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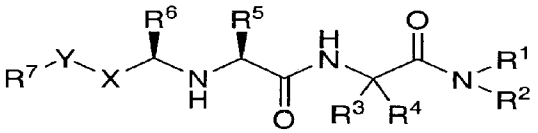
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(54) **Title:** CATHEPSIN CYSTEINE PROTEASE INHIBITORS



(I)

(57) **Abstract:** This invention relates to a novel class of compounds, represented by the formula (I) below, wherein the meanings of Rl, R2, R3, R4, R5, R6, R7, X and Y are indicated therein, which are cysteine protease inhibitors, including but not limited to, inhibitors of cathepsms K L, S and B These compounds are useful for treating diseases in which inhibition of bone resorption is indicated, such as osteoporosis, osteoarthritis and rheumatoid arthritis

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TITLE OF THE INVENTION

CATHEPSIN CYSTEINE PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, hypercalcemia of malignancy or multiple myeloma. One of the most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are a major cause of morbidity and mortality in the elderly population. As many as 50% of women and a third of men will experience an osteoporotic fracture. A large segment of the older population already has low bone density and a high risk of fractures. There is a significant need to both prevent and treat osteoporosis and other conditions associated with bone resorption. Because osteoporosis, as well as other disorders associated with bone loss, are generally chronic conditions, it is believed that appropriate therapy will typically require chronic treatment.

Cathepsins belong to the papain superfamily of cysteine proteases. These proteases function in the normal physiological as well as pathological degradation of connective tissue. Cathepsins play a major role in intracellular protein degradation and turnover and remodeling. To date, a number of cathepsin have been identified and sequenced from a number of sources. These cathepsins are naturally found in a wide variety of tissues. For example, cathepsin B, C, F, H, L, K, O, S, V, W, and Z have been cloned. Cathepsin L is implicated in normal lysosomal proteolysis as well as several diseases states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease, atherosclerosis, chronic obstructive pulmonary disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts. Increased Cathepsin B levels and redistribution of the enzyme are found in tumors, suggesting a role in tumor invasion and metastasis. In addition, aberrant Cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystisis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

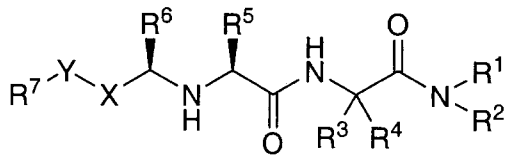
Mammalian cathepsins are related to the papain-like cysteine proteases expressed by disease-causing parasites including those from the families protozoa, platyhelminthes, nematodes and arthropodes. These cysteine proteases play an essential role in the life cycle of these organisms.

Human type I collagen, the major collagen in bone is a good substrate for cathepsin K. *See* Kafienah, W., *et al.*, 1998, *Biochem J* 331:727-732, which is hereby incorporated by reference in its entirety. *In vitro* experiments using antisense oligonucleotides to cathepsin K, have shown diminished bone resorption *in vitro*, which is probably due to a reduction in translation of cathepsin K mRNA. *See* Inui, T., *et al.*, 1997, *J Biol Chem* 272:8109-8112, which is hereby incorporated by reference in its entirety. The crystal structure of cathepsin K has been resolved. *See* McGrath, M. E., *et al.*, 1997, *Nat Struct Biol* 4:105-109; Zhao, B., *et al.*, 1997, *Nat Struct Biol* 4: 109-11, which are hereby incorporated by reference in their entirety. Also, selective peptide based inhibitors of cathepsin K have been developed *See* Bromme, D., *et al.*, 1996, *Biochem J* 315:85-89; Thompson, S. K., *et al.*, 1997, *Proc Natl Acad Sci U S A* 94:14249-14254, which are hereby incorporated by reference in their entirety. Accordingly, inhibitors of Cathepsin K can reduce bone resorption. Such inhibitors would be useful in treating disorders involving bone resorption, such as osteoporosis.

What is needed in the art are therapeutic agents to treat diseases associated with Cathepsin K activity including osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease and cancer including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma.

SUMMARY OF THE INVENTION

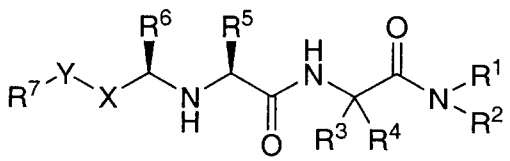
The present invention relates to compounds that are capable of treating and preventing cathepsin dependent conditions or disease states in a mammal in need thereof. One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts, stereoisomers and N-oxide derivatives thereof:



I.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention relates to compounds of the formula



wherein X is aryl or heteroaryl;

Y is aryl or heteroaryl;

R^1 is hydrogen, C_{1-6} alkyl or $O(C_{1-6}$ alkyl), which is optionally substituted with aryl or one to three halo;

R^2 is hydrogen, C_{1-6} alkyl or $O(C_{1-6}$ alkyl), which is optionally substituted with aryl or one to three halo;

R^3 is hydrogen, C_{1-6} alkyl, $(C_{1-6}$ alkyl$)SO_mR^8$, $(C_{1-6}$ alkyl$)R^8$ or $(C_{1-6}$ alkyl$)(C=O)O(C_{1-6}$ alkyl$)R^8$;

R^4 is hydrogen, C_{1-6} alkyl, $(C_{1-6}$ alkyl$)SO_mR^8$, $(C_{1-6}$ alkyl$)R^8$ or $(C_{1-6}$ alkyl$)(C=O)O(C_{1-6}$ alkyl$)R^8$;

or R^1 and R^4 can be taken together with the atoms to which they are attached and are between them to form a C_{3-8} heterocyclyl ring wherein said ring is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, $SO_m(C_{1-6}$ alkyl), SO_m(aryl) or halo;

R^5 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein said alkyl and cycloalkyl groups are optionally substituted with C_{1-6} alkyl or halo;

R^6 is C_{1-6} haloalkyl, aryl or heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted on either the carbon or heteroatom with one to three halo;

R^7 is $SO_m(C_{1-6}$ alkyl), C_{1-6} alkyl or halo;

R^8 is hydrogen, C_{1-6} alkyl or aryl;

each m is independently an integer from zero to two;

or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

In an embodiment of the invention, or X is aryl. In a further embodiment of the invention, X is phenyl.

In an embodiment of the invention, or Y is aryl. In a further embodiment of the invention, Y is phenyl.

In an embodiment of the invention, or R^1 is hydrogen.

In an embodiment of the invention, or R^2 is hydrogen.

In an embodiment of the invention, R^3 is $(C_{1-6}$ alkyl$)SO_mR^8$ or $(C_{1-6}$ alkyl$)R^8$.

In an embodiment of the invention, R^4 is hydrogen.

In an embodiment of the invention R^5 is C_{1-6} alkyl.

Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise.

Specific embodiments of the present invention include, but are not limited to:

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-alaninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucylglycinamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-methioninamide;

N^1-[(1*S*)-1-(aminocarbonyl)-3-(methylsulfonyl)propyl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-[(1*S*)-1-(aminocarbonyl)-3-phenylpropyl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-methyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1,N^1-dimethyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-methoxy-N^1-methyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-(2,2,2-trifluoroethyl)-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-benzyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-phenylalaninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-D-phenylalaninamide;

benzyl *N*-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-α-asparaginate;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-*S*-methyl-L-cysteinamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-3-(methylsulfonyl)-L-alaninamide;

N^1-(2-oxoazetidin-3-yl)-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-[2-oxo-1-(phenylsulfonyl)pyrrolidin-3-yl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-(2-oxopyrrolidin-3-yl)-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-[(3*S*)-2,5-dioxopyrrolidin-3-yl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-(1,1-dioxido-3-oxoisothiazolidin-4-yl)-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-[(3*S*)-1-(methylsulfonyl)-2-oxopyrrolidin-3-yl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-(methylsulfonyl)-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-(phenylsulfonyl)-L-methioninamide;

or a pharmaceutically acceptable salt, stereoisomers or N-oxide derivatives thereof.

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable

carrier. The invention is also contemplated to encompass a pharmaceutical composition which is comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application. These and other aspects of the invention will be apparent from the teachings contained herein.

Utilities

The compounds of the present invention are inhibitors of cathepsins and are therefore useful to treat or prevent cathepsin dependent diseases or conditions in mammals, preferably humans. Specifically, the compounds of the present invention are inhibitors of Cathepsin K and are therefore useful to treat or prevent Cathepsin K dependent diseases or conditions in mammals, preferably humans.

The compounds of the present invention have advantages over structurally similar compounds known in the art in that they have a marked improved selectivity over the other cathepsins. Specifically, the compounds of the instant invention have selectivity greater than 100000-fold vs Cathepsin B, up to 55000-fold vs. Cathepsin L and 77000-fold vs. Cathepsin S.

"Cathepsin dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more cathepsins. "Cathepsin K dependent diseases or conditions" refers to pathologic conditions that depend on the activity of Cathepsin K. Diseases associated with Cathepsin K activities include osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease and cancer including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. In treating such conditions with the instantly claimed compounds, the required therapeutic amount will vary according to the specific disease and is readily ascertainable by those skilled in the art. Although both treatment and prevention are contemplated by the scope of the invention, the treatment of these conditions is the preferred use.

