The chemistry of 1,2,3-Triazole derivatives continues to draw the attention of Synthetic organic chemistry due to their varied biological activities.

The 1,2,3-triazole ring system has been the subject of considerable research mainly due to its because of the pharmalogical properties shown by some of its derivatives.

Over the past few years, 1,2,3-triazoles have attracted the attention of organic and medicinal chemistry because of their varied biological properties, anti-HIV, anticonvulsant, anti-inflammatory, anti-tubercular and anticancer activates. The favourable properties of 1,2,3-triazole ring like moderate dipole character, hydrogen bonding capability, rigidity and stability under in vivo conditions are evidently responsible for their enhanced biological activities.

Similarly, 1,3-Benzoxazines play an important role for their diverse biological properties. A large number of synthetic derivatives of these nuclei are well documented in the literature. Isoxazole derivatives possess a wide variety of biological activities. Introduction of benzoxazine moiety on to isoxazole nucleus may enhance the activity.

A review of the recent literature concerning the synthesis of 1,2,3-triazoles and 1,3-Benzoxazines is outlined below.

1,2,3-Triazoles:

Oliva et al. reported the synthesis, characterization and evaluation of N-substituted 1,2,3-triazoles.
Ke Ding et al.\(^4\), reported the design, synthesis and in vitro Biological evaluation of 1\(H\)-1,2,3-Triazole-4-combaxamide derivatives 8 as new anti-influenza a agents targeting virus nucleoprotein.

Kumar et al.\(^5\) have been reported an azide alkyne cycloaddition en route to novel 1\(H\)-1,2,3-triazole tethered isatin conjugates with in vitro cy to toxic evaluation.
Awad, Abdel-wahab and Khidre\textsuperscript{6} have been reported the design and synthesis of 1,2,3-triazol imidazothiazoles as antimicrobial agents.

\[ \text{1,3-Benzoxazines} \]

Billmann and Dorman\textsuperscript{7} have reported that the paraformaldehyde underwent a bimolecular condensation with \( N,N'\)-bis(o-hydroxybenzyl)-ethylenediamines \textsuperscript{16} in benzene to form 1,2-bis-[3(3,4-dihydro-1,3,2\(H\)-benzoxazino]-ethane \textsuperscript{17}. The compounds \textsuperscript{2} showed bacteriostatic and fungistatic activities.
The reaction of substituted salicylanilide-isothiocyanates 18 with ethyl chloroformate in alcohol afforded 2,4-dioxobenzoxazines 19 in quantitative yields. The compounds 19 were tested against antihelmintic activity.

\[
\begin{align*}
18 & \xrightarrow{\text{CICOOEt, EtOH}} 19 \\
\end{align*}
\]

Sridhar and co-workers\(^9\) have reported the synthesis and antibacterial, antiamoebic and antitrichromal activity of pyrano[2,3-\(f\)] [1,3] benzoxazin-2-ones 21 by the reaction of 7-hydroxy-4-(2,5\(^{'}\)-nitro-2\(^{'}\)-furyl)vinyl coumarin 20 with alkyl amines and HCHO using DMF as solvent.

\[
\begin{align*}
20 & \xrightarrow{\text{R-NH\_2, HCHO, DMF}} 21 \\
\end{align*}
\]
Reaction of 2,3-bis(\(p\)-methoxyphenyl)benzofuran-6-ol 22 with formaldehyde and anilines in 1:2:1 molar ratio in ethanol furnished 8-aryl-8,9-dihydro-2,3-bis-(\(p\)-methoxyphenyl)-7\(H\)-furro[2,3-\(f\)][1,3]benzoxazines 23. The antimicrobial activities of these compounds 23 have also been tested\(^\text{10}\).

Murthy et al.\(^\text{11}\) reported the synthesis of naphtha [1,2-\(e\)] [1,3]-oxazines 25 by interaction of 3-benzalamino-5-methylisoxazoles 24 with \(\beta\)-naphthol in acetic acid.

