3.1. INTRODUCTION

3.1.1. Spiropyrrolidine-oxindoles

The heteroatom-containing spirocyclic subunits are featured in a number of naturally occurring products as well as biologically, pharmaceutically and medically active molecules. The spiropyrrolidine-oxindole moiety is one of the most important and interesting structural frameworks and is frequently found in many natural products and clinical pharmaceuticals. Spiropyrrolidine-oxindole ring systems were found in a number of alkaloids such as asrhychnophylline, spirottryprostatin B, strychnofoline and alstonidine. Many of the synthetic and naturally occurring spiropyrrolidine-oxindole derivatives exhibit biological activities such as antiviral, potential antileukemic, anticonvulsant agents, local anesthetics and inhibitors of human NK-1 receptor and potent non-peptide inhibitor of p53-MDM2.
3.1.2. Indole

Indole skeleton is present in the structure of many natural products with high structural complexities and biologically active molecules. For this reason, indole and indole derivatives have been used, continuously, in different research areas such as pharmaceuticals, fragrances, agrochemicals, pigments and material science.

One of the most important indole derivatives is an essential amino acid, tryptophan. It is one of the naturally occurring amino acids. This amino acid cannot be synthesized by the organisms but must be in human daily diet. Tryptophan plays an important role as a building block in protein biosynthesis. Tryptophan containing proteins have reducing effect on depression and insomnia related with hormonal fluctuations.

Tryptophan is a biochemical precursor to the family of tryptamines such as serotonin (5-hydroxytryptamine), a key neuro-transmitter in the central nervous system, and melatonin, a hormone that regulates function of smooth muscle in the cardiovascular and gastrointestinal systems.
Beside tryptamines, the auxins (phytohormone) are synthesized from tryptophan in human body. Auxins are essential for plant body development. These are found in nature as indole-3-acetic acid and may also be synthesized as indole-3-butyric acid.  

![Indole-3-acetic acid and Indole-3-butyric acid](image)

The indole structure is also present in the indole-3-carbinol which is an important antitumor agent. Controlled researches on the indole-3-carbinol which have been conducted on using laboratory animals and cultured cells, show that it prevents the binding of aflatoxin to DNA. As a result of this blocking, the carcinogenic effects of aflatoxins decrease. A different research also indicates that indole-3-carbinol is effective in the prevention of breast cancer via eliminating the estrogen receptor sites on the membranes of breast. In addition to these effects, some studies were also carried out on indole-3-carbinol synthesis which showed that it has positive effect on the treatment of skin cancer.

![Indole-3-carbinol](image)

There are many drugs in circulation whose structures contain the indole nucleus, including sumatriptan, a tryptamine derivative used in the treatment of
migraine headaches, indomethacin and ethodolac,\textsuperscript{13} which are used as non-steroidal anti-inflammatory drugs, and pindolol, a $\beta$-adrenoceptor antagonist.\textsuperscript{14}

Most of the indole derivatives obtained naturally, are biologically active. For example, reserpin is a antipsychotic and antihypertensive drug which was isolated from the dried root of rauwolfia serpentina (Indian snakeroot).

However, today it is rarely used because of its various side effects.\textsuperscript{15} Another example is ellipticine, an anti-tumor active compound.\textsuperscript{16} Vincristine is a mitotic
inhibitor and used in cancer chemotherapy.\textsuperscript{17} Moreover, cytotoxic eudistalbin and dihydroflustramine were found to have anti-microbial and anti-parasitic activities which were isolated from marine organisms.\textsuperscript{18}

3.1.3. Importance of 3-cyanoacetyl indole

Simple nitrogen containing heteroaromatic compounds have received much attention over many years. These pharmacophores are of paramount importance with exciting biological properties and also serve as important synthetic building blocks in drug discovery. 3-Cyanoacetyl indole is an excellent precursor for the synthesis of the compounds used in drug discovery through various reactions like cyclizations, syntheses of coumarins and other heterocycles.

3.1.4. Synthesis of various heterocycles using 3-cyanoacetyl indole

Cyanoacetylation of indoles, pyrroles and aromatic amines with the combination of cyanoacetic acid and acetic anhydride at 60-70 °C has been achieved to prepare 3-cyanoacetyl indole.\textsuperscript{19}

\[
\begin{array}{c}
\text{Ac}_2\text{O, NCCH}_2\text{COOH} \\
60-70 ^\circ\text{C, 5 min}
\end{array}
\]

3.1.5. Pyrazole

Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as azoles.\textsuperscript{20} Pyrazole is the name given by “Ludwig knorr” to this class of compounds in 1883. Pyrazole containing natural products exhibit important biological properties and a few
examples are withasomnine, pyrazofurin, formycin A, oxoformycin B, nostocine A and fluviol A.

Although scarcely found in nature, pyrazoles are known not only as potent insecticides, fungicides and monomers for the preparation of electroluminescent and thermo-resistant materials, but also as antitumor, antiviral, antimicrobial, antipsychotic, and antihistaminic agents. Pyrazoles have been the focus of much synthetic effort in the past decades due to their wide range of pharmacological and technological applications.

One example to the pyrazole-based inhibitor is helicobacter pylori dehydroorotate dehydrogenase (DHODase). Helicobacter pylori is a gram-negative microaerophilic bacterium that infects up to 50% of the World population and it resides in the acidic medium of the stomach, utilizing a high urease enzyme activity to provide a locally alkaline environment. It has been implicated in numerous gastrointestinal disorders and is associated with gastric ulcers, gastritis and gastric cancer. Other example is sildenafil that is a selective inhibitor of phosphodiesterase 5 (PDE5) and is the first agent with this mode of action for the treatment of male
erectile dysfunction that is a disease more commonly known as male impotence.\textsuperscript{29} In addition, pyrazolo[1,5] pyridines, pyrazolo [1,5] (iso)-quinolines and pyrazolo [1,5] phenanthridines show some biological activity.\textsuperscript{30} Besides the phosphodiesterase inhibitor ibudilast, a prostacyclin-mediated vasodilator and antiplatelet drug of choice for the treatment of diseases involving blood cells and vascular wall disorders. The other common uses of pyrazole heterocycles include virucides for herpes virus infection or drugs for the treatment of Alzheimer’s and Parkinson’s diseases and dementia.\textsuperscript{31}

\begin{center}
\includegraphics[width=\textwidth]{image.png}
\end{center}

3.1.6. Literature review

Larry E. Overman \textit{et al.}\textsuperscript{32} synthesized 3-acyl-3- alkylindoles by the treatment of 3-(silyloxy)acryloyl-2’(or 3S)-haloanilides with LDA followed by hydrolysis in good yields.

\begin{center}
\includegraphics[width=0.5\textwidth]{image2.png}
\end{center}

Keith Jones \textit{et al.} \textsuperscript{33} synthesized spiropyrrolidinylindoles by the reaction of indole amides with tributylstannane.
Spiropyrrolidinylxindole compounds are synthesized in moderate to excellent yield via a highly diastereoselective Cu(I)-catalysed three-component assembly reaction of an imine, diazo-compound and substituted olefin dipolarophile by Karl A. Scheidt et al.\textsuperscript{34}

A concise and efficient one-pot regio- and stereo- selective synthesis of structurally diverse spirooxindoles was constructed by simply refluxing a mixture of different types of heterocyclic ketene aminals, isatins and ethyl trifluoroacetate using catalytic piperidine reported by Jun Lin et al.\textsuperscript{35}

Ayoob Bazgir et al.\textsuperscript{36} reported the synthesis of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido [2,3-d] pyrimidine]trione derivatives by a three-component condensation reaction of barbituric acids, 1H-pyrazol-5-amines and isatins in aqueous media.
Barbas et al.\textsuperscript{37} have developed a highly rapid and efficient organocatalytic Diels-Alder reaction for the direct construction of carbazole-spirooxindole derivatives containing three or four stereocenters, including one spiro quaternary chiral center.

Ayoob Bazgir et al.\textsuperscript{38} synthesized spiro[diindenopyridine-indoline] triones and spiro[acenaphthylene-diindenopyridine]triones \textit{via} the reaction of 1,3-indandione, aromatic amines and isatins or acenaphthylene-1,2-dione using a ‘Grindstone Chemistry’ method.

Javad Mokhtari et al.\textsuperscript{39} reported the synthesis of spiro[indoline-3,4'-pyridine]-3'-carboxylate derivatives by the reaction of isatin, 1-phenyl-2-(1,1,1-triphenyl-\(\lambda^5\)-phosphanylidene)-1-ethanone, and benzylamine derivatives or aliphatic amines and alkyl acetoacetate (1,3-dicarbonyl compounds) in dry methanol under reflux conditions.
A facile and efficient one-pot three-component procedure for synthesis of novel dispirooxindolecyclo[pyrrolo[1,2-c]thiazole-6,5’-thiazolidine] derivatives without any catalysts under ultrasonic condition has been developed by Daqing Shi et al.\(^{40}\)

Thennarasu et al.\(^{41}\) has synthesized dispiropyrrolidines and dispiropyrrlizidines by intermolecular 1,3-dipolar cycloaddition of azomethine ylides obtained from 1,2-diones like isatin and acenaphthenequinone with acenaphthenone-2-ylidine ketone as a dipolarophile in methanol under reflux conditions.

