Editorial

In Silico Technologies in Drug Design, Discovery and Development

The focus of this hot topic issue is to give an overview on the current status of *in silico* technologies widely applied in drug discovery community, including QSAR, Bioisosterism, Shape-matching, Fragment-based methodologies, and *in silico* approaches for GPCRs-targeted drug discovery at a point when we witness a renaissance of the computational approach in the field. In mind that the aim of the issue is to provide a deeper analysis on the specific areas interested by discovery community, the authors contributing to the reviews are all have active research projects in the specific area they are reviewing.

With its existence over half a century, QSAR has been the single most-used computational technique and is growing further with newer algorithms and strategies. Sprous *et al.* focus on the QSAR models based on large datasets and applied to broad problems such as property modeling and target family focus library design. As a consequence of this theme, their review surveys 2D descriptors and QSAR validation methodologies as necessary background for the necessary tools used for models based on large, diverse datasets and applied not for retrospective modeling and analysis, but applied for decision making.

G-Protein coupled receptors (GPCRs) are targeted by ~30% of all marketed drugs, covering a wide range of therapeutic indications, including neurological disorders, cardiovascular diseases, metabolic diseases, inflammation and pain. The role of GPCRs in diverse signaling pathways, together with the fact that the vast majority of potential GPCR targets are still unaddressed by marketed drugs, positions this receptor family at the heart of current pharmaceutical industry efforts. Kalid *et al.* give us a comprehensive overview of the current state-of-the-art *in silico* drug-discovery in GPCR field and bring together different approaches currently being utilized for 3D structure generation with their advantages (accuracy versus speed), limitations and pitfalls. Then their attention turns to their in-house program, PREDICT^{TM}, an *ab-initio* methodology for predicting the structure of the trans-membrane (TM) portion of GPCR receptors. While structure-based drug-discovery is facilitated by the recent release of new GPCR crystal structures, it is still by no means an easy task. Therefore, they concluded their review with detailed analyses of the progresses of their diverse GPCR projects.

Bioisostere recognition has long been treated as the art of expertise in medicinal chemistry field since the discipline ever evolved. Popelier *et al.* first define the scope of bioisosterism to pairs of fragments that have similar impact on molecular activity, not whole molecules. This review provides an overall picture of the broad and increasingly varied selection of computational approaches available to find bioisosteric replacements, discusses the current status of the rational and cheminformatics approaches. Tools, such as Brood of OpenEye Scientific, the Drug Rings Database by GSK for scaffold replacement, Quantum Isostere database for linker replacement, full *ab initio* calculation, descriptor and fingerprint-based technologies, Drug Guru package from Abbott as a SMIRK-based expert system, are all been critically reviewed. Scaffold hopping is to identify alternative molecular scaffolds or 'cores' that will form the backbone of new families of compounds with similar biological activity to a known reference. Therefore, it is loosely fall into bioisostere scope. It is also reviewed with a focus on the application of SHOP and GANDI packages.

Shape complementarity plays an important role in the process of molecular recognition. In recent years, molecular shape technology has become an indispensable tool in drug discovery and development for target-to-hit, hit-to-lead and lead optimization projects, as well as in ADMET modeling. The commercialization of the ROCS (Rapid Overlay of Compound Structures) technology and the description of the USR (ultrafast shape recognition) method have marked the new state-of-the-art of molecular shape technology, and new tools integrating these ideas will ultimately make the shape technology a great complement to, sometimes a substitute for, structure-based docking tools. Zheng *et al.* give a concise review on the algorithms developed for molecular shape representation and comparison, superposition-based and superposition-free algorithms for shape matching., and their attention quickly shift to recent advances and future prospects of methods in various shape tools, including ROCS, topomer shape similarity, USR, the shape signatures method. They complete their review with a insightful summary of their practical applications.

Fragment-based methods have rapidly established their prominent presence in drug discovery. Although it is too early to have yielded a marketed drug, they have resulted in a significant number of clinical candidates and many more in preclinical development. It has long been recognized that there is no universal perfect docking program to fit all the drug discovery projects, and the screening result depends on the combination of the docking program used and the target protein. Even a slight structural change around the binding site sometimes has a large effect on the docking scores. In FBDD, the compounds are smaller than those for conventional drug screening. This makes it even harder to perform the protein–compound docking calculation. Fukunishi gives a comprehensive review on various computational methods proposed for docking-pose prediction

and their usefulness in the fragment-based drug design (FBDD). Readers who are directly involved in *in silico* FBDD will find the section of problems and solutions section especially valuable.

We hope that these reviews will convince you that *in silico* approach continues to be an exciting approach in drug discovery and the promise for significant further advances. We would like to thank all the authors for their valuable time and hard work to put this issue together. Finally I would like to thank Dr. Allen Reitz, editor-in-chief of Current Topics in Medicinal Chemistry, for providing me with this exciting opportunity, to Ms. Rhoda Weber Joseph, Associate Editor, for her constant in time editing support, and to the editorial and publication team of Bentham Science for their cooperation during the entire process of bringing this issue to the readers. I also thank readers and welcome constructive feedback that will help improve our knowledge and understanding of the field.

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