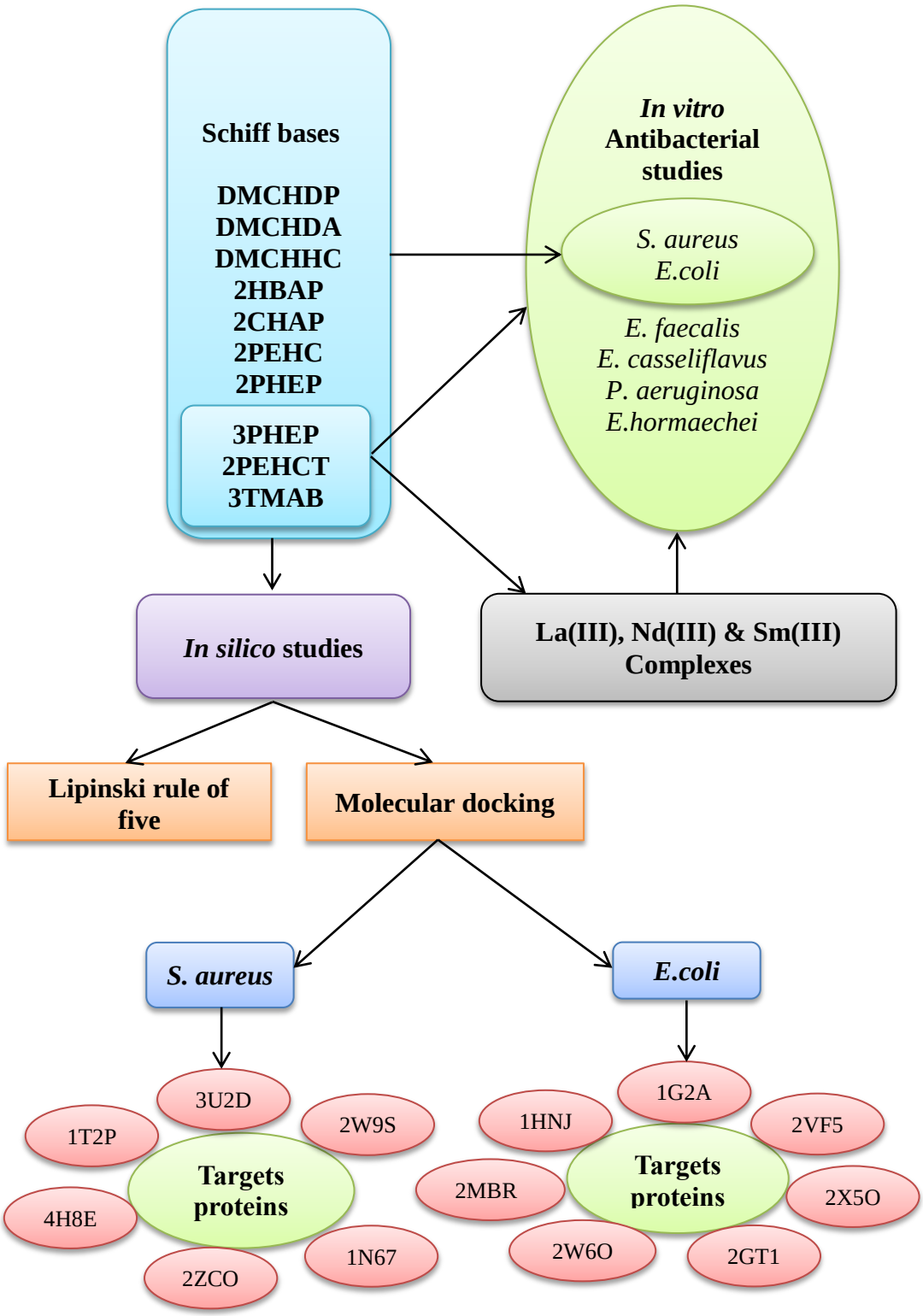
Ragi K " Structural, corrosion inhibition, chelation, biological and in silico studies of schiff bases." Thesis. Research and Postgraduate Department of Chemistry, St. Thomas' college (autonomous), University of Calicut, 2020.

PART- III

BIOLOGICAL STUDIES



CHAPTER 9
INTRODUCTION AND REVIEW

The research in the field of therapeutics is of great importance for the improvement of the quality of human life and for reducing human diseases. A vast number of diseases are caused by pathogenic organisms. Pathogens are microorganisms that are harmful to human body. Bacteria, virus, fungus, prion, protozoa, viroid etc are the different types of pathogens. Our body has the ability to defense against potential pathogens. Microbial infections are drastically increased in living beings due to multi drug resistant microorganisms. Even though a large number of antibiotics and chemotherapeutic agents are available to resist such microorganisms, the development of efficient novel chemotherapeutic agents is vital in the medical field [1-3].

Bacteria are microscopic organisms having cell walls. It is the first form of life in earth [4-5]. They have different shapes such as round, cylindrical and spiral. Round shaped bacteria are termed as cocci, whereas cylindrical and spiral bacteria are called as bacilli and spirilla respectively. Bacteriology is the branch deals with the study of bacteria. Even though they are essential in many processes like nitrogen fixation, some of them are pathogenic and cause infective diseases. Bacteria are generally categorized into two, namely gram-positive and gram-negative bacteria.

