Chapter

# Prologue: Deep Insights of Chemical Structures by Chemoinformatics Tools, Let's Think Forward!

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## 1. Introduction - Multidisciplinary context

The constant need of chemical scientists to understand complex phenomena and process and to achieve a rational structural design by controlling the synthesis to obtain compounds with improved properties or materials with enhanced quality, together with advances in information technology, has led to development of a new branch of chemistry—chemoinformatics—with strong implications in life sciences such as molecular biology or biochemistry, with major interest in medicine, pharmaceutical and food science industries.

Mainly, these interdisciplinary efforts are focused on the medical and pharmaceutical area, aiming to improve the quality and standard of life, and have applications in drug design and development of new therapeutic strategies. Chemoinformatics, as new discipline, covers a broad spectrum of aspects including all applications of information technology to chemistry involving: constructing and archiving big compound libraries (small molecules and proteins) containing structural properties and molecular descriptors, spectra, X-ray crystallography data and so on; information processing; large-scale chemical data mining; computational tools for structure and interactions visualisation, computational models for predicting interactions, to calculate properties and bioactivity, molecular docking and dynamic simulations methodologies, virtual screening, pharmacophore modelling, fragments similarity analysis, estimation of ADME (absorption, distribution, metabolism and excretion) characteristics, toxicity alerting, etc. [1–4]. The integration of chemical information and its transformation involves mathematical models and statistical data analysis.

Due to web servers and open data initiatives, large amount of chemical data from screening libraries are now available [5] and facilitate the drug discovery process. There are numerous chemoinformatics databases which contain various experimental and/or predicted properties of small molecules (ligands), peptides, proteins and data about their interactions (drug-drug interactions, ligand-protein interactions, protein-protein interactions, RNA-ligand interactions), chemical toxicity, bioactivity, adverse drug reactions, drug pathways, toxicogenomics, secondary metabolites, pharmacokinetics, etc. The existing data could help to build new structures and new models and to make new in silico predictions about physico-chemical properties and behaviour.

To raise awareness of the outstanding importance and impact of chemoinformatics research, exemplified below are some of its applications in life sciences, preponderant in medicinal chemistry.

## 2. Applications of chemoinformatics in medicinal chemistry

Novel druggable protein targets are a subject of research in order to develop new therapeutic strategies against various diseases (scleroderma, Alzheimer's disease, infections, etc.). Investigations include methods such as quantitative structure-activity relationships (QSAR), similarity search, pharmacophore modelling, molecular docking and dynamic simulations and toxicity assessment.

### 2.1 Anticancer therapy design

To fight against malignancies, new screening methods aim to identify and develop novel chemical antiproliferative agents, with promising results. As example, biomolecular modelling techniques are used to identify potential kinase inhibitor targets. The mitogen-activated protein kinase (MAPK) plays a key role in tumorigenesis; that is why it is considered a priority druggable target candidate for anticancer therapy. The interactions of cancer-related MAPK kinases and potential inhibitors are investigated by in silico tools. Molecular docking calculations are employed to predict the inhibitor-bound active sites and the binding modes for actual and potential anticancer drugs [6].

### 2.2 Parkinson's disease

Researchers' efforts to improve medication for Parkinson's disease benefit from chemoinformatics and molecular docking tools to identify new potential neuroprotective compounds able to effectively treat the disease, by inhibition of oligomerization process of α-synuclein protein. By computational techniques, the protein in its dimer and oligomer forms can be studied, and multiple molecules are subject of computational simulations in order to identify potential inhibitors of α-synuclein aggregation [7].

### 2.3 Alzheimer's disease

Chemoinformatics approaches including molecular docking, dynamic simulations, lead optimization and quantum chemical characterisation are used to achieve the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes, responsible for cholinergic dysfunctions associated with the cognitive and behavioural abnormalities in dementing illness, in order to design and develop new therapeutic agents against this disease [8–11]. Other approaches focus on the amyloid-beta aggregation process, trying to stop the formation of neurotoxic species, and the design of new inhibitors, the study being also facilitated by computational techniques such as QSAR modelling and assessment of inhibition efficiency by predicting stability and binding modes of potential inhibitors through combined computational techniques including structure-activity relationships analysis, docking and molecular dynamic simulations [12–15].

