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Computational Design of Novel Candidate Drug Molecules for Schistosomiasis

Joseph Njuguna Gichuhi* Steven Ger N Daniel Kariuki W Johnson Kinyua K
Department of Biochemistry, Jomo Kenyatta University of Agriculture and Technology
PO box 62000-00200, Nairobi, Kenya
* E-mail: joemunju@yahoo.com

Abstract
Schistosomiasis is a parasitic disease that leads to chronic ill-health. Infection is acquired from infested freshwater containing the larval forms (cercariae) of blood flukes, known as schistosomes. The three main species of the parasite that infect humans are *Schistosoma haematobium, S.japonicum,* and *S.mansoni.* Schistosomiasis affects at least 230 million people worldwide. The infection is prevalent in tropical and sub-tropical areas, in poor communities without potable water and adequate sanitation. The disease is considered as one of the Neglected Tropical Diseases and so far praziquantel is the only drug used for treatment. Should the parasites develop resistance to praziquantel, treatment would be problematic. This study incorporated a computational approach to design novel compounds with unprecedented potential as candidate drug compounds for the disease. The *Schistosoma mansoni* fatty acid binding protein was selected as a suitable drug target for its crucial role in the dependence of the parasite on its host for fatty acids. Screening for potential lead compounds was done using molecular docking software. Identified lead compounds were analyzed and optimized *in silico* for their ADMET properties then re-evaluated for suitability of their binding energies. Eight novel compounds with good predicted ADMET properties were designed and found to interact with the *S.mansoni* fatty acid binding protein with favorable binding energy, showing potential to inhibit this protein. This study opens up new possibilities in antischistosomal drug inquiry and potentiates efficacy studies of such compounds against schistosomiasis.
Keywords: computational design, antischistosomal drug inquiry, binding energy, lead optimization, ADMET properties

1. Introduction

Among human parasitic diseases, schistosomiasis also called bilharziasis ranks second after malaria in terms of socio-economic and public health importance in tropical and subtropical areas with more than 700 million people at risk (Steinman *et al*., 2006). The most common way of infection with schistosomiasis in developing countries is by wading or swimming in water bodies that are infested with snails usually of the genera Biomphalaria, Bulinus, or Oncomelania which are the natural reservoirs of the Schistosoma pathogen.

Praziquantel is the recommended treatment for schistosomiasis at 40 mg/kg body weight per dose according to the World Health Organization's factsheet. Reliance on a single drug to treat a population of over 200 million people infected and over 700 million people at risk over three continents (Steinman *et al*., 2006) seems particularly perilous when considering the threat of drug resistance.

Although widespread resistance to praziquantel has not been reported, cases of reduced susceptibility to praziquantel by schistosomes have been reported. In a study in Kisumu, Kenya, schistosomal isolates from patients that had previously been treated with praziquantel were found to be less susceptible to praziquantel than isolates from previously untreated patients (Melman *et al*., 2009). Resistance to the drug has been shown to be inducible *in vitro* (Couto *et al*., 2011) and therefore a growing concern whether resistance may develop and spread.

The Schistosoma Genome Network has published the *S.mansoni* genome sequenced using whole genome shotgun sequencing by the Pathogen Genomics group at the Wellcome Trust Sanger Institute (Berriman *et al*., 2009). Availability of genomic datasets has facilitated the identification and prioritization of drugs and drug targets in several neglected tropical disease pathogens (Crowther *et al*., 2010). Similarly, availability of this information has enabled development of new tools and resources for understanding the parasite's biological systems. This study makes use of manually drawn *S.mansoni* metabolic pathway maps in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa *et al*., 2012) to propose a putative drug target for the parasite and employs a computational approach to design candidate inhibitor compounds for the target as a plausible input in the drug development process for schistosomiasis.

2. Materials and Methods

2.1 Target selection

S.mansoni metabolic pathway maps were accessed at the KEGG website and used to identify several proteins that play crucial roles in the parasite's metabolism. These proteins were selected for their likelihood to disrupt

their respective metabolic pathways if inhibited through drug targeting.

2.2 Target validation

The presence of experimentally determined structures of the proteins was used as a criterion for target validation. Only proteins with structures in the Protein Data Bank (PDB) (Berman *et al*., 2000) were further considered suitable targets for the study. In addition, targets whose host ortholog's disruption by a designed compound through non- specific drug interactions would be highly detrimental to the host were also not further considered for drug design.

