Research Article

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A one-pot, multicomponent tandem synthesis of fused polycyclic pyrrolo[3,2-*c*]quinolinone/pyrrolizino[2,3-*c*]quinolinone hybrid heterocycles via environmentally benign solid state melt reaction

https://doi.org/10.1515/gps-2023-0043
received March 07, 2023; accepted June 18, 2023

Abstract: Structurally diverse fused polycyclic pyrrolo[3,2-*c*]quinolinone/pyrrolizino[2,3-*c*]quinolinone hybrids were synthesized to get excellent yields via a tandem multi-component reaction sequence employing an environmentally benign solid state melt reaction involving [3+2]-cycloaddition process followed by two consecutive annulation steps. Baylis–Hillman products, used as dipolarophiles, were synthesized from various substituted aryl/heteroaryl aldehydes in the presence of DABCO and methyl acrylate, while the 1,3-dipole component was derived *in situ* from indoline-2,3-dione and acyclic/cyclic amino acid *viz N*-methylglycine/L-proline. The structure of the unusual tandem products was unambiguously assigned by spectroscopic and XRD analysis. The products arose through the formation of three new rings, five new bonds, and three adjoining stereocenters with complete diastereomeric control.

Keywords: tandem multicomponent reaction, eco-friendly protocol, solid state melt reaction, pyrrolo[3,2-*c*]quinolinone/pyrrolizino[2,3-*c*]quinolinone

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1 Introduction

Expedient one-pot assembly of structurally interesting polycyclic ring systems with multiple stereogenic centers from available simple starting precursors is of great value in pharmaceutical companies [1] even in place of diversity-oriented and combinatorial synthesis [2,3]. One such methodology to achieve these goals involves the use of tandem multicomponent sequence [4], that allow the generation of multiple bonds in a one-pot synthetic transformation with noteworthy advantages such as high reaction efficacy, cost saving, convergence, elegance, facile automation, and reduction in the number of work-ups. This protocol obviates a number of isolation and purification steps resulting in enhancement of overall yield relative to classical multi-step synthetic transformations. Due to the advantages mentioned above, this protocol is environmentally friendly and excellently suited for the creation of structurally intriguing heterocycles tethering several adjoining stereocenters as well as for the synthesis of biologically attractive natural and synthetic products [5].

Three component cycloaddition reaction of 1,3-dipole with activated double bond of a dipolarophile offers a versatile methodology to construct regio and stereoselective pyrrolidine heterocycles [6–8]. The preparation of the pyrrolidine structural moiety is of particular interest due to the presence of this ring system in many bioactive natural and synthetic products and it exhibits attractive structural features and diverse bioactivity profiles rendering them as propitious synthetic targets. In addition, the pyrrolidine unit aid as very useful molecular architectures for probing the pharmacophore space using diversity-oriented synthesis which in turn leads to the development of new drug candidate [9–11].

Polycyclic compounds that comprise a pyrrolidine unit *viz* pyrroloquinoline is an important class of structural component as these analogs appear as an integral part in many natural products including melodinus alkaloids, (+) scandine, (+) meloscine (pentacyclic) [12,13] (Figure 1) which are prescribed as Chinese medicine to treat rheumatic heart disease in children. Molecules possessing the 3*H*-pyrrolo[2,3-*c*]quinoline unit such as marinoquinolines A–F and aplidiopsamine A displayed potent antimalarial activity with less toxicity to human cells [14]. Tricyclic angular heterocycle with pyrrolo[3,2-*c*]quinoline moiety showed promising biological activity [15]. For instance, antitumor properties, gastric (H+/K+)-ATPase inhibitor, aggrecanase inhibitors [16], hypotensive, anti-inflammatory activities [18–20], and significant photochemotherapeutic activity [17].

Our research team has been mainly engaged in the synthesis of bridged pyrrolidine hybrids via multi-component cycloaddition and tandem reaction protocol [21], and studies on their biological intervention in recent years, which has brought to light various biological [22–25] lead compounds. Baylis–Hillman adducts (BHAs) are useful precursor for the production of diverse natural and synthetic analogs of biological importance. In this perspective, we recently reported that unusual pyrroloquinolinone fused polycyclic analogs were synthesized from Baylis–Hillman product by tandem multicomponent cascade protocol [26].

With the above remarkable biological precedents in mind, we have now explored the synthetic utility of Baylis–Hillman product as starting precursor in the construction of novel class of heterocyclic systems comprising the pyrrolo[3,2-*c*]quinolinone/pyrrolizino[2,3-*c*]quinolinone framework through sustainable green tandem protocol involving a decarboxylative [3+2]-dipolar cycloaddition followed by a double annulation via sequential lactonization and lactamization reactions. The synthetic strategy is described in Figure 2.

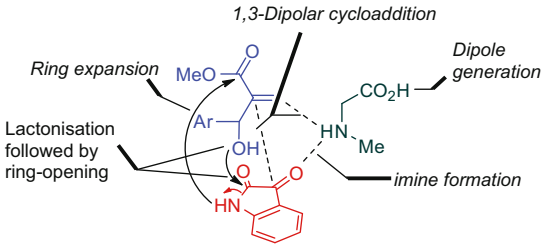


Figure 2: Synthetic strategy for the multicomponent domino protocol.

2 Experimental methods

2.1 General procedure for synthesis of aryl substituted polycyclic fused pyrrolidine derivatives, 10a–k

A mixture of BHA **3a** (1 mmol), isatin **7** (1.1 mmol) and sarcosine **8** (1.1 mmol) was placed in a round bottomed flask and melted at 180°C and kept until the reaction was completed, confirmed by TLC analysis. The crude product was recrystallized from ethyl acetate (EtOAc) and hexane to obtain the pure products **10a** as a solid.

