CHAPTER - I
SYNTHESIS AND CHARACTERISATION OF
SPIRO - OXINDOLE ANALOGUES

A. INTRODUCTION

Oxindoles that incorporate a quaternary stereogenic centre at C3 are attractive targets in organic synthesis because of their significant biological activities as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates and clinical pharmaceuticals.\(^1\)

Spirocyclic compounds are systems containing one carbon atom common to two rings and are structurally quite interesting. A spiro-oxindole core is a structural centerpiece found in a number of natural & synthetic compounds exhibits wide range of activities in a variety of disease areas. In general have been identified as anti-microbial, anti-cancer, anti mycobacterial, anti-malarial, anti-HIV ACHE inhibitor, P\(^{53}\) activity modulator anti mycobacterial & MOM2 – P\(_{53}\) interaction inhibitor anti mycobacterial.\(^2\)

They represent an important class of naturally occurring substances characterized by highly pronounced biological properties. The spirooxindole framework\(^3\) represents yet another important structural organization present in a number of bioactive natural products such as coerulescine, horsfiline, welwitindolinone A, spirotryprostatin A, elacomine, alstonisine, etc. spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of \textit{Aspergillus fumigatus}, has been identified as a novel inhibitor of microtubule
assembly and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors.\textsuperscript{4}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{images}
\caption{Examples of spirooxindoles and related compounds.}
\end{figure}

\textbf{B. SEVERAL STRATEGIES FOR THE SYNTHESIS OF SPIROOXINDOLES}

1. Gangaru Bhaskar \textit{et al.},(1984)\textsuperscript{5} reported the synthesis of novel \textit{spirooxindoles} through \textit{1,3-dipolar cycloaddition} of an azomethine ylied generated from isatin and sarcosine or l-proline with the dipolarophile 1,4-naphthoquinone followed by spontaneous dehydrogenation. All derivatives exhibited significant anti bacterial activity.

2. Syam Kumar \textit{et al.},(2001)\textsuperscript{6} described a new approach for the synthesis of \textit{spiro pyrrolidinyl oxindole alkaloids}, i.e. coerulescine and horsfiline via iodide ion induced rearrangement of [(N-aziridino methyl thio) methylene] oxindoles to the respective spiro pyrroline-2-oxindole derivatives and their subsequent \textit{one-pot reductive dethiomethylation-N-methylation}.
3. Grigg et al., (2002)\textsuperscript{7} described the formation of novel spiro-oxindoles by the combination of an intramolecular Heck reaction with a subsequent Ag(I) catalysed imine-azomethine ylide-cycloaddition cascade.

4. Feldman et al., (2004)\textsuperscript{8} described the synthesis of spirocyclic butyrolactone oxindole products by the diastereoselective pummerer based oxidative cyclization of tryptophan derivatives.


6. Nair et al., (2005)\textsuperscript{10} reported the synthesis of spirooxadiazolines from the reaction of \textit{N}-substituted isatins with the zwitterionic intermediate generated from dialkyl azodicarboxylate and triphenylphosphine.

7. Zhu et al., (2007)\textsuperscript{11} carried out a simple and efficient one-pot method for the synthesis of biologically important spiro-oxindoles by the reaction of isatin, activated methylene reagent and 1,3-dicarbonyl compounds in aqueous medium.

8. Shanmugam et al., (2006)\textsuperscript{12} reported a facile, high yield stereoselective synthesis of functionalized diastereomeric \textit{3-spiro cyclopropane – 2 - indolones} from the isomerized bromo derivative of Baylis-Hillman adducts of isatin by reductive cyclization with NaBH\textsubscript{4}.

9. Nair et al., (2006)\textsuperscript{13} reported a stereoselective synthesis of spiroannulated oxindole derivatives, an important structural unit of biologically active natural products, such as the mycotoxin triptoquivaline by \textit{N}-Heterocyclic carbene catalyzed reaction of enols and 1,2-dicarbonyl compounds.
10. Savitha. G et al., (2007)\(^1\) prepared **Spiro dihydrofuran oxindole derivatives** via \([3 + 2]\) oxidative cycloaddition of 1,3-dicarbonyl compounds to 3- (phenyl-2-oxoethylidene) -1- methyloxindole and 3 – benzylidene – 1 - methyloxindole derivatives mediated by **CAN**.

11. Shanthi. G et al., (2007)\(^2\) described a simple and efficient method for the **one-pot three-component synthesis of new spirooxindoles** under conventional and solvent **free microwave irradiation method**.

12. Redkin et al., (2007)\(^3\) synthesized **4,3'-spiro [6 - amino -5 - R - 3-methyl - 2H, 4H - pyrano [2,3 - c] pyrazolo] -2' - oxindoles** via three-component condensation of isatins with 3-methylpyrazol-5-one and respective methylene active nitriles in the presence of **basic catalysts**.

