Journal of Advanced Scientific Research
Available online through http://www.sciensage.info
ISSN
0976-9595
Review Article

A BRIEF REVIEW ON THIAZOLIDINONES AND AZETIDINONES: SYNTHESIS AND BIOLOGICAL ACTIVITIES

Babita G. Yadao*[1], Himani C. Pandhurnekar[1], Doyel M. Bhattacharya[1], Chandrashekhar P. Pandhurnekar[2]

[1]*Department of Chemistry, Dada Ramchand Bakhru Sindhu Mahavidyalaya, Nagpur, Maharashtra, India*
[2]*Department of Chemistry, Shri Ramdeobaba College of Engineering and Management, Nagpur, Maharashtra, India*
**Corresponding author: babitayadao@gmail.com*

ABSTRACT

Heterocyclic chemistry is considered as the versatile field which studies the synthesis, properties and applications of the same. These hetero molecules are in many of the natural products and have a great potential to show various biological properties and activities. Thiazolidinone, a saturated analogue of thiazole, is a five-membered ring with sulphur, carbonyl group on the fourth carbon and the most important one i.e. nitrogen which is responsible for most of the biological properties. The molecule has active 2, 3 and 5-positions, where a large number of substitutions are possible that lead to enhance the properties of the derivatives. So this molecule has been always a big target to researchers and is known to own numerous biological activities viz. anti-HIV activity, anticonvulsant, antimicrobial, anti-cancer, anti-inflammatory etc. On the same note, the cyclic azetidinone moiety has been used as a template to build many of the heterocyclic structures fused to the four-membered rings. Azetidin-2-ones have received special attention mainly due to antibacterial properties of cephalosporins and penicillin. Azetidinones is also an exceptional class of compounds which is known to possess a number of activities such as anti-inflammatory, antibacterial, tryptase inhibitory, antihyperlipidemic, human leukocyte elastase inhibitory, CNS activity, antitubercular, antihyperglycemic, pesticidal, antitumor, anticancer activity, antimicrobial, enzyme inhibitors, cholesterol absorption, cytotoxic and elastase inhibitors etc. Through this present review article, we are making a sincere effort to compile all the goodness of these two wonder moieties concerning their synthesis along with some green synthetic steps and biological activities to ease and enhance further research on them.

Keywords: Thiazolidinones, Azetidinones, Synthetic Methods and Biological Activities.

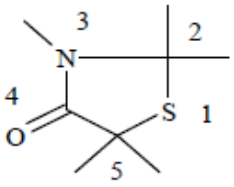
1. INTRODUCTION

Thiazolidine is the base molecule of which thiazolidin-one (Fig.a) is a derivative which belong to an important class of hetero-cyclic compounds. Thiazolidinone is a five-membered compound containing sulfur and nitrogen within the ring [1]. Number of work has been already done in the past on thiazolidinone which is of atmost importance and has provided authentic data about the same. The nucleus is well known as magic molecule or as the wonder nucleus as its different derivatives have been found to show different biological activities, in- fact almost all kinds of activities. This wonder moiety has been continuously explored and under experiment to synthesize new novel derivatives with advanced biological activities. What makes this nucleus wonderful is its 2, 3 and 5-positions where a number of group substitutions are possible that leads to enhance properties of the their analogues. Moreover the change in the substituents which are attached to the carbon atom of the methylene group or to the nitrogen atom are also responsible to synthesize new derivatives [2-5]. The carbonyl group of most of the derivatives of thiazolidinone is considerably unreactive and carry itself as it is in the derivatives. So with these so many changes possible, this molecule is always a big target to the researchers and has been found to show number of biological activities viz. antimicrobial [6-8], anticancer [9], anti-inflammatory [10-12], antiHIV [13], antiviral [15], cytoxity [16]. An adequate number of drugs are already available commercially in the market such as troglitazone, rosiglitazone, lobeglitazone and pioglita-zone and many others [17].

On the other hand, 2-Azetidinones (Fig.b) also named as β-lactams, is a four membered cyclic amide since the

nitrogen atom is attached to the β carbon relative to the carbonyl, it is formally named as so [18]. Alexander Fleming in 1928 discovered the first ever antibiotic and right after that the Cephalosporin was discovered and since then β-lactams and the chemistry of derivatives of β-lactams have gain importance and have been successfully applied as antibiotics [19].

The 2-azetidinone ring is a nucleus which is involved in the number of broad spectrum antibiotics and compounds including penicillins I, cephalosporins II, carbapenems III, monobactams etc. [20]. These all have been extensively applied as an agent which is chemotherapeutically involved in treatment of various microbial diseases and bacterial infection [21]. Azetidinones forms an irreplaceable class of compounds possessing number of biological activities such as anti-inflammatory [22], antibacterial [23], tryptase inhibitory [24], antihyperlipidemic [25], human leukocyte elastase inhibitory [26], CNS activity [27], anti-tubercular [28], anti hyperglycemic [29], pesticidal [30], antitumor, anticancer activity [31], antimicrobial [32], enzyme inhibitors [33], cholesterol absorption [34], cytotoxic and elastase inhibitors [35] etc.



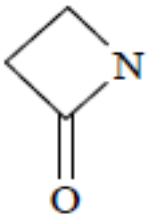


Fig. a: Thiazolidinone **Fig. b: Azetidin-2-ones**

The credit behind the exceptional activities of both these molecules and their derivatives can be the schiff bases within their structures. Schiff bases have been studied in various medicinal field and have been found to show excellent biological activities such as anticancer activity, antimicrobial, antiviral activity etc [36]. Schiff bases are involved in many of the enzymatic reaction viz they act as common enzymatic intermediates where an amine viz. the terminal group of a lysine residue go ahead to react with the ketone or aldehyde of a substrate or cofactor reversibly. The PLP which is the common enzyme cofactor forms a Schiff base with the lysine residue and is transaldiminated to the substrate(s). They have also been investigated for the inhibition of amyloid-β aggregation [37, 38].

Thiazolidinones have been synthesized by the condensation of various heterocyclic or aromatic aldehydes with 4, 4'-diamino-diphenylsulphone to yield the Schiff's bases and then the cyclocondensation of these Schiff's bases with 2-mercaptopropionic acid to provide 4-thiazoli- dinone derivatives [39]. Similarly, the reaction of the chloroacetyl chloride in triethylamine and 1, 4 dioxane with Schiff bases leads to the corresponding 2-azetidinone derivatives [40]. Hence no wonder these molecules possess those structural features to make them so efficient in showing numerous biological activities and making them suitable candidate for research. With all those outstanding characteristics discussed above, in this review article we are making an effort to compile the synthesis and the biological activities shown by various analogues of thiazolidinone and azetidinone to acknowledge their remarkable contribution in the chemistry and biomedical field so that it can be explored with ease.

2. METHODS OF SYNTHESIS OF THIAZOLIDIN ONE AND AZETIDINONE DERIVATIVES

2.1. Thiazolidinone derivatives

Ample of Synthetic methods have been placed to synthesize various derivatives of thiazolidinone including one pot or two pot as well as green synthesis routes are available. As already discussed the 2, 3 and 5 positions are the active positions and the nucleus with any single substitution possible provides excellent biological properties. The possible substituted derivatives are in general as 2-substituted thiazolidinone, thiazolidine-2,4-dione, 2,3-disubstituted thiazolidine-ones, 2,4-disubstituted thiazolidinones, dialkyl thiazolidinones, substituted 2-thiono-4 thiazolidinones etc. We are here discussing a few of them with respect to their synthesis.

