glu	Glu	Ala	Val	Lys	Ile	Lys	Gly	Ala	Ala
					805					810					815	
35	Leu	Lys	Tyr	Leu	Pro	Ser	Ile	Ile	Asn	Asp	Val	Lys	Leu	Val	Phe	Asp
				820					825					830		
40	Pro	Val	Glu	Leu	Ser	Val	Leu	Phe	Cys	Lys	Phe	Ile	Gln	Ser	Ile	Pro
			835					840					845			
45	Asp	Asn	Gln	Leu	Val	Arg	Gln	Lys	Leu	Asn	Cys	Met	Thr	Lys	Ile	Val
		850					855					860				
50	Glu	Ser	Thr	Leu	Phe	Arg	Gln	Ser	Glu	Cys	Arg	Glu	Val	Leu	Leu	Pro
	865					870					875					880
55	Leu	Leu	Thr	Asp	Gln	Leu	Ser	Gly	Gln	Leu	Asp	Asp	Asn	Ser	Asn	Lys
					885					890					895	
60	Pro	Asp	His	Glu	Ala	Ser	Ser	Gln	Leu	Leu	Ser	Asn	Ile	Leu	Glu	Val
				900					905					910		
65	Leu	Asp	Arg	Lys	Asp	Val	Gly	Ala	Thr	Ala	Val	His	Ile	Gln	Leu	Ile
			915					920					925			
70	Met	Glu	Arg	Leu	Leu	Arg	Arg	Ile	Asn	Arg	Thr	Val	Ile	Gly	Met	Asn
		930					935					940				
75	Arg	Gln	Ser	Pro	His	Ile	Gly	Ser	Phe	Val	Ala	Cys	Met	Ile	Ala	Leu
	945					950					955					960

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Leu Gln Gln Met Asp Asp Ser His Tyr Ser His Tyr Ile Ser Thr Phe
965 970 975

5 Lys Thr Arg Gln Asp Ile Ile Asp Phe Leu Met Glu Thr Phe Ile Met
980 985 990

10 Phe Lys Asp Leu Ile Gly Lys Asn Val Tyr Ala Lys Asp Trp Met Val
995 1000 1005

15 Met Asn Met Thr Gln Asn Arg Val Phe Leu Arg Ala Ile Asn Gln
1010 1015 1020

Phe Ala Glu Val Leu Thr Arg Phe Phe Met Asp Gln Ala Ser Phe
1025 1030 1035

20 Glu Leu Gln Leu Trp Asn Asn Tyr Phe His Leu Ala Val Ala Phe
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25 Leu Thr His Glu Ser Leu Gln Leu Glu Thr Phe Ser Gln Ala Lys
1055 1060 1065

Arg Asn Lys Ile Val Lys Lys Tyr Gly Asp Met Arg Lys Glu Ile
1070 1075 1080

30 Gly Phe Arg Ile Arg Asp Met Trp Tyr Asn Leu Gly Pro His Lys
1085 1090 1095

35 Ile Lys Phe Ile Pro Ser Met Val Gly Pro Ile Leu Glu Val Thr
1100 1105 1110

Leu Thr Pro Glu Val Glu Leu Arg Lys Ala Thr Ile Pro Ile Phe
1115 1120 1125

40 Phe Asp Met Met Gln Cys Glu Phe Asn Phe Ser Gly Asn Gly Asn
1130 1135 1140

45 Phe His Met Phe Glu Asn Glu Leu Ile Thr Lys Leu Asp Gln Glu
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50 Val Glu Gly Gly Arg Gly Asp Glu Gln Tyr Lys Val Leu Leu Glu
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Lys Leu Leu Leu Glu His Cys Arg Lys His Lys Tyr Leu Ser Ser
1175 1180 1185

55 Ser Gly Glu Val Phe Ala Leu Leu Val Ser Ser Leu Leu Glu Asn
1190 1195 1200

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Leu Leu Asp Tyr Arg Thr Ile Ile Met Gln Asp Glu Ser Lys Glu
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 Asn Arg Met Ser Cys Thr Val Asn Val Leu Asn Phe Tyr Lys Glu
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 10
 Lys Lys Arg Glu Asp Ile Tyr Ile Arg Tyr Leu Tyr Lys Leu Arg
 1235 1240 1245
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 Asp Leu His Arg Asp Cys Glu Asn Tyr Thr Glu Ala Ala Tyr Thr
 1250 1255 1260
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 Leu Leu Leu His Ala Glu Leu Leu Gln Trp Ser Asp Lys Pro Cys
 1265 1270 1275
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 Val Pro His Leu Leu Gln Arg Asp Ser Tyr Tyr Val Tyr Thr Gln
 1280 1285 1290
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 Gln Glu Leu Lys Glu Lys Leu Tyr Gln Glu Ile Ile Ser Tyr Phe
 1295 1300 1305
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 Asp Lys Gly Lys Met Trp Glu Lys Ala Ile Lys Leu Ser Lys Glu
 1310 1315 1320
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 Leu Ala Glu Thr Tyr Glu Ser Lys Val Phe Asp Tyr Glu Gly Leu
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 Gly Asn Leu Leu Lys Lys Arg Ala Ser Phe Tyr Glu Asn Ile Ile
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 Lys Ala Met Arg Pro Gln Pro Glu Tyr Phe Ala Val Gly Tyr Tyr
 1355 1360 1365
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 Gly Gln Gly Phe Pro Ser Phe Leu Arg Asn Lys Ile Phe Ile Tyr
 1370 1375 1380
 Arg Gly Lys Glu Tyr Glu Arg Arg Glu Asp Phe Ser Leu Arg Leu
 1385 1390 1395
 Leu Thr Gln Phe Pro Asn Ala Glu Lys Met Thr Ser Thr Thr Pro
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 Pro Gly Glu Asp Ile Lys Ser Ser Pro Lys Gln Tyr Met Gln Cys
 1415 1420 1425
 Phe Thr Val Lys Pro Val Met Ser Leu Pro Pro Ser Tyr Lys Asp
 1430 1435 1440

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	Lys	Pro	Val	Pro	Glu	Gln	Ile	Leu	Asn	Tyr	Tyr	Arg	Ala	Asn	Glu
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5	Val	Gln	Gln	Phe	Arg	Tyr	Ser	Arg	Pro	Phe	Arg	Lys	Gly	Glu	Lys
		1460					1465					1470			
10	Asp	Pro	Asp	Asn	Glu	Phe	Ala	Thr	Met	Trp	Ile	Glu	Arg	Thr	Thr
		1475					1480					1485			
15	Tyr	Thr	Thr	Ala	Tyr	Thr	Phe	Pro	Gly	Ile	Leu	Lys	Trp	Phe	Glu
		1490					1495					1500			
20	Val	Lys	Gln	Ile	Ser	Thr	Glu	Glu	Ile	Ser	Pro	Leu	Glu	Asn	Ala
		1505					1510					1515			
25	Ile	Glu	Thr	Met	Glu	Leu	Thr	Asn	Glu	Arg	Ile	Ser	Asn	Cys	Val
		1520					1525					1530			
30	Gln	Gln	His	Ala	Trp	Asp	Arg	Ser	Leu	Ser	Val	His	Pro	Leu	Ser
		1535					1540					1545			
35	Met	Leu	Leu	Ser	Gly	Ile	Val	Asp	Pro	Ala	Val	Met	Gly	Gly	Phe
		1550					1555					1560			
40	Ser	Asn	Tyr	Glu	Lys	Ala	Phe	Phe	Thr	Glu	Lys	Tyr	Leu	Gln	Glu
		1565					1570					1575			
45	His	Pro	Glu	Asp	Gln	Glu	Lys	Val	Glu	Leu	Leu	Lys	Arg	Leu	Ile
		1580					1585					1590			
50	Ala	Leu	Gln	Met	Pro	Leu	Leu	Thr	Glu	Gly	Ile	Arg	Ile	His	Gly
		1595					1600					1605			
55	Glu	Lys	Leu	Thr	Glu	Gln	Leu	Lys	Pro	Leu	His	Glu	Arg	Leu	Ser
		1610					1615					1620			
60	Ser	Cys	Phe	Arg	Glu	Leu	Lys	Glu	Lys	Val	Glu	Lys	His	Tyr	Gly
		1625					1630					1635			
65	Val	Ile	Thr	Leu	Pro	Pro	Asn	Leu	Thr	Glu	Arg	Lys	Gln	Ser	Arg
		1640					1645					1650			
70	Thr	Gly	Ser	Ile	Val	Leu	Pro	Tyr	Ile	Met	Ser	Ser	Thr	Leu	Arg
		1655					1660					1665			
75	Arg	Leu	Ser	Ile	Thr	Ser	Val	Thr	Ser	Ser	Val	Val	Ser	Thr	Ser
		1670					1675					1680			

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Ser Asn Ser Ser Asp Asn Ala Pro Ser Arg Pro Gly Ser Asp Gly
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 Ser Ile Leu Glu Pro Leu Leu Glu Arg Arg Ala Ser Ser Gly Ala
 1700 1705 1710
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 Arg Val Glu Asp Leu Ser Leu Arg Glu Glu Asn Ser Glu Asn Arg
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 15
 Ile Ser Lys Phe Lys Arg Lys Asp Trp Ser Leu Ser Lys Ser Gln
 1730 1735 1740
 Val Ile Ala Glu Lys Ala Pro Glu Pro Asp Leu Met Ser Pro Thr
 1745 1750 1755
 20
 Arg Lys Ala Gln Arg Pro Lys Ser Leu Gln Leu Met Asp Asn Arg
 1760 1765 1770
 25
 Leu Ser Pro Phe His Gly Ser Ser Pro Pro Gln Ser Thr Pro Leu
 1775 1780 1785
 Ser Pro Pro Pro Leu Thr Pro Lys Ala Thr Arg Thr Leu Ser Ser
 1790 1795 1800
 30
 Pro Ser Leu Gln Thr Asp Gly Ile Ala Ala Thr Pro Val Pro Pro
 1805 1810 1815
 35
 Pro Pro Pro Pro Lys Ser Lys Pro Tyr Glu Gly Ser Gln Arg Asn
 1820 1825 1830
 Ser Thr Glu Leu Ala Pro Pro Leu Pro Val Arg Arg Glu Ala Lys
 1835 1840 1845
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 Ala Pro Pro Pro Pro Pro Lys Ala Arg Lys Ser Gly Ile Pro
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 Thr Ser Glu Pro Gly Ser Gln
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Met Pro Pro Pro Ala Asp Ile Val Lys Val Ala Ile Glu Trp Pro Gly
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5 Ala Tyr Pro Lys Leu Met Glu Ile Asp Gln Lys Lys Pro Leu Ser Ala
20 25 30