13. Elinson, M.N. et al., (2007)\(^4\) reported an efficient electrochemistry induced catalytic multicomponent transformation of cyclic 1,3-diketones, isatin and malononitrile in alcohols in an undivided cell in the presence of **NaBr** as an electrolyte resulted in the functionalized **5, 6, 7, 8 - tetrahydro - 4H - chromene system**.

14. Gnanamani Shanthi et al., (2010)\(^5\) reported an efficient one-pot three component synthesis of novel pyrazolo phthalazinyl **spiro-oxindoles** using **L-proline** as catalyst.

15. Thelagathoti Haribabu et al., (2010)\(^6\) reported a facile one-pot synthesis of functionalized **spiro-oxindoles** via **vinyllogous aldol reaction** of vinyl malononitriles with isatin derivatives in aqueous media catalysed by **triethyl amine**.

16. Joseph J Badillo et al., (2011)\(^7\) developed a regio and stereoselective **cyclization** between isatins and 5-methoxy oxazoles using catalytic
titanium (IV) chloride to afford spiro [3, 3'- Oxindoleoxazolines] in excellent yield.

17. Oxal A. Miqdad et al., (2011)\(^{21}\) achieved the reaction of hydrozonoyl halides with exocyclic 4- arylidene-2 - methyl imidazolin- 5- one in benzene in the presence of triethylamine and synthesized spiro compounds were evaluated for \textit{in vitro} antimicrobial activity. Most of them exhibited significant antibacterial activity compared with selected standard drug.

18. Zhibin Huang et al., (2012)\(^{22}\) reported the series of novel \textit{dispiro - oxindole} derivatives via one- pot three component \textit{1,3 - dipolar cycloaddition reaction} by the condensation of isatin and \(\alpha\)-amino acid with the dipolarophile 5 - benzylidene - 1, 3 – dimethylpyrimidine - 2, 4, 6 - trione.

19. Chunhui Dai et al., (2012)\(^{23}\) reported a mild and practical synthesis of \textit{spiro - oxindole (1, 3) oxazino derivatives} from N-substituted isatins and 1,3-dicarbonyl compounds with pyridine derivative. The reaction provided good to excellent yields. Further exploration of the molecular diversity of these compounds was demonstrated through \textit{Diel’s Alder reaction}.

20. Li.Huang et al., (2012)\(^{24}\) studied the transformation of 2 - furylcarbinols into \textit{spiro furo - oxindoles} and also the skeletal rearrangement of spiro[furo - oxindoles] & spiro [thieno - Oxindoles]. The products were biologically evaluated and some of them stored promising \textit{cytotoxic activities agents} DU145 and LNCap tumor cell lines.

activity against *A549 Human lung adenocarcinoma* cancer cell lines exhibited very good anticancer activity.

22. Jun He *et al.*, (2013)\textsuperscript{26} reported an efficient synthesis of *novel dispirooxindoles* has been achieved through three-component 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* by the decarboxylative condensation of isatin and an \(\alpha\)-amino acid with the dipolarophile 5-benzylideneimidazolidine-2,4-dione. The improved procedure features mild reaction conditions, high yields, high diastereoselectivities, a one-pot procedure and operational simplicity.

C. DABCO, AS CATALYST IN ORGANIC SYNTHESIS

1,4-Diazabicyclo[2.2.2]octane (DABCO), a cage-like compound, is a small diazabicyclic molecule with weak alkalessence, medium-hindrance. It has been widely used in organic synthesis reactions and can serve as a weak base and ligand.\textsuperscript{27}

1,4-Diazabicyclo[2.2.2]octane (DABCO) has been used in many organic preparations as a good solid catalyst. DABCO has received considerable attention as an inexpensive, eco-friendly, high reactive, easy to handle and non-toxic base catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. In this review, some applications of this catalyst in organic reactions were discussed.

1,4-Diazabicyclo[2.2.2] octane (DABCO)

Few examples are listed below:
1. Silylation of hydroxyl groups

The protection and deprotection of functional groups are indispensable in the synthesis of polyfunctional compounds. The silylation of alcohols and polyols is one of the most commonly used methods for their protection\(^{28}\). Many primary, secondary, tertiary alcohols and phenolic hydroxyl groups were effectively converted to their corresponding trimethylsilyl ethers using hexamethyldisilazane in the presence of catalytic amounts of DABCO-bromine under mild conditions at room temperature with short reaction times in good to excellent yields. In comparison to other procedures reported in literature\(^{29}\), its major advantage is that a very small amount of catalyst is enough to carry the procedure.

