Phenothiazine-based anti-TB drugs

Phenothiazine, a tricyclic organic compound with formula S(CH)NH, is well known for its use as antipsychotic and antihistaminic drugs. The compound has also been reported widely as having antimicrobial activity, including anti-tubercular (anti-TB).

Phenothiazines have also demonstrated synergistic interaction with a wide spectrum of anti-microbial or anti-bacterial agents. It has been proven that thioridazine is active against multi- and extremely drug resistant forms of tuberculosis (TB).

With the chemically modified phenothiazine-based compounds of the invention, it is now possible to separate the anti-TB activity from the psychotropic activity by increasing the polarity of the molecules and hence the solubility of the compounds. This reduces their ability to cross the blood-brain barrier and thus minimises the psychotic side effects. The phenothiazine drug, Chlorpromazine, has been successfully used to treat a TB patient.

Benefits

• It retains antimicrobial activity while excluding psychotic side effects
• It is non-toxic to macrophage cells with no negative impact on the patient’s immunity

Applications

• Potential to be used alone or in combination with other anti-TB drugs, with limited side effects
• Potential to be extended to tricyclic derivatives other than phenothiazine, such as phenoxazines, phenazines, acridines, oxazepines, diazepins, xanthenes, and thioxanthenes

Market

TB sufferers worldwide, with specific focus on countries with a high incidence of TB.
Note: In 2012, 8.6 million people were diagnosed with TB globally and 1.3 million died from the disease.

Technical description

The invention is a tricyclic derivative of general formula,
where $R_1$ is an alkyl sulphonate or sulphonamide group; $R_2$ is hydrogen, a halogen, a substituted alkyl
group, a thioether or an acetyl group; $Y$ is $N$, or $C$; $X$ is $S$, $SO$, $SO_2$, $N$, $O$, $CH_2$, $C(O)$, $CO_2$, $NHCO$, and
ring $B$ is a 6, 7 or an 8 membered cycloalkyl ring. When (1) is a phenothiazine derivative, then $R_2$ is
not H.

**Intellectual Property Status**

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The IP covers modified tricyclic derivatives of phenothiazines, phenoxazines, phenazines, acridines,
oxazepines, diazepins, xanthenes, thioxanthenes and uses thereof.

The inventors are Anwar Jardine and Muazzam Jacobs.

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