ejpmr, 2017,4(8), 751-789

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MICROWAVE ASSISTED SYNTHESIS OF NOVEL SCHIFF BASES AND THEIR BIOLOGICAL EVALUATION

Syed Shah Abdus Salaam* and Naziya Mehveen

Dept of Pharmaceutical Chemistry, MESCO College of Pharmacy, Hyderabad, Telangana State.

***Corresponding Author: Syed Shah Abdus Salaam**

Dept of Pharmaceutical Chemistry, MESCO College of Pharmacy, Hyderabad, Telangana State.

Article Received on 20/06/2017 **Article Revised on 11/07/2017** **Article Accepted on 02/08/2017**

ABSTRACT

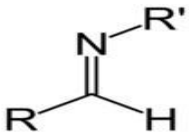
The aim of present study is to synthesise novel thiazolodinones from schiff bases of salicyladldehyde by microwave assisted method. The literature review showed that schiff bases possess a wide spectrum of biological activities such as antibacterial, anti tubercular, anti inflammatory, antiviral and antioxidant activity. Schiff bases of salicylaldehydes have also been reported as plant growth regulator and antimicrobial or antimycotic activity. Thiazolidinones found to have a broad spectrum of pharmacological properties like anti HIV, antipsychotic, anticonvulsant and antitubercular activity. In the present study, Microwave was used to make chemical synthesis more environment friendly, safe, to improve the yield and also to reduce the time consumption. The newly synthesized Schiff bases (2a and 2b) were evaluated for anticoagulant activity. Schiff bases and thiazolidinones were purified, characterized and evaluated for antibacterial and anthelmintic activities. The yield of the synthesized compounds was found to be in the range of 70-86 %. All these molecules were characterized by physical data and FT-IR, ^{1}H NMR and mass spectral analysis. The synthesized schiff bases (2a and 2b) at concentrations 10µg/ml, 20µg/ml, 40µg/ml and 80µg/ml were tested for anticoagulant activity using prothrombin time test. Time of coagulation for both the compounds was recorded and it was found out that Schiff base 2a showed better anticoagulant activity when compared to Schiff base 2b. All the synthesized compounds were tested for antibacterial activity on E.*coli* and S.*aureus*, using chloramphenicol as standard drug at concentrations of 0.1%, 0.2% and 0.3%. Amongst all the synthesized compounds, compounds 2a, and 3a showed highest activity. All the synthesized compounds were also screened for anthelmintic activity, using albendazole as standard. The compound 2a showed highest activity, 2b and 3a showed moderate activity.

KEYWORDS: Microwave assisted synthesis, schiff bases, thiazolidinones, anthelmintic and antibacterial.

1. INTRODUCTION

1.1. Schiff base

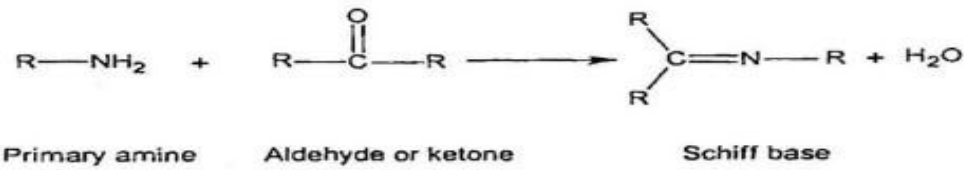
Schiff bases have been known since 1864[1] when Hugo Schiff reported the condensation of primary amines with carbonyl compounds. Schiff bases are condensation products of primary amines with carbonyl compounds. The common structural feature of these compounds is the azomethine group with a general formula RHC=N-R1, where R and R1 are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. These compounds are also known as anils, imines or azomethines. Several studies showed that the presence of a lone pair of electrons in an sp[2] hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance.[2-8]



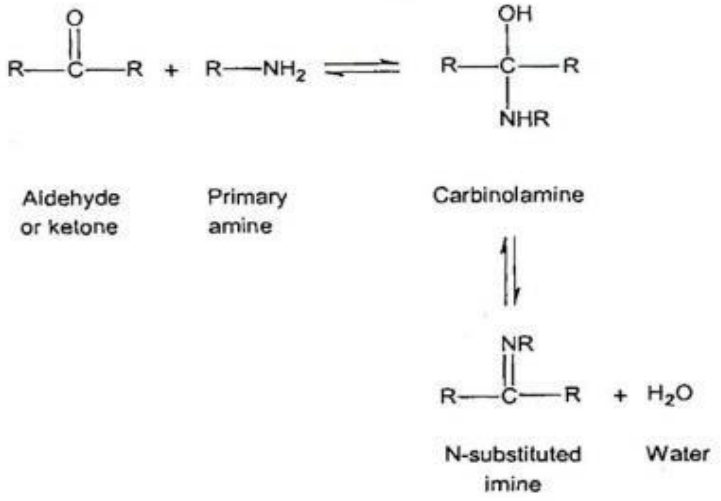
General structure of a Schiff base

1.1. a. Synthesis

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.



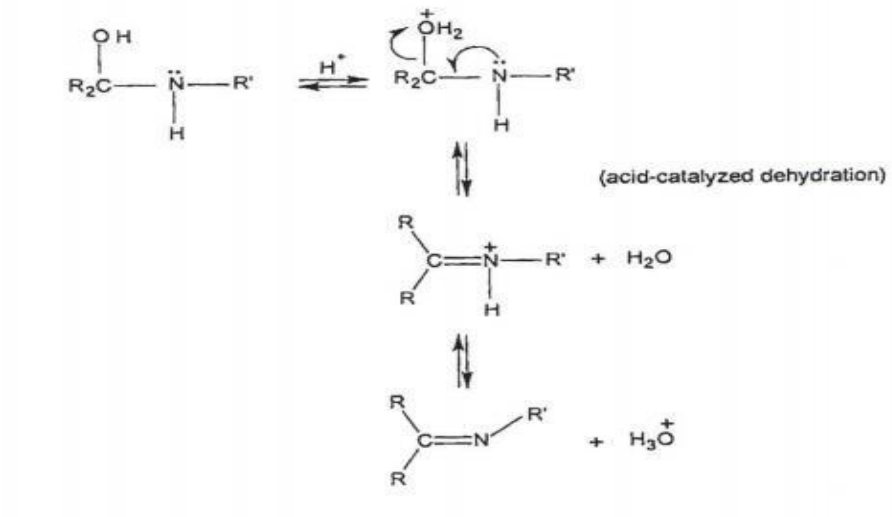
Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable[9-11] while those of aromatic aldehydes having effective conjugation are more stable.[12-15] 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.



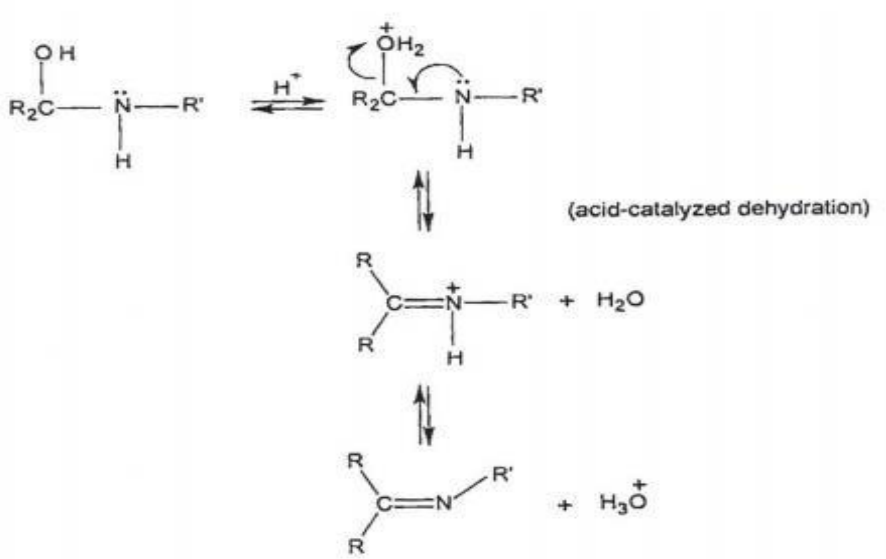
The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.

1.1. b. Mechanism

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.



1.1. c. Biological importance of Schiff bases

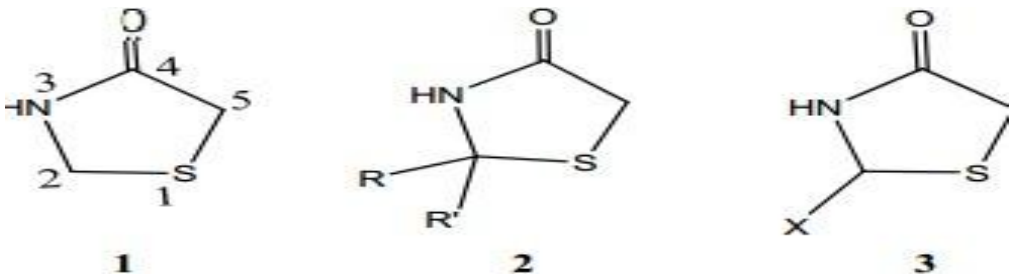
Schiff bases of salicylaldehydes have also been reported as plant growth regulators[16] and antimicrobial[17] or antimycotic[18] activity. Schiff bases also show some analytical applications. Schiff bases are characterized by the -N=CH- (imine) group which imports in elucidating the mechanism of transamination and racemination reaction in biological system.[19,20] Schiff bases are active against a wide range of organisms for example; *Candida Albicans, Escherichia coli Staphylococcus aureus, Bacillus polymxa, Trychophyton gypseum, Mycobacteria, Erysiphe graminis* and *Plasmopora viticola.*

Schiff bases have been studied for their important properties in catalysis.[21] They show catalytic activity in hydrogenation of olefins.[22] They find applications in biomimetic catalytic reactions. An interesting application of Schiff bases is their use as an effective corrosion inhibitor, which is based on their ability to spontaneously form a monolayer on the surface to be protected. Many commercial inhibitors include aldehydes or amines, but presumably due to the C=N bond the Schiff bases function more efficiently in many cases.[23]

Imines also have biological importance. An imine linkage between the aldehyde derived from vitamin A and the protein opsin in the retina of the eye plays an important role in the chemistry of vision. Schiff bases have been reported in their biological properties, such as, antibacterial, antifungal activities. Their metal[24-27] complexes have been widely studied because they have anticancer and herbicidal applications.[28-29] They serve as models for biologically important species. The Schiff bases constitute one of the most active classes of the compounds possessing diversified biological applications. The Schiff bases have been reported to possess higher degree of antitubercular, anticancer, antibacterial, anti-inflammatory, antifungal activities. Schiff bases belong to a widely used group of organic intermediates used for synthesis of pharmaceutical or rubber additives and amino protective group in organic synthesis.[30]

1.2. Thiazolidinone

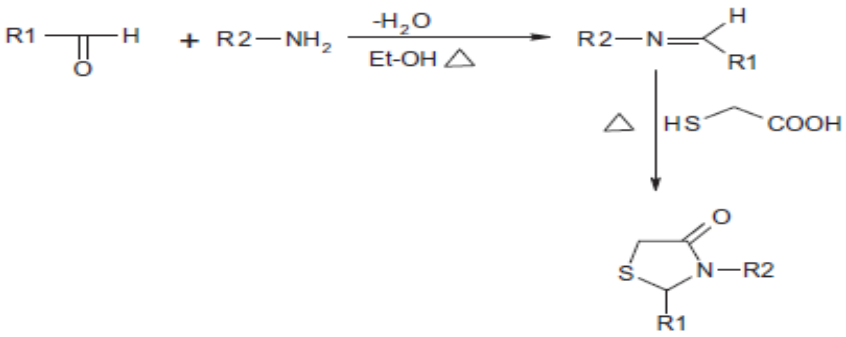
Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a moiety of choice as it possesses a broad spectrum of pharmacological activities against several targets. This array of biological response profile has attracted the attention of scientists the world over to further investigate the potential of this organic motif. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4-position (1). Substituents in the 2-, 3-, and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position (R and R' in 2 or X in 3). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by 2 and 3.



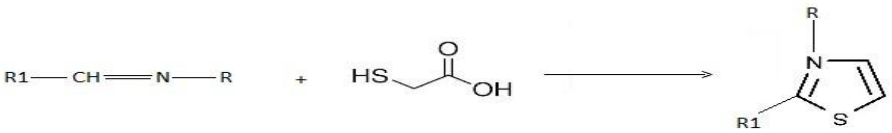
There are numerous biologically active molecules which contain various heteroatoms such as nitrogen, sulphur and oxygen, always drawn the attention of chemist over the years mainly because of their biological importance. Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5. However, its derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature. Similarly 1,3-thiazolidin-4-ones are heterocyclic nucleus that have an atom of sulfur and nitrogen at position 1 and 3, respectively and a carbonyl group at position 4 have been subjected to extensive study in the recent years.[31]

1.2. a. Synthesis

Several methods for the synthesis of 4-thiazolidinones are widely reported in the literature. The main synthetic routes to 1,3-thiazolidin-4-ones involve three components that is an amine, a carbonyl compound, and a mercapto-acid. The classical synthesis reported can be either a one- pot three-component condensation or a two-step process. The reactions begin by formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by generated sulphur nucleophile, followed by intramolecular cyclization on elimination of water.[32-34]

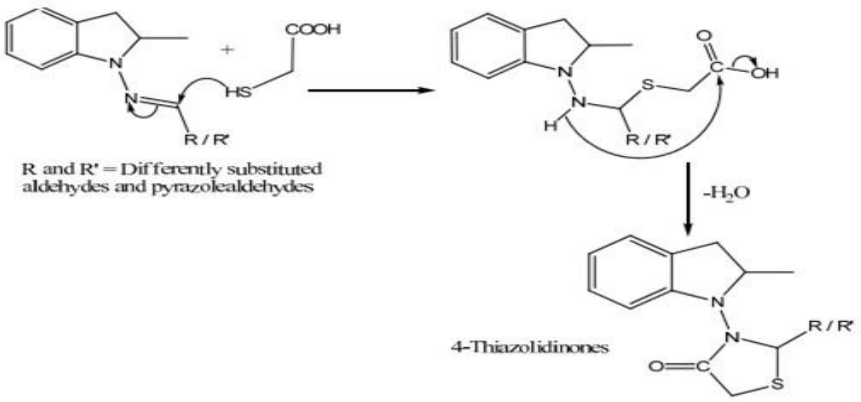


Thiazolidinones can also be synthesized by treating a Schiff base with thioglycolic acid in an organic medium.



1.2. b. Mechanism

It is based on cyclo-condensation. The reaction proceeds by the attack of mercapto acetic acid upon the C=N group, with the HS-CH2-COOH adding to the carbon atom followed by capture of the proton by nitrogen and subsequent cyclization. During the reaction an uncyclized intermediate is formed in few cases. In many instances 4-Thiazolidinones can conveniently be prepared by refluxing the mixture of thioglycolic acid and the Schiff base in benzene, dry ether or ethanol. The nucleophilic attack of the mercaptoacetic acid anion will take place on the carbon of azomethine which has got a positive character; while it is evident that the nitrogen has the negative character. Simultaneous removal of water that forms in the reaction helps in condensation and determination of the reaction time.[35]



1.2. c. Biological importance of Thiazolidinones

4-thiazolidinone is one of the most intensively investigated classes of aromatic five member heterocyclic's. These derivatives find a variety of applications ranging from antimicrobial, antitubercular, anti-inflammatory, anthelmintic, anticonvulsant, anti HIV activity, anticancer, and hypoglycemic activity. Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic researches.

The 4-thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs. 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.

It has been extensively reported that presence of arylazo, sulfamoylphenylazo-4 or phenylhydrazono moieties at different positions of the thiazolidone ring enhanced anti-microbial activity and its antibacterial activity may be due to its inhibitory activity of enzyme Mur B which is precursor acting during the biosynthesis of peptidoglycan. Numerous reports have appeared in the literature which highlights their chemistry and pharmacological uses. The thiazolidinones ring has been incorporated into a broad range of known biologically active compounds, either as a substituent group or as a replacement of another ring inspired researchers to synthesize several compounds containing this moiety.[36]

1.3. Microwave Synthesis

In inorganic chemistry, microwave technology has been used since the late 1970s, while it has only been implemented in organic chemistry since the mid-1980s. The main reasons for this increase include the availability of commercial microwave equipment intended for organic chemistry and the development of the solvent-free technique, which has improved the safety aspects, but are mostly due to an increased interest in shorter reaction times.[37]

The short reaction times and expanded reaction range that is offered by microwave assisted organic synthesis are suited to the increased demands in industry. In particular, there is a requirement in the pharmaceutical industry for a higher number of novel chemical entities to be produced, which requires chemists to employ a number of resources to reduce the time for the production of compounds. Chemistry databases, software for diversity selection, on-line chemical ordering systems, open-access and high throughput systems for analysis and high- speed, parallel and combinatorial synthesis equipment have all contributed in increasing the throughput. The common factors for these technical resources are automation and computer- aided control. They do not, however, speed up the chemistry itself. Developments in the chemistry have generally been concerned with novel highly reactive reagents in solution or on solid supports.

In general, most organic reactions have been heated using traditional heat transfer equipment such as oil baths, sand baths and heating jackets. These heating techniques are, however, rather slow and a temperature gradient can develop within the sample. In addition, local overheating can lead to product, substrate and reagent decomposition.

In contrast, in microwave dielectric heating, the microwave energy is introduced into the chemical reactor remotely and direct access by the energy source to the reaction vessel is obtained. The microwave radiation passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. If the apparatus is properly designed, the temperature increase will be uniform throughout the sample, which can lead to less by-products and/or decomposition products.

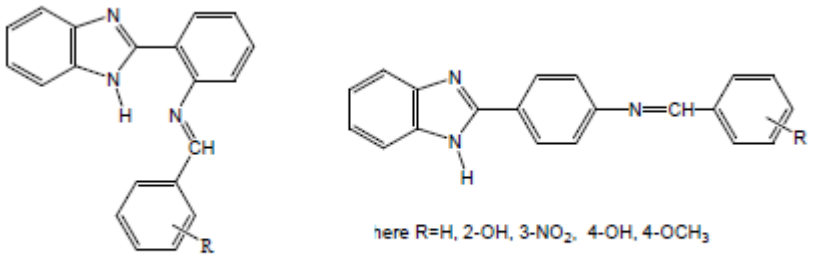
The use of microwaves as an energy source to heat reaction solutions has been shown to provide the following advantages.

- Broad applicability-few limitations as to types of synthesis chemistry.
- Increased reaction rates-1000 fold in best cases.
- Used to accelerate chemistries in both solution and solid phase reactions.
- Improved product yields.
- Moderately scalable (sub-milligram to milligram quantities).
- Can be conducted in either open or closed vessels.
- Broad dynamic temperature range.
- Green chemistry-reactions in supercritical water or solvent-less reactions.
- Can be used to accelerate the synthesis of peptides.
- Controlled method of heating.
- Rapid reaction optimization.