2. Acetal migration of 1,2 : 4,5 di-O-isopropylidene D-fructopyranose

The O-isopropylidene group has been extensively used in organic synthesis, especially in the field of carbohydrate chemistry. Acetal migration was observed when 1,2:4,5-di-O-isopropylidene-D-fructose was treated with various acyl chlorides in the presence of DABCO as a catalyst. 2,3:4,5-di-O-isopropylidene-D-fructose derivatives were isolated as the only product in high to quantitative yields. The used method had several advantages including mild conditions, good yields, and use of inexpensive catalyst.\(^{30}\)

3. Protection of carbohydrates

An efficient procedure for the regioselective tritylation of the primary hydroxyl group of aldohexopyranosides and nucleosides using trityl chloride in the presence of DABCO as a catalyst in dichloromethane has been developed.
This method eliminates the need for the use of hazardous solvents such as pyridine and DMF for such reactions.\textsuperscript{31}

4. Protection of amines: Ring opening, reactions of aziridines with amines or thiols

Efficient ring-opening of aziridines with various amines or thiols catalyzed by DABCO afforded the corresponding products in good to excellent yields under mild reaction conditions. 1 mol % of catalyst was also efficient in this reaction. It is noteworthy that this reaction could be run under the air without loss of efficiency.

5. Esterification reaction: Preparation of esters and anhydrides

A manipulatively one-pot and rapid method for the synthesis of aliphatic and aromatic ester and anhydride from acid chloride and alcohol or potassium salt of carboxylic acid under solvent-free conditions is reported. The reaction has been carried out in excellent yield and short reaction time in the presence of DABCO under solvent-free conditions. This methodology is superior from the point of view of yield, short reaction time and the easier work-up in comparison to the reported methods.\textsuperscript{32}

6. DABCO in carbon-carbon coupling: Synthesis of isoxazolines

Isoxazolines appear in numerous medicinally active compounds and natural products of biological significance.\textsuperscript{33} Activated nitrocompounds, in the presence of dipolarophiles using DABCO as an efficient catalyst undergo dehydration to afford directly isoxazoline derivatives. The advantage of this
method is simplicity. Experimental procedure and the reaction conditions are amenable to scale-up.\textsuperscript{34}

7. Synthesis of DABCO catalysed heterocyclic compounds

7.1. Bromination of various organic compounds

Tetrameric DABCO-bromine (TDB) is a powerful brominating agent but shows reasonable selectivity with certain substrates. TDB is a non-hygroscopic solid and is very stable at room temperature. It is not affected by ordinary exposure to light, air or water. It possesses ease of work-up. Stability of the reagent makes it a safe source of active bromine. The selective bromination for activated aromatic compounds and alkenes using TDB is reported. Synthesis of $\alpha$-bromo ketones and nitriles has also been achieved by using this reagent and the results are also reported. All products reported were obtained in good to excellent yields.\textsuperscript{35}

7.2. Synthesis of N-arylphthalimides

Solvent-free reactions between phthalic anhydride and aryl amines, catalyzed by DABCO in short reaction times and high yields were performed. These reactions catalyzed by DABCO, do not require any solvent or solid support, and eliminate the need of stoichiometric amount of base.\textsuperscript{36}

7.3. Synthesis of Naphthopyran derivatives

DABCO has been used as a mild and efficient catalyst for the synthesis of 2-amino-3-cyano naphthopyran derivatives via a one-pot three component reaction of aromatic aldehydes, naphthols, and malononitrile at room temperature.
The short reaction times, easy workup, good to excellent yields, and mild reaction conditions make this domino Knoevenagel–Michael reaction both practical and attractive.\textsuperscript{37}

### 7.4. Synthesis of pyrazoles and pyrazolines

1,3-Dipolar cycloaddition of ethyl diazoacetate with various activated olefins using DABCO as a catalyst under solvent-free conditions at ambient temperature to afford 3,5-disubstituted pyrazolines and pyrazoles in moderate to good yields was reported.\textsuperscript{38}

### 7.5. Synthesis of isoindol-1-yl phosphonate derivatives

$\alpha$-Amino(2-alkynyl phenyl) methyl phosphonates, which was generated from 2-alkynyl benzaldehyde, amine, and diethyl phosphate, reacted with aryl iodide at room temperature in the presence of catalytic amount of DABCO in acetone, leading to the desired isoindol-1-yl phosphonate derivatives in good to excellent yields.\textsuperscript{39}

DABCO can be used as a base catalyst in various organic reactions and we believe that a great number of acid catalyzed organic reactions could be performed by using this catalyst. From the reported results, it can be concluded that DABCO is inexpensive, convenient, easy to handle, non toxic, easily available and efficient catalyst for various organic chemistry transformations. Thus, its use has been growing rapidly.\textsuperscript{40}
D. AIM AND OBJECTIVES

The broad aim of the study was to develop a new, green synthetic route for spiro-oxindole heterocyclic and use of non-toxic catalyst to afford a diverse class of analogues by selective modification in the indole scaffold with better biocidal interest as anti-cancer profile.

The objectives of the study are

- To synthesise ten different analogues of spiro-oxindole using different isatins and vinyl malononitrile in the presence of DABCO as catalyst and to exert shorter reaction time in good yield.
- To determine the physical characteristics like appearance, melting point, Rf value and to calculate molecular weight and % yield after purification of the products by TLC and column chromatography.
- Charcterisation of the products by spectral studies like IR, \(^1\)H NMR, \(^{13}\)C NMR and Mass Spectroscopy.

