CHAPTER-IV

Water mediated synthesis of spiro chromene derivatives

4.1. Introduction

Structurally strained one sp\(^3\) carbon atom shared by two rings might be the reason for the pronounced biological activities of spiro compounds.\(^1\) The indole moiety is probably a most well-known heterocycle, which remains a common and important feature of a variety of natural products and medicinal agents.\(^2\) In addition to the presence in a natural biologically active compounds,\(^3\) some indolines spiro-annulated with heterocycles in the 3-position, have shown high biological activity.\(^4\) The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.\(^5\) For example, pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors and strychnophylline (Fig. 4.1).\(^6\) The distinct structural arrangement and the noticeable pharmacological activity displayed by the spirooxindole compounds have made them attractive synthetic targets.\(^7\)

![Diagram of strychnophylline, Pteropodine, and Isopteropodine](image)

*Fig. 4.1 Examples of naturally occurring spiro alkaloids*
Isatin and its derivatives also have interesting biological properties and are widely used as precursors for many natural products.\textsuperscript{8-12} On the basis of biological studies, the existence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal activity remarkably.\textsuperscript{13-15} Chromenes are an important group of compounds; they widely exist in plants, including edible vegetables and fruits.\textsuperscript{16} Synthetic analogues of chromene were developed over the years, some of them displaying remarkable effects as pharmaceuticals,\textsuperscript{17} including antifungal\textsuperscript{18} and antimicrobial activity.\textsuperscript{19} Among the heterocyclic spirooxindole ring systems, functionally substituted chromenes have received considerable attention due to their wide range of useful biological properties, which include spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities\textsuperscript{20} and its potential application in the treatment of human neurodegenerative disorders.\textsuperscript{21}

As presented in the Chapter - I, the need to reduce the amount of toxic waste and by-products arising from chemical process requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. The search for alternative reaction media to replace volatile, flammable, and often toxic solvents commonly employed in organic synthesis is also a priority area for the development of green chemical processes. From both environmental and economic points of view, water has emerged as the medium of choice to perform organic reactions, as it is the most environmentally acceptable, safest, and most abundant solvent.\textsuperscript{22} In addition, water generally enables facile work-up protocols, as most organic compounds, being lipophilic, are readily segregated from aqueous media. In addition, many organic reactions, that take place ‘on water’, i.e., with the reactants initially emulsionated in water, exhibit important
rate enhancements. Finally, water as a reaction medium enables novel solvation and assembly processes conferring unique selectivity and reactivity. For these reasons, the development of synthetically useful reactions that take place in water is of considerable topical interest.

Breslow’s Diels-Alder reactions in aqueous media and Mayr’s alklylation of aromatic molecules without using a Friedel-Crafts catalyst remain best examples for the water mediated organic reactions. Very recently, it has been reported that organic molecules can react on the surface of water, and in some cases, a very large enhancement in reaction rates were noticed in comparison to reactions without the solvent. High dielectric constant and cohesive energy density of water in aqueous medium showed an extraordinary effect on reaction rates. Water is a desirable solvent for chemical reactions because it is safe, nontoxic, environment friendly, readily available, and inexpensive compared to organic solvents.

The search for an efficient method for the synthesis of spiro compounds is interesting in organic synthesis, and numerous impressive successes have been recorded for the synthesis of diversely structured spiro chromenes over the past years. It is a well known fact that the multicomponent reactions pave the way to construct target compounds without isolating the intermediates by the introduction of several diversity elements in a single chemical operation. These reactions, which involve at least three different simple substrates, are powerful for the expedient building up of molecular complexity and diversity through the facile formation of several new covalent bonds in a one-pot transformation, quite closely approaching the concept of an ideal synthesis.
A quick, clean, and simple method for the synthesis of new spirooxindoles and spiroindenoquinoxaline derivatives catalyzed by indium(III) chloride under solvent-free conditions and also by thermal heating has been reported.\(^{33}\)

\[
\text{Scheme 4.1}
\]

A clean and simple one-pot three-component reaction for the synthesis of spiro chromene derivatives has been catalyzed by ammonium chloride in water.\(^{34}\)

\[
\text{Scheme 4.2}
\]

A simple procedure has been described for the synthesis of spirooxindoles in water using KAl(SO\(_4\))\(_2\)·12H\(_2\)O,\(^{35}\) an inexpensive, efficient, and recyclable catalyst.
Scheme 4.3

The Lewis acid-catalyzed,\textsuperscript{36} three-component reaction of isatin and two 1,3-dicarbonyl compounds has been reported. Reactions proceeded with high efficiency under mild reaction conditions and with good functional group tolerance to afford spirooxindole pyrano chromenedione derivatives.

