Sudan University of Science and Technology

College of Graduate Studies

Docking and QSAR Studies of Some Flouroquinolones Derivatives

(دراسة الترسية والعلاقة بين البنية التركيبية والفاعلية لبعض مشتقات الفلوروكينولونات)

A Dissertation Submitted in Partial Fulfillment for the Requirements of the Degree of Master of Science in Chemistry

By

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DEDICATION

To my beloved parent with my respect…….

To my lovely husband and daughter……

To my sisters and brothers……

My Allah bless them

ACKNOWLEDGMENT

To start with, praise to Allah and thank for giving me the strength and patience to complete this project.

I would like to thanks and gratitude **Prof.Dr. Ahmed Elsadig Mohammed**

Thanks to my loyal friend and to everyone who helped me and encouraged me.

Thanks also to all my Colleagues and Chemistry Department Staff**.**

ABSTRACT

In this study computational chemistry, drug design and docking tools were employed to discover a new class of fluoroquinolone derivatives. Fifty eight compounds were designed and made to dock into the active site of a selected receptor (4eru and 1jij); which was retrieved from protein data bank. It was found that modifications in the molecular structure of the core skeleton of fluoroquinolones structure highly affect at biological activity.It was clearly observed positions 2, 3 and 4 should not be altered as they effect directly on the basic mode of action of drug. These observations were seen in docking and QSAR derived equation. The QSAR equation was modelled from a set of experimentally active fluoroquinolones as antimicrobials. The descriptors include log P, density and refractive index.

الملخص

في هذه الدراسة تم استخدام الكيمياء الحاسوبية وتصميم الادوية وادوات الالتحام لاكتشاف فئة جديدة من مشتقات الفلوركينولون. تم تصميم ثمان وخمسين مركبا وجعلها ترسو في الموقع النشط لمستقبلة مختارة (4eru و 1jij) ؛ التي تم استيرادها من بنك بيانات البروتين. وجد ان التعديلات في البنية الجزيئية للهيكل الاساسي لهيكل الفلوروكينولونات تؤثر بشكل كبير في النشاط البيولوجي. كان من الواضح ان المواقع 2 و 3 و 4 لا ينبغي تغييرها لانها تؤثر مباشرة على طريقة عمل الدواء الاساسية. شوهدت هذه الملاجظات في الالتحام والمعادلة المشتقة من العلاقة بين البنية التركيبية والفاعلية. تم تصميم معادلة العلاقة بين البنية التركيبية والفاعلية من مجموعة من الفلوروكينولونات النشطة تجريبيا كمضادات للميكروبات.وتشمل الواصفات التى تم استخدامها في المعادلة السجل P(log P) ، الكثافة ومؤشر الانكسار.

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LIST OF ABBREVIATION:

No.	Abbreviation	Detail
1	RNA	Ribonucleic acid
2	DNA	Deoxyribionucleic acid
3	NADPH	Nicotinamide adenine dinucleotide phosphate
4	PH	Is alogarithmic scale used to specify the acidity or basicity
5	MRSA	Methicillin-resistant Staphylococcus aureus
6	E coli	Eschericha coli
7	QSPR	Quantitative structure-property relationships
8	QSAR	Quantitative structure- activity relationship
9	NMR	Nuclear magnetic resonance
10	HIV	Human immunodeficiency virus
11	FDA	Food and drug adminstration
12	$NSAID_S$	Nonsteroidal anti-inflammatory drugs
13	GABA	Gamma-aminobutyric acid
14	IC_{50}	The half maximal inhibitory concentration
15	MIC	Minimum inhibitory concentration
16	CYP1A2	Protein coding gene: cytochrome P450 Family 1 Subfamily A member 2.
17	CYP3A4	Protein coding gene: cytochrome P450 Family 3 Subfamily A member 4.
18	CYP2D6	Protein coding gene: cytochrome P450 Family 2 Subfamily D member 6.
19	ACD/ChemSketch	Molecular modeling program
20	MBC	Minimum bactericidal concentration
21	LogP	Partition coefficient
22	M.R	Molar refractivity
23	M.V	Molar volume
24	I of R	Index of refraction
25	4eru	Crystal structure of putative cytoplasmic protein ,YciF bacterial stress response protein from salmonella enterica
26	1jij	Crystal structure of staphylococcus aureustyrosyl-tRNAsynthetase in complex with class of potent and specific inhibitors

CHAPTER ONE

INTRODUCTION

1.0 Introduction:

1.1 Heterocyclic compounds:

Heterocyclic compounds are cyclic compounds in which one or more atoms are not carbon (that is hetero atoms). As hetero atom can be N, O, S, B, Al, Si, P, Sn, As, Cu. But common is N, O, or S. Heterocyclic are conveniently grouped into two classes, nonaromatic and aromatic.

Heterocyclic compounds play a major role in organic chemistry because they have different electron configurations from carbon. Heterocyclic compounds are pervasive in many areas of life sciences and technology (Gilchrist, 1997), and also include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds, as are most hallucinogens. Modern society is dependent on synthetic heterocycles for use as drugs, pesticides, dyes, and plastics.

In general, the physical and chemical properties of heterocyclic compounds are best understood by comparing them with ordinary organic compounds that do not contain heteroatoms.

1.2Quinoline:

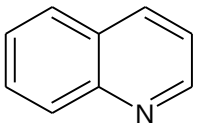
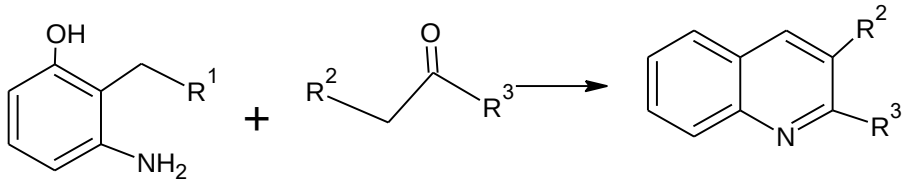


Figure (1.1): Quinoline structure

Quinoline was discovered by Runge in 1834 as one of the many components extracted from coal tar (Andersson and MacGowan,2003). While this nitrogen-

based heterocycle is not overly useful in and of itself, it is easily modified with simple to complex functionalities, giving a multitude of compounds that are widespread in the fields of medicinal and industrial chemistry.(Meldola,1913) Quinoline derivatives are pungent oily nitrogenous base C_9H_7N obtained usually by distillation of coal tar or by synthesis from aniline(Friedlaender Synthesis) that is the parent compound of many alkaloids, drugs, and dyes.

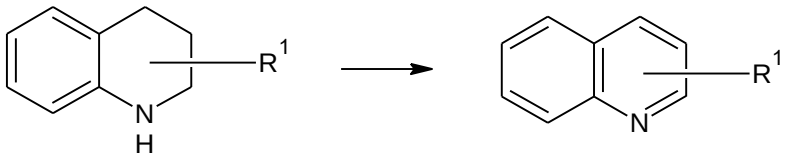


Friedlaender Synthesis

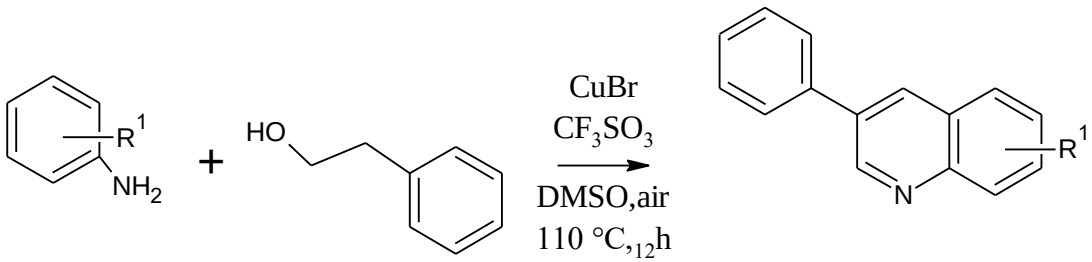
1.2.1. Synthesis of quinoline derivatives:

Quinoline derivatives can also be synthesized by:

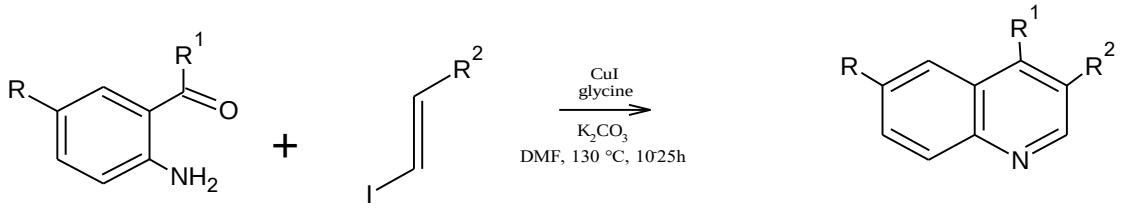
1. An aerobic dehydrogenation of various 1,2,3,4-tetrahydroquinolines to the corresponding quinolones give good yields under mild conditions by using heterogeneous cobalt as a catalyst.(Iosub and Stahl,2015)



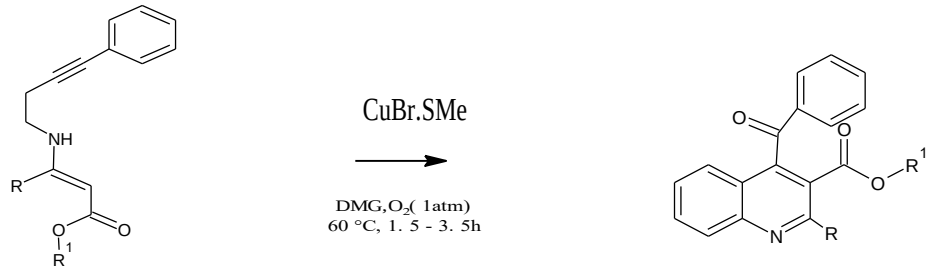
2.Direct synthesis method of substituted quinolines from anilines and aldehydes(Yan.etal,2013)



2. Can synthesis multisubstituted quinolones by an efficient cascade copper-catalyzed intermolecular Ullmann-type C-N coupling/enamine condensation reaction.



4.Cu-catalyzed aerobic cyclization of N-(2-alkynylaryl)enamine carboxylates via intramolecularcarbo-oxygenation of alkynes gives highly substituted quinolones.(Toh,etal.2012)



1.2.2. Biological activity of quinoline derivatives:

Quinoline and its fused heterocyclic derivatives tested with diverse pharmacological activity functional groups constitute an important class of compounds for new drug development. Quinoline ring has been found to possess biological activities covering antimalarial, anti-bacterial, antifungal, anthelmintic, cardiotonic, anticonvulsant, anti-inflammatory, anticancer, antimicrobial and analgesic activity.(Marella,etal.2013)

1.2.3. Mechanism of Action:

Quinoline, a hepatocarcinogen, binds to RNA, DNA and certain polyribonucleotides in the presence of NADPH and rat liver microsomes. The binding was pronounced with the help of liver microsome preparations pretreated with some inducers of the microsomal monooxygenase system. The binding reaction required NADPH and was inhibited by carbon monoxide or

aniline, and also by 7,8-benzoflavone, methyrapone or SKF 525A. These results suggested that the cytochrome P-450-linked monooxygenase system is involved in this binding process. Quinoline bound preferably to poly (A), poly(C), poly(G) and poly(X), but negligibly to poly(U) and poly(I). Most of the quinoline residues of the adducts, regardless of the kind of polynucleotides used, were released by acid or alkali at 100 °C in the form of 3 -hydroxyquinoline.This suggests that 2,3- or 3,4-epoxy derivative of quinoline is the reactive intermediate for nucleic acid modification.(Tada, etal.1980)

1.3Quinolones:

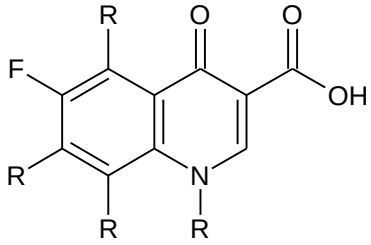


Figure (1.2): Quinolone structure

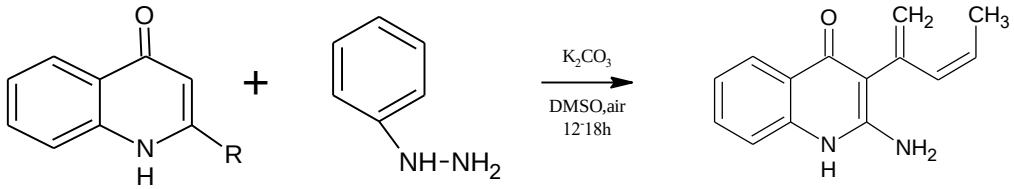
The quinolones are a family of synthetic broad-spectrum antibiotic drugs. Quinolones and derivatives have been isolated from natural sources (such as plants, animals and bacteria) and can act as natural antimicrobials and/or signaling molecules. (Andriole, 1989), (Andersson and MacGowan, 2003), (Ivanov and Budanov, 2006) (Heeb, etal.2011)

The diversity of their various ring structures, they have a number of common functional groups essential for their antimicrobial activity. For example, the quinolone nucleus contains a carboxylic acid group at position3 and an exocyclic oxygen at position 4 (hence the term 4-quinolones), which are believed to be the active DNA-gyrase binding sites. Various modifications have produced compounds with differing physical, chemical, pharmacokinetic, and antimicrobial properties.