Gram-positive bacteria

Gram-positive bacteria are a bacterium that retains the violet colour of the stain used in Gram staining method. *Bacillus thuringiensis, Staphylococcus aureus, Bacillus subtilis, Enterococcus faecalis***,** *Enterococcus casseliflavus* etc are examples for gram-positive bacteria

Staphylococcus aureus

S. aureus is a round-shaped bacterium which is a member of Firmicutes [6]. In Greek the meaning of the term Staphyle is 'bunch of grapes' and kokkos is berry. This name is given since the bacteria is forming grape like clusters. Cell wall of these species is amorphous and tough. Thickness of the cell wall is about 20-40 nm. Cytoplasm is present under the cell wall which is surrounded by cytoplasmic membrane. Major component of the cell wall is the peptidoglycan (50% of cell wall mass). The other component that contributes 40% of cell wall mass is teichoic acids. Remaining 10% of cell wall mass consists of exoproteins, surface proteins and peptidoglycan hydrolases.

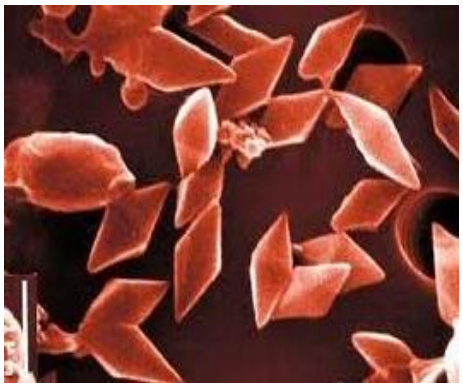


Fig. 9.1 Micrograph of *S. aureus*

Naturally this bacterium is found in nasopharynx of the human body and on skin. *S. aureus* can cause infections of nose, skin, vagina, urethra and gastrointestinal tract [7-8]. They are non-sporing, non-motile and few strains are capsulated. Nearly 50% of human population is carriers of *S. aureus*. It can grow in the temperature range 7-48.5^{0}C (optimum temperature 30-37^{0}C, pH of about 4.2-9.3 (optimum 7-7.5) and in the presence of upto 15% NaCl concentration. This helps them to grow in various food items. Micrograph of *S. aureus* is shown in Fig. 9.1.

Enterococcus faecalis

Enterococcus is a class of bacteria that is generally present in gut and bowel, vaginal tract and in oral cavity. Enterococcus when present in small amounts does not have any life threatening problems. Bacterial infection spreads throughout the body especially in people with unhealthy conditions which can cause even death [9]. Temperature range for the growth of Enterococcus is 10-42^{0}C. Of the approximately 17

types of Enterococcus species, the most common species found in human body are *E. faecalis* and *E. faecium. Enterococcus faecalis* is a gram-positive bacterium which was formerly known as *Streptococcus faecalis.* The *E. faecalis* genome consists of 3.22 million base pairs with 3,113 protein-coding genes. These bacteria will penetrate to human body through urine, blood and wounds which may cause infection [10]. Micrograph of *E. faecalis* is shown in Fig. 9.2.

Fig. 9.2 Micrograph of *E. faecalis*

Enterococcus casseliflavus

Enterococcus casseliflavus is a rare non-faecium, non-faecalis, vancomycin-resistant enterococcus (VRE) that is responsible for up to 2% of all enterococcal infections [11]. A large number of infections such as urinary tract infections, bacteremia, endocarditis, meningitis, septic arthritis, hematogenous osteomyelitis, pneumonia, pelvic, intra-abdominal and soft tissue infections will caused by enterococci. Micrograph of *E. casseliflavus* is shown in Fig. 9.3.

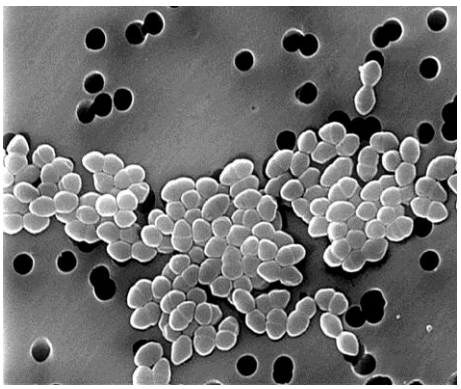


Fig. 9.3 Micrograph of *E. casseliflavus*

Gram-negative bacteria

Gram-negative bacteria are a bacterium that does not retains the violet colour of the stain used in Gram staining method. *Escherichia coli, Enterobacter aerogenes, Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter hormaechei* etc are examples for gram-negative bacteria.

Escherichia coli

In 1885 a German bacteriologist Theodor Escherich discovered *E. coli* in human colon. Normally found in intestines and in gut of some animals. They are rod-shaped, anaerobic and commonly found in intestines. It belongs to the genus Escherichia. The volume, length and diameter of the cell are 0.6–0.7 μm^3, 2.0 μm and 0.25–1.0 μm respectively. The cell wall consists of a thin peptidoglycan layer and an outer membrane. They are motile, non-caspulated, non-spore former and produce peritrichous flagella. Optimum temperature required for the growth is 15-45^{0}C. Few of them are pathogenic and the species which are not harmful will prevent colonization, helps in digestion and produce vitamin K and B_{12} [12-13]. Neonatal meningitis, urinary tract infections and gastroenteritis are the infections caused by *E. coli* in human. The symptoms are nausea, abdominal cramps, constant fatigue and diarrhea. Micrograph of *E. coli* is shown in Fig. 9.4.

