New Experimental and Computational Tools for Drug Discovery. -
Part-VII

The series of special issues “New experimental and computational tools for drug discovery” is being published by our journal as a tool to bring together in the same melting pot researchers from many diverse areas that use or develop enabling techniques for Medicinal Chemistry. As consequence, the different issues of this series have merged both experimental and computational areas of research such as Computational Chemistry, Bioinformatics, OMICS, Combinatorial Chemistry, Data Analysis, etc. with applications in Medicinal Chemistry and Drug Discovery. These areas include both experimental techniques (LC-MS/MS, FTIR, or NMR, etc.) combined or not with computational methods like Molecular Docking and Machine Learning (ML), etc. The series have published a total of six special issues until this moment (1-6). The papers included in this number follow the same line and can be summarized as follows:

Scotti et al. focused on Hepatitis C research. Hepatitis C is a disease that constitutes a serious global health problem. The aim of this study was combining structure-based and ligand-based virtual screening (VS) techniques to select potentially active molecules against four HCV target proteins from an in-house secondary metabolite dataset (SistematX). From the ChEMBL database, the authors selected four sets of 1199, 355, 290 and 237 chemical structures with inhibitory activity against different targets of HCV to create random forest models with an accuracy value higher than 82% for cross-validation and test sets. Afterward, a ligand-based virtual screen of the entire 1848 secondary metabolite database stored in SistematX (sistematx.ufpb.br) was performed. In addition, a structure-based virtual screening was also performed for the same set of secondary metabolites using molecular docking. Finally, using a consensus analysis approach combining ligand-based and structure-based VS, three alkaloids were selected as potential anti-HCV compounds [1].

Durruthy et al. focused their work on PIM-1, a kinase related to the oncogenic processes like cell survival, proliferation and multidrug resistance (MDR). In the present work, they tested a new mechanistic insight on the AZD1208 (PIM-1 specific inhibitor) under interaction with chemotherapy agents such as daunorubicin (DNR) and vincristine (VCR). In order to verify a potential cytotoxic effect based on pharmacological synergism, two MDR cell lines were used: Lucena (resistant to VCR) and FEPS (resistant to DNR), both derived from the K562 non-MDR cell line. Furthermore, they performed a molecular docking simulation to delve into the molecular mechanism of PIM-1. These results could have a pre-clinical relevance potential in the rational poly-pharmacology strategies to prevent multiple-drugs resistance in human leukemia cancer therapy [2].

Arrau et al. focused on Quillaja saponaria, which contains a high concentration of triterpene saponins that have been used for centuries as a cleansing, antiinflammatory and analgesic agents in Chilean folk medicine. In earlier studies they demonstrated, in mice, both the anti-inflammatory as well as the antinociceptive effect of the major sapogenin, quilliacid (QA). The objective of this work was to determine the antihyperalgesic effect of QA one and seven days after IP administration of complete Freund's adjuvant (CFA) in male mice using the hot plate test in the presence of complete Freund's adjuvant (HP/CFA) as an acute and chronic skeletal muscle pain model. The present study evaluated the antihyperalgesic activity of QA against acute and chronic skeletal muscle pain models in mice. The authors concluded that QA elicit dose-dependent antihyperalgesic effects against acute and chronic skeletal muscle pain, but QA is more potent than a reference drug in the early and late periods of inflammatory pain induced by CFA [3].

Tenorio et al. pointed out the harmful nature of dioxin in human health and in the whole environment. It is well known among scientists that 2, 3, 7, 8-tetrachloro dibenzo-p-dioxin (TCDD) is an environmental pollutant that causes endocrine disruption, which causes male reproductive toxicity. The objective of the present study was to evaluate the toxicity of low doses of TCDD in male CD1 mice. The results show that the body weight of the treated animals was reduced in medium and high doses (0.75, 1.5 mg / kg) with respect to the control groups. In the groups treated with TCDD, the abnormal sperm increased by 52.5% more than the control group. Significant differences in apoptosis were observed between the negative control and vehicle control, including at the median dose (0.75 mg / kg). It was concluded that at these low doses there was an impact on the quality of the mouse sperm, and an effect on apoptosis and cytotoxicity of sperm exposed to these doses of TCDD [4].

Marrero-Ponce et al. extended previously defined Graph Derivative Indices (GDIs) introducing the concepts of Higher Order Derivatives and Mixed Derivatives. The result of applying the higher order and mixed GDIs over any molecular structure allow finding Local Vertex Invariants (LOVIs) for atom-pairs, for atoms-pairs-pairs and so on. All new families of GDIs are implemented in computational software named DIVATI (acronym for Discrete DeriVAting Type Indices), a module of the
TOMOCMD-CARDD program (KeysFinder Framework). QSAR modeling of the biological activity (Log 1/K) of 31 steroids reveals that the GDIs obtained using higher order and mixed GDIs approaches yield slightly higher performance compare to previous reported approaches based on the duplex, triplex and quadruplex matrix. The higher order and mixed GDI method, appear as a promising tool in QSAR/QSPRs, similarity/dissimilarity analysis and virtual screening studies [5].

Pérez-Castillo et al. developed computational models for the identification of antimalarial hit compounds. For this, a data set suitable for the modeling of the anti-malaria activity of chemical compounds was compiled from the literature and subject to a thorough curation process. In addition, the performance of a diverse set of ensemble-based classification methodologies was evaluated and one of these ensembles was selected as the most suitable for the identification of antimalarial hits based on its virtual screening performance. During the compilation of the data set it was possible to obtain high quality data which was curated to ensure that the noise was as low as possible in the modeling process. Among the explored ensemble based methods, the one combining Genetic Algorithms for the selection of the base classifiers and Majority Vote for their aggregation showed the best performance. The results also show that ensemble modeling is an effective strategy for the QSAR modeling of highly heterogeneous datasets in the discovery of potential anti-malarial compounds [6].

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