Raghunathan et al.\(^{42}\) has recently reported the synthesis of naphthyl pyrrolidine/pyrrolizidine-spirooxindoles via azomethine ylides generated in situ from isatin/N-substituted isatin and secondary amino acids (sarcosine/L-proline) reacted with naphthylidene tetralone as a dipolarophile.
Behrouz Notash et al. have reported an efficient, one-pot, three-component procedure for the synthesis of a small library of new chiral spirooxindolopyrrolizidines with high regio-, diastereo- and enantio- selectivity, from the 1,3-dipolar cycloaddition of azomethine ylides and optically active cinnamoyl oxazolidinone.
3.2. RESULTS AND DISCUSSION

3.2.1. Synthesis of sarcosine based spirooxindoles

A broad literature survey revealed that even though there are numerous reports on the synthesis of spiropyrrolidine-oxindole, the construction of a unique spiropyrrolidine-oxindole incorporating both pyrazole and indole moiety, as these are very important in medicinal chemistry, is still limited. As part of our efforts towards the synthesis of these spiropyrrolidine-oxindoles using multicomponent 1, 3-dipolar cycloaddition reactions, herein we report a facile one pot tandem reaction of 1, 3-dipolar cycloaddition to form the spiropyrrolidine-oxindole derivatives. In this context, considering the broad biological activities of some of these oxindoles at the C3 position, we can envision that an efficient synthesis of these scaffolds is particularly promising as well as strongly desired.

![Scheme 3.1: Synthesis of spiropyrrolidine-oxindoles 4a-h](image)

To probe the feasibility of the synthesis of the moiety, preliminary experiments were performed using 1, 3-dipolar cycloaddition of azomethine ylide generated in situ via decarboxylative condensation of isatin (1 mmol), sarcosine (1 mmol) and dipolarophile (1 mmol) in a suitable solvent afforded the spirooxindoles in moderate to higher yields (Scheme 3.1).
3.2.2. Optimization of reaction condition

At the outset of the study, we have tried our best to optimize the reaction conditions by changing various solvents like methanol, toluene, acetonitrile and DMF under reflux condition. When methanol was used as a solvent, it provided maximum yield of 94\% (Table 3.1, entry 4). Among the solvents used, we were pleased to find that the cycloaddition proceeds smoothly in methanol. Theoretical investigations on role of solvents in reaction mechanism of polar cycloadditions so far have been mostly limited to applications of a simple dielectric continuum self consistent reaction field (SCRF) model\textsuperscript{20}. General conclusion is that polar solvents stabilize the zwitterionic intermediate, and thereby altering the mechanism from a concerted process in the gas phase to a stepwise one in solution \textit{via} a stable zwitterionic intermediate.

Table 3.1:
Screening of various solvents for the formation of substituted spirooxindole

<table>
<thead>
<tr>
<th>S.No</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>70</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>ACN</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>Methanol</td>
<td>65</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Ethanol</td>
<td>70</td>
<td>87</td>
</tr>
</tbody>
</table>

3.2.3. Effect of substituents in reactants

We have attempted to react various isatin derivatives with dipolarophile and sarcosine in methanol to test the wider scope of the reaction. Isatin \textbf{1 a-h} (1.0 mmol), dipolarophile \textbf{2} (1.0 mmol) and sarcosine \textbf{3} (1.1 mmol) under reflux condition in methanol for 90 min. (\textbf{Scheme 3.1}). After the reaction was completed (monitored by TLC), the reaction mixture was allowed to cool up to room temperature. Then the
resulting mixture was poured into cold water, filtered off and the resulting crude was recrystallized using ethanol to afford 82-91% pure dispiropyrrrolidine-oxindole derivatives 4a-h as shown in the Table 3.2.

Table 3.2:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isatin</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>H</td>
<td><img src="image1" alt="Image" /></td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Allyl</td>
<td>H</td>
<td><img src="image2" alt="Image" /></td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Benzyl</td>
<td>H</td>
<td><img src="image3" alt="Image" /></td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>n-Butyl</td>
<td>H</td>
<td><img src="image4" alt="Image" /></td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>Methyl</td>
<td>H</td>
<td><img src="image5" alt="Image" /></td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>Propargyl</td>
<td>H</td>
<td><img src="image6" alt="Image" /></td>
<td>84</td>
</tr>
</tbody>
</table>
3.2.4. Proposed reaction mechanism

Initially, the reaction proceeds, as described earlier, through the generation of azomethine ylide via the decarboxylative condensation of isatin 1a-h and sarcosine 3. Subsequently, we propose that when the azomethine ylide approaches towards the dipolarophile, there are two diastereoisomers possible 4a-h and 5a-h.

![Scheme 3.2: Mode of approach of azomethine ylide towards the dipolarophile.](image)

However, only one isomer was detected and the reason may be attributed to the two possible approaches of dipolarophile towards diene as shown in the Scheme 3.2. The reactions were found to be highly regioselective leading to the formation of...
only one product 4 (a-h) and the formation of the other possible regioisomer was not observed. This may be due to the unfavourable dipole–dipole repulsion between the carbonyl groups of azomethine ylide and the dipolarophile (Scheme 3.2).

3.2.5. Characterization of reaction products 4a-h

The structure of formed spirooxindole derivatives by 1, 3-dipolar cycloaddition of azomethine ylide was elucidated with the help of various spectroscopic techniques such as $^1$H NMR, $^{13}$C NMR and mass data as illustrated for compound 4 e. This was also confirmed by ORTEP of single crystal analysis of the isolated isomer.

In the $^1$H NMR (Figure 3.1) of 4e, chemical shifts in the range of 6.56–8.12 ppm confirms aromatic protons. The diastereotopic -CH$_2$ protons adjacent to-NCH appeared as a doublet at 3.69 (1H, d, J=13.5 Hz) and 3.73 (1H, d, J=13.5 Hz). The broad signals in the region at δ 4.20-4.66 ppm for two protons showed the presence of pyrrolidine ring –CH$_2$ group. Moreover, a singlet at δ 8.70 ppm showed the presence of proton attached to the pyrazole ring.

In the $^{13}$C NMR (Figure 3.2), the shift at δ 75.4 ppm corresponds to a spiro carbon and the resonances at δ 177.5 and 181.5 ppm show the presence of two amide carbonyl carbons.

A distinguished peak observed at m/z: 603.24 in the mass spectrum for [M+H]$^+$ ion further confirms the product 4 e (Figure 3.3).

The relative stereochemistry of one of the derivative 9b was determined from X-ray crystallographic analysis$^{20}$ (Figure 3.4), which unambiguously confirms the structure that deduced from spectroscopic data.
Figure 3.1: $^1$H spectrum of compound 4e

Figure 3.2: $^{13}$C spectrum of compound 4e
3.2.6. Synthesis of proline based spirooxindoles 8a-h

Having established the optimal reaction condition, we have then explored the scope and limitations of the reaction using various substituted isatins (1a-h), dipolarophile 2 and amino acids like proline (6) as shown in Scheme 3.3. It is worth
noting that the reaction proceeded cleanly within 3 h and afforded the corresponding spiropyrrolidine-oxindole products in good to excellent yields. The results were summarized in **Table 3.3.**

**Scheme 3.3: Synthesis of spiropyrrolidine-oxindoles 8(a-h).**

**Table 3.3:**

**Synthesis of spirooxindole derivatives 8a-h.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isatin</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>H</td>
<td><img src="1.png" alt="image" /></td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Allyl</td>
<td>H</td>
<td><img src="2.png" alt="image" /></td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Benzyl</td>
<td>H</td>
<td><img src="3.png" alt="image" /></td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>n-butyl</td>
<td>H</td>
<td><img src="4.png" alt="image" /></td>
<td>90</td>
</tr>
</tbody>
</table>
3.2.7. Synthesis of thioproline based spirooxindoles 9a-h

To test the wider scope of the reaction, we have reacted various substituted isatins (1a-h), dipolarophile 2 and aminoacid 7 (thioproline) as shown in Scheme 3.4. The results were summarized in Table 3.4.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Isatin</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>H</td>
<td><img src="9a.png" alt="Image" /></td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Allyl</td>
<td>H</td>
<td><img src="9b.png" alt="Image" /></td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Benzyl</td>
<td>H</td>
<td><img src="9c.png" alt="Image" /></td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>n-Butyl</td>
<td>H</td>
<td><img src="9d.png" alt="Image" /></td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>Methyl</td>
<td>H</td>
<td><img src="9e.png" alt="Image" /></td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>Propargyl</td>
<td>H</td>
<td><img src="9f.png" alt="Image" /></td>
<td>82</td>
</tr>
</tbody>
</table>
The structure of spirooxindole derivatives synthesized was elucidated with the help of various techniques such as $^1$H NMR, $^{13}$C NMR and mass data. The details are given in the experimental section 3.4.2 (4a-h), 3.4.3 (8a-h) and 3.4.3(9a-h). This method offers several advantages such as high yield, simple experimental and isolation procedures making it an efficient route to synthesis of dispiropyrrolidine-bisoxindoles which are important compounds in organic and medicinal chemistry.

3.3. ANTIMICROBIAL ACTIVITIES OF SYNTHESIZED COMPOUNDS

In the course of identifying various novel antimicrobial agents, we are particularly interested in the present work with dispirooxindole-pyrrolidine derivatives, which have been identified as a new class of antimicrobial compounds.

3.3.1. Microbial organisms

The following bacteria and fungi were used for the experiments. Bacteria; *Shigella flexneri* MTCC 1457, *Micrococcus luteus* MTCC 106, *Enterobacter aerogenes* MTCC 111, *Staphylococcus aureus* MTCC 96, *Klebsiella pneumoniae* MTCC 109, *Staphylococcus epidermidis* MTCC 3615, *Proteus vulgaris* MTCC 1771,
Salmonella typhimurium MTCC 1251 and Staphylococcus aureus (MRSA-methicillin resistant).

