



J. Chem. Pharm. Res., 2010, 2(4):309-316

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Pharmacological Profile of Benzoxazines: A Short Review

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ABSTRACT

Benzoxazine and its derivatives are used in organic synthesis for building natural and designed synthetic compounds and they have been frequently utilized as suitable skeletons for the design of biologically active compound. This review covers updated information on the most active benzoxazine derivatives that have been reported to show considerable pharmacological actions such as antimicrobial, antimycobacterial, anti-diabetic, antihypolipidaemic, and antidepressant. It can act as an important tool for chemists to develop newer benzoxazine derivatives that may prove to be better agents in terms of efficacy and safety.

Keywords: Benzoxazine derivatives, antimicrobial, antidepressant, antiplatelet.

INTRODUCTION

Since the first isolation of 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 derivatives have attracted the attention of phytochemists. These have been studied intensively as important heterocyclic system for the synthesis of biologically active compounds ranging from herbicides and fungicides to therapeutically usable drugs. A literature survey identified several benzoxazine derivatives in the development phase as potential new drugs. The versatility of the benzoxazine skeleton, in addition to its relative chemical simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds. This has led to the discovery of a wide variety of compounds that are of high interest from the point of view antimicrobial, antimycobacterial, antidiabetic and antidepressant effects among others.

Antimicrobial activity

Novel 1, 3-benzoxazinones (**1**) has been synthesized by Besson et al. [1] and their antibacterial *in vitro* activity of some derivatives was evaluated against gram -ve bacteria and gram +ve bacteria.

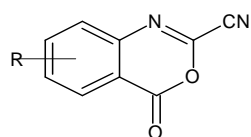
The antifungal activity of some derivatives was also studied. The experiments were performed with the following pathogenic strains: *Candida albicans* ATCC 10231, *C. glabrata* DSM 6425 and *C. tropicalis* DSM 1346.

Some 4-hydroxy-2*H*-1, 4-benzoxazin-3 (4*H*)-ones (**2**) were synthesized by Ozden *et al.* [2]. The compounds were screened for their antimicrobial activities against *S. aureus*, *E. coli* and *C. albicans*. However, on the whole, chloro substituted derivatives exhibited better activity than others. Among them, compounds having long alkyl chain on the 2 - position of the benzoxazine ring showed good antifungal activity.

Fringuelli *et al.* [3] have synthesized 1, 4-benzoxazine imidazole derivatives (**3**) and examined their possible antifungal activity. The synthesized compounds mainly showed *in vivo* activity against a murine experimental model of candidiasis but that very often lacked *in vitro* activity. Moreover, 1, 4 benzoxazine derivatives also showed immunomodulating activity.

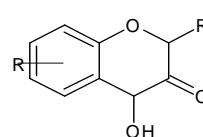
New ethyl-3, 4-dihydro-3-oxo-4, 6, 7-trisubstituted-2*H*-1, 4-benzoxazine-2-acetate derivatives (**4**) were synthesized by Alper-Hayta *et al.* [4]. Antimicrobial activity of the compounds was investigated by using the method of two-fold serial dilution technique against different gram +ve, gram -ve bacteria and some *Candida* species in comparison to standard drugs.

A series of 1,2-bis (3,4-dihydrobenzo[e][1,3]oxazin-3(4*H*)-yl)ethane derivatives (**5**) was synthesized by Mathew *et al.* [5] through an eco-friendly Mannich type condensation-cyclization reaction of phenols or naphthols with formaldehyde and primary amines in water at ambient temperature. Preliminary *in vitro* antimicrobial activity of the synthesized compounds was assessed against six pathogenic fungi, two Gram-negative and two Gram-positive bacteria. Some of the screened compounds have shown significant *in vitro* antimicrobial effect.



