Received: 11 July 2019 | Revised: 2 September 2019 | Accepted: 4 September 2019

DOI: 10.1111/cbdd.13633

REVIEW

WILEY

Medicinal chemistry of oxazines as promising agents in drug discovery

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Funding information
CAS President's International Fellowship Initiative, Grant/Award Number: 2016PM032

Abstract

Oxazines have brought much synthetic interest due to their extensive biological activities. These are the important category of heterocycles, which may be formally derived from benzene and its reduction products by convenient substitution of carbon (and hydrogen) atoms by nitrogen and oxygen. In the last few decades, oxazine derivatives have documented as worthy synthetic intermediates and also blessed with notable sedative, analgesic, anticonvulsant, antipyretic, antimicrobial, antitubercular, antimalarial, antioxidant, and anticancer activities. Nowadays, it is important to develop new classes of compounds with more effective mechanisms due to drug resistance activity in which the ability of drug to effectively treat disease can be reduced. The aim of the article is to collect and make a more generalized review on the synthesis of oxazine derivatives and their pharmaceutical and biological activities. We hope this review will provide ample references for the researchers concerned with azines in generally and oxazines in particular.

KEYWORDS

anticancer activity, anti-inflammatory, antimicrobial, antioxidant, antitubercular, oxazines

Abbreviations: AChE, human acetylcholinesterase; ADP, adenosine diphosphate; ATP, adenosine 5'-triphosphate; BACE, beta-amyloid cleaving enzyme; BSA, bovine serum albumin; BSCE, beta-secretase cleaving enzyme; CFTR, cystic fibrosis transmembrane conductance regulator; COX, cyclooxygenase; CSF, cerebral spinal fluid; DNA, deoxyribonucleic acid; DNA-PK, DNA-dependent protein kinase; DPPH, 2,2′-diphenyl-1-picrylhydrazyl; GSK-3β, glycogen synthase kinase 3β; hERG, human ether-à-go-go-related gene; HIV, human immunodeficiency virus; IC_{50}, half-maximal inhibitory concentration; IZD, inhibition zones of diameter; K_{ATP}, ATP-sensitive potassium; MAPK, mitogen-activated protein kinase; MDR, multidrug resistant; MIC, minimum inhibition concentration; MTT, (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium; NF-κB, nuclear factor kappa-B; PI3k, phosphoinositide 3-kinase; RANKL, receptor activator of nuclear factor kappa-B ligand; ROMK, renal outer medullary potassium channel; TRAAP, telomeric repeat amplification protocol; γ-GCS, human γ-glutamylcysteine synthetase.

1 | INTRODUCTION

Oxazines have attracted significant interest for past few decades, but still remain little studied compounds. These are the heterocyclic compounds having one oxygen and one nitrogen atom in a six-membered ring of doubly unsaturation. Eight existing isomers of oxazines (Eicher, Hauptmann, & Speicher, 2013) are reported depending on the relative position of the hetero atoms and double bonds. 1,2-,1,3-, and 1,4-oxazines are the O-analogues of the three isomeric diazines. The derivatives of oxazines such as dihydro-1,3-oxazine, tetrahydro-1,4-oxazine are well known. Cinnabarine and cinnabaric acid derived from biodegradation of tryptophan (Stone, Stoy, & Darlington, 2013) are the natural dioxazines. In addition, some fluorescent dyes such as Nile blue and Nile red are based on the aromatic benzophenoxazine (Figure 1).

Cope and Holly have reported first aromatic oxazines in 1944 by Mannich reactions. Fairly, less number of works has been carried out on these compounds till date. Jaiswal et al (Jaiswal, Sharma, Prikhodko, Mashevskaya, & Chaudhary, 2017) have reported a synthetic green protocol for the one-pot synthesis of functionalized 2-oxo-benzo[1,4]oxazines under ultrasound irradiation. This method gave excellent yields (up to 98%) with no side products as compared to conventional methods. Ansari et al. (2019) have used a synergistic catalysts system ZnO NPs and malic acid for the eco-friendly synthesis of oxazine derivatives. In addition, several synthetic approaches for the preparation of oxazines have been reported (Desai, Bhatt, & Joshi, 2019; Gaonkar, Nagaraj, & Nayak, 2019; Hu, Zhang, & Sun, 2019). The most common simple 1,4-oxazine is tetrahydro-1,4-oxazine (morpholine), which is a colorless liquid and miscible in water, and it has many applications in medicinal chemistry and drug discovery (Pal'chikov, 2013). Oxazine heterocycles possess peculiar significance as they establish a valuable group of natural and non-natural products and display plenteous biological activities (Mohebat, Abadi, Soltani, & Saghafi, 2016). The synthetic oxazine derivatives are well known for their promising biological properties, for example, 5-b-D-ribofuranosyl-l,3-oxazin-2,4-dione (Minimycin) is employed as an antitumor agent (Kusakabe et al., 1972), while 5-methyl-3H-1,3-oxazine-2,6-dione as a suicide inactivator of serine proteases (Figure 2; Moorman & Abeles, 1982).

These compounds also exhibit a variety of biological activities including anti-inflammation, antioxidation, PI3 kinase inhibition, and neurosedation (Lanni et al., 2007; Roy, Mitra, & Saha, 2009). Due to their enormous biological significance, these compounds could be employed for the development of new chemical entities to combat various diseases. Tetrahydro-4H-1,2-oxazines are the essential structural constituents for most of the fungicides, herbicides, and broad-spectrum bactericides (Patel & Stevenson, 1992). Oxazines are used as fundamental building blocks for many natural products (Zimmer, Collas, Roth, & Reißig, 1992). Using oxazine as synthon, one may be able to reconcile pyrroles (Nakanishi, Shirai, Takahashi, & Yoshio, 1981; Oppolzer, Bättig, & Hudlicky, 1981), pyrrolidine (Angermann, Homann, Reissig, & Zimmer, 1995), and γ-lactones (Gilchrist & Roberts, 1979) via the reductive cleavage of C-O and N-O bonds. Also, the compounds containing dihydro-1,3-oxazine ring system displayed anti-HIV (Cocuzza et al., 2001; Pedersen & Pedersen, 2000), anticancer (Hsu & Lin, 1996; Nair, Salter, Kisliuk, & Gaumont, 1983; Shoji, Otake, & Morishita, 2019), antibacterial (Prasad, Rohilla, Roy, & Nath, 2012), antifungal (Fringuelli, Pietrella, Schiaffella, Guarraci, & Perito, 2002), antithrombotic (Buckman et al., 1998), anti-inflammatory activity (Akhter, Husain, Akhter, & Khan, 2011), and its versatility as synthetic intermediate (Singh & Han, 2007). Furthermore, 6-arylbenzoxazines (Figure 3) are reported as potent non-steroidal progesterone receptor agonists (Zhang et al., 2002).

Thorough literature survey revealed that the oxazine derivatives exhibited well known pharmacological activities including antihyperglycemic (Jamal, Ansari, & Rizvi, 2009), antileishmanial (Thompson, O'Connor, Marshall,

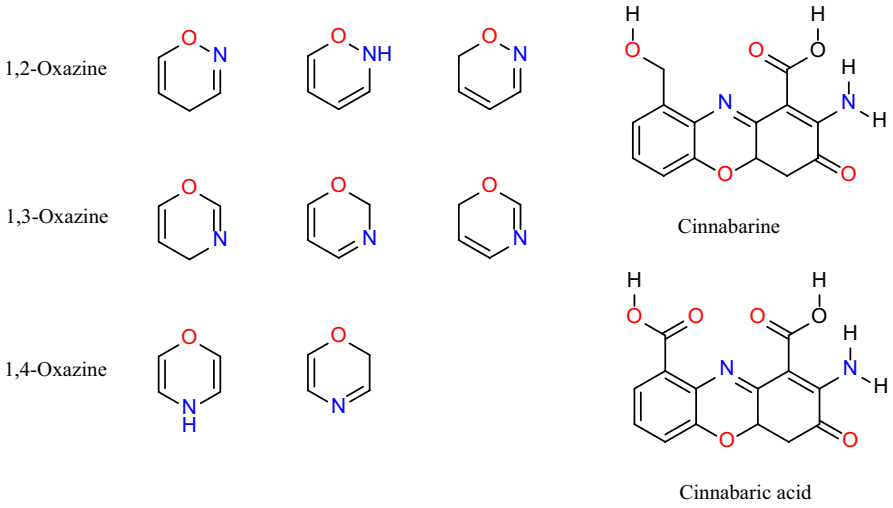
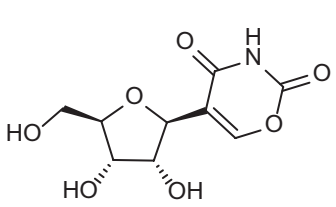
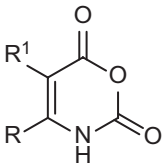


FIGURE 1 Structure of isomers of oxazines, cinnabarine, and cinnabaric acid

Yardley, & Maes, 2017), antitubercular (Kmentova et al., 2010; Ray & Roy, 2012), antiulcer (Katsura, Nishino, & Takasugi, 1991), anticancer (Nongrum et al., 2019; Zuo et al., 2012). Moreover, the oxazine derivatives have been extensively studied because of their profound biological activities including antitumor (Chylińska, Urbański, & Mordarski, 1963), antihypertensive (Kajino, Shibouta, Nishikawa, & Meguro, 1991), antibacterial (Chylińska, Janowiec, & Urbański, 1971), antifungal (Tang et al., 2012), antithrombotic and neuroprotective agent (Joyce et al., 2003). In particular, naphth-oxazine derivatives and some salts derived from oxazine derivatives advertised therapeutic potential for the treatment of Parkinson's disease (Coleman, Quinn, Traub, & Marsden, 1990; Du, Grandeury, & Jiang, 2019; Kerdesky, 2005; Stoessl, Mak, & Calne, 1985). Benzoxazine derivatives have been synthesized as promising inhibitors of monoacylglycerol lipase (Bell, Benz, & Grether, 2019). Research in the previous decades explored that oxazine moiety shows potent antitumor activity, so by inserting reductive group at different position of oxazine moiety will design hybrid compounds holding both reductive group and cytotoxic group. This will be treated as an excellent precursor for novel hypoxia-targeted compounds for cancer therapeutics and will be able to answer a myriad of questions. Considering the manifold and wide-ranging applications in pharmaceutical and biological field of these compounds, we are planned to write this review which will give an in-depth insight into various application aspects of these classes of compounds.



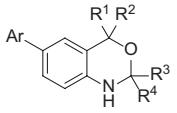
Minimycin



R= H, R^1= H
R= CH_3, R^1= H
R= H, R^1= CH_3

3H-1,3-oxazine-2,6-diones

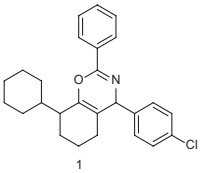
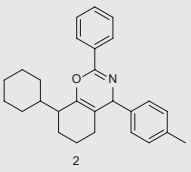
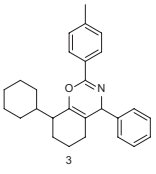
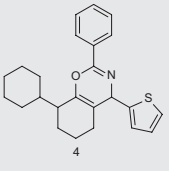
FIGURE 2 Structure of Minimycin and 3H-1,3-oxazine-2,6-dione ring system



R^1 = Me
R^2 = Me, Ph, Cyclohexyl
R^3 = Me, CF_3, $CH(CH_3)_3$, $C(CH_3)_4$, Ph, COOEt, Thien-2-yl
R^4 = H, Me

FIGURE 3 Structure of 6-arylbenzoxazines

TABLE 1 IZD in millimeters as a criterion of antibacterial and antifungal activity of some synthesis compounds at a concentration level of 10 mg/ml

Compounds	Bacteria		Fungi	
	B. thurngensis IZD (mm)	*E. coli* IZD (mm)	*B. fabae* IZD (mm)	*F. oxysporium* IZD (mm)
 1	26	33	35	32
 2	15	29	29	28
 3	20	23	25	22
 4	17	30	35	30
Streptomycin	22	30	–	–
Treflucan	–	–	36	32

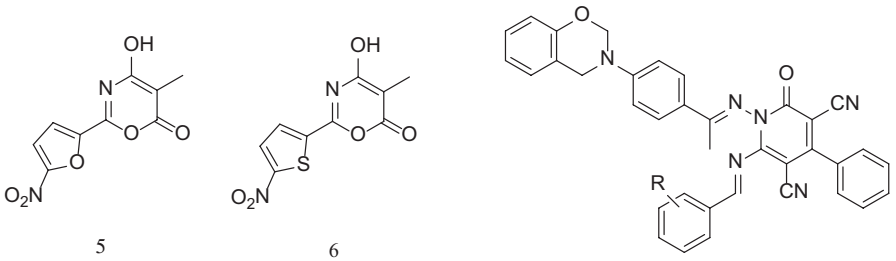


FIGURE 4 Structure of oxazine derivatives of **5**, **6,** and **7a–f**

2 | ANTIMICROBIAL STUDY

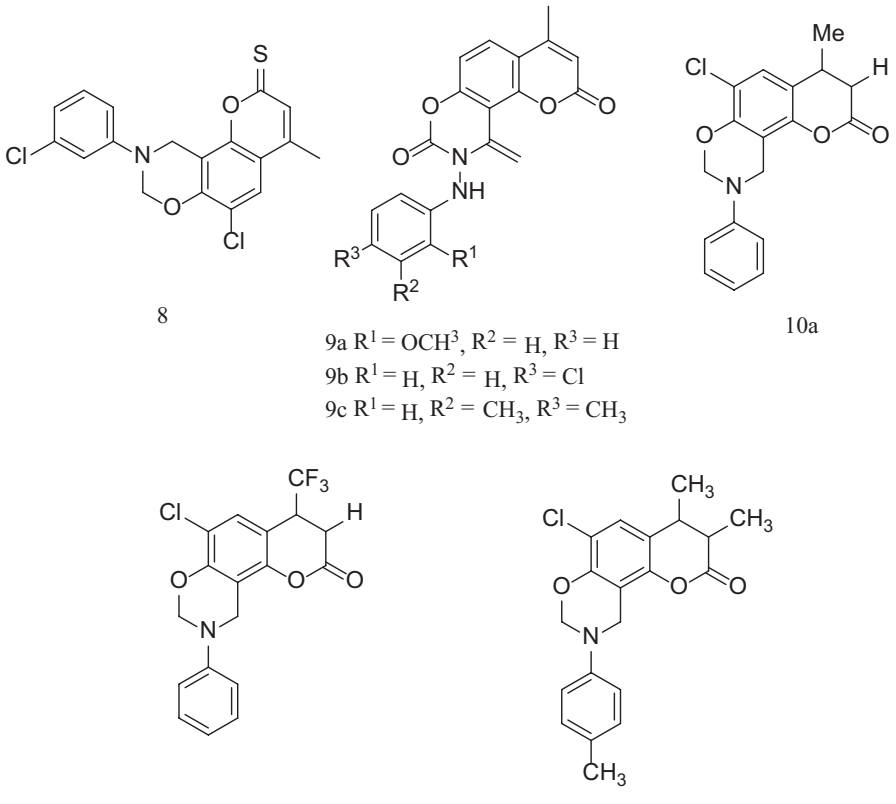
Nowadays, microbial infections are the common challenges for the researchers as large numbers of patients are at risk due to this. The lack of effective treatments and antimicrobial resistance are the main cause of this problem. Hence, the improvement of new antimicrobial agents with more effective mechanisms is vital for the public health (Rice, 2006). Oxazines and their derivatives are known to be promising antimicrobial agents. El-Bayouki, Basyouni, Khatab, Kandel, and Badawy (2017). have designed a concise, one-step procedure for synthesis of some tetrahydro-4H-benzo[1,3-e] oxazines, and β-acylamino ketone derivatives. Some selected compounds **1–4** were tested for their antimicrobial activity in nutrient agar plates and potato dextrose agar medium against *B. thurngensis*, *E. coli*, *B. fabae,* and *F. oxysporium*. Streptomycin and Treflucan were used as standard drugs. The compound **1** showed highest activity than other tested compounds (Table 1).

