Chapter-B1

B1.1 Introduction

B1.1.1 Biological significance of Oxazines

Oxazines are basically the six membered heterocyclic ring compounds with two double bonds and containing one oxygen and one nitrogen heteroatom. These can be derived from benzene and its reduction products by replacing the two carbon atoms each by one nitrogen atom and an oxygen atom. Depending upon the relative position of the hetero atoms and the relative position of the double bonds, there are three position isomers of oxazine rings viz. 1,2-, 1,3-, and 1,4-oxazines each with number of possible tautomers. The main tautomer of each class is represented as follows:

\[
\begin{align*}
\text{I} & : \text{2H-1,2-oxazine} \\
\text{II} & : \text{2H-1,3-oxazine} \\
\text{III} & : \text{4H-1,4-oxazine}
\end{align*}
\]

These heterocycles are of special interest and importance as these constitute an important class of natural and non natural products. They possess a wide array of biological properties including analgesic, sedative, anticonvulsant, antimalarial, antimicrobial, antitubercular and antipyretic. In addition to these, oxazines also possess activities such as hypolipidaemic, antiproliferative, antidiabetic and anti-inflammatory. Moreover, recent studies reveal that the bis-oxazines exhibit strong antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. Pipofezine 1 which contains the oxazine core is an important antidepressant. Substituted 1,3-oxazinylacetamide derivative 2 acts as antifungal agent.

Oxazinones act as antimicrobial and antifungal agents such as avenalumin 3, a benzoxazinone derivative is produced by oats against infection by the rust fungus \textit{Puccinia coronata avenae}. Moreover, these also act as antibacterial\textsuperscript{6}, analgesic\textsuperscript{7} and antitubercular agents\textsuperscript{2}. Thieno[2,3-\textit{d}]-1,3-oxazin-4-ones 4 act as strong CMV protease inhibitors.\textsuperscript{8} Besides this, substituted benzoxazinones have gained considerable importance in the recent years because of their potential use as anti-HIV compounds. Efavirenz (Sustiva-3) 5 contains the oxazinone moiety and is in clinical trails for the treatment of AIDS.\textsuperscript{9}

Compounds possessing the 1,4-oxazinone skeleton are found to act as 5-T\textsubscript{6} receptor antagonists, antithrombotics, bladder-selective potassium channel openers,

\begin{itemize}
\end{itemize}
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dopamine agonists and PI3 kinase inhibitors. In addition to these, the 1,4-oxazinones are used as useful intermediates for the synthesis of aza sugars.

Cyano substituted benzoxazinones 6 have been found to show strong antibacterial activity against the different strains of the gram positive and the gram negative bacteria. 4-Hydroxy-2H-1,4-benzoxazin-3(4H)-ones 7 exhibited strong antifungal activity against Staphylococcus aureus, Escherichia coli and Candida albicans. It has been found that compounds bearing long alkyl chain on the 2-position of the benzoxazines show significant antifungal activity. 2-Methylamino-4H-3,1-benzoxazin-4-ones 8 synthesised by Neumann et al. display chymase inhibitory activity.

Compounds having benzoxazine scaffold possess antitubercular activity against Mycobacterium tuberculosis and Mycobacterium kansaii. These compounds show much higher activity than the standard drug isoniazid. Benzoxazinones and their 2-substituted analogue 9 exhibit their effectiveness against collagen induced platlet aggregation.

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The thiazolidinedione derivatives of 1,3-benoxazinones of type 10 have been investigated for their antidiabetic and hypolipidaemic activity and promising results have been found for these.\textsuperscript{17}

Tetrahydro-2\textit{H}-1,3-oxazinones act as aminopropyl acting agents and as soyabean lipoxygenases.\textsuperscript{18} The 6-(2,4-diaminopyrimidinyl-5)-1,4-benoxazin-3(2\textit{H})-ones 11 are also important scaffolds and display properties such as strong rennin inhibition, good-permeability, solubility and metabolic stability. Recently a novel 12 phycotic drug SLV 314 has been discovered that contains the oxazinone core and exhibits strong serotonin antagonism.\textsuperscript{19}

Deswal \textit{et al.} have investigated these scaffolds and found that substituted benoxazinones such as 11 and 13 act as neuropeptide receptor antagonists.\textsuperscript{20} These are also used as immunodialating agents and DP receptor antagonists.\textsuperscript{21} DIBOA [2,


4-dihydroxy-2H-1,4-benoxazin-3(4H)-one] 14 exhibits strong photophysical properties.\textsuperscript{22}

\[\text{Thieno} \ [2,3-d]-1,3-\text{oxazin-4-ones} \text{ act as potent protease inhibitor. In addition to this, pyrrole fused oxazinones display strong antifungal properties.}\textsuperscript{23}\text{ Substituted 1,4 oxazinones act as antinociceptive}\textsuperscript{24}\text{, antidepressant}\textsuperscript{25}\text{ and antifungal agents}\textsuperscript{26}\text{ and also used in the treatment of Parkinson’s disease. These also find extensive applications in the physical chemistry in making laser dyes and are also used as coupling agent for oxidative hair dyes}\textsuperscript{27}\text{. Their utility also lies in the generation of}

coating films with high corrosion resistance. In line to the above mentioned properties the benoxazinone derivatives also possess diverse pharmacological properties including the anticoagulant, antiviral, herbicidal and antimicrobial properties. Some are found to be potential inhibitors of phosphoino-3-kinase-γ, chymotrypsin, pancreatic elastase.

