INTRODUCTION

This project has been aimed at the synthesis of some novel heterocyclic compounds like Schiff bases and their cyclisation to produce (Azetidinones) Beta-lactam derivatives of biological significance.

1.1 General Introduction of Schiff bases

A Schiff base is a nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme:

Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable\(^1,2\) while those of aromatic aldehydes having effective conjugation are more stable\(^3,6\).

The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating.
The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.

The mechanism of Schiff base formation is another variation on the theme of nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration.

Typically the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff bases synthesis are best carried out at mildly acidic pH.

The dehydration of carbinolamines is also catalyzed by base. This reaction is somewhat analogous to the E₂ elimination of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate.
The Schiff base formation is really a sequence of two types of reactions, i.e. *addition* followed by *elimination*.

1.2. Chemistry and Biological Importance of Schiff bases.

Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases\(^8\,^9\) by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agent to the carbon-nitrogen double bond. Reactions of this type have been put to good use in natural product synthesis.

Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base. Stereochemical investigation carried out with the aid of molecular model showed that Schiff base formed between methylglyoxal and the amino group of the lysine side chains of proteins can bent back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and oxygen atoms of the Schiff bases. In this respect pyridoxal Schiff bases derived from pyridoxal and amino acids have been prepared and studied from the biological point
of view. Transition metal complexes of such ligands are important enzyme models. The rapid development of these ligands resulted in an enhance research activity in the field of coordination chemistry leading to very interesting conclusions.

The carbon-nitrogen double bond of Schiff bases like the carbon-oxygen double bond is readily reduced by complex metal hydrides \(^{8,9}\). Reduction of this type is probably the most efficient and convenient method for the conversion of C=N into amino compounds. Thus lithium aluminium hydride in THF at room temperature (or in difficult cases at elevated temperature) smoothly reduces Schiff bases in high yield (> 90 %) to secondary amines. Sodium borohydride is an equally effective reducing agent and is preferred to lithium aluminium hydride because of its inertness to a wider range of solvent media and because of its greater specificity in that other substituents such as nitro or chloro reducible by lithium aluminium hydride are unaffected by sodium borohydride. An even more effective reagent of this type is sodium cyanoborohydride (NaBH\(_3\)CN).

Also the base catalyzed condensation of acetyl chlorides (bearing an electron withdrawing group and at least one hydrogen atom at the \(\alpha\)-position) with \(N\)-arylaldimines occurs by initial acylation at the nitrogen atom and leads to \(\beta\)-lactams of interest in penicillin chemistry [Scheme 1; (1) + (2) \(\rightarrow\) (4)]\(^{10}\).

![Scheme 1](image)

Iminium salt \(^{11}\) (R\(^2\)C=N\(^+\)R\(^3\)) at the other extremes are very rapidly hydrolyzed by water and have to be prepared under rigorously anhydrous conditions. The facility of iminium salt hydrolysis has been put to use in a synthesis of secondary amines from primary amines which involves conversion into the aldime (R\(^1\)CH=N\(^+\)R\(^2\)) and then by alkylation in to the iminium salt [R\(^1\)CH=N \(^+\)R\(^2\) (R\(^3\)) X] followed by hydrolysis
to give the secondary amines (R^2NHR^3). Because of the involvement of Schiff base hydrolysis in a number of enzyme mediated processes, the detailed mechanism of hydrolytic cleavage of carbon-nitrogen double bonds has been the subject of close scrutiny both under *in vivo* and under *in vitro* conditions^{12}. Imines hydrolysis is also a key step in the Sommelet^{13}, Stephen^{14}, Sonn-Müller^{15} and Gattermann^{16} aldehyde synthesis.

Alkoxides add in the expected fashion to Schiff bases, giving the corresponding α-alkoxy amino compounds^{9}. Addition of this type provides the key step in an elegant 'one pot' stereo specific synthesis of penicillin intermediates which can be further elaborated to new cephalosporin derivatives [Scheme 2; (5)→→(8)]^{17}. This involves the N-chlorination-dehydrochlorination of readily accessible penicillin amides (5) using t-butyl hypochloride in methanolic borate at 0°C to give acylimines (7), which adds methanol from the less hindered α-face to give the adduct (8) with the desired stereochemistry.

![Scheme 2](image)

Hydrogen sulphide reacts readily with N-substituted ketimines at low temperature (−40 to 0°C) to give initial adducts which rapidly react further to afford gemdithiols. N-arylaldimines readily add thiols in the form of their metal salts to give the expected 1,2-adducts which tend to disproportionate with net reduction of the imines to the corresponding amine and concomitant formation of the disulphide^{8,9}.

Reactions of Schiff bases with primary amines results in adducts which tend to decompose to a new imine and primary amine^{8,18}, the overall process corresponding to imine exchange. The rate of imine exchange increases with increase in the basicity of the primary amine effecting displacement. Sodamide^{18} reacts with aldimines with
formal replacement of the imidyl hydrogen to give amidines \([\text{Scheme 3; } (9) \rightarrow (10)]\). Iminium salts also readily add primary, secondary and tertiary amines with the formation of aminals (\textit{gem}-diamino compounds) or their quaternary salts\(^\text{19}\).

Schiff bases react in general with ethereal solutions of chloramines in a few hours at room temperature to give moderate to high yields (40-70\%) of diaziridines \([\text{Scheme 4; } (11) \rightarrow (13)]\)^\text{20}. This formal cycloaddition reaction has wide scope and is applicable, using chloramine itself (or the comparable reagent hydroxalamine-o-sulphonic acid), as well as \(N\)-substituted chloramines to a variety of Schiff bases derived from aldehydes and acyclic and cyclic ketones. In many cases the Schiff base can be converted \textit{in situ} into the diaziridine (yield 50-80\%) by reacting the corresponding carbonyl compound with ammonia or primary or secondary amines in the presence of hydroxalamine-o-sulphonic acid or an \(N\)-substituted hydroxalamine-o-sulphonic acid. Diazidine formation is believed to result from initial nucleophilic addition to the carbon-nitrogen double bond followed by eliminative ring closure (11)→(12)→(13).

The addition of hydrogen cyanide to Schiff bases occurs readily and provides a viable route to \(\alpha\)-amino nitriles, which can in turn be used as precursors for the synthesis (\textit{via} hydrolysis) of amino acids (Strecker synthesis)\(^\text{21}\). This reaction (which is akin to cyanohydrin formation from carbonyl compounds) is usually carried out
using anhydrous hydrogen cyanide in inert solvents such as ether or benzene. However, a more convenient procedure, which gives improved yields, is to use sodium cyanide in a phosphate buffer. Trimethyl silyl cyanide has been recommended as a safer alternative to hydrogen cyanide in the Strecker synthesis. This reagent adds to Schiff bases in the presence of catalysts such as aluminum chloride, zinc iodide or trisacetylacetonate aluminum, to give \(\alpha\)-cyano-\(N\)-trimethylsilylamines which are not isolated but are converted by neutral hydrolysis into \(\alpha\)-amino nitriles in high yield (80-90\%). Alternatively, the cyanotrimethylsilyl adducts can be converted by acidic hydrolysis directly into \(\alpha\)-amino acids.

Schiff bases lacking hydrogen atoms \(\alpha\) to the carbon-nitrogen double bond react with Grignard and organolithium reagents (alkyl and aryl) analogously to carbonyl compounds to give adducts which on hydrolytic work-up afford secondary amines in good to excellent yield (60-90\%) [Scheme 5]. Reaction occurs best with aryl amines and provides the general method for the synthesis of secondary amines. One disadvantage in this respect is that addition of organometallic reagent is subject to steric hindrance by Schiff base substituents (e.g. \(N\)-t-butyl) although substituents on the organometallic reagent do not appear to exert stearic effect. A further disadvantage is that in some cases (particularly with Grignard’s reagent) the yields of secondary amines are lowered by competing reductive dimerization of the Schiff base (14)\(\rightarrow\)(16). The scope of this amine synthesis has been widened by the use of alkylidine arenesup enamides (14; \(R_3^3=S\text{ Ar}\)) as the Schiff base component. Reaction of these substrates with organolithium reagents followed by hydrolytic work-up affords moderate to good yields (40-80\%) of secondary and tertiary alkyl primary amines (16; \(R_3^3=H\)).

![Scheme 5](image-url)
Schiff bases incapable of enolization (i.e. lacking α-hydrogen atoms) also react with Reformatsky reagent with stereo specific addition to the carbon-nitrogen double bond to give erythro-β-amino esters which can be isolated at low temperature (-10°C) but otherwise spontaneously cyclize, providing a useful synthetic route to β-lactams. Alkali metals react with fully aryl-substituted Schiff bases to give N,C-bis-metallated derivatives which can be sequentially alkylated or acylated at carbon then at nitrogen to yield mixed C,N-alkylated, acylated, or alkylated-acylated products.

The deprotonation of α-C, N-bis-alkylated Schiff base can in principle give rise either to l-aza-allyl anion or 2-aza-allyl anion. In practice deprotonation to the l-aza-allyl anion is preferred owing to its greater stability.

However, 2-aza-allyl anions are readily accessible by the deprotonation of Schiff bases containing N-alkyl substituents, and lacking α-hydrogen atoms, at low temperature (-70°C) using lithium diisopropylamide in THF [Scheme 6; (18)→(19)] or by the conrotatory ring-opening of readily accessible N-lithioaziridines (20)→(19).

(Scheme 6)

In terms of their nucleophilic reactivity, anions of this type (21) have been shown to react readily with aldehydes and ketones to afford alkylidene amino alcohols which can be dehydrated (using thionyl chloride-pyridine) or hydrolyzed (using aqueous hydrochloric acid) to provide synthetic routes to 2-azabuta-1,3-dienes (23) and β-amino alcohols (24) respectively [Scheme 7].
Reactions of anils with carbonyls-stabilized sulphonium ylides also provide a useful method for the synthesis of β-aminoalkenyl carbonyl compounds [Scheme 8; (25)+(26→(29))]. A course for these reactions involving initial nucleophilic addition followed by ring closure and subsequent ring opening of an aziridine intermediate is supported by the demonstration that, by analogy with the formation of oxirans from carbonyl compounds, anils react with dimethoxyoxosulphonium methylide to give moderate yields of aziridines.

