One-Pot Synthesis of Pyrano[3,4-*b*]chromones from Chromone-3-carbaldehyde

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Abstract: 3-Formylchromone reacts with cyclohexyl isocyanide to produce pyrano[3,4-*b*]chromone, which rearranges to 1-benzopyrano[2,3-*c*]pyridine when heated with HCl in ethanol.

Key words: 3-formylchromone, 1-benzopyran, isocyanide, pyrano[3,4-*b*]chromone, furo[3,4-*b*]chromone, molecular rearrangement, fluorophore, heterocycles, benzopyrano[2,3-*c*]pyridine

Pyrano[3,4-*b*]chromone nuclei constitute the central heterocyclic part of some naturally occurring compounds such as rotenone (**I**), 6-oxodehydrodeguelin (**II**) and elliptone (**III**, Figure 1).[1] Although rotenone and its derivatives were first known as important insecticides and piscicides, they were later reported to have anticancer activity in rodents.[2,3]

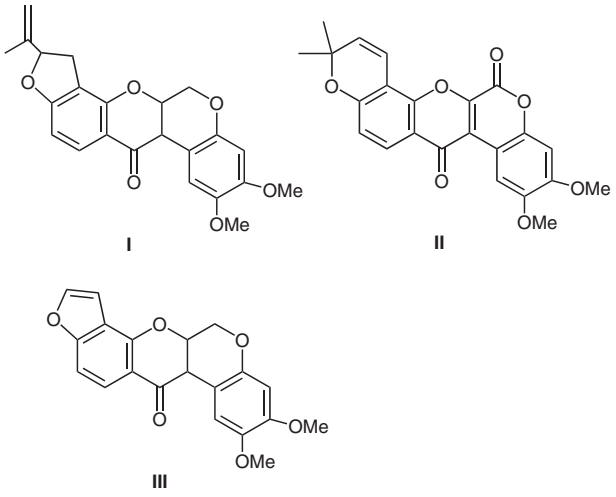

Figure 1

3-Formylchromone (**1**) is a very good substrate for the synthesis of various heterocycles. The presence of three electrophilic centres confer high reactivity, as documented in several reviews.[4] It is not only a useful building block for the synthesis of various bioactive heterocycles linked to or fused with the chromone moiety, but has also been shown to be a modifier of multidrug resistance in mouse lymphoma cells and in colo 320 colon cancer cells.[5]

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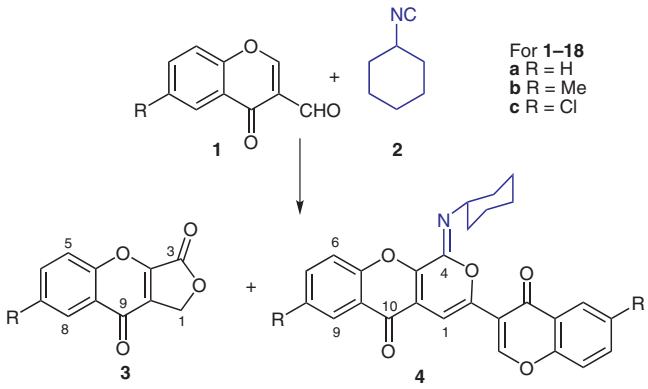
Reactions of isocyanides with α,β-unsaturated carbonyl compounds lead to the formation of furan or pyrrole derivatives.[6] Recently, reaction of isocyanides with aldehydes in the presence of boric acid has been reported to form hydroxyamides.[7] The presence of α,β-unsaturated carbonyl moiety as well as an aldehyde moiety in **1** drew our attention to study its reaction with isocyanides.

Tosylmethyl isocyanide (TOSMIC) has been reacted with **1** in presence of different bases to produce mainly 2-tosyl-4-(2-hydroxybenzoyl)pyrrole.[8] The reaction was initiated by attack of the carbanion (generated from TOSMIC) at the C-2 position of **1**. We report herein the results of the reaction of cyclohexyl isocyanide with **1**.