2. REVIEW OF LITERATURE

- Kumar *et al.* reported a new series of 2-(2-aminophenyl) benzimidazole and 2-(4-amino phenyl) benzimidazole derivatives, and their corresponding Schiff bases. Compounds were synthesized by cyclo-condensation of phenylenediamines and carboxylic acids or their derivatives (nitriles, imidates, or ortho esters) under strong acidic conditions (PPA) and at high temperatures. The synthesized compounds were screened for their *invitro* antimicrobial activities against the standard strains: *Staphylococcus aureus* (ATCC– 25923) and *Bacillus subtilis* (ATCC-6633) as Gram positive, *Escherichia coli* (ATCC- 11775) and *Pseudomonas aeruginosa* (ATCC-10145) as gram negative bacteria. Some of the compounds were found to be effective against gram positive bacteria at MIC values between 25 and 200 mg/mL and some were effective against ram negative

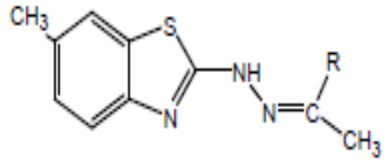
bacteria at MIC values between 25 and 200 mg/mL.[38]



here R=H, 2-OH, 3-NO_2, 4-OH, 4-OCH_3

Benzimidazole derivatives

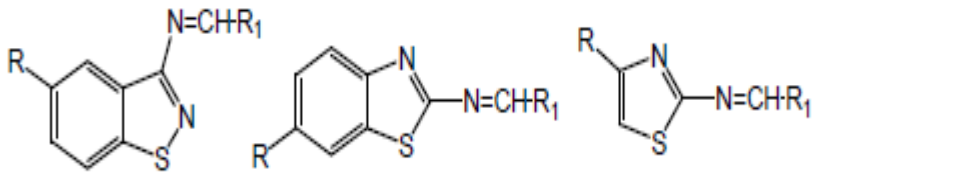
➢ Alang *et al*. described the synthesis and antibacterial activity screening of newer Schiff bases of 2-amino-6-methylbenzothiazole derivatives. *p*-tzololuidine on reacting with ammonium thiocynate yielded 2-benzothiazolamines, which on subsequent reaction with hydrazine hydrate formed hydrazino derivative. Schiff bases were obtained by reacting hydrazino derivatives with different acetophenones. All the synthesized compounds showed activity against gram positive bacteria- *Staphylococcus aureus* (MTCC 737),*Staphylococcus epidermidis* (MTCC 3615) and gram negative bacteria- *Pseudomonas aeruginosa* (MTCC 424) and *Escherichia coli* (MTCC 1687) at 1 mg/mL disc concentration.The activities of all the compounds were comparable with that of standard drug, ampicillin.[39]



where R=2-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 2-OHC_6H 4-OHC_6H, 2,5-di(OH)C_6H_3

Benzothiazole derivatives

➢ Vicini *et al.* studied a comparative evaluation of three new series of benzo[*d*]isothiazole, benzothiazole and thiazole Schiff bases. Schiff bases were synthesized by reacting the appropriate heteroarylamine with the selected aldehyde. These compounds were evaluated *in vitro* against a HIV-1 (Retrovirus), a HBV (Hepadnavirus), Yellow fever virus (YFV) and Bovine viral diarrhoea virus (BVDV). The compounds were also tested against gram positive and gram negative bacteria (*Staphylococcus aureus*, *Salmonella spp*.), various atypic mycobacterial strains (*Mycobacterium fortuitum* and *Mycobacterium smegmatis*), yeast (*Candida albicans*) and mould (*Aspergillus fumigatus*). None of the compounds showed antiviral or antimicrobial activity. The benzo[*d*]isothiazole compounds showed a marked cytotoxicity (CC50=4–9 mM) against the human CD4+ lymphocytes (MT-4) that were used to support HIV-1 growth.[40]



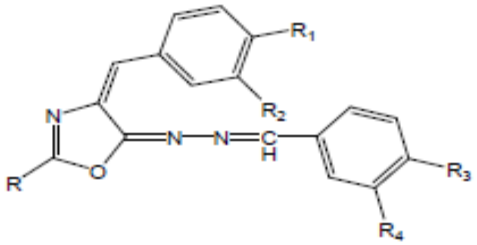
R= H, CH
R_1= 3-ClC_6H_4, 4-$OCH_3C_6H_4$, 4-OH, 5-NO_2-2 furanyl

R= H, F, -OC_2H_5
R_1=2-ClC_6H_4, 3-$NO_2C_6H_4$, 4-OHC_6H_4

R= H, -$OCH_3C_6H_4$
R_1= 3-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$

Benzothiazole & thiazole derivatives

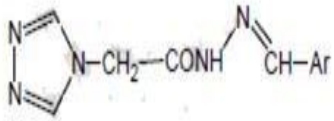
➢ Ali Syed *et al.* synthesized a novel series of Schiff bases of 2-methyl/phenyl-4- benzylidene-5-hydrazino-1,3-oxazole by condensing 2-methyl/phenyl-4-benzylidene-5- oxo-1,3-oxazole with hydrazine hydrate followed by different aromatic aldehydes. The synthesized compounds were screened for antimicrobial activities against gram positive *S. aureus*, *C. diphtheria* and Gram negative *E. coli*, *P. aeruginosa* bacterial strains. Compounds showed considerable activity when compared to the standard drug, ampicillin trihydrate.[41]



R= CH_3, C_6H_5; R_1= H, OH, OCH_3, Cl
R_2= H, OH; R_3= H, OH, OCH_3, Cl; R_4= H, OH

Oxazole derivatives

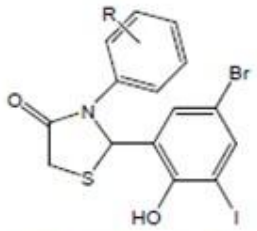
➢ Somani *et al.* reported the synthesis of newer Schiff bases of 1, 2, 4-triazolederivatives, N'-(substitutedbenzylidene)-2-(4*H*-1,2,4-triazol-4-yl) acetohydrazide. 1, 2, 4-triazole was converted to ethyl-5-N'-(1, 2, 4-triazolyl)-acetate using ethyl bromoacetate. It was then converted to corresponding hydrazide by hydrazine hydrate, which upon further treatment with various aromatic aldehydes under acidic condition afforded Schiff bases. All the synthesized compounds were screened for *in vitro* study of antibacterial efficacy against*S. aureus, P. aeruginosa and E. coli* at two different concentrations viz. 50 and 100 µg/mL using streptomycin as the standard. Compound showed good activity against all the organisms at both concentrations.[42]



Ar= C_6H_5, p-$OCH_3C_6H_4$, o-OHC_6H_4, o-ClC_6H_4, m-$NO_2C_6H_4$
furan-2-yl, 4-hydroxy-3-methoxyphenyl

Triazole derivatives

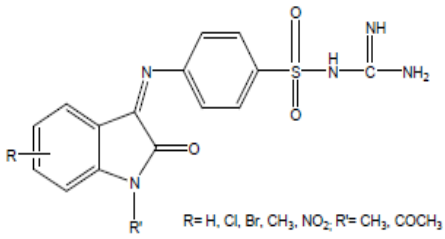
➢ Pawar and co-workers reported the synthesis and antibacterial activity of some new Schiff bases of 4-thiazolidinones. Schiff bases were synthesized by the condensation of 2-hydroxy-3-iodo-5-bromobenzaldehyde with aromatic amine in ethanol. Compounds obtained undergo cyclization with mercaptoacetic acid to afford corresponding 4- thiazolidinones. Compounds showed antibacterial activity against *E. coli*, *B. subtilis*, *S.typhi*, *S. dysentraceas* as test organisms, but none of them showed better activity than standard drug tetracycline.[43]



R= H, 2-OCH_3, 4-Cl, 4-CH_3, 2-NO_2, 4-NO_2, 4-COOH,

Thiazolidinones derivatives

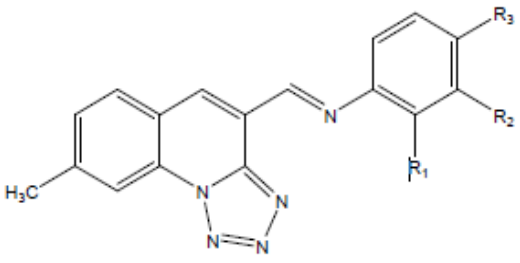
➢ Singh and co-authors synthesized some new Schiff bases of isatin and substituted isatin by condensation with 4-amino-*N*-carbamimidoylbenzene sulfonamide. The synthesized compounds were screened for antibacterial activity against three gram positive (*S. aureus*, *B. subtilis*, *B. pumulis*) and three gram negative bacterial (*E. coli*, *S. abony*, *K.pneumoniae*) strains. All the compounds exhibited significant antibacterial activity in comparison to the standard drug, sulfaguanidine against both gram positive and gram negative bacterial strains. None of the compounds exhibited significant antifungal activity comparable to standard antifungal drug, clotrimazole against *S. cerevisiae* and *C. albicans*.[44]



R= H, Cl, Br, CH_3, NO_2; R'= CH_3, $COCH_3$

Isatin sulfonamides

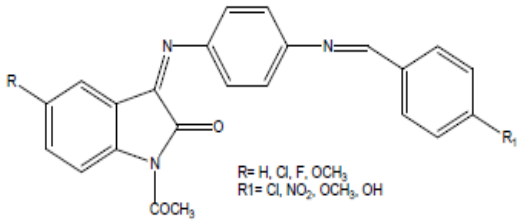
➢ Bawa *et al.* synthesized a series of 4-substituted-iminomethyltetrazolo quinoline derivatives by condensation of 4-formyl-8-methyltetrazolo quinoline with appropriate aromatic amine by refluxing in dioxane. The synthesized compounds were evaluated for anti-inflammatory and antimicrobial activities. Compounds showed moderate to good activities.[45]



R_1=R_2=R_3 = H/CH_3/F/Cl/Br/NO_2/OCH_3/CH_3 etc.

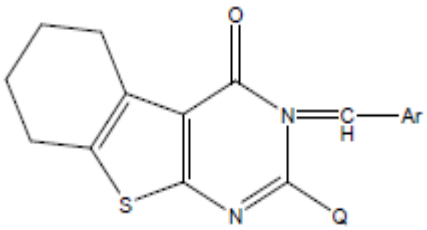
Tetrazolo quinoline derivatives

➢ Panneerselvam and coworkers synthesized a series of novel Schiff bases by condensation of 5-subsituted isatin with different substituted aromatic aldehydes. The synthesized compounds were investigated for analgesic, anti-inflammatory and antibacterial activities. The minimum inhibitory concentrations (MIC) of the compounds were also determined. Most of the synthesized compounds exhibited significant antibacterial and antifungal activities. Among the synthesized compounds, few exhibited remarkable analgesic and anti inflammatory activities.[46]



Subsituted isatin derivatives

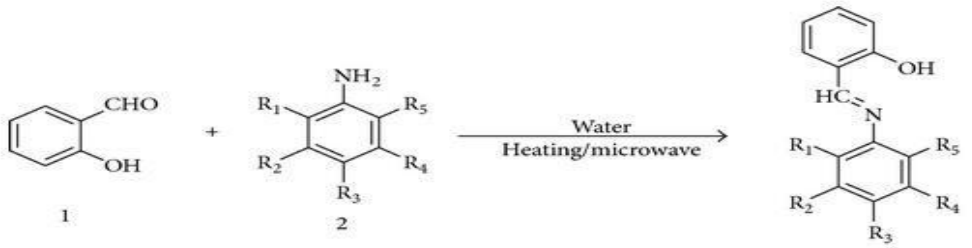
➢ Ammar *et al.* synthesized some novel thieno[2,3-*d*]pyrimidines by refluxing the compound 2-(3-aryl-4.5,6,7-tetrahydrobenzo[*b*] thiophene-2-yl)carboxamido quinoxaline with hydrazine hydrate. Further condensation with the aromatic aldehydes furnished the corresponding Schiff bases. The synthesized compounds were subjected to antibacterial activity against *S. aureus*, *E. coli*, and antifungal activity against *C. albicans*.[47]



Where Ar= C_6H_4OH-*o*, $C_6H_4OCH_3$-*o*, C_6H_4Cl-*o*
Q= quinoxalinyl-2

Quinoxaline derivatives

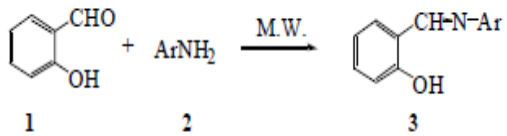
➢ Sunita Bhagat *et al.* reported the synthesis of some salicylaldehyde Schiff bases in aqueous media. The final products generate excellent yields in a one-step procedure under microwave irradiation using a suitable solvent. The structures of the synthesized compounds were confirmed by IR, ^{1}HNMR and Mass Spectra data.[48]



1 2 3(a–e)

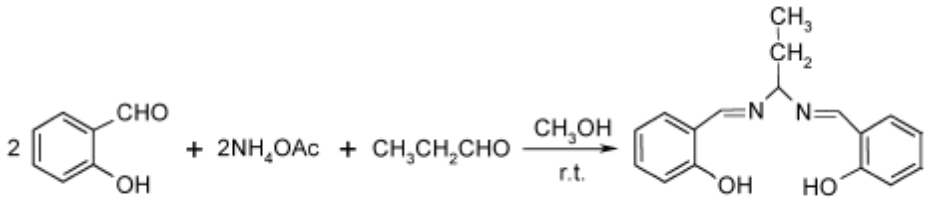
(3a) R_1 = F, R_2 = H, R_3 = F, R_4 = H, R_5 = H
(3b) R_1 = H, R_2 = H, R_3 = Cl, R_4 = H, R_5 = H
(3c) R_1 = F, R_2 = F, R_3 = F, R_4 = F, R_5 = H
(3d) R_1 = H, R_2 = H, R_3 = Br, R_4 = H, R_5 = H
(3e) R_1 = H, R_2 = H, R_3 = F, R_4 = H, R_5 = H

➢ Hai Jian Yang *et al.* reported the rapid synthesis of Schiff-base without solvent under microwave irradiation. Microwave-assisted preparations of a series of Schiff-base via efficient condensation of salicylaldehyde and aryl amines without solvent were prepared with high yield as well as environmental friendship reaction in organic synthesis.[49]

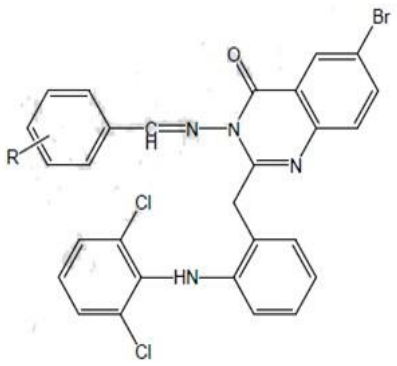


1 2 3

➢ Hossein Naeimi *et al.* reported a convenient, mild and one-pot synthesis of double schiff bases from three component reaction of salicylaldehyde, ammonium acetate and aliphatic aldehydes accelerated by NEt3 as a base. By this reaction, N,N_-bis(salicylidene)-1,1-diaminoalkanes was easily obtained in excellent yields and short reaction times under mild reaction condition.[50]



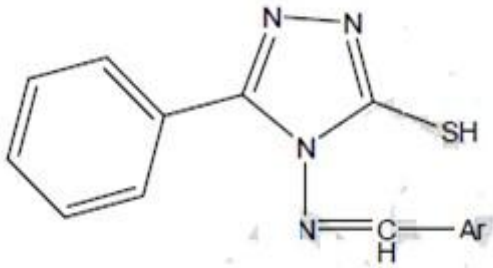
➢ Patel *et al.* reported the synthesis and antimicrobial activity of a new series of Schiff bases derived from quinazolin-4(3*H*)-one. The benzoxazinone, 6-bromo-2-[2-(2,6- dichlorophenyl)amino]benzyl-4*H*-3,1-benzoxazin-4-one was prepared by the cyclization reaction of acid chloride with 5-bromoanthranilic acid. Further reaction of benzoxazinone with hydrazine hydrate yielded 3-amino-6-bromo-2-[2-(2,6-dichlorophenyl)amino]benzylquinazolin-4(3*H*)-one, which upon subsequent condensation with different substituted aromatic aldehydes formed Schiff bases, 6-bromo-2-[2-(2,6-dichlorophenyl)amino]- benzyl-3-substituted benzylideneamino- quinazolin-4(3*H*)-ones. Compounds were screened for antibacterial activity against two gram positive bacteria (*Staphylococcus aureus*, ATCC9144 and *Bacillus subtilis*, ATCC 6633) and two gram negative bacteria (*Pseudomonas aeruginosa*, ATCC 9027 and *E. coli*, ATCC 25922); while antifungal activity was screened against *Candida albicans*, ATCC 10231 at two different concentrations 100 and 50 µg/mL. Penicillin-G was used as a standard antibacterial agent whereas amphotericine-B was used as a standard antifungal agent. Most of the synthesized Schiff bases exhibited good antibacterial activities against gram positive and gram negative bacteria, whereas antifungal activity were found to be moderate to poor.[51]



R= 2-NO_2, 3-NO_2, 2-OH, 4-OH, 2-Cl, 4-Cl, 4-OCH_3, 3,4,5-$(OCH_3)_3$, 2-OH-4-OCH_3, 4-$N(CH_3)_2$, 2-OH-4-$N(C_2H_5)_2$

Benoxazinone derivatives

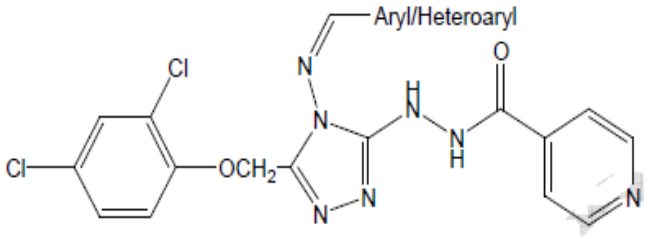
➢ Jubie *et al.* reported the synthesis of some new Schiff base of 4-(amino) -5-phenyl-4*H*- 1,2,4-triazole-3-thiol and screened them for antianxiety and antidepressant activities. The cyclisation of potassium dithiocarbazinate with hydrazine hydrate yielded the basic nucleus, 4-(amino)-5-phenyl-l-4*H*-1,2,4-triazole-3-thiol which was subjected to addition reaction with different aromatic aldehydes to obtain desired Schiff bases. Among the synthesized compounds, the Schiff bases of benzaldehyde, furfuraldehyde and 2,4- dichloro benzaldehyde showed significant activities when compared with the reference standard drug, diazepam.[52]



Ar= phenyl, 2,4-dichlorophenyl, furan-2-yl

Triazole-3-thiol derivatives

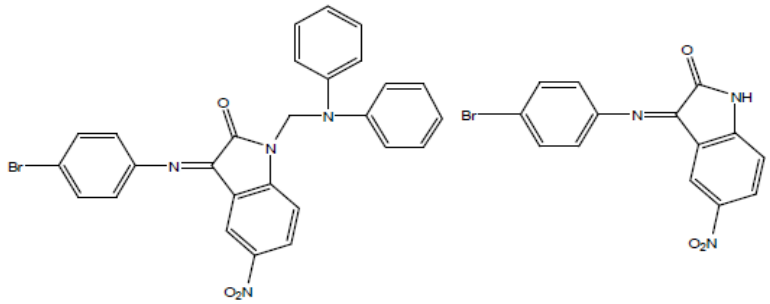
➢ Hunas Hal *et al.* reported the synthesis and antimicrobial activity of a novel series of substituted 1,2,4-triazole Schiff bases. *N*'[4-(substitutedbenzylidene)-3(2'4'dichlorophenoxymethyl)1,2,4-triazol-5-ylisonicotinyl hydrazide derivatives were synthesized by the reaction between *N*'[4-amino-3-(2'4'dichlorophenoxymethyl)1,2,4- triazol-5-ylisonicotinyl hydrazide and various aromatic aldehydes in presence of hydrochloric acid in alcohol. All the compounds were screened for antibacterial and antifungal activities using standard bacterial and fungal strains *Staphylococcus aureus* (ATCC 9144), *Bacillus subtilis*(ATCC 6633), *Pseudomonas aeruginosa* (ATCC 25668), *Escherichia coli* (ATCC 25922),*Candida albicans* (ATCC 2091), *Aspergillus niger* (ATCC 6275) *Aspergillus fumigates*(ATCC 13073) respectively. All the compounds showed moderate to good antifungal and weak antibacterial activities. Compounds were also tested for antitubercular activities by broth dilution assay method against *M. tuberculosis* H37Rv strain and showed very weak activities.[53]



Aryl/Heteroaryl: 3-NO_2, 4-NO_2, 2-OH, 4-OH, 3-OCH_3, 4-OCH_3, 4-Cl, 2,4-Cl, 4-CH_3, 4-$N(CH_3)_2$, -CH=CH-C_6H_5, 2-furyl

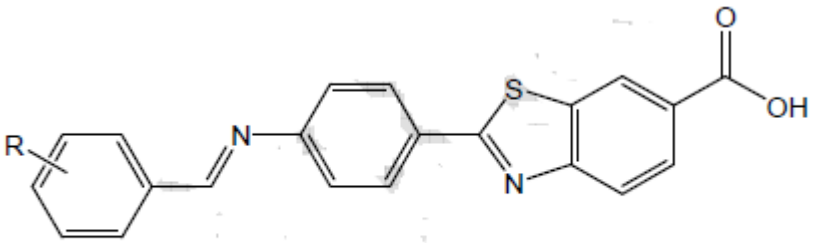
Triazol-5-ylisonicotyl hydrazide derivatives

➢ Sridhar *et al.* prepared Schiff bases and hydrazones of substituted isatin by reacting isatin and aromatic primary amines/hydrazines and determined their MIC values for antimicrobial activity against seven gram positive and seven gram negative standard pathological strains. The results of MIC values indicated that 3-(4-Bromo-phenylimino)- 1-[(diphenylamino)-methyl]-5-nitro-1,3-dihydro-indol-2-one and 3-(4-Bromo-phenylimino)-5-nitro-1,3-dihydro-indol-2-one were found to be the most active compounds of the series.[54]



Substituted isatin derivatives

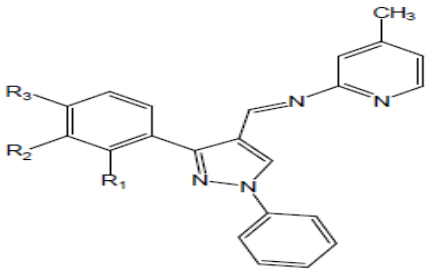
➢ Prabhu *et al.* synthesized a new series of Schiff bases of several benzothiazole derivatives. *Para-nitrobenzothiazole* carboxylic acid synthesized by Jacobson synthesis which was reduced to *para*-amino benzothiazole carboxylic acid with ammonium chloride and iron metal. The resulting product was then condensed with various aromatic or heterocyclic aldehydes in the presence of concentrated sulphuric acid as a catalyst using ethanol as solvent to yield different Schiff bases. Synthesized compounds were screened for their *in-vitro* antibacterial activity against *P.aeruginosa, E.coli, S.aureus, B.subtilis* at 100µg/ml and *in-vitro* antifungal activity against *Candida albicans and Aspergillus niger* activities at 100 µg/ml concentration. All the compounds have shown significant antibacterial activity with the reference standards, ampicillin and ketoconazole.[55]



R=H, Cl, F, NO_2, OCH_3, OH

Substituted benzothiazole derivatives

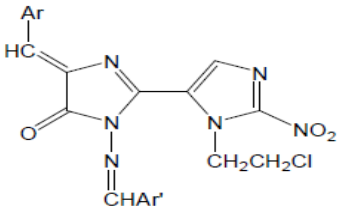
➢ Vora *et al.* prepared some new Schiff base derivatives, of N-{(1E)-[3-(mono or di- substituted aryl)-1- phenyl-1*H*-pyrazol-4-yl]methylene}-4 methylpyridin-2-amine by the acid catalyzed condensation of 3-(mono- or di-substituted aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde derivatives with 4-methylpyridin-2-amine. All the synthesized compounds were screened for their antimicrobial activities by using broth dilution method. Although compounds were found to be active against the tested antibacterial (*E. coil, P. aureginosa,S. aureus, S. pyogenus*) and antifungal strains (*C. albicans, A. niger*, and *A. clavatus*), but were less active than the standard drugs.[56]



R_1= H, OH
R_2= H, OH, NO_2
R_3= H, Cl, CH_3, NO_2, OCH_3

Pyrazol derivatives

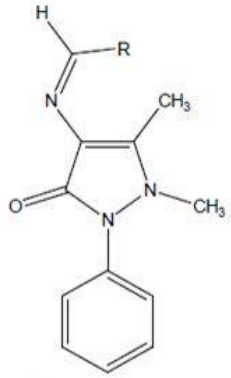
➢ Atia *et al.* reported some new imidazole Schiff bases and screened them for antibacterial activity. 3-Aminobiimidazol-4-one compounds were synthesized by the reaction of compounds, 2-[1-(2-chloroethyl)-2-nitro-1*H*-imidazole-5-yl]-4-arylidene 1,3-oxazol- 5(4*H*)-ones (prepared from oxidative cyclization of compound, ({[1-(2-chloroethyl)-2- nitro-1*H*imidazole-5-yl]carbonyl}amino) acetic acid with aromatic aldehydes) with hydrazine hydrate. The reaction of key intermediate 3-amino-3'-(2-chloroethyl)-5- arylidene-2'-nitro-3,5-dihydro-3'*H*,4*H*-2,4'-biimidazol-4-ones with aromatic aldehydes produced newer Schiff bases in high yield. The antibacterial activity of the imidazole derivatives was tested by the agar discdiffusion method against *Staph. aureus, E. coli and Proteus mirabilis* bacteria. Compounds showed good activity except few ones..[57]



Ar= 4-NO_2-C_6H_4 , 4-Br-C_6H_4 , 4Cl--C_6H_4
Ar'= 4-CH_3--C6H4 , 3-NO_2-CH_4 , 2-NO_2--C_6H_4

Imidazole derivatives

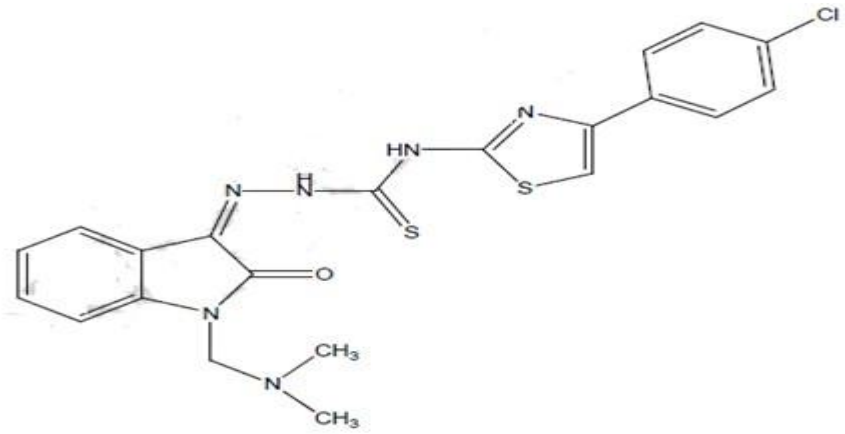
➢ Asiri *et al.* synthesized a series of 1, 5-dimethyl-2-phenyl-1, 2-dihydro-3*H*-pyrazol-3-one containing Schiff bases and screened for their antibacterial activities. 1, 5-dimethyl-2- phenyl-1, 2-dihydro-3*H*-pyrazol-3-one Schiff base derivatives were prepared by the reaction of 4-aminophenazone with different substituted aromatic aldehydes. Four compounds showed moderate to good antibacterial activity against four bacterial strains, viz.*Escherichia coli, Staphylococcus aureus, Salmonella typhimurium* and *Streptococcus pyogenes* with MIC values of 6.25 µg/ml.[58]



R= 2-Cl-C_6H_4, 2CN-C_6H_4, 2-OCH_3.C_6H_4, 4-N(CH_3)-C_6H_4 etc.