[1+2] Cycloaddition reactions of carbenes and carbenoids to Schiff bases are well documented and constitute the useful method for the synthesis of aziridines. In its simplest form, cycloaddition of this type is exemplified by the reaction of benzylidene-aniline with dichlorocarbene to give 2,2-dichloro-1,3-diphenylaziridine
in good yield (55%) [Scheme 9; (30)→(31)]. Aziridines are also the products of the reactions of Schiff bases with the Simmons-Smith reagent (methylene di-iodide/zinc-copper couple)\textsuperscript{33}.

(Scheme 9)

Cycloaddition of Schiff bases to ketenes is highly stereoselective\textsuperscript{34}, implying a concerted process. However, a two-step mechanism involving a dipolar intermediate [Scheme 10], adequately accounts for the observed stereoselectivity and is strongly supported by mechanistic studies\textsuperscript{34,35} of β-lactam (35) formation via intermediate of the type (34) from Schiff bases (32) and ketens (33).

(Scheme 10)

Cycloaddition of Schiff bases to simple isocyanates\textsuperscript{31,36,37} is preceded by the reversible formation of a zwitter ion intermediate: [Scheme 11; (36)+(37)→(38)], which in some cases\textsuperscript{36} can be isolated. The subsequent course of the reaction is then dictated both by the stability of the zwitter-ion intermediate (38) (and hence principally by the steric and electronic effects of the Schiff base substituents) and by
the operation of kinetic or thermodynamic control. Broadly, electron donating \textit{para}-substituents in the benzylidene moiety of the Schiff base (36) and low reaction temperatures, with ensuing kinetic control, favors direct ring-closure of the zwitterion (38) to the [2+2] cycloadduct (39). Conversely electron-withdrawing \textit{para}-substituents in the benzylidene nucleus of the Schiff base (36) and relatively high reaction temperatures, with consequent thermodynamic control, promote dipolar [4+2] cyclo addition of the zwitterion (38) with the Schiff base (36) or the isocyanate (37) (present in equilibrium) to give the 2:1 and 1:2 adducts (40) and (41)\textsuperscript{36,37}. The cycloaddition reactions of Schiff bases with acyl isocyanates\textsuperscript{38} and acyl isothiocyanates\textsuperscript{39} broadly follow the same pattern.

![Diagram of cycloaddition reactions](image)

(Scheme 11)

Schiff bases capable of imine-enamine tautomerism react with isocyanates to afford acyclic adducts whose formation is rationalized in terms of [2+2] cycloaddition of the isocyante (44) to the enamine tautomer followed by ring-opening of the unstable adduct formed [Scheme 12; (42) \(\rightarrow\) (45) \(\rightarrow\) (46)]\textsuperscript{36,37,40}.
The formal [2+2] cycloaddition of the carbon-nitrogen double bond to a carbon-phosphorus double bond followed by retrocycloaddition accounts\textsuperscript{41} for the ‘Wittig-like’ reaction of Schiff bases (48) with arylidene phosphoranes (47) to afford alkenes (51) and phosphinamines (52) via intermediates (49) and (50) [Scheme 13].

Schiff bases react readily with diazoalkanes (e.g. diazomethane) in the presence of catalytic amounts of methanol or water to afford $\Delta^2$-1,2,3-triazolines [Scheme 14; (54)$\rightarrow$(55)\textsuperscript{42}. Electron-withdrawing groups on the Schiff base promote this cycloaddition while electron-donating groups hinder it. These substituents effects in conjunction with the catalytic effect of methanol and water and the high regiospecificity observed, namely exclusive 1,2,3-triazoline formation as oppose to the alternative $\Delta^1$-1,2,4-triazoline formation (54)$\rightarrow$(53), are consistent with a concerted 1,3-dipolar cycloaddition involving a polar transition state in which there is maximum...
stabilization by overlap of the highest occupied molecular orbital (HOMO) in the
dipole with the lowest unoccupied molecular orbital (LUMO) in the dipolarophile\textsuperscript{31,42}.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{Scheme 14}};
\begin{scope}[every node/.style={align=center}]
\node (a) at (0,0) {\chemfig{\text{Ar}^+\text{N}=\mathit{C}^-\text{Ar} \quad \text{ArHC}^+\mathit{=N}\text{Ar}}};
\node (b) at (0,0) {\chemfig{\text{Ar}^+\text{N}=\mathit{C}^-\text{Ar} \quad \text{ArHC}^+\mathit{=N}\text{Ar}}};
\node (c) at (0,0) {\chemfig{\text{Ar}^+\text{N}=\mathit{C}^-\text{Ar} \quad \text{ArHC}^+\mathit{=N}\text{Ar}}};
\end{scope}
\end{tikzpicture}
\end{center}

Nitrile oxides add to carbon-nitrogen double bonds of Schiff bases much more
readily than to carbon-oxygen double bonds, providing a general high yield route to\n\(\Delta^2\)-1,2,4-oxadiazolines [\textbf{Scheme 15}; (56)+(57)\rightarrow(58)\]\textsuperscript{42}. The Schiff base component
\((64)\) in cycloaddition of this type can be an acyclic N-alkyl or N-aryl aldimine or
ketimine [(56; \(X = \text{alkyl or aryl}\)) or can be integral with a ring as in the
cycloaddition of nitrile oxides with \(\Delta^2\)-pyrazolines to give fused structures [(57)+(59;
\(X=\text{NR}\) \rightarrow (60; \(X=\text{NR}\))].

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{Scheme 15}};
\begin{scope}[every node/.style={align=center}]
\node (a) at (0,0) {\chemfig{\text{X} \quad \text{R}^1\text{=N} \quad \mathit{C}^-\text{N} \quad \text{R}^2 \quad \text{X} \quad \text{O}}};
\node (b) at (0,0) {\chemfig{\text{X} \quad \text{R}^1\text{=N} \quad \mathit{C}^-\text{N} \quad \text{R}^2 \quad \text{X} \quad \text{O}}};
\node (c) at (0,0) {\chemfig{\text{X} \quad \text{R}^1\text{=N} \quad \mathit{C}^-\text{N} \quad \text{R}^2 \quad \text{X} \quad \text{O}}};
\end{scope}
\end{tikzpicture}
\end{center}

The importance of electron-withdrawl in diene component is strikingly
demonstrated by the enhanced reactivity of hetero1,3-dienes in [4+2] cycloaddition in
comparison with their homo 1,3-diene counterparts. Thus acyl and thioacyl
isocyanates and acyl isothiocyanates readily undergo 1,4-cycloaddition with simple
Schiff bases to afford excellent yields of 1,3,5-oxadiazine and 1,3,5-thiadiazine
derivatives [\textbf{Scheme 16}; (61) + (62) \rightarrow (63)]\textsuperscript{31,38,39,43}.
The uncontrolled oxidation of a Schiff base with a peroxy acid results in cleavage of the carbon-nitrogen double bond to give a carbonyl compound and a nitroso compound, respectively. On the other hand, oxidation using peroxy acids at low temperature (0°C) affords an excellent synthetic route to oxaziridines [Scheme 17; (64 → 66)\(^{8,20,44}\).

Peroxy acid oxidation of Schiff base (69) [from primary amine (67) and heterocyclic aldehyde (68) to an oxaziridine (70) followed by base-catalyzed rearrangement has been shown\(^{45}\) to provide a model [Scheme 18] for the pyridoxal pyrophosphate mediated enzymatic oxidative deamination of \(\alpha\)-amino acids to pyruvic acids, which finds analogy in the well-known double bond transposition of allylic alcohols via oxiran intermediates.
Initial hydroperoxide formation also accounts for the oxidative cleavage of the Schiff base (71) from 2-aminopyridine and isobutyraldehyde, by potassium t-butoxide in dimethyl sulfoxide which affords acetone and 2-formamidopyridine (73) in high yield (80-90%). The emission of blue light associated with this oxidative transformation is consistent with the mechanism [Scheme 19] involving the formation and cleavage of a dioxetan intermediate (72) and supports a similar mechanism for bacterial luminescence.

The oxidation of Schiff bases by metal based oxidants has been most extensively investigated in the case of leadtetraacetate (LTA)\textsuperscript{44,47}. LTA oxidation of simple anils\textsuperscript{48} results in the formation of aldehyde, the arylamine, and the
corresponding azobenzene derivative. Formation of the amine and the azobenzene derivative has been attributed to the involvement of a nitrene intermediate produced by the ionic breakdown of an initially formed lead derivative [Scheme 20; (74)→(75)→(76)→(77)→(78)+(79)]. Where the anil contains, a suitable ortho substituent (hydroxyl or amino) in the N-aryl ring. LTA oxidation leads to heterocycle (benzimidazole, benzoxazole) formation [(74; Z = NHR or OH) → (80; X = NR or 0)]44,47. Lead tetraacetate dehydrogenates N-unsubstituted aldimines to the corresponding nitriles. Since the requisite aldimine can be generated in situ by reaction of an aldehyde with ammonia, this constitutes a useful method for the synthesis of nitriles from aldehydes.

