

Evaluation of magnetically recyclable nano-Fe₃O₄ as a green catalyst for the synthesis of mono- and bistetrahydro-4*H*-chromene and mono and bis 1,4-dihydropyridine derivatives

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Abstract Magnetically separable Fe_3O_4 nanoparticles were used as an environmental friendly catalyst for the synthesis of mono- and bis-tetrahydro-4*H*-chromene and mono- and bis-1,4-dihydropyridine derivatives via three-component reactions of aromatic aldehydes and malononitrile with cyclic β -dicarbonyls or cyclic β -enaminoketones respectively. These reactions were carried out in EtOH and at reflux. Fe₃O₄ nanoparticles can be magnetically separated from the reaction mixture by a magnet and recycled without significant loss of catalytic activity.

Keywords Fe_3O_4 nanoparticles \cdot Tetrahydro-4*H*-chromenes \cdot 1,4-Dihydropyridines \cdot Three-component reaction

Introduction

Multicomponent reactions (MCRs) are useful to make complex molecules with reliable synthetic yield, frequently with high stereoselectivity, and easily accessible reactants [1–3]. Improvement of MCRs can result in useful synthetic methods to produce many organic compounds potentially applicable in current organic, bioorganic, and medicinal chemistry [4–6].

Due to their unique chemical and biological properties, bis-heterocyclic compounds have attracted much attention in recent years [7–9]. Particularly, bis-

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heterocyclic compounds, which exhibit various biological activities, including antibacterial, fungicidal, tuberculostatic, and antiamoebic properties [10–12], play important roles in the drug discovery processes and analysis of drugs in late development.

In this context, the three-component reaction of aromatic aldehydes and malononitrile with cyclic β -dicarbonyls or cyclic β -enaminoketones has been one of the most well-studied MCRs in recent years. The reaction affords formation of mono- and bis-tetrahydro-4*H*-chromene and mono- and bis-1,4-dihydropyridine derivatives, respectively.

Tetrahydro-4*H*-chromenes due to their lucrative biological and pharmacological properties are used as a momentous class of heterocyclic compounds in the pharmaceutical applications such as anticancer [13], antimalarial [14], antileishmanial [15], antibacterial [16], antifungal [17], antianaphylactic [18], antiallergenic [19], diuretic [20], and hypotensive [21] agents.

Also, 1,4-dihydropyridines are of an important class of compounds with a wide range of biological activities [22]. Due to being pharmacologically active and acting as antitumor [23], calcium channel blocker [24], antitubercular [25], analgesic [26], antithrombotic [27], anti-inflammatory [28], anticonvulsant agents [29], they are of many interests.

Applications of tetrahydro-4*H*-chromene and 1,4-dihydropyridine derivatives necessitates the advancement in the environmentally friendly procedures to synthesize these compounds by three-component reaction of aromatic aldehydes and malononitrile with cyclic β -dicarbonyls or cyclic β -enaminoketones, respectively. There are various catalytic systems for the synthesis of tetrahydro-4*H*-chromene [30–39] and 1,4-dihydropyridine [40, 41] derivatives by MCR, but these systems suffer from disadvantages like the use of toxic organic solvents, costly catalysts, existence of transition metals, difficult work up, time-consuming reaction, and low yield. Thus, a simple and green synthesis of tetrahydro-4*H*-chromenes and 1,4-dihydropyridines needs to be carried out without association of these catalytic systems.

The field of nanocatalysis is a rapidly growing field, which involves the use of nanoparticles as catalysts for a variety of homogeneous and heterogeneous catalysis applications, owing to their remarkably different and unique properties, which include a high surface area, easy recovery, and nanosize [42, 43]. Nanocatalysts are esteemed as materials of enormous surface areas and with new investigation, developments may offer expanding catalytic abilities [44-46]. Heterogeneous catalysis characterizes one of the oldest commercial practices of nanoscience, nanoparticles of metals and other compounds have been extensively used for important chemical reactions. Fe₃O₄ nanoparticles (Fe₃O₄ NPs) have been used as recyclable catalysts in the development of sustainable methodologies [47] for synthesis of compounds such as xanthenes [48], oximes [49], quinoxalines [50], fused azo-linked pyrazolo[4,3-e]pyridines [51], 1,8-dioxo-decahydroacridine [52], propargylamines [53] and many more, because of their significant characteristics such as the ease of magnetic separation from the reaction mixture, non-toxicity, and being widely accessible. But Fe_3O_4 NPs has never been used in the synthesis of tetrahydro-4*H*-chromene (4a-x) and 1,4-dihydropyridine (7a-t) derivatives. Hence,

we set about to synthesize the aimed compounds in refluxing EtOH by using Fe_3O_4 NPs as a catalyst for the first time.

