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Review Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3-THIAZINES- A REVIEW

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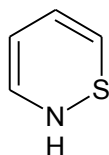
ABSTRACT

The multifaceted chemical potential of 1, 3-thiazine- a six membered motif/species containing nitrogen and sulphur in the ring has led to unabated research in their synthetic methodologies. This paper summarizes various methods viz. condensation, cyclo-addition, ring transformations etc. to procure 1,3-thiazines and their derivatives along with biological activities viz. pharmacological and agrochemical etc.

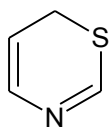
Keywords: 1, 3-Thiazine, Condensation, Ring transformation, Antimicrobial, Insecticidal activity.

INTRODUCTION

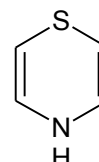
Organic compounds play a vital role in modern society and possess varied applications in different fields due to which unabated research has been going on to synthesize new organic compounds including derivatization of naturally occurring ones- nucleic acids, plant alkaloids, some vitamins, proteins, hormones etc. Synthetic heterocyclic compounds especially containing heteroatom N, S, O have enormous potential primarily as agrochemicals, drugs etc.. 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 (1-3) 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.^{2, 4, 6, 12, 13, 15-19} 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.^{2, 15} This paper mainly focuses on different synthetic procedures along with biological activities of 1,3-thiazines and their derivatives.



1,2-Thiazine
(1)



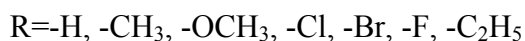
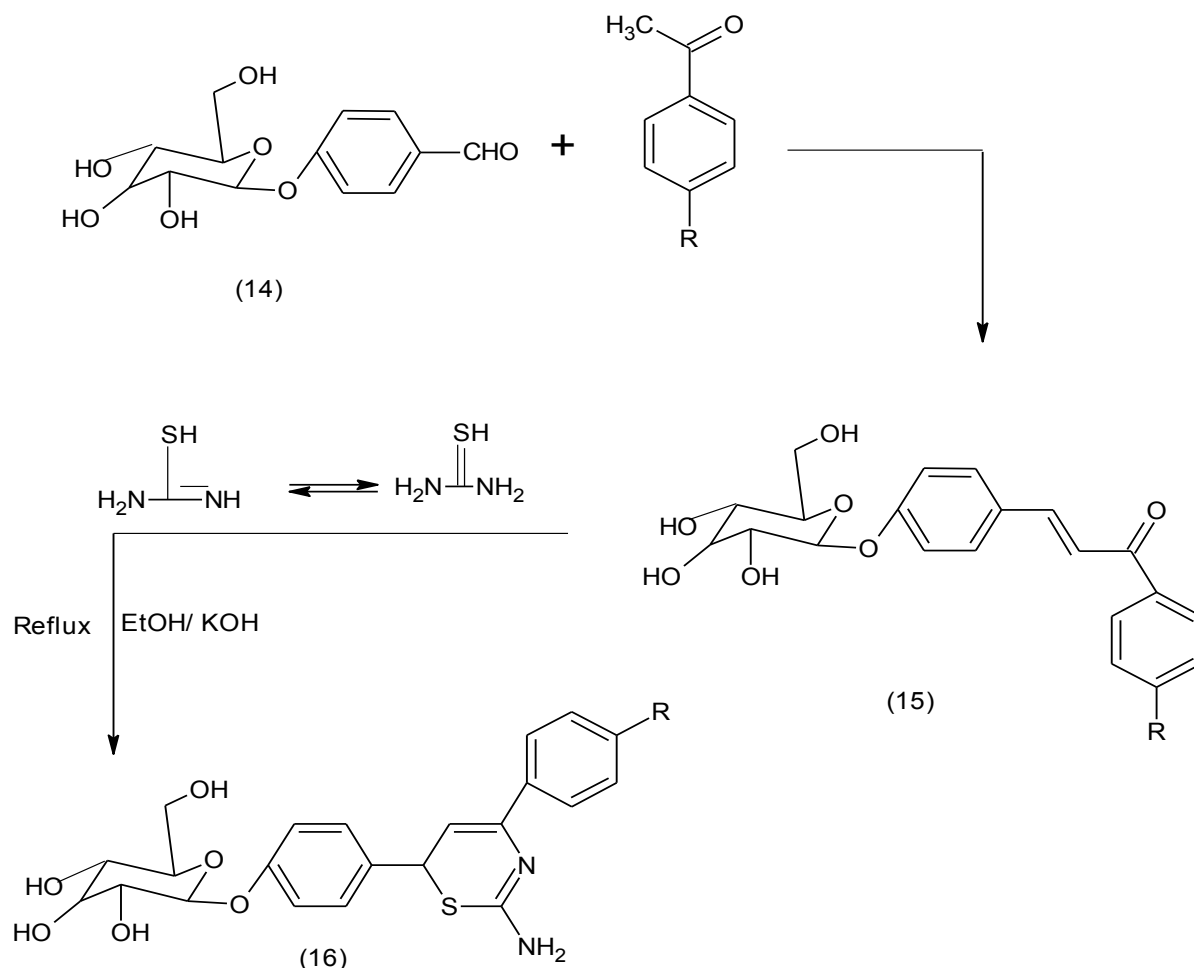
1,3-Thiazine
(2)



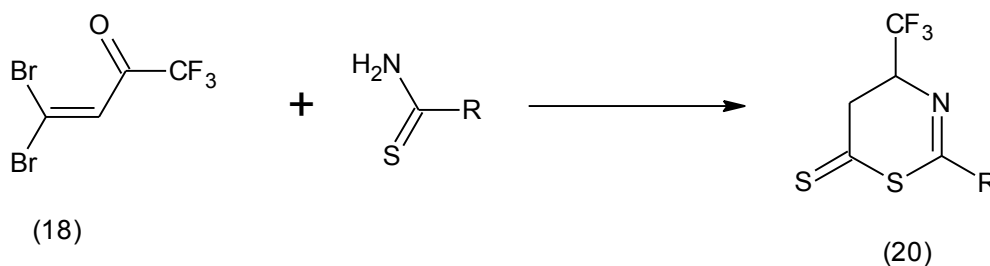
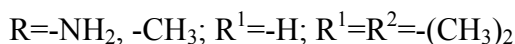
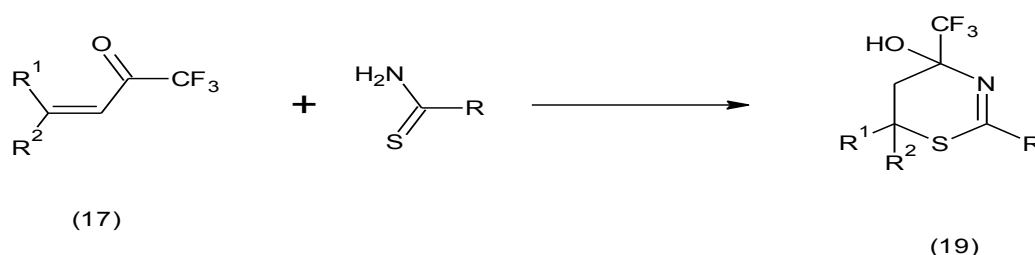
1, 4-Thiazine
(3)

1 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.

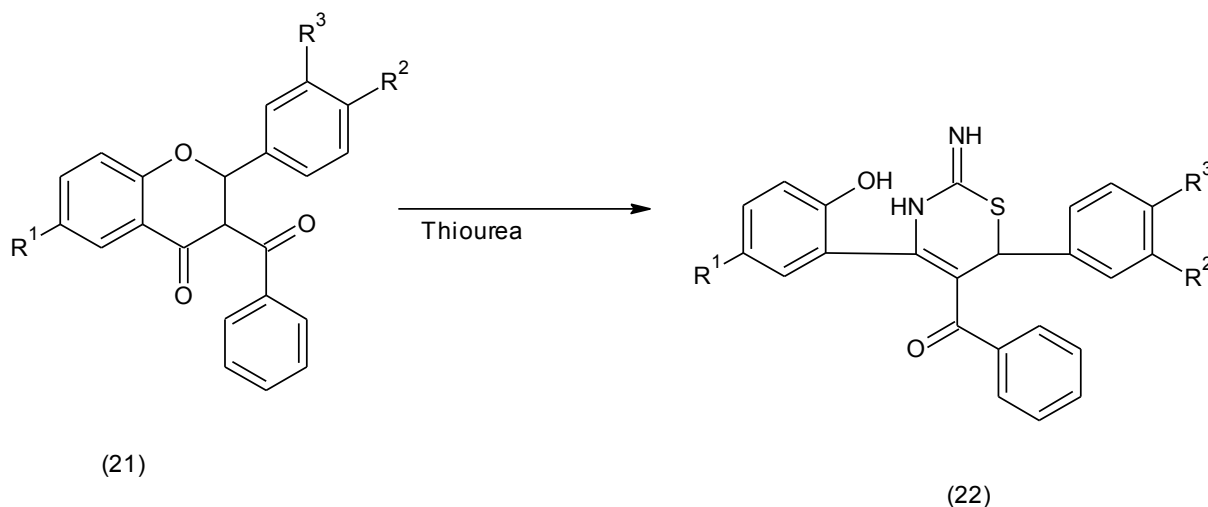
Helicid [4-formylphenyl-β-D-allopyranoside] (14) condensed with 4-substituted acetophenone to give E-(4-β-D-allopyranosyloxyphenyl)-1-(4-substituted phenyl) propenone derivatives (15). The latter undergo 1,4-Michael addition with thiourea in basic medium to yield 6H-2-amino-4-aryl-6-(4-β-D-allopyranosyloxyphenyl)-1,3-thiazine derivatives (16).⁴



On refluxing trifluoromethyl enones (17)/ β,β-dibromo-CF₃-ketones (18) with thiourea or thioacetamide in acidic medium give dihydrothiazines (19) or 1,3-thiazine derivatives (20).⁵

