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Multicomponent assembling of salicylaldehydes, malononitrile and cyanoacetamides: A simple and efficient approach to medicinally relevant 2-amino-4*H*-chromene scaffold

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ABSTRACT

Sodium hydroxide catalyzed a new multicomponent reaction of salicylaldehydes, malononitrile and cyanoacetamides under 'on-water' conditions, which results in the facile and efficient formation of the corresponding substituted 2-amino-4*H*-chromenes in 80–95% yields. The convenient approach to the substituted 2-amino-4*H*-chromenes developed here — the promising small-molecule ligands for different biomedical applications with known spasmolitic, diuretic and antianaphylactic activities — is beneficial from the viewpoint of diversity-oriented large-scale processes and represents a fast, efficient and environmentally benign 'on-water' synthetic concept for multicomponent reactions strategy.

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1. Introduction

Multicomponent reaction (MCR) strategy has sufficient advantages over conventional linear-type synthesis due to its flexible, convergent and atom-efficient nature [1,2]. In recent years, the synthesis of combinatorial small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures [3]. Thus, the success of combinatorial chemistry in drug discovery is considerably dependent on further advances in heterocyclic MCR methodology and, according to current synthetic requirements, ecologically pure MCRs such as solvent-free or 'on-water' reactions are particularly welcome.

In recent years, the concept of "privileged medicinal scaffolds"[1] [4,5] has emerged as one of the guiding principles of the drug discovery process. It involves the utilization of molecular frameworks with inherent potential for biological activity. These privileged scaffolds commonly consist of a rigid hetero ring system that assigns a well-defined orientation of appended functionalities for target recognition [6].

The chromene moiety often appears as an important structural element in both biologically active and natural compounds. It is widely performed in natural alkaloids, flavonoids, tocopherols, and anthocyanins [7]. Moreover, in recent years functionalized chromenes have played an ever-increasing role in the synthetic approaches

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[1] The term "privileged scaffolds or structures" was originally introduced by Merck researchers in their work on benzodiazepins.

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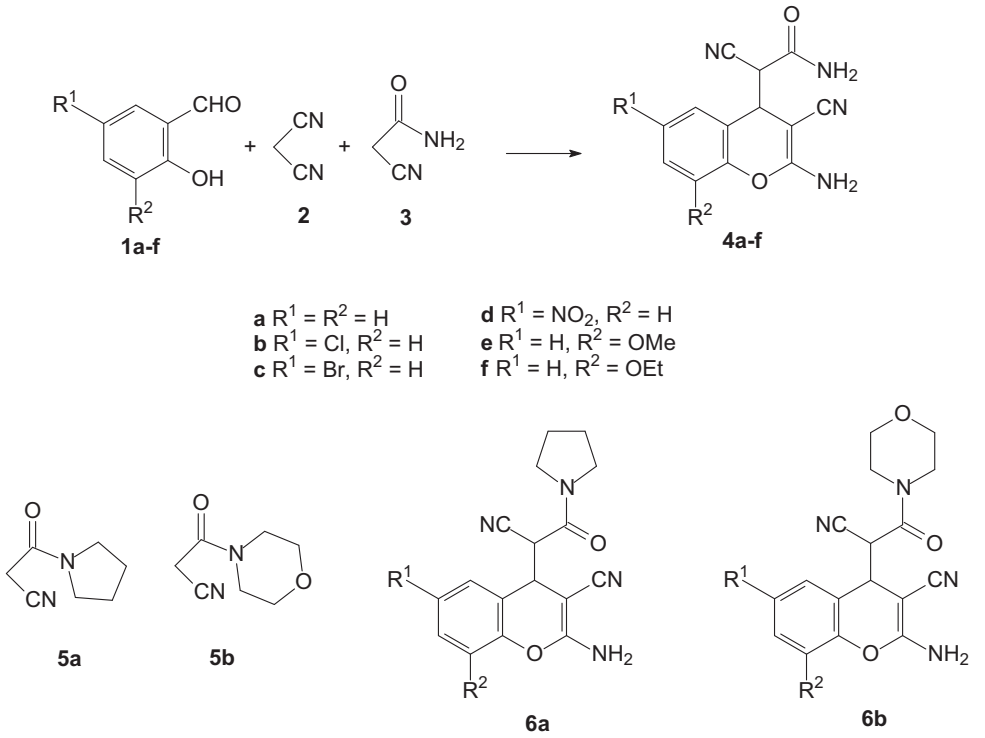


Scheme 1. Multicomponent transformation of salicylaldehydes **1**, malononitrile **2** and cyanoacetamides **3** or **5** into substituted 2-amino-4*H*-chromenes **4** or **6**.

to promising compounds in the field of medicinal chemistry [8].