Results and discussion

To optimize the reaction conditions, a methodical study considering different variables affecting the reaction time and yield was carried out for the three-component reaction of benzaldehyde **1a**, malononitrile **2**, and dimedone **3a** in the presence of Fe₃O₄ NPs as catalysts for preparing compound 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **4a** (Scheme 1). The results are shown in Table 1.

We used some polar and nonpolar solvents in this reaction for which the best results in terms of reaction time and yield of the desired product **4a** was obtained when the reaction was conducted in ethanol (Table 1, entry 1–4). We also optimized the quantity of the catalysts. The best results were obtained when the reactions were carried out in the presence of 30 mol% Fe₃O₄ NPs (Table 1, entry 5–8). We also attempted to reuse the catalyst; the catalyst was easily separated from the reaction mixture by an external magnet and reused (after washing with ethanol and dried) for three consecutive runs, and no obvious diminishing activity was observed (Table 1, entry 9–11).

Relying on our collected data, we decided to apply this method for synthesis of tetrahydro-4*H*-chromene (**4a**–**k**, **m**–**w**) and 1,4-dihydropyridine (**7a**–**d**, **f**–**i**, **k**–**n**, **p**–**s**) derivatives by a three-component reaction of aromatic aldehydes (**1a**–**k**) and malononitrile (**2**) with cyclic β -dicarbonyls (**3a**, **b**) or cyclic β -enaminoketone (**6a**–**d**) respectively, in EtOH, under reflux, and in the presence of Fe₃O₄ NPs (30 mol%) (Scheme 2; Tables 2, 3).

We were stimulated by this success, so the versatility of the reaction was explored further by extending the procedure to the synthesis of bis-tetrahydro-4*H*-chromene (**4**I, **x**) and bis-1,4-dihydropyridine derivatives (**7e**, **j**, **o**, **t**) via reaction of para phthalaldehyde (**1**I) with two equiv. malononitrile (**2**) and β -dicarbonyls (**3a**, **b**) or cyclic β -enaminoketone (**6a**–**d**) under similar conditions (Scheme 3; Tables 2, 3).

A plausible mechanism for the nano Fe_3O_4 catalyzed is illustrated in Scheme 4. The nano Fe_3O_4 facilitates the Knoevenagel condensation and Michael addition through coordination of its Fe^{3+} with O of the carbonyl group and with N from CN.



Scheme 1 Three-component reaction of benzaldehyde 1a, malononitrile 2, and dimedone 3a in the presence of Fe_3O_4 NPs as catalysts for a model reaction

Table 1 Optimization of the model reaction between	Entry	Solvent	Catalyst (mol%)	Time (min)	Yield (%)
benzaldehyde 1a, malononitrile 2, and dimedone 3a	1	EtOH	30	5	93
	2	CH ₃ CN	30	20	88
	3	EtOAc	30	35	82
	4	Toluene	30	60	65
	5	EtOH	15	22	85
	6	EtOH	20	15	87
	7	EtOH	25	10	90
	8	EtOH	35	5	93
3 T '	9 ^a	EtOH	30	6	91
^h First run	10 ^b	EtOH	30	7	90
^c Third run	11 ^c	EtOH	30	9	89



Scheme 2 Synthesis of tetrahydro-4*H*-chromene (4a-k, m-w) and 1,4-dihydropyridine (7a-d, f-i, k-n, p-s) derivatives

Conclusions

In summary, we have reported the use of magnetically separable Fe_3O_4 nanoparticles for the synthesis of mono- and bis-tetrahydro-4*H*-chromene and mono- and bis-1,4dihydropyridine derivatives via the three-component reaction of aromatic aldehydes and malononitrile with cyclic β -dicarbonyls or cyclic β -enaminoketones, respectively. These reactions were carried out in EtOH at reflux. Recycling of the catalyst, high yields, short reaction times, and clean reaction conditions are advantages of this procedure that make it a useful practical process for the synthesis of these compounds.