Scheme 4.4

A simple one-pot three component reaction involving isatin, activated methylene reagent, and 1,3-dicarbonyl compounds for the synthesis of a series of spirooxindole derivatives in water has been documented.\textsuperscript{37} Particular valuable features of this method include the higher yields of the products, broader substrate scope, mild reaction conditions, reduced environmental impact, and the straightforwardness of the procedure.
An efficient one-pot synthesis of spirooxindole derivatives by three-component reaction of isatins, malononitrile (cyanoacetic ester) and 1,3-dicarbonyl compounds in water in the presence of L-proline has been reported.\textsuperscript{38}

![Scheme 4.6](image)

Scheme 4.6

The first enantioselective organocatalytic two- and three-component reactions via a domino Knoevenagel/Michael/cyclization sequence with cupreine as catalyst have been developed.\textsuperscript{39} A wide range of optically active spiro[4H-pyran-3,3'-oxindoles] were obtained in excellent yields with good to excellent enantioselectivities from simple and readily available starting materials under mild reaction conditions.

![Scheme 4.7](image)

Scheme 4.7

It has been reported that the synthesis of spirooxindoles with fused chromenes, could be achieved through the three-component one-pot reaction in aqueous micellar media, using sodium stearate as a Lewis base-surfactant-combined catalyst.\textsuperscript{40} It has been
suggested that sodium stearate shows the favorable surfactivity, particularly, and it would act as both a base to activate the substrate molecules and a surfactant to form stable colloidal dispersion with water-insoluble substrates.

![Scheme 4.8](image)

An efficient one-pot synthesis of novel 8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3′-indoline]-2,2′,4,6(1H,3H,7H)-tetraone derivatives by a three-component condensation reaction of barbituric acids, isatins and cyclohexane-1,3-diones in refluxing water in the presence of p-TSA has been reported.\(^\text{41}\)

![Scheme 4.9](image)

Electrochemically induced catalytic multicomponent transformation of isatins, 3-methyl-2-pyrazolin-5-ones and malononitrile in ethanol in an undivided cell in the presence of sodium bromide as an electrolyte resulted in the formation of spirooxindoles with fused functionalized pyrano[2,3-c]pyrazole system in 78-99% yields.\(^\text{42}\) The developed efficient electrocatalytic approach to medicinally relevant spirocyclic [indole-3,4′-pyrano[2,3-c]pyrazoles] is beneficial from the viewpoint of
diversity-oriented large-scale processes and represents a novel example of facile environmentally benign synthetic concept for electrocatalytic multicomponent reaction strategy.

Scheme 4.10

An efficient procedure for the synthesis of biologically active 4H-chromene and N-arylquinoline derivatives has been described by using TBAF. The use of TBAF as a base has the advantages of being economically viable and more efficient for multicomponent reactions in aqueous media. The reaction system can be successfully applied to a variety of aryl aldehyde as well as isatin to synthesize a wide variety of heterocycles.

Scheme 4.11

Green catalytic protocol for the synthesis of biologically important spirooxindole derivatives has been developed in a one-pot, three-component approach involving substituted isatin, activated methylene reagent, and 3-methyl-1-
phenyl-2-pyrazolin-5-one in water under sonication.\textsuperscript{44} This report describes the use of sodium chloride as a non acidic and green catalyst for a variety of substrates.