10 Ile Ile Lys Glu Val Cys Asp Gly Trp Ser Leu Ala Asn His Glu Tyr
35 40 45

15 Phe Ala Leu Gln His Ala Asp Ser Ser Asn Phe Tyr Ile Thr Glu Lys
50 55 60

Asn Arg Asn Glu Ile Lys Asn Gly Thr Ile Leu Arg Leu Thr Thr Ser
65 70 75 80

20 Pro Ala Gln Asn Ala Gln Gln Leu His Glu Arg Ile Gln Ser Ser Ser

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					85					90					95	
5	Met	Asp	Ala	Lys	Leu	Glu	Ala	Leu	Lys	Asp	Leu	Ala	Ser	Leu	Ser	Arg
				100					105					110		
	Asp	Val	Thr	Phe	Ala	Gln	Glu	Phe	Ile	Asn	Leu	Asp	Gly	Ile	Ser	Leu
			115					120					125			
10	Leu	Thr	Gln	Met	Val	Glu	Ser	Gly	Thr	Glu	Arg	Tyr	Gln	Lys	Leu	Gln
		130					135					140				
15	Lys	Ile	Met	Lys	Pro	Cys	Phe	Gly	Asp	Met	Leu	Ser	Phe	Thr	Leu	Thr
	145					150					155					160
	Ala	Phe	Val	Glu	Leu	Met	Asp	His	Gly	Ile	Val	Ser	Trp	Asp	Thr	Phe
20					165					170					175	
	Ser	Val	Ala	Phe	Ile	Lys	Lys	Ile	Ala	Ser	Phe	Val	Asn	Lys	Ser	Ala
			180						185					190		
25	Ile	Asp	Ile	Ser	Ile	Leu	Gln	Arg	Ser	Leu	Ala	Ile	Leu	Glu	Ser	Met
			195					200						205		
	Val	Leu	Asn	Ser	His	Asp	Leu	Tyr	Gln	Lys	Val	Ala	Gln	Glu	Ile	Thr
30		210					215					220				
	Ile	Gly	Gln	Leu	Ile	Pro	His	Leu	Gln	Gly	Ser	Asp	Gln	Glu	Ile	Gln
	225					230					235					240
35	Thr	Tyr	Thr	Ile	Ala	Val	Ile	Asn	Ala	Leu	Phe	Leu	Lys	Ala	Pro	Asp
					245					250					255	
	Glu	Arg	Arg	Gln	Glu	Met	Ala	Asn	Ile	Leu	Ala	Gln	Lys	Gln	Leu	Arg
40				260					265					270		
	Ser	Ile	Ile	Leu	Thr	His	Val	Ile	Arg	Ala	Gln	Arg	Ala	Ile	Asn	Asn
			275					280					285			
45	Glu	Met	Ala	His	Gln	Leu	Tyr	Val	Leu	Gln	Val	Leu	Thr	Phe	Asn	Leu
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	Leu	Glu	Asp	Arg	Met	Met	Thr	Lys	Met	Asp	Pro	Gln	Asp	Gln	Ala	Gln
50	305					310					315					320
	Arg	Asp	Ile	Ile	Phe	Glu	Leu	Arg	Arg	Ile	Ala	Phe	Asp	Ala	Glu	Ser
					325					330					335	
55	Glu	Pro	Asn	Asn	Ser	Ser	Gly	Ser	Met	Glu	Lys	Arg	Lys	Ser	Met	Tyr

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5	Thr	Arg	Asp	Tyr	Lys	Lys	Leu	Gly	Phe	Ile	Asn	His	Val	Asn	Pro	Ala
			355					360					365			
10	Met	Asp	Phe	Thr	Gln	Thr	Pro	Pro	Gly	Met	Leu	Ala	Leu	Asp	Asn	Met
		370					375					380				
15	Leu	Tyr	Phe	Ala	Lys	His	His	Gln	Asp	Ala	Tyr	Ile	Arg	Ile	Val	Leu
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20	Glu	Asn	Ser	Ser	Arg	Glu	Asp	Lys	His	Glu	Cys	Pro	Phe	Gly	Arg	Ser
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25	Ser	Ile	Glu	Leu	Thr	Lys	Met	Leu	Cys	Glu	Ile	Leu	Lys	Val	Gly	Glu
				420					425					430		
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			435					440					445			
35	Asp	Arg	Ser	Phe	Glu	Glu	Phe	Phe	Cys	Ile	Cys	Ile	Gln	Leu	Leu	Asn
		450					455					460				
40	Lys	Thr	Trp	Lys	Glu	Met	Arg	Ala	Thr	Ser	Glu	Asp	Phe	Asn	Lys	Val
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45	Met	Gln	Val	Val	Lys	Glu	Gln	Val	Met	Arg	Ala	Leu	Thr	Thr	Lys	Pro
					485					490					495	
50	Ser	Ser	Leu	Asp	Gln	Phe	Lys	Ser	Lys	Leu	Gln	Asn	Leu	Ser	Tyr	Thr
				500					505					510		
55	Glu	Ile	Leu	Lys	Ile	Arg	Gln	Ser	Glu	Arg	Met	Asn	Gln	Glu	Asp	Phe
			515					520					525			
60	Gln	Ser	Arg	Pro	Ile	Leu	Glu	Leu	Lys	Glu	Lys	Ile	Gln	Pro	Glu	Ile
		530					535					540				
65	Leu	Glu	Leu	Ile	Lys	Gln	Gln	Arg	Leu	Asn	Arg	Leu	Val	Glu	Gly	Thr
	545					550					555					560
70	Cys	Phe	Arg	Lys	Leu	Asn	Ala	Arg	Arg	Arg	Gln	Asp	Lys	Phe	Trp	Tyr
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75	Cys	Arg	Leu	Ser	Pro	Asn	His	Lys	Val	Leu	His	Tyr	Gly	Asp	Leu	Glu
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80	Glu	Ser	Pro	Gln	Gly	Glu	Val	Pro	His	Asp	Ser	Leu	Gln	Asp	Lys	Leu

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		595					600					605				
5	Pro	Val	Ala	Asp	Ile	Lys	Ala	Val	Val	Thr	Gly	Lys	Asp	Cys	Pro	His
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10	Met	Lys	Glu	Lys	Gly	Ala	Leu	Lys	Gln	Asn	Lys	Glu	Val	Leu	Glu	Leu
	625					630					635					640
15	Ala	Phe	Ser	Ile	Leu	Tyr	Asp	Ser	Asn	Cys	Gln	Leu	Asn	Phe	Ile	Ala
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20	Pro	Asp	Lys	His	Glu	Tyr	Cys	Ile	Trp	Thr	Asp	Gly	Leu	Asn	Ala	Leu
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25	Leu	Gly	Lys	Asp	Met	Met	Ser	Asp	Leu	Thr	Arg	Asn	Asp	Leu	Asp	Thr
			675					680					685			
30	Leu	Leu	Ser	Met	Glu	Ile	Lys	Leu	Arg	Leu	Leu	Asp	Leu	Glu	Asn	Ile
		690					695					700				
35	Gln	Ile	Pro	Asp	Ala	Pro	Pro	Pro	Ile	Pro	Lys	Glu	Pro	Ser	Asn	Tyr
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35 Claims

1. A compound chosen in the group consisting in:

- 40 - 2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamide;
 - 4-[5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutanoic acid;
 - 3-(3-chlorophenyl)-7-methyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone;
 - 3-[4-(3-bromobenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoic acid;
 - N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-furamide;
 45 - 1-acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazine;
 - 3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2(3H)-furanone;
 - 3-[5-(3,4-dichlorophenyl)-2-furyl]acrylic acid;
 - (2-chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-
 2(3H)-ylidene]methyl]-6-methoxyphenoxy)acetic acid;
 - 4-[[4-(diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiadiazole;
 50 - 4-[4-phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzenediol;
 - N-(3,4-dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamide;
 - 1-[(2-hydroxyphenyl)carbonothioyl]-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol;
 - 2-methoxyethyl 4-[(4-tert-butylbenzoyl)amino]benzoate;
 - N-(2,3-dichlorophenyl)-3-(5-methyl-2-furyl)acrylamide;
 55 - N-(4-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamide;
 - 3-(2-furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-quinazolinone;
 - N-(4-ethoxyphenyl)-2-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio]acetamide;
 - 5-(4-nitrobenzylidene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one;

