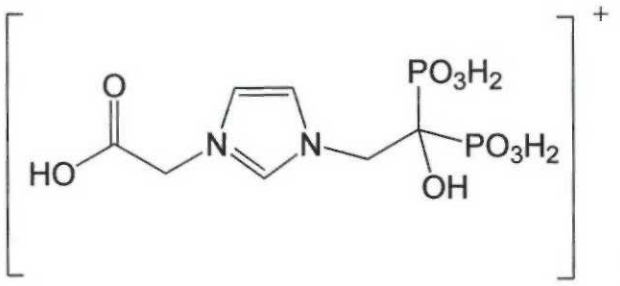
Claims:

1. A pharmaceutical dosage form comprising:

a) zoledronic acid; or

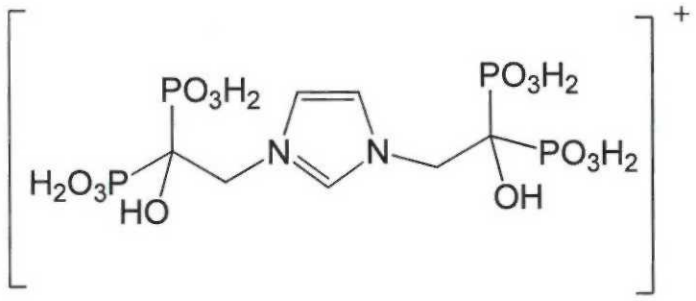
b) one of the following:

1) zoledronic acid and



(Compound 1) in an amount that is less than 0.1% w/w and greater than 0% w/w;

2) zoledronic acid and



(Compound 2) in an amount that is less than 0.1% w/w and greater than 0% w/w; or

3) zoledronic acid and a combination of Compound 1 in an amount that is less than 0.1% w/w and greater than 0% w/w, and Compound 2 in an amount that is less than 0.1% w/w and greater than 0% w/w;

wherein the dosage form is free of therapeutically active agents that are not zoledronic acid, Compound 1, or Compound 2;

wherein any amount in % w/w is based upon the total weight of zoledronic acid, Compound 1, and Compound 2; and

wherein the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4% in a human being.

2. The dosage form of claim 1, comprising about 1 mg to about 600 mg of zoledronic acid.

3. The dosage form of claim 1, comprising about 10 mg to about 300 mg of zoledronic acid.

4. The dosage form of claim 1, comprising about 20 mg to about 50 mg of zoledronic acid.

5. The dosage form of claim 1, comprising about 50 mg to about 100 mg of zoledronic acid.

6. The dosage form of claim 1, comprising about 100 mg to about 200 mg of zoledronic acid.

7. The dosage form of claim 1, wherein the dosage form is solid.

8. The dosage form of claim 1, wherein the dosage form is orally administered.

9. The dosage form of claim 1, wherein at least 10% of the weight of the dosage form is zoledronic acid.

10. The dosage form of claim 1, wherein the dosage form is suitable for administration to a human being.

11. The dosage form of claim 1, wherein the bioavailability of zoledronic acid in the dosage form is from about 1.3% to about 4% in a human being.

12. The dosage form of claim 1, wherein the bioavailability of zoledronic acid in the dosage form is from about 1.5% to about 4% in a human being.

13. The dosage form of claim 1, wherein the dosage form is a tablet.

14. The dosage form of claim 1, wherein the dosage form is a capsule.

15. The dosage form of claim 1, for use in treating complex regional pain syndrome.

16. The dosage form of claim 1, for use in treating arthritis.

17. The dosage form of claim 1, for use in treating knee pain.

18. The dosage form of claim 10, for use in treating knee pain, wherein the human being has OARSI Grade 0 or Kellgren and Lawrence Grade 0 or Grade 1 of joint space narrowing.

19. The dosage form of claim 1, for use in treating low back pain.

20. The dosage form of claim 1, for use in treating a bone marrow lesion.

21. The dosage form of claim 1, wherein the zoledronic acid is in a disodium salt form or an acid form.

22. The dosage form of claim 3, comprising about 40 mg to about 60 mg of zoledronic acid.

23. The dosage form of claim 22, comprising an equivalent of about 50 mg of zoledronic acid in a disodium salt form.

24. The dosage form of claim 23, wherein the dosage form is orally administered to a human being weekly for 6 weeks, and the resulting area under the plasma concentration curve (AUC) of zoledronic acid is about 100 ng•h/mL to about 2000 ng•h/mL in the human being.

