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BENZOXAZINE: A BIOLOGICAL STUDY OF BENZOXAZINE AND THEIR DERIVATIVES

Mohd. Rashid* Mahesh Chand and Archana Gupta

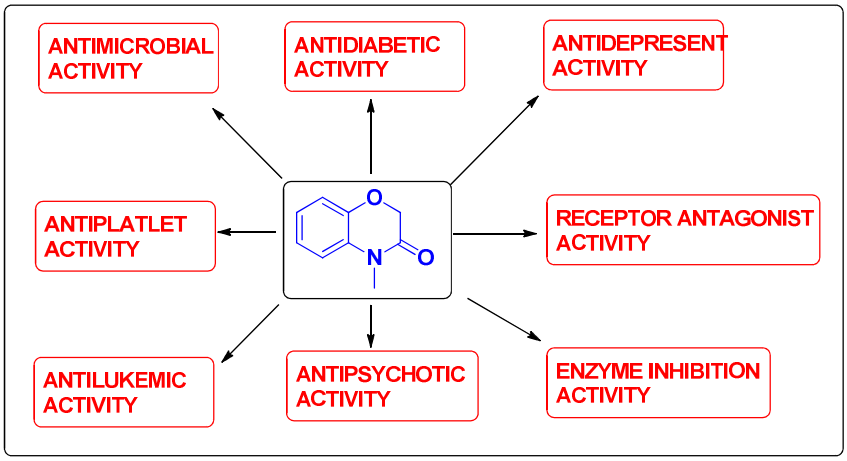
Department of Chemistry, University of Delhi, Delhi-110007
E-mail: mohd.rashid1985@gmail.com

ABSTRACT:
Benzoxazine and its derivatives are frequently utilized as suitable skeletons for the design of biologically active compound due to show their considerable pharmacological actions such as antimicrobial, antimycobacterial, anti-diabetic, antihypolipidaemic, and antidepressant. 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. 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. In this review, the biological activities of benzoxazine have been reported upto date. 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, antibacterial, anticancer and antibiotic activities.

INTRODUCTION

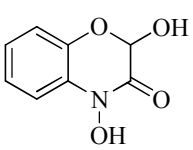
Heterocyclic compounds play a vital role in the search for new drug candidate and are essential to elucidate the chemistry of living processes. Heterocyclic compounds are well recognized for their multifaceted pharmacological behavior and as far as their relationship to medicinal chemistry is concerned, the two areas are almost inseparable. Many modern pharmaceuticals which are in regular therapeutic use are organic compounds that contain heterocyclic moiety.



Among the various heterocyclic systems benzoxazine nucleus holds a prominent place owing to their industrial and pharmaceutical uses. Literature survey revealed benzoxazine and its derivative 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.

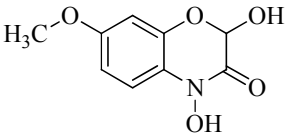
The versatility of the benzoxazine skeleton, in addition to its relative chemical simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds. This has led to the discovery of a wide variety of compounds that are of great interest from the point of view of antimicrobial, antimycobacterial, antidiabetic and antidepressant effects.[I]

Benzoxazine came in the limelight when the first isolation of 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**1**) (DIBOA)[II] and 2,4-dihydroxy-7-methoxy-2*H*-1,4 benzoxazin-3(4*H*)-one (**2**) (DIMBOA)[III] were reported. These compounds have been also isolated from roots and aerial parts of maize plant. It was found that these compounds can be further used for the synthesis of potent herbicidal and fungicidal compounds.



DIBOA

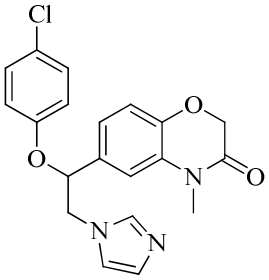
1



DIMBOA

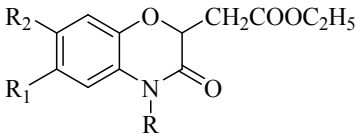
2

Fringuelli *et al.*[IV] have synthesized 6-(1-(4-chlorophenoxy)-2-(1*H*-imidazol-1-yl) ethyl)-4-methyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one **(3)** and evaluated their antibacterial and antifungal activity *in vitro* against gram -ve bacteria, gram +ve bacteria and various pathogenic strains: *Candida albicans* ATCC 10231, *C. glabrata* DSM 6425 and *C. tropicalis* DSM 1346.



