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ORIGINAL PAPER

Efficient access to novel tetra- and pentacyclic dihydroquinolin-2-ones by catalyst-free domino Knöevenagel hetero-Diels–Alder reactions from *N*-(2-formylphenyl)-*N*-methylcinnamamides and cyclic 1,3-dicarbonyls in water

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Abstract An efficient catalyst-free synthesis of novel annulated hybrid derivatives of two known scaffolds, dihydroquinolinone and pyranopyranone, pyranopyrimidinedione, pyranocoumarin or chromenone is described. *N*-(2-Formylphenyl)-*N*-methylcinnamamides underwent a one-pot domino Knöevenagel hetero-Diels–Alder reaction with dimedone, *N*,*N*-dimethylbarbituric acid, 1,3-indanedione, 4-hydroxycoumarins and 4-hydroxy-6-methyl-2*H*-pyran-2-one in water, affording the desired tetra and pentacyclic pyranoquinolinones in excellent yields.

Keywords Domino Knöevenagel hetero-Diels–Alder · Pyranoquinolinones · 1,3-Dicarbonyls

Introduction

A variety of biologically active compounds contain ubiquitous natural heterocyclic scaffolds in their molecular structure [1–8]. Whereas multistep synthetic methods were needed to prepare such compounds in the past, the number of steps was intensely reduced in recent years by using domino or cascade reactions [9–17]. Development of domino reactions in organic synthesis not only shortens the preparation methods, but also enhances the selectivity and efficiency, especially in those protocols designed toward the synthesis of fused heterocyclic scaffolds. Particularly significant in this regard is the domino Knöevenagel hetero-Diels–Alder reaction, which was developed widely by Tietze and Rackelman as an efficient process in organic synthesis, especially in the area of heterocycles and natural products [18–22]. Transformation of the precursors into the desired products including two or more rings at once, avoiding sequential chemical steps, is the main advantage of this reaction [23–27]. Part of the advantages of green chemistry such as minimizing the laboratory equipment and chemical or solvent usage together with atom economy and simple work-up methods for the construction of heterocyclic compounds with substantial molecular complexity are included in domino/cascade reactions [28–32].

As shown in Fig. 1, alkaloids of the Melodinus family, exemplified by meloscine **I** contains the dihydroquinolin-2-one (dihydroquinolone) structure (Fig. 1) [33, 34]. This structure is also found in microbial metabolites yaequinolone J1 (**II**) (Fig. 1) [35, 36]. Commercial drugs carteolol (**III**) and cilostazol (**IV**) which are used in the treatment of glaucoma [37] and peripheral vascular diseases [38], respectively, also contain the dihydroquinolin-2-one scaffold in the molecular structure (Fig. 1).

Investigation on the chemistry of fused biheterocycles has been the subject of investigation in medicinal chemistry as they are known to exhibit enhanced biological profile [39–41]. Due to the documented properties of dihydroquinolin-2-one as well as pyranoquinolinone scaffold as a privileged moiety in numerous natural products [42–44], we envisioned that synthesis of hybrid scaffolds in which dihydroquinolin-2-one is fused with pyranocoumarin [45], pyranobarbituric acid

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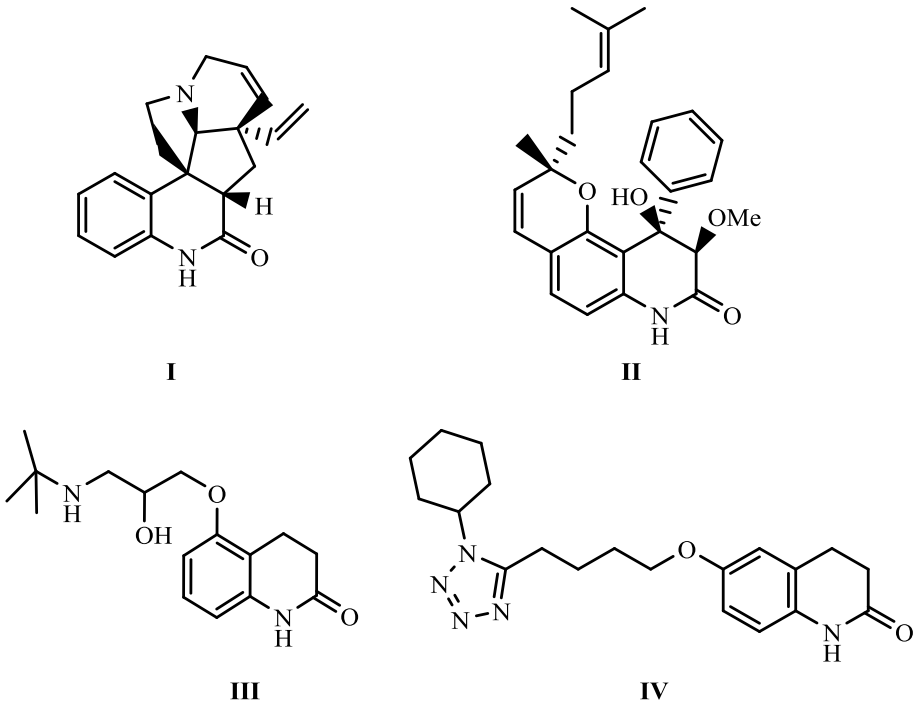


Fig. 1 Natural products and commercial drugs containing the dihydroquinolin-2-one scaffolds

[46–48], pyranopyranone [49, 50] and pyranochromenone [51, 52] should be interesting due to their individual widespread known biological activities and uses. Preparation of dihydroquinolin-2-one derivatives has been carried out in past years using different methods. Examples in this regard include silver-catalyzed reaction of *N*-methyl-*N*-phenylcinnamamide with 2-oxo-2-phenylacetic acid [53], Pd-catalyzed intra- or intermolecular carbocyclizations [54, 55], and Ir-catalyzed annulation of *N*-arylcarbamoyl chlorides with internal alkynes [56]. To the best of our knowledge, there has been no report in the literature on the intramolecular hetero-Diels–Alder reaction of a dienophile tethered to a diene moiety by an amide linkage.

As a part of our own interest in this area [57–59], herein we report the synthesis of novel tetra- and pentacyclic dihydroquinolinone annulated pyranopyranone, pyranopyrimidinedione, pyranocoumarin or chromenone derivatives via catalyst-free domino Knöevenagel hetero-Diels–Alder reaction of some *E*-*N*-(2-formylphenyl)-*N*-methylcinnamamide derivatives with cyclic 1,3-dicarbonyls such as dimedone, *N*,*N*-dimethylbarbituric acid, 1,3-indanedione, 4-hydroxy-6-methyl-2*H*-pyran-2-one and 4-hydroxycoumarins in water. Since water is an easily available and environmentally friendly solvent, a number of processes including Diels–Alder reactions have been carried out in aqueous media [60–62]. Therefore, we decided to use it as a safe solvent in our new procedure.

Experiment

General information

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Bomem B100 series spectrophotometer, in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 500 (^{1}H) and 125 MHz (^{13}C) and Bruker DRX-300-ADVANCE spectrometer at 300 (^{1}H) and 75 MHz (^{13}C). Mass spectra of the products were obtained with an HP (Agilent Technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the preparation of 15a

A mixture of *N*-(2-formylphenyl)-*N*-methylcinnamamide **4a** (0.265 g, 1.0 mmol) and 4-hydroxycoumarin (**14a**) (0.162 g, 1.0 mmol) in water (10 mL) was heated as reflux for 6 h. After completion of the reaction as evidenced by TLC, CH_2Cl_2 (20 mL) was added. The organic phase was then separated and aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried over Na_2SO_4, and the solvent was removed under reduced

pressure. The residue was recrystallized from CH_2Cl_2–EtOAc–hexane (1:2:4) to afford **15a**.