25. The dosage form of claim 23, wherein the zoledronic acid is in a hydrate form.

CLAIMS

1. A method of treating pain comprising administering a compound to relieve pain, a musculoskeletal condition, or a condition related to bone or joint, in a mammal in need thereof, wherein the compound is a RANK/RANKL antagonist, an inhibitor of osteoclast activity, or a bisphosphonate.

2. The method of claim 1, wherein the mammal is a human being.

3. The method of claim 1 or 2, comprising treating acute pain, central pain, radio-therapy or chemo-therapy associated neuropathy, ankylosing spondylitis, arthritis, axial spondyloarthritis, blood cancers, bone fracture, bone metastases from solid tumors, bone metastasis, breast cancer, cancer, central multiple sclerosis pain, Charcot's foot, chronic pain, complex regional pain syndrome, diabetic peripheral neuropathy, erosive osteoarthritis, excessive bone resorption, fibrous dysplasia, giant cell tumor of bone, HIV-associated neuropathy, hypercalcemia of malignancy, inflammatory pain, juvenile rheumatoid arthritis, leukemias, low back pain, lumbar nerve root compression, lumbosacral pain, lung cancer, metastatic bone cancer, monoradiculopathies, multiple myeloma, musculoskeletal pain, neuropathic arthropaties, neuropathic pain, non-articular rheumatism, osteoarthritis, osteogenesis imperfecta, osteoporosis, Paget's disease, Paget's disease of bone, peri-articular disorders, phantom limb pain, post-herpetic neuralgia, postoperative pain, post-stroke pain, prostate cancer, rheumatoid arthritis, SAPHO syndrome, sero-negative (non-rheumatoid) arthropathies, solid tumors or cancers, spinal cord injury, systemic lupus erythematosus, transient osteoarthritis of the hip, transient osteoporosis, transient osteoporosis of the hip, trigeminal neuralgia, tumor induced hypocalcemia, or vertebral crush fracture.

4. The method of claim 1 or 2, comprising treating arthritis.

5. The method of claim 3, comprising relieving pain associated with arthritis.

6. The method of claim 5, wherein the arthritis affects a knee, an elbow, a wrist, a shoulder, or a hip.

7. The method of claim 6, wherein the arthritis affects a knee.

8. The method of claim 1 or 2, comprising treating musculoskeletal pain.

9. The method of claim 1 or 2, comprising treating a bone marrow lesion.

10. The method of claim 9, wherein the mammal is a human being that experiences a reduction in bone marrow lesion size that is at least about 15% within about 6 months after the inhibitor of osteoclast activity is administered to the human

being.

11. The method of claim 9, wherein the mammal is a human being that experiences a reduction in bone marrow lesion size that is at least about 25% within about 6 months after the inhibitor of osteoclast activity is administered to the human being.

12. The method of claim 9, 10, or 11, wherein the bone marrow lesion affects a knee.

13. The method of claim 9, 10, 11, or 12, comprising treating a bone marrow lesion of the knee by selecting a patient having a bone marrow lesion of the knee and OARSI Grade 0 or Kellgren and Lawrence Grade 0 or Grade 1 of joint space narrowing, and administering the compound to the patient for the treatment of the bone marrow lesion.

14. The method of claim 1 or 2, comprising treating osteoarthritis.

15. The method of claim 14, wherein the osteoarthritis affects a knee.

16. The method of claim 14 or 15, comprising treating an osteolytic lesion associated with osteoarthritis.

17. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, comprising treating knee pain.

18. The method of claim 17, comprising treating moderate to severe knee pain.

19. The method of claim 17 or 18, wherein the mammal is a human being that has a normal joint space in the knee.

20. The method of claim 17, comprising treating knee pain by:

c. selecting a patient having knee pain, and:

iii. OARSI Grade 0 or Kellgren and Lawrence Grade 0 or Grade 1 of joint space narrowing, or

iv. pain intensity of 5 or greater measured using the 0-10 NRS, or 5 cm or greater using the 10 cm VAS; and

d. administering the compound to the patient.

21. The method of claim 20, comprising selecting a patient having OARSI Grade 0 or Kellgren and Lawrence Grade 0 or Grade 1 of joint space narrowing.

22. The method of claim 20, comprising selecting a patient having pain intensity of 5 or greater measured using the 0-10 NRS, or 5 cm or greater using the 10 cm VAS.

23. The method of claim 20, 21, or 22, wherein the patient experiences a

reduction in pain intensity—when using a 100 mm visual analog scale—of at least about 5 mm.

24. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17, further comprising administering a second therapeutic agent indicated for the treatment of pain or another neurological disorder.