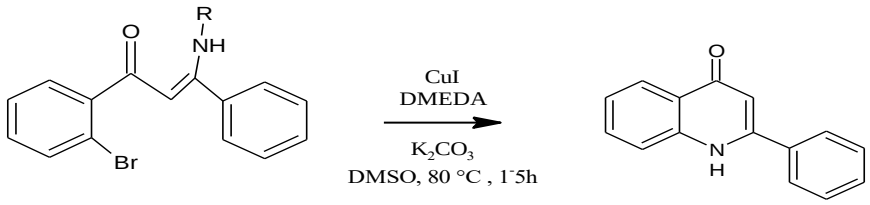
The quinolones are amphoteric and, with a few exceptions, generally exhibit poor water solubility at pH 6–8. Although the impact on therapeutic efficacy is not clear, they appear to act as weak bases in that they are much less effective in acidic than in nonacidic urine PH. In concentrated acidic urine, some quinolones form needle-shaped crystals, although this apparently has not been reported with clinical use. Liquid formulations of various quinolones for PO or parenteral administration usually contain freely soluble salts in stable aqueous solutions. Solid formulations (eg, tablets, capsules, or boluses) contain the active ingredient either in its betaine form or, occasionally, as the hydrochloride salt.(Boothe.D.M)

1.3.1. Synthesis of 4-quinolone derivatives:

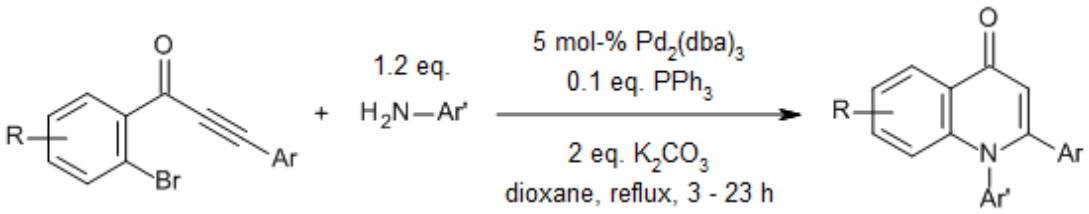
1. The use of arylhydrazines as aryl radical source and air as oxidant enables a transition-metal-free C-3-arylation of quinolin-4-ones in the presence of a base. (Ravietal, 2015)



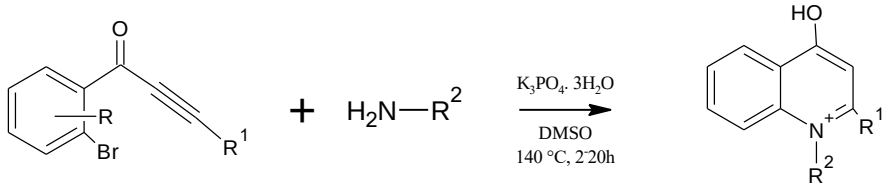
2.1,2-Disubstituted 4-quinolones have been prepared via copper-catalyzed heterocyclization of 1-(2-bromophenyl)- and 1-(2-chlorophenyl)-2-en-3-amin-1-ones, readily obtained from α,β-ynones and primary amines. Quinolone derivatives can also be directly prepared from α,β-ynones. (Bernini, etal.2009)



3. An efficient palladium-catalyzed tandem amination approach affords functionalized 4-quinolones in very good yields from easily accessible o-haloarylacetylenic ketones and primary amines. (Zhao and Xu, 2010)



4. N-Alkyl-substituted 4-quinolones are present as the key structural motif in many marketed drugs. An efficient and convenient one-step tandem amination approach affords N-alkyl-substituted 4-quinolones in high yields from easily accessible o-chloroarylacetylenic ketones and functionalized alkyl amines. (Shao, etal, 2012)



1.3.2Quinolone molecular structure-activity relationships:

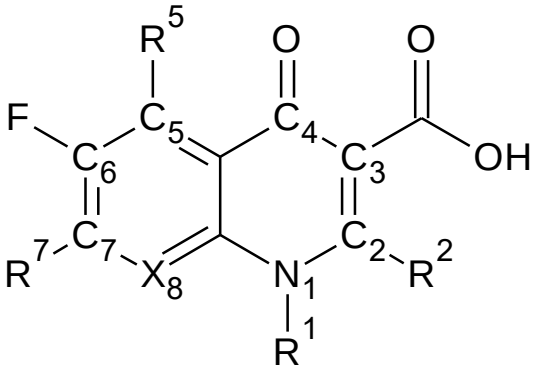


Figure (1.3):The quinolone pharmacore

Structural modifications affect both activity and toxicity and the mechanism of the quinolone antibacterial agents involves the inhibition of DNA gyrase.It is

reasonable to assume that the antibacterial cell penetration and DNA gyrase inhibiting activities.

Some molecular substitutions should not be altered as they would interface or reduce the basic mode of action of drug. These are positions 2,3 and 4; at position 2 , a hydrogen is optimal and any larger molecular addition may create a steric hindrance at the adjacent postions3 and 4 which are generally considered necessary for the binding of quinolones to DNA gyrase so any added bulk inhibits access and results in a lower level of microbiological activity . Only sulfur, incorporated into small ring has been able to replace hydrogen at the R-2postion.

The four other positions can receive a wide range of substituents. Structure activity relationships have enabled the recognition of features that lead to specific changes as below:

Position 1

This position is a part of the enzyme DNA binding complex, acyclopropyle substituent is considered the most potent modification here, followed by addition of 2,4-difluorophenyle.Most other substituent's including one with wrong stearic position can presumably lower the number of molecules capable of binding to the enzyme DNA pocket, and there for reduce potency ;because this position has some effect on the pharmacokinetics of an agent and exerts control on its overall potency.

Oxoquinolizines this is a new addition to the quinolone class, in which nitrogen replaces the carbon between ring carbons C-4 and C-5. This substitution enhances the in vitro and in vivo activity against gram-positive cocci, including methicillin-resistant S. aureus (MRSA) that are resistant to ciprofloxacin.

Position 5

Specific substituted at this position have resulted in increased activity against gram-positive bacteria. Modestly sized additions, such as an amino, hydroxyl, nitro, halo or methyl groups can markedly increase in vitro activity against gram-positive bacteria but not gram-negative bacteria. The C-5 –amino substitution may enhance absorption or tissue distribution.

Position 6

The addition of a fluorine molecule here markedly improved antimicrobial activity compared to the original quinolone agents, and gave rise to the now widely used and clinically successful fluoroquinolone compounds. The fluoro group at C-6postion seems to improve both the DNA gyrase complex binding and cell penetration.

Position 7

This position is considered to be one that directly interacts with DNA gyrase and both spectrum of activity and pharmacokinetics are controlled at this position. The optimal substituents at this position have been found to be groups that contain, at a minimum, a 5- or 6-membered nitrogen heterocycle. The most common of these are aminopyrrolidines and piperazines. Placement of aaminopyrrolidine improves gram-positive activity, whereas a piperazine generally enhances potency against gram-negative bacteria. Alkylation (-CH3) of the 5-membered or 6-membered heterocycle (pyrrolidines and piperazines, respectively) also enhances activity against gram-positive bacteria.

Position 8

This position is considered to affect overall molecular stearic configuration, pharmacokinetic and specific activity against anaerobic bacteria can also be adjusted from this position. Therefore, changes made here affect target affinity, probably by altering drug access to the enzyme or DNA binding sites. A free halogen (F or Cl) here may improve activity against anaerobes. Halogen

substituent's, as well as a methyl or methoxy also increase the in vitro activity against gram-positive cocci, even in those bacteria resistant to older fluoroquinolones. Interestingly, the R-8–substituted quinolones also exhibit enhanced bacteriostatic and lethal activities against GyrA mutants of both E. coli and Mycobacterium species. (Peterson, 2001)(Tillotson,(1996)

1.4. Ciprofloxacin:

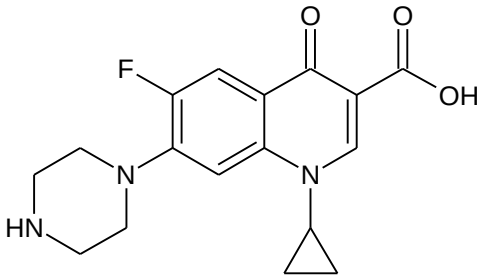


Figure (1.4) :Ciprofloxacin structure

1.4.1. History:

The first members of the quinolone antibacterial class were relatively low-potency drugs such as nalidixic acid, used mainly in the treatment of urinary tract infections owing to their renal excretion and propensity to be concentrated in urine.(Mayrer and Andriole, 1982) In 1979, the publication of a patent filed by the pharmaceutical arm of Kyorin Seiyaku Kabushiki Kaisha disclosed the discovery of norfloxacin, and the demonstration that certain structural modifications including the attachment of a fluorine atom to the quinolone ring leads to dramatically enhanced antibacterial potency.(Khan, etal. 1982) In the aftermath of this disclosure, several other pharmaceutical companies initiated research and development programs with the goal of discovering additional antibacterial agents of the fluoroquinolone class.

In 1983, the company published in vitro potency data for ciprofloxacin, a fluoroquinolone antibacterial having a chemical structure differing from that of

norfloxacin by the presence of a single carbon atom.(Wise, etal .1983) This small change led to a two- to 10-fold increase in potency against most strains of Gram-negative bacteria. Importantly, this structural change led to a four-fold improvement in activity against the important Gram-negative pathogen Pseudomonas aeruginosa, making ciprofloxacin one of the most potent known drugs for the treatment of this intrinsically antibiotic-resistant pathogen.

1.4.2.Chemical properties:

1. Ciprofloxacin is1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolone carboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4 g/mol. It is a faintly yellowish to light yellow crystalline substance. Ciprofloxacin hydrochloride is the monohydrochloride monohydrate salt of ciprofloxacin. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8 g/mol. Its empirical formula is $C_{17}H_{18}FN_3O_3HCl•H_2O$. (Madan,2004)

2. Generic Name: ciprofloxacin (oral) (SIP roe FLOX a sin)

3. Brand Names: Cipro, Cipro XR, Proquin XR.

1.4.3Medical uses:

Ciprofloxacin is a very active drug against chloroquine-sensitive and chloroquine-resistant strains of plasmodium and combinationofchloroquine with ciprofloxacin resulted in important reduction of the parasitemia . Combining of ciprofloxacin with organometallic as ferroquine showed to be good strategy for the design of novel compound which are dramatically more efficient Ciprofloxacin is an antibiotic used to treat a number of bacterial infections. This includes bone and joint infections, intra abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others. For some infections it is used in

addition to other antibiotics. It can be taken by mouth, in eye drops, or intravenously.

Ciprofloxacin is also used to treat people who have been exposed to anthrax or certain types of plague , ciprofloxacin should be used only for infections that cannot be treated with a safer antibiotic against P.falciparum. (Castro, etal.2013) Ciprofloxacin is the most widely used of the second-generation quinolones In 2010, over 20million prescriptions were written, making it the 35th-most commonly prescribed generic drug and the 5th-most commonly prescribed antibacterial in the U.S(Goossens, etal .2007)

Ciprofloxacin only treats bacterial infections; it does not treat viral infections such as the common cold. For certain uses including acute sinusitis, lower respiratory tract infections and uncomplicated gonorrhea, ciprofloxacin is not considered a first-line agent.

Ciprofloxacin occupies an important role in treatment guidelines issued by major medical societies for the treatment of serious infections, especially those likely to be caused by Gram-negative bacteria, including Pseudomonas aeruginosa. For example, ciprofloxacin in combination with metronidazole is one of several first-line antibiotic regimens recommended by the Infectious Diseases Society of America for the treatment of community-acquired abdominal infections in adults.(Solomkin., etal.2010) It also features prominently in treatment guidelines for acute pyelonephritis, complicated or hospital-acquired urinary tract infection, acute or chronic prostatitis,(Grabe, etal.2013)certain types of endocarditis,(Baddou, etal.2005) certain skin infections,(Stevens, etal .2005)and prosthetic joint infections.(Osmo, etal.2013)

1.4.4. Spectrum of activity:

Ciprofloxacin spectrum of activity includes most strains of bacterial pathogens responsible for community-acquired pneumonias, bronchitis, urinary tract

infections, and gastroenteritis.(Johannsen and Sabatine,2010)Ciprofloxacin is particularly effective against Gram-negative bacteria (such as Escherichia coli, Haemophilus influenza, Klebsiellapneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, and Pseudomonas aeruginosa), but is less effective against Gram-positive bacteria (such as methicillin-sensitive Staphylococcus aureus, Streptococcus pneumoniae, and Enterococcus faecalis) than newer fluoroquinolones.

1.4.5. Interactions:

Ciprofloxacin interacts with certain foods and several other drugs leading to undesirable increases or decreases in the serum levels or distribution of one or both drugs.