An embodiment of the invention is a method of inhibiting cathepsin activity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of treating or preventing cathepsin dependent conditions in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of inhibiting bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. Another embodiment of the invention is a method of reducing bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. A further embodiment of the invention is a method of treating abnormally increased bone turnover and bone fractures, in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the inhibition of bone resorption is known in the literature, see Stroup, G.B., Lark, M.W., Veber, DF., Bhattacharrya, A., Blake, S., Dare, L.C., Erhard, K.F., Hoffman, S.J., James, I.E., Marquis, R.w., Ru, Y., Vasko-Moser, J.A., Smith, B.R., Tomaszek, T. and Gowen, M. Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption in vivo in a nonhuman primate. J. Bone Miner. Res., 16:1739-1746; 2001; and Votta, B.J., Levy, M.A., Badger, A., Dodds, R.A., James, I.E., Thompson, S., Bossard, M.J., Carr, T., Connor, J.R., Tomaszek, T.A., Szewczuk, L., Drake, F.H., Veber, D., and Gowen, M. Peptide aldehyde inhibitors of cathepsin K inhibit bone resorption both *in vivo* and *in vitro*. J. Bone Miner. Res. 12:1396-1406; 1997.

Another embodiment of the invention is a method of treating or preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the above pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the treatment or prevention of osteoporosis, including glucocorticoid induced osteoporosis, is known in the literature, see Saftig, P., Hunziker, E., Wehmeyer, O., Jones, S., Boyde, A., Rommerskirch, W., Moritz, J.D., Schu, P., and Vonfigura, K. Impaired osteoclast bone resorption leads to osteopetrosis in cathepsin K-deficient mice. Proc. Natl. Acad. Sci. USA 95:13453-13458; 1998.

Another embodiment of the invention is a method of treating or preventing periodontal disease or tooth loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the above pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the treatment or prevention of periodontal disease or tooth loss has been discussed in the literature, see Sasaki, T., "Differentiation and functions of osteoclasts and osontoclasts in mineralized tissue resorption," Microsc Res Tech. 2003 Aug 15;61(6):483-95.

Another embodiment of the invention is a method of treating or preventing rheumatoid arthritis or rheumatoid arthritic condition in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that progressive destruction of the periarticular bone is a major cause of joint dysfunction and disability in patients with rheumatoid arthritis (RA), see Goldring SR, "Pathogenesis of bone erosions in rheumatoid arthritis". Curr. Opin. Rheumatol.

2002; 14: 406-10. Analysis of joint tissues from patients with RA have provided evidence that cathepsin K positive osteoclasts are the cell types that mediate the focal bone resorption associated with rheumatoid synovial lesion, see Hou, W-S, Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallese, EM, Goldring, SR, Bromme, D, "Comparison of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", Arthritis Rheumatism 2002; 46: 663-74. In addition, generalized bone loss is a major cause of morbidity associated with severe RA. The frequency of hip and spinal fractures is substantially increased in patients with chronic RA, see Gould A, Sambrook, P, Devlin J et al, "Osteoclastic activation is the principal mechanism leading to secondary osteoporosis in rheumatoid arthritis". J. Rheumatol. 1998; 25: 1282-9. The utility of cathepsin K inhibitors in the treatment or prevention of resorption in subarticular bone and of generalized bone loss represent a rational approach for pharmacological intervention on the progression of rheumatoid arthritis.

Another embodiment of the invention is a method of treating or preventing the progression of osteoarthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that osteoarthritis (OA) is accompanied with well-defined changes in the joints, including erosion of the articular cartilage surface, peri-articular endochondral ossification/ osteophytosis, and subchondral bony sclerosis and cyst formation, see Oettmeier R, Abendroth, K, " Osteoarthritis and bone: osteologic types of osteoarthritis of the hip", Skeletal Radiol. 1989; 18: 165-74. Recently, the potential contribution of subchondral bone sclerosis to the initiation and progression of OA have been suggested. Stiffened subchondral bone as the joint responding to repetitive impulsive loading, is less able to attenuate and distribute forces through the joint, subjecting it to greater mechanical stress across the articular cartilage surface. This in turn accelerates cartilage wear and fibrillate, see Radin, EL and Rose RM, "Role of subchondral bone in the initiation and progression of cartilage damage", Clin. Orthop. 1986; 213: 34-40. Inhibition of excessive subarticular bone resorption by an anti-resorptive agent such as a cathepsin K inhibitor, will lead to inhibition of subchondral bone turnover, thus may have a favorable impact on OA progression.

In addition to the above hypothesis, cathepsin K protein expression was recently identified in synovial fibroblasts, macrophage-like cells, and chondrocytes from synovium and articular cartilage specimens derived from OA patients, see Hou, W-S, Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallese, EM, Goldring, SR, Bromme, D, "Comparison of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", Arthritis Rheumatism 2002; 46: 663-74; and Dodd, RA, Connor, JR, Drake, FH, Gowen, M, "Expression of Cathepsin K messenger RNA in giant cells and their precursors in human osteoarthritic synovial tissues". Arthritis Rheumatism 1999; 42: 1588-93; and Konttinen, YT, Mandelin, J, Li, T-F, Salo, J, Lassus, J et al. "Acidic cysteine endoproteinase cathepsin K in the degeneration of the superficial articular hyaline cartilage in osteoarthritis", Arthritis Rheumatism 2002; 46: 953-60. These recent studies thus implicated the role of cathepsin K in the destruction of collagen type II in the articular cartilage associated with the progression

of osteoarthritis. The utility of cathepsin K inhibitors in the treatment or prevention of osteoarthritis as described in this invention thus comprise of two different mechanisms, one is on the inhibition of osteoclast-driven subchondral bone turnover, and two is on the direct inhibition of collagen type II degeneration in the synovium and cartilage of patients with OA.

Another embodiment of the invention is a method of treating periprosthetic osteolysis, in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. The use of cathepsin K inhibitors for the treatment of periprosthetic osteolysis is discussed in the literature, see, Mandelin, J., et al., "Interface tissue fibroblasts from loose total hip replacement prosthesis produce receptor activator of nuclear factor-kappaB ligand, osteoprotegerin and cathepsin K," J Rheumatol. 2005 Apr; 32(4):713-20.

Another embodiment of the invention is a method of treating bone disease, such as Paget's disease, osteogenesis imperfecta and bone lesions from multiple myeloma, in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. The use of cathepsin K inhibitors for the treatment of Paget's disease, osteogenesis imperfecta and bone lesions from multiple myeloma is discussed in the literature, see, Lipton, A., "New therapeutic agents for the treatment of bone diseases," Expert Opin Biol Ther. 2005 Jun;5(6):817-32.

Another embodiment of the invention is a method of treating cancer in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K is expressed in human breast carcinoma, prostate cancer and chordoma and has matrix degrading capabilities, see Littlewood-Evans AJ, Bilbe G, Bowler WB, Farley D, Wlodarski B, Kokubo T, Inaoka T, Sloane J, Evans DB, Gallagher JA, "The osteoclast-associated protease cathepsin K is expressed in human breast carcinoma." Cancer Res 1997 Dec 1;57(23):5386-90, . Brubaker KD, Vessella RL, True LD, Thomas R, Corey E "Cathepsin K mRNA and protein expression in prostate cancer progression." J Bone Miner Res 2003 18, 222-30, Haeckel C, Krueger S, Kuester D, Ostertag H, Samii M, Buehling F, Broemme D, Czerniak B, Roessner A. "Expression of cathepsin K in chordoma." Hum Pathol 2000 Jul;31(7):834-40.

Another embodiment of the invention is a method of treating atherosclerosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K is expressed in human atheroma and has significant elastase activity, see Sukhova GK, Shi GP, Simon DI, Chapman HA, Libby P. "Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells." J Clin Invest 1998 Aug 102, 576-83.

Another embodiment of the invention is a method of treating obesity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K mRNA is increased in adipose tissue in several mouse models of obesity and also in adipose tissue of obese human males, see Chiellini C, Costa M, Novelli SE, Amri EZ, Benzi L, Bertacca A, Cohen P, Del Prato S, Friedman JM, Maffei M. "Identification of cathepsin K as a novel marker of adiposity in white adipose tissue." J Cell Physiol 2003, 195, 309-21.

Another embodiment of the invention is a method of treating glaucoma in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amound of any of the compounds or any of the pharmaceutical compositions described above. Cathepsin K is highly expressed in the iris, cillary body and retinal pigment epithelium, and as such can be useful in the treatment of glaucoma, see Ortega, J., *et al.*, "Gene Expression of Proteases and Protease Inhibitors in the Human Ciliary Epithelium and ODM-2 cells," Exp. Eye Res (1997) **65**, 289-299; International Publication WO 2004/058238 (Alcon, Inc.).

Another embodiment of the invention is a method of treating chronic obstructive pulmonary disease in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K plays a role in lung fibrosis, see Buhling, F., *et al.*, "Pivotal role of cathepsin K in lung fibrosis," Am J Pathol. 2004 Jun;164(6):2203-16.

