Microwave Assisted Green Multicomponent Synthesis of Novel bis(2-Amino-tetrahydro-4*H*-chromene-3-carbonitrile) Derivatives Using Chitosan as Eco-friendly Basic Catalyst

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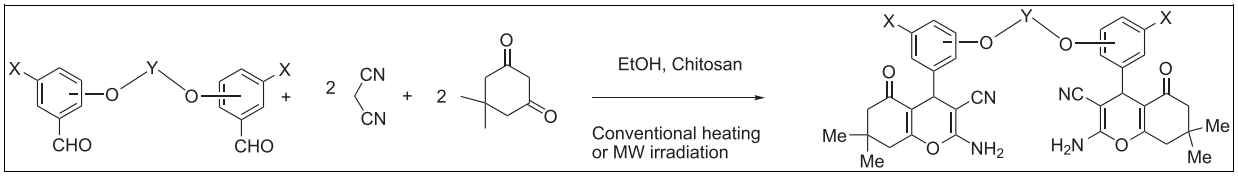

A simple, efficient, and eco-friendly procedure has been developed for the synthesis of bis(4*H*-chromene-3-carbonitrile) derivatives using chitosan as catalyst under microwave-assisted reaction conditions. For the sake of comparison, the reaction was also carried out under conventional heating in the presence of each of chitosan and piperidine as basic catalysts.

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INTRODUCTION

In the last decades, much attention has been paid to the synthesis of 4*H*-benzo[*b*]pyrans because of their wide range of biological activities [1]. They have diverse pharmacological activities such as anti-coagulant, anti-cancer, spasmolytic, diuretic, anti-ancaphylactia, and so on. [2–5]. Some 4*H*-benzo[*b*]pyran derivatives can also be used as cognitive enhancers, for the treatment of neurodegenerative disease, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia, and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [6].

Generally, these compounds have been prepared by the reaction of benzylidene-malononitrile with cyclic ketones in the presence of a catalytic amount of piperidine or in pyridine as solvent and basic catalyst [7–10].

One of the most interesting areas of research in organic synthesis is to develop new methodologies, which allow reducing the reaction time, minimum metal contamination of products, simple reaction conditions, and easy isolation of products and renewability of catalyst. Recently, much attention has been paid towards searching for environmentally friendly processes and sustainable resources. In this respect, the application of natural catalyst became an attractive strategy in organic chemistry. Among natural biopolymers, chitosan (Fig. 1) is the most widely used for catalytic applications [11–15]. The presence of both hydroxyl and amino groups make it useful as a chelating agent. It can activate the nucleophilic as well as electrophilic components of the reactions by hydrogen bonding and presence of lone pairs, respectively [16–27].

Furthermore, microwave heating has emerged as a valuable tool in organic synthesis. It leads to dramatically reduced reaction times, higher yields, and cleaner reaction profiles. Microwave irradiation has been used to improve the synthesis of a large number of organic molecules, and it is also considered as one potential and green chemical pathway to accelerate drug discovery [28–39].

Moreover, multicomponent reactions which involve more than two components are very elegant and rapid way for the synthesis of complex molecules. They reduce the number of reaction steps, minimize by products formation and thus, result in both atom and step economy [40–43].

Furthermore, attention has been increasingly paid, in recent years, to the synthesis of bis-heterocyclic compounds that exhibit various biological activities including antibacterial, fungicidal, tuberculostatic, and plant growth regulative properties [44–46]. Bis-heterocyclic compounds have also numerous applications as electrical materials [47], chelating agents, and metal ligands [48].

In connection with these findings, and in continuation of previous studies on Michael addition reactions for carrying out carbon-carbon forming reactions under both homogeneous and heterogeneous catalysis [49–53], the present study aimed at synthesis of novel bis(4*H*-benzo[*b*]pyrans) by a multicomponent reaction using chitosan as eco-friendly basic catalyst and under microwave irradiation as an efficient energetic heating source.

RESULTS AND DISCUSSION

In a preliminary study in our laboratory [54], we synthesized some bis(4*H*-chromene-3-carbonitrile) derivatives **1**

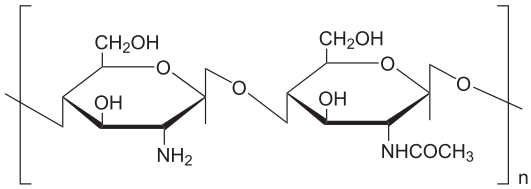


Figure 1. The chemical structure of chitosan.

by one pot, multi-component reaction of the appropriate bis-aldehydes, malononitrile, and dimedone in the presence of a catalytic amount of piperidine (Fig. 2).

