

Biocatalytic one-pot cycloaddition reactions using horseradish peroxidase

Bianca Furdui, Andreea Veronica Dediu, Ioana Otilia Ghinea, Vasilica Barbu, Steluta Gosav and Rodica Mihaela Dinica
"Dunarea de Jos" University of Galati, Romania

Statement of the Problem: The indolizine nucleus is an important scaffold for the preparation of new pharmaceuticals which is present in various biologically active compounds identified as anticancer, anti-tuberculosis, analgesic and antioxidant agents. As a result, different approaches have been reported for their synthesis. Enzymes can be used as efficient catalysts in organic synthesis, with catalytic promiscuity which exhibits their selectivity for non-natural functional group. Herein we have investigated for the first time the catalytic activity of horseradish peroxidase (HRP) for a one-pot 1, 3-dipolar cycloaddition reactions, yielding indolizine compounds starting from pyridinium heterocycles, reactive halides and alkynes. The potential toxicity of newly synthesized indolizines, have been investigated on wheat seeds germination, wheat being considered as a model for the monocotyledonous species for research in molecular biology.

Methodology & Theoretical Orientation: A number of fluorescent indolizines were prepared from pyridinium heterocycles, bromo acetophenones and alkynes via a one-pot three-component procedure using as biocatalyst the HRP commercial or extracted from *Azorella rusticana* plant. The structures of the synthesized compounds were proved by chromatographic and spectrometric analysis. The biocatalytic mechanism was investigated by computational studies. The impact of indolizine solutions on wheat seeds germination was analyzed using confocal laser microscopy. The germination rate and root length were measured five days after the treatment.

Findings: We have found that HRP could catalyze regioselective one-pot 1, 3-dipolar cycloaddition synthesis of indolizine compounds with different yields depending of the substituents of reactive halides. The cytotoxicity test of indolizines indicates that the synthesized compounds have no toxicity on wheat seeds germination.

Conclusion & Significance: A newly bio catalyzed single step green synthesis of some fluorescent indolizines has been reported. Preliminary investigations regarding the toxicity of synthesized compounds showed no toxic effect against wheat seeds germination. More complex experiments regarding the indolizine's toxicity will be performed.

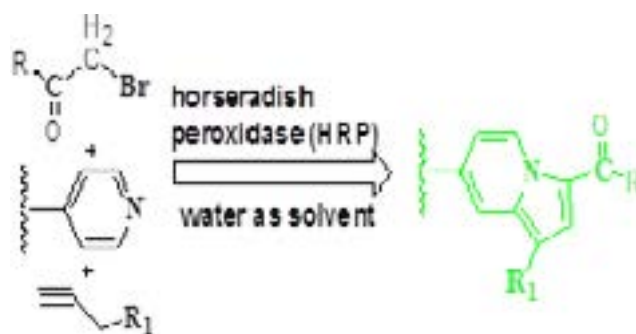


Figure 1. Biocatalytic "one-pot" indolizine synthesis

Recent Publications

1. Girija S S and Mmatli E E (2011) Recent progress in synthesis and bioactivity studies of indolizines. *European Journal of Medicinal Chemistry* 46:5237-5257.
2. Xiao-Fei G, Wen-Mei S, Xiao-Miao L, Xiao-Ju L et al. (2016) Heterothiometallic clusters as robust and efficient copper (I) catalysts for azide–alkyne [3+2] cycloadditions. *Catalysis Communications* 73:103–108.
3. Hrycay E G and Bandiera S M (2012) The monooxygenase, peroxidase, and peroxygenase properties of cytochrome P450. *Archives of Biochemistry and Biophysics* 522:71-89.
4. Wohlgemuth R, Plazl I, Znidarsic P, Gernaey K V and Woodley J M (2015) Microscale technology and biocatalytic processes: opportunities and challenges for synthesis. *Trends in Biotechnology* 33(5):302-314.
5. Jestin J L (2012) Tailor-made biocatalysts: combining thermodynamics, organic synthesis, molecular biology, biochemistry and microbiology for the design of enzyme selections. *Computational and Structural Biotechnology Journal* 2:e2012090133.

Biography

Bianca Furduliu obtained her PhD in Organic Chemistry from the University Joseph Fourier, Grenoble, France and in Chemistry from Alexandru Ioan Cuza University of Iasi, Romania, working in the field of N-heterocycles (pyridinium and indolizine) compounds with bioactive properties. Her research career was continued with a Postdoctoral fellowship at "Dunarea de Jos" University of Galati, working in the field of Biotechnology. In 1998, she joined the Department of Chemistry, Faculty of Sciences from "Dunarea de Jos" University of Galati, as Teaching Assistant. From 2014 she occupies the position of Associate Professor at the Department of Chemistry, Physics and Environment from the Faculty of Sciences and Environment of the same University. Her research is focused on the synthesis and structural and functional analysis of nitrogen heterocyclic compounds, microbiological analysis, natural extracts analysis, study of biological active compounds, and organic compounds characterization by spectral techniques (UV–VIS, IR, and NMR), HPLC, mass spectrometry, and biotechnology.

bfurduliu@ugal.ro