R = H, Cl

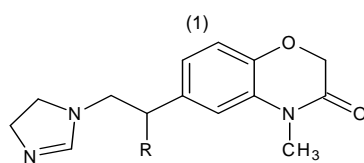
(1)



R = Cl, F, OCH₃

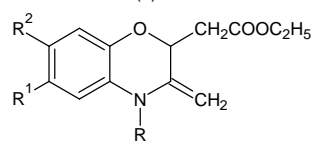
R¹ = CH₃, C₂H₅

(2)



R = OH, OC₆H₄Cl

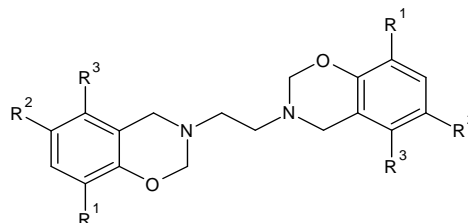
(3)



R = H, CH₃, C₂H₅ R¹ = H, Cl, CH₃

R² = H, NO₂

(4)

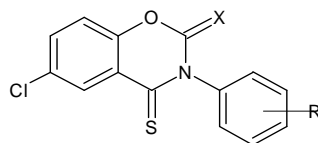


R¹, R², R³ = H, Cl, CH₃

(5)

Antimycobacterial activity

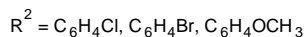
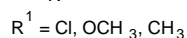
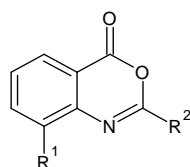
A series of 6-chloro-3-phenyl-4-thioxo-2H-1,3-benzoxazine-2(3H)-ones and a series of 6-chloro-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-diones (**6**) were synthesized by Waisser *et al.* [6]. Compounds exhibited *in vitro* activity against *Mycobacterium tuberculosis*, *M. kansasii* and *M. avium* better than or comparable to that of isoniazid.



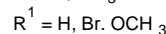
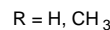
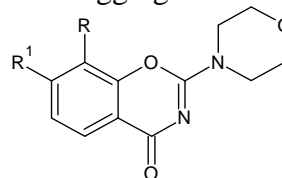
(6)

Antiplatelet aggregation activity

A series of 2, 8-disubstituted benzoxazinones (**7**) were synthesized by Hsieh *et al.* [7] and subjected to antiplatelet aggregation, inhibition of superoxide anion generation and inhibition of neutrophil elastase release assays. All of the synthesized compounds were more potent than aspirin on AA-induced platelet aggregation.



(7)

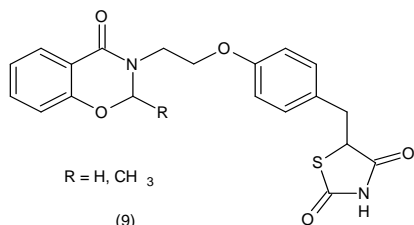


(8)

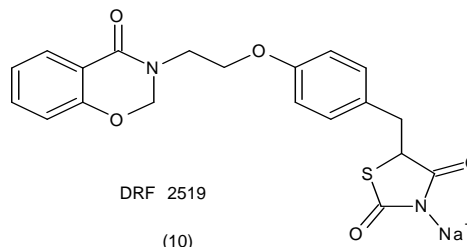
Pritchard *et al.* [8] prepared a number of 2-morpholino substituted benzoxazines (**8**) in order to test their effectiveness against ADP and collagen induced platelet aggregation.

Antidiabetic and hypolipidaemic activity

Madhavan *et al.* [9] reported the synthesis of a series of 5-[4-[2-[2, 3-benzoxazine-4-one-2-yl]ethoxy]phenyl methyl]thiazolidine-2, 4-diones (**9**) and their plasma glucose and plasma triglyceride lowering activity. Later on, they have also synthesized 2, 4-thiazolidinedione derivatives of 1, 3-benzoxazinone and evaluated them for antidiabetic and hypolipidaemic potential. DRF-2519 (**10**), a compound obtained through SAR of TZD derivatives of benzoxazinone, has shown potent dual PPAR activation.



