RESEARCH ARTICLE

Structural, functional and docking analysis against *Schistosoma mansoni* dihydroorotate dehydrogenase for potential chemotherapeutic drugs [version 1; peer review: awaiting peer review]

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Abstract

**Background:** Praziquantel, as the only drug for the treatment of schistosomiasis, is under serious threat due to the emergence of resistant strains of *Schistosoma* species. There is an urgent need to search for alternative chemotherapy to supplement or complement praziquantel. *Schistosoma* dihydroorotate dehydrogenase (DHODH) has been recommended as a druggable target for schistosomiasis chemotherapy. The development of novel molecular modeling approaches, alongside with computational tools and rapid sequencing of pathogen genomes, have facilitated drug discovery. Therefore, the aim of this study was to employ computational approaches to screen compounds against *Schistosoma mansoni* DHODH.

**Methods:** In this study, DHODH was used to blast on the latest version of DrugBank that contained 12,110 compounds, resulting in 26 drugs that can bind.

**Results:** *In silico* docking shows that 13 drugs can bind strongly with an estimated free energy of binding, total intermolecular energy and estimated inhibition constant (Ki) greater than or equal to -8.6 kcal/mol, -8.12 kcal/mol and 1.12 µM, respectively. These compounds include the approved drugs manitimus, capecitabine, brequinar analog and leflunomide.

**Conclusions:** These results indicate that these drugs have the potential for use in the control of schistosomiasis in the future.

**Keywords**
Dihydroorotate Dehydrogenase, Schistosomiasis, Drugs, Neglected Tropical Disease
Introduction

The public health impacts of schistosomiasis, caused by Schistosoma species, are second only to malaria in endemic regions and it is an important neglected tropical disease (NTD). More than 240 million people are infected with one or more Schistosoma species in the tropical or subtropical regions. Approximately 85% of these infections occur in sub-Saharan Africa. Movement of refugees and mass migration of individuals from endemic to non-endemic areas have recently expanded the areas at risk of schistosomiasis and increased disease prevalence in recent times. Around 200,000 people die from Schistosoma infections each year and many more suffer with serious disabilities. Moreover, there is great economic loss in areas where schistosomiasis is endemic. Reports have shown that over 120 million people are symptomatic, with 20 million having severe clinical disease. The disease has been reported to be endemic in 76 countries, in which approximately 4 billion people live. Involvement in agricultural work, domestic chores and recreational activities can expose them to infested water.

The control of this disease is solely dependent on the chemotherapeutic drug praziquantel, which is used to treat infected individuals. There is no effective vaccine currently. Other chemotherapy alternatives include oxamniquine and metrifonate, although these have some setbacks, such as being ineffective against all life stages of the parasite and severe side effects, which is why praziquantel is recommended. Although praziquantel is effective, relatively safe and low cost, laboratory and field studies have shown the emergence of a resistant parasite strain in certain regions. This has led to a serious search for chemotherapy alternatives for the treatment and control of schistosomiasis. Therefore, there is a need to search for alternatives using both laboratory and computational investigative methods to explore sequenced Schistosoma genomes.

The recent sequencing of Schistosoma genomes, alongside the quickly evolving field of bioinformatics, has unveiled numerous opportunities to identify and characterize important proteins, which can aid in the development of novel drugs for disease control. The application of bioinformatics tools in extracting significant meaning from the sequence data have improved our knowledge of the mode of action of proteins. Modeling protein-ligand interactions (PLIs) to determine the possible biological interactions that occur in vivo has helped in understanding protein function and predicting their mechanisms of action. PLIs are also important in the development of novel therapies and diagnostic tools.