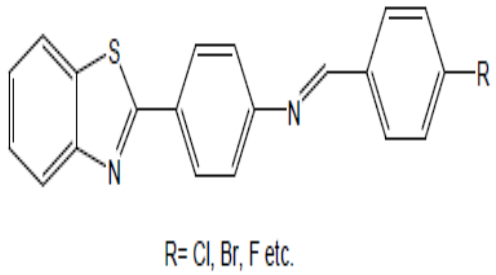
Pyrazol derivatives

➢ Pandeya *et al.* prepared a series of Schiff and Mannich bases derived from isatin derivatives and *N*-[4-(4'chloropheyl) thiazol-2-yl]thiosemicarbazide. All the synthesized compounds were screened for antimicrobial activities against 28 pathogenic bacteria, 8 pathogenic fungi and anti-HIV-1 in MT-4 cells culture. Among the synthesized compounds, one compound showed the most pronounced activity.[59]



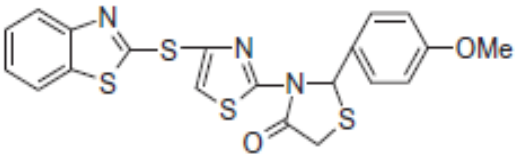
Thiazole thiosemicarbazone derivatives

➢ Hutchinson *et al.* synthesized fluorinated analogues of 2-(4-aminophenyl) benzothiazoles, among which 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole exhibited selective and potent anticancer activity..[60]

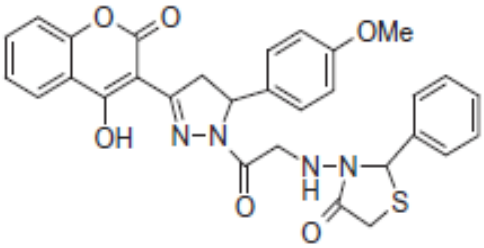


Benzothiazole derivatives

➢ Singh *et al.* studied substituted thiazolyl-thiazolidinylbenzothiazolesand showed that none of the compounds having 2-substituted 4-thiazolidinone ring showed any antibacterialactivity but compounds were potent for insecticidal activity. Electron withdrawing group at phenyl ring such as p-OCH3(a) enhanced its insecticidal activity. Compound containing the azetidinone moiety instead of thiazolidinone displayed antibacterialactivity against gram-positive bacteria *S. aureus* and *E. coli*. Thiazolidinone derivatives synthesized from chalcones of 4-hydroxycoumarin (b) showed that compounds having the methoxy group have increased antibacterial activity while azetidinones were found to be more active than thiazolidinones.[61]

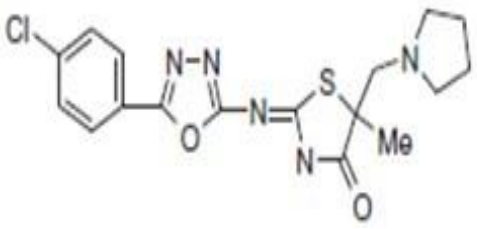


(a)

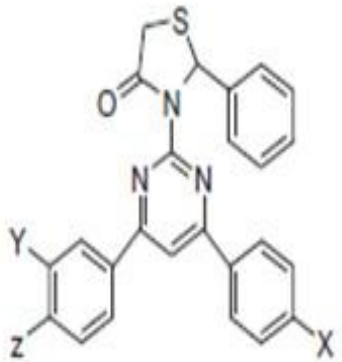


b)

➢ Kocabalkanli *et al.* synthesized Mannich bases of some 2,5-disubstituted 4- thiazolidinones and evaluated their antimicrobial activity. They reported that the most active compound had a p chlorophenyl group on the oxadiazole, a methyl and a pyrrolidinomethyl at the 5-position of the thiazolidinone (a), while the least active one has a hydrogen atom in place of a chlorine and a morpholine in place of a pyrrolidine. Further analogous of 2-phenyl-3-(4,6-diarylpyrimidin-2-yl)thiazolidin-4-ones (b,c) have been synthesized by Gopalakrishnan *et al*. and tested for their antibacterial activity against *Staphylococcus aureus*, b-hemolytic Streptococcus, *Vibrio cholera*, *Salmonella typhi*, *Shigella felxneri*, *Escherichia coli*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug. Results revealed that p-(OCH3) and p-(CH3) groups at phenyl ring attached to the pyrimidine ring exerted strong antibacterial activity against all the tested bacterial strains on the other hand compounds with electron withdrawing p-Cl and p-F functional group at phenyl ring attached to pyrimidine ring did not improved antibacterial activity.[62]



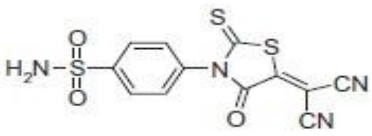
(a)



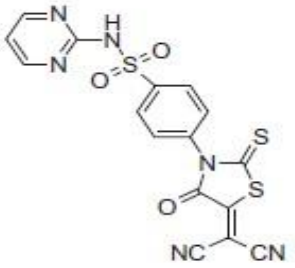
(b)X=Y=H,Z= -OCH3 ; (c) X= -OCH3, Y=Z=H

➢ El-Gaby *et al.* recently synthesized a series of 2-thioxo-4-thiazolidinones and 4,4′-bis(2- thioxo-4-thiazolidinone-3-yl)diphenylsulfone derivatives. Most of the compounds were found moderate in activity against

tested strain of bacteria. Thiazolidinones (a) with sulfamoyl and thioxo moieties were found to possess highest antibacterial activity towards *Bacillus cereus* whereas thiazolidinone derivative (b) bearing pyrimidine nucleus, sulfamoyl phenyl and thioxo moieties revealed high activity against *S. aureus.*[63]

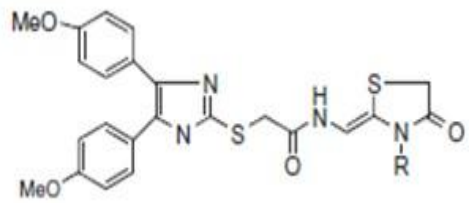


(a)



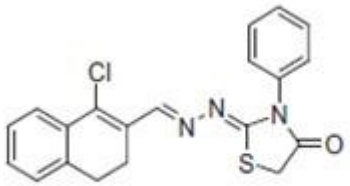
(b)

➢ Gihsoyl *et al.* synthesised and evaluated antimicrobial activity of novel derivatives of hydrazide-hydrazones, thiosemicarbazides and thiazolidinones. All the synthesized compounds were tested for antibacterial, antifungal and antimycobacterial activity against different bacteria (*S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *K. pneumonia* ATCC 4352, *P.aeruginosa* ATCC 1539, E. coli ATCC 8739, *Shigella jlexneri*, S. *typhi*, *Proteus mirabilis*, *Mycobacterium tuberculosis* H37Rv) and *C.albicans* ATCC 10231. They noted that none of the compounds (a, b) showed significant activity against the selected microorganisms.[64]

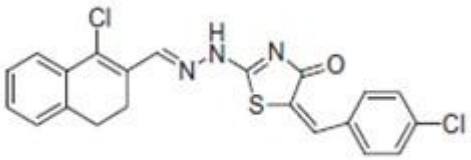


a=R= -C3H5,b=R= -C6H6

➢ Bondock *et al.* synthesized thirteen compounds and screened for antimicrobial activities against *B. subtilis*, *B. megaterium*, *E. coli*. Most of the prepared thiazolidinone derivatives (a,b) revealed comparable activity against tested strains by taking ampicillin and chloramphenicol in a concentration of 25 mg/ml as a reference drug.[65]

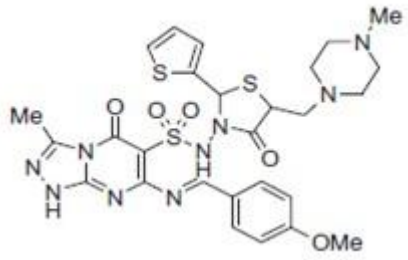


(a)



(b)

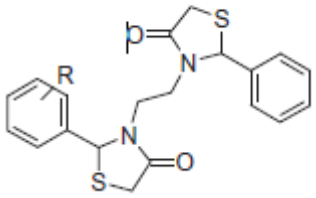
➢ Hafez *et al.* synthesized a series of substituted triazolo[4,3-a]pyrimidin-6-sulfonamide with an incorporated thiazolidinone moiety and reported for their antitumor activity. Most of the synthesized compounds were found moderate in activity and compound (a) displayed a good growth inhibitory activity on all tested 60 cell lines showing GI50 values between 5.89 and $37.1*10^{-6}$µM. In fact, the presence of 4- methylpiprazin/ morpholine on C-5 and thienyl group at C-2 of thiazolidinone seems to be very important for anticancer activity.[66]



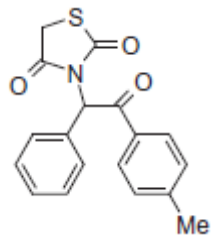
(a)

➢ Ottana *et al.* investigated 3,3'-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives (a), which

showed interesting stereoselective anti-inflammatory/analgesic activities and suggested that these derivatives might preferentially interact with inducible COX-2 isoform. Absence of 5-arylmethylidene moiety in 3-[2-(4-methylphenyl)-2-oxo-l- phenylethyl]-2,4-thiazolidinedione(b) enhanced its anti-inflammatory activity and decreased the analgesic activity. Bulkiness at NH group of 2, 4-thiazolidinedione ring either decreased or abolished the anti-inflammatory activity.[67]

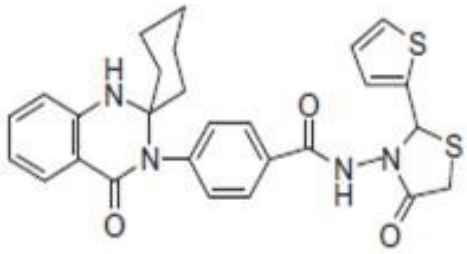


(a)



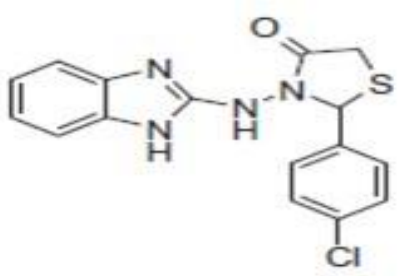
(b)

➢ Amin *et.al.* prepared several spiro [(2H,3H) quinazoline-2,10-cyclohexan]-4(1H)-one derivatives. These compounds were evaluated for their anti inflammatory, ulcerogenic and analgesic activities. Compound (a)with 2-thiophene substitution at C-2 of thiazolidinone has shown most active anti-inflammatory activity and considerable analgesic activity.[68]



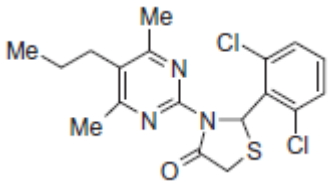
(a)

➢ Akula *et al.* synthesized 3-[1H-benzimidazole-2-yl-amino]-2-phenyl-1,3-thiazolidin-4- one derivatives and compound with 4-chloro (a) on phenyl ring showed promising depressant activity among all the tested compounds.[69]

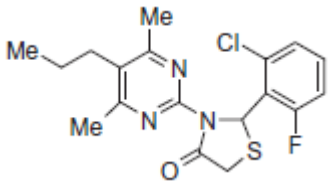


(a)

➢ Chen *et al.* prepared various 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-5-(un)substituted- pyrimidin-2-yl)-thiazolidin-4-ones. The structures of these newly synthesized compounds were confirmed by their analytical and spectral data. These compounds were also evaluated for their HIV-RT inhibitory activity. It was stated that HIV-RT inhibitory activity would be majorly affected by high value of hydrophobicity. It was reported that compound (a) and (b) having ethyl group at 5-position on N-3 position of pyrimidine ring were the most potent ones with the IC50 value of 0.26 and 0.23 lM, respectively. Their findings suggested that overall hydrophobicity of the analogues, and steric and electronic features of meta/para substituents of 3-hetero-aryl moiety on thiazolidin-4-one led to a substantial increase in antiviral activity.[70]



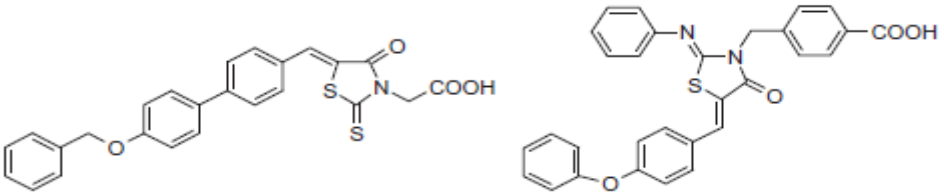
(a)



(b)

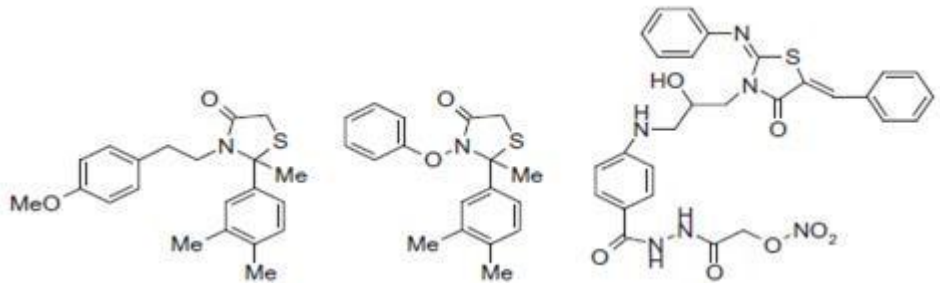
(b) Liu *et al.* studied a series of novel PTP1B inhibitors containing a thiazolidinone- substituted biphenyl scaffold and reported that introduction of the 4- oxothiazolidine-2- thione moiety showed better inhibitory activity against PTP1B. Substitution with polar group at N of thiazolidinone ring and alkyl group at the 40-position of the biphenyl scaffold led to unfavorable for bioactivity. Compound (a) have benzyl group lowered the fasting glucose levels and showed IC_{50} value of 0.48±0.07μmol/L. Replacement of carbonyl group in position 2 of the 2,4-thiazolidinedione scaffold with a phenylimino moiety enhanced its PTP1B as well as LMW-PTP inhibitory activity. Ottana et al. reported that substitution with lipophilic arylidene moiety in position 5

particularly favored the activity; phenoxy and benzyloxy groups in the para and meta positions of the 5-benzylidene group found to be better substituents for enzyme inhibition. Compound 4-{[4-oxo-5-(4-phenoxy-benzylidene)-2-phenylimino-thiazolidin-3-yl]methyl}benzoic acid showed PTP1B and LMW-PTP inhibition at IC_{50} = 1.1, 3.1 μM, respectively.[71]



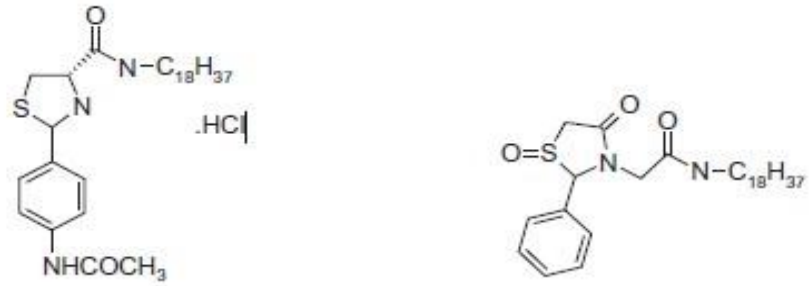
(a) (b)

➢ Jackson *et al.* reported synthesis and biological evaluation of thiazolidinone-based blockers of Kv1.5.The 3,4-dimethyl derivatives (a) (IC_{50} = 0.069 lM) and 145 (IC_{50} = 0.270 lM) were found to be the most potent compounds of this series.132 In 2009, Bhandari and co-workers discovered 2-(2-(4-(3-((5-substituted methylene)-4-oxo-2-(phenylimino)thiazolidin-3-yl)-2-hydroxypropylamino) benzoyl) hydrazinyl)-2-oxoethyl nitrate derivatives(b) and evaluated them for electrocardiographic, antiarrhythmic, vasorelaxing and antihypertensive activity as well as for in-vitro nitric oxide (NO) releasing ability and found that some of these heterocycles are very potent. Compound 2-(2-(4-(3-(5-benzyliden-4-oxo-2-(phenylimino)-thiazolidin-3-yl)-2-hydroxy propylamino)benzoyl) hydrazinyl)-2-oxoethyl nitrate (c), was found to be the most potent in this series.[72]



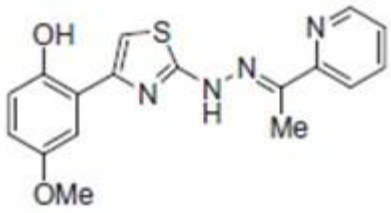
(a) **(b)** **(c)**

➢ Gududuru *et al.* tested a series of 2-arylthiazolidine-4-carboxylic acid amides for possible cytotoxic activity in prostate cancer. Compound (a) was found to be most potent and selective cytotoxic agent with IC_{50} of 0.55 lM and 38-fold selectivity in PPC-1 cells.The SAR study showed that as the chain length increased from C7 to C18, the potency also increased but further increase in the alkyl chain by one carbon unit caused a significant loss of activity, so alkyl chain with C18 unit was optimal for effectiveness of thiazolidine analogues. Replacement of the phenyl ring with an alkyl or cyclohexyl group reduced the potency while replacement with furanyl ring derivative showed equivalent cytotoxicity. The same research group designed new series of 2-aryl-4-oxo-thiazolidin-3-yl amides (b) and all synthesized compounds were evaluated against five human prostate cancer cell lines. They reported that increase in the alkyl chain enhanced the antiproliferative activity while replacement of the alkyl chain with aryl group reduced the biological activity.[73]



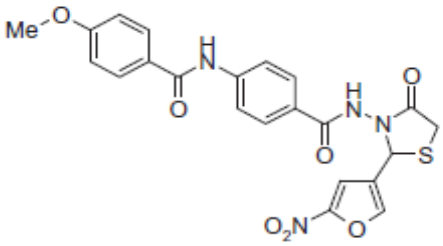
(a) **(b)**

➢ Zitouni *et al.* reported the synthesis of N-pyridyl-N0-thiazolylhydrazinederivatives. Compound (a) showed high antituberculosis activity (IC50: 6.22 lg/mL and IC90: 6.78 lg/mL), its structural details revealed that 2-pyridyl and 2-hydroxy-5-methoxyphenyl group are essential for antimycobacterial activity while 3-pyridyl, 4-pyridyl group were unfavorable for activity.[74]

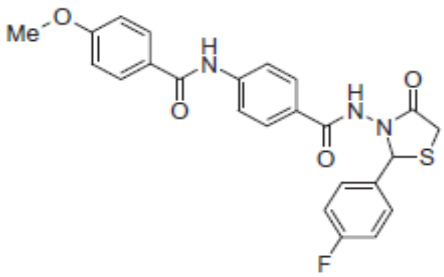


(a)