In search for a more efficient method for the synthesis of novel bis(4*H*-chromene-3-carbonitrile) derivatives of type **1**, we decided to investigate the aforementioned reaction under microwave irradiation as an efficient energetic heating source using the eco-friendly basic catalyst such as chitosan as substitute to piperidine.

For the sake of comparison, the reaction was also carried out by conventional heating in the presence of each of chitosan and piperidine as basic catalysts.

To achieve the best results for the aforementioned reaction, we studied the synthesis of **1a** by a multicomponent reaction of 2,2′-(ethane-1,2-diylbis(oxy))dibenzaldehyde **2a** with malononitrile **3** and dimedone **4**, as a model substrate using various solvents, different amounts of chitosan catalyst and different reaction times (Scheme 1). The reaction was performed under microwave irradiation (MW) as well as under conventional heating.

Initially, to find the most suitable solvent for the reaction, various solvents (EtOH, *i*-PrOH and dioxan) were used. The results indicated that ethanol was found to be the best solvent for this reaction (Table 1, entry 2).

Secondly, the optimum catalyst loading was next investigated by studying the reaction with different amounts of chitosan. The best results were obtained in the presence of 10 mol% of chitosan (Table 2, entry 5).

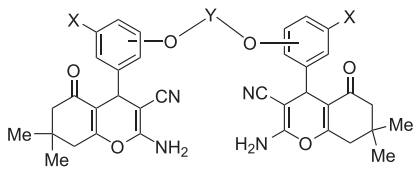


Figure 2. Bis(4*H*-chromene-3-carbonitrile) derivatives **1**.

The obtained results showed that on reducing the amount of catalyst less than 10 mol%, the yield was decreased, while increasing the amount of chitosan over this ratio did not enhance the yield of the reaction (Table 2).

Thus, the best yield, the cleanest reaction, and the most facile work-up were achieved thermally employing 10 mol% of chitosan in refluxing ethanol for 3 h or at 100° C under microwave irradiation of power 250 W.

Subsequently, with optimal condition in hand, the generality and synthetic scope of this reaction was demonstrated by synthesizing a series of bis(4*H*-chromene-

Table 1

Optimizing the yield of compound **1a.**

			(% Yield)[a,b]	
Entry	Solvent	Catalyst	Thermally	Microwave
1	Ethanol	Piperidine	87	88
2	Ethanol	Chitosan	89	92
3	*i*-PrOH	Piperidine	78	82
4	*i*-PrOH	Chitosan	82	85
5	dioxane	Piperidine	78	82
6	dioxane	Chitosan	79	80

[a]The reaction time is 3 h for thermal heating and 10 min for MW (monitored by TLC).
[b]The reaction was performed at 100°C using a microwave of power 250 W.

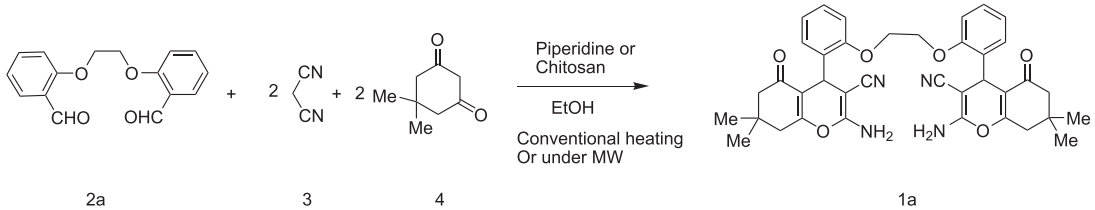
Table 2

Effect of the amount of chitosan catalyst on the synthesis of compound **1a.**

		Time		(% Yield)[a,b]	
Entry	Chitosan (mol %)	Thermally (h)	MW (min)	Thermal	MW
1	5	1	5	75	79
2	5	2	10	80	84
3	5	3	15	82	85
4	10	1	5	80	88
5	10	3	10	88	93
6	15	1	5	80	88
7	15	3	10	88	94

[a]The reaction was performed at 100°C for 10 min. using a microwave of power 250 W.
[b]The reaction was performed in ethanol for 3 h at reflux.
MW, microwave irradiation.

Scheme 1



2a 3 4 1a

3-carbonitriles) **1b-l** (linked to aliphatic and aromatic cores *via* ether linkage) (Scheme 2). Thus, different bis-aldehydes **2a-l** were well tolerated under the optimized reaction conditions and furnished the corresponding bis(4*H*-chromene-3-carbonitriles) in good yields (Table 3).