The reference cultures were obtained from Institute of Microbial Technology (IMTECH), Chandigarh, India-160036; fungi: Malassesia pachydermatis and Candida albicans MTCC 227. All the cultures were obtained from the Department of Microbiology, Christian Medical College, Vellore, Tamil Nadu, India.

3.3.2. Antimicrobial activity

Antimicrobial activities were carried out using disc diffusion method (Murray et al., 1995). Petri plates were prepared with 20 ml of sterile Mueller Hinton agar (MHA) (Hi-media, Mumbai). The test cultures were swabbed on the top of the solidified media and allowed to dry for 10 min and a specific amount of synthesized compound at 1mg/disc was added to each disc separately. The loaded discs were placed on the surface of the medium and left for 30 min at room temperature for compound diffusion. Negative control was prepared using respective solvents. Streptomycin was used as a positive control against bacteria. Ketoconazole was used as positive control for fungi. The plates were incubated for 24 h at 37°C for bacteria and for 48 h at 28°C for fungi. Zones of inhibition were recorded in millimetres and the experiment was repeated twice.

Bacterial inoculums were prepared by growing cells in Mueller Hinton broth (MHB) (HiMedia) for 24 h at 37°C. The filamentous fungi were grown on sabouraud dextrose agar (SDA) slants at 28°C for 10 days and the spores were collected using sterile double distilled water and homogenized. Yeast was grown on sabouraud dextrose broth (SDB) at 28°C for 48 h. In the present study, the antimicrobial activities of synthesized compounds were screened against nine bacteria and two
fungi using *in vitro* disc diffusion method. The results revealed that most of the synthesized compounds exhibited antimicrobial activities (Figure 3.5).

![Figure 3.5: Antimicrobial activity of synthesized compounds using disc diffusion method (Zone of inhibition in mm) (1mg/disc); Control (23)-Streptomycin - Standard antibacterial agent; Ketoconazole - Standard antifungal agent.](image)

3.3.3. Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration studies of the synthesized compounds were performed according to the standard reference methods for bacteria (Duraipandiyan and Ignacimuthu, 2009)\(^5\), for filamentous fungi (CLSI, 2008) and yeasts (NCCLS/CLSI, 2002)\(^6\). The required concentrations (1000, 500, 250, 125, 62.5, 31.25, 15.62 and 7.81µg/mL) of the compound were dissolved in DMSO (2%) and diluted to give serial two-fold dilutions that were added to each medium in 96 well plates. An inoculum of 100 from each well was inoculated. The antifungal agent ketoconazole for fungi and streptomycin for bacteria were included in the assays as positive controls. For fungi, the plates were incubated for 48 to 72 h at 28°C and for bacteria the plates were incubated for 24 h at 37°C. The MIC for fungi was defined as the lowest extract concentration, showing no visible fungal growth after incubation time. 5 µl of tested broth was placed on the sterile MHA plates for bacteria and
incubated at 28°C. The MIC for bacteria was determined as the lowest concentration of the compound inhibiting the visual growth of the test cultures on the agar plate.

![Figure 3.6: The minimum inhibitory concentration values of synthesized compounds. C-Streptomycin - Standard antibacterial agent; Ketoconazole - Standard antifungal agent.]

The MIC values of active compounds against bacteria and fungi are given in Figure 3.6. Significant MIC values were observed against gram positive and gram negative bacteria and fungi.

### 3.3.4. Docking studies

The docking analysis was developed by Auto Dock Tools (ADT) (Sanner, 1999) version 1.5.6 and Autodock version 4.2.5.1 programs; (Auto dock, Autogrid, Copyright-1989-2012) from the Scripps Research Institute [http://www.scripps.edu/mb/olson/doc/autodock](http://www.scripps.edu/mb/olson/doc/autodock). Compound 8a was docked to target protein complex 1KE4 with the protein molecule considered as a rigid body and the ligand being flexible. The search was carried out with the Lamarckian Genetic Algorithm; (Morris et al., 1998) populations of 150 individuals with a mutation rate of 0.02 evolved for 10 generations. Evaluation of the results was done by sorting the different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry, was subsequently performed and the lowest energy conformation of the more populated cluster was considered as the most trustable solution. The output was exported to ADT and Pymol (PyMOL Molecular Graphics System) for visual
inspection of the binding modes and interactions of the compounds with amino acid residues in the active sites.

The docking simulations in the active sites of AmpC beta-lactamase (PDB: 1KE4), was performed by the Auto Dock Tools (ADT) version 1.5.6 and Auto dock version 4.2.5.1 programs. The binding profile of the compound 8a docking with AmpC beta-lactamase showed two hydrogen bonds with ALA79 and GLN250 amino acids which resulted in the lowest free binding energy of -7.19 kcal/mol (Figure 3.7).

Figure 3.7: Docking studies of compound 8a
3.4. EXPERIMENTAL SECTION

3.4.1. Materials and methods

All chemicals were purchased from Sigma Aldrich, U.S.A. All melting points are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-d$_6$ using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz respectively. Mass spectra were recorded using a Thermo Finnigan LCQ Advantage MAX 6000 ESI mass spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer. Analytical TLC was performed on precoated aluminium sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck, Germany).

3.4.2. Experimental procedure for sarcosine based spiropyrrolidine-oxindoles 4a-h.

The ratios of the reactants under the optimized condition were isatin 1 a-h (1.0 mmol), dipolarophile 2 (1.0 mmol) and sarcosine 3 (1.1 mmol) under reflux in methanol for 90 min. (Scheme 3.1) and the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was brought to room temperature and then poured into cold water. The solid formed subsequently filtered off and the resulting crude was recrystallized using ethanol to afford desired product 4 (a-h) in 82-91%.

(3R,3'R,4'R)-3'-(1,3-Diphenyl-1H-pyrazol-4-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-1,2-dihydropyrrolo[3,2'-pyrrolidine]-4'-carbonitrile (4a):

$^1$HNMR (500MHz, DMSO-d$_6$): δ 3.10 (3H, S), 3.64 (1H, d, $J$=13.5 Hz), 3.73 (1H, d, $J$=13.5 Hz), 4.90 (1H, s), 6.64 (1H,d, $J$=7.50 Hz), 6.69 (1H, t, $J$=7.50 Hz), 6.82 (1H, d, $J$=8.0 Hz), 6.90-7.12 (1H, m), 7.17 (1H, t, $J$=7.50 Hz),7.21-7.30 (6H, m), 7.32-7.45
(3H, m), 7.51-7.69 (2H, m), 7.70 (1H, d, J=7.50 Hz), 8.12 (1H, d, J=7.50 Hz), 8.30 (1H, d, J=8.0 Hz), 8.68-8.75 (1H, S), 9.40 (1H, S, NH) and 10.4 (1H, s).

\(^{13}\)C NMR(125MHz, DMSO-\(d_6\)): \(\delta\) 34.3, 42.2, 57.7, 62.0, 75.5, 113.9, 122.0, 122.4, 122.7, 123.0, 123.9, 124.1, 124.7, 125.2, 126.4, 126.9, 127.6, 127.9, 128.1, 128.7, 129.0, 129.2, 129.7, 130.0, 130.6, 132.5, 134.2, 136.1, 139.9, 141.3, 154.5, 177.2 and 181.0.

ESI-MS: Molecular Weight: 588.65; m/z=589.65 [M+H]\(^+\); Anal. calcd for C\(_{37}\)H\(_{28}\)N\(_6\)O\(_2\): C, 75.49; H, 4.79; N, 14.28 and O, 5.44.

(3R,3'R,4'R)-3'-(1,3-Diphenyl-1H-pyrazol-4-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-1-(prop-2-en-1-yl)-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-4'-carbonitrile (4b):

\(^1\)H NMR (500MHz, DMSO-\(d_6\)): \(\delta\) 2.42 (1H, t, J=10.50 Hz), 2.72-2.88(1H, m), 3.10(3H, S), 3.17 (1H, d, J=10.0 Hz) 3.62 (1H, d, J=13.5 Hz), 3.74 (1H, d, J=13.5 Hz), 4.90 (1H, s), 6.62 (1H,d, J=7.50 Hz), 6.65 (1H, t, J=7.50 Hz), 6.83 (1H, d, J=8.0 Hz), 6.94-7.0 (1H, m), 7.11 (1H, t, J=7.50 Hz), 7.19-7.28 (6H, m), 7.30-7.41 (3H, m), 7.44-7.55(2H, m), 7.60 (1H, d, J=7.50 Hz), 8.00 (1H, d, J=7.50 Hz), 8.31 (1H, d, J=8.0 Hz), 8.67-8.72 (1H, s) and 9.98 (1H, s).