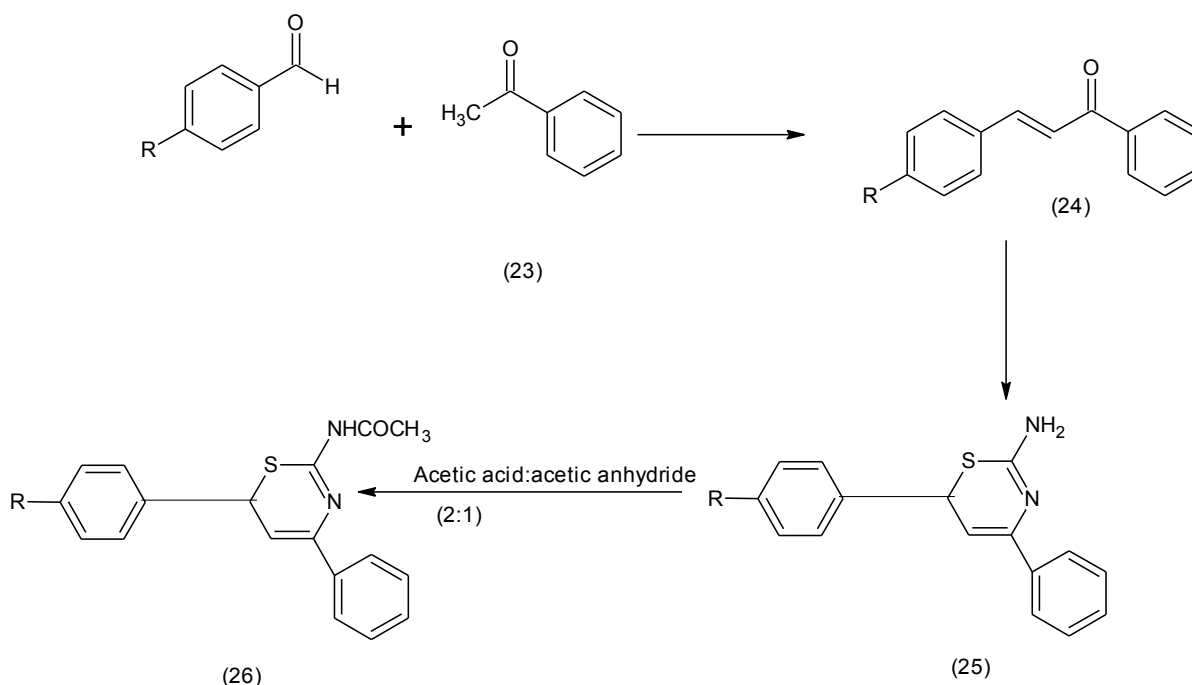


3-Benzoyl-3,4,6-trisubstituted flavanones (21) procured from 1-(2-hydroxyphenyl)-3,5-disubstituted-1,3-propanone and benzaldehyde when refluxed with thiourea in dry pyridine affords 4-(2-hydroxy-5-substitutedphenyl)-5-benzoyl-6-substitutedphenyl-2-imino-6H-2,3-dihydro-1,3-thiazine derivatives (22).⁶



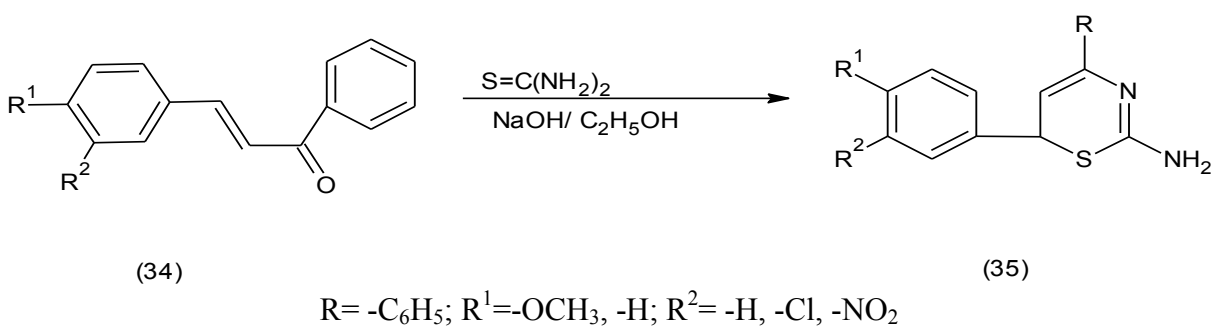
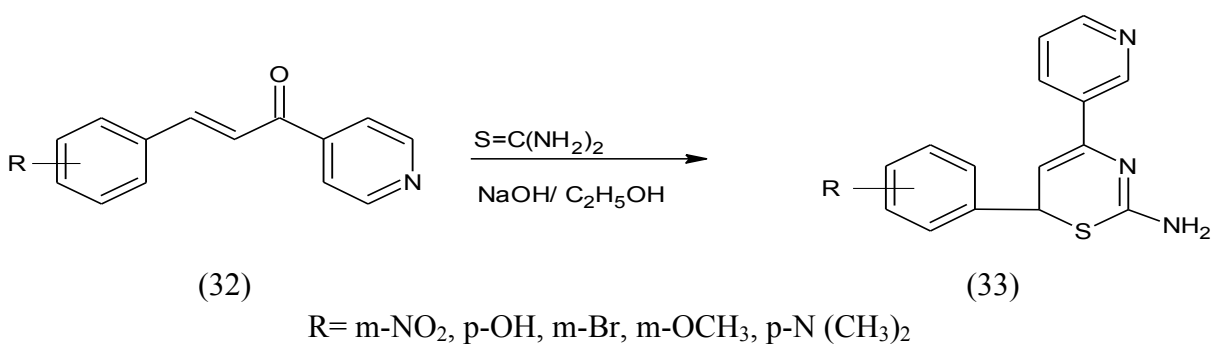
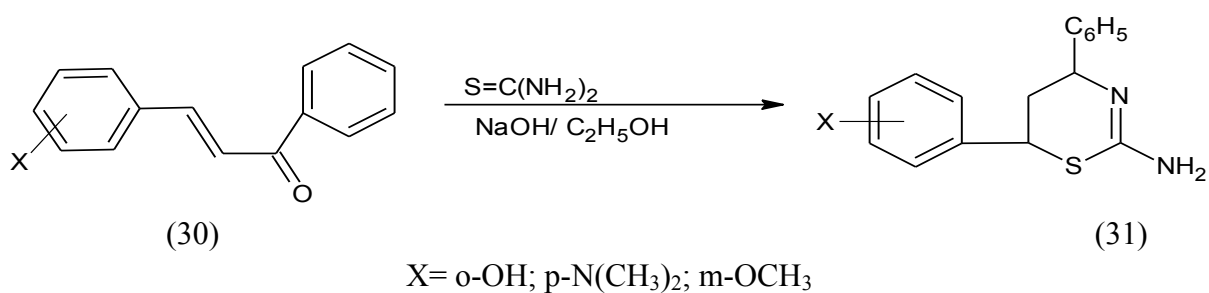
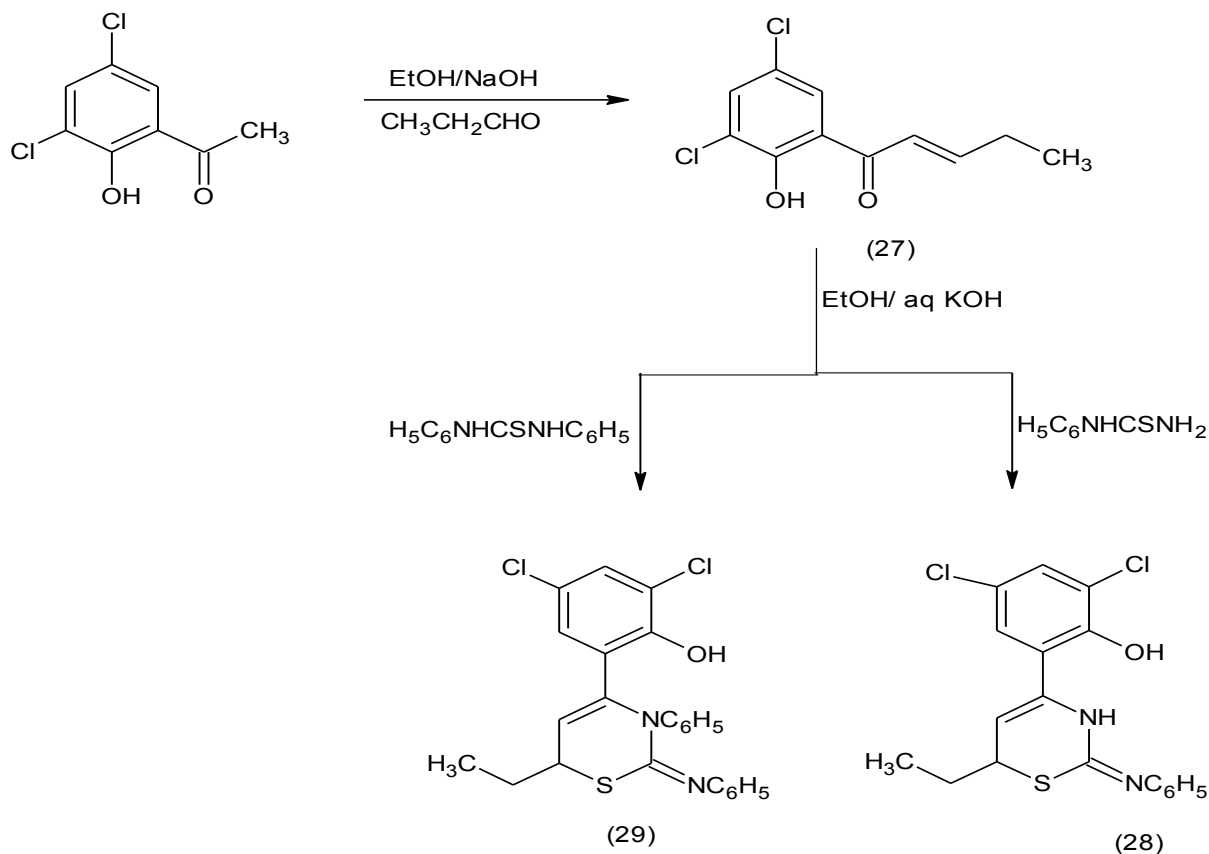
$R^1=R^2=R^3=-H$; $R^1=R^3=-H$, $R^2=-OCH_3$; $R^2=R^3=-OCH_3$; $R^1=R^3=H$, $R^2=-N(CH_3)_2$; $R^1=-CH_3$, $R^2=R^3=-H$; $R^1=-CH_3$, $R^2=-OCH_3$, $R^3=-H$; $R^2=R^3=-OCH_3$, $R^1=-CH_3$; $R^1=-CH_3$, $R^2=-N(CH_3)_2$, $R^3=-H$.

