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A diastereoselective synthesis of pyrano fused coumarins *via* organocatalytic three-component reaction†

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A new method for the synthesis of pyran fused coumarins by 3-bromo-4-hydroxycoumarins as cyclic α-halo ketones based on an organocatalyst assisted three-component tandem reaction is investigated. To the best of our knowledge, cyclic α-halo ketones have not yet been used for the synthesis of pyran fused coumarins.

Introduction

Multicomponent reactions (MCRs) have proved to be very influential and efficient bond-forming tools in organic, combinatorial and medicinal chemistry.[1] In addition to the fundamental atom economy and selectivity underlying such reactions, simpler procedures, equipment, time, and energy savings, as well as environmental friendliness have all led to a sizable effort to design and execute MCRs in both academia and industry.[2]

In recent years, the study of the biological activities of chromene and coumarin derivatives has been the aim of many scientists.[3–7] These compounds have been reported to possess a wide spectrum of biological activities like antibacterial, anticoagulant, hypothermal, anti-helminthic, and vasodilatory properties.[8–14] Coumarin is a useful building block in many natural products with remarkable biological activities and unique physical properties.[15] Coumarin and its derivatives inhibit prostaglandin biosynthesis, which involves fatty acid hydroperoxy intermediates.[16] In particular among heterocycle-fused coumarins, pyranocoumarins are an important class of heterocycles in natural compounds with broad pharmacological activities such as anti-cancer,[17] anti-hepatitis B virus,[18] anti-HIV-1,[19] anti-inflammatory,[20] antinociceptive,[21] antimicrobial and antiproliferative[22] activity. In addition they are inhibitors of measles virus replication[23] and gained importance as photoactive drugs for skin disorders.[24] Pyranocoumarins **A** are used as anti-hyperglycemic and anti-dyslipidemic agents[25] and compound **B** is an antidiabetic natural product[26] (Fig. 1). These various biological activities of pyranocoumarins encourage researchers to introduce new methodologies for synthesizing novel biologically active pyranocoumarins.[27] One of the most utilized among these various methods is the formation of a pyran ring starting from hydroxycoumarins.[28,29]

Recently, the reaction of acyclic α-halo ketones, aldehydes, and C–H acids has been shown to be powerful methods for the synthesis of polycyclic heterocycles.[30] In 2009, Chao-Guo Yan and coworkers reported the synthesis of furano fused coumarins by the reaction of 4-hydroxy coumarin, aromatic aldehydes and *p*-nitrobenzyl bromide or α-phenacyl bromide in the presence of pyridine (Scheme 1).[30a]

As part of our continuing efforts for the synthesis of heterocycles using cyclic α-halo ketones,[31] herein, we wish to report a

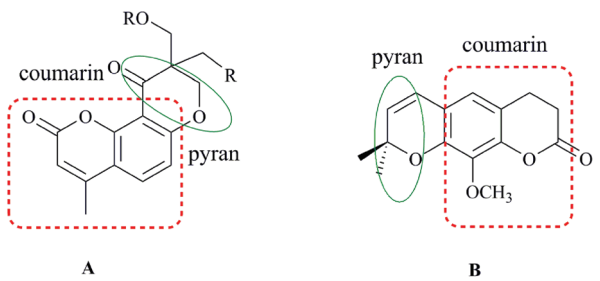
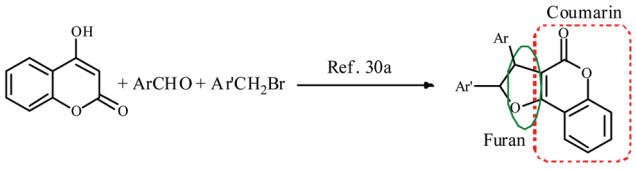


Fig. 1 Biologically active pyranocoumarins.



Scheme 1 Synthesis of furano fused coumarins by Chao-Guo Yan and coworkers.[30a]

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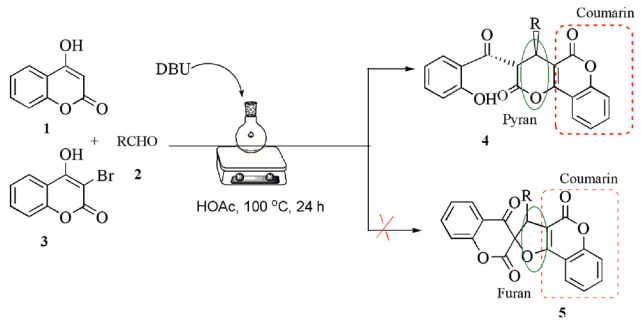


Scheme 2 Model of the reaction.

new method for the diastereoselective synthesis of pyrano fused coumarins by the reaction of 4-hydroxy coumarin **1**, aldehydes **2** and 3-bromo-4-hydroxycoumarin **3**, a cyclic α-halo ketone, *via* an organocatalytic three-component reaction (Scheme 2). It was interesting that based on recent reports,[30] the desired spiro furo fused coumarins **5** were not detected at all, while pyrano fused coumarins **4** were obtained in good yields.

Results and discussion

Initially, the three-component reaction of 4-hydroxy coumarin **1** (1 mmol), 4-nitrobenzaldehyde **2b** (1 mmol) and 3-bromo-4-hydroxycoumarin **3** (1 mmol) in the presence of various bases and solvents was investigated (Table 1). As shown in Table 1, the use of acetic acid at 100 °C in the presence of DBU (30%) allowed the formation of pyranocoumarin **4b** in 87% yield (Table 1, entry 7). It was found that when increasing the amount of DBU from 10 to 20, and 30 mol%, the isolated yield increased from 70 to 74 and 87%, respectively, and more amounts of the DBU did not improve the yield (entry 10). It should be mentioned that when the reaction was carried out in the absence of DBU the yield of the product was low (entry 12). To study the effect of temperature on the reaction, we also performed the reaction at a lower temperature. It was observed that a lower reaction temperature leads to a lower yield (entry 11).

