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A REVIEW ON 2-AZETEDINONES

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ABSTRACT

2-Azetidinone, a β-lactam four member heterocyclic compounds involved in research aimed to evaluate new products that possess interesting biological activities.2-azetidinones were highlighted as a potent mechanism based inhibitor of several enzymes like human tryptase, chymase, thrombin, leukocyte elastase, human cytomegalovirus protease and serine protease enzyme. These derivatives also known to possess antitubercular, diuretic , anti-inflammatory, antitumor, anti-HIV, anti parkinsonian, anti diabetic and vasopressin antagonist activity. The present review article focuses on the chemistry and pharmacological actions of various substituted 2-azetidinones with brief synthesis.

Key words: 2-Azetidinone, Biological activities

INTRODUCTION:

2-Azetidines have been extensively investigated by the organic chemists due to their close association with various types of biological activities [1] .It is a four-membered cyclic lactam (ß-lactam) skeleton has been recognized as a useful building block for the synthesis of large number of organic molecules by exploiting the strain energy associated with it. The Staudinger reaction ([2+2] ketene-imine cycloaddition reaction) is regarded as one of the most fundamental and versatile methods for the synthesis of structurally diverse 2-azetidinone derivatives. Azetidine-2-ones also have great importance because of the use of β-lactam derivatives as antibacterial agents recently, some other types of biological activity beside the antibacterial activity have been reported in compounds containing 2-azetidinone ring. Such biological activities include antimicrobial, anti tubercular, anti inflammatory.[2]

Chemistry of 2-Azetidinones

The β-lactam heterocycles are considered as an important contribution of science to humanity. The most widely used antibiotics such as the penicillins, cephalosporins, Carumonam, thienamycin and the nocardicins all contain β-lactam rings.[22]

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Penams: Penicillins are bicyclic structures where the β-lactam ring is fused with a fivemembered thiazolidine ring.

Penems: These differ from penams by the presence of a double bond between the C2and C3 positions. No natural penems have so far been described, but many have been synthesized in the expectation that they would combine desirable properties of penicillin sand carbapenems.

Carbapenams and Carbapenems: These compounds differ from penams and penemsby the presence of a carbon atom at position 1. Many natural and synthetic members of the group have been described, and some of them are currently used in the clinics.

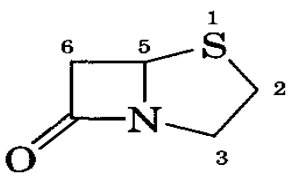
Cephems, oxacephems, and carbacephems:These compounds are characterized by the presence of a β-lactam ring fused with a six membered unsaturated ring, having at position 1 sulfur, oxygen, or a carbon atom, respectively. In particular, the Cephem class has been very prolific in generating good antibiotics, which have found extensive application in the treatment of bacterial infections.

Oxapenams. This class is generally characterized by a very weak antibacterial activity but has found therapeutic applications as inhibitors of bacterial β-lactamases. Its skeleton differs from that of penams by the presence of an oxygen atom at position 1.

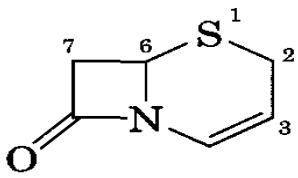
Monobactams. The monocyclic β-lactam is the simplest structure still retaining antibacterial activity.

Physical and Spectroscopic Properties

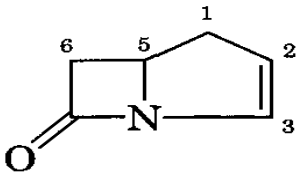
2-Azetidinone is a solid, m.p., 73- 74^0C. It is highly soluble in ethanol and chloroform. The physical state of other β-lactam varies widely with the degree and nature of the substituents. The structural data obtained from X-ray studies using sodium benzyl penicillin shows that all the four bond angles and bond distances have different values. One highly characteristic and useful property of these compounds is the infra-red absorption spectrum which provides a relative confirmation of the presence of this four-membered ring system. The carbonyl stretching frequency in an acyclic amide usually has a value of about 1735-1755 cm^{-1} (5.7-5.76 μ) in monocyclic lactams. This implies that the carbonyl group in β-lactam behaves like ester group.



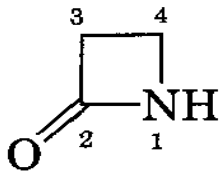
Penam



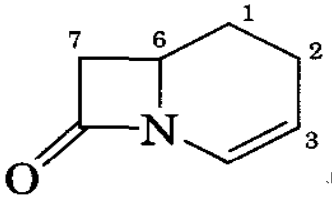
Cephem



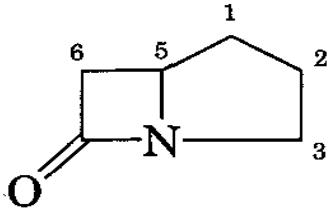
Carbapenem



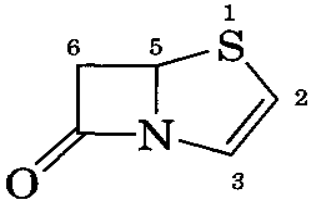
Oxacephem



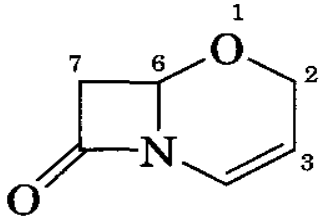
oxapenam



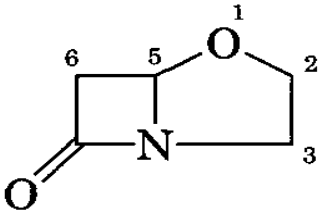
Penam



Monobactam



Carbacephem



Carbapenam

SYNTHETIC METHODS[3, 4, 5]:

Staudinger reaction and related methods:

Staudinger's ketene–mine reaction is the most common method for the synthesis of azetidinones. The reaction is carried out thermally or photo chemically using acid chlorides in the presence of triethylamine or a-diazoketones as ketene precursors.

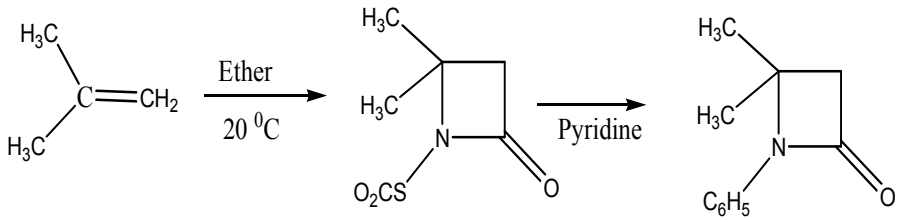
From direct cyclization of amino acids:

A commonly employed method is cyclization of free amino acids using acyl chloride, phosphorous trichloride or thionyl chloride.

