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Tetrahedron 64 (2008) 582–589
Tetrahedron
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Revisiting the reaction of β-chloroacroleins with 2-aminophenol: a new observation

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Received 27 July 2007; received in revised form 16 October 2007; accepted 26 October 2007
Available online 1 November 2007

Abstract

The reaction of β-chloroacrolein with 1 equiv of 2-aminophenol in DMF proceeds smoothly to afford 11-hydroxy derivative of chromenoquinoline in good yield. This single pot method allows for a rapid access to a variety of chromenoquinolines or oxepinoquinolines depending on the nature of β-chloroacrolein used. The structures were established by spectroscopic data and further confirmed by X-ray diffraction analysis. A plausible mechanism for this reaction has been proposed. The reaction seemed to proceed via a chloroimine species, whose intermediacy has been established, followed by the construction of the fused quinoline ring.

Keywords: β-Chloroacroleins; 2-Aminophenol; Chromenoquinoline; Oxepinoquinoline

1. Introduction

Drugs that modulate the transcriptional activity of human progesterone receptor (hPR) play important role in medicine, and over the years hPR agonists have been used therapeutically.[1] Due to the undesirable side effects caused by all the steroidal hRP modulators, a polynuclear heterocyclic framework such as chromenoquinoline (**I**, Fig. 1) has been designed and identified as an effective pharmacophore for the development of better nonsteroidal hPR agonists.[2] Additionally, this class of compounds has shown glucocorticoid receptor agonist and antagonist activity and androgen receptor antagonist activity.[3] Based on these reports that this framework can be utilized for the development of potential drugs, we became interested in the synthesis of substituted 6*H*-chromeno[4,3-*b*]quinolines (**II**) and 6,7-dihydrobenzo[2,3]oxepino[4,5-*b*]quinolines (**III**) derived from **I** (Fig. 1). The new chromenoquinolines **II** were initially designed via changing the connectivity between chromene and quinoline moiety. However, since the earlier work on **I** was limited to the effect of substituents on D and C ring,[2a] hence we focused on modifying the A and B ring also followed by the expansion of C ring as shown in Figure 1. We presumed that these compounds containing 8-hydroxyquinoline[2b] moiety might be useful for conducting structure–activity relationship (SAR) studies related to the compound **I** and that some of them might show the similar pharmacological properties to **I**. Additionally, the substituent, e.g., hydroxyl group present on the quinoline ring might help in further functionalization of **II** and **III**.

Whilst a large number of methods are known for the construction of quinoline rings, only a few have been reported for chromenoquinolines. These include (i) condensation of 2-aminobenzaldehyde with chroman-4-one,[4a–c] (ii) heating (200 °C)[4d] or irradiation[4e] of phenyl-[3-(phenylimino-methyl)-2*H*-chromen-4-yl]-amine hydrochloride, and (iii) treatment of *N*-phenyl-2-prop-2-ynyloxy-benzamide with $POCl_3$.[4f] On the other hand, 6,7-dihydro-benzo[2,3]oxepino[4,5-*b*]quinolines

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doi:10.1016/j.tet.2007.10.101

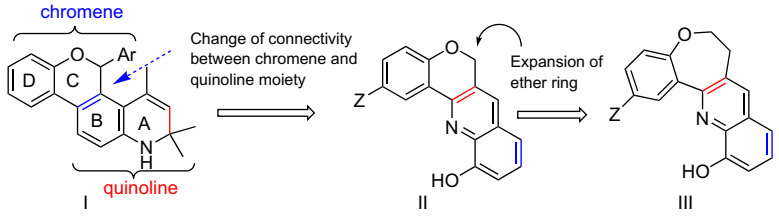


Figure 1. Design of new chromenoquinolines and oxepinoquinolines.

can be obtained via condensation of 1-(2-amino-phenyl)-ethanone hydrochloride with 3,4-dihydro-2*H*-benzo[*b*]oxepin-5-one at high temperature (140 °C).[4g] Many of these processes, however, suffer from disadvantages, such as the use of excess reagents, longer reaction time, and the low yields of products. More importantly, none of these processes appeared to be suitable for the synthesis of both **II** and **III**. Thus, development of an appropriate and general, but cost effective process, for the preparation of **II** and **III** was highly desirable. Due to our continued interest in the design and synthesis of polynuclear heterocyclic compounds of potential biological interest,[5] we have recently reported the Pd-mediated synthesis of furoquinolines via construction of the fused furan ring.[5d] Herein, we report a very simple and single pot synthesis of hydroxy derivatives of various 6*H*-chromeno[4,3-*b*]quinolines and 6,7-dihydrobenzo[2,3]oxepino[4,5-*b*]quinolines via construction of the fused quinoline moiety using β-chloroacroleins and 2-aminophenol as synthetic precursors (Scheme 1).

