Design, Synthesis and BetaIonone Based Hydroxy-Indole & Conversion to Quinoline Carboxamide Derivatives

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Abstract

The development of biologically active 3-hydroxyindoline derivatives have been widely explored as these molecules demonstrate a wide range of medicinal properties like antioxidant, anti-inflammatory and anticonvulsant. They have also been explored for their anti-microbial potential and have shown interesting results. While going through literature, it was observed that the synthetic and therapeutic potential of β-ionone based 3-hydroxyindoles have not been investigated. Already discussed in introduction, β-ionone derivatives have shown interesting antioxidant and anti-inflammatory properties. The aim of present research project is to design, synthesize and evaluate the biological potentials of β-ionone based 3-hydroxyindoles.

Keywords: Carboxamide, Quinoline, Beta-ionone, Anti-inflammatory, Biological Potential

Introduction

Antioxidants are the molecules that prevent cellular damage caused by oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from one molecule to an oxidizing agent.[1] Oxidation reactions are known to produce free radicals. These free radicals are highly reactive species which contains one or more unpaired electrons in their outermost shell. Once they are formed, the chain reaction starts. Antioxidant reacts with these free radicals and terminates this chain reaction by removing free radical intermediates

and inhibits other oxidation reactions by oxidizing themselves.[2] Though oxidation reactions are crucial for life, they can also be damaging. Plants and animals have a complex system of multiple types of antioxidants, such as vitamin C and vitamin E, as well as enzymes, such as catalase (CAT), superoxide dismutase (SOD), and various peroxidases (Hamid et al. 2010). Oxidative stress plays a key role in causing various human diseases, such as cellular necrosis, cardiovascular disease, cancer, neurological disorder, Parkinson's dementia, Alzheimer's disease, inflammatory disease, muscular dystrophy, liver disorder, and even aging (Amit and Priyadarsini 2011). Besides, there are some antioxidants in the form of micronutrients which cannot be manufactured by the body itself such as vitamin E, β-carotene, and vitamin C, and hence these must be supplemented in the normal diet[3] (Teresa et al. 2011).

The development of biologically active 3-hydroxyindoline derivatives have been widely explored as these molecules demonstrate a wide range of medicinal properties like antioxidant, anti-inflammatory and anticonvulsant.[9] They have also been explored for their anti-microbial potential and have shown interesting results. While going through literature, it was observed that the synthetic and therapeutic potential of β-ionone based 3-hydroxyindoles have not been investigated. Already discussed in introduction, β-ionone derivatives have shown interesting antioxidant and anti-inflammatory properties. The aim of present research project is to design, synthesize and evaluate the biological potentials of β-ionone based 3-hydroxyindoles as shown in Figure.

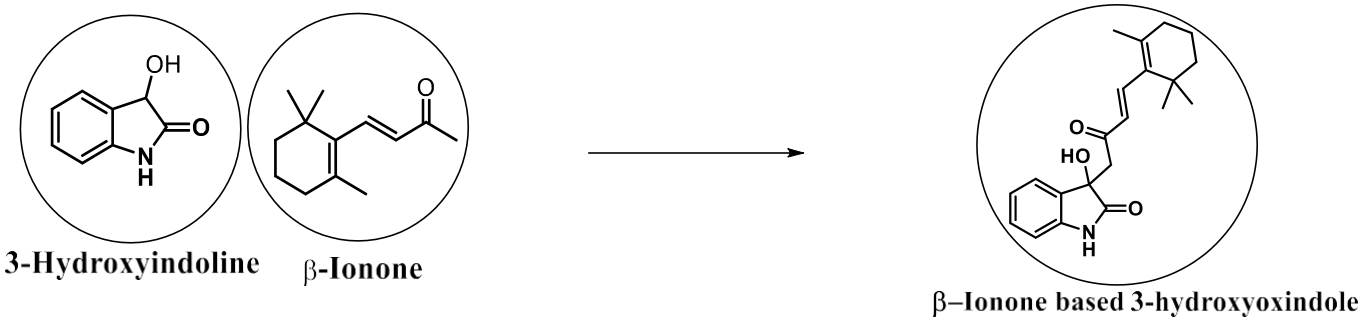
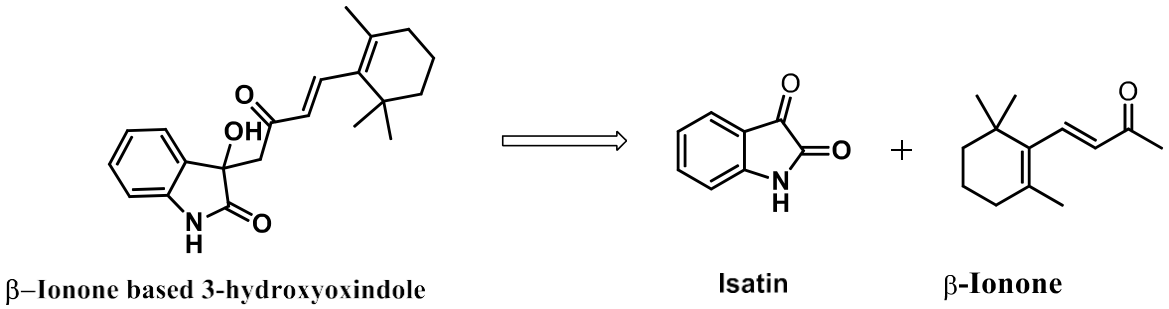


