BIOLOGICAL ACTIVITIES OF OXAZINE AND ITS DERIVATIVES: A REVIEW

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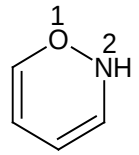
ABSTRACT

Oxazine derivatives are an important class of heterocycles, which has attracted much synthetic interest due to their wide range of biological activities. Oxazine is a heterocyclic compound can be formally derived from benzene, and its reduction products, by suitable substitution of carbon (and hydrogen) atoms by nitrogen and oxygen. In the last few years oxazine derivatives have proved to be valuable synthetic intermediates and also possess important biological activities like sedative, analgesic, antipyretic, anticonvulsant, antitubercular, antitumour, antimalarial and antimicrobial. In these days, development of drug resistance is a major problem and to overcome this situation, it is necessary to synthesize new classes of compounds. The aim of the article is to review the generalization of the collected data about the synthesis of oxazine derivatives and their activities. We hope that this work will be a definite interest for researchers concerned with azines in generally and oxazines in particular.

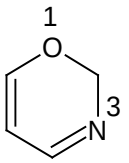
Key words: Oxazine, Antimicrobial, Antitubercular, Antitumour.

INTRODUCTION

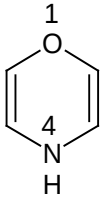
Oxazines which have been the object of the interest for the past three decades, still remain little studied compounds. Oxazines are heterocyclic compounds containing one nitrogen and one oxygen[1]. There are three isomers exist depending on the relative position of the heteroatom's and relative position of the double bonds. 1, 2-,1, 3-,and1,4- oxazines (Fig. 1) are the O- analogues of the three isomeric diazines. When the oxygen and nitrogen atoms are present the name oxazine is used and the position of the atoms are indicated by numbers.[2]



1,2- oxazine



1,3- oxazine



1,4- oxazine

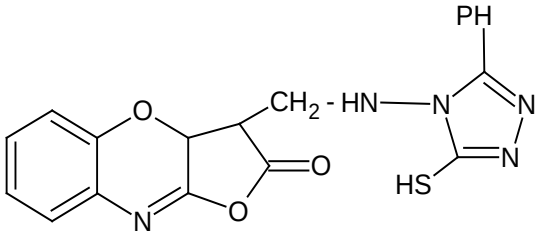
(Fig.1)

Aromatic oxazines were first synthesised in 1944 by Holly and Cope through Mannich reactions. Comparatively little work has been done on simple derivatives of these ring system and most of these concerns the reduced 1, 3 and 1, 4 compounds. The most important simple1, 4- oxazine is morpholine or tetrahydro-1, 4 oxazine, which is a colourless liquid, which is miscible with water[3].

Oxazine heterocycles have special interest because they constitute an important class of natural and non natural products and show useful biological activities[4]. Its increasing importance in pharmaceutical and biological field, through this review article, we are planned to collect synthesis of oxazine derivatives for their biological activities.

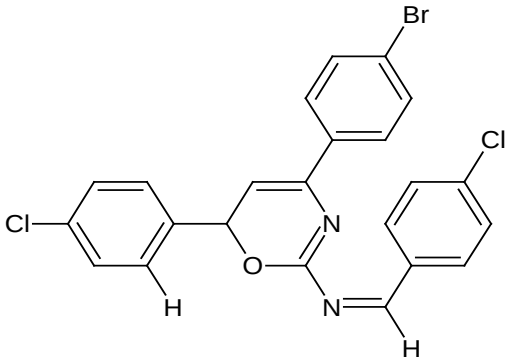
BIOLOGICAL POTENTIAL OF OXAZINE DERIVATIVES:

Bhat et. al., 2008 synthesised some new derivatives of [1, 4] oxazin-2-one (Fig.2) by reacting o-amino phenol with maleic anhydride. Further Mannich bases were synthesised from 3,3a-Dihydro-benzo(b)furo(2,3-e)[1,4]oxazine-2-one with substituted aromatic amines and amino triazole. All compounds were screened for their antitubercular, antibacterial and antifungal activity. Results suggest that 1, 4 oxazines are potential lead compounds in antitubercular, antibacterial and antifungal studies[5].



