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Sodium dodecyl sulfate catalyzed one-pot three-component synthesis of structurally diverse 2-amino-3-cyano-4-substitued-4*H*-chromenes in aqueous medium at room temperature

Bubun Banerjee,[a,b]* Anu Priya,[a] Aditi Sharma,[a] Arvind Singh,[a] and Manmeet Kaur[a]

[a]Department of Chemistry, Akal University, Talwandi Sabo, Bathinda, Punjab 151302, India
[b]Visiting Researcher, Eternal University, Baru Sahib, Himachal Pradesh 173101, India
Email: banerjeebubun@gmail.com

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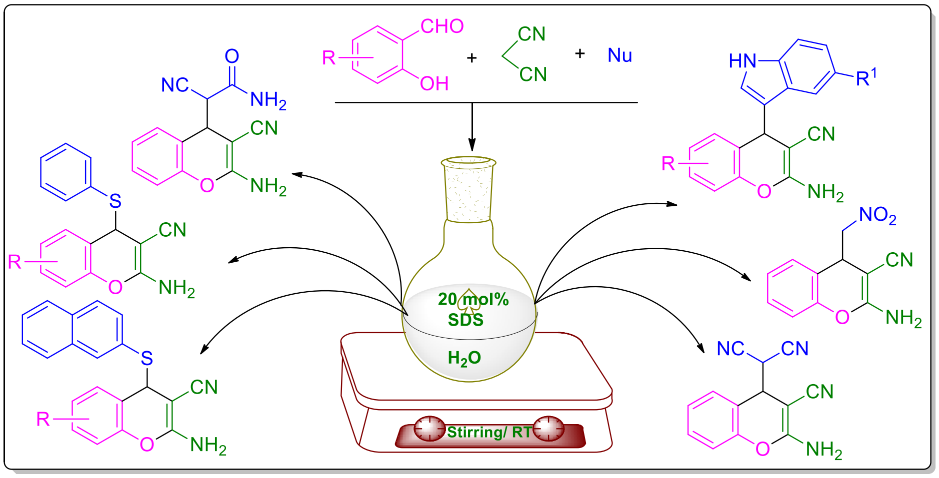
Abstract

A simple, efficient and environmentally benign method has been developed for the synthesis of a variety of 2-amino-3-cyano-4-substitued-4*H*-chromenes in excellent yields. The synthesis was accomplished via one-pot three-component reactions of salicylaldehydes, malononitrile and various nucleophiles in the presence of a catalytic amount of sodium dodecyl sulfate as a surfactant type organocatalyst in water at room temperature. All the nucleophiles afforded the desired products in excellent yields of 82-98%.



Keywords: 2-Amino-3-cyano-4-substitued-4*H*-chromenes, aqueous medium, multi-component reaction, organocatalysis, room temperature, sodium dodecyl sulfate

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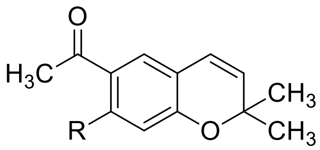
Introduction

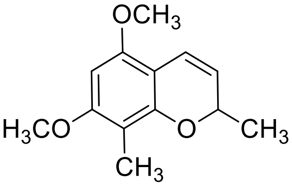
The chromene skeleton is very common in naturally occurring bioactive compounds such as encecalin (**I**) and 7-demethylencecalin (**II**) (isolated from *Encelza laciniata*, exhibits anti-insecticidal activity),[1] 5,7-dimethoxy-2-methyl-2*H*-benzopyran (**III**) (isolated from the essential oil of *Calyptranthes tricona,* exhibits anti-HIV activity),[2] lotthanongine (**IV**) and afzelechin (**V**) (isolated from *Trigonostemon reidioides*, exhibits antiseptic activity),[3] *etc.* (Figure 1). The chromene skeleton is also found in many commercially available drug molecules. Figure 2 represents a small selection of such drugs.[4-6] Many other compounds with the chromene skeleton have been reported to exhibit a wide range of pharmacological activities. Chromene derivatives, particularly 2-amino-3-cyano-chromene derivatives, have gained considerable attention due to their broad spectrum of biological efficacies which include anti-tumor, anti-proliferative, anti-cancer, apoptosis inducer, anti-HIV, IRAP inhibitor, and Bcl-2 inhibitory activities (Figure 3).[7-10] As a result, a number of methods have been developed for the synthesis of diverse 2-amino-3-cyano-chromenes using a number of homogeneous or heterogeneous catalysts under various reaction conditions.[11-16] Generally, 2-amino-3-cyano-chromenes have been synthesized from reactions between salicylaldehyde, malononitrile and various nucleophiles. A number of methods were reported for the synthesis of 2-amino-3-cyano-4-(indol-3-yl)-4*H*-chromene derivatives from the reactions of salicylaldehyde, malononitrile and indoles as nucleophile under various reaction conditions (Table 1, entries 1-14).[10,17-29] Though these reported methods possess merit, the majority suffer from common drawbacks i.e., the use of only indole derivatives as nucleophile. In a few examples metal-containing catalysts were used (Table 1, entries 1,7,9,10). Yields of the desired products were poor in some cases (Table 1, entries 3,5,13) and some required either heating (Table 1; entries 1-3,7,9,11,14) or ultrasound-assisted (Table 1; entry 12) conditions. Prolonged reaction times were also reported in some cases (Table 1; entries 4, 13). Some of the catalysts are not commercially available and thus require preparation (Table 1; entries 1,7,9). After analyzing the reported methods, we felt that there was scope to design a general method for the synthesis of a series of structurally diverse 2-amino-3-cyano-4-substitued-4*H*-chromene derivatives using a metal-free organocatalyst in water at ambient conditions.