### 2.4 Antimicrobial agents

Researchers focus their studies to block the activity of DNA gyrase and topoisomerase IV, which are essential bacterial enzymes involved in replication and recombination processes. The design of novel antibacterial agents that act against these enzymes can be realised by molecular docking techniques and bioactivity evaluation. That is the case of quinolones, which act equally against DNA gyrase and topoisomerase IV [16–19].

***Pharmacokinetics/ADMET properties*** such as absorption, distribution, metabolism, excretion and toxicity of designed structures are assessed through computational approaches too, aiming to predict the therapeutic potential of the lead compound. Biochemical properties and drug-likeness according Lipinski's rule of five (RO5) [20] and the molecular flexibility, as key descriptors to describe the oral bioavailability of drugs, are also predicted using computational tools. Thus, computer-aided drug design, coupled with in silico ADMET studies, helps to select the drug candidate molecules with possible better efficacy and less side effects (poor hepatotoxic effects).

## 3. Application in identification and quantification of substances of abuse

Recent researches report the application of chemometric tools in correlation with spectrometric techniques (near-infrared spectroscopy) for onsite analysis of cannabinoids or amphetamine compounds (with portable and handheld NIR devices). The chemometric tools allow the user to compare collection of spectra, to develop prediction models and to achieve a real-time detection of sample contamination. Such method could become an alternative way of detection of illicit drugs, determined in oral fluids, being non-invasive, rapid and accurate test, completely automated [21, 22].

## 4. Applications in food chemistry

Food chemical data sets can be manipulated and analysed also by computational resources similar with those for drugs and nutraceuticals. The interest in this area is growing because of the food-related industrial challenges. Thus, an emerging field of research has arisen: foodinformatics [23]. In silico quantitative approaches are used to assess genotoxicity and carcinogenicity of food additives (flavours, colourants, contaminants, etc.) or cosmetic ingredients [24–26], in the attempts of safety evaluation for the human health. All these computational approaches must be verified by in vitro methods.

This section is a collection of advanced studies focusing on topics of interest in the context of chemoinformatics applications in drug discovery and design of new molecules.

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## References

[1] Vogt M, Bajorath J. Chemoinformatics: A view of the field and current trends in method development. Bioorganic & Medicinal Chemistry. 2012;**20**:5317-5323

[2] Begam BF, Kumar JS. A study on Cheminformatics and its applications on modern drug discovery, international conference on modeling optimisation and computing (ICMOC 2012). Procedia Engineering. 2012;**38**:1264-1275

[3] Lo Y-C, Rensi SE, Torng W, Altman RB. Machine learning in chemoinformatics and drug discovery. Drug Discovery Today. 2018;**23**(8):1538-1546

[4] Gasteiger J. Chemoinformatics: Achievements and challenges, a personal view. Molecules. 2016;**21**(2):151. DOI: 10.3390/molecules21020151

[5] Gonzalez-Medina M, Naveja JJ, Sanchez-Cruz N, Medina-Franco JL. Open chemoinformatic resources to explore the structure, properties and chemical space of molecules. RSC Advances. 2017;**7**:54153. DOI: 10.1039/c7ra11831g

[6] Meng L, Huang Z. In silico-in vitro discovery of untargeted kinase–inhibitor interactions from kinase-targeted therapies: A case study on the cancer MAPK signalling pathway. Computational Biology and Chemistry. 2018;**75**:196-204

[7] Rondon-Villarreal P, Lopez WOC. Identification of potential natural neuroprotective molecules for Parkinson's disease by using chemometrics and molecular docking. Journal of Molecular Graphics and Modelling. 2020;**97**:107547

[8] Hassan M, Abbasi MA, Aziz-Ur-Rehaman, Siddiqui SZ, Hussain G, Shah SAA, et al. Exploration of synthetic multifunctional amides as new therapeutic agents for Alzheimer's disease through enzyme inhibition, chemoinformatic properties, molecular docking and dynamic simulation insights. Journal of Theoretical Biology. 2018;**458**:169-183

[9] Makhaeva GF, Kovaleva NV, Boltneva NP, Lushchekina SV, Rudakova EV, Stupina TS, et al. Conjugates of tacrine and 1,2,4-thiadiazole derivatives as new potential multifunctional agents for Alzheimer's disease treatment: Synthesis, quantum-chemical characterization, molecular docking, and biological evaluation. Bioorganic Chemistry. 2020;**94**:103387