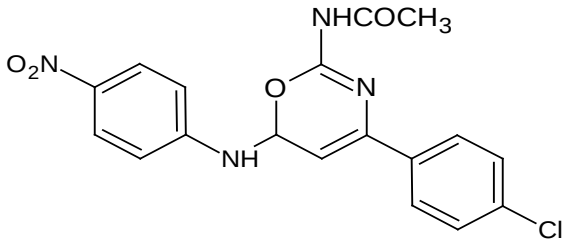
(Fig.2)

Sawant et.al., 2012 synthesised a series of Schiff bases of 1, 3-oxazines were synthesised via reaction of 1, 3-oxazine-2 amine with substituted benzaldehyde. The synthesised compounds were screened for their anticoagulant activity. Result showed that the most of the synthesised compounds exhibited significant anticoagulant activity amongst them 4-(4-Bromophenyl)-6-(4-chlorophenyl)-N [(E)-(4-chlorophenyl)-methylidene]-6H-1, 3-oxazin-2-amine (Fig. 3) was to be most active[6].



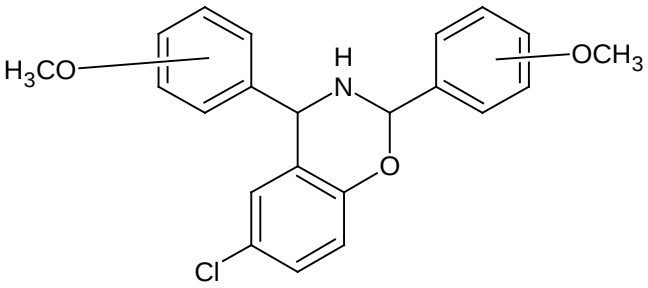
(Fig.3)

Beena et.al., 2013 synthesized a series of [6-(p-substituted aminophenyl)-4-(p-substituted phenyl)-6H- 1, 3-oxazin-yl]-acetamides via claisen-schmidth condensation. The synthesised compounds were screened for their antimicrobial activity. Among these chloro substituted 1, 3-oxazinyl acetamide derivative (Fig.4) was found to have a strong antibacterial and antifungal activity[7].



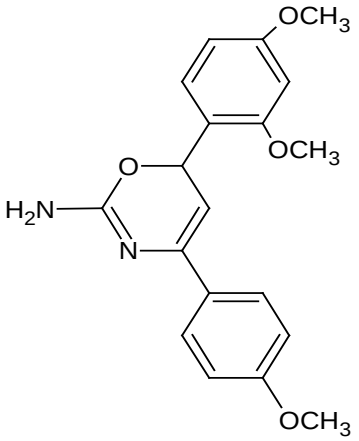
(Fig.4)

Didwagh et.al., 2013 synthesized novel one-pot synthesis of a series of 6-chloro-2, 4-diphenyl-3,4-dihydro-2H-1,3-benzoxazines derivatives (Fig.5) from the reaction of p-chlorophenol and substituted aromatic aldehyde in methanolic ammonia solution. They are screened for their antimicrobial activities. Among these compounds methoxy substituted derivatives have more antimicrobial activity than standard drugs[8].