Table 1 Optimization for synthesis of **4b**

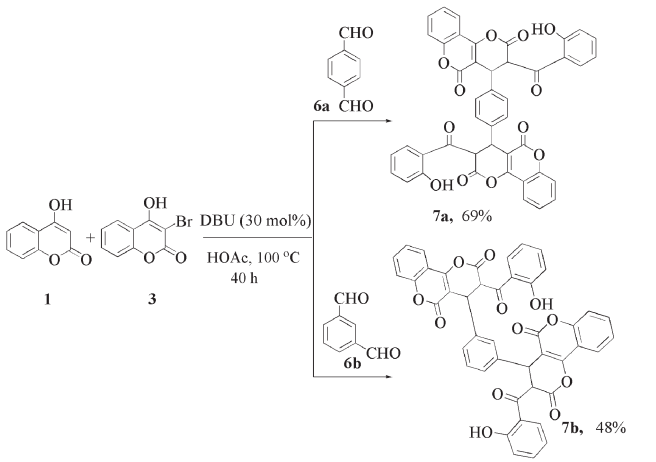
Entry	Solvent	Base (mol%)	Yield (%)[a]
1	CH_3CN (reflux)	DBU (30)	65
2	EtOH (reflux)	DBU (30)	45
3	H_2O (reflux)	DBU (30)	60
4	DMF (100 °C)	DBU (30)	50
5	THF (reflux)	DBU (30)	30
6	Toluene (reflux)	DBU (30)	50
7	HOAc (100 °C)	DBU (30)	87
8	HOAc (100 °C)	DBU (20)	74
9	HOAc (100 °C)	DBU (10)	70
10	HOAc (100 °C)	DBU (40)	88
11	HOAc (80 °C)	DBU (30)	71
12	HOAc (100 °C)	—	47
13	HOAc (100 °C)	K_2CO_3 (30)	55
14	HOAc (100 °C)	$CsCO_3$ (30)	60
15	HOAc (100 °C)	NEt_3 (30)	60
16	HOAc (100 °C)	NaOAc (30)	65
17	HOAc (100 °C)	NH_4OAc (30)	62

[a] Reaction time = 24 h.

Table 2 Synthesis of pyranocoumarins **4a–l**

Product **4**	RCHO	Yield (%)[a]
a	PhCHO	85
b	*p*-$NO_2C_6H_4CHO$	87
c	*p*-ClC_6H_4CHO	75
d	*p*-BrC_6H_4CHO	73
e	*p*-$HO_2CC_6H_4CHO$	95
f	*p*-OHC_6H_4CHO	75
g	*p*-$OMeC_6H_4CHO$	60
h	*p*-MeC_6H_4CHO	65
i	*m*-$NO_2C_6H_4CHO$	79
j	*m*-BrC_6H_4CHO	70
k	Thiophene-2-carbaldehyde	96
l	HO_2CCHO	75

[a] Isolated yields.



Scheme 3 Synthesis of bis(pyranocoumarins).

According to the optimized conditions, various aldehydes **2a–l** were selected to react with 4-hydroxy coumarin **1** and 3-bromo-4-hydroxycoumarins **3** under the optimal conditions (Table 2). The yield of the product seems to be affected by the nature of the substituents on the aldehyde, and increases when electron-withdrawing substituents are present. Reasonable yields were obtained using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents. Heterocyclic aldehydes such as thiophene-2-carbaldehyde afforded a high yield of product (**4k**) and even for glyoxylic acid, the corresponding pyranocoumarin was obtained in 75% yield (**4l**).

To further explore the potential of this protocol for new pyrano fused coumarin synthesis, we investigated a reaction involving terephthalaldehyde **6a** or isophthalaldehyde **6b** and obtained the corresponding bis(pyranocoumarins) **7a,b** in good isolated yields (Scheme 3). The mass spectrum of product **7** displayed a molecular ion peak at 748 *m*/*z*, which

was consistent with the proposed 2 : 2 : 1 adduct of 4-hydroxy coumarin **1**, 3-bromo-4-hydroxycoumarin **3** and aldehyde **6**.

The chromone scaffold forms the nucleus of flavonoids that are found naturally in fruits, vegetables, nuts, seeds, flowers, and barks.[32] Chromone is also part of the pharmacophores of a large number of molecules of medicinal significance[33] including anticancer agents such as psorospermin and pluramycin A.[34] Considering the very important biological activities of molecules containing a chromone scaffold, we hypothesize that the integration of a chromone moiety with a pyranocoumarin may result in the discovery of novel drug candidates with unknown biological activities. So, we investigated the reaction of 4-oxo-4*H*-chromene-3-carbaldehydes **8a–c** with 4-hydroxy coumarin **1** and 3-bromo-4-hydroxycoumarin **3** under same reaction conditions and obtained the desired pyranocoumarins **9a–c** containing chromone moiety in good isolated yields (Scheme 4).

It is notable that two pairs of diastereomers may be formed in the reaction. The ^{1}H-NMR spectra of the crude reaction mixture without any purification reveals a combination of two diastereomers. The *trans*-diastereoisomer is the major isomer and the *cis*-diastereoisomer is in trace amounts that can be removed by purification; therefore the reaction is diastereoselective. The expected *trans*-stereochemistry of the major diastereomer was established by the analysis of vicinal coupling constants of the two methine hydrogens as well as by NOE difference spectroscopy. In the major isomer of **4g** and **9a**, irradiation of one of the methine hydrogens gave no enhancement of the other methine hydrogen.

