Adaptable Preparation Methods and Applications of Thiazines

Rajeswari Kannuri[1], Venkanna Muripiti[2], Venkatesh Ravula[3], Shireesha Manturthi[4]. Srilakshmi Patri[5]*, Amarnath Velidandi[6]*

***Corresponding Author:** Amarnath Velidandi, Srilakshmi Patri, * **Corresponding Author email id**:velidandi@yahoo.co.in
[1,*6]Department of Chemistry, Chaitanya Deemed to be university, Warangal, Telangana State, India. [2,3,4,*5]Department of Chemistry, National Institute of Technology Warangal, Telangana State, India.

Abstract:

Thiazines are a group of heterocyclic organic compounds that are biological active compounds with different antimicrobial activities, CNS activity, and anti-cancer activity. In the literature, different methods for the synthesis of thiazine derivatives are available. In this article, we present a review of literature on the synthetic methods of various biologically active thiazine derivatives viz., synthesis of natural products containing thiazines, catalytic methods, and green synthesis and stereo-selective methods. Because of wide spread biological/pharmaceutical activities of thiazine derivatives, they play an important role in the treatment of various diseases. They are significantly active as anti-bacterial, anti-cancer agents anti-fungal, anti-neoplastic, anti-viral, anti-inflammatory, and anti-malarial. To this end as they represent an interesting class of heterocyclic compound it is important to explore further these derivatives for various applications.

Keywords: Green Synthesis, One-Pot Synthesis, Cycloadditions, Stereo-selective Synthesis, Biological activity

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Introduction:

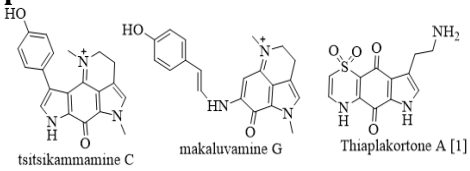
Thiazines are the six-membered heterocyclic systems with the general molecular formula C_4H_5NS. Consisting of "S" and "N" elements, these compounds are having excellent biological activity. The position of the sulfur and nitrogen may vary in different thiazene derivatives as 1,2 or 1,3 or 1,4. Thiazines can be prepared or extracted using different methods (1) Extracting from natural products. (2) With low cost by applying green synthetic protocols. (3) Using the organo metallic compounds, cyclo-addition reactions to achieve the higher yields. (4) Applying the stereo-selective synthesis to produce the active pharmacophores.

a) Thiazine contained Natural products and their synthesis:

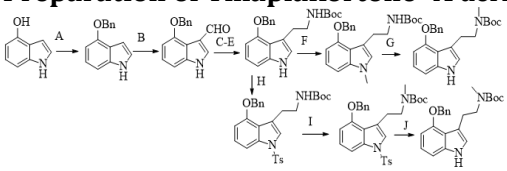
Scheme 1:

The natural product Thiaplakortone A [1] was having anti-malarial activity. A series of analogs were synthesized and their antimalarial efficiency, metabolic stability, and selectivity were evaluated Plasmodium falciparum line toward the chloroquine-sensitive (3D7), among the series four compounds (1a-d) confirmed the nano-molar activity and had been more active in competition to the standard drugs. The results in this study demonstrate that metabolic stability can be improved by the modifications of nitrogen on pyrrole.

Antimalarial (pyrroloquinone) natural products.

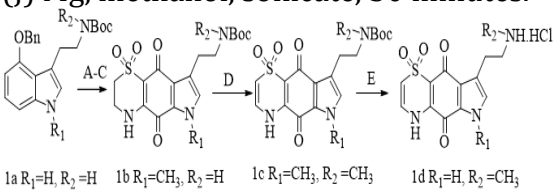


Preparation of Thiaplakortone- A derivatives:



(A) Benzyl bromide, potassium carbonate, CH_3COCH_3, heating, 36 hours; (B) phosphoryl trichloride, Dimethyl formamide, room temperature, 1 hour, potassium hydroxide, water, heating, 3 hours; (C) CH_3NO_2, Ammonium acetate, heating , 1 hour; (D) lithium aluminium hydride, tetrahydro furan, heating, 6 hours; (E)

$(Boc)_2O$, triethyl amine, tetrahydeo furan, room temperature, 16 hours; (F) methyliodide, potassium hydroxide, dimethyl sulfoxide, room temparature, 19 hours; (G) methyliodide, LiHMDS, tetrahydeo furan, room temperature, 2 hours; (H) tosyl chloride, tetrabutyl ammonium sulphide, potassium hydroxide, $PhCH_3$, Water, room temperature, 24 hours; (I) methyliodide, LiHMDS, tetrahydro furan, room temperature, 2 hours; (J) Mg, methanol, sonicate, 30 minutes.

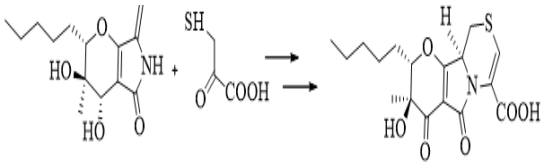


Scheme 1: (A) hydrogen, pelladium/carbon, methanol, room temperature, 24 hours; (B) Fremy's salt, sodiumdihydrogen phosphate, methyl cyanide, water, room temperature, 4 hours; (C) 2-aminoethanesulfinic acid, ethanol, methyl cyanide, water, room temperature, 16 hours; (D) oxygen, potassium hydroxide, methanol, water, 60 °C; (E) hydrogen chloride, MeOH, H_2O, room temparature, 18 hours, or 1,4-dioxane, hydrogen chloride, room temparature, 30 minutes.

Synthesis of Thiaplakortone A derivatives was simplified by the use of mild reaction conditions. Some of these derivatives showed high tolerability due to methylation and showed reduced nM drug-sensitive and therapeutic tolerant P. falciparum lines in-vitro activity. Pyrrol nitrogen N-methylation resulted in a dramatic increase in the metabolic stability of Thiaplakortone derivatives; however, no important antimalarial deficiency was noted. Such experiments are valuable for further developing new structurally adopted malaria drug compounds. [1]

Scheme 2:

As like as scheme 1, some strange thiazene derivatives developed by a natural product, the detailed structural features and estimated biosynthetic origin of the newer thiazene derivatives suggest that the compound is originated from cysteine. The endophytic fungal FT462 of Lycopodiella cernua, named paraphhaeosphaeria neglecta and analyzed by NMR and Mass spectroscopic methods. One of the isolated paraphaeosphaeride was a precursor for the new thiazene molecule, which is functioning on breast-cancer cell lines (MDA-MB-231), and can be used as anti-cancer agent.