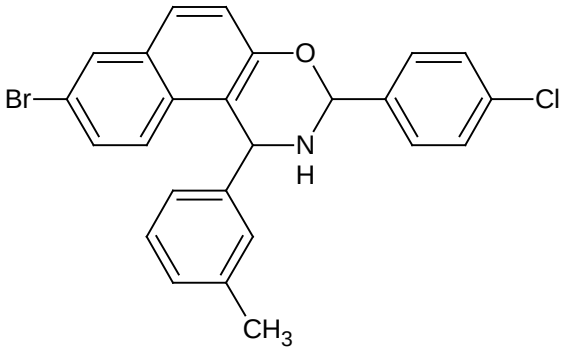
(Fig.5)

Dhanya et.al., 2013 synthesized a new series of 4-(4-substiuted phenyl)-6-substituted -6H-1, 3-oxazines from acid catalysed reaction. Claisen-schmidt condensation of substituted aromatic aldehydes with 4-substituted acetophenones yielded chalcones [(2E)-3-[(substituted phenyl)]-1-[(4-substituted) phenyl prop-2-ene-1-ones.New oxazine derivatives were synthesized by the reaction between chalcones and urea in ethanol medium in presence of concentrated HCl. The excellent antibacterial activity was exhibited by 6-[2, 4-dimethoxyphenyl]-4-(4-methoxyphenyl)-6H-1, 3-oxazin -2 amine (Fig-6) against gram +ve bacteria[9].



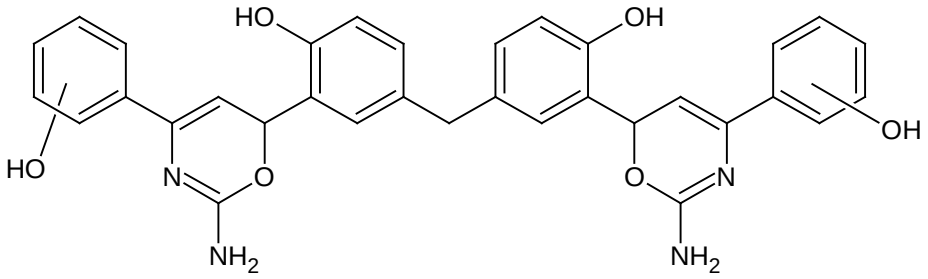
(Fig.6)

Mayekar et.al., 2011 synthesized a series of new 8-bromo -1, 3-bis (aroyl)-2, 3-dihydro-1H-naphtho [1, 2-e][1,3]oxazines. In which 6-bromonaphthol undergoes a ring closure reaction with substituted aryl and heteroaryl aldehydes to give napthoxazines derivatives. The compounds were screened for their antibacterial and antifungal activity. Compounds having fluoro, chloro and methyl substituted phenyl group attached to naphthoxazine showed promising activity. In the fungal activity study, compound 8-Bromo-1-(3-methylphenyl)-3-(4-chlorophenyl)-2, 3-dihydro-1H-naphthol [1,2-e] [1,3]oxazine (Fig.7) emerged with good activity against Aspergilus flavus[10].



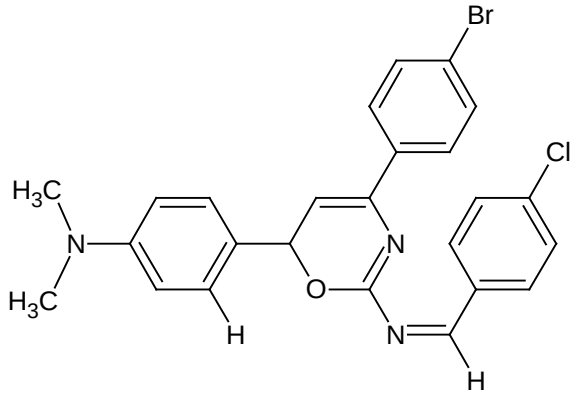
(Fig.7)

Didwagh et.al., 2013 synthesized a series of novel 2-[2-Amino-4(4-bromo phenyl)-6H-1,3-oxazine-6 yl]-4-{3-[2-amino-4(4-bromo phenyl)-6H-1,3- oxazine-6 yl]-4-hydroxy benzyl} phenol derivatives (Fig-8) were prepared from bis [3-[(E)(4-bromo phenyl)-3-oxa-1-propenyl]-4-hydroxy phenyl] methane with urea and potassium hydroxide in ethanol. The synthesized compounds were screened for their antibacterial and antifungal activity. Among these 4-hydroxy derivatives has more activity against fungal strains[11].