Cyclohexyl isocyanide (1 mmol) in CH_2Cl_2 (2 mL) was added slowly to a solution of **1a** (1 mmol) in CH_2Cl_2 (10 mL) at 0 °C with stirring under an inert atmosphere. After complete addition, the reaction mixture was allowed to come at room temperature and was stirred for eight hours. After usual workup and chromatographic separation, the reaction mixture afforded **3a** and **4a** in 5% and 15% yields, respectively (Scheme 1).



Scheme 1

Initially the structure of **3a** was established on the basis of IR and ^{1}H NMR spectroscopic analysis[9] and finally confirmed by comparing with an authentic sample.[10] A literature survey revealed that compound **3a** has been considered as a model compound in establishing the identity of clavacin and patulin antibiotics, isolated from *Aspergillus clavatus* and *Penicillium patulum*, respectively.[11] Previously compound **3a** has been synthesized either by acid-catalysed cyclisation of α-keto-β-(*o*-hydrxybenzoyl)butyrolactone, itself synthesized from *o*-hydroxy-

acetophenone and diethyl oxalate followed by hydroxymethylation and lactonisation,[11] or by heating ethyl 3-bromo-/acetoxy-methyl-4-oxochromene-2-carboxylate in a mixture of glacial acetic acid and concentrated HCl under reflux for 4 hours.[10] The structure of **4a** was established on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometric analysis.[12]

Formation of **3a** and **4a** can be rationalized as follows: isocyanide **2** attacks the C-2 position of **1** resulting in **5**, which may exist as a mixture of (*Z*)-**5** and (*E*)-**5**. Isomer (*E*)-**5** readily cyclises to iminolactone **6**, which on subsequent 1,3-hydride shift and hydrolysis produces **3a** via **7**. The other isomer (*Z*)-**5** may be intercepted by another molecule of **1** using its aldehydic oxygen to form **8**, which cyclises to **9** via the enamine tautomer **8a**. Subsequent dehydration of **9** gives iminolactone **4** (Scheme 2, path a). Formation of **4** may also be envisaged by deprotonation and reprotonation of (*Z*)-**5** to form **10** where the *Z*-configuration is further stabilized by H-bonding and may be considered as a diene. The diene moiety of **10** and the aldehydic function of **1** can undergo [4+2] cycloaddition to form **9**, leading finally to **4a** by dehydration of **9** (Scheme 2, path b).[13]

Thus, two molecules of 3-formylchromone are coupled with cyclohexyl isocyanide with the elimination of one molecule of water and in so doing generate a pyrano[3,4-*b*]chromone moiety linked to another chromone moiety.

The wide occurrences of pyrano[3,4-*b*]chromones in biologically active and naturally occurring compounds, prompted us to attempt to optimise the yield of **4** and to introduce functionalities for the synthesis of natural product analogues.