25. The method of claim 1 or 2, comprising treating musculoskeletal pain.

26. The method of claim 1 or 2, comprising treating inflammatory pain.

27. The method of claim 1 or 2, comprising treating back pain.

28. The method of claim 27, wherein the back pain comprises low back pain.

29. The method of claim 28, wherein the low back pain is related to a vertebral change.

30. The method of claim 1 or 2, comprising treating type 1 Modic changes, or type 1 and type 2 Modic changes.

31. The method of claim 30, wherein the Modic change is located at C1/2, C2/3, C3/4, C4/5, C5/6, or C6/7.

32. The method of claim 30, wherein the Modic change is located at C7/T1, T1/2, T2/3, T3/4, T4/5, T5/6, T6/7, T7/8, T8/9, T9/10, T10/11, or T11/12.

33. The method of claim 30, wherein the Modic change is located at T12/L1, L1/2, L2/3, L3/4, L4/5, or L5/S1.

34. The method of claim 1 or 2, comprising treating pain in an extremity.

35. The method of claim 1 or 2, comprising treating joint pain.

36. The method of claim 1 or 2, comprising treating muscle pain.

37. The method of claim 1 or 2, comprising treating neuropathic pain.

38. The method of claim 1 or 2, comprising treating complex regional pain syndrome.

39. The method of claim 38, wherein the complex regional pain syndrome is complex regional pain syndrome type I.

40. The method of claim 38, wherein the complex regional pain syndrome is complex regional pain syndrome type II.

41. The method of claim 1 or 2, comprising treating Paget's disease of bone.

42. The method of claim 1 or 2, comprising treating multiple myeloma.

43. The method of claim 1 or 2, comprising treating ankylosing spondylitis.

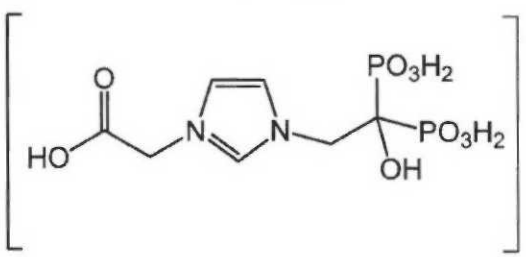
44. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40,

41, 42, or 43, wherein the compound is a RANK/RANKL antagonist, and is a polypeptide, a protein, or a nucleic acid.

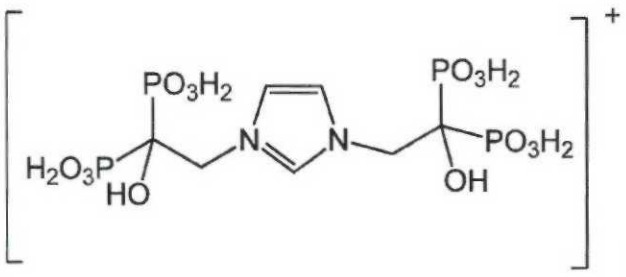
45. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is a RANK/RANKL antagonist, and is a small molecule.

46. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is a RANK/RANKL antagonist, and has a molecular weight below about 1000 Daltons.

47. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is ibrutinib, Benzo[*b*]thiophene-2-carboxamide, *N*-[3-[6-[[4-[(2*R*)-1,4-dimethyl-3-oxo-2-piperazinyl]phenyl]amino]-4,5-dihydro-4-methyl-5-oxo-2-pyrazinyl]-2-methylphenyl]-4,5,6,7-tetrahydro-, Benzamide, 4-(1,1-dimethylethyl)-*N*-[3-[8-(phenylamino)imidazo[1,2-*a*]pyrazin-6-yl]phenyl]-, Benzamide, *N*-[3-[4,5-dihydro-4-methyl-6-[[4-(4-morpholinylcarbonyl)phenyl]amino]-5-oxo-2-pyrazinyl]-2-methylphenyl]-4-(1,1-dimethylethyl)-, 2-Propenamide, *N*-[3-[[5-fluoro-2-[[4-(2-methoxyethoxy)phenyl]amino]-4-pyrimidinyl]amino]phenyl]-, 2-Pyridinecarboxamide, 4-[4-[[5-fluoro-4-[[3-[(1-oxo-2-propen-1-yl)amino]phenyl]amino]-2-pyrimidinyl]amino]phenoxy]-*N*-methyl- , AVL-101, AVL-291, AVL-292, [*N*-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide] (dasatinib), zoledronic acid, alpha-cyano-beta-hydroxy-beta-methyl-*N*-(2,5-ibromophenyl) propenamide,



(Compound 1), or



(Compound 2).

