GREEN SYNTHESIS OF THIAZINE AND OXAZINE DERIVATIVES - A SHORT REVIEW

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ABSTRACT: A survey of green synthesis of thiazines and oxazines revealed the moiety have attracted a great deal of interest of medicinal chemist, biochemist, pharmacologist and rendered as a lead molecule for designing potential bioactive agents. This review accompanying supplementary green synthetic information & its references would extend great deal of help to researchers in determining the best and most productive, economical, suggestive and clinically important compound of thiazine and oxazine derivatives which will be expected to show potent pharmacological activities. This has led to the discovery of a wide variety of compounds that are of high interest from the point of view antimicrobial, antymycobacterial, antidiabetic and antidepressant effects among others.

INTRODUCTION: Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. The large numbers of biologically active molecules that contain heterocyclic rings has play important roles in the drug discovery process and exhibit various biological activities.

A literature survey identified several thiazine and oxazine derivatives in the development phase as potential new drugs. The versatility of the thiazine and oxazine skeleton, in addition to its relative chemical simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds.

The aim of this review is generalization of the data published up to 2012 on the synthesis of Thiazines and Oxazines derivatives.

The present survey has clearly demonstrated that thiazine and oxazine may be successfully used to synthesize a wide variety of heterocycles of academic and pharmaceutical interest.

Moreover, in general, the desired compounds may be obtained in a single step with high yield. This has been noticed so far, that the modifications on thiazine and oxazine moiety displayed valuable biological activities and these modifications can be utilized to develop potentially active agents in future. Thus, the quest to explore many more modifications on thiazine and oxazine moiety needs to be continued. So we have decided to review briefly on novel green synthetic methodologies of Thiazine and Oxazine Derivatives.

Generally, we have selected synthetic methods which are related to green approach i.e. by using Microwave irradiation, Sonication, Grinding technique, Solvent free conditions, Nanoparticles, Ionic liquid etc. The reagents used for synthesis are ferric chloride, Copper nanoparticles, Cesium carbonates, Tetra phenyl phosphine, Thiourea, p-tolyl sulphonic acid, Palladium catalyst, Perchloric acid, Phosphomolybdic acid, N-Bromo succinimide, Zirconyl [IV] chloride Trioxane, 1-Benzyl-3-Methyl imidazolium hydrogen sulphate etc.

Brief review on thiazine and oxazine derivatives: Kategaonkar et al, reported ionic liquid catalyzed multicomponent synthesis of 3,4-dihydro-3-substituted-2H-naphtho[2,1-e][1,3]oxazine derivatives from 1-naphthol, various anilines and formalin at room temperature stirring. The six-membered N,O-heterocyclic skeleton was constructed via 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim][HSO4] promoted Mannich type reaction. Sawant et al, reported that a series of Schiff bases of 1, 3-oxazines were synthesized via reaction of 1, 3-oxazine-2-amine with substituted benzaldehyde. The title compounds were characterized with IR, NMR and screened for their anticoagulant activity by measuring prothrombin time by Quick’s method. The study revealed that most of the synthesized compounds exhibited significant anticoagulant activity.
Sharma et al. reported facile synthesis of differently substituted 5-benzylidene-2-aryl-5, 6-dihydro-4H-[1,3]oxazin-6-ones has been achieved by heating a mixture of substituted N-benzoyl-β-aminopropanoic acids with several aromatic aldehydes in the presence of sodium acetate and acetic anhydride. These compounds, on refluxing with o-phenylenediamine in dry benzene resulted in the formation of differently substituted 4-benzylidene-1-aryl-3,4-dihydropyrimido benzimidazoles. The synthesized compounds were characterized by elemental analysis and spectral studies (IR, 1H NMR and 13C NMR).

Taati et al., reported 2-Aryl substituted 5,6-dihydro-4H-1,3-oxazines were conveniently synthesized by the condensation of 3-aminopropanol and desired carboxylic acids under solvent-free and microwave conditions, in short reaction times, and moderate to good yields. Also a comparison was made between this method and the classical protocols using acid halides and nitrile substrates.
Chaskar et al, reported a phosphomolybdic acid catalysed novel method for the synthesis of 1,2-dihydro-1-aryl-3H-naphth[1,2-e][1,3]oxazin-3-one derivatives by a one-pot, three-component reaction of β-naphthol, aromatic aldehydes and urea in excellent yields is described.