No cyclisation of amino acids takes place on heating; rather it splits into an amine and an acid.

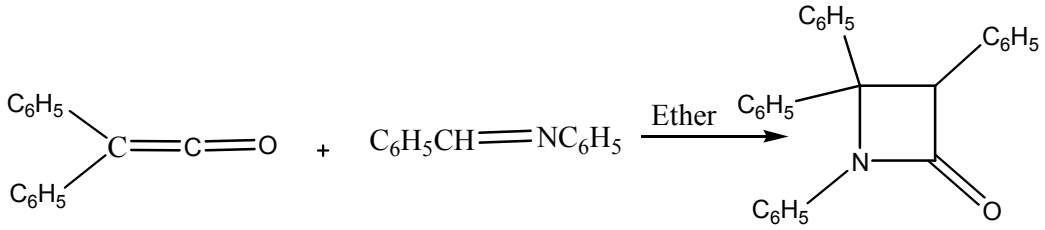
Direct combination methods:

An older technique involves the direct combination of two appropriately substituted components for instance ketenes condense with imines to form β-lactam

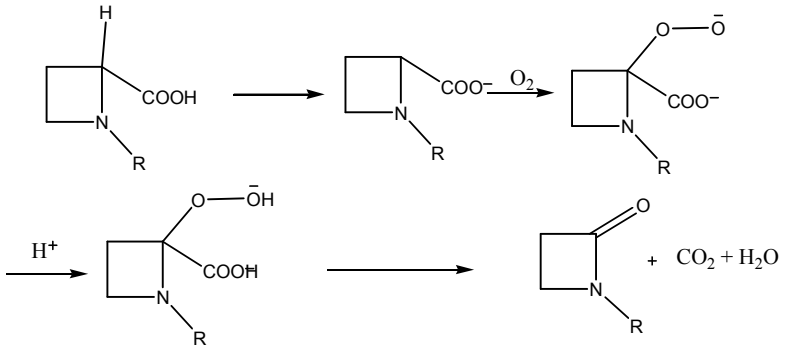


Chlorosulfonyl isocynate adds similarly with a number of alkenes to lead to the corresponding N-chlorosulfonyl-β-lactam.

The chlorosulfonyl group can easily be removed by treatment with thiophenol in pyridine.



From substituted Azetidines: N-substituted azetidine-2-carboxylic acid can be converted intoazetidinone by the following sequence involving a dicarbanion intermediate. The azetidinecarboxylic acid is treated with lithium diisopropylamide and the resultant dicarbanion isdecarboxylated oxidatively.

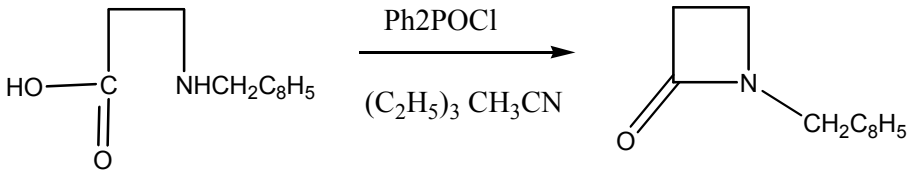


From Aziridine:

Because of ready availability of aziridine a one pot synthesis has been developed for the preparation of azetidinones. The reaction involves treatment of an aziridine derivative with lithium iodide followed by treating the reaction mixture with nickel tetra carbonyl and finally addition of solid iodine. 1-Benzyl-4-methylaziridine under these conditions gives 1-benzyl-4-methyl-2-azetidinone in 50% yield. It is noticed that the less substituted-N bond is carbonylated.

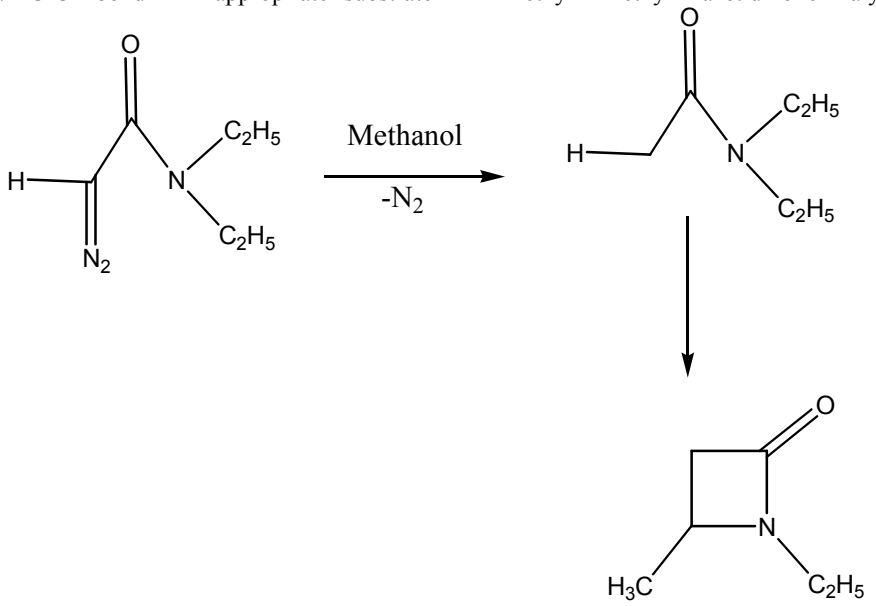
Cyclization of β-Amino Acids:

B-Amino acids cyclize cleanly in the presence of diphenylphosphoryl chloride to β-lactam. N-benzyl-3-aminobutyric acid leads to N-benzyl-2-azitidinone, in 72% yield. This reaction is solvent dependent as the yield of the product decreases by altering the solvent, THF (68%), CH_2Cl_2 (61%).



Insertion of Carbenes:

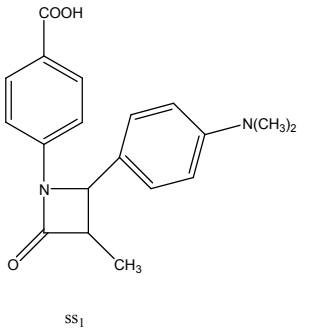
Generation and intermolecular insertion of carbons in a C-C bond in appropriate substrate results in azetidinone formation. N, N-diethyldiazoacetamide, for instance on photolysis yields 1-ethyl-4-methyl-2-azetidinone in a yield of 57%.



