Review Article

Biological Potentials of Oxazines as Promising Agents for Drug Discovery - A Short Review

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ABSTRACT

The multifaceted chemical potential of oxazines- a six-membered species containing nitrogen and oxygen in the ring has led to persistent research in the synthetic methodologies. The development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of the synthesis. Nitrogen and oxygen heterocyclic are of special interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity. A survey of biological potentials of oxazines revealed the moiety has attracted a great deal of interest of medicinal chemist, biochemist, and pharmacologist rendered as a lead molecule for designing potential bioactive agents. In the present paper, we have executed information that extends a great deal of help to determine the best and most productive, economical and clinically important compound of oxazine derivatives with antibacterial, antifungal, antimalarial, anticonvulsant, antitubercular, anti-inflammatory, anticancer, antioxidant and neurodegenerative activities.

Keywords: Aspirin; *Bacillus subtilis*; Ethambutol; Minimycin; Oxazines; Platelet aggregation inhibitors; Streptomycin.

INTRODUCTION

Organic compounds play a vital role in modern society and possess varied applications in different fields due to which unabated research has been going on to synthesize new organic compounds including derivatization of naturally occurring ones- nucleic acids, plant alkaloids, some vitamins, proteins, hormones, etc. Synthetic heterocyclic compounds especially containing heteroatoms N, S, O has enormous potential primarily as agrochemicals, drugs, etc. The versatility of the oxazine skeleton, in addition to its relative chemical simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds.[1]

Oxazines are a very important class of heterocyclic compounds, they are classified into three isomeric forms like 1,2 Oxazines, 1,3 Oxazines and 1,4 Oxazines as shown in Fig 1. They are an important class of heterocycles, which has attracted much synthetic interest due to their wide range of biological activities. Oxazine is a heterocyclic compound that 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 a sedative, analgesic, antipyretic, anticonvulsant, antitubercular, antitumor, antimalarial and antimicrobial.

Oxazines are the essential structural constituents for most of the fungicides, herbicides, and broad spectrum bactericides. They are used as fundamental building blocks for many natural products. Using oxazine as synthon, one may be able to reconcile pyrroles pyrrolidine and γ-lactones via the reductive cleavage of C-O and N-O bonds.[2] The synthetic oxazine derivatives are well known for their promising biological properties, for example, D-ribofuranosyl-l,3-oxazin-2,4-dione (Minimycin) is employed as an antitumor agent, while 3H-1,3-oxazine-2,6-dione as a suicide inactivator of serine proteases as shown in Fig 2. Due to their enormous biological significance, these compounds could be employed for the development of new chemical entities to combat various diseases. The purpose of this review was to collate literature work reported by researchers on oxazine for their various pharmacological activities and also reported recent efforts made on this moiety.

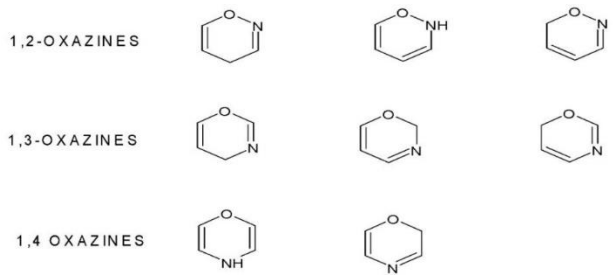
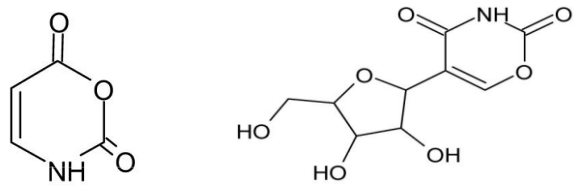


Figure 1: Structures of isomers of oxazines



3H-1,3-Oxazine-2,6-dione. Minimycin

Figure 2: Structures of minimycin and 3H-1,3-Oxazine-2,6-dione

BIOLOGICAL POTENTIALS OF OXAZINES

Antimicrobial study

Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. The lack of effective treatments and antimicrobial resistance is the main cause of microbial infections that are the common challenges for the researchers as large numbers of patients are at risk. Oxazines and their derivatives are known to be promising antimicrobial agents.