Chernov et al. (Chernov et al., 2017) have synthesized 4-hydroxy-1,3-oxazin-6-ones derivatives 5–6 that displayed prominent antimicrobial activity against *S. aureus* whereas, less active against *E. coli*. The activity decreases with opening of the oxazine ring. The study revealed that these reported compounds may be used for therapy of infectious diseases without adverse effects. The synthesis and characterization of oxazine bearing pyridine scaffold as potential antimicrobial and antibacterial activity were reported by Desai, Bhatt, Joshi, and Vaja (2017). It was observed that some derivatives compounds such as **7a–f** exhibited remarkable antibacterial potency based on substitution at benzene ring to affect their biological activities as electron-withdrawing group can increase the antibacterial activity while electron-donating group may increase antifungal activity. Compounds **7c** and **7d** displayed good inhibition over selected fungal strains (Figure 4). The 3D-QSAR study of such compounds was explained by CoMFA and CoMSIA models to get valuable information desired to improvise the biological activity. Moreover, molecular docking study against microbial *DNA gyrase* was carried out. Desai, Bhatt, and Joshi (2019) have reported the antimicrobial activity of 1-((1-(4-(2*H*-benzo[e][1,3] oxazin-3(4*H*)-yl)phenyl)ethylidene)amino)-6-((arylidene) amino)-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles. The compounds were also studied for their antimicrobial activity against *E. coli, P. aeruginosa, S. aureus, S. pyogenes, C. albicans, A. niger, and A. clavatus.* Ampicillin and Griseofulvin were used as reference drugs.

Mathew et al (Mathew, Aggarwal, Kumar, & Nath, 2014) have reported a novel 6-chloro-9-(3-chlorophenyl)-4-methyl-9,10-dihydro-2*H*,8*H*-chromeno[8,7-e][1,3]oxazine-2-thione (8) compound by Mannich-type condensation reaction. These compounds were fully characterized by using some spectral techniques. A significant zone of inhibition for the compound was obtained against *S. aureus* and *K. pneumonia*. Nagamallu, Gurunanjappa, and Kariyappa (2017) have reported the antimicrobial and antioxidant activity of some coumarin based 1,3-benzoxazine derivatives **9a–c**. The derivatives were fully characterized by several spectral techniques. These synthesized compounds flashed significant antimicrobial activity. It is also observed that the derivatives having methoxy and methyl substituents in the phenyl ring exhibited better antioxidant properties when tested. A series of novel coumarin based 1,3-oxazine derivatives **10a–c** has been synthesized by Zhang et al. through a microwave-assisted three component one-pot Mannich reaction (Zhang et al., 2016). Further, the compounds were characterized by using some spectral methods. The preliminary bioassays showed that compounds **6a–c** exhibited good antifungal activity and the most active compound was **6b** with an IC_{50} value of 2.1 nM against *B. cinerea* (Figure 5).

Also, these compounds were fully characterized by several spectral tools. New annulated heterocycles containing pyranooxazines **11a–d** obtained from reaction of 6-amino-4-substituted aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile with acetic anhydride have been reported (Elziaty, Bassioni, Hassan, Derbala, & Abdel-Aziz, 2016). These compounds were characterized by using several spectral techniques. These compounds were also evaluated

FIGURE 5 Structure of oxazine derivatives **8, 9a-c** and **10a-c**



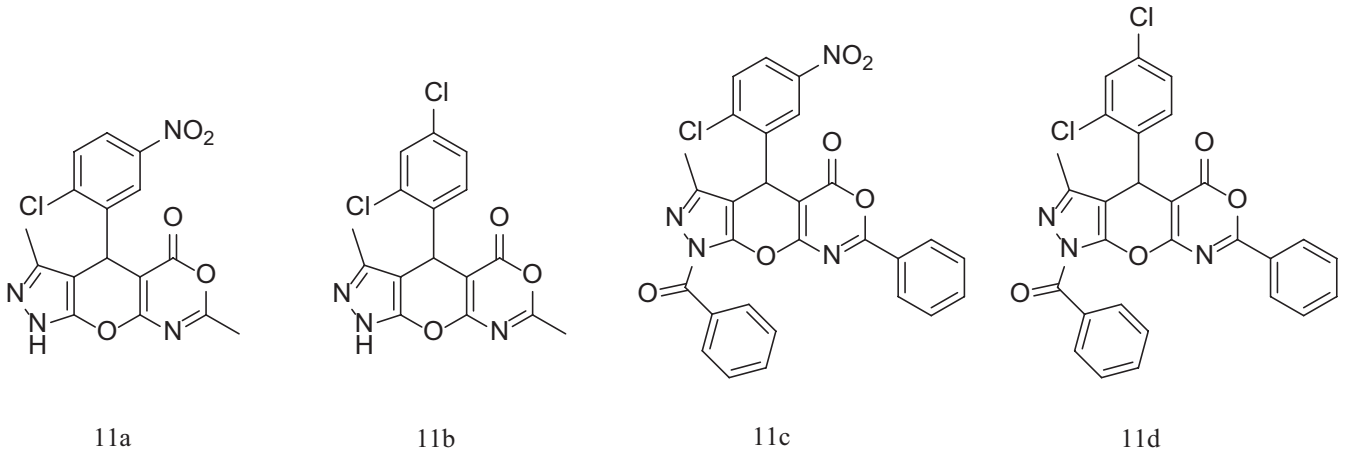
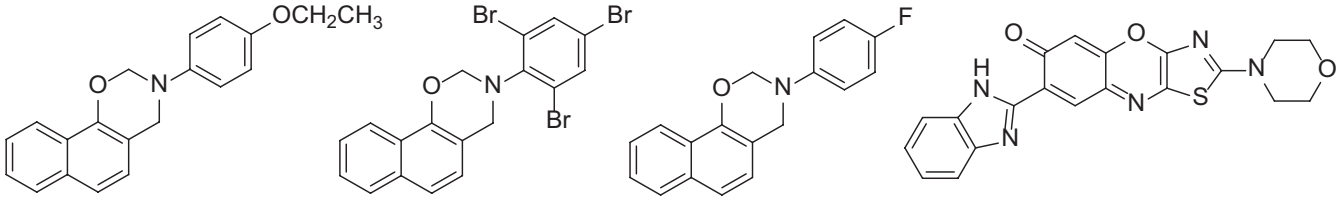


FIGURE 6 Structure of oxazine derivatives **11a–d**

for their in vitro antimicrobial efficacy against four strains, namely Gram-positive *S. aureus*, Gram-negative *P. aeruginosa*, *C. albicans* (yeast), and *A. niger* (fungus) and found significant activity. Neomycin was used as standard drug for the study (Figure 6).

The investigation of antibacterial screening for 3,4-dihydro-3-substituted-2*H*-naphtho[2,1-e][1,3]oxazine derivatives **12a–c** has been carried out against two human pathogenic bacteria including against Gram-positive *B. subtilis* and Gram-negative *E. coli* (Kategaonkar et al., 2010). All these compounds exhibited considerable and varied activity. Compound **12a** displayed 18.2 mm zone of inhibition which is more than standard Griseofluvin against *C. albicans*. A series of novel 6-(1*H*-benzo[d]imidazol-2-yl)-substituted-benzo[b][1,4]oxazin-7-one derivatives have been synthesized by Patil et al. (2015). These compounds were fully characterized by using some spectral techniques. Most of these compounds showed moderate antibacterial activity, whereas compound **13** showed good activity against all bacterial strains involving *E. coli*, *S. aureus*, *Micrococcu*s, and *B. subtilis* (Figure 7).



12a 12b 12c 13

FIGURE 7 Structure of oxazine derivatives **12a–c,** and **13**

Abou-Elmagd and Hashem (2013) have prepared 1-amidoalkyl-2-naphthols **14a–f** by using direct protocol. Ring closure of the above gave pyrazolyl- and indolyl oxazine derivatives **15a–f** while the reaction of 2-naphthol, aldehydes, and ammonia solution gave dipyrazolyl- and di-indolyl oxazine derivatives **16a–f** (Figure 8). According to antiviral test, compounds **14e** and **14f** were found to be most active compounds. Moreover, amidoalkylnaphthols **14a–e** gave high activity (Inhibition zone) and the other compounds showed moderate activities. All compounds showed no activity toward *P. aeroginosa*, *E. coli,* and *Proteus* micro-organisms.

Verma et al. (2012) have synthesized and characterized a series of 1,3-disubstituted-1*H*-naphtho[1,2-e][1,3]oxazines (Figure 9). These compounds were tested in vitro for their antimicrobial activity against some selected micro-organisms including *E. coli*, *B. subtilis,* and *S. aureus.* Compounds **17c**, **17e**, **18a**, **18c**, and **18d** showed significant antibacterial activity.

3,4-dihydro-2H-benzo[e][1,3]oxazines **19a,b** and 1,2-bis[3,4dihydrobenzo[e][1,3]oxazin-3(4H)-yl]ethanes 21 were prepared by Mathew, Kumar, Sharma, Shukla, and Nath (2010); Figure 10) through Mannich-type reaction. All the characterizations were carried out using spectral techniques. In vitro antimicrobial activity of the synthesized compounds was carried out against six pathogenic fungi species involving *C. albicans*, *C. neoformans*, *S. schenckii*, *T. mentagrophytes*, *A. fumigatus,* and *C. parapsilosis* and four bacteria species including Gram-positive bacteria involving *K. pneumonia* and *S. aureus* and two Gram-negative bacteria involving *E. coli* and *P. aeruginosa*. Compounds **19a, b** and **20a, b** showed significant in vitro antimicrobial activity.

Oxazolidinones containing dihydro-1,2-oxazine ring were synthesized by D'Andrea et al. (2005) and tested as antibacterial agents. Compound **21** proved to be most active similar to linezolid against a panel of Gram-positive bacteria including streptococci, staphylococci, and enterococci. Cu(I)-catalyzed reaction of in situ generated nitrile oxides with in situ generated N-propargyl 1,4-benzoxazine was employed to synthesis of novel derivative of 4-((3-(aryl) isoxazol-5-yl) methyl)-2*H*-benzo[b][1,4]oxazin-3(4*H*)-ones 22a-c (Iloni, Vasam, Guguloth, & Vadde, 2018). Compound **22c** has shown potent activity against *B. subtilis* and *E. coli* with MIC value 12.5 μg/mL while other compounds **22a, b** showed moderate to poor activity as compared to the standard drug streptomycin (Figure 11).

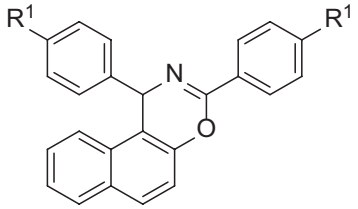
Cephalandole A was first isolated from the Taiwanese orchid Cephalanceropsis gracilis (Orchidaceae). Cephalandole A and its analogues were synthesized starting from indole by Sharma et al. (2018); Sharma et al. (2018) and proved to have potential antimicrobial and antiplatelet activity. Compounds **23a–g** (Figure 12) showed promising antimicrobial activity against the phytopathogenic bacteria and fungi, while compounds **23c**, **23e**, **23f**, and **23g** showed potent antiplatelet activity. Compound **23d**, the first aza analogue of Cephalandole A has potent antibacterial activity against *B. subtilis* and *S. griseus* strains.

Manjula, Rai, Gaonkar, Raveesha, and Satish (2009) have synthesized a new series of 5,6-dihydro-4*H*-1,2-oxazine derivatives **24a-e** via hetero Dielse–Alder reaction of α-nitroso

14 15

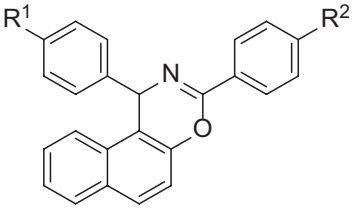
Compound	X	R
16a	1,3-diphenylpyrazolyl	NH_2
16b	1,3-diphenylpyrazolyl	CH_3
16c	1,3-diphenylpyrazolyl	Ph
16d	indolyl	NH_2
16e	indolyl	CH_3
16f	indolyl	Ph

FIGURE 8 Structure of compounds **14–16a–f**



Compound	R^1
a	H
b	CH_3
c	OCH_3
d	Cl
e	F

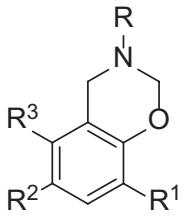
17



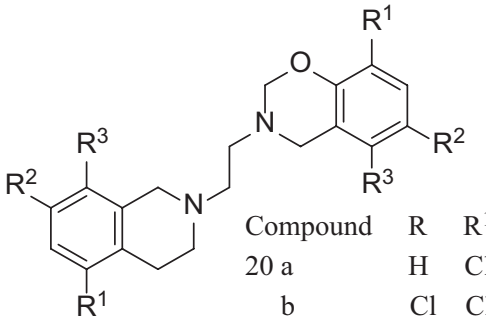
Compound	R^1	R^2
a	H	OCH_3
b	H	F
c	H	Cl
d	CH_3	F

18

FIGURE 9 Structure of compounds **17a–e** and **18a–d**

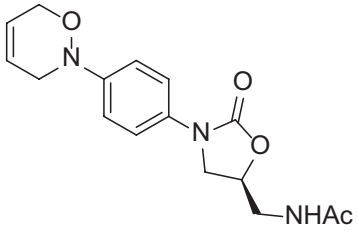


Compound	R	R^1	R^2	R^3
19 a	H	Cl	H	2-Cl-C_6H_4
b	Cl	H	Cl	2-Cl-C_6H_4



Compound	R	R^1	R^2	R^3
20 a	H	Cl	H	----
b	Cl	Cl	H	----

FIGURE 10 Structure of compounds **19a,b** and **20a,b**



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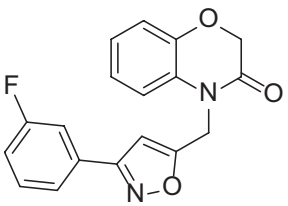
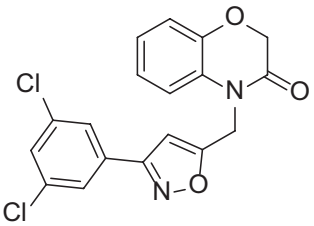
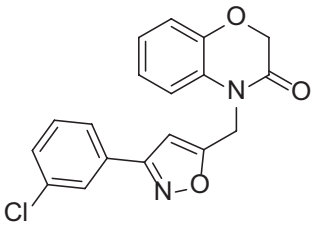


22a



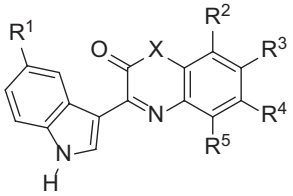
22b



22c

FIGURE 11 Structure of compounds **21** and **22a–c**

FIGURE 12 Structure of compounds **23a–g**



Compound	R^1	R^2	R^3	R^4	R^5	X
23a	H	H	H	Cl	H	O
23b	H	H	NO_2	H	H	O
23c	NO_2	H	NO_2	H	H	O
23d	H	H	H	H	H	NH
23e	H	H	H	H	H	O
23f	H	H	H	NO_2	H	O
23g	NO_2	H	H	H	H	O

olefins with alkenes and evaluated for their antimicrobial activities. These compounds were fully characterized by using several spectral techniques. These compounds exhibited significant in vitro antifungal activity. With all the four tested fungal strains including *A. flavus*, *A. niger*, *F. moniliforme,* and *F. oxysporum*, the maximum activity is shown by **24a** while **24b** and **24c** exhibited excellent activity and **24d** exhibited weak activity (Figure 13). Moreover, compound **24c** showed the maximum activity against *E. coli*, due to the due to aromatic ring, methoxy, and carboxylate groups in para positions. Compound **24e** showed excellent activity against *E. coli* due to the methoxy and benzene dioxo group in para positions.

