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Tandem one-pot synthesis of 2-arylcinnolin-6-one derivatives from arylhydrazonopropanals and acetoacetanilides using sustainable ultrasound and microwave platforms†

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Several 2-arylcinnolin-6(2*H*)-one derivatives were synthesized *via* tandem annulation of a large number of 3-oxo-2-arylhydrazonopropanals with acetoacetanilide under three different heating modes (conventional heating, ultrasound and microwave irradiation) using triethylamine in ethanol. The factors affecting the optimization of the annulation process were thoroughly studied. The annulated structures were established on the basis of ^{1}H and ^{13}C NMR and MALDI-TOF/MS spectral data as well as single crystal X-ray analysis.

Introduction

Cinnolines are a class of aromatic nitrogen-heterocyclic compounds that are also known as benzo[*c*]pyridazines. Cinnoline derivatives have attracted considerable attention as drug candidates against several diseases due to their broad spectrum biological activities.[1] They are patented as bactericides[2–4] and fungicides.[5] Cinnolin-3-one and cinnolin-4-one derivatives have also been reported to display potent antitumor,[6–8] and antifungal,[9] as well as human neutrophil elastase and STAT3 inhibitory activities[10,11] and cannabinoid CB2 agonists.[12,13] Cinnolin-5-ones were reported as atypical antipsychotic,[14] and antitumor[15] activities. In addition, cinnolin-3-carboxamides displayed ATM kinase inhibitors and were used in treating cancer[16] and as BTK (Bruton's tyrosine kinase) inhibitors.[17] Such potent biological importance of the cinnoline derivatives make them excellent templates for medicinal chemists to develop lead compounds for drug targets.

Thus, several reaction protocols have been reported for the synthesis of the cinnoline building blocks, among those protocols are the cyclization of the arylhydrazono-cyanoacetanilide,[18] Richter cyclization of *ortho*-ethynyldiazonium salts,[19–22] acid catalyzed cyclization of 3-oxo-3-aryl-2-arylhydrazonopropanals,[23] diazotization of *ortho*-substituted anilines.[24] The cinnolin-3(2*H*)-one derivatives were also synthesized by rhodium or gold catalyzed reactions of azobenzene derivatives.[25,26] To date, the only reported cinnolinone ring skeletons included cinnolin-3-one, cinnolin-4-one, cinnolin-5-one, and cinnoline-5,6-dione derivatives,[6–15,27,28] however, synthesis of cinnolin-6(2*H*)-one structures are not reported so far.

The environmentally sustainable ultrasound technique has pronounced applications in organic synthesis, medicinal chemistry, and in materials science.[29–31] The ultrasound is reported to be superior over conventional heating in organic synthesis, where formation of pure products in high yields, high selectivity, shorter reaction time and waste-minimization are among the most advantages of ultrasound techniques.[32–39] In addition, a growing interest is focused on the use of microwave irradiation methodology because it markedly assists in achieving rapid incorporation of organic synthesis into broad industrial diversities.[40–43] In continuation of our research work employed ultrasound and microwave irradiations in heterocyclic synthesis,[44–51] we envisaged in the current work a feasible simple and straightforward approach for the construction of 2-arylcinnolin-6(2*H*)-one derivatives, which would be assembled by reaction of 3-oxo-2-arylhydrazonopropanals with double equivalents of acetoacetanilide *via* aldol-condensation followed by Michael-type addition reaction. For comparison with the conventional heating, two green and energy-saving platforms; ultrasound and microwave irradiation, are applied for achieving the goals of this work. Structures of the products are examined by measuring the X-ray crystallography along with all possible spectral analyses (IR, ^{1}H and ^{13}C NMR and MALDI-TOF/MS spectral data).

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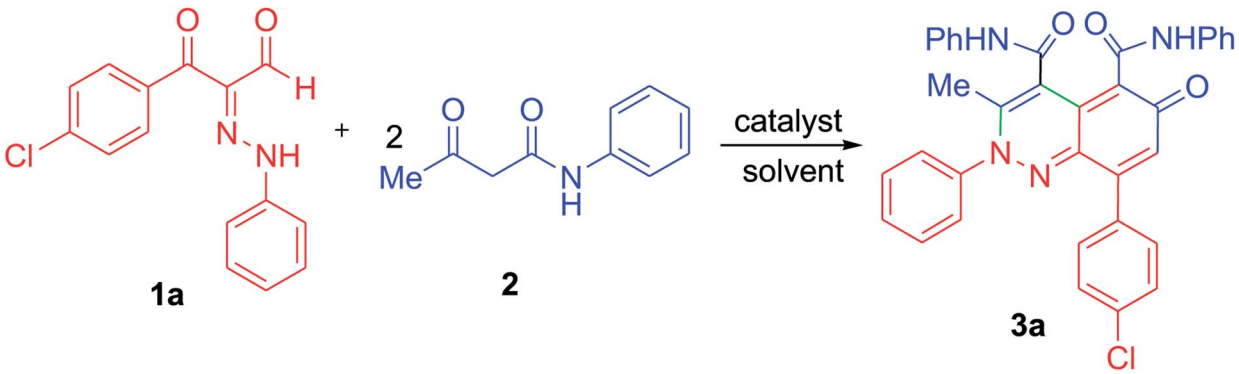
Results and discussion

At first, 3-oxo-2-arylhydrazonopropanal derivatives **1a–o** were synthesized using reported procedure in the literature.[52,53] Then, initial attempts to perform the annulation of the 3-oxo-2-phenylhydrazonopropanal **1a** with acetoacetanilide **2** in ethanol in the presence of triethylamine were conducted under conventional thermal heating. The expected pyridazine **4** or phenylazophenol **6** structures, according to the previously published protocols[54,55] could not be detected, however the assigned product was established as 2-arylcinnolin-6(2*H*)-one derivative **3a** (Scheme 1). To our delight, phenylhydrazonopropanal **1a** satisfactorily reacted with double equivalent of acetoacetanilide **2** to give the aldol-condensation followed by Michael-type addition product **3a**, through *in situ* elimination of three molecules of water during the reaction path (Scheme 1). The structure **3a** was established on the basis of IR, ^{1}H and ^{13}C NMR spectra, MALDI-TOF/MS spectrum, and X-ray diffraction data. Positive ion mode MALDI-TOF mass spectrum of **3a** exhibited molecular ion peak of the form $[M + K]^{+}$ at *m*/*z* 624.317. Optimization of the reaction of **1a** with **2** was thoroughly investigated under various reaction conditions (different solvents, bases and heating modes) and the reaction path was monitored by TLC till full conversion of the starting substrates, and the results are summarized in Table 1. The results demonstrated that these factors greatly affected the productivity of this reaction. Among several solvents used (EtOH, MeOH, i-PrOH, *n*-hexane, DMF, 1,4-dioxane), ethanol was the proper one and the reaction was also much influenced by the type of base, where various organic and inorganic bases *e.g.* Et_3N, pyridine, DBU, DABCO, $NaHCO_3$, K_2CO_3 and KOH were tested. Using ethanol as solvent and triethylamine (10 mol%) as base, the reaction of the hydrazonal **1a** with **2** under conventional heating at reflux for 4 hours resulted in 66% isolated yield, however, 70% isolated yield was obtained after 7 min of ultrasound irradiation and the yield was 75% after only



Scheme 1 Annulation of phenylhydrazonopropanal **1a** with acetoacetanilide **2**.