E. SYNTHESIS OF FUNCTIONALIZED SPIRO - OXINDOLES VIA VINYLLOGOUS ALDOL REACTION OF VINYL MALONONITRILES WITH ISATIN DERIVATIVES

i) Materials required

- Isatin and its derivatives like allyl isatin, propargyl isatin, 5-chloro isatin and isatin –N-ethyl acetate.
- Cyclohexano malononitrile, cyclopentano malononitrile
- Ethanol, ethyl acetate, petroleum ether (solvent)
- DABCO (catalyst)
- FT-IR grade KBr
- DMSO
- CDCl₃

All chemicals were purchased from Sigma Aldrich Chemicals, Germany & S.D. Fine. Chem. Limited.

**ii) Procedure**

An initial study in the synthesis of functionalized spiro-oxindoles (SV1-SV5) was performed by the treatment of vinyl malononitrile (cyclohexano malononitrile (2a) -1.0 mmol), DABCO (5 mol %)⁴¹, in H₂O:EtOH (1:1) (10 ml) at room temperature was added isatin 1a-1e and continued stirring for 30 minutes. After the reaction was complete as indicated by TLC using the solvent system ethyl acetate : petroleum ether (25:75 % v/v), the solvent mixture was evaporated under vacuo. The crude product on chromatographic purification over silica gel (Merck, 100-200 mesh, ethyl acetate: petroleum ether, 3:7 v/v) yielded the desired spiro-oxindole derivatives SV1-SV5 (Scheme-1.1) as single diastereomer. The appearance, melting point and % yield were reported as qualitative assessment of the products. The structure was assigned on the basis of spectroscopic data’s like IR, ¹H NMR, ¹³C NMR and Mass spectroscopy.

With a view to understand the generality of this methodology, the study was then successfully extended this methodology to isatin derivatives 1f-1j and another vinyl malononitrile derivative (cyclopentano malononitrile-2b) to provide representative spiro-oxindole derivatives SV6-SV10 (Scheme-1.2).
Scheme-1.1 & 1.2: Synthesis of spiro-oxindole analogues (SV1-SV10)

Substituted isatin (1a-1e) + Cyclohexano malononitrile (2a) → Spiro-oxindole analogues (SV1-SV5)

Substituted isatin (1f-1j) + Cyclopentano malononitrile (2b) → Spiro-oxindole analogues (SV6-SV10)

Scheme - 1.3: Plausible mechanism for the formation of spiro-oxindoles (SV1-SV10)
iii) Mechanism

The proposed plausible mechanism to account for the formation of spiro-
oxindoles SV1-SV10 (Scheme-3.) involves a facile deprotonation of vinyl
malononitrile to furnish a nucleophile which attacks the isatin to form an aldol
adduct. The aldol adduct on intramolecular cyclization followed by isomerization
resulted in the corresponding spirooxindole in one-pot tandem procedure.

F. RESULTS

Due to the unique pharmacological properties of spiro-oxindole
framework, the development of synthetic methods enabling facile access to this
heterocycle is still desirable. In this regard, a simple, convenient and one-pot
methodology for synthesis of functionalized spiro-oxindoles via vinylogous aldol
reaction of vinyl malononitrile with various isatin derivatives, involving tandem
construction of C–C and C–O bonds was reported. The retrosynthetic strategy for
the synthesis of spiro-oxindole will probably involve vinylogous aldol reaction
followed by cyclization. The product yield was reported in Table.1.1.
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<th>Compound Id</th>
<th>Isatin Id</th>
<th>Vinyl Malononitrile Id</th>
<th>Product Appearance</th>
<th>Mol. Weight</th>
<th>Melting Point °C</th>
<th>Rf Value</th>
<th>% Yield</th>
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<tr>
<td>SV1</td>
<td>1a</td>
<td>2a</td>
<td>Off white solid</td>
<td>293</td>
<td>191-193</td>
<td>0.26</td>
<td>70</td>
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<tr>
<td>SV2</td>
<td>1b</td>
<td>2a</td>
<td>Off white solid</td>
<td>333</td>
<td>196-198</td>
<td>0.53</td>
<td>64</td>
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<tr>
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<td>1c</td>
<td>2a</td>
<td>Off white solid</td>
<td>331</td>
<td>194-196</td>
<td>0.70</td>
<td>66</td>
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<tr>
<td>SV4</td>
<td>1d</td>
<td>2a</td>
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<td>328</td>
<td>190-192</td>
<td>0.1</td>
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<tr>
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<td>2a</td>
<td>Off white solid</td>
<td>379</td>
<td>166-168</td>
<td>0.74</td>
<td>65</td>
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<tr>
<td></td>
<td>1f</td>
<td>2b</td>
<td>Description</td>
<td>Melting Point</td>
<td>Solubility</td>
<td>ESR</td>
<td>F1</td>
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<td>SV6</td>
<td><img src="SV6.png" alt="Image" /></td>
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<td>Off white solid</td>
<td>178-180 °C</td>
<td>0.31</td>
<td>72</td>
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<td>176-178 °C</td>
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<td>81</td>
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<td>0.74</td>
<td>78</td>
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<td><img src="SV9.png" alt="Image" /></td>
<td><img src="2b.png" alt="Image" /></td>
<td>Pale brown solid</td>
<td>180-182 °C</td>
<td>0.13</td>
<td>65</td>
<td></td>
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<tr>
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<td><img src="2b.png" alt="Image" /></td>
<td>Off white solid</td>
<td>172-174 °C</td>
<td>0.79</td>
<td>69</td>
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</tr>
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</table>