Methods

Sequence retrieval, extraction of DHODH proteins and potential drugs

SchDHODH protein sequences were obtained from the NCBI protein database. The sequences were confirmed in SchistoDB for S. haematobium (two protein sequences) and GeneDB for S. mansoni (two protein sequences) and S. japonicum (one protein sequence). All sequences were obtained in FASTA format. Each of these protein sequences were used for a BLASTp search of the non-redundant protein database on NCBI, employing the protein-protein BLAST algorithm. Results with similarities above 50% and with a query coverage and expectation value of >70% and 0.0, respectively, were obtained and combined for phylogenetic tree construction. Hypothetical and unknown proteins were excluded, even when there was high identity. After combining these sequences, duplicate protein sequences were also excluded. Host DHODH protein sequences were also obtained from NCBI using the search terms as targets “Homo sapiens + DHODH”, “Mus musculus + DHODH” and “Rattus rattus + DHODH” separately. The protein sequences that had 98% similarity to the targets were retrieved for further analyses. One HsDHODH, one MnDHODH and two RrDHODH sequences were retrieved. Each SchDHODH sequence was used to search DrugBank (version 5.1.2, released 2018-12-20) for potential compounds that may bind. All settings were at default.

Functional domain analysis

Functional domains for each SchDHODH, MnDHODH and HsDHODH were computed using the normal and genomic mode of SMART. The functional domains predicted were validated using other webtools: NCBI Conserved Domains, PROSITE, InterPro and Pfam version 32.0. Default parameters were used for these analyses.

Prediction of intrinsic disorder in SmDHODH

Since, for many disordered proteins, binding affinity with their receptors is regulated by post-translational modification, SmDHODH protein was analyzed for intrinsically disordered. SmDHODH was the only protein used in this analysis because...
it was used for modeling and protein-drug interaction. PONDR, which can predict natural disordered regions in a protein sequence, was used. This was validated using other similar tools such as SLIDER webserver\(^8\) and DisEMBL Intrinsic Protein Disorder Prediction 1.5\(^9\).

**Physical and chemical properties of SchDHODHs, HsDHODHs and MmDHODHs**

Each protein’s physiochemical properties, which includes the number of residues, molecular weight and extinction coefficient were predicted using the ProtParam web tool\(^10\). These properties were validated using the PepCalc peptide property calculator and Protein Physicochemical Properties Prediction Tool (PPPPT) web tools.

**SchDHODH, HsDHODH and MmDHODH sequence alignment**

All SchDHODH, HsDHODH and MmDHODH sequences were compared by Multiple Sequence Alignment (MSA) and the conserved and deleted regions were analyzed. The MSA analysis was carried out using Clustal Omega tools in Jalview\(^11\). The MSA was analyzed for conserved properties and regions of similarity.

**Phylogenetic studies and evolutionary conservation analysis**

Phylogenetic trees were constructed using MEGA version 7 software\(^12\). The constructed phylogenetic trees were validated using Phylogeny.fr\(^13\). The tree file, in Newick format, was exported and visualized in FigTree software version 1.4.2\(^14\) for proper annotation. The pairwise distances were also estimated, using the Poisson correction model in MEGA\(^15\).

**Protein-protein interactions**

Protein-protein interactions were determined using the STRING database for functional protein association networks. Each of the SchDHODH, HsDHODH and MmDHODH protein sequences were searched on the STRING and the interactions were downloaded in jpeg format.

**3D modelling**

SmDHODH sequences were modelled using SWISS-MODEL\(^16-17\). The template 3u2o.1A, with a sequence identity of 47.95%, GMQE of 0.74 and QMEAN of -0.98 was selected as the model of choice for SmDHODH sequences.

**Molecular docking and analyses**

Molecular docking was carried out using DockingServer\(^18\) and Gasteiger partial charges were added to the ligand atoms\(^19\), as described by Kumar, 2011\(^20\). Proteins were uploaded, protein charges were calculated, and solvation parameters were calculated and cleaned. All advance docking parameters were left at default.