(9)

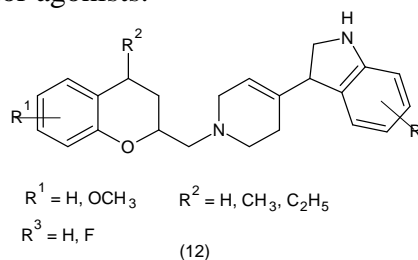
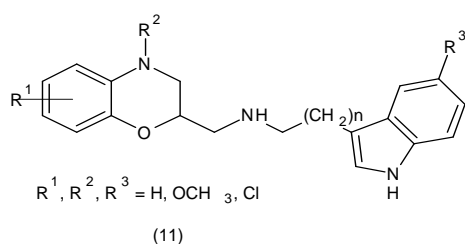


(10)

Antidepressant activity

Zhou *et al.* [10] reported the synthesis and SAR of two new classes of benzoxazine 3-indole alkyl amines (**11**) and benzoxazine 3-indole tetrahydropyridine analogs (**12**). They have discovered that the benzoxazine moiety can be utilized to embrace both the 5-HT_{1A} pharmacophore along with the SSRI and 5-HT_{1A} receptor activities. The selectivity over α 1

receptor was improved in several compounds, though most of the compounds in these two classes were found to function as 5-HT_{1A} receptor agonists.



Enzyme inhibitory activity

A series of 2-amino substituted benzoxazinones (**13**) were prepared by Neumann *et al.* [11] that potentially inhibits human CMV protease *in vitro*.

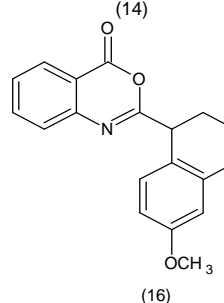
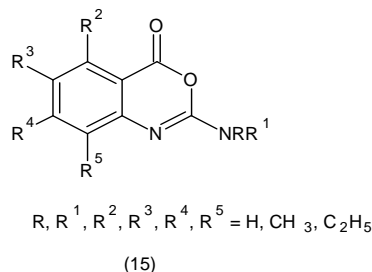
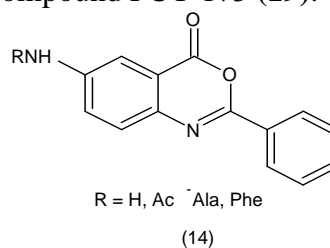
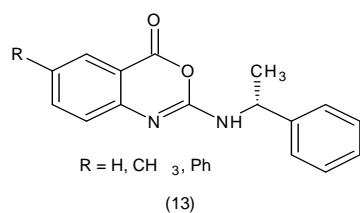
A series of 6-amino-2-phenyl-4*H*-3, 1-benzoxazin-4-one amino acyl and dipeptidyl derivatives (**14**) in which aminoacids and dipeptides are linked to the benzoxazinone moiety via an amide bond were synthesized by Colson *et al.* [12] and tested for their inhibitory activity towards human leukocyte elastase (HLE).

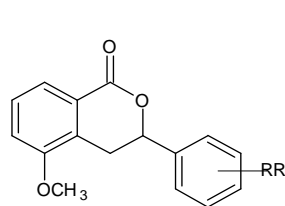
A series of 2-sec-amino-4*H*-3, 1-benzoxazin-4-ones (**15**) was evaluated by Neumann *et al.* [11] as acyl-enzyme inhibitors of human chymase.

The title 2-vinyl-4*H*-3, 1-benzoxazin-4-one (**16**) has been synthesized by Arcadi *et al.* [13] and tested for their inhibitory activity a human leukocyte elastase.

A series of 2-substituted benzoxazinones (**17**) were synthesized by Hasieh *et al.* [14] that showed significant effect to anti-human corona virus and ICAM-1 expression inhibition.

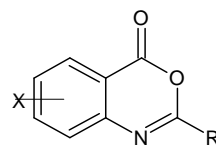
A series of 2-aryl-4*H*-3, 1-benzoxazin-4-ones (**18**) have been synthesized by Gilmore *et al.* [15] and tested for inhibitory activity against C1r serine protease. Among the synthesized compounds, some were more equipotent than the reference compound FUT-175 (**19**).





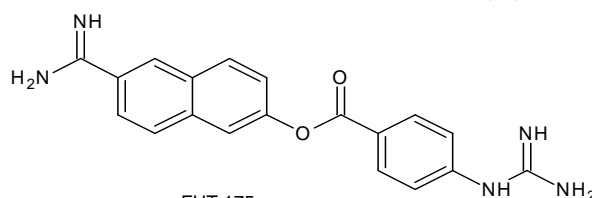
R = Br, Cl, F

(17)

X = H, CH₃

R = Ph,

(18)



FUT 175

(19)

Receptor agonist activity

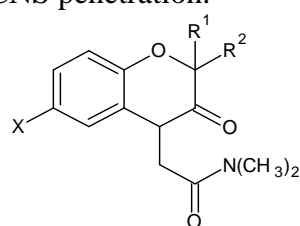
Caliendo *et al.* [16] has synthesized derivatives of cromakalim (CRK) (**20**), an important molecule which shows specific affinity towards potassium ion channel, by replacing benzopyran ring of this reference.

