SEARCH FOR NEW INHIBITORS OF THE PTERIDINE REDUCTASE (PTR1) FROM *TRYPANOSOMA BRUCEI*: STRUCTURES OF COMPLEXES WITH FOLATE ANALOGUES

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The enzymes dihydrofolate reductase-thymidylate synthase and pteridine reductase (PTR) are involved in pterin/folate dependent metabolism; together, they represent an important target for chemotherapy of parasitic leishmanias and trypanosomes. X-ray crystallography was used to elucidate the structure of PTR1 from *Trypanosoma brucei* in complex with folate analogues. Several ligands were assayed and the diffraction patterns from some dozen crystals were measured; a few were selected for a full data-set collection, later processed with computational programs. Of these, five structures were further computationally refined and validated at UEPG, the ones complexed with the ligands WSG3065 (later revealed to be absent), WSG3066, WSG3067, triamterene and cyromazin. All five structures belong to the space group $P2_1$ with unit cells around a=79Å, b=90Å, c=82Å, β=115°. Besides the expected folate analog ligands (except WSG3065), several other ligands derived from the crystal preparation were modeled either near or outside the active site. Analyses on the ligand positions and corresponding interactions with the protein are being carried out to understand modes of inhibition and to guide design of improved inhibitors.
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