CHAPTER-3

Part-1

Synthesis of glycosyl spiro chromanono pyrrolidines/pyrrolizidines through 1,3-dipolar cycloaddition reaction

3.1.1. Introduction

A number of heterocyclic compounds of biological interest containing an oxygen ring system have been prepared by the reaction of 4-chromanones. Many chromanone derivatives are used as starting materials for the synthesis of natural products such as hematoxyline,\(^1\) brazillin,\(^2\) ripariochromene,\(^3\) clausenin,\(^4,5\) and acronycine.\(^6\) It has also been used as a versatile intermediate in the synthesis of natural products calonlide(A) and inophyllum(B)\(^7\) which have been reported to have significant activity against anti-human immunodeficiency virus type 1(HIV-1).\(^8\)

Many 4-chromanone derivatives have important biological properties and their syntheses have attracted much attention.\(^9\) The 4-chromanones were claimed to be active against trichomonads, gram-positive, gram-negative bacteria and fungi. There are limited reports in the literature about the reactivity of 3-arylidene-4-chromanone as dipolarophile.

Cycloaddition reaction is one of the most important classes of reactions in synthetic organic chemistry. Within this class, 1,3-dipolar cycloaddition reaction has found a prominent place as a high-yielding and efficient, regio- and stereocontrolled method for the synthesis of many heterocyclic compounds.\(^10\) 1,3-dipolar cycloaddition reaction has been described as "the single most important method for the construction of heterocyclic five-membered ring in organic chemistry".\(^11\)

Azomethine ylide forms a classic example of 1,3-dipole. Its cycloaddition with dipolarophiles leads to the formation of pyrrolidine ring systems. The 1,3-DC reaction of
azomethine ylides with various dipolarophiles has been utilized extensively for the generation of novel heterocycles.\textsuperscript{12} Their cycloadditions to olefin or acetylene dipolarophiles give rise to the formation of two sets of carbon-carbon bonds in a single operation and results in the formation of pyrrolidines and pyrroles in which high regio and stereochemical control of the peripheral substituents can be achieved.

Raghunathan et al\textsuperscript{13} chosen (E)-3-arylidene-4-chromanones 154 as dipolarophiles for the reaction of N-metalated azomethine ylides derived from \(\beta\)-lactam imines 153. Treatment of \(\beta\)-lactam aldehydes 152 with glycine methyl ester 78 in the presence of anhydrous MgSO\(_4\) in dry dichloromethane at room temperature afforded the imines 153. These crude \(\beta\)-lactam imines when reacted with (E)-3-arylidene-4-chromanones 154 in the presence of silver acetate and triethylamine at room temperature in toluene afforded a series of novel spiropyrrolidine derivatives 155.
Raghunathan et al. have also reported the synthesis of a rare class of dispiroheterocycles, namely dispiro acenaphtheno-chromanone pyrrolidine 157 and dispiro acenaphtheno-chromanone pyrrolizidines 158 through 1,3-dipolar cycloaddition reaction of arylidene chromanones with non-stabilized azomethine ylides generated by the decarboxylative condensation reaction of acenaphthaquinone 122 with secondary amino acids.

Reaction of 3-arylidene-4-chromanones 154 with aziridine 159 in dry toluene under nitrogen atmosphere yielded a series of novel 3-aryl-5-benzoyl-1-N-cyclohexyl-2-phenyl-pyrrolidine-spiro[4.3’]4’ chromanones 160 by the regioselective cycloaddition of the 1,3-dipole across the exocyclic double bond of the arylidene chromanone in each case. 15
Raghunathan *et al* reported the synthesis of chromeno[4,3-\(b\)]pyrrolidines 162/pyrrolizidines 163 by the intramolecular cycloaddition reaction of O-allyl salicylaldehyde derivatives 161 with the azomethine ylide generated from sarcosine 16/proline 20 in anhydrous methanol in refluxing condition.\(^{16}\)

Chandrakanta *et al* reported an efficient one-pot synthesis of several novel dispirochromanopyrrolidines 165, 166 by the 1,3-DC reaction of chromone-3-carbaldehyde 164 with the azomethine ylide generated from sarcosine 16 and ninhydrin 96.\(^{17}\)

Raghunathan *et al* reported that, the bicyclic nitrone 167 when reacted with various substituted \((E)\)-3-arylidene chroman-4-ones 154 in acetonitrile under reflux conditions afforded \(\beta\)-lactam fused spiroisoxazolidine chromanones 168.\(^{18}\)
Carbohydrates and their derivatives which are useful substrates in chemical and biological fields\textsuperscript{19} are present in natural products.\textsuperscript{20} Recent studies on these glycomolecules,\textsuperscript{21} such as proteoglycans, glycoproteins,\textsuperscript{22} glycolipids,\textsuperscript{23} and antibiotics have great significance of carbohydrate parts (glycons) in molecular recognition for the transmission of biological information.\textsuperscript{24} Therefore, it is now recognized that carbohydrates takes an important role in a multitude of biological events. With this stimulating biological background, the efficient synthesis of not only carbohydrates themselves, but also carbohydrate-containing heterocycles is becoming more and more important in the field of organic chemistry and chemical biology.\textsuperscript{25} Hence, there has been renewed interest in the synthesis of carbohydrate based heterocycles.
Jean-Pierre et al\textsuperscript{26} have reported the synthesis of spiro-isoxazolines 171 and oxadiazoles 173 by the [3+2] cycloaddition reaction of \( p \)-anisonitrile oxide 170 with glucal 169 and D-glucosyl cyanide 172 respectively.

\[
\begin{align*}
\text{169} & \quad \text{ArC} &= \text{N} - \text{O} & \quad \text{170} \\
\text{172} & \quad \text{Ar} &= \text{C} - \text{N} - \text{O} & \quad \text{173}
\end{align*}
\]

Alessandro et al reported the synthesis of of [60]fulleropyrrolidine glycoconjugates 176 using 1,3-dipolar cycloaddition of \( C \)-glycosyl azomethine ylide 175 generated from sarcosine and a sugar aldehyde 174 with [60]fullerene in refluxing toluene.\textsuperscript{27}
3.1.2. Results and Discussion

In carbohydrate chemistry, 1,3-dipolar cycloadditions have gained much attention in recent years. 1,3-dipolar cycloaddition reactions of nitrones and nitrile oxides with alkenes and azides with alkynes of sugar derivatives are well known in literature. However, the cycloaddition reaction of azomethine ylides derived from carbohydrates for the synthesis of glycoheterocycles is not known and has not been utilized in organic synthesis. With a view to study the reactivity of azomethine ylide, we report here for the first time the cycloaddition reaction of the sugar derived azomethine ylide from O-benzyl sugar aldehyde with cyclic/acyclic amino acids.

In continuation of our studies in the azomethine ylide cycloaddition reaction, we have reacted 1,3-dipolar azomethine ylide generated from O-benzyl sugar aldehyde and secondary amino acid with arylidene chromanones as dipolarophiles. The dipolarophile required for the present study, 3-arylidene chromanones 154a-c were synthesized by acid catalyzed condensation of 4-chromanone 177 with various substituted benzaldehydes 178a-c (Scheme-3.1.1). The arylidene derivatives were assigned the E configuration on the basis of their NMR data in accordance with a literature report.30

![Scheme-3.1.1](image-url)
3.1.2.1: Synthesis of glycosyl chromano pyrrolidines

In a one-pot cycloaddition reaction, a mixture of O-benzyl tethered sugar aldehyde 132, sarcosine and 3-arylidene chroman-4-one 154a/b/c was refluxed in toluene. The non-stabilized azomethine ylide generated by the decarboxylative condensation reaction of sugar aldehyde 132 and sarcosine 16 underwent neat cycloaddition with 3-arylidene chroman-4-ones 154a/b/c resulting in the formation of novel spiro pyrrolidines 179a/b/c in good yields (Scheme-3.1.2). TLC analysis showed the formation of a single cycloadduct. The formation of cycloadducts and their structural elucidations were made on the basis of their spectroscopic data.

In the above reaction, the expected product 180a/b/c did not form as evidenced from spectroscopic data. The mass spectra of the product revealed a peak at m/z 474 instead of the expected m/z 617, the difference corresponds to the loss of molecule of benzyl alcohol. This was further confirmed from $^1$H NMR spectrum, which revealed the absence of signal due to benzylic protons (CH$_2$–Ph). Also, in the furanose moiety only
three protons were observed. Based on the above facts, the structure of the compound was assigned to be alkenyl sugar substituted spiro pyrrolo chromanone 179a/b/c.

The cycloadduct 179b was chosen as a representative of the series for the spectral discussion. The IR spectrum of the product 179b exhibited a peak at 1679 cm$^{-1}$ characteristic of chromanone carbonyl carbon. The absorption bands at 1554 cm$^{-1}$ and 1350 cm$^{-1}$ are attributed to the nitro group.

The $^1$H NMR spectrum of 179b (Figure 3.1.1) showed a sharp singlet at $\delta$2.40 for N-methyl protons. The furanose ring H$_1$ proton resonated as a doublet at $\delta$ 5.91 ($J = 5.4$ Hz) and H$_2$ proton resonated as a doublet of doublet at $\delta$ 5.09 ($J = 5.4, 2.4$ Hz). The H$_3$ proton was observed as a doublet at $\delta$ 5.14 ($J = 2.4$ Hz). The H$_4$ proton of the pyrrolidine ring observed as a singlet at $\delta$ 3.77 which clearly shows the regioselectivity of the cycloadduct. If other isomer had formed H$_4$ proton would have shown a doublet instead of a singlet. The H$_5$ proton resonated as a doublet of doublet at $\delta$ 3.41 ($J = 3.6 9.3$ Hz), which strongly supports the proposed regio-isomer. If other isomer had formed H$_5$ proton would have shown a doublet instead of a doublet of doublet. The N-CH$_2$- protons of the pyrrolidine ring appeared as a doublet of doublet at $\delta$ 3.08 ($J = 9.6, 3.9$ Hz), and a triplet at $\delta$2.85 ($J = 9.6$ Hz) respectively. The $^1$H NMR spectrum of the compound 179b showed two well separated doublets at $\delta$ 3.93, 4.27 with coupling constant 12.3 Hz for -CH$_2$ protons of the chromanone moiety. The aromatic protons appeared in the region $\delta$ 6.69-8.07.

