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Chemical and Pharmacological Potential of Various Substituted Thiazine Derivatives

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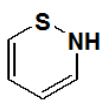
Abstract: Heterocyclic compounds have strong interest in pharmaceutical research area because of their useful pharmacological activities. Heterocyclic compounds are abundant in nature and have acquired more importance because their structural subunits are exhibit in various natural products such as vitamins, hormones, antibiotics etc. The multifaceted chemical potential of 1,3-thiazine- a six membered species containing nitrogen and sulphur in the ring has led to unabated research in their synthetic methodologies. Thiazines are six membered heterocyclic compounds which have promising pharmacological activities which have drawn the attention of scientists and researchers. It is present in the fused form with β-lactam ring in major class of antibiotics like cephalosporins which shows the prevalence of thiazines. Thiazine compounds possess variety of pharmacological activities like anti-microbial, anti-mycobacterial, antifungal, antiviral, antitumor, antipsychotic, anti-inflammatory etc. The significance of thiazine derivatives has potential pharmacological moiety and future of these derivatives in the field of drug research. Some of the pharmacological activities are briefly summarized. This article summarizes various chemical reactions like condensation, cyclo-addition, ring transformations etc. The review focuses on thethiazine derivatives with potential activities that are now in development.

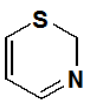
Keywords: 1,3-Thiazine, antimicrobial, biological activities, heterocyclic compounds, β-lactam ring, cephalosporins.

1 Introduction

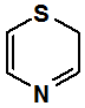
Thiazines are six member heterocycles that contain in their structure a nitrogen atom and a sulfur atom. Thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities. 1, 3-thiazines are of great importance because they form part of the framework of cephalosporins (3,6-dihydro-2H,1,3-thiazine) and also in some other medicinally important compounds like Xylazin (agonist at the α_2 class of adrenergic receptor is used for sedation, anesthesia, muscle relaxation, and analgesia in animals), Chlormezanone (used as an anxiolytic and a muscle relaxant) etc [1-3]. Thiazine-a heterocyclic compound having four carbon atoms and one nitrogen and sulphur atom at varied positions in the six membered ring exist as 1,2; 1,3; 1,4-thiazines and subsequently their derivatives having N-C-S linkage have been used as antitubercular, antibacterial, antimicrobial, antitumor, insecticidal, fungicidal, herbicidal agents, tranquilizers and various dyes etc [4-6]. Further, 1,3-thiazine core moieties have remarkable potential of anti-radiation agents.2 1,3-Thiazines are used in various organic synthesis and transformations as reaction intermediates [7]. Thiazines are organic compounds with molecular formula C_4H_5NS**.** Thiazine is a six member heterocyclic ring system, which contains two heteroatoms (N and S) placed in the heterocyclic ring. Thiazine derivatives may be 1, 2-thiazine, 1, 3-thiazine or 1, 4-thiazines [8].



1, 2-thiazine



1, 3-thiazine



1, 4-thiazines

The heterocyclic compounds which contain nitrogen and sulphur possess an enormous significance in the field of medicinal chemistry. Many researchers have synthesized different thiazines derivatives that exhibit various biological activities such as anti-tubercular, anti-fungal, anti-bacterial, analgesic, anti-inflammatory etc. Some thiazine derivatives in the development phase due to their versatility of the thiazine skeleton, its chemical simplicity and accessibility. Many compounds of thiazines were known as phenothiazines. Phenothiazines are used as vermifuge for liver stock and also as an insecticide [9].

The 1, 3 thiazine nucleus is active core of Cephalosporin which are among the widely use β lactam antibiotics A large

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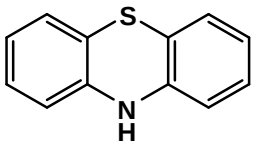
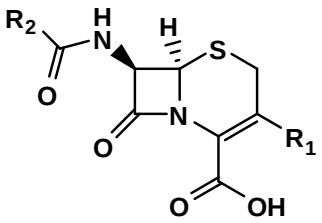
group of dyes has phenothiazine structure, including methylene blue thiazine are used for dyes, tranquillizers. Thiazine can help reduce some of that extra water weight you may be holding on to in stomach. Thiazine is a fairely basic diuretic supplement, it reduces water and increase vascularity, so it is also use as anabolic agent in medicine [10].



Phenothiazine

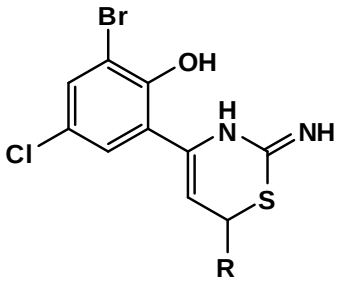


Cephalosporin

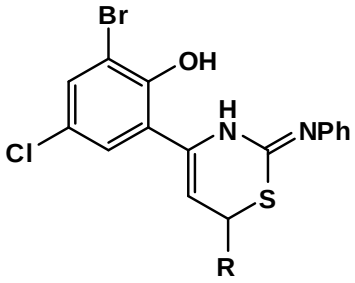
2 Biological potential of 1,3-thiazines

2.1 Antimicrobial Activity

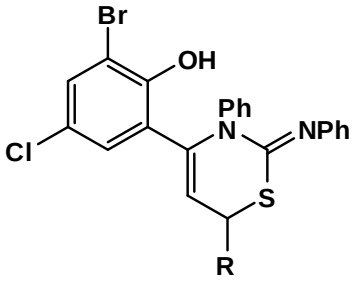
The 2-bromo-4-chloro-6-(3,6-dihydro-6-substituted-3-phenyl-2-(phenylimino)-2H-1,3-thiazin-4-yl) phenol derivatives (**1a-c**), (**2a-c**) and (**3a-c**) have been screened for their antibacterial activity against against some gram positive bacteria viz. *Staphylococcus aureus* and *Bacillus subtilus* and gram negative bacteria viz. *E.Coli* and *Pseudomonas aerugiuosa* species at conc. of 1000µm. Gentamycin is used as a standard [3].



1a-c



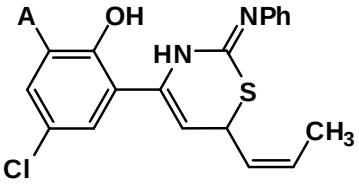
2a-c



3a-c

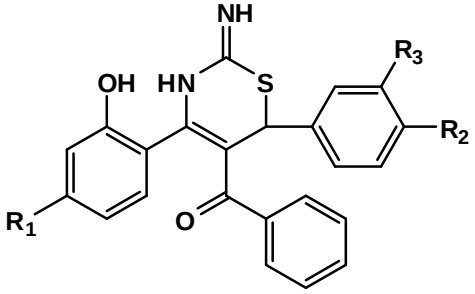
R= $-C_6H_5$, $-CH=CH-CH_3$, $-(CH_2)_3-CH_3$ **a**=benzaldehyde, **b**= crotanaldehyde, **c**=valeraldehyde

The 4-(2-hydroxy-3-bromo/nitro-5-chlorophenyl)-6-(1'-propene)-2-iminophenyl-3,6-dihydro-1,3-thiazine (**4a-b**) have been evaluated for their *in vitro* growth of inhibitory activity against *Escherichia coli, S. aureus, B. subtilis and Phaseolus argenosa.* Almost all the compounds have shown remarkable inhibitory activity against all the test pathogens [8].



4a-b A= Br/NO_2

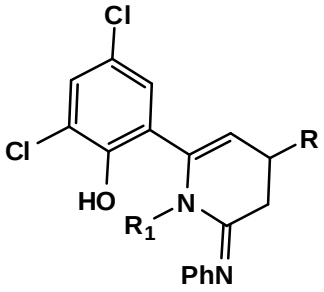
The 4-(2-hydroxy substituted phenyl)-5-benzoyl-6-(3,4-disubstituted phenyl)-2-imino-6-H-2,3-dihydro-1,3-thiazine derivatives (**5a-d**) and (**6a-d**) were evaluated for antimicrobial activity against gram positive bacteria *S. aureus* and *S. subtilus* and gram negative becteria *E.coli* and *P. aeruginosa*. With increase in number of hetero atoms the antimicrobial activity increases in the same order for all tested gram positive and gram negative bacteria [11].



Compounds 5a-d and **6a-d**

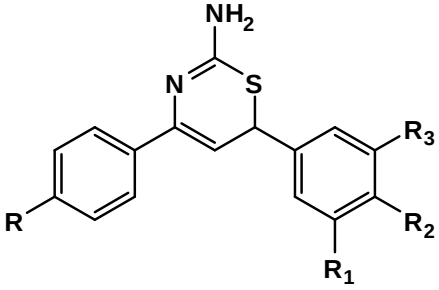
The pyrimido[2,1-b]1,3-thiazine derivatives, 6,8-bis-(substituted benzylidene-amino)-3,4,6-trihydro-pyrimido-[2,1-b][1,3]-thiazin-2-one (**7a-b**) and 6,8-bis-(substitutedbenzylidene-amino)-3-(4-chloro-benzylidene)-4,6-dihydropyrimido[2,1-b][1,3]-thiazin-2-one (**8a-b**) have been tested for their activity againest *E. coli, S. aureus, M. phlei, B. subtilis, C. albicans, A. niger* and have shown that

Compounds (11a-d)



Compd	R	R1
11a	$-CH_2CH_3$	H
11b	$-CH_2CH_3$	$-C_6H_5$
11c	$(CH_2)_5-CH_3$	**H**
11d	$(CH_2)_5-CH_3$	$-C_6H_5$

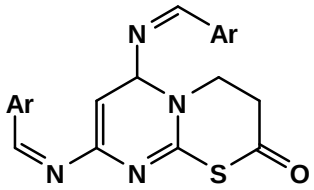
Compound 12



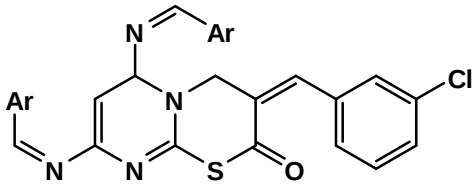
7b and **8b** were slightly active against the tested microorganisms [12].

