INNOVATIVE STRATEGIES FOR IN SILICO MODELLING OF PROMISCUOUS COMPOUNDS EVALUATED IN HIGH-THROUGHPUT SCREENING (iPEHTS)

Cod PNII-RU-TE-2014-4-0422, Contract Nr. 98/0.10.2015

Program PN II: Human Resources
Project type: Research projects for the stimulation of young independent research teams forming - TE
Contracted Unit: Institute of Chemistry Timișoara of Romanian Academy
Period: 24 months (October 2015-September 2017)

Total Value: 550 000 Lei
Amount in 2015: 84 525 Lei
Amount in 2016: 319 700 Lei
Amount in 2017: 145 775 Lei

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Abstract:

Today, high-throughput screening (HTS) has become the standard procedure to test large libraries of compounds against biological targets in early-stage drug and agrochemical discovery. It is now recognized that HTS results are heavily affected by errors due to physico-chemical and biological properties of the molecules embedded in the screening libraries. Such compounds interfere with the assays signal-detection method (fluorescent and reactive compounds, luciferase inhibitors) or form functional aggregates in the assay medium. Consequently, nonspecific or apparent activity against various, unrelated proteins in many HTS assays, generate false-positive results. The aim of this project is to develop a comprehensive methodology to predict promiscuous compounds (frequent hitters, FHs). In this endeavor we will use PubChem Bioassay (>1 million assays), a series of molecular/fragmental descriptors and state-of-the-art modelling algorithms to explore prediction models for highly reactive compounds, fluorescent compounds, luciferase inhibitors and functional aggregators. The most efficient models will establish a first integrative approach to predict FHs, which will further assist decision-making in HTS and accelerate chemical developments. Thus, the current project offers an unprecedented, systematic exploration of the limits of current-state cheminformatics tools to pursue the prediction of FHs.
Aim: *To provide an innovative methodology for the early recognition of frequent hitters (FHs) in HTS libraries, by addressing the major known problems, i.e., fluorescence, luciferase inhibition, high reactivity and functional aggregation.*

Objectives:

1. *Data sets for FH modeling.*
2. *Prediction model for luciferase modulators.*
3. *Prediction model for fluorescent compounds.*
4. *Prediction model for highly reactive compounds.*

5. *Prediction model for colloidal aggregates.*
6. *Integrative methodology for FH prediction.*

Papers:

1. Avram S., Bora A., Halip L., Curpăn R. **Modeling kinase inhibition using highly confident data sets**. J. Chem. Inf. Model., 2018, 58 (5), 957–967. FI2018 = 3.304
2. Curpăn R., Avram S., Bora A., Halip L., Bologa C., **Chemical reactivity in biological promiscuous compounds**, Revue Roumaine de Chimie, 2018, 63(7-8), 749-757. FI 2018 = 0.370
3. Borota A., Funar-Timofei S., Bora A., Curpan R., **Homology model for Tribolium castaneum smoothened receptor as potential target for pesticides**, Revue Roumaine de Chimie, 2018, 63 (7-8), 759-764 FI 2018 = 0.370
4. Maximov P.Y., Abderrahman B., Curpăn R.F., Hawsawi Y.M., Fan P., Jordan V.C. **A unifying biology of sex steroid-induced apoptosis in prostate and breast cancers**. Endocrine-Related Cancer, 2018, 25, R83-R113. FI 2018 = 5.331
5. Maximov P.Y., Abderrahman B., Fannig S.W., Sengupta S., Fan P., Curpăn R.F.,Quintana Rincon D.M., Greenland J.A., Rajan S.S., Greene G.L., Jordan V.C. **Endoxifen, 4-hydroxytamoxifen and an estrogenic derivative modulate estrogen receptor complex mediated apoptosis in breast cancer**. Mol. Pharmacol., 2018, 94(2), 812-822. FI 2018 = 3.978
6. Bora A., Avram S., Ciucanu I., Raica M., Avram S. **Predictive models for fast and effective profiling of kinase inhibitors**. J. Chem. Inf. Model., 56(5), 895-905, 2016. FI2015 = 3.657
7. Avram S, Curpan R, Bora A, Neanu C, Halip L. **Enhancing molecular promiscuity evaluation through assay profiles**. Pharm Res. 2018, 35:240, doi: 10.1007/s11095-018-2523-1. FI 2018 = 3.335

