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Developments in The Synthesis of Certain Novel [1,3]-Oxazine Derivatives and its Biological Activities

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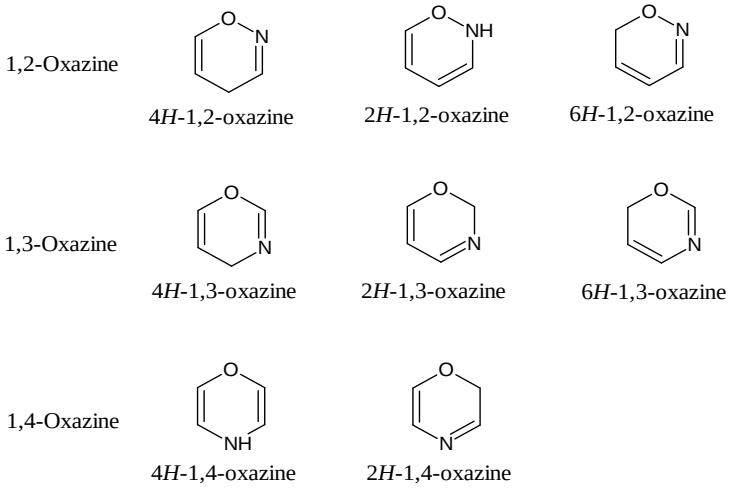
A B S T R A C T

This is a study regarding the several strategies for the synthesis of [1,3]oxazine derivatives and their pharmaceutical activities. These are one of the paramount heterocyclic classes which have drawn attention towards its synthesis because of their innumerable biological activities like antiviral, antitumour, antimalarial, antimicrobial, antitubercular and analgesics. Oxazine can be derived from benzene, and its reduction products, by substitution of carbon atoms by nitrogen and oxygen at 1,3 positions. These can be synthesised by the help of several mechanisms like Mannich reaction and Betti reaction, etc., Normally, oxazines are prepared by using expensive and toxic reagents. To reduce the cost and use of toxic reagents, novel [1,3]oxazine derivatives were synthesised by using primary amines, aldehydes, phenols and a catalyst with solvent. Currently, drug resistance is the major cause reducing the ability of the drug to treat the disease effectively. The objective of this article is to provide a precised view on the synthesis of [1,3]oxazine derivatives and their pharmaceutical and biological activities..

Keywords: oxazine, Mannich reaction, Betti reaction.

1. INDRODUCTION

The chemistry of Oxazines has generated intensive scientific studies throughout the world. Chemically, oxazines are six-membered heterocyclic compounds containing one nitrogen, an oxygen atom and two double bonds.[1] Oxazine derivatives are very important heterocyclic compounds with several biological activities.1,2- oxazines, 1,3- oxazines, 1,4- oxazines are the different types of oxazines. Naming of oxazines is followed according to IUPAC system, in which oxygen is numbered first, then the nitrogen is numbered.[1]



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The interest on 1,3-oxazine derivatives has increased recently because compounds containing dihydro[1,3]-oxazine ring system exhibited a wide spectrum of pharmacological activities and their versatility as synthetic intermediates. In addition, naphthoxazine derivatives have therapeutic potential in the treatment of Parkinson's disease.[2]

Trifluoromethyl-1,3-oxazine-2-one as a non-nucleoside reverse transcriptase inhibitor shows high activity against a variety of HIV-1 mutant strains.Hence, the studies of 1,3-oxazine derivatives have been done via the synthesis based on three-component cyclocondensation of primary aliphatic and cyclic amines with formaldehyde and substituted phenols.[2]

They have been reported to possess several biological activities such as antimicrobial activity, anti-inflammatory activity, antitubercular activity, antidiabetic activity, anticancer activity, analgesic activity, antioxidant activity, diuretic activity, antiviral activity, etc.,[3]

Apart of their biological activity, benzo-1,3-oxazines are known to be pharmacologically active and are an important group of the organic dyes.[4]

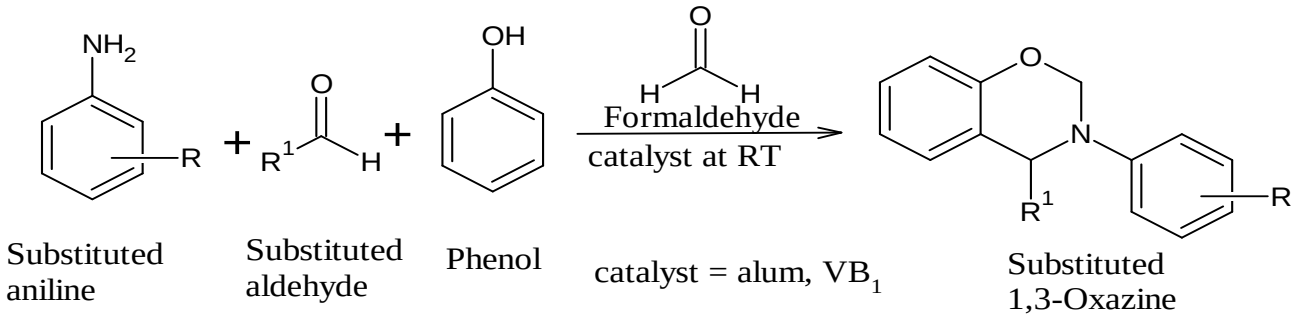
A few methods which are accessible for amalgamation of a few oxazine derivatives, even though, expensive and toxic reagents and special conditions are required. Hence, most commonly used methods are explained in this review.

