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A mini review on recent updates on pharmacological evaluations of molecules based on azetidinones and rhodanines heterocyclic nucleous

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Abstract
Azetidinones is a four member heterocyclic ring system with nitrogen as the hetero atom and a carbonyl group incorporated into it. Rhodanines is five-membered heterocyclic molecules containing thiazole nucleus with carbonyl group on fourth carbon such as rhodanine derivatives have broad spectrum of pharmacological activities. Azetidinones and rhodanines were showed wide spectrum activities including antimicrobial, anti-tubercular, anticonvulsant, anticancer, anti-inflammatory and CNS activities etc. The uses of different azetidinone and rhodanine compounds for synthesizing various biologically active compounds. Substituting the azetidinones and rhodanines with appropriate substitution for showing biological activities. Various biological activities of azetidinones and rhodanines are discussed in this article.

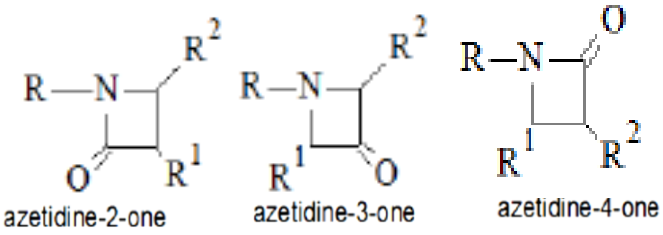
Keywords: Azetidinones, rhodanines, biological activities, heterocyclic compounds

Introduction

Allergic eye disease has been considered as a common ocular Azetidinones are carbonyl derivative of azetidine containing the carbonyl group at position 2, also called 2-azetidinone or β-lactam. These are presently used for bacterial infections. The selective inhibition during cell wall synthesis of bacteria is responsible for its unique and lethal antibacterial action [1]. The β-lactam ring is part of the core structure of several antibiotic groups like pencillins, cephalosporins, carbapenems and monobactams, hence also known as β-lactam antibiotics. Nearly all of the antibiotics work by inhibiting bacterial cell wall biosynthesis. This has a lethal effect on bacteria. Bacteria so however, contain within their population, in smaller quantities, bacteria that are resistant against β-lactam antibiotics. They achieve this by expressing one of many β-lactamase genes. More than 1000 different β-lactamase enzymes have been documented in various species of bacteria. These enzymes vary widely in their chemical structure and catalytic efficiencies. When bacterial populations have these resistant sub groups, treatment with β-lactam can result in the resistant strain becoming more prevalent and there for more virulent. It is also known for its antimicrobial activity. This molecule is also gift for patients with high cholesterol.

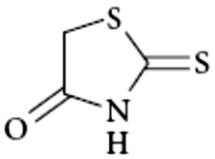
Azetidin (a), azetin (b), alpha–azetin (c) and azete (d) are the nitrogen analogues of cyclobutane, cyclobutene and cyclobutadiene respectively. Azetidines are well studied in their derivatives the azetidin-2-ones (β-lactams) have received considerable attention mainly because of the antibacterial properties of penicillin and cephalosporin [2].

Chemistry of Azetidinones: Parent heterocyclic ring of azetidinones is azetidine. Azetidine is a 4 member heterocyclic ring system with nitrogen as hetero atom. 2-Azetidinones are also known as β-lactams and it is common heterocyclic rings present in antibiotics. 2-Azetidinones consists of a carbonyl group on the second position. The β-lactams fused with thiazolidines are known as penam and β-lactams containing fused bicyclic system i.e. 3, 6-dihydro-2H-1,3-thiazine is called cepham. But this naming system was inadequate. β-lactam not fused with any other ring system is called monobactams. Depending upon the position of carbonyl group in the azetidine ring, Azetidin-2-one, Azetidin-3-one and Azetidin-4-ones are possible. The heteroatom, nitrogen in the β-lactam ring will be given the first position and carbonyl group will be given the second position. The position of carbonyl group will be given 3 and 4 position for azetidin-3-one and azetidin-4-ones respectively. Azetidin-2-ones are hydrolytically sensitive colorless solid. They have a melting point of 73- 74°c. Other simple azetidin-2-ones are low melting solids or oils [2, 3].



Five-membered heterocyclic molecules containing thiazole nucleus with carbonyl group on fourth carbon such as rhodanine derivatives have broad spectrum of pharmacological activities. In past two decades, rhodanines have emerged as potent antidiabetic agents. Some of them are clinically used such as epalrestat for the treatment of type-2 diabetes mellitus and related complications.

This is the reason why investigation or molecular modification and pharmacological evaluation of thesemolecules have attracted special attention of synthetic chemists and pharmacologists, respectively [4].



Rhodanine

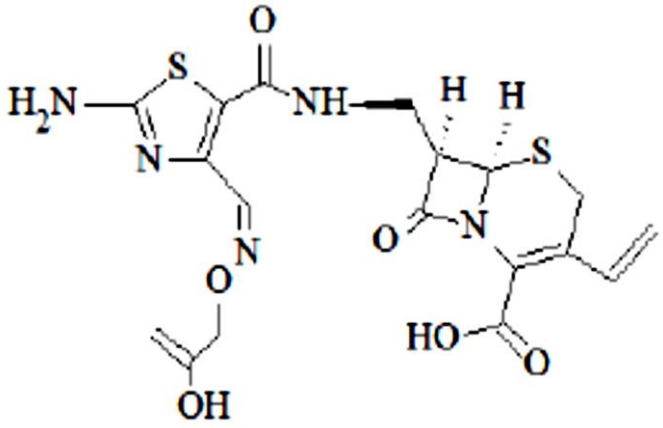
Various pharmacological protocols based on thesemolecules have been emerged extensively and in witness available in the literature. These multifaceted molecules exhibit varied type of biological activities. Some recent developments in synthesis and pharmacology of these molecules are discussed in this section.

Some β-Lactam Antibiotics

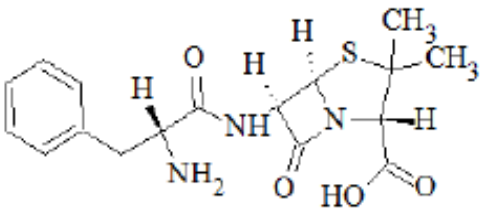
Cefixime: It is a cephalosporin [(6*R*, 7R)-7-{[2-(2-amino-1, 3-thiazol-4-yl)-2-(carboxy methoxyimino) acetyl] amino}-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2 ene-2carboxylic acid] antibiotic mainly used to treat bacterial infections. Cephalosporin antibiotics prevent the cell wall biosynthesis in bacteria. The transpeptidase reaction of peptidoglycans that takes place for the biosynthesis of cell wall will be inhibited by these antibiotics. Adverse reactions are diarrhea, dyspepsia, nausea and vomiting [2].

