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Review Article

Therapeutic Utility of 1, 3-Thiazines - Mini Review

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Abstract: 1, 3-Thiazine based compounds continue to yield promising antimycobacterial, antibacterial, antipyretic, anti-inflammatory, analgesic, antitumor, and antioxidant agents. The success of these compounds has been based on simple and cost effective synthetic routes and the presence of N-C-S linkage in its scaffold. A number of studies have been reported in the recent years to investigate different biological activities of 1, 3-thiazines. There are different classes of 1, 3-thiazines in the literature which can be divided in to natural and synthetic 1, 3-thiazines. There are several structural classes of synthetic 1, 3-thiazines such as 1, 3-thiazines as dihydro-1, 3-thiazine derivatives, 1, 3-thiazine spiro-derivatives and thioethers; 1, 3-thiazines with heterocyclic rings such as pyrimidine, pyrazole, thiazolidin-4-one and 1, 3, 5-triazine moiety; 1, 3-thiazine-2-amine, amide and hydrazides; 1, 3-thiazines with Schiff's bases. Herein natural and synthetic 1, 3-thiazine possessing molecules and their therapeutic actions are discussed.

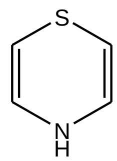
Keywords: 1.3-Thiazines; Spiro-thiazines; Thiasporines; Pyrimido-thiazines; Antidiabetic; Benzodiazepine; Anticancer; Antiinflammatory

INTRODUCTION

1, 3-Thiazine (Figure.1) containing compounds exhibit diverse set of biological activities such as antimycobacterial, antibacterial, antipyretic, anti-inflammatory, analgesic, antitumor, antioxidant and calcium channel modulatory activities [1]. As per the recent reports, around 362 FDA-approved sulphur-containing drugs are available wherein this heteroatom is found to be a part of the structure of sulphonamides, thioethers, sulfones or penicillin scaffolds [2]. Naturally occurring epicorazine, polycarbazines possess sulphur atom in their structures [3]. Recently various green synthetic methods for the preparation of 1, 3-thiazines have been reviewed and the therapeutic utility of 1, 3-thiazines and benzothiazines were also demonstrated [4]. In this review an attempt has been made to review the recent work on biological activities of 1, 3-thiazines.

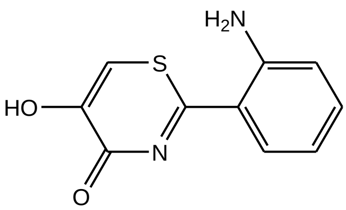
Naturally occurring 1, 3-thiazines (Thiasporines)

Natural products have been leading structures in drug development process of many therapeutic agents. Several sulphur containing compounds is available (Thiaplidiaquinones A and B) as natural products and recently thiazine and thiazole bearing natural compounds, Thiasporine A, B and C (Fig. 2a-c) were isolated from the marine-derived *Actinomycetospora chlora* SNC-032. Anticancer profile of these compounds revealed that, Thiasporine A possessing hydroxy-2-phenyl-4H-1, 3-thiazin-4-one moiety, showed cytotoxicity against a non-small-cell lung cancer cell line H2122 with an IC_{50} value of 5.4 μM. It was also reported that this compound was ineffective against other cell lines HCC366, A549, and HCC44 [5].



1, 3-thiazine

Figure (1)



Thiasporin A,B,C

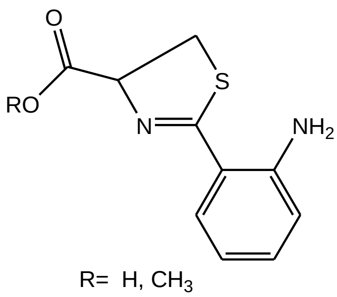


Figure (2a-c)

Molecular interactions - Role of sulphur and nitrogen

Amino acids present in the protein structure such as cysteine and methionine bearing sulfur atom in their side chains are observed to form many non-covalent interactions including H-bonds that influence structure and function of proteins. Sulfur acts as an H-bond acceptor and the S–H group behaves as H-bond donor and capable of forming a variety of H-bonds (Sulfur Center Hydrogen Bond, SCHB) [6]. This heteroatom can able to interact and establish sulphur-π bonds with aromatic aminoacids. Sulphur behaves as a weak negatively polarized atom when interacting with phenyl rings. Nitrogen (NH) acts as both H-bond acceptor and the H-bond donor and capable of forming strong H-bonds [7].

Antidiabetic activity

BACE2 (β-site APP-cleaving enzyme 2) is a protease present in the pancreas, found to play role in amyloidogenic diseases, such as AD and type 2 diabetes mellitus (T2D), caused by the accumulation of abnormally folded proteins that interfere with normal cell function [8]. Recent reports infer BACE2 as a therapeutic target for type 2 diabetes mellitus T2D which is one of the common metabolic disorders acquiring around 2.8% of the world's population [9]. 1, 3-thiazine in the form of amino dihydro and tetra hydro thiazines (Figure.3) show antidiabetic activity by selectively inhibiting BACE2 enzyme (Beta-Site APP-Cleaving Enzyme 2) **[**10, 11**].**

