

Trisodium citrate dihydrate catalyzed synthesis of fully and diversely functionalized novel piperidinone derivatives

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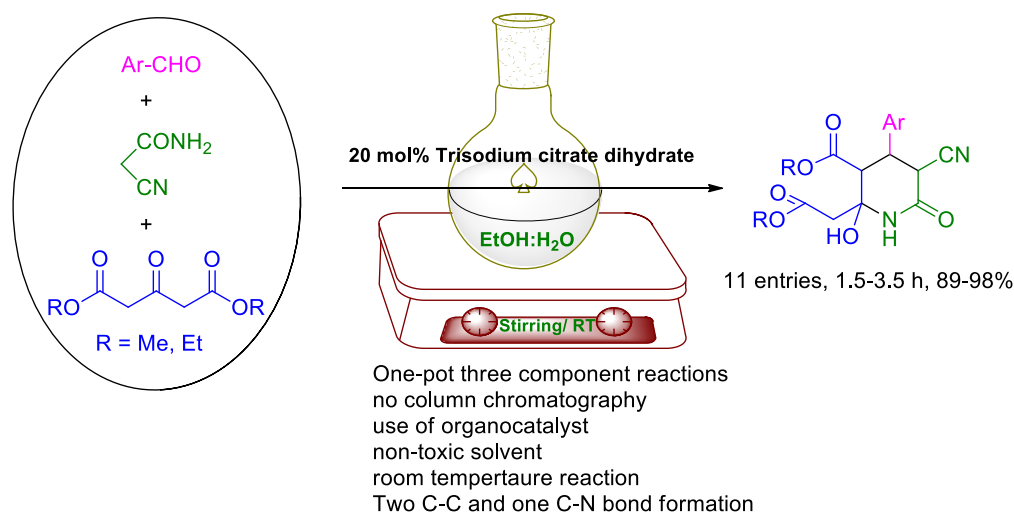
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Abstract

Piperidinones are abundantly available in many naturally occurring bioactive compounds. Many commercially available drug molecules also include a piperidinone skeleton. We have developed an easy and novel protocol for the efficient synthesis of a series of fully and diversely functionalized piperidinones from the one-pot three-component reactions of various aldehydes, cyanoacetamide and 1,3-dimethylacetonedicarboxylate or 1,3-diethylacetonedicarboxylate in the presence of a catalytic amount of trisodium citrate dihydrate as catalyst, in aqueous ethanol at ambient temperature. To the best of our knowledge this is the first developed protocol for the synthesis of these biologically promising scaffolds. This method, has many advantages such as synthesis of fully and diversely functionalized novel bioactive piperidinone derivatives, use of trisodium citrate dihydrate as an efficient metal-free organocatalyst, non-toxic solvents, high atom economy, excellent yields, gram scale synthesis, reusability of the reaction media, room temperature reaction, etc.



Keywords: Novel piperidinone derivatives; trisodium citrate dihydrate; multicomponent reactions; room temperature reactions

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Introduction

Piperidine derivatives have gained huge attention due to their significant biological importance.¹ Piperidine-containing compounds are well distributed in naturally occurring compounds having significant biological importance. Figure 1 shows a selection of naturally occurring bioactive compounds with piperidine moiety as the main building block.²⁻⁹ The piperidine skeleton is very common in commercially available drugs used for the treatment of various diseases like depression, Parkinson disease, bronchial asthma, protozoan infections, pruritic skin disorders, etc (Figure 2).¹⁰⁻²⁴ Recent studies revealed that various synthetic piperidine derivatives possess significant biological efficacies which include anticancer, farnesyltransferase (FTase) inhibitor, antioxidant, and monoamine transport inhibitor activities (Figure 3).²⁵⁻²⁸ Among many other piperidine derivatives, specifically, 2-piperidinone can be isolated from *Talinum portulacifolium*.²⁹ Many drug molecules viz., awajanomycin, tedanalactam, meloscine etc consist of a 2-piperidinone skeleton and have been used as antiasthmatic, antifungal, antimicrobial, MDM2 (murine double minute 2) inhibitor and prostaglandin agonists (Figure 4).²⁹⁻³⁴ After realizing the biological importance of piperidine and piperidinone moieties we were motivated to develop a protocol for the synthesis of a series of fully and diversely functionalized piperidinone derivatives under relatively milder conditions. In this aim we have been successful and synthesized a series of novel methyl/ethyl 4-(4-aryl)-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate derivatives in excellent yields from one-pot three-component reactions of aromatic aldehydes (**1**), cyanoacetamide (**2**) and 1,3-dimethylacetonedicarboxylate (**3a**) or 1,3-diethylacetonedicarboxylate (**3b**) by using a catalytic amount of trisodium citrate dihydrate as an efficient organocatalyst in aqueous ethanol at room temperature (Scheme 1).

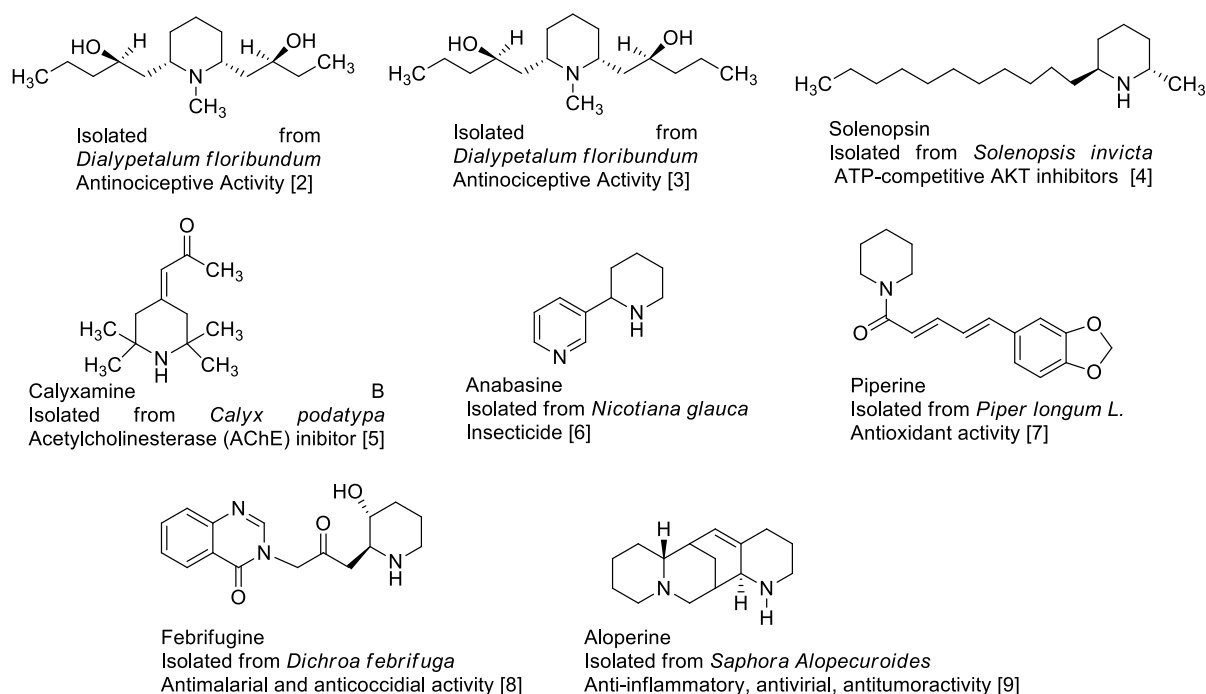


Figure 1. Some naturally occurring bioactive molecules with a piperidine skeleton.