Table 1 Optimization the reaction condition of annulation of **1a** with **2**[a]

			Conv. heating		Sonication		MW irradiation	
Entry	Base catalyst	Solvent	Yield[e] %	Time (h)	Yield[e] %	Time (min)	Yield[e] %	Time (min)
1	Et_3N[b]	EtOH	66	4	70	70	75	7
2	Et_3N[c]	EtOH	74[f]	2	79[g]	50	87[h]	5
3	Et_3N[d]	EtOH	70	3	73	60	80	6
4	Et_3N[c]	MeOH	55	6	60	80	70	10
5	Et_3N[c]	i-PrOH	68	7	72	80	80	10
6	Et_3N[c]	*n*-Hexane	28	9	30	100	40	15
7	Et_3N[c]	1,4-Dioxane	38	8	40	100	45	15
8	Et_3N[c]	DMF	42	9	45	110	55	20
9	Et_3N[c]	Toluene	34	8	37	100	42	15
10	Pyridine[c]	EtOH	55[i]	6	60[j]	80	75[k]	15
11	DABCO[c]	EtOH	30	11	35	110	41	20
12	DBU[c]	EtOH	30	11	36	110	46	20
13	$NaHCO_3$[c]	EtOH	34	9	36	90	42	12
14	K_2CO_3[c]	EtOH	38	7	40	90	45	15
15	NaOH[c]	EtOH	30	7	30	100	40	15

[a] Reaction conditions: phenylhydrazonopropanal **1a** (2 mmol), acetoacetanilide **2** (4 mmol), solvent (15 mL) and base (10–30 mol%), conventional heating at reflux for 2–11 h, ultrasound at 80 °C for 50–110 min, microwave irradiation at 80 °C (200 W) for 5–20 min. [b] Base 10 mol%. [c] Base 20 mol%. [d] Base 30 mol%. [e] Isolated yields. [f] Yield was 12% after 20 min and 50% after 80 min. [g] Yield was 30% after 20 min and 62% after 40 min. [h] Yield was 53% after 3 min. [i] Yield was 17% after 2 h. [j] Yield was 38% after 50 min. [k] Yield was 25% after 5 min.

7 min of microwave irradiation (as examined by TLC) (entry 1, Table 1). The use of 20 mol% instead of 10 mol% of triethylamine led to production of 74%, 79% and 87% isolated yields under conventional heating (2 hours), US irradiation (50 min) and MW irradiation (5 min), respectively (entry 2, Table 1). Minor shift to lower yields were observed when Et_3N was used in a higher ratio (30 mol%), where the isolated yields became 70%, 73% and 80% under thermal heating (3 hours), US (60 min) and MW (6 min), respectively (entry 3, Table 1). Very close product yields with low efficiency were obtained when MeOH or i-PrOH were employed as reaction solvent in the presence of 20 mol% of Et_3N under all heating modes (entries 4 and 5, Table 1). Replacing ethanol with aprotic solvents (*e.g.* *n*-hexane, 1,4-dioxane, DMF and toluene) led to a sharp decrease in the product yields (varied from 28–55%) after longer reaction times regardless the type of heating mode (thermal, US or MW) (entries 6–9, Table 1). Keeping ethanol solvent and replacing Et_3N by pyridine resulted in 55%, 60% and 75% isolated yields under thermal heating (6 hours), US (80 min) and MW (15 min), respectively (entry 10, Table 1). Use of other bases such as DBU, DABCO, $NaHCO_3$, K_2CO_3 and KOH could not provide satisfactory yields (varied from 30–46% yields) under all the three heating modes (entries 11–15, Table 1). From the above findings, the benefit of microwave irradiation was confirmed by high efficiency with high conversion rate compared with the low conversion rate of the reactions that were carried out under conventional heating or ultrasound. The structure of the obtained reaction product **3a** was unambiguously established by spectral analyses along with X-ray crystallography (Fig. 1).[56] Mechanistically, polar solvents absorb microwave irradiation and convert it into heat that causes bulk heating and simultaneous rising of the temperature of the reaction mixture, in sharp contrast with conventional conductive heating.[57] However, ultrasound waves cause cavitation phenomenon, that is, the creation, growth, and collapse of bubbles releasing enough energy to perform chemical reactions.[31]

Prompted by the above interesting results and under the optimized reaction conditions, generalization and scope of the reaction using different substrates were investigated as shown in Table 2. The procedure was found to be applicable to a wide range of the arylhydrazonopropanal derivatives **1a–o** with acetoacetanilide **2** (Scheme 2). Thus, annulation reaction of arylhydrazonopropanals **1a–o** with acetoacetanilide **2** was conducted using EtOH (6 mL) and Et_3N (20 mol%) under the three heating modes; conventional heating, ultrasound irradiation and microwave irradiation, afforded the corresponding 2-arylcinnolin-6(2*H*)-one derivatives **3a–o**, Scheme 2. The reaction was monitored by TLC till full conversions of the starting substrates and the isolated yields of the corresponding annulated products **3a–o** ranged from 45 to 75% (after 2–4 hours under conventional heating), from 50 and 85% yields (after 40–80 min under ultrasound), and from 60 to 90% yields (after 3–10 min of microwave irradiation) as depicted in Table 2, entries 1–15. From the structure–activity relationship point of view, it would be established, from the obtained results in Table 2, that the best yields within the shortest reaction times were obtained when R = 4-FC_6H_4 for the products **3f** and **3g** among all the tested derivatives under all heating techniques (Table 2, entries 6 and 7). In contrast, the yields of the products **3n** and **3o** (where R = CH_3) were minimum and the reaction times were longest among all the derivatives under all applied heating modes (Table 2, entries 14 and 15). The 2-arylcinnolin-6(2*H*)-one structures **3a–o** were determined from their all possible spectral data (IR, MALDI-TOF, ^1H and ^{13}C NMR spectra) and elemental analyses as mentioned in the Experimental section.