In recent times, metal-free organo-catalysis has gained considerable attention.[30] Amongst a wide variety of organocatalysts, surfactants have received much attention due to environmental friendliness.[31] Being amphiphilic in nature, surfactant compounds show surface-active properties.[31,32] This assists organic transformations in water using a surfactant as catalyst. Sodium dodecyl sulfate (SDS) is one such surfactant which has been used extensively as catalyst for the synthesis of various bioactive heterocyclic scaffolds in water.[33-37] It is commercially available, inexpensive and non-toxic. It is used in detergents, toothpastes, face wash, soap etc*.*[38] Therefore, the use of catalytic amount of sodium dodecyl sulfate for organic transformation is quite safe and does not have any toxic effect. It has been well established that multi-component reaction strategies offer many advantages like operational simplicity, reduction in waste generation, minimization of extraction and purification processes, energy, cost and manpower.[39-43]

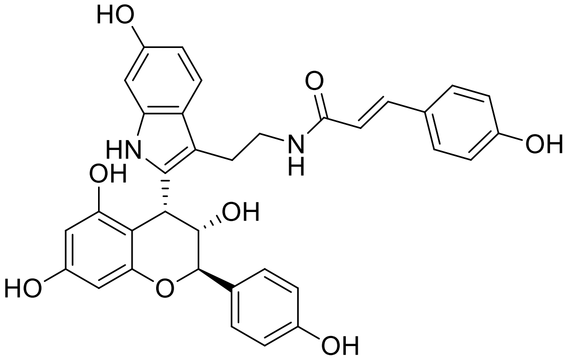
In continuation of our strong interest in organo-catalyzed reactions,[44-50] in this communication we report a simple, general method for the one-pot three-component synthesis of series of structurally diverse 2-amino-3-cyano-4-substitued-4*H*-chromenes using a catalytic amount of sodium dodecyl sulfate as an efficient, low cost, commercially available, environmentally benign metal-free surfactant type catalyst in water at room temperature.



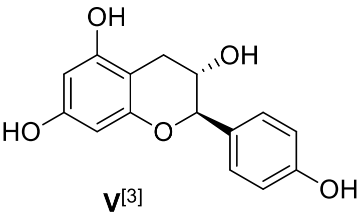
I; R = OH and **II**; R = OMe[1]



III[2]

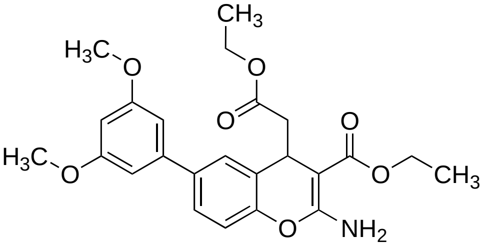


IV[3]



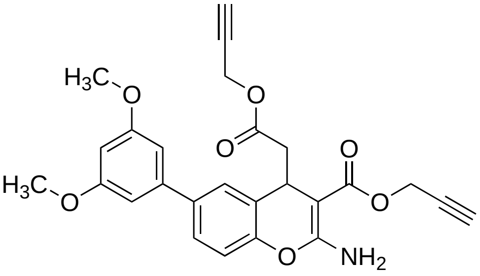
V[3]

Figure 1. Some naturally occurring bioactive compounds containing a chromene skeleton



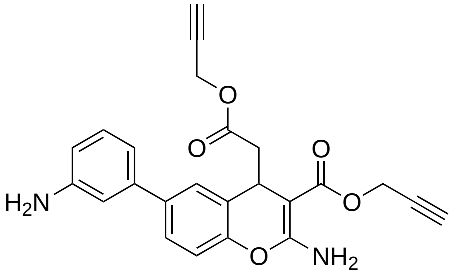
CXL017[4]

cytotoxic against multi-drug resistant cancer cell lines



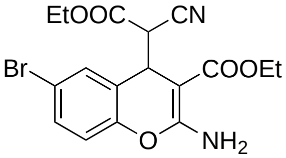
CXL035[4]

cytotoxic against multi-drug resistant cancer cell lines



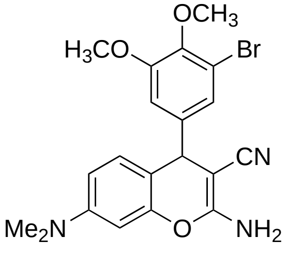
CXL055[4]

cytotoxic against multi-drug resistant cancer cell lines

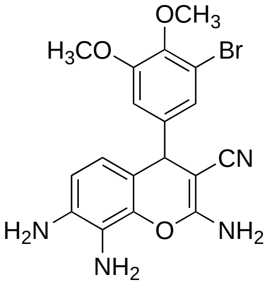


HA14-1

anti-cancer[5]
Bcl-2 inhibitor[6]

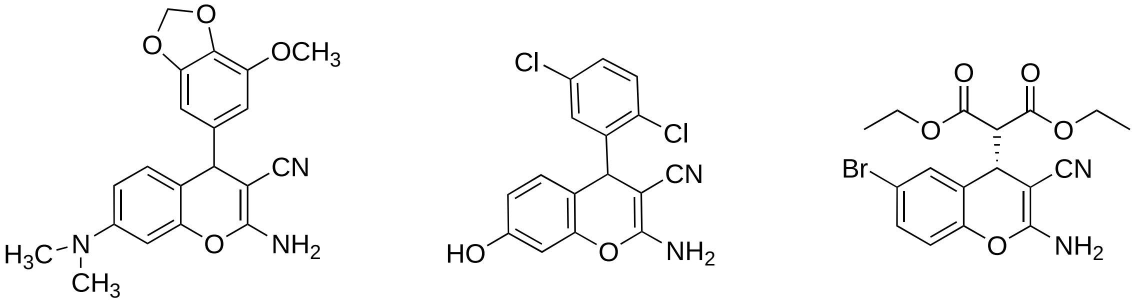


MX58151
tubulin inhibitor[6]