Table 1

Compd	R_1	R_2	R_3	Compd	R_1	R_2	R_3
5a	H	H	H	**6a**	CH_3	H	H
5b	H	OCH_3	H	**6b**	CH_3	OCH_3	H
5c	H	OCH_3	OCH3	**6c**	CH_3	OCH_3	OCH_3
5d	H	$N(CH_3)_2$	H	**6d**	CH_3	$N(CH_3)_2$	H

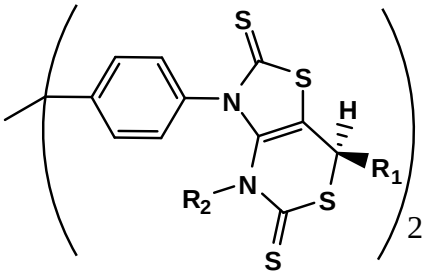


7a Ar=$-C_6H_5$ **7b** Ar=p-C_6H_4-Cl



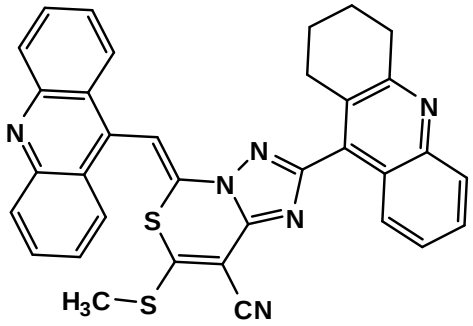
8a Ar =$-C_6H_5$ **8b** Ar =p-C_6H_4-Cl

The 4,4-bis(4,7-diaryl-2,3,4,5,7-pentahydrothiazolo(4,5-d)(1,3)-thiazine-2,5-dithion-3-yl) bibenzyls (**9a-j**) derivatives were screened for antifungal activity against *Fusarium oxysporum*, *penicillium citrinum* comparing with grisieofulvin and dathane M-45 as standards. **9c**, **9e**, **9i**, **9j** have shown best antifungalactivity [13].



Compounds 9a-9e

Some new sulfur-nitrogen heterocyclic systems 1,3-thiazines incorporating acridine and 1,2, 3,4-tetrahydroacridine (**10**) was evaluated *in vitro* for their antibacterial activities against *S. aureus (ATCC 25923)* and *S. pyogenes (ATCC 19615)* as examples of Gram positive bacteria and *Pseudomonas fluorescens (S 97)* and *P. phaseolicola (GSPB 2828)* as examples of Gram negative bacteria. It was also evaluated *in vitro* for their antifungal activities against the *Fusarium oxysporum* and *Aspergillus fumigatus* fungal strains. Cephalothin, Chloramphenicol and Cycloheximide were used as reference drugs for Gram positive bacteria, Gram negative bacteria and fungi respectively. The compounds have shown near activity as the reference [14].



Compound 10

Two series of compounds by reacting 2'-Hydroxy 3',5'-dichloro-4-ethyl chalcone and 2'-hydroxy-3',5'-dichloro-4-hexylchalcone, compound 4-(2'-hydroxy-3'5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1,3-thiazine (**11a**), 4-(2'-hydroxy-3', 5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3-phenyl-1, 3-thiazene (**11b**) and 4-(2'-hydroxy-3', 5'-dicholoro -phenyl)-6-hexyl-2-iminophenyl-1, 3-thiazene (**11c**) and 4-(2'-hydroxy-3', 5'-dichlorophenyl)-6-(hexyl)-2-iminophenyl-3-phenyl-1, 3-thiazene (**11d**). The Antibacterial activities of these compounds were studied against gram positive and gram negative pathogens like *E .Coli, S. aureus, P. aeruginosa, S. subtilus.* gentamycine as a standard. Presence of phenolic group and N, S hetero atoms increase the antibacterial activity of compound from (**5a-6a**) and (**5b-6b**) [15]. Chalcone derivatives, 2-Amino-4-substitutedphenyl-6-trisubstituted phenyl-1,3-thiazine derivatives (**12**) were screened for the antibacterial activity against cultures of two gram positive bacteria *B. cereus*, *S. aureus* and two Gram

Table 2

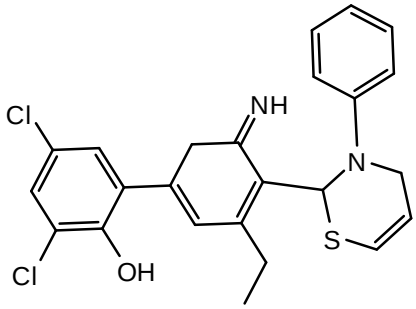
Compd	R_1	R_2	Compd	R_1	R_2
9a	C_6H_5	C_6H_5	**9f**	C_6H_5	*p*.$CH_3OC_6H_4$
9b	*p*.$CH_3OC_6H_4$	C_6H_5	**9g**	*p*.$CH_3OC_6H_4$	*p*.$CH_3OC_6H_4$
9c	*m,p*.$(CH_3O)_2C_6H_3$	C_6H_5	**9h**	*m,p*.$(CH_3O)_2C_6H_3$	*p*.$CH_3OC_6H_4$
9d	*p*.ClC_6H_4	C_6H_5	**9i**	*p*.ClC_6H_4	*p*.$CH_3OC_6H_4$
9e	*p*.$NO_2.C_6H_4$	C_6H_5	**9j**	*p*.$NO_2.C_6H_4$	*p*.$CH_3OC_6H_4$

negative bacteria *E. coli* and *Proteus vulgaris*. Penicillin and Streptomycin were used as standard drugs. The presence of chloro group at the phenyl ring increases the antibacterial activity. The activity is maximum in a compound with methoxy group at 4th position [16].

2.2 Antimicrobial Activity

The 1,3-Thiazines and their derivatives have significant antimicrobial potential against various strains of bacteria, fungi etc. The core moiety of 1,3-thiazines (C-N-S) forms an active site in antibiotics like Cephalosporins. 1,3-Thiazines derived from chalcones viz. 4-(2-hydroxy-3,5-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3phenyl-1,3-thiazine (**13**), 4-(2-hydroxy-3,5-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1,3-thiazine (**14**) etc. have been evaluated for their in vitro antimicrobial activity against various gram positive- *S. aureus*, *S. subtilus* and gram negative bacteria- *E.coli* and *P. aeruginosa* [7]. A series of 5,6-dihydro-4H-1,3-thiazine derivatives (**15**) which showed antimicrobial activity against *M. tuberculosis H37Rv* [36]. The 1,3-thiazine derivatives having acridine ring which besides showing antimicrobial activity against above mentioned species, also exhibit antibacterial activity against *S. pyogenes* and *P. fluorescens* and *P. phaseolicola* and antifungal activity against *Fusarium oxysporum* and *Aspergillus fumigates* [17]. Electron donating groups like hydroxyl and methoxy group at the fourth position of phenyl rings in the series of 6-[4-substitutephenyl]-4-phenyl-6H-1,3-thiazine-2-amines and N-[6-(4-substitutedphenyl)-4-phenyl-6H-1,3-thiazine-yl] acetamides which enhances their antimicrobial activity [18]. A series of 4-(2-hydroxy-5-substitutedphenyl)-5-benzoyl-6-substitutedphenyl-2-imino-6H-2,3-dihydro-1,3-thiazine derivatives which exhibited antimicrobial activity due to the presence of phenolic group. Its antibacterial activity has been observed to be enhanced by increasing the number of heteroatoms in the heterocyclic system [6]. Morpholine ring in the series of 4-(4-morpholinophenyl)-6-aryl-1,3-thiazin-2-amines (**16**) which showed substiantial antibacterial activity against *V. cholera* etc. and antifungal activity against various strains of fungi viz. *Rhizopus*, *M. gyseum* etc [19].

A series of 6H-2-amino-4-aryl-6-(4-β-D-allopyranosyloxyphenyl)-1,3-thiazines by Claisen Schmidst condensation which showed strong calming activity in comparison with parent helicid [4]. The 2-N-acylamino-5,6-dihydro-4H-1,3-thiazines were showed excellent NOS inhibiting activity both in vivo and in vitro and also act as antihypotensive agents in vivo [20]. The 2-arylimino-5,6-dihydro-4H-1,3-thiazines showed profound analgesic properties [21].



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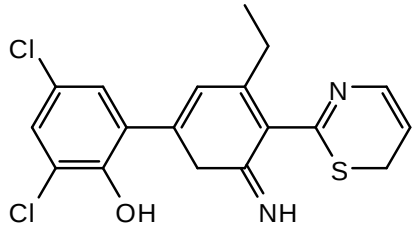

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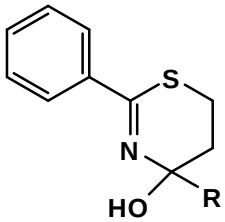
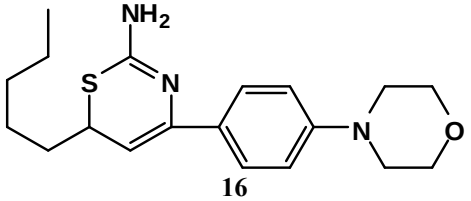


(15) 6-dihydro-4H-1,3-thiazine derivatives
R_1= -CH_3COOCH_3, -CH_3, -CH_3Cl R= -CH_3, -C_2H_5
R_2= -CH_3CN, p-$(NH_2)C_6H_4$, p-$(OH)C_6H_4$



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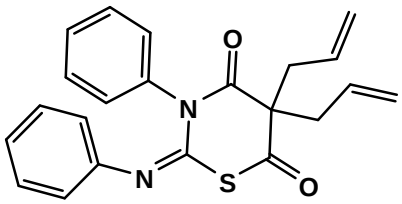
Tetrahydro-1,3-thiazines derivatives (**17**), tetrahydro [1,3]-thiazine-4-one-6-carboxylic acid (**18**), tetrahydro [1,3]-thiazin-4,6-dione derivatives, 2-(2-amino-4-phenyl-6H-1,3-thiazin-6-yl)-4-[3-(2-amino-4-phenyl-6H-1,3-thiazine-6-yl) 4-hydroxy- benzyl]phenol and 2-[2-amino-4-(4-

chlorophenyl)-6H-1,3-thiazin-6-yl]-4-hydroxybenzyl}phenol etc. have also been known to exhibit strong anti-inflammatory activity and most of them are immunotropic in nature [22-25]. Derivatives of 1,2,4-triazolo [3,2-b]-1,3-thiazine-7-ones (**19**) and amino/ guanidine thiazine derivatives besides, possessing anti-inflammatory activity, also exhibits analgesic properties [32,40]. The derivatives of 1H-pyrrolo[1,2-c][1,3]thiazine have been reported to show moderate anticonvulsant activity [26].



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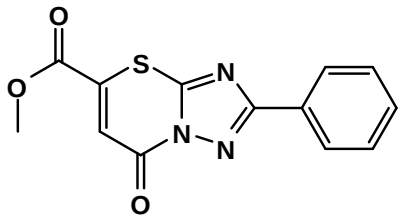

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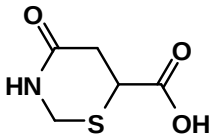

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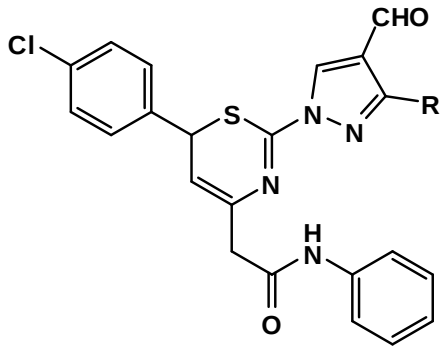
2.3 Anti-inflammatory Activity

Various 1,3-Thiazine derivatives were synthesized by reacting acetanilide derivatives with substituted aryl aldehydes to give chalcones (A and E) which are then cyclized by reacting with thiosemicarbazide to give 2-hydrazinyl 1,3-thiazine derivatives (B and F). The latter compounds were treated with substituted aryl aldehydesor ketones to give 2-arylidene hydrazinyl 1,3-thiazine derivatives. These derivatives were refluxed with Glycine in ethanol/Vilsmeir-Hack reagent (DMF: $POCl_3$) giving 2-substituted Imidazolidin-4-one 1,3-Thiazine derivatives (**20**) and 2-substituted pyrazolyl 1,3-Thiazine derivatives (**21**) respectively. All the derivatives were screened for *In-vitro* Anti Inflammatory activity. It was revealed that all compounds have shown dose dependent significant activity when compared with standard drug Diclofenac Sodium [27].