A plausible mechanistic pathway for the annulation of the hydrazonals **1a–o** with acetoacetanilide **2** was suggested as depicted in Scheme 3. First, base catalyzed aldol condensation of the active methylene of **2** with the aldehyde function of **1** followed by loss of one molecule of water led to the formation of the α,β-unsaturated carbonyl adduct **A**. Then, a second molecule of **2** attacks the adduct **A** *via* a Michael-type addition to give

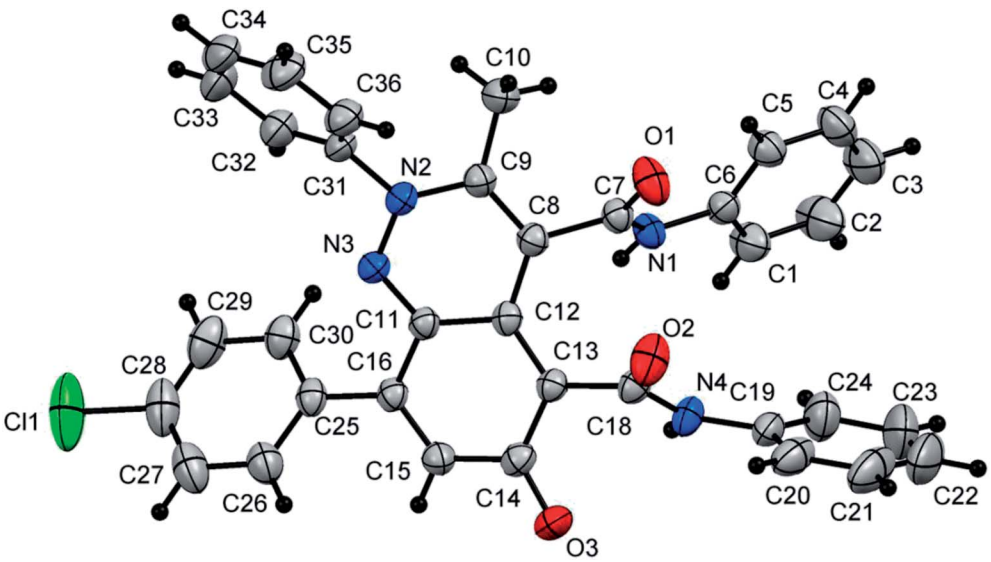


Fig. 1 ORTEP plot of the X-ray crystallographic data determined for **3a**.

Table 2 Tandem annulation of arylhydrazonopropanals **1a–o** with acetoacetanilide **2** under conventional heating, ultrasound and microwave irradiations[a]

				Conv. heating		Sonication		MW	
Entry	Product	R	Ar	Yield[b] %	Time (h)	Yield[b] %	Time (min)	Yield[b] %	Time (min)
1	**3a**	4-ClC_6H_4	C_6H_5	74	2	79	50	87	5
2	**3b**	C_6H_5	4-ClC_6H_4	70	3	74	60	75	8
3	**3c**	4-ClC_6H_4	4-BrC_6H_4	72	3	75	50	84	5
4	**3d**	4-BrC_6H_4	4-ClC_6H_4	75	2	82	40	87	3
5	**3e**	4-BrC_6H_4	4-BrC_6H_4	73	2	80[c]	60	84[d]	5
6	**3f**	4-FC_6H_4	4-ClC_6H_4	73	2	85	40	90	3
7	**3g**	4-FC_6H_4	4-BrC_6H_4	70	3	78	40	85[e]	5
8	**3h**	4-$MeOC_6H_4$	C_6H_5	63	4	68	70	74	8
9	**3i**	4-$MeOC_6H_4$	4-ClC_6H_4	62	4	65	80	72	10
10	**3j**	4-$MeOC_6H_4$	4-BrC_6H_4	65	3	70	60	80	8
11	**3k**	4-$MeOC_6H_4$	2-$NO_2C_6H_4$	58	4	62	80	72	10
12	**3l**	4-$NO_2C_6H_4$	4-ClC_6H_4	55[f]	4	60[g]	80	68[h]	10
13	**3m**	4-$NO_2C_6H_4$	4-BrC_6H_4	52	4	62	70	69	10
14	**3n**	CH_3	4-BrC_6H_4	50	4	58	80	64	10
15	**3o**	CH_3	2-$NO_2C_6H_4$	45	4	50	80	60	10

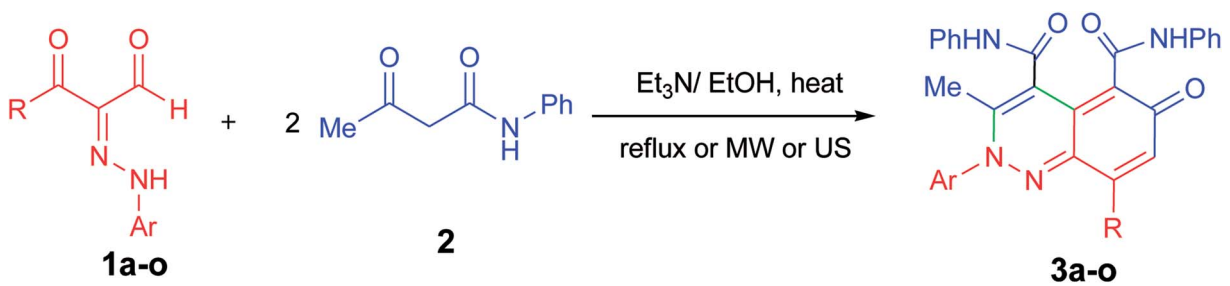
[a] Reaction condition: **1a–o** (1 mmol), acetoacetanilide (2 mmol), triethylamine (20 mol%) in EtOH (6 mL), heated under reflux for 2–4 h, ultrasound irradiation at 80 °C for 40–80 min, microwave irradiations at 80 °C (200 W) for 3–10 min. [b] Isolated yields. [c] Yield was 55% after 40 min. [d] Yield was 51% after 3 min. [e] Yield was 52% after 3 min. [f] Yield was 28% after 2 h. [g] Yield was 31% after 40 min. [h] Yield was 21% after 3 min.

the intermediate **B**, which underwent cyclization *via* nucleophilic attack of the hydrazone-NH to C=O function followed by loss of water molecule from **C** to give the pyridazine intermediate **D**. Further annulations took place by base catalyzed cyclization through C–C bond formation followed by loss of water molecule from **E** to give the intermediate **F**. Loss of hydrogen molecule through air oxidation of **F** led to the formation of the novel 6-oxo-2,6-dihydrocinnoline-4,5-dicarboxamide derivatives **3a–o**.