Ampicillin: Ampicillin **[**(2*S*, 5*R*, 6*R*)-6-([(2*R*)-2-amino-2-phenylacetyl]amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptanes] is effective towards both gram negative and gram positive bacteria. It contains an amino group which is important for it to penetrate the outer membrane of gram negative bacteria. It is classified under penicillin group of antibiotics that contains beta lactam ring. Use for treat urinary tract infections, treat otitis media and treat salmonellosis [2].

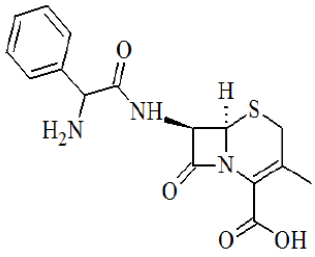
Cefalexin: Cefalexin **[**(6*R*, 7*R*)-7-{[(2*R*)-2-amino-2-phenylacetyl]amino}-3-methyl-8-oxo-5-thia-1-zabicyclo[4.2.0]oct-2-ene-2-carboxylic acid]. It is a first generation cephalosporin antibiotics. It was first marketed by Eli Lilly company under the trade name Keflex [2].



Cefixime



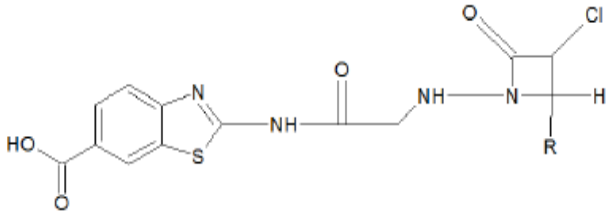
Ampicillin



Cefalexin

Biological Activities of 2-Azetidinones: Azetidinones and its derivatives possess antimicrobial, anti-bacterial, antifungal, anti-tubercular, anti-cancer, anti convulsant, enzyme inhibition and hypoglycemic action [1-3].

Anti-Bacterial Activity: The 2-{2-[3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino]acetylamino} benzothiazole-6-carboxylic acids (1) were screened for its anti-bacterial activity against *S.aureus, B.subtilus, P. aeruginosa* and *E.coli* [5]. The antibacterial screening of Nsulphonamoylphenylamino-3-chloro-4-phenylazetidin-2-ones were tested against *E.coli*, *Pseudomonas diminuta* and *Bacillus subtilus.* It was observed that N-(4'-nitro) phenylamino-3-chloro-4-(4'-dimethylamino) phenyl azetidine-2-one (2) was found to be more potent against the *E.coli* bacteria [6].



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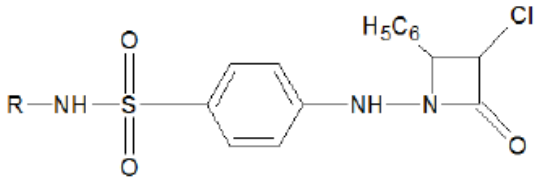
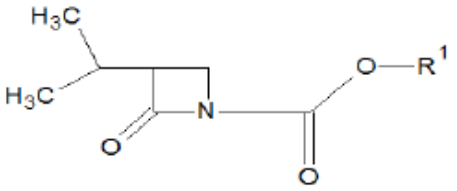


2

The N-acyl-3-alkylidenyl and 3-alkyl azetidin-2-ones (3), is a new class of monocyclic β-lactam antibacterial agents. A series of N-acyl 3-isopropyldienyl and 3-isopropyl 2- azetidinones having potent *in vitro* antibacterial activity especially against anaerobic bacteria. These compounds lack any ionizable moiety appendant to the lactam nitrogen, which distinguishes them from

other azetidinone derivatives [7]. The N-[3-chloro-2-(2-chloroquinolin-3-yl)-4-oxoazetidin-1-yl] naphtho [2,1-b] furan-2-carboxamides (4) were screened for the anti-microbial activity against *S.aureus, A.niger, P.aeruginosa* and *C.albicans* [8].



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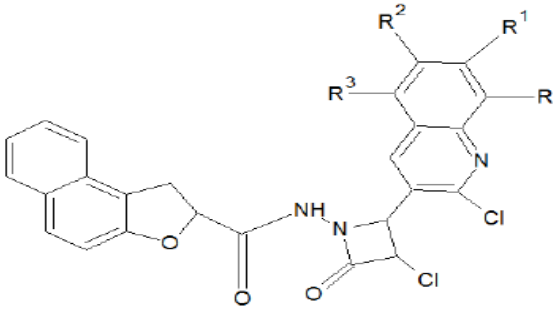
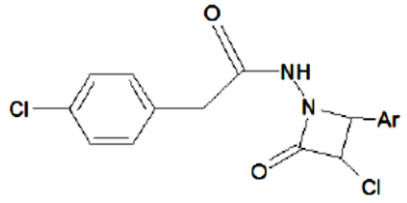


4

The synthesis of N-(3-Chloro-2-oxo-4-arylazetidinyl){4-[5oxo-2 phenyl-4-(phenylmethylene) (2-imidazolinyl]phenyl}carboxamides and N (3-chloro-2-oxo-4-arylazetidin-1-yl)-2-(4-chlorophenyl) acetamides were evaluated for its anti-bacterial activity against *E.coli* and *S.aureus.* The QSAR studies of 4-oxo-thiazolidines and 2-oxo-azetidines was carried out in terms of structural and physicochemical parameters where substituents present at position 3 of N (3-chloro-2-oxo-4-arylazetidin-1-yl)-2-(4-chlorophenyl)acetamides (5) was indicated increase in hydrophobicity or steric bulk character [9]. The azetidinone compounds were studies of their antibacterial activity. A series of compounds 4-[spiro-{4"-methylphenyl)-3'-methyl}-pyrazole]-3-chloro-1-(substitutedbenzothiazole)-2-azetidinones (6) were screened for their anti-bacterial activity against *S.aureus, B.subtilus, S.typhi* and *E.coli* [10].



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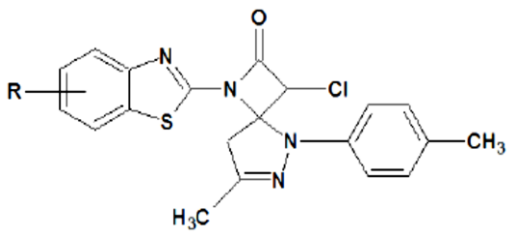
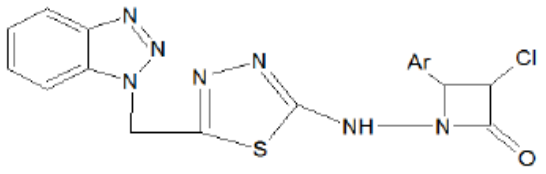


6

Some new 5-[2-{(1,2,3,-benzotriazole)-1-yl-methyl}-1'-(4'-substituted aryl-3'-chloro-2'-oxo azetidine)]-amino-1,3,4,-thiadiazoles and 5-[2-{(1,2,3,-benzotriazole)-1-yl-methyl} aryldiene hydrazino-1,3,4-thiadiazoles (7) exhibited antifungal and antibacterial activity. These compounds were screened for their anti-fungal activity against *A. niger, A. flavus, F. oxisporum* and *T. viride* and anti-bacterial activity against *B. subtilus, E. coli, K. pneumoneae* and *S.*aureus [11]. The antibacterial activity of and 2-oxo-azetidines, some aryl N-{4-oxo-2-[4-(benzyloxy) phenyl] (1,3-thiazolidineyl)} carboxamides and N-{3-chloro-2-oxo-4-[4-(benzyloxy)phenyl] azetidinyl} carboxamides (8) were screened for antibacterial activity against gram +ve and gram –ve species of bacteria [12].



