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Editorial: Insights in structural and stereochemical analysis: 2022

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Editorial on the Research Topic
Insights in structural and stereochemical analysis: 2022

With four articles, including one perspective, two reviews, and one original research article, the Research Topic Insights in Structural and Stereochemical Analysis: 2022 covers the state-of-the-art research being conducted in the analysis of the structure and 3D arrangements of natural product (NP) molecules.

In the perspective article by Lopes and da Silva, mass spectrometry and some advanced landmarks are highlighted in respect to the main challenges and impacts of the chemical characterization of complex molecular structures. In this respect, the complexity of data analysis is discussed as one of the main limitations for time-limited tasks. Moreover, the observed expansion in the mass spectral database is not sufficient for the necessary data interpretation. As emphasized by the authors, the estimated number of spectra for ESI-MS/MS in the public domain is in the order of 60,000 molecules, which is far below the chemical space, and "traditionally, most spectrometry techniques rely on database matching of previously characterized signals." Meanwhile, the importance of the recently created large public databases is acknowledged as a means of characterizing large datasets acquired in complex samples such as NP extracts. Machine learning (ML)-based methods are also examined regarding their contribution to the structural prediction of classes of molecules that are poorly represented in spectral libraries. The imaging of small molecules by MALDI-MS grants spatial mapping of *in situ* NPs, allowing a better understanding of their function and distribution. As technological advances in terms of equipment, images and MS/MS data can be simultaneously generated, allowing the direct annotation of molecules. Additionally, the introduction of a third dimension by ionic mobility reveals the possibility of single-cell analysis by spatial resolution. This perspective article by Lopes and da Silva shines light on these significant issues and all the opportunities ahead of us in NP research.

The original article of this Research Topic by Queiroz et al. is about the chemical profile of organic apolar and polar extracts from leaves and stems of *Alzatea verticillata* Ruiz & Pav. (Alzateaceae). By semipreparative LC, twelve compounds were isolated in a milligram scale, of which three were unknown. The structure elucidation of the isolated compounds was carried out based on NMR and HRMS analyses. The previously undescribed compounds included a dimeric lactone, dimethyl anemonin, and two unusual dimeric diphenyl cyclobutane dicarboxylic acids (β-truxinic derivatives). The X-ray crystallography of the new dimeric lactone revealed it as an (*S,S*), (*R,R*) racemate. This article provides a biogenetic proposal that is in line with the obtained racemate. Additionally, non-target LC-HRMS data

enabled annotation by matching with public libraries and indicated multiple derivatives belonging to shikimate, phenylpropanoid, fatty acid, terpenoid, alkaloid, and polyketide classes. The authors conclude that the presence of truxinic acid derivatives in the polar extract may account for the antipruritic use of this plant in traditional medicine.

The two review articles published in this Research Topic cover recent advances in the use computational chemistry to aid stereochemical assignments of NPs by means of chiroptical spectroscopy, and the use of ML algorithms in computation NMR predictions. The review by Zhu et al. presents valuable practical information on the correct use of computational methods to simulate chiroptical properties, such as optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD). OR, ECD, and VCD represent powerful tools to assign absolute configurations of NP molecules; however, their safe application involves the comparison of experimental data with quantum chemical simulations. Due to the structural and stereochemical complexity commonly observed in secondary metabolites, there is not a single procedure that fits all. In this respect, this review article provides the reader with comprehensive examples on the use of chiroptical methods aided by computational chemistry, either alone or in combination, highlighting their potential and pitfalls. The authors also discuss the simulation of transition states to assist the determination of absolute configuration and the use of simplified models to save computational time without reducing accuracy. Finally, the review by Cortés et al. discusses the use of computational methods to assist the interpretation of NMR data in the structural elucidation of complex NPs. NMR is one of the most important methods to determine molecular structures and, despite recent advances in instrumentation and multidimensional experiments, the problem of structural misassignments is still persistent. In this context, computational chemistry has been synergistically coupled with experimental NMR to facilitate accurate structural elucidation. Among recent advances in this field, the implementation of ML can be considered one of the most disruptive methodologies, which has revolutionized molecular simulations. This minireview provides an overview of the two main categories of ML application to computational NMR in the context of structural elucidation, namely, prediction and correlation. Both approaches are discussed with a focus on methods that combine ML with quantum NMR calculations. ML applications to NMR are expected to grow as new procedures and more powerful computers become available. The authors point out, however, that the large structural diversity found in nature associated with the lack of comprehensive and reliable experimental NMR datasets is an important challenge to overcome. Tackling such a challenge would involve improving the predictive levels of ML algorithms and solving uncertainties related to the Boltzmann population of flexible molecules.

By combining cutting-edge experimental and theoretical procedures applied to NPs, this Research Topic will certainly be a useful resource to those exploring the fascinating chemical space produced by living organisms.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors QBC and JMBJ declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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