The constitutions of compounds **1a–l** were established based on their elemental analysis and spectral data. The ^{1}H NMR spectrum of **1a** indicated the presence of two singlets integrated by 12 protons at δ 0.95 and 1.06 ppm assigned to four CH_3. In addition, it indicated two characteristic doublets at 2.11 and 2.25 ppm with coupling constant $J = 16.2$ ppm assigned to H8. The singlet signal at 2.50 ppm is assigned to H6. The pyran-H4 appeared as singlet signal at δ 4.50 ppm. Moreover, compound **1a** as

Scheme 2

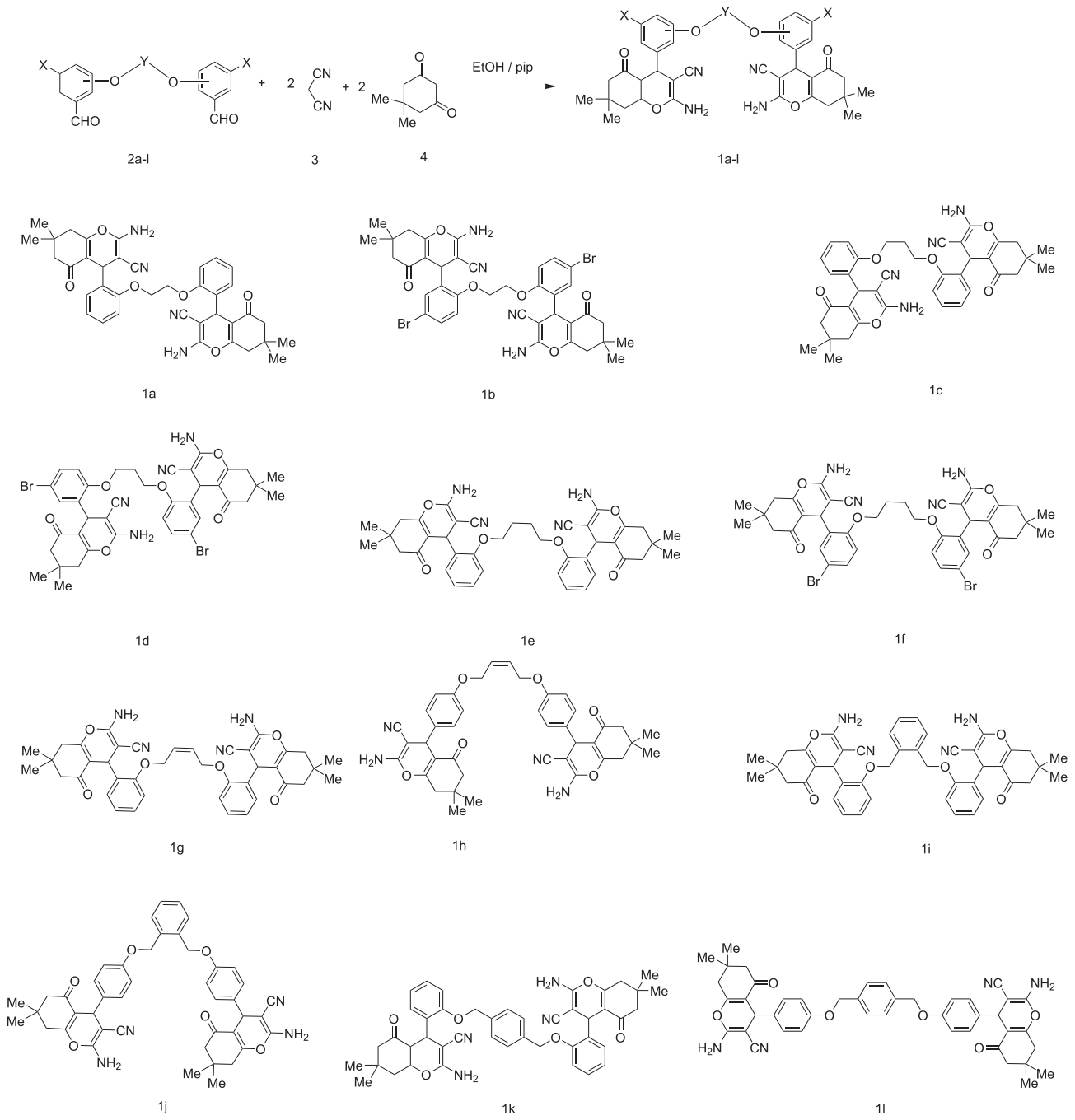


Table 3

Comparison of % yield of products **1a–l** obtained from piperidine and chitosan.