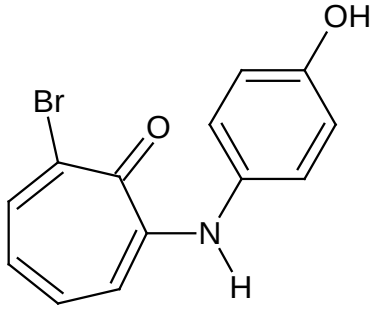
(Fig.8)

Sawant et.al., 2012 synthesized a new series of Schiff bases of 1, 3-oxazines from 4-bromo acetophenone and substituted aromatic aldehyde reacted in presence of sodium hydroxide to give substituted chalcones. Then substituted chalcones reacted with urea to produce 4-(4-bromo phenyl)-6-(substituted phenyl)-6H-1, 3-oxazine-2-amine analogues. These compounds were reacted with substituted aromatic aldehydes to produce4-(4-bromophenyl)-6-(substituted phenyl)-2-{[(1E) (substituted phenyl) methylidenene]}-6H-1, 3-oxazine-amine. They were screened for their antimicrobial activity. The present study concluded that compound4-(4-Bromophenyl)-6-(N,N-dimethylaminophenyl)-N-[(E)(4-chlorophenyl) methylidene] -6H-1, 3-oxazin -2-amine (Fig.9) were found to be most active antimicrobial compounds.[12]



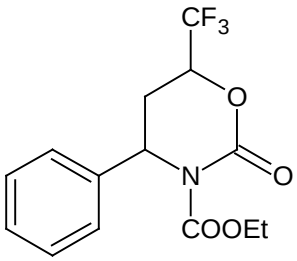
(Fig.9)

Narita et.al., 2009 synthesised twenty benzo[b]cyclohept[e] [1, 4]oxazines and their S-analogs, and 2-aminotropone derivatives and screened for their cytotoxic activity against 3 human normal cells and 4 tumour cell lines. All the synthesised compounds have moderate tumour-specific cytotoxicity. Among these, 7- bromo-2-(4-hydroxyanilino) tropone (Fig-10) showed the highest activity.[13]



(Fig.10)

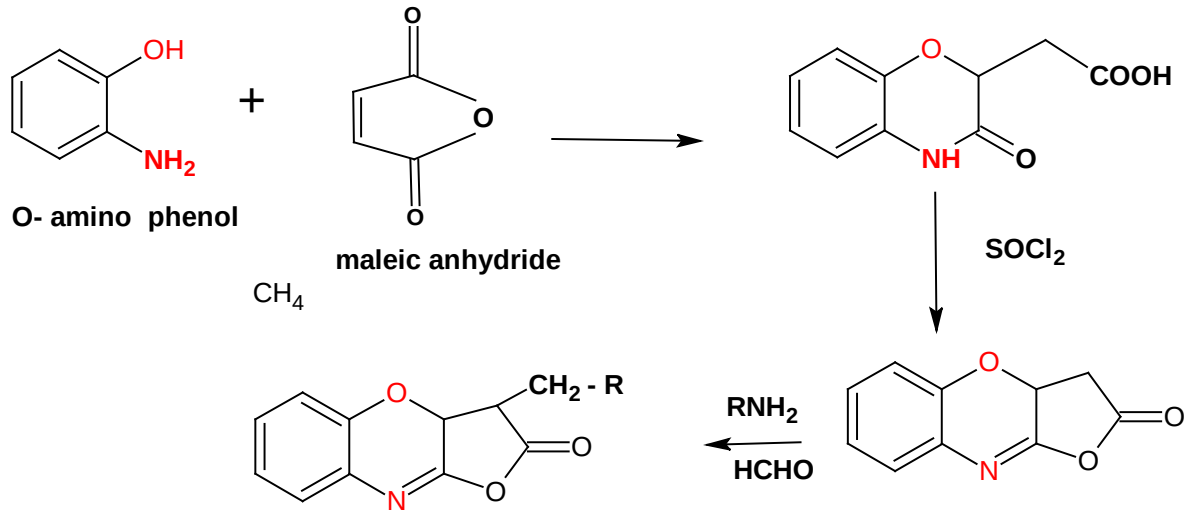
Zanatta et al., 2006 reported the reaction of beta - alkoxy- CF_3-enones with ethyl carbamate leads to formation of enamidoketones. Subsequent reduction and cyclization leads to formation of oxazines (Fig.11). They exhibited significant activity against tested microorganism strains.[14]