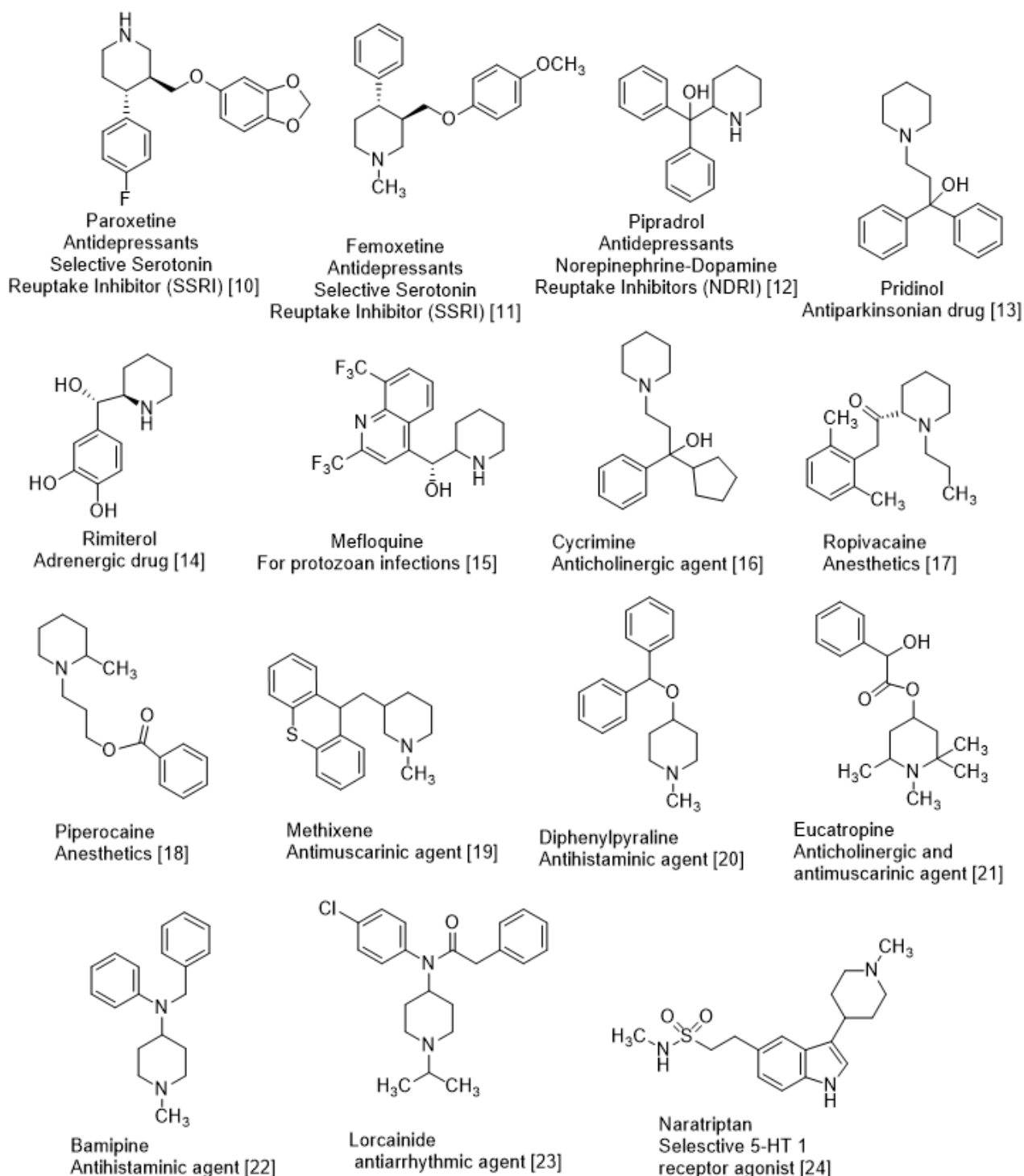


Figure 2. A sample of commercially available drugs with a piperidine moiety.

The use of multicomponent reaction strategies makes protocols more atom-economic and cost effective.³⁵⁻⁴² In addition, nowadays, use of metal-free organocatalysts for the diverse organic transformations is increasing rapidly.⁴³⁻⁴⁷ Among many others, trisodium citrate dihydrate has gained considerable attention for the synthesis of various heterocyclic scaffolds⁴⁸⁻⁵⁰ as it is a non-toxic, inexpensive and commercially available. It is fully biodegradable and used in WHO-recommended rehydrating drinks. It is also plays an important role in some medicines.⁵¹ Therefore, the use of trisodium citrate dihydrate as catalyst, even on a large scale, is safe for the environment without any hazardous effect.⁵² To the best of our knowledge, this is the first report of

the synthesis of methyl/ethyl 4-aryl-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate derivatives. Through this protocol we were able to decorate a piperidinone skeleton with five substituents, cyano, substituted phenyl, ester, hydroxyl and alkyl acetate, at four different positions.

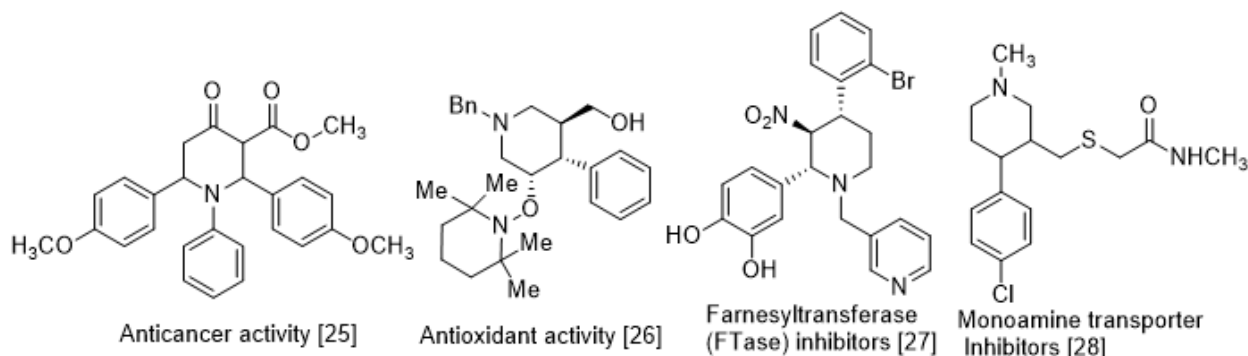


Figure 3. Some synthetic piperidine or related derivatives with important biological activities.

