GSJ: Volume 7, Issue 8, AUGUST 2019
ISSN 2320-9186

GSJ: Volume 7, Issue 8, August 2019, Online: ISSN 2320-9186
www.globalscientificjournal.com

OXAZINE AND ITS DERIVATIVES: POTENTIAL LEADS FOR DISCOVERY OF NEW AND POTENT ANTIMICROBIAL AND ANTITUBERCLOSIS DRUGS, A REVIEW.

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Abstract

Oxazines are heterocyclic compounds containing oxygen and nitrogen in the same ring which have great biological importance. Many synthetic and intermediates of oxazines show important biological activities like sedative, analgesic, antipyretic, anticonvulsant, antitubercular, antitumour, antimalarial and antimicrobial. In this era of multi-drug resistance (MDR), efforts are on accelerated to synthesized new compounds which will be helpful in combating MDR related diseases. This review focuses on the currently reported synthesized oxazine derivatives with antimicrobial and antitubercular activities. The review also X-ray the synthetic routes of these compounds. We found 132 synthesized oxazine compounds with significant antimicrobial (antibacterial and antifungal), and antitubercular activities. We hope that this review will be of great interest to Medicinal Chemists in their quest to find new active pharmaceutical ingredients for drug discovery and development.

Introduction

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Heterocyclic compounds containing oxygen and nitrogen in the same ring have been reported to be of great biological importance. Hence, the design, synthesis and characterization of these compounds with potential biological and medicinal activities from readily available starting materials in a cost and time effective manner have received significant attention in different areas of Chemistry: Medicinal, Organic, etc [1]. Oxazines and their derivatives are heterocyclic compounds containing one oxygen and one nitrogen. They are of special interest because they constitute an important class of natural and non - natural products and show useful biological activities like analgesic [2], anti-inflammatory [3], anti-leukemic [3], antimalarial [4], anticonvulsant [5] and antimicrobial activities [6], antitumor, anthelminthic, antimycobacterial, antituberculosis and Insect Growth Regulatory (IGR) activity among others [7-9].

However, 1, 3-Oxazines and its derivatives attract more attention. Benzo-1, 3-oxazines are known to be biologically active, demonstrating antimicrobial and cytotoxic [10] anti-osteoclastic bone resorption activity [11]. The 1, 4-oxazine scaffolds are a structural subunit of many naturally occurring and synthetic bioactive compounds and are known to have diverse biological activities [1]. Many isomers exist depending on the relative position of the heteroatoms and relative position of the double bonds [12], (figure 1). There are three isomers of oxazines that exists depending on the relative position of the heteroatoms and relative position of the double bonds. 1, 2- oxazines (**1**), 1, 3- oxazine (**2**), and1, 4- oxazines (**3**)

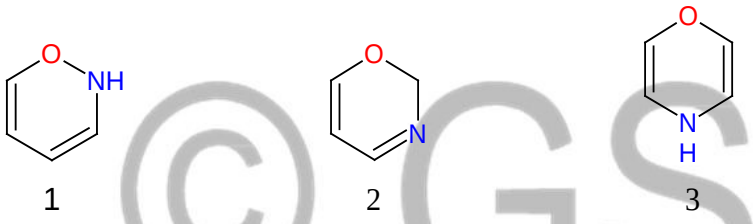
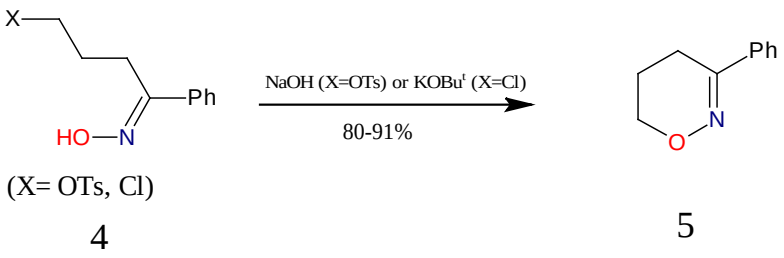


Figure 1: Different isomers of oxazines

Synthetic Routes for Oxazines

1) Intramolecular cyclization

A standard synthetic approach to 1, 2-oxazines of various types is the cyclization of an oxime bearing a side chain with an appropriate electrophilic centre. In most cases the oxime is isolated and cyclized in a separate step, but in some the oxime is made *in situ*, usually from the corresponding carbonyl compound [13].



Scheme 1: Synthesis of 1, 2-oxazines using intramolecular cyclization

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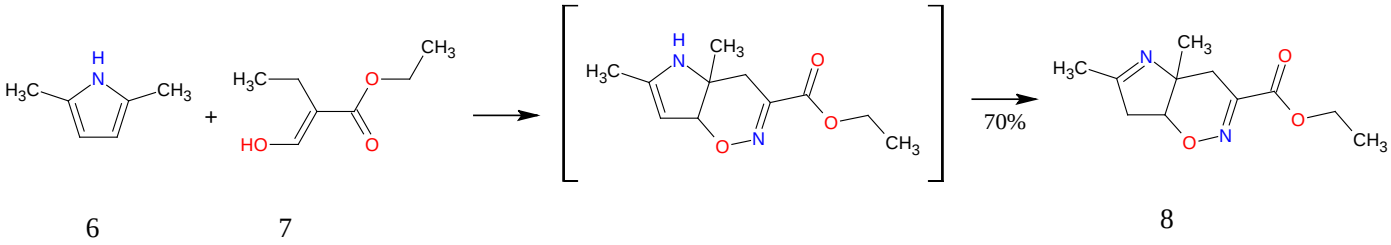
2) Synthesis involving 4-atom and 2-atom combinations:

The reactions of nitroalkenes with enolate anions and with electron-rich alkenes can be used to synthesize 1,2- oxazines [13].



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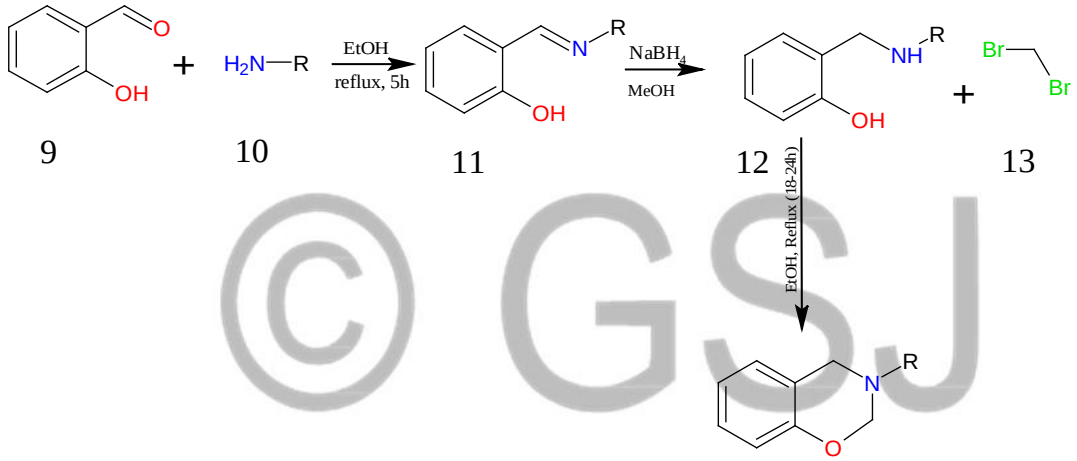
Scheme 2: Synthesis of 1, 2-oxazines involving 4-atom and 2-atom combinations

3) **Oxazines can also be prepared by the reaction between amines and aldehydes.** For example, in the synthesis of 3, 4-dihydro-2H-benzo-1, 3- benzoxazine compounds, the oxazines were formed by the reaction between benzaldehyde and an amine [14], as shown below:



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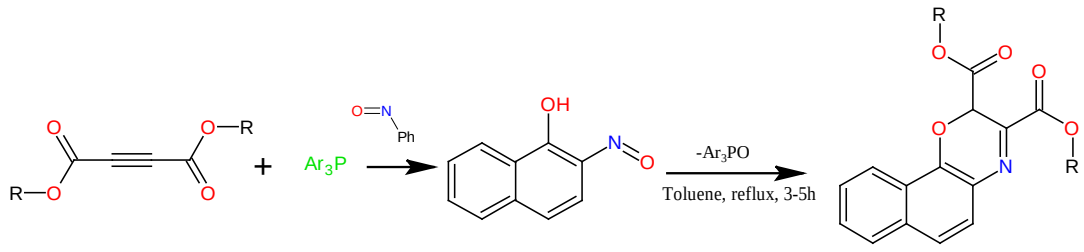
Scheme 3: Synthesis of 3, 4-dihydro-2H-benzo-1, 3- benzoxazine compounds

4) With the use of intramolecular Wittig reaction, which involves reaction between diakyl acetylenedicarboxylates and Phosphine derivatives in the presence of nitroso compounds, 1, 4-oxazines can be synthesized [1].