![Scheme 4.12](image1)

A facile, catalyst-free three component method for the synthesis of spiro[indeno[1,2-b]pyrido-[2,3-d]pyrimidine-5,3’-indolines and spiroacenaphthylene-1,4’-indeno-1,5’-pyrido[2,3-d]pyrimidines in ethanol using readily available starting materials has been achieved.\textsuperscript{45}

![Scheme 4.13](image2)

An efficient, one-pot, and pseudo four-component method for the synthesis of spiro[diindenopyridine-indoline]triones and spiro[acenaphthylene-diindenopyridine]triones has been performed using ‘Grindstone chemistry’.\textsuperscript{46}
Scheme 4.14

An atom-economical method for the preparation of spiro[diindenopyridine-indoline]-triones and spiro[acenaphthylene-diindenopyridine]-triones using readily available starting materials has been reported.47

Scheme 4.15

A clean method for the preparation of spiro[indoline-3,9-xanthene]trione derivatives has been reported using a condensation reaction of dimedone and isatins under reflux in water.48 Furthermore, a novel synthesis of spiro[acenaphthene-1,9'-xanthene]-1',2,8(2'H,5'H)-trione has been reported.

Scheme 4.16

Catalyst-free synthesis of spiro[indeno[1,2-b] pyrazolo[4,3-e]pyridine indoline] diones and spiro[acenaphthylene-indeno[1,2-b] pyrazolo[4,3-e]pyridine]diones by the three-component reaction of 1,3-indandione, pyrazol-5amines and isatins or acenaphthylene-1,2-dione in refluxing ethanol has been
reported. Reaction of 2,6-diaminopyrimidin-4(3H)-one with 1,3-indandione and isatins resulted in the formation of 1H-spiro[indeno[1,2-b]pyrido[2,3-d]pyrimidine-5,3’-indoline]-2’,4,6(11H)-triones.

\[ \text{Scheme 4.17} \]

4.2. Results and Discussion

Generally, the synthesis of spiro compound namely, 2-amino-5-oxo-7,7-dimethylspiro [(4H)-5,6,7,8-tetra-hydrochromene-4,3’-(3’H)-indol]-(1’H)-2’-one-carbonitrile has been reported by the reaction of isatin, dimedone and malononitrile in the presence of the above mentioned catalysts. However, to the best of our knowledge, there is no report on the simple and efficient method for the synthesis of spirooxindoles with fused chromenes without using any catalyst under aqueous conditions.

In this regard, we have planned to design similar type of spirooxindole chromene derivatives through a one-pot three component reaction of isatin/acenaphthenequinone/ninhydrin and cyclic 1,3-dicarbonyl compounds with active methylene esters instead of malononitrile under greener reaction conditions, with water as a reaction medium. In all the cases, we have observed very good yields.
Scheme 4.18 General scheme for the synthesis of spiromxindole chromene derivatives

<table>
<thead>
<tr>
<th>S No</th>
<th>1,3-Dicarbonyl compound</th>
<th>Catalyst(^b)</th>
<th>Time (h)</th>
<th>Reaction medium</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dimedone</td>
<td>(\text{Al}_2(\text{SO}_4)_3)</td>
<td>12</td>
<td>water</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>Dimedone</td>
<td>CAN</td>
<td>12</td>
<td>water</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>Dimedone</td>
<td>(\text{NaHCO}_3)</td>
<td>12</td>
<td>water</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Dimedone</td>
<td>Benzalkonium chloride</td>
<td>12</td>
<td>water</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>Dimedone</td>
<td>(\text{NaSO}_4)</td>
<td>12</td>
<td>water</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>Dimedone</td>
<td>(\text{NaCl})</td>
<td>12</td>
<td>water</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>Dimedone</td>
<td>CTAB</td>
<td>1</td>
<td>water</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>Dimedone</td>
<td>SLS</td>
<td>1</td>
<td>Water</td>
<td>58</td>
</tr>
<tr>
<td>9</td>
<td>Dimedone</td>
<td>---</td>
<td>1</td>
<td>Water</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: Isatin, Diethyl malonate and dimedone in the ratio of 1:1:1 under reflux conditions. \(^b\)10 mol% of catalyst.

Initially, in order to optimize the catalyst to be used, we have performed a model reaction with isatin, diethyl malonate and dimedone (Scheme 4.18) with catalysts such as aluminum sulphate, ceric ammonium nitrate (CAN), benzalkonium chloride, sodium bicarbonate, sodium sulphate, sodium chloride and also micellar catalyst such as cetyl trimethyl ammonium bromide (CTAB) and sodium lauryl sulphate (SLS) and observed that the yields were only moderate in all cases (Table - 4.1).
Scheme 4.19 Water mediated synthesis of spirooxindole chromene derivatives

