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Molecular docking study of macrocycles as Fk506-binding protein inhibitors

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ABSTRACT

To prepare for future resistance, new methods are being explored for novel treatment of malaria. The current work uses high performance docking methods to model different substrates binding into the active sites of varying *Homo sapien* and *Plasmodium* peptidyl-prolyl *cis*/*trans* isomerase enzymes and compares their subsequent docking scores. This approach has shown that the substrates ILS-920 and WYE-592 will bind less-favourably with *h*FKBP12 and *Pf*FKBP35 compared to a competing substrate rapamycin; however, the binding appears to be more favourable in *Pv*FKBP35. This could suggest a possible target for inhibition of the *Plasmodium vivax* parasite.

1. Introduction

Malaria is a world-wide epidemic affecting nearly 250 million people each year [1–3]. Of those afflicted, nearly one million are African children, and these cases nearly always result in death. It is a life-threatening disease cause by *Plasmodium* parasites. There are five types of malaria affecting humans; the most common and most deadly being *Plasmodium vivax* and *Plasmodium falciparum*, respectively. Symptoms of malaria include anemia, fever, headache, and nausea, and can be as severe as convulsions, coma, or death [3].

Although human immunity reduces the risk of severe disease due to the parasite, it does not offer complete protection. The only reliable treatment, as with many diseases, is the persistent use of drugs, or anti-malarials. Chloroquine is the typical anti-malarial used in the treatment of *P. vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and, up until the recent widespread resistance, *P. falciparum* [4,5]. Upon first being discovered, it went unused for a decade, as it was thought to be too toxic for human use. The main issue related to using chloroquine is the rapid and significant resistance developed by *P. falciparum* in recent years. This could possibly be due to mass drug administrations (MDAs) [6].

As there has yet to be a viable vaccine for malaria [7], the current treatment for all types of malaria is a potent combination of artemisinin-based combination therapy (ACTs) [2,8,9]. It is used for multi-drug resistant *P. falciparum* worldwide. Artemisinin and its derivatives can be administered orally or through intra-muscular injection, are fast acting, and have a high likelihood of curing malaria. The parasites, however, have been slowly developing resistance to artemisinin and its derivatives in Cambodia and along the Thailand border. This has led to the recommendation that artemisinin-based monotherapies no longer be used and be exclusively replaced by ACTs [10]. ACTs are typically a combination of artemisinin (or a derivative, i.e. dihydroartemisinin, artesunate, etc.) and a drug from a different class (mefloquine, piperaquine, etc.). This has led to a reduced likelihood of developing resistance.

There are several issues with the current method of treatment for malaria: the drugs are non-specific (often treating malaria as well as a variety of other diseases), the drugs can be very toxic to humans, and the parasites can develop a resistance to the drugs after a short period of time [11]. Another fear is that certain drugs that treat malaria have similar mechanisms of action in the parasite. This is a serious concern; if the parasite develops resistance to one drug's mechanism of action, it could be resistant to several others. This highlights the need for a novel malaria treatment, and the investigation of peptidyl-prolyl *cis*/*trans* isomerases may offer new insight.

Peptidyl-prolyl *cis*/*trans* isomerases (PPIases) are a powerful enzyme superfamily capable of the rapid interconversion of *cis* and *trans* amide bonds in proteins and peptides [12–14]. Although this group of enzymes was believed to be the only biocatalyst whose

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sole purpose is the *cis*/*trans* interconversion of peptide bonds, new discoveries show that PPIases are also involved in such cellular processes as apoptosis or protein synthesis. These enzymes are present in many forms of life, ranging from bacteria to mammals. They are also found in all intracellular compartments and are not tissue specific. Without the help from PPIase activity, proteins would fold improperly, take too long to fold, or never fold at all.

Fk506-binding proteins (FKBPs) are the largest and most varied of the PPIases [12–14]. Containing between 107 and 580 amino acids, they can contain between one and four domains with isomerase activity. Every FKBP has a FKBP12 binding domain, which is homologous to FKBP12 found in the human body (*h*FKBP12). This well-known domain is made from a five-strand β-sheet with an alpha helix that forms the binding site for Fk506 (tacrolimus) and rapamycin. Tacrolimus is a small molecule that binds reversibly to FKBPs and inhibits isomerase activity. The mechanism by which *h*FKBP12 isomerizes proline residues in peptide chains has now been determined [15–18].