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Scheme 4: Synthesis of 1, 4-oxazines using intramolecular Wittig reaction

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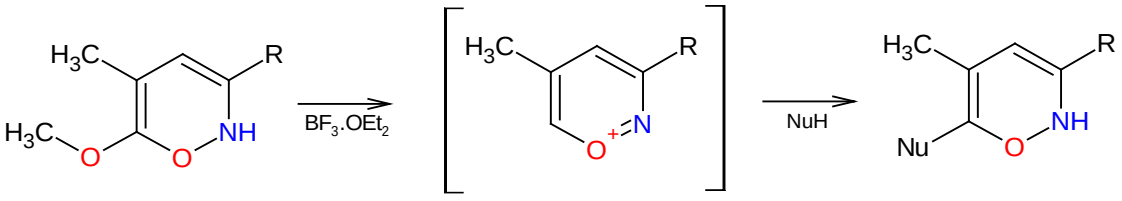
Chemistry of Oxazines

The chemistry of oxazines are vast, but listed below are chemical reactions of some 1,2-oxazines.

1. Reaction of fully Conjugated rings

6-methoxy group of the 6H-oxazines of 1,2-oxazines are readily replaced by nucleophiles in the presence of boron trifluoride etherate [13].



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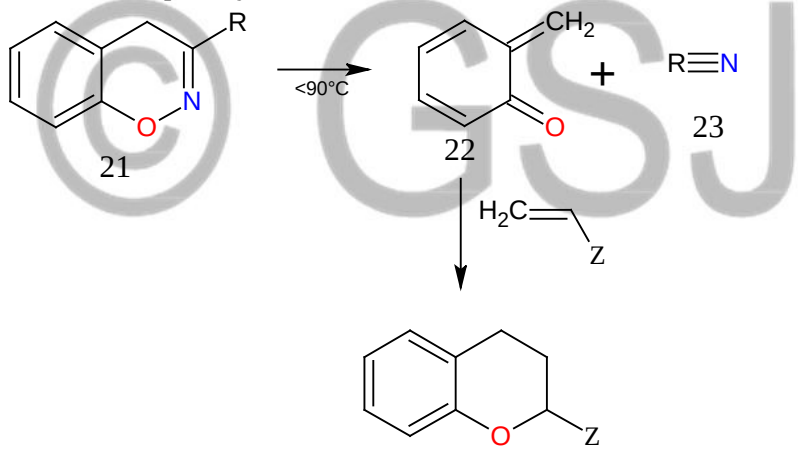
2. Reaction of Nonconjugated Rings

(a) 4H-l,2-Benzoxazines and 4H- 1,2-Oxazines

Thermal retro-Diels-Alder reaction of 3-substituted 4H-l,2-benzoxazines leads to the decomposition of these compounds on heating at, or below, 90°C to give the corresponding nitrile and o-benzoquinone methide, which can be intercepted by alkenes[13].



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(b) 5,6-Dihydro-4H-l,2-oxazines:

Some reactions of 5,6-Dihydro-4H-l,2-oxazines include:

1. Unimolecular reactions

The 3-carboxylic acids decompose, losing carbon dioxide and opening of the ring, below 100°C. 4H-Oxazines formed by cycloaddition of nitrosoalkenes to 1-methyltetrahydrocarbazole undergo the reverse reaction when heated in xylene and 5, 6- dihydro-6,6-dimethyloxazin-4-ones undergo ring contraction to pyrrolinone N-oxides under the same conditions. 5, 6-Dihydro-3-phenyl-4H-l, 2-oxazines also undergo photoinduced cleavage of the N-O bond [13].

2. Reactions with electrophiles:

5, 6-Dihydro-4H-l,2-oxazines bearing substituents at C-6 capable of stabilizing a positive charge are readily cleaved in acidic media. An example is the conversion of the dihydrooxazine to the pyrroline N-oxide by reaction with HC1 in methanol [13].

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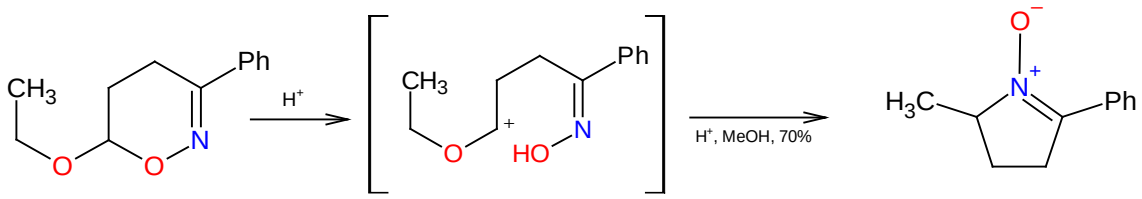

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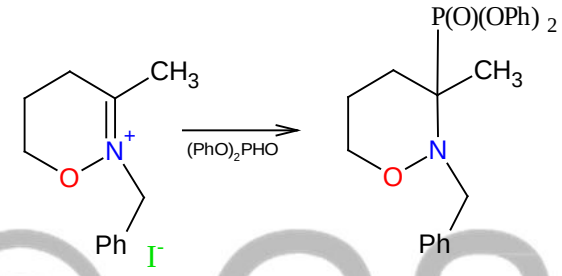
3. Reactions with nucleophiles:

The 3-position of 5, 6-dihydro-4H-l,2-oxazines is electrophilic and, when additional activation is present, a variety of nucleophiles can attack at this position. For example, a 3-nitro substituent can be displaced by nucleophiles and N-alkyloxazinium salts are attacked by nucleophiles including cyanide and diphenyl hydrogen phosphite [13].



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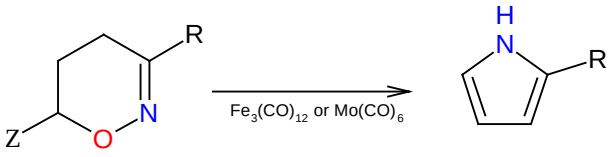
4. Reduction and reductive cleavage:

Control of reagent and conditions of reaction, can lead to 5, 6-dihydro-4H-l,2-oxazines being cleanly reduced to a variety of heterocyclic and open-chain compounds. For example, reductive deoxygenation of oxazines bearing alkoxy, trimethylsilyloxy, or dialkylamino substituents at the 6-position can be carried out using either $Fe_3(CO)_{12}$ or $Mo(CO)_6$ and the reaction leads to the formation of pyroles in good yield [13].



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Z=OAlk, $OSiMe_3$, $N(Alk)_2$

Biological Activities of Oxazines

1. Antimicrobial activities of oxazines and its derivatives

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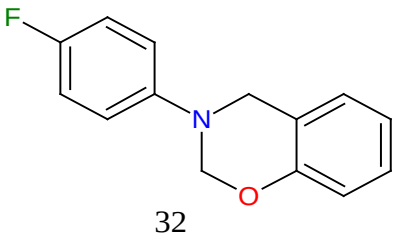
Gabbas *et al* [14], reported two 3, 4-dihydro-2H-benzo- 1, 3-oxazine derivatives and three naphtho-1, 3-oxazine derivatives synthesized using 2-hydroxybenzylamines and methylene bromide. These compounds were tested *in-vitro* for their antibacterial activity against three strains of gram positive and three strains of gram negative bacteria using the cup-plate agar diffusion method, with streptomycin (100mg/ml) as the reference antibacterial agent.