![Scheme 20](image)

The behavior of the carbon-nitrogen double bond of Schiff bases towards reducing agents broadly parallels that of the carbon-oxygen double bond. Metal-proton donor reagents (e.g. sodium, sodium amalgam, magnesium or aluminium in ethanol; zinc or aluminium in aqueous alkali; zinc in acetic acid) smoothly reduce Schiff bases (81), (prepared in situ from an aldehyde or ketone and an amine) to the corresponding amines (82)8,9. Alkali metals in inert solvents such as ether or toluene tend to promote reductive dimerization by a radical-coupling mechanism to afford diamino compounds (83) as the major products8,9,49.
Schiff bases are readily reduced to amines by hydrogenation over platinum, nickel or chromium catalysts\textsuperscript{8,9,50}. Thus, anils are reduced to secondary amines in essentially quantitative yield by hydrogenation over a platinum catalyst at 60\textdegree C. The hydrogenation of mixtures of ammonia and primary amines with alkyl and aryl aldehydes and ketones over nickel, platinum and palladium catalysts involves the \textit{in situ} reduction of Schiff bases and is a simple yet important general method for the synthesis under mild conditions of primary and secondary amines in good to excellent yield. This useful amine synthesis is applicable to polyfunctional molecules i.e. synthesis of $\alpha$-amino acids (e.g. alanine) from $\alpha$-keto acids (e.g. pyruvic acid). Asymmetric induction has also been demonstrated\textsuperscript{51} in the catalytic hydrogenation of Schiff bases and leads to chiral amines in good optical yield. A recent new method for the efficient conversion of Schiff bases into amines in excellent yield (80-90\%) under mild conditions involves reduction with alkyl silanes in the presence of transition metal catalysts [e.g. PdCl$_2$, (Ph$_3$P)$_3$RhCl]\textsuperscript{52}.

The carbon-nitrogen double bond is reduced electrolytically more readily than the carbon-oxygen double bond. Schiff bases derived from aldehydes and ketones are reducible electrolytically over a wide pH range to give the corresponding
amines. Thus the controlled potential reduction of a solution of cyclohexanone in methylamine gives N-methyl cyclohexylamine in high yield. The electrolytic reduction of N-substituted aryl aldimines and ketimines (84) occurs by the stepwise addition of two electrons and gives initially a radical anion (85) and then by protonation a radical intermediate (86) which can be further reduced to a secondary amine (87) or dimerize to a 1,2-diamino compound (88), [Scheme 22].

\[ \text{PhHC=NHPh} + e^- \rightarrow \text{PhH\tilde{C}=NPh} \]
\[ \text{(84) \rightarrow (85)} \]
\[ \text{PhCH}_2\text{NHPh} + e^- + H^+ \rightarrow \text{PhH\tilde{C}=NPh} \]
\[ \text{(87) \rightarrow (86)} \]
\[ \text{PhH\tilde{C}=NPh} \]
\[ \text{PhH\tilde{C}=NPh} \]
\[ \text{(88)} \]

(Scheme 22)

Synthesis of Schiff bases have also been reported by different authors. Ugras et al. have reported the synthesis, complexation, antifungal and antibacterial activity studies of a macro cyclic Schiff base (Scheme 23).

\[ \text{(89)} + \text{(90)} \rightarrow \text{(91)} \]

(Scheme 23)

Preparation, physical characterization and antibacterial activity of Ni (II) Schiff base complex (Scheme 24) was reported by Morad et al.

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Elzahany et al. have synthesized some transition metal complexes with Schiff bases derived from 2-formylindole, salicylaldehyde and N-amino Rhodamine. The Schiff base ligands were characterized by elemental analysis, IR, Mass, 1H NMR and electronic spectra. The free ligands and their metal complexes were also screened for antimicrobial activities against *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans*. The results indicated that the ligands do not have any activity, whereas their complexes showed more activity against the same organisms under identical experimental conditions.

Synthesis and pharmacological studies of novel Schiff bases of 4-Hydroxy-6-carboxyhydrazino benzofuran was reported by Gopal Krishna et al. (Scheme 25).
4-Chloro-2-oxo-2H-chromene-3-carbaldehyde was made to react with different anilines in rectified spirit to yield a series of Schiff bases (Scheme 26) of the type 4-chloro -3- (substituted-phenylimino) methyl) -2H-chromen-2-one. These following compounds were characterized on the basis of their spectral (IR, 1H NMR) data and evaluated for antimicrobial activity in vitro against fungi, gram positive and gram negative bacteria.

(Scheme 26)

Yi YI and coworkers have reported the synthesis and color-tunable fluorescence properties of Schiff base Zinc complexes which are used as electroluminescent materials. These authors have reported that the Schiff base Zinc complexes synthesized by them have good thermo stability, solubility and film forming capability and can be used as organic electroluminescent materials. These new complexes may afford the feasibility to realize full-color display with materials based on similar molecular structures.

(Scheme 27)
Vijey Aanandhi et al\textsuperscript{80} have reported the synthesis of a series of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted-pyridin-2-yl) thiosemicarbazide derivatives (Scheme 28). These compounds were screened for \textit{in vitro} antibacterial and antifungal activity against \textit{B. subtilis}, \textit{S. aureus}, \textit{E. coli}, \textit{P. aeruginosa}, \textit{C. albicans}, \textit{and A. niger}. All the compounds were reported to exhibit moderate to good antibacterial and antifungal activity.

![Scheme 28](image)

Karaoglan et al\textsuperscript{81} have reported the synthesis and characterization of a new Schiff base and its metal complexes. The Schiff base ligand were characterized by FT-IR, 1H-NMR, UV-Visible, Mass spectra, elemental analysis and fluorescence spectrophotometry.

Farias and Bastos\textsuperscript{82} have studied the electro chemical behavior of copper (II) complexes of the schiff’s base (111) \textit{N, N’}-ethylene bis(salicylidimine)in aqueous phosphate (pH 7) by polarographic and voltametric techniques at a mercury electrode. It is a symmetrical molecule and exhibits chiral properties.

![111](image)

Khalil et al\textsuperscript{83} were the first group to announce the possibility of using a Schiff base as an acid-base indicator. This surprising phenomenon can be considered as an interest due to the fact that Schiff bases are usually unstable in solutions and definitely
undergo hydrolysis. It was found that such a specific observation depends merely upon the chemical structure and type of the substitute of amine that reacts with aldehyde to give the Schiff base. The latter reagent 4{(4-dimethylamino-benzylidene)-amino}-benzene sulfonamide was synthesized from the condensation of sulfanilamide with p-dimethylaminobenzaldehyde. The reagent solution shows a reproducible change in its color due to the addition of acid and base. A UV-Visible spectroscopic characterization and acid-base equilibrium study of the reagent for its possible use as an indicator were investigated. The results show that the reagent is amphoteric which possesses four ionization constants $K_{a1}$, $K_{a2}$, $K_{b1}$ and $K_{b2}$ of weak dibasic and diacidic properties. It was concluded that the benzyl sulfonamide group plays a key role in the stability of the reagent towards hydrolysis and also for indicator characteristics through breaking the conjugation. Jamil and coworkers have reported the synthesis, characterization and antimicrobial activities of novel organotin schiff base compounds.

Metal complexes of Schiff bases derived from 2-furancarboxaldehyde and o-phenylenediamine and 2-thiopheneacarboxaldehyde and 2-aminothiopheneacarboxaldehyde was reported by Geindy et al. These authors have reported the ligand dissociation as well as the metal-ligand stability constants for these complexes. The synthesized ligands, in comparison to their metal complexes were also screened for their antibacterial activity against bacterial species, Escherichia coli, Pseudomonas aeruginosa and Staphylococcus Pyogones as well as fungi (Candida). The activity data reveal that the metal complexes are found to be more potent antibacterial than the parent Schiff base ligand against one or more bacterial species.
A series of biologically active pyrazine-derived Schiff base ligands (115, 116) have been synthesized by the condensation reaction of 2-aminopyrazine with salicylaldehyde and acetamidobenzylaldehyde. Then their Co(II), Ni(II) & Zn (II) complexes have been prepared. The biological evaluation of the simple uncomplexed ligand in comparison to their complexes have been determined against bacterial strains namely *Escherichia coli*, *Staphylococcus aureous* and *Pseudomonas aeruginosa*.

SARI and coworkers have reported the synthesis and antibacterial activities of some new amino acid-Schiff bases as follows:

Mixed ligand transition metal complexes of Cu+2, Ni+2 and Co+2 ions with Schiff base ligands (Scheme 29) derived from the condensation of o-hydroxy benzaldehyde with amino phenols and nitrogen donor amine bases was reported by Saidul Islam *et al*. The authors have also studied the antibacterial and antifungal activities of the compounds.
Daniel Thangadurai and Son-Ki Ihm\textsuperscript{90} have reported the synthesis, characterization, catalytic and antibacterial studies of chiral Schiff base Ruthenium complexes. These authors have tentatively proposed an octahedral structure for all the new complexes. The catalytic and antibacterial activities of these compounds have also been reported (126).

Baluja et al\textsuperscript{90} have studied the biological activities of the following Schiff base and metal complexes (Scheme 30).

(Scheme 30)
Metal complexes \(ML_2\text{Cl}_2\) where \(M\) is \(\text{Fe (II)}, \text{Co (II)}, \text{Ni(II)}, \text{Cu(II)}, \text{Zn(II)}\) or \(\text{Cd(II)}\) and \(L\) is the Schiff base formed by the condensation of 2-thiophenecarboxaldehyde with 2-aminopyridine, \(N\)-(2-thienylmethylidene)-2-aminopyridine (TNAPY) have been reported by Spinu et al\(^{91}\) (130).

\[(130)\]

Thilagavathi and coworkers\(^{92}\) have reported the synthesis (Scheme 31) of 3-{4-[4-(benzylideneamino) benzenesulfonyl]-phenyl}-2-phenylquinazolin-4(3\(H\))-one.

\[(131)\] \[(132)\] (Scheme 31)

Synthesis, characterization and electrochemical behaviour of \(\text{Cu, Co, Ni and Zn complexes derived from acetylacetone and p-anisidine was reported by Raman and coworkers}\(^{93}\). These authors have observed that the complexes synthesized by them show fairly good antimicrobial activity (133).

\[(133)\]

New Schiff base of the type, 2-[4-methyl-2-oxo-2\(H\)-chromen-7-yl)oxy]-N1-(substituted methylene)acetohydrazides were synthesized\(^{94}\) by the condensation of aryl/hetero aromatic aldehydes with 2-[(4-methyl-2-oxo-2\(H\)-chromen-7-yl)oxy] acetohydrazides under conventional and microwave conditions and characterized
through IR, \(^1\)H NMR and mass spectral data. The synthesized compounds have been screened for antimicrobial activity.

Raman et al\(^9\) have reported the synthesis of the following Schiff base ligand (134). These authors have also studied the DNA cleavage and antimicrobial activity of the Schiff base transition metal complexes.