Benzo[b][1,4]oxazin-3(4*H*)-one derivatives **25a–c** were developed by Fang et al. (2011) and evaluated for their in vitro antimicrobial activity against some selective strains including Gram-positive bacteria (*S. aureus and B. subtilis*), Gram-negative bacteria (*E. coli, P. vulgaris, P. aeruginosa*), and fungi (*C. albicans, A. aflavus*). Synthesized derivatives exhibited potency toward all tested strains but showed only week activity against fungi species. Fluorine atom may play

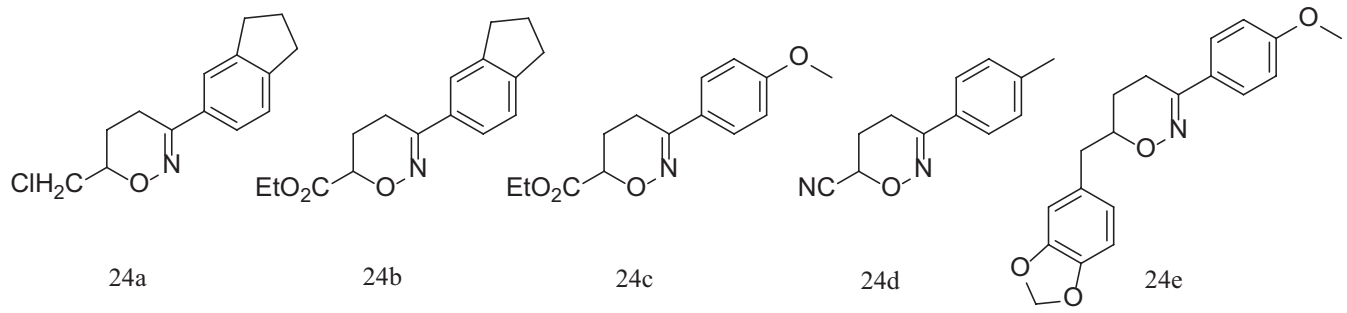


FIGURE 13 Structure of compounds **24a–e**

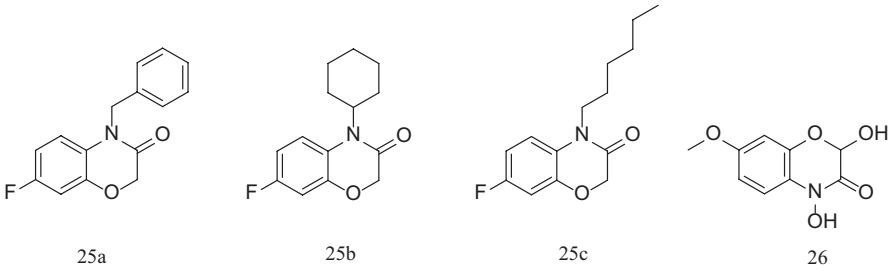


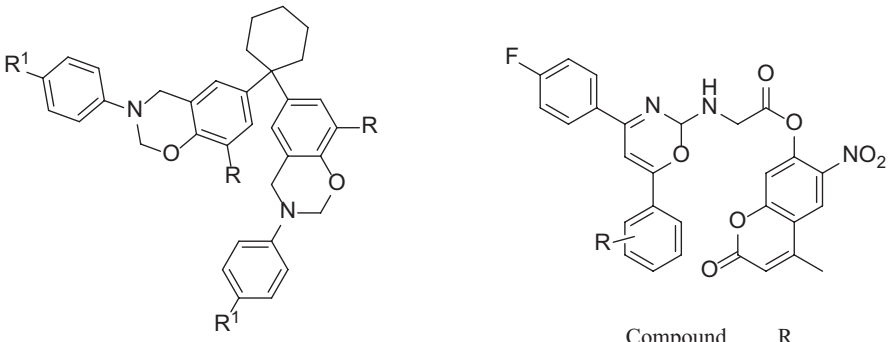
FIGURE 14 Structure of compounds **25a–c** and **26**

an important role in enhancing the antimicrobial properties. Gleńsk et al. (Gleńsk, Gajda, Franiczek, Krzyżanowska, & Biskup, 2016) have studied in vitro antimicrobial and antioxidant properties of the natural cyclic hydroxamic acid **26**. The antimicrobial activity against *S. aureus*, *E. coli,* and *S. cerevisiae* was examined by using disk diffusion method. The reported compounds were also characterized by spectral tools (Figure 14).

Reaction of substituted aniline and formaldehyde in presence of 1,4-dioxane led to bis-benoxazine derivatives **27a–d** (Lalcheta, Dhaduk, & Mendapara, 2015). These compounds were characterized by using spectral tools. Furthermore, compounds were screened against *B. subtilis*, *S. aureus*, *E. coli,* and *S. typhi* micro-organisms. All compounds proved to have comparatively good activity against all the strains. Chauhan, Patel, and Mistry (2018) have synthesized new derivatives of coumarin clubbed 4-(4-fluorophenyl)-6-substituted phenyl-2*H*-1,3-oxazin-2-amine derivatives **28a–e** and screened for their biological studies. A novel compound **28b** had excellent activity with 25 μg/ml against *E. coli* and 12.5 μg/ml against *P. aeruginosa* which is comparable to the standard drugs chloramphenicol and ciprofloxacin, whereas other compounds displayed poor activity against *S. aureus* and *S. pyogenes* (Figure 15).

Estrogen derivatives were synthesized and characterized by Figueroa-Valverde et al. (2016). These compounds were studied for their antibacterial activity against *S. typhi*. According to the results, oxazin-estradiol-3,17-diol **29** showed high decreases on the growth of *S. typhi* (Figure 16).

El Azab and Khaled (2015) have synthesized heterocyclic fused derivatives of naphtho[1,2b][1,4]oxazin-2-one derivatives **30a–g** (Figure 17) and studied their antimicrobial



Compound	R	R^1
27a	H	OH
27b	CH_3	Br
27c	Cl	OCH_3
27d	Br	OH

Compound	R
28a	2-Cl-C_6H_4
28b	4-Cl-C_6H_4
28c	4-F-C_6H_4
28d	4-CH_3-C_6H_4
28e	3-Br-C_6H_4

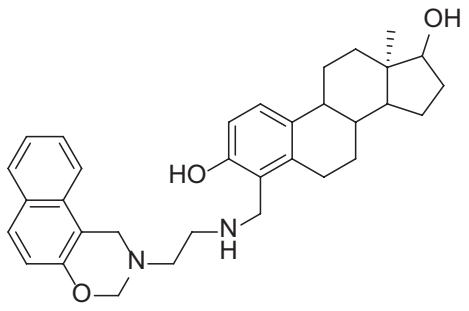
FIGURE 15 Structure of compounds **27a–d** and **28a–e**

activities against four fungal species, namely *A. fumigates, G. candidum, S. racemosum, and C. albicans* as well as against four bacterial species, namely S. *pneumoniae, P. aeruginosa, B. subtilis,* and *E. coli*. Some compounds showed highest degree antifungal and antimicrobial activity while others showed moderate to week activity.

Borgaonkar and Patil (2016) have studied the antimicrobial activity of 1,3-benzoxazine derivatives. These reported compounds were screened for their antibacterial activities against *E. coli*, *S. aureus*, *P. aureginosa*, *B. subtilis,* and antifungal activities against *A. niger*, *A. flavus, P. chrysogenum,* and *F. moniliforme*. Compound **31a** exhibited excellent antifungal activity while compounds **31b–d** were showed significant antibacterial and antifungal activities. Compounds **31e** and **31f** exhibited good antifungal activity due to chloro and iodo substituents in their structure that can enhance antifungal activity. de Brito et al. (2017) have studied the effect of two cyclohexene-fused 1,3-oxazines in different cultures involving *B. cereus*, *E. faecalis*, *E. coli*, *K. pneumoniae*, *S. enterica*, *S. marcescens*, *S. flexneri*, and *S. aureus*. Bioassays suggested that compound **32b** is more effective against bacteria than compound **32a** with lowest MIC and MBC values. This result marked that oxazines exerted direct effects on bacteria and parasite schistosomes (Figure 18).

3 | ANTITUBERCULAR STUDY

Tuberculosis (TB) is mainly caused by *M. tuberculosis*. The emergence of drug-resistant TB, multidrug-resistant TB, extensively drug-resistant TB and totally drug-resistant TB increase the alertness to eliminate TB worldwide (Hu et al., 2017). 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 drug is the common threat for the researchers nowadays. Oxazines and their derivatives are known to have excellent antitubercular activity. 2-nitroimidazooxazine derivatives **33a,b** with modification at the C-7 position were synthesized by Kang et al. (2015) These derivatives exhibited better activity



29

FIGURE 16 Structure of compound **29**

than PA-824 against *M. tuberculosis* H37Rv strain in vitro. Compound **33b** displayed most potent antimycobacterial activity with MIC = 0.050 μM. Kamble et al. (2015) have synthesized and characterized somebenzo[1,3]oxazine derivatives with their biological property. Among the synthesized compounds, compounds **34a–d** showed promising activity against *M. tuberculosis*as compared with Rifampicin and Ethambutol. The importance of chloro, nitro, and methoxy group for the manifestation of antimycobacterial activity was also discussed (Figure 19).

Tukulula et al. (2013) have reported the antiplasmodial and antimycobacterial activity of some new nitroimidazooxazine derivatives. Compounds **35a** and **35b** exhibited potent activity against the chloroquine-resistant K1 strain of *P. falciparum*. More specifically, compounds **35a** and **56b** showed IC_{50} values of 0.100 and 0.164 μM. Huang, (2005) have synthesized a new series of 2-(7-fluoro-3-oxo-4-substituted-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-6-yl)isoindoline1,3-diones analogues. These compounds were fully characterized by spectral methods. The compounds were evaluated for their herbicidal activity against velvet leaf and crab grasses. Compound **36** showed a high herbicidal activity. Two diastereomers (*S* and *R*) of the 7-methyl-nitroimidazo-oxazine **37a,b** have been synthesized and characterized by Li et al. (2008) Both derivatives showed similar activities against *M. tuberculosis* but the disadvantage of synthesized compounds is poor water solubility (Figure 20).

4 | ANTIOXIDANT STUDY

The antioxidants play a remarkable performance to decelerate the oxidative process by scavenging the free radicals, thereby prevent 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 (Scheme 1). A substance capable of donating electrons or hydrogen atom is able to convert the purple color of DPPH to its non-radical yellow color, which can be seen spectrophotometrically (Mohapatra, Das, Pradhan, Maihub, & El-ajaily, 2018).

Qamar et al. (2018) have synthesized a series of 1-(6-methyl-2-substituted phenyl-4-thioxo-4*H*-1,3-oxazin-5-yl)ethanones **38a–g** from the reaction of benzoyl isothiocyanates and acetylacetone. The free radical scavenging activity of these derivatives was performed and showed moderate antioxidant activity. These were also examined for their inhibitory activity against carbonic anhydrase II. The compound **38b** was the most potent inhibitor. Compounds **38c**, **38h**, and **38n** also performed superior inhibitory activities as compared to other synthesized

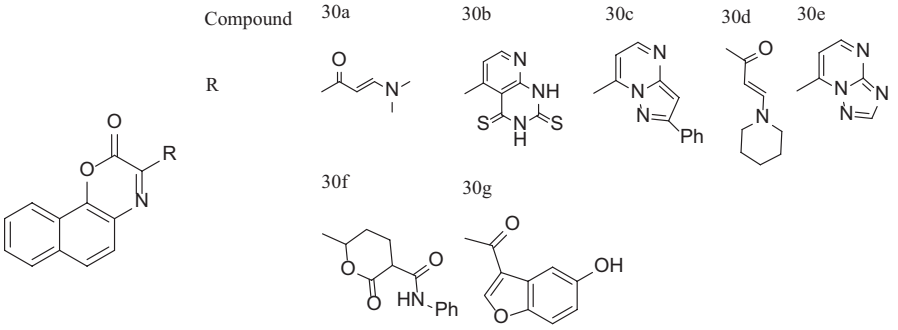
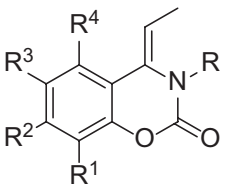
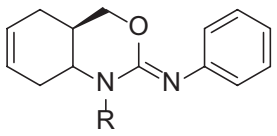


FIGURE 17 Structure of compounds **30a–g**

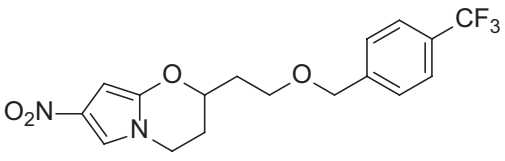


Compound	R^1	R^2	R^3	R^4	R
31a	I	H	Cl	H	C_6H_5
31b	I	H	Cl	H	Iso-C_3H_7
31c	I	H	Cl	H	n-C_4H_9
31d	H	H	Cl	H	C_6H_5
31e	H	H	Cl	H	*n*-C_4H_9
31f	I	H	CH_3	H	C_3H_7

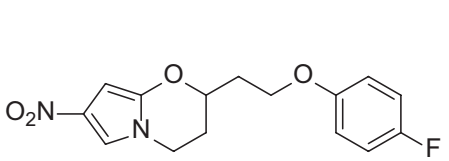


Compound	R
32a	cis, CH_2Ph
32b	trans, H

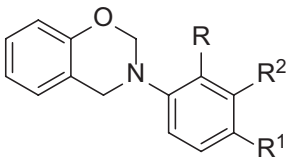
FIGURE 18 Structure of compounds **31a–f** and **32a,b**



33a



33b



	R	R^1	R^2
34a	NO_2	H	H
34b	H	NO_2	H
34c	H	OCH_3	H
34d	Cl	Cl	H

FIGURE 19 Structure of compounds **33a,b** and **34a–d**

derivatives. Zykova, Odegova Boichuk, and Galembikova (2015) have synthesized 3-substituted 4-hydroxy-6-phenyl-3,4-dihydro-2*H*-1,3-oxazines **39a,b** from 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-dione and various arylidenearylamines. These compounds were examined in vitro for their antioxidant and cytotoxic activity. Highest antioxidant activity was observed for **39a** and **39b** but did not show cytotoxic properties against normal and human tumor cells (Figure 21).

5-(2*H*-tetrazol-5-yl)-4-thioxo-2-(substituted phenyl)-4,5-dihydro-1,3-oxazin-6-ones **40a–c** (Figure 22) from 1,3-oxazine-5-carbonitriles were designed and synthesized (Qamar et al., 2019). These synthesized compounds were tested their inhibitory potential against mushroom tyrosinase. The results confirmed that all exhibited compounds have significant tyrosinase inhibitory activity while compound **40a** having 2-bromophenyl moiety was the most potent among the series. Moreover, compounds **40b** and **40c** displayed superior DPPH radical scavenging activity than other analogues.

