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Review

Pharmacological Profile of Oxazine and its Derivatives: A Mini Review

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ABSTRACT

Oxazine derivatives are significant class of heterocycle compounds, which has involved much synthetic attention due to their extensive variety of pharmacological 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, progress of drug resistance is a most important difficulty 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 expect that this effort will be a specific interest for researchers concerned with oxazine derivatives.

Keywords: Benzoxazines, Oxazine, Biological activities

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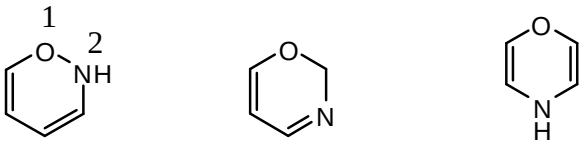
Introduction

Oxazines have interest for the past three decades and still little studied on these 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].



(Fig.1) 1,2-oxazine 1,3-oxazine 1,4-oxazine

Aromatic oxazine compounds were first prepared in 1944 by Holly and Cope by Mannich reactions method. 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 colorless liquid, which is miscible with water [3]. Oxazine heterocycles have extraordinary attention because they comprise a vital class of synthetic and natural compounds 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.

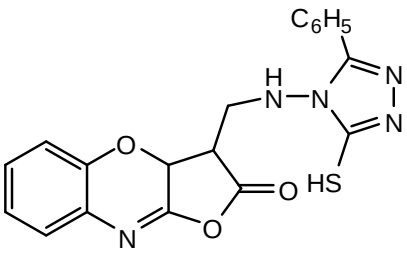
The 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one (DIBOA) and 2,4-dihydroxy-7-methoxy-(2H)-1,4-benzoxazin-3(4H)-one (DIMBOA), benzoxazine analogs have concerned the interest of phyto-chemists. These have significant heterocyclic system for the preparation of biologically active agents varying from fungicides and herbicides to usable drugs [5,6]. Several oxazine derivatives are used for the development of potential new drugs. The usefulness of the oxazine ring, in addition to its virtual chemical ease and convenience, makes these chemicals amongst the most hopeful sources of bioactive compounds. This led to the discovery of a large variety of compounds that are interest from the antiplatelet, antitumour antimicrobial, antitubercular, antidiabetic and antidepressant activities among others and various other valuable chemical and pharmacological activities [7-13].

Biological Potential Of Oxazine Derivatives:

Benzoxazine and its various derivatives are used in organic synthesis for preparation of synthetic and naturally compounds and have been utilized as suitable structural moieties for the design of pharmacologically active compound. The information on the most active benzoxazine derivatives have been showed substantial pharmacological activities loke antimicrobial, antitubercular, anti-diabetic, anti-hypolipidaemic and antidepressant. It is used as an important tool for chemists to develop new and effective benzoxazine derivatives that may prove to be better compounds in efficacy and safety [5,6].

Antimicrobial activity:

Some derivative of [1,4] oxazin-2-one (**1**), Mannich bases were prepared from 3,3a-Dihydro-benzo(b)furo(2,3-e)[1,4]oxazine-2-one with substituted aromatic amines and amino triazoles. All compounds were potential lead compounds in antitubercular, antibacterial and antifungal studies [14]. A series of [6-(p-substituted aminophenyl)-4-(p-substituted phenyl)-6H-1,3-oxazin-yl]-acetamides prepared by claisen-schmidth condensation. The synthesised compounds were showed antimicrobial activity. Among these chloro substituted 1,3-oxazinyl acetamide derivative (**2**) was found to have a strong antibacterial and antifungal activity[15].



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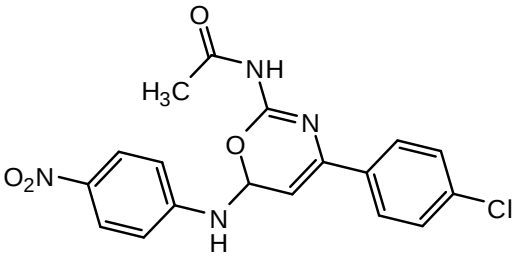
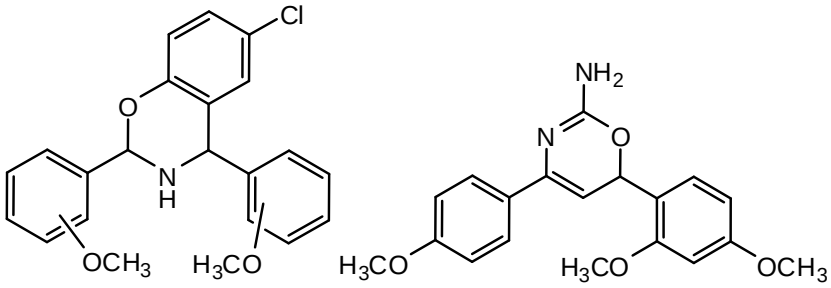