The synthesis and spermicidal activity of 1,3-benzoazoxazines 27 have been reported by Dwivedi and co-workers\(^\text{12}\). The reaction of
thymol 26 with paraformaldehyde and isopropanolamine in propanol furnished the title compounds 27.

\[
\begin{align*}
\text{R}^1 & \quad \text{OH} & \quad \text{(CH}_2\text{O)}_n \quad \text{R-NH}_2 \\
\text{26} & \quad \text{27}
\end{align*}
\]

Mellor et al.\textsuperscript{13} reported the synthesis of 1,3-oxazines 29 by involving a new methodology. Reaction of 2-methyl-4-nitroaniline 28 with excess formaldehyde and α-methylstyrene afforded 1,3-oxazines 29 in good yields.

\[
\begin{align*}
\text{NH}_2 & \quad \text{HCHO} \\
\text{28} & \quad \text{29}
\end{align*}
\]

Ramana et al.\textsuperscript{14} reported the synthesis of 2-substituted-4\textit{H}-3,1-benzoazin-4-ones 31 from \textit{N}-acylanthranilic acids 30 by heating the latter under vacuum.
Gurupadayya et al.\textsuperscript{15} have reported the synthesis and anti-inflammatory, analgesic, CNS depressant activity of 2H-3-(6'-fluoro-7'-substituted-2'-benzothiazolyl)-3,4-dihydro-1,3-benzoxazines 35.

Benzofuraryl-1,3-benzoxazin-2-ones 38 have been synthesized by adopting a new methodology from 2-acetyl benzofuran 36\textsuperscript{16}.
Bruno et al 17. reported a new one-pot preparation of \(2-N,N^1\)-dialkylamino-1,3-benzoxazines 39 and naptho[1,2-\(e\)]-1,3-oxazines 40 from corresponding \(o\)-hydroxybenzonitriles by reaction with phosgeniminium salts (\(\text{Cl}_2\text{C}=\text{NMe}_2\text{Cl}\)).
Present Work:

Heterocycles are widely utilized compounds in both phar-malogical and agriculture fields. Consequently, the development of methodologies useful for continues to attract the attention of both the academic and industrial communities.

1,2,3-triazole unit constitutes an easily accessible nucleus that is present in a number of phar-malogical compounds and displays a wide range of organic reactives, 1,2,3-Triazoles have been the subject of considerable research, mainly due to their use fullness in synthetic organic chemistry and also due to their variety of interesting biological activities, formally part of the scaffolds of antibacterial and anti cancer compounds, antiviral agents, analgesic compounds, fungicidal activity, protein tyrosine phosphatise inhibitors and assorted bio molecules (nucleosides and nucleotides).

Similarly, Isoxazole nucleus constitutes an important class of heterocyclic compound possessing diverse biological activities. The 1,3-benzoxazines are heterocycles of current interest due to their broad spectrum biological properties. Literature survey indicated that though different heterocycles carrying 1,3-benzoxazines have been made very few of them consists of isoxazole ring. Hence, a study of methylene-bis-isoxazolyl 1,3-benzoxazines have been undertaken.

In this chapter, we present the synthesis and characterization of 1,2,3-traizoles and 1,3-benzoxazines.
Section A.

I. (1-Prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43

II. [1-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl-1H-indol-3-yl] acetic acid ethyl ester 45

Section B.

I. 2-[ (5-Methyl-3-isoxazolyl)/ (3,5-dimethyl-4-isoxazolyl) imino]methyl-4-(3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)- imino] methyl-4- hydroxybenzyl) phenols 48

II. 2-[ (5-Methyl-3-isoxazolyl)/ (3,5-dimethyl-4-isoxazolyl) amino] methyl-4-(3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-amino] methyl-4-hydroxybenzyl) phenols 49

and

III. 3-[ (5-Methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-6-[3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoazines 50
Section A: Synthesis of [1-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester 45

\[
\begin{align*}
\text{41} & \quad \text{42} \quad \xrightarrow{i} \quad \text{43} \\
\text{ii} & \quad \text{44} \\
\text{45}
\end{align*}
\]

(i) DBU, CH$_3$CN, Reflux, 15 h; (ii) NaN$_3$, EtOH, Reflux, 5-7 h

44 X a) = Cl, b) = Cl, c) = Cl, d) = Br, e) = Br, f) = Br, g) = Cl

44/15 Y a) = H, b) = 4-F, c) = 4-Cl, d) = 4-Br, e) = 4-I, f) = 2-CH$_3$, g) = 4-OCH$_3$

1. (1-Prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43

The (1H-indol-3-yl)-acetic acid ethyl ester 41 reacted with 3-Bromopropynne 42 smoothly in presence of DBU in CH$_3$CN to afford corresponding (1-Prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43 in moderate to good yields.