Ciprofloxacin should not be taken with antacids containing magnesium or aluminum, highly buffered drugs (sevelamer, lanthanum carbonate, sucralfate, didanosine), or with supplements containing calcium, iron, or zinc. It should be taken two hours before or six hours after these products. Magnesium or aluminum antacids turn ciprofloxacin into insoluble salts that are not readily absorbed by the intestinal tract, reducing peak serum concentrations by 90% or more, leading to therapeutic failure. Additionally, it should not be taken with dairy products or calcium-fortified juices alone, as peak serum concentration and the area under the serum concentration-time curve can be reduced up to 40%. However, ciprofloxacin may be taken with dairy products or calcium-fortified juices as part of a meal.(Rodvol and Piscitell, 1993)(Bolhuis, etal.2011)

Ciprofloxacin inhibits the drug-metabolizing enzyme CYP1A2 and thereby can reduce the clearance of drugs metabolized by that enzyme. CYP1A2 substrates that exhibit increased serum levels in ciprofloxacin-treated patients include tizanidine, theophylline, caffeine, methylxanthines, clozapine, olanzapine, and ropinirole.. (Bolhuis, etal2011) (Janknegt,1990)

The Committee on Safety of Medicines and the FDA warn that central nervous system adverse effects, including seizure risk, may be increased when NSAIDs are combined with quinolones.(Janknegt,1990) The mechanism for this interaction may involve a synergistic increased antagonism of GABA neurotransmission.(De Sarro,. and DeSarro,.2001)(Brouwers, 1992) Ciprofloxacin is a potent inhibitor of CYP1A2, CYP2D6, and CYP3A4.(Haddad,etal. 2007)

1.4.6. Mechanism of action:

Ciprofloxacin active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, and a type II topoisomerase, topoisomerase IV, necessary to separate bacterial DNA, there by inhibiting cell division. (Drlica and Zhao,1997))(Pommier,etal.2010)

1.4.7. Pharmacokinetics:

Ciprofloxacin for systemic administration is available as immediate-release tablets, extended-release tablets, an oral suspension, and as a solution for intravenous administration. When administered over one hour as an intravenous infusion, ciprofloxacin rapidly distributes into the tissues, with levels in some tissues exceeding those in the serum. Penetration into the central nervous system is relatively modest, with cerebrospinal fluid levels normally less than 10% of peak serum concentrations. The serum half-life of ciprofloxacin is about 4–6 hours, with 50-70% of an administered dose being excreted in the urine as unmetabolized drug. An additional 10% is excreted in urine as metabolites. Urinary excretion is virtually complete 24 hours after administration. Dose adjustment is required in the elderly and in those with renal impairment.

1.5. Computational chemistry:

Computational chemistry is a branch of chemistry that uses computer simulation to assist in solving chemical problems. It uses methods of theoretical chemistry ,incorporated into efficient computer programs,to calculate the structures and properties of molecules and solids. Computers are an essential tool in modern medicinal chemistry and are important in both drug discovery and drug development.(Smithand,1997)Several major areas may be distinguished within computational chemistry:

1. Develop computer models and simulations of chemical and biochemical processes and entities.
2. Perform and interpret statistical analysis of large datasets.
3. Create visual representations of reaction pathways, molecular interactions, or other phenomena.
4. Collaborate with laboratory researchers in industrial, nonprofit, government, or academic laboratories.
5. Characterize new compounds and processes to support patent claims.
6. Help develop synthesis processes by identify and characterizing reaction pathways and identify the most likely products.
7. Apply new software and hardware capabilities for data collection and analysis.
8. Teach courses and train students.
9. Design of experiments.
10. Computational studies, used to find a starting point for a laboratory synthesis, or to assist in understanding experimental data, such as the position and source of spectroscopic peaks.
11. Computational studies, used to predict the possibility of so far entirely unknown molecules or to explore reaction mechanisms not readily studied via experiments.

12. The prediction of the molecular structure of molecules by the use of the simulation of forces, or more accurate quantum chemical methods, to find stationary points on the energy surface as the position of the nuclei is varied.
13. Storing and searching for data on chemical entities (see chemical databases).
14. Identifying correlations between chemical structures and properties (see quantitative structure–property relationship (QSPR) and quantitative structure–activity relationship (QSAR)).
15. Computational approaches to help in the efficient synthesis of compounds.
16. Computational approaches to design molecules that interact in specific ways with other molecules (e.g. drug design and catalysis).

Thus, computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects.(Counts,1987)

1.5.1. Molecular modeling:

Molecular modeling is the use of computers for the simulation of chemical entities and processes. It encompasses all theoretical methods and computational techniques used to model or mimic the behavior of molecules. The techniques are used in the fields of computational chemistry, drug design, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules and material assemblies. The simplest calculations can be performed by hand, but inevitably computers are required to perform molecular modeling of any reasonably sized system. The common feature of molecular modeling techniques is the atomistic level description of the molecular systems. This may include treating atoms as the smallest individual unit (the Molecular mechanics approach), or explicitly

modeling electrons of each atom (the quantum chemistry approach). (Parsons, etal 2005)

1.5.2. Drug design:

Drug discovery is a very time-consuming and expensive process. Estimates of the average time required to bring a drug to the market range from 12-15 years at an average cost of $600-800 million. For approximately every 10,000 compounds that are evaluated in animal studies, 10 will make it to human clinical trials in order to get 1 compound on the market.

The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bio molecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques.(Ghasemi,etal. 2016)This type of modeling is sometimes referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design.In addition to small molecules, biopharmaceuticals including peptides(Fosgerau and Hoffmann,2015)(Ciemny,etal 2018) and especially therapeutic antibodies are an increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed.

There are two major types of drug design. The first is referred to as ligand-based drug design and the second, structure-based drug design.(Reynolds,etal 2010)

1.5.3. Q.S.A.R:

Quantitative structure–activity relationship is an approach designed to find relationships between chemical structure (or structural-related properties) and biological activity (or target property) of studied compounds.

In QSAR modeling, the predictors consist of physico-chemical properties or theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. Second, QSAR models predict the activities of new chemicals.(Nantasenamat, etal.2009)(Nantasenamat, etal.2010)

Essential steps in QSAR studies:

Principal steps of QSAR/QSPR including (i) Selection of Data set and extraction of structural/empirical descriptors (ii) variable selection, (iii) model construction and (iv)validation evaluation. (Yousefinejad and Hemmateenejad, 2015)

QSAR modeling produces predictive models derived from application of statistical tools correlating biological activity (including desirable therapeutic effect and undesirable side effects) or physico-chemical properties in QSPR models of chemicals (drugs/toxicants/environmental pollutants) with descriptors representative of molecular structure or properties. QSARs are being applied in many disciplines, for example: risk assessment, toxicity prediction, and regulatory decisions(Tong, etal. 2005) in addition to drug discovery and lead optimization. (Dearden, 2003)

1.5.3.1Application of Q.S.A.R:

1.5.3.1.1Chemical:

It is well known in a particular family of chemical compounds, especially of organic chemistry, that there are strong correlations between structure and

observed properties.Astill very interesting application is the Hammett equation, Taft equation and pKa prediction methods. (Fraczkiewicz, 2013)

1.5.3.1.2. Biological:

The biological activity of molecules is usually measured in assays to establish the level of inhibition of particular signal transduction or metabolic pathways. Drug discovery often involves the use of QSAR to identify chemical structures that could have good inhibitory effects on specific targets and have low toxicity (non-specific activity). Of special interest is the prediction of partition coefficient log P, which is an important measure used in identifying "drug likeness" according to Lipinski's Rule of Five.

While many quantitative structure activity relationship analyses involve the interactions of a family of molecules with an enzyme or receptor binding site, QSAR can also be used to study the interactions between the structural domains of proteins. Protein-protein interactions can be quantitatively analyzed for structural variations resulted from site-directed mutagenesis. (Freyhult, etal.2003)

1.5.4. Docking:

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex.(Lengauerand Rare,1996)Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions.

The associations between biologically relevant molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners

may affect the type of signal produced (e.g., agonismvs.antagonism). Therefore, docking is useful for predicting both the strength and type of signal produced.

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterization of the binding behavior plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes.(Kitchen, etal 2004)

1.5.4.1Mechanics of docking:

To perform a docking screen, the first requirement is a structure of the protein of interest. Usually the structure has been determined using a biophysical technique such as x-ray crystallography or NMR spectroscopy, but can also be derive from homology modeling construction. This protein structure and a database of potential ligands serve as inputs to a docking program. The success of a docking program depends on two components: the search algorithm and the scoring function. (Kearsley,1994)

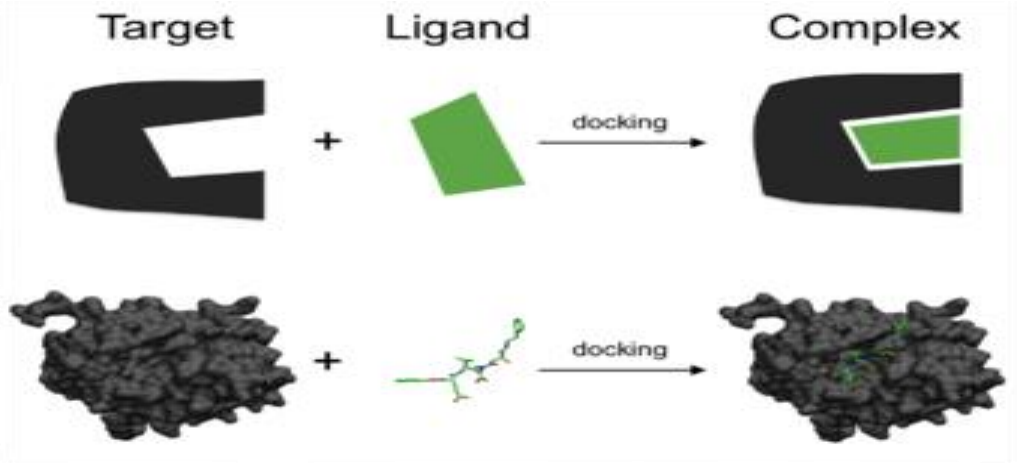


Figure (1.5) :Illustration of docking a small molecule ligand (green) to a protein target (black) producing a stable complex

1.6. Literature Review:

In the current practices of anti-infective therapy, ciprofloxacin is a popular fluoroquinolone which have a broad spectrum of activity. The available clinical evidence suggests the potentially enhanced efficacy of this drug in the treatment of various community acquired; e.g. respiratory tract, urinary tract,skin infections and sexually transmitted diseases. Various molecular modification of ciprofloxacin have been made to further improve its characteristics.

Development of the first clinically useful quinolone occurred in 1962 by George Lesher and colleagues had developed nalidixic acid.Koga ,etal. Observed that improvements in activity were achieved by modification in quinolone pharmacore at position C6 and C7 .The addition of a fluorine atom at C6 created the Fluoroquinolones which have series of benefits include: oral and parenteral dosing , increase antibacterial activity, improve pharmacokinetic profile which favor once or twice a day dosing, this resulted improved understanding of the molecule and how its structure interacts with both its target site in bacteria and metabolic systems.

(Lnce,2001) Make a review in quinolone molecular structure-activity relationships focusing in the recent data on how molecular modifications of the core of quinolone structure affect antimicrobial activity.

(Molecule 2013) A series of 7-[4-(4-(un)Substituted) piperazine-1-carbonyl]-piperazin-1-yl] derivatives of fluoroquinolone were synthesized. The results indicated that a 7-[4-(4-(benzoyl)carbopiperazin-1-yl)] piperazinyl derivative 5h and two 7-[4-(4- (benzenesulfonyl)carbopiperazin-1-yl)] piperazinyl derivatives 5k and 5l showed more promising growth inhibition of ciprofloxacin -resistant P. aeruginosa (CRPA) with MIC values as low as 16 μg/mL which is 16-fold more potent than ciprofloxacin, while most of other derivatives maintained potency against methicillin-resistant Staphylococcus aureus (MRSA). From the structure-activity point of view, the variety of piperazinyl substituents at the 7-

position of fluoroquinolone agents has disclosed the looseness of the binding pocket of the targeted type II topoisomerases and established the groundwork for further modification toward new fluoroquinolone agents useful against certain clinically resistant organisms.

Medicinal potential of ciprofloxacin and its derivatives were described by (William, etal.2013),a new class of dihaloquinolones bearing N′-aldehydoglycosylhydrazides, mercapto-1,2,4-triazole, oxadiazoline and a-amino ester precursors was reported .In vitro antimicrobial activities of these new group were tested using the Escherichia coli K 12 wild-type strain D10, a Gram-negative bacterium; wild-type Bacilliussubtilius, a Gram-positive bacterium; as well as S. aureus. As these compounds have little or no activity against the mentioned organisms, the authors concluded that the substitution of the carboxylic group of the quinolones by 1,2,4-triazolyl, 1,3,4-oxadiazolyl, a-amino ester or hydrazide derivatives of aldehydosugars does not influence the antibacterial activity. Another strategy in the search for derivatives of ciprofloxacin has been the modification of the 7-piperazinyl group. Foroumadi and colleagues reported the synthesis of a series of N-[2-(5bromothiophen-2-yl)-2-oxoethyl] and N-[2-(5bromothiophen-2-yl)-2-oximinoethyl] derivatives of piperazinyl quinolones and evaluated their antimicrobial activities against Gram-positive and Gram-negative microorganisms. These derivatives exhibit comparable or better activity against Gram positive bacteria such as S. aureus, Staphylococcus epidermidis and Bacillus subtilis than ciprofloxacin, norfloxacin and enoxacine, which were used as reference drugs.