The FKBP of particular interest to this work is FKBP35, commonly found in *P. vivax* and *P. falciparum* (*Pv*FKBP35 and *Pf*FKBP35, respectively). Due to the increasing anti-malarial resistance in these species in particular, FKBP inhibition is a novel concept for this issue: if the FKBPs can be inhibited and prevented from performing their isomerase activity, essential malarial proteins would not fold properly and the parasite would cease normal function and die. An important issue with this approach is: if the drugs inhibit FKBP35, what prevents them from inhibiting *human* FKBPs as well? It has recently been suggested that the *h*FKBP12 domain present in all FKBPs is noticeably absent from FKBP35 (Fig. 1) [19,20]. His_{87} and Ile_{90} present in *h*FKBP12 are replaced by cysteine and serine in *Plasmodium* FKBP35 active site (Cys_{106}/Ser_{109} and Cys_{105}/Ser_{108} in *Pf*FKBP35 and *Pv*FKBP35, respectively). This implies that one active site could be selectively inhibited, while leaving the other unaffected. The next step in this process would be to determine how different substrates interact in each active site and comparing these results using docking methods.

2. Docking studies

The emphasis of this work is, ultimately, to find the ideal drug candidate that will irreversibly inhibit *Pv*FKBP35 and *Pf*FKBP35 enzymes while having little affect on the *h*FKBP12 enzyme. This can be explored through the implementation of docking studies.

Docking studies allow the comparison between different substrates binding into the active site of a given enzyme. Using these methods, a variety of known available substrates (Fig. 2) can be docked into the active site of *Pv*FKBP35, *Pf*FKBP35, and *h*FKBP12 (PDB code: 3IHZ, 2VN1, 1FKJ, respectively) [20–22]. For additional completeness, the substrates were also docked into the active site of *h*FKBP12 with bound FKBP-rapamycin-associated protein (FRAP, PDB code: 1FAP) [23]. These active sites with bound natural substrates are outlined in Fig. 1. This enzyme was included as these substrates would be expected to bind favourably into this active site as well as the active sites discussed previously. This additional enzyme complex has been included to verify docking methods: rapamycin and its derivatives would be expected to bind more favourably to the Fk506-binding domain and FRAP (FKBD + FRAP) than FKBP alone, and this should be reflected in the docking scores.

For the best results, a particular substrate would give a very large negative (strongly binding) score when docked to parasitic enzymes with a non-binding or weakly-binding (large positive) score when docked to human enzymes. This would suggest a substrate could selectively inhibit *Pf*FKBP35 and *Pv*FKBP35 and could be used as a starting point for drug discovery while having little effect on the human isomerases. The substrates used for docking to the active sites are shown below, as several of these compounds have shown inhibitory responses to differing isomerases and are derivatives of previously synthesized drug candidates [20]. The goal of this study is to discover a substrate that binds very strongly with *Pv*FKBP35 or *Pf*FKBP35 while having very little or no binding affinity for the active site of *h*FKBP12. This work could be used to find exploitable differences in the protein active sites to be used in further drug development.

Comparisons of binding scores of ligands between different proteins happen very little in the described work. Much of the work described is the comparison of qualitative docking scores of ligands within certain proteins, which has been shown to be acceptable [24–26]. This work does not attempt to compare binding scores of specific ligands across proteins. The only comparisons between proteins are overall qualitative trends (i.e. Fk506 and its derivatives bind stronger than rapamycin and its derivatives, etc.), stating that changes in binding affinity of ligands within proteins is consistent across all proteins used. In this work, we are concerned with the overall qualitative trend, not with the absolute binding score.

3. Computational methods

All substrates outlined in Fig. 2 were docked into the active sites of *h*FKBP12, *h*FKBP12 binding domain and bound FRAP (FKBD + FRAP), *Pv*FKBP35 and *Pf*FKBP35 (Fig. 1, PDB codes: 1FKJ, 1FAP, 3IHZ, and 2VN1, respectively) [20–23]. The active site was defined in all enzyme systems as the residues directly interacting with the bound Fk506 substrate. This gives the docked substrates a very small active site volume, and allows for very fast docking into the chosen active site.

