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From Biomass to Medicines: a cellulose derived product as building block in the synthesis of bioactive compounds

The bio-refinery concept is based on replacing fossil fuel with biomass, having the advantage to use renewable natural raw materials. This topic is currently of interest in academic studies, industrial applications and political strategies, both for the development and for the environment conservation.

Biomass based on vegetables and wood is rich of cellulose, a glucose polymer produced by photosynthesis. It can give access to biofuels, but also to a sugar platform containing chemicals interesting for their molecular complexity. Among the applied technologies for biomass conversion, pyrolysis is a process based on heating in the absence of oxygen, often in the presence of a suitable catalyst. When lignocellulosic biomass is used as starting material, a bio-oil rich in anhydro-sugars is produced. These molecules are peculiar for their chiral nature, preserving the chirality of the natural cellulose. Briefly, a molecule is defined as chiral when it can exist as a form which is not superimposable to its mirror image, similarly to the specular property of our hands. The high added values of anhydro-sugars is in their use as chiral building blocks for the synthesis of compounds with potential application in drug discovery. The chirality is indeed an important feature of drugs, able to affect their specific interactions with receptors (e.g. proteins, enzymes, DNA) involved in a series of diseases. Receptors themselves are chiral, therefore only a specular image of the drug molecule has a correct fit in the receptor site, similarly to the case of the right hand which requires a right-handed glove.

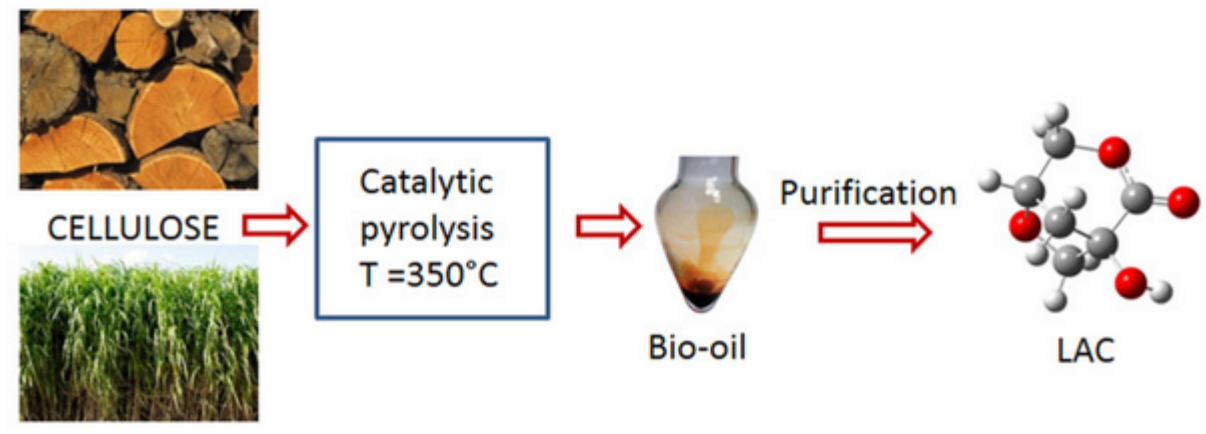

Fig. 1. Production of the anhydro-sugar LAC from cellulose pyrolysis

In the past we updated the production of an anhydro-sugar with a hydroxylactone structure, named LAC, by cellulose pyrolysis at 500°C and 350°C in the presence of different catalysts (Fig. 1). After a workup able to optimize the production of LAC and to facilitate the following purification, we evaluated its amount in the produced bio-oils by quantitative Nuclear Magnetic Resonance (NMR) and InfraRed (IR) spectroscopic methods. The highest LAC production (7.6 wt.% from cellulose) was obtained by pyrolysis at 500°C, using Sn-MCM-41as catalyst. The best alternative was given by using as catalyst the cheap and eco-friendly phyllosilicate mineral montmorillonite K10 (4.8 wt%).