To our surprise, the reaction worked well and provided good yield without any catalyst. Various dicarbonyl compounds such as diethyl malonate (5a), dibenzyl malonate (5b), di-t-butyl malonate (5c), dimethyl malonate (5d), ethyl acetoacetate (5e), methyl acetoacetate (5f), and acetyl acetone (5g) have been applied to synthesize the corresponding spirooxindole derivatives functionalized with chromene moieties (6a-6i), using water as reaction medium. In all the cases, the yields observed were very good (73 to 85%) and the products were pure (Table - 4.2). Due to the insoluble nature of dibenzyl malonate (5b) and di-t-butyl malonate (5c) in the reaction medium, they didn’t provide the respective spirooxindoles with fused chromene derivatives (entries 3 & 4 Table - 4.2).
Table - 4.2 Water mediated synthesis of spiro chromene derivatives from compounds 1a/1b/1c with 4a/4b and 5a-5g:

<table>
<thead>
<tr>
<th>S.No</th>
<th>1a/1b/1c</th>
<th>4a/4b</th>
<th>5a-5g</th>
<th>Time (h)</th>
<th>Yield(^b)(%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>4a</td>
<td>5a</td>
<td>1</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>4b</td>
<td>5a</td>
<td>1</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>4a</td>
<td>5b</td>
<td>12</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>4a</td>
<td>5c</td>
<td>12</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>4a</td>
<td>5d</td>
<td>1</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>4b</td>
<td>5d</td>
<td>1</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>4a</td>
<td>5e</td>
<td>1</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>4a</td>
<td>5f</td>
<td>1</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>4a</td>
<td>5g</td>
<td>1</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>4a</td>
<td>5a</td>
<td>1</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>4a</td>
<td>5a</td>
<td>1</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

\(^b\) Reactions were performed with 1:1:1 mmol of 1a/1b/1c : 4a/4b : 5a-5g in 10 ml of water at 80 C. \(^b\) Isolated Yield.
Scheme 4.20 Water mediated synthesis of spirowhenene indene derivatives

After obtaining successful results for isatin and 5-substituted isatins, we expected that the same type of reaction may be applicable for acenaphthenequinone (2) and ninyhydrin (3) where, the reaction failed to occur with 2 as a 1,2-dicarbonyl compound because of its limited solubility offering a very minimum yield (entries 1,3,5,7,9, Table - 4.3 ). However, the reaction worked well for ninyhydrin (3) in shorter duration with good yields as shown in Table - 4.3. The expected spirooxindole derivatives have been formed in good yields within an hour in all the cases without any by-products. The solid product formed during the reaction was easily separated by simple filtration.
Table - 4.3 Water mediated synthesis of spiro chromene indene derivatives from compounds 2/3 and 1, 3-dicarbonyl compounds\textsuperscript{a}:

<table>
<thead>
<tr>
<th>S.No</th>
<th>2/3</th>
<th>4a</th>
<th>5a-5g</th>
<th>Time (h)</th>
<th>Yield\textsuperscript{b} (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4a</td>
<td>5a</td>
<td>2</td>
<td>Trace</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4a</td>
<td>5a</td>
<td>1</td>
<td>78</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>4a</td>
<td>5d</td>
<td>1</td>
<td>Trace</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>4a</td>
<td>5d</td>
<td>1</td>
<td>77</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>4a</td>
<td>5e</td>
<td>1</td>
<td>Trace</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>4a</td>
<td>5e</td>
<td>1</td>
<td>70</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>4a</td>
<td>5f</td>
<td>1</td>
<td>Trace</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>4a</td>
<td>5f</td>
<td>1</td>
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<tr>
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<td>4a</td>
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<td>Trace</td>
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</tr>
<tr>
<td>10</td>
<td>3</td>
<td>4a</td>
<td>5g</td>
<td>1</td>
<td>73</td>
<td>---</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions were performed with 1:1:1 mmol of 2/3 : 4a : 5a-5g in 10 ml of water at 80 °C. \textsuperscript{b}Isolated yield.

4.3. Conclusion

In conclusion, we have developed the synthesis of some spiro chromene derivatives in a simple and efficient way without using any catalyst, under aqueous conditions. This method offered several advantages such as good yields, broader substrate scope with a safe, cheap, and environmentally benign procedure, making it
a useful and attractive protocol for the synthesis of these biologically important compounds.