All molecular docking calculations were performed with the FRED receptor software developed by OpenEye Scientific [27]. The scoring function used for the FRED receptor software was Chemgauss3, also developed by OpenEye Scientific [28,29]. The FRED receptor program has been shown to be a reliable docking method for quickly binding various substrates into different enzymes [24,30]. The ChemGauss3 scoring function can accurately predict binding modes and qualitatively predict binding strength for competing substrates [28,29]. This scoring function is used as a simplified protein–ligand binding energy which has been shown to be a reasonable approximation to experiment [29,30].

A high quality potential was generated for the active site for all three enzymes in the docking study. All substrates were built using Fk506 and rapamycin as a template with functional group changes performed using the Avogadro graphical interface [31]. Although all substrates are rigid macrocycles, all rotatable bonds were allowed to optimize with respect to the active site. All amino acids near the active sites were 'tweaked' to maximize hydrogen bonding potential. When residues are 'tweaked, this allows all rotatable bonds (alcohols, thiols, etc.) to change their geometry to optimize available hydrogen bonds between active site and docked substrate. All crystallographic waters were included as part of the protein. This docking method has been used previously with considerable success [24,28,30,32].

4. Results and discussion

The results of the docking study are tabulated in Table 1. Comparatively, more negative scores indicate more stabilizing forces and better binding. It is noted that while these values are likely not quantitatively accurate they likely provide a correct qualitative ordering of the ligands tested. Some important comparisons can be made between substrates.