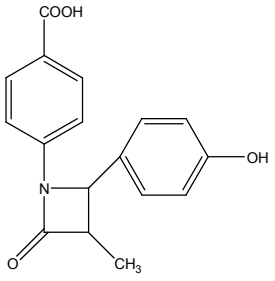
Biological Activities of 2-Azetedinones:

1. Sugumaran M et.al,[6] synthesized 2-Azetidinone and 4-Thiazolidinone derivatives from 4-Aminobenzoic acid as a starting material. They synthesized 6 derivatives using substituted aldehydes, chloro Acetyl chloride and triethylamine and gone for antimicrobial activity. It was evident that the 2- Azetidinones was more active against the bacterial strains and 4-Thiazolidinones were more active against the fungal strains.

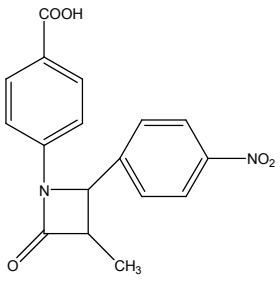
Among the synthesized derivatives ss_1, ss_3 and ss_5 shows more potent activity against the microbials. $Ss_{1\ 4}$-[3-chloro-2-[4- dimethylamino phenyl]-4- oxoazetidi-1-yl] benzoic acid was found to be more active against staphylococcus aureus(gram + bacteria). The ss_3 4-[3-chloro-2-(4-hydroxyphenyl)-4-ozoazetidin-1-yl] benzoic acid was found to be more potent against Eschericha coli (gram – Ve bacteria). The ss_5 4-[2-[4-nitrophenyl]-4- oxo-1,3- thiazolidin-3-yl] benzoic acid was found to be active against candida albicans.



ss_1

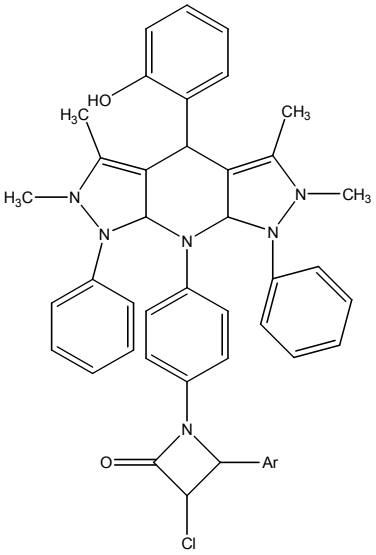


ss_3

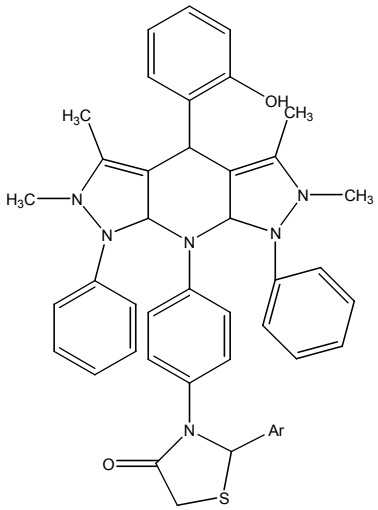


ss_5

2. Himane N. chopade et.al[7], synthesized novel bioactive Azetidinones and Thiazolidinone of 1,5- Dimethyl-2-phenyl-1H-pyrazole-3(2H-one) by using substituted aldehydes, chloro aceticacid , triethylamine , $POCl_3$ and mercaptoacetic acid. They synthesized 5 novel bioactive Azetidinones and 5 Thiazolidinones. According to the data of antimicrobial activity , it could declaimed that the compounds of the series (3a-3e) and (4a-4e) show good comparable activity against standard drugs. The biological activity of these novel bioactive Azetidinones and Thiazolidinones was studied against the panel of nine bacterial strains.

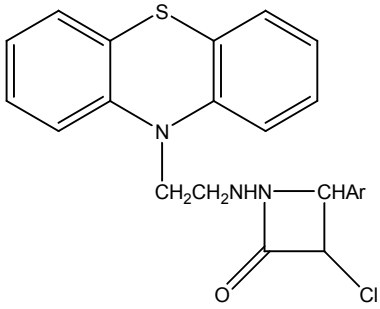


(3a-3e)

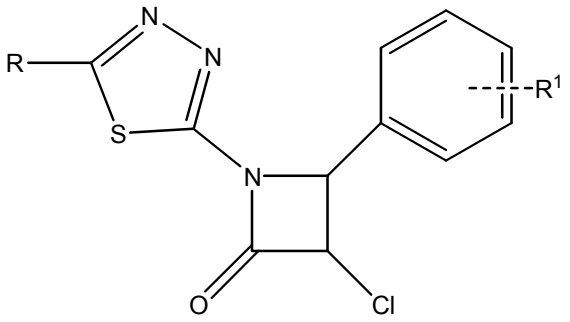


(4a-4e)

3. Sharma ritu et.al[8], synthesized 2-oxo- Azetidine dervatives of phenothiazine. They synthesized 13 derivatives of 2-oxo- Azetidine derivatives of phenothiazines. They used phenothiazine as a starting material and they used 1-bromo-2-chloro ethane, chloroacetyl chloride and acetone for the synthesis of 4(a-m) N-[2-(10H-phenothiazinyl)ethyl]-4-(phenyl)-3-chloro-2-oxo-1-iminoazetidin compounds. Later the antibacterial, antifungal and antitubercular activities of compounds 4(a-m) has been assayed in-vitro against selected gram positive bacteria. The investigation of antimicrobial data revealed that compounds (4c),(4d),(4e),(4f),(4h),(4i) and (4j) displayed highly active in the series, compounds (4b), (4g) and (4m) showed moderate activity and rest compounds show less activity against all the strains compared with the standard drugs.