New derivatives of 2-[4-(hetero) aromatic]phenyl-2-hydroxy-tetrahydro-1,4-oxazine **41a–f** were synthesized to inhibit lipid peroxidation (Kourounakis, Charitos, Rekka, & Kourounakis, 2008). Synthesized compounds were characterized by various spectral techniques. Most of the compounds showed significant antioxidant activity, which was also higher than that of the references of trolox and probucol. The study revealed that the addition of a thienyl group will improve the antioxidant activity, which is may be due to an extension of the conjugated system and the presence of sulfur atom. Chaitra and Rohini (2018) have prepared a series of novel [1,3]-oxazine derivatives of N-[4-(2-Amino-4-phenyl-6H-[1,3]oxazine-6-yl)-phenyl]-nicotinamide. The targets were evaluated for their in

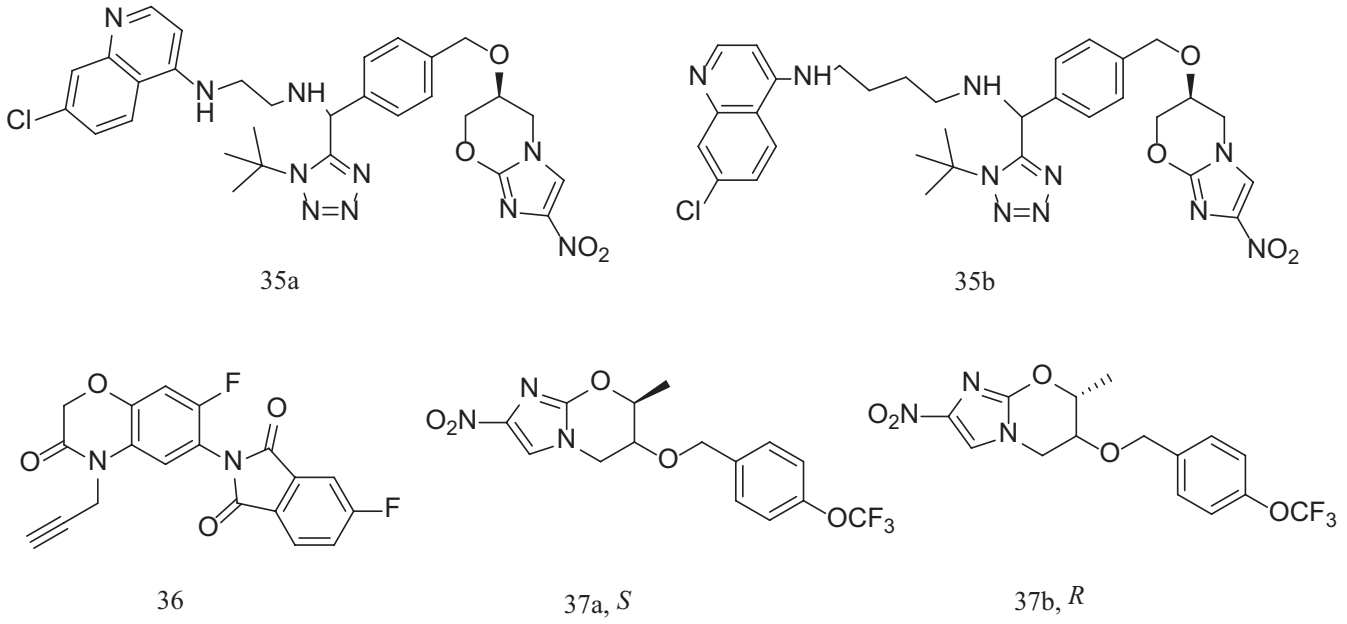
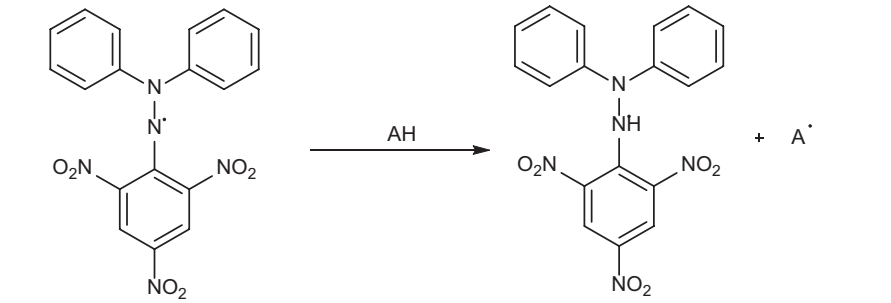


FIGURE 20 Structure of compounds **35a,b, 36** and **37a,b**

SCHEME 1 Scheme. 1 Mechanism of DPPH radical scavenging

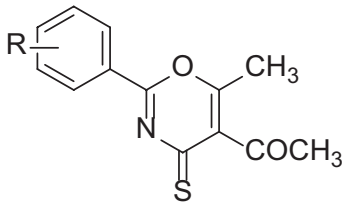


vitro anti-inflammatory activity by bovine serum albumin and protease method and antioxidant activity by DPPH and NO method. Compounds **42a** and **42b** exhibited significant activity when evaluated for BSA and protease methods for anti-inflammatory activity (Figure 23).

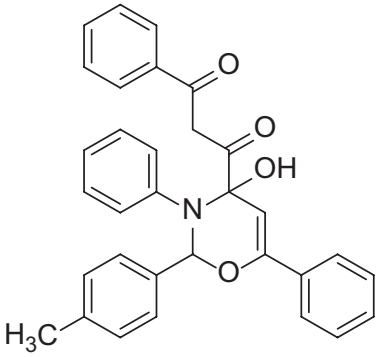
5 | ANTICANCER STUDY

Cancer, a group of diseases, which involves uncontrolled cell growth with the potential to spread. 1,735,350 new cancer cases are estimated to occur in 2018 and 609,640 might lead to death by this disease in USA (Mahal, Wu, Jiang, & Wei, 2019); therefore, the need for the development of more effective drugs for the treatment of cancer cells is the main challenge for the researchers. MTT assay is a common model for the determination of anticancer activity (Scheme 2) (Mahal, Wu, Jiang, & Wei 2017; Mohapatra et al., 2019). Converting MTT into a purple colored formazan occurred at maximum near 570 nm. The color changes from yellow to purple in case of cells die and **los**ing the ability to convert MTT into formazan including the reaction with NADH or similar reducing molecules that transfer electrons to MTT (Marshall, Goodwin, & Holt, 1995). It is still the understanding of this mechanism is not clear enough. Oxazines and their derivatives are known to have excellent anticancer properties.

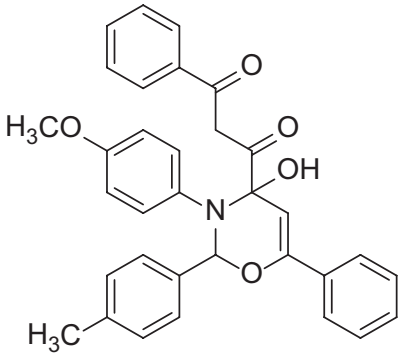
Botla, Pilli, and Koude (2017) have reported the green and catalyst-free synthesis of novel 2,3-dihydro-1*H*-benzo[2,3]benzofuro[4,5-e][1,3]oxazine derivatives **43a–c** from dibenzo[b,d]furan-2-ol, aromatic/aliphatic amines, and paraformaldehyde. Synthesized compounds exhibited good anticancer activity against lung cancer cell (A549), ovarian cancer cell (SKOV3), and breast cell (MCF7) lines. The compound **43a** displayed potent anticancer activity by inhibiting the cell proliferation of SKOV3 with an IC_{50} value at 7.5 μM, whereas **44a** and **44b** derivatives showed moderate activity against A549 with an IC_{50} value



38a	R= 4-Me	39h	2-Br
38b	4-OMe	39i	2-F
38c	2,6-OMe	39j	4-F
38d	2-Cl	39k	3-NO_2
38e	3-Cl	39l	4-NO_2
38f	4-Cl	39m	3,5-NO_2
38g	2,4-Cl	39n	1-Naph

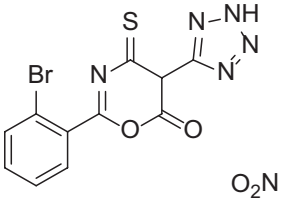


39a

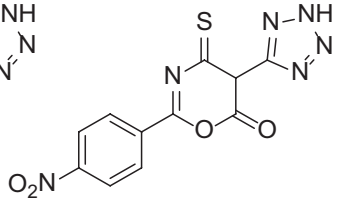


39b

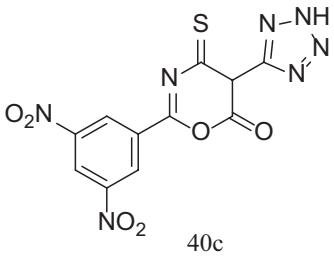
FIGURE 21 Structure of compounds **38a–n** and **39a,b**



40a

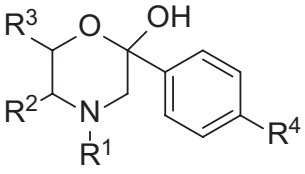


40b

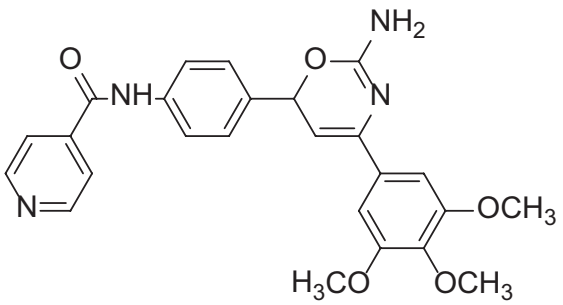


40c

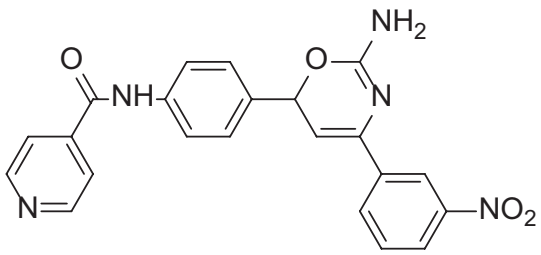
FIGURE 22 Structure of compounds **40a–c**



Compound	R^1	R^2	R^3	R^4
41a	CH_3	H	H	2-thienyl
41b	CH_3	$CH_3CH_2CH_2CH_2$	H	2-thienyl
41c	$CH_3CH_2CH_2CH_2$	H	H	2-thienyl
41d	CH_3	H	H	2-bromo-5-thienyl
41e	CH_3	$CH_3CH_2CH_2CH_2$	H	2-bromo-5-thienyl
41f	$CH_3CH_2CH_2CH_2$		H	2-bromo-5-thienyl



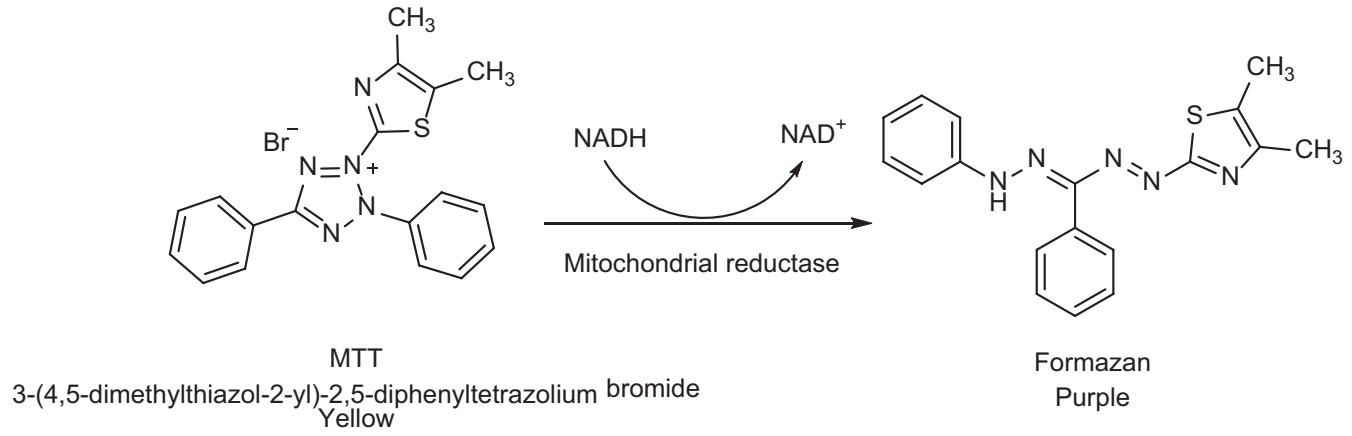
42a



42b

FIGURE 23 Structure of compounds **41a–f** and **42a,b**

ranging from 11 to 15.9 μM. Furthermore, structure relationship study is also discussed to understand the biological activity of these compounds. Maggiolini et al. (2015) have designed and synthesized two novel selective G-protein-coupled estrogen receptor (GPER) antagonists, based on a benzo[b] pyrrolo[1,2-d][1,4]oxazin-4-one structure.



SCHEME 2 Scheme. 2 Mechanism of MTT assay

The novel compounds may be useful for the dissection of the GPER signaling and the development of new pharmacological treatments in breast cancer. Compounds **44a** and **44b** made significant inhibition on the GPER-dependent signaling as selective antagonist ligands in breast cancer cells including MCF7 and SkBr3 and cancer-associated fibroblasts (CAFs; Figure 24).

Kumar et al. (2018) have synthesized pyrrolopiperazine fused with oxazines **45a–d** by the reaction of δ-alkynyl aldehydes and amines. These compounds were fully characterized and evaluated for their anti-proliferative properties in vitro using leukemia cells (K562), breast cancer cells (BT474), and breast cancer cells (MCF7). Compounds **45b** (IC_{50} 17.6 μM) and **45c** (IC_{50} < 21 μM) showed significant inhibition against human breast cancer cells. On the other hand, compound **45d** showed good activities against K562 with an IC_{50} = 3 μM and breast cancer cell BT474 with an IC_{50} = 4 μM but not in MCF7 cells (IC_{50} = 19.6 μM). A novel series of tricyclic oxazine fused quinazolines through intramolecular cyclization were reported as potent antitumor agents (Sun et al., 2016). Compounds **46a–h** demonstrated more potent activities against gastric carcinoma cell NCI-N87, epidermoid carcinoma cell A431, adenocarcinoma cell NCI-H1975, BT474, and adenocarcinoma cell Calu3 lines with IC_{50} values of 0.1 ~ 2.01 μM compared to gefitinib (IC_{50}: 0.36 ~ 1.00 μM) and erlotinib (IC_{50}: 0.75~>10 μM) (Figure 25).

Chen et al. (2014) have synthesized and characterized a series of novel tricyclic oxazine fused quinazolines **47a–h** and tested against cancer cell lines including gastric carcinoma cell NCI-N87, epidermoid carcinoma cell A431, NCI-H1975, BT474, and Calu3 lines. These reported compounds performed impressive inhibition activity against the cell lines. The activity of compound **47h** (IC_{50} = 0.046–0.24 μM) is more potent than erlotinib b (IC_{50}: 0.75–>10 μM) and gefitinib (IC_{50}: 0.36–1.00 μM) against A431, NCI-N87, BT474, Calu3. 2-oxo-benzo[1,4]oxazine analogues 4**8a–h** have been synthesized and characterized by Jaiswal et al. (2018). The cytotoxic studies of these compounds in 3T3 fibroblast cell lines were carried out and found to be non-toxic in nature. In addition, all compounds were identified as promising platelet aggregation inhibitors as compared to aspirin (Figure 26).