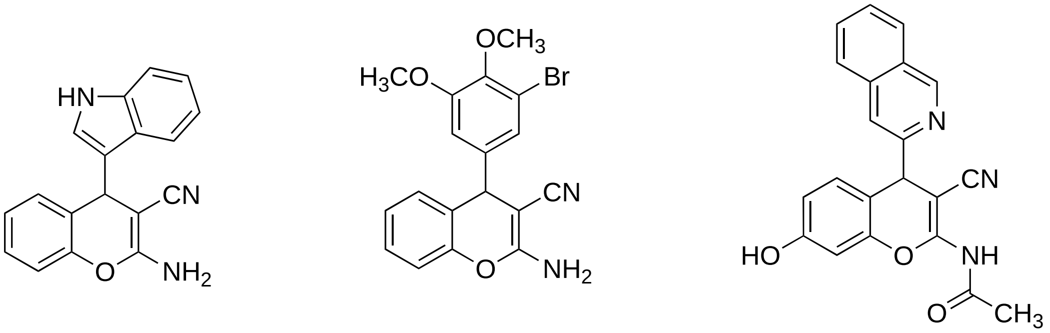


EPC2407
anti-cancer[6]

Figure 2. Commercially available drugs containing a chromene skeleton



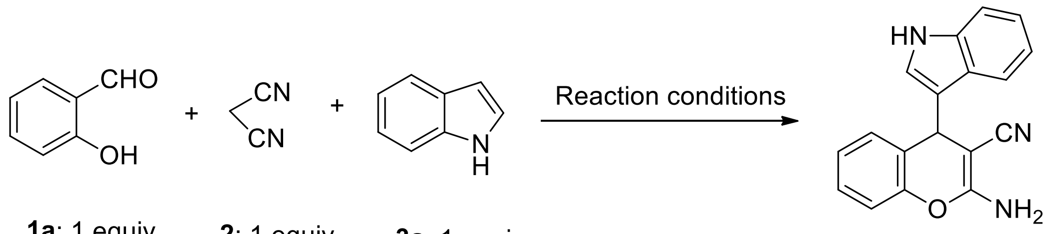
anti-tumor[7] anti-proliferative activity[8] anti-cancer and Bcl-2 inhibitor[9]



anti-HIV- IRT[10] apoptosis inducer[10] IRAP inhibitor[10]

Figure 3. Synthetic 2-amino-3-cyano-chromene derivatives with significant biological activities

Table 1. Previously reported methods for the synthesis of 2-amino-3-cyano-4-(indol-3-yl)-4*H*-chromenes



1a; 1 equiv. **2**; 1 equiv. **3a**; 1 equiv. **4a**

Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield [Ref]
1	NPGCN	H_2O	55	1 h	94%[10]
2	TBAF.3H_2O	neat	60	2 h	88%[17]
3	CD/DABCO	H_2O	60	1 h	80%[18]
4	Trisodium citrate dihydrate	EtOH-H_2O	RT	20 h	83%[19]
5	DES	neat	RT	2h	80%[20]
6	Bakers' yeast	H_2O	RT	10 min	93%[21]
7	Fe_3O_4@SiO_2@D-NHCS-Tr	neat	30	9 min	98%[22]
8	EDDF	ethylene glycol	RT	15 min	92%[23]
9	LCMNP	H_2O	80	12 h	90%[24]
10	RGO/ZnO	H_2O	RT	15 min	93%[25]
11	[DABCO-H][HSO_4]	EtOH	60	1 h	97%[26]

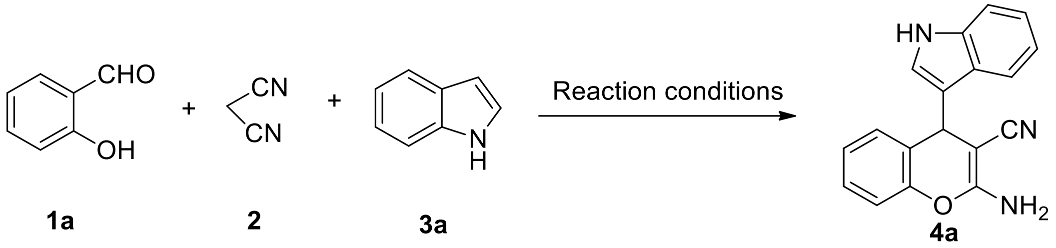
12	SPION@glutathione	H_2O	US	10 min	93%[27]
13	chiral thiourea complex	2-$CH_3C_6H_4CO_2H$	RT	3 days	72%[28]
14	[TBA][Gly]	neat	60	30 min	93%[29]
15	**SDS**	**H_2O**	**RT**	**18 h**	**94%[This work]**

NPGCN = nanocomposite of polyaniline with graphitic carbon nitride, TBAF = tetrabutylammonium fluoride, DES = choline chloride-urea (1:2), EDDF = ethylene diammonium-diformate, LCMNP = *L*-cysteine functionalized magnetic nanoparticles, SPION@glutathione = superparamagnetic iron-oxide nanoparticle, [TBA][Gly] = Tetrabutylammonium glycinate