**Solubility:** Soluble in ether, ethyl acetate, DMSO and insoluble in hexane.
Fig: 1.1. IR spectrum of 1- Allyl - 3'- amino – 2 - oxo - 6', 7', 8', 8a'-tetrahydrospiro [indoline - 3, 1' - isochromene] - 4' - carbonitrile (SV2) - C_{20}H_{19}N_{3}O_{2}.

Fig: 1.2. 1H NMR spectrum of 1- Allyl - 3'- amino – 2 - oxo - 6', 7', 8', 8a'-tetrahydrospiro [indoline - 3, 1' - isochromene] - 4' - carbonitrile (SV2) - C_{20}H_{19}N_{3}O_{2}.
Fig : 1.3. $^{13}$C NMR spectrum of 1 - Allyl - 3'- amino - 2- oxo - 6', 7', 8', 8a'-tetrahydrosipro [indoline - 3, 1' - isochromene] - 4' - carbonitrile (SV2) - C$_{20}$H$_{19}$N$_3$O$_2$.

Fig : 1.4. Mass spectrum of 1 - Allyl - 3'- amino - 2- oxo - 6', 7', 8', 8a'-tetrahydrosipro [indoline - 3, 1' - isochromene] - 4' - carbonitrile (SV2) - C$_{20}$H$_{19}$N$_3$O$_2$. 
G. DISCUSSION

The synthesis of hitherto unreported title compounds were carried out, as outlined in Schemes 1.1 & 1.2. The plausible mechanism which precede the novel green synthesis of spiro-oxindoles were shown in scheme-1.3. The appearance, molecular weight, melting point and % yield of all the synthesized compounds were shown in Table: 1.1. Spectral data’s in Fig: 1.1 - 1.4 represents that the IR measurements were done as KBr pellet for solid synthesised compounds using Perkin Elmer Spectrum RXI FT-IR. The $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ and CDCl$_3$ using TMS as an internal standard with JEOL ECA - 500 MHz NMR spectrometer. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX 6000 ESI spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on pre-coated aluminium sheets of silica gel G/ UV-254 of 0.2 mm thickness (Merck, Germany).

Thus the reaction of various isatins and other vinyl malononitrile derivative provided spiro-oxindole derivatives SV1 - SV10 in 64 - 81 % yield. In the IR spectrum of compound SV2, the peaks at 3403 and 3311 cm$^{-1}$ are diagnostic of the primary NH$_2$ group. In the $^1$H NMR spectrum, the olefinic proton of the spirofused tetrahydroisochromene ring was observed as a multiplet at $\delta$ 5.48-5.53 ppm and NH$_2$ protons resonated at $\delta$ 7.07 ppm as a sharp singlet (exchangeable with D$_2$O). In the $^{13}$C NMR spectrum, the spiro carbon was observed at $\delta$ 81.3 ppm were observed as common characteristic spectral features of all analogues. The mass spectrum of compound SV2 displayed the molecular ion peak ($M^+$) at $m/z$ 333.
H. SPECTRAL CHARACTERISATION AND
INTERPRETATION OF DATA

1. SV1.

- Molecular formula : C_{17}H_{15}N_{3}O_{2}.
- IUPAC Name : 3'- Amino- 2- oxo- 6', 7', 8', 8a'- tetrahydrospiro [indoline - 3,1'- isochromene]- 4'- carbonitrile.
- IR (KBr) : 3403, 3311, 3242, 3198, 2195, 1706, 1636, 1422, 377,763 cm^{-1}.
- $^1$H NMR (500 MHz, DMSO-d$_6$) : $\delta$ 0.39 (q, 1H, $J = 13.0$ Hz), 1.35-1.47 (m, 2H), 1.53-1.61 (m, 1H), 1.90-1.99 (m, 1H), 2.00-2.07 (m, 1H), 2.74 (d, 1H, $J = 9.9$ Hz), 5.41-5.48 (m, 1H), 6.87 (d, 1H, $J = 7.65$ Hz), 6.97 (t, 1H, $J = 7.65$ Hz), 6.99 (s, 2H), 7.07 (d, 1H, $J = 7.65$ Hz), 7.28 (t, 1H, $J = 7.65$ Hz), 10.86 (s, 1H).
- $^{13}$C NMR (125 MHz, DMSO-d$_6$) : $\delta$ 21.4, 22.8, 24.7, 37.9, 60.8, 82.3, 110.8, 114.2, 118.8, 123.2, 125.5, 125.7, 131.3, 142.9, 162.2, 170.9, 173.0.
- MS m/z = 294 M^+1.