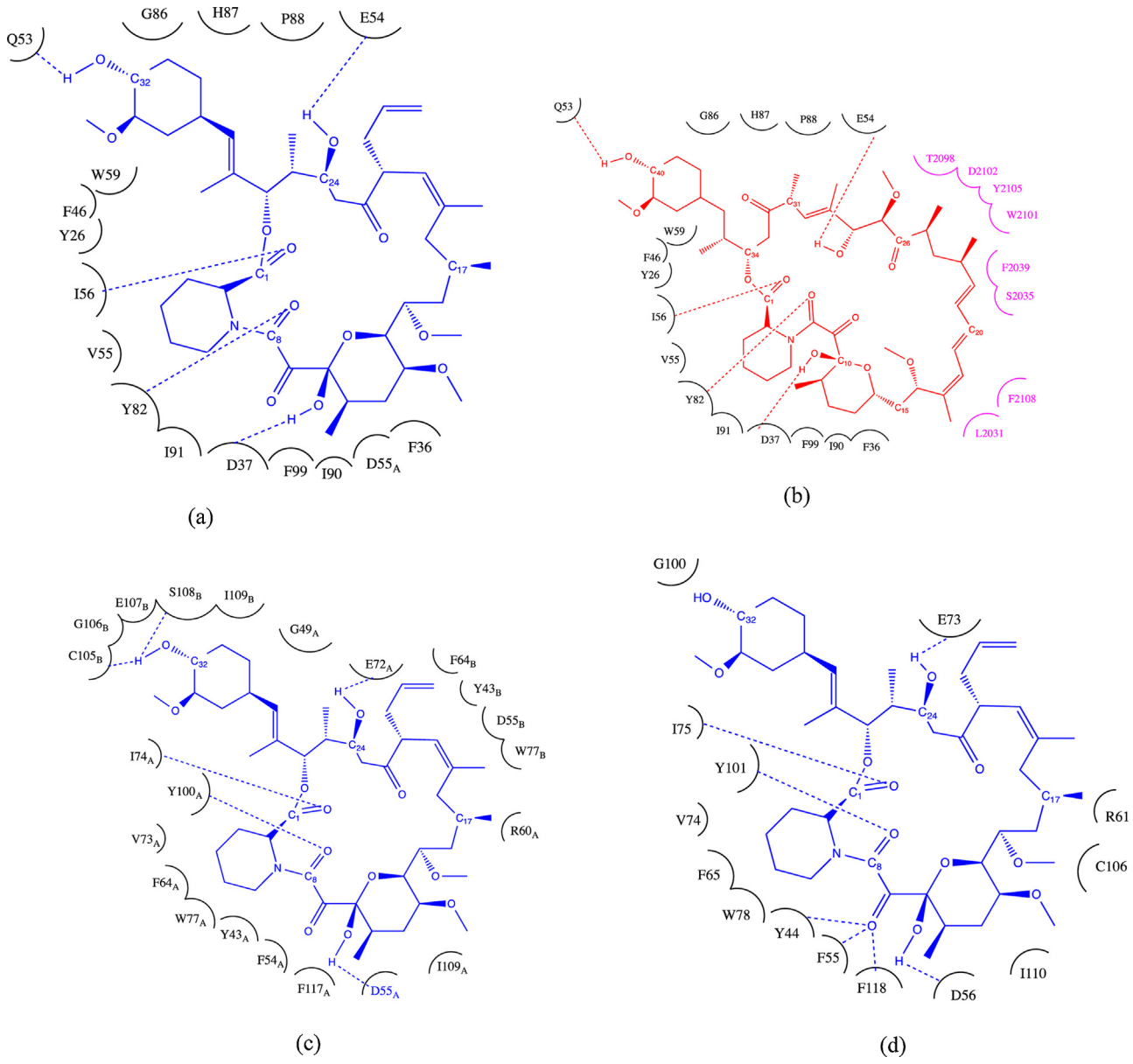

Fig. 1. Active site illustrations for (a) *h*FKBP12, (b) *h*FKBP12 + FRAP, (c) *Pv*FKBP35, and (d) *Pf*FKBP35. All active sites have bound Fk506 (blue) or rapamycin (red). Active site residues are outlined around the substrate. Purple residues represent the FRAP complex interacting with rapamycin. Residues without hashed lines represent nonpolar contact residues and hashed lines represent hydrogen bonding residues. Residues marked with "A" or "B" belong to the "A" or "B" peptide chain. These active sites were used as receptors for the docking of various macrocycles. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1. *Docking study for* h*FKBP12*

As seen in Table 1, the substrates that bind strongest in the Fk506-binding domain (FKBD) of *h*FKBP12 are Fk506 and its derivatives. All derivatives have similar docking scores, while Fk506 is given the best score. This implies that the deviations made to Fk506 are less favourable for inhibition than the original substrate. Identical binding scores of −24.32 are given for Fk520 and 18-OH-Fk520. For 13-dM(Me)-Fk520 and 13-dM(Me)-18-OH-Fk520, both have binding scores of −24.74. The marginal differences in binding score imply that the addition of an alcohol group at carbon 18 or the presence of a vinyl group at carbon 21 does not provide a significant improvement for inhibition.

Rapamycin and its derivatives bind less favourably than Fk506, as to be expected. ILS-920 and WYE-592 have identical binding scores of 34.24, which would imply that the change from alkane to alkene would have no effect on inhibition; however, it is important to remember that the Chemgauss3 scoring function only takes into account heavy atoms (except in the cases for hydrogen bond donor/acceptor). This means there is little difference for docking for an sp^3 or sp^2 carbon. For this same reason, identical scores are given to desmethoxyrapamycin and 40-Sub-1,2,3,4-tetrahydrorapamycin (−3.17). Lastly, rapamycin and WAY-179639 have identical scores (−19.3), suggesting the addition of an epoxide has little effect on inhibition. The trends for substrates with identical scores are mirrored for all enzymes used in the docking study.