In the $^1$H–$^1$H COSY spectrum of 179b, (Figure 3.1.7) the proton at $\delta$ 5.91 showed correlation with the proton at $\delta$ 5.09. Also the proton at $\delta$ 5.09 showed correlation with the proton at $\delta$ 5.14 in addition to that with the proton at $\delta$ 5.91. Hence we assigned the signals at $\delta$ 5.14 to H$_2$ and $\delta$ 5.14 to H$_3$. The stereochemistry of the cycloadduct 179b was
deduced on the basis of 2D NOESY experiments. There is no NOESY between H₄ and H₅ of 179b which clearly proved trans stereochemistry.

The ¹³C NMR spectrum of 179b (Figure 3.1.2) showed a signal at 57.51 ppm for the spiro carbon and the signal at 39.27 ppm showed the presence of N-methyl group. The N-CH₂ carbon of 179b resonated at 60.13 ppm and the O-CH₂ carbon of chromanone moiety showed signal at 68.31 ppm and were confirmed by DEPT 135 spectrum. The furanose ring attached pyrrolidine carbon showed a peak at 64.48 ppm and the peak at 49.19 ppm correspond to the benzyl attached pyrrolidine ring carbon and were confirmed by DEPT-135 (Figure 3.1.3) & ¹H-¹³C correlation spectrum (Figure 3.1.5). The furanose ring carbons showed signals at 104.74, 101.36, 81.31 and 159.98 ppm respectively which were confirmed by DEPT-135 & ¹H-¹³C correlation spectrum. The peak at 192.08 ppm corresponds to the chromanone carbonyl group. Moreover, the cycloadduct 179b exhibited a peak at m/z 519.3 (M⁺+1) in the mass spectrum (Figure 3.1.4). All these spectral characteristic features delineate the fact that the cycloaddition proceeded in a highly regioselective manner with elimination affording a single regioisomer. Similar results were observed for other products 179a and 179c. The elimination of benzyloxy group in the above reaction is well supported by literature report.³¹

3.1.2.2: Synthesis of glycosyl chromano pyrrolizidines/thiolizidines

After the successful completion of cycloaddition reaction of the azomethine ylide generated from sugar aldehyde and sarcosine with 3-arylidene chroman-4-ones, we have generated the azomethine ylides by the decarboxylative condensation reaction of sugar aldehyde and proline 20/thiazolidine-4-carboxylic acid 71 and reacted with the dipolarophile 3-arylidene chroman-4-ones 154a-c.

Refluxing a solution of 3-arylidene chroman-4-ones 154a-c in toluene with sugar aldehyde 132 and proline 20 / thiazolidine-4-carboxylic acid 71 afforded a series of spiro
pyrrolizidines/thiolizidines 181a-f (Scheme-3.1.3). The reaction gave a single product in all cases, as evidenced by TLC analysis. The cycloaddition was found to be highly regioselective in all the cases and the O-benzyl group was found to be eliminated in all cases in the final product as reported earlier in the above case.

**Scheme-3.1.3**

The products were characterized on the basis of their elemental analysis as well as $^1$H, $^{13}$C, DEPT 135, 2D NMR and mass spectral analysis. For instance, the IR spectrum of the product 181e exhibited a peak at 1684 cm$^{-1}$ characteristic of chromanone carbonyl carbon. The absorption bands at 1551 cm$^{-1}$ and 1352 cm$^{-1}$ are attributed to the presence of nitro group.

The $^1$H NMR spectrum, the compound 181e (Figure 3.1.16) showed two sets of well separated doublets at $\delta$ 3.48 ($J = 11.4$ Hz), $\delta$ 4.11 ($J = 11.4$ Hz) for -CH$_2$ protons of the thiazolidine moiety and $\delta$ 4.49 ($J = 12$ Hz), $\delta$ 4.61 ($J = 12$ Hz) for -CH$_2$ protons of the chromanone moiety. In the $^1$H NMR spectrum of 181e, the furanose ring H$_1$ proton resonated as a doublet at $\delta$ 5.86 ($J = 5.4$ Hz) and H$_2$ proton resonated as a doublet of doublet at $\delta$ 4.77 ($J = 5.4, 2.4$ Hz). The H$_3$ proton observed as a doublet at $\delta$ 5.23 ($J = 2.4$ Hz). The H$_4$ proton of the pyrrolidine ring observed as a singlet at $\delta$ 3.83 which clearly shows the regioselectivity of the cycloadduct. If other isomer had formed H$_4$ proton would have shown a doublet instead of a singlet. The H$_5$ proton of the pyrrolidine ring...
resonated as a doublet at $\delta$ 4.05 ($J = 3.6$ Hz). The $\text{H}_6$ proton of the pyrrolizidine ring resonated as a multiplet in the region $\delta$ 4.23-4.28. The stereochemistry of the cycloadduct 181e was deduced on the basis of 2D NOESY experiments. There is no NOESY between $\text{H}_4$ and $\text{H}_6$ and no NOESY between $\text{H}_4$ and $\text{H}_5$ of 181e clearly proved cis stereochemistry at the ring junction.

The off resonance decoupled $^{13}$C NMR spectrum of 181e (Figure 3.1.17) showed a signal at 58.68 ppm for the spiro carbon. The $N\text{-CH}_2\text{-S}$ carbon of 181e resonated at 55.54 ppm and $O\text{-CH}_2$ of chromanone moiety appeared at 71.69 ppm and were confirmed by DEPT 135 spectrum. The furanose ring attached pyrrolizidine carbon showed peak at 72.28 ppm and the peak at 43.11 ppm correspond to the benzyl attached pyrrolizidine ring carbon and were confirmed by DEPT-135 & $^1\text{H}$-$^{13}$C correlation spectrum. The $N\text{-CH}$ carbon of pyrrolizidine carbon resonated at 71.59 ppm and was confirmed by DEPT-135 & $^1\text{H}$-$^{13}$C correlation spectrum. The furanose ring carbons showed signals at 104.32, 99.87, 82.75 and 158.93 ppm respectively, which were confirmed by DEPT-135 (Figure 3.1.18) & $^1\text{H}$-$^{13}$C correlation spectrum. The peak at 194.70 ppm correspond to the chromanone carbonyl group.

In addition, the mass spectrum of the compound 181e (Figure 3.1.19) showed the molecular ion peak at $m/z$ 563.3 (M$^+$+1) and the compound gave satisfactory elemental analysis.

Identical results were obtained with other derivatives. The characterization, $^1\text{H}$ NMR and $^{13}$C NMR details of the glycosyl chromano pyrrolizidines/thiolizidines 181a-f is reported in experimental section.

Similarly, when a mixture of 3-arylidene chroman-4-ones 1a-c with sugar aldehyde 132 and pipecolinic acid 21 were refluxed in toluene, a series of spiro pyrrolizidines 182a-c were obtained in good yields which were formed by the
cycloaddition of the non-stabilized azomethine ylide generated by the decarboxylative condensation reaction across the exocyclic double bond of benzylidine chromanones (Scheme-3.1.4).

For instance, the IR spectrum of the product 182a exhibited a peak at 1689 cm\(^{-1}\) characteristic of chromanone carbonyl carbon. In the \(^1\)H NMR spectrum of the compound 182a showed a doublet at \(\delta\) 3.27 \((J = 3.6 \text{ Hz})\) for the \(H_5\) proton and the \(H_4\) proton of the pyrrolidine ring observed as a singlet at \(\delta\) 3.83. The \(H_6\) proton of the pyrrolizidine ring showed a multiplet in the region \(\delta\) 2.71-2.78. The –O-CH\(_2\) protons of the chromanone moiety showed two well separated doublets at \(\delta\) 3.98 and \(\delta\) 4.23 with coupling constant 12 Hz.

The \(^{13}\)C NMR spectrum of 182a showed a signal at 57.41 ppm for the spiro carbon. The \(N\)-CH carbon of 182a resonated at 68.42 ppm and \(O\)-CH\(_2\) of chromanone moiety appeared at 66.39 ppm and were confirmed by DEPT 135 spectrum. The furanose ring attached pyrrolizidine carbon showed a peak at 69.37 ppm and the peak at 45.02 ppm correspond to the benzyl attached pyrrolizidine ring carbon and were confirmed by DEPT-135 & \(^1\)H-\(^{13}\)C correlation spectrum. The peak at 192.38 ppm correspond to the chromanone carbonyl group.

In addition, the mass spectrum of the compound 182a showed the molecular ion peak at \(m/z\) 548.3 (M\(^+\)+1) and the compound gave satisfactory elemental analysis.
Identical results were obtained for other glycosyl chromano pyrrolizidines derivatives. The $^1$H NMR and $^{13}$C NMR details of the products 182a-c is reported in experimental section.

The reaction was investigated in a series of solvent systems such as acetonitrile, methanol and toluene to find the best reaction conditions. Among the solvents used toluene was found to be the best in terms of better yields and short reaction time (Table1).