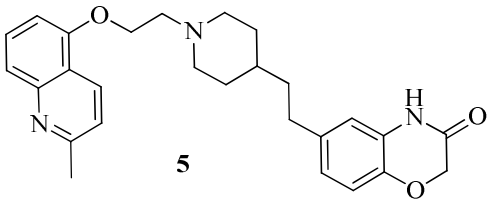
3

New ethyl-3,4-dihydro-3-oxo-4,6,7-trisubstituted-2H-1,4-benzoxazine-2-acetate derivatives (**4a-4c**) were synthesized by Alper-Hayta et al.[V] These compounds were investigated by using two-fold serial dilution technique against different gram +ve, gram -ve bacteria and some Candida species.



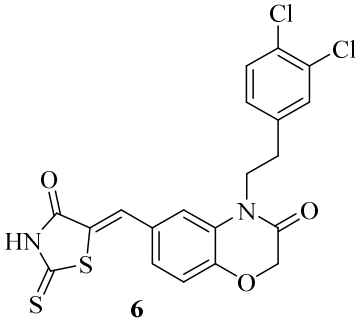
4a R = H, CH_3, C_2H_5
4b R_1 = H, Cl, CH_3
4c R_2 = H, NO_2

Derivative of benzoxazine **5** exhibited high affinities for the 5-HT1A/1B/1D receptors and inhibit the potent serotonin reuptake. It is a suitable candidate for further evaluation *in vivo* with the aim of identifying more effective antidepressant agents.[VI]



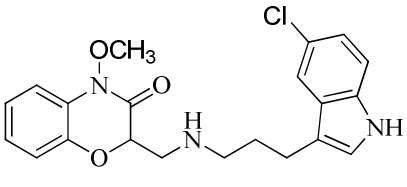
5

Compound(Z)-4-(3,4-dichlorophenethyl)-6-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-2*H*-benzo[b] [1,4]oxazin-3(4*H*)-one (**6**) has been developed as potent inhibitors of PI3Kc in enzymatic and cell based assays. This compound was subsequently profiled *in vivo* an aseptic peritonitis model of inflammatory cell migration and has also shown significant inhibition of neutrophil and monocyte migration to the infected area.[VII]

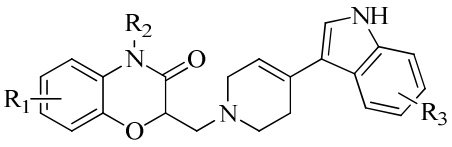


6

Synthesis and SAR study of two new classes of benzoxazine derivatives **7** and other analogs **8a-8c** was also done. It was found that the benzoxazine moiety can be utilized to embrace both the 5-HT1A pharmacophore along with the SSRI and 5-HT1A receptor activities.[VIII]

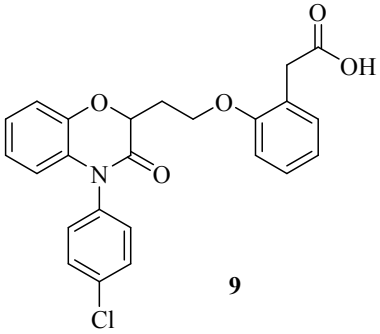


7



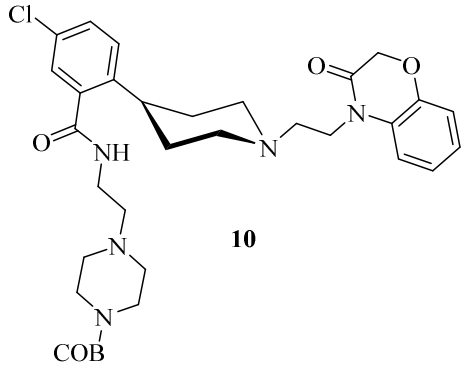
8a R_I = H, OCH_3
8b R_2 = H, CH_3, C_2H_5
8c R_3 = H, F

Compound 2-(2-(2-(4-(4-chlorophenyl)-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-2-yl)ethoxy) phenyl)acetic acid (**9)** was chosen for study early for the SAR work and it was observed that it decrease 27% plasma glucose after 5 days of oral dosing at 30 mg/kg in db/db mice. This compound also had satisfactory metabolic stability in both human liver microsomes and hepatic S9 fraction ($t_{1/2}$>50 min in each), and good oral bioavailability in rats (30 mg/kg, AUC0_24 h =308 mM-h, $t_{1/2}$ = 20 h).[IX]