3,3,8-Trimethyl-6-phenyl-3,4,6,6a,8,12b-hexahydro-1H-chromeno[3,4-c]quinoline-1,7(2H)-dione ***(6a, 7a)*** White solid, mp: 175–177 °C, yield: 0.367 g (95 %). IR (KBr) (ν_{max}, cm^{-1}): 2957, 1657, 1604, 1460, 1379, 757, 698; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 1.15$ and 1.16 (2 s, 6H, C$\underline{Me}_2^{7a}$), 1.19 and 1.27 (2 s, 6H, C$\underline{Me}_2^{6a}$), 2.42 (ABq, $J = 17.3$ Hz, 4H, 2C$\underline{CH}_2$C^{6a,7a}), 2.44 (ABq, $J = 17.1$ Hz, 4H, 2C$\underline{CH}_2$C ^{6a,7a}), 2.99–3.06 (m, 2H, $H_{6a}^{6a,7a}$), 3.27 (s, 3H, N$\underline{Me}^{6a}$), 3.30 (3H, s, N$\underline{Me}^{7a}$), 4.02 (d, $J = 13.8$ Hz, 1H, H_{12b}^{7a}), 4.43 (broad s, 1H, H_{12b}^{6a}), 4.95 (d, $J = 9.8$ Hz, 1H, H_6^{6a}), 5.01 (d, $J = 10.5$ Hz, 1H, H_6 ^{7a}), 6.90–7.45 (m, 18H, $Ar^{6a,7a}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 27.4$, 28.8 (2C), 28.9, 30.2, (2$\underline{C}$H), 30.4, 30.5, 30.7, 31.6 (4$\underline{C}H_3$), 32.7, 33.9 (2N$\underline{C}H_3$), 42.9, 43.1 (2$\underline{C}H_2$), 47.4, 47.7 (2$\underline{C}$H), 76.62, 79.78, (2O–$\underline{C}$H), 110.3, 111.0 (2C=$\underline{C}$–C=O), 115.6, 116.2, 123.6, 124.2, 125.6, 127.3, 127.7 (7CH), 128.1 (C), 128.3, 128.5, 128.7, 128.9, 129.2, 129.6 (6CH), 129.9 (C), 130.7 (CH), 137.0, 138.8, 138.9, 140.9 (4C), 166.8, 169.5 (2C=$\underline{C}$–O), 171.0, 173.3 (2N$\underline{C}$=O), 197.5, 197.8 (2$\underline{C}$=O); EI-MS: *m/z* (%): 389 (4, $M^+ + 2$), 386 (14, $M^+ + 1$), 387 (41, M^+), 360 (84), 296 (100),131(95), 103 (92), 69 (95). Anal. Calcd for $C_{25}H_{25}NO_3$ (387.18): C 77.49, H 6.50, N 3.61 %. Found: C 77.42, H 6.44, N 3.64 %. R_f (25 % EtOAc/hexane) 0.52.

3,3,8,11-Tetramethyl-6-phenyl-3,4,6,6a,8,12b-hexahydro-1H-chromeno[3,4-c]quinoline-1,7(2H)-dione ***(6b, 7b)*** White solid, mp: 207–208 °C, yield: 0.368 g (92 %). IR (KBr) (ν_{max}, cm^{-1}): 2957, 1654, 1613, 1498, 1466, 1420, 1376, 811, 758, 693; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta_H = 1.16$ and 1.17 (2 s, 6H, C$\underline{Me}_2^{6b,7b}$), 1.21 (s, 3H, C$\underline{Me}_2^{6b}$), 1.30 (s, 3H, C$\underline{Me}_2^{7b}$), 2.30 (s, 3H, C$\underline{Me}^{6b}$), 2.32 (s, 3H, C$\underline{Me}^{7b}$), 2.37–2.54 (m, 8H, 4C$\underline{CH}_2$C^{6b,7b}), 2.99 (dd, $J = 10.1$, 4.7 Hz, 1H, H_{6a}^{6b}), 3.03 (dd, $J = 13.7$, 10.5 Hz, 1H, H_{6a}^{7b}), 3.25 (s, 3H, N$\underline{Me}^{7b}$), 3.29 (s, 3H, N$\underline{Me}^{6b}$), 4.02 (d, $J = 13.7$ Hz, 1H, H_{12b}^{7b}), 4.43 (broad s 1H, H_{12b}^{6b}), 4.96 (d, $J = 10.1$ Hz, 1H, H_6^{6b}), 5.01 (d, $J = 10.5$ Hz, 1H, H_6^{7b}), 6.70 (s, 1H, Ar^{7b}), 6.77 (s, 1H, Ar^{6b}), 6.91 (d, $J = 8.3$ Hz, 1H, Ar^{7b}), 6.92 (d, $J = 8.3$ Hz, 1H, Ar^{6b}), 7.08 (dd, $J = 9.5$, 9.2 Hz, 2H, $Ar^{6b,7b}$), 7.19–7.45 (m, 10H, $Ar^{6b,7b}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 21.3$, 21.6 (2$\underline{C}H_3$), 27.3, 28.8 (2C), 28.9, 30.2 (2$\underline{C}$H), 30.4, 30.5, 30.7, 31.6 (4$\underline{C}H_3$), 32.8, 33.9 (2N$\underline{C}H_3$), 42.9, 43.2 (2$\underline{C}H_2$), 47.5, 47.9 (2$\underline{C}$H), 76.6, 79.8 (2O–$\underline{C}$H), 110.4, 111.2, 115.5, 116.1, 126.3, 127.3, 128.0, 128.1, 128.5, 128.7, 128.9, 129.0, 129.2, 129.5, 130.5, 130.7, 133.1, 133.7, 136.5, 137.1, 138.5, 139.0,166.7, 169.5 (2C=$\underline{C}$–O), 170.9, 173.2 (2N$\underline{C}$=O), 197.5, 197.7 (2$\underline{C}$=O); EI-MS: *m/z* (%): 403 (3, $M^+ + 2$), 402 (20, $M^+ + 1$), 401 (72, M^+), 384 (47), 310 (100), 254 (31), 131 (36), 103 (33). Anal. Calcd for $C_{26}H_{27}NO_3$ (401.20): C 77.78, H 6.78, N 3.49 %. Found: C 77.80, H 6.81, N 3.44 %. R_f (25 % EtOAc/hexane) 0.51.