Novel 6-aryl benzoxazines (**21**) were prepared by Zhang *et al.* [17] and examined them as progesterone receptor modulators. Compound with 2, 4, 4-trimethyl-1, 4-dihydro-2*H*-benzo[d][1, 3] oxazine core were found to be most potent PR agonist.

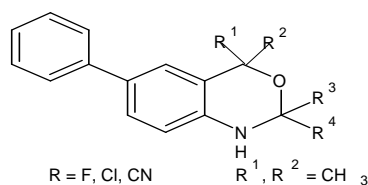
A series of benzoxazinones (**22**) were synthesized as PPAR agonists by Rybczynski *et al.* [18]. The compounds were tested as functional agonists in the induction of the *aP2* gene in preadipocytes, and the most potent compound in the series has an EC₅₀ = 0.5 μm.

A series of 3-aryl-7-hydroxy benzoxazine analogues (**23**) have been prepared and evaluated as ligands for the two estrogen receptor subtypes (ER α and ER β) by Yang *et al.* [19].

A series of 5-(piperidinyloxy) quinoline benzoxazin-3 (4*H*)-ones (**24**) have been studied by Ward *et al.* [20] as 5-HT₁ receptor ligands. These new compounds display a different pharmacological profile with potent affinity across the 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors and selectivity against the serotonin transporter. Furthermore, they have improved pharmacokinetic profiles and CNS penetration.

X = H, Cl, CH₃, NO₂, CNR¹, R² = H, CH₃

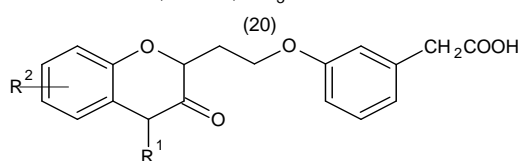
(20)



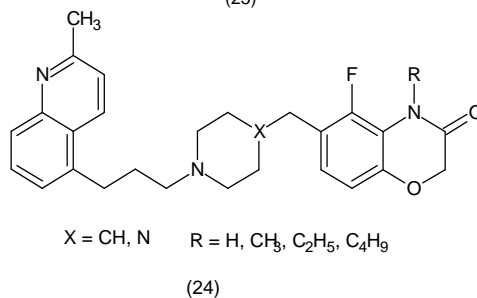
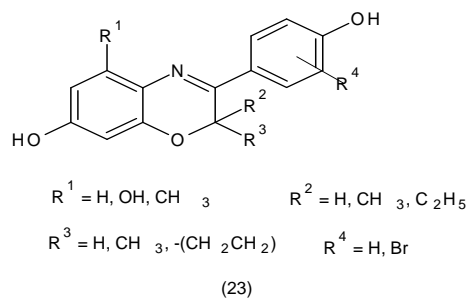
R = F, Cl, CN

R¹, R² = CH₃R³ = CH₃, CF₃, CH(CH₃)₂R⁴ = H, CH₃

(21)

R¹ = 3-ClBn, 4-CH₃Bn, 3,4-Cl₂Ph(CH₂)₂R² = H, 7-F, 7-CH₃

(22)