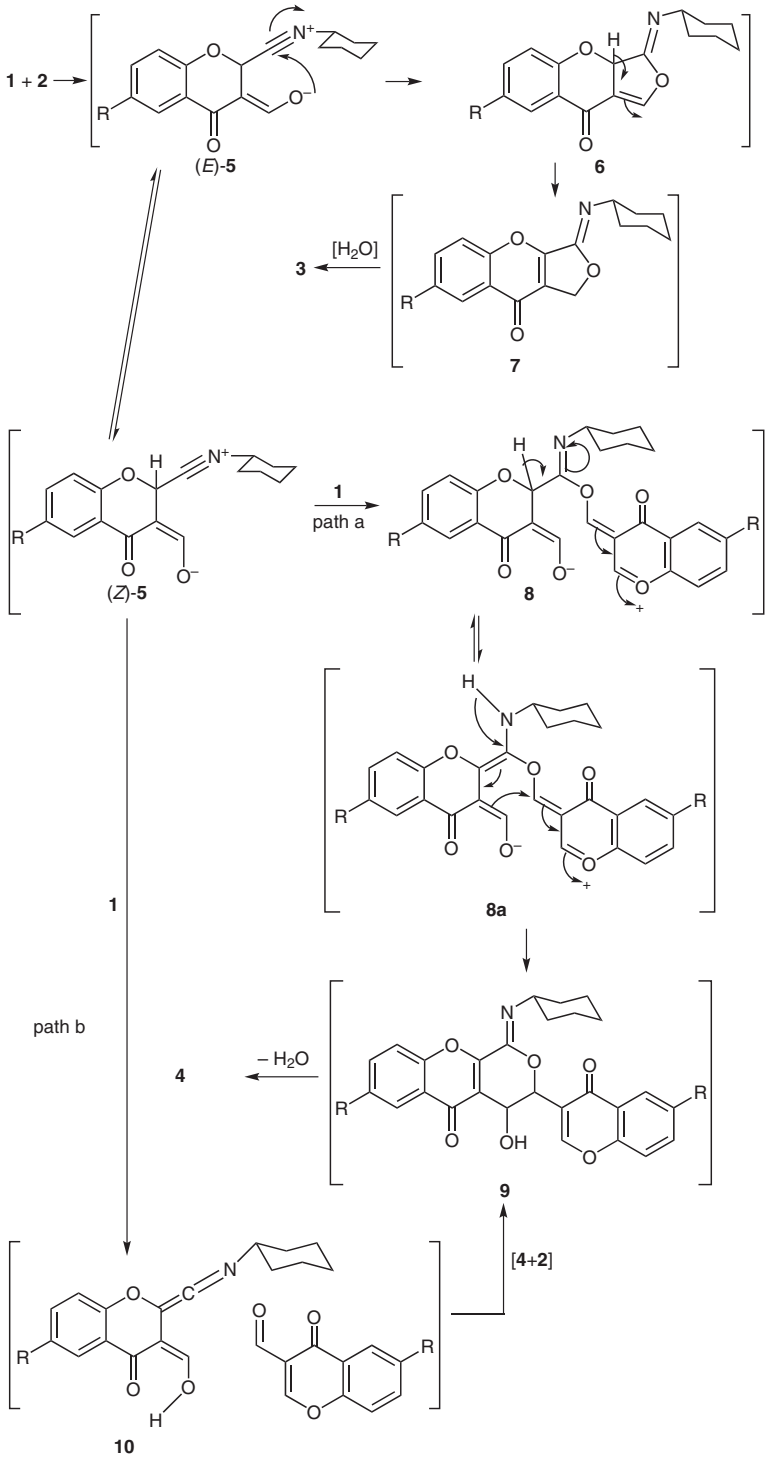
Initially the reaction was carried out in CH_2Cl_2, but the yield of **4** was poor (Table 1, entries 1–3). High-boiling apolar solvents, such as toluene or xylene, were employed as reaction media in an attempt to facilitate the [4+2] cycloaddition (Scheme 2, path b) and some improvement in the yield of **4** was noticed (enties 4–6). Encouraged by these observations, the possibility of involvement of a [4+2] cycloaddition step was further examined by adding diethyl acetylenedicarboxylate (DEAD) into the reaction mixture to act as a trap of **10**. However, addition of isocyanide **2** to a solution of **1** and DEAD in toluene or addition of a solution of **1** in toluene to a mixture of DEAD and **2** in toluene, followed by heating, produced **4** as the only isolated product in 25–28% yield. Compound **4** was isolated in better yield by heating a mixture of **1** and **2** in 1:0.6 molar ratio (the mechanism for the formation of **4** deserves 1:0.5 molar ratio) in ethanol for one hour (entries 7 and 8). When DMF was used as solvent, the reaction yielded **4** within half an hour (entry 9). Compound **4** was isolated in very good yield when the reaction was carried out in acetonitrile (entries 10–12). Better yields in polar solvents support the polar mechanism (Scheme 2, path a). It should be mentioned that compound **3** was not obtained when the reaction was carried out in toluene, ethanol, DMF, or acetonitrile. Even under high-dilution conditions (0.001 M of **1** in acetonitrile), the reaction mixture failed to produce **3**, which clearly demonstrates that formation of (*Z*)-**5** is prefered over (*E*)-**5**.