2.1.1. Method of synthesis of 2-substituted thiazolidinone

The synthesis of 2-substituted thiazolidinone involves substituted acetophenone, thiourea and iodine. This combination at 60 °C leads to intermediate which when followed by refluxing with chloroacetyl chloride in dioxane provides 2-chloroacetamido substituted thiazoles. This substituted 2-chloroacetamido leads to the formation of 2-substituted thiazolidinone derivatives when cyclized in the presence of ammonium thiocyanate (Scheme 1) [41].

2.1.2. Method of Synthesis of Thiazolidine-2,4-dione

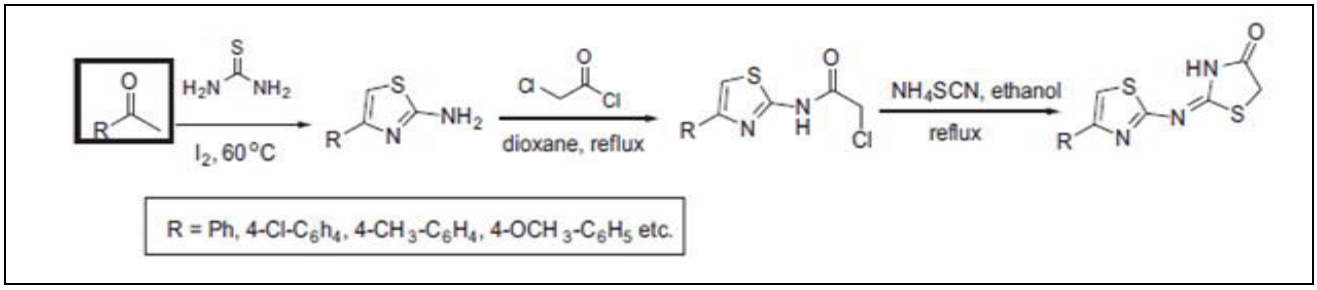
The synthesis method of thiazolidine-2, 4-dione requires the initial materials as chloroacetic acid with thiourea. The refluxing of these two together provides thiazolidine-2-4-diones which is also named as TZD as depicted in the following steps (scheme 2). The same reaction is also possible by undergoing the similar reaction conditions, first under cold reaction condition and then proceeding by microwave irradiation to provide the desired thiazolidine-2, 4-dione [42].

2.1.3. Method of Synthesis of 3-disubstituted thiazolidineones

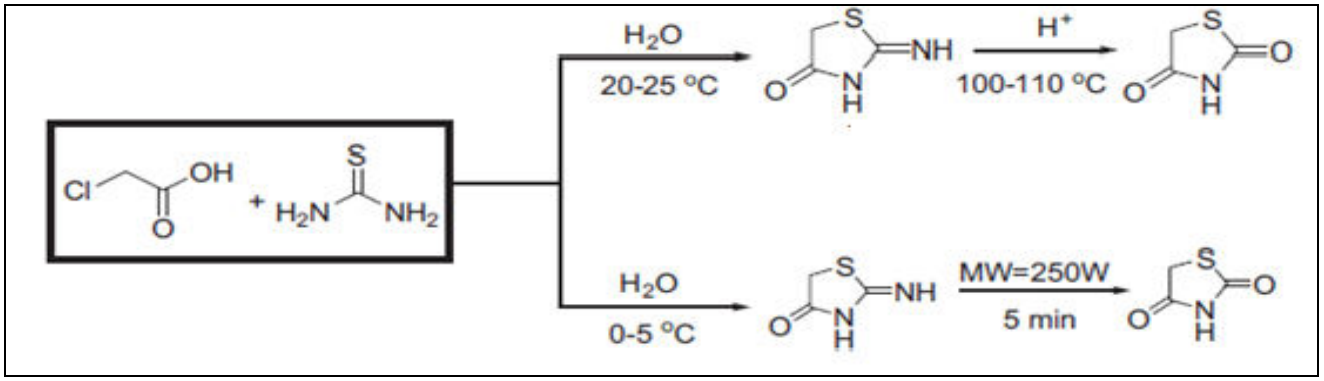
The synthetic method or route to synthesize 3-substituted thiazolidine-2, 4-dione is usually to adopt the starting material as carbonyl sulphide along with primary amine and in the presence of potassium hydroxide (Scheme 3) which results into alkyl thiocarbamates. This when treated with a haloalkanic acid and allow to undergo cyclization leads to the formation of 3-substituted TZD [43].

2.1.4. Method of Synthesis of dialkyl thiazolidin-ones

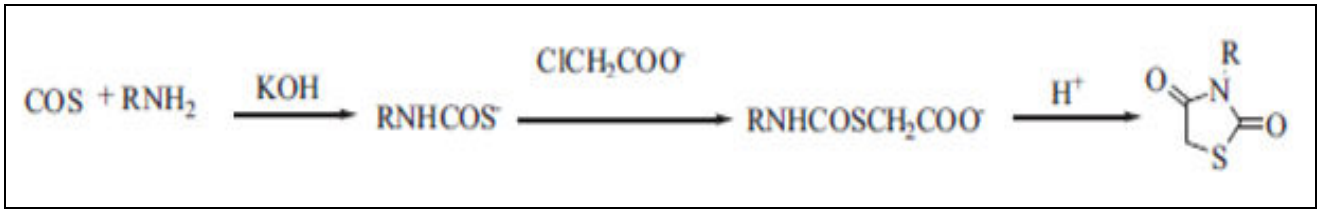
There is another substitution product which is of utmost important is 5, 5-dialkyl-thiazolidin-2-4-dione. Its synthesis requires bromoacetyl chloride or dialkyl substituted bromoacetic acid initially as the starting material. The synthesis moves forward by refluxing either of these two with thiourea along with sodium acetate in ethanol to give an intermediate so that it can be further hydrolysed and lead to the product formation as 5,5-dialkyl-thiazolidin-2,4-dione (Scheme 4) [44].



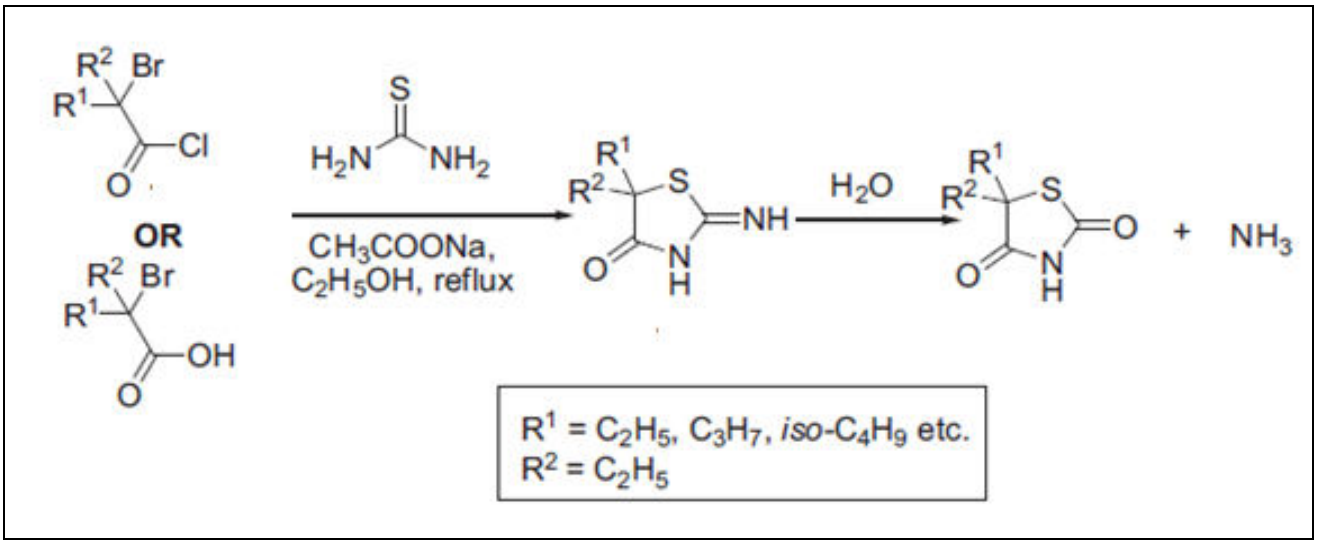
Scheme 1: Method of Synthesis of 2-substituted thiazolidinone derivatives from acetophenone