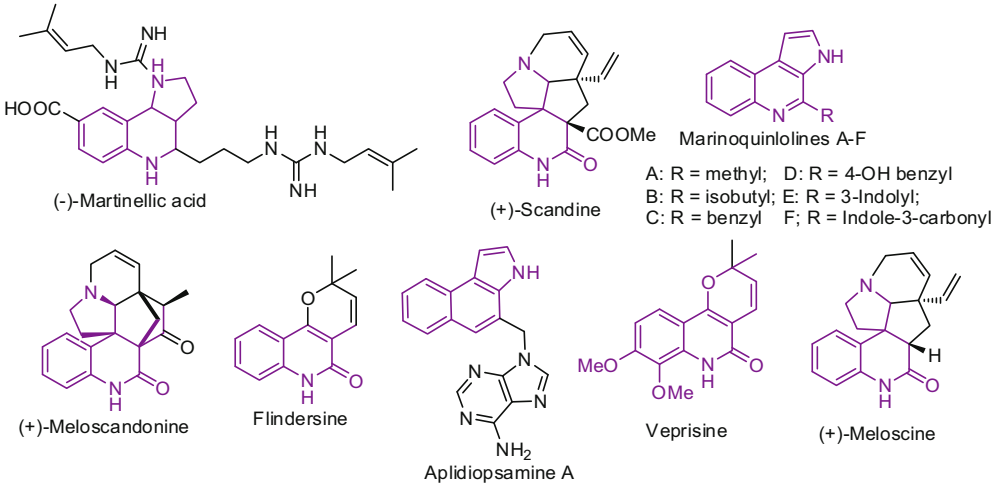


Figure 1: Biologically relevant pyrroloquinoline analogs.

2.1.1 1-Methyl-12-phenyl-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10a

IR (KBr): 1,709, 1,742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.05–2.14 (m, 1H), 2.41–2.52 (m, 1H), 2.62 (s, –NCH_3, 3H), 2.74 (q, J = 9.0, 17.7 Hz, 1H), 3.06–3.14 (m, 1H), 5.43 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.38–7.42 (m, 6H), 7.80 (d, J = 7.5 Hz, 1H), 9.78 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.7, 34.3, 52.4, 58.9, 73.1, 79.4, 114.6, 116.4, 123.8, 126.2, 128.3, 128.7, 129.9, 130.8, 134.1, 136.7, 169.9, 173.6 ppm. Mass: m/z 334 (M^+). Anal. calculated for $C_{20}H_{18}N_2O_3$: C, 71.94%, H, 5.43%, N, 8.38%; found: C, 71.99%, H, 5.50%, N, 8.35%.

2.1.2 1-Methyl-12-(2,3-dimethoxyphenyl)-1-methyl-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10b

IR (KBr): 1,715, 1,745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25–2.55 (m, 2H), 2.58 (s, –NCH_3, 3H), 2.76–2.84 (q, J = 9.0, 9.3 Hz, 1H), 3.05–3.12 (m, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 5.70 (s, 1H), 6.92–7.39 (m, 6H), 7.75 (d, J = 7.5 Hz, 1H), 9.73 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 25.9, 34.5, 52.6, 55.6, 59.1, 60.6, 73.7, 75.3, 113.2, 114.4, 116.7, 119.2, 123.3, 123.4, 126.9, 129.8, 130.6, 137.5, 146.7, 152.1, 169.2, 174.2 ppm. Mass: m/z 394 (M^+). Anal. calculated for $C_{22}H_{22}N_2O_5$: C, 66.99%, H, 5.62%, N, 7.10%; found: C, 67.02%, H, 5.66%, N, 7.15%.

2.1.3 1-Methyl-12-(3,4-dimethoxyphenyl)-1-methyl-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10e

IR (KBr): 1,715, 1,745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.04–2.16 (m, 1H), 2.47–2.57 (m, 1H), 2.61 (s, –NCH_3, 3H), 2.73 (q, J = 9.0, 17.7 Hz, 1H), 3.07–3.14 (m, 1H), 3.84 (s, 3H), 3.88 (s, 3H), 5.40 (s, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.94–7.03 (m, 3H), 7.21 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.79 (d, J = 7.5 Hz, 1H), 9.96 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.8, 34.3, 52.4, 55.8, 56.0, 59.1, 73.1, 79.2, 109.5, 110.8, 114.6, 116.4, 118.7, 123.8, 126.6, 129.9, 130.7, 136.7, 148.8, 149.2, 170.2, 173.6 ppm. Mass: m/z 394 (M^+). Anal. calculated for $C_{22}H_{22}N_2O_5$: C, 66.99%, H, 5.62%, N, 7.10%; found: C, 67.03%, H, 5.65%, N, 7.17%.

2.1.4 1-Methyl-12-(*m*-tolyl)-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10f

IR (KBr): 1,707, 1,751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.07–2.16 (m, 1H), 2.35 (s, –NCH_3, 3H), 2.42–2.52 (m, 1H), 2.61 (s, 3H), 2.73 (q, J = 9.0, 17.7 Hz, 1H), 3.06–3.14 (m, 1H), 5.39 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.15–7.28 (m, 5H), 7.41 (t, J = 6.9 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 9.74 (s, 1H, –*NH*). ^{13}C NMR (75 MHz, $CDCl_3$): 21.5, 26.7, 34.3, 52.4, 58.9, 73.1, 79.5, 114.6, 116.4, 123.4, 123.8, 126.7, 128.2, 129.5, 129.9, 130.7, 134.0, 136.7, 138.0, 169.9, 173.7 ppm. HRMS calculated for $C_{21}H_{20}N_2O_3$: 348.1547 and found 348.1543.