- (3,5-dichlorophenyl)[(phenylsulfonyl)carbonyl]amine;
- N-(2-bromophenyl)-3-(5-methyl-2-furyl)acrylamide;
- 2-(2-chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamide;
- N-[4-(4-acetyl-1-piperazinyl)phenyl]propanamide;
- 5 - 8-[(dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one;
- 4-tert-butyl-N-[1-[(2-methoxyphenyl)amino]carbonyl]-2-(2-thienyl)vinyl]benzamide;
- 2-chloro-N-(3-chloro-4-methoxyphenyl)benzamide;
- 2,6-di-tert-butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol;
- 10 - 3-benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-quinazolinone;
- 1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldehyde;
- N-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phenylurea;
- N-(3,4-dichlorophenyl)-N'-[5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl]urea;
- N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthoxy)acetamide;
- 15 - N-[4-(4-acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamide;
- N-(2-chlorophenyl)-3-(4-fluorophenyl)acrylamide;
- 1-[(dimethyl-lambda-4--sutfanylidene)amino]-2-methoxy-4-nitrobenzene;
- 5-benzylidene-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione;
- 4-ethyl-5,6-dimethyl-2-phenylpyrimidine;
- 20 - 2-(3-chlorobenzylidene)-1H-indene-1,3(2H)-dione;
- 5-[5-[(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)methyl]-2-furyl]-1H-isoindole-1,3(2H)-dione;
- N-(2,5-dimethylphenyl)-3-(4-methoxyphenyl)acrylamide;
- 2-({2-[(4-nitrophenyl)amino]ethyl}amino)ethanol;
- N-(3-methoxyphenyl)-4-propoxybenzamide;
- 25 - 2-(4-hydroxyphenyl)-3-phenyl-2,3-dihydro-4(1H)-quinazolinone;
- 4-methyl-1-(2-nitrobenzoyl)piperidine;
- 2-hydroxy-N'-[(2-methylphenyl)sulfonyl]benzohydrazide;
- 4-(1,3-benzothiazol-2-yl)butanoic acid;
- 4-(3-methylbenzylidene)-1-phenyl-3,5-pyrazolidinedione;
- 30 - 4-(2,4-dichlorophenoxy)-N-(2-ethoxyphenyl)butanamide;
- N-(2-methoxyphenyl)-N'-(phenylsulfonyl)benzenecarboximidamide;
- N-[2-(2-chloro-5-iodophenyl)-1,3-benzoxazol-5-yl]-2-methylpropanamide;
- 5-(4-butoxyphenyl)-3-cyclohexyl-1,2,4-oxadiazole;
- N-(3,4-dichlorophenyl)-N'-4H-1,2,4-triazol-4-yl urea;
- 35 - 6-chloro-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1 H)-quinolinone;
- 6-bromo-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-quinolinone; and
- N-(1H-1,2,3-benzotriazol-1-ylmethyl)-4-nitro-1,2,5-oxadiazol-3-amine for use in the treatment and/or prevention of bone loss diseases in a subject in need thereof.

40 **2.** A pharmaceutical composition comprising at least one compound chosen in the group consisting in:

- 2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamide;
- 4-[5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutanoic acid;
- 3-(3-chlorophenyl)-7-methyl-4-methylene-3,4-dihydro-2(1H)-quinazolinone;
- 45 - 3-[4-(3-bromobenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoic acid;
- N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-furamide;
- 1-acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazine;
- 3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2(3H)-furanone;
- 3-[5-(3,4-dichlorophenyl)-2-furyl]acrylic acid;
- 50 - (2-chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-ylidene]methyl]-6-methoxyphenoxy)acetic acid;
- 4-[[4-(diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiadiazole;
- 4-[4-phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzenediol;
- N-(3,4-dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamide;
- 55 - 1-[(2-hydroxyphenyl)carbonothioyl]-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol;
- 2-methoxyethyl 4-[(4-tert-butylbenzoyl)amino]benzoate;
- N-(2,3-dichlorophenyl)-3-(5-methyl-2-furyl)acrylamide;
- N-(4-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamide;

- 3-(2-furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-quinazolinone;
- N-(4-ethoxyphenyl)-2-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio]acetamide;
- 5-(4-nitrobenzylidene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one;
- (3,5-dichlorophenyl)[(phenylsulfonyl)carbonyl]amine;
- N-(2-bromophenyl)-3-(5-methyl-2-furyl)acrylamide;
- 2-(2-chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamide;
- N-[4-(4-acetyl-1-piperazinyl)phenyl]propanamide;
- 8-[[dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one;
- 4-tert-butyl-N-[1-[[2-(methoxyphenyl)amino]carbonyl]-2-(2-thienyl)vinyl]benzamide;
- 2-chloro-N-(3-chloro-4-methoxyphenyl)benzamide;
- 2,6-di-tert-butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol;
- 3-benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-quinazolinone;
- 1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldehyde;
- N-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phenylurea;
- N-(3,4-dichlorophenyl)-N'-[5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl]urea;
- N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthyl)acetamide;
- N-[4-(4-acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamide;
- N-(2-chlorophenyl)-3-(4-fluorophenyl)acrylamide;
- 1-[(dimethyl-λ⁴-sulfanylidene)amino]-2-methoxy-4-nitrobenzene;
- 5-benzylidene-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione;
- 4-ethyl-5,6-dimethyl-2-phenylpyrimidine;
- 2-(3-chlorobenzylidene)-1H-indene-1,3(2H)-dione;
- 5-[5-[[3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)methyl]-2-furyl]-1H-indole-1,3(2H)-dione;
- N-(2,5-dimethylphenyl)-3-(4-methoxyphenyl)acrylamide;
- 2-[(2-[(4-nitrophenyl)amino]ethyl)amino]ethanol;
- N-(3-methoxyphenyl)-4-propoxybenzamide;
- 2-(4-hydroxyphenyl)-3-phenyl-2,3-dihydro-4(1H)-quinazolinone;
- 4-methyl-1-(2-nitrobenzoyl)piperidine;
- 2-hydroxy-N'-[(2-methylphenyl)sulfonyl]benzohydrazide;
- 4-(1,3-benzothiazol-2-yl)butanoic acid;
- 4-(3-methylbenzylidene)-1-phenyl-3,5-pyrazolidinedione;
- 4-(2,4-dichlorophenoxy)-N-(2-ethoxyphenyl)butanamide;
- N-(2-methoxyphenyl)-N'-(phenylsulfonyl)benzenecarboximidamide;
- N-[2-(2-chloro-5-iodophenyl)-1,3-benzoxazol-5-yl]-2-methylpropanamide;
- 5-(4-butoxyphenyl)-3-cyclohexyl-1,2,4-oxadiazole;
- N-(3,4-dichlorophenyl)-N'-4H-1,2,4-triazol-4-yl urea;
- 6-chloro-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-quinolinone;
- 6-bromo-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-quinolinone; and
- N-(1H-1,2,3-benzotriazol-1-ylmethyl)-4-nitro-1,2,5-oxadiazol-3-amine and, optionally, a pharmaceutically acceptable support, for use in the treatment and/or prevention of bone loss diseases in a subject in need thereof.

3. Compound or composition for use according to any of claims 1 or 2, wherein the bone loss diseases is chosen in the group consisting of: osteoporosis, osteopenia due to bone metastases, periarticular erosions in rheumatoid arthritis, primary hyperparathyroidism, hypercalcemia of malignancy, Paget's disease of bone, periodontal disease, immobilization induced osteopenia and glucocorticoid treatment.
4. Compound or composition for use according to claim 3, wherein the bone loss disease is osteoporosis.
5. Compound or composition for use according to any of claims 1 to 4, wherein said compound is administered at a concentration of between 5 and 200 μM.
6. Compound or composition for use according to claim 5, wherein said compound is administered at a concentration of between 10 and 100 μM.

Patentansprüche

1. Verbindung, ausgewählt aus der Gruppe bestehend aus:

- 5
- 2,2,2-Trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamid;
 - 4-[5-(4-Bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobuttersäure;
 - 3-(3-Chlorophenyl)-7-methyl-4-methylen-3,4-dihydro-2(1H)-chinazolinon;
 - 3-[4-(3-Bromobenzyliden)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoesäure;
- 10
- N-2,1,3-Benzothiadiazol-4-yl-5-bromo-2-furamid;
 - 1-Acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazin;
 - 3-(3-Methoxybenzyliden)-5-(4-methylphenyl)-2(3H)-furanon;
 - 3-[5-(3,4-Dichlorophenyl)-2-furyl]acrylsäure;
 - (2-Chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-yliden]methyl]-6-methoxyphenoxy)essigsäure;
- 15
- 4-[[4-(Diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiadiazol;
 - 4-[4-Phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzoldiol;
 - N-(3,4-Dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamid;
 - 1-[(2-Hydroxyphenyl)carbonothioyl]-3-phenyl-5-(trifluormethyl)-4,5-dihydro-1H-pyrazol-5-ol;
 - 2-Methoxyethyl-4-[(4-tert-butylbenzoyl)amino]benzoat;
- 20
- N-(2,3-Dichlorophenyl)-3-(5-methyl-2-furyl)acrylamid;
 - N-(4-Fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamid;
 - 3-(2-Furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-chinazolinon;
 - N-(4-Ethoxyphenyl)-2-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio]acetamid;
 - 5-(4-Nitrobenzyliden)-2-thio-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-on;
- 25
- (3,5-Dichlorophenyl)[(phenylsulfonyl)carbonyl]amin;
 - N-(2-Bromophenyl)-3-(5-methyl-2-furyl)acrylamid;
 - 2-(2-Chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamid;
 - N-[4-(4-Acetyl-1-piperazinyl)phenyl]propanamid;
 - 8-[(Dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-on;
- 30
- 4-tert-Butyl-N-[1-[[2-methoxyphenyl]amino]carbonyl]-2-(2-thienyl)viny]benzamid;
 - 2-Chloro-N-(3-chloro-4-methoxyphenyl)benzamid;
 - 2,6-di-tert-Butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol;
 - 3-Benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-chinazolinon;
 - 1-(3,4-Dichlorobenzyl)-1H-indol-3-carbaldehyd;
- 35
- N-[5-(1-Adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phenylharnstoff;
 - N-(3,4-Dichlorophenyl)-N'-{5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl}harnstoff;
 - N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthyloxy)acetamid;
 - N-[4-(4-Acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamid;
 - N-(2-Chlorophenyl)-3-(4-fluorophenyl)acrylamid;
- 40
- 1-[(Dimethyl-lambda-4-sulfanyliden)amino]-2-methoxy-4-nitrobenzol;
 - 5-Benzyliden-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidintrion;
 - 4-Ethyl-5,6-dimethyl-2-phenylpyrimidin;
 - 2-(3-Chlorobenzyliden)-1H-inden-1,3(2H)-dion;
 - 5-[5-[(3-Methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-yliden)methyl]-2-furyl]-1H-isoindol-1,3(2H)-dion;
- 45
- N-(2,5-Dimethylphenyl)-3-(4-methoxyphenyl)acrylamid;
 - 2-({2-[(4-Nitrophenyl)amino]ethyl}amino)ethanol;
 - N-(3-Methoxyphenyl)-4-propoxybenzamid;
 - 2-(4-Hydroxyphenyl)-3-phenyl-2,3-dihydro-4(1H)-chinazolinon;
 - 4-Methyl-1-(2-nitrobenzoyl)piperidin;
- 50
- 2-Hydroxy-N'-[(2-methylphenyl)sulfonyl]benzohydrazid;
 - 4-(1,3-Benzothiazol-2-yl)buttersäure;
 - 4-(3-Methylbenzyliden)-1-phenyl-3,5-pyrazolidindion;
 - 4-(2,4-Dichlorophenoxy)-N-(2-ethoxyphenyl)butanamid;
 - N-(2-Methoxyphenyl)-N'-(phenylsulfonyl)benzolcarboximidamid;
- 55
- N-[2-(2-Chloro-5-iodophenyl)-1,3-benzoxazol-5-yl]-2-methylpropanamid;
 - 5-(4-Butoxyphenyl)-3-cyclohexyl-1,2,4-oxadiazol;
 - N-(3,4-Dichlorophenyl)-N'-4H-1,2,4-triazol-4-yl-harnstoff;
 - 6-Chloro-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-chinolinon;