\(^{13}\)C NMR(125MHz,DMSO-\(d_6\)): \(\delta\) 33.8, 34.6, 42.0, 42.2, 45.6, 57.4, 62.0, 75.6, 113.0, 122.3, 122.5, 122.8, 123.3, 123.6, 124.0, 124.5, 125.1, 126.1, 126.8, 127.2, 127.9, 128.0, 128.5, 129.3, 129.6, 129.9, 130.1, 131.0, 132.1, 134.0, 136.1, 139.4, 141.6, 154.8, 177.9, and 181.0.
ESI-MS Molecular Weight: 628.25; m/z=629.25 [M+H]^+; Anal. calcd for C_{40}H_{32}N_{6}O_{2}: C, 76.41; H, 5.13; N, 13.37 and O, 5.09

(3R,3'R,4'R)-1-Benzyl-3'-(1,3-diphenyl-1H-pyrazol-4-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-4'-carbonitrile (4c):

\[\text{H NMR (500MHz, DMSO-d_6): } \delta \ 2.93 \ (1H, t, J=8.0 Hz), \ 3.00-3.05 \ (1H, m), \ 3.10 \ (3H, S), \ 3.59 \ (1H, d, J=13.5 Hz), \ 3.69 \ (1H, d, J=13.5 Hz), \ 4.72 \ (1H, s), \ 6.48 \ (1H, d, J=7.50 Hz), \ 6.53 \ (1H, d, J=8.00 Hz), \ 6.60 \ (1H, d, J=7.50 Hz), \ 6.75 \ (2H, t, J=7.50 Hz), \ 6.85 \ (1H, d, J=7.50 Hz), \ 6.89 \ (1H, t, J=7.50 Hz),7.21 \ (2H, t, J=8.0 Hz), \ 7.30 \ (1H, t, J=7.50 Hz), \ 7.37 \ (1H, q, J=7.50 Hz), \ 7.41 \ (2H, t, J=7.50 Hz), \ 7.47 \ (3H, t, J=8.00 Hz), \ 7.52 \ (3H, d, J=7.50 Hz), \ 7.63-7.67 \ (3H, m), \ 7.80-7.84 \ (3H, m) \ and \ 8.9 \ (1H, s).\]

\[\text{C NMR (125MHz, DMSO-d_6): } \delta \ 34.2, \ 42.2, \ 55.4, \ 57.6, \ 62.3, \ 75.6, \ 113.2, \ 122.3, \ 122.5, \ 122.8, \ 123.0, \ 123.9, \ 124.2, \ 124.6, \ 125.0, \ 126.1, \ 126.4, \ 126.7, \ 127.2, \ 127.6, \ 127.8, \ 128.0, \ 128.4, \ 128.8, \ 129.1, \ 129.4, \ 129.7, \ 130.3, \ 131.2, \ 132.5, \ 133.1, \ 135.9, \ 138.2, \ 141.0, \ 154.4, \ 178.2 \ and \ 180.5.\]

ESI-MS: Molecular Weight: 678.27; m/z=679.27 [M+H]^+; Anal. calcd for C_{44}H_{34}N_{6}O_{2}: C, 77.86; H, 5.05; N, 12.38 and O, 4.71.

(3R,3'R,4'R)-1-Butyl-3'-(1,3-diphenyl-1H-pyrazol-4-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-4'-carbonitrile (4d):
\[^{1}\text{HNMR (500MHz, DMSO-\text{d}_6):} \delta \ 1.0 \ (3\text{H, t, } J=7.0 \ \text{Hz}), 1.35 \ (2\text{H, m}), 1.62-1.83 \ (4\text{H, m}), 3.10 \ (3\text{H, S}), 3.67 \ (1\text{H, d, } J=13.5 \ \text{Hz}), 3.75 \ (1\text{H, d, } J=13.5 \ \text{Hz}), 4.90 \ (1\text{H, s}), 6.63 \ (1\text{H, d, } J=7.50 \ \text{Hz}), 6.68 \ (1\text{H, t, } J=7.50 \ \text{Hz}), 6.83 \ (1\text{H, d, } J=8.0 \ \text{Hz}), 6.94-7.1 \ (1\text{H, m}), 7.10 \ (1\text{H, t, } J=7.50 \ \text{Hz}), 7.20-7.29 \ (6\text{H, m}), 7.30-7.41(3\text{H, m}), 7.54-7.65 \ (2\text{H, m}), 7.70 \ (1\text{H, d, } J=7.50 \ \text{Hz}), 8.03 \ (1\text{H, d, } J=7.50 \ \text{Hz}), 8.34 \ (1\text{H, d, } J=8.0 \ \text{Hz}), 8.69-8.72 \ (1\text{H, s}) \text{ and } 10.2 \ (1\text{H, s}).
\]

\[^{13}\text{C NMR(125MHz, DMSO-\text{d}_6): } \delta \ 13.3, 19.20, 27.6, 28.7, 34.8, 42.2, 57.7, 62.0, 75.3, 113.2, 122.3, 122.4, 122.8, 123.4, 123.9, 124.0, 124.6, 125.2, 126.1, 126.7, 127.5, 127.9, 128.1, 128.8, 129.1, 129.4, 129.7, 130.1, 130.8, 132.3, 134.6, 136.2, 139.7, 141.3, 154.4, 177.7 \text{ and } 181.3.\]

ESI-MS: Molecular Weight: 644.27; m/z=645.15 [M+H]^+; Anal. calcd for C_{41}H_{38}N_{10}O_{2}: C, 76.38; H, 5.63; N, 13.03 and O, 4.96

(3R,3'R,4'R)-3'-(1,3-Diphenyl-1H-pyrazol-4-yl)-4'-(1H-indole-3-carbonyl)-1,1'-dimethyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-4'-carbonitrile (4e):

\[^{1}\text{HNMR (500MHz, DMSO-\text{d}_6):} \delta \ 2.07 \ (3\text{H, s}), 3.20 \ (3\text{H, s}), 3.69 \ (1\text{H, d, } J=13.5 \ \text{Hz}), 3.73 \ (1\text{H, d, } J=13.5 \ \text{Hz}), 4.92 \ (1\text{H, s}), 6.61 \ (1\text{H,d, } J=7.50 \ \text{Hz}), 6.65 \ (1\text{H, t, } J=7.50 \ \text{Hz}), 6.80 \ (1\text{H, d, } J=8.0 \ \text{Hz}), 6.95-7.1 \ (1\text{H, m}), 7.15 \ (1\text{H, t, } J=7.50 \ \text{Hz}), 7.20-7.31 \ (6\text{H, m}), 7.32-7.42 \ (3\text{H, m}), 7.57-7.65 \ (2\text{H, m}), 7.73 \ (1\text{H, d, } J=7.50 \ \text{Hz}), 8.06 \ (1\text{H, d, } J=7.50 \ \text{Hz}), 8.37 \ (1\text{H, d, } J=8.0 \ \text{Hz}), 8.70-8.77 \ (1\text{H, s}) \text{ and } 10.4 \ (1\text{H, s}).\]
$^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 27.0, 34.5, 42.0, 57.9, 62.9, 75.4, 113.5, 122.3, 122.6, 122.9, 123.3, 123.9, 124.1, 124.4, 125.3, 126.0, 126.4, 127.6, 127.8, 128.2, 128.5, 129.0, 129.3, 129.5, 130.3, 130.8, 132.5, 134.4, 136.3, 139.9, 141.5, 154.6, 177.5 and 181.5.

ESI-MS: Molecular Weight: 602.68; m/z=603.24 [M+H]$^+$; Anal. calcd for C$_{38}$H$_{36}$N$_6$O$_2$: C, 75.73; H, 5.02; N, 13.94 and O, 5.31.

$(3R,3'R,4'R)$-3'-(1,3-Diphenyl-1H-pyrazol-4-yl)-4'-(1H-indole-3-carbonyl)-1'-methyl-2-oxo-1-(prop-2-yn-1-yl)-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-4'-carbonitrile (4f):

$^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.94 (1H, t, $J$=12.0 Hz), 2.48 (1H, t, $J$=11.0 Hz), 2.84-2.91 (1H, m), 3.61 (1H, d, $J$=13.5 Hz), 3.70 (1H, d, $J$=13.5 Hz), 4.89 (1H, s), 6.58 (1H, d, $J$=7.50 Hz), 6.63 (1H, t, $J$=7.50 Hz), 6.80 (1H, d, $J$=8.0 Hz), 6.85-7.12 (1H, m), 7.18 (1H, t, $J$=7.50 Hz), 7.20-7.29 (6H, m), 7.30-7.41 (3H, m), 7.47-7.65 (2H, m), 7.71 (1H, d, $J$=7.50 Hz), 8.16 (1H, d, $J$=7.50 Hz), 8.37 (1H, d, $J$=8.0 Hz), 8.60-8.72 (1H, s) and 10.1 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 28.70, 30.23, 34.0, 34.3, 42.7, 46.3, 57.1, 62.0, 75.6, 113.0, 122.2, 122.7, 123.0, 123.3, 123.7, 124.2, 124.4, 125.0, 126.1, 126.1, 127.2, 127.6, 128.0, 128.5, 129.1, 129.3, 129.7, 130.4, 130.8, 132.1, 134.0, 136.7, 139.4, 141.7, 154.9, 178.8 and 182.0.

ESI-MS: Molecular Weight: 626.70; m/z=627.44 [M+H]$^+$; Anal. calcd for C$_{46}$H$_{38}$N$_6$O$_2$: C, 76.66; H, 4.82; N, 13.41 and O, 5.11.
(3R,3'R,4'R)-4'-(5-Chloro-1H-indole-3-carbonyl)-3'-(1,3-diphenyl-1H-pyrazol-4-yl)-1'-methyl-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-4'-carbonitrile (4g):

$^1$HNMR (500MHz, DMSO-d$_6$): $\delta$ 3.12 (3H, s), 3.61 (1H, d, $J=13.5$ Hz), 3.72 (1H, d, $J=13.5$ Hz), 4.90(1H, s), 6.65 (1H,d, $J=7.50$ Hz), 6.69 (1H, t, $J=7.50$ Hz), 6.80 (1H, d, $J=8.0$ Hz), 6.93-7.12 (1H, m), 7.15 (1H, t, $J=7.50$ Hz),7.22-7.32 (5H, m), 7.34-7.45 (3H, m), 7.50-7.67 (2H, m), 7.72 (1H, d, $J=7.50$ Hz), 8.22 (1H, d, $J=7.50$ Hz), 8.35 (1H, d, $J=8. 0$ Hz), 8.68-8.75 (1H, S), 9.42 (1H, s) and 10.1 (1H, s).

