R.T.
UNIVERSITY OF DICLE
INSTITUTE OF NATURAL AND APPLIED SCIENCES

SCREENING OF ANGUCYCLINE ANTIBIOTICS AS POTENTIAL DRUG CANDIDATES AGAINST MRSA BY DOCKING ANALYSIS

Hazem Abbas Tofiq AL-BUSTANY

M.Sc. THESIS

DEPARTMENT OF BIOLOGY

DIYARBAKIR
January - 2016

T.C.
DİCLE ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ

ANGUSİKLİN ANTİBİYOTİKLERİN DOKİNG ANALİZLERİ YARDIMIYLA MRSA'YA KARŞI POTANSİYEL İLAÇ ADAYI OLARAK TARANMASI

Hazem Abbas Tofiq AL-BUSTANY

YÜKSEK LİSANS TEZİ

BİYOLOJİ ANABİLİM DALI

DİYARBAKIR
Ocak – 2016

APPROVAL OF THE THESIS

UNIVERSITY OF DICLE

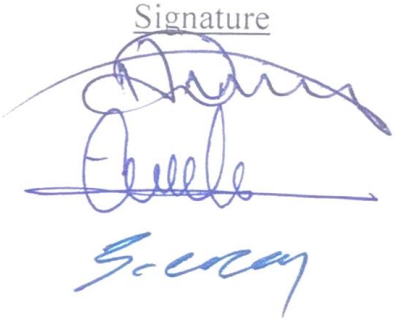
INSTITUTE OF NATURAL AND APPLIED SCIENCES

DIYARBAKIR

Screening of Angucycline Antibiotics as Potential Drug Candidates Against MRSA by Docking Analysis, Submitted by **Hazem Abbas Tofiq AL-BUSTANY** in partial fulfillment of the requirements for the degree of Master of Science in Biology/Molecular Biology.

Examination Committee:

Title	Name & Surname	Signature
Chairman	: Prof. Dr. Hasan Ç. ÖZEN	
Member (Supervisor)	: Prof. Dr. Ebru İNCE	
Member	: Yrd. Doç. Dr. Selami ERCAN	



Date of Thesis Defense: 15/01/2016

I approve accuracy of the above information.

Assoc. Prof. Dr. Mehmet YILDIRIM

MANAGER OF THE INSTITUTE

ACKNOWLEDGEMENT

I want to express my gratitude to my supervisor Prof. Dr. Ebru İNCE and co-supervisor Prof. Dr. Necmettin PİRİNÇÇİOĞLU, for their enthusiasm, inspiration and great efforts to explain things clearly and simply, in addition to their scientific advice throughout my study courses. For me this is completely new and challenge topic 'Computer Aided Drug Design' that my co-supervisor gave a step-by-step guidance and brought me most bioinformatics knowledge.

I am especially grateful to Prof. Dr. Murat KIZIL for scientific lectures in 'Medicinal Chemistry' throughout my study courses.

I am grateful for University of Dicle and the head of Biology Department Prof. Dr. A. Selçuk ERTEKİN that gives me an opportunity to continue my higher education here and such a chance to contribute a little improvement in related area.

Special thanks are extended to all friends specially Dr. Süleyman ÖZAKIN, Ekrem KUM & Hayrettin DİNÇ, for their help and support.

My deepest gratitude goes to my family for their assistance and encouragement throughout the period of study.

Finally my great thanks to all which they helped me in anyway.

Hazem Al-Bustany

CONTENTS

	Page
Acknowledgement ……..……...	I
Contents ……..……...	II
Abstract in Turkish (OZET) ……..……	IV
Abstract ……..……..…...	V
List of Tables ……..……..….	VI
List of Figures ……..…….	VII
List of Appendix ……..……	IX
Abbreviations ……...	X
1. INTRODUCTION ….…….	1
2. LITERATURE REVIEW ……	5
2.1. Current Status of MRSA ……...	5
2.2. Treatment approaches for MRSA …….	7
2.3. Targeted pathway …….	9
2.4. Secondary Metabolites …….	11
2.4.1. Function and Importance of Secondary Metabolites …….	12
2.4.2. Genetic of Secondary Metabolites …….	14
2.5. Angucycline Compounds …….	15
2.6. Actinomycetes, especially genus streptomyces (Angucyline producers) ……	17
2.7. Protein (Receptor) Structure & Function ……..	19
2.7.1. Introduction to Proteins …….	19
2.7.2. Protein Structure ……	21
2.7.3. Protein Data Bank ……..	22
2.8. Ligands …….	23
2.9. Protein-Ligand Interaction ……	23
2.9.1. Non-covalent binding ……..……	24
2.9.2. Electrostatic Interaction …….	24
2.9.3. Hydrophobic Interaction ……	25
2.9.4. Binding Affinity and Binding Site ……..…	26
2.9.5. Affinity prediction problem ……	27

2.10. Molecular Docking …….. **27**

2.10.1. AutoDock Vina ……. **28**

3. MATERIALS AND METHODS ……..……... **31**

4. RESULTS AND DISCUSSION ……..…… **39**

5. CONCLUSION ……..…….. **65**

6. REFERENCES …… **67**

APPENDIX I ……..……... **75**

APPENDIX II ……... **90**

APPENDIX III ……. **105**

APPENDIX IV ……..……... **119**

ÖZET

ANGUSİKLİN ANTİBİYOTİKLERİN DOKİNG ANALİZLERİ YARDIMIYLA MRSA'YA KARŞI POTANSİYEL İLAÇ ADAYI OLARAK TARANMASI

YÜKSEK LİSANS TEZİ

Hazem Abbas Tofiq AL-BUSTANY

DİCLE ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ
ANABİLİM DALI

2016

Metisilin-dirençli *Staphylococcus aureus* (MRSA), ağırlıklı hastane enfeksiyonlarından kaynak alan önemli bir patojendir. β-laktamlar, aminoglikozitler ve kinolonlar gibi farklı antibiyotiklere direnç geliştirmişlerdir. Bundan dolayı, MRSA enfeksiyonlarına karşı, bunların virulans faktörlerini hedef alan yeni ilaçların keşfine büyük ihtiyaç vardır. Stafiloksantin MRSA'nın bir virulans faktörü olup, bu pigmentin biyosentezinin ilk aşaması dehidroskualen sentaz (CrtM) enzimi tarafından sentezlenmektedir. Bu sebeple, CrtM, virulansı zayıflatmak suretiyle MRSA'ya karşı kullanılabilecek potansiyel bir hedef olabilir. Aktinomisetler; Gram-pozitif, filamentli bakteriler olup, farklı biyolojik aktivitelere sahip sekonder metabolitleri yüksek kapasitede üretirler. Bunlar arasında, polisiklik aromatik bileşikler olan ve tip-II poliketid sentazlar tarafından sentezlenen angusiklin antibiyotikler geniş bir yer kaplamaktadır. Bu çalışma, aktinomisetler tarafından üretilen 157 angusiklin bileşiğinin, AutoDock Vina programı kullanılarak, MRSA CrtM enzimi (PBD ID: 3ACW and 3W7F) üzerine inhibisyon etkisinin değerlendirilmesini kapsamaktadır. Doking analizleri sonucunda, incelenen bileşikler içerisinde; Moromycin A (56), Saquayamycin B (58), Saquayamycin A (145) ve Saprolmycin E (29) bileşiklerinin, enzimin substratı olan farnesyl diphosphate (doking skoru -8.3 kcal/mol) ile kıyaslandığında, CrtM ile iyi etkileşim göstererek, sırasıyla; -14.8, -14.4, -13.7 ve -13.7 kcal/mol gibi yüksek doking skorlarına sahip olduğu tespit edildi. Bununla beraber, kesin sonuçların elde edilmesi için moleküler dinamik simülasyonları ve in vitro deneylerin yapılması gerekmektedir..

Anahtar Kelimeler : Aktinomisetler, Angusiklin Antibiyotikler, MRSA, Stafiloksantin, CrtM, Moleküler Docking, AutoDock Vina.

ABSTRACT

SCREENING OF ANGUCYCLINE ANTIBIOTICS AS POTENTIAL DRUG CANDIDATES AGAINST MRSA BY DOCKING ANALYSIS

M.Sc. THESIS

Hazem Abbas Tofiq AL-BUSTANY

DEPARTMENT OF BIOLOGY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
UNIVERSITY OF DICLE

2016

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the major pathogens, mainly caused by hospital infections. It has also developed resistance to various antibiotics such as β-lactams, aminoglycosides, and quinolones. Therefore, it is necessary to discover new drugs against MRSA infections by targeting their virulent factors. It is through that staphyloxanthin is a virulent factor of MRSA as dehydrosqualene synthase (CrtM) involves in the first step of its biosynthesis. For this reason, the CrtM enzyme is a potential target against MRSA by weakening its virulence. Actinomycetes are Gram-positive, filamentous, bacteria known for their significant capacity for the production of secondary metabolites with diverse biological activities. Among these, the polycyclic aromatic compounds which are known as angucycline antibiotics are the largest group of type-II polyketide synthase. The present study involves the evaluation of the inhibitory activity of 157 actinomycete-produced angucyline compounds against MRSA CrtM enzyme (PBD ID: 3ACW and 3W7F) by docking studies. Docking analysis demonstrate that among the attempted compounds; Moromycin A (56), Saquayamycin B (58), Saquayamycin A (145) and Saprolmycin E (29) have good interactions with CrtM with higher dock scores;-14.8, -14.4, -13.7, and -13.7 kcal/mol, respectively, when compared with substrate farnesyl diphosphate (-8.3 kcal/mol) and one of current inhibitors BPH-651 (-11.5 kcal/mol). However further studies, molecular dynamic simulations and in vitro investigations are required to achieve a conclusion.

Key Words: Actinomycetes, Angucycline Antibiotics, MRSA, Staphyloxanthin, CrtM, Molecular Docking, AutoDock Vina.

LIST OF TABLES

Table No.	Description	Page
Table 3.1.	Angucycline Groups Antibiotics and their references ……..…..	**31**
Table 4.1.	Average and maximum dock scores of ligands docked to CrtM (3ACW) ……	**44**
Table 4.2.	Average of three dock score with maximum dock score of ligands docked to (3W7F) protein with MG …….……...	**48**
Table 4.3.	Average of three dock score with maximum dock score of ligands docked to (3W7F) protein without MG. ……..	**56**

LIST OF FIGURES

Figure No.	Description	Page
Figure 2.1.	Biosynthetic pathways. Staphyloxanthin biosynthesis in S. aureus …….....	**10**
Figure 2.2.	Tetrangomycin structure ……...	**16**
Figure 2.3.	The planar peptide group ……..	**22**
Figure 2.4.	Major types of non-bonded interactions in protein-ligand complexes …….	**25**
Figure 2.5.	Aryl-aryl interactions in protein structure and protein-ligand complexes. A. Edge-to-face geometry, B. Parallel stacking geometry …….	**26**
Figure 4.1.	Superimpose structure of docked inhibitor with its original BPH-651 coordinates in the complex with CrtM ……..	**39**
Figure 4.2.	Superimpose structure of docked substrate with its original farnesyl diphosphate coordinates in the complex with CrtM ……	**40**
Figure 4.3.	Superimpose structure of docked inhibitor BPH-830 with original farnesyl diphosphate coordinates in the complex with CrtM ……...	**41**
Figure 4.4.	Sructures of (a) The tetracyclic benz[a]anthracene frame; (b) Moromycin A (56); (c) Saquayamycin B (58); (d) Saquayamycin A (145); and (e) Saprolmycin E (29) ……...	**42**
Figure 4.5.	Group 1 ligands (28, 29, 155) docked to (3ACW) protein ……..	**45**
Figure 4.6.	Group 2 ligands (47, 49, 84, 88, 102) docked to (3ACW) protein ……..	**45**
Figure 4.7.	Group 3 ligands (92, 93, 95, 98) docked to (3ACW) protein ……..	**46**
Figure 4.8.	Group 4 ligands (37, 94) docked to (3ACW) protein ……..	**46**
Figure 4.9.	Group 5 ligands (11, 54, 115, 118, 119) docked to (3ACW) protein ……...	**47**
Figure 4.10.	Group 6 ligands (33, 40, 87, 133, 154) docked to (3ACW) protein …….	**47**
Figure 4.11.	Group 1 ligands (2, 13, 59, 98) docked to (3W7F) protein with MG. ……..	**50**
Figure 4.12.	Group 2 ligands (19, 28, 29, 30, 38) docked to (3W7F) protein with MG. ……..	**51**
Figure 4.13.	Group 3 ligands (41, 42, 69, 124) docked to (3W7F) protein with MG. …….	**51**
Figure 4.14.	Group 4 ligands (47, 49, 56, 58) docked to (3W7F) protein with MG. ……	**52**
Figure 4.15.	Group 5 ligands (65, 93, 123, 124, 134) docked to (3W7F) protein with MG.	**52**
Figure 4.16.	Group 6 ligands (84, 92, 145, 146, 147, 148, 151) docked to (3W7F) protein with MG. …….	**53**

Figure 4.17. Group 7 ligands (6, 7, 11, 80, 81, 102, 116, 119, 120) docked to (3W7F) protein with MG. ……. **53**

Figure 4.18. Group 8 ligands (31, 32, 33, 51, 62, 137) docked to (3W7F) protein with MG. .. **54**

Figure 4.19. Group 9 ligands (55, 107, 108, 109, 110) docked to (3W7F) protein with MG. .. **54**

Figure 4.20. Group 10 ligands (4, 34, 136, 154) docked to (3W7F) protein with MG. …… **55**

Figure 4.21. Group 11 ligands (86, 111, 115, 118) docked to (3W7F) protein with MG. …… **55**

Figure 4.22. Group 1 ligands (28, 29, 94, 141) docked to (3W7F) protein without MG. ……. **58**

Figure 4.23. Group 2 ligands (38, 56, 134, 146, 147, 148, 151, 155) docked to (3W7F) protein without MG. ……. **58**

Figure 4.24. Group 3 ligands (46, 47, 49) docked to (3W7F) protein without MG. ……. **59**

Figure 4.25. Group 4 ligands (143_PI_085, 144_PI_087) docked to (3W7F) protein without MG. …….……. **59**

Figure 4.26. Group 5 ligands (34, 42) docked to (3W7F) protein without MG. …….. **60**

Figure 4.27. Group 6 ligands (6, 7, 11, 80, 81, 88, 116, 119, 120) docked to (3W7F) protein without MG. ……. **60**

Figure 4.28. Group 7 ligands (31, 32, 33, 51, 62, 82) docked to (3W7F) protein without MG. **61**

Figure 4.29. Group 8 ligands (107, 108, 109, 110) docked to (3W7F) protein without MG…. **61**

Figure 4.30. Group 9 ligands (111, 115, 118) docked to (3W7F) protein without MG…...….. **62**

Figure 4.31. Group 10 ligands (137, 156, 157) docked to(3W7F) protein without MG…...…. **62**

LIST OF APPENDIX

Appendix No.	Description	Page
APPENDIX I	Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) …….……...	**75**
APPENDIX II	Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) ……..……...	**90**
APPENDIX III	Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) …….	**105**
APPENDIX IV	The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins …….....	**119**

ABBREVIATION

2D	: Two-Dimention
3D	: Three-Dimention
A°	: Angstrom
Ala	: Alanine
Arg	: Arginine
Asn	: Asparagine
Asp	: Aspartic Acid
AV.	: Average
CrtM	: Dehydrosqualine Synthase Enzyme
Cys	: Cysteine
Gln	: Glutamine
Glu	: Glutamic Acid
Gly	: Glycine
His	: Histidine
Ile	: Isoleucine
ITC	: Isothermal Titration Calorimetry
Leu	: Leucine
Lys	: Lysine
Max.	: Maximum
Met	: Methionine
MG.	: Magnesium
MGL Tools	: Molecular Graphics Laboratory Tools
MRSA	: Methicillin Resistant *Staphylococcus aureus*
MSSA	: Methicillin Sensitive *Staphylococcus aureus*
ORSA	: Oxacillin Resistant *Staphylococcus aureus*

PDB : Protein Data Bank

PDBQT : Protein Data Bank, Partial Charge (Q), & Atom Type (T)

Phe : Phenylalanine

Pro : Proline

QSAR : Quantitative Structural Activity Relationship

RMSD : Root Mean Square Deviation

S. aureus : *Staphylococcus aureus*

Ser : Serine

TCSs : Two-component Systems

T.B. : Tuberculosis

Thr : Threonine

Trp : Tryptophan

Tyr : Tyrosine

Val : Valine

1. INTRODUCTION

The discovery of penicillin in the 1940s revolt the fight against bacterial colony mainly *Staphylococcus aureus* infections. Shortly after its introduction isolates of penicillin-resistant *Staphylococcus aureus* were identified. Methicillin was first used in 1959 to treat these penicillin-resistant strains of *S. aureus* (Wilkinson 2010), and methicillin-resistant *S. aureus* (MRSA) were reported in the early 1960's first and are now viewed as a major hospital acquired pathogen worldwide (Batabyal *et al.* 2012). This infection is especially troublesome in hospitals, prisons and nursing homes, where patients with open wounds, invasive devices, and weakened immune systems are at greater risk of infection compared with the general public (Batabyal *et al.* 2012).

The swift rise of antimicrobial resistance among pathogens has led to a renewed interest to search for novel antimicrobial agents. The history of new drug discovery processes shows that novel skeletons have, in the majority of cases come from natural sources. They have been the source of, or inspiration for the development of chemical entities introduced as pharmaceutical. The evolution of microbial natural product collections and expansion of high-throughput screening methods have brought over researchers to use the natural product libraries in drug discoveries. Actinomycetes continue to be a productive and successful focus for natural products research, with many novel compounds with prominent pharmacological valuable (Adegboye and Babalola 2013).

Microbial natural products nowadays are the origin of most of the antibiotics in the market. There is an alarming scarcity of new antibiotics currently under development in the pharmaceutical industry. Microbial natural products still remain the most promising source of novel antibiotics, although new methods are required to improve the efficiency of the discovery process (Singh *et al.* 2014). The golden carotenoid pigment staphyloxanthin by *S. aureus* acts as a virulence factor, mainly by acting as a bacterial antioxidant which helps to the microbe avoid the reactive oxygen species which the host immune system uses to kill pathogens (Liu et al. 2008).

1. INTRODUCTION

In earlier times, secondary metabolites were defined as substances with a low molecular weight, which were not products of the primary metabolic pathway of the producing organism. As a matter of fact, it was thought that these products did not have a roll in the microbial primary functions or growth. Therefore, it was thought that production of secondary metabolites did not represent any advantage for the producing microorganism (Tabarez 2005).

Nowadays it is considered that cell investment in secondary metabolite production is almost the confirmation of a function that should give the organisms certain advantage against other members of the microbial community. In fact, secondary metabolites are accepted to be essential for the producing cell as inhibitors of other organisms that compete for the same food supply or as regulators of cellular differentiation processes. In addition, it is reported that they are indeed products of biosynthetic pathways, which have evolved to give these types of advantages (Tabarez 2005).

Actinomycetes are enthralling resource among microorganisms due to their capability to produce novel bioactive secondary metabolites with antimicrobial activities. They have proven to be effective antimicrobial agents, especially against pathogenic organisms (Adegboye and Babalola 2013). In 1940, Selman A. Waksman isolated an effective T.B. antibiotic, actinomycin and for this he got success in 1944, with the discovery of spectromycin (Demain 1998). Scientists have discovered that actinomycetes have an enormous potential to produce valuable natural products (Raczkowski 2010). Hence, they produce useful secondary metabolites of high commercial value and continue to be routinely screened for new bioactive compounds. These searches have reaches a success and approximately they provide two thirds of naturally occurring antibiotics, including many of medical importance, mainly producing over 70 % of the natural product scaffolds found in clinically used anti-infective agents (Bhat *et al.* 2013), (Gomez-Escribano *et al.* 2015). Consequently they remain essential source of new chemical diversity and main part of drug discovery. Their ingenuity and immense industrial value is extremely noteworthy (Adegboye and Babalola 2013).

There are a long time consuming and costly way in drug discovery process, computational methods attempts have been made to increase the efficiency of random screening to select a typical subset of compounds from a compound collection. This usually entails grouping (clustering) compounds with similar structure, and then choosing a few members from each cluster for screening (Silverman and Holladay 2014). Computational approaches have successfully been applied to narrow the time and cost involved in the process, with the quick increase in computational power, *in silico* methods became commonly used in the fields of structural molecular biology and structure-based drug design. Molecular docking is one of these computational techniques (Ryska 2011). Molecular docking is a computer-based, high-throughput screening method for identifying compounds of a certain structure or size (Ascencio 2010), Molecular docking may be defined as a problem of lock-and-key, where one is interested in finding the suitable orientation of a key (ligand) that will open the lock (protein) (Ryska 2011).

Knowledge about one or more known ligands or about the structure of the target itself may be used to narrow a large screening collection to a smaller set of compounds that may be more likely to hit the target. Virtual screening is the most common computational method for selection of the compounds, which involves the rapid *in silico* (by computer) assessment of large libraries of chemical structures to identify those structures that most likely bind to a drug target, such as enzyme or protein receptor. The goal is to identify new scaffolds, chiefly ones that may be in the existing collection. In computer-based analysis two components are needed: (1) a database of structures in a form that can be computationally analyzed for structural attributes and (2) a hypothesis or model of the structural attributes that are important for activity, for example, the hypothesis that structural similarities to a known active ligand should yield similarly active compounds or a hypothesis of the shape and charge density of a binding pocket that defines what features a complementary ligand structure should have (Silverman and Holladay 2014).

Furthermore, one of main tools for virtual screening procedures is docking, where a library of several compounds is “docked” against one drug target and returns the best hit. The procedure of virtual screening through docking has become essential when it is needed to test a database of thousands (or even millions) of compounds

against one or more targets in a short period of time. This search would be impossible to be reproduced experimentally at a so small economic and time cost. For this reason docking has been found to be a beneficial step in Quantitative Structural Activity Relationship (QSAR) studies, where statistical analysis is applied to thousands of drug candidates (Novotarskyi, 2013).

Docking method predicts favored orientation of one molecule to the second when they bind to form a stable complex. In the field of drug design, first molecule is usually protein (macromolecule) and the second one is ligand (small organic molecule) which is potential drug candidate. Information of favored orientation of ligand and protein can be used to predict binding affinity, and this discriminating high-affinity drug candidate from the low-affinity compounds (Ryska 2011).

Usually scoring function used in docking programs in order to recreate the chemical potentials which predict the conformation of binding. Need superficial physics-based (Coulombs energy and van der Waals forces) experimentally weighted to account for the difference in energy and free energy. Usually protein (receptor) have to be prepared by adding hydrogens and charges select site and eliminate of water and cofactors included (Pétursson 2014). Improvements in structure determination methods along with quick advances in molecular visualization tools have led to the rise of structure-aided drug design or rational drug design as an integral part of the drug discovery and development process (Dias 2011). Using of computer based analysis of molecular interaction for example protein-ligand binding becomes more necessary with the availability and expanding of molecular biological data. For this purpose, docking algorithms included a reasonably accurate model of energy and the flexibility of molecules (Pétursson 2014).

Moreover docking calculations simulate the interactions between the protein's binding site and the ligand, and these interactions give a qualitative score, and therefore the outcomes may be compared to those of biochemical assays (Tunca 2012). As a consequence, hundreds of thousands of compounds can be screened by using in silico methods. In addition these computer programs can generate the crystal structure and NMR solution structures of the target or related proteins, as well as calculating atomic homology models. Candidate drug-binding pockets can be identified as well (Ascencio 2010).

2. LITERATURE REVIEW

2.1. Current Status of MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram positive non-motile, non-facultative coccus whose infections in humans. Best environmental conditions for growth are temperatures between 15^{o}C and 45^{o}C. High concentrations of sodium chloride do not change the growth, even when concentrations reach up to 15% (Stuczen 2013). Consequently the universal occurrence of MRSA has become problem for public health (Howe *et al.* 2004), (Moghadam *et al.* 2015). It is also known as multidrug-resistant *S. aureus* and oxacillin-resistant *S. aureus* (ORSA). *S. aureus* was first identified in the late 19th century and has since been recognised as part of the natural flora of humans. It frequents the face, hands and perineum, with the most common site being the nares (nostril) (Stuczen 2013). *S. aureus* species developing, resistance to beta-lactam antibiotics are known as MRSA, they include the penicillins like methicillin, dicloxacillin, nafcillin, oxacillin, etc. and the cephalosporins (Batabyal *et al.* 2012), (Rashid *et al.* 2015). This organism is part of the natural microbiota of humans, from which clones of epidemic drug-resistant *S. aureus* have emerged (Hsu *et al.* 2015). MRSA is reported as the leading cause of wound infections in most parts of the world (Stuczen 2013). Hospital acquired infections and infections in the community (Onelum *et al.* 2015). Between 30% and 60% of the healthy population carry *S. aureus*, of which between 10% and 20% are chronically colonized (ongoing, persistent population of *S. aureus* on or in the body but in the absence of infection) (Stuczen 2013). The appearance and spread of bacterial pathogens that have become modified for existence in hospitals poses a major threat to global health systems (Hsu *et al.* 2015).

The high prevalence of MRSA colonization in diabetic foot ulcers is a consequence of antibiotic overuse and the selection of broad rather than narrow spectrum agents (Stuczen 2013).

There is another classification which known as methicillin-sensitive *S. aureus* or MSSA if the strain unable to resist these antibiotics. The development of such resistance does not cause more intrinsically virulent for the organism than strains of *S. aureus* that

have no antibiotic resistance, but resistance does make MRSA infection more difficult to treat with typical types of antibiotics and thus more dangerous (Batabyal *et al.* 2012). The glycopeptides, particularly vancomycin, have been the mainstays of therapy for MRSA, and the emergence of resistance to these agents is of great concern (Howe *et al.* 2004).

People not involved in health care backgrounds are often less aware of this silent and lethal epidemic. This lack of awareness lies in significance of hazard, perils of hospital acquired MRSA infection, and potential risk to overall health care system (Rashid *et al.* 2015). Healthy people may carry MRSA asymptomatically for long periods of time but patients with compromised immune system are at a significant greater risk of symptomatic infections (Onelum *et al.* 2015). A significant public behavioral alteration is needed in order to control this global risk as well as a well-informed public. (Rashid *et al.* 2015) The range of infections due to MRSA are manifold and are linked with worse outcome in addition to extended hospital stay, higher cost of treatment and increased mortality (Onelum *et al.* 2015).

The concept of "anti-infectious drugs" includes not only compounds that inhibit the growth of pathogenic microorganisms statically or kill them (so called chemotherapeutics or antibiotics) and vaccines but also compounds that control microbial adaptation/survival or pathogenicity, potentiate the activities of known antibiotics, or enhance the host immune system against microbial infection (Koyama *et al.* 2013). Production of β – lactamase enzyme in the affected area is the main cause of microbial resistance (Rashid *et al.* 2015). For example, β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam themselves show very weak or no antimicrobial (non-antibiotic) activity, but these compounds dramatically potentiate the antimicrobial activity of β-lactam antibiotics against β-lactamase-producing bacteria (Koyama *et al.* 2013). The choice of antibiotics as active treatment is reduced after the maturity of infection. Such methods are possibly show harmful side effects to the patient and expensive. Recent evidence supports that domestic animals like cat, dog and hen can transmit MRSA to their owners (Rashid *et al.* 2015).

In recent years, active anti-infectious compounds against MRSA have been widely searched for. Several compounds have been found to have new mechanisms of action against MRSA and are expected to be potential leads for the treatment of infection (Koyama *et al.* 2013). *S. aureus* is an extremely transmittable bacterial species found in the ecosystem. The microorganism invades the skin and enters deeper tissues. As in septicemia, it multiplies to cause a localized or systemic response (Rashid *et al.* 2015). MRSA produce a number of virulence factors which cause suppurative infections and toxinosis. Surface proteins allow bacterial attachment to the extracellular matrix of the host, specifically the proteins laminin and fibronectin, found in epithelial and endothelial tissue. Toxins produced by the bacteria damage host cell membranes and allow cell invasion. Alpha toxin is produced as a monomer that binds to the membrane of the susceptible cell. Sub-units then combine to form heptameric rings with a central pore, through which the cellular contents leak (Stuczen 2013). MRSA infections cause a huge number of deaths every year worldwide (Koyama *et al.* 2013). The patient becomes infected with the growth of its population. People who are weaker, older and sicker have weaker immune system and may get infected easily. It is also described that people may bring this infection without having any noticeable indications (Rashid *et al.* 2015).

2.2. Treatment approaches for MRSA

Microbiologists are observing an exponential growth in infectious human diseases through *S. aureus*, which is precisely known as Methicillin Sensitive *S. aureus* (MSSA). In this case, bacterial skin infections are because of the strains of Methicillin Resistant *S. aureus* (MRSA) (Rashid *et al.* 2015). According to drug bank only three antibiotics namely arbekacin, meticillin and linezolid, are approved for the treatment of MRSA. Drug targets are inadequate and there is an urgent need to find out the novel drug targets. Apart from drug target, there is also a need for good ligand preparation that would act as effective inhibitors to the novel targets without affecting human proteome. Any contaminated surfaces is the source of several kind of infections, MRSA is one of them (Balaji SR *et al.* 2014). As observed in the last decade the microbe has latency to severely resist antibiotics. The human race is facing significant morbidity caused by these lethal infections (Rashid *et al.* 2015).

Extermination (Eradication) or inhibition of staphylococcal colonization is still considered as main strategy to prevent infection and transmission of these strains. Basis behind such a strategy is that the most staphylococcal infections are caused by endogenous strains; so, existence of *S. aureus* is a major risk factor for consequent infections (Moghadam *et al.* 2015)

Increasing multiple resistances of *S. aureus* to antibiotics makes the development of new treatment routes for serious infections a matter of urgent concern (Kuroda *et al.* 2007).

MRSA is one of typical resistant strains, and research for its prevention and treatment was carried out. The idea (concept) that MRSA infection presents different signs for treatment and diagnoses of colonization is controversial, but the differential diagnosis between bacterial infection and bacterial colonization is essential to avoid unnecessary use of anti-MRSA drugs (Shigemura *et al.* 2013).

The last-resort antibiotic for the treatment of MRSA infections was vancomycin, but MRSA resistance to vancomycin has been reported too. This suggests that MRSA will likely obtain more resistance to vancomycin in the near future. Therefore, it is increasingly essential to discover new antibiotics or to devise new actions that are effective against MRSA infections (Koyama *et al.* 2013). As a consequence, clinicians across the world faced clinical challenge in controlling MRSA (Rashid *et al.* 2015).

The main component of the bacterial cell wall is peptidoglycan which is an attractive target for the development of anti-infectious agents. It forms a huge macromolecule that surrounds the cell as a single, flexible meshwork and is closely involved in cell division. The structure determines the cell shape and maintains cell integrity by protecting it against the high internal osmotic pressure. Important antibiotics have been clinically used including β-lactams and glycopeptides that target cell wall peptidoglycan synthesis (Koyama *et al.* 2013).

2.3. Targeted pathway

It is well known that MRSA produces a yellow pigment called staphyloxanthin (STX). Recently, several research groups described that STX is a virulent factor acting as an antioxidant, with its various conjugated double bonds enabling detoxification of host immune system-generated reactive oxygen species (Sakai *et al.* 2012). The first committed step in staphyloxanthin biosynthesis by *S. aureus* is dehydrosqualene synthase (CrtM) enzyme (Pelz *et al.* 2005), which catalyzes the condensation of two farnesyl diphosphates to produce the C30 species, presqualene diphosphate (Liu *et al.* 2008), (Song *et al.* 2008), which then undergoes skeletal rearrangement and further loss of diphosphate to produce dehydrosqualene (Song *et al.* 2008). Successive dehydrogenations yield 4,4′-diaponeurosporene (Pelz *et al.* 2005), which is then further oxidized, glycosylated, and esterified to give the carotenoid, staphyloxanthin (Figure 2.1) (Liu *et al.* 2008). Hence forgetting the biosynthesis of STX may provide an alternative way to develop new drug for preventing a treatment, staphyloxanthine remain infections since the lack of STX is susceptible to neutrophil killing.

The orange carotenoid staphyloxanthin is produced by most *S. aureus* strains. The staphyloxanthin biosynthesis genes are organized in an operon, crtOPQMN, with a B-dependent promoter upstream of acyl transferase (crtO) and a termination region downstream of dehydrosqualine desaturase (crtN). The functions of the five encoded enzymes are predicted on the basis of their sequence similarity to known enzymes and by product analysis of gene deletion mutants (Pelz *et al.* 2005).

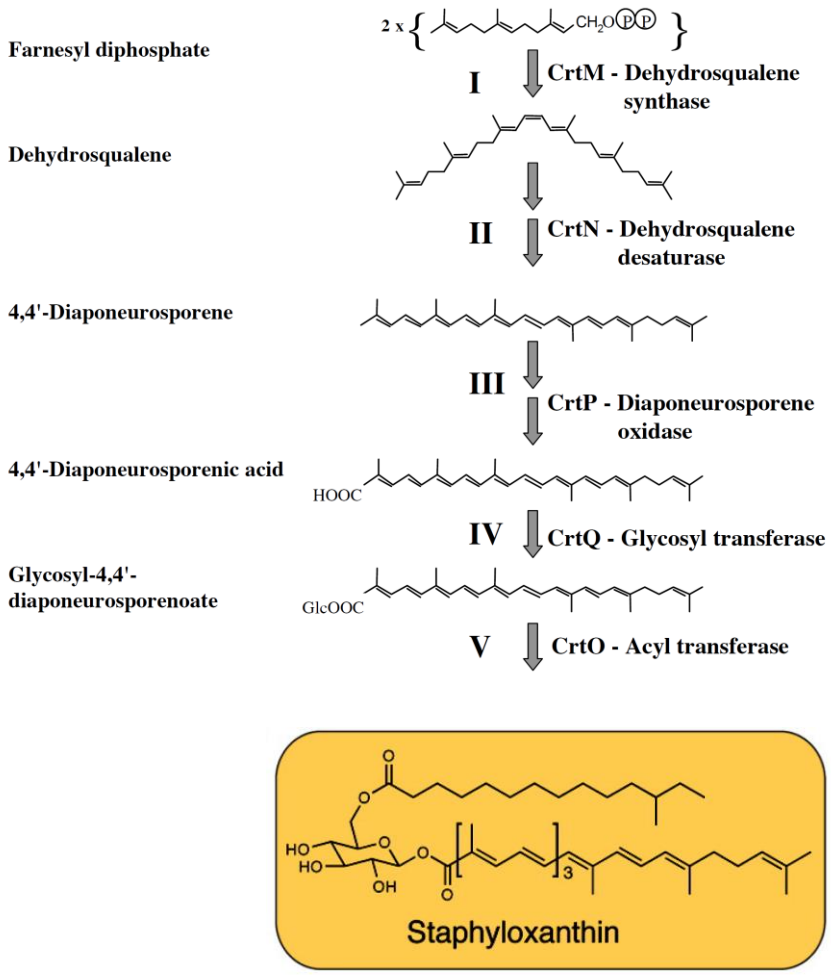


Figure 2.1. Biosynthetic pathways. Staphyloxanthin biosynthesis in *S. aureus* (Pelz et al. 2005), (Song *et al.* 2008).

The dehydrosqualene desaturase (CrtN) dehydrogenates dehydrosqualene to form the yellow, main intermediate 4,4-diaponeurosporene. Diaponeurosporene oxidase (CrtP), very likely a mixed function oxidase, oxidizes the terminal methyl group of 4,4-diaponeurosporene to form 4,4-diaponeurosporenic acid. Glycosyl transferase (CrtQ), a glycosyltransferase, esterifies glucose at the C1 position with the carboxyl group of 4,4-diaponeurosporenic acid to yield glycosyl 4,4-diaponeurosporenoate; this compound was the major product in the clone expressing crtPQMN. In the final step, the acyltransferase (CrtO) esterifies glucose at the C6 position with the carboxyl group of 12-methyltetradecanoic acid to yield staphyloxanthin (Pelz *et al.* 2005). Hence targeting are of these step is STX biosynthesis may provide a way to develop the anti-MRSA drugs.

2.4. Secondary Metabolites

Secondary metabolites are metabolic products that are not critical for vegetative growth of the producing organisms but they are considered differentiation compounds conferring adaptive roles, for example, by functioning as resistance compounds or signaling molecules in ecological interactions. They are produced at the end of the exponential phase of growth and their syntheses seriously depend on the growth conditions. Production is usually when growth is limited by the exhaustion of fundamental nutrients such as carbon or nitrogen. They are structurally different and most of them are endowed with biological activities, such as antimicrobial agents, toxins, pesticides, ionophores, bioregulators, and quorum signalling. These bioactive metabolites are extremely used as antimicrobial agents for the treatment of different diseases (Adegboye and Babalola 2013). One third of the 22,500 known microbial metabolites are the secondary metabolites of actinomycetes, mainly *Streptomyces* species (Miyaoka *et al.* 2014). Microbial secondary metabolites have been in the fırst appearance in the discovery of novel antimicrobial agents for pharmaceutical industry, and nowadays all indications suggests that novel compounds with potential therapeutic applications are still waiting to be discovered from secondary metabolites mainly those produced by actinomycetes. Actinomycetes are abundant producers of secondary metabolites with biological activities (Adegboye and Babalola 2013).

Secondary metabolites are provided by the producer organism with survival advantages in various ways, such as improving nutrient availability, acting as a metabolic defense mechanism, protecting against environmental stressors, enhancing competitive interactions with other organisms (Breitling *et al.* 2013). Secondary metabolites are organic compounds that often play an important role in defense systems of different organisms and are not directly involved in the normal growth, development or reproduction of an organism. (Davati and Najafi 2013).

Secondary metabolites usually include various chemical moieties, such as polyketide backbones, amino acid derivatives and sugars. Biosynthesis of secondary metabolite is catalyzed by a number of enzymes, usually encoded by genes. These genes occur nearby to one another in cluster. The gene cluster contains all the needed genes for the synthesis of a particular secondary metabolite. This includes: the genes that encode the biosynthetic enzymes, regulatory proteins, genes for resistance to the toxic

action of secondary metabolites and genes for secretion of the metabolites. Enzymes such as synthase (PKS) and non-ribosomal peptide synthetase (NRPS) are take part in the synthesis of secondary metabolites. Other enzymes responsible for the synthesis of other constitutive compounds, such as sugars, are often encoded by genes nearby to the gene cluster. Through processes such as elongation, synthesis, glycosylation, alkylation and oxidation, structurally different and complex metabolites are produced. The complete process of production and transportation of secondary metabolites are severely regulated by transcriptional regulators and transporters. The genes encoding for tailoring enzymes, transcriptional regulators and transporters are often located nearby to PKS and NRPS genes. The gene cluster size responsible for the synthesis of each secondary metabolite is usually between 10 -100 kb. (Adegboye and Babalola 2013).

The secondary metabolites frequently have unusual structures and their formation is regulated by nutrients, feedback control, growth rate, enzyme induction, and enzyme inactivation. These events generate signals which affect a cascade of regulatory actions resulting in chemical differentiation (secondary metabolism) and morphological differentiation (morphogenesis). The signal is often a low molecular weight inducer which acts by negative control, by binding to and inactivating a regulatory protein which normally prevents secondary metabolism and morphogenesis during rapid growth and nutrient sufficiency (Demain 1998). Regulation is affected by unique low molecular mass compounds, sigma factors, transfer RNA, and gene products formed during post-exponential growth. The synthases of secondary metabolism are often coded by clustered genes on chromosomal DNA and infrequently on plasmid DNA (Davati and Najafi 2013).

2.4.1. Function and Importance of Secondary Metabolites

Several hypotheses exist about the origin and function of secondary metabolites. The most accepted considers secondary metabolites as waste products that under the pressure of natural selection have evolved as messenger molecules which must endure long enough to shuttle between the various components of the microbial community. This fact, would explain the secondary metabolites tendency to be small organic molecules, as a natural consequence of their functions.

The presence of complex biosynthetic pathways for production of complex antibiotics suggest that they must have an important role in microbial survival, either as inhibitors of other competing organisms or as regulatory effectors during some stage of the cell differentiation process, since sensitive organisms need to evolve only a single enzyme of any several reaction types to inactivate most antibiotics (Tabarez 2005).

Nowadays, several arguments support the hypothesis that secondary metabolites improve the survival of the producer in competition with other living species. These arguments are as follows:

a) Secondary metabolites act as an alternative defense mechanism, because only the organisms lacking an immune system are prolific producers of these compounds.

b) They have sophisticated structures, complex and mechanisms of action, and energetically expensive pathways.

c) They act in the competition between microorganisms, plant and animals.

d) They are produced by biosynthetic genes clusters, which would only be selected if the product conferred a selective advantage. Some exactitudes of these genes clusters are the absence of non-functional genes and the presence of regulatory and resistance genes.

e) The production of them with antibiotic activities is temporarily related with sporulation when the cells are particularly sensitivity to competitors and requiring special protection when a nutrient runs out.

Furthermore, the wide diversity of secondary metabolites suggests a broad range of functions. Nevertheless, these functions could depend on the conditions, optimal or not, surrounding the producer microorganism. Finally, due to their crucial importance the study and exploitation of secondary metabolites continue to progress despite the lack of agreement regarding why microbes produce such chemical diversity of antimicrobial compounds (Tabarez 2005).

2.4.2. Genetics of Secondary Metabolites

The genes regulating and ensuring synthesis of secondary metabolites and their expression can be grouped in 5 classes: first, structural genes, that code for enzymes involved in the biosynthesis; second, regulatory genes, that determine the repression or induction of the structural genes; third, genes that determine the resistance of the generating organism; fourth, genes controlling the compound permeability and fifth, genes that control primary pathways. The genetic regulation of all above mentioned genes is highly complicated because many environmental and microbial factors affect the production of these compounds (Tabarez 2005)

Previous studies showed that the gene cluster responsible for the production of secondary metabolites is not found in all bacteria and even in those surviving it is not regularly distributed among them. For example *Streptomyces coelicolor* has more than 20 gene clusters for the synthesis of secondary metabolites while *Streptomyces avermitilis* has 30 gene clusters. Genome mining for new candidate secondary metabolic pathways built on clustering and co-expression has proved to be a highly successful method in microbes. This useful to expect the types of antibiotic one might expect to find after extraction and purification. With the increasing number of genome nucleotide sequence information in the Gen Bank and coming of next generation sequencing it will be possible to search for secondary metabolite gene cluster candidate in a wide range of actinomycetes (Adegboye and Babalola 2013).

Functionally related genes are on the chromosome suggesting that at least part of their evolution has occurred as a unit. Evolutionally, two types of gene clusters that produce secondary metabolites can be described: first, a gene cluster might contain many genes, some of which give rise to chemical transformations of substrates and many other that do not. This type of cluster would be indicative of a natural product which has not been selected for and which is not functional. Second, a gene cluster might contain only genes that code for enzymes of a particular biosynthetic pathway, resistance genes and regulatory factors, and no “junk” genes. This type of gene cluster indicate a natural product that has been selected for and which has had a beneficial function for the producer organism (Tabarez 2005).

2.5. Angucycline Compounds

The angucyclines are a large group of natural products (Song et al. 2015). They are a large family of actinomycete-derived polyketide antibiotics with a four-ring skeleton that constitutes the aglycone part. Angucyclines structure consist of a benz[a]anthracene core (Ren *et al.* 2011), (Abdelmuhsen *et al.* 2014), which is commonly C- or O-glycosylated with sugar (single deoxyoligosaccharide) chains of various lengths with up to six carbohydrates, as in landomycin A, the carbohydrate composition of landomycin is a repeated sequence of β-D-olivose-(4-1)-β -D-olivose-(3-1)-α-L-rhodinose attached to a phenolic oxygen of the angucycline core. The biological activities were mainly found to be depending on the length of the saccharide chain (Helaly *et al.* 2013). They have been shown to exhibit different activities of medical interest (Rohr and Thiericke, 1992) including antitumor (Kirschning *et al.* 2000), (Kharat *et al.* 2009) and antibacterial activities (Kawasaki *et al.* 2010a), (Kormanec *et al.* 2014) as well as platelet aggregation inhibitory effects (Kirschning *et al.* 2000). The first reported compounds of this class were tetrangomycin and tetrangulol (Song *et al.* 2015).

The angucycline family of antibiotics is a large and ever-growing group of secondary metabolites of microbial origin comprising more than 100 members (Ren *et al.* 2011). The first member of this group of secondary metabolites was tetrangomycin (Figure 2.2) (Kalyon *et al.* 2013). These compounds are found widely in nature and are mainly produced by soil-dwelling *Streptomyces* bacteria. The biosynthesis of angucyclines diverges from other type II aromatic polyketides by the action of the specific cyclase that closes the fourth ring of the polyketide into an angular orientation producing UWM6 (Kallio *et al.* 2008), (Patrikainen *et al.* 2012). Aromatic polyketides include a large class of natural secondary metabolites produced by certain fungi, bacteria and plants. Many of these compounds have medically important properties, and several are in clinical use (Koskiniemi *et al.* 2007).

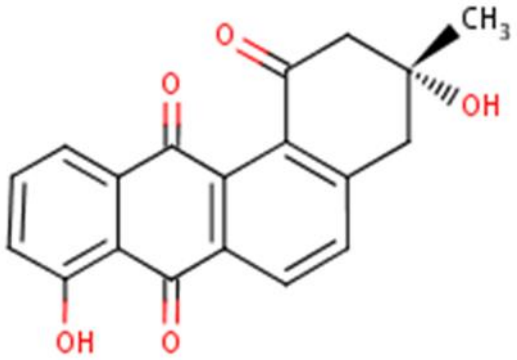


Figure 2.2. Tetrangomycin structure (Kalyon *et al.* 2013)

Aromatic polyketides are complex natural compounds well established for their biological activities and applications in medicine. They are produced by a number of different organisms, but especially *Streptomyces* bacteria have been a rich source of natural products. Angucyclines comprise a distinct group of aromatic polyketides (Rohr and Thiericke 1992), and first member of group was discovered in 1966 (Kawasaki *et al.* 2010a), but still only a few hundred structures have been described. New genetic screening studies have indicated that angucycline gene clusters are much more abundant than expected depending on traditional cultivation methods (Metsa-Ketela *et al.* 2002), which proposes that many potentially important angucyclines are yet to be discovered (Kallio *et al.* 2008).

Many of the new compounds, mainly described most recently, are from marine-derived actinomycetes, and represent new structures arising from new biosynthetic pathways. This suggests that even if marine actinomycetes are derived from terrestrial sources, they have been exposed to a new environment long enough to have evolved exceptional biosynthetic pathways of their own. The discovery of new actinomycete species producing novel chemical compounds suggests that they are metabolically active in the marine environment. Furthermore, it has become more obvious that there is great diversity of new actinomycete species within the marine environment with evidence that stems from phylogenetic analysis, metabolic requirements, morphological characteristics, and new secondary metabolite production (Raczkowski 2010).

2.6. Actinomycetes, especially genus *Streptomyces* (Angucyline producers)

Actinomycetes belong to the phylum Actinobacteria that consist of Gram positive, aerobic bacteria, were first thought to be fungi for their mycelium producing capabilities, for which the suffix "mycetes" is used (Raczkowski 2010). They are filamentous, characterized by a complex life cycle (Sharma 2014) and produce extensive branching vegetative (substrate) mycelium and aerial mycelium bearing chains of arthrospores. The substrate mycelium and spores can be pigmented, but also diffusible pigments are produced. On agar plates, they form lichenoid, leathery or butyrous colonies (Rintala 2013).

The high densities of actinomycetes in soils revealed their importance, which are one of the most significant decomposers for recalcitrant polymers such as cellulose. In addition to cellulose, *Streptomyces spp*. have shown to degrade chitin, keratin, pectin, and other hemicelluloses. These compounds can also be used as elements for their growth on artificial media. Although some pesticides inhibit their proliferation, *Nocardiopsis spp*., are known to degrade chlordane insecticides. With the ability to produce numerous antifungal compounds, actinomycetes are suspected to be associated with plant roots and hence they are believed to protect roots by using these compounds to inhibit the growth of fungal pathogens (Raczkowski 2010).

Actinomycetes produce perhaps the most diverse and most unique, unprecedented, sometimes very complicated compounds exhibiting excellent antimicrobial potency and usually low toxicity. The metabolic diversity of the actinomycetes is due to their extremely big genome, which has hundreds of transcription factors that control gene expression, allowing them to respond to specific needs (Singh *et al.* 2014). The GC-content of the DNA is 69-78 %. L-diaminopimelic acid is the characteristic compound present in the cell wall peptidoglycan of streptomycetes. The streptomycetes are able to use a wide range of organic compounds as a carbon source, with complex biological materials, such as cellulose and lignin, and can also use an inorganic nitrogen source (Rintala 2013).

Actinomycetes have provided important bioactive compounds of great commercial value and continue to be routinely screened for new bioactive substances. It

is generally accepted that the streptomycetes have a specific capacity to produce a large variety of different bioactive compounds with a wide range of activity (Singh *et al.* 2014). There are over 500 species of *Streptomyces* bacteria described by Euzeby (2008) (Raja and Prbakarana 2011). They undergo a complex process of morphological and physiological differentiation that leads to the production of exospores and specialized metabolites possessing a wide range of biological activities. While the function of many of these molecules in the natural environment is not always evident, they are believed to provide a competitive advantage to the producing organism (Gomez-Escribano *et al.* 2015).

Among the 140 defined Actinomycetes genera, only a few are responsible for the more than 10,000 bioactive compounds in clinical use (Adegboye and Babalola 2013), more than half of the 10,000 documented bioactive compounds, have offered over 50 years of interest to industry and academia (Anderson and Wellington 2001). It is representing 45% of known bioactive microbial metabolites were isolated from various actinomycetes species (Sharma 2014), and 7600 compounds are produced by Streptomyces species (74% of all actinomycetales), while the rare actinomycetes represent 26%, altogether 2500 compounds (Raja and Prbakarana 2011), (Singh *et al.* 2014).

The composition of cell wall in actinomycetes differs greatly among different groups and is of considerable taxonomic value. Four major cell wall types are distinguished in these filamentous bacteria depends on three features of peptidoglycan composition and structure, which are: diaminopimelic acid isomer on tetrapeptide side chain position 3, sugar content of peptidoglycan, and the presence of glycine in interpeptide bridges (Adegboye and Babalola 2012).

Microorganisms included in the genus *Streptomyces* that inhabit soil niches, thus facing ever changing environmental conditions and nutrient scarcity. Along evolution, this challenging environment has pushed the genus *Streptomyces* towards complex adaptive responses. Among them, two-component systems (TCSs) are the most important transduction signal mechanism in bacteria, allowing the translation of these rapid environmental or nutritional changes into a regulatory readout. Typically, TCSs

comprise a membrane-bound histidine kinase, which senses specific environmental stimuli, and a cognate regulator, which mediates the cellular response, mainly through the transcriptional regulation of target genes (Rodríguez *et al.* 2013).

It is now evident that as new molecular approaches are used to unravel the microbial community of unique marine environments, new species of actinomycetes have continued to reappear. However, these new species of actinomycetes indigenous to the marine habitat, or they derived from terrestrial run-off that are in fact a source of dormant actinomycete spores that can survive for many years (Raczkowski 2010). Bacteria belonging to the genus Streptomyces harbor a high number of TCSs in comparison with other bacterial genera, probably due to the changing environment that these organisms must inhabit (Rodríguez *et al.* 2013).

Approaches for overproduction of microbial products can be based on microbial response (elicitors, quorum sensing), genetic, ribosome, and metabolic engineering. Also, molecular genetic improvement methods include amplification of secondary metabolites biosynthetic genes, inactivation of competing pathways, disruption or amplification of regulatory genes, manipulation of secretory mechanisms, expression of a convenient heterologous protein and combinatorial biosynthesis (Davati and Najafi 2013). In 1995 more undoubted data, through the use of 16S rRNA genus-specific probe with hybridization experiments, suggested that salt marsh Streptomyces sp. strains were indigenous to the marine environment by being important proportion of the microbiota of the salt marsh environment through an entire annual cycle. Scientists revealed that Streptomyces sp. occurred dominantly in the salt marsh community and that dormant spores were not the source of their abundance (Raczkowski 2010).

2.7. Protein (Receptor) Structure and Function

2.7.1. Introduction to Proteins

The highly specific protein complex formation is an important process in biology and an integral constituent to all major biochemical pathways. The structures of these protein complexes can provide detailed understanding into the mechanisms of function, starting from disease pathogenesis, to drug action, to promoting our

understanding of innate biochemical processes. Using of the computational tools of molecular modeling, is the beginning to develop methods to predict high-resolution structures for protein complexes and assume how their functions arise from their structures (Chaudhury 2010). Multiple weak interactions stabilize protein structure, hydrophobic interactions are the major contributors to stabilizing the spherical form of most soluble proteins, ionic interactions and hydrogen bonds are optimized in the thermodynamically most stable structures (Nelson and Cox 2008).

One of the five major biological macromolecules is proteins, and they are responsible for a various biochemical processes from structure, to signaling, to catalyzing vital biochemical reactions. They are polymers of amino acids that are encoded by genes.

In the process of translation, a mRNA transcript from the nucleus is used to create the protein chain in the ribosome. After translation, this amino acid polymer (polypeptide chain) adopts the lowest free-energy conformation in solution, through a protein folding process. Most proteins fold into a very specific shape or structure, and their function is directly outcome from this structure. A typical folding energy for a protein is -10 kcal/mol, which is means that well over 99% of the protein molecules in solution adopt this lowest-free energy conformation (Chaudhury 2010).

Like protein folding, almost all protein functions come from this basic thermodynamic principle: in a given environment the protein will adopt the lowest energy conformation (Chaudhury 2010).

In almost all cases, this lowest energy conformation is highly specific structure that biologically-evolved. For example, in protein-protein binding, which are free in solution, the lowest energy conformation will be a highly specific complex between the two proteins. The energy of a given conformation is a function of numerous molecular forces that act on that conformation, these are electrostatics, van der Waals interactions, hydrogen-bonding, and solvation energies (Chaudhury 2010).

2.7.2. Protein Structure

The monomers of a polypeptide chain, are known as residues, form a polymer through peptide bonds. The polypeptide chain itself (backbone) is made up totally of an N-Cα bond, a Cα-C bond, and a C-N bond, repeated for each amino acid. The protein structure and function specificity arises from the sequence of its amino acids. Although all polypeptide chain atoms for all residues are identical, each residue in the backbone is one of 20 amino acids. Amino acids differ from one another in their side-chains, defined as those non-backbone atoms bonded to the Cα atom (Chaudhury 2010). The 20 common amino acids practically never occur in equal amounts in a protein. Some of them may occur only once or occur in large number or not at all in a given type of protein. Differences in amino acids composition and sequence leads to differences in protein function. Some differences in sequence are possible for a specific protein, with little or no effect on function. There are hundreds of individual bonds in a covalent backbone of a typical protein, free rotation is possible around many of these bonds, and as a consequence the protein can assume a huge conformation. However, each protein has a structural function or specific chemical activity, strongly suggesting that each has a unique three-dimensional structure (Nelson and Cox 2008).

The energy of a certain protein conformation is a result of molecular forces that act on and between all non-bonded atoms in that conformation. In protein biophysics the van der Waals energies, steric repulsions, electrostatic energies, solvation energies, and hydrogen bonding energies are the most significant energy contributions that favor one conformation over another. These component energy functions of the atomic positions and atom types of the atoms in the protein structure (Chaudhury 2010).

The C_α of nearby amino acid residues are separated by three covalent bonds, arranged as C_α-C-N-C_α. X-ray diffraction studies of crystals of amino acids and of dipeptides and tripeptides showed that the peptide C-N bond is a bit shorter than the C-N bond in a simple amine and that the atoms linked with the peptide bond are coplanar.

This means the existence of a partial sharing of two pairs of electrons or resonance between the carbonyl oxygen and the amide nitrogen (Figure 2.3.a). The oxygen with a partial negative charge and the nitrogen with a partial positive charge,

setting up a small electric dipole. The six atoms of the peptide group located in a single plane, with the oxygen atom of the carbonyl group trans to hydrogen atom of the amide nitrogen. Pauling and Corey concluded from these findings that the peptide C-N bonds, cannot rotate freely because of their partial double-bond character. Rotation is permitted about the N-C_α and the C_α-C bonds. The backbone of a polypeptide chain accordingly can be pictured as a series of rigid planes, with repeated planes sharing a common point of rotation at C_α (Figure 2.3.b). So the range of possible conformations for a polypeptide chain limited by the rigid peptide bonds (Nelson and Cox 2008).

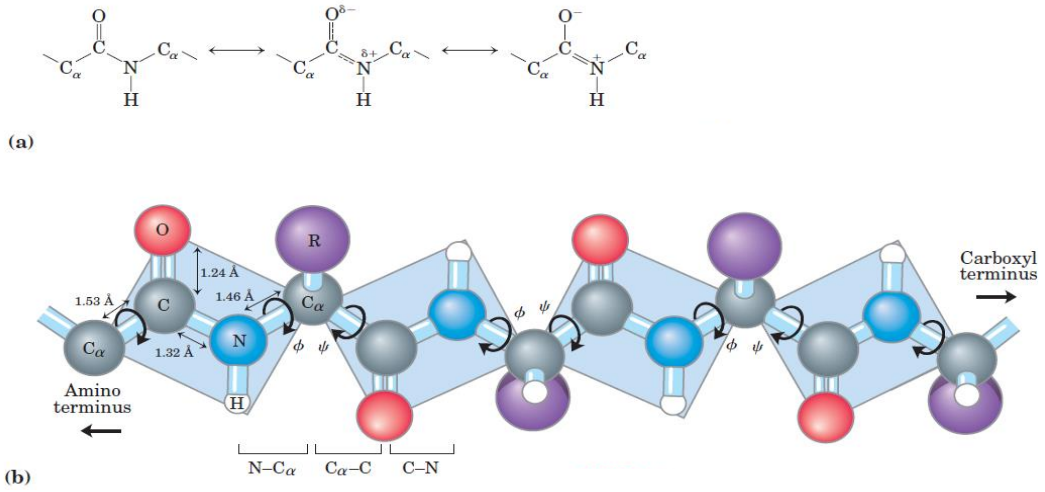


Figure 2.3. The planar peptide group. (a) Each peptide bond has some double-bond character due to resonance and hence cannot rotate. **(b)** Three bonds separate sequential α carbons in a polypeptide chain. The N-Cα and Cα-C bonds can rotate, described by dihedral angles designated ϕ and ψ, respectively. The peptide C-N bond is not free to rotate. Other single bonds in the backbone may also be rotationally hindered, depending on the size and charge of the R groups (Nelson and Cox 2008).

2.7.3. Protein Data Bank

The Protein Data Bank (PDB; www.rcsb.org) (RCSB: Research Collaborator for Structural Bioinformatics) is an archive or library of experimentally determined three dimensional structures of biological macromolecules. The information contained in this archive includes atomic coordinates, crystallographic structure factors and NMR experimental data. In addition to coordinates, each deposition also consist of the names of molecules, primary, secondary structure information, and sequence database

references, where appropriate, and ligand and biological assembly information, details information about data collection and structure solution, and bibliographic citations.

All the Protein Data Bank items are stored in a special file format - PDB. Every PDB file is demonstrated in a number of lines. Each line in the PDB item file consists of 80 columns and is self-identifying. There is a record name in the first six columns of every line. Record names are listed and explained in detail in the PDB format guide. Collection of record types which consists of one or more lines is another way to describe a PDB file (Novotarskyi 2013).

2.8. Ligands

Many proteins functions involve the reversible binding of other molecules. Ligand is a molecule bound reversibly by a protein, and may be any kind of molecule, including another protein. Binding site is the location that ligand binds on the protein, which is matching the ligand in size, shape, charge, and hydrophobic or hydrophilic character. Additionally, the interaction is specific: the protein can favor among the thousands of different molecules in its environment and selectively bind only one or a few. A certain protein may have different binding sites for several different ligands (Nelson and Cox 2008).

A ligand binds at a site on the protein called the binding site**,** which is complementary to the ligand in size, shape, charge, and hydrophobic or hydrophilic character. Furthermore, the interaction is specific: the protein can discriminate among the thousands of different molecules in its environment and selectively bind only one or a few. A given protein may have separate binding sites for several different ligands. These specific molecular interactions are crucial in maintaining the high degree of order in a living system. This discussion excludes the binding of water, which may interact weakly and nonspecifically with many parts of a protein (Nelson and Cox 2008).

2.9. Protein-Ligand Interaction

Interactions of protein-ligand have a central role in all processes in living systems. A complete understanding of protein-ligand interactions is of great interest as

it provides opportunities for therapeutic intervention and understanding function. Molecular recognition is, however, a complex interaction of several factors like inter-molecular interactions of protein, ligand and the surrounding solvent, conformational differences of binding partners and the thermodynamics of molecular association. Experimental and computational techniques have been developed over the past few decades that shed light on the role of these factors (Haider 2010).

Interactions between ligands and proteins may be regulated, usually through specific interactions with one or more additional ligands. These other ligands may cause conformational changes in the protein that affect the binding of the first ligand (Nelson and Cox 2008).

2.9.1. Non-covalent binding

The non-covalent binding of ligand (small-molecule) to proteins (receptors) is mediated by a various inter-atomic interactions. Generally, these include electrostatic and van der Waal interactions (Figure 2.4) the affinity of protein-ligand binding also greatly relies on contributions from other factors such as entropy, flexibility of receptor structure, desolvation, and the structural water molecules in the binding site (Haider 2010).

2.9.2. Electrostatic Interaction

Electrostatic interactions is a result of forces that are generally accepted to be the most important intermolecular driving factors for ligand-protein binding. Electrostatic phenomena in biomolecular systems are very complex because of the long-range nature of electrostatic forces among large numbers of interacting atoms. The existence of charged groups in proteins further complicates the situation (Tunca 2012)

Electrostatic complementary between the protein and the ligand at the binding site is very important for complex formation via electrostatic interactions such as hydrogen bonding, salt bridges, and metal interactions (Figure 2.4).

Hydrogen bonding is very important directional interaction in biological macromolecules, known for giving stability to protein structure and selectivity to

protein-ligand interactions. In general, hydrogen bonding takes place between two electronegative atoms, one of which (donor) has a covalently bound hydrogen atom and the other (acceptor) has a long pair of electrons. The strong electrostatic inter-attraction arises from attractive interaction between partial positive charge on the hydrogen atom and partial negative charge on the acceptor atom. Theoretical and experimental studies have approved an additional covalent component to hydrogen bonds also which is based on the interaction between empty (σ*) anti-bonding orbital of the hydrogen atom and highest occupied orbital of the acceptor (Haider 2010).

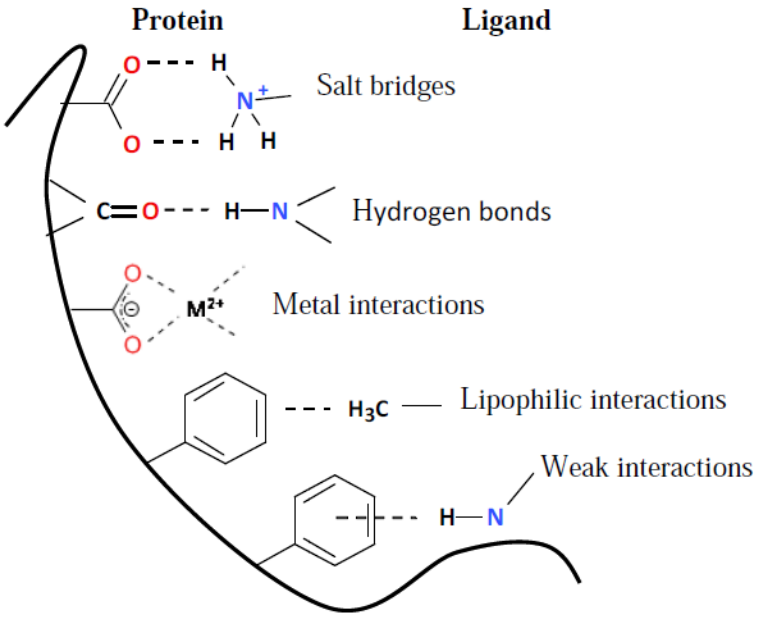


Figure 2.4. Major types of non-bonded interactions in protein-ligand complexes (Haider 2010)

2.9.3. Hydrophobic Interaction

Hydrophobic interactions include contacts between non-polar parts of the molecule (Figure 2.5). In protein-ligand complexes non-polar parts at the interacting surface are embedded or buried upon binding. This causes displacement of water molecules and this mean increasing the entropy. These types of interaction are therefore entropy-driven and have been shown to play central role in ligand binding. The burial of non-polar surface area and binding affinity relationship is well established and amounts to an affinity gain of 30 cal/mol for 1 A^2 of buried lipophilic surface area. This indicates that adjusting non-polar contacts of ligand atoms in hydrophobic protein pockets results

in strength binding. For example, Peters et al. demonstrated that improving interactions of aromatic rings in hydrophobic pocket of dipeptidyl peptidase IV resulted in 10^5 fold increase in affinity (Haider 2010).

In protein binding sites aromatic residues such as His, Phe, Trp and Tyr are frequently involved in aryl-aryl interactions. They are known to interact with each other mostly via one of two geometries: parallel displaced stacking and T-shaped edge to face interaction. Quantum mechanical studies on model system like benzene dimers have shown that these two geometries are isoenergetic. In protein structures, however, parallel displaced geometry has been more recurrently observed. Aliphatic-aromatic interactions including aromatic rings and alkyl groups are also commonly occurring interactions at non-polar interfaces. Similar to aromatic-aromatic interactions, preferable interaction geometries include parallel displaced and edge-to-face interactions. The strength of aliphatic-aromatic interactions, specially, CH-π interactions vary with increasing acidity of CH groups (Haider 2010).

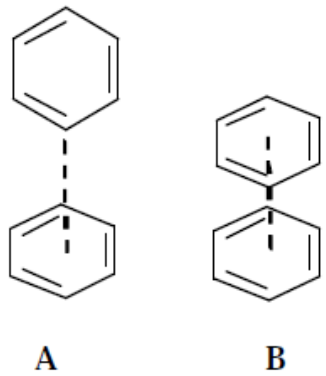


Figure 2.5. Aryl-aryl interactions in protein structure and protein-ligand complexes. A. Edge-to-face geometry, B. Parallel stacking geometry (Haider 2010)

2.9.4. Binding affinity and binding site

The binding affinity is used to describe how tightly or strongly a ligand bind to its target and is controlled by non-covalent interactions such as electrostatic and van der Waals forces, including solvation and desolvation contributions. These interactions are

important for structural and energetic recognition between ligand and target. Although covalent bonds are stronger than non-covalent interactions, small interactions accumulate to make important participations to stabilize ligand binding (Tunca 2012).

The binding site can be defined as a set of residues belonging to the protein that lies within the zone of 4.5A° from any atom of the corresponding ligand (Anand et al. 2014). For a strong ligand binding to a target, some requirements should be fulfilled: High level of steric complementarity should be between the ligand and the target protein. Ligand and the target protein surface properties should chemically complement to each other. In the meantime lipophilic parts of the protein are mostly in contact with the lipophilic parts of the ligand and polar groups are usually matching accordingly to from hydrogen bonds or ionic interactions, surface properties of both sides should match. The ligand should be in an energetically favorable conformation for stability (Tunca 2012).

2.9.5. Affinity prediction problem

The information about 3D structures of the targets and/or the ligands and the correct prediction of the binding modes and the target-ligand complex structures constitute the basis for receptor-based drug design, however understanding the protein-ligand interactions on the molecular level and the precise prediction of these interactions determine the success of a receptor-based drug project. Even though different docking algorithms are able to generate experimentally observed binding modes of ligands to protein, it is still a challenge to recognize and pick them in huge libraries and give accurate scores to rank them. The efficiency of a computational drug design method relies on the true prediction of binding affinity (Tunca 2012).