Scheme 2: Method of Synthesis of thiazolidine - 2,4-dione



Scheme 3: Method of Synthesis of 3-substituted thiazolidine -2- 4- dione



Scheme 4: Method of Synthesis of dialkyl thiazolidinones using substitituted bromoacetic acid or bromoacetyl chloride

2.1.5. Method of Synthesis of 2,3,5 substituted thiazolidinones

There are various synthetic techniques available for the method of synthesis of 2,3,5 substituted thiazolidine-2-thione derivatives. This has been synthesized through many of procedures like one pot, two component and three component methods. The reaction involves iodocyclization of carbon disulfide, an allyl amine and iodine. This reaction mixture with the temperature maintained at room temperature leads to the yield 5-iodomethyl thiazolidine-2-thones. Some reports have also described one pot synthesis which is microwave-assisted for the synthesis of 3-substituted thiazolidine-2-thione and (N-substituted rhodanines). Alkyl and benzylamine molecules could even lead into the corresponding derivative of thiazolidinone i.e. [9-(2-carboxyphenyl)-6-diethylamino-3-xanthenylidine-diethylammonium chloride (Scheme 5) [45].

2.1.6. Method of Synthesis of 2-thiono-4 thiazolidinones

The basic procedure involves the dithiocarbamates which are formed by the reaction of primary amine along with carbon disulfide in the presence of base. It reacts with haloalkanoic acid in the presence of $NaHCO_3$ to give substituted 2-thiono-4-thiazolidinones as presented in the following (Scheme 6) [46].

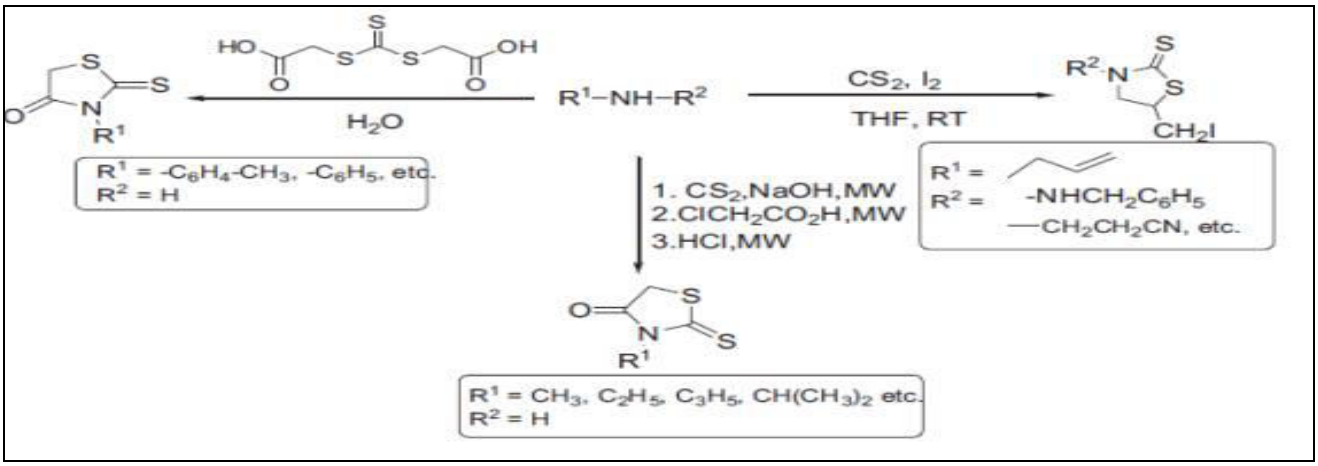
2.1.7. Method of Green Synthesis of thiazolidinone derivative by Knoevenagel condensation

The green synthesis methods approach towards the less chemicals or solvents viz. solvent less method just by grinding or microwave assisted methods have also been placed by many of the scholars. Following are some such green synthesis methods referred from some appreciating research articles.

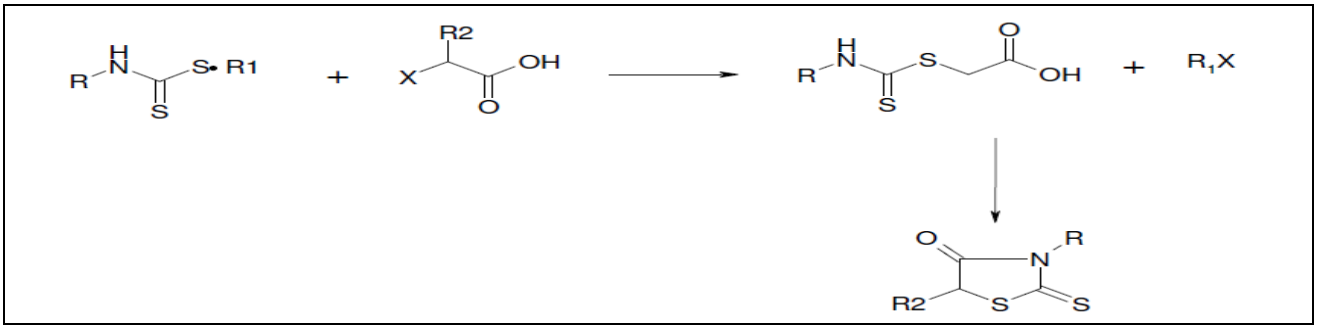
The most well used synthesis of thiazolidinone is Knoevenagel condensation which uses aromatic aldehydes and 4-thiazolidinones combined together in glacial acetic acid containing anhydrous sodium acetate (Scheme 7) [47]. In place of sodium acetate, acetic anhydride, ethanolamine and ammonium chloride in ammonia [48] have also been used.

2.1.8. Method of Green Synthesis of 5-arylidene-2,4-thiazolidinediones and 5-benzylidene rhodanines

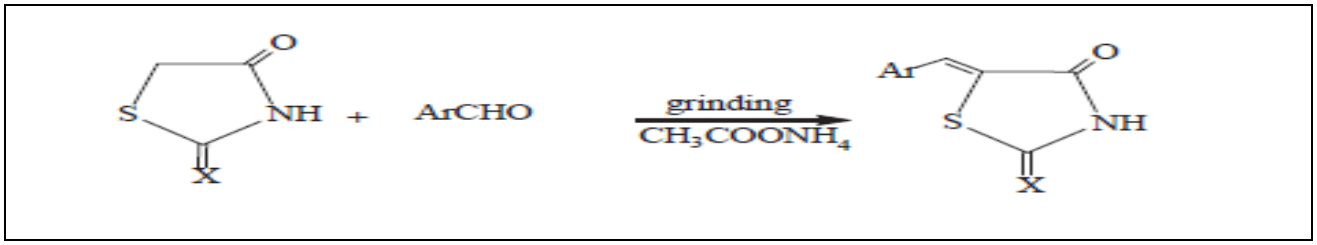
An efficient synthesis of 5-arylidene-2,4-thiazolidinediones and 5-benzylidene rhodanines by the Knoevenagel condensation of 2,4-thiazolidinedione or rhodanine with aromatic aldehydes was studied. It was allowed to proceed smoothly in the presence of tetrabutylammonium hydroxide/H_2O-EtOH to afford the corresponding products in high yields at 50°C. Also a series of dihydrothiophene derivatives were synthesized via the four component reaction of aldehyde, malonitrile, 2,4-thiazolidinedione and piperidine in the presence of Bu_4NOH as a basic ionic liquid in aqueous medium (Scheme 8). This new method offers several advantages, such as excellent yields, short reaction times, and simple procedure [49].



