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Abstract Title	In silico study of Plasmodium 1-deoxy-d-xylulose 5-phosphate reductoisomerase (DXR) for identification of novel inhibitors from SANCDB
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Reference number	ABS/19/192

Abstract

1. Abstract Title	In silico study of Plasmodium 1-deoxy-d-xylulose 5-phosphate reductoisomerase (DXR) for identification of novel inhibitors from SANCDB

2. Authors and Affiliations

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3. Abstract

Objectives
Malaria remains a major health concern with a complex parasite constantly developing resistance to the different antimalarials, threatening the efficacy of the current (Artemisinin Combination Therapy) ACT. Drugs with different mechanisms of action are ideal to decrease chances of resistance occurring. Blocking the methylerythritol phosphate pathway through 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR) inhibition fits well this profile. Previously, a promising DXR inhibitor, fosmidomycin showed poor drug-like properties. In this study, we intended to find potential inhibitors with better drug-likeness from the South African National Compound Database (SANCDB; https://sancdb.rubi.ru.ac.za) using structural bioinformatics tools.

Methods

Plasmodium spp DXR structures in its open and closed conformations were modelled using MODELLER followed by a High Throughput Virtual Screening (HTVS) with Autodock Vina of the SANCDB compounds to identify hits. Compounds' pharmacological properties using the QED (Quantitative estimate of druggability) scores from FAF-Drugs4 (Free ADME-Tox Filtering Tool) were included in the hit selection process. Finally, selected hits were submitted to 100 ns molecular dynamics (MD) simulations using GROMACS to assess the stability of the protein-ligand complexes.

Results

SANC00152 (-8.4 Kcal/mol), SANC00236 (-10.2 Kcal/mol), SANC00339 (-9.2 Kcal/mol), SANC00438 (-9.9 Kcal/mol) and SANC00570 (-8.1 Kcal/mol) were identified as hits from the docking showing good binding affinities with QED scores of 0.46, 0.68, 0.83, 0.78 and 0.68 respectively with one being the best score and zero the poorest. All compounds had different scaffolds from fosmidomycin. Finally, the different protein-hit complexes appeared to be stable during the MD simulations with Root Mean Square Deviation (RMSD) lower than 2.75 nm (maximum RMSD observed). Furthermore, these hits showed stable binding in the protein active site with ligands' RMSDs showing very low values (maximum being 0.15 nm), thus confirming their high binding affinities.

Conclusions

Five natural compounds from SANCDB were thus identified as potential DXR inhibitors.

4. Non Technical or Lay Abstract

Objectives

In this study, we intended to find potential 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR) inhibitors as antimalarial drugs from the South African National Compound Database (SANCDB; https://sancdb.rubi.ru.ac.za) using computational tools.

Methods

Plasmodium spp DXR protein structures in its open and closed forms were modelled using MODELLER followed by predictions of binding strength and poses of the SANCDB molecules to identify good binders. Compounds' drug-likeness properties given by their QED (Quantitative estimate of druggability) scores from FAF-Drugs4 (Free ADME-Tox Filtering Tool) were included in the potential drug selection process. Finally, selected potential drugs were submitted to simulation in an in vivo-like environment using GROMACS to assess the stability of drug and targets binding.

Results

Molecules SANC00152 (-8.4 Kcal/mol), SANC00236 (-10.2 Kcal/mol), SANC00339 (-9.2 Kcal/mol), SANC00438 (-9.9 Kcal/mol) and SANC00570 (-8.1 Kcal/mol) were identified as good binders from the experiment showing good binding strength and QED scores of 0.46, 0.68, 0.83, 0.78 and 0.68 respectively with one being the best score and zero the poorest. Finally, drugs showed stability in the target during the simulations with only negligible fluctuations confirming their high binding strength.

Conclusions

Five natural compounds from SANCDB were thus identified as potential drug targetting DXR.

5. Abstract's Thematic Area	Bioinformatics