2.10. Molecular Docking

Over the past 25 years, advances in structural biology have greatly changed the technique in which drugs are designed and discovered. Nowadays, rather than treating protein targets as simple black boxes, now pharmaceutical scientists are treating them as complex molecular entities that have well-defined structures with active sites that can be activated or deactivated rationally with small molecule ligands (Dias 2011).

Molecular docking is a computer simulation procedure to predict the conformation of a receptor-ligand complex, where the receptor is usually a protein and the ligand is either a small molecule or another protein. It can also be defined as a simulation process where a ligand position is estimated in a predicted or predefined binding site (Novotarskyi, 2013).

Docking studies, in general have two main aims: true structural modeling and correct binding affinity predictions. Therefore, most docking algorithms concentrate on ligand and sometimes on flexibility of protein, and explore the suitable space available to the ligand in the binding site. According to how ligand flexibility is treated, mainly search algorithms categorized in: random or stochastic method, systematic methods and simulation methods. In docking program the research algorithm can apply only a single method or a combination of different methods (Tunca 2012).

2.10.1. AutoDock Vina

AutoDock Vina (Trott and Olson 2010) is the updated member of AutoDock suite introduced in 2010. It has been developed by Dr. Oleg Trott in the Molecular Graphics Lab at The Scripps Research Institute. It differs from earlier versions in many regards, one of them the accessibility. The three-dimensional structures of molecules with polar hydrogens only, as AutoDock Vina still uses United Atom model, and a box definition is required for search space. Partial charges, pre-calculated interaction energy grids or solvation parameters are not necessary for the simulation (Reska 2011). AutoDock Vina does not provide the user with a choice of search algorithm, it uses Iterated Local search global optimizer instead. Steps consisting of mutation and subsequent local optimization are performed in this algorithm, with each step being accepted according to the Metropolis criterion. (Reska 2011)

Changes in conformation of protein may be indirect, reflecting molecular vibrations and small movements of amino acid residues throughout the protein. A protein flexing in this way is sometimes said to “breathe.” This may also be quite dramatic, with major fragments of the protein structure moving as much as several nanometers. Specific conformational changes are normally essential to a protein’s function. The binding of protein and ligand is repeatedly coupled to a conformational

change in the protein that makes the binding site to the ligand more complementary, allowing tighter binding. Ligands and proteins interactions may be regulated, usually through specific interactions with one or more extra ligands. These extra ligands may cause conformational changes in the protein acts on the binding of the first ligand (Nelson and Cox 2008).

The contact surfaces relatively small between the ligand and the protein, much smaller than in protein-protein docking. In this case, the main challenge is the ligand‘s flexibility as it can fit to the protein‘s surface in various way. Computational methods are then used to predict ligands binding affinity and conformation. This method is used to obtain leads for medical development as drug-like molecules are screened with this method (Pétursson 2014). Protein interactions with ligands, or with other proteins, or surfaces are controlled by a complex arrangement of intermolecular processes. Such interactions depend on the specificity in the binding site and the non-specific forces outside the binding pocket. The aim of various biophysical studies is to identify the molecular forces that control biological interactions and to use this known information for rationally or intelligence manipulate of the protein structure or function by modifying the protein, the interacting ligand, or both (Dias 2011).

3. MATERIALS AND METHODS

The crystal structures of dehydrosqualine synthase enzyme (CrtM) which catalysis the first committed step in staphyloxanthin biosynthesis, (PDB-ID: 3W7F, 3ACW) the former involving magnesium were downloaded from Protein Data Bank (PDB) (http://www.rcsb.org), one involves an inhibitor and the other (3W7F) involves magnesium and without magnesium. All the non-standard amino acid residues were removed from that structures and they were separately prepared as receptors and ligands using Discovery Studio 4.1 (http://accerys.com), (Maldonado-Rojas and Olivero-Verbel 2012).

MGL Tools 1.5.6 (http://mgltools.scripps.edu) was employed to prepare protein and ligand structures for molecular docking, after opening the protein the polar hydrogens added to the structures and the structures saved in (PDBQT) file format.

In present study a total of 157 ligand structures were extracted from literatures and articles comprises the angucycline antibiotics (Table 3.1) and these 2D structures are drawn by ChemDraw Pro 12.0 (www.cambridgesoft.com) and they were converted to 3D structures using Discovery Studio 4.1 (http://accerys.com) they are shown in Appendix IV for the lack of the space.

Table 3.1. Angucycline Groups Antibiotics and their references

#	Angucycline Antibiotics	References
1	Marangucycline_A	(Song et al. 2015)
2	Marangucycline_B	(Song et al. 2015)
3	Actinosporin_A	(Abdelmohsen et al. 2014), (Dashti et al. 2014)
4	Actinosporin_B	(Abdelmohsen et al. 2014), (Dashti et al. 2014)
5	Hatomarubigin_A	(Kawasaki et al. 2010a, b), (Izawa et al. 2013)
6	Hatomarubigin_B	(Kawasaki et al. 2010a, b), (Izawa et al. 2013)
7	Hatomarubigin_C	(Abdelfattah et al. 2003), (Kawasaki et al. 2010a, b), (Izawa et al. 2013)
8	Hatomarubigin_D	(Kawasaki et al. 2010a, b), (Izawa et al. 2013)
9	Hatomarubigin_E	(Kawasaki et al. 2010b), (Izawa et al. 2013)
10	Hatomarubigin_F	(Izawa et al. 2013)

Table 3.1. Angucycline Groups Antibiotics and their references (continue)

#	Angucycline Antibiotics	References
11	Rubiginone_B2	(Kawasaki et al. 2010a), (Izawa et al. 2013)
12	Warkmycin	(Helaly et al. 2013)
13	Waldiomycin	(Igarashi et al. 2013)
14	Langkocycline_A1	(Kalyon et al. 2013)
15	Langkocycline_A2	(Kalyon et al. 2013)
16	Langkocycline_A3	(Kalyon et al. 2013)
17	Langkocycline_B1	(Kalyon et al. 2013)
18	Langkocycline_B2	(Kalyon et al. 2013)
19	Fradimycin_C	(Ganesan et al. 2013)
20	UWM6	(Kallio et al. 2008), (Kharel & Rohr 2012), (Patrikainen et al. 2012)
21	Jadomycin_B	(Fan et al. 2012a, b)
22	Jadomycin_A	(Fan et al. 2012a)
23	L_digitoxosyl_dehydro-rabelomycin	(Fan et al. 2012a)
24	Dehydrorabelomycin	(Fan et al. 2012a), (Patrikainen et al. 2012)
25	Saprolmycin_A	(Nakagawa et al. 2012)
26	Saprolmycin_B	(Nakagawa et al. 2012)
27	Saprolmycin_C	(Nakagawa et al. 2012)
28	Saprolmycin_D	(Nakagawa et al. 2012)
29	Saprolmycin_E	(Nakagawa et al. 2012)
30	Saquayamycin_A	(Nakagawa et al. 2012)
31	Gaudimycin_A	(Kallio et al. 2008)
32	Gaudimycin_B	(Kallio et al. 2008)
33	Gaudimycin_C	(Kallio et al. 2008), (Patrikainen et al. 2012)
34	Aquayamycin	(Faust et al. 2000), (Igarashi et al. 2013)
35	Landomycin_A	(Kirschning et al. 2000), (Kharel & Rohr 2012)
36	Landomycin_E	(Zhu et al. 2005), (Kawasaki et al. 2010a), (Kharel & Rohr 2012)
37	Landomycin_Z	(Kharel & Rohr 2012)
38	Grincamycin	(Huang et al. 2012)
39	Grincamycin_F	(Huang et al. 2012)
40	JBIR_90	(Ueda et al. 2011)
41	JBIR_116	(Ueda et al. 2011)

Table 3.1. Angucycline Groups Antibiotics and their references (continue)

#	Angucycline Antibiotics	References
42	JBIR_91	(Ueda et al. 2011)
43	JBIR_92	(Ueda et al. 2011)
44	JBIR_93	(Ueda et al. 2011)
45	Urdamycin_A	(Rohr & Thiericke 1992), (Faust et al. 2000), (Ueda et al. 2011)
46	Urdamycin_B	(Ueda et al. 2011)
47	N05WA963A	(Ren et al. 2011)
48	N05WA963B	(Ren et al. 2011)
49	N05WA963D	(Ren et al. 2011)
50	JBIR_88	(Motohashi et al. 2010)
51	Rabelomycin	(Rohr & Thiericke 1992), (Faust et al. 2000), (Metsa-ketela et al. 2002), (Metsa-ketela et al. 2003), (Metsa-ketela et al. 2004), (Kallio et al. 2008), (Kharel et al. 2010), (Kharel & Rohr 2012), (Igarashi et al. 2013)
52	Mayamycin	(Schneemann et al. 2010)
53	8_O_methyltetrangomycin	(Maruna et al. 2010)
54	8_O_methyltetrangulol	(Maruna et al. 2010)
55	8_O_methyl_7_deoxo_7_hydroxytetrangomycin	(Maruna et al. 2010)
56	Moromycin_A	(Abdelfattah et al. 2008)
57	Moromycin_B	(Abdelfattah et al. 2008)
58	Saquayamycin_B	(Abdelfattah et al. 2008)
59	Sch_47554	(Basnet et al. 2006)
60	Sch_47555	(Basnet et al. 2006)
61	BE_23254	(Dey & Mal 2005)
62	Tetrangomycin	(Rohr & Thiericke 1992), (Zhu et al. 2005)
63	Tetrangulol	(Rohr & Thiericke 1992)
64	Ochromocinone	(Rohr & Thiericke 1992), (Kaliappan & Ravikumar 2007)
65	PI_080 (=PI-6621)	(Rohr & Thiericke 1992)
66	Urdamycin_D	(Rohr & Thiericke 1992)
67	Urdamycin_H	(Rohr & Thiericke 1992)
68	8_O_methylrabelomycin	(Rohr & Thiericke 1992)
69	Urdamycin_C	(Rohr & Thiericke 1992)
70	Urdamycin_E	(Rohr & Thiericke 1992)

Table 3.1. Angucycline Groups Antibiotics and their references (continue)

#	Angucycline Antibiotics	References
71	Urdamycin_F	(Rohr & Thiericke 1992)
72	Urdamycin_G	(Rohr & Thiericke 1992)
73	Sakyomicin_A	(Rohr & Thiericke 1992), (Igarashi et al. 2013)
74	Sakyomicin_B	(Rohr & Thiericke 1992)
75	Sakyomicin_C	(Rohr & Thiericke 1992)
76	Sakyomicin_D	(Rohr & Thiericke 1992)
77	Sakyomicin_E	(Rohr & Thiericke 1992)
78	BE_7585A	(Rohr & Thiericke 1992)
79	8_O_methylurdamycin_A	(Henkel et al. 1988)
80	Seitomycin	(Abdelfattah et al. 2003)
81	Tetrangulol methyl ether	(Abdelfattah et al. 2003)
82	SM_196B	(Rohr & Thiericke 1992), (Abdelfattah et al. 2003)
83	Saquayamycin_A1	(Alvi et al. 2000)
84	A_7884	(Alvi et al. 1999)
85	Aquamycin	(Alvi et al. 1999)
86	SM_196 A	(Rohr & Thiericke 1992)
87	C104_Aglycon	(Rohr & Thiericke 1992)
88	C104	(Rohr & Thiericke 1992)
89	3_Deoxyrabelomycin	(Rohr & Thiericke 1992)
90	6_Deoxy_8_O_methyl-rabelomycin	(Rohr & Thiericke 1992)
91	Aggreticin (OM-4842)	(Rohr & Thiericke 1992)
92	BA_12100B	(Rohr & Thiericke 1992)
93	BA_12100C	(Rohr & Thiericke 1992)
94	BA_12100D	(Rohr & Thiericke 1992)
95	BA_12100E	(Rohr & Thiericke 1992)
96	BA_12100Z1	(Rohr & Thiericke 1992)
97	BA_12100Z2	(Rohr & Thiericke 1992)
98	BA_12100Z3	(Rohr & Thiericke 1992)
99	BA_12100MY_1	(Rohr & Thiericke 1992)
100	Benzanthrin_A	(Rohr & Thiericke 1992)
101	Benzanthrin_B	(Rohr & Thiericke 1992)

Table 3.1. Angucycline Groups Antibiotics and their references (continue)

#	Angucycline Antibiotics	References
102	Capoamycin	(Rohr & Thiericke 1992)
103	De_O_acylcapoamycin	(Rohr & Thiericke 1992)
104	Elmycin_A	(Rohr & Thiericke 1992)
105	Elmycin_B	(Rohr & Thiericke 1992)
106	Elmycin_C	(Rohr & Thiericke 1992)
107	Elmycin_D	(Rohr & Thiericke 1992)
108	Elmycin_E	(Rohr & Thiericke 1992)
109	X_14881_B	(Rohr & Thiericke 1992)
110	X_14881_D	(Rohr & Thiericke 1992)
111	Emycin_A	(Rohr & Thiericke 1992)
112	SF_2315_A	(Rohr & Thiericke 1992)
113	SS_228Y	(Rohr & Thiericke 1992)
114	Fridamycin_C	(Rohr & Thiericke 1992)
115	Fujianmycin_A	(Rohr & Thiericke 1992)
116	Fujianmycin_B	(Rohr & Thiericke 1992)
117	MM_47755	(Rohr & Thiericke 1992)
118	PD116779	(Rohr & Thiericke 1992)
119	X_14881_C	(Rohr & Thiericke 1992)
120	X_14881_E	(Rohr & Thiericke 1992)
121	X_14881_A	(Rohr & Thiericke 1992)
122	Landomycin_A	(Rohr & Thiericke 1992)
123	Landomycin_B	(Rohr & Thiericke 1992)
124	Landomycin_C	(Rohr & Thiericke 1992)
125	Landomycin_D	(Rohr & Thiericke 1992)
126	PD116740	(Rohr & Thiericke 1992)
127	TAN_1085	(Rohr & Thiericke 1992)
128	Landomycin_F	(Kharel & Rohr 2012)
129	Homorabelomycin	(Kharel & Rohr 2012)
130	Prejadomycin	(Kharel & Rohr 2012)
131	Homoprejadomycin	(Kharel & Rohr 2012)
132	11_HydroxyTetrango-mycin	(Kharel & Rohr 2012)

Table 3.1. Angucycline Groups Antibiotics and their references (continue)

#	Angucycline Antibiotics	References
133	Homo_UWM6	(Kharel & Rohr 2012)
134	PI_1894B (Vineomycin A) (OS-4742A1)	(Rohr & Thiericke 1992)
135	Yoronomycin	(Rohr & Thiericke 1992)
136	Urdamycin_I	(Faust et al. 2000)
137	Urdamycin_J	(Faust et al. 2000)
138	Urdamycin_K	(Faust et al. 2000)
139	Kerriamycin_A	(Rohr & Thiericke 1992)
140	Kerriamycin_B	(Rohr & Thiericke 1992)
141	Kerriamycin_C	(Rohr & Thiericke 1992)
142	PI_083	(Rohr & Thiericke 1992)
143	PI_085	(Rohr & Thiericke 1992)
144	PI_087	(Rohr & Thiericke 1992)
145	Saquayamycin_A	(Rohr & Thiericke 1992)
146	Saquayamycin_B	(Rohr & Thiericke 1992)
147	Saquayamycin_C	(Rohr & Thiericke 1992)
148	Saquayamycin_D	(Rohr & Thiericke 1992)
149	Saquayamycin_K1	(Rohr & Thiericke 1992)
150	Saquayamycin_K2	(Rohr & Thiericke 1992)
151	Saquayamycin_K4	(Rohr & Thiericke 1992)
152	Saquayamycin_K7	(Rohr & Thiericke 1992)
153	Saquayamycin_Z	(Antal et al. 2005)
154	Retymicin	(Antal et al. 2005)
155	Vineomycin_A1	(Nakagawa & Omura 1996)
156	Azicemicin_A	(Ogasawara and Liu 2009)
157	Azicemicin_B	(Ogasawara and Liu 2009)

The docking site for the ligands on the protein was defined by establishing a cube, where is fairly simple, it involves manipulating a coloured box into the area, which includes a docking stage. The volume can be as large or as small as required. But there is an exponential increase in computation time as the volume of the box increased.

In our docking experiments we used dimensions 38 × 38 × 38 Å, covering the ligand binding site with a grid point spacing of 1.0 Å, and center grid boxes of 55.653, 12.678 and 52.021 in X, Y and Z dimensions, respectively.

Once the docking area has been defined the coordinates of the grid box in a configuration file must be written in order in the text document file which is required to supply the AutoDock Vina 1.1.2 (Trott and Olson 2010) via the command line. The configuration file also specifies the ligand molecule, the protein to dock into and the exhaustiveness of the search which can be set between 1 and 8, where 8 is the most exhaustive search. This was the present used in our docking experiments (Stevenson 2012).

AutoDock Vina (Trott and Olson 2010) was run on the Windows 8.1 operating system and all ligands (angucycline antibiotics compounds) were docked to the protein with and without magnesium. Three runs were performed for every single angucycline compound.

4. RESULTS AND DISCUSSION

First of all to validate approach of docking, inhibitor and substrate were docked and they were compared with their original x-ray structures as shown in (Figure 4.1), it demonstrate that both ligands are docked into the active site of dehydrosqualine synthase enzyme (CrtM) (PDB ID: 3ACW) in a similar manner to the original coordinates with very low RMSDs, or zero RMSD in case of substrate and farnesyl diphosphate with CrtM (PDB ID: 3W7F) as shown in (Figure 4.2).

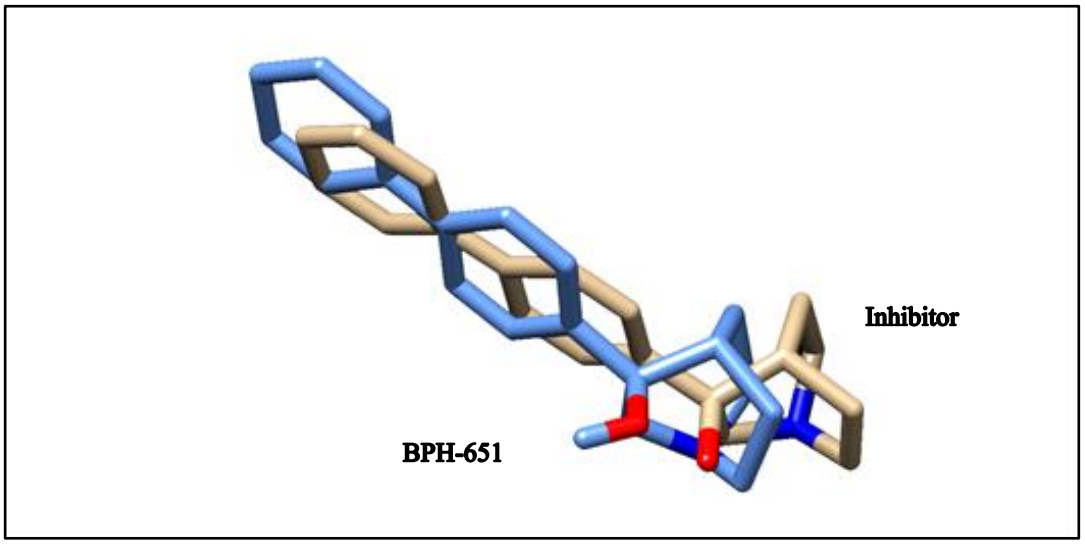


Figure 4.1. Superimpose structure of docked inhibitor with its original BPH-651 coordinates in the complex with CrtM

The active site of inhibitor BPH-651 with dock score -11.5 kcal/mol involves (Ala134, Ala157, Asn168, Gln165, Gly138, Gly161, Ile241, Leu141, Leu145, Leu160, Leu164, Phe22, Phe26, Val137) for that of farnesyl-farnesyl diphosphate the dock score -8.3 kcal/mol and involved residues are (Ala134, Ala157, Arg171, Arg265, Arg45, Asn168, Gln165, Gly138, Gly161, His18, Leu141, Leu145, Leu160, Leu164, Lys20, Phe22, Phe233, Ser19, Ser21, Tyr248, Tyr41, MG304) for CrtM. It seems that Arg45, Arg171, Arg265 are the main residues for the substrate (Appendices I, II, and III).

After seeing the success of docking protocol all ligands were successfully docked into the proteins. They were all docked into the active site where inhibitor and farnesyl diphosphate (substrate) are located.

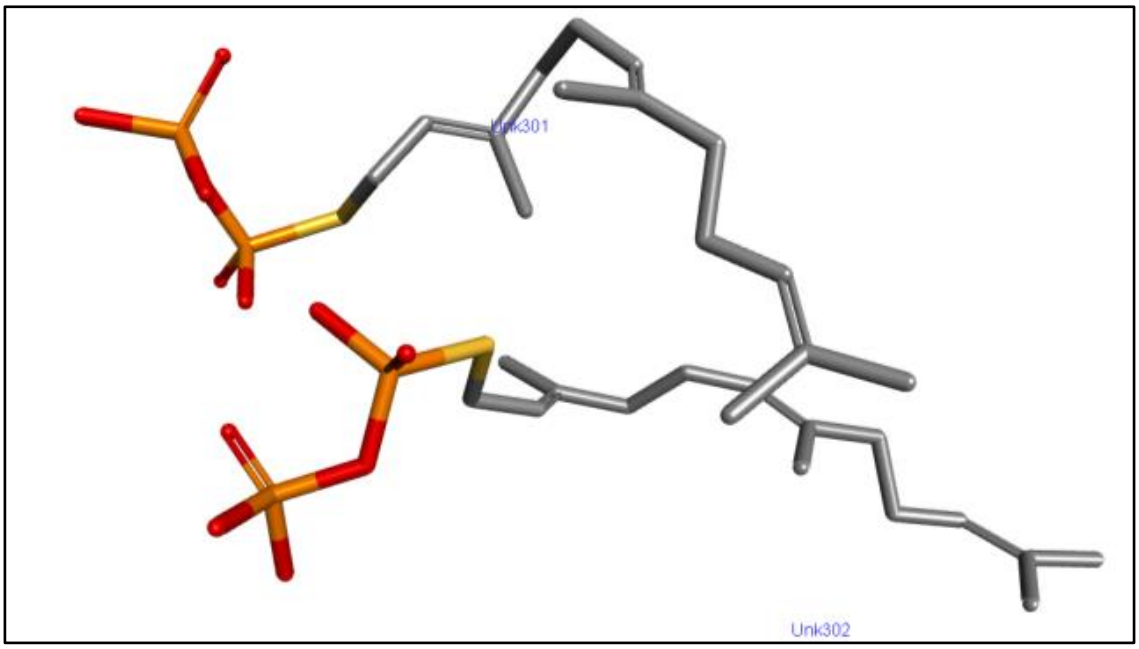


Figure 4.2. Superimpose structure of docked substrate with its original farnesyl diphosphate coordinates in the complex with CrtM

The dock scores of the inhibitor (830) and the substrate (farnesyl-farnesyl diphosphate) of CrtM (PDB ID: 2ZY1) was -9.1 and -11.5 kcal/mol respectively when docked to the active site of CrtM (3W7F), the inhibitor interact with residues (Ala134, Arg171, Arg265, Asn168, Gly161, His18, Leu141, Leu164, Lys20, Phe22, Ser19, Ser21, Tyr248, Tyr41, Val137, Val37) as illustrated in (Figure 4.3). Higher dock score of substrate to CrtM is derived from the number and type of interactions (Ala134, Ala157, Arg171, Arg265, Arg45, Asn168, Asp172, Asp48, Cys44, Gln165, Gly138, Gly161, His18, Leu141, Leu145, Leu160, Leu164, Lys20, Met15, Phe22, Phe233, Ser19, Ser21, Tyr248, Tyr41).

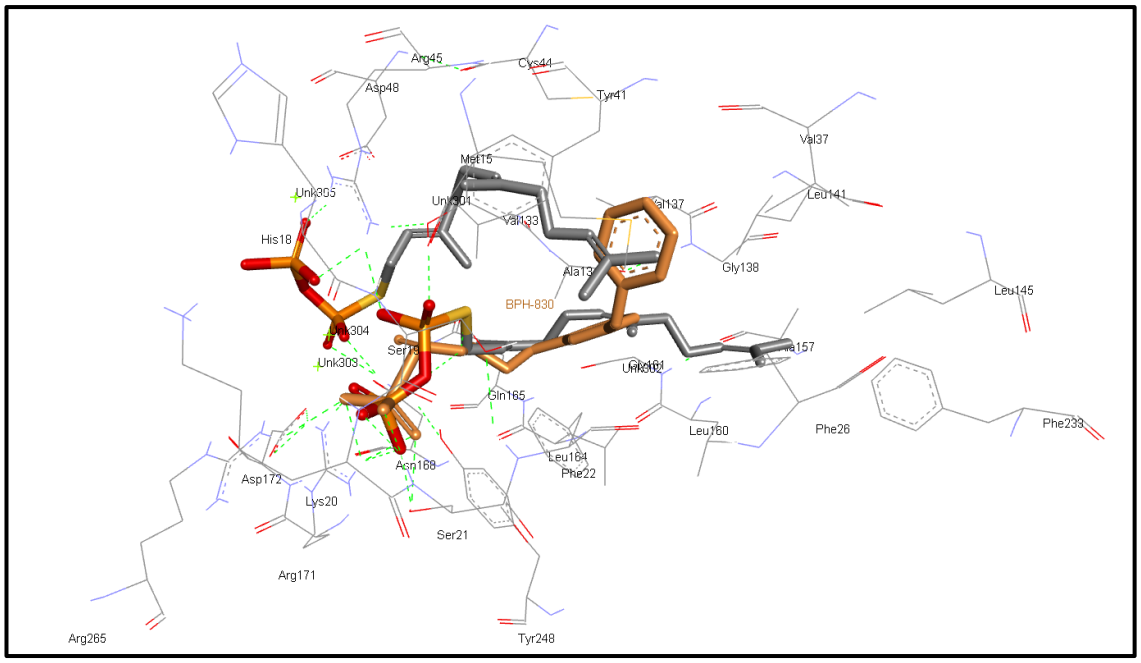
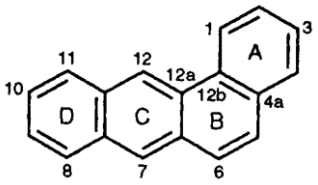
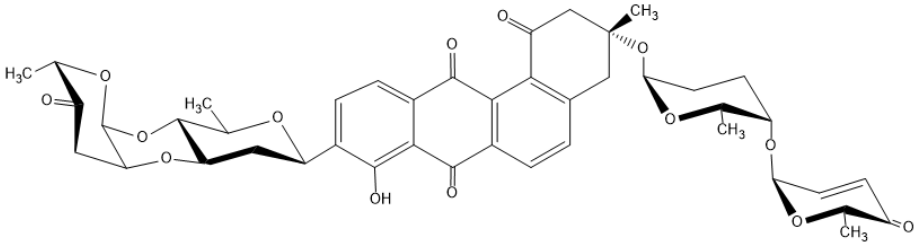


Figure 4.3. Superimpose structure of docked inhibitor BPH-830 with original farnesyl diphosphate coordinates in the complex with CrtM

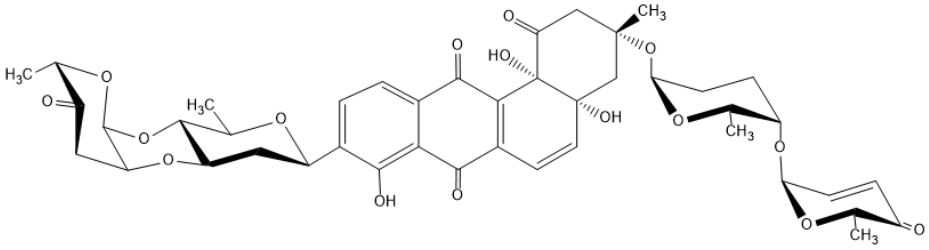
Docking analysis demonstrate that among the attempted compounds; moromycin A (56), saquayamycin B (58), saquayamycin A (145) and saprolmycin E (29) have good interactions with CrtM with higher dock scores; -14.8, -14.4, -13.7, and -13.7 kcal/mol, respectively, when compared with substrate farnesyl diphosphate -11.5 kcal/mol as shown in (Figure 4.4). It has been observed in (56) and (58) the dock scores were -14.8 and -14.4 kcal/mol respectively, the dock scores are similar as well as the structure composition almost same and there are four different sugar subunits, but in (58) there are OH group between A and B rings on Carbons (4a and 12b). But in (29) and (145) we get same dock scores -13.7 kcal/mol when we compared between them we found that there are three sugar subunits connected to D ring and the fourth sugar connected to the A ring.



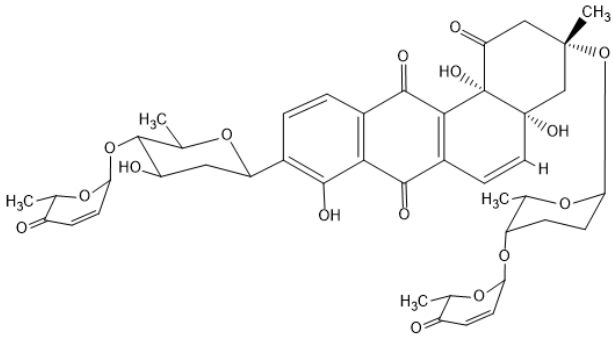
(a) The tetracyclic benz[a]anthracene frame



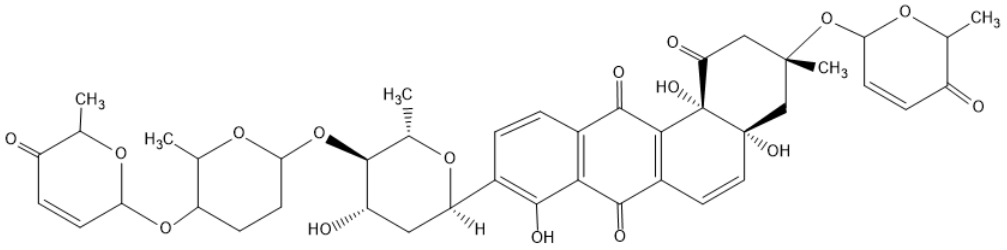
(b) Moromycin A (56) -14.8 kcal/mol



(c) Saquayamycin B (58) -14.4 kcal/mol



(d) Saquayamycin A (145) -13.7 kcal/mol



(e) Saprolmycin E (29) -13.7 kcal/mol

Figure 4.4. Sructures of (a) The tetracyclic benz[a]anthracene frame; (b) Moromycin A (56); (c) Saquayamycin B (58); (d) Saquayamycin A (145); and (e) Saprolmycin E (29)

The ligands were grouped in terms of their structure similarity, their locations in the active site of the proteins. The structures with high dock scores were explicitly shown in (Table 4.1, 4.2, 4.3) and (Figures 4.5-4.10, 4.11-4.21, 4.22-4.32) which distributed on 6, 11, 10 groups for CrtM (3ACW) and 3W7F with and without magnesium respectively.

So generally all (157) structures were successfully docked into the proteins and they were all docked into the pocket where original inhibitor and substrate were sockets, and few of them not docked, the residues involved in the interactions of the ligands with proteins are demonstrated in appendices I, II, and III.

The docking scores for the ligands presented in (Table 4.1) and (Figures 4.5 – 4.10) among the ligands, a group of them have higher docking score than the original inhibitor -11.5 kcal/mol such as in Saprolmycin_D (28), N05WA963A (47), N05WA963D (49), BA_12100E (95), BA_12100Z3 (98), which their dock score was -12.9, -12.9, -11.7, -11.7, -11.6 kcal/mol respectively.

Table 4.1: Average and maximum dock scores of ligands docked to CrtM (3ACW)

#	Angucycline Group Antibiotics	AV. Kcal/mol	Max. Dock	Interacted Residues No.	Group
0	Ligand of Protein	-11.5	-11.5	14	-
29	**Saprolmycin_E**	**-11.4**		**13**	**G1**
28	Saprolmycin_D	-12.9	-12.9	12	G1
155	**Vineomycin_A1**	**-11.5**	**-11.6**	**15**	**G1**
47	**N05WA963A**	**-12.9**	**-13.0**	**14**	**G2**
49	N05WA963D	-11.7	-12.7	15	G2
84	A_7884	-10.7	-11.7	15	G2
88	C104	-10.5	-10.5	12	G2
102	**Capoamycin**	**-10.4**	**-10.5**	**12**	**G2**
95	**BA_12100E**	**-11.7**	**-12.1**	**13**	**G3**
98	BA_12100Z3	-11.6	-11.8	15	G3
92	**BA_12100B**	**-10.8**	**-11.7**	**14**	**G3**
93	BA_12100C	-11.2	-11.7	14	G3
37	**Landomycin_Z**	**-10.2**	**-11.0**	**14**	**G4**
94	**BA_12100D**	**-10.2**	**-10.3**	**13**	**G4**
11	**Rubiginone_B2**	**-8.5**	**-8.9**	**15**	**G5**
54	8_O_methyltetrangulol	-8.6	-8.6	13	G5
118	PD116779	-8.1	-8.3	14	G5
119	X_14881_C	-7.9	-8.2	14	G5
115	**Fujianmycin_A**	**-7.9**	**-8.0**	**13**	**G5**
40	**JBIR_90**	**-9.3**	**-9.7**	**15**	**G6**
87	C104_Aglycon	-9	-9.6	15	G6
33	Gaudimycin_C	-8.4	-8.5	13	G6
154	Retymicin	-8.2	-8.5	11	G6
133	**Homo_UWM6**	**-8.1**	**-8.2**	**11**	**G6**

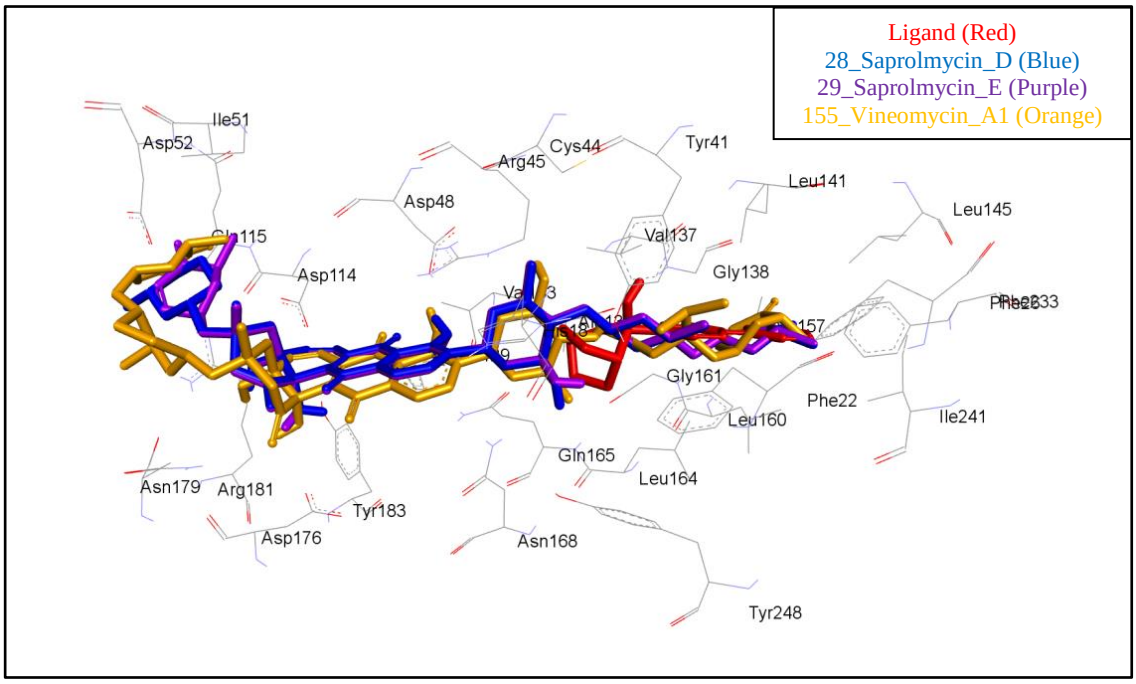


Figure 4.5. Group 1 ligands (28, 29, 155) docked to (3ACW) protein

Saprolmycin_E (29) is the best candidate with score of -13.0 kcal/mol and Vineomycin_A1 (155) is the worst of group 1 with score of -11.6 kcal/mol.

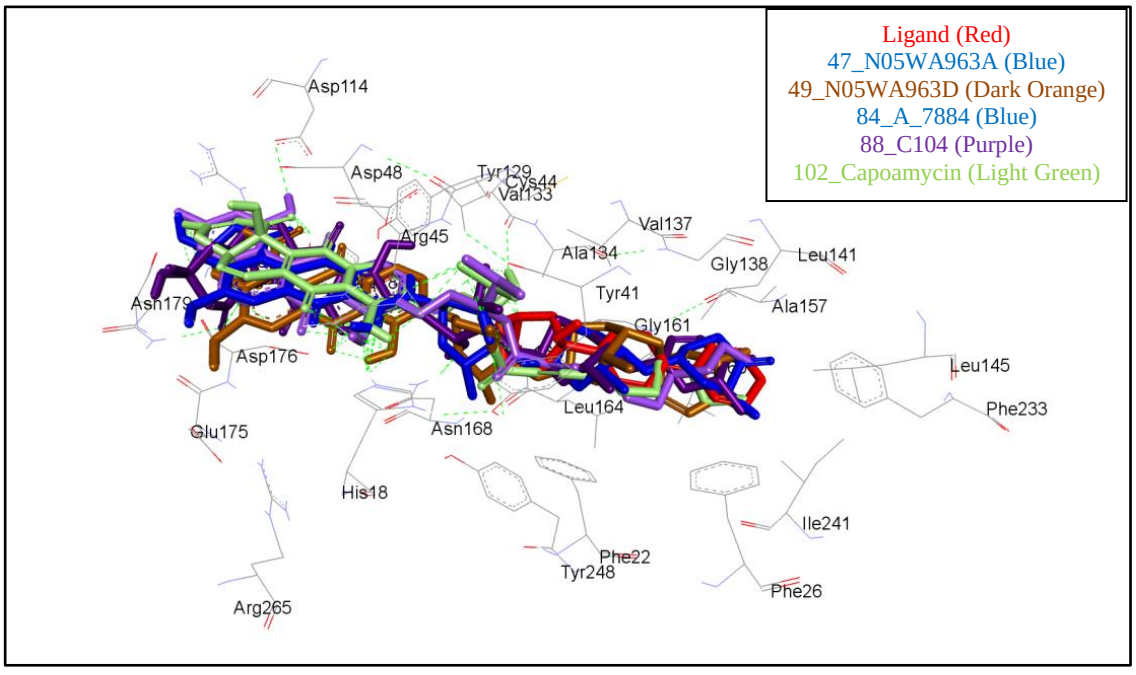


Figure 4.6. Group 2 ligands (47, 49, 84, 88, 102) docked to (3ACW) protein

N05WA963A (47) is the best candidate with score of -13.0 kcal/mol and Capoamycin (102) is the worst of group 2 with score of -10.5 kcal/mol.

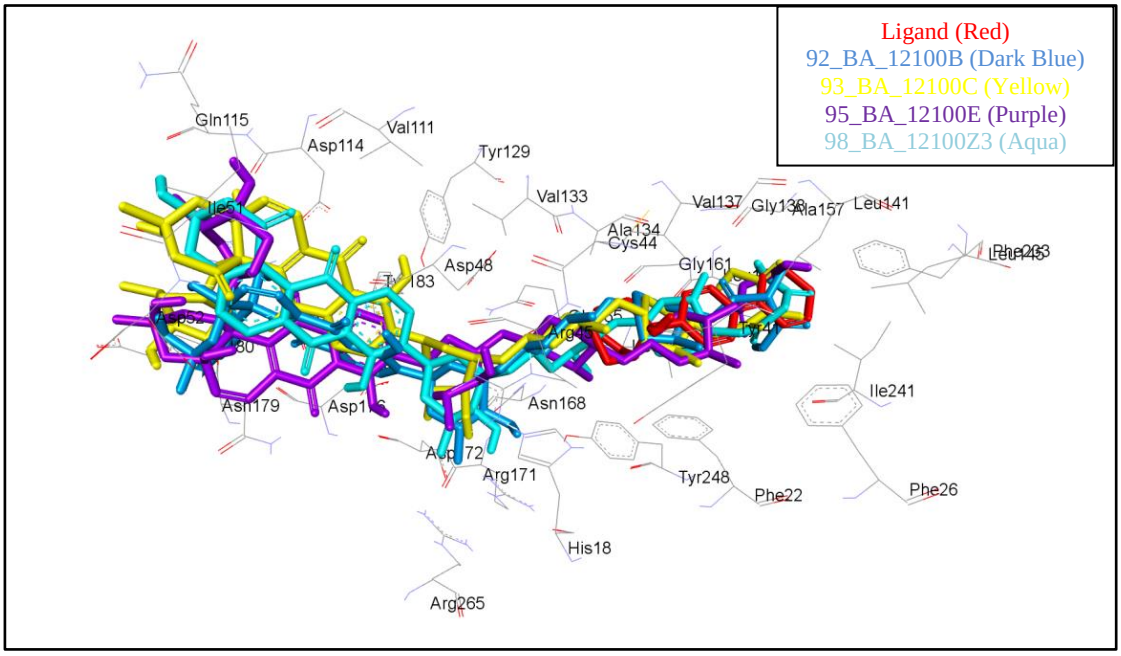


Figure 4.7. Group 3 ligands (92, 93, 95, 98) docked to (3ACW) protein

BA_12100E (95) is the best candidate with score of -12.1 kcal/mol and BA_12100B (92) is the worst of group 3 with score of -11.7 kcal/mol.

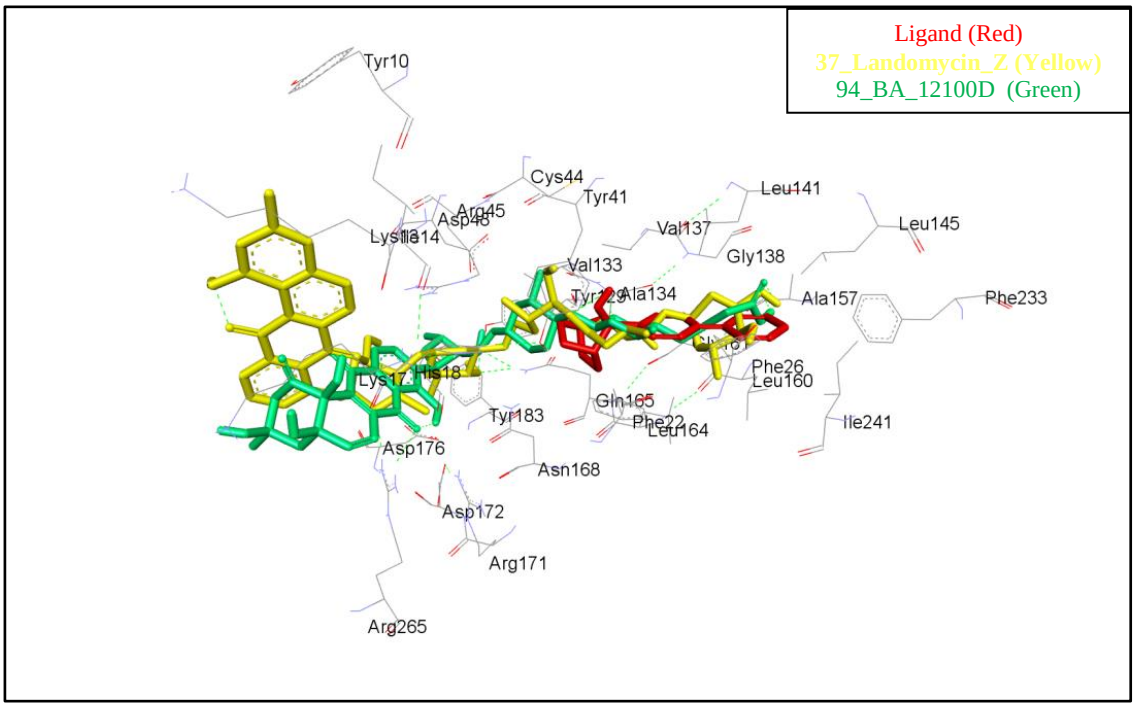


Figure 4.8. Group 4 ligands (37, 94) docked to (3ACW) protein

Landomycin_Z (37) is the best candidate with score of -11.0 kcal/mol and BA_12100D (94) is the worst of group 4 with score of -10.3 kcal/mol.

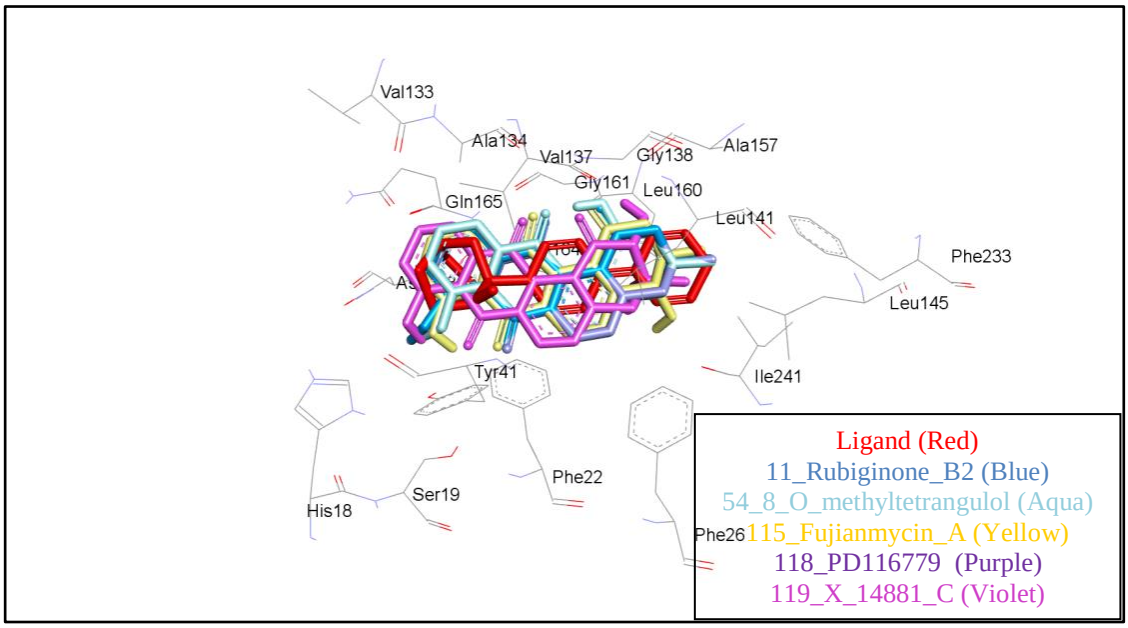


Figure 4.9. Group 5 ligands (11, 54, 115, 118, 119) docked to (3ACW) protein

Rubiginone_B2 (11) is the best candidate with score of -8.9 kcal/mol and Fujianmycin_A (115) is the worst of group 5 with score of -8.0 kcal/mol.

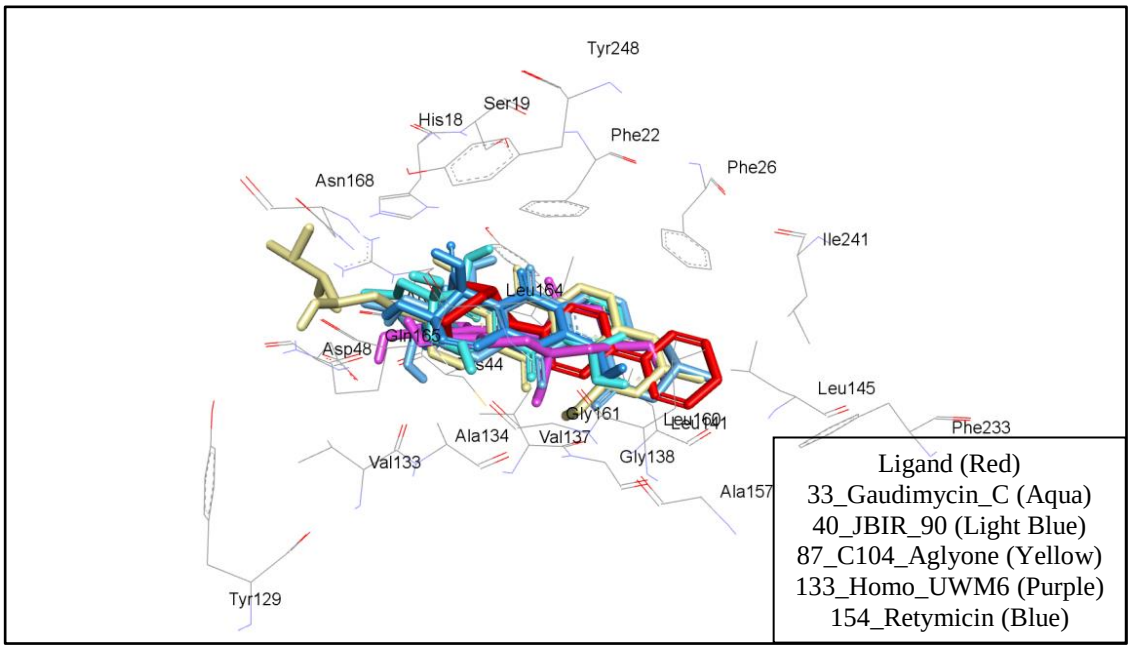


Figure 4.10. Group 6 ligands (33, 40, 87, 133, 154) docked to (3ACW) protein

JBIR_90 (40) is the best candidate with score of -9.7 kcal/mol and Homo_UWM6 (133) is the worst of group 6 with score of -8.2 kcal/mol.

The docking scores for the ligands presented in (Table 4.2) and (Figures 4.11 – 4.21) the ligands were grouped in terms of their structure similarity, their locations in the active site of the proteins, all ligands have higher docking score than the original inhibitor -8.3 kcal/mol and the dock scores are in the range of -14.8 to -8.6 kcal/mol for the protein with magnesium for more detail see Appendix II.

Table 4.2. Average of three dock score with maximum dock score of ligands docked to (3W7F) protein with MG.

#	**Angucycline Group Antibiotics**	AV. kcal/mol	Max. Dock	Interacted Residues No.	Group
0	Ligand of Protein	-8.3	-8.3	22	-
2	**Marangucycline_B**	**-13.4**	**-13.5**	**21**	**G1**
98	BA_12100Z3	-11.7	-11.8	19	G1
59	Sch_47554	-11.6	-11.7	18	G1
13	**Waldiomycin**	**-11.4**	**-11.5**	**18**	**G1**
29	**Saprolmycin_E**	**-13.5**	**-13.7**	**16**	**G2**
28	Saprolmycin_D	-13.5	-13.5	20	G2
38	Grincamycin	-12.5	-12.5	22	G2
30	Saquayamycin_A	-11.2	-11.4	23	G2
19	**Fradimycin_C**	**-11.1**	**-11.1**	**17**	**G2**
42	**JBIR_91**	**-12.5**	**-12.5**	**19**	**G3**
69	Urdamycin_C	-11.5	-12.2	17	G3
124	Landomycin_C	-11.8	-12.0	26	G3
41	**JBIR_116**	**-10.2**	**-10.2**	**19**	**G3**
56	**Moromycin_A**	**-14.8**	**-14.8**	**17**	**G4**
58	Saquayamycin_B	-13.7	-14.4	21	G4
47	N05WA963A	-12.5	-12.5	20	G4
49	**N05WA963D**	**-12.2**	**-12.2**	**20**	**G4**
134	**PI_1894B (Vineomycin A) (OS-4742A1)**	**-12.7**	**-12.7**	**24**	**G5**
65	PI_080 (=PI-6621)	-12.0	-12.1	22	G5
124	Landomycin_C	-11.8	-12.0	26	G5
123	Landomycin_B	-11.3	-11.4	22	G5
93	**BA_12100C**	**-11.0**	**-11.0**	**23**	**G5**

Table 4.2. Average of three dock score with maximum dock score of ligands docked to (3W7F) protein with MG. (continue)

#	**Angucycline Group Antibiotics**	AV. kcal/mol	Max. Dock	Interacted Residues No.	Group
146	**Saquayamycin_B**	**-13.8**	**-13.8**	**21**	**G6**
145	Saquayamycin_A	-13.7	-13.7	21	G6
148	Saquayamycin_D	-13.6	-13.6	19	G6
151	Saquayamycin_K4	-12.4	-12.4	19	G6
92	BA_12100B	-11.4	-12.3	19	G6
84	A_7884	-12.0	-12.0	18	G6
147	**Saquayamycin_C**	**-11.8**	**-11.8**	**17**	**G6**
6	**Hatomarubigin_B**	**-9.8**	**-9.8**	**15**	**G7**
7	Hatomarubigin_C	-9.7	-9.7	16	G7
81	Tetrangulol methyl ether	-9.7	-9.7	11	G7
11	Rubiginone_B2	-9.5	-9.6	14	G7
119	X_14881_C	-9.6	-9.6	14	G7
120	X_14881_E	-9.6	-9.6	12	G7
116	Fujianmycin_B	-9.5	-9.5	14	G7
102	Capoamycin	-9.4	-9.4	17	G7
80	**Seitomycin**	**-8.9**	**-9.0**	**13**	**G7**
31	**Gaudimycin_A**	**-9.8**	**-9.8**	**14**	**G8**
33	Gaudimycin_C	-9.5	-9.7	15	G8
32	Gaudimycin_B	-9.6	-9.6	16	G8
137	Urdamycin_J	-9.6	-9.6	15	G8
51	Rabelomycin	-9.3	-9.3	16	G8
62	**Tetrangomycin**	**-9.3**	**-9.3**	**16**	**G8**
108	**Elmycin_E**	**-9.6**	**-9.6**	**12**	**G9**
110	X_14881_D	-9.6	-9.6	13	G9
55	8_O_methyl_7_deoxo_ 7_hydroxytetrangomycin	-9.3	-9.3	14	G9
107	Elmycin_D	-9.1	-9.1	11	G9
109	**X_14881_B**	**-9.1**	**-9.1**	**13**	**G9**

Table 4.2. Average of three dock score with maximum dock score of ligands docked to (3W7F) protein with MG. (continue)

#	**Angucycline Group Antibiotics**	AV. kcal/mol	Max. Dock	Interacted Residues No.	Group
34	**Aquayamycin**	**-10.3**	**-10.3**	**17**	**G10**
4	Actinosporin_B	-8.7	-9.3	18	G10
154	Retymicin	-9.3	-9.3	12	G10
136	**Urdamycin_I**	**-9.2**	**-9.2**	**15**	**G10**
86	**SM_196 A**	**-9.8**	**-9.8**	**12**	**G11**
115	Fujianmycin_A	-9.5	-9.6	10	G11
118	PD116779	-9.4	-9.5	11	G11
111	**Emycin_A**	**-9.3**	**-9.4**	**11**	**G11**

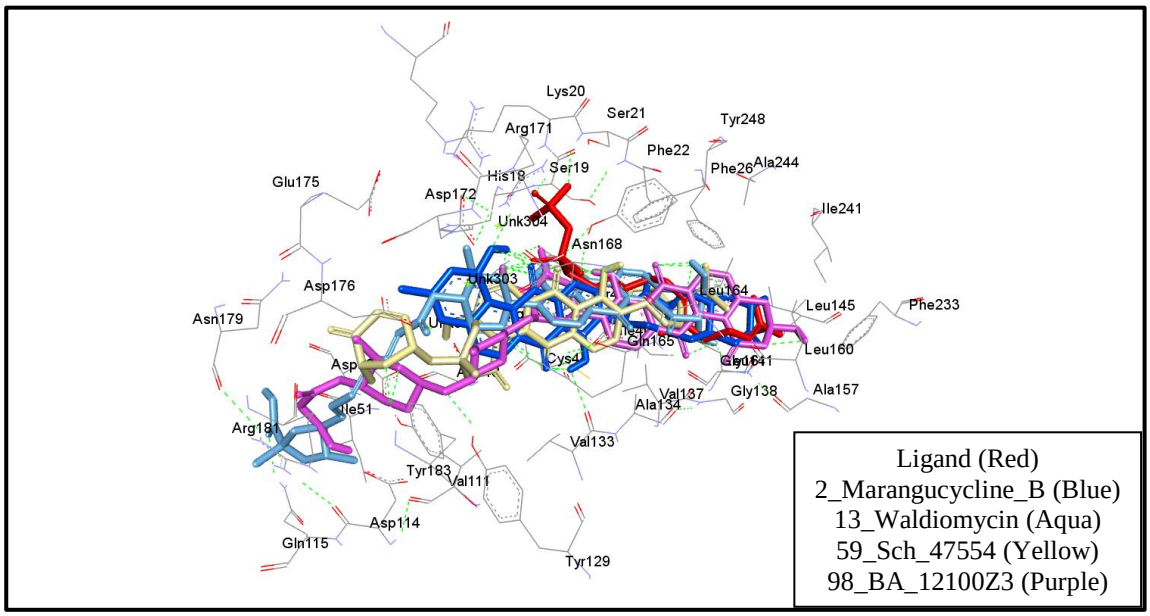


Figure 4.11. Group 1 ligands (2, 13, 59, 98) docked to (3W7F) protein with MG.

Marangucycline_B (2) is the best candidate with score of -13.5 kcal/mol and Waldiomycin (13) is the worst of group 1 with score of -11.5 kcal/mol.

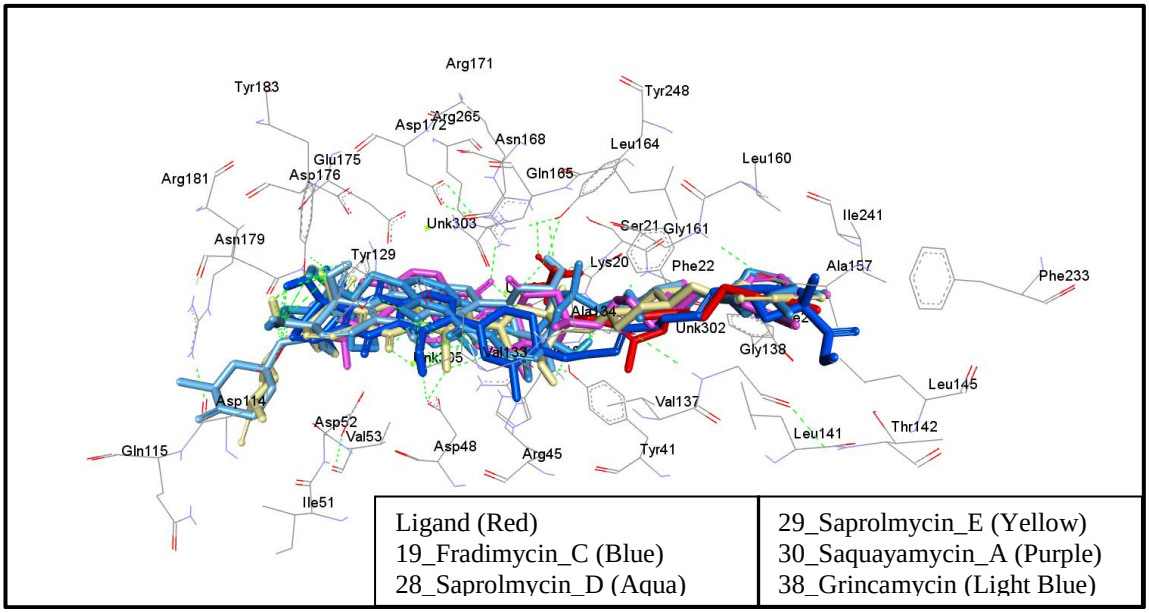


Figure 4.12. Group 2 ligands (19, 28, 29, 30, 38) docked to (3W7F) protein with MG.

Saprolmycin_E (29) is the best candidate with score of -13.7 kcal/mol and Fradimycin_C (19) is the worst of group 2 with score of -11.1 kcal/mol.

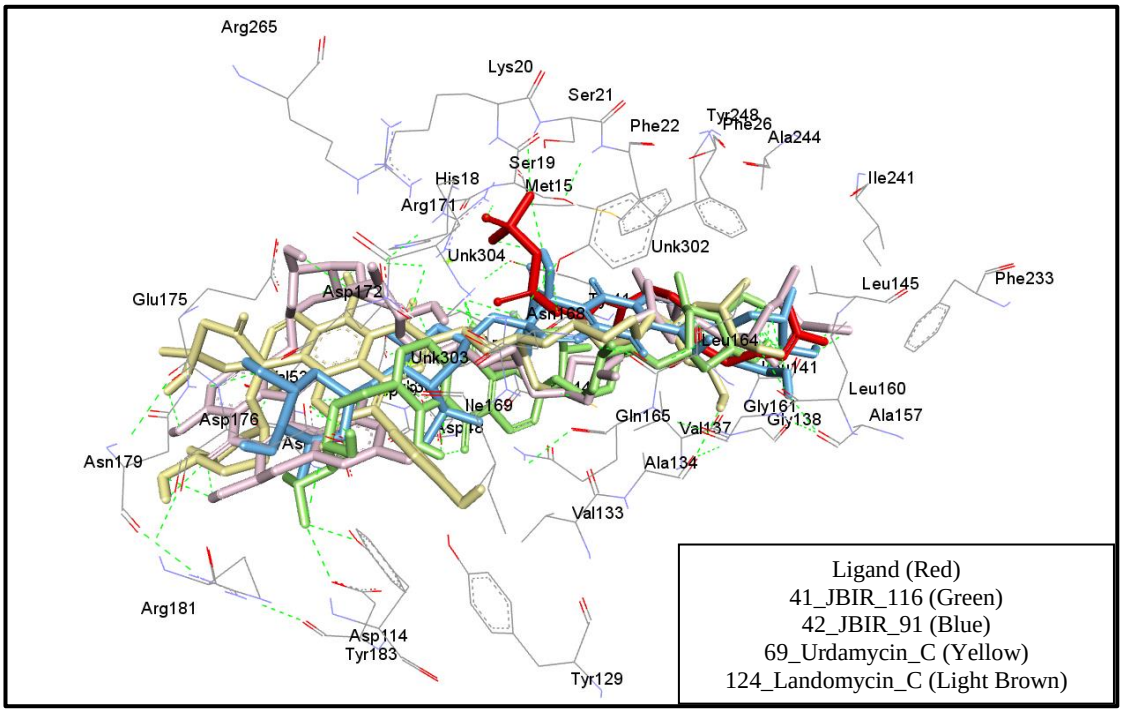


Figure 4.13. Group 3 ligands (41, 42, 69, 124) docked to (3W7F) protein with MG.

JBIR_91 (42) is the best candidate with score of -12.5 kcal/mol and JBIR_116 (41) is the worst of group 3 with score of -10.2 kcal/mol.

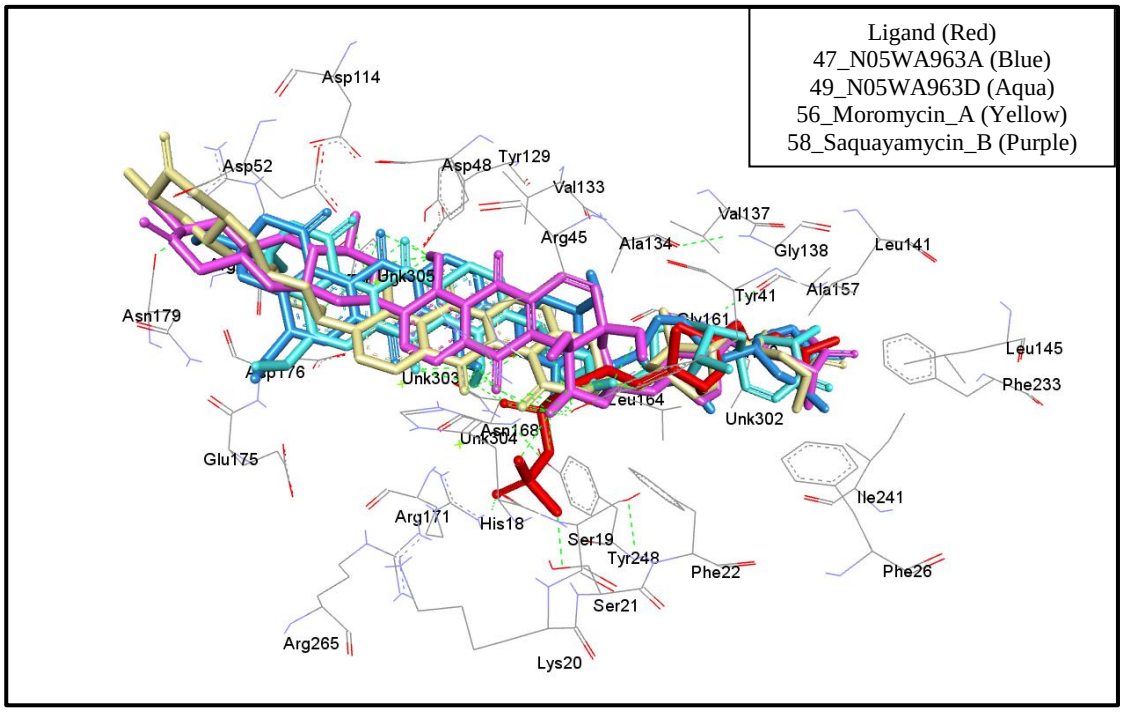


Figure 4.14. Group 4 ligands (47, 49, 56, 58) docked to (3W7F) protein with MG.

Moromycin_A (56) is the best candidate with score of -14.8 kcal/mol and N05WA963D (49) is the worst of group 4 with score of -12.2 kcal/mol.

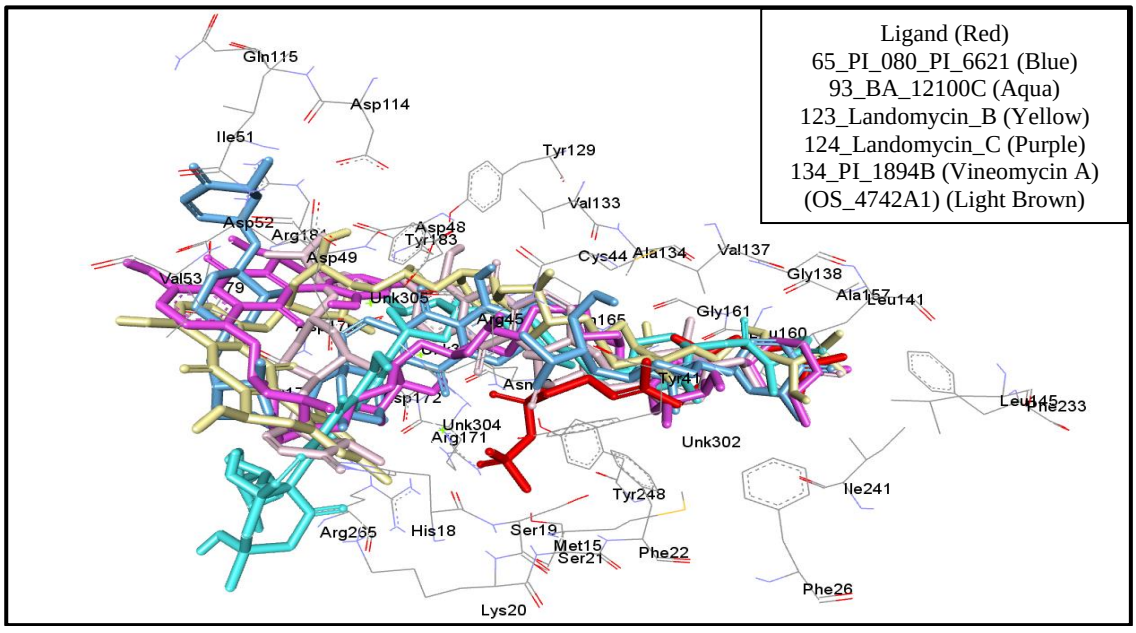


Figure 4.15. Group 5 ligands (65, 93, 123, 124, 134) docked to (3W7F) protein with MG.

PI_1894B (Vineomycin A) (OS-4742A1) (134) is the best candidate with score of -12.7 kcal/mol and BA_12100C (93) is the worst of group 5 with score of -11.0 kcal/mol.