Results and Discussion

To optimize the reaction conditions, a series of trial reactions was performed between salicylaldehyde (**1a**; 0.5 mmol), malononitrile (**2**; 0.5 mmol) and indole (**3a**; 0.5 mmol). The first reaction was carried out at room temperature in the absence of both catalyst and solvent which failed to afford the desired product even after 24 hours (Table 2, entry 1). Under catalyst-free conditions, no product was obtained even after 24 hours of stirring at room temperature either in ethanol or water as solvent (Table 2, entries 2 and 3). No desired product was isolated even after refluxing the same reaction mixture for 6 hours in water in the absence of catalyst (Table 4). These preliminary results compelled us to use some catalyst for this transformation. In continuation of our strong interest with aqueous mediated surfactant catalyzed reactions, the same reaction was performed in the presence of 10 mol% sodium dodecyl sulfate (SDS) as catalyst in aqueous medium at room temperature which resulted in a 55% yield of the desired product i.e., 2-amino-3-cyano-4-(indol-3-yl)-4*H*-chromene, after 24 hours at room temperature (Table 2, entry 5). This result showed that SDS as catalyst is effective for the present transformation, but we were not satisfied with the product yield. The amount of catalyst was increased but with 15 mol% (Table 2, entry 6) and 20 mol% SDS as catalyst without altering other conditions; after 24 hours, the yield (72%) of the product was increased with 15 mol% of SDS (Table 2, entry 6). Interestingly, with 20 mol% SDS a 94% of the desired product was obtained after 18 hours (Table 2, entry 7). Further increase of the catalyst (25 mol%) amount had no effect on the reaction rate or the product yield (Table 2, entry 8). It is relevant that by using 20 mol% of SDS as catalyst a poorer yield (60%) was obtained in water under reflux conditions (Table 2, entry 9). Further, we also carried out the same reaction in the presence of the same amount (20 mol%) of other surfactants viz., DBSA (Table 2, entry 10), CTAB (Table 2, entry 11) and CPC (Table 2, entry 12) which resulted just 12%, 48% and 33% yields of the desired product respectively, even after 18 hours at room temperature. Thus, it was concluded that the use of 20 mol% sodium dodecyl sulfate as catalyst in aqueous medium at room temperature is the best conditions for the efficient synthesis of 2-amino-3-cyano-4-(indol-3-yl)-4*H*-chromene (**4a**) from the reaction of salicylaldehyde (**1a**), malononitrile (**2**) and indole (**3**) (Table 2, entry 7).

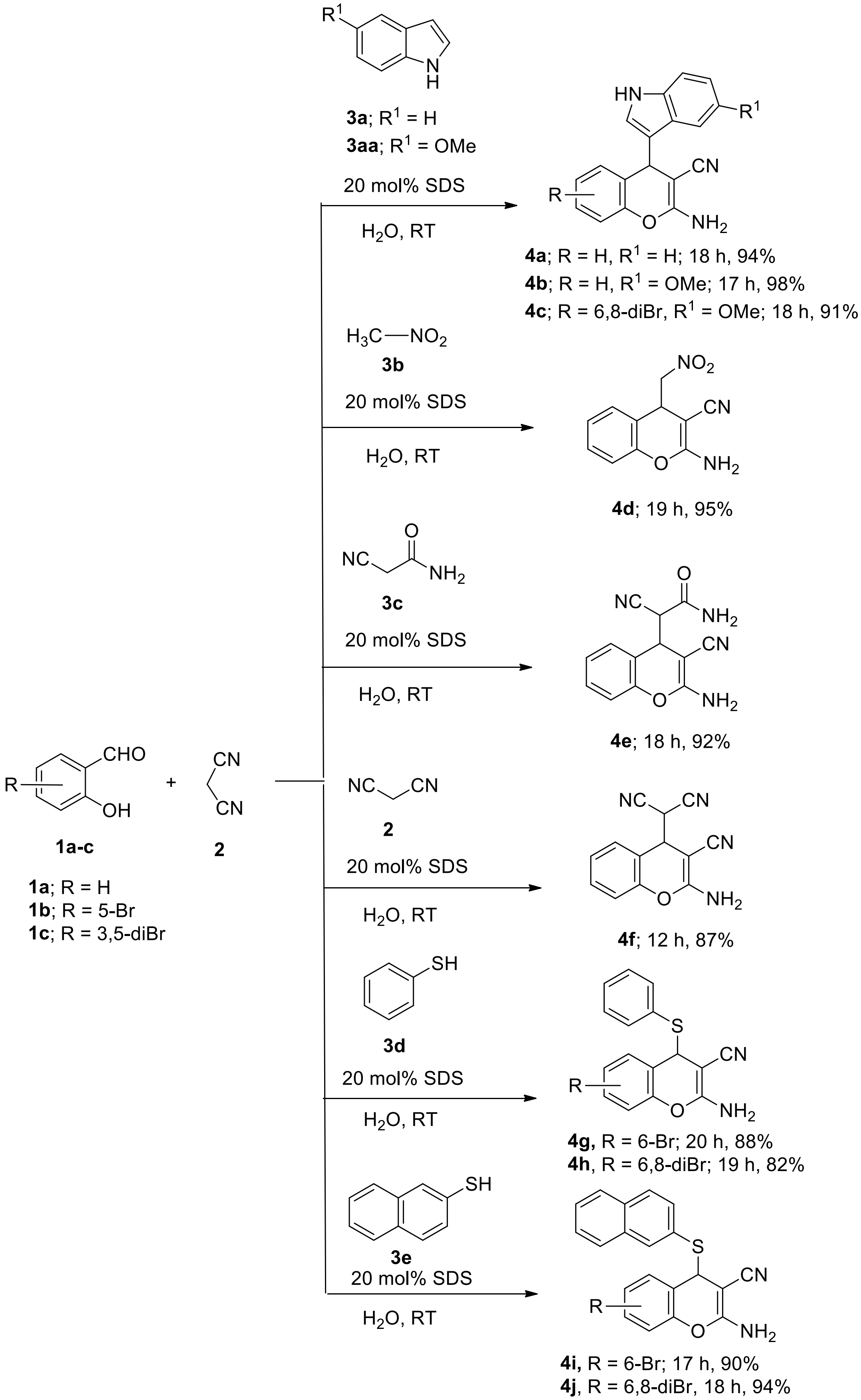
Table 2. Optimization of reaction conditions for the synthesis of 2-amino-3-cyano-4-(indol-3-yl)-4*H*-chromene



