(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
6 December 2007 (06.12.2007)

(10) International Publication Number
WO 2007/139645 A3

(51) International Patent Classification:
*C07D 275/04* (2006.01)

(21) International Application Number:
PCT/US2007/010124

(22) International Filing Date: 20 April 2007 (20.04.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/440,965 25 May 2006 (25.05.2006) US

(71) Applicant *(for all designated States except US):* **TROY TECHNOLOGY CORPORATION, INC.** [US/US]; Suite 415, 200 West Ninth Street Plaza, Wilmington, DE 19801 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only):* **LINDNER, Wolfgang** [DE/US]; 1480 Route 46, Parsippany, NJ 07054 (US).

(74) Agent: **YESUKEVICH, Robert,** A.; 8 Vreeland Road, Florham Park, NJ 07932 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, **AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,** EE, **EG,** ES, **FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD,** SE, **SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW**

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, **DK,** EE, ES, FI, FR, GB, GR, HU, IE, **IS, IT,** LT, LU, LV, MC, MT, NL, PL, PT, **RO,** SE, **SI,** SK, TR), OAPI (BF, **BJ,** CF, CG, CI, CM, GA, GN, GQ, GW, ML, **MR,** NE, SN, TD, TG).

**Declarations under Rule** 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(U))*
— *of inventorship (Rule 4.17(iv))*

**Published:**
— *with international search report*
— *with amended claims*

(88) Date of publication of the international search report:
12 September 2008

Date of publication of the amended claims: 6 November 2008

(54) Title: IMMOBILIZED l,2-BENZISOTHIAZOLIN-3-ONE

(57) Abstract: The present invention provides novel antimicrobial immobilized 1,2- benzisothiazolin-3-one/zinc oxide (BIT/ZnO) complexes useful as antimicrobial agents because of their resistance to being leached from the substrate to which they are attached. The present invention is also directed to methods for preparing the BIT/ZnO complexes, to BIT/ZnO complexes prepared by the novel methods, to methods for using the BIT/ZnO complexes to inhibit microbial growth or reduce the level of bacteria on the surface of a substrate, and to substrates protected from microbial attack by being treated with the BIT/ZnO complexes. The present invention is further directed to compositions comprising l,2-benzisothiazolin-3-one which has been immobilized with zinc oxide.

WO 2007/139645 A3

AMENDED CLAIMS
received by the International Bureau on 04 September 2008 (04.09.2008)

1. A method for making an immobilized 1,2-benzisothiazoli π-3-one/zinc oxide complex comprising the steps of:

(a) heating 1,2-benzisothiazolin-3-one and zinc chloride to reflux in a Ci-$C_4$ branched or unbranched alcohol to form a solution;

(b) cooling the solution from step (a) and adding an immobilizing effective amount of zinc oxide to the solution to form a mixture;

(c) heating the mixture from step (b) to reflux and then cooling the mixture to room temperature;

(d) filtering the mixture from step (c) to obtain a solid material which is the immobilized 1,2~benzisothiazoli π-3-one/zinc oxide complex.

2. The method of claim 1, further comprising washing the solid material from step (d) with a $C_1$-$C_4$ branched or unbranched alcohol and drying the solid material under vacuum.

3. The method of claim 1, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-o πe:zinc oxide is from about 1:20 to about 3:1.

4. A method for making a dispersion concentrate of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex comprising the steps of:

(a) forming an aqueous solution of 1,2-benzisothiazoli π-3-one and potassium hydroxide having a pH from about 7 to about 8.5;

(b) adding zinc chloride and an immobilizing effective amount of zinc oxide to the solution in step (a) to form a mixture; and

(c) milling the mixture from step (b) to form the dispersion concentrate of immobilized 1,2-benzisothiazolin-3-one/zi πc oxide complex.

5. The method of claim 4, further comprising adding a dispersing agent to the mixture in step (b) and a defoaming agent to the mixture in step (c).

AMENDED SHEET (ARTICLE 19)

6. The method of claim 4, wherein the milling in step (c) provides an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex having a particle size distribution from about 0.8μm 50% / 10μm 95% and the viscosity of the mixture is adjusted from about 400 to about 1200mPas by admixing a viscosity adjusting agent.

7. The method of claim 4, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1;20 to about 3:1.

8. A method for making a dispersion concentrate of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex comprising the steps of:

(a) forming an aqueous mixture of 1,2-benzisothiazolin-3-one, zinc chloride, and an immobilizing effective amount of zinc oxide;

(b) adjusting the pH of the mixture in step (a) to from about 7 to about 8.5; and

(c) milling the mixture from step (b) to form the dispersion concentrate of immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

9. The method of claim 8, further comprising adding a dispersing agent to the mixture in step (a) and a defoaming agent to the mixture in step (c).