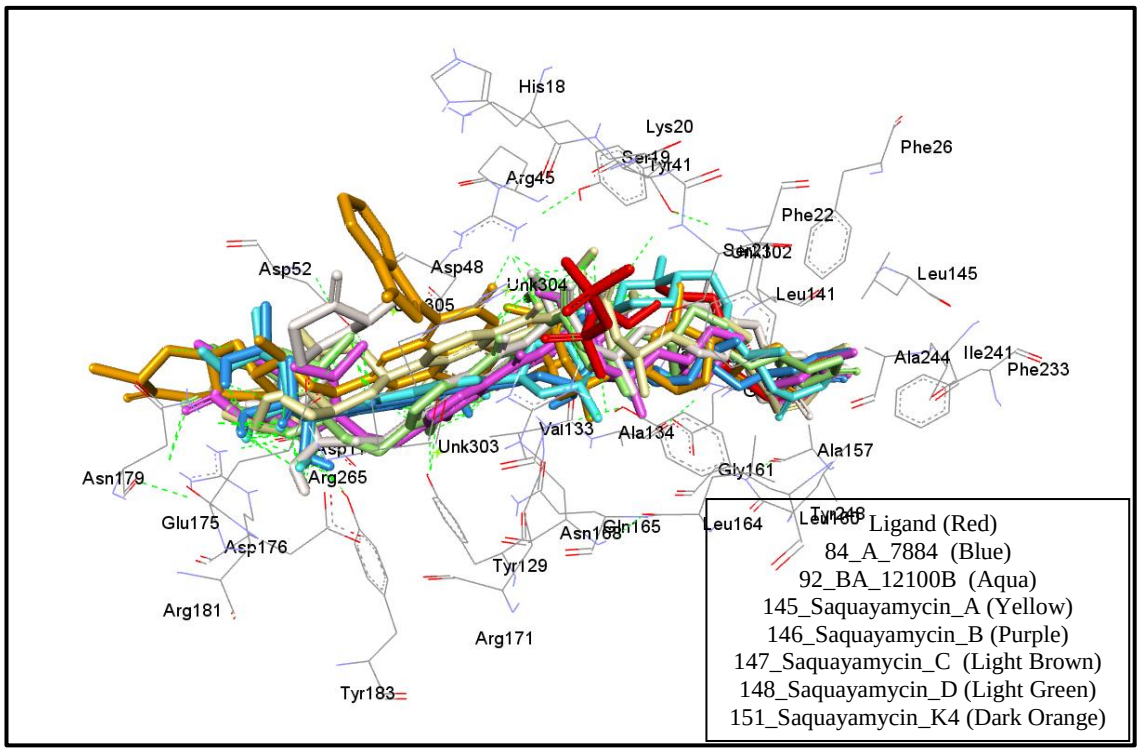


Figure 4.16. Group 6 ligands (84, 92, 145, 146, 147, 148, 151) docked to (3W7F) protein with MG.

Saquayamycin_B (146) is the best candidate with score of -13.8 kcal/mol and Saquayamycin_C (147) is the worst of group 6 with score of -11.8 kcal/mol.

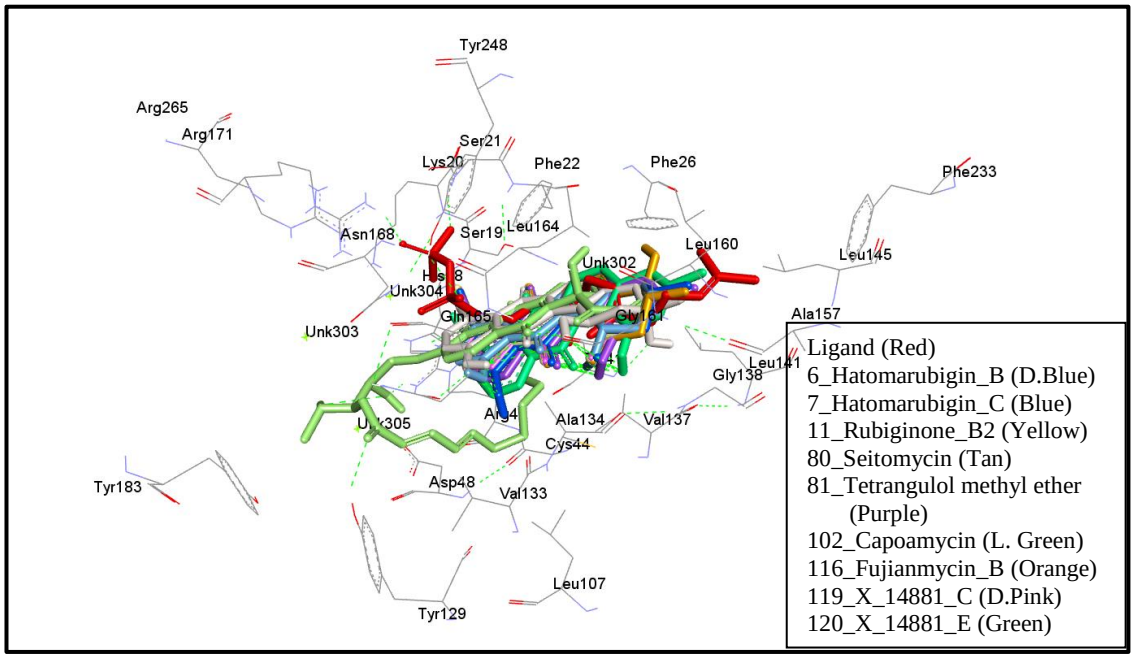


Figure 4.17. Group 7 ligands (6, 7, 11, 80, 81, 102, 116, 119, 120) docked to (3W7F) protein with MG.

Hatomarubigin_B (6) is the best candidate with score of -9.8 kcal/mol and Seitomycin (80) is the worst of group 7 with score of -9.0 kcal/mol.

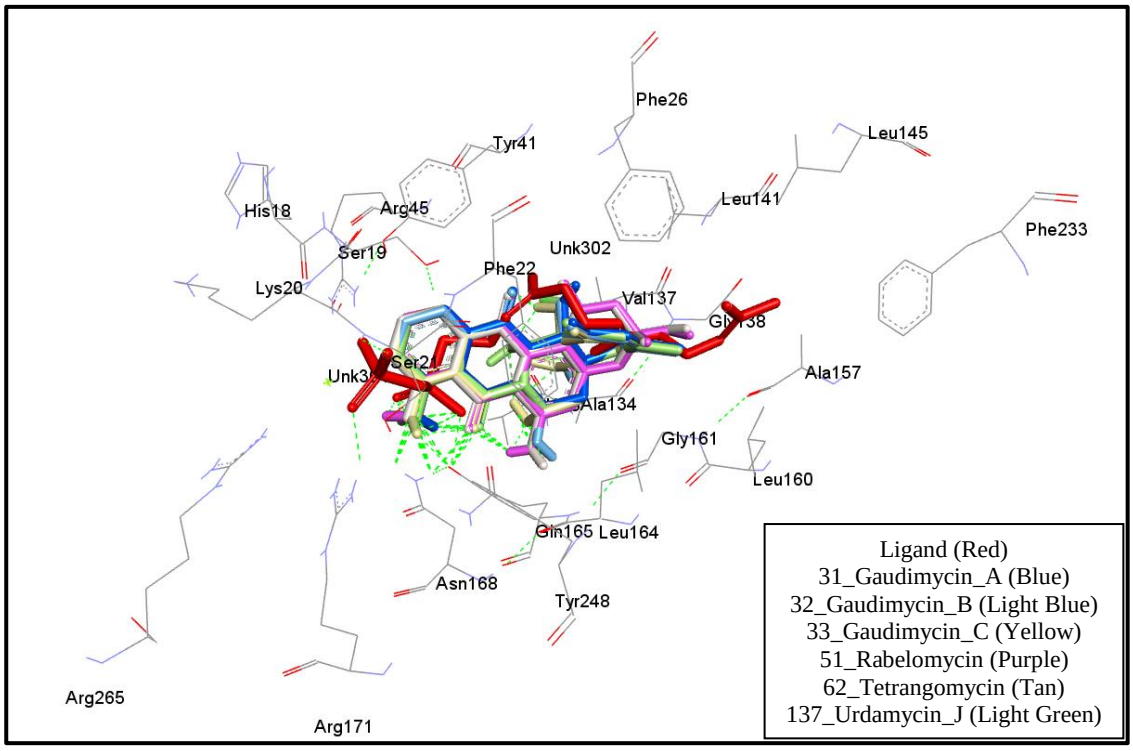


Figure 4.18. Group 8 ligands (31, 32, 33, 51, 62, 137) docked to (3W7F) protein with MG.

Gaudimycin_A (31) is the best candidate with score of -9.8 kcal/mol and Tetrangomycin (62) is the worst of group 8 with score of -9.3 kcal/mol.

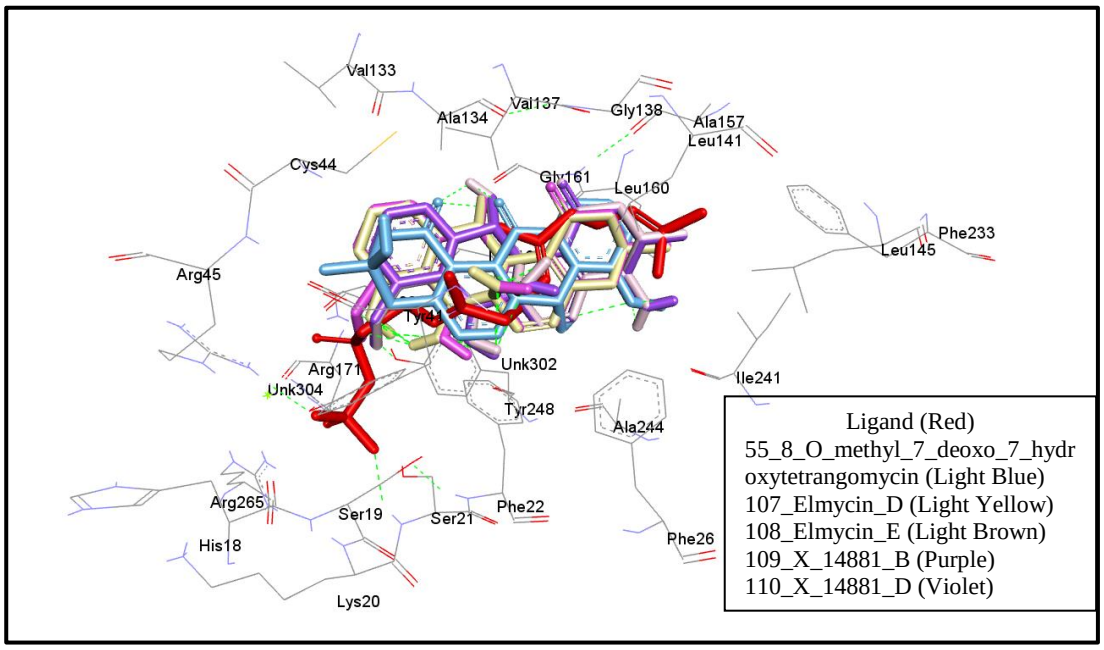


Figure 4.19. Group 9 ligands (55, 107, 108, 109, 110) docked to (3W7F) protein with MG.

Elmycin_E (108) is the best candidate with score of -9.6 kcal/mol and X_14881_B (109) is the worst of group 9 with score of -9.1 kcal/mol.

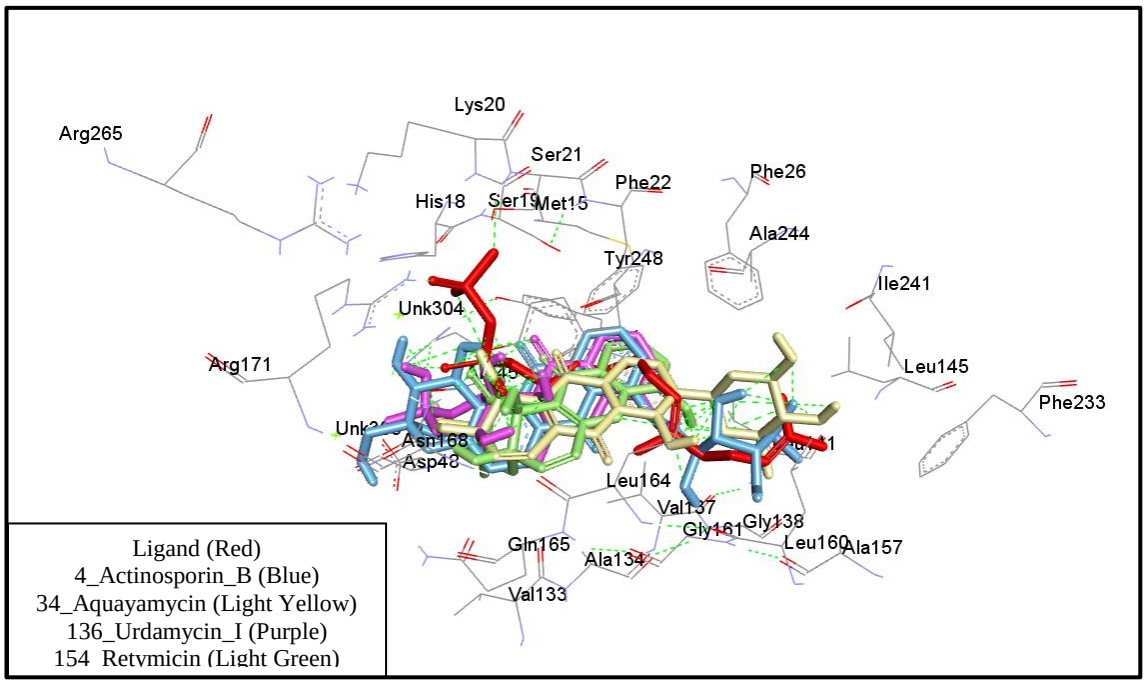


Figure 4.20. Group 10 ligands (4, 34, 136, 154) docked to (3W7F) protein with MG.

Aquayamycin (34) is the best candidate with score of -10.3 kcal/mol and Urdamycin_I (136) is the worst of group 10 with score of -9.2 kcal/mol.

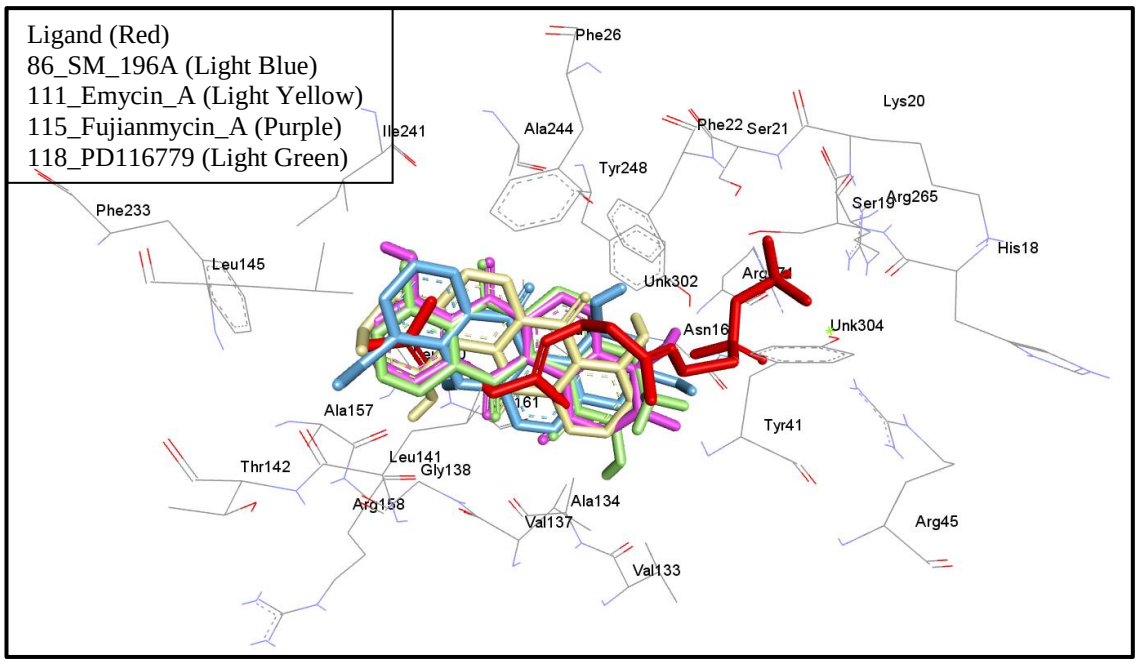


Figure 4.21. Group 11 ligands (86, 111, 115, 118) docked to (3W7F) protein with MG.

SM_196 A (86) is the best candidate with score of -9.8 kcal/mol and Emycin_A (111) is the worst of group 11 with score of -9.4 kcal/mol.

The docking scores for the ligands presented in (Table 4.3) and (Figures 4.22 – 4.32) the ligands were grouped in terms of their structure similarity, their locations in the active site of the proteins, all of the ligands have higher docking score than the original inhibitor -8.1 kcal/mol and the dock scores are in the range of -14.3 to -8.7 kcal/mol for the protein without magnesium for more detail see Appendix III.

Table 4.3. Average of three dock score with maximum dock score of ligands docked to (3W7F) protein without MG.

#	**Angucycline Group Antibiotics**	AV. kcal/mol	Max. Dock	Interacted Residues No.	Group
0	Ligand of Protein	-8.1	-8.3	20	G1
29	**Saprolmycin_E**	**-13.2**	**-13.3**	**19**	**G1**
28	Saprolmycin_D	-13.2	-13.2	18	G1
141	Kerriamycin_C	-11.9	-11.9	21	G1
94	**BA_12100D**	**-11.6**	**-11.7**	**19**	**G1**
151	**Saquayamycin_K4**	**-14.3**	**-15.0**	**24**	**G2**
56	Moromycin_A	-14.4	-14.4	18	G2
146	Saquayamycin_B	-13.6	-13.6	17	G2
148	Saquayamycin_D	-13.5	-13.6	20	G2
134	PI_1894B (Vineomycin A) (OS-4742A1)	-12.6	-12.6	24	G2
155	Vineomycin_A1	-11.9	-12.3	17	G2
38	Grincamycin	-12.2	-12.2	24	G2
147	**Saquayamycin_C**	**-11.7**	**-12.1**	**16**	**G2**
46	**Urdamycin_B**	**-12.8**	**-12.8**	**17**	**G3**
47	N05WA963A	-12.6	-12.6	14	G3
49	**N05WA963D**	**-12.3**	**-12.4**	**13**	**G3**
143	**PI_085**	**-12.6**	**-12.7**	**18**	**G4**
144	**PI_087**	**-12.4**	**-12.5**	**19**	**G4**
42	**JBIR_91**	**-12.6**	**-12.7**	**20**	**G5**
34	**Aquayamycin**	**-10**	**-10.1**	**20**	**G5**

Table 4.3. Average of three dock score with maximum dock score of ligands docked to (3W7F) protein without MG. (continue)

#	**Angucycline Group Antibiotics**	AV. kcal/mol	Max. Dock	Interacted Residues No.	Group
6	**Hatomarubigin_B**	**-9.7**	**-9.7**	**15**	**G6**
88	C104	-9.6	-9.7	14	G6
7	Hatomarubigin_C	-9.6	-9.6	16	G6
81	Tetrangulol methyl ether	-9.6	-9.6	11	G6
11	Rubiginone_B2	-9.5	-9.5	14	G6
119	X_14881_C	-9.5	-9.5	14	G6
120	X_14881_E	-9.5	-9.5	12	G6
116	Fujianmycin_B	-9.4	-9.4	14	G6
80	**Seitomycin**	**-8.8**	**-8.8**	**15**	**G6**
31	**Gaudimycin_A**	**-9.7**	**-9.7**	**15**	**G7**
33	Gaudimycin_C	-9.7	-9.7	14	G7
32	Gaudimycin_B	-9.6	-9.6	15	G7
51	Rabelomycin	-9.3	-9.3	15	G7
62	Tetrangomycin	-9.3	-9.3	15	G7
82	**SM_196B**	**-9.2**	**-9.2**	**16**	**G7**
108	**Elmycin_E**	**-9.5**	**-9.5**	**14**	**G8**
110	X_14881_D	-9.5	-9.5	13	G8
107	Elmycin_D	-9.1	-9.1	13	G8
109	**X_14881_B**	**-9.1**	**-9.1**	**15**	**G8**
115	**Fujianmycin_A**	**-9.6**	**-9.6**	**12**	**G9**
111	Emycin_A	-9.4	-9.5	13	G9
118	**PD116779**	**-9.4**	**-9.4**	**14**	**G9**
137	**Urdamycin_J**	**-9.5**	**-9.5**	**13**	**G10**
156	Azicemicin_A	-9.1	-9.1	18	G10
157	**Azicemicin_B**	**-9.0**	**-9.0**	**22**	**G10**

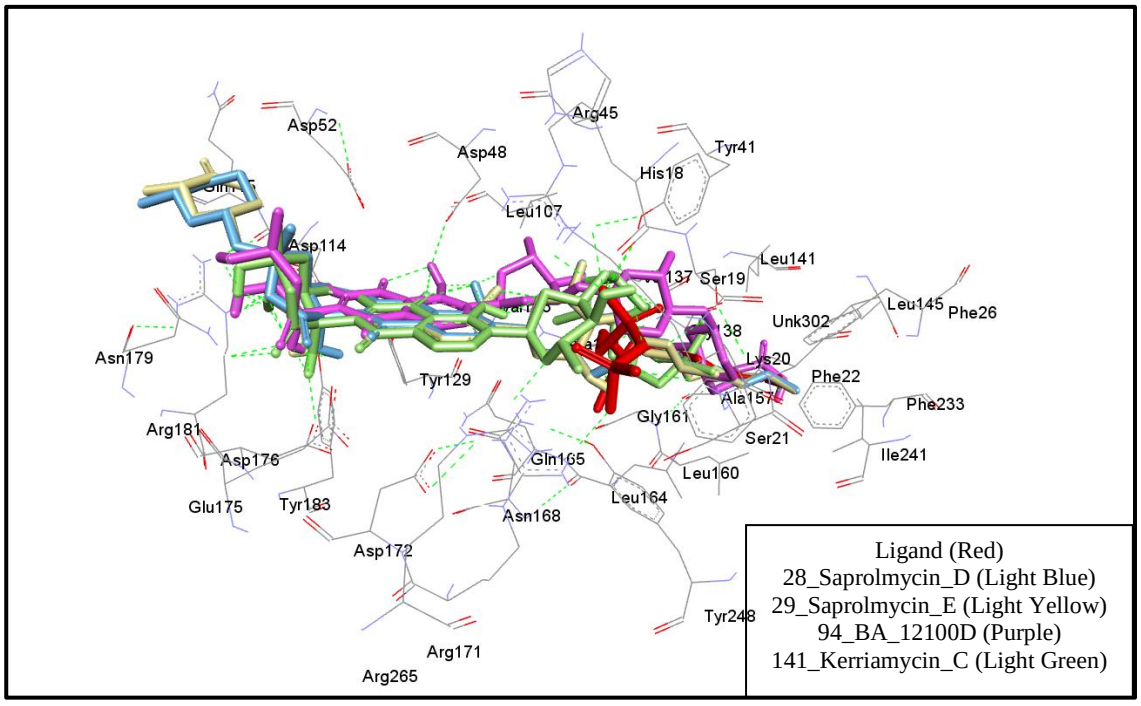


Figure 4.22. Group 1 ligands (28, 29, 94, 141) docked to (3W7F) protein without MG.

Saprolmycin_E (29) is the best candidate with score of -13.3 kcal/mol and BA_12100D (94) is the worst of group 1 with score of -11.7 kcal/mol.

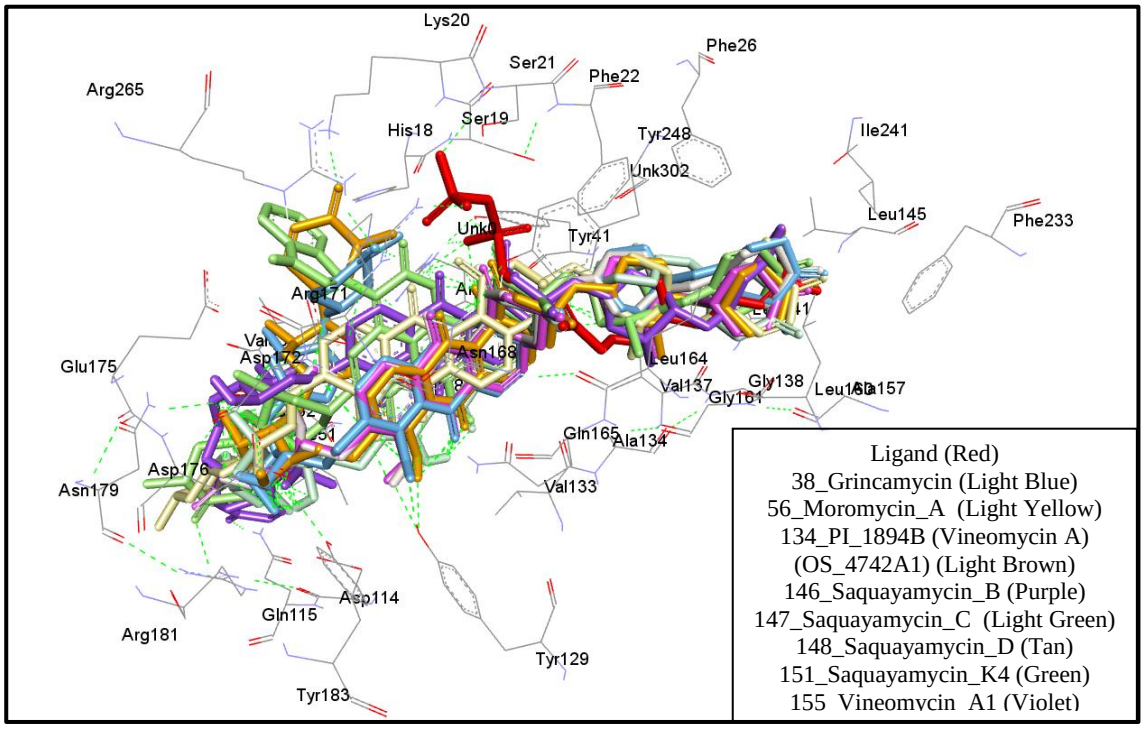


Figure 4.23. Group 2 ligands (38, 56, 134, 146, 147, 148, 151, 155) docked to (3W7F) protein without MG.

Saquayamycin_K4 (151) is the best candidate with score of -15.0 kcal/mol and Saquayamycin_C (147) is the worst of group 2 with score of -12.1 kcal/mol.

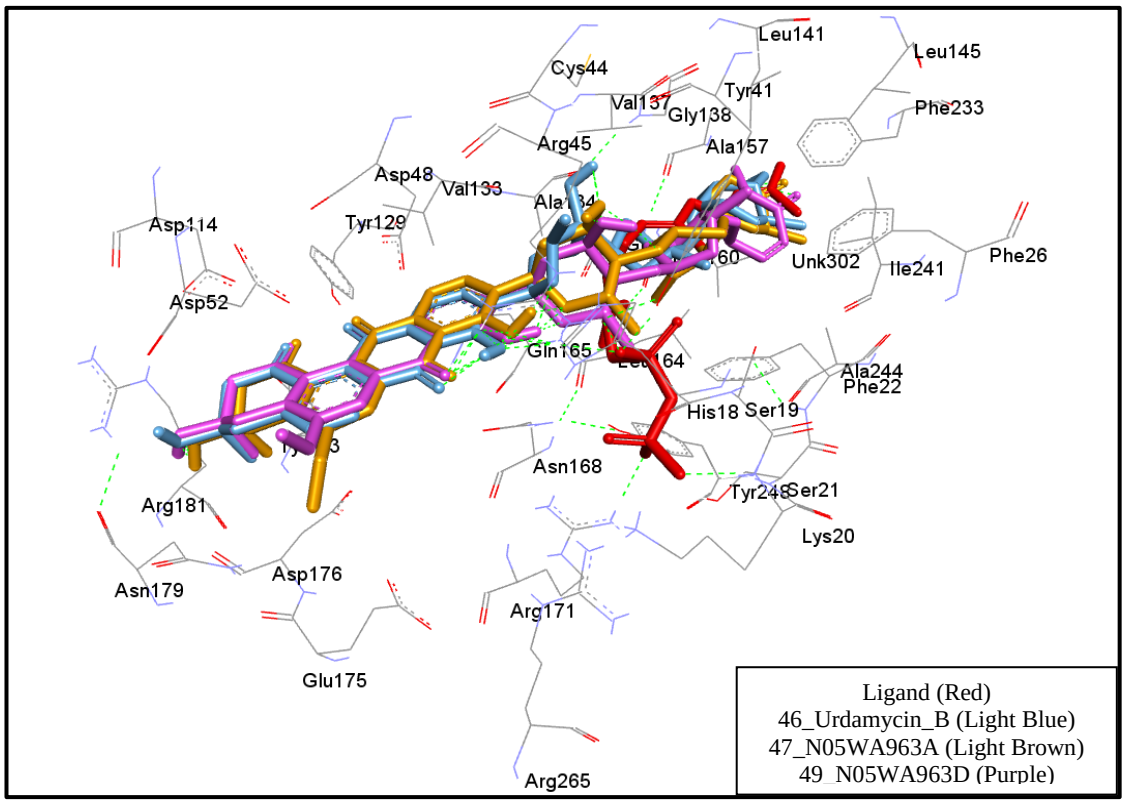


Figure 4.24. Group 3 ligands (46, 47, 49) docked to (3W7F) protein without MG.

Urdamycin_B (46) is the best candidate with score of -12.8 kcal/mol and N05WA963D (49) is the worst of group 3 with score of -12.4 kcal/mol.

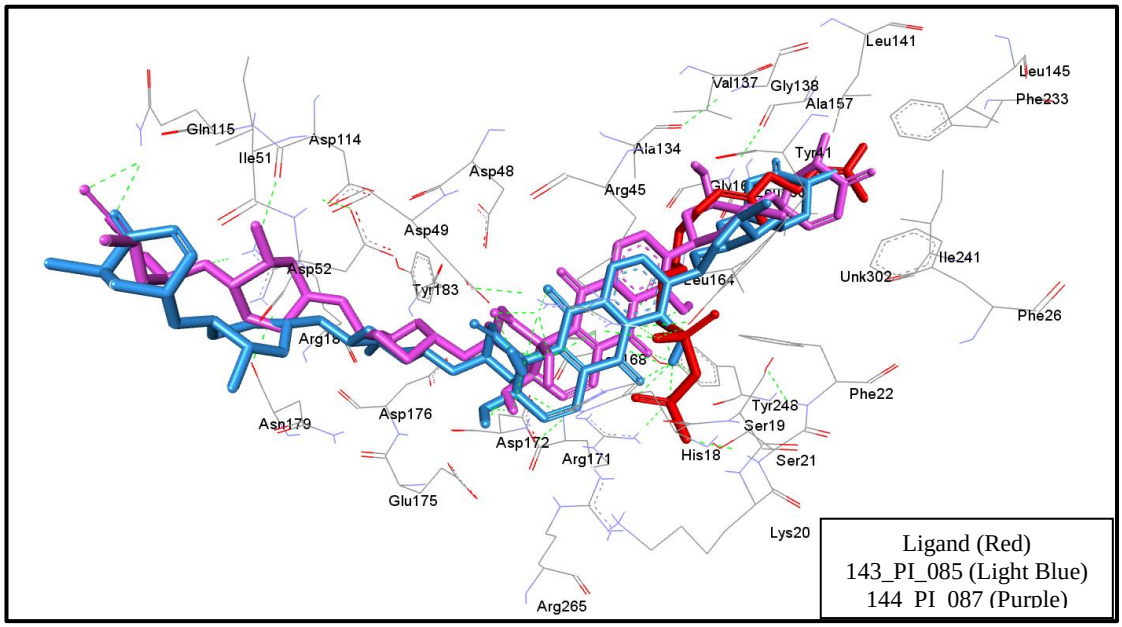


Figure 4.25. Group 4 ligands (143_PI_085, 144_PI_087) docked to (3W7F) protein without MG.

PI_085 (143) is the best candidate with score of -12.7 kcal/mol and PI_087 (144) is the worst of group 4 with score of -12.5 kcal/mol.

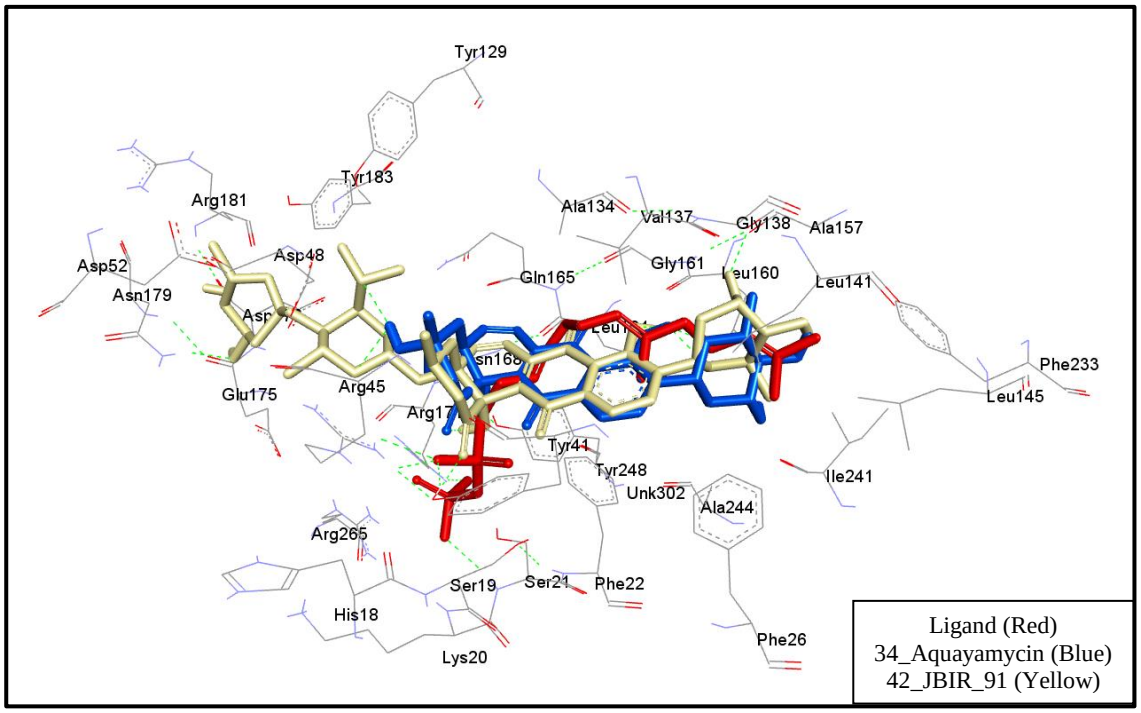


Figure 4.26. Group 5 ligands (34, 42) docked to (3W7F) protein without MG.

JBIR_91 (42) is the best candidate with score of -12.7 kcal/mol and Aquayamycin (34) is the worst of group 5 with score of -10.1 kcal/mol.

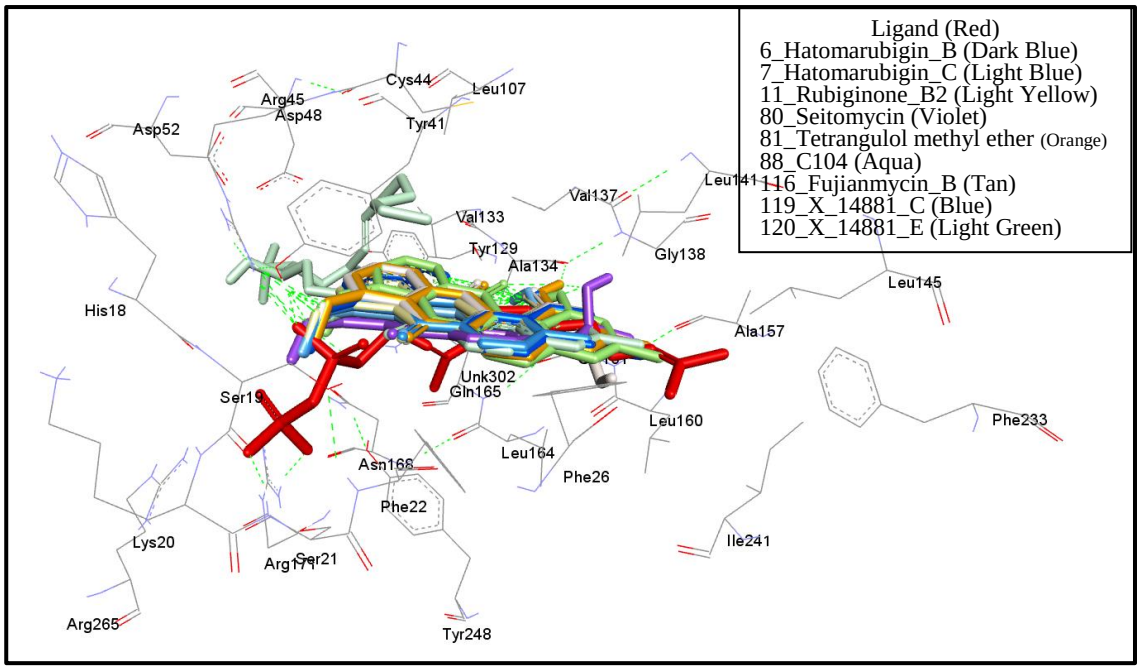


Figure 4.27. Group 6 ligands (6, 7, 11, 80, 81, 88, 116, 119, 120) docked to (3W7F) protein without MG.

Hatomarubigin_B (6) is the best candidate with score of -9.7 kcal/mol and Seitomycin (80) is the worst of group 6 with score of -8.8 kcal/mol.

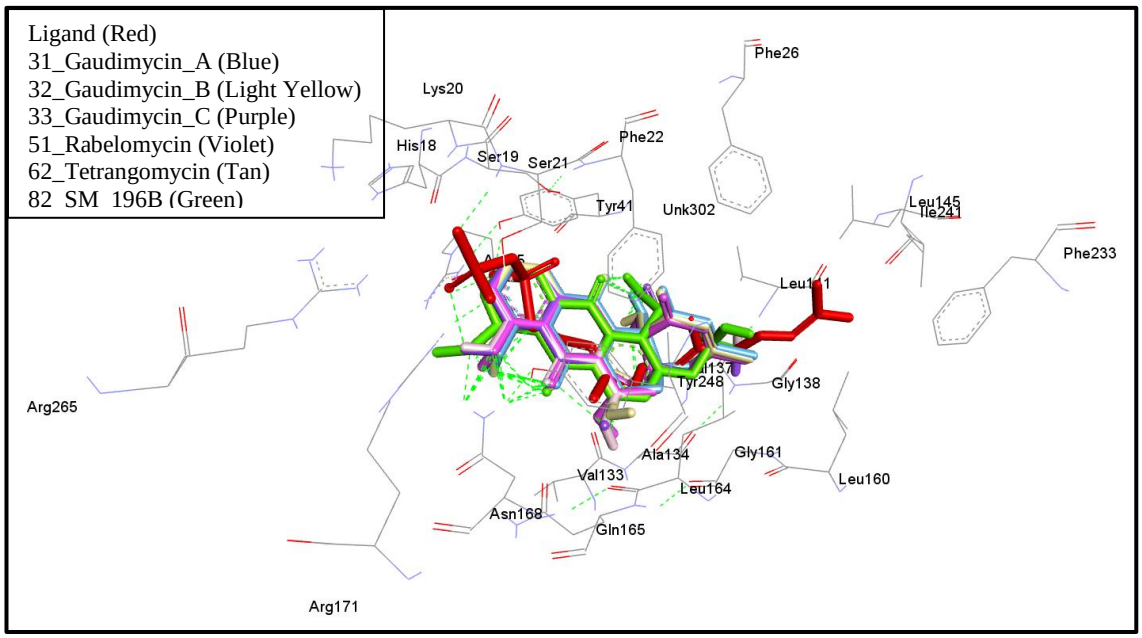


Figure 4.28. Group 7 ligands (31, 32, 33, 51, 62, 82) docked to (3W7F) protein without MG.

Gaudimycin_A (31) is the best candidate with score of -9.7 kcal/mol and SM_196B (82) is the worst of group 7 with score of -9.2 kcal/mol.

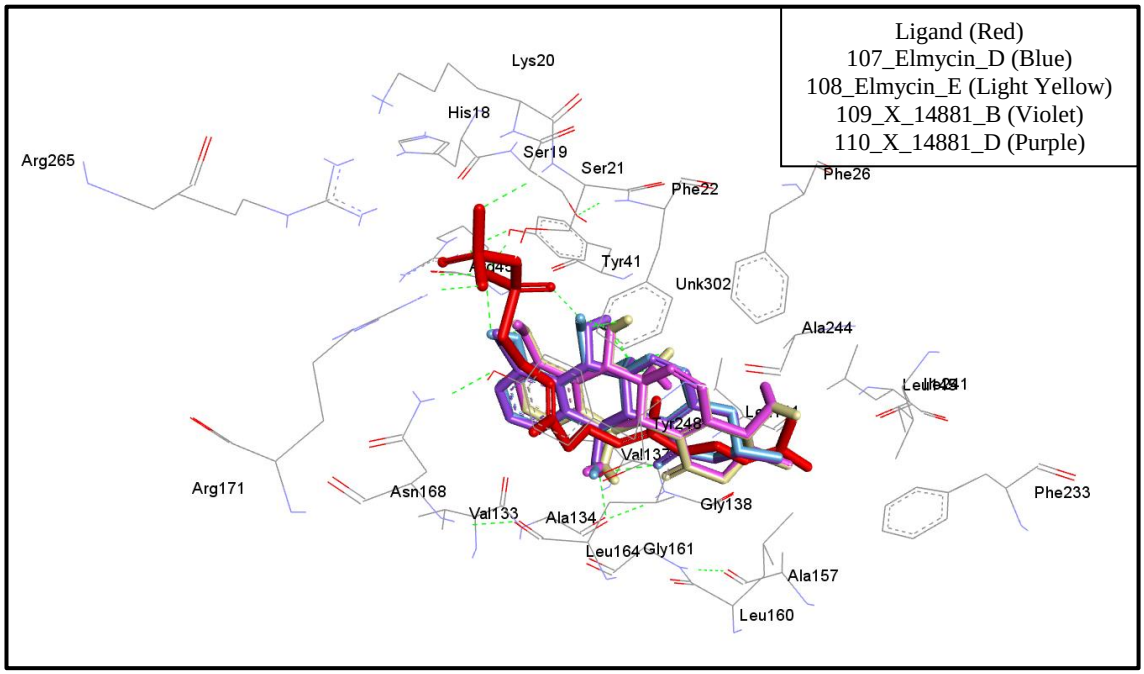


Figure 4.29. Group 8 ligands (107, 108, 109, 110) docked to (3W7F) protein without MG.

Elmycin_E (108) is the best candidate with score of -9.5 kcal/mol and X_14881_B (109) is the worst of group 8 with score of -9.1 kcal/mol.

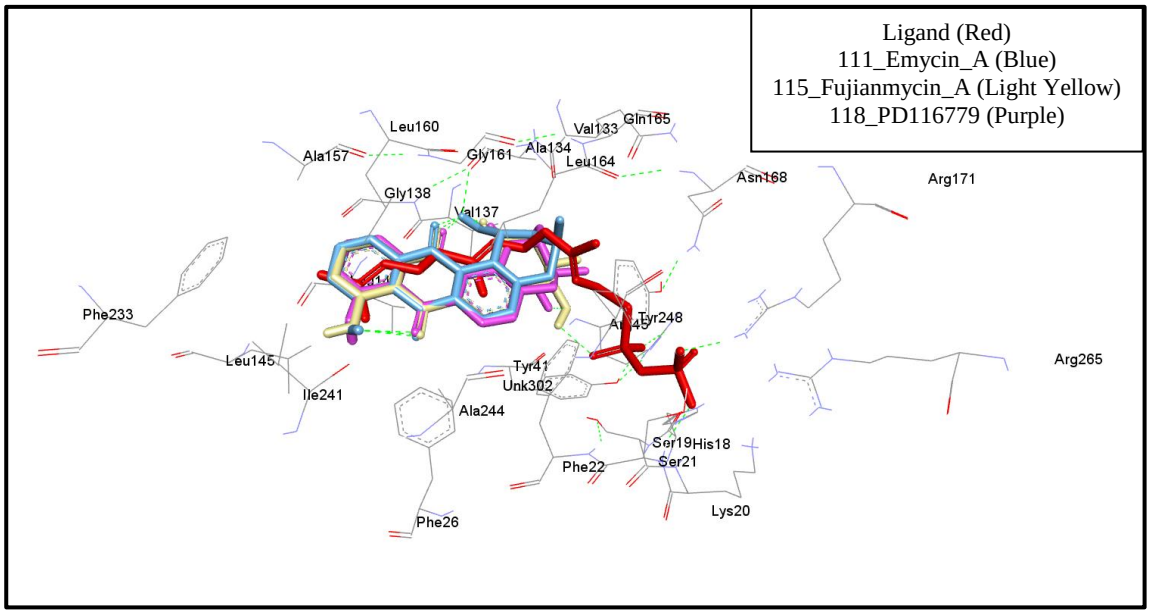


Figure 4.30. Group 9 ligands (111, 115, 118) docked to (3W7F) protein without MG.

Fujianmycin_A (115) is the best candidate with score of -9.6 kcal/mol and PD116779 (118) is the worst of group 9 with score of -9.4 kcal/mol.

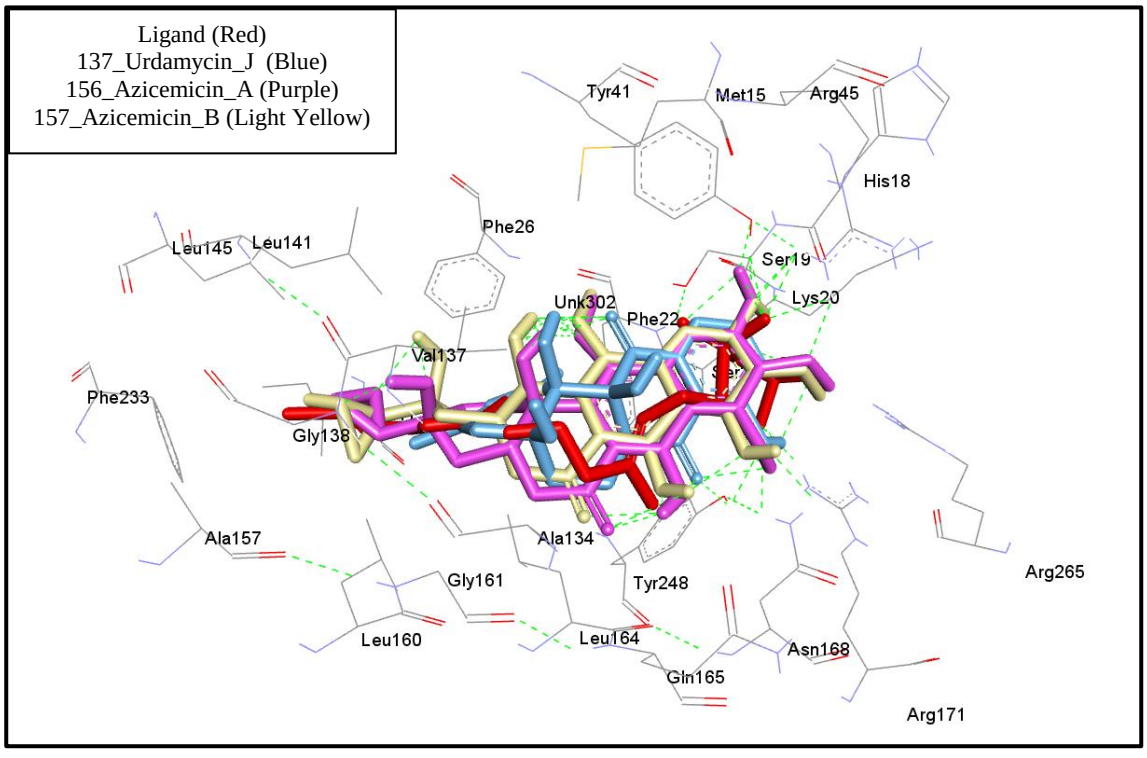


Figure 4.31. Group 10 ligands (137, 156, 157) docked to (3W7F) protein without MG.

Urdamycin_J (137) is the best candidate with score of -9.5 kcal/mol and Azicemicin_B (157) is the worst of group 10 with score of -9.0 kcal/mol.

Sakai *et al.* (2012) reported that the first member of angucycline compound tetrangomycin was found to inhibit the staphyloxanthin production by MRSA in the paper disk assay. However, the potential therapeutic target of tetrangomycin in the biosynthesis of staphyloxanthin was not clear, as reported by Ozakin *et al.* (2016) in order to investigate the potential molecular targets for tetrangomycin the molecular docking was performed using dehydrosqualine synthase enzyme (PDB ID: 2ZY1) which is catalyzed the first committed step of staphyloxanthin biosynthesis. Total dock scores were -49.55 for inhibitor 830 and -33.71 for tetrangomycin. The means of, the dock score of inhibitor 830 was higher than the dock score of tetrangomycin. Also in our study we get the same result regarding the tetrangomycin. At the same time when it is performed molecular docking using Autodock Vina for all angucycline compounds (157), it has been observed that we get higher dock scores as shown in the Appendices I, II, III, and IV, and this is because of most of the angucycline structures have large chemical structure that help them in interacting with residues that are presents in active site, and because most of interaction are electrostatic and hydrophobic as a result gives higher dock scores.

Molecular docking study was done by Kahlon *et al.* (2010) to find the binding site of SQS inhibitors within the dehydrosqualene synthase of S. aureus to inhibit its function. They used lapaquistat acetate and squalestatin analogs reported as squalene synthase (SQS) inhibitors in human and animal models but not studied in context to CrtM of S. aureus. From the frequency of residue occurrence in the formation of hydrogen bonding with inhibitors studied, it was found that the Arg45, Asp48, Asp52, Asp172, Asn168, Gln165, His18, Tyr129 are interacted comparatively with higher frequency. In our study the interacted residues of CrtM involved in the interactions with the angucycline compounds was (Ala134, Ala157, Arg171, Arg265, Arg45, Asn168, Gln165, Gly138, Gly161, His18, Leu141, Leu145, Leu160, Leu164, Lys20, Phe22, Phe233, Ser19, Ser21, Tyr248, Tyr41) It seems that Arg45, Arg171, Arg265 are the main residues for the substrate.

5 CONCLUSIONS

Docking results produced valuable information not just regarding potential use of a large class of actinomycetes based compounds as candidates against MRSA.

Docking analysis demonstrate that among the attempted compounds; Moromycin_A (56), Saquayamycin_B (58), Saquayamycin_B (146), Saquayamycin_A (145), Saprolmycin_E (29), Saquayamycin_D (148), Saprolmycin_D (28), Marangucycline_B (2), PI_1894B (Vineomycin A) (134), JBIR_91 (42), Grincamycin (38), Saquayamycin_K4 (151) are best candidates with scores of -14.8, -14.4, -13.8, -13.7, -13.7, -13.6, -13.5, -13.5, -12.7, -12.5, -12.5, 12.4 kcal/mol respectively.

However, *in vitro* tests are required to have further study regarding their activities.

It is also necessary to carry out Molecular Dynamic Simulations to have a precise information regarding the stability and dynamic behaviors of the complexes, since molecular dynamic calculations produce data to calculate binding free energies of the complexes, which are comparable with those obtained by isothermal titration calorimetry (ITC) values, which is one of the best method, determining experimental binding free energies between a receptor and a ligand.

6. REFERENCES

Abdelfattah, M., Maskey, R.P., Asolkar, R.N., Grun-Wollny, I., Laat, H. 2003. Seitomycin: Isolation, Structure Elucidation and Biological Activity of a New Angucycline Antibiotic from a Terrestrial Streptomycete. The Journal of Antibiotics, 56 (6): 539-542.

Abdelfattah, M.S., Kharel, M.K., Hitron, J.A., Baig, I., Rohr, J. 2008. Moromycins A and B, Isolation and Structure Elucidation of C-Glycosylangucycline-Type Antibiotics from Streptomyces sp. KY002. J. Nat. Prod. 7 (9): 1569–1573.

Abdelmohsen, U. R., Cheng, C., Viegelmann, C., Zhang, T., Grkovic, T., Ahmed, S., Quinn, R.J., Hentschel, U., Edrada-Ebel, R. 2014. Dereplication Strategies for Targeted Isolation of New Antitrypanosomal Actinosporins A and B from a Marine Sponge Associated-Actinokineospora sp. EG49. Marine Drugs, 12: 1220-1244.

Adegboye, M.F., Babalola, O.O. 2012. Taxonomy and ecology of antibiotic producing actinomycetes. African Journal of Agricultural Research, 7(15):2255-2261.

Adegboye, M.F., Babalola, O.O. 2013. Actinomycetes: a yet inexhaustive source of bioactive secondary metabolites. Formatex, 786-795.

Alvi, K.A., Baker, D.D., Stienecker, V., Hosken, M., Nair, B.G. 2000. Identification of Inhibitors of Inducible Nitric Oxide Synthase from Microbial Extracts. The Journal of Antibiotics. 53 (5):.496-501.

Anderson, A.S., Wellington, E.M.H. 2001. The taxonomy of Streptomyces and related genera. International Journal of Systematic and Evolutionary Microbiology, 51: 797-814.

Antal, N., Fiedler, HP., Stackebrandt, E., Beil, W., Ströch, K., Zeeck, A. 2005. Retymicin, Galtamycin B, Saquayamycin Z and Ribofuranosyllumichrome, Novel Secondary Metabolites from Micromonospora sp. Tü 6368. Journal of Antibiotics. 58(2): 95–102.

Asencio, J. 2010. Molecular docking as method to identify antibacterial compounds. Honors in Microbiology and cell science, University of Florida, Department of Microbiology and cell science. 38.

Balaji, SR., Gupta, KK., Anusha, P., Raveena, P. 2014. Molecular Docking Studies of Wide Spectrum Targets in Staphylococcus aureus - An Aim towards Finding Potent Inhibitors. Advanced Techniques in Biology & Medicine, 2 (1): 1-8.

Basnet, D. B., Oh, TJ., Vu, T.T.H., Sthapit, B., Liou, K., Lee, H.C., Yoo, J.C., Sohng, J.K. 2006. Angucyclines Sch 47554 and Sch 47555 from Streptomyces sp. SCC-2136: Cloning, Sequencing, and Characterization. Molecules and Cells. 22 (2): 154-162.

Batabyal, B., Kundu, G.K.R., Biswas, S. 2012. Methicillin-Resistant *Staphylococcus aureus*: A Brief Review. I. Res. J. Biological Sci., 1 (7): 65-71.

Bhat, S. A., Nazir, R., Malik, T.A., Shah, F. A. 2013. Secondary metabolites of actinomycetes as potential source of antibiotics. Stem Cell, 4(2): 41-46.

Breitling, R., Ceniceros, A., Jankevics, A., Takano, E. 2013. Metabolomics for Secondary Metabolite Research. Metabolites, 3: 1076-1083.

Chaudhury, S. 2010. Using Computational Protein Docking to Model the Structure and Specificity of Protein Interactions. Ph.D. Dissertation, Johns Hopkins University, Baltimore, 198.

Dashti, Y., Grkovic, T., Abdelmohsen, U.R., Hentschel, U., Quinn, R.J. 2014. Production of Induced Secondary Metabolites by a Co-Culture of Sponge-Associated Actinomycetes, Actinokineospora sp. EG49 and Nocardiopsis sp. RV163. Marine Drugs, 12: 3046-3059.

Davati, N., Najafi, M.B. 2013. Overproduction Strategies for Microbial Secondary Metabolites: A Review. Molecular Biology, 3 (1): 23-37.

Dey, S., Mal, D. 2005. Total synthesis of BE-23254, a chlorinated angucycline antibiotic. Tetrahedron Letters 46: 5483–5486.

Dias, G. F. 2011. High-Resolution Saturation Transfer Difference (STD) 1H NMR techniques and Docking simulations applied to Protein-ligand interactions. M.Sc. Thesis, Coimbra University, Department of Life Science, 164.

Fan, K., Pan, G., Peng, X., Zheng, J., Gao, W., Wang, J., Wang, W., Li, Y., Yang, K. 2012b. Identification of JadG as the B Ring Opening Oxygenase Catalyzing the Oxidative C-C Bond Cleavage Reaction in Jadomycin Biosynthesis. Chemistry & Biology 19: 1381–1390.

Fan, K., Zhang, X., Liu, H., Han, H., Luo, Y., Wang, Q., Geng M., Yang, K. 2012a. Evaluation of the cytotoxic activity of new jadomycin derivatives reveals the potential to improve its selectivity against tumor cells. The Journal of Antibiotics 65: 449-452.

Faust, B., Hoffmeister, D., Weitnauer, G., Westrich, L., Haag, S., Schneider, P., Decker, H., Kunzel, E., Rohr J., Bechthold, A. 2000. Two new tailoring enzymes, a glycosyltransferase and an oxygenase, involved in biosynthesis of the angucycline antibiotic urdamycin A in Streptomyces fradiae Tu2717. Microbiology, 146: 147–154.

Ganesan, S., Velsamy, G., Sivasudha, T., Manoharan, N. 2013. Maldi-Tof Mass Spectrum Profiling, Antibacterial and Anticancer Activity of Marin Streptomyces fradiae BDMS1, World Journal of Pharmacy and Pharmaceutical Sciences, (2) 6: 5148-5165.

Gomez-Escribano, J. P., Castro, J. F., Razmilic, V., Chandra, G., Andrews, B., Asenjo J. A., Bibb, M. J. 2015. The Streptomyces leeuwenhoekii genome: de novo sequencing and assembly in single contigs of the chromosome, circular plasmid pSLE1 and linear plasmid pSLE2. BMC Genomics, 16:485.

Haider, M.K. 2010. Computational Analysis of Protein-Ligand Interactions. Ph.D. Dissertation, University of York, Department of Chemistry. 185.

Helaly, S.E., Goodfellow, M., Zinecker, H., Imhoff, J.F., Su¨ssmuth, R.D., Fiedler, HP. 2013. Warkmycin, a novel angucycline antibiotic produced by Streptomyces sp. Acta 2930. The Journal of Antibiotics: 1–6.

Henkel, T., Ciesiolka, T., Rohr J., Zeeck, A. 1988. Urdamycins, New Angucycline Antibiotics from Streptomyces fradiae V. Derivatives of Urdamycin A. The Journal of Antibiotics. XLII (2): 299-311.

Howe, R.A., Monk, A., Wootton, M., Walsh, T. R., Enright, M. C. 2004. Vancomycin Susceptibility within Methicillin-resistant Staphylococcus aureus Lineages. Emerging Infectious Diseases, 10 (5): 855-857.

Hsu, LY., Harris, S.R., Chlebowicz, M.A., Lindsay, J.A., Koh, TH., Krishnan, P., Tan, TY., Hon, PY., Grubb, W.B., Bentley, S.D., Parkhill, J., Peacock, S.J., Holden, M.TG. 2015. Open Access Evolutionary dynamics of methicillin-resistant Staphylococcus aureus within a healthcare system, Genome Biology, 16:81.

Huang, H., Yang, T., Ren, X., Liu, J., Song, Y., Sun, A., Ma, J., Wang, B., Zhang, Y., Huang, C., Zhang, C., Ju, J. 2012. Cytotoxic Angucycline Class Glycosides from the Deep Sea Actinomycete Streptomyces lusitanus SCSIO LR32. J. Nat. Prod., 75: 202-208.

Igarashi, M., Watanabe, T., Hashida, T., Umekita, M., Hatano, M., Yanagida, Y., Kino, H., Kimura, T., Kinoshita, N., Inoue, K., Sawa, R., Nishimura, Y., Utsumi, R., Nomoto, A. 2013. Waldiomycin, a novel WalK-histidine kinase inhibitor from Streptomyces sp. MK844-mF10. The Journal of Antibiotics: 1–6.

Izawa, M., Kimata, S., Maeda, A., Kawasaki, T., Hayakawa, Y. 2013. Functional analysis of hatomarubigin biosynthesis genes and production of a new hatomarubigin using a heterologous expression system. The Journal of Antibiotics: 1–4.

Kaliappan, K.P., Ravikumar, V. 2007. Angucyclinone Antibiotics: Total Syntheses of YM-181741, (+)-Ochromycinone, (+)-Rubiginone B2, (-)-Tetrangomycin, and MM-47755. J. Org. Chem., 72: 6116-6126.

Kallio, P., Liu, Z., Mantsala, P., Niemi, J., Metsa –Ketela, M. 2008. Sequential Action of Two Flavoenzymes, PgaE and PgaM, in Angucycline Biosynthesis: Chemoenzymatic Synthesis of Gaudimycin C. Chemistry & Biology, 15: 157–166.

Kalyon, B., Tan, GY.A., Pinto, J.M., Foo, CY., Wiese, J., Imhoff, J.F., Sussmuth, R.D., Sabaratnam, V., Fiedler, HP. 2013. Langkocyclines: novel angucycline antibiotics from Streptomyces sp. Acta 3034. The Journal of Antibiotics: 1–8.

Kawasaki, T., Hirashima, R., Maruta, T., Sato, H., Maeda, A., Yamada, Y., Takeda, M., Hayakawa, Y. 2010b. Cloning and Characterization of a Gene Cluster for Hatomarubigin Biosynthesis in Streptomyces sp. Strain 2238-SVT4. Applied and Environmental Microbiology, 76 (13): 4201–4206.

Kawasaki, T., Yamada, Y., Maruta, T., Maeda A., Hayakawa, Y. 2010a. Hatomarubigin E, a biosynthetic intermediate of hatomarubigins C and a substrate of HrbU O-methyltransferase. The Journal of Antibiotics, 63: 725–727.

Kharat, K.R., Kharat, A., Hardikar, B.P. 2009. Antimicrobial and cytotoxic activity of Streptomyces sp. from Lonar Lake. African Journal of Biotechnology, 8 (23): 6645-6648.

Kharel, M.K., Pahari, P., Lian, H., Rohr, J. 2010. Enzymatic Total Synthesis of Rabelomycin, an Angucycline Group Antibiotic. Org Lett., 12(12): 2814–2817.

Kharel, M.K., Rohr J. 2012. Delineation of gilvocarcin, jadomycin, and landomycin pathways through combinatorial biosynthetic enzymology. Curr Opin Chem Biol., 16(0): 1-19.

Kirschning, A., Chen, G., Drager, G., Schuberth I., Tietze, L.F. 2000. Syntheses and Biological Evaluation of New Glyco-modified Angucyclin-antibiotics. Bioorganic & Medicinal Chemistry, 8: 2347-2354.

Kormanec, J., Novakova, R., Mingyar, E., Feckova, L. 2014. Intriguing properties of the angucycline antibiotic auricin and complex regulation of its biosynthesis. Appl Microbiol Biotechnol, 98: 45-60.

Koskiniemi, H., Metsä-Ketelä, M., Dobritzsch, D., Kallio, P., Korhonen, H., Mäntsälä, P., Schneider, G., Niemi, J. 2007. Crystal Structures of Two Aromatic Hydroxylases Involved in the Early Tailoring Steps of Angucycline Biosynthesis. J. Mol. Biol., 372: 633-648.

Koyama, N., Inokoshi, J., Tomoda, H. 2013. Review Anti-Infectious Agents against MRSA. Molecules, 18: 204-224.

Kuroda, M., Nagasaki, S., Ohta, T. 2007. Sesquiterpene farnesol inhibits recycling of the C55 lipid carrier of the murein monomer precursor contributing to increased susceptibility to b-lactams in methicillin-resistant Staphylococcus aureus. Journal of Antimicrobial Chemotherapy, 59: 425-432.

Liu, C., Liu, G.Y., Song, Y., Yin, F., Hensler, M.E., Jeng, WY., Nizet, V., Wang, A.H.J., Oldfield, E. 2008. A Cholesterol Biosynthesis Inhibitor Blocks Staphylococcus aureus Virulence. Science, 7; 319(5868): 1391-1394.

Maldonado-Rojas, W., Olivero-Verbel, J. 2012. Food-Related Compounds That Modulate Expression of Inducible Nitric Oxide Synthase May Act as Its Inhibitors. Molecules, 17: 8118-8135.

Maruna, M., Sturdikova, M., Liptaj, T., Godany, A., Muckova, M., Certik, M., Pronayova, N., Proksa, B. 2010. Isolation, structure elucidation and biological activity of angucycline antibiotics from an epiphytic yew streptomycete. Journal of Basic Microbiology, 50: 135-142.

Metsa-Ketela, M., Halo, L., Munukka, E., Hakala, J., Ma¨ntsala, P., Ylihonko, K. 2002. Molecular Evolution of Aromatic Polyketides and Comparative Sequence Analysis of Polyketide Ketosynthase and 16S Ribosomal DNA Genes from Various Streptomyces Species. Applied and Environmental Microbiology, 68 (9): 4472-4479.

Metsa-Ketela, M., Palmu, K., Kunnari, T., Ylihonko, K., Mantsala, P. 2003. Engineering Anthracycline Biosynthesis toward Angucyclines. Antimicrobial Agents and Chemotherapy, 47 (4): 1291-1296.

Metsa-ketela, M., Ylihonko, K., Mantsala, P. 2004. Partial Activation of a Silent Angucycline-type Gene Cluster from a Rubromycin β Producing Streptomyces sp. PGA64. The Journal of Antibiotics, 57 (8): 502-510.

Miyaoka, R., Hosokawa, M., Ando, M., Mori, T., Hamaguchi, H., Takeyama, H. 2014. In Situ Detection of Antibiotic Amphotericin B Produced in Streptomyces nodosus Using Raman Microspectroscopy. Mar. Drugs, 12: 2827-2839.

Moghadam, S.O., Pourmand, M.R., Davoodabadi, A. 2015. The Detection of Mupirocin Resistance and Nasal Carriage of Methicillin Resistant Staphylococcus aureus among Healthcare Workers at University Hospitals of Tehran, Iran. Iran J. Public Health, 44 (3): 361-368.

Motohashi, K., Takagi, M., Yamamura, H., Hayakawa M., Shin-ya, K. 2010. A new angucycline and a new butenolide isolated from lichen-derived Streptomyces spp.. The Journal of Antibiotics, 63: 545-548.

Nakagawa, A., Omura, S. 1996. Biosynthesis of Bioactive Microbial Metabolites and Its Application to the Structural Studies and Production of Hybrid Compounds. The Journal of Antibiotics, 49 (8): 545-548.

Nakagawa, K., Hara, C., Tokuyama, S., Takada, K., Imamura, N. 2012. Saprolmycins A–E, new angucycline antibiotics active against Saprolegnia parasitica. The Journal of Antibiotics, 65: 599-607.

Nelson, D.L., Cox, M.M. 2008. Lehninger Principles of Biochemistry, Fifth Edition, W.H. Freeman And Company, 1303, New York.

Novotarskyi, S. 2013. QSAR approaches to predict human cytochrome P450 inhibition. Ph.D. Dissertation, Technical University Munchen. 153.

Ogasawara Y., Liu, HW. 2009. Biosynthetic Studies of Aziridine Formation in Azicemicins. J Am Chem Soc., 131(50): 18066-18068.

Onelum, O., Odetoyin, B., Onipede, A., Oyelese, A. 2015. The Role of Methicillin-Resistant Staphylococcus aureus in Clinical infections in Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, South Western Nigeria. Journal of Microbiology & Experimentation, 2 (2): 1-6.

Özakin, S., Davis, R. W. Umile, T. P., Pirinccioglu, N., Kizil, M., Celik, G., Sen, A., Minbiole, K.P.C., İnce, E. 2016. The isolation of tetrangomycin from terrestrial Streptomyces sp. CAH29: evaluation of antioxidant, anticancer, and anti-MRSA activity, submitted paper.