48. The method of claim 47, wherein the RANK/RANKL antagonist is ibrutinib.

49. The method of claim 47, wherein the compound is zoledronic acid.

50. The method of claim 49, comprising orally administering a steroid and zoledronic acid to the mammal.

51. The method of claim 50, wherein the steroid is prednisone.

52. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is a nitrogen-containing bisphosphonate.

53. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is pamidronic acid.

54. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is neridronic acid.

55. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is olpadronic acid.

56. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is alendronic acid.

57. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is incadronic acid.

58. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is ibandronic acid.

59. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40,

41, 42, or 43, wherein the compound is risedronic acid.

60. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is etidronic acid.

61. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is clodronic acid.

62. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is cimadronic acid.

63. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is minodronic acid.

64. The method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the compound is tiludronic acid.

65. The method of claim 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, or 64, wherein the compound is administered about every three months, or more frequently.

66. The method of claim 65, wherein the compound is administered intravenously.

67. The method of claim 65, wherein the compound, such as zoledronic acid, is administered orally.

68. A method of delivering zoledronic acid to the blood of a mammal, comprising: orally administering zoledronic acid to a mammal in need of treatment with zoledronic acid, wherein zoledronic acid is administered only once, or there is a period of about 24 hours to about 2 years between administration of dosage forms.

69. A method of systemically delivering zoledronic acid comprising orally administering a salt enhanced dosage form to a mammal to be treated with zoledronic acid, wherein the salt enhanced dosage form comprises a disodium salt form of zoledronic acid that has an enhanced oral bioavailability in a beagle dog as compared to a diacid form of zoledronic acid.

70. A method of enhancing the oral bioavailability of zoledronic acid comprising orally administering a dosage form containing zoledronic acid in the disodium salt form.

71. A method of safely delivering zoledronic acid to the blood of a mammal through repeated oral administration comprising:

orally administering about 0.05 mg/kg to about 4 mg/kg of zoledronic acid to the mammal no more frequently than once a day and more frequently than once a week; or

orally administering about 0.1 mg/kg to about 10 mg/kg to the mammal once a week, or less frequently

wherein zoledronic acid is orally administered at least 5 times.

72. A method of safely delivering zoledronic acid to the blood of a mammal through repeated oral administration comprising:

orally administering about 0.4 mg/kg to about 4 mg/kg of zoledronic acid to the mammal no more frequently than once a day and more frequently than once a week; or

orally administering about 0.4 mg/kg to about 10 mg/kg to the mammal once a week, or less frequently.

73. The method of claim 65, 66, 67, 68, 69, 70, 71, or 72, wherein about 0.5 mg/kg to about 2 mg/kg of zoledronic acid is orally administered to the mammal daily.

74. The method of claim 73, wherein about 0.6 mg/kg to about 0.9 mg/kg of zoledronic acid is orally administered to the mammal daily.

75. The method of claim 65, 66, 67, 68, 69, 70, 71, or 72, wherein about 0.5 mg/kg to about 2 mg/kg of zoledronic acid is orally administered to the mammal weekly.

76. The method of claim 75, wherein about 0.6 mg/kg to about 0.9 mg/kg of zoledronic acid is orally administered to the mammal weekly.

77. The method of claim 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76, wherein the mammal experiences pain relief at least 24 hours after the compound is administered to the mammal.

78. The method of claim 77, wherein the mammal experiences pain relief three months after the compound is administered.

79. The method of claim 78, wherein the mammal receives about 40 mg to about 700 mg of the compound in a period of one month or less.

80. The method of claim 78, wherein the human being experiences pain relief that lasts for a duration of at least 48 hours after administration of the compound.

81. The method of claim 78, wherein the human being receives the compound no more often than once daily.

82. The method of claim 78 or 80, wherein there is a period of about 24 hours to about 7 days between administration of dosage forms.

83. The method of claim 82, wherein the compound is administered weekly.

84. The method of claim 80, wherein there is a period of about 14 days to about 28 days between administration of dosage forms.

85. The method of claim 80, wherein there is a period of at least one month between administration of dosage forms.

86. The method of claim 80, wherein about 10 mg to about 100 mg of the compound is administered to the mammal weekly.

87. The method of claim 80, wherein about 10 mg to about 250 mg of the compound is administered to the mammal monthly

88. The method of claim 77, wherein about 100 mg to about 1000 mg of the compound is administered to the mammal daily.

89. The method of claim 80, wherein there is a period of about 7 days to about 14 days between administration of dosage forms.

90. The method of claim 80, wherein the compound is administered more than once.

91. The method of claim 90, wherein zoledronic acid is orally administered to a human being in a manner that results in a bioavailability of 1.2% to about 3% in the human being.