2. SV2.

- Molecular formula : C$_{20}$H$_{19}$N$_{3}$O$_{2}$.
- IUPAC Name : 1- Allyl - 3'- amino-2- oxo- 6', 7', 8', 8a' – tetrahydrospiro [indoline - 3, 1' - isochromene] - 4'- carbonitrile.
- IR (KBr) : 3403, 3311, 3242, 3198, 2195, 1706, 1636, 1422, 1377, 763 cm^{-1}.
- $^1$H NMR (500 MHz, DMSO-d$_6$) : $\delta$ 0.42 (q, 1H, $J = 13.0$ Hz), 1.39-1.51 (m, 2H), 1.59-1.68 (m, 1H), 1.89-2.00 (m, 1H), 2.06-2.16 (m, 1H), 2.86 (d, 1H, $J = 9.9$ Hz), 4.33 (ABq, 2H, $J = 16.8$ Hz), 5.10-5.25 (m, 2H), 5.48-5.53 (m, 1H), 5.80-5.90 (m, 1H), 7.07 (s, 2H), 7.08 (d, 1H, $J = 7.65$ Hz),
7.11 (d, 1H, $J = 7.65$ Hz), 7.16 (d, 1H, $J = 7.65$ Hz), 7.41 (t, 1H, $J = 7.65$ Hz).

- **$^{13}$C NMR (125 MHz, DMSO-d$_6$):** $\delta$ 20.7, 22.2, 24.0, 38.1, 42.3, 60.3, 81.3, 109.7, 113.8, 117.3, 118.1, 123.3, 124.5, 124.6, 124.9, 130.7, 131.1, 142.7, 161.5, 170.6.
- MS m/z = 333 M$^+$.  

3. SV3.

- Molecular formula: C$_{20}$H$_{17}$N$_3$O$_2$.
- IUPAC Name: 3'-Amino-2-oxo-1-(prop-2-ynyl)-6', 7', 8', 8a'-tetrahydrospiro[indoline-3, 1'-isochromene]-4'-carbonitrile.
- IR (KBr): 3383, 3315, 3239, 2198, 1726, 1638, 1426, 1370, 760 cm$^{-1}$.
- **$^1$H NMR (500 MHz, DMSO-d$_6$):** $\delta$ 0.34 (q, 1H, $J = 11.45$ Hz), 1.33-1.44 (m, 2H), 1.50-1.59 (m, 1H), 1.85-1.93 (m, 1H), 2.00-2.11 (m, 1H), 2.82 (d, 1H, $J = 9.9$ Hz), 3.29 (t, 1H, $J = 2.3$ Hz), 4.57 (d, 2H, $J = 2.3$ Hz), 5.42-5.51 (m, 1H), 7.08 (s, 2H), 7.09 - 7.18 (m, 2H), 7.18 (d, 1H, $J = 7.65$ Hz), 7.43 (t, 1H, $J = 7.65$ Hz).
- **$^{13}$C NMR (125 MHz, DMSO-d$_6$):** $\delta$ 21.2, 22.7, 24.6, 29.5, 38.3, 60.9, 75.2, 77.9, 81.9, 110.5, 114.5, 118.7, 124.3, 125.1, 125.3, 125.4, 131.4, 142.3, 162.1, 170.8.
- MS m/z = 332 M$^++1$.  

4. SV4.

- Molecular formula: C$_{17}$H$_{14}$N$_3$O$_2$Cl.
- IUPAC Name: 3'-Amino-5-chloro-2-oxo-6', 7', 8', 8a'-tetrahydrospiro[indoline-3, 1'-isochromene]-4'-carbonitrile.
- IR (KBr): 3403, 3311, 3242, 3198, 2195, 1706 cm$^{-1}$.  

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• $^1$H NMR (500 MHz, DMSO-d$_6$) : $\delta$ 0.39 (q, 1H, $J = 13.0$ Hz), 1.37-1.47 (m, 2H), 1.55-1.63 (m, 1H), 1.89-1.97 (m, 1H), 2.00-2.08 (m, 1H), 2.74 (d, 1H, $J = 9.9$ Hz), 5.44-5.49 (m, 1H), 6.87 (d, 1H, $J = 7.65$ Hz), 7.08 (s, 2H), 7.10 (s, 1H), 7.51 (d, 1H, $J = 7.65$ Hz), 11.06 (s, 1H).