2

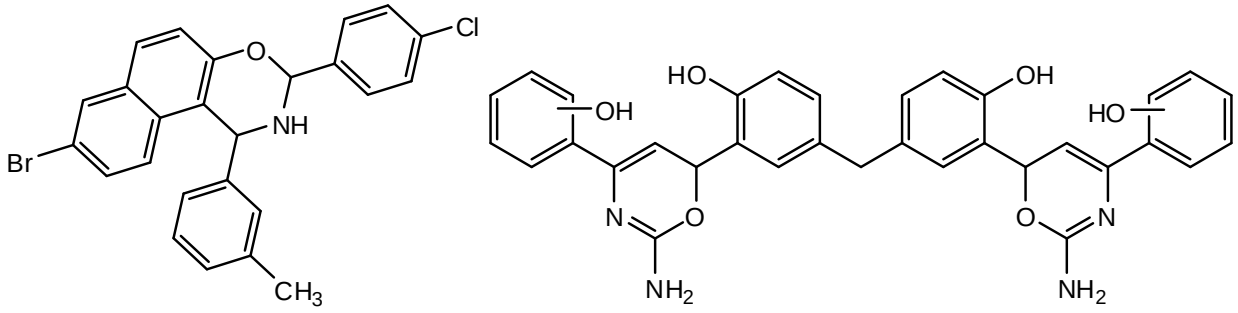
A series of 6-chloro-2,4-diphenyl-3,4-dihydro-2H-1,3-benzoxazine derivatives (**3**) were prepared from p-chlorophenol and substituted aromatic aldehyde in methanolic ammonia solution. They are screened for their antimicrobial activities. Among these compounds methoxy substituted derivatives have more antimicrobial activity than standard drugs [16] A series of 4-(4-substiuted phenyl)-6-substituted-6H-1,3-oxazines from acid catalysed reaction. The Claisen-schmidt condensation reaction of 4-substituted acetophenones with substituted aromatic aldehydes gives chalcones [(2E)-3-[(substituted phenyl)]-1-[(4-substituted) phenyl prop-2-ene-1-ones. Some oxazine derivatives were prepared 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 (**4**) against gram +ve bacteria [17].



3 **4**

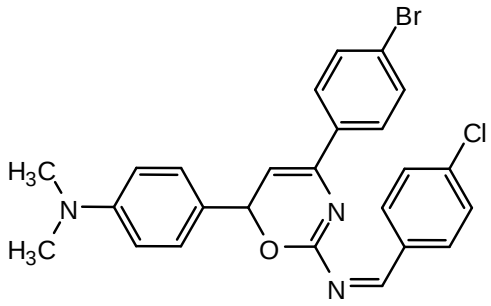
A series of 8-bromo-1,3-bis(aroyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazines, 6-bromo-naphthol undergoes a ring closure reaction with substituted heteroaryl and aryl aldehydes to give napthoxazine analogs. The compounds were screened for their antibacterial and antifungal activity. Those compounds having chloro, fluoro and methyl substituted phenyl ring attached to naphthoxazine were exhibited potential 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 (**5**) exhibited good activity against Aspergilus flavus [18]. A series of 2-[2-amino-4(4-bromo phenyl)-6H-1,3-oxazine-6-yl]-4-{3-[2-amino-4(4-bromophenyl)-6H-1,3-oxazine-6 yl]-4-hydroxy benzyl}phenol derivatives (**6**) were formed from bis[3-[(E)(4-bromo phenyl)-3-oxa-1-propenyl]-4-hydroxyphenyl]methane with urea and ethanolic potassium hydroxide. These compounds were evaluated for their antibacterial and antifungal activity. Among these 4-hydroxy derivatives has more activity against fungal strains [19].