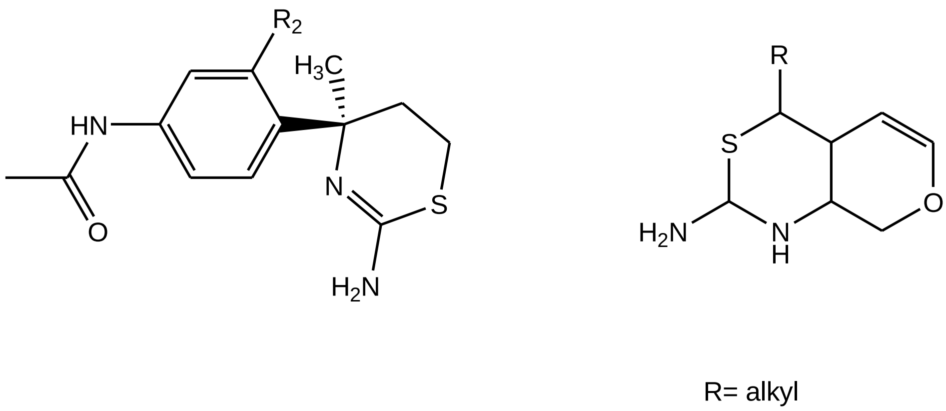
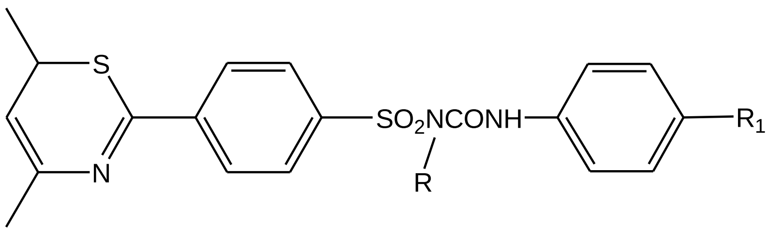


Figure (3)

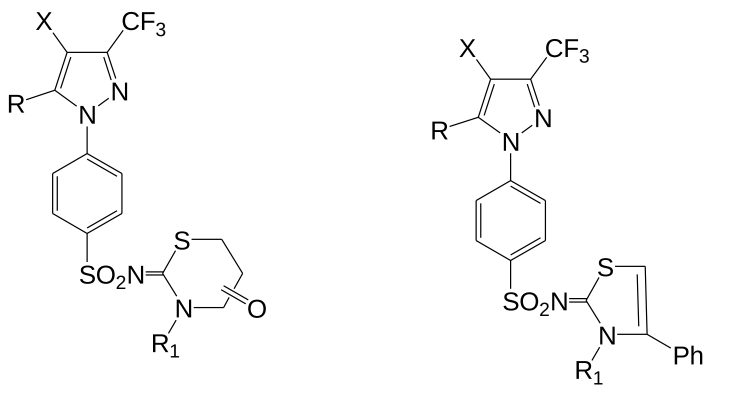
In general, sulphonyl urea derivatives possess good antidiabetic activity but these compounds have less metabolic stability. In order to get more efficient and metabolically stable compounds, Thakur et al synthesized phenylsulfonyl-substituted urea derivatives with 1, 3-thiazine moiety (Figure.4). These compounds were tested for hypoglycemic activity using oral glucose tolerance test in normal and NIDDM in STZ (streptozotocin induced type II diabetic-rat models. All the synthesized derivatives showed prominent oral hypoglycemic effect in respect of standard drug glibenclamide. Structure activity relationship showed that compounds with phenyl or 4-nitro phenyl ring on to the second amine of sulfonylurea displayed high oral hypoglycemic effect with improved metabolic stability [12].



R = Phenyl,Pheny l -4 -NO_2,Pyridin -2yl R_1=-H,-Cl,-OH,-NO_2,-OCH_3

Figure (4)

A novel series of 1.3-thiazines in the form of 4-oxo-5, 6-dihydrothiazines, 5-oxo-4, 5-dihydrothiazines and thiazolines containing sulphonyl urea derivatives were prepared (Figure.5). Trifluoromethyl substituted pyrazole ring was introduced on phenyl ring to obtain highly efficient antidiabetic compounds. In this study synthesized compounds were tested for hypoglycaemic activity using alloxan treated female albino mice and glucose was determined by the micro-colorimetric copper reduction technique. The results showed that cyclic thio-analogs showed potent antidiabetic activity than the other derivatives [13].



X= -H,-Br

R= -CH_3,-Furyl

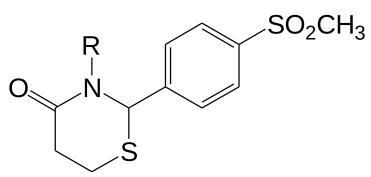
R_1=Benzyl,Napthyl,benzoyl

Figure (5)

Antiinflammatory and analgesic activity

1, 3-thiazinan-4-one derivatives with methyl sulphonyl moiety

It is well established that selective inhibition of COX-2 enzyme over COX-1enzyme is useful in the treatment of inflammation with less gastrointestinal toxicities [14]. 3-alkyl,-2-aryl-1,3-thiazinan-4-one derivatives, possessing a methylsulfonyl moiety (Figure.6) demonstrated cyclooxygenase (COX-1 & 2) inhibitory activity. Among the synthesized compounds, benzyl group possessing derivative displayed potent (IC_{50} = 0.06 μM) and selective (selectivity index > 285) inhibition than the aliphatic and cycloalkyl substituted derivatives [15].



R=Benzyl,Phenethyl,Cyclohexyl,Propyl,Butyl

Figure (6)

1, 3-thiazinones containing triazole moiety

A series of 1, 3-thiazinones containing triazole moiety (Figure.7) showed antiinflammatory and analgesic activities as well as gastrointestinal irritation liability. Among the compounds studied, compounds with chloro, nitro and naphthyl side chain showed most remarkable antiinflammatory activity in the carrageenan and serotonin induced oedema and in the inhibition of castor oil-induced diarrhea tests. The analgesic activity of these active compounds correlated with their antiinflammatory activities in the inhibition of acetic acid-induced writhing test [16].