4.4. Experimental methods: Isatin, 5-chloro isatin, 5-nitro isatin, acenaphthenequinone, ninhydrin, dimedone, 1,3-cyclohexadione, diethyl malonate, dimethyl malonate, dibenzyl malonate, di-t-butyl malonate, ethyl acetoacetate, methyl acetoacetate, acetyl acetone and all the catalysts used were purchased from Sigma-Aldrich and were used as such without further purification. The melting points of all compounds were determined with an electrothermal apparatus using capillary tube and are uncorrected. The purities of the compounds were checked by TLC using precoated silica gel plates with n-hexane:ethyl acetate (6:4) as eluent. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance spectrophotometer at 400/100 and 500/125 MHz respectively using TMS as reference. Elemental microanalyses were carried out on a Perkin-Elmer elemental analyzer Model 240C and a Thermo Finnigan analyser series Flash EA1112.

4.4.1. General procedure for the synthesis of spiro oxindole derivative (6a) using catalyst: 1.0 mmol of 1a, 1.0 mmol of 5a and 1.0 mmol of 4a were added successively to 10 mol% of catalyst (as discussed in Table - 4.1) in 10ml of water and heated with stirring at 80°C for the specified time. A solid thrown out in the reaction mass was filtered, dried and characterized by $^1$H, $^{13}$C NMR, LCMS and CHN analysis.

4.4.2. General procedure for the synthesis of spiro oxindole derivatives without catalyst (6a - 6i): 1.0 mmol of 1, 1.0 mmol of 5 and 1.0 mmol of 4 were added successively to 10ml of water and heated with stirring at 80°C for the specified time. A solid thrown out in the reaction mass was filtered, dried and characterized by $^1$H
and $^{13}$C NMR. Similar procedures have been followed for the synthesis of all other spiro derivatives and characterized by NMR and LCMS.

Ethyl 2-ethoxy-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxylate (6a): Colorless solid; mp: 160-162 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 10.17 (s, 1H); 7.19-7.15 (t, 1H); 7.08-7.07 (d, 1H); 6.90-6.86 (t, 1H); 6.78-6.76 (d, 1H); 2.21 (broad m, 4H’s); 1.91-1.89 (s, 4H’s), 1.0-0.99 (s, 12 H’s). $^{13}$C NMR (100MHz, DMSO-d$_6$) $\delta$: 196.86, 178.80, 176.79, 155.40, 153.26, 132.77, 129.64, 123.57, 121.73, 111.06, 109.89, 78.32, 65.40, 63.27, 51.49, 49.23, 39.28, 32.24, 29.84, 15.29, 14.98. LCMS (ESI) m/z calcd for C$_{23}$H$_{25}$NO$_6$ (M$^+$+ 1): 412.45 found: 412.

Ethyl 2-ethoxy-7,7-dimethyl-5'-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3'-indoline]-3-carboxylate (6b): Colorless solid; mp: 184-186 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 10.96-10.94 (s, 1H); 8.18-8.14 (d, 1H) 7.87-7.85 (s, 1H); 7.00-6.96 (d, 1H); 2.25 (m, 4H’s); 1.91-1.89 (m, 6H’s), 0.98-0.95 (m, 6H’s). LCMS (ESI) m/z calcd for C$_{21}$H$_{21}$NO$_6$ (M$^+$+ 1): 384.39 found: 384.

Methyl 2-methoxy-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxylate (6c): Colorless solid; mp: 146-148 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$: 10.18 (s, 1H); 7.19-7.16 (t, 1H); 7.09-7.07 (d, 1H); 6.90-6.83 (t, 1H); 6.79-6.77 (d, 1H); 4.21 (s, 3H’s); 3.38 (s, 3H’s); 2.22 (broad s, 4H’s); 0.99 (s, 6 H’s). $^{13}$C NMR (100MHz, DMSO-d$_6$) $\delta$: 195.0, 176.81, 174.26, 143.19, 132.76, 129.65, 123.57, 121.74, 111.06, 109.89, 78.32, 63.35, 61.27, 59.87, 56.63, 32.25, 27.94. LCMS (ESI) m/z calcd for C$_{23}$H$_{21}$NO$_6$ (M$^+$+ 1): 384.39 found: 384. Anal. calcd for C$_{21}$H$_{21}$NO$_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.89; H, 5.43; N, 3.54.
Methyl 2-methoxy-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3'-indoline]-3-carboxylate (6d): Colorless solid; mp: 170-172 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 10.25 (s, 1H); 7.25-7.17 (m, 2H’s); 6.96-6.84 (m, 2H’s); 3.45(s, 3H’s), 2.37 (s, 3H’s); 1.91-1.90 (m, 6H’s). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 196.15, 178.89, 176.92, 165.34, 162.36, 143.22, 132.93, 129.67, 123.80, 121.79, 112.51, 109.87, 78.41, 59.32, 54.37, 47.65, 32.75, 25.61, 20.85. LCMS (ESI) m/z calcd for C$_{19}$H$_{17}$NO$_6$ (M$^+$ + 1): 356.34 found: 356. Anal. calcd for C$_{19}$H$_{17}$NO$_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.35; H, 4.91; N, 3.86.