In a typical procedure (1H-indol-3-yl)-acetic acid ethyl ester 41 (0.01 mol) in acetonitrile (10 ml) and DBU (0.02 mol) was uniformly stirred for a few minutes to get homogeneous solution.
Subsequently, 3-bromo-propyne 42 (0.01 mol) was added and the whole reaction mixture was refluxed for 15 h on constant stirring. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and CH$_2$Cl$_2$ (20 ml) was added. The organic phase was washed with aqueous NH$_4$Cl solution (5%, 20 ml), dried with anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by column chromatography (CH$_2$Cl$_2$) and recrystallized from CH$_2$Cl$_2$/hexane (1:1 _v/_v). The structure of the compound formed in the reaction was confirmed as (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43. The structure of compound 18 was deduced from its micro analytical and spectral data m.p 125-127 °C. In the IR (KBr) spectrum peaks was observed at cm$^{-1}$: 3290 (C-H, H-C≡C), 3024 (Ar-H), 2962 (C-H, CH$_2$), 2210 (C≡C), 1740 (C=O), 1588 (C=C), 1210 (C-O) functional groups respectively. The $^1$HNMR (300 MHz)spectrum in CDCl$_3$ exhibited signals at $\delta$: 7.85 (1H, s, CH), 7.68-7.37 (4H, m, Ar-H), 4.26 (1H, s, H-C≡C), 4.10 (2H, s, CH$_2$), 4.04 (2H, q, $J$ = 5.6 Hz, CH$_2$), 3.85 (2H, s, CH$_2$), 1.26 (3H, t, $J$ = 5.6 Hz, CH$_3$). Its mass spectrum exhibits molecular ion [M$^+$] peak at $m/z$: 241 (M$^+$); Elemental analysis calculated for C$_{15}$H$_{15}$NO$_2$: C-74.67, H-6.27, N-5.81, O-13.26. Found: C-72.36, H-5.98, N-5.21, O-12.78.
2. Synthesis of [1-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]acetic acid ethyl ester 45

(1-Prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43 reacted with benzyl halide or substituted benzyl halide 44 in the presence of sodium azide in ethanol to afford corresponding [1-(1-Benzyl-1H-[1,2,3]triazol-4ylmethyl-1H-indol-3-yl]acetic acid ethyl ester 45 in moderate to good yields.

In a typical procedure (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43 (0.01 mol) reacted with benzyl halide 44 (0.01 mol) in presence of sodium azide (0.03 mol) in ethanol (15 mL) at reflux temperature for 5-7 h. After usual workup product was purified by column chromatography (CH$_2$Cl$_2$) and recrystallized from CH$_2$Cl$_2$/hexane (1:1 v/v).

Similar treatment of (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43 with substituted benzyl halides 44 (X = Cl, Br; Y = H, 4-F, 4-Cl, 4-Br, 4-I, 2-CH$_3$, 4-OCH$_3$) gave the corresponding [1-(1-Benzyl-1H-[1,2,3]triazol-4yl- methyl-1H- indol-3-yl]acetic acid ethyl ester 45 about 70% yields Table-I.

**IR Spectra**

The IR spectra (KBr) of [1-(1-Benzyl-1H-[1,2,3]triazol-4ylmethyl-1H-indol-3-yl]acetic acid ethyl ester 45 showed a prominent absorption peak and assigning data was given in Table-I.
$^1$HNMR Spectra

The $^1$HNMR spectra (300MHz, CDCl$_3$) of [1-(1-Benzyl-1H-[1,2,3]triazol-4ylmethyl-1H-indol-3-yl]acetic acid ethyl ester 45 was presented in Table-I.