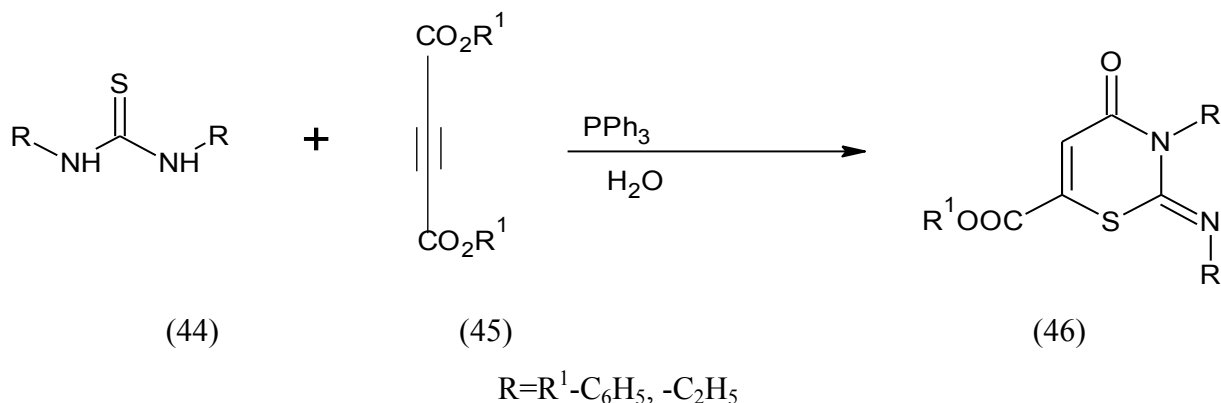
Claisen- Schmidt condensation of acetophenone (23) and aryl aldehydes yields chalcone derivatives (24) which on treatment with thiourea undergo cyclization in basic medium to yield 6-[4-substituted phenyl]-4-phenyl-6H-1,3-thiazine-2-amine derivatives (25). The latter can be acylated to give N-[6-(4-substituted phenyl)-4-phenyl-6H-1,3-thiazine-yl] acetamide derivatives (26).⁷



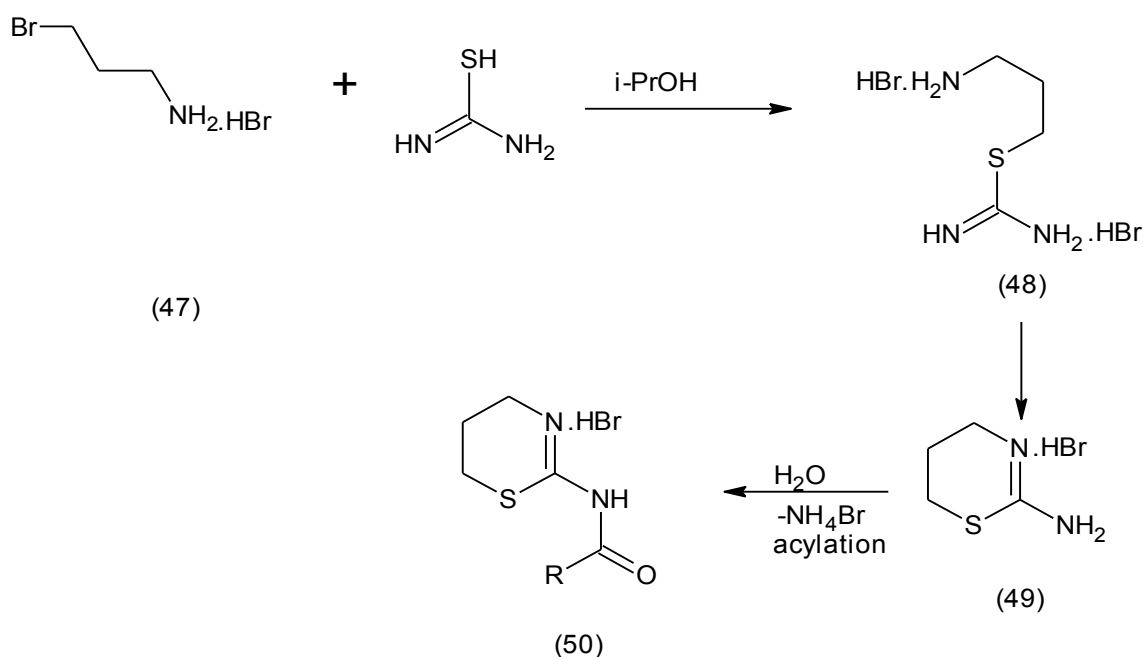
$R = -CH_3, -N(CH_3)_2, -Cl, -NO_2, -OCH_3, -OH$

Similarly, 2-hydroxy-3,5-dichloro-4-ethyl chalcone (27) when treated with phenylthiourea and diphenyl thiourea gives 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1,3-thiazine (28) and 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3-phenyl-1,3-thiazine (29) respectively.⁸ Further, mono and di-substituted chalcone derivatives (30, 32, 34) when stirred with thiourea under similar conditions yield the corresponding 1,3-thiazine derivatives (31, 33, 35).^{9, 10, 11}

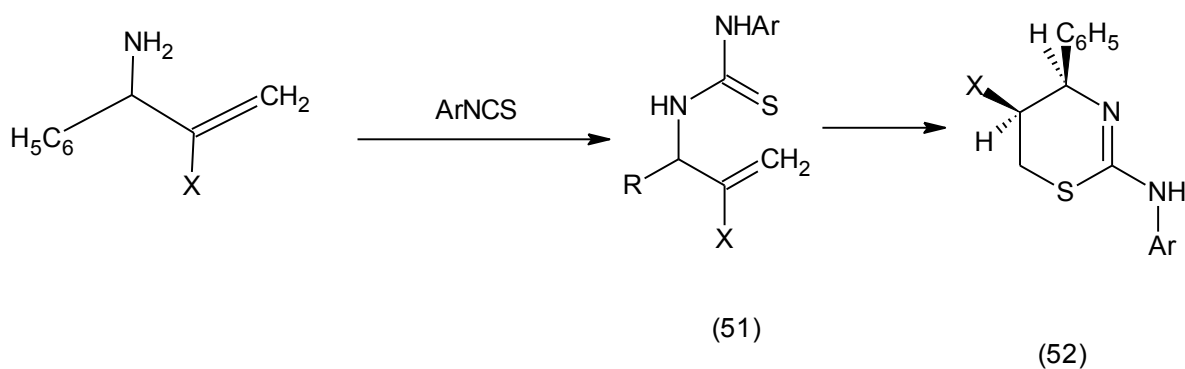




Cycloaddition of propylamine hydrobromide (47) with thiourea produces S-(aminopropyl) isothiurea dihydrobromide (48) which on heating cyclizes to 2-amino-5,6-dihydro-4H-1,3-thiazine (49). On acylation of the latter, 2-N-acylamino-5,6-dihydro-4H-1,3-thiazine hydrobromide (50) was obtained.¹⁶

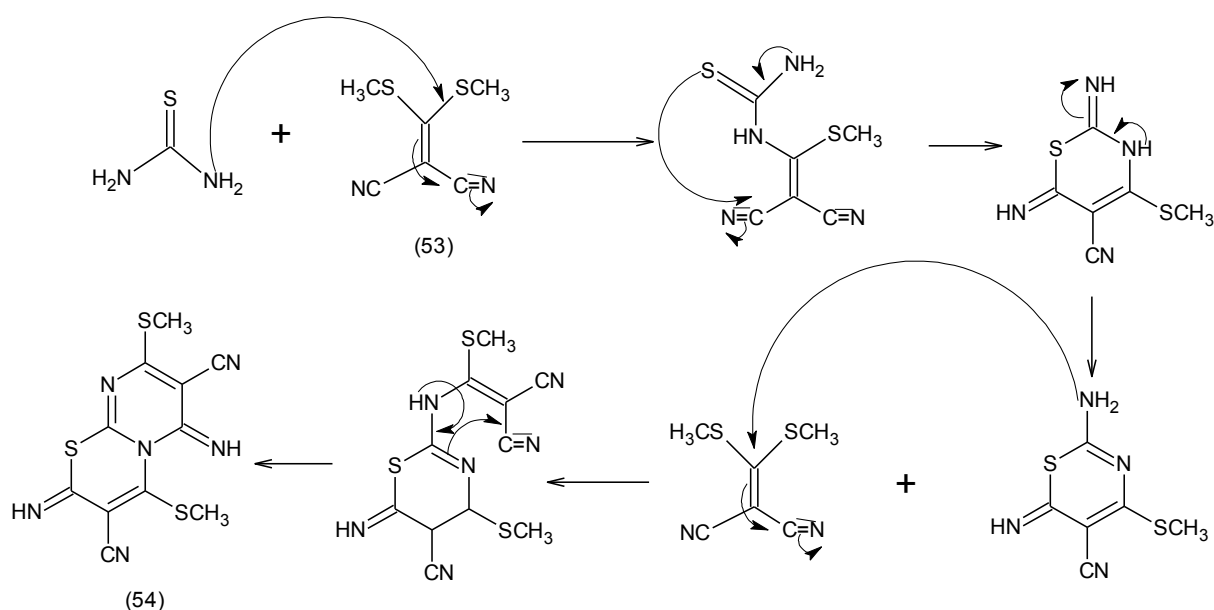


Stereoselective synthesis of 2-substituted amino-5,6-dihydro-4H-1,3-thiazines (52) involves intramolecular cyclization by sulphur-Michael reaction of allyl thiourea (51) which in turn has been prepared from allylamine and arylisothiocyanate.¹