**Results**

**Sequence retrieval of DHODHs and drugs**

In total, five SchDHODH sequences were retrieved for further analyses. One for *S. japonicum* and two proteoforms each for *S. haematobium* and *S. mansoni*. One HsDHODH sequence, two MmDHODH sequences and two RrDHODH sequences (Figure 1 and Project 1, Extended data)\(^21\) were included in the study for proper comparison as mammals, including humans, are the hosts, while rats and mice are commonly used in the laboratory for schistosomiasis studies. Of 12,110 drugs in the database, 26 compounds that can bind to SchDHODH proteins were identified and retrieved from DrugBank. These drugs were retrieved with E value: 7.46761e-71, Bit score: 224.172, query length: 379 and alignment length: 314. These results were the same for each of the SchDHODH sequences searched. All of the drugs were at the experimental phase, except flavin mononucleotide, capectabine and leflunomide, which are approved for the treatment of other diseases, and manitimus, which is still at the investigational phase. The mode of action of most of these retrieved drugs are not known, except for atovaquone, leflunomide and teriflunomide, which act as inhibitors to known proteins other than DHODH.

**Domains of DHODHs and intrinsic disorder predictions**

The protein domain analysis (see Project 3, Extended data)\(^22\) shows that all analyzed proteins have the dihydroorotate dehydrogenase domain (DHO_dh), while *Sh*DHODH proteins have dynein light domains and transmembrane helix regions, which are not seen in the other proteins. The disorder predictions show that a small fraction of the *SmDHODH* protein is disordered, as shown in Project 2, Extended data\(^23\).

**DHODHs of *S. haematobium* and *S. mansoni* evolved from a single ancestral species**

Physiochemical parameters (see Project 1, Extended data)\(^24\) and alignment (Figure 1), as well as phylogenetic analyses of all the SchDHODH sequences (Figure 2), show that the DHODH proteins of *S. haematobium* and *S. mansoni* could be evolutionary closer than that of *S. japonicum*. However, *S. japonicum* evolved 0.8928 million years ago (mya), compared to *S. haematobium* which evolved 0.8207 mya and *S. mansoni* which evolved 0.8012 mya. The last common ancestor for DHODH of both *S. haematobium* and *S. mansoni* was 0.8379 mya. The host DHODHs evolved more recently, as shown in Figure 2. These results could also explain the similarities between DHODHs that are shown in the sequence alignment (Figure 1). Mutations that occurred in *Sh*DHODHs were also observed in the *Sm*DHODHs, though there are some points where all three *Schistosoma* species shared mutation points. However, the similarities between *Sh*DHODH and *Sm*DHODH sequences do not correlate with the physiochemical parameters; *Sh*DHODH theoretical PI, extinction coefficients, instability index, aliphatic index and grand average of hydropathicity scores are more similar to *Sh*DHODH than *Sm*DHODH (see Project 1, Extended data)\(^24\).

**SchDHODHs, HsDHODHs and MmDHODHs protein-protein interaction analysis**

The prediction of possible in vivo interactions of these DHODHs showed that SchDHODH binds to NADPH (gene *Smp_166580*), putative glutamate synthase (*Smp_128380.2*) and NADH-cytochrome B5 reductase (*Smp_053230*) (Figure 2). These
Figure 1. Alignment analysis of Schistosoma dihydroorotate dehydrogenases alongside the corresponding dihydroorotate dehydrogenases of host species. Conserved amino acids across Sch DHODHs are marked and indicated in purple boxes, while across SmDODHs and ShDHODHs are marked and indicated in red boxes. The red arrows show where the mutation in SjDHODH compare to SmDODHs and ShDHODHs.
Phylogenetic tree of the dihydroorotate dehydrogenase proteins from *Schistosoma* pathogens, mice and human. All the *Sch*DHODHs shows clearly that the *Sch*DHODHs of *S. haematobium* and *S. mansoni* could be evolutionary closer compared to *S. japonicum*.