By this optimized procedure we could produce pure LAC in gram-scale, opening the access to its use in the synthesis of potentially bioactive molecules. LAC was applied to the efficient synthesis of a novel branched amino acid, interesting for the access to new peptidomimetic products. We also recognized structural similarity of this amino acid with the natural (+)-muscarine, first isolated from the mushroom *Amanita muscaria* (Fig. 2). Muscarine is important in pharmacology because, acting as a specific and competitive agonist of the acetylcholine neurotransmitter, it faithfully reproduces some of the response to stimulations of the parasympathetic nervous system. Five subtypes of muscarinic receptors (M1–M5) are known, all are found in the central nervous system, even if they are involved in cardiac function (M2) or type 2 diabetes mechanism (M3).Currently there is a renewed interest in new muscarinic analogues for the development of effective agents in the treatment of Alzheimer's disease. In addition the development of compound with a higher selectivity for a specific subtype receptor might be promising for a new drug development.

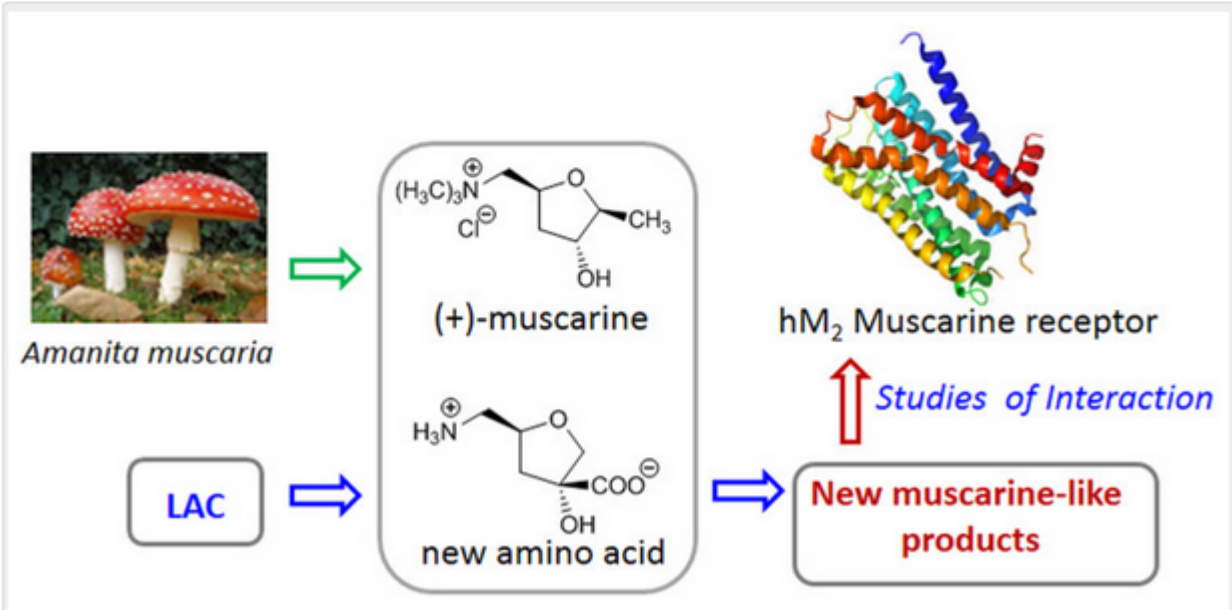

Fig. 2. Synthesis and biological evaluation of new the muscarine-like compounds synthesized from LAC via a new amino acid

In this context, we have recently obtained five new LAC-derived products structurally related to muscarine, which were investigated with respect to their binding affinity to human M_1-M_5 muscarinic acetylcholine receptors. The most active compound has shown an activity comparable to muscarine and a moderate hM_2 selectivity. This experimental data have been supported by docking calculation with hM_2 subtype receptor (3UON), based on the recent availability of its X-ray structure by Protein Data Base.

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Publication

Muscarine-like compounds derived from a pyrolysis product of cellulose.
Defant A1, Mancini I, Matucci R, Bellucci C, Dosi F, Malferrari D, Fabbri D
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