Mass spectra

The mass spectra (70 ev) of [1-(1-Benzyl-1H-[1,2,3]triazol-4ylmethyl-1H-indol-3-yl]acetic acid ethyl ester 45 was presented in Table-I.
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Y</th>
<th>IR (KBr) (\nu_{\text{max}}) in cm(^{-1})</th>
<th>(^1)H NMR (300 MHz, CDCl(_3)) (\delta) ppm</th>
<th>MS [M+]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>3036 (C-H, Ar), 2965 (C-H, CH(_2)), 2161 (N=N), 1735 (C=O), 1594 (C=C), 1220 (C=O)</td>
<td>7.81 (1H, s, CH), 7.62-7.31 (9H, m, Ar-H), 4.29 (1H, s, CH), 4.21 (2H, s, CH(_2)), 4.09 (2H, q, (J = 5.2) Hz, CH(_2)), 3.92 (2H, s, CH(_2)), 3.76 (2H, s, CH(_3)), 1.21 (3H, t, (J = 5.2) Hz, CH(_3))</td>
<td>374</td>
</tr>
<tr>
<td>2</td>
<td>4-F</td>
<td>3029 (C-H, Ar), 2970 (C-H, CH(_2)), 2167 (N=N), 1741 (C=O), 1565 (C=C), 1223 (C=O)</td>
<td>7.77 (1H, s, CH), 7.70 (2H, d, (J = 7.4) Hz, Ar-H), 7.64-7.35 (4H, m, Ar-H), 7.32 (2H, d, (J = 7.4) Hz, Ar-H), 4.20 (1H, s, CH), 4.14 (2H, s, CH(_2)), 4.01 (2H, q, (J = 5.4) Hz, CH(_2)), 3.88 (2H, s, CH(_2)), 3.72 (2H, s, CH(_2)), 1.23 (3H, t, (J = 5.4) Hz, CH(_3))</td>
<td>392</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl</td>
<td>3038 (C-H, Ar), 2962 (C-H, CH(_2)), 2172 (N=N), 1738 (C=O), 1574 (C=C), 1232 (C=O)</td>
<td>7.74 (1H, s, CH), 7.68 (2H, d, (J = 7.0) Hz, Ar-H), 7.60-7.41 (4H, m, Ar-H), 7.32 (2H, d, (J = 7.0) Hz, Ar-H), 4.24 (1H, s, CH), 4.12 (2H, s, CH(_2)), 3.96 (2H, q, (J = 6.0) Hz, CH(_2)), 3.80 (2H, s, CH(_2)), 3.68 (2H, s, CH(_2)), 1.31 (3H, t, (J = 6.0) Hz, CH(_3))</td>
<td>408</td>
</tr>
<tr>
<td>4</td>
<td>4-Br</td>
<td>3044 (C-H, Ar), 2974 (C-H, CH(_2)), 2162 (N=N), 1740 (C=O), 1565 (C=C), 1241 (C=O)</td>
<td>7.81 (1H, s, CH), 7.74 (2H, d, (J = 7.6) Hz, Ar-H), 7.61-7.36 (4H, m, Ar-H), 7.36 (2H, d, (J = 7.6) Hz, Ar-H), 4.25 (1H, s, CH), 4.21 (2H, s, CH(_2)), 4.18 (2H, q, (J = 5.8) Hz, CH(_2)), 3.91 (2H, s, CH(_2)), 3.71 (2H, s, CH(_2)), 1.41 (3H, t, (J = 5.8) Hz, CH(_3))</td>
<td>453</td>
</tr>
<tr>
<td>5</td>
<td>4-I</td>
<td>3056 (C-H, Ar), 2969 (C-H, CH(_2)), 2174 (N=N), 1744 (C=O), 1570 (C=C), 1248 (C=O)</td>
<td>7.56 (s, 1H, NH), 7.48 (d, 2H, (J = 7.4) Hz, Ar-H), 7.40-7.28 (m, 3H, pyridine), 7.36 (d, 2H, (J = 7.4) Hz, Ar-H), 4.65 (s, 1H, NH), 2.72 (s, 1H, N=CH)</td>
<td>500</td>
</tr>
<tr>
<td>6</td>
<td>2-CH(_3)</td>
<td>3062 (C-H, Ar), 2961 (C-H, CH(_2)), 2170 (N=N), 1748 (C=O), 1578 (C=C), 1252 (C=O)</td>
<td>7.78 (1H, s, CH), 7.71 (2H, d, (J = 7.6) Hz, Ar-H), 7.69-7.31 (4H, m, Ar-H), 7.29 (2H, d, (J = 7.6) Hz, Ar-H), 4.31 (1H, s, CH), 4.28 (2H, s, CH(_2)), 4.21 (2H, q, (J = 5.8) Hz, CH(_2)), 3.88 (2H, s, CH(_2)), 3.68 (2H, s, CH(_2)), 2.85 (3H, s, CH(_3)), 1.38 (3H, t, (J = 5.8) Hz, CH(_3))</td>
<td>388</td>
</tr>
<tr>
<td>7</td>
<td>4-OCH(_3)</td>
<td>3074 (C-H, Ar), 2968 (C-H, CH(_2)), 2166 (N=N), 1752 (C=O), 1578 (C=C), 1258 (C=O)</td>
<td>7.81 (1H, s, CH), 7.77 (2H, d, (J = 7.6) Hz, Ar-H), 7.70-7.36 (4H, m, Ar-H), 7.31 (2H, d, (J = 7.6) Hz, Ar-H), 4.35 (1H, s, CH), 4.30 (2H, s, CH(_2)), 4.19 (2H, q, (J = 5.8) Hz, CH(_2)), 3.78 (2H, s, CH(_2)), 3.71 (3H, s, OCH(_3)), 3.65 (2H, s, CH(_2)), 1.44 (3H, t, (J = 5.8) Hz, CH(_3))</td>
<td>404</td>
</tr>
</tbody>
</table>
Section-B: Synthesis of 3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-6-[3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoxazines 50