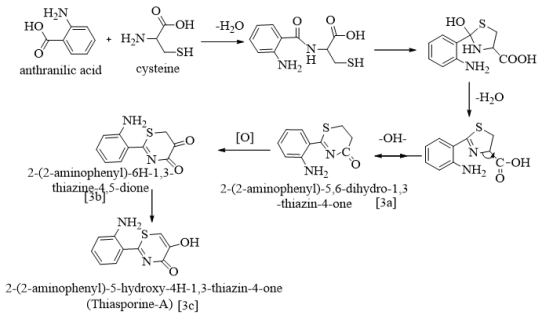


(5-hydroxy-5-methyl-6, 8-dioxo-4- Pentyl-3-oxa-12-thia-9- azatricyclotrideca -2(7), 10-diene-10-carboxylicacid) [2]

This discovery of new paraphaeosphaeride might be useful for synthetic chemists to investigate deeply for the biosynthetic pathway as well as to develop novel synthetic methods to synthesize natural products. [2]

Scheme3:

In continuation of Naturally available Thiazines and its biological property, herein discussing about Thiasporine A (natural product) isolated from Actinomycetospora chlora SNC-032 which was not found in any microorganism before, acts as anti-cancer agent and one of the starting material is cysteine in the synthesis. Thiasporine A analyzed by spectroscopic methods and predicted the biosynthetic mechanism. The biosynthetic pathway for thiasporines A–C possibly starts by amide bond formation, leading to hydroxy-thiazolidinecarboxylic acid by condensation intramolecularly in cysteine and anthranilic acid. From the intermediate removal of water, ring expansion and elimination of hydroxyl group yields the [3a].

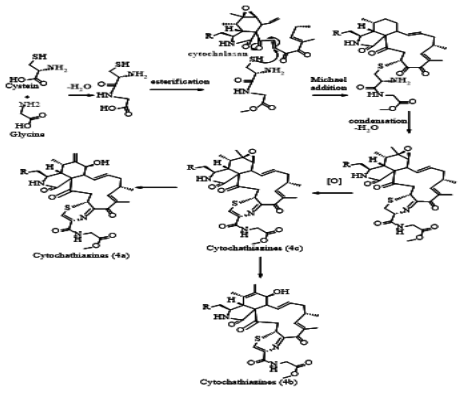


It undergoes oxidation, gives intermediate 3b, which on enolization yields the [3c] Thiasporine A. It shows cytotoxicity towards the H2122 cell line of lung cancer is an IC_{50} of 5.4 μM and shows extensive cytotoxicity on the cell line HCC44. [3]

Scheme 4:

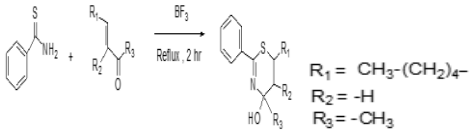
The natural compounds [1,4-thiazine derivatives], viewing their activity describing here regarding three new Cytochathiazines (4a–4c) from the coculture Chaetomium globosum, belonging to a new type of merocytochalasane and Aspergillus flavipes were isolated, it acts as anti-leukemia agent, and cysteine used in initial stage of the synthesis. These natural goods have special 2H-1,4-thiazine features for the first time. After biology evaluation, cytochathiazine B contributed to activation of caspase 3 and ADP-ribose polymerase, which decreased apoptosis in leukemia cells. There have been suggested two possible biosynthetic pathways. Dipeptide derivative 4b is produced by cysteine and glycine in one process and is esterified followed. Moreover, the addition of Michael 4b by the molecular cytochalasan is produced by the C–S bond at C-21 with a condensation to create a Schiff base after water removal by 4c.

The Schiff base subsequently oxidizes to assess the stability and development of 4c of 2H-1,4-thiazine. Finally, 4c isomerization creates 4a and 4b compounds. Cytototoxicity experiments with Cytochathiazine (4a-4c) indicate that Cytochathiazine (4b) with mild apoptosis Caspase-3 activation and PARP depletion, 9.6 and 12.5 μM of IC50 levels of NB4 and HL-60, respectively. [4]



b) Synthesis of Biologically active Thiazine derivatives:

Scheme 5:



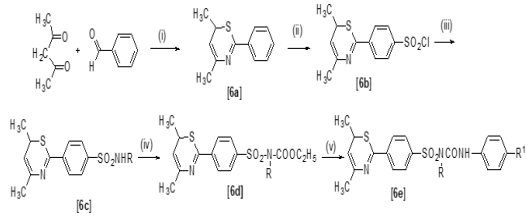
[5] [5[1]] **[5a]**

One of the Thiazine compounds medicinal application is anti-mycobacterial activity, for this series against five strains using the Microplate Alamar Blue Assay (MABA) shows moderate activity. The preparation of thiazine derivative [5a] has following stages: A mixture of [5] and [5[1]] refluxed for two hours in the presence of BF_3 (1.2 mmol), in DCM 40 mL, at 25 ^{0}C maintaining inert conditions using Ar to produce crude [5a]. Poured it into DCM, dried the extracts with Na_2SO_4 and evaporated the solvent, the recrystallization process was performed with Ether/hexane solvent system to yield the pure compound [5a]. [5]

Scheme6:

Along with anti-mycobacterial activity by thiazines, some of Thiazine sulfonamide derivatives shows Oral hypoglycemic activity displayed a significant impact on animals to reduce glucose by sulfonylurea pharmacophore. Due to this fact, scientists have studied the incorporation of numerous heterocyclic rings with sulfonylurea. The prepared fifteen derivatives of trisubstituted sulfonylurea used as anti-diabetic employing oral glucose tolerance (OGT) check and NIDDM rat version. The data chart used to evaluate the Anti-hyperglycemic impact and summarize that for the anti-diabetic drug development, the tertiary "N" containing $NH_2CONHSO_2$ is best.

Presence of NO_2 group on ring increases the activity; the unsubstituted phenyl ring is favorable.



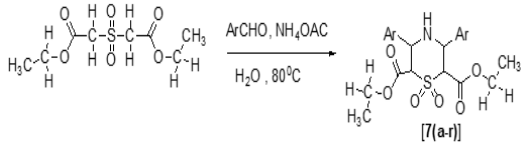
(i) NH_4CNO, AcOH, heating, 3–4 h (ii) $ClSO_3H$, 1,4 dioxane, stirring at r.t. (iii a) Pyridine, aniline (iii b) p-nitro aniline, (iii c) 2-amino pyridine, heating (iv) ClCOOEt, anhydrous K_2CO_3, CH_3COCH_3, heating 18–20 h, (v) 1^0 Amines (RNH_2), Ph-CH_3, heating 3–4 h.

Preparing [1,3] thiazine derivative by the reaction of acetylacetone, benzaldehyde and NH_4CN0 in glacial acetic acid refluxing for three to four hours produces [6a], chlorosulfonic acid with [6a] stirring at the room temperature by adding dioxane gives [6b]. In pyridine, the

formed [6b] and the amine/aniline refluxed for three to four hours to give [6c]. The ethyl chloroformate with [6c] and anhydrous K_2CO_3 in dry acetone refluxing eighteen to twenty hours leads to [6d]. Substituted primary aromatic amines and [6d] in toluene refluxed for three to four hours yields Thiazine sulfonamide derivatives [6e]. [6]

Scheme 7:

Not only the anti-mycobacterial activity, Oral hypoglycemic activity observed with thiazine compounds, the Sulfonyl thiazine derivatives act as Anti-convulsant agent's showned by mice models. The Biological studies of [7(a-r)] were powerful in the MES and/or scPTZ screens. Substitution on the ring can change the Anti-convulsant activity. To attain lower neurotoxicity of these molecules structural modifications would possibly result in the discovery of stronger anticonvulsant agents.



To produce 1,4-Sulfonyl thiazine derivatives [7(a-r)], adding benzaldehyde in water and ammonium acetate to diethyl 2,2-sulfonyldiacetate at 25 °C for 3 hours stirring at 80 °C, cooled it to 25 °C, and extracted the product with CH_3COOEt.

