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A Review of the Synthesis and Biological Activities of a Multitarget Core of Unicyclic β-Lactam

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Abstract

The most significant and fascinating publications on the synthesis of novel β-lactam compounds with various biological activities that have been released since 1977 are comprehensively covered in the current section. The various synthetic tactics that are accessible are discussed, including both new and well-established but effective and adaptable approaches. Simple changes to one or more substituents connected to the β-lactam nucleus's nitrogen and carbon atoms were taken into consideration as a different synthetic procedure for more intricate and multifunctional compounds. In this article, other marketed β-lactam derivatives are also expressed. The biological activity of this strained four-membered heterocycle is, in fact, well known and widely reviewed to be solely dependent on the type of substituent groups that alter the reactivity towards the molecular active sites, thereby increasing or decreasing the likelihood of interaction with the substrates. An overview of the most important pharmacological and biological uses of 2-azetidinones is finally presented.

Keywords: Unicyclic β-Lactam, Cyclization Procedure, Biological Significance

INTRODUCTION

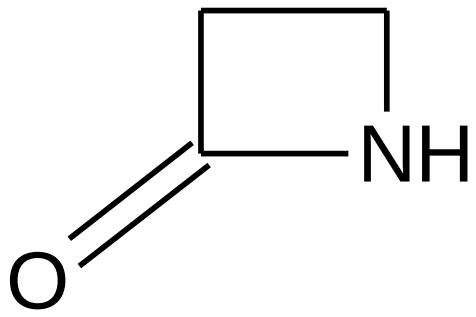
A crucial structural motif in organic chemistry and an essential component of pharmaceuticals is the beta-lactam ring[1]. It serves as a cornerstone in the synthesis[2-5] of a wide variety of physiologically active chemicals due to the peculiar reactivity and characteristics that are imparted by its particular atomic configuration. In order to fully understand the chemistry of the beta-lactam ring, this page aims to explain its production, reactivity, synthesis, biological activity and applications. After seventy years of steady advancement following Fleming's unintentional discovery of the mould that produced penicillin, the beta-lactam class of chemicals is currently the most successful example of using natural products in chemotherapy. The synthesis of cephalosporin[6-7] by Cephalosporium acremonium, the production of cephamycin, clavam, and carbapenem[8] by actinomycetes, and the production of monocyclic beta-lactam[9-12] by actinomycetes and unicellular bacteria all followed the discovery of penicillin by Penicillium chrysogenum. Each of these groups has produced items that are valuable for

medicine and has helped people throughout the world experience less pain and suffering. Research on the microbiology, biochemistry, genetics, and chemistry of these substances has continued to the present, and both lone researchers and collaborative groups from business and academia have made significant contributions. The most significant antibiotics available to medicine were made possible by the discovery of penicillin, which also ushered in the age of wonder medications. The potency, spectrum, effectiveness against resistant[13-18] infections, stability, and pharmacokinetic features of these drugs have all improved as a consequence of ongoing studies. Significant progress is being made in the study of structural and regulatory biosynthetic[19-21] genes, as well as metabolic engineering of the relevant pathways. In the clinic, novel semi-synthetic substances particularly those intended to prevent the emergence of resistance[22-23] are being investigated, and their peculiar non-antibiotic properties are being investigated. The beta-lactams are 70 years old, yet they have not reached their retirement years yet.

STRUCTURAL CHARACTERISTICS

The nitrogen atom's position in relation to the carbonyl group—at the beta-carbon position—gives the term beta-lactam its origin. This structural charecterstics[24-27] gives the ring a distinctive reactivity and adds to its significance in different chemical and biological processes.

The beta-lactam ring's conformational features[28-31] are crucial to both its functional properties and reactivity. Due to the atoms' close proximity, there is a large amount of ring strain because the bond lengths and angles are not perfect. The beta-lactam ring is more vulnerable to numerous transformations because of this strain's unique reactivity.



(azetidin-2-one)

REACTIVITY OF BETA LACTAM RING

Because of their distinct structural traits, beta-lactam rings' reactivity is an intriguing and important feature of their chemistry. The four-membered cyclic configuration of the ring's inherent strain and the polarity that the carbonyl group adds together produce a unique reactivity that serves as the basis for a wide variety of chemical reactions.Beta lactam antibiotics electrophilic behavior is influenced by the

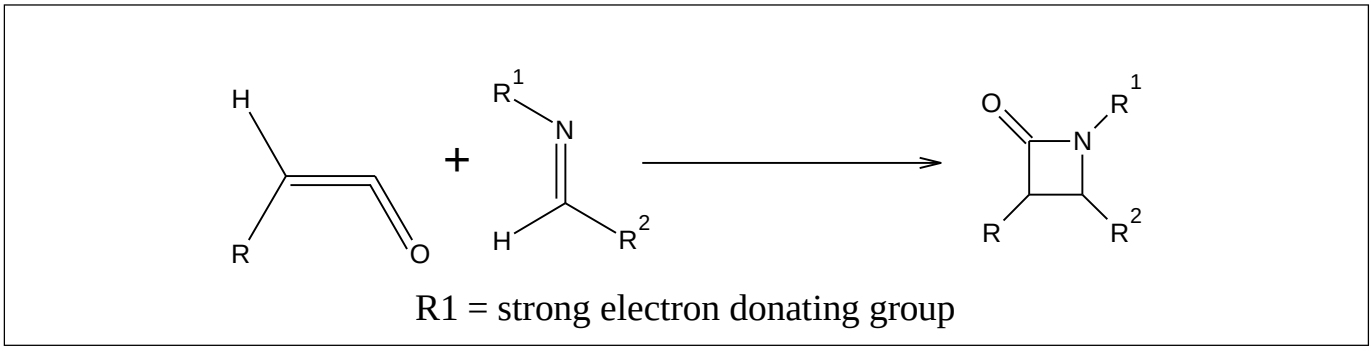
carbonyl group that is present in the beta-lactam ring. The carbonyl group's electron-withdrawing oxygen atom makes the carbonyl carbon vulnerable to nucleophilic assault by species rich in electrons. The introduction of various functional groups onto the beta-lactam scaffold is made possible by the development of new bonds as a result of this nucleophilic attack. The beta-lactam ring can be modified and reprivatized thanks to the carbonyl group's reactivity in a variety of chemical processes.The stretched structure of the beta-lactam ring permits intramolecular reactions in addition to nucleophilic attack at the carbonyl carbon. A complex molecular architecture can be produced by the ring strain by encouraging the development of additional bonds inside the ring system itself. This characteristic is frequently used in the creation of unique synthetic techniques for the creation of various substances.

BETA-LACTAM RING SYNTHESIS:

The synthesis of beta-lactam rings is a cornerstone in organic chemistry. Various methodologies have been developed to construct this essential framework.

1. The Staudinger synthesis- Scheme 1-

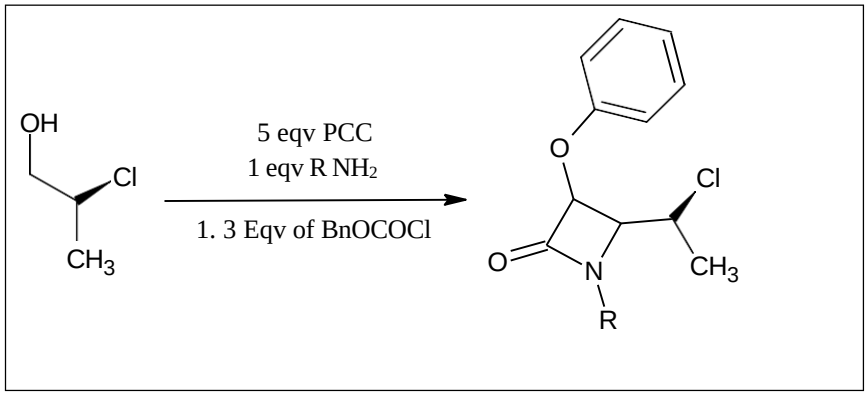
A famous chemical process called the Staudinger Synthesis produces an imine or iminophosphorane intermediate from an azide molecule and a ketone or aldehyde[32]. This reaction, which was named after its discoverer, German chemist Hermann Staudinger, is crucial both historically and practically for the synthesis of organic compounds.