11-Methoxy-3,3,8-trimethyl-6-phenyl-3,4,6,6a,8,12b-hexahydro-1H-chromeno[3,4-c]quinoline-1,7(2H)-dione ***(6c, 7c)*** White solid, mp 268–270 °C, yield: 0.408 g (98 %). IR (KBr) (ν_{max}, cm^{-1}): 2955, 1652, 1618, 1600, 1380, 1218, 1146, 1029, 760, 695; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta_H = 1.14$, 1.28 (2 s, 6H, C$\underline{Me}_2^{7c}$), 1.15, 1.19 (2 s, 6H, C$\underline{Me}_2^{6c}$), 2.36–2.49 (m, 8H, 4C$\underline{CH}_2$C^{6c,7c}), 2.98 (dd, $J = 8.1$, 4.8 Hz, 1H, H_{6a}^{6c}), 3.01 (dd, $J = 13.7$, 10.6 Hz, 1H, H_{6a}^{7c}), 3.23 (s, 3H, N$\underline{Me}^{7c}$), 3.27 (s, 3H, N$\underline{Me}^{6c}$), 3.75 (s, 6H, O$\underline{Me}^{6c,7c}$), 4.00 (d, $J = 13.7$ Hz, 1H, H_{12b}^{7c}), 4.40 (broad s, 1H, H_{12b}^{6c}), 4.93 (d, $J = 8.6$ Hz, 1H, H_6^{6c}), 5.00 (d, $J = 10.6$ Hz, 1H, H_6^{7c}), 6.48 (m, 1H, Ar^{7c}), 6.55 (broad s, 1H, Ar^{6c}), 6.76–6.81 (2dd, $J = 8.8$, 2.8 Hz, 2H, $Ar^{6c,7c}$) 6.91–6.95 (2d, $J = 8.8$ Hz, 2H, $Ar^{6c,7c}$), 7.17–7.44 (m, 10H, $Ar^{6c,7c}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 27.2$, 28.7 (2C), 29.0, 30.4 (2$\underline{C}$H), 30.5, 30.6, 30.9, 31.5 (4$\underline{C}H_3$), 32.7, 34.0 (2N$\underline{C}H_3$), 42.8, 43.1 (2$\underline{C}H_2$), 47.4, 47.7 (2$\underline{C}$H), 51.1, 55.8 (2O$\underline{C}H_3$), 76.6, 79.8 (2O–$\underline{C}$H), 110.2, 111.0, 112.0, 112.4, 112.8, 116.0, 116.5, 117.1, 127.3, 128.5, 128.8, 128.9, 129.2, 129.6, 132.3, 132.4, 134.4, 137.0, 138.9, 155.9, 156.4, 166.3, 169.2 (4C=$\underline{C}$–O), 171.1, 173.4 (2N$\underline{C}$=O), 197.4, 197.7 (2$\underline{C}$=O); EI-MS: *m/z* (%): 419 (1, $M^+ + 2$), 418 (7, $M^+ + 1$), 417 (19, M^+), 326 (48), 131 (84), 103 (73), 69 (100). Anal. Calcd for $C_{26}H_{27}NO_4$ (417.19): C, 74.80; H, 6.52; N, 3.35 %. Found: C 74.87, H 6.55, N 3.31 %. R_f (25 % EtOAc/hexane) 0.49.

2,4,8-Trimethyl-6-phenyl-6,6a,8,12b-tetrahydro-1H-pyrimido[5′,4′:5,6]pyrano[3,4-c]quinoline-1,3,7(2H,4H)-trione ***(9a, 10a)*** White solid, mp: 268–270 °C, yield: 0.382 g (95 %). IR (KBr) (ν_{max}, cm^{-1}): 2930, 1708, 1674, 1630, 1478, 1446, 1185, 760, 695; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta_H = 3.08$ (dd, $J = 13.7$, 10.6 Hz, 1H, H_{6a}^{10a}), 3.12 (dd, $J = 9.7$, 4.5 Hz, 1H, H_{6a}^{9a}), 3.28, 3.30, 3.31, 3.42, 3.44, 3.44 (6 s,18H, 6N$\underline{Me}^{9a,10a}$), 4.20 (d, $J = 13.7$ Hz, 1H, H_{12b}^{10a}), 4.50 (d, $J = 4.5$ Hz, 1H, H_{12b} ^{9a}), 5.21 (d, $J = 9.7$ Hz, 1H, H_6^{9a}), 5.24 (d, $J = 10.6$ Hz, 1H, H_6^{10a}), 7.02–7.46 (m, 18H, $18Ar^{9a,10a}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 28.6$, 28.7, 29.3, 29.4 ($4NCH_3$), 30.3, 30.5 (2$\underline{C}$H), 31.6, 34.3 (2N$\underline{C}H_3$), 47.6, 53.9 (2$\underline{C}$H), 78.9, 82.0 (2O–$\underline{C}$H), 86.8, 87.1 (2C=$\underline{C}$–C=O), 115.6, 116.2, 123.9, 124.4, 125.3, 127.1, 127.1, 127.9, 128.5, 128.7, 128.8, 129.2, 129.7, 129.9, 130.0, 136.0, 137.6, 138.5, 140.6, 141.4, 151.2, 151.3 (2MeN$\underline{C}$=ONMe), 156.7, 158.5 (2C=$\underline{C}$–O), 162.8, 163.3, 166.0, 168.8 (4NC=O); EI-MS: *m/z* (%): 404 (2, $M^+ + 1$), 403 (8, M^+), 284 (46), 131 (60), 103 (73), 97 (66), 83 (75), 69 (84), 57 (100). Anal. Calcd for $C_{23}H_{21}N_3O_4$ (403.15):

C 68.47, H 5.25, N 10.42 %. Found: C 68.42, H 5.31, N 10.47 %. R_f (25 % EtOAc/hexane) 0.47.

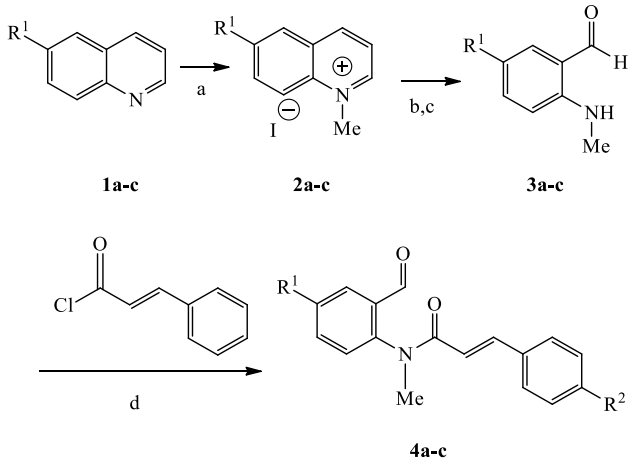
*2,4,8,11-Tetramethyl-6-phenyl-6,6a,8,12b-tetrahydro-1H-pyrimido[5′,4′:5,6]pyrano[3,4-c]quinoline-1,3,7(2H,4H)-trione (**9b, 10b**)* White solid, mp: 268–270 °C, yield: 0.391 g (94 %). IR (KBr) (ν_{max}, cm^{-1}): 2931, 1708, 1674, 1630, 1478, 1446, 1185, 760, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) $\delta_H = 2.32$ (2 s, 6H, 2C$\underline{Me}^{9b,10b}$), 3.26, 3.29, 3.35, 3.45 (6 s, 18H, 6N$\underline{Me}^{9b,10b}$), 3.04–3.11 (m, 2H, $H_{6a}{}^{9b,10b}$), 4.17 (d, $J = 13.6$ Hz,1H, H_{12b}^{10b}), 4.49 (broad s,1H, H_{12b}^{9b}), 5.18 (d, $J = 8.49$ Hz, 1H, H_6^{9b}), 5.23 (d, $J = 10.63$ Hz, 1H, H_6^{10b}), 6.84–7.44 (m, 16H, $Ar^{9b,10b}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 21.3$, 21.5 (2$\underline{C}H_3$), 28.6, 28.7, 29.2, 29.4 (4N$\underline{C}H_3$), 30.3, 30.5 (2$\underline{C}$H), 31.6, 34.3 (2N$\underline{C}H_3$), 47.4, 47.8 (2$\underline{C}$H), 78.9, 82.0 (2O–$\underline{C}$H), 86.9, 87.3 (2C=$\underline{C}$–C=O), 115.6, 116.2, 125.9, 127.0, 127.1, 128.3, 128.5, 128.8, 129.1, 129.7, 129.9, 130.0, 130.5, 133.4, 134.0, 135.9, 136.2, 137.6, 138.2, 151.4, 151.4 (2MeN$\underline{C}$(O)NMe), 156.7, 158.4 (2C=$\underline{C}$–O), 162.8, 163.3, 165.8, 168.7 (4NC=O); EI-MS: *m/z* (%): 419 (1, $M^+ + 2$), 418 (8, $M^+ + 1$), 417 (30, M^+), 131 (91), 189 (84), 103 (100), 77 (64). Anal. Calcd for $C_{24}H_{23}N_3O_4$ (417.17): C 69.05, H 5.55, N 10.07 %. Found: C 68.46, H 5.23, N 10.40 %. R_f (25 % EtOAc/hexane) 0.46.