2.1.5 1-Methyl-12-(*p*-tolyl)-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10g

IR (KBr): 1,715, 1,748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.04–2.15 (m, 1H), 2.36 (s, –NCH_3, 3H), 2.40–2.51 (m, 1H), 2.61 (s, –CH_3, 3H), 2.74 (q, J = 8.7, 17.4 Hz, 1H), 3.06–3.13 (m, 1H), 5.40 (s, 1H), 6.99 (d, J = 7.8 Hz, 1H), 7.17–7.28 (m, 5H), 7.39 (t, J = 7.8 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 9.94 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 21.2, 26.7, 34.3, 52.4, 59.0, 73.1, 79.5, 114.6, 116.4, 123.8, 126.1, 129.0, 130.7. 131.0, 135.4, 136.7, 138.5, 169.8, 173.7 ppm. Mass: m/z 349 (M^+). Anal. calculated for $C_{21}H_{20}N_2O_3$: C, 68.30%, H, 4.97%, N, 7.97%; found: C, 68.37%, H, 4.90%, N, 8.03%.

2.1.6 1-Methyl-12-(2-nitrophenyl)-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10h

IR (KBr): 1,725, 1,748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.94–2.02 (m, 1H), 2.32–2.43 (m, 1H), 2.56 (s, –NCH_3, 3H), 2.75 (q, J = 9.3, 17.4 Hz, 1H), 3.03–3.11 (m, 1H), 6.74 (s, 1H), 6.98 (d, J = 9.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.59–7.69 (m, 2H), 7.83 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.5, 34.4, 52.5, 58.3, 73.4, 74.2, 114.1, 116.3, 123.7, 126.2, 128.3, 129.7, 129.8, 129.9, 130.9, 133.6, 136.9, 146.7, 168.5, 172.9 ppm. Mass: m/z: 380 (M^+). Anal. calculated for $C_{20}H_{17}N_3O_5$: C, 63.32%, H, 4.52%, N, 11.08%; found: C, 63.37%, H, 4.49%, N, 11.12%.

2.1.7 12-(2-Bromophenyl)-1-methyl-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10j

IR (KBr): 1,708, 1,744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.92–2.06 (m, 1H), 2.42–2.51 (m, 1H), 2.61 (s, –NCH_3, 3H), 2.66–2.74 (m, 1H), 3.06–3.14 (m, 1H), 5.37 (s, 1H), 6.98–7.79 (m, 8H), 9.65 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.8, 34.2, 52.3, 58.7, 73.0, 78.7, 114.5, 116.4, 122.9, 124.0, 126.1, 127.9, 129.9, 130.9, 131.5, 133.2, 136.6, 142.2, 169.7, 173.2 ppm. Mass: m/z 412 (M^+). Anal. calculated for $C_{20}H_{17}BrN_2O_3$: C, 58.13%, H, 4.15%, N, 6.78%; found: C, 58.17%, H, 4.10%, N, 6.82%.

2.1.8 1-Methyl-12-(3-fluorophenyl)-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 10k

IR (KBr): 1,710, 1,747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.03–2.09 (m, 1H), 2.45–2.55 (m, 1H), 2.61 (s, –NCH_3, 3H), 2.75 (q, J = 9.3, 17.7 Hz, 1H), 3.08–3.15 (m, 1H), 5.41 (s, 1H), 6.99–7.09 (m, 2H), 7.17–7.23 (m, 3H), 7.32–7.45 (m, 2H), 7.78–7.80 (d, J = 7.5 Hz, 1H), 9.33 (s, 1H, N–H). ^{13}C NMR (75 MHz, $CDCl_3$): 26.9, 34.2, 52.3, 58.7, 73.1, 73.1, 76.5, 78.6, 113.3, 113.6, 114.4, 114.5, 115.5, 115.8, 116.3, 121.8, 121.9, 123.9, 129.9, 130.0, 136.6, 136.7, 136.8, 161.0, 164.3, 169.4, 173.1 ppm. Mass: m/z 352 (M^+). Anal. calculated for $C_{20}H_{17}FN_2O_3$: C, 68.17%, H, 4.86%, N, 7.95%; found: C, 68.22%, H, 4.83%, N, 8.01%.

2.2 General procedure for synthesis of polycyclic fused quinlinopyrrolizidine derivatives, 22a–e

A mixture of BHA **3c** (1 mmol), isatin **7** (1.1 mmol), and proline **21** (1.1 mmol) was placed in a round bottom flask and melted at 180°C, completion of the reaction was evidenced by thin layer chromatography (TLC), the crude product was recrystallized with EtOAc and hexane to afford the pure product **22a** as a solid.

2.2.1 14-(2-Methoxyphenyl)-7*a*,8,9,10-tetrahydro-7*H*-6*a*,11*a*-(methanooxymethano)pyrrolizino[2,3-*c*]quinoline-6,12(5*H*)-dione, 22a

IR (KBr): 1,715, 1,749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 1.35–1.41 (m, 1H), 1.61–1.75 (m, 2H), 1.99–2.20 (m, 4H), 2.64–2.70 (m, 1H), 3.62–3.71 (m, 1H), 3.75 (s, 3H), 5.81 (s, 1H), 6.86–6.89 (d, J = 8.1 Hz, 2H), 6.96–7.01 (m, 1H), 7.09–7.13 (m, 1H), 7.28–7.38 (m, 3H), 7.74–7.77 (d, J = 7.8 Hz, 1H), 10.37 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 19.9, 27.3, 28.3, 35.5, 44.0, 49.7, 53.3, 58.0, 69.9, 105.3, 109.1, 110.8, 114.8, 117.3, 118.0, 121.1, 123.5, 124.2, 125.1, 133.6, 151.0, 163.1, 170.7 ppm. Mass: m/z: 391(M^+). Anal. calculated for $C_{23}H_{22}N_2O_4$: C, 70.75%; H, 5.68%; N, 7.18%; found: C, 70.80%, H, 5.71%, N, 7.24%.