2. SYNTHESIS

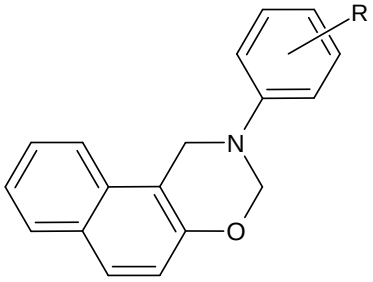
General procedure of [1,3]-Oxazine derivative:

An economical and convenient synthesis of 1,3-oxazine derivatives has been achieved by the one-pot, multicomponent condensation of *α*- or *β*-naphthol, an aniline and formaldehyde using catalyst in water as a universal solvent.[2]

The product is extracted with ethyl acetate. The organic layer is washed with brine and dried over anhydrous magnesium sulphate. By using reduced pressure the solvent is drained out to get a solid/viscous 1,3-oxazine derivatives.[2]

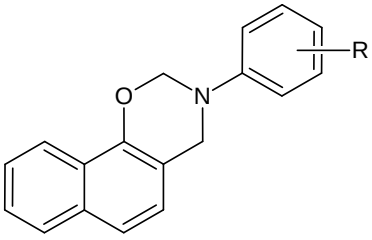


Valmik D Dhakanea*et al.*,synthesized (1,3) oxazine derivatives *via* a one-pot, three-component condensation of anilines, formaldehyde and *α*- or *β*-naphthol catalysed by thiamine hydrochloride (Vitamin B_1) in water by green method. This method is attractive for the synthesis of polysubstituted oxazine derivatives.[2]



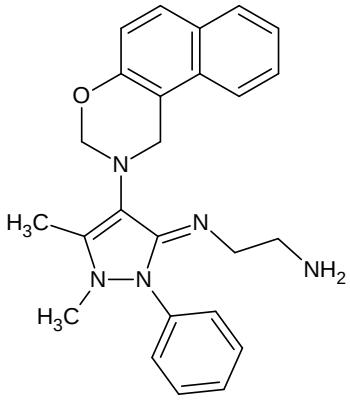
1,3-Oxazine derivative

Amol H Kategaonkar *et al.,* synthesized 3,4-dihydro-3-substituted-2*H*-naphtho[2,1-*e*] [1,3] oxazine derivatives catalysed by zirconyl (IV) chloride and evaluated its biological activity. The salient features of this method include high yields, short reaction times, cleaner reaction profile and the use of inexpensive and readily available $ZrOCl_2$ as a catalyst. The antibacterial and antifungal activities were observed in all the compounds. Most of the compounds prove even better than the standard drugs.[5]



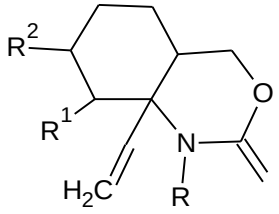
3,4-dihydro-3-substituted-2*H*-naphtho[2,1-e][1,3]oxazine derivatives

Figueroa-Valverde Lauro*et al.,* designed and synthesized two oxazine derivatives using several strategies. It is important to mention that there are reports which indicate thatcondensation of naphthol with formaldehyde and amino groups result in naphthoxazines. The methods used offer some advantages such as good yields, simple procedure, low cost, and ease of workup.[6]



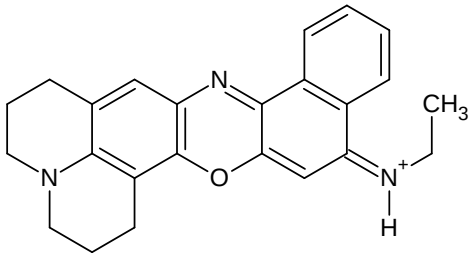
Naphthoxazines

ChitchamaiLarksarp *et al.,* prepared 1,3-oxazine derivatives by Palladium-Catalysed cycloaddition of vinyloxetanes with heterocumulenes. This process is completely regioselective and stereoselective. A particularly novel feature of the cycloaddition process is its use for the construction of bicyclic [4.4.0] systems by use of $Pd_2(dba)_3$,$CHCl_3$ and achiral ligand such as dppe.[7]