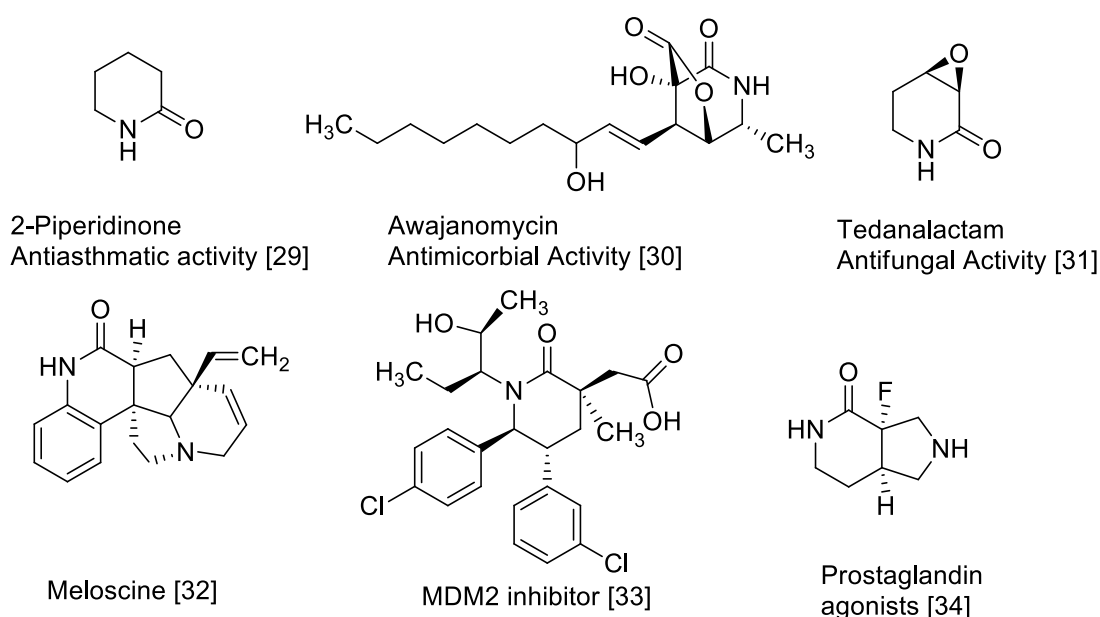


Figure 4. Some naturally occurring and synthetic bioactive piperidinone derivatives.

Results and Discussion

During optimization of the reaction conditions, a series of trial reactions between 4-chlorobenzaldehyde (**1a**; 0.5 mmol), cyanoacetamide (**2**; 0.5 mmol) and 1,3-dimethylacetonedicarboxylate (**3**; 0.5 mmol) was carried out under various reaction conditions. At the beginning, we carried out the reaction at room temperature under stirring conditions in the absence of any catalyst or solvent, but under these conditions no desired product was obtained, even after 10 hours (Table 1, entry 1). Under catalyst-free conditions, none of the desired product was obtained either in water or ethanol as the solvent even after 10 h at room temperature (Table 1, entries 2,3). After observing the poor yields under catalyst free conditions we decided to use trisodium citrate dihydrate as catalyst, in continuation of our previous strong interest. Thus, we used 20 mol %

of trisodium citrate dihydrate as catalyst for a reaction in water as solvent which afforded a 55% yield of the desired product i.e., methyl 4-(4-chlorophenyl)-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (**4a**), after 5 hours of stirring (Table 1, entry 4). Though this was a significant improvement in the yield but we were not satisfied with the yield and the reaction time. Using the same amount of catalyst, a slight improvement in the product yields was observed in ethanol (Table 1, entry 5) or methanol (Table 1, entry 6) as solvent under stirring at room temperature for 5 hours. Surprisingly, when we used aqueous-ethanol (1:1 v/v) as solvent and 20 mol % trisodium citrate dihydrate as catalyst, an excellent yield (98%) of the compound (**4a**) was obtained within just two hours (Table 1, entry 7). From these observations, we realized that aqueous ethanol may be the best suitable solvent to carry out this reaction in the presence of trisodium citrate dihydrate as catalyst. We were then interested to standardize the amount of required catalyst for that we carried out the same reaction in the presence of 15 mol % and 25 mol % trisodium citrate dihydrate as catalyst separately. No notable improvement was observed in the reaction rate with 25 mol % trisodium citrate dihydrate as catalyst (Table 1, entry 9) whereas substantial decrease in the product yield was noted with 15 mol % trisodium citrate dihydrate (Table 1, entry 8).

Without altering the other conditions, the catalytic efficiency of a number of other catalysts such as 20 mol % sodium formate (Table 1, entry 10), 20 mol % glycine (Table 1, entry 11), 20 mol % ammonium citrate (Table 1, entry 12), 20 mol % ammonium formate (Table 1, entry 13) were also screened, but all of them afforded poorer yields of the desired product, as compared to 20 mol% trisodium citrate dihydrate. Therefore, from these above experimental results, we concluded that 20 mol % of trisodium citrate dihydrate in aqueous ethanol (1:1 v/v) as solvent are the best conditions for the synthesis of methyl 4-(4-chlorophenyl)-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (**4a**) from the equimolar reaction of 4-chlorobenzaldehyde (**1a**; 0.5 mmol), cyanoacetamide (**2**; 0.5 mmol) and 1,3-dimethylacetonedicarboxylate (**3a**; 0.5 mmol) under stirring conditions at room temperature (Table 1, entry 7).

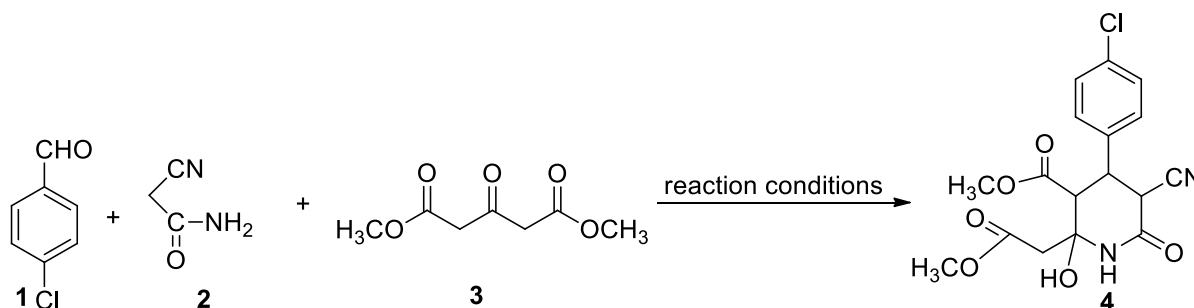
To check the effectiveness as well as the generality of our developed protocol we were then interested to synthesize some other derivatives by using some other benzaldehydes under the same optimized reaction conditions. We found that a number of substituted benzaldehydes, with both electron-withdrawing (Table 2, entries 2-5) or -donating (Table 2, entry 6) substituents, all underwent the reaction smoothly and afforded the desired products in 89-96% yields (**4b-4f**).

Under the same reaction conditions, reactions with various substituted benzaldehydes, cyanoacetamide (**2**; 0.5 mmol), 1,3-diethylacetonedicarboxylate (**3b**; 0.5 mmol) also afforded the desired products i.e. ethyl 5-cyano-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-4-aryl)-6-oxopiperidine-3-carboxylates in excellent yields (Table 2, entries 7-11). The reaction with 1,3-diethylacetonedicarboxylate (**3b**; 0.5 mmol) required a little longer time than 1,3-dimethylacetonedicarboxylate (**3a**; 0.5 mmol). We were able to synthesize methyl 4-(4-chlorophenyl)-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (**4a**, 1.71 g, 90%) in gram scale from the reaction of 4-chlorobenzaldehyde (**1a**; 5 mmol, 0.703 g), cyanoacetamide (**2**; 5 mmol, 0.420 g) and 1,3-dimethylacetonedicarboxylate (**3a**; 5 mmol, 0.87 g) using 20 mol % of trisodium citrate dihydrate (0.294 g) in 20 mL aqueous ethanol (1:1 v/v) for 5 hours. No column chromatographic purification was required. The synthesized compound was isolated pure just by simple filtration and subsequent washing with aqueous ethanol. During the gram-scale synthesis, the filtrate containing catalyst was collected quantitatively and the same was reused for another run of the same reaction. This time we isolated 73% (1.58 g) of the targeted product (**4a**) within 5 hours.