The synthetic approach to these compounds is profiled in below Scheme.

I. 2[(5-Methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-imino]methyl-4-(3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-imino]methyl-4-hydroxy benzyl) Phenols 48

Condensation of 3-amino-5-methylisoxazole 46a / 4-amino-3,5-dimethylisoxazole 46b (0.02mol) with 5,5'-methylene-bis-salicylaldehyde 47 (0.01mol) in refluxing ethanol furnished the corresponding 2[(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-imino]methyl-4-hydroxy benzyl) Phenols 48
imino)methyl-4-(3-(5-methyl-3-isoxazolyl) / (3,5-dimethyl-4-isoxazolyl) imino)methyl-4-hydroxybenzyl) phenols 48 in good yields (85%).

For example, 3-amino-5-methylisoxazole 46a (0.02 mol) and 5,5'-methylene-bis-salicylaldehyde 47 (0.01 mol) were refluxed in alcohol for 4 hr. The reaction mixture was cooled, the separated solid was filtered and recrystallized from ethanol to give Schiff's base 48 in 85% yield. The compound was assigned the structure as 2[(5-methyl-3-isoxazolyl)imino]methyl-4-(3-(5-methyl-3-isoxazolyl)imino]methyl-4-hydroxy benzyl)phenol 48a based on analytical and spectral data.

Similarly, 2[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-(3-[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-hydroxybenzyl) phenol 47b was prepared by reaction of 4-amino-3,5-dimethylisoxazole 46b with 5,5'-methylene-bis-salicylaldehyde 47 (Table-III).

The structures of the compounds 48 were established on the basis of spectral and analytical data.

**IR spectra**

The IR (KBr) spectrum of 2[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-(3-[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-hydroxy benzyl phenol 48b exhibited strong absorption bands at 3500 and 1615 cm\(^{-1}\) due to OH and C=N functional groups respectively.
**1H NMR spectra**

The 1H NMR (200 MHz, CDCl3) spectrum of 2[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-(3-[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-hydroxybenzyl) phenol 48b displayed a sharp singlet at δ 8.5 and a broad singlet at δ 12.7 assignable to –CH=N- and OH protons integrating for two protons each, respectively. Isoxazole methyls appeared as two singlets at δ 2.3 and 2.5 integrating for six protons each, methylene protons resonated at δ 3.9 as a singlet, and whereas aromatic protons are shown as complex multiplet between 6.9-7.4.

**Mass spectra**

The mass spectra (70eV) of 2[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-(3-[(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-hydroxybenzyl) phenol 48b exhibited molecular ion [M+H]+ peak at m/z 445.

**II. 2[(5-Methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl) amino]methyl-4-(3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl) amino)methyl-4-hydroxybenzyl) phenols 49**

The reduction of iminomethyl phenols 48 (0.01 mol) with sodium borohydride (0.05 mol) furnished the corresponding amino methyl phenols 28 in good yields.