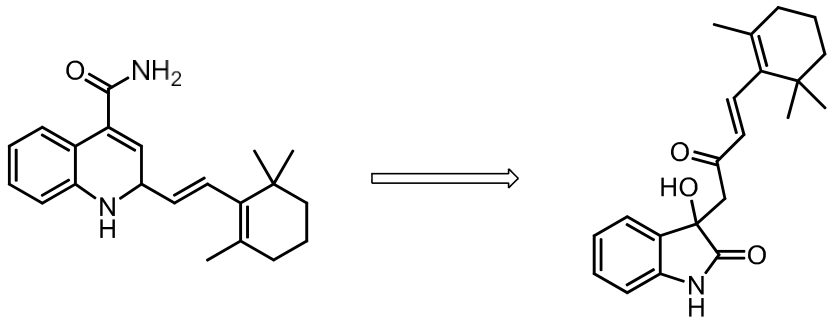
Figure: Design of β-ionone based 3-hydroxyindoles.

As a part of our research plan aimed at developing new synthetic methodologies for the creation of biologically important molecules, we propose to synthesize beta-ionone based 3-hydroxyl oxy-indole derivatives. A synthetic protocol for synthesis of a series of designed moleculeswith optimization of reaction protocol will be developed. A retrosynthetic scheme is shown below.



Scheme: Retrosynthetic scheme

As we have already developed protocol in our laboratory to convert 3-hydroxyoxindole derivative to quinoline-4-carboxamide derivative as shown below.

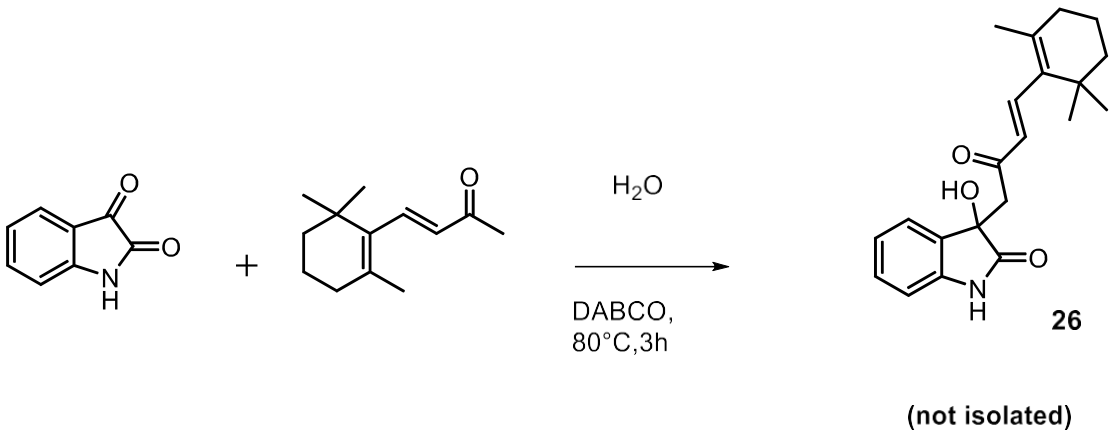


Results and Discussion

The present section describes the design, synthesis and characterization of β-ionone based3-hydroxy oxy-indole derivatives. The details of reaction planning and experimental execution willbe discussed in this section.

Synthesis of β-ionone based 3-hydroxyoxindole

As water has been shown an excellent solvent for isatin based aldol type of reactions already demonstrated in our research group, we initially attempted the synthesis of β-ionone based 3-hydroxyoxindole by reaction of isatin and β-ionone using water as solvent and DABCO as base. Unfortunately, there was no product obtained even after heating the reaction mixture to 80^{o}C. The possible reason for reaction failure may be due to solubility of the substrate. The reaction was also attempted in various organic solvents which also didn't yield the expected product.



Scheme. Synthesis of β-ionone based 3-hydroxyoxindole.

We paid our attention towards use of surfactant for the reaction as surfactants have been widely used in reactions using water as solvent. Accordingly, the reaction was performed with isatin (1eq) and beta-ionone (1 eq.) in H_2O as solvent and DABCO as a base using SLS as surfactant. The reaction was stirred for 2.5 hour when TLC indicated the complete consumption of starting precursor. The solid precipitated out from the reaction mixture was purified by column chromatography to provide white pure product. The structure of product was confirmed by NMRand mass spectral analysis**.**

Role of Surfactant Sodium Lauryl Sulphate (SLS) in Reaction

As the reaction proceeded smoothly with the use of surfactants, it is quite appropriate to discuss role of surfactant in the reaction.Surfactants (or 'surface active agents') are organic compounds with at least one lyophilic. ('solvent-loving') group and one lyophobic ('solvent- fearing') group in the molecule. If the solvent in which the surfactant is to be used is water or an aqueous solution, then the respective terms 'hydrophilic' and 'hydrophobic' are used. In the simplest terms, a surfactant contains at least one non-polar group and one polar (or ionic) group.

Two phenomena result from these opposing forces within the same molecule: adsorption and aggregation. For example, in aqueous media, surfactant molecules will migrate to air/water and solid/water interfaces and orientate in such a fashion as to minimise, as much as possible, the contact between their hydrophobic groups and the water. This process is referred to as 'adsorption' and results in a change in the properties at the interface.