Benzo[1,4]oxazin-3(4H)ones are also called as 5- hydroxytryptamine receptors and selective potassium channel openers. 6{2-[2-Aryl-4-(5-quinolinyl)1-piperazinyl]ethyl}-2H-1,4-benoxazin-3(4H)-ones act as highly potent 5-HT1 receptor antagonists and have high degree of selectivity against the potassium channels.

Naphthoxazines especially the ones containing the 1,3-oxazine moiety fused at its [e] face with naphthalene moiety at 1,2 positions possess strong antibacterial

activity. The other fused combinations involving the other faces \([b,c,d]\) of 1,3-oxazine or other positions of naphthalene are invisible in literature. 1,4-Oxazines and 1,2-oxazines nucleus fused with naphthalene are also very rarely known and are very less studied as far as their synthesis and chemistry is involved. Naphthoxazinones are used in the preparation of phosphinic ligands for asymmetric catalysis and also help in the treatment of Parkinson’s disease. Moreover, these can be used as intermediates in the synthesis of \(N\)-substituted amino alcohols and in the enantioselective synthesis of chiral amines. The 1, 3- \(O, N\) heterocycles have great synthetic potential owing to the tautomeric nature of the bonds. As a part of our program to synthesise biologically active heterocyclic compounds using multicomponent reactions and owing to a wide range of biological and pharmaceutical properties of naphthoxazinones, it was contemplated to synthesise this naphthoxazinone nucleus bearing 1,3-oxazine moiety condensed in it using some efficient, simpler and ecofriendly catalysts such as potash alum.

**B1.1.2 Reported methods for the synthesis of naphthoxazines involving 1,3-oxazines**

A one-pot synthesis involving the condensation of 2-naphthol with aral aldehydes at room temperature stirring in presence of ammonia and methanol yielded the naphthoxazinone nucleus in good yields **(Scheme-1)**.

![Scheme-1](image)

A Greener method employing the montmorillonite clay has been reported by S. Kantevari et al. **(Scheme-2).**

Three component reaction of β-naphthol, arylaldehyde and urea catalysed by phosphomolybidic acid in DMF to yield naphthoxazines has been reported by A. Chaskar et al. (Scheme-3).\(^{42}\)

In an alternative procedure, naphthoxazines were obtained in good yields by A. Kumar et al. using the copper based nano-particles (Scheme-4).\(^{43}\)

A new approach using the silica supported on perchloric acid has been utilised for the synthesis of naphthoxazinones (Scheme-5).\(^{44}\)


In a straight forward synthesis of naphthoxazines have been reported by X. Zhu et al.\textsuperscript{45} by using tris(triphenylphosphine) ruthenium (II) based catalyst (Scheme-6).

M. Dabri et al.\textsuperscript{38} have devised the microwave radiation assisted method for the synthesis of naphthoxazines (Scheme-7).

An efficient synthesis of naphthoxazines has been achieved by using guanidine hydrochloride as reported by A. Olyaei et al.\textsuperscript{46} (Scheme-8).

Synthesis of naphthoxazininones has been proposed by F. Nemati et al.\(^\text{47}\) by using the wet cyanuric chloride (Scheme-9).

\[
\text{ArCHO} + \text{OH} + \text{H}_2\text{N} - \text{NH}_2 + \text{X} = \text{O}, \text{S} \\
\begin{array}{c}
\text{150 °C}
\end{array}
\longrightarrow
\text{ArH} - \text{NHX} - \text{O} \\
\text{Scheme-9}
\]

Treatment of aminonaphthols with phosgene in presence of triethylamine generates the condensed naphthoxazinones (Scheme-10).\(^\text{48}\)

\[
\text{R} - \text{NH}_2 + \text{OH} + \text{COCl}_2, \text{Et}_3\text{N} \\
\text{toluene, r.t.} \\
\longrightarrow
\text{R} - \text{H}, \text{Ph} \\
\text{Scheme-10}
\]

Another approach for the synthesis of naphthoxazines is by using the molecular iodine (Scheme-11).\(^\text{49}\)

\[
\text{OH} + \text{CHO} + \text{H}_2\text{N} - \text{NH}_2 + \text{I}_2, \text{Hot plate} \\
\text{5 min} \\
\longrightarrow
\text{R} - \text{H}, \text{Ph} \\
\text{Scheme-11}
\]

Synthesis of naphthoxazines has also been achieved by using zinc triflate in refluxing acetonitrile (Scheme-12).\(^\text{50}\)

