Design and synthesis of molecular hybrids between drugs for dermatological disorders or wound healing and H_2S donors

The research topic concerns the development of molecular hybrids of clostebol and other drugs for the treatment of skin wounds, as well as JAK kinase inhibitors and anti-inflammatory drugs approved for the treatment of dermatological diseases, with chemical entities capable of H_2S slow releasing, either enzymatically or chemically, in a way that mimics physiological conditions.

There are a great number of skin pathologies, which moreover always have a particular impact on the patient, if only because they are "visible" and because of the resulting aesthetic concerns. Some are on a hereditary basis or at least have a familial basis (psoriasis, vitiligo, atopic dermatitis, neurofibromatosis), others result from exposure to sunlight (skin cancers such as melanoma) or radiation, and still others are on an infectious basis from bacteria and viruses. The most common symptoms of skin diseases are itching, pain, and burning. Signs, on the other hand, include depigmentation, scarring, blisters, scabs, excoriations, ulcers, etc.

Along with nitric oxide (NO) and carbon monoxide (CO), hydrogen sulfide (H_2S) is recognized as a vital gaseous transmitter. Acting as an antioxidant, it can counteract oxidative species such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) while also protecting the skin from oxidative stress.

The anti-inflammatory effect of H_2S and its participation in the resolution of inflammation at the dermal level has been described by countless in vitro and in vivo studies. H_2S donors result in reduced inflammatory response, lower expression of TNF-α and IFN-γ, and fewer neutrophils recruited at the level of skin lesions. In addition, H_2S also plays an important role in the pruritus gene response. These same studies have also demonstrated the role of H_2S in accelerating the healing process of skin wounds.

A special focus will be devoted to the derivatization of JAK kinase inhibitors, an innovative and promising class of drugs that have been studied and used in the treatment of dermatological diseases, guaranteeing surprising results especially in the treatment of vitiligo, atopic dermatitis, and alopecia. These premises support the goal of the largely multidisciplinary project aimed at the synthesis, characterization and preclinical evaluation of the proposed molecular hybrids with optimal pharmacokinetic requirements for cutaneous use.