Likewise, an alternative way of limiting the contact between the hydrophobic groups and the water is for the surfactant molecules to aggregate in the bulk solution with the hydrophilic 'head groups' orientated towards the aqueous phase. These aggregates of surfactant molecules vary in shape depending on concentration and range in shape from spherical to cylindrical to lamellar (sheets/layers).

The aggregation process is called 'micellisation' and the aggregates are known as 'micelles'. Micelles begin to form at a distinct and frequently very low concentration known as the 'critical micelle concentration' or 'CMC'.

In simple terms, in aqueous media, micelles result in hydrophobic domains within the solution whereby the surfactant may solubilize or emulsify particular solutes. Hence, surfactants will modify solution properties both within the bulk of the solution and at interfaces. The hydrophilic portion of a surfactant may carry a negative or positive charge, both positive and negative charges or no charge at all. These are classified respectively as anionic, cationic, amphoteric (or 'zwitterionic') or non-ionic surfactant.

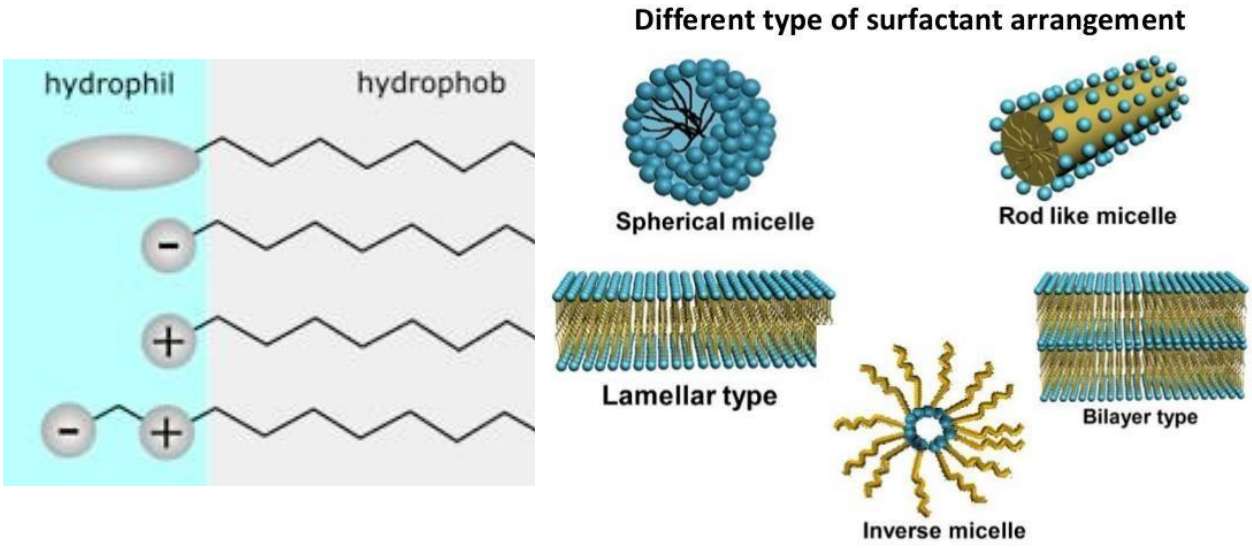


Figure: Micelle configuration

Optimization of Surfactants

Earlier I have tried this reaction in water without adding surfactant results no reaction .Later on I tried with surfactant and reaction proceeds well. I have also tried several surfactant such as Tween 80, Span 20, Cetrimide, Sodium Lauryl sulphate, SDS. It has been found

reaction proceeds well in SLS (Sodium Lauryl sulphate) in less amount of time.

S.No.	**Surfactant**	**Solvent**	**Time**	**Yield(%)**
1	Tween 80	H_2O	3h	70
2	Span 20	H_2O	5h	65
3	**SLS**	**H_2O**	**2.5h**	**85**
4	Lecithin	H_2O	4h	60
5	Cetrimonium Chloride	H_2O	6h	67

Several reactions were performed in order to find optimal reaction conditions in various solvents like water, ethanol, acetonitrile, THF, dimethylsulfoxide, dimethylformamide. After the completion of reaction, the maximum yield was found by using water in minimum reaction time.

S. No.	**Solvent**	**Temp. (^oC)**	**Time (h)**	**Time (h)**
1	**H_2O**	**80**	**2.5h**	**87%**
2	C_2H_5OH	80	7h	60%
3	CH_3CN	80	10h	55%
4	$(CH_3)_2SO$	80	15h	65%
5	$(CH_3)_2NCH$	80	13h	71%

Optimization of solvents.

Optimization of Bases

We tried this reaction in various bases such as DABCO, DBU, Et_3N, Pyridine, Piperidine, K_2CO_3, NaOH, DMAP. The reaction proceeded well in DABCO in less amount of time with highest yield so DABCO has chosen for furthure reaction. Bases and their respective yield is enlisted below with time at table.

S.No.	Sovent	Base	Temp. (^oC)	Time (h)	Yield(%)
01	**H_2O**	**DABCO**	**80**	**2.5**	**77**
02	H_2O	DMAP	80	5	30
03	H_2O	DBU	80	3	60
04	H_2O	Et_3N	80	5	20
05	H_2O	Pyridine	80	5	35
06	H_2O	Piperidine	80	5	35
07	H_2O	K_2CO_3	80	3	20
08	H_2O	NaOH	80	3	15

Series of Molecule

After the optimization of reaction conditions, a series of 8 molecules were synthesized by changing substitution on isatin like 5-chloroisatin, 5-bromoisatin, 5-methoxyisatin, 5-flouroisatin, 7-flouroisatin, 5-iodoisatin, N-phenylisatin, N-methylisatin.