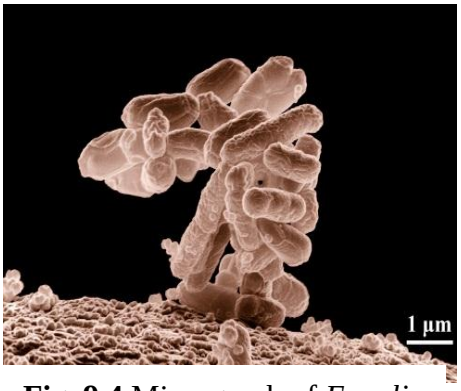


Fig. 9.4 Micrograph of *E. coli*

Pseudomonas aeruginosa

It is a rod-shaped gram-negative bacterium, 0.5-0.6 by 1.5 microns which are aerobic, motile with polar flagella, non-spore forming, nonfermentive, toxigenic and invasive. They appear as singly or in pairs or as short chains. This bacterium is considered as opportunistic and it infects urinary tract, wounds, burns and cause blood infections [14]. It is generally known for its high resistant capacity to antibiotics [15] and for its characteristic water-soluble pigment as pyoverdine

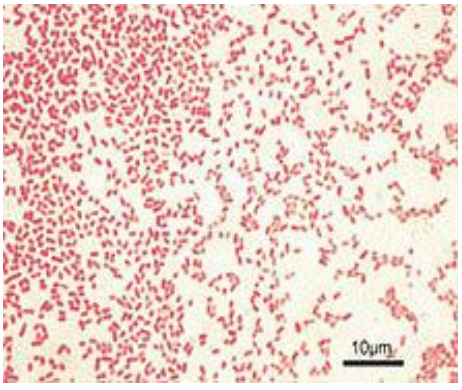


Fig. 9.5 Micrograph of *P. aeruginosa*

(yellow and fluorescent), pyocyanin (blue), pyomelanin (brown) and pyorubin (red). Temperature of about 37^0C or 42^0C is favorable for its growth. In 1882 it is first isolated from green pus by Gessard. They have fruity, sweet-grape smell, sometimes corn/taco-like odor. They are found in hot tubs, moist environment such as water and soil, fresh fruits and vegetables, lakes, rivers, streams, respiratory therapy equipment, dialysis tubing, catheters and portable water sources like sinks and showers. Micrograph of *P. aeruginosa* is shown in Fig. 9.5.

Enterobacter hormaechei

Enterobacter hormaechei is a new species belongs to *Enterobacteriaceae* family. It is previously called as Enteric Group 75 [16]. *Enterobacter hormaechei* is named in honor of Estenio Hormaeche, a Uruguayan microbiologist who (with P. R. Edwards) proposed and defined the genus Enterobacter. They are rod shaped, anaerobic, motile and non-spore forming. It is a member of coliform group of bacteria. Optimum temperature for the growth is 44.5^0C in the presence of bile salts. It can cause infections in respiratory and urinary tracts. They are oxidase reductase, ferment glucose with acid production and reduce nitrates to nitrites. Micrograph of *E. hormaechei* is shown in Fig. 9.6

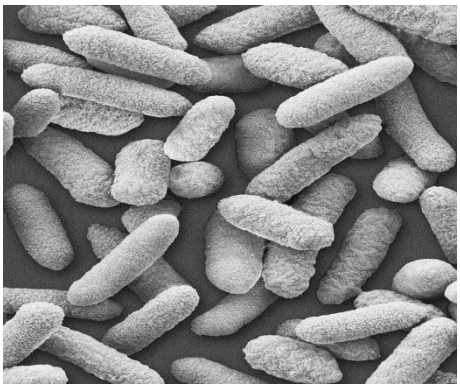


Fig. 9.6 Micrograph of *E. hormaechei*

Gram's method

Gram's method is used to classify the bacteria into two groups based on the difference in the cell walls [17]. This technique was named after a Danish bacteriologist Hans Christian Gram. Gram-positive bacteria consist of a thick peptidoglycan layer whereas in gram-negative bacteria peptidoglycan layer is thin and contains two outer

layers. In this method the bacteria is first stained with crystal violet dye and washed with absolute alcohol and water. Then it is again stained with a pink coloured dye safranin. A gram-positive bacterium retains the violet colour whereas a gram-negative bacterium gets the pink colour. This is due to the structural dissimilarity of the bacterial cell wall. A thick peptidoglycan layer present in the cell wall of gram-positive bacteria is responsible for retaining the violet colour of the dye. In the case of gram-negative bacteria the layer present outside the lipid will never bind the violet stain and get washed away during the staining processes. Schematic representation of Gram's test is shown in Fig. 9.7.

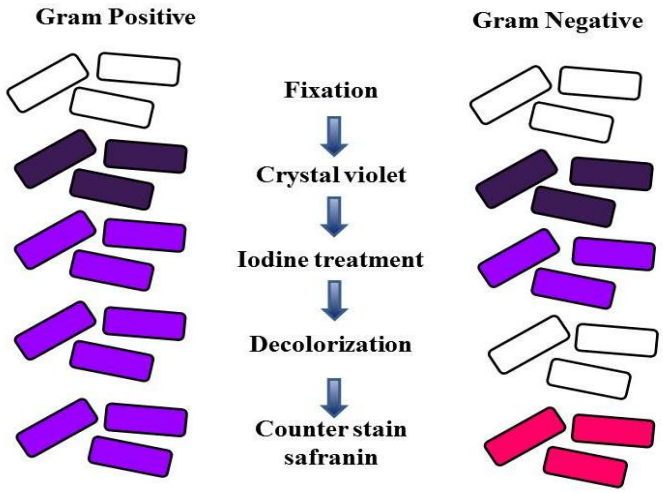


Fig. 9.7 Representation of Gram's test

Factors affecting the growth of bacteria

There are several factors that control the growth of bacteria. Nutrient concentration, pH, temperature, presence of salt and ions, gaseous concentration and light are some of the factors influencing the bacterial growth.