R1 = strong electron donating group

Scheme 2

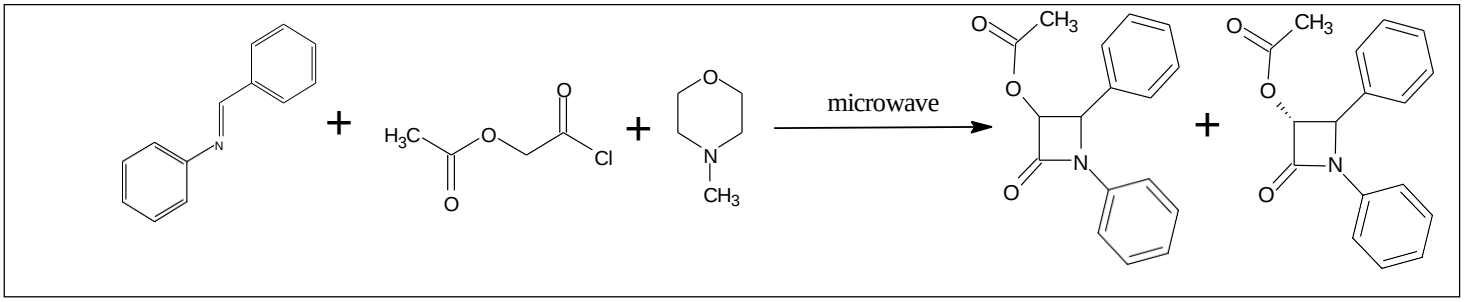
It has been reported that chiral 2-azetidinones can be produced in one pot, starting with (2S)-chloro-1-propanol. The (2S)-chloropropanal was obtained by treating this latter with 5 equivalents of pyridinium chlorochromate in dichloromethane at room temperature, and it was then treated with 1 equivalent of amine and 1.5 equivalents of MgSO4 to produce the (S)-N-(2chloropropylidene)amines. Finally, under Staudinger conditions, the corresponding -lactams were produced by reacting the chloropropylideneamines with 1.3 equivalents of benzyloxyacetyl chloride.



Microwave assisted beta lactam Synthesis

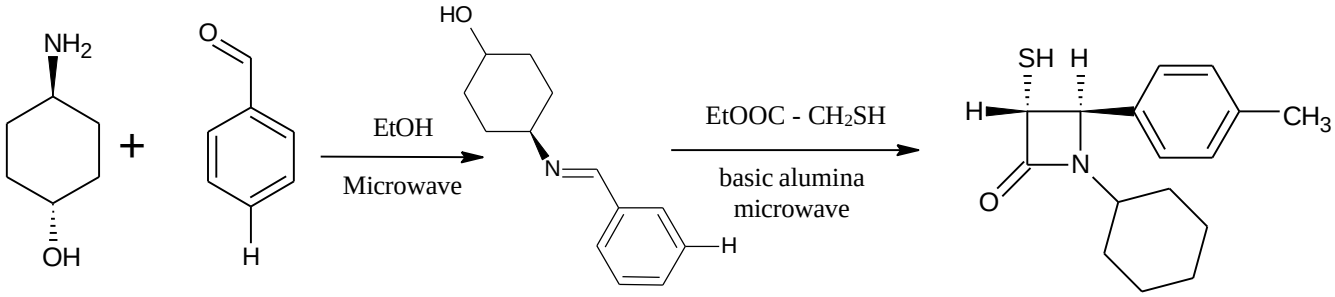
Scheme 3-

With the use of a CEM automated microwave and a mixture of cis and trans -lactams, diarylimine was reacted with acetoxy acetyl chloride in the presence of N-methylmorpholine, and a 70% yield was produced. A combination of two -lactams was created within 10 minutes using a microwave-induced technique at modest power settings. Regardless of the solvent employed, the reaction occurs at -78 degrees Celsius with the sole result being available at ambient temperature. The microwave power settings, reaction temperature, and solvent type all affect the ratio of -lactam production. Trans-lactam production is favoured by high temperature and power settings. Notably, trans -lactam production is favoured by non-polar solvent.



Scheme 4-

When 4 amino cyclo hexanol reacts with benzaldehyde in the presence of ethanol while being microwave assisted, an intermediate is created that, when exposed to the microwave in the presence of basic alumina, transforms into (3R,4R).-1-cyclohexyl-

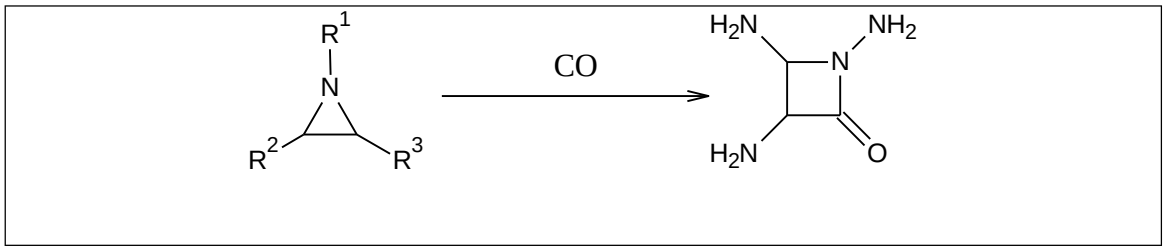


4-(4-methylphenyl)beta lactam ring-containing derivative -3-sulfanylazetidin-2-one.

Alper Reaction –

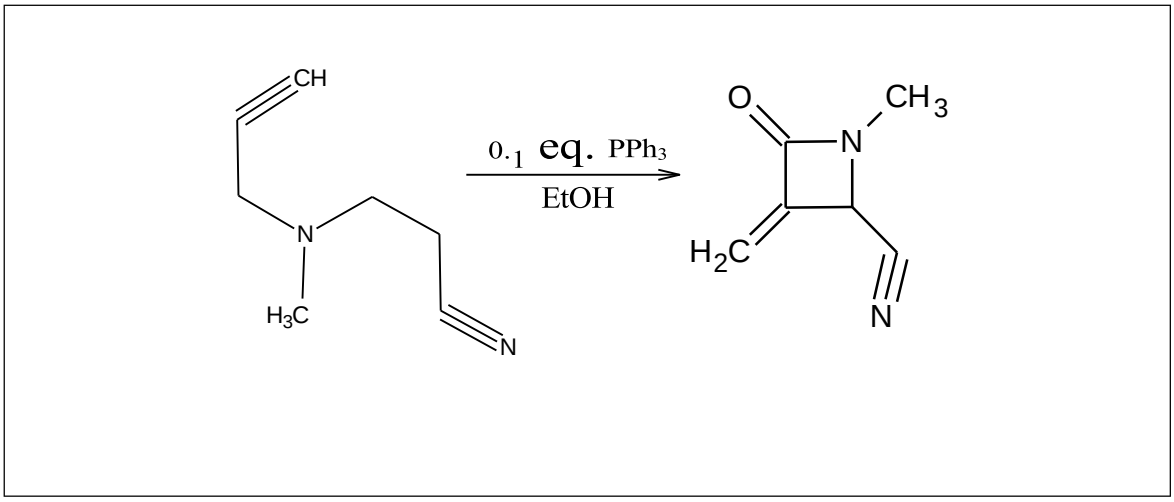
Scheme 5-

The ring expansion of aziridines by metal-catalyzed carbon monoxide (CO) insertion occurs during the Alper Reaction[33].