**Table-1:** Cycloaddition reaction of O-benzyl tethered sugar aldehyde and cyclic/acyclic amino acid with 3-arylidene chroman-4-ones under different solvent conditions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Toluene</th>
<th>Methanol</th>
<th>Acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time(h)</td>
<td>Yield (%)</td>
<td>Time(h)</td>
</tr>
<tr>
<td>179a</td>
<td>8</td>
<td>64</td>
<td>9</td>
</tr>
<tr>
<td>179b</td>
<td>8</td>
<td>66</td>
<td>9</td>
</tr>
<tr>
<td>179c</td>
<td>8</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td>181a</td>
<td>8</td>
<td>64</td>
<td>9</td>
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<td>181b</td>
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<td>181c</td>
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<td>181d</td>
<td>8</td>
<td>61</td>
<td>9</td>
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<tr>
<td>181e</td>
<td>8</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>181f</td>
<td>8</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>182a</td>
<td>8</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>182b</td>
<td>8</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td>182c</td>
<td>8</td>
<td>62</td>
<td>9</td>
</tr>
</tbody>
</table>
CONCLUSION

To conclude this chapter we have accomplished the synthesis of some novel complex sugar fused spiro pyrrolidines/pyrrolizidines/thioazolidines of biological interest with high stereo and regioselectivity by intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylide generated from O-benzyl substituted sugar aldehyde and cyclic/acyclic amino acid with 3-arylidene chroman-4-ones under different solvent conditions.
3.1.3. Experimental

3.1.3.1: General Considerations

IR spectra were recorded on an ABB BOMEN FT-IR instrument. $^1$H NMR spectra were recorded in CDCl$_3$ using TMS as an internal standard on a Bruker 300 spectrometer at 300 MHz. $^{13}$C NMR was recorded on a Bruker 300 spectrometer at 75 MHz. Mass spectra were recorded by Thermo Finnigan (LCQ) Amax 6000 ESI mass spectrometer. Elemental analysis was carried out using Perkin-Elmer CHNS 2400B instrument.

Column chromatography was performed on silica gel (ACME, 100-200 mesh). Routine monitoring of the reactions were made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 0.25 mm thickness and visualized with iodine. The organic extracts of crude products were dried over anhydrous Na$_2$SO$_4$. Solvents were reagent grade and were purified according to standard procedures.

The starting materials namely sarcosin, proline, pipecolinic acid and chromanone were purchased commercially and used as such.

3.1.3.2: Preparation of 3-arylidene chroman-4-one 154a-c

To a solution of chromanone (1.48 g, 10 mmol), aromatic aldehyde (11 mmol) in ethanol (10 ml) con HCl (4 ml) was added. The mixture was refluxed for 2-4 hours till the disappearance of the chromanone as evidenced by TLC. On cooling the solid separated was filtered washed with ethanol and the pure compound was obtained by crystallization from ethanol in 70-85 % yield.

3.1.3.3: General procedure for synthesis of cycloaducts 179a-c, 181a-f and 182a-c

To a solution of $O$-benzyl tethered sugar aldehyde 132 (1 mmol), sarcosine 16/ proline 20/ thiazolidine-4-carboxylic acid /pipecolinic acid 21 (1 mmol) and 3-arylidene
chroman-4-one 154a-c (1 mmol) was refluxed in dry toluene for 5-8 h at 110 °C using Dean-Stark apparatus. After the completion of reaction as indicated by TLC, toluene was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane: EtOAc (99:1) as eluent.

3.1.3.3.1: (2'S,3S,4'R)-4'-(4-chlorophenyl)-2'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxide]-5'-yl)-1'-methylspiro[chroman-3,3'-pyrrolidin]-4-one (179a)

Pale yellow liquid. Yield; 64%. IR (KBr); 1689 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz); δ 1.48 (br s, 10H), 2.39 (s, 3H), 2.72 (t, J = 9.3 Hz, 1H), 2.98 (dd, J = 3.6, 9.3 Hz, 1H), 3.37 (dd, J = 3.6, 9.3 Hz, 1H), 3.64 (s, 1H), 3.89 (d, J = 12 Hz, 1H), 4.16 (d, J = 12 Hz, 1H), 4.97 (dd, J = 2.4, 5.4 Hz, 1H), 5.08 (d, J = 2.4 Hz, 1H), 5.89 (d, J = 5.4 Hz, 1H), 6.60-8.00 (m, 8H). ¹³C NMR (75 MHz); ppm 22.17, 22.59, 24.02, 34.98, 36.02, 38.17, 47.14, 55.18, 59.93, 62.79, 69.54, 82.03, 99.94, 103.84, 112.09, 116.81, 120.74, 121.59, 122.54, 123.37, 123.79, 126.64, 127.97, 129.93, 136.37, 147.03, 147.94, 158.83, 193.01. MS (ESI); m/z 508.1 (M⁺+1). Anal.Calcd for; C₂₉H₃₀ClNO₅; C, 68.56; H, 5.95; N, 2.76%. Found; C, 68.62; H, 5.99; N, 2.42%.

3.1.3.3.2: (2'S,3S,4'R)-2'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxide]-5'-yl)-1'-methyl-4'-(4-nitrophenyl)spiro[chroman-3,3'-pyrrolidin]-4-one (179b)

Pale yellow liquid. Yield; 66%. IR (KBr); 1342, 1520, 1690 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz); δ 1.49 (br s, 10H), 2.40 (s, 3H), 2.85 (t, J = 9.3 Hz, 1H), 3.08 (dd, J = 3.6, 9.3 Hz, 1H), 3.41 (dd, J = 3.6, 9.3 Hz, 1H), 3.77 (s, 1H), 3.93 (d, J = 12.3 Hz, 1H), 4.27 (d, J = 12.3 Hz, 1H), 5.09 (dd, J = 2.4, 5.4 Hz, 1H), 5.14 (d, J = 2.4 Hz, 1H), 5.91 (d, J = 5.4 Hz, 1H), 6.69-8.07 (m, 8H). ¹³C NMR (75 MHz); ppm 22.89, 22.91, 23.81, 35.94, 36.49, 39.27, 48.19, 57.51, 60.13, 64.48, 68.33, 81.31, 101.36, 104.74,
111.63, 116.50, 117.99, 120.59, 122.18, 122.77, 122.95, 127.30, 128.63, 129.44, 135.45, 146.06, 147.46, 157.43, 159.98, 192.08. MS (ESI); \( m/z 519.1 \) (M\(^+\)+1). Anal.Calcd for; C\(_{29}\)H\(_{30}\)N\(_2\)O\(_7\); C, 67.17; H, 5.83; N, 5.40%. Found; C, 67.24; H, 5.81; N, 5.32%.

3.1.3.3.3: (2\(^S\),3\(^S\),4\(^R\))-2'-(3\(^a\),6\(^a\)-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole ]-5'-yl)-1'-methyl-4'-(3-nitrophenyl)spiro[chroman-3,3'-pyrrolidin]-4-one(179c)

Pale yellow liquid. Yield; 62%. IR (KBr); 1344, 1521, 1690 cm\(^{-1}\);

\(^1\)H NMR (CDCl\(_3\), 300 MHz); \( \delta 1.47 \) (br s, 10H), 2.42 (s, 3H), 2.87 (t, \( J = 9.3 \) Hz, 1H), 3.07 (dd, \( J = 3.9, 9.3 \) Hz, 1H), 3.40 (dd, \( J = 3.9, 9.3 \) Hz, 1H), 3.797 (s, 1H), 3.88 (d, \( J = 12.3 \) Hz, 1H), 4.30 (d, \( J = 12.3 \) Hz, 1H), 5.11 (dd, \( J = 2.4, 5.4 \) Hz, 1H), 5.24 (d, \( J = 2.4 \) Hz, 1H), 5.87 (d, \( J = 5.4 \) Hz, 1H), 6.72-7.96 (m, 8H). \(^13\)C NMR (75 MHz); ppm 22.83, 22.88, 28.67, 35.96, 36.39, 39.35, 48.15, 57.48, 59.72, 64.01, 68.32, 81.39, 101.11, 104.61, 11.43, 117.04, 120.63, 121.14, 123.15, 123.73, 126.59, 127.01, 127.31, 133.26, 134.48, 135.44, 141.63, 157.64, 192.20. MS (ESI); \( m/z 519.2 \) (M\(^+\)+1). Anal.Calcd for; C\(_{29}\)H\(_{30}\)N\(_2\)O\(_7\); C, 67.24; H, 5.81; N, 5.32%.

3.1.3.3.4: (1\(^R\),2\(^S\),3\(^S\),7\(^a\)R)-1'-(4-chlorophenyl)-3'-(3\(^a\),6\(^a\)-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-1',3',5',6',7',7\(^a\)'-hexahydoxypro[chroman-3,2'-pyrrolizin]-4-one (181a)

Pale yellow liquid. Yield; 64%. IR (KBr); 1686 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 300 MHz); \( \delta 1.42 \) (br s, 10H), 1.69-1.76 (m, 2H), 1.84-1.90 (m, 2H), 1.99-2.07 (m, 1H), 2.17-2.22 (m, 1H), 2.74-2.83 (m, 1H), 3.57 (d, \( J = 3.6 \) Hz, 1H), 3.76 (s, 1H), 4.02 (d, \( J = 12 \) Hz, 1H), 4.39 (d, \( J = 12 \) Hz, 1H), 5.17 (dd, \( J = 2.4, 5.4 \) Hz, 1H), 5.32 (d, \( J = 2.4 \) Hz, 1H), 5.93 (d, \( J = 5.4 \) Hz, 1H), 6.63-7.96 (m, 8H). \(^13\)C NMR (75 MHz); ppm 21.74, 22.08, 23.74, 24.48, 28.34, 33.04, 34.19, 44.72, 56.42, 60.02, 68.39, 69.47, 70.76, 81.48, 99.49,
3.1.3.3.5. (1'R,2'S,3'S,7a'R)-3'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d]
[1,3]dioxole]-5'-yl)-1'-(4-nitrophenyl)-1',3',5',6',7',7a'-hexahydrospiro[chroman-3,2'-
pyrrolizin]-4-one (181b)

Pale yellow liquid. Yield; 65%. IR (KBr); 1685 cm\(^{-1}\). \(\text{H NMR} (\text{CDCl}_3, 300 \text{ MHz}); \delta 1.51 \text{ (br s, 10H)}, 1.67-1.75 \text{ (m, 2H)}, 1.81-1.90 \text{ (m, 2H)}, 1.98-2.05 \text{ (m, 1H)}, 2.27-2.33 \text{ (m, 1H)}, 3.01-3.10 \text{ (m, 1H)}, 3.57 \text{ (d, } J = 3.6 \text{ Hz, 1H)}, 3.82 \text{ (s, 1H)}, 3.97 \text{ (d, } J = 12 \text{ Hz, 1H)}, 4.28 \text{ (d, } J = 12 \text{ Hz, 1H)}, 4.94 \text{ (dd, } J = 2.4, 5.4 \text{ Hz, 1H)}, 5.21 \text{ (d, } J = 2.4 \text{ Hz, 1H)}, 5.93 \text{ (d, } J = 5.4 \text{ Hz, 1H)}, 6.59-8.02 \text{ (m, 8H)}. 13C NMR (75 MHz); ppm 20.94, 21.37, 22.48, 23.82, 28.35, 34.02, 35.41, 42.82, 54.47, 59.82, 67.39, 69.42, 70.72, 82.34, 100.12, 103.41, 113.92, 117.41, 121.42, 122.71, 123.39, 125.17, 125.62, 126.24, 127.19, 130.34, 132.74, 146.49, 149.32, 157.32, 191.97. MS (ESI); \(m/z\) 545.4 (M\(^{+}\)+1). Anal.Calcd for; C\(_{31}\)H\(_{32}\)N\(_{2}\)O\(_7\); C, 68.37; H, 5.92; N, 5.14%. Found; C, 68.42; H, 5.98; N, 5.02%.

