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# Synthesis of some complex pyrano[2,3-*b*]- and pyrido[2,3-*b*]quinolines from simple acetanilides via intramolecular domino hetero Diels–Alder reactions of 1-oxa-1,3-butadienes in aqueous medium

Biswajita Baruah, Pulak J. Bhuyan *

*Medicinal Chemistry Division, North East Institute of Science & Technology, Jorhat 785006, India*

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ABSTRACT

Some complex pyrano[2,3-*b*]- and pyrido[2,3-*b*]quinolines were synthesized from simple acetanilides via intramolecular domino hetero Diels–Alder reactions of 1-oxa-1,3-butadienes using water as solvent.



## 1. Introduction

The importance of quinoline and its annelated derivatives is well recognized by synthetic and biological chemists. Compounds possessing this ring system have wide applications as drugs and pharmaceuticals.[1] Pyrano- and pyridoquinolines are two important classes of compounds that constitute the basic frameworks of a number of alkaloids of biological significance, for example, geibalasine, ribalinine, flindersine, etc. (Fig. 1).[2] Therefore, considerable efforts have been directed towards the preparation and synthetic manipulation of these molecules. As a result, a number of compounds have been obtained with diverse biological activities.[3]

The development of resource and eco-friendly process in terms of sustainable chemistry has become a focal point in chemical research in recent years. Diels–Alder reactions involve cyclic electron shifts and ring closure where the number of σ-bonds increase at the expense of π-bonds without the loss of any fragment and yet result in the formation of the desired cyclic compound. In the present world of green chemistry, such chemical processes with high atom economy have received a growing interest from the scientific community. Hetero Diels–Alder reactions are becoming a mainstay of heterocyclic and natural product synthesis.[4] Especially efficient are those cycloaddition where the heterodienes are formed in situ (domino hetero Diels–Alder).[5] Among these reactions, the domino oxa-1,3-butadiene Diels–Alder reaction is highly useful method for the synthesis of dihydropyrans.[6]

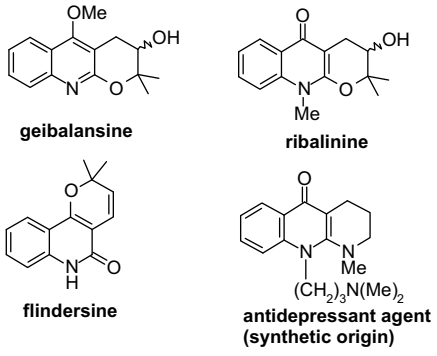


**Figure 1.**

The use of environmentally benign solvents like water represents very powerful green chemical technology procedures from both the economical and synthetic point of view.[7] They not only reduce the burden of organic solvent disposal, but also enhance the rate of many organic reactions.

As part of our continued interest on quinolines[8] and synthesis of diverse heterocyclic compounds[9] of biological significance, we report here the synthesis of some novel complex pyrano[2,3-*b*]- and pyrido[2,3-*b*]quinolines from simple acetanilides via intramolecular domino hetero Diels–Alder reactions involving 1-oxa-1,3-butadienes in aqueous medium (Scheme 1).

## 2. Results and discussion

Acetanilides **1** were chosen as the parent molecules in our reaction strategy (Scheme 1). The 2-chloro-3-formyl quinolines **2** were prepared from **1** by our own method.[8a] Thus acetanilide **1a** (R=H) on treatment with the Vilsmeier reagent (DMF–$POCl_3$) gave 2-chloro-3-formyl quinoline **2a** in excellent yield (80%). The reaction of **2a** with prenyl alcohol in presence of sodium hydroxide (50% aqueous solution) under phase transfer catalytic condition was

* Corresponding author. Tel.: +91 0376 2370121.
*E-mail address:* pulak_jyoti@yahoo.com (P.J. Bhuyan).

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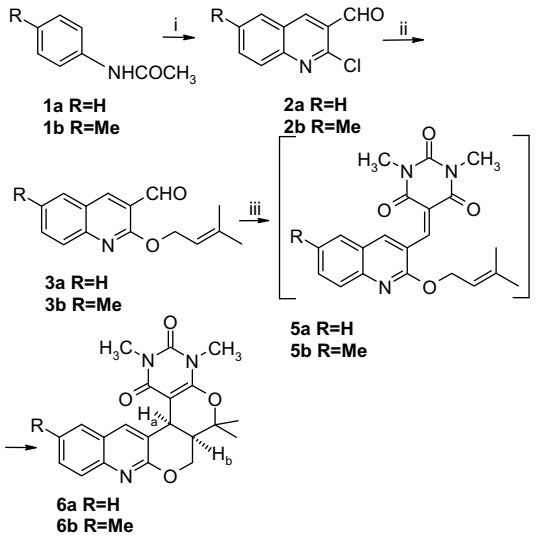