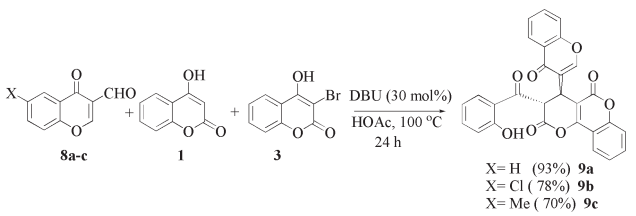
To demonstrate the key role of 3-bromo-4-hydroxycoumarins **3** in the reaction, we investigated the reaction of 4-hydroxy coumarin **1** with aromatic aldehydes **2a,b** in the same reaction conditions. The pyranocoumarins **4a,b** were not detected at all, while biscoumarin salts **10a,b** were obtained in <30% yield (Scheme 5). When this reaction was carried out with equimolar amounts of the DBU salts **10a,b** were obtained in moderate yields.

When we introduced the reaction of salicylaldehyde **11a** with 4-hydroxy coumarin **1** and 3-bromo-4-hydroxycoumarin **3** under the same reaction conditions, it was interesting that the desired pyranocoumarin **13** was not observed, while 7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)chromeno[4,3-*b*]chromen-6-(7*H*)-one **12a** was obtained in 60% yield (Scheme 6). It was found when the reaction was carried out in refluxing acetic acid that the product **12a** was obtained in 75% yield after 30 h.

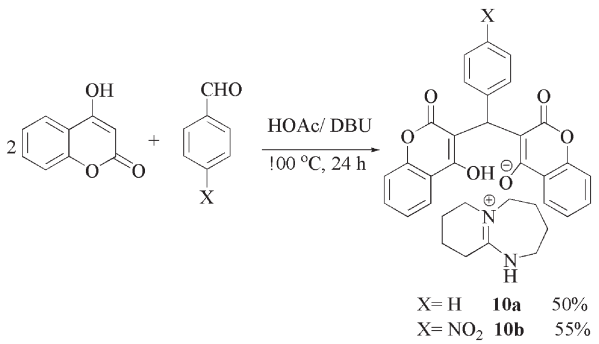
Therefore, the reaction of various 2-hydroxybenzaldehydes **11a–f**, 4-hydroxycoumarin **1** and 3-bromo-4-hydroxy coumarin **3** in the presence of DBU (30%) in refluxing acetic acid affords 7-(4-hydroxy-2-oxo-2H-chromen-3-yl)chromeno[4,3-b]chromen-6(7H)-ones **12a–f** in good isolated yields (Table 3).

The structures all of the products were deduced from their IR, ^{1}H, and ^{13}C NMR spectra and elemental analysis. The structure of **12f** was confirmed by single-crystal X-ray analysis (Fig. 2).

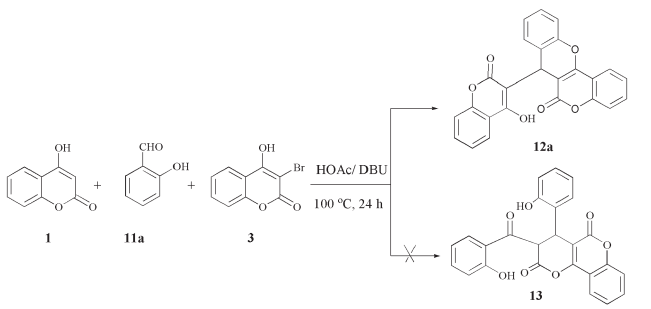
It is known that DBU promotes sequential Michael, aldol, dehydration and dealkoxycarbonylation.[35] Also, DBU in acidic conditions, facilitates Knoevenagel condensation *via* hydrogen bonding to aldehydes.[36] There are some examples of DBU hydrogen bonding to substrates and some examples of the use of DBU as a nucleophile.[37] Catalysis employing hydrogen bonding for substrate activation has been shown to be an effective and versatile strategy in a wide variety of transformations.[38] Therefore, the plausible mechanism for the formation of products **4** and **12** are depicted in Scheme 7. First,



Scheme 4 Synthesis of pyranocoumarins containing a chromone moiety **9**.



Scheme 5 Synthesis of biscoumarin salt **10**.



Scheme 6 Synthesis of 7-(2-oxo-2*H*-chromen-3-yl)chromeno[4,3-*b*]chromen-6-(7*H*)-one **12a**.

Table 3 Synthesis of 7-(2-oxo-2*H*-chromen-3-yl)chromeno[4,3-*b*]chromen-ones **12**

Product **12**	X	Yield (%)
a	H	75
b	5-Br	65
c	4-OMe	69
d	5-OMe	85
e	3-OH	50

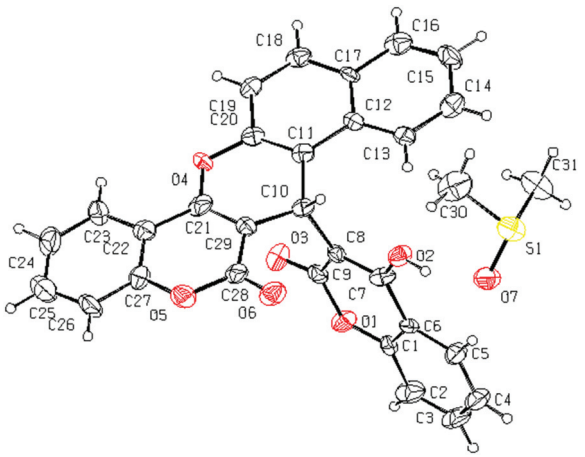
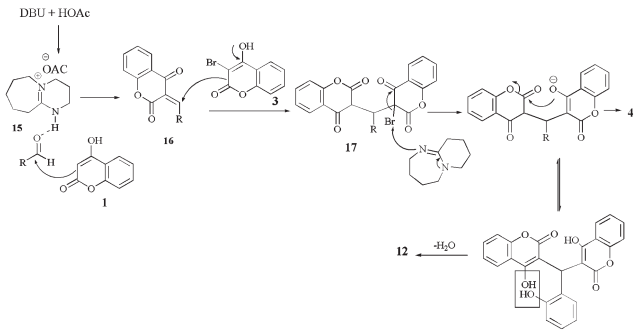


Fig. 2 ORTEP diagram of product **12f**.