➢ Kucukguzel *et al.* reported antimycobacterial activity of substituted 4-thiazolidinones and found those only compounds (a) and (b) showed 90 and 98% inhibitions at 6.25 µg /ml, respectively.[75]

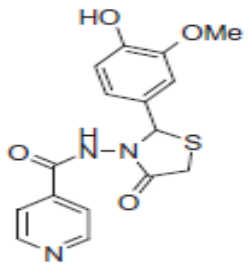


(a)

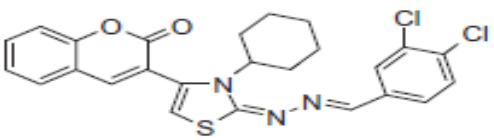


(b)

➢ Jaju and co-workers had synthesized isonicotinylhydrazidederivatives and screened their in vitro antimycobacterial activity against *M. tuberculosis* H37Rv using alamar-blue susceptibility test. They found that the antitubercular activity was considerably affected by various substituents on the aromatic ring of 4-thiazolidinone and it was proved by the fact that compounds with no substitution at the aromatic ring did not show any considerable activity. The hydroxyl and methoxyl group on aromatic ring substituted compound (a) was found to be more active (MIC = 0.31 lg/mL). Karali et al. tested 4-(3- coumarinyl)-3-cyclohexyl-4-thiazolin-2-one benzylidene hydrazone derivatives for antitubercular activity. Most of the compounds showed less than 90% inhibition and considered to be inactive and compound (b) showed maximum inhibition of 42%.[76]

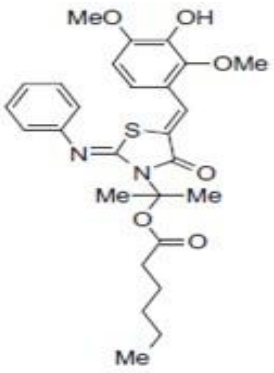


(a)

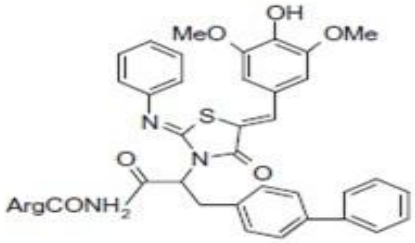


(b)

(a) Kline *et al.* have carried out the synthesis of some novel trisaryl substituted 2-imino-5-arylidenethiazolidin-4-one derivatives and evaluated for their inhibitory activity of bacterial type III secretion in *Salmonella enterica*. The results indicated that compound and (b) acted directly to disrupt a protein-protein interaction. Analogous having N-3 carbalkoxy substituent (a) was shown to have significant degree of SipA inhibition at concentrations of lM or less and the activity of compound (b) was due to the presence of combination of a cationic group and a functional group having the potential for hydrophobic interactions.[77]

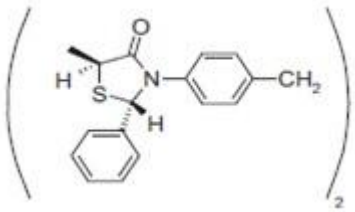


(a)

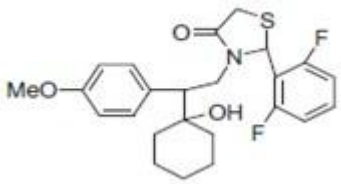


(b)

➢ Siddiqui *et al*. studied fungicidal activity of 4, 4′-bis(200-aryl-500-methyl/unsubstituted- 400-oxo-thiazolidin-300-yl) bibenzyl against *Fusarium oxysporium* and *Penicillium citrinum*. The results demonstrated that the presence of 5-methyl oxothiazolidine nucleus with the bibenzyl nucleus (a) caused complete inhibition of mycelial growth of the test fungi and enhanced the fungicidal activity of these compounds. Further substitution on phenyl ring on thiazolidinone did not improve its fungicidal activity. Presence of two fluorine atoms at 2nd and 6th positions of 2-phenylthiazolidin- 4-one (b) bearing a venlafaxine moiety represented more potent antibacterial and antifungal agents.[78]

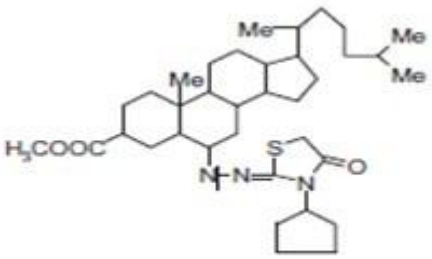


(a)

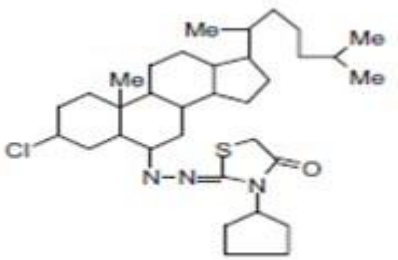


(b)

➢ Khan and Yusuf synthesized steroidal (cholesterol) derivatives of thiazolidinone and evaluated against bacteria such as *S.aureus, S. pyogenes, S. typhimurium* and *E. coli*. Compounds having acetoxy (a) and chloro (b) substituents on the 3b-position of the steroidal thiazolidinone ring showed maximum potency.[79]

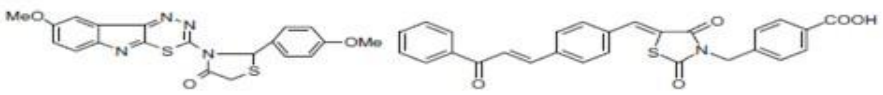


(a)



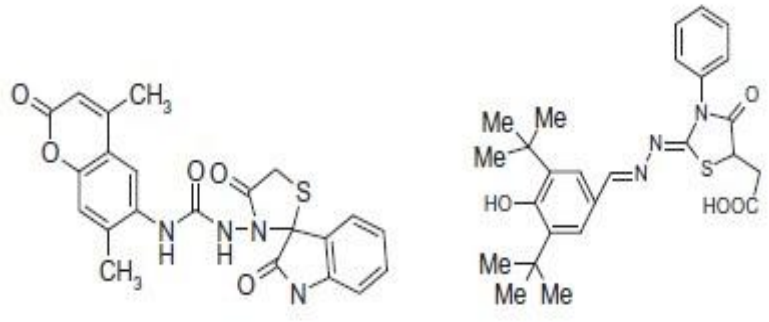
(b)

➢ Kumar *et al.* synthesized a variety of new indolylthiadiazino-azetidinones and indolylthiadiazino-thiazolidinone. Out of eight indolylthiadiazino-thiazolidinone derivatives only 5-methoxy-2,3-[2′-(2″-methoxy-phenyl-4″-oxo-1″,3″-thiazolidin-3″-yl)- 1′,3′,4′-thiadiazino]indoles (a) showed moderate antibacterial activity, but none of the compounds was found to be more active than 5-methoxy-2,3-[20-(300-chloro-200-oxo- 400-methoxy-phenyl-100-azetidinyl)-10,30,40-thiadiazino]indoles.A number of chalcone derivatives bearing the 2,4-thiazolidinedione and benzoic acid moieties has been evaluated for antimicrobial activity against six gram-positive bacteria and tested compounds did not exhibited any activity against gram-negative strains. From this series compound (b) was the best against multi drug resistant gram-positive bacterial strains (MRSA CCARM 3167, 3506; QRSACCARM 3505, 3519) with MIC values in the range of 0.5–2 l gm/ml, which showed eight-fold more potency than norfloxacin and 64-fold more activity than oxacillin. SAR study explained that free carboxyl group at para position and Cl, Br and –OCH3 groups at ortho position seem to be enhanced antibacterial activity.[80]



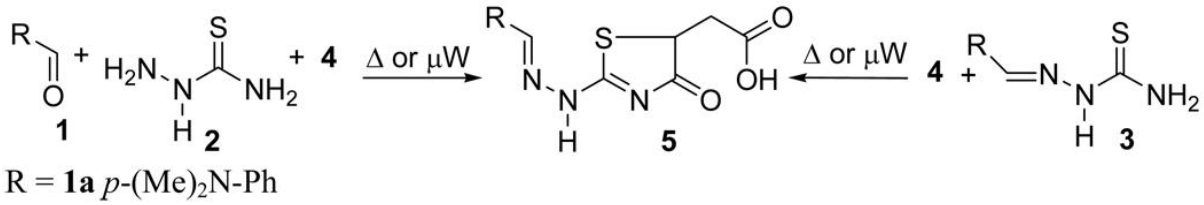
(a) **(b)**

➢ Mulwad and Mir reported antibacterial activity of N-[coumarin-6-yl] spiro- indoloazetidin-2-ones/thiazolidin-4-ones derivatives. Thiazolidinone ring instead of azetidinone did not show significant activity, coumarin ring substituted with methyl group at 4th and 7th position attached with 2-isatin-4-thiazolidinone ring (a) showed moderate antibacterial activity against *S. aureus* and *B. subtilis*. Aquino *et al*. synthesized a series of 2-[(phenylmethylene) hydrazono]-4-oxo-3-phenyl-5-thiazolidineacetic acids for their anti-T. gondii and antimicrobial activities.4-Thiazolidinone derivatives were initially tested for antimicrobial activity by the disc diffusion method and it was found that compound (b) revealed the best activities against *S.aureus*, *S. faecalis*, *B. subtilis* reduced and the percentage of infected cells and mean number of tachyzoites per cell in 2 lM concentration.[81]

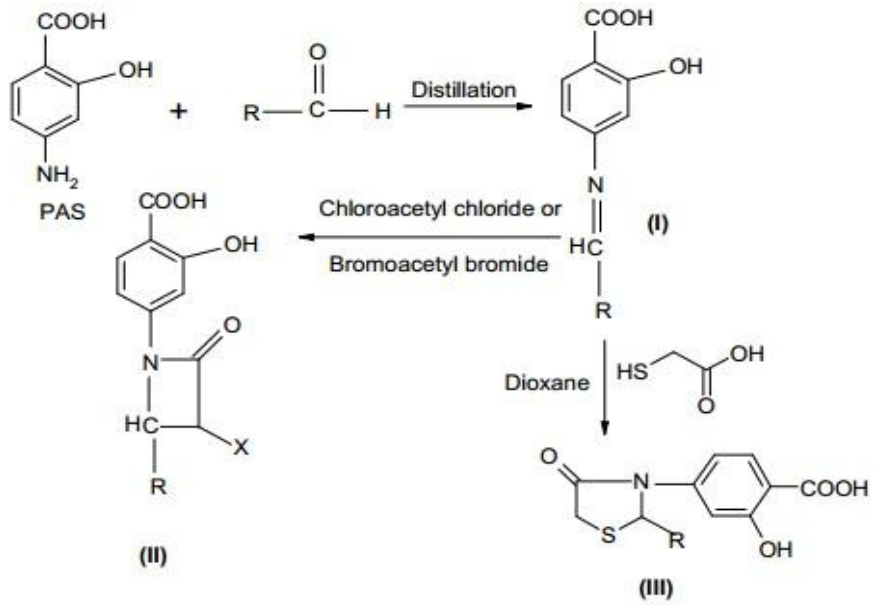


(a) **(b)**

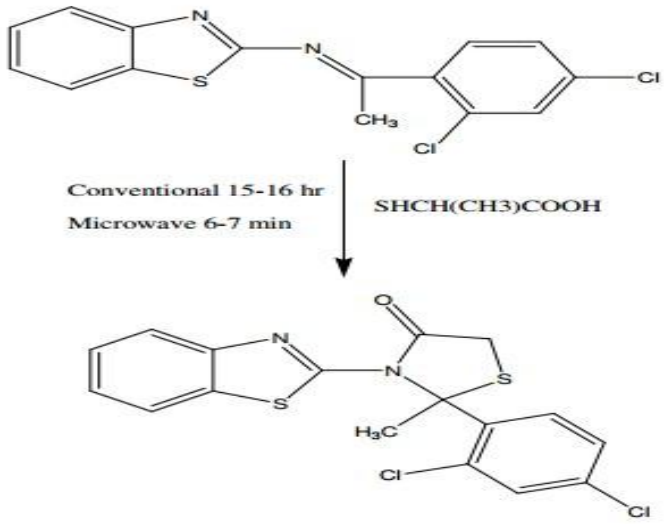
➢ Cecilia Saiz *et al.* developed a tandem method for the synthesis of 2-hydrazolyl-4- thiazolidinones from commercially available materials in a 3 component reaction. The reaction connects aldehydes, thiosemicarbazides and maleic anhydride, effectively assisted by microwave irradiation. The synthesis of a new type of compound, 2- hydrazolyl-5, 5-diphenyl-4-thiazolidinone, obtained by treatment of thiosemicarbazone with benzil in basic media is also reported. HOMO/LUMO energies, orbital coefficients and charge distribution were used to explain the proposed reaction mechanism. Microwave heating for the synthesis of thiazolidinone resulted in a significantly better yield compared to thermal conditions. Microwave irradiation also allowed for a faster conversion.[82]



➢ S.J.Wadher *et al.* synthesized Schiff base and 4-thiazolidinones of amino salicylic acid and their derivatives and tested their antimicrobial acivity. The novel molecules were synthesized and evaluated for antimicrobial studies. The synthesized compounds were screened for their *in vitro* antimicrobial activity. The structure of synthesized compounds was established on the basis of their spectral (IR, ^{1}H NMR and mass) data. The purity of the synthesized compounds was confirmed by TLC.[83]



➢ Mulay Abhinit *et al***.** reviewed the chemistry, synthesis, spectral studies and applications of 4-thiazolidinones. Work done by many researchers was explored. The literature revealed that 4- thiazolidinone has diverse biological potential, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. The anticancer and anti HIV activities are the most encouraging activities for the pharmacists. Also the research in anticonvulsant, FSH and CFTR inhibitory activity gave positive results.[84]



4-Thiazolidinone synthesis

3. AIM AND OBJECTIVE

Schiff bases of heterocyclic compounds are interesting class of organic compounds, being studied over the years and reported to possess a wide spectrum of biological activities such as antibacterial, anti tubercular, anti inflammatory, antiviral and antioxidant activity. Schiff bases of salicylaldehydes have also been reported as plant growth regulator and antimicrobial or antimycotic activity. Schiff bases also show some analytical applications. Although a number of anticoagulant, antiplatelet, antibacterial and antifungal drugs are available in the market, the search for new molecules still continues because of the need for less costly drugs and drugs with minimal side effects. Thiazolidinones have been synthesized and screened for possible antimicrobial activity. Thiazolidinones have a broad spectrum of pharmacological properties like anti HIV, antipsychotic, anticonvulsant and antitubercular activity. In view of the above mentioned facts and need to develop some novel biologically important compounds and utilizing environmental friendly methods, an attempt has been made.

- To synthesize Schiff bases from salicylaldehyde by using a microwave as depicted in Scheme I.
- To purify the new compounds by recrystallization.
- To synthesize Thiazolidinones using the above

Schiff bases.

- To purify the new compounds by recrystallization.
- To characterize the new compounds by physical and spectral data (TLC, IR, ^{1}H NMR and Mass spectral analysis).
- To screen the Schiff bases for *in-vitro* anticoagulant activity.
- To screen Schiff bases and thiazolidinones for *in-vitro* antibacterial and anthelmintic activities by standard protocol available in literature.

4. EXPERIMENTAL SECTION

4.1. Methodology

The present work is based on Schiff base reaction which involves reaction between different amines with salicylaldehyde without using a solvent to get imines. Schiff bases were screened for anticoagulant activity and using these Schiff bases, thiazolidinones were synthesized and were screened for *in vitro* antibacterial activity and anthelmintic activity.

Chemicals and Reagents

The chemicals and reagents (Table 1) used in the present project were of AR and LR grade, procured from S.D-Fine Chem.Ltd.

Table no.1 List of chemicals and reagents.

Salicylaldehyde	DL Isoleucine
3 aminobenzoic acid	acetone
Ethanol	methanol
Tetrahydrofuran	Silica gel G
Dimethylformamide	Charcoal
Thioglycolic acid	n-hexane

Analytical Techniques

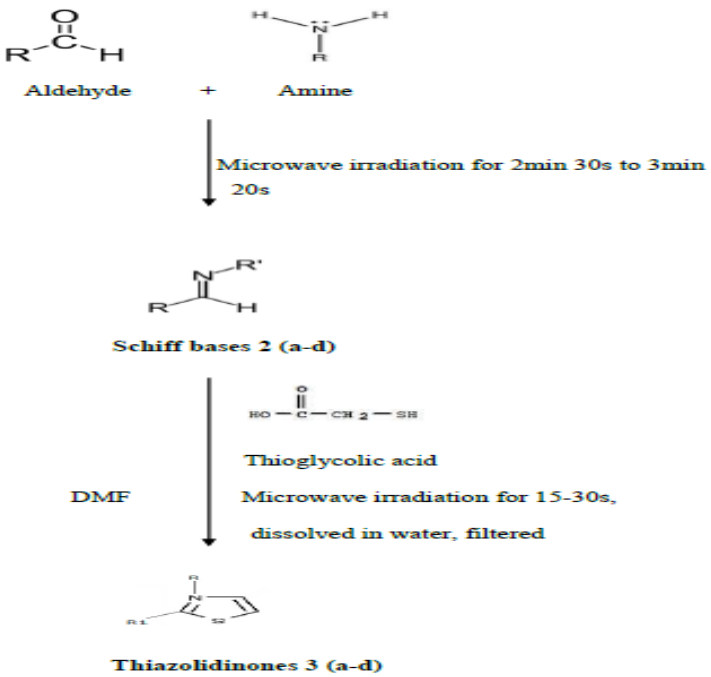
1. **Physical data:** Melting points of the synthesized compounds were recorded using melting point apparatus with open capillary tubes.
2. **Thin Layer Chromatography:** Purity of the compounds was determined by thin layer chromatography using silica gel G as stationary phase and various combinations of methanol: water: tetrahydrofuran in the ratio 2:2:1.
3. **Instrumentation:** The techniques employed for the characterization of the synthesized compounds were IR, ^{1} H NMR and Mass spectral analysis.

a. **IR spectra**: The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of 400- 4000cm^{-1} using KBr pellets and values are reported in cm^{-1} and the spectra were interpreted.

b. **^{1} H- NMR:** ^{1} H–NMR spectra were recorded on DPX-200 MHz NMR spectrometer using DMSO-d6 and chemical shifts (δ) are reported in parts per million down field from internal reference tetramethylsilane (TMS) and the spectra were interpreted.

c. **Mass spectra:** Mass spectra were recorded on Mass spectrophotometer (model Shimadzu) by LC-MS and the spectra were interpreted.

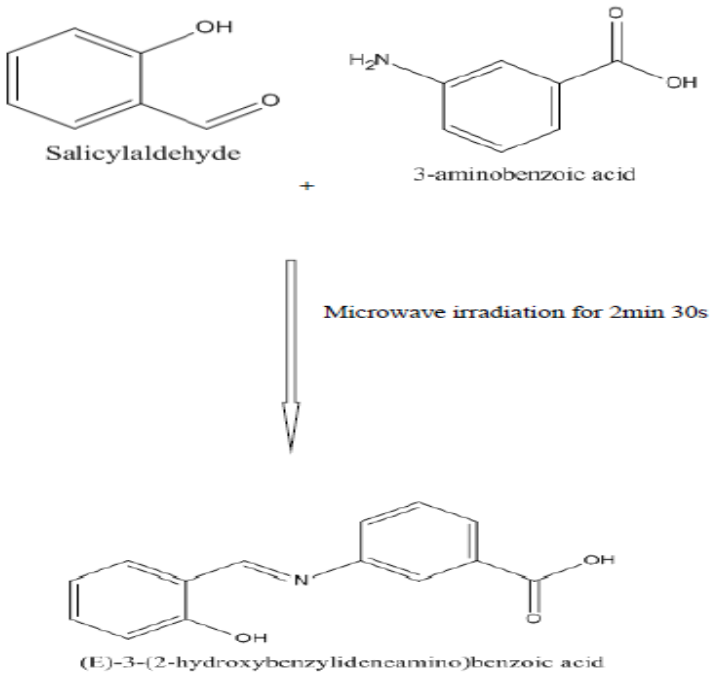
SCHEME I



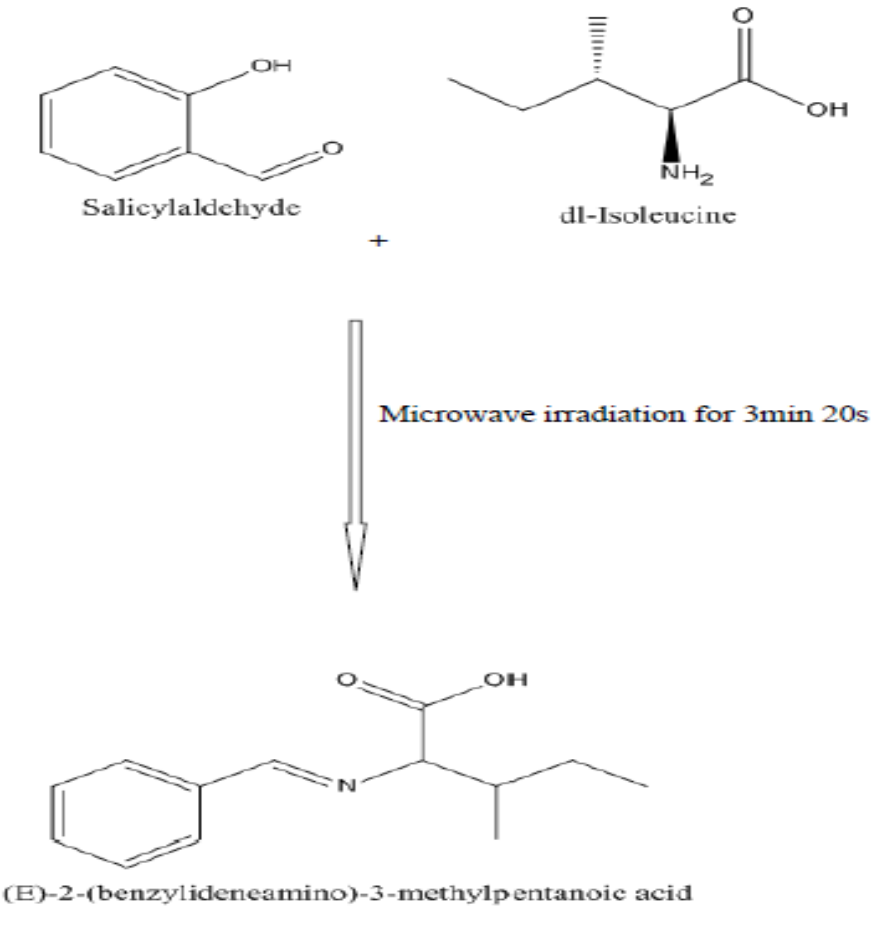
Aldehyde: R= C6 H5 OH (phenol)/ C6 H6 (benzene)
Amine: R= C6 H5 OH (phenol)/ C5 H5 N (pyridine)