$^{13}$C NMR(125MHz, DMSO-d$_6$): $\delta$ 34.1, 42.0, 57.5, 62.3, 75.1, 113.4, 122.3, 122.4, 122.7, 123.1, 123.7, 124.4, 124.9, 125.1, 126.8, 127.2, 127.6, 127.8, 128.0, 128.6, 129.3, 129.5, 129.7, 130.1, 130.5, 132.0, 134.7, 136.4, 139.7, 141.3, 154.3, 177.7 and 180.7.

ESI-MS: Molecular Weight: 623.17; m/z=624.17 [M+H]$^+$; Anal. calcd for C$_{37}$H$_{25}$ClN$_6$O$_2$: C, 71.32; H, 4.37; Cl, 5.69; N, 13.49 and O, 5.14.

(3R,3'R,4'R)-3'-(1,3-Diphenyl-1H-pyrazol-4-yl)-1'-methyl-4'-(5-nitro-1H-indole-3-carbonyl)-2-oxo-1,2-dihydrospiro[indole-3,2'-pyrrolidine]-4'-carbonitrile (4h):

$^1$HNMR (500MHz, DMSO-d$_6$): $\delta$ 3.20 (3H, S), 3.67 (1H, d, $J=13.5$ Hz), 3.70 (1H, d, $J=13.5$ Hz), 4.90 (1H, s), 6.55 (1H,d, $J=7.50$ Hz), 6.64 (1H, t, $J=7.50$ Hz), 6.76 (1H, d, $J=8.0$ Hz), 6.93-7.12 (1H, m), 7.13 (1H, t, $J=7.50$ Hz),7.21-7.37 (5H, m), 7.38-7.49 (3H, m), 7.54-7.65 (2H, m), 7.72 (1H, d, $J=7.50$ Hz), 8.22 (1H, d, $J=7.50$ Hz), 8.35 (1H, d, $J=8. 0$ Hz), 8.68-8.73 (1H, S), 9.47 (1H, s, NH) and 9.92 (1H, s).
\(^{13}\)C NMR (125MHz, DMSO-\(d_6\)): \(\delta\) 34.4, 42.7, 57.0, 62.1, 75.3, 113.2, 122.0, 122.4, 122.6, 123.4, 123.7, 124.5, 124.9, 125.0, 126.4, 127.4, 127.6, 127.9, 128.2, 128.6, 129.0, 129.4, 129.7, 130.3, 130.7, 132.2, 134.6, 136.0, 139.5, 141.7, 154.0, 177.5 and 180.4;

ESI-MS: Molecular Weight: 633.65; \(m/z=634.51[M+H]^+\); Anal. calcd for C\(_{37}\)H\(_{27}\)N\(_7\)O\(_4\): C, 70.13; H, 4.29; N, 15.47 and O, 10.10.

3.4.3. Experimental procedure for proline based spiropyrrolidine-oxindoles 8a-h

The ratios of the reactants under the optimized condition was isatin 1 a-h (1.0 mmol), dipolarophile 2 (1.0 mmol) and proline 6 (1.1 mmol) under reflux in methanol for 90 min. (Scheme 3.3) and the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature and then poured into cold water. The solid formed subsequently filtered off and the resulting crude was recrystallized using ethanol to afford 80-92 % (Table 3.3).

\(1'R,2'R,3'R\)-2'-\((1,3\text{-Diphenyl-1H-pyrazol-4-yl})\)-1'-(1H-indole-3-carbonyl)-2-oxo-1,1\',2,2',5,6',7',7'a-octahydropyrrolo[indo-3,3'-pyrrolizine]-1'-carbonitrile (8a):

\(^1\)HNMR (500MHz, DMSO-\(d_6\)): \(\delta\) 1.95-2.07 (1H, m), 2.15-2.27(1H, m), 2.48 (1H, t, \(J=7.5\) Hz), 3.25 (1H, q, \(J=8.0\) Hz), 3.51(1H, qt, \(J=7.5\) Hz), 3.53 (1H, d, \(J=12.0\) Hz), 3.79 (1H, q, \(J=6.5\) Hz), 4.78 (1H, s), 6.50(1H, d, \(J=7.5\) Hz), 6.72 (1H, t, \(J=7.5\) Hz), 6.87 (1H, d, \(J=7.5\) Hz),
Hz), 6.90-7.12 (1H, m), 7.17 (1H, t, J=7.5 Hz), 7.19-7.29 (6H, m), 7.30-7.43 (3H, m), 7.50-7.67 (2H, m), 7.72 (1H, d, J=7.5 Hz), 8.23 (1H, d, J=7.5 Hz), 8.27 (1H, d, J=8.0 Hz), 9.60 (1H, s) and 9.89 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-d$_6$): δ 31.2, 33.0, 41.4, 54.3, 56.7, 62.3, 75.1, 113.9, 122.0, 122.4, 122.9, 123.1, 123.7, 123.9, 124.6, 124.9, 125.5, 126.1, 126.7, 127.7, 128.6, 128.9, 129.2, 129.7, 130.1, 130.5, 130.9, 132.0, 133.7, 135.4, 139.7, 141.6, 154.8, 177.6 and 181.5;

ESI-MS: Molecular Weight: 614.69; m/z=615.56 [M+H]$^+$; Anal. calcd for C$_{39}$H$_{38}$N$_6$O$_2$: C, 76.20; H, 4.92; N, 13.67 and O, 5.21.

$^{1}$R,2$^R$,3R)-2'-[(1,3-Diphenyl-1H-pyrazol-4-yl)-1'-(1H-indole-3-carbonyl)-2-oxo-1-(prop-2-en-1-yl)-1',2,2',5',6',7',7'a-octahydrospiro[indole-3,3'-pyrrolizine]-1'-carbonitrile (8b):

$^{1}$HNMR (500MHz, DMSO-d$_6$): δ 1.95-2.10 (1H, m), 2.15-2.19 (1H, m), 2.41 (1H, t, J=10.50 Hz), 2.86-2.97 (1H, m), 3.59 (1H, d, J=10.0 Hz), 3.90-3.98 (1H, m), 4.20 (1H, d, J=10.0 Hz), 4.40-4.51 (2H, m), 4.61-4.80 (1H, m), 4.87 (1H, d, J=10.0 Hz), 4.94 (1H, S), 5.41-5.55 (1H, m), 6.65 (1H, d, J=7.5 Hz), 6.69 (1H, t, J=7.5 Hz), 6.79 (1H, d, J=7.5 Hz), 6.91-7.11 (1H, m), 7.14 (1H, t, J=7.5 Hz), 7.20-7.33 (6H, m), 7.34-7.44 (3H, m), 7.52-7.69 (2H, m), 7.73 (1H, d, J=7.5 Hz), 8.21 (1H, d, J=7.5 Hz), 8.39 (1H, d, J=8.0 Hz), 8.73-8.79 (1H, s) and 10.2 (1H, s).

$^{13}$C NMR (125MHz, DMSO-d$_6$): δ 31.2, 33.9, 34.7, 42.0, 45.4, 54.0, 56.9, 62.2, 75.7, 113.1, 119.9, 120.0, 122.3, 122.5, 122.8, 123.0, 123.6, 124.1, 124.7, 125.1, 125.9,
126.3, 127.1, 127.9, 128.2, 128.4, 129.1, 129.4, 129.9, 130.5, 130.9, 132.3, 134.1, 136.1, 139.6, 141.2, 154.9, 176.7 and 181.6.

ESI-MS: Molecular Weight: 654.75; m/z=655.63 [M+H]+; Anal. calcd for C_{42}H_{34}N_{6}O_{2}: C, 77.04; H, 5.23; N, 12.84 and O, 4.89.

(1'R,2'R,3R)-1-Benzyl-2'-(1,3-diphenyl-1H-pyrazol-4-yl)-1'-(1H-indole-3-carbonyl)-2-oxo-1,1',2,2',5',6',7',7'a-octahydrospiro[indole-3,3'-pyrrolizine]-1'-carbonitrile (8c):

^{1}H{NMR} (500MHz, DMSO-d_{6}): \delta 90.2-1.4 (1H, m), 2.16-2.18 (1H, m), 2.46 (1H, t, J=10.50 Hz), 2.59-2.78 (1H, m), 2.82 (1H, t, J=8.0 Hz), 3.03-3.05 (1H, m), 3.46 (1H, d, J=10.0 Hz), 3.64 (1H, d, J=7.5 Hz), 6.65 (1H, t, J=7.5 Hz), 6.71 (1H, d, J=7.5 Hz), 6.89-7.19 (1H, m), 7.22 (1H, t, J=7.5 Hz), 7.24-7.30 (6H, m), 7.40-7.47 (3H, m), 7.52-7.67 (2H, m), 7.65 (1H, d, J=7.5 Hz), 8.20 (1H, d, J=7.5 Hz), 8.29 (1H, d, J=8.0 Hz), 8.40-8.81 (1H, s) and 10.5 (1H, s).

^{13}C{NMR}(125MHz, DMSO-d_{6}): \delta 33.5, 34.2, 42.0, 54.4, 55.7, 56.1, 62.6, 75.1, 113.4, 119.7, 122.1, 122.5, 122.7, 123.4, 123.6, 124.4, 124.7, 125.0, 126.0, 126.4, 127.1, 127.4, 127.7, 128.0, 128.4, 128.7, 128.9, 129.0, 129.5, 130.4, 131.3, 132.6, 134.2, 135.4, 136.0, 138.9, 141.1, 154.7, 177.0 and 181.4.

