[P9] Diversity-Oriented Target-focused Synthesis (DOTS) : A hit optimization strategy combining molecular modeling and automated synthesis platform

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We report an original approach for generic hit-to-lead optimization and design of selective chemical probes that combines molecular modeling coupled to an automated synthesis robotic platform and a high throughput laboratory workstation (referred as DOTS). The full process has been set-up without any intermediary purification processes.

The *in silico* optimization strategy relies on 2 main steps: 1) the design of a diversity-oriented target-focused chemical library using medicinal chemistry relevant reactions[1] and a collection of commercially available building blocks; 2) the virtual screening of this chemical library using S4MPLE, a conformational sampling tool, able to deal with hundreds of intra/intermolecular degrees of freedom in the context of one (conformer enumeration) or more molecules (docking)[2]. S4MPLE relies on a Lamarckian genetic algorithm and significant flexibility may be enabled (e.g. ligands, target side chains and backbone). Energy calculations are based on the AMBER force field and its generalized version GAFF for ligands. This two-step *in silico* protocol has been validated using the FXa case study leading to very good agreement with published data[3] (*i.e.* the known inhibitor was correctly generated, accurately positioned in the binding site and ranked within the top 1%).

The DOTS approach has been applied to the design of potent selective bromodomain (BRD) inhibitors. Bromodomains and extra terminal domain (BET) family of proteins are small interaction modules that emerged as druggable epigenetic targets due to their role in cancer. We recently identified through mid throughput screening an acetylated-mimic xanthine derivative selectively inhibiting BRD4-BD1[4]. We first generated a xanthine-focused chemical library of ≈7000 compounds using a Williamson-like reaction and a collection of building blocks. Interestingly, the original selective inhibitor was correctly generated and ranked at the top 1%. Following this very encouraging result, about 50 building blocks were purchased to prepare a representative set of compounds from the top 1%. The compounds have been synthetized using our automated robotic platform from Chemspeed. The Accelerator Synthetizer SLT100 allows the efficient synthesis of the focused library in 96 well plates that can be directly transferred to our Labcyte Access/Echo® Laboratory Workstation to assess the compounds for their ability to disrupt bromodmain/histone complexes using the homogeneous time-resolved fluorescence (HTRF®) technology. IC_{50} measured by HTRF and selectivity profiles for the best compounds will be presented.

References:

[1] M. Hartenfeller, M. Eberle, P. Meier, C. Nieto-Oberhuber, K. H. Altmann, G. Schneider, E. Jacoby, S. Renner, J Chem Inf Model 2011, 51, 3093-3098.
[2] L. Hoffer, C. Chira, G. Marcou, A. Varnek, D. Horvath, Molecules 2015, 20, 8997-9028; L. Hoffer, J. P. Renaud, D. Horvath, J Chem Inf Model 2013, 53, 836-851.
[3] M. Nazaré, H. Matter, D. W. Will, M. Wagner, M. Urmann, J. Czech, H. Schreuder, A. Bauer, K. Ritter, V. Wehner, Angew Chem Int Ed Engl 2012, 51, 905-911.
[4] B. Raux, Y. Voitovich, C. Derviaux, A. Lugari, E. Rebuffet, S. Milhas, S. Priet, T. Roux, E. Trinquet, J. C. Guillemot, S. Knapp, J. M. Brunel, A. Y. Fedorov, Y. Collette, P. Roche, S. Betzi, S. Combes, X. Morelli, J Med Chem 2016, 59, 1634-1641.