Four proteins bind to each other; however, it is unclear whether they form a complex. *Sch*DHODHs have an inhibitory effect on orotate phosphoribosyltransferase (*Smp_050540*), which has an inhibitory transcriptional regulation on aspartate carbamoyltransferase (*Smp_186670*) and vice versa. *Hs*DHODH and *Mm*DHODHs non-specifically bind to collapsin response mediator protein 1 (Crmp1) and different proteoforms of dihydropyrimidinase (Dpys). However, *Hs*DHODH and *Mm*DHODHs have an inhibitory role on carbamoyl-phosphate synthetase (Cps1) and uridine monophosphate synthetase (Umps).

Docking of selected ligands against modelled *Sch*DHODH protein structure

*Smp*DHODH was selected for modeling and protein-drug interaction studies as a representative for the three *Sch*DHODHs, since sequence alignment and phylogenetic analysis showed that they are all closely related. The modelled *Smp*DHODH used for docking against the 26 potential compounds is shown in Figure 4. After the molecular docking, 13 drugs had a binding affinity of less than -6 kcal/mol, suggesting a strong bond, with *Sch*DHODH (Table 1 and Figure 5) and details of these interactions are shown in Figure 6. The results show that 3-[[3-fluoro-3’-methoxybiphenyl-4-yl]amino]carbonyl]thiophene-2-carboxylic acid (accession number DB07976) and 3-[[3-fluoro-3’-methoxybiphenyl-4-yl]amino]carbonyl]thiophene-2-carboxylic acid (accession number DB07978) have the highest binding affinity, with an estimated free energy of binding (kcal/mol) of -10.18 and -10.66, respectively. Leflunomide (accession number DB01097) and N-anthracen-2-yl-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine (accession number DB08006) both have an estimated free energy of binding of -8.12. The *Sch*DHODH protein residues that interact with the different drugs in Table 1, are shown stick while drugs cartoon. It was observed that *Smp*DHODH interacts with the various compounds using hydrogen bonds, polar, hydrophobic, pi-pi, halogen and other forms of bonding.

Discussion

In the present study, known drugs that are either approved for treatment or at the experimental stage were searched as targets of DHODHs. Of those searched, 13 had a strong binding affinity. Binding affinity of less than -6 kcal/mol is regarded a strong bond. The strength of hydrogen, polar, pi-pi, halogen and hydrophobic bonding between the drugs and the *Smp*DHODH shows
The stability of the ligand inside the binding pocket. Based on the interaction properties of the ligand-protein complex, all the drugs have strong affinity, however, drug **DB07978** (2-{(2,3,5,6-tetrafluoro-3'-(trifluoromethoxy)biphenyl-4-yl)amino}carbonyl)cyclopenta-1,3-diene-1-carboxylic acid) and **DB07976** (3-{{3-fluoro-3'-methoxybiphenyl-4-yl)amino}carbonyl}thiophene-2-carboxylic acid) have the strongest free energy of binding among all the drugs screened.

One of the drugs with a high affinity (estimated free energy of binding of -9.56) to SmDHODH is flavin mononucleotide (accession number **DB03247**) (vitamin B2). This compound is naturally present in most food and used as a food additive. Riboflavin supplementation has been known to increase the efficiency of cell energy metabolism. Manitimus (accession number **DB06481**) was also identified by the docking experiment as a potential drug for schistosomiasis. It is an efficacious

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**Figure 3.** Interaction of proteins with (a) SmDHODH (b) HaDHODH and (c) MmDHODH.