Scheme 7 Proposed mechanism.

salt **15** is formed *in situ* by the acid–base reaction of DBU and HOAc. Then a hydrogen bond is formed between the aldehyde **2** and **15**. This activated aldehyde reacts with 4-hydroxy coumarin **1** by Knoevenagel condensation. Then Michael addition of 3-bromo-4-hydroxycoumarin **3** to intermediate **16** affords intermediate **17**. Finally, nucleophilic attack of DBU on **17**, followed by cyclization produces the corresponding pyranocoumarin **4**. The formation of product **12** can be rationalized by enolization of **17**, followed by elimination of one molecule of H_2O (Scheme 7).

Conclusions

In this paper for the first time, the three-component reaction of 3-bromo-4-hydroxycoumarins as a cyclic α-bromo ketone, aldehydes and 4-hydroxy coumarin using a DBU/HOAc system for the diastereoselective synthesis of pyrano fused coumarins is reported. Reaction of 3-bromo-4-hydroxycoumarins with salicylaldehydes and 4-hydroxycoumarins resulted in the formation of 7-(2-oxo-2*H*-chromen-3-yl)chromeno[4,3-*b*]chromenone derivatives. Prominent among the advantages of this new method are novelty, operational simplicity, good yields and the easy work-up procedures employed. This synthesis serves as a nice addition to group-assistant-purification (GAP) chemistry in which purification *via* chromatography and recrystallization can be avoided, and the pure products were obtained simply by washing the crude products with methanol.

Experimental section

General methods

Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were taken with a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a 70 MHz spectrometer using broadband proton decoupling. Chemical shifts are expressed in parts per million using the middle resonance of DMSO as an internal standard. Mass spectra were recorded on a JEOL MAT312 mass spectrometer or Agilent 5973 network mass selective detector operating at an ionization potential of 70 eV. Elemental analyses for C, H and N were performed using a Heraeus CHN–O– Rapid analyzer.

All chemicals were purchased from Merck or Aldrich and were used without further purification. Known 3-bromo-4-hydroxycoumarin was prepared by the procedure reported previously.[39]

General procedures for the synthesis of 4a–4l

A mixture of aldehyde (1.0 mmol), 4-hydroxy coumarin (0.16 g, 1.0 mmol), 3-bromo-4-hydroxycoumarin (0.24 g, 1 mmol) in HOAc (2 mL) in the presence of DBU (0.05 g, 30 mol%) was heated at 100 °C for 24 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with methanol (5 ml) to afford the pure product **4**.

3-(2-Hydroxybenzoyl)-4-phenyl-3,4-dihydropyrano[3,2-*c*]-chromene-2,5-dione (4a)

White powder (85%); mp 215–217 °C. IR (KBr) (ν_{max}/cm^{-1}): 3049, 1716, 1637, 1613. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.54 (1H, bs, CH), 6.56 (1H, bs, CH), 6.91–7.88 (13H, m, H–Ar), 10.93 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 49.4, 93.6, 105.5, 112.1, 117.2, 117.8, 119.9, 120.3, 123.5, 125.0, 127.7, 127.9, 129.1, 131.0, 133.8, 136.4, 141.2, 155.1, 158.7, 159.6, 166.8, 194.9. MS, *m*/*z*: 412 (M$^+$). Anal. Calcd for $C_{25}H_{16}O_6$: C, 72.81; H, 3.91. Found: C, 72.70; H, 3.84.

3-(2-Hydroxybenzoyl)-4-(4-nitrophenyl)-3,4-dihydropyrano-[3,2-*c*]chromene-2,5-dione (4b)

Cream powder (87%); mp 210–212 °C. IR (KBr) (ν_{max}/cm^{-1}): 3073, 1721, 1646, 1606. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.76 (1H, d, *J* = 3.54 Hz, CH), 6.62 (1H, d, *J* = 3.69 Hz, CH), 6.94–8.22 (12H, m, H–Ar), 10.86 (1H, s, OH). MS, *m*/*z*: 457 (M$^+$). Anal. Calcd for $C_{25}H_{15}NO_8$: C, 65.65; H, 3.31; N, 3.06. Found: C, 65.57; H, 3.37; N, 3.14. (Due to very low solubility of the product 4b, we cannot report the ^{13}C NMR date for this product).

4-(4-Chlorophenyl)-3-(2-hydroxybenzoyl)-3,4-dihydropyrano-[3,2-*c*]chromene-2,5-dione (4c)

White powder (75%); mp 191–193 °C. IR (KBr) (ν_{max}/cm^{-1}): 3055, 1722, 1647, 1605. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.56 (1H, bs, CH), 6.55 (1H, d, J = 3.72 Hz, CH), 6.92–7.88 (12H, m, H–Ar), 10.89 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 48.8, 93.5, 105.2, 112.0, 117.2, 117.8, 119.7, 120.4, 123.6, 125.1, 129.0, 129.7, 131.0, 132.4, 133.9, 136.4, 140.3, 155.1, 158.7, 159.6, 167.0, 194.4. MS, m/z: 446 (M$^+$). Anal. Calcd for $C_{25}H_{15}ClO_6$: C, 67.20; H, 3.38. Found: C, 67.13; H, 3.30.