**Scheme 1.** (i) DMF–$POCl_3$, 80 °C, (ii) prenyl alcohol/TBAB/NaOH, (iii) *N*,*N*-dimethyl barbituric acid (**4a**).

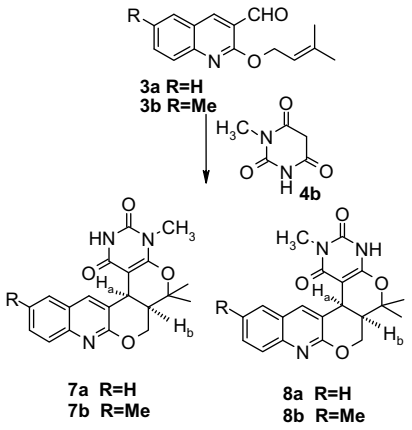
found to be the most suitable method to introduce the dienophile in compound **2a** and to prepare **3a**. Following the Tietze protocol of domino Knoevenagel hetero Diels–Alder reaction, **3a** was reacted with *N*,*N*-dimethylbarbituric acid (**4a**) in presence of piperidine at room temperature using water as solvent. The intermediate Knoevenagel adduct **5a** was observed by TLC control and appearance of the yellow colour within 15 min. It was not isolated and allowed to cyclise at room temperature which after 3 h stirring gave the cis fused pentacyclic pyrano[2,3-*b*]quinoline derivative **6a** with high yield 80% and diastereoselectivity (>99%). The structure of the compound was ascertained from the spectroscopic data. $^1$H NMR spectra showed the absence of the prenylic protons at $\delta$ 4.16 (d, 2H), 5.27 (t, 1H) and the presence of two another *N*-Me protons at $\delta$ 3.30 and 3.36 as singlets. The cis-fusion at the ring junction of **6a** is strongly supported by the coupling constant of 4.77 Hz between the two hydrogens $H_a$ and $H_b$ in the $^1$H NMR spectrum. Similarly compound **6b** was synthesized and characterized (Table 1).

**Table 1**
Synthesis of pyrano[2,3-*b*]quinolines **6**, **7**, **8**, **10** and **12**

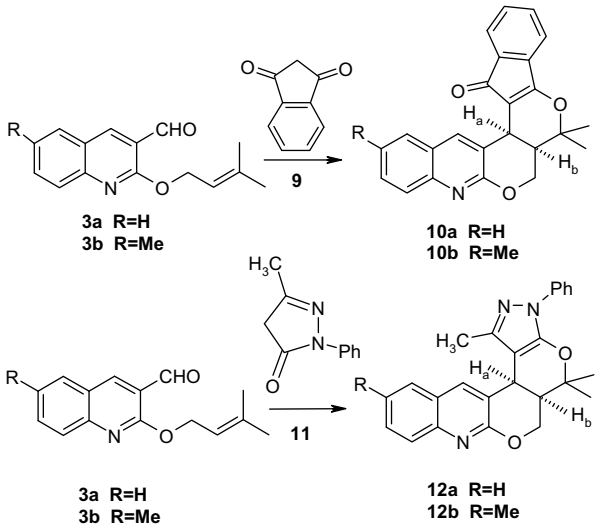
| Product | R | Time (h) | Yield (%) | Mp (°C) |
|---|---|---|---|---|
| **6a** | H | 3 | 80 | 274–276 |
| **6b** | Me | 3 | 76 | 287–288 |
| **7a** | H | 4.5 | 45 | 312–314 |
| **7b** | Me | 4.5 | 45 | 320–322 |
| **8a** | H | 4.5 | 30 | 310–312 |
| **8b** | Me | 4.5 | 25 | 316–318 |
| **10a** | H | 3 | 75 | 274–276 |
| **10b** | Me | 3 | 70 | 288–290 |
| **12a** | H | 4 | 80 | 197–199 |
| **12b** | Me | 4 | 74 | 210–212 |

When the reaction was studied by utilizing *N*-methyl barbituric acid **4b** with compound **3** two regioisomeric cycloadducts **7** & **8** were formed (Scheme 2). Obviously it is because of the two possible oxabutadiene sites of the Knoevenagel condensed product formed from the reaction of unsymmetrical barbituric acid **4b** with **3a**. Thus the reaction of **3a** with **4b** gave the two isomers **7a** and **8a** in a ratio of 3:2 and in 75% yield. The structures of the compounds were ascertained from the spectroscopic data and elemental analysis. The compound **7a** showed a broad singlet at $\delta$ 8.90 for the NH proton whereas **8a** showed the presence of the NH proton at $\delta$ 4.89. Similarly compound **7b** and **8b** were synthesized and characterized (Table 1).

The reaction was then extended by utilizing other cyclic dicarbonyl compounds viz. 1,3-indanedione **9** and 3-methyl-1-phenyl-2-



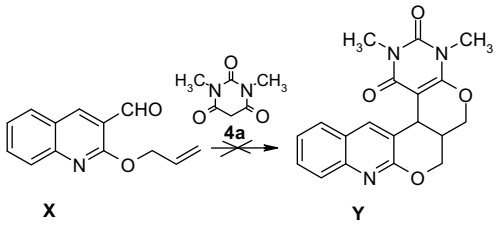

**Scheme 2.**




**Scheme 3.**

pyrazolin-5-one **11** to generate the oxabutadiene system which after cyclisation resulted the products **10** and **12** respectively (Scheme 3, Table 1).

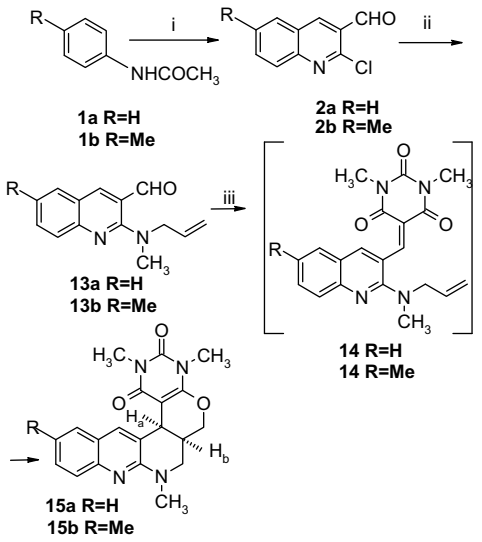
Aldehydes **X** obtained from the reaction of **2** with allyl alcohol instead of prenyl alcohol were found to react with *N*,*N*-dimethyl barbituric acid **4a** to afford the Knoevenagel adduct which could not be transformed to the hetero Diels–Alder adduct **Y** even on heating at 200 °C for 48 h (Scheme 4).