Oral presentations:

1. Curpăn R, Avram S., Bora A., Halip L. In-silico modeling of promiscuous compounds in high-throughput screening. 11th European Conference on Theoretical and Computational Chemistry, EUCO-TCC, 4-7 September 2017, Barcelona, Spain, Book of Abstracts, p. 62, OC26, comunicare orală.
2. Curpăn R., Avram S., Bora A., Halip L., Kurunczi L. Biological promiscuity modeled using in-silico tools. The 10th Edition of New Trends and Strategies in the Chemistry of Advanced Materials with Relevance in Biological systems, Technique and Environmental Protection, 8-9 June 2017, Timisoara, Romania, Book of Abstracts, ISSN 2065-0760, pag 18, L11, lecture.

Posters:

1. Curpăn R., Avram S., Bora A., Halip L., Minimizing false-positive rates in high-throughput screening: predictors for fluorescent compounds, 11th European Conference on Theoretical and Computational Chemistry, EUCO-TCC, 4-7 September 2017, Barcelona, Spain, Book of abstracts, pag. 114, P20.
2. Bora A., Halip L., Curpăn R., Avram S. Minimizing false-positive rates in high throughput screening (HTS): prediction of luciferase inhibitors. 11th European Conference on Theoretical and Computational Chemistry, EUCO-TCC, 4-7 September 2017, Barcelona, Spain, Book of abstracts, pag. 106, P12.
3. Avram S., Bora A., Halip L., Curpăn R. Development of reliable prediction models for the efficient profiling of kinase inhibitors. 11th European Conference on Theoretical and

Computational Chemistry, EUCO-TCC, 4-7 September 2017, Barcelona, Spain, Book of abstracts, pag. 103, P09.

4. Bora A., Avram S., Halip L., Curpăn R. Description of PUBCHEMKININA: a comprehensive dataset of kinase inactive compounds. 11th European Conference on Theoretical and Computational Chemistry, EUCO-TCC, 4-7 September 2017, Barcelona, Spain, Book of abstracts, pag. 171, P77.
5. Halip L., Avram S., Bora A., Curpăn R. Mapping the chemical space of kinase inhibitors. 11th European Conference on Theoretical and Computational Chemistry, EUCO-TCC, 4-7 September 2017, Barcelona, Spain, Book of abstracts, pag. 105, P31.
6. Bora A., Halip L., Curpăn R., Avram S. A survey of electronic properties influence on biological activity of flavonoids. The 10th Edition of the Symposium New Trends And Strategies In The Chemistry Of Advanced Materials With Relevance In Biological Systems, Technique And Environmental Protection, 08-09 June, 2017, Timişoara, Romania, Book of abstracts, ISSN: 2065-0760, pag. 67, P32.
7. Avram S., Bora A., Curpăn R., Halip L. The computation of prediction intervals in kinase inhibitor modelling. The 10th Edition of the Symposium New Trends And Strategies In The Chemistry Of Advanced Materials With Relevance In Biological Systems, Technique And Environmental Protection, 08-09 June, 2017, Timişoara, Romania, Book of abstracts, ISSN: 2065-0760, pag. 95, P44.
8. Halip L., Avram S., Bora A., Curpăn R. A novel tool for the chemical space mapping of biological active compounds. The 10th Edition of the Symposium New Trends And Strategies In The Chemistry Of Advanced Materials With Relevance In Biological Systems, Technique And Environmental Protection, 08-09 June, 2017, Timişoara, Romania, Book of abstracts, ISSN: 2065-0760, pag. 56, P23.
9. Curpăn R., Avram S., Halip L., Bora A., Ursu O., Bologa C., Oprea T.I. Chemical reactivity in biological promiscuous compounds 21st EuroQSAR Where Molecular Simulations Meet Drug Discovery, September 4-8, 2016, Verona, Italy, Book of Abstracts, p.134, P053.
10. Avram S., Bora A., Halip L., Curpan R. Measuring the prediction errors for kinase inhibitor models 21st EuroQSAR - 21st European Symposium on Quantitative Structure-Activity Relationship - Where Molecular Simulations Meet Drug Discovery 4-8September 2016, Verona, Italia, Book of abstracts, pag.96, P015.
11. Bora A., Avram S., Halip L., Curpan R. PubChemKinIna: a consistent dataset of kinase inactive compounds 21st EuroQSAR - 21st European Symposium on Quantitative Structure-Activity Relationship - Where Molecular Simulations Meet Drug Discovery 4-8September 2016, Verona, Italia, Book of abstracts, pag.110, P029.
12. Halip L., Avram S., Bora A., Curpăn R., Ursu O., Bologa C., Oprea T.I. Virtual biological fingerprints for mining kinase inhibitors 21st EuroQSAR Where Molecular Simulations Meet Drug Discovery, September 4-8, 2016, Verona, Italy, Book of Abstracts, p. 190, P109.
13. Avram S., Bora A., Curpan R., Halip L., Dragos B., Mioc M., Kurunczi L. Versatile biological fingerprints for mining large chemical libraries The 9th Edition of the Symposium New trends and strategies in the chemistry of advanced materials with relevance in biological systems, technique and environmental protection, 09-10 June, 2016, Timişoara, Romania, Book of abstracts, ISSN: 2065-0760, pag. 80, P38.
14. Curpăn R., Neanu C., Avram S., Bora A., Halip L., Kurunczi L., Bologa C. Semiempiric quantum-chemical methods used in the prediction of biological promiscuity