In a typical case, to the Schiff’s base viz., 2-[(5-methyl-3-isoxazolyl)imino]methyl-4-(3-(5-methyl-3-isoxazolyl)imino]methyl-
4-hydroxybenzyl)phenol 48a (0.01 mol) dissolved in dichloromethane, sodium borohydride (0.05 mol) dissolved in methanol was added and the contents are stirred for 1hr at room temperature. The solid separated on pouring the reaction mixture on to ice-cold water was filtered and crystallized from ethanol. The product was assigned the structure as 2[(5-methyl-3-isoxazolyl)amino]methyl-4-(3-(5-methyl-3-isoxazolyl) amino]methyl-4-hydroxybenzyl) phenol 49a on the basis of spectral data.

Similar treatment of other Schiff’s base 48b (R= 3,5-dimethyl-4-isoxazolyl) with NaBH₄ gave the corresponding 2[(3,5-dimethyl-4-isoxazolyl)amino]methyl-4-(3-(3,5-dimethyl-4-isoxazolyl)amino]methyl-4-hydroxybenzyl) phenol 49b (Table-III). The structure of the compounds 49 were confirmed by their spectroscopic (IR, ¹H NMR and MS) and analytical data.

**IR spectra**

The IR (KBr) spectrum of 2-[3,5-dimethyl-4-isoxazolyl]-amino]methyl-4-(3-(3,5-dimethyl-4-isoxazolyl)amino]-methyl-4-hydroxy benzyl)phenol 49b showed strong absorption bands at 3378, 3200 cm⁻¹ assignable to –NH and –OH functional group stretching vibrations respectively.
1H NMR spectra

1H NMR spectra (200 MHz, CDCl$_3$) of 2[(3,5-dimethyl-4-isoxazolyl)amino]methyl-4-(3-(3,5-dimethyl-4-isoxazolyl)amino]methyl-4-hydroxybenzyl) phenol 49b exhibited two singlets at δ 3.9 and 4.2 due to NH and NCH$_2$ protons integrating for two and four protons respectively confirming reduction. The isoxazole methyls, OH protons and aromatic protons appeared at δ 2.1, 2.2, 9.4 and 6.5-7.0 respectively.

Mass spectra

The mass spectra (70eV) of 2[(3,5-dimethyl-4-isoxazolyl)amino]methyl-4-(3-(3,5-dimethyl-4-isoxazolyl)amino]methyl-4-hydroxybenzyl) phenol 49b exhibited the molecular ion peak [M+H]$^+$ at m/z 449 confirming the reduction of Schiff’s base.

III. 3-(5-Methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-6-[3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoxazines 50

Aminomethyl phenols 49 underwent smooth ring closure involving internal Mannich reaction, on treatment with formaldehyde (2 moles) to give the corresponding methylene-bis-isoxazolyl-1,3-benzoxazines 50 in good yields.

For example, a mixture of 49a (R= 5-methyl-3-isoxazolyl) (0.01 mol) and formaldehyde (0.02 mol) were heated in methanol for 6hr. The reaction mixture was poured on to ice-cold water. The separated
solid was filtered and recrystallized from ethanol to afford 3-(5-methyl-3-isoxazolyl)-6-[3-(5-methyl-3-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoxazine 50a in 80 % yield.

A similar method was used for the preparation of other member of the series 50b (R= 3,5-dimethyl-4-isoxazolyl) (Table-III).

The structural assignments to the compounds 50 were based on their elemental analyses and spectral (IR, 1H NMR and MS) data.

**IR spectra**

The IR (KBr) spectrum of 3-(3,5-dimethyl-4-isoxazolyl)-6-[3-(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoxazine 50b exhibited characteristic absorption bands at 2990 and 2930 cm\(^{-1}\) due to CH\(_2\)N and CH\(_2\)O stretching vibrations respectively.