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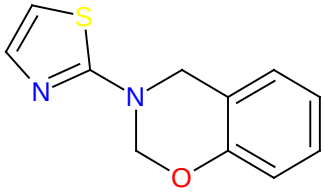

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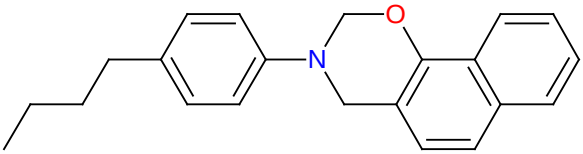

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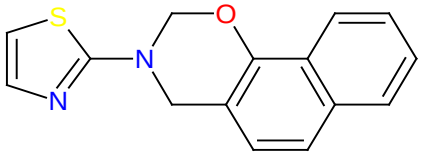

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The results of the antibacterial activity against three strains of gram positive bacteria and three strains of gram negative bacteria as compared to 100 mg/ml streptomycin which was used as the standard can be seen in table 1. From the result **32** was reported to exhibit good activity against *Bacillus subtilis*, B29, and *Staphylococcus epidermidis*, S273. The compound also showed very good activity against *Acinetobacter anitratus*, A9, and excellent activity against *Escherichia coli*, E266, and only a moderate activity against *Staphylococcus aureus*, S276. **33** was reported to exhibit moderate activity against *Bacillus subtilis*, B29, *Staphylococcus epidermidis*, S273, and *Escherichia coli*, E266. **34** was reported to exhibit very good activity against all the strains of gram positive bacteria. It showed very good activity against *Acinetobacter anitratus*, A9, and an excellent activity against *Escherichia coli* E266. **35** was reported to exhibit only moderate activity against *Bacillus subtilis*, B29.

Table 1: Antibacterial activities of 3, 4-dihydro-2h-benzo- and naphtho-1, 3-oxazine derivatives [14]

Inhibition Zone Diameter (mm)						
Antimicrobial activity against gram positive bacteria				Antimicrobial activity against gram negative bacteria		
Compd	*B. subtilis* (B29)	*S aureus*, S276	*S epidermidis*, S273	*P aeruginosa*, ATCC 15442	*E coli*, E266	*A anitratus* A9
32	18.67	14.00	18.67	8.67	28.00	25.33
33	12.00	13.00	10.00	10.33	14.67	14.67
34	22.67	24.67	22.67	16.00	38.67	25.33
35	12.67	11.00	8.00	8.33	10.00	12.00
Standard	28.00	33.00	34.00	31	30	36.33
Standard (Streptomycin 100mg/ ml)						

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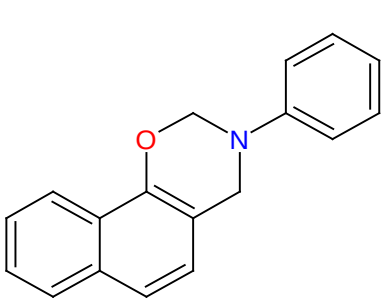
Kategaonkar et al.[15], reported nine 3,4-dihydro-3-substituted-2H naphtho[2,1 *e*][1,3]oxazines, synthesized by the reaction between formalin ,aromatic amine and 1-naphthol in the presence of $ZrOCl_2$. The antibacterial and antifungal activities were reported to have been evaluated by screening the compounds by standard method, Agar cup plate method, against a panel of human pathogenic microorganisms: one Gram positive (*Bacillus subtilis* NCIM 2250), one Gram negative (*Escherichia coli* ATCC 25922) were used, while for the antifungal assay, (*Candida albicans* MTCC 277) and (*Aspergillus niger* NCIM 545) were used for the studies.



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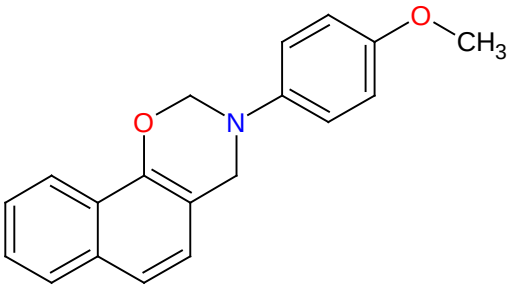

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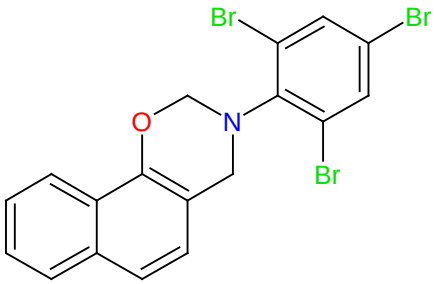

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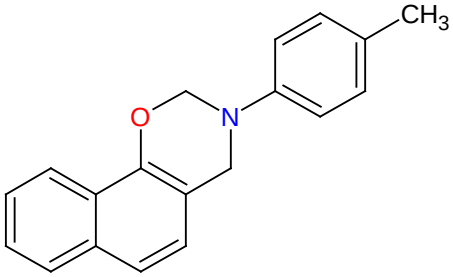

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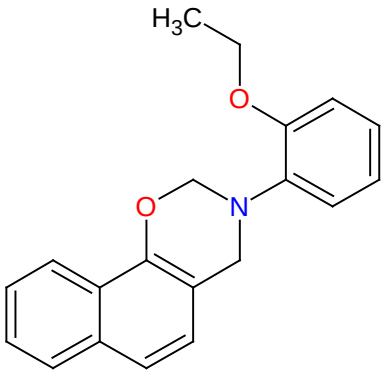

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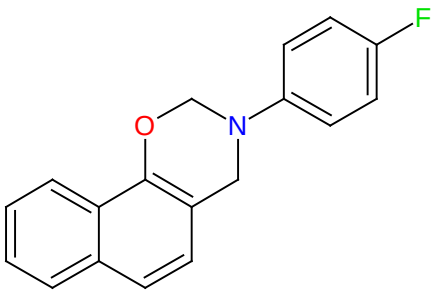

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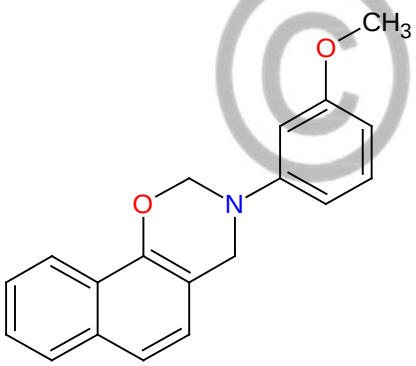

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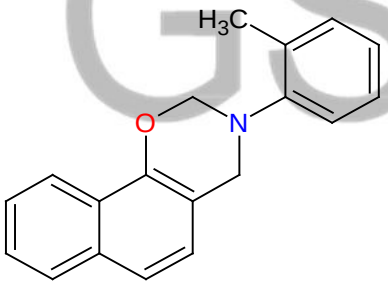

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Kategaonkar *et al.* [15], reported that the results of the antibacterial screening data revealed that all the tested compounds showed considerable and varied activity against the two human pathogenic bacteria. **38, 39** and **42** showed the zone of inhibition (18.0 mm each) as that of the standard streptomycin (17.6 mm) against *B. subtilis.* Against *E. coli*, the synthesized compounds have not shown significant activity.

The antifungal activity of compounds **36-44** clearly indicates that **38** exhibited zone of inhibition which is more than that of standard Griseofluvin against C. *albicans*. Against A. *niger*, **43** showed zone of inhibition close to that of standard Griseofluvin.

Table 2: Antimicrobial activity of 3,4-dihydro-3-substituted-2*H*-naphtho[2,1 *e*][1,3]oxazines [15]

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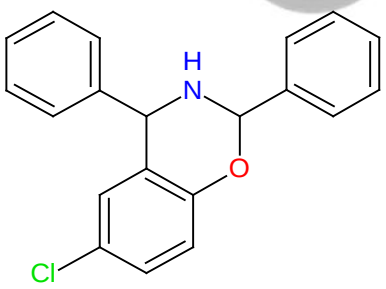
Compound	*Bacillus subtilis*	*Escherichia coli*	*Candida albicans*	*Aspergillus niger*
	ZI*a*(MIC)*b*	ZI(MIC)	ZI(MIC)	ZI(MIC)
36	14.0(25)	13.4(15)	12.4(25)	14.1(15)
37	16.0(10)	13.6(25)	13.0(20)	12.4(25)
38	18.0(10)	12.0(15)	18.2(10)	14.0(15)
39	18.0(10)	14.0(15)	12.2(15)	13.2(20)
40	15.0(20)	13.2(15)	14.2(20)	11.1(25)
41	14.0(15)	12.0(20)	15.6(15)	14.2(15)
42	18.0(10)	13.2(15)	14.0(15)	15.4(10)
43	12.2(15)	13.4(25)	16.0(10)	16.1(10)
44	14.4(20)	13.0(15)	13.8(15)	12.1(25)
Strept.	17.6(10)	17.3(10)	n.t[c]	n.t
Gris.	n.t	n.t	17.2(10)	16.9(10)

Ddiwagh and Piste [16] reported nine 6-chloro-2,4- diphenyl 3,4-dihydro-2H-1,3-benzoxazine derivatives, synthesized by the reaction between P-Chlorophenol in methanol, aromatic aldehyde and methanolic ammonia. The Antibacterial activity was screened against two gram positive bacteria *Staphylococcus aureus, Bacillus subtilis* and two gram negative bacteria *Escherichia coli, Pseudomonas aeruginosa* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL. As reported in table 3, antifungal activity was also screened against *Candida albicans, Aspergillus niger* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL.