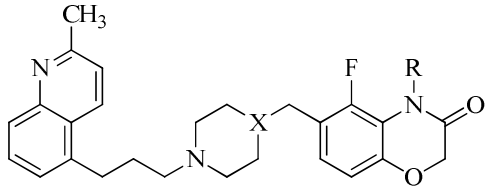
9

Compound **10** was selected for *in vivo* evaluation because it has criteria of excellent potency at both rat and human UT receptors, while the rat (2 mg/kg) showed $t_{1/2}$ = 127 min and C_{max} = 553 ng/ml. This compound was examined in the U-II-induced earflushm model in rats to demonstrate that it could block a U-II-mediated effect.[X]



10

A series of benzoxazine analogues **11** have been prepared and evaluated as ligands for the two estrogen receptor subtypes (ERα and ERβ).[XI]

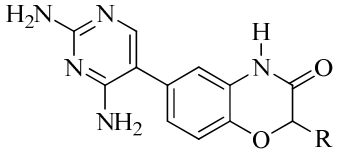


11

X = CH, N

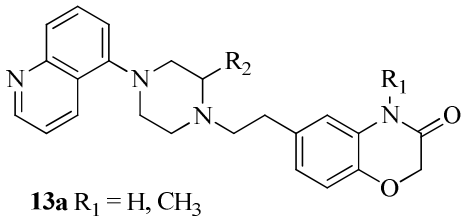
R = H, CH_3, C_2H_5, C_4H_9

Design and synthesis of a series of 6-(2,4 diaminopyrimidinyl)-1,4-benzoxazin-3-ones (**12)** as orally bioavailable inhibitors as rennin have been reported. It was found that compound with 2-methyl & 2-aryl substitution pattern exhibit potent rennin inhibition and good permeability, solubility and metabolic stability.[XII]



12 R = CH_3, C_2H_5, C_4H_9

A series of compounds 8-(2-(4-Aryl-1-piperazinyl) ethyl)-2*H*-1,4-benzoxazin-3(4*H*)-ones **(13a-13b)** were identified as highly potent 5-HT1A/B/D receptor antagonists and showed high degree of selectivity over hERG potassium channels.[XIII]

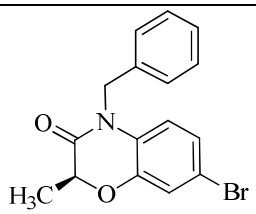
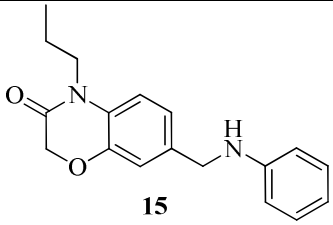


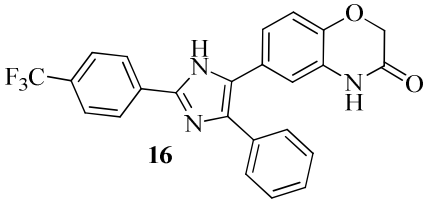
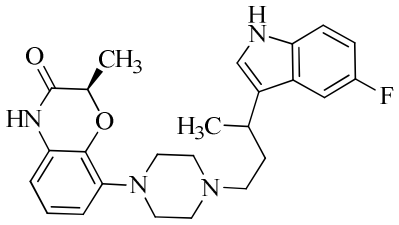
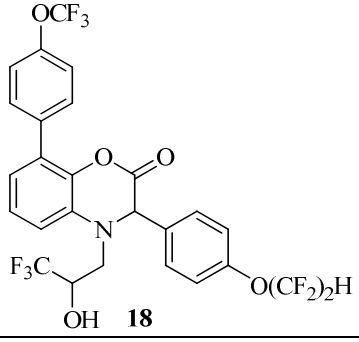
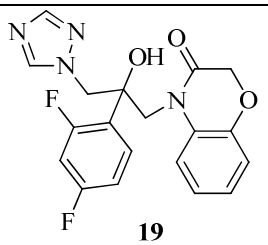
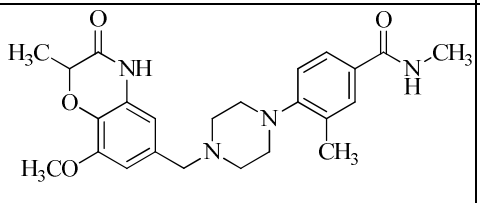
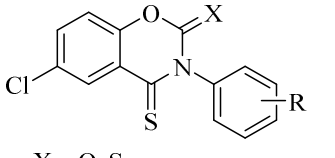
13a R_1 = H, CH_3

