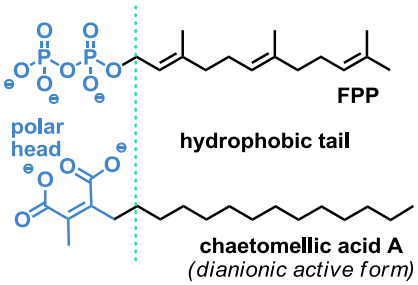
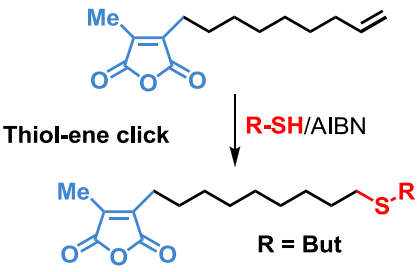
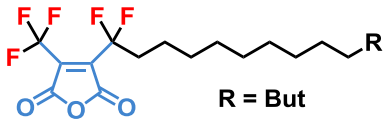
Medicinal Chemistry

F. Bellesia, F. Ghelfi, M. C. Menziani, F. Roncaglia







Fluorinated chaetomellic anhydrides A

(H replacement is at methyl and/or methylene bound to the ring)

RESEARCH TOPIC

AKI (Acute Kidney Injury) from ischemia-reperfusion. Study of the molecular mechanisms which cause short- and long-term modifications of function and renal structure, and prevention of the ischemic damage through the inhibition of the pathway Ras/ERK1/2.

External collaborations:

Prof. Massimo Sabbatini (Dip. di Patologia Sistematica, Univ. degli Studi di Napoli "Federico II"),
Prof. C. Dale Poulter (Department of Chemistry, University of Utah, USA),
Prof. A. Clark (Department of Chemistry, University of Warwick, UK).

Techniques and instrumentation:

reactions under controlled atmosphere, transition metal catalysis, click-reactions, analytical and preparative chromatography, enzymatic inhibition assays, molecular modeling, GC-MS, HRMS, NMR, mini-pilot plant.

The inhibition of the Ras/ERK1/2 pathway by chaetomellic-A acid (ACA) has a beneficial effect on acute ischemia-reperfusion injury in rats, preserving either renal function and histology.[1] ACA appears thus as a lead molecule for the development of drugs, targeted to clear up the acute kidney injury, following an ischemic damage. It is a natural product and was isolated, as anhydride, in 1993 from fermented systems of *Chetomella Acutiseta*: it inhibits (IC_{50} = 55 nM)[2] recombinant human FPTase.[3] The anhydride, just under the mild basic conditions of biological fluids, is readily hydrolyzed to the dicarboxylate anion, the real biologically active form.
The goal of our research is to identify more stable and more active ACA analogues, through the preparation of a tailored small library of 3-alkyl-4-metilfuran-2,5-diones, which will be synthesized through the radical cyclization of 6-member cyclic *N*-2,2-dichloropropanoyl-*N*,*S*-ketene acetals.[4,5] The method is highly versatile, as it makes possible the building of analogues through a thiol-ene coupling (a "click" reaction).[6] To note that the FTase inhibition assays with a representative sulphurated analogue, prepared for the validation of the synthetic path, gave an amazing result.[7] On this basis, we will investigate the influence on the enzymatic activity of: *i*) position and number of S atoms, *ii*) length of the sulphurated chain, *iii*) presence of aromatic substituents, ramifications or heteroatoms (N, O) at the tail end, and *v*) replacement of S with atoms of the same group (O, Se or Te). Because of its unique physicochemical properties, we have also projected to insert F atoms on the polar head of ACA.
Synthesized substances will be tested "*in vitro*" and "*in vivo*". From the experimental results we also try to understand if there is a correlation between the inhibitory activity on the FPTase and the anti-ischemic action. If so, molecular modelling studies will help us to drive ensuing structural adjustment to secure more active synthetic chetomellic acids. For those compounds with interesting pharmacological features, the respective DL_{50} will be also determined.
A parallel chemical effort to further improve the synthesis (reduce its cost) will be carried out, especially studying: *i*) the preparation and the use of open thioimidates as starting material, and *ii*) the possibility of running the key radical cyclization with an inverted procedure.[7]

Bibliography

1) Sabbatini, M.; Santillo, M.; Pisani, A.; Paternò, R.; Uccello, F.; Serù, R.; Matrone, G.; Spagnoulo, G.; Andreucci, M. *Am. J. Physiol., Renal Physiol.* **2006**, *290*, F1408. 2) Scholte, A. A.; Eubanks, L. M.; Poulter, C. D.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 763. 3) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Goetz, M. A.; Jenkins, R. G.; Nallin-Omstead, M.; Silverman, K. C.; Bills, G. F.; Mosley, R. T.; Gibbs, J. B.; Albers-Schonberg, G.; Lingham, R. B. *Tetrahedron* **1993**, *49*, 5917. 4) Pattarozzi, M.; Ghelfi, F.; Roncaglia, F.; Pagnoni, U. M.; Parsons, A. F. *Synlett* **2009**, 2172. 5) Comia, A.; Felluga, F.; Frenna, V.; Ghelfi, F.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F.; Spinelli, D. *Tetrahedron* **2012**, *68*, 5863. 6) Bellesia, F.; Choi, S.; Felluga, F.; Fiscaletti, G.; Ghelfi, F.; Menziani, C.; Poulter, C. D.; Roncaglia, F.; Sabbatini, M.; Spinelli, D. *Bioorg. Med. Chem.* **2013**, *21*, 348. 7) Casolari, R.; Felluga, F.; Frenna, V.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Spinelli, D. *Tetrahedron* **2011**, *67*, 408.

CONTACTS

Prof. Franco Ghelfi
franco.ghelfi@unimore.it
Tel. +39 059 205 5049
Sito web del gruppo