*11-Methoxy-2,4,8-trimethyl-6-phenyl-6,6a,8,12b-tetrahydro-1H-pyrimido[5′,4′:5,6]pyrano[3,4-c]quinoline-1,3,7(2H,4H)-trione (**9c, 10c**)* White solid, mp: 268–270 °C, yield: 0.424 g (98 %). IR (KBr) (ν_{max}, cm^{-1}): 2941, 1700, 1671, 1630, 1496, 1460, 1038, 757, 696; ^1H NMR (500 MHz, $CDCl_3$) $\delta_H = 3.07$ (dd, $J = 13.6$, 10.7 Hz, 1H, H_{6a}^{10c}), 3.12 (dd, $J = 10.2$, 4.7 Hz, 1H, H_{6a}^{9c}), 3.27 (s, 3H, N$\underline{Me}^{10c}$), 3.30 (s, 3H, N$\underline{Me}^{9c}$), 3.31 (s, 3H, N$\underline{Me}^{10c}$), 3.35, 3.44 (2 s, 6H, 2N$\underline{Me}^{9c}$), 3.45 (3H, s, N$\underline{Me}^{10c}$), 3.77 (s, 3H, O$\underline{Me}^{10c}$), 3.78 (3H, s, O$\underline{Me}^{9c}$), 4.18 (d, $J = 13.6$ Hz, 1H, H_{12b}^{10c}), 4.49 (d, $J = 4.7$ Hz, 1H, H_{12b}^{9c}), 5.16 (d, $J = 9.8$ Hz, 1H, H_6^{9c}), 5.24 (d, $J = 10.7$ Hz, 1H, H_6^{10c}), 6.84–7.44 (m, 16H, $Ar^{9c,10c}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 28.6$, 28.7, 29.2, 29.4 (4N$\underline{C}H_3$), 30.4, 30.6 (2$\underline{C}$H), 32.0, 34.4 (2N$\underline{C}H_3$), 47.6, 53.8 (2$\underline{C}$H), 55.9, 56.0 (2O$\underline{C}H_3$), 79.0, 82.1 (2O-$\underline{C}$H), 86.8, 87.1 (2C=$\underline{C}$–C=O), 111.8, 112.5, 116.5, 116.9, 117.1, 127.2, 128.5, 128.8, 129.1, 129.7, 130.0, 131.6, 132.2, 134.1, 135.8, 137.6, 151.3, 151.4 (2MeN$\underline{C}$=ONMe), 156.2, 156.5 (2CH_3O-$\underline{C}$=C), 158.5, 162.8 (2C=$\underline{C}$–O), 163.3, 165.4, 167.0, 168.4 (4N$\underline{C}$=O); EI-MS: *m/z* (%): 435 (3, $M^+ + 2$), 434 (21, $M^+ + 1$), 433 (79, M^+), 303 (50), 189 (84), 131 (100), 103 (49). Anal. Calcd for $C_{24}H_{23}N_3O_5$ (433.16): C 66.50, H 5.35, N 9.69 %. Found: C 66.43, H 5.38, N 9.57 %. R_f (25 % EtOAc/hexane) 0.47.

*5-Methyl-7-phenyl-6a,7-dihydroindeno[2′,1′:5,6]pyrano[3,4-c]quinoline-6,13(5H,13bH)-dione(**12, 13**)* *5-Methyl-7-phenyl-6a,7-dihydroindeno[2′,1′:5,6]pyrano[3,4-c]quinoline-6,13(5H,13bH)-dione(**12, 13**)* Brown solid, mp: 239–241 °C, yield: 0.349 g (89 %); IR (KBr) (ν_{max}, cm^{-1}): 1670, 1626, 1589, 750, 700; ^1H NMR (500 MHz, $CDCl_3$) $\delta_H = 3.16$ (dd, $J = 13.2$, 10.6 Hz, 1H, H_{6a}^{13}), 3.26 (dd, $J = 10.5$, 7.9 Hz, 1H, H_{6a}^{12}), 3.31 (s, 3H, N$\underline{Me}^{12}$), 3.36 (s, 3H, N$\underline{Me}^{13}$), 4.14 (d, $J = 13.2$ Hz, 1H, H_{13b}^{13}), 4.24 (d, $J = 7.9$ Hz, 1H, H_{13b}^{12}), 5.30 (d, $J = 10.5$ Hz, 1H, H_7^{12}), 5.44 (d, $J = 10.6$ Hz, 1H, H_7^{13}), 7.01–7.63 (m, 26H, $Ar^{12,13}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 26.0$, 31.8 (2$\underline{C}$H), 36.1, 37.6 (2N$\underline{C}H_3$), 55.6, 57.6 (2$\underline{C}$H), 76.5, 79.3 (2O-$\underline{C}$H), 103.5, 104.1, 106.1, 107.0, 108.0, 109.2, 111.9, 114.1, 114.7, 118.8, 119.1, 119.5, 121.2, 121.6, 122.0, 124.9, 125.0, 126.1, 126.2, 126.4, 126.5, 127.1, 128.3, 129.2, 129.3, 129.6, 130.0, 130.9, 131.1, 132.5, 134.9, 136.0, 136.2, 137.2, 155.0, 156.0 (2C=$\underline{C}$–O), 162.6, 177.9 (2N$\underline{C}$=O), 189.5, 190.4 (2$\underline{C}$=O); EI-MS: *m/z* (%): 395 (1, $M^+ + 2$), 394 (3, $M^+ + 1$), 393 (12, M^+), 159 (100), 131 (58), 103 (36), 77 (21). Anal. Calcd for $C_{26}H_{19}NO_3$ (393.14): C, 79.37; H, 4.87; N, 3.56 %. Found: C 79.40, H 4.85, N 3.57 %. R_f (25 % EtOAc/hexane) 0.57.

*2-Methyl-14-phenyl-14,14a-dihydrochromeno[3′,4′:5,6]pyrano[3,4-c]quinoline-1,7(2H,6bH)-dione (**15a**)* Withe solid, mp: 263–265 °C, yield: 0.343 g (85 %). IR (KBr) (ν_{max}, cm^{-1}): 3412, 2923, 1794, 1702, 1681, 1621, 766; ^1H NMR (300 MHz, $CDCl_3$) $\delta_H = 3.23$ (dd, $J = 13.6$, 10.6 Hz, 1H, H_{14a}), 3.32 (s,3H, N$\underline{Me}$), 4.33 (d, $J = 13.6$ Hz, 1H, H_{6b}), 5.31 (d, $J = 10.6$ Hz, 1H, H_{14}), 7.05–7.73 (m, 13H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta_C = 29.9$ ($\underline{C}$H), 34.2 (N$\underline{C}H_3$), 47.4 ($\underline{C}$H), 79.9 (O-$\underline{C}$H), 100.2, 115.4 (2C), 115.9, 116.5 (2CH), 123.2 (C), 123.5, 124.0, 124.6, 127.7, 128.2, 128.3, 128.6, 128.7 (9CH), 128.9 (C), 129.0, 132.4 (2CH), 137.9, 140.3 (2C), 152.8, 161.9 (2C=$\underline{C}$–O), 163.0 (O$\underline{C}$=O), 168.5 (N$\underline{C}$=O); EI-MS: *m/z* (%): 411 (4, $M^+ + 2$), 410 (23, $M^+ + 1$), 409 (83, M^+), 392 (40), 318 (88), 131 (100), 103 (68), 77 (37). Anal. Calcd for $C_{26}H_{19}NO_4$ (409.13): C, 76.27; H, 4.68; N, 3.42 %. Found: C 76.24, H 4.61, N 3.45 %. R_f (25 % EtOAc/hexane) 0.53.