2.4 Antimicrobial and Anti-Inflammatory

A series of novel bischalcones by the reaction of 5,5'-methylene-bissalicylaldehyde with various acetophenones, subsequent treatment with thiourea or guanidine resulted to the corresponding bis-thiazines or bispyrimidines. The Antibacterial, Antifungal and Anti-inflammatory activities of the compounds have also been evaluated.



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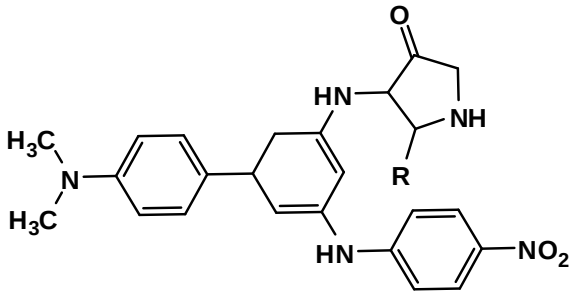
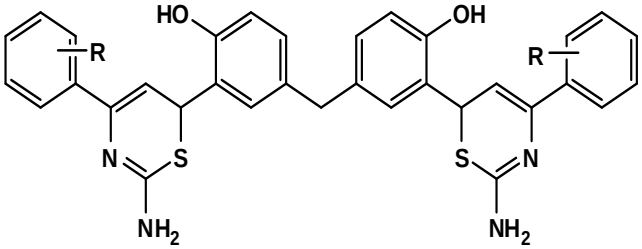


21

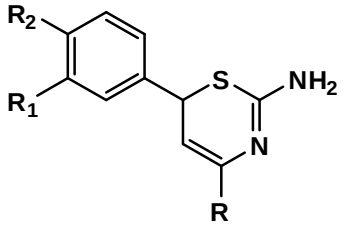
The compounds 4a-f were screened for their antibacterial activity against human pathogenic bacteria *E. coli, S. aureus* and *B. subtilis.* streptomycin/ neomycin was used as antibacterial standard. The compound **22b** is highly active against all the three organisms. Compound **22e** is highly active against *E. coli, S. aureus* and compound **22f** is highly active against *E. coli, B. subtilis.* The compound **22a** is almost inactive against all the three organisms. The antifungal activity was compared with the known antibiotic fluconazole the compound **22e** is highly active against *C. albicans*. Remaining compounds showed moderate activity. Compounds (**22b, 22c**) were screened for their anti-inflammatory activity using rat paw edema method. Ibuprofen was used as standard anti-inflammatory drug. These compounds were showed 22.01, 42.02 % of inhibition respectively, whereas standard ibuprofen showed 44% of inhibition [28].



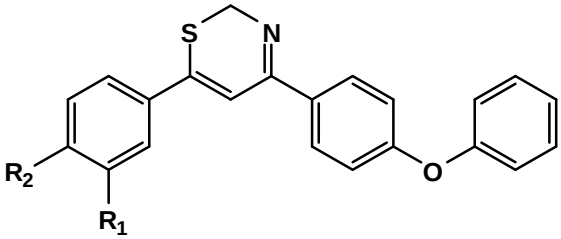
R= 22a H; **22b** 4-OCH_3; **22c** 4-Cl; **22d** 4-NO_2; **22e** 4-Br; **22f** 2-Cl

Some thazines derivatives from various Chalcones (**23**) were subjected to antimicrobial screening by cup plate method for

zone of inhibition. The Antibacterial activity was tested against various gram positive (*B. subtilis, S. aureus*) and Gram negative bacteria (*E.coli, K. pneumonia*) and anti fungal activity against various fungal strains (*C. albians, A. niger*). They are compared with standard drugs Ampicillin and Ketoconazole and Anti-inflammatory activity by In-Vitro HRBC Membrane Stabilization method taking Ibuprofen as standard drug. Many of the compounds show comparable activity with that of standard (Ampicillin and Ketoconazole) and have highly significant activity when compared with standard drug Ibuprofen [29]. Chalcones comprising diphenyl ether moiety by Claisen Schmidt condensation of 3-phenoxy benzaldehyde with substituted acetophenones, The compounds (**24**) screened for antitubercular, antibacterial, antifungal and anti-inflammatory activities [30].



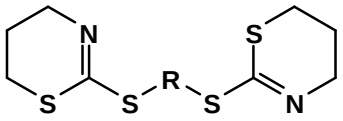
23a-c R_1 R_2 R **23a** -OCH_3, H, -C_6H_5; **23b** H, -Cl,-C_6H_5; **23c** H -NO_2 -C_6H_5



24

2.5 Anti cancer Activity

A series of novel multithioether derivatives by the combining thiazoline and thiazine with dibromides. The synthesized derivatives (**25a-g**) were tested for antitumor activity. The *in vitro* antitumor activities of the synthesized target compounds were done against A-549 (human lung cancer cell) and Bcap-37 (human breast cancer cell) which were evaluated by the standard MTT assay. The data revealed that compound **25g** possessed higher anti- tumor activities [31].



Compound 25a-g

The 3,4-disubstituted-7,8-dihydro-6H-imidazo[2,1-b][1,3]thiazines. The structures of imidazo [2,1-b][1,3]thiazine derivatives. The cytotoxicities of the compounds on both of noncancer (F2408) and cancer (5RP7) cells were measured by 3-(4,5-dimethyl-thiazollyl-2)-2,5-diphenyltetrazolium (MTT) assay [32].

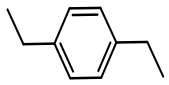
25a= -CH_2-CH_2-

25b= -CH_2-CH_2-CH_2-

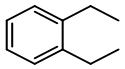
25c= -CH_2-CH_2-CH_2-CH_2-

25d= -CH_2-CH=CH-CH_2-

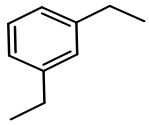
25e=



25f=

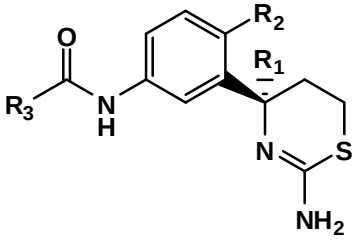


25g=



2.6 Anti-diabetic Activity

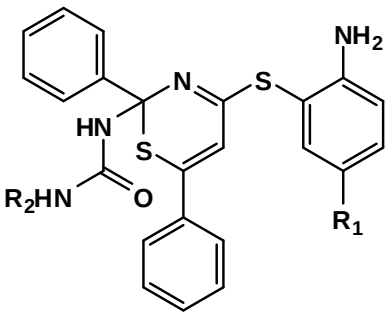
The use of aminodihydrothiazines (**26**) as well as their pharmaceutically acceptable salts and pharmaceutical compositions containing them are used for the treatment or prevention of diabetes, particularly type 2 diabetes by selective inhibition of BACE2 [33].



26

2.7 Anti-Inflammatory, Analgesic and Ulcerogenic Activity

A series of chalcones and 2-substituted guanidino-4-(2'-amino-5'-substitued phenyl) mercapto-6-phenyl-1,3-thiazine derivatives (**27a-h**), the compounds were showed Antiinflammatory, Analgesic and Ulcerogenic activities comparable to that of Indomethacin and Aspirin respectively. It was revealed that **4a**, **4d**, **4e** and **4f** showed moderate anti-inflammatory activity **4d**, **4e** and **4f** showed good to excellent analgesic activity and all compounds have shown mild ulcerogenic activity [34].

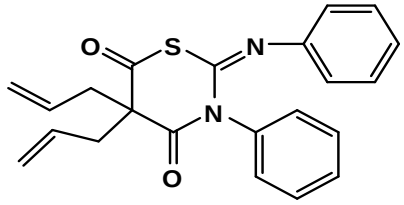


Compounds 27a-h R1 R2= 27a H, H; **27b** H, -C_6H_5; 27c H, P-OCH_3-C_6H_4; **27d** H, P-Br-C_6H_4 ;

27e -CH_3, H; **27f** -CH_3, -C_6H_5; **27g** -CH_3, P-OCH_3-C_6H_4; **27h** -CH_3, P-Br-C_6H_4

2.8 Anti-Inflammatory and Immunotropic Activity

Anti-inflammatory and Immunosuppressive activity of a series of derivatives of tetrahydro[1,3]-thiazines which were obtained as a result of condensation of some N,N1-derivatives of thiocarbamide and malonyl dichlorides. The 1,3-thiazine derivatives, 5,5-diallyl-2-phenylimino-3-phenyl-2,3,4,5-tetrahydro-[1,3]-thiazine-4,6-dione (**28**) and 5,5-diethyl-2-phenyl-imino-3-naphtyl-2,3,4,5-tetrahydro-[1,3]-thiazine-4,6-dione (**29**) exhibited anti-inflammatory activity. The compounds also contained the immunotropic component, either stimulatory or suppressive; Some interdependence between chemical structure and biological activity in the group of the investigated 1, 3-thiazines derivatives was observed [35].



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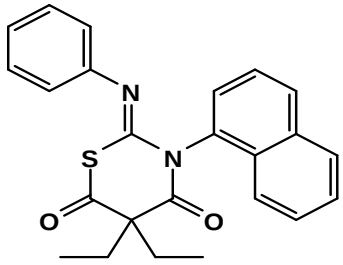


29

2.9 Anti-anxiety, Anti convulsant and Spontaneous motor activity

The reaction of 2-(_-hydroxyethyl)-pyrrolidine with isothiocyanates giving rise to thiourea derivatives which are cyclized on refluxing in hydrobromic acid to yield N-(3,4,4a,5,6,7- hexa-hydro-1H-pyrrolo [1,2-c] [1,3]thiazin-1-ylidene)-aryl (alkyl)amines (**30**). Compounds were screened for Antianxiety, Anticonvulsant and Spontaneous motor activities [36].

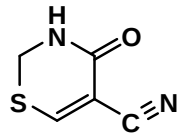
30

2.10 Tuberculostatic and Circulatory Activities

Condensed triazole-thiazine derivatives were obtained in reaction of the corresponding 5-substituted 1,2,4-triazole-3-thiones with epichlorohydrin in alkaline medium. Tuberculostatic and circulatory activities of the compounds were also studied [37].