**Scheme 4.**

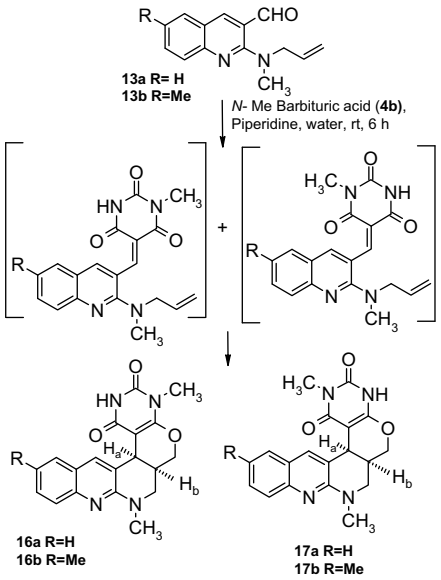
In order to synthesize the pyrido[2,3-*b*]quinoline derivatives, the dienophile site was prepared from **2** by treatment with *N*-allyl methyl amine in presence of $K_2CO_3$ under refluxing condition in DMF for 4 h (Scheme 5). Thus the reaction of **2a** with *N*-allyl methyl amine in presence of $K_2CO_3$ afforded the compound **13a**. The compound **13a** on treatment with *N*,*N*-dimethylbarbituric acid **4a** in prsence of piperidine as catalyst and water as solvent at room temperature afforded the hetero Diels–Alder cycloadduct, **15a** in

5 h and in 70% yield. The formation of the orange-red intermediate **14a** was observed in TLC plate in 15 min. It could not be isolated which cyclised at room temperature after 5 h stirring to the cis-fused pentacyclic pyrido[2,3-*b*]quinoline derivative **15a** giving high yield (70%). The structure of the compound was determined from the spectroscopic data. $^1$H NMR spectra showed the absence of the allylic protons at $\delta$ 5.98 (m, 1H), 5.32 (d, 2H), 3.53 (d, 2H) and the presence of two *N*-Me protons at $\delta$ 3.31 and 3.35 as singlets. The cis-fusion at the ring junction of **15a** was confirmed from the coupling constant of 4.53 Hz between $H_a$ and $H_b$ in the $^1$H NMR spectrum.



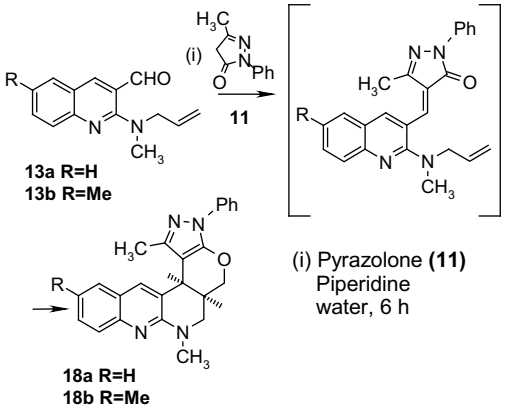

**Scheme 5.** (i) DMF–$POCl_3$, 80 °C. (ii) *N*-allyl methyl amine, $K_2CO_3$, DMF, (iii) *N*,*N*-dimethyl barbituric acid (**4a**).

As in the earlier case when *N*-methyl barbituric acid **4b** was reacted with **13a** two products **16a** and **17a** were formed in the ratio 3:2 (Scheme 6). The two products could be separated by column chromatography giving a combined yield of 70%. The structures of the compounds were determined from the spectroscopic data. The $^1$H NMR spectra of the compounds showed the cis-fusion at the ring junction for both the isomer **16a** and **17a**. The $^1$H NMR spectra of **16a** showed a broad singlet at $\delta$ 8.83 for NH proton whereas **17a** showed a broad singlet at $\delta$ 4.90 for the NH proton.




**Scheme 6.**

The reaction was then studied by condensing pyrazolone **11** with **13a** which afforded exclusively the cis-adduct **18a** in good yield (Scheme 7). Similarly compound **18b** was synthesized by utilizing **13b** with **11**. The structures of the compounds were determined from the spectroscopic data and elemental analysis (Table 2).




**Scheme 7.**

**Table 2**
Synthesis of pyrido[2,3-*b*]quinolines **15**, **16**, **17** and **18**

| Product | R | Time (h) | Yield (%) | Mp (°C) |
|---|---|---|---|---|
| **15a** | H | 5 | 70 | 167–168 |
| **15b** | Me | 5 | 65 | 187–189 |
| **16a** | H | 6 | 42 | 267–269 |
| **16b** | Me | 6 | 39 | 297–299 |
| **17a** | H | 6 | 28 | 265–266 |
| **17b** | Me | 6 | 26 | 294–296 |
| **18a** | H | 6 | 55 | 155–157 |
| **18b** | Me | 6 | 52 | 170–172 |

However, we failed in the reaction to replace the chloro group of **2a** by simple *N*-phenyl allyl-amine in the presence of base, e.g., $Na_2CO_3$, $NaHCO_3$ even at elevated temperature.