3.1.3.3.6: (1'S,2'R,3'R,7a'S)-3'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d]
[1,3]dioxole]-5'-yl)-1'-(3-nitrophenyl)-1',3',5',6',7',7a'-hexahydrospiro[chroman-3,2'-
pyrrolizin]-4-one (181c)

Pale yellow liquid. Yield; 61%. IR (KBr); 1685 cm\(^{-1}\). \(\text{H NMR} (\text{CDCl}_3, 300 \text{ MHz}); \delta 1.49 \text{ (br s, 10H)}, 1.74-1.86 \text{ (m, 2H)}, 1.88-1.97 \text{ (m, 2H)}, 2.12-2.19 \text{ (m, 1H)}, 2.22-2.28 \text{ (m, 1H)}, 3.17-3.25 \text{ (m, 1H)}, 3.74 \text{ (d, } J = 3.6 \text{ Hz, 1H)}, 3.92 \text{ (s, 1H)}, 4.08 \text{ (d, } J = 12.3 \text{ Hz, 1H)}, 4.29 \text{ (d, } J = 12.3 \text{ Hz, 1H)}, 4.87 \text{ (dd, } J = 2.4, 5.4 \text{ Hz, 1H)}, 5.17 \text{ (d, } J = 2.4 \text{ Hz, 1H)}, 5.89 \text{ (d, } J = 5.4 \text{ Hz, 1H)}, 6.67-7.98 \text{ (m, 8H)}. 13C NMR (75 MHz); ppm 22.07, 22.74,
23.18, 25.78, 28.77, 34.41, 34.98, 44.17, 56.32, 58.39, 67.48, 69.07, 69.98, 81.94, 99.48, 100.87, 112.82, 117.02, 121.32, 123.17, 123.59, 124.71, 126.05, 128.42, 130.12, 134.49, 136.39, 142.24, 149.37, 158.39, 192.02. MS (ESI); m/z 545.4 (M^+1). Anal. Calcd for C_{31}H_{32}N_{2}O_{7}; C, 68.37; H, 5.92; N, 5.14%. Found; C, 68.42; H, 5.98; N, 5.02%.

3.1.3.3.7: (3S,5'S,7'R,7a'S)-7'-(4-chlorophenyl)-5'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-3',5',7',7a'-tetrahydro-1'H-spiro[chroman-3,6'-pyrrolo[1,2-c]thiazol]-4-one(181d)

Pale yellow liquid. Yield; 61%. IR (KBr); 1679 cm^{-1}. $^1$H NMR (CDCl$_3$, 300 MHz); $\delta$ 1.52 (br s, 10H), 2.28 (dd, $J = 5.1, 9.0$ Hz, 1H), 3.07 (dd, $J = 5.1, 9.0$ Hz, 1H), 3.41 (d, $J = 11.4$ Hz, 1H), 3.79 (s, 1H), 3.88 (d, $J = 3.9$ Hz, 1H), 4.09 (d, $J = 11.4$ Hz, 1H), 4.21-4.27 (m, 1H), 4.42 (d, $J = 12$ Hz, 1H), 4.67 (d, $J = 12$ Hz, 1H), 4.81 (dd, $J = 2.4, 5.4$ Hz, 1H), 5.17 (d, $J = 2.4$ Hz, 1H), 5.89 (d, $J = 5.4$ Hz, 1H), 6.59-7.97 (m, 8H). $^{13}$C NMR (75 MHz); ppm 22.75, 23.17, 24.57, 35.79, 37.04, 45.12, 54.49, 58.77, 69.48, 70.94, 71.48, 82.48, 100.24, 113.74, 117.37, 120.94, 122.45, 123.79, 125.17, 125.49, 126.32, 127.45, 131.40, 136.29, 140.42, 146.32, 158.17, 192.39. MS (ESI); m/z 552.5 (M^+1). Anal. Calcd for C$_{30}$H$_{30}$ClNO$_5$S; C, 65.27; H, 5.48; N, 2.54%. Found; C, 65.34; H, 5.55; N, 2.42%.

3.1.3.3.8: (3S,5'S,7'R,7a'S)-5'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-7'-(4-nitrophenyl)-3',5',7',7a'-tetrahydro-1'H-spiro[chroman-3,6'-pyrrolo[1,2-c]thiazol]-4-one(181e)

Pale yellow liquid. Yield; 67%. IR (KBr); 1684, 1551, 1352cm^{-1}. $^1$H NMR (CDCl$_3$, 300 MHz); $\delta$ 1.53 (br s, 10H), 2.39 (dd, $J = 5.1, 9.3$ Hz, 1H), 3.37 (dd, $J = 5.1, 9.3$ Hz, 1H), 3.48 (d, $J = 11.4$ Hz, 1H), 3.83 (s, 1H), 4.05 (d, $J = 3.6$ Hz, 1H), 4.11 (d, $J = 11.4$ Hz, 1H), 4.23-4.28 (m, 1H), 4.49 (d, $J = 12$ Hz, 1H), 4.61 (d, $J = 12$ Hz, 1H), 4.77 (dd, $J =$
2.4, 5.4 Hz, 1H), 5.23 (d, J = 2.4 Hz, 1H), 5.86 (d, J = 5.4 Hz, 1H), 6.82-8.09 (m, 8H).

$^{13}$C NMR (75 MHz); ppm 23.57, 23.72, 24.69, 35.42, 37.26, 43.11, 44.10 55.53, 58.68, 71.59, 71.69, 72.78, 82.74, 99.83, 104.32, 113.27, 117.78, 123.77, 125.90, 127.75, 128.21, 128.63, 129.65, 136.62, 136.98, 146.14, 153.34, 167.12, 194.70. MS (ESI); m/z 563.3 (M$^+$+1).

Anal. Calcd for; C$_{30}$H$_{30}$N$_2$O$_7$S; C, 64.04; H, 5.37; N, 4.98%. Found; C, 64.12; H, 5.41; N, 4.87%.

3.1.3.3.9: (3S,5'S,7'R,7a'S)-5'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-7'-(3-nitrophenyl)-3',5',7',7a'-tetrahydro-1'H-spiro[chroman-3,6'-pyrrolo[1,2-c]thiazol]-4-one (181f)

Pale yellow liquid. Yield; 67%. IR (KBr); 1684, 1552, 1351 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz); $\delta$ 1.49 (br s, 10H), 2.37 (dd, J = 5.1, 9.6 Hz, 1H), 3.32 (dd, J = 5.1, 9.6 Hz, 1H), 3.49 (d, J = 11.4 Hz, 1H), 3.79 (s, 1H), 3.98 (d, J = 3.6 Hz, 1H), 4.09 (d, J = 11.4 Hz, 1H), 4.21-4.27 (m, 1H), 4.50 (d, J = 12 Hz, 1H), 4.76 (d, J = 12 Hz, 1H), 5.06 (dd, J = 2.4, 5.4 Hz, 1H), 5.21 (d, J = 2.4 Hz, 1H), 5.88 (d, J = 5.4 Hz, 1H), 6.62-8.01 (m, 8H). $^{13}$C NMR (75 MHz); ppm 22.91, 23.32, 25.19, 32.79, 34.52, 44.02, 56.12, 59.12, 68.91, 69.48, 70.02, 82.39, 101.49, 113.38, 117.12, 121.19, 122.37, 124.38, 125.27, 125.82, 126.42, 128.32, 131.39, 136.32, 141.30, 145.49, 158.52, 191.98. MS (ESI); m/z 563.2 (M$^+$+1).

Anal. Calcd for; C$_{30}$H$_{30}$N$_2$O$_7$S; C, 64.04; H, 5.37; N, 4.98%. Found; C, 64.12; H, 5.41; N, 4.87%. 

\[\text{O}_2\text{N} \]

\[\text{H} \]

\[\text{O} \]

\[\text{O} \]

\[\text{S} \]
3.1.3.3.10: \((1'R,2'S,3'S,8a'R)-1'-(4-chlorophenyl)-3'-(3a',6a'-dihydrospiro \[cyclo\text{hexane-1,2'-furo} \[3,2-d]\[1,3]\text{dioxole-5'-yl}]\)-3',5',6',7',8',8a'-hexahydro-1'H-spiro[chroman-3,2'-indolizin]-4-one (182a)

Pale yellow liquid. Yield; 60%. IR (KBr): 1689 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 300 MHz); \(\delta\) 1.43 (br s, 10H), 1.57-1.62 (m, 3H), 1.71-1.82 (m, 2H), 1.89-1.94 (m, 1H), 2.02-2.08 (m, 1H), 2.24-2.30 (m, 1H), 2.71-2.78 (m, 1H), 3.27 (d, \(J = 3.6\) Hz, 1H), 3.62 (s, 1H), 3.98 (d, \(J = 12\) Hz, 1H), 4.23 (d, \(J = 12\) Hz, 1H), 4.87 (dd, \(J = 2.4, 5.4\) Hz, 1H), 5.17 (d, \(J = 2.4\) Hz, 1H), 5.88 (d, \(J = 5.4\) Hz, 1H), 6.59-8.10 (m, 8H). \(^{13}\)C NMR (75 MHz); ppm 20.21, 21.52, 21.98, 23.52, 25.52, 27.62, 31.39, 33.32, 45.02, 49.32, 57.41, 66.39, 68.42, 69.37, 82.19, 100.31, 113.07, 117.35, 121.42, 122.34, 123.37, 125.17, 125.59, 126.31, 127.17, 130.72, 133.49, 138.37, 142.39, 157.59, 192.38. MS (ESI); \(m/z\) 548.3 (M\(^+\)+1). Anal. Calcd for: C\(_{32}\)H\(_{34}\)ClNO\(_5\); C, 70.13; H, 6.25; N, 2.56%. Found; C, 70.22; H, 6.34; N, 2.42%.