Schiff base: R= C_6H_5OH (phenol)/ C_6H_6 (benzene), R^1= C_6H_5OH (phenol)/C_5H_5N (pyridine)
Thiazolidinones: R^1= C_6H_5OH (phenol)/ C_6H_6 (benzene), R= C_6H_5OH (phenol)/ C_5H_5N (pyridine)

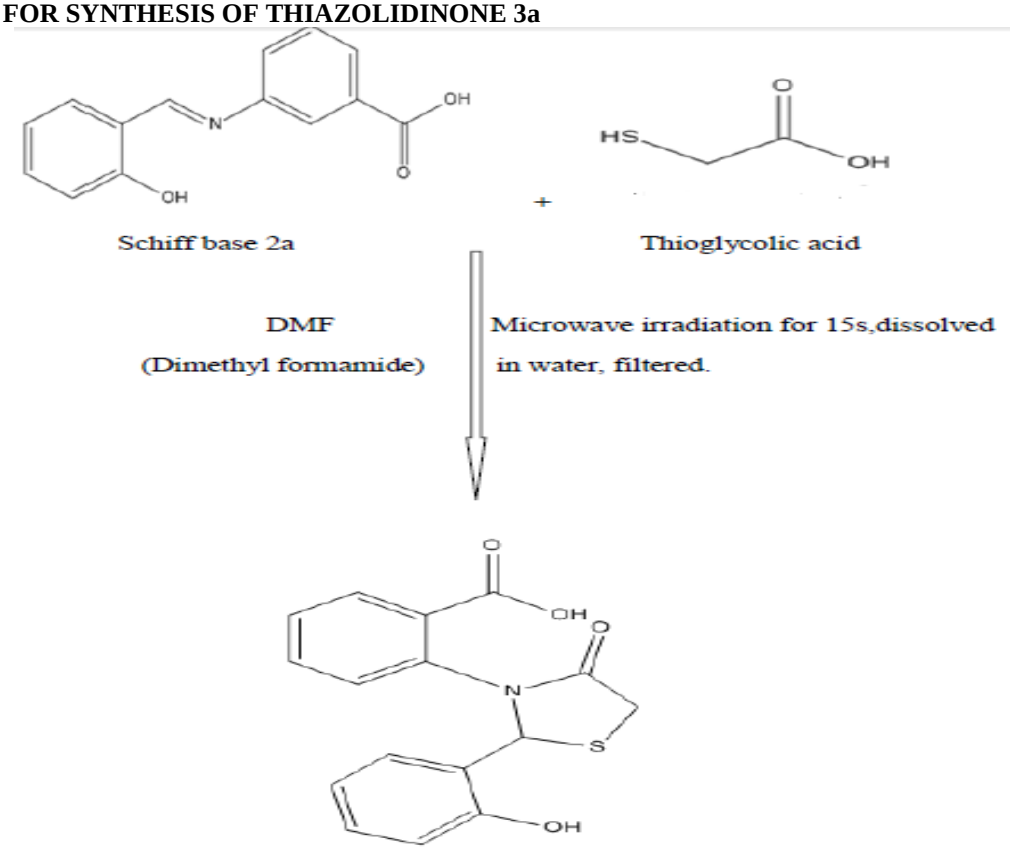
SCHEME FOR INDIVIDUAL COMPOUNDS SCHEME FOR SYNTHESIS OF SCHIFF BASE 2a



SCHEME FOR SYNTHESIS OF SCHIFF BASE 2b

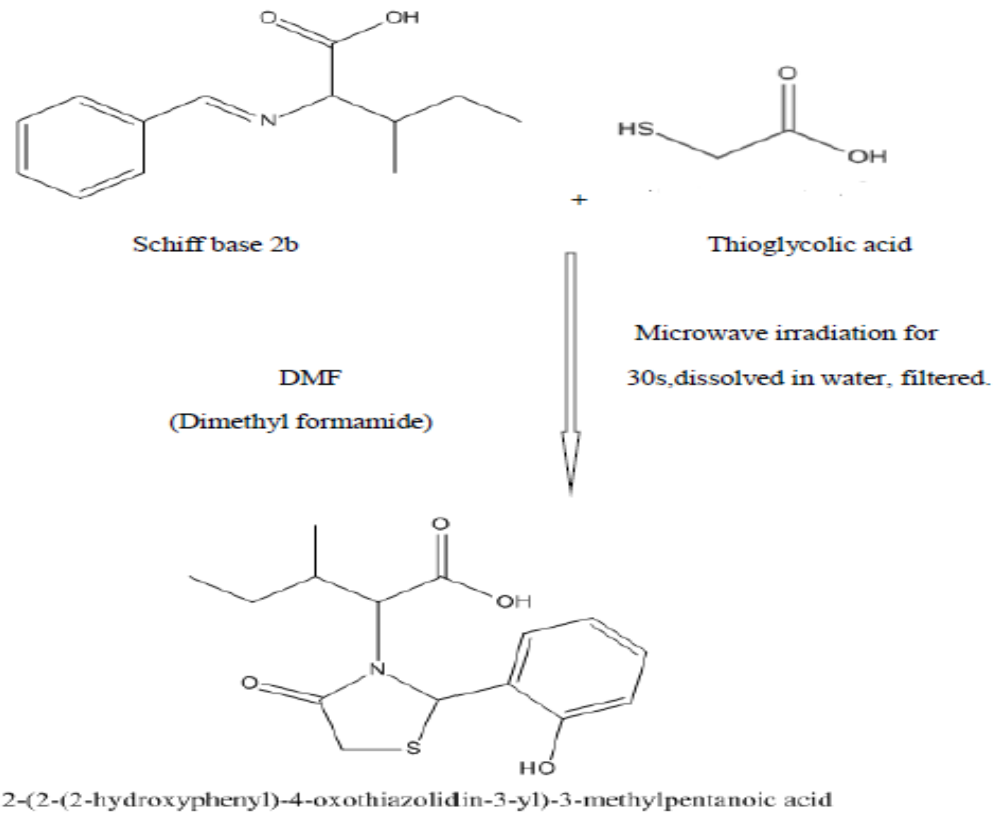


SCHEME FOR SYNTHESIS OF THIAZOLIDINONE 3a



2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzoic acid

SCHEME FOR SYNTHESIS OF THIAZOLIDINONE 3b



2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid

4.2. General procedures: Synthesis of Schiff base 2a

1.06 ml of salicylaldehyde and 1.37g of 3-aminobenzoic acid were taken in a clean and dry conical flask and subjected to microwave irradiation for 2min 30s giving 10s pulses to synthesize 0.01 mole of the compound. The product was then cooled and recrystallized using ethanol and to get pure crystals of the product. Melting point was determined using melting point apparatus with open capillary tubes. TLC was performed to determine the Rf value.

Synthesis of Schiff base 2b

1.06 ml of salicylaldehyde and 1.31g of DL Isoleucine were taken in a clean and dry conical flask and subjected to microwave irradiation for 3min 20s giving 10s pulses to synthesize 0.01 mole of the compound. The product was then cooled and recrystallized using tetrahydrofuran to get pure crystals of the product. Melting point was determined using melting point apparatus with open capillary tubes. TLC was performed to determine the Rf value.

Table no. 2: Physical data of Schiff bases.

Code	Mol.F	Mol.wt (g.mol-1)	M.P(oC)	%Yield
2a	C14H11NO3	241	163	86
2b	C13H17NO	219	185-190	70

Synthesis of Thiazolidinone 3a.

The above synthesized Schiff base 2a (0.01 mole) was taken in a clean and dry conical flask. To this 0.7 ml of dimethylformamide (0.01 mole) was added. 0.7 ml of thioglycolic acid (0.01 mole) was added slowly to the above contents and subjected to microwave irradiation for 15 s. To this solution ice cold water was added immediately when the solution was still hot. The product was filtered, dried and recrystallized with ethanol to get pure crystals of the product. Melting point was determined using melting point apparatus with open capillary tubes. TLC was performed to determine the Rf value.

Synthesis of Thiazolidinone 3b.

The above synthesized Schiff base 2b (0.01 mole) was taken in a clean and dry conical flask. To this 0.7 ml of dimethylformamide (0.01 mole) was added. 0.7 ml of thioglycolic acid (0.01 mole) was added slowly to the above contents and subjected to microwave irradiation for 30s. To this solution ice cold water was added immediately when the solution was still hot. The product was filtered, dried and recrystallized with ethanol to get pure crystals of the product. Melting point was determined using melting point apparatus with open capillary tubes. TLC was performed to determine the Rf value.

Table no. 3 Physical data of Thiazolidinones.

Code	Mol.F	Mol.wt (g.mol-1)	M.P. (oC)	% Yield
3a	C16H13NSO4	315	215	84
3b	C15H19NSO4	309	247	75

4.3. Biological Activity

1. Antibacterial activity

Even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents. Such a fact is cause for concern, because of the number of patients in hospitals who have suppressed immunity, and due to new bacterial strains, which are multi- resistant. Consequently, new infections can occur in hospitals resulting in high mortality.[85]

The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future is still uncertain. Therefore, actions must be taken to reduce this problem, for example, to control the use of antibiotic, develop research to better understand the genetic mechanisms of resistance, and to continue studies to develop new drugs, either synthetic or natural. The ultimate goal is to offer appropriate and efficient antimicrobial drugs to the patient.

Antibacterials are drugs used to treat infections caused due to bacteria, by either inhibiting their growth or by killing them. In view of the above mentioned problems, an attempt was made to synthesize new Schiff bases and thiazolidinones and tested their antibacterial activity.

Procedure

The synthesized Schiff bases and thiazolidinones were screened for antibacterial activity using two cultures, *E.coli* for gram negative species and *Staphylococcus. aureus* for gram positive. The compounds were tested by agar well diffusion assay. The cultures were prepared 24hrs prior to testing the antibacterial activity. Nutrient agar medium was prepared and sterilized in an autoclave for 45 minutes. This medium was inoculated with the above cultures and then poured into different petriplates under a laminar airflow chamber in an aseptic room. The medium was allowed to solidify. Using aseptic borers, small holes were made at equal distances in the petri plates. The synthesized compounds were dissolved in ethanol to make 10, 20 and 30 µg/ml concentration solutions. The standard drug solution was also prepared in concentrations of 10, 20 and 30 µg/ml. Using aseptic borers, holes were made in the media at equal distances. These holes were filled with the above solutions using an automatic pipette. Ethanol was used as control.

The petriplates were placed in a refrigerator for a short period of time and then transferred to an incubator where they were incubated in an inverted position at 37^0 C for

24hrs. These petriplates were then observed for zone of inhibition and the distance was measured in mm. The zone of inhibition for different test compound and standard drug are tabulated in the table no 8.

2. Anthelmintic Activity

Helminthes infections are among the most widespread infections in humans, distressing a huge population of the world. Although the majority of infections due to helminthes are generally restricted to tropical regions and cause enormous hazard to health and contribute to the prevalence of undernourishment, anaemia, eosinophilia and pneumonia. Parasitic diseases cause ruthless morbidity affecting principally population in endemic areas. The gastro-intestinal helminthes becomes resistant to currently available anthelmintic drugs therefore there is a foremost problem in treatment of helminthes diseases.[86-87]

Anthelmintics are drugs that are used to treat infections due to parasitic worms. This includes both flat worms,e.g. flukes, tapeworms and roundworms, i.e. nematodes. They are of huge importance for human tropical medicine and for veterinary medicine. The World Health Organization estimates that a staggering 2 million people harbor parasitic worm infections.[88-89]

Despite the prevalence of parasitic worms, anthelmintic drug discovery is the poor relation of the pharmaceutical industry. The simple reason is that the nations which suffer most from these tropical diseases have little money to invest in drug discovery and therapy. It comes as no surprise therefore that the drugs available for human treatment were first developed as veterinary medicines.

Procedure

The synthesized Schiff bases and thiazolidinones were screened for anthelmintic activity using *Pheretima Posthuma* (earthworms). 11 earthworms of nearly equal size were placed in control, standard and test compound's solutions at room temperature. Normal saline was used as control. The standard drug used was albendazole. The standard drug and test compound were dissolved in minimum quantity of ethanol and adjusted the volume upto 10ml with normal saline solution to get the concentrations 0.1%, 0.2% and 0.5%w/v.

The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug.

The time taken by earthworms to become motionless was noted as paralysis time. To ascertain the death of motionless earthworms, they were frequently applied with external stimuli, which stimulates and induces movement in earthworms, if alive. The mean lethal time and paralysis time of the earthworms for different test compounds and standard drug are tabulated in the table no 9.

3. Anticoagulant activity

Anticoagulants are medicines that prevent the blood from clotting as quickly or as effectively as normal. Anticoagulants are used to treat and prevent blood clots that may occur in blood vessels. Blood clots can block an artery or a vein (blood vessels). A blocked artery stops blood and oxygen from getting to a part of our body. The tissue supplied by a blocked artery becomes damaged, or dies, and this results in serious problems such as a stroke or heart attack. A blood clot in a large vein, such as a deep vein thrombosis (a clot in the leg vein), can lead to serious problems such as a pulmonary embolism (a clot that travels from the leg vein to the lungs).[90]

A number of anticoagulants are available including: warfarin, acenocoumarol, phenindione, dabigatran, aspirin and rivaroxaban. However, due to its side effects like bleeding and other disadvantages like its chemical inhomogeneity and the variability of its physiological activities, an important field of research are alternatives to genuine anticoagulants.

Despite the prevalence of these anticoagulants, they suffer from common side effects like haemorrhages, headaches, backpain, nose bleeds *etc*.

Therefore the aim of the present study was to develop newer Schiff bases with anticoagulant activity and to minimize the side effects and the cost associated with the presently available anticoagulants.

Procedure

The synthesized Schiff bases (2a and 2b) were screened for anticoagulant activity by prothrombin time test. The prothrombin time test (also known as the pro test or PT test) is a useful screening procedure for the extrinsic coagulation mechanism including the common pathway. It detects deficiencies in factor II, V, VII, and X. The prothrombin time test is frequently used to follow oral anticoagulant therapy that inhibit factors II, VII, IX and X. The normal prothrombin time ranges between 11-15 seconds.

Collection of blood sample

The blood sample was obtained from an individual having normal prothrombin time, not suffering from any cardiovascular diseases (hypertension, congestive heart failure, coagulation disorders such as, Hemophilia A or B) or diabetes, not recently using nonsteroidal anti inflammatory drugs, not obese or smokers and free from dyslipidemic disorders and placed separately in container containing tri-sodium citrate to prevent the clotting process. Centrifugation (15 minutes at rate 3000 rpm) was carried out to separate the blood cells from plasma in order to obtain pure platelet plasma (ppp) for prothrombin time test. The obtained plasma sample was poured separately in plane containers using automatic pipette and stored at room temperature.[91-92]

Collection of blood and Plasma re-calcification

0.2 ml plasma, 0.1 ml of Schiff base of different concentrations and CaCl2 [(25 *mili* M) thereby reversing the effect of citrate which enables the blood to clot again] were added together in a clean fusion tube and incubated at 37^0 C in water bath. For control experiment Schiff base solution was replaced by same volume of 0.9% saline water. The clotting time of Schiff bases (2a and 2b) were recorded with stopwatch by tilting the test tubes every 5 seconds. This time is called the prothrombin time.[93-94] The Schiff bases (2a and 2b) were dissolved in methanol to make 10, 20, 40 and 80 µg/ml concentration solutions.

Time of coagulation of Schiff bases 2a and 2b at different concentrations are tabulated in table no 10 and table no 11 respectively.

5. RESULTS AND DISCUSSION

Chemistry

As a result of microwave assisted synthesis, it was observed that the reaction was completed in a short time with higher yields compared to the conventional method. Schiff bases and thiazolidinones show a wide spectrum of pharmacological applications. The synthesis of all compounds was carried out as depicted in Scheme – I. Novel Schiff bases were obtained by microwave irradiation of different aryl amines with different aldehydes. These Schiff bases were then treated with thioglycolic acid in the presence of DMF (dimethyl formamide) in a microwave to give thiazolidinones. The resulting compounds were purified by recrystallization using ethanol and methanol.

The synthesized compounds were characterized by both physical and spectral data like ^{1}H-NMR, Mass spectra and FT-IR. Schiff bases were evaluated for anticoagulant activity. Newly synthesized compounds were evaluated for antibacterial and anthelmintic activities.

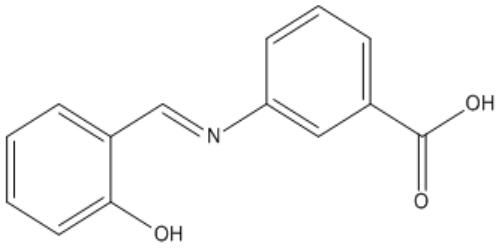
The synthesized novel Schiff bases were characterized from the spectral analysis, it is revealed that, IR shows presence of C=N peak at around 1600cm^{-1} for all the Schiff bases.IR also shows presence of –OH peak at around 3300cm^{-1} for Schiff bases containing –OH group. ^{1}H-NMR shows chemical shift (δ) of protons in –COOH at around 13ppm, Ar-OH at around 9 ppm and Ar-H at around 6-8 ppm.

The synthesized novel thiazolidinones bases were characterized from the spectral analysis, it is revealed that, IR shows presence of C=O peak at around 1700cm^{-1} and presence of N-CH-S peak at around 730cm^{-1} for all the thiazolidinones. ^{1}H-NMR shows chemical shift (δ) of protons in –COOH at around 13 ppm, Ar-OH at around 9 ppm and 6.7-7.9 ppm.

All the compounds showed characteristic base peak for M+1 peak and the mass spectra of all the synthesized compounds obeying the nitrogen rule.

Physical characterization of synthesized compounds:

Compound 2a

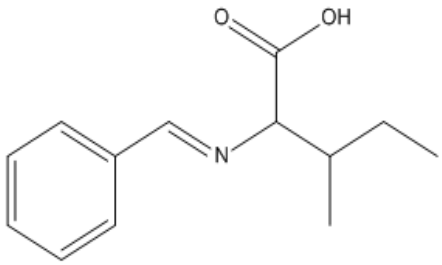


(E)-3-(2-hydroxybenzylideneamino)benzoic acid

Table no: 4 Physical characterization data of compound 2a.

IUPAC Name	(E)-3-(2-hydroxybenzylideneamino)benzoic acid
Mol.F	C14H11NO3
Mol.wt	241 g mol-1
M.P	163 oC
Solubility	Methanol and ethanol
TLC solvent	Methanol : Water :Tetrahydrofuran-2:2:1
Rf value	0.65
% Yield	86%

Compound 2b.

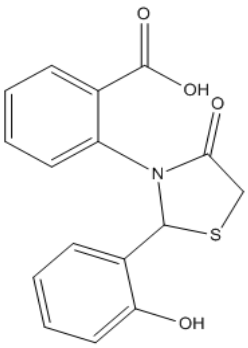


(E)-2-(benzylideneamino)-3-methylpentanoic acid

Table no: 5 Physical characterization of compound 2b.

IUPAC Name	(E)-2-(benzylideneamino)-3-methylpentanoic acid
Mol.F	C13H17NO2
Mol.wt	219 g mol-1
M.P	185-190 oC
Solubility	Tetrahydrofuran
TLC solvent	Methanol : Water :Tetrahydrofuran-2:2:1
Rf value	0.56
% Yield	70%

Compound 3a

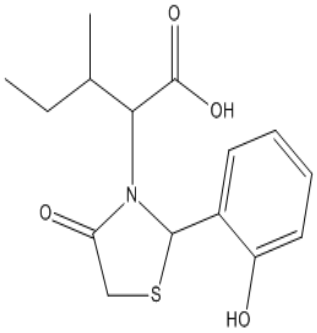


2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzoic acid

Table no: 6 Physical characterization data of compound 3a.

IUPAC Name	2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid
Mol.F	C16H13NSO4
Mol.wt	315 g mol-1
M.P.	215 oC
Solubility	Ethanol
TLC solvent	Methanol : Water : Tetrahydrofuran-2:2:1
Rf value	0.43
% Yield	84%

Compound 3b

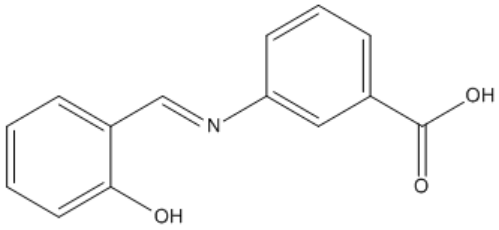


2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid

Table no: 7 Physical characterization data of compound 3b.

IUPAC Name	2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid
Mol.F	C15H19NSO4
Mol.wt	309 g mol-1
M.P	247 o C
Solubility	Ethanol
TLC solvent	Methanol : Water : Tetrahydrofuran-2:2:1
Rf value	0.34
% Yield	75%

Chemical characterization data of synthesized compounds: Compound 2a.