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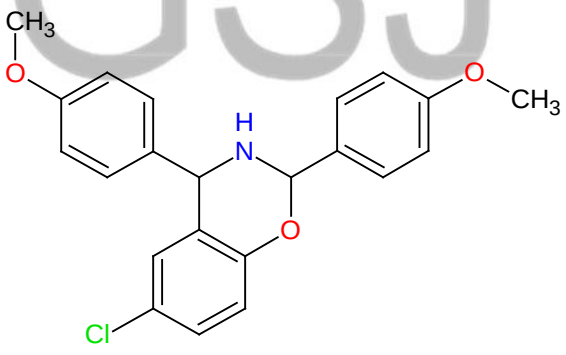

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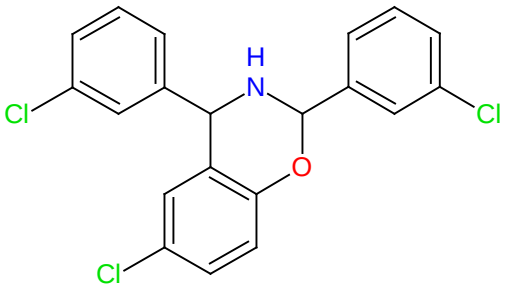

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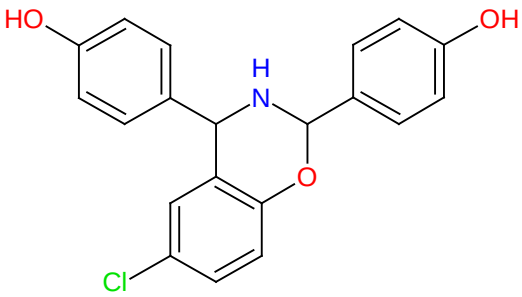

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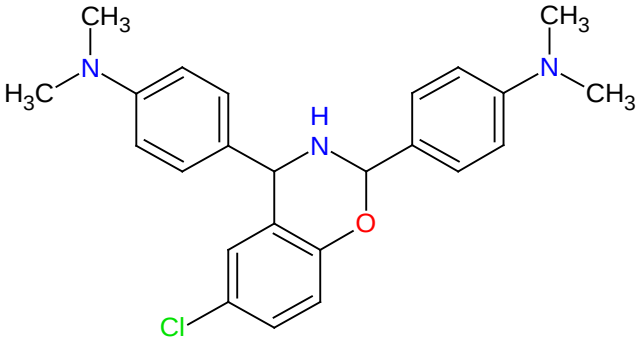

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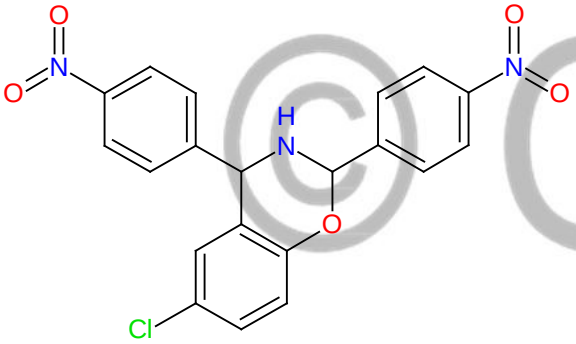

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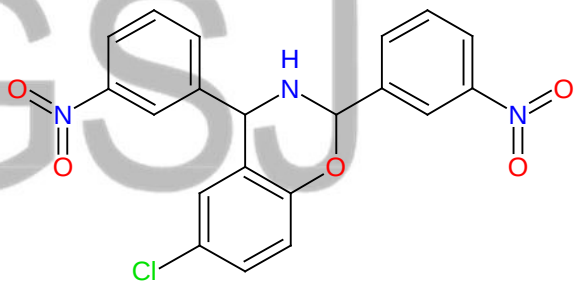

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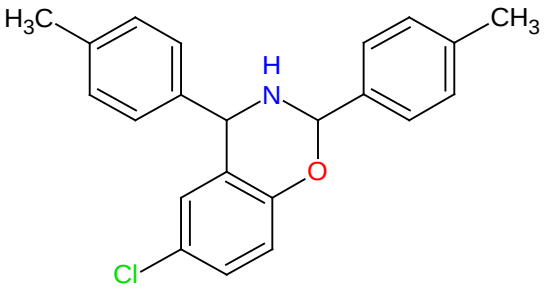

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The reported results of the antibacterial screening data revealed that most of the compounds exhibited good to moderate antitbacterial activity against the tested microorganisms. The **46**, **47** and **51** showed good activity against various pathogens as compared to standard drug Streptomycin and Griseofulvin. **45**, **49**, **50**, **52**, **53** exhibited moderate activities as compared to standard drugs. The antifungal activity of **48-52** showed good activity against *Candida albican*, *Aspergillus niger*. **45**, **47**, **48**, **52** exhibited moderate activities as compared to standard drugs.

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Table 3: Antimicrobial activity of 6-chloro-2,4- diphenyl 3,4-dihydro-2H-1,3-benzoxazine derivatives [16]

Compound	Antibacterial				Antifungal	
	S. Aureus	*B. Subtilis*	*E. Coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
45	9	11	7	5	9	7
46	15	19	17	9	17	15
47	16	13	21	17	7	8
48	14	18	16	17	6	7
49	9	7	10	5	15	12
50	6	9	8	12	13	15
51	15	19	19	18	16	13
52	7	10	5	9	13	11
53	11	7	5	8	7	9
Strept.	17	20	22	19	-	-
Gris.	-	-	-	-	21	17

Anusha *et al*. [17], reported ten schiff's base derivatives of oxazine from chalcones, which were synthesized in three stages: first, synthesis of the chalcones by dissolving equimolar mixtures of benzoaldehyde and Acetophenone in minimum amount of alcohol, with the slow addition of NaOH to give the chalcones; the second stage involves dissolving equimolar mixture of the chalcones formed from stage one and urea in ethanolic sodium hydroxide to give the oxazines; stage three involves the addition of mixture of Oxazine derivatives and appropriate aromatic aldehydes in ethanol, with the addition of 2-3 drops of $TiCl_4$ to give the Schiff base derivatives. The antibacterial activity of the schiff's base derivatives of oxazine was tested, against four different strains of bacteria by agar diffusion method (cup-plate method); three Gram-Positive Bacteria: *Bacillus subtilis, Bacillus Pumilus* and *Staphylococcus aureus;* two Gram-Negative Bacteria: *Escherichia coli* and *Pseudomonas aeruginosa,* using Ampicillin as a standard antibiotic for comparison.

