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## MAZA - New methods for azamacrocycles

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Axis 1 Activities 1.3.b - Smart Health



Technologies and processes for the preparation of active pharmaceutical ingredients and diagnostic contrast media require constant technological adaptation to meet the ever-increasing demands for quality, safety, reliability and environmental compatibility. The industrial complex of Torviscosa has well-established high technological capacities in the chemical field, and, since the opening of the Bracco-Spin production site, these skills, as well as those that the regional university network, are available for the development of medical and pharmaceutical applications.

Contrast media are the main tools that allow a clear and easily interpretable imaging in NMR diagnostics. The main contrast agents for nuclear magnetic resonance diagnostics use poly-aza-macrocycles as binders of gadolinium, the principal component. Despite the importance and the impressive number of studies that have been conducted on poly-aza-macrocyclic preparation, a synthetic method is not currently available that fully complies with the aforementioned market requirements. On the other hand, recent technologies, both in catalytic chemistry and plant engineering, now permit the adaptation of published procedures and significant synthetic technological improvements.

The project goal is to introduce into the synthesis of 1,4,7,10-tetraazacyclododecane (Ciclene), which is the key intermediate for the preparation of NMR contrast agents (Gadobutrol, Gadoteric Acid and Gadoteridol), the recent technological achievements that some of the project partners have developed, and, in particular, the catalytic alkylation techniques for amines with alcohols (W. Baratta et al., Chem. Eur. J. 2017, 23, 14416) and methods of continuous reactions (WO2013 / 156,973). These modifications of the synthesis of Ciclene should lead to an innovative process, and address the needs for quality, safety, reliability and environmental compatibility.

One of the project's partners, Bracco Imaging, is today one of the world's largest producers of contrast media for NMR, able to implement the project results industrially with a substantial impact on the strategic site of Torviscosa.

The project aims to achieve an innovative process for the production of Ciclene that meets the following specifications:

- confinement of reagents with critical toxicity characteristics for industrial management and for the pharmacological use of the final product;

- better atomic efficiencies compared to the methods already in use, and, consequently, lower environmental impact due to a reduced ratio between quantity of waste by-products and of main product;
- compliance with the operational guidelines for Good Manufacturing Practices;
- competitive manufacturing costs in comparison to alternative processes currently in use.

#### Innovative features & competitive advantage

The current synthetic paths for the Cyclene preparation start from very simple raw materials, polyamines and amino alcohols, with low molecular weight. The critical point resides in the fact that in order to link them together to obtain the aza-cycle it is necessary to use huge quantities of protecting groups that increase the molecular weight of process intermediates, generating large quantities of wastes and requiring high reaction volumes. The economic result is that, while starting materials cost about 10 €/kg value, the final product cost is in the range of one thousand €/kg. Moreover, some intermediates have highly mutagenic properties, so that their handling is troublesome and costly.

The new process should overcome these drawbacks. The approach of controlling the selectivity of carbon-nitrogen bond formation should reduce the use of protecting groups, reducing the production of wastes. The systematic use of continuous operations should produce the characteristic effect of “process intensification” that is one of the advantages offered by these technologies. A second, very important advantage, is that continuous operations work in stationary state, allowing a feedforward logic of control, that avoids the production of “out of specification” products.

Improvements of the new process will allow a less costly production of Cyclene, and the economic advantage could be transferred to the derived MRI contrast media. Patent protection of the new technology should reaffirm the position as market leader for the producer.

Improvements of the new process should allow a reduction of Cyclene production cost of about 40% compared to the more common processes industrially in operation. This result can be achieved only by developing a continuous production process.

The expected results are possible by exploiting the complementarity of the skills and capabilities of the project partners, all located in Friuli:

- the analytical assets of Bracco Imaging-CRB laboratory, located in the Science Area Park, specialized in the structural analysis of contrast media;
- the experience of Udine University, Departments DI4A e DPIA, in the design of selective hydrogenation catalysts;
- the ability of Serichim in the development of complex chemical processes, based on continuous technologies.

The industrial implementation of the project results is oriented to the Torviscosa industrial complex where the synergies within companies create significant advantages. In particular the Project MAZA results will first be exploited for the needs of the local partner, Bracco Imaging.