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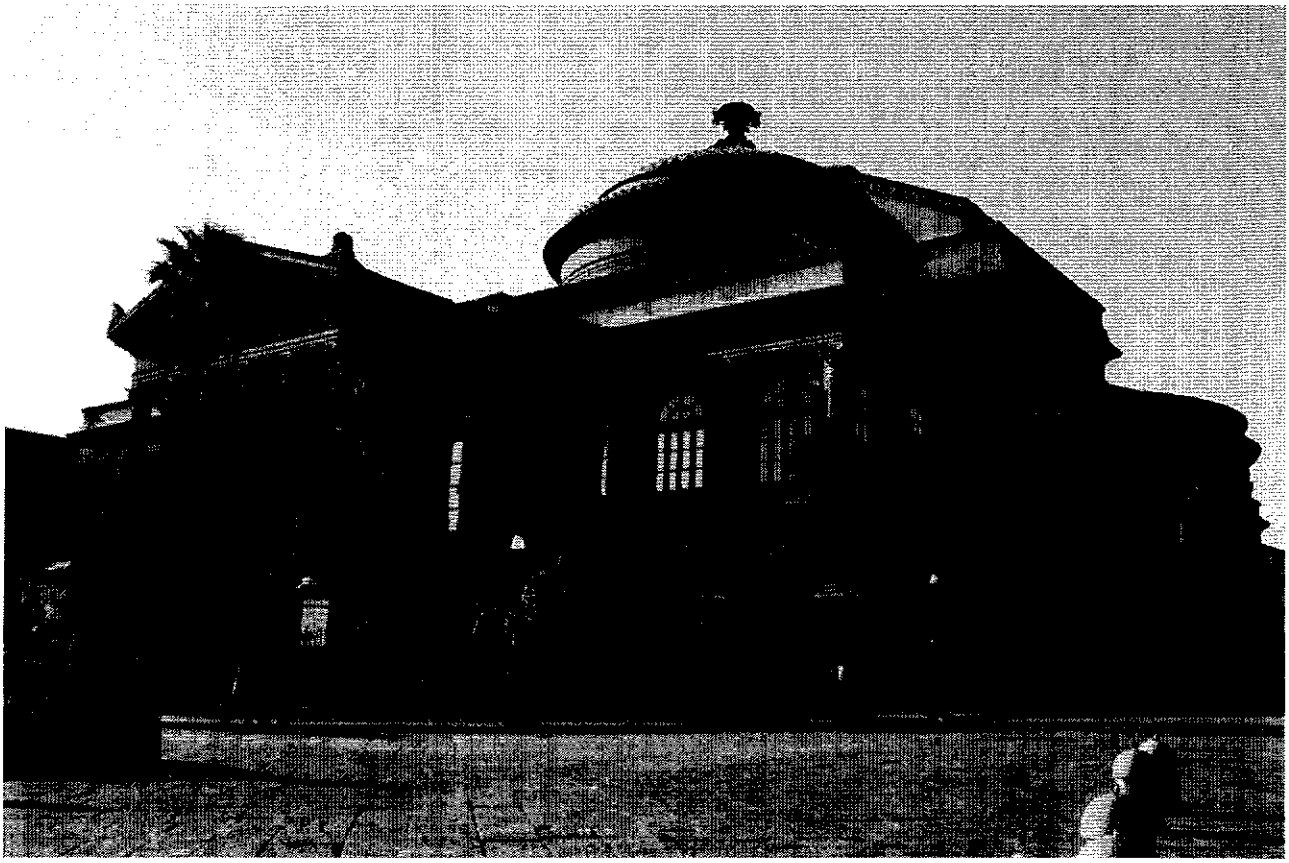

BOOK OF ABSTRACTS

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New topoisomerase I inhibitors with condensed-azaindole structure

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The variety of therapeutic approaches for cancer and a better knowledge about the mechanisms of neoplastic transformation increase the survival against many types of tumours. Despite of these improvements, cancer always constitutes one of the principal cause of death; so it is necessary to find out new drugs to introduce in therapy. Polycyclic nitrogen heterocycles can be good pharmacophores for classes of antineoplastic drugs because of their potential ability to bind to DNA by intercalating between the base pairs of the DNA duplex. Many 1,2,3-triazine and cinnoline derivatives are well known compounds endowed with a wide range of biological properties such as antineoplastic activity.(1-4) In our attempts to search for novel antitumor agents, we extended our interest to the 7-azaindole[1,2-c][1,2,3]benzotriazines and 7-azaindole[3,2-*c*]cinnolines with the aim of evaluating their antitumor activity. Five derivatives tested by the National Cancer Institute exhibited antitumor activity against the total number of the 60 cell lines panel from micromolar to nanolar concentrations. We evaluated the mode of cellular death through a series of flow cytometry experiments. Annexin V/PI test together with the cell cycle analysis showed that these compounds induce cell death by apoptosis. The involvement of some cellular organelles, such as mitochondria and lysosomes, in inducing apoptosis was also evaluated through some well known flow cytometry tests (JC-1 staining and ROS production for mitochondrial participation and AO uptake method for lysosomal one). Results indicate that mitochondria were clearly implicated in test compounds cell death. Moreover, since the resistance onset is one of the main problems for classical anticancer drugs, their cytotoxic activity was also studied in some P-glycoprotein over-expressing cell lines and their antiproliferative effect was maintained. Their mechanism of action was investigated: first of all, the affinity for DNA was studied by different spectroscopic and electrophoretic techniques but only one of them acts as a DNA intercalator. Well-known cancer chemotherapeutic agents, such as anthracyclines, camptothecin, and amsacrine, characterized by planar polycyclic systems, are able to interfere with DNA-processing enzymes (topoisomerases I and II) by forming a ternary complex involving the drug, the DNA, and the enzyme (9). DNA cleavage reactions with human topoisomerase I were carried out in presence of various concentrations of compounds to verify a possible inhibition of the enzyme activity. Results suggested that these molecules act as poisons of topoisomerase I.

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