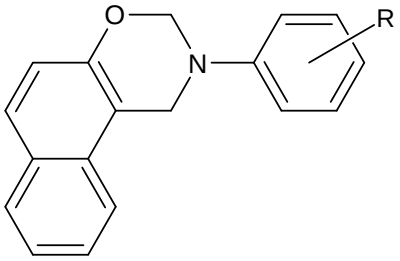
1,3-Oxazine derivative
*= halogens (Cl,F)
R^1 = alkyl group
R^2 =alkyl group

S Arda Ozturkcans *etal.,* prepared new 1,3-oxazine derivatives Mannich-type aminoalkylation reaction of 2-naphthol was applied in the presence of ammonia. The biologically active results obtained showed that 1,3-di(2-naphthyl)-2,3-dihydro-1*H*-naphto[1,2-*e*] [1,3] oxazine has anti-mutagenic activity in *S. typhimurium* TA1535, and *E. coli* WP2uvrA strains at three concentrations.[8]



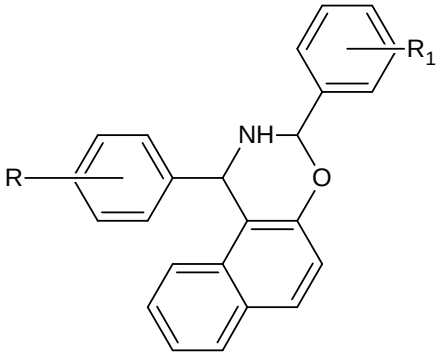
1,3-Di(2-naphthyl)-2,3-dihydro-1*H*-naphto[1,2-e][1,3]oxazine

Sandip A *et al*., synthesized various [1,3] oxazine compounds from aryl amines using alum as a catalyst and water as solvent. The remarkable advantages offered by this method are the use of safer catalyst, solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields.[9]



1,3-Oxazine derivative

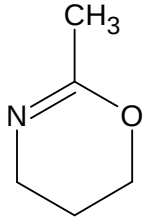
Zuhal Turgut *et al.,* synthesizedsubstituted aminobenzylnaphthols from moderate to good yields by the reactions of 2-naphthols with appropriate aldehydes. Some new 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-*e*]- [1,3] oxazines that are expected to show biological activities, were obtained by the ring closure reactions of these aminobenzylnaphthols and various aldehydes.[10]



1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-e]- [1,3]oxazine derivatives

Microwave-assisted synthesis of dihydro1,3- Oxazines

Mollo*et al.,* synthesised 1,3-oxazines by microwave irradiation of amido alcohols in the presence of polyphosphoric acid esters (PPA). Trimethylenic amido alcohols were converted into appropriate cyclic imidates in better yields when PPA were applied.[11]



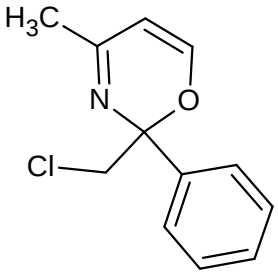
2-alkyl-5,6-dihydro-4*H*-1,3-oxazine

Reaction condition and yield

R	Reaction condition	Yield (%)
4-$OCH_3C_6H_4$	5 min, 70℃	85%
4-$CH_3C_6H_4$	5 min, 70℃	96%
2-$CH_3C_6H_4$	5 min, 90℃	84%
4-ClC_6H_4	5 min, 70℃	92%
4-$NO_2C_6H_4$	5 min, 70℃	91%
2-$NO_2C_6H_4$	5 min, 90℃	78%
2-FC_6H_4	3 min, 90℃	65%
2,4-$Cl_2C_6H_4$	3 min, 90℃	27%
$C_6H_5CH_2$	10 min, 90℃	35%

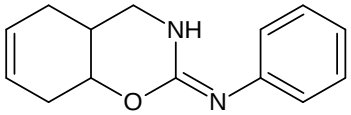
By using Gold(I)-Catalyst:

Lonca*et al.,* synthesised 1,3-oxazine by denitrogenation cyclization of halo-substituted alkyl azides using the gold precursor. Firstly, *α*-propargyloxy-*β*-fluoroalkylazide reacted with three different gold complexes: $[Ph_3PAu(NCCH_3)]SbF_6$, $[IprAu\ (NCCH_3)]SbF_6$ and $[XPhosAu(NCCH_3)]SbF_6$. All the mentioned gold complexes produce 2*H*-1,3-oxazine by 6-endo-dig azide-yne cyclization, out of which $[XPhosAu\ (NCCH_3)]SbF_6$ has more reactivity. The Me_4tBuXPhos ligand has showed higher reaction rate and yield. The greater reaction rate was obtained by replacing the SbF_6– counter-anion in the gold complex with the more coordinating NTf2-. The reaction is completed within 20 min after accelerated by counter anion replacement, by getting same range of yield.[12]



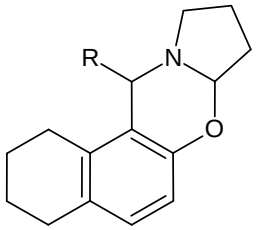
2-(halomethyl)-4-alkyl-2-phenyl-2*H*-1,3-oxazine