	Yield (%)				Yield (%)		
	Piperidine (Method A)	Chitosan (Method B)	(Method C)		Piperidine (Method A)	Chitosan (Method B)	(Method C)
Entry	Thermal	Thermal	MW	Entry	Thermal	Thermal	MW
1a	87[a]	88	93	**1g**	84	82	87
1b	78[a]	76	82	**1h**	83	87	90
1c	84[a]	86	89	**1i**	87[a]	89	91
1d	76	78	83	**1j**	85[a]	87	93
1e	83[a]	84	87	**1k**	86[a]	91	92
1f	82	80	84	**1l**	82[a]	88	90

[a]These compounds were prepared in our laboratory under conventional heating method and the results has been submitted for publication [54].
MW, microwave irradiation.

well as compounds **1b**, **1i** and **1k** also featured the methylene ether linkage OCH_2 as multiplet or two separate doublets signals in the region 3.98–4.30 ppm, although their precursors **2a**,**2b**,**2i** and **2k** exhibit singlet signals for these protons. This suggests that the generated asymmetric centre (in the dihydropyran rings) is close enough to this CH_2 group. On the other hand, the two methylene ether linkage OCH_2 resonance appears as a singlet in compounds **1j** and **1l** which indicate that the asymmetric center is not close enough to effect such splitting.

The reaction represents a typical cascade reaction in which the arylidenemalononitrile derivatives **5**, containing the electron-poor C–C double bond, is firstly produced by Knoevenagel condensation of the bis-aldehydes **2** with two moles of malononitrile **3**. Compounds **5** then react with two moles of dimedone **4** yielding the final isolable products **1** (Scheme 3, method D, Table 4). In support of this view, we managed to isolate the Knoevenagel condensation products, bis-arylidenemalononitrile derivatives **5a-l** (Scheme 3).

Table 4

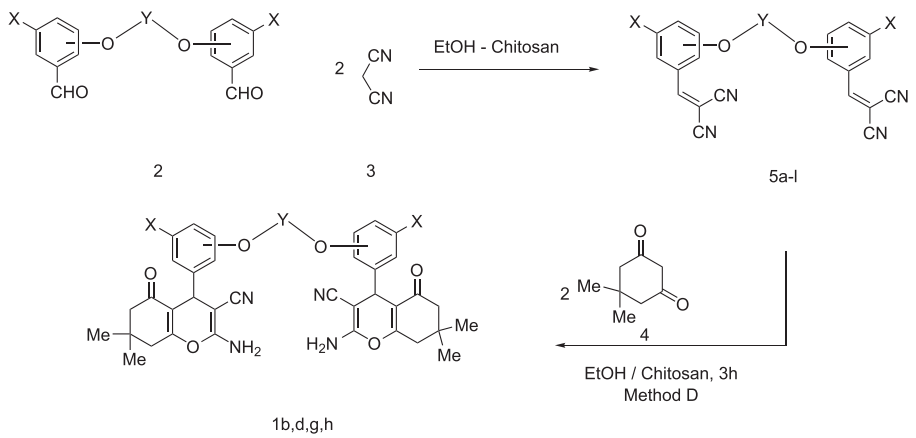
Synthesis of **1b**,**d**,**g**,**h** through the reaction of **5b**,**d**,**g**,**h** with dimedone **4** (Method D).

Compound	% Yield	Compound	% Yield
1b	74	**1g**	77
1d	80	**1h**	80

CONCLUSION

We have reported an easy, efficient, and green protocol for the synthesis of bis-chromenes thermally and under microwave irradiation conditions. The use of chitosan as heterogeneous and reusable catalyst suggests a good prospect for the industrial applicability of this process. The present methodology offers very attractive features such as reduced reaction times and economic viability of the catalyst. The use of microwave reduced the time required for the reaction to 10 min as compared with 3–5 h required by conventional techniques.

Scheme 3



EXPERIMENTAL

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^{1}H NMR) and at 75 MHz ^{13}C NMR. Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography was performed using pre-coated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Microwave experiments were carried out using a CEM Discover Labmate microwave apparatus (300 W with ChemDriver Software).

General procedure for the synthesis of compound 1a–l.

Method A. To a mixture of bisaldehydes **2a-l** (1 m*M*), malononitrile **3** (2.2 m*M*) and dimedone **4** (2.2 m*M*), in absolute ethanol (15 mL) was added piperidine (0.2 mL), and the mixture was heated at reflux for 3 h. The crude solid was isolated and recrystallized from the proper solvent.

Method B. To a mixture of bisaldehydes **2a-l** (1 m*M*), malononitrile (2.2 m*M*) and dimedone **4** (2.2 m*M*) in absolute ethanol (15 mL) was added chitosan (0.1 g), and the mixture was heated at reflux for 3 h. The crude solid was isolated and recrystallized from the proper solvent.

Method C. A mixture of bisaldehydes **2a-l** (1 m*M*), malononitrile (2.2 m*M*) and dimedone **4** (2.2 m*M*) and chitosan (0.1 g) in ethanol (5 mL) in a closed vessel was irradiated in a focused microwave reactor for 10 min at 100°C (250 W). The crude solid was isolated and recrystallized from the proper solvent.