El-Bayouki *et al.,* 2017 have designed a concise, one-step procedure for the synthesis of some tetra hydro-4H-benzo [1, 3-e] oxazines and β-acylamino ketone derivatives. Some selected compounds (1–4) as shown in Fig 3 were tested for their antimicrobial activity in nutrient agar plates and potato dextrose agar medium against *B. thuringiensis, E. coli, B. fabae, and F. oxysporum*. Streptomycin and Treflucan were used as standard drugs.[3]

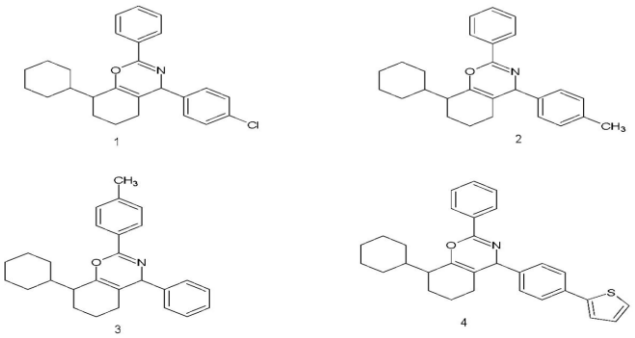


Figure 3: Structures of compounds 1-4

Gabbas *et al.,* 2016 reported 1, 3-oxazine derivatives (5-7) as shown in Fig 4 were synthesized using 2-hydroxy benzyl amines and methylene bromide. These compounds were tested in-vitro for their antibacterial activity against three strains of gram-positive and three strains of gram-negative bacteria using the cup-plate agar diffusion method, with streptomycin (100mg/ml) as the reference antibacterial agent.[4]

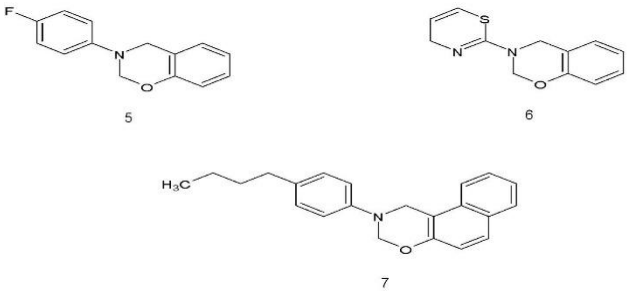


Figure 4: Structures of compounds 5-7

The results of the antibacterial activity against three strains of gram-positive bacteria and three strains of gram-negative bacteria as compared to 100 mg/ml streptomycin which was used as the standard. From the result 5 was reported to exhibit good activity against *Bacillus subtilis* and *Staphylococcus epidermidis*. The compound also showed very good activity against *Acineto bacteranitratus* and excellent activity against *Escherichia coli* and only moderate activity against Staphylococcus aureus. 6was reported exhibiting moderate activity against *Bacillus subtilis, Staphylococcus epidermidis* and *Escherichia coli.* Compound 7 was reported to exhibit very good activity against all the strains of gram-positive bacteria. It showed a very good activity against *Acinetobacteranitratus* and an excellent activity against *Escherichia coli*.

Antitubercular study

Tuberculosis (TB) is mainly caused by *Mycobacterium tuberculosis*. It is estimated that one-third of the world's population is TB-infected, with 8 million new cases annually and 3.1 million die annually. TB is currently the leading killer of youths, women and AIDS patients in the world. Isoniazid is a frontline anti-TB drug, but unfortunately, bacterial strains resist INH at an alarming rate. Hence, the development of more effective anti-TB drugs is a common threat for researchers nowadays. Oxazines and their derivatives are known to have excellent antitubercular activity.

Kamble *et al.,* 2015 have synthesized and characterized somebenzo [1,3] oxazine derivatives with their biological property. Among the synthesized compounds, compounds (8-11) as shown in Fig 5 showed promising activity against M. tuberculosis as compared with Rifampicin and Ethambutol. The importance of chloro, nitro, and methoxy groups for the manifestation of antimycobacterial activity was also discussed.[5]

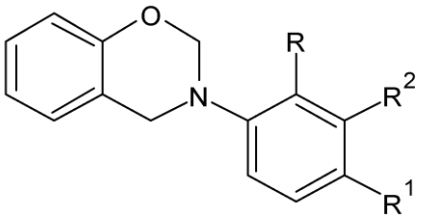


Figure 5: Structures of compounds 8-11

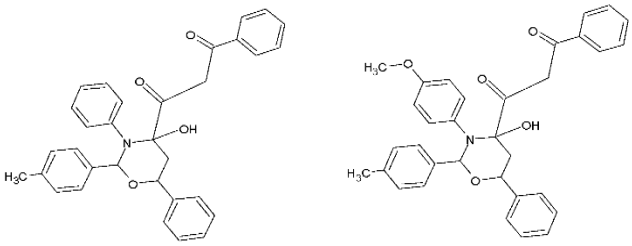
Antioxidant study

The antioxidants play a remarkable performance to decelerate the oxidative process by scavenging the free radicals, thereby preventing the extent of damage to the cell walls. The efficacy of antioxidants is determined by their free radical scavenging activity. DPPH contains an odd electron and is used for scavenging activity.