2. Results and discussion

Recently, condensation followed by cyclization of heterocyclic β-chloroaldehydes with 2-aminophenol has been studied, which led to the formation of 1,5-benzoxazepines in good yields.[6] Accordingly, we reacted 4-chloro-2*H*-chromene-3-carboxaldehyde (**1a**) with 1.1 equiv of 2-aminophenol (**2a**) in DMF (5 mL) at 25 °C for 1.0 h followed by heating the reaction mixture at 120 °C for 4 h. To our surprise, the corresponding 1,5-benzoxazepine (**3aa**) was not isolated from the reaction mixture (Scheme 2). Based on analytical data [^{1}H (Fig. 2) and ^{13}C NMR, Mass {*m*/*z* 250.3 (M+1, 100%)},

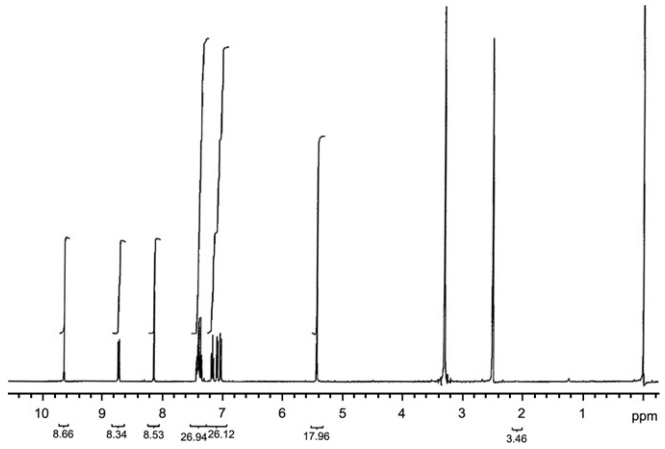
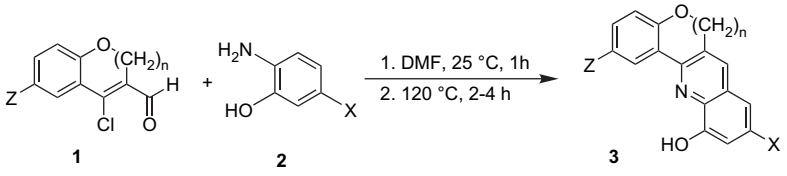


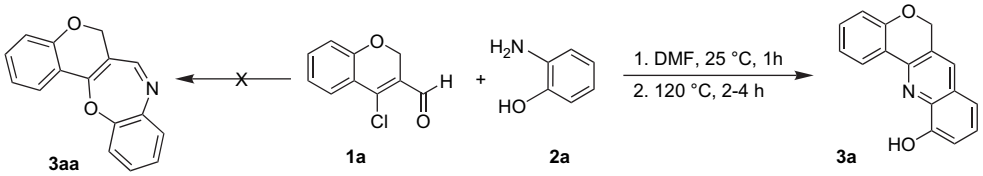
Figure 2. ^{1}H NMR (in DMSO-d_6) spectra of 6*H*-chromeno[4,3-*b*]quinoline-11-ol (**3a**).

and a broad peak at 3364 cm^{-1} in IR spectra due to the phenolic OH], the product isolated after usual work up and purification was identified as 6*H*-chromeno[4,3-*b*]quinoline-11-ol (**3a**, $C_{16}H_{11}NO_2$). This was supported by the molecular structure of 2-bromo-6*H*-chromeno[4,3-*b*]quinolin-11-ol (**3e**) being confirmed by X-ray analysis (Fig. 3).[7]

We were delighted to isolate the chromenoquinoline derivative where the fused quinoline ring seemed to have formed via an unprecedented pathway under the reaction condition studied (see later for mechanistic discussion). Thus, encouraged by these results we then decided to assess the generality and scope of this one-pot process. A variety of 2-aminophenols (**2**) were employed in this reaction and a range of 6*H*-chromeno[4,3-*b*]quinoline derivatives (**3a**–**f**) were synthesized



Scheme 1. Reaction of β-chloroacroleins with 2-aminophenol.