![Schiff base ligand](image)

Chittilappilly and Yusuff\(^9\) have reported the synthesis, characterization and biological properties of ruthenium Schiff base complexes derived from 3-hydroxy quinoxaline-2-carboxaldehyde and salicylaldehyde (135).

![Ruthenium complex](image)

Two new Schiff base ligand containing cyclobutane and thiazole rings 4-(1-methyl-1-mesitylcyclobutane-3yl)-2-(2,4dihydroxybenzylidenehydrazino)Thiazole and 4-(1-methyl-1-mesitylcyclobutane-3-yl)-2-(2-hydroxy-3-methoxybenzylidenehydrazino)thiazole and their mononuclear complexes with Co(II), Cu(II), Ni(II) and Zn(II) in EtOH was reported by Cukurovali and co workers\(^9\) (Scheme 32).
Hearn and Cynamon\textsuperscript{98} have reported the synthesis and antitubercular activity of Schiff base of the following type.

\textsuperscript{(143)}

Nair and coworkers\textsuperscript{99} have studied the synthesis and antibacterial activity of some Schiff base complexes. The Schiff bases (143) showed greater activity than their metal complexes.
Vanden Ancker et al\textsuperscript{100} have reported the synthesis of the following bis-imine Schiff bases (Scheme 33). These authors have claimed that bis-imine Schiff bases are obtained in high yield (>95\%) when aliphatic diamine/aldehyde condensation reactions are carried out under solvent-free conditions or in polypropylene glycol (PPG) as a recyclable reaction medium with negligible waste.

![Scheme 33](image)

Potentially heptadentate tripodal Schiff-base ligand (146) have been prepared\textsuperscript{101} and characterized by various spectroscopic methods such as IR, FAB-MS and NMR.

![Image of 146](image)

Dong-Hoon Won and coworkers\textsuperscript{102} have studied the synthesis and crystal structure of the following Schiff base macrocycles bearing thiophene (147).
Shabani et al.\textsuperscript{103} have reported the synthesis, characterization and anti-tumor activity of Iron Schiff base complexes. Iran Sheikhshoaie and Samira\textsuperscript{104} have reported the synthesis, characterization and nonlinear optical properties of the following Schiff bases (Scheme 34).

(147)

(148)

(149)

(150)

(151)
Gao and Zheng\textsuperscript{105} have reported the synthesis of optically active Schiff base ligand (155) derived from condensation of 2-hydroxyacetophenone and 1,2-diaminocyclohexane.

Synthesis of Schiff bases of naptha[1,2-d]thiazol-2-amine and metal complexes of 2-(2-hydroxy)benzylideneaminonaphthathiazole as potential antimicrobial agent (Scheme 35) was reported by Faizul and coworkers\textsuperscript{106}. 
Ibrahim and Sharif\textsuperscript{107} have studied the synthesis, characterization of following Schiff bases (Scheme 36) which can be used as fluorometric analytical reagents.
Gudasi et al\textsuperscript{108} have reported the synthesis, characterization and biological studies of dioxouranium and thorium complexes of Schiff base (Scheme 37) derived from 2-amino pyridine and acetophenones.

![Diagram of reaction](image)

(Scheme 37)

More et al\textsuperscript{109} have reported the synthesis of the following Schiff base (169). These authors have studied the proton ligand stability constant of the Schiff bases and the formation constants of their transition metal complexes.

![Diagram of compound 169](image)

(Bag et al\textsuperscript{110} have synthesized a series of Schiff bases of benzidene and examined the mercuration reaction (Scheme 38).)

![Diagram of reaction and compound 173](image)

(Scheme 38)
Following two (174,175) new Schiff bases and transition metal complexes derived from 2, 3-diminopyridine (DAPY) and ortho-vanillin have been synthesized\textsuperscript{111} and characterized by elemental analysis, magnetic susceptibility measurements, IR and NMR spectra. The Schiff bases and most of the metal complexes display antibacterial activity.

\begin{align*}
\text{(174)} & \quad \text{(175)}
\end{align*}

Rajendran and Karvembu\textsuperscript{112} have reported the synthesis of following Schiff bases derived from 3-amino-2\textit{H}pyran[2,3-\textit{b}]quinolin-2-ones. The synthesized Schiff base (Scheme 39) compounds were screened against the fungal strains, such as Aspergillus niger and Fusarium sp..

\begin{align*}
\text{(Scheme 39)}
\end{align*}

Rosu \textit{et al}\textsuperscript{113} have reported the synthesis of Cu complexes derived from following Schiff base ligands (178, 179) obtained by the condensation of 2-hydroxy-benzaldehyde or terephthalic aldehyde with 4-aminoantipyrine.
Jarrahpour et al.\textsuperscript{114} have reported the synthesis of twelve new bis-Schiff bases of istatin, benzylisatin and 5-fluoroisatin by the condensation with primary aromatic amines (Scheme 40).
The UV visible spectra of some Schiff bases derived from 2-aminopyridine and 2-aminopyrazine have been investigated in acetonitrile and toluene. The compounds (183, 184) were in tautomeric equilibrium in polar and non polar solvents. This was suggested by Asiri et al\textsuperscript{115}.

![Chemical Structures](183-184)

Sivakumar et al\textsuperscript{116} have reported the proton dissociation constant of the ligand and the stability of the complexes of Co(II), Ni(II), Zn(II), Cd(II), Hg(II) and Pb(II) ions with 2-phenyl-3-(2'-hydroxy-5'-benzylidene)-quinazoline-4-(3H)-one. The proton-ligand and metal-ligand stability constants of the complexes have been determined pH metrically by the Calvin Bjerrum titration technique (Scheme 41).

![Chemical Structure](185-187)

(Scheme 41)

Wei et al\textsuperscript{117} synthesized a pair of iso structural azido or thiocyanato bridged centre of symmetric dinuclear copper (II) complexes derived from the Schiff base ligand, 4-nitro-2-[(2-diethylaminoethylimino)methyl]phenol (188). These compounds are characterized by elemental analysis, IR spectra and single X-ray diffraction. The antimicrobial activities of the complexes have been tested.

![Chemical Structure](188)

Natarajan Raman et al\textsuperscript{118} have reported the synthesis of a novel 14-membered
macrocyclic Schiff base (189) derived from 3-cinnamalidene-acetanalide and o-phenylenediamine which acts as a tetradentate and strongly conjugated ligand to form a cationic solid complex with Cu(II)/Ni(II)/Co(II) and Zn(II). The ligand and the complexes were characterized by the usual spectral and analytical techniques. The antimicrobial tests were also recorded and gave good results in the presence of metal ions in the ligand system.

An investigation dealing with the impact of the following Schiff base (190) derived from anthranilic acid and acetoacetanilide and its copper complex on instar larvae of Spodopetra litura was done by Raman et al.119.

Twenty Schiff bases of 2-amino-5-1,3,4-oxadiazoles have been synthesized with different aromatic aldehydes.120 The antibacterial properties of the compounds were investigated against Proteus mirabilis and Basillus subtilus. A series of 4-substituted-emoni-methyltetrazolo[1,5-a]quinoline with appropriate aromatic amine by refluxing in dioxane. They have been evaluated for their anti-inflammatory and antimicrobial activities (Scheme 42).
Biyala et al\textsuperscript{122} have studied the synthesis of mono basic bidentate Schiff base complexes of palladium and platinum from 1H-indol-2,3-dione thiosemicarbazone. These complexes were characterized on the basis of elemental analysis, molecular weight determination, 1H NMR and UV spectral studies. Antimicrobial effects of both the ligands (194,195), and their complexes on different species of pathogenic fungi and bacteria have been recorded and these are found to possess significant fungicidal and bactericidal properties.

Synthesis, crystal structures and antimicrobial activities of two thiocyanato-bridged dinuclear copper complexes derived from 2,4-dibromo-6-[(2-diethylaminoethlimino) methyl] phenol and 4-nitro-2-[(2-thylamino ethyl-imino)methyl]phenol was proposed by Zhe Hong\textsuperscript{123}. These complexes have been characterized by physico-chemical and spectroscopic methods. These are found to be antimicrobial. In-vitro antibacterial and antifungal activities of five different amino acid Schiff bases derived from the reaction of 2-hydroxy-1-naphthaldehyde with glycine, L-alanine, L-phenylalanine, L-histidine, L-tryptophane and the manganese(III) complexes of these bases were investigated by Sakiyan et al\textsuperscript{124}. The in-vitro activities against some Gram positive and Gram negative bacteria and fungi were determined.

Tarafder et al\textsuperscript{125} have reported the synthesis of complexes of a tridentate schiff base from the condensation of S-benzyldithiocarbazate with salicylaldehyde. These complexes have been characterized by elemental analysis and spectral analysis. Square planar structures are proposed for the Ni and Cu complexes. These authors have also studied the antimicrobial tests which indicate that Schiff base and five of the
metal complexes of Cu, Ni, U, Zr and Sb are strongly active against bacteria. The Schiff base exists in tautomeric form (196, 197).

Ispir et al\textsuperscript{126} have reported the synthesis of Schiff base ligands (198, 199) containing -SiOH\textsubscript{3} or -SiOCH\textsubscript{2}CH\textsubscript{3} groups, 4-([(3-trimethoxysilanepropyl) imino]methyl)benzene-1,3-diol and 4-([(3-triethoxysilanepropyl) imino]methyl)benzene-1,3-diol from 2,4-dihydroxy-benzaldehyde and 3-amino propyltrimethoxysilane and 3-aminopropyl-triethoxysilane.

Singh\textsuperscript{127} proposed a reaction of bis(triorganotin)oxide with Schiff bases derived by condensation of heterocyclic ketones, 2-acetylfuran and 2-acetylthiophene with various sulfa drugs. The structures of the complexes have been established by spectral studies. Molar conductance measurements were carried out for the Schiff bases. The results of antimicrobial effects of some representative complexes on different species of pathogenic fungi and bacteria have also been recorded.

