# Handling Compound Promiscuity in CZ-Openscreen

Hanzlík Adam1, 2, Voršilák Milan 1,2, Škuta Ctibor2, Bartůněk Petr 2

1 UCT Prague

2 CZ-Openscreen

High Throughput Screening (HTS) is a cornerstone of early-stage drug discovery, enabling rapid evaluation of extensive chemical libraries for biological activity against specific targets. While HTS significantly accelerates the discovery process compared to traditional manual assays, its heightened sensitivity often results in a high incidence of false positives. These artifacts can lead to costly and unproductive follow-up studies. False positives typically stem from assay technology interference or non-specific interactions with biological targets. Over time, problematic compounds exhibiting such behaviors have been categorized using terms such as *nuisance compounds*, *promiscuous compounds*, *PAINS* (Pan-Assay Interference Compounds)(1), *frequent hitters*(2), and *aggregators*(3). To mitigate their impact, researchers have developed filtering strategies including SMARTS-based substructure searches, similarity-based filtering to known nuisance compounds, and machine learning approaches.

In this work, we present a methodology for annotating, visualizing, and estimating the likelihood of compound promiscuity based on primary screening data generated at CZ-Openscreen. Leveraging rich metadata from ScreenX—CZ-Openscreen’s laboratory information management system—such as assay format and detection technology (e.g., fluorescence or luminescence), we aim to reduce experimental noise and provide more informative annotations. This methodology is currently being integrated into the ScreenX platform to support the design and evaluation of future HTS campaigns, ultimately enhancing data quality and decision-making in early drug discovery.

1. Baell JB, Holloway GA. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. Journal of Medicinal Chemistry. 2010;53(7):2719-40.

2. Stork C, Chen Y, Šícho M, Kirchmair J. Hit Dexter 2.0: Machine-Learning Models for the Prediction of Frequent Hitters. Journal of Chemical Information and Modeling. 2019;59(3):1030-43.

3. Irwin JJ, Duan D, Torosyan H, Doak AK, Ziebart KT, Sterling T, et al. An Aggregation Advisor for Ligand Discovery. Journal of Medicinal Chemistry. 2015;58(17):7076-87.