2.2.2 14-(4-Methoxyphenyl)-7*a*,8,9,10-tetrahydro-7*H*-6*a*,11*a*-(methanooxymethano)pyrrolizino[2,3-*c*]quinoline-6,12(5*H*)-dione, 22b

IR (KBr): 1,715, 1,745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37–1.42 (m, 1H), 1.58–1.75 (m, 2H), 2.08–2.22 (m, 4H), 2.66–2.73 (m, 1H), 3.61–3.69 (m, 1H), 3.81 (s, 3H), 5.41(s, 1H), 6.87–6.90 (m, 2H), 7.01–7.04 (m, 1H), 7.19–7.43 (m, 4H), 7.90–7.93 (d, J = 7.5 Hz, 1H), 9.81 (s, 1H, N–H). ^{13}C NMR (75 MHz, $CDCl_3$): 25.0, 32.1, 35.4, 49.2, 55.2, 59.4, 63.4, 76.8, 80.4, 113.8, 115.3, 116.0, 124.7, 126.5, 127.1, 129.5, 130.8, 137.1, 159.9, 170.5, 175.6 ppm. Mass: m/z: 391 (M^+). Anal. calculated for $C_{23}H_{22}N_2O_4$: C, 70.75%; H, 5.68%; N, 7.18%; found: C, 70.80%, H, 5.65%, N, 7.23%.

2.2.3 14-(*o*-Tolyl)-7*a*,8,9,10-tetrahydro-7*H*-6*a*,11*a*-(methanooxymethano)pyrrolizino[2,3-*c*]quinoline-6,12(5*H*)-dione, 22c

IR (KBr): 1,715, 1,744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.41–1.55 (m, 1H), 1.63–1.83 (m, 2H), 2.04–2.19 (m, 3H), 2.25 (s, 3H), 2.35–2.47 (m, 1H), 2.67–2.72 (m, 1H), 3.67–3.76 (m, 1H), 5.68 (s, 1H), 7.08–7.45 (m, 7H), 7.86 (d, J = 7.5 Hz, 1H), 10.34 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 19.1, 25.0, 32.0, 34.4, 49.1, 59.0, 63.4, 77.1, 77.3, 114.9, 116.2, 124.1, 125.7, 126.7, 128.6, 129.1, 130.6, 130.9, 132.3, 135.6, 137.9, 169.6, 175.9 ppm. Mass: m/z: 375 (M^+). Anal. calculated for $C_{23}H_{22}N_2O_3$: C, 73.98%; H, 5.92%; N, 7.48%; found: C, 74.05%, H, 5.96%, N, 7.53%.

2.2.4 14-(3,4-Dimethoxyphenyl)-7*a*,8,9,10-tetrahydro-7*H*-6*a*,11*a*-(methanooxymethano)pyrrolizino[2,3-*c*]quinoline-6,12(5*H*)-dione, 22d

IR (KBr): 1,712, 1,755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01–1.08 (m, 1H), 1.28–1.36 (m, 2H), 1.66–1.89 (m, 4H), 2.29 (t, J = 6.3 Hz, 1H), 3.19–3.32 (m, 1H), 3.51(s, 6H), 5.01(s, 1H), 6.50–7.02 (m, 6H), 7.41 (d, J = 7.8 Hz, 1H), 10.30 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$): 24.8, 31.9, 34.9, 48.9, 55.6, 55.6, 58.7, 63.0, 76.3, 79.8, 109.1, 110.8, 114.4, 116.0, 118.0, 123.4, 127.1, 128.4, 130.3, 138.0, 148.4, 148.8, 168.8, 175.5 ppm. HRMS (ESI) exact mass calculated for $C_{24}H_{24}N_2O_5$ $[M + H]^+$: 421.1758, Found: 421.1754. Mass: m/z: 420 (M^+). Anal. calculated for $C_{24}H_{24}N_2O_5$: C, 68.56%; H, 5.75%; N, 6.66%; found: C, 68.64%, H, 5.79%, N, 6.70%.

2.2.5 14-(Benzo[*d*][1,3]dioxol-5-yl)-7*a*,8,9,10-tetrahydro-7*H*-6*a*,11*a*-(methanooxymethano)pyrrolizino[2,3-*c*]quinoline-6,12(5*H*)-dione, 22e

Mp: 245–248°C; IR (KBr): 1,715, 1,749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 1.35–1.44 (m, 1H), 1.63–1.83 (m, 2H), 2.06–2.23 (m, 4H), 2.69 (t, J = 6.6 Hz, 1H), 3.59–3.68 (m, 1H), 5.34 (s, 1H), 5.97(s, 2H), 6.78–7.40 (m, 6H), 7.86 (d, J = 7.5 Hz, 1H), 9.80 (s, 1H, *N–H*). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 24.0, 31.0, 34.2, 48.2, 58.2, 62.3, 75.7, 79.2, 100.2, 105.5, 107.1, 114.0, 115.0, 118.4, 112.3, 127.3, 128.2, 129.7, 136.5, 146.7, 146.8, 168.5, 174.5 ppm. HRMS calculated for $C_{23}H_{20}N_2O_5$: 404.1345 and found 404.1344.

2.3 General procedure for synthesis of heterarylpyrrolo[3,2-*c*]quinolinone/pyrrolizino[2.3-*c*]quinoline hybrids, 23 and 24

A mixture of BHA **5**/**6** (1 mmol), isatin **7** (1.1 mmol), and *N*-methylglycine **8**/proline **21** (1.1 mmol) was placed in a round bottom flask and melted at 180°C until completion of the reaction is evidenced by TLC analysis. After completion of the reaction, the crude product was recrystallized with 5 mL of EtOAc and hexane mixture (1:4 ratio) which successfully provided the pure product **23/24** as a solid.