Brito*et al.,* synthesised (2*Z*)-*N*-phenyl-1,4,4a,5,8,8a-hexahydro-2*H*-3,1-benzoxazin-2-imine from ester derivative with benzoyl chloride and lithium aluminium hydride again reacted with phenyl isothiocyanates in toluene followed by the treatment with methyl iodide and KOH in methanol. *Cis* and *trans* derivatives were obtained from *cis* and *trans* ester derivatives, simultaneously.[13]



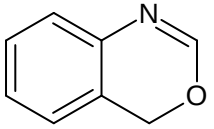
(2*E*)-*N*-phenyl-3,4,4a,5,8,8a-hexahydro-2*H*-1,3-benzoxazin-2-imine

Deb*et al.,* synthesised benzoxazine by the reaction oxygenation of iodine-tert butyl hydroperoxide. This method was metal free reaction and resulted in very good yield in short time.[14]

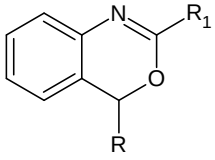


R=Ph, 4-ClPh,4-OMePh,H

Chao chen*et al.,* synthesised 2,4-disubstituted-4*H*-3,1-benzoxazines by using a catalyst copper(I) in the reaction cascade annulation of nitriles, aldehydes and diaryliodonium salts.[15]



4*H*-3,1-benzoxazine



2,4-disubstituted-4*H*-3,1-benzoxazine

Anti-inflammatory activity and Anti-oxidant activity:

Chaitra G*et al.,* substituted 1,3-oxazine were synthesised with the help of an intermediate Chalcone and performed an anti-inflammatory activity **Table 1** by comparing with the standard Indomethacin using *invitro* analysis in two methods, one is Bovine serum albumin (BSA) method and the other Protease inhibition assay method. Anti-oxidant activity **Table 2**by comparing with ascorbic acid as standard using *invitro* analysis in two methods, one is Diphenyl picryl hydrazide (DPPH) method and the other is nitric oxide (NO) method. Among all the synthesised products *N*-{4-[2-amino-4-(3,4,5-trimethoxy-phenyl)-6*H*-[1,3]oxazine-6-yl]-phenyl}-nicotinamide and *N*-{4-[2- amino-4-(3-nitro-phenyl)-6*H*-[1,3]oxazine-6-yl]-phenyl}-nicotinamide methane has significant anti-inflammatory activity and anti-oxidant activity.[16]

Table1: Anti-inflammatory activity

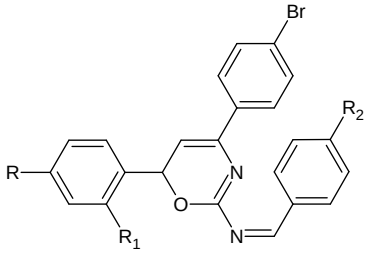
Compound	Percentage Inhibition (%)				
	Protease method			BSA method	
	(100µg/ml)	(50 µg/ml)	(10 µg/ml)	(100µg/ml)	(200 µg/ml)
Indomethacin	89.32	69.31	30.15	78.01	94.8
N-{4-[2-amino-4-(3,4,5-trimethoxy-phenyl)-6*H*-[1,3]oxazine-6-yl]-phenyl}-nicotinamide	77.74	71.43	67.64	66.6	86.6
N-{4-[2- amino-4-(3-nitro-phenyl)-6*H*-[1,3]oxazine-6-yl]-phenyl}-nicotinamide methane	86.34	68.91	68.77	73.3	86.6

Table2: Anti-oxidant activity

Compound	Percentage Inhibition (%)					
	DPPH method			NO method		
	(100 µg/ml)	(50 µg/ml)	(10 µg/ml)	(100 µg/ml)	(50 µg/ml)	(10 µg/ml)
Ascorbic acid	99.25	95.41	90.5	81.112	80.4	78.81
N-{4-[2-amino-4-(3,4,5-trimethoxy-phenyl)-6*H*-[1,3]oxazine-6-yl]-phenyl}-nicotinamide	94.7	94.4	94	81.11	81.73	81.11
N-{4-[2- amino-4-(3-nitro-phenyl)-6*H*-[1,3]oxazine-6-yl]-phenyl}-nicotinamide methane	90	85	84.6	81.11	81.11	81.11

Anticoagulant activity:

Sawant*et al.,* reported a series of Schiff's bases of 1,3-oxazines were synthesized by the reaction between 1,3-oxazine-2-amine and substituted benzaldehydes. Majority of the synthesized compounds resulted in anticoagulant activity**Table 3**, among all the compounds, 4-(4-bromophenyl)-6-(4-chlorophenyl)-*N* [(*E*)-(4-chlorophenyl)-methylidene]- 6*H*-1,3-oxazin-2-amine was higher active compound.[17]



