**Supplemental Data S1**

XL file

**Supplemental Data S2**

*Method and results for Homology model and docking for Zika virus envelope protein*.

**Homology model**

The following sequence of the Zika virus envelope protein (E) was taken from the polyprotein [1], where the part corresponding to E is from residues 291-592, while the IG-like domain III is from residues 601-693 as shown below

ircigvsnrd

301 fvegmsggtw vdvvlehggc vtvmaqdkpt vdielvtttv snmaevrsyc yeasisdmas

361 dsrcptqgea yldkqsdtqy vckrtlvdrg wgngcglfgk gslvtcakfa cskkmtgksi

421 qpenleyrim lsvhgsqhsg mivndtghet denrakveit pnspraeatl ggfgslgldc

481 eprtgldfsd lyyltmnnkh wlvhkewfhd iplpwhagad tgtphwnnke alvefkdaha

541 krqtvvvlgs qegavhtala galeaemdga kgrlssghlk crlkmdklrl kgvsyslcta

601 aftftkipae tlhgtvtvev qyagtdgpck vpaqmavdmq tltpvgrlit anpviteste

661 nskmmleldp pfgdsyivig vgekkithhw hrsgsti

SwissModel [2] was used to construct a homology model using the Dengue crystal structure 4gsx as a template (58.69 identity) [3-6].

The complete homology model of subunit A was then used in Discovery Studio (Biovia, San Diego, CA) and the ‘prepare protein’ protocol was used before the ‘Dock ligands’ protocol. Selected molecules were initially docked using a docking sphere of 13 angstroms. The proposed binding site was centered on residues 270-277 and a site sphere created (coordinates 17.07, -21.94, 25.70) with 13 Å diameter. The protocol included 10 hotspots and docking tolerance (0.25). The FAST conformation method was also used along with steepest descent minimization with CHARMm. Further parameters followed the default settings. Out of 3 compounds of interest initially docked, pyronaridine had the highest LibDockScore scoreof 142**.** Quinacrine – (a known FDA approved drug that has shown activity against Dengue (IC50 0.55uM –[7]) has a docking score of 128. The well known antiviral Ribavirin has a docking score of 101. These predictions suggest that Quinacrine may be targeting this protein and that other antimalarials may also be worth testing.

The Prestwick chemical library [8] of 1280 molecules was first filtered to remove salts then this was docked in the protein as described above.

The top 10 docked molecules from the Prestwick chemical library (Data S3), as identified using the best scored conformation, includes 3 antivirals: ritonavir, indinavir and saquinavir. Selected antimalarials from the Prestwick chemical library (Data S4) suggest that these molecules may be worth further testing *in vitro* versus Zika virus given their availability (alongside pyronaridine and quinacrine).

**Supplementary Data S3. The top 10 docked molecules from the Prestwick chemical library**

|  |  |
| --- | --- |
| **Molecule** | **LibDock Score** |
| Colistin | 180.85 |
| Ritonavir | 180.76 |
| Pepstatin A | 171.92 |
| Indinavir | 170.23 |
| Deferoxamine | 168.53 |
| Lanatoside C | 165.79 |
| Dihydroergotamine | 161.16 |
| Saquinavir | 161.02 |
| Nadide | 160.40 |
| Avermectin B1a | 159.79 |

**Supplementary Data S4. Selected antimalarials docked in the Prestwick chemical library**

|  |  |
| --- | --- |
| **Molecule** | **LibDockScore** |
| Halofantrine | 152.27 |
| Quinidine | 111.02 |
| Amodiaquine | 108.83 |
| Chloroquine | 108.80 |
| Mefloquine | 99.01 |
| Primaquine | 95.77 |

**Supplementary Data S5. PDB file for homology model**

**Supplementary Data S6. Prestwick library compounds docked in protein**

**Supplemental References**

1. Anon. *Zika virus polyprotein*. Available from: <http://www.ncbi.nlm.nih.gov/protein/AHZ13508.1>.

2. Anon. *SwissModel*. Available from: <http://swissmodel.expasy.org/>.

3. Biasini, M., et al., *SWISS-MODEL: modelling protein tertiary and quaternary structure using evolutionary information.* Nucleic Acids Res, 2014. **42**(Web Server issue): p. W252-8.

4. Arnold, K., et al., *The SWISS-MODEL workspace: a web-based environment for protein structure homology modelling.* Bioinformatics, 2006. **22**(2): p. 195-201.

5. Kiefer, F., et al., *The SWISS-MODEL Repository and associated resources.* Nucleic Acids Res, 2009. **37**(Database issue): p. D387-92.

6. Guex, N., M.C. Peitsch, and T. Schwede, *Automated comparative protein structure modeling with SWISS-MODEL and Swiss-PdbViewer: a historical perspective.* Electrophoresis, 2009. **30 Suppl 1**: p. S162-73.

7. Shum, D., et al., *High-content assay to identify inhibitors of dengue virus infection.* Assay Drug Dev Technol, 2010. **8**(5): p. 553-70.

8. Anon. *Prestwick chemical library*. Available from: (<http://www.prestwickchemical.com/prestwick-chemical-library.html>.