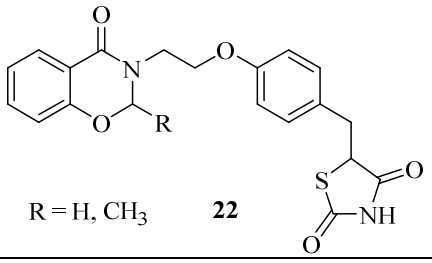
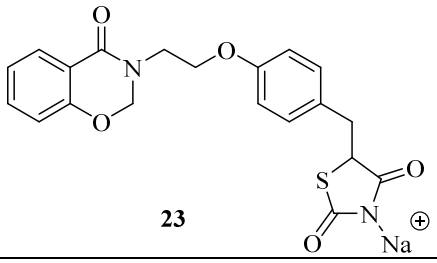
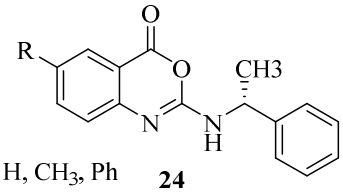
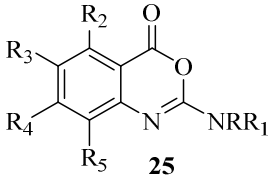
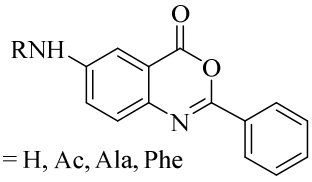
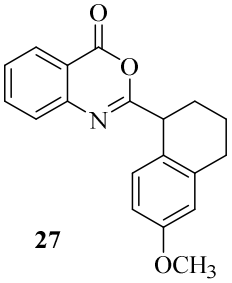
13b R_2 = CH_3, C_2H_5

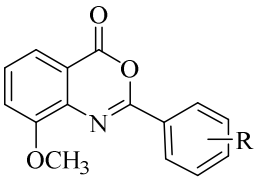
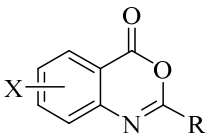
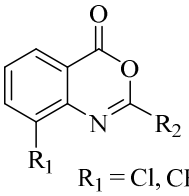
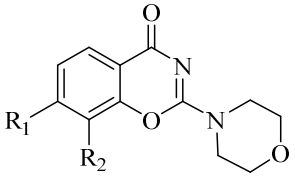
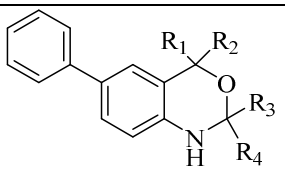
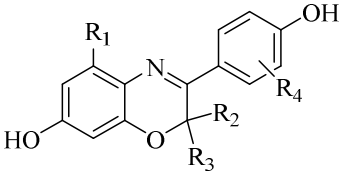
Besides above, some other biologically important benzoxazine containing compounds have been summarized in **Table-II**.

Table-II

S.No.	Compound	Structure	Activity
1	(S)-4-Benzyl-7-bromo-2-methyl-2*H*-benzo[b] [1,4]oxazin-3(4*H*)-one	 **14**	Antifungal[XIV]
2	7-((Phenylamino)methyl)-4-propyl-2*H*-benzo[b] [1,4]oxazin-3(4*H*)-one	 **15**	Antiplatelet aggregation[XV]