Another embodiment of the invention is a method of treating parasitic infections in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that mammalian cathepsins are related to the papain-like cysteine proteases which play an important role in the life cycle of these parasites. Such parasites are involved in the diseases of malaria, American trypanosomiasis, African trypanosomiasis, leishmaniasis, giardiasis, trichomoniasis, amoebiasis, schistosomiasis, fascioliasis, paragonimiasis and intestinal roundworms, see Lecaille F, Kaleta J, Bromme D., Human and parasitic papain-like cysteine proteases: their role in physiology and pathology and recent developments in inhibitor design. Chem Rev 2002 102, 4459-88.

Another embodiment of the invention is a method of treating severe acute respiratory syndrome (SARS) in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Another embodiment of the invention is a method of treating metastatic bone disease in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that osteoclasts are responsible for bone resorption and that bone destruction and hypercalcemia induced by metastatic tumors are carried out by osteoclasts. Accordingly, the inhibition

of osteoclasts can prevent bone destruction and bone metastasis, see Miyamoto, T. and Suda, T., "Differentiation and function of osteoclasts," Keio J Med 2003 Mar;52(1):1-7.

Another embodiment of the invention is administering to a mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above for the treatment of mammalian diseases associated with cathepsin S including Alzheimer's disease, atherosclerosis, chronic obstructive pulmonary disease, cancer and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts. It is known in the literature that cathepsin S activity is associated with the above disease states, see Munger JS, Haass C, Lemere CA, Shi GP, Wong WS, Teplow DB, Selkoe DJ, Chapman HA. Lysosomal processing of amyloid precursor protein to A beta peptides: a distinct role for cathepsin S. Biochem J 1995 311, 299-305, Sukhova GK, Zhang Y, Pan JH, Wada Y, Yamamoto T, Naito M, Kodama T, Tsimikas S, Witztum JL, Lu ML, Sakara Y, Chin MT, Libby P, Shi GP. Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice. J Clin Invest 2003 111, 897-906, Zheng T, Zhu Z, Wang Z, Homer RJ, Ma B, Riese RJ Jr, Chapman HA Jr, Shapiro SD, Elias JA. Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin-dependent emphysema. J Clin Invest 2000 106,1081-93, Shi GP, Sukhova GK, Kuzuya M, Ye Q, Du J, Zhang Y, Pan JH, Lu ML, Cheng XW, Iguchi A, Perrey S, Lee AM, Chapman HA, Libby P. Deficiency of the cysteine protease cathepsin S impairs microvessel growth. Circ Res 2003 92, 493-500, Nakagawa TY, Brissette WH, Lira PD, Griffiths RJ, Petrushova N, Stock J, McNeish JD, Eastman SE, Howard ED, Clarke SR, Rosloniec EF, Elliott EA, Rudensky AY. Impaired invariant chain degradation and antigen presentation and diminished collagen-induced arthritis in cathepsin S null mice. Immunity 1999 10,207-17.

Exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of osteoporosis in a mammal in need thereof. Still further exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of: bone loss, bone resorption, bone fractures, metastatic bone disease and/or disorders related to cathepsin functioning.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. For oral use of a

therapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. For oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

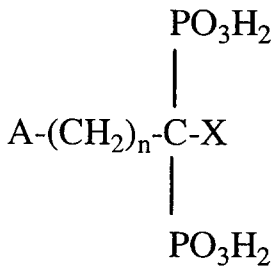
The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

The instant compounds are also useful in combination with known agents useful for treating or preventing osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia

of malignancy, and multiple myeloma. Combinations of the presently disclosed compounds with other agents useful in treating or preventing osteoporosis or other bone disorders are within the scope of the invention. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved. Such agents include the following: an organic bisphosphonate; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; Vitamin D; a synthetic Vitamin D analogue; a Nonsteroidal anti-inflammatory drug; a selective cyclooxygenase-2 inhibitor; an inhibitor of interleukin-1 beta; a LOX/COX inhibitor; and the pharmaceutically acceptable salts and mixtures thereof. A preferred combination is a compound of the present invention and an organic bisphosphonate. Another preferred combination is a compound of the present invention and an estrogen receptor modulator. Another preferred combination is a compound of the present invention and an androgen receptor modulator. Another preferred combination is a compound of the present invention and an osteoblast anabolic agent.

"Organic bisphosphonate" includes, but is not limited to, compounds of the chemical formula



wherein n is an integer from 0 to 7 and wherein A and X are independently selected from the group consisting of H, OH, halogen, NH_2, SH, phenyl, C_1-C_{30} alkyl, C_3-C_{30} branched or cycloalkyl, bicyclic ring structure containing two or three N, C_1-C_{30} substituted alkyl, C_1-C_{10} alkyl substituted NH_2, C_3-C_{10} branched or cycloalkyl substituted NH_2, C_1-C_{10} dialkyl substituted NH_2, C_1-C_{10} alkoxy, C_1-C_{10} alkyl substituted thio, thiophenyl, halophenylthio, C_1-C_{10} alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, imidazopyridinyl, and benzyl, such that both A and X are not selected from H or OH when n is 0; or A and X are taken together with the carbon atom or atoms to which they are attached to form a C_3-C_{10} ring.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C_1-C_{30} substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH_2, C_1-C_{10} alkyl or dialkyl substituted NH_2, OH, SH, and C_1-C_{10} alkoxy.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Non-limiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra- C_1-C_{10} -alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. More preferred are sodium salts. Non-limiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 5 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 5 mg of alendronic acid.

Non-limiting examples of bisphosphonates useful herein include the following:

Alendronate, which is also known as alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, alendronate sodium or alendronate monosodium trihydrate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronate is described in U.S. Patents 4,922,007, to Kieczykowski *et al.*, issued May 1, 1990; 5,019,651, to Kieczykowski *et al.*, issued May 28, 1991; 5,510,517, to Dauer *et al.*, issued April 23, 1996; 5,648,491, to Dauer *et al.*, issued July 15, 1997, all of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (incadronate, formerly known as cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem 32*, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

1-hydroxy-2-imidazo-(1,2-a)pyridin-3-yethylidene (minodronate).

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Breliere et al., October 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zoledronate).

Nonlimiting examples of bisphosphonates include alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, and zolendronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially a sodium, potassium, calcium, magnesium or ammonium salt of alendronic acid. Exemplifying the preferred bisphosphonate is a sodium salt of alendronic acid, especially a hydrated sodium salt of alendronic acid. The salt can be hydrated with a whole number of moles of water or non whole numbers of moles of water. Further exemplifying the preferred bisphosphonate is a hydrated sodium salt of alendronic acid, especially when the hydrated salt is alendronate monosodium trihydrate.

It is recognized that mixtures of two or more of the bisphosphonate actives can be utilized.

The precise dosage of the organic bisphosphonate will vary with the dosing schedule, the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 μg/kg body weight and preferably about 10 to about 2000 μg/kg of body weight. For alendronate monosodium trihydrate, common human doses which are administered are generally in the range of about 2 mg/day to about 40 mg/day, preferably about 5 mg/day to about 40 mg/day. In the U.S. presently approved dosages for alendronate monosodium trihydrate are 5 mg/day for preventing osteoporosis, 10 mg/day for treating osteoporosis, and 40 mg/day for treating Paget's disease.

In alternative dosing regimens, the bisphosphonate can be administered at intervals other than daily, for example once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly

dosing. In a once weekly dosing regimen, alendronate monosodium trihydrate would be administered at dosages of 35 mg/week or 70 mg/week.

"Selective estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, estrogen, progestogen, estradiol, droloxifene, raloxifene, lasofoxifene, TSE-424, tamoxifen, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

An "estrogen receptor beta modulator" is a compound that selectively agonizes or antagonizes estrogen receptor beta (ERβ Agonizing ERβ increases transcription of the tryptophan hydroxylase gene (TPH, the key enzyme in serotonin synthesis) via an ERβ mediated event. Examples of estrogen receptor beta agonists can be found in PCT International publication WO 01/82923, which published on November 08, 2001, and WO 02/41835, which published on May 20, 2002, both of which are hereby incorporated by reference in their entirety.

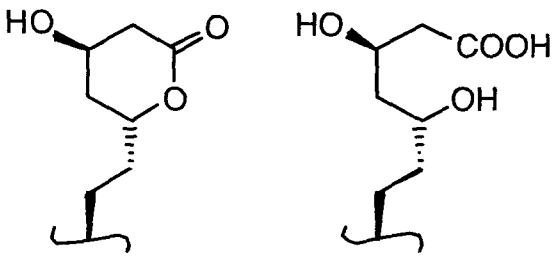
"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"An inhibitor of osteoclast proton ATPase" refers to an inhibitor of the proton ATPase, which is found on the apical membrane of the osteoclast, and has been reported to play a significant role in the bone resorption process. This proton pump represents an attractive target for the design of inhibitors of bone resorption which are potentially useful for the treatment and prevention of osteoporosis and related metabolic diseases. See C. Farina et al., "Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone antiresorptive agents," DDT, 4: 163-172 (1999)), which is hereby incorporated by reference in its entirety.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural

formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone I

Open-Acid II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

As used above, "integrin receptor antagonists" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of$\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. H.N. Lode and coworkers in PNAS USA 96: 1591-1596 (1999) have observed synergistic effects between an antiangiogenic αv integrin antagonist and a tumor-specific antibody-cytokine (interleukin-2) fusion protein in the eradication of spontaneous tumor metastases. Their results suggested this combination as having potential for the treatment of cancer and metastatic tumor growth. $\alpha_v\beta_3$ integrin receptor antagonists inhibit bone resorption through a new mechanism distinct from that of all currently available drugs. Integrins are heterodimeric transmembrane adhesion receptors that mediate cell-cell and cell-matrix interactions. The α and β integrin subunits interact non-covalently and bind extracellular matrix ligands in a divalent cation-dependent manner. The most abundant integrin on osteoclasts is $\alpha_v\beta_3$ (>10^7/osteoclast), which appears to play a rate-limiting role in cytoskeletal organization important for cell migration and polarization. The $\alpha_v\beta_3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of macular degeneration, inhibition of arthritis, and inhibition of cancer and metastatic growth.

