

Title	New generation trimethylangelicin (TMA) analogues for selective modulation of defective CFTR or inflammation
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Project description:

TMA was recently identified as a promising anti-inflammatory molecule for CF lung disease, with additional properties as potentiator and corrector of mutated F508del CFTR protein.

The major objective is to synthesize TMA analogs with the aim to find new anti-inflammatory agents (with NF- κ B inhibitory activity) and/or CFTR function modulators, useful for CF lung disease, with equal or higher activity in the respect to the parent TMA, but with low or absent DNA photo-binding properties. Hence, the goals of the project can be outlined in: 1) design and synthesis of a library of TMA analogs to identify a lead compound with optimized properties, 2) test of photoreactivity, 3) test of the anti-inflammatory activity and of the effects as CFTR function modulators, 4) derivation of structure-activity relationships to rationalize the structural determinants required to obtain selective anti-inflammatory properties, selective CFTR modulatory properties and dual anti-inflammatory/CFTR modulatory activity.

Expected results. Identification of novel candidates with improved anti-inflammatory and/or CFTR function modulating properties with reduced photoreactivity for the treatment of the chronic lung pathology of patients affected by CF.

Recent Publications in the specific field:

M Borgatti, A Chilin, et al. *Eur. J. Med. Chem.*, **46**, 4870-7 (2011) DOI:

10.1016/j.ejmech.2011.07.032

G Marzaro, ... A Chilin, *J. Med. Chem.* **67**, 373-83 (2013) DOI: 10.1021/jm3009647

G Marzaro, ... A Chilin, *Molecular Diversity* **19**, 551-61 (2015) DOI: 10.1007/s11030-015-9586-2

I. Lampronti, A Chilin, *Mediators of inflammation*, 2017, submitted.

Collaborations/Network:

Dr. GIULIO CABRINI and Dr. MARIA CRISTINA DECHECCHI - Laboratory of Molecular Pathology - University Hospital of Verona (for testing analogues on rescue and potentiation of defective CFTR and for immune response).

Prof. ROBERTO GAMBARI - Department of Life Sciences and Biotechnology, Laboratory of Biochemistry and Molecular Biology, University of Ferrara (for testing analogues on the anti-inflammatory properties).

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