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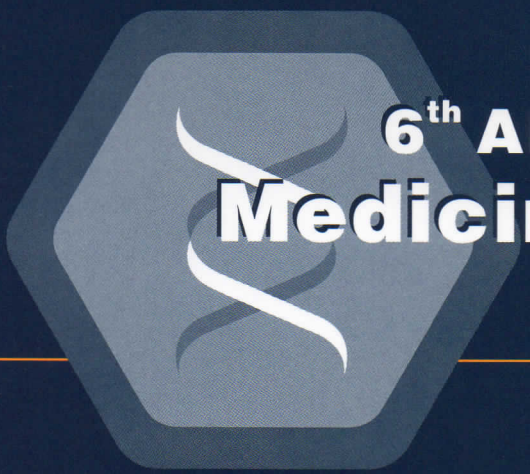

ABSTRACTS FROM THE

6th AFMC International Medicinal Chemistry Symposium

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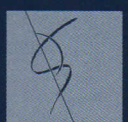

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r modeling as a tool for the design of drug es

to Farmaco Chimico Tecnologico, Via Aldo Moro 4,

utational methodologies are today a well-estab-
d essential tool in drug discovery. Computer-
g design (CADD) approaches mainly depends
owledge of the 3D structure of the target under
his is known, then structure-based drug design
es can be applied (such as docking experi-
Otherwise, ligand-based drug design methods
sed (e.g. QSAR or 3D-QSAR models, pharma-
models, etc), based on the analysis of a number
s known to act with a common mechanism of
ithin the drug development process, CADD was
plied during the lead/drug optimization phase,
e to provide both qualitative and quantitative
activity relationships, and to get further insight
node of action of many biologically active com-
However, in recent years, the development of
rary design and virtual screening approaches
CADD to play an important role also in the early
e drug development process (i.e., hit and/or lead
). Virtual screening (VS, also referred to as *in*
ening) makes use of computational models able
te a specific biological activity of compounds to
er existing databases or virtual libraries, and to
olecules provided with activity against the target
st. Likewise traditional drug design, also VS
es can be structure- or ligand-based, depending
ailable information about the three-dimensional
of the target.
al CADD successful approaches to the drug dis-
ocess are presented, derived from dealing with
iological targets.
example of ligand-based drug design, a 3D-
odel was generated starting from a collection of
A_1 adenosine receptor antagonists, with the aim
the design of new compounds by predicting
activity. Moreover, an homology modeling
led us to the development of a receptor model
redict the activities of new compounds.
e other hand, a structure-based and a ligand-
S procedure were elaborated and successfully
r the research of lead compounds for anti-HIV-1
ubercular therapy, respectively. In detail, a novel
HIV-1 integrase inhibitors was identified making
th a receptor-based pharmacophoric model and
experiments, whereas two compounds endowed
esting activity against *Mycobacterium tuberculo-*
found through a combined process of virtual
sign and virtual screening.

OP-12

Modeling Strategies Used to Support the Discovery of Caspase-3 Inhibitors

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The current work outlines modeling strategies used to support the discovery of potent caspase-3 inhibitors. First, a group of caspase DEVD aldehyde crystal structure complexes were aligned. Caspases-1, 3, 7, and 8 were considered. Residues proximal to DEVD aldehyde define the binding pockets of the various caspases. It was found that SER 343 and PHE 381B in the S3 and S4 pockets were exclusive to caspase-3. Therefore targeting ligand interactions with these residues provides a general recipe for making caspase-3 selective ligands. Selective or pan inhibition, however, is better understood by examination of the detailed interactions that ligands make with the caspase proteins. To show how this is done in a qualitatively fashion, two well-known ligands were modeled into the caspase-3 and caspase-7 binding pockets. These molecules were M13 (potent at Caspase-3, not at caspase-7) and M826 (potent at both caspase-3 and caspase-7). A visual inspection of the modeled geometries suggests that in the case of M13 the key residue for caspase-3 selectivity over caspse-7 is ASN_342. In the case of M826 the key residue for potency at both caspase-3 and caspase-7 is ARG_341. For an ultimate understanding of the ligand-protein binding one must map some kind of binding thermodynamics onto modeled geometries. Therefore, a methodology was derived for the calculation of ligand-caspase binding free energies associated with modeled geometries. The methodology was validated by showing that calculated binding free energy differences correlated reasonably well (R^2 = 0.87) with experimentally determined K_i ratios for a set of pyrimidoindolone (3,4-dihydropyrimido (1,2-a) indol-10 (2H)-one) caspase-3 inhibitors. We believe this broad approach (identification of target residues, visual examination of ligand-protein interactions, and binding free energy calculation) can be useful for the effective design of selective or pan caspase inhibitors.