3 Other Activities

Structural activity studies on Classic Galactosemia which is a rare human disease associated with the accumulation of a toxic level of galactose-1-phosphate (gal-1P) caused by the inherited deficiency of galactose-1-phosphate uridyl transferase (GALT) activity. To reduce the toxic level of gal-1P in patients, identification is one by high-throughput screening, over 200 small molecule GALK inhibitors. 4-oxo-3,4-dihydro-2H-1,3-thiazine-5-carbonitrile (**31**) scaffold have been selected for further structure activity relationship characterization, lead optimization with regards to potency and efficacy in order to reduce gal-1P accumulation in patient cells [38] Three series of compounds by reacting 2-Hydroxy-3,5-dichloro acetophenone with three aldehydes like chlorobenzaldehyde, Nitrobenzaldehyde and butyraldehyde giving three compounds where they are reacted with Thiourea, Phenylthiourea and Diphenyl thiourea giving three series of compounds. Like 4-(2-hydroxy-3,5-dichlorophenyl)-6-(4-chlorophenyl)-2-imino-3,6-dihydro-1,3-thiazine, 4-(2-hydroxy-3,5-di-chlorophenyl)-6-(4-chlorophenyl)-2-imino phenyl-3,6-dihydro- 1,3-thiazine and 4-(2-hydroxy-3,5-dichlorophenyl)-6-(4-chlorophenyl)-2-iminophenyl-6-hydro-3-phenyl-1,3-thiazine (**32a-c**). Growth promoting activity on some flowering plants viz. *Papaver rhoeas, Dianthus chinensis, Candy tuft, Calendula officinalise, Gladiola tristis, Gaillardia is done.* The experimental set up of the study was divided into I) Seed Treatment II) Field Experiment When the comparison of morphological characters was made between those of treated and control groups plants, it was interesting to note that all the plants exhibited significant shoot growth, and considerable increase in the number of leaves as compared to those of untreated ones [39].



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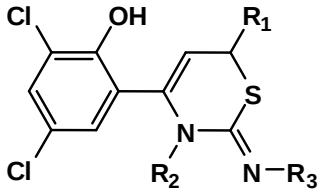
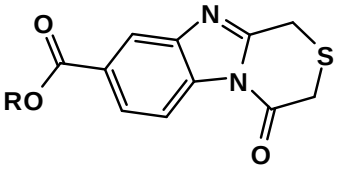
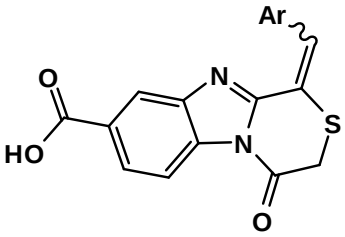


32 Where R= C_6H_5-NO_2, C_6H_5-Cl, $(CH_2)_3$-CH_3, **32a**: R_2=R_3= H; **32b**: R_2= H, R_3=C_6H_5- **32c**: R_2=R_3= C_6H_5-

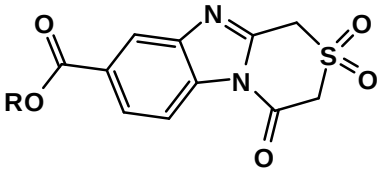
The 1,3-thiazines by refluxing the mixture of 2-Hydroxy-3-



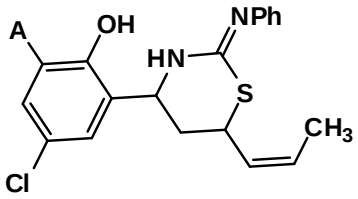
35R=H;**36**R=C_2H_5



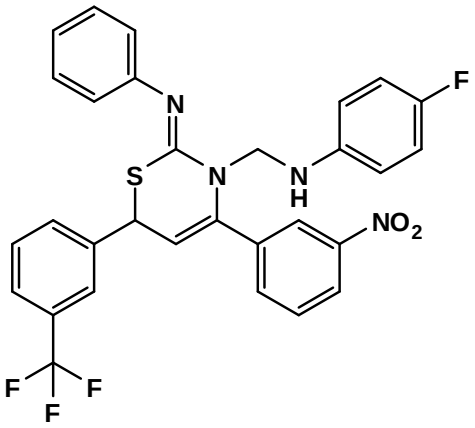
37 R=H **38**R=C_2H_5



39R=-3-Pyridinyl **40** R=-Benzo[1,3] dioxol; **41**R=-1H -3-indolyl



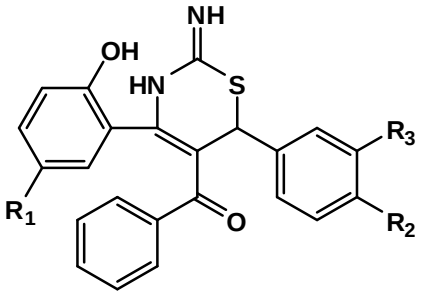
33 A=Br/NO_2



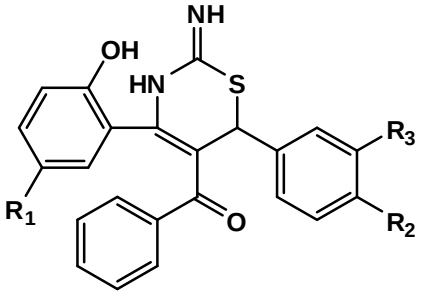
34

The 1,3-dihydro-4H-benzo[4',5']imidazole [2,1c] [1,4] thiazine-4-one-8-carboxylic acid derivatives were tested against antiviral activity of compound (**35-41**) were tested against their herpes simplex virus 1. Compounds (**35** and **41**) have possessed potent activity as they inhibited virus propagation by 94.7% and 91.3 % at a dose of 50mg respectively. Compound 80 and 84 showed higher potentssive than acyclovir at dose of 20mcg and 50 mcg [42].

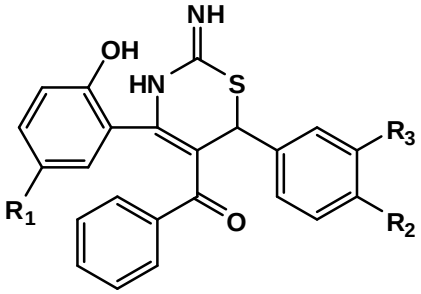
The 1,3 thiazine derivatives from thiourea first by using 2-Hydroxy acetophenone as starting material and second by using 2-Hydroxy 5-methyl acetophenone as starting material. Got 4-(2-Hydroxy phenyl)-5-benzoyl-6-phenyl or 4-alkoxy phenyl or 4-dimethyl amino phenyl or 4-dimethyl amino phenyl-2-imino-6-H-2,3-dihydro-1,3-thiazine (**42a-c**), second series starting material is 2-hydroxy -5-methylacetophenone and got 4-(2-Hydroxy-5-methyl phenyl)-5-benzoyl-6-phenyl-2-imino-6 H-2,3 dihydro 1,3 thiazine (**42a'-c'**). All these compounds are tested against anti-microbial studies. The antimicrobial activity increased with increasing the number of heterocyclic ring [43].



42a, 42a'



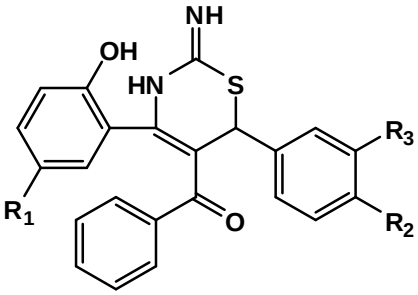
42b, 42b'



42c, 42c'

A series of eight 5,6–dihydro-4-H-1,3-thiazine derivatives (**43**) by BF_3Et_2O-catalysed reaction of selected an α,β-unsaturated ketoneswith thiobenzamide at room temperature. The anti-mycobacterial activities of these compounds are determined against *Mycobacterium tuberculosis* H37Rv using Alamar blue method. (one compound got 97 % of anti-Tb activity at 6.25mg/ml) [44].

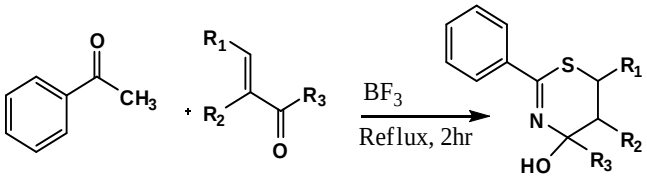
A series of novel chalcones from different benzaldehydes with various Acetophenones .The resulted chalcones were treated with thiourea leading to the formation of corresponding thiazines (**44-58**) in good yields. The compounds were screened for the antibacterial activity [45].



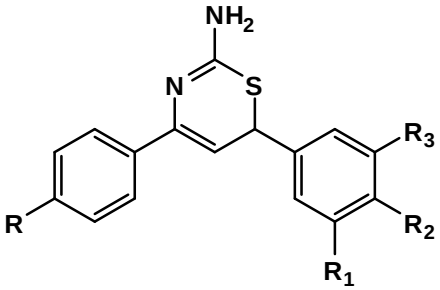
42d,42d'

Compd R_1 R_2 R_3

42a H, H, H 42a' CH_3, H, H 42b H, OCH_3, H 42b' CH_3, OCH_3, H 42c H, OCH_3, OCH_3 42c' CH_3, OCH_3, OCH_3 42d H, $N(CH_3)_2$, H 42d' CH_3, $N(CH_3)_2$, H



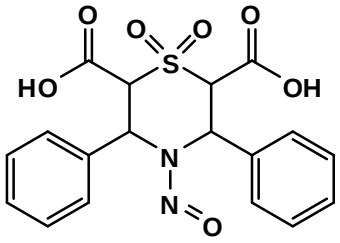
Compound 43



Compound 44-58

R R_1 R_2 R_3= **44** H H H H; **45** H H Cl H; **46** H H OCH_3 H; **47** H OCH_3 OCH_3 H; **48** H OCH_3 OCH_3 OCH_3; **49** Cl H H H; **50** Cl H Cl H; **51** Cl H OCH_3 H; **52** Cl OCH_3 OCH_3 H; **53** Cl OCH_3 OCH_3 OCH_3; **54** CH_3 H H H; **55** CH_3 H Cl H; **56** CH_3 H OCH_3 H; **57** CH_3 OCH_3 OCH_3 H; **58** CH_3 OCH_3 OCH_3 OCH_3

The N-nitroso-2, 6-dicarboxy-3,5-diaryltetrahydro-1,4-thiazine-1,1dioxides (**59**) were tested against anti-bacterial and antifungal activity. The compound exhibits potent antifungal activity [46]. An amine and amide derivatives having 2,6-di-tert-butyl phenol moiety (**60**), all most all are anti-oxidants and it reduces acute inflammation and inhibit COX-1 and lipoxygenase activity. The 2,6-di-tert-butyl-1,4-thiomorpholine-4-yl methyl phenol is having most potent anti-inflammatory activity [47]. A series of chalcones and substituted guanidino-4-(2'-amino-5'-substitued phenyl) mercapto-6-phenyl-1,3-thiazineand. The new synthesized drug exhibits anti-inflammatory, analgesic, and ulcer genic activities compared to that of standards indomethacin and acetylsalicylic acid, respectively [48].