Raman et al\textsuperscript{128} have reported the synthesis of Schiff bases (200) of 4-aminoantipyrine neutral complexes of Cu (II) from salicylidine-4-aminoantipyrine
and PhNH₂ substituted anilines. These authors confirmed their structure using IR, UV-visible, 1H NMR and 13C-NMR spectra.

Schiff bases of some biological interest have also been studied by some other authors.¹²⁹⁻¹³⁴
AZETIDINONES (BETA-LACTAMS)

The β-lactams are 4-membered cyclic amides derived from 3-aminopropanoic acids. Though the first member synthesized by Staudinger in 1907, the β-lactams as a class acquired importance since the discovery of penicillin which contains β-lactam unit as an essential structural feature of its molecule, this interest continued unabated because of the therapeutic importance of β-lactam antibiotics and recent finding of new naturally occurring β-lactams. As a result of vigorous research, a vast literature has been accumulated over the years, and the chemistry of azetidinones continues to be blossoming field.

Recent years have seen a resurgence of interest in the development of stereo and enatioselective methodologies. The utility of azetidinones as synths for various biologically active compounds, as well as their recognition as cholesterol absorption inhibitors and enzyme inhibitors has given impetus to these studies.

The β-lactams are 4-membered cyclic amides derived from 3-aminopropanoic acids. Though the first member synthesized by Staudinger in 1907, the β-lactams as a class acquired importance since the discovery of penicillin which contains β-lactam unit as an essential structural feature of its molecule. In the late 1990s, several groups reported novel methodologies for the synthesis of azetidinones of potential biological activities by applying known methods.

2.1. Chemistry of Azetidinones

In the literature, monocyclic β-lactams are usually referred to as azetidin-2-ones or 2-oxoazetidine, based on the nomenclature of the parent heterocycle, azetidine. However, the trivial names penam for the fused β-lactam (201 a) and cephem for the bicyclic system (202 a) are also used. Similarly, the term o-penam, o-cephem, azapenam and azacephem were coined for the bicyclic β-lactam (201 b), (202 b), (201 c) and (202 c) respectively. This trivial system of nomenclature is inadequate, especially in the case of fused β-lactams having no bridge head nitrogen atom, and in those having no heteroatom at position 1 or alterations in the positions of the hetero atom of the non β-lactam ring. This discrepancy can be removed by adopting a new system in which fused β-lactams (203) and (204) may be called “Alkanam” and “isoalkanam” respectively. Thus, β-lactams containing 7, 8 and 9
atoms in the bicyclic system (203) may be given generic names, heptanam, octanam, nonanam and so on, using the corresponding latin roots. The numbering system as shown in (201 d) and (202 d) is in conformity with the convention followed in the case of penam-cephem nomenclature. Thus, the conventional penam will be termed as 1-thiaheptanam, and cephem as 1-thiaoctanam according to this system. Similarly, the fused β-lactams of the type (204) may be termed as isoheptanam, isoctanam, isononanam and so on, depending on the number of atoms in the bicyclic system. The numbering of ring atoms in this case may be the one used for azetidin-2-ones, and is shown in (205).

A bicyclic β-lactam containing a double bond in the ring system may be given the corresponding generic name derived from the collective name “Alkenam” or “Isoalkenam” depending on the mode of fusion of the rings. For stereo description of the molecule, the terms “α” and “β” denoting the configuration of the substituents, which may be below or above the plane of the β-lactam ring, may be used as in case of steroids.

**Construction of β-lactam ring**

There are diverse synthetic routes to β-lactams and in principle the 4-membered heterocycle could be constructed by the formation of one, two, three or all four bonds of the ring system during the process of cyclisation.
Cyclisation of 3-aminopropanoic acid derivatives

Five 1,3,4-triaryiazetidin-2-ones (207) were prepared by treating (206) with benzenesulfonyl chloride and alkali. Saponification of 2, 2-disubstituted-3-benzamido propanoic acid esters (208) was found to give β-lactams besides the acid derivatives\(^\text{172}\). The cyclisation is possibly initiated by removal of the amidic proton, followed by Dieckmann reaction (Scheme 43).

\[
\begin{align*}
R_2 & \quad R_3 - C - CH(R_4) - COOH \\
& \quad NH - R_4 \\
R_3 & = H, R_1 = R_2 = R_4 = \text{Aryl} \\
\end{align*}
\]

(Scheme 43)

Bicyclic β-lactams such as penicillins\(^\text{173,174}\), cephalosporin\(^\text{175}\) analogs\(^\text{176,177}\) and the compound (210)\(^\text{178}\) were synthesized by this method, using carbodimides as Cyclising agents.

\[
\begin{align*}
\text{PhCO} - \text{NH} & \quad \text{COOBu-1} \\
\text{Saponification} & \quad \text{Acidification} \\
\text{PhCO} - N & \quad \text{o} \\
\end{align*}
\]

Blinkovsky et al\(^\text{179}\) have suggested the synthesis of beta-lactam antibiotics containing alpha-aminophenylacetyl group in the acyl moiety catalyzed by D-phenylglycyl-beta-lactamide amidohydrolase.
Carlos Cativiela et al\textsuperscript{180} have reported the asymmetric Synthesis of Beta-lactams by Diastereoselective Alkylation of Chiral 2-Cyano Esters.

**Addition of imines**

The first $\beta$-lactam was prepared by the ketene-imine interaction. Usually ketenes are generated \textit{in situ} by dehydrohalogenation of suitable acetyl chlorides in the presence of a tertiary base. Also, photolysis and thermal decomposition of diazoketones were employed for generating ketenes, which were trapped by imines to give $\beta$-lactams. Thermal fragmentation of acetylenic ethers to aldoketenes was also reported.

The choice of ketene precursor is important, because it gives $\beta$-lactams with a suitable group at the carbon atom $\alpha$ to the $\beta$-lactam carbonyl function\textsuperscript{154}. The structural requirements of the imines are difficult to define due to the inconsistency in the results obtained from different procedures. Imidylchlorides, $o$-alkyloximes and phenylhydrazones did not give azetidin-2-ones. Addition of diphenyl ketenes on acyl hydrazones is reported to give $\beta$-lactams. Imines such as (210 a) and (210 b) gave (211 a) and (211 b), on treatment with diphenyl- and dimethylketenes respectively\textsuperscript{153}. Tert-butylcyanoketenes with imino ethers gave $\beta$-lactam (211 c)\textsuperscript{181}. Diphenyl ketenes with imines (210 d) gave $\beta$-lactams (211 d), but their reactivity and yields varied considerably with change in the substituents in the aromatic ring. Conjugated diimines\textsuperscript{182,183} and carbodiimides\textsuperscript{154} also gave $\beta$-lactams with suitable ketenes (Scheme 44).

\begin{align*}
\text{R}_1&-\text{C}=\text{N}-\text{R}_3 & & \text{R}_1&-\text{C}=\text{O} & & \text{R}_1&-\text{C}=\text{N} \text{R}_3
\end{align*}

(a) R\textsubscript{1} = morpholine, R\textsubscript{2} = H, R\textsubscript{3} = Ph, R\textsubscript{4} = R\textsubscript{5} = Me or Ph  
(b) R\textsubscript{1} = Ph, R\textsubscript{2} = Me\textsubscript{S}-, R\textsubscript{3} = Ph, R\textsubscript{4} = R\textsubscript{5} = Me or Ph  
(c) R\textsubscript{1} = H, R\textsubscript{2} = -OMe, R\textsubscript{3} = R\textsubscript{4} = t\textsubscript{-}Bu, R\textsubscript{5} = CN  
(d) R\textsubscript{1} = R\textsubscript{3} = Substitutedphenyl, R\textsubscript{2} = H, R\textsubscript{4} = R\textsubscript{5} = Ph

(Scheme 44)
Reactions of isocyanates

Diazomethane was found to give β-lactams (213) when treated with phenyl- and p-bromophenylisocyanates\textsuperscript{184}. Indolyl-3-isocyanate reacted similarly\textsuperscript{152}.

\[
\text{ArN=CO + 2CH\textsubscript{2}N\textsubscript{2}} \rightarrow \overset{-2N\textsubscript{2}}{\text{O}} \text{N-Ar}
\]

(Scheme 45)

Ring expansion of 3-membered rings

The aziridine (214) in the presence of thionylchloride or oxalylchloride rearranges to β-lactam (215) in benzene, possibly via a mixed anhydride which undergoes ring expansion. The conversion is stereospecific and yields are good\textsuperscript{185} (Scheme 46).

(Ring contraction of 5-membered rings)

Photolytic Wolf rearrangement of 3-diazopyrrolidine-2,4-diones (216), in the presence of tert-butylcarbazate afforded β-lactams (217)\textsuperscript{186,187}. This method was extended to the synthesis of azetidin-2-one (218), which was found to be biologically inactive\textsuperscript{188}. The fused system (219) under similar conditions produced (220), which was found to be highly unstable\textsuperscript{189} (Scheme 47).
Passerini reaction

The reaction of carbonyl compounds with 3-aminopropanoic acids, followed by treatment with a suitable isocyanide afforded β-lactam derivatives. This is an extension of the Passerini reaction and it was useful for the preparation of monocyclic and bicyclic β-lactams (222) and (223) respectively. The reaction envisages formation of a cyclic compound (221) which on transannular acyl migration gave the β-lactam (222). It is noteworthy that the configuration of newly formed asymmetric center in the penicillin analog (223) is predetermined by the steric disposition of the reacting molecule (Scheme 48).
Rearrangement reactions

There were several cycloadducts which undergo thermal or photochemical fragmentation, generating ketenes and imines which recombine to give β-lactams. This method is of limited use because of the drastic conditions involved and possible side reactions. Beckmann rearrangement of o-sulfonyloximes (224) was reported to give novel β-lactams (225) but now the revised structure has been proposed\textsuperscript{154}.

\[\text{O} \quad \text{NO} \quad \text{SO}_2\text{Ph} \]
\[R = \text{OMe, OEt or H} \]

(224)

Reactions of Beta-lactams

Cleavage of the β-lactam bond

The β-lactam bond undergoes rupture in the presence of an alkali, acid and β-lactamase, yielding 3-aminopropanoic acids. By selective degradation the natural β-lactams could afford useful amino acids. In the presence of dry hydrogen chloride, a β-amino acid hydrochloride is generated. For example, the compound (226) gave (227) on treatment with hydrogen chloride in methylene chloride\textsuperscript{190}. Similarly, the β-lactam may be cleaved by imines\textsuperscript{191} (Scheme 49).

\[\text{CONH-CH-CH}_2\text{Ph} \quad \text{COOMe} \quad \text{ClO}_2\text{C-CH}_2 \quad \text{NH}_3^+ \quad \text{CH} \quad \text{CO-NH-CH} \quad \text{COOMe} \]

(Scheme 49)

Cleavage of the 2,3-bond in azetidin-2-ones

1-Haloazetidin-2-ones (228) undergo photolytic or thermolytic cleavage to give isocyanates (229) capable of undergoing secondary cyclisation under suitable conditions\textsuperscript{192}. Similarly, 3-azidoazetidin-2-one (230) on refluxing in diglyme, underwent ring expansion through 2,3-bond cleavage\textsuperscript{193} (Scheme 50).
Cleavage of 5,6-bond in penicillin

Rearrangement of penicillin to penilloic acid (233) involves cleavage of the 5,6-bond\(^{186}\) (Scheme 51). Similar bond cleavage was observed in penicillin-1-oxide\(^{195}\).