5 **6**

Some Schiff bases of 1,3-oxazines from 4-bromo acetophenone and substituted aromatic aldehyde reacted with sodium hydroxide to give substituted chalcones. These substituted chalcones reacted with urea and give 4-(4-bromo phenyl)-6-(substituted phenyl)-6H-1,3-oxazine-2-amine derivatives. These compounds were reacted with substituted arylaldehydes to give 4-(4-

bromophenyl)-6-(substitutedphenyl)-2-{[(1E)(substitutedphenyl)methylidenene]}-6H-1,3-oxazine-amine and were screened for their antimicrobial activity. The compound 4-(4-bromo-phenyl)-6-(N,N-dimethylaminophenyl)-N-[(E)(4-chlorophenyl) methylidene]-6H-1,3-oxazin-2-amine (**7**) were found to be most active antimicrobial compounds [20]. 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 (**8**). They exhibited significant activity against tested microorganism strains [21].



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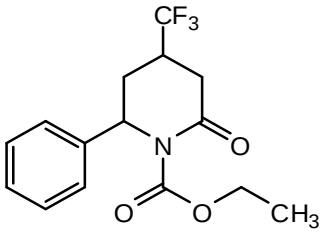
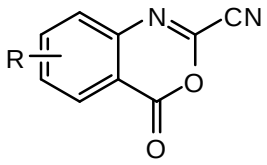
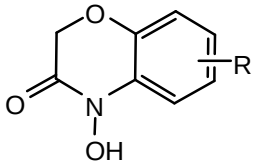


8

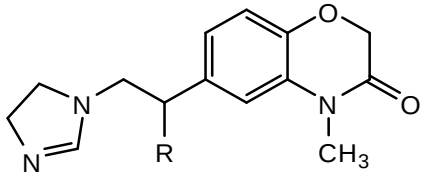
Novel 1, 3-benzoxazinones **(9)** has been tested for their in vitro antibacterial activity against Gram negative (G-ve) bacteria and Gram positive (G +ve) bacteria and antifungal activity of some derivatives were also studied [22] against Candida albicans ATCC 10231, C. glabrata DSM 6425 and C. tropicalis DSM 1346. Some 4-hydroxy-2H-1,4-benzoxazin-3(4H)-ones **(10)** were tested for their antimicrobial activities against S. aureus, E. coli and C. albicans. However, chloro substituted derivatives were exhibited better activity than others [23]. Among them, compounds having long alkyl chain on the 2- position of the benzoxazine ring were exhibited good antifungal activity. The 1,4-benzoxazine imidazole derivatives **(11)** were tested for their possible antifungal activity. These compounds mainly showed in vivo activity against candidiasis [24]. The 1,4 benzoxazine derivatives were exhibited immunomodulating activity. The ethyl-3, 4-dihydro-3-oxo-4,6,7-trisubstituted-2H-1,4-benzoxazine-2-acetate derivatives **(12)** [25] were showed antimicrobial activity against different G+ve, G-ve bacteria and some Candida species in comparison to reference drugs. A series of 1,2-bis(3,4-dihydrobenzo[e][1,3]oxazin-3(4H)-yl) ethane derivatives **(13)** were [26] tested in vitro antimicrobial activity against six pathogenic fungi, two G-ve and two G+ve bacteria. Some of the compounds have shown significant in vitro antimicrobial activity.



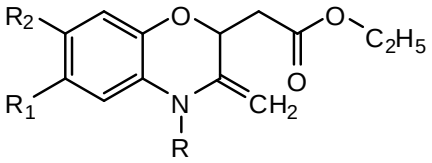
9 R = H, Cl



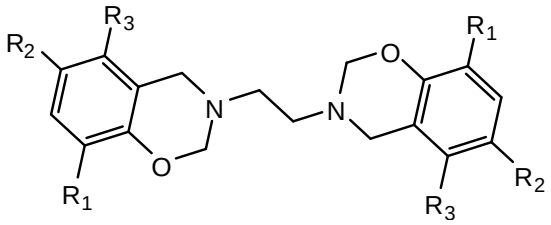
10 R = Cl. F, OCH_3 R_1= CH_3, C_2H_5



11 R = OH, OC_6H_4Cl



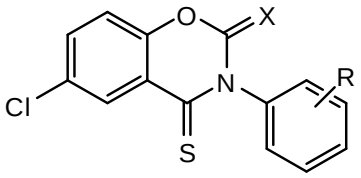
12 R= H, CH_3, C_2H_5



13 R_1,R_2,R_3= H,Cl, CH_3

R_1= H, Cl, CH_3, R_2= H, NO_2

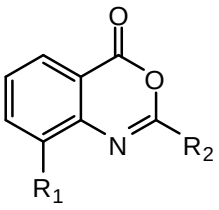
Series of 6-choloro-3-phenyl-4-thioxao-2H-1,3-benzoxazine-2(3H)-ones and 6-choloro-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-diones **(14)** were exhibited in vitro activity against Mycobacterium tuberculosis, M. kansasii and M. avium better than or comparable to reference drug Isoniazid [27].