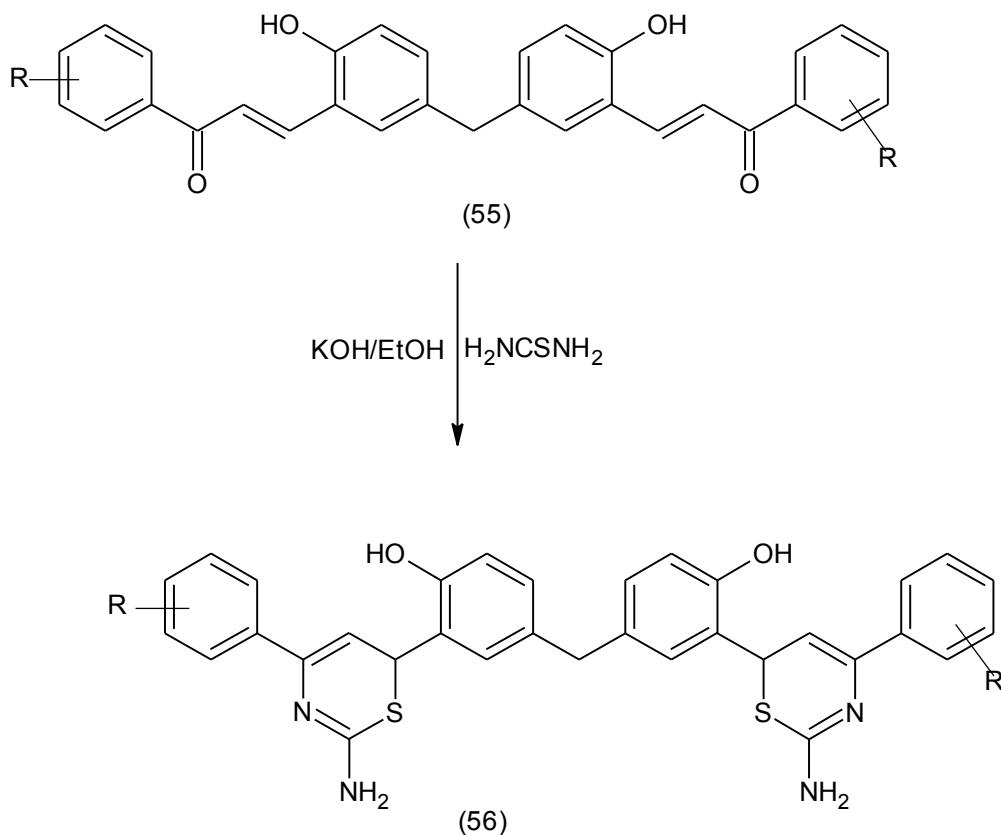
On refluxing (methylthio) methylene malanonitrile (53) with thiourea in the presence of anhydrous potassium carbonate for 12 hours produces 2,6-dihydro-2,6-diimino-4,8-bis(methylthio) pyrimido [2,1-

b)[1,3] thiazine-3,7-dicarbonitrile (54). 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 (scheme-1).¹⁸



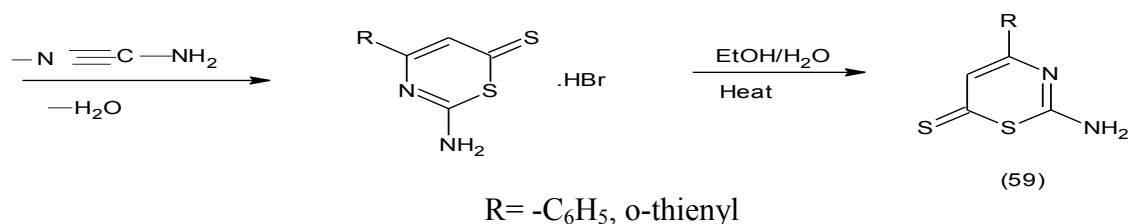
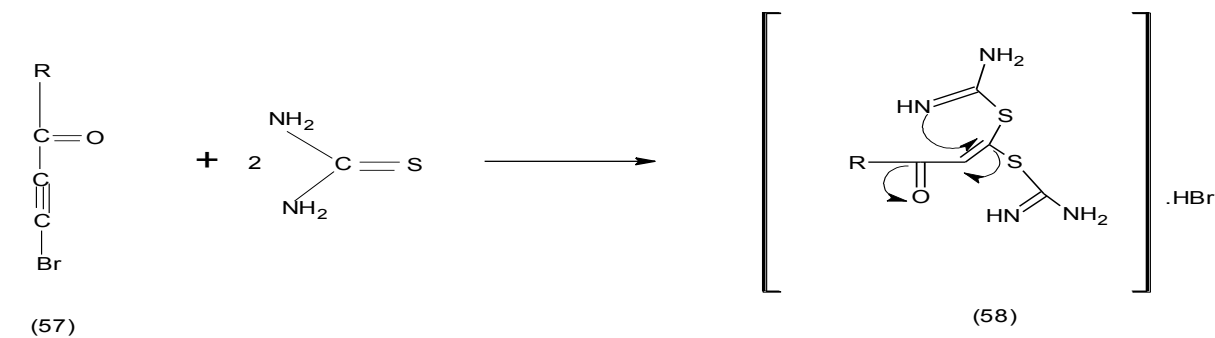
Scheme-1

Bis[3-[(E)-3(4-substitutedphenyl)-3-oxo-1-propenyl]-4-hydroxyphenyl] methane (55) on treating with thiourea followed by cyclization in ethanolic KOH produces bis- thiazine derivatives (56).¹⁹

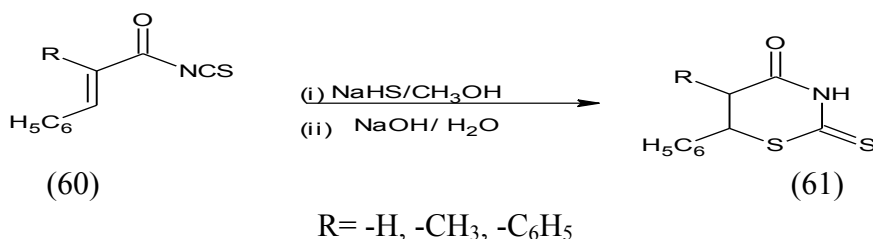


R= -H, p-OCH₃, p-Cl, p-NO₂, p-Br, o-Cl

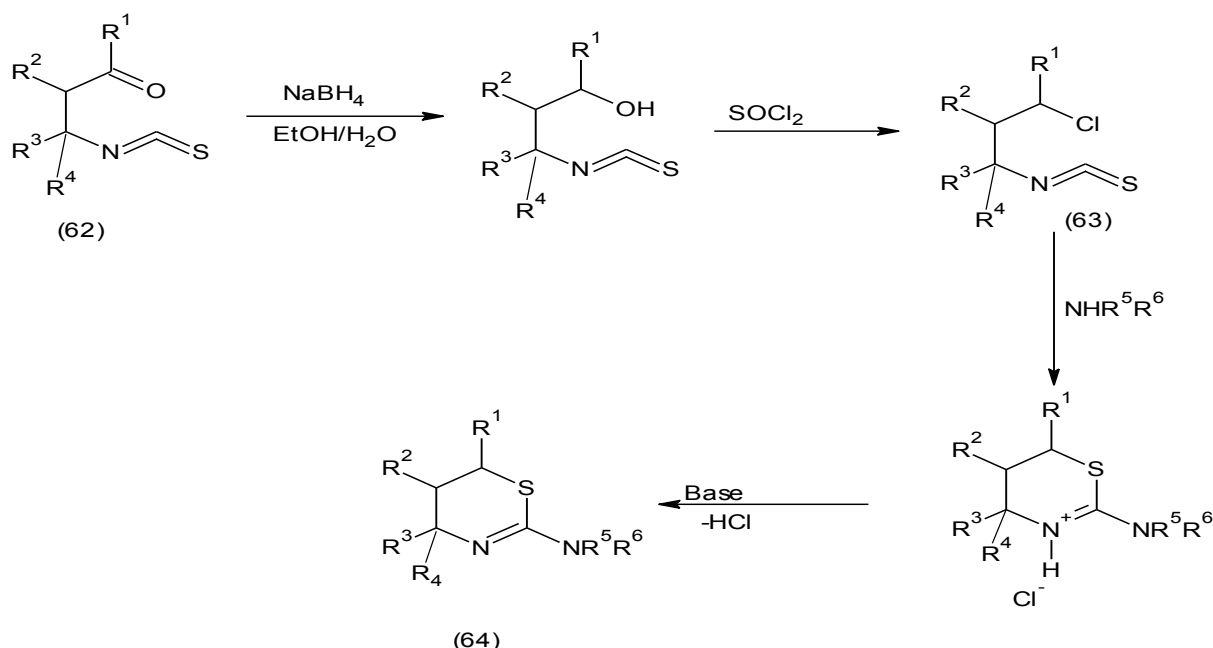
1-Acyl-2-bromoacetylene derivatives (57) when treated with thiourea in the presence of glacial acetic acid produce α -oxoketene mercaptals (58). The latter in BF₃.Et₂O, with the removal of cyanamide and water undergoes intramolecular cyclization to give 1,3-thiazine-6-thione hydrobromide which on recrystallization with water-alcohol yields pure substituted 2-amino-1,3-thiazine-6-thiones (59).²⁰