Cleavage of the 1,4-bond in azetidin-2-ones and collapse of the bridge in bicyclic Beta-lactams

β-Lactams bearing a C-4 hetero atom are unstable and easily undergo 1,4-bond cleavage\(^{196}\). For example, the 4-mercaptoazetidin-2-one (234) changes to isothiazolinone (235) in 40% yield, on treatment with dimethylsulfoxide\(^{197}\) (Scheme 52).
Fragmentation of Beta-lactams

Monocyclic Beta-lactams on photolysis or thermolysis break up into ketenes and imines or alkenes and isocyanates, depending on the substituents present in the molecule and which ever fragmentation is energetically profitable. This process is essentially a case of retrocycloaddition. Reagent induced fragmentation leads to diverse products, depending on the substituents and reagents used. Fragmentation of penicillin and cephalosporin occurred on treatment with trifluoroacetic acid, the fragments being amido ketenes, and \( \Delta^2 \)-thiazoline and \( \Delta^2 \)-1,3-thiazine derivatives respectively. Sometimes the fragment formed as primary products may undergo secondary reactions. For example, \( \beta \)-lactam on retro Michael reaction, gave (237) and subsequently (238) and (239) (Scheme 53).

(Scheme 53)

Enzyme catalyzed fragmentation of benzylpenicillin was reported. It is noteworthy that the azido group in \( \beta \)-lactam (240 a) on reduction with Adam’s catalyst and subsequent-acylation with phenoxyacetylchloride and triethylamine afforded the 6-phenoxy compound (240 c). Such an unusual result may be explained only on the assumption that the 6-amino compound (240 b) undergoes fragmentation and generates a \( \Delta^2 \)-thiazoline, which then reacts with phenoxyacetyl chloride and triethylamine in the usual way.

(240)
2.2. Biological Importance of Beta-lactam Derivatives.

2.2.1. Beta-lactam derivatives as antimicrobial agents.

Azetidine and their derivatives have been extensively explored for their applications in the field of medicine\(^{205-209}\). Likewise, azetidin-2-ones are of great importance because of β-lactam derivatives as an antibacterial agent\(^{210-214}\). Recently, incorporation of these compounds have witnessed a great upsurge in the treatment of tuberculosis and other chemotherapeutic diseases\(^{215}\). Sharma et al.\(^{216}\) reported synthesis and antibacterial activity of some N-sulphonamoylphenylamino-3-chloro-4-phenylazetidin-2-ones. Most of the compounds exhibited significant antibacterial activity. Comp.1 [4(5,6 dimethoxy pyrimidino sulphonamoyl)phenylamino]-3-chloro-4-phenylazetidin-2-one (241) has been found to be very potent compound against *E. coli*.

\[
\begin{align*}
\text{RNHSO}_2 & \text{Ph} \\
\text{NH} & \text{N} \\
\text{N} & \text{Cl} \\
\end{align*}
\]

\[R = 4,5\text{-dimethoxy pyrimidyl}\]

A series of 1-[5-(N\(^{10}\)-phenothiazinomethyl)-1,3,4-thiadiazol-2'-yl]-4-substituted-2-azetidinones as antifungal agents have been reported by Rawat et al.\(^{217}\). All the compounds were screened for their antifungal activity against the fungi *Candida albicans*, *Rhizopus oryzae* and *Crystosporium pannical*\(^{218}\). The fungicidal data indicated that all the compounds were moderately to highly toxic. The toxicity of compounds depends upon the nature and position of the substituents at the aryl moiety. Compound (242) displayed promising antifungal activity.

\[
\begin{align*}
\text{S} & \text{N} \\
\text{CH}_2 & \text{N} \\
\text{S} & \text{Ph} \\
\text{Ph} & \text{Ph} \\
\end{align*}
\]

Shah et al.\(^{219}\) synthesized azetidinones (243) from hydrazine thieno [3,2-d]pyrimidines as potential antimicrobial agents. All the products have been evaluated for their *in vitro* growth inhibitory activity against several microbes like *B. megatilis*,

49
B. subtilis, E. coli, A. aerogens and A. awamori. Most of the compounds exhibited maximum activity in the range of 21-27 mm against A. aerogens. Other compounds showed either moderate or less activity against these organisms. None of the compounds synthesized was found to exhibit significant activity against B. subtilis.

Parmar et al\textsuperscript{220} reported synthesis of azetidinones from hydrazinopyrimidine as potential antimicrobial agents. All the products were evaluated for their in vitro growth inhibitory activity against several microbes like B. megaterium, B. subtilis, E. coli, P. fluorescens and A. awamori. All the compounds exhibited mild to moderate antimicrobial activity against all microorganisms except (244) which exhibited promising activity with ampicillin and chloramphenicol against P. fluorescens.

Antimicrobial activity of azetidin-2-ones has also been reported by various authors\textsuperscript{221-228}. 
Mechanism of action of Beta-lactam derivatives as Antimicrobial agents.

Beta-lactams inhibit cell wall synthesis (Figure No. 1). The peptidoglycan is composed of sugars and amino acids. The sugar components consist of alternating residues of N-acetyl glucosamine and N-acetyl muramic acid residues. Peptide chain of 3-5 amino acids is attached with N-acetyl muramic acid. The peptide chain can be cross linked to peptide chain of another strand forming mesh like layer by transpeptidase. Beta-Lactams bind to PBPs which catalyse transpeptidation reaction. They inhibit transpeptidation (final stage in the synthesis of cell wall) (Figure No. 2).

![Figure No. 1]
2.2.2. Beta-lactam derivatives as antitubercular agents.

Synthesis and antitubercular activity of Beta-lactam derivatives\textsuperscript{229-232}, has been reported by different authors. The representative compounds were tested \textit{in vitro} for their anti-tubercular activity against \textit{M. tuberculosis H37Rv}. The data were compared with standard drug Rifampin. All the compounds showed moderate antituberculcer activity against \textit{M. tuberculosis}.

Patel \textit{et al}\textsuperscript{233} have reported synthesis and antitubercular activity of 2-[4-(4-substitutedphenyl)-3-chloro-2-azetidinon-1-yl]-4-[2-(4-chlorobenzene sulphone -mido)-phenyl] thiazoles (245). Primary screening of the compounds for antitubercular activity was conducted at 12.5 mcg/ml against \textit{M. tuberculosis H37Rv}. Compounds demonstrating at least 99% inhibition in the primary screening were tested at lower concentrations against this microorganism to determine actual minimum inhibitory concentration. The antitubercular activity data showed that most of the azetidinone derivatives exhibited 100% inhibition in the primary screen at 12.5 mcg/ml concentration.

(Figure No. 2) Peptidoglycan synthesis
Vashi et al.\textsuperscript{234} have reported synthesis and antitubercular activity of 2-azetidinones bearing thymol moiety. The products displayed moderate to good tuberculostatic activity. Synthesis and antitubercular activity of 2-(4-aryl-3-chloro-2-azetidinon-1-yl-amino)-6-(4-chlorophenyl)-5-cyano-3-N-methyl-3,4dihydropyrimidin-4-ones is reported by Modha et al.\textsuperscript{235} All the products displayed mild to moderate antitubercular activity against \textit{M. tuberculosis}. Compound (246) was the most active member of this series.

\textbf{2.2.3. Beta-lactam derivatives as anti-inflammatory agents.}

Several such comp. like 1-[5-(carbazolymethyl)-1,3,4-thiadiazol-2-yl]-4-(substituted phenyl) -3-chloro-2-oxo-azetidines have been synthesized and evaluated for their anti-inflammatory activity by Srivastava et al.\textsuperscript{236} All the compounds displayed mild to moderate anti-inflammatory activity except compound (247) that showed anti-inflammatory activity that was comparable to standard drug phenylbutazone.
Several comp. like 1-[5-(N\textsuperscript{10}-2-chlorophenothiazinomethyl)-1,3,4-thiadiazol-2-yl]-4-(substituted phenyl)-3-chloro-2-oxoazetidines have been synthesized and evaluated for their anti-inflammatory activity by Srivastava et al\textsuperscript{237}. All the compounds tested for anti-inflammatory activity exhibited mild to moderate activity. The compound (248) was the most potent and active member of this series. It displayed comparable anti-inflammatory activity but lesser than the standard phenylbutazone.