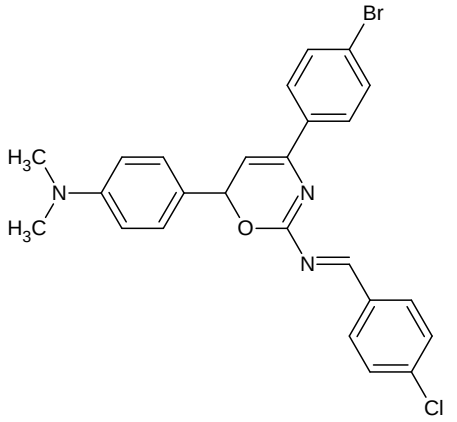
1,3-oxazine-2-amine derivative

Table3: Anticoagulant activity

compound	R	R_1	R_2	Prothrombin time (time in sec)
Control	-	-	-	25.66
Standard	-	-	-	122.5
A	NO_2	H	NO_2	113.33
B	H	OH	NO_2	115.5
C	Cl	H	Cl	120.16
D	NO_2	H	OCH_3	106.33
E	$N(CH_3)_2$	H	OCH_3	118.12

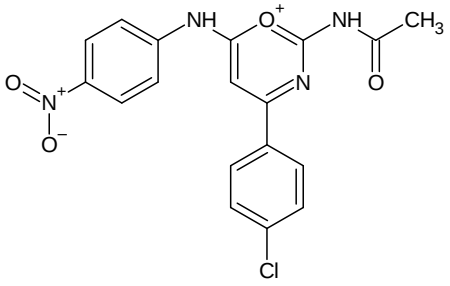
Antimicrobial activity:

Sawant*et al.,* reported a series of Schiff's bases 1,3-oxazines from reaction between 4-bromo acetophenone and substituted aromatic aldehyde reacted in presence of sodium hydroxide to result in substituted chalcones which are reacted with urea to produce 4-(4-bromo phenyl)-6-(substituted phenyl)-6*H*-1, 3-oxazine2-amine analogues. Again reacted with substituted aromatic aldehydes to produce4-(4- bromophenyl)-6-(substituted phenyl)-2-{[(1*E*) (substituted phenyl) methylidenene]}-6*H*-1, 3-oxazine-amine. Most of the synthesised compounds showed antimicrobial activity. 4-(4- Bromophenyl)-6-(*N*,*N*-dimethylaminophenyl)-*N*-[(*E*)(4-chlorophenyl) methylidene]-6*H*-1, 3-oxazin -2-amine was most active antimicrobial compounds.[1]



4-(4-Bromophenyl)-6-(*N*,*N*-dimethylaminophenyl)-*N*-[(*E*)(4-chloro phenyl) methylidene]-6*H*-1, 3-oxazin -2-amine

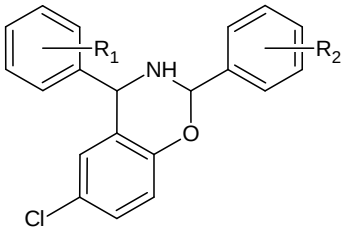
Beena*et al.,* by claisen-schmidth conednsation reaction synthesised a series of [6-(*p*-substituted aminophenyl)-4-(*p*-substituted phenyl)-6*H*- 1, 3- oxazin-yl]-acetamides. Most of the synthesized compounds resulted in antimicrobial activity. Amongst them chloro substituted 1, 3-oxazinyl acetamide derivative showed strong antibacterial and antifungal activity.[18]



2-acetamido-4-(4-chlorophenyl)-6-(4-nitroanilino)-1,3-oxazin-1-ium

Didwagh*et al.,* reported a series of 6-chloro-2,4-diphenyl-3,4-dihydro-2*H*-1,3-benzoxazinesderivatives by reacting *p*-chlorophenol with substituted aromatic aldehyde in methanolic ammonia solution through one pot synthesis. Compounds synthesised were screened for *in vitro*antimicrobial activitywith the help of cup plate method mentioned in **Table 4**. *Staphylococcus aureus, Bacillus subtilis* are two-gram positive bacteria and *Escherichia coli*, *Pseudomonas aeruginosa* are two-gram negative bacteria were screened for antibacterial activity. By measuring the zone of inhibition on nutrientagar

medium at the concentration of 100µg/ml.*Candida albicans*, *Aspergillus niger* were screened for antifungal activity by measuring the zone of inhibition by using nutrient medium such as agar plates at the concentrations of 100µg/ml. Nutrient agar mediumwas a culture medium, DMSO(Dimethylsulphoxide) was a solvent used as control for antimicrobial activity. Amongst all methoxy substituted derivatives resulted in higher activity than the standard drug Streptomycin and Griseofulvin.[19]