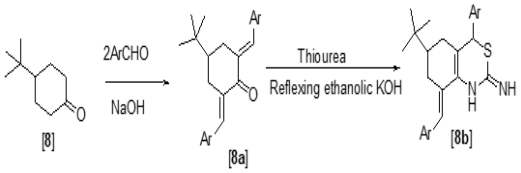
Anhydrous Na_2SO_4 is used to dehydrate the organic layer. Concentrated the solution to obtain crude product under the reduced pressure, recrystallized it with ethanol. [7]

Scheme 8:

When compare the biological activity of this scheme seems same activity with scheme 7. The Anticonvulsant activity employed by 1,3 thiazine derivatives is evaluated using maximal electron shocks (MES) method using diazepam as standard reference.

Using Molinspiration and Orisis program, the liophilicity, the drug likeness, and solubility parameters of the compound [8b] were evaluated. The toxicity prediction of [8b] carried in silico using Mol soft and ALOGPS software. Softwares like Mol soft and ALOGPS 2.1 used for prediction of the toxicity. Methoxy and isopropyl groups contained compounds stronger among all the compounds; hydroxyl groups (lipophilic) have been least. The halogenated thiazines have been exhibited the same activity.

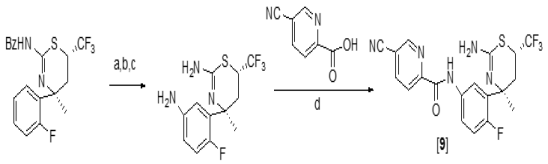
The dihydroxy phenyl substitution was comparatively less active in the series. The Structure-activity relationship study reveals that [8b] was very important for the activity. The presence of -OH groups on the aromatic rings has reduced the activity. A mainly substituted electron-donating, hydrophobic group like methoxy, alkyl groups enhances the anticonvulsant activity.



To prepare the 1,3-thiazine derivatives of [8b], 50 ml of ethyl alcohol, 4-tert-butylcyclohexanone (0.01 mol), substituted ArCHO (0.02 mol) and 30 mL of 10% sodium hydroxide were taken at 20-25 °C. At 500 rpm for 2 hours, stirred this reaction mixture and then the reaction mixture is kept stand at 0-4 °C for 8 hours to form a residue. Filtering and washing the residue with cool water, drying followed by recrystallising with DMF yields [8b] crystals with yellow color.[8]

Scheme 9:

In addtion to biological activity mentioned for derivatives of Thiazine in above schemes this scheme explores flouoro substituted thiazine derivatives activity, which can be used as BACE1 inhibitors that critically influence in addition to different pharmaceutical profiles.



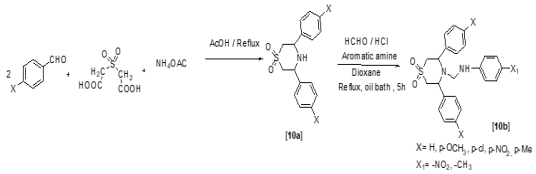
(a) NH_2NH_2, ethyl alcohol, 25 °C; (b) sulphuric acid, nitric acid, CF_3COOH, −10 °C; (c) Iron, ammonium chloride, Ph-CH_3/water, 80–90 °C, 79% over 3 steps; (d) aqueous hydrogen chloride, EDC·HCl, methanol, 25 °C.

(b) A novel synthesis of 6-tri flouro substituted thiazine [9] produced selectively with excessive yield from chemo-selective reaction

of substituted thiourea by using DAST (N,N-Diethylaminosulfur trifluoride). [9]

Scheme 10:

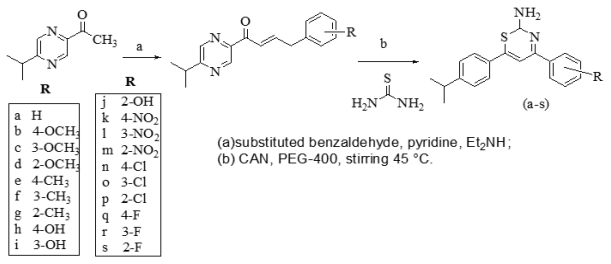
Besides, of before mentioned schemes activity, Anti-bacterial activity of sulfonyl thiazine derivatives [10b] against EC, KP, SA, BS were studied. Among the series, four compounds show good anti-bacterial and anti-fungal activity.



The synthesis of [1,4] thiazine derivatives from sulfonyl di acetic acid, substituted aldehyde and ammonium acetate refluxed in acetic acid to give [10a], condensing it with the HCHO and para substituted aniline. It is then refluxed in HCl and dioxane leads to a compound [10b]. [10]

Scheme 11:

In conjunction with schemes [5-10] thiazines activity, herein mentioned newer pyrazino thiazine derivative anti HIV activity, tested against HIV-1, H1N1, EV71and B3 viruses via enzyme-based assay reveals substantial activity, and one of the compounds (k) has potential activity towards HIV-1 virus. Compound (d) has good activity towards H1N1 virus. The computational studies of these molecules supporting that the designed molecules, which are having excellent bonding energy with respective protein to show better activity.



R		R	
a	H	j	2-OH
b	4-OCH_3	k	4-NO_2
c	3-OCH_3	l	3-NO_2
d	2-OCH_3	m	2-NO_2
e	4-CH_3	n	4-Cl
f	3-CH_3	o	3-Cl
g	2-CH_3	p	2-Cl
h	4-OH	q	4-F
i	3-OH	r	3-F
		s	2-F

Condensation reaction between Pyrazino ketones with substituted Aldehydes produces Pyrazine chalcones. Treated it with thio urea in presence of ceric ammonium nitrate, poly ethylene glycol-400 as solvent and stirred the mixture at 45^{o}c yielded 1, 2 thizine derivatives. [11]

Scheme 12:

1,3-Thiazinediones with phenyl- and naphthyl-substitution causing cell death and shows anti leukemia activity.[12]

Scheme 13:

A new synthetic approach of Pipothiazine compounds, and their neuroleptic activity discussed in this work. [13]

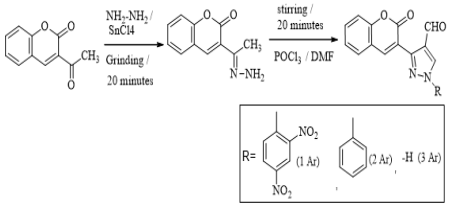
Scheme 14:

2-amino-1,3-thiazines synthesized and screened for antituberculosis activity against Mycobacterium tuberculosis and tested for cytotoxic activity against cancer cell lines by MTT colorimetric assay. [14]

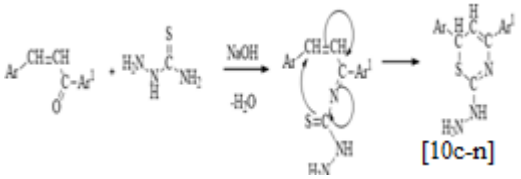
Scheme 15:

Preparation of phenothiaze by multi-step process and they have anti-inflammatory, and anticancer activity, Molecular docking results shows these derivatives can acts as pharmaceutically active. [15]

Sheme 15a:



Plausible mechanism:



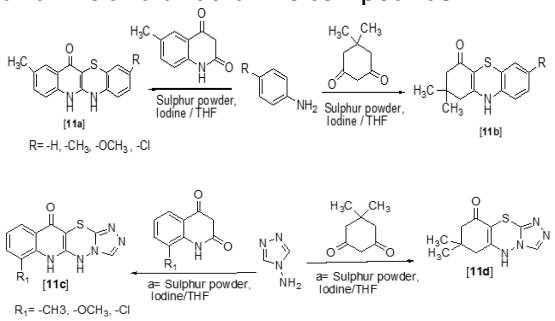
The synthesis of hydragenyl thiazines from chalcone and thiosemicarbazide in the presence of sodium hydroxide on heating. Insilico investigations indicate that two compounds have greater pharmacological similarities. The larvicidal effect of one compound against brine shrimp eggs (Artemia cysts) at various doses is outstanding. [15a]

c) Green approach towards synthesis of Thiazines:

Scheme 16:

The conventional methods mostly having expensive chemicals (or) more time takes to

complete the reaction. To overcome these circumstances given the need for green chemistry to save energy with high efficiency and environmentally benign process carried out with the sonication technique for this series of reactions. It was found that the sonication method proved better than the existing techniques and fast method to synthesize thiazine and thiadiazine compounds.



(Ultrasound method): One milli mole of iodine as catalyst, carbostyrils (CAB) (50 mmole), different substitutions on amines (50 mmole) and powdered "S" (15.6 mmole) in THF (5 mL) for 25 min kept in sonicating machine, TLC is used to monitor the reaction.

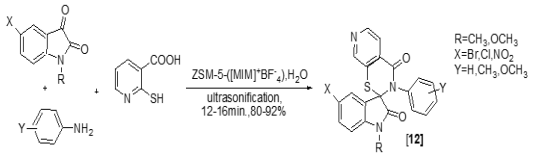
On Cooling solid formed is filtered, washed warm dilute hydrogen chloride and recrystallized from carbon disulphide/AcOH to yield pure [11a]. Preparation of the organic derivatives, Sonication Technique with Ultrasound is having a predominant role to get high yields with the low reaction time. When compared with general techniques it is having more credentials. [16]

Scheme 17:

As mentioned green approaches in the scheme - 12, in this scheme discussing other approaches especially Ultrasound-promoted, aqueous-mediated preparation of heterocyclic spiro derivatives was carried out using extraordinary ZSM-5 zeolite and Brønsted-acid ionic liquids as Catalyst. The conventional, and MW strategies having low yield of derivatives.

The yield was improved in the presence of ultrasonication with renewable catalyst. Upto five cycles catalyst can applicable where as a huge loss of catalytic activity was discovered in the presence of MWs.

After completion of reaction, catalyst in response medium under MWs appeared as brownish and decomposed ionic liquid. Ultrasound has been selected to prepare heterocyclic spiro derivatives because of RTILs high efficiency, for this reason there is a scope for similar improvement in the activation technique.



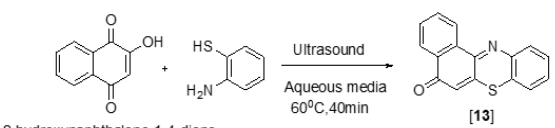
The significance of an aqueous mediated one-pot synthesis by sonochemistry to prepare heterocyclic spiro derivatives using substituted indole di one, amines, and a pair of mercaptonicotinic acid was reported. The Yields depend on substrate/IL molar ratios 1:1 (92%), 1:1.5 (82%). The reaction yield changed into higher towards low chain length (IL) cation ([MIM]$^+$BF4$^-$) compare with ionic liquids with the large chain lengths in a condensation reaction while using the different ZSM-5 zeolite supported Brønsted acidic (IL). In this reaction six solvent systems were studied 1) toluene, 2) DMF 3) glacial Acetic acid, 4) $PhCH_3$+ triflouroacetic acid,

5) dioxane + $ZnCl_2$, 6) H_20. It was observed that in aqueous medium-high yields with less reaction time and presence of ionic liquid catalyst, water plays a role as promoter. Applications of this method for the synthesis of spiro-ring systems is a simple, eco-friendly, convenient and would be relevant in higher the yield without usage of any dehydrating agents, with clean purification. It can be used for a large scale in the field of combinatorial chemistry for drug discovery. [17]

Scheme 18:

As like as the above schemes, herein this scheme describing the efficient, eco-friendly method for the production of 5H-benzo [a] phenothiazin-5-one from 2-Hydroxynaphthalene-1,4-dione and 2–Amino thiophenol with high yields by using ultrasound irradiation.

The advantages of this method are (A) water used as solvent, (B) less time takes to complete the reaction with simple workup. Density Functional Theory (DFT) and Time-Dependent Density Functional Theory (TDDFT) computations used for evaluate, prepared thiazine's photophysical properties.



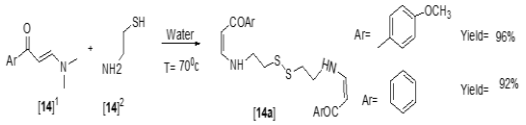
A great concurrence can be observed among computational studies on vertical excitation as well as the emission values and experimental study on the absortion-emission values. To obtaining materials dye-sensitized sun cells (DSSCs) (organic digital devices), the favored HOMO/LUMO hole is important for easy donation of HOMO or LUMO electrons.

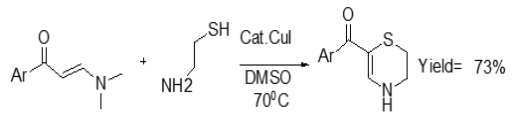
Compound [13] acts as chromophore and the characterization done by Electronic vertical excitation and emission spectra (TDDFT), IR spectra. [18]

Scheme19:

Present scheme also one of the environmentally benign approach as schemes 12,13 and 14, the transamination, oxidative S–S coupling, aqueous conditions between the $[14]^2$ with $[14]^1$ preferably forming the [14a] and [14b] is reported by J.P. Wan etal. In the organic synthesis and preparation of bioactive molecule, disulfide-functionalized enaminones with S-S bond having a crucial role.

Using CuI catalyst in dimethyl sulfoxide transamination and (SP^2) C- H bond thiolation to form a yellow coloured solid [14b].



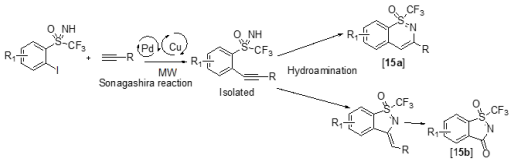


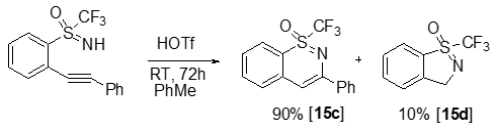
[14b]

To the formation of enamino disulfide, the reaction of $[14]^2$ with $[14]^1$ performed in water (as solvent), at 70 °c temperature, catalyst-free reaction leads to form product with higher yields and it is observed that the effect of substituents on the substrate is negligible. The availability of amino thiols is less hence, fewer of compounds prepared, which were, resembled [14a] and [14b]. [19]

Scheme 20:

Discussing scheme is an eco friendly approach like before mentioned schemes to produce 1,2 thiazines derivatives, incorporating the S-trifluoromethyl sulfoximine in 1,2-benzothiazine analogs and benzoisothiazole is carried out recently by Emanuel M.J etal., starting with a stable precursor and catalytic controlled manner cyclization. For selectivity, closer to the 5 or 6 ring the selection of the catalyst is essential. Trifluoromethylating Adachi reagent transform of one of the benzothiazines. A source of radical CF_3 under photo-redox catalysis is the primary use of this reagent.