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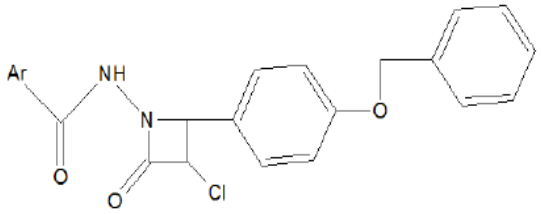
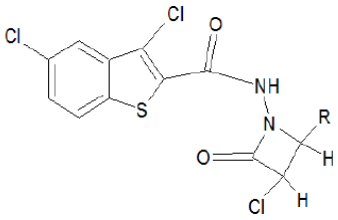


8

The4-Aryl-3-chloro-1-(3',5'-dichloro-2'benzo(b)thiophenoylamino)-2-azetidinones were evaluated for their antimicrobial activity against *E. coli, S. aureus, P. vulgaris* and *A. niger.* The 2-(substituted benzalhydrazinocarbonyl)-3,5-chlorobenothiophene (9) compound was exhibited gud activity [13]. The QSAR studies on 2-azetidinones bearing benzothiophene (10) as potential anti-tubercular agents. Some common important feature i.e., bulky substitution and the high nucleophilicity nature of the molecules, favorable for anti-tubercular activity [14]. The biological activity of 2-azetidinones, these compounds were screened and found to posses moderate to potent antitubercular activities [15]. The antimicrobial activity of 2-azetidinones (11) from selective ester cleavage in 1,3,3-trisubstituted 4-[2'-(odiarylacyl) hydroxyphenyl]-2-azetidinones. Treatment of the 1,3,3-trisubstituted 4-[2'-(O diarylacyl)hydroxyphenyl]-2-azetidinones with sodium hydroxide in ethanol at room temperature lead to selective cleavage of the ester linkage in the substrates forming new 1,3,3-trisubstituted 4-(2'-hydroxyphenyl)-2-azetidinones [16].



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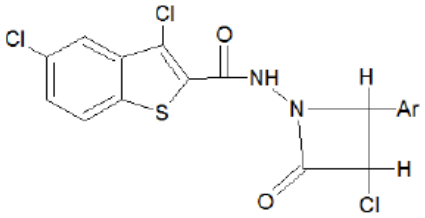

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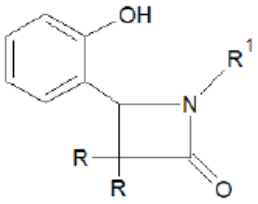
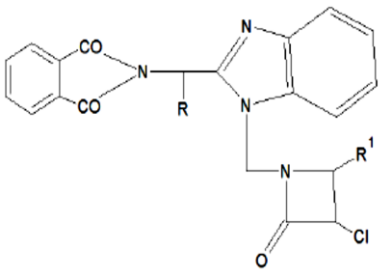


11

In vitro microbial studies of some azetidinones derivatives. Various substituted 3-chloro-4-(substitutedphenyl)-1-{4-[7-chloro-2-(3-chloropropyl)-4-oxoquinazolin-3(4H)-yl}azetidin-2-ones (12) were tested for antimicrobial studies and showed significant activity at low and high concentration as compared to standard [17]. The antimicrobial screening of N-substituted-3-chloro-4-dithiocarbamato azetidin-2-ones. All the compounds were evaluated for their *in-vitro* growth inhibitory activity against *P. diminuta, B. subtilis, E. coli, S. Aureus, R. rhodochrous.* All the compounds were showed significant antibacterial activity. *N*-[4'-(*N*'-4,6-Dimethyl pyrimidinyl)sulphonamoyl amino phenyl]-3-chloro-4-dithiocarbamato azetidin-2-one (13) has been found to be more potent antimicrobial agent against *B. subtilis* [18].



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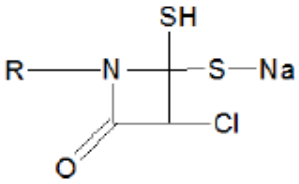

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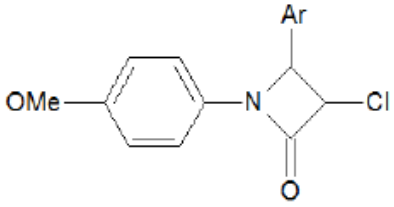
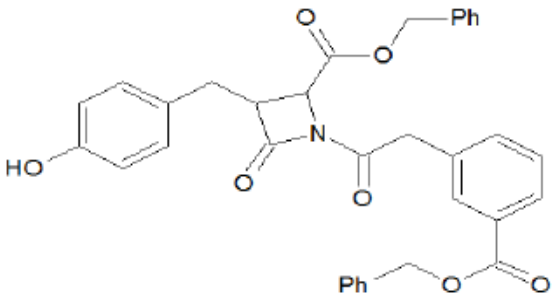


14

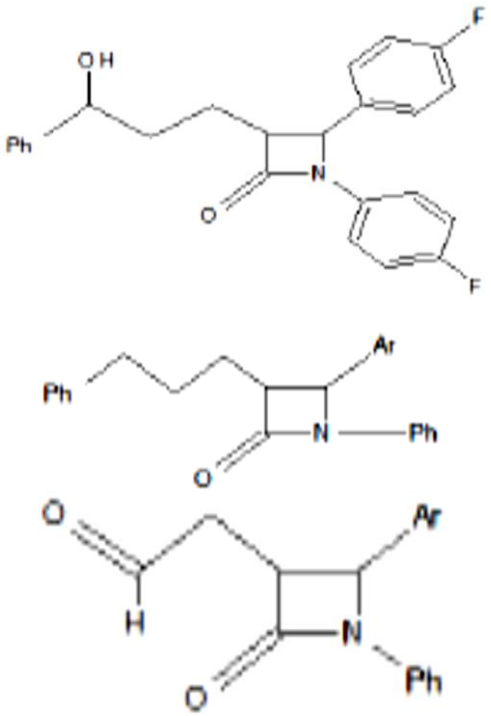
The antimicrobial evaluation of some 2-azetidinone derivatives. The compounds were evaluated for their anti-microbial activity against *S .faecalis, S. aureus, P. aeruginosa* and *E. coli.* Among the derivatives 2,4 dimethyl amino phenyl at 2nd position showed good activity against all species. The activity were attributed to C=O, C-N linkages of 2-azetidinone [19].