In conclusion we have reported the synthesis of some complex pyrano[2,3-*b*]- and pyrido[2,3-*b*]quinolines from simple acetanilides and via intramolecular domino hetero Diels–Alder reactions involving 1-oxa-1,3-butadienes. The reactions were performed in aqueous medium and products were isolated simply by filtration almost in the pure form.

## 3. Experimental

### 3.1. General

All reagents and solvents were of reagent grade and were used without drying. The IR spectra were recorded on Perkin–Elmer system-2000 FTIR spectrometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker Avance-DPX 300 MHz and 75 MHz FT NMR in $CDCl_3$ using TMS as an internal standard. LRMS were recorded in Bruker Daltonics ESQUIRE 3000 LC ESI ion trap mass spectrometer. Elemental analyses were performed on Perkin–Elmer-2400 spectrometer at the Analytical Chemistry Division, NEIST, Jorhat. Analytical TLC and column chromatography were performed using E. Merck aluminum-backed silica gel plates coated with silica gel G and E. Merck silica gel (100–200 mesh); Melting points (uncorrected) were determined on a Buchi B-540 apparatus.

### 3.2. General procedure for the synthesis of 2-chloro-3-formylquinolines 2

$POCl_3$ (9 mL, 98.28 mmol) was added dropwise from a droping funnel to DMF (2.7 mL, 34.65 mmol) taken in a round bottom flask

keeping the temperature at 0–5 °C. The mixture was allowed to stir for about 5 min. Acetanilide **1a** (1.4 g, 10.37 mmol) was then added to the reaction mixture and heated the resulting solution for 8 h (75–80 °C). The reaction mixture was cooled to room temperature and then poured into crushed ice under stirring condition. A pale yellow compound appeared at once. The precipitate thus appeared was filtered and washed with water and dried. The crude compound was then recrystallised from ethylacetate. **2a**. Yield 1.59 g (80%), mp 148–149 °C. Similarly compound **2b** was synthesized. **2b**. Yield 1.71 g (82%), mp 124–125 °C.

### 3.3. General procedure for the synthesis of 2-prenyloxy-3-formylquinolines 3

In a round bottom flask containing 10 mL of 50% aqueous NaOH solution was added prenyl alcohol (0.6 mL, 10 mmol) and catalytic amount of tetrabutyl amonium bromide. To this added a solution of 2-chloro-3-formyl quinoline **2a** (1.53 g, 8 mmol) in dichloromethane (10 mL) and allowed to stirred the reaction mixture for 5 h. The organic layer was separated and washed 2–3 times with water. The solvent was evaporated and the crude product thus formed was separated by means of column chromatography (5% EtOAc/hexane). The structure of the compound was determined from the spectroscopic data. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.71 (s, 3H), 1.75 (s, 3H), 4.16 (d, $J$=4.7 Hz, 2H), 5.27 (t, $J$=4.6 Hz, 1H), 7.27–8.76 (m, 5H), 10.56 (s, 1H). **3a**. Yield 1.01 g (52%), mp 65 °C. Similarly compound **3b** was synthesized and characterized. **3b**. Yield 1.05 g (50%), mp 62 °C.

### 3.4. Experimental procedure for the synthesis of pyrano[2,3-*b*]quinolines

To an aqueous solution of 2-prenyloxy-3-formylquinolines **3** (1 mmol) in a 100 mL round bottom flask added 1 mmol of active methylene compound **4**/**9**/**11** and 1 drop of piperidine and then allowed to stir at room temperature. The reaction mixture becomes yellow within 15 min which shows the formation of the Knoevenagel condensed product. Stiring was continued for 3–4.5 h. The product **6**/**10**/**12** appeared as yellowish/brownish/white compound in the reaction mixture. The compound was filtered and recrystallised (20% EtOH/$CHCl_3$). Yields 70–80%. In the reaction of **3** with **4b** two products were formed. The solid product obtained in this reaction was filtered and separated by column chromatography (EtOAc). The structure of the compounds were confirmed as regioisomers **7** & **8** from the spectroscopic data.

**6a**: Light yellow solid. Yield=300 mg (80%); mp=274–276 °C; $R_f$ (90% EtOAc/pet. ether) 0.21. IR (KBr): 3014.3, 2958.4, 1704.1, 1655.7, 756.9 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.56 (s, 6H, $OCMe_2$), 2.83–3.11 (m, 1H, $H_b$), 3.30 (s, 3H, NMe), 3.36 (s, 3H, NMe), 3.70 (d, $J$=4.7 Hz, 1H, $H_a$), 4.15 (d, $J$=4.8 Hz, 2H, $OCH_2$), 7.48–7.57 (m, 1H, Ar), 7.67–7.79 (m, 2H, Ar), 7.96–8.10 (m, 1H, Ar), 8.17 (s, 1H, Ar). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 27.87, 28.27, 28.54, 29.37, 33.56, 54.61, 85.88, 116.38, 126.55, 127.14, 127.77, 130.91, 138.03, 145.23, 150.14, 153.62, 154.43, 161.58, 166.11, 166.50. ESI-MS $m/z$ (%): 380.1 $(M+H)^+$ (100). Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.07. Found: C, 66.36; H, 5.64; N, 11.10.