4-(4-Bromophenyl)-3-(2-hydroxybenzoyl)-3,4-dihydropyrano-[3,2-c]chromene-2,5-dione (4d)

White powder (73%); mp 216–218 °C. IR (KBr) (ν_{max}/cm^{-1}): 3049, 1714, 1646, 1604. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.54 (1H, bs, CH), 6.55 (1H, d, J = 3.09 Hz, CH), 6.91–7.88 (12H, m, H–Ar), 10.88 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 48.9, 93.4, 105.2, 112.0, 117.2, 117.8, 119.9, 120.4, 121.0, 123.6, 125.1, 130.1, 131.0, 131.9, 133.9, 136.4, 140.8, 155.1, 158.7, 159.6, 167.0, 194.4. MS, m/z: 492 (M$^+$, ^{81}Br), 490 (M$^+$, ^{79}Br). Anal. Calcd for $C_{25}H_{15}BrO_6$: C, 61.12; H, 3.08. Found: C, 61.01; H, 2.96.

4-(3-(2-Hydroxybenzoyl)-2,5-dioxo-2,3,4,5-tetrahydropyrano-[3,2-*c*]chromen-4-yl)benzoic acid (4e)

White powder (95%); mp 250–252 °C. IR (KBr) (ν_{max}/cm^{-1}): 3192, 1726, 1680, 1637. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.64 (1H, d, J = 3.24 Hz, CH), 6.56 (1H, d, J = 3.51 Hz, CH), 6.92–7.94 (12H, m, H–Ar), 10.88 (1H, s, OH), 12.93 (1H, bs, OH exchange with solvent). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 49.3, 93.2, 105.2, 112.0, 117.2, 117.8, 119.9, 120.4, 123.6, 125.1, 128.1, 129.1, 130.2, 130.3, 131.1, 133.9, 136.4, 146.2, 155.1, 158.7, 159.6, 167.1, 167.5, 194.3. MS, m/z: 456 (M$^+$). Anal. Calcd for $C_{26}H_{16}O_8$: C, 68.42; H, 3.53. Found: C, 68.51; H, 3.45.

3-(2-Hydroxybenzoyl)-4-(4-hydroxyphenyl)-3,4-dihydropyrano-[3,2-*c*]chromene-2,5-dione (4f)

Cream powder (75%); mp 263–265 °C. IR (KBr) (ν_{max}/cm^{-1}): 3279, 1688, 1646, 1605. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.42 (1H, bs, CH), 6.49 (1H, bs, CH), 6.71–7.94 (12H, m, H–Ar), 9.44 (1H, s, OH), 10.96 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 49.0, 93.8, 105.7, 112.1, 115.8, 117.2, 117.8, 119.8, 120.2, 123.5, 125.0, 128.7, 131.0, 131.3, 133.7, 136.4, 155.1, 157.2, 158.7, 159.7, 162.7, 166.5, 195.4. MS, m/z: 428 (M$^+$). Anal. Calcd for $C_{25}H_{16}O_7$: C, 70.09; H, 3.76. Found: C, 70.22; H, 3.69.

3-(2-Hydroxybenzoyl)-4-(4-methoxyphenyl)-3,4-dihydropyrano-[3,2-*c*]chromene-2,5-dione (4g)

White powder (60%); mp 198–200 °C. IR (KBr) (ν_{max}/cm^{-1}): 3059, 1720, 1644, 1610. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 3.73 (3H, s, CH$_3$), 4.47 (1H, bs, CH), 6.53 (1H, d, J = 3.57 Hz, CH), 6.88–7.88 (12H, m, H–Ar), 10.94 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 48.9, 55.5, 93.7, 105.6, 112.1, 114.5, 117.2, 117.8, 119.9, 120.2, 123.5, 125.0, 128.8, 131.0, 133.1, 133.8, 136.4, 155.1, 158.7, 159.0, 159.7, 166.6, 195.2. MS, m/z: 442 (M$^+$). Anal. Calcd for $C_{26}H_{18}O_7$: C, 70.58; H, 4.10. Found: C, 70.45; H, 4.01.

3-(2-Hydroxybenzoyl)-4-p-tolyl-3,4-dihydropyrano[3,2-*c*]-chromene-2,5-dione (4h)

White powder (65%); mp 199–201 °C. IR (KBr) (ν_{max}/cm^{-1}): 3055, 1721, 1643, 1607. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 3.73 (3H, s, CH$_3$), 4.48 (1H, d, J = 3.57 Hz, CH), 6.52 (1H, d, J = 3.75 Hz, CH), 6.88–7.88 (12H, m, H–Ar), 10.93 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 48.9, 55.5, 93.7, 105.6, 112.1, 113.6, 114.5, 117.2, 117.8, 119.9, 120.2, 123.5, 125.0, 128.8, 131.0, 133.1, 133.8, 136.4, 155.1, 159.0, 159.7, 195.2. MS, m/z: 426 (M$^+$). Anal. Calcd for $C_{26}H_{18}O_6$: C, 73.23; H, 4.25. Found: C, 73.30; H, 4.19.

3-(2-Hydroxybenzoyl)-4-(3-nitrophenyl)-3,4-dihydropyrano-[3,2-*c*]chromene-2,5-dione (4i)

Cream powder (79%); mp 206–208 °C. IR (KBr) (ν_{max}/cm^{-1}): 3079, 1718, 1646, 1607. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.81 (1H, bs, CH), 6.63 (1H, d, J = 3.61 Hz, CH), 6.93–8.18 (12H, m, H–Ar), 10.82 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 48.8, 93.4, 104.9, 112.0, 117.2, 117.7, 119.9, 120.5, 122.8, 123.6, 125.1, 130.7, 131.1, 134.0, 134.6, 136.4, 143.6, 148.3, 155.2, 158.7, 159.5, 167.3, 193.9. MS, m/z: 457 (M$^+$). Anal. Calcd for $C_{25}H_{15}NO_8$: C, 65.65; H, 3.31; N, 3.06. Found: C, 65.73; H, 3.23; N, 3.17.