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- 6-Bromo-4-phenyl-3-[3-(3,4,5-trimethoxyphenyl)acryloyl]-2(1H)-chinolinon; und
- N-(1H-1,2,3-Benzotriazol-1-ylmethyl)-4-nitro-1,2,5-oxadiazol-3-amin zur Verwendung bei der Behandlung und/oder Prävention von Knochenschwunderkrankungen in einem behandlungsbedürftigen Subjekt.

5 2. Pharmazeutische Zusammensetzung, umfassend mindestens eine Verbindung, ausgewählt aus der Gruppe bestehend aus:

- 2,2,2-Trichloro-N-(1,1-dioxido-2,3-dihydro-3-thienyl)-N-(4-methylphenyl)acetamid;
- 4-[5-(4-Bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobuttersäure;
- 10 - 3-(3-Chlorophenyl)-7-methyl-4-methylen-3,4-dihydro-2(1H)-chinazolinon;
- 3-[4-(3-Bromobenzyliden)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoesäure;
- N-2,1,3-Benzothiadiazol-4-yl-5-bromo-2-furamid;
- 1-Acetyl-4-(2-chloro-4-nitrophenyl)-2-methylpiperazin;
- 3-(3-Methoxybenzyliden)-5-(4-methylphenyl)-2(3H)-furanon;
- 15 - 3-[5-(3,4-Dichlorophenyl)-2-furyl]acrylsäure;
- (2-Chloro-4-[[5-(2-chlorophenyl)-6-(ethoxycarbonyl)-7-methyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-yliden]methyl]-6-methoxyphenoxy)essigsäure;
- 4-[[4-(Diphenylmethyl)-1-piperazinyl]sulfonyl]-2,1,3-benzothiadiazol;
- 4-[4-Phenyl-5-(2-thienyl)-1H-imidazol-2-yl]-1,2-benzoldiol;
- 20 - N-(3,4-Dimethoxyphenyl)-4-[methyl(phenylsulfonyl)amino]benzamid;
- 1-[[2-Hydroxyphenyl]carbonothioyl]-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol;
- 2-Methoxyethyl-4-[[4-tert-butylbenzoyl]amino]benzoat;
- N-(2,3-Dichlorophenyl)-3-(5-methyl-2-furyl)acrylamid;
- N-(4-Fluorophenyl)-3-[3-(trifluoromethyl)phenyl]acrylamid;
- 25 - 3-(2-Furylmethyl)-2-(2-hydroxyphenyl)-2,3-dihydro-4(1H)-chinazolinon;
- N-(4-Ethoxyphenyl)-2-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio]acetamid;
- 5-(4-Nitrobenzyliden)-2-thio-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-on;
- (3,5-Dichlorophenyl)[(phenylsulfonyl)carbonyl]amin;
- N-(2-Bromophenyl)-3-(5-methyl-2-furyl)acrylamid;
- 30 - 2-(2-Chlorophenoxy)-N-[2-chloro-5-(trifluoromethyl)phenyl]acetamid;
- N-[4-(4-Acetyl-1-piperazinyl)phenyl]propanamid;
- 8-[(Dimethylamino)methyl]-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-on;
- 4-tert-Butyl-N-[1-[[[2-methoxyphenyl]amino]carbonyl]-2-(2-thienyl)viny]benzamid;
- 2-Chloro-N-(3-chloro-4-methoxyphenyl)benzamid;
- 35 - 2,6-di-tert-Butyl-4-(2,3-dihydro-1H-perimidin-2-yl)phenol;
- 3-Benzyl-2-(2,6-dichlorophenyl)-2,3-dihydro-4(1H)-chinazolinon;
- 1-(3,4-Dichlorobenzyl)-1H-indol-3-carbaldehyd;
- N-[5-(1-Adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phenylharnstoff;
- N-(3,4-Dichlorophenyl)-N'-{5-[(4-methylphenoxy)methyl]-1,3,4-thiadiazol-2-yl}harnstoff;
- 40 - N-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-(1-naphthyloxy)acetamid;
- N-[4-(4-Acetyl-1-piperazinyl)phenyl]-4-ethoxy-3-nitrobenzamid;
- N-(2-Chlorophenyl)-3-(4-fluorophenyl)acrylamid;
- 1-[(Dimethyl-lambda-4-sulfanylidene)amino]-2-methoxy-4-nitrobenzol;
- 5-Benzyliden-1-(2-chlorophenyl)-2,4,6(1H,3H,5H)-pyrimidintrion;
- 45 - 4-Ethyl-5,6-dimethyl-2-phenylpyrimidin;
- 2-(3-Chlorobenzyliden)-1H-inden-1,3(2H)-dion;
- 5-[5-[(3-Methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-yliden)methyl]-2-furyl]-1H-isoindol-1,3(2H)-dion;
- N-(2,5-Dimethylphenyl)-3-(4-methoxyphenyl)acrylamid;
- 2-({2-[(4-Nitrophenyl)amino]ethyl}amino)ethanol;
- 50 - N-(3-Methoxyphenyl)-4-propoxybenzamid;
- 2-(4-Hydroxyphenyl)-3-phenyl-2,3-dihydro-4(1H)-chinazolinon;
- 4-Methyl-1-(2-nitrobenzoyl)piperidin;
- 2-Hydroxy-N'-[(2-methylphenyl)sulfonyl]benzohydrazid;
- 4-(1,3-Benzothiazol-2-yl)buttersäure;
- 55 - 4-(3-Methylbenzyliden)-1-phenyl-3,5-pyrazolidindion;
- 4-(2,4-Dichlorophenoxy)-N-(2-ethoxyphenyl)butanamid;
- N-(2-methoxyphenyl)-N'-(phenylsulfonyl)benzolcarboximidamid;
- N-[2-(2-Chloro-5-iodophenyl)-1,3-benzoxazol-5-yl]-2-methylpropanamid;

- 5-(4-Butoxyphényl)-3-cyclohexyl-1,2,4-oxadiazol;
 - N-(3,4-Dichlorophényl)-N'-4H-1,2,4-triazol-4-yl-harnstoff;
 - 6-Chloro-4-phényl-3-[3-(3,4,5-triméthoxyphényl)acryloyl]-2(1H)-chinolinon;
 - 6-Bromo-4-phényl-3-[3-(3,4,5-triméthoxyphényl)acryloyl]-2(1H)-chinolinon; und
 - N-(1H-1,2,3-Benzotriazol-1-ylmethyl)-4-nitro-1,2,5-oxadiazol-3-amin und
- wahlweise einem pharmazeutisch akzeptablem Träger zur Verwendung bei der Behandlung und/oder Prävention von Knochenschwunderkrankungen in einem behandlungsbedürftigen Subjekt.

3. Verbindung oder Zusammensetzung zur Verwendung nach einem der Ansprüche 1 oder 2, wobei die Knochenschwunderkrankung ausgewählt ist aus der Gruppe bestehend aus: Osteoporose, Osteopenie aufgrund von Knochenmetastasen, periartikuläre Erosionen in rheumatoider Arthritis, primären Hyperparathyreoidismus, maligner Hyperkalzämie, Paget-Knochenerkrankung, periodontaler Erkrankung, immobilisierungsinduzierter Osteopenie und Glucocorticoidbehandlung.

4. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 3, wobei die Knochenschwunderkrankung Osteoporose ist.

5. Verbindung oder Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei die Verbindung in einer Konzentration von zwischen 5 und 200 μ M verabreicht wird.

6. Verbindung oder Zusammensetzung zur Verwendung nach Anspruch 5, wobei die Verbindung in einer Konzentration von zwischen 10 und 100 μ M verabreicht wird.

