MOLECULAR CHAPERONES AND STAT5 AS NEW ANTITUMOR AGENTS

Molecular chaperones (heat shock proteins, Hsp) are involved in many mechanisms that regulate cell functions. They assist other proteins to fold properly in the cytoplasm, and stabilize mitochondria, thus containing the release of pro-apoptotic factors. These mechanisms are often overexpressed in cancer cell lines causing chemotherapy resistance, so inhibitors of molecular chaperones may find application as therapeutic agents.
Some molecular chaperones, such as Hsp90 and 75 (TRAP1), are also involved in the mitochondrial activation of apoptosis, which is known to be inhibited in tumor cell lines by the overexpression of Hsp molecules. Based on this, mitochondrial vehiculation of Hsp inhibitors might represent a possible target for new antitumor drugs.
The STAT5 proteins regulate cell cycle, apoptosis and proliferation of different cells through the influence on gene transcription. STAT5 proteins are suggested to play an important role in leukaemogenesis, as they are constitutively activated in some haematooncologic diseases. For this reason, inhibition of STAT5 proteins may represent a valuable treatment option for this type of cancers. It has been demonstrated that structural analogs of the neuroleptic pimozide are able to interfere with cell growth in some myelocytic leukemias lines, which is typical of Jak/STAT system overexpression.

GOALS

- Design and synthesis of new derivatives as potential inhibitors of Hsp family, with particular regard to mitochondrial Hsp75.
- Synthesis and biological evaluation of a potential class of antitumor drugs acting through inhibition of activated STAT5, with the aim of finding alternative therapeutic options to bypass imatinib resistance in the treatment of myelocytic leukemias.

INSTRUMENTS AND METHODS
Common techniques and equipment of a synthetic organic laboratory. Use of chromatographic (preparative HPLC, flash chromatography) and analytic techniques (mass spectrometry, NMR, IR) for the purification, identification and characterization of the synthesized compounds. Structural optimization based on literature data and preliminary biological test results of the new compounds.

MAIN SUBJECTS
Medicinal chemistry

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