**Figure 4.** Modelled SmDHODH protein.
<table>
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<td>1</td>
<td>DB07978 2-([(2,3,5,6-TETRAFLUORO-3'-TRIFLUOROMETHOXY)BIPHENYL-4-YL]AMINO)CARBONYL]CYCLOPENTA-1,3-DIENE-1-CARBOXYLIC ACID</td>
<td>Experimental</td>
<td>-10.66</td>
<td>15.3</td>
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<td>DB07976 3-[[3'-FLUORO-3'-METHOXYBIPHENYL-4-YL]AMINO]CARBONYL]THIOPHENE-2-CARBOXYLIC ACID</td>
<td>Experimental</td>
<td>-10.18</td>
<td>34.56</td>
<td>-11.34</td>
<td>-0.35</td>
<td>-11.69</td>
<td>94</td>
<td>806.017</td>
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<td>3</td>
<td>DB03247 Flavin mononucleotide</td>
<td>Approved, Investigational</td>
<td>-9.56</td>
<td>97.67</td>
<td>-9.38</td>
<td>1.06</td>
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<td>4</td>
<td>DB07977 3-[[3,5-DIFLUORO-3'-TRIFLUOROMETHOXYBIPHENYL-4-YL]AMINO]CARBONYL]THIOPHENE-2-CARBOXYLIC ACID</td>
<td>Experimental</td>
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<td>110.54</td>
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<td>-10.95</td>
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<td>DB07975 2-([(3,5-DIFLUORO-3'-TRIFLUOROMETHOXYBIPHENYL-4-YL]AMINO]CARBONYL]CYCLOPENT-1-ENE-1-CARBOXYLIC ACID</td>
<td>Experimental</td>
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<td>DB04583 5-Carbamoyl-1,1''-4',1''-terphenyl-3-carboxylic acid</td>
<td>Experimental</td>
<td>-8.89</td>
<td>305.65</td>
<td>-9.93</td>
<td>0.14</td>
<td>-10.07</td>
<td>18</td>
<td>777.123</td>
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<td>7</td>
<td>DB08008 5-methyl-N-[4-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine</td>
<td>Experimental</td>
<td>-8.69</td>
<td>425.74</td>
<td>-8.95</td>
<td>-0.04</td>
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<td>DB01101 Caperceptabine</td>
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<td>-10.02</td>
<td>-0.31</td>
<td>-10.33</td>
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<td>DB03480 Brequinar Analog</td>
<td>experimental</td>
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<td>approved, Investigational</td>
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<td>1.12</td>
<td>-8.88</td>
<td>-0.03</td>
<td>-8.91</td>
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<td>13</td>
<td>DB08006 N-anthracen-2-yl-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine</td>
<td>experimental</td>
<td>-8.12</td>
<td>1.13</td>
<td>-8.21</td>
<td>0.09</td>
<td>-8.12</td>
<td>43</td>
<td>751.241</td>
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and well tolerated drug for kidney transplant patients. It is a novel compound with multiple mechanisms of action\(^{60,61}\). One mechanism is via the suppression of \textit{de novo} pyrimidine biosynthesis, inhibiting the action of dihydroorotate dehydrogenase and consequently inhibiting cell proliferation\(^{62}\).

Another promising drug is capecitabine (accession number DB01101), which is a chemotherapy medication used to treat numerous types of neoplasms, including those of the breast, esophagus, larynx and gastrointestinal and genitourinary tracts. Capecitabine is a prodrug and is enzymatically converted to fluorouracil (an antimitabolite) in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue\(^{63-65}\). Leflunomide (accession number DB01097) is an approved immunosuppressive disease-modifying antirheumatic drug that has been in use for the treatment of rheumatoid arthritis and psoriatic arthritis for more than 10 years. Its mode of action is via pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase\(^{66-70}\).

Conclusions

There is an urgent need to search for and develop novel drugs that can be used in the treatment of schistosomiasis to complement treatment with praziquantel as there are growing number of reports of praziquantel-resistant \textit{Schistosoma} strains in the laboratory as well as in the field. Furthermore, there are no efficient vector control strategies. \textit{SmDHODH} has been proposed as druggable target in the \textit{de novo} pyrimidine biosynthesis pathway for schistosomiasis chemotherapy. We used the \textit{SmDHODH} sequence to search for all possible inhibiting compounds from the DrugBank database and found 13 with the potential to bind efficiently. If these compounds, which are already approved or...
Figure 6. The binding site of the interaction between the SmDHODH protein and the retrieved compounds. 