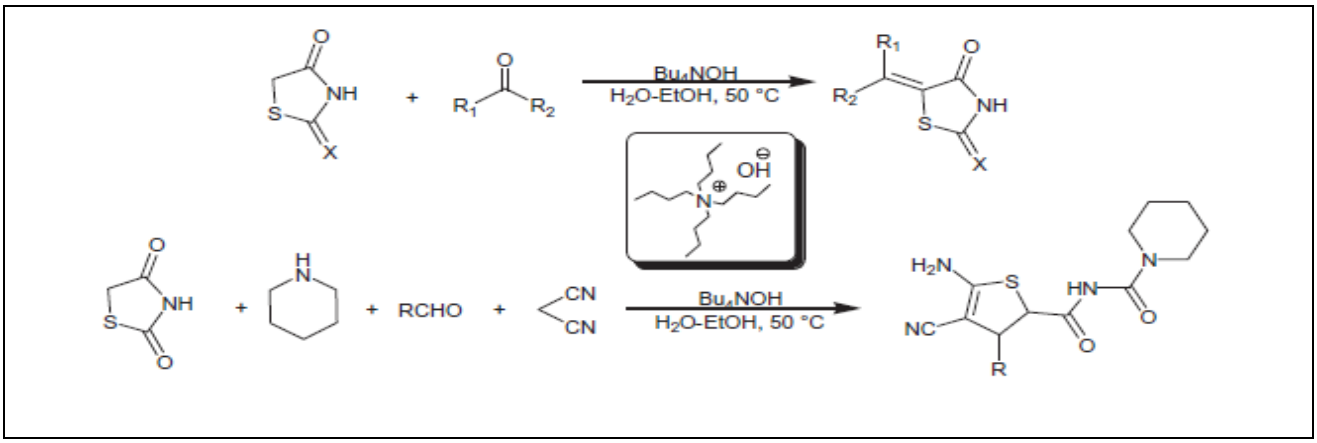
Scheme 5: Method of Synthesis of 5-iodomethyl and 3-substituted thiazolidine -2- thiones



Scheme 6 : Method of Synthesis of 2-thiono-4thiazolidinones



Scheme 7: Thiazolidinone derivative by Knoevenagel Condensation

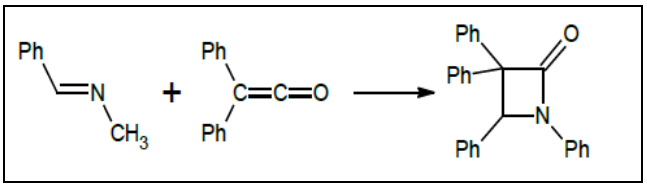


Scheme 8: Method of Synthesis of 5-arylidene-2,4-thiazolidinediones and 5-benzylidene rhodanines

2.2. Azetidinones derivatives

2.2.1. Method of Synthesis of first β-lactam

In the year 1907, the team of Hermann Staudinger prepared the first synthetic β-lactam. He had performed a [2+2] Cycloaddition. They have used Schiff base of aniline along with benzaldehyde with diphenylketene (Scheme 9) [50].

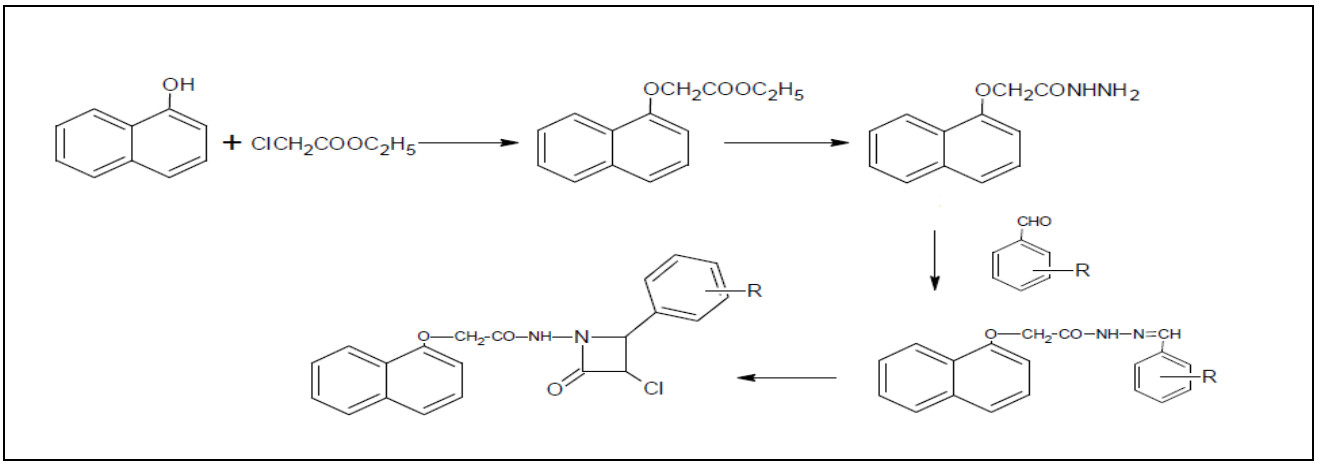


Scheme 9: Synthesis of first synthetic β -lactam

2.2.2. Method of Synthesis of 4methyl-2H-benzo-chromen-2-one

Kumar and the co-workers [51] have reported the systemic synthesis of 4-methyl-2H-benzochromen-2-one through α-Naphthol. For this process they have used ethyl acetoacetate along with bismuth trichloride to obtain the desired product (Scheme 10). The product then obtained was oxidized after which, what obtained is 2-oxo-2H-benzochromene-4-carbaldehyde. This was then allowed to condense with aromatic primary amines to obtain Schiff bases. These Schiff bases thus obtained were allowed to react with acid chlorides in the presence of a base in toluene to give 1, 3, 4-substituted 2-azetidinones.

With these initial attempts to prepare various Azetidinone analogues, great attention was dragged towards its exceptional biological activities and a number of analogues were synthesized by many researchers and team. Following are some analogues representing some of the recently placed new substituted derivatives of azetidinone which have been found to show excellent biological activities.



Scheme 10: Synthesis of 4-methyl-2H-benzochromen-2-one

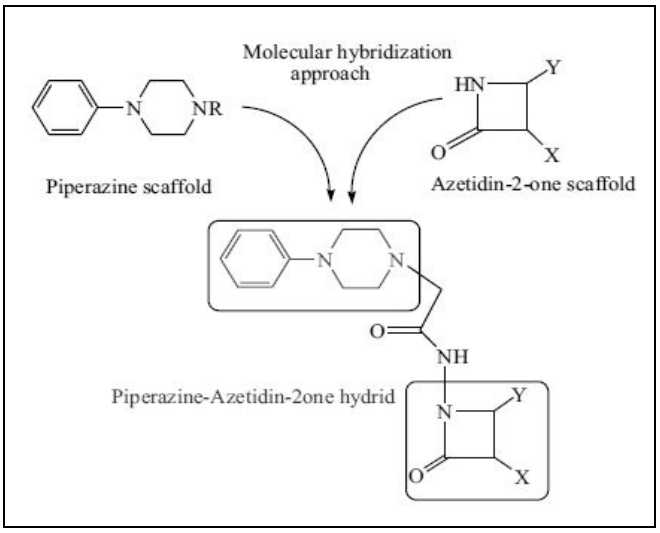
2.2.3. Method of Synthesis of 4-[3-chloro-2-(5-nitro-furan-2-yl)-4-oxo-azetidin-1-yl]-N-pyrimidin-2-yl-benzenesulfonamide

Hussam Hamza Salman et al, in 2014 [52] have synthesized 4-[(5-Nitro-furan-2-yl-methyle-ne)-amino]-N-pyrimidin-2-yl-benzenesulfonamide as schiff base and then taking approximate 0.01 mole of it, it has been treated with triethyl amine (0.02 mole) and this mixture was dissolved in dry 1,4-dioxane (25 ml). To this α-chloroacetyl chloride (0.02 mole) was then added in dropwise or in small portions with vigorous stirring for 20 min at room temperature. This mixture, after refluxing for 3 hrs, was left to room temperature and then was mixed with crushed-ice. This leads to formation of precipitate. The precipitate thus obtained was recrystallized with the help of ethanol giving the derivative of azetidinone which was named as 4-[3-chloro-2-(5-nitro-furan-2-yl)-4-oxo-azetidin-1-yl]-N-pyrimidin-2-yl-benzenesulfonamide.