Method D. A mixture of bis-arylidenemalononitrile derivatives **5b**, **5d**, **5g,** and **5h** (1 m*M*) and dimedone **4** (2.2 m*M*) in absolute ethanol (15 mL) was heated at reflux in presence of chitosan (0.1 g) for 3 h. The crude solid was isolated and recrystallized from the proper solvent to give **1b**, **1d**, **1g,** and **1h**, respectively.

4,4′-((Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1a). Pale yellow crystals (dioxan / ethanol), mp 277–279°C, IR (KBr): ν = 3435, 3350 (NH_2), 2194 (CN), 1668 (CO) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.95 (s, 6H, $2CH_3$), 1.06 (s, 6H, $2CH_3$), 2.11 (d, 2H, H8, J = 16.2 Hz), 2.25 (d, 2H, H8, J = 16.2 Hz), 2.50 (s, 4H, H6), 4.27–4.30 (m, 4H, 2-OCH_2), 4.50 (s, 2H, pyran H-4), 6.86–7.22 (m, 12H, ArH + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 646 [M$^+$], *Anal*. Calcd for $C_{38}H_{38}N_4O_6$: C, 70.57; H, 5.92; N, 8.66. Found: C, 70.63; H, 5.87; N, 8.83.

Compound **1a** was obtained in 85% yield using general procedure D.

4,4′-((Ethane-1,2-diylbis(oxy))bis(5-bromo-2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1b). Pale yellow crystals (dioxan / ethanol), mp 265–268°C, IR (KBr): ν = 3436, 3350 (NH_2), 2195 (CN), 1682 (CO) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.95 (s, 6H, $2CH_3$), 1.08 (s, 6H, $2CH_3$), 2.04–2.42 (m, 4H, H8), 2.50 (s, 4H, H6), 4.24–4.35 (m, 4H, 2-OCH_2), 4.50 (s, 2H, pyran H-4) 6.78-7.22 (m, 10H, ArH + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 804 [M$^+$], *Anal*. Calcd for $C_{38}H_{36}Br_2N_4O_6$: C, 56.73; H, 4.51; Br, 19.86; N, 6.96. Found: C, 56.67; H, 4.59; Br, 19.78; N, 6.78.

4,4′-((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1c). Pale yellow crystals (dioxan / ethanol), mp 240–242°C, IR (KBr): ν = 3396, 3305 (NH_2), 2186 (CN), 1654 (CO) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.93 (s, 6H, $2CH_3$), 1.04 (s, 6H, $2CH_3$), 2.0–2.25 (m, 6H, H8 + CH_2), 2.50 (s, 4H, H6), 4.03–4.21 (m, 4H, 2-OCH_2), 4.46 (s, 2H, pyran H-4), 6.81–7.13 (m, 12H, ArH + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 660 [M$^+$], *Anal*. Calcd for $C_{39}H_{40}N_4O_6$: C, 70.89; H, 6.10; N, 8.48. Found: C, 70.93; H, 6.02; N, 8.51.

4,4′-((Propane-1,3-diylbis(oxy))bis(5-bromo-2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1d). Pale yellow crystals (dioxan / ethanol), mp 267–270°C, IR (KBr): ν = 3422, 3326 (NH_2), 2189 (CN), 1670 (CO) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.92 (s, 6H, $2CH_3$), 1.04 (s, 6H, $2CH_3$), 2.04–2.28 (m, 6H, H8 + 2 CH_2), 2.50 (s, 4H, H6), 4.15–4.02 (m, 4H, 2-OCH_2), 4.46 (s, 2H, pyran H-4) 6.93–7.31 (m, 10H, ArH + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 818 [M$^+$], *Anal*. Calcd for $C_{39}H_{38}Br_2N_4O_6$: C, 57.23; H, 4.68; Br, 19.52; N, 6.84. Found: C, 57.41; H, 4.79; Br, 19.45; N, 6.95.

4,4′-((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1e). Pale yellow crystals (dioxan / ethanol), mp 215–217°C, IR (KBr): ν = 3326 (NH_2), 2191 (CN), 1660 (CO) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.96 (s, 6H, $2CH_3$), 1.06 (s, 6H, $2CH_3$), 1.94–2.45 (m, 8H, H8 + $2CH_2$), 2.50 (s, 4H, H6), 3.98–4.05 (m, 4H, 2-OCH_2), 4.49 (s, 2H, pyran H-4), 6.77–7.17 (m, 12H, ArH + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 674 [M$^+$], *Anal*. Calcd for $C_{40}H_{42}N_4O_6$: C, 71.20; H, 6.27; N, 8.30. Found: C, 71.31; H, 6.36; N, 8.27.