Table 2 Three-component reaction of aromatic aldehydes (1a-k), malononitrile (2) and dimedone (3a) or 1,3-cyclohexanedione (3b)



4a-k, m-w



Compd. no.	R	Ar	Time (min)	Yield (%)	M. P. observed (°C)	M. P. reported (°C)
4a	Me	C ₆ H ₅	5	93	231–232	234–236 [30]
4b	Me	4-Cl-C ₆ H ₄	4	94	215-217	216–218 [30]
4c	Me	2,4-(Cl) ₂ -C ₆ H ₃	4	95	175-178	178–179 [32]
4d	Me	4-Br-C ₆ H ₄	5	94	221-222	222–224 [<mark>30</mark>]
4e	Me	$4-NO_2-C_6H_4$	4	95	181–182	180–182 [30]
4f	Me	4-CH ₃ -C ₆ H ₄	6	91	218-220	219–221 [30]
4g	Me	4-CH ₃ O-C ₆ H ₄	7	90	200-202	201–203 [30]
4h	Me	4-OH-C ₆ H ₄	9	88	225-228	226-228 [30]
4i	Me	Furan-2-yl	9	90	221-222	220-222 [30]
4j	Me	Thiophen-2-yl	10	89	227-229	226–228 [30]
4k	Me	Pyridin-3-yl	10	89	206-207	206-207 [38]
41	Me	p-Phthalaldehyde	13	88	>300 (dec.)	>300 (dec.) [39]
4m	Н	C ₆ H ₅	6	92	230-231	229–231 [32]
4n	Н	4-Cl-C ₆ H ₄	5	93	223-226	225–227 [32]
4o	Н	2,4-(Cl) ₂ -C ₆ H ₃	4	94	220-222	221–223 [32]
4p	Н	$4-Br-C_6H_4$	5	93	248-250	248-250 [38]
4q	Н	$4-NO_2-C_6H_4$	4	94	234–237	235–237 [32]
4r	Н	4-CH ₃ -C ₆ H ₄	7	91	223-225	224–226 [31]
4s	Н	4-CH ₃ O-C ₆ H ₄	8	89	189–191	190–192 [32]
4t	Н	$4-OH-C_6H_4$	10	87	256-258	257–259 [31]
4u	Н	Furan-2-yl	12	89	237-239	237–239 [38]
4v	Н	Thiophen-2-yl	13	88	210-211	210-211 [38]
4 w	Н	Pyridin-3-yl	13	88	229-230	229–230 [38]
4x	Н	p-Phthalaldehyde	15	88	>300 (dec.)	

Experimental section

General

Melting points were measured on a Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Brucker FT-IR Tensor 27 infrared spectrophotometer. ¹H NMR and spectra were recorded on a Avance III 400 MHz

Table 3 Three-component reaction of aromatic aldehydes $(1a\mathchar`-g),$ malononitrile (2) and cyclic enaminoketones $(6a\mathchar`-d)$





7a-d, f-i, k-n, p-s



Compd. no.	R	R'	Ar	Time (min)	Yield (%)	M. P. observed (°C)	M. P. reported (°C)
7a	Me	Н	C ₆ H ₅	12	91	262–264	265–267 [40]
7b	Me	Н	$4-CH_3O-C_6H_4$	15	89	279-281	279–281 [41]
7c	Me	Н	4-Br-C ₆ H ₄	10	92	210 (dec.)	210 (dec.) [41]
7d	Me	Н	Pyridin-3-yl	13	90	248-250	
7e	Me	Н	p-Phthalaldehyde	15	89	191 (dec.)	
7f	Me	C_6H_5	C ₆ H ₅	10	92	244-245	246-248 [40]
7g	Me	C_6H_5	$4-CH_3-C_6H_4$	12	91	243-245	243-245 [41]
7h	Me	C_6H_5	4-Br-C ₆ H ₄	8	93	269-271	269–271 [41]
7i	Me	C_6H_5	Pyridin-3-yl	11	91	265-267	
7j	Me	C_6H_5	p-Phthalaldehyde	13	90	200 (dec.)	
7k	Н	Н	C ₆ H ₅	15	90	254 (dec.)	254 (dec.) [41]
71	Н	Н	$4-CH_3-C_6H_4$	17	89	269-271	269–271 [41]
7m	Н	Н	4-Cl-C ₆ H ₄	12	92	296–298	296–298 [41]
7n	Н	Н	Pyridin-3-yl	15	89	287-289	
7o	Н	Н	p-Phthalaldehyde	17	88	260 (dec)	
7p	Н	C_6H_5	C ₆ H ₅	12	91	110 (dec.)	110 (dec.) [41]
7q	Н	C_6H_5	4-CH ₃ -C ₆ H ₄	15	89	235 (dec.)	235 (dec.) [41]
7r	Н	C_6H_5	4-Cl-C ₆ H ₄	10	93	228-230	228-230 [41]
7s	Н	C_6H_5	Pyridin-3-yl	13	90	237–238	
7t	Н	C_6H_5	<i>p</i> -Phthalaldehyde	15	89	230 (dec.)	