Scheme 6-

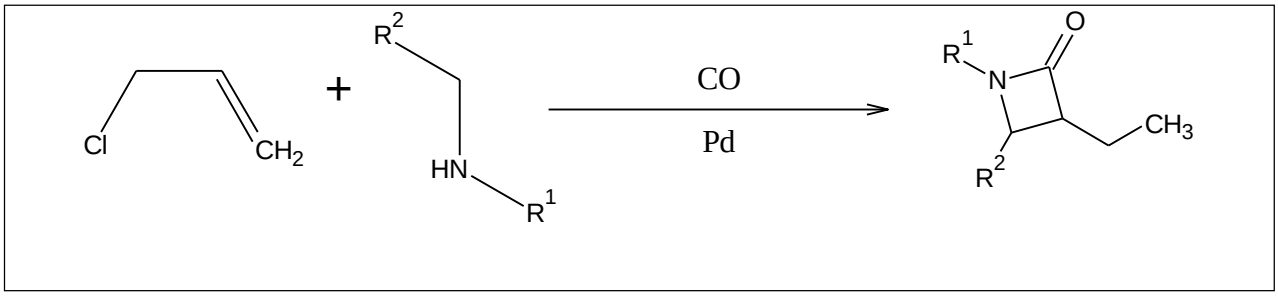
The Cu(I)-catalyzed intramolecular C-N coupling of amides with vinyl bromides allowed for a versatile and extremely effective synthesis of 4-alkylidene-2-azetidinones. Under copper catalysis, it was discovered that this 4-exo ring closure was essentially favored over other cyclization processes (5-exo, 6-exo, and 6-endo).



Torii Reaction-

Scheme 7-

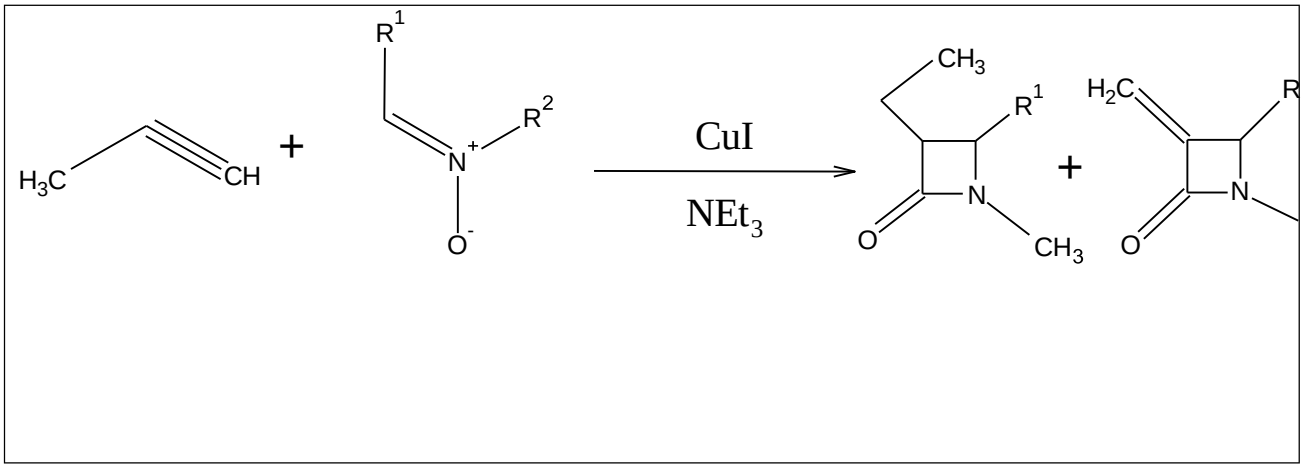
The Torii Reaction's [2+2] cycloaddition of alpha-amino nitriles and ketenes is a crucial step in the creation of -lactam rings. Organic chemists can gain a lot from this reaction to access a variety of beta-lactam compounds for application in the synthesis of natural products and medicinal chemistry.



The Kinugasa reaction-

Scheme 8-

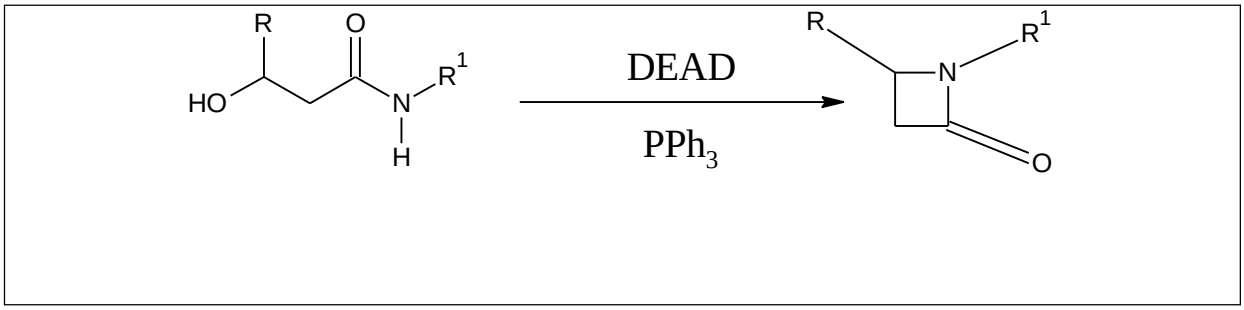
Use of copper salts as catalysts in the Kinugasa Reaction, a versatile chemical reaction, couples nitrones with propargyl moieties. Valuable beta-lactam molecules are created as a result of this reaction. The Kinugasa Reaction is especially renowned for its capacity to produce -lactams, significant structural motifs present in a variety of natural products and biologically active substances. The process offers a simple starting material, mild reaction conditions, and a straightforward and effective pathway to these molecules.



Mitsunobu reaction-

Scheme 9-

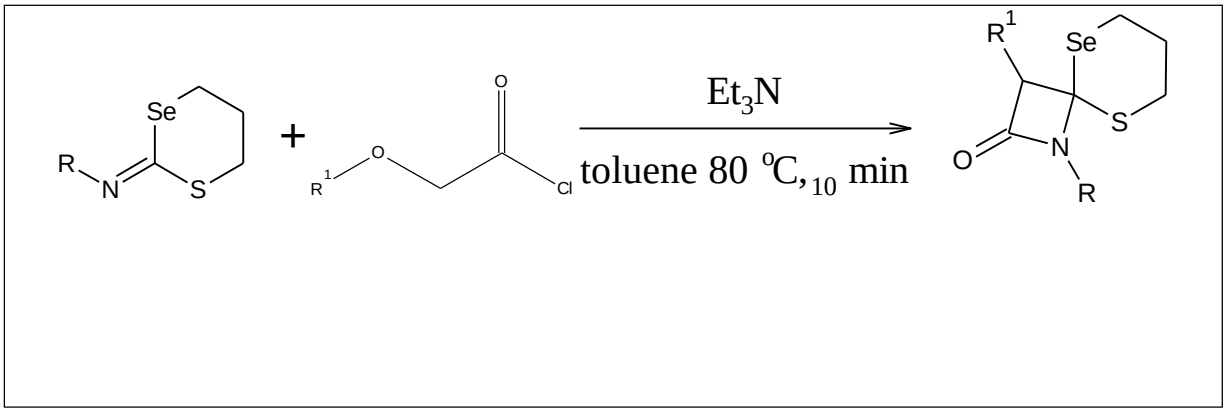
It is an intramolecular cyclization reaction of amides in presence of DEAD Diethyl azo dicarboxylate) and PPh3 (triphenyl phosphine) to give beta-lactam.