4.2. *Docking study for* h*FKBP12 + FRAP*

Rapamycin and Fk506 are both immunosuppressive drugs that can bind to FKBP12 and inhibit its PPIase activity. The

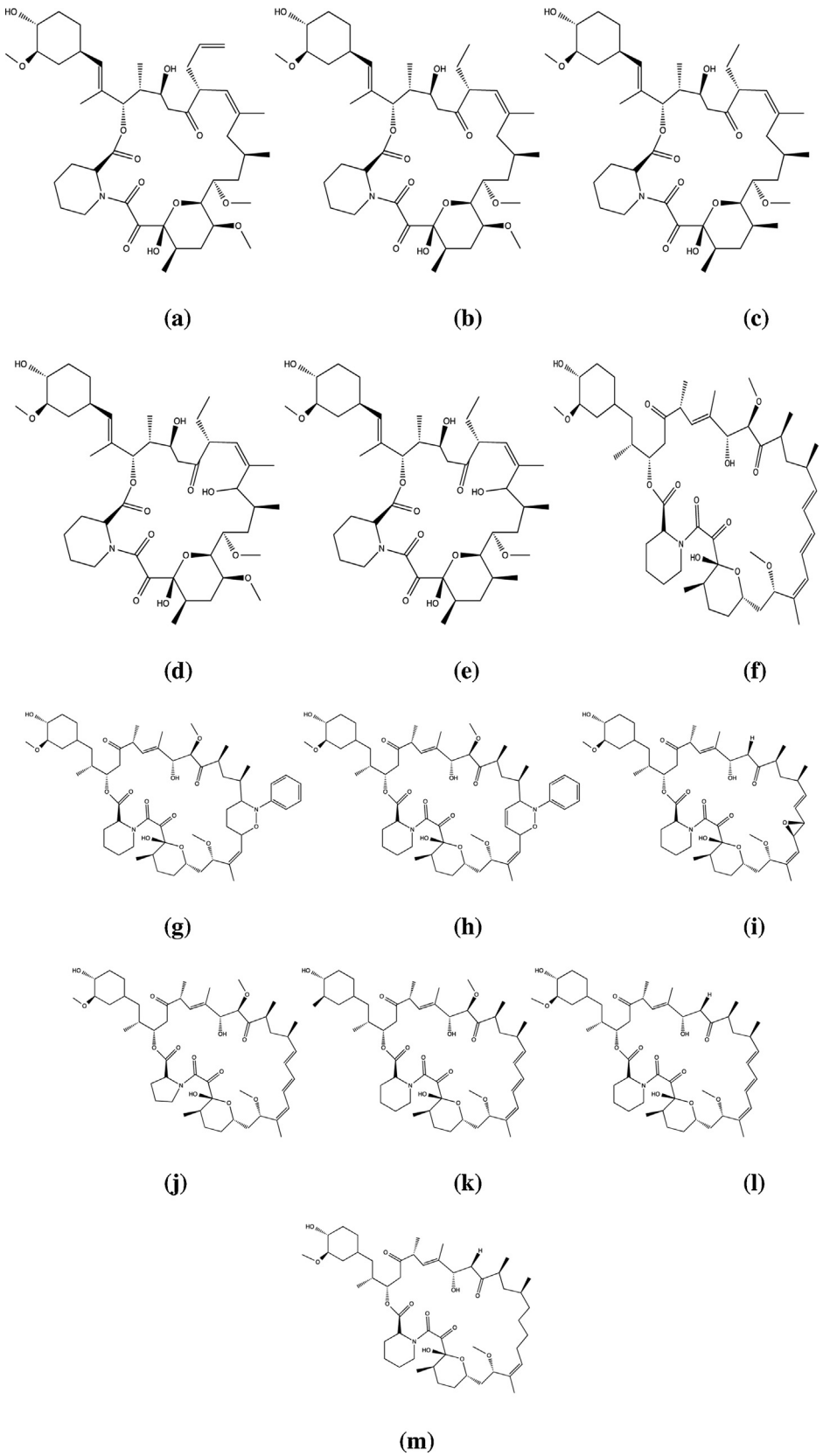

Fig. 2. Substrates used in docking study: (a) Fk506, (b) Fk520, (c) 13-dM(Me)-Fk520, (d) 18-OH-Fk520, (e) 13-dM(Me)-18-OH-Fk520, (f) rapamycin, (g) ILS-920, (h) WYE-592, (i) WAY-179639, (j) prolylrapamycin, (k) desmethylrapamycin, (l) desmethoxyrapamycin, (m) 40-Sub-1,2,3,4-tetrahydrorapamycin. These substrates were docked into the active sites of *h*FKBP12, *h*FKBP12 + FRAP, *Pv*FKBP35 and *Pf*FKBP35 and the docking scores compared.