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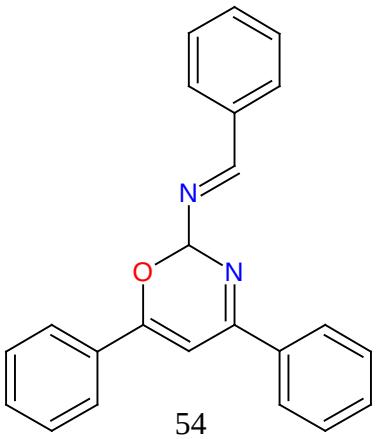

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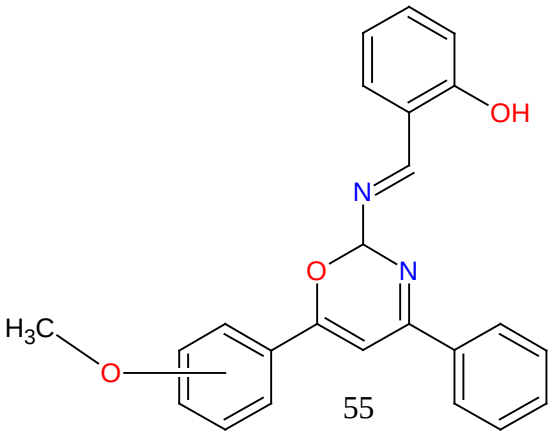

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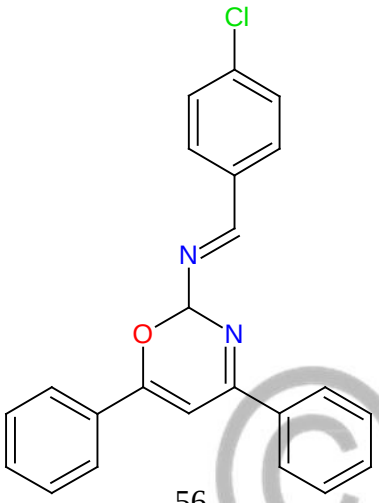

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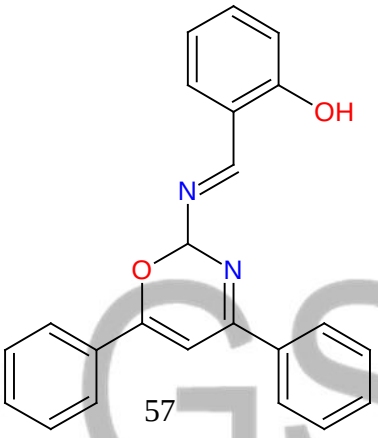

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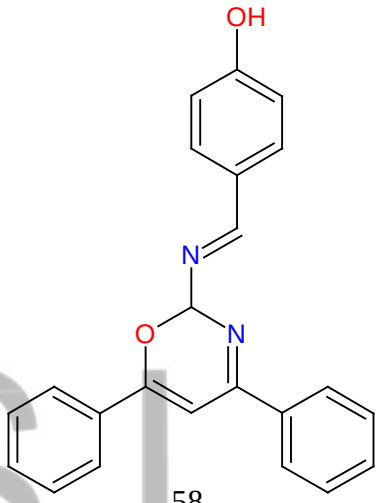

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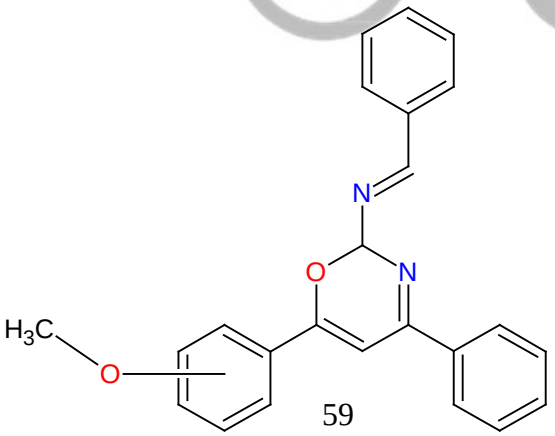

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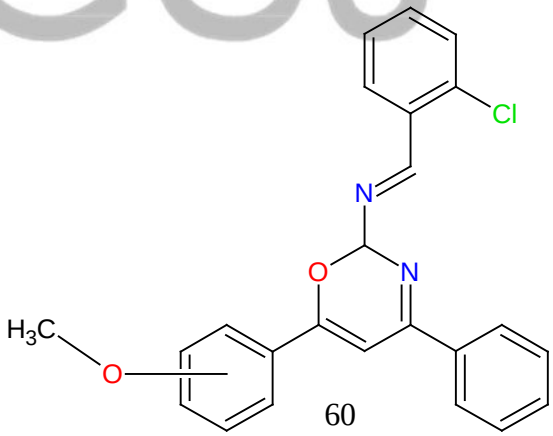

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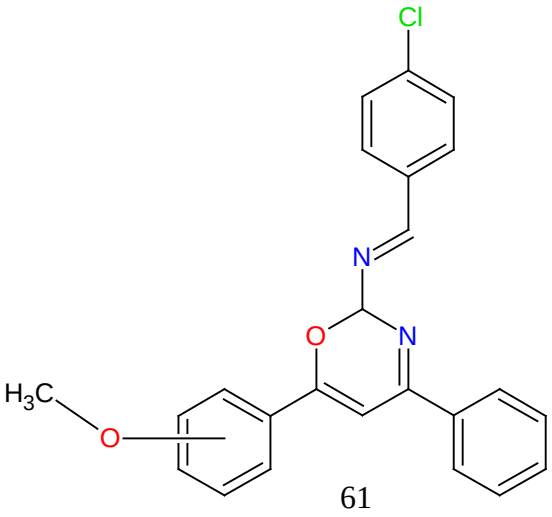

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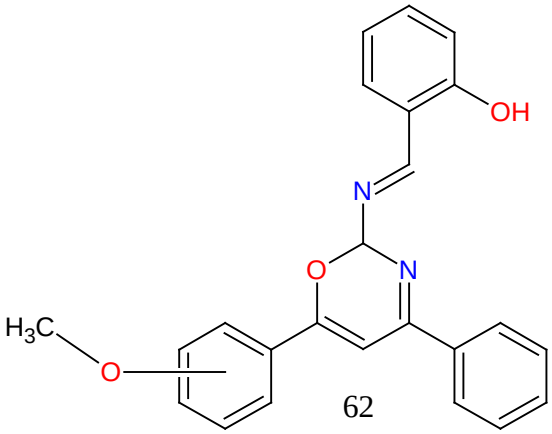

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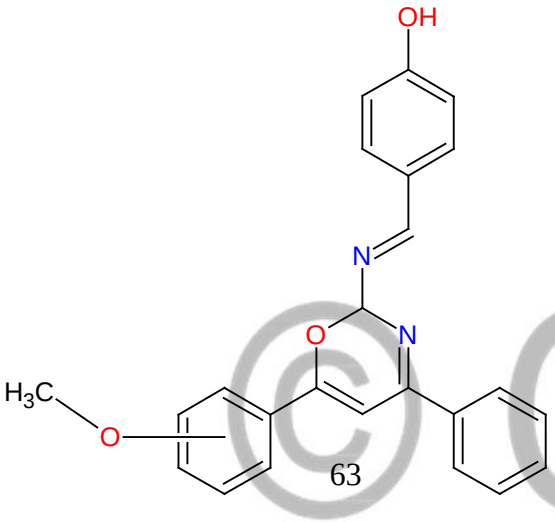

63

The Schiff base oxazine derivatives showed promising antimicrobial activity. The most potent antibacterial compound found to be **60**, showing good antibacterial activity against all the tested organisms. **62** and **63** were found to posess good antibacterial activity against the organisms: *Eschertia coli* and *Pseudomonas aeruginosa* at 100g/ml concentration.

Table 4: Antibacterial activity of schiff's base derivatives of oxazine [17]

Zone of Inhibition in mm										
Compd.	*S.aureus*		*B.subtilis*		*B.pumilis*		*E.coli*		*P.aureginosa*	
	50g	100g	50g	100g	50g	100g	50g	100g	50g	100g
54	6	14	5	12	4	12	4	13	6	13
55	9	18	8	18	9	18	9	19	9	18
56	6	14	7	16	6	15	6	14	16	7
57	8	17	7	16	7	16	6	15	7	16
58	7	16	6	16	6	15	7	17	8	17

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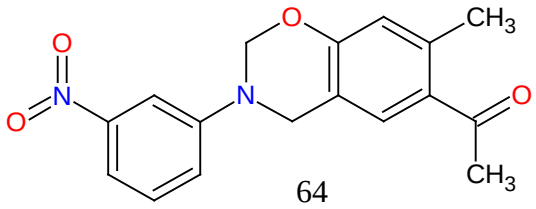
59	6	5	7	16	16	15	6	14	16	14
60	16	7	8	17	8	17	16	10	6	15
61	7	17	6	16	6	15	7	16	8	17
62	10	21	9	19	9	18	9	19	10	20
63	10	20	9	19	10	21	10	20	10	22
Ampicilin	14	22	13	21	14	23	15	22	14	23

Akhter *et al*. [18], reported ten 1-(3-Phenyl-3,4-Dihydro-2H-1,3-Benzoxazin- 6-yl)-Ethanone derivatives, which showed good antimicrobial activity. The 1-(3-Phenyl-3,4-Dihydro-2H-1,3-Benzoxazin- 6-yl)-ethanone derivatives were prepared by reacting formaldehyde in a solution of aromatic primary amine with 2 or 4-hydroxy acetophenone. The compounds were screened for their antibacterial activity against E. *coli*, S. *aureus* and B. *subtilis* bacterial strains, and antifungal activity against A. *niger* by cup plate method using ofloxacin and fluconazole as standards, respectively.