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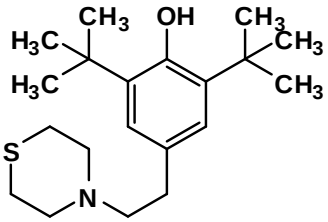

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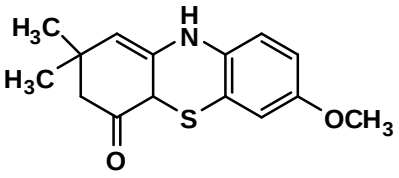
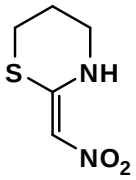


61

Agrochemical Uses of 1,3-Thiazine Derivatives

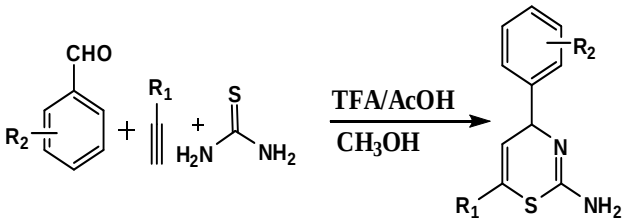
Tetrahydro-2-(nitromethylene)-2H-1,3-thiazine (Nitromethylene) possess strong insecticidal properties (**62**) [42]. Perhydro dervivatives of 1,3-thiazine have obtained patent for their insecticidal properties against various nematodes[49].



62

Thus, variously substituted 1,3-thiazine derivatives procured largely through cyclo-condensations and few ring transformations have great synthetic utility, particularly for the synthesis of different heterocyclic systems. Besides having synthetic applications, these have also been remarkably known for their biological activities viz. pharmaceutical, agrochemical etc.

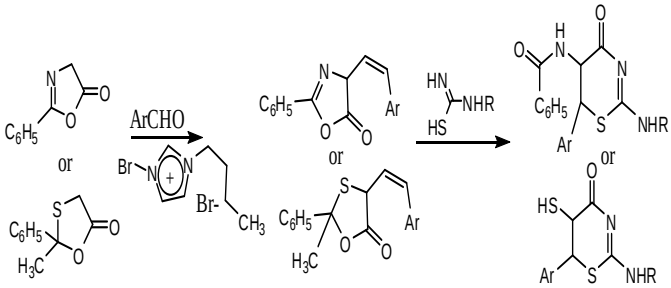
For the synthesis of 1,3-thiazines, thiourea has been the major reactant in most of the synthetic procedures. Sulphur and nitrogen of thiourea have been placed in 1,3-thiazine ring by various cyclo-condensation, ring transformation, addition reactions etc. with different reactants to produce variety of 1,3-thiazines. One pot reaction of aryl aldehydes with thiourea give 4H-1,3-thiazine derivative (**63**) in excellent yield [50].



Compound 63

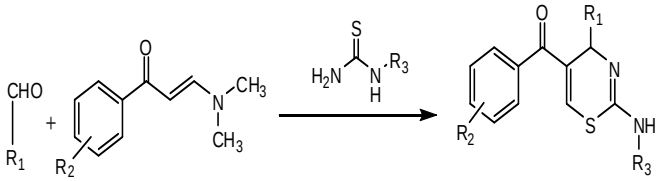
R_1= -C_6H_5, p-F-C_6H_5; R_2= -H, p-CH_3, p-F, p-CH_3O, p-Cl, p-NO_2, m-NO_2

The 1-Butyl-3-methyl-1H-imidazol-3-ium bromide promoted Knoevenagel condensation of aromatic aldehyde with masked amino acid, 2-phenyl-1,3-oxazol-5-one and mercapto acid, 2-methyl-2-phenyl-1,3-oxathiolan-5-one to yield 4-benzylidene-2-phenyloxazol-5-one and 4-benzylidene-2-methyl-2-phenyl-1,3-oxathiolan-5-one respectively. These on treatment with thiourea gives Michael adduct which undergo ring transformation to produce diasteromer of 2,5-diamino-1,3-thiazine-4-ones or 2-amino-5-mercapto-1,3-thiazine-4-ones [4].



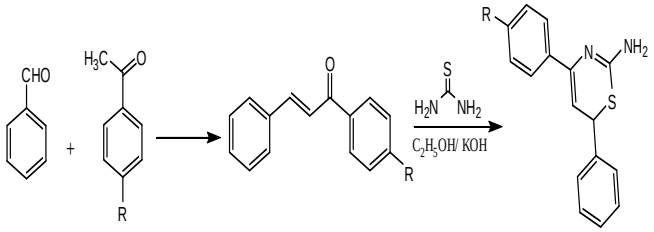
67 Ar= -C_6H_5, p-Cl-C_6H_4, p-CH_3O-C_6H_4, p-$(CH_3)_2N$-C_6H_4; R= -H, -C_6H_5

Multicomponent reaction of aldehydes, enaminone and thiourea in the presence of trimethyl silyl chloride (TMSCl) yield substituted 1,3-thiazine derivatives [51].



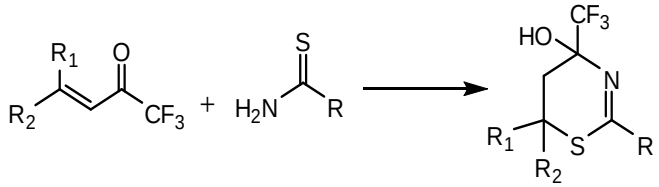
68 R_1= alkyl, aryl; R2=R3= -H, alkyl, aryl.

Helicid [4-formylphenyl-β-D-allopyranoside] condensed with 4-substituted acetopheno-ne to give E-(4-β-D-allopyranosyloxyphenyl)-1-(4-substituted phenyl) propenone derivatives. the latter undergo 1,4-Michael addition with thiourea in basic medium to yield 6H-2-amino-4-aryl-6-(4-β-D-allopyrano-syloxyphenyl)-1,3-thiazine derivatives [5].

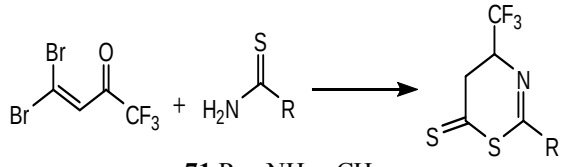


69 R=-H, -CH_3, -OCH_3, -Cl, -Br, -F, -C_2H_5

On refluxing trifluoromethyl enones/β,β-dibromo-CF_3-ketones with thiourea or thioacetamide in acidic medium give dihydrothiazines or 1,3-thiazine derivatives [52].

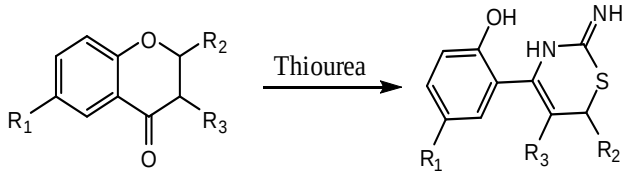


70 R=-NH_2, -CH_3; R_1=-H; R_1=R_2=-$(CH_3)_2$



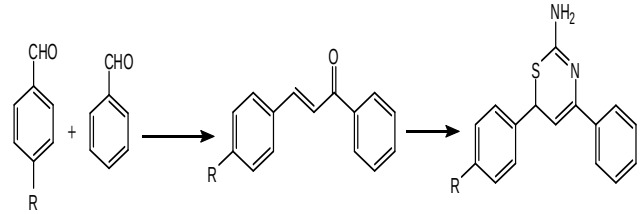
71 R= -NH_2, -CH_3

The 3-Benzoyl-3,4,6-trisubstituted flavanones procured from 1-(2-hydroxyphenyl)-3,5-disubstituted-1,3-propandione and benzaldehyde when refluxed with thiourea in dry pyridine affords 4-(2-hydroxy-5-substitutedphenyl)-5-benzoyl-6-substitutedphenyl-2-imino-6H-2,3-dihydro-1,3-thiazine derivatives[6].



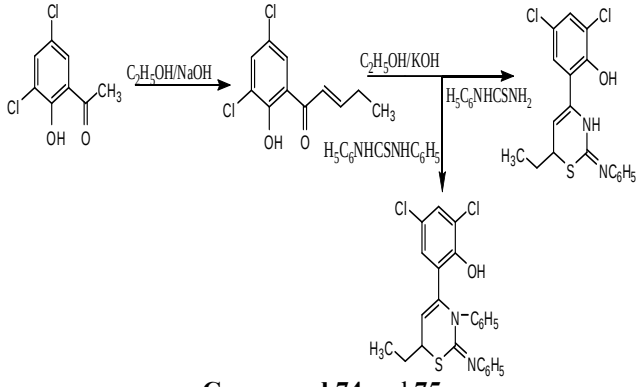
Compound 72

Claisen-Schmidt condensation of acetophenone and aryl aldehydes yields chalcone derivatives which on treatment with thiourea undergo cyclization in basic medium to yield 6-[4-substituted phenyl]-4-phenyl-6H-1,3-thiazine-2-amine derivatives. The latter can be acylated to give N-[6-(4-substituted phenyl)-4-phenyl-6H-1,3-thiazine-yl] acetamide derivatives [18].

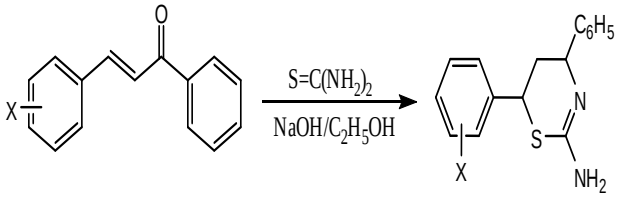


73 R= -CH_3, -$N(CH_3)_2$, -Cl, -NO_2, -OCH_3, -OH

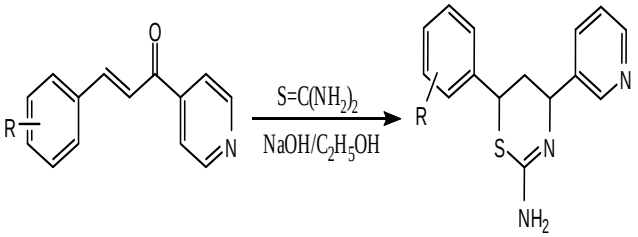
Similarly, 2-hydroxy-3,5-dichloro-4-ethyl chalcone when treated with phenylthiourea and diphenyl thiourea gives 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1,3-thiazine and 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3-phenyl-1,3-thiazine respectively [53]. Further, mono and di-substituted chalcone derivatives when stirred with thiourea under similar conditions yield the corresponding 1,3-thiazine derivatives [54,55].