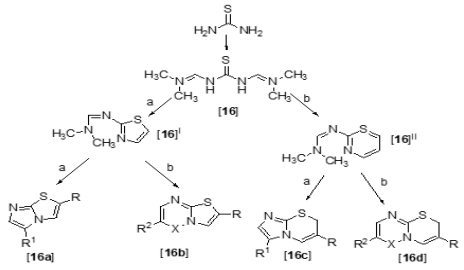
Using Sonogashira reaction, *ortho*-alkynyl *S*-trifluoromethyl *S*-arylsulfoximines through microwave activation was the first and efficient preparation. In the second step, the non-cyclized sulfoximines were isolated with high yields and controlled the hydroamination cyclization reaction.

The cyclization mechanism can be clarified by DFT calculations to understand its regioselectivity. [20]

d) Fewer synthetic approaches of Thiazine derivatives and their properties:

Scheme 21:

This scheme is performed with cyclo addition path way to produce 1,3 thiazines derivatives, Thiourea reaction with DMF gives Intermediate [16], it is used for the preparation of 16^I and 16^{II}, and reaction of these compounds with bromo ketones and ketenes produces [16a, 16b, 16c, and 16d]. It is simple versatile pathway and regioselective route to these significant heterocyclic compounds.



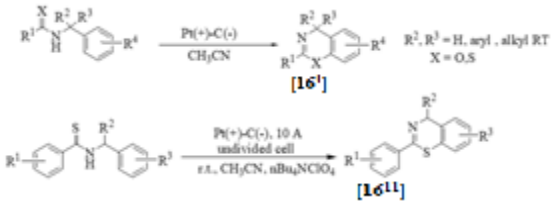
a=alfa bromo ketone, b=ketene(X=CO) or acrylic dienophiles($X=CH_2$)

Acrolein was used as a dienophile, in which the drug was exposed to a slight deterioration (20-30 percent), while the testing was performed on

the amidine side chains. The issue with ketone was identified that dual condensation happens before full absorption of the original content owing to the introduction of [4+2] cyclo addition between this diénophile and the subsequent thiazine, therefore the ring was turned into a big side product (15%). For amidin reaction with acrylic dienophile gives thiazine derivatives. The ring formation with [4 + 2] cycloaddition and removal of amine performed in mild concentrations, the derivatives expected were obtained regioselectively. [21]

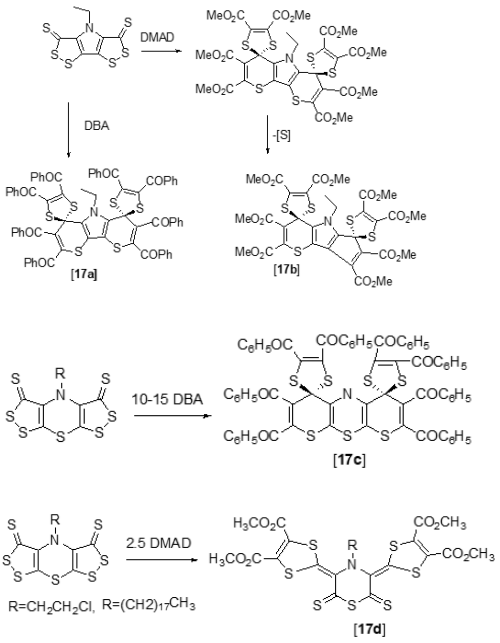
Scheme 22:

Electro-organic synthesis of 1,3-benzothiazines by electrochemical intra-molecular dehydrogenative coupling reaction of thioamides is a trend using Platinum and graphite as anode and cathode.



To generate benzothiazine followed by dehydrogenation, cyclization, oxidation, and degradation with high yields at 25° c by stirring. Monitoring the reaction with TLC at 254 nm in fluorescence light, the crude product is purified by the column chromatography. [22]

Scheme 23:

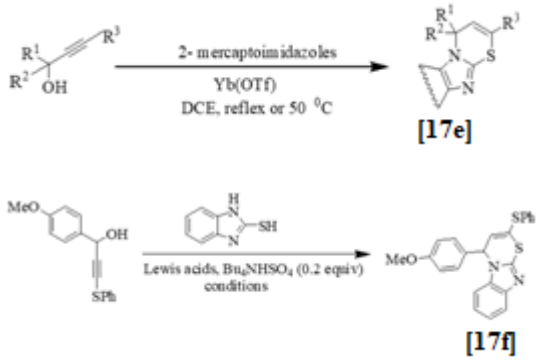


As like as scheme-17 herein this scheme consists cyclo-addition reaction to produce 1,4 –thiazine derivatives. The newer polysulfur-nitrogen derivatives that might be interest for synthesizing moieties bearing more than one 1,3-dithioles which can further give many derivatives consisting of thiazine-di-thiones may display multiplied antitumor activity.

The spiro compound 17c, fused moiety 17d prepared from bis 1, 2-dithiole-3-thiones using DBA and DMAD. In Heterocyclic fused structures consisting hydrophobic natured amphiphiles easy for encapsulation capability by self-assembly structure. Different ratios of reactants are used for this reaction and it shows significant selectivity as well as reactivity. From these products, it is easy to prepare desired targetable compounds because of active sites. [23]

Scheme 24:

This Scheme is also a cycloaddition approach like schemes [21, 23] towards the preparation of 1,3 thiazine derivative.



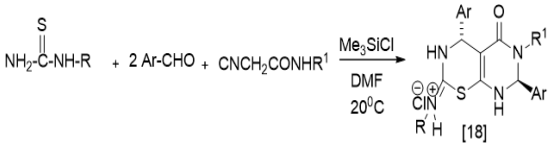
A novel approach to produce high yields of thiazino imidazoles with Yb catalysed stereo-selective, [3+3] cyclization reaction between “S”& “Se” contained propargyl alcohols and “S” contained imidazoles. [24]

Scheme 25:

Present discussing scheme is about the synthesis of 1,3-thiazine derivative with acid catalysed, microwave assisted solid phase Bigineelli reaction starting with mixture of trimethyl silyl chloride and dimethyl formamide at r.t, cyanoacetamides with benzaldehyde and thiourea (1:2 molar ratio) leads to the thiazinopyrimidine.

It is observed that the yields of the reaction are more when the nucleophilcity of the substituent on urea is more and the urea with the least nucleophilic substituent does not undergo

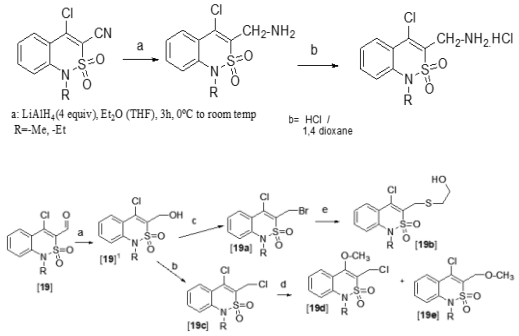
reaction. In this scheme cyano substituted pyrimidine formation takes place, it gives many fused heterocyclic structures with S, N and O. Ethers of Boron, Lanthanide halide, Yetarbium triflates, Zirconium halides, Bismuth halides, Lithium halides, Lithium halates, Manganese acetate, Ceric ammonium nitrate, Ferric chloride, Nickel chloride, Ruthinim chloride, Sumerium iodide can be used as catalysts. Synthesis and purification is easy to produce [18] contained library of compounds for Calcium channel modulators, adrenergic receptor antagonists, mitotic kinesine inhibitors antiviral and antibacterial agents.