**1H NMR spectra**

The 1H NMR spectra (200 MHz, CDCl\(_3\)) of 3-(3,5-dimethyl-4-isoxazolyl)-6-[3(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoxazine 50b displayed two distinct singlets at δ 4.2 and 5.0 integrating for four protons each, due to newly formed 1,3-benzoxazine CH\(_2\)N and CH\(_2\)O ring protons respectively. The methylene protons appeared as a singlet at δ 3.8, whereas isoxazole methyls integrating for six protons each and aromatic protons appeared at 2.1, 2.2 and 6.7-7.1 respectively.
**13C NMR spectrum** (75 MHz, CDCl₃+DMSO-d₆, δ ppm) of 50a

11.88 (C-6″), 12.08 (C-6″), 40.26 (PhCH₂Ph), 43.08 (C-4), 46.59 (C-4), 92.63 (C-2), 93.09 (C-2), 116.14 (C-4″), 116.37 (C-4″), 116.50 (Ar-C), 119.58 (Ar-C), 119.70 (Ar- C), 125.10 (Ar-C), 126.56 (Ar-C), 127.76 (Ar-C), 128.46 (Ar-C), 129.97 (Ar-C), 131.72 (Ar-C), 132.30 (Ar-C), 133.58 (Ar-C), 151.37 (C-3″), 153.06 (C-3″), 164.23 (C-5″), 164.75 (C-5″), 167.85 (C-8′), 169.47 (C-8′).

**Mass spectra**

The mass spectra (70eV) of 3-(3,5-dimethyl-4-isoxazolyl)-6-[3-(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoxazine 50b displayed molecular ion [M+H]+ peak at m/z 473 confirming cyclization.

**Conclusion**

In conclusion, we have achieved the synthesis of new isoxazolyl 1,3-benzoxazines and also novel methylene-bis-isoxazolyl-1,3-benzoxazines by utilizing minimum number of steps and by easily adoptable method, where in isoxazole is coupled with 1,3-benzoxazine.
Experimental

Section-A:

I. Synthesis of (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43

The mixture of (1H-indol-3-yl)-acetic acid ethyl ester 41 (0.01 mol) in acetonitrile (10 ml) and DBU (0.02 mol) was uniformly stirred for a few minutes to get homogeneous solution. Subsequently, 3-bromopropyne 42 (0.01 mol) was added and the whole reaction mixture was refluxed for 15 h on constant stirring. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and CH₂Cl₂ (20 ml) was added. The organic phase was washed with aqueous NH₄Cl solution (5%, 20 ml), dried with anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography (CH₂Cl₂) and recrystallized from CH₂Cl₂/hexane (1:1 v/v) to obtain pure (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester 43

II. Synthesis of [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives 45

The mixture of compound 43 (0.01 mol), sodium azide (0.03 mol) and benzyl halide or substituted benzyl halide 44 (0.01 mol) in ethanol solvent (15 ml) was constantly stirred at reflux temperature for 5-7 h. After accomplishment of the reaction (examined by TLC), the reaction mixture was poured in ice-cold water and obtained solid was filtered off, washed with H₂O, then with hexane and dried under vacuum. The crude product was purified by column
chromatography (CH$_2$Cl$_2$/EtOH 98:2 \(v/v\)) and recrystallized from CH$_2$Cl$_2$/hexane (1:1 \(v/v\)) to afford [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives 45 in pure form.

Other compounds 45 in this series were prepared similarly and their characterization data are recorded in Table-II.

**Section-B:**

**Synthesis of 3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-6-[3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl]methyl-3,4-dihydro-2H-1,3-benzoxazines 34**

I. 5,5'-Methylene-bis-salicylaldehyde 47$^{24}$

To a solution of salicylaldehyde (2 mol) in glacial acetic acid (10 ml), formaldehyde (1mol) and 2 drops of conc. sulphuric acid was added and the contents are stirred for overnight at ambient temperature. The reaction mixture was poured on to ice-cold water and kept a side for a day. The separated solid on addition of diethyl ether is filtered and purified by crystallization from ethanol. m.p. 136 °C.
II. 2[(5-Methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)imino]methyl-4-(3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-imino)methyl-4-hydroxybenzyl) phenols 48

A mixture of 3-amino-5-methylisoxazole 46a (0.02 mol) and 5-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde 47 (0.01 mol) was taken in methanol (15 ml) and the contents were refluxed for 4 hr. The solid that separated on cooling was filtered and recrystallized from ethanol 48a.

Other member 48b in this series was prepared similarly and their characterization data are recorded in Table-III.

III. 2[(5-Methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)amino]methyl-4-(3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-amino)methyl-4-hydroxybenzyl] phenols 49

To iminomethyl phenol 48a (0.01 mol) dissolved in dichloromethane (10 ml), sodium borohydride (0.05 mol) dissolved in methanol (10 ml) was added and the contents were stirred for 1 hr at room temperature. The reaction mixture was poured onto water. The separated solid was filtered and crystallized from ethanol to get amino methyl phenol 49a.