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\[
\begin{align*}
\text{Condensation of } & \beta\text{-naphthol, arylaldehyde with urea in presence of titanium tetrachloride yields naphthoxazinone derivatives in quantitative yields (Scheme-13).}^{51} \\
& \text{(Scheme-13)} \\
& \text{In another procedure, synthesis of various substituted naphthoxazinones have been attained using } \alpha\text{-naphthol by A. Kumar et al.}^{52} \text{ by using micelles in water (Scheme-14).} \\
& \text{(Scheme-14)} \\
& \text{J. S. Ghomi et al.}^{53} \text{ have reported the synthesis of naphthoxazinones using ferric chloride and nano particle supported silica (NPs) under solvent free conditions (Scheme-15).}
\end{align*}
\]

B1.2 Potash alum catalysed synthesis of naphthoxazinones and their characterisation

B1.2.1 Genesis:

Multicomponent reactions are finding increasing interest in the synthesis of biologically important compounds as these have tremendous advantages mainly the quality of building up of molecules with simplicity and brevity. Moreover, these offer advantages such as convergence, productivity, ease of execution and generally high yields of products are obtained.  

Aromatic oxazines were first synthesized in 1944 by Holly and Cope through Mannich reactions from phenols, formaldehyde and amines. Only a few methods are available in the literature for the synthesis of aromatic condensed oxazinones. The procedures generally involved in the preparation of these compounds employed harsh conditions and hazardous reagents such as phosgene, triethylamine, POCl₃ and the alternative procedures have generally resulted in low yields.

In recent years, alum is extensively used for catalysing organic synthesis because it is a nontoxic, inexpensive, ecofriendly and easy handling catalyst. Other advantages include mild acidity, involatibility, incorrositivity, insolubility in common organic solvents and so forth. Because of the numerous advantages associated with potash alum, it was thought worthwhile to employ it in the synthesis of naphthoxazinones. Though two types of naphtho-1,3-oxazines thereotically expected from the reaction of β-Naphthol, aryl or heteryl aldehyde and urea using potash alum

as catalyst, yet only one type was produced and the formation of the product was exclusive. The only angular product, naphtho[1,2-e][1,3]oxazine analogue was generated and no traces of the linear product naphtho[2,3-e][1,3]oxazine were identified and hence proving that these types of cyclic condensations were not competing with each other and the formation of product was entirely exclusive. With α-Naphthol using same reagents and catalyst under slightly changed conditions, the formation of only one expected angular product naphtho[2,1-e][1,3]oxazine derivative was achieved. A very little work has been reported in literature using α-naphthol. So, we have achieved the one pot three component synthesis of 4-aryl/hetaryl-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one derivatives 34 and 1-aryl/hetaryl-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one derivatives 36 using α-naphthol and β-naphthol respectively as substrates under very mild inexpensive and easier to handle conditions with very good results, excellent yields and promising coupling.

B1.2.2 Results and discussion

Grinding thoroughly a mixture of α-naphthol 31, appropriate aromatic/heteryl aldehyde 32 and urea 33 in the mole ratio of 1:1:1 followed by refluxing of the molten mass at 140 °C for 2 hours in the presence of a catalytic amount of potash alum without using any solvent afforded the naphthoxazine-2-one products 34 in good yield as shown in Scheme-16. Using β-naphthol 35 and other related substrates the naphthoxazin-3-one derivatives 36 were obtained also in good yield under solvent free conditions in the presence of a catalytic amount of potash alum under slightly different conditions of temperature and duration i.e., at 125 °C for 1.5 hr as shown in Scheme-17. This proved to be the best set of conditions whereas other changed conditions of catalyst, temperature and duration in both the cases have also been attempted. (Table-1)
The structure of the compound 36a was arrived at by spectral means. The $^1$H NMR showed a multiplet in the range of δ 7.4-7.9 corresponding to eleven protons indicating the presence of three aromatic rings. Further, a doublet at δ 6.3 indicated the presence of one benzylic proton. A broad singlet at δ 8.4 (D$_2$O exchangeable) was the most diagnostic signal of the compound and indicated the presence of one NH proton. All these features of $^1$H NMR coupled with the appearance of peaks at 1735 and 3235 cm$^{-1}$ in the IR spectrum spoke in favour of the formation of 1-phenyl-2,3–dihydro-$^1$H-naphtho[1,2-$e$][1,3]-oxazin-3-one. The structure was further confirmed by the mass spectrum analysis which showed a peak at 276 (M+H)$^+$. Further the CHNS analysis data of the compound further supported our observation and confirmed the cyclisation process along with the coupling reaction.

**Table-1: Catalyst scan for the reaction**

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<th>Catalyst</th>
<th>Yield(%)</th>
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<td>LiCl</td>
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<td>4</td>
<td>NiCl$_2$</td>
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$^a$ isolated yields.
### Table-2: Physical data of the compounds 34 and 36.

