Tranylcypromine derivative useful as inhibitors of histone demethylases LSD1 and LSD2.

KEYWORDS

- TRANYLCYPRO-MINE DERIVATIVE
- HISTONE DEMETHYLASES
- GENE TRANSCRIPTION
- CELL DIFFERENTIATION AND PROLIFERATION

AREA

- PHARMACEUTICAL

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Patent Type
Patent for invention.

Co-Ownership
Sapienza University of Rome 33%, University of Pavia 33%,
University degli Studi of Milan 17%,
European Institute of Oncology Foundation (IEO) 17%.

Inventors
Antonello Mai, Saverio Minucci, Andrea Mattevi.

Industrial & Commercial Reference
Compounds useful in the prevention and / or treatment of diseases (eg. cancer, viral diseases).

Time to Market
The product has been fully developed tested and is now available on the market for its applications.

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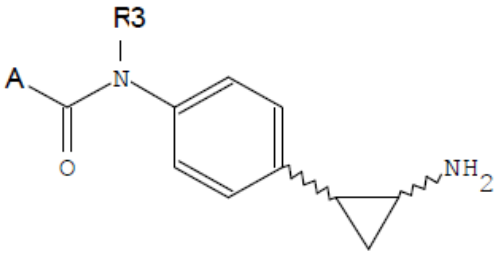

(I) General Formula

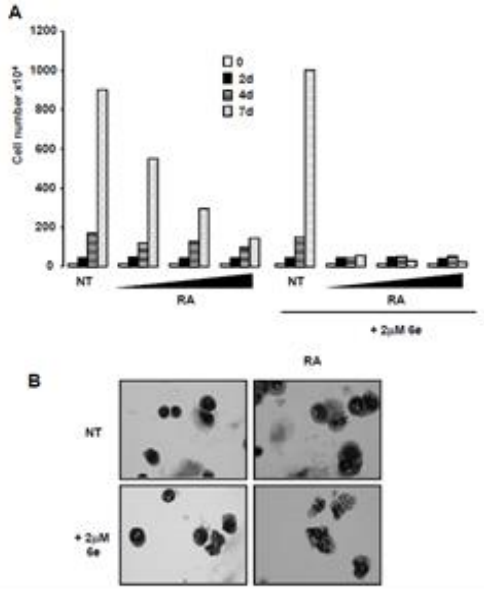

Fig. 1 Biological evaluation of 6e. (A) 6e synergizes with retinoic acid (RA) in inhibiting cell growth.

Abstract
Tranylcypromine derivatives useful as therapeutic agents, particularly for the prevention and/or treatment of diseases and conditions associated with the activity of histone demethylases LSD1 and LSD2, such as the diseases characterized by deregulation of gene transcription, cell differentiation and proliferation (e.g. tumors, viral infections). These compounds belong to the structural formula (I) wherein A and R_3 as defined in the specification.
The invention also relates to the preparation of these compounds, as well as to compositions containing them and to therapeutic use thereof.

Publications

- Minucci S, Mattevi A, Mai A. et al. Biochemical, structural, and biological evaluation of tranylcypromine derivatives as inhibitors of histone demethylases LSD1 and LSD2. J Am Chem Soc. 2010 May 19;132(19):6827-33. doi: 10.1021/ja101557k.
- Minucci S, Mattevi A, Mai A. et al. Pure Diastereomers of a Tranylcypromine-Based LSD1 Inhibitor: Enzyme Selectivity and In-Cell Studies. ACS Med Chem Lett. 2014 Dec 8;6(2):173-7. doi: 10.1021/ml500424z.

Tranylcypromine derivative useful as inhibitors of histone demethylases LSD1 and LSD2.

Technical Description

The present invention is directed towards compounds that are endowed with LSD1 and/or LSD2 histone demethylases inhibiting activity and are useful in the prevention or therapy of diseases and conditions associated with the activity of the LSD1 and/or LSD2 histone demethylases.

The invention is directed also to methods of preparing said compounds, compositions containing them and therapeutic use thereof.

The invention discovered that tranylcypromine derivatives of general formula (I), and derivatives thereof, are endowed with histone demethylases LDS 1/2 inhibiting activity.

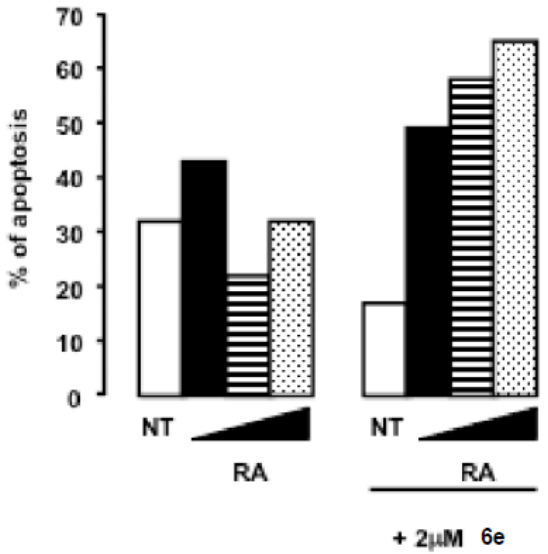

Fig. 2 6e synergizes with retinoic acid (RA) in inducing apoptosis in NB4 cells.

Technologies & Advantages

The reported inhibitors show marked effects on cell differentiation and an unprecedented synergistic activity with antileukemia drugs (ATRA).

These data demonstrate that these LSD1/2 inhibitors are of potential relevance for the treatment of promyelocytic leukemia and, more generally, as tools to alter chromatin state with promise of a block of tumor progression.

Applications

Therapeutic agents for the prevention and treatment of diseases characterized by deregulation of gene transcription, cell differentiation and proliferation.

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