Table 1 Synthesis of Iminolactone **4** under Different Conditions

Entry	R	Solvent	Reaction conditions	Time (h)	Product	Mp (°C)	Yield (%)
1	H	anhyd CH_2Cl_2	0 °C to r.t., Ar atm.	8	**4a**[a]	274–76	10
2	Me	anhyd CH_2Cl_2	0 °C to r.t., Ar atm.	8	**4b**	302–04	11
3	Cl	anhyd CH_2Cl_2	0 °C to r.t., Ar atm.	6	**4c**[b]	296–98	15
4	H	PhMe	reflux	2	**4a**	274–76	25
5	Me	PhMe	reflux	2	**4b**	300–02	22
6	Me	xylene	reflux	2	**4b**	300–02	25
7	H	EtOH	reflux	1	**4a**	272–74	40
8	Me	EtOH	reflux	1	**4b**	302	45
9	H	DMF	100–110 °C	0.5	**4a**	274–76	50
10	H	MeCN	reflux	0.5	**4a**	274–76	68
11	Me	MeCN	reflux	0.5	**4b**	300–02	70
12	Cl	MeCN	reflux	0.5	**4c**	296–98	75

[a] Compound **3a**, mp 240–42 °C (lit.[10] mp 242–43 °C) was isolated in 5% yield along with **4a**.
[b] Compound **3c**, mp 244–46 °C was isolated in 9% yield along with **4c**.

Compound **4** possesses a chromone moiety linked to a pyrano[3,4-*b*]-1-benzopyran motif and forms a conjugated π-system, which can undergo intramolecular charge transfer upon excitation and may act as a fluorophore,



Scheme 2

which is indeed supported by spectroscopic measurements. The absorption spectrum of **4** ($1.0 \cdot 10^{-6}$ M in $CHCl_3$, Figure 2) showed absorption at λ = 285–295 nm with a low absorbance and its emission spectrum ($1.90 \cdot 10^{-7}$ M in $CHCl_3$, Figure 3) showed a strong emission band at λ = 470 nm ($\varepsilon = 3.77 \cdot 10^6$).

Comparing the basic structure of rotenone (**I**), dehydrodeguelins (**II**), and elliptone (**III**, Figure 1), it is clear that a hydroxyl group at the 7-position of **4** is needed for the synthesis of rotenone analogues. 7-Hydroxychromone-3-carbaldehyde **12** was synthesized from resacetophenone (**11**) by Vilsmeier–Haack reaction.[14] Compound **13** was obtained in moderate yield by heating **12** with **2** in acetonitrile (Scheme 3).[15]

In an attempt to obtain an analogue of 6-oxodehydrodeguelin (**II**, Figure 1) by hydrolysing the imino function of