• $^{13}$C NMR (125 MHz, DMSO-d$_6$) : $\delta$ 21.8, 22.7, 24.6, 37.9, 60.8, 81.9, 113.8, 114.6, 114.9, 125.1, 126.3, 127.8, 134.19, 142.3, 149.2, 162.1, 172.5.

• MS m/z = 329 M$^+$$+1$, 331 M$^+$$+3$.

5. SV5.

• Molecular formula : C$_{21}$H$_{21}$N$_3$O$_4$.

• IUPAC Name : Ethyl 2- (3 ' - amino - 4' - cyano - 2 - oxo - 6', 7', 8', 8a' - tetrahydrospiro [indoline - 3, 1' - isochromene] -1 – yl ) acetate.

• IR (KBr) : 3401, 3321, 3226, 2201, 1731,1637,1381,760cm$^{-1}$.

• $^1$H NMR (500 MHz, DMSO-d$_6$) : $\delta$ 0.37 (q, 1H, $J = 13.0$ Hz), 1.16 (t, 3H, $J = 6.85$ Hz), 1.41-1.50 (m, 2H), 1.53-1.61 (m, 1H), 1.84-1.91 (m, 1H), 2.00-2.07 (m, 1H), 2.81 (d, 1H, $J = 10.7$ Hz), 4.11 (q, 2H, $J = 6.85$ Hz), 4.60 (s, 2H), 5.43-5.49 (m, 1H), 7.05 (s, 2H), 7.05-7.12 (m, 2H), 7.13 (d, 1H, $J = 7.65$ Hz), 7.37 (t, 1H, $J = 7.65$ Hz).

• $^{13}$C NMR (125 MHz, DMSO-d$_6$) : $\delta$ 14.5, 21.3, 22.7, 24.7, 38.3, 47.7, 60.9, 61.8, 81.8, 110.0, 114.5, 118.7, 124.1, 124.9, 125.3, 125.5, 131.3, 143.2, 162.1, 167.9, 171.7.

• MS m/z = 380 M$^+$$+1$.

6. SV6.

• Molecular formula : C$_{16}$H$_{13}$N$_3$O$_2$. 
• IUPAC Name: 3- Amino - 2'- oxo-7, 7a - dihydro - 6H - spiro [cyclopenta [c] pyran - 1, 3' - indoline] - 4 - carbonitrile.

• IR (KBr) : 3413, 3323, 3230, 2173, 1725, 1623, 1421, 1093, 755 cm⁻¹.

• ¹H NMR (500 MHz, CDCl₃): δ 0.79-0.83 (m, 1H), 1.85-1.87 (m, 1H), 2.26-2.28 (m, 1H), 2.35-2.38 (m, 1H), 3.35 (t, 1H, J = 8.0 Hz), 5.40-5.51 (m, 1H), 5.81 (s, 2H), 6.89 (d, 1H, J = 7.65 Hz), 6.90 (t, 1H, J = 7.65 Hz), 7.14 (d, 1H, J = 7.65 Hz), 7.24 (t, 1H, J = 7.65 Hz), 10.18 (s, 1H).

• ¹³C NMR (125 MHz, CDCl₃): δ 24.3, 31.4, 46.2, 59.1, 83.2, 110.0, 116.3, 118.2, 122.5, 124.6, 125.5, 129.5, 130.2, 141.8, 162.5, 173.2.

• MS m/z = 280 M⁺+1.

7. SV7.

• Molecular formula: C₁₆H₁₃N₃O₂.

• IUPAC Name: 1'- Allyl - 3 - amino - 2'- oxo -7, 7a- dihydro - 6H- spiro [ cyclopenta [c] pyran - 1, 3'- indoline] - 4 - carbonitrile.

• IR (KBr) : 3411, 3327, 3232, 2945, 2217, 1717, 1607, 1363, 758 cm⁻¹.

• ¹H NMR (500 MHz, DMSO-d₆): δ 0.60-0.68 (m, 1H), 1.73-1.78 (m, 1H), 2.15-2.20 (m, 1H), 2.31-2.37 (m, 1H), 3.21 (t, 1H, J = 7.7 Hz), 4.31 (ABq, 2H, J = 16.8 Hz), 5.07 (d, 1H, J = 16.05 Hz), 5.15 (d, 1H, J = 9.15 Hz), 5.28-5.32 (m, 1H), 5.81-5.89 (m, 1H), 7.06-7.13 (m, 3H), 7.34 (s, 2H), 7.37 (t, 1H, J = 7.65 Hz).

• ¹³C NMR (125 MHz, DMSO-d₆): δ 25.0, 31.8, 42.1, 46.8, 57.8, 82.6, 110.4, 114.5, 117.4, 118.7, 123.9, 124.7, 125.6, 131.4, 131.6, 131.7, 143.3, 163.3, 171.3.

• MS m/z = 320 M⁺+1.
8. SV8.