[10] Hassan M, Abbasi MA, Aziz-Ur-Rehaman, Siddiqui SZ, Shahzadi S, Raza H, et al. Designing of promising medicinal scaffolds for Alzheimer's disease through enzyme inhibition, lead optimization, molecular docking and dynamic simulation approaches. Bioorganic Chemistry. 2019;**91**:103138

[11] Dhanjal JK, Sharma S, Grover A, Das A. Use of ligand-based pharmacophore modeling and docking approach to find novel acetylcholinesterase inhibitors for treating Alzheimer's. Biomedicine & Pharmacotherapy. 2015;**71**:146-152

[12] Safarizadeh H, Garkani-Nejad Z. Molecular docking, molecular dynamics simulations and QSAR studies on some of 2-arylethenylquinoline derivatives for inhibition of Alzheimer's amyloid-beta aggregation: Insight into mechanism of interactions and parameters for design of new inhibitors. Journal of Molecular Graphics and Modelling. 2019;**87**:129-143

[13] Eskici G, Gur M. Computational design of new peptide inhibitors for amyloid beta (Aβ) aggregation in Alzheimer's disease: Application of a novel methodology. PLOS One.

2013;**8**(6):e66178. DOI: 10.1371/journal.pone.0066178

[14] Tran L, Kaffy J, Ongeri S, Ha-Duong T. Binding modes of a glycopeptidomimetic molecule on Aβ protofibrils: Implication for its inhibition mechanism. ACS Chemical Neuroscience. 2018;**9**(11):2859-2869. DOI: 10.1021/acschemneuro.8b00341

[15] Tonali N, Kaffy J, Soulier JL, Gelmi ML, Erba E, Taverna M, et al. Structure-activity relationships of β-hairpin mimics as modulators of amyloid β-peptide aggregation. European Journal of Medicinal Chemistry. 2018;**154**:280-293. DOI: 10.1016/j.ejmech.2018.05.018

[16] Pintilie L, Stefaniu A, Nicu AI, Caproiu MT, Maganu M. Synthesis, antimicrobial activity and docking studies of novel 8-chloro-quinolones. Revista de Chimie (Bucharest). 2016;**67**(3):438-445

[17] Pintilie L, Stefaniu A, Nicu AI, Maganu M, Caproiu MT. Design, synthesis and docking studies of some novel fluoroquinolone compounds with antibacterial activity. Revista de Chimie (Bucharest). 2018;**69**(4):815-822

[18] Strahilevitz J, Hooper DC. Dual targeting of topoisomerase IV and Gyrase to reduce mutant selection: Direct testing of the paradigm by using WCK-1734, a new fluoroquinolone, and ciprofloxacin. Antimicrobial Agents and Chemotherapy. 2005;**49**(5):1949-1956

[19] Collin F, Karkare S, Maxwell A. Exploiting bacterial DNA gyrase as a drug target: Current state and perspectives. Applied Microbiology and Biotechnology. 2011;**92**:479-497. DOI: 10.1007/s00253-011-3557-z

[20] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews. 2001;**46**:3-26

[21] Risoluti R, Gullifa G, Buiarelli F, Materazzi S. Real time detection of amphetamine in oral fluids by MicroNIR/Chemometrics. Talanta. 2020;**208**:120456

[22] Risoluti R, Gullifa G, Battistini A, Materazzi S. Monitoring of cannabinoids in hemp flours by MicroNIR/Chemometrics. Talanta. 2020;**211**:120672

[23] Martinez-Mayorga K, Medina-Franco JL, editors. Foodinformatics: Applications of Chemical Information to Food Chemistry. 2014th ed. Cham, Heidelberg, New York, Dordrecht, London: Springer. ISBN 978-3-319-10225-2; ISBN 978-3-319-10226-9 (eBook). DOI 10.1007/978-3-319-10226-9

[24] Tcheremenskaia O, Battistelli CL, Giuliani A, Benigni R, Bossa C. In silico approaches for prediction of genotoxic and carcinogenic potential of cosmetic ingredients. Computational Toxicology. 2019;**11**:91-10

[25] Benigni R. Towards quantitative read across: Prediction of Ames mutagenicity in a large database. Regulatory Toxicology and Pharmacology. 2019;**108**:104434

[26] Kruhlak NL, Contrera JF, Benz RD, Matthews EJ. Progress in QSAR toxicity screening of pharmaceutical impurities and other FDA regulated products. Advanced Drug Delivery Reviews. 2007;**59**:43-55