2.3 Target structure preparation

Three dimensional structures of *S.mansoni* fatty acid binding protein were retrieved from the PDB and visualized using the Pymol molecular graphics program (Pymol.org, 2012). Co-crystalized ligand molecules in the downloaded structures were identified and used to define the target's binding site. The 3D Ligand Site server (Wass *et al*., 2010) was used to identify the binding sites of any structures that had no ligands.

2.4 Ligand preparation

A library of ligands was generated from 755 carboxylic acids downloaded in MDL mol format (Dalby *et al*., 1992) from LipidBank (Yasugi and Seyama, 2007). The MarvinSketch program (Chemaxon.com) was used to add explicit hydrogen atoms to these structures and subsequently to clean their 3-Dimensional structures. The open source program OpenBabel (O'Boyle *et al*., 2011) was used to convert the MDL mol structures of these molecules molecule into a single SDF file (Dalby *et al*., 1992).

2.5 Library screening

The Arguslab molecular docking software (Planaria Software LLC, 2004) was used to dock all ligands in the library to the target's binding site through the programs implementation of the ArgusDock exhaustive search docking engine. All ligands were treated as flexible molecules and evaluated for ligand-target interaction energies using the software's in-built Ascore scoring function. The search space was automatically calculated by Arguslab and grids of resolution 0.4 angstroms were generated and used in the docking run.

2.6 Lead identification

Only ligands with estimated interactions energies lower than that of the co-crystallized ligands i.e. Oleic acid Arachidonic acid were selected from the library screening process as lead compounds.

2.7 ADMET analysis

The (Absorption, Distribution, Metabolism, Excretion and Toxicity) ADMET properties of each lead compound were estimated using the OSIRIS Property Explorer tool (Actelion Pharmaceuticals Ltd, 1999). The structure of each compound was manually drawn on the tool's java based web applet for on-the-fly calculations of the cLogP, solubility, molecular weight, drugscore, druglikeness and toxicity risks for mutagenic, tumorigenic, irritant and reproductive effective properties.

2.8 Lead optimization

Functional side groups were introduced on the lead compounds through hydrogen substitutions in a manner that improved the ADMET properties of each compound using the OSIRIS Property Explorer. The structures of all optimized compounds were generated and saved as MDL mol format files using ChemAxon's Marvinsketch program.

2.9 Nomenclature and docking of optimized compounds

IUPAC names for optimized compounds were generated from their structures using Chemaxon's Marvinsketch program. The MDL mol structure files of these compounds were combined into a single SDF file using OpenBabel. This file was used as a ligand database for docking the optimized compounds into the binding site of the target protein to evaluate their interaction energy.

2.10 Prediction of Biological activity

The biological activity of optimized compounds that had lower interaction energy than arachidonic acid with the target protein was predicted using the Prediction of Activity Spectra for Substances (PASS) online server (Laguni *et al*., 2000). The MDL mol file of each compound was uploaded individually to the server for prediction.

3. Results

3.1 Target selection and validation

Ten *S.mansoni* genes were selected as possible antischistosomal drug targets through analysis of the parasite's metabolic pathways in KEGG. These genes play crucial roles in the parasite and were deemed as good targets for drug action against the parasite as shown in Table 1.

Table 1. Selected putative targets.

Putative target	KEGG accession	Process	PDB structure
Ryanodine receptor	Smp_101180	Muscle contraction	-
Mevalonate kinase	Smp_042980	Mevalonate pathway	-
Phosphomevalonate kinase	Smp_072460	Mevalonate pathway	-
Hexokinase	Smp_043030	Glycolysis	1BDG
Phosphopyruvate hydratase	Smp_024110	Glycolysis	-
Hydroxymethylglutaryl CoA reductase	Smp_138590	Mevalonate pathway	-
Methionyl aminopeptidase	Smp_142010.2 Smp_011120	Protein degradome	-
Rab 6	Smp_176050	Cellular transport	-
Fatty acid binding protein	Smp_095360.1	Fatty acid transport	1VYG, 1VYF, 1POA
Calmodulin	Smp_018940	Phosphatidylinositol signaling system	-

Despite the high viability of the selected proteins as drug targets in the parasite, we screened off those without experimentally determined structures as a measure of minimizing errors in docking that could arise from incorrect protein folding and incorrect orientation of binding site residues in modelled structures. Although a structure for hexokinase was present in the PDB, we avoided this target because of the high likelihood that a compound designed to disrupt its function would also disrupt mammalian hexokinase owing to the similar nature of substrate, binding sites and mechanism of catalysis between the two. Interference with glycolysis in mammalian host could cause variations in blood glucose levels that might be detrimental especially to individuals at high risk of glucose metabolism disorders.