Methyl 2,7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3'-indoline]-3-carboxylate (6f): Colorless solid; mp: 188-190 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 10.18 (s, 1H); 7.17 (t, 1H); 7.08-7.06 (d, 1H); 6.90-6.88 (t, 1H); 6.78-6.76 (d, 1H); 4.87 (s, 3H’s); 2.38 (broad s, 7H’s (2CH$_2$ + CH$_3$)); 0.99 (s, 6 H’s). $^{13}$C NMR (100MHz, DMSO-d$_6$) δ: 197.80, 178.62, 176.80, 143.19, 132.45, 129.65, 123.57, 121.74, 111.05, 109.89, 78.31, 50.0, 32.24. 30.21, 27.15. LCMS (ESI) m/z calcd for C$_{23}$H$_{21}$NO$_5$ (M$^+$ + 1): 368.40 found: 368. Anal. calcd for C$_{23}$H$_{21}$NO$_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.51; H, 5.85; N, 3.76.

3-Acetyl-2,7,7-trimethyl-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (6g): Colorless solid; mp: 158-160 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 10.16 (s, 1H); 7.17-7.13 (t, 1H); 7.07-7.05 (d, 1H); 6.88-6.84 (t, 1H); 6.77-6.75 (d, 1H); 3.38 (s, 3H’s); 2.19-2.07 (broad s, 7H’s); 0.99 (s, 6 H’s). $^{13}$C NMR (100MHz, DMSO-d$_6$) δ: 195.84, 192.10, 176.81, 155.38, 154.73, 143.18, 132.75, 129.65, 123.57, 121.74, 111.04, 109.89, 52.37, 50.82, 39.32, 32.59, 28.42, 19.56.
Ethyl 5'-chloro-2-ethoxy-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydropyro
[chromene-4,3'-indoline]-3-carboxylate (6h): Colorless solid; mp: 168-170 °C; \(^1\)H NMR (400 MHz, DMSO-d6) δ: 10.96-10.94 (s, 1H); 8.18-8.14 (d, 1H) 7.87-7.85 (s, 1H); 7.00-6.96 (d, 1H); 2.25-2.08 (m, 4H's); 1.75-1.71 (m, 4H's); 0.99-0.97 (s, 12 H's).

Ethyl 2-ethoxy-2',5-dioxo-5,6,7,8-tetrahydropyro[chromene-4,3'-indoline]-3-carboxylate (6i): Colorless solid; mp: 186-188 °C; \(^1\)H NMR (500 MHz, DMSO-d6) δ: 10.96 (s, 1H); 8.26-8.23 (d, 1H) 7.89-7.86 (s, 1H); 7.04-7.00 (d, 1H); 2.35-2.18 (m, 4H's); 1.85-1.82 (m, 4H's); 1.03-0.99 (s, 12 H's).

Ethyl 2-ethoxy-7,7-dimethyl-1',3',5-trioxo-1',3',5,6,7,8-hexahydropyro [chromene-4,2'-indene]-3-carboxylate (7a): Colorless solid; mp: 174–176 °C; \(^1\)H NMR (400 MHz, DMSO-d6) δ: 7.87-7.66 (m, 4H's); 2.32-2.04 (m, 8H's); 1.026-0.84 (d, 12H's). \(^13\)C NMR (100 MHz, DMSO-d6) δ: 197.48, 192.11, 175.88, 147.21, 136.60, 134.60, 131.83, 125.37, 123.41, 112.96, 111.77, 83.06, 73.21, 72.15, 69.58, 68.43, 51.60, 37.60, 33.55, 28.75, 27.76. \(^13\)C DEPT (135 MHz, DMSO-d6) δ: CH₂ carbon: 51.57, 37.62 and CH carbon: 136.59, 131.83, 125.39, 123.39, 28.82, 27.76. LCMS (ESI) m/z calcd for C₂₄H₂₄O₇ (M⁺+ 1): 425.44 found: 425.