![Chemical Structure](image)

\textbf{2.2.4. Beta-lactam derivatives as anticancer agents.}

Shah. et al\textsuperscript{238} thoroughly analysed the mechanism of inhibiton of human leukocyte elastase (HLE) by a monocyclic lactam. This work led to the identification of 4-[(4-carboxyphenyl)-oxy]-3,3-diethyl-1-[(phenylmethyl) amino] carbonyl] -2-azetidinone as the first orally active inhibitor of human leucocyte elastase (HLE). Analogues with different substituents on the urea-N were synthesized and evaluated for their activity \textit{in vitro} against HLE as well as \textit{in vivo} in a hamster lung haemorrhage model. Compounds with a methyl or methoxy group in the para position of the benzene ring were very potent in both assays. Park et al\textsuperscript{239} synthesized and evaluated two known phenolic metabolites of paclitaxel. The C3-phenolic metabolite of paclitaxel was prepared from 7-(triethylsilyl)-baccatin III and enantioenriched N-benzoyl-2-azetidinone. The C2 –phenolic metabolite was synthesized from paclitaxel via selective C2 debenzoylation reacylation. Both the metabolites were found to have good anticancer activity. Spletstoser et al\textsuperscript{240} synthesized and evaluated a novel paclitaxel derivatives. The synthesis involved the preparation of an azide-containing C-13 side chain through a Staudinger cycloaddition followed by a growth and a variety of other cell lines. Compounds inhibited tubulin polymerization with potencies commensurate with their cytotoxic activity and a more lipase-mediated kinetic resolution through which azetidinone in 99% cc was obtained. Coupling of the...
enantiopure side chain precursor to 7-TES-baccatin and subsequent silyl ether deprotection afforded 3'-[(4-azidophenyl)-3'-dephenyl paclitaxel, which was shown to be as active as paclitaxel in tubulin assembly and cytotoxicity assays. A series of novel 1,4-diaryl-2-azetidinones was synthesized by Sun et al²⁴¹ using stereo specific staudinger reaction as conformationally restricted analogues of combrestatin because molecular modeling studies suggested close geometric similarities. They were evaluated for cytotoxicity against a number of human tumor and normal cell lines. Strong potencies were observed, with the best compound exhibiting IC₅₀'s of 25-74 nm against human neuroblastoma IMR 32 cell soluble aniline-containing analogue was found to be very effective in inhibiting the growth of AR42J rat pancreatic tumors when transplanted into the nude mice. Boge et al²⁴² synthesized and evaluated novel cyclohexyl analogues of taxol and taxotere. Compound 2-(cyclohexyl carbonyl)-2-debenzoylbaccatin was prepared from baccatin by hydrogenation. Subsequent coupling of 2-(cyclohexyl carbonyl)-2-debenzoylbaccatin with N-t-BOC-3-[(tert-butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone, followed by removal of the protecting groups afforded 2-(cyclohexyl carbonyl)-2-debenzyoxyl taxotere. In a similar synthetic sequence, 3'-cyclohexyl-3'-dephenyl taxol was prepared from N-benzoyl-3-[(tert-butylidimethylsilyl) oxy]-4-cyclohexyl-2-azetidinone and (triethylsilyl) baccatin. The taxol analogue, in which all three taxol phenyl groups were substituted by a cyclohexyl moiety, was synthesized in one step from taxol via hydrogenation. All analogues exhibited strong activity in the microtubule assembly assay and cytotoxicity comparable to taxol against B16 melanoma cells. Different authors²⁴³-²⁵¹ have reported the Synthesis of anticancer Beta-lactams & their mechanism of action.

2.2.5. Beta-lactam derivatives as cholesterol lowering agents.

Fluorescent analogues of the cholesterol absorption inhibitor (CAI), have been synthesized by Burnett et al²⁵² as enantiomers. Biological testing revealed that they were potent cholesterol absorption inhibitors (CAI’s) and were suitable tools for the investigation of the azetidinone cholesterol absorption inhibiting mechanism of action. Ezetimibe²⁵³, 1-(4-fluorophenyl) - (3R) -[3-(4-fluorophenyl) - (3S) hydroxyl-propyl] - (4S)-(4-hydroxyphenyl)-2-azetidinone potentially and selectively inhibited the intestinal absorption of cholesterol, thereby reducing plasma cholesterol in
preclinical models of hypercholesterolemia. In rhesus monkeys fed a diet containing 375mg/day of cholesterol, 0.1mg/kg of ezetimibe completely prevented the doubling of plasma cholesterol normally induced under these dietary conditions (ED$_{50}$=0.0005mg/kg). Low-density lipoprotein (LDL) cholesterol was dose dependently reduced, while high-density lipoprotein (HDL) cholesterol and plasma triglyceride were unchanged. Clader et al$^{254}$ synthesized a series of azetidinone cholesterol absorption inhibitors (CAI) and compounds were evaluated for their activity to inhibit hepatic cholesteryl ester formation in a cholesterol fed hamster model. Although originally designed as acyl CoA: cholesteryl acyl transferase (ACAT) inhibitors, comparison of in vivo potency with in vitro activity in a microsomal ACAT assay indicated no correlation between activity in these two models. Examination of the in vivo activity of a range of compounds has revealed clear structure-activity relationships consistent with a well defined molecular target. Two derivatives, of a novel cholesterol absorption inhibitors were glucuronidated with the help of glucuronyl transferase derived from bovine and dog liver microsomes. An efficient procedure for the iodination was developed on an analytical scale to be used for the preparation of a radioactive$^{255}$ glucuronide. Different authors$^{256-258}$ have reported the Beta-lactam derivatives as cholesterol lowering agents.

2.2.6. Beta-lactam derivatives as human tryptase & chymase inhibitors.

Sutton et al$^{259}$ prepared a series of non guanidine N1-activated C4-carboxy azetidinone tryptase inhibitors by solid phase methodology to quickly assess the SAR associated with the distal functionality on the N1-activating group. From these studies, potent inhibitors with improved specificity were discovered. Qian et al$^{260}$ synthesized a highly stereo selective novel tryptase inhibitor. Key to this synthesis was the discovery and development of a high diastereo selective demethoxy carbonylation of diester to form the trans-azetidinone. Derivatives of 3-benzylazetidine-2-one were designed and evaluated as a novel series of chymase inhibitors by Aoyama et al$^{261}$. Structure activity relationship of 3-benzylazetidine-2-ones led to compounds, which exhibited 3.1nm inhibition of human chymase and enhancement of stability in human plasma (t$_{1/2}$=6hrs). Bisacchi et al$^{262}$ synthesized a number of potent azetidinone tryptase inhibitors in which the guanidine moiety at the
ring C-3 position is replaced with primary or secondary amine or amino pyridine functionality. These compounds were found to be highly potent tryptase inhibitors, which has excellent selectivity against trypsin and most other related serine proteases. Different authors\textsuperscript{263,264} have reported the Beta-lactam derivatives as human tryptase & chymase inhibitors.

\section*{2.2.7. Beta-lactam derivatives as anti-hepatitis agents.}

Hepatitis A virus (HAV) 3C enzyme is a picornaviral cysteine proteinase involved in the processing of the initially synthesized viral poly protein is therefore important for viral maturation and infectivity. Although it is a cysteine proteinase, this enzyme has a topology similar to those of the chymotrypsin like serine proteinases. Since the enzyme recognizes peptide substrates with a glutamine residue at the P(1) site, a number of ketone-containing glutamine compounds analogous to nanomolar inhibitors of cathepsin k were synthesized by Ramtohul \textit{et al}\textsuperscript{265} and tested for inhibition against HAV 3C proteinase. In addition, a 3-azetidinone scaffold was incorporated into the glutamine fragment but gave only modest inhibition. However, introduction of a phthalhydrazido group alpha to ketone moiety gave significant better inhibitors with IC\textsubscript{50} values ranging from 13 to 104 µm, presumably due to the effect of intra molecular hydrogen bonding to the ketone. Lall \textit{et al}\textsuperscript{266} synthesized a number of serine and threonine beta-lactones and were tested against HAV 3C proteinase. The D-N-Cbz-serine beta-lactones displayed competitive reversible inhibition with a K(i) value of 1.50 \times 10^{-6} M. Its enantiomer, L-N-Cbz-serine beta-lactone is an irreversible inactivator with K(\text{inact}) = 0.07\text{min}^{-1}, K(\text{lota}) = 1.84 \times 10^{-4} M and K(\text{inact}) / K(\text{lota}) = 3800 M^{-1}\text{min}^{-1}. Mass spectrometry and HMQC NMR studies using \textsuperscript{13}C-labelled L-N-Cbz-serine beta-lactone showed that inactivation of the enzyme occurs by nucleophilic attack of the cysteine thiol (cys-172) at the beta-position of the oxetanone ring. Although the N-Cbz-serine beta-lactones displayed potent inhibition, other related analogues with an N-Cbz side chain, such as the five-membered ring homoserine gamma-lactones, the four-membered ring beta-lactam, 2-methylene oxetane, cyclobutanone and 3-azetidinone, failed to give significant inhibition of HAV 3C proteinase, thus the importance of the beta-lactone ring for binding has been demonstrated.
2.2.8. Beta-lactam derivatives reduces ethanol consumption in alcohol-preferring rats.

Changes in glutamatergic transmission affect many aspects of neuroplasticity associated with ethanol and drug addiction. For instance, ethanol and drug seeking behavior is promoted by increased glutamate transmission in key regions of the motive circuit. Youssef Sari et al. hypothesized that because glutamate transporter 1 (GLT1) is responsible for the removal of most extracellular glutamate, up-regulation or activation of GLT1 would attenuate ethanol consumption. Behavioral drinking, statistical analyses revealed a significant reduction in daily ethanol, but not sucrose, consumption following Ceftriaxone (CEF) treatment. During the post treatment period, there was a recovery of ethanol intake across days. Dose-dependent increases in water intake were manifest concurrent with the CEF-induced decreases in ethanol intake. Nevertheless, CEF did not affect body weight. An examination of a subset of the CEF-treated ethanol-drinking rats, on the third day post CEF treatment, revealed increases in GTL1 expression levels within the prefrontal cortex and nucleus accumbens. These results indicate that CEF effectively reduces ethanol intake, possibly through activation of GLT1, and may be a potential therapeutic drug for alcohol addiction treatment.