SYNTHESIS OF SPIRO FUSED BETA LACTAM

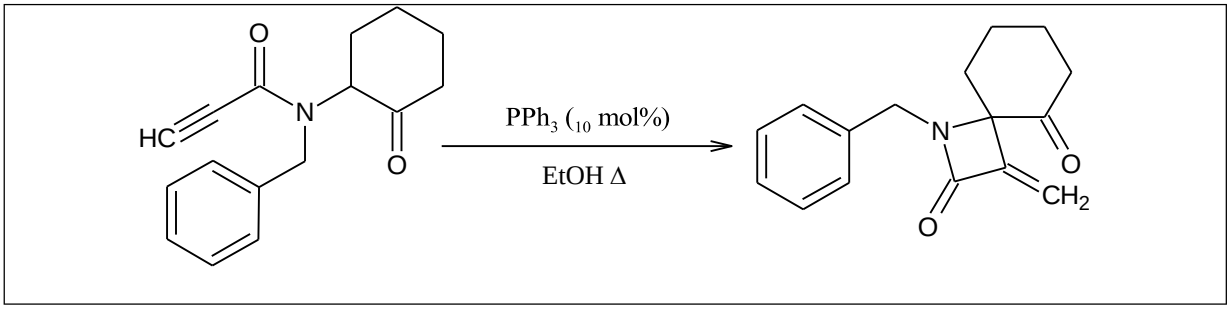
Scheme 10-

Z/E isomers of -selenium substituted exocyclic imines with different types of acyl chlorides, such as methoxy-, choro-, propionyl-, phenyl-, cyclohexyl-, phenoxy-, and p-chlorophenoxyacetyl chloride, have been used to study the synthesis of Spiro-fused seleno-lactams. Spiro-lactams were produced in high yields as stereoisomer mixes by the reaction of exocyclic imines with acetyl chlorides.



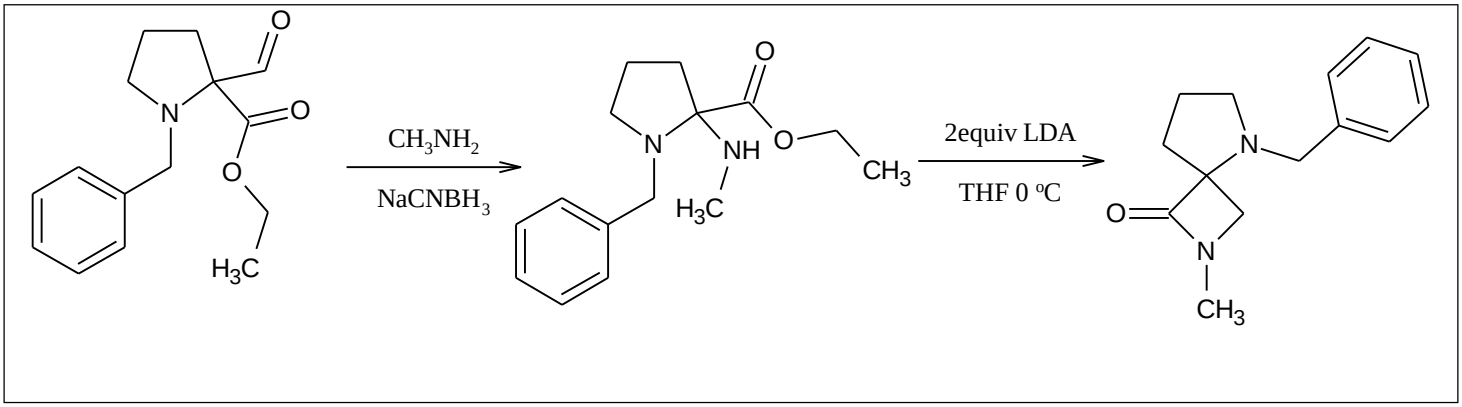
Scheme 11-

Propiolamide was converted to the equivalent spiro-3-methyleneazetidin-2-one in ethanol under reflux by cycling it with triphenylphosphine as a catalyst. The presence of steric hindrance during the 4-exo cyclization stage may provide an explanation for the low yield of Spiro-beta-lactam.



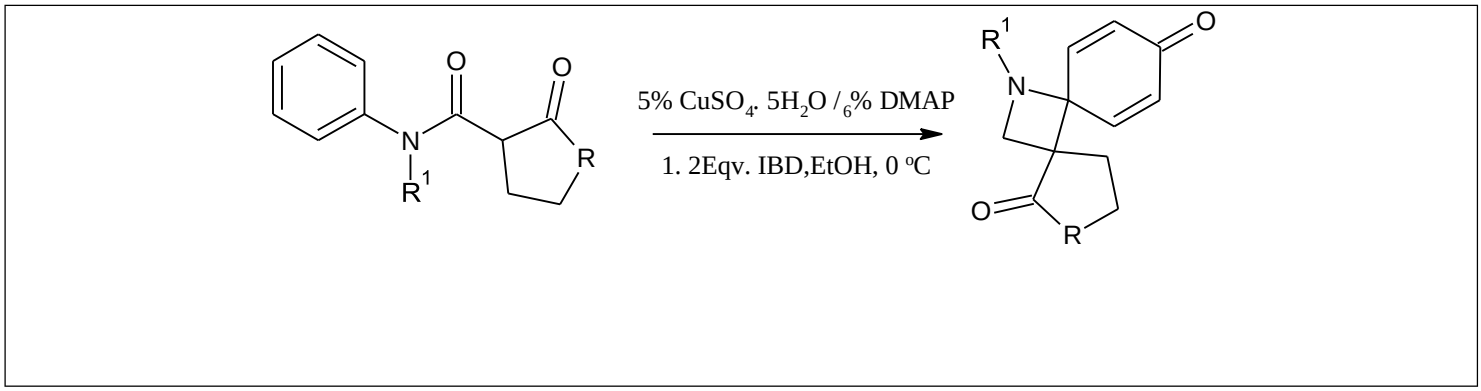
Scheme 12-

The -amino ester was produced by treating pyrrolidine aldehyde with the reducing agent NaCNBH3 and methylamine. The required Spiro--lactam was then produced by cyclizing the molecule with two equivalents of the strong base LDA (Lithium diisopropylamide).



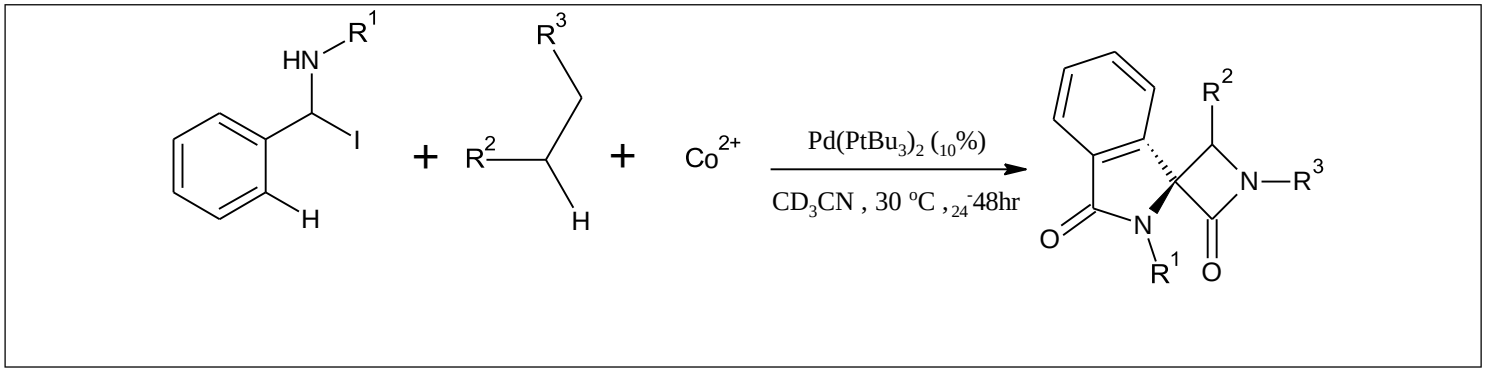
Scheme 13-

the synthesis of several spiro-4-cyclohexadienone β -lactams with cyclopentanone, γ-lactone and γ -lactam side chains on their C3 position beginning with the matching amides.



Scheme 14-

the multi-component palladium-catalyzed synthesis of Spiro cyclic –beta lactams with participation of imines, ortho-iodo-substituted aryl imines, and CO. By using X-ray analysis, the structure of the resultant Spiro cyclic -lactams, exhibiting a trans orientation of the aromatic units, was confirmed.