Entry	Catalyst (mol%)	Solvent	Condition	Time (h)	Yield (%)[a,b]
1	catalyst-free	neat	RT	24	-
2	catalyst-free	EtOH	RT	24	-
3	catalyst-free	H_2O	RT	24	-
4	catalyst-free	H_2O	reflux	6	-
5	SDS (10)	H_2O	RT	24	55
6	SDS (15)	H_2O	RT	24	72
7	**SDS (20)**	$\mathbf{H_2O}$	**RT**	**18**	**94**
8	SDS (25)	H_2O	RT	18	94
9	SDS (20)	H_2O	reflux	11	60
10	DBSA (20)	H_2O	RT	18	12
11	CTAB (20)	H_2O	RT	18	48
12	CPC (20)	H_2O	RT	18	33

[a]Reaction conditions: salicylaldehyde (**1a**, 0.5 mmol), malononitrile (**2**, 0.5 mmol) and indole (**3a**, 0.5 mmol) in the absence or presence of surfactants such as sodium dodecyl sulfate (SDS), 4-Dodecylbenzenesulfonic acid (DBSA, cetyl trimethylammonium bromide (CTAB) and cetylpyridinium chloride (CPC) as catalyst in 3 mL of water or ethanol as solvent at room temperature. [b]Isolated yields.

Under the optimized reaction conditions, we were able to synthesize another two 2-amino-3-cyano-4-(indol-3-yl)-4*H*-chromene derivatives (**4b-c**) from the reactions of salicylaldehyde (**1a**) or substituted salicylaldehyde (**1c**; 0.5 mmol), malononitrile (**2**; 0.5 mmol) and 5-methoxyindole (**3aa**; 0.5 mmol) in excellent yields (91-98%) (Scheme 1). Using the same catalytic amount of sodium dodecyl sulfate as catalyst in water, 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitrile (**4d**) was achieved in excellent yield (95%) from the reaction of salicylaldehyde (**1a**) malononitrile (**2**; 0.5 mmol) and nitromethane (**3b**; 0.5 mmol) at room temperature (Scheme 1). Under the same reaction conditions, use of cyanoacetamide (**3c**) as nucleophile afforded the corresponding product (**4e**) in excellent yield (92%). Synthesis of 2-(2-amino-3-cyano-4-(4*H*-chromen-4-yl)malononitrile (**4f**) was achieved under the same optimized reaction conditions from the reactions of one equivalent of salicylaldehyde (**1a**; 0.5 mmol) and two equivalents of malononitrile (**2**; 1 mmol). To check the generality of our developed protocol we were interested to use thiols as nucleophiles to prepare 2-amino-3-cyano-4-substitued-4*H*-chromene derivatives. To our delight, under the same optimized reaction conditions, one-pot three-component reactions of 5-bromosaliclaldehyde (**1b**; 0.5 mmol)/3,5-dibromosalicylaldehyde (**1c**; 0.5 mmol), malononitrile (**2**; 1 mmol) and thiophenol (**3d**; 1 mmol) or 2-naphthalenethiol (**3e**; 1 mmol) also underwent smooth reaction and afforded the corresponding 2-amino-4-(phenylthio)-4*H*-chromene-3-carbonitriles (**4g**-**4h**) or 2-amino-4-(naphthalen-2-ylthio)-4*H*-chromene-3-carbonitriles (**4i**-**4j**) in good yields (Scheme 1).



Scheme 1. Synthesis of a series of various 2-amino-3-cyano-4-substitued-4*H*-chromene derivatives using a catalytic amount of SDS as catalyst in water at room temperature

All the synthesized products were isolated pure just by simple filtration and subsequent washing with aqueous ethanol. No column chromatographic purification was required. It is noteworthy that we were also able to synthesize 2-amino-4-(5-methoxy-1*H*-indol-3-yl)-4*H*-chromene-3-carbonitrile (**4b**; 1.38 g, 87%) on a gram scale after 20 hours of at room temperature from the reactions of 5 mmol salicylaldehyde (**1a**; 0.61 g), 5 mmol malononitrile (**2**; 0.33 g) and 5 mmol 5-methoxyindole (**3aa**; 0.74g) using 20 mol% sodium dodecyl sulfate (0.288 g) in 20 ml water. All the synthesized compounds were well characterized by the detailed physical as well as spectroscopic analyses of ^{1}H NMR, ^{13}C NMR and HRMS. A plausible mechanism for the formation of 2-amino-3-cyano-4-substitued-4*H*-chromene derivatives is shown in Figure 4. The first intermediate (**I1**) would be formed *via* the Knoevenagel condensation reaction between salicylaldehyde and malononitrile. Next, the intermediate **I1** would undergo cyclization to form the second intermediate (**I2**) which upon nucleophilic addition would lead to the observed products.