Bruker spectrometer. The cyclic enaminoketones **6a–d** [54] were prepared from according to procedures described in the literature.

Preparation of Fe₃O₄ nanoparticles

To a solution of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (2.5 g) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (6 g) in 30 mL deionized water was added dropwise 1.0 mL of concentrated hydrochloric acid at room temperature. The solution was added into 300 mL of 1.5 mol/L NaOH, and then the solution was stirred vigorously at 70 °C until precipitation. Afterwards, the prepared magnetic nanoparticles were separated magnetically, washed with deionized water, and then dried at 70 °C for 8 h [48].



Scheme 3 Synthesis of bis-tetrahydro-4H-chromene (4l, x) and bis-1,4-dihydropyridine (7e, j, o, t) derivatives

General procedure for the preparation of mono- and bis-tetrahydro-4H-chromene (4a-x) and mono- and bis-1,4-dihydropyridine (7a-t) derivatives

A mixture of aromatic aldehydes **1a–k** (2 mmol) [if para phthalaldehyde **11** (1 mmol)], malononitrile **2** (2 mmol), cyclic β -dicarbonyls **3a**, **b** or cyclic β -enaminoketones **6a–d** (2 mmol) and Fe₃O₄ nanoparticles (30 mol%) in ethanol (10 mL) was refluxed for the time reported in Table 2, 3 (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as an eluent). After completion of the reaction, the catalyst was separated magnetically from the reaction mixture. Then the reaction mixture was poured into ice-cold water; the crude product was filtered, dried, and recrystallized from ethanol.

4,4'-(1,4-Phenylene)bis(2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (4x) Yellow powder; IR (KBr, v_{max}/cm^{-1}): 3456, 3392 (NH₂), 2192 (CN), 1680 (C=O), 1593 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 7.38 (s, 4H, CH-Ar), 7.04 (s, 4H, 2NH₂), 4.11 (s, 2H, 2CH), 3.31–1.32 (m, 12H, 6CH₂). ¹³C NMR (100 MHz, DMSO-d₆): 195.21 (C=O), 163.27 (C2), 157.12 (C8a), 146.47 (C-Ar), 128.63 (CH-Ar), 121.11 (C4a), 114.08 (CN), 62.25 (C3), 48.98 (CH₂), 43.87 (CH₂), 37.89 (C4), 26.14 (CH₂). Anal. calcd. for C₂₆H₂₂N₄O₄: C, 68.71; H, 4.88; N, 12.33 %. Found: C, 68.49; H, 4.69; N, 12.14 %.

2-*Amino*-7,7-*dimethyl*-5-*oxo*-4-(*pyridin*-3-*yl*)-1,4,5,6,7,8-*hexahydroquinoline*-3*carbonitrile* (7*d*) Yellow powder; IR (KBr, v_{max}/cm^{-1}): 3472, 3360, 3312 (NH₂, NH), 2192 (CN), 1699 (C=O), 1606 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 9.07 (s, 1H, NH), 8.27 (s, 1H, CH-Ar), 7.78–7.25 (m, 3H, CH-Ar), 5.38 (s, 2H, NH₂), 4.43 (s, 1H, CH), 2.27 (d, 1H, ²J_{HH} = 4 Hz, CH), 2.21 (d, 1H, ²J_{HH} = 4 Hz, CH),



Scheme 4 Plausible mechanism for the nano Fe₃O₄ catalyzed

2.07 (d, 1H, ${}^{2}J_{HH} = 8$ Hz, CH), 1.78 (d, 1H, ${}^{2}J_{HH} = 8$ Hz, CH), 1.07 (s, 3H, CH₃), 0.91 (s, 3H, CH₃). 13 C NMR (100 MHz, DMSO-d₆): 192.21 (C=O), 164.78 (C2), 158.14 (C8a), 153.25, 137.02, 135.14, 130.54, 128.11, 124.32 (C4a), 114.21 (CN), 63.70 (C3), 49.74 (CH₂), 41.89 (CH₂), 38.25 (C4), 35.28 (CMe₂), 32.21 (CH₃), 28.98 (CH₃). Anal. calcd. for C₁₇H₁₈N₄O: C, 69.37; H, 6.16; N, 19.03 %. Found: C, 69.15; H, 5.98; N, 18.84 %.