Scheme 2. Reaction of 4-chloro-2*H*-chromene-3-carboxaldehyde (**1a**) with 1.1 equiv of 2-aminophenol (**2a**).

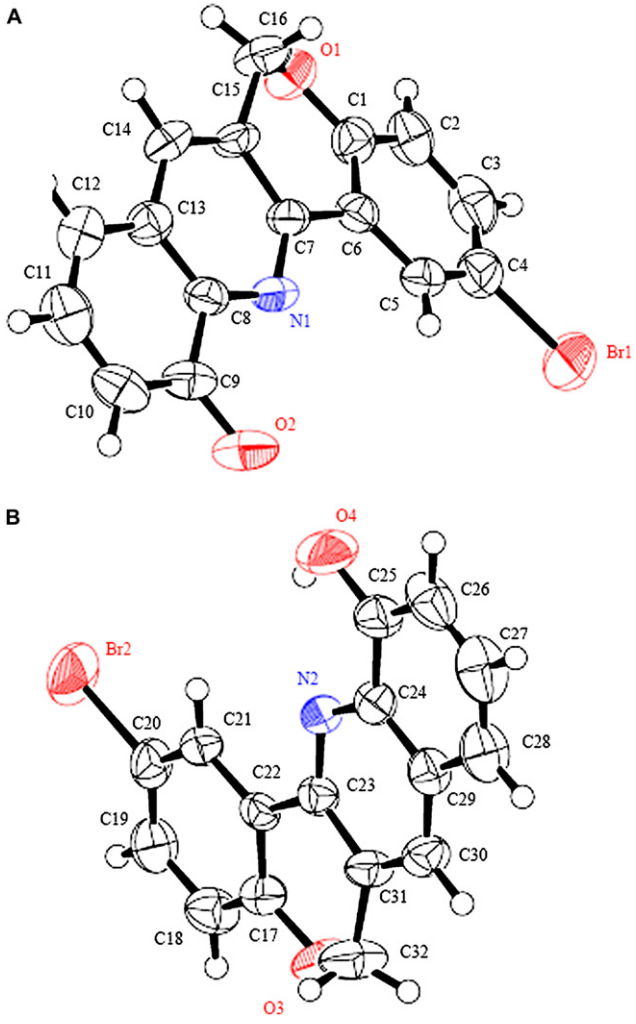


Figure 3. X-ray crystal structure of **3e** (ORTEP diagram). Displacement ellipsoids are drawn at 50% probability level for non-hydrogen atoms.

(Table 1) in good yields. As evident from Table 1, all the 2-aminophenols participated in this reaction smoothly and the yields of the products were remarkably similar irrespective of the presence of electron donating/withdrawing groups on the aniline ring (entry 1 vs entries 3–5, Table 1). No other significant side products including 1,5-benzoxazepine were isolated. Generally, all the reactions were carried out in DMF at 120 °C instead of refluxing DMF.[6] However, the use of other solvents, e.g., ethanol was investigated and found to be less effective in terms of yield of the product (entry 2, Table 1). The methodology was extended successfully to prepare the hydroxy derivatives of 6,7-dihydrobenzo[2,3]oxepino[4,5-*b*]quinoline (**3g–i**) in good yields (entry 8–10, Table 1). Thus β-chloroacroleins appeared to be useful synthetic precursors for the preparation of 6*H*-chromenoquinolines (**3a–f**) and 6,7-dihydrobenzo[2,3]oxepino[4,5-*b*]quinolines (**3g–i**). All the β-chloroacroleins (**1**) were readily prepared from the corresponding ketones by a Vilsmeier–Haack–Arnold reaction[8] according to Scheme 3. All the 2-aminophenols used are commercially available.