Nutrition concentration

The presence of substance promoting the growth of bacteria in the culture media will enhance the growth of bacteria. Nutrient concentration required for the growth of various bacteria is different. Rate of bacterial growth increases upto a certain level with increase in concentration of nutrient. After that the growth rate remains constant.

pH

Change in pH will affect the ionic properties of its cell. Therefore change in pH will affect the growth of bacteria. The suitable pH for the bacterial growth is in the range 6.5-7.5.

Temperature

Temperature range of about 0 to 85^0C is suitable for the survival of bacteria. The death rate of bacteria will be enhanced when the temperature is suddenly reduced, and even kill the bacteria at a lower temperature. If the water content in the medium where bacterial growth is high, low temperature is required to kill the bacteria. Bacteria are categorized into three depending on temperature range required for the growth as psychrophilic, mesophilic and thermophilic (Table 9.1).

Table 9.1 Classification of bacteria based on the temperature range required for the growth

Temperature (^{0}C)	Psychrophilic	Mesophilic	Thermophilic.
Minimum	0^0C	5-25^0C	25-45^0C
Optimum	15^0C	18-45^0C	55^0C
Maximum	30^0C	30-50^0C	60-93^0C

Minimum temperature and maximum temperature are the lowest and highest temperature that allows the growth of bacteria. Optimum temperature is the temperature at which bacterial growth is maximum. Solidification of cell membrane occurs below minimum temperature and denaturation of enzymes and cellular proteins occur above maximum temperature. As a result there is no bacterial growth below minimum and above maximum temperature. The optimum temperature for psychrophilic, mesophilic and thermophilic bacteria are 15^0C, 18-45^0C and 55^0C respectively.

Salt and ions

Metal ions like Zn^{2+}, Ca^{2+}, Fe^{2+}, K^{+} etc are required by the bacteria for the synthesis of enzymes and proteins. NaCl is not required for most bacteria however for halophilic bacteria such as *Archeobacteria*, high salt concentration is required.

Gaseous concentration

Oxygen and CO_2 has an important role in the growth of bacteria. O_2 is needed for aerobic respiration. Hence obligate aerobic bacteria will sustain in the presence of O_2 whereas it is harmful to anaerobic bacteria. CO_2 is required for capnophilic bacteria such as *Helicobacter pylori* and *Campylobacter.*

Light

Visible light is not harmful to bacterial cells whereas non visible rays like infrared and UV-visible rays have an adverse effect on bacterial cells.

Antibacterial agents

Antibiotics are the commonly used antibacterial agents [18]. They are substances generated by one microorganism that selectively inhibits the growth of another. They inhibit by disrupting different targets present in the bacteria and cell surface, by blocking the growth of new proteins and by inhibiting DNA replication. They are classified into various groups such as beta-lactams, glycopeptides, macrolides and ketolides, aminoglycosides, tetracyclines and glycylcyclines, quinolones, lincosamides, streptogramins, oxalidinones, lipopeptides, polymixins, ansamycins and sulfa drugs. The examples of antibiotics belong to these groups and their mechanism of action is shown in Table 9.2. Structure of antibiotics penicillin and ampicillin are given in Fig. 9.8 and 9.9 respectively.

Table 9.2 Classification of antibiotics with examples and their mechanism of action

Group	Examples	Mechanism of action
Beta-lactams	Penicillins, Cephalosporins, Carbapenems, Ampicillin	Inhibit cell wall synthesis
Glycopeptides	Vancomycin, Teichoplanin, Telavancin	
Macrolides and ketolides	Azithromycin, Telithromycin, Erythromycin, Clarithromycin	Inhibit protein synthesis
Aminoglycosides	Gentamicin, Amikacin, Tobramycin, Netilmicin, Streptomycin	
Tetracyclines and Glycylcyclines	Tetracycline, Tigecycline, Doxycycline, Minocycline	
Lincosamides	Clindamycin	
Streptogramins	Quinupristin/ dalfopristin	
Oxalidinones	Linezolid	
Ansamycins	Rifampicin	
Lipopeptides	Daptomycin	Destroys cell membrane structure
Polymixins	Colistin Polymixin B	
Sulfa drugs	Sulfamethoxazoletrimehoprim	Inhibit DNA synthesis
Quinolones	Ciprofloxacin, Norfloxacin Levofloxacin, Moxifloxacin	Inhibit DNA gyrase