Plausible mechanism of the reaction

The reaction undergoes via enolization mechanism firstly DABCO picks proton from beta-ionone generate enolate then further react with electrophilic C3 position of isatin moreover protonation takes place formed 3-substituted 3- hydroxyl oxy-indole.

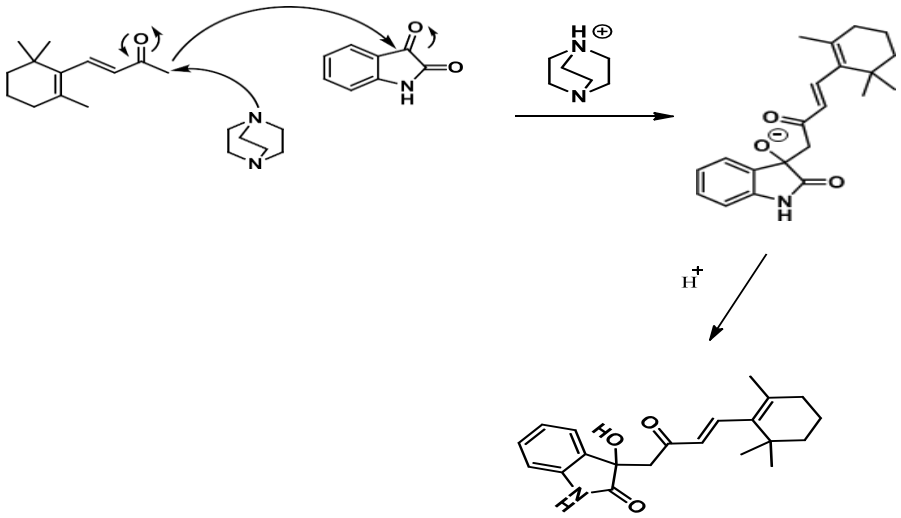
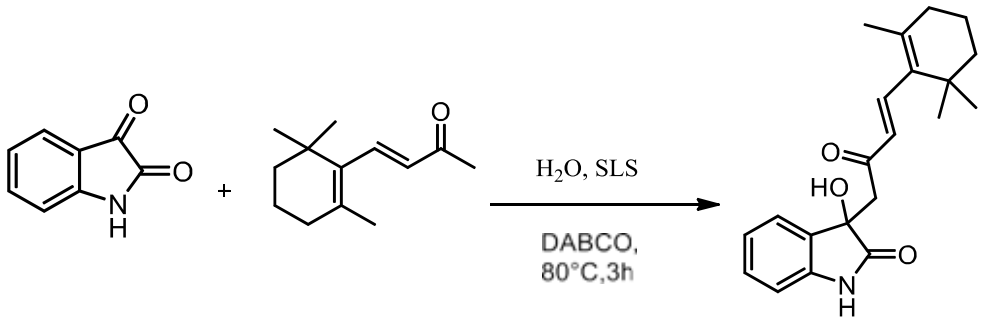


Figure . Mechanism of the reaction.

Synthesis of beta-ionone based 3-hydroxyoxindole

The reaction was performed with isatin (1eq.) and beta-ionone (1 eq.) in H_2O as solvent and DABCO as a base using SLS as surfactant. The reaction was stirred for 2.5 hour when TLC indicated the complete consumption of starting precursor. The solid precipitated out from the reaction mixture was purified by column chromatography to provide white pure product. The structure of product was confirmed by NMR spectra**.**

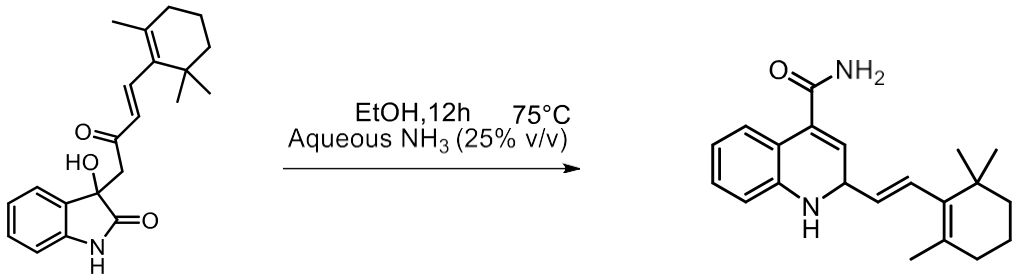


. Synthesis of (E)-3-hydroxy-5-methyl-3-(2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-1-yl)indolin-2-one.

Step 2.

Synthesis of (E)-2-(2-(2,6,6-trimethylcyclohex-1-en-1yl)vinyl)-1,2 dihydroquinoline-4-carboxamide from 3-hydroxyoxindole

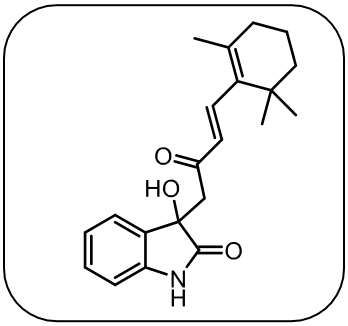
For the synthesis of vinyl-1, 2-dihydroquinoline-4-carboxamide, the 3-hydroxyindoline was reacted with ammonia solution (25% v/v) using ethanol as solvent at 80°C. The reaction after heating for 12 hours the reaction shows the consumption of stating precursor checked by TLC It also shown the formation of florescent product. Later on workup was performed by using ethylacetate and water further more column chromatography was performed at (1:1) ethylacetate hexane. All the characteristic peaks of 3-Hydroxyindoline of NH at and CH_2 at were not present in proton NMR of the product which confirms that cyclisation has occurred and product has been formed.