A series of [1,3]oxazino fused acridines **49a–f** were prepared by Ouberai et al. (Ouberai et al., 2006), and their cytotoxic activity was conducted against HT29 colon carcinoma cell line. The substituent located in position 2 of the oxazine ring may play important role in increasing the bioactivity. Basappa et al. (2010) have designed and synthesized a novel

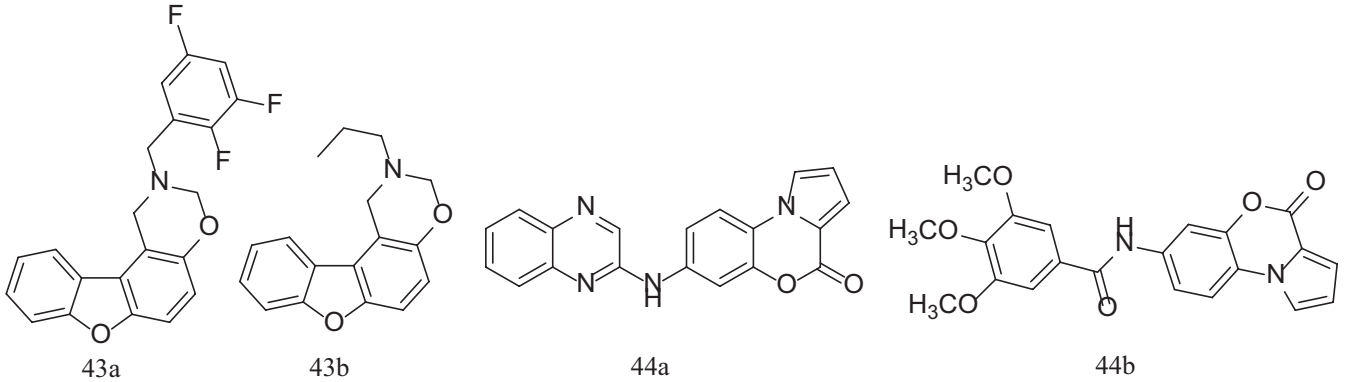


FIGURE 24 Structure of compounds **43a,b** and **44a,b**

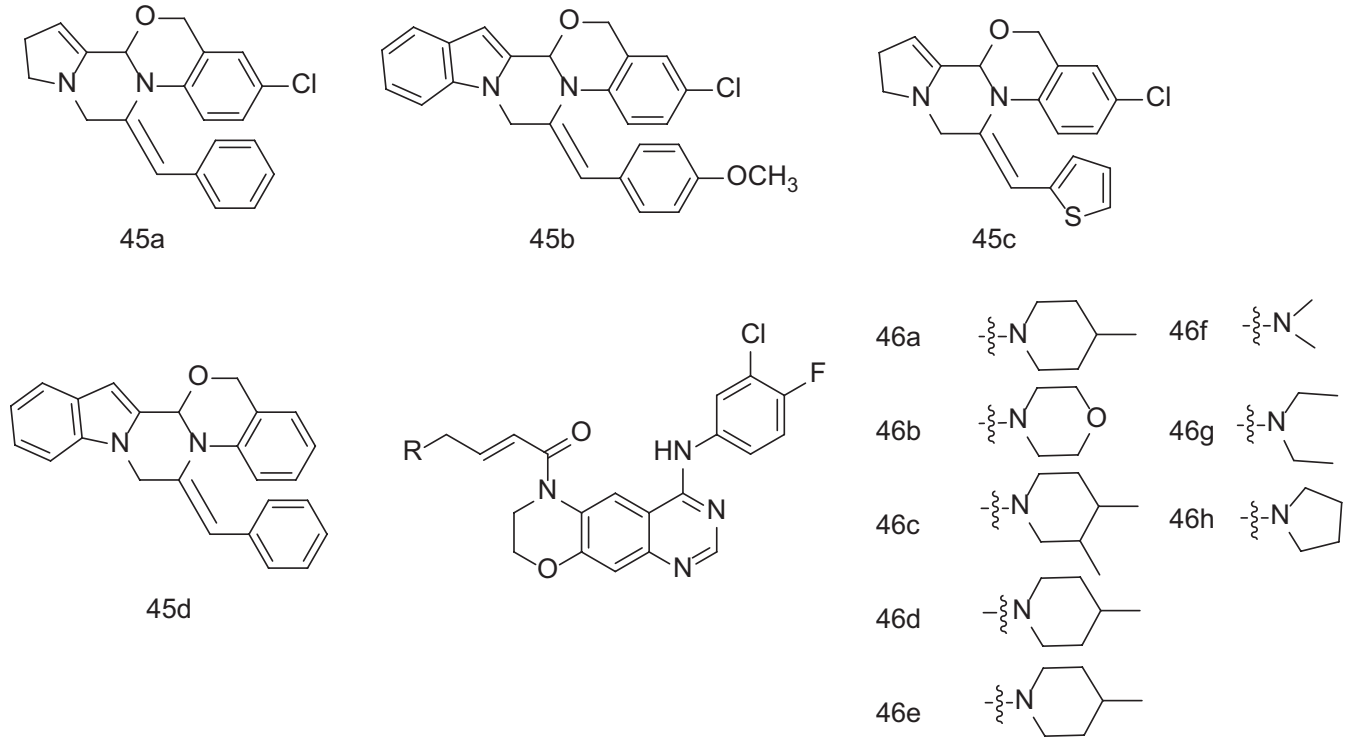
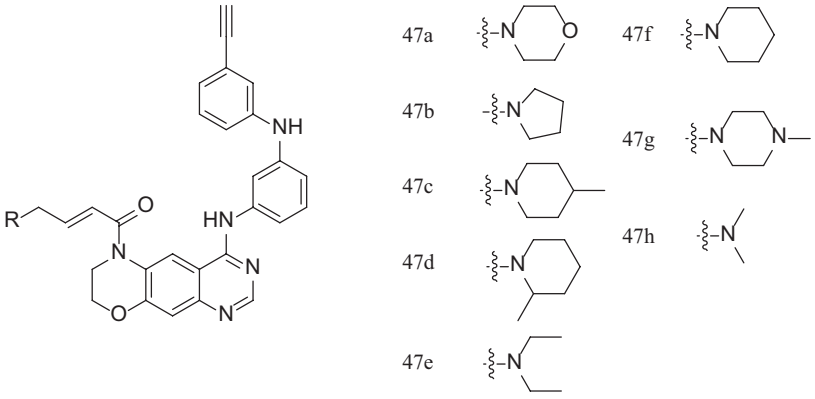


FIGURE 25 Structure of compounds **45a–d** and **46a–h**



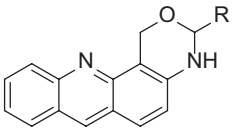
Compound	R^1	R^2	R^3	R^4	R^5	R^6
48a	Br	H	H	CH_3	H	Br
48b	Br	H	H	H	NO_2	H
48c	OCH_3	H	H	CH_3	H	Br
48d	Cl	Cl	H	CH_3	H	Br
48e	F	H	H	CH_3	H	Br
48f	H	H	NO_2	H	H	H
48g	Cl	H	NO_2	H	H	H
48h	Br	H	NO_2	H	H	H

FIGURE 26 Structure of compounds **47a–h** and **48a–h**

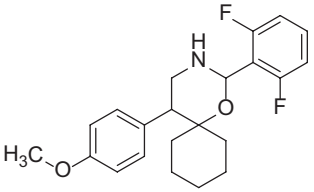
pyranoside mimetic compound, namely DMBO 2-(2,6-difluorophenyl)-5-(4-methoxyphenyl)-1-oxa-3-azaspiro[5.5]undecane (50). This compound showed strong anti-proliferation activity of tumor necrosis factor (TNF-α) of ovarian cancer cells (OVSAHO) with an IC_{50} value of 16 μM and with an IC_{50} value of 13 μM against osteosarcoma cell line (LM8G7) (Figure 27).

Morrison, Al-Rawi, Jennings, Thompson, and Angove (2016) have described the synthesis of a series of 8-aryl-2-morpholino-4*H*-benzo[e][1,3]oxazin-4-ones with potent activity against PI3K and DNA-PK. The compounds were evaluated for their anti-proliferative activity, in which compound **51a** showed strong anti-proliferative activity (GI% at 10 μM = 92) against renal cancer cell lines (A498)

FIGURE 27 Structure of compounds **49a–f** and **50**



Compound	R
49a	CH_3
49b	CH_2Cl
49c	CH_2Br
49d	$CH_2O\text{-}CH_2Ph$
49e	Ph
49f	*p*-Ph-NO_2



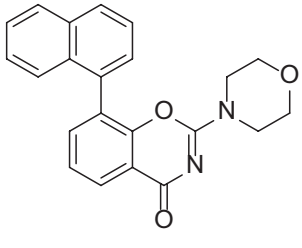
50

and the compound **51b** displayed strong activity with IC_{50} = 0.034 μM and 170-fold more selective over the PI3K inhibitor. New derivatives of 1-aryl-2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazine bearing an arylsulfonamide moiety **52a–h** were synthesized and characterized by Mansouri et al. (2017) Compound **52e** showed most potency against MCF7 (IC_{50} = 16.14 μM) and colorectal carcinoma cell lines (HCT116) with an IC_{50} value of 19.72 μM while **52f** displayed strong activity against MCF7 (IC_{50} = 15.22 μM) and HCT116 (IC_{50} = 18.72 μM). Synthesized compounds were found less toxic on the normal cells of PBMC rather than cancer cell lines (Figure 28).

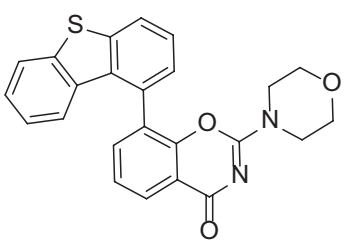
A series of naphth-oxazine derivatives **53a–h** have been synthesized and characterized by using various spectral tools (Bouaziz et al., 1991). These reported compounds were studied in vitro on leukemia cell (L1210), breast cancer cell (MDA-MB231) lines. The whole compounds showed significant cytotoxic activity toward both L1210 (IC_{50} = 0.174–1.137 μM) and MDA-MB231 (IC_{50} = 0.046–2.91 μM) cells. Three compounds **53a,b,h** were found to be more cytotoxic than 5-hydroxy naphthalene-1,8-carbolactone toward L1210. Tests on MDA-MB231 cells revealed a lower activity for all compounds compared to 5-hydroxy naphthalene-1,8-carbolactone. A Mannich-type condensation was used to synthesize new derivatives of dihydro furonaphth[1,3]oxazine **54a–e**. All synthesized compounds were screened for in vitro cytotoxic activity toward L1210, MDA-MB, and prostate cancer cell lines (PC3). Among them, compound **54b** showed a significant activity against L1210 cells with an IC_{50} value of 2.995 μM and compound **54c** showed potency activity (IC_{50} = 2.256 μM) against L1210 cells (Benameur, Bouaziz, Nebois, Bartoli, & Boitard, 1996). A series of 2*H*-benzo[b][1,4]oxazine derivatives were synthesized and characterized by Das Madhukumar Anguiano and Mani (2009). These compounds were examined for their biological activities on liver hepatocellular cell lines (HepG2) under normoxic and hypoxic conditions. Compounds **55a,b** specifically inhibit hypoxic cancer cell growth on HepG2 cells with an IC_{50} value of 87 μM and IC_{50} value of 10 ± 3.7 μM, respectively (Figure 29).

The anticancer activity of a novel series of oxazinyl isoflavonoids has been reported (Wang, Hou, Wu, & Yu, 2012). These compounds were fully characterized by several spectral methods. Also, the compounds were tested against ovarian cancer cell line (SKOV3), prostate cancer cell line (DU145), and leukemic cell line (HL-60). Furthermore, the cellular potency of the compounds **56a,b** was determined and found to be greater than phenoxodiol. Gupta et al. (2016) have synthesized a novel series of 3,4-dihydro-2*H*-1,3-oxazine derivatives of bakuchiol through Mannich-type condensation-cyclization reaction. The newly synthesized compounds were tested against leukemia, breast, colon and pancreatic cancer cell lines. Most of the compounds including compound **57** displayed greater cytotoxic profile than the parent molecule (Figure 30).

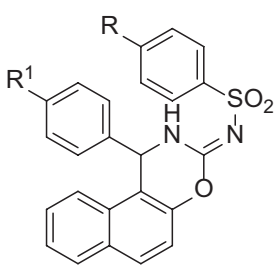
The oxazine substituted 9-anilinoacridine derivatives **58a–f** have been synthesized and characterized by Kalirajan Kulshrestha Sankar and Jubie (2012). These derivatives were examined for their antioxidant and anticancer activity against Dalton's lymphoma ascites cell lines (DLA). Compounds **58a**, **d**, **e**, and **f** have shown remarkable anticancer activity as topoisomerase II inhibitors. In addition, the derivatives displayed interesting antioxidant activity when compared to standard ascorbic acid (Figure 31).



51a

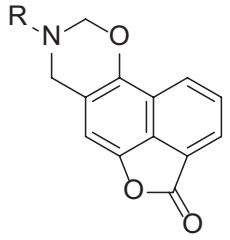


51b

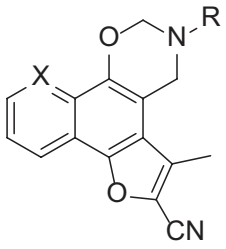


Compound	R	R^1
52a	*P*-Cl	H
52b	*P*-CH_3	*P*-CH_3
52c	*P*-Cl	*P*-CH_3
52d	*P*-OCH_3	*P*-i_{Propyl}
52e	H	*P*-Cl
52f	*P*-Cl	*P*-Cl
52g	*P*-OCH_3	*P*-Cl
52h	*P*-Cl	*P*-OCH_3

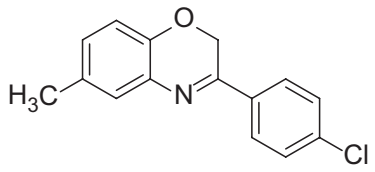
FIGURE 28 Structure of compounds **51a,b** and **52a–h**



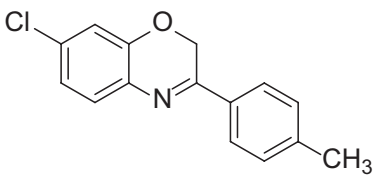
Compound	R
53a	C_6H_5
53b	*p*-Cl-C_6H_4
53c	*p*-CH_3-C_6H_4
53d	C_6H_5-CH_2
53e	*p*-Cl-C_6H_4-CH_2
53f	*p*-CH_3O-C_6H_4-CH_2
53g	C_6H_5-$CHCH_3$
53h	CH_3CHCH_2



Compound	R
54a	C_6H_5-CH_2
54b	*p*-CH_3O-C_6H_4-CH_2
54c	CH_3CHCH_2
54d	$CH_2CH_2N(CH_3)_2$
54e	$C(CH_3)_3$

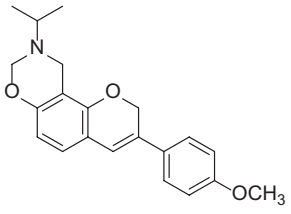


55a

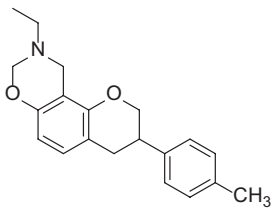


55b

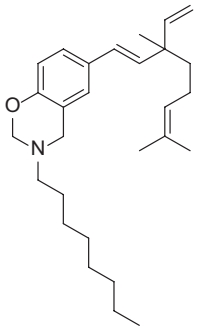
FIGURE 29 Structure of compounds **53a–h**, **54a–e,** and **55a,b**