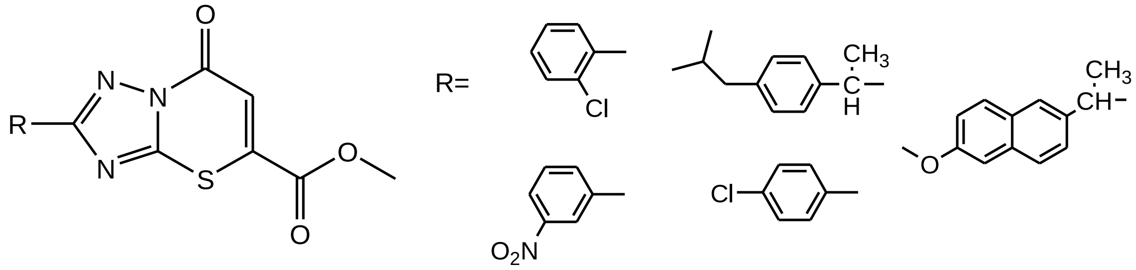
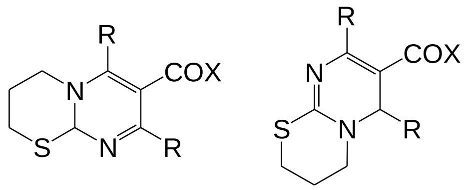


Figure (7)

Pyrimido-thiazine derivatives

A series of racemic pyrimido-thiazine derivatives (Figure.8) were synthesized and evaluated for their antiinflammatory and antipyretic activities. Among the synthesized compounds, derivatives with electron releasing methyl and 4-methoxy phenyl substituents were found to be the most potent in rat carrageen and yeast fever assays. Therapeutic activity of these derivatives was found to be comparable to acetylsalicylic acid and aminophenazone in an antiinflammatory model and an antipyretic test. These compounds did not inhibit prostaglandin biosynthesis *in vitro*. The authors also demonstrated low reactivity of these derivatives as calcium channel blockers [17].



X=-OCH_3,-OC_2H_5,-NHPh
R=-CH_3,-C_2H_5,-C_6H_5,-C_6H_4-NO_2,-C_6H_4-OCH_3
R_1=-CH_3,-C_6H_5

Figure (8)

1, 3-thiazines with imidazolidine moiety

Synthesis of 1, 3-thiazinones containing imidazolidine moiety (Figure.9) was carried out by Srikanth et al. These compounds were reported to have significant *in vitro* anti inflammatory activity in the models such as membrane stabilization and haemolytic tests [18].

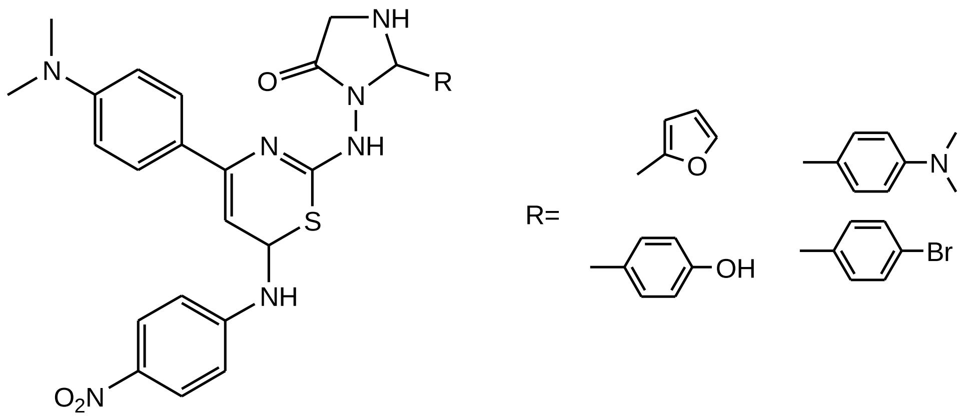
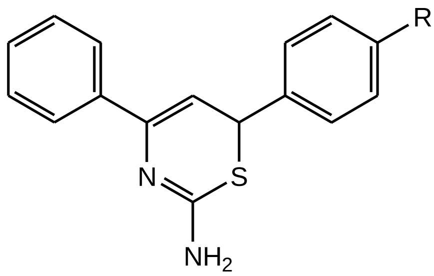


Figure (9)

1, 3-Thiazine-2-amine derivatives

Gomathi *et al* studied analgesic and anti-inflammatory effects of 1, 3-thiazine-2-amine derivatives (Figure.10) using tail clip method and carrageenan induced rat paw edema methods. The test compounds were found to be active in both the animal models when compared with the effect of standard drug diclofenac sodium, suggesting the significance of disubstitution with phenyl rings and free amino group [19].



R=F,Cl

Figure (10)

Anticancer activity

Pathophysiology of all cancers involves the malfunction of genes controling cell growth and division. According to recent estimates from the International Agency for Research on Cancer (IARC), the global burden is expected to grow at a rapid rate in the coming years [20].

Thioethers derivatives

A series of novel thiazoline and thiazine multithioether derivatives (Figure.11) were tested for antitumor activity. The *in vitro* antitumor activities of the compounds against A-549 (human lung cancer cell) and Bcap-37 (human breast cancer cell) were evaluated by the standard MTT (3-(4, 5-dimethyl-thiazollyl-2)-2, 5-diphenyltetrazolium assay. Among the synthesized compounds, few were found to have good anticancer activity against A-549 and Bcap-37 cell lines [21].

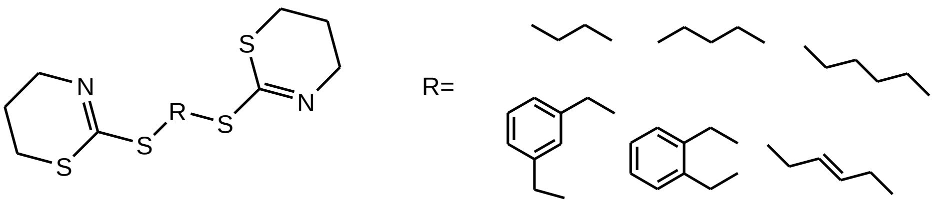


Figure (11)

1, 3-Thiazines and thiazolone derivatives containing pyrazole moiety

Abdelhamid *et al.* synthesized *a* novel series of 1, 3-thiazines and thiazolone derivatives containing pyrazole moiety (Figure.12) and evaluated for their antitumor activity against human breast carcinoma (MCF-7) cell lines using colorimetric viability assay. Results revealed that all the synthesized compounds showed concentration dependent inhibitory activity. The introduction of a methoxy group at the 4-position of phenyl group was found to be unfavourable and introduction of chlorine atom was found to be favorable for the antitumor activity [22].