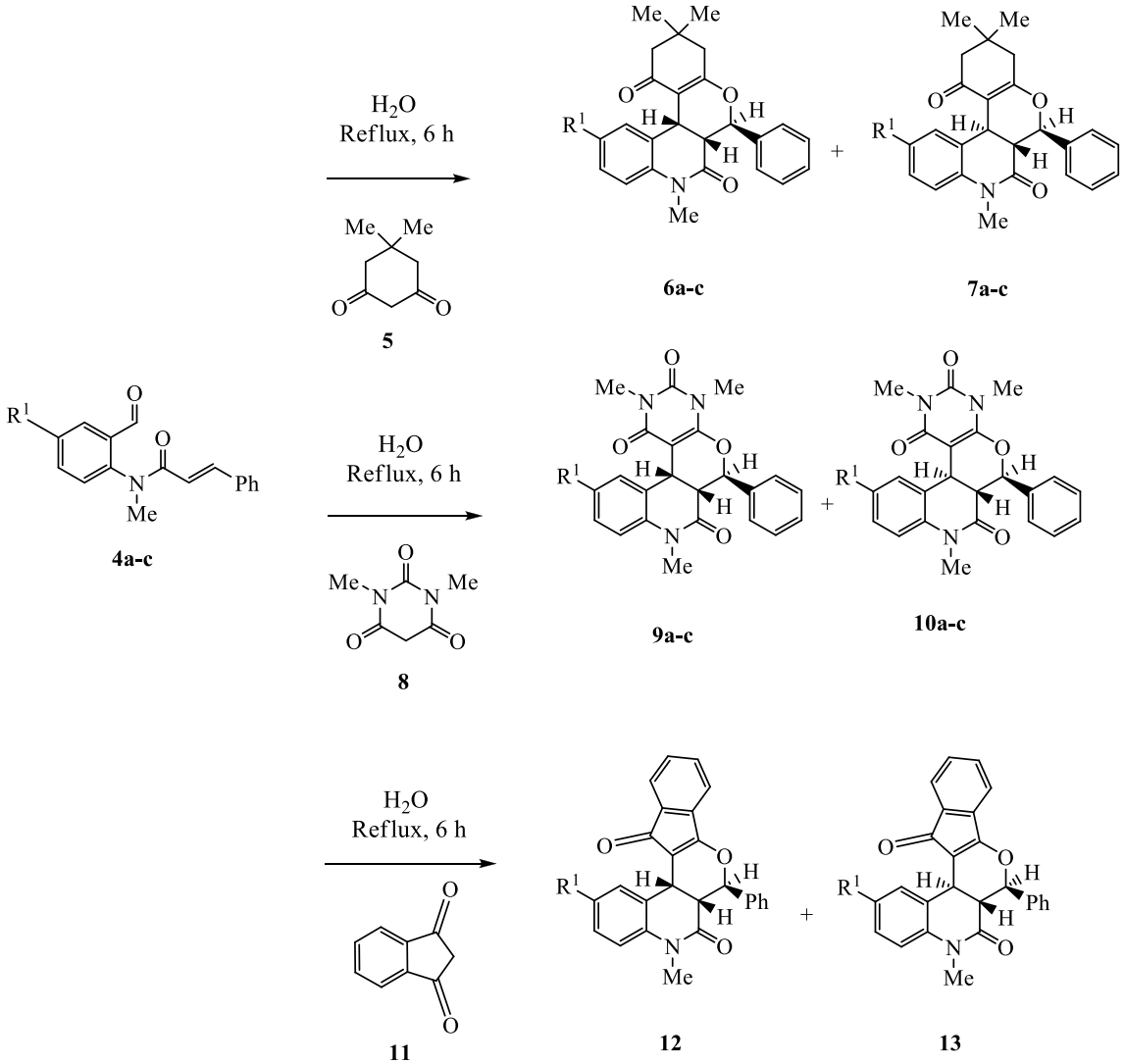
*11-(Tert-butyl)-2-methyl-14-phenyl-14,14a-dihydrochromeno[3′,4′:5,6]pyrano[3,4-c]quinoline-1,7(2H,6bH)-dione(**15b**)* White solid, mp: 289–291 °C, yield: 0.446 g (96 %). IR (KBr) (ν_{max}, cm^{-1}): 1718, 1677, 1620, 985, 750; ^1H NMR (500 MHz, $CDCl_3$) $\delta_H = 1.31$ (s, 9H, C$\underline{Me}$3), 3.22 (dd, $J = 13.6$ Hz, 1H, 10.3, H_{14a}), 3.33 (s, 3H, N$\underline{Me}$), 4.33 (d, $J = 13.6$ Hz, 1H, H_{6b}), 5.31 (d, $J = 10.3$ Hz, 1H, H_{14}), 7.06–7.68 (m, 12H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta_C = 30.4$ ($\underline{C}$H), 31.7



Scheme 1 Synthesis of compounds **4a**–**c**

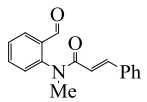
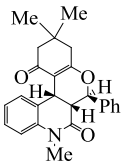
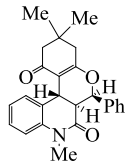
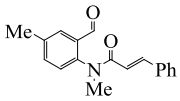
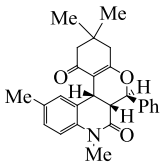
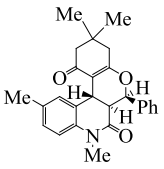
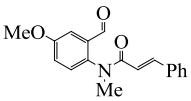
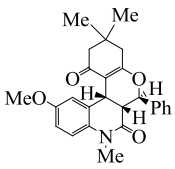
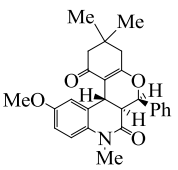
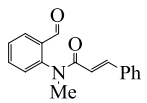
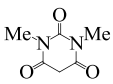
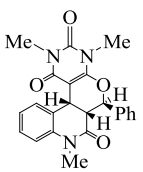
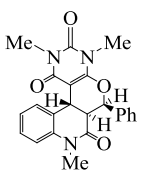
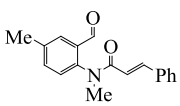
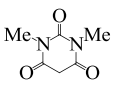
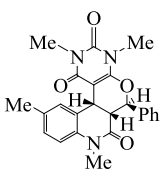
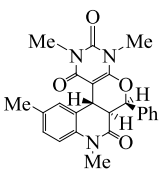
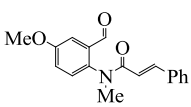
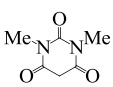
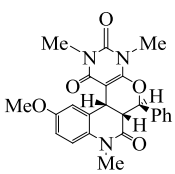
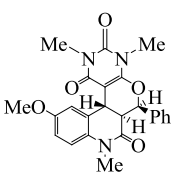
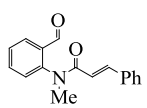
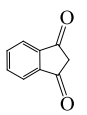
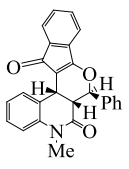
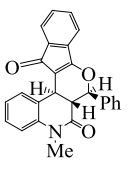
(C(CH$_3$)$_3$), 34.7 (C(CH$_3$)$_3$), 35.1 (NCH$_3$), 48.0 (CH), 80.3 (O-CH), 100.4, 115.2 (2C), 116.4, 116.7, 119.5, 123.9, 125.0, 128.1, 128.7, 128.8 (8CH), 129.2 (C), 129.4, 130.5 (2CH), 138.44, 140.7 (2C), 147.8 (C-t-Bu), 151.3, 162.6 (2C=C–O), 163.8 (OC=O), 169.1 (NC=O); EI-MS: *m/z* (%): 467 (2, $M^+ + 2$), 466 (6, $M^+ + 1$), 465 (18, M^+), 374 (17), 131 (100), 103 (74), 77 (52). Anal. Calcd for $C_{30}H_{27}NO_4$ (465.19): C, 77.40; H, 5.85; N, 3.01 %. Found: C 77.41, H 5.83, N 2.99 %. R_f (25 % EtOAc/hexane) 0.51.