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<th>S.No.</th>
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<th>Aldehyde (32)</th>
<th>Product (34a-i, 36a-i)</th>
<th>M.pt. (°C)</th>
<th>Time (hr)</th>
<th>Yield(^a) (%)</th>
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### Chapter-B1: One-pot synthesis of differently fused naphthoxazinones using potash alum

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*Isolated yields*
Formation of 4-aryl-3,4-dihydro-2H-naptho[2,1-e][1,3]-oxazin-2-ones 34 can be explained by the possible mechanism (Scheme 18).

![Scheme 18](image)

The reaction can be mechanistically considered to proceed through the Schiff's base type of compounds (N-arylideneureas) formed in situ by reaction of an aldehyde with urea. The subsequent addition of the α-naphthol to these aryldieneureas, followed by cyclisation might have afforded the corresponding products and ammonia (Scheme-18). Alum in the reaction simply acts as a Lewis acid catalyst increasing the electrophilicity of the carbonyl carbon.

B1.2.3 Experimental:

B1.2.3.1 General Considerations:

All experiments were performed in oven dried glass apparatus. The melting points were determined in open capillary tubes on Perfit melting point apparatus and are uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC) using silica gel pre-coated aluminium sheets (60 F254, Merck). Visualisation of spots was effected by exposure to iodine vapoours and Dragendroff reagent. Column chromatography was performed on silica gel (60-120 and 100-200 mesh) and compounds were eluted with graded solvent systems of petroleum ether and ethyl acetate. The IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer using KBr discs (νmax in cm⁻¹). ¹H and ¹³C NMR spectra
were recorded on Bruker Ac-400 (400 & 100 MHz respectively). The abbreviations s, d, t, q, m in spectra refer to singlet, doublet, triplet, quartet and multiplet respectively.

EIMS were recorded on Bruker Micro mass VG-7070 mass spectrometer. Elemental analysis was performed on Leco CHNS 932 analyser. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as internal standard and expressed in δ scale, J is expressed in Hertz. Commercial grade solvents were purified and dried as per established procedure before use.

B1.3.3.2 General experimental procedure for the synthesis of 4-Aryl/heteroyl-3,4-dihydro-2H-naptho[2,1-e][1,3]-oxazin-2-ones 34 and 1-Aryl/heteroyl-2,3-dihydro-1H-naptho[1,2-e][1,3]oxazin-3-ones 36.

A mixture of α-naphthol 31 (1mmol), aryl/hetero aldehyde (1mmol) 32 and urea (1mmol) 33 was finely mixed by grinding thoroughly. The reaction was placed in a screw-capped vial and heated without any solvent at 140 °C in the presence of catalytic amount of potash alum (0.1 mmol) for two hours. After cooling the reaction mixture was washed with water, separated by filtration, dried and then recrystallised from AcOEt-hexane (1:2) to afford the pure products 34 in good yield. The compounds 36 were synthesised by a similar procedure by using β-naphthol instead of α-naphthol and under slightly different conditions of time and temperature (1.5 hours at 125 °C). All the compounds belonging to both the series were obtained following the similar procedure with monitoring of temperature and time duration.

B1.2.4 Spectroscopic Details:

4-Phenyl-3,4–dihydro-2H-naptho[2,1-e][1,3]-oxazin-2-ones (34a):

**Physical state**: White solid.

![Chemical Structure](image)

**IR (KBr, cm⁻¹)**: 825, 1112, 1170, 1392, 1725, 2282, 2371, 3452.

**¹H NMR (CDCl₃, 400 MHz)**: δ 5.1 (s, 1H, H-4), 7.4-7.9 (m, 11 H, ArH’s), 8.31(s, 1H, NH).

**¹³C NMR (CDCl₃, 100 MHz)**: δ 51.4, 118.2, 120.1, 121.3, 125.4, 126.3, 126.5, 127.2, 128.5, 128.9, 129.2, 129.5, 142.7, 143.4, 149.4.
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Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{NO}_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.48; H, 4.62; N, 4.98. EIMS ($m/z$) = 276 (M+H)$^+$. 

4-(p-Methylphenyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34b):

Physical state: Creamish solid.

IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 1371, 1425, 1728, 3242.

$^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 2.28 (s, 3H, CH$_3$), 5.98 (s, 1H, H-4), 7.20-7.69 (m, 8H, ArH’s), 7.85 (d, 1H, $J=7.8$ Hz, ArH), 8.05 (d, 1H, $J=7.8$ Hz, ArH), 8.78 (s, 1H, NH).

$^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 24.4, 51.4, 118.1, 120.2, 122.4, 125.8, 126.2, 127.3, 128.3, 129.3, 129.7, 132.7, 135.9, 139.8, 143.6, 157.8.

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{NO}_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.18; H, 5.08; N, 4.32. EIMS ($m/z$) = 290 (M+H)$^+$. 

4-(p-Methoxyphenyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34c):

Physical State: White solid.

IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 834, 920, 1025, 1114, 1172, 1253, 1382, 1512, 1732, 2962.

$^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 3.73 (s, 3H, OCH$_3$), 5.4 (s, 1H, H-4), 7.5-8.6 (m, 10H, ArH’s), 8.21 (s, 1H, NH).