4-(3-Bromophenyl)-3-(2-hydroxybenzoyl)-3,4-dihydropyrano-[3,2-*c*]chromene-2,5-dione (4j)

Cream powder (70%); mp 148–150 °C. IR (KBr) (ν_{max}/cm^{-1}): 3048, 1728, 1652, 1609. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.61 (1H, d, J = 3.99 Hz, CH), 6.61 (1H, d, J = 4.11 Hz, CH), 6.92–7.88 (12H, m, H–Ar), 10.93 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 48.9, 93.3, 105.1, 112.1, 117.2, 117.5, 117.8, 119.9, 120.4, 122.3, 123.5, 123.6, 125.1, 126.9, 130.5, 130.8, 131.1, 133.9, 136.4, 143.9, 155.1, 158.7, 159.6, 167.1, 194.4. MS, m/z: 492 (M$^+$, ^{81}Br), 490 (M$^+$, ^{79}Br). Anal. Calcd for $C_{25}H_{15}BrO_6$: C, 61.12; H, 3.08. Found: C, 61.20; H, 3.15.

3-(2-Hydroxybenzoyl)-4-(thiophen-2-yl)-3,4-dihydropyrano-[3,2-*c*]chromene-2,5-dione (4k)

Cream powder (96%); mp 210–212 °C. IR (KBr) (ν_{max}/cm^{-1}): 3049, 1721, 1637, 1603. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.90 (1H, d, J = 2.31 Hz, CH), 6.56 (1H, d, J = 2.43 Hz, CH), 6.92–7.87 (11H, m, H–Ar), 11.07 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 44.5, 93.6, 105.0, 111.9, 117.3, 117.8, 119.9, 120.3, 123.6, 125.1, 125.8, 127.6, 131.1, 134.1, 136.4, 143.8, 155.1, 158.6, 159.7, 166.9, 194.3. MS, m/z: 418 (M$^+$). Anal. Calcd for $C_{23}H_{14}O_6S$: C, 66.02; H, 3.37. Found: C, 65.91; H, 3.28.

3-(2-Hydroxybenzoyl)-2,5-dioxo-2,3,4,5-tetrahydropyrano[3,2-*c*]-chromene-4-carboxylic acid (4l)

Cream powder (75%); mp 254–256 °C. IR (KBr) (ν_{max}/cm^{-1}): 3178, 1729, 1698, 1647. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.07 (1H, d, J = 3.99 Hz, CH), 6.69 (1H, d, J = 3.99 Hz, CH),

6.94–7.83 (8H, m, H–Ar), 11.28 (1H, s, OH), 13.13 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 49.0, 90.7, 100.9, 111.7, 117.3, 117.8, 120.0, 120.2, 123.5, 125.2, 131.0, 134.3, 136.5, 155.0, 158.3, 159.5, 168.0, 172.0, 193.1. MS, *m*/*z*: 380 (M^+). Anal. Calcd for $C_{20}H_{12}O_8$: C, 63.16; H, 3.18. Found: C, 63.10; H, 3.24.

4,4′-(1,4-Phenylene)bis(3-(2-hydroxybenzoyl)-3,4-dihydropyrano-[3,2-c]chromene-2,5-dione) (7a)

Cream powder (69%); mp 210–212 °C. IR (KBr) (ν_{max}/cm^{-1}): 3079, 1721, 1648, 1602. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.56 (2H, bs, CH), 6.46–6.55 (2H, bs, CH), 6.96–7.85 (20H, m, H–Ar), 10.95 (1H, s, OH), 11.01 (1H, s, OH). MS, *m*/*z*: 748 (M^+). MS, *m*/*z*: 746 (M^+). Anal. Calcd for $C_{44}H_{26}O_{12}$: C, 70.78; H, 3.51. Found: C, 70.67; H, 3.57. (Due to very low solubility of the product 7a, we cannot report the ^{13}C NMR date for this product).

4,4′-(1,3-Phenylene)bis(3-(2-hydroxybenzoyl)-3,4-dihydropyrano-[3,2-c]chromene-2,5-dione) (7b)

Cream powder (48%); mp 216–218 °C. IR (KBr) (ν_{max}/cm^{-1}): 3065, 1710, 1645. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.59 (2H, d, CH, *J* = 3.84 Hz), 6.49 (2H, d, CH, *J* = 3.87 Hz), 6.88–7.09 (6H, m, H–Ar), 7.19–7.22 (2H, m, H–Ar), 7.33–7.84 (16H, m, H–Ar), 10.89 (2H, s, OH). MS, *m*/*z*: 746 (M^+). Anal. Calcd for $C_{44}H_{26}O_{12}$: C, 70.78; H, 3.51. Found: C, 70.65; H, 3.45. (Due to very low solubility of the product 7b, we cannot report the ^{13}C NMR date for this product).

3-(2-Hydroxybenzoyl)-4-(4-oxo-4*H*-chromen-3-yl)-3,4-dihydropyrano[3,2-*c*] chromene-2,5-dione (9a)

White powder (93%); mp 247–249 °C. IR (KBr) (ν_{max}/cm^{-1}): 3055, 1710, 1638. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.65 (1H, d, *J* = 4.59 Hz, CH), 6.66 (1H, d, δ_H 4.65 Hz, CH), 6.93–8.04 (13H, m, H–Ar), 8.44 (1H, s,=CH), 10.96 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 42.3, 89.9, 101.9, 112.2, 117.2, 117.8, 118.9, 119.9, 120.5, 121.8, 123.8, 125.0, 125.4, 126.0, 131.3, 133.7, 134.8, 136.6, 155.0, 155.9, 156.2, 158.8, 159.9, 167.5, 176.1, 195.8. MS, *m*/*z*: 480 (M^+). Anal. Calcd for $C_{28}H_{16}O_8$: C, 70.00; H, 3.36. Found: C, 70.09; H, 3.31.