Among the different types of chromene systems, 2-amino-4*H*-chromenes (or 2-amino-4*H*-benzo[*b*]pyranes) are of particular utility as they belong to privileged medicinal scaffolds serving for the generation of small-molecule ligands with highly pronounced spasmolitic, diuretic, anticoagulant, and antianaphylactic activities [9]. The current interest in 2-amino-4*H*-chromene derivatives bearing nitrile functionality arises from their potential application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis, and in cancer therapy [10].

In the course of our studies on the electrochemical transformations of organic compounds [11], we have successfully applied the electrocatalytic procedure to form a 2-amino-4*H*-chromene scaffold from salicylaldehydes and two different C–H acids [12].

Recently, we have also accomplished solvent-free and 'on water' transformations of salicylaldehydes and malononitrile [13] or cyanoacetates [14], salicylaldehyde, malononitrile and cyanoacetates [15], nitroalkanes [16] or pyrazolin-5-ones [17] into substituted 2-amino-4*H*-chromenes. But an efficient convenient and ecologically reasonable procedure for the synthesis of substituted 2-amino-4*H*-chromenes based on multicomponent reaction of salicylaldehydes, malonitrile and cyanoacetamides has yet to be developed. Considering our preliminary results in the field of solvent-free and 'on water' reactions of carbonyl compounds and C–H acids, we were prompted to design a convenient and facile environmentally benign chemical methodology for the efficient synthesis of the new type of the substituted 2-amino-4*H*-chromenes based on the multicomponent reaction of salicylaldehydes, malononitrile and cyanoacetamides.

2. Results and discussion

As it follows from the introduction, we were prompted to design a convenient facile and ecologically reasonable methodology for the efficient synthesis of new substituted

Table 1
Multicomponent transformation of salicylaldehyde **1a**, malononitrile **2** and cyanoacetamide **3** into 2-amino-4*H*-chromene **4a**[a].

Entry	Catalyst, % mol	Solvent	Time, h	Tempera-ture, °C	Yield (%)[b]
1	NaOAc, 5	–	0.25	20	25
2	KF, 5	–	0.25	20	30
3	Na_2CO_3, 5	–	0.25	20	28
4	NaOH, 5	–	0.25	20	35
5	NaOH, 5	–	0.5	20	58
6	NaOH, 10	–	0.5	20	60
7	NaOH, 5	H_2O[c]	1.0	60	71
8	NaOH, 5	H_2O[c]	2.0	60	83
9	NaOH, 5	H_2O[c]	3.0	60	95[d]

[a] 5 mmol of salicylaldehyde **1a**, 5 mmol of malononitrile **2**, 5 mmol of cyanoacetamide **3**.
[b] ^1H NMR data.
[c] 3 mL H_2O.
[d] Isolated yield.

Table 2
On-water multicomponent transformation of salicylaldehydes **1a-f**, malononitrile **2** and cyano-acetamides **3**, **5a**,**b** into 2-amino-4*H*-chromenes **4a-f**, **6a**,**b**[a].

Entry	Salicylaldehyde	R^1	R^2	Cyanoacetamide	Product	Yield (%)[b]
1	**1a**	H	H	**3**	**4a**	95 (3:1)
2	**1b**	Cl	H	**3**	**4b**	90 (7:5)
3	**1c**	Br	H	**3**	**4c**	81 (2:1)
4	**1d**	NO_2	H	**3**	**4d**	85 (6:1)
5	**1e**	H	MeO	**3**	**4e**	88 (2:1)
6	**1f**	H	EtO	**3**	**4f**	80 (3:1)
7	**1a**	H	H	**5a**	**6a**	82 (8:1)
8	**1a**	H	H	**5b**	**6b**	87 (1:1)

[a] 5 mmol of salicylaldehyde **1**, 5 mmol of malononitrile **2**, 5 mmol of cyanoacetamide **3**, **5a** or **5b**, 3 mL H_2O, 60 °C, 3 h.
[b] Isolated yield, in parentheses ratio of diastereomers.