2. On stirring isothiocyanate (60) 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 (61).²¹



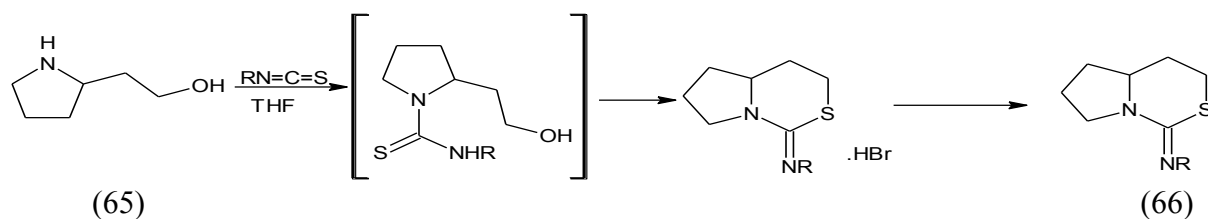
1,3-Isothiocyanato ketones (62) get reduced with NaBH₄ to give 1,3-isothiocyanato alcohols which subsequently react with thionyl chloride to produce 3-chloro-1-isothiocyanatoalkane derivatives (63). The latter in methanol and ammonia treated with NaOH yield 2-amino-4,4,6-trisubstituted-5,6-dihydro-4H-1,3-thiazine (64) (scheme-2).²²



R¹=R²=R⁴=-H, R³=-Me; R¹=R²=-Me, R³, R⁴=-H; R¹=R³=R⁴=-Me, R²=-H; R¹=R²=R³=R⁴=-CH₃; R⁵=R⁶=H; R⁵=-Bn, R⁶=-H; R¹=-C₆H₅, t-Bu; R²=-OCH₃, -H; R³=-H, -OCH₃, -CH₃

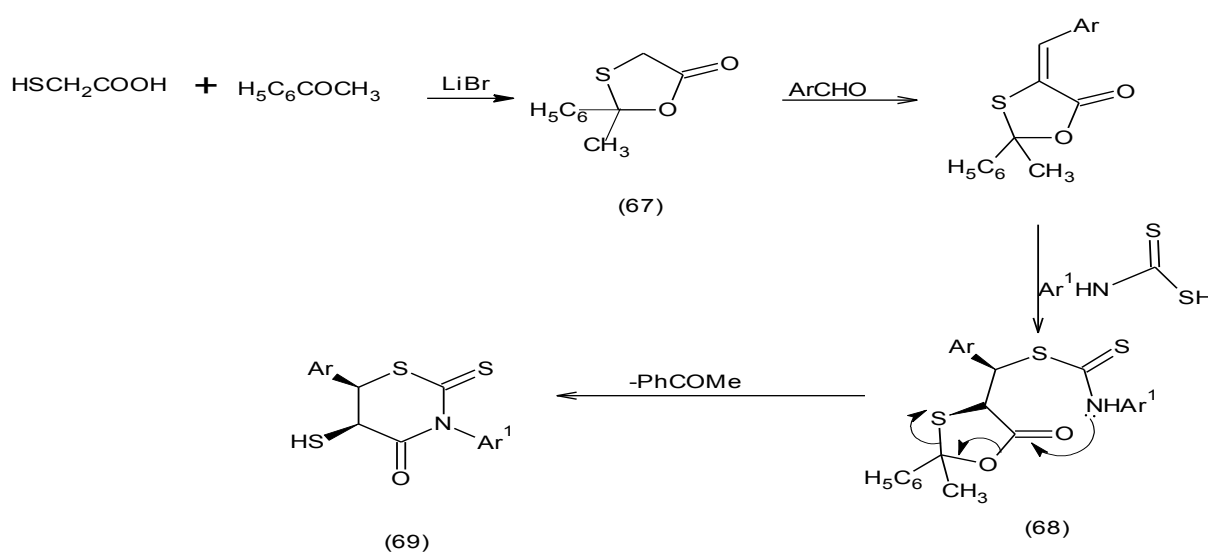
Scheme-2

2-(β -Hydroxyethyl)-pyrrolidine (65) 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) (66).²³



R = -CH₃, -C₂H₅, cyclo-C₆H₁₁, -CH₂C₆H₅, -C₆H₄, p-CH₃-C₆H₄, p-CH₃O-C₆H₄, p-Br-C₆H₄, p-Cl-C₆H₄

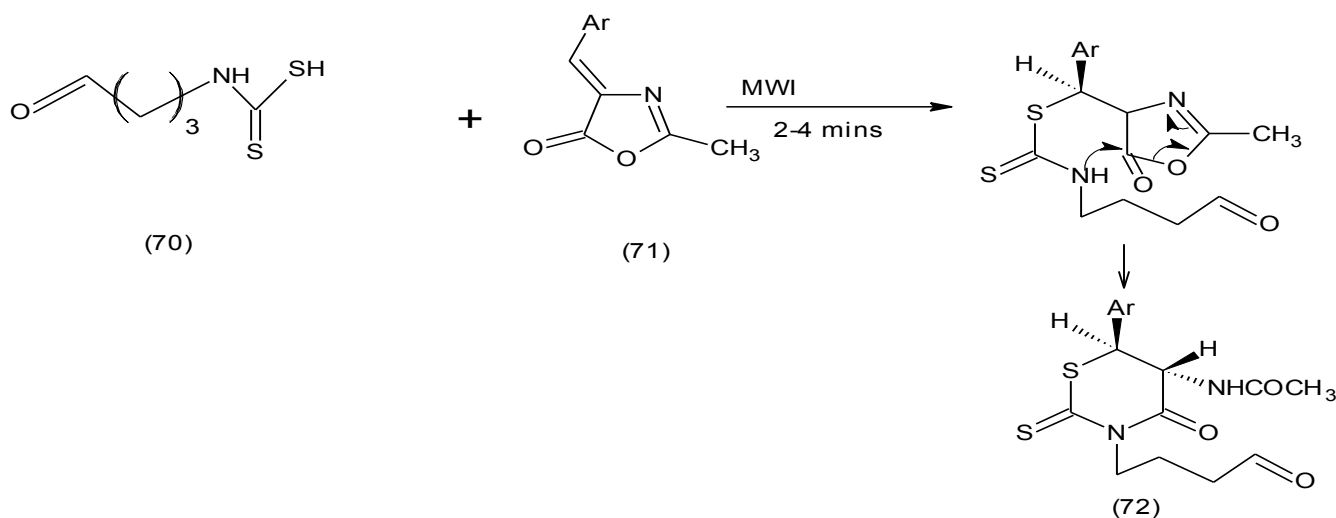
One pot diastereoselective reaction of 2-methyl-2-phenyl-1,3-oxathiolan-5-one (67), aromatic aldehyde and N-aryldithiocarbamic acid in microwave yields Michael adduct (68). The latter undergo ring transformation to produce polyfunctionalised 3,6-diaryl-5-mercaptoperhydro-2-thioxo-1,3-thiazine-4-ones (69) (scheme-3).²⁴



Ar = -Ph, p-Cl-C₆H₄, p-MeO-C₆H₄; Ar¹ = -Ph, o-Me-C₆H₄, p-MeO-C₆H₄

Scheme-3

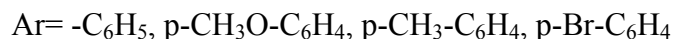
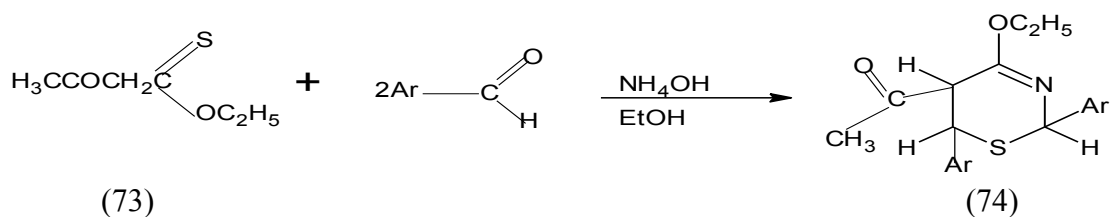
(4-Oxo-butyl)-dithiocarbamic acid (70) and 4-arylidene-5(4H)-oxazolones (71) in microwave with montmorillonite K-10 clay yield N-[3-(3-hydroxymethyl-4-oxo-butyl)-4-oxo-6-aryl-2-thioxo-[1,3]thiazinan-5-yl]-acetamide derivatives (72) (scheme-4).²⁵



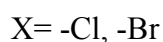
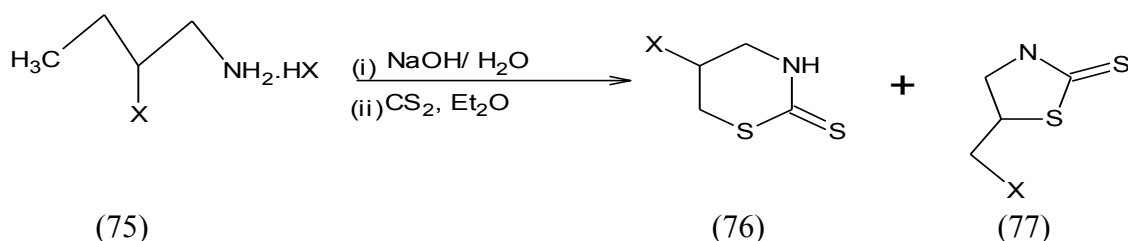
Ar = -C₆H₅, p-CH₃O-C₆H₄, p-HO-C₆H₄, p-Cl-C₆H₄, p-NO₂-C₆H₄