4,4′-((Butane-1,4-diylbis(oxy))bis(5-bromo-2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1f). Pale yellow crystals (dioxan / ethanol), mp 238–240°C, IR (KBr): ν = 3428, 3316 (NH_2), 2188 (CN), 1682 (CO) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.93 (s, 6H, $2CH_3$), 1.04 (s, 6H, $2CH_3$), 1.89–2.28 (m, 8H, H8 + $2CH_2$), 2.50 (s, 4H, H6), 3.96–4.02 (m, 4H, 2-OCH_2), 4.45 (s, 2H, pyran H-4), 6.94–7.35 (m, 10H, ArH + $2NH_2$),MS (EI, 70 eV): *m/z* (%) = 832 [M$^+$], *Anal*. Calcd for $C_{40}H_{40}Br_2N_4O_6$: C, 57.70; H, 4.84; Br, 19.19; N, 6.73. Found: C, 57.83; H, 4.72; Br, 19.28; N, 6.78.

4,4′-((But-2-ene-1,4-diylbis(oxy))bis(2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1g). Pale yellow crystals (dioxan / ethanol), mp 252–255°C, IR (KBr): $\nu = 3404$, 3325 (NH_2), 2197 (CN), 1682 (CO) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): $\delta = 0.94$ (s, 6H, $2CH_3$), 1.03 (s, 6H, $2CH_3$), 2.07 (d, 2H, H8, $J = 16.2$ Hz), 2.26 (d, 2H, H8, $J = 16.2$ Hz), 2.50 (s, 4H, H6), 4.49–4.62 (m, 4H, pyran H-4 + 2-OCH_2), 6.09 (s, 2H, vinyl), 6.77–7.15 (m, 12H, ArH + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 672 [M^+], *Anal*. Calcd for $C_{40}H_{40}N_4O_6$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.52; H, 5.78; N, 8.26.

4,4′-((But-2-ene-1,4-diylbis(oxy))bis(4,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1h). Pale yellow crystals (dioxan / ethanol), mp 185–187°C, IR (KBr): ν = 3396, 3329 (NH_2), 2194 (CN), 1678 (CO) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): $\delta = 0.94$ (s, 6H, $2CH_3$), 1.03 (s, 6H, $2CH_3$), 2.06 (d, 2H, H8, $J = 16.2$ Hz), 2.21 (d, 2H, H8, $J = 16.2$ Hz), 2.50 (s, 4H, H6), 4.12 (s, 2H, pyran H-4), 4.54 (s, 4H, 2-OCH_2), 6.03 (s, 2H, vinyl), 6.84–7.36 (m, 12H, ArH + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 672 [M^+], *Anal*. Calcd for $C_{40}H_{40}N_4O_6$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.51; H, 5.76; N, 8.28.

4,4′-(((1,2-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1i). Pale yellow crystals (dioxan / ethanol); Mp = 224–226°C; IR (KBr): $\nu = 3443$, 3335 (NH_2), 2189 (CN), 1677 (CO) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): $\delta = 0.93$ (s, 6H, $2CH_3$), 0.94 (s, 6H, $2CH_3$), 2.0, 2.27 (2d, 4H, H8, $J = 15.9$ Hz), 2.50 (s, 4H, H6), 4.55 (s, 2H, pyran H-4), 5.11, 5.26 (2d, 4H, 2-OCH_2, $J = 11.7$ Hz), 6.81–7.61 (m, 16H, Ar-H + $2NH_2$); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 27.3$, 28.1, 30.1, 31.5, 38.6, 50.1, 57.6, 67.4, 112.0, 112.4, 119.8, 120.5, 127.8, 128.1, 129.0, 129.2, 132.3, 135.6, 155.9, 158.6, 162.5, 195.6. MS (EI, 70 eV): *m/z* = 723 [M^+], *Anal*. Calcd for $C_{44}H_{42}N_4O_6$: C, 73.11; H, 5.86; N, 7.75. Found: C, 73.22; H, 5.95; N, 7.67.

4,4′-(((1,2-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1j). Pale yellow crystals (dioxan / ethanol), mp 162–164°C, IR (KBr): $\nu = 3383$, 3332 (NH_2), 2192 (CN), 1677 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 0.94$ (s, 6H, $2CH_3$), 1.03 (s, 6H, $2CH_3$), 2.07, 2.12 (2d, 4H, H8, $J = 15.9$ Hz), 2.50 (s, 4H, H6), 4.12 (s, 2H, pyran H-4), 5.17 (s, 4H, 2-OCH_2), 6.92–7.51 (m, 16H, Ar-H + $2NH_2$), MS (EI, 70 eV): *m/z* (%) = 722 [M^+], *Anal*. Calcd for $C_{44}H_{42}N_4O_6$: C, 73.11; H, 5.86; N, 7.75. Found: C, 73.27; H, 5.75; N, 7.93.