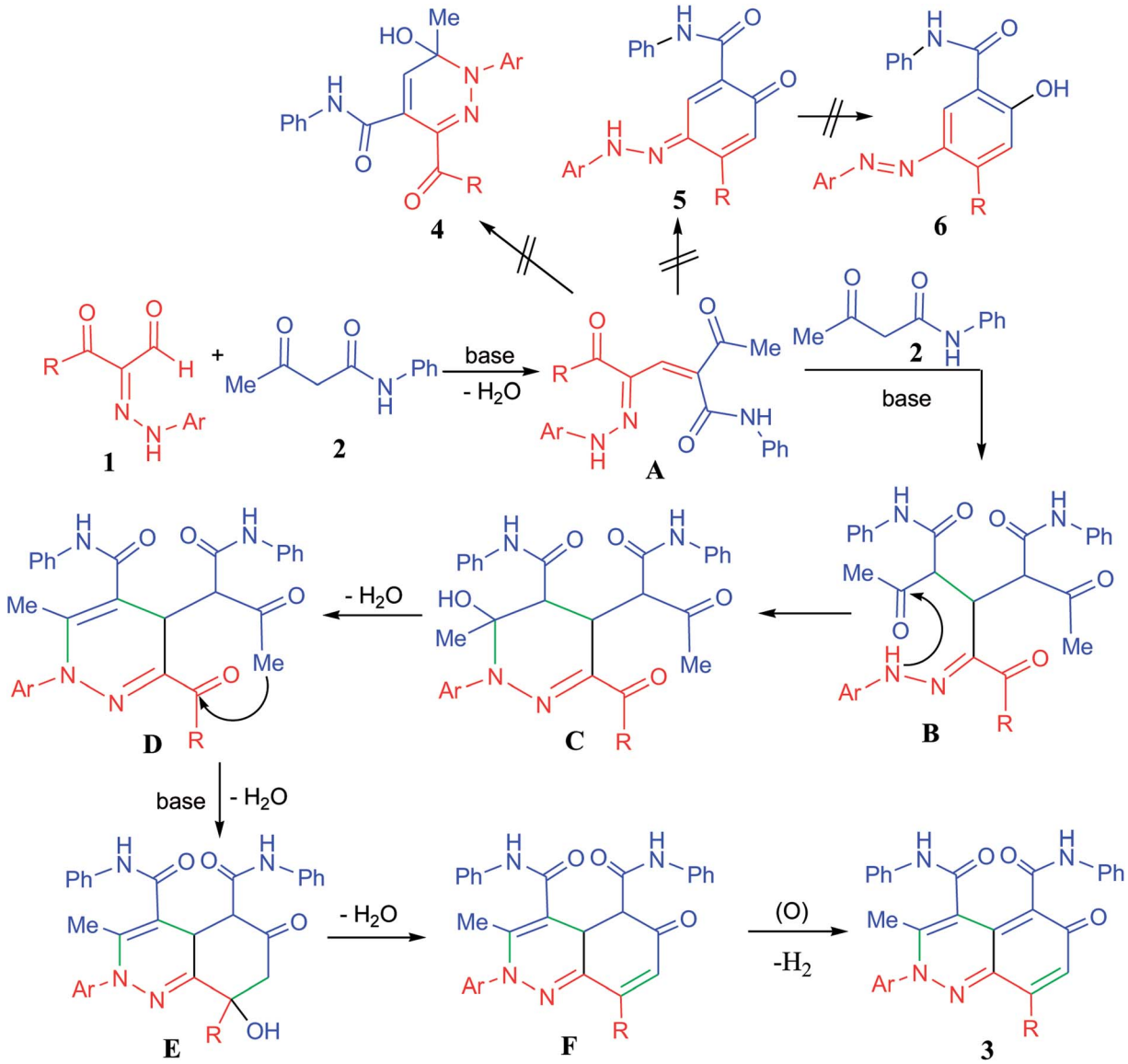
Experimental section

General

Melting points were recorded on a Griffin melting point apparatus and are reported uncorrected. IR spectra were recorded using KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^{1}H-NMR (600 MHz) and ^{13}C-NMR (150 MHz) spectra were recorded at 25 °C using DMSO-d_6 as solvent with TMS as internal standard on a Bruker DPX 400 or 600 superconducting NMR spectrometer. Chemical shifts are reported in ppm. Low-resolution electron impact mass spectra [MS (EI)] was performed using a high resolution GC-MS (DFS) thermo spectrometer at 70.1 eV using magnetic sector mass analyzer. Follow up of the reactions was made by using thin layer chromatography (TLC). Microwave experiments were carried out using a CEM Discover LabMate® microwave apparatus (300 W with ChemDriver software; Matthews, NC). Reactions were conducted under microwave irradiation in heavy-walled Pyrex tubes fitted with PCS caps (closed vessel under pressure). The X-ray crystal structures were determined by using a Rigaku R-AXIS RAPID diffractometer and Bruker X8 Prospector and the collection of single crystal data was made at room temperature by using Cu-Kα radiation. The data were collected at room temperature. The structures were solved by using direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The structures were solved and refined using the Bruker SHELXTL Software Package (Structure solution program-SHELXS-97 and Refinement program-SHELXL 97).[58] Data were corrected for the absorption effects using the multi-scan method (SADABS). Sonication was performed in MKC6, Guyson ultrasonic bath (Model-MKC6, operating frequency 38 kHz ± 10% and an



Scheme 2 Annulation of arylhydrazonopropanals **1a–o** with acetoacetanilide **2**.



Scheme 3 Proposed mechanism for the annulation pathway.

output power of 110 watts) with digital timer (6 s to 100 min) and heater allows solution heating to be set from 20 to 80 °C in 1 °C increments. The inside tank dimensions are 150 × 300 × 150 mm (length × width × depth) with a fluid capacity of 6 L.

Molecular weight determination using MALDI-TOF/MS

Determination of molecular weight was achieved using MALDI-TOF/MS (Bruker, model ultraflexXtreme). All the analyses were examined in positive mode using a reflectron time of flight mass spectrometer. Data processing was performed using Bruker flexAnalysis. The instrument was calibrated with peptide calibration standard.

The sample was prepared as following: the matrix α-cyano-4-hydroxycinnamic acid (HCCA) was purchased from Sigma Aldrich. All reagents were used without any further purification. HCCA was dissolved in mixture of acetonitrile : water : trifluoroacetic acid (70 : 30 : 0.1). All samples were dissolved in chloroform. Deposition of the samples on target pate was done as follows: 5 L of the sample was mixed with 5 L of the matrix (1 : 1 ratio). The solution mixture was placed on the target plate and allowed to dry at room temperature.