2.3.1 1-Methyl-12-(thiophen-2-yl)-2,3-dihydro-1*H*-3*a*,9*b*-(methanooxymethano)pyrrolo[3,2-*c*]quinoline-4,10(5*H*)-dione, 23

Mp: 233–235°C; IR (KBr): 1,710, 1,747 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$): δ 2.24–2.23 (m, 1H), 2.59 (s, –NCH_3, 3H), 2.63–2.79 (m, 2H), 3.09–3.16 (m, 1H), 5.62 (s, 1H), 6.96–7.05 (m, 2H), 7.17–7.23 (m, 2H), 7.34 (d, J = 5.1 Hz, 1H), 7.45 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 8.98 (s, 1H, *N*–*H*). ^{13}C NMR (75 MHz, $CDCl_3$): 27.3, 34.2, 52.4, 59.1, 73.0, 77.2, 114.5, 116.2, 123.8, 126.0, 126.2, 126.9, 129.9, 130.8, 136.3, 136.5, 168.9, 172.9 ppm. Mass: *m*/*z*: 341 (M^+). Anal. calculated for $C_{18}H_{16}N_2O_3S$: C, 63.51%, H, 4.74%, N, 8.23%; found: C, 63.57%, H, 4.70%, N, 8.25%.

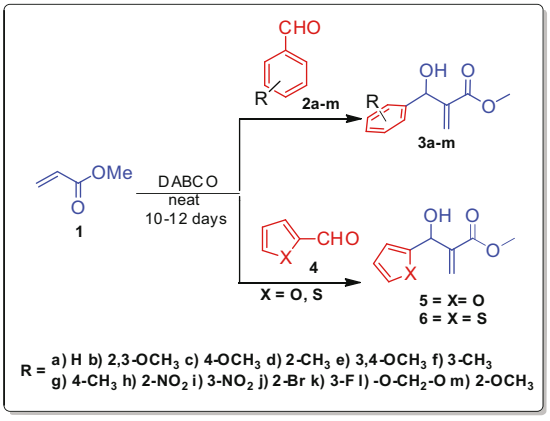
2.3.2 14-(Furan-2-yl)-7*a*,8,9,10-tetrahydro-7*H*-6*a*,11*a*-(methanooxymethano)pyrrolizino[2,3-*c*]quinoline-6,12(5*H*)-dione, 24

IR (KBr): 1,709, 1,749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39–1.48 (m, 1H), 1.65–1.75 (m, 2H), 2.09–2.17 (m, 2H), 2.53–2.71 (m, 3H), 3.68–3.73 (m, 1H), 5.29 (s, 1H), 6.39 (s, 1H), 6.52–7.79 (m, 6H), 10.11 (s, 1H, *N*–*H*).^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 25.2, 32.4, 35.1, 49.4, 58.1, 63.6, 75.1, 76.3, 110.4, 110.5, 114.3, 116.2, 124.0, 129.0, 130.7, 138.0, 143.6, 147.2, 168.0, 175.2 ppm. Mass: *m*/*z* 350 (M^+). Anal. calculated for $C_{20}H_{18}N_2O_4$: C, 68.56%; H, 5.18%; N, 8.10%; found: C, 68.62%, H, 5.22%, N, 8.04%.

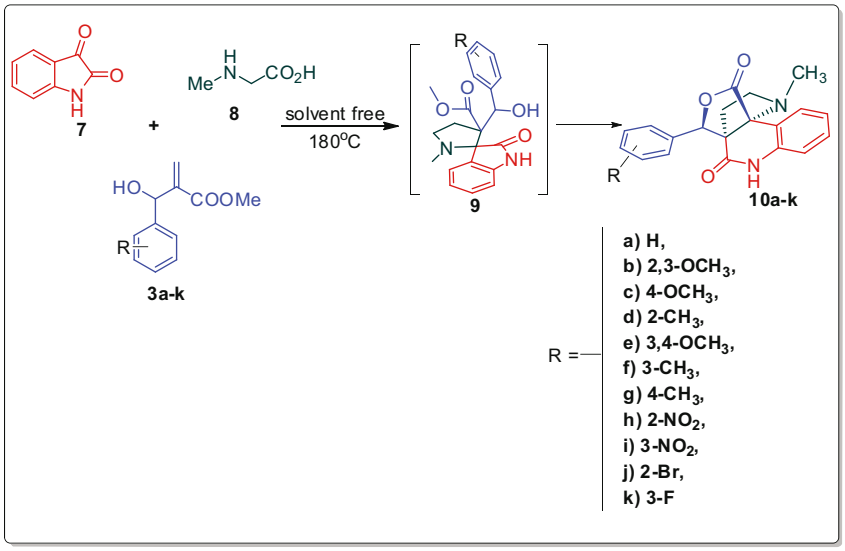
3 Results and discussion

To begin with, the preparation of BHA *viz* various substituted methyl 2-(hydroxy(phenyl)methyl)acrylate **3**/methyl 2-(furan-2-yl(hydroxy)methyl)acrylate **5**/methyl 2-(hydroxy (thiophen-2-yl)methyl)acrylate **6** was achieved from the reactions of appropriate aryl/heteroaryl aldehyde in the presence of DABCO and methyl acrylate based on protocol reported in the literature [27] (Scheme 1).

