Molecular modeling and QSAR studies of a set of diazaborines – an experimental class of antibacterial agents

Pasqualoto, K.F.M.* and Ferreira, M. M. C. - *kerlyfmp@iqm.unicamp.br*

Laboratory for Theoretical and Applied Chemometrics, Institute of Chemistry, UNICAMP, Campinas-SP, Brazil

Keywords: Molecular Modeling, QSAR, Diazaborines, Ligand-Based Design, Enoyl-ACP Reductase.

Introduction

Diazaborines (DBs) represent a group of antibacterial agents of which the important structural element is a heterocyclic 1,2-diazine ring containing a boron as a third hetero atom. The arene group can be benzene, naphthalene, thiophene, furan and pyrrole. The antibacterial activity is confined almost exclusively to Gram-negative bacteria.[1,2] Recently, the molecular target of DBs was identified as an enoyl-acp reductase (ENR). ENR catalyzes the last reductive step in the cyclic process of fatty acid elongation, and it is considered the key enzyme of the bacterial fatty acid synthase (FAS II) pathway. The presence of the cofactor nicotinamide adenine dinucleotide (NAD) is required for both the inhibition and the binding of DBs to the ENR enzyme.[2] The analysis of the X-ray crystallographic structures of ENR-NAD-DBs complexes revealed the formation of a covalent bond between the 2'-hydroxyl of the nicotinamide ribose and the boron atom of the ligands to generate a tight, noncovalently bound bisubstrate analogue (Fig. 1).[3] In this study, molecular modeling and QSAR methodologies were applied to a set of fifty-one DB derivatives aiming the rational design of new antibacterial/antimycobacterial agents.

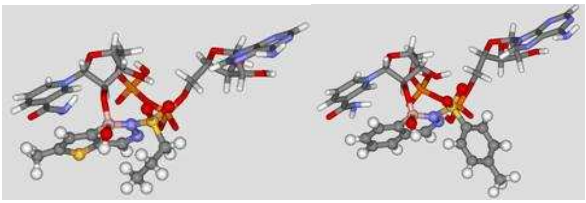

Figure 1. Three dimensional adduct models, thieno-DB/NAD and benzo-DB/NAD, from 1dfh and 1dfg PDB complexes, respectively.

Results e Discussion

A set of fifty-one DB derivatives were selected from ref. [1]. Biological activities were evaluated as the minimum inhibitory concentration, MIC (µg/mL), against *E. coli* Δ120 at 310 K. These data were converted to molar units and then expressed in negative logarithmic units, pMIC (-log MIC). The range of activity for the analogues is more than 3 pMIC units (3.22 to 5.87). The 3D models of each DB derivative in their neutral forms were constructed using the HyperChem 7.5 software. The crystallized structures of the thieno-DB/NAD and benzo-DB/NAD adducts (Fig. 1) were used as reference geometries in the building up of the investigated ligands. Each model was energy-minimized using MM+ force field without any restriction (HyperChem 7.5). Partial atomic charges were computed employing the AM1 semiempirical method. The MOLSIM 3.2 program was also used to optimize the ligands geometry. The molecular dynamics (MD) simulations protocol included 100,000 steps with a step size of 1 fs at 310 K (T of the biological assay) (MOLSIM 3.2). An output trajectory file was saved every 20 simulation steps, resulting in 5,000 conformations. The lowest-energy conformation of each ligand was selected and its solvation and hydrogen bonding energy contributions were calculated. Electrostatic potential partial atomic charges (Chelpg) were obtained using the *ab initio* method HF/6-31G* (Gaussian 03). Thermodynamic descriptors from MD simulations and other calculated descriptors (electronic, lipophilic, steric and structural), totalizing 28 independent variables, were considered in the construction of QSAR models. Partial least squares (PLS) regression and genetic function approximation (GFA),[4] implemented in WOLF 5.5 program, were used as fitting functions. Preliminary analysis detected one outlier in the investigated set. The best QSAR model (training set, N = 39; q^2 = 0.59; r^2 = 0.86; LSE = 0.11; and LOF = 0.16) was validated employing the *leave-multi-out* and *y-randomization* methods. Its external prediction power (test set, N = 11) was 90.9%.

Conclusions

Thermodynamic descriptors, molecular volume and the electrostatic charge of sulfur atom in DBs organossulfonyl side chain present important contributions for the antibacterial activity. These findings must be considered for designing new antibacterial/antimycobacterial agents.

Acknowldgements

The authors are grateful to FAPESP for the financial support.

[1]Grassberger, M. A.; Turnowsky, F.; Hildebrandt, J., *J.Med.Chem.* **1984**, 27, 947; [2]Pasqualoto, K.F.M.; Ferreira, M.M.C. *QSAR Comb. Sci.* **2006**, 25, 629; [3]Baldock, C.; de Boer, G. J.; Rafferty, J. B.; Stuitje A.R.; Rice, D.W., *Biochem. Pharmacol.* **1998**, 55, 1541; [4]Rogers, D.; Hopfinger, A.J., *J. Chem. Inform. Comput. Sci.* **1994**, 34, 854.