Mechanistically, the present two-step reaction in a single pot seems to proceed via (a) generation of a 4-chloroimine in situ at low temperature in the initial step, (b) followed by the construction of fused quinoline ring at elevated temperature in the next step to afford the observed product **3**. A plausible mechanism showing the formation of compound **3** from a 4-chloroimine is depicted in Scheme 4. To prove the intermediacy of 4-chloroimine, the reaction of **1a** with **2a** was carried out in DMF at 25 °C for 1.0 h where the corresponding 4-chloroimine (**4**) was isolated in 75% yield (Scheme 5). The spectral data of the solid product (mp 156–157 °C) obtained was found to be identical in all respects as reported earlier (lit. mp 156–158 °C).[6] It is interesting to note that the reaction of **1a** with 2 equiv of aniline in chloroform at room temperature afforded the corresponding enaminoimine in 80% yield, which on pyrolysis (200 °C) furnished 6*H*-chromeno[4,3-*b*]-quinoline.[4a] Since the formation of enaminoimine was not observed in the present case perhaps due to the use of lesser quantity (1.0 equiv) of **2a**, the intermediacy of enaminoimine can be ruled out. Moreover, isolation of 6*H*-chromeno[4,3-*b*]-quinoline-11-ol (**3a**) in 80% yield from compound **4** when heated at 120 °C for 4 h (Scheme 4) clearly suggests that the reaction proceeds via a chloroimine intermediate. Thus, once generated in situ the chloroimine undergoes intermolecular cycloaddition at elevated temperature as shown in Scheme 3. The fused tetrahydro pyrimidine intermediate (**X-1**) formed then collapsed to chroman-4-ylideneamine species (**X-2**), which as a result of intra-molecular rearrangement followed by aromatization furnish **3** with the regeneration of chloramine thereby completing the reaction cycle.[9,10]

3. Conclusions

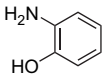
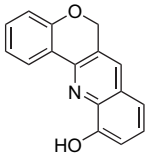
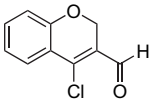
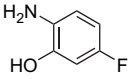
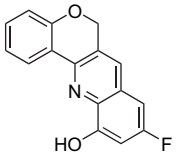
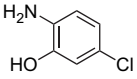
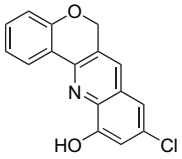
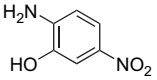
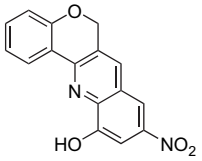
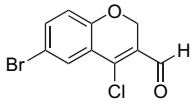
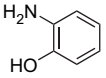
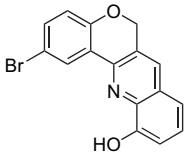
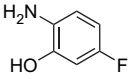
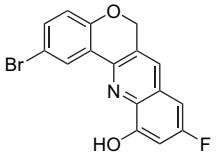
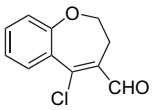
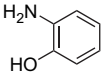
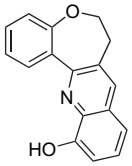
In conclusion, the reaction of β-chloroacroleins with 2-aminophenols in DMF was investigated, which yielded chromenoquinolines and oxepinoquinolines thereby providing an easy method for the synthesis of these compounds. Contrary to the earlier report[6] no 1,5-benzoxazepine derivative was isolated under the present reaction conditions. The single step procedure described here could be attractive as it is simple, easy to handle, and does not involve the use of expensive reagents or catalysts. The process is also free from the use of excess 2-aminophenol or photochemical conditions and found to be general for the synthesis of quinoline based polynuclear heterocycles. Therefore, the process may prove to be a powerful tool in the direct synthesis of chromenoquinoline/oxepinoquinolines based agents of potential pharmacological interest, preparation of which via other route may require lengthy synthetic procedure. Moreover, this design may be applicable to generate diversity-based library of polynuclear heterocyclic compounds.

4. Experimental

4.1. General

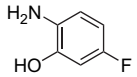
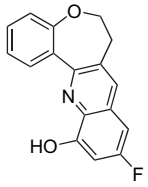
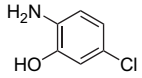
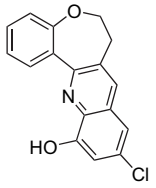
Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Flash

Table 1
Synthesis of 6*H*-chromeno quinolines (**3a–f**) and 6,7-dihydrobenzo[2,3]oxepino[4,5-*b*]quinolines (**3g–i**)[a]

Entry	β-Chloroacroleins (**1**)	Aminophenols (**2**)	Products[b] (**3**)	Yield[c] (%)
1		 **2a**	 **3a**	79
2[d]				30
3	 **1a**	 **2b**	 **3b**	69
4		 **2c**	 **3c**	70
5		 **2d**	 **3d**	65
6	 **1b**	 **2e**	 **3e**	71
7		 **2f**	 **3f**	66
8	 **1c**	 **2g**	 **3g**	77