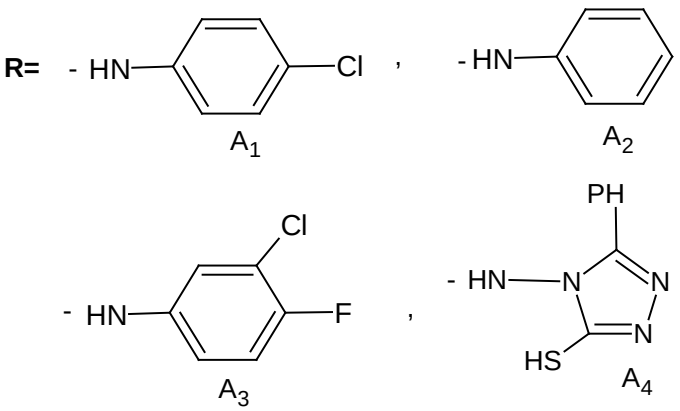


(Fig. 11)

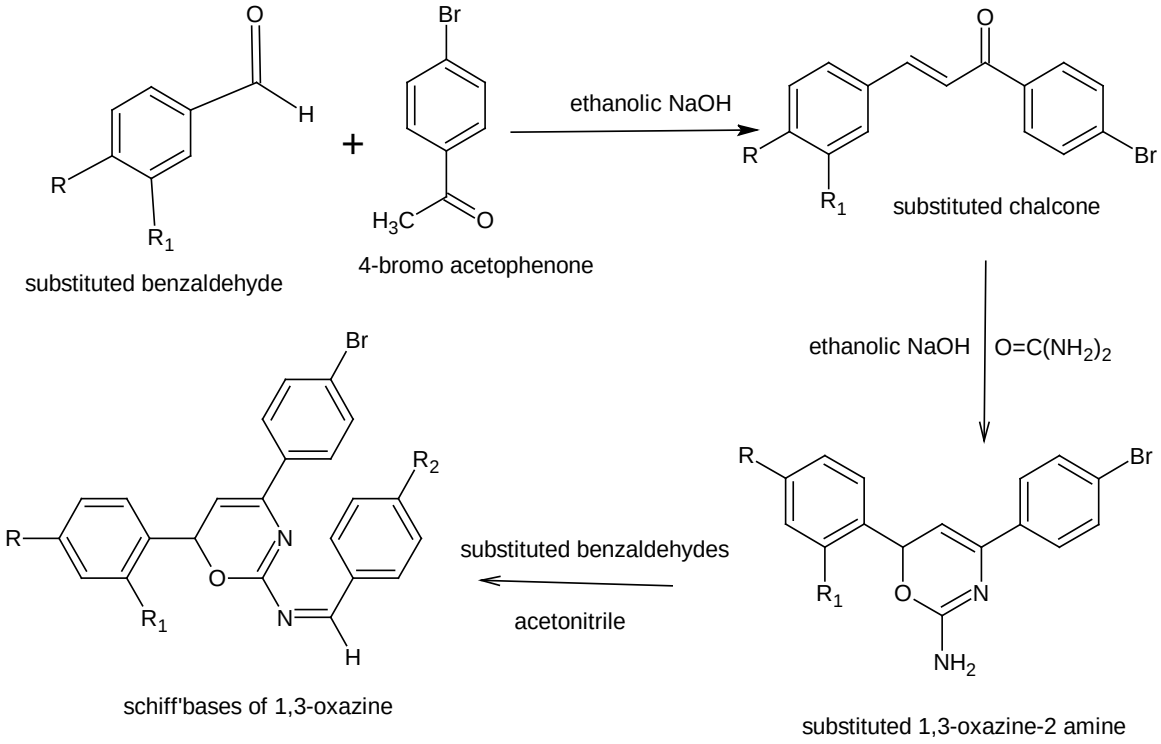
STRATEGIES EMPLOYED FOR THE SYNTHESIS OF OXAZINE DERIVATIVES:

(1) Synthesised of [1, 4] oxazin-2-one derivatives[5]





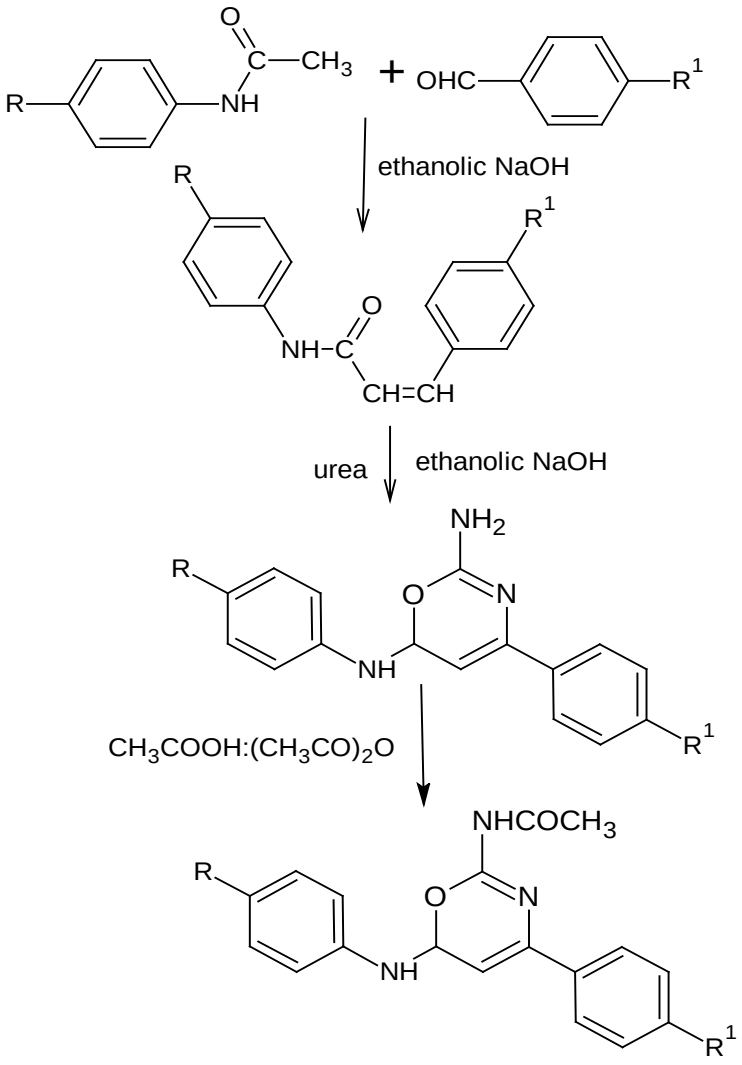
(2) Synthesis of Schiff bases of 1, 3- oxazines.[6]



Various substituents used for Schiff bases of 1, 3-oxazine:

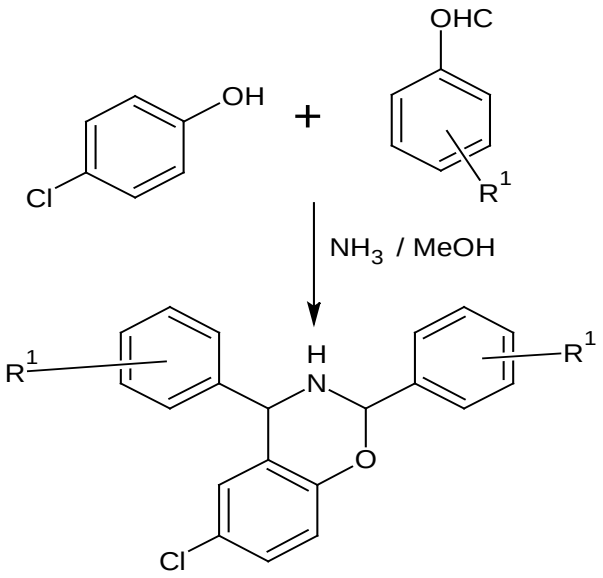
compound	R	R_1	R_2
1.	**Cl**	**H**	**NO_2**
2.	NO_2	H	NO_2
3.	H	OH	NO_2
4.	Cl	H	Cl
5.	H	OH	Cl

(3) Synthesis of [6-(p-substituted amino phenyl)-4-(p-substituted phenyl)-6H-1, 3-oxazin-yl]-acetamide[7].



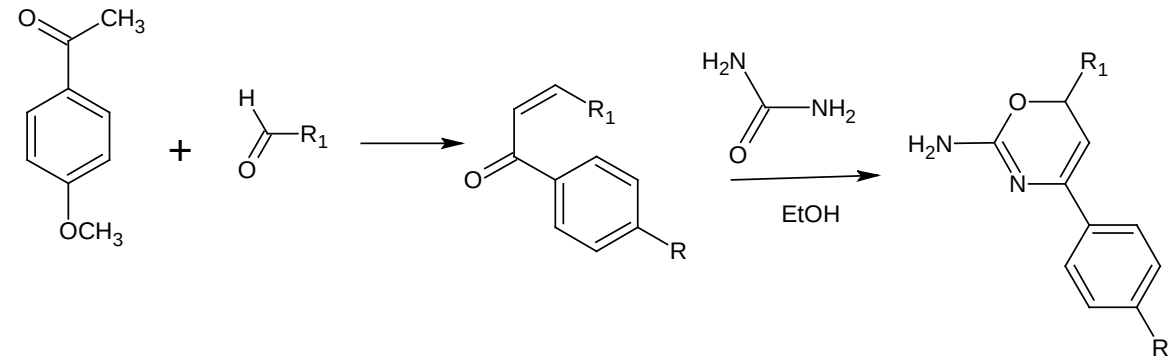
R	R_1
H	$N(CH_3)_2$
NO_2	Cl
NO_2	H
NO_2	OCH_3
NO_2	NO_2

(4) Synthesis of 6-chloro-2, 4-diphenyl-3, 4-dihydro-2H-1, 3-benzoxazines derivatives.[8]