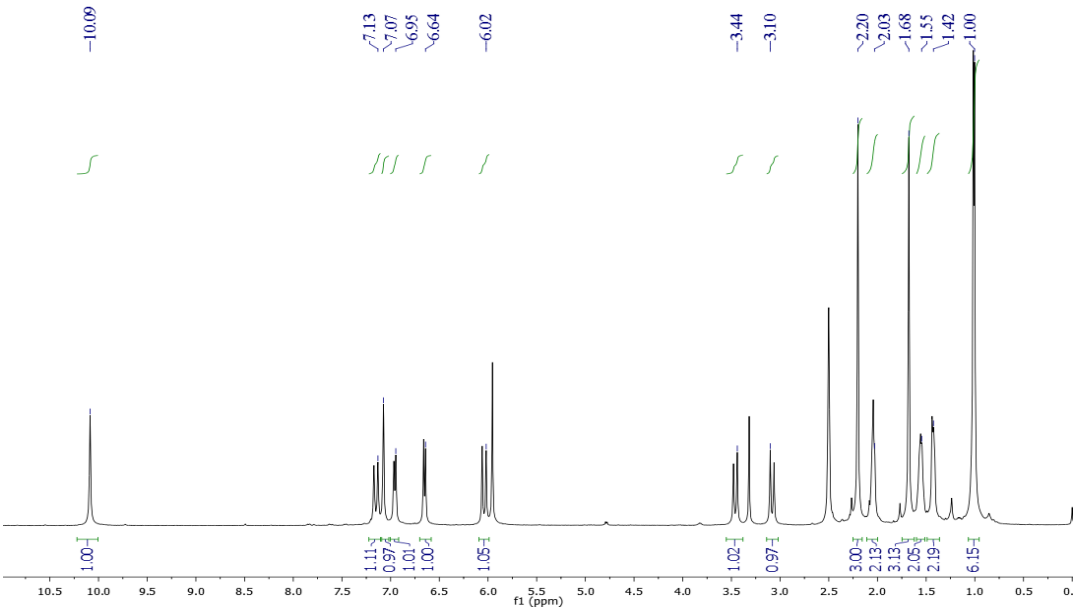


Synthesis of (E)-2-(2-(2,6,6-trimethylcyclohex-1-en-1yl)vinyl)-1,2 dihydroquinoline-4-carboxamide from 3-hydroxyoxindole.

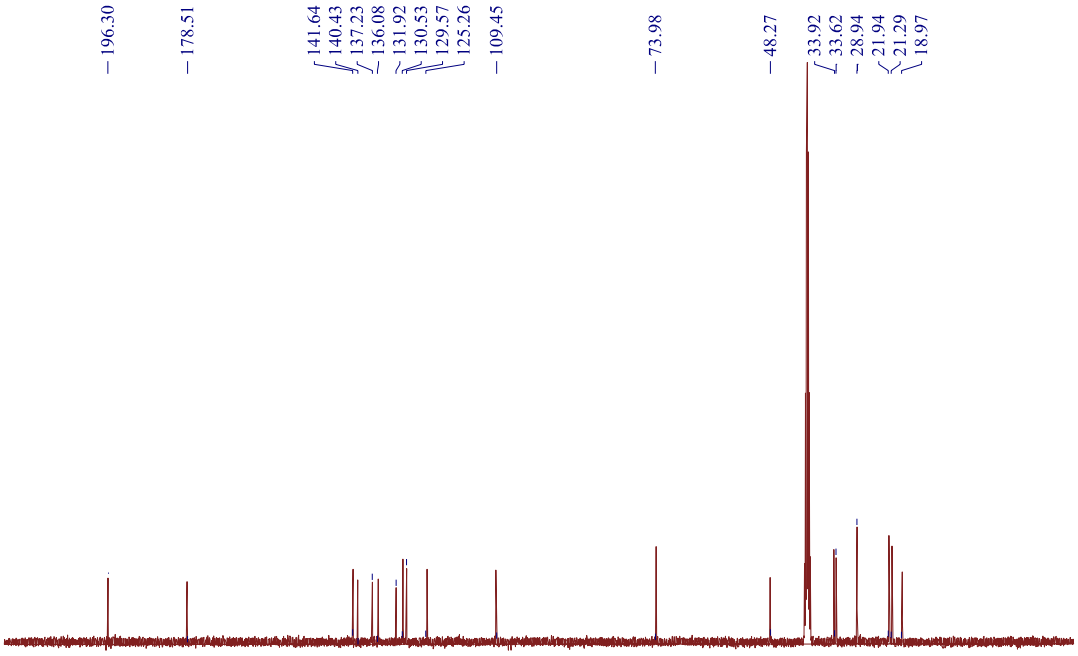
- **Characterization data for compounds**