2.2.4. Method of Synthesis of N-(3-chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-2-(4-phenylpiperazin-1-yl) acetamide

An another study by Rashmin Khanam et al [53] reported that few 2-azetidione derivatives associated with 1-Phenylpiperazine were synthesized by them with strict reaction conditions (Scheme 11). The synthesized derivatives were properly studied and also these were

characterized by various latest techniques. They were also studied with various parameters like their in-vitro anti-proliferative activities and induction of apoptosis etc. Among all the derivatives, the compound named as *N*-(3-chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-2-(4-phenylpiperazin-1-yl) acetamide was found to show good biological activity.



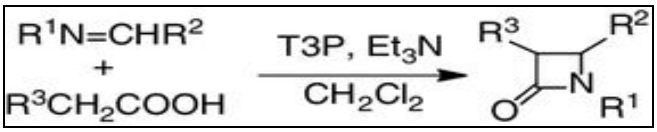
Scheme 11: General structure of piperazine clubbed with azetidin-2-one derivatives

They have provided the synthesis route for the preparation as, to a solution form of N′-(4-substitutedbenzylidene)-2-(4-phenylpiperazin-1-yl) acetohydrazide in dioxane, triethylamine and chloroaetylchloride have to be added carefully with continuous stirring and dropwise addition. While doing so, the temperature should be maintained at 0-5°C. Maintaining the temperature is an essential condition. After refluxing the reaction solution mixture for 24 h, it was then transfered into crushed ice. The precipitate so obtained was then recrystallized using mixture of solvents (DCM/methanol).

A number of another intersting new series like, series of *N*-(arylidene)hydrazinoacetyl sulphonamides[54], series of analogues of 3-chloro-1-{[2-(6-nitro-1H-indazol-1-yl)ethyl] amino}-4-(substituted phenyl)-2-azetidinones [55], series of compound of 4-(2'-hydroxy-3'-chloro-5'-ethyl phen-1'-yl)-1-(4'-tolyl)-3-chloro-2-azetidinone [56] have also been prepared and have been found to show excellent biological activities

2.2.5. Method of Green Synthesis of β-lactams by [2+2] ketene-imine cycloaddition

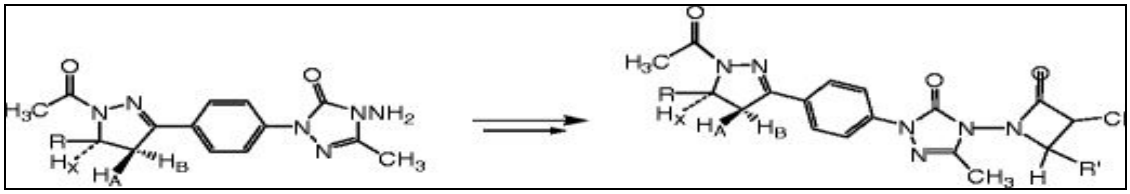
Zarei M. [57] had studied and reported a series of analogues of β-lactams. The scheme adopted by them was cycloaddition i.e. [2+2] ketene-imine cyclo-addition. They had used the substituted forms of acetic acids and imines where propylphosphonic anhydride had been used in the form of acid activator. They found excellent yields by their way (Scheme 12). The products obtained were spirocyclic, monocyclic and the β-lactams analogues found were known to be 3-electron withdrawing.



Scheme 12: Method of synthesis of β-lactams: [2+2] by ketene-imine cycloaddition

2.2.6. Method of Green Synthesis of 1-amino-2-aryl-3-oxo-1,2,4- triazoles

An another magnificiant green approach has been attempted [58, 59] were schiff bases had been prepared using 1-amino-2-aryl-3-oxo-1,2,4- triazoles along with $Mg(ClO4)_2$ which is acting as a catalyst in the system (Scheme 12). The products were then treated in a solvent free condition with chloroacetyl chloride which led them towards the azetidinones derivatives with exceptional yields. The synthesized compounds were screened for many activities viz towards their penetration as how much they have the penetration strength into biological membranes (clogP) and its utility as drug. Their drug score was even calculated. They were also tested for their biological activity viz and antimicrobial activities antitubercular activities.



Scheme 12: Azetidinones using 1-amino-2-aryl-3-oxo-1,2,4- triazoles and Mg $(ClO4)_2$

3. BIOLOGICAL ACTIVITIES OF THIAZOLIDIN ONE AND AZETIDINONE DERIVATIVES

3.1. Biological activities of Thiazolidinone derivatives

3.1.1. Anti HIV activity

A series of analogues of 2,3-diaryl-1,3-thiazolidin-4-ones (Fig.1) were reported showing antiviral properties [60-62]. An another series of analogues of 2-adamantyl-substituted thiazolidin-4-ones(Fig.2) have also been evaluated and have been found to active in CEM Cell cultures against HIV-I(III B) and HIV-2(ROD) [63].

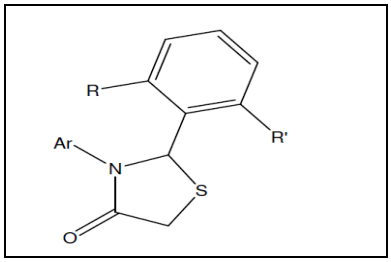


Fig. 1: Derivative of Thiazolidinone: 2,3-diaryl-1,3-thiazolidin-4-ones

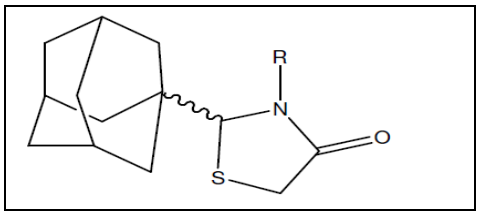


Fig. 2: Derivative of Thiazolidinone: 2-adamantyl-substituted thiazolidin-4-ones

3.1.2. Anti Convulsant

The researchers have done many synthesis and characterization to evaluate the anticonvulsant properties of thiazolidinone derivatives specially for those derivatives who have substitution on 2,3,5 positions. They have found a series of N,N'-bis (arylidene) di -hydrazide(Fig.3) and bis(4-thiazolidin-one) (Fig.4) who have been found to show Anti Convulsantactivity. Upto 80% protection was observed in the pentylenetetrazole seizures [64].

3.1.3. Antimicrobial

Brown et al have studied on antimicrobial activity of the newly synthesized 2-(ptolylimino)-3-(4-tolyl)-5-[5-(3,4-dichlorophenyl)-2-furylidene]-4thiazolidinone (Fig.5). Their many derivatives were screened. The study was most of the time *in vitro* towards antimicrobial activity. The derivatives were studied against bacterial strains such as *S. aureus, P. vulgaris, E. coli, B. mega* and as a result remarkabale inhibition have been observed in compounds having groups R=2-methoxyphenyl, phenyl, 3-methylphenyl 4-nitrophenyl substituents [65].

