

A Short Note on Interaction Energy Analysis of Nonclassical Antifolates with *Pneumocystis carinii* Dihydrofolate Reductase

Abstract

The x-ray structure of the *Pneumocystis carinii* dihydrofolate reductase (DHFR): trimethoprim: NADPH ternary complex obtained from the Protein Databank was used as a structural template to generate models for the following complexes. *P. carinii*

DHFR: piritrexim: NADPH, *P. carinii* DHFR: epiroprim: NADPH, and *P. carinii* DHFR: trimetrexate: NADPH. Each of these complexes, including the original trimethoprim complex was then modeled in 60 angstrom cubes of explicit water and minimized to a rms gradient between 1.0 to 3.0 x 10⁻⁵ kcal/angstrom. Subsequently, each antifolate structure was subdivided into distinct substructural regions. The minimized complexes were used to calculate interaction energies for each intact antifolate and its corresponding substructural regions with the *P. carinii* DHFR binding site residues, the DHFR protein, the solvated complex (which consists of *P. carinii* DHFR, NADPH, and solvent water), solvent water alone, and NADPH. Antifolate substructural regions which contained nitrogen and carbon atoms in an aromatic environment (i. e. the pteridyl, pyridopyrimidinyl, and diaminopyrimidinyl subregions) contributed most to the stability of antifolate interactions, while interaction energies for the hydrocarbon aromatic rings, methoxy, and ethoxy groups were much less stable.

Keywords: antifolates • interaction energy • DHFR binding

Introduction

Pneumocystis carinii respiratory illness (PCP) may be a common infection in patients with AIDS. A very important therapeutic explanation for the treatment of psychotropic drug is that the inhibition of dihydropteroate synthase (an accelerator of the folacin synthesis pathway in microorganisms) and also the inhibition of dihydrofolate enzyme (DHFR). The principal treatment for psychotropic drug is that the antifolate, trimethoprim (TMP) together with Gantanol, associate matter of dihydropteroate synthase [1]. Trimetrexate (TMQ) or piritrexim (PTX) is also used to treat patients. United Nations agency don't reply to or cannot tolerate the TMP: sulfamethoxazole combination. Current treatment regimens for psychotropic drug area unit generally hampered by undesirable adverse reactions in some patients and by poor property between the human and *P. carinii* DHFR molecules. As a result, varied investigations have focused on the event of improved and additional selective inhibitors of *P. carinii* DHFR relative to the human DHFR [2]. It ought to be noted that antifolates area unit structurally complicated molecules consisting of distinct substructural regions or modules which the event of latest antifolates usually involves the structural modification of associate existing antifolate structure. Consequently, modification of existing antifolate structures essentially involves modification of 1 or additional antifolate substructural regions. For example, Piper et. al. synthesized analogs of trimetrexate (TMQ) and piritrexim (PTX) with modified phenyl teams. Normally these analogs consisted of changes within the phenyl cluster substituents and their positions round the phenyl ring. They ascertained that phenyl teams with polar substituents resulted

Ertan Şahin*

Faculty of Medicine, Gaziantep University, Turkey

*Author for correspondence:
er_ahin@yahoo.com

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in improved antifolate binding. Those phenyl teams that contained a methoxy group and a methyltrifluoro cluster as substituents were higher to the *P. carinii* DHFR than analogs whose phenyl subregions contained less polar substituents. To boot, TMQ analogs with carboxyl containing teams connected to the phenyl subregion additionally usually showed improved binding to *P. carinii* DHFR however not essentially improved property relative to the human DHFR. When modification of the TMQ phenyl subregion failed to increase the polarity of the phenyl subregion, binding to the *P. carinii* DHFR wasn't improved. Moreover, if the binding of every Int. J. Mol. Sci. 2002, 3 1190 substructural region might be evaluated severally, those substructural regions that contribute less to overall binding may then be targeted for structural modification so as to boost antifolate binding [3].

Description

The pteridyl and pyridopyrimidinyl teams of PTX and TMQ, severally and also the diaminopyrimidinyl teams of TMP and EPM area unit the foremost contributors to the soundness of their respective antifolate interactions with the solvated *P. carinii* DHFR complicated. The carbon atoms of each of those subregions consequently showed favorable interactions with binding web site and NADPH and the atomic number 7 atoms of those subregions showed unfavorable interactions with binding web site and NADPH [4]. To boot, the carbon atoms usually showed unfavorable interactions with water and the atomic number 7 atoms usually showed stable interactions with water. Since the binding web site of the *P. carinii* DHFR

may be a hydrophobic surroundings these observations indicate that the aromatic carbon atoms create favorable interactions with hydrophobic organic compound facet chains of the *P. carinii* DHFR binding web site and hydrophobic regions of NADPH, whereas the atomic number 7 atoms of those subregions Int. J. Mol. Sci. 2002, 3 1200 make comparatively favorable interactions with water solvent molecules. These results additionally counsel that the pteridyl and pyridopyrimidinyl regions of PTX and TMQ and also the diaminopyrimidinyl subregions of TMP and EPM area unit anchored to the *P. carinii* DHFR complicated via each hydrophobic and hydrophilic interactions [5].

Conflict of Interests

None

Acknowledgments

None

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