**6b**: Yellowish white solid. Yield=298 mg (76%); mp=274–276 °C; $R_f$ (90% EtOAc/pet. ether) 0.20. IR (KBr): 3014.3, 2958.4, 1704.1, 1655.7, 756.9 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.56 (s, 6H, $OCMe_2$), 2.34 (s, 3H, Me), 2.86–3.14 (m, 1H, $H_b$), 3.31 (s, 3H, NMe), 3.36 (s, 3H, NMe), 3.80 (d, $J$=4.9 Hz, 1H, $H_a$), 4.13 (d, $J$=4.2 Hz, 2H, $OCH_2$), 7.39–7.98 (m, 4H, Ar). $^{13}$C (75 MHz, $CDCl_3$): $\delta$ 21.98, 27.64, 28.31, 28.22, 29.42, 33.48, 54.75, 86.00, 116.12, 126.30, 127.41, 127.79, 131.01, 138.11, 145.17, 150.20, 153.49, 154.41, 161.50, 166.14, 166.39. ESI-MS $m/z$ (%): 394.2 $(M+H)^+$ (100). Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.22; H, 5.83; N, 10.73.

**7a**: Brown solid. Yield=164 mg (45%); mp=312–314 °C; $R_f$ (EtOAc) 0.18. IR (KBr): 3415.8, 3010.9, 2954.0, 1702.5, 1656.2, 755.6 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.57 (s, 6H, $OCMe_2$), 2.94–3.10 (m, 1H, $H_b$), 3.33 (s, 3H, NMe), 3.84 (d, $J$=4.9 Hz, 1H, $H_a$), 4.12 (d, $J$=4.8 Hz, 2H, $OCH_2$), 7.12–7.96 (m, 5H, Ar), 8.90 (s, 1H, NH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 27.85, 28.23, 29.32, 32.92, 54.40, 85.11, 117.10, 126.29, 127.16, 127.81, 130.75, 137.99, 145.41, 149.86, 153.68, 154.44, 161.20, 166.10, 166.45. ESI-MS $m/z$ (%): 366.3 $(M+H)^+$ (100). Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.81; H, 5.19; N, 11.45.

**7b**: Brownish white solid. Yield=169 mg (45%); mp=320–322 °C; $R_f$ (EtOAc) 0.20. IR (KBr): 3418.0, 3012.2, 2955.7, 1702.6, 1657.4, 756.8 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.56 (s, 6H, $OCMe_2$), 2.35 (s, 3H, Me), 2.96–3.10 (m, 1H, $H_b$), 3.34 (s, 3H, NMe), 3.89 (d, $J$=4.5 Hz, 1H, $H_a$), 4.15 (d, $J$=4.3 Hz, 2H, $OCH_2$), 7.02–7.82 (m, 4H, Ar), 8.91 (s, 1H, NH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 20.86, 27.80, 28.39, 29.37, 32.96, 54.91, 86.01, 117.70, 126.21, 127.10, 127.42, 130.51, 138.05, 145.33, 149.69, 153.78, 154.40, 161.87, 166.27, 166.49. ESI-MS $m/z$ (%): 380.4 $(M+H)^+$ (100). Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.07. Found: C, 66.54; H, 5.51; N, 11.10.

**8a**: Dark brown solid. Yield=110 mg (30%); mp=310–312 °C; $R_f$ (EtOAc) 0.16. IR (KBr): 3442.0, 3015.1, 2954.8, 1702.5, 1624.8, 758.1 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.56 (s, 6H, $OCMe_2$), 2.96–3.08 (m, 1H, $H_b$), 3.37 (s, 3H, NMe), 3.90 (d, $J$=4.0 Hz, 1H, $H_a$), 4.14 (d, $J$=4.1 Hz, 2H, $OCH_2$), 4.89 (s, 1H, NH), 7.01–8.11 (m, 5H, Ar). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 27.92, 28.81, 29.54, 32.86, 54.33, 84.80, 116.89, 126.43, 127.429, 127.91, 130.74, 138.01, 145.42, 149.95, 153.49, 154.23, 161.21, 166.11, 166.57. ESI-MS $m/z$ (%): 366.1 $(M+H)^+$ (100). Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.77; H, 5.16; N, 11.57.

**8b**: Dark brown solid. Yield=95 mg (25%); mp=317–319 °C; $R_f$ (EtOAc) 0.17. IR (KBr): 3444.6, 3014.9, 2956.7, 1704.3, 1627.3, 758.9 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.56 (s, 6H, $OCMe_2$), 2.33 (s, 3H, Me), 2.94–3.06 (m, 1H, $H_b$), 3.37 (s, 3H, NMe), 3.90 (d, $J$=4.1 Hz, 1H, $H_a$), 4.16 (d, $J$=4.2 Hz, 2H, $OCH_2$), 4.89 (s, 1H, NH), 7.09–8.05 (m, 4H, Ar). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.10, 27.34, 28.45, 29.67, 32.88, 54.75, 84.09, 116.62, 126.49, 127.42, 127.89, 130.44, 138.47, 145.33, 149.90, 153.88, 154.27, 161.11, 166.06, 166.73. ESI-MS $m/z$ (%): 380.4 $(M+H)^+$ (100). Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.07. Found: C, 66.43; H, 5.63; N, 11.11.