ESI-MS: Molecular Weight: 704.81; m/z=705.66 [M+H]+; Anal. calcd for C_{46}H_{36}N_{6}O_{2}: C, 78.39; H, 5.15; N, 11.92 and O, 4.54.

(1'R,2'R,3R)-1-Butyl-2'-(1,3-diphenyl-1H-pyrazol-4-yl)-1'-(1H-indole-3-carbonyl)-2-oxo-1,1',2,2',5',6',7',7'a-octahydrospiro[indole-3,3'-pyrrolizine]-1'-carbonitrile (8d):
$^1$H NMR (500MHz, DMSO-$d_6$): $\delta$ 1.1 (3H, t, $J=7.0$ Hz), 1.40 (2H, m), 1.62-1.90 (4H, m), 1.96-2.07 (1H, m), 2.15-2.22 (1H, m), 2.55(1H, t, $J=7.5$ Hz), 3.30 (1H, q, $J=8.0$ Hz), 3.47 (1H, qt, $J=7.5$ Hz), 3.70 (1H, d, $J=12.0$ Hz), 3.90 (1H, q, $J=6.5$ Hz), 4.95 (1H, s), 6.60 (1H, d, $J=7.5$ Hz), 6.64 (1H, t, $J=7.5$ Hz), 6.85 (1H, d, $J=7.5$ Hz), 6.96-7.08 (1H, m), 7.14 (1H, t, $J=7.5$ Hz), 7.20-7.34 (6H, m), 7.36-7.45 (3H, m), 7.58-7.65 (2H, m), 7.74 (1H, d, $J=7.5$ Hz), 8.06 (1H, d, $J=7.5$ Hz), 8.38 (1H, d, $J=8.0$ Hz), 8.74-8.76 (1H, s) and 10.4-10.6 (1H, s).

$^{13}$C NMR(125MHz, DMSO-$d_6$): $\delta$ 13.5, 19.22, 27.7, 29.0, 31.2, 34.1, 42.0, 54.5, 56.8, 62.9, 75.4, 113.3, 122.3, 122.6, 122.8, 123.2, 123.5, 123.8, 124.0, 124.4, 125.5, 126.1, 126.4, 127.5, 127.7, 128.5, 129.1, 129.4, 129.6, 130.1, 130.7, 132.4, 134.3, 136.2, 139.8, 141.5, 154.6, 177.5 and 181.6.

ESI-MS: Molecular Weight: 670.80; m/z=671.58 [M+H]$^+$; Anal. calcd for C$_{43}$H$_{38}$N$_6$O$_2$: C, 76.99; H, 5.71; N, 12.53 and O, 4.77.

(1’R,2’R,3R)-2’-(1,3-Diphenyl-1H-pyrazol-4-yl)-1’-(1H-indole-3-carbonyl)-1-methyl-2-oxo-1,1’-2,2’,5’,6’,7’,7’-a-octahydrospiro[indole-3,3’-pyrrolizine]-1’-carbonitrile (8e):

$^1$H NMR (500MHz, DMSO-$d_6$): $\delta$ 1.92-2.09 (1H, m), 2.12 (3H, s), 2.17-2.20 (1H, m), 2.59 (1H, t, $J=7.5$ Hz), 3.20 (1H, q, $J=8.0$ Hz), 3.42 (1H, qt, $J=7.5$ Hz), 3.69 (1H, d, $J=12.0$ Hz), 3.97 (1H, q, $J=6.5$ Hz), 4.87 (1H, s), 6.57 (1H, d, $J=7.5$ Hz), 6.70 (1H, t, $J=7.5$ Hz), 6.82
(1H, d, J=7.5 Hz), 6.91-7.01 (1H, m), 7.10 (1H, t, J=7.5 Hz), 7.17-7.21 (6H, m), 7.32-7.40 (3H, m), 7.51-7.69 (2H, m), 7.70 (1H, d, J=7.5 Hz), 8.16 (1H, d, J=7.5 Hz), 8.32 (1H, d, J=8.0 Hz), 8.71-8.79 (1H, s) and 10.2 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 21.7, 31.0, 33.7, 41.3, 54.0, 56.1, 62.5, 75.6, 113.7, 122.1, 122.4, 122.8, 123.0, 123.3, 123.5, 124.1, 124.7, 125.0, 126.2, 126.9, 127.2, 127.9, 128.9, 129.0, 129.9, 130.0, 130.4, 130.7, 132.1, 134.0, 135.9, 138.1, 141.9, 154.0, 177.2 and 181.0;

ESI-MS: Molecular Weight: 628.72 m/z = 629.54 [M+H]$^+$; Anal. calcd for C$_{40}$H$_{32}$N$_{6}$O$_2$: C, 76.41; H, 5.13; N, 13.37 and O, 5.09.

(1'R,2'R,3R)-2'-(1,3-Diphenyl-1H-pyrazol-4-yl)-1'-(1H-indole-3-carbonyl)-2-oxo-1-(prop-2-yn-1-yl)-1',2',2',5',6',7',7'a-octahydrospiro[indole-3,3'pyrrolizine]-1'-carbonitrile (8f):

$^1$H NMR (500 MHz, DMSO-$d_6$): δ 1.91 (1H, t, J=12.0 Hz), 1.94-2.11 (1H, m), 2.15-2.18 (1H, m), 2.47 (1H, t, J=11.0 Hz), 2.81-2.90 (1H, m), 2.40 (1H, t, J=10.50 Hz), 2.85-2.89 (1H, m), 3.45 (1H, d, J=10.0 Hz), 3.71-3.99 (1H, m), 4.15 (1H, d, J=10.0 Hz), 4.18-4.29 (1H, m, s), 6.53 (1H, d, J=7.5 Hz), 6.66 (1H, t, J=7.5 Hz), 6.71 (1H, d, J=7.5 Hz), 6.86-7.12 (1H, m), 7.13 (1H, t, J=7.5 Hz), 7.20-7.29 (6H, m), 7.31-7.41 (3H, m), 7.58-7.71 (2H, m), 7.71 (1H, d, J=7.5 Hz), 8.29 (1H, d, J=7.5 Hz), 8.36 (1H, d, J=8.0 Hz), 8.39-8.54 (1H, s) and 9.97 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 28.58, 30.10, 31.1, 33.7, 34.5, 411, 53.9, 56.0, 612, 75.5, 113.9, 118.9, 122.1, 122.3, 122.5, 123.1, 123.5, 124.0, 124.7, 125.1, 126.7,
126.9, 127.1, 127.3, 128.6, 128.9, 129.4, 129.7, 130.1, 131.8, 132.2, 133.9, 135.2,
138.5, 141.9, 154.7, 178.6 and 182.7;

ESI-MS: Molecular Weight: 652.25 m/z=653.10 [M+H]^+; Anal. calcd for C_{42}H_{32}N_{6}O_{2}
: C, 77.28; H, 4.94; N, 12.87 and O, 4.90.

(1'R,2'R,3R)-5-Chloro-2'-(1,3-diphenyl-1H-pyrazol-4-yl)-1'-(1H-indole-3-
carbonyl)-2-oxo-1,1',2,2',5',6',7',7'a-octahydrospiro[indole-3,3'-pyrrolizine]-1'-
carbonitrile (8g):

![](image)

$^1$H NMR (500MHz, DMSO-d$_6$): $\delta$ 1.93-2.09 (1H, m),
2.14-2.28 (1H, m), 2.40 (1H, t, $J=7.5$ Hz), 3.27 (1H, q, 
$J=8.0$ Hz), 3.47 (1H, qt, $J=7.5$ Hz), 3.50 (1H, d, 
$J=12.0$ Hz), 3.74 (1H, q, $J=6.5$ Hz), 4.65 (1H, s), 6.58 
(1H, d, $J=7.5$ Hz), 6.70 (1H, t, $J=7.5$ Hz), 6.82 (1H, d, 
$J=7.5$ Hz), 6.92-7.10 (1H, m), 7.13 (1H, t, $J=7.5$ Hz), 7.15-7.27 (6H, m), 7.30-7.47 
(2H, m), 7.54-7.61 (2H, m), 7.70 (1H, d, $J=7.5$ Hz), 8.27(1H, d, $J=7.5$ Hz), 8.34 (1H, 
d, $J=8.0$ Hz), 9.58 (1H, s) and 9.97 (1H, s).

$^{13}$C NMR (125MHz, DMSO-d$_6$): $\delta$ 31.1, 33.9, 41.6, 54.9, 56.0, 62.7, 75.7, 113.7,
122.5, 122.7, 122.9, 123.4, 123.7, 124.0, 124.5, 124.9, 125.3, 126.0, 126.6, 127.9,
128.5, 128.8, 129.4, 129.7, 130.5, 130.7, 131.5, 132.7, 133.8, 135.0, 139.6, 141.3,
154.6, 177.9, 182.1;

ESI-MS: Molecular Weight: 649.13; m/z=650.10; [M+H]^+; Anal. calcd for
C_{39}H_{29}ClN_{6}O_{2} : C, 72.16; H, 4.50; Cl, 5.46; N, 12.95; O, 4.93.