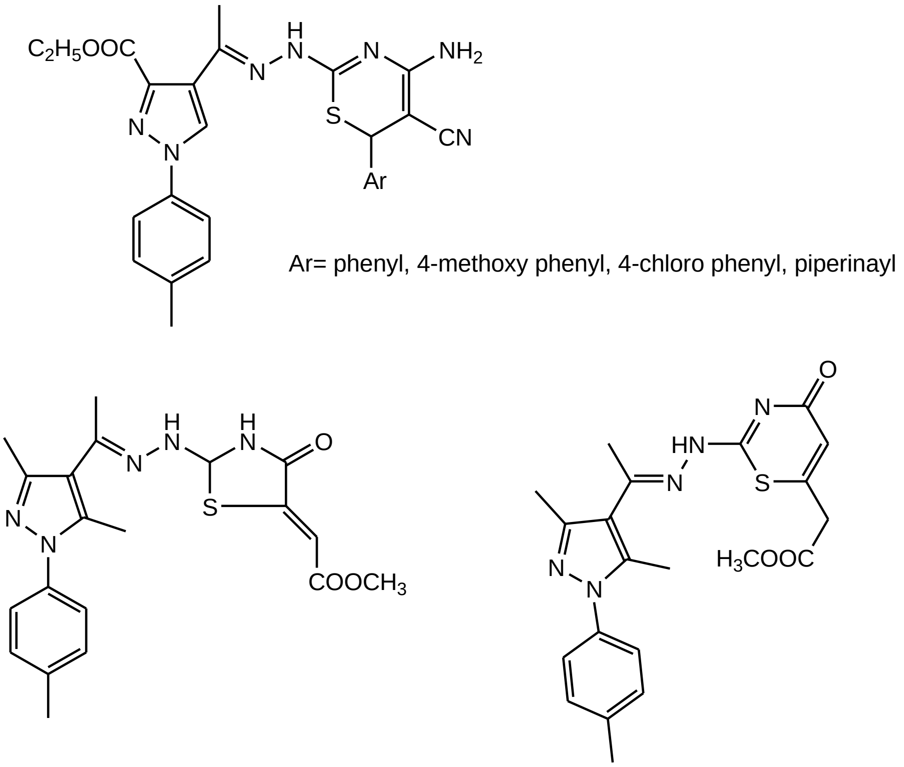


Figure (12)

Antitubercular activity

15, 6-dihydro-4H-1, 3-thiazine derivatives

Mycobacterium tuberculosis is responsible for tuberculosis infection, and the emergence in recent years of multi-resistant strains has made it a serious challenge in terms of international public health. Annually 10 million new cases of tuberculosis appear and about two million people die each year as a consequence of the disease [23-24]. A series of 5,6-dihydro-4H-1,3-thiazine derivatives (Figure. 13) was synthesized using selected α,β-unsaturated ketones and thiobenzamide at room temperature. The antimycobacterial activities of these compounds were determined against Mycobacterium tuberculosis H37Rv (ATCC 27294) using the Alamar blue assay. Antitubercular activity profile of the compounds was found to be good and especially derivatives with alkyl groups, methyl and ethyl exhibited high activity at a concentration of 6.25 mg/ ml [25].

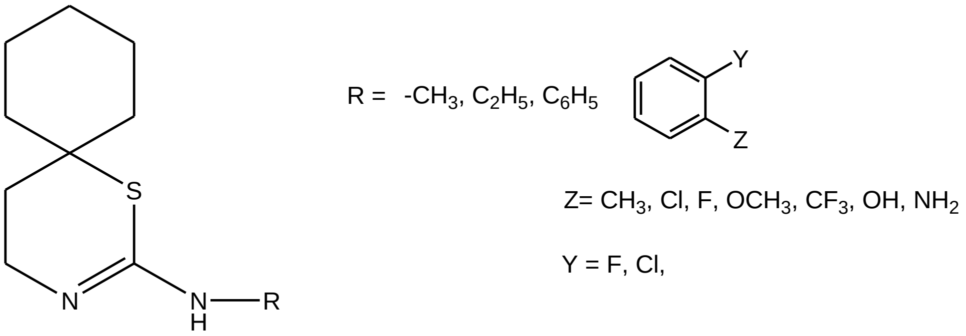


Figure. (13)

Anti viral activity

1, 3-thiazine derivatives as hydrazides

A series of novel thiazoles and 1, 3-thiazine derivatives (Figure.14) were synthesized using ethyl 3-(1-(2-thiocarbamoylhydrazono) ethyl)-1, 5-diphenyl-1*H*-pyrazole-4-carboxylate with hydrazonoyl halides and aryliden-emalononitriles. These compounds were tested against Vero-cell culture and against Herpes simplex virus type 1 (HSV-1) using the standard drug aphidicolin. These studies revealed that compounds with phenyl or 4-methoxy phenyl group present as substituent groups were active as antiviral compounds. The results also showed that derivatives containing 6-membered thaizine ring were more active than derivatives with 5-membered thaizine scaffold [26].

