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# Aqueous $NH_3$-mediated syntheses of 2-styrylquinoline-4-carboxamides by domino ring opening cyclization strategy

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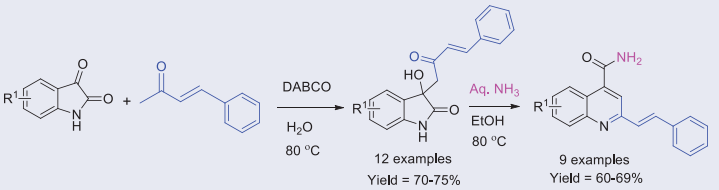
**ABSTRACT**

A straightforward and efficient protocol for the synthesis of medicinally relevant 2-styrylquinoline-4-carboxamide has been developed by aqueous ammonia-mediated domino ring-opening and cyclization strategy of 3-hydroxyoxindole. The starting precursors 3-hydroxyoxindoles were easily prepared through organocatalytic "on water" reaction of isatin and benzalacetone in high yields. The wide substrate scope with operationally simple experimental procedures provides an opportunity to create library of 2-styrylquinoline-4-carboxamide derivatives.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
Ammonia; cyclization; 3-hydroxyoxindole; isatin; quinoline-4-carboxamide

## Introduction

The broad-spectrum biological profile of quinoline derivatives enlists them as one of the most sought after chemical entities in medicinal chemistry for the development of new clinical candidates.[1] The widespread occurrence of this privileged scaffold in natural products,[2] pharmaceuticals[3] and agrochemicals has garnered great interest among synthetic as and medicinal chemists. Particularly, quinoline-4-carboxamide with aryl substitution at 2-position has been predominantly discovered with diverse chemotherapeutic activities such as antimalarial,[4] antibacterial,[5] antiviral[6] and anticancer.[7] DD107498, a quinoline-4-carboxamide derivative, demonstrates potent antimalarial activity against multiple life-cycle stages of the Plasmodium parasite with acceptable safety profile and good pharmacokinetic properties (Figure 1).[8] The molecular target

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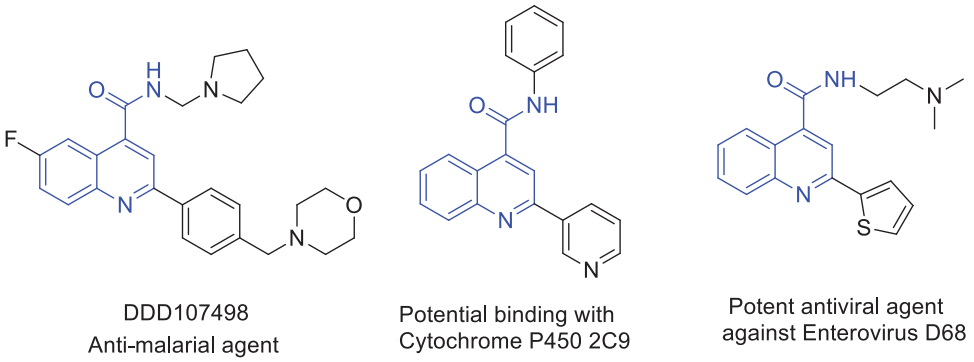
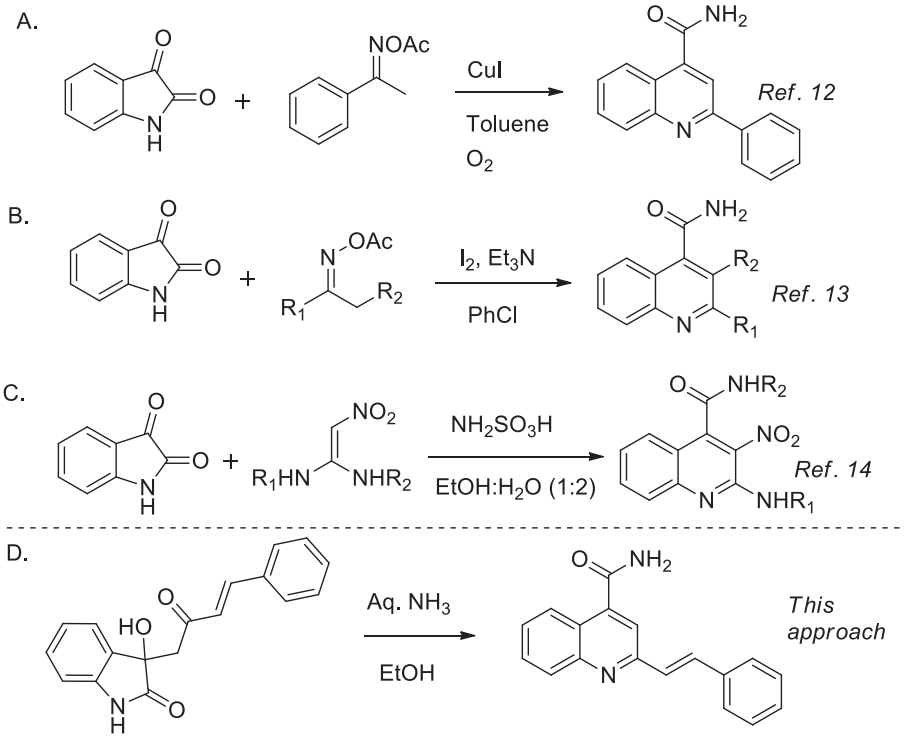