Patrikainen, P., Kallio, P., Fan, K., Klika, K.D., Shaaban, K.A., Mantsala, P., Rohr, J., Yang, K., Niemi, J., Metsa-Ketela, M. 2012. Tailoring Enzymes Involved in the Biosynthesis of Angucyclines Contain Latent Context-Dependent Catalytic Activities. Chemistry & Biology, 19: 647-655.

Pelz, A., Wieland, KP., Putzbach, K., Hentschel, P., Albert, K., Goutz, F. 2005. Structure and Biosynthesis of Staphyloxanthin from Staphylococcus aureus. The Journal of Biological Chemistry, 280 (37): 32493–32498.

Pétursson, B. 2014. The promiscuity of alkaline phosphatase against nucleotides and sugar phosphates. Computational analysis and kinetics. B.Sc. Project, Sigillium University Island, Haskoli, 70.

Raczkowski, J.V. 2010. Biodiversity of Actinomycetes Associated with Caribbean Sponges of Puerto Rico, and Their Metabolic Profiles. M.Sc. Thesis, University of North Carolina Wilmington, 137.

Raja, A., Prabakarana, P. 2011. Actinomycetes and Drug – An Overview. American Journal of Drug Discovery and Development, 1(2): 75-84.

Rashid, A., Rashid, A., Rashid, H., Qureshi, U.R. 2015. Curbing Methicillin Resistant Staphylococcus aureus: Challenges and Options in Drug Therapy. iMedPub, Vol. 6 No. 1:3.

Ren, X., Lu, X., Ke, A., Zheng, Z., Lin, J., Hao, W., Zhu, J., Fan, Y., Ding, Y., Jiang Q., Zhang, H. 2011. Three novel members of angucycline group from Streptomyces sp. N05WA963. The Journal of Antibiotics, 64: 339-343.

Rintala, H. 2013. Steptomycetes in Indore Environments – PCR Base Detection and Diversity. Ph.D. Dissertation, University of Kuopio, Department of Environmental Sciences, Kuopio. 70.

Rohr, J., Thiericket, R. 1992. Angucycline Group Antibiotics. Natural Products, 9 (2): 103-137.

Ryška, J. 2011. Docking study of matrix metalloproteinase inhibitors. Bachelor Thesis, Masaryk University, Faculty of Science, Beno. 50.

Sakai, K., Koyama, N., Fukuda, T., Mori, Y., Onaka, H., Tomoda, H. 2012. Search Method for Inhibitors of Staphyloxanthin Production by Methicillin-Resistant Staphylococcus aureus. Biol. Pharm. Bull., 35(1): 48-53.

Schneemann, I., Kajahn, I., Ohlendorf, B., Zinecker, H., Erhard, A., Nage, K., Wiese, J., Imhoff, J.F. 2010. Mayamycin, a Cytotoxic Polyketide from a Streptomyces Strain Isolated from the Marine Sponge Halichondria panicea. J. Nat. Prod., 73 (7): 1309-1312.

Sharma, M. 2014. Actinomycetes: Source, Identification, and Their Applications. Int. J. Curr. Microbiol. App. Sci., 3(2): 801-832.

Shigemura, K., Osawa, K., Mukai, A., Yoshida, H., Fujisawa, M., Arakawa, S. 2013. Anti-MRSA drug use and antibiotic susceptibilities of MRSA at a university hospital in Japan from 2007 to 2011. The Journal of Antibiotics, 66: 273-276.

Silverman, R.B., Holladay, M. W. 2014. The organic chemistry of drug design and drug action. Academic Place, Third edition, 521, Amestrdam.

Singh, L.S., Sharma, H., Talukdar, N. C. 2014. Production of potent antimicrobial agent by actinomycete, Streptomyces sannanensis strain SU118 isolated from phoomdi in Loktak Lake of Manipur, India. BMC Microbiology, 14:278.

Song, Y., Lin, FY., Yin, F., Hensler, M., Poveda, C.A.R., Mukkamala, D., Cao, R., Wang, H., Morita, C.T., Pacanowska, D.G., Nizet, V., Oldfield, E. 2008. Phosphonosulfonates Are Potent, Selective Inhibitors of Dehydrosqualene Synthase and Staphyloxanthin Biosynthesis in Staphylococcus aureus. Journal of Medicinal Chemistry, XXXX, xxx, (xx): A-M.

Song, Y., Liu, G., Li, J., Huang, H., Zhang, X., Zhang, H., Ju, J. 2015. Cytotoxic and Antibacterial Angucycline- and Prodigiosin- Analogues from the Deep-Sea Derived Streptomyces sp. SCSIO 11594. Marine Drugs, 13: 1304-1316.

Stevenson, C. 2012. Database mining studies on protein-peptide and protein-protein interactions. Ph.D. Dissertation, University of Edinburgh, Structural Biochemistry Group Institute of Structural and Molecular Biology, 271.

Stuczen, M. 2013. Conventional and Molecular Approaches for Bacterial Identification and Quantification in Chronic Wounds. Ph.D. Dissertation, Manchester Metropolitan University, Faculty of Science and Engineering, 296.

Tabarez, M. R. 2005. Discovery of the new antimicrobial compound 7-O-malonyl macrolactin. Ph.D. Dissertation, Technischen Universität Carolo-Wilhelmina, Gemeinsamen Naturwissenschaftlichen Fakultät, 166.

Trott, O., Olson, A.J. 2010. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. Journal of Computational Chemistry, 31(2): 455-461.

Tunca, G. 2012. A virtual screening procedure combining pharmacophore filtering and molecular docking with the LIE method. Ph.D. Dissertation, University of Autonoma, Institute of Biotechnology and Biomedicine, Barcelona. 153.

Ueda, J., Izumikawa, M., Mukai, A., Nagai, A., Hwang, JH., Takagi, M., Shin-ya, K. 2011. New angucycline C-glycosides from Streptomyces sp. RI33. The Journal of Antibiotics, 64: 367–372.

Wilkinson, K. 2010. Use of Accelerated Hydrogen Peroxide Skin Cleanser to Reduce Methicillin-resistant *Staphylococcus aureus* Colonization in Clients of the Calgary Drop-In and Rehab Centre. M.Sc. Thesis, University of Kalgary, Department of Community Health Science, Calgary. 194.

Zhu, L., Ostash, B., Rix, U., Nur-e-Alam, M., Mayers, A., Luzhetskyy, A., Mendez, C., Salas, J.A., Bechthold, A., Fedorenko, V., Rohr, J. 2005. Identification of the Function of Gene lndM2 Encoding a Bifunctional Oxygenase-Reductase Involved in the Biosynthesis of the Antitumor Antibiotic Landomycin E by Streptomyces globisporus 1912 Supports the Originally Assigned Structure for Landomycinone. J Org Chem. 21; 70(2): 631-638.

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol)

#		0	58	47	29	28	56	49	143	39	148
Compound Name Docked to Protein (3ACW)	3ACW with its ligand From PDB	Ligand of Protein	Saquayamycin_B	N05WA963A	Saprolmycin_E	Saprolmycin_D	Moromycin_A	N05WA963D	P1_085	Grincamycin_F	Saquayamycin_D
Run1		-11.5	-12.1	-12.9	-13.0	-12.9	-12.1	-12.7	-12.7	-12.6	-12.4
Run2		-11.5	-12.0	-12.9	-10.6	-12.9	-12.7	-9.9	-10.5	-12.6	-12.3
Run3		-11.5	-13.3	-13.0	-10.6	-12.9	-12.7	-12.6	-11.2	-11.4	-12.3
AV.		-11.5	-12.5	-12.9	-11.4	-12.9	-12.5	-11.7	-11.5	-12.2	-12.3
Dock		-11.5	-13.3	-13.0	-13.0	-12.9	-12.7	-12.7	-12.7	-12.6	-12.4
Residues that interacts with the original ligand & Residues that interacts with the ligands	14	14	10	14	13	12	9	15	9	15	8
	Ala134	Ala134	Ala134	Ala134			Ala134	Ala134	Ala134	Ala134	
	Ala157	Ala157			Ala157			Ala157		Ala157	
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138		Gly138	
	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	
	His18		His18	His18	His18	His18	His18	His18	His18	His18	His18
		Ile241		Ile241	Ile241	Ile241		Ile241		Ile241	
	Leu141	Leu141	Leu141	Leu141			Leu141	Leu141	Leu141	Leu141	Leu141
	Leu145	Leu145		Leu145	Leu145	Leu145		Leu145		Leu145	
	Leu160	Leu160		Leu160	Leu160	Leu160		Leu160		Leu160	
	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22	Phe22
	Phe26	Phe26		Phe26	Phe26	Phe26		Phe26		Phe26	Phe26
	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Unk1001	Unk1001	Arg181	Ala157	Arg181	Ala157	Arg181	Arg181	Arg181	Ser19	Arg181
	HOH474	Phe233	Arg45	Arg181	Arg45	Arg181	Arg45	Arg265	Arg45	Tyr129	Arg45
		Tyr41	Asn179	Arg45	Asn179	Arg45	Asn179	Arg45	Asn179	Tyr183	Asn179
		Val133	Asp114	Asn179	Asp114	Asn179	Asp114	Asn179	Asp114	Tyr248	Asp114
			Asp176	Asp114	Asp176	Asp114	Asp176	Asp176	Asp176	Tyr41	Asp176
			Asp48	Asp176	Asp48	Asp176	Asp48	Asp48	Asp48	Val133	Asp48
			Asp52	Asp48	Asp52	Asp48	Asp52	Glu175	Asp52	Ile51	Asp52
			Gln115	Phe233	Cys44	Asp52	Gln115	Tyr129	Cys44	Arg171	Gln115
			Gly55	Tyr129	Gln115	Gln115	Gly55	Tyr183	Gln115	Arg181	Gly161
			Ile51	Tyr183	Ile51	Phe233	Ile51	Tyr248	Gly55	Arg265	Gly55
			Tyr129	Tyr248	Phe233	Tyr129	Tyr129	Tyr41	His116	Arg45	Ile51
			Tyr183	Tyr41	Tyr129	Tyr183	Tyr183	Val133	Ile51	Asn179	Tyr129
			Tyr248	Val133	Tyr183	Tyr248	Tyr41		Tyr129	Asp114	Tyr183
			Val133		Tyr41	Tyr41			Tyr183	Asp172	Tyr248
					Val133	Val133			Tyr41	Asp176	Tyr41
									Val133	Asp48	Val133
										Asp52	
										Cys44	
										Gln115	

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	146	145	65	96	95	71	151	25	98	1	139
Compound Name Docked to Protein (3ACW)	Saquayamycin_B	Saquayamycin_A	PI_080 (=PI-6621)	BA_12100Z1	BA_12100E	Urdamycin_F	Saquayamycin_K4	Saprolmycin_A	BA_12100Z3	Marangucycline_A	Kerriamycin_A
Run1	-12.2	-11.8	-12.2	-12.1	-12.1	-11.9	-11.9	-11.8	-11.2	-11.7	-11.6
Run2	-12.1	-12.1	-11.6	-12.1	-11.1	-12.0	-11.9	-11.8	-11.7	-10.4	-10.5
Run3	-12.0	-12.2	-12.2	-11.4	-12.0	-12.0	-11.9	-11.8	-11.8	-11.7	-11.7
AV.	-12.1	-12.0	-12.0	-11.9	-11.7	-12.0	-11.9	-11.8	-11.6	-11.3	-11.3
Dock	-12.2	-12.2	-12.2	-12.1	-12.1	-12.0	-11.9	-11.8	-11.8	-11.7	-11.7
Residues that interacts with the original ligand & Residues that interacts with the ligands	10	9	15	9	13	9	9	10	15	10	8
	Ala134	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134	Ala134	Ala134
			Ala157		Ala157				Ala157		
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138	Gly138	Gly138	Gly138	Gly138		Gly138	Gly138	Gly138		Gly138
	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161
	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18
			Ile241						Ile241		
	Leu141	Leu141	Leu141		Leu141			Leu141	Leu141	Leu141	
			Leu145		Leu145				Leu145		
			Leu160		Leu160	Leu160			Leu160		
	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
			Phe26		Phe26				Phe26	Phe26	
	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Arg181	Arg181	Arg171	Arg171	Arg181	Arg181	Arg171	Arg181	Arg171	Arg181	Arg171
	Arg45	Arg45	Arg181	Arg181	Arg45	Arg265	Arg181	Arg45	Arg181	Arg45	Arg181
	Asp114	Asn179	Arg265	Arg265	Asn179	Arg45	Arg265	Asn179	Arg265	Asn179	Arg265
	Asp176	Asp114	Arg45	Arg45	Asp114	Asn179	Arg45	Asp114	Arg45	Asp114	Arg45
	Asp48	Asp176	Asn179	Asn179	Asp48	Asp114	Asn179	Asp176	Asp114	Asp48	Asn179
	Asp52	Asp48	Asp114	Asp114	Asp52	Asp48	Asp114	Asp48	Asp48	Tyr129	Asp114
	Gln115	Asp52	Asp172	Asp48	Gln115	Asp52	Asp176	Asp52	Asp52	Tyr183	Asp52
	Gly55	Gln115	Asp176	Asp52	Ile51	Gln115	Asp48	Gln115	Gln115	Tyr248	Gln115
	Ile51	Gly55	Asp48	Cys44	Tyr129	Ile51	Gln115	Ile51	Tyr248	Tyr41	Glu175
	Tyr129	Ile51	Asp52	Gln115	Tyr183	Tyr183	Glu180	Tyr129	Val111	Val133	Ile51
	Tyr183	Tyr129	Tyr129	Tyr41	Tyr248	Tyr41	Tyr129	Tyr183	Val133		Leu141
	Tyr41	Tyr183	Tyr183	Val111	Tyr41	Val111	Tyr183	Tyr248	Ile51		Tyr248
	Val133	Tyr248	Tyr248	Ile51	Val111		Tyr248	Tyr41			Tyr41
		Tyr41	Tyr41		Val133		Tyr41	Val133			Val111
		Val133	Val111				Val133				Val133
		Val137	Val133								

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	93	92	84	30	38	155	147	144	57	140	36
Compound Name Docked to Protein (3ACW)	BA_12100C	BA_12100B	A_7884	Saquayamycin_A	Grincamycin	Vineomycin_A1	Saquayamycin_C	PI_087	Moromycin_B	Kerriamycin_B	Landomycin_E
Run1	-10.3	-11.7	-10.5	-11.6	-11.6	-11.6	-11.5	-11.5	-11.4	-11.4	-11.3
Run2	-11.5	-9.7	-10.0	-11.6	-11.6	-11.4	-11.4	-11.3	-11.4	-10.7	-10.6
Run3	-11.7	-11.1	-11.7	-11.6	-11.6	-11.6	-11.4	-10.5	-11.4	-9.6	-10.9
AV.	-11.2	-10.8	-10.7	-11.6	-11.6	-11.5	-11.4	-11.1	-11.4	-10.6	-10.9
Dock	-11.7	-11.7	-11.7	-11.6	-11.6	-11.6	-11.5	-11.5	-11.4	-11.4	-11.3
Residues that interacts with the original ligand & Residues that interacts with the ligands	14	14	15	10	9	15	8	8	9	8	12
	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134
	Ala157	Ala157	Ala157			Ala157					
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138			Gly138	Gly138	Gly138
	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161		Gly161
	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18
		Ile241	Ile241			Ile241					
	Leu141	Leu141	Leu141	Leu141		Leu141			Leu141		Leu141
	Leu145	Leu145	Leu145			Leu145					
	Leu160	Leu160	Leu160			Leu160					Leu160
	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
	Phe22		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22
	Phe26	Phe26	Phe26	Phe26		Phe26					Phe26
	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Arg181	Arg171	Arg181	Arg181	Arg171	Arg181	Arg171	Arg181	Arg181	Arg181	Arg171
	Arg265	Arg181	Arg45	Arg45	Arg181	Arg45	Arg181	Arg45	Arg45	Arg265	Arg181
	Arg45	Arg265	Asn179	Asn179	Arg45	Asn179	Arg45	Asn179	Asp114	Arg45	Arg265
	Asn179	Arg45	Asp114	Asp114	Asn179	Asp114	Asn179	Asp114	Asp48	Asn179	Arg45
	Asp114	Asn179	Asp176	Asp176	Asp114	Asp176	Asp114	Asp176	Tyr129	Asp114	Asn179
	Asp172	Asp114	Asp48	Asp48	Asp172	Asp48	Asp172	Asp48	Tyr183	Asp48	Asp172
	Asp48	Asp176	Phe233	Asp52	Asp176	Asp52	Asp176	Asp52	Tyr41	Asp52	Asp176
	Asp52	Asp48	Tyr129	Gln115	Asp48	Cys44	Asp48	Gln115		Cys44	Asp48
	Gln115	Asp52	Tyr183	Ile51	Asp52	Gln115	Asp52	Gly55		Gln115	Asp49
	Glu180	Cys44	Tyr41	Tyr129	Ile51	Ile51	Gln115	His116		Glu180	Cys44
	Ile51	Tyr248	Val133	Tyr183	Tyr129	Tyr129	Ile51	Ile51		Ile51	Glu175
	Tyr129	Tyr41		Tyr41	Tyr183	Tyr183	Tyr129	Tyr129		Tyr248	Tyr183
	Tyr41	Val133		Val133	Tyr41	Tyr41	Tyr183	Tyr183		Tyr41	Tyr248
	Val111				Val111	Val133	Tyr248	Tyr248		Val111	Tyr41
	Val133				Val133		Tyr41	Tyr41		Val133	Val133
							Val133	Val133			

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	2	26	152	27	37	124	134	19	13	97	83
Compound Name Docked to Protein (3ACW)	Marangucycline_B	Saprolmycin_B	Saquayamycin_K7	Saprolmycin_C	Landomycin_Z	Landomycin_C	PI_1894B (Vineomycin A) (OS-4742A1)	Fradimycin_C	Waldiomycin	BA_12100Z2	Saquayamycin_A1
Run1	-11.3	-11.2	-11.2	-11.0	-11.0	-9.7	-10.9	-10.9	-10.9	-10.9	-10.8
Run2	-11.3	-11.2	-9.9	-10.9	-11.0	-11.0	-10.9	-10.9	-10.9	-10.6	-10.8
Run3	-10.0	-11.2	-10.2	-11.1	-8.6	-9.7	-10.8	-10.8	-10.7	-10.9	-10.8
AV.	-10.9	-11.2	-10.4	-11.0	-10.2	-10.1	-10.9	-10.9	-10.8	-10.8	-10.8
Dock	-11.3	-11.2	-11.2	-11.1	-11.0	-11.0	-10.9	-10.9	-10.9	-10.9	-10.8
Residues that interacts with the original ligand & Residues that interacts with the ligands	7	3	7	4	14	3	10	5	11	8	8
					Ala134		Ala134			Ala134	Ala134
					Ala157				Ala157		
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165
					Gly138		Gly138				
					Gly161		Gly161	Gln165	Gly161		
	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18
	Leu141		Leu141		Leu141		Leu141		Leu141		
					Leu145						
					Leu160				Leu160		
	Leu164		Leu164		Leu164		Leu164		Leu164	Leu164	Leu164
			Phe22		Phe22		Phe22	Phe22	Phe22	Phe22	Phe22
	Phe26				Phe26				Phe26	Phe26	Phe26
	Val137		Val137	Val137	Val137		Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Arg171	Arg181	Arg171	Arg181	Arg171	Arg171	Arg171	Arg171	Arg181	Arg171	Arg181
	Arg181	Arg45	Arg265	Arg45	Arg265	Arg265	Arg181	Arg45	Arg45	Arg265	Arg45
	Arg45	Asn179	Arg45	Asn179	Arg45	Arg45	Arg265	Asp48	Asn179	Arg45	Asn179
	Asn179	Asp114	Asn179	Asp114	Asp172	Asn179	Arg45	Cys44	Asp114	Asp172	Asp114
	Asp114	Asp172	Asp176	Asp172	Asp176	Asp114	Asn179	Glu269	Asp176	Asp176	Asp176
	Asp48	Asp176	Asp48	Asp176	Asp48	Asp176	Asp114	Lys20	Asp48	Asp48	Asp48
	Tyr129	Asp48	Asp52	Asp48	Cys44	Asp48	Asp172	Lys270	Asp52	Lys17	Gly161
	Tyr183	Asp52	Glu175	Asp52	Ile14	Asp49	Asp176	Lys273	Ile51	Lys20	Tyr129
	Tyr41	Gln115	Ser19	Gln115	Lys13	Asp52	Asp48	Phe267	Tyr129	Lys273	Tyr183
		Ile51	Tyr129	Ile51	Lys17	Glu175	Asp49	Ser19	Tyr183	Ser19	Tyr41
		Tyr129	Tyr183	Tyr129	Phe233	Ile251	Asp52	Ser21	Tyr41	Ser21	Val133
		Tyr183	Tyr248	Tyr183	Tyr10	Ile51	Glu175	Tyr248		Tyr129	
		Tyr41	Tyr41	Tyr41	Tyr129	Lys17	Ile51	Tyr41		Tyr248	
		Val133	Val133	Val133	Tyr41	Lys20	Tyr129	Val133		Tyr41	
						Lys273	Tyr183	Val268			
						Phe267	Tyr248				
						Ser21	Tyr41				
						Tyr129					
						Tyr183					
						Val111					
						Val133					
						Val268					

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	142	123	35	46	88	102	59	94	72	150	122
Compound Name Docked to Protein (3ACW)	PI_083	Landomycin_B	Landomycin_A	Urdamycin_B	C104	Capoamycin	Sch_47554	BA_12100D	Urdamycin_G	Saquayamycin_K2	Landomycin_A_122
Run1	-10.5	-10.4	-10.7	-10.4	-10.5	-10.4	-10.3	-9.9	-10.3	-10.2	-9.9
Run2	-10.8	-10.8	-10.7	-10.4	-10.5	-10.4	-10.1	-10.3	-10.3	-10.2	-10.1
Run3	-10.4	-8.7	-10.7	-10.7	-10.5	-10.5	-10.3	-10.3	-9.4	-10.2	-9.8
AV.	-10.6	-10.0	-10.7	-10.5	-10.5	-10.4	-10.2	-10.2	-10.0	-10.2	-9.9
Dock	-10.8	-10.8	-10.7	-10.7	-10.5	-10.5	-10.3	-10.3	-10.3	-10.2	-10.1
Residues that interacts with the original ligand & Residues that interacts with the ligands	10	14	4	10	12	12	10	13	4	2	4
	Ala134	Ala134		Ala134		Ala134	Ala134				
		Ala157			Ala157			Ala157			
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165		Gln165
	Gly138	Gly138			Gly138		Gly138	Gly138			
	Gly161	Gly161		Gly161			Gly161	Gly161			
	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18
		Ile241				Ile241					
	Leu141	Leu141		Leu141	Leu141	Leu141	Leu141	Leu141			
		Leu145			Leu145	Leu145		Leu145			
		Leu160			Leu160	Leu160		Leu160			
	Leu164	Leu164		Leu164	Leu164	Leu164	Leu164	Leu164			
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22
				Phe26	Phe26	Phe26		Phe26			
	Val137	Val137		Val137	Val137	Val137	Val137	Val137			
Residues that NOT interacts with the original ligand	Arg181	Arg171	Arg181	Arg181	Arg181	Arg181	Arg181	Arg171	Arg171	Arg171	Arg171
	Arg45	Arg181	Arg265	Arg265	Arg45	Arg45	Arg45	Arg265	Arg181	Arg181	Arg265
	Asn179	Arg265	Arg45	Arg45	Asn179	Asn179	Asn179	Arg45	Arg265	Arg265	Arg45
	Asp114	Arg45	Asn179	Asn179	Asp114	Asp114	Asp114	Asp48	Arg45	Arg45	Asp114
	Asp176	Asn179	Asp114	Asp114	Asp48	Asp48	Asp176	Lys17	Asn179	Asp114	Asp48
	Asp48	Asp114	Asp176	Asp176	Cys44	Cys44	Asp48	Tyr129	Asp114	Asp172	Asp49
	Asp52	Asp48	Asp48	Asp48	Tyr129	Tyr129	Tyr129	Tyr183	Asp172	Asp176	Asp52
	Gln115	Asp52	Asp49	Asp52	Tyr183	Tyr183	Tyr183	Tyr41	Asp48	Asp48	Ile251
	Gly55	Gln115	Asp52	Gln115	Tyr41	Tyr41	Tyr248	Val133	Asp52	Asp49	Lys20
	Ile51	Ile51	Glu175	Ile51	Val133	Val133	Tyr41		Gln115	Lys17	Lys273
	Tyr129	Phe233	Ile14	Tyr183			Val111		Ile51	Lys20	Phe267
	Tyr183	Phe26	Lys13	Tyr41			Val133		Tyr129	Lys273	Ser21
	Tyr41	Tyr129	Lys17	Val133					Tyr183	Phe267	Tyr129
	Val133	Tyr248	Tyr10						Tyr248	Ser19	Tyr183
		Tyr41	Tyr129						Tyr41	Ser21	Tyr248
		Val111	Tyr183						Val111	Tyr183	Tyr41
			Tyr248							Tyr248	Val133
			Tyr41								Val268
			Val111								
			Val133								

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	125	3	45	78	141	91	40	41	42	8	23
Compound Name Docked to Protein (3ACW)	Landomycin_D	Actinosporin_A	Urdamycin_A	BE_7585A	Kerriamycin_C	Aggreticin (OM-4842)	JBIR_90	JBIR_116	JBIR_91	Hatomarubigin_D	L_digitoxosyl_dehydrorabelomycin
Run1	-10.0	-9.9	-9.9	-9.9	-9.8	-9.8	-9.6	-8.4	-9.1	-9.5	-9.1
Run2	-9.7	-9.9	-9.4	-8.9	-9.6	-9.1	-8.6	-9.7	-8.7	-9.6	-9.5
Run3	-7.9	-9.9	-9.3	-9.4	-9.6	-9.8	-9.7	-9.7	-9.7	-9.6	-9.6
AV.	-9.2	-9.9	-9.5	-9.4	-9.7	-9.6	-9.3	-9.3	-9.2	-9.6	-9.4
Dock	-10.0	-9.9	-9.9	-9.9	-9.8	-9.8	-9.7	-9.7	-9.7	-9.6	-9.6
Residues that interacts with the original ligand & Residues that interacts with the ligands	9	5	10	3	11	11	15	9	4	7	4
	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134		Ala134	
							Ala157				
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138		Gly138		Gly138	Gly138	Gly138	Gly138			
	Gly161		Gly161		Gly161	Gly161	Gly161	Gly161			
	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18	His18
							Ile241				
			Leu141		Leu141	Leu141	Leu141				
							Leu145				
							Leu160				
	Leu164		Leu164		Leu164	Leu164	Leu164	Leu164		Leu164	
	Phe22		Phe22		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	
					Phe26	Phe26	Phe26				
	Val137	Val137	Val137		Val137	Val137	Val137	Val137		Val137	Val137
Residues that NOT interacts with the original ligand	Arg171	Arg171	Arg171	Arg171	Arg171	Tyr129	Arg45	Arg171	Arg181	Arg171	Arg181
	Arg265	Arg181	Arg181	Arg265	Arg265	Tyr183	Asp48	Arg181	Arg45	Arg181	Arg265
	Arg45	Arg265	Arg265	Arg45	Asp172	Tyr248	Cys44	Arg265	Asn179	Arg265	Asp114
	Asn179	Arg45	Arg45	Asn179	Glu269	Tyr41	Phe233	Arg45	Asp114	Arg45	Asp172
	Asp114	Asn179	Asn179	Asp114	Lys20	Val111	Tyr41	Asn179	Asp172	Asn179	Asp176
	Asp172	Asp114	Asp114	Asp172	Lys270	Val133	Val133	Asp114	Asp176	Asp114	Asp48
	Asp176	Asp172	Asp176	Asp176	Lys273	Arg181		Asp172	Asp48	Asp172	Tyr129
	Asp48	Asp176	Asp48	Asp48	Phe267	Arg45		Asp176	Asp52	Asp176	Tyr183
	Cys44	Asp48	Asp52	Asp49	Ser19	Asn179		Asp48	Gln115	Asp48	Val133
	Glu175	Asp52	Gln115	Asp52	Ser21	Asp114		Asp49	Gly55	Asp52	
	Tyr248	Cys44	Glu180	Gln115	Tyr248	Asp176		Asp52	Ile51	Ile51	
	Tyr41	Glu175	Ile51	Glu175	Tyr41	Asp48		Gln115	Tyr129	Tyr129	
	Val133	Ile51	Tyr248	Ile169	Val268	Cys44		Ile51	Tyr183	Tyr183	
		Thr110	Tyr41	Ile51				Glu175	Tyr41	Tyr248	
		Tyr129	Val133	Tyr129				Tyr129	Val133	Tyr41	
		Tyr183		Tyr183				Tyr183		Val133	
		Tyr41		Val111				Tyr41			
		Val111						Val111			
		Val133						Val133			

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	87	149	12	103	60	128	73	11	34	127	54
Compound Name Docked to Protein (3ACW)	C104_Aglycon	Saquayamycin_K1	Warkmycin	De_O_acylcapoamycin	Sch_47555	Landomycin_F	Sakyomicin_A	Rubiginone_B2	Aquayamycin	TAN_1085	8_O_methyltetrangulol
Run1	-8.8	-9.4	-8.9	-9.0	-9.1	-8.1	-8.3	-8.1	-8.7	-8.3	-8.6
Run2	-8.6	-9.4	-9.3	-9.1	-8.9	-9.1	-8.9	-8.6	-8.6	-8.7	-8.6
Run3	-9.6	-8.5	-9.3	-9.1	-8.9	-9.0	-8.7	-8.9	-8.6	-8.3	-8.6
AV.	-9.0	-9.1	-9.2	-9.1	-9.0	-8.7	-8.6	-8.5	-8.6	-8.4	-8.6
Dock	-9.6	-9.4	-9.3	-9.1	-9.1	-9.1	-8.9	-8.9	-8.7	-8.7	-8.6
Residues that interacts with the original ligand & Residues that interacts with the ligands	14	8	12	3	6	8	3	15	5	6	13
	Ala134	Ala134	Ala134			Ala134		Ala134	Ala134	Ala134	Ala134
	Ala157							Ala157			Ala157
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	
	Gly138							Gly138			Gly138
	Gly161	Gly161	Gly138			Gly161		Gly161			Gly161
	His18	His18	Gly161	His18	His18	His18	His18	His18	His18	His18	His18
			His18					Ile241			Ile241
	Leu141		Leu141					Leu141			Leu141
	Leu145							Leu145			Leu145
	Leu160		Leu160					Leu160			Leu160
	Leu164	Leu164	Leu164		Leu164	Leu164		Leu164		Leu164	Leu164
	Phe22	Phe22	Phe22		Phe22	Phe22		Phe22			Phe22
	Phe26		Phe26					Phe26			Phe26
	Val137	Val137	Val137		Val137	Val137		Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Arg45	Arg171	Arg181	Arg181	Arg181	Arg45	Arg171	Phe233	Arg265	Arg171	Tyr41
	Asp48	Arg181	Arg45	Arg45	Arg45	Asp114	Arg265	Tyr41	Arg45	Arg265	Val133
	Tyr129	Arg265	Asn179	Asp114	Asn179	Asp48	Arg45	Val133	Asn179	Arg45	Phe233
	Tyr41	Arg45	Asp114	Asp48	Asp114	Cys44	Asp114		Asp172	Asp114	
	Val133	Asn179	Asp176	Asp52	Asp48	Ile51	Asp172		Asp176	Asp48	
		Asp114	Asp48	Gln115	Asp49	Tyr129	Asp176		Asp48	Tyr129	
		Asp176	Asp49	Ile51	Cys44	Tyr41	Asp48		Cys44	Val111	
		Asp48	Asp52	Tyr129	Tyr129	Val133	Tyr129		Glu175	Val133	
		Asp52	Cys44	Val111	Tyr183		Tyr183		Tyr129		
		Cys44	Gln115	Val133	Tyr248		Tyr41		Tyr183		
		Glu175	Ile51		Tyr41		Val133		Val133		
		Tyr129	Tyr129								
		Tyr183	Tyr183								
		Tyr41	Tyr41								
		Val133	Val111								
			Val133								

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	48	99	21	33	154	120	85	31	74	118	52
Compound Name Docked to Protein (3ACW)	N05WA963B	BA_12100MY_1	Jadomycin_B	Gaudimycin_C	Retymicin	X_14881_E	Aquamycin	Gaudimycin_A	Sakyomicin_B	PD116779	Mayamycin
Run1	-8.6	-8.3	-8.5	-8.5	-8.0	-8.5	-8.4	-8.3	-8.3	-8.3	-8.2
Run2	-8.3	-8.3	-8.5	-8.3	-8.5	-7.2	-8.4	-8.3	-8.3	-7.7	-8.2
Run3	-8.6	-8.6	-8.5	-8.3	-8.0	-7.5	-8.4	-8.4	-8.3	-8.2	-8.2
AV.	-8.5	-8.4	-8.5	-8.4	-8.2	-7.7	-8.4	-8.3	-8.3	-8.1	-8.2
Dock	-8.6	-8.6	-8.5	-8.5	-8.5	-8.5	-8.4	-8.3	-8.3	-8.3	-8.2
Residues that interacts with the original ligand & Residues that interacts with the ligands	12	4	1	13	11	13	6	11	2	14	3
	Ala134			Ala134	Ala134	Ala134	Ala134	Ala134		Ala134	
	Ala157			Ala157		Ala157				Ala157	
	Asn168	Asn168	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165		Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138			Gly138		Gly138		Gly138		Gly138	
	Gly161			Gly161	Gly161	Gly161		Gly161		Gly161	
	His18	His18		His18	His18	His18	His18	His18		His18	His18
						Ile241					
	Leu141			Leu141	Leu141	Leu141		Leu141		Leu141	
						Leu145				Leu145	
	Leu160			Leu160	Leu160	Leu160				Leu160	
	Leu164			Leu164	Leu164	Leu164	Leu164	Leu164		Leu164	
	Phe22			Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	
				Phe26	Phe26	Phe26		Phe26		Phe26	
	Val137	Val137		Val137	Val137	Val137		Val137		Val137	
Residues that NOT interacts with the original ligand	Arg171	Arg181	Arg181	Arg45	Arg45	Phe233	Asn179	Arg45	Arg45	Tyr41	Arg171
	Arg45	Arg45	Asn179	Asp48	Tyr248	Tyr41	Asp172	Asp48	Asp114	Val133	Arg265
	Asp176	Asn179	Asp114	Ser19	Tyr41	Val133	Arg265	Tyr248	Asp48		Asn179
	Asp48	Asp114	Asp172	Tyr248	Val133		Arg45	Tyr41	Asp52		Asp114
	Tyr129	Asp48	Asp176	Tyr41			Asp176	Val133	Ile51		Asp172
	Tyr41	Cys44	Asp48	Val133			Asp48		Tyr129		Asp176
	Val133	Leu107	Asp52				Glu175		Tyr183		Asp48
		Tyr129	Gln115				Tyr129		Val111		Asp52
		Tyr183	Ile51				Tyr183		Val133		Glu175
		Tyr41	Tyr129				Tyr248				Ile51
		Val133	Tyr183				Tyr41				Tyr129
			Val111				Val133				Val111
			Val133								Val133

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	75	61	77	113	133	101	100	14	119	4	114
Compound Name Docked to Protein (3ACW)	Sakyomicin_C	BE_23254	Sakyomicin_E	SS_228Y	Homo_UWM6	Benzanthrin_B	Benzanthrin_A	Langkocycline_A1	X_14881_C	Actinosporin_B	Fridamycin_C
Run1	-8.2	-8.2	-8.2	-8.1	-8.2	-7.9	-7.8	-7.8	-7.4	-8.1	-8.0
Run2	-8.2	-8.1	-8.2	-8.2	-7.8	-8.1	-7.9	-8.2	-8.2	-8.0	-8.0
Run3	-8.2	-8.2	-8.1	-8.1	-8.2	-8.2	-8.2	-7.8	-8.2	-8.0	-8.0
AV.	-8.2	-8.2	-8.2	-8.1	-8.1	-8.1	-8.0	-7.9	-7.9	-8.0	-8.0
Dock	-8.2	-8.2	-8.2	-8.2	-8.2	-8.2	-8.2	-8.2	-8.2	-8.1	-8.0
Residues that interacts with the original ligand & Residues that interacts with the ligands	2	2	2	2	11	3	2	3	14	3	3
					Ala134				Ala134		
									Ala157		
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
					Gly138				Gly138		
					Gly161				Gly161		
			His18			His18		His18	His18	His18	His18
									Ile241		
					Leu141				Leu141		
									Leu145		
					Leu160				Leu160		
					Leu164				Leu164		
					Phe22				Phe22		
					Phe26				Phe26		
					Val137						
Residues that NOT interacts with the original ligand	Arg181	Asp114	Arg181	Arg181	Arg45	Arg171	Arg181	Arg181	Phe233	Arg171	Arg171
	Arg265	Asp176	Arg45	Asp114	Asp48	Arg265	Asn179	Arg265	Tyr41	Arg181	Arg265
	Arg45	Asp48	Asp114	Asp172	Cys44	Arg45	Asp114	Arg45		Arg265	Arg45
	Asn179	Asp52	Asp48	Asp176	Tyr41	Asn179	Asp172	Asn179		Arg45	Asp114
	Asp114	Ile51	Asp49	Asp48	Val133	Asp114	Asp176	Asp114		Asp114	Asp48
	Asp176	Tyr129	Asp52	Ile51		Asp172	Asp48	Asp172		Asp172	Tyr129
	Asp48	Tyr183	Tyr129	Tyr129		Asp176	Asp49	Asp176		Asp176	Val111
	Asp49	Val111	Tyr183	Tyr183		Asp48	Asp52	Asp48		Asp48	Val133
	Glu175	Val133	Val111	Val111		Asp52	Gln115	Asp49		Gln115	
	Tyr129		Val133	Val133		Gln115	Ile51	Asp52		Ile169	
	Tyr183					Glu175	Tyr129	Gln115		Ile51	
	Val133					Ile51	Val111	Ile51		Tyr129	
						Tyr129	Val133	Ser50		Tyr183	
						Tyr183		Tyr129		Val111	
						Val111		Tyr183		Val133	

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	137	132	129	76	115	156	50	51	62	112	53
Compound Name Docked to Protein (3ACW)	Urdamycin_J	11_HydroxyTetrangomycin	Homorabelomycin	Sakyomicin_D	Fujianmycin_A	Azicemicin_A	JBIR_88	Rabelomycin	Tetrangomycin	SF_2315_A	8_O_methyltetrangomycin
Run1	-8.0	-8.0	-7.8	-8.0	-8.0	-8.0	-7.5	-7.9	-7.9	-7.8	-7.8
Run2	-7.9	-8.0	-8.0	-7.9	-8.0	-7.6	-8.0	-7.9	-7.9	-7.9	-7.9
Run3	-8.0	-7.9	-8.0	-7.9	-7.7	-8.0	-7.7	-7.9	-7.9	-7.9	-7.9
AV.	-8.0	-8.0	-7.9	-7.9	-7.9	-7.9	-7.7	-7.9	-7.9	-7.9	-7.9
Dock	-8.0	-8.0	-8.0	-8.0	-8.0	-8.0	-8.0	-7.9	-7.9	-7.9	-7.9
Residues that interacts with the original ligand & Residues that interacts with the ligands	11	4	5	2	13	7	5	3	3	10	3
	Ala134		Ala134		Ala134	Ala134	Ala134			Ala134	
					Ala157						
	Asn168	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138				Gly138					Gly138	
	Gly161				Gly161					Gly161	
	His18	His18	His18		His18	His18	His18	His18	His18	His18	His18
	Leu141				Leu141						
					Leu145						
					Leu160						
	Leu164				Leu164	Leu164				Leu164	
	Phe22				Phe22	Phe22	Phe22			Phe22	
	Phe26				Phe26					Phe26	
	Val137	Val137	Val137		Val137	Val137				Val137	
Residues that NOT interacts with the original ligand	Arg45	Arg171	Arg171	Arg171	Phe233	Arg171	Arg181	Arg171	Arg171	Arg45	Arg181
	Asp48	Arg265	Arg265	Arg181	Ser19	Arg265	Arg45	Arg265	Arg265	Asp48	Arg45
	Tyr248	Arg45	Arg45	Asn179	Tyr41	Arg45	Asn179	Asp114	Asp114	Cys44	Asn179
	Tyr41	Asn179	Asn179	Asp114	Val133	Asp172	Asp176	Asp172	Asp172	Tyr41	Asp176
	Val133	Asp172	Asp172	Asp172		Asp48	Asp48	Asp48	Asp48	Val133	Asp48
		Asp176	Asp176	Asp176		Ser19	Tyr129	Tyr129	Ile51		Tyr129
		Asp48	Asp48	Tyr129		Tyr248	Tyr183	Val111	Tyr129		Tyr183
		Glu175	Glu175	Tyr183		Tyr41	Tyr41	Val133	Val111		Val133
		Tyr129	Tyr129			Val133	Val133		Val133		
		Tyr183	Tyr183								
		Val133	Val133								

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	131	90	55	22	82	157	20	80	105	116	117
Compound Name Docked to Protein (3ACW)	Homoprejadomycin	6_Deoxy_8_O_methylrabelomycin	8_O_methyl_7_deoxo_7_hydroxytetrangomycin	Jadomycin_A	SM_196B	Azicemicin_B	UWM6	Seitomycin	Elmycin_B	Fujianmycin_B	MM_47755
Run1	-7.8	-7.7	-7.9	-7.7	-7.8	-7.9	-7.8	-7.8	-7.8	-7.8	-7.7
Run2	-7.8	-7.9	-7.7	-7.9	-7.9	-7.4	-7.8	-7.8	-7.8	-7.6	-7.7
Run3	-7.9	-7.9	-7.7	-7.6	-7.2	-7.4	-7.8	-7.8	-7.7	-7.8	-7.8
AV.	-7.8	-7.8	-7.8	-7.7	-7.6	-7.6	-7.8	-7.8	-7.8	-7.7	-7.7
Dock	-7.9	-7.9	-7.9	-7.9	-7.9	-7.9	-7.8	-7.8	-7.8	-7.8	-7.8
Residues that interacts with the original ligand & Residues that interacts with the ligands	9	3	13	2	12	6	9	3	3	5	3
	Ala134		Ala134		Ala134	Ala134	Ala134			Ala134	
			Ala157		Ala157						
		Asn168	Asn168	Asn168		Asn168		Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138				Gly138		Gly138				
	Gly161		Gly161		Gly161		Gly161				
		His18	His18		His18	His18		His18	His18	His18	His18
			Ile241								
	Leu141		Leu141		Leu141		Leu141				
			Leu145		Leu145						
			Leu160		Leu160						
	Leu164		Leu164		Leu164		Leu164				
	Phe22		Phe22		Phe22	Phe22	Phe22				
	Phe26		Phe26		Phe26		Phe26				
	Val137				Val137	Val137	Val137			Val137	
Residues that NOT interacts with the original ligand	Arg45	Arg181	Tyr248	Arg171	Phe233	Arg171	Arg45	Arg181	Arg171	Asp176	Arg181
	Asp48	Arg45	Tyr41	Arg45	Tyr41	Arg265	Asp48	Arg265	Arg265	Asp48	Arg45
	Cys44	Asn179		Asn179	Val133	Arg45	Cys44	Arg45	Arg45	Tyr129	Asn179
	Tyr41	Asp176		Asp114		Asn179	Tyr41	Asn179	Asp172	Tyr183	Asp176
	Val133	Asp48		Asp172		Asp172	Val133	Asp176	Asp176	Tyr41	Asp48
		Tyr129		Asp176		Asp176		Asp48	Asp48	Val133	Tyr129
		Tyr183		Asp48		Asp48		Tyr129	Glu175		Tyr183
		Val133		Asp49		Glu175		Tyr183	Tyr129		Val133
				Ile51		Tyr129		Val133	Tyr183		
				Tyr129		Tyr248					
				Tyr183		Tyr41					
						Val133					

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	106	111	136	7	9	63	64	6	32	104	135
Compound Name Docked to Protein (3ACW)	Elmycin_C	Emycin_A	Urdamycin_I	Hatomarubigin_C	Hatomarubigin_E	Tetrangulol	Ochromocinone	Hatomarubigin_B	Gaudimycin_B	Elmycin_A	Yoronomycin
Run1	-7.6	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.5	-7.5	-7.6
Run2	-7.6	-7.7	-7.7	-7.7	-7.7	-7.7	-7.6	-7.6	-7.7	-7.7	-8.1
Run3	-7.8	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.5	-7.5
AV.	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.6	-7.6	-7.7
Dock	-7.8	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.6
Residues that interacts with the original ligand & Residues that interacts with the ligands	2	10	8	4	4	2	11	3	4	6	12
		Ala134	Ala134				Ala134		Ala134	Ala134	Ala134
		Ala157					Ala157				Ala157
	Asn168		Asn168	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168	Asn168
	Gln165		Gln165	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165
							Gly138				Gly138
		Gly161					Gly161				Gly161
			His18	His18	His18			His18	His18	His18	His18
							Ile241				
		Leu141	Leu141				Leu141				Leu141
		Leu145					Leu145				
		Leu160					Leu160				
		Leu164	Leu164				Leu164				Leu164
		Phe22	Phe22				Phe22			Phe22	Phe22
		Phe26					Phe26				Phe26
		Val137	Val137	Val137	Val137					Val137	Val137
Residues that NOT interacts with the original ligand	Arg181	Gly138	Arg45	Arg171	Arg171	Asp114	Tyr41	Arg171	Arg171	Arg171	Arg45
	Asp114	Tyr41	Asp48	Arg265	Arg265	Asp172		Arg265	Arg45	Arg265	Asp48
	Asp172	Val133	Tyr41	Asp172	Arg45	Asp176		Asp114	Asn179	Arg45	Tyr248
	Asp176		Val133	Asp176	Asp172	Asp48		Asp172	Asp172	Asp172	Tyr41
	Asp48			Asp48	Asp176	Ile51		Asp176	Asp176	Asp48	Val133
	Ile51			Tyr129	Asp48	Tyr129		Asp48	Asp48	Glu175	
	Tyr129			Tyr183	Tyr129	Val111		Tyr129	Glu175	Tyr248	
	Tyr183			Tyr248	Tyr183	Val133		Tyr183	Tyr129	Tyr41	
	Val111			Tyr41	Tyr248			Tyr41	Tyr183	Val133	
				Val133	Tyr41			Val133	Val133		
					Val133						

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	130	86	68	89	5	108	24	10	121	107	126
Compound Name Docked to Protein (3ACW)	Prejadomycin	SM_196 A	8_O_methylrabelomycin	3_Deoxyrabelomycin	Hatomarubigin_A	Elmycin_E	Dehydrorabelomycin	Hatomarubigin_F	X_14881_A	Elmycin_D	PD116740
Run1	-7.8	-7.6	-7.6	-7.6	-7.4	-7.5	-7.5	-7.5	-7.5	-7.5	-7.3
Run2	-7.6	-7.6	-7.6	-7.6	-7.7	-7.5	-7.5	-7.4	-7.5	-7.4	-7.3
Run3	-7.8	-7.6	-7.6	-7.6	-7.6	-7.5	-7.5	-7.5	-7.3	-7.4	-7.3
AV.	-7.7	-7.6	-7.6	-7.6	-7.6	-7.5	-7.5	-7.5	-7.4	-7.4	-7.3
Dock	-7.6	-7.6	-7.6	-7.6	-7.6	-7.5	-7.5	-7.5	-7.5	-7.5	-7.3
Residues that interacts with the original ligand & Residues that interacts with the ligands	6	4	3	2	14	4	2	2	6	4	2
	Ala134				Ala134	Ala134					
					Ala157						
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
					Gly138						
					Gly161						
	His18	His18	His18		His18	His18			His18	His18	
					Ile241						
					Leu141						
					Leu145						
					Leu160						
					Leu164				Leu164		
	Phe22				Phe22				Phe22		
					Phe26						
	Val137	Val137							Val137	Val137	
Residues that NOT interacts with the original ligand	Arg171	Arg171	Arg265	Val111	Phe233	Arg181	Asp114	Asn179	Arg45	Arg265	Arg181
	Arg265	Arg265	Arg45	Val133	Tyr41	Arg45	Asp172	Asp114	Asp48	Arg45	Asn179
	Arg45	Arg45	Asn179	Tyr129		Asn179	Asp176	Asp172	Tyr41	Asn179	Asp114
	Asp172	Asp172	Asp172	Asp114		Asp176	Asp48	Asp176	Val133	Asp176	Asp172
	Asp176	Asp176	Asp176	Asp48		Asp48	Ile51	Asp48		Asp48	Asp176
	Asp48	Asp48	Asp48	Asp52		Tyr129	Tyr129	Ile51		Glu175	Asp48
	Tyr129	Tyr183	Tyr129	Ile51		Tyr183	Val111	Tyr129		Tyr129	Ile51
	Tyr41	Tyr248	Tyr183			Val133	Val133	Val111		Tyr183	Tyr129
	Val133	Tyr41	Val133					Val133		Val133	Tyr183
		Val133	Val137								Val111

APPENDIX I

Docking score and interacted residue of protein (3ACW) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	110	109	81	69	70	79	43	44	15	16	17
Compound Name Docked to Protein (3ACW)	X_14881_D	X_14881_B	Tetrangulol methyl ether	Urdamycin_C (Not Docked)	Urdamycin_E (Not Docked)	8_O_methylurdamycin_A (Not Docked)	JBIR_92 (Not Docked)	JBIR_93 (Not Docked)	Langkocycline_A2 (Not Docked)	Langkocycline_A3 (Not Docked)	Langkocycline_B1 (Not Docked)
Run1	-7.4	-7.2	-7.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Run2	-7.2	-7.2	-7.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Run3	-7.1	-7.2	-7.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AV.	-7.2	-7.2	-7.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dock	-7.2	-7.2	-7.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Residues that interacts with the original ligand & Residues that interacts with the ligands	13	4	3	0	0	0	0	0	0	0	0
	Ala134										
	Ala157										
		Asn168	Asn168								
		Gln165	Gln165								
	Gly138										
	Gly161										
	His18	His18	His18								
	Ile241										
	Leu141										
	Leu145										
	Leu160										
	Leu164										
	Phe22										
	Phe26										
	Val137	Val137									
Residues that NOT interacts with the original ligand	Gly135	Arg265	Arg45								
	Phe233	Arg45	Asn179								
	Tyr41	Asn179	Asp176								
	Val133	Asp176	Asp48								
		Asp48	Tyr129								
		Glu175	Tyr183								
		Tyr129	Val133								
		Tyr183									
		Val133									

APPENDIX I
Docking score and interacted residue of protein (3ACW)
with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

	Residues that NOT interacts with the original ligand		Residues that interacts with the original ligand & Residues that interacts with the ligands		Dock	AV.	Run3	Run2	Run1	Compound Name Docked to Protein (3ACW)	#
				0	0.0	0.0	0.0	0.0	0.0	Langkocycline_B2 (Not Docked)	18
				0	0.0	0.0	0.0	0.0	0.0	Saquayamycin_Z (Not Docked)	153
				0	0.0	0.0	0.0	0.0	0.0	Urdamycin_D (Not Docked)	66
				0	0.0	0.0	0.0	0.0	0.0	Urdamycin_H (Not Docked)	67
				0	0.0	0.0	0.0	0.0	0.0	Urdamycin_K (Not Docked)	138

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol)

#		0	56	58	8	146	145	29	148	27	28
Compound Name Docked to Protein 3W7F with MG	3W7F_FromPDB Part A	Ligand of Protein	Moromycin_A	Saquayamycin_B	Hatomarubigin_D	Saquayamycin_B	Saquayamycin_A	Saprolmycin_E	Saquayamycin_D	Saprolmycin_C	Saprolmycin_D
Run1		-8.3	-14.8	-13.3	-14.2	-13.8	-13.7	-13.7	-13.6	-13.6	-13.5
Run2		-8.2	-14.8	-13.3	-14.2	-13.8	-13.7	-13.4	-13.6	-13.6	-13.5
Run3		-8.3	-14.8	-14.4	-14.2	-13.8	-13.7	-13.4	-13.6	-13.6	-13.5
AV		-8.3	-14.8	-13.7	-14.2	-13.8	-13.7	-13.5	-13.6	-13.6	-13.5
Dock		-8.3	-14.8	-14.4	-14.2	-13.8	-13.7	-13.7	-13.6	-13.6	-13.5
Residues that interacts with the original ligand & Residues that interacts with the ligands	32	23	17	21	18	21	20	16	19	17	20
	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134
	Ala157	Ala157	Ala157	Ala157		Ala157	Ala157	Ala157	Ala157		Ala157
	Arg171	Arg171			Arg171						Arg171
	Arg265	Arg265									
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45		Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Asp172				Asp172						
	Asp48			Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48
	Cys44				Cys44					Cys44	
	Gln165	Gln165	Gln165	Gln165	Gln165				Gln165	Gln165	Gln165
	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138
	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161		Gly161	Gly161
	His18	His18				His18					
	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
	Leu145	Leu145	Leu145	Leu145		Leu145	Leu145	Leu145	Leu145		Leu145
	Leu160	Leu160	Leu160	Leu160		Leu160	Leu160	Leu160	Leu160		Leu160
	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
	Lys20	Lys20									
	Met15										
	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22		Phe22	Phe22	Phe22
	Phe233	Phe233		Phe233		Phe233	Phe233	Phe233			Phe233
	Ser19	Ser19				Ser19	Ser19				
	Ser21	Ser21									
	Tyr248	Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	Tyr248	Tyr248		Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41	
	Unk303			Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303
	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304		Unk304	Unk304	Unk304
	Unk305		Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305
	Val133			Val133	Val133			Val133	Val133	Val133	
	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Unk301	Unk302	Arg181	Arg181	Arg181	Arg181	Arg181	Arg181	Arg181	Asn179	Arg181
	Unk302		Asn179	Asn179	Asn179	Asn179	Asn179	Asn179	Asn179	Asp114	Asn179
	HOH401		Asp176	Asp52	Asp114	Asp114	Asp114	Asp114	Asp176	Asp176	Asp114
	HOH402		Asp52	Ile241	Asp176	Asp52	Asp176	Asp176	Asp52	Asp52	Asp176
	HOH403		Ile241	Phe26	Asp52	Ile241	Asp52	Asp52	Ile241	Phe26	Asp52
	HOH404		Phe233	Tyr129	Phe26	Phe26	Glu175	Gln115	Phe26	Tyr129	Gln115
	HOH405		Phe26	Tyr183	Tyr129	Tyr129	Ile241	Ile241	Tyr129	Tyr183	Ile241
	HOH406		Tyr129		Tyr183	Tyr183	Phe26	Ile51	Tyr183		Phe26
	HOH407		Tyr183				Tyr129	Phe26			Tyr129
	HOH408						Tyr183	Tyr129			Tyr183
								Tyr183			

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	2	26	143	134	38	42	57	47	151	25	71
Compound Name Docked to Protein 3W7F with MG	Marangucycline_B	Saprolmycin_B	PI_085	PI_1894B (Vineomycin A) (OS-4742A1)	Grincamycin	JBIR_91	Moromycin_B	N05WA963A	Saquayamycin_K4	Saprolmycin_A	Urdamycin_F
Run1	-13.2	-13.3	-12.4	-12.7	-12.5	-12.5	-12.5	-12.4	-12.4	-12.3	-12.2
Run2	-13.5	-13.3	-12.8	-12.7	-12.5	-12.5	-12.5	-12.5	-12.4	-12.3	-12.3
Run3	-13.5	-13.3	-13.0	-12.7	-12.5	-12.5	-12.5	-12.5	-12.4	-12.3	-12.2
AV	-13.4	-13.3	-12.7	-12.7	-12.5	-12.5	-12.5	-12.5	-12.4	-12.3	-12.2
Dock	-13.5	-13.3	-13	-12.7	-12.5	-12.5	-12.5	-12.5	-12.4	-12.3	-12.3
Residues that interacts with the original ligand & Residues that interacts with the ligands	21	12	18	24	22	19	14	20	19	18	19
	Ala134		Ala134	Ala134	Ala134		Ala134	Ala134			Ala134
	Ala157			Ala157	Ala157	Ala157		Ala157	Ala157	Ala157	
	Arg171		Arg171								Arg171
	Arg265			Arg265					Arg265		
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Asp172		Asp172				Asp172				Asp172
	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48
		Cys44	Cys44								Cys44
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138			Gly138	Gly138	Gly138		Gly138	Gly138	Gly138	
	Gly161			Gly161		Gly161	Gly161	Gly161	Gly161	Gly161	Gly161
				His18	His18				His18		
	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
	Leu145			Leu145	Leu145	Leu145		Leu145			
	Leu160			Leu160	Leu160	Leu160		Leu160	Leu160	Leu160	
	Leu164		Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
				Lys20	Lys20						
		Met15	Met15								Met15
			Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
				Phe233	Phe233	Phe233		Phe233			
						Ser19				Ser19	Ser19
	Tyr248		Tyr248	Tyr248	Tyr248	Tyr248		Tyr248	Tyr248		
		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41	Tyr41
	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk304	Unk303	Unk303
	Unk304		Unk304	Unk304	Unk304	Unk304		Unk304		Unk304	Unk304
	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305
	Val133	Val133		Val133	Val133			Val133	Val133	Val133	
	Val137	Val137	Val137	Val137	Val137		Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Asp176	Asn179	Arg181	Arg181	Arg181	Arg181	Arg181	Arg181	Arg181	Arg181	Asp176
	Glu175	Asp114	Asp114	Asn179	Asn179	Asn179	Asn179	Asn179	Asn179	Asn179	Asn179
	Ile241	Asp176	Asp176	Asp114	Asp114	Asp176	Asp114	Asp114	Asp52	Asp114	Asp114
	Phe26	Asp52	Asp52	Asp176	Asp176	Glu175	Asp52	Glu175	Glu175	Asp176	Arg181
		Ile40	Gln115	Asp52	Asp52	Ile241	Phe26	Asp52	Phe26	Asp52	Asp52
		Phe26	Glu175	Glu175	Glu175	Phe26	Tyr129	Ile241	Tyr129	Phe26	Ile51
		Tyr129	Ile40	Ile241	Ile241	Tyr129	Tyr183	Phe26	Tyr183	Tyr129	Phe26
		Tyr183	Phe26	Phe26	Phe26	Tyr183		Tyr129		Tyr183	Tyr129
		Val37	Tyr129	Tyr129	Tyr129			Tyr183			Tyr183
			Tyr183	Tyr183	Tyr183						Val37
			Val37								

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	144	92	49	141	69	72	65	97	84	37	124
Compound Name Docked to Protein 3W7F with MG	PI_087	BA_12100B	N05WA963D	Kerriamycin_C	Urdamycin_C	Urdamycin_G	PI_080 (=PI-6621)	BA_12100Z2	A_7884	Landomycin_Z	Landomycin_C
Run1	-12.2	-11.4	-12.2	-12.2	-10.2	-12.1	-12.0	-11.4	-12.0	-12.0	-11.6
Run2	-12.3	-10.5	-12.2	-12.2	-12.2	-12.1	-11.8	-11.0	-12.0	-12.0	-12.0
Run3	-12.2	-12.3	-12.2	-12.2	-12.1	-12.1	-12.1	-12.1	-12.0	-12.0	-11.7
AV	-12.2	-11.4	-12.2	-12.2	-11.5	-12.1	-12.0	-11.5	-12.0	-12.0	-11.8
Dock	-12.3	-12.3	-12.2	-12.2	-12.2	-12.1	-12.1	-12.1	-12	-12	-12
Residues that interacts with the original ligand & Residues that interacts with the ligands	14	19	20	20	17	20	22	17	18	16	26
	Ala134	Ala134	Ala134		Ala134	Ala134		Ala134	Ala134		Ala134
		Ala157	Ala157	Ala157	Ala157		Ala157	Ala157	Ala157		Ala157
			Arg171	Arg171		Arg171	Arg171				Arg171
						Arg265	Arg265				Arg265
	Arg45		Arg45	Arg45	Arg45	Arg45	Arg45			Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
				Asp172		Asp172	Asp172				Asp172
	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48
				Cys44		Cys44	Cys44			Cys44	
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
		Gly138	Gly138	Gly138	Gly138		Gly138	Gly138	Gly138		Gly138
	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161		Gly161
										His18	His18
		Leu141	Leu141	Leu141		Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
		Leu145	Leu145	Leu145			Leu145		Leu145		Leu145
		Leu160	Leu160	Leu160	Leu160		Leu160	Leu160	Leu160		Leu160
	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
										Lys20	
						Met15					Met15
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
		Phe233							Phe233		Phe233
						Ser19					Ser19
	Tyr248	Tyr248	Tyr248		Tyr248			Tyr248		Tyr248	
	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303
	Unk304		Unk304	Unk304	Unk304	Unk304	Unk304			Unk304	Unk304
	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305
		Val133		Val133	Val133		Val133	Val133	Val133		Val133
	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Arg181	Ala244	Asp52	Asn179	Ala244	Asp176	Arg181	Arg181	Arg181	Arg181	Asn179
	Asn179	Arg181	Arg181	Asp176	Arg181	Asp52	Asp176	Asn179	Asn179	Asp49	Arg181
	Asp114	Asn179	Glu175	Glu175	Asn179	Glu175	Asn179	Asp114	Asp114	Asp52	Asp176
	Asp176	Asp114	Asn179	Ile241	Asp176	Phe26	Asp114	Asp176	Asp176	Asn179	Asp49
	Asp52	Asp176	Asp114	Leu107	Asp52	Tyr129	Asp52	Asp52	Asp52	Asp114	Asp52
	Gln115	Asp52	Ile241	Phe26	Glu175	Tyr183	Gln115	Phe26	Ile241	Asp176	Glu175
	Gly55	Glu139	Phe26	Tyr129	Ile169	Val37	Glu175	Tyr129	Phe26	Glu175	Ile241
	Ile51	Ile241	Tyr129	Tyr183	Phe26		Ile241	Tyr183	Tyr129	Phe26	Phe26
	Ile57	Phe26	Tyr183		Tyr129		Ile51		Tyr183	Tyr129	Tyr129
	Tyr129	Tyr129			Tyr183		Phe26			Tyr183	Tyr183
	Tyr183	Tyr183			Val53		Val53			Val37	Val53
										Val53	

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	46	39	95	147	98	140	59	35	91	96	150
Compound Name Docked to Protein 3W7F with MG	Urdamycin_B	Grincamycin_F	BA_12100E	Saquayamycin_C	BA_12100Z3	Kerriamycin_B	Sch_47554	Landomycin_A	Aggreticin (OM-4842)	BA_12100Z1	Saquayamycin_K2
Run1	-11.9	-11.5	-11.9	-11.8	-11.6	-11.7	-11.6	-11.5	-11.6	-11.6	-11.6
Run2	-11.9	-11.9	-10.9	-11.8	-11.6	-11.7	-11.7	-11.3	-11.6	-11.6	-11.6
Run3	-11.9	-11.9	-11.7	-11.8	-11.8	-11.7	-11.6	-11.7	-11.6	-11.6	-11.6
AV	-11.9	-11.8	-11.5	-11.8	-11.7	-11.7	-11.6	-11.5	-11.6	-11.6	-11.6
Dock	-11.9	-11.9	-11.9	-11.8	-11.8	-11.7	-11.7	-11.7	-11.6	-11.6	-11.6
Residues that interacts with the original ligand & Residues that interacts with the ligands	17	21	19	17	19	18	18	19	20	19	9
		Ala134	Ala134		Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	
		Ala157		Ala157	Ala157						
	Arg171	Arg171	Arg171			Arg171		Arg171	Arg171	Arg171	
	Arg265							Arg265	Arg265		
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Asp172		Asp172					Asp172	Asp172	Asp172	
	Asp48	Asp48	Asp48	Asp48	Asp48		Asp48	Asp48	Asp48	Asp48	Asp48
			Cys44			Cys44	Cys44	Cys44	Cys44	Cys44	
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
				Gly138	Gly138						
		Gly161	Gly161	Gly161	Gly161	Gly161	Gly161		Gly161	Gly161	
	His18	His18						His18			His18
	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141		Leu141	Leu141	
				Leu145	Leu145						
		Leu160		Leu160	Leu160		Leu160				
		Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	
		Lys20						Lys20			Lys20
			Met15						Met15	Met15	
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	
					Phe233						
	Ser19	Ser19	Ser19			Ser19				Ser19	
	Tyr248	Tyr248		Tyr248		Tyr248	Tyr248	Tyr248			
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	
	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303
	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304	Unk304
	Unk305	Unk305	Unk305	Unk305		Unk305	Unk305	Unk305	Unk305	Unk305	Unk305
				Val133	Val133	Val133	Val133	Val133	Val133		
	Val137	Val137	Val137		Val137	Val137	Val137		Val137	Val137	
Residues that NOT interacts with the original ligand	Asn179	Arg181	Arg181	Arg181	Ala244	Arg181	Ala244	Ala244	Asp176	Arg181	Asn179
	Asp114	Asn179	Asn179	Asn179	Arg181	Asn179	Asn179	Arg181	Asp52	Asp114	Asp114
	Asp176	Asp176	Asp114	Asp114	Asn179	Asp114	Asp176	Asn179	Glu175	Asn179	Asp176
	Asp52	Asp49	Asp176	Asp176	Asp114	Asp176	Asp52	Asp114	Ile40	Asp176	Asp49
	Glu175	Asp52	Asp52	Asp52	Asp176	Asp52	Ile40	Asp49	Phe26	Asp52	Asp52
	Phe26	Gln115	Gln115	Glu175	Asp52	Ile169	Phe26	Asp52	Tyr129	Phe26	Glu175
	Tyr129	Glu175	Ile51	Ile241	Ile241	Tyr129	Tyr129	Glu175	Tyr183	Tyr129	Lys17
	Tyr183	Gly55	Phe26	Phe26	Ile51	Tyr183	Tyr183	Phe26	Val37	Tyr183	Tyr129
		Ile51	Tyr183	Tyr129	Phe26			Tyr129		Val37	Tyr183
		Phe26	Val111	Tyr183	Tyr129			Tyr183			Val53
		Tyr129	Val37		Tyr183			Val53			
		Tyr183									
		Tyr54									
		Val53									