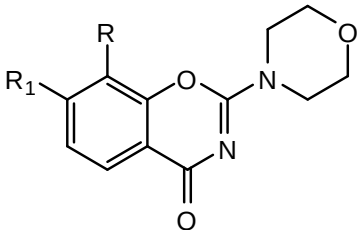


14 X = O, S R = H, CH_3, Cl

Antiplatelet aggregation activity:

A series of 2,8-disubstituted benzoxazinones **(15)** were tested as antiplatelet aggregation, inhibition of superoxide anion generation and inhibition of neutrophil elastase release method [28]. All of these compounds were more potent than aspirin on AA-induced platelet aggregation. Some 2-morpholino substituted benzoxazines **(16)** were effective against ADP and collagen induced platelet aggregation [29].



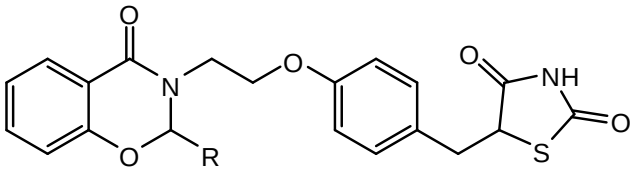


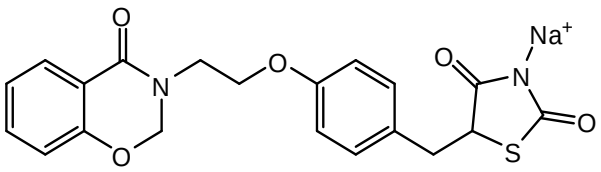
15 R_1= Cl, OCH_3, CH_3 **16** R=H,CH_3; R_1=H, Br.OCH_3

R_2= C_6H_4Cl, C_6H_4Br, $C_6H_4OCH_3$

Antidiabetic and hypolipidaemic activity:

A series of 5-[4-[2-[2,3-benzoxazine-4-one-2-yl]-ethoxy]phenylmethyl]thiazolidine-2,4-diones **(17)** exhibited plasma glucose and plasma triglyceride lowering activity. The 2,4-thiazolidinedione derivatives of 1,3-benzoxazinone were tested for antidiabetic and hypolipidaemic potential. The DRF-2519 **(18),** a thiazide (TZD) derivative of benzoxazinone has shown potent dual PPAR activation [30].

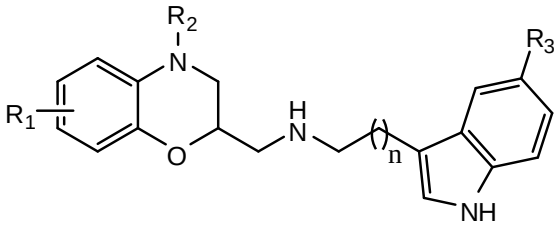


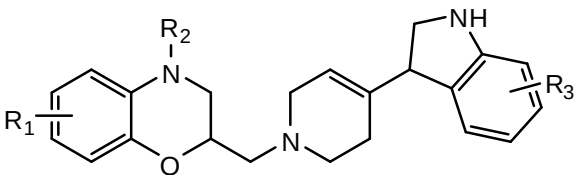


17 R = H, CH_3 **18** DRF 2519

Antidepressant activity:

Two new classes of benzoxazine 3-indole alkyl amines **(19)** and benzoxazine 3-indole tetrahydropyridine analogs **(20)** can be utilized to embrace both the 5-HT1A pharmacophore along with the SSRI and 5-HT1A receptor activities. The selectivity over α1 receptor was improved in some compounds. Most of the compounds in these two classes were act as 5-HT1A receptor agonists [31].