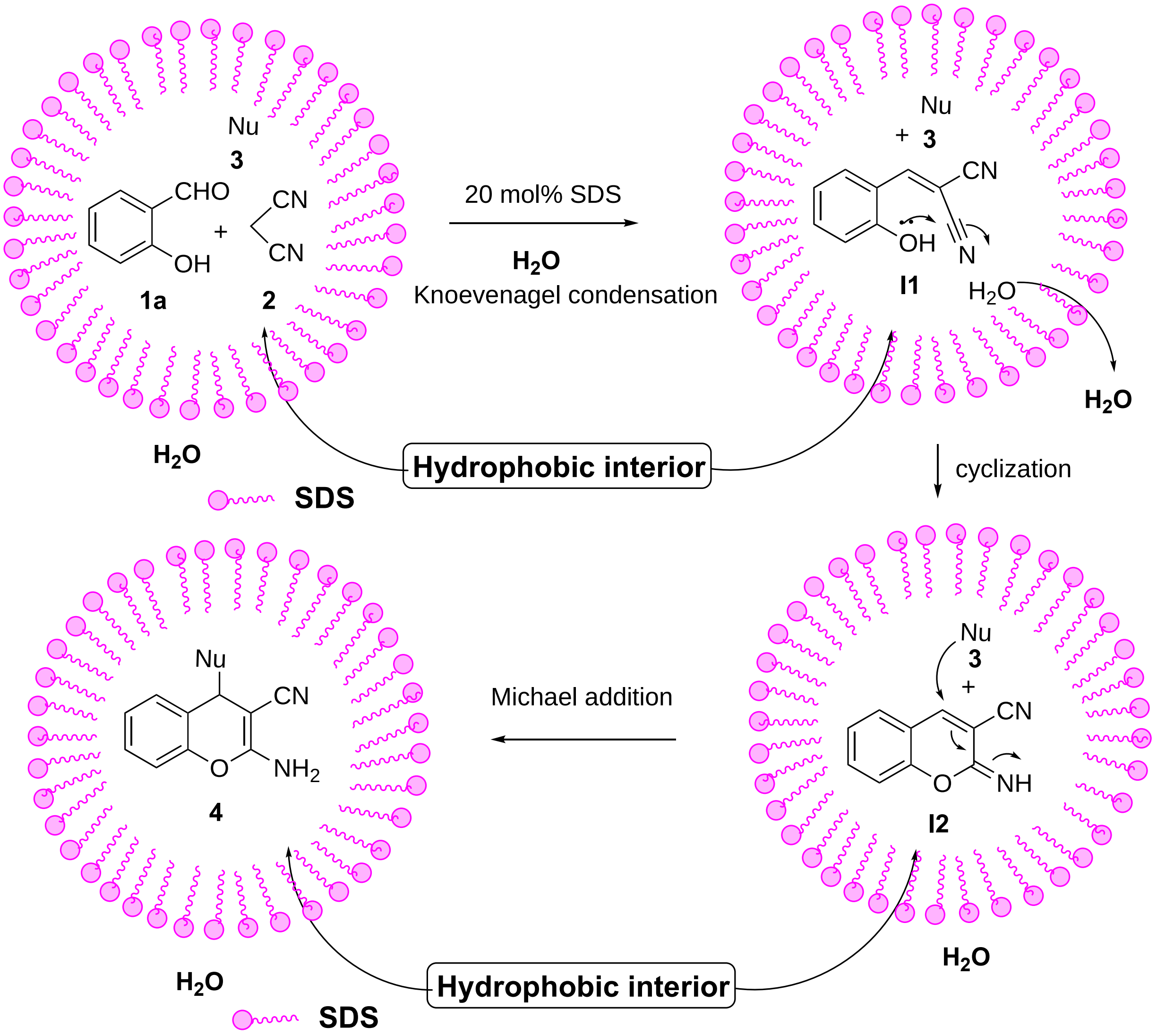


Figure 4. Plausible mechanism for the aqueous mediated SDS catalyzed synthesis of 2-amino-3-cyano-4-substituted-4*H*-chromenes

Conclusions

In conclusion we have developed a simple, efficient, environmentally benign, general and practical method for the synthesis of a series of structurally diverse biologically promising 2-amino-3-cyano-4-substitued-4*H*-chromene derivatives *via* one-pot three-component reactions of salicylaldehydes, malononitrile and various nucleophiles such as indoles, nitromethane, cyanoacetamide, malononitrile, thiophenol, 2-naphthalenethiol in the presence of a catalytic amount of sodium dodecyl sulfate as a surfactant type catalyst in water at room temperature. All the products were isolated pure just by simple filtration, avoiding column chromatography. Use of a green solvent, low cost commercially available surfactant type catalyst, excellent yields, easy isolation procedure, and gram scale production are some of the major advantages of this developed protocol.

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 F_{254} (Merck) plates. ^{1}H and ^{13}C NMR spectra were obtained at 500 MHz Jeol (JNM ECX-500) NMR machines with $CDCl_3$ or DMSO-d_6 as solvent. Mass spectra (TOF-MS ES^+) were measured on a Bruker Impact HD QTOF Micro mass spectrometer.

General procedure for synthesis of 2-amino-3-cyano-4-substituted-4*H*-chromenes (4a-4j). In a clean screw-cap test tube, a magnetic stir bar, salicylaldehyde (**1a**; 0.5 mmol), malononitrile (**2**; 0.5 mmol), 2.5 ml water and 20 mol% sodium dodecyl sulfate were aadded sequentially. The whole reaction mixture was then stirred at rt (30-35 °C) for 30 min. To the resultant mixture, 0.5 mmol of various nucleophiles (**3a**) such as indoles/ nitromethane/ cyanoacetamide/ thiophenol/ 2-naphthalenethiol were added and the stirring was continued for appropriate range of time as mentioned in Scheme 1. Under the same optimized reaction conditions synthesis of 2-(2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile (**4f**) was also achieved from the reactions of one equivalent of salicylaldehyde (**1**; 0.5 mmol) and two equivalents of malononitrile (**2**; 1 mmol). The completion of the reaction was confirmed by TLC with petroleum ether-EtOAc mixture (1:1) as the eluent. After completion of the reaction the desired products were isolated pure just by simple filtration. The structures of all the synthesized compounds were determined by the detailed spectral analysis including ^{1}H NMR, ^{13}C NMR and HRMS analysis.