A plausible mechanism of this transformation is shown in Figure 5. It was assumed that the reactions of aldehydes and cyanoacetamide generated the Knoevenagel condensation products in situ (I-1) under the influence of a catalytic amount of trisodium citrate dihydrate. Without isolating the intermediate, in the same

vessel, an equimolar amount of 1,3-dimethylacetonedicarboxylate (**3a**) or 1,3-diethylacetonedicarboxylate (**3b**) was added. The enol form of the compound (**3'**) was then attacked the *in situ* formed Knoevenagel adduct to generate the 2nd intermediate (**I-2**) which on further cyclization afforded the desired products (**4**).

Table 1. Optimization of the reaction conditions for the synthesis of methyl 4-(4-chlorophenyl)-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate



Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%) ^{a,b}
1	Catalyst-free	Neat	10	-
2	Catalyst-free	H ₂ O	10	trace
3	Catalyst-free	EtOH	10	trace
4	Trisodium citrate dihydrate (20)	H ₂ O	5	55
5	Trisodium citrate dihydrate (20)	EtOH	5	75
6	Trisodium citrate dihydrate (20)	MeOH	5	69
7	Trisodium citrate dihydrate (20)	EtOH:H ₂ O	2	98
8	Trisodium citrate dihydrate (15)	EtOH:H ₂ O	2	75
9	Trisodium citrate dihydrate (25)	EtOH:H ₂ O	2	96
10	Sodium formate (20)	EtOH:H ₂ O	2	73
11	Glycine (20)	EtOH:H ₂ O	2	55
12	Ammonium citrate (20)	EtOH:H ₂ O	2	77
13	Ammonium formate (20)	EtOH:H ₂ O	2	62

^aReaction conditions: 4-chlorobenzaldehyde (**1a**; 0.5 mmol), cyanoacetamide (**2**; 0.5 mmol) and 1,3-dimethylacetonedicarboxylate (**3**; 0.5 mmol) in the absence or presence of catalyst in neat/4 mL of water/ethanol/aqueous ethanol as solvent at room temperature (28-35 °C). ^bIsolated yields.

Table 2. Synthesis of alkyl-4-aryl-5-cyano-2-hydroxy-2-(2-alkoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate derivatives

Entry	Ar	R	Product	Time (h)	Yield (%) ^{a,b}
1	4-ClC ₆ H ₄ (1a)	Me	4a	2	98
2	2-NO ₂ C ₆ H ₄ (1b)	Me	4b	1.5	90
3	4-NO ₂ C ₆ H ₄ (1c)	Me	4c	2.5	94
4	3-CNC ₆ H ₄ (1d)	Me	4d	2	91
5	4-CNC ₆ H ₄ (1e)	Me	4e	2	95
6	3,4,5-(OMe) ₃ C ₆ H ₂ (1f)	Me	4f	2	98
7	2-NO ₂ C ₆ H ₄ (1b)	Et	4g	2	89
8	4-CNC ₆ H ₄ (1e)	Et	4h	2.5	93
9	4-NO ₂ C ₆ H ₄ (1c)	Et	4i	3	91
10	2,4-Cl ₂ C ₆ H ₄ (1g)	Et	4j	3.5	94
11	3,4,5-(OMe) ₃ C ₆ H ₂ (1f)	Et	4k	3	98

^aReaction conditions: substituted benzaldehydes (**1**; 0.5 mmol), cyanoacetamide (**2**; 0.5 mmol) and 1,3-dimethylacetonedicarboxylate (**3a**; 0.5 mmol) or 1,3-diethylacetonedicarboxylate (**3b**; 0.5 mmol) in the presence of 20 mol % of trisodium citrate dihydrate as catalyst in aqueous ethanol at room temperature (28-35 °C). ^bIsolated yields

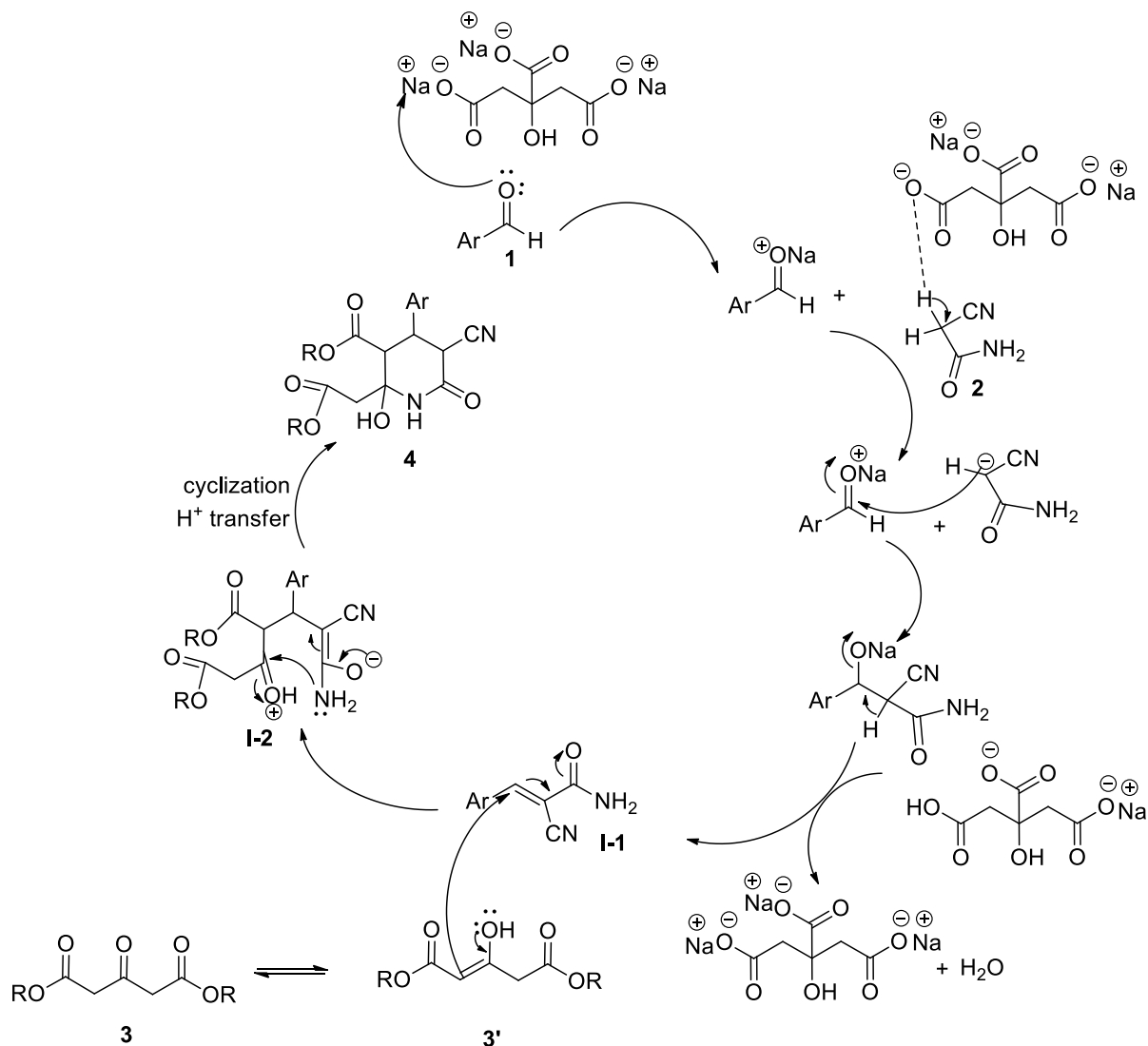


Figure 5. Proposed mechanism for the synthesis of alky 4-aryl-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate.