**Figure 1.** Selected biologically active quinoline-4-carboxamide derivatives.

for DD107498 is Translation elongation factor 2 (eEF2) which is responsible for the GTP-dependent translocation of the ribosome along with messenger RNA. Similarly, a novel series of quinoline-4-carboxamide derivatives have been shown to interact with Cytochrome P450 enzymes which plays a key role in metabolic reactions of endogenous and exogenous substrates (Figure 1).[9] Very recently, the quinoline-4-carboxamide analogs were discovered as potent antiviral agents against Enterovirus D68 against respiratory as well as neuronal infections (Figure 1).[10]

Many efforts have taken center stage for the synthesis of 4-functionalized quinolines over the decades with conventional and frequently used name reactions like Pfitzinger, Skraup, Doebner-von Miller, Conrad-Limpach-Knorr.[11] However, many of these reactions encounter severe limitations like harsh reaction conditions and low yield compelling researchers to discover an alternative synthetic strategy for quinoline-4-carboxamides. Very recently, O-acyl oxime has been employed as a starting precursor for direct access to quinoline-4-carboxamide. For example, the copper-catalyzed coupling of O-acyl oxime with isatin yielded quinoline derivatives in excellent yield (Scheme 1A).[12] Along a similar line, the coupling of isatin with iodine-triggered N-centered radical of oxime acetate provided straightforward quinoline-4-carboxamide (Scheme 1B).[13] The multi-substituted quinoline-4-carboxamides were efficiently obtained in good to excellent yields utilizing 1,1-enediamine in a reaction with isatin (Scheme 1C).[14] Owing to widespread biological significance, the development of synthetic methods for the direct access of quinoline-4-carboxamide is urgently warranted.

The 3-hydroxyoxindole derivatives have found wide application in medicinal chemistry due to their diverse biological activities with many derivatives currently under preclinical evaluation.[15] Our research program is primarily focused on the design and development of synthetic methods leading to oxindole based heterocyclic scaffold of medicinal relevance.[16] We have recently demonstrated the synthesis of 3-hydroxyoxindole derivatives and their synthetic transformation to quinoline-4-carboxamide.[17] In continuation, we planned to explore the synthetic utility of 3-hydroxyoxindole as a template for direct access to quinoline-4-carboxamides. Herein, we wish to report a straight forward domino ring-opening cyclization strategy of 3-hydroxyoxindoline leading to direct access of quinoline-4-carboxamides (Scheme 1D).