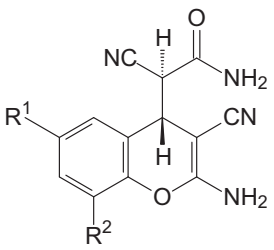
2-amino-4*H*-chromenes based on the multicomponent reaction of salicylaldehydes, malononitrile, and cyanoacetamides.

Thus, in the present study we report on the new multicomponent transformation of salicylaldehydes **1a–f**, malononitrile **2** and cyanoacetamides **3**, **5a**,**b** into substituted 2-amino-4*H*-chromene **4a–f**, **6a**,**b** (Scheme 1, Tables 1 and 2).

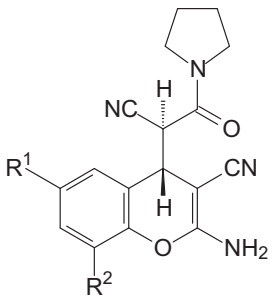
The solvent-free reaction of aldehyde **1a**, malononitrile **2** and cyanoacetamide **3** in the presence of NaOAc, KF, Na_2CO_3 or NaOH with 15 min grinding (entries 1-4, Table 1) resulted in the formation of 2-amino-4*H*-chromenes **4a** in the 25, 30, 28 and 35% yields, respectively. Under increasing reaction time (30 min) in the presence of NaOH, 2-amino-4*H*-chromene **4a** was obtained in 58% yield. An increasing quantity of NaOH had no sufficient influence on the yield of **4a** (entry 5, Table 1).

Under 'on-water' conditions in the presence of NaOH at 60 °C, 2-amino-4*H*-chromene **4a** was formed in 71, 83 and 95% yields in 1, 2 and 3 h of reaction time (entries 7–9, Table 1). It should be mentioned that compared to the only known previous synthesis of **4a**, which was carried out using the same reagents by electrochemical induction in an alcohol as the solvent [12], chromene **4a** under 'on-water' conditions was obtained in higher yield (95 instead of 73%) and with a higher diastereomeric ratio (3:1 instead of 1:1), using an easier methodology.

Under optimum conditions 'on-water' reaction thus found (5 mol% of NaOH as catalyst, 60 °C, 3 h reaction time) substituted 2-amino-4*H*-chromenes **4a-f** and **6a**,**b**

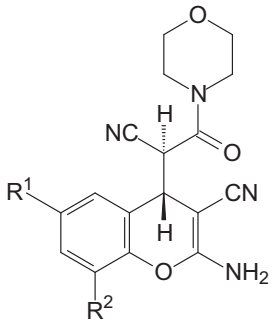


(*R*,*S*)*- **4a-f**



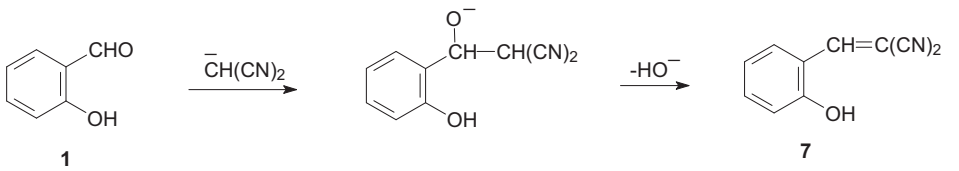
(*R*,*S*)*- **6a**

a $R^1 = R^2 = H$
b $R^1 = Cl$, $R^2 = H$
c $R^1 = Br$, $R^2 = H$
d $R^1 = NO_2$, $R^2 = H$
e $R^1 = H$, $R^2 = OMe$
f $R^1 = H$, $R^2 = OEt$



(*R*,*S*)*- **6b**

Fig. 1. Proposed configuration for the more abundant diastereoisomers of **4a–f**, **6a** and **6b**.