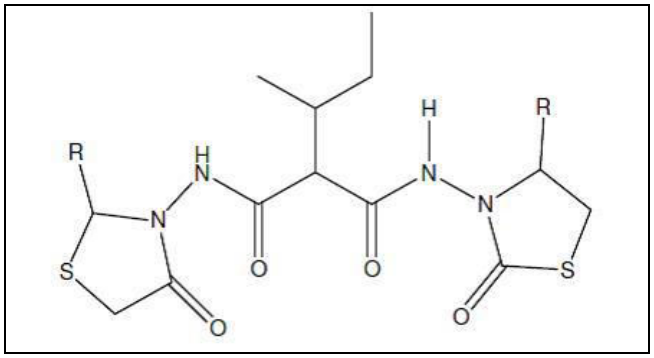


Fig. 3: Derivative of Thiazolidinone: N,N'-bis (arylidene)dihydrazide

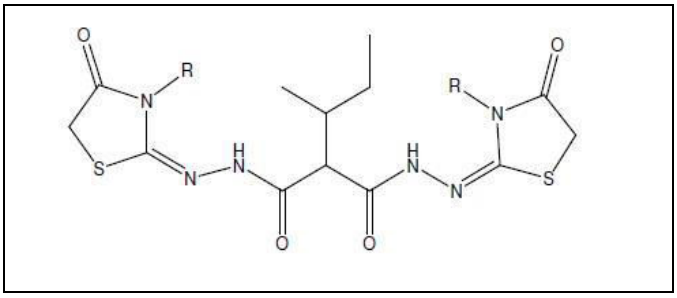


Fig. 4: Derivative of Thiazolidinone: bis(4-thiazolidinone)

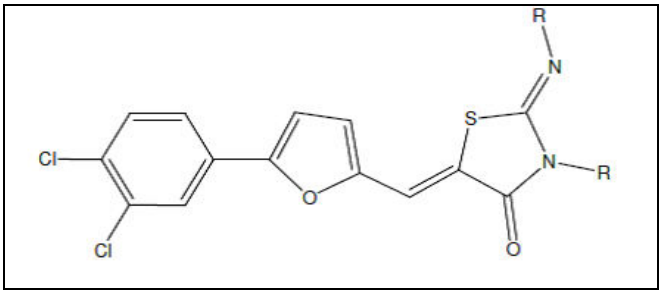


Fig. 5: Derivative of Thiazolidinone: 2-(p-tolylimino)-3-(4-tolyl)-5[5-(3,4-dichlorophenyl)-2-furylidene]-4-thiazolidinone

3.1.4. Anticancer

The thiazolidinone derivatives were excellent and have classical application in the treatment of cancer. Some of the cytoselective compounds were selected from 372 thiazolidinone analogues or derivatives (Fig.6) simply by

considering the iterative library approaches. These derivatives were studied for their biological activities. It was found that many of them selectively were able to kill its paclitaxel-resistant variant H460taxR and cancer cell line H460 at an IC50 between 0.21 and 2.93 M and interestingly they have found to be have no negative or very less toxic effect to normal human fibroblasts at concentrations up to 195 M [66].

Gududuru and the co-workers have worked on a series of analogues of 2-aryl-4-oxothiazolidin-3-yl amides and found these derivatives to inhibitprostate cancer cells. some derivatives of them have been found effective against killing the prostate cancer cells.It has also been found that they have enhanced selectivity as compared to the serine amide phosphates [67].

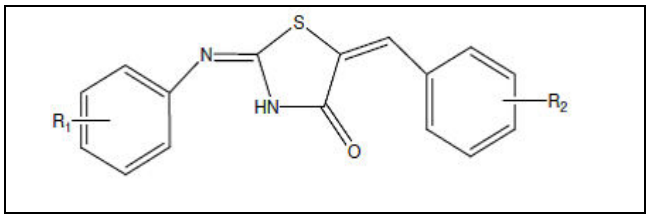


Fig. 6: Derivative of Thiazolidinone having anti-cancer activity

3.1.5. Antiinflammatory

Sparatore F et al have worked on a series of 2, 3-disubstituted-1,3 thiazolidin-4-one derivatives (Fig.7) and found them as anti-inflammatory [68]. Similarly Kumar A et al [69] and the co-workers have also attempted the synthesis of series of 3-[4'-(pchlorophenyl)-thiazol-20-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethyl] 6-bromo-quinazolin-4-ones (Fig.8). Among all the synthesized derivatives few have been found to show anti-inflammatory activity according to biological activity shown by the derivatives.

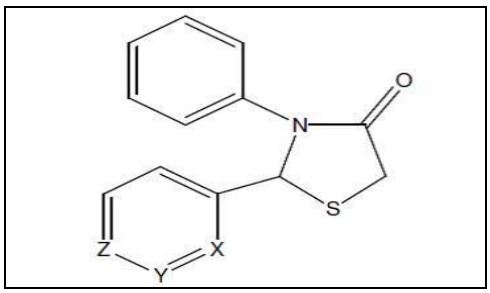


Fig. 7: Derivative of Thiazolidinone: series of 2,3-disubstituted-1,3-thiazolidin-4-one derivatives

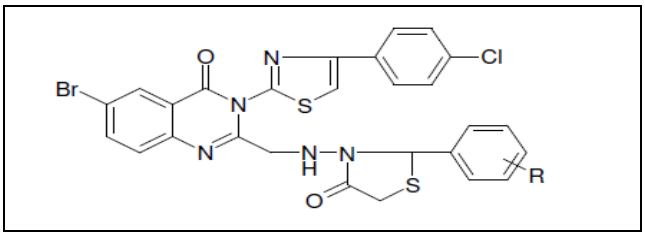


Fig. 8: Derivative of Thiazolidinone: 3-[4'-(pchlorophenyl)-thiazol-20-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethyl] 6-bromoquinazolin-4-ones

3.2. Biological activities of Azetidinones

3.2.1. Antimicrobial

Junneet al. [70] have reported a series in which they have prepared analogues of 3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1(substitutedphenyl) azetidin-2-one (Fig.9).Their derivatives have been studied by them to confirm the antibacterial activity against various bacterial strains for example against E. coli, Xanthomonascitri, B. subtilis and Erwiniacarotovora and many more. Their derivatives have been found to exhibit excellent and approximate equal activities and in some cases they have been found to show even more active against the bacteria whichever are used for confirming the activities, except B. subtilisas which have been not found accurate as according to the standard expectations.

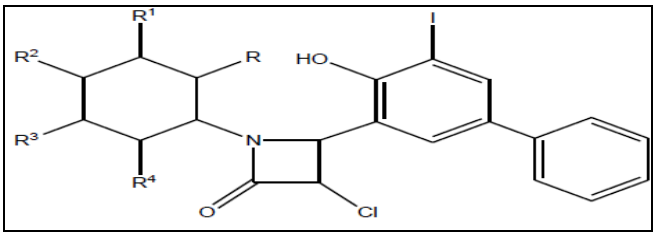


Fig. 9: Derivative of azetidinone: 3-chloro-4-(4-hydroxy-5-iodobiphenyl-3-yl)-1(substituted-phenyl) azetidin-2-one

3.2.2. Antitubercular Activity

S. Hussain et al. [71] have worked with several derivatives of azetidinone. Among that the analogues found by them, the derivative analogues of N-[3-chloro-4-(aryl)-2-oxoazetidin-1-y]-pyridine-4-carboxamides (Fig.10) were found to meet the expectations**.** The derivatives were screened for various types of antimicrobacterial activity. Almost all of these derivatives were found to exhibit excellent antiubercular activities.