- a) 2-(((2,3,5,6-TETRAFLUORO-3’-(TRIFLUOROMETHOXY)BIPHENYL-4-YL)AMINO)CARBONYL)CYCLOPENTA-1,3-DIENE-1-CARBOXYLIC ACID (Accession Number: DB07978);
- b) 3-(((3-FLUORO-3’-METHOXYBIPHENYL-4-YL)AMINO)CARBONYL)THIOPHENE-2-CARBOXYLIC ACID (Accession Number: DB07976);
- c) 3-(((3,5-DIFLUORO-3’-(TRIFLUOROMETHOXY)BIPHENYL-4-YL)AMINO)CARBONYL)THIOPHENE-2-CARBOXYLIC ACID (Accession Number: DB07977);
- d) Flavin mononucleotide (Accession Number: DB03247);
- e) 2-(((3,5-DIFLUORO-3’-(TRIFLUOROMETHOXY)BIPHENYL-4-YL)AMINO)CARBONYL)CYCLOPENT-1-ENE-1-CARBOXYLIC ACID (Accession Number: DB07975);
- f) 5-Carbamoyl-1,1‘:4’,1''-terphenyl-3-carboxylic acid (Accession Number: DB04583);
- g) 5-methyl-N-[4-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-a]pyrimidin-7-amine (Accession Number: DB08008);
- h) Manitimus (Accession Number: DB06481);
- i) Capecitabine (Accession Number: DB01101);
- j) Brequinar Analog (Accession Number: DB03480);
- k) (2Z)-N-biphenyl-4-yl-2-cyano-3-cyclopropyl-3-hydroxyprop-2-enamide (Accession Number: DB08169);
- l) Leflunomide (Accession Number: DB01097);
- m) N-anthracen-2-yl-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-amine (Accession Number: DB08006).

in experimental stages, are tested in a wet laboratory experiment against the Schistosoma parasite and any are found to be effective, they could be easier than novel compounds to approve to supplement praziquantel for the control of schistosomiasis in the future.

Data availability

Underlying data
SICHGC02326 protein [Schistosoma japonicum], Accession number AAW26221: https://identifiers.org/ncbiprotein/AAW26221

Dihydroorotate dehydrogenase (quinone), mitochondrial [Schistosoma haematobium], Accession number KGB36135: http://identifiers.org/ncbiprotein/KGB36135

Dihydroorotate dehydrogenase (quinone), mitochondrial [Schistosoma haematobium], Accession number XP_012795900: https://identifiers.org/ncbiprotein/XP_012795900

dihydroorotate dehydrogenase [Schistosoma mansoni], Accession number CCD78646: http://identifiers.org/ncbiprotein/CCD78646
dihydroorotate dehydrogenase [Schistosoma mansoni], Accession number XP_018651255: https://identifiers.org/ncbi/protein/XP_018651255

dihydroorotate dehydrogenase (quinone), mitochondrial precursor [Mus musculus], Accession number NP_064430: http://identifiers.org/ncbi/protein/NP_064430

Chain A, DIHYDROOROTATE DEHYDROGENASE [Rattus rattus], Accession number 1UUM_A: http://identifiers.org/ncbi/protein/47169292

Chain B, DIHYDROOROTATE DEHYDROGENASE [Rattus rattus], Accession number 1UUM_B: http://identifiers.org/ncbi/protein/47169293

Crystal structure of human dihydroorotate dehydrogenase at 1.7 Å resolution [Homo sapiens], Accession number 5K9D: https://identifiers.org/pdb/5K9D

References


Extended data

Figshare: Extended data 1_Physicochemical Properties.docx. https://doi.org/10.6084/m9.figshare.8019683.v1

Figshare: Prediction of intrinsic disorder of SmDHODH.docx https://doi.org/10.6084/m9.figshare.8050541.v1

Figshare: Extended data 3_Protein domain analysis of DHODHs of the Schistosoma sp and Host.docx https://doi.org/10.6084/m9.figshare.8051777.v1

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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