$^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 24.4, 51.4, 114.6, 114.7, 118.2, 120.7, 121.3, 126.2, 126.4, 127.8, 129.4, 132.7, 135.4, 143.4, 156.3, 158.4.

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{NO}_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.67; H, 4.38; N, 4.03. EIMS ($m/z$) = 306 (M+H)$^+$. 

4-(3,4-Dimethoxyphenyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34d):

Physical State: White solid.

IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 872, 1452, 1734, 3145.

$^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 3.73 (s, 3H,
Chapter-B1: One-pot synthesis of differently fused naphthoxazinones using potash alum

OCH₃), 3.78 (s, 3H, OCH₃), 5.37 (s, 1H, H-4), 7.6-7.9 (m, 9H, ArH’s), 8.72 (s, 1H, NH).

¹³C NMR (DMSO-d₆, 100 MHz): δ 51.7, 56.3, 113.4, 118.4, 120.3, 121.3, 121.5, 125.6, 125.8, 126.5, 126.7, 127.3, 132.7, 143.5, 147.4, 150.4, 157.7.

Anal. Calcd. for C₂₀H₁₇NO₄: C, 71.63; H, 5.11; N, 4.18. Found: C, 70.23; H, 4.56; N, 3.92. EIMS (m/z) = 336 (M+H)+.

4-(p-Chlorophenyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34e):

**Physical State:** Off-white solid.

**IR (KBr, νmax cm⁻¹):** 734, 1452, 1734, 3146, 3224.

**¹H NMR (DMSO-d₆, 400 MHz):** δ 5.24 (s, 1H, H-4), 7.5-8.6 (m, 10H, ArH’s), 8.21 (s, 1H, NH).

**¹³C NMR (DMSO-d₆, 100 MHz):** δ 53.4, 117.3, 120.3, 121.4, 123.5, 125.6, 127.9, 128.1, 129.3, 129.4, 130.8, 133.6, 142.2, 147.9, 149.6.

Anal. Calcd. for C₁₈H₁₂ClNO₂: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.06; H, 3.14; N, 4.28. EIMS (m/z) = 310, 312 (M+H)+.

4-(p-Bromophenyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34f):

**Physical State:** Light brown solid.

**IR (KBr, νmax cm⁻¹):** 735, 1465, 1718, 3189.

**¹H NMR (DMSO-d₆, 400 MHz):** δ 6.17 (s, 1H, H-4), 6.9 (d, 2H, ArH’s), 7.23-7.69 (m, 8H, ArH’s), 8.9 (s, 1H, NH).

**¹³C NMR (DMSO-d₆, 100 MHz):** δ 53.4, 114.0, 117.34, 123.5, 125.6, 127.9, 128.6, 129.1, 129.2, 129.3, 129.4, 130.8, 132.5, 133.0, 142.2, 147.9, 149.1.

Anal. Calcd. for C₁₈H₁₂BrNO₂: C, 61.04; H, 3.41; N, 3.95. Found: C, 60.37; H, 2.68; N, 3.63. EIMS (m/z) = 355, 357 (M+H)+.
4-(p-Nitrophenyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34g):

Physical State: Yellow solid.

\[
\text{IR (KBr, } \tilde{\nu}_{\text{max}} \text{ cm}^{-1}) : 822, 926, 1115, 1224, 1342, 1734, 2952, 3124.
\]

\[
^{1}H \text{ NMR (DMSO-d}_6, 400 \text{ MHz)} : \delta 6.5 \text{ (s, 1H, H-4), 7.4-7.9 \text{ (m, 10 H, ArH's), 8.1 (s, 1H, NH).}
\]

\[
^{13}C \text{ NMR (DMSO-d}_6, 100 \text{ MHz)} : \delta 51.3, 118.2, 120.2, 121.1, 121.6, 125.3, 126.4, 126.5, 127.2, 129.3, 132.3, 132.5, 143.7, 148.2, 157.8.
\]

Anal. Calcd. for C_{18}H_{12}N_{2}O_{4}: C, 67.50; H, 3.78; N, 8.75. Found: C, 66.45; H, 3.12; N, 8.15. EIMS (m/z) = 321(M+H)^{+}.

4-(3-Indolyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34h):

Physical state: Dark grey solid.

\[
\text{IR (KBr, } \tilde{\nu}_{\text{max}} \text{ cm}^{-1}) : 742, 1374, 1576, 1723, 3245.
\]

\[
^{1}H \text{ NMR (DMSO-d}_6, 400 \text{ MHz)} : \delta 5.9 \text{ (s, 1H, H-4), 5.17 (s, 1H, H-4), 6.18 (s, 1H, H-4), 7.67-7.85 \text{ (m, 8H, ArH's), 7.92 (d, 1H, ArH'), 8.13 (d, 1H, ArH), 8.8 (s, 1H, NH), 9.82 (s, 1H, NH).}
\]

\[
^{13}C \text{ NMR (DMSO-d}_6, 100 \text{ MHz)} : \delta 53.4, 101.7, 111.4, 118.3, 119.3, 120.4, 121.3, 123.4, 125.1, 125.8, 126.1, 126.5, 127.3, 128.1, 132.5, 135.1, 136.4, 143.2, 157.7.
\]

Anal. Calcd. for C_{20}H_{14}N_{2}O_{2}: C, 76.42; H, 4.49; N, 8.91. Found: C, 75.32; H, 4.34; N, 8.21. EIMS (m/z) = 315 (M+H)^{+}.