Scheme 2. Knoevenagel adduct **7** formation.

were obtained in 80–95% yields (Table 2). As practically pure 2-amino-4*H*-chromenes **4a–f** and **6a**,**b** were formed at the end of the reaction, the reaction mixture was only filtered off in the end of the process, washed with water, and dried to isolate pure substituted 2-amino-4*H*-chromenes **4a–f** and **6a**,**b**. The liquid phase after filtration (solution of NaOH in water) was used three times in the synthesis of 2-amino-4*H*-chromene **4a**, with a slight decrease of the yield in the last experiment to 85%.

According to ^{1}H and ^{13}C NMR analysis, the 2-amino-4*H*-chromenes **4a–f**, **6a**,**b** thus obtained were mixtures of two diastereoisomers (Table 2, entries 1–8). From the thermodynamic point of view, the more abundant diastereoisomer should possess a (*R**, *S**)-configuration (Fig. 1). For compounds **4a** and **6b**, NMR HSQCED and HMBC spectra were recorded to establish the position of all C-atoms. The comparison of experimental and calculated [18] NMR ^{13}C spectra indicated a (*R**, *S**)-configuration for the main isomer of **4a** and for the main isomer of **6b** (Fig. 1).

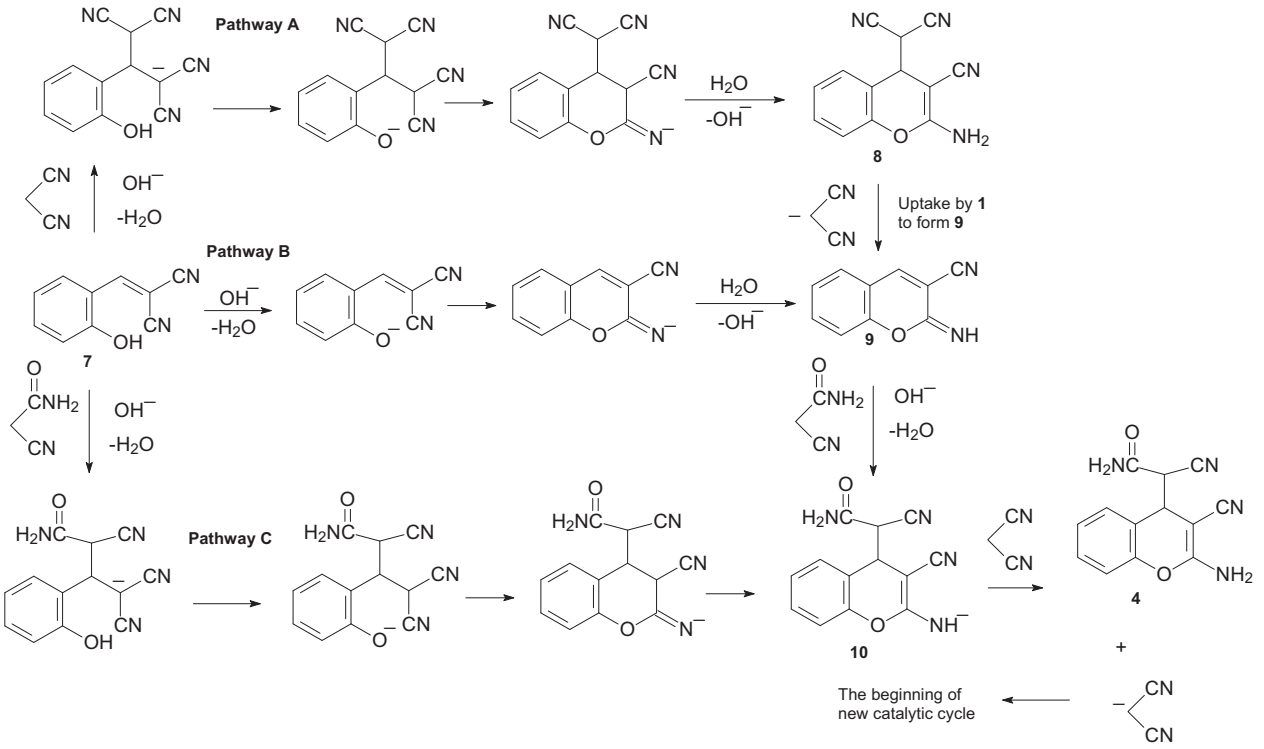
With the above results taken into consideration and the mechanistic data on the solvent-free cascade formation of 2-amino-4*H*-chromene scaffold from salicylaldehydes and malononitrile [12], the following mechanism for 'on-water' sodium hydroxide catalyzed multicomponent transformation of salicylaldehydes **1**, malononitrile **2**, and cyanoacetamide **3** into substituted 2-amino-4*H*-chromenes **4** is proposed.