"An osteoblast anabolic agent" refers to agents that build bone, such as PTH. The intermittent administration of parathyroid hormone (PTH) or its amino-terminal fragments and analogues have been shown to prevent, arrest, partially reverse bone loss and stimulate bone formation in animals and humans. For a discussion refer to D.W. Dempster et al., "Anabolic actions of parathyroid hormone on bone," Endocr Rev 14: 690-709 (1993). Studies have demonstrated the clinical benefits of parathyroid hormone in stimulating bone formation and thereby increasing bone mass and strength. Results were reported by RM Neer et al., in New Eng J Med 344 1434-1441 (2001).

In addition, parathyroid hormone-related protein fragments or analogues, such as PTHrP-(1-36) have demonstrated potent anticalciuric effects [see M.A. Syed et al., "Parathyroid hormone-related protein-(1-36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy," JCEM 86: 1525-1531 (2001)] and may also have potential as anabolic agents for treating osteoporosis.

"Vitamin D" includes, but is not limited to, vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol), which are naturally occurring, biologically inactive precursors of the hydroxylated

biologically active metabolites of vitamin D: 1α-hydroxy vitamin D; 25-hydroxy vitamin D, and 1α ,25-dihydroxy vitamin D. Vitamin D_2 and vitamin D_3 have the same biological efficacy in humans. When either vitamin D_2 or D_3 enters the circulation, it is hydroxylated by cytochrome P_{450}-vitamin D-25-hydroxylase to give 25-hydroxy vitamin D. The 25-hydroxy vitamin D metabolite is biologically inert and is further hydroxylated in the kidney by cytochrome P450-monooxygenase, 25 (OH) D-1α -hydroxylase to give 1,25-dihydroxy vitamin D. When serum calcium decreases, there is an increase in the production of parathyroid hormone (PTH), which regulates calcium homeostasis and increases plasma calcium levels by increasing the conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D.

1,25-dihydroxy vitamin D is thought to be reponsible for the effects of vitamin D on calcium and bone metabolism. The 1,25-dihydroxy metabolite is the active hormone required to maintain calcium absorption and skeletal integrity. Calcium homeostasis is maintained by 1,25-dihydroxy vitamin D by inducing monocytic stem cells to differentiate into osteoclasts and by maintaining calcium in the normal range, which results in bone mineralization by the deposition of calcium hydroxyapatite onto the bone surface, see Holick, MF, "Vitamin D photobiology, metabolism, and clinical applications," in *Endocrinology*, 3rd ed., 990-1013 (1995), edited by DeGroot L, *et al.* However, elevated levels of 1α,25-dihydroxy vitamin D_3 can result in an increase of calcium concentration in the blood and in the abnormal control of calcium concentration by bone metabolism, resulting in hypercalcemia. 1α,25-dihydroxy vitamin D_3 also indirectly regulates osteoclastic activity in bone metabolism and elevated levels may be expected to increase excessive bone resorption in osteoporosis.

"Synthetic vitamin D analogues" includes non-naturally occurring compounds that act like vitamin D.

"Nonsteroidal anti-inflammatory drugs" or NSAIDs, inhibit the metabolism of arachidonic acid to proinflammatory prostaglandins via cyclooxygenase (COX)-1 and COX-2. Nonlimiting examples of NSAIDs include: aspirin, ibuprofen, naproxen, diclofenac, etodolac, fenoporfen, flubiprofen, indomethacin, ketoprofen, ketorolac, meloxicam, nabumetone, oxaprozin, piroxicam, sulindac, tolmetin, diflunisal, meclofenamate and phenylbutazone.

A "selective cyclooxygenase-2 inhibitor," or COX-2 inhibitor, refers to a type of nonsteroidal anti-inflammatory drug (NSAID), that inhibit the COX-2 coenzyme, which contributes to pain and inflammation in the body. Nonlimiting examples of COX-2 inhibitos include: celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib and lumiracoxib.

An "inhibitor of interleukin-1 beta" or IL-1β refers to in inhibitors of IL-1, which is a soluble factor produced by monocytes, macrophages, and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. Nonlimiting examples of IL-1β inhibitors include diacerein and rhein.

A "LOX/COX inhibitor" refers to an inhibitor or all three of the major enzymes involved in arachidonic acid pathway - namely, 5-LOX, COX-1 and COX-2. A nonlimiting example of a LOX/COX inhibitor is licofelone.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents. The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985, which is incorporated by reference herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The terms "treating" or "treatment" of a disease as used herein includes: preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

The term "bone resorption," as used herein, refers to the process by which osteoclasts degrade bone.

The present invention also encompasses a pharmaceutical composition useful in the treatment of osteoporosis or other bone disorders, comprising the administration of a therapeutically

effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for a cathepsin dependent condition. Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds of the present invention can be used in combination with other agents useful for treating cathepsin-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating cathepsin-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

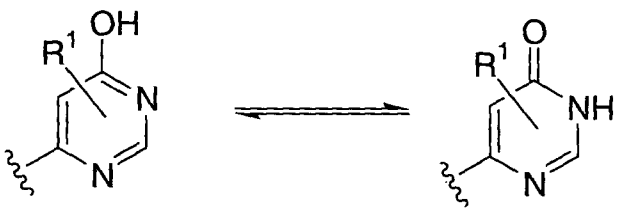
The scope of the invention therefore encompasses the use of the instantly claimed compounds in combination with a second agent selected from: an organic bisphosphonate; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; Vitamin D; a synthetic Vitamin D analogue; a Nonsteroidal anti-inflammatory drug; a selective

cyclooxygenase-2 inhibitor; an inhibitor of interleukin-1 beta; a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof.

These and other aspects of the invention will be apparent from the teachings contained herein.

Definitions

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



A B

When any variable (e.g. R^1, R^2, R^3 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having one to ten carbon atoms unless otherwise specified. For example,

C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear, branched, or cyclic arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

The term "haloalkyl" means an alkyl radical as defined above, unless otherwise specified, that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyl, dichloroethyl, and the like.

The term "cycloalkyl" or "carbocycle" shall mean cyclic rings of alkanes of three to eight total carbon atoms, unless otherwise indicated, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 12 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolinyl, methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolinyl, isoquinolinyl, oxazolyl, and tetrahydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered nonaromatic ring, unless otherwise specified, containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S, SO, or SO_2 and includes bicyclic groups. "Heterocyclyl" therefore includes, but is not limited to the following: piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also emcompassed by this definition.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, $CH(CH_3)$ $CH_2CH(CH_3)$Ph, and so on.

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed inorganic or organic acids. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19, hereby incorporated by reference. The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

For purposes of this specification, the following abbreviations have the indicated meanings:

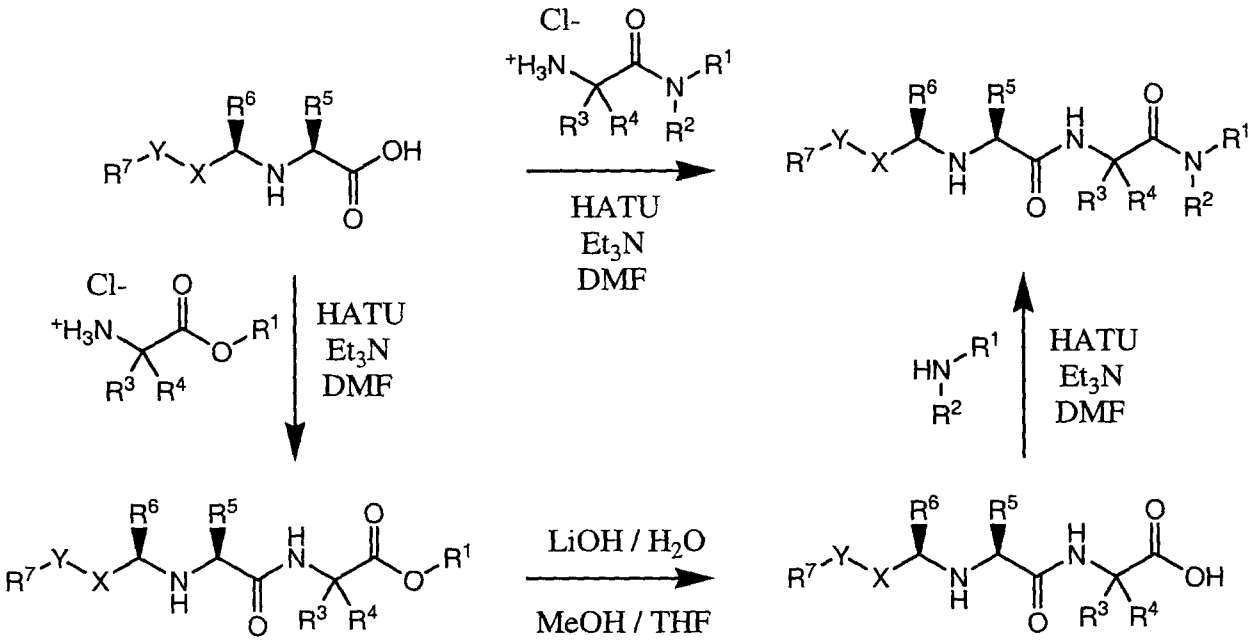
DMF	=	N,N-dimethylformamide
Et_3N	=	triethylamine
HATU	=	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
LiOH	=	lithium hydroxide