Experimental Section

General. Melting points were recorded on a Digital Melting Point Apparatus (Model No. MT-934) and are uncorrected. TLC was performed on silica gel 60 F254 (Merck) plates. ¹H and ¹³C NMR spectra were obtained at 500 MHz Jeol (JNM ECX-500) NMR machines with CDCl₃/DMSO-*d*₆ as the solvent. Mass spectra (TOF-MS ES⁺) were measured on a Bruker Impact HD QTOF Micro mass spectrometer. All the chemicals were purchased from Sigma Aldrich and used without further purification.

General procedure for the synthesis of alkyl-4-aryl-5-cyano-2-hydroxy-2-(2-alkoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate derivatives (4a-4k). In a clean reaction tube, a magnetic stir bar, substituted benzaldehyde (1; 0.5 mmol), cyanoacetamide (2; 0.5 mmol), 20 mol % trisodium citrate dihydrate and aqueous ethanol (1:1 v/v; 4 mL) were added in a sequential manner. Then the reaction tube was placed on a magnetic stirrer and the reaction mixture was allowed to stir vigorously at room temperature for 1 h. In this process a white coloured material was formed. After that, 1,3-dimethylacetonedicarboxylate (3a) (0.5 mmol) or 1,3-

diethylacetonedicarboxylate (**3b**) (0.5 mmol) was added the stirring was continued for the time mentioned in Table 2, monitored by TLC. On completion, white products precipitated out which were isolated pure by simple filtration and subsequent washing with aqueous ethanol. The structure of the each purified fully and diversely functionalised piperidinone scaffold was confirmed by the detailed physical as well as spectroscopic characterization techniques including FT-IR, ^1H NMR, ^{13}C NMR and HRMS analyses.

Methyl 4-(4-chlorophenyl)-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (4a). Light yellow solid, yield 98%; mp 142 °C; FTIR (cm^{-1}): 3421, 1726, 1682, 1359, 1219, 1087, 615, 507, 434; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} /ppm: 8.67 (s, 1H, -NH), 7.39 (d, J 8.5 Hz, 2H, aromatic H), 7.33 (d, J 8.5 Hz, 2H, aromatic H), 6.57 (s, 1H, -OH), 4.33 (d, J 12 Hz, 1H, -CH), 3.91 (t, J 12.5 Hz, 1H, -CH), 3.69 (d, J 12.5 Hz, 1H, aromatic H), 3.62 (s, 3H, -OCH₃), 3.33 (s, 3H, -OCH₃), 2.82 (dd, J 17 Hz, 2H, -CH₂); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ_{C} /ppm: 170.22, 169.88, 168.84, 162.94, 159.07, 138.59, 132.82, 130.49 (2C), 129.09 (2C), 80.75, 52.57, 52.14, 52.07, 43.11, 41.97; HRMS (ESI-TOF) m/z : For $\text{C}_{17}\text{H}_{17}\text{ClN}_2\text{O}_6$ Calcd. $[\text{M}]^+$ 380.0775; Found $[\text{M-H}]^-$ 379.0355.

Methyl 5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-4-(2-nitrophenyl)-6-oxopiperidine-3-carboxylate (4b). Light yellow solid, yield 90%; mp 153-155 °C; FTIR (cm^{-1}): 3423, 2355, 1681, 1344, 1218 848, 699, 617; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} /ppm: 8.80 (s, 1H, -NH), 7.88-7.86 (m, 1H, aromatic H), 7.77-7.69 (m, 2H, aromatic H), 7.52-7.49 (m, 1H, aromatic H), 6.79 (s, 1H, OH), 4.65-4.63 (m, 2H, -CH), 3.71-3.69 (m, 1H, -CH), 3.68 (s, 3H, -OCH₃), 3.26 (s, 3H, -OCH₃), 2.88 (dd, J 17 Hz, 2H, -CH₂); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ_{C} /ppm: 170.25, 168.73, 167.74, 162.86, 151.05, 134.05, 133.74, 129.48, 128.96, 124.96, 116.66, 80.74, 53.61, 52.41, 52.11, 42.94, 40.94; HRMS (ESI-TOF) m/z : For $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_8$ Calcd. $[\text{M} + \text{Na}]^+$ 414.1016; Found $[\text{M} + \text{Na}]^+$ 414.1050.

Methyl 5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-4-(4-nitrophenyl)-6-oxopiperidine-3-carboxylate (4c). Light yellow solid, yield 94%; mp 140 °C; FTIR (cm^{-1}): 3423, 2355, 1681, 1344, 1218, 848, 699, 617; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} /ppm: 8.75 (s, 1H, -NH), 8.19 (d, J 9 Hz, 2H, aromatic H), 7.61 (d, J 8.5 Hz, 2H, aromatic H), 6.64 (s, 1H, -OH), 4.46 (d, J 12.5 Hz, 1H, -CH), 4.09 (t, J 12.5 Hz, 1H, -CH), 3.81 (d, J 12.5 Hz, 1H, aromatic H), 3.63 (s, 3H, -OCH₃), 3.32 (s, 3H, -OCH₃), 2.85 (dd, J 17 Hz, 2H, -CH₂); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ_{C} /ppm: 170.20, 168.68, 162.63, 147.59 (2C), 147.18, 130.02, 124.32 (2C), 124.12 (2C), 117.13, 117.10, 80.83, 52.11, 40.62, 40.46; HRMS (ESI-TOF) m/z : For $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_8$ Calcd. $[\text{M} + \text{Na}]^+$ 414.1016; Found $[\text{M} + \text{Na}]^+$ 414.1050.

Methyl 5-cyano-4-(3-cyanophenyl)-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (4d). White solid, yield 91%; mp 163 °C; 3422, 2355, 1722, 1679, 1348, 1216, 619, 548, 458; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} /ppm: 8.77 (s, 1H, -NH), 7.81 (s, 1H, aromatic H), 7.75 (d, J 8 Hz, 1H, aromatic H), 7.75 (d, J 8 Hz, 1H, -CH), 7.55 (d, J 8 Hz, 1H, -CH), 6.65 (s, 1H, -OH), 4.47 (d, J 12 Hz, 1H, -CH), 3.99 (t, J 12.5 Hz, 1H, -CH), 3.75 (d, J 12.5 Hz, 1H, -CH), 3.63 (s, 3H, -OCH₃), 3.32 (s, 3H, -OCH₃), 2.83 (dd, J 17 Hz, 2H, -CH₂); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ_{C} /ppm: 170.17, 168.75, 162.81, 141.18, 134.14, 132.20, 132.00 (2C), 119.10, 117.24, 112.10, 80.76, 52.27 (2C), 52.09 (2C), 42.97, 41.60; HRMS (ESI-TOF) m/z : For $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_6$ Calcd. $[\text{M}]^+$ 371.1117; Found $[\text{M-H}]^-$ 370.0476.

Methyl 5-cyano-4-(4-cyanophenyl)-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (4e). White solid, yield 95%; mp 151 °C; FTIR (cm^{-1}): 3422, 2355, 1722, 1679, 1348, 1216, 619, 548, 458; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} /ppm: 8.73 (s, 1H, -NH), 7.81 (d, J 8.5 Hz, 2H, aromatic H), 7.52 (d, J 8 Hz, 2H, aromatic H), 6.61 (s, 1H, -OH), 4.43 (d, J 12 Hz, 1H, -CH), 4.02 (t, J 12.5 Hz, 1H, -CH), 3.77 (d, J 12 Hz, 1H, aromatic H), 3.63 (s, 3H, -OCH₃), 3.32 (s, 3H, -OCH₃), 2.84 (dd, J 17 Hz, 2H, -CH₂); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ_{C} /ppm: 170.18, 168.71, 162.72, 145.15, 133.05 (2C), 129.80 (2C), 119.03, 117.15, 111.20, 80.81, 52.23 (2C), 52.07 (2C), 43.06, 41.54; HRMS (ESI-TOF) m/z : For $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_6$ Calcd. $[\text{M}]^+$ 371.1117; Found $[\text{M-H}]^-$ 370.0476.