4-(6-Chloro-4-oxo-4*H*-chromen-3-yl)-3-(2-hydroxybenzoyl)-3,4-dihydropyrano[3,2-*c*]chromene-2,5-dione (9b)

White powder (78%); mp 260–262 °C. IR (KBr) (ν_{max}/cm^{-1}): 3065, 1710, 1645. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 4.65 (1H, d, CH, *J* = 5.13 Hz), 6.64 (1H, d, CH, *J* = 4.71 Hz), 6.93–6.96 (2H, m, H–Ar), 7.45–7.52 (3H, m, H–Ar), 7.72–7.90 (5H, m, H–Ar), 7.97 (1H, s, H–Ar), 8.49 (1H, s,=CH), 10.93 (1H, s, OH). MS, *m*/*z*: 514 (M^+). Anal. Calcd for $C_{28}H_{15}ClO_8$: C, 65.32; H, 2.94. Found: C, 65.43; H, 2.87. (Due to very low solubility of the product 4b, we cannot report the ^{13}C NMR date for this product).

3-(2-Hydroxybenzoyl)-4-(6-methyl-4-oxo-4*H*-chromen-3-yl)-3,4-dihydropyrano[3,2-*c*]chromene-2,5-dione (9c)

White powder (70%); mp 267–269 °C. IR (KBr) (ν_{max}/cm^{-1}): 3045, 1710, 1631. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 2.49 (3H, s, CH$_3$), 4.64 (1H, d, CH, *J* = 4.86 Hz), 6.64 (1H, d, CH, *J* = 5.25 Hz), 6.93–6.96 (2H, m, H–Ar), 7.43–7.84 (9H, m, H–Ar), 8.39 (1H, s,=CH), 10.93 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 20.4, 41.8, 89.6, 101.5, 111.7, 116.7, 117.4, 118.2, 119.5, 120.1, 121.2, 122.9, 123.1, 124.2, 124.5, 130.9, 133.3, 135.2, 135.3, 136.1, 154.1, 154.6, 155.3, 158.4, 159.4, 167.0, 175.6, 195.5. MS, *m*/*z*: 494 (M^+). Anal. Calcd for $C_{29}H_{18}O_8$: C, 70.44; H, 3.67. Found: C, 70.37; H, 3.63.

2,3,4,5,7,8,9,10-Octahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-6-ium 3-((4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-nitrophenyl)methyl)-2-oxo-2*H*-chromen-4-olate (10a)

White powder (55%); mp 128–130 °C. IR (KBr) (ν_{max}/cm^{-1}): 3436, 2936, 1686, 1648. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 1.61 (6H, bs, CH$_2$), 1.89 (2H, bs, CH$_2$), 2.60 (2H, bs, CH$_2$), 3.22 (2H, bs, CH$_2$), 3.45 (2H, bs, CH$_2$), 3.51 (2H, bs, CH$_2$), 3.91 (1H, bs, NH overlap with solvent), 6.34 (1H, bs, CH), 7.24–8.07 (12H, m, H–Ar), 9.46 (1H, bs, OH). Anal. Calcd for $C_{34}H_{31}N_3O_8$: C, 66.99; H, 5.13. N, 6.89. Found: C, 66.86; H, 5.21; N, 6.78.

2,3,4,5,7,8,9,10-Octahydro-1H-pyrido[1,2-a][1,3]diazepin-6-ium 3-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-2-oxo-2H-chromen-4-olate (10b)

White powder (50%); mp 123–125 °C. IR (KBr) (ν_{max}/cm^{-1}): 3434, 2936, 1684, 1645. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 1.62 (5H, bs, CH$_2$), 1.76 (2H, bs, CH$_2$), 2.62 (3H, bs, CH$_2$), 3.22 (2H, bs, CH$_2$), 3.45 (2H, bs, CH$_2$), 3.51 (2H, bs, CH$_2$), 3.91 (1H, bs, NH overlap with solvent), 6.34 (1H, bs, CH), 7.24–8.07 (12H, m, H–Ar), 9.46 (1H, OH). Anal. Calcd for $C_{34}H_{32}N_2O_6$: C, 72.32; H, 5.71. N, 4.96. Found: C, 72.20; H, 5.64; N, 4.87.

General procedures for the synthesis of 12a–12e

A mixture of salicylaldehyde (1.0 mmol), 4-hydroxy coumarin (0.16 g, 1.0 mmol), 3-bromo-4-hydroxycoumarin (0.25 g, 1 mmol) in HOAc (3 mL) in the presence of DBU (0.05 g, 30 mol%) was refluxed in HOAc for 30 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with methanol (5 ml).

7-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)chromeno[4,3-*b*]chromen-6(7*H*)-one (12a)

White powder (75%); mp 247–249 °C. IR (KBr) (ν_{max}/cm^{-1}): 3256, 1718, 1700, 1633. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 5.72 (1H, s, CH), 7.13–8.05 (12H, m, H–Ar), 12.18 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 29.6, 114.2, 116.5, 116.6, 116.9, 122.6, 123.0, 124.0, 124.1, 124.2, 124.3, 124.9, 125.7, 128.7, 129.0, 132.6, 132.9, 149.5, 152.4, 152.6, 156.6, 160.8, 161.1. MS, *m*/*z*: 410 (M^+). Anal. Calcd for $C_{25}H_{14}O_6$: C, 73.17; H, 3.44. Found: C, 73.09; H, 3.37.