3.1.3.3.11: \((1'R,2'S,3'S,8a'R)-3'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo\[3,2-d]]\[1,3]\text{dioxole-5'-yl}]\)-1'-(4-nitrophenyl)-3',5',6',7',8',8a'-hexahydro-1'H-spiro[chroman-3,2'-indolizin]-4-one (182b)

Pale yellow liquid. Yield; 62%. IR (KBr). 1682, 1554, 1349 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 300 MHz); \(\delta\) 1.50 (br s, 10H), 1.61-1.74 (m, 3H), 1.84-1.97 (m, 3H), 2.07-2.14 (m, 1H), 2.26-2.31 (m, 1H), 3.12-3.16 (m, 1H), 3.54 (d, \(J = 3.9\) Hz, 1H), 3.91 (s, 1H), 4.12 (d, \(J = 12.3\) Hz, 1H), 4.29 (d, \(J = 12.3\) Hz, 1H), 4.92 (dd, \(J = 2.4, 5.4\) Hz, 1H), 5.08 (d, \(J = 2.4\) Hz, 1H), 5.91 (d, \(J = 5.4\) Hz, 1H), 6.61-7.98 (m, 8H). \(^{13}\)C NMR (75 MHz); ppm 20.17, 21.97, 22.12, 23.48, 27.42, 28.49, 33.48, 34.41, 45.22, 52.12, 57.83, 66.17, 68.25, 69.81, 82.38, 100.77, 113.92, 116.91, 121.29, 123.37, 124.48, 125.32, 125.69, 127.12, 129.39, 131.42, 133.27,
139.12, 141.27, 144.48, 158.37, 191.23. MS (ESI); m/z 559.4 (M⁺+1). Anal.Calcd for; C₃₂H₃₄N₂O₇; C, 68.80; H, 6.13; N, 5.01%. Found; C, 68.90; H, 6.18; N, 4.91%.

3.1.3.3.12: (1'R,2'S,3'S,8a'R)-3'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-1'-(3-nitrophenyl)-3',5',6 ',7',8',8a'-hexahydro-1'H-spiro[chroman-3,2'-indoline]-4-one(182c)

Pale yellow liquid. Yield; 62%. IR (KBr); 1682 1553, 1349cm⁻¹. ¹H NMR (CDCl₃, 300 MHz); δ 1.47 (br s, 10H), 1.59-1.76 (m, 3H), 1.81-1.95 (m, 3H), 2.11-2.16 (m, 1H), 2.32-2.37 (m, 1H), 2.79-2.85 (m, 1H), 3.24 (d, J = 3.6 Hz, 1H), 3.82 (s, 1H), 4.08 (d, J = 12 Hz, 1H), 4.29 (d, J = 12 Hz, 1H), 4.76 (dd, J = 2.4, 5.4 Hz, 1H), 4.98 (d, J = 2.4 Hz, 1H), 5.89 (d, J = 5.4 Hz, 1H), 6.59-8.01 (m, 8H). ¹³C NMR (75 MHz); ppm 21.11, 22.17, 22.37, 24.41, 26.92, 29.47, 31.32, 32.35, 42.71, 50.17, 56.12, 66.18, 69.39, 70.19, 83.02, 99.83, 103.82, 113.81, 116.72, 121.71, 122.61, 123.42, 123.71, 125.51, 125.92, 128.39, 131.27, 136.62, 146.22, 158.42, 193.07. MS (ESI); m/z 559.4 (M⁺+1). Anal.Calcd for; C₃₂H₃₄N₂O₇; C, 68.80; H, 6.13; N, 5.01%. Found; C, 68.90; H, 6.18; N, 4.91%.
3.1.4. References


CHAPTER-3

Part-2

Synthesis of glycosyl spirooxindoles through 1,3-dipolar cycloaddition reaction

3.2.1. Introduction

Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. Spiro-oxindole ring systems are central skeletons for numerous alkaloids and pharmacologically important compounds. Hence, there has been a renewed interest towards the synthesis of such interesting compounds. Gelsemine, pseudotabersonine, morroniside, (±)formosanine, (±)isoformosanine, (±)mitraphylline, (±)isomitraphylline, (±)rhyynchophylline, (±)isorhynchophylline, vincatine etc. are some of the alkaloids containing the spiro-oxindole ring systems.

The spiropyrrolidinyloxindole ring systems are also found to be present in a number of alkaloids like horsfiline, spirotryprostatin A and B. Of particular interest the spiro[pyrrolidin-3,3'-oxindole] ring system constitutes the core structural element found in a large family of alkaloids and unnatural compounds exhibiting important biological activities as exemplified by those shown in figure 3.1. The significant biological activity and recent synthetic advances of these natural products have encouraged the development of biologically promising analogues that are often more efficacious and selective than the original natural products. The privileged spirooxindole skeletons have high potential as core elements for the development of related compounds leading to medicinal agents. The derivatives of spiro-oxindole rings find wide biological applications as antimicrobial agents (Figure 15).
Figure 15

- Spirotryprostatin A (183)
- Isocorynoxeine (184)
- Alstonidine (185)
- Cytotoxic Spirotryprostatin Analog (186)
- R=2-hydroxyethoxy Schreiber's Lead Compound (187)
- Tryprostatin (188)
- MI-219 (189)
- Strychnoxindole alkaloid (190)
- Horsfiline (191)
- Vincatine (192)
- Cell cycle inhibitor (193)
- Pseudotabersonine (194)
Nyerges et al. have reported the reaction of oxoindolin-3-ylidene 195 with the non-stabilized azomethine ylide 196 (generated by the desilylation method from N-benzyl-N-(methoxymethyl)-N-[(trimethylsilyl)methyl]amine) at room temperature to give spirooxindole derivative 197.

![Chemical Reaction Diagram]

Our group has reported the synthesis of a series of spirooxindolo nitro pyrrolidine 199 and pyrrolizidine 200 by the reaction of azomethine ylide generated from isatin, sarcosine 16/proline 20 with various p-substituted nitrostyrenes 198.

![Chemical Reaction Diagram]
The azomethine ylide generated from isatin 101 and sarcosine 16 has been effectively subjected to cycloaddition with unusual dipolarophiles, arylidene heptanones / octanone 201 and arylidene octahydro / decahydro cycloalka[d] thiazolo[3,2a] pyrimidine-3-ones 203 to give novel spiroheterocycles 202 and 204.\(^7\)

Sebabar et al\(^8\) have reported the asymmetric synthesis of spirotryprostatin 208 in good yield by the cycloaddition reaction of azomethine ylide generated from diphenyl morpholine-2-one 205 and 3-methoxy-3-methyl butanal 206 with various substituted dipolarophiles 207.

Perumal et al\(^9\) reported the 1,3-dipolar cycloaddition of azomethine ylides, generated in situ from the reaction of isatin 101 and phenylglycine 209 with bis arylidine piperidinone 210 to afford dispiropyrrolidine 211 in good yield.
Pardasani *et al*¹⁰ have reported the synthesis of a series of spirooxindolo thiapyrrolizidines 215 and thiazolidine fused pyrrolines 213 by the reaction of the azomethine ylide generated from isatin and thiazolidine-4-carboxylic acid with various substituted alkenes 214 and alkynes 212.

Recently Raghunathan *et al* have utilized the Baylis-Hillman adduct of ninhydrin 216 in the dipolar cycloaddition reaction of azomethine ylide generated by the condensation of sarcosine 16 and proline 20 with isatin 101 to give novel spirooxindolo pyrrolidine 217 and spiro pyrrolizidine 218.¹¹
Hazra et al.\textsuperscript{12} have reported that the spirooxindolo pyrrolidines 220 and pyrrolizidines 221 could be synthesized by the azomethine ylide cycloaddition reaction of isatin 101 and proline 20/sarcosine 16 with andrographolide 219 under microwave irradiation.

1,3 dipolar cycloaddition of Knoevenagel adduct of isatin-malanonitrile 222 with azomethine ylides derived from sarcosine 16/proline 20 gave the corresponding spiropyrrrolidines 224, 225 and spiropyrrolizidines 226, 227 in moderate to good yield.\textsuperscript{13}

Carbohydrates are one of the most important classes of organic compounds in nature. In recent years, much attention has been focused on the synthesis and development of glycosidase inhibitors\textsuperscript{14} because of an increasing awareness of the vital role played by carbohydrates in biological process. A variety of carbohydrate-derived heterocyclic compounds have been synthesized and found to act as potent inhibitor of
various glycosidases. Among these, substituted pyrrolidines have biologically important properties as glycosidase inhibitors.\textsuperscript{15}

1,3-DC reaction of azomethine ylide is a powerful tool for the synthesis of a variety of natural products containing a pyrrolidine structure. Although many investigations have been made to exploit carbohydrate as a template for 1,3-DC reaction involving azide, nitrone, and nitrile oxide, there are only very few reports involving azomethine ylide in the literature and the synthetic utility of azomethine ylide reaction has not been well exploited in carbohydrate chemistry.