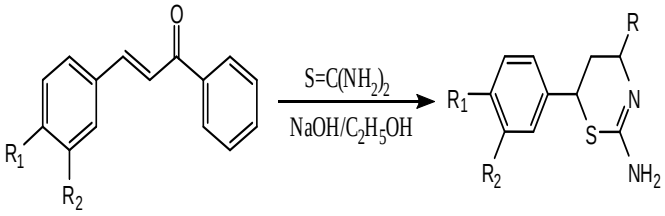
Compound 74 and **75**



Compound 76

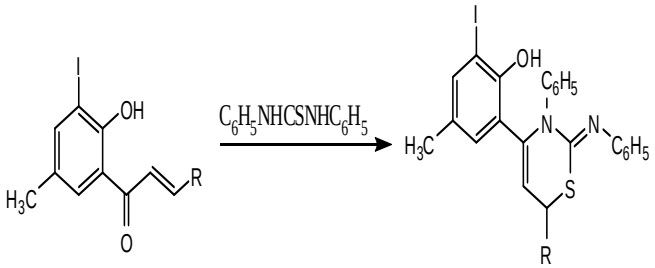


Compound 77



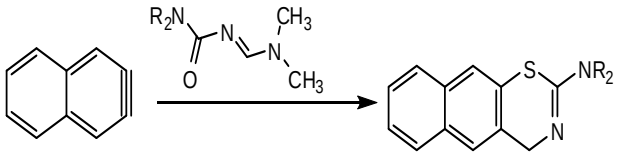
Compound 78
R= m-NO_2, p-OH, m-Br, m-OCH_3, p-N $(CH_3)_2$
R= -C_6H_5; R_1=-OCH_3, -H; R_2= -H, -Cl, -NO_2

Furthermore, chalcone derivatives on refluxing with diphenyl thiourea in basic medium with few drops of piperidine give 1,3-thiazine derivatives in better yields [56].



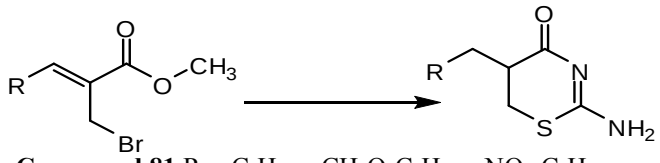
Compound 79 R= -C_6H_5, -C_6H_5-OCH_3, -C_6H_5-Cl, -C_6H_5-OH, -HC=HC-C_6H_5, -C_4H_3O

Diels Alder adduct-benzyne intermediate which aromatized with N1,N1-disubstituted-N2-(dimethylaminomethylidene) thiourea by electron release from S and NR_2 to give. The latter undergoes NMe_2 anion displacement and subsequent 1,3-hydride shift to provide disubstituted-amino-4H-naptho[2,3-e]-1,3-thiazine derivatives [57].



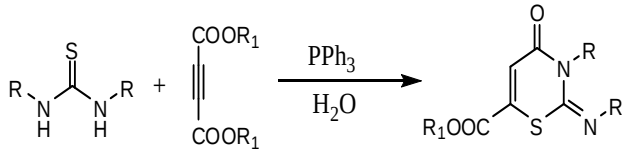
Compound 80 R=-C_2H_5, -$(CH_2)_4$, -$(CH_2)_5$, -CH-$(CH_2)_2O(CH_2)_2$

Allylic bromide undergoes nucleophilic reaction and cyclization with thiourea in basic medium to yield 2-amino-1,3-thiazine-4-ones through the intermediacy of isothiuronium salt [58].



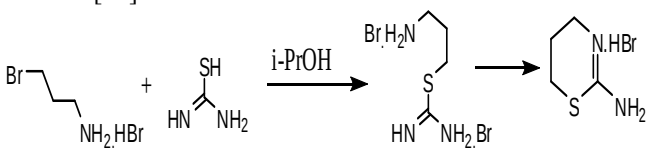
Compound 81 R= -C_6H_5, p-CH_3O-C_6H_4, p-NO_2-C_6H_4, o-Cl-C_6H_4, o-$C_{10}H_7$, -CH_3, -CH_3CH_2.

Dialkylthioureas on treatment with electron deficient acetylenic esters and triphenyl-phosphine as catalyst yield 2H-1,3-thiazine derivative [7].



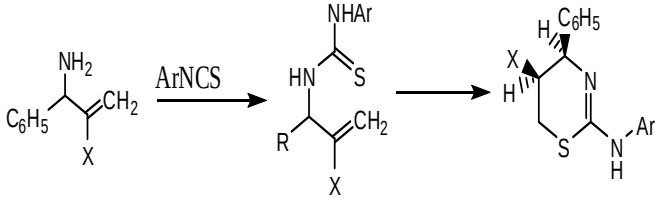
Compound 82 R=R_1-C_6H_5, -C_2H_5

Cycloaddition of propylamine hydrobromide with thiourea produces S-(aminopropyl) isothiourea dihydrobromide which on heating cyclizes to 2-amino-5,6-dihydro-4H-1,3-thiazine [20].



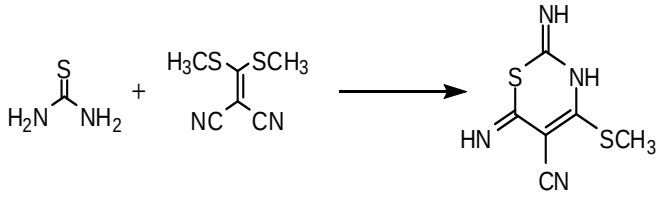
83 R=-CH_3, -C_6H_5, -Cyclohexyl, -adamantyl

Stereoselective synthesis of 2-susbstituted amino-5,6-dihydro-4H-1,3-thiazines involves intramolecular cyclization by sulpha-Michael reaction of allyl thiourea which in turn has been prepared from allylamine and arylisothiocyanate [1].



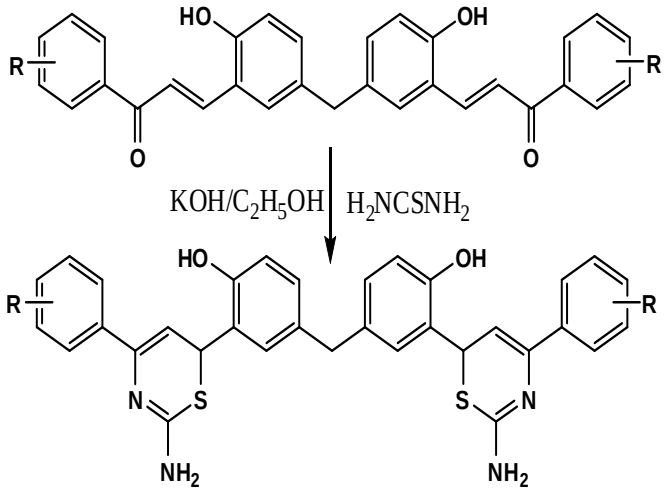
Compound 84 X= -CO_2Me, -CN; Ar= -C_6H_5, p-ClC_6H_4, O-BrC_6H_4

On refluxing (methylthio) methylene malanonitrile with thiourea in the presence of anhydrous potassium carbonate for 12 hours produces 2,6-dihydro-2,6-diimino-4,8-bis(methylthio) pyrimido [2,1-b][1,3] thiazine-3,7-dicarbonitrile. The proposed mechanism revealed that the latter having 2-methylthio group, an activated nitrogen and an electron withdrawing cyano group enhances the reactivity towards nucleophile to give substituted 1,3-thiazines [59,60].



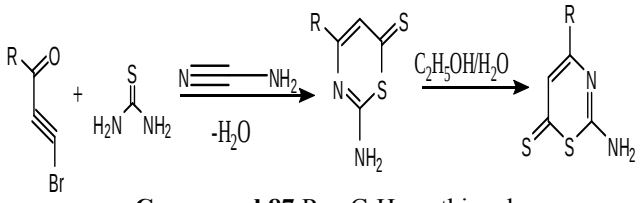
Compound 85

Bis[3-[(E)-3(4-substitutedphenyl)-3-oxo-1-propenyl]-4-hydroxyphenyl] methane on treating with thiourea followed by cyclization in ethanolic KOH produces bis- thiazine derivatives [23].



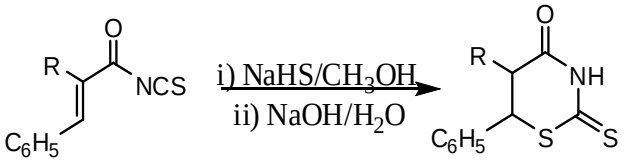
Compound 86 R= -H, p-OCH_3, p-Cl, p-NO_2, p-Br, o-Cl

The 1-Acyl-2-bromoacetylene derivatives when treated with thiourea in the presence of glacial acetic acid produce α-oxoketene mercaptals. The latter in $BF_3.Et_2O$, with the removal of cyanamide and water undergoes intramolecular cyclization to give 1,3-thiazine-6-thione hydrobromide which on recrystallization with water-alcohol yields pure substituted 2-amino-1,3-thiazine-6-thiones [61].



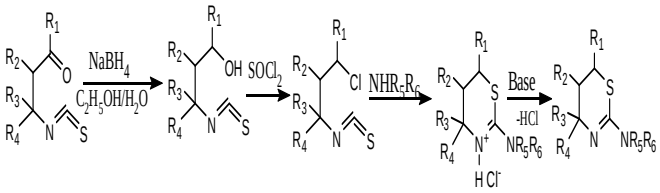
Compound 87 R= -C_6H_5, o-thienyl

On stirring isothiocyanate in methanol with solution of sodium hydrogen sulfide gives 2-substituted 3-phenyl-3-(thiocarbamoylthio)propanoate which by alternate cyclization in basic medium yields 5-substituted 6-phenyl-2-thioxo-tetrahydro-4H-1,3-thiazine-4-ones [62].



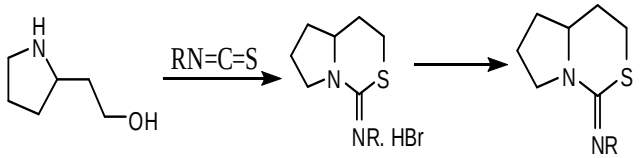
Compound 88 R= -H, -CH_3, -C_6H_5

1,3-Isothiocyanato ketones get reduced with $NaBH_4$ to give 1,3-isothiocyanato alcohols which subsequently react with thionyl chloride to produce 3-chloro-1-isothiocyanatoalkane derivatives. The latter in methanol and ammonia treated with NaOH yield 2-amino-4,4,6-trisubstituted-5,6-dihydro-4H-1,3-thiazine [63].



Compound 89 R_1=R_2=R_4=-H, R_3=-Me; R_1=R_2=-Me, R_3, R_4=-H; R_1=R_3=R_4=-Me, R_2=-H; R_1=R_2=R_3=R_4=-CH_3; R_5=R_6=H; R_5=-Bn, R_6=-H; R_1= -C_6H_5, t-Bu; R_2= -OCH_3, -H; R_3= -H, -OCH_3, -CH_3

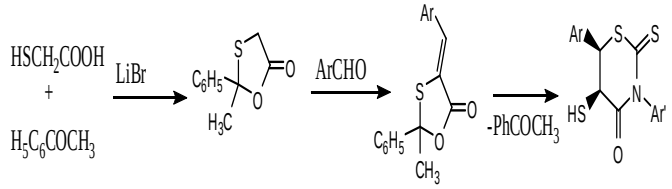
2-(β-Hydroxyethyl)-pyrrolidine on refluxing with isothiocyanate derivative in THF gives an intermediate thiourea derivative which by intramolecular cyclization produces N-(3,4,4a,5,6,7-hexahydro-1H-pyrrolo[1,2-c][1,3]thiazin-1-ylidene [26].