3.2 Target structure preparation

Two crystallographic (1VYG and 1VYF) and one NMR (2POA) structures of *S.mansoni* fatty acid binding protein were retrieved from the PDB. The three structures were visualized in Pymol to reveal co-crystalized ligands: arachidonic acid and oleic acid in 1VYG and 1VYF respectively, whereas the structure 2POA did not have any ligand (Figure1).

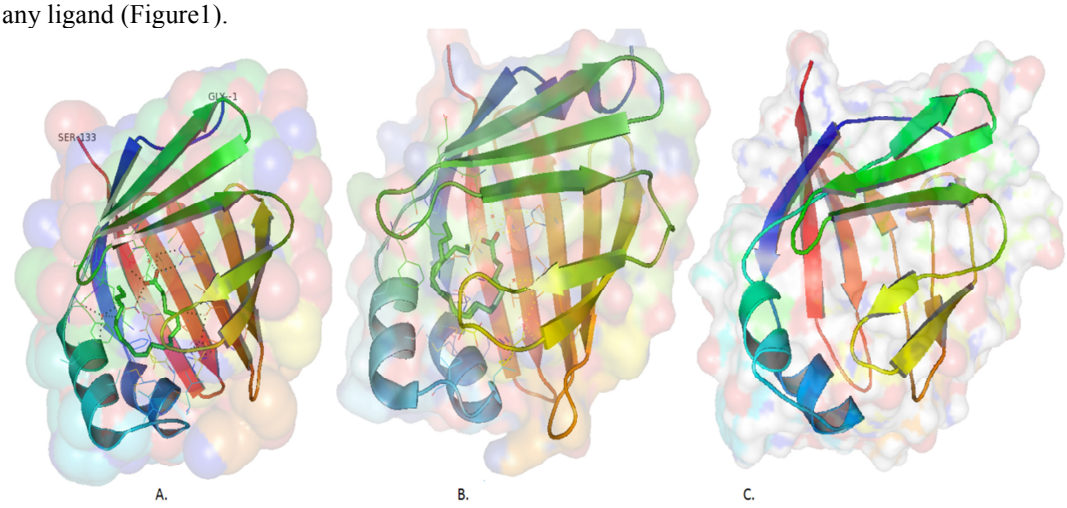

Figure 1: Structures of target protein as visualized in Pymol. A: IVYG with arachidonic acid visible in the protein's binding site. B: IVYF with oleic acid visible in the binding site. C: 2POA with no ligand. The ribbon structures are colored red through blue from the carboxylic to the amino terminal ends. The molecular surfaces of the protein are also shown with similar coloring of residues along the chain.

3.3 Binding site selection

The Pymol program was also used to identify binding site residues in the structures. Residues in the binding site of oleic acid in the structure 1VYF were PHE16, VAL19, MET20, LEU23, VAL25, THR29, ILE32, GLY33, VAL36, PRO38, THR53, GLU54, PHE57, LYS58, SER75, ASP76, ARG78, GLN96, THR103, ILE105, ARG107, THR116, VAL118, ARG127 andTYR129 while the same residues were also in the binding site of arachidonic acid in the structure 1VYG with an addition of LEU 60 (Figure 2). Binding site residues in 2POA were predicted by the 3D Ligand Site Server as follows: 16PHE, 23LEU, 35VAL, 28ALA, 29THE, 30ARG, 32ILE, 33GLY, 36VAL, 51MET, 57PHE, 58LYS, 62VAL, 70PHE, 72GLU, 74THR, 75SER, 76ASP, 78ARG, 84VAL, 94GLN, 96GLN, 98ASP, 103THR, 105ILE, 107ARG and 127ARG. More than 60 percent of these residues were common for all the three ligands and occur in the same cavity in the target protein. The binding site of arachidonic acid in the structure 1VYG was set up for all docking calculations.