1.(E)-3-hydroxy-5-methyl-3-(2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-1-yl)indolin-2-one m.p.165-167 oC; 90% as white solid; IR (cm-1) OH(3744), NH(3172), C=O (1695); 1H NMR (400 MHz, DMSO) δ 10.09 (s, 1H), 7.15 (d, J = 16.3 Hz, 1H), 7.07 (s, 1H), 6.96 (d, J = 7.7 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.04 (d, J = 16.3 Hz, 1H), 3.48 (s, 1H), 3.06 (s, 1H), 2.20 (s, 3H), 2.03 (s, 2H), 1.68 (s, 3H), 1.55 (d, J = 4.4 Hz, 2H), 1.43 (d, J = 5.7 Hz, 2H), 1.01 (d, J = 5.0 Hz, 6H). 13C NMR (101 MHz, DMSO) δ 196.30 (s), 141.64 (s), 140.57 (s), 137.21 – 137.01 (m), 135.92 (s), 131.88 (s), 130.48 (s), 129.57 (s), 125.08 (s), 73.84 (s), 48.34 (s), 34.10 (s), 33.62 (s), 28.94 (s), 21.82 (s), 21.13 (s), 18.84 (s) (ESI) m/z for C21H27NO3 [M + H]+, calcd., 353.199, found: 353.199. (26f)





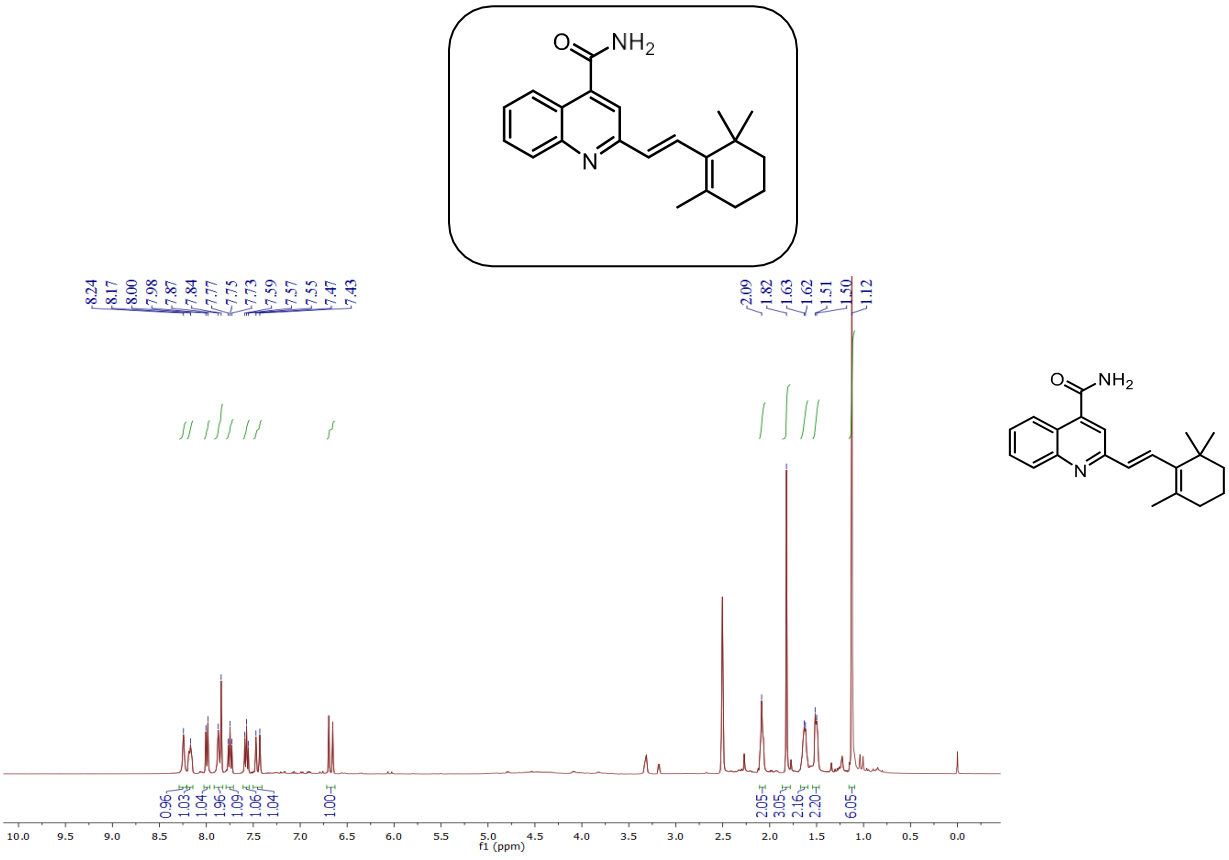
1H NMR of (E)-3-hydroxy-3-(2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-1-yl)indolin-2-one.