Compound 90 R= -CH_3, -C_2H_5, cyclo-C_6H_{11}, -$CH_2C_6H_5$, -C_6H_4, p-CH_3-C_6H_4, p-CH_3O-C_6H_4, p-Br-C_6H_4, p-Cl-C_6H_4

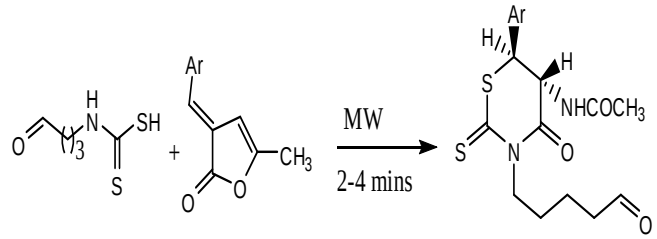
One pot diasteroselective reaction of 2-methyl-2-phenyl-1,3-oxathiolan-5-one, aromatic aldehyde and N-

aryldithiocarbamic acid in microwave yields Michael adduct. The latter undergo ring transformation to produce polyfunctionalised 3,6-diaryl-5-mercaptoperhydro-2-thioxo-1,3-thiazine-4-ones [64].



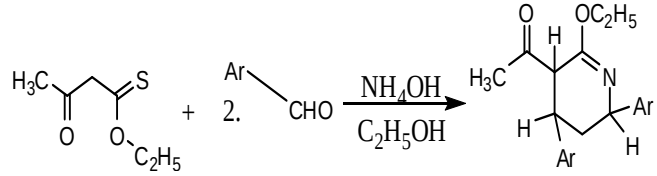
Compound 91 ar= -Ph, p-Cl-C_6H_4, p-MeO-C_6H_4; Ar1= -Ph, o-Me-C_6H_4, p-MeO-C_6H_4

The (4-Oxo-butyl)-dithiocarbamic acid and 4-arylidene-5(4H)-oxozolones in microwave with montmorillonite K-10 clay yield N-[3-(3-hydroxymethyl-4-oxo-butyl)-4-oxo-6-aryl-2-thioxo-[1,3]thiazinan-5-yl]-acetamide derivatives[65].



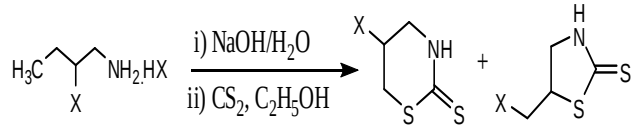
Compound 92 Ar= -C_6H_5, p-CH_3O-C_6H_4, p-HO-C_6H_4, p-Cl-C_6H_4, p-NO_2-C_6H_4

Cyclocondensation of acetothioacetic acid-O-ethyl ester with aromatic aldehydes and aqueous ammonia produces oil of symmetrical 5-acetyl-2,6-diaryl-4-ethoxy-5,6-dihydro-2H-1,3-thiazine derivatives [66].



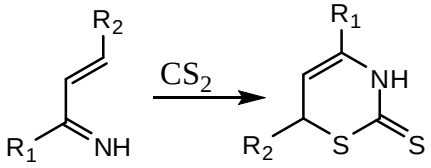
Compound 93 Ar= -C_6H_5, p-CH_3O-C_6H_4, p-CH_3-C_6H_4, p-Br-C_6H_4

On heating 2,3-dihalopropylaminehydrohalide with carbon disulfide produces mixture of 5-halo-3,4,5,6-tetrahydro-1,3-thiazine-2-thiones and 5-halomethylthiazolidine-2-thiones. It has not been quite an efficient method as latter yields mixture of cyclic dithiocarbamates [67].



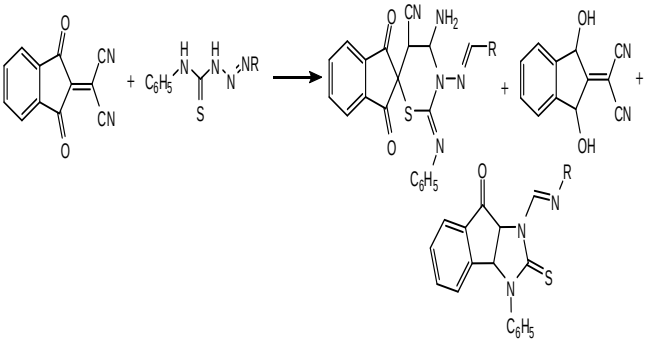
Compound 94 X= -Cl, -Br

Subsequent Horner-Wadsworth-Emmons reaction with aldehyde to give 1-azadiene intermediate. The latter undergoes hetero Diels-Alder reaction with carbon disulphide to afford 3,6-dihydro-2H-1,3-thiazine-2-thiones [68].



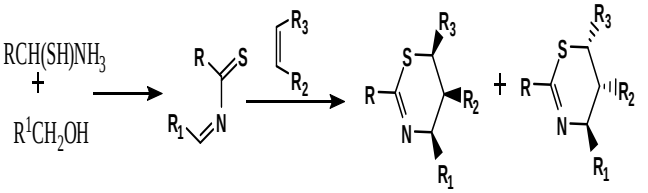
Compound 95 R_1, R_2= -C_6H_5, -iC_3H_7, 2,6-$(CH_3)_2$-C_6H_3, p-F_3C-C_6H_4, p-CH_3O-C_6H_4, p-Br-C_6H_4, o-Br-C_6H_5

The (2-Dicyanomethylidene)indan-1,3-dione on stirring with (substituted) alkenylidene-hydrazine carbothioamide and their derivatives in ethylacetate produces dioxospiroindene[1,3] thiazine derivatives along with byproducts [69].



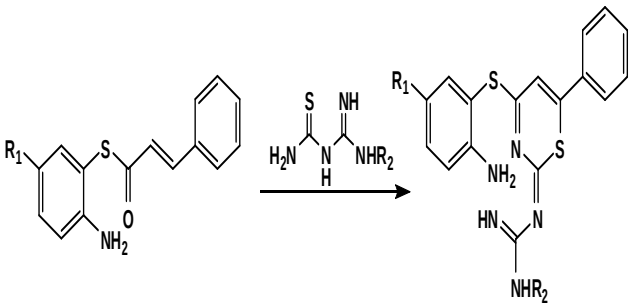
Compound 96 R=C_6H_5-CH=CH, o-OCH_3-C_6H_4-CH=CH, CH_3-$(CH_2)_2$-CH=CH, CH_3-CH=CH, $CH(CH_3)_2$

The N-thioacyl imine heterodiene derivatives procured from thioacetamide and aromatic aldehyde undergoes hetero Diels-Alder reaction with alkenes to give mixture of isomers of 1,3- thiazine derivative [70].



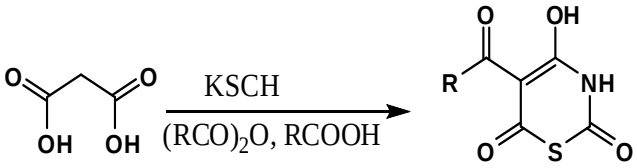
Compound 97 R=-C_6H_5, -CH_3; R_1= -C_6H_5, p-Me-C_6H_4, p-Cl-C_6H_4, p-Br-C_6H_4, p-NO_2-C_6H_4, o-CH_3O-C_6H_4, m-HO-C_6H_4, m-Br-C_6H_4, m-NO_2-C_6H_4, 1-naphthyl, m-thienyl; R_2=-H, -$(CH_2)_4$, -$(CH_2)_6$, -$(CH_2CH_2)_2CH_2$; R_3= n-C_4H_9, -Ph, -(CH_2)2Br, -$(CH_2)_2CO_2Et$, -$(CH_2)_2CO_2H$

The 1-(2-Amino-5-substituted phenyl) mercapto-3-(substituted) phenyl-2-propen-1-one from 2-amino thiophenol on refluxing with substituted amidinothiocarbamides in basic medium for 4-5 hours produce 2-substituted guanidine-4-(2-amino-5-substituted phenyl)mercapto-6-phenyl-1,3-thiazines and it has also been an efficient method for synthesizing 2-amino-4-(2-amino-5-substituted phenyl)mercapto-6-(substituted) phenyl pyrimidine derivatives [71].



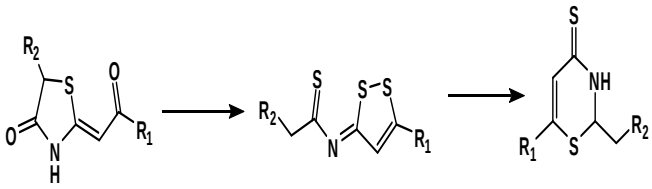
Compound 98 r_1= -H, -CH_3; R_2= -H, -C_6H_5, p-OCH_3-C_6H_4, p-Br-C_6H_4

Malonic acid reacts with potassium thiocyanate, acid anhydride in the presence of carboxylic acid to give 5-acyl-4-hydroxy-2H-1,3-thiazine-2,6(3H)-dione [72].



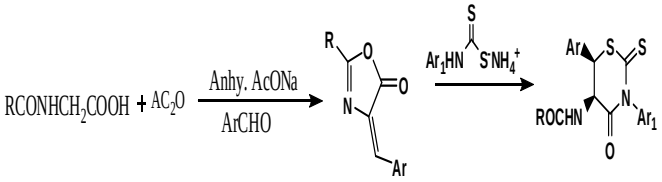
Compound 99 R= -CH_3, -C_2H_5, -C_3H_7

The 1,2-Dithioles from 4-oxothiazolidines when treated with sodium borohydride in ethanol produce 1,3 thiazine derivatives [73].



Compound 100 R_1= -COC_6H_5; R_2= -H, -CH_3, -$CH_2CO_2C_2H_5$

N-acylglycine on treatment with anhydrous sodium acetate, acetic anhydride and arylaldehyde gives an intermediate azalactone. The latter undergoes Michael addition with N-aryldithiocarbamate in microwave to yield an adduct in which the lone pair of nitrogen attacks the carbonyl carbon which by alternate cyclization produces 5-acylamino-3,6-diarylperhydro-2-thioxo-1,3-thiazine-4-one [74].