(*continued on next page*)

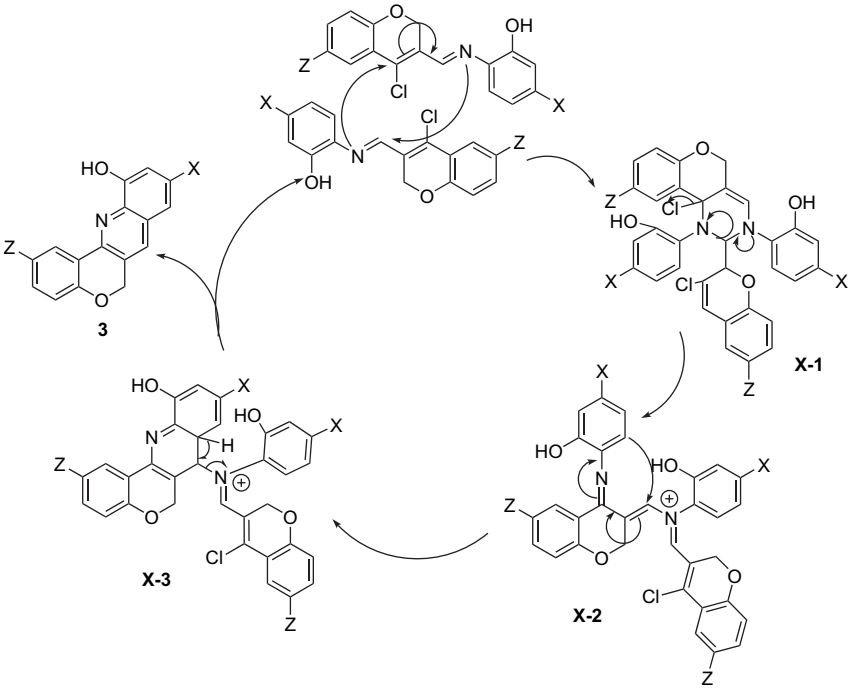
Table 1 (*continued*)

Entry	β-Chloroacroleins (**1**)	Aminophenols (**2**)	Products[b] (**3**)	Yield[c] (%)
9		 **2h**	 **3h**	77
10		 **2i**	 **3i**	74

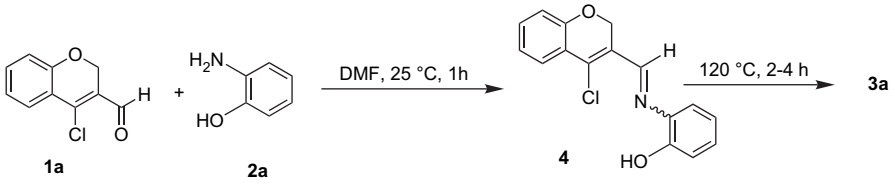
[a] All the reactions were carried out by using **1** (1.0 equiv), **2** (1.1 equiv), DMF at 25 °C for 1 h, and then at 120 °C for 2–4 h.
[b] Identified by ^{1}H NMR, IR, and MS.
[c] Isolated yields.
[d] Ethanol was used as a solvent.

Scheme 3. Preparation of β-chloroacroleins (**1**).

chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 solution using 200 and 400, and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as br (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined using a Buchi melting point B-540 apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case:



Scheme 4. Proposed reaction mechanism.



Scheme 5. Preparation of 4-chloroimine (**4**) followed by **3a**.

column, mobile phase (range used), flow rate, detection wavelength, and retention times. All the reagents used are commercially available except β-chloroacroleins that were prepared according to a known procedure.[8]

*4.2. Synthesis of 6H-chromenoquinolines (**3a–f**) and 6,7-dihydrobenzo[2,3]oxepino[4,5-b]quinolines (**3g–i**): general procedure*

To a solution of the 4-chloro-2*H*-3-chromenecarboxaldehyde (2.57 mmol) in DMF (5 mL) was added 2-aminophenol (280 mg, 2.57 mmol) at 25 °C under a nitrogen atmosphere. The resulting solution was stirred at 25 °C for 1.0 h under a nitrogen atmosphere. The resulting reaction mixture was then stirred at 120 °C for 2–4 h. After completion of the reaction (as indicated by TLC, mobile phase: 20% ethyl acetate/petroleum ether), solvent was removed under reduced pressure and the residue was purified by column chromatography using light petroleum ether/ethyl acetate to furnish the desired product.