Subsequently, a model tandem reaction was investigated by refluxing a mixture of BHA **3a**, indoline-2,3-dione **7**, and *N*-methylglycine **8** in MeOH for 8 h. The reaction afforded 20% isolated yield of the unusual rearranged product **10a** and 65% of the expected spiro cycloadduct **9a** (Scheme 2 and Table 1). Since our interest was more on the synthesis of the rearranged product **10a**, to improve its yield, the tandem protocol was explored under different solvent conditions including MeCN, dioxane, toluene, and xylene and the results are presented in Table 1. The reaction in all these solvents failed to afford **10a** even after longer reaction time, alternatively the expected cycloadduct **9a** was obtained. Ultimately, the reaction was performed under solid state melt reaction (SSMR) conditions in the absence of solvent, as SSMR is an environmentally benign and economically attractive synthetic strategy to prepare complex heterocycles without using expensive, flammable, toxic, and hazardous solvents [28]. Thus, an equimolar mixture of compounds **7**, **8**, and **3a** was melted under solvent free condition at 180°C, whereupon a quantitative yield of the rearranged product **10a** was obtained in 5 min (Scheme 2 and Table 1). It was observed that 180°C was the optimum temperature for getting maximum yield of the rearranged product **10a**. Increasing the temperature (200°C) became detrimental to the reaction, while lowering the temperature (80°C) had no significant effect on the reaction. The most remarkable observation of this protocol is that the unusual rearranged adduct was achieved in maximum yield and in the absence of column purification, as the pure product could be attained by recrystallization technique.



Scheme 1: Synthesis of BHAs.



Scheme 2: Synthesis of pyrrolo[3,2-*c*]quinolinone hybrid heterocycles.

Table 1: Optimization of reaction conditions for the synthesis of **10a**

Entry	Solvent	Temperature	Time	Yield (%) of the products[a]	
				Spiro adduct (9a)	Rearranged product (10a)
1	Methanol	Reflux	8 h	65	20
2	Acetonitrile	Reflux	8.5 h	82	—
3	Toluene	Reflux	10 h	78	—
4	Xylene	Reflux	8 h	79	—
5	Dioxane	Reflux	8 h	75	—
6	None	80°C[b]	2 h	—	—
7	None	100°C[b]	1 h	53	40
8	None	140°C[b]	30 min	20	70
9	None	180°C[b]	5 min	—	97

[a]Isolated yield of pure products.
[b]Reactants melted at the mentioned temperature.

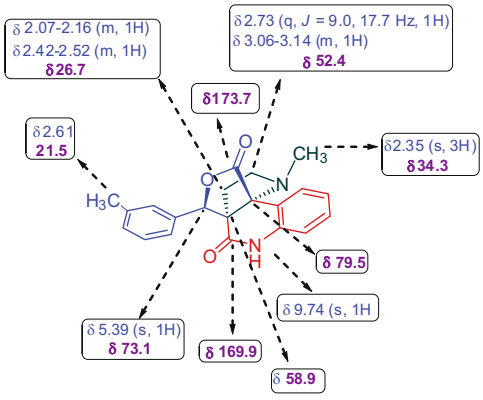


Figure 3: Chemical shift of **10f**.

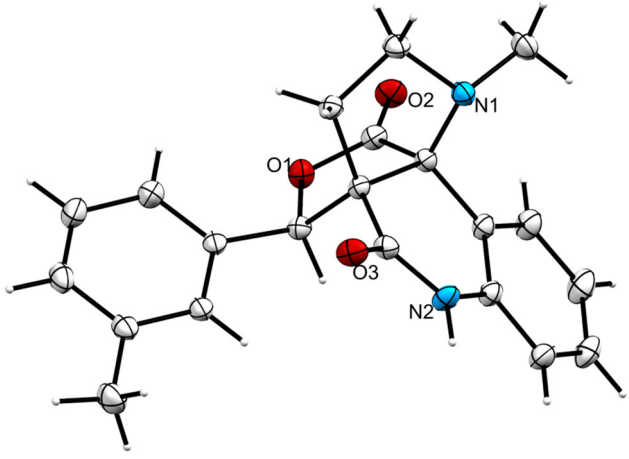


Figure 4: ORTEP diagram of pyrroloquinolinone hybrid **10f**.

