Although providing certain advantages over the use of MTC, the synthesis of LMT.2HCl under certain conditions may result in $CH_3Cl$ being trapped within the crystal. This then needs to be removed since $CH_3Cl$ is toxic and levels need to be kept below safety levels.

Furthermore LMT.2HBr contains bromide ions. This is in principle less desirable since bromide is toxic either at high levels or with chronic dosing and, at lower levels, can causes side effects such as confusion in patients.

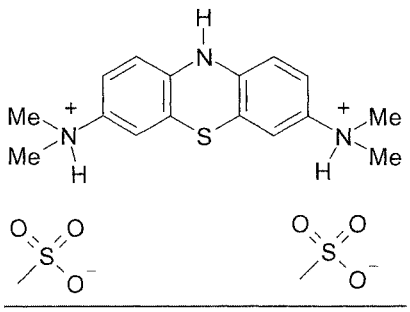
Therefore it can be seen the provision of further salts of methylthioninium compounds, having one or more desirable properties over those already known, would be a contribution to the art.

Furthermore the provision of novel formulations of methylthioninium compounds which enhance stability, absorption, and\or otherwise improve their effectiveness as therapeutics would be a contribution to the art.

## SUMMARY ~~OF THE INVENTION~~

The present inventors have now identified a new class of stable phenothiazine diaminium compounds which have improved properties as compared to previously disclosed diaminophenothiazine compounds and salts.

In one aspect, there is provided a pharmaceutical composition comprising a compound of the following formula:



and a pharmaceutically acceptable carrier or diluent, for use in the treatment or prophylaxis of a protozoal disease, skin cancer or melanoma; or a viral or bacterial disease.

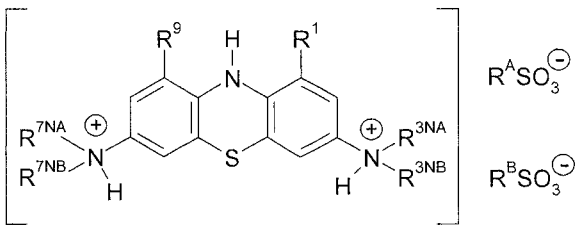
In another aspect, there is provided use of a pharmaceutical composition according to the present invention in the manufacture of a medicament for use in the treatment or prophylaxis of skin cancer or melanoma. In a further aspect, there is provided use of a pharmaceutical composition according to the present invention in the manufacture of a medicament for use in the treatment or prophylaxis of a viral, bacterial or protozoal disease condition.

The properties of the compounds are described hereinafter, whereby it can be seen that in preferred ~~embodiments~~examples the ~~invention~~present disclosure can provide one or more of improved physical, pharmacokinetic, biochemical or other beneficial properties.

In other ~~aspects~~examples the present inventors also provide novel formulations of 3,7-diamino-10H-phenothiazinium salts.

In one ~~aspect~~example the present ~~invention~~disclosure provides certain compounds, specifically, certain phenothiazine diaminium compounds, as described herein.

The compound may be selected from compounds of general formula (I):



(I)

wherein:

each of $R^1$ and $R^9$ is independently selected from: -H, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, and halogenated $C_{1-4}$alkyl;

each of $R^{3NA}$ and $R^{3NB}$ is independently selected from: -H, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, and halogenated $C_{1-4}$alkyl;

each of $R^{7NA}$ and $R^{7NB}$ is independently selected from: -H, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, and halogenated $C_{1-4}$alkyl;

and wherein:

each of $R^A$ and $R^B$ is independently selected from:

$C_{1-4}$alkyl, halogenated $C_{1-4}$alkyl, and $C_{6-10}$aryl;

*or*

$R^A$ and $R^B$ are linked to form a group $R^{AB}$, wherein $R^{AB}$ is selected from:

$C_{1-6}$ alkylene and $C_{6-10}$ arylene;

and pharmaceutically acceptable salts thereof.