Receptor antagonist activity

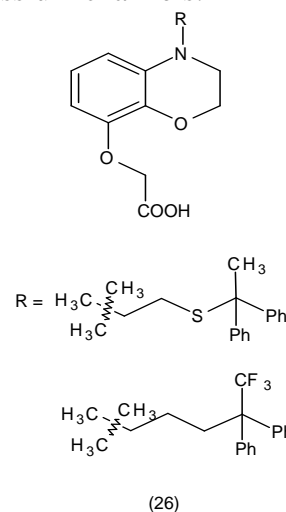
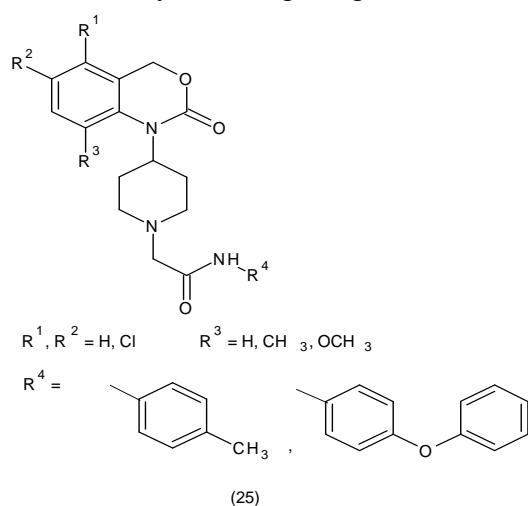
Deswal *et al.* [21] has established the QSAR for 30 benzoxazinone (**25**) derivatives acting as neuropeptide Y Y5 receptor antagonists.

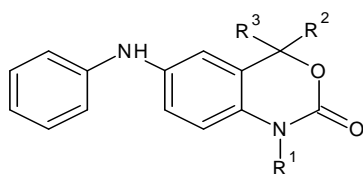
Ohno *et al.* [22] reported the synthesis of a novel series of 3, 4-dihydro-2*H*-benzo [1, 4]oxazine-8-yl-oxyacetic acid derivatives (**26**). The compounds were screened to block the TXA2 receptor and found as a novel treatment in the antithrombotic and the cardiovascular fields avoiding hypotensive side effects.

Kern *et al.* [23] previously reported 6-aryl benzoxazine-2-ones (**27**) as PR modulators. In the continuation of this work, they examined the SAR of new 6-aryl amino benzoxazinones and found the compounds with benzoxazine-2-thione core as PR antagonists.

Powell *et al.* [24] reported the design and synthesis of a series of 6-(2, 4 diaminopyrimidinyl)-1, 4-benzoxazin -3-ones (**28**) as orally bioavailable small molecule inhibitors as rennin. Compounds with a 2-methyl-2-aryl substitution pattern exhibit potent rennin inhibition and good permeability-solubility and metabolic stability.

Bromidge *et al.* [25] have identified 8-[2-(4-Aryl-1-piperazinyl) ethyl]-2*H*-1, 4-benzoxazin-3(4*H*)-ones (**29**) as highly potent 5-HT1A/B/D receptor antagonists with and without additional serT activity and a high degree of selectivity over hERG potassium channels.

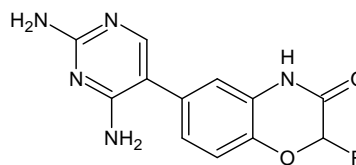




$R^1, R^2 = H, CH_3, C_2H_5$

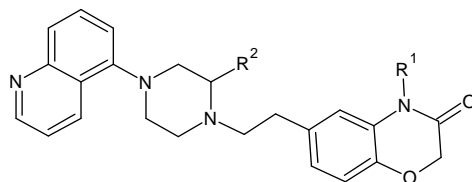
$R^3 = CH_3, C_2H_5, \text{Thien-2-yl}$

(27)



$R = CH_3, C_2H_5, C_4H_9$

(28)



$R^1 = H, CH_3$

$R^2 = CH_3, C_2H_5$

(29)

Current aspects of Benzoxazines

A new series of 1, 3-Benzoxazines were synthesized, characterized (1H NMR and ^{13}C NMR) and evaluated for their pesticidal activity by Shakil *et al.* [26] and the synthesized compounds were found to be promising and provides new array of synthetic chemicals to be utilized as pesticides. Novel 1, 4 benzoxazines compounds have been identified by Wang *et al.* [27] that are protective in tissue culture and in vivo model of neurodegeneration.

Recently a novel benzoxazine deivative 6-amino-2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine (ABO) has been discovered by Dong *et al.* [28] that could improve the proliferation of human umbilical vein endothelial cells (HUVECs) without basic fibroblast growth factor (bFGF) and serum.

CONCLUSION

This has been noticed so far, that the modifications on benzoxazine 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 benzoxazine moiety needs to be continued.

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