**10a**: Yellowish brown solid. Yield=277 mg (75%); mp=274–276 °C; $R_f$ (EtOAc) 0.15. IR (KBr): 2922.6, 1708.5, 1655.1, 771.6 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.57 (s, 6H, $OCMe_2$), 2.83–3.11 (m, 1H, $H_b$), 3.70 (d, $J$=4.7 Hz, 1H, $H_a$), 4.15 (d, $J$=4.8 Hz, 2H, $OCH_2$), 7.27 (s, 1H, Ar), 7.37 (d, $J$=7.2 Hz, 1H, Ar), 7.41–7.50 (m, 1H, Ar), 7.52 (d, $J$=6.9 Hz, 1H, Ar), 7.65 (t, $J$=7.3 Hz, 1H, Ar), 7.76 (d, $J$=7.2 Hz, 1H, Ar), 7.84 (d, $J$=7.1 Hz, 1H, Ar), 7.96 (d, $J$=8.0 Hz, 1H, Ar), 8.04 (s, 1H, Ar). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 25.87, 30.12, 34.52, 58.01, 79.95, 105.82, 118.97, 121.64, 122.92, 123.07, 126.95, 127.79, 130.31, 130.60, 132.54, 135.37, 135.69, 138.86, 141.20, 144.90, 155.14, 169.98, 180.61. ESI-MS $m/z$ (%): 370.4 $(M+H)^+$ (100). Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.12; H, 5.01; N, 3.73.

**10b**: Crimson white solid. Yield=268 mg (70%); mp=274–276 °C; $R_f$ (EtOAc) 0.12. IR (KBr): 2924.0, 1709.1, 1655.4, 772.1 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.57 (s, 6H, $OCMe_2$), 2.45 (s, 3H, Me), 2.84–3.12 (m, 1H, $H_b$), 3.72 (d, $J$=4.2 Hz, 1H, $H_a$), 4.14 (d, $J$=4.7 Hz, 2H, $OCH_2$), 7.35 (d, $J$=7.3 Hz, 1H, Ar), 7.42 (s, 1H, Ar), 7.54 (d, $J$=7.9 Hz, 1H, Ar), 7.67 (t, $J$=7.8 Hz, 1H, Ar), 7.78 (d, $J$=7.4 Hz, 1H, Ar), 7.85 (d, $J$=7.2 Hz, 1H, Ar), 7.98 (d, $J$=7.7 Hz, 1H, Ar), 8.05 (s, 1H, Ar). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 20.92, 25.81, 30.43, 34.76, 58.21, 79.81, 105.77, 118.68, 121.40, 123.09, 123.12, 127.10, 127.89, 130.42, 130.62, 132.64, 135.51, 135.86, 138.59, 141.31, 145.21, 155.23, 169.84, 180.44. ESI-MS $m/z$ (%): 384.3 $(M+H)^+$ (100). Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.27; H, 5.56; N, 3.60.

**12a**: Dirty white solid. Yield=318 mg (80%); mp=197–199 °C; $R_f$ (EtOAc) 0.72. IR (KBr): 3065.2, 2953.6, 1595.9, 1513.2, 772.2 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.56 (s, 6H, $OCMe_2$), 2.64 (s, 3H, NCMe), 3.02–3.23 (m, 1H, $H_b$), 4.11 (d, $J$=4.4 Hz, 2H, $OCH_2$), 4.29 (d, $J$=4.9 Hz, 1H, $H_a$), 7.13–8.06 (m, 10H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 14.51, 27.22, 33.41, 54.65, 86.11, 102.20, 121.31, 125.49, 126.10, 127.48, 127.79, 128.43, 129.53, 130.96, 137.65, 139.81, 146.12, 148.22, 153.47, 166.70. ESI-MS $m/z$ (%): 398.7 $(M+H)^+$ (100). Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.55; H, 5.83; N, 10.57. Found: C, 75.47; H, 6.90; N, 10.61.

**12b**: Light brown solid. Yield=329 mg (80%); mp=210–212 °C; $R_f$ (EtOAc) 0.65. IR (KBr): 3064.8, 2954.1, 1593.4, 1510.4, 773.5. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.56 (s, 6H, $OCMe_2$), 2.35 (s, 3H, Me), 2.65 (s, 3H, NCMe), 3.04–3.25 (m, 1H, $H_b$), 4.12 (d, $J$=4.9 Hz, 2H, $OCH_2$), 4.30 (d, $J$=4.5 Hz, 1H, $H_a$), 7.26–8.13 (m, 9H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 13.96, 21.12, 27.21, 33.44, 54.66, 86.85, 102.11, 121.39, 125.40, 126.80, 127.62, 127.91, 128.54, 129.28, 130.40, 137.10, 139.17, 146.78, 148.64, 153.66, 166.31. ESI-MS $m/z$ (%): 412.9 $(M+H)^+$ (100). Anal. Calcd for $C_{26}H_{25}N_3O_2$: C, 75.89; H, 6.12; N, 10.21. Found: C, 75.80; H, 6.22; N, 10.27.

### 3.5. Typical experimental procedure for the synthesis of 13

In a simple experimental procedure, equimolar amounts of 2-chloro-3-formyl quinoline **2a** (2 mmol) and *N*-allyl methyl amine (2 mmol) were taken in a round bottom flask containing 5 mL of DMF. 2 mmol of $K_2CO_3$ was added to the reaction mixture and refluxed for 4 h. The reaction mixture was cooled to room temperature and poured into crushed ice under continuous stirring. It was then extracted with dichloromethane, dried with anhydrous $Na_2SO_4$, evaporated under reduced pressure and purified by preparative TLC (5% EtOAc/hexane) to furnish **13a** (176 mg, 60%). The structure of the compound was determined from the spectroscopic data. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.10 (s, 3H), 3.53 (d, $J$=4.4 Hz, 2H), 5.32 (d, $J$=4.0 Hz, 2H), 5.98–6.07 (m, 1H), 7.20–8.47 (m, 5H), 10.54 (s, 1H).