Another ~~aspect~~example of the ~~invention~~disclosure pertains to processes for synthesizing a compound as described above.

Another ~~aspect~~example of the ~~invention~~disclosure pertains to a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable carrier or diluent.

Another ~~aspect~~example of the ~~invention~~disclosure pertains to a method of preparing a pharmaceutical composition comprising admixing a compound as described herein and a pharmaceutically acceptable carrier or diluent.

Another ~~aspect~~example of the ~~invention~~disclosure pertains to a pharmaceutical composition in solid dosage form, comprising a compound as described herein and further comprising at least one diluent suitable for dry compression, and optionally one or more other excipients.

Another ~~aspect~~example of the ~~invention~~disclosure pertains to a process for the manufacture of a pharmaceutical composition by a dry compression method, said composition being a solid dosage form comprising a compound as described herein, at least one diluent suitable for dry compression, and optionally one or more other excipients.

Another ~~aspect~~example of the ~~invention~~disclosure pertains to a free-flowing, cohesive powder, comprising a compound as described herein and at least one diluent suitable for dry compression, and optionally one or more other excipients, said powder being capable of being compressed into a solid dosage form.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to a method of reversing and/or inhibiting the aggregation of a protein (e.g., a tau protein, a synuclein, etc.), for example, aggregation of a protein associated with a neurodegenerative disease and/or clinical dementia, comprising contacting the protein with an effective amount of a compound or composition as described herein. Such a method may be performed in vitro, or in vivo.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to a method of treatment or prophylaxis of a disease condition in a subject comprising administering to said subject a prophylactically or therapeutically effective amount of a compound as described herein, preferably in the form of a pharmaceutical composition, preferably a pharmaceutical composition in solid dosage form, as further described herein.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to a compound or composition as described herein for use in a method of treatment or prophylaxis (e.g., of a disease condition) of the human or animal body by therapy.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to use of a compound or composition as described herein, in the manufacture of a medicament for use in the treatment or prophylaxis of a disease condition.

In some ~~embodiments~~examples, the disease condition is a disease of protein aggregation.
In some ~~embodiments~~examples, the disease condition is a tauopathy, e.g., a neurodegenerative tauopathy, e.g., Alzheimer's disease or other disease described hereinafter.
In some ~~embodiments~~examples, the disease condition is skin cancer, e.g., melanoma.
In some ~~embodiments~~examples, the disease condition is a viral, bacterial or protozoal disease condition, e.g., Hepatitis C, HIV, West Nile Virus (WNV), or malaria.

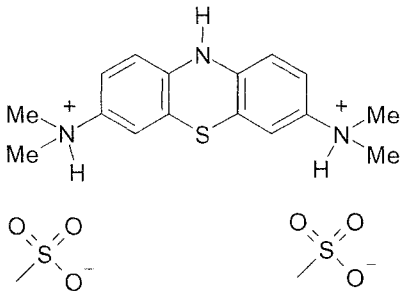
Another ~~aspect~~example of the present ~~invention~~disclosure pertains to a method of inactivating a pathogen in a sample (for example a blood or plasma sample), comprising the steps of introducing a compound or composition as described herein, into the sample, and then exposing the sample to light.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to a kit comprising (a) a compound as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the compound or composition.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

CLAIMS

1. A pharmaceutical composition comprising a compound of the following formula:



and a pharmaceutically acceptable carrier or diluent,

for use in the treatment or prophylaxis of a protozoal disease, skin cancer or melanoma; or a viral or bacterial disease.

2. A pharmaceutical composition according to claim 1 which is a solid dosage form comprising the compound and at least one diluent suitable for dry compression.

3. A pharmaceutical composition according to claim 2, wherein the solid dosage form dissolves to an extent of at least 80% within 30 minutes as evaluated by a standard pharmacopeial method as defined in United States Pharmacopeia (USP) General Chapter <711>.