The 9th Edition of New Trends and Strategies in the Chemistry of Advanced Materials with Relevance in Biological systems, Technique and Environmental Protection, 9-10 June 2016, Timisoara, Romania, Book of abstracts, ISSN 2065-0760, pag. 53, P15.

15. Mioc M., Bora A., Ramona CURPĂN1, Liliana HALIP1, Sorin AVRAM1, Ludovic KURUNCZI
    Modeling the kinase bioactivity space
    The 9th Edition of New Trends and Strategies in the Chemistry of Advanced Materials with Relevance in Biological systems, Technique and Environmental Protection, 9-10 June 2016, Timisoara, Romania, Book of abstracts, ISSN 2065-0760, pag. 95, P47.
16. Bogdan DRAGOŞ, Alina BORA, Ramona CURPĂN, Liliana HALIP, Sorin AVRAM, Ludovic KURUNCZI
    A kinome-based evaluation of bio-selective flavonoids
    The 9th Edition of New Trends and Strategies in the Chemistry of Advanced Materials with Relevance in Biological systems, Technique and Environmental Protection, 9-10 June 2016, Timisoara, Romania, Book of abstracts, ISSN 2065-0760, pag. 89, P43.

Lectures:

1. Curpăn R., Avram S., Bora A., Halip L., Dragoş B., Mioc M., Kurunczi L. Innovative cheminformatics tool to predict biological promiscuity
   The 9th Edition of New Trends and Strategies in the Chemistry of Advanced Materials with Relevance in Biological systems, Technique and Environmental Protection, 9-10 June 2016, Timisoara, Romania, Book of abstracts, p. 64, ISSN 2065-0760, pag 30, L9, lecture.
2. Curpăn R, Avram S., Bora A., Halip L., Dragos B., Mioc M., Kurunczi L. Chemoinformatics tool for biological promiscuity prediction
   Actual Trends in Chemoinformatics, 7 July 2016, Timişoara, Romania.

Software development

- MPP, Molecular Promiscuity Predictor – free application available on the project page, (http://chembioinf.ro/en/Grants/)
  used for the prediction of compounds with false-positive potential in high volume biological testing (HTS) and/or nonselective / nonspecific.

Human resource training within the project

- Supporting the PhD candidate Mioc Marius Nicolae in the preparation and elaboration of his PhD thesis titled: "Design, synthesis and evaluation of new bioactive compounds, potential drugs for signaling pathways active in colon cancer" publicly presented on 30.08.2017 at IOD - Institutul de Chimie Timişoara al Academiei Române.

Progress reports:

Stage I: Report (pdf)
Stage II: Report (pdf)
Stage III: Report (pdf)