Antimicrobials are products that kill micro-organisms or keep them from multiplying (reproducing) or growing. They are most commonly used to prevent or treat disease and infections due to microorganisms.

Antibiotics are compounds of natural, semi-synthetic, or synthetic origin which inhibit growth of microorganisms without significant toxicity to the human or animal host. Penicillin [I] is a classic example of an antibiotic: it is produced by Penicillium fungi but has the ability to kill a number of bacteria and is, therefore, an effective antibiotic (and also an antimicrobial) when used appropriately to treat organisms that are susceptible to its effects.

Microbes are organisms too small for the eye to see and are found everywhere on Earth. There are many types of microbes: bacteria, viruses, fungi, and parasites. While most microbes are harmless and even beneficial to living organisms, some can cause disease among humans, other animals, and plants. These disease-causing microbes are called pathogens; sometimes they are referred to as “germs” or “bugs.” All types of microbes have the ability to develop resistance to the drugs created to destroy them, becoming drug-resistant organisms.

Although the definition of "antibiotic" doesn't specifically say that they are only effective against bacteria, the vast majority of antibiotics are used primarily to kill or inhibit the growth of bacteria. The term “antibacterials”, being the largest and most widely known and studied class of antimicrobials, is often used interchangeably with the term “antimicrobials”.

Extensive use of antibiotics has led to the emergence of multi-drug resistant microbial pathogen. [1] This highlights the incessant need for the development of new classes of
antimicrobial agents and alterations of known drugs in such a way that would allow them to retain their physiological action along with combating resistively by the pathogens. The designs of the proposed chemotherapeutic agents are particularly beneficial due to their distinctive mode of action which can avoid cross resistance to known drugs.

Chemotherapy has been spectacularly successful, yet the final solution is not here because some therapeutic agents have been withdrawn due to their high toxicity and the development of resistant to these agents by certain microbial strains. Following are the ways by which microbial cells might develop resistance: (A) The target enzyme is over produced, so that the drug does not inhibit the biochemical reaction completely. (B) The drug target is altered so that the drug cannot bind to the target. (C) The entry of the drug is prevented at the cell membrane/cell wall level. (D) Some microbial enzymes that convert an inactive drug to its active form are inhibited. (E) The cell secretes some enzymes to the extracellular medium, which degrade the drug.

Thus a satisfactory chemotherapeutic agent must:

- Destroy or prevent the activity of a microbe without harming the host cells.
- Be able to come in contact with the microbe by penetrating the cells and tissues of the host in effective concentrations.
- Leave unaltered the host’s natural defense mechanisms, such as phagocytosis and the production of antibodies.

The era of chemotherapy revolutionized the field of medicine. Syphilis is the first known disease for which a chemotherapeutic agent SALVARSAN [II] was used.

![Chemical Structure of SALVARSAN II]
Chloramphenicol [III] is a broad spectrum antibiotic, effective against a wide variety of Gram ‘−ve’ and ‘+ve’ organisms.[2]

Chloramphenicol

Clotrimazole [IV] have been found to possess broad-spectrum antifungal activity [3]

Clotrimazole

In organic synthesis, Imines reactions are useful in making carbon nitrogen bonds compounds containing azomethine group (-CH=N-). [Fig-1]

The possibility of having a lone pair of electrons in either π or sp² hybridized orbital or trigonally hybridized nitrogen in the >C=N group is of the fundamental chemical and
biological importance. Heterocyclic systems containing mainly nitrogen, sulphur and oxygen atom constitute a large class of compounds of biological and medicinal interest. [4]

Recent literature has explored the biological importance of various structural derivatives of heterocyclic compounds. Since 1864 [5] up to now, Imines have become increasingly important mainly due to their stability, ease of preparation, structural variability and variety of applications. On the other hand, Imines, the condensed products of aromatic amines with aromatic aldehydes, have been known to possess a wide variety of biological applications like antibacterial, antifungal, antitumor, analgesic and anti-inflammatory activities. [6, 7] It has been observed that several Imines show fungicidal [8], anti-inflammatory [9], antibacterial [10], antiviral [11], antioxidant [12], anticancer [13], antibacterial, [14] antifungal. [15]