(E)-3-(2-hydroxybenzylideneamino)benzoic acid

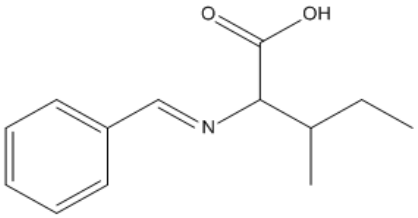
IR data

Functional group	Frequency in cm-1
C=N stretching	1603.88
CH=N stretching	1501.65
OH stretching	3089.13
COOH stretching	2995.58
Aromatic C-H stretching	2570.26

H^{1}NMR data

Protons	δ in ppm
COOH	s(12.8)
Ar-H	m(7.4-7.9)
Ar-OH	s(9.0)
CH	m(6.9-7.0)

Compound 2b



(E)-2-(benzylideneamino)-3-methylpentanoic acid

IR data

Functional group	Frequency in cm-1
C=N stretching	1594.23
CH=N stretching	1499.72
C-H stretching	3119.03
COOH stretching	2581.83
Aromatic C-H stretching	2850.91

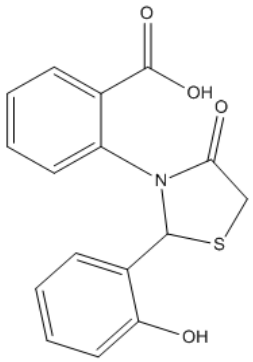
H^{1}NMR data.

Protons	δ in ppm
COOH	s(13.7)
Ar-H	m(6.6-8.6)
CH3	s(0.9)
CH2	m(1.2-1.3)
CH	s(2.5)
CH	s(3.9)

MASS data

Molecular weight	Fragmentation
219	248(35)
	219(50)
	203(30)
	175(40)

Compound 3a.



2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzoic acid

IR data

Functional group	Frequency in cm-1
C=O stretching	1725.46
N-CH-S stretching	741.00
OH stretching	3311.92
Aromatic C-H stretching	2982.08
COOH stretching	2493.10

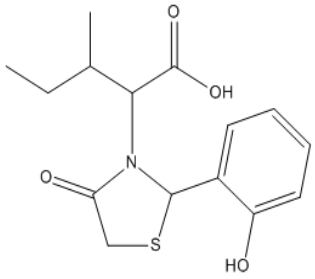
H[1] NMR data

Protons	δ in ppm
COOH	s(12.8)
Ar-OH	s(9.0)
Ar-H	m(7.4-7.9)
CH	m(6.97-7.01)
CH2	s(3.6)

MASS data

Molecular weight	Fragmentation
315.34	315.34(60)
	279.5(45)
	136.5(25)
	95.6(40)

Compound 3b.



2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid

H[1]NMR data

Protons	δ in ppm
Ar-OH	s(5.5)
Ar-H	m(6.7-7.7)
CH3	m(0.88-0.9)
CH3	m(1.26-1.29)
CH2	s(3.9)
CH	s(2.5)
CH	s(5.5)
CH	s(4.2)

MASS data

Molecular weight	Fragmentation
309.38	309.38(80)
	239.5(50)
	201.5(50)
	180.5(40)

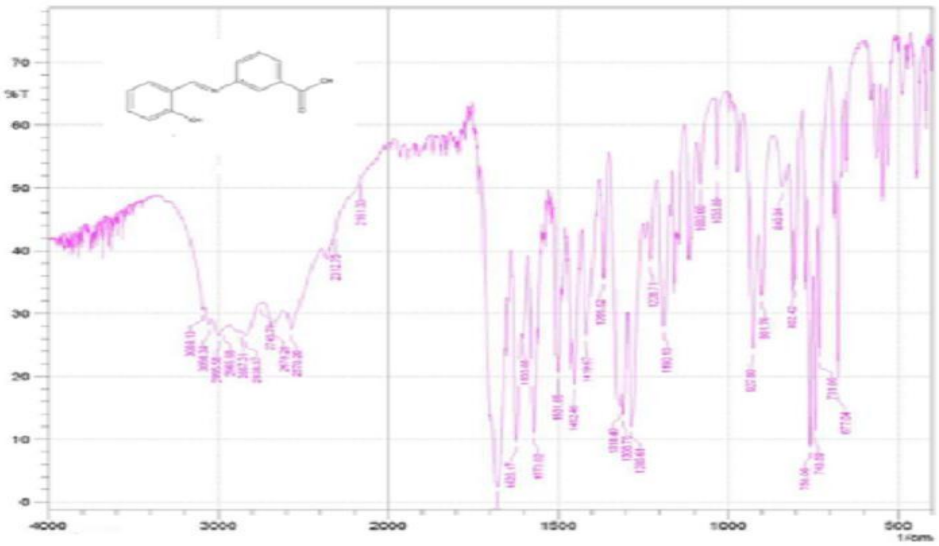


Figure 1: FT-IR spectra of (E)-3-(2-hydroxybenzylideneamino)benzoic acid (Schiff base 2a)

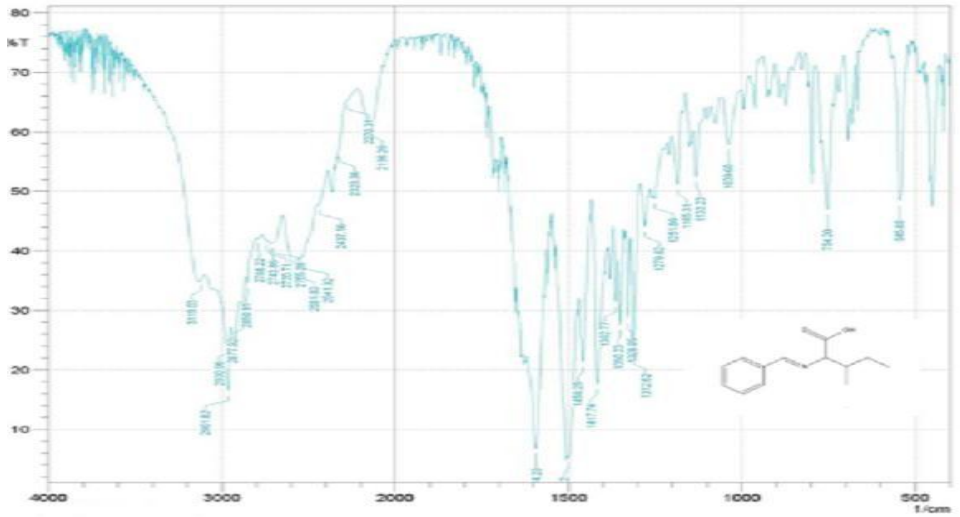


Figure 2: FT-IR spectra of 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzoic acid (Schiff base 2b)

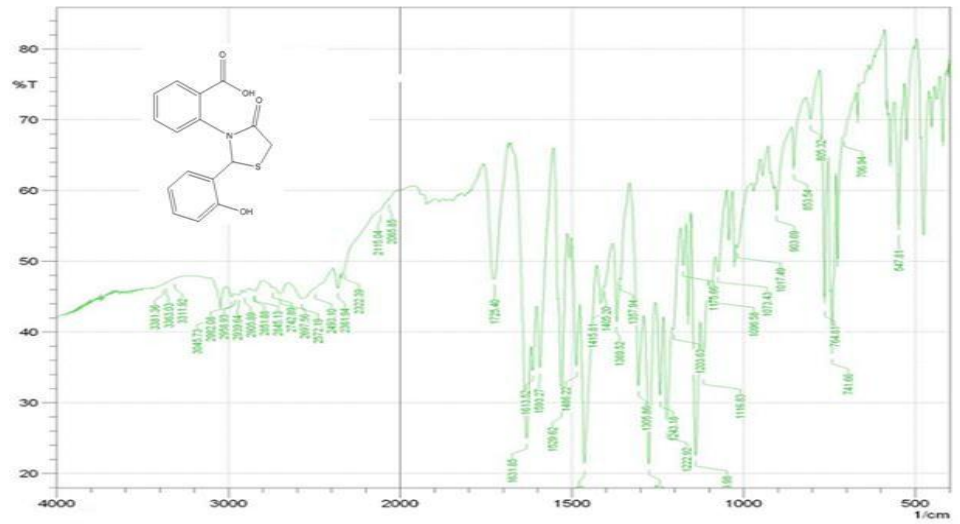


Figure 3: FT-IR spectra of 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzoic acid. (Thiazolidinone 3a)

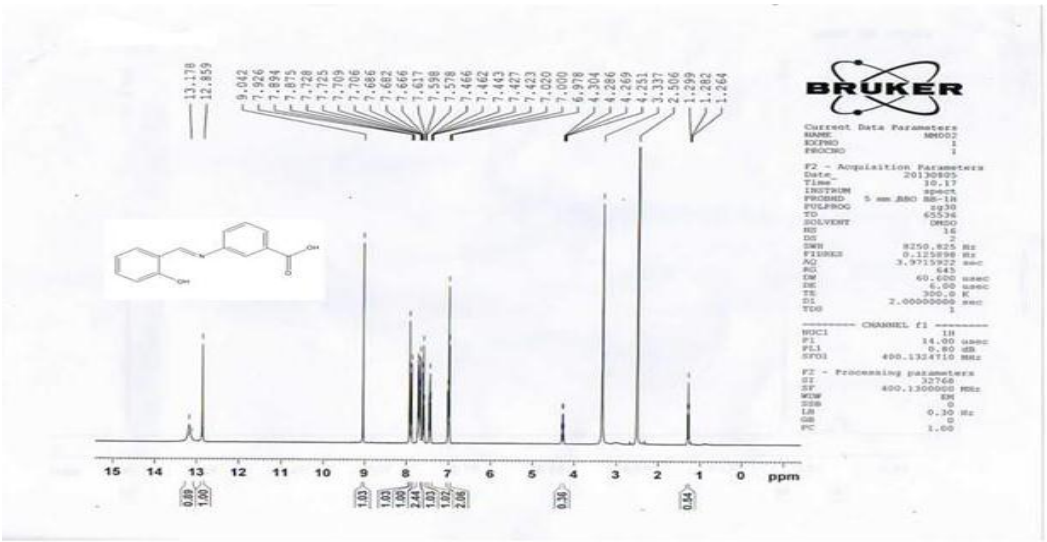


Figure 4: H^{1}NMR spectra of (E)-3-(2-hydroxybenzylideneamino) benzoic acid (Schiff base 2a)

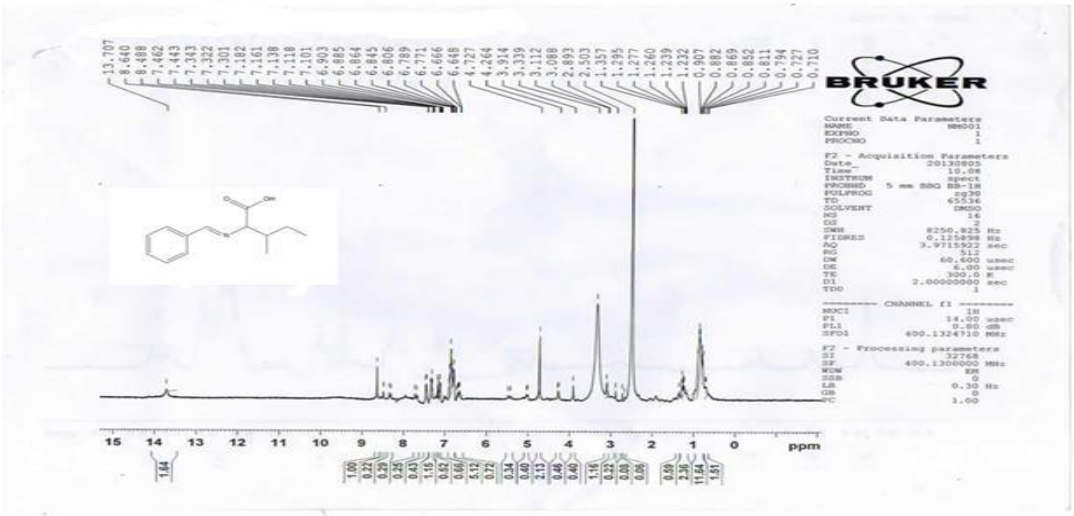


Figure 5: H[1]NMR spectra of (E)-2-(benzylideneamino)-3-methylpentanoic acid (Schiff base 2b).

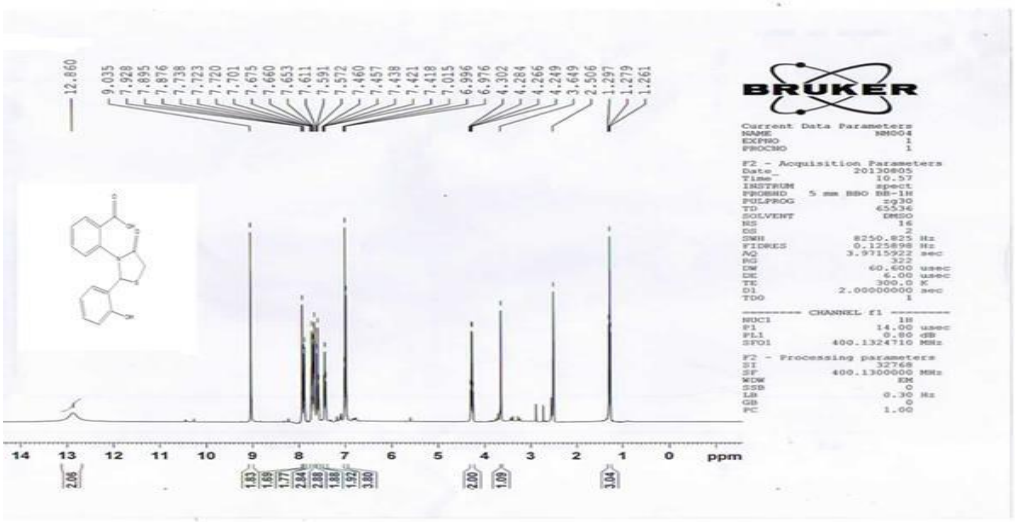


Figure 6: H[1]NMR spectra of 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid (Thiazolidinone 3a)

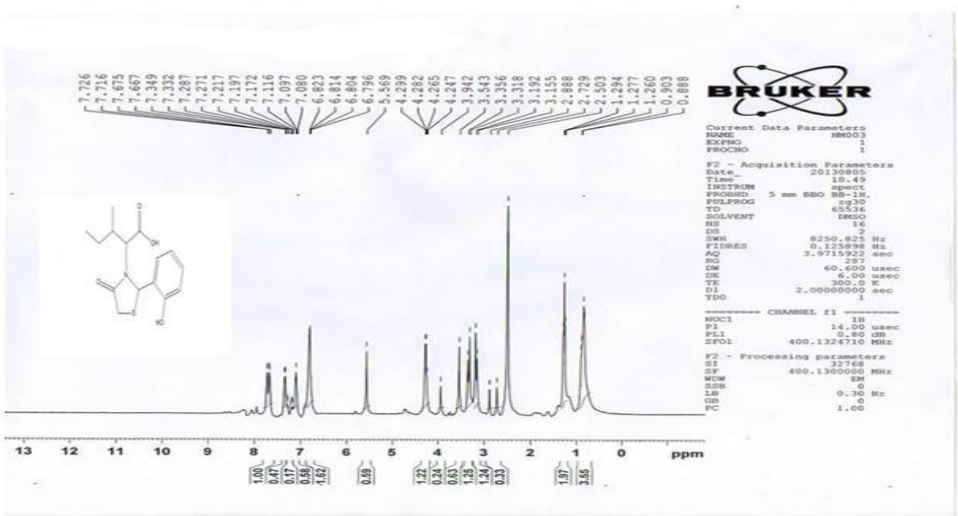


Figure 7: H[1] NMR spectra of 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3- methylpentanoic acid (Thiazolidinone 3b)

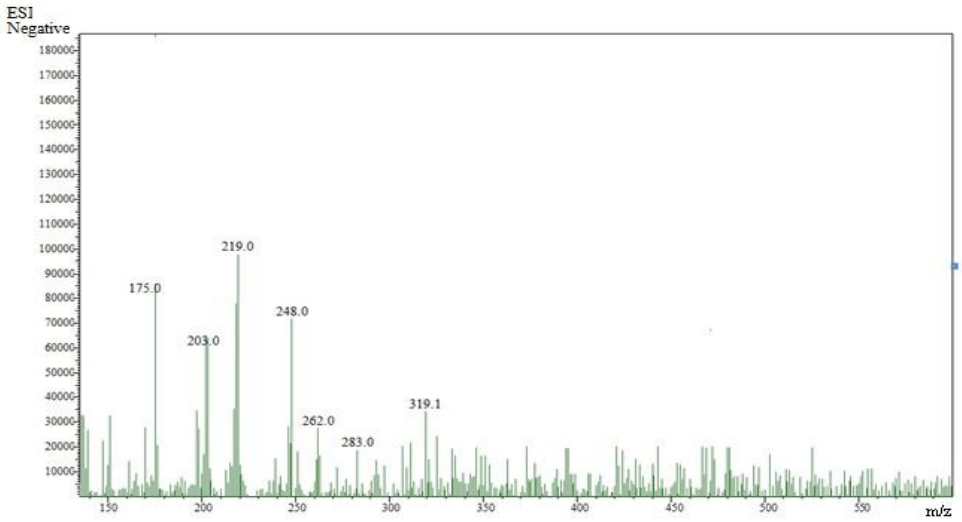


Figure 8: Mass spectra of (E)-2-(benzylideneamino)-3-methylpentanoic acid (Schiff base 2b)

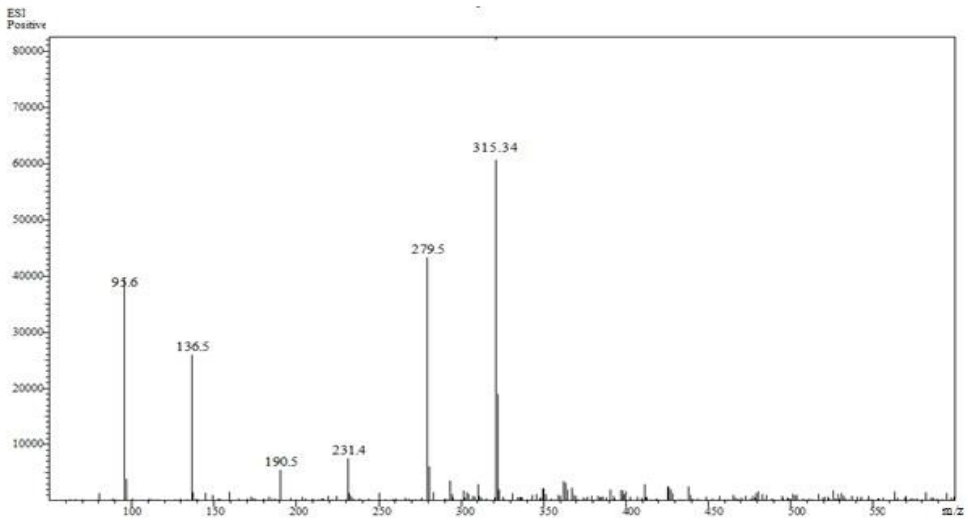


Figure 9: Mass spectra of 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid: (Thiazolidinone 3a)

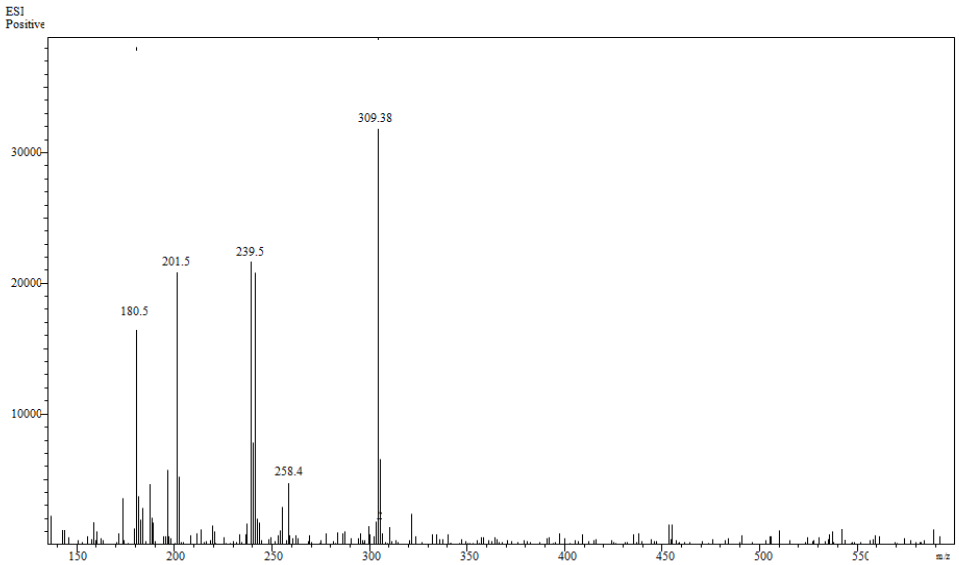


Figure 10: Mass spectra of 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid (Thiazolidinone 3b)

Antibacterial activity

The synthesized compounds (2a-3b) were evaluated for antibacterial activity on E.*coli* and S.*aureus* for gram negative and gram positive species respectively. All compounds showed antibacterial activity. Among the compounds tested, all the compounds showed significant zone of inhibition compared to standard drug chloramphenicol at (10, 20 and 30 µg/ml) concentration of compounds.

Table no: 8 Antibacterial activities of novel Schiff bases and Thiazolidinones.