9-Bromo-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)chromeno[4,3-*b*]-chromen-6(7*H*)-one (12b)

White powder (65%); mp > 260 °C. IR (KBr) (ν_{max}/cm^{-1}): 3276, 1710, 1674, 1629. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 3.23–3.51 (1H, bs, OH), 5.70 (1H, s, CH), 7.30–8.07 (11H, m, H–Ar). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 29.6, 114.0, 116.6, 116.8, 116.9, 117.0, 119.0, 123.0, 124.4, 124.5, 125.0, 125.3, 131.2, 131.6, 132.7, 133.0, 149.0, 152.3, 152.7, 156.4, 160.6, 161.7, 161.7. MS, *m*/*z*: 489 (M$^+$, ^{81}Br), 487 (M$^+$, ^{79}Br). Anal. Calcd for $C_{25}H_{13}BrO_6$: C, 61.37; H, 2.68. Found: C, 61.25; H, 2.73.

7-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-10-methoxychromeno-[4,3-*b*]chromen-6(7*H*)-one (12c)

White powder (69%); mp 262 °C. IR (KBr) (ν_{max}/cm^{-1}): 3212, 1736, 1674. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 3.61 (1H, bs, OH), 5.66 (1H, s, CH), 6.71–8.41 (11H, m, H–Ar), 12.01 (1H, bs, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 28.61, 55.90, 101.7, 112.3, 114.2, 114.3, 116.6, 116.9, 117.0, 123.0, 124.1, 124.3, 124.9, 129.6, 132.5, 132.9, 150.2, 152.4, 152.6, 156.6, 159.5, 160.9. MS *m*/*z* 440 (M$^+$). MS, *m*/*z*: 440 (M$^+$). Anal. Calcd for $C_{26}H_{16}O_7$: C, 70.91; H, 3.66. Found: C, 70.80; H, 3.58.

7-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-9-methoxychromeno-[4,3-*b*]chromen-6(7*H*)-one (12d)

White powder (85%); mp > 260 °C. IR (KBr) (ν_{max}/cm^{-1}): 3064, 1703, 1666, 1608. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 3.78 (1H, bs, OH), 5.69 (1H, s, CH), 6.66–8.08 (11H, m, H–Ar), 12.16 (1H, bs, OH). MS, *m*/*z*: 440 (M$^+$). Anal. Calcd for $C_{26}H_{16}O_7$: C, 70.91; H, 3.66. Found: C, 70.84; H, 3.61. (Due to very low solubility of the product **12d**, we cannot report the ^{13}C NMR date for this product).

11-Hydroxy-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)chromeno-[4,3-*b*]chromen-6(7*H*)-one (12e)

White powder (50%); mp 247–249 °C. IR (KBr) (ν_{max}/cm^{-1}): 3404, 1683, 1607. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 3.40 (1H, bs, OH overlap with solvent), 5.70 (1H, s, CH), 6.61–8.32 (11H, m, H–Ar), 9.85 (1H, s, OH), 12.13 (1H, bs, OH). MS, *m*/*z*: 426 (M$^+$). Anal. Calcd for $C_{25}H_{14}O_7$: C, 70.42; H, 3.31. Found: C, 70.52; H, 3.25. (Due to very low solubility of the product **12e**, we cannot report the ^{13}C NMR date for this product).

7-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)benzo[*f*]chromeno[4,3-*b*]-chromen-6(7*H*)-one (12f)

Cream powder (85%); mp 260 °C. IR (KBr) (ν_{max}/cm^{-1}): 3212, 1728, 1661, 1610. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 6.16 (1H, s, CH), 7.25–8.35 (14H, m, H–Ar), 12.49–12.51 (1H, bs, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 114.1, 116.2, 116.6, 116.9, 117.4, 123.1, 123.2, 124.3, 124.9, 125.4, 127.7, 129.1, 129.6, 131.4, 132.7, 132.9, 152.4, 152.6, 160.9. MS, *m*/*z*: 460 (M$^+$). Anal. Calcd for $C_{29}H_{16}O_6$: C, 75.65; H, 3.50. Found: C, 75.54; H, 3.45.

X-ray data for 12f

$C_{29}H_{16}O_7$(DMSO), M = 538.56 g mol^{-1}, triclinic system, space group $P\bar{1}$, a = 10.399(3), b = 11.235(3), c = 13.089(3) Å, β = 101.40(2)°, V = 1277.6(6) Å^3, Z = 2, Dc = 1.400 g cm^{-3}, μ(Mo–Kα) = 0.177 mm^{-1}, crystal dimension of 0.20 × 0.16 × 0.15 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the X-STEP32 suite of programs. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.1168, wR_2 = 0.2969 and S = 1.006 with 356 parameters using 5003 independent reflection (θ range = 1.74–26.00°). Hydrogen atoms were located from expected geometry and were not refined.

The X-ray diffraction measurements were made on a STOE IPDS-II diffractometer with graphite monochromated Mo–Kα radiation. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 5003 unique reflections. Data were collected at a temperature of 298(2) K to a maximum 2θ value of 52.00° and in a series of ω scans in 1° oscillations and integrated using the Stoe X-AREA[40] software package. The numerical absorption coefficients, μ, for Mo–Kα radiation is 0.177 mm^{-1}. A numerical absorption correction was applied using X-RED[41] and X-SHAPE[42] software. The data were corrected for Lorentz and polarizing effects. The structure was solved by direct methods and refined on F^2 by a full-matrix least-squares procedure. All hydrogen atoms were added at ideal positions and constrained to ride on their parent atoms, with $U_{iso}(H)$ = 1.2U_{eq}. All refinements were performed using the X-STEP32 crystallographic software package.[43] Complete crystallographic data for compound **12f** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 876614.

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