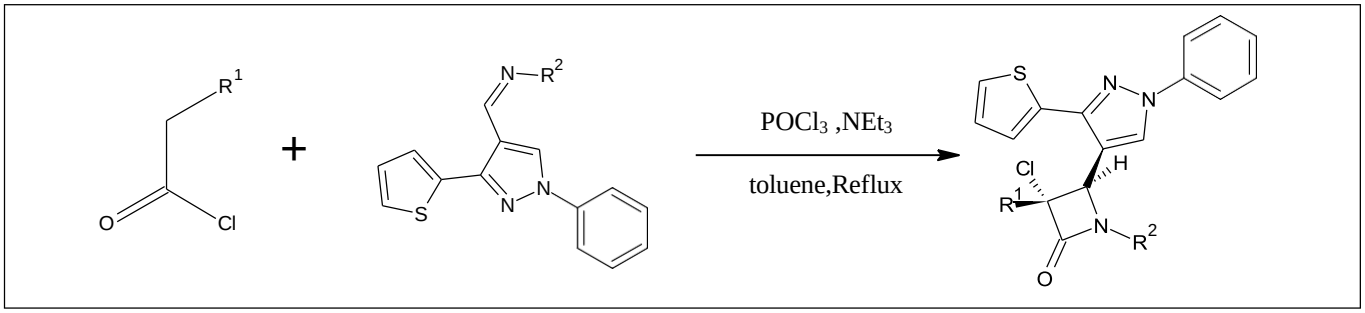


ASYMMETRIC CYCLOADDITION PROCEDURE CATALYSED TO PRODUCE BETA-LACTAMS.

Scheme 15-

Ketene-imine cycloaddition reactions-

In the presence of NEt3 or POCl3/NEt3, (thiophenyl) pyrazol substituted Schiff's bases and 2-substituted ethanoic acid or acid chloride derivatives undergo a Staudinger cycloaddition process to produce the desired beta lactam product.



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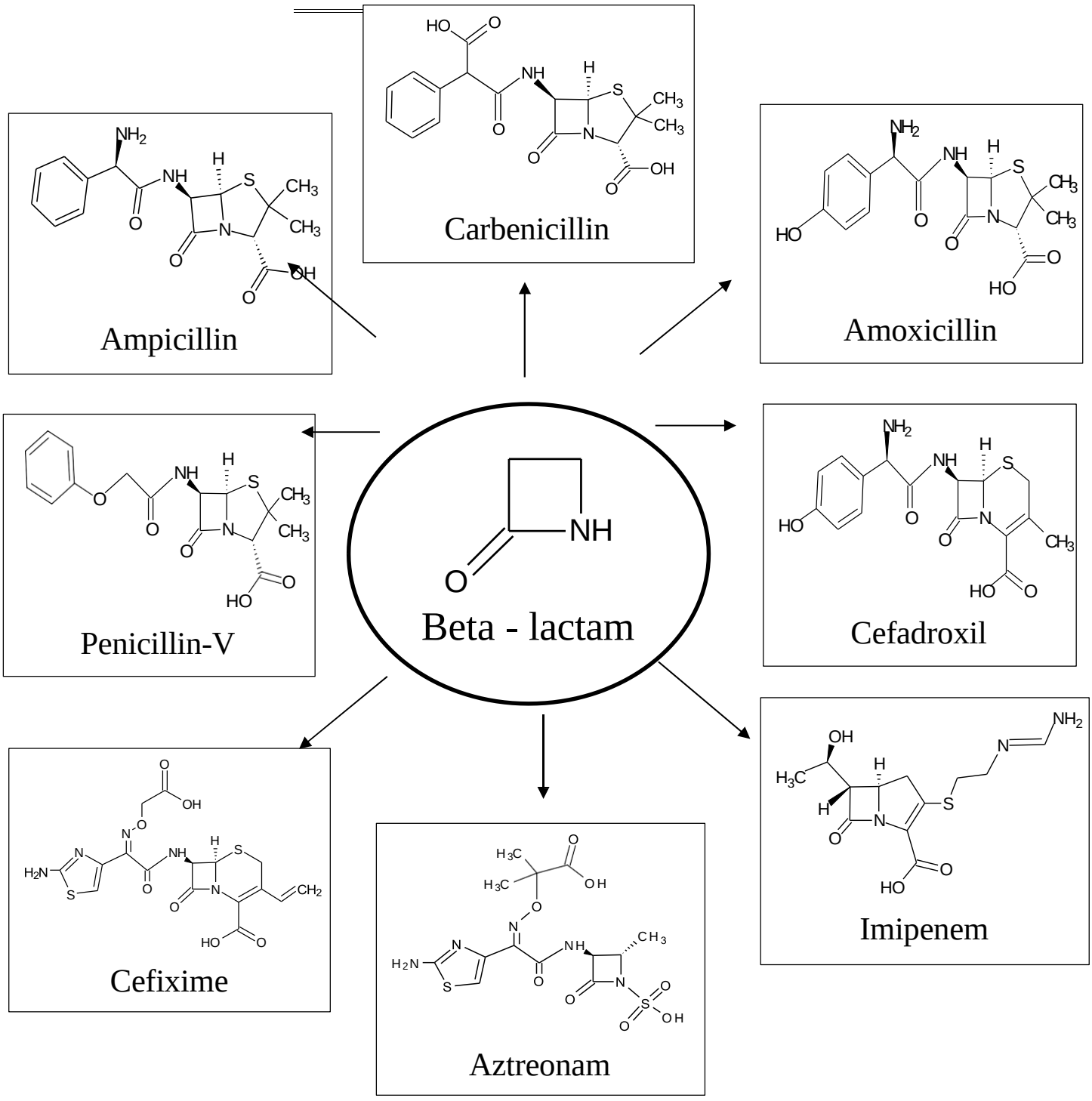


BIOLOGICAL ACTIVITIES OF BETA-LACTAM

An important class of four-membered heterocyclic compounds with a variety of biological functions is made up of azetidine[34-35] and its derivatives. The 2-azetidinone derivatives of azetidines are also known as β-lactams or 2-azetidinones.

Penicillin[36], cephalosporins[37], carbapenems[38,39], clavulanic acid[40], and tazobactams[41] are examples of β-lactam antibiotics that have been used extensively as chemotherapy to treat bacterial infections and microbiological disorders.

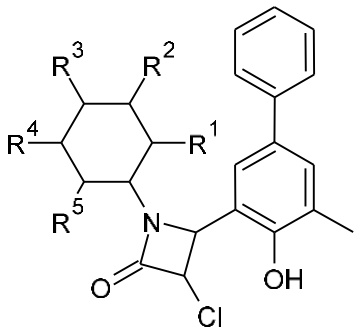
BIOLOGICAL IMPORTANCE

The beta-lactam ring plays a critical role in the manufacture of antibiotics because of its strained and reactive character. This ring is a characteristic of beta-lactam antibiotics, which include penicillin's, cephalosporin's, carbapenem, monobactam. The penicillin-binding proteins (pbps)[42], which are essential for bacterial cell wall construction, are the target enzymes for these antibiotics, and the stretched ring shape improves their affinity for attaching to them. This contact prevents the production of cell walls, which causes bacterial cell lysis and ultimately results in the death of the Microorganisms. Additionally, the manufacture of peptidomimetics and enzyme inhibitors uses the beta-lactam scaffold. Additionally, interest in the utilization of beta-lactam-containing compounds as organo catalysts[43-44] has increased due to their catalytic potential.

BIOLOGICAL ACTIVITIES: -

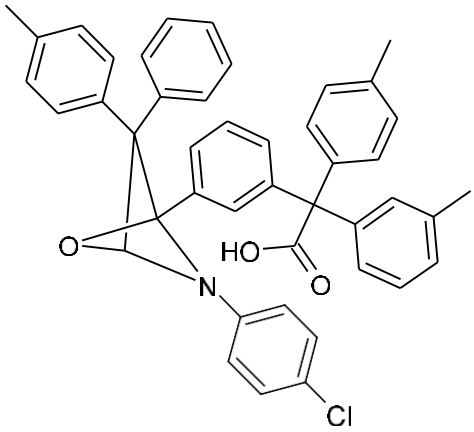
ANTIBACTERIAL ACTIVITY: -

a) Using penicillin G as the reference antibiotic for comparison, a variety of 3-chloro-4-(4 - hydroxy - 5- iodo biphenyl - 3 - yl) -1 (substituted phenyl) azetidin-2-one 15 derivatives[45] are tested for antibacterial activity against Xanthomonas citri, E. coli, Erwinia carotovora, and B. With the exception of B. subtilis, some of the compounds were shown to be almost as active as or more active than the standard against all of the tested microorganisms.