S.No	COMPOUND	ZONE OF INHIBITION Distance in mm					
		E.coli			S.aureus		
		10µg/ml	20µg/ml	30µg/ml	10µg/ml	20µg/ml	30µg/ml
1	Ethanol (control)	2	3	5	1	2	4
2	Chloramphenicol (std)	20	23	27	19	25	27
3	2a	17	18	20	12	17	20
4	2b	16	18	19	13	14	17
5	3a	17	19	22	14	18	20
6	3b	12	15	16	12	14	16

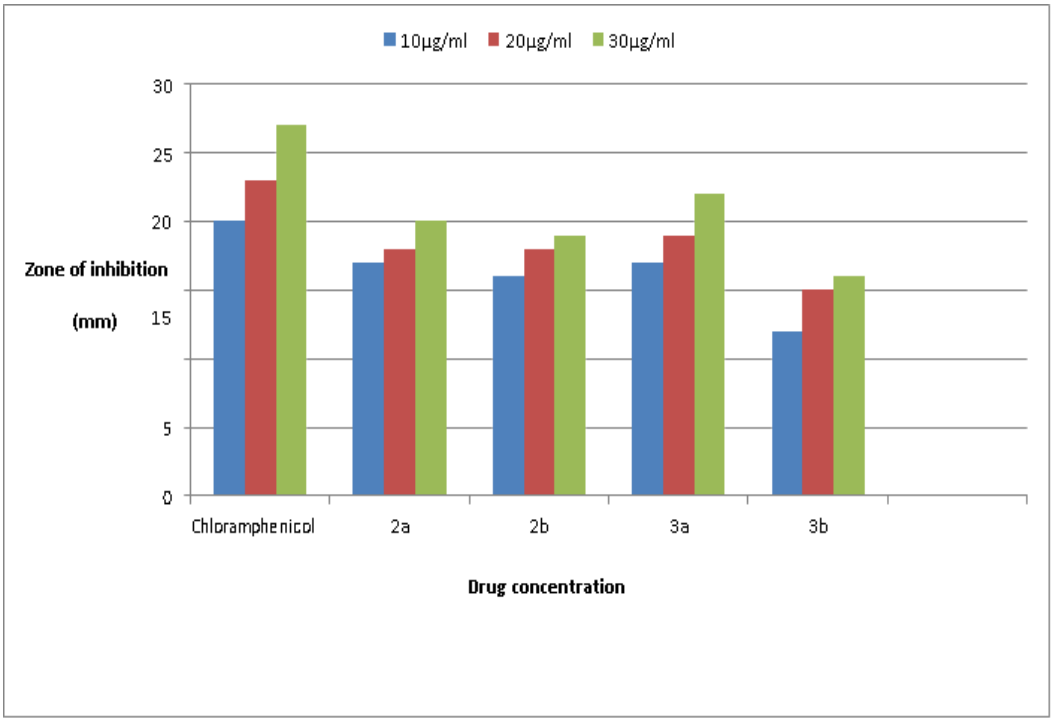


Figure 11: Antibacterial activity *E.coli* (gram negative)

Graphical representation of antibacterial activity against gram negative bacteria *E.coli*. of compounds (2a, 2b, 3a, 3d).
Where **2a:-** (E)-3-(2-hydroxybenzylideneamino) benzoic acid.
2b:- (E)-2-(benzylideneamino)-3-methylpentanoic acid.
3a:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid.
3b:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid.

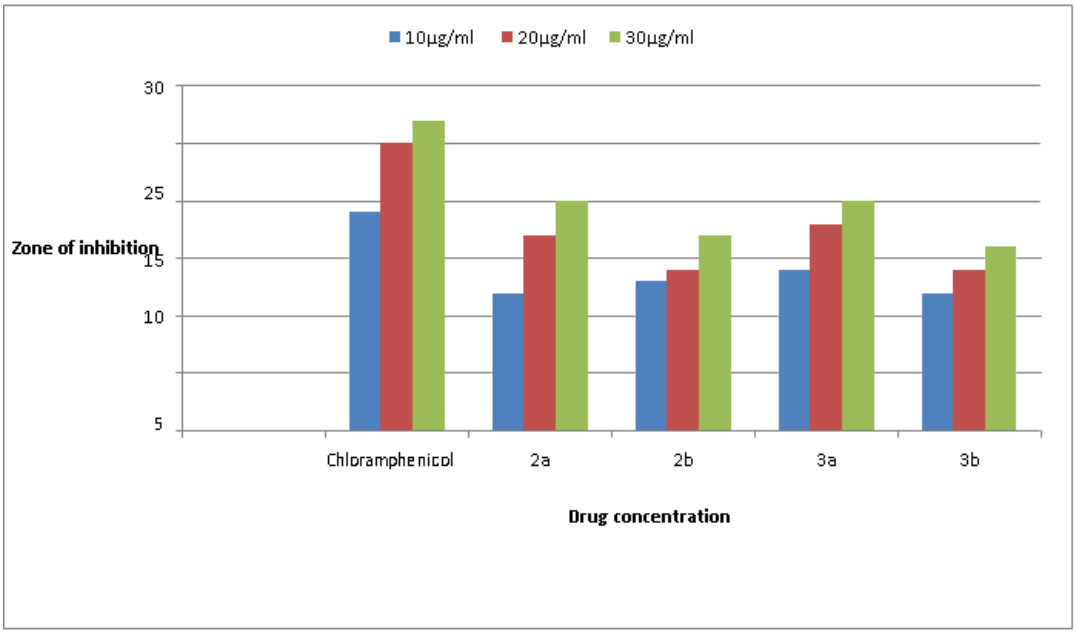


Figure 12: Antibacterial activity *S.aureus* (gram positive).

Graphical representation of antibacterial activity against gram positive bacteria *S.aureus* of compounds (2a, 2b, 3a, 3b).
Where **2a:-** (E)-3-(2-hydroxybenzylideneamino) benzoic acid
2b:- (E)-2-(benzylideneamino)-3-methylpentanoic acid
3a:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid
3b:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid.

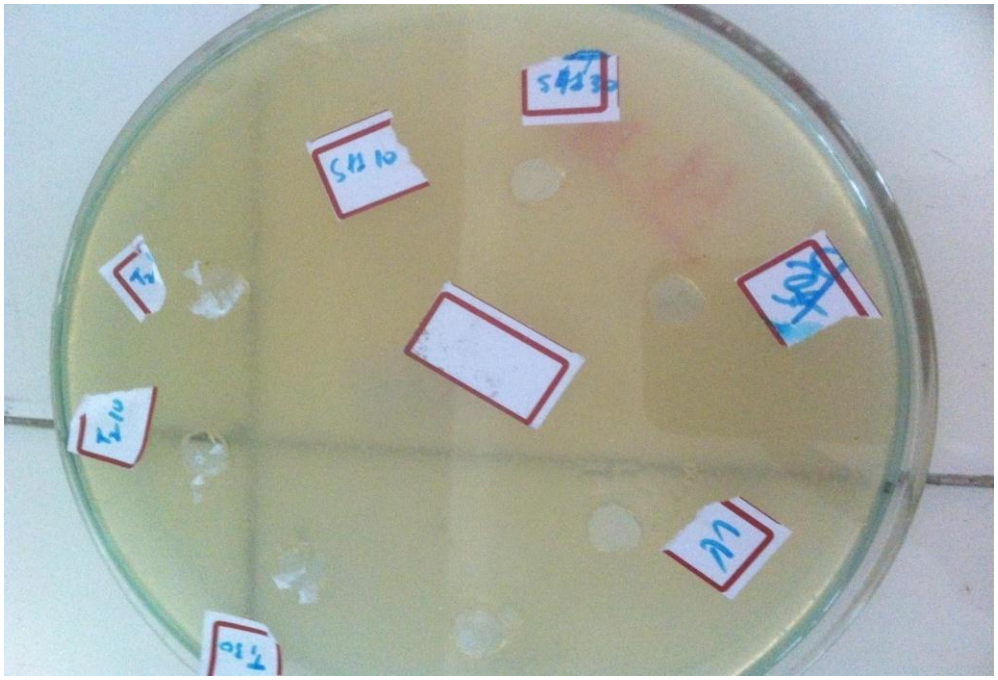


Figure 13: Photograph of various novel Schiff bases and thiazolidinones-Antibacterial activity against gram negative bacteria *(E.coli*).

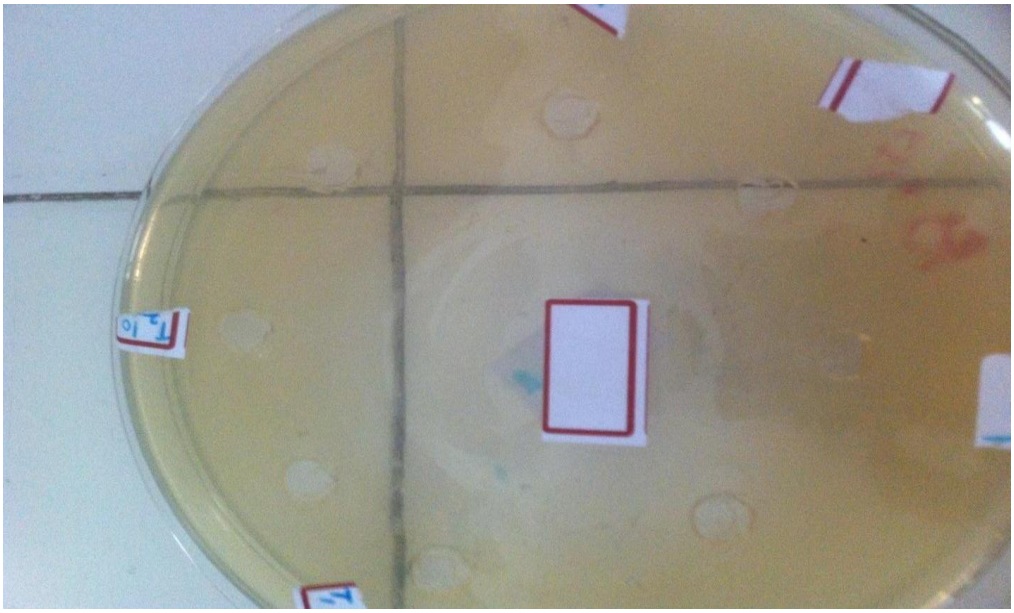


Figure 14: Photograph of various novel Schiff bases and thiazolidinones-Antibacterial activity against gram positive bacteria (*S.aureus*).

Anthelmintic activity

The synthesized compounds (2a-3b) were evaluated for anthelmintic activity on Indian earthworms (*Pherethima posthuma)*. All compounds showed anthelmintic activity. Among the compounds tested, all the compounds showed significant paralytic time for earthworms compared to standard drug albendazole at (0.1%, 0.2% and 0.5%) concentration of compounds.

Table no 9: Anthelmintic activities of novel Schiff bases and thiazolidinones.

S.No.	Name	Time in minutes					
		For paralysis			For death		
		% Drug concentration			% Drug concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
1	Control	-	-	-	-	-	
2	Albendazole	14	12	9	42	32	25
3	2a	29	23	10	50	43	37
4	2b	24	17	11	45	37	28
5	3a	27	17	13	53	47	31
6	3b	28	24	14	51	44	36

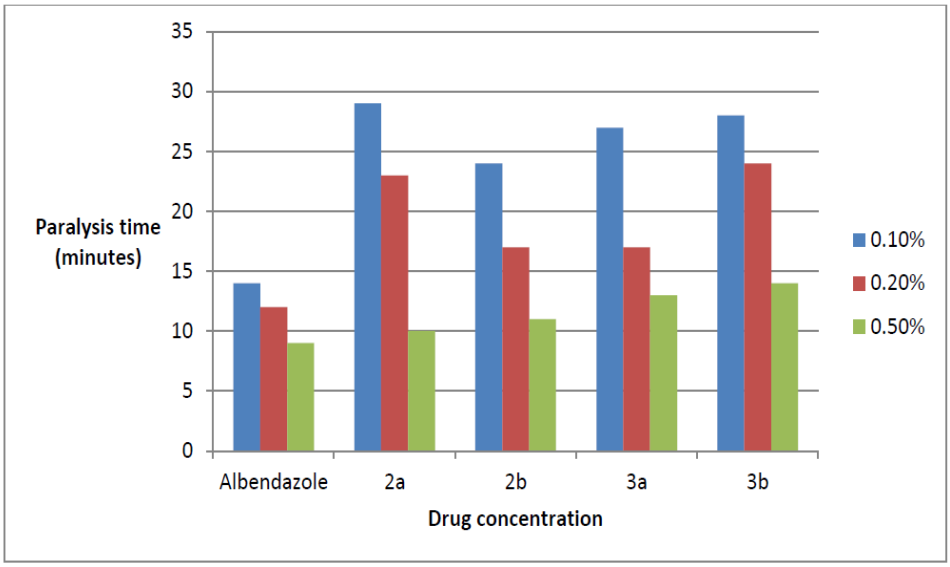


Figure 15: Anthelmintic activity.

Graphical representation of anthelmintic activity of compounds (2a, 2b, 3a, 3b)). Where **2a:-** (E)-3-(2-hydroxybenzylideneamino) benzoic acid.
2b:- (E)-2-(benzylideneamino)-3-methylpentanoic acid.
3a:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid.
3b:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid.

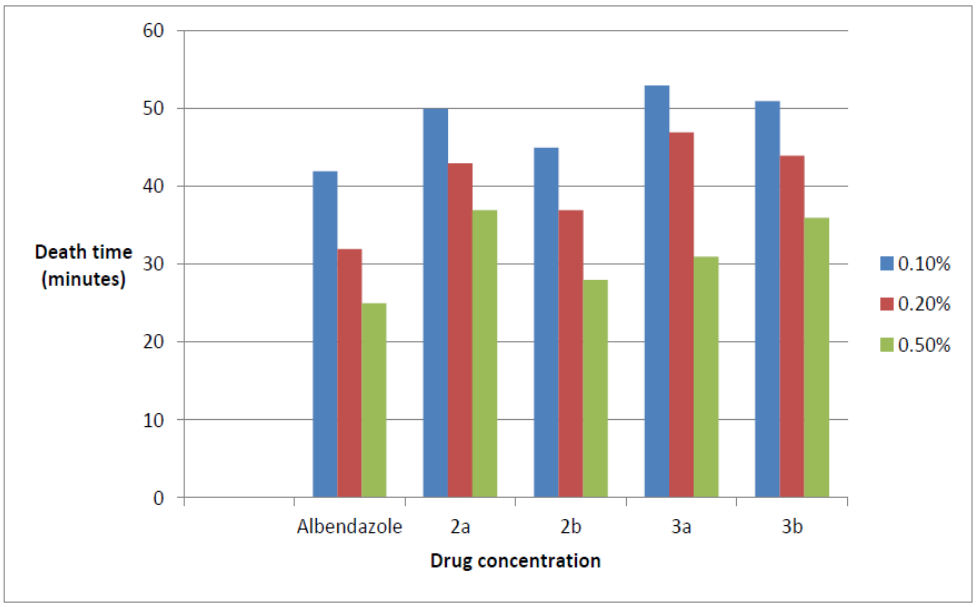


Figure 16: Anthelmintic activity.

Graphical representation of Anthelmintic activity of compounds (2a, 2b, 3a, 3b). Where **2a:-** (E)-3-(2-hydroxybenzylideneamino) benzoic acid.
2b:- (E)-2-(benzylideneamino)-3-methylpentanoic acid.
3a:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid.
3b:- 2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-methylpentanoic acid.

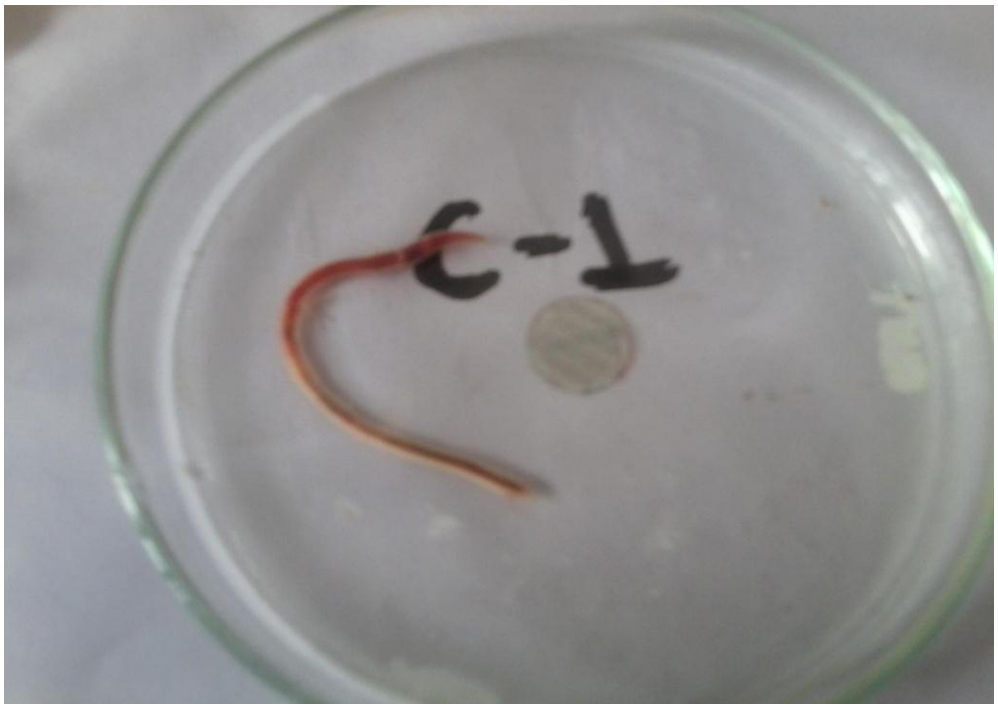


Figure 17: Photograph of various novel Schiff bases and thiazolidinones- Anthelmintic activity.

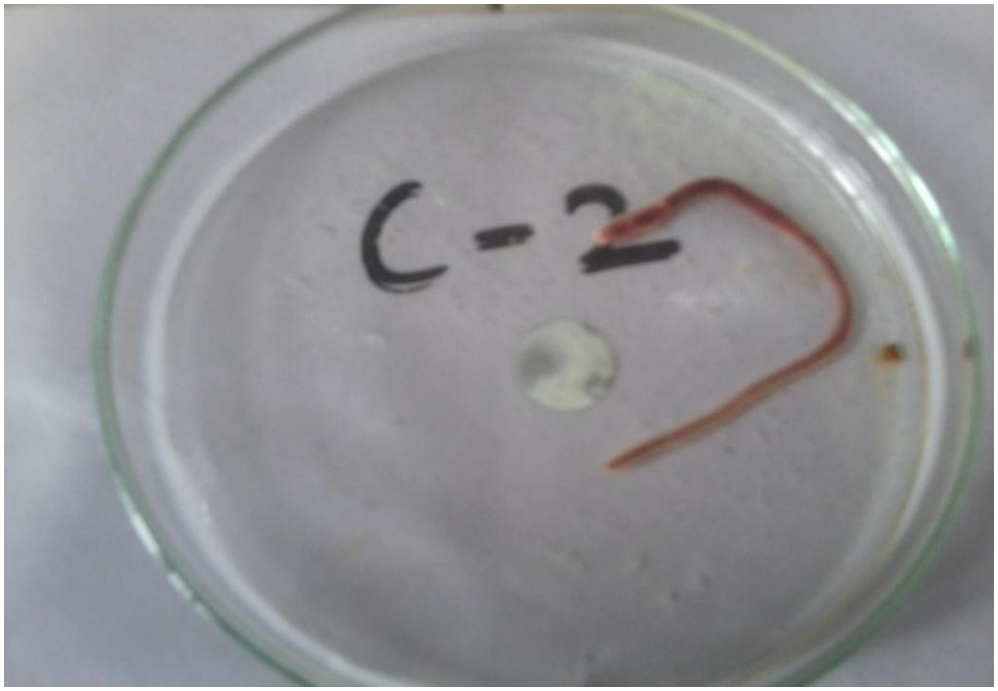


Figure 18: Photograph of various novel Schiff bases and thiazolidinones- Anthelmintic activity.

Anticoagulant activity

The synthesized Schiff bases (2a and 2b) were screened for *invitro* anticoagulant activity using prothrombin time test.10µg/ml, 20µg/ml, 40µg/ml and 80µg/ml concentrations of compounds (2a and 2b) were prepared. Time of coagulation at different concentrations was recorded for both the compounds. From the time of coagulation of the compounds it was found out that Schiff base 2a possess better anticoagulant activity when compared to Schiff base 2b.

Table no: 10 Determination of coagulation time of Schiff base 2a.

S.No.	Name of compound	Amount of plasma	Amount of extract	Calcium chloride solution	Time of coagulation
1.	Control	0.2ml	0.1ml	0.3ml	1min
2.	Schiff base 2a(10µg/ml)	0.2ml	0.1ml	0.3ml	6min 23s
3.	Schiff base 2a(20µg/ml)	0.2ml	0.1ml	0.3ml	7min 12s
4.	Schiff base 2a(40µg/ml)	0.2ml	0.1ml	0.3ml	8min 10s
5.	Schiff base 2a(80µg/ml)	0.2ml	0.1ml	0.3ml	9min 19s

Table no: 11 Determination of coagulation time of Schiff base 2b.

S.No.	Name of compound	Amount of plasma	Amount of extract	Calcium chloride solution	Time of coagulation
1.	Control	0.2ml	0.1ml	0.3ml	1min
2.	Schiff base 2b(10µg/ml)	0.2ml	0.1ml	0.3ml	5min 53s
3.	Schiff base 2b(20µg/ml)	0.2ml	0.1ml	0.3ml	6min 25s
4.	Schiff base 2b(40µg/ml)	0.2ml	0.1ml	0.3ml	6min 44s
5.	Schiff base 2b(80µg/ml)	0.2ml	0.1ml	0.3ml	7min 39s

The IR data showed the presence of major functional groups present in the synthesized compounds, ^{1}H-NMR data showed the chemical shift of protons and Mass spectral analysis confirmed the molecular weight of the synthesized compounds.

The synthesized Schiff bases were screened for anticoagulant, antibacterial and anthelmintic activities and thiazolidinones were screened for antibacterial and anthelmintic activities. Schiff base **2a** ((E)-3-(2-hydroxybenzylideneamino) benzoic acid) showed better anticoagulant, antibacterial and anthelmintic activities compared to Schiff base 2b and thiazolidinone **3a** (2-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzoic acid) showed better antibacterial and anthelmintic activities compared to thiazolidinone 3b.

Antibacterial, anthelmintic and anticoagulant activities seen in Schiff bases (2a and 2b) is due to the presence of highly reactive azomethine group (RHC=N-R1). Presence of phenolic hydroxyl group in Schiff base 2a is also important for biological activity particularly

antibacterial activity.