2-Amino-4-(1*H*-indol-3-yl)-4*H*-chromene-3-carbonitrile (**4a**). Yellow solid, yield 94%; mp 166–168 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 10.84 (s, 1H, -NH), 7.29 (d, *J* 8.5 Hz, 1H, aromatic H), 7.23 (d, *J* 1 Hz, 1H, aromatic H), 7.20 (d, *J* 7.5 Hz, 1H, aromatic H), 7.15 (t, *J* 11 Hz, 1H, aromatic H), 7.04 (d, *J* 7.5 Hz, 1H, aromatic H), 6.99 (t, *J* 12 Hz, 2H, aromatic H), 6.95 (t, *J* 11.25 Hz, 1H, aromatic H), 6.82 (t, *J* 11.25 Hz, 1H, aromatic H), 6.70 (s, 2H, -NH_2), 4.95 (s, 1H, -CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 160.6, 148.9, 137.5, 129.8, 128.3, 125.8, 124.9 (2C), 124.3, 123.6, 121.5, 121.3, 119.2, 119.0, 116.3, 112.3, 56.9, 32.9; HRMS (ESI-TOF) *m/z*: For $C_{18}H_{13}N_3O$ Calcd. $[M+Na]^+$ 310.0956; Found $[M+Na]^+$ 310.0869.

2-Amino-4-(5-methoxy-1*H*-indol-3-yl)-4*H*-chromene-3-carbonitrile (**4b**). Off white solid, yield 98%; mp 185–187 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H/ppm 7.93 (s, 1H, -NH), 7.22 (d, *J* 9 Hz, 1H, aromatic H), 7.18 (t, *J* 11.25 Hz, 1H, aromatic H), 7.11 (t, *J* 4.25 Hz, 2H, aromatic H) 7.03-6.98 (m, 2H, aromatic H), 6.80 (dd, *J* 8.75 Hz, 2.5 Hz, 1H, aromatic H), 6.77 (d, *J* 2 Hz, 1H, aromatic H), 5.02 (s, 1H, -CH), 4.56 (s, 2H, -NH_2), 3.73 (s, 3H, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C/ppm 170.4, 164.1, 158.3, 153.9, 152.1, 148.8, 132.1, 129.6, 128.1, 125.1, 123.2, 122.9, 116.1, 112.1, 112.0, 101.4, 61.5, 55.8, 32.7; HRMS (ESI-TOF) *m/z*: For $C_{19}H_{15}N_3O_2$ Calcd. $[M+Na]^+$ 340.1062; Found $[M+Na]^+$ 340.0804.

2-Amino-6,8-dibromo-4-(5-methoxy-1*H*-indol-3-yl)-4*H*-chromene-3-carbonitrile (**4c**). Yellow solid, yield 91%; mp 213-215 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 10.82 (d, *J* 2.5 Hz, 1H, -NH) 7.71 (d, *J* 2.5 Hz, 1H, aromatic H), 7.27 (d, *J* 3 Hz, 1H, aromatic H), 7.22 (t, *J* 6 Hz, 2H, aromatic H), 7.03 (s, 2H, $-NH_2$), 6.72 (d, *J* 2 Hz, 1H, aromatic H), 6.70-6.68 (m, 1H, aromatic H), 5.00 (s, 1H, -CH), 3.64 (s, 3H, $-OCH_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 160.2, 153.5, 145.4, 133.6, 132.5, 131.6, 128.4, 124.4, 120.6, 118.3, 116.5, 113.1, 111.3, 110.9, 100.9, 100.3, 56. 8, 55.7, 33.3; HRMS (ESI-TOF) *m/z*: For $C_{19}H_{13}Br_2N_3O_2$ Calcd. $[M]^+$ 475.1334; Found $[M-H]^-$ 473.9489.

2-Amino-4-(nitromethyl)-4*H*-chromene-3-carbonitrile (**4d**). Off white solid, yield 95%; mp 139–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H/ppm 7.32-7.29 (m, 1H, aromatic H), 7.18-7.13 (m, 2H, aromatic H), 7.03 (d, *J* 8.5 Hz, 1H, aromatic H), 4.85 (s, 2H, $-NH_2$), 4.61 (dd, *J* 12.25 Hz, 4.5 Hz, 1H, $-CH_2$), 4.49 (dd, *J* 12.5 Hz, 7.5 Hz, 1H, $-CH_2$), 4.36 (dd, *J* 7.25 Hz, 4.5 Hz, 1H, -CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C/ppm 161.8, 149.3, 129.7, 127.9, 125.8, 118. 8, 118.7, 116.9, 80.3, 54.2, 34.8; HRMS (ESI-TOF) *m/z*: For $C_{11}H_9N_3O_3$ Calcd. $[M+Na]^+$ 254.0542; Found $[M+Na]^+$ 254.0508.

2-(2-Amino-3-cyano-4*H*-chromen-4-yl)-2-cyanoacetamide *(***4e**). Off white solid, yield 92%; mp 168-169 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.78 (s, 1H), 7.52 (s, 1H), 7.32 (t, *J* 11.25 Hz, 1H, aromatic H), 7.22 (d, *J* 7.5 Hz, 1H, aromatic H), 7.14 (s, 2H, $-NH_2$), 7.11 (d, *J* 7.5 Hz, 1H, aromatic H), 7.04 (d, *J* 8 Hz, 1H, aromatic H), 4.21 (d, *J* 5 Hz, 1H, -CH), 3.88 (d, *J* 5 Hz, 1H, -CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 179.2, 165.4, 163.6, 150.4, 129.8, 129.2, 124.9, 119.9, 117.3, 116.6, 51.9, 48.1, 37.3; HRMS (ESI-TOF) *m/z*: For $C_{13}H_{10}N_4O_2$ Calcd. $[M+Na]^+$ 277.0701; Found $[M+Na]^+$ 277.0937.