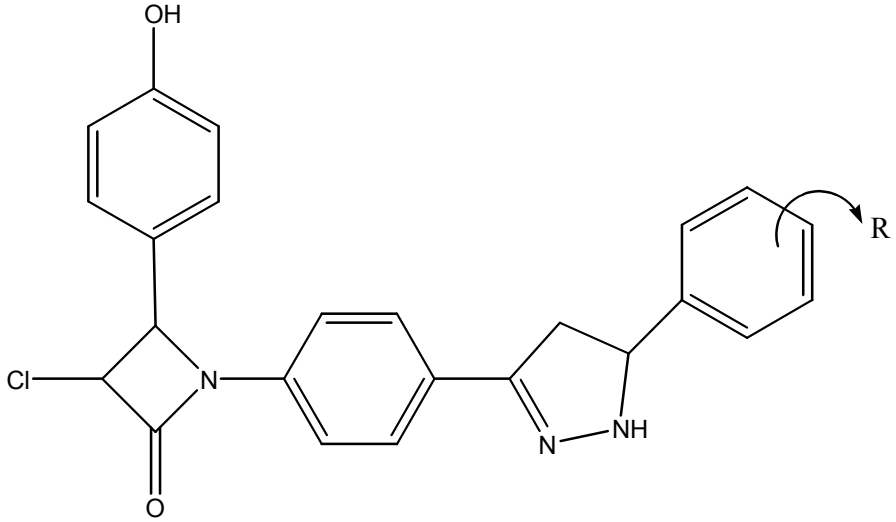
4. Killarimath et.al[9], synthesized newer Azetidinones. They synthesized a series of 3-chloro-4-(substituted) phenyl[1,3,4] thiadiazol-2-yl] azetidin-2-one(VI a-n) derivatives by the cyclo addition of N-[(1E)-phenylmethylene]-5-pyridin-3-yl-1,3,4- thiadiazol-2-amine(V a-n)n with chloro acetyl chloride in presence of triethyl amine catalyst. Docking studies has been carried out by using Hex software for all the compounds. The result of the docking studies clearly confirms that compoundsVI e, VI g, VI k and VI m are active against the tuberculosis and VI l and VI n compound showed potent antitubercular activity. The antimycobacterial activities of compounds VI a-n were assessed against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA). In the series VI a-n, compounds VI e, VI g, VI k, VI l, VI m and VIn showed better antitubercular activity compared to all thestandard drugs pyrazinamide, streptomycin and ciprofloxacin and compounds VI d, VI f, VI i and VI j showed similar activity compared to standard streptomycin.



R= Nicotinic acid, isonicotonic acid

R^1= H, 2-Cl, 4-Cl, 2-OCH_3, 4-OCH_3, , 2-OH,4-OH

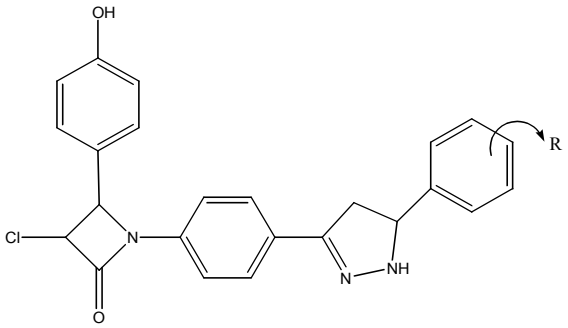
5. Shah shailesh H et.al[10], synthesized azetdin-2-one containing pyrazoline derivatives. A new series of 3-chloro-1-[4-[5-dihydro-pyrazol-3-yl]phenyl]-4-(4-hydroxyphenyl) azetdin-2-one with 99% hydrazine hydrate. The antimicrobial activity studies were carried to the newly synthesized derivatives. The compound (**4a**) have shown better activity against E. coli and S. pyogenus, while (**4e**) have Shown better activity against E.coli, while rest of all compound possessed good activity against S.aureus. Compound (**4f**) is found to be good antifungal activity against C. albicans, against standard drugs Greseofulvin. While rest of all derivatives are poor against A. Niger and A. clavatus.

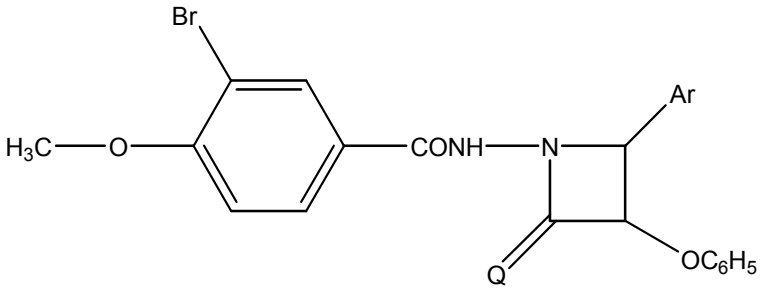


6. Vildan Adar Guner et.al[11]. performed antimicrobial activity of previously synthesized 4- substituted-styryl-2-azetidinones. In this study, antimicrobial activity of previously synthesized 1-(Substituted phenyl)-4-(substituted styryl)-2-azetidinones(3a-i) have been examined. All compounds have been tested against Gram(+) and Gram(-) bacteria and yeasts. Their antimicrobial activity was determined as MIC values. The inhibitory effect is found against Gram (-) bacteria. Compounds 3a.3b,3c and 3d were particularly interesting against *Pseudomonas aeruginosa*.

7. Ujjwal Sahoo et.al[12], synthesized certain novel azetdinone derivatives. He synthesized 8 derivatives. They used 3-bromo-4-methoxy benzoyl hydrazine, ethanol and glacial acetic acid ,benzyl hydrazine, triethylamine, N,N-dimethylformamide and phenoxy acetyl chloride for the synthesis of 3-phenoxy-4-(substituted phenyl)-1-(3'-bromo-4'-methoxy benzamide) azetidin-2-ones 3(a-h). He performed evaluation of antibacterial and antifungal activity. He studied antibacterial activity against Staphylococcus aureus, Escherichia coli, bacillus subtilis and Pseudomonash aeruginosa by the ditch-plate technique and for antifungal activity against *Aspergilus niger* and *Candida albicans* by paper disc diffusion method. Among the compounds tested, 3b, 3c and 3h showed good antibacterial activity as compared with standard ciprofloxacin and rest of the compounds showed moderate activity.