Raghunathan et al\textsuperscript{16} reported the 1,3-dipolar cycloaddition (1,3-DC) reaction of unique dipolarophile \textsuperscript{228} (\(\alpha,\beta\)-unsaturated lactone) derived from D-glucose/D-galactose with the azomethine ylide generated in situ from isatin/\(N\)-substituted isatin and secondary amino acids (sarcosine \textsuperscript{16}/proline \textsuperscript{20}) to give the corresponding cycloadduct \textsuperscript{230} / \textsuperscript{229}.

Raghunathan et al\textsuperscript{17} also reported the sugar-derived spirooxindolopyrrolidines \textsuperscript{232} and \textsuperscript{233} by 1,3-dipolar cycloaddition (1,3-DC) reaction of the dipolarophiles \textsuperscript{231a} and \textsuperscript{231b} derived from galactose with azomethine ylide generated \textit{in situ} from isatin \textsuperscript{101} and sarcosin \textsuperscript{16}.
The same group reported the synthesis of ferrocenyl $\beta$-C-glycosydic spiropyrrolidines 235 through 1,3-dipolar cycloaddition reaction of carbohydrate derived C-gluco and manno-pyranoside dipolarophiles 234 with the azomethine ylide generated in situ from isatin 101 and sarcosin 16.\(^{18}\)

The reaction was extended to the synthesis of ferrocenyl $\beta$-C-ribofuranoside spiropyrrolidine 237 by the cycloaddition reaction of ferrocenyl derivative of $\beta$-C-ribofuranoside 236 with isatin 101 and sarcosin 16.
3.2.2. Results and discussion

The foregoing introduction exemplifies clearly the versatility of 1,3-dipolar cycloaddition reaction of azomethine ylide for the construction of biologically interesting spiro-oxindole derivatives. To broaden the scope of 1,3-DC reactions in the construction of complex polycyclic oxindole spiro ring systems and to evaluate the biological applications of the products, we have undertaken a systematic study of 1,3-dipolar cycloaddition of azomethine ylide derived from O-benzyl tethered sugar aldehyde and cyclic/acyclic amino acid with 4-(E)-3-phenacylidene oxindoles.

The required dipolarophiles, 4-(E)-3-phenacylidene oxindoles 240a/b were prepared as per the literature procedures,\(^1\) by the condensation of isatin with various substituted acetophenones 238a/b in refluxing ethanol in the presence of diethylamine. The alcohol 239a/b initially obtained was dehydrated with glacial acetic acid and conc. hydrochloric acid to give phenacylidene oxindoles 240a/b in good yield (Scheme-3.2.1).
3.2.2.1: Synthesis of glycosyl spiro pyrrolidin-3,3’-oxindoles

*O*-Benzyl tethered sugar aldehyde 132 when reacted with sarcosine 16 and 4-(*E*-)3-phenacylidene oxindole 240a/b in refluxing toluene yielded novel glycosyl spiro pyrrolidin-3,3’-oxindoles 242a/b through cycloaddition reaction of azomethine ylide generated from sugar aldehyde and sarcosine with 4-(*E*-)3-phenacylidene oxindole (Scheme-3.2.2).

The TLC analysis showed the formation of only one product. NMR and mass spectral data of the product did not match with the expected structure 241a. The mass spectra of the product revealed a peak at *m/z* 487 instead of the expected *m/z* 595, the difference corresponds to the loss of molecule of benzyl alcohol. This was further confirmed from *^1^H* NMR spectrum, which revealed the absence of signal due to benzylic protons (CH$_2$–Ph). Also, in the furanose moiety only three protons were observed. Based on the above facts, the structure of the compound was assigned to be the alkenyl sugar fused oxindole 242a.
The structure and regiochemistry of the cycloadducts were established by IR, $^1$H, $^{13}$C, DEPT 135, 2D NMR spectra and mass spectrometric studies. For instance, the IR spectrum of the cycloadduct 242a showed characteristic bands at 1682 and 1703 cm$^{-1}$ which correspond to the benzoyl and amide carbonyl groups respectively.

The $^1$H NMR spectrum of 242a (Figure 3.2.1) showed a sharp singlet at $\delta$ 2.43 for $N$-methyl protons. The furanose ring H$_1$ proton resonated as a doublet at $\delta$ 5.23 ($J = 5.4$ Hz) and H$_2$ proton resonated as a doublet of doublet at $\delta$ 4.60 ($J = 5.4$, 2.4 Hz). The H$_3$ proton observed as a doublet at $\delta$ 4.91 ($J = 2.4$ Hz). The H$_4$ proton of the pyrrolidine ring observed as a singlet at $\delta$ 3.46 which clearly showed the regioselectivity of the cycloadduct. If other isomer had formed H$_4$ proton would have shown a doublet instead of a singlet. The H$_5$ proton resonated as a doublet of doublet at $\delta$ 4.48 ($J = 9.6$, 3.9 Hz), which strongly supports the proposed regio-isomer. If the other isomer had formed H$_5$ proton would have shown a doublet instead of a doublet of doublet. The $N$-CH$_2$- protons of the pyrrolidine ring appeared as a doublet of doublet at $\delta$ 4.12 ($J = 9.6$, 3.9 Hz), and a triplet at $\delta$ 2.75 ($J = 9.6$ Hz).

In the $^1$H–$^1$H COSY spectrum of 242a (Figure 3.2.7) the proton at $\delta$ 5.23 (anomeric proton, H-1) showed correlation with the proton at $\delta$ 4.60. Also the proton at $\delta$ 4.60 showed correlation with the proton at $\delta$ 4.91 and with the proton at $\delta$ 5.23. Hence we assigned the signals at $\delta$ 4.60 to H$_2$ and $\delta$ 4.91 to H$_3$. The stereochemistry of the cycloadduct 242a was deduced on the basis of 2D NOESY experiments. There is no NOESY between H$_4$ and H$_5$ of 242a clearly proved trans stereochemistry.

The $^{13}$C NMR spectrum of 242a (Figure 3.2.3) showed a signal at 60.29 ppm for the spiro carbon and the signal at 41.28 ppm shows the presence of $N$-methyl group. The $N$-CH$_2$ carbon of 242a resonated at 55.93 ppm and was confirmed by DEPT 135 spectrum. The furanose ring attached pyrrolidine carbon showed a peak at 72.72 ppm and
the peak at 52.29 ppm correspond to the benzyol attached pyrrolidine ring carbon and were confirmed by DEPT-135 (Figure 3.2.4) & \(^1\text{H}-^{13}\text{C}\) correlation spectrum (Figure 3.2.5). The furanose ring carbons shows signals at 105.45, 100.65, 82.30 and 157.99 ppm respectively which were confirmed by DEPT-135 & \(^1\text{H}-^{13}\text{C}\) correlation spectrum. The peaks at 197.26 and 178.74 ppm correspond to the benzyol and amide carbonyl groups. Moreover, the cycloadduct 242a exhibited a peak at \(m/z\) 487.1 (M\(^+\)+1) in the mass spectrum (Figure 3.2.10). All these spectral features delineate the fact that the cycloaddition proceeded in a highly regioselective manner with elimination affording a single regioisomer. Similar results were observed for other glycosyl spiro pyrrolidin-3,3'-oxindole 242b.

3.2.2.2: Synthesis of glycosyl spiro pyrrolizidin/thiolizidine-3,3'-oxindoles

To widen the scope of the above cycloaddition reaction, we have generated the 1,3-dipole azomethine ylide from proline 20/thiazolidine-4-carboxylic acid 71/pipocolinic acid 39 with the sugar aldehyde and reacted with 4-(E)-3-phenacylidene oxindole 240a/b in refluxing toluene to give glycosyl spiro pyrrolizidin/thiolizidine-3,3'-oxindoles as a single product in each case. The cycloaddition was found to be regioselective in all cases and we obtained a series of sugar substituted oxindoles 243a/b, 244a/b and 245a/b. (Scheme-3.2.3-3.2.5)
The products were characterized on the basis of their elemental analysis as well as $^1$H, $^{13}$C, DEPT-135, 2D NMR and mass spectral analysis. The IR spectrum of 243b displayed the absorption peaks corresponding to the proposed structure. The peak appeared at 1684 cm$^{-1}$ was due to the benzoyl carbonyl carbon and the amide carbonyl showed peak at 1705 cm$^{-1}$.

In the $^1$H NMR spectrum of 243b (Figure 3.2.18) the furanose ring $H_1$ proton resonated as a doublet at $\delta$ 5.19 ($J = 5.4$ Hz) and $H_2$ proton resonated as a doublet of doublet at $\delta$ 4.69 ($J = 5.4$, 2.4 Hz). The $H_3$ proton was observed as a doublet at $\delta$ 5.11 ($J = 2.4$ Hz). The $H_4$ proton of the pyrrolidine ring observed as a singlet at $\delta$ 3.95 which clearly showed the regioselectivity of the cycloadduct. If other isomer had formed $H_4$ proton would have shown a doublet instead of a singlet. The $H_5$ proton of the pyrrolidine ring resonated as a doublet at $\delta$ 4.56 ($J = 8.7$ Hz). The $H_6$ proton of the pyrrolizidine ring resonated as a multiplet in the region $\delta$ 4.10-4.15 and the singlet at $\delta$ 2.24 is due to the
Ph-CH\textsubscript{3} protons. Multiplets in the region δ 1.57-1.66, 1.95-2.05, 2.68-2.75 and 3.01-3.07 were observed for the -CH\textsubscript{2} and N-CH\textsubscript{2} protons of the pyrrolizidine ring. The stereochemistry of the cycloadduct 243b was deduced on the basis of 2D NOESY experiments. There is no NOESY between H\textsubscript{4} and H\textsubscript{5} of 243b which clearly proved trans stereochemistry.