4. A pharmaceutical composition according to claim 2 or claim 3, wherein said at least one diluent is selected from microcrystalline cellulose, mannitol, calcium salts and sugars.

5. A pharmaceutical composition according to claim 4 wherein the sugar is selected from: lactose, sucrose, dextrose and maltodextrin.

6. A pharmaceutical composition according to any one of claims 2 to 5, further comprising at least one disintegrant selected from crosslinked polyvinylpyrrolidone, sodium starch glycolate, crosslinked sodium carboxymethyl cellulose, or pregelatinized starch.

7. A pharmaceutical composition according to any one of claims 2 to 6 wherein the solid dosage form is film-coated.

8. A pharmaceutical composition according to any one of claims 2 to 7 further comprising an acid having a pK1 of greater than 1.5, optionally wherein the acid is selected from maleic acid, phosphoric acid, ascorbic acid, sorbic acid, aspartic acid and sialic acid.

9. A pharmaceutical composition according to claim 8, further comprising a carrier selected from mannitol, a cellulosic material, a starch, or mixtures thereof.

10. A pharmaceutical composition according to any one of claims 2 to 9 characterised in that said composition comprises particles of which more than 10% have a size greater than 10 microns.

11. A pharmaceutical composition according to any one of claims 2 to 9 comprising a carrier having a particle shape which is averse to water.

12. A pharmaceutical composition according to any one of claims 1 to 11 for use in the treatment of prophylaxis of a viral disease selected from Hepatitis C, HIV, and West Nile Virus

13. A pharmaceutical composition according to any one of claims 1 to 11 for use in the treatment of prophylaxis of malaria.

14. Use of a pharmaceutical composition according to any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment or prophylaxis of skin cancer or melanoma.

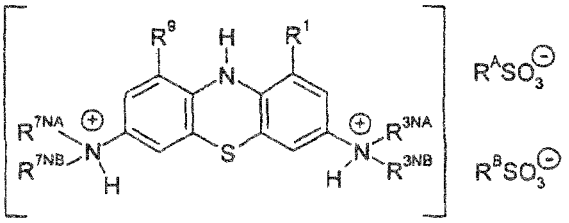
15. Use of a pharmaceutical composition according to any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment or prophylaxis of a viral, bacterial or protozoal disease condition.

16. Use of a pharmaceutical composition according to claim 15 in the manufacture of a medicament for use in the treatment or prophylaxis of a viral disease selected from Hepatitis C, HIV, and West Nile Virus.

17. Use of a pharmaceutical composition according to claim 15 in the manufacture of a medicament for use in the treatment or prophylaxis of malaria.

CLAIMS

1. A compound selected from compounds of general formula (I):



(I)

wherein:

each of $R^1$ and $R^9$ is independently selected from: -H, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, and halogenated $C_{1-4}$alkyl;

each of $R^{3NA}$ and $R^{3NB}$ is independently selected from: -H, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, and halogenated $C_{1-4}$alkyl;

each of $R^{7NA}$ and $R^{7NB}$ is independently selected from: -H, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, and halogenated $C_{1-4}$alkyl;

and wherein:

each of $R^A$ and $R^B$ is independently selected from:

$C_{1-4}$alkyl, halogenated $C_{1-4}$alkyl, and $C_{6-10}$aryl;

*or*

$R^A$ and $R^B$ are linked to form a group selected from:

$C_{1-6}$ alkylene and $C_{6-10}$ arylene;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein each of $R^A$ and $R^B$ is independently $C_{1-4}$alkyl.

3. A compound according to claim 1 wherein each of $R^A$ and $R^B$ is independently methyl.

4. A compound according to any one of claims 1 to 3 wherein each of $R^1$ and $R^9$ is independently -H.

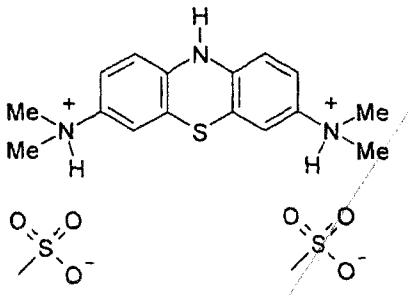
5. A compound according to any one of claims 1 to 4 wherein each of $R^{3NA}$ and $R^{3NB}$ and is independently $C_{1-4}$alkyl.