Compound 101

4 Conclusion

The above informational data got from the literature gives an idea that thiazines are an important class of heterocyclic and their significances are challenging in disease of various infections .A survey of thiazine revealed that the moiety have possess a great deal of interest to the medicinal chemist and biochemist and can be taken as a lead molecule for designing potential bioactive compounds and thiazine derivatives have various pharmacological activities This review gives an idea to the researchers in determining the best and most productive, economical suggestive and clinically important compounds of thiazines. I hope that my brief review will help all those are interested to research in this class of heterocyclic compounds to develop potent pharmacologically active drugs in the field of medicinal chemistry. 1,3-thiazines are versatile molecules which require further research regarding synthesis and elucidation of mechanism of action of different derivatives by conducting *invivo* & *invitro* studies and QSAR development studies to bring the potential effects.

References

[1] Simerpreet and C.S Damanjit, *Pharmacophore.* **4(3)**, 70-88 (2013).

[2] G. Vincent, B.V Mathew, J. Joseph, M. Chandran, A.R Bhat and K.K Kumar, *Inter J Pharm & Chem Sci*, **3(2)**, 341-348 (2014).

[3] S. Jupudi, K. Padmini, P. Jaya Preethi, P.V.P Deepak Bharadwaj and P. Vengal Rao, *Asian J. Res. Pharm. Sci.* **3(4)**, 170-177 (2013).

[4] V.K Rai, B.S Yadav and L.S.D Yadav, *Tetrahedron*. **65,** 1306-1315 (2009).

[5] L. Fu, Y. Li, D. Ye and S. Yin, *Chem Nat. Compd.* **46 (2)**, 169-172 (2010).

[6] F.H.Z Haider, *J. Chem. Pharm. Res.* **4(4)**, 2263-2267 (2012).

[7] Z. Hossaini, M. Nematpour and I. Yavari, *Monatsh Chem.* **41**, 229–232 (2010).

[8] R.S Ganorkar, R.P Ganorkar and V.V Parhate, *Rasayan J Chem.* **6(1)**, 65-67 (2013).

[9] S. Didwagh and B.P Pravina, *Inter. J. Pharm. Sci & Res.* **4(6)**, 2045-2061 (2013).

[10] Simerpreet and S.D Cannoo, *Pharmacophore.* **4(3)**, 70-88 (2013).

[11] F. Haider and Z. Haider, *J. Chem. & Pharm. Res.* **4(4)**, 2263-2267 (2012).

[12] H.H Sayed, A.H Shamroukh and A.E Rashad, *Acta Pharm*, **56**, 231–244, (2006).

[13] I.R Siddiqui and P.K Singh, *Indian J. Chem.* **46B**, 499-504 (2007).

[14] T.A El-Sayed and A.M El-Kazak, *Eur. J. Chem.* **1(1)**, 2010: 23 (2010).

[15] S.P Rathod, A.P Charjan and P.R Rajput, *Rasayan J. Chem.* **3(2)**, 363-367 (2010).

[16] K. B Kumar et al, *J. Pharm Res.* **4(1)**, 274-275 (2011).

[17] T-S. Ali and A.M El-Kazak, *Eur. J. Chem.* **1(1)**, 6-11 (2012).

[18] L.P Bhangale, R.L Sawant and J.B Wadekar, *Int. J. Drug Design Dis.* **2(4)**, 637-641 (2011).

[19] J. Thansu, V. Kanagarajan and M. Gopalakrishnan, *J. Enzym Inhib. Med. Chem.* **25(6)**, 756-764 (2010).

[20] V.M Fedoseev, A.A Mandrugin, T.P Trofimova, O.N Zefirova et al, *Moscow Uni. Chem B*+. **63(5)**, 274-277 (2008).

[21] H. Kai, Y. Koriyama, Y. Morioka, K. Okamoto et al. *Bioorg Med Chem Lett*, **18(24)**, 6444-6447 (2008).

[22] H.A Al-Difar and M.J Elarfi, *Sci. Revs. Chem. Commun.* **2(2)**, 103-107 (2012).

[23] A. Nagaraj and C.S Reddy, *J. Iran Chem. Soc.* **5(2)**, 262-267 (2008).

[24] T. Jakobiec, B.S.H Kowalczyk, H. Matczak and T. Zawisza, *Arch. Immunol. Ther. Exp. (Warsz)*, **29 (2)**, 235-248 (1981).

[25] T. Jakobiec, H. Matczakowa, E. Wagner and T. Zawisza, *Arch. Immunol. Ther. Exp. (Warsz)*, **26 (1-6)**, 943-949 (1978).

[26] E. Jagodzinska, T.S Jagodzinski, S. Rump and A. Wesolowska. *Acta Polomac Pharma- Drug Res*, **60(1)**, 67-74 (2003).

[27] S. Jupudi et al, *Inter. J. Res. Pharm & Chem.* **3(2)**, 213-220 (2013).

[28] C.S Reddy and A. Nagara, *J. Iran. Chem. Soc.* **5(2)**, 262-267 (2008).

[29] R. Kalirajan et al. *Inter. J. Chem. Tech & Res.* **1(1)**, 27-34 (2009).

[30] R.H Udupi, A.R Bhat and J. Jacob, *Indian J. Heterocyclic Chem.* **15**, 89 (2005).

[31] W. Wang, B. Zhao, C. Xu and W. Wu, *Inter. J. Org. Chem.* **2**, 117-120 (2012).

[32] A. Meriç, Z. Ncesu and I. Hatipoglu, *Med. Chem. Res.* **17(1)** 30-41 (2008).

[33] B. Benardeau and H. Wang. 2-Aminodihydro [1,3] Thiazines as Bace 2 Inhibitors For the Treatment of Diabetes. Patent scope, world intellectual property organization. 165p, (2011).

[34] V.V Dabholkar and S.D Parab, *Hetero. Chem. Lett.* **1(2)**, 176-188 (2011).

[35] Zawisza. *Natural center for biotechnol Inform*, **29(2)**, 235-48 (1981).

[36] T.S Jagodzinski, *Acta Pol Drug Res*, **60(1)**, 67-74 (2003).

[37] H. Foks et al, *Pharmazie*, **47(10)**, 770-773 (1992).

[38] I. Sina et al, *Med. Chem. Lett.* 34, (2011).

[39] V. Hushare et al, *Inter J. Pharm Tech & Res.* **5(2)**, 420-425 (2013).

[40] S.G Ram, P.G Rajesh and V.V Parhate, *Rasayan J. Chem.* **6**, 65-67, (2013).

[41] G.S Dipansu and B.P Mander, *Inter. J. Health Pharm. Sci.* **1(1)**, 27-33 (2012).

[42] A.G Shadia, Shweekar and E.I Naemel, *Arch. Pharm. Chem. Life Sci.* **11**, 255-263 (**2011**).

[43] H.Z.H Farooque, *J. Chem. & Pharm. Res.* **4(4)**, 2263-2267 (2012).

[44] M. Koketsu, *Eur. J. Pharm. Sci*. **15**, 307-310 (2002).

[45] P. Varalakshmi Devi, G.P Ramesh, K. Keerthi and G. Ramkrishna, *J. Pharm. Res.* **4(1)**, 274-275 (2011).

[46] E. Naushad and R. Panugonda, *Med. Chem. Res.* **21**, 2056-2063 (2012).

[47] A.R Eleni, N.Z George, A.M Gavalas, T.E Phaedra and N. Panos, *Bioorg & Med Chem*, **14**, 5616–5624 (2006).

[48] V.D Vijay, *The Pharma Res.* **5(1)**, 127-143 (2011).

[49] J. D Bourzat, D. Farge, A. Leger and G. Ponsinet. *U.S. patent 4271156 A*, 1981.

[50] S. Huang, Y. Pan, A. Wu and Y. Zhu, *Organic letters.* **7(17)**, 3797-3799 (2005).

[51] E.M.A.A El-Taweel and M.H Elnagd, *J. Heterocyclic Chem.* **38**, 981 (2001).

[52] E.S Balenkova and V.G Nenajdenko, *Arkivoc*, (**i**), 246-328 (2011).

[53] A.P. Charjan, P.R Rajput and S.P Rathod, *Rasayan J. Chem.* **3(2)**, 363-367 (2010).

[54] M.A Kadhim, *J. Uni. Anbar. for Pure Sci.* **4(3)**, 1000 (2010).

[55] B. Gowramma, S. Jubie, R. Kalirajan, S.U Sivakumar et al, *Int. J. ChemTech Res.* **1(1)**, 27-34 (2009).

[56] A.S. Dighade and S.R Dighade, *Der Pharma Chemica.* **4(5)**, 1863-1867 (2012).

[57] E.D. Biehl and R. Sathunuru, *Arkivoc.* (xiv), 51-60 (2004).

[58] A.J Bortoluzzi, L. Fernandes, M. Ferreira, M.M Sá et al, *Arkivoc.* **(xi)**, 303-321 (2010).

[59] S. Batra, S. Bhowmik and A. Mishra, *RSC Adv.* **1,** 1237-1244 (2011).

[60] P.V Sambhaji and B.S Shivraj, *Organic Chem. Curr. Res.* **1(5)**, 1-3 (2012).

[61] T.E Glotova, T.N Kamarova, V.A Lopyrev and A.S Nakhmanovich, *Russ. Chem B*+. **49(11)**, 1917-1918 (2000).

[62] M. Dzurilla, V. Ficeri, D. Koscik, R. Kraus et al, *Chcm Papers.* **44(1)**, 45-50 (1990).

[63] A.S Fisyuk, N.V Peretokin and B.V Unkovsky, *Chem. Heterocycl. Compd.* **39(6)**, 802-808 (2003).

[64] V.K Rai, L,S,D Yadav and S. Yadav, *Tetrahedron.* **61**, 10013-10017 (2005).

[65] I.R Siddiqui, J. Singh and P.K Singh and V. Srivastava, *Indian J. Chem.* **49B**, 512-520 (2010).

[66] G. Duburs, A. Mishnev, J. Ozols, B. Vigante et al, *Chem. Heterocycl. Compd.* **36(7)**, 862-869 (2000).

[67] V.M Fedoseev, S.E Tkachenko and P.T Trofimova, *Chem Heterocycl Compd.* **38(12)**, 1533-1534 (2002).

[68] M. Helliwell, E. Janssen, A, Kruithof, M.L Ploeger et al, *Molecules.* **17**, 1675-1685 (2012).

[69] F.F Abdel-Latif, A.A Hassan, S.M Mostafa, A.M Nour El-Din et al, *Chemical Papers*, **66(4)**, 295–303 (2012).

[70] R. Legay, J.F Lohier, F. Peudru, V. Reboul V et al, *Tetrahedron.* **68**, 9016-9022 (2012).

[71] V.V Dabholkar and S.D Parab, *Tetrahedron*. **1(2)**, 176-188 (2011).

[72] B.A BIvin, A.V Moskvin and V.N Yuskovets, *Russ J. Gen. Chem*, 2004, **74(2**), 312-313 (2004).

[73] E. Kleinpeter, R. Markovic, A. Rašovic A and Steel PJ. *Tetrahedron.* **63(9)**, 1937-1945 (2007).

[74] A. Singh and L.D.S Yadav, *Tetrahedron Lett.* 2003, **44**, 5637-5640 (2003).