### 3.6. Experimental procedure for the synthesis of pyrido[2,3-*b*]quinolines

To an aqueous solution of 2-prenyloxy-3-formylquinolines **13** (1 mmol) added 1 mmol of active methylene compound **4**/**11** and 1 drop of piperidine and then allowed to stir at room temperature. The reaction mixture becomes orange-red within 15 min which shows the formation of the Knoevenagel condensed product. Stirring was continued for 5–6 h. The product **15**/**18** appeared as yellowish white compound in the reaction mixture. The compound was filtered and recrystallised (20% EtOH/$CHCl_3$). Yields 50–70%.

In the reaction of **13** with **4b** two products were formed. The products were separated by column chromatography (70% EtOAc/pet. ether). The structures of the compounds were confirmed as regioisomers **16** and **17** from the spectroscopic data.

**15a**: Brownish white colour solid; Yield=255 mg (70%); mp=167–168 °C; $R_f$ (70% EtOAc/pet. ether) 0.30. IR (KBr): 3011.2, 2955.8, 1704.5, 1654.7, 756.4 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.70–2.90 (m, 1H, $H_b$), 2.95 (s, 3H, NMe), 3.31 (s, 3H, NMe), 3.35 (s, 3H, NMe), 3.48 (d, $J$=1.5 Hz, 2H, $NCH_2$), 3.92 (d, $J$=4.5 Hz, 1H, $H_a$), 4.11 (d, $J$=4.9 Hz, 2H, $OCH_2$), 7.26–7.89 (m, 5H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 27.68, 28.25, 29.17, 32.45, 39.41, 44.22, 51.03, 115.29, 125.45, 127.31, 129.81, 130.52, 137.92, 145.69, 150.25, 153.71, 154.89, 160.21, 166.05, 166.28. ESI-MS $m/z$ (%): 365.1 $(M+H)^+$ (100). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.84; H, 5.62; N, 15.40.

**15b**: Brown colour solid: Yield=245 mg (65%); mp=187–189 °C; $R_f$ (70% EtOAc/pet. ether) 0.27. IR (KBr): 3010.6, 2952.6, 1702.7, 1659.2, 755.8 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.39 (s, 3H, Me), 2.71–2.91 (m, 1H, $H_b$), 2.96 (s, 3H, NMe), 3.28 (s, 3H, NMe), 3.33 (s, 3H, NMe), 3.47 (d, $J$=1.8 Hz, 2H, $NCH_2$), 3.96 (d, $J$=4.2 Hz, 1H, $H_a$), 4.10 (d, $J$=4.7 Hz, 2H, $OCH_2$), 7.24–7.84 (m, 4H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 22.27, 27.46, 28.15, 29.31, 32.41, 39.52, 44.14, 51.08, 115.64, 125.41, 127.39, 129.62, 130.71, 137.90, 145.81, 150.49, 153.70, 155.02, 160.41, 166.15, 166.48. ESI-MS $m/z$ (%): 379.3 $(M+H)^+$ (100). Anal. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.80. Found: C, 66.71; H, 5.92; N, 14.71.

**16a**: Pinkish white colour solid. Yield=147 mg (42%); mp=267–269 °C; $R_f$ (70% EtOAc/pet. ether) 0.25. IR (KBr): 3414.3, 3011.2, 2955.8, 1704.7, 1654.7, 756.4 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$), 2.89–2.92 (m, 1H, $H_b$), 3.09 (s, 3H, NMe), 3.31 (s, 3H, NMe), 3.71 (d, $J$=4.4 Hz, 2H, $NCH_2$), 3.92 (d, $J$=4.9 Hz, 1H, $H_a$), 4.06 (d, $J$=4.6 Hz, 2H, $OCH_2$), 7.17 (s, 1H, Ar), 7.27 (t, $J$=7.2 Hz, 1H, Ar), 7.52 (t, $J$=7.5 Hz, 1H, Ar), 7.65 (s, 1H, Ar), 7.75 (s, 1H, Ar), 8.83 (s, 1H, NH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 27.36, 28.29, 32.42, 35.21, 43.98, 53.92, 116.11, 125.26, 127.43, 129.52, 130.68, 137.59, 145.49, 150.14, 153.61, 154.93, 160.43, 166.18, 166.48. ESI-MS $m/z$ (%): 351.4 $(M+H)^+$ (100). Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.21; H, 5.10; N, 15.92.

**16b**: Brownish white colour solid. Yield=142 mg (39%); mp=297–299 °C; $R_f$ (70% EtOAc/pet. ether) 0.23. IR (KBr): 3431.2, 3014.7, 2957.1, 1702.3, 1657.0, 756.9 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.36 (s, 3H, Me), 2.89–2.92 (m, 1H, $H_b$), 3.04 (s, 3H, NMe), 3.33 (s, 3H, NMe), 3.69 (d, $J$=4.2 Hz, 2H, $NCH_2$), 3.91 (d, $J$=4.9 Hz, 1H, $H_a$), 4.04 (d, $J$=4.7 Hz, 2H, $OCH_2$), 7.14–7.64 (m, 4H, Ar), 8.83 (s, 1H, NH). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 21.91, 27.33, 28.32, 33.02, 35.31, 43.77, 53.81, 116.21, 126.16, 127.51, 129.44, 131.08, 137.69, 145.17, 150.10, 153.67, 154.97, 160.19, 166.22, 166.49. ESI-MS $m/z$ (%): 365.7 $(M+H)^+$ (100). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.85; H, 5.61; N, 15.41.