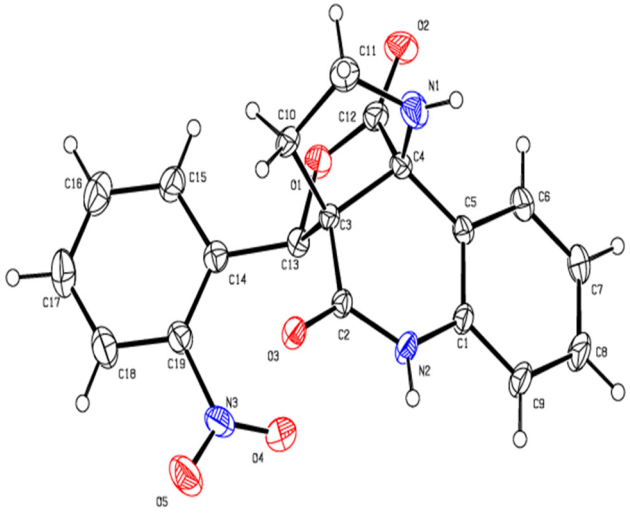
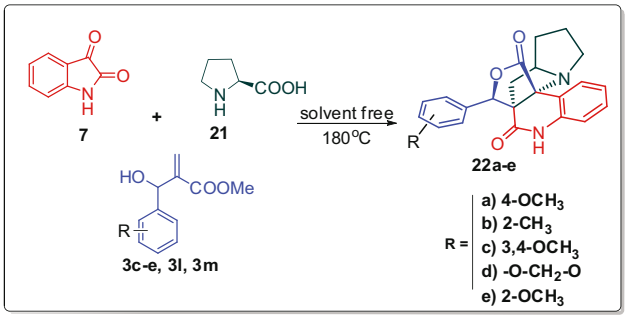
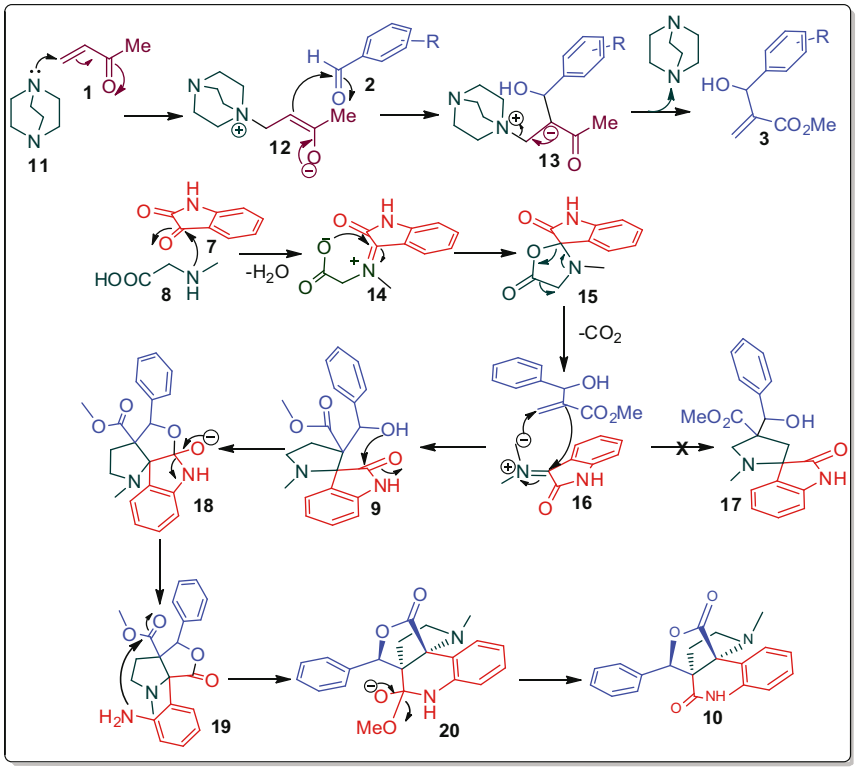


Figure 5: ORTEP diagram of **10h**.

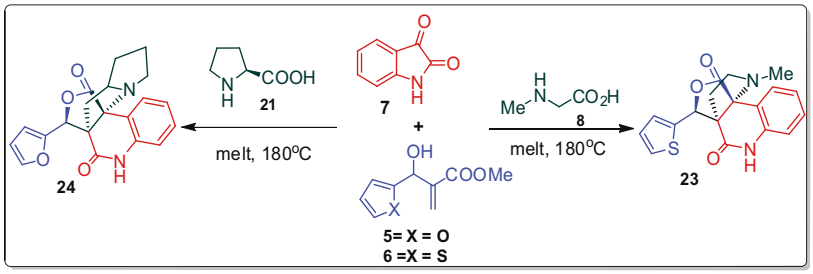


Scheme 4: Synthesis of pyrrolizino[2,3-*c*]quinolinone hybrids.

The structure of the product **10** was carefully ascertained by spectroscopic data (Supplementary material) (Figure 3). In the ^{1}H and ^{13}C NMR spectrum of compound **10f**, no peak for ester–OCH_3 and –OH could be found that are in accordance with the construction of the rearranged adduct. In the ^{1}H NMR spectrum of **10f**, the protons of the –NCH_3 and lactam –*NH* exhibited as singlets at δ 2.35 and 9.74 ppm. The signals at δ 2.73 and δ 3.06–3.14 ppm as quartet and multiplet were due to –NCH_2 protons of the pyrrolidine. In the ^{13}C NMR of **10f**, the peaks at δ 173.7 and 169.9 ppm were assigned to lactone and quinolinone rings carbonyl carbon, respectively. The carbon signals at δ 58.9 and 73.1 were assigned to two quaternary carbons. Further, two methylene units appeared at δ 26.7 and 52.4 ppm in the negative region of the DEPT 135 spectrum. The structures of other products were also determined by similar straightforward method. The stereo and regiochemistry of pyrroloquinolinone hybrids **10f** and **10h** have been unambiguously elucidated by XRD analysis in Figures 4 and 5 [29,30].



Scheme 3: A feasible mechanism for the formation of pyrroloquinoline hybrids.



Scheme 5: Synthesis of heterarylpyrrolo[3,2-*c*]quinolinone/pyrrolizino[2.3-*c*]quinoline hybrids.

The persuasive mechanism for the construction of the polycyclic hybrid heterocycles in the one pot operation is shown in Scheme 3. The acrylate upon reaction with DABCO affords the intermediate **12**, which further reacts with aryl aldehyde **2** to furnish the appropriate BHA **3** via intermediate **13**. The reaction of diketone **7** and *N*-methyl glycine **8**, affords the 1,3-dipole **16** via intermediates **14** and **15** by spontaneous decarboxylation and dehydration. The 1,3-dipole **16** adds regioselectively to the dipolarophile **3** to give the cycloadduct **9** in preference over **17**. Presumably,