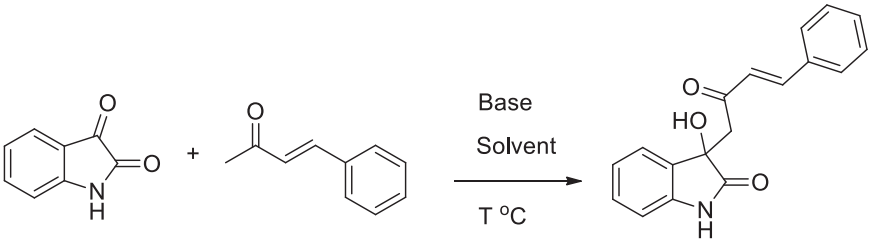

**Scheme 1.** Synthetic approaches for quinoline-4-carboxamide derivatives.

## Results and discussion

To implement our strategy, the reaction of isatin **1a** was attempted with benzalacetone **2a** in aqueous media similar to our previous observation.[17] With DABCO as a base, the desired product **3a** was isolated in 75% yield after 1.5 h of reaction (Table 1, entry 1). Further to obtain the optimal conditions, the reaction was performed with isatin **1a** and benzalacetone **2a** as a model substrate with varying solvent and base. The reaction in aprotic organic solvents like $CH_3CN$, DCE, DMF, Toluene, THF resulted in poor yield (32–15%) of desired product **3a** (Table 1, entries 2–6). However, the good yield of product **3a** (65–70%) was obtained in protic solvents like MeOH and EtOH (Table 1, entries 7–8). Advantageously, no chromatographic purification was required for product **3a** as it precipitated out in the reaction mixture. The attempt of reaction with organic bases like DMAP, DBU, $Et_3N$, pyridine, piperidine furnished desired product **5a** in low yields (Table 1, entries 9–13). The use of inorganic bases like $K_2CO_3$ and NaOH was also not fruitful and resulted into a lower conversion (Table 1, entries 14–15).

With the optimized reaction conditions in hand, we next turned our attention toward exploring the generality and scope of the synthetic protocol. Isatin containing both electron-donating (5-Me and 5-OMe) and electron-withdrawing (5-F, 5-Cl, and 5-Br) groups on the oxindole afforded 3-substituted-3-hydroxyoxindole derivatives **3a–l** in good to the excellent yield of 60–80% (Figure 2). The spectral data of known 3-hydroxyoxindole derivatives (**3a**, **3c**, **3f**, **3j**) were found in complete agreement with literature data.[18]

**Table 1.** Optimization of reaction conditions[a] for **3a**.




**1a** **2** **3a**

| Entry | Solvent | Base | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $H_2O$ | DABCO | 80 | 1.5 | 75 |
| 2 | $CH_3CN$ | DABCO | 80 | 5 | 32 |
| 3 | DCE | DABCO | 80 | 5 | 25 |
| 4 | DMF | DABCO | 120 | 5 | 30 |
| 5 | Toluene | DABCO | 100 | 5 | 15 |
| 6 | THF | DABCO | 60 | 5 | 26 |
| 7 | MeOH | DABCO | 65 | 2 | 65 |
| 8 | EtOH | DABCO | 75 | 2 | 70 |
| 9 | $H_2O$ | DMAP | 80 | 5 | 30 |
| 10 | $H_2O$ | DBU | 80 | 3 | 60 |
| 11 | $H_2O$ | $Et_3N$ | 80 | 5 | 20 |
| 12 | $H_2O$ | Pyridine | 80 | 5 | 35 |
| 13 | $H_2O$ | Piperidine | 80 | 5 | 35 |
| 14 | $H_2O$ | $K_2CO_3$ | 80 | 3 | 20 |
| 15 | $H_2O$ | NaOH | 80 | 3 | 15 |

[a]Reaction conditions: **1a** (1.36 mmol) **2a** (1.36 mmol), DABCO (1.36 mmol) water (10 mL); [b]Isolated yield

With 3-hydroxyoxindole derivatives in hands, we next planned to perform a reaction of **3a** with aqueous $NH_3$. Like our previous observation,[15] the reaction of **3a** with $NH_4OAc$ in boiling EtOH didn't work out for this reaction as only traces of product **4a** were observed. As aqueous ammonia is used as source of nitrogen, we turned our attention toward use of ammonia. Accordingly, **3a** was treated with an excess of 25% (*v*/*v*) aqueous $NH_3$ as nitrogen source in EtOH at 80$^o$C which provided product **4a** in 69% yield (Table 1, entry 1). Further, the attempt was made to enhance the yield of reaction by performing reactions in several solvents (Table 2). The reaction of **3a** in MeOH and $CH_3CN$ yielded **4a** with moderate yield of 55 and 45%, respectively (Table 2, entries 2–3) whereas the use of water and THF as solvent was unfruitful and no desired product was obtained (Table 2, entries 4–5).