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	13	142	1	83	123	30	155	149	19	139	93
Compound Name Docked to Protein 3W7F with MG	Waldiomycin	PI_083	Maranguycycline_A	Saquayamycin_A1	Landomycin_B	Saquayamycin_A	Vineomycin_A1	Saquayamycin_K1	Fradimycin_C	Kerriamycin_A	BA_12100C
Run1	-11.5	-11.4	-11.4	-11.4	-11.4	-11.3	-11.2	-11.2	-11.1	-11.1	-11.0
Run2	-11.4	-11.3	-11.4	-11.4	-11.3	-11.0	-11.3	-11.3	-11.1	-11.1	-11.0
Run3	-11.4	-11.5	-11.4	-11.4	-11.3	-11.4	-11.3	-11.3	-11.1	-11.1	-11.0
AV	-11.4	-11.4	-11.4	-11.4	-11.3	-11.2	-11.3	-11.3	-11.1	-11.1	-11.0
Dock	-11.5	-11.5	-11.4	-11.4	-11.4	-11.4	-11.3	-11.3	-11.1	-11.1	-11
Residues that interacts with the original ligand & Residues that interacts with the ligands	18	16	16	11	22	23	17	16	17	15	23
	Ala134		Ala134	Ala134	Ala134	Ala134			Ala134	Ala134	Ala134
					Ala157	Ala157			Ala157		Ala157
	Arg171	Arg171	Arg171			Arg171	Arg171	Arg171		Arg171	Arg171
	Arg265		Arg265		Arg265	Arg265					Arg265
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45		Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
	Asp172	Asp172	Asp172			Asp172	Asp172	Asp172			Asp172
		Asp48		Asp48	Asp48	Asp48	Asp48	Asp48	Asp48		Asp48
		Cys44			Cys44		Cys44	Cys44			
	Gln165	Gln165	Gln165	Gln165	Gln165		Gln165		Gln165		Gln165
	Gly138				Gly138	Gly138			Gly138	Gly138	Gly138
	Gly161		Gly161		Gly161	Gln165		Gln165	Gly161	Gly161	Gly161
					His18						His18
		Leu141	Leu141	Leu141	Leu141	Leu141			Leu141	Leu141	Leu141
					Leu145	Leu145			Leu145		Leu145
	Leu141				Leu160	Leu160			Leu160	Leu160	Leu160
	Leu164	Leu164	Leu164		Leu164	Leu164			Leu164	Leu164	Leu164
					Lys20	Lys20					Lys20
		Met15					Met15				
	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22		Phe22	Phe22
					Phe233	Phe233			Phe233		
	Ser19		Ser19				Ser19	Ser19			
						Tyr248	Tyr248	Tyr248		Tyr248	Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41			Tyr41	Tyr41	Tyr41		
	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303
	Unk304	Unk304	Unk304		Unk304	Unk304	Unk304	Unk304		Unk304	Unk304
	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305
					Val133	Val133	Val133	Val133	Val133		
	Val137	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Asp114	Arg181	Arg181	Arg181	Asn179	Asn179	Arg181	Asn179	Arg181	Arg181	Asp176
	Arg181	Asn179	Asn179	Asn179	Asp114	Asp176	Asn179	Asp114	Asn179	Asn179	Asp49
	Asp176	Asp114	Asp176	Asp114	Asp176	Asp52	Asp114	Asp176	Asp114	Asp52	Glu175
	Asp52	Asp176	Asp52	Asp176	Asp52	Glu175	Asp176	Asp52	Asp176	Glu175	Phe26
	Gln115	Asp52	Glu175	Asp52	Glu175	Ile241	Asp52	Glu175	Asp52	Phe26	Tyr129
	Ile51	Gln115	Phe26	Tyr129	Ile241	Phe26	Gln115	Leu107	Glu175	Val53	Tyr183
	Phe26	Glu175	Tyr183	Tyr183	Phe26	Val53	Gly55	Tyr129	Ile241		
	Tyr183	Phe26			Tyr129		Ile51	Tyr183	Phe26		
	Val111	Tyr129			Tyr183		Phe26		Thr142		
		Tyr183			Val53		Tyr129		Tyr129		
		Val37					Tyr183		Tyr183		
							Tyr54				
							Val53				

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	36	152	21	122	94	23	77	128	125	40	34
Compound Name Docked to Protein 3W7F with MG	Landomycin_E	Saquayamycin_K7	Jadomycin_B	Landomycin_A_122	BA_12100D	L_digitoxosyl_dehydrorabelomycin	Sakyomicin_E	Landomycin_F	Landomycin_D	JBIR_90	Aquayamycin
Run1	-11.0	-10.9	-10.5	-10.9	-10.9	-10.8	-10.7	-10.4	-10.4	-10.4	-10.3
Run2	-11.0	-10.9	-10.9	-10.5	-10.2	-10.8	-10.6	-10.4	-10.4	-10.1	-10.3
Run3	-11.0	-10.9	-10.9	-10.5	-10.3	-10.8	-8.8	-10.4	-10.4	-10.4	-10.3
AV	-11.0	-10.9	-10.8	-10.6	-10.5	-10.8	-10.0	-10.4	-10.4	-10.3	-10.3
Dock	-11	-10.9	-10.9	-10.9	-10.9	-10.8	-10.7	-10.4	-10.4	-10.4	-10.3
Residues that interacts with the original ligand & Residues that interacts with the ligands	15	11	17	19	17	12	15	20	15	11	17
	Ala134		Ala134		Ala134		Ala134	Ala134			Ala134
					Ala157						Ala157
		Arg171		Arg171			Arg171	Arg171			Arg171
				Arg265							
	Arg45	Arg45	Arg45	Arg45			Arg45	Arg45	Arg45		Arg45
	Asn168	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
		Asp172							Asp172		
	Asp48	Asp48	Asp48	Asp48		Asp48	Asp48	Asp48	Asp48	Asp48	Asp48
	Cys44		Cys44	Cys44	Cys44	Cys44	Cys44	Cys44	Cys44	Cys44	
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165
					Gly138			Gly138			Gly138
			Gly161		Gly161			Gly161			Gly161
		His18		His18				His18			
				Leu141	Leu141		Leu141	Leu141	Leu141	Leu141	Leu141
					Leu145						
					Leu160						Leu160
	Leu164		Leu164	Leu164	Leu164		Leu164	Leu164	Leu164		Leu164
		Lys20		Lys20							
			Met15			Met15	Met15				
	Phe22		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
					Phe233						
								Ser19			Ser19
	Tyr248		Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248		Tyr248
	Tyr41		Tyr41	Tyr41		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Unk303	Unk303	Unk303	Unk303	Unk303	Unk303			Unk303	Unk303	
	Unk304	Unk304	Unk304	Unk304			Unk304	Unk304	Unk304		Unk304
	Unk305	Unk305	Unk305	Unk305	Unk305	Unk305		Unk305	Unk305	Unk305	
	Val133		Val133	Val133	Val133	Val133	Val133	Val133		Val133	
	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	
Residues that NOT interacts with the original ligand	Ala244	Asn179	Leu107	Asn179	Arg181	Asp176	Ile40	Leu107	Asn179	Asp176	Ala244
	Asp176	Asp114	Phe26	Asp114	Asn179	Asp52	Phe26	Tyr129	Asp176	Asp52	Phe26
	Asp52	Asp176	Tyr129	Asp52	Asp114	Leu107	Val37	Val111	Asp52	Ile169	Ile241
	Glu175	Asp49	Tyr183	Glu175	Asp176	Phe26			Glu175	Phe26	
	Phe26	Asp52	Val111	Ile40	Asp48	Tyr129			Ile40	Tyr129	
	Tyr129	Lys17		Lys17	Asp52	Tyr183			Phe26	Tyr183	
	Tyr183	Tyr129		Phe26	Glu175				Tyr129	Val37	
		Tyr183		Tyr129	Ile241				Val37		
		Val53		Tyr183	Leu107						
				Val37	Phe26						
				Val53	Thr142						
					Tyr129						
					Tyr183						
					Val111						

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	87	78	75	85	45	41	3	103	63	60	22
Compound Name Docked to Protein 3W7F with MG	C104_Aglycon	BE_7585A	Sakyomicin_C	Aquamycin	Urdamycin_A	JBIR_116	Actinosporin_A	De_O_acylcapoamycin	Tetrangulol	Sch_47555	Jadomycin_A
Run1	-10.3	-10.2	-10.3	-10.2	-10.2	-10.1	-10.0	-10.1	-10.1	-9.6	-8.8
Run2	-10.3	-10.3	-9.2	-10.2	-10.2	-10.2	-10.2	-10.1	-10.1	-9.2	-9.3
Run3	-10.3	-10.2	-9.2	-10.2	-10.2	-10.2	-10.0	-10.1	-9.8	-10.0	-10.0
AV	-10.3	-10.2	-9.6	-10.2	-10.2	-10.2	-10.1	-10.1	-10.0	-9.6	-9.4
Dock	-10.3	-10.3	-10.3	-10.2	-10.2	-10.2	-10.2	-10.1	-10.1	-10	-10
Residues that interacts with the original ligand & Residues that interacts with the ligands	10	21	15	18	16	19	11	12	9	18	14
		Ala134		Ala134	Ala134	Ala134				Ala134	Ala134
				Ala157							
		Arg171	Arg171				Arg171			Arg171	
		Arg265	Arg265				Arg265				
		Arg45	Arg45	Arg45	Arg45	Arg45	Arg45			Arg45	
		Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
		Asp172									
	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48		Asp48		Asp48	Asp48
	Cys44	Cys44	Cys44	Cys44		Cys44		Cys44	Cys44		Cys44
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
				Gly138		Gly138					
		Gly161		Gly161	Gly161	Gly161				Gly161	Gly161
	Leu141		Leu141	Leu141	Leu141	Leu141			Leu141	Leu141	
				Leu145							
				Leu160		Leu160					
		Leu164	Leu164	Leu164	Leu164	Leu164			Leu164	Leu164	Leu164
	Met15							Met15		Met15	Met15
	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
				Phe233							
		Ser19			Ser19			Ser19			
		Ser21									
		Tyr248	Tyr248			Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Unk303	Unk303			Unk303	Unk303	Unk303			Unk303	
		Unk304	Unk304	Unk304	Unk304	Unk304	Unk304			Unk304	Unk304
		Unk305		Unk305	Unk305	Unk305	Unk305	Unk305		Unk305	
	Val133	Val133	Val133	Val133	Val133	Val133		Val133		Val133	Val133
	Val137	Val137	Val137	Val137	Val137	Val137		Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Asn168	Arg181	Leu107	Ile241	Arg181	Arg181	Arg181	Asp114	Ile40	Ala244	Leu107
	Asp176	Asp114	Phe26	Leu107	Asn179	Asp114	Asn179	Asp52	Phe26	Arg181	Phe26
	Phe26	Asp176	Val111		Asp114	Asp176	Asp114	Phe26	Val37	Asn179	Val111
	Tyr129	Asp52			Asp176	Asp52	Asp176	Thr110		Asp176	
	Tyr183	His18			Asp52	Phe26	Asp52	Tyr129		Asp52	
	Val37	Leu107			Gln115	Tyr129	His18	Tyr183		Ile40	
		Tyr129			Glu175	Tyr183	Ile169	Val111		Phe26	
		Tyr183			Ile51		Lys20			Tyr129	
		Val111			Phe26		Ser19			Tyr183	
					Tyr129		Ser21			Val37	
					Tyr183		Tyr129				
					Val111		Tyr183				

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	88	64	112	52	6	31	135	86	70	81	99
Compound Name Docked to Protein 3W7F with MG	C104	Ochromocinone	SF_2315_A	Mayamycin	Hatomarubigin_B	Gaudimycin_A	Yoronomycin	SM_196 A	Urdamycin_E	Tetrangulol methyl ether	BA_12100MY_1
Run1	-9.9	-9.9	-9.3	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.7	-9.7
Run2	-9.9	-9.9	-9.9	-9.8	-9.8	-9.8	-9.8	-9.8	-9.7	-9.7	-9.7
Run3	-9.9	-9.7	-9.9	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.7	-9.7
AV	-9.9	-9.8	-9.7	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.7	-9.7
Dock	-9.9	-9.9	-9.9	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.7	-9.7
Residues that interacts with the original ligand & Residues that interacts with the ligands	17	10	12	16	15	14	14	12	19	11	11
	Ala134				Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	
								Ala157			
				Arg171		Arg171					
				Arg265							
	Arg45		Arg45	Arg45	Arg45	Arg45	Arg45		Arg45	Arg45	
	Asn168	Asn168	Asn168	Asn168		Asn168	Asn168		Asn168		Asn168
				Asp172							
	Asp48			Asp48					Asp48		Asp48
	Cys44	Cys44	Cys44						Cys44		Cys44
	Gln165	Gln165	Gln165	Gln165	Gln165		Gln165		Gln165		Gln165
					Gly138	Gly138		Gly138	Gly138	Gly138	
	Gly161				Gly161	Gly161		Gly161	Gly161	Gly161	
					His18	His18			His18		
	Leu141	Leu141	Leu141		Leu141		Leu141	Leu141	Leu141	Leu141	
								Leu145			
					Leu160			Leu160		Leu160	
	Leu164	Leu164	Leu164		Leu164	Leu164	Leu164	Leu164	Leu164		
		Met15	Met15				Met15		Met15		Met15
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
								Phe233			
	Ser19		Ser19	Ser19	Ser19	Ser19	Ser19			Ser19	
				Ser21							
		Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	Tyr248	Tyr248		
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41	Tyr41
	Unk303			Unk303					Unk303		Unk303
	Unk304			Unk304	Unk304	Unk304	Unk304		Unk304	Unk304	
	Unk305			Unk305					Unk305		Unk305
	Val133			Val133	Val133		Val133				Val133
	Val137	Val137	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Asp52	Phe26	Ile40	Asp114	Phe26	Phe26	Phe26	Ile241	Arg181	Phe26	Arg181
	Leu107	Val37	Phe26	Asp176				Phe26	Asn179		Leu107
	Phe26		Val37	Asp52				Thr142	Asp176		Phe26
	Tyr129			Leu107					Asp52		Tyr129
	Tyr183			Tyr129					Glu175		Tyr183
				Tyr183					Ile169		Asp114
				Val111					Phe26		Asp52
									Tyr129		
									Tyr183		
									Val53		

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	54	104	7	105	48	89	33	32	137	110	120
Compound Name Docked to Protein 3W7F with MG	8_O_methyltetrangulol	Elmycin_A	Hatomarubigin_C	Elmycin_B	N05WA963B	3_Deoxyrabelomycin	Gaudimycin_C	Gaudimycin_B	Urdamycin_J	X_14881_D	X_14881_E
Run1	-9.7	-9.7	-9.7	-9.7	-9.6	-9.7	-9.7	-9.6	-9.6	-9.6	-9.6
Run2	-9.7	-9.7	-9.6	-9.6	-9.6	-9.7	-9.2	-9.6	-9.6	-9.6	-9.6
Run3	-9.7	-9.7	-9.7	-9.6	-9.7	-9.5	-9.7	-9.6	-9.6	-9.6	-9.6
AV	-9.7	-9.7	-9.7	-9.6	-9.6	-9.6	-9.5	-9.6	-9.6	-9.6	-9.6
Dock	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.6	-9.6	-9.6	-9.6
Residues that interacts with the original ligand & Residues that interacts with the ligands	9	9	16	14	12	8	15	16	15	13	12
		Ala134	Ala134	Ala134			Ala134	Ala134	Ala134	Ala134	Ala134
			Ala157							Ala157	
				Arg171			Arg171	Arg171	Arg171		
			Arg45	Arg45	Arg45	ARG45	Arg45	Arg45	Arg45		Arg45
	Asn168	Asn168		Asn168	Asn168		Asn168	Asn168	Asn168		
		Asp48		Asp48	Asp48						
	Cys44										
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165			
			Gly138				Gly138	Gly138	Gly138	Gly138	Gly138
			Gly161				Gly161	Gly161	Gly161	Gly161	Gly161
			His18				His18	His18	His18		
	Leu141		Leu141		Leu141	LEU141				Leu141	Leu141
										Leu145	
			Leu160							Leu160	Leu160
	Leu164	Leu164	Leu164	Leu164	Leu164	LEU164	Leu164	Leu164	Leu164	Leu164	
				Met15							
	Phe22	Phe22	Phe22	Phe22	Phe22	PHE22	Phe22	Phe22	Phe22	Phe22	Phe22
			Ser19				Ser19	Ser19	Ser19	Ser19	Ser19
	Tyr248	Tyr248		Tyr248	Tyr248	TYR248	Tyr248	Tyr248	Tyr248		
	Tyr41		Tyr41	Tyr41	Tyr41	TYR41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
					Unk303						
			Unk304	Unk304			Unk304	Unk304	Unk304		Unk304
					Unk305						
		Val133	Val133	Val133				Val133	Val133	Val133	Val133
	Val137	Val137	Val137	Val137	Val137	VAL137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Phe26	Phe26	Phe26	Phe26	Asp52	VAL37				Ile241	Phe26
	Val37	Tyr129			Phe26	MET15				Phe26	
					Tyr129	ASN168					
					Tyr183	CYS44					
						PHE26					

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	9	61	132	130	119	108	11	115	116	10	133
Compound Name Docked to Protein 3W7F with MG	Hatomarubigin_E	BE_23254	11_HydroxyTetrangomycin	Prejadomycin	X_14881_C	Elmycin_E	Rubiginone_B2	Fujianmycin_A	Fujianmycin_B	Hatomarubigin_F	Homo_UWM6
Run1	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.4	-9.5	-9.5	-9.5
Run2	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.5	-9.6	-9.5	-9.5	-9.5
Run3	-9.6	-9.6	-9.6	-9.6	-9.5	-9.5	-9.5	-9.6	-9.5	-9.5	-9.5
AV	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.5	-9.5	-9.5	-9.5	-9.5
Dock	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.5	-9.5	-9.5
Residues that interacts with the original ligand & Residues that interacts with the ligands	11	11	11	8	14	12	14	10	14	12	12
	Ala134		Ala134		Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134
					Ala157	Ala157	Ala157	Ala157	Ala157		
	Arg45		Arg45		Arg45		Arg45		Arg45	Arg45	
											Asn168
	Asp48	Asp48	Asp48	Asp48						Asp48	Asp48
	Cys44	Cys44	Cys44	Cys44						Cys44	Cys44
	Gln165	Gln165	Gln165	Gln165						Gln165	Gln165
					Gly138	Gly138	Gly138	Gly138	Gly138		
	Gly161				Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161
					His18		His18		His18		
	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	
								Leu145			
					Leu160	Leu160	Leu160	Leu160	Leu160		
	Leu164	Leu164	Leu164		Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
		Met15								Met15	
		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22
					Ser19	Ser19	Ser19		Ser19		
		Tyr248									Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41	Tyr41
					Unk304		Unk304		Unk304		
	Val133	Val133	Val133	Val133		Val133				Val133	Val133
	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Phe26	Ile40	Phe26	Leu107	Phe26	Ala244	Phe26	Ala244	Phe26	Phe26	Leu107
		Leu107		Phe26		Phe26		Ile241			Phe26
		Phe26		Val37				Phe26			
		Val37									

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	131	113	129	118	102	76	106	24	5	74	111
Compound Name Docked to Protein 3W7F with MG	Homoprejadomycin	SS_228Y	Homorabelomycin	PD116779	Capoamycin	Sakyomicin_D	Elmycin_C	Dehydrorabelomycin	Hatomarubigin_A	Sakyomicin_B	Emycin_A
Run1	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.3	-9.4	-9.4
Run2	-9.5	-9.5	-9.5	-9.3	-9.4	-9.4	-9.4	-9.4	-9.3	-9.4	-9.1
Run3	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.3	-9.4	-9.1	-9.4
AV	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.4	-9.3	-9.3	-9.3
Dock	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4
Residues that interacts with the original ligand & Residues that interacts with the ligands	11	10	10	11	17	12	7	9	9	13	11
				Ala134	Ala134	Ala134		Ala134		Ala134	Ala134
				Ala157							Ala157
					Arg45	Arg45	Arg45			Arg45	
	Asn168		Asn168		Asn168		Asn168			Asn168	
	Asp48	Asp48	Asp48		Asp48	Asp48	Asp48	Asp48	Asp48		
	Cys44	Cys44	Cys44		Cys44	Cys44		Cys44	Cys44	Cys44	
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	
				Gly138							Gly138
				Gly161	Gly161						Gly161
		Leu141		Leu141	Leu141	Leu141			Leu141	Leu141	Leu141
				Leu145							Leu145
				Leu160							Leu160
		Leu164		Leu164	Leu164	Leu164		Leu164		Leu164	Leu164
	Met15		Met15							Met15	
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22	Phe22
											Phe233
	Ser19	Ser19			Ser19						
	Tyr248		Tyr248						Tyr248	Tyr248	
	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41		Tyr41	Tyr41	Tyr41	
					Unk303		Unk303				
					Unk304						
					Unk305	Unk305	Unk305				
	Val133	Val133	Val133	Val133	Val133	Val133	Val133	Val133	Val133	Val133	
	Val137	Val137	Val137	Val137	Val137	Val137		Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Leu107	Leu107	Phe26	Ala244	Leu107	Phe26	Arg181	Phe26	Leu107	Ile40	Ala244
	Phe26	Phe26	Val37	Ile241	Phe26		Asn179		Phe26	Phe26	Arg158
	Tyr129			Phe26	Tyr129		Asp114		Tyr129	Val37	Ile241
					Tyr183		Asp176		Val37		Phe26
							Asp52				
							Tyr129				
							Tyr183				

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	73	51	62	55	53	154	50	68	114	4	136
Compound Name Docked to Protein 3W7F with MG	Sakyomicin_A	Rabelomycin	Tetrangomycin	8_O_methyl_7_deoxo_7_hydroxytetrangomycin	8_O_methyltetrangomycin	Retymicin	JBIR_88	8_O_methylrabelomycin	Fridamycin_C	Actinosporin_B	Urdamycin_I
Run1	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-8.5	-9.2
Run2	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.2
Run3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-8.4	-9.2
AV	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-8.7	-9.2
Dock	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.2
Residues that interacts with the original ligand & Residues that interacts with the ligands	18	16	16	14	12	12	11	11	11	18	15
	Ala134	Ala134	Ala134	ALA134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134
				ALA157						Ala157	
	Arg171	Arg171	Arg171								
	Arg265										
	Arg45	Arg45	Arg45	ARG45		Arg45		Arg45	Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168			Asn168	Asn168
	Asp48				Asp48		Asp48	Asp48	Asp48	Asp48	Asp48
	Cys44			Cys44	Cys44		Cys44	Cys44	Cys44		
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138	Gly138	Gly138	Gly138				Gly138	Gly138	Gly138	
	Gly161	Gly161	Gly161	Gly161				Gly161	Gly161	Gly161	
		His18	His18								
	Leu141	Leu141	Leu141	LEU141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
										Leu145	
				LEU160						Leu160	
		Leu164	Leu164	LEU164		Leu164		Leu164	Leu164	Leu164	
											Met15
	Phe22	Phe22	Phe22	PHE22	Phe22	Phe22	Phe22			Phe22	Phe22
	Ser19	Ser19	Ser19	SER19	Phe26	Ser19				Ser19	Ser19
	Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	Tyr248				Tyr248
	Tyr41	Tyr41	Tyr41	TYR41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Unk304	Unk304	Unk304			Unk304				Unk304	Unk304
							Unk305			Unk305	Unk305
	Val133			VAL133	Val133	Val133	Val133				Val133
	Val137	Val137	Val137	VAL137	Val137		Val137	Val137	Val137	Val137	Val137
							no 2D				
Residues that NOT interacts with the original ligand	Leu107			ALA244	Val37	Phe26	Phe26			Phe26	Phe26
	Phe26			ILE241			Tyr129				
				PHE26			Val37				

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	109	157	82	107	90	117	126	121	80	156	14
Compound Name Docked to Protein 3W7F with MG	X_14881_B	Azicemicin_B	SM_196B	Elmycin_D	6_Deoxy_8_O_methylrabelomycin	MM_47755	PD116740	X_14881_A	Seitomycin	Azicemicin_A	Langkocycline_A1
Run1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-8.9	-8.9	-8.8
Run2	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.0	-8.9	-8.7
Run3	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-8.9	-8.9	-8.9	-8.9
AV	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.0	-8.9	-8.9	-8.8
Dock	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9	-8.9	-8.9
Residues that interacts with the original ligand & Residues that interacts with the ligands	13	13	11	11	10	10	10	9	13	14	17
	Ala134	Ala134		Ala134					Ala134		Ala134
	Arg45	Arg45	Arg45		ARG45	Arg45	Arg45		Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
		Asp48	Asp48		ASP48	Asp48	Asp48			Asp48	Asp48
		Cys44	Cys44		Cys44	Cys44		Cys44		Cys44	Cys44
		Gln165					Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138			Gly138					Gly138		
	Gly161			Gly161	Gly161	Gly161			Gly161		
	Leu141		Leu141	Leu141	LEU141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
	Leu160			Leu160							
	Leu164			Leu164	LEU164	Leu164	Leu164	Leu164	Leu164		Leu164
		Met15								Met15	Met15
	Phe22	Phe22	Phe22	Phe22	PHE22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
	Ser19			Ser19					Ser19		
	Tyr248	Tyr248	Tyr248				Tyr248	Tyr248		Tyr248	Tyr248
		Tyr41	Tyr41	Tyr41	TYR41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
		Unk303								Unk303	Unk303
			Unk304						Unk304	Unk304	Unk304
			Unk305				Unk305			Unk305	Unk305
	Val133	Val133		Val133							Val133
	Val137	Val137	Val137	Val137	VAL137	Val137		Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Phe26	Asp172	Phe26	Phe26	PHE26	Phe26	Phe26	Phe26	Phe26	Asp176	Ile40
		Leu107	Val37					Val37	His18	Phe26	Phe26
		Phe26								Tyr129	Val37
		Tyr129								Tyr183	
		Tyr183									

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	12	100	101	20	127	15	16	17	18	43	44
Compound Name Docked to Protein 3W7F with MG	Warkmycin	Benzanthrin_A	Benzanthrin_B	UWM6	TAN_1085	Langkocycline_A2 (Not Docked)	Langkocycline_A3 (Not Docked)	Langkocycline_B1 (Not Docked)	Langkocycline_B2 (Not Docked)	JBIR_92 (Not Docked)	JBIR_93 (Not Docked)
Run1	-8.8	-8.2	-8.7	-8.7	-8.6	0.0	0.0	0.0	0.0	0.0	0.0
Run2	-8.2	-8.3	-8.7	-8.7	-8.6	0.0	0.0	0.0	0.0	0.0	0.0
Run3	-8.8	-8.8	-8.7	-8.5	-8.7	0.0	0.0	0.0	0.0	0.0	0.0
AV	-8.6	-8.4	-8.7	-8.6	-8.6	0.0	0.0	0.0	0.0	0.0	0.0
Dock	-8.8	-8.8	-8.7	-8.7	-8.7	0	0	0	0	0	0
Residues that interacts with the original ligand & Residues that interacts with the ligands	16	17	12	13	11	0	0	0	0	0	0
		Ala134									
	Arg171	Arg171		Arg171	Arg171						
	Arg265		Arg265								
	Arg45	Arg45	Arg45	Arg45	Arg45						
	Asn168	Asn168	Asn168	Asn168	Asn168						
		Asp172		Asp172							
	Asp48	Asp48	Asp48	Asp48							
	Cys44	Cys44		Cys44							
	Gln165	Gln165	Gln165	Gln165	Gln165						
	His18				His18						
	Leu141										
	Lys20		Lys20		Lys20						
		Phe22	Phe22		Phe22						
		Ser19	Ser19								
		Tyr248			Tyr248						
	Tyr41	Tyr41	Tyr41	Tyr41							
	Unk303	Unk303		Unk303	Unk303						
	Unk304	Unk304	Unk304	Unk304	Unk304						
	Unk305	Unk305	Unk305	Unk305	Unk305						
	Val133	Val133	Val133	Val133							
	Val137	Val137		Val137							
Residues that NOT interacts with the original ligand	Asp49	Asp176	Asn179	Glu175	Arg181						
	Asn179	Glu175	Asp176	Leu107	Asn179						
	Asp176	His18	Asp49	Tyr129	Asp176						
	Asp52	Leu107	Asp52		Tyr183						
	Glu175	Tyr129	Glu175								
	Tyr129	Tyr183	Tyr129								
	Tyr183		Tyr183								
	Val53		Val53								

APPENDIX II

Docking score and interacted residue of protein (3W7F with MG)
with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

Residues that NOT interacts with the original ligand		Residues that interacts with the original ligand & Residues that interacts with the ligands		Dock	AV	Run3	Run2	Run1	Compound Name Docked to Protein 3W7F with MG	#
			0	0	0.0	0.0	0.0	0.0	Urdamycin_D (Not Docked)	66
			0	0	0.0	0.0	0.0	0.0	Urdamycin_H (Not Docked)	67
			0	0	0.0	0.0	0.0	0.0	8_O_methylurdamycin_A (Not Docked)	79
			0	0	0.0	0.0	0.0	0.0	Urdamycin_K (Not Docked)	138
			0	0	0.0	0.0	0.0	0.0	Saquayamycin_Z (Not Docked)	153

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol)

#		0	151	56	58	8	146	148	2	27	39
Compound Name Docked to Protein 3W7F without MG	3W7F with its ligand From PDB Part A	Ligand of Protein	Saquayamycin_K4	Moromycin_A	Saquayamycin_B	Hatomarubigin_D	Saquayamycin_B	Saquayamycin_D	Marangucycline_B	Saprolmycin_C	Grincamycin_F
Run1		-8.2	-14.9	-14.4	-14.2	-13.9	-13.6	-13.5	-13.4	-13.3	-13.2
Run2		-8.3	-13.1	-14.4	-14.1	-13.9	-13.6	-13.5	-13.4	-13.4	-13.2
Run3		-7.9	-15.0	-14.4	-14.4	-13.9	-13.6	-13.6	-13.4	-13.4	-13.3
AV.		-8.1	-14.3	-14.4	-14.2	-13.9	-13.6	-13.5	-13.4	-13.4	-13.2
Dock		-8.3	-15.0	-14.4	-14.4	-13.9	-13.6	-13.6	-13.4	-13.4	-13.3
Residues that interacts with the original ligand & Residues that interacts with the ligands	29	21	24	18	21	15	17	20	20	15	25
	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134
	Ala157		Ala157	Ala157	Ala157		Ala157	Ala157	Ala157		Ala157
	Arg171	Arg171	Arg171		Arg171	Arg171	Arg171		Arg171		Arg171
	Arg265	Arg265	Arg265				Arg45				Arg265
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Asn168	Arg45	Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168	Asn168
	Asp172		Asp172		Asp172	Asp172	Asp172	Asp172	Asp172		Asp172
	Asp48		Asp48		Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48
	Cys44					Cys44				Cys44	Cys44
	Gln165			Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	
	Gly138		Gly138	Gly138	Gly138		Gly138	Gly138	Gly138	Gly138	Gly138
	Gly161		Gly161	Gly161	Gly161	Gly161	Gly161		Gly161	Gly161	Gly161
	His18	His18	His18								His18
		Ile241	Ile241	Ile241	Ile241			Ile241	Ile241		Ile241
	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
	Leu145	Leu145	Leu145	Leu145	Leu145		Leu145	Leu145	Leu145		Leu145
	Leu160	Leu160	Leu160	Leu160	Leu160		Leu160	Leu160	Leu160		Leu160
	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
	Lys20	Lys20	Lys20								Lys20
	Met15										
	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22	Phe22	Phe22
	Phe233	Phe233		Phe233				Phe233			
		Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26
	Ser19	Ser19	Ser19								Ser19
	Ser21	Ser21									Ser21
	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	Tyr248		Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41
	Val133		Val133		Val133	Val133		Val133	Val133	Val133	
	Val137	Val137	Val137	Val137	Val137	Val137		Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Unk301		Arg181	Arg181	Arg181	Asn179	Arg181	Arg181	Asp176	Asn179	Arg181
	Unk302	Unk302	Asn179	Asn179	Asn179	Asp114	Asn179	Asn179	Tyr129	Asp114	Asn179
	HOH401		Asp176	Asp176	Asp114	Arg181	Asp114	Asp114		Asp176	Asp114
	HOH402		Asp52	Asp52	Asp176	Asp176	Asp176	Asp176		Asp52	Asp176
	HOH403		Glu175	Tyr129	Asp52	Asp52	Asp52	Asp52		Tyr129	Asp52
	HOH404			Tyr183	Tyr129	Tyr129	Gln115	Tyr129		Tyr183	Gln115
	HOH405				Tyr183	Tyr183	Ile51	Tyr183			Glu175
	HOH406						Tyr129				Tyr129
	HOH407						Tyr183				Tyr183
	HOH408										

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	29	28	152	150	26	46	145	42	143	134	47	144
Compound Name Docked to Protein 3W7F without MG	Saprolmycin_E	Saprolmycin_D	Saquayamycin_K7	Saquayamycin_K2	Saprolmycin_B	Urdamycin_B	Saquayamycin_A	JBIR_91	PI_085	PI_1894B (Vineomycin A) (OS-4742A1)	N05WA963A	PI_087
Run1	-13.1	-13.2	-13.0	-13.0	-13.0	-12.8	-12.7	-12.3	-12.7	-12.6	-12.5	-12.3
Run2	-13.3	-13.2	-13.0	-13.0	-13.0	-12.8	-12.8	-12.7	-12.7	-12.6	-12.6	-12.3
Run3	-13.1	-13.2	-13.0	-13.0	-13.0	-12.8	-12.4	-12.7	-12.3	-12.6	-12.6	-12.5
AV.	-13.2	-13.2	-13.0	-13.0	-13.0	-12.8	-12.6	-12.6	-12.6	-12.6	-12.6	-12.4
Dock	-13.3	-13.2	-13.0	-13.0	-13.0	-12.8	-12.8	-12.7	-12.7	-12.6	-12.6	-12.5
Residues that interacts with the original ligand & Residues that interacts with the ligands	19	18	22	16	11	17	21	20	18	24	14	19
	Ala134	Ala134	Ala134	Ala134		Ala134		Ala134		Ala134		Ala134
	Ala157	Ala157				Ala157	Ala157	Ala157	Ala157	Ala157		Ala157
	Arg171		Arg171	Arg171			Arg171	Arg171	Arg171	Arg171		Arg171
			Arg265	Arg265					Arg265	Arg265		Arg265
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168	Asn168		Asn168
			Asp172									Asp172
	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp172	Asp48	Asp48	Asp48
					Cys44	Cys44					Cys44	
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Asp48	Gln165	Gln165	
	Gly138	Gly138	Gly138	Gly138		Gly138	Gly138	Gly138	Gly138	Gly138	Gly138	Gly138
	Gly161	Gly161	Gly161			Gly161	Gly161	Gly161	Gly161	Gly161	Gly161	Gly161
			His18	His18			His18			His18		
	Ile241	Ile241				Ile241	Ile241	Ile241		Ile241	Ile241	Ile241
	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
	Leu145	Leu145					Leu145	Leu145		Leu145	Leu145	Leu145
	Leu160	Leu160				Leu160	Leu160	Leu160	Leu160	Leu160	Leu160	Leu160
	Leu164	Leu164	Leu164			Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
			Lys20	Lys20						Lys20		
					Met15							
	Phe22	Phe22	Phe22			Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
	Phe233	Phe233				Phe233		Phe233		Phe233		
	Phe26	Phe26	Phe26		Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26
			Ser19	Ser19			Ser19	Ser19	Ser19			
			Ser21	Ser21			Ser21					
	Tyr248	Tyr248	Tyr248	Tyr248			Tyr248	Tyr248	Tyr248	Tyr248		Tyr248
			Tyr41	Tyr41	Tyr41		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	
			Val133	Val133	Val133	Val133				Val133		
	Val137	Val137	Val137	Val137	Val137	Val137	Val137		Val137	Val137		Val137
Residues that NOT interacts with the original ligand	Arg181	Arg181	Arg181	Arg181	Asn179	Arg181	Arg181	Arg181	Arg181	Arg181	Ala244	Arg181
	Asn179	Asn179	Asn179	Asn179	Asp114	Asn179	Asn179	Asn179	Asn179	Asn179	Arg181	Asp114
	Asp114	Asp114	Asp176	Asp176	Asp176	Asp114	Asp52	Asp176	Asp176	Asp176	Asn179	Asp176
	Asp176	Asp176	Asp52	Asp52	Asp52	Asp176	Tyr183	Asp52	Asp49	Asp52	Asp114	Asp52
	Asp52	Asp52	Glu175	Glu175	Ile40	Asp52		Glu175	Asp52	Tyr129	Asp176	Gln115
	Gln115	Gln115	Tyr129	Tyr129	Tyr129	Tyr129		Tyr129	Gln115	Tyr183	Asp52	Ile51
	Tyr129	Tyr129	Tyr183	Tyr183	Tyr183	Tyr183		Tyr183	Glu175	Val53	Glu175	Tyr183
	Tyr183	Tyr183			Val37				Ile51		Tyr129	
											Tyr183	

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	49	65	37	155	124	57	38	59	35	147	25	142
Compound Name Docked to Protein 3W7F without MG	N05WA963D	PI_080 (=PI-6621)	Landomycin_Z	Vineomycin_A1	Landomycin_C	Moromycin_B	Grincamycin	Sch_47554	Landomycin_A	Saquayamycin_C	Saprolmycin_A	PI_083
Run1	-12.3	-12.4	-12.3	-12.3	-12.2	-12.2	-12.2	-12.1	-12.1	-12.1	-12.0	-12.0
Run2	-12.4	-11.8	-11.9	-11.0	-12.2	-12.2	-12.2	-12.1	-12.0	-11.5	-12.0	-12.0
Run3	-12.3	-11.1	-12.3	-12.3	-12.2	-12.2	-12.1	-12.1	-12.0	-11.5	-12.0	-12.0
AV.	-12.3	-11.8	-12.2	-11.9	-12.2	-12.2	-12.2	-12.1	-12.0	-11.7	-12.0	-12.0
Dock	-12.4	-12.4	-12.3	-12.3	-12.2	-12.2	-12.2	-12.1	-12.1	-12.1	-12.0	-12.0
Residues that interacts with the original ligand & Residues that interacts with the ligands	13	21	18	17	19	10	24	14	18	16	16	14
		Ala134		Ala134			Ala134			Ala157		
	Ala157	Ala157		Ala157			Ala157				Ala157	
		Arg171	Arg171		Arg171		Arg171	Arg171	Arg171			Arg171
		Arg265	Arg265		Arg265		Arg265		Arg265			
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45		Arg45	Arg45	Arg45	Arg45
		Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
		Asp172	Asp172		Asp172		Asp172	Asp172				Asp172
	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48
			Cys44		Cys44				Cys44			Cys44
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165			Gln165	Gln165
	Gly138	Gly138		Gly138			Gly138	Gly138		Gly138	Gly138	
		Gly161		Gly161			Gly161	Gly161	Gln165	Gly161	Gly161	
			His18		His18		His18		His18			
	Ile241	Ile241		Ile241			Ile241			Ile241		
	Leu141	Leu141	Leu141		Leu141		Leu141	Leu141		Leu141	Leu141	Leu141
	Leu145	Leu145					Leu145			Leu145		
	Leu160	Leu160		Leu160			Leu160	Leu160		Leu160	Leu160	
	Leu164	Leu164	Leu164	Leu164	Leu164		Leu164	Leu164		Leu164	Leu164	Leu164
			Lys20		Lys20				Lys20			
						Met15			Met15			Met15
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22	Phe22
				Phe233			Phe233					
	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26
				Ser19	Ser19				Ser19		Ser19	
			Ser21						Ser21			
		Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248		Tyr248	Tyr248		
	Tyr41		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
		Val133			Val133		Val133	Val133	Val133		Val133	
		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val133	Val137	Val137
Residues that NOT interacts with the original ligand	Ala244	Arg181	Arg181	Arg181	Asn179	Arg181	Arg181	Arg181	Arg181	Arg181	Arg181	Arg181
	Arg181	Asn179	Asn179	Asn179	Asp114	Asp114	Asn179	Asn179	Asn179	Asn179	Asn179	Asn179
	Asn179	Asp114	Asp114	Asp114	Asp52	Asp52	Asp114	Asp176	Asp114	Asp114	Asp114	Asp176
	Asp114	Asp176	Asp176	Asp176	Glu175	Tyr129	Asp176	Asp52	Asp176	Asp176	Asp176	Asp52
	Asp176	Asp49	Asp52	Asp52	Ile40	Tyr183	Asp52	Ile40	Asp52	Asp52	Asp52	Gln115
	Asp52	Asp52	Glu175	Gln115	Tyr129		Tyr129	Tyr129	Glu175	Gln115	Tyr129	Glu175
	Tyr129	Tyr129	Ile40	Glu175	Tyr183		Tyr183	Tyr183	Leu107	Ile51	Tyr183	Ile51
	Tyr183	Tyr183	Tyr129	Ile51	Val37		Val53	Val37	Tyr129	Tyr129		Tyr129
		Val53	Tyr183	Leu145					Tyr183	Tyr183		Tyr183
			Val37	Tyr183					Val111			Val37
									Val53			

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	69	141	84	92	94	1	123	122	13	149	72	98
Compound Name Docked to Protein 3W7F without MG	Urdamycin_C	Kerriamycin_C	A_7884	BA_12100B	BA_12100D	Marangucycline_A	Landomycin_B	Landomycin_A_122	Waldiomycin	Saquayamycin_K1	Urdamycin_G	BA_12100Z3
Run1	-11.9	-11.9	-11.8	-11.8	-11.7	-11.5	-11.5	-11.5	-11.3	-11.3	-10.1	-11.2
Run2	-12.0	-11.9	-11.8	-11.8	-11.6	-11.5	-11.4	-11.4	-11.1	-10.5	-10.1	-11.2
Run3	-12.0	-11.9	-11.9	-11.8	-11.6	-11.5	-11.5	-11.4	-11.3	-10.6	-11.3	-11.2
AV.	-12.0	-11.9	-11.8	-11.8	-11.6	-11.5	-11.5	-11.4	-11.2	-10.8	-10.5	-11.2
Dock	-12.0	-11.9	-11.9	-11.8	-11.7	-11.5	-11.5	-11.5	-11.3	-11.3	-11.3	-11.2
Residues that interacts with the original ligand & Residues that interacts with the ligands	13	21	19	19	19	12	25	19	17	17	14	17
	Ala134	Ala134	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134		
		Ala157	Ala157		Ala157		Ala157					
		Arg171		Arg171			Arg171	Arg171	Arg171	Arg171	Arg171	Arg171
		Arg265		Arg265			Arg265	Arg265	Arg265	Arg265	Arg265	Arg265
	Arg45	Arg45	Arg45	Arg45	Arg45		Arg45	Arg45	Arg45	Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
		Asp172		Asp172		Asp172	Asp172	Asp172	Asp172	Asp172		Asp172
	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48
						Cys44		Cys44				
	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
	Gly138	Gly138	Gly138		Gly138		Gly138		Gly138			
	Gly161	Gly161	Gly161	Gly161	Gly161		Gly161		Gly161			
		His18		His18			His18	His18		His18		His18
			Ile241		Ile241		Ile241					
		Leu141	Leu141		Leu141	Leu141	Leu141		Leu141			Leu141
			Leu145		Leu145		Leu145					
	Leu160		Leu160		Leu160		Leu160					
	Leu164	Leu164	Leu164	Leu164	Leu164		Leu164	Leu164	Leu164	Leu164		
				Lys20			Lys20	Lys20		Lys20	Lys20	
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
			Phe233		Phe233		Phe233					
	Phe26	Phe26	Phe26		Phe26	Phe26	Phe26		Phe26	Phe26		Phe26
		Ser19		Ser19				Ser19	Ser19	Ser19	Ser19	Ser19
				Ser21				Ser21		Ser21	Ser21	Ser21
	Tyr248	Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	Tyr248
		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41
		Val133	Val133	Val133	Val133	Val133	Val133	Val133			Val133	Val133
	Val137	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Arg181	Arg181	Asp114	Arg181	Arg181	Asp176	Asp176	Arg181	Arg181	Asn179	Arg181	Asp114
	Asn179	Asn179	Asp176	Asp114	Asn179	Asp52	Asp52	Asn179	Asp114	Asp176	Asn179	Asp176
	Asp176	Asp114	Asp52	Asp49	Asp114	Ile40	Tyr129	Asp114	Asp176	Asp52	Asp114	Asp52
	Asp52	Asp176	Tyr129	Asp52	Asp176	Tyr129	Tyr183	Asp176	Asp52	Glu175	Asp176	Glu175
	Glu175	Asp52	Tyr183	Glu175	Asp52	Tyr183	Val53	Asp49	Gln115	Tyr129	Asp52	Tyr129
	Ile169	Glu175		Tyr129	Leu107	Val37		Asp52	Ile51	Tyr183	Thr110	Tyr183
	Tyr129	Tyr129		Tyr183	Tyr129			Glu175	Tyr183		Tyr129	Val111
	Tyr183	Tyr183			Tyr183			Leu107	Val111		Tyr183	
	Val53							Tyr129			Val111	
								Tyr183				
								Val111				
								Val53				

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	93	97	78	71	83	36	95	30	96	91	139	21
Compound Name Docked to Protein 3W7F without MG	BA_12100C	BA_12100Z2	BE_7585A	Urdamycin_F	Saquayamycin_A1	Landomycin_E	BA_12100E	Saquayamycin_A	BA_12100Z1	Aggreticin (OM-4842)	Kerriamycin_A	Jadomycin_B
Run1	-11.1	-10.8	-11.2	-11.1	-11.1	-11.0	-11.1	-10.6	-10.9	-10.9	-10.7	-9.7
Run2	-11.2	-10.8	-11.1	-11.1	-11.1	-11.1	-11.1	-11.0	-10.9	-10.9	-10.6	-9.7
Run3	-10.8	-11.2	-10.0	-11.1	-11.1	-11.0	-10.7	-10.6	-10.9	-10.9	-10.6	-10.7
AV.	-11.0	-10.9	-10.8	-11.1	-11.1	-11.0	-11.0	-10.7	-10.9	-10.9	-10.6	-10.0
Dock	-11.2	-11.2	-11.2	-11.1	-11.1	-11.1	-11.1	-11.0	-10.9	-10.9	-10.7	-10.7
Residues that interacts with the original ligand & Residues that interacts with the ligands	14	10	20	19	10	21	15	14	18	13	12	15
		Ala134	Ala134	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134		Ala134
				Ala157								
	Arg171		Arg171	Arg171		Arg171	Arg171	Arg171	Arg171		Arg171	
	Arg265		Arg265	Arg265		Arg265	Arg265		Arg265		Arg265	
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
			Asp172	Asp172					Asp172			
	Asp48	Asp48	Asp48		Asp48	Asp48	Asp48	Asp48		Asp48	Asp48	Asp48
		Cys44	Cys44			Cys44		Cys44				Cys44
	Gln165		Gln165		Gln165	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165
				Gly138								
		Gln165	Gly161	Gly161		Gly161			Gly161	Gly161		Gly161
	His18		His18			His18	His18		His18		His18	
				Leu141	Leu141	Leu141		Leu141	Leu141	Leu141		
				Leu160								
			Leu164	Leu164		Leu164			Leu164	Leu164		Leu164
	Lys20		Lys20			Lys20	Lys20		Lys20			
								Met15				Met15
	Phe22	Phe22		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
			Phe22	Phe26		Phe26			Phe26			Phe26
	Ser19		Ser19	Ser19		Ser19	Ser19		Ser19	Ser19	Ser19	
	Ser21		Ser21	Ser21		Ser21	Ser21		Ser21		Ser21	
	Tyr248		Tyr248	Tyr248		Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41
	Val133	Val133	Val133		Val133	Val133	Val133	Val133			Val133	Val133
		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137		Val137
Residues that NOT interacts with the original ligand	Asn179	Arg181	Asn179	Ala244	Arg181	Ala244	Asn179	Arg181	Arg181	Arg181	Arg181	Leu107
	Asp114	Asn179	Asp176	Asn179	Asn179	Asp176	Asp114	Asn179	Asn179	Asn179	Asn179	Tyr129
	Asp49	Asp114	Asp49	Asp176	Asp114	Tyr129	Asp172	Asp114	Asp114	Asp114	Asp114	Tyr183
	Asp52	Asp176	Glu175	Asp52	Asp176	Tyr183	Asp52	Asp176	Asp52	Asp176	Asp176	Val111
	Glu175	Asp52	Leu107	Glu175	Asp52		Glu175	Asp52	Glu175	Asp52	Asp49	
	Tyr129	Gln115	Tyr183	Tyr183	Tyr129		Tyr129	Gln115	Tyr183	Glu175	Asp52	
	Tyr183	Leu107	Val111	Val53	Tyr183		Tyr183	Ile51	Val53	Tyr129	Glu175	
	Val111	Tyr129	Val53				Val111	Tyr129		Tyr183	Tyr129	
	Val53	Tyr183						Tyr183			Tyr183	
											Val53	

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	23	128	77	75	73	125	40	140	87	41	60	19
Compound Name Docked to Protein 3W7F without MG	L_digitoxosyl_dehydrorabelomycin	Landomycin_F	Sakyomicin_E	Sakyomicin_C	Sakyomicin_A	Landomycin_D	JBIR_90	Kerriamycin_B	C104_Aglycon	JBIR_116	Sch_47555	Fradimycin_C
Run1	-10.5	-10.4	-10.0	-10.3	-10.3	-10.2	-10.1	-10.2	-9.9	-10.2	-10.0	-10.1
Run2	-10.5	-10.4	-10.4	-10.2	-10.1	-10.2	-10.2	-9.9	-10.2	-9.6	-10.1	-10.0
Run3	-10.5	-10.4	-10.4	-10.3	-10.1	-10.2	-10.2	-10.2	-10.2	-8.5	-10.0	-10.0
AV.	-10.5	-10.4	-10.3	-10.3	-10.2	-10.2	-10.2	-10.1	-10.1	-9.4	-10.0	-10.0
Dock	-10.5	-10.4	-10.4	-10.3	-10.3	-10.2	-10.2	-10.2	-10.2	-10.2	-10.1	-10.1
Residues that interacts with the original ligand & Residues that interacts with the ligands	12	18	16	17	15	18	10	19	12	19	14	12
		Ala134	Ala134	Ala134				Ala134	Ala134	Ala134		
										Ala157		
	Arg171	Arg171	Arg171	Arg171	Arg171	Arg171		Arg171		Arg171	Arg171	Arg171
				Arg265	Arg265	Arg265		Arg265				
		Arg45	Arg45	Arg45	Arg45	Arg45		Arg45		Arg45		Arg45
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
								Asp172		Asp172	Asp172	
	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48	Asp48		Asp48	Asp48	Asp48	Asp48
	Cys44	Cys44	Cys44			Cys44	Cys44		Cys44	Cys44	Cys44	Cys44
	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165
		Gly138						Gly138		Gly138		
		Gly161	Gly161	Gly161				Gly161		Gly161		
		His18		His18	His18	His18		His18				His18
		Leu141	Leu141			Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	
		Leu164	Leu164	Leu164	Leu164	Leu164		Leu164		Leu164	Leu164	
				Lys20	Lys20	Lys20		Lys20				Lys20
	Met15		Met15						Met15		Met15	
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	
	Phe26		Phe26		Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	
		Ser19			Ser19	Ser19		Ser19				
				Ser21	Ser21	Ser21		Ser21				
	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248		Tyr248		Tyr248		Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Val133	Val133	Val133	Val133			Val133		Val133	Val133	Val133	Val133
	Val137	Val137	Val137	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Asp176	Leu107	Ile40	Tyr129		Ile40	Asp176	Ala244	Asp176	Arg181	Arg181	Arg181
	Ile169	Tyr129	Leu107			Val37	Asp52	Arg181	Ile40	Asn179	Asn179	Asn179
	Tyr129	Val111	Val37				Ile169	Asn179	Tyr129	Asp176	Asp176	Asp114
	Tyr183						Tyr129	Asp52	Tyr183	Glu175	Asp52	Asp176
							Tyr183	Glu175	Val37	Tyr129	Ile40	Asp49
							Val37	Tyr183		Tyr183	Leu107	Asp52
								Val53			Tyr129	Leu107
											Tyr183	Tyr129
											Val37	Tyr183
												Val53

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	34	85	3	45	100	63	103	24	102	101	154	86
Compound Name Docked to Protein 3W7F without MG	Aquayamycin	Aquamycin	Actinosporin_A	Urdamycin_A	Benzanthrin_A	Tetrangulol	De_O_acylcapoamycin	Dehydrorabelomycin	Capoamycin	Benzanthrin_B	Retymicin	SM_196 A
Run1	-9.8	-10.1	-10.0	-10.0	-10.0	-9.6	-9.9	-9.9	-9.8	-9.8	-9.8	-9.8
Run2	-10.1	-9.0	-10.0	-10.0	-9.8	-10.0	-9.9	-9.9	-9.9	-9.8	-9.8	-9.8
Run3	-10.1	-10.1	-10.0	-10.0	-10.0	-10.0	-9.9	-9.9	-9.4	-9.8	-9.8	-9.8
AV.	-10.0	-9.7	-10.0	-10.0	-9.9	-9.9	-9.9	-9.9	-9.7	-9.8	-9.8	-9.8
Dock	-10.1	-10.1	-10.0	-10.0	-10.0	-10.0	-9.9	-9.9	-9.9	-9.8	-9.8	-9.8
Residues that interacts with the original ligand & Residues that interacts with the ligands	20	18	18	16	19	10	11	10	21	17	16	15
	Ala134	Ala134	Ala134	Ala134	Ala134				Ala134	Ala134	Ala134	Ala134
	Ala157	Ala157							Ala157			Ala157
	Arg171		Arg171	Arg171	Arg171				Arg171	Arg171	Arg171	
			Arg265	Arg265	Arg265				Arg265	Arg265	Arg265	
	Arg45	Arg45	Arg45	Arg45	Arg45				Arg45	Arg45	Arg45	
	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168	Asn168
			Asp172		Asp172				Asp172			
	Asp48	Asp48	Asp48	Asp48	Asp48		Asp48		Asp48	Asp48		
		Cys44	Cys44			Cys44	Cys44	Cys44	Cys44	Cys44		
	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	Gln165	
	Gly138	Gly138							Gly138			Gly138
	Gly161	Gly161		Gly161	Gly161				Gly161		Gly161	Gly161
					His18					His18	His18	
	Ile241	Ile241										Ile241
	Leu141	Leu141	Leu141	Leu141		Leu141		Leu141	Leu141			Leu141
	Leu145	Leu145										Leu145
	Leu160	Leu160							Leu160			Leu160
	Leu164	Leu164		Leu164	Leu164	Leu164		Leu164	Leu164	Leu164	Leu164	Leu164
			Lys20		Lys20					Lys20		
							Met15					
	Phe22		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
	Phe233	Phe233										Phe233
	Phe26	Phe26	Phe26			Phe26	Phe26	Phe26	Phe26		Phe26	Phe26
	Ser19		Ser19	Ser19	Ser19					Ser19	Ser19	
			Ser21		Ser21					Ser21	Ser21	
	Tyr248			Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248	Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	
		Val133	Val133	Val133	Val133		Val133		Val133			
		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val133	Val137	Val137
Residues that NOT interacts with the original ligand	Ala244	Leu107	Asp176	Arg181	Asp176	Ile40	Asp114	Val37	Ala244	Asp52		Thr142
			Leu107	Asn179	Asp52	Val37	Asp52			Leu107		
			Tyr129	Asp114	Glu175		Thr110			Tyr129		
			Tyr183	Asp176	Tyr129		Tyr129					
				Asp52	Tyr183		Tyr183					
				Glu175			Val111					
				Tyr129								
				Tyr183								

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	70	112	64	99	6	31	33	135	88	89	54	7
Compound Name Docked to Protein 3W7F without MG	Urdamycin_E	SF_2315_A	Ochromocinone	BA_12100MY_1	Hatomarubigin_B	Gaudimycin_A	Gaudimycin_C	Yoronomycin	C104	3_Deoxyrabelomycin	8_O_methyltetrangulol	Hatomarubigin_C
Run1	-9.8	-9.8	-9.8	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.6	-9.6
Run2	-9.8	-9.8	-9.8	-9.7	-9.7	-9.7	-9.7	-9.7	-9.6	-9.7	-9.7	-9.6
Run3	-9.8	-9.8	-9.8	-9.7	-9.7	-9.7	-9.7	-9.7	-9.6	-9.5	-9.6	-9.6
AV.	-9.8	-9.8	-9.8	-9.7	-9.7	-9.7	-9.7	-9.7	-9.6	-9.6	-9.6	-9.6
Dock	-9.8	-9.8	-9.8	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.6
Residues that interacts with the original ligand & Residues that interacts with the ligands	13	12	11	17	15	15	14	13	14	11	10	16
				Ala134	Ala134	Ala134	Ala134	Ala134	Ala134			Ala134
												Ala157
	Arg171			Arg171		Arg171	Arg171					
	Arg265			Arg265								
	Arg45	Arg45		Arg45	Arg45	Arg45	Arg45	Arg45	Arg45			Arg45
	Asn168	Asn168	Asn168	Asn168		Asn168	Asn168	Asn168		Asn168	Asn168	
	Asp172											
	Asp48								Asp48			
		Cys44	Cys44						Cys44	Cys44	Cys44	
	Gln165	Gln165	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165	Gln165
					Gly138	Gly138	Gly138		Gly138			Gly138
				Gly161	Gly161	Gly161	Gly161		Gly161			Gly161
	His18			His18	His18	His18	His18					His18
		Leu141	Leu141	Leu141	Leu141			Leu141	Leu141	Leu141	Leu141	Leu141
					Leu160							Leu160
	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164	Leu164		Leu164	Leu164	Leu164
	Lys20			Lys20								
		Met15	Met15					Met15		Met15		
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
		Phe26	Phe26	Phe26	Phe26	Phe26		Phe26	Phe26	Phe26	Phe26	Phe26
				Ser19	Ser19	Ser19	Ser19	Ser19	Ser19			Ser19
				Ser21								
	Tyr248	Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	Tyr248		Tyr248	Tyr248	
		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Val133				Val133	Val133			Val133			Val133
		Val137	Val137		Val137	Val137	Val137	Val133	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Asp176	Ile40	Val37	Ala244					Asp52	Val37	Val37	
	Asp49	Val37							Leu107			
	Asp52								Tyr129			
	Tyr129											
	Tyr183											
	Val53											

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	32	115	61	104	81	52	11	108	119	9	110	133
Compound Name Docked to Protein 3W7F without MG	Gaudimycin_B	Fujianmycin_A	BE_23254	Elmycin_A	Tetrangulol methyl ether	Mayamycin	Rubiginone_B2	Elmycin_E	X_14881_C	Hatomarubigin_E	X_14881_D	Homo_UWM6
Run1	-9.6	-9.6	-9.5	-9.5	-9.6	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5
Run2	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5
Run3	-9.6	-9.6	-9.6	-9.6	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5
AV.	-9.6	-9.6	-9.6	-9.6	-9.6	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5
Dock	-9.6	-9.6	-9.6	-9.6	-9.6	-9.6	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5
Residues that interacts with the original ligand & Residues that interacts with the ligands	15	12	12	10	11	11	14	14	14	13	13	13
	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134	Ala134
		Ala157					Ala157	Ala157	Ala157		Ala157	
	Arg171					Arg171						
						Arg265						
	Arg45				Arg45	Arg45	Arg45		Arg45	Arg45		
	Asn168		Asn168	Asn168		Asn168						Asn168
						Asp172						
			Asp48	Asp48						Asp48		Asp48
			Cys44							Cys44		Cys44
	Gln165		Gln165	Gln165		Gln165				Gln165		Gln165
	Gly138	Gly138			Gly138		Gly138	Gly138	Gly138	Gly138	Gly138	
	Gly161	Gly161			Gly161		Gly161	Gly161	Gly161	Gly161	Gly161	
	His18					His18	His18		His18			
		Ile241						Ile241				
		Leu141	Leu141		Leu141		Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
		Leu145										
		Leu160			Leu160		Leu160	Leu160	Leu160		Leu160	
	Leu164	Leu164		Leu164			Leu164	Leu164	Leu164	Leu164	Leu164	Leu164
			Met15									
	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22		Phe22	Phe22
		Phe26	Phe26	Phe26	Phe26		Phe26	Phe26	Phe26	Phe26	Phe26	Phe26
	Ser19				Ser19		Ser19	Ser19	Ser19		Ser19	
	Tyr248		Tyr248	Tyr248								Tyr248
	Tyr41		Tyr41		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Val133		Val133	Val133		Val133		Val133		Val133	Val133	Val133
	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand		Ala244	Ile40	Tyr129		Asp114		Ala244				Leu107
			Leu107			Asp176						
			Val37			Asp52						
						Glu175						
						Tyr129						
						Tyr183						

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	137	10	120	132	130	111	105	116	118	131	113	48
Compound Name Docked to Protein 3W7F without MG	Urdamycin_J	Hatomarubigin_F	X_14881_E	11_HydroxyTetrangomycin	Prejadomycin	Emycin_A	Elmycin_B	Fujianmycin_B	PD116779	Homoprejadomycin	SS_228Y	N05WA963B
Run1	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4
Run2	-9.5	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.3
Run3	-9.5	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4
AV.	-9.5	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4
Dock	-9.5	-9.5	-9.5	-9.5	-9.5	-9.5	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4
Residues that interacts with the original ligand & Residues that interacts with the ligands	13	12	12	12	9	13	15	14	14	12	9	11
	Ala134	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134			
						Ala157		Ala157	Ala157			
	Arg171						Arg171					
	Arg45	Arg45	Arg45	Arg45			Arg45	Arg45				Arg45
	Asn168						Asn168			Asn168		Asn168
		Asp48		Asp48	Asp48		Asp48			Asp48	Asp48	Asp48
		Cys44		Cys44	Cys44					Cys44	Cys44	
		Gln165		Gln165	Gln165	Gln165	Gln165			Gln165	Gln165	Gln165
	Gly138		Gly138			Gly138		Gly138	Gly138			
	Gly161	Gly161	Gly161			Gly161	Gly161	Gly161	Gly161			
	His18							His18				
						Ile241			Ile241			
		Leu141	Leu141	Leu141	Leu141	Leu141		Leu141	Leu141			Leu141
						Leu145			Leu145			
			Leu160			Leu160		Leu160	Leu160			
	Leu164	Leu164		Leu164		Leu164	Leu164	Leu164	Leu164		Leu164	Leu164
							Met15			Met15		
	Phe22		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22
		Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26	Phe26
	Ser19		Ser19					Ser19		Ser19		
	Tyr248						Tyr248			Tyr248		Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41		Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
		Val133	Val133	Val133	Val133		Val133		Val133	Val133	Val133	
	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand					Leu107	Ala244			Ala244	Leu107	Leu107	Asp176
					Val37							Asp52
												Tyr129
												Tyr183
												Val37

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	129	22	127	55	62	76	5	114	51	82	20	53
Compound Name Docked to Protein 3W7F without MG	Homorabelomycin	Jadomycin_A	TAN_1085	8_O_methyl_7_deoxo_7_hydroxytetrangomycin	Tetrangomycin	Sakyomicin_D	Hatomarubigin_A	Fridamycin_C	Rabelomycin	SM_196B	UWM6	8_O_methyltetrangomycin
Run1	-9.3	-9.4	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.2	-9.2	-9.2
Run2	-9.3	-9.2	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.2	-9.2	-9.2
Run3	-9.4	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.2	-9.2	-9.2	-9.2
AV.	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.2	-9.2	-9.2
Dock	-9.4	-9.4	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.3	-9.2	-9.2	-9.2
Residues that interacts with the original ligand & Residues that interacts with the ligands	11	15	18	16	15	12	11	11	15	16	15	12
			Ala134	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134	Ala134	Ala134
				Ala157								
		Arg171	Arg171		Arg171				Arg171	Arg171	Arg171	
		Arg265	Arg265							Arg265	Arg265	
		Arg45	Arg45	Arg45	Arg45	Arg45		Arg45	Arg45	Arg45	Arg45	
	Asn168	Asn168	Asn168		Asn168		Asn168		Asn168	Asn168	Asn168	Asn168
			Asp172									
	Asp48	Asp48	Asp48			Asp48	Asp48	Asp48				Asp48
	Cys44	Cys44		Cys44		Cys44	Cys44	Cys44				Cys44
	Gln165	Gln165	Gln165		Gln165	Gln165	Gln165	Gln165	Gln165		Gln165	Gln165
				Gly138	Gly138			Gly138	Gly138	Gly138		
				Gly161	Gly161			Gly161	Gly161	Gly161		
		His18	His18		His18				His18	His18	His18	
				Ile241								
	Leu141			Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141
				Leu160				Leu164		Leu160		
			Leu164	Leu164	Leu164	Leu164			Leu164	Leu164		
		Lys20	Lys20									
			Met15									
	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22		Phe22	Phe22	Phe22	Phe22
	Phe26		Phe26	Phe26		Phe26	Phe26				Phe26	Phe26
		Ser19	Ser19	Ser19	Ser19				Ser19	Ser19	Ser19	
		Ser21	Ser21								Ser21	
	Tyr248				Tyr248		Tyr248		Tyr248	Tyr248	Tyr248	Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
	Val133	Val133	Val133	Val133		Val133	Val133					Val133
	Val137	Val137		Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand	Tyr129	Tyr129	Tyr129	Ala244			Leu107					Val37
							Tyr129					
							Val37					

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	68	12	106	156	109	74	126	107	50	117	90	14
Compound Name Docked to Protein 3W7F without MG	8_O_methylrabelomycin	Warkmycin	Elmycin_C	Azicemicin_A	X_14881_B	Sakyomicin_B	PD116740	Elmycin_D	JBIR_88	MM_47755	6_Deoxy_8_O_methylrabelomycin	Langkocycline_A1
Run1	-9.2	-9.2	-9.2	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-8.7
Run2	-9.2	-9.1	-9.2	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1
Run3	-9.2	-9.2	-9.0	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.0	-9.0
AV.	-9.2	-9.2	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-8.9
Dock	-9.2	-9.2	-9.2	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1	-9.1
Residues that interacts with the original ligand & Residues that interacts with the ligands	11	15	12	18	15	14	14	13	11	11	11	19
	Ala134		Ala134	Ala134	Ala134	Ala134	Ala134	Ala134		Ala134	Ala134	Ala134
		Arg171		Arg171			Arg171					Arg171
		Arg265		Arg265								Arg265
	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45	Arg45		Arg45	Arg45	Arg45
		Asn168		Asn168	Asn168	Asn168	Asn168		Asn168			Asn168
		Asp172										
	Asp48	Asp48	Asp48			Asp48			Asp48	Asp48	Asp48	Asp48
	Cys44		Cys44			Cys44			Cys44	Cys44	Cys44	
	Gln165	Gln165	Gln165	Gln165		Gln165	Gln165		Gln165	Gln165	Gln165	Gln165
	Gly138			Gly138	Gly138		Gly138	Gly138		Gly138	Gly138	
	Gly161			Gly161	Gly161		Gly161	Gly161		Gly161	Gly161	Gly161
		His18		His18								His18
	Leu141			Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	Leu141	
				Leu160	Leu160			Leu160				
	Leu164	Leu164	Leu164	Leu164	Leu164		Leu164	Leu164		Leu164	Leu164	Leu164
		Lys20										Lys20
				Met15		Met15						
		Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22	Phe22			Phe22
			Phe26		Phe26	Phe26	Phe26	Phe26	Phe26			Phe26
		Ser19	Ser19	Ser19	Ser19		Ser19	Ser19				Ser19
		Ser21										Ser21
		Tyr248		Tyr248	Tyr248	Tyr248	Tyr248		Tyr248			Tyr248
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41
			Val133		Val133	Val133		Val133	Val133			Val133
	Val137		Val137	Val137	Val137	Val137		Val137	Val137	Val137	Val137	Val137
Residues that NOT interacts with the original ligand		Asn179				Ile40			Tyr129			
		Asp114				Val37			Val37			
		Asp176										
		Asp52										
		Glu175										
		Tyr129										
		Tyr183										
		Val53										

APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

#	157	136	121	80	4	15	16	17	18	43	44	66
Compound Name Docked to Protein 3W7F without MG	Azicemicin_B	Urdamycin_I	X_14881_A	Seitomycin	Actinosporin_B	Langkocycline_A2 (Not Docked)	Langkocycline_A3 (Not Docked)	Langkocycline_B1 (Not Docked)	Langkocycline_B2 (Not Docked)	JBIR_92 (Not Docked)	JBIR_93 (Not Docked)	Urdamycin_D (Not Docked)
Run1	-9.0	-9.0	-8.8	-8.8	-8.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Run2	-9.0	-9.0	-9.0	-8.8	-8.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Run3	-9.0	-9.0	-9.0	-8.8	-8.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AV.	-9.0	-9.0	-8.9	-8.8	-8.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dock	-9.0	-9.0	-9.0	-8.8	-8.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Residues that interacts with the original ligand & Residues that interacts with the ligands	22	11	12	15	21	0	0	0	0	0	0	0
	Ala134	Ala134		Ala134	Ala134							
	Ala157											
	Arg171				Arg171							
	Arg265				Arg265							
	Arg45			Arg45	Arg45							
	Asn168	Asn168	Asn168	Asn168	Asn168							
					Asp172							
			Cys44									
	Gln165	Gln165	Gln165	Gln165	Gln165							
	Gly138			Gly138	Gly138							
	Gly161			Gly161	Gly161							
	His18			His18	His18							
	Leu141		Leu141	Leu141	Leu141							
	Leu145											
	Leu160											
	Leu164	Leu164	Leu164	Leu164	Leu164							
	Lys20				Lys20							
	Met15	Met15	Met15									
	Phe22	Phe22	Phe22	Phe22	Phe22							
	Phe26	Phe26	Phe26	Phe26	Phe26							
	Ser19			Ser19	Ser19							
					Ser21							
	Tyr248	Tyr248	Tyr248		Tyr248							
	Tyr41	Tyr41	Tyr41	Tyr41	Tyr41							
		Val133	Val133	Val133	Val133							
	Val137	Val137	Val137	Val137	Val137							
Residues that NOT interacts with the original ligand			Val37		Ala244							