Scheme-4

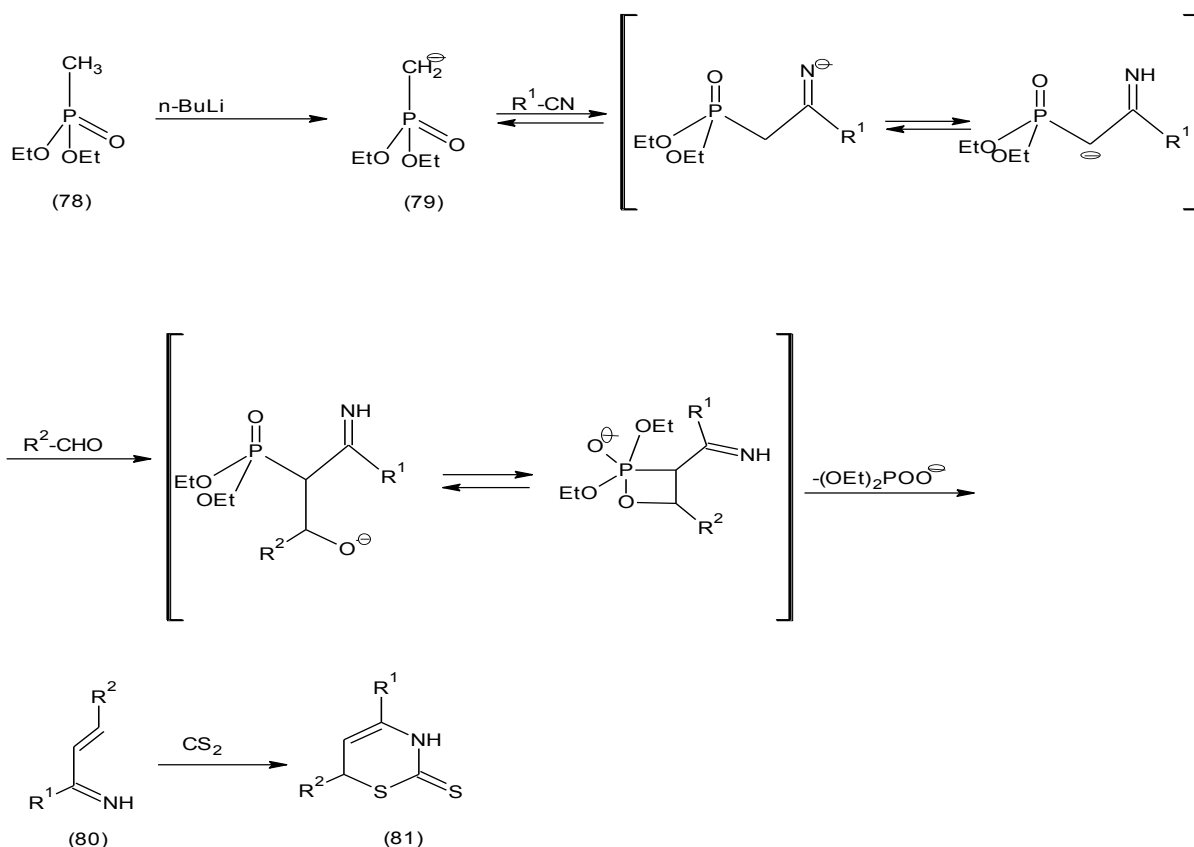
4. Cyclocondensation of acetothioacetic acid-O-ethyl ester (73) with aromatic aldehydes and aqueous ammonia produces oil of symmetrical 5-acetyl-2,6-diaryl-4-ethoxy-5,6-dihydro-2H-1,3-thiazine derivatives (74)²⁶.



5. On heating 2,3-dihalopropylaminehydrohalide (75) with carbon disulfide produces mixture of 5-halo-3,4,5,6-tetrahydro-1,3-thiazine-2-thiones (76) and 5-halomethylthiazolidine-2-thiones (77). It has not been quite an efficient method as latter yields mixture of cyclic dithiocarbamates.²⁷

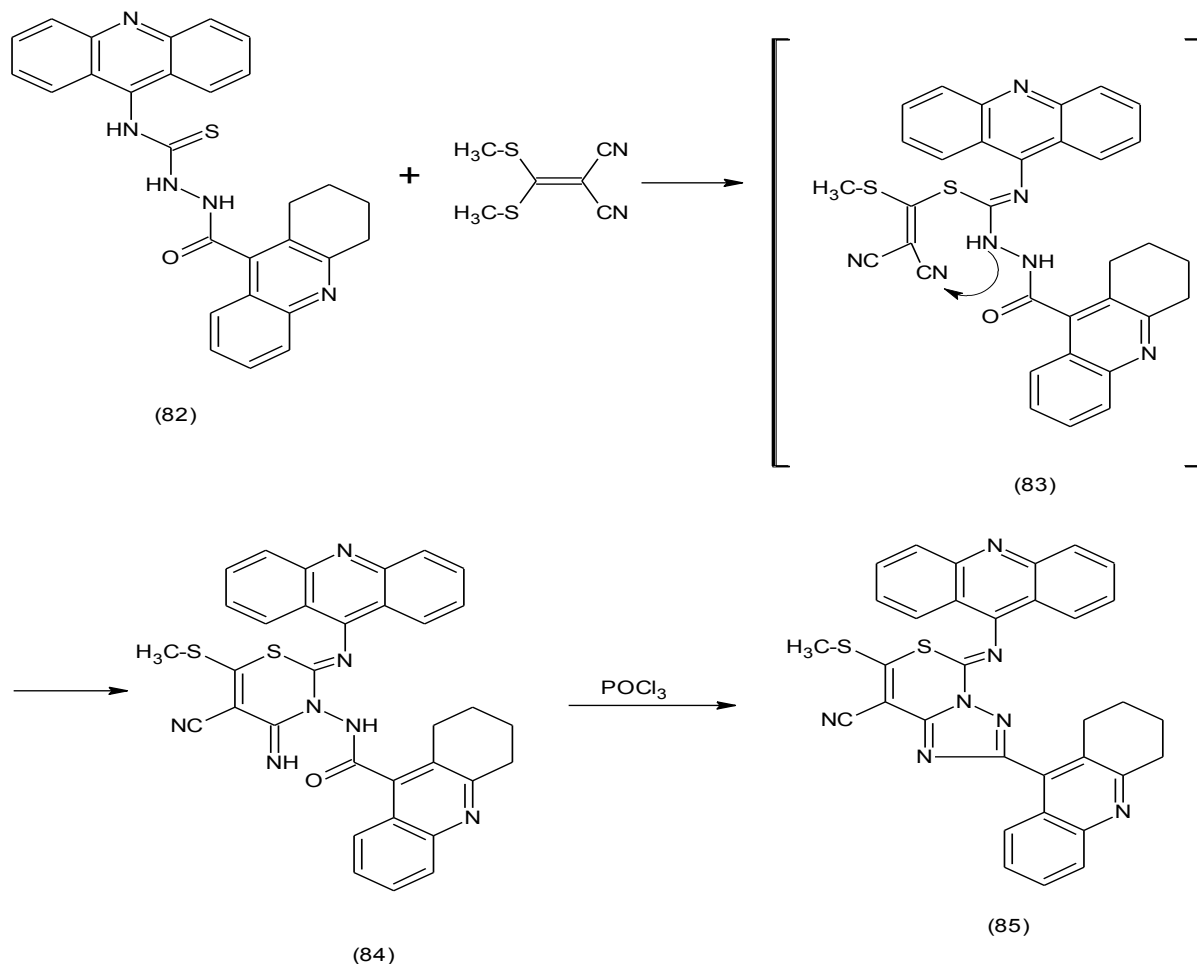


Diethyl methylphosphonate (78) on treating with n-butyllithium produces deprotonated diethyl methylphosphonate (79) which undergoes nucleophilic reaction with nitrile carbon of aryl nitrile followed by proton shift and subsequent Horner-Wadsworth-Emmons reaction with aldehyde to give 1-azadiene intermediate (80). The latter undergoes hetero Diels-Alder reaction with carbon disulphide to afford 3,6-dihydro-2H-1,3-thiazine-2-thiones (81) (scheme-5).²⁸