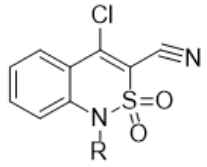
This sort of huge spectrum of organic activity permits attention of the dihydropyrimidine was having an important role. [25]

Scheme 26:

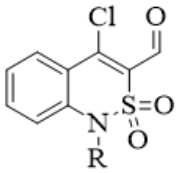
Herein this scheme elevating the synthesis of benzo[e] [2, 1] thiazine chloro aldehyde and chloro nitriles from Thiazine nitriles or Thiazine aldehydes. The derivatives of benzo[e] [2, 1] thiazine chloro aldehyde and chloro nitriles also reported which have potential biological and pharmaceutical application.



a: sodium borohydride(2.5 equiv), methanol, 2 hours, r.t.; *b:* thionyl chloride (4 equiv), benzene, 3 hours, 0 °C to 25 °C; *c*: Hydrogen bromide (50%), 5 hours, heating; *d*: sodium methoxide/methanol, 2 hours, reflux; *e*: thioethanol 1.5 equivalents, potassiumcarbonate, 1,4-dioxane, tri ethyl amine, 2 hours, heating.



4-chloro-1H-benzo[c][1,2] thiazine-3-carbonitrile 2,2-dioxide



Benzo[e][2,1]thiazine-4-chloro -3-carbaldehydes

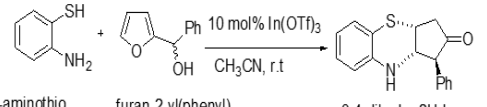
R= -Me, -Et,-nPr,-nBu,-Bn,

The reduction of [19] with sodium borohydride to yield the compound [19][1], reacting the [19] [1] with $SOCl_2$ in dry benzene gives [19c].

The compound [19] [1] and concentrated hydrobromic acid refluxed to produce the derivatives of [19a]. The compound [19a] had been heated with SH $(CH_2)_2OH$ and N $(Et)_3$ in dioxane leads to [19b], refluxed [19c] with sodium methoxide in methanol for two hours to give [19d] and [19e]. [26]

Scheme 27:

Present scheme is expertise by the application of the Piancatelli rearrangement through an aza-Piancatelli rearrangement/Michael reaction to produce 1, 4-Benzothiazine [20] derivatives. The reaction of [20][1] with [20][11] in the presence of indium triflates as catalyst and CH_3CN as solvent. At 25 °C produces [20] with 86% yield. Among the reaction with numerous Lewis acid catalysts, $In(OTf)_3$ shows good results according to reaction time and yield when compare between $InCl_3$, $InBr_3$, $In(OTf)_3$, $CeCl_3.7H_2O$ and $Al(OTf)_3$. Amid the strong acid catalysts Brønsted acids, Phosphomolybdic acid acts better compare to heteropoly acids, K10 clay.



2-aminothio Phenol [20][1]

furan-2-yl(phenyl) methanol [20][11]

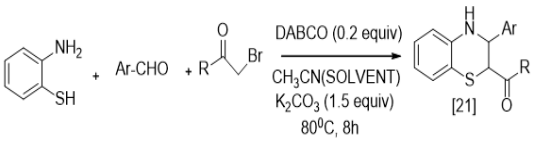
3,4-dihydro-2H-benzo [b][1,4]thiazine [20]

Among the solvents, acetonitrile having more significance than 1, 2- dichloroethane and tetrahydrofuran. To perform this conversion

essential condition is 10 mol% In $(OTf)_3$ in acetonitrile. Halogen substitution on [20][1] gives higher yield of [20] than methyl substitution on [20][1]. [27]

Scheme 28:

Now discussing scheme explains the preparation of 1,4 thiazine derivatives [21], diazabicyclo [2.2.2] octane (0.2 mmole) as catalyst, K_2CO_3 (1.5 mmole) as base, in CH_3CN as solvent, Phenacyl bromide (1 mmole), *O*-aminothiophenol (1 milli mole) and aryl aldehyde (1 milli mole) stirred in an oil bath at 80 °C for 8 hours. The product is extracted by the addition of dichloro methane (3 × 20 mL) and washed with water. The organc layer was dried with Sodium sulphate, filtered, and applied vacuum to evaporate the solvent. By using silica gel (300–400 mesh) in flash chromatography with ethyl acetate and hexane (1:20, v/v) as the mobile phase to extract preferred product. The ring activating groups gave low yields than ring deactivating groups on benzene ring of halogenated aromatic ketones. The reaction of diazabicyclo [2.2.2] octane and phenacyl bromides generates quaternary salt, the addition of potassium carbonate leads to deprotonation to produce the carbanion.

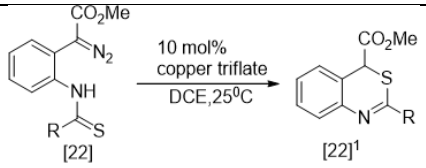


Ar=C_6H_5, R=C_6H_5

Condensation of 2-aminobenzenethiol and aromatic aldehydes gives imines, which are in situ and thermodynamically desired product forms by cyclization, and regeneration of the catalyst takes place. This method can be applicable for preparing annulated heterocyclic aromatic compounds, which are used in medicinal chemistry. [28]

Scheme 29:

Present scheme illustrate that inserting the Carbon–Sulphur intramolecularly in [22] to produce 1,3 benzothiazine derivative [22][1] using $Cu(OTf)_2$ as catalyst.

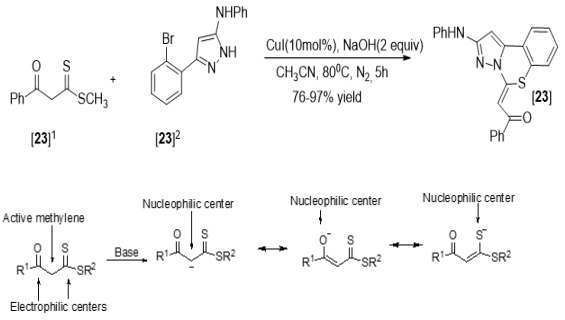


To optimize the reaction, copper triflate effective in terms of rate of reaction than the scandinium triflate, indium triflate, bismuth triflate, copper acetate, copper sulphate and copper iodide.