Haider et al, reported the synthesis and antimicrobial screening with spectral analysis of some 1,3-thiazines have been carried out in two series, first series starting material is 2-hydroxyacetophenone and obtained 4-(2-hydroxy phenyl)-5-benzoyl-6-phenyl or 4-alkoxy phenyl or 4-dimethyl amino phenyl -2-imino -6-H-2,3 dihydro 1,3-thiazine(4a,4a’,4a”,4a”). Second series starting material is 2-hydroxy- 5- methyl acetophenone we got 4-(2-hydroxy -5-methyl phenyl)-5-benzoyl-6-phenyl-2-imino-6 H- 2,3 dihydro-1,3-thiazine and respected derivatives as written above (4b,4b’,4b”,4b”’) from thiourea. All these compounds have been analyzed by melting point, IR, 1H NMR. All the synthesized compounds are tested for their antimicrobial activities.
Safaei-Ghomi et al, reported an efficient green route for the preparation of naphthoxazinones, applying a three-component one-pot condensation reaction of 2-naphthol, aromatic aldehyde and urea in the presence of nano silica supported ferric chloride under solvent-free conditions has been developed. The present procedure offers several advantages such as short reaction time, simple workup, recovery and reusability of the catalyst 7.

Kumar et al, reported an efficient methodology employing copper nanoparticles for the preparation of 2-naphthol condensed 1,3 oxazin derivatives employing one-pot condensation reaction in the presence of K$_2$CO$_3$ and Copper nanoparticles in PEG-400 is described which offers several advantage 8.

Sekhar et al, reported commercially available N-Bromo succinimide (NBS)is reported as an extremely efficient catalyst for the synthesis of 2-aryl/hetero aryl-5, 6-dihydro-4H-1,3-oxazines by ultrasound irradiation of 3-aminopropanol with different aryl/ heteroaryl aldehydes took place in one pot under aqueous medium at 70°C, gives high yields in shorter reaction time. The reaction proceeded with extremely high efficiency under mild conditions and gave good yields. The proposed methods were found to be suitable and accurate for rapid synthesis of substituted 5, 6-dihydro-4H-1,3-oxazines derivatives available 9.

Ahangar et al, reported that 1,2-Dihydro-1-aryl naphtho[1,2-e][1,3]oxazine-3-one derivatives were synthesized in high yields using a facile and one-pot condensation of 2-naphthol, aromatic aldehydes and urea catalyzed by perchloric acid supported on silica under thermal solvent free conditions 10.
Hua et al., reported highly efficient synthesis of substituted benzo[1,4]oxazin-3-ones and pyrido [1,4] oxazin-2-ones under microwave irradiation via Smiles rearrangement. Substituted benzo[1,4]oxazin-3-ones and pyrido [1,4]oxazin-2-ones were obtained by treatment of substituted 2-chlorophenols or 2-chloropyridols with N-substituted 2-chloroacetamide in the presence of potassium carbonate in MeCN and subsequent exposure to cesium carbonate in DMF. All the reactions which take 2-10 hours under conventional condition were completed successfully within a few minutes under microwave irradiation giving moderate to excellent yields.

Baltorka et al., synthesized Nano-SiO$_2$ solid acid efficiently and selectively catalyzed the cyclocondensation reaction of arylnitriles with 3-amino-1-propanol or 1, 3-diaminopropane to afford their respective 2-substituted oxazines and tetrahydropyrimidines in high yields under thermal conditions and microwave irradiation. This methodology works effectively for the selective synthesis of mono-1, 3-oxazines and mono-tetrahydropyrimidines from dinitriles. The catalyst could be recycled and reused several times without a noticeable decrease in its activity.