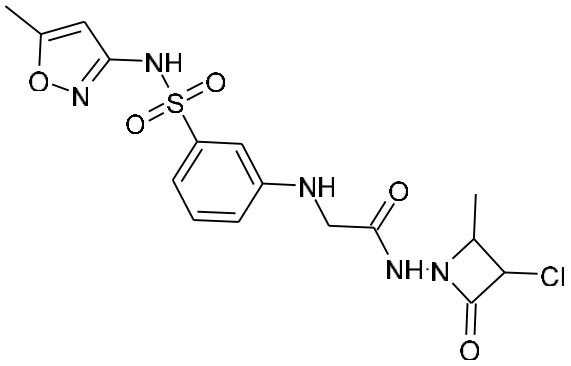


R^1, R^2, R^3, R^4, R^5 = H,H,NO_2,H,I ; H,I,H,NO_2;
H,H,I,H,Cl ; H,H, Cl,H,I ;
Cl, H,I,H,Cl ; I,H,Me,H,I;
I,H,NO_2,H,I ; Me,I,H,NO_2,H;
H,H,COOH,H,I; I,H,H,NO_2,H
H,H,H,Cl,I ; H,H,I,H,COOH

b) A number of novel 2-azetidinone compounds were produced through the thermal breakdown of 2-diazo-1, 2- di aryl ethanones[46] and the interactions of N-salicylidene amines with di aryl ketenes. The products were tested for their antibacterial and antifungal activity against Saccharomyces cerevisiae, Candida mycoderma, E. coli, P. aeruginosa, B. subtilis, and S. aureus. The compounds showed mediocre to excellent.



c) VariousN-[3-chloro-4-(4-substitutedphenyl)-2-oxoazetin-1-yl]Sulfadiazine and sulfamethoxazole are used as the starting materials for the production of -2- (N'-5-methyl-3-isoxazolyl) sulphonamides[47], which are then screened. The compounds were tested against four different bacterial cultures, including S. aureus, E. coli, P. aeruginosa, and B. subtilis, as well as one fungus culture, C. a0lbicans, for their antibacterial and antifungal properties. Standards for antibacterial and antifungal activity included griseofulvin, ampicillin, and sulfadiazine. Some of the synthetic compounds had exceptional antibacterial and antifungal activity that were on par with those of common pharmaceuticals.

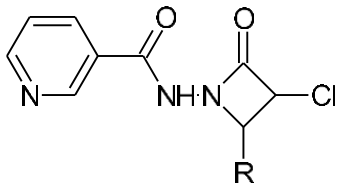


R= 2- OHph
4- OMeh
4-NMe_2Ph

ANTI TUBERCULAR ACTIVITY: -

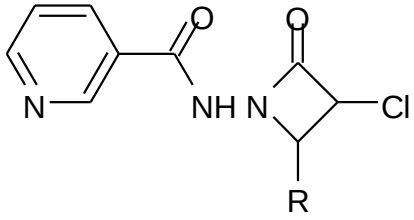
The leading cause of death worldwide continues to be tuberculosis (TB), which is typically caused by Mycobacterium tuberculosis. About 8.7 million cases of TB were reported in 2011, and 1.4 million individuals died from the disease; 0.43 million of the fatalities were due to HIV-associated TB.

a) A number of N-[3-chloro-4-(aryl)-2-oxoazetidin-1-y]-pyridine-4-carboxamides[48] were tested for their ability to inhibit the growth of the standard strain H37Rv and two additional human strains, Human strain-I and Human strain-II, which were obtained from tuberculosis patients with pulmonary involvement. Isoniazid was the go-to medication. Significant antimycobacterial activity was displayed by the substances.



R= Aromatic
4-OHPh
4-MePh
4-OMePh
4-NMePh

b) The creation of brand-new N-(3-chloro-2-oxo-4- substitutedazetidin-1-yl) isonicotinamide derivatives[49] and their analysis using QSAR as antimycobacterial drugs against M. tuberculosis H37Rv. As reference standards, rifampicin and isoniazid were utilized. The substitution pattern of the aryl and heteryl group at C-4 in relation to antimycobacterial activity has been compared, and it has been found that electron donating groups give better activity while electron withdrawing groups cause less activity.

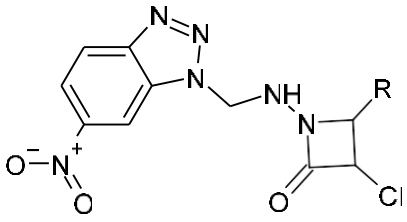


R= Aromatic
4-ClPh
4-NO_2Ph
4-OHPh

4-OH-3-OMePh
2-OHPh
4-OMePh

4-NMe_2Ph, Ph, Furfuryl etc.

c) From 6-nitro-1H-indazole, a novel series of 3-chloro-1-[2-(6-nitro-1Hindazol-1-yl) ethyl] amino-4-(substituted-phenyl)- 2-azetidinones[50] were produced in four steps. Isoniazid and rifampicin were used as reference drugs for the evaluation of antitubercular activity against M. tuberculosis (H37Rv strain). The results showed that compounds with nitro groups were more active than those with chloro or bromo groups. It was discovered that the order of the activity was NO2 > Cl > Br > H.

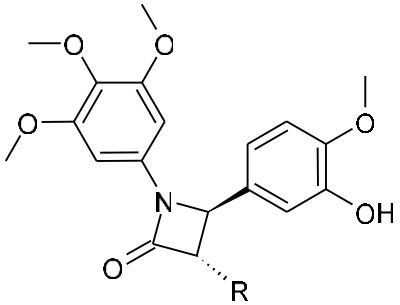


R= Ph,4-ClPh, 3-ClPh,2-ClPh,
4-BrPh,3-BrPh,2-BrPh,
4-NO_2Ph,3-NO_2Ph

ANTI CANCER ACTIVITY: -

Cancer is characterized as a condition in which a collection of aberrant cells proliferates uncontrollably while disobeying the normal laws of cell division. In actuality, the tumor-spreading process known as metastatis is to blame for over 90% of cancer-related fatalities. Both innate (such as inherited mutations, hormones, and immunological disorders) and acquired (such as cigarettes, food, radiation, and infectious organisms) factors contribute to the development of cancer.

A number of azetidin-2-ones substituted at positions 1, 3, and 4 of the azetidinone ring scaffold have also been created and their antiproliferative, cytotoxic, and tubulin-binding properties have been tested. The 3-(2-thienyl) analog I and 3-(3-thienyl) analog II[51], which had IC50 values of 7 nM and 10 nM, respectively, and are comparable to combretastatin A-4, showed the best potency in human MCF-7 breast cancer cells among a variety of heterocyclic derivatives. Normal mouse breast epithelial cells showed no sign of harm. The antiproliferative activity was considerably reduced in the micromolar range when larger, bulkier groups, such as 3-naphthyl derivative and 3-benzothienyl derivative, were present at the 3-position.

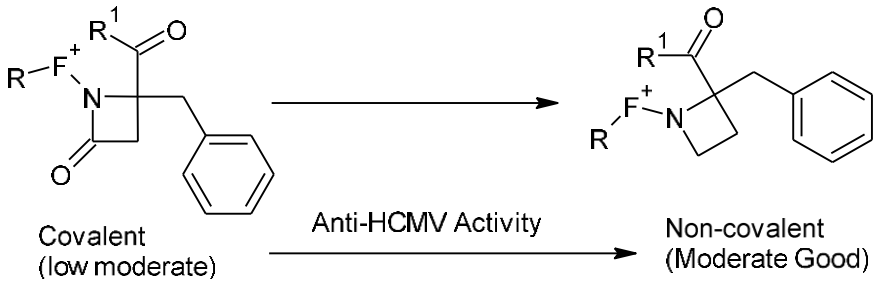


R= 2-thienyl(I)
3-thienyl(II)

HUMAN CYTOMEGALO VIRUS PROTEASE ACTIVITY: -

The herpes virus family includes the common human cytomegalovirus (HCMV). HCMV can appear severely in people whose immune systems have been compromised by a disease, such as late-stage malignancies and AIDS, or by immunosuppressive therapy after organ transplantation, despite the fact that the majority of infections are asymptomatic.