MeOH	=	methanol
PG	=	protecting group
PyBOP	=	Benzotriazole-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
rt	=	room temperature
sat. aq.	=	saturated aqueous
THF	=	tetrahydrofuran
tlc	=	thin layer chromatography
Me	=	methyl

The novel compounds of the present invention can be prepared according to the following general procedures using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

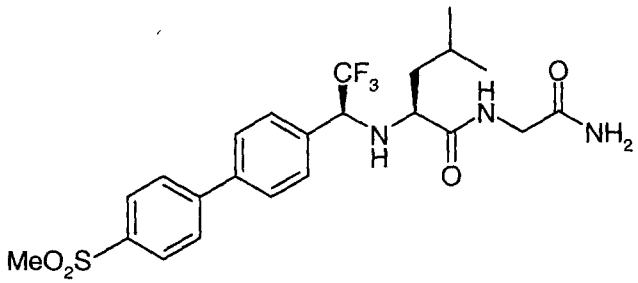
Compounds of the present invention can be prepared according to Scheme 1, as indicated below. Thus, an α-amino amide may be coupled to a carboxylic acid using a coupling reagent such as HATU or PyBOP to form a compound of the present invention. Alternatively, using the same reaction conditions, α-amino esters can be coupled to a carboxylic acid to provide an ester intermediate which is saponified using standard hydrolysis conditions. Finally this acid is converted to an amide by using the appropriate amine in the presence of coupling reagents such as HATU or PyBOP to form a compound of the present invention.

SCHEME 1



EXAMPLE 1

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucylglycinamide

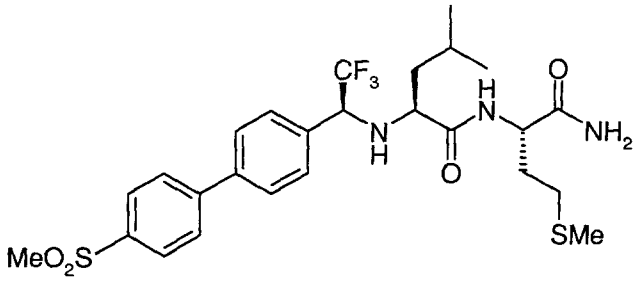


To an ice-cold mixture of N-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucine from WO200375836, Example 8, Step 6, (148 mg, 0.33 mmol), HATU (292 mg, 0.77 mmol) and L-glycinamide hydrochloride (102 mg, 0.92 mmol) in DMF (1 mL) was added dropwise triehylamine (175 µL, 1.26 mmol). The resulting solution was stirred and allowed to reach r.t. over 2 hours. The reaction mixture was partitioned between EtOAc and half-saturated aqueous sodium bicarbonate, the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (70:30 EtOAc/Hexane to 100% EtOAc) to give the title compound as a white solid.

^{1}H NMR (500 MHz, CD_3COCD_3) δ 0.96 (6H, dd), 1.53 (2H, m), 1.95 (1H, m), 2.6 (1H, m), 3.19 (3H, s), 3.57 (1H, bq), 3.78 (2H, m), 4.55 (1H, m), 6.43 (1H, b), 6.86 (1H, b), 7.58 (1H, b), 7.68 (2H, d), 7.78 (2H, d), 7.97 (2H, d), 8.06 (2H, d).

EXAMPLE 2

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-methioninamide

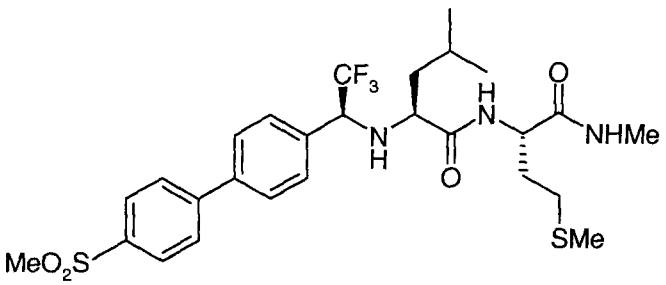


Using the procedure described for the preparation of Example 1 where L-methioninamide hydrochloride was substituted for L-glycinamide hydrochloride, the title compound was obtained as a white solid.

^{1}H NMR (500 MHz, CD_3COCD_3) δ 0.93 (6H, dd), 1.50 (2H, m), 1.78 (1H, m), 1.95 (2H, m), 1.99 (3H, s), 2.38 (2H, m), 2.68 (1H, m), 3.16 (3H, s), 3.52 (1H, bq), 4.45 (2H, m), 6.44 (1H, b), 6.90 (1H, b), 7.53 (1H, bd), 7.66 (2H, d), 7.78 (2H, d), 7.97 (2H, d), 8.04 (2H, d).

EXAMPLE 3

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-*N*^{1}-methyl-L-methioninamide



Step 1 Methyl *N*-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-methioninate

Using the procedure described for the preparation of Example 1 where L-methionine methyl ester hydrochloride was substituted for L-glycinamide hydrochloride, the title compound was obtained as a white solid.

Step 2 *N*-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-methionine

To an ice-cold solution of methyl *N*-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-methioninate from step 1 (100 mg, 0.17 mmol) in THF (2 mL) and methanol (0.5 mL) was added 1N lithium hydroxide (0.25 mL, 0.25 mmol). The resulting solution was stirred at room temperature for 18 hours and then partitioned between EtOAc and 0.1N HCl. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography

(10:90:1 EtOH/EtOAc/AcOH) and then crystallized in EtOAc/Hexane (1:2) to give the title compound as a white solid.

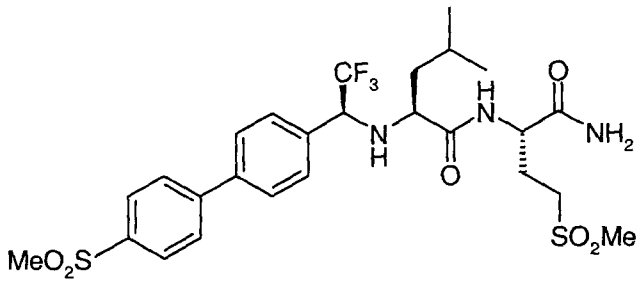
Step 3 *N*-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-methyl-L-methioninamide

Using the procedure described for the preparation of Example 1 where L-methylamine hydrochloride was substituted for L-glycinamide hydrochloride, the title compound was obtained as a white solid.

^{1}H NMR (500 MHz, CD_3COCD_3) δ 0.92 (6H, dd), 1.48 (2H, m), 1.74 (1H, m), 1.92 (2H, m), 1.98 (3H, s), 2.37 (2H, t), 2.65 (1H, m), 2.68 (3H, d), 3.17 (3H, s), 3.51 (1H, m), 4.37 (1H, m), 4.43 (1H, m), 7.09 (1H, b), 7.52 (1H, bd), 7.66 (2H, d), 7.77 (2H, d), 7.97 (2H, d), 8.03 (2H, d).

EXAMPLE 4

N^1-[(1*S*)-1-(aminocarbonyl)-3-(methylsulfonyl)propyl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide

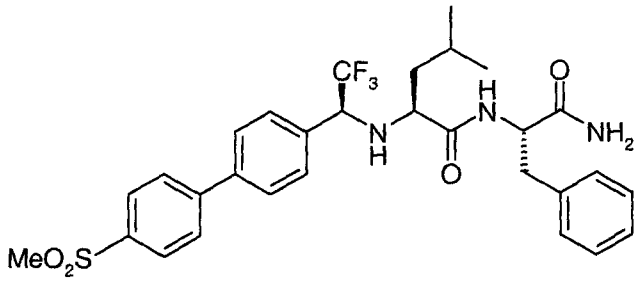


Step1 To an ice-cold solution of *N*-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-methioninamide from Example 2 (405 mg, 0.7 mmol) in dichloromethane (5 mL) and methanol (1 mL) was added magnesium bis(monoperoxiphthalate) hexahydrate 80% (521 mg, 0.84 mmol). The resulting suspension was stirred at room temperature for 30 min. It was then partitioned between EtOAc and water and the organic layer was dried over Na_2SO_4 and concentrated. It was purified by flash chromatography (100% EtOAc to 10:90 EtOH/EtOAc) and then by crystallisation in EtOAc/hexane (2:1) to give the title compound as a white powder.