4-(2-Furyl)-3,4-dihydro-2H-naphtho[2,1-e][1,3]oxazin-2-one (34i):

Physical state: Dark grey solid.

\[
\text{IR (KBr, } \tilde{\nu}_{\text{max}} \text{ cm}^{-1}) : 725, 1457, 1734, 3027.
\]

\[
^{1}H \text{ NMR (DMSO-d}_6, 400 \text{ MHz)} : \delta 5.17 \text{ (s, 1H, H-4), 6.1-6.2 \text{ (m, 2H, ArH's), 7.2-7.6 \text{ (m, 5H, ArH's), 7.8-8.1 \text{ (m, 2H, ArH's), 8.4 (d, 1H, NH).}
\]
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\[ ^{13}C \text{ NMR (DMSO-}d_6, 100 \text{ MHz)}: \delta 53.5, 106.5, 110.4, 120.1, 121.3, 125.7, 126.1, 126.5, 127.3, 132.7, 142.1, 143.7, 152.5, 157.8. \]

**Anal. Calcd. for** \( \text{C}_{16}\text{H}_{11}\text{NO}_3 \): C, 72.45; H, 4.18; N, 5.28. Found: C, 72.02; H, 3.82; N, 5.08. **EIMS** \((m/z) = 266 (\text{M}+\text{H})^+ \).

1-Phenyl-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36a):

Physical state: White solid.

\[ \text{IR (KBr, } \nu_{\text{max}} \text{ cm}^{-1}): 827, 1113, 1170, 1223, 1392, 1727, 2281, 2371, 3235, 3454. \]

\[ ^1\text{H NMR (CDCl}_3+\text{DMSO-}d_6, 400 \text{ MHz)}: \delta 6.3 \text{ (d, 1H, H1), 7.4-7.9 (m, 11H, ArH’s), 8.43 (s, 1H, NH).} \]

\[ ^{13}\text{C NMR (CDCl}_3+\text{DMSO-}d_6, 100 \text{ MHz)}: \delta 54.3, 112.7, 116.3, 122.1, 124.9, 126.7, 127.1, 129.2, 130.1, 141.7, 147.2, 149.1. \]

**Anal. Calcd. for** \( \text{C}_{18}\text{H}_{13}\text{NO}_2 \): C, 78.53; H, 4.76; N, 5.09. Found: C, 78.52; H, 4.72; N, 5.2. **EIMS** \((m/z) = 276 (\text{M}+\text{H})^+ \).

1-(4-Methylphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36b):

Physical state: White solid.

\[ \text{IR (KBr, } \nu_{\text{max}} \text{ cm}^{-1}): 872, 1152, 1390, 1512, 1723, 2362, 3137, 3242. \]

\[ ^1\text{H NMR (CDCl}_3+\text{DMSO-}d_6, 400 \text{ MHz)}: \delta 2.23 \text{ (s, 3H, CH}_3), 5.97 \text{ (d, 1H, H-1), 7.12 (d, 1H, ArH), 7.23 (d, 1H, ArH), 7.7-7.9 (m, 8H, ArH’s), 8.3 (s, 1H, NH).} \]

\[ ^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz)}: \delta 20.8, 55.7, 112.4, 116.7, 122.7, 124.9, 126.7, 127.1, 128.5, 129.2, 129.7, 130.2, 130.7, 138.2, 147.3, 149.7, 149.8. \]

**Anal. Calcd. for** \( \text{C}_{19}\text{H}_{15}\text{NO}_2 \): C, 78.87; 5.23; N, 4.84. Found: C, 77.13; H, 4.37; N, 3.62. **EIMS** \((m/z) = 290 (\text{M}+\text{H})^+ \).
1-(4-Methoxyphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36c):

**Physical State:** Pale yellow solid.

![Chemical Structure 1]

$\text{IR (KBr, } \nu_{\text{max}} \text{ cm}^{-1})$: 745, 832, 1025, 1113, 1172, 1225, 1512, 1732, 2967, 3152.

$^1\text{H NMR (CDCl}_3, 400 \text{ MHz})$: δ 3.73 (s, 3H, OCH$_3$), 6.1 (s, 1H, H-1), 6.8 (d, 2H, ArH’s), 7.15 (d, 2H, ArH’s), 7.3-7.9 (m, 6H, ArH’s), 8.5 (s, 1H, NH).

$^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz})$: δ 55.2, 55.7, 112.7, 114.2, 117.3, 122.8, 125.1, 127.2, 128.1, 129.2, 130.4, 131.2, 134.2, 147.5, 159.7, 161.3.