(1'R,2'R,3R)-2'-(1,3-Diphenyl-1H-pyrazol-4-yl)-1'-(5-nitro-1H-indole-3-
carbonyl)-2-oxo-1,1',2,2',5',6',7',7'a-octahydrospiro[indole-3,3'-pyrrolizine]-1'-
carbonitrile (8h):
Chapter 3

\[ \text{H NMR (500MHz, DMSO-d}_8\text{): } \delta 1.98-2.07 (1H, m), 2.10-2.21 (1H, m), 2.35 (1H, t, J=7.5 Hz), 3.20 (1H, q, J=8.0 Hz), 3.42 (1H, t, J=7.5 Hz), 3.52 (1H, d, J=12.0 Hz), 3.71 (1H, q, J=6.5 Hz), 4.69 (1H, s), 6.61 (1H, d, J=7.5 Hz), 6.76 (1H, t, J=7.5 Hz), 6.81 (1H, d, J=7.5 Hz), 6.90-7.15 (1H, m), 7.17 (1H, t, J=7.5 Hz), 7.19-7.25 (6H, m), 7.32-7.45 (2H, m), 7.51-7.59 (2H, m), 7.66 (1H, d, J=7.5 Hz), 8.25 (1H, d, J=7.5 Hz), 8.30 (1H, d, J=8.0 Hz), 9.53 (1H, s) and 9.92 (1H, s).

\[ \text{C NMR (125MHz, DMSO-d}_8\text{): } \delta 31.9, 33.0, 41.3, 54.7, 56.7, 62.1, 75.3, 113.3, 122.1, 122.6, 122.9, 123.1, 123.6, 124.3, 124.8, 124.9, 125.2, 126.1, 126.7, 127.1, 128.3, 128.6, 129.1, 129.6, 130.1, 130.9, 131.2, 132.5, 133.4, 135.2, 139.2, 141.0, 154.1, 177.3 and 182.4.

ESI-MS: Molecular Weight: 659.69; m/z=660.22 [M+H]^+; Anal. calcd for C_{39}H_{29}N_{7}O_{4}: C, 71.01; H, 4.43; N, 14.86 and O, 9.70.

3.4.3. Experimental procedure for thioproline based spiropyrrolidinone-oxindoles 9a-h

The ratios of the reactants under the optimized condition was isatin 1 a-h (1.0 mmol), dipolarophile 2 (1.0 mmol) and thioproline 7 (1.1 mmol) under reflux in ethanol for 90 min. (Scheme 3.4) and the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was allowed to room temperature for a while and then poured into cold water. The solid formed subsequently filtered off and the resulting crude was recrystallized using ethanol to afford 82-93 % (Table 3.4).
(3R,6'R,7'R)-6'-(1,3-Diphenyl-1H-pyrazol-4-yl)-7'-(1H-indole-3-carbonyl)-2-oxo-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9a):

$^1$H NMR (500MHz, DMSO-d$_6$): $\delta$ 2.42 (1H, t, $J=10.50$ Hz), 2.82-2.89 (1H, m), 3.51 (1H, d, $J=10.0$ Hz), 3.87-3.95 (1H, m), 4.10 (1H, d, $J=10.0$ Hz), 4.35-4.51(1H, m S), 6.63 (1H, d, $J=7.5$ Hz), 6.70 (1H, t, $J=7.5$ Hz), 6.79 (1H, d, $J=7.5$ Hz), 6.84-7.15 (1H, m), 7.19 (1H, t, $J=7.5$ Hz), 7.21-7.30 (6H, m), 7.35-7.42 (3H, m), 7.50-7.74 (2H, m), 7.78 (1H, d, $J=7.5$ Hz), 8.12 (1H, d, $J=7.5$ Hz), 8.25 (1H, d, $J=8.0$ Hz), 9.35 (1H, s) and 10.1 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-d$_6$):$\delta$ 34.7, 42.1, 54.4, 56.0, 62.7, 74.9, 113.2, 119.4, 122.1, 122.7, 122.9, 123.0, 123.6, 124.5, 124.7, 125.4, 126.4, 126.9, 127.4, 127.7, 128.0, 128.4, 129.1, 129.9, 130.1, 131.5, 132.7, 134.0, 135.3, 138.6, 141.7, 154.0, 178.7 and 181.1.

ESI-MS: Molecular Weight: 632.73 m/z=634.51 [M+H]$^+$; Anal. calcd for C$_{38}$H$_{28}$N$_6$O$_2$S : C, 72.13; H, 4.46; N, 13.28 and O, 5.06; S, 5.07.

(3R,6'R,7'R)-6'-(1,3-Diphenyl-1H-pyrazol-4-yl)-7'-(1H-indole-3-carbonyl)-2-oxo-1-(prop-2-en-1-yl)-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9b):

$^1$HNMR (500MHz, DMSO-d$_6$): $\delta$ 2.49 (1H, t, $J=10.50$ Hz), 2.84-2.91(1H, m), 3.55 (1H, d, $J=10.0$ Hz), 3.91-3.98 (1H, m), 4.02 (1H, d, $J=10.0$ Hz), 4.42-4.54 (2H, m), 4.74-4.82 (1H, m), 4.89 (1H, d, $J=10.0$ Hz), 4.99 (1H, S), 5.46-5.55 (1H, m), 6.62 (1H, d, $J=7.5$ Hz), 6.67 (1H, t, $J=7.5$ Hz), 6.89 (1H, d, $J=7.5$ Hz), 6.97-7.09 (1H, m), 7.15 (1H, t, $J=7.5$ Hz),
7.21-7.32 (6H, m), 7.34-7.43 (3H, m), 7.58-7.66 (2H, m), 7.75 (1H, d, J=7.5 Hz), 8.08 (1H, d, J=7.5 Hz), 8.36 (1H, d, J=8.0 Hz), 8.71-8.76 (1H, s) and 10.6 (1H, s).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 34.0, 42.2, 45.9, 54.2, 56.3, 62.8, 75.3, 113.3, 119.4, 119.6, 122.3, 122.6, 122.9, 123.4, 123.9, 124.0, 124.3, 125.4, 126.0, 126.5, 127.6, 127.8, 128.2, 128.6, 129.1, 129.3, 129.6, 130.3, 130.9, 132.5, 134.3, 136.2, 139.9, 141.6, 154.7, 177.3 and 181.4.

ESI-MS: Molecular Weight: 672.79 m/z=673.62 [M+H]$^+$; Anal. calcd for C$_{41}$H$_{32}$N$_6$O$_2$S : C, 73.19; H, 4.79; N, 12.49; O, 4.76 and S, 4.77.

(3R,6'R,7'R)-1-Benzyl-6'- (1,3-diphenyl-1H-pyrazol-4-yl)-7'- (1H-indole-3-carbonyl)-2-oxo-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9c):

$^1$HNMR (500MHz, DMSO-$d_6$): $\delta$ 2.47 (1H, t, J=10.50 Hz), 2.61-2.89 (1H, m), 2.87(1H, t, J=8.0 Hz), 3.02-3.05 (1H, m), 3.52 (1H, d, J=10.0 Hz), 3.71 (1H, d, J=7.5 Hz), 6.67 (1H, t, J=7.5 Hz), 6.84 (1H, d, J=7.5 Hz), 6.89-7.18 (1H, m), 7.21 (1H, t, J=7.5 Hz), 7.25-7.33 (6H, m), 7.37-7.43 (3H, m), 7.49-7.67 (2H, m), 7.69 (1H, d, J=7.5 Hz), 8.22 (1H, d, J=7.5 Hz), 8.29 (1H, d, J=8.0 Hz), 8.40-8.78 (1H, s) and 10.1 (1H, s).

$^{13}$C NMR(125MHz, DMSO-$d_6$): $\delta$ 34.0, 42.2, 54.5, 55.7, 56.3, 62.9, 75.4, 113.9, 119.0, 122.2, 122.5, 122.8, 123.4, 123.9, 124.4, 124.9, 125.3, 126.0, 126.5, 127.3, 127.6, 127.9, 128.0, 128.3, 128.5, 128.9, 129.1, 129.7, 130.1, 131.5, 132.9, 134.3, 135.0, 136.6, 138.9, 141.2, 154.9, 177.1 and 181.6.

ESI-MS: Molecular Weight: 722.85 m/z=723.74 [M+H]$^+$; Anal. calcd for C$_{45}$H$_{34}$N$_6$O$_2$S : C, 74.77; H, 4.74; N, 11.63; O, 4.43 and S, 4.44.
(3\text{R,6'\text{R,7'\text{R}}})-1\text{-butyl-6'-(1,3\text{-Diphenyl-1H-pyrazol-4-yl})-7'-(1H\text{-indole-3-carbonyl})-2-oxo-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9d):

$^1$HNMR (500MHz, DMSO-d$_6$): $\delta$ 1.2 (3H, t, $J$=7.0 Hz), 1.31 (2H, m), 1.60-1.88 (4H, m), 2.42 (1H, t, $J$=10.50 Hz), 2.81-2.89 (1H, m), 3.58 (1H, d, $J$=10.0 Hz), 3.77-3.91 (1H, m), 4.10 (1H, d, $J$=10.0 Hz), 4.37-4.57 (1H, m), 6.58 (1H, d, $J$=7.5 Hz), 6.76 (1H, t, $J$=7.5 Hz), 6.81 (1H, d, $J$=7.5 Hz), 6.87-7.14 (1H, m), 7.20 (1H, t, $J$=7.5 Hz), 7.22-7.31 (6H, m), 7.34-7.40 (3H, m), 7.47-7.61 (2H, m), 7.69 (1H, d, $J$=7.5 Hz), 8.10 (1H, d, $J$=7.5 Hz), 8.32 (1H, d, $J$=8.0 Hz), 8.44-8.73 (1H, s) and 10.3 (1H, s).

