Drug Design and Development for Neglected Diseases

Neglected diseases have been a great challenge for Public Health for many poor countries. About one billion people are infected worldwide with one or more of the 20 diseases considered neglected according to the WHO. Although tuberculosis and malaria are not considered by some world organisms as neglected -- they have more investments than most of the other diseases, they fit the concept of diseases that affect neglected populations. Furthermore, the problem of high level of drug resistance related to tuberculosis and malaria is a threat that the public health must strongly tackle, otherwise they can strongly compromise the quality of life of populations.

Most of the neglected diseases face the trouble of the scarcity chemotherapeutic armamentarium available. For this very reason, the design and development of new drug candidates are urgently needed.

Therefore, the aim of this issue was to present some important contributions of researchers mainly from the academia about the drug design and discovery of bioactive compounds on neglected diseases. The research works have been contributed by important and specialized Brazilian and foreign groups dedicated to the search for new bioactive compounds to treat some of the most important Neglected Diseases worldwide. The diseases involved in this issue are: Chagas disease, leishmaniasis, malaria, tuberculosis, dengue, schistosomiasis. Well-known molecular targets and new ones are comprehended in the subtopics in general. Then, rational design, especially SBDD – Structure Based Drug Design – is the subject of some topics, and, in addition, LBDD – Ligand Based Drug Design is involved in others. Molecular modification as bioisosterism, molecular hybridization and prodrug design are used as approach to design some leads and hits, described for their potential activity on neglected diseases. Polypharmacology and also drug repositioning are discussed concerning their importance on neglected diseases.

I am grateful to Prof. Atta-ur-Rahaman, Editor of Current Medicinal Chemistry, for the opportunity of editing this special issue, giving the importance that this topic deserves in the context of drug design and development. I am also indebted to the authors for their participation in this issue, discussing about the works they have developed in their laboratories against neglected diseases.

Obtaining selective compounds against protozoan parasites has been a challenge for those who work on drug design for neglected diseases. Martins-Teixeira, Morotti and Carvalho [1] reviewed the main differences between a complex glycosylphosphatidylinositon(GPI) anchor biosynthesis of parasites and mammalian. The use of this complex by parasites seems to be more frequent than in the case of higher eukaryotes. The function of this anchor in parasites was discussed in terms of being the targets for therapy against parasitic diseases. The structural variations, which implies in the selectivity for parasitic cells over mammalian cells were also discussed. Is important to emphasize that the advances in the studies as selective drug discovery against the enzymes involved in the biosynthesis of the GPI anchors have also been explained.

The paper of Lima Leite et al. [2] explores the concept of privileged scaffolds, as phthalimide, isatine, indole, thiosemicarbazone, thiazole and thiasolidinone, found in leads and drug candidates for neglected tropical diseases. Thiosemicarbazone was found to be the most investigated and the most versatile. This review covers 15 years, from 2002 to 2016, of search in the literature and points out that some neglected tropical diseases were highlighted in this period. Compounds for Chagas disease, malaria, tuberculosis, schistosomiasis, leishmaniasis, dengue, human African trypanosomiasis and toxoplasmosis were highlighted in this period, with an emphasis on antitrypanosomal and antiplasmodial activity. Many of the compounds were shown to be promising drug candidates and others can be leads for optimization of new chemotherapeutic agents for neglected tropical diseases. The scaffolds presented can be an inspiration for new drug design.

Repositioning has been strongly stimulated as a promising approach for neglected tropical diseases. Andrade et al. [3] reviewed the aspects of chemogenomics, which are directly involved in the identification of potential ligands for all potential targets for neglected tropical diseases as leishmaniasis, schistosomiasis, malaria and human African trypanosomiasis. The current methodological development towards repositioning approach using computational
ligand- and structure-based chemogenomics is presented and the advances are highlighted for some neglected tropical diseases. In addition, successful examples are described, including those from the group, presenting the aspects that may deserve attention and the possible solutions.

New targets for malaria were reviewed by Aguiar et al. [4], towards the urgent need for new and better antimalarial agents. Genetically and clinically validated plasmodial proteins were highlighted. Many enzymes, involved in mechanisms hemoglobin hydrolysis, the invasion process, elongation factors for protein synthesis, pyrimidine biosynthesis, posttranslational modifications such as prenylation, phosphorylation and histone acetylation, generation of ATP in mitochondrial metabolism and aminoacylation of RNAs, were described. Those studies are now possible because of the parallel development of advanced methods, using genetics as well as computational approaches, which provide the deep knowledge of drug targets in many aspects. Based on the foregoing information, the authors presented the progress and the challenges, which must be faced in order to develop new drugs to malaria. In addition, the perspectives towards this objective were also discussed.

Molecules as 1,2,3- and 1,2,4-triazole have shown potential activity against neglected diseases, such as Chagas disease, malaria, leishmaniasis and tuberculosis. Mantoani et al. [5] reviewed some compounds that can be considered for lead optimization. In addition, they present chemical characteristics and synthesis of triazole rings. Those molecules, mainly when linked to other heterocyclic rings, which allows chemical diversity and functionality, presented promising application to those neglected diseases.

Vieira, Santos and Ferreira [6] highlighted the relevance of cysteine proteases as targets for the design of inhibitors as promising antiparasitic agents. These enzymes have been validated through the years of research and this paper reviewed the recent results of structure-based drug design using two important proteases, cruzain and falcipain, as targets for Chagas disease and malaria inhibitors, respectively. In addition, the combination of computational and synthetic approach was presented as hit optimization strategies. The paper expands the scope of application of the rational design to schistosomiasis, leishmaniasis and babesiosis. A neurodegenerative disease, i.e. Alzheimer’s disease, was also included in the review as it was associated to physiopathological roles of human cysteine proteases, as recently discovered. The repositioning approach linked to cysteine proteases was also discussed.

The current and future prospects of nitro compounds as drugs for trypanosomiasis and leishmaniasis are presented in the interesting paper of Patterson and Fairlamb [7]. Monocyclic and bicyclic nitroheterocyclic compounds have raised interest nowadays for some neglected diseases, as human African trypanosomiasis and Chagas disease, besides visceral leishmaniasis. Some monocyclic nitrocompounds, such as nifurtimox, benznidazole and fexinidazole, as well as the bicyclic compounds pretomanid and delamanid are recognized as prodrugs, which need enzymatic biotransformation through nitroreductases to show their activity. The different mechanisms by which these enzymes, NTR1 - activating monocyclic nitro derivatives, and NTR2, biotransforming bicyclic derivatives - act are presented. In addition, the pharmacokinetics and pharmacodynamics, as well as the structure-activity of the compounds are discussed.

Aguilera et al. [8] reviewed the polypharmacology strategy as an alternative to solve the problems of Chagas disease treatment. It is worth noticing that there are only two drugs available for this disease and they are not effective in the chronic phase of the disease. Furthermore, they are used alone, in monotherapy. Polypharmacology, which consists of a combination of compounds that interact with different targets in different biochemical pathways, mainly to achieve efficacy and to overcome the resistance in some infections, is gaining interest nowadays. Therefore, different classes of compound combinations, as reviewed, such as ergosterol biosynthesis inhibitors, anti-inflammatories, cardiac dysfunction drugs, trypanothione reductase inhibitors, and vitamins, among others, including some natural products, are presented in this paper as a strategy to be used for combating Chagas disease.

**REFERENCES**


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