Next, the scope and limitation of the substrate were investigated with optimized reaction conditions. The reaction demonstrated a wide range of substrate scope as isatin containing both electron-withdrawing (5-F, 5-Cl, and 5-Br) and electron-donating (5-Me and 5-OMe) groups on the oxindole successfully yielded 2-styrylquinoline-4-carboxamides **4a–i** in good yield (Figure 3). The unsubstituted isatin derivative **4a** was obtained with 69% yield. In general, the yield of desired product was found more in case of electron-withdrawing group (5-Cl and 5-Br) than electron-donating group (5-Me and 5-OMe). Probably, electron-withdrawing group helps in cleavage of N–CO bond (mentioned in reaction mechanism). the The spectral data of **4a** was found in complete agreement with literature data.[10] Further, the reaction of **3a** with hydrazine and hydrazide as a source of amide nitrogen failed to provide expected product leading

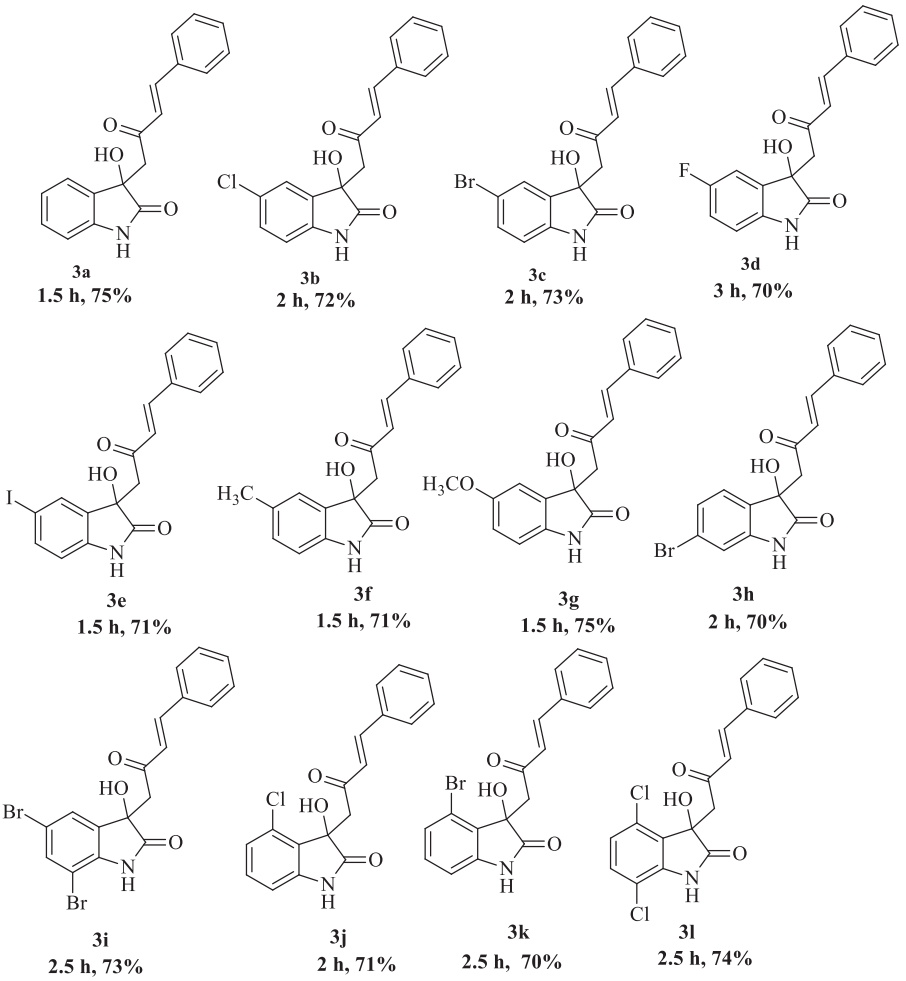
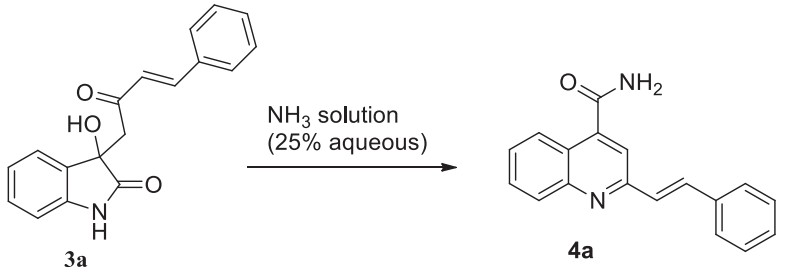