6. A compound according to claim 5 wherein each of $R^{3NA}$ and $R^{3NB}$ is independently methyl.

7. A compound according to any one of claims 1 to 6 wherein each of $R^{7NA}$ and $R^{7NB}$ is independently $C_{1-4}$alkyl.

8. A compound according to claim 7 wherein each of $R^{7NA}$ and $R^{7NB}$ is independently methyl.

9. A compound according to claim 1 which is of the following formula:



or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

10. A compound according to any one of claims 1 to 9 in crystalline form.

11. A compound according to claim 9 in crystalline form, having a crystal structure as represented by Figures 11-16.

12. A compound according to any one of claims 1 to 11 in substantially purified form.

13. A composition comprising a compound according to any one of claims 1 to 12 and a pharmaceutically acceptable carrier or diluent.

14. A process for preparing a pharmaceutical composition comprising admixing a compound according to any one of claims 1 to 12, and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition as claimed in claim 13 which is a solid dosage form comprising the compound according to any one of claims 1 to 12 and at least one diluent suitable for dry compression.

16. A composition according to claim 15 wherein the solid dosage form is produced by direct compression.

17. A composition according to claim 15 wherein the solid dosage form is produced by dry granulation.

18. A composition according to any one of claims 15 to 17, wherein the solid dosage form dissolves to an extent of at least 80% within 30 minutes as evaluated by a standard pharmacopeial method as defined in United States Pharmacopeia (USP) General Chapter <711>.

19. A composition according to any one of claims 15 to 18, wherein said at least one diluent is selected from microcrystalline cellulose, lactose, mannitol, calcium salts such as, calcium phosphate dibasic, calcium sulphate, calcium carbonate, and sugars such as lactose, sucrose, dextrose and maltodextrin.

20. A composition according to any one of claims 15 to 19, further comprising at least one disintegrant.

21. A composition according to claim 20 wherein the disintegrant is selected from crosslinked polyvinylpyrrolidone (crospovidone), sodium starch glycolate, crosslinked sodium carboxymethyl cellulose (sodium croscarmellose), or pregelatinized starch.

22. A composition according to any one of claims 15 to 21 wherein the solid dosage form is film-coated.

23. A composition according to any one of claims 15 to 22 further comprising an acid having a pK1 of greater than 1.5.

24. A composition according to claim 23, wherein the acid is selected from maleic acid, phosphoric acid, ascorbic acid, sorbic acid, aspartic acid and sialic acid.

25. A composition according to claim 23 or claim 24, further comprising a carrier selected from mannitol, a cellulosic material, a starch, or mixtures thereof.

26. A composition according to any one of claims 15 to 25 characterised in that said composition comprises particles of which more than 10% have a size greater than 10 microns.

27. A composition according to any one of claims 15 to 25 comprising a carrier having a particle shape which is averse to water, such as Elcema TM , ethylcellulose, mannitol, or Starch 1500 TM.

28. A free-flowing, cohesive powder comprising a compound according to any one of claims 1 to 12 and at least one diluent suitable for dry compression and optionally one or more other excipients, said powder being capable of being compressed into a solid dosage form.

29. A process as claimed in claim 14 for the manufacture of a pharmaceutical composition, which process comprises dry compression of an intimate powder mixture comprising the compound according to any one of claims 1 to 12 with at least one diluent suitable for dry compression and optionally one or more other excipients.

30. A process according to claim 29, wherein the process comprises a direct compression process wherein said compound, at least one diluent, and optional excipients are blended together in solid particulate form to create said intimate mixture and then compressed using a tablet machine.