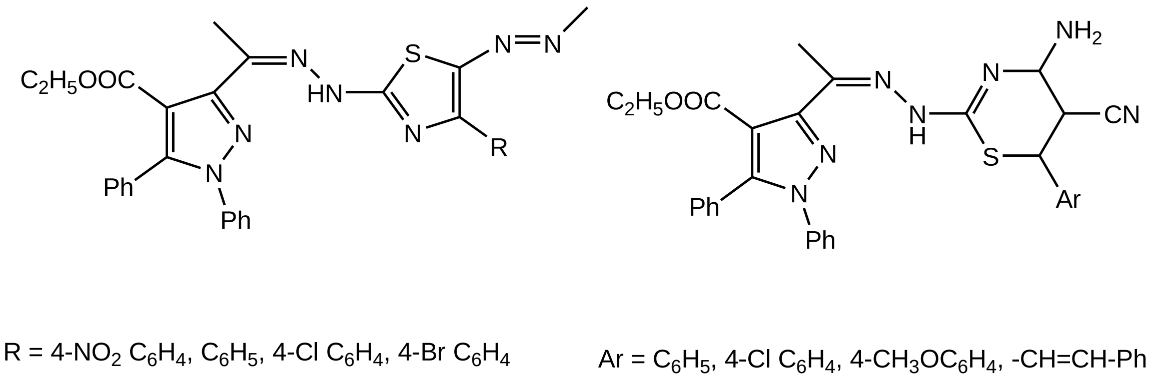


Figure (14)

Neuroprotector activity

1, 3-thiazine spiro-derivatives

Different spiro-derivatives of 1, 3-thiazine (Figure. 15) were synthesized as potential neuroprotectors agents. The derivatives were synthesized using electron releasing alkyl alkoxy, hydroxy and amine groups, electron withdrawing halogen atoms such fluoro, chloro and trifluoromethyl groups. The structure activity relationship showed that the inhibitory activity depends on the position of the substituents. Among the synthesized spiro-thiazines, derivatives with ethyl- and isopropyl- groups demonstrated high inhibitory ability. It is also reported that these spiro scaffolds compounds are capable to block the glutamate induced calcium ion uptake [27].

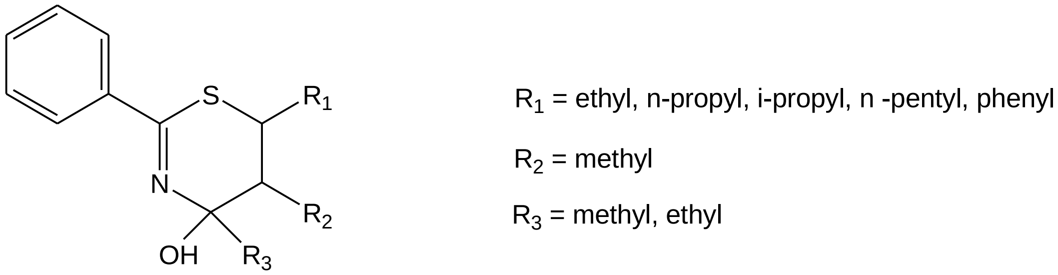


Figure (15)

Anticonvulsant activity

1, 3-thiazine derivatives substituted with naphthyl ring

Ravindar B et al synthesized a series of 1, 3-thiazine derivatives (Figure.16) containing naphthyl ring and evaluated them for anticonvulsant activity. These compounds were screened for anticonvulsant activity using pentylenetetrazole-induced seizures test wherein they showed good anticonvulsant activity and results also showed that 1,3-thiazines were more potent than chalcones. Highest anticonvulsant activity was obtained for the compound containing 4-fluorophenyl substituent on the thiazine ring [28].

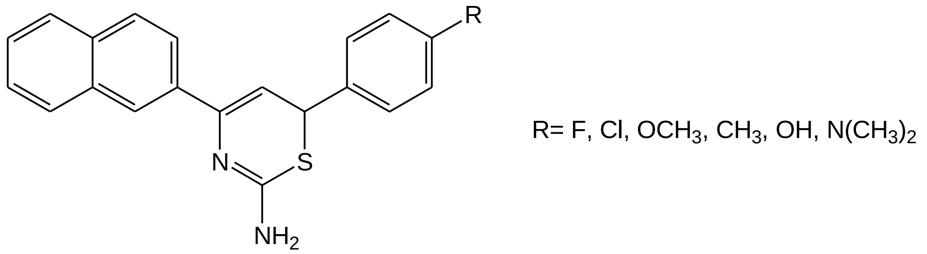


Figure (16)

Amines with pyrrolo - 1,3-thiazine nucleus

In search of central nervous system active compounds, Jagodzinski et al. synthesized different alkyl and aryl amines containing pyrrolo-1, 3-thiazine nucleus (Figure.17). The results of the anticonvulsant activity showed that aryl amines were found to be more potent than alkyl derivatives. Within the tested compounds, chloro phenyl substituted derivative had less toxicity and high potency in the pentylenetetrazole-induced seizures test. These hybrid compounds were also screened for antianxiety and spontaneous motor activities using different animal models and proved to be active [29].

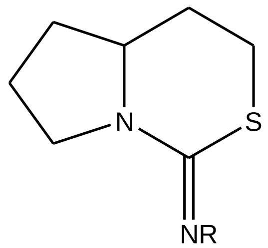


Figure (17)

Growth promoting activity

1, 3-thiazine derivatives as hydrazides

Hushare *et al* studies growth promoting effects of 1, 3-thiazine derivatives (Figure.18) on some flowering plants such as *Papaver rhoeas, Dianthus chinensis, Candy tuft* and *Calendula officinalise.* It was observed that morphological characters of treated groups plants exhibited significant shoot growth, and considerable increase in the number of leaves than that of untreated ones [30].