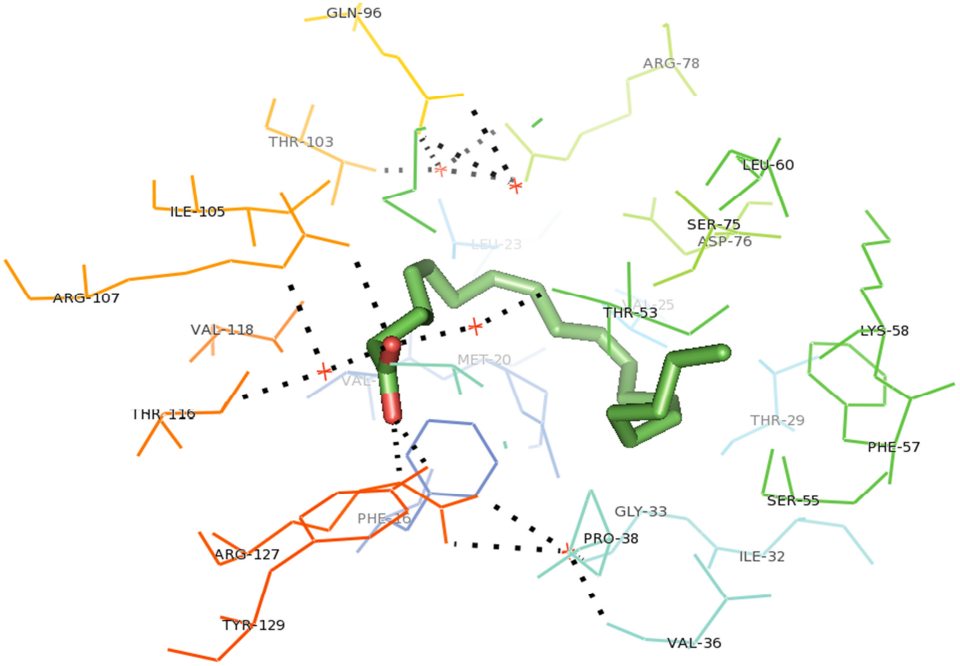

Figure 2: Binding site residues in 1VYG. Arachidonic acid is rendered as stick while amino acid residues are rendered as wireframe. Hydrogen bonds are shown as black dotted lines and water molecules as red crosses.

3.4 Library screening

A total of 35 out of the 755 carboxylic acids screened consistently showed lower interaction energy than arachidonic acid with the *S.mansoni* fatty acid binding protein and were selected as lead compounds (Table 2).

3.5 ADMET analysis

Each of the selected lead compounds was evaluated for various ADMET properties using the OSIRIS property explorer as shown in Table 2.

Table 2: Binding energy and predicted ADMET properties of the selected lead compounds.

LipidBank Id.	Interaction energy Kcal/mol	cLogP	Solubility	Molecular weight	Drug likeness	Drug score	Toxicity risk
DFA0024	-13.9093	10.23	-6.4	368	-25.22	0.14	none
DFA0025	-14.0123	10.7	-6.67	382	-25.22	0.13	none
DFA0026	-14.0975	11.16	-6.94	396	-25.22	0.13	none
DFA0030	-14.584	13.02	-8.02	452	-25.22	0.11	none
DFA0031	-14.6176	13.48	-8.29	466	-25.22	0.1	none
DFA0032	-15.9191	13.95	-8.56	480	-25.22	0.1	none
DFA0033	-15.0982	14.41	-8.83	494	-25.22	0.1	none
DFA0034	-15.7452	14.87	-9.1	508	-25.22	0.09	none
DFA0035	-16.4189	15.34	-9.37	522	-25.22	0.09	none
DFA0036	-17.1863	15.8	-9.64	536	-25.22	0.09	none
DFA0037	-16.0922	16.27	-9.91	550	-25.22	0.09	none
DFA0038	-16.4506	16.73	-10.18	564	-25.22	0.08	none
DFA0132	-14.4781	9.88	-6.17	366	-28.97	0.14	none
DFA0133	-14.5945	10.8	-6.71	394	-28.97	0.13	none
DFA0134	-14.3868	10.8	-6.71	394	-28.97	0.14	none
DFA0135	-14.4871	11.73	-7.25	422	-28.97	0.12	none
DFA0136	-14.8182	12.66	-7.79	450	-28.97	0.11	none
DFA0137	-15.2025	13.59	-8.33	478	-28.97	0.1	none
DFA0170	-13.9464	8.59	-5.4	336	-24.85	0.17	none
DFA0213	-13.7482	6.95	-4.41	304	-10.1	0.22	none
DFA0216	-14.5648	7.87	-4.95	332	-23.27	0.19	none
DFA0217	-14.6828	7.87	-4.95	332	-25.56	0.19	none
DFA0218	-14.4056	7.87	-4.95	332	-20.74	0.11	irritant
DFA0219	-14.0697	6.59	-4.18	302	-8.9	0.19	moderate risk irritant
DFA0221	-14.7107	7.52	-4.72	330	-17.53	0.2	none
DFA0222	-14.6792	7.52	-4.72	330	-10.83	0.12	high risk irritant
DFA0223	-14.8789	7.52	-4.72	330	-20.74	0.12	High risk irritant
DFA0224	-14.3433	7.16	-4.49	328	-10.83	0.13	High risk irritant
DFA0225	-15.3845	8.09	-5.03	356	-10.83	0.11	High risk irritant
DFA0247	-13.7912	10.79	-6.61	396	-13.29	0.13	none
DFA0253	-14.6216	13.36	-8.18	466	-11.17	0.1	none
DFA0257	-14.4959	11.03	-6.62	408	-16.9	0.06	high risk mutagenic, moderate risk reproductive effective
DFA8086	-14.0613	6.04	-4.33	336	-13.28	0.05	high risk mutagenic, tumorigenic and irritant
DFA8133	-13.8034	5.93	-4.01	320	-17.88	0.26	none
DFA8157	-14.1638	5.85	-4.06	318	-17.13	0.27	none