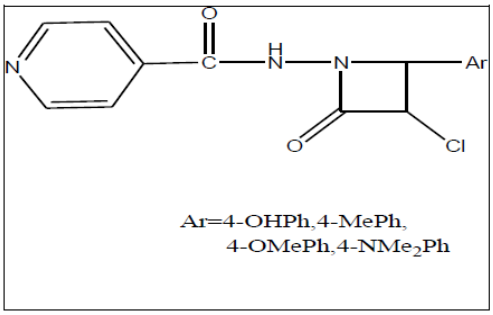


Fig. 10: Derivative of azetidinone: N- [3-chloro-4-(aryl)-2-oxoazetidin-1-y]-pyridine-4-carboxamides

3.2.3. Anticancer

O'Boyle and the team [72] have reported a series of synthesis of azetidin-2-ones where each time they substituted the molecule with the positions 1, 3 and 4 (Fig.11). A number of derivative synthesized in this series were found to be exhibit significant activity in cancer treatment specifically they were found to effective with the MDA-MB-231 breast cancer cells and they also work well with the line panel in the NCI60.

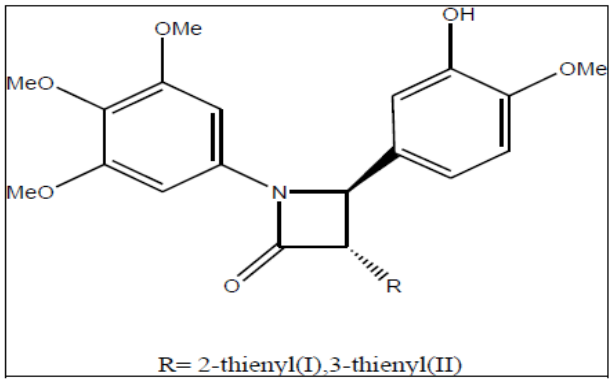


Fig. 11: A series of azetidin-2-ones with substitution at 1,3,4 positions

3.2.4. Antidiabetic Activity

Reddy and the team [73] have synthesized a series of N1-benzothiazolyl-3- chloro-1,5,6-triazaspiro [3.4] oct-6-en-2-ones. They have first prepared Schiff bases by the stepwise condensation of 3-methyl-1-phenyl-5-pyrazolone along with aminobenzothiazole. Out of many derivatives prepared by them, 3-chloro-1-(6-fluoro-7-p-tolylaminobenzothiazol-2-yl)-7-methyl-5-phenyl-1,5,6-triazaspiro[3.4]-oct-6-en-2-one (Fig.12) has found to be following the expected characteristics and its activity was almost comparable to the standard.

Other than these some other novel series have also been reported by various researchers and the azetidinone derivative have also been found to exhibit inhibitory activity of chymase and tryptase [74], inhibitory activity of human leukocyte [75], anti-inflammatory activities, analgesic activities [76], antiparkinsonian activity [77] and D. human cytomegalovirus protease activity [78,79] also.

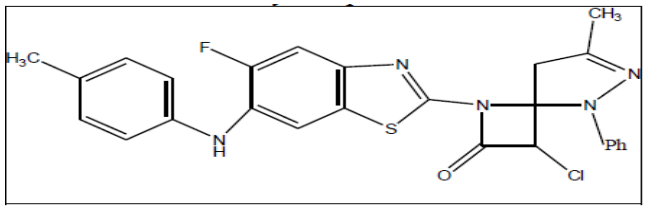


Fig. 12: Derivative of azetidinone: 3-chloro-1-(6-fluoro-7- p-polylaminobenzothiazol-2-yl)-7-methyl-5-phenyl-1,5,6-triazaspiro[3.4]-oct-6-en-2-one

4. CONCLUSIONS

The Chemistry of both the molecules, thiazolidinone and azetidinone analogues takes a prestigious place in organic and medicinal chemistry due to their ketonic structure and presence of Schiff bases which is a smoothly adapted structure in the field of drugs and making them so important that though already a lot of work has been done, still there are numerous opportunities to work with them. So, the review on their synthesis together with the biological activities can provide compact information in a single place and be a step to motivate towards this evergreen concept for researchers and chemists to work with them more and more for further development.

5. ACKNOWLEDGEMENT

The authors would like to express their gratitude to Head of Institution and Department for their constant support and guidance

Conflict of Interest

The authors confirm that the contents of this review article present no conflicts of interest.

6. REFERENCES

1. Sahiba N, Sethiya A, Soni J, Agarwal D, Agarwal S, *Top in Cur Chem*, 2020; **378**:34.
2. Zhang Q, Zhou H, Zhai S, Yan B, *Curr Pharm Des*, 2010; **16:**1826-1842.