Sundari et al., reported synthesis of 3,5-diaryl tetrahydro-N-[(4'-nitroanilino)methyl-thiazine-1,1-dioxide and N-[(4'-methylanilino)methyl]-1,4-thiazine-1,1-dioxides by condensing 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide with formaldehyde and 4 nitroaniline/4-methylaniline in the presence of hydrochloric acid is reported. The structures of the synthesized compounds have been confirmed by elemental and spectral analysis. The preliminary screening of the compounds for their biological activities gives significant results.
Wang et al, reported a series of novel multithioether derivatives were synthesized by the combination of thiazoline and thiazine with dibromo-mides and their structures were characterized by IR, $^1$H NMR, MS and elemental analysis. The synthesized derivatives were tested for antitumor activity $^{14}$.

Dighade et al, reported that six different Chalcones I(a)-I(f) were synthesized by condensing 2-hydroxy-3-iodo-5-methyl acetophenone with six different aromatic aldehydes in ethanol using NaOH. These chalcone were cyclized with diphenyl thiourea in ethanol yielding IIa-IIf. The synthesized compounds were characterized by I.R., NMR spectral analysis $^{15}$. 

\[ \text{HOOC-CH}_2\text{CH}_2\text{-COOH} + \text{NH}_2\text{OAc} \]

\[ \text{NH}_2\text{OAc} \]

\[ \text{AcOH/ reflux} \]

\[ \text{HCHO/HCl} \]

\[ \text{Aromatic amine} \]

\[ \text{Dioxan} \]

\[ \text{Reflux, oil bath, 5h} \]

\[ X = \text{H, p-OCH}_3, \text{p-Cl, p-NO}_2, \text{p-Me}. \]

\[ X' = \text{NO}_2, \text{CH}_3 \]

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\[ X' = \text{NO}_2, \text{CH}_3 \]
Yavari et al, reported a one-pot synthesis of alkyl 3,4-dihydro-4-oxo-2H-1,3-thiazine-6-carboxylates from dialkyl acetylenedicarboxylates and N,N0-diethyldithiourea in the presence of triphenylphosphine (20 mol%) is described.

Kadhim reported a series of novel Azachalcone compounds were prepared by the reaction of 3-acetyl pyridine with different aromatic aldehydes. Azachalcone was reacted with thiourea to give good yields of thiazines, all the new compounds were characterized by I.R, U.V and TLC. Also the Biological Activities of these compounds against anti-bacterial and anti-fungal were evaluated. Some of these compounds gave good activity.
Yadav et al, reported a novel three-component expeditious synthesis of 3,6-diaryl-5-mercapto perhydro-2-thioxo-1,3-thiazin-5-ones from 2-methyl-2-phenyl-1,3-oxathiolan-5-one, an aromatic aldehyde and an N-aryldithiocarbamic acid. The synthesis is diastereoselective and involves tandem Knoevenagel, Michael and ring transformation reactions under solvent-free microwave irradiation in a one-pot procedure.

Bolognese et al, synthesized Oxazine by condensation of 2-aminophenols and quinolin-5,8-dione in acetic acid.

El-Sharief et al, reported refluxing 1,4-phenylenedicarbamothioyl cyanide with two moles of salicylic acid or methyl salicylate in DMF containing a catalytic amount of triethylamine, 3,3'-((1,4-phenylene)bis(2-thioxo-2,3-dihydro-benzo [e][1,3]oxazine-4-one) was obtained.
According to Ramjith et al., fluoro, chloro 2-acetyl benzimidazole were prepared by the microwave induced reaction between 3-chloro-4-fluorobenzene-1, 2-diamine and lactic acid, followed by oxidation with potassium permanganate and aluminum oxide. The chalcone derivative of fluoro, chloro 2-acetyl benzimidazole were prepared by the condensation with different aldehydes and the resulting compounds were cyclized with thiourea, to get the thiazine derivatives of fluoro, chloro benzimidazole. The synthesized compounds have been characterized and confirmed by TLC, elemental analysis, IR, and $^1$H NMR spectroscopy and screened for their antibacterial and analgesic activity. Compounds containing electron withdrawing groups in the substituted Benzimidazole thiazine were found to show potent analgesic and antibacterial activities.\(^{21}\)
Zanatta et al, reported the reaction of beta-alkoxy-CF₃-enones with ethyl carbamate leads to formation of enamidoketones. Subsequent reduction and cyclization leads to formation of oxazines. They exhibited significant activity against tested microorganism strains.\(^22\)