3.6 Lead optimization

Several compounds (Table 3) were generated through hydrogen group substitutions on the lead compounds. Substitution of hydrogen atoms at various positions in the structures of lead compounds was guided by the overall effect that each substitution produced on the compounds' ADMET properties. The best possible properties attained for the optimized compounds are shown in Table 4. In addition, the topological polar surface area of each compound was calculated using Chemaxon's Marvinsketch program (Table4). These compounds were docked to the target protein to evaluate their interaction energies (table 5). The IUPAC names for the optimized compounds are shown in table 5.

Table 3: Structures of compounds generated from lead optimization.

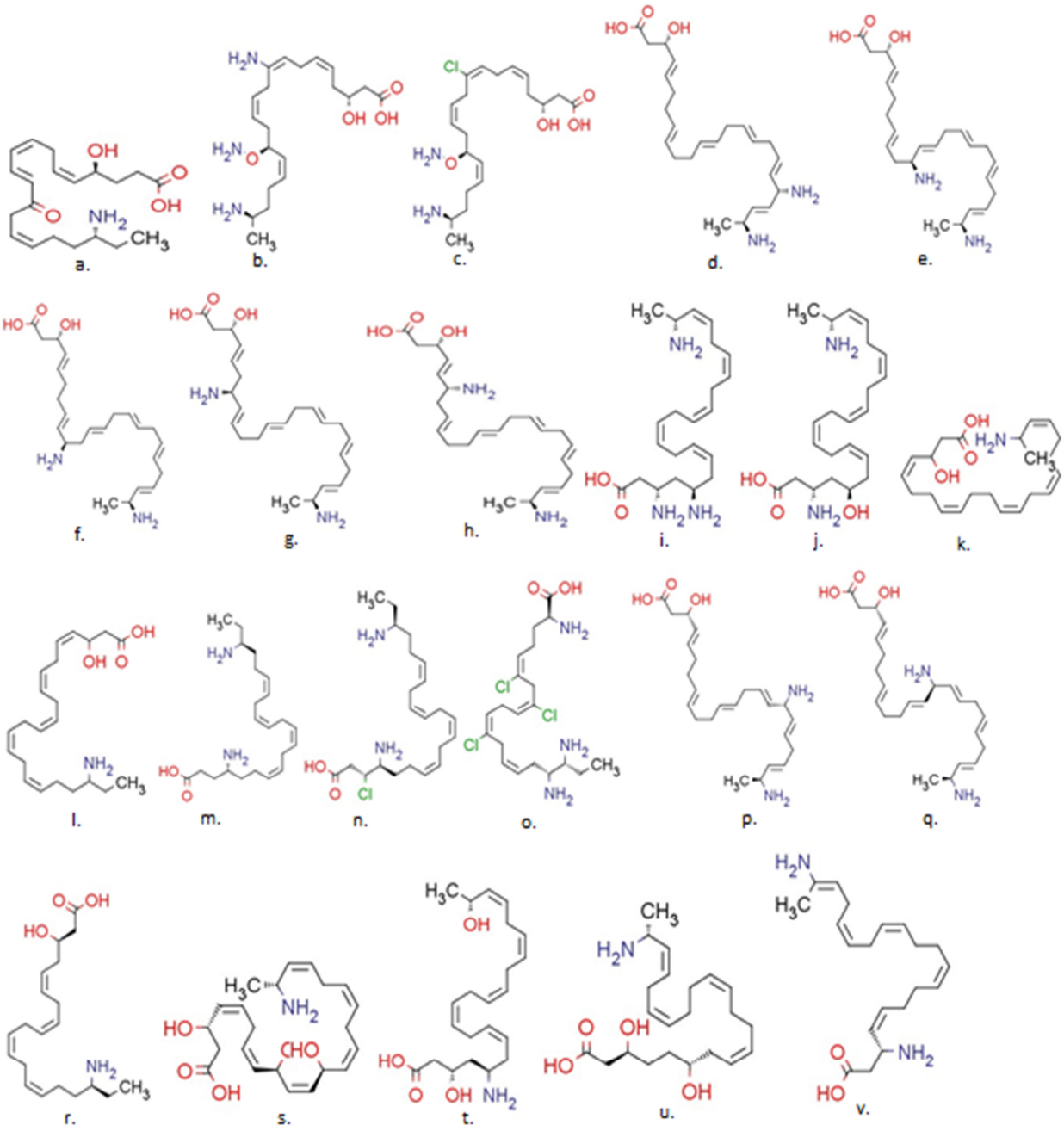

Table 4: Predicted ADMET properties of generated compounds.

lead	Derived compound	cLogP	Solubility	Molecular weight	Drug likeness	Drug score	Toxicity risk	TPSA