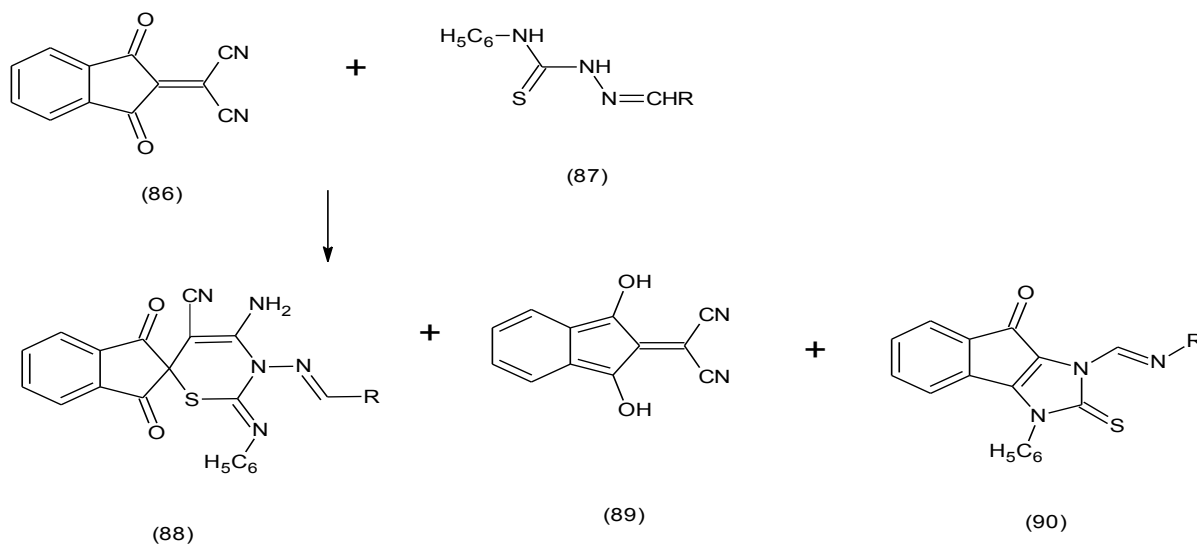


Scheme-5

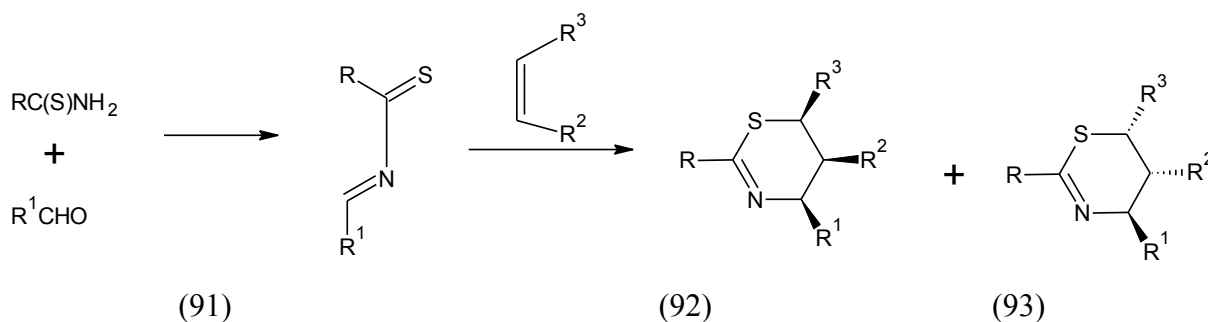
6. 4-(Acridine-9-yl)-1-(1,2,3,4-tetrahydroacridine-9-ylcarbonyl) thiosemicarbazide (82) on refluxing with [bis(methylthio) methylene]malononitrile yields intermediate (83) which in situ by intramolecular cyclization of NH functional group with CN group produces N-[2-(9-acridinylimino)-5-cyano-4-imino-6-(methylthio)-2H-1,3-thiazin-3(4H)-yl]-1,2,3,4-tetrahydro-roacridine-9-carboxamide (84). The latter on treatment with POCl₃ gives 5-(9-acridinylimino)-7-(methylthio)-2-[1,2,3,4-tetrahydroacridine-9-yl]-[1,2,4] triazolo[1,5-c][1,3] thiazine-8-carbonitrile (85).²⁹



8. (2-Dicyanomethylidene)indan-1,3-dione (86) on stirring with (substituted) alkenylidenehydrazinecarbothioamide (87) and their derivatives in ethylacetate produces dioxospiroindene[1,3]thiazine derivatives (88) along with byproducts (89-90).³⁰

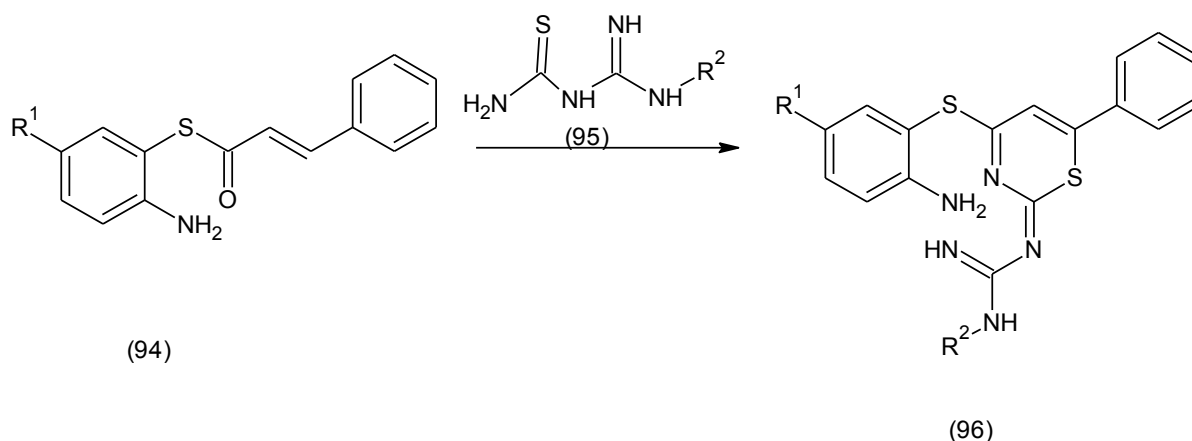


9. N-thioacyl imine heterodiene derivatives (91) procured from thioacetamide and aromatic aldehyde undergoes hetero Diels-Alder reaction with alkenes to give mixture of isomers of 1,3- thiazine derivative (92-93).³¹



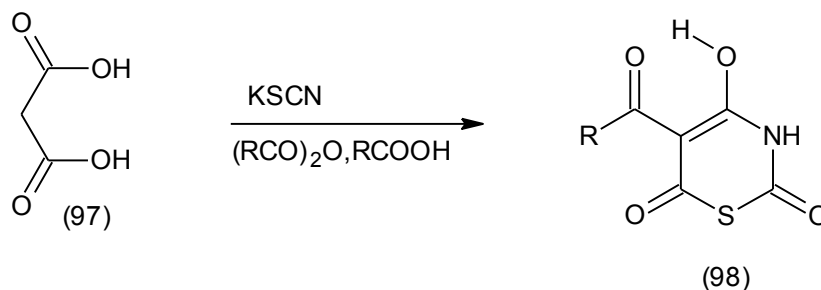
R = -C₆H₅, -CH₃; R¹ = -C₆H₅, p-Me-C₆H₄, p-Cl-C₆H₄, p-Br-C₆H₄, p-NO₂-C₆H₄, o-CH₃O-C₆H₄, m-HO-C₆H₄, m-Br-C₆H₄, m-NO₂-C₆H₄, 1-naphthyl, m-thienyl; R² = -H, -(CH₂)₄, -(CH₂)₆, -(CHCH₂)₂CH₂; R³ = n-C₄H₉, -Ph, -(CH₂)₂Br, -(CH₂)₂CO₂Et, -(CH₂)₂CO₂H

10. 1-(2-Amino-5-substituted phenyl) mercapto-3-(substituted) phenyl-2-propen-1-one (94) from 2-amino thiophenol on refluxing with substituted amidinothiocarbamides (95) in basic medium for 4-5 hours produce 2-substituted guanidine-4-(2-amino-5-substituted phenyl)mercapto-6-phenyl-1,3-thiazines (96) and it has also been an efficient method for synthesizing 2-amino-4-(2-amino-5-substituted phenyl)mercapto-6-(substituted) phenyl pyrimidine derivatives.³²



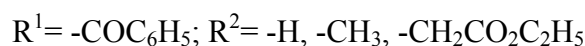
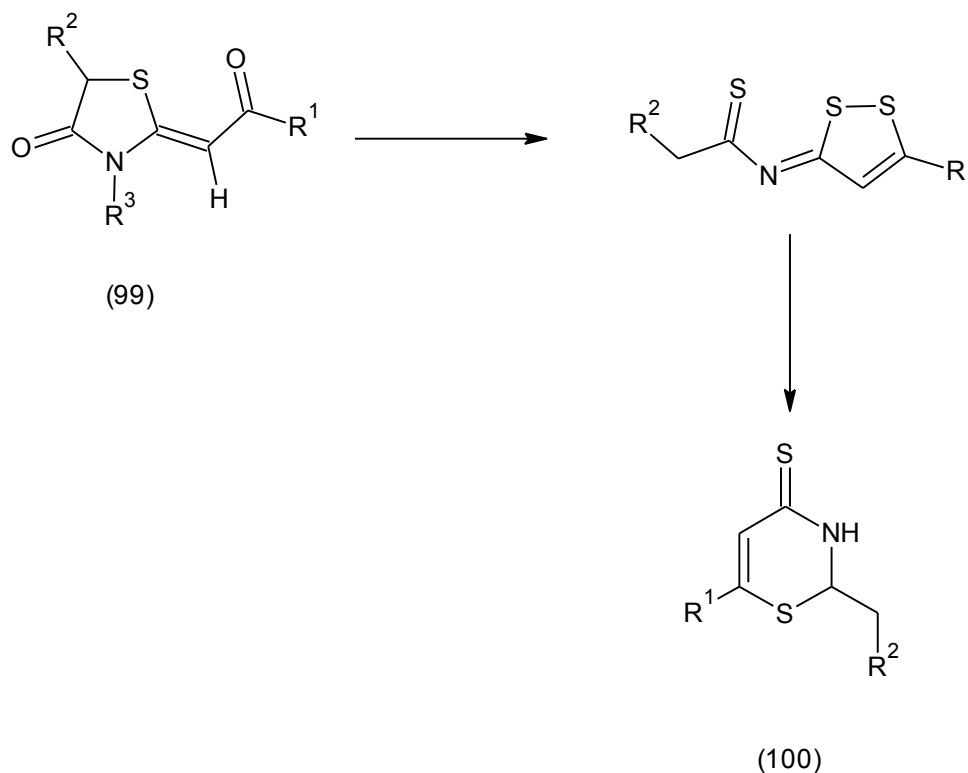
R¹ = -H, -CH₃; R² = -H, -C₆H₅, p-OCH₃-C₆H₄, p-Br-C₆H₄

Malonic acid (97) 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 (98).³³

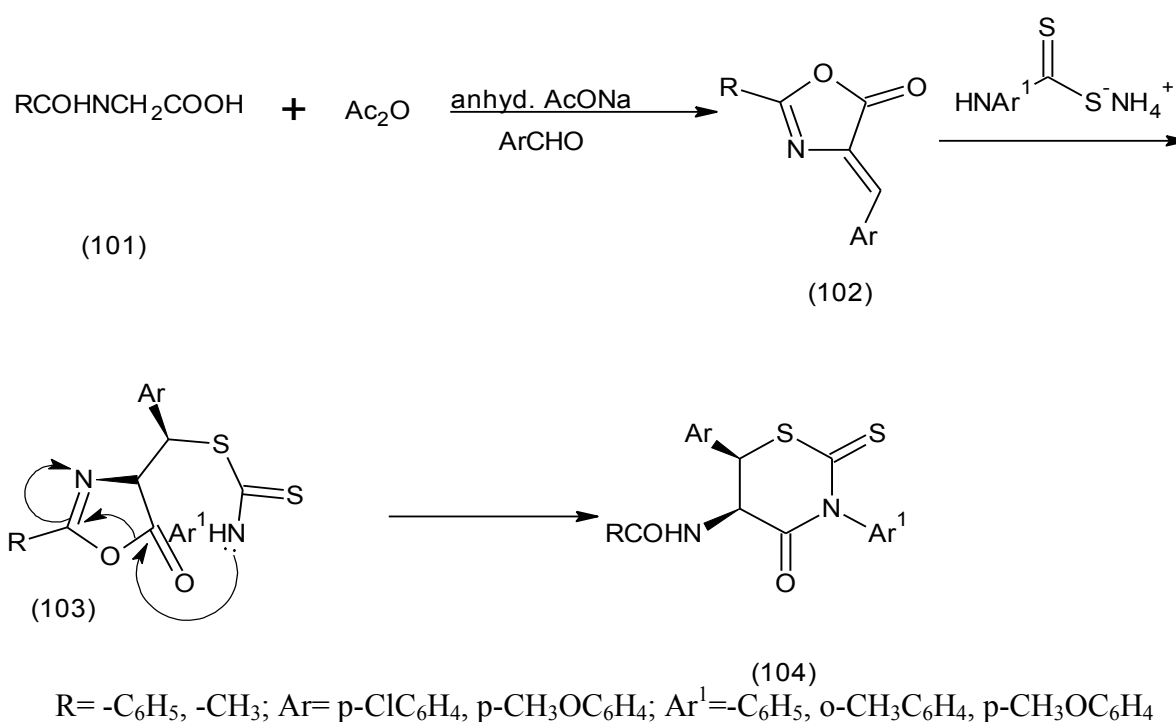


R = -CH₃, -C₂H₅, -C₃H₇

10. 1,2-Dithioles from 4-oxothiazolidines (99) when treated with sodium borohydride in ethanol produce 1,3 thiazine derivatives (100).³⁴