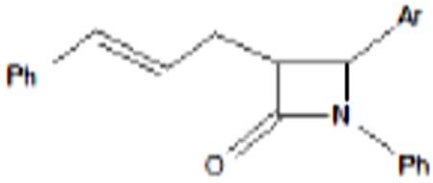
Anti-Cancer Activity: Specific antigen inhibiting activity of 2-azetidinones (15). The active site region was investigated for specific interacting functionality and a binding model postulated for the novel 2-azetidinone acyl enzyme inhibitor which was used as a lead compound in this study [20].



15

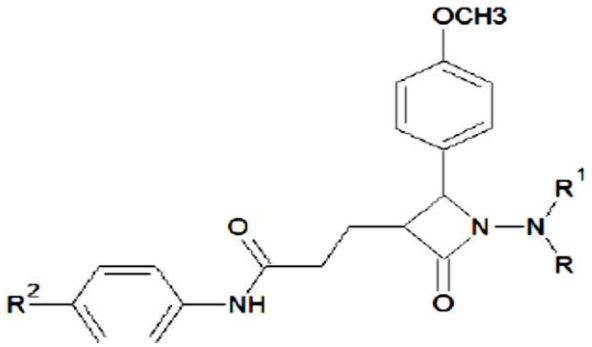
Antihyperlipidemic Activity: The use of nitrones in the synthesis of potential antihypercholesterolemic and antibacterial mono and tricyclic β-lactams (16). The hydroxyethyl group at C-3 of a number of monocyclic β-lactams is elaborated to the appropriate side chain meant for acting as cholesterol absorption inhibitor without perturbing the sensitive β-lactam moiety [21].





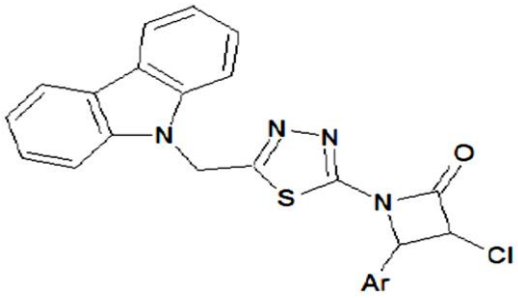
16

The azetidinone derivatives with hydrazine substitutions on nitrogen and their ability to inhibit cholesterol absorption and antibacterial activity were evaluated. Some derivatives of 2-azetdinone derivatives (17) as cholesterol absorption inhibitors were synthesized. Most of them showed comparable effects in lowering the levels of total cholesterol in the of serum cholesterol-fed hamsters and anti-bacterial screening reveal that all the compounds showed moderate to good anti-bacterial activity against *S. aureus* [22].



17

Anticonvulsant activity: Some 2-arylidenylamino-5-(carbazolylmethyl)-1, 3, 4-thiadiazoles and 1-[5'-(carbazolylmethyl)-1', 3', 4'-thiadiazol-2'-yl)]-4-(substituted phenyl)-3-chloro-2-oxo-azetidines (18) were evaluated for their antimicrobial, anticonvulsant and anti-inflammatory activity [23].



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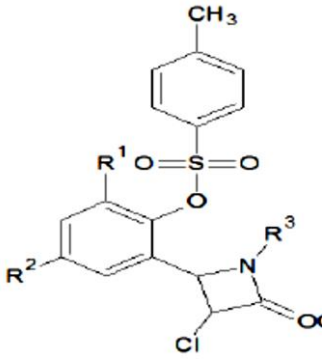
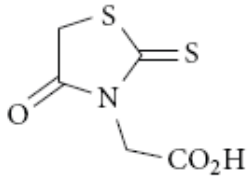
CNS activity: Some azetidin-2-ones as C.N.S modulating agents which were evaluated for hypolipidemic and antihyperglycemic activity based on the predictions made by the computer software Prediction of Activity Spectra for Substances (PASS) [24].

Antiinflammatory activity: The N-Substituted-3-chloro-2-azetidinones were screened for its anti-inflammatory action [25]. The azetdin-2-one derivatives containing aryl sulfonate moiety (19) with anti-inflammatory and anti-microbial activity [26].



19

Biological activities of Rhodanine derivatives: The rhodanine containing molecules of pharmaceutical interest and found pharmacological importance of these molecules is limited because of poor solubility of rhodanine derivatives in water (exception of rhodanine-3-acetic acids). However, these compounds exhibit a broad range of significant biological activities [27]. Rhodanine-3-acetic acid (RAA) 20 was prepared in 1908 [4] and condensation products of the acid with various aldehydes, namely [(5*Z*)-(5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)] acetic acids 21 were reported [4]. These type of molecule exhibited potential antitubercular [28, 29], antifungal [30–33], pesticidal [34, 35], antihypertensive [36], and anticancer [37, 38] activities. Compounds of rhodanine-3-acetic acid with pyridinecarbaldehydes were possess potential antibacterial and antifungal activities. The {(5*Z*)-[4-Oxo-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-3-yl]}acetic acid 22 were patented as a drug for the treatment of metabolic bone diseases. It stimulate parathyroid hormone receptor-mediated cAMP formation and could be useful for the local and systemic treatment of rheumatoid arthritis, osteoarthritis, and degenerative arthrosis [39-41].



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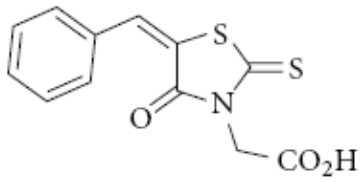

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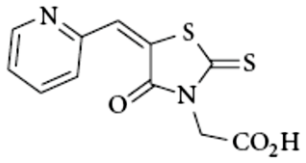
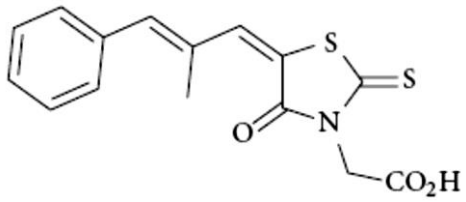


22

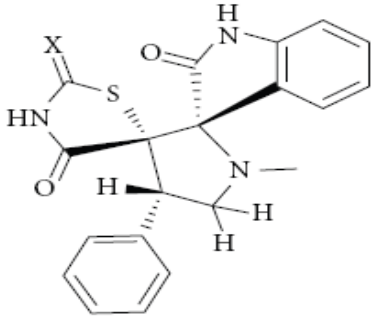
Trypanocidal activity of substituted rhodanine-3-acetic acids has been reported [42]. The only rhodanine acetic acid derivative that has been used clinically is the aldose reductase inhibitor epalrestat 23. It was used to slow eye damage associated with diabetes and to prevent diabetic peripheral neuropathy [43, 44]. Aldose reductase is not the only enzyme inhibited by rhodanine carboxylic acids. Many other enzymes are also inhibited by the derivatives of this structural class and may be responsible for their various biological effects [45].Other rhodanine-based

molecules have also been popular as small molecule inhibitors of numerous targets such as hepatitis C viral (HCV) NS3 protease [46], antidiabetic mechanism [47], aldose reductase [48], β-lactamase [49, 50], histidine decarboxylase [51], and JNK Stimulatory Phosphatase-1 (JSP-1) [52]. This section is a brief account on synthesis and biological effects and recent developments of newly prepared potential drugs based on nitrogen-sulphur containing heterocycles having rhodanine nucleus.