DFA0225	d, e, f, g, h, p, q	3.97	-3.99	402	-4.61	0.34	none	109.57
DFA0223	j	3.4	-3.67	376	-1.49	0.44	none	109.57
DFA0223	i	2.86	-3.75	375	-1.94	0.43	none	115.36
DFA0223	t	3.93	-3.6	377	-0.63	0.48	none	103.78
DFA0221	l	4.95	-4.0	361	-4.07	031	none	83.55
DFA0217	n	4.58	-4.63	396	-4.81	0.29	none	89.34
DFA0217	m	4.77	-4.3	362	-7.02	0.3	none	89.34
DFA0222	k	4.95	-4.0	361	-4.58	0.3	none	83.55
DFA0224	s	2.56	-2.97	391	-0.68	0.54	none	124.01
FA8157	a	3.28	-3.34	349	-3.86	0.4	none	100.62
DFA0219	v	4.61	-3.86	332	-6.7	0.33	none	89.34
DFA8086	c	3.68	-4.38	400	-2.81	0.35	none	118.8
DFA8086	b	2.58	-3.7	381	-3.01	0.41	none	144.82
DFA0213	r	4.38	-3.69	335	-3.92	0.35	none	83.55
DFA0213	o	4.3	-5.51	451	-14.66	0.24	none	115.36
DFA0218	u	4.29	-3.83	379	-4.35	0.34	none	103.78

TPSA-Topological Polar Surface Area

Table 5: IUPAC naming and interaction energies of generated compounds.