\[
\begin{array}{c}
\text{CHO} + \text{NC} \text{CONH}_2 \xrightarrow{\text{p-TSA, EtOH, Reflux}} \text{ArHN} \text{S} \text{NHCOOEt} \\
\text{CHO} + \text{NC} \text{CONH}_2 \xrightarrow{\text{p-TSA, EtOH, Reflux}} \text{ArHN} \text{S} \text{NHCOOEt}
\end{array}
\]

\[\text{Ar} = \text{Ph}, \text{PhCH}_2-\]

Aly et al, recently demonstrated that 1,4-diphenylbut-2-yn-1,4-dione reacted with \text{N}-substituted hydrazinocarbothioamides to form the corresponding \[N^\prime\text{-(2E)}\text{-}6\text{-benzyol}\text{-}4\text{-phenyl}2\text{H}-1\text{-3-thiazin-2-yldene}\text{-}substituted hydrazides \[\text{[A]}\text{ a-e}\text{.}\]

Shaker et al, reported that the 2,2\(^\prime\)\text{-}(1,4-phenylene) bis\text{(3,4-dihydro-2H-1,3-thiazine)} have been synthesized by the cyclocondensation of terephthalaldehyde with 2 equivalents of in the presence of catalytic amounts of \text{p}-toluenesulfonic acid in boiling ethanol. High yields of the products also resulted when the reaction was performed in boiling glacial acetic acid.\(^24\)

\[
\text{CHO} + \text{NC} \text{CONH}_2 \xrightarrow{\text{p-TSA, EtOH, Reflux}} \text{ArHN} \text{S} \text{NHCOOEt} \\
\text{CHO} + \text{NC} \text{CONH}_2 \xrightarrow{\text{p-TSA, EtOH, Reflux}} \text{ArHN} \text{S} \text{NHCOOEt}
\]

\[\text{Ar} = \text{Ph}, \text{PhCH}_2-\]

Gupta et al, reported one post synthesis for the compound containing 1,4-thiazine hetrocyclic ring. They prepared 1,2,4\text{-Trichloro-7- fluoro-9-}
methyl\text{-}phenothiazin-3\text{-one from condensation reaction of 2-Amino-5-fluoro-3methyl- benzenethiol and 2,3,5,6- Tetrachloro-[1,4] benzoquinone.}\(^25\).
Kudryavtsev et al, reported the condensation of 5-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thione with benzene-1,4-diylbisacryloyl chloride gave 5,5′-(1,4-phenylene)bis(5H[1,2,4]triazolo[5,1-b][1,3]thiazin-7(6H)-one)\textsuperscript{26}.

Basin et al, synthesized, 4-chloro-2-cyclohexyl-6, 7-dimethoxy-2H-1, 2-benzothiazine-1,1-dioxide from 3,4-dimethoxy chalcone. The reaction was preceded with chloro sulfonation of chalcone followed by amination and epoxidation under basic conditions\textsuperscript{27}.

Harmata et al, reported a new synthetic method for the preparation of benzothiazines and benzisothiazoles containing a sulfoximine functional group. The reaction of S-2-bromophenyl-S-methyl sulfoxoimine was conducted in the presence of a palladium catalyst which resulted in the formation of both 1, 2-benzothiazines and 1,2-benzisothiazoles. A preference for the former was seen with alkyl alkynes, while the later were preferentially formed with alkyl arenes\textsuperscript{28}.