56a

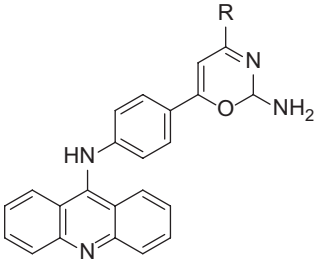


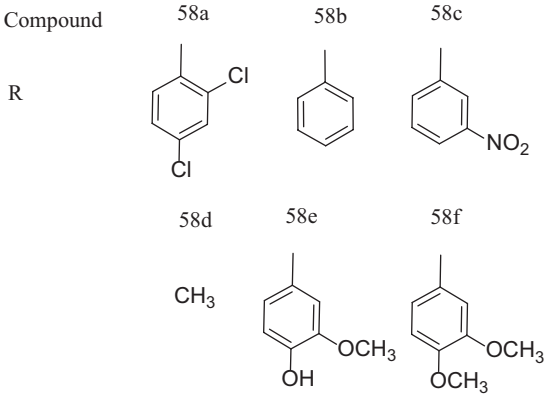
56b



57

FIGURE 30 Structure of compounds **56a,b** and **57**



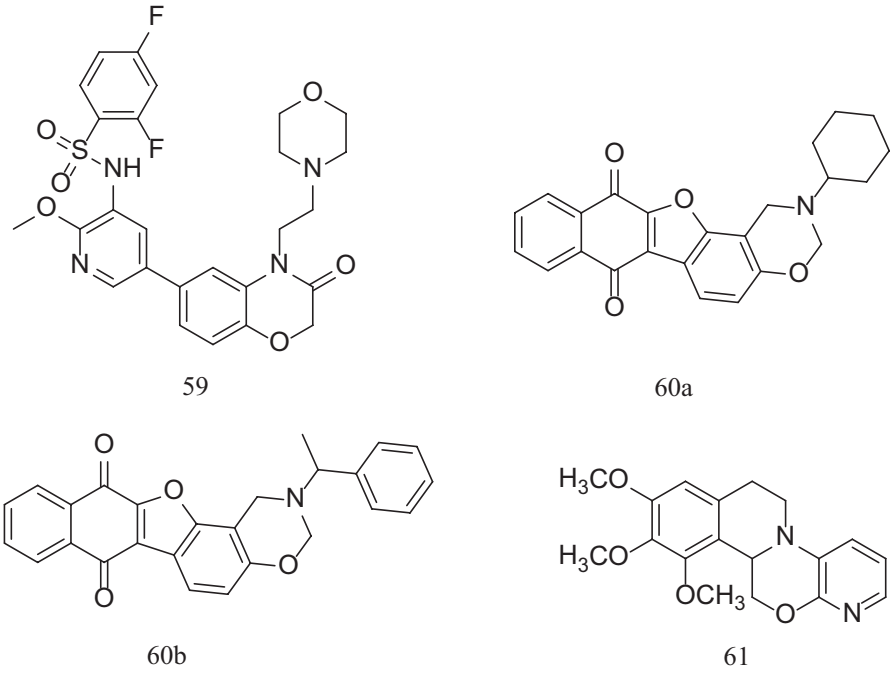


Compound	58a	58b	58c
R			
	58d	58e	58f
	CH_3		

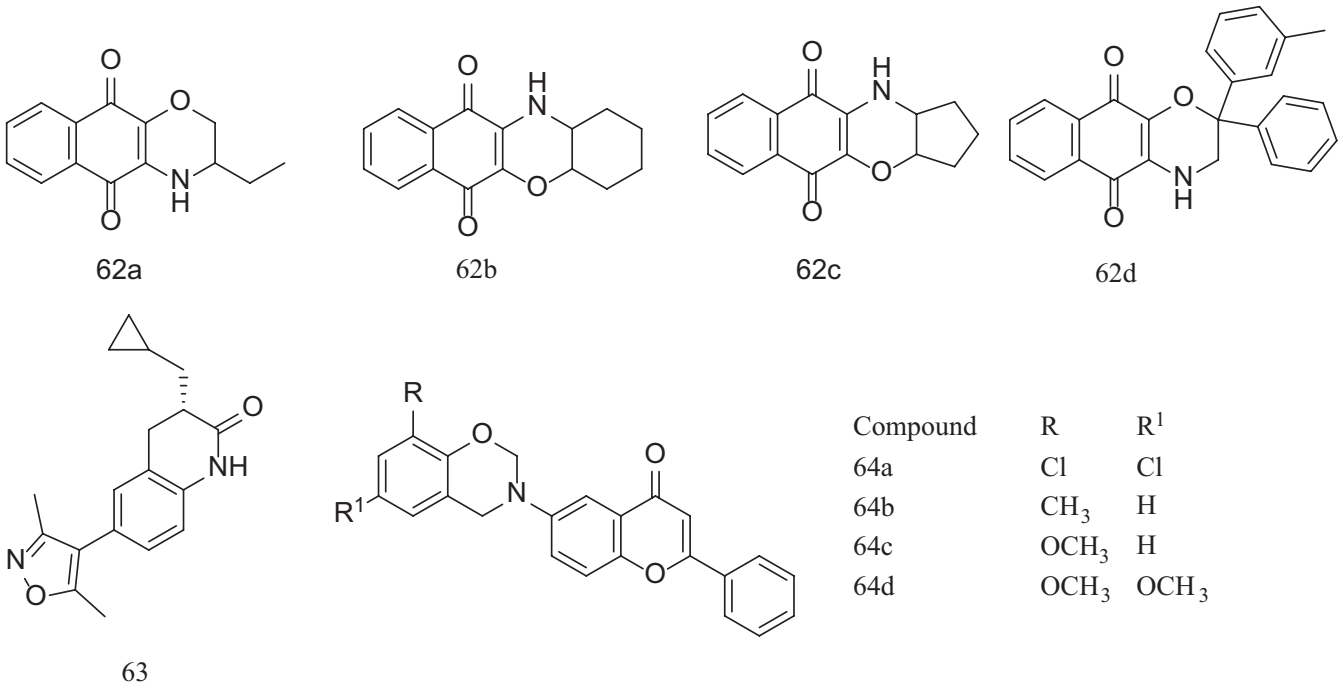
FIGURE 31 Structure of compounds **58a–f**

Dong et al. (2018) were designed and synthesized two series of 2*H*-benzo[b][1,4]oxazin derivatives containing sulfonamide substituted pyridyl group. The reported compounds were tested for their anti-proliferative activities against HCT116, MDA-MB231, and gastric cancer cell lines (SNU638) cancer cell lines. Compound **59** exhibited more potent anti-proliferative activity. The compound is also tested for its cytotoxic effects on normal human cells and found much less inhibitory activity against normal lung cells (MRC5) with an IC_{50} = value of 32.8 μM and normal human umbilical vein endothelial (HUVEC) with an IC_{50} value of 15.6 μM. The anti-proliferative effects of some commercially available oxazine analogues have been examined by Amato et al. (2019) using a library of well-characterized G4-binder.

FIGURE 32 Structure of compounds **59, 60a,b,** and **61**



59 60a 60b 61



62a 62b 62c 62d

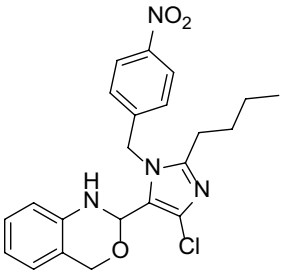
63

Compound	R	R^1
64a	Cl	Cl
64b	CH_3	H
64c	OCH_3	H
64d	OCH_3	OCH_3

FIGURE 33 Structure of compounds **62a–d, 63,** and **64a–d**

The study confirmed that these compounds were able to bind several G4 structures. Moreover, the assays also convinced that these compounds produced effective DNA damage in low μM range. Compound **60b** is less cytotoxic than compound **60a** on normal cells. Ma et al. (2006) have synthesized Pyridooxazine–tetrahydroisoquinoline derivatives for inhibitors of multidrug resistance modulating activity. Compound **61** with trimethoxy groups on phenyl ring displayed high cytotoxic and multidrug resistance modulating activity (Figure 32).

You et al. (2018) were proceeded a convenient synthesis of 3,4-dihydro-2*H*-naphtho [2,3-b] [1,4] oxazine-5,10-diones **62a–d** via copper-catalyzed intramolecular C-O/C-C coupling reaction and tested for activities and exhibited good inhibitory activities against A549. Xue et al. (2018) have synthesized and characterized a new series of benzoxazinone-containing



65

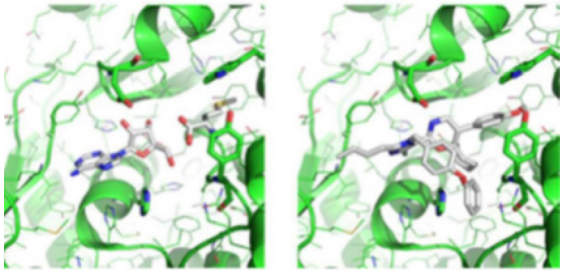
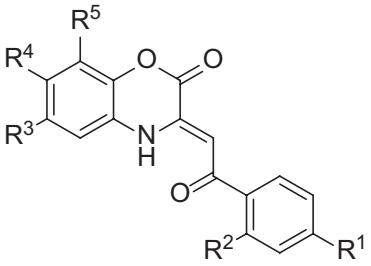


FIGURE 34 Structure of compounds **65** and molecular interactions with methionyl-tRNA synthetase



Compound	R^1	R^2	R^3	R^4	R^5
66a	OCH_3	H	H	H	H
66b	H	H	NO_2	H	H
66c	H	H	Cl	H	H
66d	F	H	CH_3	H	H
66e	H	H	CH_3	H	Br
66f	F	H	CH_3	H	Br
66g	NO_2	H	CH_3	H	H
66h	F	H	NO_2	H	H
66i	Cl	Cl	H	NO_2	H
66j	Br	H	H	NO_2	H

FIGURE 35 Structure of compounds **66a–j**

3,5-dimethylisoxazole derivatives based on structural analysis of BET bromodomain inhibitors. The compound **63** binds in the acetyl-lysine binding site of bromodomain-containing protein 4 (BRD4(1)) with an IC_{50} value of 100 nM and shown promising therapeutic effects in a human prostate 22Rv1 carcinoma tumor xenograft model. Garg et al. (2013) have described the synthesis of 1,3-benzoxazine derivatives having flavones moiety at 3-position **64a–d**. The derivatives were explored in vitro against MCF7 cell lines and found to be most potent. Furthermore, molecular docking studies of these compounds were also carried out, which is in good agreement with the experimental results (Figure 33).

The biological studies of a series of 1,3-oxazines, benzoxazines scaffolds against human methionyl-tRNA synthetase (MRS) has been reported (Bharathkumar et al., 2015). The compound **65** proved to be potent and significantly suppressed the proliferation of lung carcinoma and colon cancer cells (Figure 34).

Ultrasound-assisted irradiation was employing to prepare new derivatives (Sharma et al., 2018; Sharma et al., 2018) of C-3 tethered 2-oxo-benzo[1,4]oxazines **66a–j**. The in vitro cytotoxic study of these compounds was carried out in MTT assay. The study displayed non-toxic nature of the compounds **66a** and **66b** in non-cancerous 3T3 fibroblast cell lines (Figure 35).

The design and cytotoxic activity of a series of ethyl 3-oxo-2-(substituted-phenylamino)-3,4-dihydro-2*H*-benzo[b][1,4]oxazine-6-carboxylates **67a–e** has been reported by Lin et al. (2016) The in vitro cytotoxicity against eleven cancers and one normal cell line was carried out and found to be highly cytotoxic with growth inhibition values of 0.34 to >50 μM (Figure 36).

A series of 3-ferrocenyl-2-ferrocenylmethyl-2-morpholino-2H-areno[1,4]oxazines **68a–f** have been synthesized and characterized by García, Flores-Álamo, Martínez-Klimova, Ramírez Apan, and Klimova (2018) The compounds were screened in vitro against six human cancer cell lines including HCT15, MCF7, K562, PC3, glioblastoma cell (U251), and lung cancer cell (SKLU1) lines using sulforhodamine-B assay as described in the protocols established by the National Cancer Institute (Monks et al., 1991; Skehan et al., 1990). Some of the compounds displayed significant cytotoxic activity. This study will help to develop better and safer therapeutic antitumor agents (Figure 37).

6 | ANTI-INFLAMMATORY STUDY

Anti-inflammatory agents play an important role in reducing inflammation in the body and acute and chronic inflammatory conditions. 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.

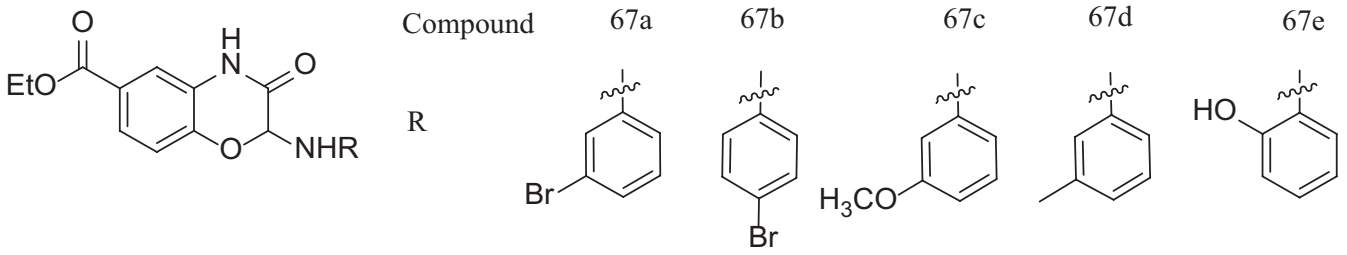
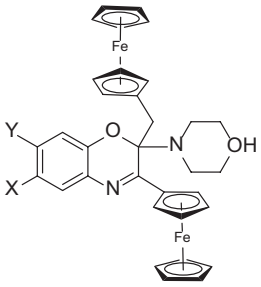


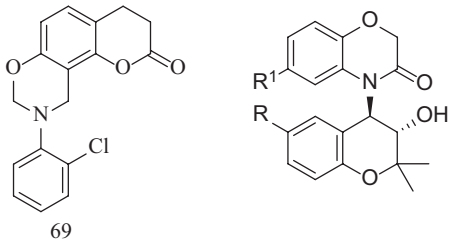
FIGURE 36 Structure of compounds **67a–e**

FIGURE 37 Structure of compounds **68a–f**



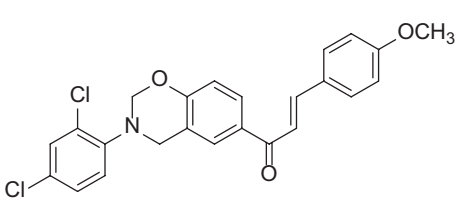
Compound	68a	68b	68c	68d	68e	68f
X	H	CH_3	^tBu	Cl	NO_2	CH=HC
Y	H	CH_3	^tBu	Cl	NO_2	

Zhang, Li, Cao, Tian, and Quan (2017) have studied the effect of new derivatives of tetrahydro-2*H*,8*H*-chromeno[8,7-e][1,3]oxazin-2-one on lipopolysaccharide (LPS)-induced cytokine levels in mouse macrophage cells (RAW264.7). The results showed that the compound of 9-(2-chlorophenyl)-3,4,9,10-tetrahydro-2*H*,8*H*-chromeno[8,7-e][1,3]oxazin-2-one (**69**) could inhibit inflammatory responses via suppression of the NF-κB and MAPK signaling pathways. 3-hydroxy-2,2-dimethylchroman-4-yl)-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one derivatives 70a-f have been synthesized and characterized by various spectral methods (Bano, Barot, Jain, & Ghate, 2015). The biological activities of these compounds were evaluated for K_{ATP} channel opener as antihypertensive activity. Compounds **17a**, **17b**, **17c**, and **17d** have exhibited around 40% inhibition of COX1 as compared to the inhibition of COX2. Compounds **17e** and **17f** displayed notable inhibition activity more than 50% of COX-2 compared with the inhibition of COX1 at a concentration of 0.3 mg/ml. New benzoxazine derivatives have been reported by solvent-free microwave thermolysis (Akhter, Habibullah, et al., 2011). These compounds were tested for their anti-inflammatory activity. Compound **71** exhibited 74.87% in rat paw edema, 57.38% of protection against acetic acid-induced writhing, 0.08 of severity index (SI) of gastric damage compared to 82.33 value of ibuprofen. Some novel oxazine derivatives have been synthesized and characterized by using Bi_2O_3 catalyst (Srinivas et al., 2015). The biological activities were also carried out. According to the study, compound **72** was most potent having high degree of selectivity in inhibition toward COX2

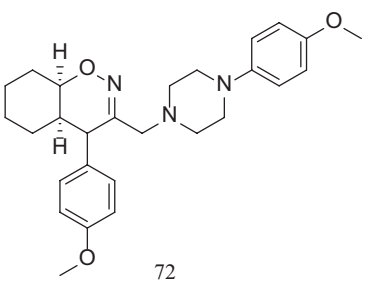


69

Compound	R	R^1
70a	Br	NO_2
70b	NO_2	Br
70c	NH_2	Cl
70d	NO_2	Cl
70e	NH_2	NO_2
70f	NO_2	NO_2



71



72

FIGURE 38 Structure of compounds **69, 70a–f, 71,** and **72**

over COX1. This study may be helpful in developing new COX2 specific inhibitors (Figure 38).