Methyl 5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxo-4-(3,4,5-trimethoxyphenyl)piperidine-3-carboxylate (4f). White solid, yield 98%; mp 181-182 °C; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ_{H} /ppm: 8.65 (s, 1H, -NH), 6.59 (s, 2H, aromatic H), 6.61 (s, 1H, -OH), 4.41 (d, J 12 Hz, 1H, -CH), 3.80 (t, J 12.5 Hz, 1H, -CH), 3.73 (s,

6H, 2X -OCH₃), 3.64 (d, *J* 8.5 Hz, 1H, -CH), 3.62 (s, 3H, -OCH₃), 3.61 (s, 3H, -OCH₃), 3.36 (s, 3H, -OCH₃), 2.79 (dd, *J* 16.5 Hz, 2H, -CH₂); ¹³C NMR (125 MHz, DMSO-*d*₆) δ_c/ppm: 170.25, 169.07, 163.31, 153.21 (2C), 137.23, 135.07, 117.65, 105.99, 80.67, 60.48 (2C), 56.49 (2C), 52.84 (2C), 52.14, 52.09, 43.06, 41.99); HRMS (ESI-TOF) *m/z*: For C₂₀H₂₄N₂O₉ Calcd. [M+Na]⁺ 459.1482; Found [M+Na]⁺ 459.1274.

Ethyl 5-cyano-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-4-(2-nitrophenyl)-6-oxopiperidine-3-carboxylate (4g). Light yellow solid, yield 89%; mp 161-163 °C; FTIR (cm⁻¹): 3742, 3307, 3153, 2361, 1738, 1356, 1053, 649, 537, 436; ¹H NMR (500 MHz, DMSO-*d*₆) δ_H/ppm: 8.76 (s, 1H, -NH), 7.89 (d, *J* 8.5 Hz, 1H, aromatic H), 7.76-7.71 (m, 1H, aromatic H), 7.70 (d, *J* 8 Hz, 1H, aromatic H), 7.51 (td, *J* 17 Hz, *J* 8 Hz, *J* 7.5 Hz, 1H, aromatic H), 6.71, (s, 1H, OH), 4.69-4.59 (m, 2H, -CH), 4.11-4.060 (m, 2H, -OCH₂), 3.80-3.77 (m, 1H, -CH), 3.71-3.67 (m, 2H, -OCH₂), 2.88 (d, *J* 17 Hz, 1H, -CH₂), 2.76 (d, *J* 17 Hz, 1H, -CH₂), 1.17 (t, *J* 7 Hz, 3H, -OCH₃), 0.78 (t, *J* 7 Hz 3H, -OCH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ_c/ppm: 169.74, 168.21 (2C), 162.86, 134.07, 133.99, 129.39, 128.96, 125.02, 116.64, 80.74, 61.17, 60.70, 53.41, 41.15, 40.56, 33.43, 14.58, 13.91; HRMS (ESI-TOF) *m/z*: For C₁₉H₂₁N₃O₈ Calcd. [M+Na]⁺ 442.1329; Found [M+Na]⁺ 442.1194.

Ethyl 5-cyano-4-(4-cyanophenyl)-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-6-oxopiperidine-3-carboxylate (4h). Light yellow solid, yield 93%; mp 155 °C; FTIR (cm⁻¹): 3741, 3304, 3192, 2361, 1733, 1318, 1060, 721, 526, 437; ¹H NMR (500 MHz, DMSO-*d*₆) δ_H/ppm: 8.78 (s, 1H, -NH), 7.82 (d, *J* 8 Hz, 2H, aromatic H), 7.51 (d, *J* 8.5 Hz, 2H, aromatic H), 6.60 (s, 1H, OH), 4.57-4.33 (d, *J* 12 Hz, 1H, -CH), 4.10-4.078 (m, 2H, -OCH₂), 4.00 (t, *J* 12.5 Hz, 1H, -CH), 3.85-3.81 (m, 1H, -CH), 3.75-3.70 (m, 2H, -OCH₂), 2.88 (d, *J* 17 Hz, 1H, -CH₂), 2.76 (d, *J* 17 Hz, 1H, -CH₂), 1.77 (t, *J* 7 Hz, 3H, -OCH₃), 0.82 (t, *J* 7 Hz, 3H, -OCH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ_c/ppm: 169.67, 168.19 (2C), 162.76, 145.20, 133.07 (2C), 129.89, 119.22, 119.072, 111.10, 107.99, 80.78, 60.94, 60.70, 51.95, 43.03, 41.58, 14.59, 14.03; HRMS (ESI-TOF) *m/z*: For C₂₀H₂₁N₃O₈ Calcd. [M+K]⁺ 438.1430; Found [M+K]⁺ 438.1109.

Ethyl 5-cyano-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-4-(4-nitrophenyl)-6-oxopiperidine-3-carboxylate (4i). Light yellow solid, yield 91%; mp 162 °C; FTIR (cm⁻¹): 3742, 3307, 3153, 2361, 1738, 1356, 1053, 649, 537, 436; ¹H NMR (500 MHz, DMSO-*d*₆) δ_H/ppm: 8.76 (s, 1H, -NH), 8.20 (d, *J* 9 Hz, 2H, aromatic H), 7.61 (d, *J* 8.5 Hz, 2H, aromatic H), 6.61 (s, 1H, OH), 4.45 (d, *J* 12.5 Hz, 1H, -CH), 4.11-4.06 (m, 2H, -OCH₂, 1H, -CH), 3.85-3.71 (m, 2H, -OCH₂, 1H, -CH), 2.89 (d, *J* 17 Hz, 1H, -CH₂), 2.78 (d, *J* 17 Hz, 1H, -CH₂), 1.87 (t, *J* 7 Hz, 3H, -CH₃), 0.84 (t, *J* 7 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ_c/ppm: 169.70, 168.15, 162.65, 147.58, 147.23, 130.22 (2C), 124.17 (2C), 117.14, 80.84, 61.01, 60.72, 52.04, 43.10, 41.61 (2C), 14.58, 14.04; HRMS (ESI-TOF) *m/z*: For C₁₉H₂₁N₃O₈ Calcd. [M+Na]⁺ 442.1329; Found [M+Na]⁺ 442.1194

Ethyl 5-cyano-4-(2,4-dichlorophenyl)-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-6-oxopiperidine-3-carboxylate (4j). White solid, yield 94%; mp 174 °C; FTIR (cm⁻¹): 3741, 3377, 3297, 2360, 1717, 1519, 1355, 1054, 625, 518, 436; ¹H NMR (500 MHz, DMSO-*d*₆) δ_H/ppm: 8.70 (s, 1H, -NH), 7.60 (d, *J* 2 Hz, 1H, aromatic H), 7.48 (d, *J* 8.5 Hz, 1H, aromatic H), 7.43 (dd, *J* 2 Hz, 1H, aromatic H) 6.66 (s, 1H, OH), 4.60 (d, *J* 12 Hz, 1H, -CH), 4.31 (d, *J* 12 Hz, 1H, -CH), 4.12-4.08 (m, 2H, -OCH₂), 3.87-3.83 (m, 1H, -CH), 3.76-3.71 (m, 2H, -OCH₂), 2.90 (d, *J* 16.5 Hz, 1H, -CH₂), 2.78 (d, *J* 17 Hz, 1H, -CH₂), 1.18 (t, *J* 7 Hz, 3H, -CH₃), 0.84 (t, *J* 7 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ_c/ppm: 169.77, 168.16, 162.74, 136.91, 136.03, 133.22, 129.72, 128.42, 117.47, 116.75, 80.83, 60.96, 60.71, 52.54, 43.26, 41.59 (2C), 14.57, 13.96; HRMS (ESI-TOF) *m/z*: For C₁₉H₂₀Cl₂N₂O₆ Calcd. [M+Na]⁺ 465.0596; Found [M+Na]⁺ 465.0704