*11-Chloro-2,10-dimethyl-14-phenyl-14,14a-dihydrochromeno[3′,4′:5,6]pyrano[3,4-c]quinoline-1,7(2H,6bH)-dione(**15c**)* Yellow solid, mp: 283–285 °C, yield: 0.438 g (96 %). IR (KBr) (ν_{max}, cm^{-1}): 1726, 1664, 1619, 756, 699; ^{1}H NMR (500 MHz, CDCl$_3$) $\delta_H = 2.49$ (s, 3H, CMe), 3.23 (dd, $J = 13.6$, 10.6 Hz, 1H,



Scheme 2 Synthesis of dihydroquinolinones **6a–c/7a–c/9a–c/10a–c** and **12/13**

Table 1 Results obtained for the preparation of **6a–c/7a–c**, **9a–c/10a–c** and **12/13** in H_2O

Entry	Reactants		Yeild (%)	Isomeric ratio (%)	
1	 **4a**	 **5**	95	 **6a** (48)	 **7a** (52)
2	 **4b**	 **5**	92	 **6b** (59)	 **7b** (41)
3	 **4c**	 **5**	98	 **6c** (56)	 **7c** (44)
4	 **4a**	 **8**	95	 **9a** (53)	 **10a** (47)
5	 **4b**	 **8**	94	 **9b** (70)	 **10b** (30)
6	 **4c**	 **8**	98	 **9c** (33)	 **10c** (68)
7	 **4a**	 **11**	89	 **12** (37)	 **13** (63)

H_{14a}), 3.33 (s, 3H, NMe), 4.31 (d, J = 13.6 Hz, 1H, H_{6b}), 5.31 (d, J = 10.6 Hz, 1H, H_{14}), 7.07–7.69 (m, 11H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 21.1 (CH_3), 30.4 (CH), 34.6 (NCH_3), 47.7 (CH), 80.5 (O-CH), 100.6, 114.8 (2C), 116.4, 118.9, 123.3, 123.9, 125.0, 128.2, 128.7, 128.8, 128.9 (9CH), 129.6, 130.7, 138.2, 140.7, 141.9 (5C), 151.5, 162.1 (2C=C–O), 162.6 (OC=O), 168.9 (NC=O); EI-MS: *m/z* (%): 459 (3, M^+ + 2), 458 (2, M^+ + 1), 457 (8, M^+), 374(23), 131 (100), 103 (69), 77 (46). Anal. Calcd for $C_{27}H_{20}ClNO_4$ (457.11): C, 70.82; H, 4.40; N, 3.06 %. Found: C 70.84, H 4.39, N 3.05 %. R_f (25 % EtOAc/hexane) 0.51.

*2,5-Dimethyl-14-phenyl-14,14a-dihydrochromeno[3′,4′:5,6]pyrano[3,4-c]quinoline-1,7(2H,6bH)-dione(**15d**)* Withe solid, mp: 321–322 °C, yield: 0.393 g (93 %). IR (KBr) (ν_{max}, cm^{-1}): 3039, 2916, 1794, 1702, 1671, 1610, 763; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 2.32 (s, 3H, CMe), 3.20 (dd, J = 13.6, 10.6 Hz, 1H, H_{14a}), 3.29 (s, 3H, NMe), 4.29 (d, J = 13.6 Hz, 1H, H_{6b}), 5.28 (d, J = 10.6 Hz, 1H, H_{14}), 6.93–7.75 (m, 12H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 21.5 (CH_3), 30.3 (CH), 34.7 (NCH_3), 48.0 (CH), 80.3 (O-CH), 100.8, 115.9 (2C) 116.2, 116.3, 123.6, 124.5, 125.6, 128.5, 128.7, 128.8 (8CH), 129.0 (C), 129.5, 132.8 (2CH), 133.6, 138.4, 138.5 (3C), 153.2, 162.4 (2C=C–O), 163.4 (OC=O), 168.9 (NC=O); EI-MS: *m/z* (%): 425 (4, M^+ + 2), 424 (23, M^+ + 1), 423 (83, M^+), 391 (38), 317 (85), 131 (100), 103 (66), 77 (35). Anal. Calcd for $C_{26}H_{19}NO_4$ (423.15): C, 73.79; H, 4.82; N, 3.19 %. Found: C 73.74, H 4.79, N 3.21 %. R_f (25 % EtOAc/hexane) 0.53.

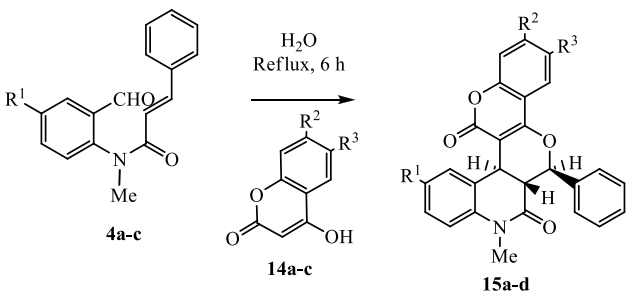
*3,8-Dimethyl-6-phenyl-6,6a-dihydropyrano[3′,4′:5,6]pyrano[3,4-c]quinoline-1,7(8H,12bH)-dione(**17a, 18a**)* Yellow solid, mp: 251–253 °C, yield: 0.343 g (92 %). IR (KBr) (ν_{max}, cm^{-1}): 3414, 3167, 2361, 1713, 1608, 1641, 759; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 2.27 (s, 3H, CMe^{17a}), 2.27 (s, 3H, CMe^{18a}), 3.14 (dd, J = 13.5, 10.5 Hz, 2H, $H_{6a}^{17a,18a}$), 3.28 (s, 3H, NMe^{17a}), 3.31 (s, 3H, NMe^{18a}), 4.15 (d, J = 13.6 Hz, 1H, H_{12b}^{17a}), 4.29 (d, J = 13.5 Hz, 1H, H_{12b}^{18a}), 5.14 (d, J = 10.5 Hz, 1H, H_6^{17a}), 5.33 (d, J = 10.5 Hz, 1H, H_6^{18a}), 5.87 (s, 1H, $C=CH^{17a}$), 6.19 (s, 1H, $C=CH^{18a}$), 7.05 (dd, J = 7.7, 7.5 Hz, 2H, $Ar^{17a,18a}$), 7.12 (d, J = 7.6 Hz, 2H, $Ar^{17a,18a}$), 7.22 (d, J = 7.5 Hz, 2H, $Ar^{17a,18a}$), 7.30 (dd, J = 8.1, 7.5 Hz, 2H, $Ar^{17a,18a}$), 7.39–7.51 (m,10H, $Ar^{17a,18a}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 19.1, 19.8 ($2CH_3$), 29.8, 30.5 (2CH), 33.5, 33.7 ($2NCH_3$), 47.0, 47.3 (2CH), 79.4, 81.6 (2O-CH), 97.6, 98.6, 100.5, 112.9, 114.1, 115.2, 115.8, 123.4, 124.7, 125.2, 126.9, 127.6, 128.0, 128.3, 128.4, 128.5, 128.7, 129.2, 129.7, 137.0, 138.0, 140.3, 161.1, 161.8, 163.7, 165.0 (4C=C–O), 167.6, 168.3 (2OC=O), 168.6, 179.9 (2NC=O); EI-MS: *m/z* (%): 375 (2, M^+ + 2), 374 (17, M^+ + 1), 373 (64, M^+), 131 (100), 103 (77), 77 (59), 43 (36). Anal. Calcd for $C_{23}H_{19}NO_4$ (373.13): C, 73.98; H, 5.13; N, 3.75 %. Found: C 73.95, H 5.14, N 3.71 %. R_f (25 % EtOAc/hexane) 0.45.