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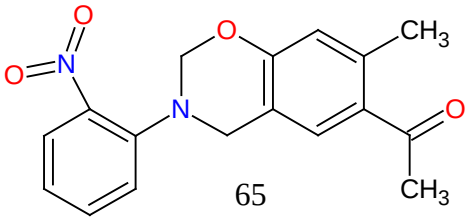

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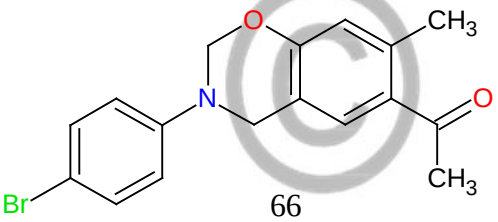

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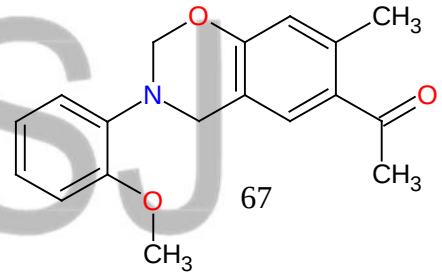

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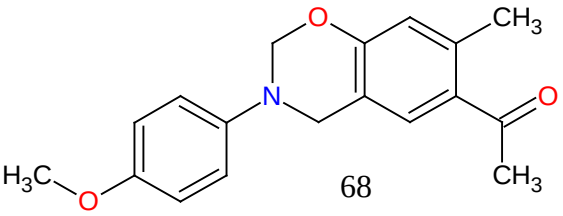

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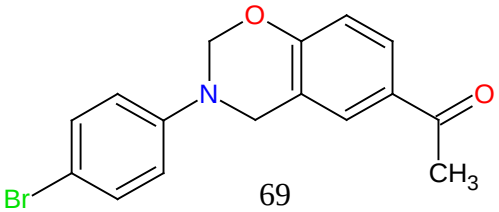

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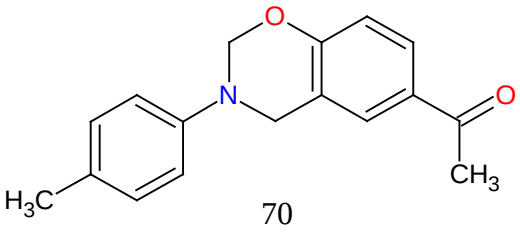

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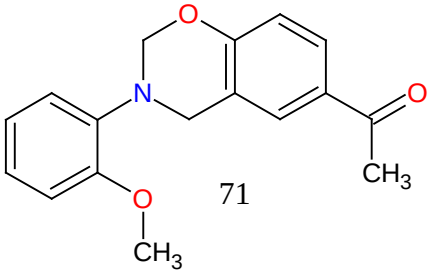

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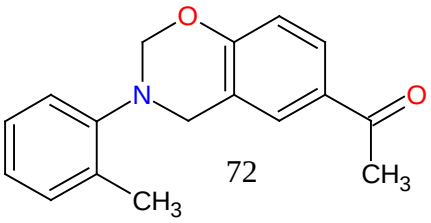

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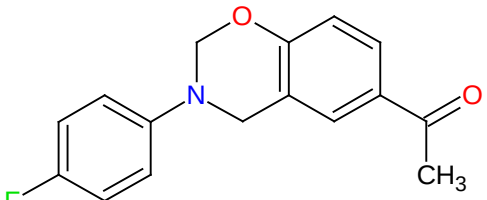

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Table 5: Antimicrobial activity of 1-(3-Phenyl-3,4-Dihydro-2H-1,3-Benzoxazin- 6-yl)-Ethanone derivatives [18]

Zone of Inhibition (50µg/ml)				
Compound	**Antifungal activity**	**Antibacterial activity**		
	A. niger	***S. aureus***	***E. coli***	***B. subtilis***
64	10	16	11	4
65	12	21	17	8
66	19	25	20	12
67	11	17	15	6
68	13	12	9	12
69	8	15	9	8
70	11	19	12	7
71	18	20	15	10
72	10	13	10	7
73	20	22	18	11
Ofl	-	26	22	19
Flu	22	-	-	-
Ofl is ofloxacin and Flu is fluconazole				

All the test compounds inhibited E. *coli,* S. *aureus* and A. *niger* but only **66**, **68** and **73** were potent in inibiting growth of *B. subtilis.* **66**, **61** and **73** showed zone of inhibition comparable to standard drugs.

Dhanya *et al*. [12], reported the antimicrobial activity of six 1,3-oxazines synthesized by the reaction between chalcone in alcohol and urea, with a subsequent addition of HCl. The antibacterial activity of the compounds was carried out dissolving in DMSO at a concentration of 100µg/mL and evaluated against *Staphylococus aureus* representing Gram-positive bacteria and *Escherichia coli* representing Gram-negative bacteria, using Tetracycline as a reference drug. They were also tested using Nutrient agar media plated on petri-plates. The antifungal activity was evaluated at 100 µg/mL against *Aspergillus niger*, using Ketaconazole as a reference drug. QSAR studies was carried out by

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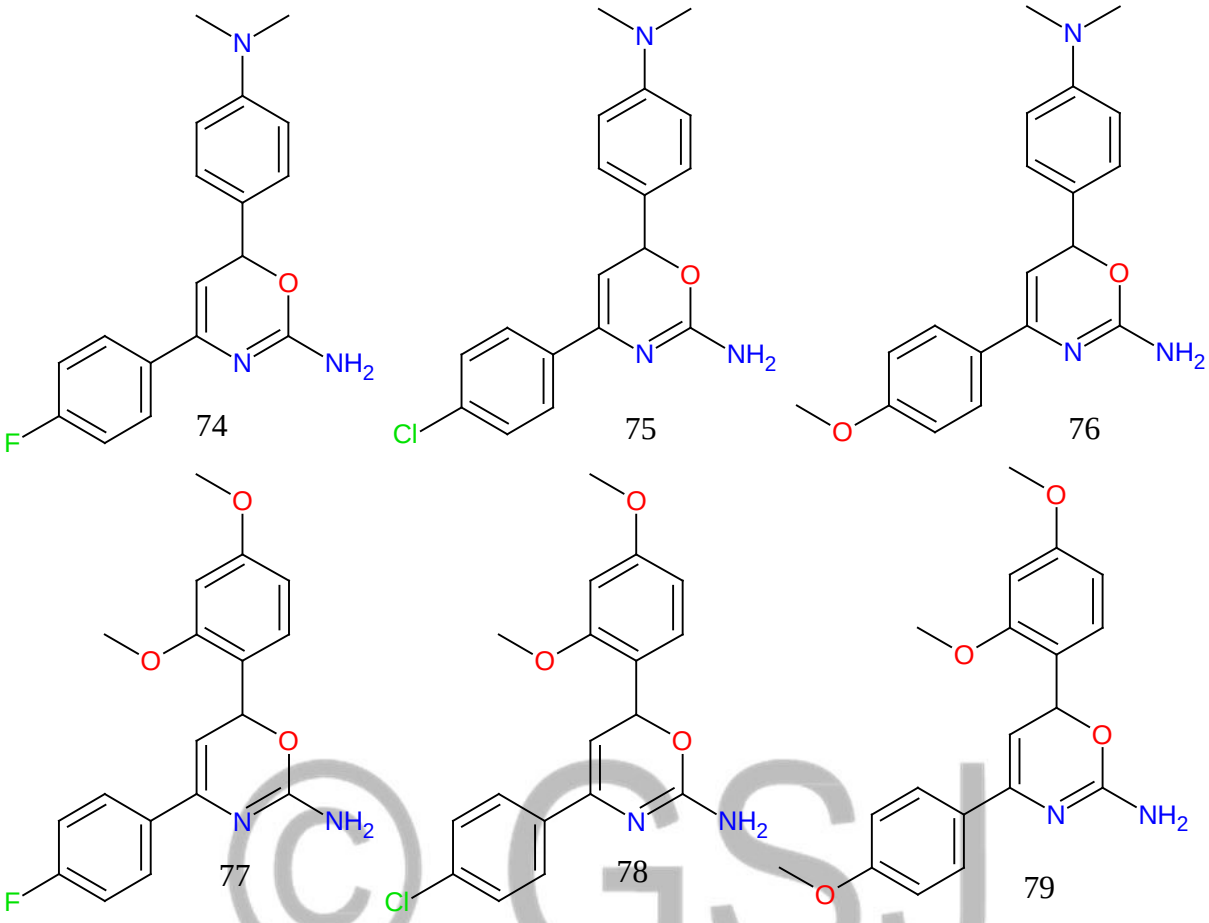
Dhanya *et al.* [12] to correlate the experimentally obtained antimicrobial activity of the 1,3-oxazines with their predicted antimicrobial activity using the tool Easy QSAR.