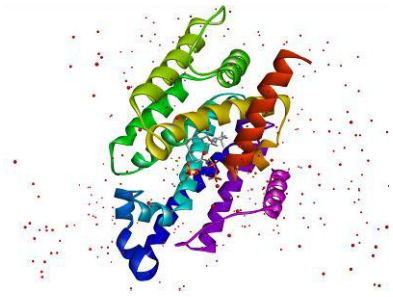
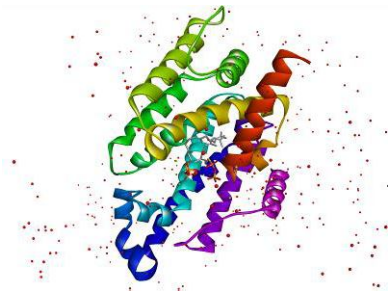
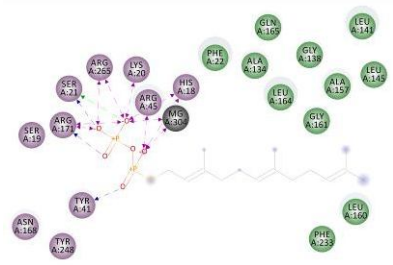
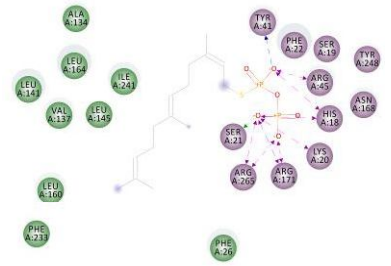
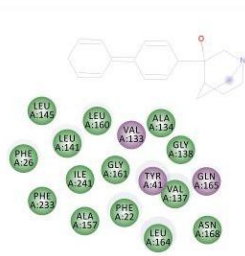
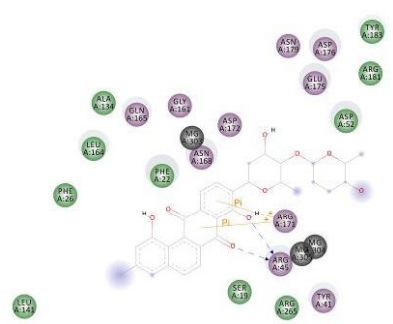
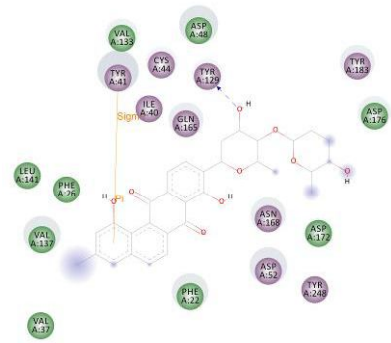
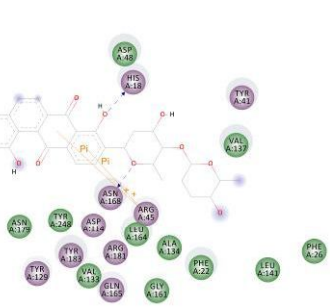
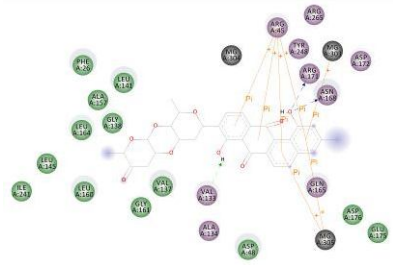
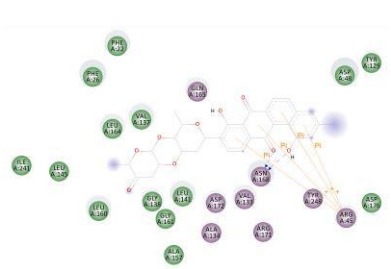
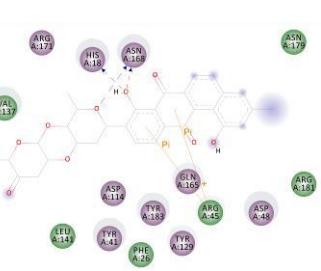
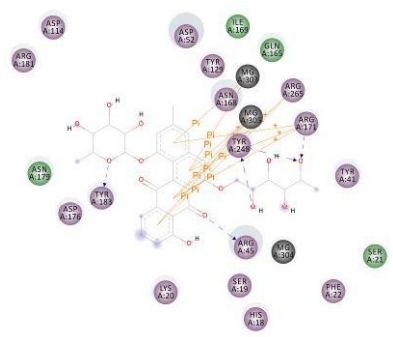
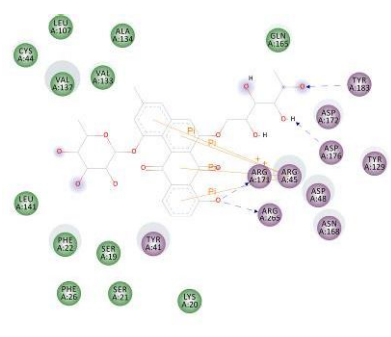
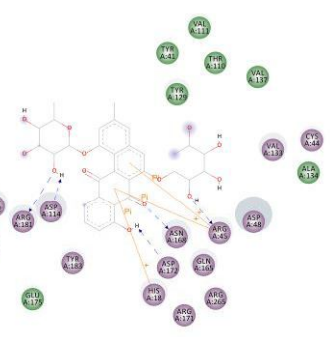
APPENDIX III

Docking score and interacted residue of protein (3W7F without MG) with the Angucycline Group Antibiotics (ligands), and the arrangements are according to dock scores (kcal/mol) (continue)

Residues that NOT interacts with the original ligand		Residues that interacts with the original ligand & Residues that interacts with the ligands		Dock	AV.	Run3	Run2	Run1	Compound Name Docked to Protein 3W7F without MG	#
	0		0	0.0	0.0	0.0	0.0	0.0	Urdamycin_H (Not Docked)	67
	0		0	0.0	0.0	0.0	0.0	0.0	8_O_methylurdamycin_A (Not Docked)	79
	0		0	0.0	0.0	0.0	0.0	0.0	Urdamycin_K (Not Docked)	138
	0		0	0.0	0.0	0.0	0.0	0.0	Saquayamycin_Z (Not Docked)	153

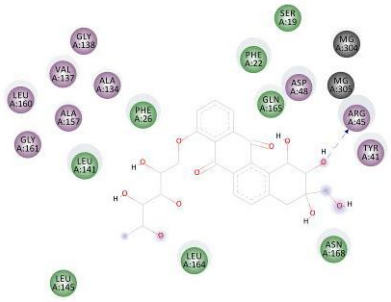
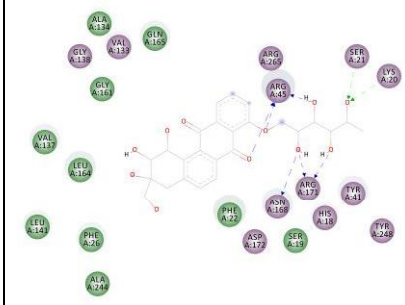
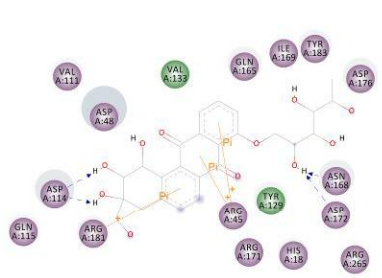
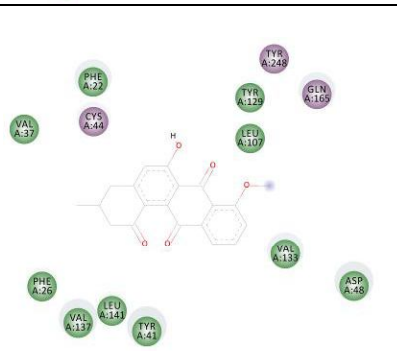
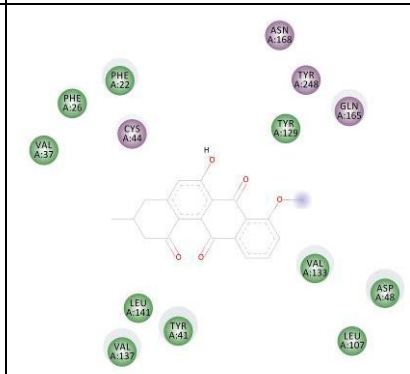
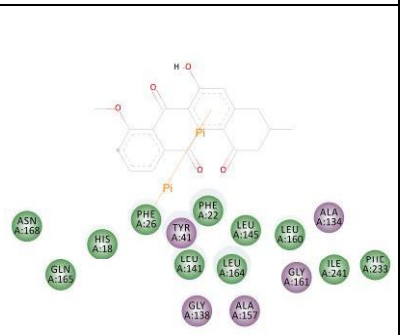
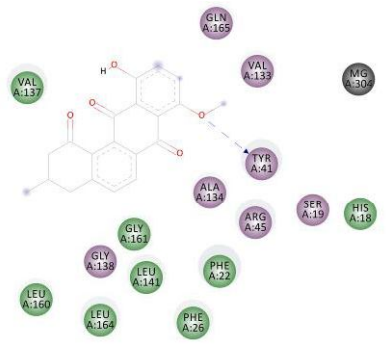
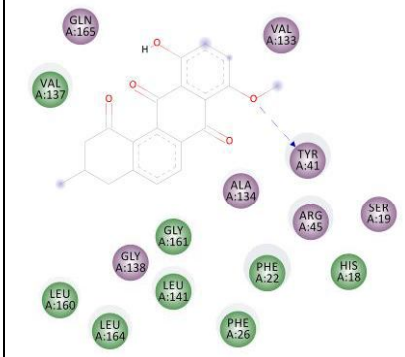
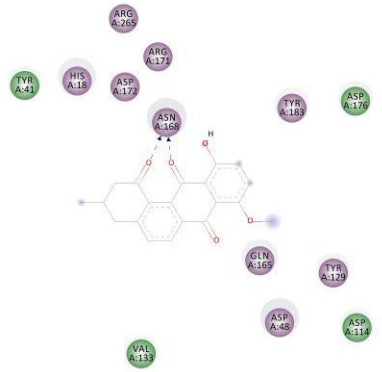
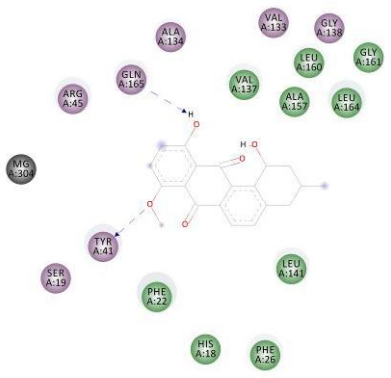
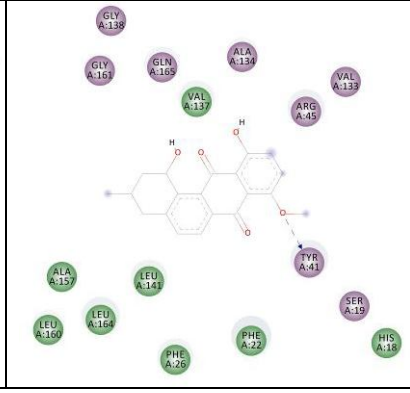
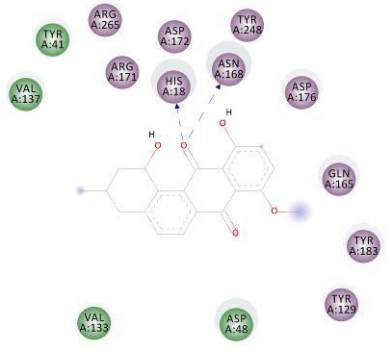
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
	Protein & Ligand From PDB			
0	Ligand of protein (Docked Ligand)			
1	Marangucycline_A			
2	Marangucycline_B			
3	Actinosporin_A			

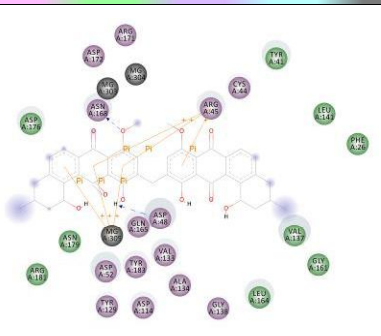
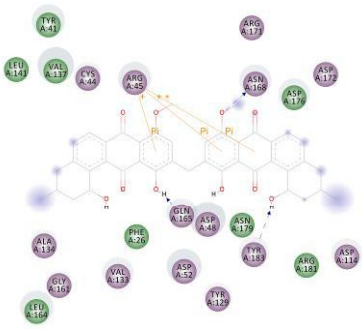
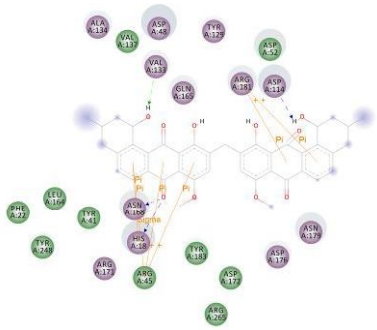
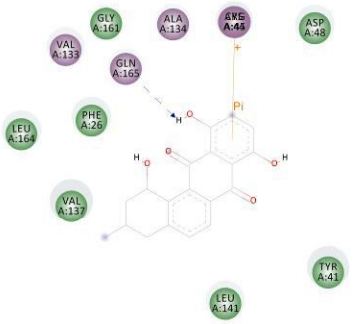
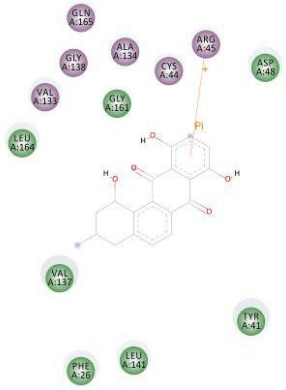
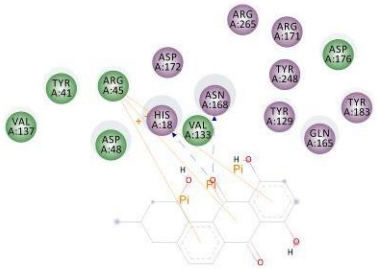
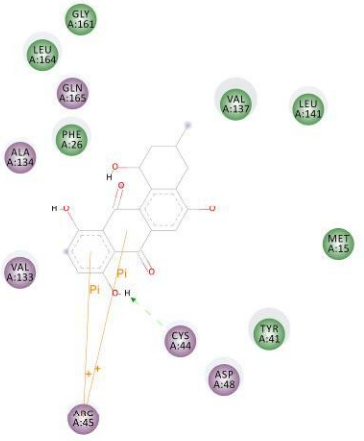
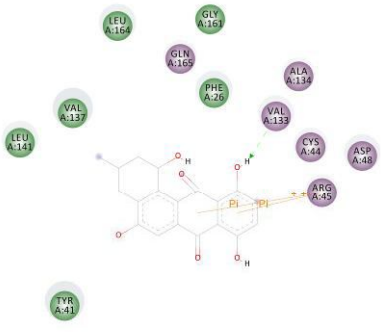
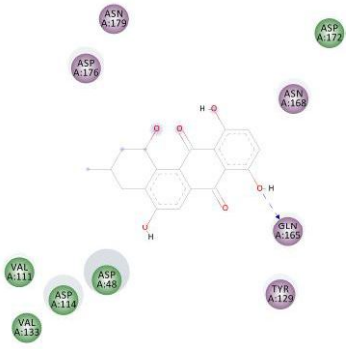
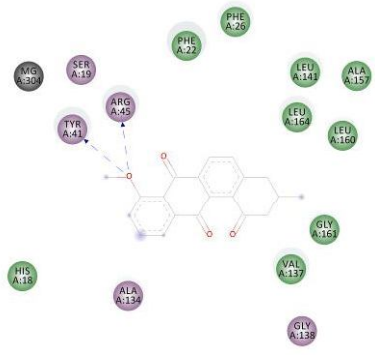
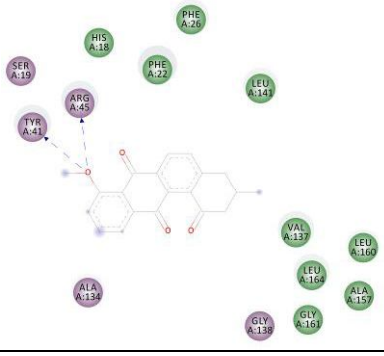
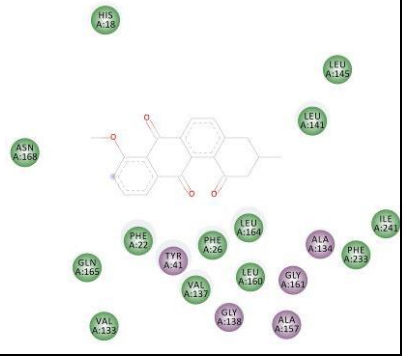
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
4	Actinosporin_B			
5	Hatomarubigin_A			
6	Hatomarubigin_B			
7	Hatomarubigin_C			

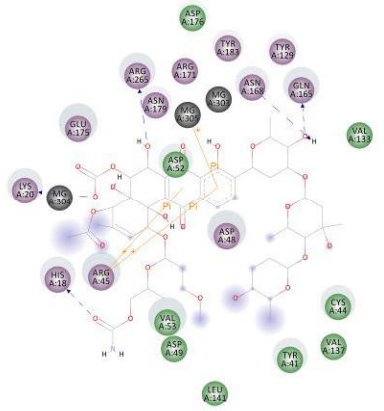
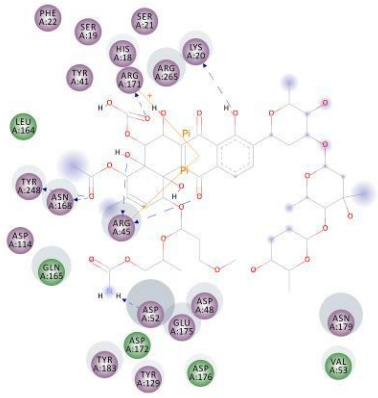
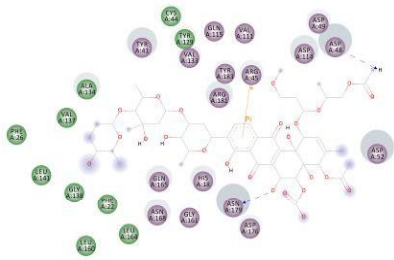
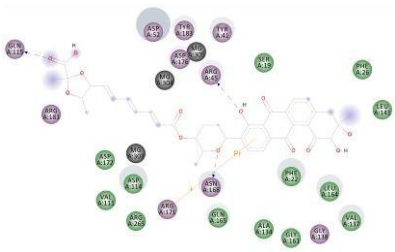
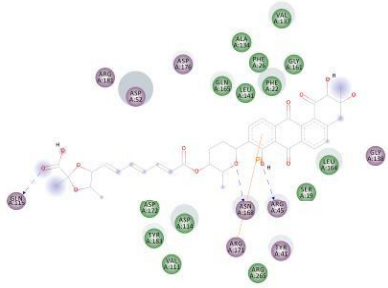
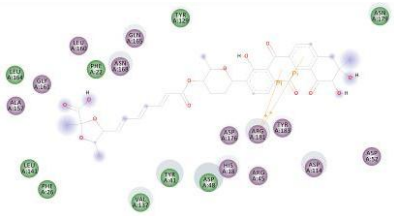
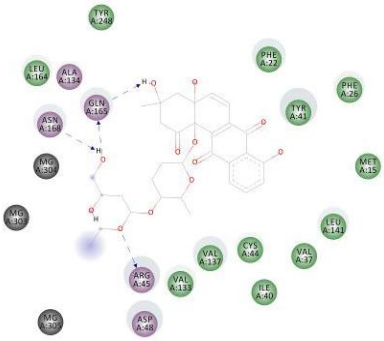
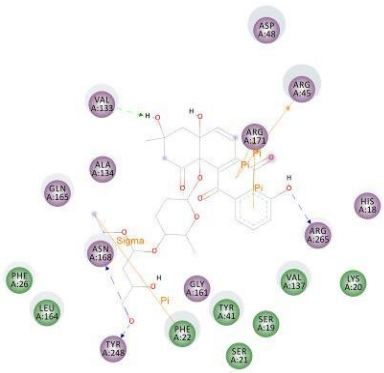
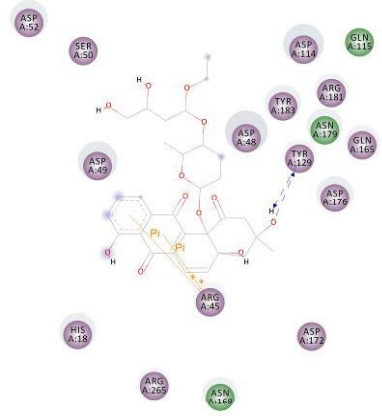
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
8	Hatomarubigin_D			
9	Hatomarubigin_E			
10	Hatomarubigin_F			
11	Rubiginone_B2			

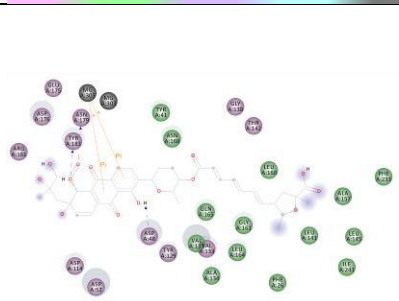
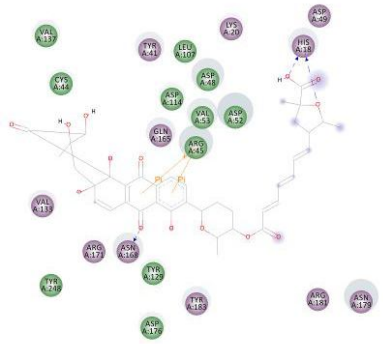
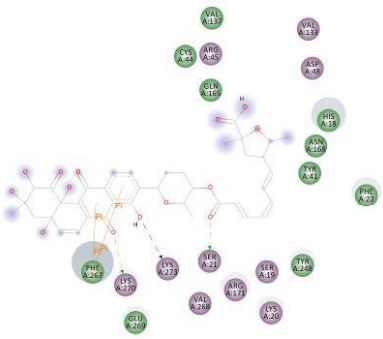
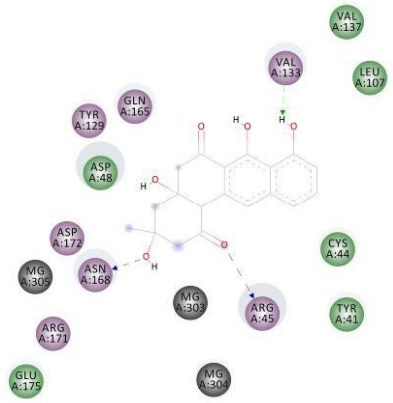
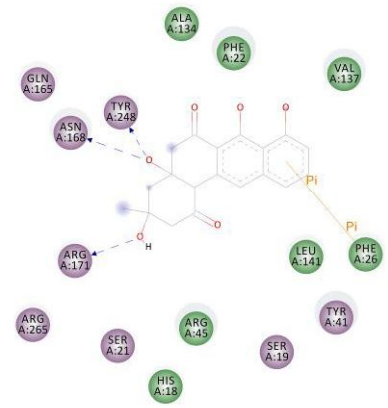
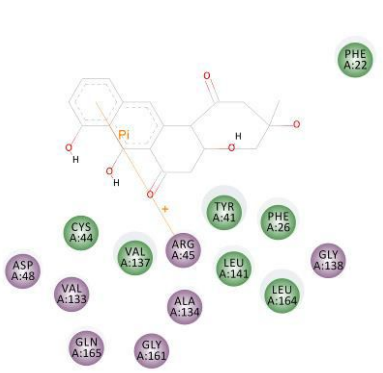
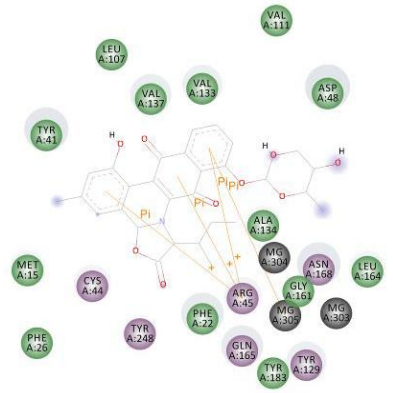
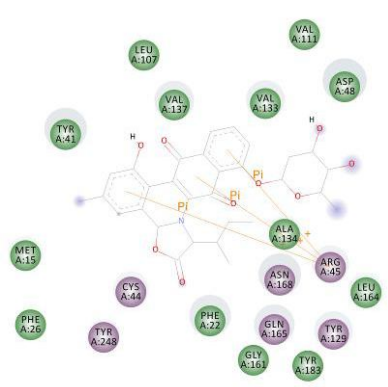
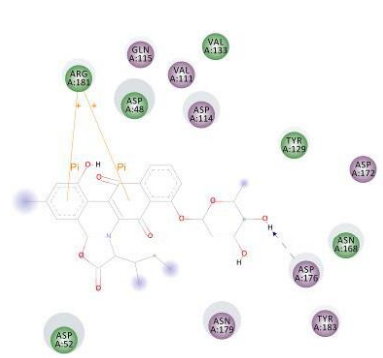
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
12	Warkmycin			
13	Waldiomycin			
14	Langkocycline_A1			
15		Langkocycline_A2	Not Docked	Not Docked
16		Langkocycline_A3	Not Docked	Not Docked
17		Langkocycline_B1	Not Docked	Not Docked
18		Langkocycline_B2	Not Docked	Not Docked

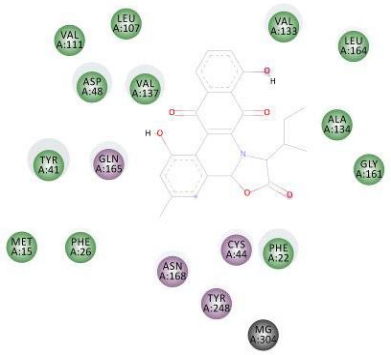
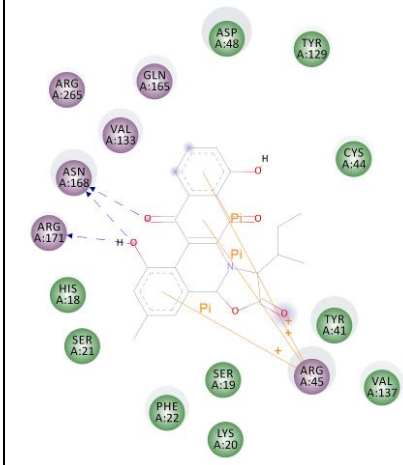
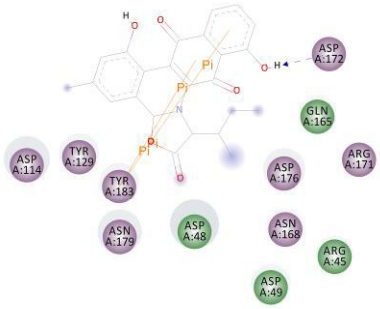
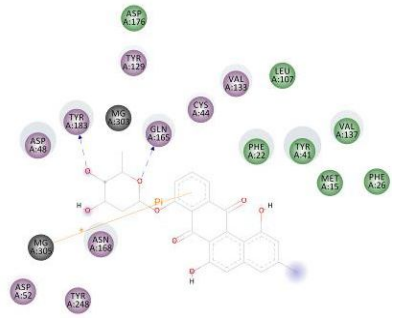
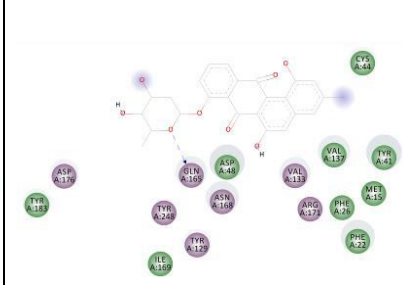
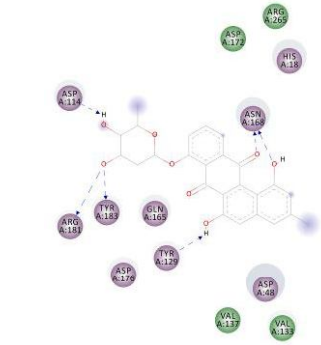
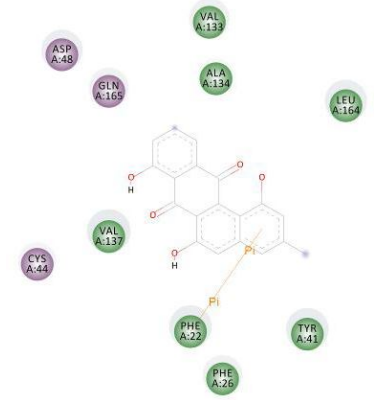
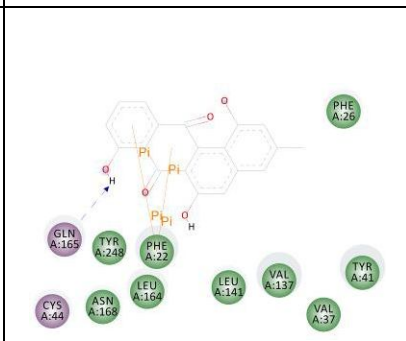
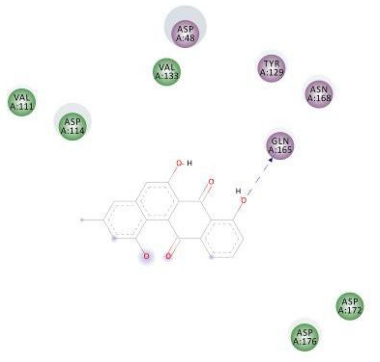
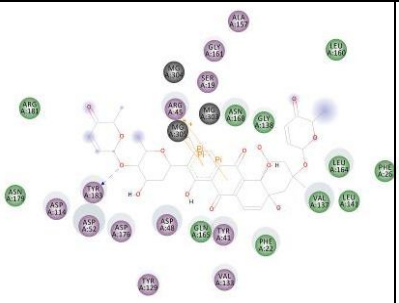
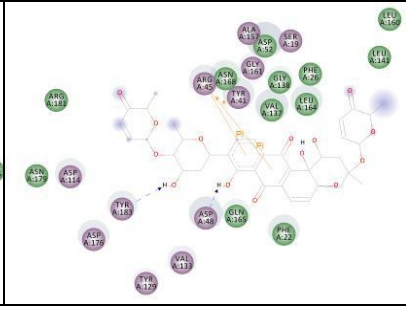
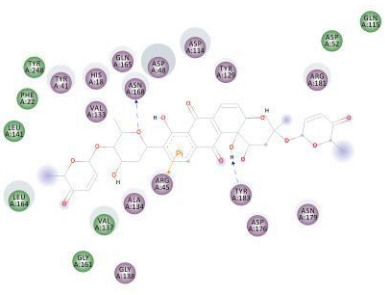
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
19	Fradimycin_C			
20	UWM6			
21	Jadomycin_B			

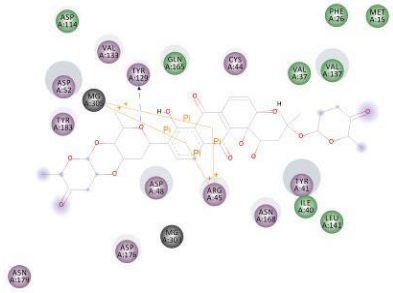
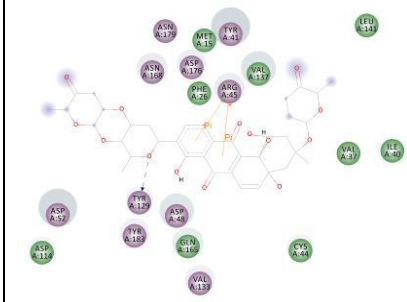
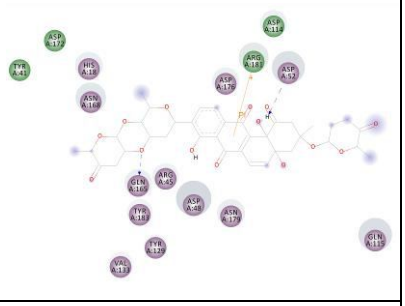
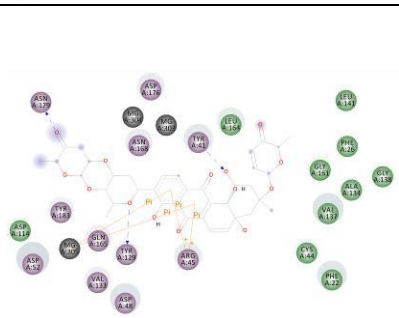
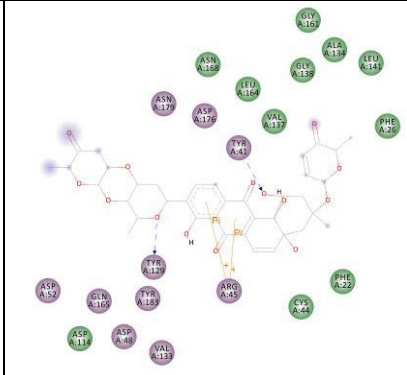
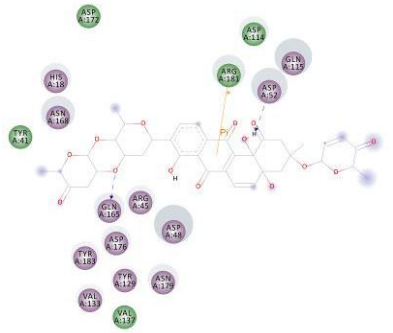
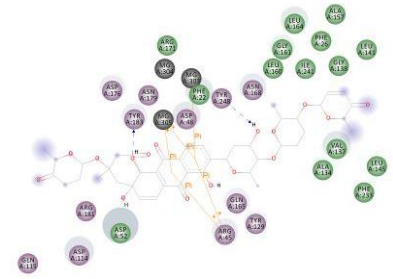
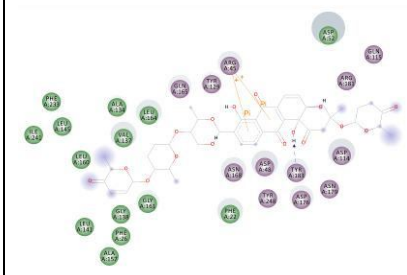
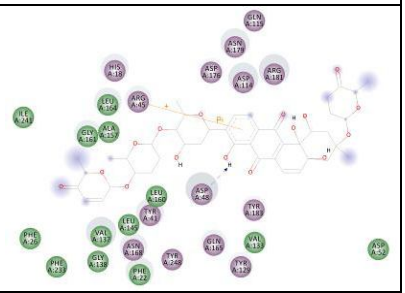
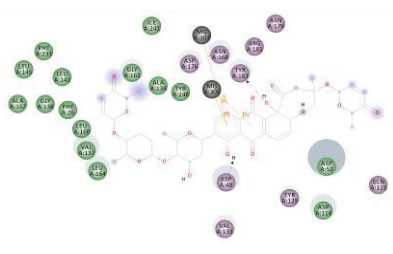
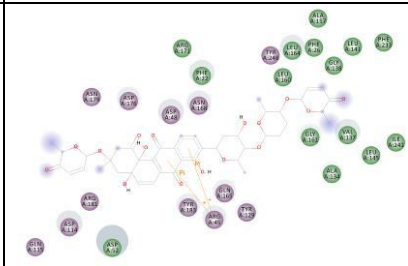
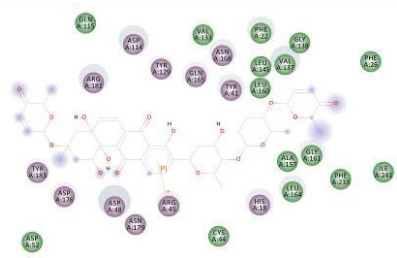
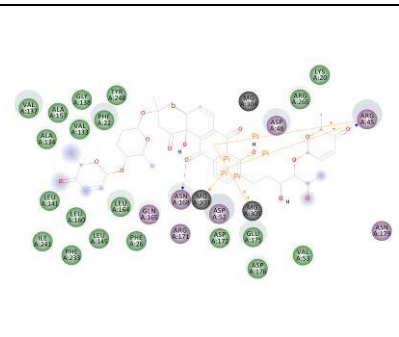
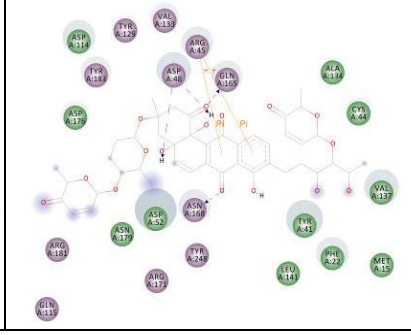
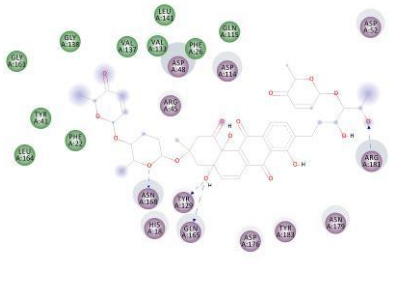
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
22	Jadomycin_A			
23	L_digitoxosyl_dehydrorabelomycin			
24	Dehydrorabelomycin			
25	Saprolmycin_A			

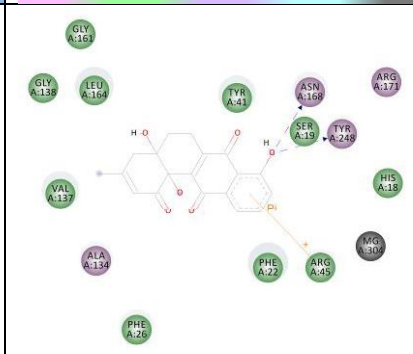
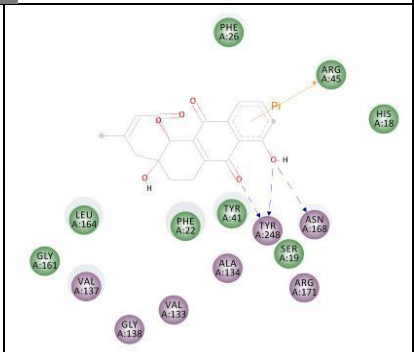
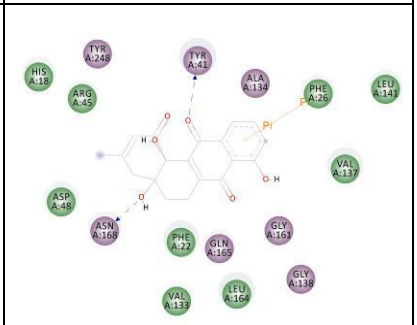
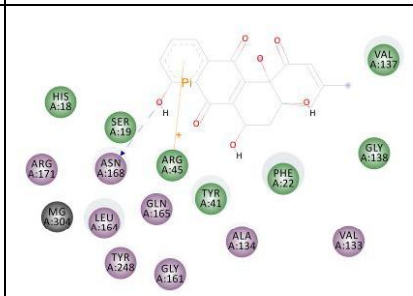
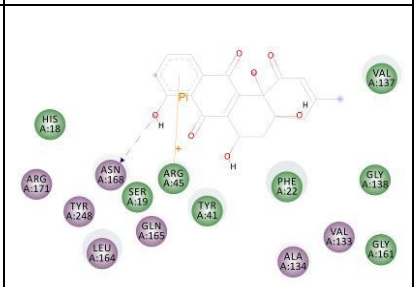
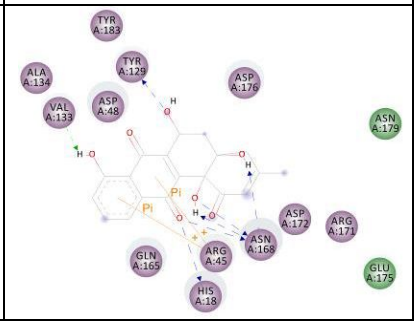
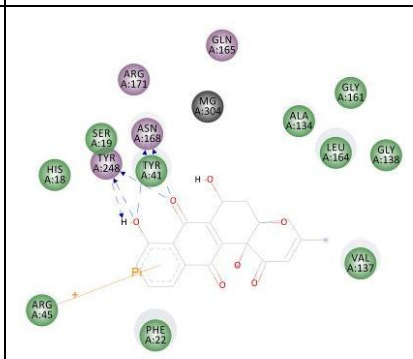
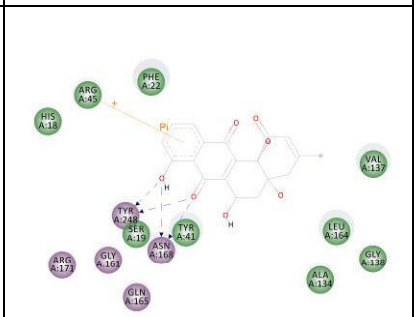
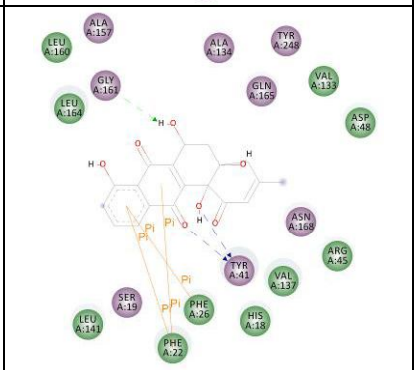
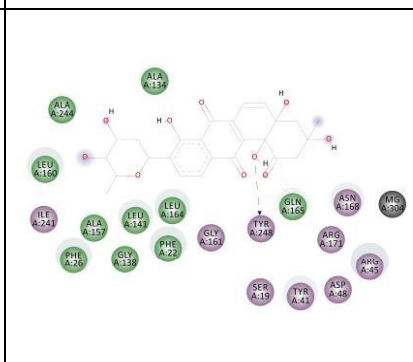
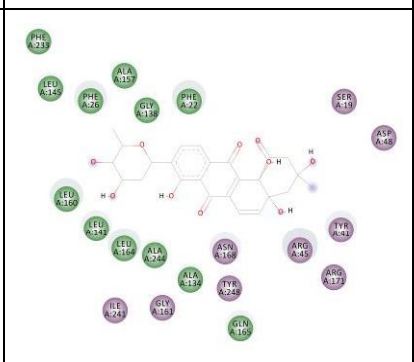
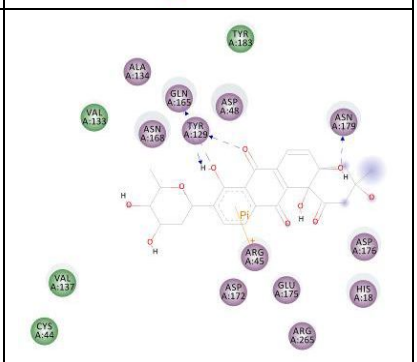
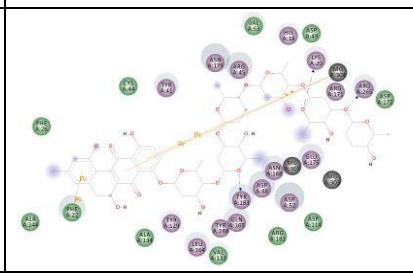
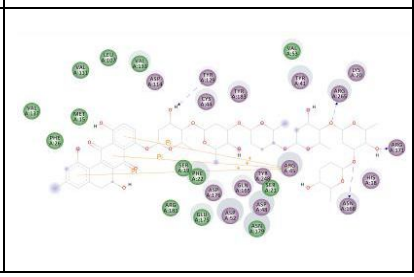
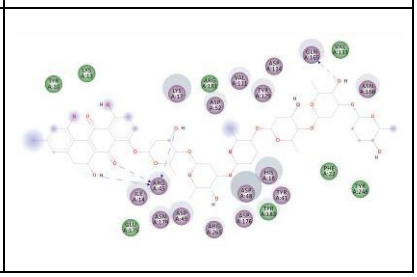
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
26	Saprolmycin_B			
27	Saprolmycin_C			
28	Saprolmycin_D			
29	Saprolmycin_E			
30	Saquayamycin_A 30_11.6			

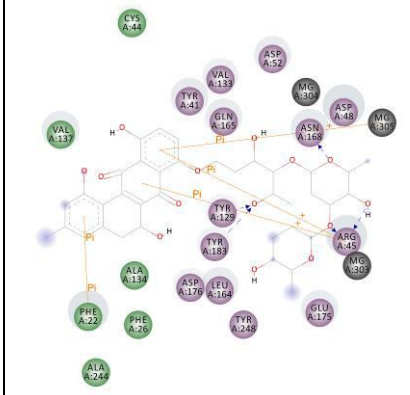
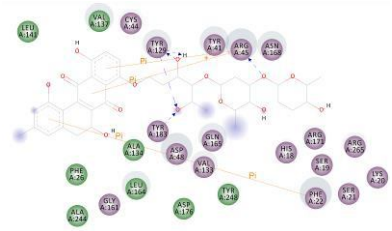
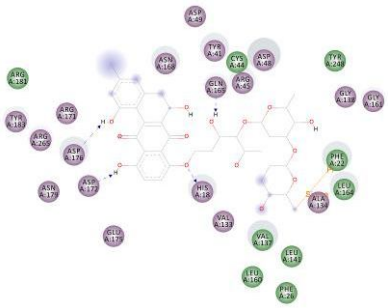
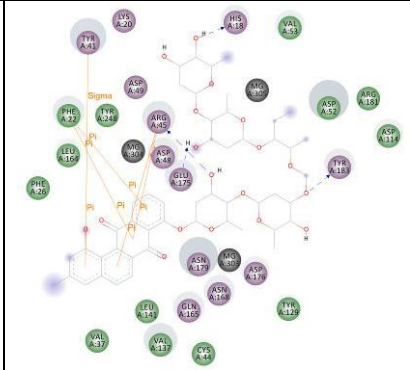
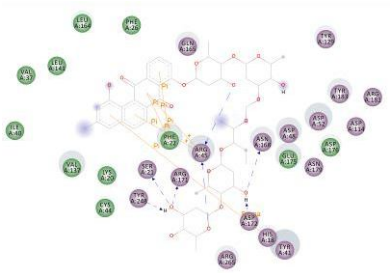
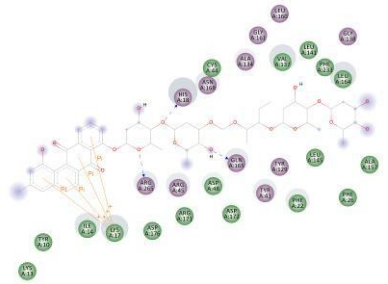
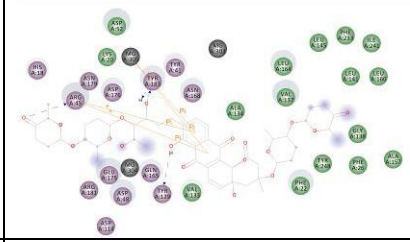
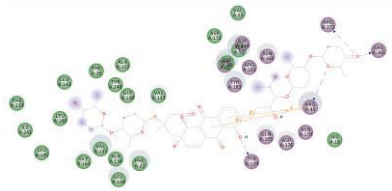
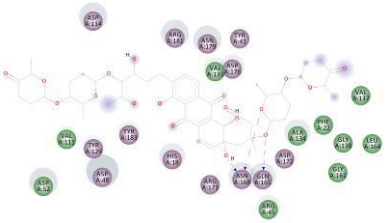
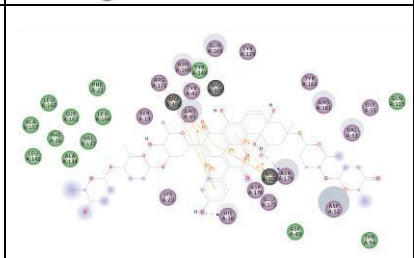
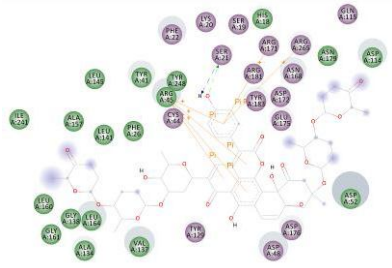
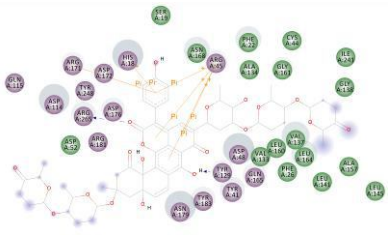
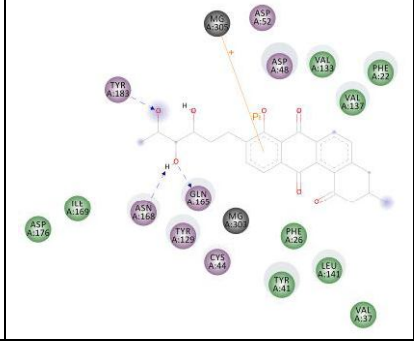
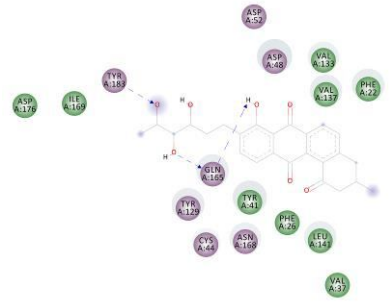
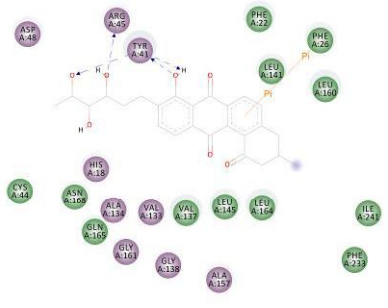
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
31	Gaudimycin_A			
32	Gaudimycin_B			
33	Gaudimycin_C			
34	Aquayamycin			
35	Landomycin_A 35 10.7			

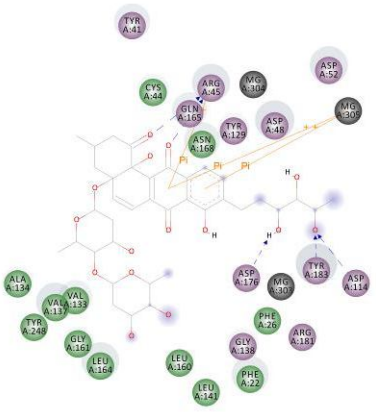
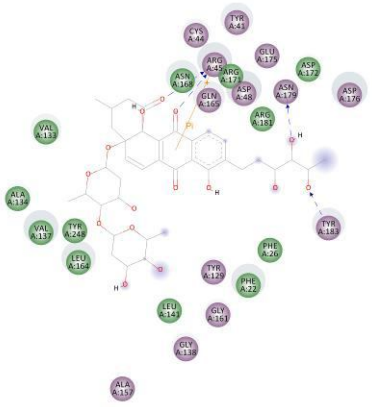
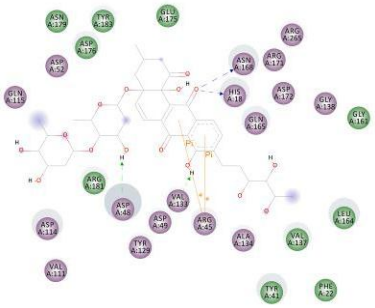
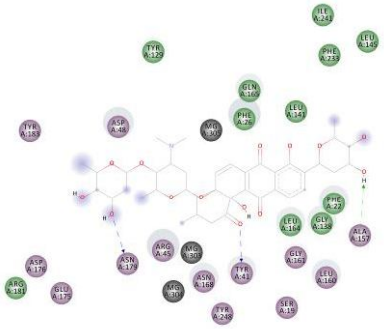
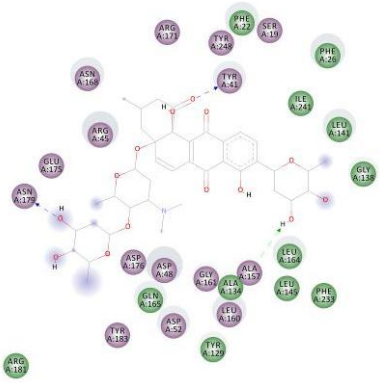
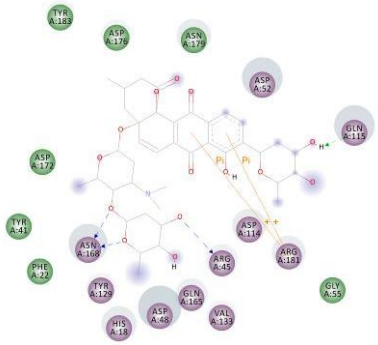
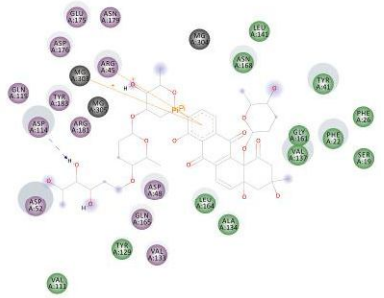
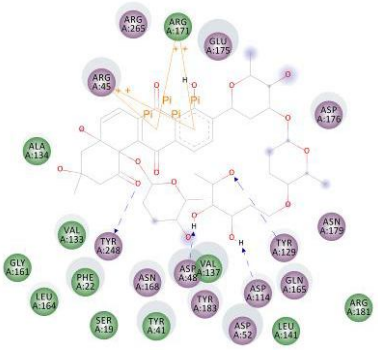
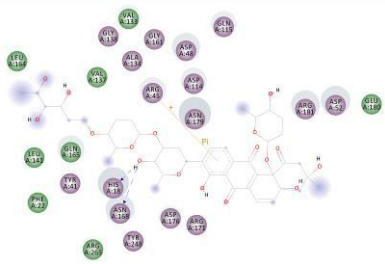
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
36	Landomycin_E			
37	Landomycin_Z			
38	Grincamycin			
39	Grincamycin_F			
40	JBIR_90			

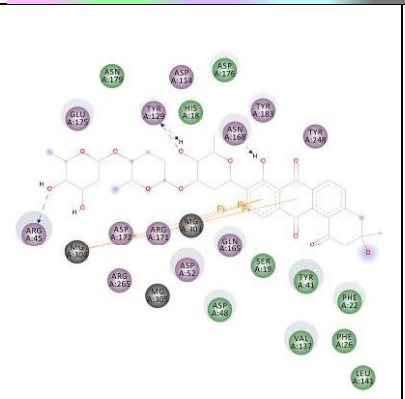
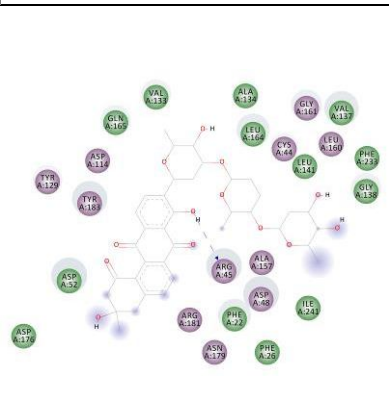
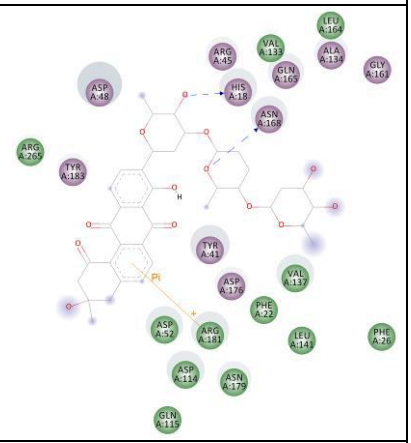
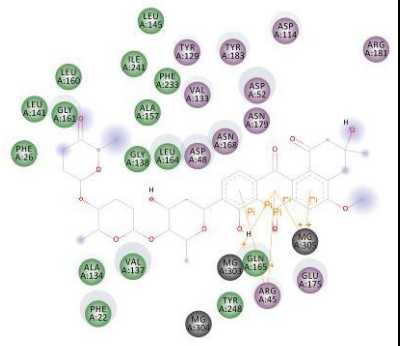
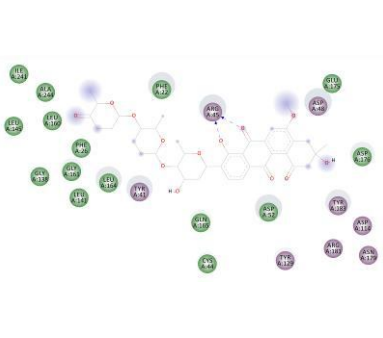
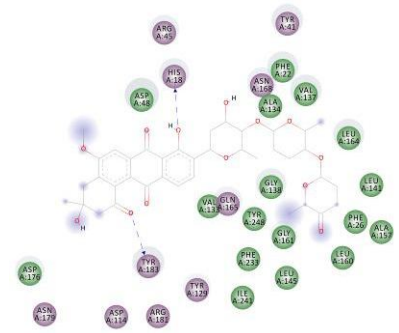
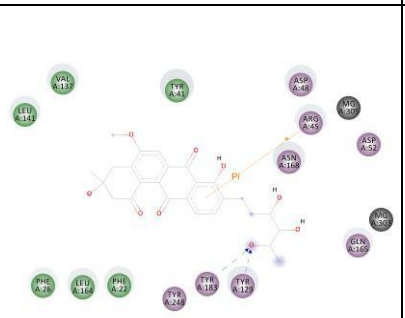
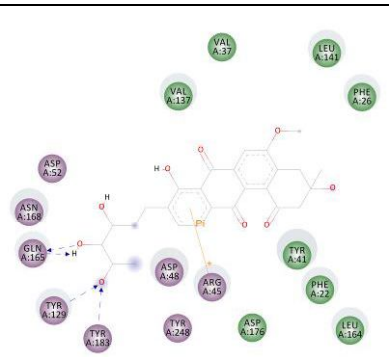
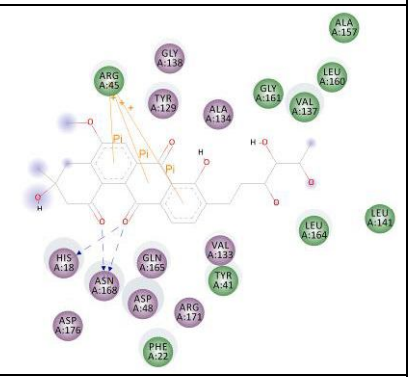
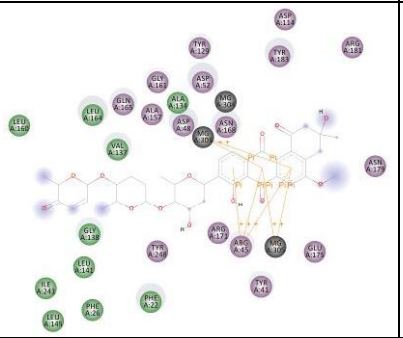
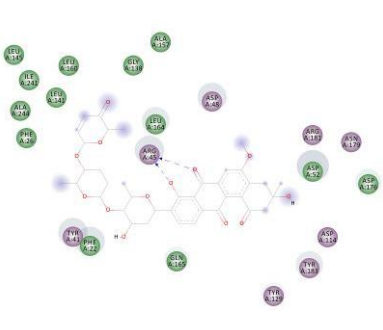
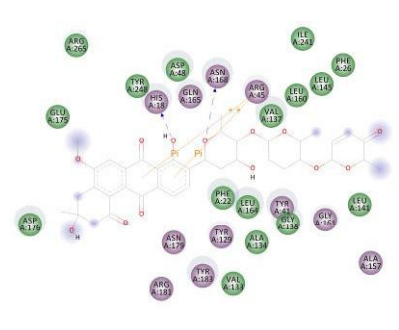
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
41	JBIR_116			
42	JBIR_91			
43		JBIR_92	Not Docked	Not Docked
44		JBIR_93	Not Docked	Not Docked
45	Urdamycin_A			

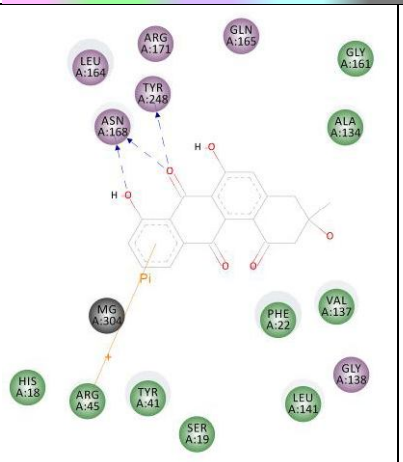
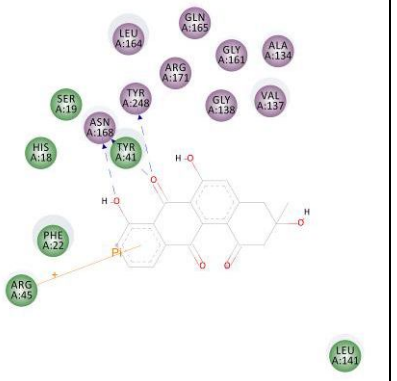
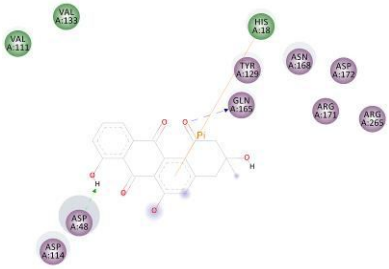
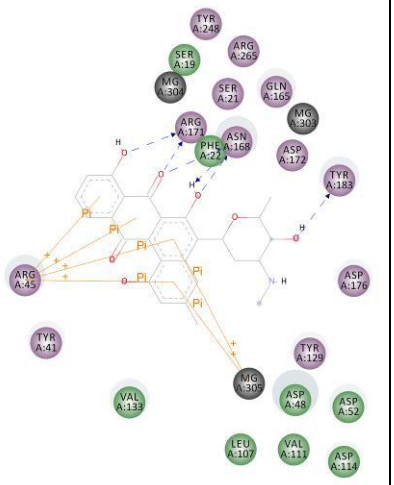
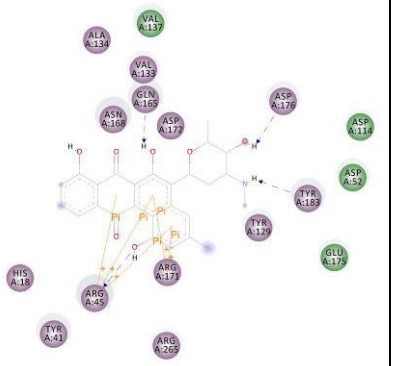
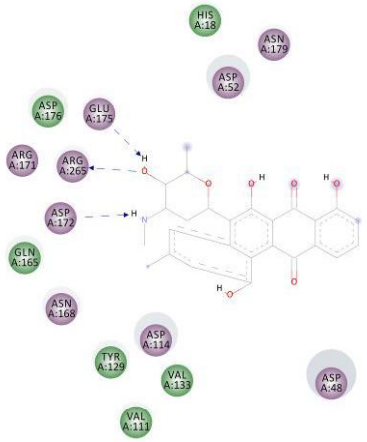
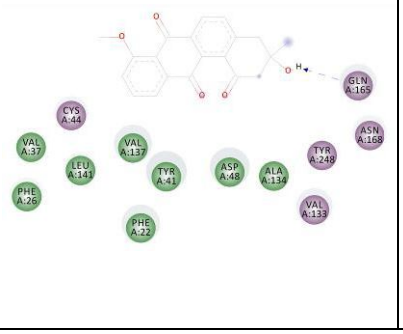
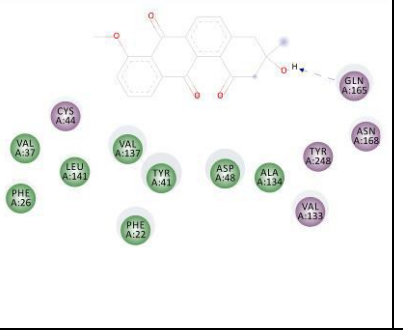
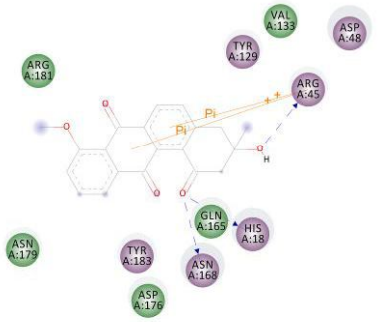
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
46	Urdamycin_B			
47	N05WA963A			
48	N05WA963B			
49	N05WA963D			
50		JBIR_88	Not Docked	Not Docked

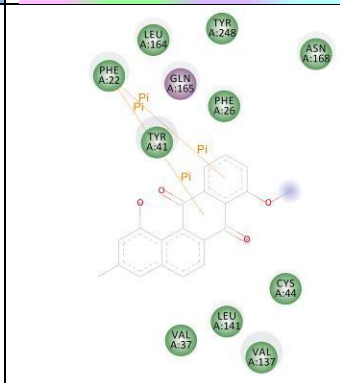
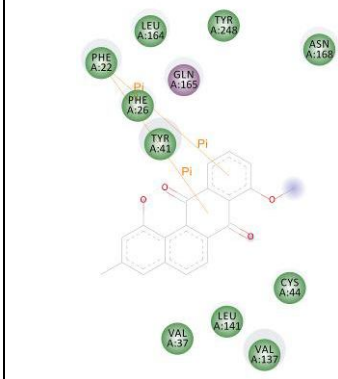
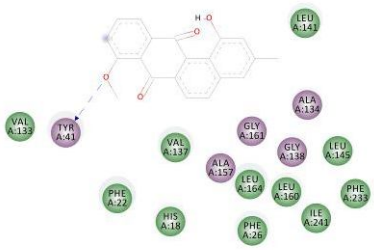
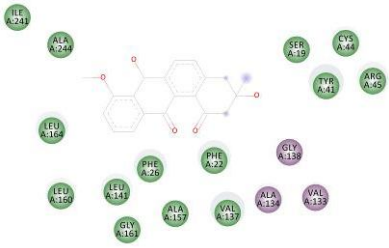
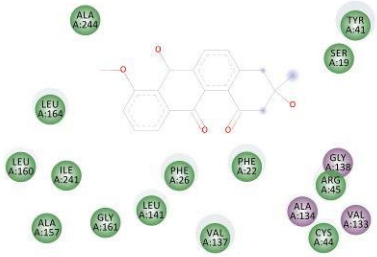
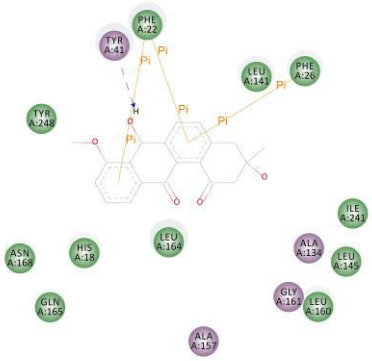
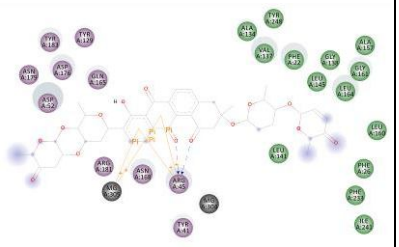
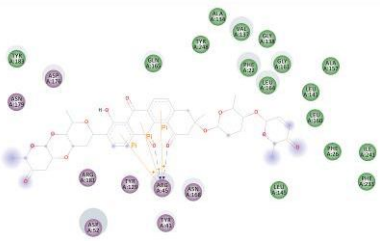
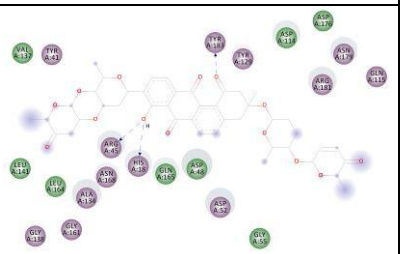
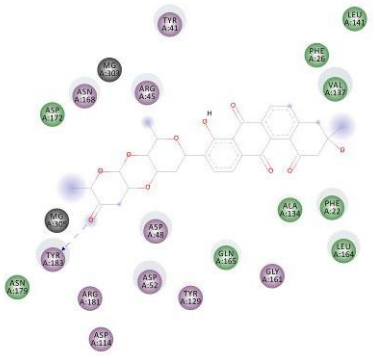
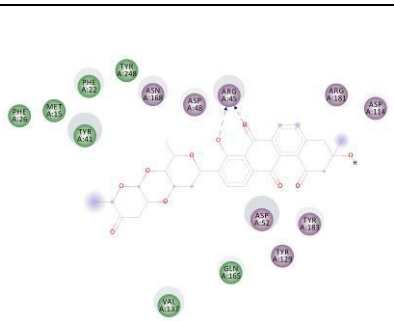
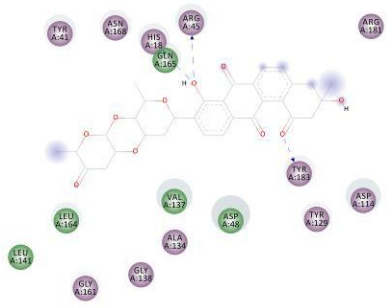
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
51	Rabelomycin			
52	Mayamycin			
53	8_O_methyltetrangomycin			