In presence of the five mol% $Rh_2(OAc)_4$ as catalyst seems better for cyclisation. Among the solvents, DCE shows good performance for cyclisation than the dichloromethane, toluene, and tetrahydrofuran. [29]

Scheme 30:

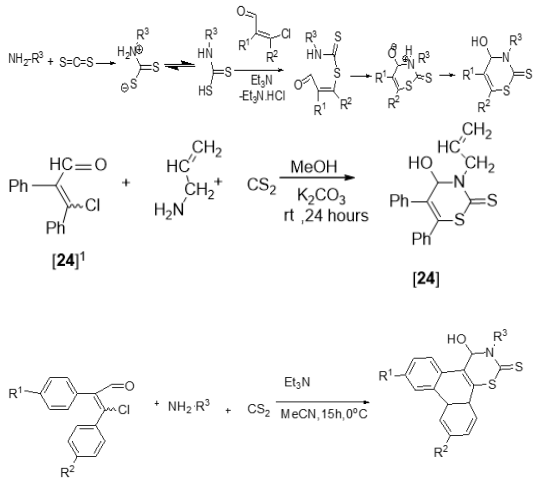
This scheme explains about the usage of Ullmann coupling reactions of the [23][1], [23][2], Sodium hydroxide as base, Methyl cyanide as solvent, Cu acts as catalyst at 80 °C below in N_2 atmosphere gives chemo-selective benzothiazine [23] product. The [23][1] consists of two electron deficient and three electron rich positions, these are acting as reactive centers. Due to these centers different types of heterocycles with "S" atom forms.



The yield of reactions depends upon the 5th position of pyrazolic ring, 89-94% yield with aryl amino substitution bearing either electron-withdrawing or electron-donating group. The yield 84% with primary amino substitution, seventy-six percent yielded with pyrazole unsubstituted 5th position. The reaction yields enhance by "F" group on phenyl ring fused to pyrazole. An application of this method is mild conditions, easy purification, higher yield, and CuI/extra-ligand-free catalyst. [30]

Scheme 31:

In this scheme application of Pictet-Spengler-type cyclization leads to diverse annulated polycyclic systems to prepare thiazine derivative.

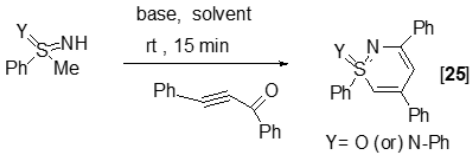


[24]^1 [24]

The preferred [24] to be synthesized from [24]^1 with prop-2-en-1-amine, carbon disulfide, MeOH as solvent, potassium carbonate as base at 25^{o}c under MCR (multicomponent reaction). [31]

Scheme 32:

Herein this scheme proposed that One-pot synthesis of 1,2 thiazine derivatives followed by Michael addition/ cyclization/ condensation sequence by one equivalent weight of sulfoximine, $CsCO_3$ (2.1 equivalent weight), and molecular sieves 4 A^0 in dimethylsulphoxide 2 mL, the resulting mixture stirred for 15 minutes, in an argon atmosphere at ambient temperature. 1-phenyl butyne1-one (1.5 equivalent weight) was added and stirred it for five hours at 80 °C. Later $NaHCO_3$ solution (15 mL) added and extracted compound using CH_2Cl_2 (30X10 mL).

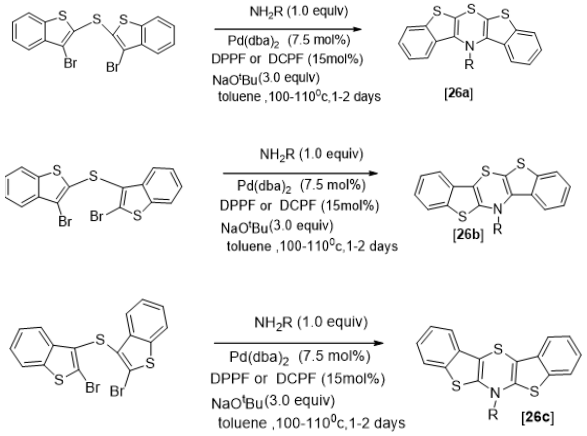


Anhydrous magnesium sulfate used for drying organic layers and evaporation of solvent by reduced pressure. Applying the flash chromatography CH_3-$(CH_2)_3$-CH_3/ethyl-acetate used as a mobile phase for the purification of the desired [25] derivatives. [32]

Scheme 33:

Now discussing scheme exploring the preparation method preferably by two fold *Buchwald-Hartwig* amination of benzothieno [1,4] thiazine (BBTT) [26a-26c] and its properties. The structures by using UV/Vis and fluorescence spectroscopy three regioisomeric have been examined in the solution. The cyclic voltammetry (BBTT)s show two chemical reversible oxidation methods. Syn-anti and anti-anti BBTTs are Nernstian reversible in the first and second oxidations.

The first oxidation is quasi-reversible for syn-syn BBTT, second oxidation is Nernstian reversible. For the first and second oxidations of N-phenyl BBTT regioisomers potentially low. The first oxidation potentials are shifted anodically for 26a.

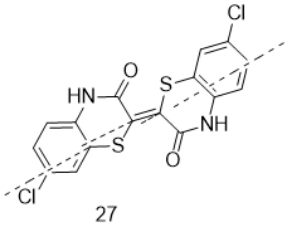


The absorption bands at larger wavelength of the anti-anti derivatives were in red shift resulting from the extra planar shape the interactions between the hetero atoms of the 1,4-thiazine and ∏-systems is multiplied by X-ray analysis, NICS(0) and NICS(1) calculations for the diagnosis of three planar anti-aromatic, anti-anti BBTTs. This study leads to small singlet-triplet separations, the optical and material properties of novel multifunctional ∏-systems. [33]

Scheme 34:

Present scheme instructing that Thiazine-indigo based pigments were recently reported. The chlorinated thiazine indigo (THI) crystal structure that appears crimson colour where as in solution it seems as pale yellow was used to analyse the electronic nature of the dye. Intermolecular H-bonding appears between N-H

group of one molecules and oxygen of the carbonyl group of another molecule. The transition dipoles existed as opposite corners present in crystal form gives maximum wavelength. THI absorption bands appeared at UV region with larger wavelength 524 nm. The large bathochromic shift after the crystallisation will usually be due to excitonic interactions, arranged diagonally along with the piling axis on the molecular surface.



27

The chemical structure of chlorinated thiazine indigo (THI) can be analysed by solid state XRD and absorption spectra. [34]

Scheme 35:

Yogesh etal proposed first Ir(III)-catalyzed preparation of 1,2-benzothiazines C–H functionalization of sulfoximines with a-diazocarbonyl compounds. The applications of this protocol have mild simple reaction conditions, various functional groups can be inserted, and products formed with high yields. [35]

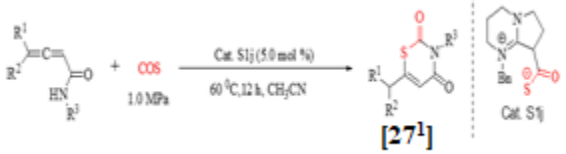
Scheme 36:

Synthesis of 4*H*-thiazine ring can be performed by by intramolecular cyclizations; reaction of thioureas /thioamides with Michael acceptors; thioureas reaction with malonic acid; reaction of 3-mercaptoacrylamides wit carbonyl compounds/Michael acceptors, and also hetero-Diels–Alder reactions. [36]

e) Stereo selective synthesis of Thiazines:

Scheme 37:

This scheme explore that the preparation of thiazine diones with simple conditions, stereo selective, organo catalytic and COS incorporation.