^{1}H NMR (500 MHz, CD_3COCD_3) δ 0.93 (6H, dd), 1.50 (2H, m), 1.92 (1H, m), 2.02 (1H, m), 2.25 (1H, m), 2.67 (1H, m), 2.89 (3H, s), 3.03 (2H, m), 3.17 (3H, s), 3.52 (1H, m), 4.48 (2H, m), 6.58 (1H, b), 7.02 (1H, b), 7.66 (1H, bd), 7.68 (2H, d), 7.78 (2H, d), 7.97 (2H, d), 8.03 (2H, d).

EXAMPLE 5

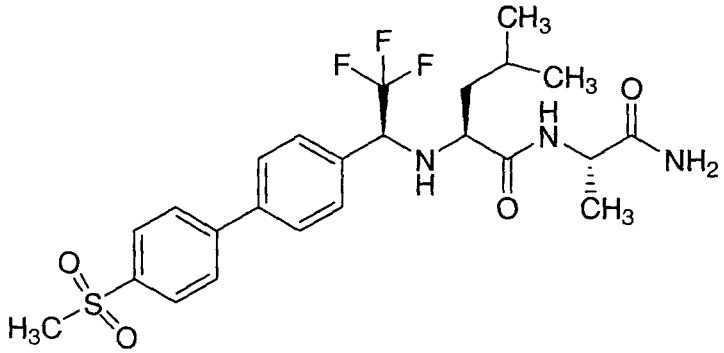
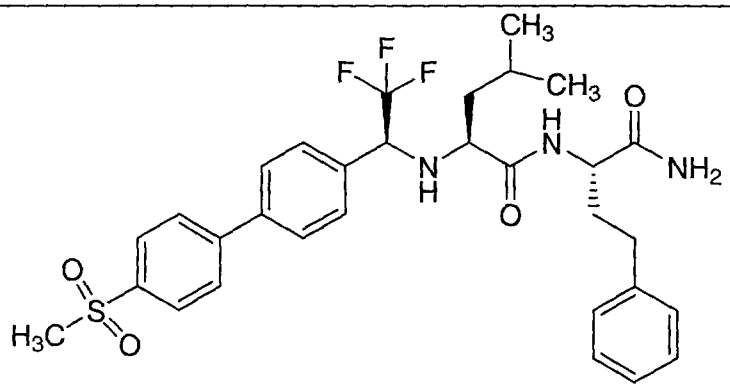
N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-phenylalaninamide

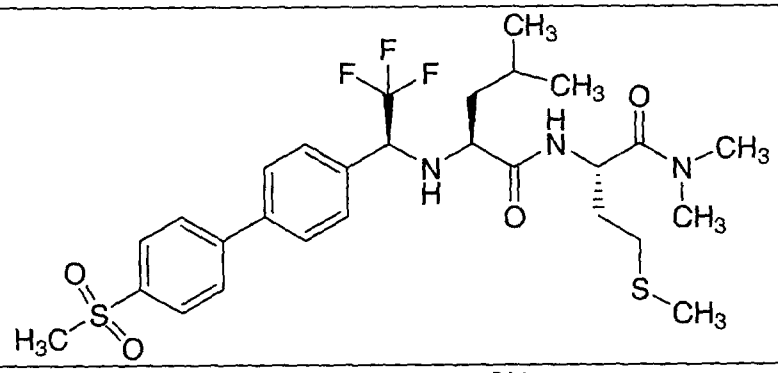
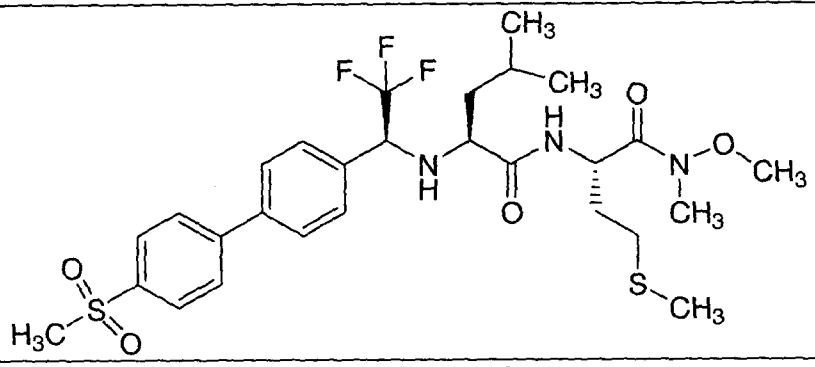
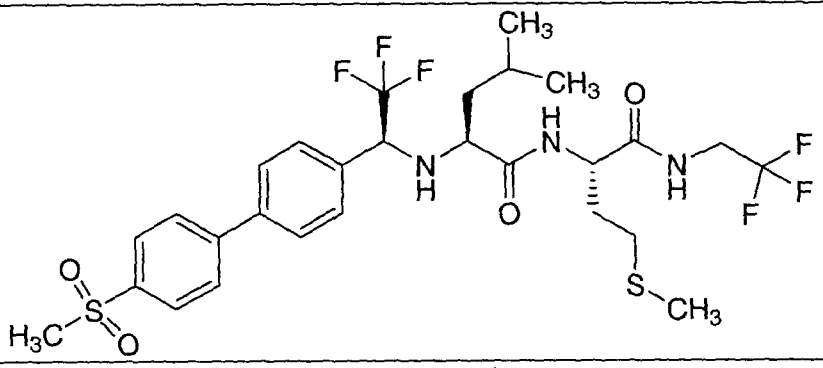
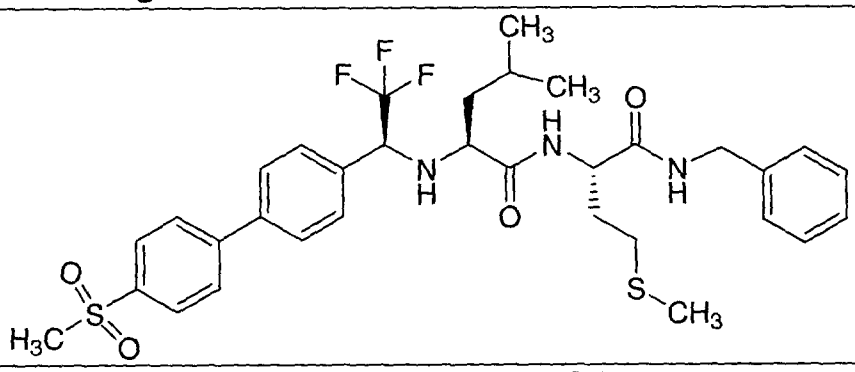
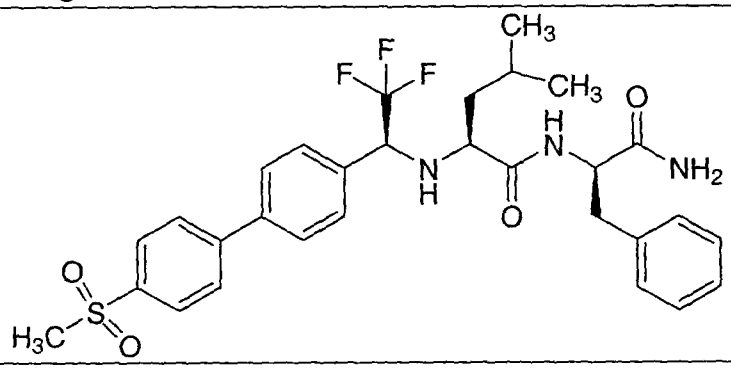