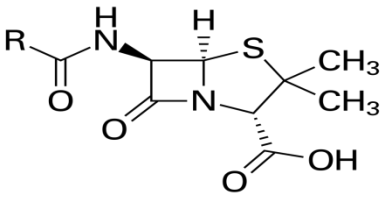


Fig. 9.8 Structure of Penicillin

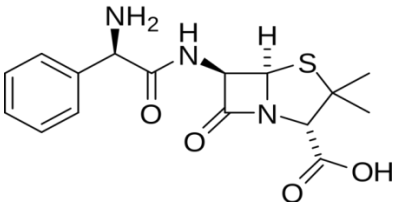


Fig. 9.9 Structure of Ampicillin

Molecular docking

Molecular docking is a key tool in the field of molecular biology and modern drug design. It is an *in silico* approach used to explore drug-receptor interactions [19-21]. Main aim is to predict the best-fit orientation of the drug molecule that binds to a specified protein target of interest in order to find out the activity and affinity of the drug molecule. Computer-aided drug design is a fast, automatic and very low cost process that can be done either by structure based drug design (SBDD) or ligand based drug design (LBDD) [22]. Ligand based drug design is an indirect method which have been used

when a series of ligand molecules having good activity is known and structural information about target is not available. Methods employed for this are pharmacophore modelling and quantitative structure activity relationship (QSAR). Former model designed to identify the ligand structures needed for target binding and the latter one is to suggest molecular similarity and biological activity. QSAR is based on the principle that structurally similar chemicals are likely to have similar physicochemical and biological properties. Structure based drug design is mainly based on the three dimensional structure of the target. If any target is not available it can be created by using homology modeling. Using the structure of the target, we can predict the binding affinity of drug molecules to the target. The most common method used for SBDD is molecular docking.

The vital steps involved in docking are prediction of conformation, position and orientation of the ligands within the target sites and evaluation of binding energy. Its default search function is based on Lamarckian Genetic Algorithm (LGA), a hybrid genetic algorithm with local optimization that uses a parameterized free-energy scoring function to estimate binding energy. Docking efficiency is high if the location of binding site is known before docking. In the lack of information about binding site, online severs or cavity detection programs such as POCKET, GRID, PASS, SurfNet and MMC have been used to identify active sites within target proteins. Docking without any idea about the active site is called blind docking. Schematic representation of docking procedure is shown in Fig. 9.10.

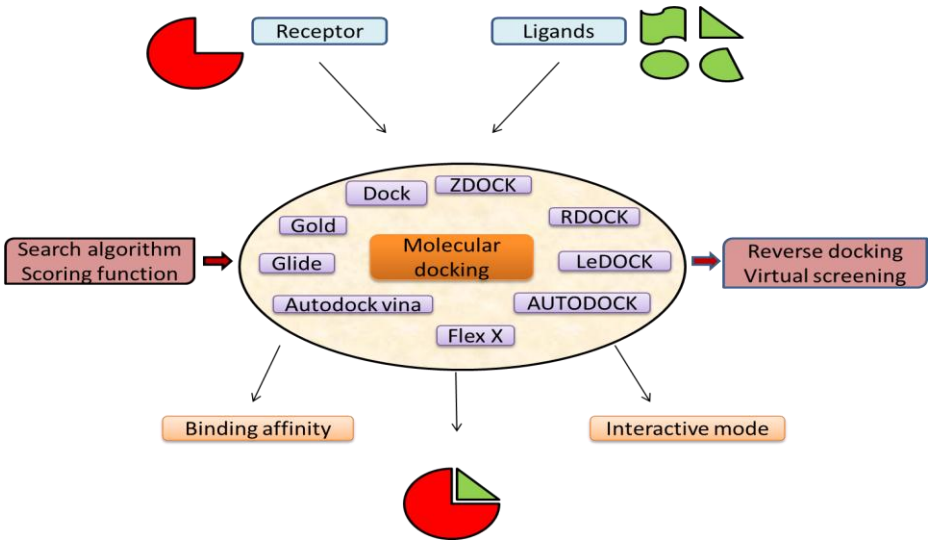


Fig. 9.10 Schematic representation of docking procedure

Schiff bases and its metal complexes as antibacterial agents – A review

Schiff base ligands and their metal chelates have wide application in the field of biology. They are found to be effective antibacterial, antifungal, antimalarial, antiinflammatory, antioxidant agents. Its ability to prevent the bacterial growth is well reported.

S. A. Patil and coworkers synthesized and characterized Cu(II), Co(II) and Ni(II) complexes of the Schiff bases derived from 8-acetyl-7-hydroxy-4-methylcoumarin and meta substituted thiosemicarbazides [23]. Characterization was done using spectral, thermal, magnetic and cyclic voltammetric studies. The antibacterial (*Escherichia coli*, *Bascillus subtilis*, *Staphilococcus aureus*, and *Salmonella typhi*), antifungal (*Aspergillus Niger*, *Candida albicans* and *Cladosporium*) and DNA cleavage activities of the complexes were also evaluated. It is found that Schiff bases and complexes are active against *E. coli*, *S. aureus* and *S. typhi*. All complexes exhibited enhanced activity against *S. typhi*. Another important observation is that antifungal activity of the Schiff bases and complexes is high compared to their antibacterial activity.

B. K. Singh et al. investigated antimicrobial activity of the Schiff base 2-aminophenol-pyrrole-2-carboxaldehyde and its Cd(II), Zn(II), Pb(II) and Sn(II)

complexes against two bacterium *E. coli* and *S. aureus* using agar well-diffusion method [24]. Coordination of ligand with metal was established using IR and NMR (^{1}H) spectroscopy. Chloramphenicol is used as the standard antibiotic to compare the activity of synthesized compounds. Ligand, Zn(II) and Cd(II) complexes are more active against *E. coli* whereas other complexes are active against *S. aureus.* Also the activity of Zn(II) complexes were higher than other complexes in both bacterial strains.