Revendications

1. Composé sélectionné dans le groupe consistant en :

- 2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thiényl)-N-(4-méthylphényl)acétamide ;
- acide 4-[5-(4-bromophényl)-3-(4-nitrophényl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxo-butanoïque ;
- 3-(3-chlorophényl)-7-méthyl-4-méthylène-3,4-dihydro-2(1H)-quinazolinone ;
- acide 3-[4-(3-bromobenzylidène)-3-méthyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoïque ;
- N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-furamide ;
- 1-acétyl-4-(2-chloro-4-nitrophényl)-2-méthylpipérazine ;
- 3-(3-méthoxybenzylidène)-5-(4-méthylphényl)-2(3H)-furanone ;
- acide 3-[5-(3,4-dichlorophényl)-2-furyl]acrylique ;
- acide (2-chloro-4-[[5-(2-chlorophényl)-6-(éthoxycarbonyl)-7-méthyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-ylidène]méthyl]-6-méthoxyphénoxy)acétique ;
- 4-[[4-(diphénylméthyl)-1-pipérazinyl]sulfonyl]-2,1,3-benzothiadiazole ;
- 4-[4-phényl-5-(2-thiényl)-1H-imidazol-2-yl]-1,2-benzènediol ;
- N-(3,4-diméthoxyphényl)-4-[méthyl(phénylsulfonyl)amino]benzamide ;
- 1-[(2-hydroxyphényl)carbonothioyl]-3-phényl-5-(trifluorométhyl)-4,5-dihydro-1H-pyrazol-5-ol ;
- 2-méthoxyéthyl 4-[(4-tert-butylbenzoyl)amino]benzoate ;
- N-(2,3-dichlorophényl)-3-(5-méthyl-2-furyl)acrylamide ;
- N-(4-fluorophényl)-3-[3-(trifluorométhyl)phényl]acrylamide ;
- 3-(2-furylméthyl)-2-(2-hydroxyphényl)-2,3-dihydro-4(1H)-quinazolinone ;
- N-(4-éthoxyphényl)-2-[[5-(4-méthoxyphényl)-1,3,4-oxadiazol-2-yl]thio]acétamide ;
- 5-(4-nitrobenzylidène)-2-thioxo-3-[3-(trifluorométhyl)phényl]-1,3-thiazolidin-4-one ;
- (3,5-dichlorophényl)[(phénylsulfonyl)carbonyl]amine ;
- N-(2-bromophényl)-3-(5-méthyl-2-furyl)acrylamide ;
- 2-(2-chlorophénoxy)-N-[2-chloro-5-(trifluorométhyl)phényl]acétamide ;
- N-[4-(4-acétyl-1-pipérazinyl)phényl]propanamide ;
- 8-[(diméthylamino)méthyl]-9-hydroxy-2-méthyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
- 4-tert-butyl-N-[1-[[2-méthoxyphényl]amino]carbonyl]-2-(2-thiényl)viny]benzamide ;
- 2-chloro-N-(3-chloro-4-méthoxyphényl)benzamide ;
- 2,6-di-tert-butyl-4-(2,3-dihydro-1H-périmidin-2-yl)phénol ;
- 3-benzyl-2-(2,6-dichlorophényl)-2,3-dihydro-4(1H)-quinazolinone ;
- 1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldéhyde ;

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- N-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phénylurée ;
- N-(3,4-dichlorophényl)-N'-{5-[(4-méthylphénoxy)méthyl]-1,3,4-thiadiazol-2-yl}urée ;
- N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphtyloxy)acétamide ;
- N-[4-(4-acétyl-1-pipérazinyl)phényl]-4-éthoxy-3-nitrobenzamide ;
- N-(2-chlorophényl)-3-(4-fluorophényl)acrylamide ;
- 1-[(diméthyl-lambda-4-sulfanylidène)amino]-2-méthoxy-4-nitrobenzène ;
- 5-benzylidène-1-(2-chlorophényl)-2,4,6(1H,3H,5H)-pyrimidinetrione ;
- 4-éthyl-5,6-diméthyl-2-phénylpyrimidine ;
- 2-(3-chlorobenzylidène)-1H-indène-1,3(2H)-dione ;
- 5-{5-[(3-méthyl-5-oxo-1-phényl-1,5-dihydro-4H-pyrazol-4-ylidène)méthyl]-2-furyl}-1H-isoindole-1,3(2H)-dione ;
- N-(2,5-diméthylphényl)-3-(4-méthoxyphényl)acrylamide ;
- 2-({2-[(4-nitrophényl)amino]éthyl}amino)éthanol ;
- N-(3-méthoxyphényl)-4-propoxybenzamide ;
- 2-(4-hydroxyphényl)-3-phényl-2,3-dihydro-4(1H)-quinazolinone ;
- 4-méthyl-1-(2-nitrobenzoyl)pipéridine ;
- 2-hydroxy-N'-[(2-méthylphényl)sulfonyl]benzohydrazide ;
- acide 4-(1,3-benzothiazol-2-yl)butanoïque ;
- 4-(3-méthylbenzylidène)-1-phényl-3,5-pyrazolidinedione ;
- 4-(2,4-dichlorophénoxy)-N-(2-éthoxyphényl)butanamide ;
- N-(2-méthoxyphényl)-N'-(phénylsulfonyl)benzèncarboximidamide ;
- N-[2-(2-chloro-5-iodophényl)-1,3-benzoxazol-5-yl]-2-méthylpropanamide ;
- 5-(4-butoxyphényl)-3-cyclohexyl-1,2,4-oxadiazole ;
- N-(3,4-dichlorophényl)-N'-4H-1,2,4-triazol-4-yl urée ;
- 6-chloro-4-phényl-3-[3-(3,4,5-triméthoxyphényl)acryloyl]-2(1H)-quinolinone ;
- 6-bromo-4-phényl-3-[3-(3,4,5-triméthoxyphényl)acryloyl]-2(1H)-quinolinone ; et
- N-(1H-1,2,3-benzotriazol-1-ylméthyl)-4-nitro-1,2,5-oxadiazol-3-amine pour son utilisation dans le traitement et/ou la prévention de maladies de perte osseuse chez un sujet le nécessitant.

2. Composition pharmaceutique comprenant au moins un composé sélectionné dans le groupe consistant en :

- 2,2,2-trichloro-N-(1,1-dioxido-2,3-dihydro-3-thiényl)-N-(4-méthylphényl)acétamide ;
- acide 4-[5-(4-bromophényl)-3-(4-nitrophényl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxo-butanoïque ;
- 3-(3-chlorophényl)-7-méthyl-4-méthylène-3,4-dihydro-2(1H)-quinazolinone ;
- acide 3-[4-(3-bromobenzylidène)-3-méthyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]benzoïque ;
- N-2,1,3-benzothiadiazol-4-yl-5-bromo-2-furamide ;
- 1-acétyl-4-(2-chloro-4-nitrophényl)-2-méthylpipérazine ;
- 3-(3-méthoxybenzylidène)-5-(4-méthylphényl)-2(3H)-furanone ;
- acide 3-[5-(3,4-dichlorophényl)-2-furyl]acrylique ;
- acide (2-chloro-4-[[5-(2-chlorophényl)-6-(éthoxycarbonyl)-7-méthyl-3-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-2(3H)-ylidène]méthyl]-6-méthoxyphénoxy)acétique ;
- 4-[[4-(diphénylméthyl)-1-pipérazinyl]sulfonyl]-2,1,3-benzothiadiazole ;
- 4-[4-phényl-5-(2-thiényl)-1H-imidazol-2-yl]-1,2-benzènediol ;
- N-(3,4-diméthoxyphényl)-4-[méthyl(phénylsulfonyl)amino]benzamide ;
- 1-[(2-hydroxyphényl)carbonothioyl]-3-phényl-5-(trifluorométhyl)-4,5-dihydro-1H-pyrazol-5-ol ;
- 2-méthoxyéthyl 4-[(4-tert-butylbenzoyl)amino]benzoate ;
- N-(2,3-dichlorophényl)-3-(5-méthyl-2-furyl)acrylamide ;
- N-(4-fluorophényl)-3-[3-(trifluorométhyl)phényl]acrylamide ;
- 3-(2-furylméthyl)-2-(2-hydroxyphényl)-2,3-dihydro-4(1H)-quinazolinone ;
- N-(4-éthoxyphényl)-2-[[5-(4-méthoxyphényl)-1,3,4-oxadiazol-2-yl]thio]acétamide ;
- 5-(4-nitrobenzylidène)-2-thioxo-3-[3-(trifluorométhyl)phényl]-1,3-thiazolidin-4-one ;
- (3,5-dichlorophényl)[(phénylsulfonyl)carbonyl]amine ;
- N-(2-bromophényl)-3-(5-méthyl-2-furyl)acrylamide ;
- 2-(2-chlorophénoxy)-N-[2-chloro-5-(trifluorométhyl)phényl]acétamide ;
- N-[4-(4-acétyl-1-pipérazinyl)phényl]propanamide ;
- 8-[(diméthylamino)méthyl]-9-hydroxy-2-méthyl-4H-pyrido[1,2-a]pyrimidin-4-one ;
- 4-tert-butyl-N-[1-[[2-méthoxyphényl]amino]carbonyl]-2-(2-thiényl)viny]benzamide ;
- 2-chloro-N-(3-chloro-4-méthoxyphényl)benzamide ;