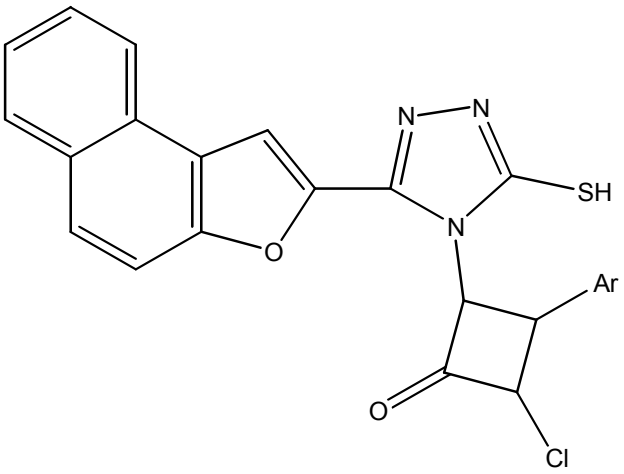
	R^1	R^2	R^3
a	Ph	H	Ph
b	Ph	OMe	Ph
c	Ph	Cl	Ph
d	Ph	Me	Ph
e	H	H	Ph
f	H	OMe	Ph
g	H	Me	Ph
h	H	Cl	Ph
i	H	OMe	Cl





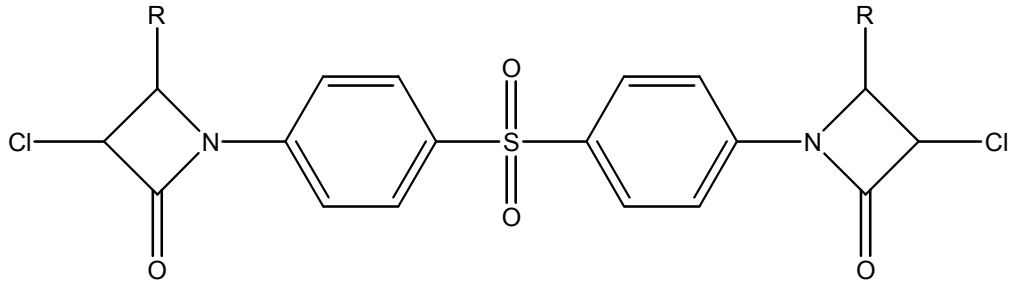
Ar; 3c=4-hydroxy-3-methoxy pheny 3b = 4-hydroxyphenyl3h= 2- furyl

8. VP.Vaidya et.al[13], synthesized azetidinones involving 3-mercapto-4-amino-5-naptho[2,1-b] furan-1,2,4-triazole. He also performed pharmacological investigation.he used naptho [2,1-b]furan 2-carbohydrazide as a starting material. The newly synthesized (4a-f) compounds were evaluated for antibacterial, antifungal and antipyretic activities. The compounds 4b, 4d and 4e displayed significant antibacterial activity. Rest of the compounds exhibited substantial activity against both the organisms. It is observed that electron withdrawing groups resulted in enhancement of activity. The compounds 4b and 4d showed promising antifungal activity, whereas remaining compounds are found to be considerable active. In this case also electron withdrawing groups have much more pronounced effect on antifungal activity. The compounds 4a-f exhibited Excellent anti inflammatory activity. compounds 4a-f possess substantial analgesic activity and remaining compounds exhibited significant activity. The compounds 4b, 4d and 4e, were found to display promising diuretic activity and remaining compounds possessed moderate activity. Presence of electron donating groups in compound 4b may be responsible for the enhanced activity.



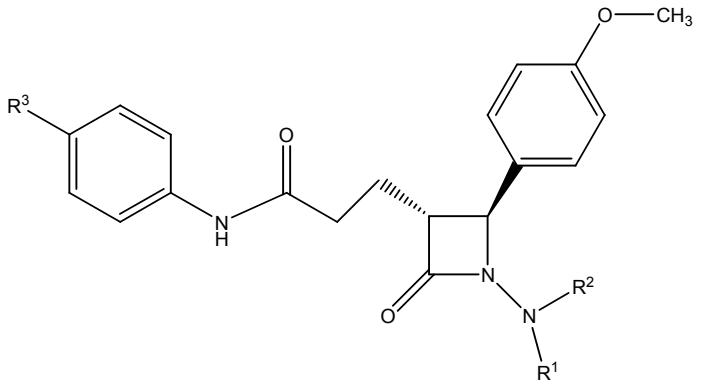
	Ar
a	C_6H_5
b	4-OCH_3-C_6H_5
C	2-Cl-C_6H_5
d	4-Cl-C_6H_5
e	4-NO_2-C_6H_5
f	furfuryl

9. Mehta Parul D et.al[14], performed QSAR study of some novel 2-azetidinone series for their antibacterial activity against Bacillus Subtilis. From the detail study of 2D QSAR it was observed that the descriptors which are highly correlated with the biological activity of 2-azetidinone series are hydrogen counts. SddsN(nitro)E-index and T_T_Cl_3. Hydrogen counts and SddsN(nitro)Eindex showed negative contribution to the biological activity while T_T_Cl_3 showed positive contribution to the biological activity. It can be concluded that antibacterial activity of 4,4'-bis [3- chloro-4-aryl-azetidin-2-one-1-yl] diphenyl sulphone derivatives against B.subtilis is strongly influenced by the electrotopological parameter, element count and alignment independent descriptors. This data was used for the synthesis of new antibacterial agents.

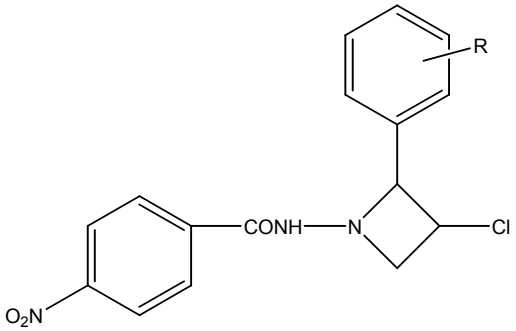


R= heterocyclic or substituted aryl ring

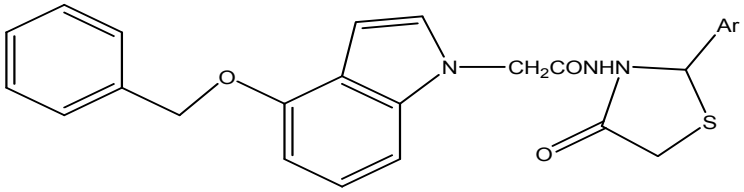
10. N.B.Charbe et.al[15], synthesized some novel 2-azetidinone derivatives. They used methoxy benzaldehyde and substituted hydrazine, isopropanol and glutaric anhydride for the synthesis. They synthesized 9 derivativesof novel 2-azetidinones. He also performed cholesterol absorption inhibition and antibacterial activity. The cholesterol absorption inhibition activites were evaluated. Most of them showed comparable effects in lowering the levels of total cholesterol in the serum. However the compounds with the phthalazine and 1,3-dinitrobenzene substituted hydrazine showed comparable cholesterol inhibition. The compounds 1,2,5 and 4 showed moderate antibacterial activity 6,9,8,7 and 3 showed good antibacterial when compared with lincomycin against S,aureus.