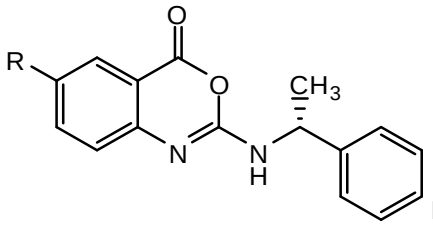


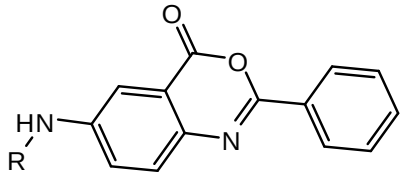
19 R_1,R_2,R_3=H, OCH_3, Cl **20** R_1= H, OCH_3; R_2= H, CH_3, C_2H_5; R_3=H,F

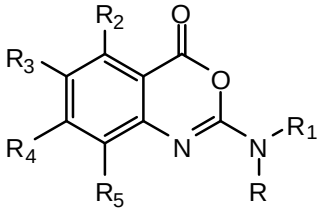
Enzyme inhibitory activity:

A series of 2-amino substituted benzoxazinones **(21)** were potentially inhibits human CMV protease in vitro [32]. A series of 6-amino-2-phenyl-4H-3,1-benzoxazin-4-one amino acyl and

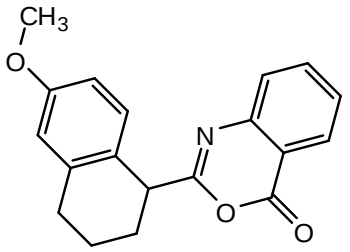
dipeptidyl derivatives **(22),** amino acids and dipeptides are linked to the benzoxazinone by an amide bond [33] and tested for their inhibitory effect towards human leukocyte elastase (HLE). A series of 2-sec-amino-4H-3, 1-benzoxazin-4-ones **(23)** was tested as acyl-enzyme inhibitors of human chymase [33]. The 2-vinyl-4H-3, 1-benzoxazin-4-one **(24)** has been tested for their inhibitory activity a human leukocyte elastase [34]. A series of 2-substituted benzoxazinones **(25)** were exhibited significant anti-human corona virus and ICAM-1 expression inhibition [35]. A series of 2-aryl-4H-3,1-benzoxazin-4-ones **(26)** have been tested for inhibitory activity against C1r serine protease. Among these compounds, some were more equipotent than the reference compound FUT-175 **(27)** [36].

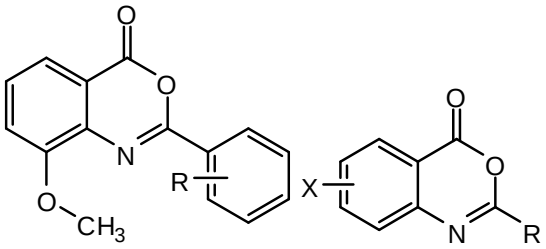


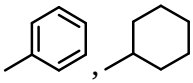


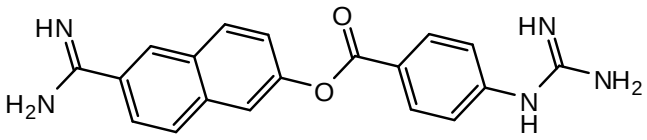


21 R = H, CH_3, C_6H_5 **22** R=H, CH_3CO, Ala, Phe **23**R,R_1,R_2,R_3,R_4,R_5=H,CH_3,C_2H_5





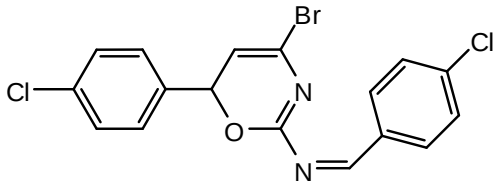
24 **25** R=Cl,Br,F **26** X=H, CH_3; R= 



27 FUT 175

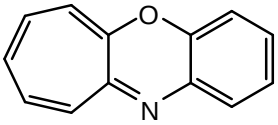
Anticoagulant activity:

A series of Schiff bases of 1,3-oxazines were prepared from 1,3- oxazine-2 amine and substituted benzaldehydes. The most of the compounds were showed considerable anticoagulant effect and the compound 4-(4-Bromophenyl)-6-(4-chlorophenyl)-N [(E)-(4-chlorophenyl)-methylidene]-6H-1,3-oxazin-2-amine (**28**) was the most active compound [37].