Ethyl 5-cyano-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-6-oxo-4-(3,4,5-trimethoxyphenyl)piperidine-3-carboxylate (4k). White solid, yield 98%; mp 197 °C; FTIR (cm⁻¹): 3741, 3305, 3155, 2361, 1725, 1517, 1317, 1054, 627, 519, 435; ¹H NMR (500 MHz, DMSO-*d*₆) δ_H/ppm: 8.67 (s, 1H, -NH), 6.59 (s, 2H, aromatic H), 6.49 (s, 1H, OH), 4.39 (d, *J* 12.5 Hz, 1H, -CH), 4.11 (m, 2H, -OCH₂), 3.88-3.79 (m, 2H, -OCH₂, 1H, -CH), 3.72 (s, 6H, 2 x -OCH₃), 3.6 (t, 3H, -OCH₃, 1H, -CH), 2.85 (d, *J* 16.5 Hz, 1H, -CH₂), 2.70 (d, *J* 17 Hz, 1H, -CH₂), 1.19-1.165 (m, 3H, -CH₃), 0.83 (t, *J* 7

Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ_C/ppm: 169.71, 168.55, 164.54, 163.30, 153.18, 137.30, 135.05, 117.66, 106.05, 80.68, 78.71, 60.74, 60.64, 60.49, 56.47, 52.64 (2C), 43.24, 42.12 (2C), 14.54, 14.12; HRMS (ESI-TOF) *m/z*: For C₂₂H₂₈N₂O₉ Calcd. [M+Na]⁺ 487.1693; Found [M+Na]⁺ 487.1756.

Conclusions

In conclusion, we have developed an easy, efficient and novel protocol for the synthesis of a series of fully and diversely functionalized piperidinone derivatives *via* one-pot three-component reactions of substituted benzaldehydes, cyanoacetamide and 1,3-dimethylacetonedicarboxylate/1,3-diethylacetonedicarboxylate in the presence of 20 mol % trisodium citrate dihydrate as catalyst in aqueous ethanol at ambient temperature. This is the first report of the synthesis of these biologically promising scaffolds. Benzaldehydes with both electron-donating as well as -withdrawing substituents are well tolerated under the developed conditions and afford the desired products in excellent yields. Through this protocol we were able to decorate the piperidinone skeleton with five different substituents such as cyano, substituted benzene rings, ester, hydroxyl and alkyl acetate at four different positions. The desired products were formed through the formation of two new C-C and one C-N bonds. Synthesis of fully and diversely functionalized novel bioactive scaffolds, excellent yields, high atom economy, use of trisodium citrate dihydrate as an efficient metal-free organocatalyst, non-toxic solvents, gram scale synthesis, reusability of the reaction media, energy efficiency, one-pot three-component synthesis, high atom economy are some of the notable advantages of this newly developed protocol.

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Supplementary Material

Scanned spectra including FTIR, ¹H-NMR, ¹³C-NMR and HRMS of all the synthesized scaffolds are given in Supporting Information.

References

1. Frolov, N. A.; Vereshchagin, A. N. *Int. J. Mol. Sci.* **2023**, *24*, 2937.
<https://doi.org/10.3390/ijms24032937>
2. Saify, Z. S.; Khan, K. M.; Haider, S. M.; Zeeshan, Shah, S. T. A.; Saeed, M.; Shekhani, M. S. Voelter, W. *Zeitschrift für Naturforschung B*, **1999**, *54*, 1327-1336.
<https://doi.org/10.1515/znb-1999-1017>

3. Krebs, H. C.; Ramiarantsoa, H. *Phytochemistry*, **1998**, *48*, 911-913.
[https://doi.org/10.1016/S0031-9422\(97\)00929-1](https://doi.org/10.1016/S0031-9422(97)00929-1)
4. Arbiser, J. L.; Kau, T.; Konar, M.; Narra, K.; Ramchandran, R.; Summers, S. A.; Vlahos, C. J.; Ye, K.; Perry, B. N.; Matter, W.; Fischl, A.; Cook, J.; Silver, P. A.; Bain, J.; Cohen, P.; Whitmire, D.; Furness, S.; Govindarajan, B.; Bowen, J. P. *Blood*, **2007**, *109*, 560-565.
<https://doi.org/10.1182/blood-2006-06-029934>
5. Meza-León, R. L.; Dávila-García, A.; Sartillo-Piscil, F.; Quintero, L.; Rivadeneyra, M.S.; Cruz-Gregorio, S. *Tetrahedron Lett.* **2013**, *54*, 6852-6854.
<https://doi.org/10.1016/j.tetlet.2013.10.022>
6. Kuete, V. In *Toxicological Survey of African Medicinal Plants* **2014**, 611-633. Elsevier.
<https://doi.org/10.1016/B978-0-12-800018-2.00021-2>
7. Gorgani, L.; Mohammadi, M.; Najafpour, G. D. Nikzad, M. *Compt. Rev. Food Sci. Food Saf.* **2017**, *16*, 124-140.
<https://doi.org/10.1111/1541-4337.12246>
8. Gill, J.; Sharma, A. *Drug Discov. Today* **2022**, *27*, 2586–2592
<https://doi.org/10.1016/j.drudis.2022.05.020>
9. Cheng, Y.; Rauf, A.; Pan, X. *Med. Chem.* **2022**, *22*, 729–742.
<https://doi.org/10.2174/1389557521666210831155426>
10. Germann, D.; Ma, G.; Han, F.; Tikhomirova, A. Brittain, H. G.; Ed. *Profiles of drug substances, excipients, and related methodology.* **2013**, *38*, 367-406.
<https://doi.org/10.1016/B978-0-12-407691-4.00008-3>
11. Wei, P.; Kaatz, G. W.; Kerns, R. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3093-3097.
<https://doi.org/10.1016/j.bmcl.2004.04.018>
12. White, M. W.; Archer, J. R. *Novel Psychoactive*, **2013**, 233-259.
<https://doi.org/10.1016/B978-0-12-415816-0.00010-9>
13. Richter, M.; Donath, F.; Wedemeyer, R. S.; Warnke, A.; Horstmann, A.; Peschel, C. *Int. J. Clin. Pharmacol. Ther.* **2021**, *59*, 471-477.
<https://doi.org/10.5414/CP203900>
14. Evans, M. E.; Shenfield, G. M.; Thomas, N.; Walker, S. R. Paterson, J. W. *Xenobiotica*, **1974**, *4*, 681-692.
<https://doi.org/10.3109/00498257409052083>
15. *The International Encyclopedia of Adverse Drug Reactions and Interactions*, **2016**, 790-798.
16. Tacke, R.; Kornek, T.; Heinrich, T.; Burschka, C.; Penka, M.; Pülm, M.; Keim, C.; Mutschler, E.; Lambrecht, G. *J. Organomet. Chem.* **2001**, *640*, 140-165.
[https://doi.org/10.1016/S0022-328X\(01\)01179-2](https://doi.org/10.1016/S0022-328X(01)01179-2)
17. Hansen, T. G. *Expert Rev. Neurother.* **2004**, *4*, 781-791.
<https://doi.org/10.1586/14737175.4.5.781>
18. Tiedt, T. N.; Albuquerque, E. X.; Bakry, N. M.; Eldefrawi, M. E.; Eldefrawi, A. T. *Mol. Pharmacol.* **1979**, *16*, 909-921.
19. Brittain, H.G. *Analytical Profiles of Drug Substances and Excipients*. Academic Press. **1994**, ISBN: 9780080861180
20. Lapa, G. B.; Mathews, T. A.; Harp, J.; Budygin, E. A.; Jones, S. R. *Eur. J. Pharmacol.* **2005**, *506*, 237-240.
<https://doi.org/10.1016/j.ejphar.2004.11.017>
21. Smith, S. E. *The Lancet*, **1971**, *298* (7729), 837-839.
[https://doi.org/10.1016/S0140-6736\(71\)90218-2](https://doi.org/10.1016/S0140-6736(71)90218-2)