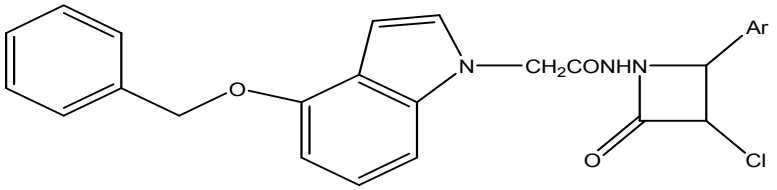


11. S.k.Gawande et al[16]., synthesized some 2-azetidinone derivatives from4-Nitroethyl benzoate by microwave method. They synthesized 5 derivatives of 2-azetidinone. All the synthesized derivatives are evaluated for antimicrobial activity. From the microbial study it can be concluded that compounds bearing chloro, methoxy groups are more potent than remaining substituted compounds against gram (+) and gram (-) bacterias. This method using microwave irradiation to synthesis 2-azetidinone derivatives offers significant improvement over existing procedures. This reproducible technique affords various azetidin-2-one derivatives with short reaction times and excellent yield and without formation of undesirable products.



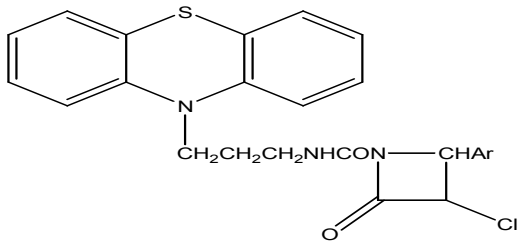
12. Piyush vyas et al[17]., Synthesized azetidinone derivatives and thiazolidine derivatives of (4-benzyloxy)-1H-indole. They synthesized 8 derivatives of each azetidinones and thiazolidines. The synthesized compounds are screened for antibacterial and antifungal activities.antibacterial activity of all the compounds against gram + bacteria(Bacillus subtilis and staphylococcus aureus) and gram – bacteria(E.coli, Salmonella and klebsiella promiee) by agar cup plate method using ampicillin as a standard.5b, 5c, 6b and6c showed more active against the above microbes. The fungicidal activity also studied in vtro. Among all the compounds 5a,5c,5d and 6c showed more activity as antifungal.



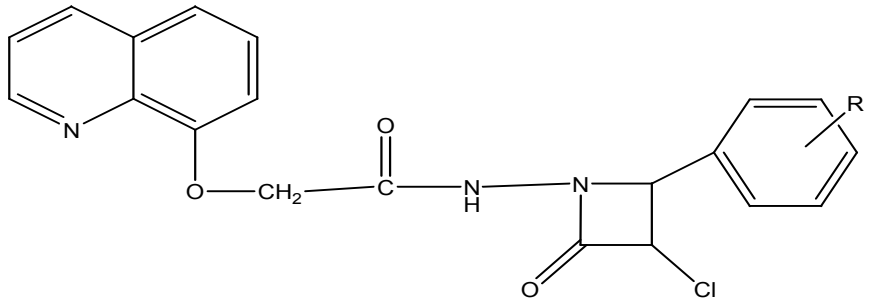


Where Ar; phenyl, 4-bromo phenyl, 4-chloro phenyl,4- nitro phenyl, 4- methoxy phenyl.

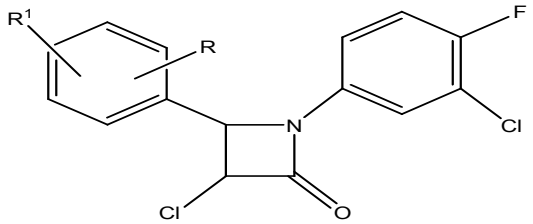
13. Pushkal Samdhiya et al[18]., synthesized 2-Azetidinone derivatives of phenothiazine. They synthesized 13 derivatives of 2- azetidinone. They used phenothiazine as a starting material. The synthesized compounds are screened for their biological study. The investigation of antimicrobial(antibacterial, antifungal and antitubercular) activities data revealed that the compounds 4b, 4e, 4f, 4h, 4i and 4j displayed excellent activity, the compound 4c, 4g, and 4m showed moderate activity and rested compounds showed less activity compared with standard drugs.



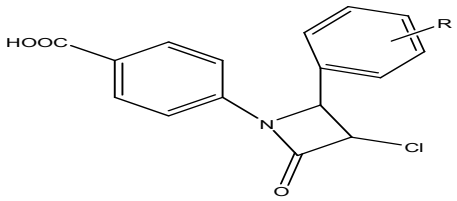
14. Maitya S et al[19].. synthesizedsome novel beta lactum condensed bioactive 2-azetidinone derivatives as prospective antimicrobial agent. They synthesized 10 derivatives by using 8-hydroxy quinolone as a starting material. All the synthesized compounds were subjected to antimicrobial activity. The antibacterial activity against cultures of staphylococcus aureus, Bacillus Subtilius, Pseudomonasaeruginosa and Escherichia coli and antifungal activity against candida albicans using modified broth dilution method. From screening results, it has been observed that final compounds 4c, 4e and 4h possess significant activity against E.coli compounds 4g and 4h possess extremely significant activity against E.coli. Final compounds 4d, 4e, 4f, 4g, 4h and 4i possess significant activity against S. aureus. Compounds 4b, 4c, 4d, 4e, 4f, 4i and 4j were shown to possess significant activity against B.Subtilis while compounds 4b possess extremely significant activity. The remaining compounds of the entire series possess poor antibacterial activity. Antifungal screening data showed that final compounds 4a, 4c, 4e, 4f and 4i possess significant activity. While compounds 4f possess excellent significant activity against candida albicans.



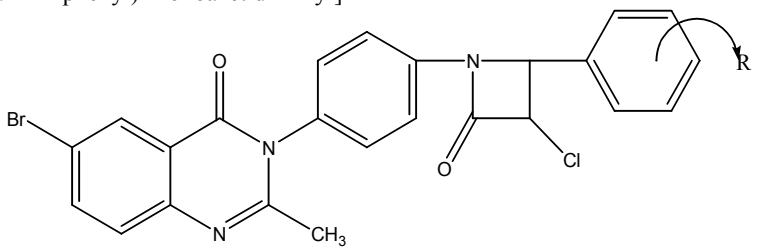
15. Basavaraj M Dinnimath et al[20]., synthesized chloro , fluro, phenyl, substituted azetidin-2-one by microwave method. They used substituted aldehyde as a starting material. They synthesized 10 derivatives of 2-azetidinone. The synthesized compounds were screened for their antibacterial, antifungal and antitubercular agents whereas moderate activity as antibacterial agent compared with standard. The change in their activity is mainly due to the substituents especially electronegative on the phenyl rings. Az_3 shown moderate activity as antibacterial agent against S.aureus mild against E.coli. Az_4 has shown mild to moderate activity against both the strains when compared to standard drug ciprofloxacin. Az_3 has shown good antifungal activity against C.albicans moderate activity against A.fumigatus,Az_8 has shown moderate antifungal activity both the strains when compared to standard drug Flucanazole.