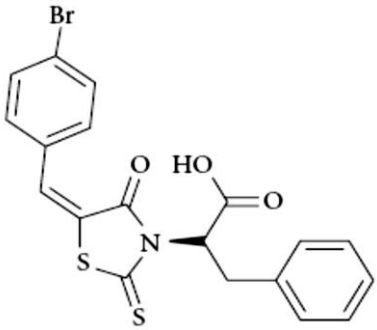
Epalrestat 23

Antidiabetic activity: A series of dispiropyrrolidines**,** compound 24 exhibited attractive antidiabetic properties and are more effective than rosiglitazone in ameliorating stress conditions [53].



24

Antiapoptotic activity: A series of BH3I-1 based dimeric modulators of 25. The over expression of antiapoptotic Bcl-2 proteins which protects cells from apoptosis is one mechanism for tumours to acquire drug resistance. The dimeric modulators 26-27 have enhanced binding activity against antiapoptotic Bcl-2 proteins and proved dimerization of monomeric modulators is one practical approach to enhance the bioactivity of Bcl-2 antagonists [54].



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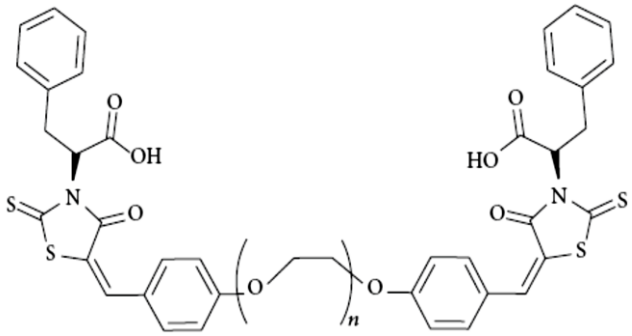
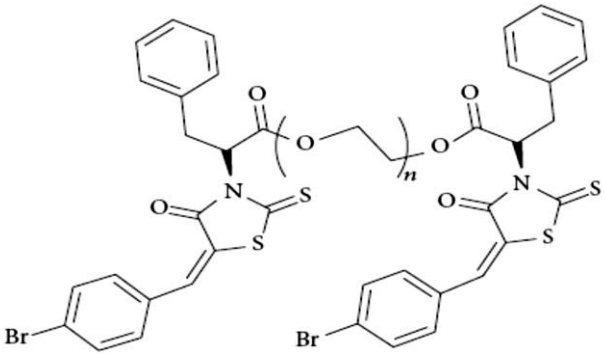
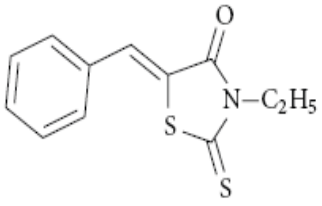


26 n = 1, 2, 3

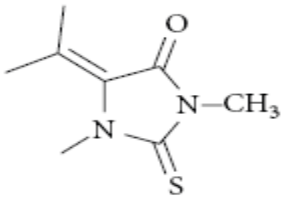


27 n = 1, 2, 3

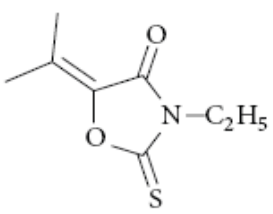
The 5-isopropylidiene derivatives of 5-benzilidene-3-ethyl rhodanine (BTR-1) 28, 3-dimethyl-2-thio-hydantoin (ITH-1) 29, and 3-ethyl-2-thio-2,4-oxazolidinedione (ITO-1) 30 and tested their chemotherapeutic properties. They found all the compounds induced cytotoxicity in a time- and concentrationdependentmanner on leukemic cell line, CEM [55]. Among these compounds, BTR-1 28 was found to be manifold more potent in inducing cytotoxicity than ITH-1 29 and ITO-1 30 with an IC_{50} value of <10 μM and affected cell division by inducing a block at S phase, which finally led to the activation of apoptosis. The 5-isopropylidene-3-ethyl rhodanine 31 found that rhodanine ITR 31 treatment led to cytotoxicity in leukemic cell line, CEM, by inducing apoptosis [56].



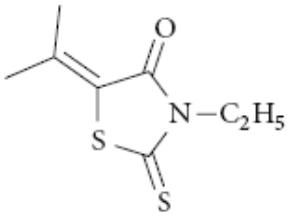
28BTR-1



29 ITH-1

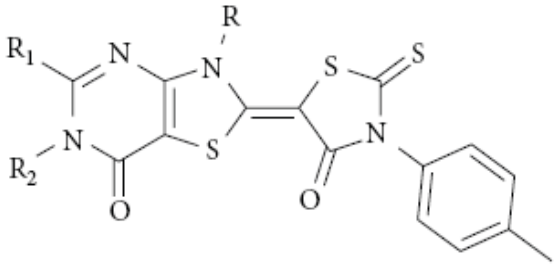


30 ITO-1

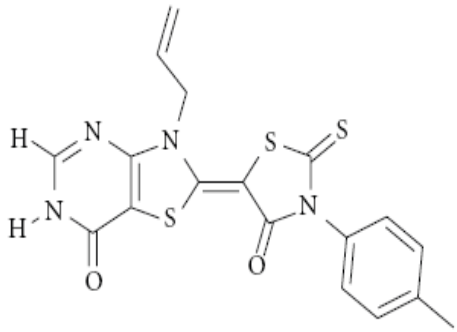


31 ITR

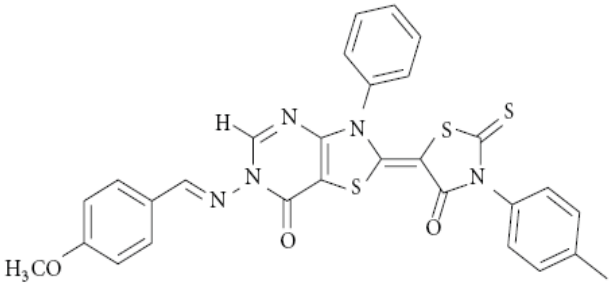
Antimicrobial activity: Compound thiazolo[4,5-dlpyrimidines with rhodanines 32 were tested for antimicrobial screening and they found antifungal activity against *Aspergillus niger* and *Penicillium* sp. with MIC <50–<25 μg/mL. The compound 33 is th emost active against *A. niger* while compound 34 is the most active against *Penicillium* sp.; and 5-fold less active than the standard antibiotic clotrimazole. The presence of an alkyl group at position 3 of the thiazolo-pyrimidine ring 33 is superior to that of other aromatic substituents; also the introduction of an arylideneamino group at position 6 of 34 enhanced the antifungal activity [57].