The off resonance decoupled \textsuperscript{13}C NMR spectrum of 243b (Figure 3.2.19) showed a signal at 61.22 ppm for the spiro carbon. The N-CH\textsubscript{2} carbon of 243b resonated at 52.75 ppm and was confirmed by DEPT 135 spectrum (Figure 3.2.20). The furanose ring attached pyrrolizidine carbon showed a peak at 69.92 ppm and the peak at 56.97 ppm correspond to the benzoyl attached pyrrolizidine ring carbon and were further confirmed by DEPT-135 & \textsuperscript{1}H-\textsuperscript{13}C correlation spectrum. The N-CH carbon of pyrrolizidine carbon resonated at 63.73 ppm and was confirmed by DEPT-135 & \textsuperscript{1}H-\textsuperscript{13}C correlation spectrum. The furanose ring carbons shows signal at 103.91, 97.43, 80.13 and 158.18 ppm respectively, which were confirmed by DEPT-135 and \textsuperscript{1}H-\textsuperscript{13}C correlation spectrum. The peaks at 194.37 and 175.12 ppm correspond to the benzoyl and amide carbonyl groups.

In addition, the mass spectrum of the compound 243b (Figure 3.2.21) showed the molecular ion peak at m/z 527.1 (M\textsuperscript{+}+1) and the compound gave satisfactory elemental analysis.

Identical results were obtained with other glycosyl spiro pyrrolizidin/thiolizidine-3,3'-oxindoles. The \textsuperscript{1}H NMR and \textsuperscript{13}C NMR details of the products 243a/b, 244a/b and 245a/b are reported in experimental section.

The reaction was investigated in a series of solvent systems such as acetonitrile, methanol and toluene to find the best reaction conditions. Among the solvents used toluene was found to be the best in terms of better yields and short reaction time (Table-3.2.1).
Table 3.2.1: Cycloaddition reaction of O-benzyl tethered sugar aldehyde and cyclic/acyclic amino acid with 4-(E)-3-phenacylidene oxindoles under different solvent conditions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Toluene</th>
<th>Methanol</th>
<th>Acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time(h)</td>
<td>Yield (%)</td>
<td>Time(h)</td>
</tr>
<tr>
<td>242a</td>
<td>6</td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td>242b</td>
<td>6</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td>243a</td>
<td>6</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>243b</td>
<td>6</td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td>244a</td>
<td>6</td>
<td>61</td>
<td>8</td>
</tr>
<tr>
<td>244b</td>
<td>6</td>
<td>61</td>
<td>8</td>
</tr>
<tr>
<td>245a</td>
<td>6</td>
<td>64</td>
<td>8</td>
</tr>
<tr>
<td>245b</td>
<td>6</td>
<td>60</td>
<td>8</td>
</tr>
</tbody>
</table>
CONCLUSION

To conclude this chapter we have accomplished the synthesis of some novel complex sugar fused spiroisoxazolidinyl heterocycles of biological interest with high stereo and regioselectivity by intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylide generated from O-benzyl tethered sugar aldehyde and cyclic/acyclic amino acid with 4-(E)-3-phenacylidene oxindoles under different solvent conditions.
3.2.3. Experimental

3.2.3.1: General Considerations

IR spectra were recorded on an ABB MB3000 FT-IR instrument. $^1$H NMR spectra were recorded in CDCl$_3$ using TMS as an internal standard on a Bruker 300 spectrometer at 300 MHz. $^{13}$C NMR was recorded on a Bruker 300 spectrometer at 75 MHz. Mass spectra were recorded in Thermo Finnigan (LCQ) Amax 6000 ESI mass spectrometer. Elemental analysis was carried out using Perkin-Elmer CHNS 2400B instrument.

Column chromatography was performed on silica gel (ACME, 100-200 mesh). Routine monitoring of the reactions were made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 0.25 mm thickness and visualized with iodine. The organic extracts of crude products were dried over anhydrous Na$_2$SO$_4$. Solvents were reagent grade and were purified according to standard procedures.

The starting materials namely sarcosin, proline, pipecolinic acid isatin and acetophenone were purchased commercially and used as such.

3.2.3.2: General procedure for synthesis of 4-(E)-3-phenacylidene oxindole (240a-b)

Stage 1: Preparation of 1,3-Dihydro-3-hydroxy-3-(4-phenyl-2-oxoethylidene)-indol-2(1H)-ones (239a/b)

An equimolar mixture of indole 2,3-dione (10 mmol, 1.47 g) and acetophenone (10 mmol, 1.38 g) was refluxed on a water bath for 4-5 h in absolute ethanol (15 ml) containing 3-5 drops of diethylamine. On cooling, yellow coloured crystals separated out which were filtered and recrystallized from methanol to give white needles of 239a/b.
Stage 2. 1,3-Dihydro-3-[2-(4-phenyl)-2-oxoethylidene]indol-2(1H)-one (240a/b)

The alcohol 239a/b (10 mmol, 1.47 g) was refluxed with a mixture of glacial acetic acid (15 ml) and conc. hydrochloric acid (5 ml) on a water bath for 1 h. The reaction mixture was cooled to room temperature. A red colored compound separated out which was filtered and recrystallized from ethanol to give red needles of 240a/b.

3.2.3.3: Preparation of thiazolidine-4-carboxylic acid 71:

To a solution of cysteine hydrochloride (0.05 mol) in ethanol: water mixture (1:1), potassium acetate (0.07 mol) and then (0.14 mol) formaldehyde solution were added. After vigorous stirring (3 hours), a white precipitate was formed. The resulting precipitate of thiazolidine carboxylic acid was filtered, washed with ethanol and was recrystallised from ethanol to give pure product in 65% yield. m.p: 196 °C.

3.2.3.4: General procedure for synthesis of cycloadducts 242a/b, 243a/b, 244a/b and 245a/b

To a solution of O-benzyl tethered sugar aldehyde 132 (1 mmol), sarcosine/ proline/thiazolidine-4-carboxylic acid /pipecolinic acid (1 mmol) and 4-(E)-3-phenacylidene oxindole 240a/b (1 mmol) were added and refluxed in dry toluene for 5-8 h at 110 °C using Dean-Stark apparatus. After the completion of reaction as indicated by TLC, toluene was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane: EtOAc (9:1) as eluent.
3.2.3.4.1: (2'S,3S,4'S)-4'-benzoyl-2'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-1'-methylspiro[indoline-3,3'-pyrrolidin]-2-one (242a)

Pale yellow liquid. Yield; 62%; IR (KBr); 1682, 1703 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz); δ 1.42 (br s, 10H), 2.43 (S, 3H), 2.75 (t, J = 9.6 Hz, 1H), 3.46 (s, 1H), 4.12 (dd, J = 9.6, 3.9 Hz, 1H), 4.48 (dd, J = 9.6, 3.9 Hz, 1H), 4.60 (dd, J = 5.4, 2.4 Hz, 1H), 4.91 (d, J = 2.4 Hz, 1H), 5.23 (d, J = 5.4 Hz, 1H), 6.29 (d, J = 7.8 Hz, 1H), 6.77-7.29 (m, 8H), 7.71 (s, 1H). ¹³C NMR (75 MHz); ppm 23.56, 23.95, 24.86, 37.0, 37.44, 41.26, 52.29, 55.93, 60.29, 72.72, 82.60, 100.56, 105.45, 108.40, 113.01, 121.80, 122.42, 126.64, 127.82, 127.89, 128.11, 128.29, 132.44, 137.17, 140.21, 157.99, 178.74, 197.26. MS (ESI); m/z 487.13 (M⁺+1). Anal.Calcd for; C₂₉H₃₀N₂O₅; C, 78.03; H, 5.73; N, 7.58%. Found; C, 78.12; H, 5.81; N, 7.42%.

3.2.3.4.2: (2'S,3S,4'S)-2'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-1'-methyl-4'-(4-methylbenzoyl)spiro[indoline-3,3'-pyrrolidin]-2-one (242b)

Pale yellow liquid. Yield; 66%. IR (KBr); 1680, 1704 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz); δ 1.42 (br s, 10H), 2.19 (s, 3H), 2.43 (s, 3H), 2.73 (t, J = 9.6 Hz, 1H), 3.46 (s, 1H), 4.09 (dd, J = 9.6, 3.9 Hz, 1H), 4.46 (dd, J = 9.6, 3.9 Hz, 1H), 4.60 (dd, J = 5.4, 2.4 Hz, 1H), 4.91 (d, J = 2.4 Hz, 1H), 5.23 (d, J = 5.4 Hz, 1H), 6.31 (d, J = 7.8 Hz, 1H), 6.74-7.22 (m, 7H), 7.67 (s, 1H). ¹³C NMR (75 MHz); ppm 21.53, 23.57, 23.95, 24.87, 29.68, 37.07, 37.44, 41.32, 51.81, 56.14, 60.44, 72.86, 82.31, 100.60, 105.47, 108.39, 113.03, 121.76, 126.65, 127.59, 127.78, 127.92, 128.05, 128.45, 128.54, 128.77, 134.57, 140.14, 143.27, 157.29, 178.70, 196.64. MS (ESI); m/z 501.20 (M⁺+1). Anal.Calcd for; C₃₀H₃₂N₂O₅; C, 71.98; H, 6.44; N, 5.60%. Found; C, 72.12; H, 6.51; N, 5.42%.
3.2.3.4.3: \((1'S,2'S,3'S,7a'S)-1'-benzoyl-3'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d]\(1,3\)dioxole]-5'-yl)-1',3',5',6',7',7a'-hexahydrospiro[indoline-3,2'-pyrrolizin]-2-one\) (243a)

Pale yellow liquid. Yield: 63%. IR (KBr): 1687, 1702 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 300 MHz); \(\delta\) 1.45 (br s, 10H), 1.49-1.58 (m, 2H), 1.86-1.97 (m, 2H), 2.57-2.64 (m, 1H), 2.94-3.01 (m, 1H), 3.87 (s, 1H), 3.99-4.07 (m, 1H), 4.48 (d \(J = 8.4\) Hz, 1H), 4.70 (dd, \(J = 5.4, 2.4\) Hz, 1H), 5.09 (d, \(J = 2.4\) Hz, 1H), 5.18 (d, \(J = 5.4\) Hz, 1H), 6.32 (d, \(J = 7.5\) Hz, 1H), 6.73-7.29 (m, 8H), 7.81 (s, 1H). \(^{13}\)C NMR (75 MHz); ppm 22.17, 22.54, 24.48, 25.31, 27.86, 33.59, 34.48, 51.69, 56.10, 60.57, 62.38, 68.93, 80.37, 98.42, 103.31, 105.93, 11.24, 118.39, 122.84, 123.31, 124.49, 125.12, 125.72, 125.91, 126.18, 127.13, 127.43, 128.41, 131.51, 135.81, 140.57, 157.38, 176.31, 196.22. MS (ESI); \(m/z\) 513.23 (M\(^{+1}\)). Anal. Calcd for: C\(_{31}\)H\(_{32}\)N\(_2\)O\(_5\); C, 72.64; H, 6.29; N, 5.47%. Found: C, 72.73; H, 6.32; N, 5.35%.

