Notch inhibitors for the treatment of T-cell acute Lymphoblastic Leukemia.

KEYWORDS

- NOTCH SIGNALING INHIBITORS
- SMALL MOLECULES
- NATURAL COMPOUNDS
- LEUKEMIA
- CANCER THERAPY
- TARGETED THERAPY
- NOTCH-DEPENDENT DISEASE THERAPY

AREA

- PHARMACEUTICS

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Patent Type
Patent for invention.

Co-Ownership
Sapienza University of Rome 60%, Italian Institute of Technology Foundation of Genoa 40%.

Inventors
Rocco Palermo, Mattia Mori, Luca Tottone, Francesca Ghirga, Nadezda Zhdanoskaya, Cinzia Ingallina, Francesca Giulimondi, Deborah Quaglio, Bruno Botta, Isabella Screpanti.

Industrial & Commercial Reference

Pharmaceutical industry focused on novel therapeutic approaches in Notch-dependent diseases.

Time to Market

Preclinical development (in vitro assay) of novel Notch inhibitors endowed with a naturally occurring scaffold.

Availability
Cession, License and Collaboration.

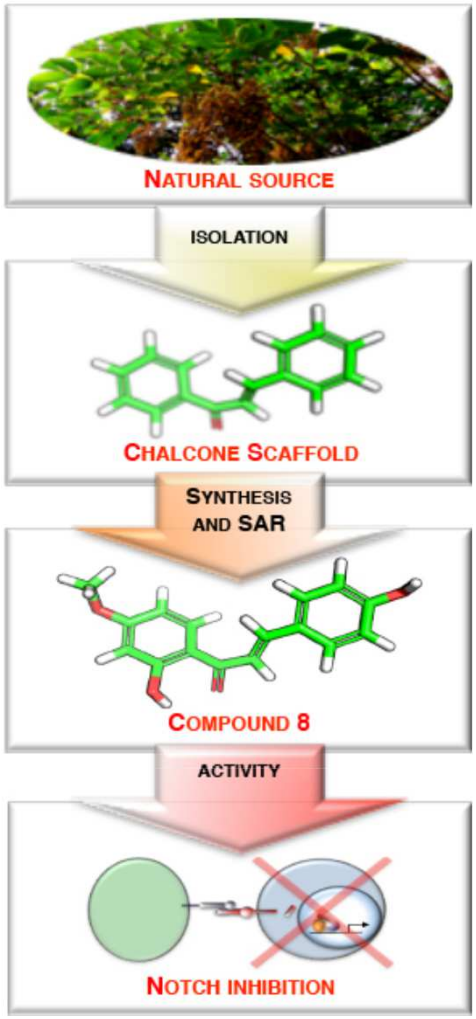

Fig.1 Compound 8 is a novel calcone derivative with potent Notch-inhibitor activity.

Abstract
A library of about 1000 natural products has been clustered through cheminformatics approach. By functional and biological analysis of the representative compounds of the 8 most populated clusters of the library for their strength in inhibiting Notch signaling and cell growth of human T-ALL cell lines, a novel naturally occurring Notch inhibitor, called C, has been identified.
Several chemical derivatives of C have been designed and synthesized to afford structure-activity relationships (SAR) and to develop a more potent Notch inhibitor, named 8.
Treatments with low micro-molar concentration of compound 8 exert Notch inhibitory and anti-proliferative effects in human T-ALL cell lines.

Publications

- Mori M., Tottone L., Quaglio D., Zhdanovskaya N., Ingallina C., Fusto M., Ghirga F., Peruzzi G., Crestoni M.E., Simeoni F., Giulimondi F., Talora C., Botta B., Screpanti I., Palermo R. Identification of a novel chalcone derivative that inhibits Notch signaling in T-cell acute lymphoblastic leukemia. Scientific Reports 7, Article number: 2213 (2017); doi:10.1038/ s41598-017-02316-9.

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Technical Description

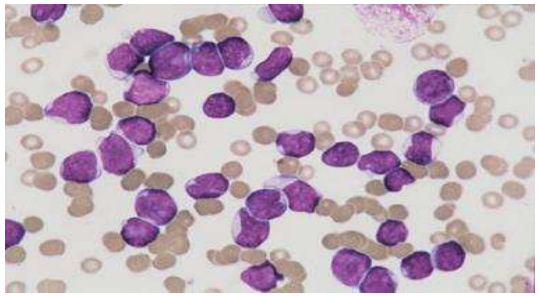
Chalcone-based bioactive Notch blocking agents have been developed.

Several chemical derivatives of the initial hit compound have been designed and synthesized to afford structure-activity relationships (SAR) and to develop a more potent Notch-blocking lead compound.

Low micromolar (single-digit) doses of the lead compound are able to decrease Notch signaling activity and to abrogate cell proliferation in several human T-ALL cell lines.

Notably this compound is not able to affect proliferation of Notch-independent cell lines.

Fig. 2 T-cell acute lymphoblastic leukemia.
(Image adapted from http://emedicine.medscape.com/article/990113-overview).



Technologies & Advantages

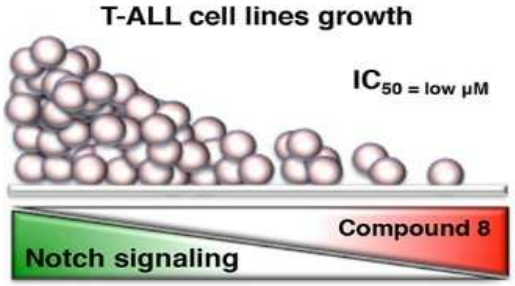
Given the number of deregulated Notch signaling-related diseases and cancers, other than T-ALL leukemia, there is an urgent need to develop novel efficient and safe Notch-blocking therapies.
Most promising pharmacologic approaches to block Notch signaling are focused on the inhibition of the enzymatic activity of the gamma secretase complex by small molecules (GSIs). Although these approaches exert efficient anti-Notch and antitumor activities, their clinical application is limited by primary resistance and by severe side effects. Another class of Notch inhibitors under development is represented by the monoclonal antibodies (mAbs) either against specific Notch receptors or ligands that interfere with the Notch ligand-receptor interaction. Unfortunately, current therapeutic mAbs are associated with drawbacks, including inadequate pharmacokinetics and tissue accessibility, limited duration of action, undesired immune reactions and high costs of production. The targeting of Notch signaling by small molecules of natural origin, such as chalcone-based agents, promises to improve the Notch related therapies in terms of delivery, cancer progression retention, blood clearance and also in terms of cost.

Applications

This invention refers to novel and potent small molecules endowed with a naturally occurring scaffold possessing Notch-inhibitor and anti-growth activities in T-ALL cell lines, providing novel guidelines for future development of chalcone-based bioactive Notch blocking agents useful in the treatment as single agents, or in combination with standard anti-cancer drugs in T-ALL.

The use of these molecules could be potentially extensible even in those contexts of solid and hematologic cancers and non-oncologic diseases (i.e. vascular diseases) in which the aberrant Notch pathway activation contributes to the development of the pathology and to the resistance to conventional treatments.

Fig. 3 Compound 8 inhibits Notch signaling and T-ALL human cell lines growth.



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