32 R=C_6H_5, $CH_3C_6H_4$, $CH_3CH=CH_2$;

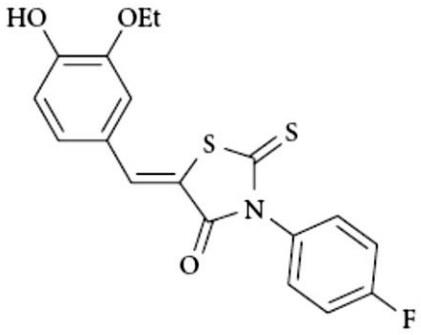


33 R_1=H, CH_3; R_2 = H, CH_3.

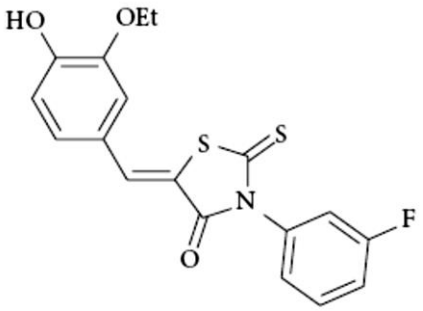


34

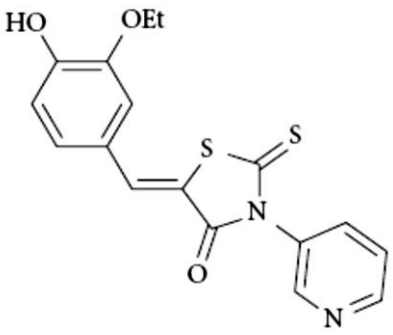
The aryl rhodanines 35–38 did not exhibit antibacterial activity against any of the bacterial strains tested and are not cytotoxic against HeLa cells. Their study revealed that the aryl rhodanines 35–38 specifically inhibit the early stages of biofilm development by preventing attachment of the bacteria (specifically inhibit biofilm formation of *S. aureus, S. epidermidis, Enterococcus faecalis, E. faecium,* and *E. gallinarum* but not the Gramnegative species *P. aeruginosa* or *Escherichia coli.*) to surfaces [58].



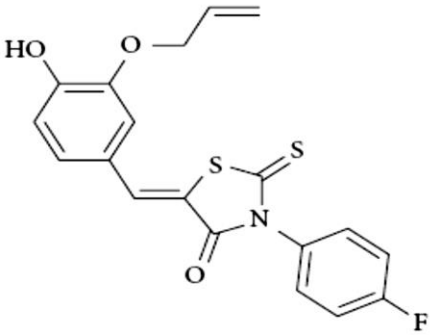
35MBX-1240



36MBX-1246

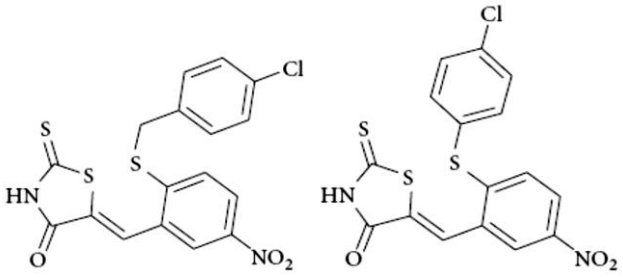


37 MBX-1384

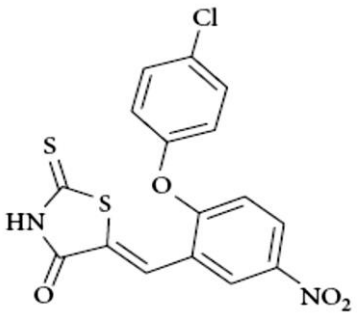


38 MBX-1427

The benzylidene rhodanines 39–41 as novel inhibitors of uridine diphospho-Nacetylmuramate/L-alanine ligase. The compounds 39–41 exhibit selective whole-cell activity against the Gram-positive methicillin resistant *S. aureus* (MRSA) but not against the Gram-negative *E. coli*. They also evaluated their cytotoxic effect on mammalian Chinese hamster ovary (CHO) cells [59].

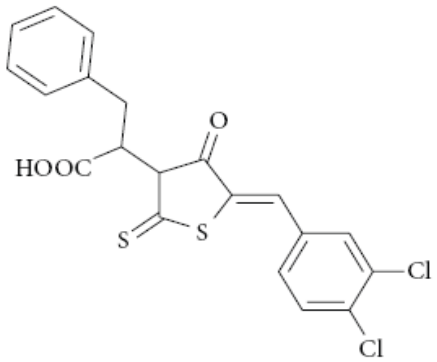


39 **40**



41

A series of glycine and phenylalanine-derived rhodanine analogs and evaluated their anti-MRSA activity. The antibacterial activity of compounds 42 and 43 against a panel of MRSA strains was significantly greater than that of the antibiotics penicillin G and ciprofloxacin. The compound 43 exhibited only a 2–4-fold higher MIC value than that of vancomycin. The phenylalanine derived compounds 42 and 43 are promising templates for the development of new drugs to treat MRSA infections [60].



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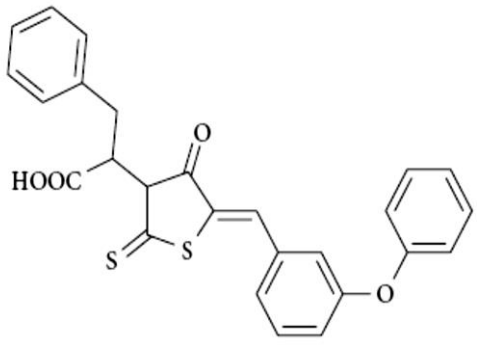
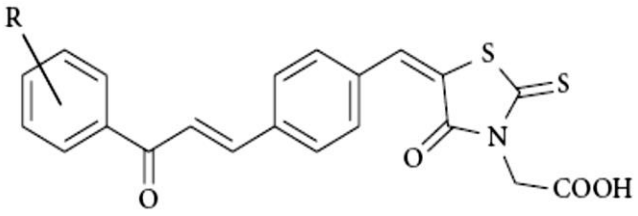


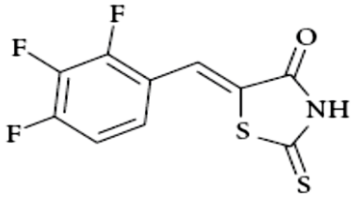
43

Several hybrid compounds 44 having chalcone and rhodanine-3-acetic acid units and tested these compounds for their antibacterial activity. Some compounds exhibited great antimicrobial activities against Gram-positive bacteria (including the multidrug-resistant clinical isolates) as active as the standard drug norfloxacin and less active than oxacillin [61].



44 R = 4-CH_3, 2, 4-$(CH_3)2$, 3-OCH_3, 4-OCH_3, H, 2-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 2,4-$(Cl)_2$,
2-Br, 3-Br, 4-Br, 3-F, 4-NO_2, 3-OCH_2OCH_3, 4-OCH_2OCH_3, 4-$NHCOCH_3$.

