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Editorial

Structure-Based Discovery of Natural Product-Like Protein Inhibitors

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Natural products have been refined over evolutionary timescales for optimal interactions with biomolecules, and they have historically been considered as an important source of new drugs [1-4]. Unfortunately, natural products had fallen somewhat out of favour in pharmaceutical research over the past few decades due to the rise of automated combinatorial synthesis techniques that could generate large compound libraries in a rapid manner [5]. The screening of natural extracts became less desirable by comparison, owing to issues associated with sample collection, hit identification and dereplication. However, it was soon realized that the compounds generated by combinatorial chemistry, though great in number, were constrained in structural diversity due to the limited number of reaction types that can be employed. In contrast, natural products offer diverse chemical scaffolds that are rarely found in purely synthetic compounds. As such, natural compounds do not adhere closely to the Lipinski rules, and their use in screening may offer interesting hits distinct from those obtained using synthetic or combinatorial libraries.

Meanwhile, the rising costs of high-throughput screening (HTS) of large chemical libraries and the synthesis of chemical analogues of the hit compounds are problems that have burdened the pharmaceutical industry worldwide, in addition to increasingly stringent regulatory and safety issues. Under this regime, virtual screening has emerged as an attractive and powerful technique that could complement traditional HTS technologies [6,7]. The virtual screening of chemical libraries could potentially weed out non-binding candidates *in silico*, thus greatly reducing the costs associated with chemical synthesis and *in vitro* screening. In this context, the combination of virtual screening and natural products represents a potent synergy that could allow the astonishing diversity of natural compounds to be harnessed in an efficient manner.

Virtual screening can be broadly classified into structure-based and ligand-based approaches. In the former, knowledge of the target binding site obtained from X-ray crystallographic or NMR studies is used to construct a three-dimensional model that can be used for molecular docking or pharmacophore generation [8]. By comparison, ligand-based methods typically aim to identify structural motifs that are important for bioactivity by considering sets of known active and inactive molecules. Our own group has focused on the structure-based docking approach which, while generally considered to be more computationally demanding, can be used with new or orphan targets that have few known ligands. Moreover, molecular docking may be used to study the mode of the ligand-target interaction in order to rationally design analogues of hit compounds with improved potency and selectivity. A few recent examples of the use of structure-based docking methods to identify natural product or natural product-like protein inhibitors are presented below.

NEDD8-activating enzyme (NAE) controls the specific degradation of proteins regulated by cullin-RING ubiquitin E3 ligases, and has been considered as an attractive molecular target for the development of anti-cancer drugs. In 2011, our research group reported the discovery of the natural product-like 6,6”-biapigenin as only the second inhibitor of NAE using molecular docking [9], demonstrating the use of the technique in identifying ligands of novel protein targets. Later on, our group identified a dipeptide-conjugated deoxyvasicinone derivative as an inhibitor of NAE by virtual screening of over 90,000 compounds from the ZINC database of natural products [10]. Molecular modelling analysis suggested that both 6,6”-biapigenin and the deoxyvasicinone derivative acted as non-covalent competitive inhibitors of NAE by blocking the ATP-binding domain.

Protein-protein interactions play central roles in cellular signalling cascades, but have historically been considered to be difficult to target by small molecules due to their relatively large and amorphous interfaces [11,12]. Our group was the first to utilise structure-based techniques to identify natural product-like inhibitors of tumor necrosis factor-α (TNF-α), which is a pro-inflammatory cytokine dysregulated in a number of human inflammatory and autoimmune diseases [13]. The molecular docking compound furnished two molecules which targeted the binding site of the TNF-α dimer, thereby blocking the entry of the third subunit to form the biologically active trimer complex. Additionally, our group has recently discovered novel small molecule inhibitors of signal transducer and activator of transcription 3 dimerisation from a database of over 90,000 natural products and natural product-like compounds by molecular docking [14]. These studies demonstrate that structure-based docking can be effective for discovering novel modulators of protein-protein interactions from natural product databases.

Towards the future, the continual identification of new protein-protein interactions in the emerging field of interactomics offers new targets for therapeutic intervention that could potentially be addressed by natural products. Moreover, the knowledge that protein-protein

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interactions are often governed by "hot spots" [15,16], which are key amino residues that are responsible for most of the binding energy of the interaction, can allow computational power to be more efficiently harnessed, as the search area for *in silico* screening can be restricted to the critical regions. Additionally, the continuing exploration of biological lifeforms, particularly of rare microbial or marine species, will offer heretofore undiscovered chemical scaffolds that can be efficiently screened, at low cost, by virtual screening. Finally, improved knowledge in structural biology as well as the development of more powerful computational algorithms could also enhance the utility of molecular docking techniques for the high-throughput virtual screening or structure-based rational design of natural product-like inhibitors. Challenges notwithstanding, we believe that this exciting field will continue to thrive and mature in the years to come.

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