Bunker et al, prepared a series of 1, 2-benzothiazine derivatives. They claimed that these compounds were useful in treating the elevated blood pressure and hypertension as endothelin antagonists\textsuperscript{29}.
According to Kacem Y et al, the same author in different article have also reported the synthesis of 3-substituted-2H-1,2-naphthothiazin-4(3H)-one 1,1-dioxides via ortho-metalation reaction. Different N,N-diisopropyl-2-aminoamides prepared from α-amino acids, were converted to 3-substituted-2H-1,2-naphthothiazin-4(3H)-one 1,1-dioxides in the presence of an excess of lithium di-isopropyl amide giving yields ranging from 21 to 70%. The key steps were the naphthyl sulfonyl ortho-deprotonation based on the directed ortho-metalation reaction followed by a regiospecific intra-molecular cyclization reaction.

Zia-ur-Rehman et al., working during the year 2005 in Applied Chemistry Research Centre of the PCSIR Laboratories Lahore, Pakistan, efficiently made use of ionic liquids for preparing 1,2-benzothiazine 1,1-dioxide derivatives. An environment friendly method has been described for the synthesis of various 2-alkyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxides starting from N-alkylation of sodium o-benzosulfimide in an ionic liquid for the first time. Ring cleavage and ring closure of the resulting product were achieved in a single step in a cost-effective solvent (methanol),...
followed by $N$-alkylation of resulting alkyl 4-hydroxy-$2H$-1, 2-benzothiazine-3-carboxylate in ionic liquid while boron triflouride was used as a catalyst along with molecular sieves in carboxamide formation step $^{31}$.

Recently, Harmata et al, have reported palladium catalyzed synthesis of 1,2-benzothiazine 1,1-dioxides using alkynes. The reaction of $S$-2-bromophenyl-$S$-methylsulfoximine with terminal alkynes in the presence of a palladium catalyst resulted in the formation of both 1,2-benzothiazines and 1,2-benzoisothiazoles. A preference for the former was seen with alkylalkynes, while the latter were preferentially formed with alkynylarenes $^{32}$.

Kategaonkar et al, reported an efficient and novel one-pot synthesis of new 3, 4-dihydro-3-substituted-$2H$-naphtho[2,1-$e$][1,3]oxazine derivatives from 1-naphthol, various anilines and formalin at room temperature grinding is presented. The six-membered $N$, $O$-heterocyclic skeleton was constructed via zirconyl(IV) chloride promoted Mannich type reaction. In vitro antimicrobial activities of synthesized compounds have been investigated against Gram-positive Bacillus subtilis, Gram negative Escherichia coli and two fungi Candida albicans and Aspergillus niger in comparison with standard drugs. The results of preliminary bioassay indicate that some of title compounds possess significant antibacterial and antifungal activity $^{33}$.

Nagaraj et al, prepared a series of bis – chalcone by reaction of 5,5 – methylene –bis – salicyaldehyde with various acetophenone, subsequent treatment of Bis –chalcone with thiourea or guanidine resulted to the corresponding bis –thiazines or bis –pyrimidines in good yields. The antibacterial, antifungal and anti-inflammatory activities of the compounds have been evaluated $^{34}$. 
Elarfi et al., reported Chalcone derivatives were synthesized by reaction of some benzaldehyde derivatives with acetophenone, then the products obtained were allowed to react with urea, thiourea and hydroxylamine, to give the heterocyclic derivatives of oxazine, thiazine and isoxazole, respectively. The final products have been characterized by elemental analysis, IR and proton NMR spectra. These compounds were also screened for their antibacterial activities.\(^\text{35}\)
CONCLUSION: The informational data, available in literature so far, rendered thiazine and oxazine, a significantly important class of heterocycle and their applications are challenging in disease of various infections. A survey of thiazine and oxazine revealed the moieties have attracted a great deal of interest of medicinal chemist and biochemist and rendered as a lead molecule for designing potential bioactive agents. Also, its derivatives are reported including broad-spectrum pharmacological activities.

This review accompanying supplementary information & its references would extend great deal of help to researchers in determining the best and most productive, economical, suggestive and clinically important compounds of thiazine and oxazine.

Further, we can conclude that many other derivatives of thiazine and oxazine can be synthesized which will be expected to show potent pharmacological activities. We hope that, our brief review will assist all those interested in this promising class of heterocyclic compounds to reach decisions in the choice of targets and tasks for further investigations.

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