As a first step, the NaOH-initiated deprotonation of malononitrile leads to the formation of the malononitrile anion:

$$CH_2(CN)_2 \xrightarrow{NaOH} \bar{C}H(CN)_2$$

Then a Knoevenagel condensation of the malononitrile anion and salicylaldehyde **1** takes place, with elimination of the hydroxide anion and formation of benzylidenemalononitrile **7** (Scheme 2, [19]).

Next, three reaction pathways are possible for Knoevenagel adduct **7** (Scheme 3).



Scheme 3. Mechanism of multicomponent transformation of salicylaldehydes **1**, malononitrile **2** and cyanoacetamides **3** into substituted 2-amino-4*H*-chromenes **4**.

The Michael addition of malononitrile to the Knoevenagel adduct **7** followed by intramolecular cyclization leads to the corresponding (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **8** (pathway A).

(2-Amino-3-cyano-4*H*-chromen-4-yl)malononitrile **8** was detected in the reaction mixture when the solvent-free reaction of salicylaldehyde **1**, malononitrile **2** and cyanoacetamide **3** in the presence of NaOH was completed in shorter reaction times (1 h and 2 h) in 13% and 5% yields based on the starting salicylaldehyde **1**.

Recently, O'Callaghan et al. have noted that in alcoholic solution, (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **8** could exist in equilibrium with the corresponding 2-imino-2*H*-chromene-3-carbonitrile **9** and malononitrile under certain reaction conditions [20]. If such an equilibrium exists in our case, the uptake of stronger C–H acid (malononitrile in our case) from the equilibrium by salicylaldehyde **1** could facilitate the base-promoted addition of weaker C–H acid **3** (cyanoacetamide) to 2-imino-2*H*-chromene **9**, which results in the full conversion of **8** into the desired 2-amino-4*H*-chromene **4**.

3. Conclusions

Thus, sodium hydroxide as a catalyst can produce under 'on-water' conditions the selective multicomponent transformation of salicylaldehydes, malononitrile and cyanoacetamides into substituted 2-amino-4*H*-chromenes in excellent yields, from 80 to 95%. This new process opens an efficient and convenient multicomponent way to create substituted 2-amino-4*H*-chromenes — promising compounds for different biomedical applications.

This 'on-water' multicomponent catalytic procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes. This efficient approach to substituted 2-amino-4*H*-chromenes represents a new synthetic concept for the modern synthesis of bioactive compounds that integrates a multicomponent strategy with 'on-water' reaction procedure, and allows for the combination of the synthetic virtues of MCR with ecological benefits of 'on-water' reactions; therefore, it makes the MCR strategy a step closer to a notion of "ideal synthesis" [21].

4. Experimental

4.1. General remarks

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance II-300 spectrometer at ambient temperature. Chemical shifts values are relative to Me_4Si. IR spectra were registered with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass-spectra (EI = 70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer. High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The internal calibration was done with Electrospray Calibrant Solution (Fluka). A syringe injection was used for solutions in acetonitrile, or methanol, (flow rate 3 μL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C. All chemicals were purchased from commercial sources.

4.2. General procedure

A mixture of salicylaldehyde **1** (5 mmol), malononitrile (0.33 g, 5 mmol), cyanoacetamide (5 mmol), and sodium hydroxide (0.02 g, 0.5 mmol) in water (5 mL) was stirred at 60 °C for 3 h. Then the reaction mixture was allowed to cool. The resulting solid was filtered off, rinsed twice with cold water (2 mL × 5 mL), and then dried to give the corresponding pure 2-amino-4*H*-chromene.