31. A process according to claim 30, wherein said at least one diluent is selected from microcrystalline cellulose, lactose, mannitol, calcium salts such as, calcium phosphate dibasic, calcium sulphate, calcium carbonate, and sugars such as lactose, sucrose, dextrose and maltodextrin.

32. A process according to claim 30, wherein said at least one diluent is a granulated product prepared by moist granulation of one or more excipients.

33. A process according to claim 32, comprising a step of wet massing one or more excipients using a granulating fluid, and drying to form said granulated product.

34. A process according to claim 29, wherein the process comprises a dry granulation process wherein said compound, at least one diluent, and optional excipients are formed into a compressed mass, milled and then compressed using a tablet machine.

35. A process according to any one of claims 28 to 33 further comprising the step of applying a film coating to the resultant tablets.

36. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of the human or animal body by therapy.

37. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of a disease of protein aggregation.

38. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of a tauopathy.

39. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of Alzheimer's disease (AD), Pick's disease, progressive supranuclear palsy (PSP), frontotemporal dementia (FTD), FTD with parkinsonism linked to chromosome 17 (FTDP 17), frontotemporal lobar degeneration (FTLD) syndromes; disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), pallido-ponto-nigral degeneration (PPND), Guam-ALS syndrome, pallido nigro luysian degeneration (PNLD), cortico-basal degeneration (CBD), dementia with argyrophilic grains (AgD), dementia pugilistica (DP) or chronic traumatic encephalopathy (CTE), Down's syndrome (DS), dementia with Lewy bodies (DLB), subacute sclerosing panencephalitis (SSPE), MCI, Niemann-Pick disease, type C (NPC), Sanfilippo syndrome type B (or mucopolysaccharidosis III B (MPS III B)), or myotonic dystrophies (DM), DM1 or DM2.

40. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of Alzheimer's disease.

41. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of Parkinson's disease.

42. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of PSP, ALS, or FTLD.

43. A compound or composition according to any one of claims 1 to 12 for use in a method of treatment or prophylaxis of Huntington's disease or other polyglutamine disorder, such as spinal bulbar muscular atrophy (Kennedy disease), dentatorubropallidoluysian atrophy or spinocerebellar ataxias.

44. A compound or composition according to any one of claims 1 to 12 or 15 to 27 for use in a method of treatment or prophylaxis of skin cancer or melanoma; or a viral, bacterial or protozoal disease condition.

45. A compound or composition for use according to claim 44 wherein the viral, bacterial or protozoal disease is selected from Hepatitis C, HIV, West Nile Virus (WNV) and malaria.

46. Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of a disease of protein aggregation.

47. Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of a tauopathy.

48. Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of Alzheimer's disease (AD), Pick's disease, progressive supranuclear palsy (PSP), frontotemporal dementia (FTD), FTD with parkinsonism linked to chromosome 17 (FTDP 17), frontotemporal lobar degeneration (FTLD) syndromes; disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), pallido-ponto-nigral degeneration (PPND), Guam-ALS syndrome, pallido nigro luysian degeneration (PNLD), cortico-basal degeneration (CBD), dementia with argyrophilic grains (AgD), dementia pugilistica (DP) or chronic traumatic encephalopathy (CTE), Down's syndrome (DS), dementia with Lewy bodies (DLB), subacute sclerosing panencephalitis (SSPE), MCI, Niemann-Pick disease, type C (NPC), Sanfilippo syndrome type B (or mucopolysaccharidosis III B), or myotonic dystrophies (DM), DM1 or DM2.

49. Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of Alzheimer's disease.

50 Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of Parkinson's disease.

51 Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of PSP, ALS or FTLD.

52. Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of Huntington's disease or other polyglutamine disorder, such as spinal bulbar muscular atrophy (Kennedy disease), dentatorubropallidoluysian atrophy or spinocerebellar ataxias.