*3,8,11-Trimethyl-6-phenyl-6,6a-dihydropyrano[3′,4′:5,6]pyrano[3,4-c]quinoline-1,7(8H,12bH)-dione (**17b**)* Withe solid, mp: 266–267 °C, yield: 0.371 g (96 %); IR (KBr) (ν_{max}, cm^{-1}): 3034, 2921, 1704, 1678, 1559, 812, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 2.28 (s, 3H, CMe), 2.34 (3H, s, CMe), 3.09 (dd, J = 13.6, 10.6 Hz, 1H, H_{6a}), 3.25 (s, 3H, NMe), 4.12 (d, J = 13.6 Hz, 1H, H_{12b}), 5.12 (d, J = 10.6 Hz, 1H, H_6), 5.88 (s,1H, C=CH), 6.09–7.04 (m, 8H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 20.3, 21.5 ($2CH_3$), 30.3 (CH), 34.0 (NCH_3), 47.7 (CH), 79.9 (O-CH), 98.1 (C), 101.0 (C=CH), 116.2, 125.7, 128.4, 128.5, 128.8 (5CH), 128.9 (C), 129.4 (CH), 133.5, 138.3, 138.5 (3C), 162.2, 164.2 (2C=C–O), 168.1 (OC=O), 169.0 (NC=O); EI-MS: *m/z* (%): 389 (2, M^+ + 2), 388 (17, M^+ + 1), 387 (64, M^+), 145 (100), 117 (72), 77 (62), 43 (31). Anal. Calcd for $C_{23}H_{19}NO_4$ (387.15): C, 74.40; H, 5.46; N, 3.62 %. Found: C 74.45, H 5.46, N 3.61 %. R_f (25 % EtOAc/hexane) 0.45.

Results and discussion

Initially, *N*-methyl-2-aminobenzaldehydes (**3a**–**c**) were prepared on the basis of the reported method starting from quinolines **1a**–**c** in three steps (Scheme 1) [63]. Subsequent treatment of (*E*)-cinnamoyl chloride with **3a**–**c** in the presence of pyridine in CH_2Cl_2 for 48 h afforded **4a**–**c** in 43–61 % [64]. The structures of **4a**–**c** were identical with those of the authentic samples.

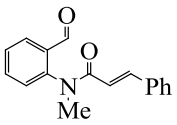
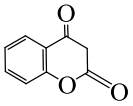
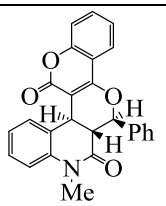
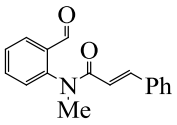
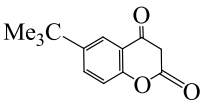
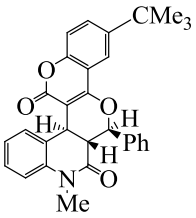
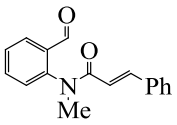
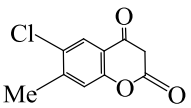
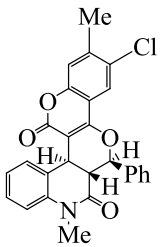
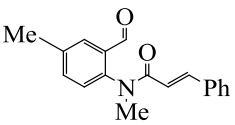
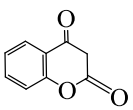
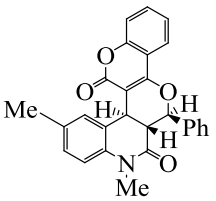
Compounds **4a**–**c** were then treated with dimedone **5**, *N*,*N*-dimethylbarbituric acid (**8**), 1,3-indanedione (**11**), 4-hydroxycoumarins (**14a**–**c**) and



Scheme 3 Synthesis of dihydroquinolinones **15a**–**d**

4-hydroxy-6-methyl-2*H*-pyran-2-one **(16)** in H_2O. The reaction proceeded smoothly at reflux and was complete within 6 h as indicated by TLC. The mixture was cooled to room temperature, and the organics were extracted using CH_2Cl_2. Evaporation of the solvent under reduced pressure followed by recrystallization from dichloromethane-ethyl acetate-hexane mixture afforded the desired 3,3,8-trimethyl-6-phenyl-3,4,6,6a,8,12b-hexahydro-1*H*-chromeno[3,4-c]quinoline-1,7(2*H*)-diones (**6a–c/7a–c**), 2,4,8-trimethyl-6-phenyl-6,6a,8,12b-tetrahydro-1*H*-pyrimido[5′,4′:5,6]-

Table 2 Results obtained for the preparation of **15a–d** in H_2O

Entry	Aldehyde	1,3-dicarbonyl	Product (%)
1	 **4a**	 **14a**	 **15a (85)**
2	 **4a**	 **14b**	 **15b (96)**
3	 **4a**	 **14c**	 **15c (96)**
4	 **4b**	 **14a**	 **15d (93)**

pyrano[3,4-c]quinoline-1,3,7(2*H*,4*H*)-triones (**9a–c/10a–c**), 5-methyl-7-phenyl-6a,7-dihydroindeno[2′,1′:5,6]pyrano[3,4-*c*]quinoline-6,13(5*H*,13b*H*)-diones (**12/13**) (Scheme 2; Table 1), 2-methyl-14-phenyl-14,14a-dihydrochromeno[3′,4′:5,6]pyrano[3,4-c]quinoline-1,7(2*H*,6b*H*)-diones (**15a–d**) (Scheme 3; Table 2), and 3,8-dimethyl-6-phenyl-6,6a-dihydropyrano[3′,4′:5,6]pyrano[3,4-*c*]quinoline-1,7(8*H*,12b*H*)-diones (**17a–b/18a**) (Scheme 4) [65]. The structure of products were deduced by elemental analysis, MS, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Unambiguous evidence for the proposed structures of **7c** and **10c** [66] was finally obtained by single-crystal X-ray diffraction analysis (Figs. 2, 3).

The stereochemical outcome of the cycloaddition is dependent on the geometries of the diene as well as the dienophile. For example, while the *trans* stereochemistry of the resultant pyran PhCH-CH bond emerges from the *trans* geometry of the dienophile, the stereochemistry of the pyran-fused CH–CH bond depends on the transition state structure of the cycloadditions. It seems justified that the *trans–trans* and *cis–trans* annulated products are expected to be formed via *exo*-transition state **I** and *endo*-transition state **II**, respectively (Scheme 5) [22]. The formation of both *trans–trans* and *cis–trans* annulated products in the case of dimedone **5**, *N*,*N*- dimethylbarbituric acid (**8**) and 1,3-indanedione (**11**) supports the implication of *exo*- and *endo*- transition states **I** and **II** in these processes. On the other hand, diastereoselective formation of **15a–d** and **17a–b** indicates that reactions in the case of coumarins **14a–c** and pyrone **16** have proceeded via *exo*-transition state **I**. The *trans* fusion of the ring junction in **7a–c**, **10a–c**, **13**, **15a–d** and **17a–b** was further confirmed by considering coupling constants which appeared as doublet and double of doublet as J = 13.6–13.8 Hz and J = 13.6–13.8, 10.3–10.6 Hz, respectively. Particularly significant is the participation of C=C–CO as well as C=C–CO–O moieties as heterodiene part in the formation of **17a–b**, processes which have been observed previously [58, 67].