Cyclic voltammetry (CV) and antimicrobial activity of Cu^{II}, Mn^{II}, Co^{II}, Ni^{II}, VO^{II} and Zn^{II} complexes of two Schiff bases acetoacetanilido-4-aminoantipyrinyl-2-aminophenol and acetoacetanilido-4-aminoantipyrinyl-2-aminothiophenol were carried out by N. Raman et al [25]. Structure of the metal complexes were confirmed by spectroscopic techniques (IR, UV, ^{1}H NMR and ESR), magnetic moment measurement and microanalytical data. Microorganisms used for the antimicrobial acivity were *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Salmonella typhi, Shigella fleneri, Rhizoctonia bataicola, Klebsiella pneumoniae* and *Aspergillus niger*.

V. B. Badwaik and co-workers synthesized Fe(II), Ni(II), Cd(II), Mn(II), Cu(II), UO_2(VI), Zn(II) and Co(II) complexes of Schiff base derived from glycine and 2-hydroxy-5-methylacetophenone [26]. Characterization was done using IR, ESR, electronic spectroscopic techniques, electrical conductance, analytical, thermogravimetric analysis and magnetic susceptibility measurements. Anitibacterial activity is tested against both gram-positive and gram-negative bacterium using disc diffusion method. 10 mg/L is the concentration of the compounds taken for the study in DMSO. Both ligand and complexes have less activity than the standard antibiotic streptomycin. Inhibitory power of the ligand enhanced upon chelation.

Z. H. Chohan et al. synthesized Schiff base derived from amino-5-hydroxypyridine and salicylaldehyde and its Co(ll), Ni(ll) Cu(ll), and Zn(ll) metal

complexes [27]. Characterization was done on the basis of analytical, physical and spectral data. *S. aureus*, *Klebsiella pneumonae*, *E. coli*, *Proteus vulgaris* and *P. aeruginosa* were the bacterial strains used for screening antibacterial activity. Effect of anions in the antibacterial activity of the complexes was also monitored by preparing same metal complexes having different anions such as nitrate, chloride, acetate and sulphate. Activity of the complexes is enhanced when the anion are present in the order nitrate>oxalate>chloride>sulphate.

The synthesis and characterization of two novel Schiff bases N,N'-bis (acetophenone)ethylenediamine, N,N'-bis(4-nitrobenzaldehyde)ethylenediamine and their transition metal complexes (Zn(II) and Cd(II)) were done by A. Prakash and co-workers [28]. IR spectra indicate the bonding of ligand with metal through acetate and azomethine moiety. The *in vitro* studies were carried out to determine the antibacterial potential of the synthesized ligands and metal chelates. Both ligands and complexes are found to possess good antibacterial properties.

The antibacterial activity (*in vitro)* of the Schiff base N,N'bis(pyrrole-2-carbaldehyde)ethylenediamine and its Ni(II), Mn(II), Cu(II) and Co(II) complexes were evaluated using the bacterial strains *E. coli* and *S.aureus* by B. K. Singh et al [29]. Spectral, electrochemical and magnetic studies were used for characterization. The *in vitro* inhibitory activity of the metal chelates were high than the ligand. Also Ni(II) complex was found to more active than the other complexes.

Ti(III), Mn(III), MoO(V), Ru(III), V(III), MoO_2(VI), and UO_2(VI) complexes of the Schiff base derived from 2-aminophenol and 1-phenyl-2,3-dimethyl-4-(4-iminopentan-2-one)-pyrazolin-5-one were synthesized and characterized by A. Saxena and co-workers [30]. Geometry of all the complexes is found to octahedral. Antibacterial activity of both ligand and complexes were done against *B. subtilis* and *S. aureus.* The

nature of metal ion has influence on antibacterial activity. Order of activity against *B. subtilis* and *S. aureus* was Mn(III) > MoO(V) > MoO_2(VI) > Ru(III) > UO_2(VI) > V(III) > Ti(III) and MoO(V) > MoO_2(VI) > UO_2(VI) > Ru(III) > Mn(III) > V(III) > Ti(III) respectively

L. Lekha and co-workers synthesized Sm(III), Pr(III), Tb(III), Gd(III), Yb(III) and Er(III) complexes of sodium salt of 2-[(5-bromo-2-hydroxy-benzylidene)-amino]-3-hydroxypropionic acid [31]. General formula of the complexes was $[Ln(L)(NO_3)_2(H_2O)]NO_3$. Elemental analysis, UV–Vis, conductivity measurements, fluorescence study, FT-IR and mass spectrometry were used as characterization techniques. Antibacterial activity of the Schiff base and complexes were also carried out against *E. coli, P. aeruginosa, P. vulgaris* and *S. aureus* by means of agar diffusion method. Results showed that the activity of the Ln(III) complexes of the ligand is high compared to the corresponding ligand. That is activity is enhanced upon chelation. Also the Sm(III) and Gd(III) complexes showed exceptional activity compared to other complexes.

Seven Ln(III) complexes of the tetradentate Schiff base (N,N'-bis(1-naphthaldimine)-o-phenylenediamine) was synthesized and their antibacterial activity against *Staphylococcus aureus, Shigella dysenteriae, Escherichia coli, Serratia marcescens* and *Pseudomonas aeruginosa* using micro-broth dilution and agar well diffusion was done by W. M. Al Momani et al [32]. La(III), Nd(III) and Gd(III) complexes were more active than two standard antibiotics used against *Pseudomonas aeruginosa.* Pr(III) and La(III) complexes were effective against *Staphylococcus aureus* whereas complex of Sm(III) is effective against Serratia marcescens. Minimum inhibitory concentration observed is 1.95-250.00 μg/mL. Dy(III) and Er(III) showed no remarkable activity in comparison with the two standard antibiotics used.

