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Nitrogen heterocycles: Antimycobacterial, anticancer and antileishmanial activity

Over the past decades, nitrogen heterocyclic derivatives, especially five and six member ring, were reported as valuable scaffolds in medicinal chemistry, showing variously biological activities such as antiviral and anticancer, antituberculosis, antimicrobials, antifungus, anti-inflammatory, antihypertensive, diuretics, antithrombics, anticoagulants, antidepressant, anxiolytics, anticonvulsant, analgesic, etc.

As part of our ongoing research in the field of nitrogen heterocyclic derivatives, we present herein some core results obtained by our group in the field of nitrogen heterocycles derivatives, focused on chemistry and their pharmacological potential applications as anticancer, antituberculosis and other antimicrobials, leishmaniasis. Our design has had in mind to get compounds with at least two biological activities.

As far for anticancer activity, several classes of nitrogen heterocycles (diazols, fused azine and diazine, mono- and bis-indolizines, 1,10- 1,7- and 4,7- phenanthroline) was designed, synthesized, and tested. Some of the compounds have a significant and selective anticancer activity against Melanoma, Renal cancer, Brest cancer and Lung cancer. As to the mechanism, our classes of compounds belong to DNA-intercalators, either via covalent bonding interactions (alkylators) either via non-bonding interactions (intercalations between base pairs, minor/major groove binding, G-quadruplex interactions). The molecular docking experiments suggests important clues concerning the mechanism of actions of our five and six member ring azaheterocyclic derivatives.

Design, synthesis and antimycobacterial activity of some new classes of nitrogen heterocycles (namely azine and bis-azine, diazine and bis-diazine, mono- and bis- indolizines, phenanthroline) is presented. The primary cycle high throughput screening reveals that some compounds are potent inhibitors against *Mycobacterium tuberculosis* (*Mtb*), their antitubercular activity being superior to the second-line antitubercular drug Pyrimethamine and Cycloserine. The MIC, MBC, LORA, intracellular (macrophage) drug screening, and MTT cell proliferation, indicate, for some of our compounds, the intracellular drug effectiveness against *Mtb*, the lack of toxicity, a significant activity against both replicating and non-replicating Mtb, a bactericidal mechanism of action, excellent solubility in microbiological medium. For the most active compounds, a complete ADMET studies have been performed (these including Plasma Protein Binding, Caco-2 Permeability, Cytochrome P450 Inhibition, In vitro microsomal Stability, HepG2 Cytotoxicity) with very good and promising results.

Design, synthesis and antileishmanial activity of several classes of nitrogen heterocycles (fused and nonfused diazine and diazols) is presented. The antileishmanial assay against Leishmania donovani intramacrophage amastigote reveal a very good and promising activity for some compounds.

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Biography

Ionel I Mangalagiu is a professor of organic and medicinal chemistry and Vice-Rector with research at "Alexandru Ioan Cuza" University of Iasi, Romania. Previously, he has served as Dean, Vice-Dean, Head of Organic Chemistry Department, etc. at Faculty of Chemistry. He has nearly 30 years of experience in the research, focused in the area of Heterocycles Compounds. He has over 150 papers, 13 patents, 3 international chapter books, etc. He was Visiting Professor and/or invited speaker to prestigious foreign universities (Ludwig Maximilianus University Munchen and Technische Universität Braunschweig, University of Florence, Universite D'Angers), awarded with numerous prizes and honours: DAAD and NATO award, "Costin D. Nenitescu Medal" (Romanian Society of Chemistry), "Al.I.Cuza University Award in Research", Special Award of Croatian Association of Inventors, etc. Web site: http://teclu.chem.uaic.ro/mangalagiu; Additional web site: http://a302.chem.uaic.ro/.

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