2.2.9. Beta-lactams decreases acquisition of and motivation to respond for cocaine, but not sweet food, in mice.

No medication is approved to treat cocaine addiction, but mounting evidence by Ward et al. reported that glutamate-directed approaches may reduce cocaine dependence and relapse. The glutamate transporter subtype 1 activator, ceftriaxone, disrupts acquisition of cocaine self-administration, motivation to self-administer cocaine, and conditioned place preference in mice. Repeated ceftriaxone (200 mg/kg) reduced the ability of mice to acquire cocaine and the motivation to self-administer cocaine after successful acquisition without affecting acquisition of or motivation for sweet food. Repeated ceftriaxone had no effect on cocaine-conditioned place preference. These results suggest that a β-lactam antibiotic reduces the direct reinforcing strength of cocaine without producing nonspecific deficits in conditioned learning processes.
2.2.10. Artesunate enhances the antibacterial effect of beta-lactam derivatives.

Yao et al.\textsuperscript{260} suggested that although artemisute itself had no antibacterial ability, artemisute significantly increased the antibacterial effect of β-lactam antibiotics against E. coli ATCC 35218. Artesunate increased daunomycin accumulation within E. coli in a dose-dependent manner and reduced the mRNA expression of AcrAB-TolC, an important multidrug efflux system for Gram-negative bacteria. The bacterial number was significantly reduced by as-ODN targeting AcrB, but did not further decrease after additional artemisute treatment. In contrast, artemisute lost its enhancement of β-lactam antibiotics against E. coli AG100A, a strain lacking the gene encoding AcrAB.

2.2.11. Genetic determinants involved in the susceptibility of Pseudomonas aeruginosa to beta-lactam antibiotics.

Alvarez-Ortega et al.\textsuperscript{270} suggested that the resistome of P. aeruginosa for three β-lactam antibiotics, namely, ceftazidime, imipenem, and meropenem, was deciphered by screening a comprehensive PA14 mutant library for mutants with increased or reduced susceptibility to these antimicrobials. Confirmation of the phenotypes of all selected mutants was performed by E-test. Of the total of 78 confirmed mutants, 41 demonstrated a reduced susceptibility phenotype and 37 a super susceptibility (i.e., altered intrinsic resistance) phenotype, with 6 mutants demonstrating a mixed phenotype, depending on the antibiotic. Only three mutants demonstrated reduced (PA0908) or increased (glnK and ftsK) susceptibility to all three antibiotics. Overall, the mutant profiles of susceptibility suggested distinct mechanisms of action and resistance for the three antibiotics despite their similar structures. More detailed analysis indicated important roles for novel and known β-lactamase regulatory genes, for genes with likely involvement in barrier function, and for a range of regulators of alginate biosynthesis.

2.2.12. Allergy to beta-lactam antibiotics

Ponvert et al.\textsuperscript{271} suggested, studies based on skin and challenge tests have shown that 12–60% of children with suspected beta-lactam hypersensitivity were
allergic to beta-lactams. Responses in skin and challenge tests were studied in 1865 children with suspected beta-lactam allergy\textsuperscript{272} (i) to confirm or rule out the suspected diagnosis; (ii) to evaluate diagnostic value of immediate and non-immediate responses in skin and challenge tests; (iii) to determine frequency of beta-lactam allergy in those children, and (iv) to determine potential risk factors for beta-lactam allergy. The work-up was completed in 1431 children, of whom 227 (15.9\%) were diagnosed allergic to beta-lactams. Beta-lactam hypersensitivity was diagnosed in 50 of the 162 (30.9\%) children reporting immediate reactions and in 177 of the 1087 (16.7\%) children reporting non-immediate reactions (p < 0.001). The likelihood of beta-lactam hypersensitivity was also significantly higher in children reporting anaphylaxis, serum sickness-like reactions, and (potentially) severe skin reactions such as acute generalized exanthematic pustulosis, Stevens–Johnson syndrome, and drug reaction with systemic symptoms than in other children (p < 0.001). Skin tests diagnosed 86\% of immediate and 31.6\% of non-immediate sensitizations. Cross-reactivity and/or cosensitization among beta-lactams was diagnosed in 76\% and 14.7\% of the children with immediate and non-immediate hypersensitivity, respectively. The number of children diagnosed allergic to beta-lactams decreased with time between the reaction and the work-up, probably because the majority of children with severe and worrying reactions were referred for allergological work-up more promptly than the other children. Sex, age, and atopy were not risk factors for beta-lactam hypersensitivity. In conclusion, it is confirmed in numerous children that (i) only a few children with suspected beta-lactam hypersensitivity are allergic to beta-lactams; (ii) the likelihood of beta-lactam allergy increases with earliness and/or severity of the reactions; (iii) although non-immediate-reading skin tests (intradermal and patch tests) may diagnose non-immediate sensitizations in children with non-immediate reactions to beta-lactams (maculopapular rashes and potentially severe skin reactions especially), the diagnostic value of non-immediate-reading skin tests is far lower than the diagnostic value of immediate-reading skin tests, most non-immediate sensitizations to beta-lactams being diagnosed by means of challenge tests; (iv) cross-reactivity and/or cosensitizations among beta-lactams are much more frequent in children reporting immediate and/or anaphylactic reactions than in the other children; (v) age, sex and personal atopy are not significant risk factors for beta-lactam hypersensitivity; and (vi) the number of children with diagnosed allergy to beta-lactams (of the immediate-type hypersensitivity especially) decreases with time between the reaction and...
allergological work-up. Immunologic cross-reactivity of aztreonam with other beta-lactam antibiotics has been studied by Saxon et al\textsuperscript{273} and Rodilla et al\textsuperscript{274}.

2.2.13. Integrated detection of extended-spectrum beta-lactam resistance.

Different ways of bacterial resistance\textsuperscript{278-286} have been shown in (Figure No. 3), Leinberger et al\textsuperscript{275} suggested that extended-spectrum beta-lactamases (ESBL) of the TEM, SHV, or CTX-M type confer resistance to beta-lactam antibiotics in Gram-negative bacteria. The activity of these enzymes against beta-lactam antibiotics and their resistance\textsuperscript{276,277} against inhibitors can be influenced by genetic variation at the single-nucleotide level. He suggested the development and validation of an oligonucleotide microarray for the rapid identification of ESBLs in Gram-negative bacteria by simultaneously genotyping bla\textsubscript{TEM}, bla\textsubscript{SHV}, and bla\textsubscript{CTX-M}. The array consists of 618 probes that cover mutations responsible for 156 amino acid substitutions. As this comprises unprecedented genotyping coverage, the ESBL array has a high potential for epidemiological studies and infection control. With an assay time of 5 h, the ESBL microarray also could be an attractive option for the development of rapid antimicrobial resistance tests in the future. The validity of the DNA microarray was demonstrated with 60 blinded clinical isolates, which were collected during clinical routines. Fifty-eight of them were characterized phenotypically as ESBL producers. The chip was characterized with regard to its resolution, phenotype-genotype correlation, and ability to resolve mixed genotypes. ESBL phenotypes could be correctly ascribed to ESBL variants of bla\textsubscript{CTX-M} (76%), bla\textsubscript{SHV} (22%), or both (2%), whereas no ESBL variant of bla\textsubscript{TEM} was found. The most prevalent ESBLs identified were CTX-M-15 (57%) and SHV-12 (18%).

Rawls et al\textsuperscript{287} suggested that β-Lactam antibiotics enhance cellular glutamate uptake. As increased glutamatergic transmission is a primary mediator of opiate dependence, tested the hypothesis that a β-lactam antibiotic (ceftriaxone) prevents development of morphine physical dependence in rats. Morphine (20 mg/kg) was injected twice daily for 10 days to induce physical dependence. Naloxone (10 mg/kg) administration 1, 48, and 96 h after the last morphine injection induced a withdrawal syndrome characterized by the appearance of wet-dog shakes, teeth chattering, eye blinking, jumping, and paw tremor. Ceftriaxone (150, 200 mg/kg) injected once daily during chronic morphine exposure inhibited each naloxone-precipitated withdrawal sign. Ceftriaxone efficacy persisted even after the 96 h-naloxone (10 mg/kg) injection. These results suggest that β-lactam antibiotics inhibit processes leading to development of morphine physical dependence.
2.2.15. **Synergistic antibacterial effect of Beta-lactam derivatives with silver nano-particles.**

Ping et al\textsuperscript{288} The bactericidal action of silver nanoparticles and amoxicillin on *Escherichia coli* is studied, respectively. Increasing concentration of both amoxicillin (0–0.525 mg ml\textsuperscript{-1}) and silver nanoparticles (0–40 µg ml\textsuperscript{-1}) showed a higher antibacterial effect. *Escherichia coli* cells have different bactericidal sensitivity to them. When amoxicillin and silver nanoparticles are combined, it results in greater bactericidal efficiency on *Escherichia coli* cells than when they were applied separately.

2.2.16. **Beta-lactam derivatives offer neuroprotection.**

Glutamate is the principle excitatory neurotransmitter in nervous system. Inactivation of synaptic glutamate is handled by glutamate transporter (GLT1). Animal studies show that the GLT1 is important for normal excitatory synaptic transmission, while its dysfunction is implicated in acute and chronic neurological disorders including stroke, brain tumours and epilepsy. It has been discovered that may β-lactam antibiotics are potent stimulators of GLT1,Glutamate transporter are important in preventing glutamate neurotoxicity\textsuperscript{289}.

2.2.17. **Bacteriological antagonism between acylureidopenicillins & cephalosporins, and combination of different antibiotics.**

An antagonism is described by Grimm\textsuperscript{290} between cefoxitin and azlocillin by means of agar-diffusion test and checker-board titrations of MIC. This phenomenon is attributed to beta-lactamase-induction by cefoxitin. Cefuroxime is less antagonistic, and cefotaxime is indifferent in combination with azlocillin. Combination of mezlocillin and azlocillin with cephalosporin antibiotics has been studied by Neu et al\textsuperscript{291} for their synergistic effects. Amdinocillin in combination with another beta-lactam antibiotic (ampicillin, cephalothoin, cefamandole or cefoxitin) was studied by Rosten et al\textsuperscript{292}. 

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