CHAPTER II

A novel oxidative decarboxylation-synthesis of 2-amino-1,2-dihydroisoquinoline-3(4H)-one and its amide derivatives from tetrahydroisoquinoline-3-carboxylic acid

II.A. Introduction

Mesoionic compounds are distinct types of heterocycles which belong to the class of non-benzenoid aromatics. Sydnone, the representative mesoionic compound has been extensively studied because of its unusual structure, chemical properties and synthetic utility. Sydnone is used as a versatile synthon in heterocyclic synthesis.

Literature has indicated that sydnones have gained significant interest through the discovery of an array of useful biological properties (e.g., as antibacterial,\(^1\) antineoplastic\(^2\) and anti-inflammatory\(^3\) agents), which has driven the development of new functionalisation methods. Similarly, sydnones act as useful and novel precursors for pyrazoles (through cycloaddition with alkynes), which has also served to drive research into their functionalisation and cycloaddition chemistry.

II.B. Synthesis of Sydnones

Classically, sydnones are synthesized in just two steps from  \(N\)-substituted amino acids.  \(N\)-Nitrosation followed by cyclodehydration generally furnishes the mesoionic products in good-to-excellent yields. Whilst this is the most common method, several improvements or alternatives have been introduced. Of particular note, the employment of trifluoroacetic anhydride (TFAA) has superseded the use of acetic anhydride, largely due to an increased rate of cyclisation. Turnbull et al. have described nitrosation using isoamyl nitrite (IAN) for acid-sensitive starting materials. Thoman and Voaden reported the use of charcoal to improve the purity of the isolated products, which was evidenced by the isolation of a colourless solid (\(N\)-phenyl sydnone is usually isolated as tan crystals).

Azarifar et al. have reported several one-pot syntheses of sydnones. One approach employs dibromo-dimethylhydantoin (DBH). This one-pot procedure avoids isolation of the toxic nitrosamine intermediate and makes use of cheap commercially
available materials. Moreover, they report good yields for the formation of a range of sydnones across all methods.

Classical sydnone preparation

\[
\begin{align*}
\text{R}^1 & \quad \text{H} & \quad \text{N} & \quad \text{R}^2 \\
\text{OH} & \quad \text{O} & \quad \text{NaNO}_2 & \quad \text{Conc. HCl} & \quad (\text{CH}_3\text{CO})_2\text{O} \\
\end{align*}
\]

Alternative nitrosation

Improved Cyclodehydration

II.C. Synthesis of 2-amino-1,2-dihydroisoquinoline-3(4H)-one:

A convenient method of synthesizing 2-amino-1,2-dihydroisoquinoline-3(4H)-one and its amide derivatives 2.7 and 2.9a-k are described through sydnone intermediate 2.6 derived from TIC 2.4 (tetrahydroisoquinoline-3-carboxylic acid) under acidic conditions in good yield.

In the literature the title compounds 2.7 or 2.9a-k have been synthesised from homophthalic acid in five steps. N-phenylsydnone has been reported to give phenyl hydrazine on treatment with HCl. Sydnone derived from proline refluxed with propiolic acid in xylene gave the corresponding cyclic hydrazide. These reports revealed that the mechanism of formation of the hydrazine and hydrazide product
suggested that 2.7 or 2.9a-k could be easily accessed through the sydnone intermediate 2.6. In continuation of our work, 2-amino-1,2-dihydroisoquinoline-3(4H)-one 2.7 and their amide derivatives were listed in Table 2.1.

The commercially available TIC 2.4 was treated with NaNO₂ in HCl to generate the N-nitroso compound 2.5, which on subsequent reaction with trifluoroacetic anhydride gave the corresponding sydnone 2.6. Sydnone 2.6 was treated with concentrated HCl under reflux condition for 12 h to give the corresponding N-amino compound 2.7 in good yield (II.F.) (Scheme 2.1). The structure of the compound was confirmed by mass, IR and NMR spectral data.

Scheme 2.1

This sequence of reactions posed several scale-up problems. The first reaction, the nitrosation, proceeded well. The product was isolated by extraction with methyl tert-butyl ether (MTBE), followed by the azeotropic drying of the resulting crude product with toluene. Conversion of nitroso compound 2.5 to sydnone 2.6 by reaction with trifluoroacetic anhydride in diethyl ether was very cumbersome- it did not give us the described 96% yield. Instead, the yield was in the range of 68-70%. Diethyl ether was not acceptable for scale-up, and the purification of the product required chromatography on silica gel to remove the generated trifluoroacetic acid. Also, as sydnone 2.6 is water soluble, aqueous workup had to be avoided or minimized to reduce the loss of the sydnone in an extractive procedure. We had to find an alternative solvent and neutralization procedure.
After many experiments, we found that performing the reaction in acetonitrile resulted in complete conversion within 2h. The neutralization was performed with powdered potassium carbonate. The resulting mixture was concentrated to dryness, producing a glasslike substance, which was thoroughly suspended in methylene chloride. The methylene chloride suspension was filtered to remove the residual potassium carbonate and potassium trifluoroacetate. This procedure enabled us to isolate sydnone 2.6 in 91% yield as a crystalline, low-melting solid;

After further optimization, the conditions for the synthesis of the sydnone were modified as follows: The reaction between N-nitroso compound (after azeotropic drying) and trifluoroacetic anhydride was performed in DCM, and the trifluoroacetic acid generated was neutralized using a concentrated aqueous solution of potassium carbonate. The sydnone 2.6, was extracted with dichloromethane, and the combined organic extracts were evaporated azeotropically to remove residual water. The sydnone 2.6, was isolated as a dark-colored, low-melting solid in an overall yield of 60-80% from 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid.

These reaction conditions were carried out successfully on a 10 gm scale. According to the results, N-nitroso compound 2.5 has a decomposition exotherm at 68°C; sydnone 2.6 has a significant decomposition exotherm at 180 °C. All operations with intermediates 2.5 and 2.6 were therefore performed below the decomposition temperatures by at least 30 °C. We carried out all solvent evaporations under vacuum with a bath temperature at or below 35 °C. The reaction of the sydnone 2.6 with acetic acid under reflux for 6h gave the corresponding amide 2.9a in good yield (II.F). We then turned our attention to a few other carboxylic acids. The reaction of 2.6 with one equivalent of carboxylic acid 2.8a-k in refluxing xylene for 6–7h gave amide derivatives 2.9a–k of hydrazide 2.7 in good yield (Scheme 2.2, Table 2.1).
To confirm the structure of the compound, the reaction of 2.6 with (E)-2-(4-dimethylamino) phenyl-3-phenylacrylic acid 2.8j was carried out and the resulting the amide (2.9j), structure was determined using single crystal X-ray diffraction analysis (II.F) (Fig.2.1). Structures of the compounds 2.9 (a–k) were determined using NMR and mass spectrum (II.F). The pKa of the carboxylic acid did not change the rate or the yield of the reaction.

**Table 2.1: Reaction of compound 2.6 with carboxylic acids 2.8 (a-k) and their yields**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Carboxylic acids 2.8 (a-k)</th>
<th>Time (h)</th>
<th>Yielda (%)</th>
<th>Mp b (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9a</td>
<td>Acetic acid</td>
<td>5</td>
<td>73</td>
<td>184-186</td>
</tr>
<tr>
<td>2.9b</td>
<td>Benzoic acid</td>
<td>6</td>
<td>68</td>
<td>194-196</td>
</tr>
<tr>
<td>2.9c</td>
<td>4-Fluorobenzoic acid</td>
<td>5</td>
<td>75</td>
<td>220-224</td>
</tr>
<tr>
<td>2.9d</td>
<td>E-2,3-diphenylacrylic acid</td>
<td>5</td>
<td>87</td>
<td>156-158</td>
</tr>
<tr>
<td>2.9e</td>
<td>3,4-dimethoxybenzoic acid</td>
<td>5</td>
<td>71</td>
<td>204-206</td>
</tr>
<tr>
<td>2.9f</td>
<td>Thiophene-2-carboxylic acid</td>
<td>5</td>
<td>89</td>
<td>202-204</td>
</tr>
<tr>
<td>2.9g</td>
<td>Cinnamic acid</td>
<td>6</td>
<td>69</td>
<td>154-158</td>
</tr>
<tr>
<td>2.9h</td>
<td>Phenylacetic acid</td>
<td>6</td>
<td>65</td>
<td>144-148</td>
</tr>
<tr>
<td>2.9i</td>
<td>4-F-phenylacetic acid</td>
<td>5</td>
<td>89</td>
<td>175-177</td>
</tr>
<tr>
<td>2.9j</td>
<td>(E)-2-(4- dimethyl amino) phenyl-3-phenyl acrylic acid</td>
<td>5</td>
<td>91</td>
<td>163-166</td>
</tr>
<tr>
<td>2.9k</td>
<td>4-fluoro cinnamic acid</td>
<td>5</td>
<td>78</td>
<td>189-192</td>
</tr>
</tbody>
</table>
Fig. 2.1: X-ray structure of the compound 2.9j

The proposed mechanism of the reaction is as shown in scheme 2.3. The first step of the reaction is protonation of 2.6 to give I which on subsequent addition of water gives II. The intermediate II on protonation gives III which undergoes spontaneous decarboxylation to give 2.7.

II.C.1. Proposed Mechanism for the formation of 2.7

Scheme 2.3

The formation of 2.9 can be explained by addition of carboxylate ion to I after initial protonation as shown in scheme 2.4, followed by decarboxylation and intramolecular acyl transfer to give VII which on tautomerism gives 2.9.
II.C.2. Proposed Mechanism for the formation of 2.9

![Mechanism diagram](image)

II.D. Synthesis of substituted phenyl acrylic acids

Phenyl acrylic acids also called as stilbene carboxylic acids are contributing a significant role in the medicinal chemistry because of their extensive applications. This type of stilbene carboxylic acids are used as starting materials for the synthesis of antimicrobial drugs. These compounds can be prepared by special organic methods, for example, Reformatszkij, Suzuki, Wadsworth–Emmons, and Witting reactions. Another most significant reaction type is the perkin reaction in good yield. Here aromatic aldehydes react with phenyl acetic acid derivatives under basic condition, providing substituted stilbene carboxylic acids with high E-selectivity. This type of carboxylic acid groups demonstrate intermolecular hydrogen bonding that leads to dimeric structures. These smaller interactions also enhance the hydrolysis of these compounds that favours the permeation through lipid layer and hence improve the biological activity.\(^{10}\) We have synthesized and characterized a number of different substituted phenyl acrylic acids.

The methodology of synthesis is described as follows. The reaction was carried out by dissolving equimolar amounts of respective aldehydes and substituted phenyl acetic acids in 10 mL acetic anhydride that acts as a dehydrating agent. The basic medium was provided by triethylamine. Following the additions, the temperature was slowly raised to 50°C and these conditions were sustained for 2 hours. After that, 10% HCl and 20 mL of H\(_2\)O were added and an additional 2 hours of stirring was carried out at cold conditions. The precipitated product was filtered off and washed...
with water repeatedly to ensure the complete removal of traces of acetic acid and acetic anhydride. Slow evaporation of the solvent at room temperature over days yielded fine crystals that were subsequently washed with acetone.

The preparation of substituted phenyl acrylic acids.

![Scheme 2.5](image)

Table 2.2: Substituted Phenyl acrylic acids 2.12a-z

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R1 (2.10a-z)</th>
<th>R2 (2.11a-z)</th>
<th>Time (h)</th>
<th>Yielda (%)</th>
<th>Mp b (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.12a</td>
<td>4-SCH3 - phenyl</td>
<td>4-F-phenyl</td>
<td>1</td>
<td>62</td>
<td>163-166</td>
</tr>
<tr>
<td>2.12b</td>
<td>4-CN-phenyl</td>
<td>4-F-phenyl</td>
<td>1.5</td>
<td>63</td>
<td>171-174</td>
</tr>
<tr>
<td>2.12c</td>
<td>3,4-diOCH3-Phenyl</td>
<td>4-F-phenyl</td>
<td>1</td>
<td>60</td>
<td>183-186</td>
</tr>
<tr>
<td>2.12d</td>
<td>3,4-diOCH3-Phenyl</td>
<td>2-F-phenyl</td>
<td>1</td>
<td>61</td>
<td>162-165</td>
</tr>
<tr>
<td>2.12e</td>
<td>Phenyl</td>
<td>4-N,N-diCH3-Phenyl</td>
<td>1</td>
<td>68</td>
<td>174-178</td>
</tr>
<tr>
<td>2.12f</td>
<td>Phenyl</td>
<td>2-Cl-4-F-Phenyl</td>
<td>1</td>
<td>70</td>
<td>173-176</td>
</tr>
<tr>
<td>2.12g</td>
<td>Phenyl</td>
<td>p-Tolyl</td>
<td>1.5</td>
<td>73</td>
<td>164-167</td>
</tr>
<tr>
<td>2.12h</td>
<td>3,4-di-F-Phenyl</td>
<td>p-Anisyl</td>
<td>1.3</td>
<td>72</td>
<td>169-172</td>
</tr>
<tr>
<td>2.12i</td>
<td>3,4-di-F-Phenyl</td>
<td>2-Thiophenyl</td>
<td>1</td>
<td>75</td>
<td>178-181</td>
</tr>
<tr>
<td>2.12j</td>
<td>Phenyl</td>
<td>Naphthyl</td>
<td>1.2</td>
<td>71</td>
<td>189-192</td>
</tr>
<tr>
<td>2.12k</td>
<td>3-NO2-Phenyl</td>
<td>4-F-phenyl</td>
<td>1</td>
<td>64</td>
<td>187-190</td>
</tr>
<tr>
<td>2.12l</td>
<td>2-NO2-Phenyl</td>
<td>4-F-phenyl</td>
<td>1</td>
<td>60</td>
<td>192-195</td>
</tr>
<tr>
<td>2.12m</td>
<td>3,4-diOCH3-Phenyl</td>
<td>3-Cl-Phenyl</td>
<td>1</td>
<td>62</td>
<td>165-168</td>
</tr>
<tr>
<td>2.12n</td>
<td>4-F-phenyl</td>
<td>3-Indolyl</td>
<td>1</td>
<td>67</td>
<td>193-196</td>
</tr>
</tbody>
</table>
In addition, the emerging area of research are directed towards the development of novel antimicrobial agents. In our continuing effort aimed synthesis of amides at gathering the two bioactive entities like tetrahydroisoquinoline with substituted stilbene carboxylic acid for the purpose of evaluating the antimicrobial and antioxidant potentials.

\[
\begin{array}{cccc}
\text{2.12o} & \text{Phenyl} & 2-\text{F-phenyl} & 1.5 & 66 & 159-162 \\
\text{2.12p} & \text{Phenyl} & 2-\text{Cl-phenyl} & 1 & 63 & 160-163 \\
\text{2.12q} & \text{Phenyl} & 4-\text{F-phenyl} & 1 & 70 & 168-171 \\
\text{2.12r} & \text{Phenyl} & 4-\text{OCH}_3-\text{phenyl} & 1.3 & 72 & 156-159 \\
\text{2.12s} & 4-\text{F-phenyl} & 4-\text{OCH}_3-\text{phenyl} & 1 & 71 & 148-151 \\
\text{2.12t} & \text{Phenyl} & \text{phenyl} & 1 & 75 & 166-168 \\
\text{2.12u} & \text{Phenyl} & 4-\text{CH}_3-\text{phenyl} & 1 & 71 & 162-164 \\
\text{2.12v} & 2-\text{thiophene} & 4-\text{OCH}_3-\text{phenyl} & 1.2 & 68 & 155-158 \\
\text{2.12w} & 4-\text{F-phenyl} & 4-\text{CH}_3-\text{phenyl} & 1 & 66 & 156-159 \\
\text{2.12x} & 4-\text{F-phenyl} & 4-\text{F-phenyl} & 1 & 78 & 164-167 \\
\text{2.12y} & 4-\text{formyl benzoic ester} & 4-\text{F-phenyl} & 1.5 & 72 & 188-191 \\
\text{2.12z} & \text{Phenyl} & 3-\text{CH}_3 & 1.2 & 76 & 176-179 \\
\end{array}
\]

\( ^a \) Isolated yield \(^b \) Uncorrected

To expand the scope of the reaction, we undertook a systematic study of the reaction of sydnone derived from TIC with various substituted stilbene carboxylic acids. This cyclic hydrazide is a very useful precursor for the synthesis of various heterocyclic compounds. Structure of the synthesized compound (2.9j) were confirmed by recording their Mass, IR, \(^1\)H NMR, \(^{13}\)C NMR as shown in experimental data.

\[ \text{Scheme 2.6} \]

To expand the scope of the reaction, we undertook a systematic study of the reaction of sydnone derived from TIC with various substituted stilbene carboxylic acids. This cyclic hydrazide is a very useful precursor for the synthesis of various heterocyclic compounds. Structure of the synthesized compound (2.9j) were confirmed by recording their Mass, IR, \(^1\)H NMR, \(^{13}\)C NMR as shown in experimental data.
Table 2.3. Synthesis of compounds 2.13a-o by conventional method

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>Time (h)</th>
<th>Yield a (%)</th>
<th>Mp b (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.13a</td>
<td>4-SCH₃-phenyl</td>
<td>4-F-phenyl</td>
<td>6</td>
<td>92</td>
<td>168-171</td>
</tr>
<tr>
<td>2.13b</td>
<td>4-CN-phenyl</td>
<td>4-F-phenyl</td>
<td>5</td>
<td>89</td>
<td>161-164</td>
</tr>
<tr>
<td>2.13c</td>
<td>3,4-diOCH₃-Phenyl</td>
<td>4-F-phenyl</td>
<td>8</td>
<td>87</td>
<td>171-173</td>
</tr>
<tr>
<td>2.13d</td>
<td>3,4-diOCH₃-Phenyl</td>
<td>2-F-phenyl</td>
<td>6</td>
<td>88</td>
<td>166-168</td>
</tr>
<tr>
<td>2.13e</td>
<td>Phenyl</td>
<td>4-N,N-diCH₃-Phenyl</td>
<td>5</td>
<td>93</td>
<td>163-166</td>
</tr>
<tr>
<td>2.13f</td>
<td>Phenyl</td>
<td>2-Cl-4-F-Phenyl</td>
<td>6</td>
<td>88</td>
<td>174-176</td>
</tr>
<tr>
<td>2.13g</td>
<td>Phenyl</td>
<td>p-Tolyl</td>
<td>7</td>
<td>86</td>
<td>180-183</td>
</tr>
<tr>
<td>2.13h</td>
<td>3,4-di-F-Phenyl</td>
<td>p-Anisyl</td>
<td>5</td>
<td>89</td>
<td>186-188</td>
</tr>
<tr>
<td>2.13i</td>
<td>3,4-di-F-Phenyl</td>
<td>2-Thiophenyl</td>
<td>7</td>
<td>87</td>
<td>178-181</td>
</tr>
<tr>
<td>2.13j</td>
<td>Phenyl</td>
<td>Naphthyl</td>
<td>6</td>
<td>91</td>
<td>173-175</td>
</tr>
<tr>
<td>2.13k</td>
<td>3-NO₂-Phenyl</td>
<td>4-F-phenyl</td>
<td>5</td>
<td>86</td>
<td>159-161</td>
</tr>
<tr>
<td>2.13l</td>
<td>2-NO₂-Phenyl</td>
<td>4-F-phenyl</td>
<td>7</td>
<td>88</td>
<td>156-158</td>
</tr>
<tr>
<td>2.13m</td>
<td>3,4-diOCH₃-Phenyl</td>
<td>3-Cl-Phenyl</td>
<td>5</td>
<td>94</td>
<td>169-171</td>
</tr>
<tr>
<td>2.13n</td>
<td>4-F-phenyl</td>
<td>3-Indolyl</td>
<td>6</td>
<td>91</td>
<td>175-177</td>
</tr>
<tr>
<td>2.13o</td>
<td>Phenyl</td>
<td>2-F-phenyl</td>
<td>7</td>
<td>89</td>
<td>158-160</td>
</tr>
</tbody>
</table>

a Isolated yield  b Uncorrected
II.E. Results and Discussion

The compound 2.13e was synthesized by reaction of sydnone 2.6 with (2E)-2-[4-(dimethylamino) phenyl]-3-phenylprop-2-enoic acid 2.12e under reflux condition, for 5h. Which have been proved by the presence of band in compound 2.13e showed absorption at 3368 cm$^{-1}$ which is due to the -NH stretching and 1678 cm$^{-1}$ due to the amide stretching. $^1$H NMR spectral studies of compounds 2.13e showed a singlet appeared at $\delta$ 2.93 which is due to the presence of $N,N$-dimethyl group. A singlet appeared at $\delta$ 3.70 ppm which is due to CH$_2$ protons of (COCH$_2$) group. Methylene protons (-NCH$_2$) is observed as a singlet at $\delta$ 4.69 ppm. An aromatic proton was observed as a doublet in the region of (6.71-7.28) ppm and alkenic protons observed as a singlet at $\delta$ 7.20 ppm. Amide proton appeared as a singlet, at $\delta$ 9.87 ppm. The Mass spectrum of compound 2.13e showed molecular ion peak at m/z = 412.2 (M$^+$+1). The characteristic resonance peaks assigned provided the expected results. In $^{13}$C NMR, 36.96 ppm is due to the $N,N$-dimethyl carbon. A distinctive peak in $\delta$ 166.75-167.40 ppm range is assigned to carbon attached to the oxygen atom. All the aromatic carbon signals appeared in $\delta$ 112.19-149.92 ppm range confirming the proposed structure of the compound 2.13e. All the synthesized compounds 2.13(a-o) screened for their antimicrobial and antioxidant activity, results will be discussed in chapter IV and V respectively.

In conclusion we have developed a simple synthesis of 2-amino-1,2-dihydroisoquinoline-3(4H)-one 2.7 from sydnone 2.6 derived from tetrahydroisoquinoline-3-carboxylic acid 2.4 in good yields. The reaction is further explored with different carboxylic acids to give the corresponding amide derivatives in good yields.

II.F. Experimental data

General procedure for the synthesis of 2-amino-1,2-dihydroisoquinoline-3(4H)-one(2.7): Sydnone 2.6 (0.5 g, 1 mmol) was taken in 20 mL of conc.HCl and stirred overnight under reflux. After completion of the reaction, conc.HCl was evaporated using rotavapour at 50 °C. Resulting crude product was taken in ethylacetate (50 mL) and sonicated for 10 min and filtered to give the product as its HCl salt 2.7. Isolated as pale yellow solid. yield 91%. Mp 94-98 °C; IR $\nu_{max}$ (KBr) 1682, 1639, 3382 cm$^{-1}$;
^1H NMR (400 MHz, CDCl₃) δH 3.79 (s, 2H), 4.81 (s, 2H), 7.23-7.34 (m, 4H); ^13C NMR (400MHz, DMSO) δC 35.52, 51.08, 125.75, 126.73, 127.53, 127.73, 129.61, 130.65, 166.94; Mass (M⁺ +1) = 163.

Procedure for the synthesis of compound (2.9a): Sydnone 2.6 (1 equiv) was taken in 15 mL of acetic acid 2.8a (1 equiv) and stirred overnight under reflux. After completion of the reaction, acetic acid was evaporated using rotavapour at 50 °C to dryness to give the product 2.9a as yellow solid yield 73%. Mp 184-186 °C; IR νmax (KBr) 1653, 1694, 3552 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δH 1.90 (s, 3H), 3.72 (s, 2H), 4.64 (s, 2H), 7.22-7.29 (m, 4H), 10.23 (s, 1H); ^13C NMR (400MHz, DMSO) δC 20.52, 36.93, 53.59, 125.44, 126.44, 127.17, 127.36, 131.65, 131.77, 166.87, 168.22; Mass (M⁺ +1) = 205.1

X-ray crystal data of compound 2.9j: Compound 2.9j have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number is CCDC – 829819. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/contents/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

Crystal data for compound 2.9j : C₂₆H₂₅N₃O₂, M = 411.49, monoclinic, space group P2₁/c, a = 14.7503(6) Å, b = 10.3737(4) Å, c = 14.1677(5) Å, β = 96.176(2)°, U= 2155.29(14) Å³, Z = 4, μ = 0.081 mm⁻¹, 16224 reflections collected, 2641 independent reflections, Rint = 0.0364, final R indices [I > 2σ(I)] R₁ = 0.0430, wR₂ = 0.1068, R indices (all data) R₁ = 0.0631, wR₂ = 0.1289. CCDC – 829819.

General Methods:

Synthesis of substituted phenyl acrylic acids 2.12a-z:

To a solution of substituted phenyl acetic acids 2.11a-z (1 equiv) and acetic anhydride (2 equiv) followed by triethylamine (3 equiv) added drop by drop to get clear solution and stirring was continued for 15 min. To this substituted aromatic aldehydes (2 equiv) added drop by drop and stirring was continued for 2 hours at RT. Reaction progress was monitored by TLC. After completion, the reaction mixture poured into the
ice water and acidified by 1:1 HCl to get solid. Crude solid was dissolved by ethyl acetate and this layer was basified by using 2N NaOH solution. Aqueous layer was washed by ethyl acetate two times to remove excess aldehydes. Aqueous layer was acidified by using 1:1 HCl to get pure solid and it was filtered, dried at the vacuum pump.

**Preparation of 2,3-Bis-(4-fluoro-phenyl)-acrylic acid 2.12x:**

To a solution of 4-fluoro phenyl acetic acid 2.11x (5g, 32.44 mmol, 1 equiv), 4-fluoro benzaldehyde 2.10x (4 mL, 32.44 mmol, 1 equiv) and triethylamine (13.6 mL, 97.31 mmol, 3 equiv) in acetic anhydride (50 mL). After 2 hours, purification, compound 2.12x (4.2 g, 50%): IR $\nu_{\text{max}}$ (KBr) 1682, 3064 cm$^{-1}$; Mass = 261.1 (M$^+$+1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.06-7.14 (4H, m, Ar-H); 7.20-7.29 (4H, m, Ar-H); 7.78 (1H, s, =CH); 12.77 (1H, s, -COOH).

**General procedure for the synthesis of compounds 2.9a-k and 2.13a-o:**

Sydnone 2.6, (1 mmol) and xylene (30 mL) were charged to a double necked 100 mL round-bottomed flask, equipped with a water cooled condenser. The stirred solution was purged with nitrogen and heated to 140-145°C and carboxylic acid 2.8a-k and 2.12a-z (1 mmol) was added slowly over a period of 15 minutes. The reaction was held at 140-145°C for 6 h. After completion of the reaction, the solvent was removed and the product was purified by column chromatography using hexane-ethylacetate mixture (6:4) as eluent to afford the product. Spectroscopic data for representative 2-amino-1,2-dihydroisoquinoline-3(4H)-one 2.7 and its amide derivatives 2.13a-o are given below.

**N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzamide 2.9b:**

Pale brown solid. Yield 88%. Mp 194-196°C; IR $\nu_{\text{max}}$ (KBr) 1654, 1694, 3267 cm$^{-1}$; $^1$H NMR ( 400 MHz, DMSO ) $\delta$H 3.76 (s, 2H), 4.78 (s, 2H),7.25-7.33 (m, 4H), 7.51-7.55 (m, 2H), 7.59-7.63 (1H, m), 7.89-7.91 (2H, m), 10.88 (1H, s); $^{13}$C NMR (400MHz, DMSO) $\delta$C 37.05, 53.67, 125.46, 126.45, 127.19, 127.38, 127.51, 128.54, 131.63, 131.79, 132.10, 165.11, 167.07; Mass (M$^+$+1) = 267.1
4-fluoro-\(N\)-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzamide 2.9c:

Pale brown solid. Yield 75%. Mp 220-224\(^0\)C; IR \(\nu_{\text{max}}\) (KBr) 1643, 1684, 3435 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 3.77 (s, 2H), 4.78 (s, 2H), 7.26-7.33 (m, 4H), 7.36-7.40 (m, 2H), 7.96-7.99 (m, 2H), 10.93 (s, 1H); \(^1\)C NMR (400MHz, DMSO) \(\delta\) 37.04, 53.66, 115.50, 115.72, 125.46, 126.46, 127.20, 127.40, 128.55, 128.58, 130.24, 130.33, 131.63, 131.78, 163.10, 164.10, 165.58, 167.10; Mass (M\(^+\) +1) = 285.1

\((E)\)-\(N\)-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2,3-diphenylacrylamide 2.9d:

Pale brown solid. Yield 87%. Mp 156-158\(^0\)C; IR \(\nu_{\text{max}}\) (KBr) 1646, 1682, 3258 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 3.77 (s, 2H), 4.85 (s, 2H), 7.03 (m, 2H), 7.14-7.24 (m, 3H), 7.25-7.28 (m, 1H) 7.32-7.33 (m, 2H) 7.37-7.46 (m, 2H), 7.47-7.49 (m, 4H), 7.91 (s, 1H), 10.47 (s, 1H); \(^1\)C NMR (400MHz, DMSO) \(\delta\) 23.29, 37.00, 49.92, 53.55, 125.44, 126.43, 126.57, 127.17, 127.33, 128.06, 128.14, 128.32, 128.60, 128.85, 129.48, 129.56, 129.76, 131.58, 131.76, 134.67, 134.76, 134.97, 135.36, 166.68, 166.84; Mass (M\(^+\) +1) = 369.1

3,4-dimethoxy-\(N\)-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzamide 2.9e:

Pale brown solid. Yield 71%. Mp 204-206\(^0\)C; IR \(\nu_{\text{max}}\) (KBr) 1654, 1682, 3436 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 3.76 (s, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 4.77 (s, 2H), 7.08 (d, 1H, J = 8 Hz), 7.28-7.32 (m, 4H), 7.49 (d, 1H, J = 4 Hz), 7.55 (d, 1H, J = 12 Hz), 10.75 (1H, s); \(^1\)C NMR (400MHz, DMSO) \(\delta\) 37.09, 53.77, 55.55, 55.64, 110.63, 111.01, 121.05, 124.15, 125.45, 126.44, 127.17, 127.37, 131.66, 131.88, 148.31, 151.89, 164.62, 167.14; Mass (M\(^+\) +1) = 327.1

\(N\)-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)thiophene-2-carboxamide 2.9f:

Pale brown solid. Yield 89%. Mp 202-204\(^0\)C; IR \(\nu_{\text{max}}\) (KBr) 1654, 1677, 3436 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 3.76 (s, 2H), 4.77 (s, 2H), 7.21-7.33 (m, 5H), 7.86-7.89 (m, 2H), 10.93 (1H, s); \(^1\)C NMR (400MHz, DMSO) \(\delta\) 37.04, 53.83, 125.46, 126.47, 127.19, 127.41, 128.23, 129.43, 131.59, 131.75, 132.07, 136.76, 160.16, 167.19; Mass (M\(^+\) +1) = 273.1
N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)cinnamamide 2.9g:

Pale brown solid. Yield 69%. Mp 154-158°C; IR ν max (KBr) 1655, 1689, 1638, 3209 cm⁻¹; ¹H NMR ( 400 MHz, DMSO ) δ H 3.74 (s, 2H), 4.74 (s, 2H), 6.70 (d, 1H, J = 16 Hz), 7.26-7.28 (m, 4H), 7.44-7.45 (m, 3H), 7.57 (d, 1H, J = 16 Hz), 7.62-7.64 (m, 2H), 10.51 (s, 1H); ¹³C NMR (400MHz, DMSO) δ C 36.95, 53.65, 119.09, 125.50, 126.47, 127.21, 127.40, 127.83, 129.08, 130.03, 131.65, 131.74, 134.49, 164.01, 166.97; Mass (M⁺ +1) = 293.1

N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylacetamide 2.9h:

Pale brown solid. Yield 78%. Mp 144-148°C; IR ν max (KBr) 1651, 1686, 3436 cm⁻¹; ¹H NMR ( 400 MHz, DMSO ) δ H 3.34 (s, 2H), 3.69 (s, 2H), 4.64 (s, 2H), 7.21-7.26 (m, 5H), 7.27-7.33 (m, 4H), 10.57 (s, 1H); ¹³C NMR (400MHz, DMSO) δ C 36.88, 53.46, 125.44, 126.39, 126.54, 127.13, 127.32, 128.28, 129.07, 131.57, 131.65, 135.43, 166.83, 169.03; Mass (M⁺ +1) = 281.1

2-(4-fluorophenyl)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetamide 2.9i:

Pale brown solid. Yield 89%. Mp 175-177°C; IR ν max (KBr) 1651, 1686, 3436 cm⁻¹; ¹H NMR ( 400 MHz, DMSO ) δ H 3.53 (s, 2H), 3.69 (s, 2H), 4.64 (s, 2H), 7.13-7.18 (m, 2H), 7.22-7.26 (m, 4H), 7.34-7.37 (m, 2H), 10.53 (s, 1H); ¹³C NMR (400MHz, DMSO) δ C 36.87, 53.46, 114.91, 115.12, 125.45, 126.41, 127.14, 127.34, 130.89, 130.97, 131.56, 131.64, 159.93, 162.33, 166.87, 169.00 Mass (M⁺ +1) = 299.1

(E)-2-(4-(dimethylamino)phenyl)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-3 phenylacrylamide 2.9j:

Pale brown solid. Yield 89%. Mp 163-166°C; IR ν max (KBr) 1678, 1698, 3368 cm⁻¹; ¹H NMR ( 400 MHz, DMSO ) δ H 2.93 (s, 6H), 3.70 (s, 2H), 4.69 (s, 2H), 6.71 (d, 2H, J = 12 Hz), 7.05 (d, 2H, J = 8 Hz), 7.13-7.15 (m, 2H), 7.22-7.23 (m, 3H), 7.25-7.28 (m, 5H), 9.87 (1H, s); ¹³C NMR (400MHz, DMSO) δ C 36.96, 53.51, 112.19, 122.02, 125.44, 126.40, 127.16, 127.30, 128.14, 128.27, 129.59, 130.33, 131.68, 131.59, 131.76, 133.12, 134.99, 135.39, 149.92, 166.75, 167.40; Mass (M⁺ +1) = 412.2
(E)-3-(4-fluorophenyl)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acrylamide 2.9k:

Pale brown solid. Yield 89%. Mp 189-192°C; IR ν max (KBr) 1654, 1682, 1738, 3419 cm⁻¹; ¹H NMR (400 MHz, DMSO) δH 3.74 (s, 2H), 4.74 (s, 2H), 6.64 (d, 1H, J = 16 Hz), 7.24-7.32 (m, 6H), 7.57 (d, 1H, J = 16 Hz), 7.69-7.72 (m, 2H), 10.51 (s, 1H); ¹³C NMR (400MHz, DMSO) δC 36.92, 53.62, 115.93, 116.14, 118.94, 125.47, 126.44, 127.19, 127.37, 130.02, 130.10, 131.10, 131.13, 131.61, 131.70, 139.65, 161.77, 163.94, 164.23, 166.94; Mass (M⁺ +1) = 311.1

2-(4-Fluoro-phenyl)-3-(4-methylsulfanyl-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13a:

IR ν max (KBr) 1691, 1733, 3298 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δH 2.44 (s, 3H), 3.77 (s, 2H), 4.85 (s, 2H), 6.92 (2H, d, J=12 Hz), 7.03 (d, 2H, J=12Hz) 7.15-7.26 (4H, m), 7.39-7.42 (m, 3H), 7.52 (s, 1H), 7.84 (s, 1H), 9.89 (s, 1H); ¹³C NMR (400MHz, DMSO) δC 23.3, 37.0, 49.9, 53.6, 115.9, 116.1, 125.2, 125.4, 126.4, 126.6, 127.2, 127.4, 128.1, 128.6, 130.3, 130.7, 131.8, 132.7, 135.2, 139.7, 160.8, 163.3, 166.4, 166.8; Mass (M⁺ +1) =432.5

3-(4-Cyano-phenyl)-2-(4-fluoro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13b:

IR ν max (KBr) 1667, 1693, 2228, 3331 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δH 3.78 (s, 2H), 4.87 (s, 2H), 6.94 (2H, d, J=12 Hz), 7.07 (d, 2H, J=8Hz), 7.17-7.28 (4H, m), 7.42-7.51 (m, 3H), 7.56 (s, 1H), 7.84 (s, 1H), 9.92 (s, 1H); ¹³C NMR (400MHz, DMSO) δC 37.2, 49.9, 54.6, 116.7, 116.9, 125.2, 125.4, 126.5, 126.9, 127.2, 127.6, 128.1, 128.6, 130.7, 130.8, 131.8, 132.7, 135.9, 139.8, 160.8, 164.2, 166.5, 166.9; Mass (M⁺ +1) =411.4.

3-(3,4-Dimethoxy-phenyl)-2-(4-fluoro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13c:

IR ν max (KBr) 1664, 1692, 3276 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δH 3.40 (s, 2H), 3.70 (s, 2H), 3.72 (s, 3H), 4.68 (2H, s), 6.49 (d, 1H, J=2 Hz), 6.56 (d, 1H, J=4Hz), 6.87 (d, 1H, J=8Hz), 7.23-7.31 (m, 8H), 7.47 (s, 1H), 9.89 (s, 1H); ¹³C NMR (400MHz, DMSO) δC 36.6, 52.4, 56.1, 111.5, 111.7, 115.4, 122.5, 125.5, 125.9,127.2,
127.4, 128.0, 128.5, 129.4, 132.3, 132.4, 141.2, 149.0, 149.7, 162.1, 165.9, 174.2; Mass (M$^+$ +1) = 445.5.

3-(3,4-Dimethoxy-phenyl)-2-(2-fluoro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13d:

IR $\nu_{\text{max}}$ (KBr) 1661, 1691, 3331 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 3.32 (s, 3H), 3.69 (s, 2H), 3.73 (s, 3H), 4.68 (2H, s), 6.49 (d, 1H, $J$=4 Hz), 6.88 (d, 1H, $J$=8Hz), 7.25-7.33 (m, 7H), 7.48 (s, 1H), 7.61 (s, 1H), 10.07 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta_C$ 37.1, 53.6, 54.7, 55.4, 111.5, 116.2, 123.4, 124.1, 125.1, 125.5, 126.4, 126.8, 127.2, 127.3, 130.6, 131.6, 131.8, 132.2, 137.7, 148.1, 149.7, 158.6, 161.0, 165.6, 166.8; Mass (M$^+$ +1) = 445.5.

(E)-2-(4-(dimethylamino)phenyl)-N-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-3-phenyl acrylamide 2.13e:

Isolated as pale brown solid. Yield 89%. Mp. 163-166°C; IR $\nu_{\text{max}}$ (KBr) 1678, 1698, 3368 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 2.93 (s, 6H), 3.70 (s, 2H), 4.69 (s, 2H), 6.71 (d, 2H), 7.05 (d, 2H), 7.13 (d, 2H), 7.22-7.23 (m, 3H), 7.25-7.28 (m, 5H), 9.87 (1H, s); $^{13}$C NMR (400MHz, DMSO) $\delta_C$ 36.96, 53.51, 112.19, 122.02, 125.44, 126.40, 127.16, 127.30, 128.14, 128.27, 129.59, 130.33, 131.68, 131.59, 131.76, 133.12, 134.99, 135.39, 149.92, 166.75, 167.40; Mass (M$^+$ +1) = 412.2.

2-(2-Chloro-4-fluoro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenylacrylamide 2.13f:

IR $\nu_{\text{max}}$ (KBr) 1599, 1660, 3436, 2924 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 3.72 (s, 2H), 4.69 (s,2H), 6.51 (2H, s), 6.79 (d, 1H, $J$=4Hz), 6.89 (d, 1H, $J$=8Hz), 7.28-7.32 (5H, m), 7.48 (s, 1H), 7.61 (s, 2H), 9.86 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta_C$ 36.6, 52.4, 113.6, 117.8, 125.9, 127.2, 127.4, 127.9, 128.5, 128.6, 129.4, 130.9, 132.4, 132.7, 138.2, 141.2, 163.5, 165.9; Mass (M$^+$ +1) =420.9.

N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-2-p-tolyl-acrylamide 2.13g:

IR $\nu_{\text{max}}$ (KBr) 1696, 1677, 3370 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 2.37 (s, 3H), 3.78 (s, 2H), 4.81 (s,2H), 7.05 (2H, d, $J$=4Hz), 7.13-7.22 (m, 2H), 7.25-7.28 (2H, m), 7.37 (d, 2H, $J$=8Hz), 7.37-7.51 (m, 5H), 7.91 (s, 1H), 9.89 (s, 1H); $^{13}$C NMR
3-(3,4-Difluoro-phenyl)-2-(4-methoxy-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl) - acrylamide 2.13h:

IR $\nu_{\max}$ (KBr) 1691, 1733, 3298 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 3.85 (s, 3H), 3.78 (s, 2H), 4.87 (s, 2H), 6.94 (2H, d, J=12 Hz), 7.05 (d, 2H, J=8Hz) 7.17-7.28 (4H, m), 7.39-7.40 (m, 3H), 7.38-7.41 (m, 3H), 7.51 (s, 1H), 7.84 (s, 1H), 9.87 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta$c 36.6, 52.6 55.8, 112.6, 114.3, 122.4, 125.2, 125.9, 126.0, 127.4, 129.2, 130.2, 132.3, 132.4, 138.2, 141.2, 148.6, 149.2, 159.8, 165.9, 174.2; Mass (M$^+$ +1) = 434.5.

3-(3,4-Difluoro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-thiophen-2-yl- acrylamide 2.13i:

IR $\nu_{\max}$ (KBr) 1688, 1732, 3365 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 3.76 (s, 2H), 4.86 (s,2H), 6.57 (1H, d, J=4 Hz), 6.78 (d, 1H, J=8Hz), 6.98-7.13 (2H, m), 7.15-7.19 (m, 3H), 7.22-7.27 (m, 2H), 7.58 (d, 1H, J=4Hz), 7.85 (s, 1H), 9.86 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta$c 36.8, 52.7, 112.8, 125.2, 125.9, 126.2, 127.2, 127.4, 127.8, 128.3, 129.4, 130.2, 132.4, 136.8, 141.2, 145.7, 148.6, 149.4, 165.8, 174.2; Mass (M$^+$ +1) = 410.5

2-Naphthalen-2-yl-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide 2.13j:

IR $\nu_{\max}$ (KBr) 1651, 1681, 3436 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 3.78 (s, 2H), 4.83 (s,2H), 7.04 (d, 1H, J=8Hz), 7.17-7.26 (4H, m), 7.27-7.28 (4H, m), 7.37 (d, 2H, J=4Hz), 7.39-7.50 (m, 5H), 7.92 (s, 1H), 9.82 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta$c 36.6, 52.4, 123.5, 125.0, 125.8, 126.2, 126.4, 127.4, 127.6, 127.8, 127.9, 128.2, 128.4, 128.6, 129.6, 132.3, 132.4, 135.2, 133.2, 133.6, 138.2, 141.4, 165.9, 174.2; Mass (M$^+$ +1) = 418.5
2-(4-Fluoro-phenyl)-3-(3-nitro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13k:

IR $\nu_{\text{max}}$ (KBr) 1699, 1750, 3465 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 3.78 (s, 2H), 4.87 (s, 2H), 6.97 (2H, d, J=12 Hz), 7.05 (d, 2H, J=8Hz), 7.17-7.28 (4H, m), 7.41-7.44 (m, 3H), 7.57 (s, 1H), 7.85 (s, 1H), 9.87 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta_c$ 36.9, 49.9, 53.5, 116.2, 123.1, 123.8, 125.4, 126.5, 127.2, 127.5, 128.1, 128.5, 129.5, 129.9, 130.6, 130.7, 131.6, 131.8, 133.1, 133.2, 134.6, 147.6, 160.9, 163.4, 166.0, 166.8; Mass (M$^+$ +1) = 431.4

2-(4-Fluoro-phenyl)-3-(2-nitro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13l:

IR $\nu_{\text{max}}$ (KBr) 1697, 1734, 3437 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 3.76 (s, 2H), 4.87 (s, 2H), 6.54 (s, 1H), 6.73 (d, 1H, J=8Hz), 6.92 (d, 2H, J=12Hz), 7.17-7.28 (m, 3H), 7.39-7.43 (3H, m), 7.57 (s, 1H), 7.87 (s, 1H), 9.89 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta_c$ 36.7, 49.9, 53.8, 115.3, 124.2, 124.8, 124.8, 125.4, 126.7, 127.5, 128.1, 128.5, 129.5, 129.9, 130.9, 132.8, 133.1, 133.2, 133.4, 134.1, 136.0, 147.8, 160.9, 163.5, 166.3, 166.9; Mass (M$^+$ +1) = 431.4

2-(3-Chloro-phenyl)-3-(3,4-dimethoxy-phenyl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13m:

IR $\nu_{\text{max}}$ (KBr) 1660, 1694, 2924 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 3.48 (3H, s), 3.78 (2H, s), 3.86 (3H, s), 4.86 (2H, s), 6.39 (1H, d, J=4 Hz), 6.75 (1H, d, J=8 Hz), 6.79 (2H, s), 7.15-7.49 (7H, m), 7.86 (s, 1H), 9.86 (s, 1H); $^{13}$C NMR (400MHz, DMSO) $\delta_c$ 37.0, 53.5, 54.8, 55.4, 111.4, 112.1, 124.4, 124.6, 125.4, 125.4, 126.4, 126.6, 126.7, 127.2, 127.3, 127.8, 128.1, 128.6, 128.7, 131.6, 131.8, 135.6, 138.1, 148.1, 149.8, 165.7, 166.8; Mass (M$^+$ +1) = 461.9

3-(4-Fluoro-phenyl)-2-(1H-indol-3-yl)-N-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acrylamide 2.13n:

IR $\nu_{\text{max}}$ (KBr) 1674, 1698, 2924,3317 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 3.78 (s, 2H), 4.88 (s, 2H), 6.61 (1H, d, J=4 Hz), 6.78 (d, 1H, J=8Hz), 7.18-7.29 (5H, m), 7.38-7.42 (m, 3H), 7.51 (s, 1H), 7.87 (s, 1H), 9.89 (s, 1H), 11.01 (s, 1H); $^{13}$C NMR
(400MHz, DMSO) δc  23.9, 37.0, 53.5, 114.7, 115.4, 116.1, 119.9, 123.4, 124.5, 125.0, 125.4, 126.4, 127.2, 127.4, 127.7, 128.4, 131.4, 131.6, 131.9, 135.4, 136.9, 160.8, 163.3, 165.5, 166.8, 169.7; Mass (M^+ +1) =425.5

2-(2-Fluoro-phenyl)-N-(3-oxo-3,4-dihydro-1H-isouquinolin-2-yl)-3-phenyl-acrylamide

2.13o:

IR νmax (KBr) 1644, 1703, 3435 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δH 3.78 (s, 2H), 4.86 (s,2H), 7.05 (d, 2H, J=8Hz), 7.13-7.27 (3H, m), 7.28-7.32 (m, 2H), 7.37 (d, 2H, J=4Hz), 7.41-7.47 (m, 4H), 7.91 (s, 1H), 9.82 (s, 1H); ¹³C NMR (400MHz, DMSO) δc 36.7, 52.6, 115.4, 121.9, 124.3, 125.9, 127.2, 127.4, 127.8, 128.0, 128.5, 128.7, 129.2, 129.5, 132.4, 132.6, 135.2, 141.8, 156.9, 165.2, 174.2; Mass (M^+ +1) =386.4
II. G. Supporting information

Fig. 2.1 Mass spectrum of 2-Amino-1,4-dihydro-2H-isoquinolin-3-one

Fig. 2.2 IR spectrum of 2-Amino-1,4-dihydro-2H-isoquinolin-3-one
Fig. 2.3 $^1$H NMR spectrum of 2-Amino-1,4-dihydro-2$H$-isoquinolin-3-one

Fig. 2.4 $^{13}$C NMR spectrum of 2-Amino-1,4-dihydro-2$H$-isoquinolin-3-one
**Fig. 2.5** Mass spectrum of $N$-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

**Fig. 2.6** $^1$H-NMR spectrum of $N$-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide
Fig. 2.6.1 $^1$H-NMR (D$_2$O) spectrum of N-(3-Oxo-3,4-dihydro-$H$-isoquinolin-2-yl)-acetamide

Fig. 2.7. IR spectrum of N-(3-Oxo-3,4-dihydro-$H$-isoquinolin-2-yl)-acetamide
Fig. 2.8 $^{13}$C-NMR spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

Fig. 2.9 Mass spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide
Fig. 2.10. IR spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide

Fig. 2.11. $^1$H-NMR spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide
Fig. 2.11. $^1$H-NMR spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide

Fig. 2.12 $^{13}$C-NMR spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide
Fig. 2.13. Mass spectrum of 2-(4-Dimethylamino-phenyl)-N-(3-oxo-3,4-dihydro-1H-isquinolin-2-yl)-3-phenyl-acrylamide

Fig. 2.14. 1H-NMR spectrum of 2-(4-Dimethylamino-phenyl)-N-(3-oxo-3,4-dihydro-1H-isquinolin-2-yl)-3-phenyl-acrylamide
Fig. 2.14.1. $^1$H-NMR spectrum of 2-(4-Dimethylamino-phenyl)-N\(^\text{3}\)-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide

Fig. 2.15. IR spectrum of 2-(4-Dimethylamino-phenyl)-N\(^\text{3}\)-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-acrylamide
Fig. 2.16. $^{13}$C-NMR spectrum of 2-(4-Dimethylamino-phenyl)-$N$-(3-oxo-3,4-dihydro-$1H$-isoquinolin-2-yl)-3-phenyl-acrylamide

Fig. 2.16.1. $^{13}$C-NMR spectrum of 2-(4-Dimethylamino-phenyl)-$N$-(3-oxo-3,4-dihydro-$1H$-isoquinolin-2-yl)-3-phenyl-acrylamide
Fig. 2.17. Mass spectrum of $N\text{-}(3\text{-}O\text{xo\text{-}3,4\text{-}dihydro\text{-}1H\text{-}isoquinolin\text{in\text{-}2\text{-}yl\text{-}2\text{-}phenyl\text{-}acetamide}}$.

Fig. 2.18. IR spectrum of $N\text{-}(3\text{-}O\text{xo\text{-}3,4\text{-}dihydro\text{-}1H\text{-}isoquinolin\text{in\text{-}2\text{-}yl\text{-}2\text{-}phenyl\text{-}acetamide}}$.
Fig 2.19. $^1$H-NMR spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-phenyl-acetamide

Fig 2.19.1. $^1$H-NMR (D$_2$O) spectrum of N-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-phenyl-acetamide
Fig. 2.20 $^{13}$C-NMR spectrum of $N$-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-phenyl-acetamide
Fig. 2.21. Mass spectrum of \(N\)\(^{\circ}\)-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-thiophen-2-yl-acetamide

Fig. 2.22. IR spectrum of \(N\)\(^{\circ}\)-(3-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-thiophen-2-yl-acetamide
Fig. 2.23. $^1$H-NMR spectrum of $N$-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-thiophen-2-yl-acetamide

Fig. 2.23.1. $^1$H-NMR spectrum of $N$-(3-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-2-thiophen-2-yl-acetamide
Fig. 2.24. $^{13}$C-NMR spectrum of N-(3-Oxo-3,4-dihydro-1H-isquinolin-2-yl)-2-thiophen-2-yl-acetamide.
REFERENCES


