SYNTHESIS AND ACTIVITY OF PROTEASOME INHIBITORS

The proteasome is a multicatalytic protease complex which takes an active part in the ubiquitin-proteasome (UPP) metabolic pathway of proteolysis in eukaryote cells. Fundamental cell functions are related to the degradation of proteins which are involved in processes such as cell cycle and differentiation, apoptosis and generation, and transcriptional regulation. Many natural and synthetic compounds have been evaluated as inhibitors of proteasome. In vitro and in vivo studies have demonstrated that proteasome inhibitors show anti-proliferative and pro-apoptotic activities towards solid and hematologic tumors. Other proteasome inhibitors have been tested against inflammation- and immune-associated disorders.

GOALS

The project aims at the synthesis of new potent and selective proteasome inhibitors, with satisfactory pharmacokinetic properties, to be used in new therapeutic protocols. It follows previous development of many classes of peptide-based proteasome inhibitors bearing *C*-terminal suitable pharmacophoric units that are able to interact with the catalytic threonine through a Michael-type addition. At present, we are studying the design and synthesis of new peptide-based proteasome inhibitors featuring a ketoamide moiety as the *C*-terminal pharmacophoric unit. Some of these molecules significantly act as reversible inhibitors of the catalytic subunits of the enzymatic complex. Potential therapeutic applications of such analogs should not suffer from the undesired side effects that are displayed by irreversible inhibitors, that instead covalently bind to the enzymatic complex active subsites. In the future, suitable structure modifications are expected to enable the development of more potent and specific inhibitors of proteasome.

INSTRUMENTS AND METHODS

Solution- and solid-phase synthesis. Combinatorial chemistry techniques. Purification techniques, such as flash chromatography and preparative HPLC. Mass spectrometry, analytical HPLC, NMR, IR techniques to determine either structure or purity of final compounds.

MAIN SUBJECTS

Pharmaceutical chemistry, organic chemistry, biochemistry

RESEARCH GROUP

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