Synthesis of 6-oxo-2,6-dihydrocinnoline-4,5-dicarboxamide derivatives 3a–o

General method A. To a mixture of the appropriate arylhydrazonopropanal **1a–o** (2 mmol) and acetoacetanilide **2** (0.71 g, 4 mmol) in the appropriate solvent (EtOH, MeOH, i-PrOH, *n*-hexane, DMF or 1,4-dioxane) (15 mL), triethylamine (0.06 mL, 20 mol%) was added portion-wise. The mixture was heated at refluxing temperature till the starting substrates were almost completely consumed as followed up by TLC, then left to cool to room temperature. The solvent was removed under reduced pressure to give yellow or orange colored solid products. The solid products were recrystallized from dimethylformamide

(DMF)/ethanol to afford the corresponding 6-oxo-cinnoline-4,5-dicarboxamide derivatives **3a–o** as pure products.

General method B. A mixture of the appropriate arylhydrazonopropanal **1a–o** (2 mmol) and acetoacetanilide **2** (0.71 g, 4 mmol) and triethylamine (0.06 mL, 20 mol%) in the appropriate solvent (EtOH, MeOH, i-PrOH, *n*-hexane, DMF or 1,4-dioxane) (15 mL) was mixed thoroughly. The mixture was sonicated in a MKC6, Guyson ultrasonic bath (Model-MKC6, operating frequency 38 kHz ± 10% and an output power of 110 W) for 40–80 min at 80 °C during which time the starting substrates were almost completely consumed as followed up by TLC, then left to cool to room temperature. The solvent was removed under reduced pressure to give yellow or orange colored solid products. The solid products were recrystallized from dimethylformamide (DMF)/ethanol to afford the corresponding 6-oxo-cinnoline-4,5-dicarboxamide derivatives **3a–o** as pure products.

General method C. A mixture of the appropriate arylhydrazonopropanal **1a–o** (2 mmol) and acetoacetanilide **2** (0.71 g, 4 mmol) and triethylamine (0.06 mL, 20 mol%) in the appropriate solvent (EtOH, MeOH, i-PrOH, *n*-hexane, DMF or 1,4-dioxane) (15 mL) was mixed thoroughly in a process glass vial. The vial was capped properly, and thereafter, the mixture was heated under microwave irradiating conditions at 80 °C and 200 W for the appropriate reaction time as listed in Table 2. Then mixture was then left to cool to room temperature and the solvent was removed under reduced pressure to give yellow or orange colored solid products. The solid products were recrystallized from dimethylformamide (DMF)/ethanol to afford the corresponding 6-oxo-cinnoline-4,5-dicarboxamide derivatives **3a–o** as pure products.

*8-(4-Chlorophenyl)-3-methyl-6-oxo-N^4,N^5,2-triphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3a**).* Orange crystals, mp 268–270 °C; IR (KBr): ν/cm^{-1} 3259 (NH), 1683, 1654 (C=O); ^{1}H NMR (DMSO-d$_6$): δ = 2.35 (s, 3H, CH$_3$), 6.95 (t, J = 6.9 Hz, 1H, Ar–H), 7.06 (t, J = 6.6 Hz, 1H, Ar–H), 7.11 (m, 3H, Ar–H), 7.24 (t, J = 7.8 Hz, 2H, Ar–H), 7.46–7.47 (m, 2H, Ar–H), 7.49–7.50 (m, 2H, Ar–H), 7.55–7.62 (m, 3H, Ar–H), 7.64 (d, J = 4.2 Hz, 4H, Ar–H), 7.66–7.68 (m, 2H, Ar–H), 10.48 (s, 1H, NH), 10.55 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.35 (CH$_3$), 115.17, 119.48, 119.79, 123.50, 124.20, 125.94, 127.33, 127.97, 128.09, 128.36, 129.78, 131.90, 133.46, 134.43, 135.41, 138.74, 139.43, 141.73, 142.56 (Ar–C) 162.59, 164.20, 178.96 (C=O). MALDI-TOF: calcd for [M + K]$^+$ m/z = 624.128, found m/z = 624.317. Anal. calcd for $C_{35}H_{25}ClN_4O_3$: C, 71.85; H, 4.31; N, 9.58 found: C, 71.77; H, 4.39; N, 9.61. Crystal data, $C_{35}H_{25}ClN_4O_3$, M = 585.04, monoclinic, a = 15.5696(6) Å, b = 19.6736(7) Å, c = 9.4182(3) Å, α = 90°, β = 95.241(3)°, γ = 90°, V = 2872.83(18) Å^3, T = 296(2) K, space group: $P121/c1$, Z = 4, calculated density = 1.353 g cm^{-3}, no. of reflection measured 24 182, θ_{max} = 66.51°, $R1$ = 0.0800.[56]

*2-(4-Chlorophenyl)-3-methyl-6-oxo-N^4,N^5,8-triphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3b**).* Yellow crystals, mp 270–271 °C; IR (KBr): ν/cm^{-1} 3249 (NH), 1677, 1660 (C=O); ^{1}H NMR (DMSO-d$_6$): δ = 2.36 (s, 3H, CH$_3$); 6.97 (t, J = 7.2 Hz, 1H, Ar–H), 7.07–7.15 (m, 2H, Ar–H), 7.13 (t, J = 7.8 Hz, 2H, Ar–H), 7.25 (t, J = 8.1 Hz, 2H, Ar–H), 7.42–7.49 (m, 5H, Ar–H), 7.56 (d, J = 7.8 Hz, 2H, Ar–H), 7.65 (d, J = 8.4 Hz, 2H, Ar–H), 7.63–7.72 (m, 4H, Ar–H), 10.48 (s, 1H, NH), 10.56 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.33(CH$_3$), 115.41, 119.49, 119.79, 122.54, 123.53, 123.95, 127.23, 127.92, 127.98, 128.11, 128.39, 128.59, 129.79, 130.11, 134.49, 135.23, 135.58, 138.75, 139.47, 140.59, 141.32, 141.59, 143.32 (Ar–C), 162.55, 164.23, 178.80 (C=O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 607.151, [M + K]$^+$ m/z = 623.128, found m/z = 607.50 and 623.458; anal. calcd for $C_{35}H_{25}ClN_4O_3$: C, 71.85; H, 4.31; N, 9.58. Found: C, 71.71; H, 4.40; N, 9.51.

