STRUCTURAL MODELS OF MARMESININE REFINED AGAINST SINGLE-CRYSTAL AND HRPD DATA

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Marmesinine – $C_{20}H_{24}O_9$, coumarin β-D-glucoside derivative – appears in several plants – e.g. Ruta graveolens, playing role of biocontrolling, antipathogenic compound. Marmesinine was first isolated by Reisch in 1970. Its molecular structure was assigned using NMR spectroscopy by Duddeck and coworkers (1993). In spite of development in separation techniques – marmesinine is difficult to crystallize, appearing as 'amorphous powder' (Kitayama, 2001). The crystal structure of marmesinine was determined from single microcrystal diffraction and, independently, from powder diffraction – with the aim of comparing the conformations and precision of both structural models. The single crystal experiment (CAD-4 diffractometer, copper radiation), yielded lattice parameters a = 7.8503, b = 5.9850, c = 40.579 Å, α = β = γ = 90°, in $P2_12_12_1$ space group. The structure was solved and refined to R = 0.035, and could serve as good reference for powder methods. The powder diffraction experiments (Grochowski, Serda, Baehtz, Knapp, 2001), were done on the B2 beamline of DESY-HASYLAB (Hamburg) using wavelength 1.3572 Å and a channel-cut type analyzer crystal. The pattern was indexed with TREOR90 giving lattice parameters a = 7.8449(3), b = 5.9903(2), c = 40.598(2) Å, α = β = γ = 90° with figure of merit M20=158, F20=506. The effective resolution of the data (d = 1.75 Å) was limited by the sample, hence structure solution was attempted by global optimization rather than direct methods. Structure solution was carried out by simulated annealing, using the program DASH ver. 2.0. Several simulated annealing runs were tried to achieve the global minimum.

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Keywords: MARMESININE, COUMARIN, HRPD

43 YEARS OF CINCHONA ALKALOID X-RAY CRYSTALLOGRAPHY: ARE THERE ANY SECRETS LEFT?

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Cinchona alkaloids (C. a.) belong to the oldest natural therapeutics, known and used in Europe since 1630. They are also very interesting both from the chemical (stereospecific reactions) and crystallographic (intermolecular interactions) points of view. First X-ray crystal data for some C. a., were determined in 1959 [1], while the absolute configuration of quinidine was reported in 967 [2]. Recently we found in CSDS about 90 crystal structures of C. a. and their derivatives.

The most important problems solved in result of the X-ray structure analysis concerned:

i) conformations observed in crystals versus energetically preferred conformations of isolated molecules,

ii) conformational behavior of different diastereoisomers,

iii) effect of protonation and esterification on conformation and other parameters of molecular geometry,

iv) interactions of C. a. molecules with the crystalline environment via hydrogen bonds and π - π stacking.

Essential for understanding the structure - biological activity relationships are the studies of inactive threo epimers of C. a. and of metal - C. a. interactions. Among still unsolved questions the most urgent seem to be the mode of C. a. interactions with biological macromolecules and relatively low stereospecificity of their active diastereoisomers towards various biological targets.

References

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Keywords: **CINCHONA ALKALOIDS, CONFORMATION, HYDROGEN BONDS**

CRYSTALLOGRAPHIC INSIGHT INTO MECHANISMS OF QUINOLONES ACTIONS

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Quinolones are common antibacterial agents consisting N1-substituted 4-oxo-1,4-dihydroquinoline with an acidic function at C3. Two main models of their actions have been proposed in the literature. One model is based on quinolones interactions with gyrase-DNA complex (through hydrogen bonds with guanine) and the other on intercalation. Also binding with phosphate oxygens of DNA via magnesium bridge has been considered. As a detailed molecular mechanism of antibacterial quinolones action as well as crystal structure of gyrase are not known, information from crystal structures of quinolones and their analogs is very valuable. The most important observations are: (1) Quinolones occur in the crystal state predominantly in a neutral form with intramolecular hydrogen bond 'locking' acidic H atom of carboxylic group. It assures good permeability of quinolones through cell membranes. (2) Quinolones show strong preference for stacking in dimers of antiparallel orientations. The observation leads to modification of existing (Shen) model of quinolone - DNA interactions and suggest that the most probable place of quinolone binding is GC/CG region. Therefore we have designed new analogs of quinolones interacting through hydrogen bonds with cytosine. The compounds showed antibacterial activity similar to that of nalidixic acid. (3) We have shown that substituents making partial negative charges at carbonyl oxygens larger have higher activity. It supports a model of quinolones interactions with DNA through hydrogen bonds with guanine.

Keywords: **QUINOLONES HYDROGEN BONDS QUINOLONE-DNA INTERACTIONS**

HIV-1 NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS - STRUCTURAL BASED DRUG DESIGN

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One of the goals of contemporary medicinal chemistry is to obtain active inhibitors of enzymes of HIV. Inhibition of one of such essential enzymes should provide effective means of blocking replication of HIV-1 - the etiological agent of AIDS. Structural investigation is a very crucial part of the development of potent antiviral drugs.

We aim to determine the crystal structure of several non-nucleoside inhibitors of HIV-1 reverse transcriptase (RT). We found that derivatives of 2,6-difluorobenzyl benzimidazole inhibit HIV-1 RT and could be looked at as members of non-nucleoside inhibitors (NNRTI). These inhibitors are also known as butterfly inhibitors because their common characteristic is the presence of two π-electron moieties with a slant orientation. One of the crucial geometrical parameters is the dihedral angle between the planes of the π-electron systems. There is a specific optimal value for this parameter and only the compounds, which meet it, are potentially active. The active conformation determines the optimal torsion angles within the 2,6-difluorobenzyl and the 2,6-difluorphenyl. We found that different substituents at the C4 position of the benzimidazole moiety had dramatically varied anti-viral activity. The crucial parameters for activity are the size of the substituent, polar and hydrophobic distribution of the spatial regions, and orientation of the substituents in respect to the benzymidazol ring.

Structural data is very useful to determine the correlation between the three-dimensional structure of inhibitor and its biological activity. It is also a good base for modeling enzyme-inhibitor interaction and designing new much more active compounds.

Keywords: **HIV-1 NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS DRUG DESIGN STRUCTURAL INVESTIGATION**