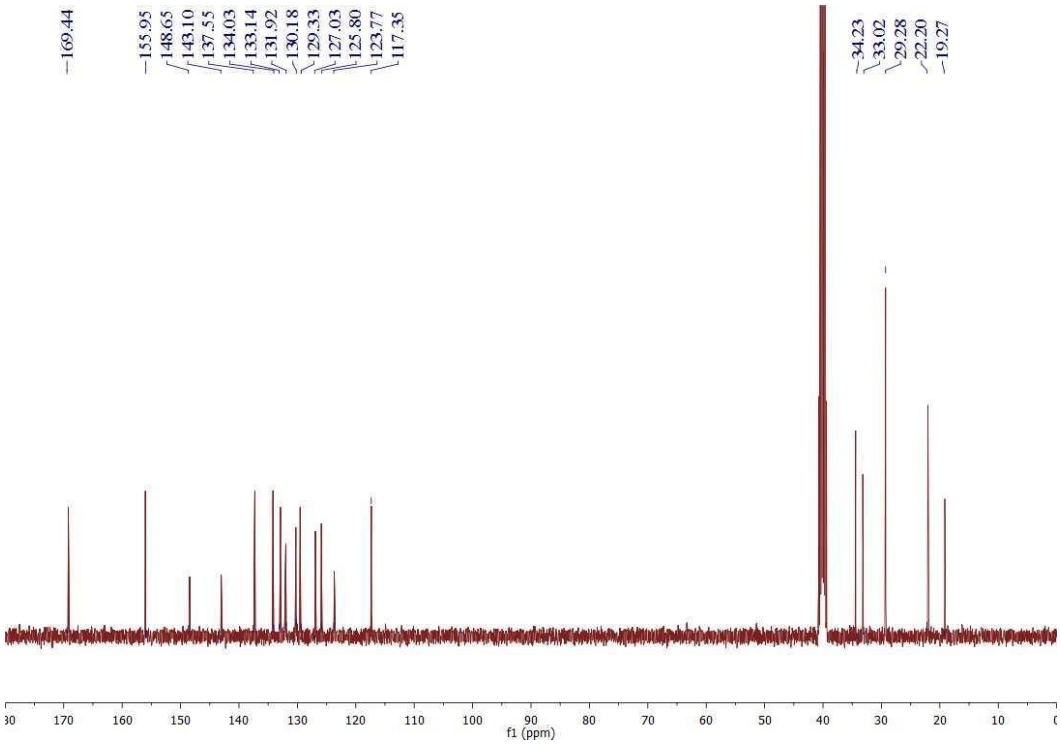
13C NMR of (E)-3-hydroxy-3-(2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-1-yl)indolin-2-one**.**

2.(E)-2-(2-(2,6,6-trimethylcyclohex-1-en-1yl)vinyl)-1,2-dihydroquinoline-4-carboxamide from 3-hydroxyoxindole Light brown solid,

78%, m.p.: 84- 86 °C, IR (cm-1) 3743,3198 2919,1697; 1H NMR (400 MHz, DMSO) δ 8.24 (s, 1H), 8.17 (s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 12.3 Hz, 2H), 7.75 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 16.4 Hz, 1H), 6.67 (d, J = 16.4 Hz, 1H), 2.09 (s, 2H), 1.82 (s, 3H), 1.62 (d, J = 5.0 Hz, 2H), 1.51 (d, J = 6.0 Hz, 2H), 1.12 (s, 6H). 13C NMR (101 MHz, DMSO) δ 169.20 (s), 156.01 (s), 148.65 (s), 143.03 (s), 137.28 (s), 134.41 – 134.22 (m), 131.92 (s), 130.53 (s), 129.89 (s), 127.13 – 126.93 (m), 126.19– 125.99 (m), 123.77 (s), 34.48 (s), 33.27 (s), 29.28 (s), 21.98 (s), 19.15 (s). (ESI) m/z for C21H24N2O [M + H]+, calcd., 320.188, found: 320.188.



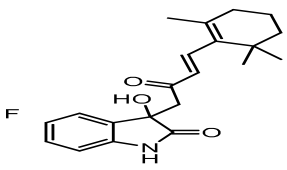
[1]H NMR of (E)-2-(2-(2,6,6-trimethylcyclohex-1-en-1-yl)vinyl)quinoline-4-carboxamide.