**Figure 2.** Substrate scope for 3-substituted-3-hydroxyoxindole derivatives.

**Table 2.** Optimization of reaction conditions[a] for **4a**.




| Entry | Solvent | Temp. (*oc*) | Time (h) | Yield (%)b (4a) |
|---|---|---|---|---|
| 1 | EtOH | 75 | 6 | 69 |
| 2 | MeOH | 65 | 8 | 55 |
| 3 | $CH_3CN$ | 80 | 10 | 45 |
| 4 | $H_2O$ | 80 | 10 | No product |
| 5 | THF | 60 | 10 | No product |

[a]Reaction conditions: **3a** (0.68 mmol), 1.0 mL of aq. $NH_3$ (25% *v/v*), EtOH (10 mL); [b]Isolated yield

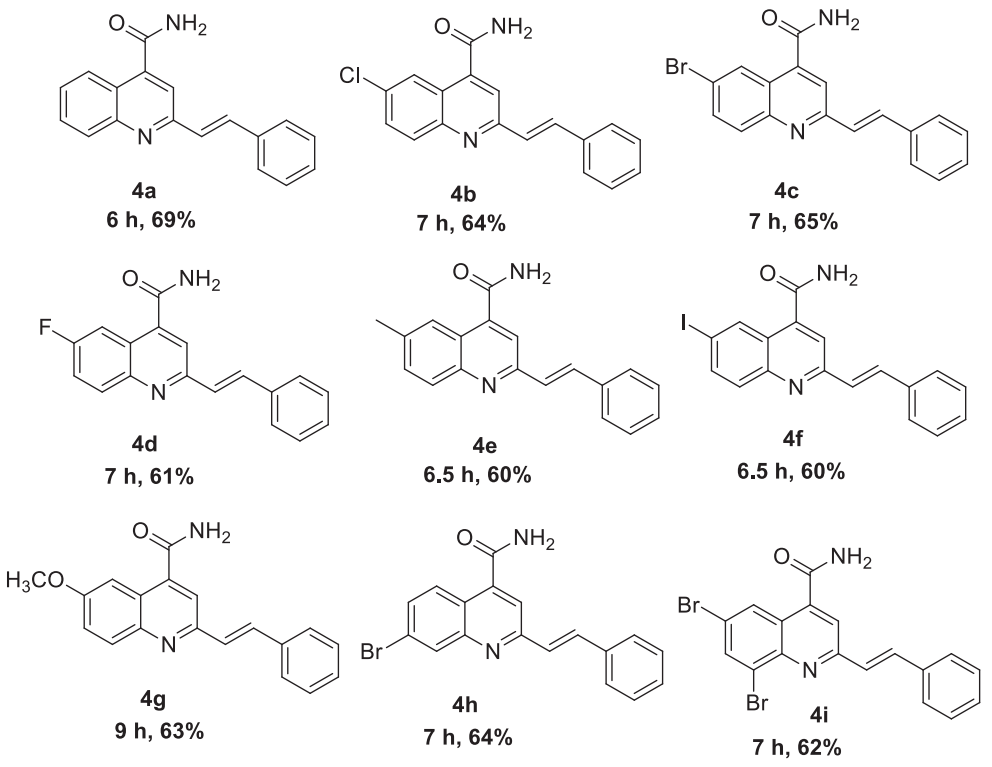
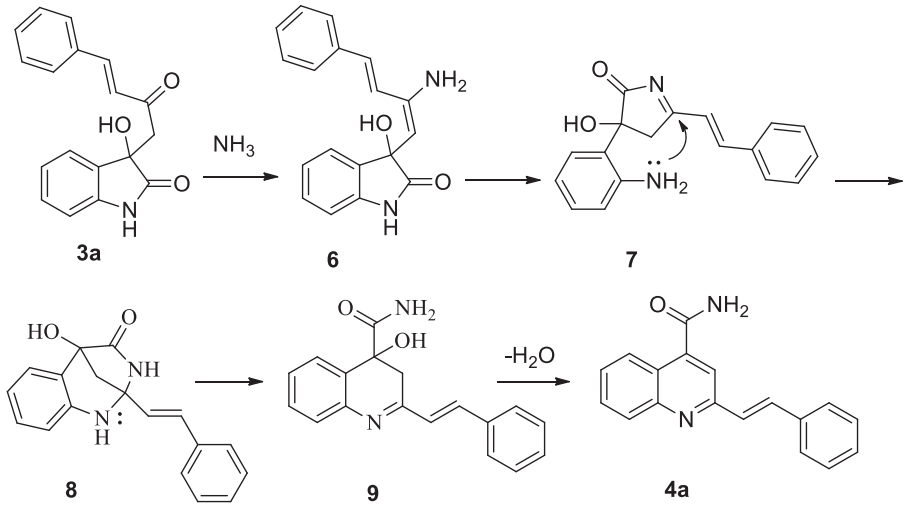