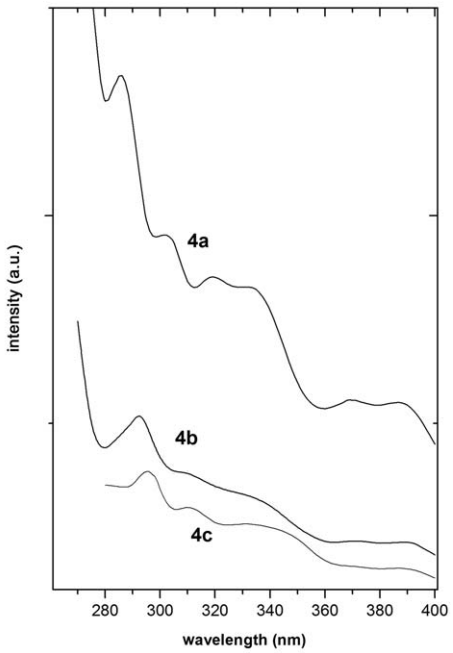


Figure 2

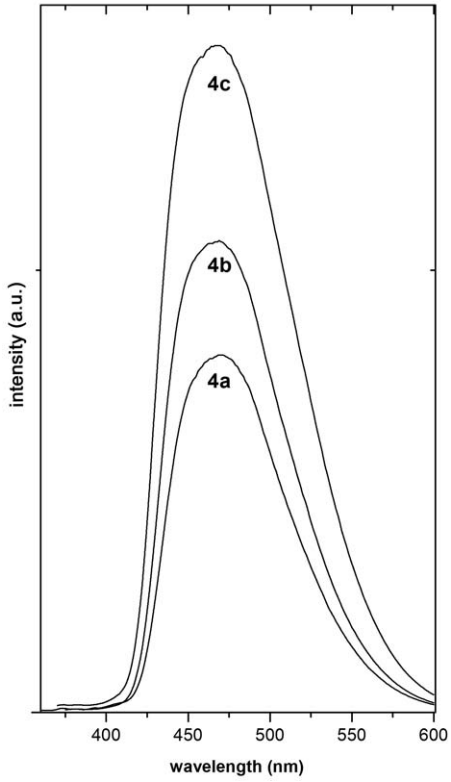
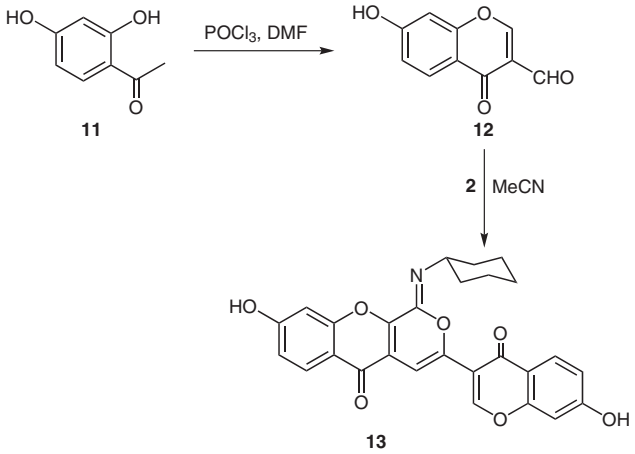


Figure 3

4, it was dissolved in concentrated H_2SO_4 and then poured into ice water, but a black insoluble mass was obtained. However, on heating an ethanolic solution of **4** for two hours in the presence of a trace amount of aqueous HCl, the iminolactone **4** rearranged to lactam **17**[16] (Table 2, Scheme 4) along with an insoluble product, which could not be characterised due to its insolubility. Formation of



Scheme 3

17 may be rationalised by the initial protonation on the vinyl ether moiety of **4** to form **14**, which undergoes hydrolytic cleavage to form **16** via **15**. Recyclisation of **16** followed by dehydration produces **17**.

Table 2 Acid-Catalysed Rearrangement of Iminolactone **4** to Lactam **17**

Entry	R	Product	Mp (°C)	Yield (%)
1	H	**17a**	>300	33
2	Me	**17b**	260–62	35
3	Cl	**17c**	>300	40

In conclusion, we have developed an efficient and direct route for the preparation of pyrano[3,4-*b*]chromones, which constitutes the central part of the rotenones and also have reported an acid-catalysed iminolactone–lactam rearrangement associated with this system.