*2-(4-Bromophenyl)-8-(4-chlorophenyl)-3-methyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3c**).* Pale yellow crystals, mp 274–276 °C; IR (KBr): ν/cm^{-1} 3251 (NH), 1676 (C=O); ^{1}H NMR (DMSO-d$_6$): δ = 2.35 (s, 3H, CH$_3$); 6.95 (t, J = 7.25 Hz, 1H, Ar–H), 7.06 (t, J = 7.2 Hz, 1H, Ar–H), 7.10–7.13 (m, 3H, Ar–H), 7.24 (t, J = 7.8 Hz, 2H, Ar–H), 7.45 (d, J = 7.2 Hz, 2H, Ar–H), 7.50 (d, J = 8.4 Hz, 2H, Ar–H), 7.53 (d, J = 7.8 Hz, 2H, Ar–H), 7.61 (d, J = 8.4 Hz, 2H, Ar–H), 7.67 (d, J = 8.4 Hz, 2H, Ar–H), 7.85 (d, J = 8.4 Hz, 2H, Ar–H), 10.44 (s, 1H, NH), 10.55 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.39 (CH$_3$), 115.56, 119.52, 119.82, 122.59, 123.56, 123.16, 123.58, 124.04, 127.22, 128.03, 128.13, 128.15, 128.41, 131.94, 132.80, 133.55, 134.36, 135.39, 138.74, 139.45, 140.40, 141.63, 141.73, 142.03 (Ar–C), 162.55, 164.18, 178.68 (C=O). MALDI-TOF: calcd for [M + K]$^+$ m/z = 703.034, found 703.713; anal. calcd for $C_{35}H_{24}BrClN_4O_3$: C, 63.31; H, 3.64; N, 8.44. Found: C, 63.28; H, 3.72; N, 8.49.

*8-(4-Bromophenyl)-2-(4-chlorophenyl)-3-methyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3d**).* Orange crystals, mp 276–278 °C; IR (KBr): ν/cm^{-1} 3247 (NH), 1674 (C=O); ^{1}H NMR (DMSO-d$_6$): δ = 2.34 (s, 3H, CH$_3$), 6.95 (t, J = 7.2 Hz, 1H, Ar–H), 7.06 (t, J = 7.2 Hz, 1H, Ar–H), 7.11 (m, 3H, Ar–H), 7.24 (t, J = 8.1 Hz, 2H, Ar–H), 7.46 (d, J = 7.8 Hz, 2H, Ar–H), 7.54 (d, J = 7.8 Hz, 2H, Ar–H), 7.60–7.65 (m, 4H, Ar–H), 7.67–7.73 (m, 4H, Ar–H), 10.44 (s, 1H, NH), 10.54 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.37 (CH$_3$), 115.54, 119.49, 119.79, 122.24, 122.56, 123.55, 124.00, 127.22, 128.11, 129.85, 130.94, 132.21, 134.55, 134.73, 135.36, 138.73, 139.44, 140.31, 141.29, 141.67, 142.07 (Ar–C), 162.53, 164.15, 179.43 (C=O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 686.937, [M + K]$^+$ m/z = 703.045, found m/z = 687.294 and 703.261; anal. calcd For $C_{35}H_{24}BrClN_4O_3$: C, 63.31; H, 3.64; N, 8.44. Found: C, 63.38; H, 3.60; N, 8.41.

*2,8-Di(4-bromophenyl)-3-methyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3e**).* Pale yellow solid, mp 268–270 °C; IR (KBr): ν/cm^{-1} 3250 (NH), 1676 (C=O); ^{1}H NMR (DMSO-d$_6$): δ = 2.34 (s, 3H, CH$_3$), 6.95 (t, J = 7.5 Hz, 1H, Ar–H), 7.06 (t, J = 7.5 Hz, 1H, Ar–H), 7.10–7.13 (m, 3H, Ar–H), 7.24 (t, J = 7.8 Hz, 2H, Ar–H), 7.46 (d, J = 7.8 Hz, 2H, Ar–H), 7.54 (d, J = 7.8 Hz, 2H, Ar–H), 7.59–7.65 (m, 6H, Ar–H), 7.86 (d, J = 9 Hz, 2H, Ar–H), 10.44 (s, 1H, NH), 10.54 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.37 (CH$_3$), 115.55, 119.49, 119.79, 122.24, 122.56, 123.15, 123.55, 124.01, 127.20, 128.11, 128.14, 128.39, 130.94, 132.20, 132.79, 134.72, 135.35, 138.72, 139.44, 140.31, 141.60, 141.71, 142.05 (Ar–C), 162.52, 164.15, 178.65 (C=O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 729.011, found 729.03; anal. calcd for $C_{35}H_{24}Br_2N_4O_3$: C, 59.34; H, 3.41; N, 7.91. Found: C, 59.22; H, 3.49; N, 7.84.

*2-(4-Chlorophenyl)-8-(4-fluorophenyl)-3-methyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3f**).* Yellow

solid, mp 271–273 °C; IR (KBr): ν/cm^{-1} 3277 (NH), 1659 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.35 (s, 3H, CH$_3$), 6.95 (t, J = 7.5 Hz, 1H, Ar–H), 7.06 (t, J = 7.2 Hz, 1H, Ar–H), 7.09 (s, 1H, Ar–H), 7.12 (t, J = 7.8 Hz, 2H, Ar–H), 7.22–7.29 (m, 4H, Ar–H), 7.45 (d, J = 7.2 Hz, 2H, Ar–H), 7.55 (d, J = 7.2 Hz, 2H, Ar–H), 7.67–7.72 (m, 6H, Ar–H), 10.46 (s, 1H, NH), 10.55 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.38 (CH$_3$), 114.86, 115.00, 115.44, 119.51, 119.80, 122.57, 123.56, 124.01, 127.25, 127.92, 128.12, 128.41, 129.83, 131.87, 131.89, 132.26, 132.31, 134.51, 135.26, 138.75, 139.46, 140.54, 141.33, 141.61, 142.20 (Ar–C), 162.59, 164.20, 178.75 (C═O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 626.031, found 626.317; anal. calcd for $C_{35}H_{24}ClFN_4O_3$: C, 69.71; H, 4.01; N, 9.29. Found: C, 69.65; H, 4.15; N, 9.23.

*2-(4-Bromophenyl)-8-(4-fluorophenyl)-3-methyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3g**).* Yellow crystals, mp 267–269 °C; IR (KBr): ν/cm^{-1} 3274 (NH), 1676 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.35 (s, 3H, CH$_3$); 6.95 (t, J = 7.2 Hz, 1H, Ar–H), 7.06 (t, J = 7.5 Hz, 1H, Ar–H), 7.09 (s, 1H, Ar–H), 7.12 (t, J = 7.8 Hz, 2H, Ar–H), 7.22–7.29 (m, 4H, Ar–H), 7.47 (d, J = 7.2 Hz, 2H, Ar–H), 7.55 (d, J = 7.2 Hz, 2H, Ar–H), 7.61 (d, J = 8.4 Hz, 2H, Ar–H), 7.68–7.71 (m, 2H, Ar–H), 7.85 (d, J = 9 Hz, 2H, Ar–H), 10.46 (s, 1H, NH), 10.57 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.38 (CH$_3$), 114.85, 114.99, 115.45, 119.50, 122.55, 123.10, 123.53, 124.02, 127.24, 128.11, 128.14, 128.39, 131.87, 132.24, 132.29, 132.76, 135.25, 138.75, 139.45, 140.54, 141.54, 141.74, 142.19, 161.54, 162.27 (Ar–C) 163.17, 164.19, 178.75 (C═O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 669.091, found 669.316; anal. calcd for $C_{35}H_{24}BrFN_4O_3$: C, 64.92; H, 3.74; N, 8.65. Found: C, 64.85; H, 3.66; N, 8.77.

