Editorial

Effect of Stereochemistry in Medicinal Chemistry and Drug Discovery

Although in 1986 E.J. Ariens wrote "Stereochemistry: a source of problems in medicinal chemistry", chirality dominates in nature, in biological systems (i.e. aminoacids, receptors, enzymes) and in disposition and metabolic processes in which receptors and enzymes are involved. The complexity of biological systems, together with the different pharmacological and pharmacokinetic properties of enantiomers prompt medicinal chemists to take advantage in new asymmetric synthesis and in separation technologies. Beyond the groundbreaking strategies of drug design in which efficacy and safety should be hold imperative, the development of dynamic theoretical models, which taking account the stereoselectivity and the asymmetry of the target, emerged as needful tools to improve pharmacological therapies. Despite the true difficulty to develop new chiral drugs or new molecules with elevate stereoselectivity, chirality keep affecting both the modern pharmaceutical industry and drug discovery.

Stereochemistry represents a challenge to improve the activity and/or to reduce toxicity of drugs throughout the rise of new theoretical and synthetic strategies. This issue offers an useful overview and entry point into the discussion of stereochemistry and its consequences for drug development.

The review paper of *Daniel Kenyon et al.* gives a very detailed and highly informative description of the regulatory guidelines regarding chirality of drugs and the changes in drug development resulting from these. Moreover, this paper includes an examination of some of the practical concerns of stereochemistry in drug discovery campaigns highlighting the need to address chirality in the early of drug discovery process.

The review of *Subhash Basak et al* is an overview of some theoretical methods useful to assess the importance of chirality in behaviour of molecules useful in pharmacology, agrochemistry and environmental toxicology. In particular, this paper detailed analyses different mathematical models to predict the properties of chiral drugs throughout the numerical characterization of chiral compounds.

This issue carries on with the effects of stereoselectivity and the role played by chiral centers in the interaction with different biological targets such as enzymes (i.e. kinase inhibitors), and nuclear receptors (i.e. PPAR, VDR). The clinical importance of stereochemistry has been clearly discussed in other two reviews that provide hope in the fight against tubercolosis and cancer, two globally health problems, not yet overcome.

The *Sessel & Fernandez* manuscript outlines the need for the combined use of computational methods, biomolecular structure and bioinformatics in rationally drug design. Biomolecular structure and bioinformatics are described as essential instruments to design novel drugs with increased selectivity. The application proposed by Sessel & Fernandez in the field of drug specificity is on modelling molecular filters to specifically target kinases with cancer-related mutations.

The review article by *Thomas Craig et al*. talks about the key role played by stereochemistry in the interaction with several pharmacological targets, and in particular with kinases which are involved in the cellular signalling pathway. This paper discusses the effects induced by the introduction of chiral centers in terms of potency and selectivity of new small kinase inhibitors

The review article by *Kozikowski et al.* summarizes the importance of stereochemistry in anti-TB drug activity and in the discovery and development of anti-TB drug candidates. The authors focus on the advantages in potency, efficacy and selectivity obtained by the development of single enantiomers of chiral drugs in the discovery of novel anti-TB agents .

The review article by *Fulvio Loiodice et al.* is a detailed discussion of the influence of stereochemistry on PPAR activation, focusing on the PPAR binding mode and how chirality affects it. To better explain and comprehend the PPAR stereoselectivity, the authors suggest the application of cristallization methods together with the analysis of the complexes formed by PPAR and their ligands. The differences between several ligands targeted PPAR as well as the pharmacophore and the role played by the stereogenic centers in the PPAR-ligand complexes are discussed.

The review article by *Chiellini & De Luca* focuses on the stereochemistry aspect on vitamin D analogs and their interaction with VDR (Vitamin D Receptor). In particular, this paper outlines the main structural modifications of vitamin D skeleton as the main tool to elucidate the role played by aminoacids within the binding pocket to anchor the ligands. The strategy reported here is based on the understanding of the structure activity relationship of vitamin D analogs which represent one of the most important resource for researchers in this field.

The review of *Taliani et al.* summarises the structural requirements needed to obtain TSPO ligands with high affinity and selectivity. Because of the lack of crystallographic data due to the difficulty of isolate this receptor, this paper elucidate the structural requirements on the basis of a detailed analysis of the SAR of TSPO ligands designed and tested.

The review of *Rasmus et al* focuses on the stereochemical and conformational aspects related to the activity of glutamate receptors. Both the stereochemical and the conformational considerations were reported on the basis of biostructural knowledges of the agonist binding pockets based on structure-activity relationship of ionotropic glutamate receptors. This

review highlights the influence of stereochemistry in the ligand fitting with the receptor as well as in the conformational space of the ligand.

I would like to thank all the authors for their excellent contributions and participation in this issue and all the Referees who contributed to improve the quality of the whole issue. I am also grateful to the editor-in-chief, Dr. Allen Reitz, for the invitation and the opportunity to arrange this special issue as guest editor.

Taking into account the ever growing needs for new and more efficacious drugs and the evident existence of a high degree of stereoselectivity within the complexity of the targeted biological system, I hope this issue will provide useful tools to pursue and develop new and more specific strategies for satisfing the prime demands of the pharmacological therapy: the safety and the efficacy.

This issue may represent an useful guide for the medicinal chemistry research community and other related fields in the future.

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