Antibacterial activity of solvent DMSO against the test organisms was investigated and was found to be nil. **76** and **78** showed excellent antibacterial activity against E. *coli*. **77** and **78** showed moderate antibacterial activity, whereas **79** showed high sensitivity against *S. aureus*. **75** and **79** demonstrated excellent antifungal activity by inhibiting spore germination of A. *niger*. The structure-antimicrobial activity relationship of the synthesized compounds revealed that the compounds with methoxy and chloro substituents in the phenyl ring exhibited maximum antimicrobial activity. This can be attributed to the increased dipole moment in C-X bond which might have enhanced the intermolecular interactions and might have augmented the antimicrobial property of the molecule.

Table 6: Antimicrobial activity of 1,3-oxazines [12]

Compound	***S. aureus***			***E. coli***			***A. niger***		
	ZOI	Observed Log ZOI	Predicted Log ZOI	ZOI	Observed Log ZOI	Predicted Log ZOI	ZOI	Observed Log ZOI	Observed Log ZOI
74	0	0	0	11	2.4	2.53	14	2.639	2.72
75	0	0	0	13	2.56	2.45	20	2.996	2.81
76	0	0	0	22	3.09	3.1	0	0	-
77	12	2.48	2.49	0	0	-	0	0	-
78	12	2.28	2.48	24	3.18	3.16	16	2.773	2.90
79	21	3.04	3.04	0	0	-	19	2.994	2.88

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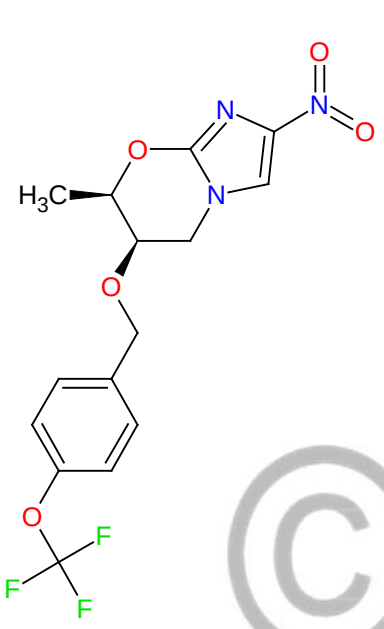
Antitubercular Properties

Working on the improvement of the clinical drug, PA-824, Li *et al*. [19], reported the synthesis of **80** and **81** which are analogues of PA-824, by adding NaH to a solution of (6S,7S)-7-Methyl-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-6-ol or (6S,7R)-7-methyl-2-nitro- 6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-6-ol respectively and 4-(trifluoromethoxy)-benzylbromide in anhydrous DMF at 45˚C. The synthesized compounds were tested for their antitubercular properties and compared to PA-824 under aerobic conditions, using the broth dilution method for MIC and log phase Mtb cultures for minimum anerobicidal concentration (MAC), as shown in the table **7**:



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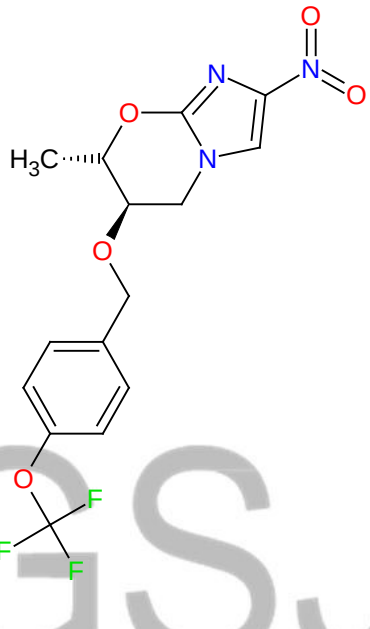

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Table 7: Antitubercular Activities of PA-824 and 7-methyl analogues [19]

Compound	**H3R7v MIC (µM)**	**H3R7v MAC (µM)**	**H3R7v-T3 MIC (µM)**	**H3R7v-5A1 MIC (µM)**	**H3R7v-T2 MIC (µM)**
PA-824	0.4	8-16	>100	>100	>100
7-(S)-methyl-824 (*cis*)	0.2-0.4	16	>100	>100	>100
7-(R)-methyl-824 (*trans*)	0.2	8-16	>100	>100	>100

Activity of the 7-methyl analogues was reported to demonstrate that the nitroreductase accept at least small substituents at the 7-position, suggesting that further derivatives at the 7-position of the oxazine may be fruitfully explored to improve their activity.

Sutherland *et al.* [20] reported series of 2-Nitroimidazooxazines which showed antitubercular peoperties, and compared them with a reference clinical trial drug, PA-824, with respect to their antitubucular activites and solubility. The compounds were constructed by coupling the chiral 2-nitroimidazooxazine alcohol with various halomethyl-substituted arylheterocycles, by cycloadditions to a propargyl ether derivative of this alcohol, or by Suzuki couplings on haloheterocyclic methyl ether

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derivatives and includes; the 5-arylthiophene derivatives, 2-aryl-1-methylimidazole derivatives, 3-aryl-1- methylpyrazole derivatives, 3-arylisoxazole derivatives, 1-aryl-4-linked, 2-aryl-4-linked, and 2-aryltetrazole analogues. These compounds **(82 - 131)** were evaluated for their ability to inhibit *Mycobaterium tuberculosis* (M. tb) in two assays: the MABA (aerobic) assay, which was used to evaluate the activity of compounds against replicating M. tb and the LORA (anaerobic) assay (luminescence-based low-oxygen-recovery assay) screened for activity against bacteria in a non-replicating state that models clinical persistence. The activity of the compounds was quantified by the minimum inhibitory concentration (MIC) which was compared to a predicted MIC value gotten using equation 1:

$$\text{Log}\,(MIC_{MABA}) = -0.25\text{CLogP} - 0.52\sum\sigma - 0.014 \quad \text{..... equation 1[20]}$$