4,4'-(1,4-Phenylene)bis(2-amino-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile) (7e) Yellow powders; IR (KBr, v_{max}/cm^{-1}): 3472, 3296, 3232 (NH₂, NH), 2176 (CN), 1648 (C=O), 1590 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 8.98 (s, 2H, 2NH), 7.71 (s, 4H, CH-Ar), 5.27 (s, 4H, 2NH₂), 4.43 (s, 2H, 2CH), 2.51 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 2.35 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 2.18 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 1.61 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 1.01 (s, 6H, 2CH₃), 0.92 (s, 6H, 2CH₃). ¹³C NMR (100 MHz, DMSO-d₆): 193.92 (C=O), 167.87 (C2), 160.34 (C8a), 144.70 (C–Ar), 128.82 (CH-Ar), 121.20 (C4a), 114.08 (CN), 61.28 (C3), 52.48 (CH₂), 46.91 (CH₂), 43.74 (C4), 32.04 (CMe₂), 30.26 (CH₃), 27.77 (CH₃). Anal. calcd. for $C_{30}H_{32}N_6O_2$: C, 70.84; H, 6.34; N, 16.52 %. Found: C, 70.63; H, 6.16; N, 16.33 %.

2-Amino-7,7-dimethyl-5-oxo-1-phenyl-4-(pyridin-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7i) Pale orange powders; IR (KBr, v_{max}/cm^{-1}): 3392, 3312 (NH₂), 2192 (CN), 1670 (C=O), 1587 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 8.12–7.07 (m, 9H, CH-Ar), 5.53 (s, 2H, NH₂), 4.43 (s, 1H, CH), 2.23 (d, 1H, ²J_{HH} = 4 Hz, CH), 2.18 (d, 1H, ²J_{HH} = 4 Hz, CH), 2.01 (d, 1H, ²J_{HH} = 8 Hz, CH), 1.77 (d, 1H, ²J_{HH} = 8 Hz, CH), 0.93 (s, 3H, CH₃), 0.85 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-d₆): 192.65 (C=O), 166.05 (C2), 160.06 (C8a), 157.05, 152.25, 135.29, 133.15, 132.47, 131.62, 131.27, 126.25, 123.58, 121.20 (C4a), 114.32 (CN), 62.69 (C3), 49.78 (CH₂), 43.58 (CH₂), 39.02 (C4), 35.87 (CMe₂), 31.76 (CH₃), 29.54 (CH₃). Anal. calcd. for C₂₃H₂₂N₄O: C, 74.57; H, 5.99; N, 15.12 %. Found: C, 74.35; H, 5.80; N, 14.92 %.

4,4'-(1,4-Phenylene)bis(2-amino-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile) (7j) Yellow powders; IR (KBr, v_{max}/cm^{-1}): 3472, 3328 (NH₂), 2192 (CN), 1638 (C=O), 1590 (C=C). ¹H NMR (400 MHz, DMSOd₆): 7.63–7.58 (m, 8H, CH-Ar), 7.43 (d, 2H, ³J_{HH} = 4 Hz, CH-Ar), 7.24 (d, 4H, ³J_{HH} = 4 Hz, CH-Ar), 5.32 (s, 4H, 2NH₂), 4.47 (s, 2H, 2CH), 2.20 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 2.15 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 2.07 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 1.77 (d, 2H, ²J_{HH} = 8 Hz, 2CH), 0.89 (s, 6H, 2CH₃), 0.77 (s, 6H, 2CH₃). 13C NMR (100 MHz, DMSO-d₆): 194.90 (C=O), 165.04 (C2), 151.08 (C8a), 150.19, 144.41, 136.24, 130.27, 129.71, 126.78, 121.01 (C4a), 113.78 (CN), 60.57 (C3), 49.28 (CH₂), 46.56 (CH₂), 40.93 (C4), 35.91 (CMe₂), 31.98 (CH₃), 28.85 (CH₃). Anal. calcd. for C₄₂H₄₀N₆O₂: C, 76.34; H, 6.10; N, 12.72 %. Found: C, 76.13; H, 5.91; N, 12.54 %.