*4.2.1. 6H-Chromeno[4,3-b]quinolin-11-ol (**3a**)*

Light yellow solid; R_f 0.50 (25% ethyl acetate/*n*-hexane); mp 139–140 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.65 (br s, 1H, −OH), 8.74 (dd, J=7.8, 1.9 Hz, 1H), 8.15 (s, 1H), 7.44–7.37 (m, 3H), 7.19–7.02 (m, 3H), 5.43 (s, 2H); IR (cm^{-1}, KBr) 3364, 1604, 1567; *m/z* (ES mass) 250.3 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 156.9, 153.2, 146.3, 137.9, 131.9, 131.4, 128.1, 127.3, 126.2, 125.5, 122.7, 122.1, 117.6, 117.1, 111.3, 67.5 (CH_2); HPLC 99.74%, column: ZORBAX XDB-C8 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/15, 25/90, 30/90, 31/35; flow: 1.0 mL/min; UV 215 nm, retention time 19.44 min; HRMS: calcd for $C_{16}H_{12}NO_2$ 250.0868, found 250.0866.

*4.2.2. 9-Fluoro-6H-chromeno[4,3-b]quinolin-11-ol (**3b**)*

Cream solid; R_f 0.56 (25% ethyl acetate/*n*-hexane); mp 142–144 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.26 (br s, 1H, −OH), 8.72 (dd, J=7.8, 1.9 Hz, 1H), 8.13 (s, 1H), 7.46–7.38 (m, 1H), 7.20–7.15 (m, 2H), 7.06–6.96 (m, 2H), 5.43 (s, 2H); IR (cm^{-1}, KBr) 3351, 1638, 1608, 1122; *m/z* (ES mass) 268.4 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 160.5, 156.8, 155.3, 145.8, 135.6, 131.9, 131.1, 128.2, 126.6, 126.1, 122.5, 122.1, 117.0, 101.6, 100.9, 67.4 (CH_2); HPLC: 98.47%, column: Luna C18 (2) (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/35, 25/80, 35/80, 36/35; flow 1.0 mL/min; UV 220 nm, retention time 18.1 min; HRMS: calcd for $C_{16}H_9NO_2F$ 266.0617, found 266.0612.

*4.2.3. 9-Chloro-6H-chromeno[4,3-b]quinolin-11-ol (**3c**)*

Light yellow solid; R_f 0.62 (25% ethyl acetate/*n*-hexane); mp 150–152 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.96 (br s, 1H, −OH), 8.75 (dd, J=7.5, 1.4 Hz, 1H), 8.36 (s, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.50–7.43 (m, 1H), 7.20–7.17 (m, 1H), 7.01–7.04 (m, 2H), 5.52 (s, 2H); IR (cm^{-1}, KBr) 3378, 1603, 1583, 1108; *m/z* (ES mass) 284.2 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 157.1, 152.7, 147.0, 138.5, 132.4, 128.1, 127.1, 126.8, 126.4, 125.3, 122.1, 122.1, 118.7, 117.1, 111.5, 67.4 (CH_2); HPLC: 99.64%, Column: Luna C18 (2) (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/35, 25/80, 35/80, 36/35; flow: 1.0 mL/min; UV 220 nm, retention time: 21.3 min; HRMS calcd for $C_{16}H_{11}NO_2Cl$ 284.0478, found 284.0477.

*4.2.4. 9-Nitro-6H-chromeno[4,3-b]quinolin-11-ol (**3d**)*

Light yellow solid; R_f 0.55 (25% ethyl acetate/*n*-hexane); mp 270–272 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.63 (br s, 1H, −OH), 8.74 (dd, J=7.8, 1.6 Hz, 1H), 8.45 (s, 1H), 8.42 (d, J=2.4 Hz, 1H), 7.4 (d, J=2.4 Hz, 1H), 7.5–7.46 (m, 1H), 7.23–7.2 (m, 1H), 7.07 (dd, J=8.1, 0.8 Hz, 1H), 5.49 (d, J=1.1 Hz, 2H); IR (cm^{-1}, KBr) 3401, 1607, 1573, 1491, 1335, 1121; *m/z* (ES mass) 293.1 (M−1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 157.5, 154.4, 148.7, 145.3, 140.7, 133.7, 133.1, 127.3, 126.8, 126.6, 122.3, 122, 117.2, 114.3, 104.5, 67.3 (CH_2); HRMS: calcd for $C_{16}H_9N_2O_4$ 293.0562, found 293.0565.