10. The method of claim 8, wherein the milling in step (c) provides an immobilized 1,2-benzisothiazoli π-3-one/zinc oxide complex having a particle size distribution from about 0.8μm 50% / 10μm 95% and the viscosity of the mixture is adjusted from about 400 to about 1200mPas by admixing a viscosity adjusting agent.

11. The method of claim 8, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

12. A method for making a dispersion concentrate of an immobilized 1,2-benzisothiazoli π-3-one/zinc oxide complex comprising the steps of:

(a) forming an aqueous mixture of 1,2-benzisothiazolin-3-one and an immobilizing effective amount of zinc oxide; and

(b) milling the mixture from step (a) to form the dispersion concentrate of immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

AMENDED SHEET (ARTICLE 19)

13. The method of claim 12, further comprising adding a dispersing agent to the mixture in step (a) and a defoaming agent to the mixture in step (b).

14. The method of claim 12 wherein the milling in step (b) provides an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex having a particle size distribution from about 0.8μm 50% / 10μm 95% and the viscosity of the mixture is adjusted from about 400 to about 1200mPas by admixing a viscosity adjusting agent.

15. The method of claim 12 wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

16. An immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

(a) heating 1,2-benzisothiazolin-3-one and zinc chloride to reflux in a C1-$C_4$ branched or unbranched alcohol to form a solution;

(b) cooling the solution from step (a) and adding an immobilizing effective amount of zinc oxide to the solution to form a mixture;

(c) heating the mixture from step (b) to reflux and then cooling the mixture to room temperature;

(d) filtering the mixture from step (c) to obtain a solid material which is the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

17. The complex preparable by the method of claim 16, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

18. A dispersion which includes an aqueous phase and particles composed of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

(a) forming an aqueous solution of 1,2-benzisothiazolin-3-one and potassium hydroxide having a pH from about 7 to about 8.5;

(b) adding zinc chloride and an immobilizing effective amount of zinc oxide to the solution in step (a) to form a mixture; and

(c) milling the mixture from step (b) to form a dispersion which includes an aqueous phase and particles composed of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

19. The method of claim 18, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

20. A dispersion which includes an aqueous phase and particles composed of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

(a) forming an aqueous mixture of 1,2-benzisothiazolin-3-one, zinc chloride, and an immobilizing effective amount of zinc oxide;

(b) adjusting the pH of the mixture in step (a) to from about 7 to about 8.5; and

(c) milling the mixture from step (b) to form a dispersion which includes an aqueous phase and particles composed of animmobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

21. The complex preparable by the method of claim 20, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

22. An immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

(a) forming an aqueous mixture of 1,2-benzisothiazolin-3-one and an immobilizing effective amount of zinc oxide; and

(b) milling the mixture from step (a) to form the dispersion concentrate of immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

23. The complex preparable by the method of claim 22, wherein the weight to weight ratio of 1,2-benzisothiazolin~3-one:zinc oxide is from about 1:20 to about 3:1.

24. A method for protecting a substrate from antimicrobial infestation which comprises treating the substrate with an antimicrobially effective amount of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

AMENDED SHEET (ARTICLE 19)

(a) heating 1,2-benzisothiazolin-3-one and zinc chloride to reflux in a $C_{1-4}$ branched or unbranched alcohol to form a solution;

(b) cooling the solution from step (a) and adding an immobilizing effective amount of zinc oxide to the solution to form a mixture;

(c) heating the mixture from step (b) to reflux and then cooling the mixture to room temperature;

(d) filtering the mixture from step (c) to obtain a solid material which is the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

25. The method of claim 24, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

26. A method for protecting a substrate from antimicrobial infestation which comprises treating the substrate with an antimicrobially effective amount of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

(a) forming an aqueous solution of 1,2-benzisothiazolin-3-one and potassium hydroxide having a pH from about 7 to about 8.5;

(b) adding zinc chloride and an immobilizing effective amount of zinc oxide to the solution in step (a) to form a mixture; and

(c) milling the mixture from step (b) to form the dispersion concentrate of immobilized 1,2-benzisothiazoli-3-one/zinc oxide complex.

27. The method of claim 26, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

28. A method for protecting a substrate from antimicrobial infestation which comprises treating the substrate with an antimicrobially effective amount of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

(a) forming an aqueous mixture of 1,2-benzisothiazolin-3-one, zinc chloride, and an immobilizing effective amount of zinc oxide;

(b) adjusting the pH of the mixture in step (a) to from about 7 to about 8.5; and

(c) milling the mixture from step (b) to form the dispersion concentrate of immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

29. The method of claim 28, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1 .

30. A method for protecting a substrate from antimicrobial infestation which comprises treating the substrate with an antimicrobially effective amount of an immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising the steps of:

(a) forming an aqueous mixture of 1,2-benzisothiazoli π-3-one and an immobilizing effective amount of zinc oxide; and

(b) milling the mixture from step (a) to form the dispersion concentrate of immobilized 1,2-beπzisothiazolin-3-one/zinc oxide complex.