S. Alghool et al. synthesized the Schiff base (3,5-di-tert-butyl-2-hydroxybenzyl) amino]acetic acid and its La(III), Gd(III), Ce(IV), Sm(III) and Nd(III) complexes [33]. Characterization was done by elemental analyses, IR, UV-visible, FAB-mass, magnetic measurement, molar conductance measurements and NMR spectral studies. Antibacterial and antifungal activity of the complexes was also evaluated. Antibacterial activity was screened against the bacterial strains *S. aureus* and *E. coli* whereas the antifungal activity was screened against *A. flavus* and *C. albicans*. Tetracycline and Amphotericin B are the standard antibiotics used in antibacterial and antifungal studies respectively. Results showed that the activity of the complexes was less compared to that of ligands.

Synthesis, characterization and antibacterial activity of the seven lanthanide complexes of a tridentate Schiff base derived from 2-aminopyrimidine and 2-hydroxyacetophenone were carried out by K. Mohanan and co-workers [34]. Luminescence, thermal decomposition, XRD and DNA cleavage study was also conducted. *E. coli*, *B. magaterium*, *S. typhi* and *S. aureus* were the bacterial species used for the study. Both the ligand and complexes have *in vitro* growth inhibitory activity with MIC values in the range 20–60 μg/mL. The *in vitro* growth inhibitory activity of the complexes were high than ligands.

Z. A. Taha et al. synthesized eight novel Ln(III) complexes (Ln(III) = Dy, Nd, Gd, Tb, Sm, Er, Pr and La) of bis-(salicyladehyde)-1,3-propylenediimine and characterized using elemental analysis, molar conductivity measurements, spectral studies and thermogravimetric analysis (TGA) [35]. Sm(III), Dy(III) and Tb(III) ions have characteristic luminescence, which indicates that the ligand is efficient for absorbing and transfer energy to metal. Most of the Ln(III) complexes have antibacterial activity against various pathogenic bacteria and are higher than the corresponding ligand. This is attributed to the increase in lipophilic nature of the metal when coordinated with

ligand. Activity of ligand is high against *Pseudomonas aereuguinosa* and *S. dysenteriae* whereas inactive against *P. vulgaris*. Also many of the complexes are more active than the standard antibiotics such as cephalexin and cephradine.

A novel Schiff base by the condensation of 3-aminopyridine and 8-formyl-7-hydroxy-4-methyl-coumarin and its nine Ln(III) complexes were synthesized by V. Mutalik et al [36]. In addition to characterization studies, fluorescence study, antibacterial, antifungal and antitubercular activities were also studied. *E. coli* and *S. aureus* were the bacterial strains whereas *C. Albicans* and *A. Niger* were the fungi used for the study. Antimicrobial activity of the complexes was found to be greater than that of ligand.

Nine novel lanthanide complexes of the Schiff base 5-bromosalicylidene -4-amino-3-mercapto-1,2,4-triazine-5-one (BrSAMT) having the general formula $[Ln(L)(ONO_2)(H_2O)_2]$ were synthesized and characterized by A. S. Ramasubramanian and co-workers [37]. Spectral, magnetic, thermal and molar conductance studies confirmed the coordination sites of the ligand. Antibacterial activity against gram-negative bacteria such as *E. coli, Salmonella typhi, Shigella flexneri* and *Pseudomonas aeruginosa* was shown by La, Yb and Eu complexes.

S. Alghool et al. synthesized and characterized an amino acid Schiff base N-(2-hydroxybenzyl)-L-methionine acid and its La(III), Th(IV) and Ce(IV) complexes [38]. Structure of the compounds was confirmed by elemental, spectral and molar conductivity measurements. Both ligand and complexes were screened for antifungal and antibacterial activity. Antibacterial activity was screened against the bacterial strains *S. aureus* and *E. coli* whereas the antifungal activity was screened against *A. flavus* and *C. albicans*. Tetracycline and amphotericin B were the standard antibiotics used in antibacterial and

antifungal studies respectively. Results showed that the activity of the complexes is less compared to that of ligands.

Molecular docking studies with proteins as targets – A review

A series of 3-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4H-chromen-4-ones were synthesized and characterized by Vidya S. Dofe et al [39]. The characterization was done by IR, NMR (^{1}H and ^{13}C) and Mass spectroscopy. All the compounds were subjected to *in vitro* antibacterial study against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus subtilis* and antifungal activity against *Candida tropicalis*, *Candida albicans* and *Candida glabrata* by micro broth dilution method. Molecular docking study was also done to elucidate the binding at the active site. Docking studies were carried out using Glide v6.2 and the results showed that there is a good binding interaction.

A. Bharathi and co-workers synthesized six novel dihydropyrimido[4,5-*a*]acridin-2-amines and the structures were analysed using FTIR, EIMS, NMR (^{1}H and ^{13}C) and single crystal XRD studies [40]. The molecular docking and *in vitro* antidiabetic activity of the compounds on α–glucosidase and α-amylase activity were also evaluated. Docking studies were performed using AutoDock 4.0. The *in vitro* studies are in good agreement with docking studies.