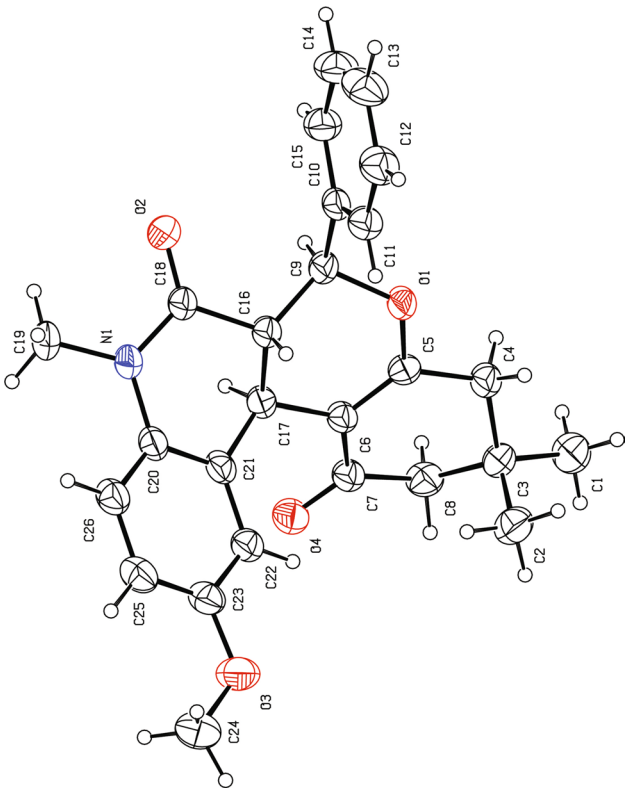


Fig. 2 X-ray crystal structure of compound **7c**

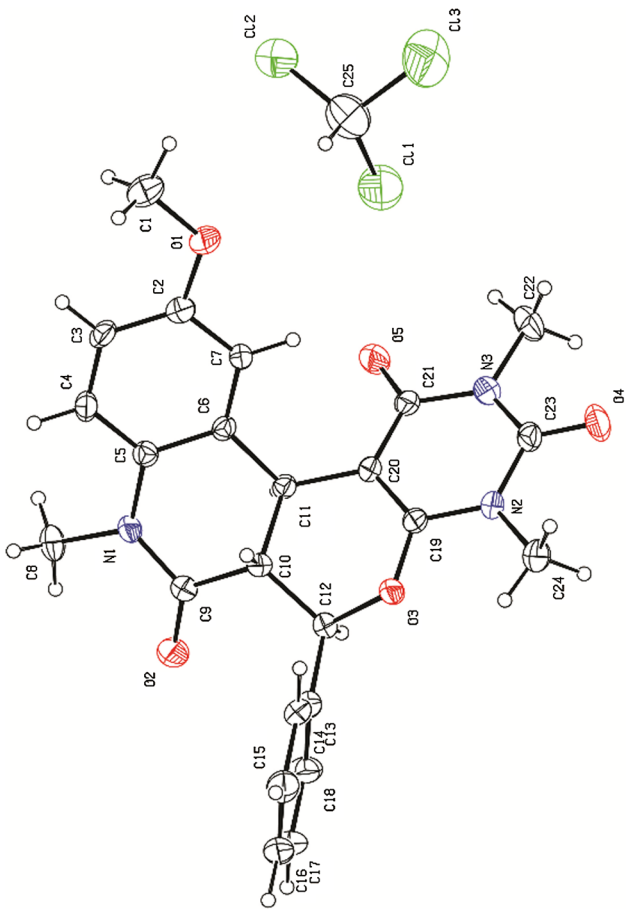
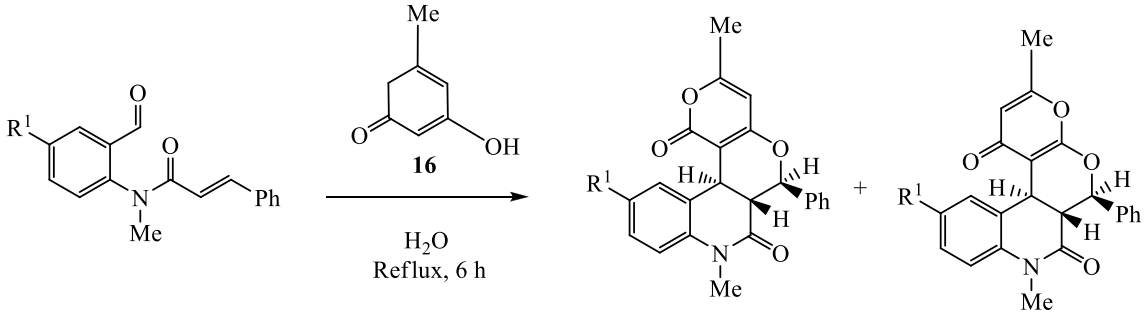
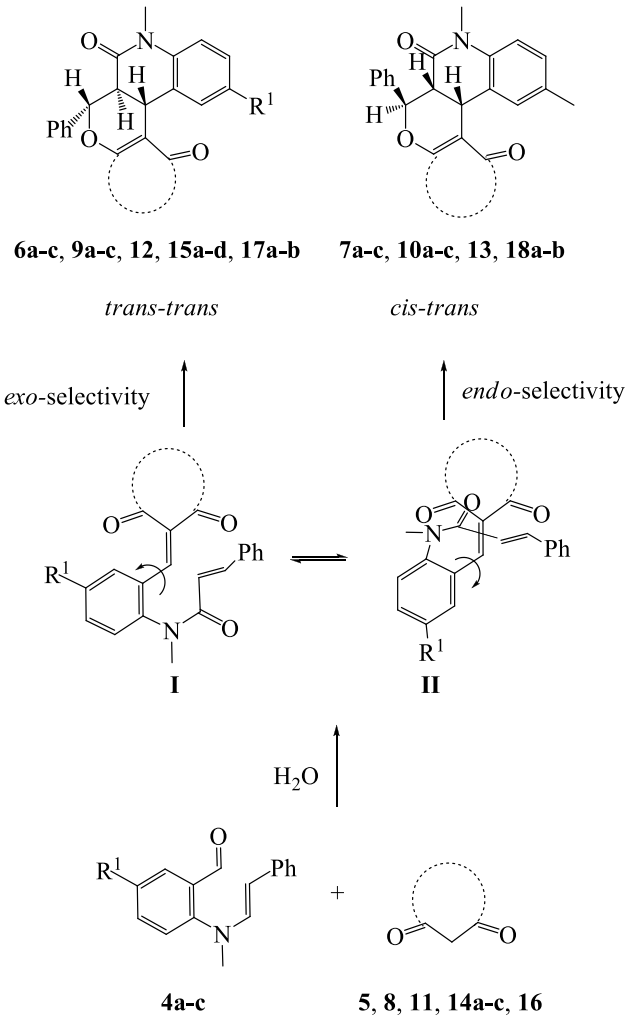


Fig. 3 X-ray crystal structure of compound **10c**



R^1	Yield (%)	Isomer ratio	
H (**4a**)	92	**17a** (64)	**18a** (36)
Me (**4b**)	96	**17b** (93)	**18b** (-)

Scheme 4 Results obtained for the formation of **17a–b/18a**



Scheme 5 Suggested mechanism for the formation of products

Conclusion

In conclusion, a number of synthesized bifunctional starting materials containing an aldehyde and an unsaturated amide groups underwent a one-pot catalyst-free domino Knöevenagel hetero-Diels–Alder reaction, respectively, with dimedone, *N*,*N*-dimethylbarbituric acid, 1,3-indanedione, 4-hydroxycoumarins and 4-hydroxy-6-methyl-2*H*-pyran-2-one in water, giving novel annulated hybrid derivatives of two known scaffolds, dihydroquinolinone and pyranopyranone, pyranopyrimidinedione, pyranocoumarin or chromenone in excellent yields. These new structures broaden the scaffolds that are accessible through domino hetero-Diels–Alder reactions, and many of them may represent interesting pharmacophores.

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