*8-(4-Anisyl)-3-methyl-6-oxo-N^4,N^5,2-triphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3h**).* Orange crystals, mp 242–244 °C; IR (KBr): ν/cm^{-1} 3260 (NH), 1687, 1653 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.35 (s, 3H, CH$_3$), 3.79 (s, 3H, OCH$_3$), 6.96 (t, J = 7.5 Hz, 1H, Ar–H), 7.00 (d, J = 9 Hz, 1H, Ar–H), 7.07–7.14 (m, 4H, Ar–H), 7.24 (t, J = 7.8 Hz, 2H, Ar–H), 7.38–7.48 (m, 4H, Ar–H), 7.57–7.61 (m, 4H, Ar–H), 7.64–7.82 (m, 3H, Ar–H), 7.95 (d, J = 7.8 Hz, 2H, Ar–H), 11.84 (br. s, 2H, 2NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.45 (CH$_3$), 55.77 (OCH$_3$), 113.43, 113.56, 114.24, 114.91, 115.37, 116.61, 119.57, 119.87, 122.59, 124.18, 125.83, 126.07, 127.90, 128.46, 129.85, 131.57, 132.42, 138.89, 139.29, 141.63, 142.70 (Ar–C), 162.67, 164.42, 188.79 (C═O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 603.201, found 603.327; anal. calcd for $C_{36}H_{28}N_4O_4$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.40; H, 4.74; N, 9.77.

*8-(4-Anisyl)-2-(4-chlorophenyl)-3-methyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3i**).* Orange crystals, mp 225–227 °C; IR (KBr): ν/cm^{-1} 3313 (NH), 1705, 1642 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.34 (s, 3H, CH$_3$), 3.79 (s, 3H, OCH$_3$), 6.95 (t, J = 7.8 Hz, 1H, Ar–H), 7.00 (d, J = 8.4 Hz, 2H, Ar–H), 7.04 (s, 1H, Ar–H), 7.07 (d, J = 7.2 Hz, 1H, Ar–H), 7.12 (t, J = 7.8 Hz, 2H, Ar–H), 7.24 (t, J = 7.8 Hz, 2H, Ar–H), 7.47 (d, J = 7.2 Hz, 2H, Ar–H), 7.56 (d, J = 7.8 Hz, 2H, Ar–H), 7.60 (d, J = 8.4 Hz, 2H, Ar–H), 7.68–7.73 (m, 4H, Ar–H), 10.50 (s, 1H, NH), 10.53 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.35 (CH$_3$), 55.18 (OCH$_3$), 113.50, 115.18, 119.49, 119.79, 122.53, 123.51, 123.91, 127.34, 127.73, 127.93, 128.12, 128.39, 129.82, 131.50, 134.45, 138.78, 139.46, 140.68, 141.36, 141.46, 142.93, 159.70 (Ar–C), 162.66, 164.28, 178.95 (C═O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 637.162, [M + K]$^+$ m/z = 653.136, found 637.488 and 653.447; anal. calcd For $C_{36}H_{27}ClN_4O_4$: C, 70.30; H, 4.42; N, 9.11. Found: C, 70.40; H, 4.55; N, 9.18.

*8-(4-Anisyl)-2-(4-bromophenyl)-3-methyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3j**).* Orange crystals, mp 252–254 °C; IR (KBr): ν/cm^{-1} 3268 (NH), 1678, 1659 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.34 (s, 3H, CH$_3$), 3.79 (s, 3H, OCH$_3$), 6.97 (t, J = 7.5 Hz, 1H, Ar–H), 7.02 (d, J = 8.4 Hz, 2H, Ar–H), 7.07 (t, J = 7.5 Hz, 2H, Ar–H), 7.12 (t, J = 7.8 Hz, 2H, Ar–H), 7.24 (t, J = 7.8 Hz, 2H, Ar–H), 7.46 (d, J = 7.8 Hz, 2H, Ar–H), 7.55–7.62 (m, 6H, Ar–H), 7.86 (d, J = 8.4 Hz, 2H, Ar–H), 10.49 (s, 1H, NH), 10.54 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.39 (CH$_3$), 55.20 (OCH$_3$), 113.52, 115.24, 119.51, 119.80, 122.56, 123.08, 123.54, 123.92, 127.32, 127.74, 128.14, 128.19, 128.42, 131.52, 132.78, 134.41, 138.80, 139.49, 140.70, 141.42, 141.80, 142.95, 159.72 (Ar–C), 162.68, 164.30, 178.96 (C═O). MALDI-TOF: calcd for [M + H]$^+$ m/z = 661.127, found 661.456; anal. calcd for $C_{36}H_{27}BrN_4O_4$: C, 65.56; H, 4.13; N, 8.49. Found: C, 65.40; H, 4.23; N, 8.58.

*8-(4-Anisyl)-3-methyl-2-(4-nitrophenyl)-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3k**).* Orange crystals, mp 248–250 °C; IR (KBr): ν/cm^{-1} 3274 (NH), 1661 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.35 (s, 3H, CH$_3$), 3.78 (s, 3H, OCH$_3$), 6.92–7.02 (m, 5H, Ar–H), 7.13 (t, J = 7.8 Hz, 2H, Ar–H), 7.22–7.31 (m, 4H, Ar–H), 7.47 (m, 2H, Ar–H), 7.54–7.58 (m, 3H, Ar–H), 7.89 (t, J = 7.8 Hz, 1H, Ar–H), 8.01 (s, 1H, Ar–H), 8.36 (d, J = 7.8 Hz, 1H, Ar–H), 10.40 (br. s, 1H, NH), 10.64 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.39 (CH$_3$), 55.19 (OCH$_3$), 113.40, 113.61, 119.43, 119.52, 119.78, 119.93, 122.46, 122.69, 123.59, 123.54, 126.68, 127.54, 128.07, 128.10, 128.32, 128.41, 128.73, 130.91, 131.52, 131.94, 134.53, 134.85, 135.37, 138.63, 139.54, 141.43, 141.95, 142.95, 144.05, 159.58, 159.64 (Ar–C), 162.20, 164.64, 179.15(C═O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 648.186, found 648.439; anal. calcd for $C_{36}H_{27}N_5O_6$: C, 69.11; H, 4.35; N, 11.19. Found: C, 69.22; H, 4.42; N, 11.26.