31. The method of claim 30, wherein the weight to weight ratio of 1,benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1 .

32. An antibacterial composition that is suitable for providing antibacterial activity on the surface of a solid comprising 1,2-benzisothiazolin-3-one which has been immobilized as part of a 1,2-benzisothiazolin-3-one/zinc oxide complex.

33. The composition of claim 32, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1 .

34. The composition of claim 33, wherein the weight to weight ratio of 1,2-beπzisothiazolin-3-o πe:zinc oxide is from about 1:5 to about 1:1.

35. The composition of claim 34, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zi πc oxide is from about 1:3 to about 2:3.

36. An immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method which comprises:

providing a mixture which includes an immobilizing effective amount of zinc oxide; a liquid phase including water, a $C_1$-$C_4$ branched or unbranched alcohol, or a mixture thereof; and an antimicrobial agent dissolved in the liquid phase and selected from the group consisting of 1,2-benzisothiazolin-3-one, salts of 1,2-benzisothiazolin-3-o πe, and mixtures thereof; and

precipitating the antimicrobial agent to produce an immobilized 1,2-benzisothiazolin-3-o πe/zinc oxide complex.

37. The complex preparable by the method of claim 36, wherein the weight to weight ratio of the antimicrobial agentzinc oxide is from about 1:20 to about 3:1 .

38. The complex preparable by the method of claim 37, wherein the weight to weight ratio of the antimicrobial agentzinc oxide is from about 1:5 to about 1:1.

39. The complex preparable by the method of claim 36, wherein the liquid phase includes is water.

40. The complex preparable by the method of claim 39, wherein the liquid phase has a pH of about 7 to about 8.5.

41. The complex preparable by the method of claim 36, wherein the mixture includes a zinc compound selected from the group consisting of zinc chloride, zinc bromide, zinc acetate, zinc formate, and zinc nitrate and mixtures thereof.

42. The complex preparable by the method of claim 41, wherein the mixture includes zinc chloride.

43. The complex preparable by the method of claim 41, wherein the mixture includes zinc acetate.

44. The complex preparable by the method of claim 36, which is in the form of particles having a particle size distribution in the range of about 0.8 micrometer 50% / 3.5 micrometer 95% to about 19 micrometer 50% / 79 micrometer 95%.

45. The complex preparable by the method of claim 36, wherein the liquid phase includes methanol, ethanol, isopropanol, n-propanol, n-butanol, sec-butanol, or a mixture thereof, and the antimicrobial agent is precipitated by cooling the mixture.

46. The complex preparable by the method of claim 36, in which includes at least about 40% immobilized 1,2-benzisothiazolin-3-one, based upon the 1,2-benzisothiazolin-3-one used to prepare the complex.

47. The complex preparable by the method of claim 36, in which the infrared spectrum does not include a band at 1645 $cm^{-1}$.

48. The complex preparable by the method of claim 47, in which the infrared spectrum does not include a band at 1055 or 880 $cm^{-1}$.

49. The complex preparable by the method of claim 48, which has an infrared spectrum that includes bands at 910, 899 and 797 $cm^{-1}$.

50. The complex preparable by the method of claim 36, in which the antimicrobial agent is precipitated by cooling, neutralizing or milling the mixture.

51. The complex preparable by the method of claim 48, in which the antimicrobial agent is precipitated by cooling or neutralizing the mixture.

52. The complex preparable by the method of claim 48, in which the antimicrobial agent is precipitated by milling the mixture.

53. An immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising:

providing a mixture including 1,2-benzisothiazolin-3-one, zinc chloride, an immobilizing effective amount of zinc oxide, and a liquid phase which includes a $C_1$-$C_4$ branched or unbranched alcohol; and

cooling the mixture and recovering a solid material which includes the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

54. An immobilized 1,2-benzisothiazolin-3-on θ/zinc oxide complex preparable by a method comprising:

providing a mixture including zinc chloride, an immobilizing effective amount of zinc oxide, and an aqueous solution having a pH from about 7 to about 8.5 which includes 1,2-benzisothiazolin-3-one; and

milling the mixture to produce a dispersion concentrate including the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

55. An immobilized 1,2-beπzisothiazolin-3-one/zinc oxide complex preparable by a method comprising:

providing an aqueous mixture including water, 1,2-benzisothiazolin-3-o πe and an immobilizing effective amount of zinc oxide; and

milling the mixture produce a dispersion concentrate of the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

56. An immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex preparable by a method comprising:

providing an aqueous mixture having a pH of about 7 to about 8.5 which includes water, 1,2-benzisothiazolin-3-one, zinc chloride and an immobilizing effective amount of zinc oxide; and

milling the mixture to produce a dispersion concentrate which includes the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex.