3.2.3.4.4: \((1'S,2'S,3'S,7a'S)-3'-(3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-1'-(4-methylbenzoyl)-1',3',5',6',7',7a'-hexahydrospiro[indoline-3,2'-pyrrolizin]-2-one\) (243b)

Pale yellow liquid. Yield: 62%. IR (KBr): 1684, 1705 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 300 MHz); \(\delta\) 1.46 (br s, 10H), 1.57-1.66 (m, 2H), 1.95-2.05 (m, 2H), 2.24 (s, 3H), 2.68-2.75 (m, 1H), 3.01-3.07 (m, 1H), 3.95 (s, 1H), 4.10-4.15 (m, 1H), 4.56 (d, \(J = 8.7\) Hz, 1H), 4.69 (dd, \(J = 5.4, 2.4\) Hz, 1H), 5.11 (d, \(J = 2.4\) Hz, 1H), 5.19 (d, \(J = 5.4\) Hz, 1H), 6.42 (d, \(J = 7.5\) Hz, 1H), 6.85-7.35 (m, 7H), 7.79 (s, 1H). \(^{13}\)C NMR (75 MHz); ppm 19.41, 21.81, 21.85, 22.76, 24.18, 29.92, 34.90, 35.39, 52.75, 56.97, 61.22, 63.73, 69.92, 80.13, 97.43, 103.91, 106.53, 110.02, 119.78, 123.75, 125.30, 125.75, 125.88. 126.01, 126.12, 126.29, 126.75, 132.63, 137.85, 141.54, 158.18, 175.12, 194.37. MS (ESI); \(m/z\)
527.13 (M$^+$+1). Anal. Calcd for; C$_{32}$H$_{34}$N$_2$O$_5$; C, 72.98; H, 6.51; N, 5.32%. Found; C, 73.12; H, 6.59; N, 5.17%.

3.2.3.4.5: (3S,5'S,7'S,7a'R)-7'-benzoyl-5'-((3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-3',5',7',7a'-tetrahydro-1'H-spiro[indoline-3,6'-pyrrolo[1,2-c]thiazol]-2-one (244a)

Pale yellow liquid. Yield; 61%. IR (KBr); 1689, 1702 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz); $\delta$ 1.42 (br s, 10H), 2.80 (d, $J = 6$ Hz, 2H), 3.41-3.49 (m, 1H), 3.73 (d, $J = 3$ Hz, 1H), 3.79 (d, $J = 3$ Hz, 1H), 3.97 (s, 1H), 4.20 (d, $J = 9$ Hz, 1H), 4.65 (dd, $J = 5.4$, 2.4 Hz, 1H), 5.12 (d, $J = 2.4$ Hz, 1H), 5.29 (d, $J = 5.4$ Hz, 1H), 6.41 (dd, $J = 7.5$ Hz, 1H), 6.79-7.51 (m, 8H), 8.12 (s, 1H). $^{13}$C NMR (75 MHz); ppm 22.17, 22.54, 24.48, 25.31, 27.86, 33.59, 34.48, 51.69, 56.10, 60.57, 62.38, 68.93, 80.37, 98.42, 103.31, 105.93, 11.24, 118.39, 122.84, 123.31, 124.49, 125.12, 125.72, 125.91, 126.18, 127.13, 127.43, 128.41, 131.51, 135.81, 140.57, 157.38, 180.31, 196.22. MS (ESI); $m/z$ 531.14 (M$^+$+1). Anal. Calcd for; C$_{30}$H$_{30}$N$_2$O$_5$S; C, 67.90; H, 5.70; N, 5.28%. Found; C, 67.98; H, 5.81; N, 5.12%.

3.2.3.4.6: (3S,5'S,7'S,7a'R)-5'-((3a',6a'-dihydrospiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-7'-(4-methylbenzoyl)-3',5',7',7a'-tetrahydro-1'H-spiro[indoline-3,6'-pyrrolo[1,2-c]thiazol]-2-one (244b)

Pale yellow liquid. Yield; 61%. IR (KBr); 1686, 1707 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz); $\delta$ 1.42 (br s, 10H), 2.24 (s, 3H), 2.88 (d, $J = 6$ Hz, 2H), 3.33-3.42 (m, 1H), 3.71 (d, $J = 3$ Hz, 1H), 3.77 (d, $J = 3$ Hz, 1H), 3.99 (s, 1H), 4.12 (d, $J = 9.3$ Hz, 1H), 4.66 (dd, $J = 5.4$, 2.4 Hz, 1H), 5.09 (d, $J = 2.4$ Hz, 1H), 5.24 (d, $J = 5.4$ Hz, 1H), 6.39 (d, $J = 7.5$ Hz, 1H), 6.85-7.50 (m, 7H), 8.34 (s, 1H). $^{13}$C NMR (75 MHz); ppm 21.85, 23.94, 24.00, 24.85, 37.01, 37.60, 39.44, 39.04, 59.04, 59.99, 60.88, 67.77, 69.30, 82.08,
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100.02, 106.10, 109.10, 113.22, 121.95, 124.55, 125.54, 126.90, 127.07, 127.92, 128.10, 128.54, 132.99, 133.51, 136.88, 141.62, 159.23, 180.37, 196.92. MS (ESI); m/z 545.21 (M+1). Anal.Calcd for; C$_{31}$H$_{32}$N$_2$O$_5$S; C, 68.36; H, 5.92; N, 5.14%. Found; C, 68.48; H, 5.99; N, 5.02%.

3.2.3.4.7: (1'S,2'S,3'S,8a'S)-1'-benzoyl-3'-((3a',6a'-dihydropiro[cyclohexane-1,2'-furo [3,2-d][1,3]dioxole]-5'-yl)-3',5',6',7',8',8a'-hexahydro-1'H-spiro[indoline-3,2'-indolizin]-2-one (245a)

Pale yellow liquid. Yield; 64%. IR (KBr); 1690, 1706 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz); $\delta$ 1.45 (br s, 10H), 1.64-1.81 (m, 3H), 1.91-2.08 (m, 3H), 2.48-2.53 (m, 1H), 2.87-2.95 (m, 1H), 3.56 (s, 1H), 3.82-3.89 (m, 1H), 4.18 (d, J = 8.4 Hz, 1H), 4.48 (dd, J = 5.4, 2.4 Hz, 1H), 4.94 (d, J = 2.4 Hz, 1H), 5.09 (d, J = 5.4 Hz, 1H), 6.36 (d, J = 7.5 Hz, 1H), 6.61-7.32 (m, 8H), 7.76 (s, 1H). $^{13}$C NMR (75 MHz); ppm 20.02, 21.31, 21.79, 23.18, 24.41, 26.35, 31.07, 32.81, 50.39, 54.17, 60.32, 61.77, 68.85, 81.02, 97.83, 103.17, 106.02, 112.10, 117.79, 119.34, 121.89, 122.39, 122.78, 122.91, 123.52, 125.59, 126.25, 127.07, 127.34, 128.19, 130.94, 134.72, 140.41, 156.92, 177.07, 198.12. MS (ESI); m/z 527.15 (M+1). Anal.Calcd for; C$_{32}$H$_{34}$N$_2$O$_5$S; C, 72.98; H, 6.51; N, 5.32%. Found; C, 73.12; H, 6.59; N, 5.22%.

3.2.3.4.8: (1'S,2'S,3'S,8a'S)-3'-((3a',6a'-dihydropiro[cyclohexane-1,2'-furo[3,2-d][1,3]dioxole]-5'-yl)-1'-(4-methylbenzoyl)-3',5',6',7',8',8a'-hexahydro-1'H-spiro[indoline-3,2'-indolizin]-2-one (245b)

Pale yellow liquid. Yield; 60%. IR (KBr); 1684, 1705 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 300 MHz); $\delta$ 1.40 (br s, 10H), 1.59-1.63 (m, 2H), 1.79-1.87 (m, 2H), 1.94-2.07 (m, 2H), 2.23 (s, 3H), 2.51-2.58 (m, 1H), 2.92-3.03 (m, 1H), 3.76 (s, 1H), 3.93-4.01 (m, 1H), 4.27 (d, J = 8.7 Hz, 1H), 4.53 (dd, J = 5.4, 2.4 Hz, 1H), 5.02 (d, J = 2.4 Hz, 1H), 5.23 (d, J = 5.4 Hz, 1H), 6.32 (d, J =
7.5 Hz, 1H), 6.71-7.40 (m, 7H), 7.72 (s, 1H). $^{13}$C NMR (75 MHz); ppm 20.11, 20.37, 21.54, 22.17, 24.27, 25.09, 28.37, 32.17, 33.21, 51.17, 55.79, 61.18, 63.02, 69.84, 81.83, 98.12, 103.75, 106.54, 113.12, 118.19, 120.37, 121.54, 123.12, 123.41, 123.54, 123.84, 125.74, 126.78, 130.02, 131.82, 140.89, 157.02, 178.09, 197.17. MS (ESI); $m/z$ 541.23 (M$^+$+1). Anal. Calcd for; C$_{33}$H$_{36}$N$_2$O$_5$; C, 73.31; H, 6.71; N, 5.18%. Found; C, 73.42; H, 6.81; N, 5.02%. 
3.2.4. References