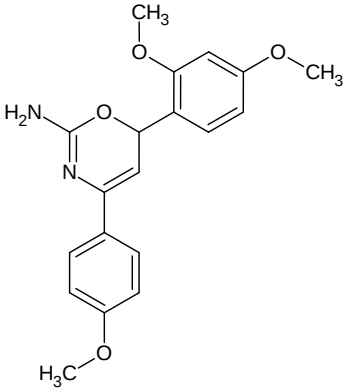


6-chloro-2,4-diphenyl-3,4-dihydro-2*H*-1,3-benzoxazines derivatives

Table4: Antimicrobial activity

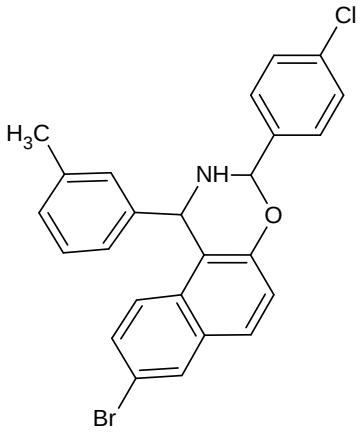
Compound (100µg/ml)	**R_1,R_2**	**Antibacterial**				**Antifungal**	
		Staphylococcus aureus	***Bacillus subtilis***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Candida albicans***	***Aspergillus niger***
a	OCH_3	15	19	17	09	17	15
b	4-Cl	16	13	21	17	07	08
c	2-Cl	14	18	16	17	06	07
d	4-NO_2	15	19	19	18	16	13
Streptomycin	-	17	20	22	19	-	-
Griesofulvin	-	-	-	-	-	21	17

Dhanya*et al.*, reported a series of 4-(4-substiuted phenyl)-6-substituted -6*H*-1, 3-oxazines by Claisen-schmidt condensation of substituted aromatic aldehydes reacted with 4-substituted acetophenones resulted in chalcones [(2*E*)-3-[(substituted phenyl)]-1-[(4-substituted) phenyl prop-2-ene-1- ones. 6-[2, 4- dimethoxyphenyl]-4-(4-methoxyphenyl)-6*H*-1, 3-oxazin -2 amine showed an excellent antibacterial activity against gram +ve bacteria.[20]



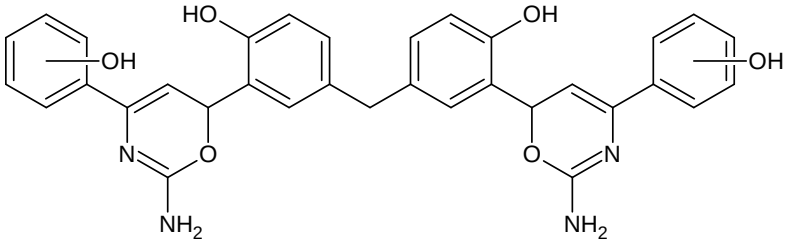
6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-6*H*-1,3-oxazin-2-amine

Mayekar*et al.*, reported a series of 8-bromo -1, 3-bis (aroyl)-2, 3-dihydro-1*H*-naphtho [1, 2- e] [1,3] oxazines. All the synthesized compounds resulted in antibacterial and antifungal activity.Among them, 8-Bromo-1-(3-methylphenyl)- 3-(4-chlorophenyl)-2,3-dihydro-1*H*-naphthol[1,2-e] [1,3]oxazine showed an excellent antimicrobial activity against *Aspergilusflavus*.[21]



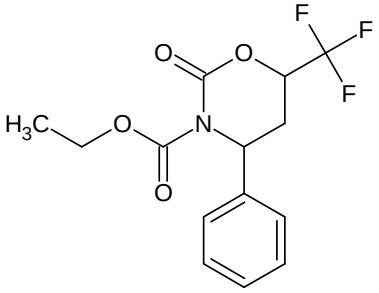
8-bromo-3-(4-chlorophenyl)-1-(3-methylphenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine

Didwagh*et al.,* reported a series of 2-[2-amino-4(4-bromo phenyl)-6*H*-1,3-oxazine-6 yl]-4-{3- [2-amino-4(4-bromo phenyl)-6*H*-1,3- oxazine-6 yl]-4-hydroxy benzyl} phenol derivatives synthesised from bis [3-[(*E*)(4-bromo phenyl)-3-oxa-1-propenyl]-4-hydroxy phenyl] methane with urea and potassium hydroxide in ethanol. All the synthesised compounds showed antibacterial and antifungal activity, among them 4-hydroxy derivatives has greater activity against fungal strains.[22]



2-[2-amino-4(4-bromophenyl)-6*H*-1,3-oxazine-6yl]-4-{3-[2-amino-4(4-b romo phenyl)-6*H*-1,3- oxazine-6 yl]-4-hydroxy benzyl} phenol