DPPH is a stable free radical which accepts a proton or an electron to become a stable diamagnetic molecule, viz. Hydrazine. A substance capable of donating electrons or hydrogen atoms can convert the purple color of DPPH to its non-radical yellow color, which can be seen spectrophotometrically.

Zykova *et al.,* 2015 have synthesized 3-substituted 4-hydroxy-6-phenyl-3,4-dihydro 2H-1, 3-oxazines(12-13) as shown in Fig 6 from 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-dione and various arylidene aryl amines. These compounds were examined *in vitro* for their antioxidant and cytotoxic activity. The highest antioxidant

activity was observed for 12 and 13 but did not show cytotoxic properties against normal and human tumor cells.[6]



12 13

Figure 6: Structures of compounds 12 and 13

Anticancer activity

Cancer is a life-threatening disease characterized by the abnormal cell growth of cancerous cells and they invade and spread into other cells. Normal cells can receive signals that determine whether they differentiate or undergo apoptosis. Cancerous cells are powerless to receive these signals and unable to control their differentiation and apoptosis, resulting in the uncontrollable growth of damaged cells. Metastasis, the cancer spreading process is the core of cancer death. Mutations in DNA mislead the normal cellular process by the production of some proteins which leads to cancer.

MTT assay is a common model for the determination of anticancer activity. Converting MTT into a purple-colored formazan occurred at a maximum near 570 nm as shown in Fig 7. The color changes from yellow to purple in case cells die and lose the ability to convert MTT into formazan. Oxazines and their derivatives are known to have excellent anti-cancer properties.

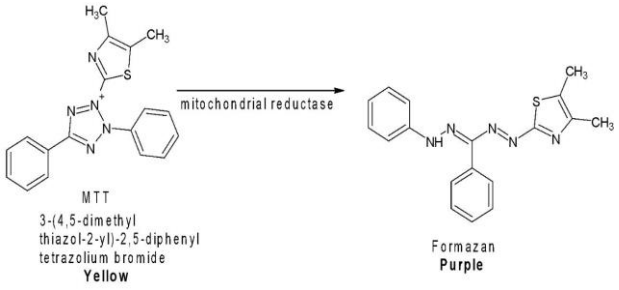
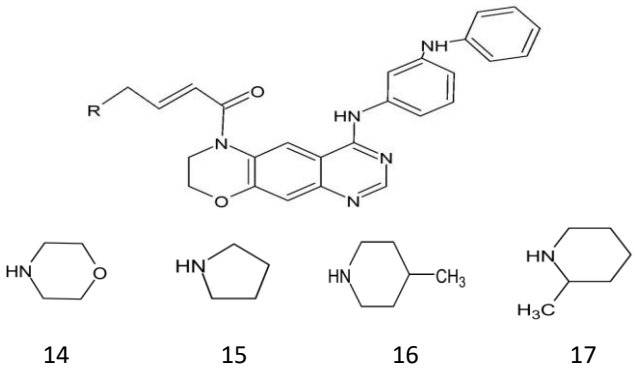


Figure 7: Scheme for conversion of MTT to Formazan

Chen *et al.,* 2014 have synthesized and characterized a series of novel tricyclic oxazine fused quinazolines 14-17 as shown in Fig 8and tested against cancer cell lines including gastric carcinoma cell NCI-N87, epidermoid carcinoma cell A431, NCIH1975, BT474, and Calu3 lines These reported compounds performed impressive inhibition activity against the cell lines. The activity of compound 17 (IC50 = 0.046–0.24 µM) is more potent than erlotinib b (IC50: 0.75>10µM) and gefitinib (IC50: 0.36–1.00 µM) against A431, NCI-N87, BT474, Calu 3. 2-oxo-benzo [1,4]oxazine analogs.[7]



14 15 16 17

Figure 8: Structures of compounds 14-17

Jaiswal *et al.,* 2017 have synthesized different derivatives (18-20) as shown in Fig 9 and characterized the cytotoxic studies of these compounds in 3T3 fibroblast cell lines that were carried out and found to be non-toxic. Besides, all compounds were identified as promising platelet aggregation inhibitors as compared to aspirin. Substituents are presented in Table 1.[8]