Acknowledgment

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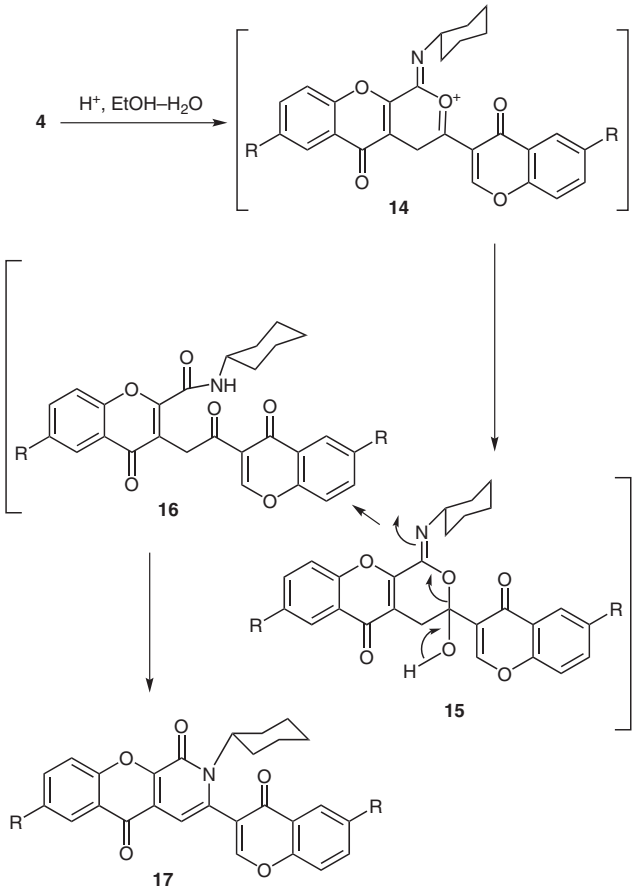

Scheme 4

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(9) **Analytical Data of 1*H*-Furo[3,4-*b*]-1-benzopyran-3,9-dione (3a)**
White crystalline solid, mp 240–42 °C (lit.[11] 242–43 °C). IR (KBr): 2978, 1775, 1642 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.23 (s, 2 H, CH_2), 7.56 (br t, *J* = 7.2 Hz, 1 H, 7-H), 7.69 (br d, *J* = 8.4 Hz, 1 H, 5-H), 7.81–7.87 (m, 1 H, 6-H), 8.30 (br d, *J* = 7.2 Hz, 1 H, 8-H).