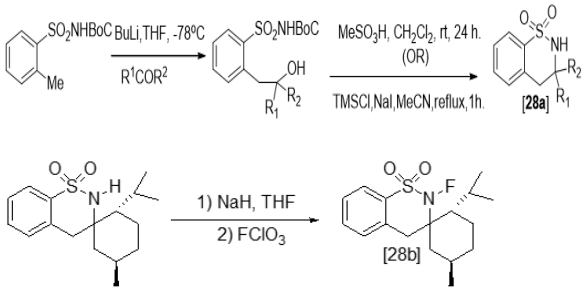


[27[1]]

By Lewis Base-COS catalyzed [4+2] annulation effectively carry out at 60 °C and 1.0 MPa of COS. It showed the highest activity with 96% yield. [37]

Scheme 38:

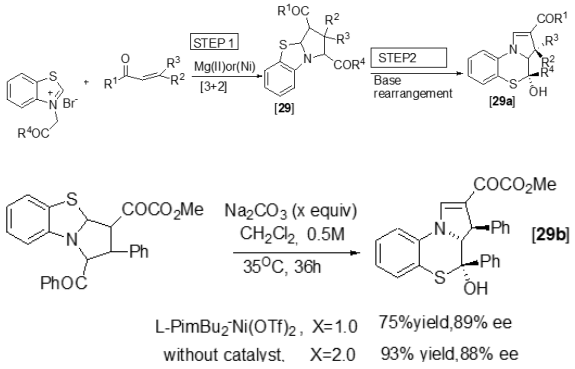
Present scheme explains the stereo-selective synthesis of 1,2 thiazine di one derivatives.



[28a] can be prepared by novel method, for the cyclisation, tri methyl silyl chloride, sodium iodide, methyl cyanide, CH_3SO_3H to be used. From [28a] spiro asymmetric fluorinated compound [28b] can be prepared with ee 70%. [38]

Scheme 39:

As like as scheme-36, this scheme explains the enantio-selectve synthesis of Benzothiazine derivatives.

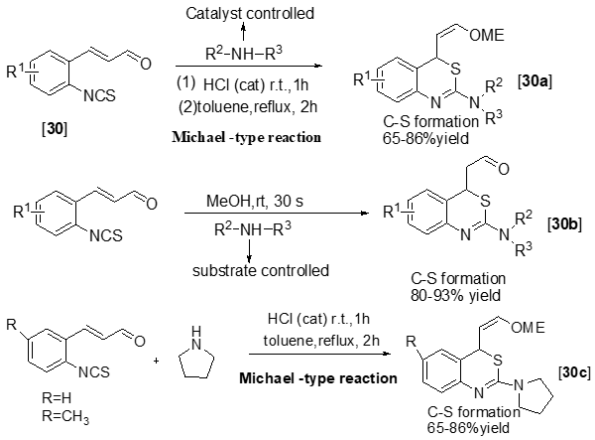


The quaternary salt of thiazole in presence of Nickel triflate chiral catalyst and sodium carbonate produces [29]; Rearrangement of [29] in presence of base produces enantio-selective compound [29a] with high yield. X-ray crystallography studies reveal the structure of the [29a]. [39]

Scheme 40:

Similarly, to the schemes [32, 33] herein discussed stereo-selective synthetic protocol for the benzothiazine derivatives. For achieve these

important heterocycles, a few tremendous protocols were dedicated. The most widely employed techniques are the addition/cyclisation protocols for the domino Michael. To widen the chemoselective
reactions, to construct those valuable heterocyc lic moieties, a catalyst controlled green chemo selective reaction to synthesis [30a] with excessive yields using [30] under mild conditions. In this domino reaction, [30b] could be acquired while substrate controlled reaction the amines are secondary amines (SA) with [30]. The domino reaction between the compound [30], cyclic secondary amine at room temperature in THF, absence of catalysts to afford the favored product [30c] in high yields. In the mechanism 2° amine attacks [30] and forms thiourea as intermediate; intramolecular michael addition produces its corresponding thiazine derivatives.



Due to less solubility, the formation of the product is not expected with water as solvent. The Methanol as the solvent shows a higher yield when compared with other solvents.

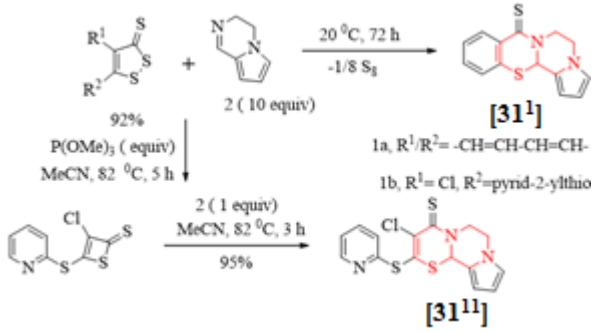
The Domino reaction, applicable for electron-deficient and electron-efficient groups on [30] having more scope for synthesis, very less time takes for this reaction of newer thiazine derivatives with higher yields in absence of toxic metals as catalysts. In the Green approach, nucleophile attacks on gamma position of beta-gamma unsaturated cinnamaldehyde to give product within 5 minutes by the formation C-S bond.

In the one-pot synthesis of methoxy vinyl substituted thiazine, HCl used as catalyst, toluene used as solvent it leads to Michael type of product instead of aldol type of product with more selectivity. [40]

Scheme 41:

As mentioned all above schemes here-in ring forming is a stereo selective, partly saturated, racemic mixture of solid, non-planar policy-heterocycles, rich in "S" and "N" from readily accessible heterocyclic groups.

Single pot, 2 step reaction, thioles and fused thioles are substituted with -NH_2CH_2- to produce 1, 3 thiazine. In a number of instances, in situ "S" extrusion from 1,4-thiazines has been found to give rise to new pyrrolo-fused structures. Here-in ring forming is a stereo selective, partly saturated, racemic mixture of solid, non-planar policy-heterocycles, rich in "S" and "N" from readily accessible heterocyclic groups.



Single pot, 2 step reaction, thioles and fused thioles are substituted with -NH_2CH_2- to produce 1, 3 thiazine. In a number of instances, in situ "S" extrusion from 1,4-thiazines has been found to give rise to new pyrrolo-fused structures. The medicinal applications of pyrazolo thiazones extended to the spectrum of non-cyclic imine reactions in this phase. [41]

Conclusions:

In the nature thiazine based derivatives available in wide range as fungi, plants, marine derivatives, and extraction of these compounds are discussed in [1-4]. The biological activity of thiazine derivatives [5-15] as anti-mycobacterial agents, hypoglycemic effect, anti-convulsant agents, and BACE-1 inhibitor because of these reasons thiazine derivatives may have the crucial role in the medicinal chemistry. To protect the environment green chemistry approach is a better pathway, [16-20] indicating sonication technique, microwave irradiating technique and aqueous mediated synthesis of thiazine derivatives. To enhance the yield and rate of reaction solvent and catalyst is playing a major role, for the preparation of thiazine based derivatives [21-36] various catalysts like

$In(OTf)_3$ and DABCO, solvents like DCM, CH_3CN used. Viewing the importance of the stereochemistry of the molecules in biological activity for the preparation of thiazines asymmetric synthesis, chiral catalysis, and chemo-selective synthesis discussed in [37-41]. This review is helpful for researchers who want to implement newer thiazines in different aspects in terms of biology and physico chemical properties.

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