*4.2.5. 2-Bromo-6H-chromeno[4,3-b]quinolin-11-ol (**3e**)*

Light yellow solid; R_f 0.54 (25% ethyl acetate/*n*-hexane); mp 182–184 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.89 (br s, 1H, -OH), 8.99 (d, J=2.7 Hz, 1H), 8.16 (s, 1H), 7.56–7.53 (m, 1H), 7.43 (t, J=8.1 Hz, 1H), 7.37 (dd, J=8.3, 1.3 Hz, 1H), 7.11 (d, J=1.3 Hz, 1H), 7.09–7.0 (m, 1H) 5.46 (s, 2H); IR (cm^{-1}, KBr) 3363, 1610, 1559; *m/z* (ES mass) 327.8 (M^+, 50%), 329.8 (M+2, 50%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 155.9, 153.4, 144.9, 137.9, 134.1, 131.5, 128.4, 128.3, 127.7, 124.9, 124.5, 119.3, 117.5, 114.2, 111.5, 67.6 (CH_2); HPLC 98.8%, column: ZORBAX XDB-C8 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/15, 25/90, 30/90, 31/35; flow: 1.0 mL/min; UV 215 nm, retention time: 22.98 min; HRMS calcd for $C_{16}H_9NO_2Br$ 325.9817, found 325.9817.

*4.2.6. 2-Bromo-9-fluoro-6H-chromeno[4,3-b]-quinolin-11-ol (**3f**)*

Light yellow solid; R_f 0.56 (25% ethyl acetate/*n*-hexane); mp 203–205 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.43 (s, 1H), 8.97 (d, J=2.4 Hz, 1H), 8.1 (s, 1H), 7.54 (dd, J=8.6, 2.4 Hz, 1H), 7.19 (d, J=2.7 Hz, 1H), 7.17 (d, J=2.7 Hz, 1H), 7.01–6.98 (m, 2H), 5.45 (d, J=0.8 Hz, 2H); IR (cm^{-1}, KBr) 3359, 3069, 1641, 1615, 1125; *m/z* (ES mass) 346.0 (M$^+$, 100%), 347.9 (M+2, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 160.8, 155.8, 155.5, 144.4, 135.6, 134.2, 131.3, 128.6, 128.3, 126.2, 124.4, 119.4, 114.3, 101.8, 100.9, 67.6 (CH_2); HPLC: 99.1%, column: Luna C18 (2) (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/35, 25/80, 35/80, 36/35; flow: 1.0 mL/min; UV 220 nm, retention time: 22.3 min; HRMS: calcd for $C_{16}H_8NO_2FBr$ 344.9801, found 344.9813.

*4.2.7. 6,7-Dihydrobenzo[2,3]oxepino[4,5-b]-quinoline-12-ol (**3g**)*

Light yellow solid; R_f 0.50 (25% ethyl acetate/*n*-hexane); mp 150–152 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.53 (br s, 1H, –OH), 8.23 (s, 1H), 8.06 (dd, J=7.5, 1.6 Hz, 1H), 7.52–7.42 (m, 2H), 7.4–7.32 (m, 2H), 7.18 (dd, J=7.8, 1.1 Hz, 1H), 7.40 (dd, J=7.5, 1.6 Hz, 1H), 4.53 (t, J=6.2 Hz, 2H), 3.0 (t, J=6.2 Hz, 2H); IR (cm^{-1}, KBr) 3381, 3352, 1601, 1567; *m/z* (ES mass) 264.1 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 155.1, 154.7, 153.2, 137.6, 134.8, 133.4, 131.9, 130.9 (2C), 127.9, 127.5, 124.1, 122.0, 117.1, 110.9, 75.9 (CH_2), 31.7 (CH_2); HPLC 99.9%, Column: ZORBAX XDB-C8 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/15, 25/90, 30/90, 31/35; flow: 1.0 mL/min; UV 215 nm, retention time: 13.5 min; HRMS: calcd for $C_{17}H_{14}NO_2$ 264.1025, found 264.1017.

