

Abstract

One of the main goal of modern medicinal chemistry is the development of new agents able to modulate biological targets involved in inflammation and cancer processes. In this context, my PhD project was focused on the exploration and structural optimization of various chemical moieties able to interfere with two targets involved in both processes. In particular, two biological targets were selected: Heat shock protein 90 (Hsp90) and microsomal Prostaglandin E₂ Synthase-1 (mPGES-1). The results obtained can be divided into two sections in accordance with the target of interest.

a) Exploration and structural optimization of DHPM core in order to guide the synthesis of new and more potent Hsp90 C-terminal inhibitors.

Hsp90 is a molecular chaperone involved in the maturation and stabilization of a wide range of client proteins that play a crucial role in the development, survival and proliferation of cancer cells. In the literature there are several compounds capable of inhibiting this molecular chaperone. The most part of these compounds inhibit the protein through modulation of the N-terminal domain. However, this type of modulation involves a well-known heat shock response, a cytoprotective mechanism that as a final result leads to the increase of cytosolic levels of heat shock proteins with consequent cell survival. Therefore, the modulation of C-terminal domain of Hsp90 represents a better strategy for the development of new antitumor agents, since, they do not induce heat shock response. In an attempt to discover new modulators of the C-terminal domain of Hsp90 and taking into account the structure of the first synthetic inhibitor of this domain, a 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivative, two more generations of DHPM derivatives have been synthesized. Relatively to the second generation of DHPM derivatives, the synthesis was focused on the influence of the chemical functionalization of aromatic ring at C4 position of DHPM core, while the third generation has been designed with the aim to functionalize the C2 position of the core. The exploration and optimization processes of DHPM core led to the identification of novel and more potent inhibitors of the C-terminal domain of Hsp90.

b) Identification of new mPGES-1 inhibitors.

mPGES-1 is an inducible enzyme that catalyzes the terminal step of the biosynthesis of PGE₂ from the PGH₂ precursor. The inhibition of this enzyme appears to be a promising strategy for the identification of novel anti-inflammatory agents, because, the use of selective inhibitors would

allow to overcome the classical side effects of traditional anti-inflammatory drugs. Moreover, mPGES-1 is overexpressed in a wide variety of human cancers and for this reason it has emerged as an attractive biological target for anticancer drug discovery. In order to identify new molecular platforms able to interact with the target protein three collections of compounds (carbazoles, biaryl compounds and 5-pyrazolones) were synthesized. Biological evaluation revealed the identification of five biaryl compounds (**60-64**) as new chemical entities that inhibit mPGES-1 activity with promising IC₅₀ values (ranging 0.18-1.64 μM).