4,4′-(((1,4-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1k). Pale yellow crystals (dioxan / ethanol), mp 250–252°C, IR (KBr): $\nu = 3333$, 3314 (NH_2), 2191 (CN), 1687 (CO) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): $\delta = 0.93$ (s, 6H, $2CH_3$), 0.98 (s, 6H, $2CH_3$), 2.02, 2.23 (2d, 4H, H8, $J = 15.9$ Hz), 2.50 (s, 4H, H6), 4.60 (s, 2H, pyran H-4), 5.04, 5.13 (2d, 4H, 2-OCH_2, $J = 11.7$ Hz), 6.79–7.16 (m, 12H, Ar-H), 7.55 (s, 4H, $2NH_2$). MS (EI, 70 eV): *m/z* (%) = 722 [M^+], *Anal*. Calcd for $C_{44}H_{42}N_4O_6$: C, 73.11; H, 5.86; N, 7.75. Found: C, 73.26; H, 5.73; N, 7.69.

4,4′-(((1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (1l). Pale yellow crystals (dioxan / ethanol), mp 236–238°C, IR (KBr): $\nu = 3407$, 3324 (NH_2), 2193 (CN), 1681 (CO) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): $\delta = 0.95$ (s, 6H, $2CH_3$), 1.03 (s, 6H, $2CH_3$), 2.07, 2.12 (2d, 4H, H8, $J = 16.2$ Hz), 2.50 (s, 4H, H6), 4.13 (s, 2H, pyran H-4), 5.05 (s, 4H, 2-OCH_2), 6.90–7.07 (m, 12H, Ar-H), 7.45 (s, 4H, $2NH_2$); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 26.8$, 28.3, 31.7, 34.7, 38.6, 50.0, 58.5, 69.0, 112.9, 114.5, 119.7, 120.1, 127.7, 128.2, 136.7, 137.0, 157.0,158.4,162.1,195.6. MS (EI, 70 eV): *m/z* (%) = 722 [M^+], *Anal*. Calcd for $C_{44}H_{42}N_4O_6$: C, 73.11; H, 5.86; N, 7.75. Found: C, 73.25; H, 5.94; N, 7.87.

General procedure of synthesis of compound 5a-l. To a mixture of bis-aldehydes **2a-l** (1 m*M*) and malononitrile **3** (2.2 m*M*) in ethanol (20 mL) was added chitosan (0.1 gm) and the mixture was set at reflux for 3 h. The crude solid was isolated and recrystallized from the proper solvent.

2,2′-(((Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(methanylylidene))-dimalononitrile (5a). Pale yellow crystals mp 243–245°C [55].

2,2′-(((Ethane-1,2-diylbis(oxy))bis(5-bromo-2,1-phenylene))bis-(methanylylidene))dimalononitrile (5b). Pale yellow crystals (87%), (dioxan / ethanol), mp 258–260°C, IR (KBr): $\nu = 2195$ (CN) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): $\delta = 4.56$ (s, 4H, 2-OCH2), 7.31 (d, 2H, Ar-H, $J = 8.7$ Hz), 7.82 (d, 2H, Ar-H, $J = 8.7$ Hz), 8.09 (s, 2H, Ar-H), 8.42 (s, 2H, vinyl-H). MS (EI, 70 eV): *m/z* (%) = 524 [M^+], *Anal*. Calcd for $C_{22}H_{12}Br_2N_4O_2$ C, 50.41; H, 2.31; Br, 30.49; N, 10.69. Found: C, 50.59; H, 2.43; Br, 30.39; N, 10.54.

2,2′-(((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis-(methanylylidene))dimalononitrile (5c). Pale yellow crystals (dioxan / ethanol), mp = 258–260°C [55].

2,2′-(((Propane-1,3-diylbis(oxy))bis(5-bromo-2,1-phenylene))bis-(methanylylidene))dimalononitrile (5d). Pale yellow crystals (86%, dioxan), mp 187–189°C, IR (KBr): $\nu = 2192$ (CN) cm^{-1}, MS (EI, 70 eV): *m/z* (%) = 538 [M^+], *Anal*. Calcd for $C_{23}H_{14}Br_2N_4O_2$: C, 51.33; H, 2.62; Br, 29.69; N, 10.41. Found: C, 51.42; H, 2.78; Br, 29.83; N, 10.35.

2,2′-(((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methanylylidene))-dimalononitrile (5e). Pale yellow crystals (84%, dioxan), mp 210–212°C, IR (KBr): $\nu = 2220$ (CN) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.90$ (s, 4H, 2 CH_2), 4.22 (s, 4H, 2-OCH_2), 7.11–7.99 (m, 8H, Ar-H), 8.41 (s, 2H, vinyl-H). MS (EI, 70 eV): *m/z* (%) = 394 [M^+], *Anal*. Calcd for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found: C, 73.19; H, 4.67; N, 14.31.