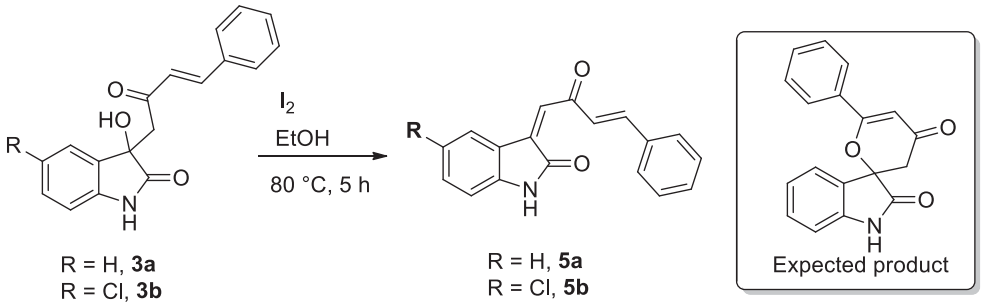

**Figure 3.** Substrate scope for 2-styrylquinoline-4-carboxamides.




**Scheme 2.** The plausible reaction mechanism

to the complex reaction mixture. The reason of this failure is not very clear but possibly ammonia being small in size may be able to perform the required transformation.

For the reaction mechanism, we observed a similar reactivity pattern as our previous observation with ammonium acetate.[15] Based on the outcome of the product and our earlier findings, a plausible mechanism for the formation of **4a** from **3a** is proposed in




**Scheme 3.** Reaction of 3-hydroxyindole with $I_2$

Scheme 2. The ammonia attacks on carbonyl of enone of **3a** leading to the formation of enamine **6**. The amine of **6** then cyclizes with amide carbonyl of oxindole to produce pyrrole-2-one **7**. The further attack of $NH_2$ of aniline on imine of pyrrole-2-one **7** possibly yields benzodiazepinone **8** which after ring-opening and release of amide group provides 4-hydroxydihydroquinoline **9**. Finally, the elimination of water leads to the formation of product **4a.**

To transform 3-hydroxyindole **3a** into spirooxindole pyran skeleton, the iodocyclization strategy was attempted with $I_2$ in EtOH as solvent (Scheme 3). To our surprise, the dehydrated product **5a** was obtained as a red solid in 80% yield. Under similar conditions, the compound **3 b** was also transformed to product **5a** in 75% yield. This could be a utilized as a practical and simple method to dehydrate 3-hydroxyoxindole to conjugated indoline-2-one derivatives which otherwise requires harsh conditions. The possible mechanism could be activation of hydroxyl group by iodine that triggers elimination of water to provide conjugated product. The application of other reagents like Eaton's reagent and $FeCl_3$ with **3a** in $CH_3CN$ also led to the formation of dehydrated product **5a** in 60 and 70% yield respectively. The reason behind formation of product **5a** could be thermodynamic stability of conjugated enone system.