In another study, they examined a series of N-(5-benzylthio-1,3,4-thiadiazol-2-yl) and N-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl) derivatives of piperazinyl quinolone and evaluated them for antibacterial activity against different microorganisms. Among the synthesized compounds, 7-(4-(5-(4-

nitrobenzylthio)-1,3,4thiadiazol-2-yl)piperazin-1-yl)-1-cyclopropyl6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) exhibited high activity against Gram-positive bacteria. The structure activity relations of this series indicates that both the structure of the benzyl unit and the S or SO_2 linker dramatically impact antibacterial activity.

Talathetal. Evaluated a series of 7-[4-(5amino-1,3,4 thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolone derivatives . The compounds were evaluated for their in vitro antibacterial activity against some Gram positive and Gram-negative bacteria and antitubercular activity against M. tuberculosis H37Rv strain by the broth dilution assay method. The antibacterial data of the tested ciprofloxacin derivate indicated that the synthesized compound showed better activity against the Gram-positive bacteria S. aureus, E. faecelis and Bacillus sp. compared with the reference drug (ciprofloxacin), and also showed moderate in vitro antitubercular activity against M. tuberculosis. Nieto et al. carried out quantitative structure–activity relationships of benzenesulfonamide-fluoroquinolones throughHansch analyses. These showed a linear correlation of the activity with electronic and steric parameters, concluding that small electron-donor groups would increase the in vitro activity against Gram-positive bacteria, and that hydrophobic properties played a minor role when activity is measured as minimum inhibitory concentration. The quantitative structure–activity relationships analyses also reinforced previous biological findings regarding the presence of new interactions with target topoisomerases.

Ciprofloxacin derivatives have been tested against tumor cell lines and HIV. Shaharyar,2007 reported fluoroquinolone with oxadiazole, 1-cyclopropyl-6-fluoro-3-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-7-piperazino-1,4-dihydro 4-quinolinone, was found to be the most active compound in vitro with a IC_{50} of 9.0 μg/mL. Sriram,etal.2007 synthesized a series of new tetracycline derivatives

by reacting appropriate tetracyclines, formaldehyde and secondary amino (piperazino) function of fluoroquinolones, and evaluated as anti-HIV, anti-mycobacterial activities and HIV-1 integrase enzyme inhibition studies .This study reported that combining tetracyclines and fluoroquinolones resulted in both anti-HIV and anti-tubercular activities, and specifically was found to be promising for the treatment of AIDS, as shown by excellent anti-HIV and anti-mycobacterial activity.

1.7.Objective:

1.7.1. Main Objective

The main objective of the conducted study is to use quantitative structure–activity relationships (QSARs) to design a new group of quinolones that could be antimicrobial.

1.7.2. Specific Objectives

1. To undertake quantitative structure–activity relationships (QSARs) study for fluoroquinolones as anti-microbial agent
2. To design a derivative of fluoroquinolones.
3. To predict biological activity of designed compounds by using the equation of QSAR.

CHAPTER TWO

EXPERIMENTAL

2.0 Materials and Methods

2.1. ACD lab program (Software):

ACD/lab (2018) program was used to draw structure and calculate their properties.

2.1.1General method of ACD/lab program

The main program page consists of the toolbar and taskbar and there were two options:1-ChemSketch and 3-3D-view .Option 1-ChemSketch have two modes, name by Structure and Draw. Structure mode was used to draw chemical molecules, while Draw mode was used to create and edit graphical objects. Upon startup, the Draw Normal mode and Carbon were automatically selected, by clicking and dragging the cursor, C-C bonds were created. The change was made by selecting a heteroatom from the element list in the left toolbar and clicking on an atom in the structure to replace it. Bond lengths and bond angle standardized by clicking on Clean Structure from option Tools in the taskbar. The properties of the drown structures were calculated by using appropriate option in the toolbar and then copied into ChemSketch window as a text field. By selecting a structure and clicking on generate Name for structure in tools the IUPAC name was generated as a text field.

This procedure was used to draw all derivatives structure and equations in this project.

2.2. Minitab (Software):

Minitab18 package was used to perform multiple linear regression and to obtain QSAR equation.

2.2.1. General method of Minitab program

Minitab program was used to perform a multiple linear regression analysis to get the equation which we can use to predict the biological activity of our derivatives

structure, by select from toolbar: Stat ► Regression ► Regression ►Fit Regression Model. The response and the predictor(s) variable were specified, and selection were conformed. Next, back up to the Main Menu which regression has run.

2.2.2. Multiple linear regression and QSAR equations:

A series of 7-[4-(4-(un)substituted) piperazine-1-carbonyl]-piperazin-1-yl]derivatives of Fluoroquinolonewere drown by ACD/lab and their properties were calculated to get the mathematical formula which related biological activity with structure (QSAR equations) .

Table NO. (2.1): ACD/Lab of 7-(4-carbo- piperazin-4-yl) derivatives of fluoroquinolones and their biological activity (MBC: minimum bactericidal concentration mg/l)):

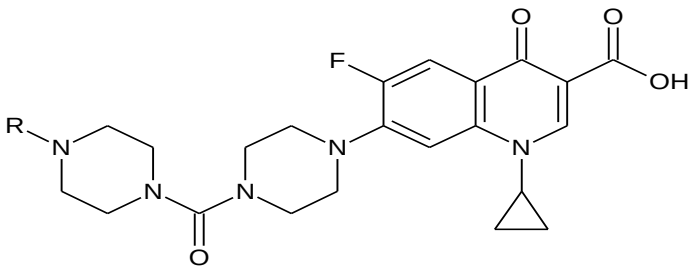
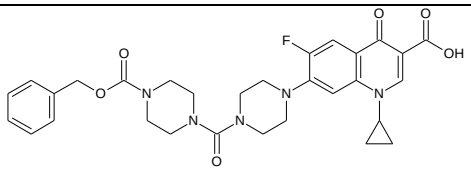
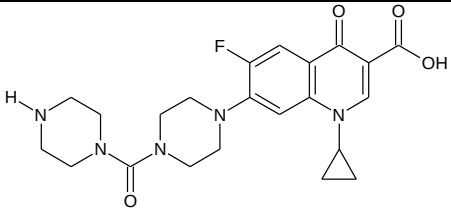
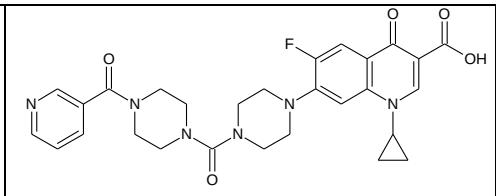
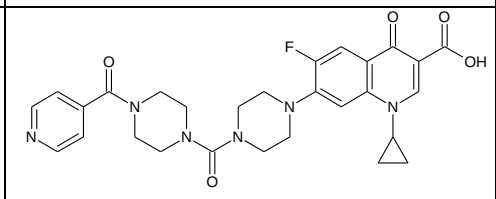
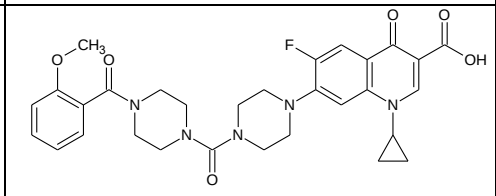
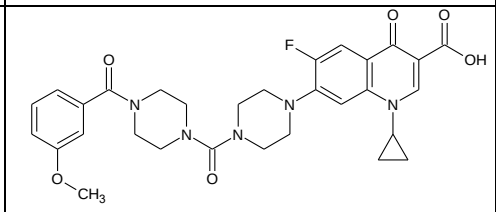
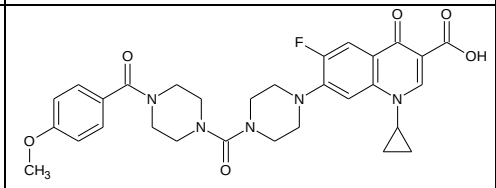
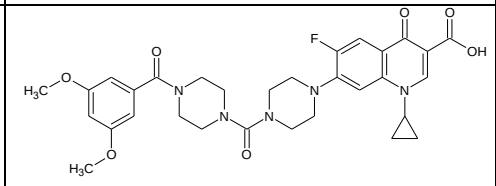
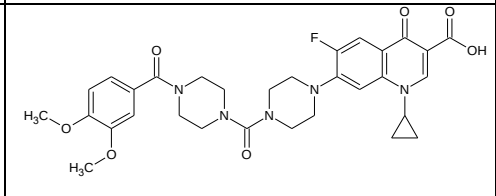
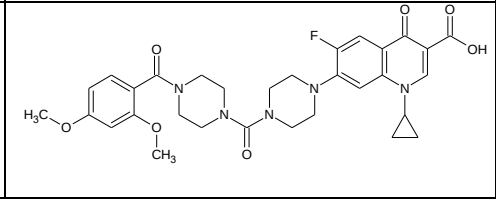
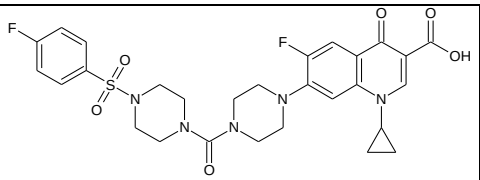
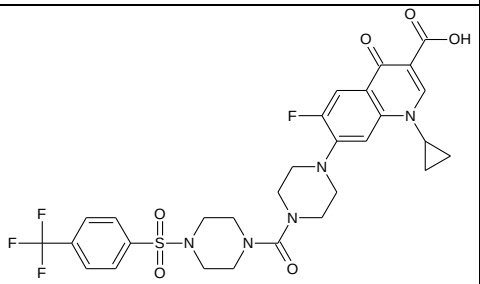
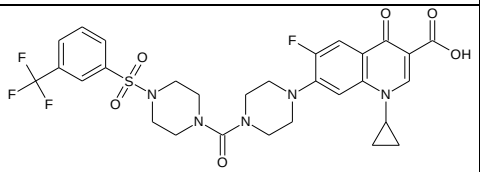


Figure (2.1): Structure of 7-(4-carbo- piperazin-4-yl)

No.	Structure	MBC Mg/l	-Log MBC	Log P	Molar Refractivity	Molar Volume	Index of Refraction	Surface Tension	Densi
1		128	-2.11	2.17	147.06	395.9	1.665	72.6	1.45
2		128	-2.11	0.43	111.40	302.6	1.657	71.0	1.46

3		4	-0.6	0.23	139.36	367.9	1.682	77.3	1.49
4		0.25	0.6	0.32	139.36	367.9	1.682	77.3	1.49
5		1	0	1.21	147.94	398.6	1.664	70.2	1.44
6		16	-1.2	1.50	147.94	398.6	1.664	70.2	1.44
7		4	-0.6	1.46	147.94	398.6	1.664	70.2	1.44
8		16	-1.2	1.95	154.62	422.6	1.652	67.7	1.43
9		16	-1.2	1.94	154.62	422.6	1.652	67.7	1.43
10		16	-1.2	1.62	154.62	422.6	1.652	67.7	1.43

11		16	-1.2	2.43	147.37	389.1	1.681	72.9	1.54
12		64	-1.81	3.08	152.25	418.4	1.648	65.8	1.55
13		128	-2.11	3.01	152.25	418.4	1.648	65.8	1.55

2.2.3.QSAR equations:

By using general Minitab procedure and by choosing randomly descriptors as independent variable and plotted against biological activity as dependent variable a number of QSAR equations were obtained the best of them were:

- -log MBC = -117-1.25 log P+ 0.01 M.R +0.02 M.V +71.0 I of R -0.221 Surface Tension +4.9 Density.
  With R2 = 0.8205
- -log MBC = -118-1.248 log P +0.02064 M.V + 72.0 I of R – 0.221 Surface Tension + 4.85 Density
  With R2 = 0.8205
- -log MBC = -18.71 – 1.193 log P +0.066 M.R +6.63 Density
  With R2 = 0.7582
- -log MBC = -41.9 -0.758 log P + 0.0509 M.R +20.8 I of R
  With R2 =0.7371

- -log MBC=-7.46 – 0.764 log P + 0.172 M.R -0.0444 M.V

  With R2 =0.7358

Table No (2.2) descriptors used to perform Multiple Linear Regressions to generate QSAR equation:

- -Log MBC = -117-1.25 Log P+ 0.01 M.R +0.02 M.V +71.0 I of R -0.221 Surface Tension + 4.9 Density.