Table 1
Results obtained from docking study of various substrates into the Fk506-binding domain (FKBD) of *h*FKBP12, *Pv*FKBP35, *Pf*FKBP35, as well as the binding domain of *h*FKBP12 with the FKBP12-rapamycin-associated protein (FRAP). A strong interaction between substrate and receptor is shown with a large negative docking score while weakly or non-interacting substrates will have a positive docking score.

Substrate	*h*FKBP12		*Pv*FKBP35	*Pf*FKBP35
	FKBD	FKBD + FRAP	FKBD	FKBD
Fk506	−25.21	−87.53	−110.06	−103.41
Fk520	−24.32	−89.07	−104.56	−102.37
13-dM(Me)-Fk520	−24.74	−91.97	−110.93	−100.65
18-OH-FK520	−24.32	−89.07	−104.56	−102.37
13-dM(Me)-18-OH-Fk520	−24.74	−91.97	−110.93	−100.65
Rapamycin	−1.93	−150.17	−33.24	−33.64
ILS-920	34.24	−120.09	−67.28	−10.74
WYE-592	34.24	−120.09	−67.28	−10.74
WAY-179639	−1.93	−150.17	−33.24	−33.64
Prolylrapamycin	−3.11	−148.29	−24.73	−28.52
Desmethylrapamycin	−4.16	−153.67	−29.56	−32.93
Desmethoxyrapamycin	−3.17	−149.70	−31.61	−35.30
40-Sub-1,2,3,4-tetrahydrorapamycin	−3.17	−149.70	−31.61	−35.30

rapamycin-FKBP12 complex can bind with the FKBP12-rapamycin-associated protein (FRAP, PDB code: 1FAP) in humans. This will cause cell-cycle arrest. Rapamycin will bind into a hydrophobic binding pocket of both FKBP12 and FRAP, forming a dimer.

Rapamycin binds much more favourably with FKBD + FRAP than Fk506 (−150.17 compared to −87.53); this is expected, as it has been experimentally shown that the Fk506–FKBP12 complex will not bind FRAP. This is shown through the comparatively low docking score. The best substrate to bind and inhibit the FKBD + FRAP is desmethylrapamycin with a docking score of −153.67, suggesting that the substitution of a methyl group for the ether at carbon 41 improves binding affinity, and the addition of the bulky groups at carbon 19 lowers binding affinity, as with ILS-920 and WYE-592 (−120.09).

4.3. *Docking study for* Pv*FKBP35 and* Pf*FKBP35*

Docking all substrates into the active sites of *Pv*FKBP35 and *Pf*FKBP35 yields comparative results. In both enzymes, Fk506 and its derivatives have better scores than rapamycin and its derivatives, with Fk506 being the best inhibitor for both enzymes with a docking score of −110.06 and −103.41, respectively. One anomaly was found while docking ILS-920 and WYE-592 to both enzymes. The docking scores of ILS-920 and WYE-592 are far more favourable than rapamycin in *Pv*FKBP35 (−67.28 compared to −33.24), while the same substrates are far less favourable than rapamycin in *Pf*FKBP35 (−10.74 compared to −33.64). While these active sites are conserved, there is evidence to suggest that the *Pv*FKBP35 active site can favourably accommodate a bulky group at carbon 19 while this is detrimental for inhibition of *Pf*FKBP35.

5. Conclusions

Of particular interest is the difference in docking score for ILS-920 and WYE-592 in the *Plasmodium* FKBP35 enzymes. The current work suggests *Pf*FKBP35 cannot favourably accommodate a bulky group on carbon 19, while this addition seems to improve inhibition for *Pv*FKBP35. It is also important to note the change from rapamycin to ILS-920 or WYE-592 (the addition of a nitrosobenzylated moiety) in *h*FKBP12 results in a decrease in docking score. This would suggest the addition of a bulky moiety on carbon 19 could lead to novel inhibitors of *P. vivax* without negatively affecting the most common *Homo sapien* Fk506-binding protein binding domain. These results provide insight into the molecular interactions that in turn may be important for the development of anti-malaria drugs.

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