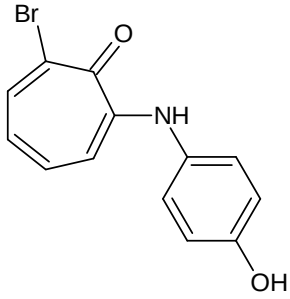
Zanatta*et al.,* synthesized oxazines by reduction and cyclization from enamidoketones resulted in the reaction between beta - alkoxy- CF_3-enones with ethyl carbamate. All the synthesised compounds were showed a significant activity against micro-organisms.[23]



ethyl 2-oxo-4-phenyl-6-(trifluoromethyl)-1,3-oxazinane-3-carboxylate

Tumour-Specific Cytotoxicity:

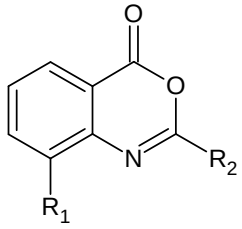
Narita*et al.,* reported twenty benzo[*b*]cyclohept[*e*][1, 4]oxazines and their S-analogs, and 2- aminotropone derivatives. All the synthesised compounds showed moderate tumour-specific cytotoxicity amongst them 7- bromo-2-(4-hydroxyanilino) tropone is more active compound.[24]



2-bromo-7-(4-hydroxyanilino)cyclohepta-2,4,6-trien-1-one

Antiplatelet aggregation activity:

PHsieh*et al.,* reported a series of 2,8-disubstituted benzoxazinones which showed an antiplatelet activity, inhibition of superoxide anion generation and inhibition of neutrophil elastase release method.[25]

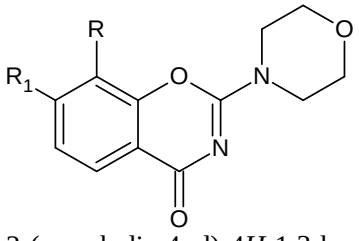


2,8-disubstituted-4*H*-3,1-benzoxazin-4-one

R_1= Cl, OCH_3,CH_3

R_2=C_6H_4Cl, C_6H_4Br, $C_6H_4OCH_3$

KMPritchard*et al.,* synthesised compounds has showed more potent activity than aspirin on AA-induced platelet aggregation. Few 2-morpholino substituted benzoxazines resulted as effective against ADP and collagen induced platelet aggregation.[26]

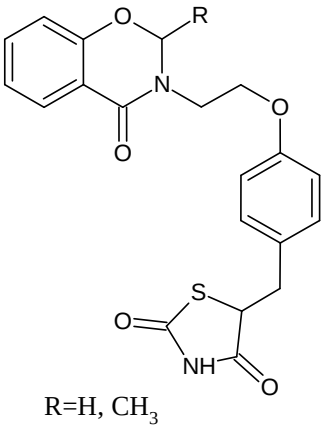


7,8-disubstituted-2-(morpholin-4-yl)-4*H*-1,3-benzoxazin-4-one

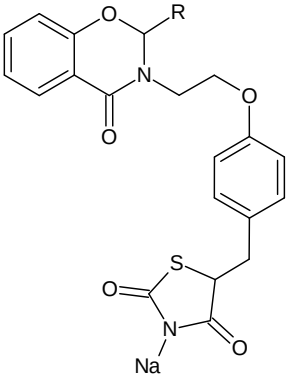
R=H,CH_3; R_1=H,Br,OCH_3

Antidiabetic and hypolipidaemic activity:

GRMadhavan*et al.,* reported a series of 5-[4-[2-[2,3-benzoxazine-4-one-2-yl]-ethoxy]phenylmethyl]thiazolidine-2,4-diones resulted in plasma glucose and plasma triglyceride lowering activity. Few synthesised compounds showed potent dual PPAR activation.[27]



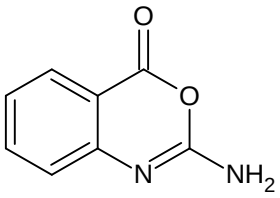
R=H, CH_3



R=H,CH_3

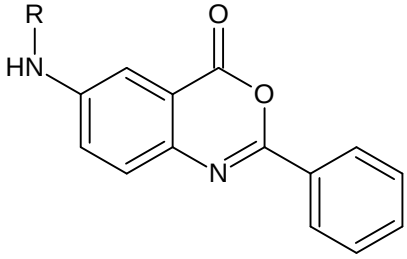
Enzyme inhibitory activity:

UNeumann*et al.,* reported a series of 2-amino substituted benzoxazinones results in inhibition of human CMV protease *in vitro*.[28]



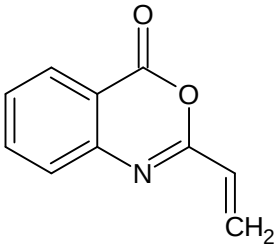
2-amino substituted-4*H*-3,1-benzoxazin-4-one

EColson*et al.,* synthesised a series of 6-amino-2-phenyl-4*H*-3,1-benzoxazin-4-one amino acyl and dipeptidyl derivatives, amino acids and dipeptides are linked to the benzoxazinone by an amide bond and tested for their inhibitory effect towards human leukocyte elastase (HLE). A series of 2-sec-amino-4*H*-3, 1-benzoxazin-4-ones was tested as acyl-enzyme inhibitors of human chymase.[29]