**17a**: Dark brown colour solid. Yield=98 mg (28%); mp=265–266 °C; $R_f$ (70% EtOAc/pet. ether) 0.22. IR (KBr): 3441.9, 2954.0, 1702.1, 1625.9, 759.2 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.75–2.87 (m, 1H, $H_b$), 3.12 (s, 3H, NMe), 3.32 (s, 3H, NMe), 3.70 (d, $J$=4.1 Hz, 2H, $NCH_2$), 3.94 (d, $J$=4.4 Hz, 1H, $H_a$), 4.02 (d, $J$=5.9 Hz, 2H, $OCH_2$), 4.90 (s, 1H, NH), 7.16–7.26 (m, 2H, Ar), 7.54 (t, $J$=7.7 Hz, 1H, Ar), 7.66 (d, $J$=7.7 Hz, 1H, Ar), 7.74 (s, 1H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 27.35, 28.30, 32.40, 35.18, 43.97, 54.01, 116.20, 125.14, 127.40, 129.55, 130.54, 137.62, 145.30, 150.32, 153.66, 154.99, 160.80, 166.25, 166.55. ESI-MS $m/z$ (%): 351.2 $(M+H)^+$ (100). Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.21; H, 5.09; N, 15.92.

**17b**: Brown colour solid. Yield=95 mg (26%); mp=294–296 °C; $R_f$ (70% EtOAc/pet. ether) 0.21. IR (KBr): 3440.5, 2953.2, 1704.0, 1627.3, 758.1 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.37 (s, 3H, Me), 2.78–2.91 (m, 1H, $H_b$), 3.02 (s, 3H, NMe), 3.31 (s, 3H, NMe), 3.68 (d, $J$=4.1 Hz, 2H, $NCH_2$), 3.84 (d, $J$=4.4 Hz, 1H, $H_a$), 4.0 (d, $J$=5.9 Hz, 2H, $OCH_2$), 4.92 (s, 1H, NH), 7.28 (d, $J$=7.6 Hz, 1H, Ar), 7.54 (t, $J$=7.7 Hz, 1H, Ar), 7.66 (s, 1H, Ar), 7.74 (d, $J$=7.5 Hz, 1H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 22.01, 27.33, 28.39, 32.42, 35.49, 43.08, 54.21, 116.14, 125.22, 127.50, 129.35, 131.01, 137.82, 145.10, 150.33, 153.48, 155.06, 161.10, 166.21, 166.32. ESI-MS $m/z$ (%): 365.3 $(M+H)^+$ (100). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.82; H, 5.47; N, 15.45.

**18a**: Brown solid. Yield=210 mg (55%); mp=155–157 °C; $R_f$ (70% EtOAc/pet. ether) 0.35. IR (KBr): 3066.2, 2924.0, 1596.6, 1519.1, 754.1 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.65 (s, 3H, NCMe), 2.95 (s, 3H, NMe), 3.23–3.45 (m, 1H, $H_b$), 3.70 (d, $J$=4.4 Hz, 2H, $NCH_2$), 4.11 (d, $J$=4.3 Hz, 2H, $OCH_2$), 4.36 (d, $J$=4.1 Hz, 1H, $H_a$), 7.09 (d, $J$=7.3 Hz, 1H, Ar), 7.18–7.42 (m, 4H, Ar), 7.52 (d, $J$=7.7 Hz, 1H, Ar), 7.63 (s, 1H, Ar), 7.66 (d, $J$=7.6 Hz, 1H, Ar), 7.82 (d, $J$=8.4, 1H, Ar), 7.95 (s, 1H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 13.49, 26.23, 31.48, 38.14, 44.42, 54.92, 96.61, 121.30, 125.21, 125.42, 127.40, 127.76, 128.33, 129.45, 130.93, 137.40, 139.03, 145.89, 148.01, 153.26, 166.47. ESI-MS $m/z$ (%): 383.4 $(M+H)^+$ (100). Anal. Calcd for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80; N, 14.65. Found: C, 75.43; H, 5.74; N, 14.69.

**18b**: Dark brown solid. Yield=206 mg (52%); mp=170–172 °C; $R_f$ (70% EtOAc/pet. ether) 0.30. IR (KBr) 3064.9, 2926.7, 1589.6, 1525.0, 755.7 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 2.34 (s, 3H, Me), 2.65 (s, 3H, NCMe), 2.95 (s, 3H, NMe), 3.24–3.45 (m, 1H, $H_b$), 3.71 (d, $J$=4.6 Hz, 2H, $NCH_2$), 4.09 (d, $J$=4.9 Hz, 2H, $OCH_2$), 4.34 (d, $J$=4.2 Hz, 1H, $H_a$), 7.09 (d, $J$=7.3 Hz, 1H, Ar), 7.15–7.41 (m, 4H, Ar), 7.60 (s, 1H, Ar), 7.69 (t, $J$=7.7 Hz, 1H, Ar), 7.82 (d, $J$=7.4 Hz, 1H, Ar), 7.95 (s, 1H, Ar). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 13.42, 21.97, 26.25, 31.48, 38.17, 44.34, 54.95, 96.60, 121.55, 125.32, 125.55, 127.38, 127.71, 128.40, 129.47, 130.94, 137.44, 139.01, 145.84, 148.11, 153.17, 166.48. ESI-MS $m/z$ (%): 397.5 $(M+H)^+$ (100). Anal. Calcd for $C_{25}H_{24}N_4O$: C, 75.73; H, 6.10; N, 14.13. Found: C, 75.79; H, 6.15; N, 14.02.

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