OP-13

Molecular modelling studies on some eukaruotic topoisomerase II enzyme inhibitor fused heterocyclic compounds

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Since the activity of topoisomerases is essential for several cellular processes such as replication, transcription, and chromosome condensation, investigation of the inhibitory activities of eukaryotic topoisomerases is widely used in anticancer drug development. Topoisomerase II (Topo II) is the target for some of the most active anticancer drugs such as etoposide, teniposide, and doxorubicin used in the treatment of human malignancies [1-3].

Many pharmacological studies have resolved receptor active/binding sites using numerous computational 3D-quantitative structure-activity relationship (3D-QSAR) techniques [4]. These methods utilize relevant conformers of ligands to suggest functional groups, the geometry of structural features, and regions of electrostatic and steric interactions essential for activity or fit to the receptor binding/active site.

In previously research paper, inhibition effect of some novel benzazole derivatives on eukaryotic Topo II were investigated [5].

In this study, we applied the CoMFA (Comparative Molecular Field Analysis) [6] and the CoMSIA (comparative molecular similarity indices analysis) [7] as the 3D-QSAR applications using the Sybyl 7.0 [8] Software in SGI workstation for the lead optimization to the training set of compounds having the eukaryotic Topo II inhibitory activities as log 1/C values.

Moreover, three-dimensional pharmacophore hypotheses were built from a set of some Topo II inhibitor benzazoles by using the program Catalyst/HipHop [9].

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OP-14

A fast empirical scoring method for docking and virtual screening

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The docking and scoring paradigm can be considered as the combination of two separate problems. The first aspect is a geometric, or more broadly an informatics problem: how can we place a solid object (ligand) within a "cavity" of another solid (protein) or close to another molecule in a well-defined Cartesian space? The second one is a more intriguing chemical problem: how can we properly predict the free energy of binding considering all the possible contributions involved in biological interactions?

The availability of computational fast methods to score all the solutions found by a docking or virtual screening software is of paramount importance. But the scoring function must be a "complete" scoring function, able to consider all the contribution in a binding process, biological or organic process, where leading forces are weak forces.

In this work we present an empirical scoring function, HINT, based on experimental LogP data, which is able to consider enthalpic and entropic contributions to $\Delta G°$ of binding, the role of the solvent, water, the right protonation state of the systems to generate much more realistic models.

Some case studies will be illustrated highlighting qualities and limits.

OP-15

A Comparative Molecular Field Analysis (CoMFA) Study of Flavonoids Active Against HT-29 Colon Carcinoma

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Flavonoids have been found in various food items as the plant origin. In vitro, flavonoids have the well-known antiproliferative property for varieties of cancer cells. Many efforts for the development of chemopreventive or therapeutic agents for cancer from natural products were performed over the last several decades. In this research, a series of 31 flavonoids, which show the cytotoxicity against human colon carcinoma (HT-29) were analyzed using comparative molecular field analysis (CoMFA) for generating the hypothetic pharmacophore model. To perform the systematic molecular modeling study of these flavonoids, a conformational search was determined with the precise dihedral angle analysis of the flavone. Then, CoMFA was performed based on the energy-minimized conformer of the flavone by using several different alignments. In CoMFA, the steric and electrostatic field vari-