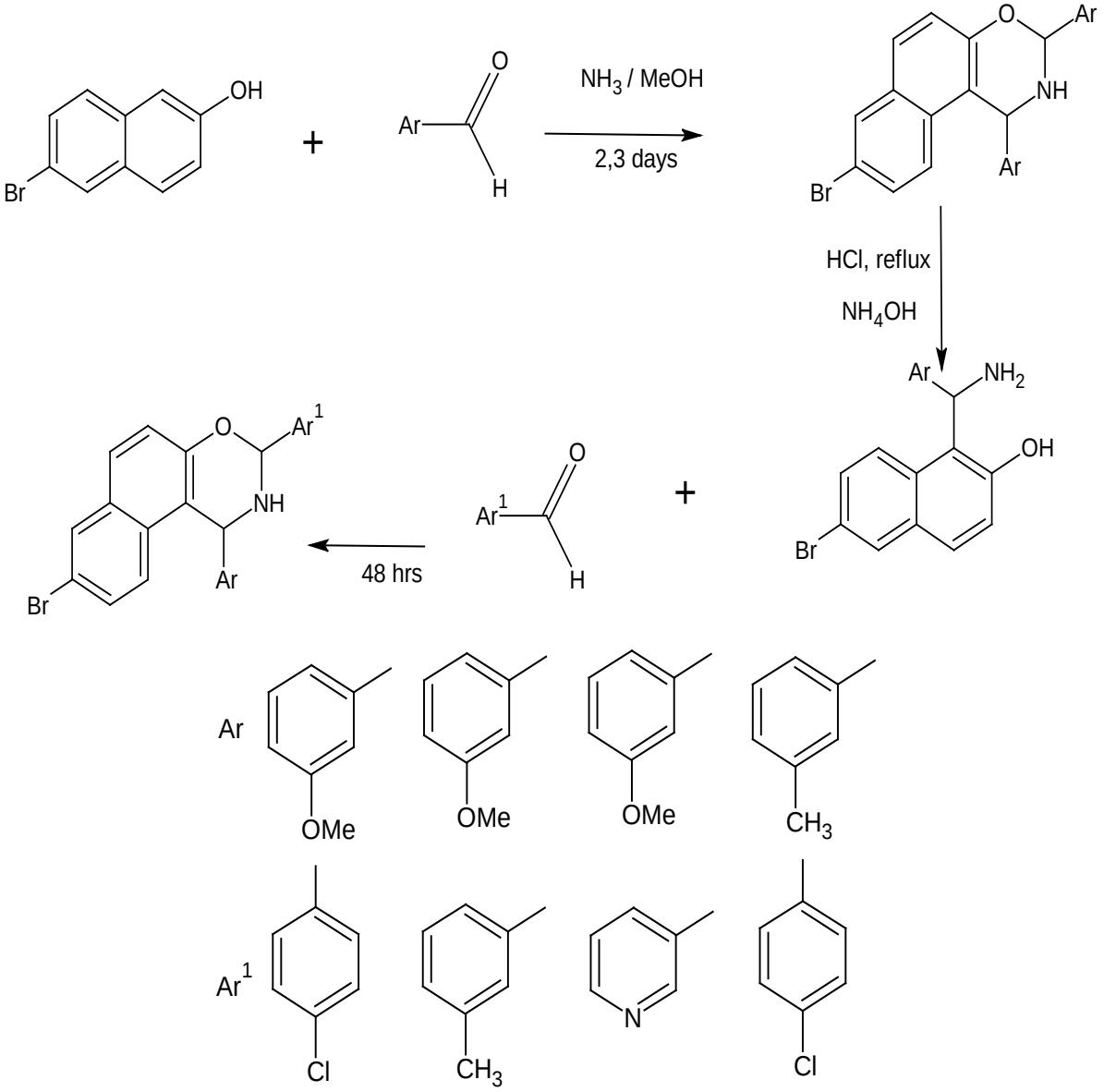
R_{1-} C_6H_5, 4-$OCH_3C_6H_4$, $NO_2C_6H_4$, $CH_3C_6H_4$.

(5) Synthesis of 4-(4-substituted phenyl)-6-substituted -6H-1, 3-oxazines[9].



R_1	R
4-dimethyl amino phenyl	F
4-dimethyl amino phenyl	Cl
2,4-dimethoxy phenyl	OCH_3
2,4-dimethoxy phenyl	F
2,4-dimethoxy phenyl	Cl

(6) Synthesis of 8-bromo -1, 3-bis (aroyl)-2, 3-dihydro-1H-naphtho[1,2-e][1,3] oxazines[10].



CONCLUSION

Oxazine and related heterocyclic compounds were reported to have antimycobacterial, antibacterial, antifungal, anticoagulant, anticancer, antioxidant, and cytotoxic activities. It has been found that oxazine derivative can be synthesized in a number of ways. So this review article can extend the synthetic utility of new heterocyclic oxazine derivatives. Therefore, biological significance of oxazine compounds could be utilized for the development of new chemical entities to various diseases.

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