3. Havrylyuk D, Zimenkovsky B, Vasylenko O, Lesyka R, *J Heterocycl Chem*, 2013; **50:**55-62.
4. Osmaniye D, Levent S, Ardıç CM, Atlı O, Ozkay Y, Kaplancıklı ZA et al. *Phos Sulf Sili Rel Elem*, 2017; **193:**249-256.
5. El-Gaby MSA, Ismail ZH, Abdel-Gawad SM, Aly HM, Ghorab MM, *Phos Sulf Sili Rel Elem*, 2019; **184:**2645-2654.
6. Agarwal S, Agarwal DK, Gautam N, Agarwal K, Gautam DC, *J Kor Chem Soc*, 2014; **58:**33-38.
7. Sankar PS, Divya K, Padmaja A, Padmavathi V, *Med Chem*, 2017; **7:**340-347.
8. Deep A, Kumar P, Narasimhan B, Ramasamy K, Mani V, Mishra RK, Majeed ABA, *Curr Top Med Chem*, 2015; **15:**990-1002.
9. Patel KH, Mehta AG, E J Chem, 2006; **3(13):**267-273.
10. Geronikaki AA, Lagunin AA, Hadjipavlou-Litina DI, Eleftheriou PT, Filimonov DA, Poroikov VV et al. *J Med Chem*, 2008; **51:**1601-1609.
11. Ma L, Xie C, Ma Y, Liu J, Xiang M, Ye X et al. *J Med Chem*, 2011 ; **54:** 2060-2068.
12. Barros CD, Amato AA, de Oliveira TB, Iannini KBR, da Silva AL, da Silva TG et al, *Bioorg Med Chem*, 2011; **18:**3805-3811.
13. Jiang S, Tala SR, Lu H, Abo-Dya NE, Avan I, Gyanda K et al, *J Med Chem*, 2011; **54:**572-579.
14. Nitsche C, Schreier VN, Behnam MAM, Kumar A, Bartenschlager R, Klein CD, *J Med Chem*, 2013; **56:**8389-8403.
15. Romine JL, St. Laurent DR, Leet JE, Martin SW, Serrano-Wu MH, Yang F et al, *ACS Med Chem Lett*, 2011; **2:**224-229.
16. Janovec L, Sabolova D, Kozurkova M, Paulikova H, Kristian P, Ungvarsky J et al, *Bioconjugate Chem*, 2007; **18:**93-100.
17. Jaehyun B, Taegyun P, Hyeyoung K, Minyoung L, Bong-Soo C, *Diabetes Metab J*, 2021; **45(3):** 326-336.
18. Tidwell, Thomas T, *Angew Chem Int Ed*, 2008; **47 (6):** 1016.
19. Brabandt WV, Dejaegher Y, Kimpe ND, *Pure Appl Chem,* 2005; **77(12):** 2061-2071.
20. Mehta PD, Pathak AK, *Int J Pharm Tech Research*, 2012; **4(2):** 676-688.
21. Bandyopadhyay D, Cruz J, Yadav RN, Banik BK, *Molecules,* 2012; **17:**11570 - 11584.
22. Kumar A, Rajput CS, *Eur J Med Chem*, 2009; **44:** 83-90.
23. Chavan AA, Pai NR, *Molecules*, 2007; **12(11):** 2467-2477.
24. Bisacchi GS, Slusarchyk WA, *Bioorg Med Chem Lett*, 2004; **14:** 2227-2231.
25. Goel RK, Mahajan MP, Kulkarni SK, J Pharm and Pharma Sci, 2004; **7(1):**80-83.
26. Stephane G, Moreno G, Georges D, Jacqueline M, *Bio &Med Chem,* 2004; **12:** 129-138.
27. Goel RK, Singh A, Naidu PS, Mahajan MP, Kulkarni SK, *J Pharm and Pharmac Sci,* 2005; **8:** 182-189.
28. Narute AS, Khedekar PB, Bhusari KP, *Ind J Chem*, 2008; **47B:**586-591.
29. Goel RK, Mahajan MP, Kulkarni SK, *J Pharm and Pharmac Sci*, 2004; **7(1):**80-83.
30. Madhu G, Jayaveera KN, Ravindranath LK, Santosh Kumar B, Nagarjuna R, *Int J Chem Tech Res*, 2013; **5(5):** 2381-2389.
31. Veinberg G, Shestakova I, Vorona M, Kanepe I, Lukevics E, *Bioorg Med Chem Lett,* 2004; **14(1):** 147-150.
32. Banik BK, Banik I, Becker FF, *Bioorg Med Chem,* 2005; **13:** 3611 - 3622. 14.
33. Beauve C, Bouchet M, Touillaux R, Fastrez J, Marchand-Brynaert, *J Chem Informat,* 2000; 31(4).
34. Wang Y, Zhang H, Huang W, Kong J, Zhou J, Zhang B et al. *Euro J Med Chem*, 2009; **44(4):** 1638-1643.
35. Gerard S, Dive G, Clamot B, Touillaux R, Marchand-Brynaert, *J Tetrahedron,* 2002; **58:** 2423-2433.
36. Iacopetta D, Ceramella J, Catalano A, Saturnino C, Bonomo MG, Franchini C, Sinicropi MS et al. *Appl Sci* 2021; **11:**1877.
37. Punekar NS, *ENZYMES: Catalysis, Kinetics and Mechanisms*, *Springer,* Singapore, 2018; eBook ISBN978-981-13-0785-0.
38. Archana, Sachin S, *Drug Res (Stuttg),* 2019; **69(8):**445-450.
39. Elkanzi NAA, Solieman HA, Khalafallah AK, *Phos Sulf Sili,* 2007; **182:**1483-1496.
40. Salama EE, *BMC Chem*, 2020; **14(1):**30
41. Chadha N, Bahia MS, Kaur M, Silakari O, *Bioorg Med Chem*, 2015; **23(13):**2953-2974.
42. Doran WJ, Shonle HA, *J Org Chem,* 1988; **3(3):**193-197.
43. Manjal SK, Kaur R, Bhatia R, Kumar K, Singh V, Shankar R et al, *Bioorg Chem*, 2017; **75:**406-423.
44. Halimehjani Z, Marjani K, Ashouri A, *Tetra Lett*, 2012; **53(27):**3490-3492.

45. Cunico W, *Tetra Lett,* 2007; **48:**6217-6220.
46. Vijayakumar R, Ilango K, Arunkumara S, Puratchikody A, *Int J Chem Sci,* 2008; **6(3):** 1213-1222.
47. Shah SH, Patel PS, *Res J Chem Sci,* 2012; **2(7):** 62-68.
48. Metwally NH, Rateb NM, Zohdi HF, *Gr Chem Lett rev*, 2011, **4(3):**225-228.
49. Iwao J, Tomino K, *J Pharm Soc Japan* ,1956; **76:**755.
50. Tidwell, Hugo TT, *Ang Chemie Int Ed*, 2008; **47 (6):** 1016.
51. Kumar S, Kumar P, Sati N, *J Pharm Bioallied Sci*, 2012; **4(3):** 246-249.
52. Hussam HS, Munther Abdul A, Alyaa AA, *Misan J Aca St,* 2014.
53. Khanam R, Kumar R, Hejazi II, Shahabuddin S, Meena R, Jayant V et al, *Apoptosis,* 2018; **23(2):**113-131.
54. Dragostin OM, Lupascu F, Vasile C, Mares M, Nastasa V, Moraru RF, Pieptu D et al. *Molecules,* 2013; **18(4):**4140-57.
55. Pushkal S, Sharma R, Srivastava SK, Srivastava SD, *quim. nova*, 2012; **35(5):**914-919.
56. Kamal V, H. B. Naik, *E-J Chem*, 2004; **1(5):**272-276.
57. Maaroof Z, *Springer-Verlag Wien, Chemical Monthly*, 2014; **145(9):**1495-1499.
58. Taj T, Kambale RR, Gireesh T, Badami BV, *J Chem Sci,* 2011; **123(5):** 657-666.
59. Marton J, Enisz J, Hosztafi S, Tmar T, *J Bioorg Med Chem Letters,* 2001; **11(37):**1793-1796.
60. Ardeshir K, Hojat V, Maryam S, Hossein A, *J Sul Chem*, 2014; **35(3):** 270-278.
61. Monforte P, *Bioorg Med Chem Letters*, 2001; **11:**1793-1796.
62. Rao, *IL Farmaco*, 2002; **57:**747-751.
63. Rao, *IL Farmaco*, 2004; **59:**33-39.
64. Balzarini J, Orzeszko-Krzesińska B, Maurin JK, Orzeszko A, *Eur J Med Chem*, 2009; **44(1):** 303-11.
65. Brown FC, Bradsher CK, Bond SM, *Ind Eng Chem*, 1953; **45:**1030.
66. Zhou H, Wu S, Zhai S, Liu A, Sun Y, Li R et al, *J Med Chem,* 2008; **51(5):**1242-51.
67. Gududuru V, *Bioorg Med Chem Lett*, 2004; **14:**5289-5293.
68. Vazzana I, Terranova E, Mattioli F, Sparatore F, *Arkivoc*, 2004; **(v):**364-374.
69. Kumar A, Rajput CS, Bhati SK, *Bioorg Med Chem*, 2007; **15:** 3089-3096.
70. Junne SB, Kadam AB, Zangade SB, Shinde SL, Vibhute YB, *Int Multidiscip Res J*, 2012; **2:**44-47.
71. Hussain S, Jadhav S, Rai M, Farooqui M., *Int J Drug Des Discov*, 2011; **2:**527-532**.**
72. Niamh O'B, Miriam C, Lisa MG, Orla B, *J Med Chem*, 2010; **53(24):**8569-84.
74. Reddy D, Jamullamudi R, *Pharma Chemica*, 2013; **5:**235-240.
75. Bisacchi GS, Slusarchyk WA, Bolton SA, Hartl KS, Jacobs G, Mathur A et al, *Bioorg. Med. Chem. Lett,* 2004; **14:**2227-2231.
76. Cainelli G, Galletti P, Garbisa S, Giacomini D, Sartorb L, Quintavalla A, *Bioorg Med Chem*, 2005; **13:** 6120-6132.
77. Santosh SC, Puranik M, Virupaksha AB, Haldar A, Ingle VN, Chandrashekhar DU et al, *Bioorg Med Chem Lett*, 2010; **20:** 3640-3644.
78. Kumar S, Kaur H, Kumar A, *Arab J Chem*, 2012; **5:**475-484.
79. Navarro GG, De Vega MJP, Lopez MTG, Andrei G, Snoeck R, Clercq ED et al, *J Med Chem*, 2005; **48:** 2612-2621.
80. Singh GS, Mbukwa E, Pheko T, *ARKIVOC*, 2007; **9:**80-90.