Vanillin (4-hydroxy-3-methoxy benzaldehyde) is one of the most important widely used flavoring materials worldwide. [16–18] Synthetic vanillin is used in both food and non-food applications, in fragrances and as a flavoring in pharmaceutical preparations. Currently, approximately 50% of the worldwide production of synthetic vanillin is used as an intermediate in the chemical and pharmaceutical industries for the production of herbicides, antifoaming agents or drugs such as papaverine, l-dopa, methyldopa and the antimicrobial agent, trimethoprim. [19] Konstantinovic et al [20] synthesized vanillin Imines. [V]

![Vanillin Imines](image)

Imines derived [VI & VII] from vanillin having the central molecule with morpholine and sulphamethoxazole as the side chain, showed marked inhibition against the investigated bacteria and appeared to be promising antimicrobial agents. [21]
Imines containing heterocyclic scaffolds have been known to possess a wide range of biological and pharmacological activities for a long time. Biologically relevant Imines derived from a diverse group of heterocyclic scaffolds have been intensively investigated. It is strongly believed that the specific −C=N grouping (imine) is an important structural requirement for the bioactivity of Imines. The pharmacological potential of several heterocyclic scaffolds (pharmacophores) and their combined biological effect with an active moiety i.e., imino (−CH=N−) have been extensively studied. Nowadays, the research field dealing with Imine co-ordination chemistry has expanded enormously. The importance of Imine complexes of bio-inorganic chemistry, bio-medical applications, supra-molecular chemistry, catalysis and material sciences, separation and encapsulation processes and formation of compounds with unusual properties and structures has been well recognized and reviewed. Prasad et al synthesized a Imine [VIII] derived from amine derivative 1-(2-amino-5-chlorophenyl)-2,2,2, trifluoroethane-1,1-diol hydrochloride with aldehydes such as Isovanillin, Pyridine 2-Carboxyaldehyde, 2-Carboxybenzaldehyde and 3-hydroxy-4-methyl benzaldehyde study their antibacterial and antifungal activities. [22]
An Imines behaves as a Flexi-dentate ligand and commonly co-ordinates through the Oxygen atom of the de-protonated phenolic group and the N atom of azomethine group. [23] In Imine, azomethine nitrogen and other donor atoms like oxygen play a vital role in co-ordination chemistry. Hence an attempt is made to study the interaction of reduced Imine with transition metals of biological interest and to investigate the coordination chemistry of such interactions. Gamet et al described the synthesis and characterization of reduced Imine and its metal complexes. [24] Moreover antibacterial and analgesic activity of reduced Imine metal complexes is also evaluated and compared with the standards. [25] Aromatic aldehydes especially with an effective conjugation system, form stable Imines, whereas aliphatic aldehydes are unstable and readily polymerize. [26] Imine ligands with aldehydes are formed more readily than with ketone (carbonyl carbon). Imines have very flexible and different structures. A wide range of Imine compounds and their behavior studied because these compounds have very flexible and diverse structure. [27] Vaidehi et al synthesized a series of 4-Nitro Imines [IX] by condensation of 4-nitro aniline with substituted aromatic aldehydes and evaluate their antioxidant, antibacterial activities. [28]

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{N} \quad \text{==CH} \quad \text{R} \\
\text{IX}
\end{align*}
\]

Sobola et al [29] synthesized and evaluated antimicrobial activity of some Imine [X] derived from 2-hydroxy-3-methoxybenzaldehyde(o-vanillin)/2-hydroxybenzaldehyde (salicylaldehyde) and ortho-substituted anilines (R = Cl, Br, CH₃ and OCH₃).

\[
\begin{align*}
\text{X}
\end{align*}
\]
Imines have been found to be active against Gram ‘+ve’ and Gram ‘–ve’ organisms. Imine having chloro substitution derived from 4-amino-6-arylmethyl-3-mercapto-1,2,4-trizine-5(4H)-ones with substituted benzaldehydes possessed highest degree of antifungal activity against *C. albicans* [30] Imines bearing chloro [XI] and methoxy [XII] substitution have shown enhanced antibacterial and antifungal activities. [31-34]

Imines and their derivatives has been a research subject [35-38] owing to their pharmacological characteristics and striking complexometric behavior. These properties allow them to play apivotal role in various biological activities [39-41] viz., antibacterial [42] antifun[43], anti-carcenogenic [44], antitubercular [45], anticonvulsant [46], anti-HIV [47], antiamoebic [48], anti-inflammatory [49], antinociceptive [50], antimouse hepatitisvirus (MHV) [51] inhibition of herpes simplexvirus type-1(HSV-1) and adenivirus type 5(AD-5) [52], antimalarial [53] pesticidale thymidine phosphorylase inhibitors [54] antitumor [55] and herbicidal [56].

