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EDITED AND REVIEWED BY
José L. Medina-Franco,
National Autonomous University of Mexico, Mexico

*CORRESPONDENCE
Yudibeth Sixto-López,
syudibeth@hotmail.com
Kuldeep K. Roy,
kuldeepkroy@gmail.com

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Editorial: Use of computational tools for designing epigenetic drugs

Yudibeth Sixto-López[1]*, Abdullahi Ibrahim Uba[2] and Kuldeep K. Roy[3]*

[1]Departamento de Química Farmacéutica y Orgánica, Facultad de Farmacia, Universidad de Granada, Granada, Spain, [2]Department of Molecular Biology and Genetics, Istanbul AREL University, Istanbul, Türkiye, [3]Department of Pharmaceutical Sciences, School of Health Sciences and Technology, UPES, Dehradun, Uttarakhand, India

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Editorial on the Research Topic
Use of computational tools for designing epigenetic drugs

Epigenetics is a term that refers to all those modifications to gene expression due to the interaction of genes with the environment. These modifications do not imply any changes in DNA sequences and may be heritable (Bollati and Baccarelli, 2010). In recent years, the association between epigenetic imbalance and human disease has been widely described in diseases such as cancer, metabolic disorders, neurodegenerative diseases, and immune disorders, among others. This has opened the opportunity to develop new drugs targeting epigenetic changes (Feehley et al., 2023).

Drug discovery is a large endeavor that involves the application of different methods and expertise, including harnessing the power of computational tools to speed up the process while concurrently reducing the cost of the undertaking. This Research Topic presents four original articles that employed such methods and tools to improve epigenetic drug discovery (Lu et al., 2018; Sixto-López and Correa-Basurto, 2021).

Flores-León et al. employed an approach that allows for the calculation of the on-target residence time (τ_{calc}) of nucleoside DOT1L (Human epigenetic enzyme disruptor of telomeric silencing 1-like) inhibitors. τ-Random Acceleration Molecular Dynamics (τRAMD) was used to estimate τ of urea-containing inhibitors and it was compared with reported experimental data. A high correlation was reported ($R^2 = 0.87$). Additionally, conventional all-atom MD simulation was done to obtain the starting structures for τRAMD and to study the interaction profile of the inhibitors at the DOT1L catalytic site. Using this combined approach, the authors offer a reliable method that predicts the nucleoside τ and the interaction profile.

Salifu et al. identified possible inhibitors of acetyl-coenzyme A (CoA) carboxylase and enoyl-acyl carrier reductase, two enzymes belonging to the fatty acid synthetic pathway of *P. falciparum*. Indirectly, CoA carboxylase participates in epigenetic regulation, and the CoA carboxylase inhibition leads to increased histone acetylation since this histone acetylation is dependent on the generation of acetyl-CoA by metabolic processes such as fatty acid synthesis (Galdieri and Vancura, 2012). Salifu et al., through the combination of in-house Per Residue Energy Decomposition (PRED) based Pharmacophore method, molecular

docking, ADMET, and MD simulation techniques to identified hit compounds from the ZINCPharmer database that favorably bound to the studied enzymes for further possible treatment of malaria disease.

Regarding infectious disease, tuberculosis (TB) represents a global health problem. It is one of the top ten causes of death in the world (Agbota et al., 2023). Additionally, there are TB strains that have become multidrug resistant, which decreases the efficacy and increases the toxicity of the available treatments. In search for novel anti-TB targets, Akinnuwesi et al., presented an interesting review where innovative approaches of computational biology, particularly metabolomics analysis, to study the TB's metabolism network were discussed.

Finally, Prado-Romero et al. discovered a novel non-nucleoside-based DNA methyltransferase 1 (DNMT1) inhibitor. The compound, F447-0397 consists of a chemical scaffold that had not been previously reported as a DNMT1 inhibitor. In addition, F445-0397 shows moderate DNMT1 activity but the novel moiety makes it an interesting molecule to further explore to optimize its structure and in consequence its inhibitory activity. The development was possible through the combination of consensus molecular docking with *de novo* ligand-based design complemented with similarity searching. The developer docking approach yields good agreement with experimental enzymatic inhibition in agreement with reported data, which makes the reported method reliable.

Finally, this Research Topic showcases novel and innovative approaches in epigenetic drug discovery, especially those in which computational approaches are used as part of their development protocol, thereby reducing the existing research gaps that usually hinder the achievement of more effective and affordable treatments for vulnerable populations worldwide. We thank all the contributors.

Author contributions

YS-L: Conceptualization, Writing–original draft. AU: Data curation, Formal Analysis, Writing–review and editing. KR: Data curation, Writing–review and editing.

Conflict of interest

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