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Editorial: The protagonism of bioanalytical methods in high-throughput drug discovery

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Editorial on the Research Topic
The protagonism of bioanalytical methods in high-throughput drug discovery

Protein-ligand interactions are essential for the regulation of biological processes, such as signal transduction, gene regulation, cellular metabolism, and immunoreaction. The term ligand encompasses nucleic acids, cofactors, metals, other proteins, peptides, amino acids, lipids, and drugs. Protein function can be regulated by its interaction with specific ligands through different mechanisms. Protein-ligand interaction studies are crucial for understanding the regulation of the biological function of proteins, elucidating potential biological targets, as well as discovering bioactive compounds in the drug development process. Within this context, this Research Topic aims to highlight different aspects of analytical techniques as a useful tool to develop new, rapid, and reliable ligand screening assays.

Two original research manuscripts, one review, and one mini-review on analytical assays for ligand screening are collected in this Research Topic, covering assays for ornithine decarboxylase inhibitor screening, on-flow enzymatic inhibitor screening through liquid chromatography methods, liquid chromatography coupled to mass spectrometry (LC-MS) method to screen human kallikrein (KLKs) inhibitors, and a study on salt concentration to improve the separation performance of biomarkers for transporter protein inhibition. In the following paragraphs, each published manuscript is presented and briefly described.

The ornithine decarboxylase (ODC) enzyme belongs to the polyamine biosynthetic pathway, catalyzing the decarboxylation of ornithine to putrescine. Polyamines (putrescine, spermidine, and spermine) are essential growth factors in eukaryotic cells, but their high levels are associated with carcinogenesis (Gerner and Meyskens, 2004) and Alzheimer's disease (Mäkitie et al., 2010). Consequently, ODC is considered a biological target for developing new drugs for the treatment of several diseases. Tinoco et al. (2022) summarized the methods based on radiolabeling, colorimetric assays using auxiliary enzymes to detect CO_2 or H_2O_2 release, chromatographic-based methods with putrescine derivation, mass spectrometry, circular dichroism, and fluorescence techniques. The authors highlight the demand for the development of high-throughput assays for the screening of ODC inhibitors. Since ornithine and putrescine (substrate and product) cannot be directly monitored by spectroscopic techniques, derivation or conversion procedures into spectrophotometrically detectable species are mandatory, resulting in low throughput assays.

Kallikreins (KLKs) are a subgroup of the serine protease enzyme family that play a crucial role in biological fluids (plasma kallikrein, KLK 1B) and tissues (tissue KLK, KLK-15). Unregulated levels of KLK expression may be associated with various diseases. For instance, KLK 1B plasmatic high concentrations or hyperactivity perpetuates cardiovascular disease (Kolte and Shariat-Madar, 2016). Other examples of KLK-related diseases include Alzheimer's and Parkinson's disease (Diamandis et al., 2000), inflammatory skin disorders (Di Paolo et al., 2021), and cancer (Kryza et al., 2016). The manuscript published by De Carvalho et al. in the present Research Topic describes the KLK immobilization on Sepharose-NHS as a micro-column for the development of an offline screening assay. KLK activity was monitored by quantifying the formed product (7-amino-4-methyl coumarin, AMC). After conducting kinetic assays, the method was validated for screening purposes using leupeptin as a reference inhibitor. Immobilized KLK exhibited stability through several cycles and it represents a promising alternative to the traditional fluorescence microplate assays.

Enzyme inhibition is known as an approach to the development of new drugs for the treatment of several pathological conditions, such as inflammation, diabetes, microbial infections, HIV, neglected diseases, and others (Geronikaki, 2020). Therefore, the development of analytical assays for high-throughput screening assays that enable the evaluation of large libraries as potential enzyme inhibitors can accelerate the drug development process (de Moraes et al.). In this realm, on-flow assays based on liquid chromatography (LC) can be highlighted. De Oliveira et al. summarized the applications of on-flow LC-based assays for monitoring the enzyme catalytic activity and the affinity/retention ligands. Since most of the applications use the immobilized biological target, immobilization methods and solid supports for enzyme immobilization are discussed. Activity- and affinity-based assays, including frontal affinity chromatography, zonal affinity chromatography, and ligand fishing applications are presented. The versatility of on-flow set-ups, the possibility of automation, and enzyme reuse are highlighted as the main factors associated with the emerging success of LC-based on-flow screening assays.

Taurine and glycochenodeoxycholate sulfate (GCDCA-S) can be used as probes for evaluating pharmacokinetic drug-drug interactions (DDI) involving renal organic anion transporters OAT1 and OAT3 inhibition in humans (Tsuruya et al., 2016). Both molecules are highly polar, hydrophilic compounds, and incompatible with conventional reverse phase LC mode. Wouters et al. reported the use of high salt concentrations to improve separation performance with suppressor technology in LC-MS using hydrophilic interaction liquid chromatography (HILIC) separation. The use of high salt concentration solvent modifiers to tune resolution and subsequently mitigate the MS incompatibility of high molar ammonium acetate was achieved by a post-column mobile phase modulation approach. The proposed method resulted in an up to a 10-fold increase in detection sensitivity.

The published manuscripts on this Research Topic nicely highlight some of the state-of-the-art achievements and challenges concerning the contribution of bioanalytical methods in high-throughput drug discovery. It is our hope that this Research Topic will encourage readers to apply different bioanalytical technologies to advanced applications in medicinal chemistry.

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 declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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