Bromotenoxim [XIII] [57], one of the most important herbicide containing the imine group is used for selective weed control in cereal crops.
Imines of aliphatic aldehydes are unstable and readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. Several derivatives of imines have been used as drugs and have been proved effective bacteriocides, pesticides, fungicides and insecticides [58] Abbas et al [59] synthesized and analyzed biological activity of sulfadimidine–imine complexes [XIV].

Salicylaldehyde and o-amino benzoic acid compounds are capable to form complexes with transition metal ions in the form of imines. Morad et al [60] prepared and studied the antibacterial activity of the prepared imine complex derived from salicylaldehyde and o-amino benzoic acid [XV].
Patel et al [61] synthesized a new series of 4,4’-methylene-bis-(N-substituted benzylidene-2,6-dibromo aniline) [XVI] obtained by condensation of 4,4’-methylene bis (2,6-dibromo aniline) with different various substituted aromatic aldehyde. All the synthesized compounds were tested for their antimicrobial activities.

![XVI]

Dapsone (4, 4’-diaminodiphenylsulphone), a sulphone analog, has been proved to be a powerful antimicrobial agent. Wadher et al synthesized imines of dapsone [XVII] and their derivatives as antimicrobial agents [62].

![XVII]

Priya et al [63] reported the synthesis and antimicrobial activities Schiff base complexes [XVIII] derived from salicylaldehyde and various aniline derivatives.

![XVIII]

Organic solid-state reactions have now emerged as a new area of chemical research because of its tremendous applications in variety of disciplines and in industries [64–69]. Solid-state reactions are eco-friendly and in many cases they occur faster than those in the presence of a solvent. Recently, it has been reported [70] that in many organic solid-state
reactions liquid phase also appears as a result of the formation of low melting eutectic mixtures or one of the reaction products is a liquid. Singh et al [71] reported the study of solid-state reaction between vanillin and p-anisidine to form imines. [XIX]

![XIX](image)

Matar et al [72] synthesized and explored antimicrobial activity of some imines derived from benzaldehydes and 3,3’-diaminodipropylamine. [XX]

![XX](image)

Vivekanand et al [73] have synthesized new Imines by the reaction between 3-((5-chloro-2-phenyl-1Hindole-3-amine and 2-thioxo-1,2-dihydroquinoline-3-carbaldehyde [XXI] and evaluated their antioxidant properties by DPPH free radical, scavenging activity, DNA-cleavage and antimicrobial activities.

![XXI](image)

Heterocyclic compounds are an integral part of the chemical and life sciences and constitute a considerable quantum of the modern research that is being currently pursued throughout the world. Jeyaraman and Avila et al have reviewed the importance of heterocyclic and bicyclic compounds as intermediates in the synthesis of several
physiologically active compounds. [74] These compounds are also found to be useful as intermediates for the synthesis of a variety of heterocyclic compounds. [75]

Thiazolidinones are the derivatives of an important group of heterocyclic compounds containing sulfur and nitrogen in a five-membered ring [Fig-2]. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as ‘wonder nucleus’ because it gives out different derivatives with all different types of biological activities.