- 2,6-di-tert-butyl-4-(2,3-dihydro-1H-périmidin-2-yl)phénol ;
 - 3-benzyl-2-(2,6-dichlorophényl)-2,3-dihydro-4(1H)-quinazolinone ;
 - 1-(3,4-dichlorobenzyl)-1H-indole-3-carbaldéhyde ;
 - N-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-N'-phénylurée ;
 - N-(3,4-dichlorophényl)-N'-[5-[(4-méthylphénoxy)méthyl]-1,3,4-thiadiazol-2-yl]urée ;
 - N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(1-naphtyloxy)acétamide ;
 - N-[4-(4-acétyl-1-pipérazinyl)phényl]-4-éthoxy-3-nitrobenzamide ;
 - N-(2-chlorophényl)-3-(4-fluorophényl)acrylamide ;
 - 1-[[diméthyl-lambda-4-sulfanylidène]amino]-2-méthoxy-4-nitrobenzène ;
 - 5-benzylidène-1-(2-chlorophényl)-2,4,6(1H,3H,5H)-pyrimidinetrione ;
 - 4-éthyl-5,6-diméthyl-2-phénylpyrimidine ;
 - 2-(3-chlorobenzylidène)-1H-indène-1,3(2H)-dione ;
 - 5-[5-[(3-méthyl-5-oxo-1-phényl-1,5-dihydro-4H-pyrazol-4-ylidène)méthyl]-2-furyl]-1H-isoindole-1,3(2H)-dione ;
 - N-(2,5-diméthylphényl)-3-(4-méthoxyphényl)acrylamide ;
 - 2-({2-[(4-nitrophényl)amino]éthyl}amino)éthanol ;
 - N-(3-méthoxyphényl)-4-propoxybenzamide ;
 - 2-(4-hydroxyphényl)-3-phényl-2,3-dihydro-4(1H)-quinazolinone ;
 - 4-méthyl-1-(2-nitrobenzoyl)pipéridine ;
 - 2-hydroxy-N'-[(2-méthylphényl)sulfonyl]benzohydrazide ;
 - acide 4-(1,3-benzothiazol-2-yl)butanoïque ;
 - 4-(3-méthylbenzylidène)-1-phényl-3,5-pyrazolidinedione ;
 - 4-(2,4-dichlorophénoxy)-N-(2-éthoxyphényl)butanamide ;
 - N-(2-méthoxyphényl)-N'-(phénylsulfonyl)benzèncarboximidamide ;
 - N-[2-(2-chloro-5-iodophényl)-1,3-benzoxazol-5-yl]-2-méthylpropanamide ;
 - 5-(4-butoxyphényl)-3-cyclohexyl-1,2,4-oxadiazole ;
 - N-(3,4-dichlorophényl)-N'-4H-1,2,4-triazol-4-yl urée ;
 - 6-chloro-4-phényl-3-[3-(3,4,5-triméthoxyphényl)acryloyl]-2(1H)-quinolinone ;
 - 6-bromo-4-phényl-3-[3-(3,4,5-triméthoxyphényl)acryloyl]-2(1H)-quinolinone ; et
 - N-(1H-1,2,3-benzotriazol-1-ylméthyl)-4-nitro-1,2,5-oxadiazol-3-amine, et,
- facultativement, un support pharmaceutiquement acceptable pour son utilisation dans le traitement et/ou la prévention de maladies de perte osseuse chez un sujet le nécessitant.

3. Composé ou composition pour leur utilisation selon l'une quelconque des revendications 1 et 2, dans lesquels la maladie de perte osseuse est sélectionnée dans le groupe consistant en : l'ostéoporose, l'ostéopénie due aux métastases osseuses, les érosions péri-articulaires dans la polyarthrite rhumatoïde, l'hyperparathyroïdie primaire, l'hypercalcémie maligne, la maladie de Paget des os, une parodontopathie, l'ostéopénie induite par l'immobilisation et un traitement par glucocorticoïdes.
4. Composé ou composition pour leur utilisation selon la revendication 3, dans lesquels la maladie associée à une perte osseuse est l'ostéoporose.
5. Composé ou composition pour leur utilisation selon l'une quelconque des revendications 1 à 4, dans lesquels ledit composé est administré à une concentration comprise entre 5 et 200 µM.
6. Composé ou composition pour leur utilisation selon la revendication 5, dans lesquels ledit composé est administré à une concentration comprise entre 10 et 100 µM.

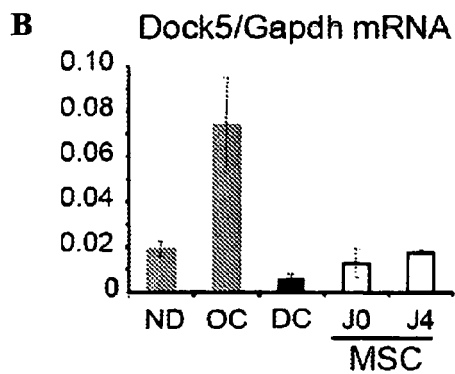
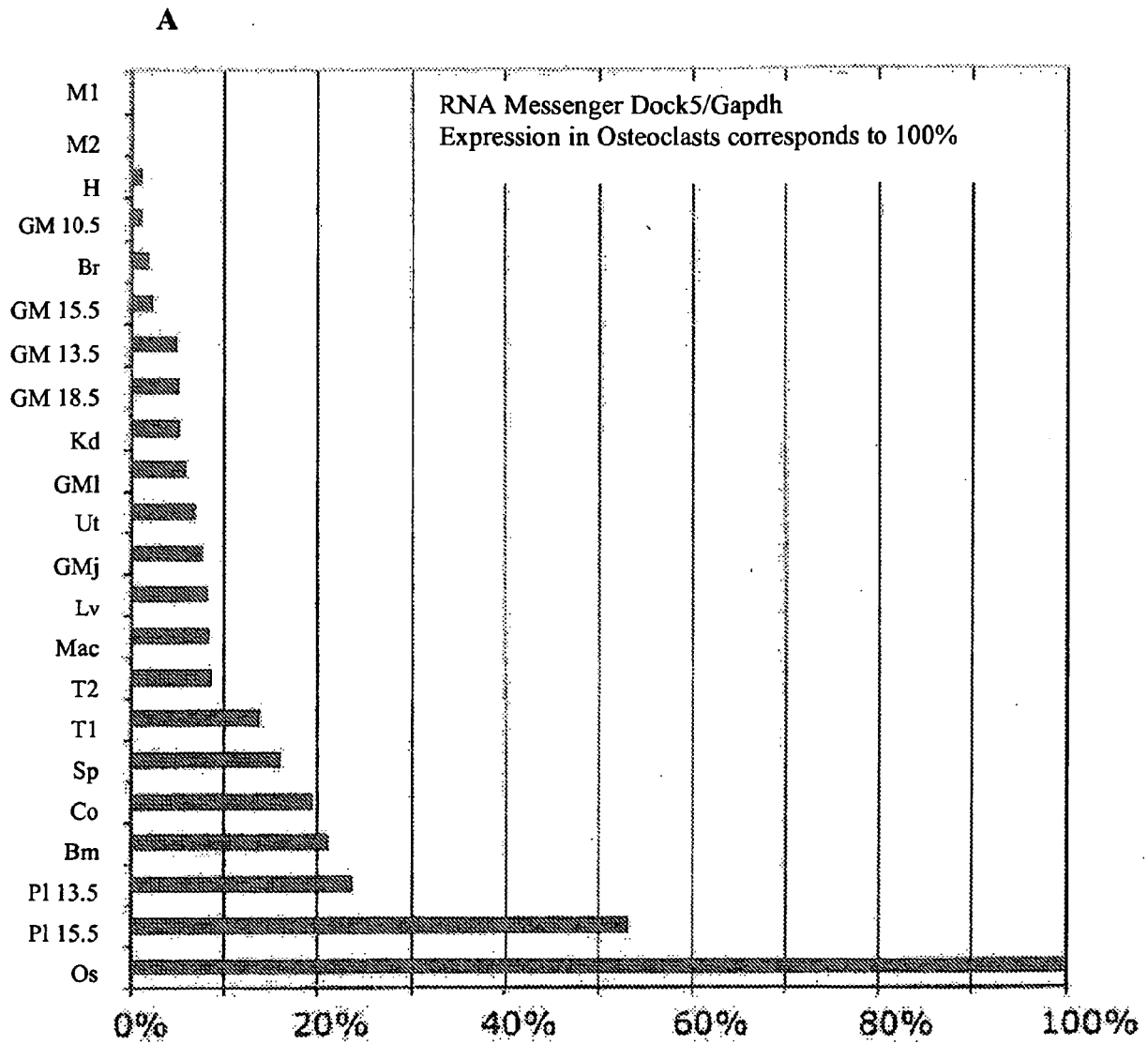