2,2′-(((Butane-1,4-diylbis(oxy))bis(5-bromo-2,1-phenylene))bis-(methanylylidene))dimalononitrile (5f). Pale yellow crystals (83%), (dioxan / ethanol), mp 268–270°C, IR (KBr):

ν = 2188 (CN) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ = 1.96 (s, 4H, $2CH_2$), 4.21 (s, 4H, 2-OCH_2), 7.20–8.07 (m, 6H, Ar-H), 8.35 (s, 2H, vinyl-H. MS (EI, 70 eV): *m/z* (%) = 549 [M^+], *Anal*. Calcd for $C_{24}H_{16}Br_2N_4O_2$ C, 52.20; H, 2.92; Br, 28.94; N, 10.15. Found: C, 52.16; H, 2.81; Br, 28.83; N, 10.28.

2,2′-(((But-2-ene-1,4-diylbis(oxy))bis(2,1 phenylene))bis(methanylylidene))-dimalononitrile (5g). Pale yellow crystals (83%), (dioxan / ethanol), mp 212–213°C, IR (KBr): ν = 2223 (CN) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ = 4.79 (s, 4H, 2-OCH_2), 6.16 (s, 2H, vinyl-H), 7.12–8.0 (m, 8H, Ar-H), 8.48 (s, 2H, vinyl-H). MS (EI, 70 eV): *m/z* (%) = 392 [M^+], *Anal*. Calcd for $C_{24}H_{16}N_4O_2$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.38; H, 4.07; N, 14.37.

2,2′-(((But-2-ene-1,4-diylbis(oxy))bis(4,1-phenylene))bis(methanylylidene))-dimalononitrile (5h). Pale yellow crystals (77%), (dioxan / ethanol), mp 194–196°C, IR (KBr): ν = 2219 (CN) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ = 4.77 (s, 4H, 2-OCH_2), 6.10 (s, 2H, vinyl-H), 7.20 (d, 4H, Ar-H, J = 7.8 Hz), 7.96 (d, 4H, Ar-H, J = 7.8 Hz), 8.37 (s, 2H, vinyl-H), MS (EI, 70 eV): *m/z* (%) = 392 [M^+], *Anal*. Calcd for $C_{24}H_{16}N_4O_2$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.53; H, 4.23; N, 14.41.

2,2′-((((1,2-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis-(methanylylidene))dimalononitrile (5i). Pale yellow crystals (91%), (dioxan / ethanol), mp 172–174°C, IR (KBr): ν = 2224 (CN) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ = 5.41 (s, 4H, 2-OCH_2), 7.13–8.23 (m, 12H, Ar-H), 8.26 (s, 2H, vinyl-H). MS (EI, 70 eV): *m/z* (%) = 442 [M^+], *Anal*. Calcd for $C_{28}H_{18}N_4O_2$: C, 76.01; H, 4.10; N, 12.66. Found: C, 76.15; H, 4.21; N, 12.54.

2,2′-((((1,2-phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(methanylylidene))dimalononitrile (5j). Pale yellow crystals (82%), (dioxan / ethanol), mp 126–128°C, IR (KBr): ν = 2221 (CN) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 442 [M^+], *Anal*. Calcd for $C_{28}H_{18}N_4O_2$: C, 76.01; H, 4.10; N, 12.66. Found: C, 76.11; H, 4.23; N, 12.42.

2,2′-((((1,4-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis-(methanylylidene))dimalononitrile (5k). Pale yellow crystals (90%), (dioxan / ethanol), mp 215–217°C, IR (KBr): ν = 2224 (CN) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ = 5.27 (s, 4H, 2-OCH2), 7.22 (d, 4H, Ar-H, J = 8.4 Hz), 7.50 (s, 4H, Ar-H), 7.96 (d, 4H, Ar-H, J = 8.4 Hz), 8.38 (s, 2H, vinyl-H). MS (EI, 70 eV): *m/z* (%) = 442 [M+], *Anal*. Calcd for $C_{28}H_{18}N_4O_2$: C, 76.01; H, 4.10; N, 12.66. Found: C, 76.17; H, 4.18; N, 12.58.

2,2′-((((1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis-(methanylylidene))dimalononitrile (5l). Pale yellow crystals (89%), (dioxan / ethanol), mp 150–152°C, IR (KBr): ν = 2221 (CN) cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6): δ = 5.28 (s, 4H, 2-OCH_2), 7.18–8.39 (m, 13H, Ar-H + vinyl-H). MS (EI, 70 eV): *m/z* (%) = 442 [M^+], *Anal*. Calcd for $C_{28}H_{18}N_4O_2$: C, 76.01; H, 4.10; N, 12.66. Found: C, 76.15; H, 4.19; N, 12.61.

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