Antibacterial activity for a series of rhodanine-, rhodanine-N-acetic acid-based compounds bearing an ylidene substituent at position 5, the most potent compound of the series, (*Z*)-5-(2,3,4-trifluorobenzylidene)rhodanine 45, inhibited the growth of *S. aureus* at 0.5mg/mL and MRSA at 32 mg/mL [62]. The rhodanine-3-acetic acid-based compounds 46-47 were described as inhibitors of fungal protein: mannosyl transferase 1 (PMT1). The 5-[[3-(1-phenylethoxy)-4-(2-phenylethoxy)phenyl] methylene]-4-oxo-2-thioxo-3-thiazolidineacetic acid 48 was inhibited *C. albicans* PMT1 with IC_{50} in the range 0.2–0.5 μM. Members of the series are effective in inducing changes in morphology of *C. albicans in vitro* that have previously been associated with loss of the transferase activity. The compounds 46-47 could serve as useful tools for studying the effects of protein O-mannosylation and its relevance in the search for novel antifungal agents [63].



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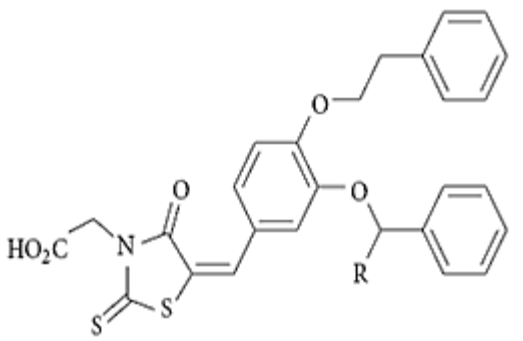
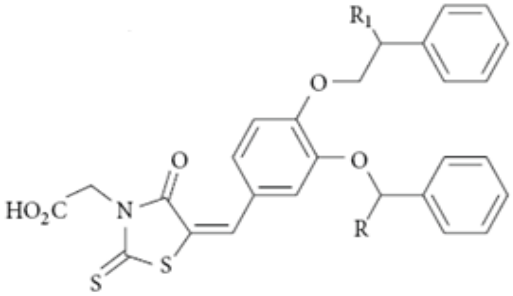
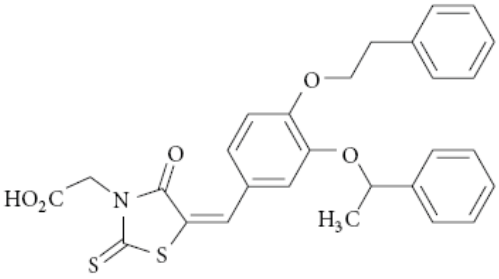


46R= Me, Et, i-Pr, CH_2OH, $CONH_2$, $CON(n\text{-}Pr)_2$.

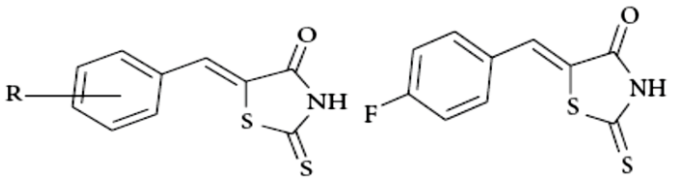


47 R = Me, Et. R_1=H, CF_3, Me

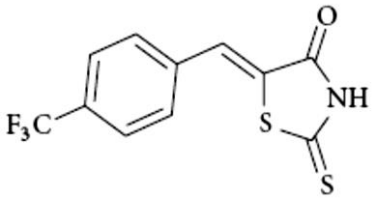


48

The benzylidene-rhodanines **49** which act as antifungal agents, compounds **50** and **51** showed fungicidal activity and are the most active against *Candida genus* and *C. neoformans* including clinical isolates. Other compounds of this series showed a very good activity against dermatophytes [64].



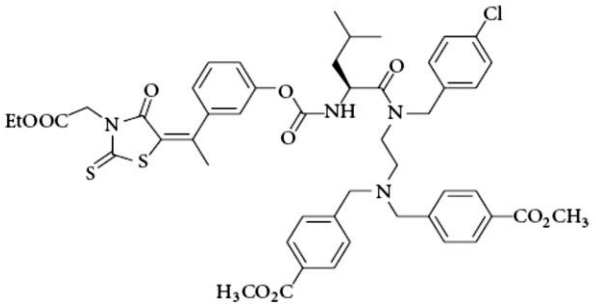
49 R = H, 4-Cl, 4-Br, 4-F, 4-CF_3,



51

2-F, 2-CF_3, 4-CH_3, 4-OCH_3,
3, 4-OCH_2O-, 3, 4, 5-tri-CH_3O,
2-pyridyl, 3-pyridyl, 4-pyridyl.

Antihepatitis C Virus (HCV) activity: The arylalkylidene rhodanines 52-53 inhibit HCVNS3 protease at moderate concentrations. They claimed these rhodanine derivatives are better inhibitors of serine proteases such as chymotrypsin and plasmin. The selectivity of aryl-methylidene rhodanines 52-53 with bulkier andmore hydrophobic functional groups increases by 13- and 25-fold towards HCV NS3 protease, respectively [65].



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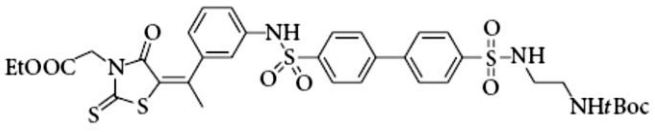
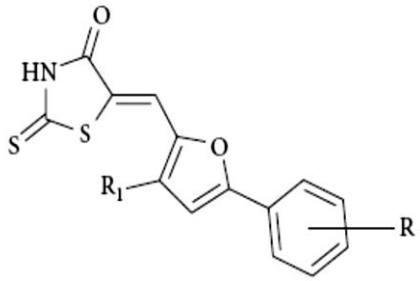


53

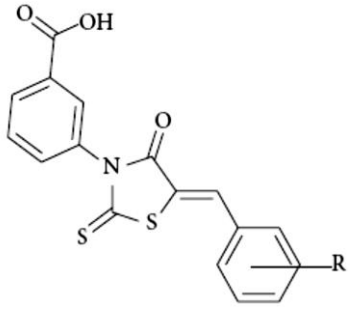
HIV-1 Integrase Inhibitor activity: Biologically evaluated rhodanine-based compounds 54 and identified these exhibiting anti-HIV-1 integrase activity and moderate inhibition of HIV-1 cell replication [66].