2-*Amino*-5-*oxo*-4-(*pyridin*-3-*yl*)-1,4,5,6,7,8-*hexahydroquinoline*-3-*carbonitrile* (**7n**) Pale yellow powders; IR (KBr, v_{max}/cm^{-1}): 3456, 3392, 3232 (NH₂, NH), 2192 (CN), 1680 (C=O), 1593 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 8.81 (s, 1H, NH), 8.03 (s, 1H, CH-Ar), 7.68–7.33 (m, 3H, CH-Ar), 5.75 (s, 2H, NH₂), 4.41 (s, 1H, CH), 2.31–1.74 (m, 6H, 3CH₂). ¹³C NMR (100 MHz, DMSO-d₆): 192.25 (C=O), 166.02 (C2), 160.14 (C8a), 156.22, 148.27, 141.59, 137.47, 131.22, 120.75 (C4a), 113.14 (CN), 62.02 (C3), 48.01 (CH₂), 37.12 (CH₂), 36.58 (C4), 27.03 (CH₂). Anal. calcd. for C₁₅H₁₄N₄O: C, 67.65; H, 5.30; N, 21.04 %. Found: C, 67.43; H, 5.12; N, 20.85 %.

4,4'-(1,4-Phenylene)bis(2-amino-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile) (70) Yellow powders; IR (KBr, v_{max}/cm^{-1}): 3392, 3328, 3232 (NH₂, NH), 2176 (CN), 1657 (C=O), 1600 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 8.90 (s, 2H, 2NH), 6.97 (s, 4H, CH-Ar), 5.56 (s, 4H, 2NH₂), 4.84 (s, 2H, 2CH), 2.77–1.28 (m, 12H, 6CH₂). ¹³C NMR (100 MHz, DMSO-d₆): 193.89 (C=O), 169.41 (C2), 159.96 (C8a), 149.80 (C–Ar), 128.67 (CH-Ar), 121.25 (C4a), 115.09 (CN), 62.21 (C3), 49.82 (CH₂), 43.70 (CH₂), 36.54 (C4), 25.82 (CH₂). Anal. calcd. for $C_{26}H_{24}N_6O_2$: C, 69.01; H, 5.35; N, 18.57 %. Found: C, 68.80; H, 5.17; N, 18.38 %.

2-Amino-5-oxo-1-phenyl-4-(pyridin-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7s) Cream powders; IR (KBr, v_{max}/cm^{-1}): 3392, 3328 (NH₂), 2192 (CN), 1658 (C=O), 1593 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 8.23 (s, 1H, CH-Ar), 7.99–7.35 (m, 8H, CH-Ar), 5.78 (s, 2H, NH₂), 4.42 (s, 1H, CH), 3.13–1.87 (m, 6H, 3CH₂). ¹³C NMR (100 MHz, DMSO-d₆): 191.97 (C=O), 166.48 (C2), 160.15 (C8a), 150.12, 142.35, 138.72, 135.28, 134.34, 132.19, 131.79, 128.86, 125.68, 121.14 (C4a), 113.78 (CN), 62.61 (C3), 49.47 (CH₂), 40.25 (CH₂), 39.59 (C4), 28.26 (CH₂). Anal. calcd. for C₂₁H₁₈N₄O: C, 73.67; H, 5.30; N, 16.36 %. Found: C, 73.45; H, 5.12; N, 16.17 %.

4,4'-(1,4-Phenylene)bis(2-amino-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3carbonitrile) (7t) Yellow powders; IR (KBr, v_{max}/cm^{-1}): 3408, 3328 (NH₂), 2176 (CN), 1638 (C=O), 1596 (C=C). ¹H NMR (400 MHz, DMSO-d₆): 7.36–7.32 (m, 6H, CH-Ar), 7.20 (d, 2H, ³J_{HH} = 4 Hz, CH-Ar), 7.99 (s, 4H, CH-Ar), 5.03 (s, 4H, 2NH₂), 4.24 (s, 2H, 2CH), 2.26–1.41 (m, 12H, 6CH₂). ¹³C NMR (100 MHz, DMSO-d₆): 195.15 (C=O), 165.12 (C2), 152.34 (C8a), 150.91, 144.58, 136.23, 130.04, 129.66, 126.82, 121.25 (C4a), 114.05 (CN), 60.48 (C3), 49.11 (CH₂), 42.74 (CH₂), 35.95 (C4), 27.76 (CH₂). Anal. calcd. for C₃₈H₃₂N₆O₂: C, 75.48; H, 5.33; N, 13.90 %. Found: C, 75.27; H, 5.15; N, 13.72 %.

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