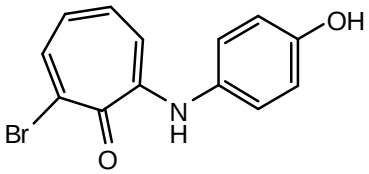


28

Some benzo[b]cyclohept[e][1,4]oxazines, their S-analogs and 2-aminotropone derivatives were tested for their cytotoxic activity against 3 human normal cells and 4 tumour cell lines. All the compounds have moderate tumour-specific cytotoxicity. Among these, 7-bromo-2-(4-hydroxy-anilino)tropone (**29**) was showed the highest activity [38].



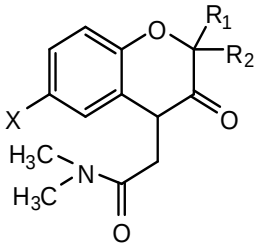
29 benzo[b]cyclohept[e][1,4]oxazine

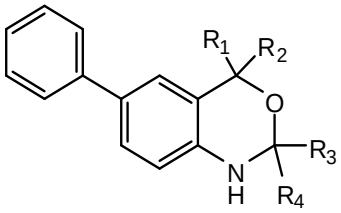


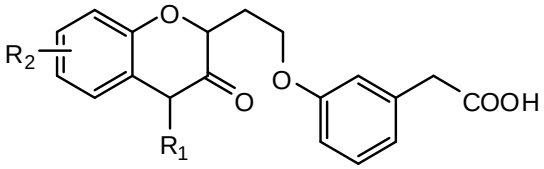
7-bromo-2-(4-hydroxyanilino)tropone

Receptor agonist activity:

The cromakalim (CRK) **(30)** derivatives were showed particular affinity towards potassium ion channel, by replacing benzopyran ring [39], 6-aryl benzoxazines **(31)** were prepared [40] and tested them as progesterone receptor modulators. Compound with 2, 4, 4-trimethyl-1,4-dihydro-2H-benzo[d][1,3]-oxazine core were found most potent PR agonist. A series of benzoxazinones **(32)** were exhibited PPAR agonists activity [41]. The functional agonists in the induction of the aP2 gene in preadipocytes, the potent compound in the series has an EC_{50}=0.5μm. A series of 3-aryl-7-hydroxy benzoxazine analogues **(33)** have been evaluated as ligands for the two estrogen receptor subtypes (ERα and ERβ) [42]. A series of 5-(piperidinylethyloxy)quinoline benzoxazin-3(4H)-ones **(34)** have been tested as 5-HT1 receptor ligands [43]. These compounds exhibited different potent affinity across the 5-HT1A, 5-HT1B and 5-HT1D receptors and selectivity against the serotonin transporter.

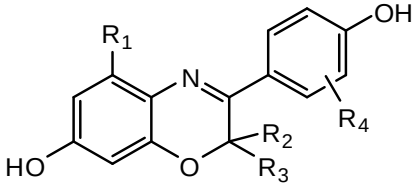


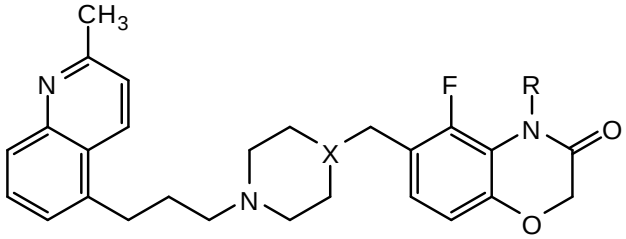




30X=H,Cl,CH_3,NO_2,CN **31**R=F,Cl,CN; R_1,R_2=CH_3 **32**R_1=3-ClBn,4-CH_3Bn,3,4-Cl_2Ph$(CH_2)_2$

R_1, R_2= H,CH_3 R_3=CH_3, CF_3, $CH(CH_3)_2$ R_4=H, CH_3 R_2= H, 7-F, 7-CH_3



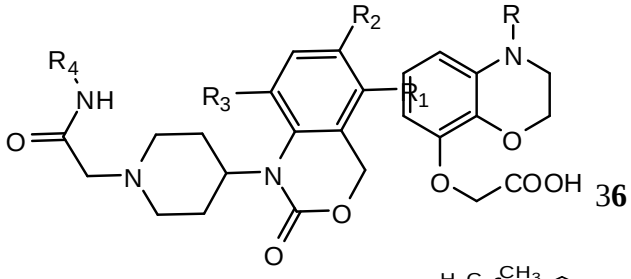


33 R_1= H,OH,CH_3; R_2=H, CH_3, C_2H_5 **34** X= CH, N R =H, CH_3, C_2H_5, C_4H_9

R_3= H, CH_3, -(CH_2CH_2); R_4= H, Br

Receptor antagonist activity:

Some benzoxazinone **(35)** derivatives act as neuropeptide YY5 receptor antagonists [44]. A series of 3,4-dihydro-2H-benzo[1,4]oxazine-8yl-oxyacetic acid derivatives **(36)** were screened to block the TXA2 receptor and found as antithrombotic and avoiding hypotensive side actions [45]. The 6-aryl benzoxazine-2-ones **(37)** act as PR modulators, the 6-aryl amino benzoxazinones and compounds with benzoxazine-2-thione were core as PR antagonists [46]. A series of 6-(2,4-diaminopyrimidinyl)-1,4-benzoxazin-3-ones (**38**) were orally bioavailable molecule inhibitors as rennin. Compounds with a 2-methyl-2-aryl substitution exhibited potent rennin inhibition and good permeability-solubility and metabolic stability [47]. The 8-[2-(4-Aryl-1-piperazinyl) ethyl]-2H-1,4-benzoxazin-3(4H)-ones **(39)** act as highly potent 5-HT1A/B/D receptor antagonists with and without additional serT effect and a exhibited high degree of selectivity over hERG potassium channels [48].



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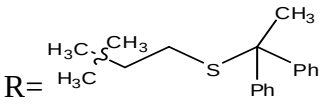
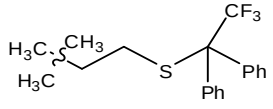
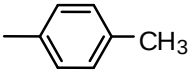
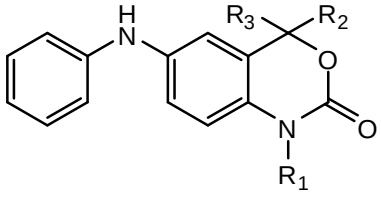




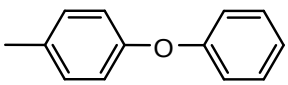
35R_1, R_2=H,Cl; R_3=H,CH_3, OCH_3

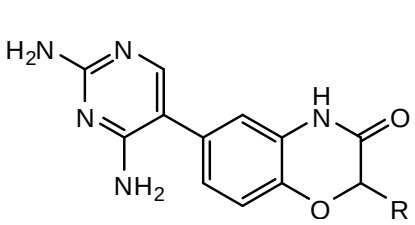
R_4=  ,

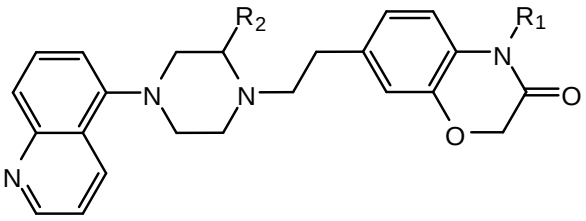


37 R_1,R_2=H, CH_3, C_2H_5

R_3= CH_3, C_2H_5, Thien-2-yl



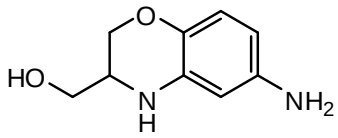




38 R=CH_3, C_2H_5, C_4H_9 **39** R_1=H, CH_3 R_2=CH_3, C_2H_5

Pesticidal activities:

A series of 1,3-Benzoxazines were evaluated for their pesticidal activity [49] and compounds were found to be potential and provides new array of compounds to be developed as pesticides. The 1,4-benzoxazine compounds [50] were protective in tissue culture and neuro-degeneration. A benzoxazine derivative 6-amino-2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine (**40)** [51] could improve the proliferation of human umbilical vein endothelial cells without basic fibroblast growth factor and serum.



40

Conclusion:

Oxazine and related heterocyclic compounds were reported to have antitubercular, 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. The alterations on benzoxazine moiety exhibited important pharmacological activities and these alterations can be employed to development of potentially active compounds in future. Therefore, the operation to explore many more alterations on benzoxazine ring needs to be carrying on.

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