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(12) **Preparation of 2-(4-Oxo-4*H*-1-benzopyran-3-yl)-4-(*N*-cyclohexylimino)pyrano[3,4-*b*]-1-benzopyran-10-ones 4a–c**
Cyclohexyl isocyanide (0.065 g, 0.6 mmol) was added to a solution of **1** (1 mmol) in MeCN (15 mL). The resultant mixture was heated under reflux for 30 min when a solid began to separate. The reaction mixture was cooled, and the separated solid was filtered off. The solid was further crystallised from chloroform–light PE (4:1) to afford a yellowish green solid.
Compound **4a**: yield 0.15 g (68%); mp 274–76 °C. IR (KBr): 3070, 2931, 1664, 1611 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27–1.35 (m, 1 H, cyclohexyl H), 1.39–1.52 (m, 2 H, cyclohexyl H), 1.58–1.66 (m, 2 H, cyclohexyl H), 1.77–1.95 (m, 5 H, cyclohexyl H), 3.89–4.02 (m, 1 H, NCH), 7.18 (s, 1 H, 1-H), 7.41–7.45 (m, 1 H, ArH), 7.48–7.50 (m, 2 H, ArH), 7.65–7.76 (m, 3 H, ArH), 8.31 (br d, *J* = 8.0 Hz, 1 H, 5′-H), 8.34 (br d, *J* = 7.8 Hz, 1 H, 9-H), 8.73 (s, 1 H, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 (3″-C, 5″-C), 25.7 (4″-C), 33.6 (2″-C, 6″-C), 58.1 (1″-C), 97.0 (1-C), 118.1 (8′-C), 119.0 (6-C), 119.7 (10a-C), 120.2 (3′-C), 123.8 (4′a-C), 124.9 (9a-C), 125.2 (6′-C), 126.1 (8-C), 126.5 (5′-C, 9-C), 133.6 (7′-C), 134.5 (7-C), 144.2 (2′-C), 146.9 (2-C), 153.1 (4a-C), 155.7 (4-C), 155.9 (5a-C), 156.4 (8′a-C), 172.2 (10-C), 174.8 (4′-C). MS: *m/z* = 440 [M$^+$ + H], 462 [M$^+$ + Na]. Anal. Calcd for $C_{27}H_{21}NO_5$: C, 73.79; H, 4.82; N, 3.19. Found: C, 73.90; H, 4.89; N, 3.11.
Compound **4b**: yield 0.16 g (70%); mp 300–302 °C. IR (KBr): 3059, 2925, 1669, 1616 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.77 (m, 6 H, cyclohexyl H), 1.88–1.97 (m, 4 H, cyclohexyl H), 2.47 (s, 3 H, $ArCH_3$), 2.50 (s, 3 H, $ArCH_3$), 3.88–3.95 (m, 1 H, NCH), 7.17 (s, 1 H, 1-H), 7.38 (d, *J* = 8.7 Hz, 1 H, 6-H), 7.47 (br d, *J* = 8.7 Hz, 1 H, 7-H), 7.54 (d, *J* = 8.4 Hz, 1 H, 8′-H), 7.60 (br d, *J* = 8.4 Hz, 1 H, 7′-H), 8.08 (br s, 1 H, 9-H), 8.12 (br s, 1 H, 5′-H), 8.71 (s, 1 H, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (2 × CH_3), 24.9 (3″-C, 5″-C), 25.6 (4″-C), 33.5 (2″-C, 6″-C), 58.1 (1″-C), 97.1 (1-C), 117.8 (8′-C), 118.8 (6-C), 119.4 (10a-C), 120.0 (3′-C), 123.3 (4′a-C), 124.4 (9a-C), 125.8 (5′-C), 125.9 (9-C), 134.9 (7′-C), 135.3 (7-C), 135.9 (6′-C), 136.3 (8-C), 144.0 (2′-C), 147.2 (2-C), 153.1 (4a-C), 154.1 (8′a-C), 154.6 (5a-C), 155.7 (4-C), 172.4 (10-C), 175.1 (4′-C). MS: *m/z* = 468 [M$^+$ + H], 490 [M$^+$ + Na]. Anal. Calcd for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.39; N, 3.00. Found: C, 74.39; H, 5.42; N, 2.93.
Compound **4c**: yield 0.19 g (75%); mp 296–298 °C. IR (KBr): 3061, 2929, 1672, 1606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26–1.77 (m, 6 H, cyclohexyl H), 1.89–1.93 (m, 4 H, cyclohexyl H), 3.88–3.95 (m, 1 H, NCH), 7.10 (s, 1 H, 1-H), 7.45 (d, *J* = 8.7 Hz, 1 H, 6-H), 7.61 (dd, *J* = 8.7, 1.8 Hz, 1 H, 7-H), 7.65–7.69 (m, 2 H, ArH), 8.24 (d, *J* = 1.8 Hz, 1 H, 9-H), 8.27 (br s, 1 H, 5′-H), 8.70 (s, 1 H, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (3″-C, 5″-C), 25.6 (4″-C), 33.5 (2″-C, 6″-C), 58.3 (1″-C), 96.9 (1-C), 119.6 (8′-C), 119.9 (6-C), 120.0 (10a-C), 120.7 (3′-C), 124.5 (4′a-C), 125.7 (9a-C), 125.9 (8-C, 6′-C), 131.4 (5′-C), 132.4 (9-C), 134.0 (7′-C), 134.9 (7-C), 144.1 (2′-C), 146.6 (2-C), 153.2 (4a-C), 154.1 (8′a-C), 154.6 (5a-C), 155.8 (4-C), 171.1 (10-C), 173.8 (4′-C). MS: *m/z* = 512 [M$^+$ + 4], 510 [M$^+$ + 2], 508 [M$^+$]. Anal. Calcd for $C_{27}H_{19}NCl_2O_5$: C, 63.79; H, 3.77; N, 2.76. Found: C, 63.68; H, 3.72; N, 2.67.