22. Neidlein, R.; Kleiser, M. *Arzneimittel-forschung*, **1987**, *37*, 337-339.
23. Keefe, D. L. *Am. J. Card.* **1984**, *54*, 18-21.
[https://doi.org/10.1016/0002-9149\(84\)90819-1](https://doi.org/10.1016/0002-9149(84)90819-1)
24. Mathew, N. T.; Asgharnejad, M.; Peykamian, M.; Laurenza, A. *Neurology*, **1997**, *49*, 1485-1490.
<https://doi.org/10.1212/WNL.49.6.1485vv>
25. Aeluri, R.; Alla, M.; Bommena, V. R.; Murthy, R.; Jain, N. *Asian J. Org. Chem.* **2012**, *1*, 71-79.
<https://doi.org/10.1002/ajoc.201200010>
26. Kim, J. H.; Shyam, P. K.; Kim, M. J.; Lee, H. J.; Lee, J. T.; Jang, H.Y. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3119-3121
<https://doi.org/10.1016/j.bmcl.2016.04.092>
27. Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hughes, P. F.; Turkington, S.; Kanda, Y. *J. Med. Chem.* **2003**, *46*, 2467-2473.
<https://doi.org/10.1021/jm020522k>
28. He, R.; Kurome, T.; Giberson, K. M.; Johnson, K. M.; Kozikowski, A. P. *J. Med. Chem.* **2005**, *48*, 7970-7979
<https://doi.org/10.1021/jm050694s>
29. Mamillapalli, V.; Shaik, A. R.; Avula, P. R. *J. Res. Pharm.* **2020**, *24*, 334-340.
<https://doi.org/10.35333/jrp.2020.155>
30. Jang, J. H.; Kanoh, K.; Adachi, K.; Shizuri, Y. *J. Nat. Prod.* **2006**, *69*, 1358-1360.
<https://doi.org/10.1021/np060170a>
31. Majik, M. S.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, *74*, 6378-6381.
<https://doi.org/10.1021/jo901143b>
32. Selig, P.; Bach, T. *Angew. Chem., Int. Ed.*, **2008**, *47*, 5082-5084.
<https://doi.org/10.1002/anie.200800693>
33. Rew, Y.; Sun, D.; Gonzalez-Lopez De Turiso, F.; Bartberger, M. D.; Beck, H. P.; Canon, J.; Chen, A.; Chow, D.; Deignan, J.; Fox, B. M. Gustin, D. *J. Med. Chem.* **2012**, *55*, 4936-4954.
<https://doi.org/10.1021/jm300354j>
34. Tran, A. P. Honors College Theses, University of Massachusetts Boston **2015**.
<https://doi.org/10.1021/jm300354j>
35. Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085-2093.
<https://doi.org/10.2174/0929867023368719>
36. Kaur, G.; Devi, P.; Thakur, S.; Kumar, A.; Chandel, R.; Banerjee, B. *ChemistrySelect.* **2018**, *3*, 9892-9910.
<https://doi.org/10.1002/slct.201801887>
37. Banerjee, B.; Kaur, M.; Sharma, V.; Gupta, V. K.; Kaur, J.; Sharma, A.; Priya, A.; Singh, A. *Res. Chem. Intermed.* **2023**, *49*, 4639-4670.
<https://doi.org/10.1007/s11164-023-05064-w>
38. Banerjee, B.; Brahmachari, G. *J. Chem. Res.* **2014**, *38*, 745-750.
<https://doi.org/10.3184/174751914X14177132210020>
39. Banerjee, B.; Kaur, M.; Sharma, A.; Singh, A.; Priya, A.; Gupta, V. K.; Jaitak, V. *Curr. Green Chem.* **2022**, *9*, 162-173.
<https://doi.org/10.2174/2213346110666221212152202>
40. Sharma, A.; Singh, A.; Priya, A.; Kaur, M.; Gupta, V. K.; Jaitak, V.; Banerjee, B. *Synth. Commun.* **2022**, *52*, 1614-1627.
<https://doi.org/10.1080/00397911.2022.2101378>

41. Basu, B.; Banerjee, B. *Multicomponent Synthesis: Bioactive Heterocycles*, Berlin, Boston: De Gruyter, 2024. <https://doi.org/10.1515/9783110985313>
42. Banerjee, B.; Priya, A.; Kaur, M.; Sharma, A.; Singh, A.; Gupta, V. K.; Jaitak, V. *Cat. Lett.* **2023**, *153*, 3547-3560. <https://doi.org/10.1007/s10562-022-04256-0>
43. Banik, B. K.; Banerjee, B. *Organocatalysis: A Green Tool for Sustainable Developments*, Berlin, Boston: De Gruyter, **2022**. <https://doi.org/10.1515/9783110732542>
44. Banerjee, B.; Singh, A.; Sharma, A.; Priya, A.; Kaur, M.; Kaur, G.; Kumar, V. *Arkivoc*, **2022**, 100-118. <https://doi.org/10.24820/ark.5550190.p011.895>
45. Banerjee, B.; Bhardwaj, V.; Kaur, A.; Kaur, G.; Singh, A.; *Curr. Org. Chem.* **2019**, *23*, 3191-3205. <https://doi.org/10.2174/1385272823666191121144758>
46. Brahmachari, G.; Banerjee, B. *Curr. Organocatal.* **2016**, *3*, 93–124. <https://doi.org/10.2174/2213337202666150812230830>
47. Banerjee, B. *Curr. Org. Chem.* **2018**, *22*, 208–233. <https://doi.org/10.2174/1385272821666170703123129>
48. Brahmachari, G.; Banerjee, B. *Asian J. Org. Chem.* **2016**, *5*, 271–286. <https://doi.org/10.1002/ajoc.201500465>
49. Kaur, M.; Priya, A.; Sharma, A.; Singh, A.; Banerjee, B. *Synth. Commun.* **2022**, *52*, 1635-1656. <https://doi.org/10.1080/00397911.2022.2090262>
50. Banerjee, B.; Singh, A.; Sharma, A.; Priya, A.; Kaur, M.; Gupta V. K. *Polycycl. Aromat. Compd.* **2024**, *44*, 3747-3760 <https://doi.org/10.1080/10406638.2023.2238869>
51. Pierce, D. A.; Rocco, M. V. *Pharmacotherapy: J. Human Pharmacol. Drug Ther.*, **2010**, *30*, 1150-1158. <https://doi.org/10.1592/phco.30.11.1150>
52. Gruber, C. M. Halbeisen, W. A. *J. Pharmacol. Exp. Ther.* **1948**, *94*, 65–67.

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