Antibacterial and anthelmintic activities seen in thiazolidinones (3a and 3b) are mainly due to the presence of thiazolidine ring. Presence of N-CH-S grouping and phenolic hydroxyl groups in thiazolidinones (3a and 3b) confers the presence of anthelmintic and antibacterial activities.

6. CONCLUSION

The objective of the present work was to employ microwave for the synthesis of some novel Schiff bases and novel thiazolidinones Schiff bases have been reported to possess higher degree of antitubercular, anticancer, antibacterial, anti-inflammatory, antifungal activities and even thiazolidinones find a variety of applications ranging from antimicrobial, antitubercular, anti- inflammatory, anthelmintic, anticonvulsant, Anti HIV activity, Anticancer, and hypoglycemic activity. Microwave was used microwave to make chemical synthesis more environment friendly, safe, to improve the yield and also to reduce the time consumption. This method is safe, more environment friendly and by using this method compounds can be synthesized in absence of solvents. Microwave synthesis gives improved product yields, provides controlled method of heating and also increases reaction rates.

The newly synthesized Schiff bases (2a and 2b) were evaluated for anticoagulant activity. Schiff bases and thiazolidinones were purified, characterized and evaluated for antibacterial and anthelmintic activities. The yield of the synthesized compounds was found to be in the range of 70-86 %. All these molecules were characterized by physical data and FT-IR, ^{1}H NMR and mass spectral analysis. The functional groups in the title compounds were indicated by their IR spectra. The no. of protons in the compound was confirmed by their ^{1}H NMR spectra. The structure of title compounds were confirmed by their Mass spectra.

The synthesized Schiff bases (2a and 2b) at concentrations 10µg/ml, 20µg/ml, 40µg/ml and 80µg/ml were tested for anticoagulant activity using prothrombin time test. Time of coagulation for both the compounds was recorded and it was found out that Schiff base **2a** showed better anticoagulant activity when compared to Schiff base **2b.**

All the synthesized compounds were tested for antibacterial activity on E.*coli* and S.*aureus*, using chloramphenicol as standard drug at concentrations of 0.1%, 0.2% and 0.3%. Amongst all the synthesized compounds, compounds **2a,** and **3a** showed highest activity.

All the synthesized compounds were also screened for anthelmintic activity, using albendazole as standard. The compound **2a** showed highest activity, **2b** and **3a** showed moderate activity.

From the data of antibacterial and anthelmintic activity of Schiff bases and thiazolidinones it is clearly concluded that the synthesized compounds are having good antibacterial and anthelmintic activities. The data of anticoagulant activity of Schiff bases also showed that the synthesized Schiff bases possess good anticoagulant activity.

7. ACKNOWLEDGEMENTS

On this occasion of successful completion of my work, I offer my salutations to the Almighty, with whose showering of blessings, this task was ventured without any hindrance. It affords me an immense pleasure to acknowledge with gratitude the help and guidance rendered to me by a host of people, whom, I owe a substantial measure for the completion of this project.

It is with pleasure of immense gratitude that I express my most cordial and humble thanks to my esteemed research Guide, **Mr. SURESH, Scientist Glochem industries pvt. ltd,** for his valuable guidance, keen interest, perennial inspiration and everlasting encouragement. I shall forever remain indebted to him for having inculcated in me a quest for excellence, a spirit of diligence and perseverance, a sense of humility, honesty and respect for the moral and ethics which govern our sciences and without whom this work would not have seen the light of the day.

It gives me an immense pleasure and pride to express my deep sense of gratitude and respect for my teacher and Guider **(Mrs.) P. Madhuri, Asst Professor** at **Sultan-U-Uloom College of Pharmacy**, Hyderabad and for his evergreen expertise and inspiring guidance throughout the period of my project work. I am indebted to **Dr. J. Venketashwara Rao** for enlightening me on the finer skills of dealing with synthetic problems. I consider myself fortunate to be associated with him.

I take this opportunity to reveal my gratitude, regards and sincere thanks to Miss.Sharmila Sutradhar and faculty of Sultan-Ul-Uloom college of pharmacy for their guidance, constant encouragement and valuable suggestions throughout this course. I am very much thankful for their unflinching support, affection, which helped me a lot in exploring my abilities and made it possible for me to carry out the present work which otherwise, would be very difficult.

I am indebted to my seniors, research scholars Mr. Adil Shareef, Ms. Shabnam Dobani for their restless and patient support throughout my work period. I have the pleasure of collaborating with them for my thesis work.

It gives me a great pleasure to express my thanks to my Sultan-Ul-Uloom friends Mohsin abbas Khambaty, Shaik Md Muzakir, Faisal Ahmed, syed wajahat ullah, mirza fathe ullah baig and many more for their constant support, encouragement during the entire period of my research.

I would like to present my sincere thanks towards Analysis Departments for their support and helping me in analysis of my work and making it possible for me to carry out the present work which otherwise, would be very difficult. I am at loss of words while thanking my Family for their support, sacrifice and pain they have taken in bringing me up to this position. Finally, I take this opportunity to thank one and all who have directly or indirectly helped me in completing this task.

8. REFERENCES

1. Z. Cimerman, S. Miljanic and N. Galic, *Croatica Chemica Acta*, 2000; 73(1): 81- 95.
2. P. Singh, R. L. Goel and B. P. Singh, *J. Indian Chem. Soc*, 1975; 52: 958.
3. B. F. Perry, A. E. Beezer, R. J. Miles, B. W. Smith, J. Miller and M. G. Nascimento, Microbois, 1988; 45: 181.
4. Elmali, M. Kabak and Y. Elerman, J. *Mol. Struct*, 2000; 477: 151.
5. P. R. Patel, B. T. Thaker and S. Zele, *Indian J. Chem*, 1999 38A: 563.
6. M. Valcarcel and M. D. Laque de Castro, Flow-Throgh Biochemical Sensors, Elsevier, 1994, Amsterdam.
7. U. Spichiger-Keller, Chemical Sesors and Biosensors for Medical and Biological Applications, Wiley-VCH, 1998; Weinheim.
8. J. F. Lawrence and R. W. Frei, Chemical Derivatization in Chromatography, Elsevier, 1976, Amsterdam.
9. K.N. Campbell, H. Sommers and B.K. Campbell, J. Am. Chem. Soc, 1944; 66: 82.
10. J. Hine and C.Y.Yeh, J. Am. Chem. Soc, 1967; 89: 2669.
11. I.A.Savich, A.K.Pikaev, I.A.Lebedev and V.I.Spitsyn., Vestnik. Moskov, Univ, 1956; 11: 225.
12. H.Tazoki and K.Miyano, J.Chem, Soc., 1959; 9769.
13. D.N.Robertson, U.S.P, 1960; 2: 920,101.
14. C.M.Brewster, J.Am.Chem.Soc, 1924; 46: 2463.
15. C.Munir,S.M. Yousaf and N. Ahmad, J. Chem. Soc. Pak, 1985; 7: 301.
16. G.H. Alt (Monsanto Co.), US. 4.226.615; *Chem. Abstr*, 1980; 94: 26155.
17. Y. Hamada, I. Takeuchi, Y. Ita, S. Matsui and T. Ita, Yakugaku Zasslzi, 1981; 101: 633.
18. *Chem. Abstr*, 1981; 95: 181559.
19. M. Ismail, *Indian J. Pharm. Sei*, 1986; 45: 121.
20. *Chem. Abstr*, 1987; 107: 175589.
21. K.Y. Lau, A. Mayr, K.K. Cheung, Inorg. *Chem. Acta*, 1999; 285: 223.
22. A.S, Shawali, N.M.S. Harb and K.O. Badahdah, J. *Heterocylic Chem*, 1985; 22: 1397.
23. M.M. Hernandes, M.L. Mckee, T.S. Keizer, B.C. Yeaswood and D.A. Atwood, J. Chem. Soc., Dalton Trans, 2002; 410.
24. G. H. Olie, and S. Olive, Springer, Berlin, 1984.
25. S. Li, S. Chen, H.Ma, R. Yu and D. Liu, Corros. Sci, 1999; 41: 1273.
26. www.shodhganga.inflibnet.ac.in
27. D.R. Williams, *Chem. Rev*, 1972; 72: 203.
28. Campos, J.R. Anacona and M.M. Campos-Vallette, Mian group Metal chem, 1999; 22: 283.
29. N. Sari, S. Arslan, E. Logoglu and I. Sakiyan, *G.U.J. Sci*, 2003; 16: 283.
30. M. Verma, S.N. Pandeya, K N. Singh, J P. *Stabler and Acta Pharm*, 2004; 54: 49.
31. P.G. Cozzi, *Chem. Soc. Rev*, 2004; 410.
32. S. Chandra, J. Sangeetika, *J. Indian Chem. Soc*, 2004; 81: 203.
33. Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. Chem. Rev, 1981; 81: 175.
34. Markovic, R.; Stodanovic, M. Heterocycles, 2005; 56: 2635.
35. Pawar, R. B.; Mulwad, V. V. Chem Heterocycl. Compd, 2004; 40: 219.
36. Ocal, N.; Aydogan, F.; Yolacan, C.; Turgut, Z. J. Heterocycl. Chem, 2003; 40: 721.
37. Eltsov, O. S.; Mokrushin, V. S.; Belskaya, N. P.; Kozlova, N. M. Rus. Chem. Bull., Int. Edn, 2003; 52: 461.
38. Abhishek Kumar Jain, Ankur Vaidya, Veerasamy Ravichandran Sushil Kumar Kashaw and Ram Kishore Agrawal, Recent developments and biological activities of thiazolidinone derivatives: A review, Bioorganic & Medicinal Chemistry, 2012.
39. Microwave assisted organic synthesis,Tetrahedron, 5 Nov 2001; 57(45): 9225- 9283.
40. Chhonker YS, Veenu B, Hasim SR, Kausik N, Kumar D, Kumar P. Synthesis and pharmacological evaluation of some new 2-phenyl benzimidazoles derivatives and their Schiff's bases. E-J Chem, 2009; 6(S1): S342-S346.
41. Alang G, Kaur R, Kaur G, Singh A, Singla P. Synthesis and antibacterial activity of some new benzothiazole derivatives. Acta Pharmaceutica Sciencia, 2011; 52: 213-218.
42. Vicini P, Geronikaki A, Incerti M, Busonera B, Poni G, Cabras CA, Colla PA. Synthesis and Biological Evaluation of Benzo[*d*] isothiazole, Benzothiazole and Thiazole Schiff's Bases. Bioorg Med Chem, 2003; 11: 4785–4789.
43. Dabholkar VV, Ali Syed SAS. Synthesis of Novel Oxazoles and Their Hydrazones. Rasayan J Chem, 2010; 3(4): 761-765.
44. Munj PP, Somani RR, Chavan AV. Synthesis and biological evaluation of some newer triazole based Schiff's bases. Der Pharma Chemica, 2010; 2(1): 98-103.
45. Kenderekar PS, Siddiqui RF, Patil PS, Bhusare SR, Pawar RP. Synthesis and Antibacterial Activity of Schiff's bases and 4-Thiazolidinones. Indian J Pharm Sci, 2003; May-June: 313.
46. Singh UK, Pandeya SN, Sethia SK, Pandey M, Singh A, Garg A, Kumar P. Synthesis and Biological Evaluation of Some Sulfonamide Schiff's Bases. Int J Pharm Sci Drug Res, 2010; 2(3): 216-218.
47. Bawa S, Kumar S. Synthesis of Schiff's bases of 8-methyltetrazolo [1,5-*a*] quinoline as potential anti-

inflammatory and antimicrobial agents. Indian J Chem, 2009; 48B: 142- 145.
48. Panneerselvam P, Ravi Sankar Reddy, Kumarasamy Murali and Natesh Ramesh Kumar. Synthesis, analgesic, anti-inflammatory and antimicrobial activities of some novel Schiff's bases of 5-subsituted Isatin. Der Pharma Chemica, 2010; 2(1): 28-37.
49. Ammar YA, Ismail MMF, El-Gaby MSA, Zahran MA. Some reactions with quinoxaline- 2,3-dicarboxylic acid anhydride: Novel synthesis of thieno[2,3-*d*]pyrimidines and pyrrole[3,4-*b*]quinoxalines as antimicrobial agents. Indian J Chem, 2001; 41B: 1486-1491.
50. Sunita Bhagat, Nutan Sharma and Tejpal Singh Chundawat, Synthesis of Some Salicylaldehyde – Based Schiff Bases in Aqueous Media. *Journal of Chemistry*, 2013, Article ID 909217.
51. Hai Jian YANG, Wen Hua SUN, Zi Long LI, Zhi MA, The Rapid Synthesis of Schiff-Base Without Solvent Under Microwave Irradiation. *Chinese Chemical Letters*, 2002; 13(1): 3–6.
52. Hossein Naeimi and Khadigeh Rabiei, Convenient, Mild and One-Pot Synthesis of Double Schiff Bases from Three Component Reaction of Salicylaldehyde, Ammonium Acetate and Aliphatic Aldehydes Accelerated by NEt3 as a Base. *Journal of the Chinese Chemical Society*, 2007; *54*: 1293-1298.
53. Patel NB, Patel JC. Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3*H*)-one. Arabian J Chem, 2011; 4(4): 403-411.
54. Jubie S, Sikdar P, Antony S, Kalirajan R, Gowramma B, Gomathy S, Elango K. Synthesis and biological evaluation of some Schiff's bases of 4-(amino)-5-phenyl-l-4*H*- 1,2,4-triazole-3-thiol. Pak J Pharm Sci, 2011; 24(2): 109-112.
55. Hunas HR, Ronad PK, Maddi V, Darbhamulla S, Kamdod M. Synthesis and Biological Activities of *N*'[4-(substituted benzylideneamino)-3-(2'4-dichlorophenoxymethyl)-1,2,4- triazol-5-yl)] isonicotinyl hydrazide. Int J Drug Desig Discov, 2010; 1(1): 107-113.
56. Sridhar SK, Saravanan M, Ramesh A. Synthesis and antibacterial screening of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur J Med Chem, 2001; 36: 615-625.
57. Prabhu PP, Pande S, Shastry CS. Synthesis and Biological Evaluation of Schiff's Bases of Some New Benzothiazole Derivatives as Antimicrobial Agents. Int J Chem Tech Res, 2011; 3(1): 185-191.
58. Vora JJ, Vasava SB, Parmar KC, Chauhan SK, Sharma SS. Synthesis, Spectral and Microbial Studies of Some Novel Schiff Base Derivatives of 4-Methylpyridin-2-amine. E-J Chem, 2009; 6(4): 1205-1210.
59. Atia AJK. Synthesis and Antibacterial Activities of New Metronidazole and Imidazole Derivatives. Molecules, 2009; 14: 2431-2446.
60. Asiri AM, Khan SA. Synthesis and Anti-Bacterial Activities of Some Novel Schiff's Bases Derived from Aminophenazone. Molecules, 2010; 15: 6850-6858.
61. Pandeya SN, Sriram D, Nath G, De Clerq E. Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff's and Mannich bases derived from isatin derivatives and *N*- [4-(4'-chlorophenyl) thiazol-2-yl] thiosemicarbazide. Eur J Pharm Sci, 1999; 9: 25-31.
62. Gouveia, F. L.; Oliveira, R. M. B.; Oliveira, T. B.; Silva, I. M.; Nascimento, S. C.; Sena, K. X. F. R.; Albuquerque, J. F. C. Eur. J. Med. Chem, 2009; 44: 2038.
63. Singh, T.; Srivastava, V. K.; Saxena, K. K.; Goel, S. L.; Kumar, A. Arch. Pharm. Chem. Life Sci. 2006, 339, 466. Pawar, R. B.; Mulwad, V. V. Chem. Heterocyclic. Comp, 2004; 40: 219.
64. Kocabalkanli, A.; Ates, A.; Otuk, G. Arch. Pharm. Pharm. Med. Chem, 2001; 334: 35.
65. El-Gaby, M. S. A.; El-Hag Ali, G. A. M.; El-Maghraby, A. A.; Abd El-Rahman, M. T.; Helal, M. H. M. Eur. J. Med. Chem, 2009; 44; 4148.
66. Gihsoyl, A.; Terzioglul, N.; Otuk, G. Eur. J. Med. Chem, 1997; 17: 181.
67. Bondock, S.; Khalifa, W.; Fadda, A. A. Eur. J. Med. Chem, 2007; 42: 948.
68. Hafez, H. N.; El-Gazzar, A. B. A. Bioorg. Med. Chem. Lett, 2009, 19: 4143.
69. Ali, A. M.; Saber, G. E.; Mahfouz, N. M.; EI-Gendy, M. A.; Radwan, A. A.; Hamid, M. A. Arch. Pharm. Res, 2007; 30: 1186.
70. Amin, K. M.; Kamel, M. M.; Anwar, M. M.; Khedr, M.; Syam, Y. N. Eur. J. Med. Chem, 2010; 45: 2117.
71. Akula, G.; Srinivas, B.; Vidyasagar, M.; Kandikonda, S. Int. J. Pharm. Tech. Res, 2011; 3: 360.
72. Chen, H.; Bai, J.; Jiao, L.; Guo, Z.; Yin, Q.; Li, X. Bioorg. Med. Chem, 2009; 17: 3980.
73. Ottana, R.; Maccari, R.; Ciurleo, R.; Paoli, P.; Jacomelli, M.; Manao, G.; Camici, G.; Laggner, C.; Langer, T. Bioorg. Med. Chem, 1928; 17.
74. Bhandari, S. V.; Bothara, K. G.; Patil, A. A.; Chitre, T. S.; Sarkate, A. P.; Gore, S. T.; Dangre, S. C.; Khachane, C. V. Bioorg. Med. Chem, 2009; 17: 390.
75. Gududuru, V.; Hurh, H.; Dalton, J. T.; Miller, D. D. Bioorg. Med. Chem. Lett, 2004; 14: 5289.
76. Turan-Zitouni, G.; Kaplancikli, Z. A.; Ozdemir, A. Eur. J. Med. Chem, 2010; 45: 2085.
77. Kucukguzel, S. G.; Oruc, E. E.; Rollas, S.; Sahin, F.; Ozbek, A. Eur. J. Med. Chem, 2002; 37: 197.
78. Jaju, S.; Palkar, M.; Maddi, V.; Ronad, P. K.; Mamledesai, S.; Satyanarayana, D.; Ghatole, M. Arch. Pharm. Chem. Life Sci. 2009, 342, 723. Karali, N.; Kocabalkanlı, A; Gursoy, A.; Ates, O., II Farmaco, 2002; 57: 589.
79. Kline, T.; Felise, H. B.; Barry, K. C.; Jackson, S. R.; Nguyen, H. V.; Miller, S. I. J. Med. Chem, 2008; 51: 7065.
80. Kavitha, C. V.; Basappa, S.; Swamy, N.;

Mantelingu, K.; Doreswamy, S.; Sridhar, M. A.; Prasad, J. S.; Rangappa, K. S. Bioorg. Med. Chem, 2006; 14: 2290.
81. Khan, S. A.; Yusuf, M. Eur. J. Med. Chem, 2009; 44: 2597.
82. Liu, X.; Zheng, C.; Sun, L.; Liu, X.; Piao, H. Eur. J. Med. Chem, 2011; 46: 3469.
83. Mulwad, V. V.; Mir, A. A. J. Kor. Chem. Soc, 2008; 52: 649.
84. Cecilia Saiz, Chiara Pizzo, Eduardo Manta, Peter Wipf, and S. Graciela Mahler, Microwave assisted tandem reactions for the synthesis of 2-hydrazolyl-4-thiazolidinones, *Tetrahedron Lett*, 2009 February 25; 50(8): 901–904.
85. Ozcan Kocyigit, Ahmed N. Kursunlu, Ersin Guler, Complexation properties and synthesis of a novel Schiff Base with triphenylene nucleus. *Journal of Hazardous Materials*, 15 November 2010; 183: 1-3, 334-340.
86. Navin B. Patel and Sarvil D. Patel, Synthesis and *in vitro* antimicrobial study of Schiff base and thiazolidinone of 1-cyclopropyl-6-fluoro-7-[4-(2,3-dichlorophenyl)piperizin-1- yl]- 4-quinolin. *Acta Poloniae Pharmaceutica ñ Drug Research*, 2010; 67(1): 45-53, ISSN 0001-6837.
87. Gislene G. F. Nascimento; Juliana Locatelli; Paulo C. Freitas; Giuliana L. Silva, Antibacterial activity of plant extracts and phytochemicals on antibiotic resistant bacteria, *Brazilian Journal of Microbiology*, 2000; 31: 247-256.
88. Bundy D A. Immunoepidemiology of intestinal helminthic infection I: The global burden of intestinal nematode disease. *Trans Royal Soc Trop Med Hyg*, 1994; 8: 259-261.
89. Tagbota S, Townson S. Antiparasitic properties of medicinal and other naturally occurring products, *Adv Parasitol*, 2001; 50: 199-205.
90. Sondhi SM., Shahu R., Magan Archana. *Indian Drugs*, 1994; 31(7): 317-320.
91. Bharathi, D.; Hemalatha, S.; devadass, G.; Kumar, P.R.; Shanmugasundaram, P.; Vijey Ananandhi, M.; Synthesis, Characterization and invitro Anti inflammatory and Anthelmenthic activities of 1,3.4-Oxadiazole. *International Journal of Chem Tech Research* CODEN(USA): IJCRGG ISSN: 0974-4290, Oct-Dec 2010; 2(4): 1867-1890.
92. M.S. Sirridge, R. Shannon, Hematology Principles and Procedures, Lea & Febiger, Philadelphia, 1993; 6th ed., 202-278.
93. R.Biggs, R. McFarlane, Human Blood Coagulation and their disorders, Blackwell Scientific Publications, Oxford, 1962; 430-436.
94. R Hull, H Hirsh, R Jay, *New England Journal of Medicine*, 1982; 307: 1676-81.
95. EA BuLoeliger, AMHV Besselaar, Lewis, SM, *Archives of Internal Medicine*, 1985; 53: 148-154.
96. R.W. Colman, J. Hirsh, V. J. Marder, Haemostasis and Thrombosis, Basic Principle and Clinical Practice, Lippincott Company, J.B, 1994; 759-762.