7 | NEURODEGENERATIVE STUDY

The amino-1,4-oxazine-derived BACE-1 inhibitors has been synthesized and characterized by Veenstra et al. (2018). All the compounds displayed nanomolar activity for the inhibition of Ab release in comparison with biochemical enzyme inhibition assay. Compound **73** fixed the in vitro results by dose-dependently reducing A neurotoxic β-amyloid (Aβ) levels in mice (IC_{50} = 8 nM). A novel 2-ethoxy-4,5-diphenyl-1,3-oxazine-6-one (**74**) has been designed and characterized by Ansari et al. (Ansari, Khodagholi, Amini, & Shaerzadeh, 2011). The biological study proved that this compound could increase heat shock proteins Hsp70 and Hsp32 levels. Pretreatment of the cells with this reported compound also increases γ-GCS level and antioxidant enzyme activities. A novel series of chiral oxazino-indoles **75a–d** have been prepared and characterized by Chen, Tao, et al. (2016). These compounds performed serious neuroprotective effects against $Aβ_{25–35}$-induced neuronal damage. The results clearly indicated that the synthesized compounds displayed robust neuroprotective effects against $Aβ_{25–35}$ induced neurotoxicity. (Figure 39).

The synthesis and structure relationship study of a series of BACE inhibitors containing oxazines have been reported by Low et al. (2018) Aβ peptide is a responsible of Alzheimer's disease (AD) in which produced by β-secretase enzyme and BACE inhibitors can be recuced the levels of Aβ in the AD brain. The derivative 76 was confirmed as a potent (IC_{50} = 15 nM) BACE inhibitor with acceptable absorption, distribution, metabolism, and excretion properties. In vivo, it also exhibited a notable reduction of brain and CSF Ab40 levels. The synthesis and characterization of novel oxazine-based BACE1 inhibitors **77a,b** have been reported by Fuchino et al. (2018) to improve brain penetration by lowering amidine basicity. According to the study, the compounds demonstrated significant Aβ reduction. Potent 6-substituted 5-fluoro-1,3-dihydro-oxazine β-secretase (BACE1) inhibitors have been developed by Nakahara et al. (2018) via active conformation stabilization. Compound 78 inhibited hERG and displayed high P-gp efflux with robust Aβ reduction. The compound also performed significant Aβ reduction at a dose of no more than 0.16 mg/kg in dog (Figure 40).

Rombouts et al. (2015) have developed the synthesis of novel 1,4-oxazineanalogues. These were found to have potent in vitro inhibition in enzymatic and cellular BACE1 assays. The newly synthesized derivatives **79a** and **79b** demonstrated to be orally bioavailable, centrally active and which exhibited robust lowering of brain and cerebrospinal fluid (CSF Aβ) levels, respectively, in mouse and dog models. Allison et al. (Allison & Mani, 2017) have developed gram-scale synthesis of β-secretase 1 (BACE 1). Inhibitor in which overcame the use of hazardous, expensive reagents, and numerical chromatographic purifications that led to poor overall yield (<2%). Compound **80** was proved to be one of the most promising and selected for further bioactivity evaluation (Figure 41).

Osteoarthritis (OA) is a common degenerative joint disease. Ho et al. (2019) have reported the anti-osteoarthritis effects of 3-(4-chloro-2-fluorophenyl)-6-(2,4-difluorophenyl)-2H-benzo[*e*] [1,3]oxazine-2,4(3H)-dione (Cm-02) and 6-(2,4-difluorophenyl)-3-(3,4-difluorophenyl)-2H-benzo[*e*] [1,3] oxazine-2,4(3H)-dione (Ck-02). Anti-osteoarthritic effects were determined in terms of protein and mRNA levels associated with the pathogenesis of OA. The results demonstrated that both Cm-02 and Ck-02

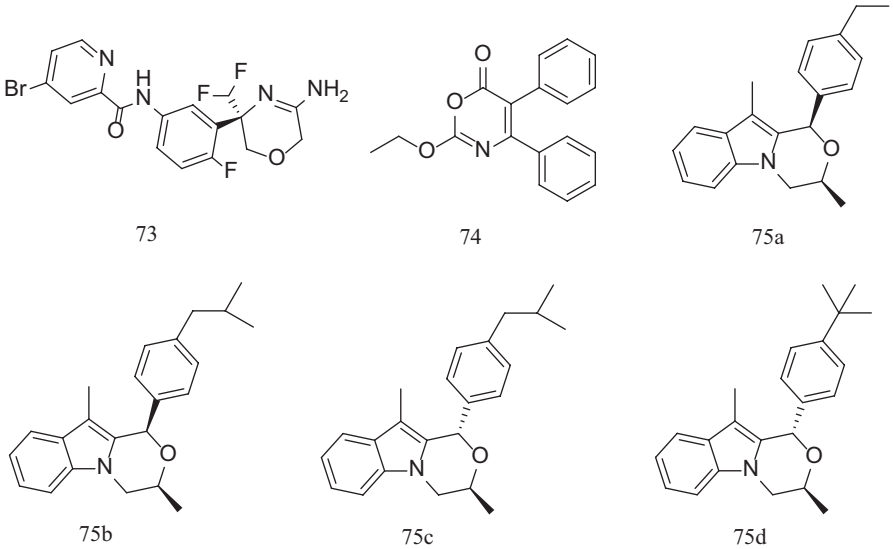


FIGURE 39 Structure of compounds **73**, **74,** and **75a–d**

FIGURE 40 Structure of compounds **76, 77a,b,** and **78**

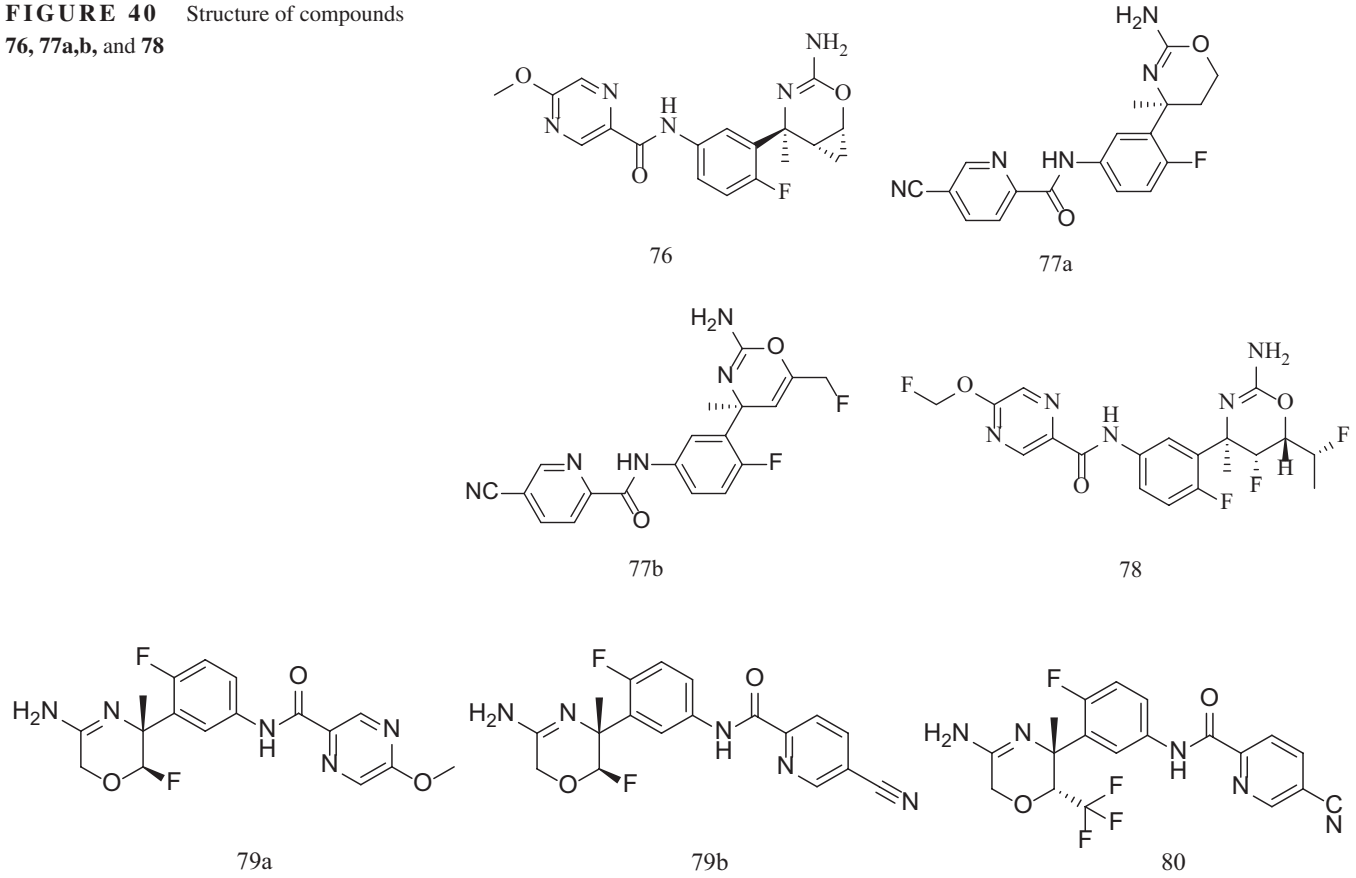


FIGURE 41 Structure of compounds **79a,b** and **80**

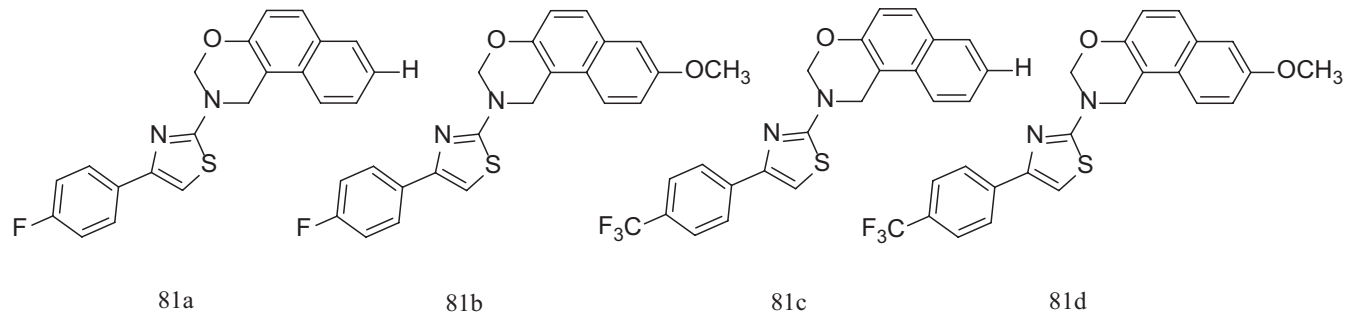


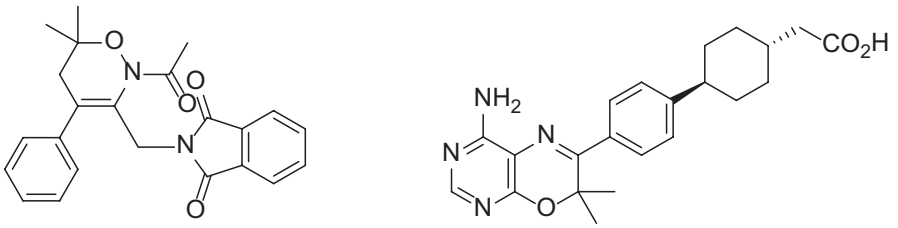
FIGURE 42 Structure of compounds **81a–d**

have potent anti-inflammatory activities and the ability to protect cartilage in an OA cell model, which will be very useful for the therapeutic treatment of OA.

8 | MISCELLANEOUS STUDY

A novel series of 2-thiazolyl substituted-2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazine derivatives **81a–d** have been developed (Gawali et al., 2018) on the basis of structure activity relationships. The inhibitory effect on HIV-1 reverse transcriptase (RT) enzyme activity was studied. The synthesized compounds (Figure 42) inhibited potent activity of HIV-1 RT at low concentration and demonstrated a better therapeutic index (TI) than known HIV-1 RT inhibitors such as Zidovudine and Efavirenzb.

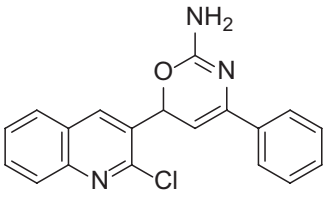
Oxazine-based small molecule targeting 5-LOX and AChE was designed and developed (Sukhorukov et al., 2014). The most active compound **82** displayed significant inhibitory activity toward 5-LOX and AChE. A potent and selective diacylglycerol acyltransferase 1 (DGAT1) inhibitor 1 containing a pyrimidooxazine core and a phenylcyclohexylacetic acid substituent (IC_{50} = 40 nM) was reported (Fox, Sugimoto, Iio, Yoshida, & Zhang, 2014). Inhibitor 83



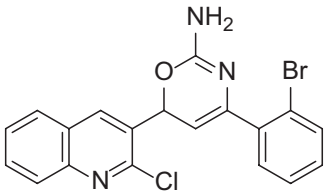
82

83

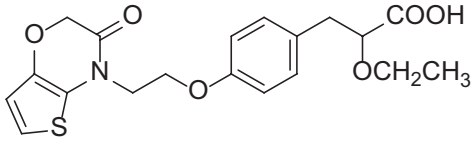
FIGURE 43 Structure of compounds **82, 83,** and **84a,b**



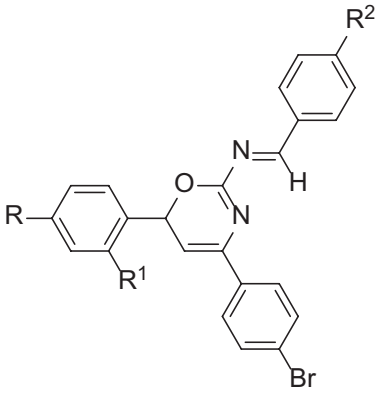
84a



84b



85



Compound	R	R^1	R^2
86a	NO_2	H	NO_2
86b	H	OH	NO_2
86c	Cl	H	Cl
86d	$N(CH_3)_2$	H	Cl
86e	NO_2	H	OCH_3
86f	$N(CH_3)_2$	H	OCH_3

FIGURE 44 Structure of compounds **85** and **86a–f**

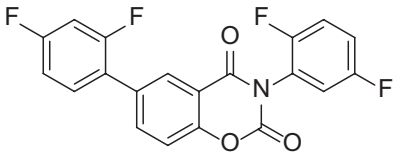
acted as a promising preclinical candidate to form 2-hydroxy metabolite in cynomolgus monkeys. Tiwari, Meshram, and Ali (2011) have developed a series of 6-(2-chloroquinolin-3-yl)-4 substituted phenyl-6-*H*-1,3-oxazin-2-amines in two reaction step including Claisen–Schmidt reaction. Compounds **84a,b** were found to have better antimalarial activity than chloroquine against resistant strain of *P. falciparum* (Figure 43).