G. Sabbagh et al. carried out docking studies of fifty flavonoids with β-ketoacyl acyl carrier proteinsynthase I (KAS I) present in *E. coli* using iGemdock v2.1 [41]. Among the flavonoids taken, two of them named isorhamnetin and genistein are found to exhibit binding energy of about −132.42 kcal/mol and −135.76 kcal/mol. This is comparable with the binding energy of the standard drugs cerulenin (−99.64 kcal/mol) and thiolactomicin (-90.26 kcal/mol). They are also found to obey Lipinski rule of five to predict druglikeness.

Antibacterial activity of fourteen novel qunioline based chalcones obtained by the condensation of 2,7-dichloro-8-methyl-3-formyl quinoline and acetophenone/ acetylthiophenes, were carried out against 3 gram-positive and 3 gram-negative bacteria by M. I. Abdullah et al [42]. Bioassay and computational (theoretical and docking) studies were also carried out. The chalcones having bromo or choro substituent are found to have high antibacterial activity. Docking study showed that the binding energy of chalcones having high interaction with DNA gyrase is -8.18 and -8.88 kcal/mol respectively.

Antifungal and antibacterial studies of the imidazole and pyrazole based compounds prepared by one-pot reaction, was carried out by F. Abrigach and co-workers [43]. Results showed that the compounds have efficient antifungal activity rather than antibacterial activity. This observation is also supported by lipophilicity study and structure-activity relationship analysis (SAR). In order to understand the interactions between ligand and the target molecule molecular docking study and homology modeling was conducted on compounds having higher activity against the fungus *Fusarium oxysporum f.sp. albedinis*.

J. N. Sangshetti and co-workers synthesized some linezolid-like Schiff bases and screened for their biofilm inhibition activity against *Pseudomonas aeruginosa* [44]. Out of these nine Schiff bases two of them are found to exhibiting high inhibition activity compared to standard linezolid. Also they are more potent than ciprofloxacin. Hence they are good antibacterial agents. Docking study of these highly active Schiff bases was also carried out against PqsD enzyme of *P. aeruginosa.* ADME analysis was also conducted and the results showed that they have capacity to develop as oral drug.

K. Gullapelli et al. synthesized oxadiazinanes and triazinane and conducted antibacterial analysis by means of well diffusion method against gram-positive and

gram-negative bacterial strains [45]. Results showed that they are good antibacterial agents. Molecular docking studies of the compounds were also done with the protein targets *DNA gyrase subunit b* and *topoisomerase II.* Results of docking study are in agreement with the antibacterial activity of the compounds.

Five 2-substituted 4-(2,5-dichlorothienyl)-1,3-thiazoles were synthesized, characterized and subjected to antibacterial and antifungal activity by B. K. Sarojini and co-workers [46]. The results showed that the thiazoles 4-(2,5-dichlorothien-3-yl)-2-amino-1,3-thiazole and 4-(2,5-dichlorothien-3-yl)-2-(8-quinolinyl)-1,3-thiazole are excellent antibacterial and antifungal inhibitors. Docking study was also carried out by taking L-glutamine: D-fructose-6-phosphate amidotransferase [GlcN-6-P] as target molecule. From the results it is clear that the 4-(2, 5-dichlorothien-3-yl)-2-(8-quinolinyl)-1,3-thiazole has lower binding energy and good inhibition capacity of GlcN-6-P.

G. Gomathi and co-workers synthesized methyl 3–[(E)–(2–hydroxy–1-naphthyl)methylidene]carbazate by means of slow evaporation solution growth technique [47]. Proton NMR, powder XRD, FT-RAMAN, UV-VIS-DRS analysis, FT-IR and fluorescence studies were carried out. From UV-VIS-DRS and fluorescence studies it was clear that the compound has bluish green emission property. Antimicrobial activity of the compound was screened against pathogenic bacteria such as *Streptococcus faecalis, Shigella dysenteriae, Bacillus cereus, Vibrio Cholerae* and fungi such as *Candida glabrata, Candida krusei* and *Candida albicans.* Docking studies showed that the compound has good binding affinity towards human estrogen receptor.

Scope and aims of present investigations

In addition to significant roles in catalysis and organic synthesis Schiff base ligands and their metal complexes have a wide variety of applications in biological, industrial, analytical and clinical fields. Coordination chemistry of lanthanides and its

complexes have aroused much interest since, chemistry of lanthanides is a promising research area inspired by a wide variety of applications. On account of the excellent coordination nature of Schiff bases to the rare earth ions, the coordination chemistry of rare earth complexes of Schiff bases are interesting and their role in chemical, industrial and medical field are enough to recognize them as worthwhile for the synthesis of new complexes.

Therefore in the present course of investigation it is proposed to carry out analysis of antibacterial activity of the Schiff base ligands 3PHEP, 2PEHCT and 3TMAB and some of their lanthanide (III) complexes against six pathogens such as *S. aureus, E. faecalis, E. casseliflavus, E. coli, P. aeruginosa* and *E. hormaechei***.** Ampicillin was taken as the standard antibiotic to compare the growth inhibitory power of the ligands and complexes. Molecular docking studies of all the ten Schiff base ligands were also proposed to conduct using AutoDock 4.2 in order to understand the mechanism by which the Schiff base molecules inhibit the growth of bacteria. Six target proteins from *S. aureus* and seven target proteins from *E. coli* were selected for this purpose. Drug ability of the Schiff bases is also to be preliminarily screened using Lipinski rule of five.