*2-(4-Chlorophenyl)-3-methyl-8-(4-nitrophenyl)-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3l**).* Orange crystals, mp 249–251 °C; IR (KBr): ν/cm^{-1} 3251 (NH), 1668 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.35 (s, 3H, CH$_3$), 6.95 (t, J = 7.5 Hz, 1H, Ar–H), 7.07 (t, J = 7.5 Hz, 1H, Ar–H), 7.12 (t, J = 7.5 Hz, 2H, Ar–H), 7.22–7.25 (m, 3H, Ar–H), 7.47 (d, J = 7.8 Hz, 2H, Ar–H), 7.55 (d, J = 7.8 Hz, 2H, Ar–H), 7.68–7.72 (m, 4H, Ar–H), 7.94 (d, J = 8.4 Hz, 2H, Ar–H), 8.26 (d, J = 8.4 Hz, 2H, Ar–H), 10.41 (s, 1H, NH), 10.56 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): δ = 19.87 (CH$_3$), 116.44, 119.99, 120.30, 123.09, 123.47, 124.09, 124.59, 127.61, 128.40, 128.61, 128.89, 130.37, 131.98, 135.07, 136.70, 139.18, 139.92, 140.66, 141.72, 142.35, 142.64, 147.86 (Ar–C), 162.92, 164.55, 178.84 (C═O). MALDI-TOF: calcd for [M + Na]$^+$ m/z = 652.136, found 652.859; anal. calcd for $C_{35}H_{24}ClN_5O_5$: C, 66.72; H, 3.84; N, 11.12. Found: C, 66.66; H, 3.95; N, 11.29.

*2-(4-Bromophenyl)-3-methyl-8-(4-nitrophenyl)-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3m**).* Orange solid, mp 302–304 °C; IR (KBr): ν/cm^{-1} 3259 (NH), 1668 (C═O); ^{1}H NMR (DMSO-d$_6$): δ = 2.36 (s, 3H, CH$_3$), 6.96–7.26 (m, 7H, Ar–H), 7.47 (d, J = 7.2 Hz, 2H, Ar–H), 7.56 (d, J = 7.8 Hz, 2H, Ar–H), 7.60–7.65 (m, 2H, Ar–H), 7.86–7.95 (m, 4H, Ar–H), 8.27 (d, J = 7.8 Hz, 1H, Ar–H), 8.34 (d, J = 7.8 Hz, 1H, Ar–H), 10.45 (s, 1H,

NH), 10.57 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 19.39 (CH_3), 115.70, 115.81, 119.52, 119.82, 121.76, 122.60, 122.98, 123.16, 123.21, 123.60, 124.03, 124.69, 127.20, 128.12, 128.40, 130.78, 131.08, 131.48, 132.81, 135.92, 136.85, 138.74, 139.44, 140.35, 140.45, 141.66, 142.28, 143.46, 147.41 (Ar–C), 162.28, 164.18, 178.68 (C=O). MALDI-TOF: calcd for $[M + Na]^+$ m/z = 698.038, found 698.295; anal. calcd For $C_{35}H_{24}BrN_5O_5$: C, 62.32; H, 3.59; N, 10.38. Found: C, 62.26; H, 3.46; N, 10.42.

*2-(4-Bromophenyl)-3,8-dimethyl-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3n**).* Orange crystals, mp 222–223 °C; IR (KBr): ν/cm^{-1} 3240 (NH), 1658, 1640 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.95 (t, J = 6.9 Hz, 1H, Ar–H), 6.99 (s, 1H, Ar–H), 7.06 (t, J = 7.5 Hz, 1H, Ar–H), 7.12 (t, J = 7.5 Hz, 2H, Ar–H), 7.23 (t, J = 7.8 Hz, 2H, Ar–H), 7.45 (d, J = 7.2 Hz, 2H, Ar–H), 7.55 (d, J = 7.2 Hz, 2H, Ar–H), 7.66 (d, J = 7.8 Hz, 2H, Ar–H), 7.91 (d, J = 7.8 Hz, 2H, Ar–H), 10.43 (s, 1H, NH), 10.47 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 16.88 (CH_3), 19.27 (CH_3), 114.32, 119.49, 119.77, 122.50, 123.16, 123.49, 123.61, 127.44, 128.11, 128.38, 132.86, 135.14, 138.80, 139.47, 140.68, 141.58, 141.92, 142.27 (Ar–C), 162.66, 164.30, 179.51 (C=O). MALDI-TOF: calcd for $[M + Na]^+$ m/z = 589.085, found 589.513; anal. calcd For $C_{30}H_{23}BrN_4O_3$: C, 63.50; H, 4.09; N, 9.87. Found: C, 63.55; H, 4.14; N, 9.76.

*3,8-Dimethyl-2-(2-nitrophenyl)-6-oxo-N^4,N^5-diphenyl-2,6-dihydrocinnoline-4,5-dicarboxamide (**3o**).* Orange crystals, mp 176–178 °C; IR (KBr): ν/cm^{-1} 3260 (NH), 1677 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.37 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.06 (t, J = 7.2 Hz, 2H, Ar–H), 7.11–7.14 (m, 2H, Ar–H), 7.31 (t, J = 8.1 Hz, 2H, Ar–H), 7.57 (d, J = 8.4 Hz, 2H, Ar–H), 7.73–7.75 (m, 2H, Ar–H), 7.83 (s, 2H, Ar–H), 7.92–7.94 (m, 2H, Ar–H), 8.12 (d, J = 8.4 Hz, 2H, Ar–H), 11.52 (s, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ = 24.50 (CH_3), 30.17 (CH_3), 115.02, 116.84, 119.06, 119.50, 120.96, 121.22, 123.39, 125.70, 128.74, 130.02, 133.55, 135.22, 136.12, 138.87, 139.15, 141.13 (Ar–C) 165.02, 197.16, 202.83 (C=O). MALDI-TOF: calcd for $[M + Na]^+$ m/z = 556.159, found 556.233; anal. calcd For $C_{30}H_{23}N_5O_5$: C, 67.53; H, 4.35; N, 13.13. Found: C, 67.59; H, 4.28; N, 13.24.

Conclusions

A feasible and efficient one-pot tandem annulation of the hydrazonals **1a–o** with acetoacetanilide **2** was performed under three different heating modes (conventional heating, ultrasound and microwave irradiation) and resulted in the formation of a series of novel class of the 2-arylcinnolin-6(2*H*)-one derivatives **3a–o**. Microwave irradiation proved to be superior and efficient tool over ultrasound and conventional heating, for the promotion of such annulation reactions using ethanol as solvent and Et_3N as a base.

Conflicts of interest

There are no conflicts to declare.

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