53. Use of a compound or composition according to any one of claims 1 to 12 or 15 to 27 in the manufacture of a medicament for use in the treatment or prophylaxis of skin cancer or melanoma; or a viral, bacterial or protozoal disease condition.

54. Use according to claim 53, wherein the viral, bacterial or protozoal disease is selected from Hepatitis C, HIV, West Nile Virus (WNV) and malaria.

55. A method of treatment or prophylaxis of a disease of protein aggregation in a subject comprising administering to said subject a prophylactically or therapeutically effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

56. A method of treatment or prophylaxis of a tauopathy in a subject comprising administering to said subject a prophylactically or therapeutically effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

57. A method of treatment or prophylaxis of Alzheimer's disease in a subject comprising administering to said subject a prophylactically or therapeutically effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

58. A method of treatment or prophylaxis of Parkinson's disease in a subject comprising administering to said subject a prophylactically or therapeutically effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

59. A method of treatment or prophylaxis of PSP, ALS or FTLD in a subject comprising administering to said subject a prophylactically or therapeutically effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

60. A method of treatment or prophylaxis of Huntington's disease or other polyglutamine disorder, such as spinal bulbar muscular atrophy (Kennedy disease), dentatorubropallidoluysian atrophy or spinocerebellar ataxias in a subject comprising administering to said subject a prophylactically or therapeutically effective amount of a compound according to any one of claims 1 to 12 or 15 to 27.

61. A method of treatment or prophylaxis of skin cancer or melanoma; or a viral, bacterial or protozoal disease in a subject, comprising administering to said

subject a prophylactically or therapeutically effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

62. A method according to claim 61, wherein the viral, bacterial or protozoal disease is selected from Hepatitis C, HIV, West Nile Virus (WNV) and malaria.

63. A method of reversing and/or inhibiting the aggregation of a protein comprising contacting the protein with an effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

64. A method of reversing and/or inhibiting the aggregation of a protein in the brain of a mammal, which aggregation is associated with a disease state, the treatment comprising the step of administering to said mammal in need of said treatment, a prophylactically or therapeutically effective amount of a compound or composition according to any one of claims 1 to 12 or 15 to 27.

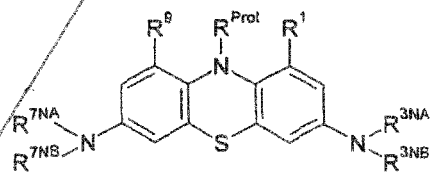
65. A method of inactivating a pathogen in a sample, comprising the steps of introducing a compound according to any one of claims 1 to 12 into the sample, and then exposing the sample to light.

66. A process for the preparation of a compound according to any one of claims 1 to 12 from a *N*-protected 3,7-diamino-10H-phenothiazine, comprising the steps of:

ring amino deprotection (DP); and

salt formation (SF).

67. A process according to claim 66, wherein the *N*-protected 3,7-diamino-10H-phenothiazine is a compound of formula (II):




(II)

wherein $R^{Prot}$ is an amine protecting group and $R^1$, $R^9$, $R^{3NA}$, $R^{3NB}$, $R^{7NA}$, $R^{7NB}$, $R^A$ and $R^B$ are as previously defined.

68. A process according to claim 67, wherein $R^{Prot}$ is acyl.

69. A process according to any one of claims 66 to 68, wherein ring amino deprotection (DP) and salt formation (SF) are performed simultaneously.

70. A process according to claim 69, wherein ring amino deprotection (DP) and salt formation (SF) comprise treatment of the *N*-protected 3,7-diamino-10H-phenothiazine with at least one sulfonic acid.

71. A process according to claim 70, wherein ring amino deprotection (DP) and salt formation (SF) comprise treatment of the *N*-protected 3,7-diamino-10H-phenothiazine with methanesulfonic acid and water, in an organic solvent, to produce the *bis*(methanesulfonate) salt.