4.2.1. 2-(2-amino-3-cyano-4H-chromen-4-yl)-2-cyanoacetamide (4a)

White solid (1.21 g, 95%); diastereomeric ratio 3:1; mp 169–171 °C; ν_{max} (KBr): 3431, 3337, 2937, 2190, 1680, 1650, 1606, 1428 cm^{-1}; HRMS (ESI): found *m/z* 277.0688; calcd for $C_{13}H_{10}N_4NaO_2$ $[M+Na]^+$ 277.0696; major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.94 (d, $^3J_{H,H}$ = 5.2 Hz, 1H, CH), 4.26 (d, $^3J_{H,H}$ = 5.2 Hz, 1H, CH), 7.05–7.45 (m, 6H, Ar, NH_2), 7.59 (s, 1H, $CONH_2$), 7.86 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.9, 47.7, 51.5, 116.2, 116.9, 119.4, 119.8, 124.5, 128.7, 129.4, 149.9, 163.1, 165.0 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.95 (d, $^3J_{H,H}$ = 4.7 Hz, 1H, CH), 4.29 (d, $^3J_{H,H}$ = 4.7 Hz, 1H, CH), 7.05–7.45 (m, 6H, Ar, NH_2), 7.53 (s, 1H, $CONH_2$), 7.73 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.9, 48.7, 50.0, 116.2, 116.9, 119.8, 120.9, 124.9, 128.4, 129.1, 149.8, 163.1, 164.8 ppm.

4.2.2. 2-(2-amino-6-chloro-3-cyano-4H-chromen-4-yl)-2-cyanoacetamide (4b)

White solid (1.30 g, 90%); diastereomeric ratio 7:5; mp 158–159 °C; ν_{max} (KBr): 3405, 3312, 2935, 2202, 1676, 1649, 1600, 1424 cm^{-1}; HRMS (ESI): found *m/z* 311.0301; calcd for $C_{13}H_9ClN_4NaO_2$ $[M+Na]^+$ 311.0306; major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.04 (d, $^3J_{H,H}$ = 4.4 Hz, 1H, CH), 4.29 (d, $^3J_{H,H}$ = 4.4 Hz, 1H, CH), 7.11 (d, $^3J_{H,H}$ = 8.8 Hz, 1H, Ar), 7.26 (s, 2H, NH_2), 7.39 (dd, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,H}$ = 2.3 Hz, 1H, Ar), 7.52 (d, $^4J_{H,H}$ = 2.3 Hz, 1H, Ar), 7.56 (s, 1H, $CONH_2$), 7.70 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.8, 48.5, 49.5, 116.7, 117.5, 119.4, 122.8, 128.0, 128.2, 129.0, 148.6, 162.8, 164.6 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.98 (d, $^3J_{H,H}$ = 5.1 Hz, 1H, CH), 4.27 (d, $^3J_{H,H}$ = 5.1 Hz, 1H, CH), 7.12 (d, $^3J_{H,H}$ = 8.8 Hz, 1H, Ar), 7.28 (d, $^4J_{H,H}$ = 2.5 Hz, 1H, Ar), 7.30 (s, 2H, NH_2), 7.41 (dd, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,H}$ = 2.5 Hz, 1H, Ar), 7.68 (s, 1H, $CONH_2$), 7.88 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.6, 47.4, 51.0, 116.7, 118.0, 119.4, 121.3, 128.2, 128.3, 129.2, 148.7, 162.8, 164.8 ppm.

4.2.3. 2-(2-amino-6-bromo-3-cyano-4H-chromen-4-yl)-2-cyanoacetamide (4c)

White solid (1.35 g, 81%); diastereomeric ratio 1:2; mp 171–173 °C; ν_{max} (KBr): 3440, 3324, 2935, 2191, 1675, 1643, 1595, 1428 cm^{-1}; HRMS (ESI): found *m/z* 354.9794; calcd for $C_{13}H_9BrN_4NaO_2$ $[M+Na]^+$ 354.9801; major

diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.04 (d, $^3J_{H,H}$ = 4.2 Hz, 1H, CH), 4.29 (d, $^3J_{H,H}$ = 4.2 Hz, 1H, CH), 7.05 (d, $^3J_{H,H}$ = 8.7 Hz, 1H, Ar), 7.26 (s, 2H, NH_2), 7.51 (d, $^3J_{H,H}$ = 8.7 Hz, 1H, Ar), 7.56 (s, 1H, $CONH_2$), 7.66 (s, 1H, Ar), 7.70 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.7, 47.4, 49.6, 116.2, 118.4, 119.4, 123.2, 130.9, 131.0, 131.8, 149.1, 162.7, 164.6 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.98 (d, $^3J_{H,H}$ = 4.9 Hz, 1H, CH), 4.27 (d, $^3J_{H,H}$ = 4.9 Hz, 1H, CH), 7.06 (d, $^3J_{H,H}$ = 8.7 Hz, 1H, Ar), 7.30 (s, 2H, NH_2), 7.41 (s, 1H, Ar), 7.54 (d, $^3J_{H,H}$ = 8.7 Hz, 1H, Ar), 7.69 (s, 1H, $CONH_2$), 7.87 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.4, 47.4, 51.1, 115.9, 116.7, 119.4, 121.7, 130.9, 131.1, 132.1, 149.2, 162.7, 164.7 ppm.

