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~~

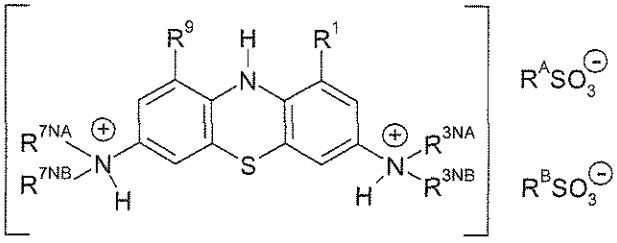
The present inventors have now identified a new class of stable phenothiazine diaminium compounds which have improved properties as compared to previously disclosed diaminophenothiazine compounds and salts.

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

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

In one embodiment~~aspect~~ the present disclosure~~invention~~ 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 embodiment~~aspect~~ of the present disclosure~~invention~~ pertains to processes for synthesizing a compound as described above.

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

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

Another embodiment~~aspect~~ of the present disclosure~~invention~~ 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 embodiment~~aspect~~ of the present disclosure~~invention~~ 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.

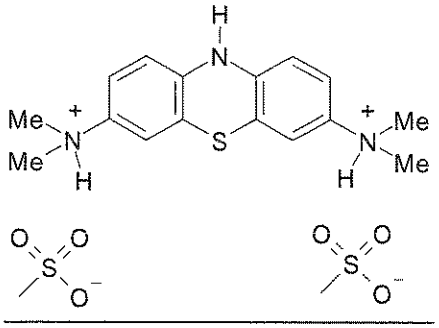
Another embodiment~~aspect~~ of the present disclosure~~invention~~ pertains to a free-flowing, cohesive powder, comprising a compound as described herein and at least one diluent suitable for dry compression, and optionally one or more other excipients, said powder being capable of being compressed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

Another embodimentaspect of the present disclosureinvention 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 embodimentaspect of the present disclosureinvention 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 embodimentaspect of the present disclosureinvention 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 embodimentaspect of the present disclosureinvention 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 one aspect, there is provided the use of a compound which is of the following formula:



or a pharmaceutically acceptable salt, solvate, or hydrate thereof in the manufacture of a medicament for use in the treatment or prophylaxis of a disease of protein aggregation.

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

Another embodimentaspect of the present disclosureinvention 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 embodimentaspect of the present disclosureinvention 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 embodimentaspect of the present disclosureinvention will also pertain to other embodimentaspects of the present disclosureinvention.