Compound No.	-Log MBC	Log P	M.R	M.V	I of R	Surface Tension	Density
1	-2.11	2.17	147.06	395.9	1.665	72.6	1.458
2	-2.11	0.43	111.40	302.6	1.657	71.0	1.465
3	-0.6	0.23	139.36	367.9	1.682	77.3	1.491
4	0.6	0.32	139.36	367.9	1.682	77.3	1.491
5	0	1.21	147.94	398.6	1.664	70.2	1.448
6	-1.2	1.50	147.94	398.6	1.664	70.2	1.448
7	-0.6	1.46	147.94	398.6	1.664	70.2	1.448
8	-1.2	1.95	154.62	422.6	1.652	67.7	1.437
9	-1.2	1.94	154.62	422.6	1.652	67.7	1.437
10	-1.2	1.62	154.62	422.6	1.652	67.7	1.437
11	-1.2	2.43	147.37	389.1	1.681	72.9	1.546
12	-1.81	3.08	152.25	418.4	1.648	65.8	1.557
13	-2.11	3.01	152.25	418.4	1.648	65.8	1.557

Table No (2.3) descriptors used to perform Multiple Linear Regression to generate QSAR equation

-log MBC = -118.5 - 1.248 Log P + 0.02064 M.V + 72.0 I of R - 0.221 Surface Tension + 4.85 Density

Compound No.	-Log MBC	Log P	M.V	I of R	Surface Tension	Density
1	-2.11	2.17	395.9	1.665	72.6	1.458
2	-2.11	0.43	302.6	1.657	71.0	1.465
3	-0.6	0.23	367.9	1.682	77.3	1.491
4	0.6	0.32	367.9	1.682	77.3	1.491
5	0	1.21	398.6	1.664	70.2	1.448
6	-1.2	1.50	398.6	1.664	70.2	1.448
7	-0.6	1.46	398.6	1.664	70.2	1.448
8	-1.2	1.95	422.6	1.652	67.7	1.437
9	-1.2	1.94	422.6	1.652	67.7	1.437
10	-1.2	1.62	422.6	1.652	67.7	1.437
11	-1.2	2.43	389.1	1.681	72.9	1.546
12	-1.81	3.08	418.4	1.648	65.8	1.557
13	-2.11	3.01	418.4	1.648	65.8	1.557

Table No (2.4) descriptors used to perform Multiple Linear Regressions to generate QSAR equation:

-log MBC = -18.71 - 1.193 Log P + 0.0667 M.R + 6.63 Density

Compound No.	-Log MBC	Log P	M.R	Density
1	-2.11	2.17	147.06	1.458
2	-2.11	0.43	111.40	1.465
3	-0.6	0.23	139.36	1.491

4	0.6	0.32	139.36	1.491
5	0	1.21	147.94	1.448
6	-1.2	1.50	147.94	1.448
7	-0.6	1.46	147.94	1.448
8	-1.2	1.95	154.62	1.437
9	-1.2	1.94	154.62	1.437
10	-1.2	1.62	154.62	1.437
11	-1.2	2.43	147.37	1.546
12	-1.81	3.08	152.25	1.557
13	-2.11	3.01	152.25	1.557

Table No (2.5) descriptors used to perform Multiple Linear Regressions to generate QSAR equation:

-log MBC = -7.46 - 0.764 Log P + 0.1720 M.R - 0.0444 M.V
R^2 =0.7385

Compound No.	-Log MBC	Log P	Molar Refractivity	Molar Volume
1	-2.11	2.17	147.06	395.9
2	-2.11	0.43	111.40	302.6
3	-0.6	0.23	139.36	367.9
4	0.6	0.32	139.36	367.9
5	0	1.21	147.94	398.6
6	-1.2	1.50	147.94	398.6

7	-0.6	1.46	147.94	398.6
8	-1.2	1.95	154.62	422.6
9	-1.2	1.94	154.62	422.6
10	-1.2	1.62	154.62	422.6
11	-1.2	2.43	147.37	389.1
12	-1.81	3.08	152.25	418.4
13	-2.11	3.01	152.25	418.4

Table No (2.6) descriptors used to perform Multiple Linear Regressions to generate QSAR equation:

-log MBC = -41.9 - 0.758 Log P + 0.0509 M.R + 20.8 I of R

R^2 =0.7371

Compound No.	-Log MBC	Log P	Molar Refractivity	Index of Refraction
1	-2.11	2.17	147.06	1.665
2	-2.11	0.43	111.40	1.657
3	-0.6	0.23	139.36	1.682
4	0.6	0.32	139.36	1.682
5	0	1.21	147.94	1.664
6	-1.2	1.50	147.94	1.664
7	-0.6	1.46	147.94	1.664
8	-1.2	1.95	154.62	1.652
9	-1.2	1.94	154.62	1.652

10	-1.2	1.62	154.62	1.652
11	-1.2	2.43	147.37	1.681
12	-1.81	3.08	152.25	1.648
13	-2.11	3.01	152.25	1.648

Table No (2.7) descriptors used to perform Multiple Linear Regression to generate QSAR equation:

-log MBC =-11.49-0.774 log P +0.0535 M.R +0.0543 Surface Tension

R^2 =0.6984

Compound No.	-Log MBC	Log P	Molar Refractivity	Surface Tension
1	-2.11	2.17	147.06	72.6
2	-2.11	0.43	111.40	71.0
3	-0.6	0.23	139.36	77.3
4	0.6	0.32	139.36	77.3
5	0	1.21	147.94	70.2
6	-1.2	1.50	147.94	70.2
7	-0.6	1.46	147.94	70.2
8	-1.2	1.95	154.62	67.7
9	-1.2	1.94	154.62	67.7
10	-1.2	1.62	154.62	67.7
11	-1.2	2.43	147.37	72.9
12	-1.81	3.08	152.25	65.8
13	-2.11	3.01	152.25	65.8

Table No (2.8) descriptors used to perform Multiple Linear Regression to generate QSAR equation:

-Log MBC = -56.1 - 0.756 Log P + 0.01870 M.V + 29.4 I of R

R^2 =0.7375

Compound no.	-Log MBC	Log P	Molar Volume	Index of Refraction
1	-2.11	2.17	395.9	1.665
2	-2.11	0.43	302.6	1.657
3	-0.6	0.23	367.9	1.682
4	0.6	0.32	367.9	1.682
5	0	1.21	398.6	1.664
6	-1.2	1.50	398.6	1.664
7	-0.6	1.46	398.6	1.664
8	-1.2	1.95	422.6	1.652
9	-1.2	1.94	422.6	1.652
10	-1.2	1.62	422.6	1.652
11	-1.2	2.43	389.1	1.681
12	-1.81	3.08	418.4	1.648
13	-2.11	3.01	418.4	1.648

2.3 Molecular Operating Environment(MOE) program:

MOE program was used to detect protein – ligand binding sites and effective docking for the highest activity which calculated from QSAR equation.

2.3.1. Preparation of protein:

MOE was used to prepare the protein that was selected (2Val of E coli) , first test the active site by select from toolbar : compute►simulation►dock► site►?. Then similar chain and water molecule were removed by select from right option: SEQ►detectedit►delete selected chain . Then protein wasisolated and become ready for docking.

2.3.2. Preparation of ligand(compound):

MOE was used to prepare the designed derivatives by select from toolbar: file ►open to get compound, then select: compute ►conformation ►conformational search ►Edit;to minimize energy of compound to become ready for docking.

2.3.3. Docking:

MOE was used for docking process by opening protein which prepared firstly then select from the toolbar : compute ► simulation ► Dock ;window which opened were select : ligand ► MDP file ► Browse ; to get compound, and refinement ► forcefield ► Run .The result of running were export and saved as JPG.

CHAPTER THREE

RESULTS AND DISCISSION

3.0Results and Discussion:

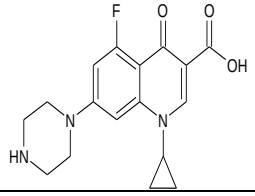
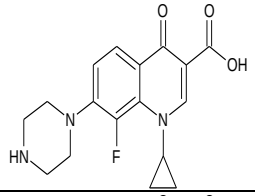
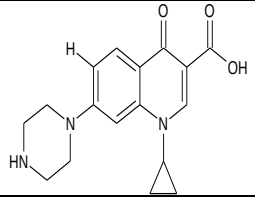
3.1Result:

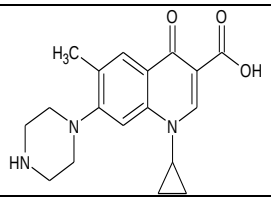
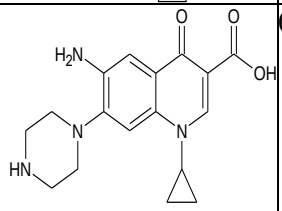
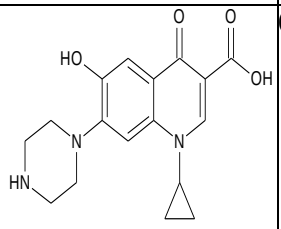
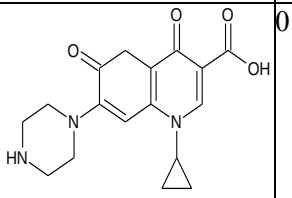
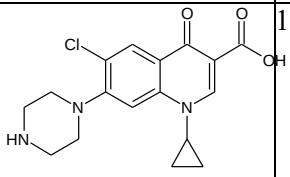
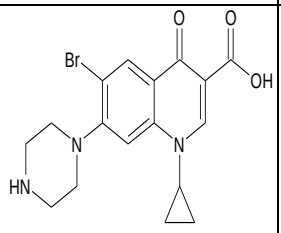
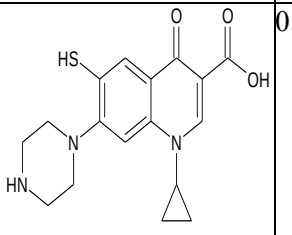
Structures of a series of (58) derivatives of ciprofloxacin were drown by ACD/lab and their properties were calculated (log P, Molar Refractivity, Molar Volume, Index of Refraction and Density) and biological activity was predicted by using equation:

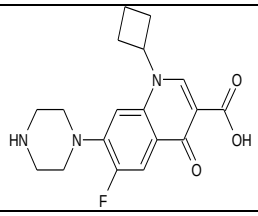
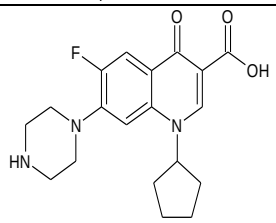
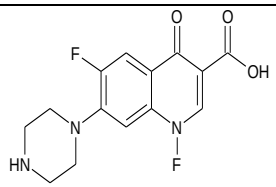
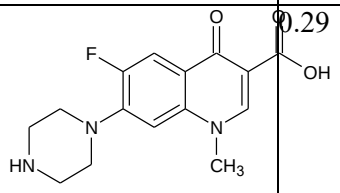
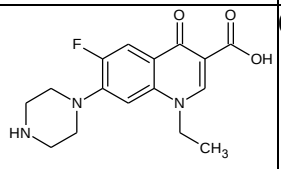
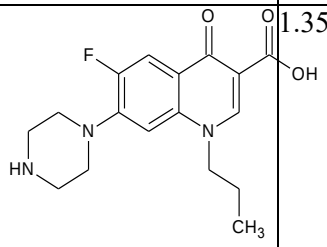
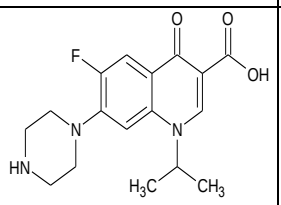
-log MBC = -117-1.25 log P+ 0.01 M.R +0.02 M.V +71.0 I of R -0.221 Surface Tension +4.9 Density.

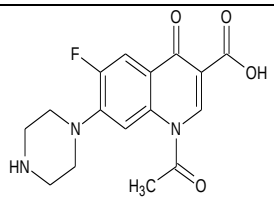
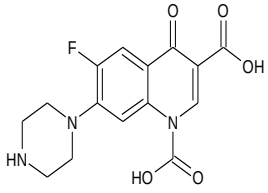
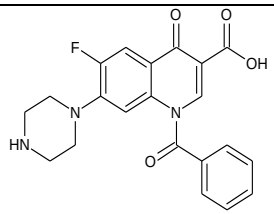
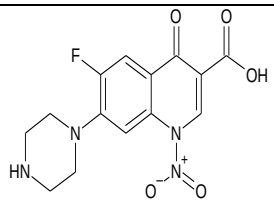
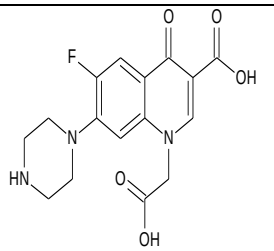
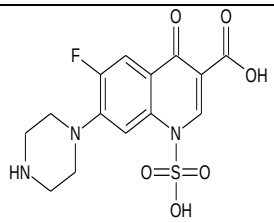
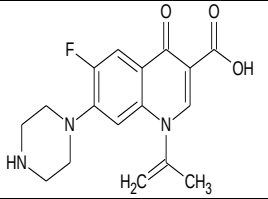
With $R^2 = 0.8205$

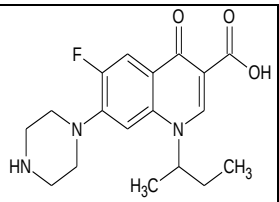
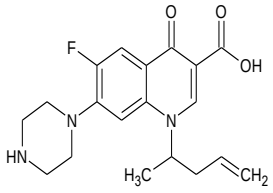
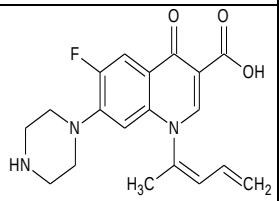
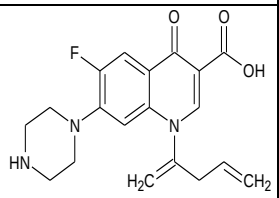
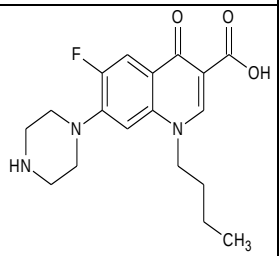
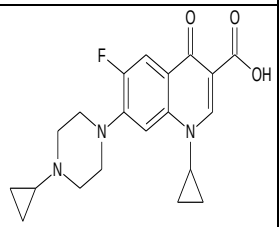
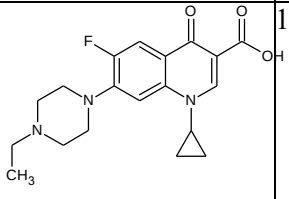
Table No. (3.1) ACD/Lab results of some Ciprofloxacin (1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolone carboxylic acid) derivatives and their calculated activity from QSAR equation:

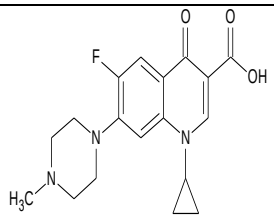
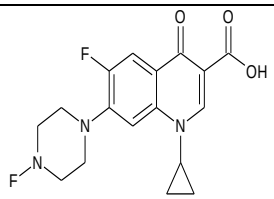
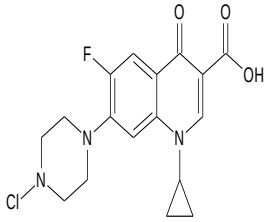
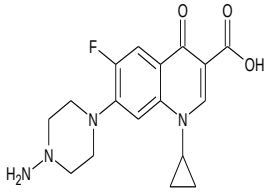
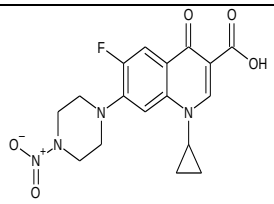
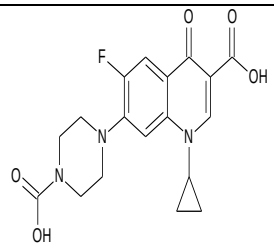
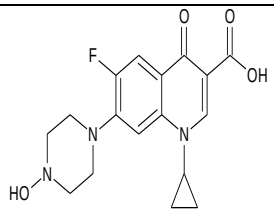
No.	substituent	Log P	Molar Refractivity ± 0.3 cm^3	Molar Volume ± 3.0cm^3	Index of Refraction ± 0.02	Surface Tension ± 3.0 dyne/cm	Density ± 0.06 g/cm^3	Biological activity (MBC)	-log MBC
1.		0.64	83.25	226.7	1.655	67.4	1.461	462.38	2.665
2.		0.65	83.25	226.7	1.655	67.4	1.461	475.88	2.6775
3.		0.29	83.26	222.5	1.671	69.4	1.408	75.35	1.8771

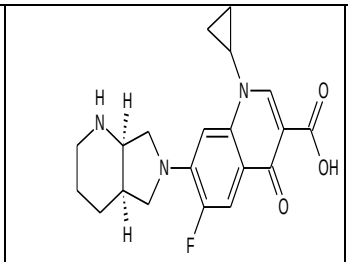
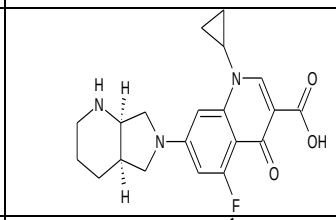
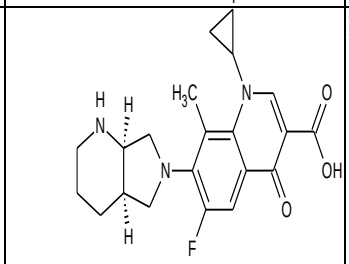
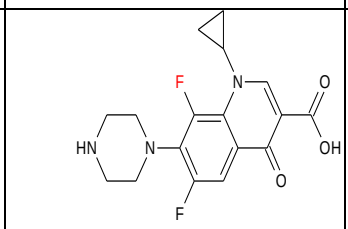
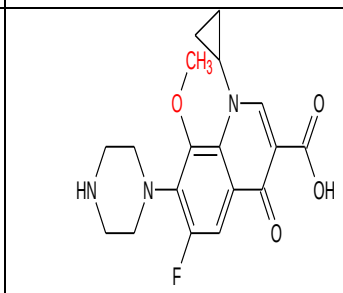
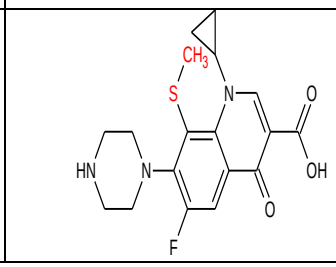
4.		0.75	88.08	238.8	1.659	66.0	1.37	231.58	2.3647
5.		0.99	87.49	224.8	1.706	79.0	1.460	111.07	2.0456
6.		0.36	85.14	220.9	1.697	78.4	1.490	52.36	1.719
7.		0.55	84.68	222.2	1.687	74.2	1.480	58.33	1.7659
8.		1.25	88.15	234.4	1.675	70.5	1.483	240.88	2.3818
9.		1.42	90.95	238.7	1.687	71.2	1.643	9.98	0.999
10.		0.59	91.43	235.1	1.705	75.7	1.468	3.74	0.5732

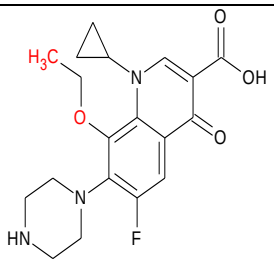
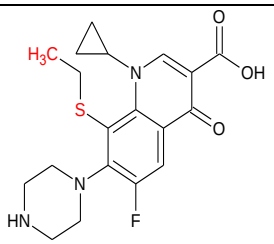
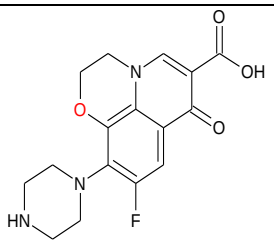
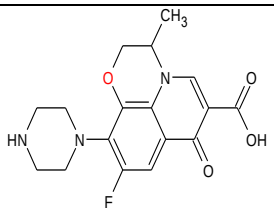
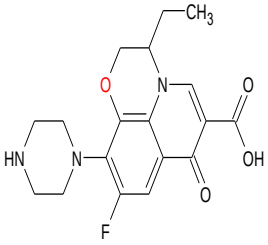
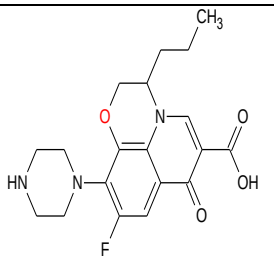
11.		1.22	87.86	244.4	1.637	63.3	1.412	3998.52	3.6019
12.		1.78	92.48	262.2	1.623	60.0	1.370	23227.36	4.3666
13.		1.03	72.79	197.9	1.656	68.9	1.560	4059.75	3.6085
14.		0.29	76.08	219.8	1.608	55.8	1.388	3700.84	3.5683
15.		0.82	80.70	237.4	1.595	53.1	1.344	23442.29	4.3745
16.		1.35	85.33	253.9	1.586	51.8	1.312	338064.84	5.5292
17.		1.17	85.24	251.9	1.591	52.8	1.322	33269.55	5.5221

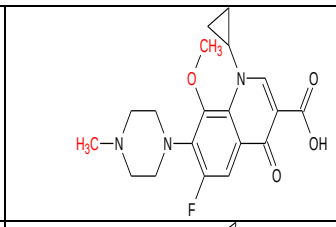
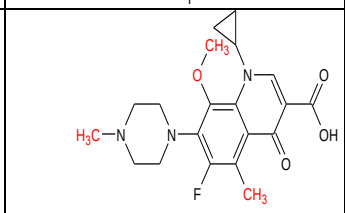
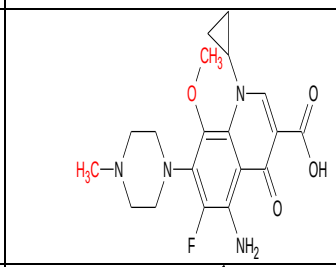
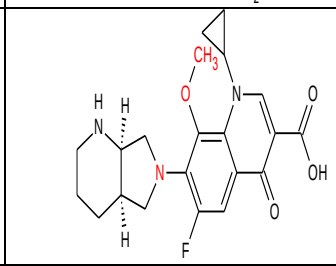
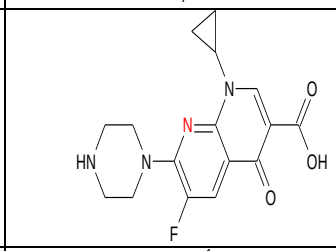
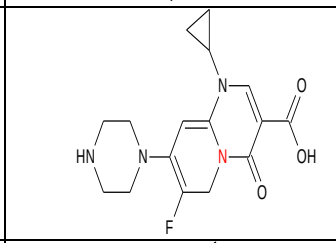
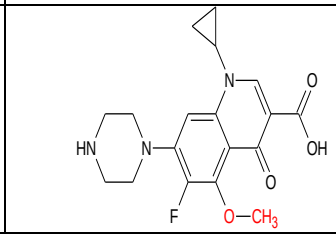
18.		0.10	80.58	231.1	1.614	61.1	1.442	850.16	2.9295
19.		0.23	77.48	212.1	1.651	74.5	1.58	5918.34	3.7722
20.		1.65	101.02	276.8	1.650	63.0	1.427	198.52	2.297
21.		0.45	76.71	204.6	1.695	84.2	1.640	852.31	2.9306
22.		0.26	82.26	232.0	1.627	66.7	1.505	5147.54	3.716
23.		0.45	83.03	209.4	1.723	97.2	1.77	1045.68	3.0194
24.		0.28	84.75	245.4	1.607	54.4	1.350	803.34	2.9049

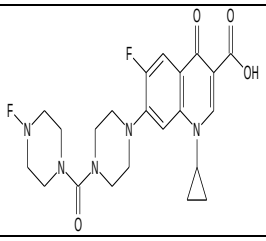
25.		1.70	89.87	268.4	1.584	51.5	1.293	143218.79	5.1659
26.		1.91	94.23	280.0	1.587	51.0	1.283	141905.5	5.1525
27.		0.82	94.07	272.0	1.608	53.1	1.313	599.38	2.7777
28.		1.02	93.74	273.5	1.601	52.4	1.306	2385.61	3.3776
29.		1.88	89.97	270.4	1.579	50.6	1.284	545506.59	5.7368
30.		1.71	95.35	248.6	1.692	76.9	1.493	574.38	2.7592
31.		1.88	92.80	259.3	1.634	62.0	1.385	13724.61	4.1375

32.		1.35	88.18	241.7	1.649	65.5	1.428	2349.63	3.371
33.		0.87	84.85	227.1	1.669	69.9	1.53	140.9	2.1489
34.		1.14	89.56	233.5	1.693	74.8	1.56	34.93	1.5432
35.		0.54	87.02	229.3	1.683	76.1	1.510	139.6	2.1449
36.		0.29	90.77	233.7	1.704	83.5	1.60	25.72	1.4103
37.		0.39	89.58	234.0	1.691	84.7	1.603	512.23	2.712
38.		0.62	85.06	218.7	1.705	85.3	1.587	371.88	2.5704

39.		1.53	95.14	260.9	1.649	63.3	1.423	479.4	2.6807
40.		1.52	95.14	260.9	1.649	63.3	1.423	465.8	2.6682
41.		1.99	99.96	277.2	1.640	60.9	1.390	1418.4	3.1518
42.		1.05	83.25	230.9	1.640	65.5	1.512	3081.06	3.4887
43.		0.72	89.93	250.7	1.636	63.3	1.441	668.96	2.8254
44.		1.13	97.14	252.9	1.694	73.4	1.49	10.70	1.0295

45.		1.25	94.56	267.2	1.625	61.5	1.404	4071.93	3.6098
46		1.66	101.77	269.0	1.680	70.8	1.45	86.92	1.9391
47		0.34	81.63	212.1	1.695	77.8	1.57	33.50	1.525
48		0.15	86.23	228.9	1.677	72.5	1.51	20.12	1.3037
49		0.68	90.86	245.1	1.663	69.7	1.47	146.93	2.1671
50		1.21	95.50	261.3	1.651	67.3	1.430	947.98	2.968

51		1.41	94.86	265.7	1.632	62.2	1.412	2852.996	3.4553
52		1.87	99.68	282.0	1.624	59.9	1.380	7457.62	3.8726
53		0.31	99.09	268.0	1.661	69.6	1.456	22.53	1.3528
54		1.60	101.82	284.9	1.633	60.5	1.408	648.78	2.8121
55		0.39	81.34	219.9	1.661	74.0	1.510	1995.72	3.3001
56		-0.74	83.94	220.4	1.686	72.1	1.510	32.11	1.5067
57		0.50	89.93	250.7	1.636	63.63	1.441	355.14	2.5504

58		0.63	113.84	289.5	1.688	77.5	1.540	3.91	0.5926

3.1.2.The result of docking:

Docking is used to predict the binding orientation for the (5) compounds which have high predicted biological activity to their protein targets (4eru and 1jij) and the results were illustrate in figures bellow**.**

