



**Interuniversity National Consortium
"Chemistry for Environment"**

**A project named
"Syntheses Of Active Pharmaceutical Principles With Tetrazolic Structure"
A collaboration INCA – Dinamite-Dipharma S.p.A. to train young graduates**

The cooperation between NCA and Dinamite Dipharma S.p.A. begun in October 2003 with the project called "Original Syntheses Of Active Pharmaceutical Principles With Tetrazolic Structure", which aims to train two graduated researchers in the field of organic synthesis of active pharmaceutical principles, involving high-level safety and environmental problems.

The project realized and organized by INCA is connected to the Dinamite Dipharma's strategy, which aims to train new experts in emerging technologies in order to make them become part of the research and development sectors. This should help to keep the company competitiveness at a high level, within the general pharmaceutical market.

The participants will carry on activities at the Department of Chemistry for Materials and Chemical Engineering of Polytechnic of Milano (curators Prof. Attilio Citterio, project manager, and Prof. Sergio Auricchio), and at Dipharma's facilities. (person in charge Mr. Pietro Allegrini). The course is intended to transfer know-how within the specific innovative field of Green Chemistry, and management capabilities to complete participants' professional knowledge. This would possibly make them able to become project leaders and will facilitate research activities for synthesis and analysis, also yielding working flexibility.

The course is divided into macro-phases, each one with a specific educational aim, i.e. technical-scientific education¹, management education, and practical education². The course duration is 2,000 hours, it focuses on process innovations related to drug synthesis. Lessons are on synthetic chemistry and chemical engineering, laboratory practice, consultation of literature and data banks of patents, laboratory activities on chemical and analytical synthesis (NMR, MS, IR, X-ray, DSC, and TGA), safe preparation of macro-samples, and training at a pilot plant. The aim is to deliver information on all innovation problems related to the specific field of pharmaceutical "bulk" production, with a particular care for safety of processes involving hazardous and toxic substances, and the development of safe technologies. The two participants will also have the chance to take part to international specialization courses to complete their professional training. They will exchange information with European and extra-European researchers working in these specific fields.

The particular aim of all laboratory experimental activities will be the preparation of innovative solutions for safe syntheses of tetrazolic derivatives. Such heterocycles have become very popular during the last few years, greatly extending the range of their applications³. Dipharma's interest on such compounds is limited to pharmaceutical field and is based on the availability of proper plants to treat hazardous and toxic substances, and the development of safe processes. Many alternative synthetic methods for tetrazolic molecules are known, but all of them are intrinsically dangerous

¹ With modules for bibliographic research, analytical chemistry, synthetic chemistry, green chemistry, and chemical engineering.

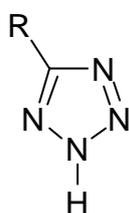
² Laboratory research activities.

³ E.g. in the pharmaceutical field as lyophilic spacers and substitutes of carboxylic acids, but also in the specific field of explosives, in photography, for data storage systems, and as precursors of other heterocycles.

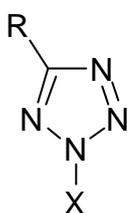
because of the use of toxic and/or explosive raw materials, the involvement of some intermediates and/or critical reaction conditions, and the instability of final products to heat and light.

For those reasons the participants will be specifically trained on:

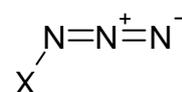
- Development of safety conditions when using inorganic and organic azides.
- Design of systems for control and abatement of nitrohydric acid.
- Finding substitutes of azides for the tetrazolic synthesis.
- Development of "green" protective groups for positively charged nitrogen atoms of tetrazoles.
- Design of catalytic systems with a high-efficiency level for the cyclizing of tetrazoles derived for carboxylic acids and nitriles.
- Use of environmentally compatible solvents for the conventional synthesis of tetrazoles via cycloaddition of azides and nitriles.



1-H Tetrazole



Tetrazole X-protected



Azide X-substituted

All possible innovations found during the studying phase will be tested on a macro-sample scale, in order to assess their real potential for application to industrial production and to evaluate possible engineering and safety problems not revealed during laboratory tests.

The course ends with a final exam to determine the professional level reached by participants. The judging committee will be formed by professors, experts from INCA, and researchers working from Dipharma. Besides an oral test, the committee will also base its conclusions on monthly reports and detailed evaluation forms about performed educational activities.