2-(2-Amino-3-cyano-4*H*-chromen-4-yl)malononitrile (**4f**). White solid, yield 87%; mp 153-155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H/ppm 7.53 (s, 2H, $-NH_2$), 7.48 (d, *J* 6 Hz, 1H, aromatic H), 7.43 (t, *J* 9.75 Hz, 1H, aromatic H), 7.28 (t, *J* 9. 5 Hz, 1H, aromatic H), 7.14 (d, *J* 7 Hz, 1H, aromatic H), 5.08 (d, *J* 2.5 Hz, 1H, -CH), 4.59 (d, *J* 2.5 Hz, 1H, -CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 163. 9, 150.2, 130.6, 129.3, 125.5, 119.8, 118.4, 116.8, 113.5, 113.4, 49.3, 37.6, 32.9; HRMS (ESI-TOF) *m/z*: For $C_{13}H_8N_4O$ Calcd. $[M+K]^+$ 275.0335; Found $[M+K]^+$ 275.0289.

2-Amino-6-bromo-4-(phenylthio)-4*H*-chromene-3-carbonitrile (**4g**). White solid, yield 88%; mp 181-183 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.41 (d, *J* 2.5 Hz, 1H, aromatic H), 7.36-7.31 (m, 2H, aromatic H), 7.21 (t, *J* 7.5 Hz, 2H, aromatic H), 7.08 (s, 2H, $-NH_2$), 7.01 (dd, *J* 10.5 Hz, 1 Hz, 2H, aromatic H), 6.73 (d, *J* 9 Hz, 1H, aromatic H), 5.30 (s, 1H, -CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 162.43, 136.6, 131.8, 131.7 (2C), 129.6 (2C), 129.7 (2C), 124.4 (2C), 124.0, 118.3, 116.3, 53.6, 46.7; HRMS (ESI-TOF) *m/z*: For $C_{16}H_{11}BrN_2OS$ Calcd. $[M+Na]^+$ 380.9673; Found $[M+Na]^+$ 381.3114.

2-Amino-6,8-dibromo-4-(phenylthio)-4*H*-chromene-3-carbonitrile (**4h**). Light Yellow solid, yield 82%; mp 171–173 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.74 (d, *J* 2 Hz, 1H, aromatic H), 7.49 (d, *J* 7.5 Hz, 1H, aromatic H), 7.41 (d, *J* 2 Hz, 1H, aromatic H), 7.37-7.34 (m, 3H, aromatic 1H & $-NH_2$), 7.26-7.22 (m, 2H, aromatic H), 6.99 (dd, *J* 8.25 Hz, 1 Hz 1H, aromatic H), 5.34 (s, 1H, -CH), ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 162.1, 145.9, 136.7, 134.2, 130.0 (2C), 129.9, 129.2 (2C), 128.1, 127.7, 119.5, 116.4, 110.5, 53.8, 47.0; HRMS (ESI-TOF) *m/z*: For $C_{16}H_{10}Br_2N_2OS$ Calcd. $[M+H]^+$ 436.8959; Found $[M+H]^+$ 436.8742.

2-Amino-6-bromo-4-(naphthalen-2-ylthio)-4*H*-chromene-3-carbonitrile (**4i**). White solid, yield 90%; mp 181-183 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.87-7.86 (m, 1H, aromatic H), 7.74 (d, *J* 8.5 Hz, 2H, aromatic H), 7.62 (s, 1H, aromatic H), 7.51-7.48 (m, 2H, aromatic H), 7.46 (d, *J* 2.5 Hz, 1H, aromatic H), 7.35 (dd, *J* 8.5 Hz, 2.5

Hz, 1H, aromatic H), 7.09 (dd, *J* 8.5 Hz, 1.5 Hz, 1H, aromatic H), 7.04 (s, 2H, $-NH_2$), 6.66 (d, *J* 8.5 Hz, 1H, aromatic H); 5.40 (s, 1H, -CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 162.4, 148.8, 136.5, 133.5, 133.2, 132.9, 131.9, 131.7, 128.6, 128.4, 128.3, 128.0, 127.4, 126.9, 124.5, 119.9, 118.2, 116.4, 53.9, 47.0; HRMS (ESI-TOF) *m/z*: For $C_{20}H_{13}BrN_2OS$ Calcd. $[M+Na]^+$ 432.2888; Found $[M+Na]^+$ 432.9574.

2-Amino-6,8-dibromo-4-(naphthalen-2-ylthio)-4H-chromene-3-carbonitrile (**4j**). Off White solid, yield 94%; mp 173-175 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.88-7.86 (m, 1H, aromatic H), 7.76 (d, *J* 8.5 Hz, 1H, aromatic H), 7.72 (d, *J* 2.5 Hz, aromatic H), 7.51-7.49 (m, 2H, aromatic H), 7.43 (d, *J* 2.5 Hz, 1H, aromatic H), 7.20 (s, 2H, $-NH_2$), 7.07 (dd, *J* 8.5 Hz, 1.5 Hz, 1H, aromatic H) 5.43 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 162.1, 145.9, 136.4, 134.2, 133.5, 133.3, 132.8, 131.1, 129.8, 128.5, 128.3, 128.1, 127.6, 127.0, 125.9, 119.6, 116.5, 110.6, 53.9, 47.3; HRMS (ESI-TOF) *m/z*: For $C_{20}H_{12}Br_2N_2OS$ Calcd. $[M+Na]^+$ 511.1848; Found $[M+Na]^+$ 510.8708.

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Supplementary Material

Characterization data with scanned spectra (^{1}H and ^{13}C NMR and HRMS) of all the synthesized compounds are available in the supplementary material file associated with this manuscript.

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