Figure (3.1) interaction between compound 2 and receptor 4eru

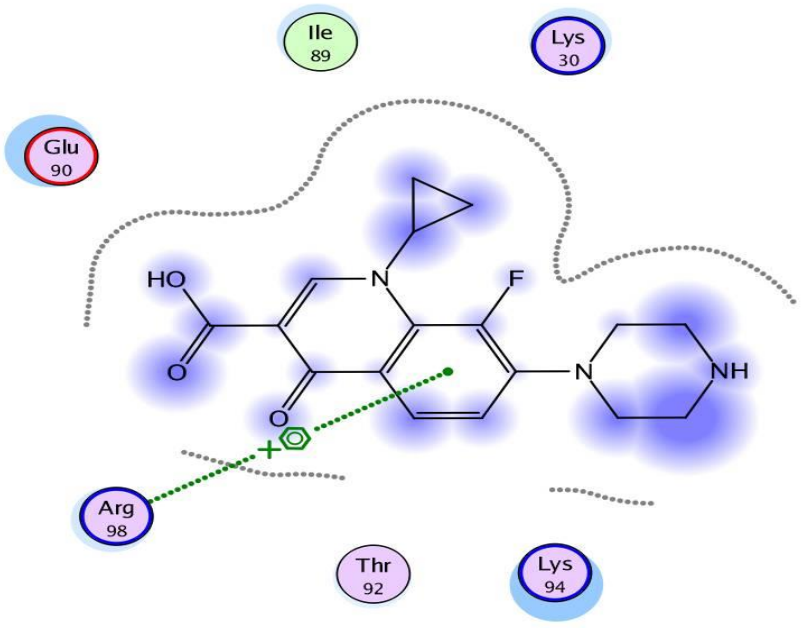


Figure (3.2) interaction between compound 2 and receptor 1jij

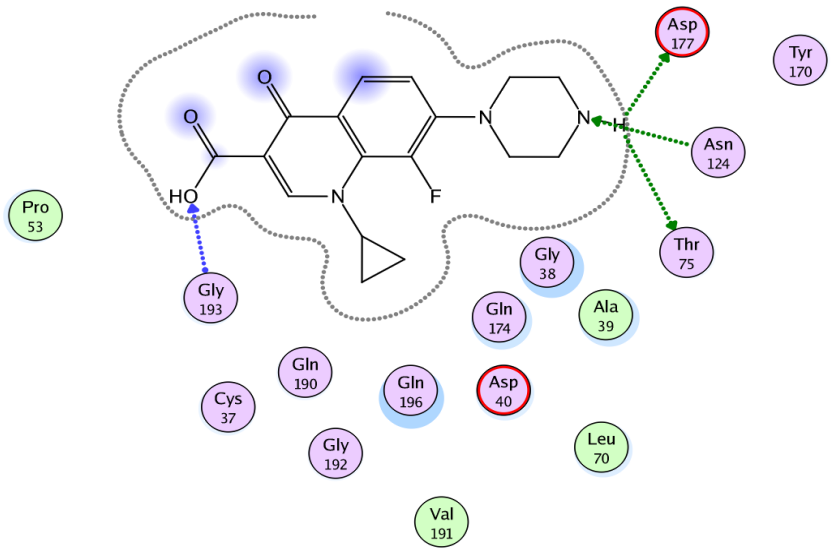


Figure (3.3) interaction between compound 12 and receptor 4eru

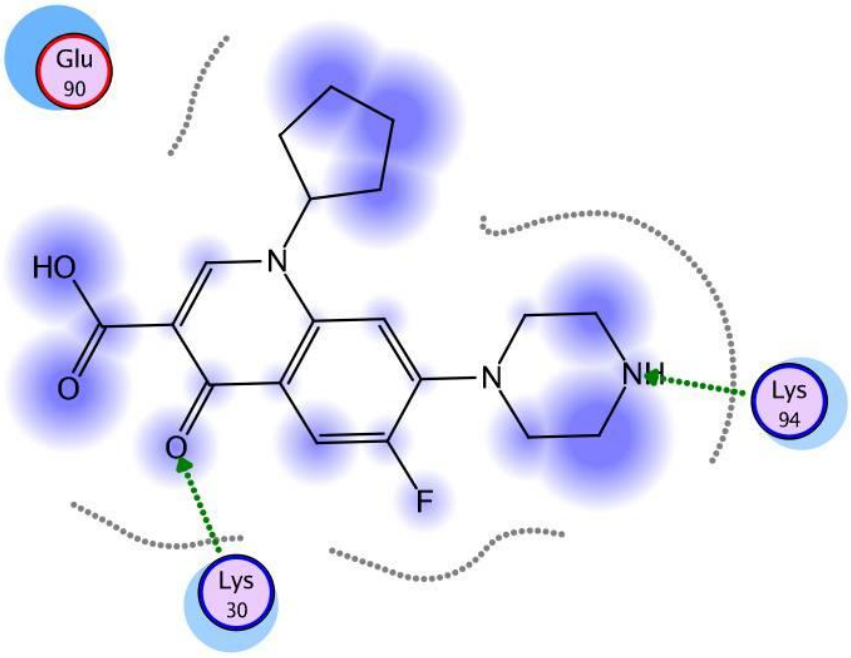


Figure (3.4) interaction between compound 12 and receptor 1jij

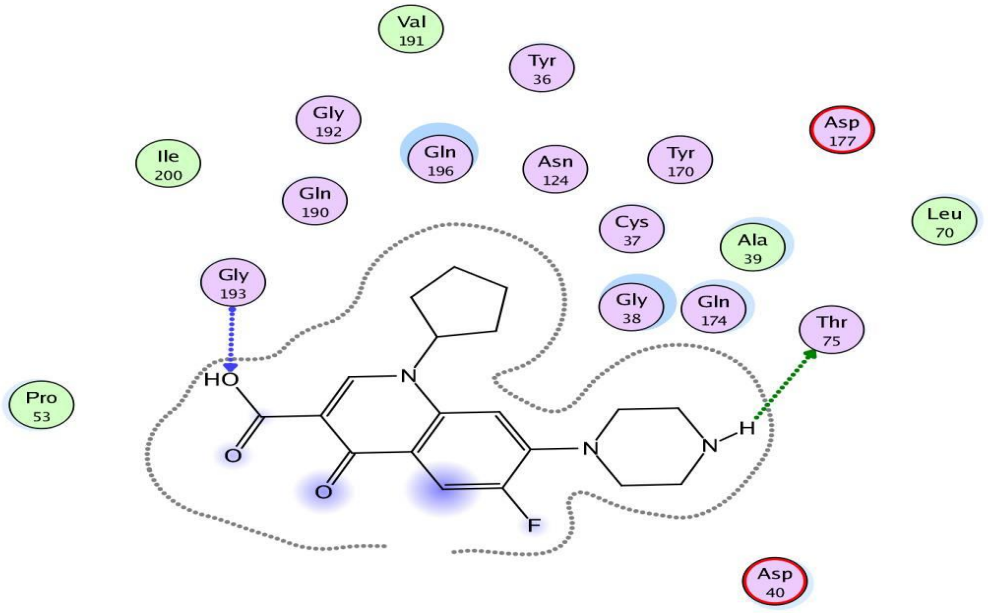


Figure (3.5) interaction between compound 26 and receptor 4eru

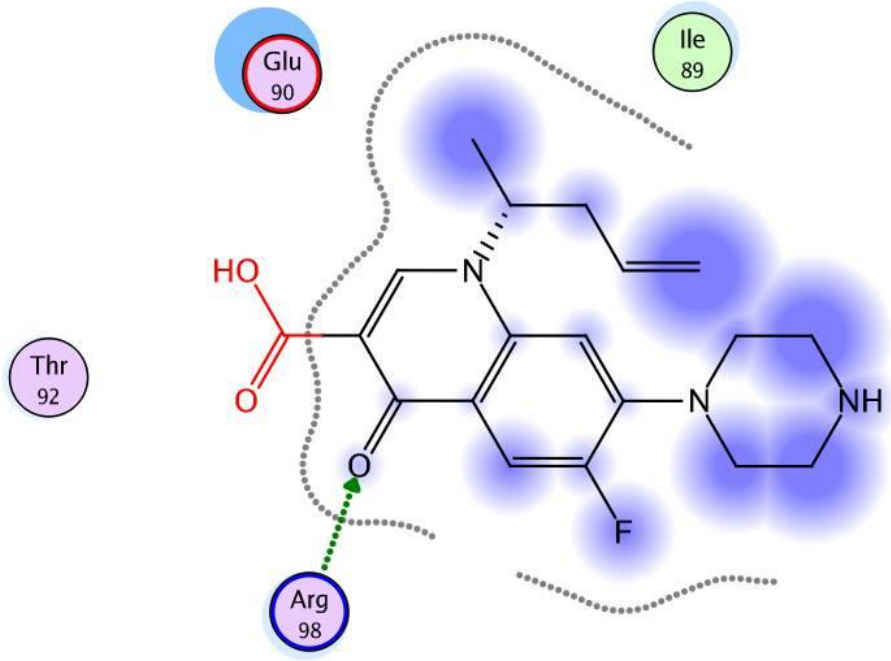


Figure (3.6) interaction between compound 26 and receptor 1jij

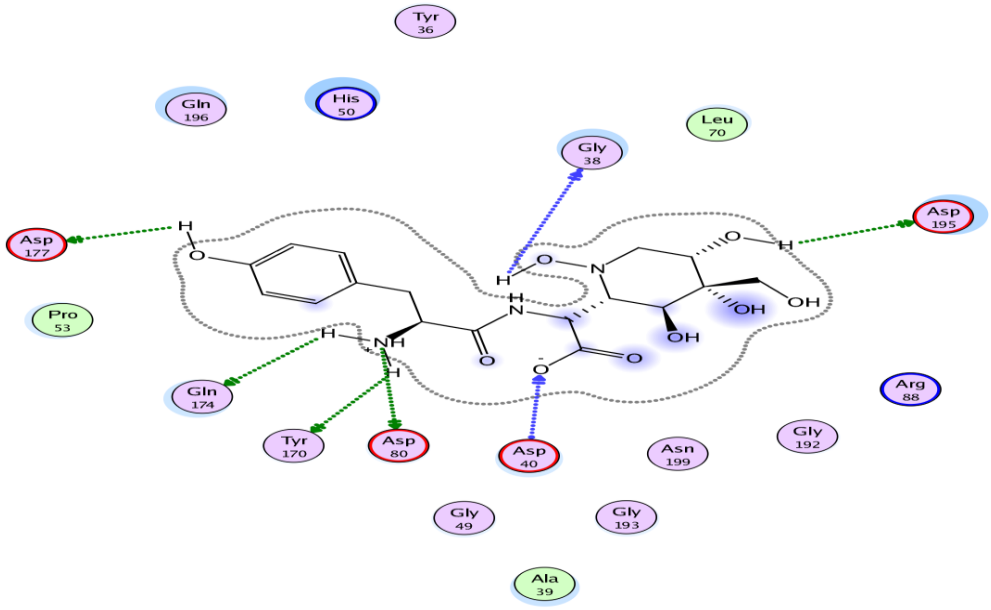


Figure (3.7) interaction between compound 29 and receptor 4eru

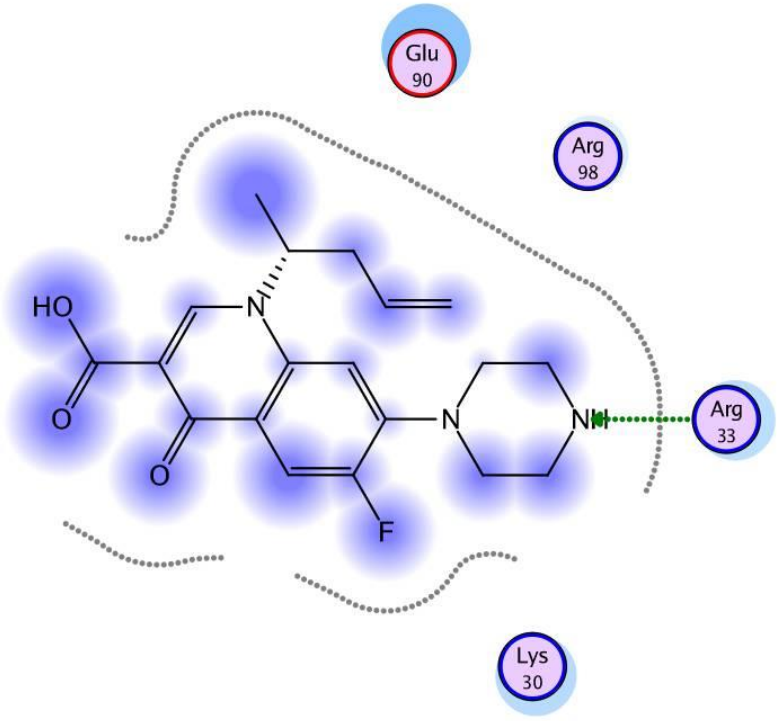


Figure (3.8) interaction between compound 29 and receptor 1jij

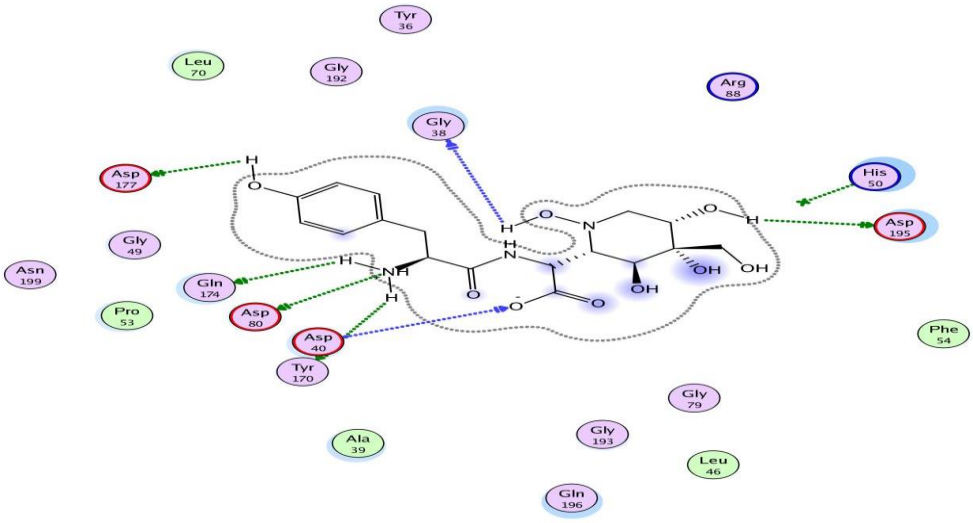


Figure (3.9) interaction between compound 25 and receptor 4eru

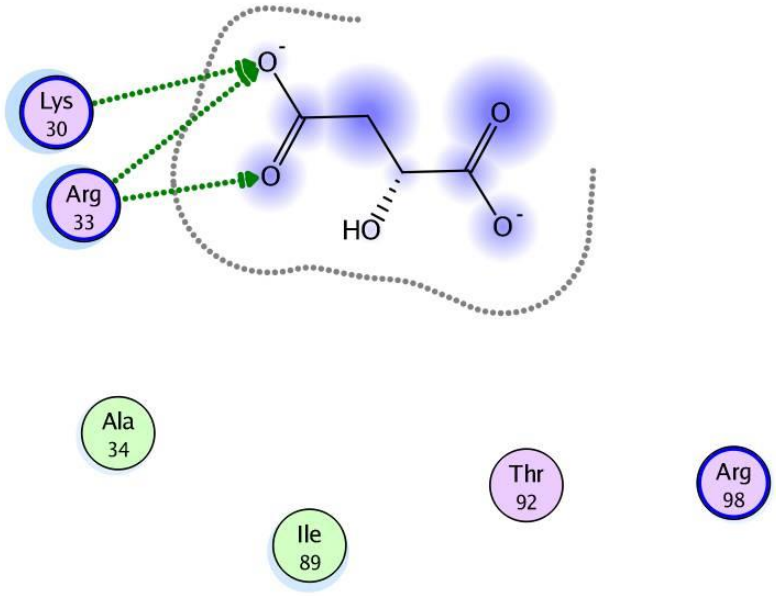


Figure (3.10) interaction between compound 25 and receptor 1jij

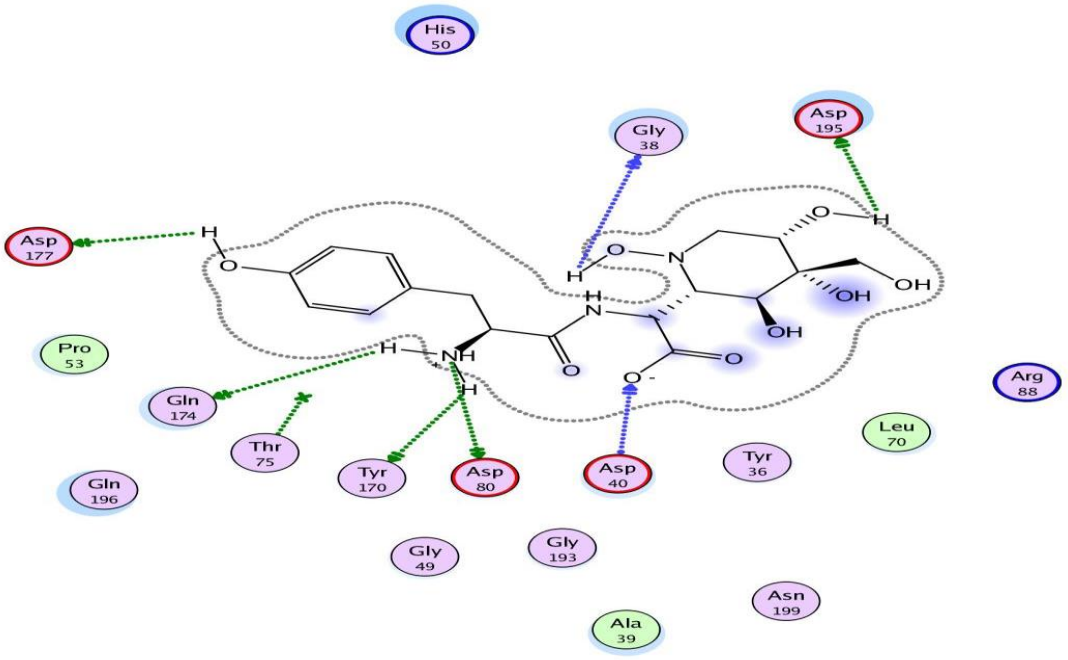
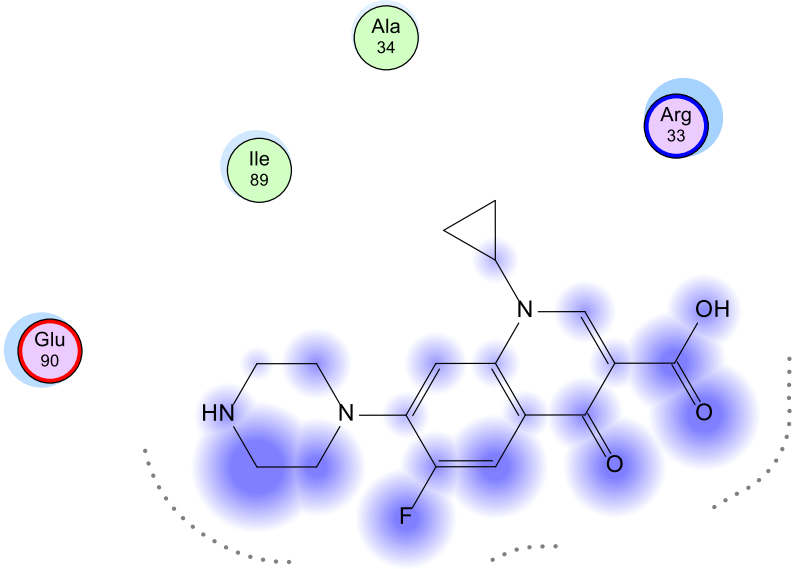


Figure (3.11) interaction between Ciprofloxacin and receptor 4eru



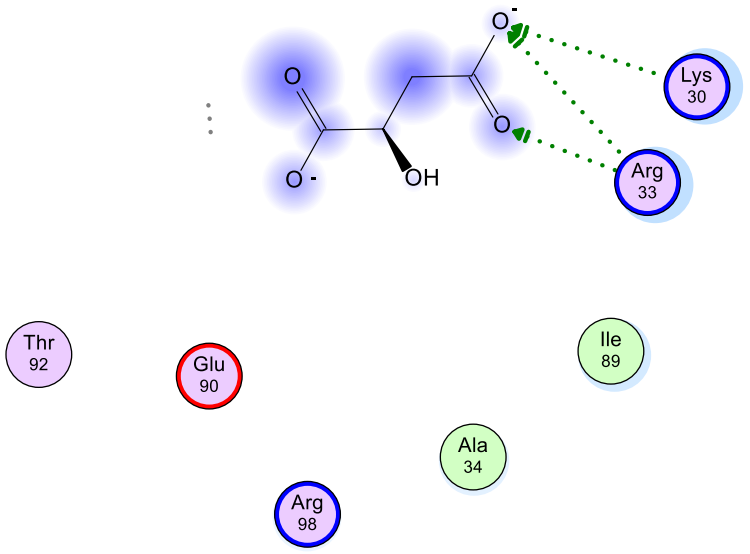
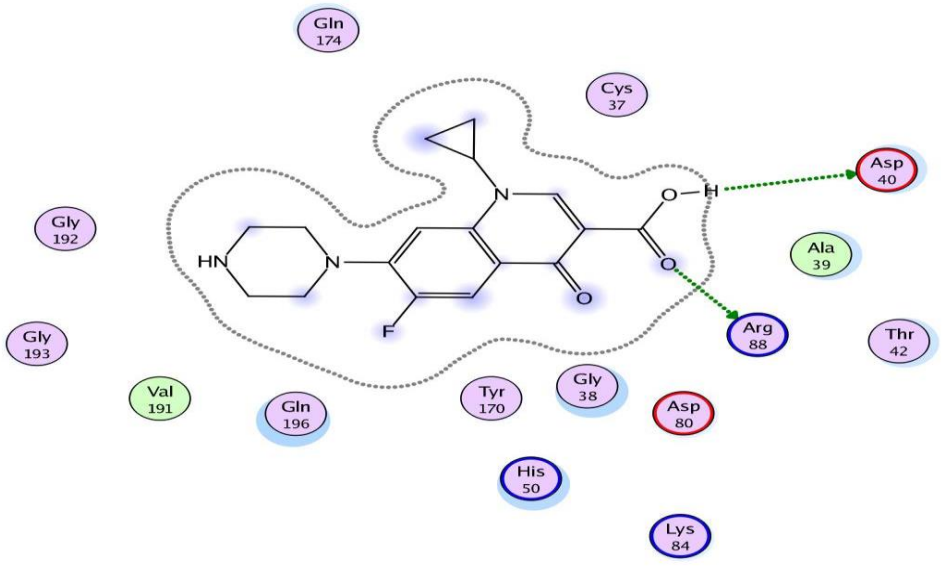


Figure (3.12) interaction between Ciprofloxacin and receptor 1jij



3.2. Discussion:

Quinolones are a group of synthetic antibacterial that effectively inhibit DNA replication and are commonly used as treatments for many infections. The presence of a fluorine atom to the original quinolone compounds usually at position 7;yielded new class of drugs the fluoroquinolones, highly active against diverse microorganism. Fluoroquinolone derivatives are large group with abroad range of biological activities, and much continuous effort has gone into the structural modification of the fluoroquinolone framework to provide newer congeners with improved potency and efficacy to conquer the fluoroquinolone-resistant pathogens commonly encountered. Based on the structure-activity relationships of fluoroquinolones that have been well addressed, substituent at the 7-position of the fluoroquinolone skeleton greatly influence their antimicrobial spectrum, potency, and even safety.

3.2.1Regression analysis:

Regression analysis is a powerful statistical method that allows to examine the relationship between two or more variable of interest. While there are many types of regression analysis, at their core they all examine the influence of one or more independent variables on dependent variable.

In this study a regression was performed by using Minitab procedure and by choosing randomly descriptors as independent variable and plotted against biological activity as dependent variable a number of QSAR equations were obtained allows to determine that factors can be ignored and how these factors influence each others.