Figure 1

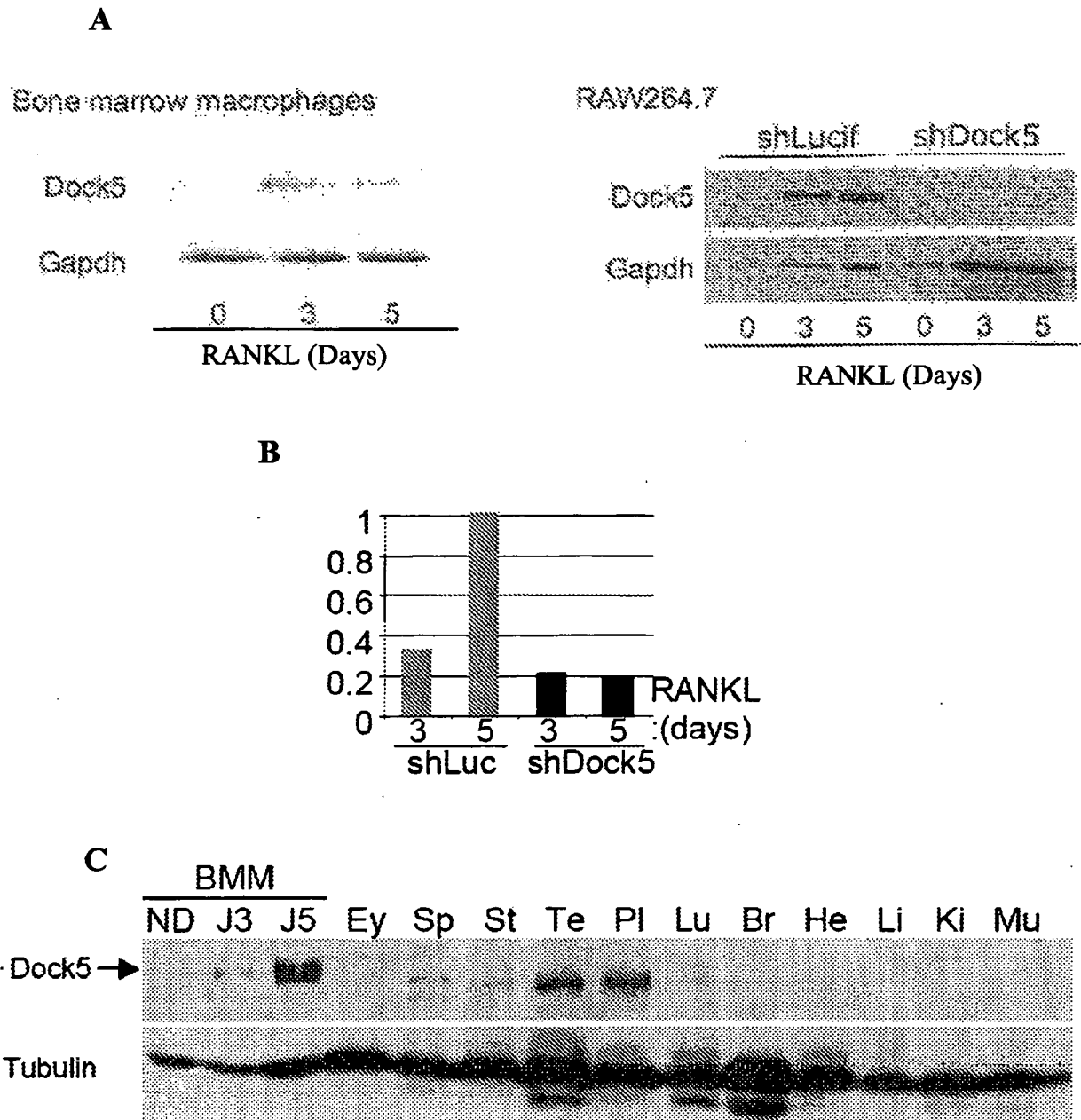


Figure 2

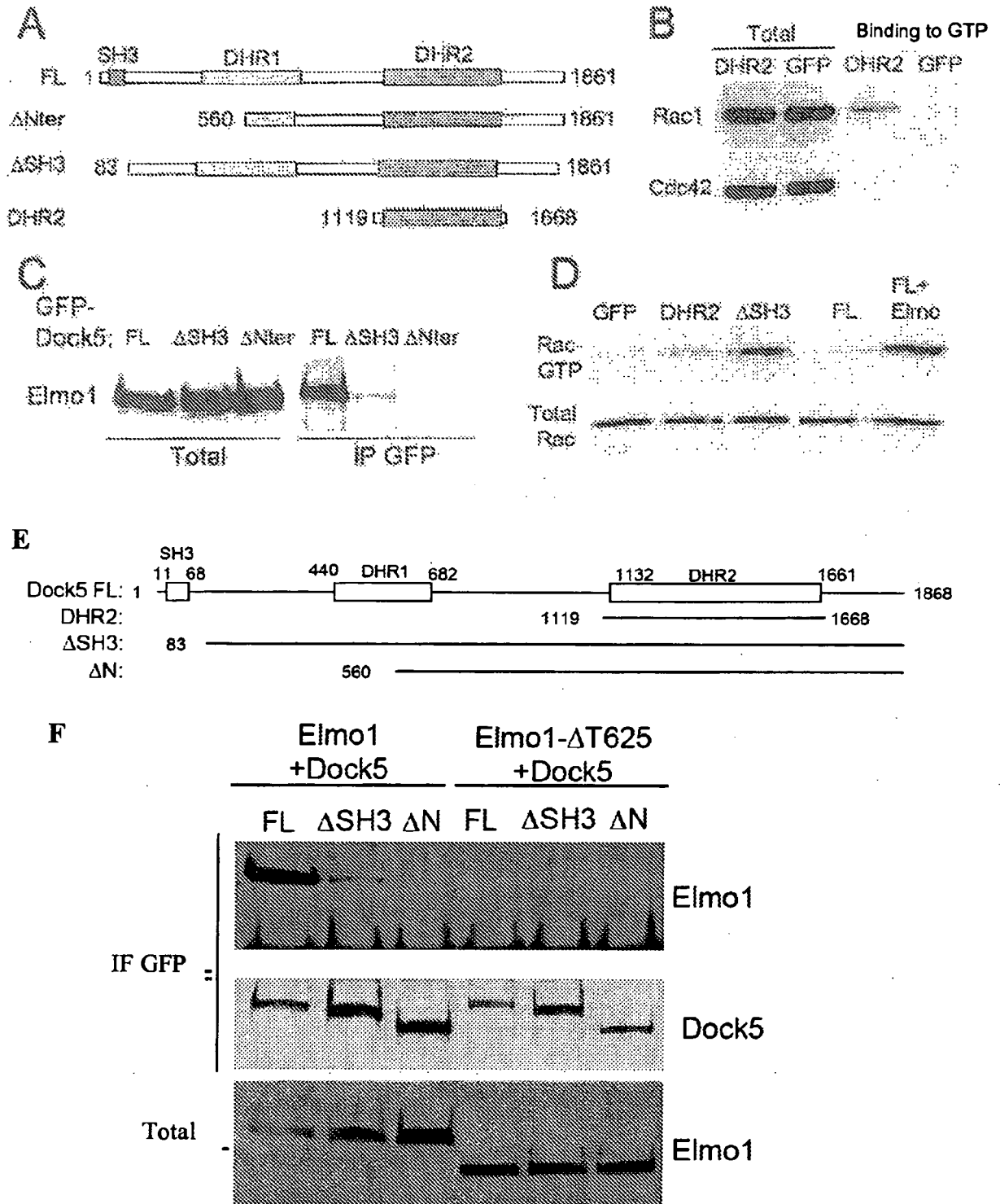
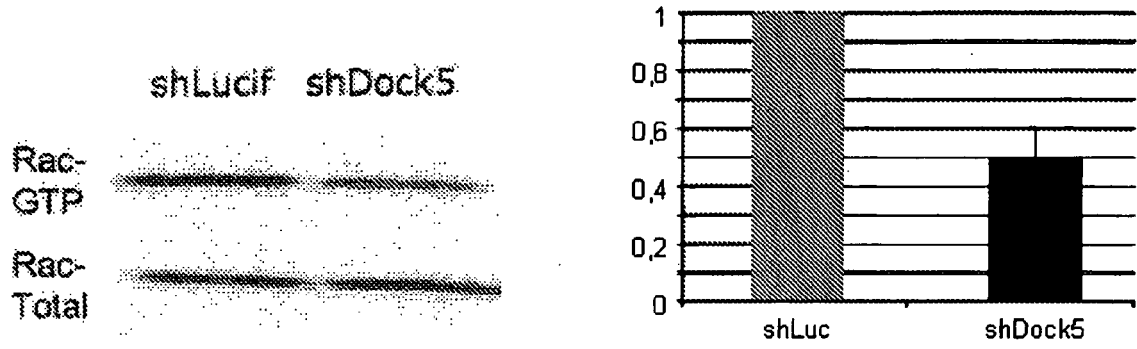