**Anal. Calcd.** for C$_{19}$H$_{15}$NO$_3$: C, 74.74; H, 4.95; N, 4.59. **Found:** C, 73.96; H, 4.34; N, 4.25. **EIMS** ($m/z$) = 306 (M+H)$^+$.  

1-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36d):

**Physical state:** White solid.

![Chemical Structure 2]

$\text{IR (KBr, } \nu_{\text{max}} \text{ cm}^{-1})$: 735, 1362, 1462, 1705, 3247.

$^1\text{H NMR (DMSO-d$_6$, 400 MHz})$: δ 3.73 (s, 3H, OCH$_3$), 3.79 (s, 3H, OCH$_3$), 5.27 (s, 1H, H-1), 7.13-7.97 (m, 9H, ArH’s), 8.79 (s, 1H, NH).

$^{13}\text{C NMR (DMSO-d$_6$, 100 MHz})$: δ 43.5, 49.8, 56.7, 113.4, 115.9, 118.7, 121.5, 122.5, 123.2, 126.7, 128.3, 128.8, 130.3, 133.7, 136.5, 151.7, 157.7, 158.8.

**Anal. Calcd.** for C$_{20}$H$_{17}$NO$_4$: C, 71.63; H, 5.11; N, 4.18. **Found:** C, 70.87; H, 4.78; N, 3.25. **EIMS** ($m/z$) = 336 (M+H)$^+$.  

1-(4-Chlorophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36e):

**Physical state:** White solid.

![Chemical Structure 3]

$\text{IR (KBr, } \nu_{\text{max}} \text{ cm}^{-1})$: 831, 925, 997, 1117, 1180, 1226, 1390, 2964, 3147.

$^1\text{H NMR (CDCl}_3+\text{DMSO-d$_6$, 400 MHz})$: δ 6.7 (d, 1H, $J = 2.4$ Hz, H-1), 7.2-7.6 (m, 7H, ArH’s), 7.6 (d, 1H, $J = 7.8$ Hz, ArH), 7.8 (d, 2H, 9.8 Hz, ArH’s), 8.7 (s, 1H, NH).  

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Chapter-B1: One-pot synthesis of differently fused naphthoxazinones using potash alum
Chapter-B1: One-pot synthesis of differently fused naphthoxazinones using potash alum

$^{13}$C NMR (CDCl$_3$+DMSO-$d_6$, 100 MHz): $\delta$ 53.4, 112.8, 116.4, 122.5, 124.8, 127.3, 128.5, 128.7, 128.8, 130.1, 130.4, 132.9, 141.5, 147.5, 149.3.

Anal. Calcd. for C$_{18}$H$_{12}$ClNO$_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.15; H, 3.34; N, 4.05. EIMS ($m/z$) = 310, 312 (M+H$^+$).

1-(4-Bromophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36f):

Physical state: Brown solid.

IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 930, 1112, 1180, 1224, 1392, 1732, 2962, 3148.

$^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 6.8 (d, 1H, $J$=2.4Hz, H-1), 7.2-7.3 (m, 7H ArH’s), 7.6 (d, 1H, $J$=7.2 Hz, ArH), 7.8 (d, 2H, $J$=7.8 Hz, ArH’s), 8.7 (s, 1H, NH).

$^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 59.3, 113.3, 118.3, 120.2, 122.4, 123.1, 126.4, 128.3, 128.4, 130.5, 132.3, 132.4, 133.5, 141.7, 141.8, 157.8.

Anal. Calcd. for C$_{18}$H$_{12}$BrNO$_2$: C, 61.04; H, 3.41; N, 3.95. Found: C, 60.49; H, 3.23, N, 3.02. EIMS ($m/z$) = 354, 346 (M+H$^+$).

1-(4-Nitrophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36g):

Physical state: Yellow solid.

IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 752, 823, 927, 1114, 1224, 1342, 1521, 1732, 2952, 3137.

$^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 6.4 (d, H-1, $J$ = 8.6 Hz, H-1) 7.4-7.5 (m, 3H, ArH’s), 7.6 (d, 2H, ArH’s), 7.8 (d, 1H, ArH), 7.97 (d, 1H, $J$=7.2 Hz, ArH), 8.1 (d, 1H, ArH), 8.19 (d, 2H, ArH’s), 9.5 (s, 1H, NH).

$^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 55.3, 112.4, 117.1, 122.3, 124.6, 125.4, 127.8, 128.3, 129.1, 132.4, 147.7, 148.3, 150.2.

Anal. Calcd. for C$_{18}$H$_{12}$N$_2$O$_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 66.82; H, 2.98; N, 8.03. EIMS ($m/z$) = 321 (M+H$^+$).
1-(3-Indolyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36h):

Physical state: Grey solid.

IR (KBr, \( \nu_{\text{max}} \) cm\(^{-1} \)): 728, 1472, 1568, 1732, 3026.

\(^1\)H NMR (DMSO-d\(_6\), 400 MHz): \( \delta \) 5.9 (s, 1H, H-1), 6.84 (d, 2H, ArH’s), 7.67-7.85 (m, 9H, ArH’s), 8.3 (s, 1H, NH), 9.87 (s, 1H, NH).