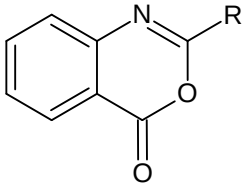
6-amino-2-phenyl-4*H*-3,1-benzoxazin-4-one aminoacyl derivatives

AArcadi*et al.,* synthesised a compound 2-vinyl-4*H*-3,1-benzoxazin-4-one has been tested for its inhibitory activity a human leukocyte elastase.[30]



2-ethenyl-4*H*-3,1-benzoxazin-4-one

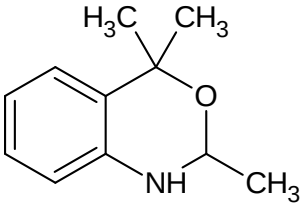
JLGilmore*et al.,* synthesised a series of 2-aryl-4*H*-3,1-benzoxazin-4-ones have been tested for inhibitory activity against C1r serine protease. Among these compounds, few are more equipotent than the reference compound FUT-175.[31]



R=Ph,C_6H_{11}

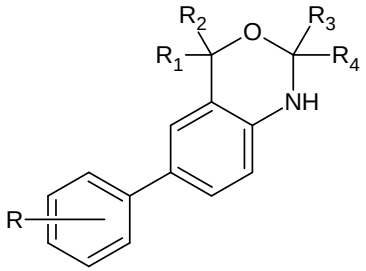
Receptor agonist activity:

P.Zhang*et al.,* synthesised 6-aryl benzoxazines and screened for the activity progesterone receptor modulators. Compound with 2, 4, 4-trimethyl-1,4-dihydro-2*H*-benzo[*d*][1,3]-oxazine core resulted in potent PR agonist activity.[32]



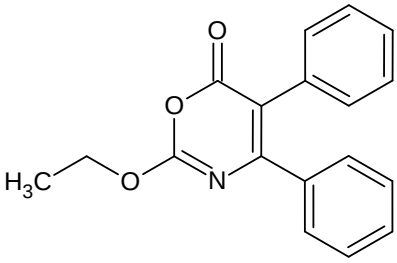
2,4,4-trimethyl-1,4-dihydro-2*H*-3,1-benzoxazine

E.Ward*et al.,* synthesised a series of 5-(piperidinylethyloxy)quinoline benzoxazine-3(4*H*)-ones has screened as 5-HT1 receptor ligands.[33]



R=F, Cl, CN
R_1,R_2=CH_3
R_3=CH_3, CF_3, $CH(CH_3)_2$
R_4=H, CH_3

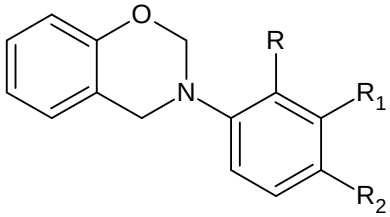
Ansari*et al.,* synthesised 2-ethoxy-4,5-diphenyl- 1,3-oxazine-6-one.Screening of the synthesised compound resulted in increase heat shock proteins Hsp70 and Hsp32 levels. The pre-treatment of the cells with the Ansari *et al.,* synthesised compound alsoincreases the γ-GCS level and antioxidant enzyme activities.[34]



2-ethoxy-4,5-diphenyl-6*H*-1,3-oxazin-6-one

Antitubercular activity:

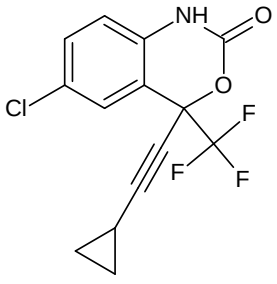
Kamble*et al.,* reported a series of benzo [1,3] oxazine derivatives, few of the synthesised compounds resulted in higher activity more than Rifampicin and Ethambutol against *M. tuberculosis*.[35]



3-(2,3,4-trisubstitutedphenyl)-3,4-dihydro-2*H*-1,3-benzoxazine

Anti-viral activity:

R Gawali*et al.*,reportedthe synthesis, docking studies and biological screening of 2-thiazolyl substituted -2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazines as potent HIV-1 reverse transcriptase inhibitors. Few of these derivatives are more active than (s)-6-chloro-4-cyclopropylethynyl-1,4-dihydro-4-trifluoromethyl-2H-[3,1]-benzoxazin2-one also known as Efavirenz(Sustiva)which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of Human Immunodeficiency Virus (HIV).[36,37]



6-chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one

6. CONCLUSION

Certain [1,3]-oxazine derivatives were reported to have antiplatelet aggregation, antitubercular, anti-inflammatory, antidiabetic, hypolipidemic, antimycobacterial, antibacterial, antifungal, anticoagulant, antioxidant, and cytotoxic activities. It can be noted that 1,3-oxazine derivatives can be synthesised in several ways.Thusthis review article include various methods of synthesis and the physiological activities.

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