In this antimicrobial agents research program a series of ciprofloxacin derivatives were designed and their activities (MBCs) were calculated using quantitative structure activity relationship equation which obtained and was found a number of designed compound have higher biological activity than ciprofloxacin.

There was recent study that modified the structure of ciprofloxacin at the 7 -position and provided 7-(4-carbo- piperazin-4-yl) derivatives with improved antimicrobial activities compared to the prevailing ciprofloxacin. 7-[4-Carbopiperazin-4-(3,5-dimethoxybenzoyl)-yl] derivative and 7-[4-carbo-piperazin-4-(4-trifluoromethoxybenzenesulfonyl)-yl] derivative showed an impressive selective potency against a clinic isolate of CRPA and also maintained activities against MRSA, demonstrating that the delicate manipulation at the 7-position of the fluoroquinolone framework can still be a suitable ways to obtain new, broad spectrum fluoroquinolones, against especially the Gram-negative pathogens and certain drug-resistant strains.

Computers become essential tool in both drug discovery and drug development, by which time and material are saved. Computational chemistry based on selecting a set of compounds of known activities to drive quantitative structure activity relationship equation which enable finding relationship between observed properties of structure and biological activities; as a result new chemical structures were design which could have a good inhibitory effects on specific targets and have low toxicity.

Molecular docking is the process that involves placing molecules in appropriate configurations to interact with a receptor to form stable complex. Molecular docking is a natural process which occurs within seconds in a cell. Docking is frequently used to predict the binding orientation of drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. In this study we use molecular docking to achieve an optimized conformation for our designed compounds (ligand) and two type of proteins: (4eru) and (1jij) and the free energy of the overall system is minimized ,as illustrate in figure (3.1 - 3.10) there are more binding site particularly in compound 25,26 and 29 than in ciprofloxacin .

3.3Conclusion:

It was found that the structural modification in pharmacore of fluoroquinolone (figure 1.3) affect directly in biological activity , some molecular substitutions should not be altered as they interface or reduce the basic mode of action of compounds , these are position 2,3 and 4.

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