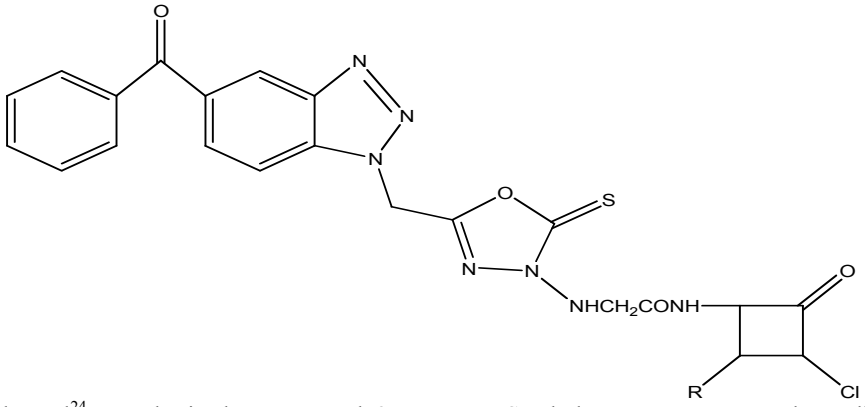
16. Pratap Y Pawar et al[21]., synthesized some new azetidinone derivatives. They synthesized 10 derivatives of 2-azetidinones by using 4-amino benzoic and substituted aromatic aldehyde. The synthesized compounds were evaluated for in vitro anticonvulsant activity against by MEs method and also evaluated for neurotoxicity study. Most of the compounds exhibited mild to moderate anticonvulsant activity. The results reveals that among the tested compounds 2b, 2d and 2i were found to have better activity. Whereas the 2a and 2c have moderate activity among the tested compounds 2a, 2g and 2h exhibited neurotoxicity.



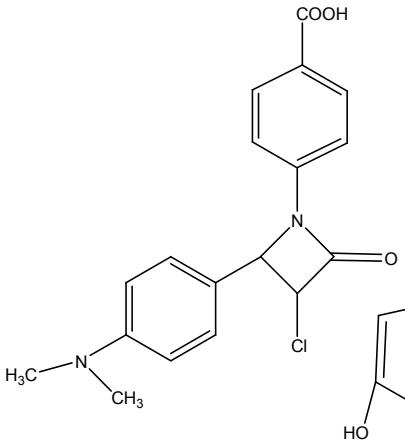
17. Patel PS et al [22]., synthesized 3-{4-[3-chloro-2-(substituted phenyl)-4-oxoazetidin-1yl]phenyl}-6-bromo-2-methyl quinazoline-4-one as a staring material. They synthesized 10 derivatives of 3-{4-[3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl] phenyl}-6-bromo-2-methylquinazolin-4-one. These synthesized compounds showed good activity against the bacterialstrains.



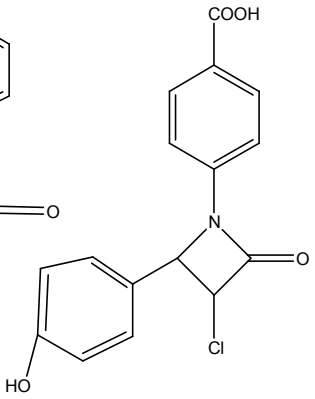
18. Pandaya K M et al[23]., synthesized some novel azetidinone derivatives. They synthesized 3 derivatives of 2-((5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thiano-1,3,4-oxodiazol-3(2H)-yl)amino)-N-(3-chloro-2-substituted-4-oxoazetidin-1-yl)acetamide. They used 2-(5-((5-benzoyl-1H-benzo[d]1,2,3]triazol-1-yl)methyl)2-thiano-1,3,4-oxodiazol-3(2H)-yl) acetohydrazide as a starting material. The synthesized compounds were subjected to biological evaluations. The compounds were evaluated for antibacterial and antifungal activites. The activity studies suggest that novel azetidinone derivatives had showed moderate antibacterial and antifungal activity. The activity of betalactums was greatly influenced by substituents or fused rings. Based on the above observation ,it may be postulated the presence of nitro and methoxy group on the azetidinone may be responsible for significant antimicrobial activity.



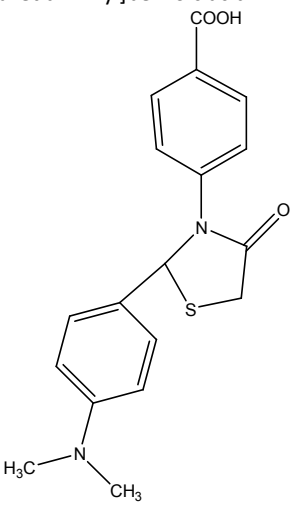
19. A.V.G.S.Prasad et al[24]., synthesized some novel 2-azetidinone and 4-thiazolidinone derived from 4-nitro benzoic acid Schiff bases. They synthesized 2 derivatives of 2-azetidinones and 4-thiazolidinones. Antimicrobial activity of the synthesized compound was screened using the disc diffusion method against selected pathogens such as Escherichia coli, Staphylococcus aureus and candida albicans. The synthesized compounds therefore, present a new scaffold that can be used to yield potent antimicrobial compounds. It can be concluded that these compounds certainly holds great promise towards good active leads in medicinal chemistry.