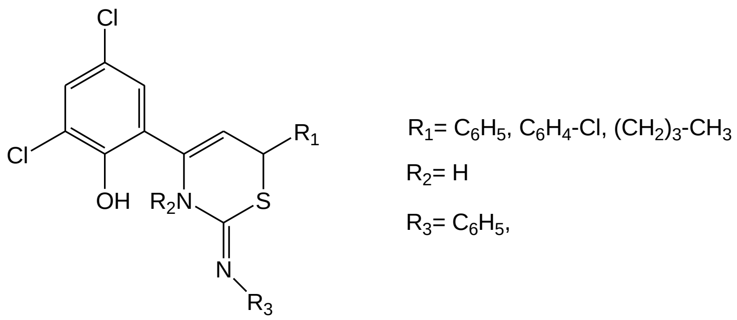


Figure (18)

iNOS inhibitory activity

Acylamino-1, 3-thiazine derivatives

2-Amino-5, 6-dihydro-4*H*-1, 3-thiazine (Figure.19) is a potent inhibitor of NO synthase (NOS). 2-*N*-Acylamino-5, 6-dihydro-4*H*-1, 3-thiazine derivatives (Figure.20) exhibited *in vitro* and *in vivo* iNOS-inhibiting activity. The iNOS inhibitory activity was performed *in vitro* by radiometric method with the use of [^{3}H]-*L*-arginine (a natural substrate of NO synthase). The acylated derivative was proved to be highly potent antihypotensive and the authors patented the derivative as a potential antihypotensive agent [31].

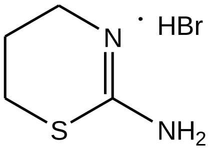


Figure (19)

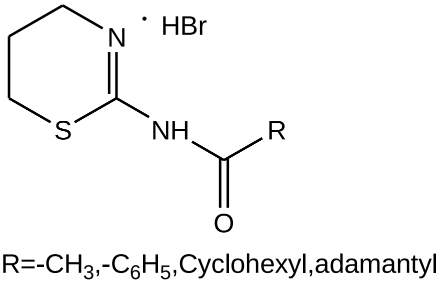


Figure (20)

Anti infective activity

Their impact of infectious diseases high in developing countries due to the emergence of widespread drug resistance which resulted in the increase demand for novel antimicrobial compounds.1, 3-Thiazines which are disubstituted with phenyl rings or phenyl and biphenyl ring or phenyl and 4-bromo naphthyl ring exhibited good antimicrobial activity. Ceftibuten (Figure.21); is broad-spectrum cephalosporin contains 1,3-thiaizne scaffold in its structure which led to the synthesis and antimicrobial evaluation studies of 1,3-thiaizne bearing compounds. Antimicrobial 1, 3-thiazines are linked to aryl thiazolidin-4-one or contain free amino group or N-acetamido substituent groups.

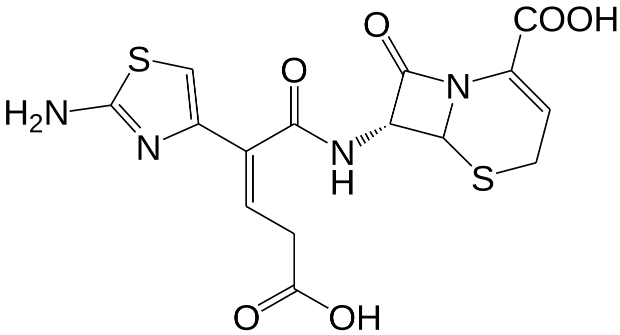
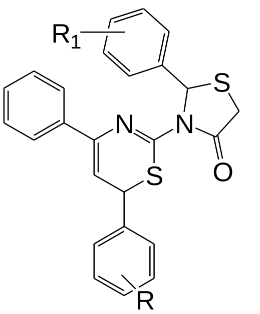


Figure (21)

1, 3-Thiazines with thiazolidin-4-one moiety

A series of 3-(4,6-diphenyl-6H-1,3-thiazin-2-yl)-2-(4-methoxyphenyl) thiazolidin-4-one derivatives (Figure.22) were synthesized and their antimicrobial activity was tested against several gram negative and positive organisms. These compounds showed good antibacterial activity, indicating the important contribution of thiazolidin-4-one substitution [32].

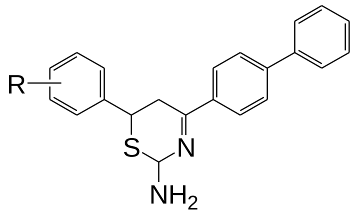


R= C_6H_5	R_1= 4 -$OCH_3C_6H_4$
R= C_6H_5	R_1= 2 - Cl C_6H_4
R= C_6H_5	R_1= 4 - Cl C_6H_4
R= 4-OCH_3 C_6H_4	R_1= 4 -$OCH_3C_6H_4$
R= 4-OCH_3 C_6H_4	R_1= 2 - Cl C_6H_4
R= 4-OCH_3 C_6H_4	R_1= 4 - Cl C_6H_4

Figure (22)

1, 3-Thiazines with biphenyl ring

Biphenyl substituted 1, 3-thiazines (Figure.23) exhibited *in vitro* antibacterial activity when tested against gram-positive organisms (*Staphylococcus aureus* and *Bacillus subtilis*) and gram-negative (*Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) organisms by the conventional agar dilution procedures [33].



R=H,2-OCH$_3$,4-OCH$_3$,2-Cl,4-Cl

Figure (23)

1, 3-Thiazines with 1, 3, 5-triazine moiety

Novel hybrid 1,3-thiazine-1,3,5-triazine derivatives (Figure.24) were synthesized and screened for antibacterial activity by Singh et al. These hybrid compounds were active against bacteria, especially derivatives possessing nitro groups and nitro and hydroxyl groups showed good potency against gram negative as well s gram positive bacteria. Molecular docking studies demonstrated that these derivatives showed good binding affinity towards eubacterial ribosomal decoding A site (Escherichia coli 16S rRNA A site) [34].