S.No.	Compound	Structure	Activity
3	6-(4-Phenyl-2-(4-(trifluoro methyl)phenyl)-1*H*-imidazol-5-yl)-2*H*-benzo[b] [1,4]oxazin-3(4*H*)-one	 **16**	Antileukemic agent[XVI]
4	(2R)-8-(4-(3-(5-Fluoro-1*H*-indol-3-yl)butyl)piperazin-1-yl)-2-methyl-2*H*-benzo[b] [1,4] oxazin-3(4*H*)-one	 **17**	Antipsychotic[XVII]
5	1,1,1-Trifluoro-3-(3-(4-(1,1,2,2-tetrafluoroethoxy) phenyl)-8-(4-(trifluoro methoxy)phenyl)-2*H*-benzo[b][1,4]oxazin-4(3*H*)-yl)propan-2-ol	 **18**	Cholesteryl ester transfer protein inhibitors[XVIII]
6	4-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-2*H*-benzo[b] [1,4] oxazin-3(4*H*)-one	 **19**	Inhibitors of Candida strains[XIX]
7	4-(4-((8-Methoxy-2-methyl-3-oxo-3,4-dihydro-2*H*-benzo[b] [1,4]oxazin-6-yl)methyl) piperazin-1-yl)-*N*,3-dimethyl benzamide	 **20**	Poly(ADP-ribose) polymerase inhibitors[XX]
8	6-Choloro-3-phenyl-4-thioxao-2*H*-1, 3-benzoxazine-2(3*H*)-ones and a series of 6-choloro-3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones	 X = O, S R = H, CH_3,Cl **21**	Antimycobacterial activity[XXI]

S.No.	Compound	Structure	Activity
9	5-[4-[2-[2, 3-Benzo xazine-4-one-2-yl] ethoxy]phenyl methyl] thiazolidine-2,4-diones	 R = H, CH_3 **22**	Plasma glucose and plasma triglyceride lowering activity[XXII]
10	Monosodium(II) mono(2,4-dioxo-5-(4-(2-(4-oxo-2H-benzo[e] [1,3]oxazin-3(4H)-yl) ethoxy)benzyl)thiazolidi n-3-ide)	 **23**	Antidiabetic and hypolipidaemic Potential[XXII]
11	2-Amino substituted benzoxazinones	 R = H, CH_3, Ph **24**	Potentially inhibits human CMV protease[XXIII]
12	2-Sec-amino-4*H*-3, 1-benzoxazin-4-ones	 **25** R, R_1, R_2, R_3, R_4, R_5 = H, CH_3, C_2H_5	Acyl-enzyme inhibitors of human chymase[XXIII]
13	6-Amino-2-phenyl-4*H*-3, 1-benzoxazin-4-one amino acyl and dipeptidyl derivatives	 R = H, Ac, Ala, Phe **26**	Inhibitory activity towards human leukocyte elastase (HLE)[XXIV]
14	2-Vinyl-4*H*-3, 1-benzoxazin-4-one	 **27**	Inhibitory activity a human leukocyte elastase[XXV]

S.No.	Compound	Structure	Activity
15	2-Substituted benzoxazinones	 **28** R = Br, Cl, F	Anti-human corona virus and ICAM-1 expression inhibition[XVI]
16	2-Aryl-4*H*-3, 1-benzoxazin-4-ones	 **29** X = H, CH_3 R = Ph, cyclochexane	Inhibitory activity against C1r serine protease[XVII]
17	2, 8-Disubstituted benzoxazinones	 **30** R_1 = Cl, CH_3, OCH_3 R_2 = PhCl, PhBr, $PhOCH_3$	Antiplatelet aggregation activity[XVIII]
18	2-Morpholino substituted benzoxazines	 R_1 = H, CH_3 R_2 = H, Br, OCH_3 **31**	Effectiveness against ADP and collagen induced platelet aggregation[XXIX]
19	Novel 6-aryl benzoxazines	 R_1, R_2 = CH_3 R_3 = CH_3, CF_3, $CH(CH_3)_2$ **32** R_4 = H, CH_3	Potent Progesterone Receptor agonist[XXX]
20	3-Aryl-7-hydroxy benzoxazine analogues	 R_1 = H, OH, CH_3 R_2 = H, CH_3, C_2H_5 **33** R_3 = H, CH_3, -(CH_2CH_2) R_4 = H, Br	Estrogen receptor subtypes (ERα and ERβ)[XXXI]

CONCLUSION

Benzoxazine and their derivatives have a wide range of biological and pharmacological activities such as anti-tumor, anti-inflammatory, anti-oxidant, anti-bacterial, anti cancer and receptor antagonist. Benzoxazine have become the research hot point based on their different treatment effects to diseases and less damage to normal cells. We have made efforts to summarize various biological activities of benzoxazine, in this communication which will help to gets an efficient way of understanding about biological profile of benzoxazine and which can further aid the process of drug design developments.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests regarding the publication of this paper.

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