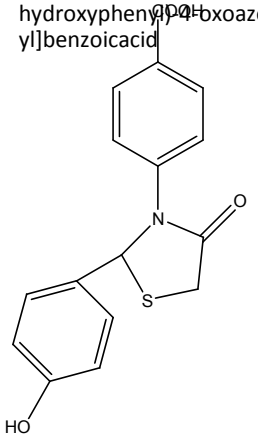
SSA1 4-[3-Chloro-2-[4-dimethylaminophenyl] -4-oxo-azetidin-1-yl]benzoic acid



SSA2 4-[3-Chloro-2-(4-hydroxyphenyl)-4-oxoazetidi-1-yl]benzoicacid

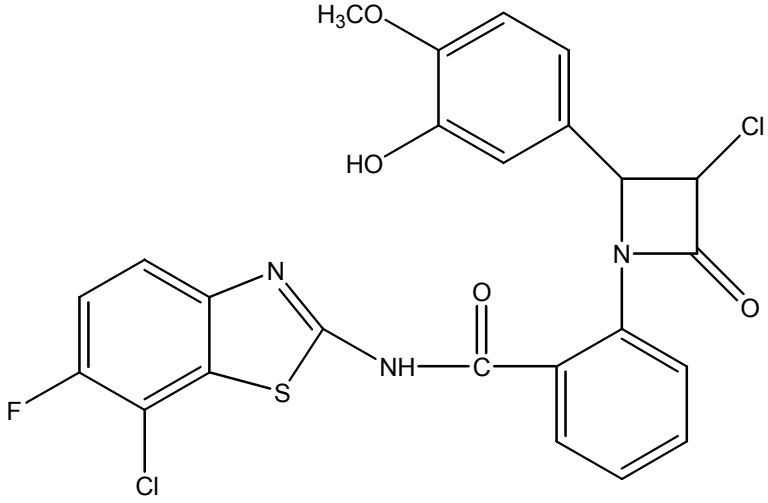


SST1 4-[2-[4-Dimethyl aminophenyl]-4-oxo-1,3-thiazolidin-3-yl]benzoicacid

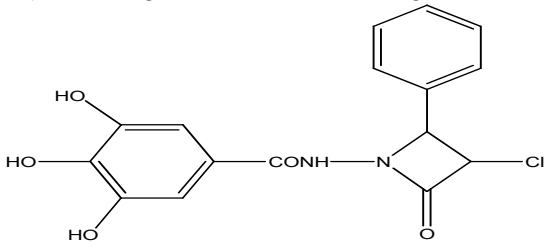


SST2 4-[2-[4-Hydroxy phenyl]-4-oxo1,3-thiazo-lidin-3-yl]benzoic acid

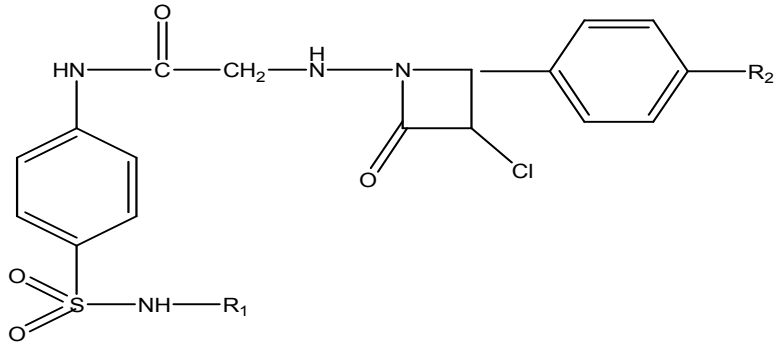
20. Vijaya kumar MM J et al[25]., synthesized novel N-Substituted-3- Chloro-2- Azetdinones as potential anticonvulsant agents. They synthesized 12 derivatives by using 4-fluro-3-chloro aniline as a starting material. These newly synthesized heterocyclics showed promising anticonvulsant activity using PTZ induced method. The anticonvulsant activity using the concentrations at low and high compared to standard. Among compounds A_3, A_7, A_5 and A_{12} showed significant anticonvulsant activity.



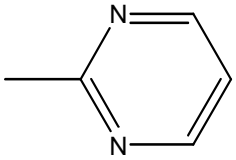
21. K Ilango et al[26]., synthesized some novel trihydroxy benzamido azetidin-2-one derivatives. They used propyl gallate as a starting material. They synthesized 15 derivatives of 2- azetidinone derivatives. They performed evaluation test to know their antimicrobial and antitubercular activity.from the above results it was concluded that theCompounds 3f, 3g, 3k and 3o were active, among the compounds in the series (3a-o), exhibiting antibacterial and antifungal activities as



22. Dragos pieptu et. al[27]., synthesized new azetidinones with sulfonamides and they performed biological activities. These derivatives are synthesized by using sulfadiazine and sulfisoazole as starting material. They used chloroactyl chloride and hydrazine hydrate for the preparation. They synthesized 12 derivatives of azetidinones. The synthesized compounds were evaluated for antimicrobial activity and for antioxidant activity. The N(arylidene)hydrazinoacetyl derivative of sulfadiazine (compound **4a2**) was the most active compound, as it was active on Staphyloccoccus epidermidis, Enterococcus faecalis and Pseudomonas aeruginosa. Thecompounds **4a1** , **4a4** and **4b5** were active against Pseudomonasaeruginosa. All tested compounds are more active than sulfanilamide, but less active than ampicillin used as positive controls. In the *N*-(arylidene)hydrazinoacetyl series of sulfadiazine (compounds **4a1**–**6**) it was observed that the most active compounds were those which resulted from reaction of condensation with 4-hydroxybenzaldehyde (compound **4a5**) and 4-nitrobenzaldehyde (compound **4a6**). The values of EC50 for these compoundswere 0.0510 ± 0.0036 (compound **4a5**) and 0.0503 ± 0.0025 (compound **4a6**), which means that they are about 50 times more active than sulfadiazine (EC50 = 2.6140 ± 0.0301). Concerning the azetidinone series the most active compound was **5a5**, which is the analogue of **4a5** in the azetidinone series. This compound is approximately 28 time more active (EC50 = 0.0945 ± 0.0085) then sulfadiazine (EC50 = 2.6140 ± 0.0301) . The ferric reducing power of the compounds resulting through modulation of sulfisoxazole is lower than that of the the analogues of the sulfadiazine series. In reference to sulfisoxazole (**1b**), all tested compounds **4b1**–**6**, **5b1**–**6** are more active. The most active compounds were **4b5** [*N*-(arylidene)hydrazinoacetyl series] and **5b5** (azetidinone series), which have in their structure the 4-hydroxyphenyl radical. These compounds are 46 times (**4b5**, EC50 = 0.0210 ± 0.0065) and 10 times (**5b5**, EC50 = 0.0935 ± 0.0098) more active, respectively, than sulfisoxazole. Although their antimicrobial potential was reduced, they shown excellent antioxidant properties; for some of them the potential is comparable with the antioxidant activity of ascorbic acid. These results support the antioxidant potential of the synthesized compounds and their applications in several disease mediated by reactive oxygen species (ROS) including the healing of the wounds. $5_{a(1-6)}$ and $5_{b(1-6)}$



R_1 =



$R_{2=}$ H, F, Cl, Br, OH,-NO_2

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