N-acylglycine (101) on treatment with anhydrous sodium acetate, acetic anhydride and arylaldehyde gives an intermediate azalactone (102). The latter undergoes Michael addition with N-aryldithiocarbamate in microwave to yield an adduct (103) 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 (104) (scheme-6).³⁵

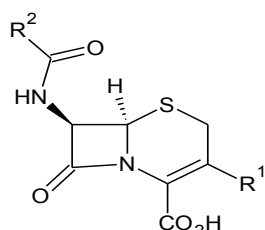


Scheme-6

BIOLOGICAL POTENTIAL OF 1, 3-THIAZINES

Antimicrobial Activity

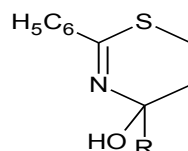
1,3-Thiazines and their derivatives have significant antimicrobial potential against various strains of bacteria, fungi etc.. The core moiety of 1,3-thiazines (C-N-S) forms an active site in antibiotics like Cephalosporins (105). 1,3-Thiazines derived from chalcones viz. 4-(2-hydroxy-3,5-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3-phenyl-1,3-thiazine (29), 4-(2-hydroxy-3,5-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1,3-thiazine (28) etc. have also been evaluated for their in vitro antimicrobial activity against various gram positive- *Streptococcus aureus*, *S.subtilis* and gram negative bacteria- *E.coli* and *P.aeruginosa* [S.P.Rathod *et al.* (2010)].¹⁵ Mamoru Koketsu *et al.*, 2002 synthesized series of 5,6-dihydro-4H-1,3-thiazine derivatives³⁶ (106) which showed antimicrobial activity against *M. tuberculosis H37Rv*. Tarik EL-Sayed Ali *et al.*, 2010 synthesized 1,3-thiazine derivatives having acridine ring (85) which besides showing antimicrobial activity against above mentioned species, also exhibit antibacterial activity against *Streptococcus pyogenes* and *Pseudomonas fluorescens* and *Pseudomonas phaseolicola* and antifungal activity against *Fusarium oxysporum* and *Aspergillus fumigates*.²⁹ Ramesh L. Sawant *et al.*, 2011 introduced electron donating groups like hydroxyl and methoxy group at the fourth position of phenyl rings in the series of 6-[4-substitutedphenyl]-4-phenyl-6H-1,3-thiazine-2-amines (25) and N-[6-(4-substitutedphenyl)-4-phenyl-6H-1,3-thiazine-yl] acetamides (26) which enhances their antimicrobial activity⁷. Farooque Haider Zulfeqar Haider, 2012 synthesized series of 4-(2-hydroxy-5-substitutedphenyl)-5-benzoyl-6-substitutedphenyl-2-imino-6H-2,3-dihydro-1,3-thiazine derivatives (22) which exhibits 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 Thanusu J *et al.*, 2010 introduced morpholine ring in the series of 4-(4-morpholinophenyl)-6-aryl-1,3-thiazin-2-amines (107) which showed substantial antibacterial activity against *V.cholera* etc. and antifungal activity against various strains of fungi viz. *Rhizopus*, *M. gyseum*³⁷ etc.



$R^1 = -CH_3COOCH_3, -CH_3, -CH_3Cl$

$R^2 = -CH_3CN, p-(NH_2)C_6H_4, p-(OH)C_6H_4$

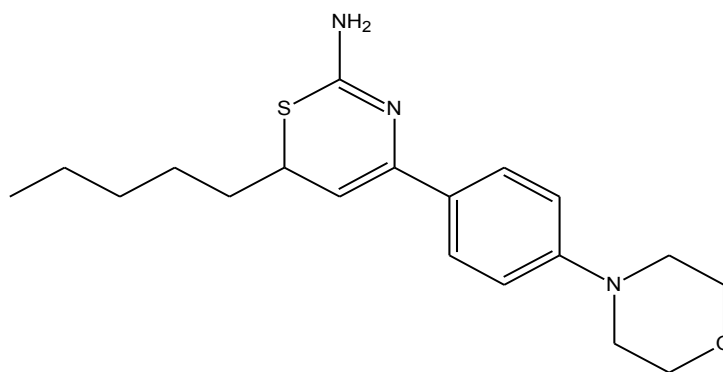
(105)



5, 6-dihydro-4H-1,3-thiazine derivative

$R = -CH_3, -C_2H_5$

(106)

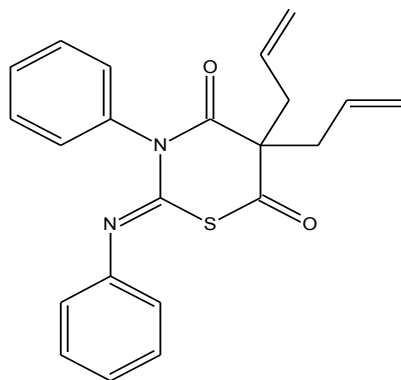


4-(4-morpholinophenyl)-6-amyl-1, 3-thiazine-2-amine

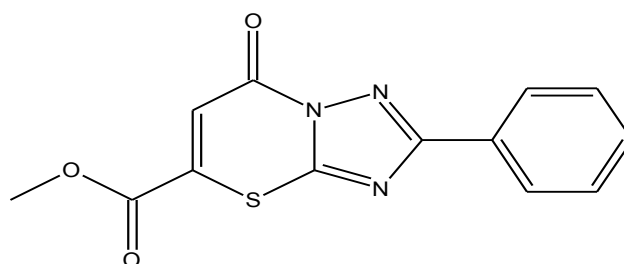
(107)

Other Activities of 1, 3-Thiazines

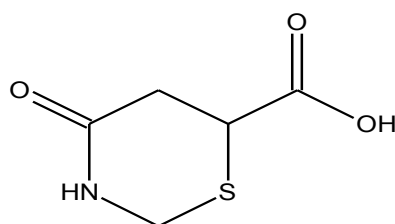
Li Fu *et al.*, 2010 procured series of 6H-2-amino-4-aryl-6-(4-β-D-allopyranosyloxyphenyl)-1,3-thiazines (16) by Claisen Schmidt condensation which show strong calming activity in comparison with parent helicid.⁴ T.P.Trofimova *et al.*, 2008 gave a reaction scheme to synthesize 2-N-acylamino-5,6-dihydro-4H-1,3-thiazines (50) which showed excellent NOS inhibiting activity both in vivo and in vitro and also act as antihypotensive agents in vivo.¹⁶ Kai H *et al.*, 2008 synthesized 2-arylimino-5,6-dihydro-4H-1,3-thiazines which show profound analgesic properties.³⁸ Tetrahydro-1,3-thiazines derivatives (108), tetrahydro [1, 3]-thiazine-4-one-6-carboxylic acid (109), 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-hydroxybenzyl]phenol and 2-[2-amino-4-(4-chlorophenyl)-6H-1,3-thiazin-6-yl]-4-hydroxybenzyl}phenol (56) etc. have also been known to exhibit strong anti-inflammatory activity and most of them are immunotropic in nature [Zawisza T *et al.*, (1978&1981); R. Kalirajan *et al.* (2009), A. Nagaraj *et al.* (2008)].^{9, 19, 39, 41} Derivatives of 1,2,4-triazolo [3, 2-b]-1,3-thiazine-7-ones (110) and amino/ guanidine thiazine derivatives (96) besides, possessing anti-inflammatory activity, also exhibits analgesic properties [Tozkoparan B *et al.* (2002); Vijay V. Dabholkar *et al.* (2011)].^{32,40} The derivatives of 1H-pyrrolo [1, 2-c] [1,3] thiazine (66) have been reported to show moderate anticonvulsant activity [Tadeusz S. Jagodzinski *et al.*, 2003].²³



5,5-diallyl-2-phenylimino-3-phenyl-2,3,4,5-tetrahydro-[1, 3]-thiazine-4,6-dione
(108)



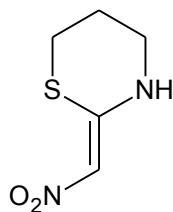
5-carbomethoxy-2-phenyl-7H-1,2,4-triazolo[3,2-b]-1, 3-thiazine-7-one
(109)



Tetrahydro[1, 3]-thiazine-4-one-6-carboxylic ac
(110)

Agrochemical Uses of 1,3-Thiazine Derivatives

Tetrahydro-2-(nitromethylene)-2H-1,3-thiazine (Nitromethylene) possess strong insecticidal properties (111)[Margulies, L et al. (1988)]⁴². Perhydro derivatives of 1,3-thiazine have obtained patent for their insecticidal properties against various nematodes [Jean-dominique bourzat et al. (1981)]⁴³.



(111)

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.

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