## Conclusions

In summary, we have developed a direct and efficient method for synthesis of 2-styryl-quinoline-4-carboxamides through domino ring-opening and cyclization strategy of 3-hydroxyoxindoles. Utilizing this method, a library of quinoline-4-carboxamide derivatives was rapidly generated with good to a very good yield of products. The primary amide functionality of quinoline ring provides ample opportunity for further transformation into medicinally relevant therapeutic agents and work along this line is currently in progress.

## Experimental part

### *General*

All the chemicals and reagents such as isatin, benzalacetone, 25% aqueous ammonia solution, DABCO, etc. were purchased from commercial suppliers unless otherwise stated. All the NMR spectra were recorded in DMSO-$d_6$, 500 MHz for $^1$H and 125 MHz

for $^{13}C$ on JEOL 500 MHz instrument or 300 MHz for $^{1}H$ and 75 MHz for $^{13}C$ BrukerAvance DPX-300. The chemical shifts are reported in ppm relative to DMSO-$d_6$ as internal standards. Integrals are in accordance with assignments and coupling constants are given in Hz. The HRMS data were recorded on Agilent-6530 QTOF/LCMS instrument using electrospray ionization (ESI). All the infrared spectra were recorded using Alpha-Bruker IR spectrometer in ATR mode and wavelengths ($\nu$) are reported in $cm^{-1}$. Melting points were recorded using melting point apparatus by LABINDIA and are uncorrected. All the reactions were performed in heating conditions and progress of reaction was monitored by use of thin layer chromatography (TLC) performed on plates coated with Silicagel 60 $F_{254}$ with 0.2 mm thickness. Visualization was achieved by a combination of ultraviolet light (254 nm), potassium permanganate and iodine chamber. Column chromatography was performed using silica gel 100–200 mesh (Merck). The yields refer to quantities obtained after purification by column chromatography.

### General procedure for synthesis of (E)-3-hydroxy-3-(2-oxo-4-phenylbut-3-en-1-yl)indolin-2-one (3a)

To a stirred mixture of isatin (**1a**) (200 mg, 1.36 mmol) in 10 mL of water, benzalacetone (**2a**) (198 mg, 1.36 mmol) and DABCO (152 mg, 1.36 mmol) were added and reaction mixture allowed to stir vigorously at 80 °C for 1.5 hours. After the TLC indicated complete consumption of starting material, the reaction mixture was filtered and product **3a** was collected as white solid.

### Spectroscopic data for product 3a (E)-3-hydroxy-3-(2-oxo-4-phenylbut-3-en-1-yl)indolin-2-one (3a):

Yield (75%) white solid, mp 160–162$^{o}$C (dec.). IR (solid) $\tilde{\nu}$ = 3261, 3058, 1705, 1646, 1471, 1336, 1186, 1057, 976, 745, 687 $cm^{-1}$. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta = 10.23$ (s, 1H, NH), 7.70–7.62 (m, 2H, Ar-H), 7.54 (d, $J = 16.3$ Hz, 1H, =CH), 7.46–7.38 (m, 3H, Ar-H), 7.26 (d, $J = 1.3$ Hz, 1H, Ar-H), 7.15 (td, $J = 7.6$, 1.3 Hz, 1H, Ar-H), 6.88 (td, $J = 7.5$, 1.0 Hz, 1H, Ar-H), 6.80–6.71 (m, 2H, 1 Ar-H, 1 = CH), 6.04 (s, 1H, OH), 3.64 (d, $J = 16.4$ Hz, 1H, $CH_2$), 3.22 (d, $J = 16.4$ Hz, 1H, $CH_2$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta = 196.2$, 178.1, 142.6, 142.4, 134.2, 131.4, 130.5, 128.9, 128.4, 126.3, 123.7, 121.1, 109.3, 73.1, 47.6. DEPT-135 (75 MHz, DMSO-$d_6$) $\delta = 142.5$, 130.5, 128.9, 128.4, 126.3, 123.7, 121.1, 109.3, 47.6 ($CH_2$). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{16}NO_3$ 294.1130; found 294.1126.[18]