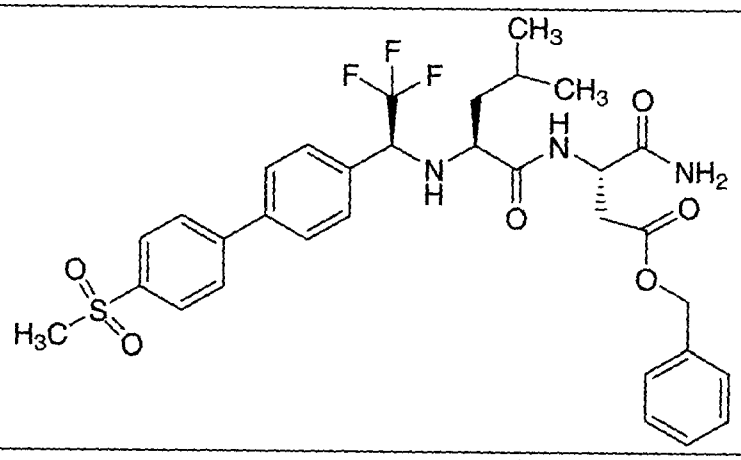
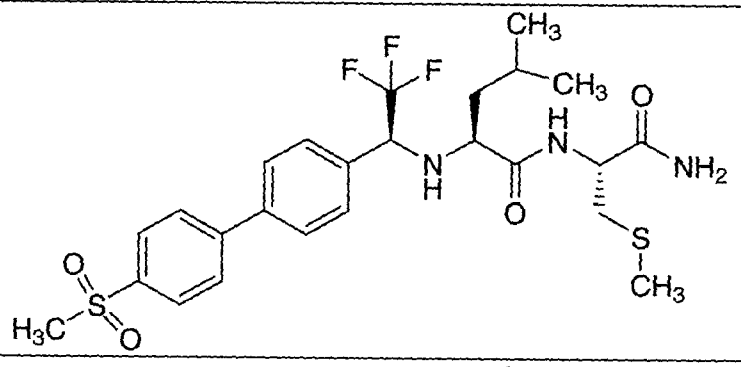
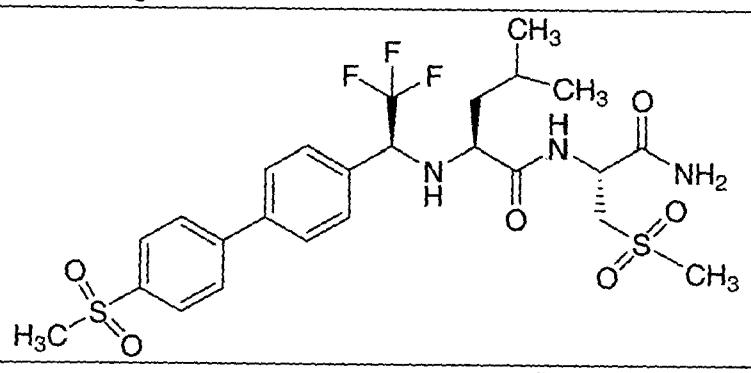
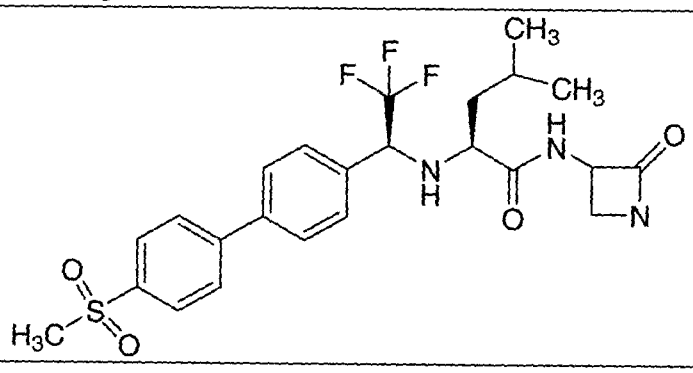
Using the procedure described for the preparation of Example 1 where L-phenylalaninamide hydrochloride was substituted for L-glycinamide hydrochloride, the title compound was obtained as a white solid.

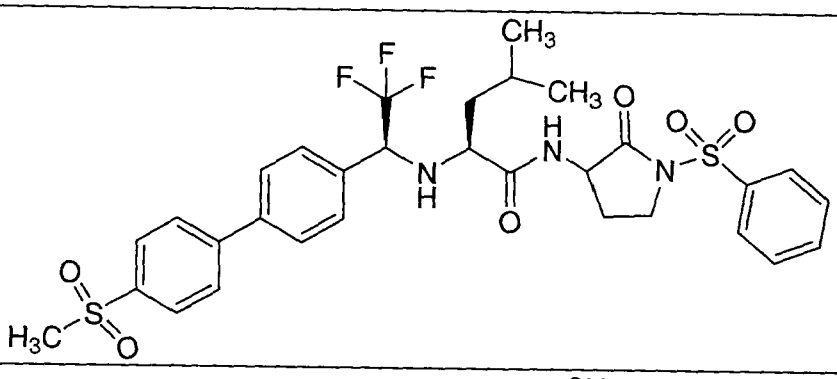
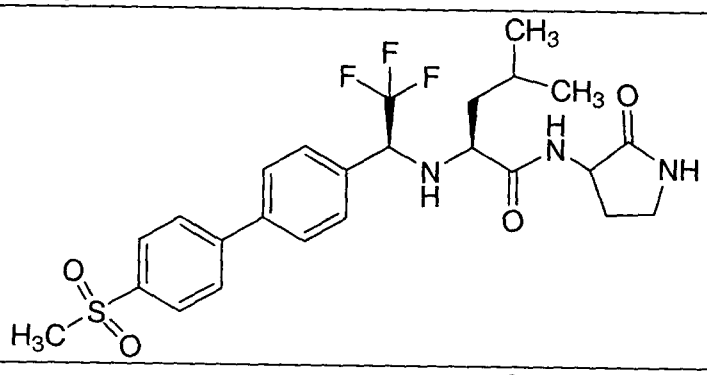
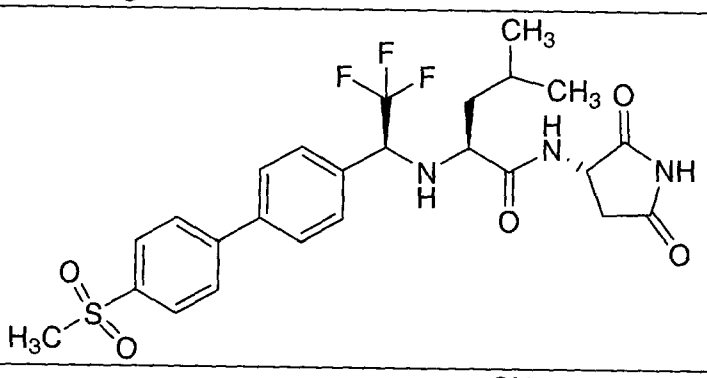
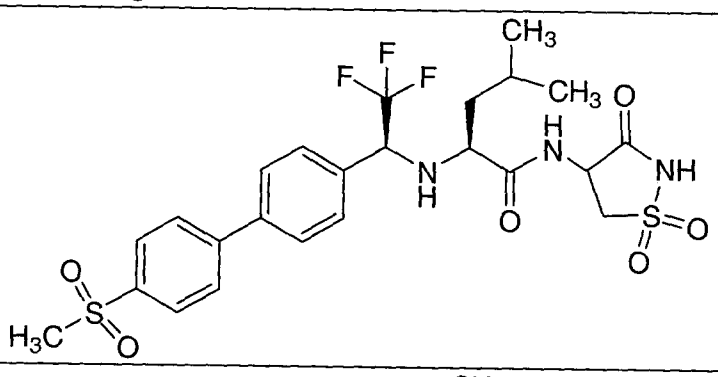
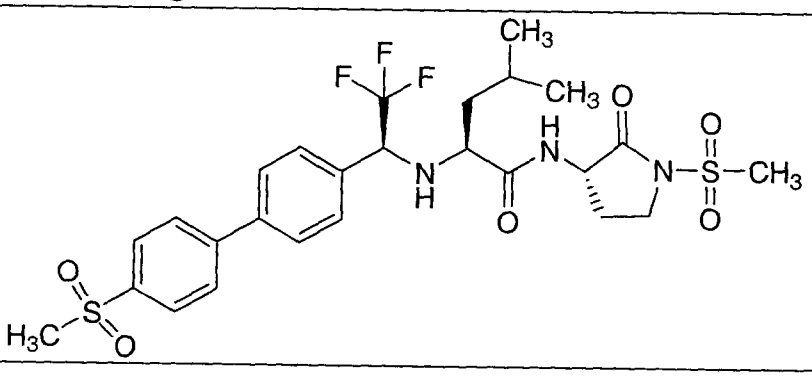
^{1}H NMR (500 MHz, CD_3COCD_3) δ 0.88 (6H, dd), 1.38 (2H, m), 1.85 (1H, m), 2.44 (1H, b), 2.78 (1H, dd), 3.08 (1H, dd), 3.17 (3H, s), 3.47 (1H, b), 4.05 (1H, m), 4.64 (1H, m), 6.45 (1H, b), 6.87 (1H, b), 7.25 (5H, m), 7.47 (2H, d), 7.54 (1H, d), 7.72 (2H, d), 7.91 (2H, d), 8.02 (2H, d).

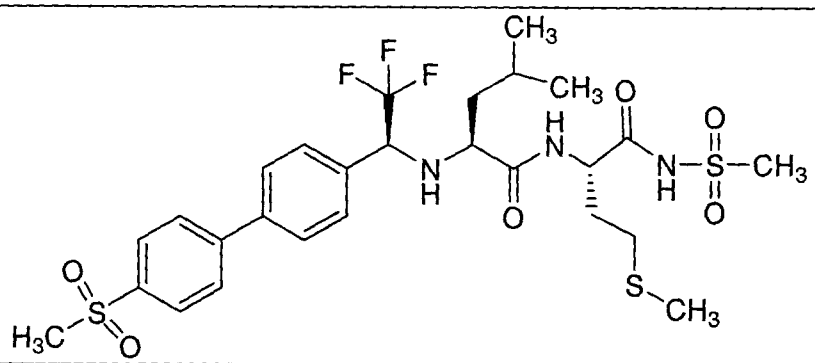
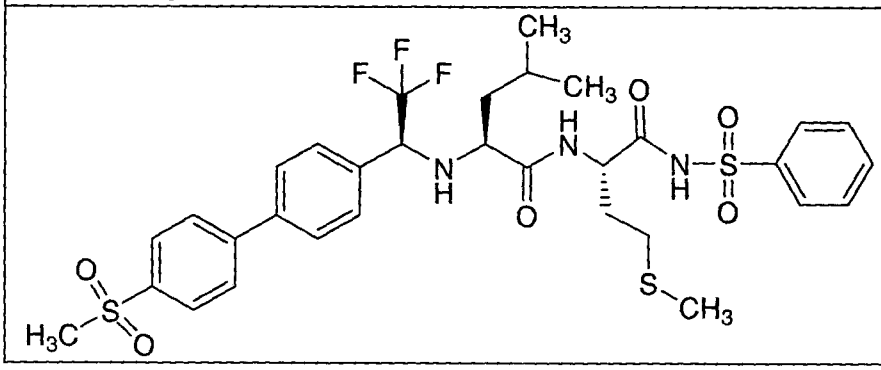
Using the methods described above, the following compounds were prepared:

COMPOUND	CHARACTERIZATION
	MS (+ESI) 514.3 (M + 1).
	MS (+ESI) 604.4 (M + 1).