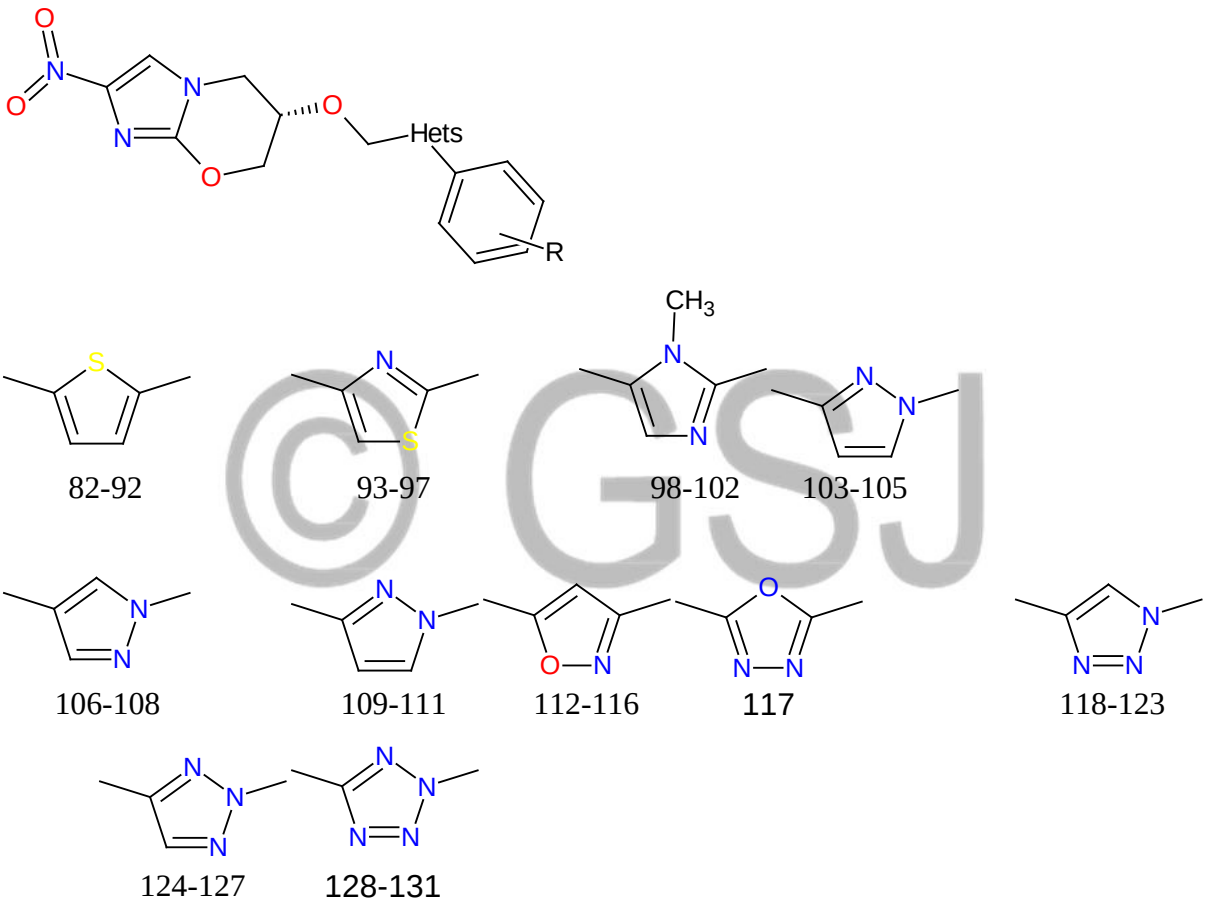

Table 8: Summary of Mean MICs for Compound Subsets [20]

Compound	Subseries	n[a]	Mean MICs (µM)			
			Observed		Predicted	
			MABA	LORA	MABA	Ratio[b]
82-92	(2,5)-thiophene	5	0.24	1.6	0.17	1.4
93-97	(2,4)-thiazole	5	0.76	2.4	0.19	4.0
98-102	(2,5)-1-Me-imidazole	5	1.6	>22	0.52	3.1
103-105	(3,5)-1-Me-pyrazole	3	0.16	2.9	0.45	1 /2.8
106-108	(1,4)-pyrazole	3	0.50	2.7	0.45	1.1

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109-111	(1,3)-pyrazole	3	0.068	2.9	0.45	1 / 6.6
112-116	(3,5)-isoxazole	5	0.94	2.8	0.56	1.7
117	(2,5)-1,3,4-oxadiazole	1	2.4	17	0.75	3.2
118-123	(1,4)-1,2,3-triazole	5	0.63	6.7	0.52	1.2
124-127	(2,4)-1,2,3-triazole	3	0.0833	1.7	0.54	1 /6.5
128-131	(2,5)-tetrazole	3	0.18	2.o	0.56	1 /3.1
[a]Number of compounds from which mean MICs were calculated. [b]ratio is observed/predicted value.						

Four heterocyclic subseries (5-arylthiophene, 3-arylisoxazole, 1-aryl-4-linked-pyrazole, and 1-aryl-4-linked- 1,2,3-triazole derivatives) showed aerobic (MABA) potencies similar to those expected based on their lipophilicities (Table 2), three subseries (2-arylthiazole, 2-aryl-1-methylimi- dazole, and 5-aryl-1,3,4-oxadiazole derivatives) showed slightly poorer MABA activities than predicted (3- to 4-fold), while a further four subseries(3-aryl-1-methylpyrazole,1-aryl- 3-linked-pyrazole, 2-aryl-4-linked-triazole, and 2-aryl-5- linked-tetrazole analogues) were 3- to 7-fold more potent than expected (MABA assay). Of these latter four, the 1-aryl-3- linked-pyrazoles, class F, and the 2-aryltetrazoles, class K, provided compounds with both lower lipophilicities and modestly (2-fold) improved aqueous solubilities, compared to the original biphenyl analogues. Interestingly, from an anaerobic (LORA) potency perspective, only two heterocyclic subseries (2-aryl-1-methylimidazole and 5-aryl-1,3,4-oxadiazole derivatives) were significantly different from the MLB analogues (5- to >7-fold less active).

A subset of the compounds was evaluated for their stabilities in a metabolism screen with human and mouse liver microsome preparations. These compounds were further evaluated for their antitubercular effects in a mouse model of acute M. tb infection, using a once daily oral dose of 100 mg/kg for 5 days a week for 3 weeks, PA-824 was employed as an internal standard, with activity recorded as the ratio of the fold decrease in colony forming units (CFUs) recovered from the lungs of compound-treated mice compared to the corresponding fold CFU decrease achieved by treatment with PA-824.

Table 9: Microsomal Stability and in Vivo Efficacy Data for Selected Analogues [20]

Compound	**Subseries**	**Substituent**	**Microsomes (% remaining at 1 h)**		
			H[a]	M[b]	*In vivo* efficacy[c] (ratio vs PA-824)
83	(2,5)-thiophene	CN	85	54	0.02
90	(2,5)-thiophene	3-aza, 4 CF_3	85	77	2.3
105	(3,5)-1-Me-pyrazole	OCF_3	86	81	12
108	(1,4)-pyrazole	OCF_3	87	64	15
111	(1,3)-pyrazole	OCF_3	87	67	41
121	(1,4)-1,2,3-triazole	OCF_3	99	74	0.34
131	(2,5)-tetrazole	OCF_3	97	81	4.3
[a]Pooled human liver microsomes. [b]Pooled CD-1 mouse liver microsomes. [c]Fold reduction in lung CFUs for compound compared with the fold CFU reduction for 1 in a mouse model of acute TB infection					

All compounds assayed were found to be very stable toward human microsomes (>80% remaining after incubation at 37ºC for 1 h), and most (except perhaps the thiophene analogue **83**) were adequately stable toward mouse microsomes. For their antitubercular activities, the most active compound was the 1-aryl-3-linked- pyrazole, **111**, which showed a 41-fold greater efficacy than PA-

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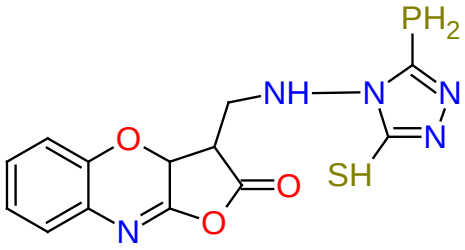
824 in this model. Two further compounds, the 3-aryl-1-methyl- pyrazole, **105**, and the 2-aryltetrazole, **131**, also showed significant *in-vivo* activity in this assay (respectively 12-fold and 4-fold greater than PA-824).

A new derivative of [1, 4] oxazin-2-one, **132** was synthesized [21]. The biosynthesis was carried out by reacting o-amino phenol with maleic anhydride. This compound was screened for its antitubercular, antibacterial and antifungal activity. The results further confirm that 1, 4 oxazines are potential lead compounds in antitubercular, antibacterial and antifungal studies



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Conclusion

Oxazine derivatives having significant antimicrobial and antitubercular activities were reviewed. This current reported synthesized oxazine derivatives with antimicrobial and antitubercular activities could open up a new frontier to Medicinal Chemists in their quest to find new active pharmaceutical ingredients for drug discovery and development.

Conflicts of Interest: The authors declared that no conflict of interest.

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