$^{13}$C NMR(125MHz, DMSO-d$_6$): $\delta$ 13.7, 19.32, 27.0, 28.2, 34.9, 42.7, 54.4, 56.0, 56.2, 75.9, 113.7, 119.1, 122.3, 122.7, 122.9, 123.2, 123.9, 124.4, 124.9, 125.2, 126.0, 126.5, 127.5, 127.4, 128.3, 128.7, 129.1, 129.8, 130.5, 131.0, 132.7, 134.2, 135.0, 138.3, 1415, 154.0, 178.6 and 180.8.

ESI-MS: Molecular Weight: 688.83 m/z=689.58 [M+H]$^+$; Anal. calcd for C$_{42}$H$_{36}$N$_6$O$_2$S : C, 73.23; H, 5.27; N, 12.20; O, 4.65 and S, 4.65.

(3\text{R,6'\text{R,7'\text{R}}})-6'-(1,3\text{-Diphenyl-1H-pyrazol-4-yl})-7'-(1H\text{-indole-3-carbonyl})-1-methyl-2-oxo-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9e):

$^1$HNMR (500MHz, DMSO-d$_6$): $\delta$ 2.10 (3H, S), 2.46 (1H, t, $J$=10.50 Hz), 2.80-2.89 (1H, m), 3.50(1H, d, $J$=10.0 Hz), 3.87-3.96 (1H, m), 4.00(1H, d, $J$=10.0 Hz), 4.39-4.50 (1H, m), 6.61 (1H, d, $J$=7.5 Hz), 6.71 (1H, t, $J$=7.5 Hz), 6.79 (1H, d, $J$=7.5 Hz), 6.87-7.11 (1H, m), 7.17 (1H, t, $J$=7.5 Hz), 7.25-7.30 (6H, m), 7.31-7.42 (3H, m), 7.55-7.70
(2H, m), 7.73 (1H, d, J=7.5 Hz), 8.18 (1H, d, J=7.5 Hz), 8.26 (1H, d, J=8.0 Hz), 8.51-8.62 (1H, s) and 10.1 (1H, s).

$^{13}$C NMR (125MHz, DMSO-$d_6$): δ 27.0, 34.2, 42.0, 54.7, 56.5, 62.2, 75.8, 113.2, 119.5, 122.0, 122.5, 122.9, 123.2, 123.7, 124.1, 124.7, 125.6, 126.1, 126.7, 127.3, 127.6, 128.1, 128.4, 129.0, 129.3, 130.0, 131.2, 132.3, 134.0, 135.1, 138.6, 141.9, 154.2, 178.1 and 180.2.

ESI-MS: Molecular Weight: 646.75 m/z=647.63 [M+H]$^+$; Anal. calcd for C$_{39}$H$_{30}$N$_6$O$_2$S : C, 72.43; H, 4.68; N, 12.99; O, 4.95 and S, 4.96.

(3R,6'R,7'R)-6'-(1,3-Diphenyl-1H-pyrazol-4-yl)-7'-((1H-indole-3-carbonyl)-2-oxo-1-(prop-2-yn-1-yl)-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9f):

$^1$H NMR (500MHz, DMSO-$d_6$): δ 1.92 (1H, t, J=12.0 Hz), 2.49 (1H, t, J=11.0 Hz), 2.84-2.91 (1H, m), 2.44 (1H, t, J=10.50 Hz), 2.82-2.87 (1H, m), 3.47(1H, d, J=10.0 Hz), 3.77-3.96 (1H, m), 4.10 (1H, d, J=10.0 Hz), 4.29-4.34 (1H, m), 6.59 (1H, d, J=7.5 Hz), 6.68 (1H, t, J=7.5 Hz), 6.73 (1H, d, J=7.5 Hz), 6.83-7.09 (1H, m), 7.13 (1H, t, J=7.5 Hz), 7.20-7.29 (6H, m), 7.31-7.41 (3H, m), 7.58-7.71 (2H, m), 7.77 (1H, d, J=7.5 Hz), 8.20 (1H, d, J=7.5 Hz), 8.32 (1H, d, J=8.0 Hz), 8.49-8.59 (1H, s) and 9.95 (1H, s).

$^{13}$C NMR(125MHz, DMSO-$d_6$): δ 28.60, 30.13, 33.9, 34.0, 41.7, 53.5, 56.1, 61.9, 75.4, 113.0, 119.1, 122.0, 122.3, 122.7, 123.0, 123.4, 123.9, 124.9, 125.2, 126.4, 126.9, 127.0, 127.3, 128.3, 128.8, 129.1, 129.7, 130.4, 131.2, 132.0,133.8, 135.8, 138.0, 141.4, 154.9, 178.9 and 182.1.
ESI-MS: Molecular Weight: 670.78 m/z = 671.63 [M+H]+; Anal. calcd for C_{41}H_{38}N_{6}O_{5}S: C, 73.41; H, 4.51; N, 12.53; O, 4.77 and S, 4.78.

(3R,6'R,7'R)-7'-(5-Chloro-1H-indole-3-carbonyl)-6'-(1,3-diphenyl-1H-pyrazol-4-yl)-2-oxo-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9g):

\begin{center}
\includegraphics[width=0.5\textwidth]{structure}
\end{center}

^1\text{HNMR} (500MHz, DMSO-d_6): \( \delta \) 2.41 (1H, t, \( J = 10.50 \) Hz), 2.80-2.89 (1H, m), 3.50 (1H, d, \( J = 10.0 \) Hz), 3.86-3.95 (1H, m), 4.12 (1H, d, \( J = 10.0 \) Hz), 4.34-4.50 (1H, m), 6.65 (1H, d, \( J = 7.5 \) Hz), 6.72 (1H, t, \( J = 7.5 \) Hz), 6.82 (1H, d, \( J = 7.5 \) Hz), 6.84-7.14 (1H, m), 7.22 (1H, t, \( J = 7.5 \) Hz), 7.24-7.33 (6H, m), 7.36-7.42 (2H, m), 7.54-7.78 (2H, m), 7.83 (1H, d, \( J = 7.5 \) Hz), 8.12 (1H, d, \( J = 7.5 \) Hz), 8.24 (1H, d, \( J = 8.0 \) Hz), 9.57 (1H, s) and 10.2 (1H, s).

^1\text{C NMR} (125MHz, DMSO-d_6): \( \delta \) 34.7, 42.1, 54.4, 56.0, 62.7, 74.9, 113.2, 119.4, 122.1, 122.7, 122.9, 123.0, 123.6, 124.5, 124.7, 125.4, 126.4, 126.9, 127.4, 127.7, 128.0, 128.4, 129.1, 129.9, 130.1, 131.5, 132.7, 134.0, 135.3, 138.6, 141.7, 154.0, 178.7 and 181.1.

ESI-MS: Molecular Weight: 667.17 m/z = 668.12 [M+H]+; Anal. calcd for C_{38}H_{27}ClN_{6}O_{5}S: C, 68.41; H, 4.08; Cl, 5.31; N, 12.60; O, 4.80 and S, 4.81.

(3R,6'R,7'R)-6'-(1,3-Diphenyl-1H-pyrazol-4-yl)-7'-(5-nitro-1H-indole-3-carbonyl)-2-oxo-1,2,3',6',7',7'a-hexahydro-2'H-spiro[indole-3,5'-pyrrolo[2,1-b][1,3]thiazole]-7'-carbonitrile (9h):

^1\text{HNMR} (500MHz, DMSO-d_6): \( \delta \) 2.43 (1H, t, \( J = 10.50 \) Hz), 2.80-2.87 (1H, m), 3.43 (1H, d, \( J = 10.0 \) Hz), 3.85-3.90 (1H, m), 4.15(1H, d, \( J = 10.0 \) Hz), 4.30-4.52 (1H, m), 6.61(1H, d, \( J = 7.5 \) Hz), 6.74 (1H, t, \( J = 7.5 \) Hz), 6.85 (1H, d, \( J = 7.5 \) Hz), 6.89-7.19 (1H,
m), 7.22 (1H, t, J=7.5 Hz), 7.26-7.35 (6H, m), 7.38-7.42 (2H, m), 7.52-7.76 (2H, m), 7.80 (1H, d, J=7.5 Hz), 8.14 (1H, d, J=7.5 Hz), 8.29 (1H, d, J=8.0 Hz), 9.50 (1H, s) and 10.0 (1H, s).

$^{13}$C NMR (125MHz, DMSO-d$_6$): $\delta$ 34.5, 42.3, 54.7, 56.7, 62.3, 75.9, 113.7, 118.8, 122.4, 122.8, 122.9, 123.9, 123.9, 124.5, 124.5, 125.0, 126.6, 126.8, 127.2, 127.7, 128.1, 128.4, 129.5, 129.9, 130.6, 131.9, 132.4, 134.3, 135.9, 138.0, 141.5, 154.4, 178.4 and 181.6.

ESI-MS: Molecular Weight: 677.73 m/z = 678.45 [M+H]$^+$; Anal. calcd for C$_{38}$H$_{27}$N$_7$O$_4$S : C, 67.34; H, 4.02; N, 14.47; O, 9.44 and S, 4.73.
3.5. CONCLUSIONS

In conclusion, we have demonstrated an efficient and facile synthesis of an array of dispiropyrrolidine-oxindoles via a three component 1, 3-dipolar cycloaddition reaction. The advantages of this process include using simple starting materials and the reaction proceeds under mild conditions. This opening up useful new synthetic route in medicinal chemistry and synthetic chemistry. The products were isolated by recrystallization without involving tedious process like column chromatography.
3.6. REFERENCES


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