*4.2.8. 10-Fluoro-6,7-dihydrobenzo[2,3]oxepino[4,5-b]-quinoline-12-ol (**3h**)*

Light yellow solid; R_f 0.52 (25% ethyl acetate/*n*-hexane); mp 190–192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.16 (br s, 1H, –OH), 8.21 (s, 1H), 8.04 (dd, J=7.7, 1.8 Hz, 1H), 7.51–7.47 (m, 1H), 7.36–7.32 (m, 1H), 7.18 (dd, J=7.8, 1.1 Hz, 2H), 6.97 (dd, J=10.7, 2.7 Hz, 1H), 4.53 (t, J=6.2 Hz, 2H), 2.98 (t, J=6.2 Hz, 2H); IR (cm^{-1}, KBr) 3312, 1604, 1568, 1126; *m/z* (ES mass) 282.1 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 160.6, 155.5, 154.7 (2C), 154.5, 135.2, 134.5, 133.1, 130.9, 130.8, 128.0, 124.1, 121.9, 101.2, 100.3, 75.8 (CH_2), 31.7 (CH_2); HPLC: 99.5%, column: Luna C18 (2) (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/35, 25/80, 35/80, 36/35; flow: 1.0 mL/min; UV 220 nm, retention time: 15.2 min; HRMS calcd for $C_{17}H_{11}FNO_2$ 280.0774, found 280.0771.

*4.2.9. 10-Chloro-6,7-dihydrobenzo[2,3]oxepino[4,5-b]-quinoline-12-ol (**3i**)*

Light yellow solid; R_f 0.60 (25% ethyl acetate/*n*-hexane); mp 187–189 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.93 (br s, 1H, –OH), 8.44 (s, 1H), 8.09 (dd, J=7.8, 1.9 Hz, 1H), 7.6–7.48 (m, 2H), 7.39–7.32 (m, 1H), 7.21–7.08 (m, 2H), 4.57 (t, J=6.3 Hz, 2H), 3.09 (t, J=6.3 Hz, 2H); IR (cm^{-1}, KBr) 3310, 1600; *m/z* (ES mass) 298.3 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 156.0, 154.9, 152.8, 138.0, 133.3, 132.8, 131.4, 131.3, 131.1, 127.3, 125.1, 124.2, 122.1, 118.2, 111.2, 75.9 (CH_2), 31.8 (CH_2); HRMS: calcd for $C_{17}H_{13}NO_2Cl$ 298.0635, found 298.0644.

Acknowledgements

The authors thank Dr. V. Dahanukar and Mr. A. Mukherjee for their encouragement and the analytical group for spectral data. Mr. R.B. thanks CPS-DRL, Hyderabad, India for allowing him to pursue this work as a part of his Ph.D. program.

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7. Single crystals suitable for X-ray diffraction of **3e** were grown from methanol. The compound crystallizes in triclinic space group *P*-1 with the unit cell parameters a=10.841(3) Å, b=11.643(2) Å, c=12.127(3) Å, α=83.52(7)°, β=89.004(8)°, γ=62.70(5)°, V=1350(6) Å^3 and Z=4. The intensity data was collected on a Rigaku Mercury CCD area detector with graphite monochromated Mo Kα (λ=0.7107 Å) radiation. The structure was solved by direct methods (SIR92) and refined by least squares method. The residual factors are R_1=0.049 and Rw=0.1185 for 4576 observed reflections. Due to the change in the conformation of the 'chromeno' ring the independent molecules A and B differ, which is indicated by the difference in the torsion angles C14C15C16O1

(−144.6(5)) and C30C31C32O3 (−157.1(4)), respectively. The phenolic OH of A showed an intermolecular hydrogen bonding with the hydroxyl oxygen of B. Crystallographic data (excluding structure factors) for **3e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 644669.

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9. The intermediacy of 4-arylamino-2*H*-chromene-3-carbaldehyde has been proposed during photochemical transformation of 4-chloroimine to chromenoquinoline.[4e] While intermediacy of a similar species cannot be ruled out in the present case we, however, failed to detect or isolate a corresponding carbaldehyde intermediate under the condition employed during our synthesis of compound **3**. Preparation of this intermediate from **1a** for further studies was also not successful.
10. In an alternative pathway the reaction may proceed via protonated imine intermediate, which then reacts with a second molecule of the 2-aminophenol by addition–elimination of HCl to form the N–C bond.[4d] The beta-amino imine, when protonated, would be able to undergo ring-closure and then subsequent aromatization to give compound **3** with regeneration of the 'second' 2-aminophenol molecule. We thank the reviewer for bringing this to our notice.