- Molecular formula : $C_{19}H_{15}N_{3}O_{2}$.
- IUPAC Name : 3 - Amino - 2'- oxo -1- (prop - 2 - ynyl) -7, 7a - dihydro - 6H- spiro [cyclopenta [c] pyran - 1, 3'- indoline]- 4 - carbonitrile.
- IR (KBr) : 3369, 3311, 3247, 2129, 1713, 1609, 1516, 1342, 773 cm$^{-1}$.
- $^1$H NMR (500 MHz, DMSO-d$_6$) : $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 0.32 (q, 1H, $J = 11.42$ Hz), 1.48-1.56 (m, 1H), 1.84-1.91 (m, 1H), 1.98 -2.08 (m, 1H), 2.82 (d, 1H, $J = 9.9$ Hz), 3.29 (t, 1H, $J = 2.3$ Hz), 4.57 (d, 2H, $J = 2.3$ Hz), 5.42-5.51 (m, 1H), 7.08 (s, 2H), 7.09-7.18 (m, 2H), 7.18 (d, 1H, $J = 7.65$ Hz), 7.43 (t, 1H, $J = 7.65$ Hz).
- $^{13}$C NMR (125 MHz, DMSO-d$_6$) : $\delta$ 21.1, 22.6, 29.5, 38.3, 60.9, 75.2, 77.9, 81.9, 110.5, 114.5, 118.7, 124.3, 125.1, 125.3, 125.4, 131.4, 142.3, 162.1, 170.8.
- MS m/z = 318 M$^{+}$+1.


- Molecular formula : $C_{16}H_{12}N_{3}O_{2}Cl$.
- IUPAC Name : 3 - Amino - 5 - chloro- 2' – oxo - 7,7a- dihydro- 6H- spiro [cyclopenta [c] pyran- 1, 3'- indoline] - 4 - carbonitrile.
- IR (KBr) : 3465, 3396, 3202, 3172, 2155, 1706,1683 cm$^{-1}$
- $^1$H NMR (500 MHz, DMSO-d$_6$) : $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 0.38 (q, 1H, $J = 12.8$ Hz), 1.54-1.61 (m, 1H), 1.89-1.96 (m, 1H), 1.98-2.06 (m, 1H), 2.74 (d, 1H, $J = 9.9$ Hz), 5.44-5.49 (m, 1H), 6.87 (d, 1H, $J = 7.65$ Hz), 7.08 (s, 2H), 7.10 (s, 1H), 7.51 (d, 1H, $J = 7.65$ Hz), 11.06 (s, 1H).
- $^{13}$C NMR (125 MHz, DMSO-d$_6$) : $\delta$ 21.7, 22.6, 37.9, 60.8, 81.9, 113.8, 114.6, 114.9, 125.1, 126.3, 127.8, 134.19, 142.3, 149.2, 162.1, 172.5.
• MS m/z = 315 M²⁺1.

10. SV10.

• Molecular formula : C₂₀H₁₉N₃O₄.
• IUPAC Name : Ethyl 2 - (3 – amino - 4 – cyano -2'- oxo -7,7a – dihydro - 6H- spiro [cyclopenta [c] pyran - 1, 3' - indoline] -1'- yl) acetate.
• IR (KBr) : 3364, 3313, 3227, 2195, 1724, 1640, 1575, 1425, 1190,761 cm⁻¹.
• ¹H NMR (500 MHz, DMSO-d₆) : δ 0.60-0.69 (m, 1H), 1.16 (t, 3H, J = 6.9 Hz), 1.70-1.75 (m, 1H), 2.10-2.15 (m, 1H), 2.26-2.33 (m, 1H), 3.20 (t, 1H, J = 7.7 Hz), 4.10 (q, 2H, J = 6.9 Hz), 4.60 (s, 2H), 5.23-5.25 (m, 1H), 7.05-7.10 (m, 3H), 7.35 (s, 2H), 7.38 (d, 1H, J = 7.65 Hz).
• ¹³C NMR (125 MHz, DMSO-d₆) : δ 14.5, 25.0, 31.7, 41.7, 47.1, 57.8, 61.8, 82.5, 110.0, 114.6, 118.7, 124.1, 124.5, 125.6, 131.4, 131.6, 143.3, 163.3, 167.8, 171.8.
• MS m/z = 366 M²⁺1.

I. CONCLUSION

A novel, one-pot green method was developed for the synthesis of functionalized spiro-oxindoles in a sequential tandem procedure by using vinyl malononitriles as vinylogous nucleophiles in aldol reaction on isatin. A systematic variation of the substituents at the possible N⁴th, 5th in tetrahydrospiro[indoline-3,1'-isochromene] and spiro[cyclopenta[c]pyran-1,3'-indoline scaffolds led to a wide variety of structural analogues. It also facilitated in reducing the usage of organic solvents and the reaction time. Use of non-toxic eco-friendly catalyst and easy separation in good to excellent yield was an added advantage of this method. The IR, ¹H NMR, ¹³C NMR, and MS data confirmed the proposed structure of the synthesized compounds.
J. REFERENCES