Compound	**IUPAC Name**	**Interaction energy**
a	(4S,5Z,8Z,10E,14Z,18R)-18-amino-4-hydroxy-12-oxoicosa-5,8,10,14-tetraenoic acid	-12.9082
b	(3R,5Z,8E,11Z,14S,15Z,19R)-9,19-diamino-14-(aminooxy)-3-hydroxyicosa-5,8,11,15-tetraenoic acid	-12.692
c	(3R,5Z,8E,11Z,14S,15Z,19R)-19-amino-14-(aminooxy)-9-chloro-3-hydroxyicosa-5,8,11,15-tetraenoic acid	-12.5987
d	(3S,4E,8E,12E,15E,18E,20S,21E,23S)-20,23-diamino-3-hydroxytetracosa-4,8,12,15,18,21-hexaenoic acid	-15.5521
e	(3S,4E,8E,11S,12E,15E,18E,21E,23S)-11,23-diamino-3-hydroxytetracosa-4,8,12,15,18,21-hexaenoic acid	-14.6348
f	(3S,4E,8E,10R,12E,15E,18E,21E,23S)-10,23-diamino-3-hydroxytetracosa-4,8,12,15,18,21-hexaenoic acid	-15.44
g	(3S,4E,7S,8E,12E,15E,18E,21E,23S)-7,23-diamino-3-hydroxytetracosa-4,8,12,15,18,21-hexaenoic acid	-14.5169
h	(3S,4E,6R,8E,12E,15E,18E,21E,23S)-6,23-diamino-3-hydroxytetracosa-4,8,12,15,18,21-hexaenoic acid	-13.7576
i	(3S,5R,7Z,10Z,13Z,16Z,19Z,21R)-3,5,21-triaminodocosa-7,10,13,16,19-pentaenoic acid	-13.4618
j	(3S,5R,7Z,10Z,13Z,16Z,19Z,21R)-3,21-diamino-5-hydroxydocosa-7,10,13,16,19-pentaenoic acid	-13.5923
k	(3S,4Z,8Z,12Z,15Z,19Z,21R)-21-amino-3-hydroxydocosa-4,8,12,15,19-pentaenoic acid	-13.8649
l	(3S,4Z,7Z,10Z,13Z,16Z,20S)-20-amino-3-hydroxydocosa-4,7,10,13,16-pentaenoic acid	-13.5934
m	(4R,7Z,10Z,13Z,16Z,20S)-4,20-diaminodocosa-7,10,13,16-tetraenoic acid	-13.4261
n	(3R,4S,7Z,10Z,13Z,16Z,20S)-4,20-diamino-3-chlorodocosa-7,10,13,16-tetraenoic acid	-13.5759
o	(2S,5E,8E,11E,14Z,17R,18R)-2,17,18-triamino-6,8,12-trichloroicosa-5,8,11,14-tetraenoic acid	-13.4181
p	(3S,4E,8E,12E,15E,17S,18E,21E,23S)-17,23-diamino-3-hydroxytetracosa-4,8,12,15,18,21-hexaenoic acid	-14.6651
q	(3S,4E,8E,12E,14R,15E,18E,21E,23S)-14,23-diamino-3-hydroxytetracosa-4,8,12,15,18,21-hexaenoic acid	-15.8855
r	(3R,5Z,8Z,11Z,14Z,18S)-18-amino-3-hydroxyicosa-5,8,11,14-tetraenoic acid	-13.4304
s	(3S,4Z,7Z,9R,10Z,12S,13Z,16Z,19Z,21R)-21-amino-3,9,12-trihydroxydocosa-4,7,10,13,16,19-hexaenoic acid	-13.2826
t	(3S,5R,7Z,10Z,13Z,16Z,19Z)-5-amino-3,21-dihydroxydocosa-7,10,13,16,19-pentaenoic acid	-13.0026
u	(3S,6R,8Z,12Z,16Z,19Z,21R)-21-amino-3,6-dihydroxydocosa-8,12,16,19-tetraenoic acid	-13.3608
v	(3R,4Z,8Z,12Z,15Z,18E)-3,19-diaminoicosa-4,8,12,15,18-pentaenoic acid	-12.8736

3.8 Biological Activity Prediction

Generated compounds that had lower interaction energy than arachidonic acid were selected as potential competitive inhibitors of the target protein. Their likely biological activities were predicted for numerous categories evaluated by the PASS server. The two likely biological activities predicted with highest probability values for these compounds is shown in Table 6.

Table 6: Predicted biological activities of compounds with low interaction energies.

Compound	Pa	Pi	Biological Activity
d, k, p and q	0.932	0.003	Beta-adrenergic receptor kinase inhibitor
	0.932	0.003	G-protein-coupled receptor kinase inhibitor
e, f, g, and h	0,909	0,004	Beta-adrenergic receptor kinase inhibitor
	0,909	0,004	G-protein-coupled receptor kinase inhibitor

Pa- probability of being active, Pi- probability of being inactive

4. Discussion

Schistosomes are incapable of *de novo* synthesis of sterols or free fatty acids and must use complex precursors from the host (Brouwers *et al*., 1997). *S.mansoni* fatty acid binding protein was selected as a putative target that can be inhibited to block the parasite's mechanism of reliance on the host for fatty acid biosynthesis. Coincidentally, this protein has been studied as a target for vaccine development because it possesses cross-reactive, discontinuous epitopes principally derived from amino acids in the C-terminal portions of its structure (Ramos *et al*., 2009). Inhibiting this protein would hamper synthesis of cell membranes and protein modification of the parasite which depend on uptake and transport of fatty acids from the host. There is minimal probability of producing adverse effects in the host through non-specific interaction of an inhibitor of this protein with host orthologs. It has been reported that pharmacologically blocking adipocyte fatty acid binding protein in mice alleviates both acute liver injury and non-alcoholic steatohepatitis (Hoo *et al*., 2012). Similarly, inhibiting fatty-acid-binding protein 4 (Adipocyte protein 2) has been found to treat diabetes and atherosclerosis in mouse models (Furuhashi *et al*., 2004). However, the nature of effects produced by the designed novel drug compounds need to be ascertained through testing in animal models.