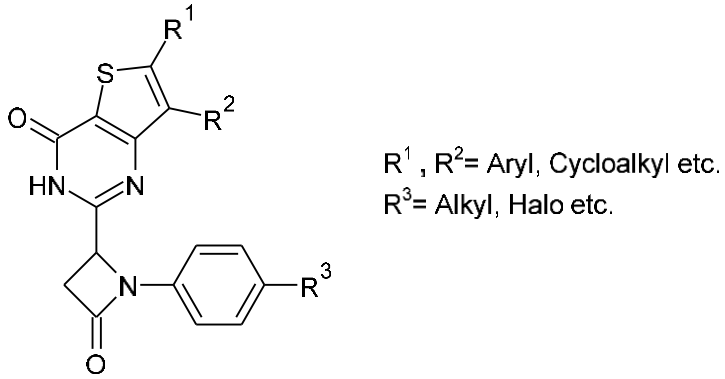
A series of phenylalanine-derived -lactams with 4-carboxylate moiety were created and may be suitable for further interactions with the guanidine group of the Arg165/Arg166 residues[52] of the viral protease. At 10–50 mM, some of the compounds in this series exhibited anti–HCMV action, although with rather substantial toxicity. Strict conditions for anti-HCMV activity included the presence of aromatic 1-acyl groups and a certain hydrophobic character in the vicinity of the 4-carboxylate.



CHOLESTEROL ABSORPTION INHIBITORY ACTIVITY: -

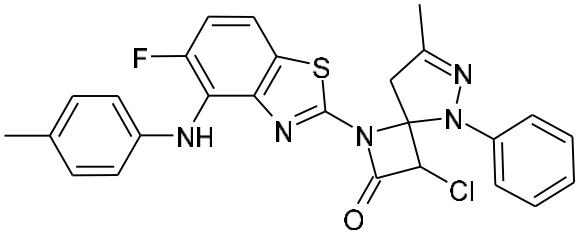
One of the key risk factors for atherosclerosis, associated cardiovascular illnesses, and stroke (and is closely related to mortality and morbidity) is elevated lipid levels. One of the main strategies used to prevent coronary heart disease and stroke is lipid reduction.

A number of unique 2- [1-(substitutedphenyl) - 4-oxo-azetidin-2-yl] compounds[53] have been created from thieno[2, 3-d]-5, 6-disubstitutedpyrimidin-4(3H)-ones. The compounds are 2-substituted thieno [2, 3-d]-pyrimidin-4-ones, which have the potential to be antihyperlipidemic, having the structural characteristics of an azetidin-2-one moiety. They are thienopyrimidine derivatives of -lactams. Wistar albino rats were used to test the compounds' ability to decrease cholesterol. Some of them had noticeable effects on lipid levels.



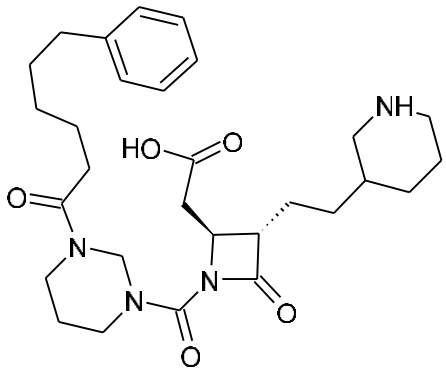
ANTI DIABETIC ACTIVITY: -

The metabolic illness known as diabetes mellitus (DM) is brought on by a problem with insulin secretion, action, or both. Chronic hyperglycemia brought on by an insulin shortage also causes problems with protein, lipid, and carbohydrate metabolism. A compound was created by first condensing 3-methyl-1-phenyl-5-pyrazolone[54] with aminobenzothiazole to create a Schiff base, then cyclizing that base with ClCOCH2Cl to create a -lactam that was then combined with various primary and secondary amines. With acarbose serving as the control for comparison, this was tested for anti-diabetic effectiveness utilizing an amylase inhibitory activity based on colorimetric technique. The chemical 3-chloro-1-(6-fluoro-7-p-tolylaminobenzothiazol-2-yl) is one of them.Triazaspiro[3.4]: -7-methyl-5-phenyl-1,5,6One demonstrated the required activity.



TRYPTASE AND CHYMASE INHIBITORY ACTIVITY: -

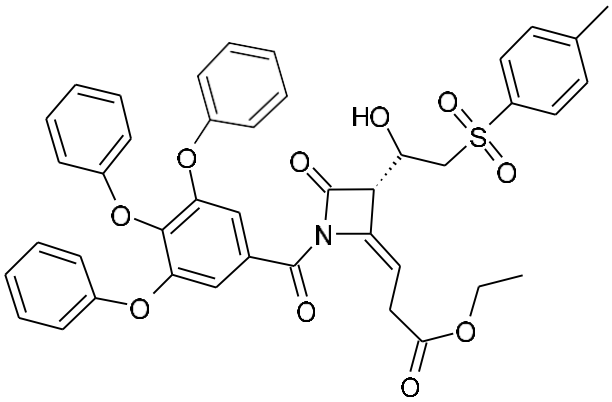
Serine proteases called tryptase and chymase are almost exclusively found in the secretory granules of mast cells. They make up the majority of the protein products in mast cell granules, which contain roughly 50% protein overall. The synthesis of a number of potent β -lactam tryptase inhibitors were carried out in which the guanidine moiety at the ring C-3 position of BMS-363131 and BMS- 363130 was replaced with primary or secondary amine or aminopyridine functionality and found that one of the compound BMS-354326 25[55] having an IC50 for tryptase of 1.8 nM, displayed excellent selectivity against trypsin and most other related serine proteases.



HUMAN LEUKOCYTE ELASTASE INHIBITORY ACTIVITY: -

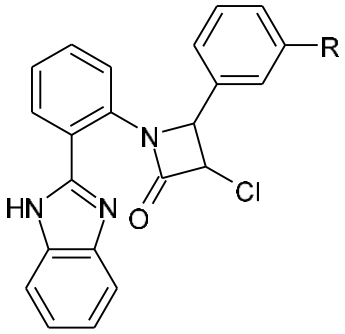
The serine protease known as human leukocyte elastase (HLE) is located in the neutrophil's azurophilic granules. Other names for it include human neutrophil elastase. Elastin and other components of connective tissue can be broken down by them. Acute and long-term inflammatory disorders of the lungs have been linked to an imbalance between HLE and its endogenous inhibitors and the resulting excessive elastin proteolysis.

An N-galloyl-4-alkylidenbeta-lactam[3-[1-(tertbutyldimethylsilanyloxy)ethyl][56] was the most effective substance against elastase. In contrast, a 4-alkyliden b-lactam arylated on the C-3 hydroxy side chain (3, 5-bisbenzyloxy- 4 - hydroxy benzoicacid-1-(2-ethoxycarbonylmethylene-2-oxoazetidin-3-yl)ethyl-ester) with an IC50 of 4 mM was the most effective against MMP-2. High levels of elastase and MMPs inhibition were independently exerted by separate molecules among the 35 drugs evaluated.



ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY: -

The significant heterocyclic -lactam nuclei have been coupled with a variety of heterocyclic templates to produce hybrid structures. The analgesic and anti-inflammatory effects of a series of 1-(2-(1H-benzimidazol-2-yl) phenyl) - 3 - chloro - 4 - (un/substituted phenyl) azetidin-2-ones[57] on acetic acid-induced writhing in mice and carrageenan-induced paw edema in rats were examined. Compared to the common medication nimesulide, one of the compounds (R 14 Cl) shown greater analgesic and anti-inflammatory activity. Synthesized compounds were docked into the active sites of the enzyme COX-II in order to test binding mechanisms and binding affinities. In silico docking analysis and biological screening show a strong connection.

