Doctoral Thesis Abstract: Design, Synthesis and Characterization of Biologically Active Heterocyclic Organic Compounds.

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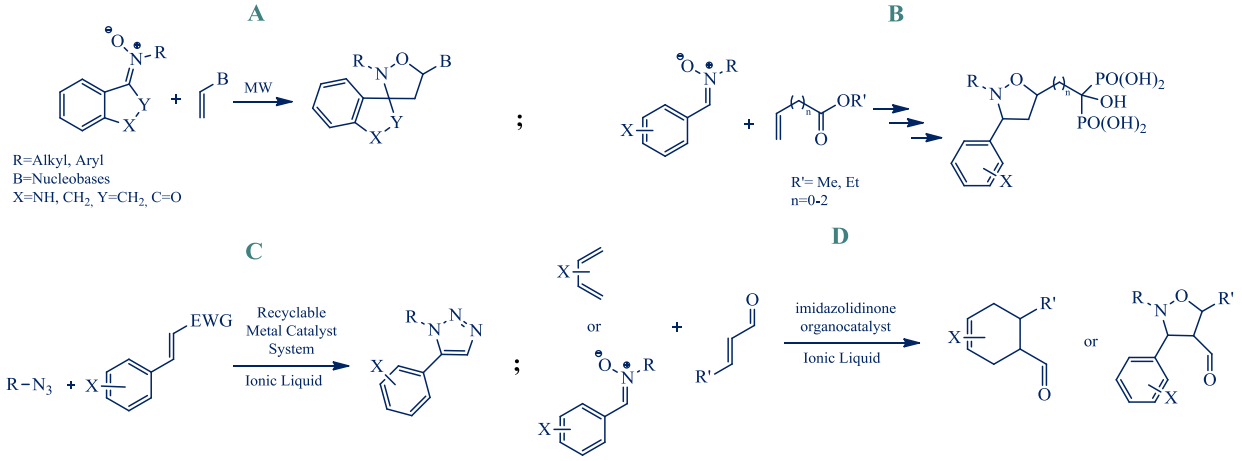
The discovery of new pharmacological agents is one of the biggest challenges for the current research. In recent years, the synthesis of heterocycles has been developed by pericyclic reactions[1] in which the product cycloadduct is an interesting pharmacophore that could be the future in biology and pharmacology fields. These pharmacologically active heterocycles can be indolyl or indanyl spiroisoxazolidine *N,O*-Nucleosides, isoxazolidin-*gem*-bisphosphonic acids and 1,2,3-Triazoles. Isoxazolidines are five-membered cyclic molecules that mimic natural nucleosides exerting antiviral and antitumoral activity. The addition of a *gem*-bisphosphonate group on the isoxazolidine ring increases the cytotoxicity of the obtained substrates that can be applied in clinical treatment of bone metastases and osteoporosis. The 1,2,3-triazole nucleus represents a significant class of biologically active nitrogen compounds that exhibit the important biological properties, such as antibacterial, anticancer, antivirus, and antituberculosis. In addition, organocatalysis exploits the small organic molecules to increase the speed of the reactions; expecially the covalent catalysis mediated by iminium ion has been used in various applications.



In this doctoral thesis numerous synthesis of all classes of molecules descrived above are reported. In particular, the Solvent-Free Microwave assisted 1,3-dipolar cycloaddition reaction for the synthesis of indolyl or indanyl spiroisoxazolidine *N,O*-Nucleosides (**A)** is described.[2] The reactions are conducted with short time (order of minutes), high diastereoselectivity and excellent yields. Moreover, the ketonitrone precursors are synthesized with same methodology.[3,4] In addition, the synthesis of the isoxazolidin-*gem*-bisphosphonic acids is carried out by a multistep reactions in which the isoxazolidine ring is obtained by solvent-free microwave assisted 1,3-dipolar cycloaddition (**B**).[5] The 1,2,3-triazoles are obtained by using of a eco-friendly recyclable system ($Er(OTf)_3$/Ionic Liquid/H_2O) in high yields and excellent regioselectivity, furnishing only 1,5 regioisomers (**C**). Moreover, the system can be reused for several cycles without loss of catalytic activity. Finally, the synthesis of a new imidazolidinone organocatalyst namely (*5S*)-2,2,3-trimethyl-5-thiobenzyl-4-imidazolidinone is described. The eco-friendly catalytic system is represented by organocatalyst/ionic liquid/H_2O that was tested on Diels-Alder and 1,3-dipolar cycloaddition betweed an α,β-unsaturated aldehyde and various dienes or 1,3-dipoles, isolating target products in high yields and excellent diastereo- and enantioselectivity (**D**).[6] Some of this compounds are been biologically tested and have demonstrated good results while others are currently being tested.

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3. Loredana Maiuolo, Pedro Merino, Vincenzo Algieri, Monica Nardi, Marialuisa Di Gioia, Beatrice Russo, Ignacio Delso, Matteo Antonio Tallarida, Antonio De Nino, *RSC Advances*, **2017**, 7, 48980-48988.
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5. Pedro Merino, Loredana Maiuolo, Ignacio Delso, Vincenzo Algieri, Antonio De Nino, Tomas Tejero, *RSC Advances*, **2017**, 7, 10947-10967.
6. Antonio De Nino, Loredana Maiuolo, Pedro Merino, Monica Nardi, Antonio Procopio, David Roca-López, Beatrice Russo, Vincenzo Algieri, *ChemCatChem*, **2015**, 7, 830-835.