![Fig-2](image)

4-Thiazolidinone derivatives have attracted continuing interest over the years because of their diverse biological activities, such as anti-inflammatory, antiproliferative, antiviral, anticonvulsant, antidiabetic, antihyperlipidemic, cardiovascular, antitubercular, antifungal, and antibacterial. Compounds such as; ralitoline (anti-convulsant), etozoline (anti-hypertensive), pioglitazone (hypoglycemic) and thiazolidomycin (activity against *streptomyces* species), based on this pharmacophore are already in the market. In recent years, 4-thiazolidinone derivatives with anti-tumor activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, pro-state and breast cancers cell lines have become a promising area of research. Different researchers have reviewed the progress on the scaffold from time to time. [76-81]

N and S heterocyclic compounds and their derivatives have been intensely explored for their applications in the field of antimicrobials and have been found to be the key component of many biologically active compounds such as cephalosporin. [XXII] The richest sources of diversity for the medicinal chemists are small heterocyclic rings, which in addition to exhibiting biological activity, may often serve as rigid scaffolds for further display of functionalities. Thiazole and thiazolidine derivatives belong to an important family of these heterocyclic compounds and display diverse pharmacological activities. [82-85]
4-thiazolidinones are derivatives of thiazolidine with carbonyl group at the 4th position and formed by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclisation with elimination of water. Moreover, the greatest difference in structure and property is exerted by the group attached to the carbon atom. p-anisidine, an aniline derivative have been found to be biologically interesting compound for many years. Since bulky substitution at all positions of 4-thiazolidinones have been reported and known to possess biological activity. Jubie and his group synthesized some 4-thiazolidinones of p-anisidine [XXIII] and screened for antitubercular, antimicrobial and cytotoxicity studies. [86]

Zhang et al synthesized 2,3-disubstituted-1,3 thiazolidin-4-one derivatives via the three-component reaction of aldehyde, amine and mercaptoacetic acid in 1-butyl-3-methylimidazolium hexafluorophosphate without any catalyst. This procedure was simple, efficient and straightforward and no aqueous work-up is needed. A series of novel pyrimidine nucleoside-thiazolidin-4-one [XXIV] hybrids can be prepared. [87]
Desai et al has carried out the microwave assisted synthesis of thiazolidinone from the Imines by using thiolactic acid. The products [XXV] were synthesized by conventional and microwave synthesis. [88]

![XXV]

Literature survey reveals that several substituted thiazolidinones have been prepared from different synthetic routes. [89-99] The main synthetic routes to 1,3-thiazolidin-4-ones involve three components (an aldehyde, an amine and mercaptoacetic acid), either in a one or two-step process. The reactions proceed by initial formation of an imine, which undergoes attack by the sulfur nucleophile, followed by intramolecular cyclization on elimination of water. The most common protocol to remove the water is by azeotropic distillation. Dicyclohexyl-carbodiimide (DCC), which is extensively used in peptide synthesis dehydration, strongly promotes the dehydration here too. Some improved protocols have also been reported by wherein N,N-dicyclohexylcarbodiimide/2(1Hbenzotriazo-1-yl)-1,1,3,3tetramethyl-uraniumhexafluorophospate is used as a dehydrating agent to accelerate the intramolecular cyclization.

![XXVI]

Thiazolidinones are an important class of heterocyclic compounds known for their potential pharmaceutical applications [100]. In the development of an efficient procedure for the synthesis of some new thiazolidinone derivatives, literature reported the synthesis of key intermediate4-[4(4-aminophenylamino)-6-dimethylamino-[1,3,5]triazin-2-yl]oxy]1-methyl-
1H-quinolin-2-one which contain quinolone derivative. Quinolone derivatives are used as anticancer \[ \text{[101]} \], anti-HIV \[ \text{[102]} \], anti-tumor \[ \text{[103]} \], anti-inflammatory \[ \text{[104]} \] and antithyroid agents. \[ \text{[105]} \] On account of the prominent biological applications of 1,3,5-triazines an quinolones, the intermediate compound seems to be a good candidate to fulfill our objective via its condensation with different aldehydes to afford imine and further cyclisation to get thiazolidinones. Piperazines and substituted piperazines are important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry. \[ \text{[106-108]} \] Literature survey ascribes that Mannich reaction for thiazolidinone derivatives are important and these types of derivatives possess significant biological activities. \[ \text{[109]} \] In view of these conceptions, Patel et al \[ \text{[110]} \] synthesized thiazolidinone derivatives attached with N–ethylpiperazine. \[ \text{[XXVII]} \] All the novel derivatives have been screened for their antimicrobial activity.