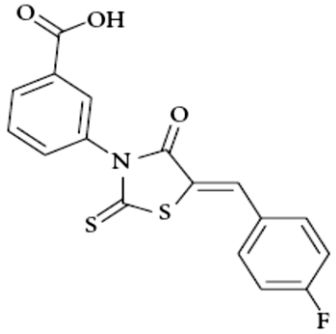
54

R = 4-CO_2H, 5-OH; 4Cl, 5-CO_2H; 2-Cl, 4-CO_2H, 5-OMe, 2, 3-OH, 5-CO2H;
4-CO_2H, 5-OH; 4CO2H, 5-OH R_1 = H, Me, OMe

Anti-Inflammatory activity: The evaluation of rhodanine-based compounds 55 as inhibitors of JSP-1. The SAR studies demonstrated that stronger electron-withdrawing functional groups appended to the aryl-benzylidene position provided analogs with the greatest potencies as illustrated by compound 56. Compound 56 has also reversible and competitive bind with substrate and showed a high degree of enzyme selectivity against other phosphatases. A series of rhodanine derivatives as novel inhibitors of phosphodiesterase-4 (PDE4). Structures 57 and 58 displayed the most significant activity of the compounds, being some 20- and 24-fold more potent than lead compound 59 [67].



55 R = H, 4-OH, 4-CH_3, 4-CH_3O, 4-F, 4-NO_2, 4-COOH.



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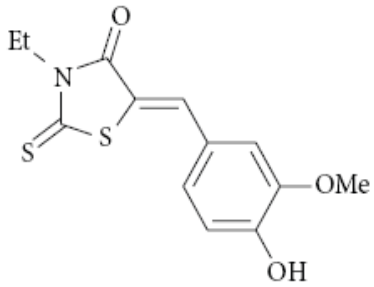

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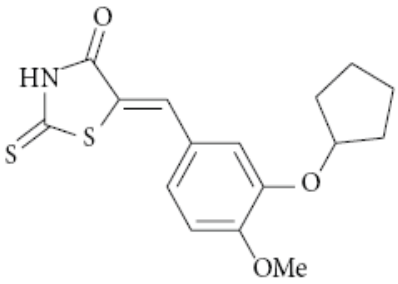

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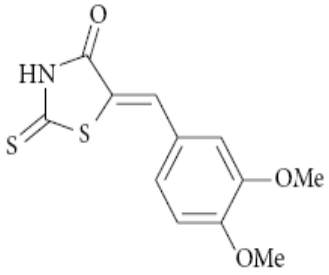
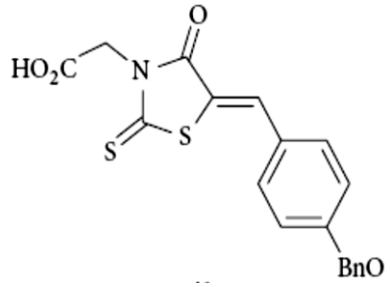


59

Anti-Sleeping Sickness activity: The first molecular inhibitors of dolicholphosphate mannose synthase (DPMS), a mannosyltransferase critically involved in glycoconjugate biosynthesis in *T. brucei*. The thiazolidinones 60, 61, and 62 in particular are promising candidates for development because of their respective activities against trypanosomal DPMS and GPI anchor biosynthesis. They reported that these DPMS inhibitors prevent the biosynthesis of glycosyl phosphatidylinositol (GPI) anchors and possess trypanocidal activity against live trypanosomes. Drug-like molecules 60–62 with activity against *Trypanosoma brucei* are urgently required as potential therapeutics for the treatment of African sleeping sickness [68].



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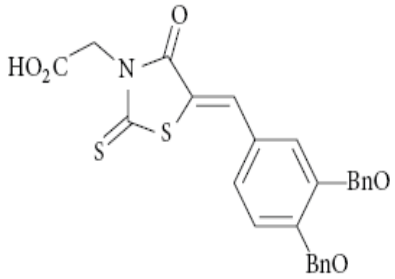

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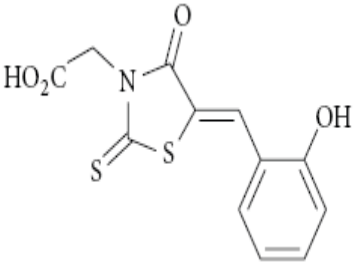
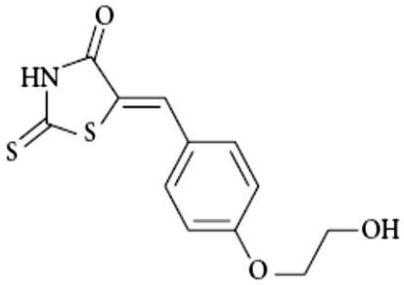


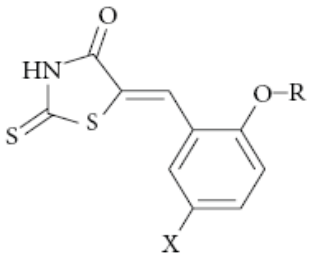
62

Tyrosinase Inhibitors activity: A series of dihydropyrimidin-(2H)-one analogues and rhodanine derivatives were evaluated for their inhibitory effects on the diphenolase activity of mushroom tyrosinase. Some of the compounds exhibited significant inhibitory activities. Compound 63 bearing a hydroxyethoxyl group at position-4 of phenyl ring exhibited the most potent tyrosinase inhibitory activity with IC_{50} value of 0.56mM. The inhibition mechanism analysis of compound 63 demonstrated that the inhibitory effect of the compound on the tyrosinase was irreversible. Such compounds might be served as lead compounds for further designing new potential tyrosinase inhibitors [69].

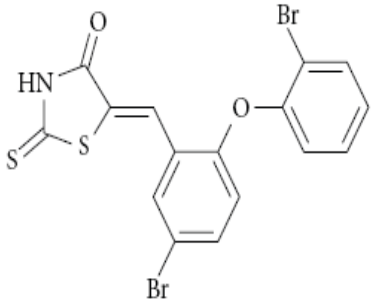


63

PRL-3 Inhibitors activity: A series of rhodanine derivatives 64 for their ability to inhibit oncolytic phosphatase (PRL-3). Benzylidene rhodanine derivative 64 showed good biological activity, while compound 65 is found to be the most active in this series exhibiting IC50 value of 0.9 Lm*in vitro* and showed a reduced invasion in cell-based assay [70].



64



65

R = H, Benzyl, CH_3SO_2, Pyridin-3-yl-methyl,
2-Chlorobenzyl, 2-Bromobenzyl, 4-Bromobenzyl.
X = Br, H, Phenyl, Benzofuran-3-yl.

Conclusion

Several of molecules based on azetidinones and rhodanines have been synthesized and evaluated with improved pharmacological activities. The literature reveals the various diverse biological activities like antimicrobial, anticancer, anticonvulsant, antihyperlipidemic, and anti-inflammatory properties. A variety of drugs in market today possess azetidinones and rhodanines β-lactam moiety and many ongoing research is focused on developing newer drugs. Hence it can be concluded that azetidinones and rhodanines derivatives have a great potential as bioactive molecules. Due to wide range of pharmacological activities and clinically used, these molecules have attracted much attention and encouraged the chemists and biologists to be extensive investigations or molecular manipulations, and as a result further improved protocol with better observation is still under progress.

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