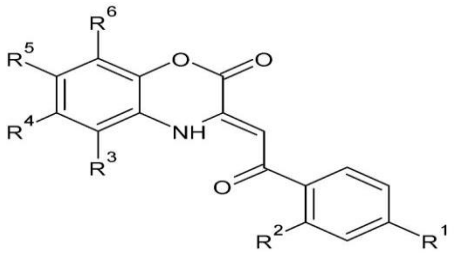


Figure 9: Structures of compounds 18-20

Table 1: Substituents for compounds 18-20

Compounds	R1	R2	R3	R4	R5	R6
18	Br	H	H	CH_3	H	Br
19	Br	H	H	H	NO_2	H
20	OCH_3	H	H	CH_3	H	Br

Anti-inflammatory activity

Anti-inflammatory is the property of a substance or treatment that reduces inflammation or swelling. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system to block pain signaling to the brain. The development of more selective, tolerable and efficacious agents able to control the inflammatory process is being vigorously pursued due to their undesirable side and adverse effects. Aspirin and Ibuprofen are common anti-inflammatory drugs. Oxazines and their derivatives are known to have excellent anti-inflammatory activity.

Bano *et al.,* 2015 have been synthesized (21-24) as shown in Fig 10 and characterized by various spectral methods. The biological activities of these compounds were evaluated for the KATP channel opener as an antihypertensive activity. Compounds have exhibited around 40% inhibition of COX1 as compared to the inhibition of COX2. Substituents are presented in Table 2.[9]

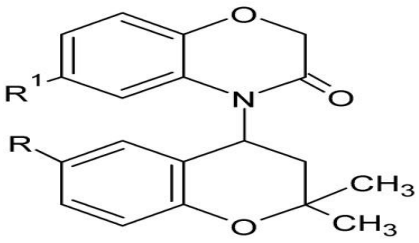


Figure 10: Structures of compounds 21-24

Table 2: Substituents for compounds 21-24

Compounds	R1	R2
21	Br	NO_2
22	NO_2	Br
23	NO_2	Cl
24	NO_2	Cl

Neurodegenerative disorder

Neurodegeneration is the progressive loss of structure or function of neurons, including the death of neurons. Many neurodegenerative diseases – including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, fatal familial insomnia. Such diseases are incurable, resulting in progressive degeneration and/or death of neuron cells.

Rombouts *et al.,* 2015 have developed the synthesis of novel 1,4-oxazine analogs. These were found to have potent in vitro inhibition in enzymatic and cellular BACE1 assays. The newly synthesized derivatives (25 and 26) as shown in Fig 11demonstrated to be orally bioavailable, centrally active and which exhibited robust lowering of the brain and cerebrospinal fluid (CSF Aβ) levels, respectively, in mouse and dog models.[10]

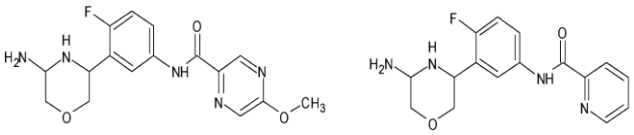


Figure 11: Structures of compounds 25 and 26

Novel 2-ethoxy-4,5-diphenyl- 1,3-oxazine-6-one (27) as shown in Fig 12 has been designed and characterized by Ansari *et al.,* 2019. The biological study proved that this compound could increase heat shock proteins Hsp70 and Hsp32 levels. The pretreatment of the cells with this reported compound also increases the γ-GCS level and antioxidant enzyme activities.[11]

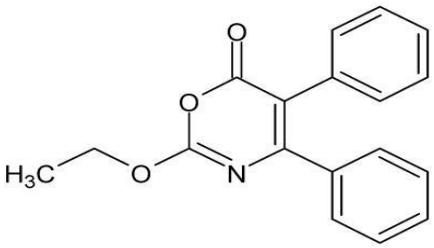


Figure 12: Structure of compound 27

CONCLUSION

The data available in literature so far, rendered oxazine, an important class of heterocyclic compounds. This review includes information that would extend a great deal of help to researchers in determining the best and most productive, economical and clinically important compounds of oxazine. The biological activities of oxazines including antimicrobial, antitubercular, antioxidant, anti-inflammatory, anticoagulant and anticancer activities are undoubtedly beneficial to human health. Moreover, these compounds also act as anti-inflammatory agents to reduce inflammation. Some of these compounds are also used for the treatment of neurodegenerative. The current survey of works carried out in oxazine derivative revealed that these moieties have attracted a great deal of interest of medicinal chemists and biochemists and rendered them like a lead molecule for designing potential bioactive agents. Further, we can conclude that many other derivatives of oxazine can be synthesized which will be expected to show potent pharmacological activities.

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Conflict of Interest: None declared.