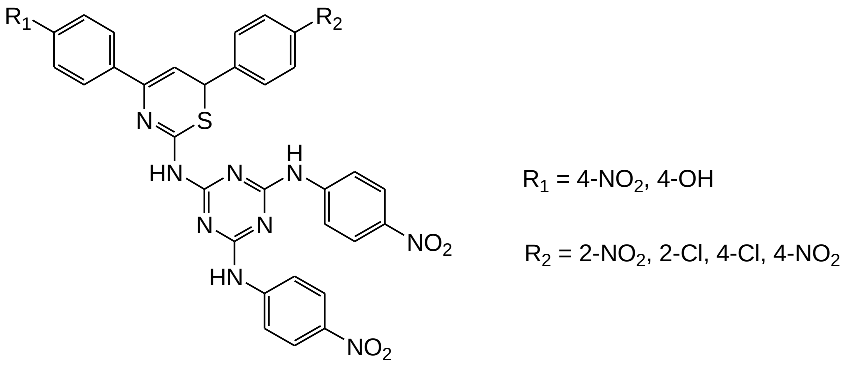
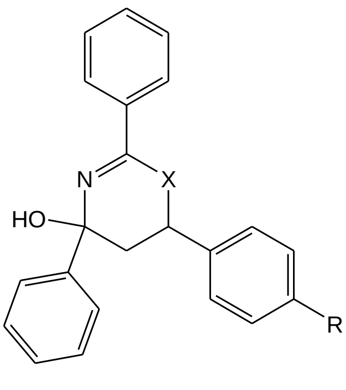


Figure (24)

In study by Tony et al, molecular docking was carried out for the derivatives of 1, 3 thiazines and 1, 3 oxazines (Figure. 25) to predict binding affinity towards cytochrome p450 14 α- sterol demethylase from mycobacterium tuberculosis. The results indicated that the 1, 3 thiazines exhibited good affinity (-12.135kcal/mol to-14.2547 kcal/mol) than the derivatives of 1, 3 oxazines (-11.3042kcal/mol to -13.0389kcal/mol). Among the compounds studied, methyl substituted 1, 3 thiazine showed highest affinity towards the enzyme [35].



X= S, O R= CH$_3$,Cl, F

Figure (25)

1, 3-Thiazines with schiffs bases

Pitchai *et al* synthesized a series of 1.3-thiazine derivatives possessing schiffs bases in their structure (Figure. 26), using thiourea and various chalcones derived by Clasien-Schimdt reaction between various schiff bases of p-amino-acetophenone and p-chloro-benzaldehyde and studied their antimicrobial activity using disc diffusion method. Among the synthesized compounds methoxy derivative showed good antibacterial activity and it was observed that these derivatives were active as antibacterial agents than antifungal agents [36]

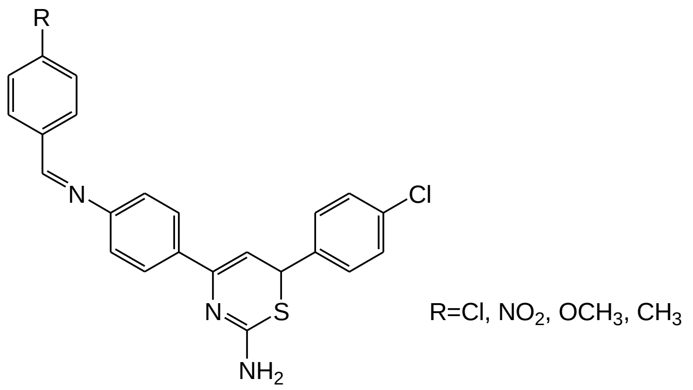


Figure (26)

4-Phenyl-2-substituted-amino-thiazines

A novel series of 4-phenyl-2-substituted-amino-thiazines (Figure. 27) were synthesized using chalcones and phenylthiourea and diphenyl thiourea. Antibacterial activity was determined using gram positive and gram-negative pathogens. Among the two series of compounds, good activity was obtained for the derivatives possessing n-hexyl side chain than the other derivatives [37].

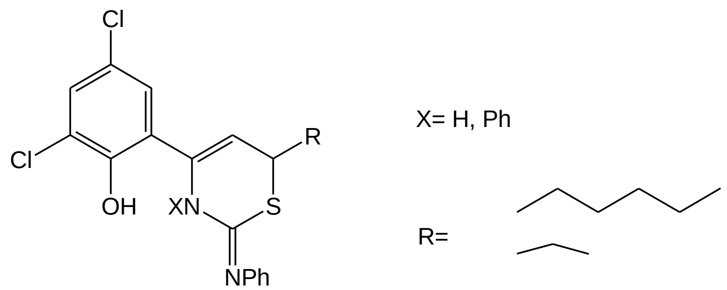


Figure (27)

1, 3-Thiazines with bromo-naphthyl ring

Prakash *et al* synthesized 4-bromo naphthyl containing 1,3-thiazine derivatives with various electron releasing and electron withdrawing substituent groups on phenyl ring (Figure. 28). In this study, antimicrobial activity was evaluated against *Aspergillus flavus*, *Penicillium chrysogenum* and *Aspergillus niger* and different gram positive and gram negative bacteria. Among the synthesized compounds, unsubstituted derivative and methoxy containing derivatives exhibited better antifungal activity than the standard amphotericin-B. These compuods were also active against *Klebsiella pneumoniae* and good antibacterial activity was observed with methoxy and bromine possessing derivatives [38].