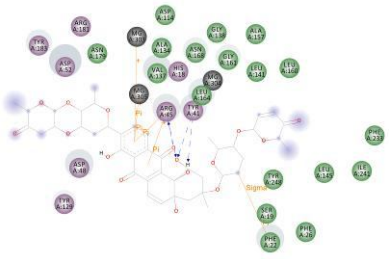
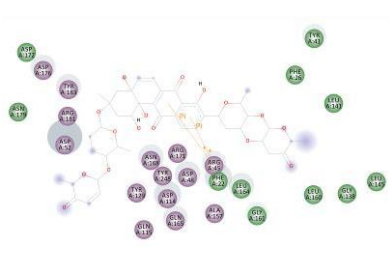
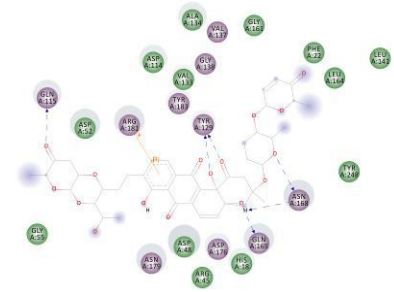
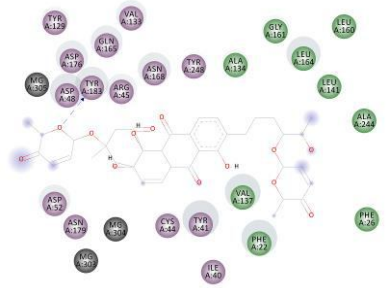
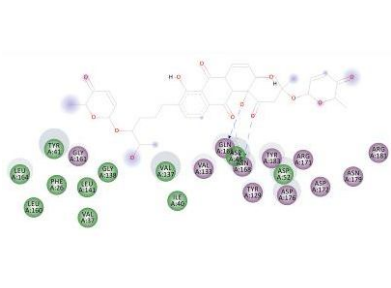
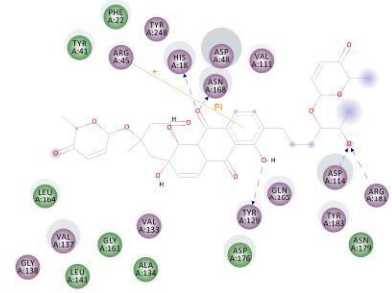
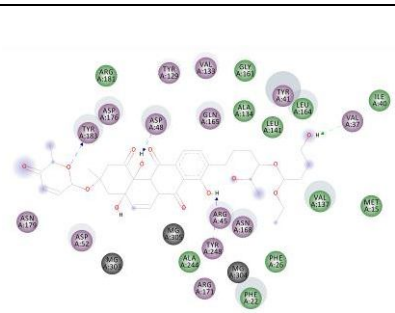
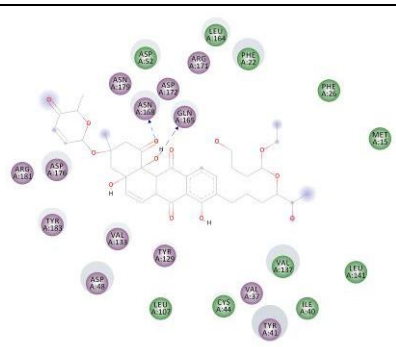
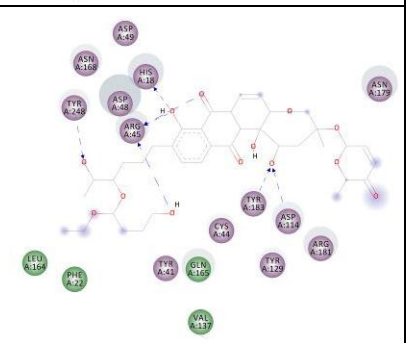
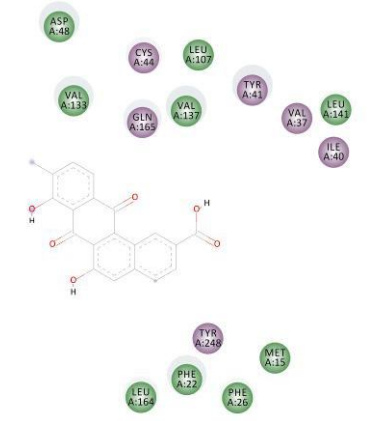
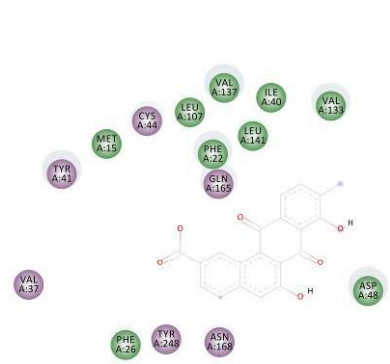
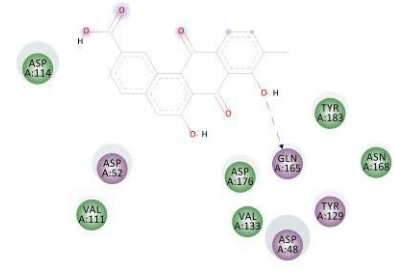
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
54	8_O_methyltetrangulol			
55	8_O_methyl_7_deoxo_7_hydroxytetrangomycin			
56	Moromycin_A			
57	Moromycin_B			

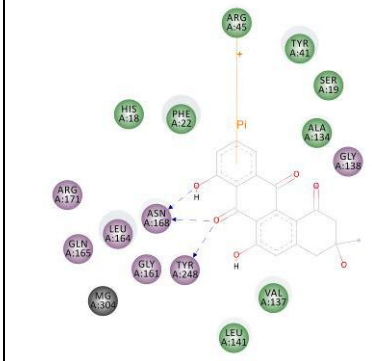
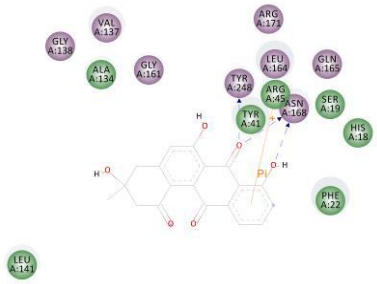
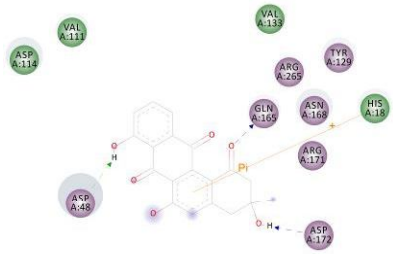
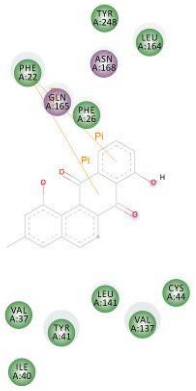
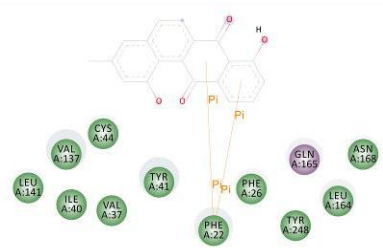
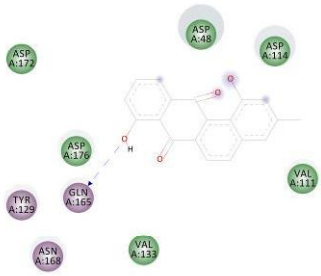
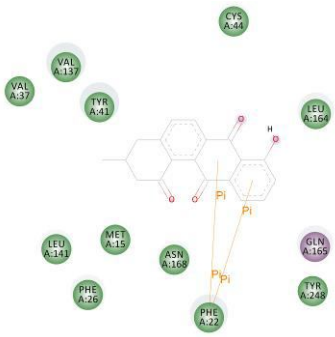
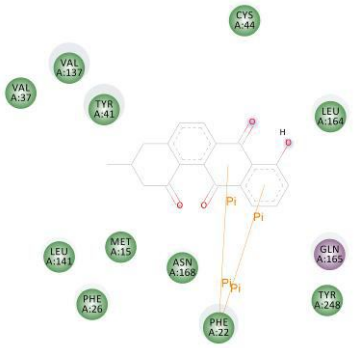
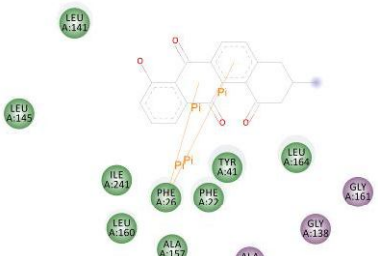
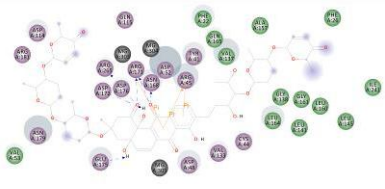
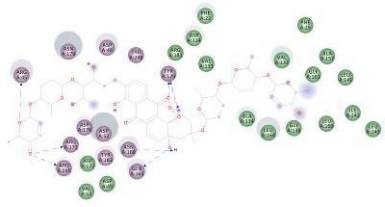
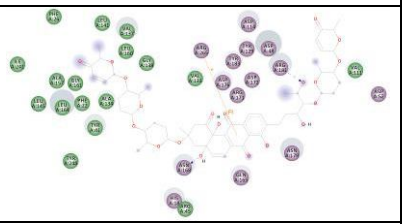
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
58	Saquayamycin_B			
59	Sch_47554			
60	Sch_47555			
61	BE_23254			

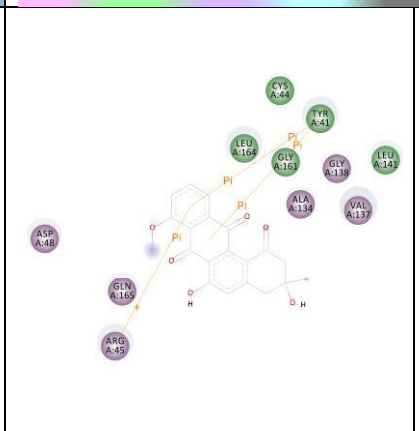
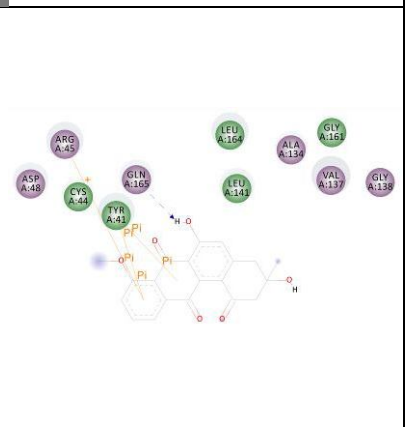
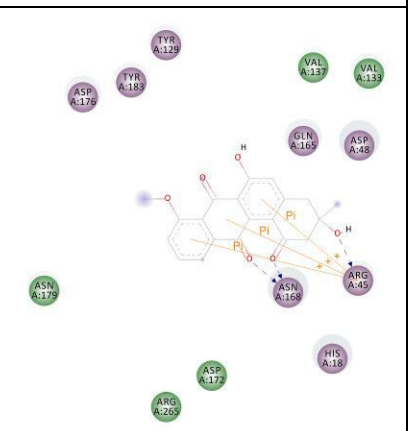
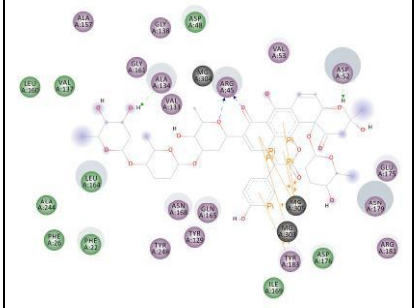
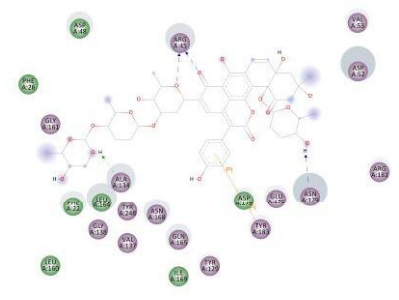
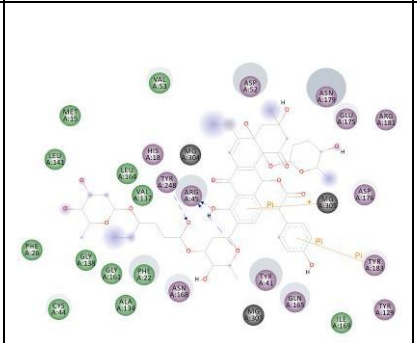
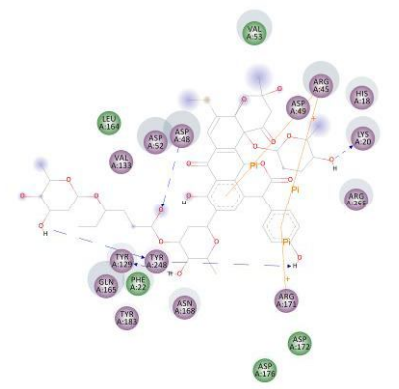
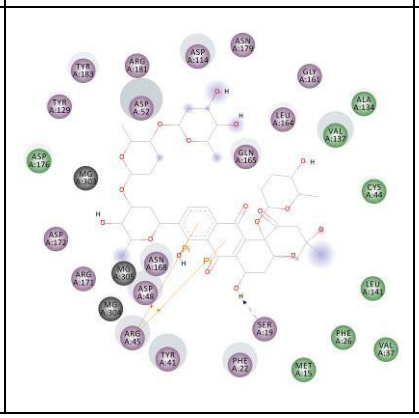
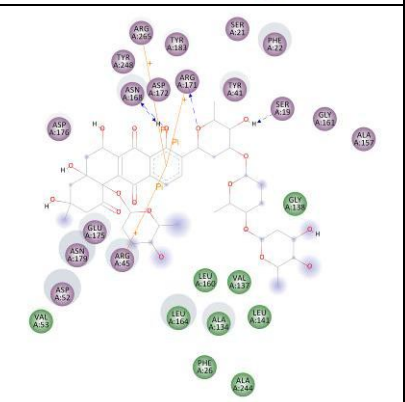
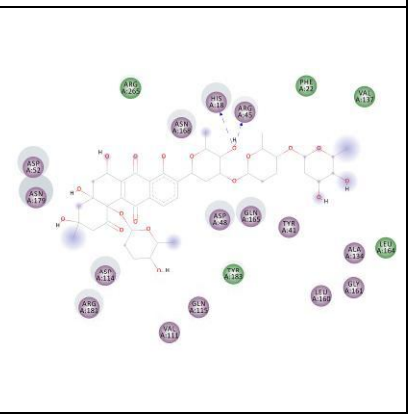
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
62	Tetrangomycin			
63	Tetrangulol			
64	Ochromocinone			
65	PI_080 (=PI-6621)			
66		Urdamycin_D	Not Docked	Not Docked
67		Urdamycin_H	Not Docked	Not Docked

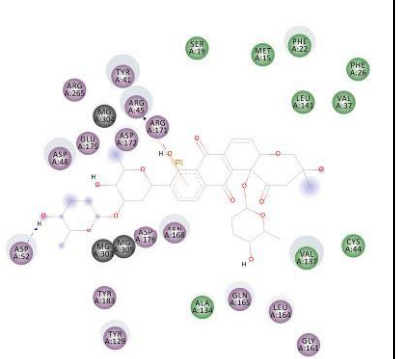
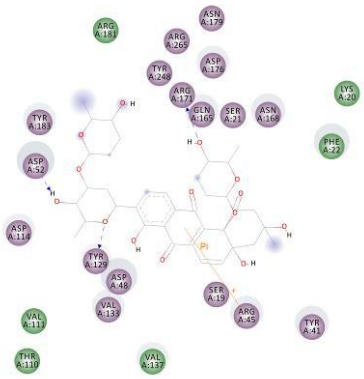
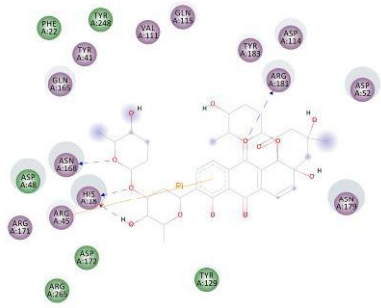
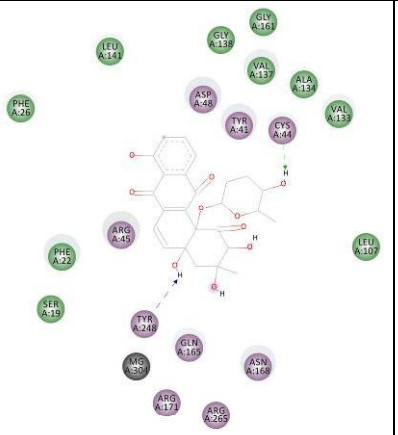
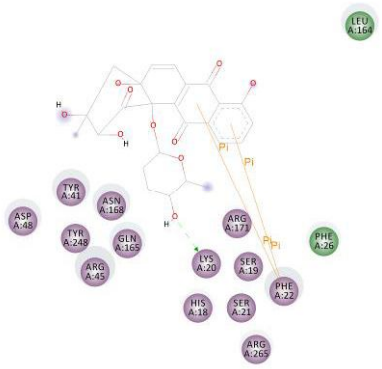
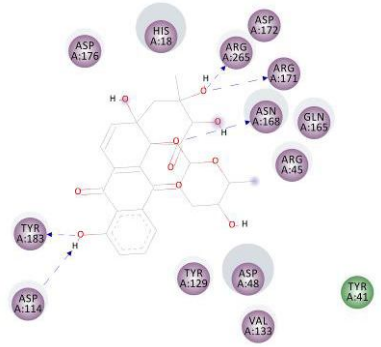
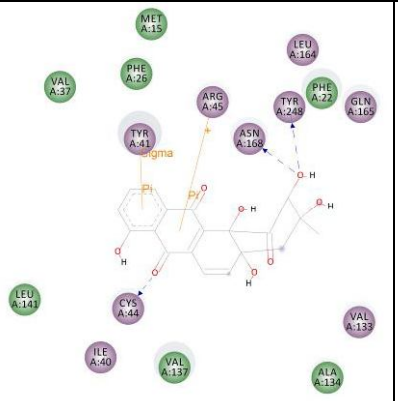
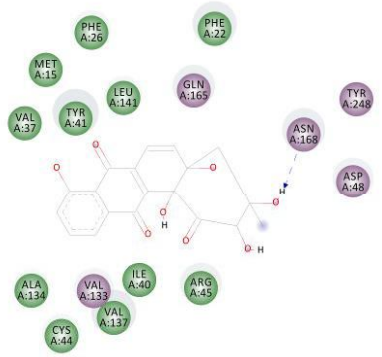
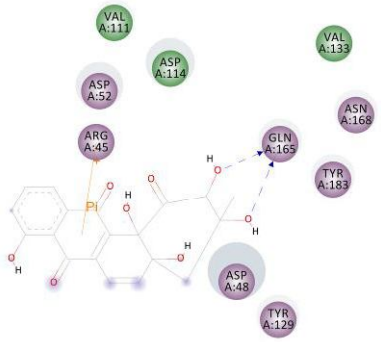
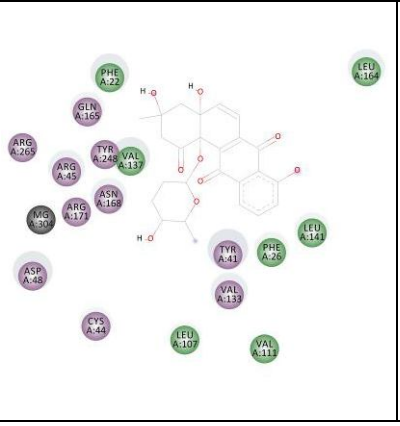
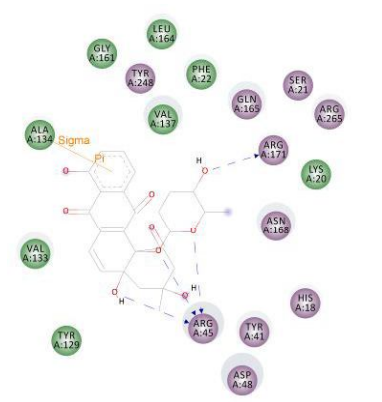
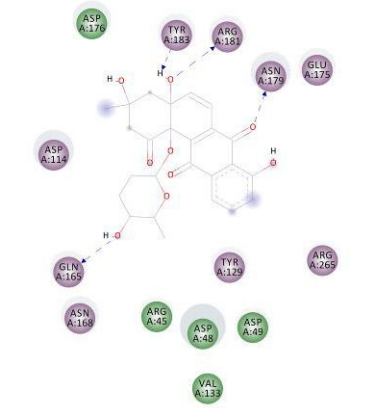
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
68	8_O_methylrabelomycin			
69	Urdamycin_C			Not Docked
70	Urdamycin_E			Not Docked
71	Urdamycin_F			

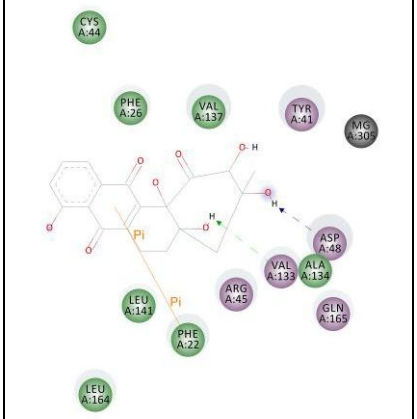
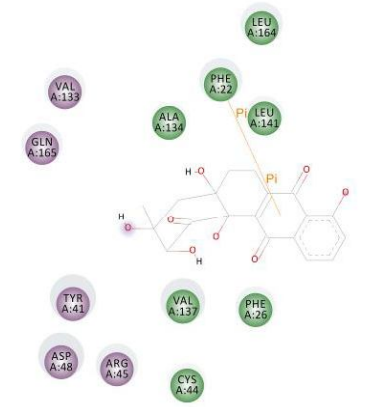
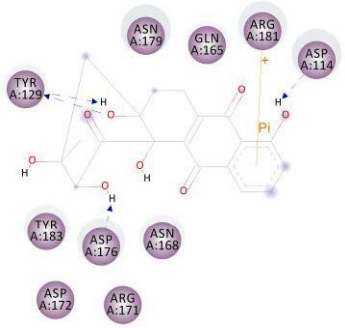
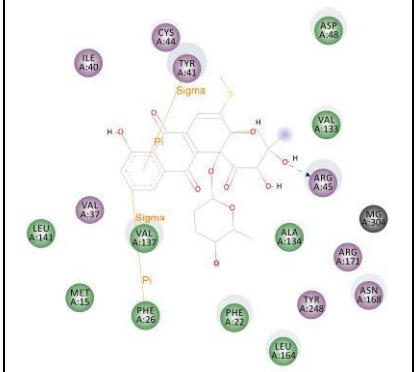
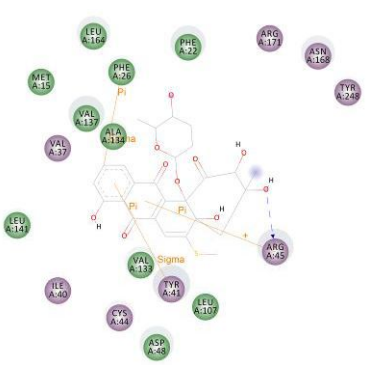
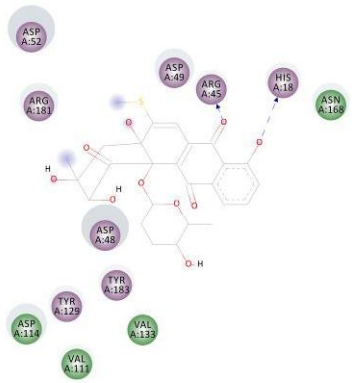
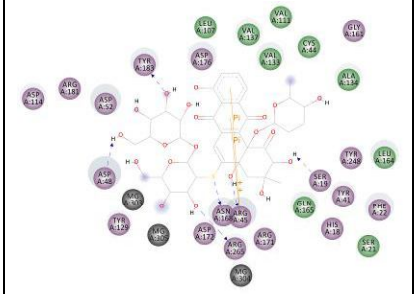
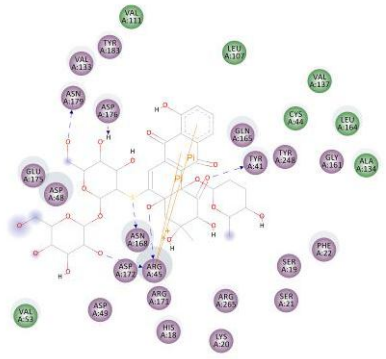
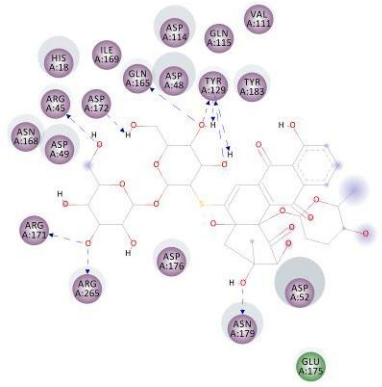
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
72	Urdamycin_G			
73	Sakyomicin_A			
74	Sakyomicin_B			
75	Sakyomicin_C			

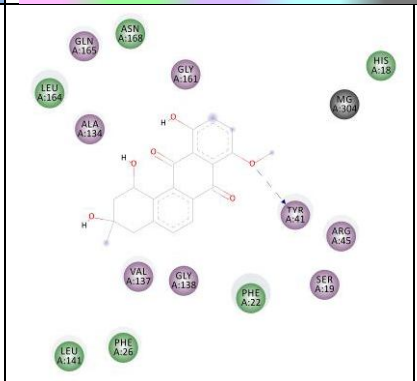
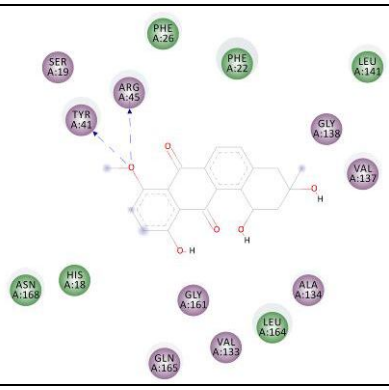
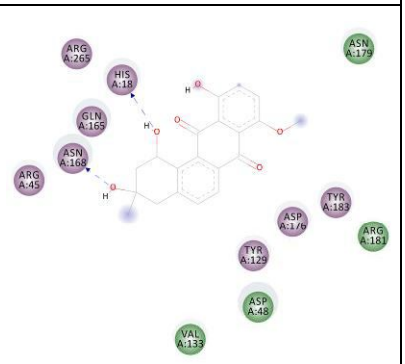
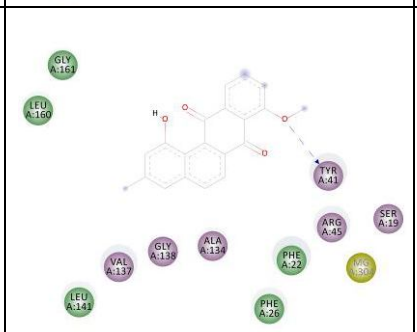
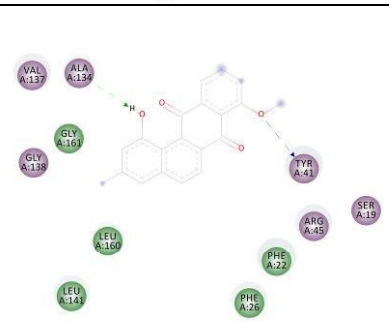
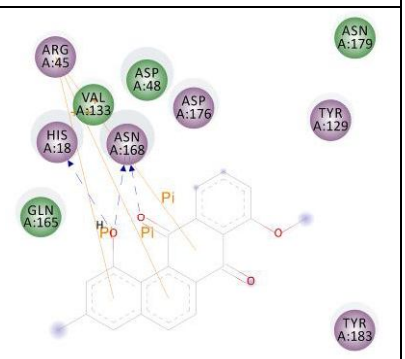
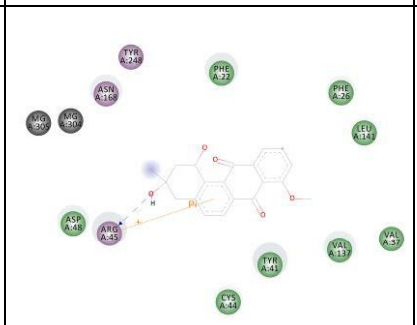
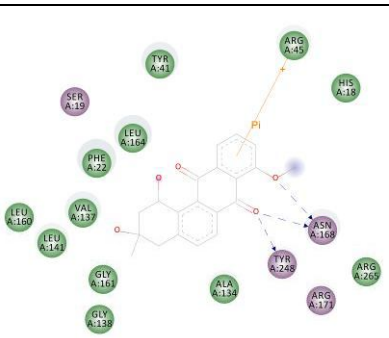
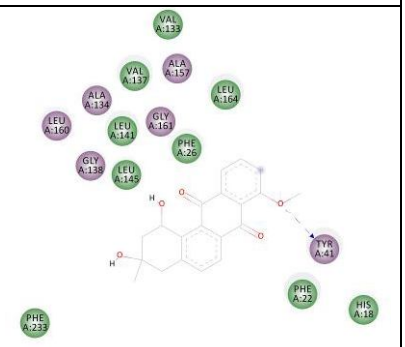
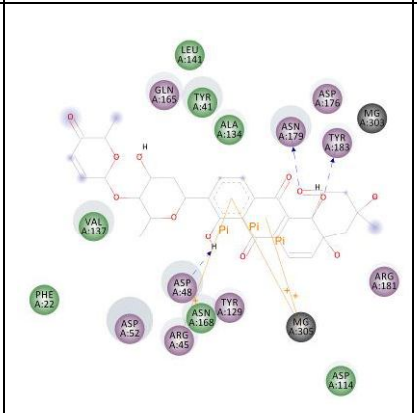
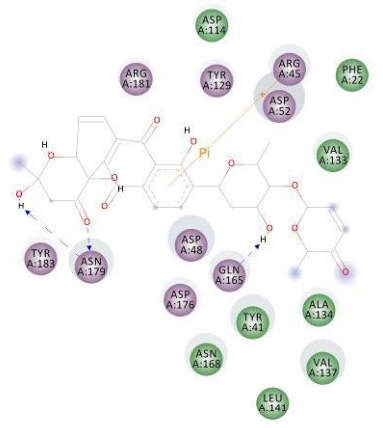
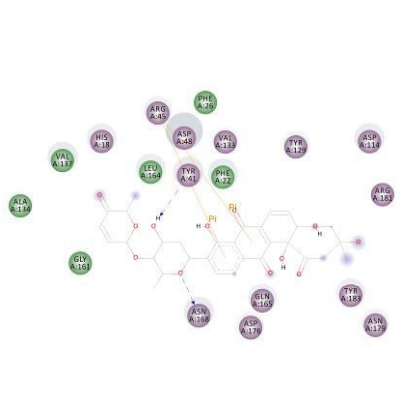
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
76	Sakyomicin_D			
77	Sakyomicin_E			
78	BE_7585A			
79		8_O_methylurdamycin_A	Not Docked	Not Docked

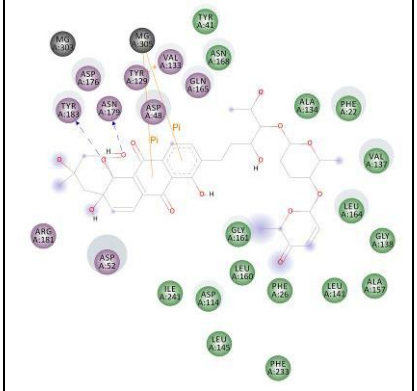
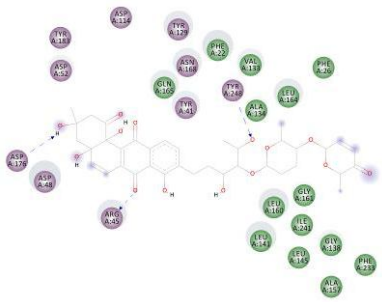
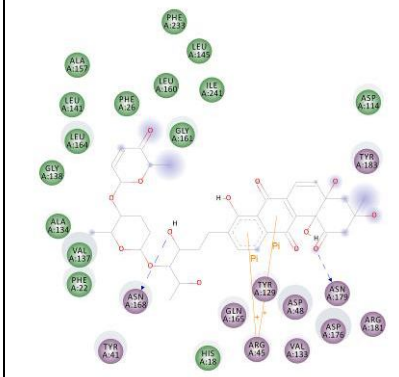
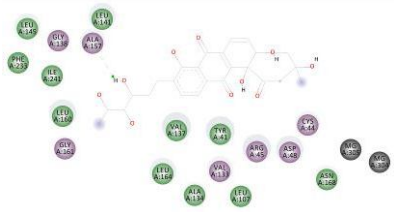
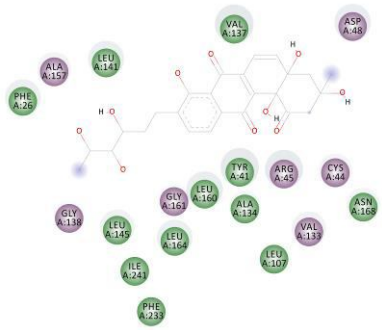
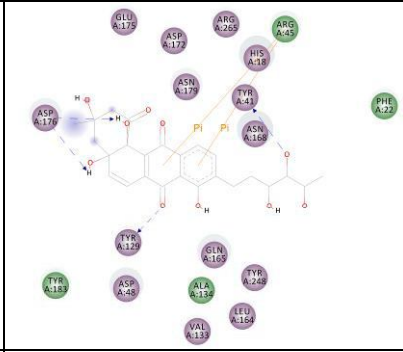
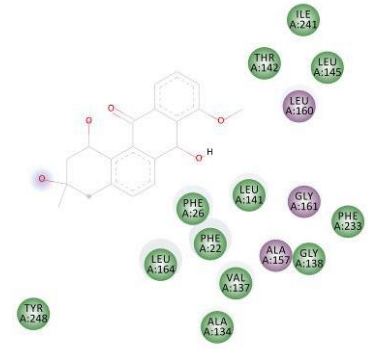
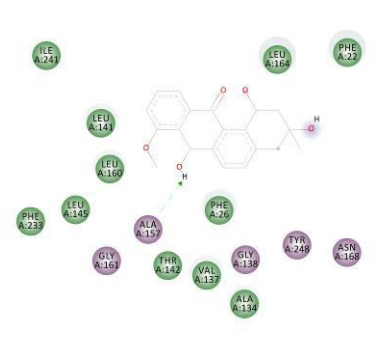
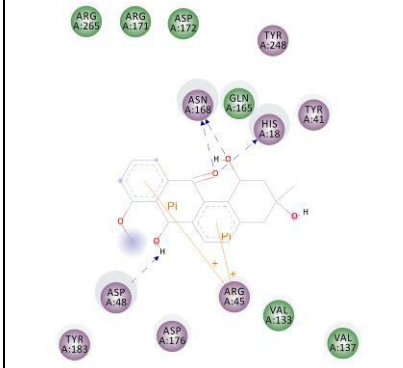
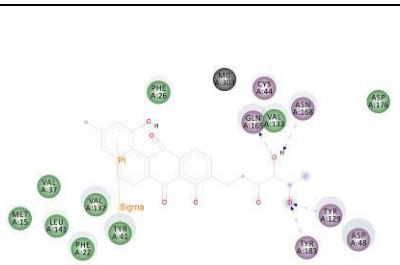
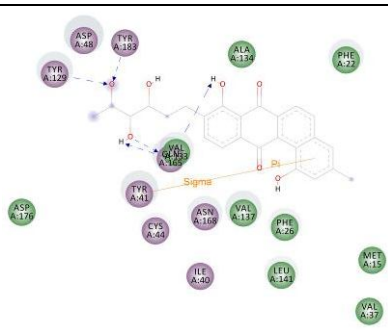
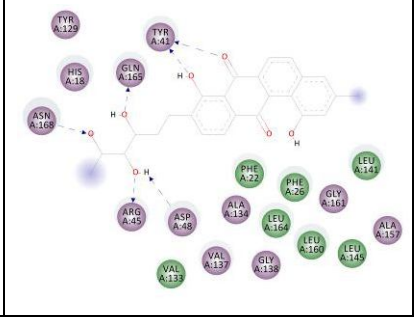
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
80	Seitomycin			
81	Tetrangulol methyl ether			
82	SM_196B (1b)			
83	Saquayamycin_A1			

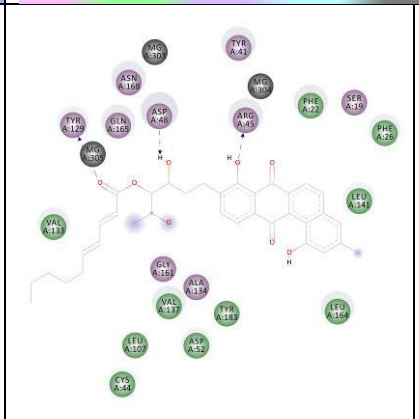
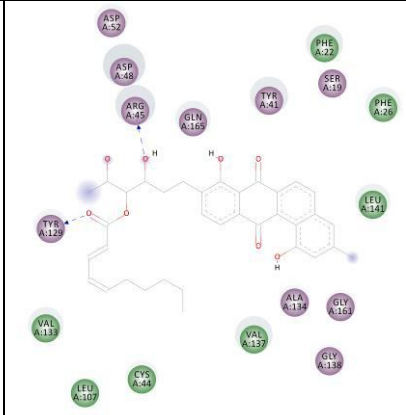
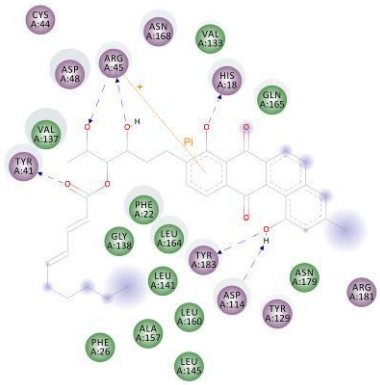
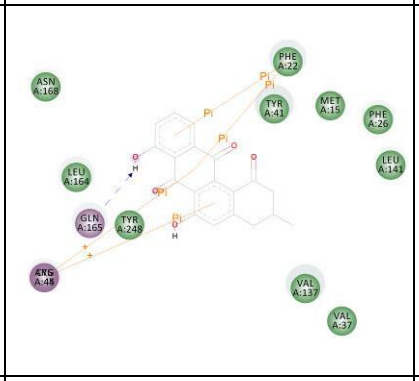
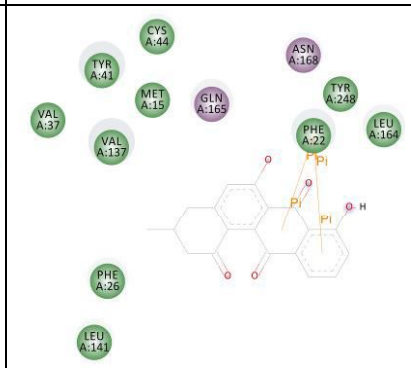
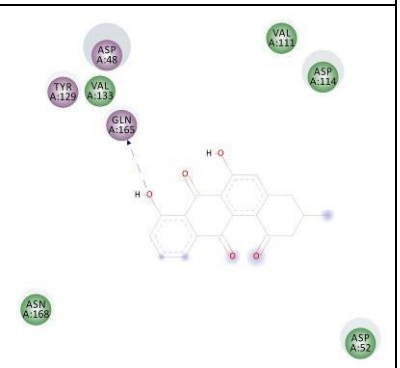
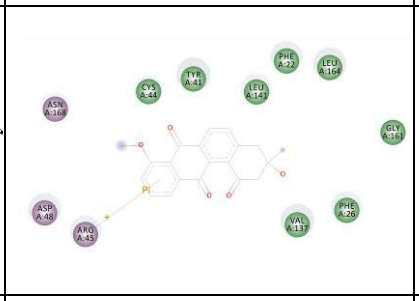
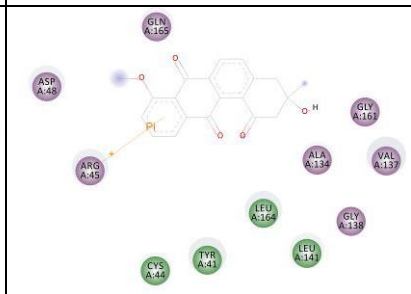
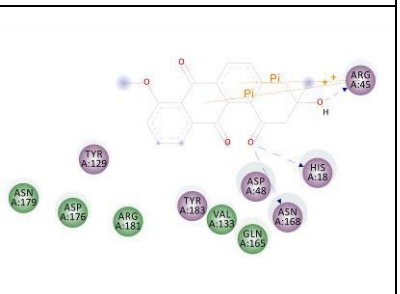
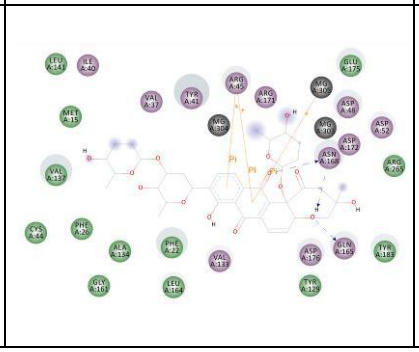
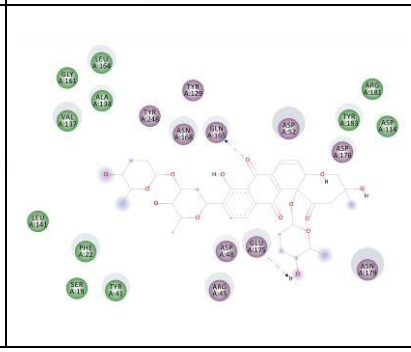
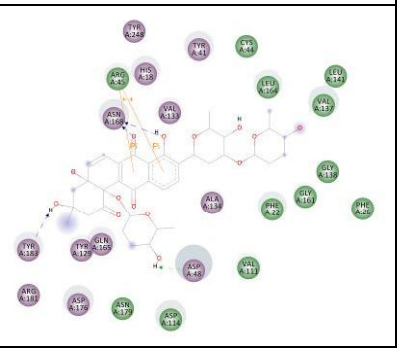
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
84	A_7884			
85	Aquamycin			
86	SM_196A			
87	C104_Aglycon			

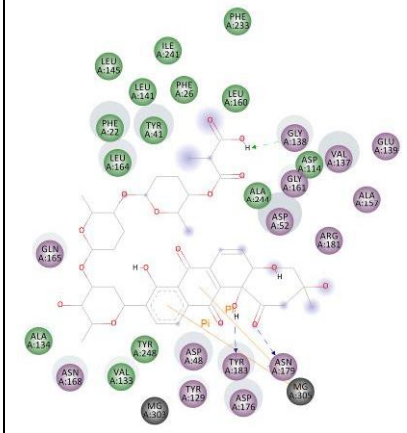
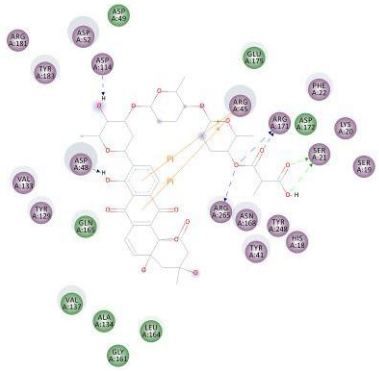
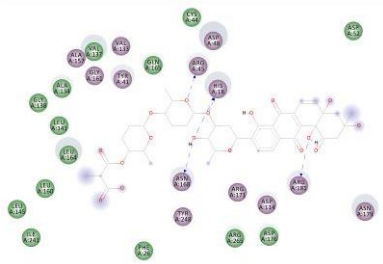
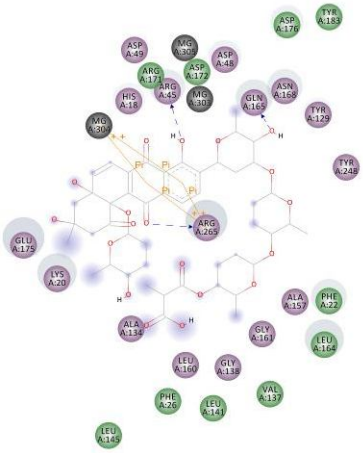
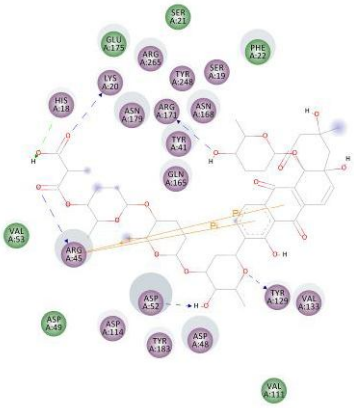
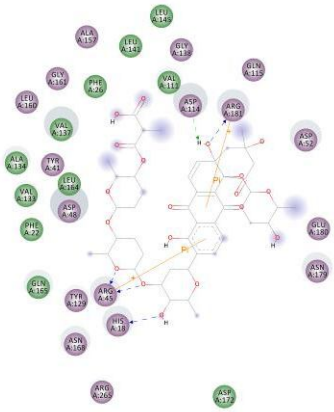
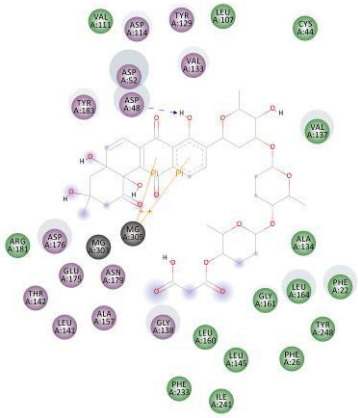
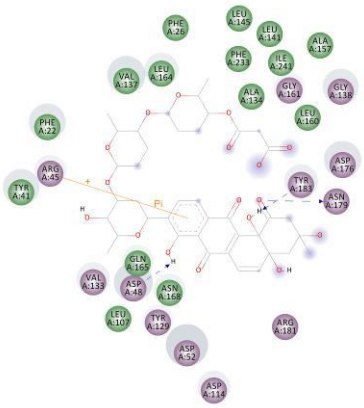
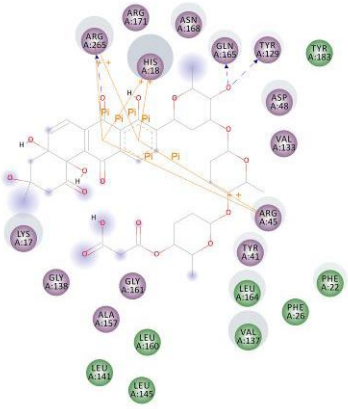
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
88	C104			
89	3_Deoxyrabelomycin			
90	6_Deoxy_8_O_methylrabelomycin			
91	Aggreticin (OM-4842)			

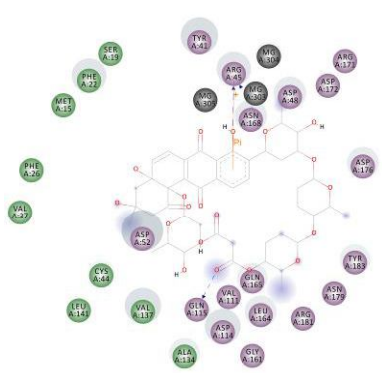
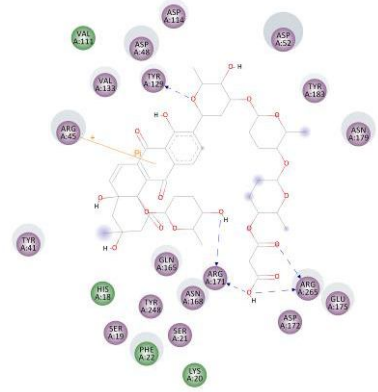
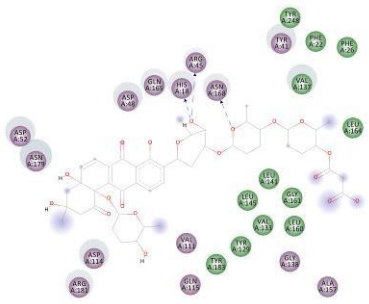
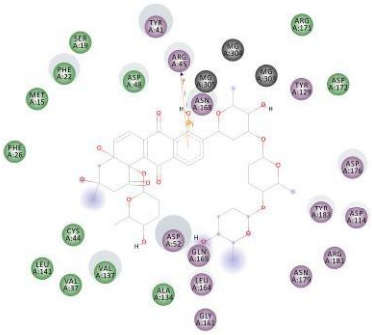
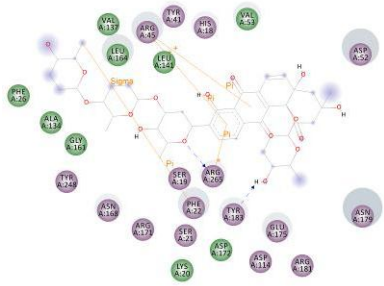
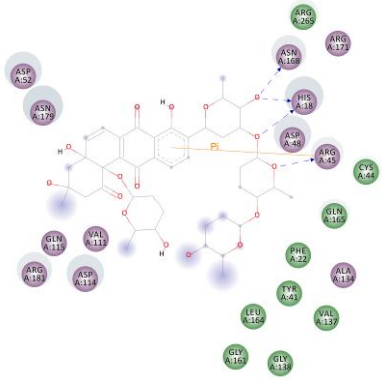
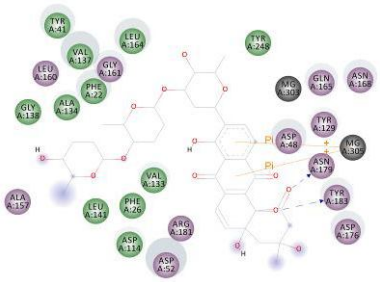
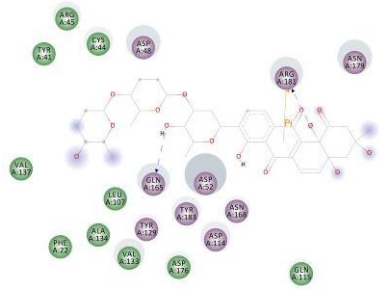
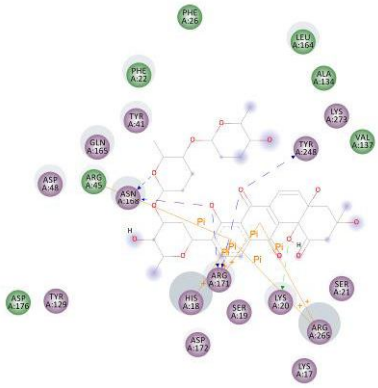
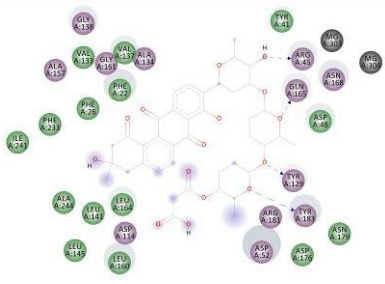
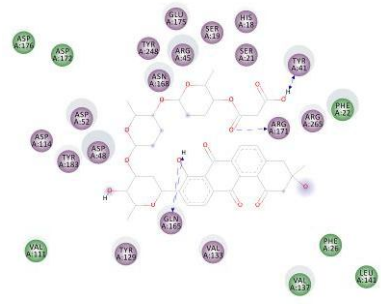
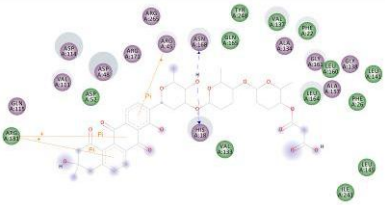
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
92	BA_12100B			
93	BA_12100C			
94	BA_12100D			

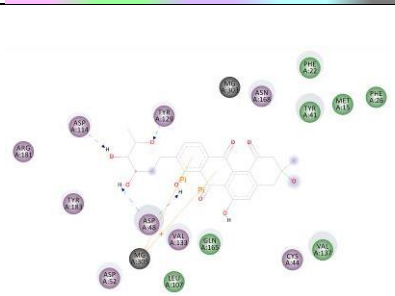
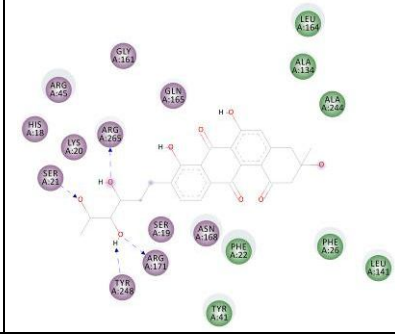
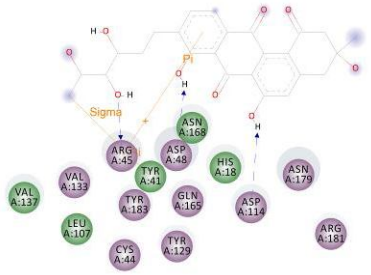
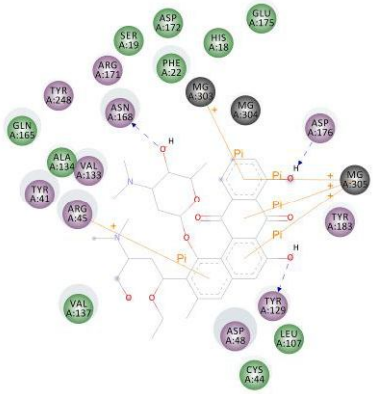
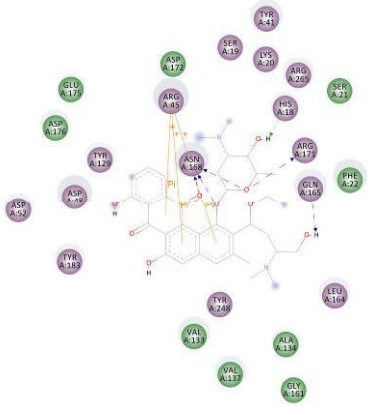
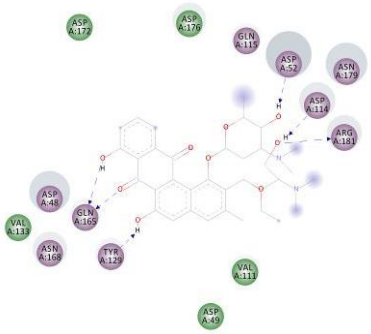
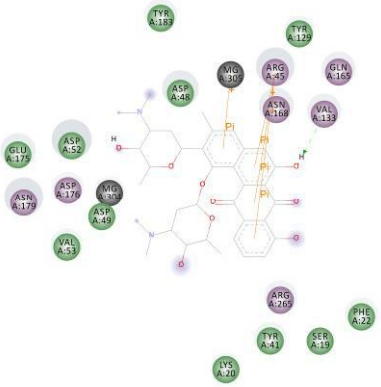
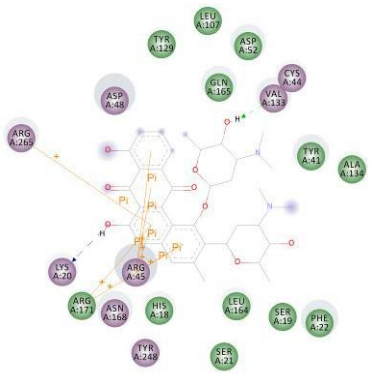
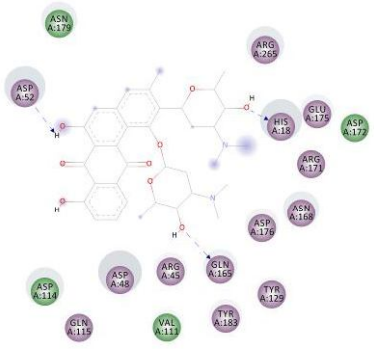
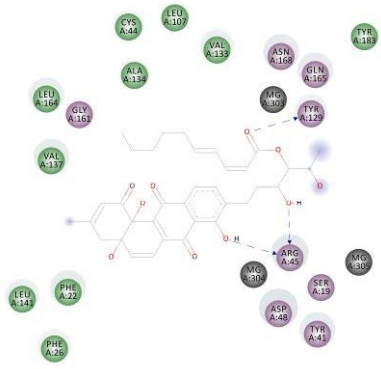
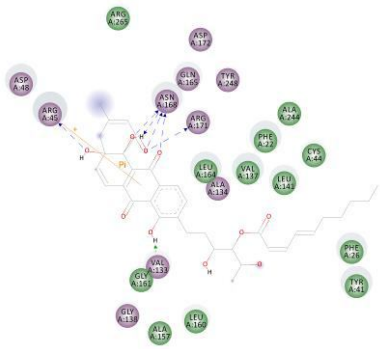
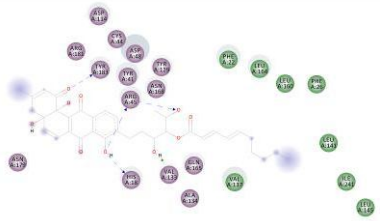
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
95	BA_12100E			
96	BA_12100Z1			
97	BA_12100Z2			
98	BA_12100Z3			

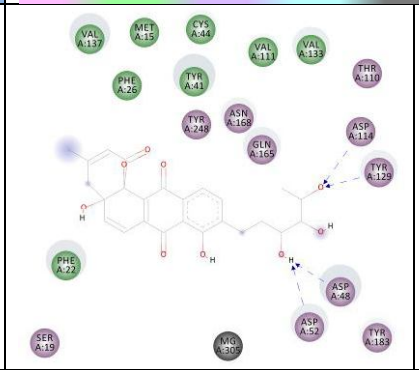
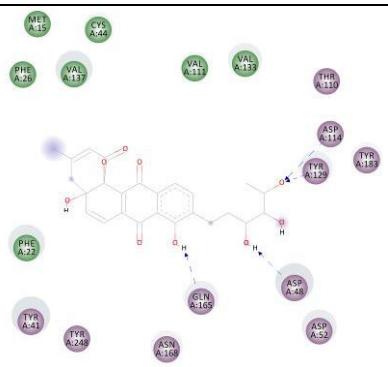
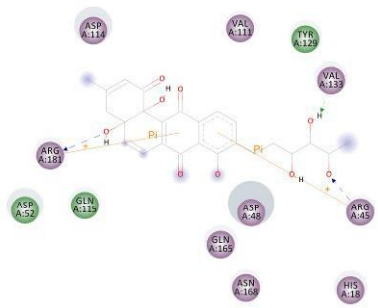
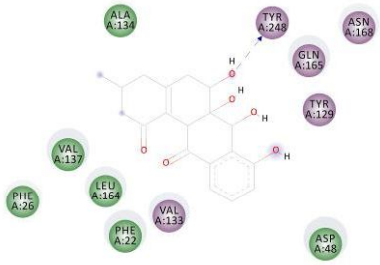
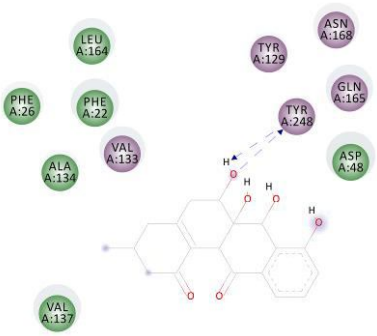
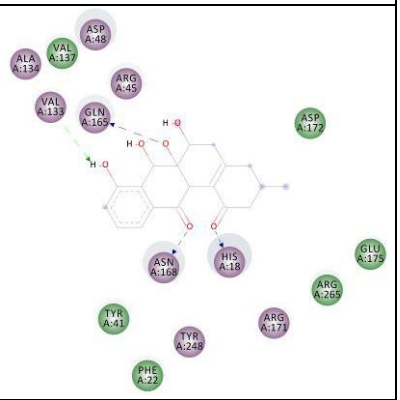
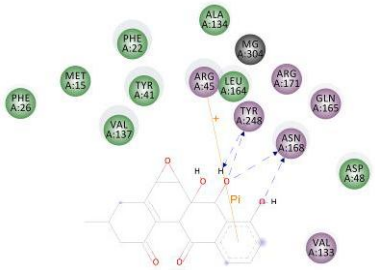
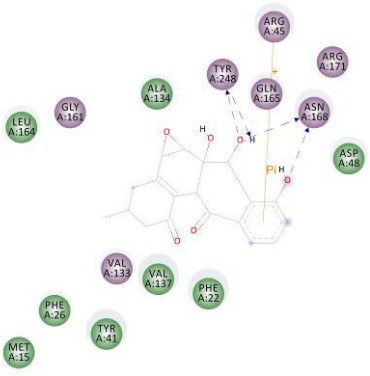
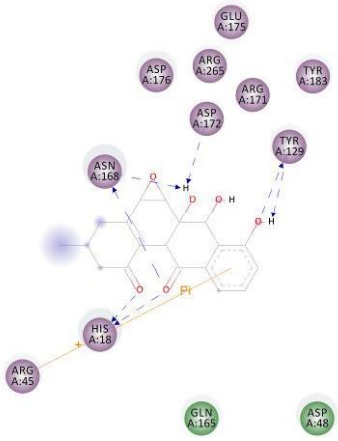
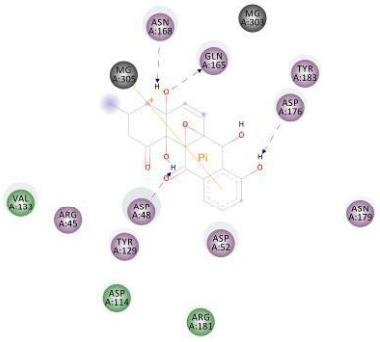
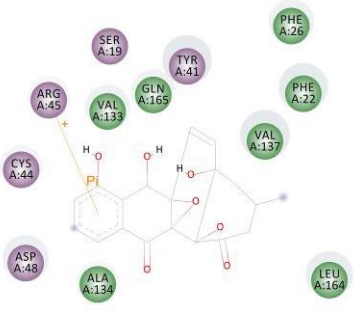
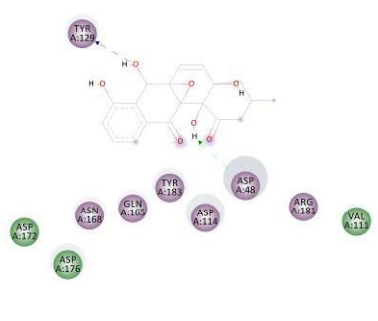
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
99	BA_12100MY_1			
100	Benzanthrin_A			
101	Benzanthrin_B			
102	Capoamycin			

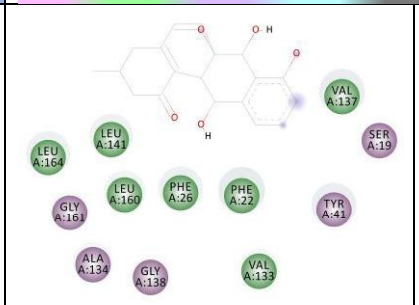
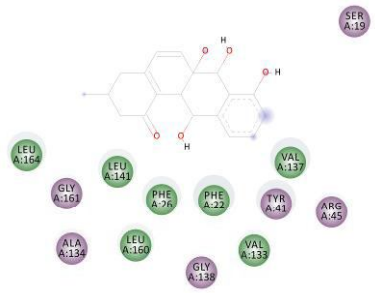
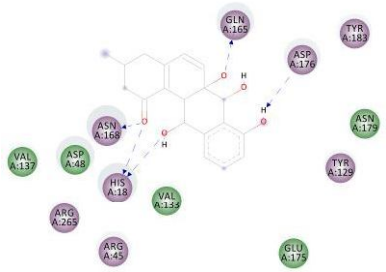
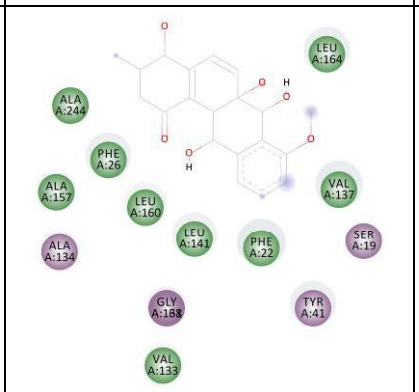
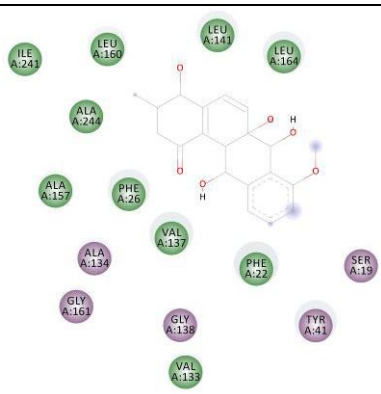
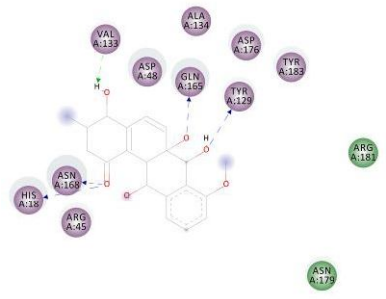
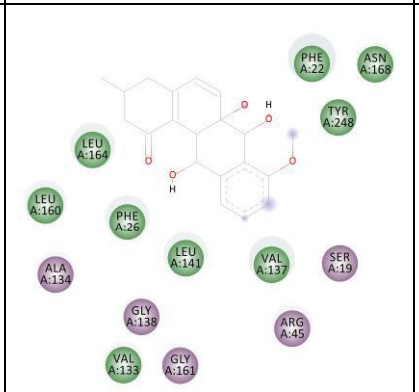
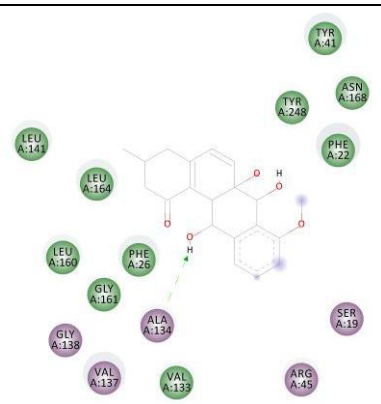
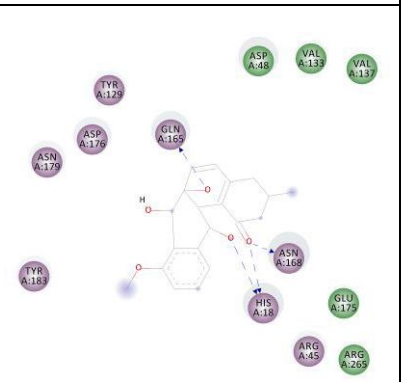
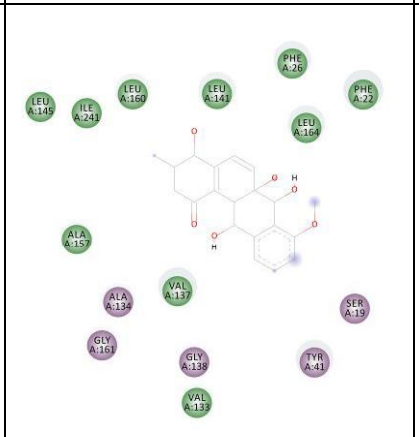
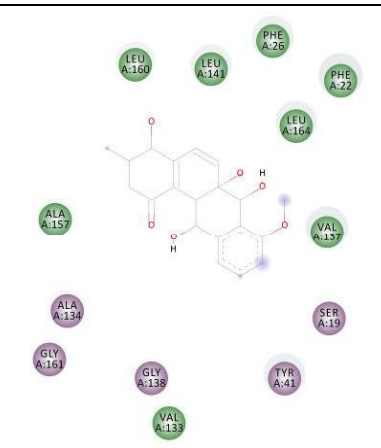
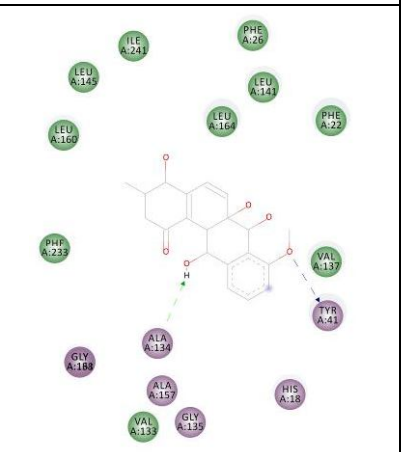
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
103	De_O_acylcapoamycin			
104	Elmycin_A			
105	Elmycin_B			
106	Elmycin_C			