57. A 1,2-benzisothiazolin-3-one/zinc oxide complex that resists decomposition by methanol at room temperature; which complex comprises carbon, hydrogen, nitrogen, oxygen, sulfur and zinc; and

which complex, when blended with methanol at room temperature for 15 minutes, yields an amount of 1,2-benzisothiazolin-3-one per unit mass of the complex which is less than about 50% of the amount of 1,2-benzisothiazolin-3-one per unit mass initially measurable by hydrolysis and extraction of the complex;

whereby the complex resists decomposition by methanol *at* room temperature.

58. A method for protecting a substrate from antimicrobial infestation which comprises treating the substrate with an antimicrobially effective amount of the complex of claim 57.

59. A 1,2-benzisothiazolin-3-one/zinc oxide complex that resists decomposition by water at room temperature; which complex comprises carbon, hydrogen, nitrogen, oxygen, sulfur and zinc;

which complex, when incorporated in a dried film of a water-based paint and immersed in water at room temperature for 8 hours, retains an amount of hydrolyzable and extractable 1,2-benzisothiazolin-3-one per unit mass of the complex that is at least about 40% of the amount of 1,2-benzisothiazolin-3-one per unit mass initially measurable by hydrolysis and extraction of the complex in the dried film;

whereby the complex resists decomposition by water at room temperature.

60. A method for protecting a substrate from antimicrobial infestation which comprises treating the substrate with an antimicrobially effective amount of the complex of claim 59.

61. A 1,2-benzisothiazolin-3-one/zinc oxide which complex comprises carbon, hydrogen, nitrogen, oxygen, sulfur and zinc; and

which complex has an infrared spectrum that includes bands at 910, 899 and 797 $cm^{-1}$.

62. The complex of claim 61 in which the infrared spectrum does not include a band at 1645, 1055 or 880 $cm^{-1}$.

63. A method for protecting a substrate from antimicrobial infestation which comprises treating the substrate with an antimicrobially effective amount of the complex of claim 61.

64. 1,2-Benzisothiazolin-3-one or a salt thereof characterized in that it has been immobilized on zinc oxide.

65. Composition according to claim 64, wherein the weight to weight ratio of 1,2-benzisothiazolin-3-one:zinc oxide is from about 1:20 to about 3:1.

66. Composition according to any one of claims 64 to 65 wherein the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex is having a particle size distribution from about 0.8 µm 50%/10 µm 95%.

67. Composition according to any one of claims 64 to 65 wherein the immobilized 1,2-benzisothiazolin-3-one/zinc oxide complex is having a particle size distribution from about 2.5 µm 50%/4 µm 95%.

68. Composition according to any one of claims 64 to 67, comprising a further component from the group consisting of antimicrobial agents and fungicidal film preservatives.

69. Composition according to claim 67 wherein the further component is selected from methylbenzimidazol-2-ylcarbamate, 3-iodo-2- propynyl butyl carbamate, zinc pyrithione, 5-chloro-2-(2,4- dichlorophenoxy)phenol), 2-n-octylisothiazolin-3-one, 4,5-dichloro-2-n-octylisothiazolin-3-one, 2,4,5,6,tetrachloroisophthalonitril, 3-benzo[b]thieπ-2-yl-5,6-dihydro-1 ,4,2-oxathiazine 4-oxide, zinc bis(dimethyldithio-carbamate), tetramethylthiuram disulfide, 2-n-butyl-benzisothiazolin-3-one, silver and silver compounds, zinc silver zeolite compounds, silver chloride on titanium dioxide and nano-scale silver.

70. Composition according to any one of claims 64 to 69 further comprising adjuvants selected from the group consisting of organic binding agents, auxiliary solvents, processing additives, fixatives, plasticizers, UV-stabilizers or stability enhancers, water-soluble or water-insoluble dyes, color pigments, siccatives, corrosion inhibitors, antisettlement agents, anti-skinning agents, and complex basic salts of carboxylic acids.

71. Use of a composition according to any one of claims 64 to 70 as antimicrobial agent.

72. Use according to claim 71 wherein the composition is used for the protection of aqueous based paints and coatings, adhesives, joint cements, sealants, caulks, printing inks, metal working fluids, polymer emulsions, pigment dispersions, aqueous industrial products, lubricants, or caulkings.