Other member 49b in this series was prepared similarly and their characterization data are presented in Table-III.
IV. 3-[5-Methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-6-[3-(5-methyl-3-isoxazolyl)/(3,5-dimethyl-4-isoxazolyl)-3,4-dihydro-2H-1,3-benzoxazin-6-yl] methyl -3,4-dihydro-2H-1,3-benzoxazines 50

Aminomethyl phenol 49a (0.01 mol) and formalin (37%, 2ml) was taken in methanol and refluxed for 6hr (monitored with TLC). The reaction mixture was poured on to ice-cold water, the separated solid was filtered and recrystallized from ethanol to get pure 1,3-benzoxazine 50a.

Other number 50b in this series was prepared similarly and their characterization data are presented in Table-III.
**Table-II** - Characterization data of [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Y</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Mol. Formula</th>
<th>Found (%) (Calcd)</th>
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<tr>
<td>1.</td>
<td>H</td>
<td>112-124</td>
<td>74</td>
<td>C_{22}H_{22}N_{4}</td>
<td>70.57  5.92  14.96</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>(69.23  5.26  13.56)</td>
</tr>
<tr>
<td>2.</td>
<td>4-F</td>
<td>130-132</td>
<td>70</td>
<td>C_{22}H_{22}FN_{4}O_{2}</td>
<td>67.33  5.39  14.28</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(66.21  5.06  13.65)</td>
</tr>
<tr>
<td>3.</td>
<td>4-Cl</td>
<td>162-164</td>
<td>74</td>
<td>C_{22}H_{21}ClN_{4}O_{2}</td>
<td>64.62  5.18  13.70</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(63.20  4.89  12.65)</td>
</tr>
<tr>
<td>4.</td>
<td>4-Br</td>
<td>154-156</td>
<td>72</td>
<td>C_{22}H_{21}BrN_{4}O_{2}</td>
<td>58.29  4.67  12.36</td>
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<tr>
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<td></td>
<td>(57.46  4.25  11.95)</td>
</tr>
<tr>
<td>5.</td>
<td>4-I</td>
<td>147-149</td>
<td>75</td>
<td>C_{22}H_{21}BrN_{4}O_{2}</td>
<td>52.81  4.23  11.20</td>
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<td>(51.36  4.02  10.87)</td>
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<td>6.</td>
<td>2-CH3</td>
<td>133-135</td>
<td>77</td>
<td>C_{23}H_{24}N_{4}O_{2}</td>
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<td>(70.41  5.89  13.98)</td>
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<td>7.</td>
<td>4-OCH3</td>
<td>141-143</td>
<td>74</td>
<td>C_{23}H_{24}N_{4}O_{3}</td>
<td>68.30  5.98  13.05</td>
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<td>(67.69  5.25  12.95)</td>
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### Table-III. Characterization data of compounds 48, 49 and 50

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Mol. Formula</th>
<th>Found(%) (Calcd.)</th>
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<td>5.71 13.33</td>
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<td>C 66.96</td>
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<td></td>
<td></td>
<td>C 67.56</td>
<td>5.40 12.61</td>
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<td>C 68.64</td>
<td>5.93 11.86</td>
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</table>

**48a** 5-methyl-3-isoxazolyl 119-21 85 C_{23}H_{24}N_{4}O_{4} (66.38 4.78 13.40)

**48b** 3,5-dimethyl-4-isoxazolyl 127-29 85 C_{23}H_{24}N_{4}O_{4} (67.51 5.47 12.57)

**49a** 5-methyl-3-isoxazolyl 132-34 70 C_{23}H_{24}N_{4}O_{4} (65.73 5.78 13.38)

**49b** 3,5-dimethyl-4-isoxazole 145-47 75 C_{23}H_{28}N_{4}O_{4} (66.94 6.20 12.56)

**50a** 5-methyl-3-isoxazolyl 141-43 80 C_{23}H_{24}N_{4}O_{4} (67.58 5.46 12.65)

**50b** 3,5-dimethyl-4-isoxazolyl 161-63 75 C_{27}H_{28}N_{4}O_{4} (68.62 5.90 11.92)
References:


