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DISSERTATION

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Jalli Venkataprasad

Student Number 14595701

Ph.D. SUPERVISOR

Professor. Akihiko Tsuge

Efficient synthesis of valuable heterocyclic compounds using multi-component reactions

Abstract

Synthetic protocols involving easy handling process, atom economy, ambient reaction conditions, short reaction times, inexpensive and less hazardous catalyst always have been attractive. Multi-component reaction is a chemical reaction, in which three or more starting materials react to form the product in an atom economy manner and ease of access to complex molecules in one-pot certainly belong to this class. A contemporary challenge in the world is environmental pollution. Multi component reactions are certainly one of the solutions for this problem due to the less release of chemical wastage compared with classical bicomponent reaction protocols and it is being considered as one of the green technology. I have also tried to use water as a reaction solvent to synthesize heterocyclic compounds because water is cheaper, green solvent and highly abundant in nature. I have synthesized various valuable heterocyclic compounds using multicomponent reactions.

Compounds possessing pyrrolo[2,3-c]pyridone backbone have been used to control the cell proliferation in breast cancer and p38 kinase inhibitors. Wang Le *et. al.,* also have reported molecules having pyrrolo[2,3-c]pyridone backbone as BRD4 receptor inhibitors to control breast cancer. Considering the importance of these molecules, we have demonstrated an efficient, mild and multicomponent protocol for the synthesis of novel heterocyclic compounds possessing pyrrolo[2,3-c]pyridone backbone by using Ugi four component reaction and post condensation of Ugi adduct. This method offers several advantages such as easy handling procedure, atom economy, short reaction time and huge molecular library can be synthesized by changing the substituents on four independent starting materials. In previous reported methods for pyrrolo[2,3-c]pyridones, expensive metal catalysts were used, where as in present method we used

inexpensive PTSA catalyst. Various anilines substituted with Iodo, bromo, chloro, methyl, methoxy at different positions on aniline were used in Ugi 4CR. And also phenyl glyoxylic acids substituted with methoxy, ethoxy, methyl and chloro were used in combinations with t-butyl and cyclohexyl isocyanides. In all cases the reaction proceeded smoothly and yielded the corresponding pyrrolo[2,3-c]pyridone derivatives in good to excellent yields. Considering these advantages we hope this methodology will be useful for medicinal chemists in drug discovery process. All the products were characterized by using NMR (1H and 13C) spectroscopy and FAB mass. One of the products was further characterized with X-ray diffraction analysis.

Coumarin analogs having both coumarin and furan heterocycles have gained the considerable attention of researchers due to their significant properties as anti-leishmania panamensis, dyes and fluorescent sensors. Coumarin analogs with furan heterocycle isolated from the plants origin such as microminutin, micromelin, psoralen, 8-methoxypsoralen have important properties in medicinal chemistry and bio photochemistry. It is well documented that by introducing a heteroaromatic substituent at 3-position the absorption and emission maxima of coumarin scaffold can be improved because of extended π conjugation and consequently their optoelectronic properties can be improved. Based on this phenomenon a variety of 3-heteroaryl coumarin derivatives have been synthesized and evaluated for their optoelectronic properties. Considering the broad range of applications of furyl coumarin derivatives, we have demonistrated an efficient and facile synthesis of 3-furyl coumarin derivatives by reaction of 4-chloro-3-formylcoumarin, secondary amines, dialkyl acetylenedicarboxylates and diversely substituted isocyanides using four component one pot reaction. All the products were isolated as yellow color fluorescent solids by column chromatography in quantitative yield and characterized with ^{1}H NMR, C^{13} NMR, IR and FAB mass.

Spiro compounds having dipyrrole namely Amathaspiramide A, Mytraginine psuedoindoxyl as shown below was proven to have prominent antiviral and anticancer properties. Very few reports were there in the literature for the synthesis of spiro [indole-2,2'-pyrroles] bearing spiro carbon at C-2 position. Considering this as an opportunity, we have developed an efficient and facile method for the synthesis of novel spiro[indole-2,2'-pyrroles] from N-methyl-3-isatin imines, t-butyl isocyanide and dialkyl acetylenedicarboxylate has been achieved by [3+2] cyclo addition reaction. The notable advantages of this protocol are operational simplicity, easily available starting materials, available diversity of each component, catalyst free and easy work procedure employed. We believed in this protocol will help in developing novel spiro heterocyclic compounds using C-2 carbon atom of isatin. All the products were purified by column chromatography as yellow solids and confirmed with ^{1}H NMR, ^{13}CNMR, FAB mass, IR. One of the compound was further confirmed with X-ray analysis.

Imidazo[1,2-a]pyridines have been valuable to organic and medicinal chemists due to the interesting structure and numerous applications in pharmaceutical Industry. The molecules possessing imidazo[1,2-a]pyridine core structure have been used as anticancer, anti-inflammatory, antibacterial, antiprotozonal and antiviral agents. Additionally, they were also used for the treatment of gastric disease and heart disease. They have been found in drug candidates such as Minodronic acid used for the treatment of osteoporosis, Zolpidem used for the treatment of insomnia and some brain disorders, Zolmidine used for the treatment of peptic ulcers and gastro esophageal reflux disease and Olprinone used for the treatment of acute heart failure. Considering these applications, New coumarin derivatives having imidazo[1,2-a]pyridine heterocycle moiety were synthesized by the condensation of 4-morpholino-3-formyl coumarin, diversely substituted 2-amino pyridine and isocyanides under catalyst free, water mediated

reaction conditions. All the products were characterized by using IR, NMR (1H and 13C) spectroscopy and HRMS spectrometry. Product 4b was further characterized with X-ray diffraction analysis. All the products have showed UV-Visible absorbance in between 234 nm to 248 nm and emissions were observed in between 412 nm to 544 nm.

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Chapter 1

Introduction

1. Overview of multicomponent reactions

Multi-component reaction is a chemical reaction, in which more than two starting materials react to form the product in an atom economy manner. Multi-component reactions belong to green chemistry. Using multi-component synthesis methods many complex heterocyclic molecules have been synthesized with ease, atom economy manner, therefore it is believed that multi-component methods reduce the chemical waste by reducing the number of chemical synthesis steps.[1-4] In the contemporary world one of the major global problems is environmental pollution. Pharmaceutical industry, which is dedicated for the drug discovery is one of the major polluter causing environmental pollution by releasing chemical waste into the environment. So, the major challenge for the pharmaceutical industries is to keep focus on developing sustainable, environmental benign chemical methods for the synthesis of pharmaceutically active compounds. In this context, multi-component reactions, in which chemical waste is considerably reduced by reducing the number of chemical synthesis steps, attracted the chemists. On the other hand, water mediated and catalyst free protocols for the synthesis valuable heterocyclic compounds have been attracting great attention because such methodologies also reduces the generation of organic waste, water is abundant, inexpensive, non toxic and environmental benign solvent.[5] Another notable advantage of multi-component reactions is that within short reaction time huge molecular library can be synthesized by varying substituent on each individual starting material. Because of these advantages, multi-component reactions have been extensively used in medicinal chemistry and materials chemistry.[6]

In this context Isocyanide based multi-component reactions such as passerini three component reaction,[7] Ugi four-component reaction and intramolecular Ugi four centre three-component reactions have been extensively used for the synthesis of various heterocyclic molecules.[8] In my graduation research, I have used Ugi four-component reaction followed by the condensation reaction for the synthesis of various substituted pyrrolo[2,3-c]pyridone analog derivatives.

Another notable isocyanide based multicomponent reaction is that addition of isocyanides to electron deficient alkynes such as dialkylacetylene dicarboxylate generated a 1,3-dipolar intermediate,[9-10] which was captured in situ by 1,2-dipolar nucleophiles such as carbonyl functional groups generated a furan heterocycles was extensively used for the synthesis of various substituted furan derivatives.[11] In my graduation research I have employed this strategy and synthesized various substituted 3-furyl coumarin derivatives and evaluated their photophysical properties.

Another important multicomponent reaction is Groebke-Blackburn-Bienayme reaction, involved one-pot condensations of aldehydes, isonitriles, and 2-aminopyridines generates the imidazo[1,2-a]pyridine derivatives in one pot. It is the well known and extensively used multicomponent reaction for the synthesis of imidazo[1,2-a]pyridine derivatives.[12-15] This reaction was proved to compatible to variety of aromatic and heteroaromatic aldehydes. In my graduation research, I have used 4-thiomorpholino-3-formyl coumarin as aldehyde component and performed Groebke-Blackburn-Bienayme type condensation to synthesisze imidazo[1,2-a]pyridine derivatives in aqueous medium under refluxing conditions.

2. Pyrrolo[2,3-c]pyridone derivatives

Pyrrolo[2,3-c]pyridone is a fused heterocyclic system possessing both pyrrole and pyridone. Compounds possessing pyrrolo[2,3-c]pyridone backbone have been used to control the cell proliferation in breast cancer and p38 kinase inhibitors.[16-17] Wang Le *et. al.,* also have reported molecules having pyrrolo[2,3-c]pyridone backbone as BRD4 receptor inhibitors to control breast cancer. Despite very important properties of these molecules in medicinal chemistry, not much research has been done for the development of efficient protocols to their synthesis. Vander Eycken *et. al.,* have reported the synthesis of pyrrolo[2,3-c]pyridinone with carbonyl group at slightly different position employing Ugi reaction followed by gold(I) catalyzed intramolecular hydroarylation using N-methyl-2-pyrrole carbaldehyde and N-methyl-3-pyrrole carbaldehyde.[18-19] However this methodology requires longer reaction times (72h including two steps) and expensive gold catalysts were employed for the cyclization step. As part of my graduation research, herein we established a simple procedure for the synthesis of pyrrolo[2,3-c]pyridones using Ugi reaction followed post cyclization of Ugi adduct under acidic conditions.

3. 3-Furyl coumarin derivatives

Coumarin analogs have been considered as important class of heterocyclic compounds due to their significant applications as anticoagulant,[20] antibacterial,[21] antihypertensive,[22] anti-tubercular,[23] antifungal,[24] anticancer,[25] HIV protease inhibition,[26] Laser dyes and fluorescent properties.[27] Similarly Furan ring is found in many pharmaceutically important substances like furanose form in carbohydrate, alkaloid pylocarpine and furacilin antibiotics. Coumarin analogs having both coumarin and furan heterocycles have gained the considerable attention of researchers due to their significant properties as anti-leishmania panamensis,[28] dyes and

fluorescent sensors.[29] Coumarin analogs with furan heterocycle isolated from the plants origin such as microminutin, micromelin, psoralen, 8-methoxypsoralen have important properties in medicinal chemistry and bio photochemistry.[30] It is well documented that by introducing a heteroaromatic substituent at 3-position the absorption and emission maxima of coumarin scaffold can be improved because of extended π conjugation and consequently their optoelectronic properties can be improved.[31] Based on this phenomena a variety of 3-heteroaryl coumarin derivatives have been synthesized and evaluated for their optoelectronic properties.[32] 3-furyl coumarin falls under this class with extended π conjugation. Thus the structural features and the wide spectrum of applications of furyl coumarin analogs have prompted the intense research by the chemists to develop novel, simple and efficient methods for their synthesis.

4. Spiro[indole-2,2'-pyrrole] derivatives

Spiro compounds having both indole and pyrrole nucleus is found to be the key structural unit in many natural products such as Spirotriprostrain A, Spirotriprostrain B and Horsfiline, which were proven to have anticancer activity. Spiro compounds having dipyrrole namely Amathaspiramide A, Mytraginine psuedoindoxyl as shown below was proven to have prominent antiviral and anticancer properties.[33]
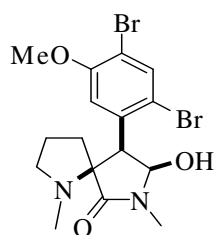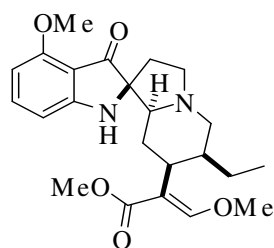
Amathaspiramide A   Mytraginine psuedoindoxyl

In my graduation research, we have demonstrated a novel three component [3+2] cyclo addition reaction for the synthesis of spiro [indole-pyrazoles] using C-2 carbon atom of isatin.

5. imidazo[1,2-c]pyridine derivatives possessing coumarin

imidazo[1,2-a]pyridines have been valuable to organic and medicinal chemists due to the interesting structure and numerous applications in pharmaceutical Industry.[34]The molecules possessing imidazo[1,2-a]pyridine core structure have been used as anticancer, anti-inflammatory, antibacterial, antiprotozonal and antiviral agents. Additionally, they were also used for the treatment of gastric disease and heart disease. They have been found in drug candidates such as Minodronic acid, Zolpidem, Zolmidine. In the present study we have used 4-morpholino-3-formyl coumarin as aldehyde component and performed Groebke-Blackburn-Bienayme type condensation to synthesisze imidazo[1,2-a]pyridine derivatives. As part of our ongoing research for the synthesis bioactive novel heterocycles using isocyanide based multicomponent reactions, here in we report the one-pot multicomponent synthesis of novel imidazo[1,2-a]pyridine derivatives having 4-hydroxy coumarin.

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Chapter 2

Efficient synthesis of novel pyrrolo[2,3-c]pyridone derivatives using Ugi for-component reaction followed by acid assisted condensation reaction

Abstract:

An efficient, mild and multicomponent protocol for the synthesis of novel heterocyclic compounds possessing pyrrolo[2,3-c]pyridone backbone was achieved by using Ugi 4CR and post condensation of Ugi adduct. This method offers many advantages such as easy handling procedure, atom economy, short reaction time and huge molecular library can be synthesized by changing the substituents on four independent starting materials. This methodology was also successfully employed to the electron deficient anilines and phenyl glyoxylic acids having CF3 group. All the products were characterized by using NMR (1H and 13C) spectroscopy and FAB mass. Product **6g** was further characterized with X-ray diffraction analysis.

1.   Introduction

Synthetic protocols involving easy handling process, atom economy, ambient reaction conditions, short reaction times, inexpensive and less hazardous catalyst always have been attractive. Multicomponent reaction is a chemical reaction, in which three or more starting materials react to form the product in an atom economy manner and ease of access to complex molecules in one-pot certainly belong to this class.[1-2] Ugi reaction is a

multicomponent reaction involving the condensation of aldehydes, amines, carboxylic acids and isocyanides to form the corresponding diamides adducts. Ugi multicomponent reaction have emerged as an important tool for the chemists because of its vast applications in chemistry.[3] Post condensation transformations of Ugi product also emerged as important tools to the chemists due to numerous applications in the synthesis of biologically important fused heterocyclic systems.[4-10] For example, the pharmacologically important 1,4-benzodiazepin-2-one analogs were achieved by using Ugi four component reaction followed by deprotection and cyclization reactions. Also various fused tetrazoles, peptidomimetic 3-carboxamide-1,4-benzodiazepin-5-ones were reported by using Ugi reaction and post modification of Ugi adduct.[11-13] Pyrrolo[2,3-c]pyridone is a fused heterocyclic system possessing both pyrrole and pyridone.

Compounds possessing pyrrolo[2,3-c]pyridone backbone have been used to control the cell proliferation in breast cancer and p38 kinase inhibitors.[14-15] Wang Le *et. al.,* also have reported molecules having pyrrolo[2,3-c]pyridone backbone as BRD4 receptor inhibitors to control breast cancer.[15] However not much research have been done for the development of efficient protocols to get these molecules. Vander Eycken *et. al.,* have reported the synthesis of pyrrolo[2,3-c]pyridinone with carbonyl group at slightly different position employing Ugi reaction followed by gold(I) catalyzed intramolecular hydroarylation using N-methyl-2-pyrrole carbaldehyde and N-methyl-3-pyrrole carbaldehyde.[16-17]However this methodology requires longer reaction times (72h including two steps) and expensive gold catalysts were employed for the cyclization step.

As part of our continuous research towards the development of efficient methods for the synthesis of valuable heterocyclic systems using multicomponent reactions, herein we

established a simple procedure for the synthesis of pyrrolo[2,3-c]pyridones using Ugi reaction followed post cyclization of Ugi adduct under acidic conditions. Earlier, we have reported the synthesis of novel spiro[indol-2,2'-pyrroles] and 3-furyl coumarin derivatives using isocyanide based multicomponent reactions.[18-19]

2. RESULTS AND DISCUSSION

We took 2-formyl pyrrole (1), t-Butyl isocyanide (2a), phenyl glyoxylic acid (3a) and 4-bromo aniline (4a) as model substrates to demonstrate Ugi 4-CR. The Ugi 4-CR was successfully performed by using 2-formyl pyrrole (1), t-Butyl isocyanide (2a), phcenyl glyoxylic acid (3a) and 4-bromo aniline (4a) in methanol at ambient temperature for 60 min.
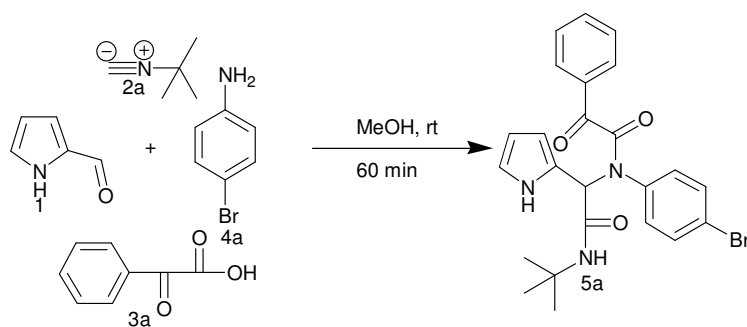
Scheme 1 Synthesis of Ugi adduct 5a

The precipitated white solid was filtered off, washed with ice cooled methanol (3 ml). This adduct was further investigated to synthesize pyrrolo[2,3-c]pyridone.

The Ugi adduct was further subjected to condensation under different reaction conditions in order to get the pyrrolo[2,3-c]pyridone analogs. The results were summarized in **Table 1**. While the reaction was conducted under basic reaction conditions using NaOH, Na_2CO_3, K_2CO_3 and NaH in methanol solvent using at 50^oC for 24h (**Table 1.** Entrys 1-4), traces of the expected product formation was observed. The condensation of Ugi adduct was smoothly happened under acidic reaction condition. When the PTSA

was employed as catalyst in methanol at 50°C for 1h, the yield of the product was 96% (**Table 1.** Entry 5). When 50 mol% PTSA was used as catalyst same amount of product formation was observed (**Table 1.** Entry 6).

Table 1. Optimization of the reaction conditions for condensation of the Ugi adduct[a]
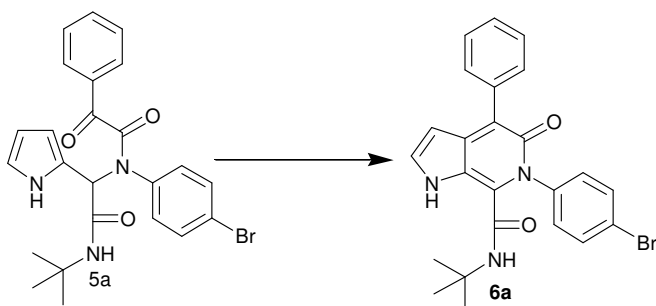
Entry	Catalyst	Reaction conditions	Time (h)	Yield (%)[b]
1	NaOH	MeOH	24	traces
2	K_2CO_3	MeOH	24	traces
3	Na_2CO_3	MeOH	24	traces
4	NaH	THF	24	traces
5	PTSA	MeOH	1	96
6	PTSA[c] (50mol%)	MeOH	1	96
7	PTSA[c] (10mol%)	MeOH	5	70
8	CH_3COOH	MeOH	1	60
9	TBAB	MeOH	1	10

[a]Reaction conditions: All the reactions were performed at 50°C and 1 equivalent of catalyst was loaded

[b]Isolated yields

On the other hand, When 10 mol% PTSA was used as catalyst 70% of product formation was observed in 5h (**Table 1.** Entry 7). Ugi adduct condensation was also occurred using acetic acid, TBAB. The yield of the product was 60 % and 10 % respectively (**Table 1.** Entrys 8, 9). From the optimization reaction conditions 50 mol% PTSA was found to be the best catalyst to carry out the condensation of Ugi adduct to pyrrolo[2,3-c]pyridone derivative with significantly short reaction time and quantitative yield. To explore the tolerance of these conditions, the reaction was further explored to different Ugi adducts synthesized by varying anilines, phenyl glyoxylic acids and isocyanides. The results were summarized in **Table 2**.

Table 2. Synthesis of pyrrolo[2,3-c]pyridone analogs
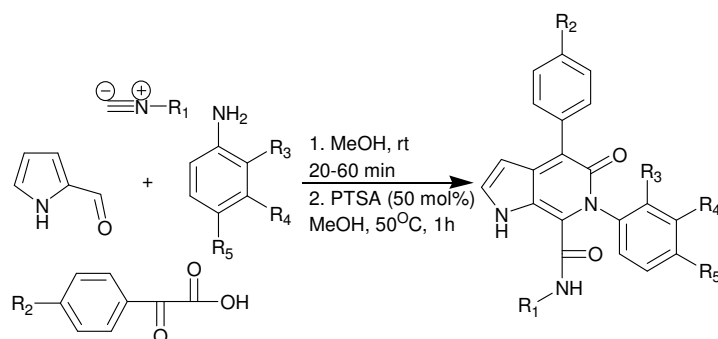
Entry	Ugi adduct (5a-5x)[a]	Pyrrolo[2,3-c]pyridone (6a-6z)[b]
1	**5a**, 90%	**6a**, 96%

2

5b, 88%

6b, 97%

3

5c, 84%

6c, 98%

4

5d, 84%

6d, 94%

5

5e, 80%

6e, 94%

6

5f, 93%

6f, 93%

7

5g, 98%

6g, 95%

8

5h, 90%

6h, 93%

9

5i, 92%

6i, 97%

10

5j, 86%

6j, 97%

11

5k, 90%

6k, 96%

12

5l, 84%

6l, 97%

13

5m, 82%

6m, 96%

14

5n, 88%

6n, 97%

15

5o, 90%

6o, 97%

16

5p, 89%

6p, 94%

17

5q, 82%

6q, 92%

18

5r, 84%

6r, 94%

19

5s, 90%

6s, 98%

20

5t, 86%

6t, 98%

21

5u, 85%

6u, 98%

22

5v, 85%

6v, 97%

23

5w, 86%

6w, 96%

24

5x, 82%

6x, 96%

25

5y, 86%

6y, 91%

26

5z, 81%

6z, 81%
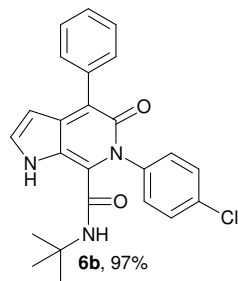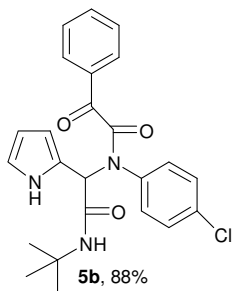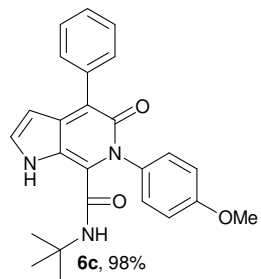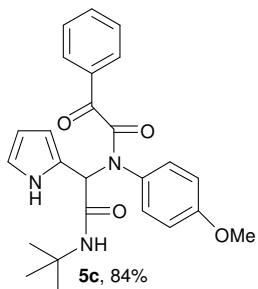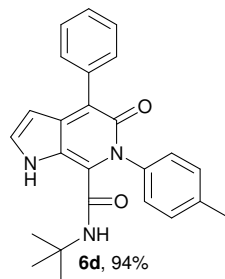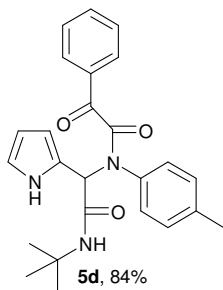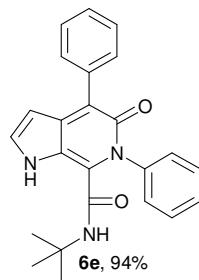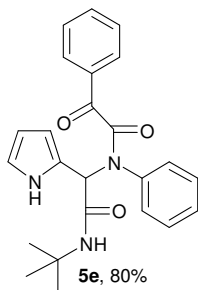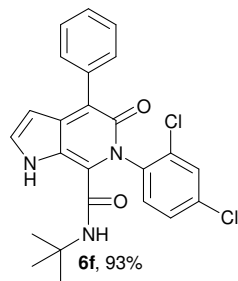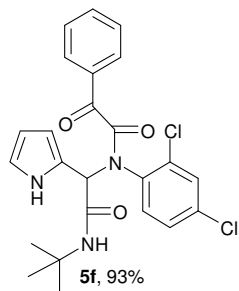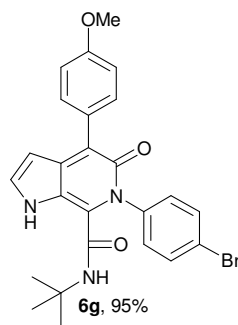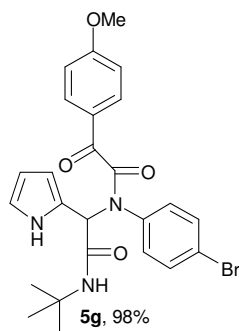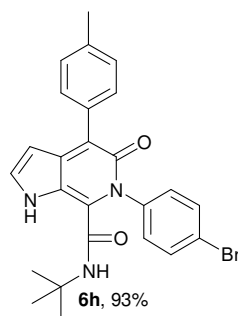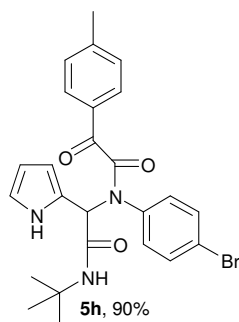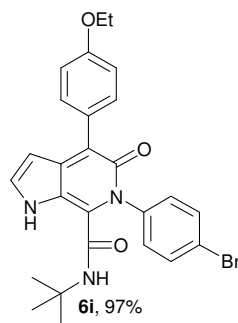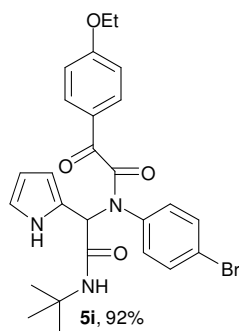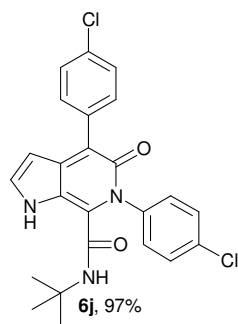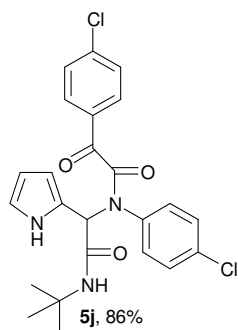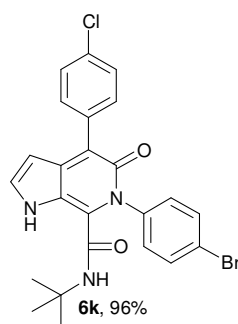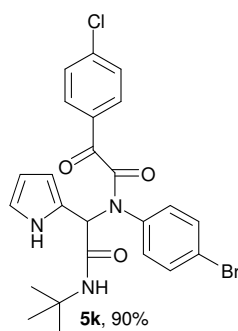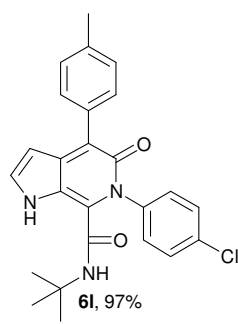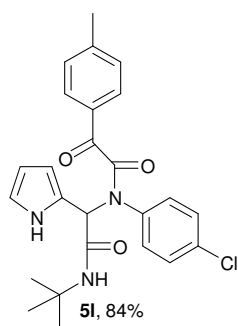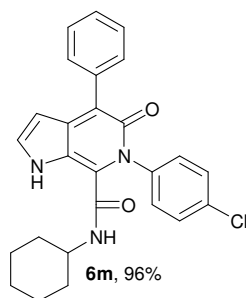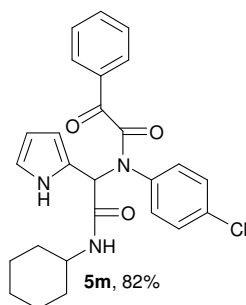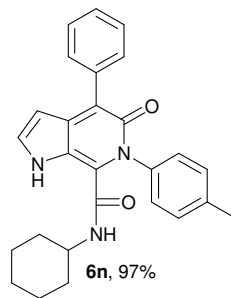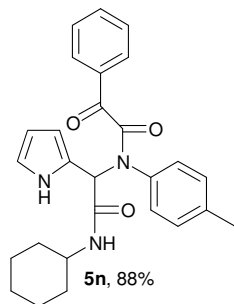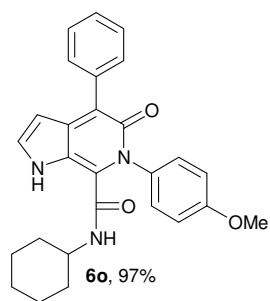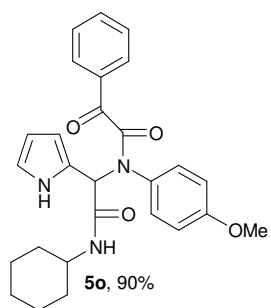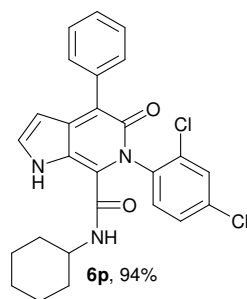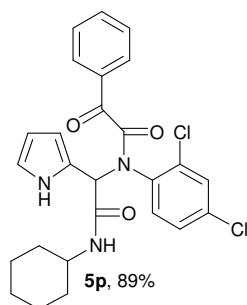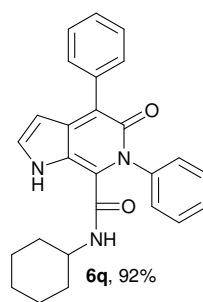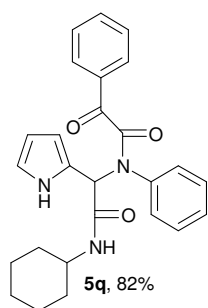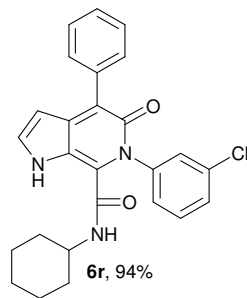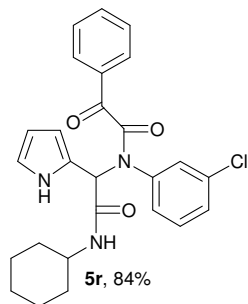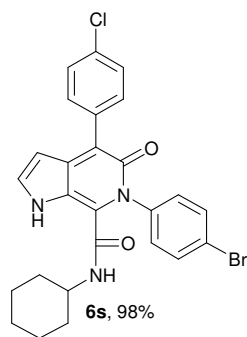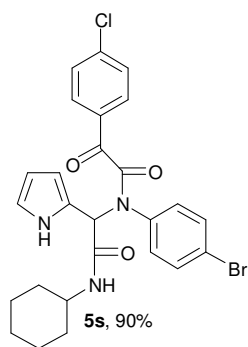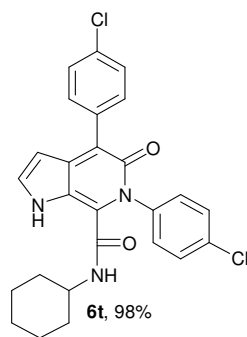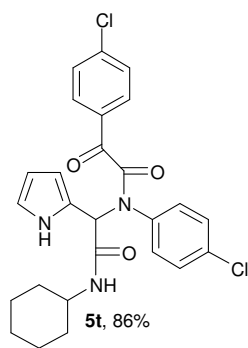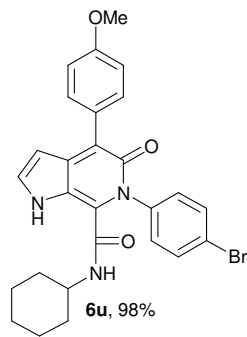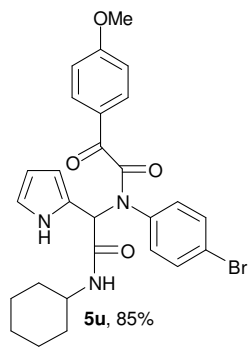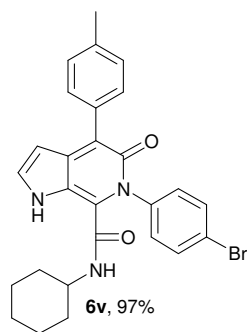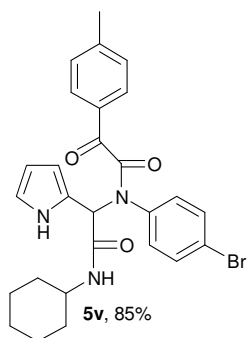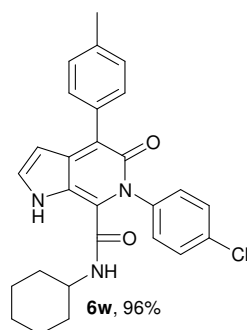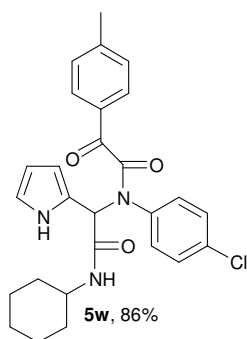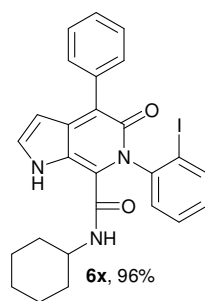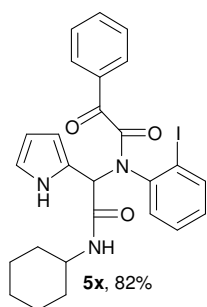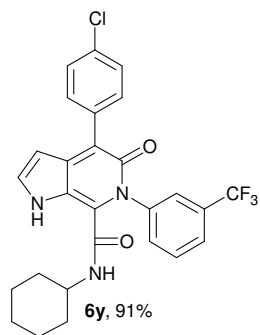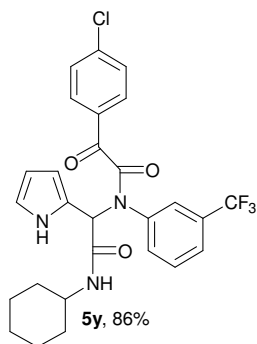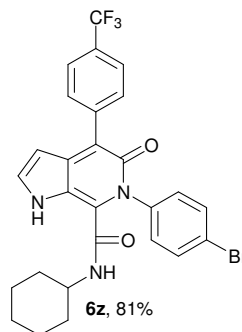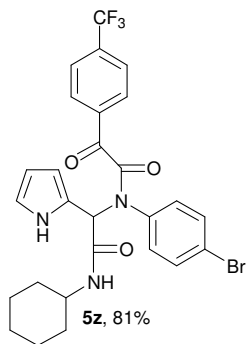
[a]yields refer to precipetated solids and all the reactions were run on 1 mmol scale

[b]yields refer to precipetated solids

Various anilines substituted with Iodo, bromo, chloro, methyl, methoxy at different positions on aniline were used in Ugi 4CR. And also phenyl glyoxylic acids substituted with methoxy, ethoxy, methyl and chloro were used in combinations with t-butyl and cyclohexyl isocyanides. We also have attempted the reaction using anilines and phenyl glyoxylic acids having electron-deficient aryl group, such as -ArNO2 and -ArCF3. When the reaction was performed with aniline having CF3 group and phenyl glyoxylic acid having CF3 group, the reaction proceeded smoothly and yielded the corresponding pyrrolo[2,3-c]pyridone derivatives in 91 % (Entry 25) and 81 % (Entry 26) respectively. However, when the reaction was performed with aniline having NO2, Ugi 4CR itself did not happened, may due to the presence of NO2 group imine formation was not happened. When the reaction was performed with phenyl glyoxylic acids having NO2 group, Ugi 4CR proceeded smoothly, but cyclization step was not happened even after refluxing for 14h. In all the cases Ugi 4CR and post condensation of Ugi adduct proceeded smoothly, resulted the corresponding Ugi adduct and pyrrolo[2,3-c]pyridone in quantitative yields (91-98%). First step (Ugi 4CR) of this protocol, all the products were precipitated as white color solids and second step that is PTSA catalyzed post condensation of

Ugi adduct, after the reaction on addition of water the final products were precipitated. All the products were characterized by using NMR (1H and 13C) spectroscopy and FAB mass spectrometry. One of the final product **6g** was further characterized with X-ray diffraction analysis. Good crystals suitable for X-ray diffraction analysis were obtained using slow evaporation method in MeOH solvent. The ortep diagram of the molecule **6g** is shown in Figure 1. One water molecule was found in crystal structure of final product **6g.** For clarity the water molecule was not shown in ortep diagram.
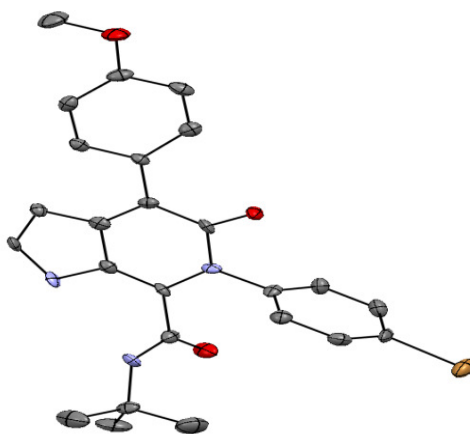
Figure 1. Ortep diagram of final product **6g**, ellipsoids were drawn with 50% probability

From the experimental results, the possible mechanism for the formation of pyrrolopyridone was depicted as follows. To explain the possible pathway for the formation of pyrrolopyridone, the Ugi adduct of the final compound **6a** was taken as model substrate. The possible path way for the formation of product **6a** was shown in **scheme 2.** Ugi adduct **5a** was activated by the addition of PTSA catalyst. Initially α-keto group of Ugi adduct was protonated and subsequently electrophilic addition on pyrrole ring generated the intermediate **I**. This intermediate **I**, undergoes dehydration under same catalytic condition yields the final product **6a**.
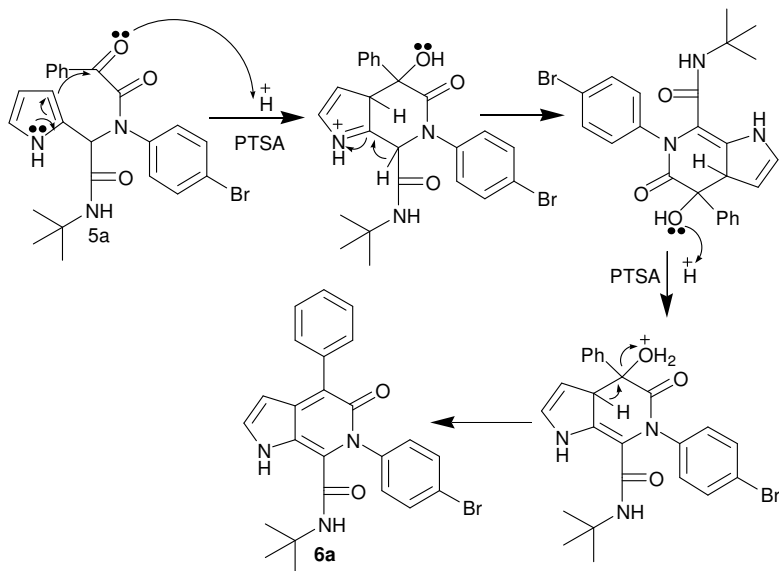
Scheme 1 Possible reaction mechanism for the synthesis of pyrrolo[2,3-c]pyridone

3.   Experimental section

General

 All reagents were purchased from TCI and Sigma Aldrich and used without further purification. All the products were characterized by ^{1}H NMR, C[13] NMR, IR, and Fab-Mass analysis. The NMR spectra were recorded on a Bruker AMX-500 MHz instrument at room temperature in DMSO-d_6 using TMS as an internal reference. Melting points were determined by AS ONE instrument. X-ray data for the compound **6g** was collected at room temperature using a Bruker Apex II KY CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Crystallographic data of **6g** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1484244 contains the supplementary crystallographic data for this paper.

Experimental procedure for the synthesis of Ugi adducts (5a-5x):

Pyrrole-2-carbaldehyde (1 mmol), corresponding aniline (1 mmol), substituted phenylglyoxylic acid (1.2 mmol) and isocyanide (1 mmol) were taken in 3 ml methanol. This mixture was stirred at room temperature for 20-60 min. During the stirring, white color precipitate formation was observed. The precipitated Ugi adducts were filtered off and washed with ice cooled methanol (2 ml) to get pure products. No precipitate formation was observed for Ugi adducts 5c, 5d, 5m and 5q. These Ugi adducts were purified by column chromatography using 20% EtOAc/Hexane. In other cases, the volatiles were removed under reduced pressure. All the products were isolated in good yields ranging from 80-93%.

Experimental procedure for the PTSA catalyzed synthesis of pyrrolo[2,3-c]pyridone derivatives (6a-6x):

Ugi adduct (1 mmol, 5a-5x) was taken in 5ml methanol. To this PTSA (50mol %) was added and heated at 50°C for 1h. Methanol was removed under reduced pressure and water was added to the reaction mixture. Filtered the yellow solid precipitated and thoroughly washed with water to remove PTSA catalyst completely. The yellow solid was run flash column chromatography using 5% DCM/MeOH. The yields are almost quantitative ranging from 91-98%.

2-(2-{1-[N-(4-bromophenyl)-2-oxo-2-phenylacetamido]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5a)

White solid, yield 90%; δ_H (500 MHz CDCl$_3$) 1.38 (9 H, s), 5.51 (1 H, s), 5.79 (1 H, s), 6.14 (1 H, m), 6.20 (1 H, m), 6.76 (1 H, m), 7.04 (2 H, m), 7.24 (2 H, m), 7.48 (2 H, t, J=6.4 Hz), 7.59 (1 H, t, J=5.9 Hz), 7.96 (2 H, m), 9.44 (1 H, s); δ_C (125 MHz, CDCl$_3$) 28.61, 51.91, 61.87, 108.21, 111.50, 120.13, 123.02, 123.61, 128.93, 129.79, 130.96, 132.27, 133.14, 134.67, 138.04, 167.06,

167.93, 189.84; HRMS-FAB(m/z) calcd for $C_{24}H_{24}BrN_3O_3$ ([M + H]$^+$) 481.3698, found 481.3690.

2-(2-{1-[N-(4-chlorophenyl)-2-oxo-2-phenylacetamido]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5b)

White solid, yield 88%; δ_H (500 MHz CDCl$_3$) 1.39 (9 H, s), 5.54 (1 H, s), 5.82 (1 H, s), 6.13 (1 H, m), 6.19 (1 H, m), 6.75 (1 H, m), 7.09 (4 H, m), 7.48 (2 H, t, J=6.2 Hz), 7.58 (1 H, m), 7.96 (2 H, m), 9.45 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 28.61, 51.91, 61.90, 108.30, 111.49, 120.12, 123.63, 128.93, 129.28, 129.77, 130.65, 133.15, 134.65, 134.84, 137.52, 167.09, 168.00, 189.86; HRMS-FAB(m/z) calcd for $C_{24}H_{24}ClN_3O_3$ ([M + H]$^+$) 436.9185, found 436.9193.

2-(2-{1-[N-(4-methoxyphenyl)-2-oxo-2-phenylacetamido]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5c)

White solid, yield 84%; δ_H (500 MHz CDCl$_3$) 1.39 (9 H, s), 3.67 (3 H, s), 5.57 (1 H, s), 5.89 (1 H, s), 6.12-6.14 (2 H, m), 6.59 (2 H, m), 6.73 (1 H, m), 7.03 (2 H, m), 7.45 (2 H, m), 7.56 (1 H, m), 7.96 (2 H, m), 9.46 (1 H, s); δ_C (125 MHz, CDCl$_3$) 28.62, 51.79, 55.28, 61.65, 108.07, 111.21, 114.10, 119.96, 124.03, 128.79, 129.69, 130.61, 131.24, 133.32, 134.38, 159.51, 167.34, 168.29, 190.26; HRMS-FAB(m/z) calcd for $C_{25}H_{27}N_3O_4$ ([M + H]$^+$) 432.4997, found 432.4988.

2-(2-{1-[N-(4-methylphenyl)-2-oxo-2-phenylacetamido]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5d)

White solid, yield 84%; δ_H (500 MHz CDCl$_3$) 1.38 (9 H, s), 2.20 (3 H, s), 5.50 (1 H, s), 5.82 (1 H, s), 6.13-6.20 (2 H, m), 6.75 (1 H, m), 6.91 (2 H, m), 7.01 (2 H, m), 7.43-7.47 (2 H, m), 7.55-7.58 (1 H, m), 7.98 (2 H, m), 9.51 (1 H, s); δ_C (125 MHz, CDCl$_3$) 21.95, 28.60, 51.88, 61.75, 108.27, 111.44, 120.08, 122.95, 123.68, 129.67, 129.91, 130.76, 130.92, 132.25, 145.91, 167.13, 168.11, 189.46; HRMS-FAB(m/z) calcd for $C_{25}H_{27}N_3O_3$ ([M + H]$^+$) 416.5003, found 416.5013.

2-(2-{1-[N-phenyl-2-oxo-2-phenylacetamido]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5e)

White solid, yield 80%; δ_H (500 MHz CDCl$_3$) 1.39 (9 H, s), 5.54 (1 H, s), 5.83 (1 H, s), 6.13-6.20 (2 H, m), 6.74 (1 H, m), 6.74-7.16 (5 H, m), 7.46 (2 H, m), 7.56 (1 H, m), 7.98 (2 H, m), 9.51 (1 H, s); δ_C (125 MHz, CDCl$_3$) 28.62, 51.82, 62.27, 119.97, 124.13, 128.74, 128.80, 129.09, 129.12, 129.76, 133.32, 134.41, 139.16, 167.18, 168.18, 190.05; HRMS-FAB(m/z) calcd for C$_{24}$H$_{25}$N$_3$O$_3$ ([M + H]$^+$) 402.4737, found 402.4744.

2-(2-{1-[N-(2,4-dichlorophenyl)-2-oxo-2-phenylacetamido]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5f)

White solid, yield 93%; δ_H (500 MHz CDCl$_3$) 1.37 (9 H, s), 5.54 (1 H, s), 5.97 (1 H, m), 6.06 (1 H, s), 6.68 (2 H, m), 7.00 (2 H, m), 7.11 (2 H, m), 7.46 (2 H, m), 7.57 (1 H, m), 7.97 (2 H, m); δ_C (125 MHz, CDCl$_3$) 28.63, 52.03, 65.02, 115.83, 122.86, 124.81, 128.87, 129.88, 131.73, 131.82, 132.87, 133.13, 134.60, 136.05, 156.54, 167.70, 168.14, 190.41; HRMS-FAB(m/z) calcd for C$_{25}$H$_{23}$Cl$_2$N$_3$O$_3$ ([M + H]$^+$) 471.3632, found 471.3625.

2-(2-{1-[N-(4-bromophenyl)-2-oxo-2-(4-methoxyphenylacetamido)]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5g)

White solid, yield 98%; δ_H (500 MHz CDCl$_3$) 1.38 (9 H, s), 3.87 (3 H,s), 5.48 (1 H, s), 5.78 (1 H, s), 6.75 (1 H, m), 6.94 (2 H, m), 7.06 (2 H, m), 7.26 (2 H, m), 7.96 (2 H, d, J=8.05 Hz), 9.48 (1 H, s); δ_C (125 MHz, CDCl$_3$) 28.61, 51.87, 55.60, 62.17, 108.26, 111.45, 114.29, 120.12, 122.87, 123.82, 126.29, 130.84, 132.24, 132.32, 138.43, 164.76, 167.15, 168.36, 188.46; HRMS-FAB(m/z) calcd for C$_{25}$H$_{26}$BrN$_3$O$_4$ ([M + H]$^+$) 511.3858, found 511.3866.

2-(2-{1-[N-(4-bromophenyl)-2-oxo-2-(4-methlphenylacetamido)]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5h)

White solid, yield 90%; δ_H (500 MHz CDCl$_3$) 1.38 (9 H, s), 2.10 (3 H, s), 5.53 (1 H, s), 5.82 (1 H, s), 6.13 (1 H, m), 6.19 (1 H, m), 6.74 (1 H, m), 7.03 (2 H, m), 7.26 (4 H, m), 7.86 (2 H, d, J=6.2 Hz), 9.46 (1 H, s); δ_C (125 MHz, CDCl$_3$) 21.95, 25.60, 51.88, 61.76, 108.27, 111.44, 120.08, 122.95, 123.68, 129.67, 129.91, 130.76, 130.92, 132.25, 145.91, 167.13, 168.11, 184.46; HRMS-FAB(m/z) calcd for C$_{25}$H$_{26}$BrN$_3$O$_3$ ([M + H]$^+$) 495.3964, found 495.3972.

2-(2-{1-[N-(4-bromophenyl)-2-oxo-2-(4-ethoxyphenylacetamido)]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5i)

White solid, yield 92%; δ_H (500 MHz CDCl$_3$) 1.38 (9 H, s), 1.45 (3 H, t), 4.07-4.11 (2 H, q), 5.53 (1 H, s), 5.83 (1 H, s), 6.12-6.16 (2 H, m), 6.74 (1 H, m), 6.92 (2 H, m), 7.05 (2 H, m), 7.26 (2 H, m), 7.94 (2 H, m), 9.49 (1 H, s); δ_C (125 MHz, CDCl$_3$) 14.62, 28.60, 51.86, 61.97, 63.95, 108.25, 111.42, 114.70, 120.08, 122.86, 123.77, 126.06, 130.91, 132.20, 132.31, 138.30, 164.23, 167.19, 168.39, 188.47; HRMS-FAB(m/z) calcd for C$_{26}$H$_{28}$BrN$_3$O$_4$ ([M + H]$^+$) 525.4223, found 525.4232.

2-(2-{1-[N-(4-chlorophenyl)-2-oxo-2-(4-chlorophenylacetamido)]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5j)

White solid, yield 86%; δ_H (500 MHz CDCl$_3$) 1.37 (9 H, s), 5.47 (1 H, s), 5.74 (1 H, s), 6.12-6.17 (2 H, m), 6.76 (1 H, m), 7.11 (4 H, m), 7.45 (2 H, m), 7.95 (2 H, m), 9.43 (1 H, s); δ_C (125 MHz, CDCl$_3$) 28.59, 51.95, 62.55, 108.37, 111.63, 120.26, 123.53, 129.38, 129.41, 130.53, 131.16, 131.52, 134.97, 137.58, 141.33, 166.90, 167.67, 188.70; HRMS-FAB(m/z) calcd for C$_{24}$H$_{23}$Cl$_2$N$_3$O$_3$ ([M + H]$^+$) 471.3632, found 471.3645.

(2-{1-[N-(4-bromophenyl)-2-oxo-2-(4-chlorophenylacetamido)]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5k)

White solid, yield 90%; δ_H (500 MHz CDCl$_3$) 1.37 (9 H, s), 5.44 (1 H, s), 5.71 (1 H, s), 6.77 (1 H, m), 7.06 (2 H, m), 7.28 (2 H, m), 7.46 (2 H, m), 7.96 (2 H, m), 9.42 (1 H, s); δ_C (125 MHz, CDCl$_3$) 28.59, 51.95, 62.64, 108.38, 111.65, 120.29, 123.14, 123.60, 129.39, 130.77, 131.19, 131.52, 132.44, 141.34, 166.87, 167.63, 188.65; HRMS-FAB(m/z) calcd for C$_{24}$H$_{23}$BrClN$_3$O$_3$ ([M + H]$^+$) 515.8145, found 515.8156.

2-{1-[N-(4-chlorophenyl)-2-oxo-2-(4-methylphenylacetamido)]-2-*tert*-butylamino-2-oxoethyl}-1*H*-pyrrol (5l)

White solid, yield 84%; δ_H (500 MHz CDCl$_3$) 1.38 (9 H, s), 2.40 (3 H, s), 5.57 (1 H, s), 5.86 (1 H, s), 6.12-6.18 (2 H, m), 6.76 (1 H, m), 7.08 (4 H, m), 7.25-7.26 (2 H, m), 7.86 (2 H, m), 9.46 (1 H, s); δ_C (125 MHz, CDCl$_3$) 21.92, 28.60, 51.88, 61.59, 108.27, 111.41, 120.03, 123.65, 129.66, 129.89, 130.69, 130.76, 134.76, 137.49, 145.90, 167.17, 168.16, 189.52; HRMS-FAB(m/z) calcd for C$_{25}$H$_{26}$ClN$_3$O$_3$ ([M + H]$^+$) 450.9451, found 450.9442.

2-{1-[N-(4-chlorophenyl)-2-oxo-2-phenylacetamido]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5m)

White solid, yield 82%; δ_H (500 MHz CDCl$_3$) 1.11-1.94 (10 H, m), 3.87 (1 H, m), 5.58 (1 H, s), 5.81 (1 H, d), 6.12-6.17 (2 H, m), 6.77 (1 H, m), 7.09-7.14 (4 H, m), 7.45-7.48 (2 H, m), 7.58 (1 H, m), 7.99 (2 H, m), 9.51 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.68, 25.42, 32.74, 48.97, 61.91, 108.31, 111.65, 120.29, 123.52, 128.93, 129.33, 129.83, 130.63, 133.07, 134.68, 134.86, 137.66, 166.82, 168.15, 189.97; HRMS-FAB(m/z) calcd for C$_{26}$H$_{26}$ClN$_3$O$_3$ ([M + H]$^+$) 462.9558, found 462.9548.

2-{1-[N-(4-methylphenyl)-2-oxo-2-phenylacetamido]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5n)

White solid, yield 97%; δ_H (500 MHz CDCl$_3$) 1.12-1.92 (10 H, m), 2.20 (3 H, s), 3.89 (1 H, m), 5.49 (1 H, s), 5.74 (1 H, d), 6.13-6.19 (2 H, m), 6.78-6.94 (3 H, m), 7.05-7.07 (2 H, m), 7.44-7.54 (2 H, m), 7.54-7.57 (1 H, m), 8.02 (2 H, m), 9.55 (1 H, s); δ_C (125 MHz, CDCl$_3$) 21.06, 24.68, 25.45, 32.76, 48.85, 62.48, 108.08, 111.45, 120.12, 124.17, 128.76, 128.78, 129.81, 129.86, 133.29, 134.38, 136.78, 138.82, 166.95, 168.41, 190.21; HRMS-FAB(m/z) calcd for C$_{27}$H$_{29}$N$_3$O$_3$ ([M + H]$^+$) 442.5376, found 442.5362.

2-{1-[N-(4-methoxyphenyl)-2-oxo-2-methylphenylacetamido]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5o)

White solid, yield 90%; δ_H (500 MHz CDCl$_3$) 1.12-1.67 (10 H, m), 3.67 (3 H, s), 3.87 (1 H, m), 5.55 (1 H, s), 5.81 (1 H, s), 6.19 (2 H, m), 6.62 (2 H, m), 6.77 (1 H, m), 7.08 (2 H, m), 7.45 (2 H, m), 7.57 (1 H, m), 7.98 (2 H, m), 9.51 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.69, 25.45, 32.78, 48.84, 55.29, 62.05, 108.09, 111.40, 114.18, 120.00, 124.00, 128.80, 129.78, 130.52, 133.26, 134.40, 159.52, 167.05, 168.47, 190.36; HRMS-FAB(m/z) calcd for C$_{27}$H$_{29}$N$_3$O$_4$ ([M + H]$^+$) 458.5370, found 458.5360.

2-{1-[N-(2,4-chlorophenyl)-2-oxo-2-phenylacetamido]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5p)

White solid, yield 89%; δ_H (500 MHz CDCl$_3$) 1.14-1.92 (10 H, m), 3.86 (1 H, m), 5.54 (1 H, s), 5.97 (1 H, m), 6.06 (1 H, d), 6.68-6.70 (2 H, m), 7.00-7.02 (2 H, m), 7.09-7.11 (2 H, m), 7.43-7.46 (2 H, m), 7.55-7.58 (1 H, m), 7.97 (2 H, m), 9.46 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.67, 25.40, 32.72, 49.04, 65.02, 115.83, 122.86, 124.81, 128.87, 129.88, 131.73, 131.82, 132.87, 133.13, 134.60, 136.05, 156.54, 167.70, 168.14, 190.41; HRMS-FAB(m/z) calcd for C$_{26}$H$_{25}$Cl$_2$N$_3$O$_3$ ([M + H]$^+$) 497.4005, found 497.4017.

2-{1-[N-phenyl-2-oxo-2-phenylacetamido]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5q)

White solid, yield 82%; δ_H (500 MHz CDCl$_3$) 1.14-1.93 (10 H, m), 3.88 (1 H, m), 5.53 (1 H, s), 5.77 (1 H, d), 6.13-6.19 (2 H, m), 6.78 (1 H, m), 7.13-7.20 (5 H, m), 7.43-7.46 (2 H, m), 7.54-7.57 (1 H, m), 8.00 (2 H, m), 9.57 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.68, 25.44, 32.75, 48.89, 62.47, 108.13, 111.54, 120.19, 124.05, 128.77, 128.81, 129.04, 129.17, 129.83, 133.23, 134.45, 139.44, 166.92, 168.34, 190.16; HRMS-FAB(m/z) calcd for C$_{26}$H$_{27}$N$_3$O$_3$ ([M + H]$^+$) 428.5110, found 428.5122.

2-{1-[N-(3-chlorophenyl)-2-oxo-2-phenylacetamido]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5r)

White solid, yield 84%; δ_H (500 MHz CDCl$_3$) 1.12-1.92 (10 H, m), 3.87 (1 H, m), 5.48 (1 H, s), 5.73 (1 H, d), 6.14-6.21 (2 H, m), 6.80 (1 H, m), 7.05-7.16 (3 H, m), 7.26 (1 H, m), 7.46-7.49 (2 H, m), 7.57-7.59 (1 H, m), 8.02 (2 H, m), 9.54 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.67, 25.42, 32.73, 49.00, 62.66, 108.32, 111.80, 120.40, 123.63, 127.43, 128.93, 129.12, 129.21, 129.85, 130.03, 133.09, 134.68, 140.69, 166.69, 168.21, 189.86; HRMS-FAB(m/z) calcd for C$_{26}$H$_{26}$ClN$_3$O$_3$ ([M + H]$^+$) 462.9558, found 462.9568.

2-{1-[N-(4-bromophenyl)-2-oxo-2-(4-chlorophenylacetamido)]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5s)

White solid, yield 90%; δ_H (500 MHz CDCl$_3$) 1.35-1.91 (10 H, m), 3.85 (1 H, m), 5.48 (1 H, s), 5.71 (1 H, d), 6.14-6.17 (2 H, m), 6.79 (1 H, m), 7.07-7.08 (2 H, m), 7.26-7.30 (2 H, m), 7.44-7.46 (2 H, m), 7.98 (2 H, m), 9.47 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.67, 25.40, 32.72, 49.04, 62.53, 108.38, 111.82, 120.46, 123.18, 123.44, 129.41, 130.73, 131.23, 131.44, 132.50, 138.34, 141.37, 167.75, 168.65, 188.74; HRMS-FAB(m/z) calcd for C$_{26}$H$_{25}$BrClN$_3$O$_3$ ([M + H]$^+$) 541.8158, found 541.8166.

2-{1-[N-(4-chlorophenyl)-2-oxo-2-(4-chlorophenylacetamido)]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5t)

White solid, yield 86%; δ_H (500 MHz CDCl$_3$) 1.11-1.91 (10 H, m), 3.87 (1 H, m), 5.49 (1 H, s), 5.73 (1 H, d), 6.13-6.17 (2 H, m), 6.79 (1 H, m), 7.13 (4 H, m), 7.46 (2 H, m), 7.98 (2 H, m), 9.47 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.67, 25.40, 32.72, 49.03, 62.51, 108.30, 111.80, 120.43, 123.45, 129.40, 129.48, 130.47, 131.22, 131.45, 135.01, 137.74, 141.36, 166.68, 167.81, 188.78; HRMS-FAB(m/z) calcd for C$_{26}$H$_{25}$Cl$_2$N$_3$O$_3$ ([M + H]$^+$) 497.4005, found 497.4020.

2-{1-[N-(4-bromophenyl)-2-oxo-2-(4-methoxyphenylacetamido)]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5u)

White solid, yield 85%; δ_H (500 MHz CDCl$_3$) 1.10-1.92 (10 H, m), 3.85 (1 H, m), 3.86 (3 H, s), 5.51 (1 H, s), 5.76 (1 H, d), 6.13-6.16 (2 H, m), 6.78 (1 H, m), 6.93 (2 H, m), 7.09 (2 H, m), 7.25 (2 H, m), 7.99 (2 H, m), 9.53 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.68, 25.42, 32.72, 48.96, 55.58, 62.21, 108.27, 111.62, 114.31, 120.30, 122.90, 123.69, 126.21, 130.80, 132.30, 132.39, 138.58, 164.78, 166.90, 168.52, 188.57; HRMS-FAB(m/z) calcd for C$_{27}$H$_{28}$BrN$_3$O$_4$ ([M + H]$^+$) 537.4330, found 537.4342.

2-{1-[N-(4-bromophenyl)-2-oxo-2-(4-methylphenylacetamido)]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5v)

White solid, yield 85%; δ_H (500 MHz CDCl$_3$) 1.16-1.91 (10 H, m), 2.40 (3 H, s), 3.86 (1 H, m), 5.54 (1 H, s), 5.78 (1 H, d), 6.13-6.18 (2 H, m), 6.77 (1 H, m), 7.06 (2 H, m), 7.25 (4 H, m), 7.89 (2 H, m), 9.50 (1 H, s); δ_C (125 MHz, CDCl$_3$) 21.96, 24.68, 25.42, 32.72, 48.94, 61.89, 108.28, 111.60, 120.27, 122.98, 123.61, 129.69, 129.97, 130.68, 130.86, 132.32, 138.36, 145.95, 166.84, 168.27, 189.56; HRMS-FAB(m/z) calcd for C$_{27}$H$_{28}$BrN$_3$O$_3$ ([M + H]$^+$) 521.4336, found 521.4321.

2-{1-[N-(4-chlorophenyl)-2-oxo-2-(4-methylphenylacetamido)]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol **(5w)**

White solid, yield 86%; δ_H (500 MHz CDCl$_3$) 1.12-1.93 (10 H, m), 2.40 (3 H, s), 3.86 (1 H, m), 5.57 (1 H, s), 5.82 (1 H, d), 6.12-6.17 (2 H, m), 6.76 (1 H, m), 7.13 (4 H, m), 7.25 (2 H, m), 7.89 (2 H, m), 9.51 (1 H, s); δ_C (125 MHz, CDCl$_3$) 21.96, 24.69, 25.43, 32.74, 48.94, 61.75, 108.27, 111.58, 120.23, 123.58, 129.29, 129.68, 129.95, 130.62, 130.68, 134.78, 137.73, 145.93, 166.88, 168.33, 189.62; HRMS-FAB(m/z) calcd for C$_{27}$H$_{28}$ClN$_3$O$_3$ ([M + H]$^+$) 476.9823, found 476.9837.

2-{1-[N-(2-iodophenyl)-2-oxo-2-(4-methylphenylacetamido)]-2-cyclohexylamino-2-oxoethyl}-1*H*-pyrrol (5x)

White solid, yield 82%; δ_H (500 MHz CDCl$_3$) 1.11-1.95 (10 H, m), 3.86 (1 H, m), 5.53 (1 H, s), 5.76 (1 H, d), 6.13-6.18 (2 H, m), 6.78 (1 H, m), 7.06-7.08 (2 H, m), 7.25-7.27 (2 H, m), 7.45-7.48 (2 H, m), 7.57-7.60 (1 H, m), 7.99 (2 H, m), 9.49 (1 H, s); δ_C (125 MHz, CDCl$_3$) 24.68, 25.42, 32.75, 48.97, 62.09, 108.32, 111.69, 120.34, 123.05, 123.56, 128.95, 129.86, 130.86, 132.38, 133.07, 134.70, 138.34, 166.77, 168.11, 184.91; HRMS-FAB(m/z) calcd for C$_{26}$H$_{26}$IN$_3$O$_3$ ([M + H]$^+$) 554.4075, found 554.4087.

N-(tert-Butyl)-4-phenyl-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6a)

Yellow solid, yield 96%, mp 177-181°C; δ_H (500 MHz DMSO-d$_6$) 1.08 (9 H, s), 6.16 (1 H, s), 7.27-7.68 (10 H, m), 8.34 (1 H, d, J= 8.01 Hz), 10.81 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 28.24, 51.62, 98.81, 113.53, 121.48, 121.92, 126.84, 128.17, 128.32, 130.09, 131.68, 131.71, 137.29, 139.41, 139.82, 142.0, 157.65, 159.90; HRMS-FAB(m/z) calcd for C$_{24}$H$_{22}$BrN$_3$O$_2$ ([M + H]$^+$) 462.0915, found 462.0925.

N-(tert-Butyl)-4-phenyl-6-(4-chlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6b)

Yellow solid, yield 97%, mp 173-177°C; δ_H (500 MHz DMSO-d_6) 1.07 (9 H, s), 6.16 (1 H, s), 7.26-7.65 (10 H, m), 8.34 (1 H, s), 10.80 (1 H, s); δ_C (125 MHz, DMSO-d_6) 28.24, 51.61, 98.79, 121.88, 126.83, 128.16, 128.38, 128.74, 130.08, 131.35, 133.01, 137.31, 138.97, 139.86, 141.99, 157.73, 159.91; HRMS-FAB(m/z) calcd for $C_{24}H_{22}ClN_3O_2$ ($[M + H]^+$) 418.1435, found 418.1445.

N-(tert-Butyl)-4-phenyl-6-(4-methoxyphenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6c)

Yellow solid, yield 98%, mp 162-164°C; δ_H (500 MHz DMSO-d_6) 1.07 (9 H, s), 3.8 (3 H, s), 6.25 (1 H, s), 7.02-7.81 (9 H, m), 8.35 (1 H, d, J= 8.01 Hz), 11.34 (1 H, s); δ_C (125 MHz, DMSO-d_6) ; 28.33, 51.76, 55.93, 99.76, 114.06, 122.60, 125.97, 127.41, 128.54, 130.31, 130.35, 131.97, 136.30, 138.12, 140.33, 141.80, 146.14, 159.38, 159.67; HRMS-FAB(m/z) calcd for $C_{25}H_{25}N_3O_3$ ($[M + H]^+$) 414.1924, found 414.1935.

N-(tert-butyl)-4-phenyl-6-(4-methylphenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6d)

Yellow solid, yield 98%, mp 156-160°C; δ_H (500 MHz DMSO-d_6) 1.05 (9 H, s), 2.38 (3 H, s), 6.23 (1 H, s), 6.23-7.76 (10 H, m), 8.31 (1 H, d, J= 8.05 Hz), 11.16 (1 H, s); δ_C (125 MHz, DMSO-d_6) 21.25, 28.27, 51.67, 99.43, 113.83, 122.41, 125.97, 127.21, 128.40, 128.53, 129.04, 129.21, 129.72, 130.14, 136.66, 137.0, 138.10, 138.21, 140.08, 141.79, 156.02, 159.55; FAB: HRMS-FAB(m/z) calcd for $C_{25}H_{25}N_3O_2$ ($[M + H]^+$) 398.1942, found 398.1950.

N-(tert-Butyl)-4-phenyl-6-phenyl-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6e)

Yellow solid, yield 97%, mp 150-154°C; δ_H (500 MHz DMSO-d_6) 1.04 (9 H, s), 6.30 (1 H, s), 7.27-7.66 (11 H, m), 8.26 (1 H, d, J= 8.15 Hz), 10.94 (1 H, s); δ_C (125 MHz, DMSO-d_6) ; 28.27, 51.50, 98.69, 113.40, 121.78, 126.72, 128.12, 128.32, 128.67, 129.54, 130.09, 137.53, 139.49, 140.12, 141.80, 157.90, 160.02; FAB: HRMS-FAB(m/z) calcd for $C_{25}H_{25}N_3O_2$ ([M + H]$^+$) 384.1838, found 384.1849.

N-(tert-Butyl)-4-phenyl-6-(2,4-dichlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6f)

Yellow solid, yield 97%, mp 182-184°C; δ_H (500 MHz DMSO-d_6) 1.14 (9 H, s), 6.20 (1 H, s), 7.26-7.79 (9 H, m), 8.43 (1 H, d, J= 8.10 Hz), 10.80 (1 H, s); δ_C (125 MHz, DMSO-d_6) ; 28.24, 51.82, 98.84, 113.53, 121.96, 126.91, 127.81, 127.94, 128.19, 129.49, 130.03, 132.35, 133.98, 134.64, 137.09, 137.29, 140.21, 142.44, 157.17, 159.46; HRMS-FAB(m/z) calcd for $C_{24}H_{21}ClN_3O_2$ ([M + H]$^+$) 353.3480, found 353.3488.

N-(tert-Butyl)-4-(4-methoxyphenyl)-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6g)

Yellow solid, yield 98%, mp 165-168°C; δ_H (500 MHz DMSO-d_6) 1.08 (9 H, s), 3.79 (3 H, s), 6.16 (1 H, s), 6.96-7.68 (9 H, m), 8.30 (1 H, d, J= 8.01 Hz), 10.72 (1 H, s); δ_C (125 MHz, DMSO-d_6) 28.24, 51.58, 55.52, 98.84, 113.62, 121.38, 122.04, 127.55, 129.48, 131.21, 131.68, 139.45, 139.54, 141.60, 157.80, 158.25, 160.04; HRMS-FAB(m/z) calcd for $C_{25}H_{24}BrN_3O_3$ ([M + H]$^+$) 493.3805, found 493.3816.

N-(tert-Butyl)-4-(4-methylphenyl)-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6h)

Yellow solid, yield 96% mp 190-194°C; δ_H (500 MHz DMSO-d_6) 1.07 (9 H, s), 2.36 (3 H, s), 6.26 (1 H, s), 7.20-7.67 (9 H, m), 8.31 (1 H, d, J= 8.01 Hz), 10.74 (1 H, s); δ_C (125 MHz,

DMSO-d$_6$) 21.37, 28.21, 51.59, 98.85, 113.68, 121.41, 121.96, 127.90, 128.75, 129.94, 131.68, 134.34, 135.94, 139.50, 139.58, 141.83, 157.76, 159.99; HRMS-FAB(m/z) calcd for C$_{25}$H$_{24}$BrN$_3$O$_3$ ([M + H]$^+$) 477.3805, found 477.3811.

N-(tert-butyl)-4-(4-ethoxyphenyl)-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6i)

Yellow solid, yield 97%, mp 163-167°C; δ_H (500 MHz DMSO-d$_6$) 1.07 (9 H, s), 1.36 (2 H, t, J= 6.95 Hz), 4.08 (2 H, q, J= 5.55 Hz), 6.16 (1 H, s), 6.94-7.69 (9 H, m), 8.30 (1 H, d, J= 8.05 Hz), 10.71 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 15.20, 28.24, 51.57, 98.86, 113.63, 114.08, 121.37, 122.04, 127.51, 129.35, 131.21, 131.67, 139.42, 139.55, 141.57, 157.51, 157.80. 160.04; HRMS-FAB(m/z) calcd for C$_{25}$H$_{24}$BrN$_3$O$_3$ ([M + H]$^+$) 507.4071, found 507.4082.

N-(tert-Butyl)-4-(4-chlorophenyl)-6-(4-chlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6j)

Yellow solid, yield 97%, mp 239-242°C; δ_H (500 MHz DMSO-d$_6$) 1.07 (9 H, s), 6.21 (1 H, s), 7.39-7.69 (9 H, m), 8.39 (1 H, s), 10.94 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 28.24, 51.68, 98.73, 111.89, 121.87, 125.97, 128.23, 128.51, 128.99, 131.32, 131.80, 133.16, 136.11, 138.75, 140.24, 141.92, 157.41, 159.72; HRMS-FAB(m/z) calcd for C$_{24}$H$_{21}$ClN$_3$O$_2$ ([M + H]$^+$) 453.3480, found 453.3492.

N-(tert-butyl)-4-(4-chlorophenyl)-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6k)

Yellow solid, yield 96%, mp 266-270°C; δ_H (500 MHz DMSO-d$_6$) 1.07 (9 H, s), 6.20 (1 H, s), 7.30-7.69 (9 H, m), 8.35 (1 H, d, J= 8.05 Hz), 10.90 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 28.23, 51.66, 98.66, 111.86, 121.58, 121.83, 128.21, 128.85, 131.07, 131.66, 131.74, 136.18, 139.25,

140.20, 141.91, 157.51, 159.76; HRMS-FAB(m/z) calcd for $C_{24}H_{21}BrClN_3O_2$ ([M + H]$^+$)
497.7993, found 497.7999.

N-(tert-butyl)-4-(4-methylphenyl)-6-(4-chlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6l)

Yellow solid, yield 97%, mp 129-132°C; δ_H (500 MHz DMSO-d$_6$) 1.07 (9 H, s), 2.51 (3 H, s),
6.15 (1 H, s), 7.20-7.61 (9 H, m), 8.31 (1 H, d, J= 8.05 Hz), 10.74 (1 H, s); δ_C (125 MHz,
DMSO-d$_6$) 21.35, 28.24, 51.59, 98.85, 113.66, 121.94, 128.72, 128.75, 129.94, 131.35, 132.96,
134.34, 135.95, 139.04, 139.59, 140.12, 141.83, 157.81, 159.99; HRMS-FAB(m/z) calcd for
$C_{25}H_{24}ClN_3O_2$ ([M + H]$^+$) 432.9298, found 432.9291.

N-cyclohexyl-4-phenyl-6-(4-chlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6m)

Yellow solid, yield 96%, mp 190-194°C; δ_H (500 MHz DMSO-d$_6$) 0.95-1.57 (10 H, m), 3.49 (1
H, sex), 6.15 (1 H, d, *J*= 1.81 Hz), 7.26-7.65 (10 H, m), 8.65 (1 H, d, J= 8.05 Hz), 10.94 (1 H, s);
δ_C (125 MHz, DMSO-d$_6$) 24.59, 25.54, 31.80, 48.91, 98.73, 113.47, 121.89, 126.83, 128.03,
128.16, 128.76, 130.08, 131.28, 133.11, 137.30, 138.77, 139.75, 141.88, 157.78, 159.63; HRMS-
FAB(m/z) calcd for $C_{26}H_{24}ClN_3O_2$ ([M + H]$^+$) 444.9405, found 444.9413.

N-cyclohexyl-4-phenyl-6-(4-methylphenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6n)

Yellow solid, yield 97%, mp 169-173°C; δ_H (500 MHz DMSO-d$_6$) 0.94-1.56 (10 H, m), 2.35 (3
H, s), 3.47 (1 H, m), 6.15 (1 H, d, *J*= 1.81 Hz), 7.19-7.65 (9 H, m), 8.57 (1 H, d, J= 8.05 Hz),
10.86 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 21.19, 24.61, 25.56, 31.83, 48.22, 98.61, 113.30,
121.80, 126.69, 128.11, 128.53, 129.10, 129.11, 130.09, 137.34, 137.59, 139.33, 141.61, 157.96,
159.75; HRMS-FAB(m/z) calcd for $C_{27}H_{27}N_3O_2$ ([M + H]$^+$) 424.5223, found 424.5231.

N-cyclohexyl-4-phenyl-6-(4-methoxyphenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6o)

Yellow solid, yield 97%, mp 150-154°C; δ_H (500 MHz DMSO-d_6) 0.95-1.59 (10 H, m), 3.47 (1 H, m), 3.79 (3 H. s), 6.15 (1 H, d, J= 1.81 Hz), 6.99-7.65 (10 H, m), 8.58 (1 H, d, J= 8.05 Hz), 10.98 (1 H, s); δ_C (125 MHz, DMSO-d_6) 24.61, 25.56, 31.90, 48.22, 55.91, 98.70, 113.24, 113.91, 121.79, 126.74, 128.14, 128.91, 130.09, 130.39, 132.53, 137.49, 139.58, 141.59, 157.85, 159.72; HRMS-FAB(m/z) calcd for $C_{27}H_{27}N_3O_3$ ([M + H]$^+$) 440.5217, found 440.5226.

N-cyclohexyl-4-phenyl-6-(2,4-dichlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6p)

Yellow solid, yield 98%, mp 139-142°C; δ_H (500 MHz DMSO-d_6) 0.95-1.56 (10 H, m), 3.52 (1 H, m), 6.25 (1 H, d, J= 1.81 Hz), 7.31-7.84 (9 H, m), 8.40 (1 H, d, J= 8.05 Hz), 10.98 (1 H, s); δ_C (125 MHz, DMSO-d_6) 24.74, 25.57, 31.82, 48.63, 98.81, 122.09, 126.93, 127.46, 127.92, 128.20, 129.55, 130.02, 132.44, 134.53, 137.04, 137.06, 140.19, 142.33, 157.20, 159.14; HRMS-FAB(m/z) calcd for $C_{26}H_{23}Cl_2N_3O_2$ ([M + H]$^+$) 479.3854, found 479.3864.

N-cyclohexyl-4-phenyl-6-phenyl-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6q)

Yellow solid, yield 96%, mp 199-202°C; δ_H (500 MHz DMSO-d_6) 0.87-1.58 (10 H, m), 3.43 (1 H, m), 6.15 (1 H, d, J= 1.81 Hz), 7.25-7.66 (11 H, m), 8.58 (1 H, d, J= 8.05 Hz), 10.90 (1 H, s); δ_C (125 MHz, DMSO-d_6) 24.27, 25.54, 31.82, 48.27, 98.64, 113.35, 121.84, 126.74, 128.12, 128.38, 128.42, 128.67, 129.44, 130.09, 137.50, 139.45, 139.89, 141.68, 157.89, 159.70; HRMS-FAB(m/z) calcd for $C_{26}H_{25}N_3O_2$ ([M + H]$^+$) 410.4957, found 410.4966.

N-cyclohexyl-4-phenyl-6-(3-chlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6r)

Yellow solid, yield 96%, mp 199-203°C; δ_H (500 MHz DMSO-d_6) 0.95-1.59 (10 H, m), 3.48 (1 H, ,m), 6.16 (1 H, d, J= 1.81 Hz), 7.13-7.69 (10 H, m), 8.68 (1 H, d, J= 8.05 Hz), 10.97 (1 H, s); δ_C (125 MHz, DMSO-d_6) 24.59, 25.55, 31.83, 48.32, 98.76, 113.55, 122.02, 126.87, 127.86, 128.16, 128.30, 128.56, 129.60, 130.08, 130.39, 132.94, 137.23, 139.88, 141.13, 141.95, 157.74, 159.57; HRMS-FAB(m/z) calcd for $C_{26}H_{24}N_3O_2$ ([M + H]$^+$) 444.9405, found 444.9419.

N-cyclohexyl-4-(4-chlorophenyl)-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6s)

Yellow solid, yield 98%, mp 266-270°C; δ_H (500 MHz DMSO-d_6) 0.95-1.59 (10 H, m), 3.49 (1 H, m), 6.19 (1 H, d, J= 1.81 Hz), 7.28-7.69 (9 H, m), 8.68 (1 H, d, J= 8.05 Hz), 11.0 (1 H, s); δ_C (125 MHz, DMSO-d_6) 24.56, 25.54, 31.78, 48.30, 98.59, 111.82, 121.69, 121.92, 128.19, 128.50, 128.19, 128.50, 131.06, 131.58, 131.76, 131.78, 136.18, 139.06, 140.12, 141.79, 157.58, 159.49; HRMS-FAB(m/z) calcd for $C_{26}H_{23}BrClN_3O_2$ ([M + H]$^+$) 523.8365, found 523.8376.

N-cyclohexyl-4-(4-chlorophenyl)-6-(4-chlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6t)

Yellow solid, yield 98%, mp 272-276°C; δ_H (500 MHz DMSO-d_6) 0.93-1.59 (10 H, m), 3.49 (1 H, m), 6.19 (1 H, d, J= 1.81 Hz), 7.35-7.70 (9 H, m), 8.67 (1 H, d, J= 8.05 Hz), 11.04 (1 H, s); δ_C (125 MHz, DMSO-d_6) 24.57, 25.53, 31.79, 48.32, 98.59, 111.81, 128.19, 128.58, 128.80, 131.06, 131.25, 131.78, 133.21, 136.19, 138.61, 140.12, 141.79, 157.63, 159.49; HRMS-FAB(m/z) calcd for $C_{26}H_{23}Cl_2N_3O_2$ ([M + H]$^+$) 479.3852, found 479.3864.

N-cyclohexyl-4-(4-methoxyphenyl)-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6u)

Yellow solid, yield 98%, mp 162-166°C; δ_H (500 MHz DMSO-d$_6$) 0.95-1.56 (10 H, m), 3.40 (1 H, m), 6.15 (1 H, d, J= 1.81 Hz), 6.96-7.66 (9 H, m), 8.61 (1 H, d, J= 8.05 Hz), 10.85 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 24.60, 25.55, 31.80, 48.30, 98.80, 113.56, 113.62, 121.51, 129.45, 131.21, 131.60, 131.70, 139.33, 139.42, 141.49, 157.81, 158.26, 159.73; HRMS-FAB(m/z) calcd for C$_{27}$H$_{26}$BrN$_3$O$_3$ ([M + H]$^+$) 519.4178, found 519.4189.

N-cyclohexyl-4-phenyl-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6v)

Yellow solid, yield 97%, mp 180-184°C; δ_H (500 MHz DMSO-d$_6$) 0.95-1.59 (10 H, m), 2.35 (3 H, s), 3.47 (1 H, m), 6.23 (1 H, d, J= 1.81 Hz), 7.20-7.66 (9 H, m), 8.62 (1 H, d, J= 8.05 Hz), 10.88 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 21.35, 24.59, 25.55, 31.80, 48.29, 98.81, 113.67, 121.54, 122.07, 127.55, 128.75, 129.93, 131.60, 131.71, 134.31, 135.97, 139.29, 141.72, 157.77, 159.69; HRMS-FAB(m/z) calcd for C$_{27}$H$_{26}$BrN$_3$O$_2$ ([M + H]$^+$) 503.4184, found 503.4193.

N-cyclohexyl-4-(4-methylphenyl)-6-(4-chlorophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6w)

Yellow solid, yield 98%, mp 166-170°C; δ_H (500 MHz DMSO-d$_6$) 0.93-1.59 (10 H, m), 2.34 (3 H, s), 3.48 (1 H, m), 6.14 (1 H, d, J= 1.81 Hz), 7.21-7.81 (8 H, m), 8.61 (1 H, d, J= 8.05 Hz), 10.88 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) 21.35, 24.59, 25.54, 31.80, 48.30, 98.80, 113.65, 122.05, 127.63, 128.74, 129.93, 131.27, 133.06, 134.32, 135.96, 138.83, 139.54, 141.71, 157.82, 159.69; HRMS-FAB(m/z) calcd for C$_{27}$H$_{26}$ClN$_3$O$_2$ ([M + H]$^+$) 458.9671, found 458.9681.

N-(cyclohexyl)-4-phenyl-6-(2-iodophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6x)

Light yellow solid, yield 95%, mp 162-164°C; δ_H (500 MHz DMSO-d$_6$) 0.91-1.80 (10 H, m), 3.48 (1 H, m), 6.28 (1 H, d, J= 1.81 Hz), 7.12-7.95 (11 H, m), 8.67 (1 H, d, J= 8.01 Hz), 11.34 (1

H, s); δ_C (125 MHz, DMSO-d$_6$) ; 14.45, 21.26, 22.54, 48.58, 99.45, 114.19, 122.73, 125.97, 127.31, 128.46, 128.57, 128.99, 130.03, 130.62, 136.51, 138.21, 139.34, 140.55, 142.04, 142.59, 145.99, 155.49, 158.58; HRMS-FAB(m/z) calcd for $C_{26}H_{24}IN_3O_2$ ([M + H]$^+$) 536.3912, found 536.3924.

N-(tert-Butyl)-4-(4-chlorophenyl)-6-(3-trifluoromethylphenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6y)

Yellow solid, yield 91%, mp 125-129°C; δ_H (500 MHz DMSO-d$_6$) 0.94 (9 H, s), 6.14 (1 H, d, J= 5 Hz), 7.37-7.74 (9 H, m), 8.26 (1 H, s), 10.85 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) ; 28.10, 51.59, 98.70, 111.99, 121.96, 125.44, 126.47, 128.20, 128.62, 130.18, 131.13, 131.81, 133.84, 136.07, 140.41, 140.59, 142.10, 157.67, 159.72; HRMS-FAB(m/z) calcd for $C_{25}H_{21}ClF_3N_3O_2$ ([M + H]$^+$) 486.9012, found 486.9025.

N-(cyclohexyl)-4-(4-trifluoromethylphenyl)-6-(4-bromophenyl)-5-oxo-1H-pyrrolo[2,3-c]pyridone-7-carboxamide (6z)

yellow solid, yield 87%, mp 145-149°C; δ_H (500 MHz DMSO-d$_6$) 0.97-1.57 (10 H, m), 3.48 (1 H, m), 6.25 (1 H, d, J= 1.81 Hz), 7.29-7.91 (9 H, m), 8.69 (1 H, d, J= 8.01 Hz), 11.13 (1 H, s); δ_C (125 MHz, DMSO-d$_6$) ; 24.55, 25.52, 31.76, 48.32, 98.55, 111.22, 121.78, 121.84, 125.04, 129.29, 130.58, 131.58, 131.81, 138.92, 140.54, 141.80, 142.03, 157.61, 159.38; HRMS-FAB(m/z) calcd for $C_{27}H_{23}BrF_3N_3O_2$ ([M + H]$^+$) 557.3897, found 557.3888.

4.   Conclusions

In conclusion we have demonstrated a mild, efficient and multicomponent protocol for the synthesis of novel pyrrolo[2,3-c]pyridone molecules. This method offers several advantages such as easy handling procedure, atom economy, short reaction time and huge molecular library can

be synthesized by changing the substituents on four independent starting materials. In previous reported methods for pyrrolo[2,3-c]pyridones, expensive metal catalysts were used, where as in present method we used inexpensive PTSA catalyst. Considering these advantages we hope this methodology will be useful for medicinal chemists in drug discovery process.

Acknowledgements

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Chapter 3

One pot four component synthesis of novel 3-furyl coumarin derivatives

Abstract:

Efficient and facile synthesis of 3-furyl coumarin derivatives has been achieved by reaction of 4-chloro-3-formylcoumarin, secondary amines, dialkyl acetylenedicarboxylates and diversely substituted isocyanides using four component one pot reaction. All the products were isolated as yellow color fluorescent solids by column chromatography in quantitative yield and characterized with ^{1}H NMR, C^{13} NMR, IR and FAB mass.

1.   Introduction

Coumarin analogs have been considered as important class of heterocyclic compounds due to their significant applications as anticoagulant,[1] antibacterial,[2] antihypertensive,[3] anti-tubercular,[4] antifungal,[5] anticancer,[6] HIV protease inhibition,[7] Laser dyes and fluorescent properties.[8] Similarly Furan ring is found in many pharmaceutically important substances like furanose form in carbohydrate, alkaloid pylocarpine and furacilin antibiotics. Coumarin analogs having both coumarin and furan heterocycles have gained the considerable attention of researchers due to their significant properties as anti-leishmania panamensis,[9] dyes and fluorescent sensors.[10] Coumarin analogs with furan heterocycle isolated from the plants origin such as microminutin, micromelin, psoralen, 8-methoxypsoralen have important properties in medicinal chemistry and bio photochemistry.[11] It is well documented that by introducing a heteroaromatic substituent at 3-position the absorption and emission maxima of coumarin

scaffold can be improved because of extended π conjugation and consequently their optoelectronic properties can be improved.[12] Based on this phenomena a variety of 3-heteroaryl coumarin derivatives have been synthesized and evaluated for their optoelectronic properties.[13] 3-furyl coumarin falls under this class with extended π conjugation. Thus the structural features and the wide spectrum of applications of furyl coumarin analogs have prompted the intense research by the chemists to develop novel, simple and efficient methods for their synthesis.

There are many reports in literature for the synthesis of 3-furyl coumarin derivatives. These involve the condensation of substituted salicylaldehydes and furyl acetonitriles with subsequent hydrolysis of the resulting 2-imino coumarin intermediates in acidic medium,[14] NBS bromination of coumarin at 3-position followed by Suzuki-Miyaura cross-coupling reaction with furano boronic acids,[15] condensation of 4-chloromethyl coumarins with salicylaldehydes in DMF in the presence of potassium carbonate[16] and condensation of phenol with 2-furyl acid chloride,[17] followed by Fries rearrangement with benzoyl chloride under PTC conditions and condensation of coumarin chalcone hybrid with benzoyl chloride using TPP catalyst.[18]
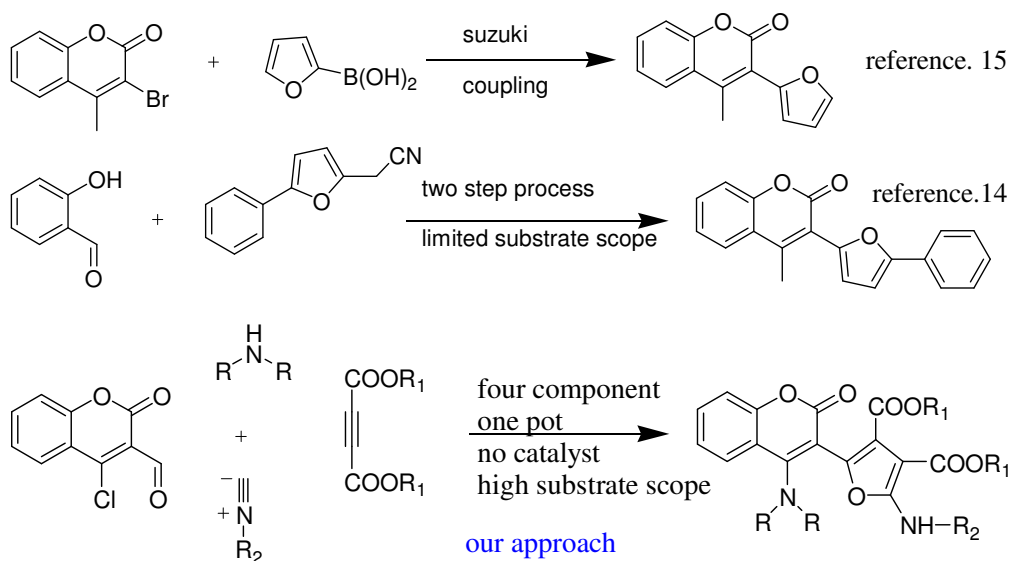
Scheme 1. Comparison of previous reports with our approach

Most of the above protocols involved multistep synthesis, metal catalyst, high temperatures, limited substrate scope, tedious workup and long reaction times.

A contemporary challenge in the world is environmental pollution. Multi component reactions are certainly one of the solutions for this problem due to the less release of chemical wastage compared with classical bicomponent reaction protocols and it is being considered as one of the green technology. Previously we have reported the efficient and convenient synthesis of novel 2-benzazepines and chromeno quinolines using green technology platforms.[19] In this article, we have envisaged a four component one pot reaction using 4-chloro-3-formyl coumarin, secondary amines, dialkyl acetylene dicarboxylate, and isocyanides. The reaction proceeded smoothly and yielded the desired products in good to excellent yields (83 to 88%).

2. **Results and Discussion**

Initial attempts by us to successfully synthesize 3-furyl coumarin derivatives by three component reaction using 4-chloro-3-formyl coumarin, dimethyl acetylenedicarboxylate and *tert*-butyl isocyanide met with failure. Even when the reaction was conducted at reflux condition did not yield the desired compounds. Previous reports suggest that that 1,3-dipolar generated by the addition of electron deficient alkynes and isocyanides reacts with carbonyl functional group, results in furan derivatives.[20] But, unfortunately in our case the reaction proceeded to generate a lot of unwanted products as observed by TLC, without the desired product. We envisaged that the problem could be because of chloride of 4-chloro-3-formyl coumarin, as the chloride is a labile group in 4-chloro-3-formyl coumarin molecule, which was known to undergo substitution

reactions readily with nucleophiles, hence resulting in many spots on TLC in our case. To our satisfaction substitution of chloride with morpholine, followed by three component reaction generated the desired product (85%). Finally a four component reaction using 4-chloro-3-formyl coumarin, morpholine, t-butyl isocyanide and dimethyl acetylenedicarboxylate generated the desired product in good yield.

Table 1. Screening of solvents for the synthesis of 3-furyl coumarin with 4-chloro-3-formyl coumarin, morpholine, dimethyl acetylenedicarboxylate and t-butyl isocyanide [a]
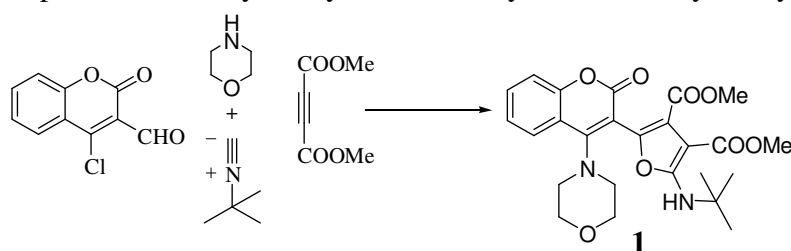
Entry	Solvent	T (^{0}C)	Time(h)	Yield [b](%)
1	EtOH	80	8	NR[c]
2	MeOH	80	8	NR[c]
3	DMF	80	8	NR
4	DCM	60	8	40
5	CHCl$_3$	60	8	40
6	THF	80	8	50
7	Toluene	80	3	80
8	Benzene	80	2.5	85

[a] carried out using 4-chloro-3-formyl coumarin (1 mmol), morpholine (2 mmol), dimethyl acetylenedicarboxylate (1 mmol), and t-butyl isocyanide (1 mmol) under N$_2$, [b] isolated yields,
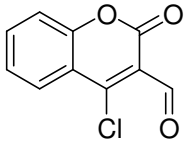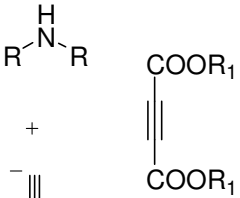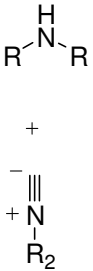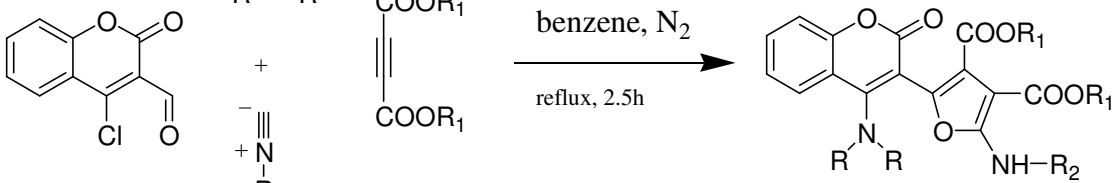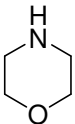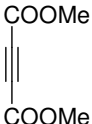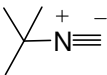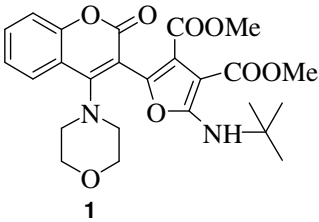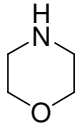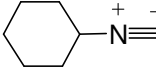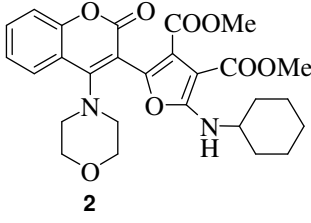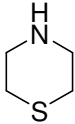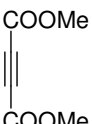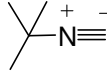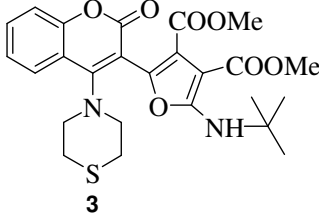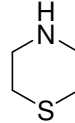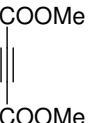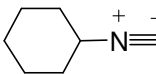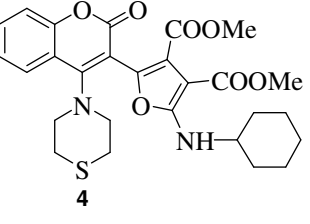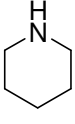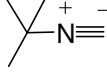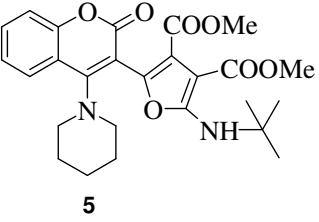
The order of addition of reactants was initially 4-chloro-3-formyl coumarin (1 eq) and morpholine (2 eq) taken and stirred at reflux for 2 min in benzene under N_2. Subsequently dimethyl acetylenedicarboxylate and t-butyl isocyanide were added and refluxed for 2.5h.

To choose the best solvent for conducting the reaction, we have optimized the reaction in different solvents under different conditions. No product formation was observed in polar solvents like EtOH, MeOH and DMF at room temperature as well as refluxed at 80^0C for 8h (**Table 1**, entries **1**-**3**). Poor to moderate yields were observed in $CHCl_3$, DCM and THF (Table 1, entries **4**-**6**). Very good yields were observed in benzene and toluene (**Table 1**, entries 7-**8**). Among all the screened solvents benzene was found to be the more effective solvent with 85% yield with short reaction time.

Under the optimized reaction conditions, a variety of secondary amines, dialkyl acetylenedicarboxylates and isocyanides were employed to evaluate the substrate scope of the reaction. All the reactions proceeded very smoothly under optimized reaction conditions. All the 3-furanyl coumarins **1**-**14** were obtained in good yields. All the compounds reported in this paper are novel, characterized with ^{1}H NMR, C^{13} NMR, IR and FAB mass.

When the reaction was performed using pentyl isocyanide, diethyl acetylenedicarboxylate, 4-chloro-3-formyl coumarin and Morpholine (or) thiomorpholine, we have not observed usual reaction product in these cases.

Table 2. Synthesis of novel 3-furyl coumarins

Entry	Secondary amine	Dialkylacetylene dicarboxylate	Isocyanide	3-Furyl coumarin (1-14)	Yield (%) [a]
1	morpholine (H-N, O)	COOMe / COOMe	t-Bu-N≡C	**1**	85
2	morpholine (H-N, O)	COOMe / COOMe	cyclohexyl-N≡C	**2**	85
3	thiomorpholine (H-N, S)	COOMe / COOMe	t-Bu-N≡C	**3**	80
4	thiomorpholine (H-N, S)	COOMe / COOMe	cyclohexyl-N≡C	**4**	88
5	piperidine (H-N)	COOMe / COOMe	t-Bu-N≡C	**5**	84

#	Amine	Alkyne	Isocyanide	Product	Yield
6	piperidine (N–H)	COOMe / COOMe (DMAD)	cyclohexyl N⁺≡⁻	**6**	84
7	Me–N(H)–Me	COOMe / COOMe	t-Bu–N⁺≡⁻	**7**	84
8	morpholine (N–H)	COOEt / COOEt	t-Bu–N⁺≡⁻	**8**	83
9	Me–N(H)–Me	COOEt / COOEt	t-Bu–N⁺≡⁻	**9**	87
10	thiomorpholine (N–H)	COOEt / COOEt	cyclohexyl N⁺≡⁻	**10**	83
11	piperidine (N–H)	COOEt / COOEt	t-Bu–N⁺≡⁻	**11**	85

12	H N (piperidine)	COOEt / COOEt (alkyne)	cyclohexyl-N≡	(structure **12**) with COOEt, COOEt, piperidine N, NH-cyclohexyl	85
13	H N / O (morpholine)	COOEt / COOEt (alkyne)	pentyl-N≡	(structure **13**) COOEt, COOEt, EtOOC, EtOOC, C=N	80
14	H N / S (thiomorpholine)	COOEt / COOEt (alkyne)	pentyl-N≡	(structure **14**) COOEt, COOEt, EtOOC, EtOOC, C=N	80

a Isolated yields

It was further reacted with another molecule of dipolar intermediate formed by the addition of pentyl isocyanide and diethylacetylene dicarboxylate (**Scheme 3**) formed ketenimine furyl coumarin analogs (products **13**, **14**) respectively and the yield of final product was 40%. When the reaction was conducted by using two equivalents of pentyl isocyanide, diethyl acetylenedicarboxylate as shown (**Scheme 2**), the yield of the final product ketenimine furyl coumarin was increased from 40 to 80%.

This product formations were supported by literature reports, where secondary amines reacts with dipolar intermediate generated by the addition of electron withdrawing alkynes and isocyanides to form ketenimine products.[21]

Scheme 2[a]. Representation of the formation of products 13, 14
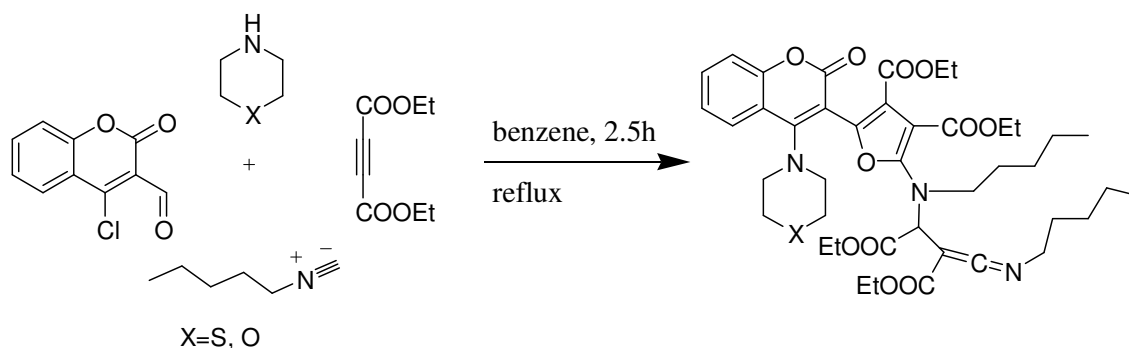
[a] Reaction was performed using pentyl isocyanide (2 mmol), diethylacetylene dicarboxylate (2 mmol), morpholine (or) thiomorpholine (2 mmol) and 4-chloro-3-formyl coumarin (1 mmol)

We have not observed such kinds of products, when the reaction was attempted using t-butyl isocyanide and cyclohexyl isocyanide. The reason could be because of steric hindrance of bulky t-butyl and cyclohexyl groups might be prevented the attack of second molecule of dipolar intermediate. Molecule 1 was crystallized in ethyl acetate solvent. From the SXRD data, it was concluded that molecule 1 was crystallized in monoclinic form along with ethyl acetate solvent molecule with p21/c space group. The ortep diagram of molecule is shown below (**Fig. 1**).
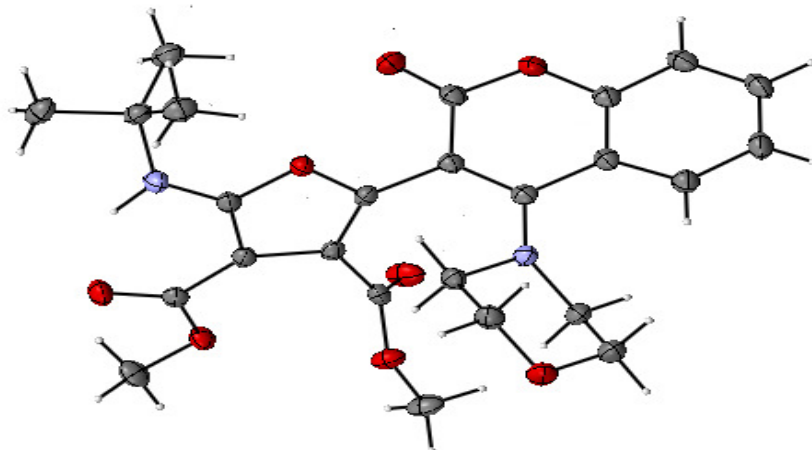
Fig 1.ORTEP plot for the X-ray crystal structure of 1 at 50% probability

The synthesized compounds (1-14) were further evaluated for their optoelectronic properties. We have measured the UV-Vis absorption and fluorescence emissions of compounds 1-14 (Fig. 2 and Fig. 3). The concentrations of 3-furyl coumarin derivatives were 2.0×10^{-4} mol/L for absorption in MeOH solvent. The results are summarized in Table 3. The shapes of absorption spectra of all the compounds are very similar to each other. The absorption spectra (Fig 2) have showed absorption maxima from 295 nm to 322 nm for all the compounds in methanol solvent.

Table 3. UV-Visible absorption and fluorescence of compounds 1-14[a]

Compound	λ_{abs}/nm	λ_{ex}/nm	λ_{em}/nm
1	299	358	456
2	300	355	461
3	297	366	440
4	308	362	454
5	304	355	446
6	298	357	465
7	303	355	472
8	298	357	457
9	322	354	476
10	295	351	463
11	298	355	445
12	300	357	444
13	320	372	501
14	322	371	496

[a] The concentration of all the samples were 2.0×10^{-4} mol/L in Methanol solvent
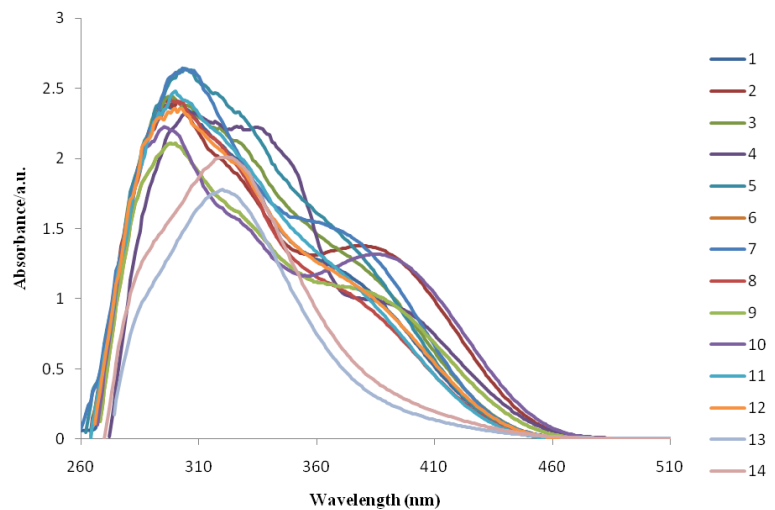
Figure 2. Absorption spectra of compounds 1-14 in MeOH solvent
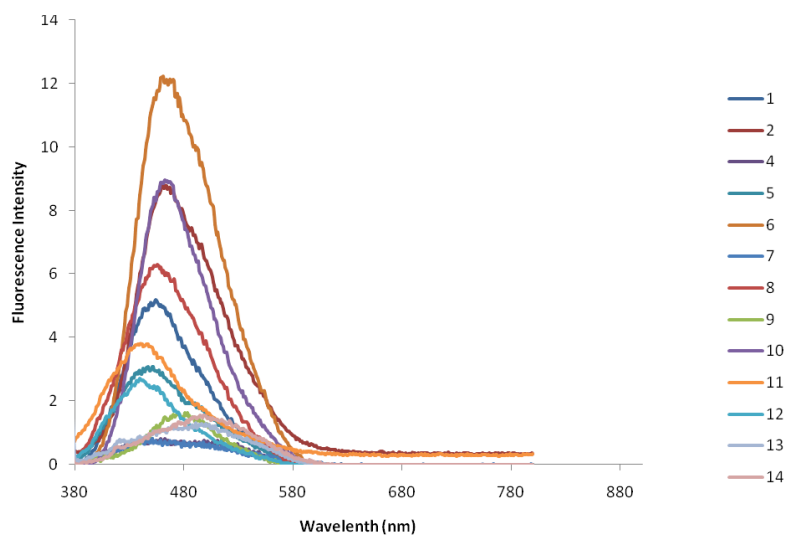
Figure 3. Emission spectra of compounds 1-14 in MeOH

With the above results in hand, we would like to propose the plausible mechanism for the above reaction. The first step of the reaction was nucleophilic displacement of chloride group with secondary amine as shown in Scheme 3.
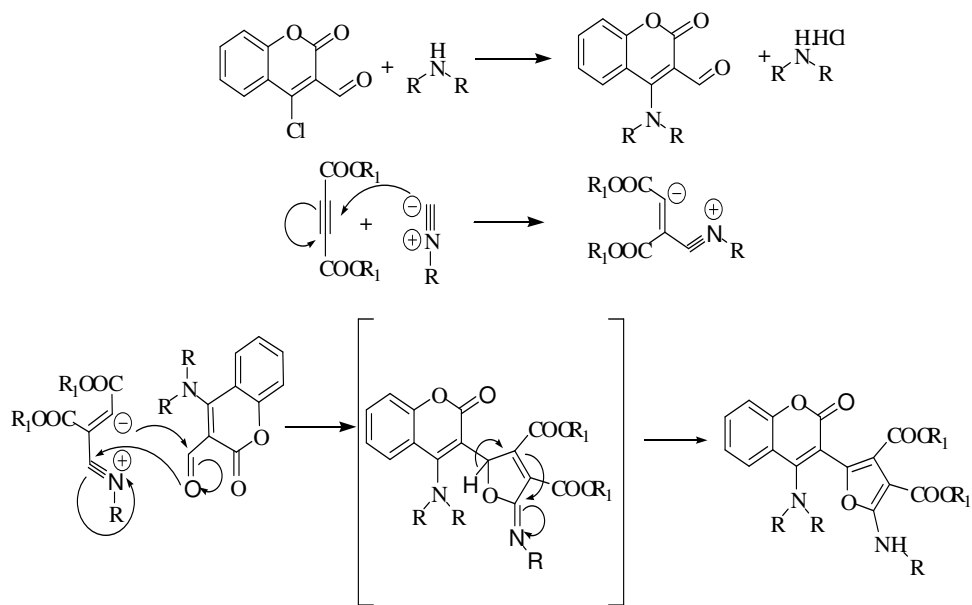
Scheme 3. Plausible reaction mechanism for the formation of 3-furyl coumarin

On the basis of well-established chemistry of isocyanides reactivity with dialkyl acetylenedicarboxylate, a zwitter ionic intermediate was expected. This zwitter ionic intermediate was added to carbonyl function of coumarin formed an intermediate, which finally undergoes rearrangement to form the final product.

3. **Experimental**

All reagents were purchased from TCI and Sigma Aldrich and used without further purification. All the products were characterized by ^{1}H NMR, C^{13} NMR, IR, and Fab-Mass analysis. The NMR spectrum was recorded on a Bruker AMX-500 MHz instrument at room temperature in CDCl$_3$ using TMS as an internal reference. Melting points were determined by AS ONE instrument. Absorption spectrum was measured by using JASCO V-550 UV/VIS Spectrophotometer and Fluorescence spectrum was measured by using Hitachi F-2500 Fluorescence Spectrophotometer. X-ray data for the compound were collected at room

temperature using a Bruker Apex II KY CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Crystallographic data of **1** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1424464 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

General procedure for the synthesis of 3-furyl coumarin derivatives:

A solution of 4-chloro-3-formyl coumarin (1 mmol) and secondary amine (2 mmol) were stirred at reflux for 2 min in benzene under N_2. To this solution dialyl acetylenedicarboxylate (1 mmol), isocyanide (1 mmol) were added and refluxed at 80^0C for 2.5h. The volatiles were removed under reduced pressure. The crude reaction mixture was subjected to column chromatography using EtOAc/Hexane mobile phase. All the products were isolated as yellow color fluorescent solids in very good yields.

4-morpholino-3-(2-N-t-butylamino-3,4-dimethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (1).

Yellow color solid, mp 133-136 °C; IR: ν_{max}(KBr) 3288, 1732, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.69 (1 H, J =1.2 Hz, dd) 7.54 (m, 1 H), 7.34 (1 H, J =1.0 Hz, dd), 7.29 (m, 1 H), 7.02 (1 H, s), 3.85 (4 H, J =4.55 Hz, t), 3.78 (3 H, s), 3.75 (3 H, s), 3.25 (4 H, m), 1.43 (9 H, s); δ_C (125 MHz, CDCl$_3$) 165.4, 163.9, 162.7, 161.2, 159.5, 153.7, 138.1, 132.2, 125.3, 123.2, 118.6, 117.8, 117.5, 102.7, 87.3, 67.0, 52.7, 52.0, 51.1, 30.1; LCMS: MH$^+$, 484. Anal. Calcd. For C$_{25}$H$_{28}$N$_2$O$_8$**:** C, 61.94; H, 5.86; N, 5.78. Found**:** C, 61.95; H, 5.83; N, 5.80.

4-morpholino-3-(2-N-cyclohexylamino-3,4-dimethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (2).

Yellow color solid, mp 109-112 °C; IR; ν_{max}(KBr) 3288, 1733, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.69 (1 H, J =1.4 Hz, dd), 7.52 (1 H, m), 7.34 (1 H, J =1.0 Hz, dd), 7.28 (1 H, m), 6.78 (1 H, J =6.8 Hz, d), 3.88 (4 H, J =4.5 Hz, t), 3.79 (3 H, s), 3.78 (3 H, s), 3.19 (4 H, J =4.5 Hz, t), 2.05 (3 H, m), 1.76 (2 H, m), 1.61(1 H, m), 1.34 (3 H, m); δ_C (125 MHz, CDCl$_3$) 165.2, 164.0, 162.1, 160.9, 159.1, 153.5, 137.6, 132.1, 125.1, 123.8, 119.2, 117.8, 103.7, 86.5, 67.0, 52.1, 51.1, 51.0, 33.7, 33.7, 25.3, 24.6; LCMS: MH$^+$, 510. Anal. Calcd. For C$_{27}$H$_{30}$N$_2$O$_8$: C, 63.50; H, 5.92; N, 5.51. Found**:** C, 63.50; H, 5.90; N, 5.53.

4-thiomorpholino-3-(2-N-t-butylamino-3,4-dimethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (3).

Yellow color solid, mp 107-109 °C; IR; ν_{max}(KBr) 3288, 1732, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.69 (1 H, J =1.2 Hz, dd), 7.52 (1 H, J =8 Hz, t), 7.28-7.33 (2 H, J =1.0 Hz, dd), 7.05 (1 H, s), 3.78 (3 H, s), 3.75 (3 H, s), 3.39-3.48 (4 H, m), 2.77-2.81 (4 H, m), 1.44 (9 H, s); δ_C (125 MHz, CDCl$_3$) 165.6, 163.9, 163.0, 161.2, 160.6, 153.4, 138.2, 132.4, 125.1, 123.7, 118.7, 118.1, 117.7, 103.6, 87.8, 53.2, 52.7, 51.8, 51.3, 28.0; LCMS: MH$^+$, 500. Anal. Calcd. For C$_{25}$H$_{28}$N$_2$O$_7$S: C, 59.90; H, 5.69; N, 5.64. Found**:** C, 59.85; H, 5.71; N, 5.67.

4-thiomorpholino-3-(2-N-cyclohexylamino-3,4-dimethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (4).

Yellow color solid, mp 86-88 °C; IR; ν_{max}(KBr) 3288, 1732, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.82 (1 H, J =1.2 Hz, dd), 7.70 (1 H, J =6.8 Hz, d), 7.32

(1 H, m), 7.25 (1 H, m), 6.81 (1 H, J =7.2 Hz, d), 3.79 (3 H, s), 3.75 (3 H, s), 3.38-3.41 (4 H, m), 2.78-2.83 (4 H, m), 1.62 (1 H, m), 1.17-1.38 (10 H, m); δ_C (125 MHz, CDCl$_3$) 162.2, 162.1, 161.4, 160.7, 159.6, 153.4, 146.9, 134.1, 133.7, 132.0, 126.4, 126.1, 124.9, 119.2, 118.6, 117.9, 105.3, 87.0, 60.9, 56.1, 52.9, 52.0, 51.1, 33.8, 28.7, 27.9, 25.3, 24.6; LCMS: MH$^+$, 526. Anal. Calcd. For C$_{27}$H$_{30}$N$_2$O$_7$S: C, 61.50; H, 5.82; N, 5.32. Found: C, 61.55; H, 5.75; N, 5.34.

4-piperidino-3-(2-N-t-butylamino-3,4-dimethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (5).

Yellow color solid, mp 92-94 °C; IR; ν_{max}(KBr) 3288, 1732, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.72 (1 H, J =1.2 Hz, dd), 7.51 (1 H, J =6.9 Hz, t), 7.32 (1 H, m), 7.26 (1 H, m), 7.0 (1 H, s), 3.78 (3 H, s), 3.73 (3 H, s), 3.08-3.22 (4 H, m), 1.73 (6 H, m), 1.43 (9 H, s); δ_C (125 MHz, CDCl$_3$) 165.6, 164.2, 162.7, 161.6, 160.6, 153.6, 139.2, 131.9, 125.5, 123.5, 118.2, 118.0, 118.0, 101.4, 87.2, 60.4, 52.6, 52.3, 51.9, 51.0, 30.0, 26.3, 24.0, 14.2; LCMS: MH$^+$, 482. Anal. Calcd. For C$_{26}$H$_{30}$N$_2$O$_7$: C, 64.68; H, 6.29; N, 5.83. Found: C, 64.70; H, 6.28; N, 5.82.

4-piperidino-3-(2-N-cyclohexylamino-3,4-dimethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (6).

Yellow color solid, mp 93-96 °C; IR; ν_{max}(KBr) 3288, 1732, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.71 (1 H, J =1.0 Hz, dd), 7.50 (1 H, J =6.5 Hz, t), 7.30 (1 H, m), 7.26 (1 H, m), 6.76 (1 H, J =7.2 Hz, d), 3.79 (3 H, s), 3.75 (3 H, s), 3.11-3.15 (4 H, m), 2.01 (3 H, m), 1.59-1.73 (11 H, m), 1.33-1.36 (3 H, m) ; δ_C (125 MHz, CDCl$_3$) 165.4, 164.1, 162.1, 161.3, 160.3, 153.5, 138.8, 131.8, 125.3, 123.6, 118.5, 118.3, 117.6, 102.4, 86.4, 60.4,

52.2, 51.9, 51.4, 51.3, 33.7, 26.2, 25.3, 24.6, 24.1, 14.2; LCMS: MH$^+$, 508. Anal. Calcd. For C$_{28}$H$_{32}$N$_2$O$_7$: C, 66.10; H, 6.35; N, 5.53. Found**:** C, 66.11; H, 6.36; N, 5.51.

4-N-dimethylamino-3-(2-N-t-butylamino-3,4-dimethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (7).

Yellow color solid, mp 66-68 °C; IR; ν_{max}(KBr) 3288, 1732, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.88 (1 H, J =1.2 Hz, dd), 7.51 (1 H, J =6.4 Hz, t), 7.31 (1 H, m), 7.24 (1 H, m), 6.97 (1 H, s), 3.77 (3 H, s), 3.74 (3 H, s), 2.98 (6 H, s), 1.42 (9 H, s); δ_C (125 MHz, CDCl$_3$) 165.7, 164.1, 162.7, 161.3, 160.4, 153.6, 139.0, 132.0, 126.4, 123.5, 117.8, 99.9, 86.9, 60.4, 52.6, 52.2, 51.1, 43.4, 29.8; LCMS: MH$^+$, 441. Anal. Calcd. For C$_{23}$H$_{26}$N$_2$O$_7$: C, 62.43; H, 5.90; N, 6.35. Found**:** C, 62.40; H, 5.95; N, 6.33.

4-morpholino-3-(2-N-t-butylamino-3,4-diethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (8).

Yellow color solid, mp 102-105 °C; IR; ν_{max}(KBr) 3288, 1732, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.69 (1 H, J =1.0 Hz, dd), 7.54 (1 H, m), 7.34 (1 H, J =1.2 Hz, dd), 7.28 (1 H, m), 7.04 (1 H, s), 4.24 (4 H, m), 3.86 (4 H, J =4.5 Hz, q), 3.21-3.36 (4 H, m), 1.43 (9 H, s), 1.32 (3 H, J =6.5 Hz, t), 1.26 (3 H, J =5.7 Hz, t); δ_C (125 MHz, CDCl$_3$) 165.1, 164.0, 162.7, 161.2, 160.6, 153.5, 137.8, 132.1, 125.1, 123.8, 119.0, 118.0, 117.8, 104.0, 87.5, 60.7, 59.7, 53.1, 52.6, 30.5, 27.9, 14.1, 13.9; LCMS: MH$^+$, 512. Anal. Calcd. For C$_{27}$H$_{32}$N$_2$O$_8$: C, 63.25; H, 6.29; N, 5.49. Found: C, 63.29; H, 6.27; N, 5.47.

4-N-dimethylamino-3-(2-N-t-butylamino-3,4-diethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (9).

Yellow color solid, mp 158-160 °C; IR; ν_{max}(KBr) 3288, 1735, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.77 (1 H, J =1.2 Hz, dd), 7.50 (1 H, J =6.5 Hz, t), 7.32 (1 H, m), 7.25 (1 H, m), 6.98 (1 H, s), 4.24 (4 H, J =4.7 Hz, q), 2.98 (6 H, s), 1.42 (9 H, s), 1.28-1.31 (3 H, J =6.2 Hz, t), 1.22-1.24 (3 H, s); δ_C (125 MHz, CDCl$_3$) 165.4, 164.1, 162.8, 161.6, 159.9, 153.8, 138.5, 131.9, 126.8, 123.4, 118.4, 117.8, 99.4, 87.4, 60.9, 59.4, 52.3, 43.4, 29.4, 14.4, 14.3; LCMS: MH$^+$, 469. Anal. Calcd. For C$_{25}$H$_{30}$N$_2$O$_7$: C, 63.78; H, 6.45; N, 5.97. Found: C, 63.82; H, 6.40; N, 5.98.

4-thiomorpholino-3-(2-N-cyclohexylamino-3,4-diethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (10).

Yellow color solid, mp 89-91 °C; IR; ν_{max}(KBr) 3288, 1734, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.69 (1 H, J =1.2 Hz, dd), 7.52 (1 H, J =6.4 Hz, t), 7.30 (1 H, m), 7.28 (1 H, m), 6.80 (1 H, J =7.2 Hz, d), 4.24-4.26 (4 H, J =4.4 Hz, q), 3.37-3.40 (4 H, m), 2.78-2.82 (4 H, m), 1.74-1.78 (3 H, m), 1.59-1.61 (1 H, m), 1.25-1.36 (13 H, m); δ_C (125 MHz, CDCl$_3$) 165.1, 163.7, 162.0, 160.9, 159.9, 153.0, 137.0, 131.7, 124.9, 124.1, 119.8, 118.8, 117.7, 105.4, 86.6, 60.6, 59.5, 52.7, 51.9, 34.7, 28.3, 24.7, 24.3, 14.6, 13.9; LCMS: MH$^+$, 554. Anal. Calcd. For C$_{29}$H$_{34}$N$_2$O$_7$S: C, 62.80; H, 6.15; N, 5.08. Found: C, 62.78; H, 6.19; N, 5.06.

4-piperidino-3-(2-N-t-butylamino-3,4-diethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (11).

Yellow color solid, mp 71-73 °C; IR; ν_{max}(KBr) 3288, 1734, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.71 (1 H, J =1.0 Hz, dd), 7.52 (1 H, J =6.6 Hz, t), 7.31 (1 H, m), 7.30 (1 H, m), 7.01 (1 H, s), 4.18-4.23 (4 H, J =4.4 Hz, q), 3.08-3.29 (4 H, m), 1.64-1.72 (6 H, m), 1.43 (9 H, s), 1.32 (3 H, J =6.2 Hz, t), 1.24 (3 H, J =5.7 Hz, t); δ_C (125 MHz,

CDCl$_3$) 165.2, 164.0, 162.7, 161.6, 160.6, 153.6, 138.7, 131.8, 125.5, 123.5, 118.4, 118.1, 101.6, 87.3, 60.8, 59.3, 52.5, 52.2, 30.0, 26.3, 24.0, 14.2, 14.1; LCMS: MH$^+$, 510. Anal. Calcd. For C$_{28}$H$_{34}$N$_2$O$_7$: C, 65.83; H, 6.75; N, 5.49. Found: C, 65.84; H, 6.70; N, 5.49.

4-piperidino-3-(2-N-cyclohexylamino-3,4-diethylcarboxylate-5-furyl) 2H-1-Benzopyran-2-one (12).

Yellow color solid, mp 78-80 °C; IR; ν_{max}(KBr) 3288, 1735, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.71 (1 H, J =1.2 Hz, dd), 7.51 (1 H, J =6.6 Hz, t), 7.31 (1 H, m), 7.26 (1 H, m), 6.77 (1 H, J =7.2 Hz, d), 4.20-4.26 (4 H, m), 3.14 (4 H, J =6.2 Hz, t), 1.58-1.74 (11 H, m), 1.23-1.37 (12 H, m), 1.24 (3 H, J =5.7 Hz, t); δ_C (125 MHz, CDCl$_3$) 165.0, 163.9, 162.1, 161.4, 160.4, 153.4, 138.2, 131.8, 125.3, 123.6, 118.9, 118.3, 117.5, 102.4, 86.6, 60.8, 59.6, 52.3, 52.2, 51.3, 33.7, 26.4, 25.3, 24.5, 24.1, 14.2, 14.1; LCMS: MH$^+$, 536. Anal. Calcd. For C$_{30}$H$_{36}$N$_2$O$_7$: C, 67.10; H, 6.76; N, 5.27. Found: C, 67.13; H, 6.78; N, 5.22.

4-morpholino-3-[2-N-pentyl-N-(4-pentylimino-1,2-diethyl-3-ketenimine dicarboxylate) -5-furyl] 2 H-1-Benzopyran-2-one (13).

Yellow color semi solid; IR; ν_{max}(KBr) 2079, 1733,1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.69 (1 H, J =1.2 Hz, dd), 7.52 (1 H, m), 7.33 (1 H, J =1.0 Hz, dd), 7.28 (1 H, m), 6.73 (1 H, s), 4.11-4.29 (8 H, m), 3.86 (4 H, J =6.7 Hz, t), 3.06-3.19 (4 H, bm), 1.52-1.65 (6 H, m), 1.17-1.37 (22 H, m), 0.88 (6 H, m); δ_C (125 MHz, CDCl$_3$) 162,15, 162.11, 161.69, 161.38, 160.70, 160.18, 153.86, 132.40, 131.15, 125.60, 125.33, 123.83, 123.72, 117.83, 117.76, 117.16, 66.94, 62.22, 61.17, 60.91, 53.64, 51.68, 50.67, 49.83, 31.06, 29.73, 29.00, 27.80, 22.58, 14.13, 14.04, 13.96, 13.91; LCMS: MH$^+$, 793. Anal. Calcd. For C$_{42}$H$_{55}$N$_3$O$_{12}$: C, 63.50; H, 6.98; N, 5.31. Found: C, 63.54; H, 6.94; N, 5.33.

4-thiomorpholino-3-[2-N-pentyl-N-(4-pentylimino-1,2-diethyl-3-ketenimine dicarboxylate) - 5-furyl] 2 H-1-Benzopyran-2-one (14).

Yellow color semi solid; IR; ν_{max}(KBr) 2079, 1733, 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.69 (1 H, m), 7.54 (1 H, m), 7.32 (2 H, m), 6.78 (1 H, s), 4.11-4.29 (8 H, m), 3.38 (4 H, bm), 2.80 (4 H, t), 1.53-1.65 (6 H, m), 1.17-1.37 (22 H, m), 0.89 (6 H, m); δ_C (125 MHz, CDCl$_3$) 163.13, 162.15, 162.10, 161.69, 160.70, 160.18, 153.87, 132.39, 131.20, 125.60, 123.72, 119.03, 117.76, 117.16, 66.94, 62.22, 61.27, 61.17, 60.90, 53.64, 51.68, 50.66, 49.83, 31.05, 29.72, 28.98, 27.80, 27.45, 22.58, 22.48, 14.13, 14.06, 14.04, 13.95; LCMS: MH$^+$, 809. Anal. Calcd. For C$_{42}$H$_{55}$N$_3$O$_{11}$S: C, 62.30; H, 6.80; N, 5.20. Found: C, 62.27; H, 6.86; N, 5.18.

4. Conclusions

In conclusion, we have reported a mild and efficient synthesis of 3-furyl coumarins via four component one pot reaction. The protocol afforded all the products as yellow color solids after column chromatography in good to excellent yields.

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Chapter 4

Synthesis of novel spiro[indole-2,2'-pyrroles] using isocyanide based multicomponent reaction

Abstract:

An efficient and facile method for the synthesis of novel spiro[indole-2,2'-pyrroles] from N-methyl-3-isatin imines, t-butyl isocyanide and dialkyl acetylenedicarboxylate has been achieved by [3+2] cyclo addition reaction. All the products were purified by column chromatography as yellow solids and confirmed with ^{1}H NMR, ^{13}CNMR, FAB mass, IR. Compound 11 was further confirmed with X-ray analysis.

1. Introduction

Isatin derivatives have several pharmacological and biological properties such as anti-HIV,[1] anticancer,[2] anti-mycobacterial,[3] anti-inflammatory,[4] and anticonvulsant activities.[5] Isatin found to be a prevalent motif in several alkaloids,[6] drugs,[7] dyes,[8] pesticides and analytical reagents. Spiro compounds having both indole and pyrrole nucleus is found to be the key structural unit in many natural products such as Spirotriprostrain A, Spirotriprostrain B and Horsfiline, which were proven to have anticancer activity. [9] Because of the versatile reactivity of the isatin various methods have been developed for the synthesis of spiro [indole-pyrazoles] using multi component reactions.[10] However most of these methods were involved the C-3 carbon of isatin in the formation of spiro heterocycle. Spiro compounds having dipyrrole namely Amathaspiramide A, Mytraginine psuedoindoxyl as shown below was proven to have prominent

antiviral and anticancer properties.[11] Very few reports were there in the literature for the synthesis of spiro [indole-pyrazoles] bearing spiro carbon at C-2 position. [12]

The reported method involved the multistep organic synthesis, used metal catalysts and tedious workup procedures. As a consequence and our passion towards the synthesis of novel heterocycles using multi component reactions, in this article we investigated an efficient and simple route for the synthesis of novel spiro [indole-2,2'-pyrazoles] bearing spiro carbon at C-2 position. Previously we have reported the novel heterocycles like benzazepine, chromeno [4, 3-b] quinolin-6-ones, chromeno-pyrimidine-N-oxides and chromeno [4, 3-b] pyridine-2, 5-diones. [13]
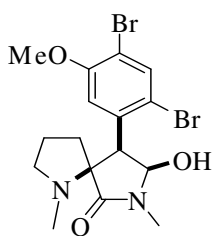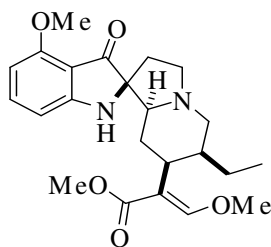
Amathaspiramide A   Mytraginine psuedoindoxyl

Herein we have demonstrated a novel three component [3+2] cyclo addition reaction for the synthesis of spiro [indole-pyrazoles] using C-2 carbon atom of isatin.

2. Results and Discussions

It was already reported in the literature N-methyl isatin reacts with zwitterionic intermediates generated by the addition of isocyanides to electron withdrawing alkynes, such as dialkyl acetylenedicarboxylate to form spirooxindoles.[14] We wanted to attempt the similar reaction using C-2 carbon of isatin. For this purpose we have protected the C2 carbon of isatin by means of ketal formation using ethylene glycol. Now, we have attempted a three component

reaction using the protected N-methyl isatin, dimethyl acetylenedicarboxylate and t-butyl isocyanide in benzene solvent. We have observed many spots in TLC. Hence, we have changed the protecting group to imine using different anilines. We have attempted a three component reaction by blocking the reactive C-3 carbonyl carbon atom of isatin by means of forming imine with 4-chloroanilines.

Table 1. Effect of solvents for the synthesis of spiro[indole-2,2'-pyrroles] with N-methyl-3-(4-chloro phenyl) isatin imine, dimethyl acetylenedicarboxylate and t-butyl isocyanide
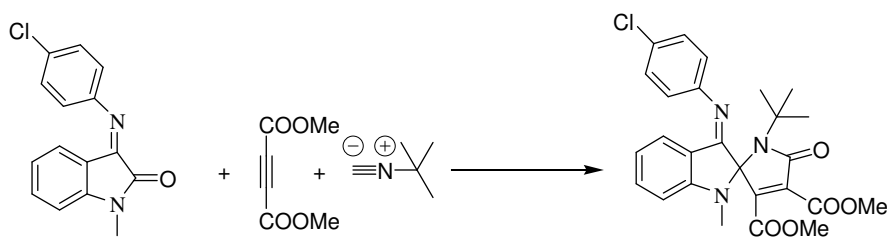
Entry	Solvent	T (^{0}C)	Time (h)	Yield (%)
1	EtOH	80	24	NR[c]
2	MeOH	80	24	NR
3	DCM	60	24	20[b]
4	CHCl3	60	24	20
5	THF	80	24	50
6	Toluene	80	24	60
7	Benzene	80	12	70

[a] All the reactions were performed with 1 mmol of each reactant and 10ml of solvent

To establish three component protocol, we have carried out a three component reaction using N-methyl isatin-3-(4-chlorophenyl) imine, dimethyl acetylenedicarboxylate and t-Butyl isocyanide in toluene solvent under refluxing conditions for 24h (Table 1, Entry. 6). After column chromatography we have obtained the final product as a yellow solid with 60% yield.

To optimize the reaction conditions we have screened the same reaction in different solvents and different conditions (Table 1). The choice of the solvent played profound effect on the reaction yields. No product formation was observed in polar solvents like MeOH, EtOH (Table 1, Entry. 1, 2). Halogenated solvents like $CHCl_3$, DCM (Table 1, Entry. 3, 4) less yields were observed. Among all the solvents screened benzene (Table 1, Entry. 7) was found to be the best solvent with 70% yield with less reaction time.

With the optimized reaction conditions in hand, we have demonstrated the reaction with different substituted N-methyl isatin imines and dialkyl acetylene dicarboxylates as shown in Table 2. We have attempted the reaction with various substituted N-methyl isatin imines, reaction went smoothly yielded 40-71%.

Table 2. Synthesis of novel spiro [indole-2,2'-pyroles] scaffolds
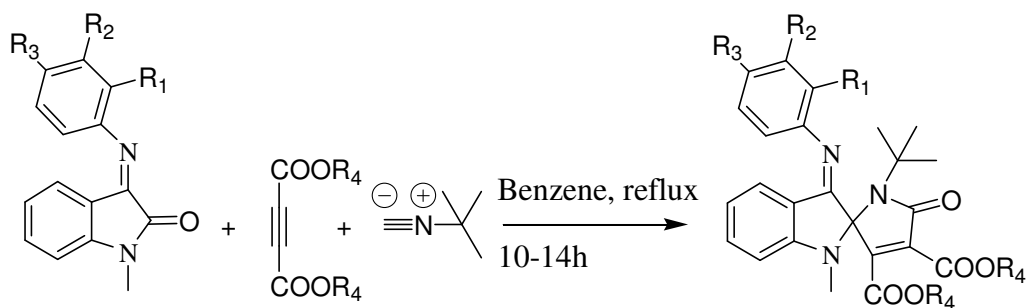
Entry	N-methyl isatin imine	Dialkyl acetylenedicarboxylate	Spiro [indole-2,2'-pyroles] (1-12)	Yield (%)[a]
1				70
2				70
3				40
4				60

COOMe
COOMe

	Substrate	Dipolarophile	Product	Yield
5	Cl, Cl (2,4-dichlorophenyl) N=; N-Me isatin imine (=O)	COOMe / COOMe	Cl, Cl; =N; N-tBu; O; COOMe; COOMe; N-Me	40
6	Cl (3-chlorophenyl) N=; N-Me isatin imine (=O)	COOEt / COOEt	Cl; =N; N-tBu; O; COOEt; COOEt; N-Me	60
7	Cl (4-chlorophenyl) N=; N-Me isatin imine (=O)	COOEt / COOEt	Cl; =N; N-tBu; O; COOEt; COOEt; N-Me	71
8	Br (4-bromophenyl) N=; N-Me isatin imine (=O)	COOEt / COOEt	Br; =N; N-tBu; O; COOEt; COOEt; N-Me	71
9	4-methylphenyl N=; N-Me isatin imine (=O)	COOEt / COOEt	4-methylphenyl; =N; N-tBu; O; COOEt; COOEt; N-Me	60

10

COOEt

COOEt

45

11

COOEt

COOEt

60

12

COOEt

COOEt

45

13[c]

COOEt

COOEt

70

---

[a]Isolated yield after column chromatography

[c]Reaction was performed using pentyl isocyanide

Substrates like N-methyl isatin-3-(4-bromophenyl) imine, N-methyl isatin-3-(4-chlorophenyl) imine, N-methyl isatin-3-(3-chlorophenyl) imine, N-methyl isatin-3-(phenyl) imine were reacted smoothly yielded the products as yellow solids (Table 2. Entry 1, 2, 4, 6, 7, 8, 9, 11) with 60-71%. Substrates like N-methyl isatin-3-(2-chlorophenyl) imine, N-methyl isatin-3-(2,4-dichlorophenyl) imine were less reactive yielded the products as yellow solids (Table 2. Entry 3, 5, 10, 12) with 40-45%. The reason for low yields of the reaction with substrates isatin-3-(2-chlorophenyl) imine, N-methyl isatin-3-(2, 4-dichlorophenyl) imine could be steric hindrance of ortho substitution with t-butyl group. The reaction was also successful with pentyl isocyanide (Table 2. Entry 13). We had successfully regenerated the isatin carbonyl of final product 13(Scheme 1) using 2M aq.HCl in THF at room temperature.
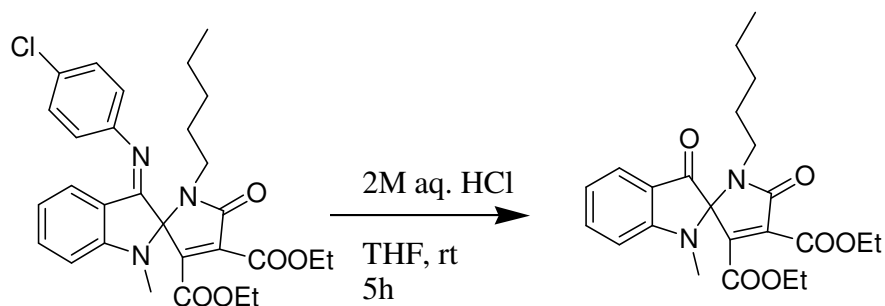
Scheme 1. Hydrolysis of product 13 to retain isatin carbonyl

All the products are novel characterized with ^{1}H NMR, ^{13}CNMR, FAB mass and IR. Structure of the product **11** was further confirmed by X-ray analysis of as shown in Figure 1. Good crystals were obtained for compound **11** in DCM solvent suitable for XRD. The molecule does not contain any hydrogen bonding from the X-ray analysis. The molecule was crystallized in a racemic form with two molecules in the unit cell and it has triclinic system with space group p-1.
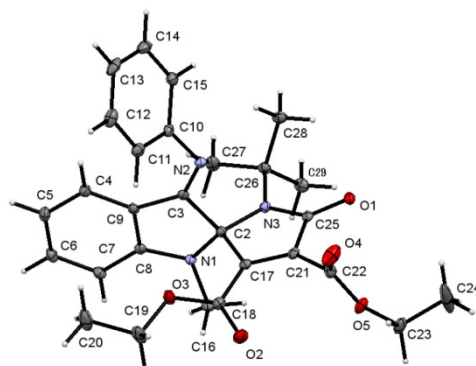
Fig 1.ORTEP plot for the X-ray crystal structure of 11 at 30% probability

On the basis of well-established chemistry of isocyanides I reactivity with dialkyl acetylenedicarboxylate II, initial step was the formation of zwitter ionic species as shown in scheme 1. This was reacted with activated N-methyl isatin imine amide carbonyl III expected to form a spiro Oxindole IV. This undergoes iminolactones-lactam rearrangement formed the final product spiro[indole-2,2'-pyrroles].
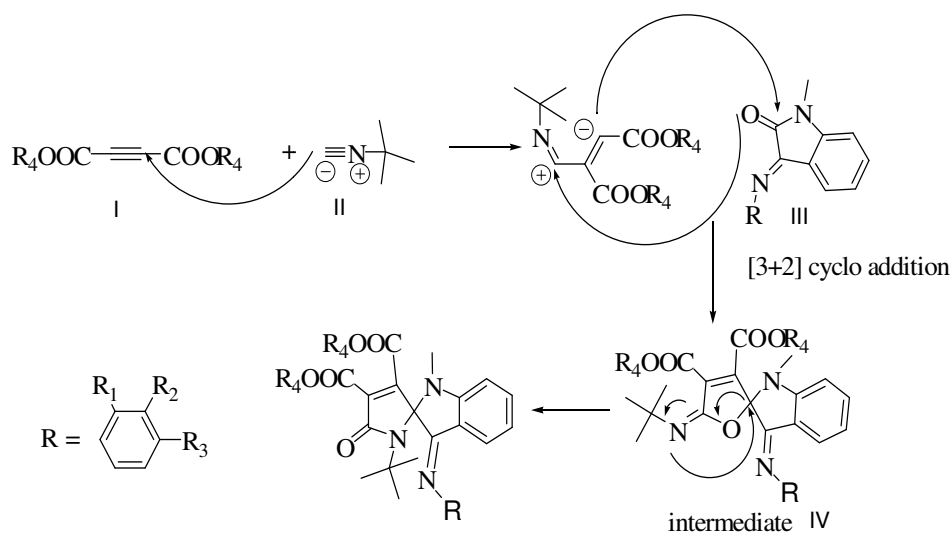
Scheme 2. Plausible reaction mechanism for the formation of spiro [indole-2,2'-pyrazoles]

3. Experimental

All reagents were purchased from TCI and Sigma Aldrich and used without further purification. N-methyl isatin imines were synthesized according to the procedure reported in the literature. All the products were characterized by ^{1}H NMR, C^{13} NMR, IR, and Fab-Mass analysis. The NMR spectra were recorded on a Bruker AMX-500 MHz instrument at room temperature in CDCl$_3$ using TMS as an internal reference. Melting points were determined by AS ONE instrument. X-ray data for the compound were collected at room temperature using a Bruker Apex II KY CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Crystallographic data of **11** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1037350 contains the supplementary crystallographic data for this paper

General procedure for the synthesis of spiro[indole-2,2'-pyrroles] (1-12):

A solution of substituted N-methyl isatin imine (1 mmol), t-Butyl isocyanide (1 mmol) and dimethyl (or) diethyl acetylenedicarboxylate (1 mmol) in 10ml benzene were refluxed for 10-14h. After completion of the reaction monitored by TLC, volatiles were removed under reduced pressure. The crude reaction mixture was subjected to column chromatography using (SiO2, 15% EtOAc/n-Hexane) yielded 40-71% as yellow color solids in most reactions and some cases as yellow color semi solids were obtained.

General procedure for the synthesis of isatin imines:

A mixture of Isatin (1 mmol) and substituted aniline (1 mmol) were added into 10 ml of absolute ethanol containing a few drops of glacial acetic acid in a 50-ml round bottom flask. The reaction mixture was refluxed for 6h and recrystallized from ethanol to obtain pure products

Synthesis of N-methyl isatin ketal:

A mixture of N-methyl isatin imine (1 mmol) and ethylene glycol (1.2 mmol) were taken in 10 ml benzene. To this catalytic amount of PTSA was added and refluxed for 10h. Benzene was removed and N-methyl isatin ketal was isolated as a white color solid using column chromatography.

Procedure for the hydrolysis of product 13:

Compound 13 (1 mmol) was taken in 10 ml of 2M aq. HCl in THF and stirred at room temperature for 5h. The reaction mixture was basified with 20% $NaHCO_3$ and extracted with EtOAC, product was isolated as yellow color solid using column chromatography using 20% EtOAC/Hexane.

Spiro[indole-2,2'-pyrazole]-3-(4-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 1. Yellow color solid, mp 163-166 °C; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.48 (2 H, m), 7.30 (1 H, m), 6.77 (2 H, m), 6.64 (1 H, d), 6.61 (1 H, d), 6.47 (1 H, m), 3.90 (3 H, s), 3.63 (3 H, s), 2.82 (3 H, s), 1.49 (9 H, s); δ_C (125 MHz, CDCl$_3$) 167.9, 165.5, 163.9, 161.8, 161.2 155.2, 149.7, 146.5, 135.3, 135.0, 131.1, 126.4, 119.7, 118.6, 117.8, 116.9, 108.0, 88.1, 56.5, 53.0, 27.98; LCMS: MH$^+$, 496.16. Anal. Calcd. For C$_{26}$H$_{26}$ClN$_3$O$_5$**:**C, 62.93; H, 5.24; Cl, 7.12; N, 8.45; O, 16.10. Found**:**C, 62.95; H, 5.23; Cl, 7.14; N, 8.47; O, 16.13.

Spiro[indole-2,2'-pyrazole]-3-(4-bromophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 2. Yellow color solid, mp 200-202 °C; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.32 (2 H, m), 7.29 (1 H, m), 6.81 (2 H, m), 6.63 (1 H, d), 6.59 (1 H, d), 6.47 (1 H, m), 3.90 (3 H, s), 3.63 (3 H, s), 2.82 (3 H, s), 1.49 (9 H, s); δ_C (125 MHz CDCl$_3$) 165.6, 163.7, 161.6, 161.2, 155.5, 149.2, 146.7, 135.0, 134.7, 129.3, 129.1,

126.7, 119.4, 118.2, 117.8, 108.2, 88.5, 57.5, 52.88, 52.88, 27.7; LCMS: MH$^+$, 541.17.Anal. Calcd. For C$_{26}$H$_{26}$ClN$_3$O$_5$**:** C, 57.77; H, 4.87; Br, 14.77; N, 7.80; O, 14.80. Found**:** C, 57.79; H, 4.85; Br, 14.75; N, 7.82; O, 14.80.

Spiro[indole-2,2'-pyrazole]-3-(2-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 3. Yellow color solid, mp 148-152 °C; **IR:** ν$_{max}$(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ$_H$ (500 MHz CDCl$_3$) 7.31 (1 H, dd), 7.25 (1 H, m), 7.17 (1 H, m), 7.03 (1H, m), 6.79 (1 H, d), 6.58 (1 H, d), 6.39 (2 H, m), 3.84 (3 H, s), 3.52 (3 H, s), 2.77 (3 H, s), 1.47 (9 H, s); δ$_C$ (125 MHz CDCl$_3$) 164.5, 163.7, 160.9, 159.8, 154.7, 146.7, 134.1, 129.17, 126.7, 125.4, 123.9, 122.5, 118.1, 117.6, 116.9, 107.1, 87.4, 51.4, 50.3, 26.81; LCMS: MH$^+$, 496.16.Anal. Calcd. For C$_{26}$H$_{26}$ClN$_3$O$_5$**:** C, 62.93; H, 5.24; Cl, 7.12; N, 8.45; O, 16.10. Found**:** C, 62.95; H, 5.23; Cl, 7.14; N, 8.47; O, 16.13.

Spiro[indole-2,2'-pyrazole]-3-(3-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester (4). Yellow color solid, mp 195-197 °C; **IR:** ν$_{max}$(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ$_H$ (500 MHz CDCl$_3$) 7.31 (2 H, t), 7.14 (1 H, m), 6.86 (1 H, t), 6.76 (1 H, d), 6.62 (1 H, m), 6.58 (1 H, t), 6.47 (1 H, t), 3.90 (3 H, s), 3.64 (3 H, s), 2.83 (3 H, s), 1.50 (9 H, s); δ$_C$ (125 MHz CDCl$_3$) 165.5, 163.9, 161.5, 161.2, 155.5, 151.9, 146.7, 135.1, 135.1, 130.6, 126.8, 124.0, 118.1, 118.0, 117.8, 116.3, 108.2, 88.5, 57.5, 52.88, 52.8, 28.0; LCMS: MH$^+$, 496.16.Anal.Calcd. For C$_{26}$H$_{26}$ClN$_3$O$_5$**:** C, 62.93; H, 5.24; Cl, 7.12; N, 8.45; O, 16.10. Found**:** C, 62.95; H, 5.23; Cl, 7.14; N, 8.47; O, 16.13.

Spiro[indole-2,2'-pyrazole]-3-(2,4-dichlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 5. Yellow color solid, mp 146-148 °C; **IR:** ν$_{max}$(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ$_H$ (500 MHz CDCl$_3$) 7.46 (1 H, m), 7.30 (1 H, m), 7.23 (1 H, m), 6.80 (1H, d), 6.65 (1 H, d), 6.52 (2 H, m), 3.94 (3 H, s), 3.59 (3 H, s), 2.82 (3 H, s), 1.52 (9 H, s);

δ_C (125 MHz CDCl$_3$) 165.5, 163.9, 161.5, 161.2, 155.5, 151.9, 146.7, 135.1, 135.1, 130.6, 126.8, 124.0, 118.12, 118.09, 117.8, 116.3, 116.1, 108.2, 88.5, 57.5, 53.0, 27.7; **LCMS:** MH$^+$, 529.12.Anal.Calcd. For C$_{26}$H$_{25}$Cl$_2$N$_3$O$_5$**:** C, 58.84; H, 4.77; Cl, 13.38; N, 7.95; O, 15.06. Found**:** C, 58.86; H, 4.75; Cl, 13.39; N, 7.90; O, 15.08.

Spiro[indole-2,2-'pyrazole]-3-(3-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester <u>**6.**</u> Yellow color solid, mp 138-140 °C; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.28-7.32 (2 H, m), 7.14 (1 H, m), 6.87 (1 H, t), 6.76 (1 H, m), 6.63 (1H, d), 6.55 (1H, d), 6.47 (1H, m), 4.37 (2 H, q), 4.08 (2 H, q), 2.83 (3 H, s), 1.51 (9 H, s), 1.37 (3 H, t), 0.99 (3 H, t); δ_C (125 MHz CDCl$_3$) 165.7, 164.1, 161.2, 160.7, 155.6, 152.0, 146.2, 135.3, 135.1, 130.7, 126.9, 124.0, 118.3, 118.1, 117.8, 116.1, 108.2, 88.4, 62.1, 57.4, 27.8, 14.2, 13.5; **LCMS:** MH$^+$, 524.01.Anal.Calcd. For C$_{28}$H$_{30}$ClN$_3$O$_5$**:** C, 64.18; H, 5.77; Cl, 6.77; N, 8.02; O, 15.27. Found**:** C, 64.16; H, 5.75; Cl, 6.75; N, 8.04; O, 15.27.

Spiro[indole-2,2-'pyrazole]-3-(4-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester <u>**7.**</u>Yellow color semi solid; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.34 (2 H, m), 7.29 (1 H, t), 6.82 (2 H, d), 6.62 (2 H, d), 6.46 (1 H, t), 4.37 (2 H, q), 4.08 (2 H, q), 2.83 (3 H, s), 1.50 (9 H, s), 1.36 (3 H, t), 0.97 (3 H, t); δ_C (125 MHz CDCl$_3$) 165.7, 163.9, 161.2, 160.7, 155.6, 149.3, 146.2, 135.3, 134.9, 129.6, 129.2, 126.7, 119.3, 118.4, 117.6, 108.1, 88.5, 62.1, 57.4, 27.79, 14.2, 13.5; **LCMS:** MH$^+$, 524.01.Anal.Calcd. For C$_{28}$H$_{30}$ClN$_3$O$_5$**:** C, 64.16; H, 5.79; Cl, 6.75; N, 8.04; O, 15.27. Found**:** C, 64.18; H, 5.77; Cl, 6.77; N, 8.024 O, 15.25.

Spiro[indole-2,2-'pyrazole]-3--(4-bromophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester <u>**8.**</u>Yellow color semi solid; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.49 (2 H, t), 7.30 (1 H, t), 6.77 (2 H, m), 6.62 (1 H, d), 6.58 (1

H, d), 6.47 (1 H, t), 4.38 (2 H, q), 4.08 (2 H, q), 2.82 (3 H, s), 1.50 (9 H, s), 1.37 (3 H, t), 0.98 (3 H, t); δ_C (125 MHz CDCl$_3$) 165.6, 163.8, 161.1, 160.7, 155.5, 149.7, 146.2, 135.2, 134.9, 132.5, 126.7, 119.7, 118.3, 117.6, 116.8, 108.1, 88.4, 62.1, 28.0, 14.0, 13.5; LCMS: MH$^+$, 568.46. Anal.Calcd. For C$_{28}$H$_{30}$BrN$_3$O$_5$: C, 59.16; H, 5.32; Br, 14.06; N, 7.39; O, 14.07. Found: C, 59.14; H, 5.32; Br, 14.08; N, 7.37; O, 14.09.

Spiro[indole-2,2-'pyrazole]-3-(4-methylphenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester 9. Yellow color semi solid; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.24 (1 H, m), 7.18 (2 H, d), 6.77 (2 H, d), 6.59 (2 H, t), 6.42 (1 H, t), 4.37 (2 H, q), 4.07 (2 H, q), 2.82 (3 H, s), 2.37 (3 H, s), 1.51 (9 H, s), 1.36 (3 H, t), 0.96 (3 H, t); δ_C (125 MHz CDCl$_3$) 165.7, 163.0, 161.30, 160.8, 155.3, 148.2, 135.2, 134.4, 133.4, 130.0, 129.7, 126.8, 118.8, 117.6, 117.4, 115.2, 107.8, 88.5, 62.04, 57.3, 28.0, 14.2, 13.5; LCMS: MH$^+$, 503.59. Anal.Calcd. For C$_{29}$H$_{33}$N$_3$O$_5$: C, 69.17; H, 6.60; N, 8.34; O, 15.89. Found:C, 69.17; H, 6.60; N, 8.34; O, 15.89.

Spiro[indole-2,2-'pyrazole]-3-(o-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester 10. Yellow color solid, mp 160-162 °C; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.30 (2 H, m), 7.18 (1 H, m), 6.83(1 H, t), 6.66 (1 H, d), 6.53 (1 H, d), 6.55 (1 H, d), 6.47 (1 H, m), 4.36 (2 H, q), 4.08 (2 H, q), 2.82(3 H, s), 1.50 (9 H, s), 1.37 (3 H, t), 0.99 (3 H, t); δ_C(125 MHz CDCl$_3$) 165.7, 164.1, 161.1, 160.7, 155.6, 152.1, 146.2, 135.2, 135.1, 135.1, 130.6, 126.9, 126.8, 124.0, 118.3, 118.1, 117.8, 116.1, 108.2, 88.4, 62.13, 62.0, 57.4, 27.8, 14.2, 14.1; LCMS: MH$^+$, 524.01. Anal.Calcd. For C$_{28}$H$_{30}$ClN$_3$O$_5$: C, 64.16; H, 5.75; Cl, 6.77; N, 8.04; O, 15.25. Found: C, 64.16; H, 5.79; Cl, 6.77; N, 8.04; O, 15.25.

Spiro[indole-2,2-'pyrazole]-3-(phenyl)imine-3',4'-dicarboxylic acid-1'-t-butyl-5'-one ethyl ester 11. Yellow color solid, mp 184-186 °C; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.38 (2 H, t), 7.28 (1 H, m), 7.16 (1 H, t), 6.87 (2 H, m), 6.61 (1 H, d), 6.49 (1 H, d), 6.41 (1 H, t), 4.37 (2 H, q), 4.07 (2 H, q), 2.83 (3 H, s), 1.52 (9 H, s), 1.36 (3 H, t), 0.97 (3 H, t); δ_C (125 MHz CDCl$_3$) 165.7, 163.2, 161.3, 160.8, 155.4, 150.9, 146.2, 135.3, 134.6, 129.53, 126.8, 124.0, 118.7, 117.7, 117.5, 107.9, 88.5, 62.0, 57.4, 27.8, 14.2, 13.5; LCMS: MH$^+$, 489.56.Anal.Calcd. For C$_{28}$H$_{31}$N$_3$O$_5$**:** C, 68.69; H, 6.36; N, 8.58; O, 16.36. Found**:** C, 68.69; H, 67.38; N, 8.58; O, 16.36

Spiro[indole-2,2'-pyrazole]-3-(2,4--dichlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester 12. Yellow color semi solid ; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.46 (1 H, m), 7.34 (1 H, m), 7.23 (1 H, dd), 6.65 (2 H, d), 6.49-6.56 (2 H, m), 4.39 (2 H, q), 4.04 (2 H, q), 2.84 (3 H, s), 1.52 (9 H, s), 1.37 (3 H, t), 0.93 (3 H, t); δ_C (125 MHz CDCl$_3$) 165.6, 164.5, 161.45, 160.35, 156.0, 146.4, 135.4, 133.6, 129.9, 129.4, 128.0, 126.4, 124.5, 120.1, 118.6, 118.0, 108.3, 88.4, 62.2, 57.5, 27.5, 14.1, 14.1; LCMS: MH$^+$, 558.45.Anal.Calcd. For C$_{28}$H$_{29}$Cl$_2$N$_3$O$_5$**:** C, 60.22; H, 5.23; Cl, 12.72; N, 7.50; O, 14.32. Found**:** C, 60.20; H, 5.23; Cl, 12.72; N, 7.48; O, 14.36.

Spiro[indole-2,2'-pyrazole]-3-(4--chlorophenyl)imine-3',4'-dicarboxylicacid-1'-pentyl-5'-one ethyl ester 13. Yellow color solid, mp 116-119 °C ; **IR:** ν_{max}(KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.31-7.34 (3 H, m), 6.75-6.77 (2 H, m), 6.67 (1 H, d), 6.57 (1 H, m), 6.48 (1 H, t), 4.39 (2 H, q), 4.12 (2 H, q), 3.22 (2 H, t), 2.75 (3 H, s), 1.60 (4 H, m), 1.39 (3 H, t), 1.26 (2 H, m), 1.04 (3 H, t), 0.83 (3 H, t); δ_C (125 MHz CDCl$_3$) 165.0, 163.6, 161.4, 160.2, 156.9, 149.1, 143.9, 137.8, 135.1, 129.6, 129.3, 126.7, 119.5, 117.7, 107.9, 87.3, 62.3, 62.0, 40.6, 29.2, 27.9, 22.2, 14.1, 13.9, 13.6; LCMS: MH$^+$, 558.45.Anal.Calcd. For

$C_{28}H_{29}Cl_2N_3O_5$**:** C, 60.22; H, 5.23; Cl, 12.72; N, 7.50; O, 14.32. Found**:** C, 60.20; H, 5.23; Cl, 12.72; N, 7.48; O, 14.36. LCMS: MH$^+$, 537. Anal.Calcd. For $C_{29}H_{32}ClN_3O_5$**:** C, 64.72; H, 5.99; Cl, 6.61; N, 7.81; O, 14.87. Found**:** C, 64.74; H, 5.99; Cl, 6.59; N, 7.79; O, 14.89

Analytical data for Hydrolyzed compound:

Spiro[indole-2,2'-pyrazole]-3-one-3',4'-dicarboxylicacid-1'-pentyl-5'-one ethyl ester. Yellow color solid, mp 236-240 °C ; **IR:** ν_{max}(KBr) 1740, 1736, 1660, 1618, 1240, 1041 cm^{-1}; δ_H (500 MHz CDCl$_3$) 7.59 (1 H, t), 7.64 (1 H, dd), 6.82-6.87 (2 H, m), 4.42 (2 H, q), 4.04 (2 H, q), 3.22 (2 H, t), 2.75 (3 H, s), m), 1.44 (2 H, m), 1.38 (3 H, t), 1.22 (4 H, m), 0.97 (3 H, t); δ_C (125 MHz CDCl$_3$) 192.38, 165.06, 161.20, 159.61, 145.78, 140.40, 138.88, 125.59, 119.9, 118.79, 108.79, 85.61, 62.42, 62.14, 40.72, 28.97, 28.27, 27.75, 22.07, 14.05, 13.81, 13.34; LCMS: MH$^+$, 428. Anal.Calcd. For $C_{23}H_{26}N_2O_6$**:** C, 64.45; H, 6.59; N, 6.56; O, 22.40. Found**:** C, 64.47; H, 6.61; N, 6.54; O, 22.38

4. Conclusion

An efficient and environmental friendly method for the synthesis of novel spiro[indole-2,2'-pyrroles] using readily available starting materials is reported. The notable advantages of this protocol are operational simplicity, easily available starting materials, available diversity of each component, catalyst free and easy work procedure employed. We believed in this protocol will help in developing novel spiro heterocyclic compounds using C-2 carbon atom of isatin.

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Chapter 5

Catalyst free, water mediated synthesis of 2,3-disubstituted imidazo[1,2-a]pyridines derivatives using three-component reaction and evaluation of their photophysical properties
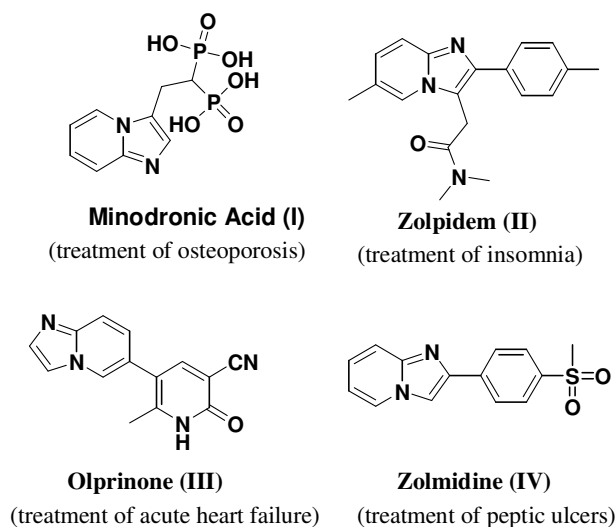
Abstract:

New coumarin derivatives having imidazo[1,2-a]pyridine heterocycle moiety were synthesized by the condensation of 4-morpholino-3-formyl coumarin, diversely substituted 2-amino pyridine and isocyanides under catalyst free, water mediated reaction conditions. All the products were characterized by using IR, NMR (1H and 13C) spectroscopy and HRMS spectrometry. Product 4b was further characterized with X-ray diffraction analysis. All the products have showed UV-Visible absorbance in between 234 nm to 248 nm and emissions were observed in between 412 nm to 544 nm.

1. Introduction

In the contemporary world one of the major problems that the world is facing is environmental pollution. Pharmaceutical industry is one of the polluter causing environmental pollution. So, the major challenge for the pharmaceutical industries is to keep focus on developing sustainable, environmental benign chemical methods for the synthesis of pharmaceutically active compounds. In this context, water mediated and catalyst free protocols for the synthesis valuable heterocyclic compounds have been attracting great attention because such methodologies reduces the generation of organic waste, water is abundant, inexpensive, non toxic and environmental benign solvent.[1]

Imidazo[1,2-a]pyridines have been valuable to organic and medicinal chemists due to the interesting structure and numerous applications in pharmaceutical Industry [1-12]. The molecules possessing imidazo[1,2-a]pyridine core structure have been used as anticancer [13-15], anti-inflammatory [16-17], antibacterial [18-19], antiprotozonal [20-22] and antiviral [23-25] agents. They have been found in drug molecules such as Minodronic acid (I), Zolpidem (II), Zolmidine (III) and Olprinone (IV).

Minodronic Acid (I)
(treatment of osteoporosis)

Zolpidem (II)
(treatment of insomnia)

Olprinone (III)
(treatment of acute heart failure)

Zolmidine (IV)
(treatment of peptic ulcers)

Figure 1. Examples of bioactive drugs containing imidazo[1,2-a]pyridine structure

As part of our research objectives to develop environmental benign methods for the synthesis of valuable heterocyclic compounds, herein, we would like to report the synthesis and photophysical properties of novel coumarin derivatives having imidazo[1,2-a]pyridine heterocycle moiety with extended π conjugation. Previously we reported the synthesis of novel benzazepinone derivatives using water as a reaction solvent [26]. There were already few methods available for the synthesis of coumarin derivatives having imidazo[1,2-a]pyridine heterocycle moiety (Scheme 1).
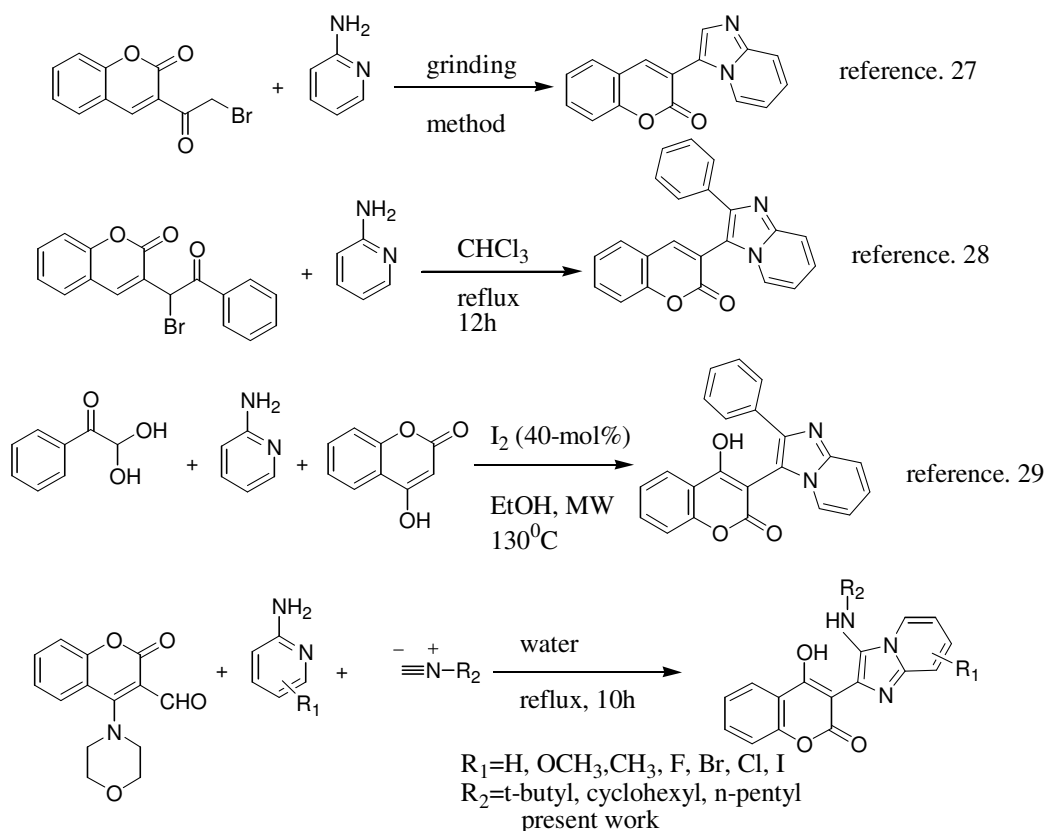
**Scheme 1.** Comparison of previous reports with our approach

These methods involved the reaction of bromoacetyl coumarin with 2-aminopyridines [27], condensation between 2-aminopyridines and 3-(2-(4-bromophenyl)-2-oxoethyl)-2H-chromen-2-one [28], multicomponent reaction of arylglyoxals, cyclic 1,3-dicarbonyls and 2-aminopyridine [29]. However, these methods have disadvantages like poor solubility of products in organic solvents, limited substrate scope and harsh reaction conditions were used.

2. Results and discussions

Groebke-Blackburn-Bienayme reaction is the most familier, widely used general reaction for the generation of imidazo[1,2-a]pyridine derivatives [30-32], it involved one-pot condensations of aldehydes, isonitriles, and 2-aminopyridines.

Table 1. Condensations of 4-morpholino-3-formyl coumarin, 2-amino pyridine and t-butyl isocyanide under different reaction conditions
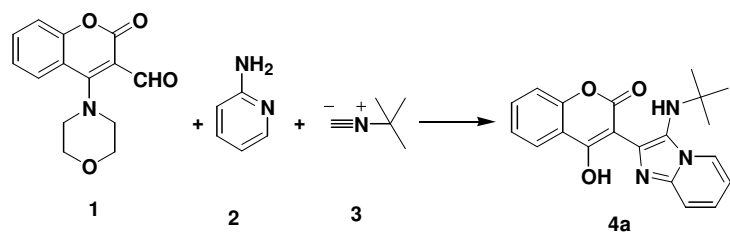
Entry	Solvent	Catalyst	Time (h)	Yield (%)[b]
1	EtOH	Et$_3$N	1	20
2	Benzene	Et$_3$N	1	20
3	Benzene	Et$_3$N	1	10
4	EtOH	PTSA	1	50
5	Benzene	PTSA	3	70
6	Water	PTSA (30mol %)	3	85
7	Water	NC[c]	10	91

[a]Reaction conditions: all the reactants were taken 1mmol each and reaction was performed under reflux in a given solvent, except entries 6, 1 equivalent catalyst was used

[b]Isolated yields

[c]No catalyst

In the present study, we have performed the Groebke-Blackburn-Bienayme reaction to synthesize the novel coumarin analogs using 4-morpholino-3-formyl coumarin as aldehyde component. Initially, to choose best reaction conditions to conduct the reaction, we have performed a three component condensation reaction using 4-morpholino-3-formyl coumarin, 2-amino pyridine and t-Butyl isocyanide under different reaction conditions (Table 1). The choice of the solvent and catalyst showed significant effect on the rate of the reaction. Low yields were observed under basic reaction conditions irrespective of solvent choice (Table 1, Entry. 1-3). On the other hand, when the reaction was performed in EtOH and Benzene solvents using PTSA catalyst, moderate yields were observed (Table 1, Entry. 4, 5).
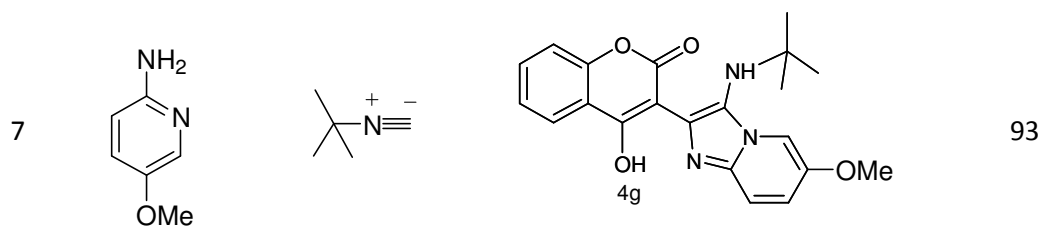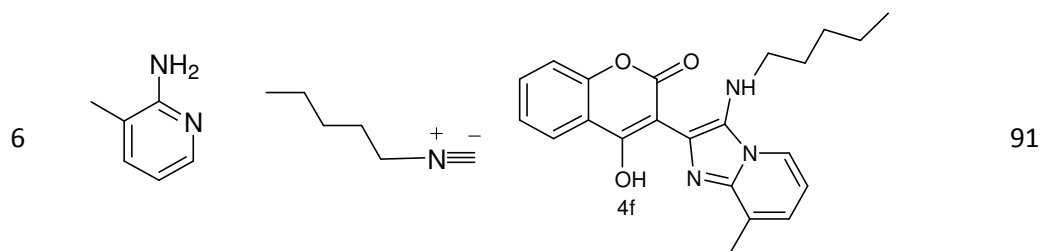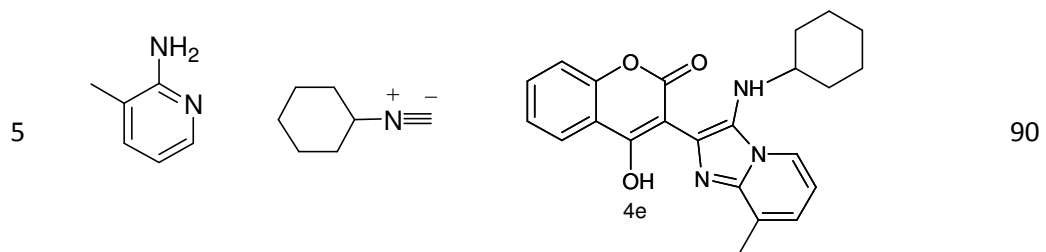
The reaction proceeded smoothly in water solvent using 30% PTSA catalyst, 85% of the product 4a formation was observed (Table 1, Entry. 6). When the same reaction was conducted in water without PTSA catalyst and refluxed for 10h, 91% of the product 4a formation was observed (Table 1, Entry.7). From the optimization reaction conditions, water was selected as a best solvent to conduct the reaction. With the optimization conditions in hand, further to explore the substrate scope of the reaction, a wide variety of 2-aminopyridines, isocyanides were reacted under optimized reaction conditions keeping the 4-morpholino-3-formyl coumarin constant. The results are summarized in Table 2. Various 2-aminopyridines possessing –Me, -oMe, -I, -Br, -Cl in different positions were reacted under the optimized reaction conditions and in all these cases moderate to excellent yield were observed (50-93%). Isocyanides possessing t-butyl, cyclohexyl, and n-pentyl groups were reacted in combination with various 2-aminopyridines. From the experimental results, it was concluded that electronic factors showed significant effect on the rate of this reaction. When the reaction was performed with 2-aminopyridine having –Cl, -Br, -I groups, less yields were obtained compare to unsubstituted 2-aminopyridines or its derivatives

having electron donating groups. Very good yields were obtained with unsubstituted 2-aminopyridines and 2-aminopyridines with electron releasing groups –Me, -OMe. Substituents on isocyanides have no effect on the rate of the reaction.
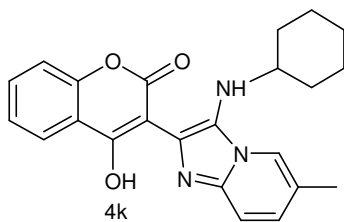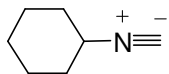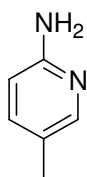
Table 2.Synthesis of coumarin derivatives having imidazo[1,2-a]pyridine (4a-4q)

R_1=H, OCH$_3$, CH$_3$, F, Br, Cl, I
R_2=t-butyl, cyclohexyl, n-pentyl
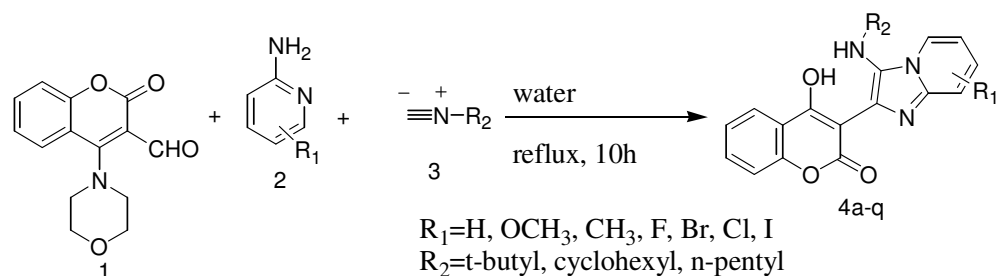
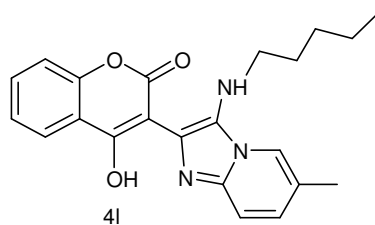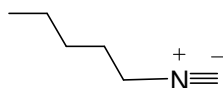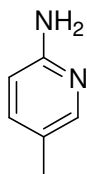| Entry	Amino pyridine	Isocyanide	Coumarin derivative (4a-4q)	Yield (%) [a]
1			4a	91
2			4b	90
3			4c	91
4			4d	93

Entry	Amine	Isocyanide	Product	Yield
5	3-methyl-2-aminopyridine	cyclohexyl isocyanide	4e	90
6	3-methyl-2-aminopyridine	pentyl isocyanide	4f	91
7	5-methoxy-2-aminopyridine	tert-butyl isocyanide	4g	93
8	5-methoxy-2-aminopyridine	cyclohexyl isocyanide	4h	92
9	5-methoxy-2-aminopyridine	pentyl isocyanide	4i	90
10	5-methyl-2-aminopyridine	tert-butyl isocyanide	4j	90

11	
4k	90
12	
4l	90
13	
4m	80
14	
4n	70
15	
4o	70
16	
4p | 60 |

| 17 | | | 4q | 50 |
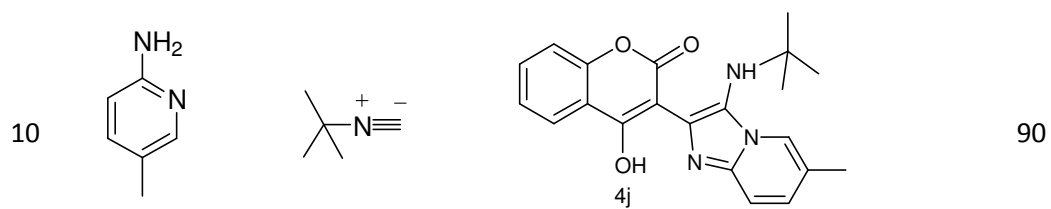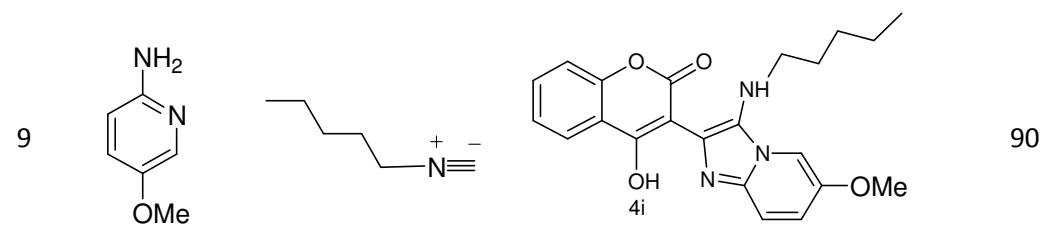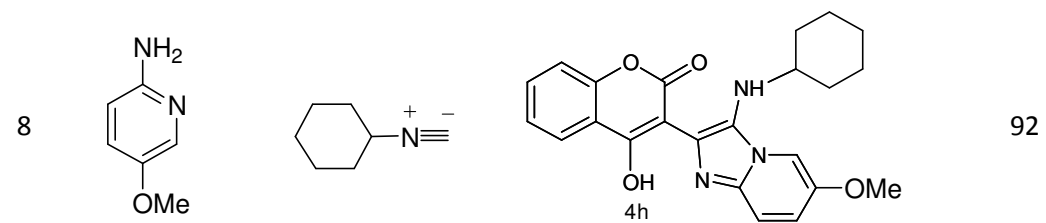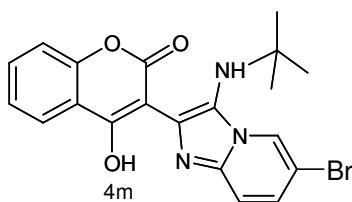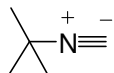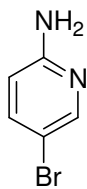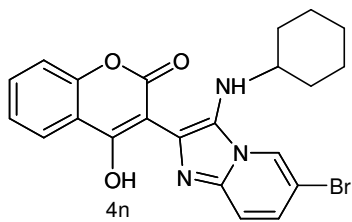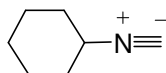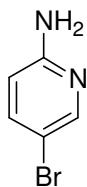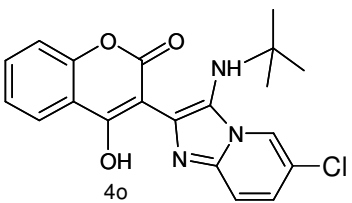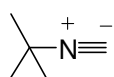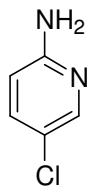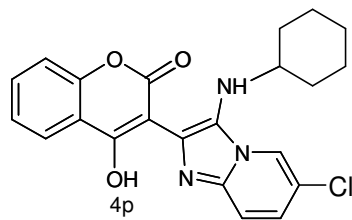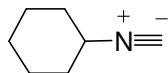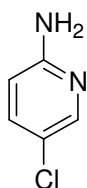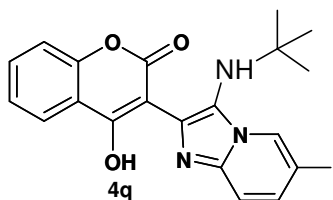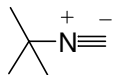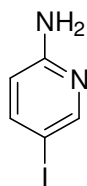
The reaction was not successful with 2-aminopyridine with –NO$_2$ substitution. The reason for this may be due to the strong electron withdrawing effect of –NO$_2$ group. All these products were fully characterized with IR, ^{1}H NMR, ^{13}C NMR and with elemental analysis. One of the products **4b** further characterized with X-ray diffraction analysis. The ortep diagram of this product is shown in Figure 1.
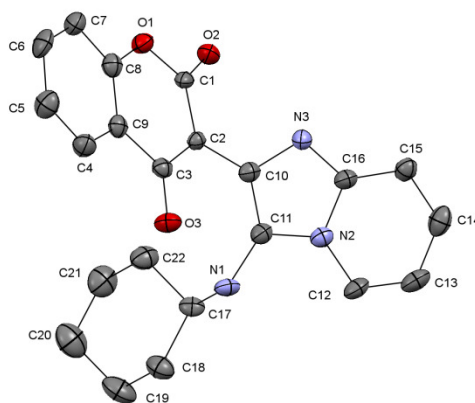
Figure 1. Ortep plot for the X-ray crystal structure of product **4b** with 50% probability

Based on the above results and related reports [30-32], we would like propose the plausible reaction mechanism for the formation of final products 4a-4q. We took 4-morpholino-3-formyl coumarin, 2-aminopyridine and t-butyl isocyanide as model substrates to explain the plausible mechanism for the formation of product **4a.** The first step of the reaction is imine formation. 4-morpholino-3-formyl coumarin (1) reacts with 2-aminopyridine (2) gives intermediate A, this reacts with t-butyl isocyanide gives intermediate B. Intermediate B undergoes intramolecular cyclization gives intermediate C. This undergoes intramolecular 1,3-hydride shift followed by the deprotection of morpholine group resulted the final product 4a.
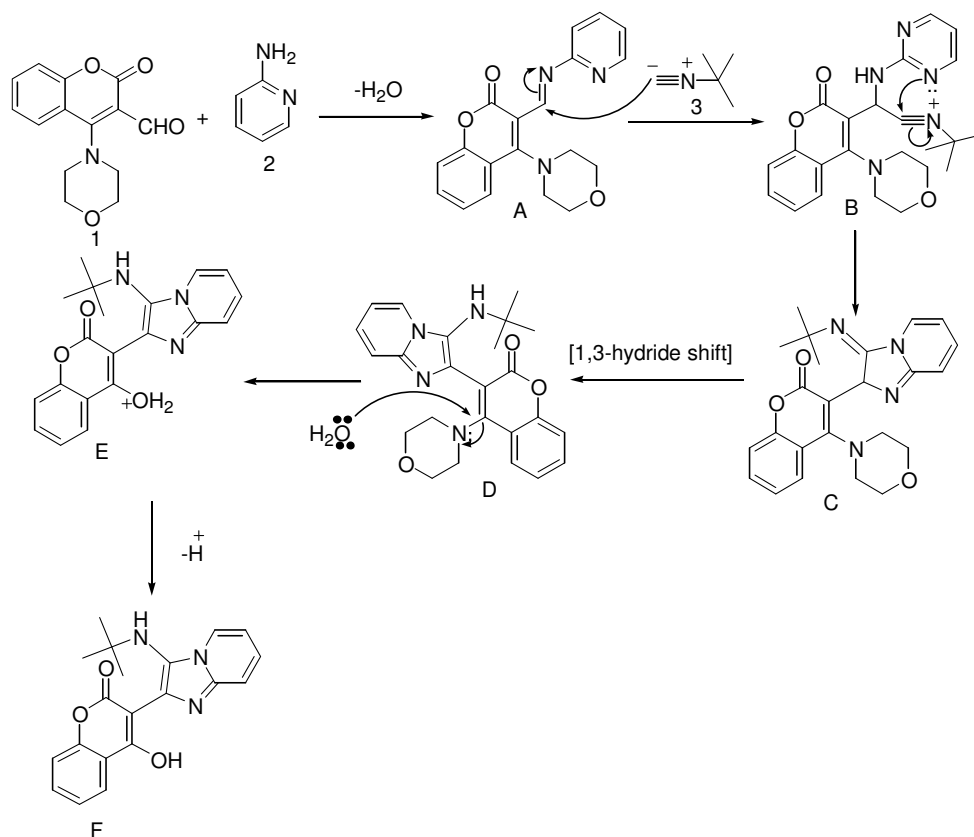
Scheme 2. Plausible reaction mechanism for the synthesis of imidazo[1,2-a]pyridine

The synthesized compounds (4a-4q) were further evaluated for their optoelectronic properties. We have measured the UV-Vis absorption and fluorescence emissions of compounds 4a-4q in MeOH solvent. The concentrations of coumarin derivatives were 2.0×10^{-4} mol/L for absorption in MeOH solvent. The results are summarized in Table 3. All the compounds have showed UV-Visible absorbance in between 234 nm to 248 nm and emissions were observed in between 412 nm to 544 nm.

Table 3. UV-Visible absorption and fluorescence of compounds 4a-4q

Compound	λ_{abs}/nm	λ_{ex}/nm	λ_{em}/nm
4a	234	396	462
4b	240	447	544
4c	242	397	455
4d	236	390	431
4e	238	398	434
4f	246	395	482
4g	248	375	412
4h	234	379	415
4i	240	374	415
4j	238	394	437
4k	247	402	441
4l	245	401	440
4m	238	402	498
4n	243	430	518
4o	234	395	512
4p	243	415	475
4q	248	397	469

[a] The concentration of all the samples were 2.0×10^{-4} mol/L in Methanol solvent

3. Experimental

All reagents were purchased from TCI and Sigma Aldrich and used without further purification. N-methyl isatin imines were synthesized according to the procedure reported in the literature. All the products were characterized by ^{1}H NMR, C^{13} NMR, IR, and Fab-Mass analysis. The NMR spectra were recorded on a Bruker AMX-500 MHz instrument at room

temperature in CDCl$_3$ using TMS as an internal reference. Melting points were determined by AS ONE instrument. X-ray data for the compound were collected at room temperature using a Bruker Apex II KY CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Crystallographic data of **4b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1440029 contains the supplementary crystallographic data for this paper.

General procedure for the synthesis of coumarin derivatives having imidazo[1,2-a]pyridine (4a-4q):

A solution of 4-morpholino-3-formyl coumarin (1 mmol), corresponding 2-aminopyridine (1 mmol) and isocyanide (1 mmol) were taken in 15 ml water solvent and refluxed for 10h. The reaction mixture was cooled to room temperature. Filtered off the solid products precipetated and passed through filter column using 50% EtOAc/Hexane mobile phase. All the products were isolated good yields ranging from 60-93%.

4-Hydroxy-3-(3-(N-t-butylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4a).

White color solid, mp 249-253°C; IR: ν$_{max}$(KBr) 3095, 2966, 1733, 1586, 1521, 1462 cm^{-1}; δ$_H$ (500 MHz DMSO-d$_6$) 1.01 (9 H, s), 5.24 (1 H, s), 7.26-7.28 (2 H, m), 7.36-7.38 (1 H, m), 7.52-7.55 (1 H, m), 7.75-7.78 (1 H, m), 7.85 (1 H, m), 8.01 (1 H, *J*= 1.35 Hz, dd), 8.77 (1 H, *J*= 6.75 Hz, d); δ$_C$ (125 MHz, CDCl$_3$) 29.6, 56.8, 88.4, 111.7, 116.1, 116.4, 122.5, 123.3, 124.8, 124.9, 125.6, 127.8, 131.1, 131.9, 136.2, 153.8, 163.4, 173.5; HRMS-FAB(m/z) calcd for C$_{20}$H$_{19}$N$_3$O$_3$ ([M + H]$^+$) 348.3833, found 348.3845.

4-Hydroxy-3-(3-(N-cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4b).

Yellow color solid, mp 222-225°C; IR: ν$_{max}$(KBr) 3164, 2927, 1734, 1586, 1521, 1462 cm^{-1}; δ$_H$

(500 MHz CDCl$_3$) 1.11-1.30 (5 H, m), 1.53-1.84 (5 H, m), 2.68 (1 H, sex), 4.72 (1 H, d), 7.12-7.14 (1 H, m), 7.26-7.31 (2 H, m), 7.44-7.47 (1 H, m), 7.50-7.54 (1 H, , m), 7.59-7.61 (1 H, m), 8.11-8.13 (1 H, J=1.35 Hz, dd), 8.30 (1 H, J=6.7 Hz, d); δ_C (125 MHz, CDCl$_3$) 25.2, 25.6, 33.8, 56.6, 56.7, 90.9, 112.3, 114.5, 116.4, 120.4, 123.4, 123.5, 124.9, 125.7, 127.5, 131.8, 134.6, 135.8, 153.4, 163.7, 173.5; HRMS-FAB(m/z) calcd for C$_{22}$H$_{21}$N$_3$O$_3$ ([M + H]$^+$) 374.4206, found 374.4214.

4-Hydroxy-3-(3-(N-pentylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4c). Yellow color solid, mp 168-172°C; IR: ν_{max}(KBr) 3165, 2928, 1730, 1658, 1630 cm^{-1}; δ_H (500 MHz CDCl$_3$) 0.83-0.87 (3 H, J=7.15 Hz, t), 1.24-1.37 (4 H, m), 1.54-1.60 (2 H, J=7.1Hz, quin), 2.87 (2 H, J=6.65 Hz, t), 6.03 (1 H, s), 7.10-7.13 (1 H, J=6.8 Hz, t), 7.23-7.29 (2 H, m), 7.41-7.43 (1 H, m), 7.48-7.51 (1 H, m), 7.70 (1 H, J=8.45 Hz, d), 8.09 (1 H, J=1.45 Hz, dd), 8.27 (1 H, J=6.8 Hz, d); δ_C (125 MHz, CDCl$_3$) 14.01, 22.5, 29.2, 30.1, 48.4, 90.6, 112.5, 114.6, 116.3, 120.6, 122.9, 123.4, 125, 126.3, 127.2, 127.6, 131.8, 134.8, 153.4, 163.9, 173.6; HRMS-FAB(m/z) calcd for C$_{21}$H$_{21}$N$_3$O$_3$ ([M + H]$^+$) 362.4099, found 362.4087.

4-Hydroxy-3-(8-methyl-3-(N-t-butylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4d). White color solid, mp 250-254°C; IR: ν_{max}(KBr) 3247, 2956, 1729, 1657, 1594 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.11 (9 H, s), 2.62 (3 H, s), 5.41 (1 H, s), 6.99-7.02 (1 H, J=6.85 Hz, t), 7.25-7.32 (3 H, m), 7.51-7.52 (1 H, m), 8.11-8.13 (1 H, J=1.5 Hz, dd), 8.45-8.47 (1 H, J=6.6 Hz, d); δ_C (125 MHz, CDCl$_3$) 15.8, 29.5, 57.3, 91.1, 114.1, 116.5, 120.3, 121.9, 122.4, 123.5, 124.7, 124.8, 127.6, 130.3, 131.9, 135.5, 153.5, 163.3, 173.8; HRMS-FAB(m/z) calcd for C$_{21}$H$_{21}$N$_3$O$_3$ ([M + H]$^+$) 362.4099, found 362.4086.

4-Hydroxy-3-(8-methyl-3-(N-cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4e). Yellow color solid, mp 176-178°C; IR: ν_{max}(KBr) 3279, 2929, 1730, 1647, 1604 cm^{-1};

δ_H (500 MHz CDCl$_3$) 1.11-1.31 (5 H, m), 1.54-1.84 (5 H, m), 2.63 (3 H, s), 2.68 (1 H, m), 6.02 (1 H, J=8.5 Hz, d), 7.01-7.04 (1 H, J=3.2 Hz, t), 7.22-7.32 (3 H, m), 7.51-7.54 (1 H, m), 8.11-8.14 (2 H, m); δ_C (125 MHz, CDCl$_3$) 15.9, 25.3, 25.6, 33.7, 56.6, 91.4, 114.4, 116.5, 120.0, 121.3, 122.5, 123.5, 124.6, 125.8, 126.6, 127.6, 131.8, 134.8, 153.3, 163.3, 173.3; HRMS-FAB(m/z) calcd for C$_{23}$H$_{23}$N$_3$O$_3$ ([M + H]$^+$) 388.4471, found 389.4486.

4-Hydroxy-3-(8-methyl-3-(N-pentylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4f). Yellow color solid, mp 102-104°C; IR: ν_{max}(KBr) 3297, 2946, 1717, 1669, 1540 cm^{-1}; δ_H (500 MHz CDCl$_3$) 0.85-0.88 (3 H, J=7.25 Hz, t), 1.24-1.37 (4 H, m), 1.56-1.62 (2 H, J=7.1 Hz, quin), 2.60 (3 H, s), 2.85-2.89 (2 H, J=3.65 Hz, q), 6.20-6.22 (1 H, J=6.8 Hz, t), 6.99-7.02 (1 H, J=6.85 Hz, t), 7.19-7.20 (1 H, m), 7.23-7.30 (2 H, m), 7.49-7.53 (1 H, m), 8.08-8.10 (2 H, J=1.15 Hz, dd); δ_C (125 MHz, CDCl$_3$) 14.1, 15.9, 22.6, 29.2, 30.1, 48.6, 91.4, 114.5, 116.4, 119.9, 120.8, 122.6, 123.5, 124.6, 126.5, 127.1, 131.8, 134.7, 153.2, 163.3, 173.1; HRMS-FAB(m/z) calcd for C$_{22}$H$_{23}$N$_3$O$_3$ ([M + H]$^+$) 376.4364, found 376.4375.

4-Hydroxy-3-(6-methoxy-3-(N-t-butylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4g). White color solid, mp 188-190°C; IR: ν_{max}(KBr) 3276, 2966, 1734, 1652, 1528 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.08 (9 H, s), 3.86 (3 H, s), 5.26 (1 H, s), 6.77 (1 H, m), 7.00 (1 H, s), 7.21-7.24 (2 H, m), 7.46-7.49 (1 H, m), 8.12 (1 H, J=1.45 Hz, dd), 8.39 (1 H, J=7.4 Hz, d); δ_C (125 MHz, CDCl$_3$) 29.5, 56.3, 56.8, 90.1, 90.8, 108.6, 116.2, 121.9, 123.1, 124.0, 125.1, 125.3, 127.3, 131.4, 137.7, 153.6, 161.4, 174.6; HRMS-FAB(m/z) calcd for C$_{21}$H$_{21}$N$_3$O$_4$ ([M + H]$^+$) 378.4093, found 378.4080.

4-Hydroxy-3-(6-methoxy-3-(N-cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4h). Yellow color solid, mp 192-194°C; IR: ν_{max}(KBr) 3259, 2927, 2853, 1734, 1663, 1595 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.10-1.25 (5 H, m), 1.52-1.83 (5 H, m), 2.62 (1 H, m), 3.85 (3

H, s), 5.72 (1 H, J=8.45 Hz, d), 6.78 (1 H, J=7.1 Hz, d), 7.00 (1 H, s), 7.21-7.26 (2 H, m), 7.46-

7.49 (1 H, m), 8.12 (1 H, J=7.8 Hz, d); δ_C (125 MHz, CDCl$_3$) 25.2, 25.6, 33.7, 56.3, 57.4, 89.9,

91.00, 109.1, 116.2, 121.6, 123.2, 124.9, 125.1, 125.2, 131.4, 136.8, 153.4, 160.9, 164.2, 174.2;

HRMS-FAB(m/z) calcd for C$_{21}$H$_{21}$N$_3$O$_4$ ([M + H]$^+$) 404.4465, found 404.4482.

4-Hydroxy-3-(6-methoxy-3-(N-pentylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one

(4i). Yellow color solid, mp 130-134°C; IR: ν_{max}(KBr) 3262, 1919, 1730, 1663, 1595 cm^{-1}; δ_H

(500 MHz CDCl$_3$) 0.81-0.84 (3 H, J=7.15 Hz, t), 1.23-1.35 (4 H, m), 1.51-1.57 (2 H, J=7.4 Hz,

quin), 2.80-2.84 (2 H, J=6.85 Hz, q), 3.84 (3 H, s), 5.87 (1 H, J=7.1 Hz, t), 6.76-6.78 (1 H, J=2.3

Hz, dd), 7.02 (1 H, s), 7.21-7.26 (2 H, m), 7.45-7.49 (1 H, m), 8.07-8.11 (2 H, m); δ_C (125 MHz,

CDCl$_3$) 13.9, 22.5, 29.2, 29.9, 48.9, 56.2, 89.7, 91.1, 109.1, 116.1, 121.6, 123.2, 123.8, 124.0,

125.2, 126.1, 131.4, 136.8, 153.4, 160.9, 164.3, 174.2 ; HRMS-FAB(m/z) calcd for C$_{22}$H$_{23}$N$_3$O$_4$

([M + H]$^+$) 392.4358, found 392.4371.

4-Hydroxy-3-(6-methyl-3-(N-t-butylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one

(4j). White color solid, mp 232-235°C; IR: ν_{max}(KBr) 3202, 2973, 1730, 1635, 1607 cm^{-1}; δ_H

(500 MHz CDCl$_3$) 1.11 (9 H, s), 2.44 (3 H, s), 5.36 (1 H, s), 7.22-7.29 (2 H, m), 7.33-7.34 (1 H,

J=7.55 Hz, d), 7.60-7.61 (1 H, J=9 Hz, d), 8.10-8.11 (1 H, J=1.5 Hz, dd), 8.39 (1 H, s); δ_C (125

MHz, CDCl$_3$) 18.4, 29.5, 57.2, 90.4, 111.1, 116.4, 121.4, 122.2, 123.2, 124.5, 124.6, 125.2,

129.5, 131.6, 131.7, 134.3, 153.7, 164.2, 174.7; HRMS-FAB(m/z) calcd for C$_{22}$H$_{23}$N$_3$O$_4$ ([M +

H]$^+$) 362.4099, found 362.4070.

4-Hydroxy-3-(6-methyl-3-(N-cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-

one (4k). Yellow color solid, mp 242-244°C; IR: ν_{max}(KBr) 3212, 2932, 2854, 1717, 1684, 1653

cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.13-1.29 (5 H, m), 1.53-1.84 (5 H, m), 2.45 (3 H, s), 2.67 (1 H, m),

5.89 (1 H, J=8.5 Hz, d), 7.24-7.25 (1 H, m), 7.28-7.31 (2 H, m), 7.48-7.50 (1 H, m), 7.54-7.56 (1

H, J=9.1 Hz, d), 8.06 (1 H, s), 8.10-8.11 (1 H, J=1.45 Hz, dd); δ_C (125 MHz, CDCl$_3$) 18.5, 25.6, 33.7, 56.7, 90.4, 111.4, 116.4, 120.9, 121.1, 123.3, 124.8, 125.0, 125.4, 127.4, 130.7, 131.7, 133.3, 153.4, 163.6, 174.1; HRMS-FAB(m/z) calcd for C$_{23}$H$_{23}$N$_3$O$_3$ ([M + H]$^+$) 388.4471, found 388.4487.

4-Hydroxy-3-(6-methyl-3-(N-pentylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one

(4l). Yellow color solid, mp 102-104°C; IR: ν_{max}(KBr) 3297, 2946, 1717, 1669, 1540 cm^{-1}; δ_H (500 MHz CDCl$_3$) 0.84-0.86 (3 H, J=7.1 Hz, t), 1.24-1.37 (4 H, m), 1.56-1.62 (2 H, J=7.1Hz, quin), 2.45 (3 H, s), 2.85-2.86 (2 H, J= 3.44 Hz, q), 6.11 (1 H, J=6.2 Hz, t), 7.24-7.30 (3 H, m), 7.48-7.54 (2 H, m), 8.04 (1 H, s), 8.09-8.11 (1 H, J=1.35 Hz, dd); δ_C (125 MHz, CDCl$_3$) 14.0, 14.2, 18.4, 22.5, 29.2, 30.0, 48.3, 90.4, 111.5, 116.3, 120.8, 123.4, 124.9, 125.0, 126.4, 126.6, 130.5, 131.7, 133.1, 153.4, 163.9, 174.1; HRMS-FAB(m/z) calcd for C$_{22}$H$_{23}$N$_3$O$_3$ ([M + H]$^+$) 376.4364, found 376.4390.

4-Hydroxy-3-(6-bromo-3-(N-t-butylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one

(4m). Yellow solid, mp 232-235°C; IR: ν_{max}(KBr) 3179, 2966, 1734, 1684, 1644 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.12 (9 H, s), 5.21 (1 H, s), 7.29-7.33 (2 H, m), 7.39-7.41 (1 H, m), 7.48-7.50 (1 H, m), 7.54-7.56 (1 H, m), 8.07-8.08 (1 H, m), 8.62 (1 H, s); δ_C (125 MHz, CDCl$_3$) 29.5, 57.3, 99.6, 114.4, 116.5, 123.8, 124.3, 124.5, 125.6, 130.0, 132.1, 132.3, 136.0, 140.1, 148.7, 153.2, 157.0, 168.4; HRMS-FAB(m/z) calcd for C$_{20}$H$_{18}$BrN$_3$O$_3$ ([M + H]$^+$) 427.2793, found 427.2768.

4-Hydroxy-3-(6-bromo-3-(N-cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4n). Yellow color solid, mp 216-218°C; IR: ν_{max}(KBr) 3177, 3095, 2966, 1734, 1684, 1652 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.15-1.30 (5 H, m), 1.56-1.82 (5 H, m), 2.69 (1 H, J=7.2 Hz, t), 5.80 (1 H, d), 7.29-7.37 (5 H, m), 7.42-7.44 (1 H, m), 8.29 (1 H, s); δ_C (125 MHz, CDCl$_3$) 25.2, 25.6, 33.8, 56.6, 94.0, 108.3, 114.8, 116.4, 118.1, 123.1, 123.9, 124.4, 126.7, 129.1, 129.7, 132.2,

135.1, 153.0, 162.5, 169.8 ; HRMS-FAB(m/z) calcd for $C_{22}H_{20}BrN_3O_3$ ([M + H]$^+$) 453.3166, found 453.3182.

4-Hydroxy-3-(6-chloro-3-(N-t-butylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one

(4o). White color solid, mp 232-235°C; IR: ν_{max}(KBr) 3180, 3097, 2964, 1730, 1684, 1652 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.10 (9 H, s), 5.21 (1 H, s), 7.26-7.33 (3 H, m), 7.53-7.57 (2 H, m), 8.07-8.08 (1 H, J=1.45 Hz, dd), 8.52 (1 H, s); δ_C (125 MHz, CDCl$_3$) 29.7, 57.2, 93.6, 114.0, 116.4, 121.9, 122.1, 123.7, 124.6, 125.8, 128.2, 132.1, 132.2, 135.5, 153.2, 163.0, 170.7; HRMS-FAB(m/z) calcd for $C_{20}H_{18}ClN_3O_3$ ([M + H]$^+$) 382.8280, found 382.8299.

4-Hydroxy-3-(6-chloro-3-(N-cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one (4p). White color solid, mp 205-207°C; IR: ν_{max}(KBr) 3256, 2926, 1715, 1656 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.14-1.29 (5 H, m), 1.55-1.82 (5 H, m), 2.67 (1 H, m), 5.79-5.81 (1 H, J=7.4 Hz, d), 7.25-7.32 (3 H, m), 7.50-7.55 (2 H, m), 8.05-8.06 (1 H, J=1.05 Hz, dd), 8.19 (1 H, s); δ_C (125 MHz, CDCl$_3$) 25.2, 25.6, 33.8, 56.6, 93.6, 114.4, 116.4, 118.4, 120.9, 122.1, 123.8, 124.5, 126.8, 127.2, 129.7, 132.2, 134.8, 153.1, 162.7, 170.2; HRMS-FAB(m/z) calcd for $C_{22}H_{20}ClN_3O_3$ ([M + H]$^+$) 408.8653, found 408.8677.

4-Hydroxy-3-(6-iodo-3-(N-t-butylamino)imidazo[1,2-a]pyridin-2-yl)-2H-chromen-2-one

(4q). Yellow color solid, mp 232-234°C; IR: ν_{max}(KBr) 3177, 3095, 2966, 1734, 1684, 1652 cm^{-1}; δ_H (500 MHz CDCl$_3$) 1.10 (9 H, s), 5.22 (1 H, s), 7.30-7.35 (4 H, m), 7.50-7.57 (2 H, m), 8.74 (1 H, s); δ_C (125 MHz, CDCl$_3$) 28.5, 56.2, 109.8, 113.3, 115.4, 122.7, 123.6, 124.1, 128.1, 131.1, 133.9, 134.6, 144.3, 152.2, 152.7, 156.3, 162.3, 170.1; HRMS-FAB(m/z) calcd for $C_{20}H_{18}IN_3O_3$ ([M + H]$^+$) 474.2798, found 474.2766.

4. Conclusion

In conclusion, we have reported an efficient, catalyst free and water mediated synthesis of new coumarin derivatives having imidazo[1,2-a]pyridine moiety using Groebke-Blackburn-Bienayme condensation reaction. Various 2-amino pyridine derivatives and isocyanides were used in this reaction. The final structure of the final product **4b** was confirmed with X-ray diffraction analysis. The notable advantages of this protocol are water was employed as a reaction solvent, operational simplicity, easily available starting materials and no catalyst was employed.

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Achievements

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7. Tetsuji Moriguchi1, Tatsuya Egami, Daisuke Yakeya, **Venkataprasad Jalli**, Kenji Yoza, Akihiko Tsuge. Synthesis and Crystal Structure Determination of 4',9',4",9"-Tetra-*t*-Butyl-1',6',1",6"-Tetramethoxy-2,5-Dithia[3.3]Metabiphenylophane. *Crystal Structure Theory and Applications*. 2016, 5, 56-62.

8. Tetsuji Moriguchi, Makoto Higashi, Daisuke Yakeya, **Venkataprasad Jalli**, Akihiko Tsuge, Tatsuo Okauchi, Shuichi Nagamatsu, Wataru Takashima. Synthesis, characterization and air stable semiconductor properties of thiophene-condensed pyrene derivatives. *J. Mol. Structure*. 2017, 1127, 413-418.

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10. Tetsuji Moriguchi1, Keiichi Mitsumoto, Yuki Nishizawa, Daisuke Yakeya, **Venkataprasad Jalli** and Akihiko Tsuge. Syntheses, Characterization and DFT Analysis of Two Novel Thiaheterohelicene Derivatives. *Crystal Structure Theory and applications*. 2016, 5, 63-73.

Conference Presentations

1. **Venkataprasad Jalli**, Suvratha Krishnamurthy, Tetsuji Moriguchi and Akihiko Tsuge, "Synthesis of novel spiro[indole-pyrazoles] using isocyanide based multi component reaction", 10th International symposium on bio-organic chemistry, Pune, India, January, 2015, poster presentation (PP 068).

2. **Venkataprasad Jalli**, Suvratha Krishnamurthy, Tetsuji Moriguchi and Akihiko Tsuge, "Efficient synthesis of novel spiro[indole-2,2'-pyrazoles]", Kyushu branch chemical symposium, Kitakyushu, Japan, 27th June, 2015, Poster presentation (OC-3-0004).

3. Suvratha Krishnamurthy, **Venkataprasad Jalli**, Tetsuji Moriguchi, Koji Araki and Akihiko Tsuge, "Chemoenzymatic synthesis of 4-hydroxyproline and 5-hydroxypipecolicacid through epoxide cyclization", Kyushu branch chemical symposium, Kitakyushu, Japan, 27th June, 2015, Poster presentation (OC-3-0003).

4. **Venkataprasad Jalli**, Tetsuji Moriguchi and Akihiko Tsuge, "Synthesis of novel fluorescent 3-furyl coumarin materials using multicomponent protocol ", International symposium on nanoscience, nanotechnology and advanced materials, Visakhapatnam, India, December 14-17, 2015, poster presentation (P-SYN-116).