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IA, database of known ligands of aminoacyl-tRNA synthetases

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Abstract The IA database contains 240 structures of known inhibitors of aminoacyl-tRNA synthetases. Structures can be downloaded in different file formats (mol, sdf, smile, png). The search engine offers possibility of searching for the ligands with a given functional group. Additionally, one can search for ligands that act on selected synthetases and from particular references. The data include information which synthetase a given ligand inhibits together with the inhibition constant (IC_{50}) if known. Database is freely available at http://ia.bioinfo.pl/

Keywords Aminoacyl-tRNA synthetases · Aminoacyl-tRNA synthetases inhibitors · Molecular docking · Virtual high throughput screening

Introduction

Aminoacyl-tRNA synthetases (AA-RS) are a group of enzymes that ensure the fidelity of transfer of genetic information from the DNA into the protein [1]. They are found in all living organisms and catalyze the esterification of a particular tRNA with its cognate amino acid. Their key mode of action is graphically depicted in Fig. 1.

AA-RS fulfill many criteria indispensable for good antibacterial agents [2], among others they are crucial for viability, different for procariotic and eucariotic organism and share a common catalytic cite. These and other advantages cause that AA-RS constitute an appealing molecular target for drug design for compounds active against pathogenic bacteria. Moreover it seems possible to create selective drugs which do not act on host aminoacyl-tRNA synthetases.

Inhibition of these enzymes is possible in every stage [3]. In the first stage, substrate-binding can be interrupted by analogues of amino acids. In the second stage it is possible to generate mimetic of the enzyme-bound reaction intermediate (AA-AMP). As the result no AA-tRNA is synthesized so finally it will lead to the interruption of a polypeptide chain elongation and inhibition of cell growth.

Currently, rational drug design often proceeds via structure based virtual screening of possible inhibitors. Sometimes the process is facilitated by a feedback from experimental measurements. In such case the collection of compounds that are known to act as inhibitors facilitates the discovery of agents of a desired activity. Our database of molecules known to inhibit enzymatic activities of aminoacyl-tRNA synthetases gathers experimental data from various sources and can be used to find other molecules which can be potential inhibitors and test their usefulness using methods like virtual screening or molecular docking.

Methods and database overview

We searched for known inhibitors of aminoacyl-tRNA synthetases in articles published from 2001 to 2006, found by PubMed search engine. Reviews published before 2001

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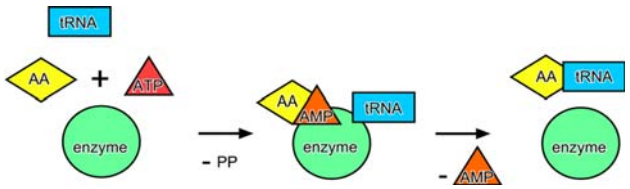

Fig. 1 In the first ATP dependent stage amino acid (AA) is recognized by the enzyme and carboxyl group of amino acid is activated as aminoacyl-AMP (AA-AMP) is formed. In the second stage amino acid moiety is transferred to its cognate tRNA creating aminoacyl-tRNA (AA-tRNA), a substrate for synthesis of proteins

were also taken into account in creation of the database of inhibitors of aminoacyl-tRNA synthetases.

Molecules 0000–0239 were obtained from 22 papers [2–23]. Next Marvin applets [24] were used to create files with 3D structures of these compounds in 'mol' format and to convert structures between different file types. Two conformations were chosen for each molecule. The conformation A is the one of the lowest energy in Marvin's optimization with Dreiding force field [25]. The conformation B is the conformation whose RMSD (root mean square deviation) from the conformer A is the largest in the set of conformations generated by Marvin's molconvert utility.

The presented database is composed of 240 molecules known from literature to inhibit enzymatic activity of aminoacyl-tRNA synthetases. The geometries of all these molecules are available in two different conformations. The MySQL database is equipped with a search engine to search for molecules having desired functional groups, i.e. possessing a given smile's substring. It is also possible to define up to two substrings and use %, AND or OR operators. Additionally, one can search for ligands that act on selected synthetases and from particular references. The data include information which synthetase a given ligand inhibits together with the inhibition constant (IC_{50}) if known.

Conclusions

We presented here the database containing the structures of 240 known inhibitors of aminoacyl-tRNA synthetases ready to search and download, as well as experimental information on these inhibitors. The 3D geometries of ligands, after downloading, can be easily used for various computational tests like molecular docking [26–28] or virtual high throughput screening [29–31] experiments. Furthermore, the IA database can be easily expanded and updated to include more data on aminoacyl-tRNA synthetases inhibitors.

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