92. The method of claim 90, wherein the zoledronic acid is administered in a manner that results in a bioavailability of 1.5% to 3% in the human being.

93. The method of claim 90, wherein zoledronic acid is administered daily for 2 to 7 consecutive days.

94. The method of claim 90, wherein the compound is administered once weekly for a period of six weeks.

95. The method of claim 90, wherein the compound comprises zoledronic acid, and the weekly dose is between about 25 mg and about 75 mg.

96. The method of claim 90, wherein about 10 mg to about 100 mg of zoledronic acid is orally administered daily.

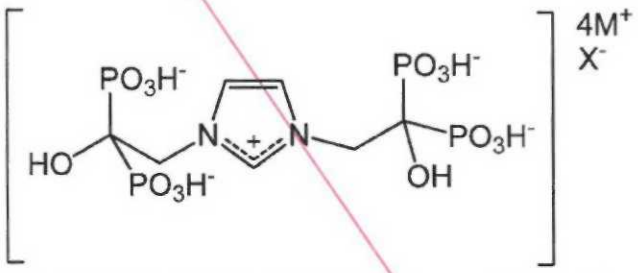
97. The method of claim 90, wherein about 40 mg to about 50 mg of zoledronic acid is orally administered daily.

98. The method of claim 90, wherein about 50 mg of zoledronic acid is orally administered daily.

99. The method of claim 90, wherein about 50 mg to about 100 mg of zoledronic acid is orally administered daily.

100. The method of any preceding claim, wherein zoledronic acid is administered with Compound 1 and/or Compound 2; Compound 1 is less than 0.1% of the total weight of zoledronic acid, Compound 1, and Compound 2; and Compound 2 is less than 0.1% of the total weight of zoledronic acid, Compound 1, and Compound 2.

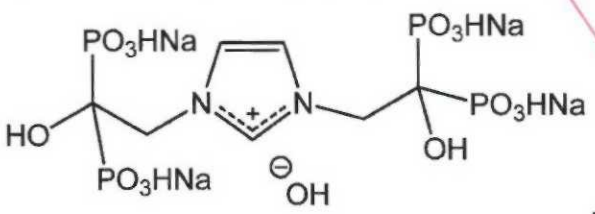
101. A compound represented by a formula:



wherein X^- is F^-, Br^-, Cl^-, I^-, OH^-, or acetate; and

M^+ is Na^+, K^+, or NH_4^+.

102. The compound of claim 101, further represented by a formula,



103. The compound of claim 102, wherein the compound is in a hydrate form.

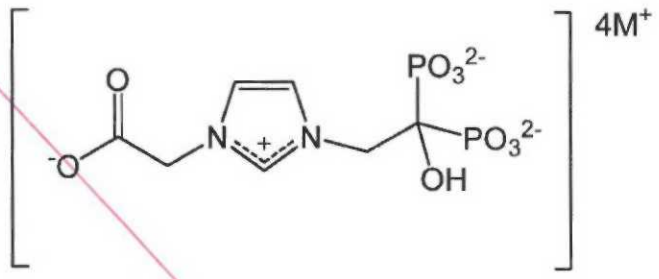
104. A dosage form comprising the compound of claim 101, 102, or 103.

105. The dosage form of claim 104, wherein the compound is no more than 0.1% (w/w) of the total amount of therapeutically active agent in the dosage form.

106. The dosage form of claim 104, wherein the compound is at least 20% of the total amount of therapeutically active agent in the dosage form.

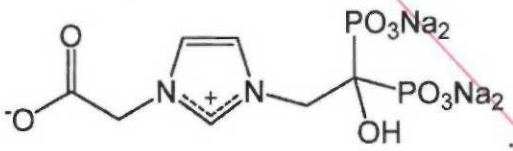
107. The dosage form of claim 104, wherein the compound is at least 90% of the total amount of therapeutically active agent in the dosage form.

108. A compound represented by a formula:



wherein M^+ is Na^+, K^+, or NH_4^+.

109. The compound of claim 108, wherein the compound is further represented by a formula,



110. The compound of claim 109, wherein the compound is in a hydrate form.

111. A dosage form comprising the compound of claim 108, 109, or 110.

112. The dosage form of claim 111, wherein the compound is no more than 0.1% (w/w) of the total amount of therapeutically active agent in the dosage form.

113. The dosage form of claim 111, wherein the compound is at least 20% of the total amount of therapeutically active agent in the dosage form.

114. The dosage form of claim 111, wherein the compound is at least 90% of the total amount of therapeutically active agent in the dosage form.