	MS (+ESI) 602.3 (M + 1).
	MS (+ESI) 618.3 (M + 1).
	MS (+ESI) 656.3 (M + 1).
	MS (+ESI) 664.0 (M + 1).
	MS (+ESI) 590.3 (M + 1).

	MS (+ESI) 648.4 (M + 1).
	MS (+ESI) 560.1 (M + 1).
	MS (+ESI) 592.1 (M + 1).
	MS (+ESI) 512.1 (M +1).

	MS (+ESI) 666.3 (M +1).
	MS (+ESI) 526.2 (M +1).
	MS (+ESI) 540.2 (M +1).
	MS (+ESI) 576.1 (M +1).
	MS (+ESI) 604.2 (M + 1).

	MS (+ESI) 652.2 (M + 1).
	MS (+ESI) 714.1 (M + 1).

Pharmaceutical Composition

As a specific embodiment of this invention, 100 mg of *N*-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucylglycinamide, is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0, hard-gelatin capsule.

The compounds disclosed in the present application exhibited activity in the following assays. In addition, the compounds disclosed in the present application have an enhanced pharmacological profile relative to previously disclosed compounds.

ASSAYS

Cathepsin K Assay

Serial dilutions (1/3) from 500 μM down to 0.0085 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μL of DMSO from each dilution were added to 50 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μL of human cathepsin K (0.4 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =355 nm; Emλ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin L Assay

Serial dilutions (1/3) from 500 μM down to 0.0085 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μL of DMSO from each dilution were added to 50 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μL of human cathepsin L (0.5 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =355 nm; Emλ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin B Assay

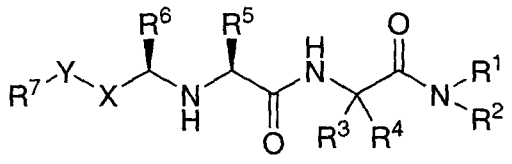
Serial dilutions (1/3) from 500 μM down to 0.0085 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μL of DMSO from each dilution were added to 50 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μL of human cathepsin B (4.0 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =355 nm; Emλ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin S Assay

Serial dilutions (1/3) from 500 μM down to 0.0085 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μL of DMSO from each dilution were added to 50 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μL of human cathepsin S (20 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =355 nm; Emλ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

WHAT IS CLAIMED IS:

1. A compound of the formula



wherein X is aryl or heteroaryl;
Y is aryl or heteroaryl;
R^1 is hydrogen, C_{1-6} alkyl or $O(C_{1-6}$ alkyl), which is optionally substituted with aryl or one to three halo;
R^2 is hydrogen, C_{1-6} alkyl or $O(C_{1-6}$ alkyl), which is optionally substituted with aryl or one to three halo;
R^3 is hydrogen, C_{1-6} alkyl, $(C_{1-6}$ alkyl$)SO_mR^8$, $(C_{1-6}$ alkyl$)R^8$ or $(C_{1-6}$ alkyl$)(C{=}O)O(C_{1-6}$ alkyl$)R^8$;
R^4 is hydrogen, C_{1-6} alkyl, $(C_{1-6}$ alkyl$)SO_mR^8$, $(C_{1-6}$ alkyl$)R^8$ or $(C_{1-6}$ alkyl$)(C{=}O)O(C_{1-6}$ alkyl$)R^8$;
or R^1 and R^4 can be taken together with the atoms to which they are attached and are between them to form a C_{3-8} heterocyclyl ring wherein said ring is optionally substituted with one or two substituents independently selected from C_{1-6} alkyl, $SO_m(C_{1-6}$ alkyl), SO_m(aryl) or halo;
R^5 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein said alkyl and cycloalkyl groups are optionally substituted with C_{1-6} alkyl or halo;
R^6 is C_{1-6} haloalkyl, aryl or heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted on either the carbon or heteroatom with one to three halo;
R^7 is $SO_m(C_{1-6}$ alkyl), C_{1-6} alkyl or halo;
R^8 is hydrogen, C_{1-6} alkyl or aryl;
each m is independently an integer from zero to two;
or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

2. The compound of Claim 1 wherein X is aryl and Y is aryl; or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

3. The compound of Claim 2 wherein X is phenyl and Y is phenyl; or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

4. The compound of Claim 3 wherein R^1 is hydrogen and R^2 is hydrogen; or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

5. The compound of Claim 3 wherein R^3 is $(C_{1-6}$ alkyl$)SO_mR^8$ or $(C_{1-6}$ alkyl$)R^8$ and R^4 is hydrogen; R^5 is C_{1-6} alkyl; or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

6. The compound of Claim 1 selected from:

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-alaninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucylglycinamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-methioninamide;

N^1-[(1*S*)-1-(aminocarbonyl)-3-(methylsulfonyl)propyl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-[(1*S*)-1-(aminocarbonyl)-3-phenylpropyl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-methyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1,N^1-dimethyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-methoxy-N^1-methyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-(2,2,2-trifluoroethyl)-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-benzyl-L-methioninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-phenylalaninamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-D-phenylalaninamide;

benzyl *N*-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-L-α-asparaginate;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-*S*-methyl-L-cysteinamide;

N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-3-(methylsulfonyl)-L-alaninamide;

N^1-(2-oxoazetidin-3-yl)-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-[2-oxo-1-(phenylsulfonyl)pyrrolidin-3-yl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-(2-oxopyrrolidin-3-yl)-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-[(3*S*)-2,5-dioxopyrrolidin-3-yl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N^1-(1,1-dioxido-3-oxoisothiazolidin-4-yl)-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;
N^1-[(3*S*)-1-(methylsulfonyl)-2-oxopyrrolidin-3-yl]-N^2-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;
N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-(methylsulfonyl)-L-methioninamide;
N-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucyl-N^1-(phenylsulfonyl)-L-methioninamide;
or a pharmaceutically acceptable salt, stereoisomer or N-oxide derivative thereof.

7. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

8. The use of a compound of Claim 1 in the preparation of a medicament useful for the treatment of: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof a therapeutically effective amount of a compound according to Claim 1.

9. A pharmaceutical composition comprising a compound of Claim 1 and another agent selected from the group consisting of: an organic bisphosphonate, an estrogen receptor modulator, an estrogen receptor beta modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, or an osteoblast anabolic agent, vitamin D, a synthetic Vitamin D analogue, a Nonsteroidal anti-inflammatory drug, a selective cyclooxygenase-2 inhibitor, an inhibitor of interleukin-1 beta, a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof.

10. The use of a compound of Claim 1 and another agent selected from the group consisting of: an organic bisphosphonate, an estrogen receptor modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, an osteoblast anabolic agent, vitamin D, a synthetic Vitamin D analogue, a Nonsteroidal anti-inflammatory drug, a selective cyclooxygenase-2 inhibitor, an inhibitor of interleukin-1 beta, a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof, in the preparation of a medicament useful for the treatment of: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone

fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001654

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07C 317/32*** (2006.01) , ***A61K 31/165*** (2006.01) , ***C07D 207/14*** (2006.01) , ***C07D 207/48*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: ***C07C 317/32*** (2006.01) , ***A61K 31/165*** (2006.01) , ***C07D 207/14*** (2006.01) , ***C07D 207/48*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, STN and Delphion.
Keywords: cathepsin and cysteine.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2535366 (MERCK FROSST CANADA LTD.) 10 March 2005 (10-03-2005) Examples 16 and 19.	1-10
Y	See whole document.	1-10
Y	CA 2535359 (MERCK FROSST CANADA LTD.) 3 March 2005 (03-03-2005) Example 1.	1-10

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2006 (06-12-2006)	22 January 2007 (22-01-2007)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Sandra Nevill 819- 934-6732

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001654

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [ ] Claim Nos. :
because they relate to subject matter not required to be searched by this Authority, namely :

2. [ ] Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

In order for a claim to compounds using a Markush formula to be regarded as uniform, the claimed compounds should have in common a structural moiety which is distinctive in view of the prior art. The structural moiety common to all the presently claimed compounds is the unit R7-Y-X-CR6-NH-R5-(CO)-NH-CR3R4. However such a moiety is to be found in the compounds disclosed in D2. The subject matter of claims 1-10 appear to lack unity of invention.

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2535366	10-03-2005	AU2004268707 A1	10-03-2005
		CN1842515 A	04-10-2006
		EP1660436 A1	31-05-2006
		WO2005021487 A1	10-03-2005
CA2535359	03-03-2005	AU2004266740 A1	03-03-2005
		CN1839114 A	27-09-2006
		EP1673336 A1	28-06-2006
		WO2005019161 A1	03-03-2005