CHEMICAL REACTIVITY - MAJOR CAUSE OF FALSE RESULTS IN HIGH THROUGHPUT SCREENING?

Project PN II PD, Contract no. 174/2010

Project Title: Chemical reactivity - major cause of false results in high throughput screening?

Project: PN-II-RU-PD-502, Contract no. 174/5.08.2010

Program PN II: Human Resources

Project Type: Project for Postdoctoral Research (PD)

Contracting Unit: UEFISCDI (Executive Unity for Financing the Superior Education, Research, Development and Innovation)

Contractor: Institute of Chemistry Timisoara of Romanian Academy

Period: 24 months (August 2010 - May 2011; July 2013 - July 2014)

Total amount: 257.200 RON

2010: 44.000 RON

2011: 106.700

2012: -

2013: 63.000 RON

2014: 39.000 RON

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Web-based application to highlight possible promiscuous compounds from PubChem database.
Chemical Reactivity and Biological Promiscuity

Abstract:
Currently, computational chemistry and chemoinformatics have reached a high level of development and complexity allowing them to provide the proper tools that can be successfully employed in the discovery of new lead structures with high affinity towards the biological target of interest and good biodisponibility properties. The next step in the process is leads optimization to drugs.
Regarding the theme's competence domain, this grant proposal belongs to the field of rational drug design. Careful study of main stream publications published in the field from the last decade, has laid stress on the lack of thoroughly analyses which could explain the biological promiscuity of compounds (active in multiple assays and against different targets), main source of false hits in high throughput screening (HTS). In the framework of the project, we are planning to perform a retrospective analysis of the active compounds published in Pubchem. The main motivation of

the analysis is to evaluate compound's promiscuity through biological results and to establish a correlation between the biological behavior of a compound and its chemical reactivity. The later property is estimated with the help of reactivity indexes. The outcome of this analysis will be a list of compounds which should be avoided in the future from the list of compounds annotated as active from primary screening outcome. This list will be published on a website which will be created by us.

The main goal:

This proposal uses the computational chemistry methods to test the hypothesis that electrophile compounds and free radical generators are the major source of false positive results in high-throughput screening (HTS). This technique is one of the most utilized and expensive approach which has been used in the pharmaceutical industry to identify bioactive molecules. For this reason, the recognition and detection of false active compounds in early stages of the new drugs design will substantially accelerate the discovery process, allowing the subsequent efforts to be guided on the development of true active compounds against the pharmacological target of interest.

Objectives:

1. To evaluate if compounds which are annotated active in different types of biological assays have an electrophile or redox character, showing an increased reactivity and being a potential source of false active compounds in subsequent screenings.
2. To develop and establish the working methodology so that the best models that correlate the biological promiscuity with chemical reactivity will be built and selected.

Current state of research:
Scientific report of the research activity for 2010: Report
Scientific report of the research activity for 2011: Report
Scientific report of the research activity for July – December 2013: Report
Scientific report of the research activity for January – July 2014: Report

Conferences:

1. Ramona CURPĂN, Cristian BOLOGA. Reactivity descriptors for biological active compounds, Proceedings of the 12th Timisoara`s Academic Days, 26-27 Mai 2011, Timişoara, Romania.
2. Ramona CURPĂN, Cristian BOLOGA. A DFT Approach to Explain the Biological Behavior of Some Pubchem Compounds, International Conference of Physical Chemistry ROMPHYSCHEM 15, 11-13 September 2013, Bucharest, Romania.
3. Ramona Curpăn, Sorin Avram, Robert Vianello, Cristian Bologa. Biological promiscuity of HTS hits evaluated via chemical reactivity descriptors, New trends and strategies in the chemistry of advanced materials with relevance in biological systems, technique and environmental protection, 7th Edition, June 5-6 2014, Timişoara.

Publications:

1. Ramona Curpăn, Sorin Avram, Robert Vianello, Cristian Bologa. Exploring the biological promiscuity of high-throughput screening hits through DFT calculations. Bioorg. Med. Chem. 2014, 22, 2461-2468, DOI: 10.1016/j.bmc.2014.02.055. (FI2012 = 2.903)

2. Ifeyinwa Obiorah, Surojeet Sengupta, Ramona Curpan, V. Craig Jordan. Defining the Conformation of the Estrogen Receptor Complex That Controls Estrogen-Induced Apoptosis in Breast Cancer, Molecular Pharmacology 2014, 85(5), 789-799, DOI: 10.1124/mol.113.089250. (FI2012 = 4.411)
3. Philipp Y. Maximov, Daphne J. Fernandes, Russell E. McDaniel, Cynthia B. Myers, Ramona F. Curpăn, V. Craig Jordan. Influence of the length and positioning of the antiestrogenic side chain of endoxifen and 4-hydroxytamoxifen on gene activation and growth of estrogen receptor positive cancer cells, Journal of Medicinal Chemistry, 2014, 57(11), 4569-4583, DOI: 10.1021/jm500569h. (FI2012 = 5.614)
4. Ramona Curpăn, Sorin Avram, Robert Vianello, Cristian Bologa. Biological promiscuity of HTS hits evaluated via chemical reactivity descriptors, under review, Rev. Roum. Chim.

Publications mentioning the project to the Aknowledgements section:

1. Sergiu A. Chicu, Melania Munteanu, Ioana Citu, Codruta Şoica, Cristina Dehelean, Cristina Trandafirescu, Simona Funar-Timofei, Daniela Ionescu, Georgeta M. Simu. The Hydractinia Echinata test-system. III: Structure-toxicity relationship study of some azo-, azo-anilide, and diazonium salt derivatives, Molecules, 2014, 19(7), 9798-9817, DOI:10.3390/molecules19079798, (FI2012 = 2.428).
2. Mihaela F. Petric, Manuela E. Crisan*, Yurii M. Chumakov, Richard A. Varga, Andreea Micle, Ion Neda, Gheorghe Ilia. Structural and Ab Initio studies on the polymorphism of iminophosphorane (CH3C6H4)3P=NP[(=O)(OPh)2], under review, New Journal of Chemistry, submission ID NJ-ART-07-2014-001171, (FI2012 = 2.966)