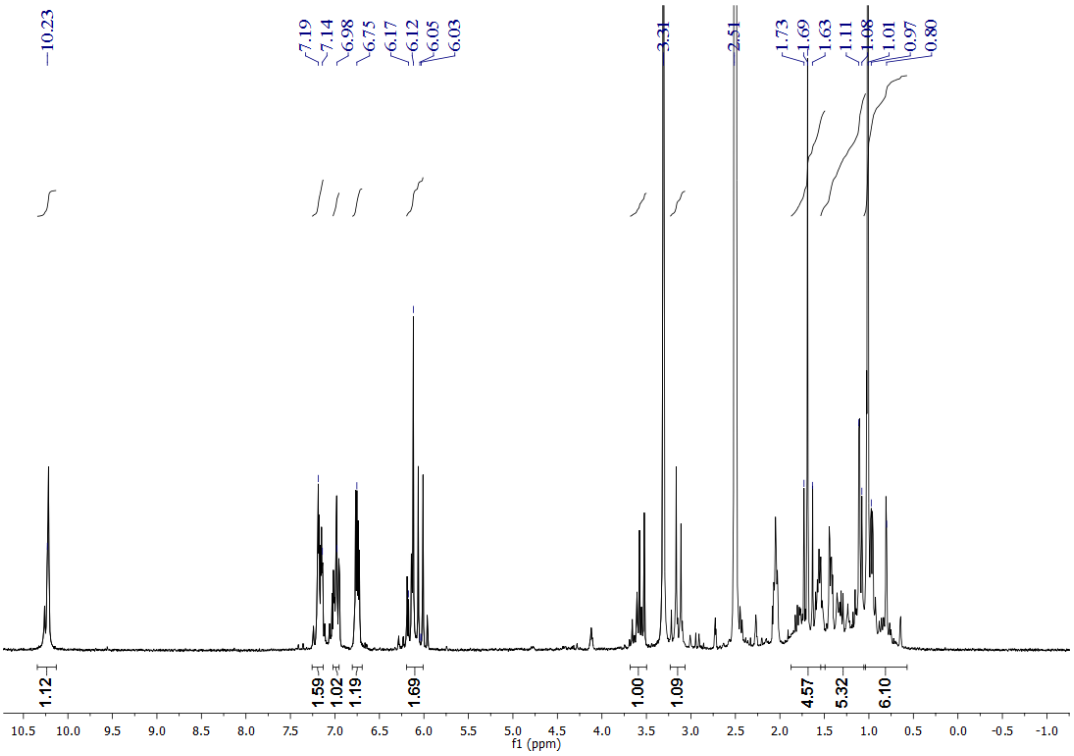


13C NMR of (E)-2-(2-(2,6,6-trimethylcyclohex-1-en-1-yl)vinyl)quinoline-4-carboxamide.

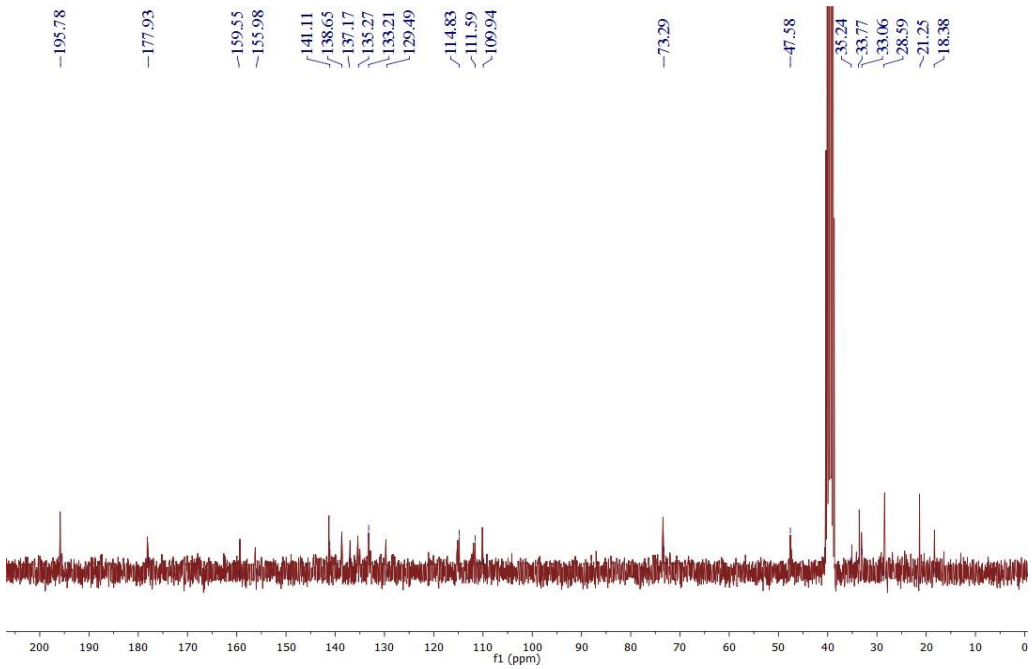
3.(E)-5-fluoro-3-hydroxy-3-(2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-1-yl)indolin-2-one m.p.195-197 oC; 90% as brown solid

1H NMR (300 MHz, DMSO) δ 10.23 (s, 1H), 7.16 (d, J = 13.9 Hz, 2H), 6.98 (s, 1H), 6.75 (s, 1H), 6.75 (s, 1H), 6.19 – 6.01 (m, 2H), 3.68 – 3.50 (m, 1H), 3.23 – 3.07 (m, 1H), 1.87 – 1.49 (m, 5H), 1.10 (d, J = 10.3 Hz, 5H), 1.06 –0.57 (m, 6H). 13C NMR (75 MHz, DMSO) δ 195.78, 177.93, 159.55, 155.98, 141.11, 138.65, 137.17, 135.27, 133.21, 129.49, 114.83, 111.59, 109.94, 73.29, 47.58, 35.24, 33.77, 33.06, 28.59, 21.25, 18.38.13C NMR (75 MHz, DMSO) δ 141.60, 130.19, 115.77, 112.66, 110.51, 33.36, 29.08, 22.01, 19.20. (ESI) m/z for C21H24FNO3 [M + H]+, calcd., 357.331, found:357.331. (26d)





^{1}H NMR of(E)-5-fluoro-3-hydroxy-3-(2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-1- yl)indolin-2-one .



^{13}CNMR of (E)-5-fluoro-3-hydroxy-3-(2-oxo-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-1-yl)indolin-2-one .

Conclusions and Summary

An easy and efficient synthetic protocol for the access of cyclic beta-ionone substituted 3-Hydroxy oxindole derivatives was developed by two component reaction of isatin and beta-ionone in water SLS as surfactant and DABCO as base. Based on the above methodology, a series of beta-ionone based 3-hydroxyoxindoles were synthesized, purified and fully characterized. Second step also planned and we have synthesized beta-ionone based quinoline - 4- carboxamide in ammonia ethanol as a solvent .There are 7 molecules were synthesized *in silico* to predict the physicochemical and drug-likeness properties of the molecules.

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