Novel phenyl acetic acid and α-hydroxy propionic acid based Thieno[3,2-b][1,4]oxazinone derivatives were synthesized by Das et al. (2003). In vivo study demonstrated that compound **85** showed higher potency in which has both glucose- and lipid-lowering properties. Schiff bases of 1, 3-oxazine derivatives **86a–f** have been synthesized and characterized from 1,3-oxazine-2-amine and substituted benzaldehydes (Ramesh, Mahesh, & Jyoti, 2012). Newly synthesized derivatives were examined for their anticoagulant activity by Quick's method. The compounds showed significant anticoagulant activity (Figure 44).

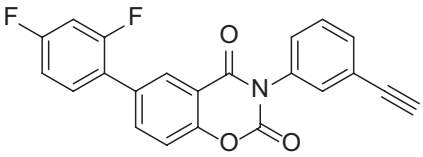
A series of 6-(2,4-difluorophenyl)-3-phenyl-2*H*-benzo[e][1,3]oxazine-2,4(3*H*)-dione derivatives have been synthesized and characterized by Lee et al. (2015) These compounds were tested for their inhibitory effects on osteoclast activities by using telomere repeat amplification protocol assay. The study revealed that targets **87a** and **87b** presented more potent osteoclast-inhibitory activities. Koini et al. (2012) have synthesized the microwave-assisted 6-substituted-5,7,8-trimethyl-1,4-benzoxazines-ones **88a–k** by Suzuki-Miyaura cross coupling method. Compounds **88b** and **88j** showed high activity with IC_{50} = 1.21 μM and 0.86 μM, respectively, as potential agents against toxoplasmosis (Figure 45).

The synthesis of 2-(N substituted-3-aminopyridine)-substituted-1,3-benzoxazines **89a–c** has been reported by Ihmaid et al. (Ihmaid, Al-Rawi, Bradley, Angove, & Robertson, 2012) These compounds were studied for their DNA-PK inhibition and antiplatelet activity. DNA-PK inhibition data for 2-morpholino-substituted-1,3-benzoxazines displayed

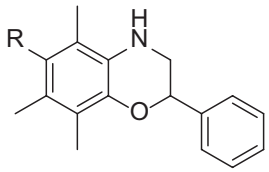
FIGURE 45 Structure of compounds **87a,b,** and **88a–k**



87a

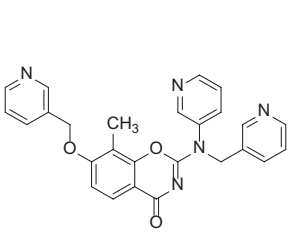


87b

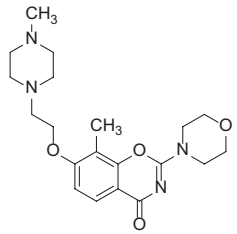


Compound	R
88a	*o*-Me-OPh
88b	*m*-Me-OPh
88c	*P*-Me-OPh
88d	(*E*)-styryl
88e	4-vinylphenyl
88f	2-furyl
88g	2-thienyl
88h	2-naphthyl
88i	*P*-CF_3-Ph
88j	*P*-butylphenyl
88k	butyl

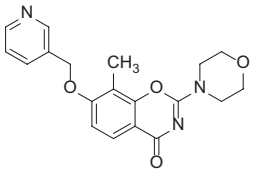
FIGURE 46 Structure of compounds **89a–c**



89a

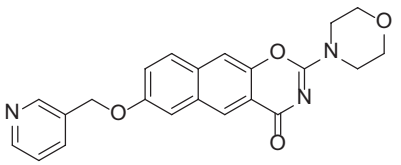


89b

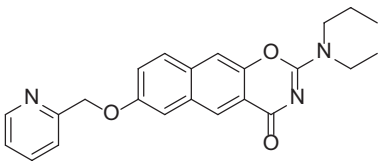


89c

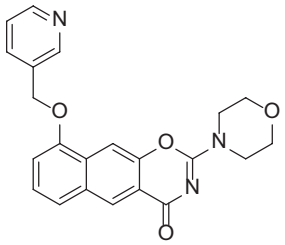
FIGURE 47 Structure of compounds **90a–d**



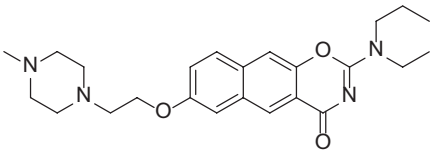
90a



90b



90c

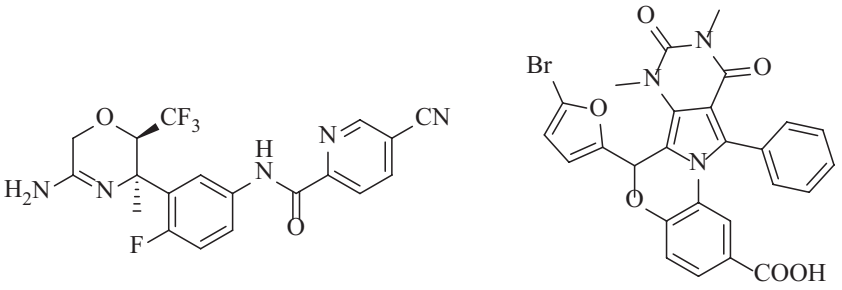


90d

significant activity. Compound **89b** exhibited greater inhibition of DNA-PK over PI3K (Figure 46).

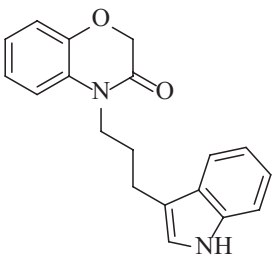
Morpholino-substituted-1,3-naphth-oxazines (Figure 47) have been synthesized and evaluated for their homology modeling, DNA-PK inhibition, and antiplatelet activity (Ihmaid et al., 2011). IC_{50} for the compound **90a** was 55 μM due to inhibitory effect on human platelet aggregation induced by collagen. Moreover, DNA-PK activity was measured and showed that the most active are **90b** (IC_{50} = 0.091 μM), **90c** (IC_{50} = 0.191 μM), and **90d** (IC_{50} = 0.331 μM).

A series of 1,4-oxazine BACE1 inhibitors have synthesized and characterized by Gijsen et al. (Gijsen et al.,

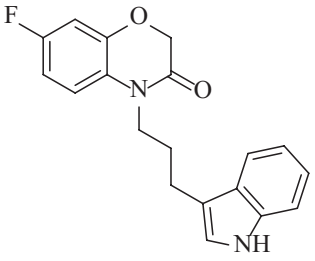


91

92

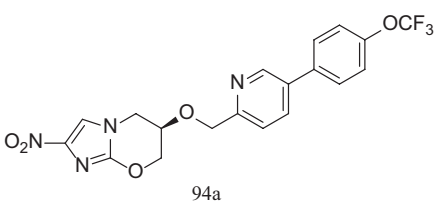


93a

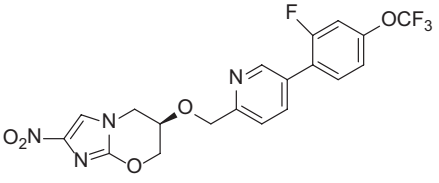


93b

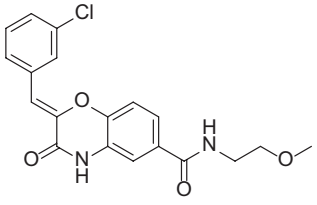
FIGURE 48 Structure of compounds **91, 92,** and **93a,b**



94a



94b

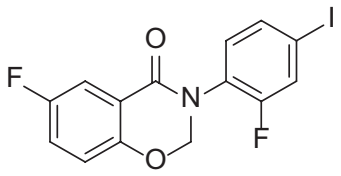


95

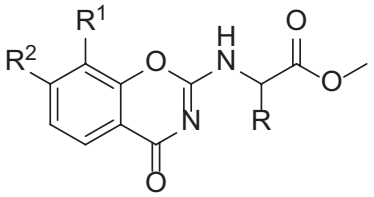
FIGURE 49 Structure of compounds **94a,b** and **95**

2018). Compound **91** having CF_3 group (electron-withdrawing) resulted in good in vivo efficacy with a sufficient cardiovascular safety margin. The effect of replacement of 2-fluoro substituent with other groups was discussed. Benzopyrimidopyrrolo-oxazinedione of the CFTR inhibitors has been designed and synthesized by Snyder, Tradtrantip, Yao, Kurth, and Verkman (2011). Modification of pyrimido-pyrrolo-quinoxalinedione including bromine substitution to form compound **92** which inhibited CFTR with IC_{50} ~8 nM compared to pyrimido-pyrrolo-quinoxalinedione and showed >10-fold greater metabolic stability and much greater polarity/aqueous solubility. A series of indole-benzoxazinones (Family I) and benzoxazine-arylpiperazine derivatives (Family II) have been synthesized and characterized by Méndez-Rojas et al. (2018). These compounds were tested for their potential AChE inhibitory properties and displayed effective inhibitory profiles with Ki values of 20.3 ± 0.9 μM for **93a** and 20.2 ± 0.9 μM for **93b** (Figure 48).

Investigating 900-compound pretomanid analogues including several hits through head-to-head assessments in a Leishmania donovani mouse model have been studied by Thompson et al. (Thompson et al., 2018). Compounds **94a** and **94b** indicated significant activity and found to be potent inhibitors of hERG. Virtual screening of commercially purchased small molecule repository of 50,000 drug-like compounds using validated docking protocol for identification of potential GSK-3β inhibitors has been studied by Joshi, Gupta, and Vishwakarma (2017). GSK-3β is widely excepted molecular target for number of diseases such as diabetes, cancer, and Alzheimer's disease. The virtual screening efforts led to identify 95 class of GSK-3β inhibitor with an IC_{50} value of 1.6 μM (Figure 49).



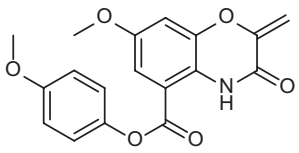
96



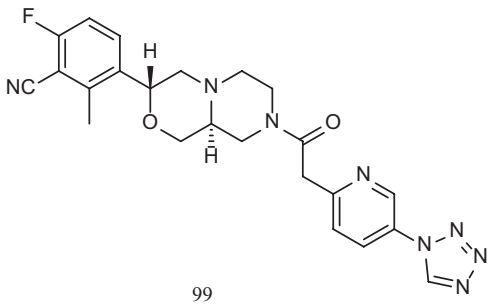
Compound	R^2	R^1	R
97a	H	Ph	$CH_2CH(CH_3)_2$
97b	OCH_3	H	CH_3
97c	H	CH_3	$CH(CH_3)_2$
97d	OH	CH_3	CH_2Ph

FIGURE 50 Structure of compounds **96** and **97a–d**

FIGURE 51 Structure of compounds **98** and **99**

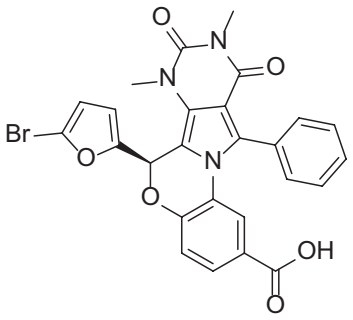


98

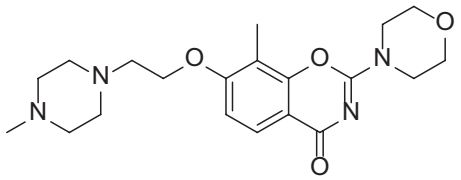


99

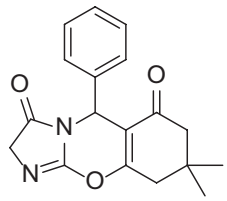
FIGURE 52 Structure of compounds **100** and **101**



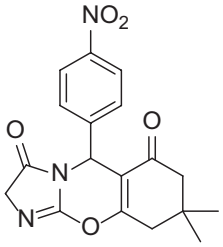
100



101



102a



102b

FIGURE 53 Structure of compounds **102a,** and **102b**

Chen, Lee, et al. (2016), Chen, Tao, et al. (2016) have reported the design and synthesis of a series of salicylanilide analogues and their corresponding derivatives. These compounds were tested for their anti-osteoclastogenic activities of a potent anti-restorative. Compound **96** displayed most potent inhibitory effects on RANKL-induced osteoclast formation with no remarkable cytotoxic effects. A series of L- or LD-2-amino acid ester (substituted)-benz[1,3]oxazines **97a–d** have been synthesized and characterized by Ihmaid, Fitzgibbon, and Al-Rawi (2015). Some of these compounds showed weak inhibition on DNA-PK and platelet aggregation. Furthermore, these compounds were also acted as effective chemo-sensitizers (Figure 50).

Development of benzo[1,4]oxazines has been reported by Warner, Cheng, Yildiz, and Linington (2015) and compound **98** dispersal agents against Vibrio cholera. Structure–activity relationships study demonstrated the importance of existing amidic proton and exocyclic alkene for compound activity. New ROMK inhibitors have been synthesized by Zhu et al. (2016). The reported compounds "Acyl octahydropyrazino [2,1-c][1,4]oxazines" showed comparable ROMK potency and significant pharmacokinetic properties. In addition, compound **99** also showed significantly improved half-life in the preclinical species (Figure 51).

Some of benzopyrimido-pyrrolo-oxazinediones such as enantiomerically pure (R)-isomer 100 inhibits the CFTR by competition with ATP (Kim et al., 2015). Molecular simulations showed lower binding energy for the (R) versus (S) stereoisomers and this result convinced that (R)-isomer could bind near the canonical ATP binding site. A series of 2-morpholino-substituted-1,3-benzoxazines have been synthesized and characterized by Pritchard et al. (Pritchard, Al-Rawi, & Bradley, 2007). These derivatives were evaluated for their activity against ADP- and collagen-induced platelet aggregation. The presence of a methyl or phenyl group at C-8 position of 2-morpholino benzoxazines is very important for antiplatelet activity. Compound **101** displayed most potent activity against both ADP- and collagen-induced platelet aggregation (Figure 52).

Significant anticonvulsant activity was confirmed for novel imidazo-[1,3]-oxazine derivatives **102a,b.** Synthesized compounds were successfully prepared through solvent-free reaction of hydrazine hydrate, aromatic aldehyde, and 5,5-dimethylcyclohexane-1,3-dione (El-Ansary, Hassan, Rahman, Farag, & Hamed, 2016; Figure 53).

9 | CONCLUSION

The chemistry of oxazines gains much synthetic interest due to their plethora of applications in diverse and promising areas. The biological activities of oxazines including antimicrobial, antitubercular, antioxidant, 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 and Alzheimer's diseases. These compounds exhibited significant anticoagulant and antiplatelet activity. The literature study revealed that these compounds show potent antiresorptive activity for treating of osteoclastic diseases. Benzopyrimido-pyrrolooxazinediones are potential development candidates for antisecretory therapy of polycystic kidney disease. These compounds reduce cystogenesis in a model of polycystic kidney disease. Furthermore, the oxazine derivatives displayed marked blood glucose and triglyceride lowering activities in mice models. Also, it presents better antimalarial activity than chloroquine against resistant strain of *P. falciparum.* In addition, some of these compounds displayed potent inhibition of HIV-1 RT activity at low concentration. This will be very useful for the development of HIV-1 inhibitors. Considering these wide-ranging applications, it is envisaged that this review will provide ample references for the researchers to do further research in this area.

ACKNOWLEDGMENTS

Ahmed Mahal acknowledges the Chinese Academy of Sciences (CAS) for support through the CAS President's International Fellowship Initiative (2016PM032).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests in this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Zinad DS, Mahal A, Mohapatra RK, Sarangi AK, Pratama MRF. Medicinal chemistry of oxazines as promising agents in drug discovery. *Chem Biol Drug Des*. 2019;00:1–32. https://doi.org/10.1111/cbdd.13633