\(^13\)C NMR (DMSO-d\(_6\), 100 MHz): \( \delta \) 49.0, 111.1, 112.1, 118.9, 119.3, 122.1, 122.5, 122.9, 123.2, 126.4, 127.5, 128.3, 128.5, 133.5, 136.5, 151.9, 157.8.

Anal. Calcd. for C\(_{20}\)H\(_{14}\)N\(_2\)O\(_2\): C, 76.42; H, 4.49; N, 8.91. Found: C, 76.37; H, 4.38; N, 8.74. EIMS (m/z) = 315 (M+H)

1-(2-Furyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazin-3-one (36i):

Physical state: Grey solid.

IR (KBr, \( \nu_{\text{max}} \) cm\(^{-1} \)): 1362, 1480,1745, 3247.

\(^1\)H NMR (DMSO-d\(_6\), 400 MHz): \( \delta \) 5.07 (s, 1H, H-1), 6.1-6.2 (m, 2H, ArH’s), 6.8-7.2 (m, 4H, ArH’s), 7.5-7.6 (m, 3H, ArH’s), 8.79 (s, 1H, NH).

\(^13\)C NMR (DMSO-d\(_6\), 100 MHz): \( \delta \) 43.5, 105.9, 110.1, 115.9, 118.7, 122.5, 123.2, 126.7,128.2, 128.5, 128.8, 133.7, 141.5, 151.2, 151.7, 157.5.

Anal. Calcd. for C\(_{16}\)H\(_{11}\)NO\(_3\):C, 72.45; H, 4.18; N, 5.28. Found: C, 71.06; H, 3.57; N, 4.72. EIMS (m/z) = 266 (M+H)

B1.2.5 Pharmacological report of the synthesised compounds

Antibacterial and antifungal activities of the synthesised compounds were performed using the microdilution method against two gram positive strains \textit{Staphylococcus aureus} ATCC 29213, Methicillin Resistant \textit{Staphylococcus aureus} 15187), two gram negative strains (\textit{Escherichia coli} ATCC 25922, \textit{Pseudomonas aeruginosa} ATCC-9027), two yeast strains (\textit{Candida albicans} ATCC 22019, \textit{Candida albicans} V-01-27853) and two filamentous fungi (\textit{Asperigillus fumigates} LSI-II, \textit{Asperigillus niger} ATCC 16404). Antibacterial testing was performed in Muller Hinton Broth (Becton- Dickenson, Cockeysville, MD, USA) where as for antifungal testing RPMI 1640 with L-glutamine (Sigma-Aldrich, St. Louis, MO, USA) buffered to pH 7.0 supplemented with 0.165 M 3-(N-morphilino)propanesulphonic acid(MOPS) [Sigma-Aldrich] was used. The stock solution of the compounds was prepared in DMSO. The MIC (Minimum Inhibitory Concentration of the compounds was determined by a serial two fold diluting the solution in the above mentioned media in 100 µL volume in 96 well U bottom micro litre plate. The final concentrations of compounds ranged from 128 to 0.25 µg/ml. Amphotericin B and Ciprofloxacin [16 to 0.03 µg/ml](both from Sigma-Aldrich) were used as standard antifungal and antibacterial agents respectively. The bacterial and fungal suspension of the overnight grown bacterial and fungal cultures was prepared in sterile normal saline and the density was adjusted to 0.5 McFarland. The bacterial cultures were further diluted and added in 100µl volume at final inoculums of 1× 10^{5} CFU/ml. For fungal cultures 1×10^{3} CFU/ml was used. The plates were incubated at 37°C for 24 hr for bacteria and at 26°C for 48 hr for fungal cultures. The plates were read visually


and the minimum concentration of the compound showing no turbidity was recorded as MIC.

**B1.2.5.1 Activity results**

Table-3: MIC determination of the compounds for antibacterial activity

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<tr>
<th>Entry</th>
<th>Compound</th>
<th>MIC(µg/ml)</th>
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Table-4: MIC determination of the compounds for antifungal activity

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Most of the prepared compounds were tested for their antibacterial activity against the two types of bacterium, one gram positive bacterium *Staphylococcus aureus* and one gram negative bacterium *Escherichia coli*. Regarding the antifungal activity, the compounds were screened against the two yeast strains (*Candida albicans ATCC 22019, Candida albicans V-01-27853*) and two filamentous fungi strains (*Asperigillus fumigates LSI-II, Asperigillus niger ATCC 16404*). The preliminary screening was carried out by measuring MIC values in µg/ml. The data is summarised in the **Table-3** and **Table-4**. It was found that the compounds 34e, 34h, 36e and 36h exhibited mild antibacterial activity whereas the rest of the compounds did not show any significant antibacterial activity. Concerning the antifungal activity, it was found that the compounds 34e, 34h, 34i, 36e, 36h and 36i exhibited mild antifungal activity whereas the rest of the compounds were found inactive for the fungal species screened. Ciprofloxacin and Amphotericin-B were used as standard antibiotics in the present study.