Methyl 2-methoxy-7,7-dimethyl-1',3',5-trioxo-1',3',5,6,7,8-hexahydropyro [chromene-4,2'-indene]-3-carboxylate (7b): Colorless solid; mp: 182-184 °C; \(^1\)H NMR (400 MHz, DMSO-d6) δ: 7.87-7.67 (d, 4H's); 3.38 (s, 3H's); 2.32-2.08 (m, 7H's); 1.02-0.85 (d, 6H's). \(^13\)C NMR (100 MHz, DMSO-d6) δ: 197.43, 192.09, 175.91, 136.61, 131.78, 125.32, 123.40, 112.81, 111.72, 83.06, 51.59, 37.55, 33.50, 28.75, 27.76. LCMS (ESI) m/z calcd for C₂₂H₂₀O₇ (M⁺+ 1): 397.39 found: 397. Anal. calcd for C₂₂H₂₀O₇: C, 66.66; H, 5.09. Found: C, 66.18; H, 5.16.
Ethyl  2,7,7-trimethyl-1',3',5-trioxo-1',3',5,6,7,8-hexahydrospiro[chromene-4,2'-indene]-3-carboxylate (7c): Colorless solid; mp: 186-188 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta:\) 7.86-7.72 (d, 4H’s); 3.37 (s, 2H’s); 2.32-2.07 (m, 7H’s); 1.00-0.85 (d, 9H’s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta:\) 197.38, 192.16, 175.92, 147.16, 136.59, 134.62, 131.80, 125.38, 123.41, 112.89, 111.74, 83.04, 51.6, 37.60, 28.73, 27.75, 15.34, 14.67. LCMS (ESI) m/z calcd for C\(_{23}\)H\(_{22}\)O\(_6\) (M\(^{+}\) 1): 395.42 found: 395. Anal. calcd for C\(_{23}\)H\(_{22}\)O\(_6\): C, 70.04; H, 5.62. Found: C, 70.21; H, 5.56.

Methyl  2,7,7-trimethyl-1',3',5-trioxo-1',3',5,6,7,8-hexahydrospiro[chromene-4,2'-indene]-3-carboxylate (7d): Colorless solid; mp: 194-196°C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta:\) 7.88-7.66 (d, 4H’s); 3.61-3.37 (s, 3H’s); 2.32-2.09 (m, 4H’s); 1.03-0.85 (d, 9H’s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta:\) 197.39, 192.07, 175.94, 136.58, 131.82, 125.34, 111.71, 83.00, 51.60, 37.65, 33.48, 28.62.

3-Acetyl-2,7,7-trimethyl-7,8-dihydrospiro[chromene-4,2'-indene]-1',3',5(6H)-trione (7e): Colorless solid; mp: 208-210 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta:\) 7.86-7.71 (d, 4H’s); 3.31 (s, 3H’s); 2.29-2.07 (m, 4H’s); 1.09-0.84 (d, 9H’s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta:\) 197.41, 192.16, 178.94, 136.60, 131.81, 125.33, 123.40, 112.80, 82.97, 51.59, 37.56, 33.49, 28.70, 27.76.
Some representative NMR spectra

Fig. 4.2 $^1$H and $^{13}$C NMR spectra of 6c
Fig. 4.3 $^1$H and $^{13}$C NMR spectra of 6f
Fig. 4.4 $^1$H NMR spectrum of 6g
Fig. 4.5 $^1$H and $^{13}$C NMR spectra of 7a
Fig. 4.6 DEPT $^{13}$C NMR spectrum of 7a
Fig. 4.7 $^{13}$C NMR spectrum of 7b
Fig. 4.8 $^1$H and $^{13}$C NMR spectra of 7c
Fig. 4.9 $^1$H and $^{13}$C NMR spectra of 7d
References