Docking calculations revealed that arachidonic acid interacts more readily with the target protein than oleic acid. The two fatty acids had interaction energies of -13.7482kcal/mol and -12.6204 kcal/mol respectively in the library screening docking run. This observation is coherent with previous findings (Angelucci *et al*., 2004) which suggested that the target protein's binding site is optimized to fit arachidonic acid. We therefore used arachidonic acid as a reference ligand and screened for compounds with the ability to interact more readily with the protein. Out of the 35 carboxylic acids that had lower interaction energies than arachidonic acid, only 11 could sufficiently be optimized to conform to a pharmacophore model. Those with molecular weights greater than 450 were screened out in line with the observation that 80% of all traded drugs have a molecular weight less than 450 daltons (Actelion Pharmaceuticals Ltd, 1999) whereas it was not possible to generate optimized compounds for the rest without violating one or more of Lipinski's rule of five (Lipinski, 2004). Eight optimized compounds were found to interact with the target protein at lower binding energy than arachidonic acid through docking, suggesting a capability to inhibit this protein. The eight compounds: d, e, f, g, h, k, p and q can be deduced to be orally active and well absorbed by passive diffusion across cell membranes because they comply with all criteria of the Lipinski's rule of five. In addition, the topological polar surface areas of all the eight compounds is well below 140 $Å^2$ inferring ability to permeate cell membranes and intestinal mucosa. These compounds are however unlikely to cross the blood brain barrier because their topological polar surface areas are above 70$Å^2$, which is a good property because none of the parasitic stages of schistosomes get localized in the central nervous system. The predicted aqueous solubility values of these compounds are at the lower bounds when compared to majority of traded drugs which have values greater than -4 (Actelion Pharmaceuticals Ltd, 1999). However, measures to increase solubility could be employed if bioavailability of the drug at a determined dosage is found to be low. Such methods include micronization (Bladgen *et al*., 2007), nanosuspension (Muller *et al*., 2000), preparation of binary eutectic mixtures (Liu *et al*., 2006), solid dispersion (Sekiguchi and Obi, 1961) and hydrotrophy (Roy and Moulik, 2002). The PASS online server predicted numerous possible biological activities for the eight compounds. The highest probability predicted for all the eight compounds was the inhibition of beta-adrenergic receptor kinase. This inhibition has been employed to reverse cardiac dysfunction in failing cardiomyocytes (Eckhart and Koch 2002) and therefore would not present a major challenge as an adverse effect in a mammalian host body system. Similarly, these compounds were predicted with high probability to have inhibitory activity on G-protein-coupled receptor kinase, an activity that has been shown to have cardioprotective effects (Fu *et al*., 2013). However, the actual biological activity that any of these compounds possess can only be ascertained experimentally especially considering the possibility that pharmacological activity may be destroyed in first pass metabolism.

The success of computational drug design cannot be fully appreciated unless complemented by experimental testing. Theoretical concepts and ideological premises employed in *in silico* drug design have to be evaluated for experimental evidence of drug activity and associated effects for the drug to be useful towards its intended purpose. The novel compounds d, e, f, g, h, k, p and q can therefore be synthesized and tested in vitro for activity against schistosomes as well as in animal models for efficacy and biological activity. In addition, these compounds can also be synthesized and tested in animal models for their predicted inhibitory activity on Beta-adrenergic receptor kinase and G-protein-coupled receptor kinase in order to evaluate their possible use in cardioprotective strategies.

5. Conclusion

The *S.mansoni* genome has a promising potential of presenting novel drug targets that can be exploited for anti-schistosomal drug design. Alternative drug development for schistosomiasis is necessary to alleviate over-reliance on praziquantel and also to mitigate against limitations in therapeutic management of the disease should the parasites develop resistance to praziquantel. In the present study, a few key targets in the parasite have been evaluated and eight novel compounds with potential to competitively inhibit the *S.mansoni* fatty acid binding protein designed. These compounds can therefore be evaluated as candidate drug compounds in strategy to incapacitate the parasite from proper utilization of fatty acids from the host. Although theoretical and computational evidence suggest good anti-schistosomal prospects for these compounds, in vitro and in vivo testing for activity and efficacy are the surest means of ascertaining their contribution to anti-schistosomal drug discovery and development. These compounds can therefore be synthesized and tested experimentally for their pharmacological activity.

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