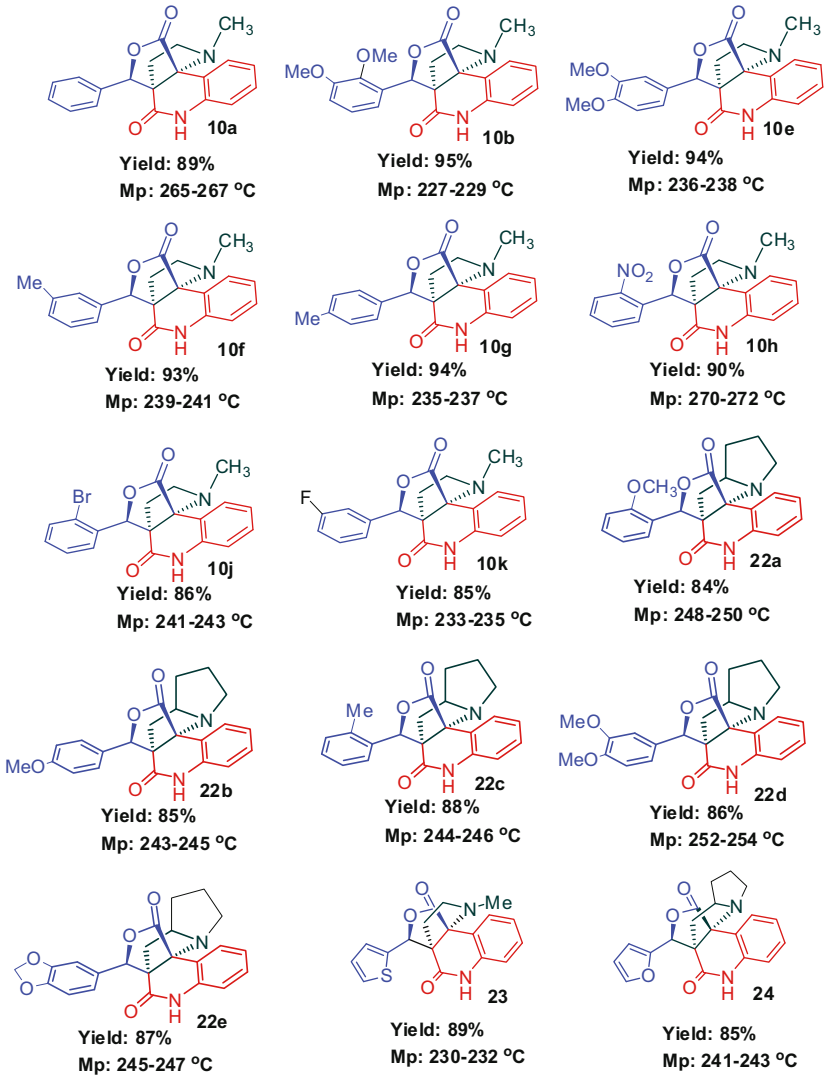


Figure 6: Pyrrolo[3,2-*c*]quinolinone and pyrrolizino[2,3-*c*]quinolinone hybrids.

the hydroxyl group of **9** was reacted with the imido carbonyl of the isatin moiety leading to the construction of lactone **19** via **18.** The condensation between the amino group of intermediate **19** with the ester function ultimately affords the final product **10** via subsequent elimination of the methoxy unit.

The construction of structurally fascinating polycyclic pyrrolizinoquinoline hybrids **22a–e** were further realized through the tandem reaction of BHA **3** with indoline-2,3-dione **7** and L-proline **21** as described in Scheme 4. This reaction under the optimized conditions led to the formation of aryl substituted polycyclic pyrrolizino[2,3-*c*]quinolinone hybrids in good yields (Scheme 4).

To broaden the scope of this tandem transformation, the reaction was also investigated with different BHAs generated from heteroaryl aldehydes (pyrrole-2-carboxaldehyde and furan-2-carboxaldehyde) as shown in Scheme 1. Thus, the reaction involving the azomethine ylide generated *in situ* from decarboxylative condensation of isatin **7** and *N*-methylglycine **8**/L-proline **21**, under optimized condition led to the formation of heteroaryl substituted polycyclic pyrrolo[3,2-*c*]quinolinone/pyrrolizinoquinolinone hybrids **23** and **24** in good yield (Scheme 5). The structure of these products was confirmed by spectroscopic data. All these reactions afforded angularly fused, quinolin-2-olactone in excellent yields and the results are described in Figure 6.

4 Conclusion

In conclusion, we report herein the synthesis of a library of hitherto unexplored new classes of pyrrolo[3,2-*c*]quinolinone/pyrrolizino[2,3-*c*]quinolinone hybrid heterocycles through single-pot three component tandem green transformation involving a cycloaddition reaction and a consecutive lactonization and lactamization. Notable features of this protocol include the following: (a) solvent free reaction involving solid reactants, (b) products formed in shortest reaction time, (c) pure products obtained without column chromatographic purification, (d) environmentally benign green protocol, (e) products obtained in excellent yields. The products were obtained by single stereoisomers with high stereoselectivity which was confirmed by spectroscopic and XRD analyses.

Acknowledgements: Authors thank the Department of Science and Technology (DST), New Delhi for financial support. Suresh Mani and Rajesh Raju would like to thank the CSIR, New Delhi for SRF Fellowship. Rajesh Raju would like to thank the UGC New Delhi for BSR Faculty Fellowship.

Funding information: The project was funded by Researchers Supporting Project Number (RSP2023R143), King Saud University, Riyadh, Saudi Arabia.

Author contributions: Suresh and Rajesh Raju: conceptualization, investigation, supervision, formal analysis, methodology, validation, writing – original draft, and visualization; Natarajan Arumugam: conceptualization, investigation, validation, writing – original draft, and visualization; Abudulrahman I. Almansour: project administration, visualization, and writing – review and editing; Raju Suresh Kumar: methodology, validation, and writing – review and editing; Karthikeyan Perumal: investigation, formal analysis, and methodology

Conflict of interest: The Authors state no conflict of interest.

Data availability statement: All materials for this study are presented in this article and available on request to the corresponding author.

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[30] Crystallographic data (including structure factors) for the compound 10i in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 993215. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].