Figure 3

A



B

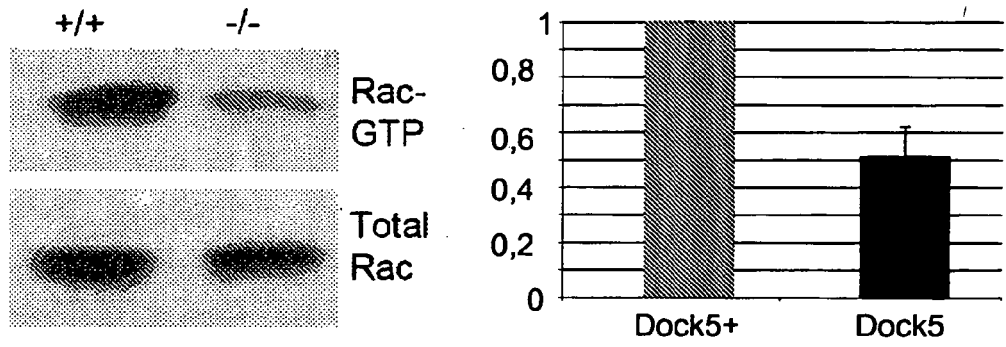


Figure 4

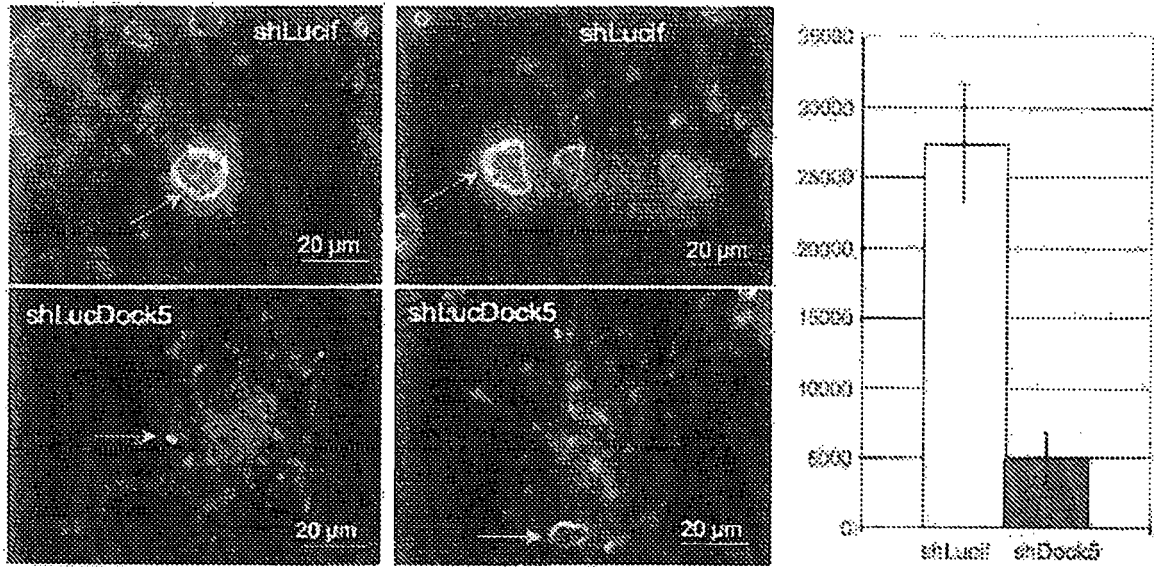


Figure 5

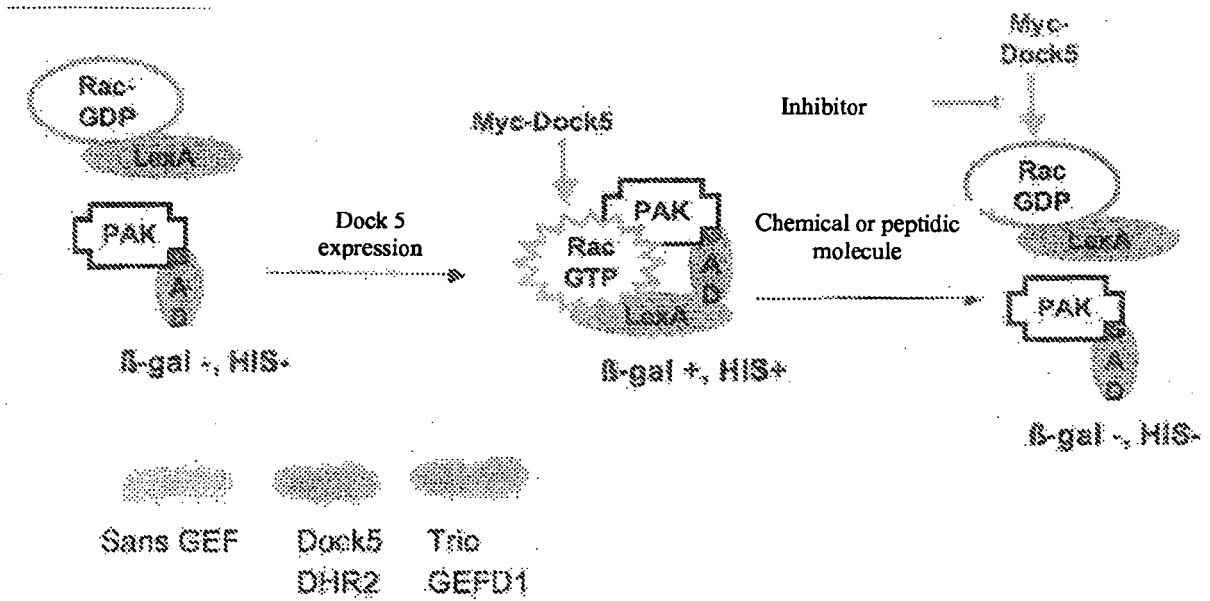
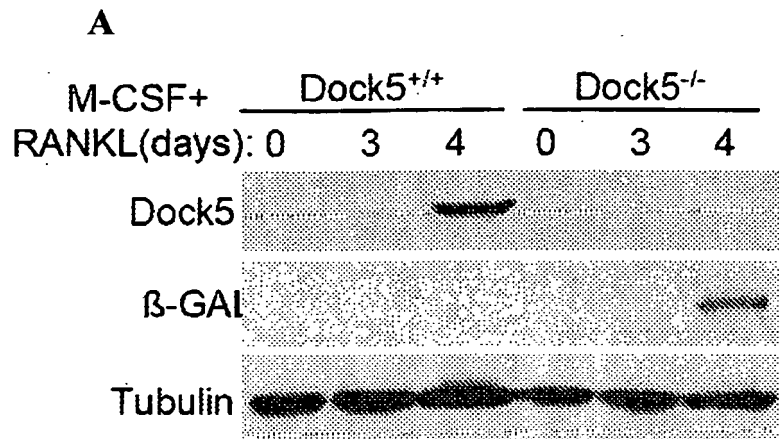
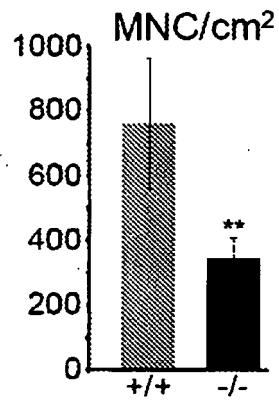


Figure 6



B



C

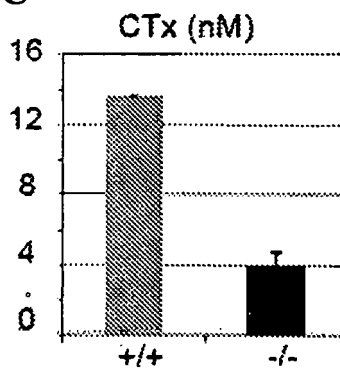
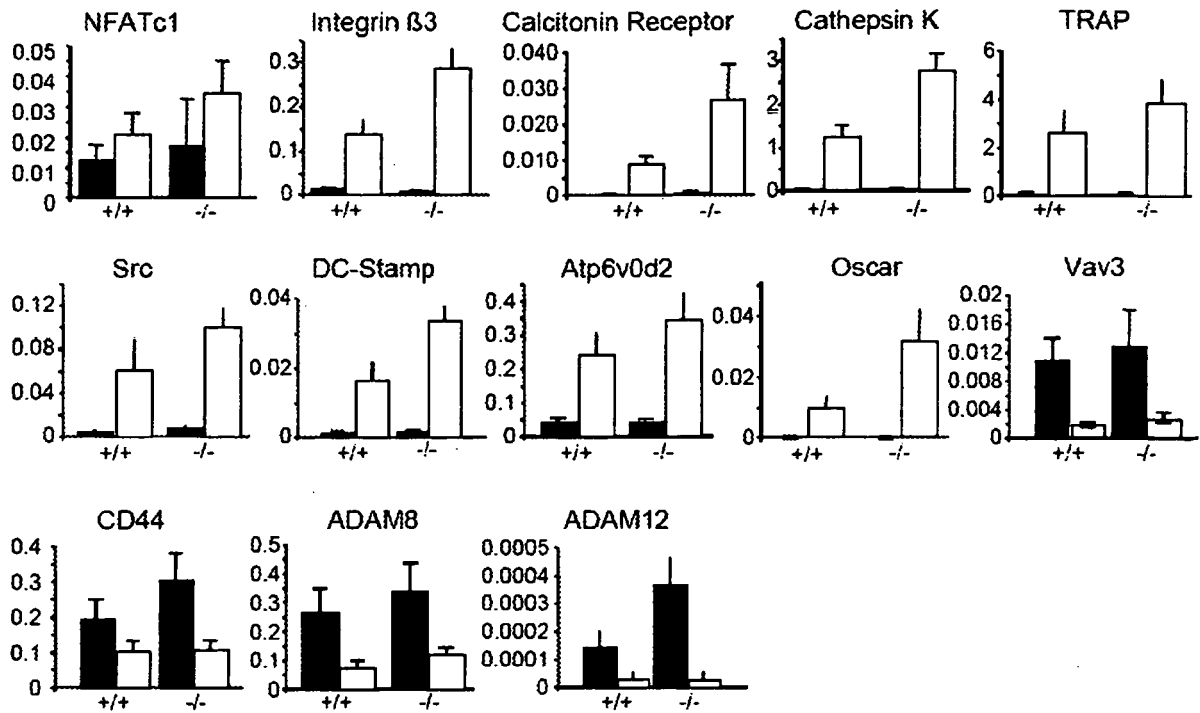
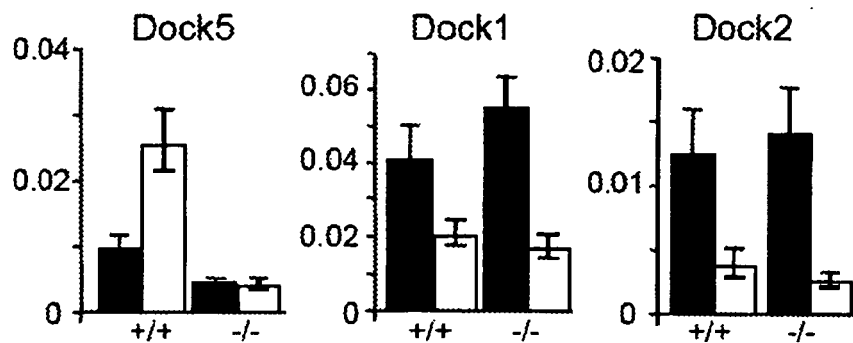


Figure 7

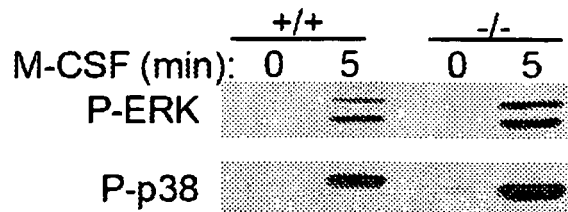
A



B



C



D

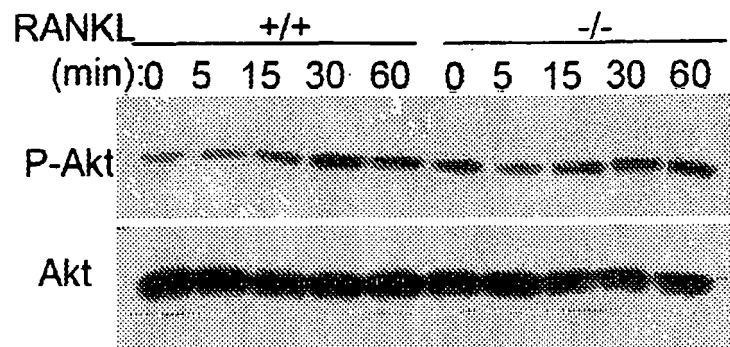


Figure 8

REFERENCES CITED IN THE DESCRIPTION

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