![XXVII](image)

1,3,4-thiadiazoles and 1,3-thiazoles and their derivatives exhibit various biological activities such as antitubercular \[ \text{[111]} \], antimicrobial \[ \text{[112-114]} \], anti-inflammatory \[ \text{[115-117]} \], antiviral, \[ \text{[118]} \] anticonvulsant, \[ \text{[119]} \] antihypertensive \[ \text{[120,121]} \], local anesthetic \[ \text{[122]} \], anticancerous, \[ \text{[123,124]} \] antihypoglycemic \[ \text{[125]} \] and cytotoxic activities \[ \text{[126-131]} \]. Nandini and his group studied antifungal and antimicrobial activities of some synthetic compounds \textit{viz}: 5-arylidene-2-imino-4-thiazolidinones \[ \text{[XXVIII]} \] and found that the compounds bearing chloro, bromo and hydroxyl moieties show promising biological activity. \[ \text{[132]} \]
One pot three component synthesis containing aldehyde, thiourea and chloroform to give 2-amino-4-thiazolidinone derivatives [XXIX] was also reported [133]. Various imino-thiazolidinones were developed by using different reagents with different reaction conditions.

Nicotinic acid and its amides proved to be powerful antimicrobial agent. Quantitative structure activity relationship (QSAR) studies have also been performed on the basis of the fact that the biological activity of a compound is a function of its physicochemical properties. Sharma *et al* synthesized N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide derivatives [XXX] and studied QSAR analysis [134].
Garnaik et al [135] synthesized a series of 2-(benzothiazolyl2’)azino-5-arylidene-4-thiazolidinone derivatives. [XXXI]

\[ \text{XXXI} \]


\[ \text{XXXII} \]

Rosiglitazone [XXXIII] and pioglitazone [XXXIV], the two thiazolidinone based drugs have been found to be the most potent antidiabetic agents. [137]

\[ \text{XXXIII} \]
Looking to the efficacy of these pharmacores, it was a thought of interest to combine all the above mentioned biolabile moieties together in a molecular framework in order to curtail the pandemic of drug resistance and to observe the additive effect of these drugs towards antimicrobial activity. Keeping this rationale in view the present piece of research work records the experiments, conducted the observations made and the inferences drawn by me with the following major objectives within the chapters:-

**Chapter 1: General Introduction**

It includes a general review on synthesis and biological activity of imines and 4-thiazolidinones compounds.

**Chapter 2: Synthesis of Imines analogues**

Synthesis of a new series of imines was conducted to make the progress for the succeeding steps.

\[
\text{XXXIV}
\]

\[
\text{HC}=\text{N}-\begin{array}{c}
\text{R} \\
\text{R}_1 \\
\text{OCH}_3
\end{array}
\]

**2a-2h, 3a-3h**

R = H, CH$_3$ (p-, m-), OCH$_3$ (p-), Cl (p-, m-), F (p-), NO$_2$(p-)

R$^1$ = OCOCH$_3$ (2a-2h), OH (3a-3h)
Chapter 3: Synthesis of 4-Thiazolidinone analogues

Quite a good number of 5-membered heterocyclic compounds have been synthesized by incorporating 4-thiazolidinone core in the –CH=N– linkage of imines.

\[
\text{\begin{center}
\begin{array}{c}
\text{\includegraphics[width=0.6\textwidth]{chemical_structure.png}}
\end{array}
\end{center}
}\]

4a-4h, 5a-5h

\[R= \text{H, CH}_3(p-,m-), \text{OCH}_3(p-), \text{Cl}(p-,m-), \text{F}(p-), \text{NO}_2(p-)\]

\[R^1= \text{OCOCH}_3(4a-4h), \text{OH}(5a-5h)\]

Chapter 4: In-vitro Antimicrobial Efficacy Test

Screening of some of the synthesized compounds was performed in order to ascertain their in-vitro antimicrobial activity against bacterial pathogens namely \textit{S. aureus, B. subtilis, E.coli and P.aeruginosa} taking chloramphenicol as the standard drug and fungal pathogens namely \textit{C. albicans, C. tropicalis, A. flavus and A. niger} taking clotrimazole as the standard drug.
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Chapter 1 General Introduction

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