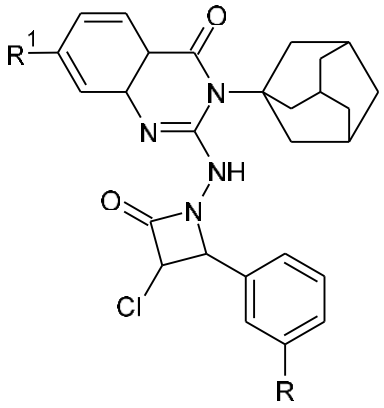


R = H; 2-Cl; 4-F; 2-OH; 4-OH; 2-NO; 4-OMe

ANTI PARKINSONIAN ACTIVITY: -

One of the most prevalent progressive neurological degenerative conditions is Parkinson's disease. In addition to the more recently highlighted non-motor dysfunctions, it is characterized by motor dysfunction such as resting tremor, slowness of movements (bradykinesia), trouble beginning movements (akinesia), rigidity, gait disruption, and postural instability.

A series of 3-amantadinyl-2-[(4-(substituted-phenyl) - 3- chloro - 2 - oxoazetidin - 1 -yl) methylamino] quinazolin-4(3H)-ones[58] are tested for their ability to treat parkinsonism. These substances nearly had the same antitwitching effects as L-dopa. The newly synthesized chemicals also underwent testing for an approximation of the lethal dose (LD50), and it was discovered that the LD50 value was more than 1000 mg/kg.



R^1=H ,R= 3,4-OMe; 2-Cl; 2-Br; 2-OMe; 3-OMe-4-OH; H

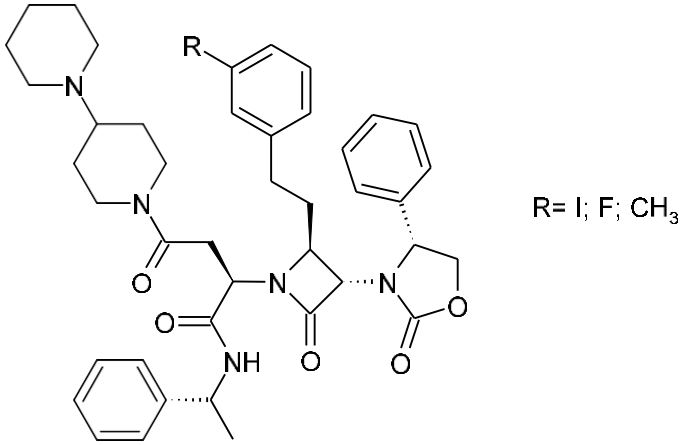
R^1=Br, R^2= 3,4-OMe; 2-Cl; 2-Br; 2-OMe; 3-OMe-4-OH; H

VASOPRESSIN ANTAGONIST: -

Only neurosecretory cells in the central nervous system (CNS) may produce the cyclic non-apeptide arginine vasopressin (AVP). There are three unique AVP receptor subtypes—V1a, V1b, and V2—of which the brain mostly contains V1a, with particularly high concentrations in the cerebral cortex, limbic system, hypothalamus, and brainstem. This precursor should provide access to both the PET (18F, 11C) and SPECT (123I) derivatives of SRX246. (R)-4-[1,4-Bipiperidin]- 10 yl-2-((2R,3S)-2-((E)-3-substitutedstyryl) - 4 - oxo-3-((S)azetidin-1-yl)-2-oxo-4-phenyloxazoli din-3-yl)[59] A highly effective and selective hV1a antagonist is 4-oxo-N-((R)-1)-phenylethyl)butanamides.

These results provide the opportunity to launch a more thorough inquiry employing appropriate

imaging tracers into the function of the human vasopressin V1a receptor in numerous CNS processes. A versatile biologically significant scaffold and synthon for numerous medically significant molecules, -lactam is a desirable target for medicinal chemists worldwide.

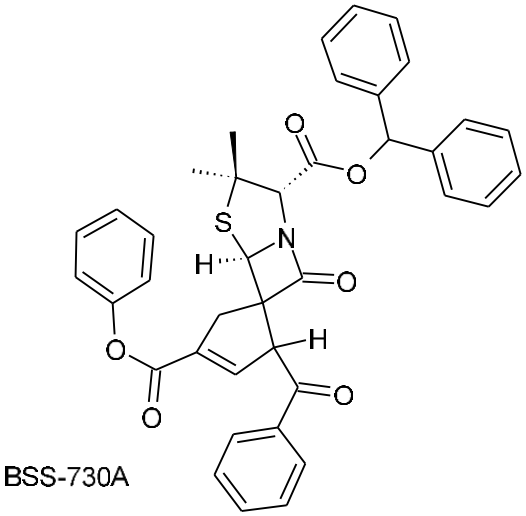


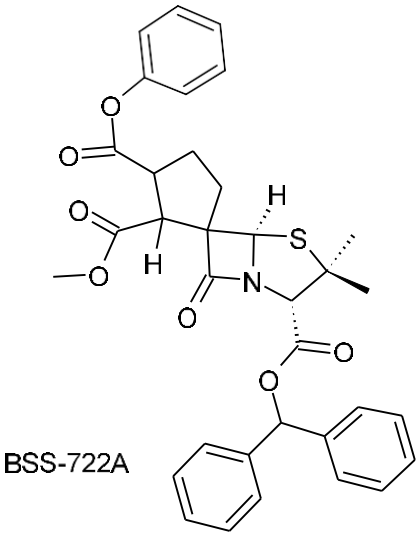
ANTI HIV ACTIVITY: -

Three compounds with antiviral activity, BSS-593, BSS-722A, and BSS-730A, were discovered after the activity of spiro-beta-lactams was assessed in TZM-bl cells in a single-round infectivity assay against numerous HIV-1 and HIV-2 isolates.

While BSS-593 was a weak inhibitor of the primary HIV-1 isolate and had no effect on HIV-2, BSS-722A and BSS-730A[60] were highly active against both HIV-1 and HIV-2 isolates.

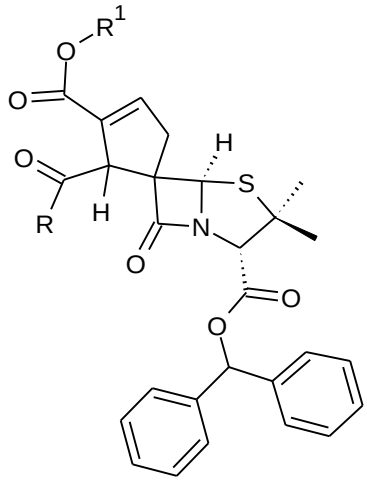
Eight primary HIV-2 isolates that were drug-resistant as well as the control 03PTHCC19 isolate, which is responsive to all currently available antiretroviral medications, were used to assess the effectiveness of BSS-730A. Against all, BSS-730A was quite active. The findings imply that BSS-730A might be helpful in treating infections brought on by HIV isolates that are multidrug resistant.





ANTI PLASMODIAL ACTIVITY: -

Three spiro--lactams with stronger anti-HIV activity, BSS-593, BSS-730A, and BSS-722A, as well as two inactive derivatives, BSS-452 and BSS-1026, were tested for their ability to prevent P. berghei hepatic infection in vitro. BSS-452 and BSS-1026, two molecules without anti-HIV action, also lacked anti-Plasmodium activity, but BSS-593, BSS-730A, and BSS-722A, three compounds with anti-HIV activity, were likewise effective against P. berghei liver stages.It was determined that the substance with the greatest antiplasmodial activity was spiro-lactam BSS-730A[61].



a) R= p-halophenyl with R^1=p-MeOBn
=> Decrease in P.berghei hepatic stage activity

b) R=P-Flurophenyl with R^1=P-MeOBn
=> 1.6-fold increase for P.falciparum blood stage activity.

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