### General procedure for synthesis of (E)-2-styrylquinoline-4-carboxamide (4a)

To a stirred mixture of (*E*)-3-hydroxy-3-(2-oxo-4-phenylbut-3-en-1-yl)indolin-2-one **(3a)** (200 mg, 0.68 mmol) in 10 mL of ethanol, 1 mL of aqueous ammonia solution (25% *v/v*) was added and allowed to stir vigorously at 75 °C. After the TLC indicated the complete consumption of starting material after 6 hours of reaction, the solution was concentrated under reduced pressure to get brown solid. The crude mixture was

purified by column chromatography using ethyl acetate:hexane (4:6) as an eluent to afford to get **4a** as white solid.

### *Spectroscopic data for product 4a (E)-2-styrylquinoline-4-carboxamide (4a):*

Yield (69%) white solid. mp 214–216°C (dec.). IR (solid) $\tilde{\nu}$ = 3622, 3045, 2684, 1666, 1584, 1392, 1042 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta = 8.28$ (*s*, 1H), 8.18 (dd, $J = 8.4$, 1.4 Hz, 1H), 8.05 (d, $J = 8.3$ Hz, 1H), 7.94 (d, $J = 2.6$ Hz, 2H), 7.88 (*s*, 1H), 7.83–7.71 (*m*, 3H), 7.61 (ddd, $J = 8.3$, 6.8, 1.3 Hz, 1H), 7.55 (*s*, 1H), 7.51–7.41 (*m*, 2H), 7.37 (*t*, $J = 7.2$ Hz, 1H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta = 168.6$, 155.2, 148.0, 142.7, 136.1, 134.6, 129.9, 129.0, 128.8, 128.8, 128.3, 127.3, 126.7, 125.4, 123.2, 117.3. DEPT-135 NMR (75 MHz, DMSO-$d_6$) $\delta$ 134.6, 129.9, 129.0, 128.8, 128.8, 128.3, 127.3, 126.7, 125.4, 117.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O$ 275.1184; found 275.1190.[10]

### *General synthesis of (Z)-3-((E)-2-oxo-4-phenylbut-3-en-1-ylidene)indolin-2-one (5a)*

To a stirred mixture of (*E*)-3-hydroxy-3-(2-oxo-4-phenylbut-3-en-1-yl)indolin-2-one **(3a)** (200 mg, 0.68 mmol) in 10 mL of ethanol, and 2.0 equivalent of iodine was added and allowed to stir vigorously at 75 °C for 5 hours. The reaction mixture was washed with aqueous sodium thiosulfate solution and extracted with EtOAc three times. The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to get crude reaction mixture as red solid. The solid was purified by column chromatography using ethyl acetate:hexane (3:7) as an eluent to afford to get **5a** as a red solid.

### *Spectroscopic data for product 5a (Z)-3-((E)-2-oxo-4-phenylbut-3-en-1-ylidene)indolin-2-one (5a)*

Yield (80%) red solid. mp 175–176 °C (dec.). $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.76 (*s*, 1H, NH), 8.36 (d, $J = 7.7$ Hz, 1H), 7.85 − 7.75 (*m*, 3H), 7.50 − 7.44 (*m*, 3H), 7.43 − 7.32 (*m*, 3H), 6.99 (*t*, $J = 7.7$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H).$^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$ 190.5, 169.0, 145.6, 145.0, 136.7, 134.9, 133.6, 131.6, 129.6, 129.5, 128.4, 128.3, 127.9, 122.3, 120.8, 110.8. DEPT-135 NMR (DMSO-$d_6$) $\delta$ 145.0, 133.6, 131.6, 129.6, 129.5, 128.4, 128.3, 127.9, 122.3, 110.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{14}NO_2$ 276.1025; found 276.1031.

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## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Author contributions

The manuscript was prepared by the contribution of all authors.

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