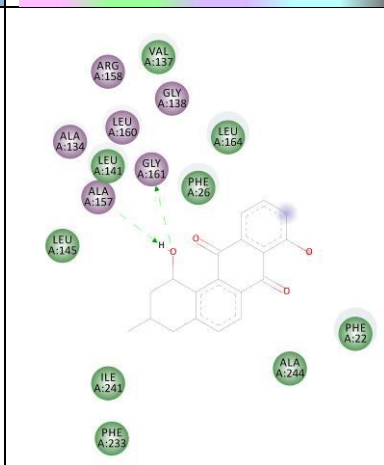
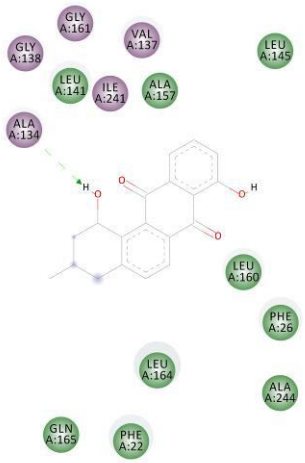
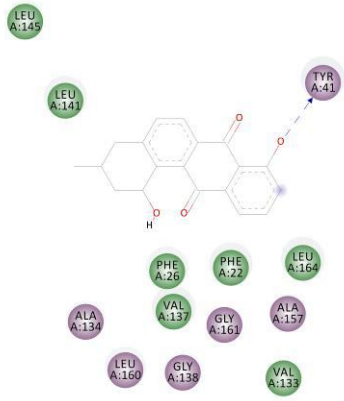
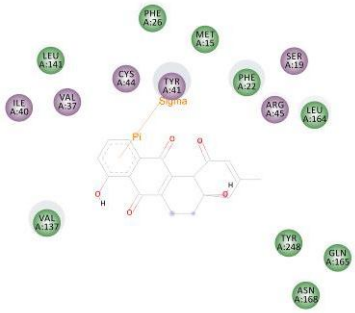
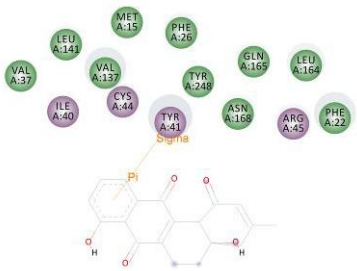
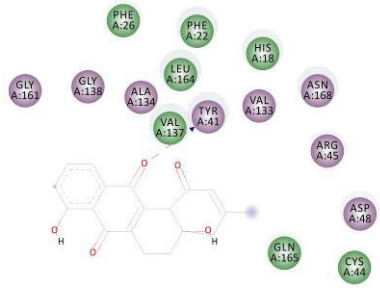
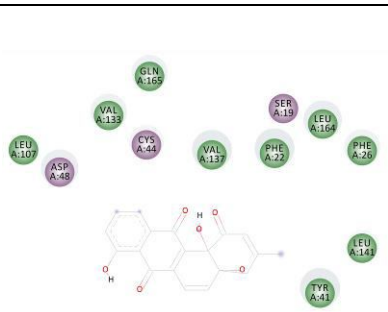
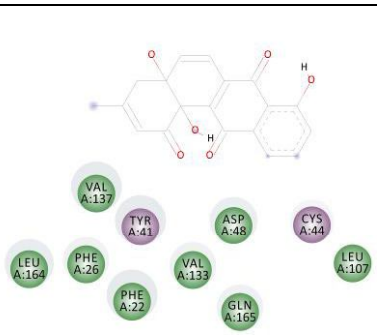
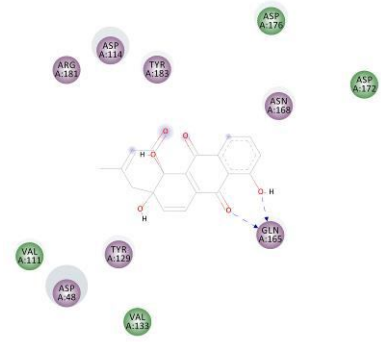
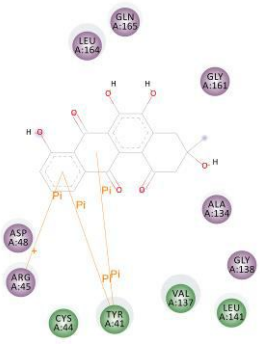
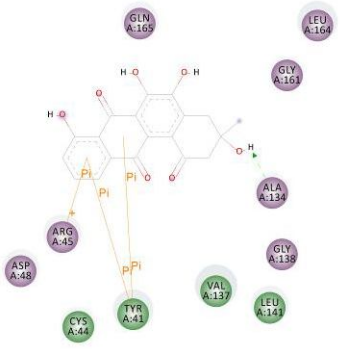
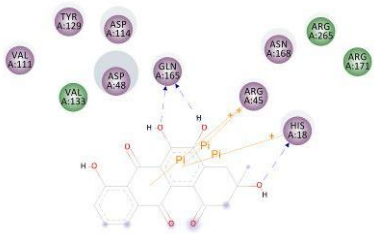
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
107	Elmycin_D			
108	Elmycin_E			
109	X_14881_B			
110	X_14881_D			

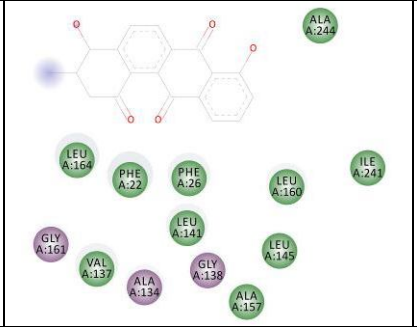
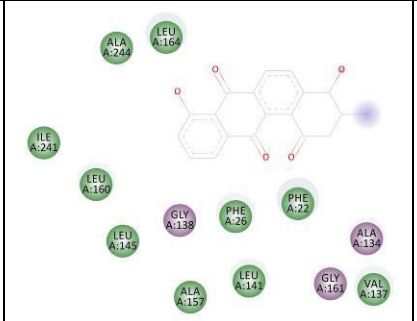
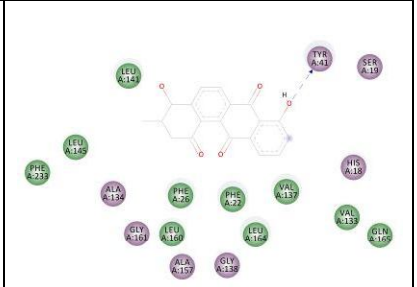
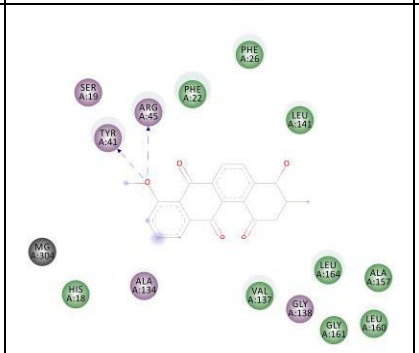
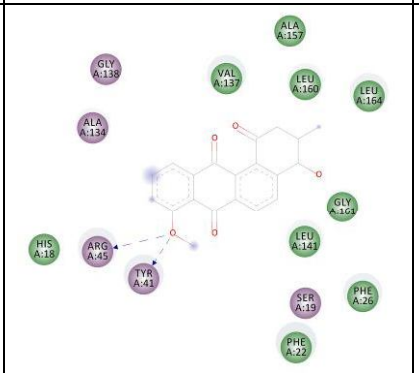
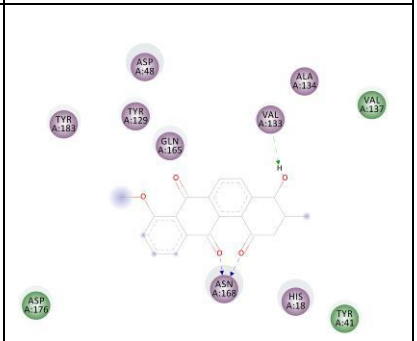
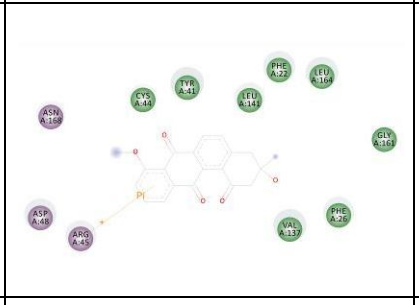
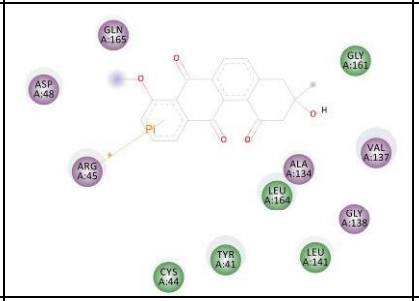
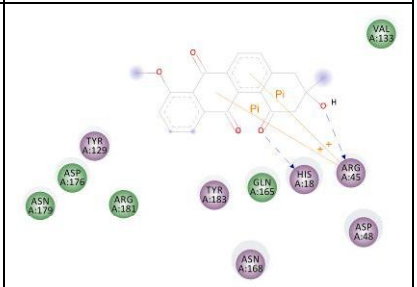
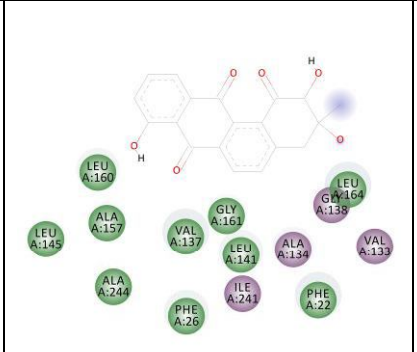
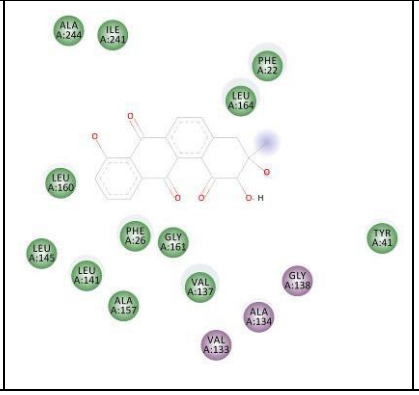
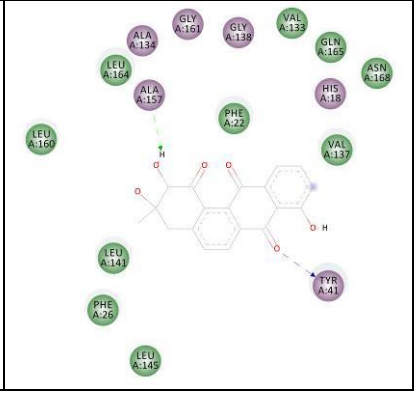
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
111	Emycin_A			
112	SF_2315_A			
113	SS_228Y			
114	Fridamycin_C			

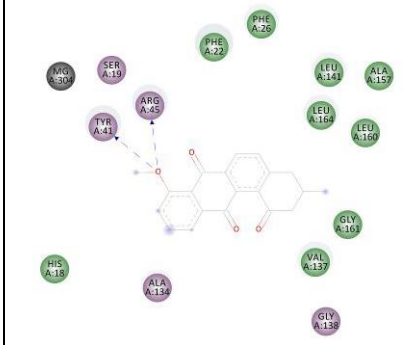
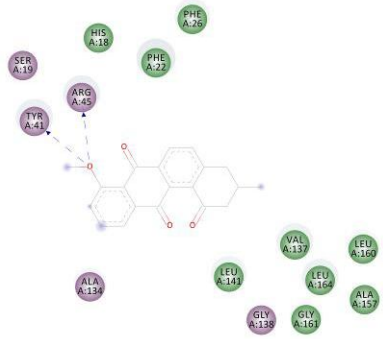
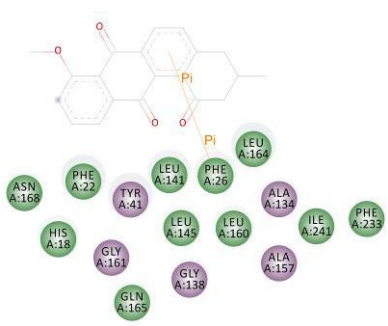
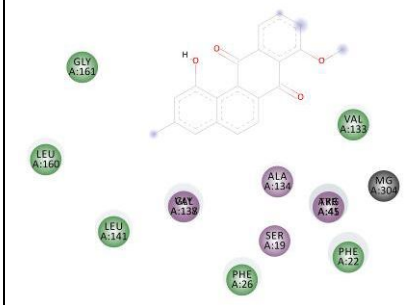
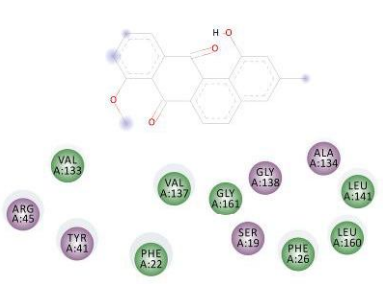
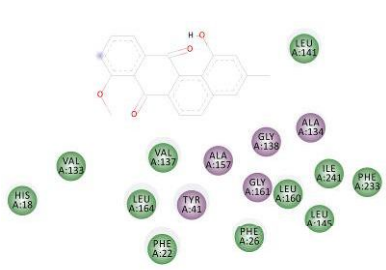
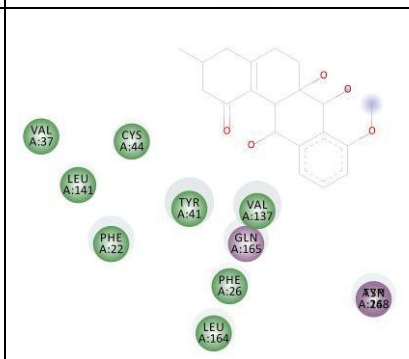
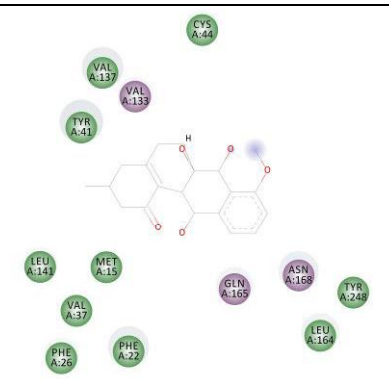
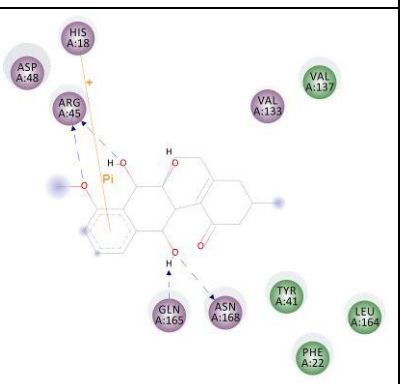
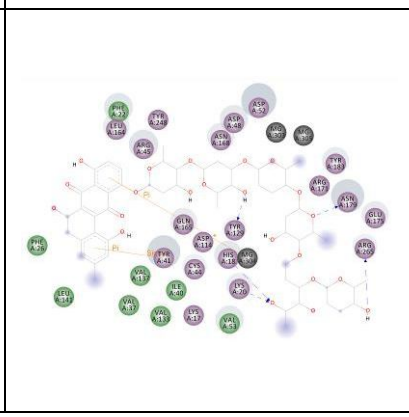
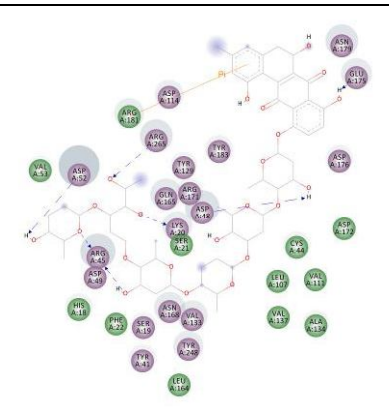
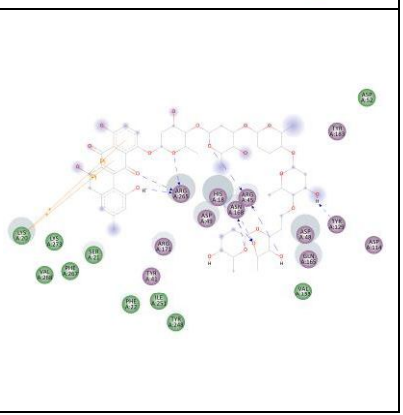
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
115	Fujianmycin_A			
116	Fujianmycin_B			
117	MM_47755			
118	PD116779			

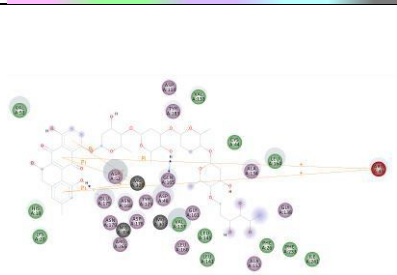
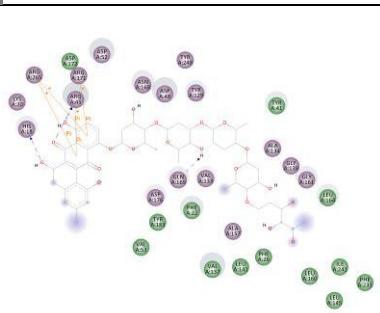
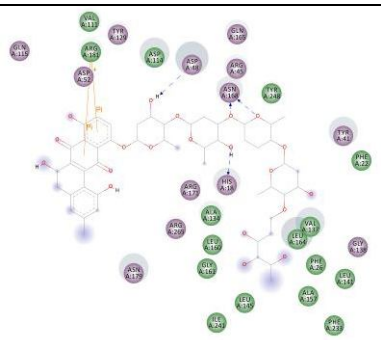
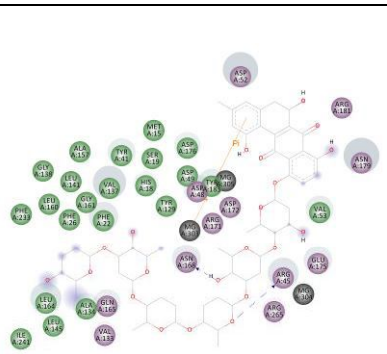
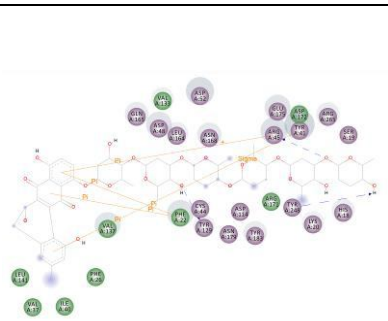
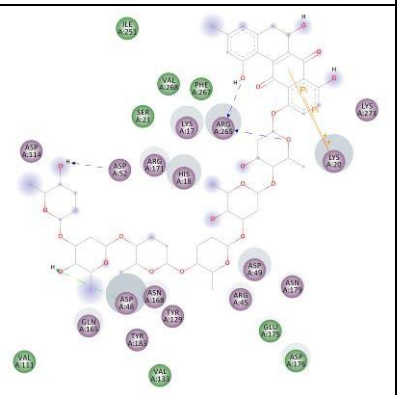
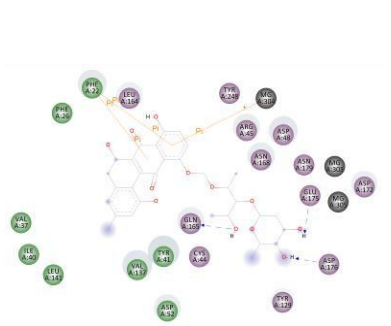
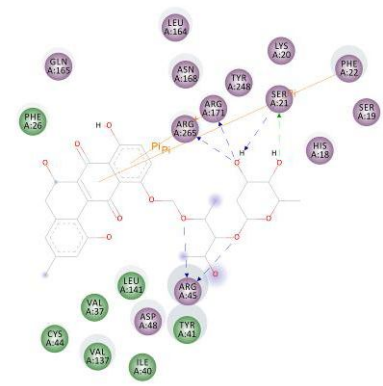
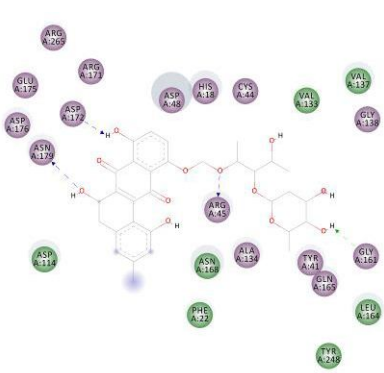
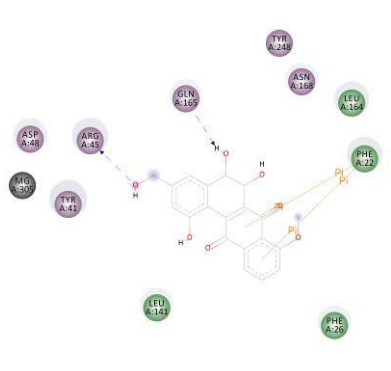
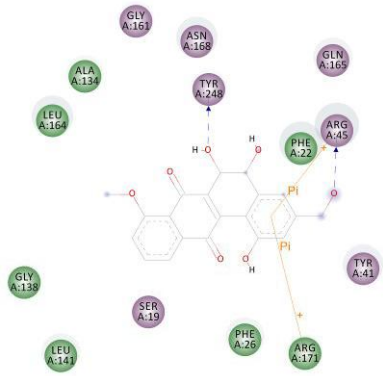
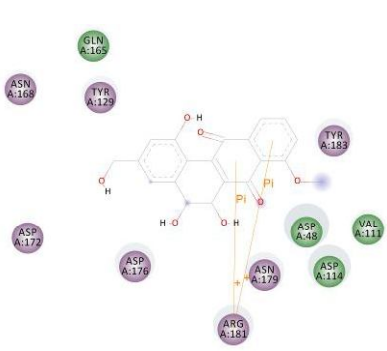
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
119	X_14881_C			
120	X_14881_E			
121	X_14881_A			
122	Landomycin_A 122			

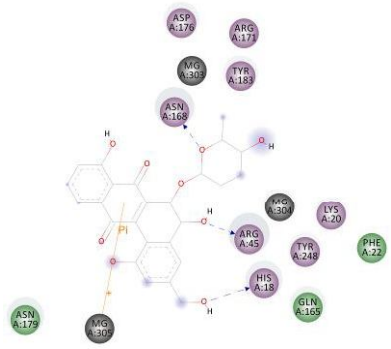
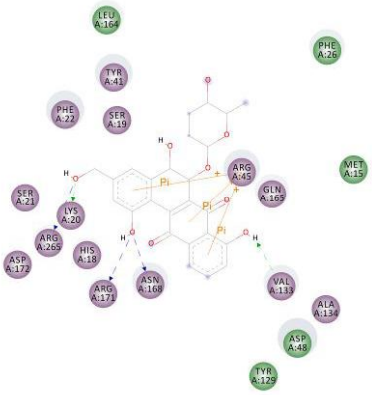
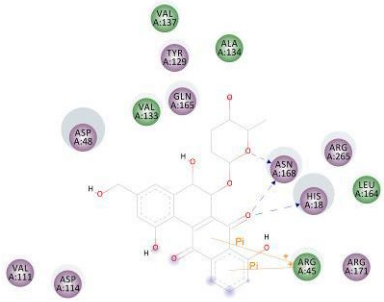
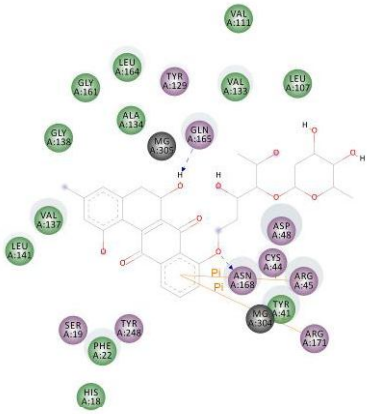
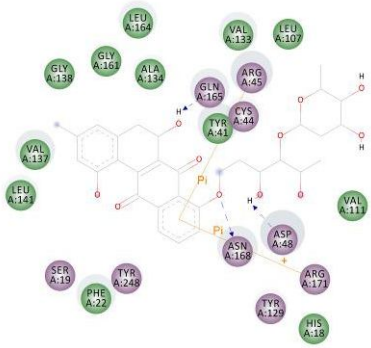
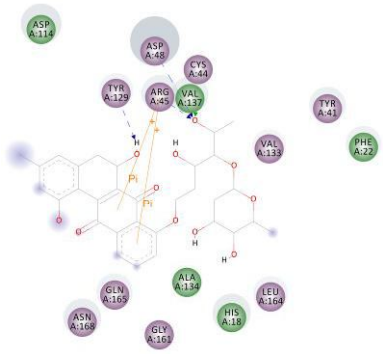
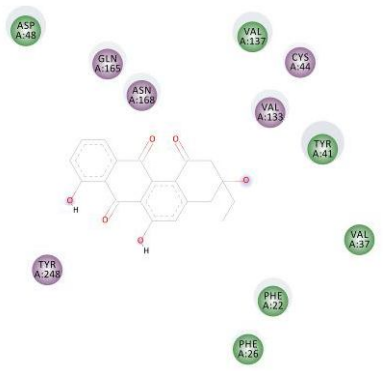
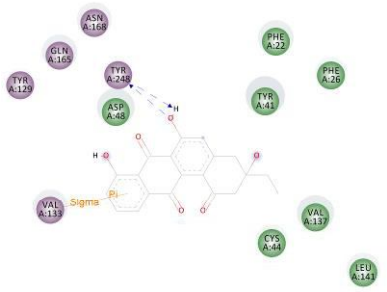
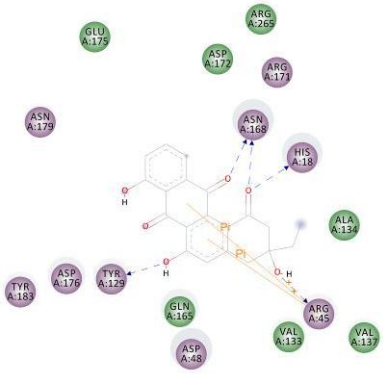
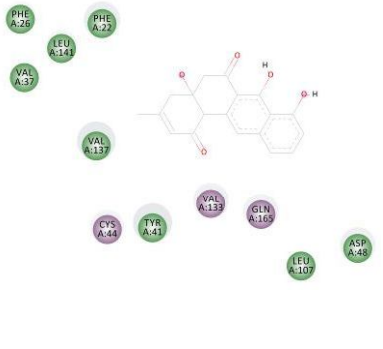
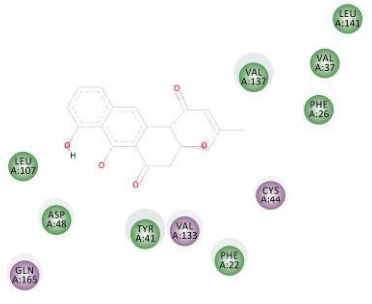
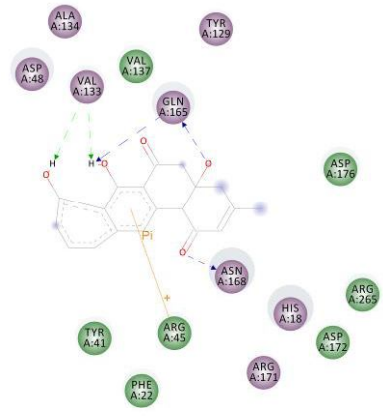
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
123	Landomycin_B			
124	Landomycin_C			
125	Landomycin_D			
126	PD116740			

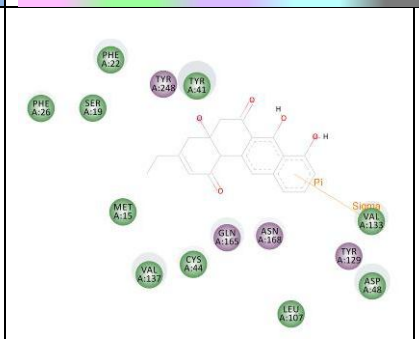
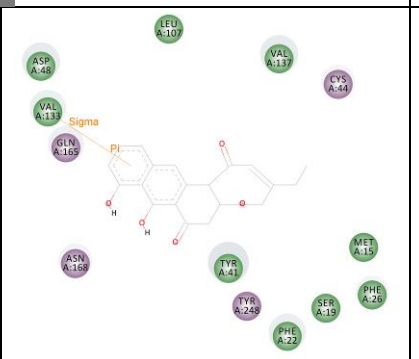
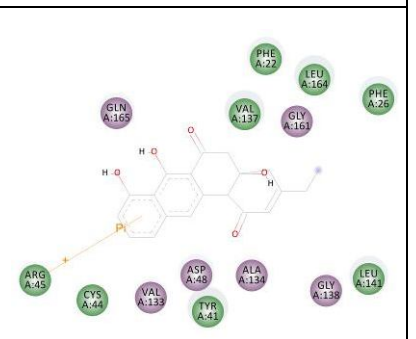
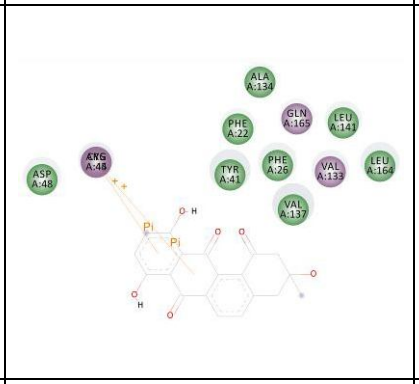
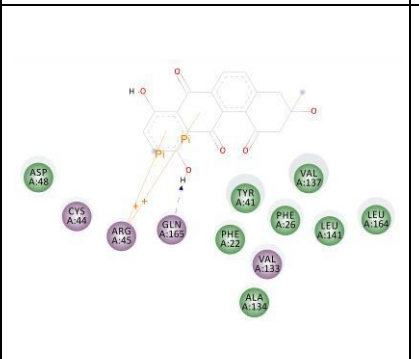
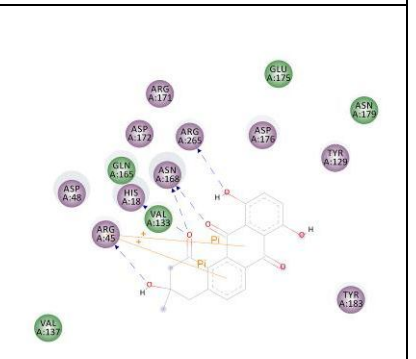
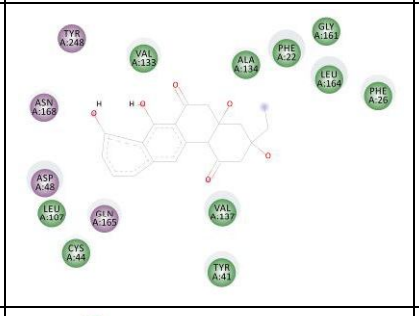
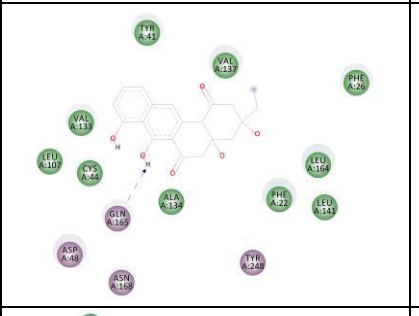
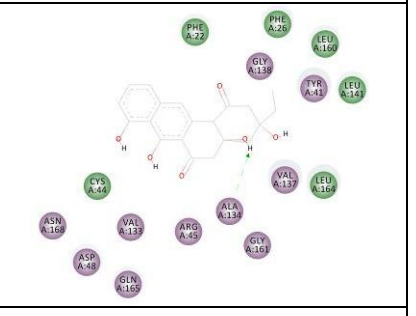
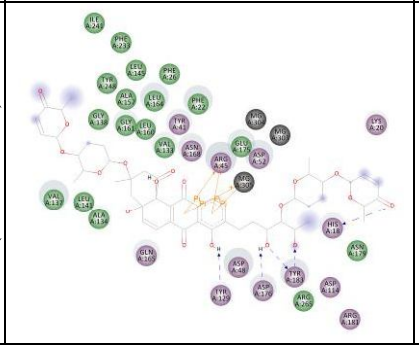
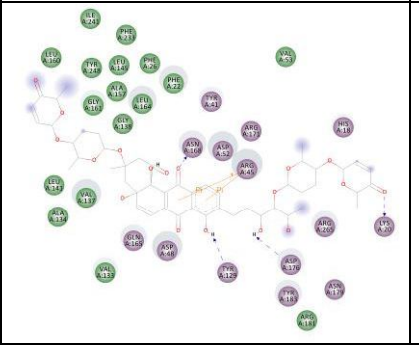
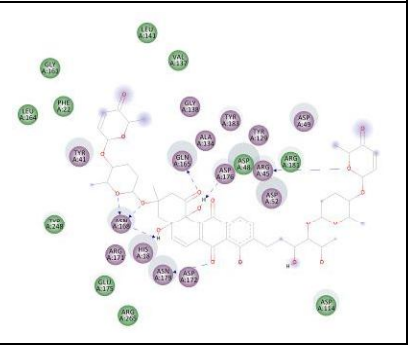
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	**Covalent Bond, Water, Metal**
127	TAN_1085			
128	Landomycin_F			
129	Homorabelomycin			
130	Prejadomycin			

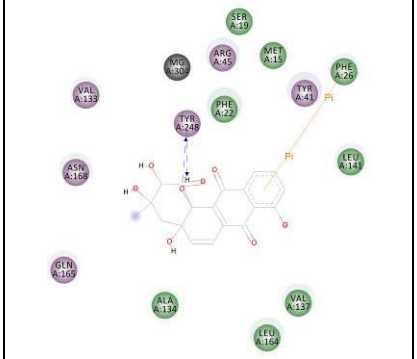
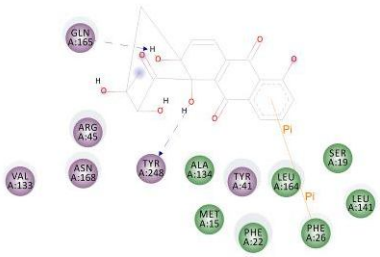
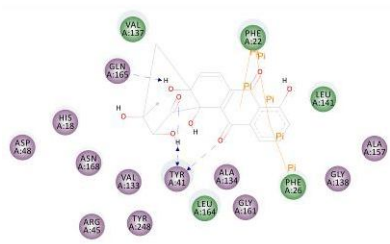
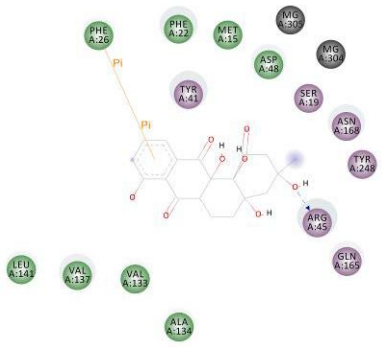
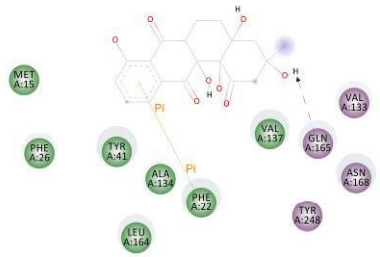
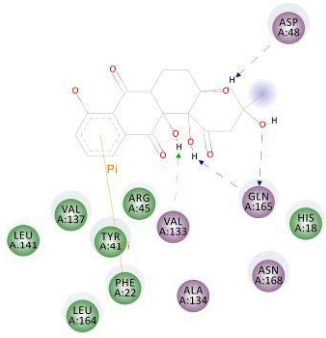
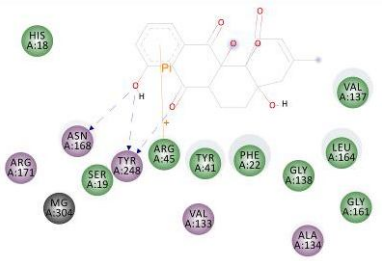
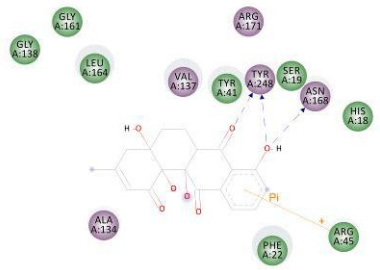
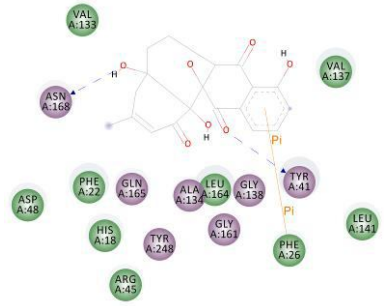
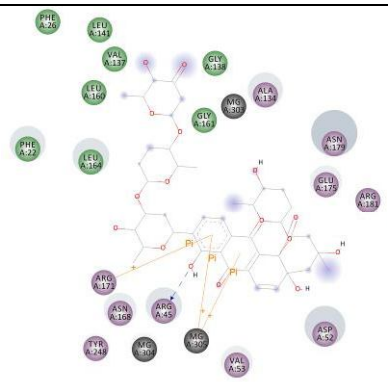
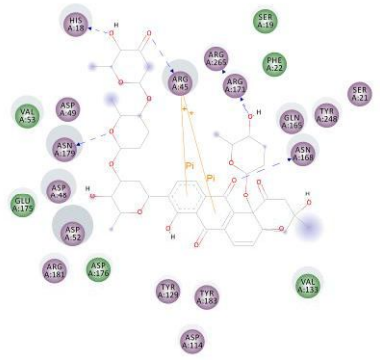
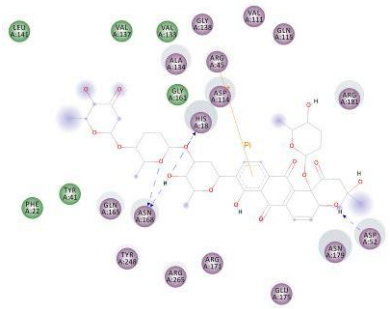
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
131	Homoprejadomycin			
132	11_HydroxyTetrangomycin			
133	Homo_UWM6			
134	PI_1894B (Vineomycin A) (OS-4742A1)			

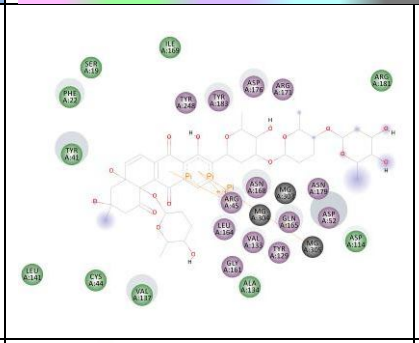
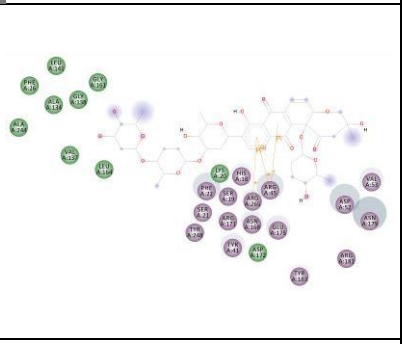
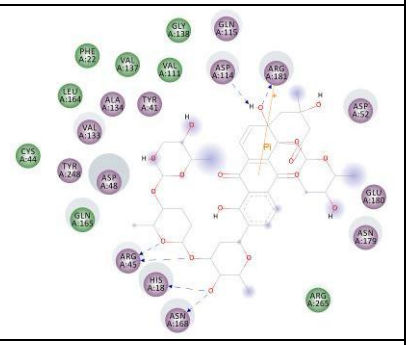
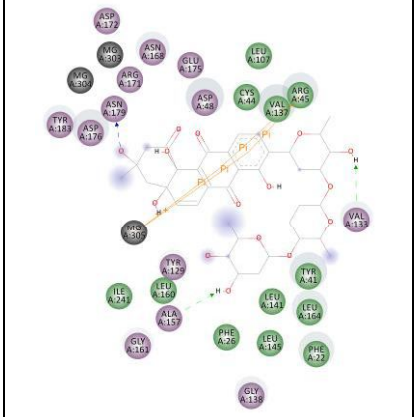
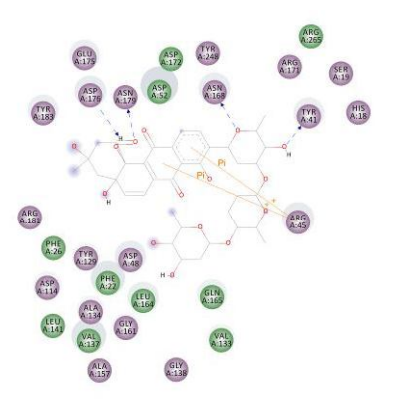
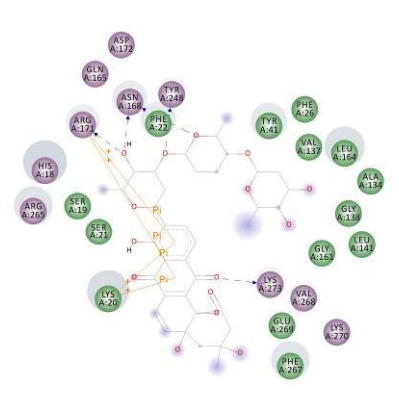
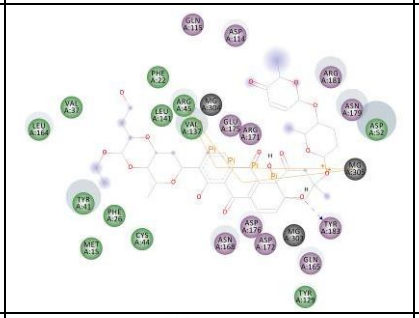
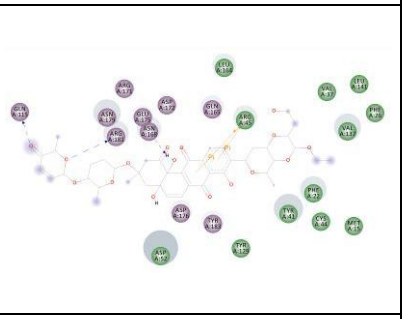
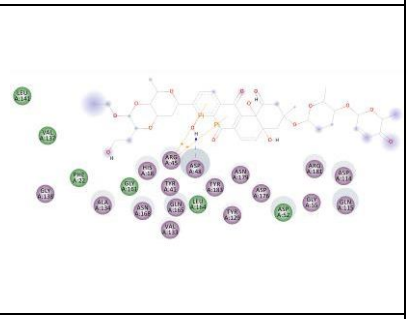
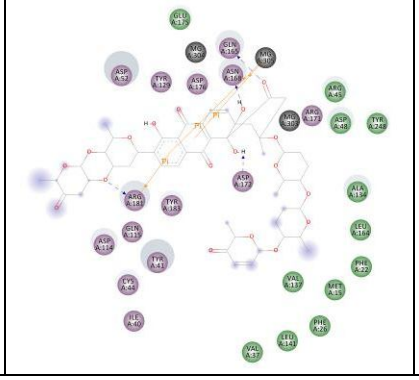
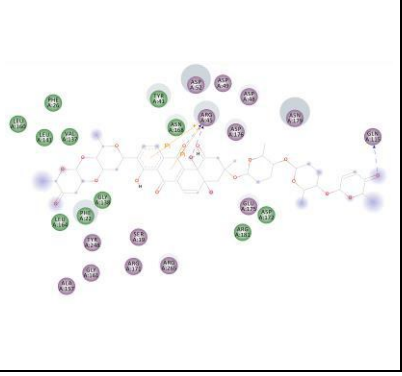
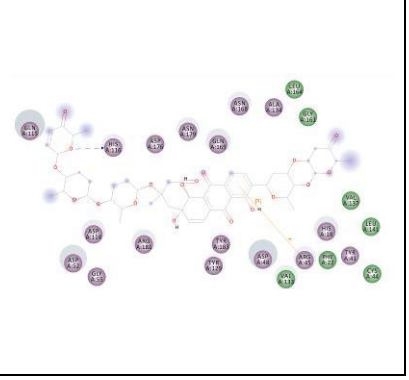
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
135	Yoronomycin			
136	Urdamycin_I			
137	Urdamycin_J			
138		Urdamycin_K	Not Docked	Not Docked
139	Kerriamycin_A			

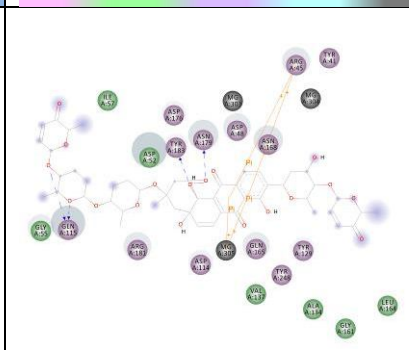
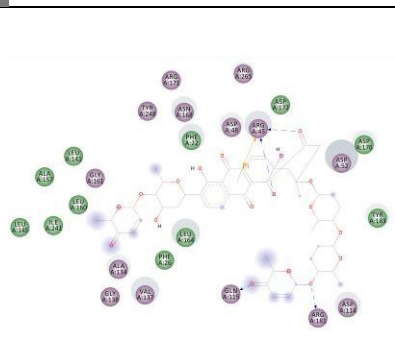
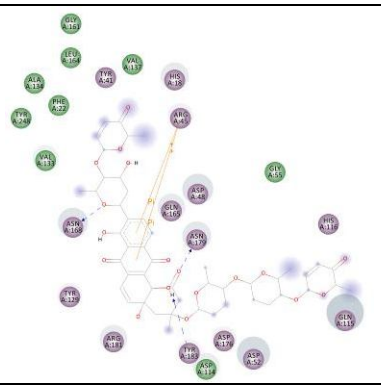
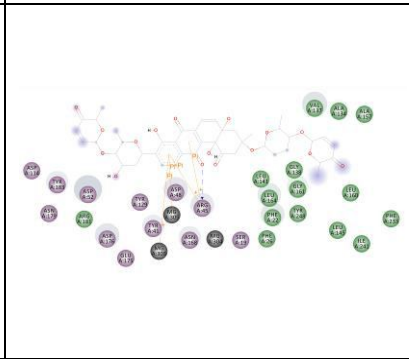
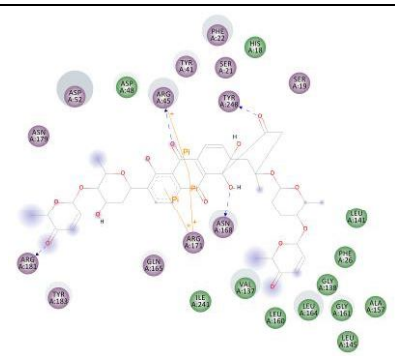
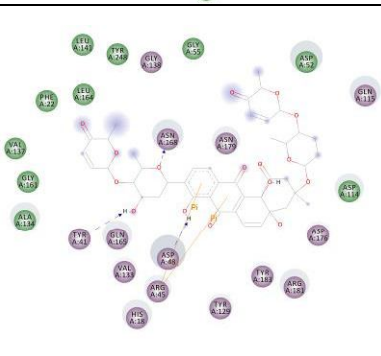
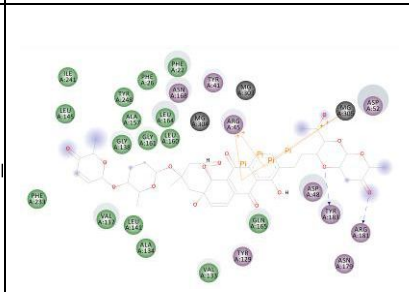
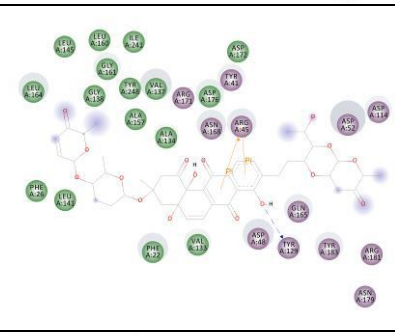
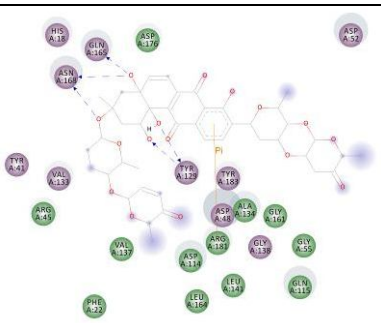
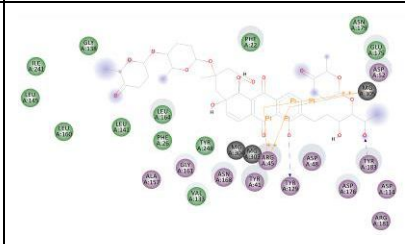
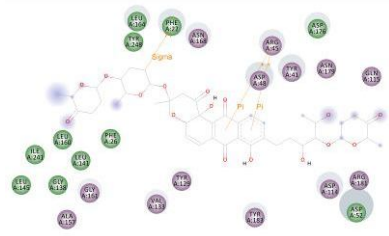
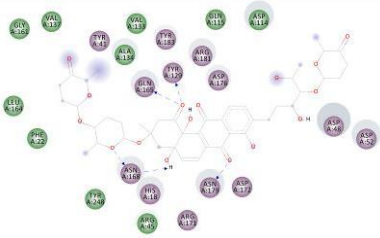
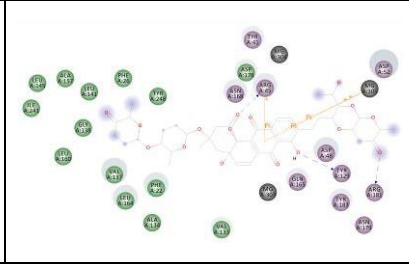
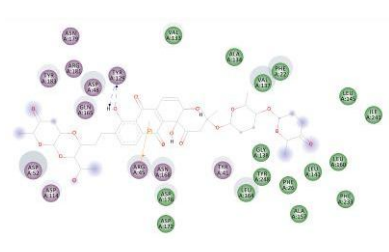
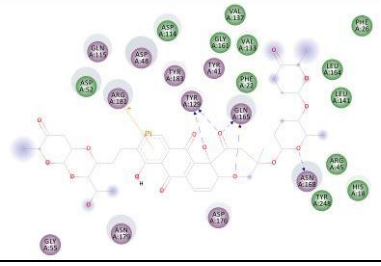
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
140	Kerriamycin_B			
141	Kerriamycin_C			
142	PI_083			
143	PI_085			

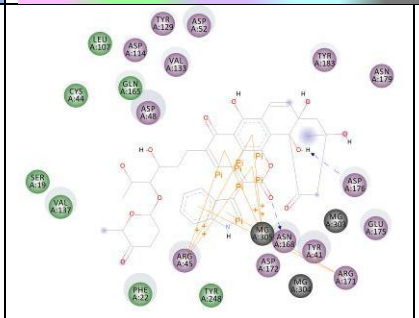
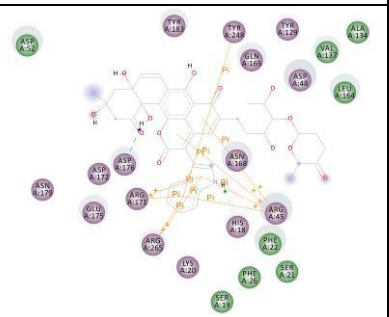
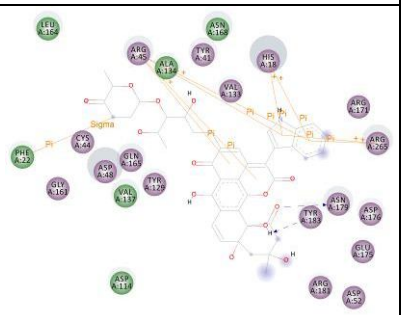
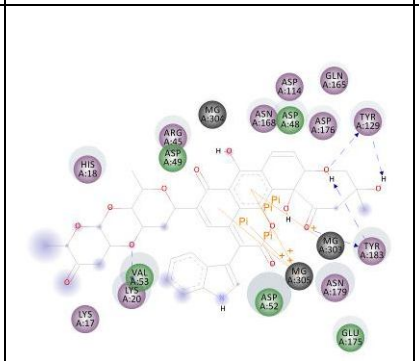
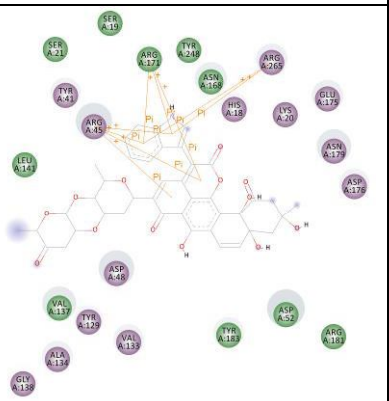
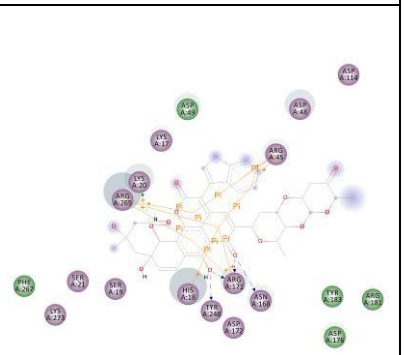
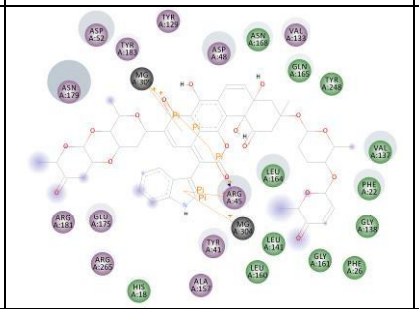
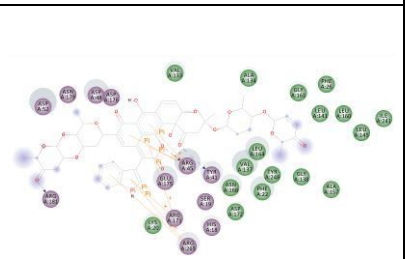
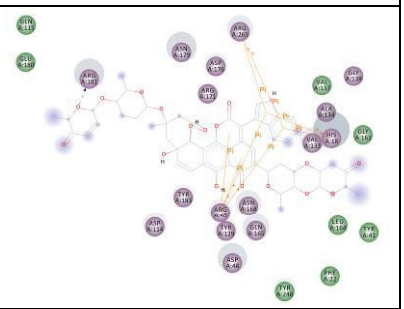
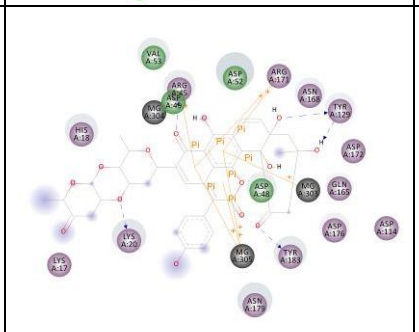
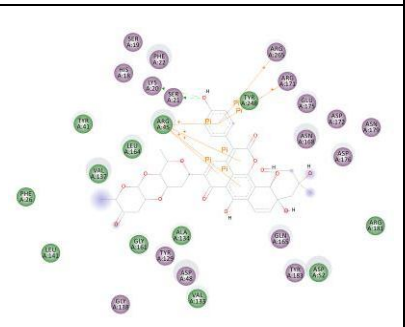
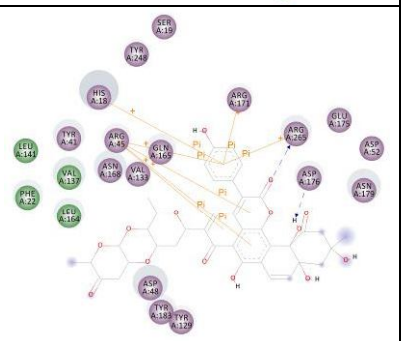
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
144	PI_087			
145	Saquayamycin_A			
146	Saquayamycin_B 146_13.2			
147	Saquayamycin_C			
148	Saquayamycin_D			

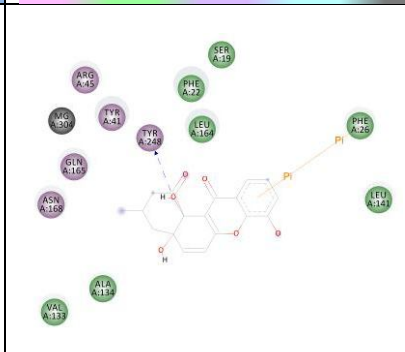
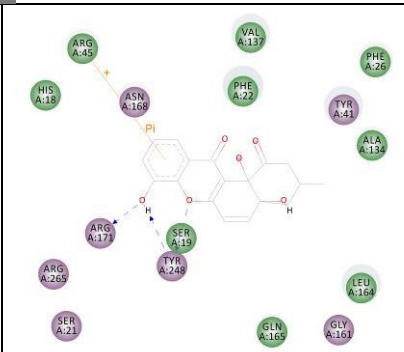
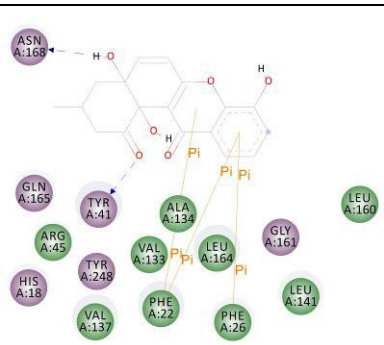
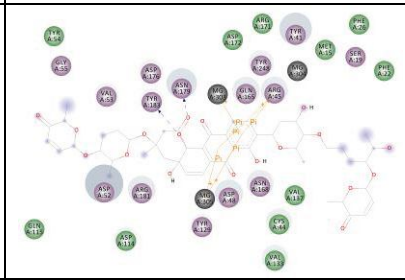
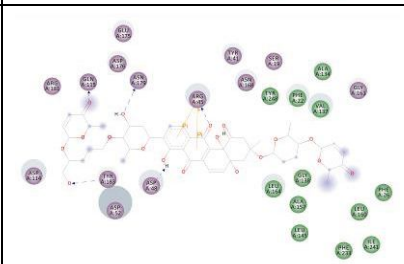
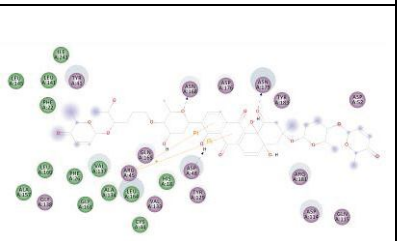
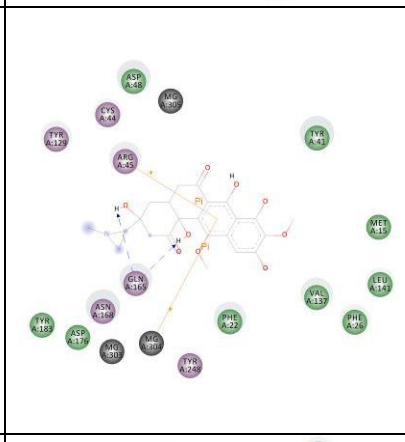
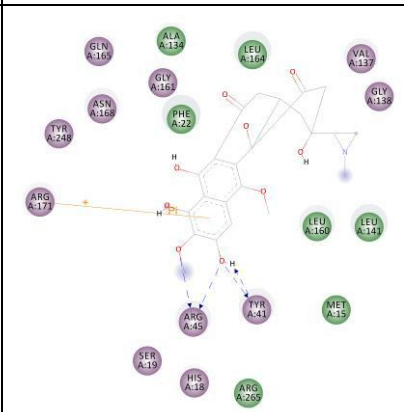
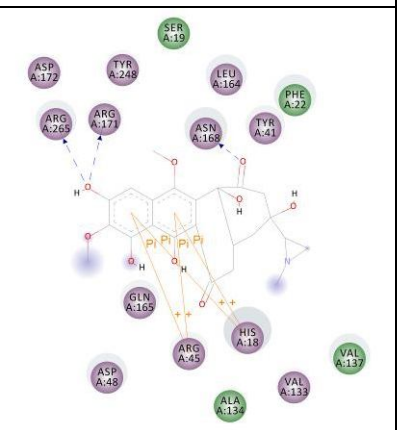
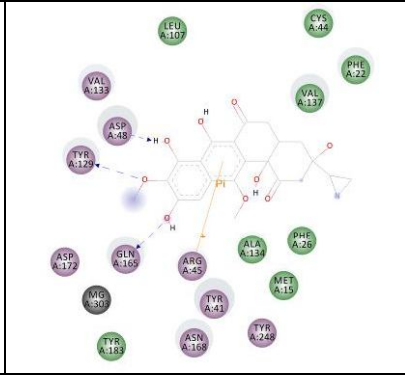
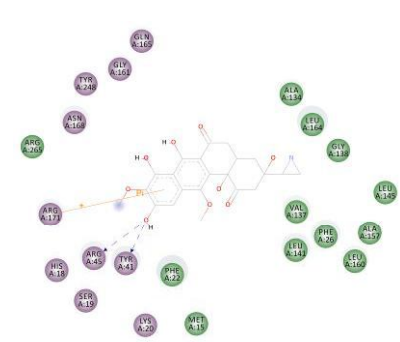
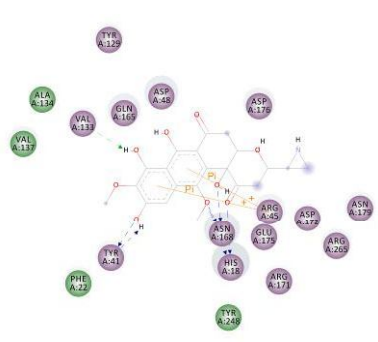
APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
149	Saquayamycin_K1			
150	Saquayamycin_K2			
151	Saquayamycin_K4			
152	Saquayamycin_K7			
153		Saquayamycin_Z	Not Docked	Not Docked

APPENDIX IV

The 2D Interactions Between Docked Angucycline Group Antibiotics (Ligands) with Proteins (continue)

Code	Name	3W7F With MG	3W7F Without MG	3ACW
			Electrostatic, Van der Waals,	Covalent Bond, Water, Metal
154	Retymicin			
155	Vineomycin_A1			
156	Azicemicin_A			
157	Azicemicin_B			

Curriculum Vitae

Personal Information:

Name:	Al-Bustany, Hazem Abbas Tofiq
Permanent Address:	Erbil – Rasty Q. – St. 150/3/566
Date of Birth:	19th Feb., 1975
Nationality:	IRAQI
Marital Status:	Marred with one child
Blood Group:	B^+
E-mail Address:	albustany@gmail.com
Office Address:	College of Medicine, Hawler Medical University, Erbil, IRAQ
Passport No.:	A2345211

Graduation and Degrees:

2001 – 2002 (B.Sc. in Biology) College of Science, Dept. of Biology, Salahaddin University, Erbil-Iraq.

1996 – 1997 (Diploma in Physiotherapy) Erbil Technical Institute, Medical Part, Dept. of Physiotherapy.

1994 – 1995 High School Certificate, Baccalaureate Exam. for Secondary Schools (Scientific Section).

Certifications:

Jul. 2013 Certificate of International Computer Driving License (ICDL Course) Started from 03/06/2013 to 08/07/2013, Salahaddin University-Erbil, Iraq.

Sep. to Dec.2012 Microsoft Office Specialist (M.O.S.) Courses: MS-Word 2010, MS-Excel 2010, MS-Access 2010, MS-Power Point 2010, MS-Outlook 2010, and Comp TIA Network+, certificate from Information Technology Academy (ITA) KRG, Iraq.

Summary of the relevant works:

1- College of Medicine, Hawler Medical University, Erbil-IRAQ.
- ·From 11/2006 till now, Senior Biologist in Dept. of Anatomy & Histology\ Working in lab of Medical Biology as a Demonstrator.

2- Presidency of Hawler Medical University, Erbil-IRAQ.
- .From 11/2005 to 10/2006, Biologist.

3- College of Nursing, University of Salahaddin, Erbil-IRAQ.
- ·From 2/2004 to 11/2005, Biologist \ Working in labs of Biology, Physiology, Biochemistry as a Demonstrator.

4- Erbil Technical Institute\ Medical Part \ Dept. of Physiotherapy, Erbil-IRAQ.
- ·From 7/2003 to 1/2004, Assistant Biologist\ Working in labs of Physiotherapy, Biology, and Physiology.

Language skills:

Mother Tongue Kurdish, fluency in English, Arabic, & Turkish languages.

Languages	Reading	Writing	Speaking
English	Excellent	Excellent	Good
Arabic	Excellent	Excellent	Excellent
Turkish	Good	Fair	Good

T.C.
DİCLE ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ
YÜKSEK LİSANS / DOKTORA TEZ ÇALIŞMASI İNTİHAL RAPORU FORMU

ÖĞRENCİ BİLGİLERİ	
ADI VE SOYADI	Hazem Abbas Tofiq AL-BUSTANY
ÖĞRENCİ NO	13801303
EĞİTİM – ÖĞRETİM YILI	2015-2016
YARIYIL	☒ Güz ☐ Bahar
ANABİLİM DALI	Biyoloji
PROGRAM	☒ Yüksek Lisans ☐ Doktora ☐ Tezsiz Yüksek Lisans (Dönem Projesi)
TEZ KONUSU	SCREENING OF ANGUCYCLINE ANTIBIOTICS AS POTENTIAL DRUG CANDIDATES AGAINST MRSA BY DOCKING ANALYSIS
İNTİHAL RAPORU BİLGİLERİ	
RAPOR TÜRÜ	☐ Tez Savunma Sınavı Öncesi ☒ Tez Savunma Sınavı Sonrası
SAYFA SAYISI	171
BENZERLİK ORANI	%15
RAPORLAMA TARİHİ	26/02/2016

Yukarıda başlığı/konusu gösterilen tez çalışmamın kapak sayfası, giriş, ana bölümler, sonuç ve tartışma kısımlarından oluşan toplam 171 sayfalık kısmına ilişkin, 26/02/2016 tarihinde şahsım/tez danışmanım tarafından *Turnitin* adlı intihal tespit programından aşağıda belirtilen filtrelemeler uygulanarak alınmış olan intihal raporuna göre, tezimin benzerlik oranı %15 'tür.

Uygulanan filtrelemeler:

☒ Kabul/Onay sayfaları hariç,
☒ Kaynakça hariç
☐ Alıntılar hariç/dâhil
☒ Diğer

Dicle Üniversitesi Fen Bilimleri Enstitüsü Lisansüstü Programlarda Tez Çalışması İntihal Raporu Uygulama Esasları'nı inceledim ve bu Uygulama Esasları'nda belirtilen azami benzerlik oranlarına göre tez çalışmamın herhangi bir intihal içermediğini; aksinin tespit edilmesi durumunda doğabilecek her türlü hukuki sorumluluğu kabul ettiğimi ve vermiş olduğum bilgilerin doğru olduğunu beyan ederim.

Gereğini saygılarımla arz ederim.

H. Albustany

Hazem Abbas Tofiq AL-BUSTANY

12/04/2016

Prof. Dr. Ebru İNCE
Tez Danışmanı

12/04/2016

Prof. Dr. A. Selçuk ERTEKİN
Anabilim Dalı Başkanı