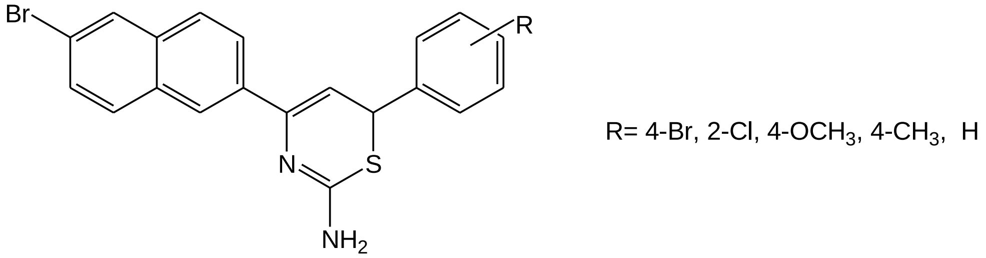


Figure (28)

1, 3-Thiazines with nitro-substituted phenyl ring

A series of nitro-substituted 1,3 thiazines (Figure. 28) were synthesized by the condensation of 2-hydroxy-3-nitro-5-chlorochalcones with thiourea, phenylthiourea and diphenylthiourea in ethanolic KOH solution. These derivatives were screened for their antibacterial activity against *S. aureus*, *B. subtilus*, *E. coli* and *P. Aerugiuosa* [39]. Similarly bromo substituted compounds were found to be effective antibacterial agents several strains [40].

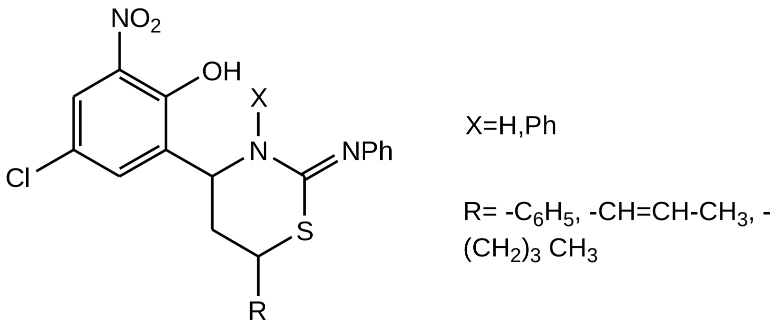


Figure (28)

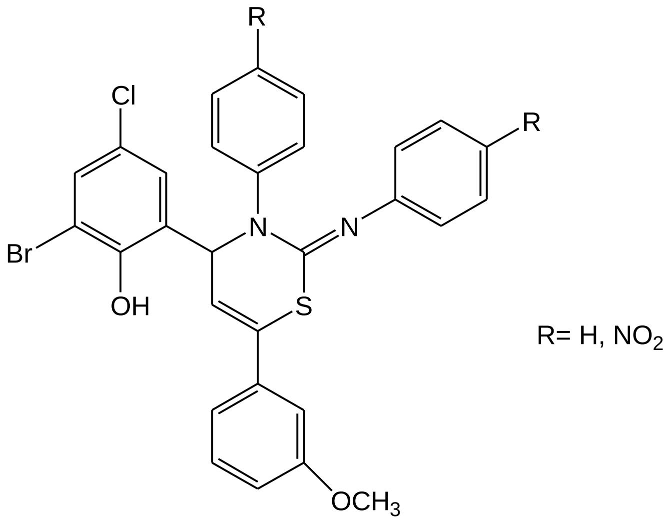


Figure (29)

Acetamido 1, 3-thiazines

A series of acetamido-1, 3 thiazines (Figure. 30) were synthesized and screened for their antibacterial and antifungal activity using disc diffusion method. Among the synthesized compounds, derivative with electron withdrawing substitutents such as chloro and nitr**o** groups shown good antibacterial and antifungal activity [40].

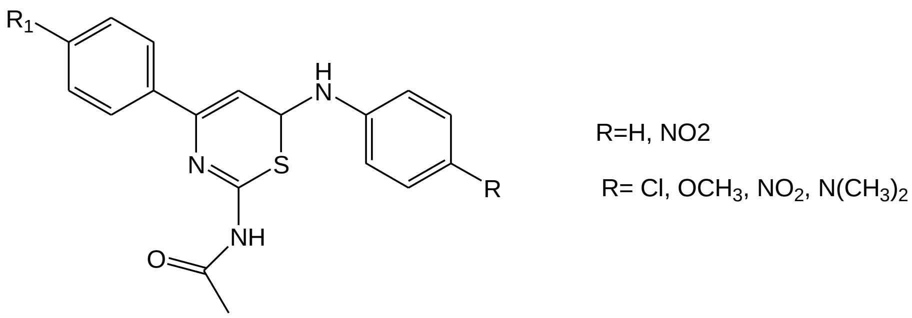


Figure (30)

Benzodiazepine receptor binding affinity

Fused 2-Thiohydantoin derivatives

A series of fused 2-thiohydantoin derivatives (Figure. 31) were synthesized and evaluated for their affinity towards benzodiazepine receptors (GABA). The structure of one of the synthesized compounds with cinnamoyl moiety was examined using crystallography in this study. All the synthesized compounds showed good affinity for the benzodiazepine receptors [42].

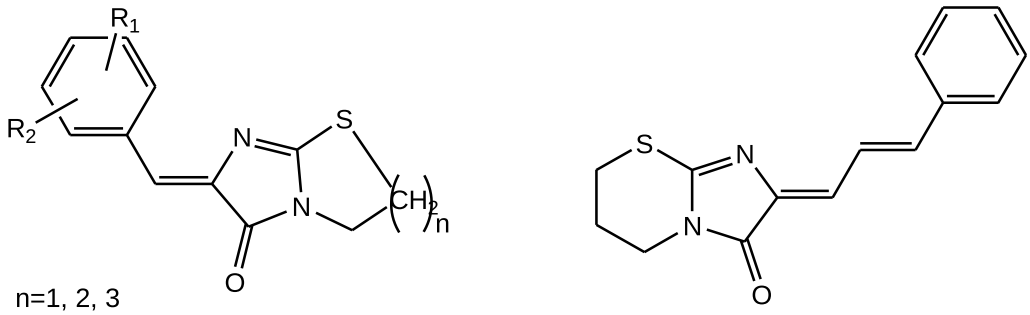


Figure (31)

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