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(15) **2-(7-Hydroxy-4-oxo-4*H*-1-benzopyran-3-yl)-7-hydroxy-4-(*N*-cyclohexylimino)pyrano[3,4-*b*]-1-benzopyran-10-one (13)**
Yield 51%; mp 310–312 °C. IR (KBr): 3436, 1660, 1629, 1458 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14–1.28 (m, 1 H, cyclohexyl H), 1.30–1.52 (m, 4 H, cyclohexyl H), 1.57–1.72 (m, 1 H, cyclohexyl H), 1.80–1.97 (m, 4 H, cyclohexyl H), 3.86–4.06 (m, 1 H, NCH), 6.87 (s, 1 H, 1-H), 6.91 (br s, 1 H, 8′-H), 6.95 (br d, *J* = 8.7 Hz, 1 H, 6′-H), 7.02

(br d, J = 8.4 Hz, 1 H, 8-H), 7.05 (br s, 1 H, 6-H), 7.98 (d, J = 8.7 Hz, 1 H, 5′-H), 8.04 (d, J = 8.4 Hz, 1 H, 9-H), 8.70 (s, 1 H, 2′-H), 11.01 (br s, 2 H, 2 × OH). MS: m/z = 472 [M^+ + H], 494 [M^+ + Na]. Anal. Calcd for $C_{27}H_{21}NO_7$: C, 68.78; H, 4.49; N, 2.97. Found: C, 68.97; H, 4.35; N, 2.90.

(16) **3-Cyclohexyl-8-methyl-2-(6-methyl-4-oxo-4*H*-1-benzopyran-3-yl)-1-benzopyrano[2,3-*c*]pyridine-4,10-dione (17b)**

Yield 35%; mp 260–262 °C. IR (KBr): 2924, 1715, 1664, 1611, 1482 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.50 (m, 3 H, cyclohexyl H), 1.73–1.76 (m, 1 H, cyclohexyl H), 1.88–2.92 (m, 4 H, cyclohexyl H), 2.34–2.48 (m, 2 H, cyclohexyl H), 2.35 (s, 3 H, $ArCH_3$), 2.49 (s, 3 H, $ArCH_3$), 4.12–4.29 (m, 1 H, NCH), 6.83 (s, 1 H, 1-H), 7.44 (d, J = 8.4 Hz, 1 H, 6-H), 7.50–7.59 (m, 3 H, ArH), 7.78 (s, 1 H, 2′-H), 7.96 (br s, 1 H, 9-H), 8.07 (br s, 1 H, 5′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (CH_3), 21.0 (CH_3), 25.1 (4″-C), 26.2 (3″-C, 5″-C), 29.9 (2″-C, 6″-C), 54.2 (1″-C), 107.6 (1-C), 117.7 (3′-C), 118.1 (6-C), 118.4 (8′-C), 120.0 (10a-C), 123.5 (9a-C), 125.0 (4′a-C), 125.4 (9-C), 126.3 (5′-C), 132.0 (2-C), 134.8 (7-C), 135.3 (8-C), 135.5 (7′-C), 136.1 (6′-C), 153.3 (5a-C), 154.6 (8′a-C), 155.3 (4a-C), 155.4 (2′-C), 159.5 (4-C), 171.7 (10-C), 176.6 (4′-C). MS: m/z = 468 [M^+ + H], 490 [M^+ + Na]. Anal. Calcd for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.39; N, 3.00. Found: C, 74.70; H, 5.52; N, 2.88.