*4.2.4. 2-(2-amino-3-cyano-6-nitro-4H-chromen-4-yl)-2-cyanoacetamide (**4d**)*

White solid (1.27 g, 85%); diastereomeric ratio 6:1; mp 183–184 °C; ν_{max} (KBr): 3439, 3312, 2931, 2192, 1680, 1648, 1595, 1421 cm^{-1}; HRMS (ESI): found *m/z* 322.0542; calcd for $C_{13}H_9N_5NaO_4$ $[M + Na]^+$ 322.0547; major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.12 (d, $^3J_{H,H}$ = 4.0 Hz, 1H, CH), 4.45 (d, $^3J_{H,H}$ = 4.0 Hz, 1H, CH), 7.32 (d, $^3J_{H,H}$ = 9.0 Hz, 1H, Ar), 7.44 (s, 2H, NH_2), 7.59 (s, 1H, $CONH_2$), 7.79 (s, 1H, $CONH_2$), 8.21 (dd, $^3J_{H,H}$ = 9.0 Hz, $^4J_{H,H}$ = 2.5 Hz, 1H, Ar), 8.45 (d, $^4J_{H,H}$ = 2.5 Hz, 1H, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.8, 48.6, 49.6, 116.6, 117.6, 119.0, 122.0, 124.8, 124.9, 143.8, 154.3, 162.2, 164.5 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.07 (d, $^3J_{H,H}$ = 5.0 Hz, 1H, CH), 4.45 (d, $^3J_{H,H}$ = 5.0 Hz, 1H, CH), 7.40 (d, $^3J_{H,H}$ = 9.3 Hz, 1H, Ar), 7.48 (s, 2H, NH_2), 7.72 (s, 1H, $CONH_2$), 7.89 (s, 1H, $CONH_2$), 8.28 (dd, $^3J_{H,H}$ = 9.3 Hz, $^4J_{H,H}$ = 2.5 Hz, 1H, Ar), 8.50 (d, $^4J_{H,H}$ = 2.5 Hz, 1H, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.5, 47.3, 51.1, 116.6, 117.9, 119.2, 120.5, 125.1, 125.2, 143.4, 154.3, 162.2, 164.6 ppm.

*4.2.5. 2-(2-amino-3-cyano-8-methoxy-4H-chromen-4-yl)-2-cyanoacetamide (**4e**)*

White solid (1.25 g, 88%); diastereomeric ratio 2:1; mp 161–163 °C; ν_{max} (KBr): 3425, 3352, 2898, 2182, 1692, 1641, 1581, 1220 cm^{-1}; HRMS (ESI): found *m/z* 307.0799; calcd for $C_{14}H_{12}N_4NaO_3$ $[M + Na]^+$ 307.0802; major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H, CH_3), 3.91 (d, $^3J_{H,H}$ = 4.7 Hz, 1H, CH), 4.25 (d, $^3J_{H,H}$ = 4.7 Hz, 1H, CH), 6.90–7.30 (m, 5H, Ar, NH_2), 7.52 (s, 1H, $CONH_2$), 7.71 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.1, 48.5, 49.9, 55.7, 111.7, 116.8, 119.6, 119.7, 121.8, 124.6, 139.1, 147.1, 163.0, 164.7 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H, CH_3), 3.89 (d, $^3J_{H,H}$ = 5.2 Hz, 1H, CH), 4.21 (d, $^3J_{H,H}$ = 5.2 Hz, 1H, CH), 6.75–7.35 (m, 5H, Ar, NH_2), 7.58 (s, 1H, $CONH_2$), 7.84 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.0, 47.6, 51.4, 55.7, 112.1, 116.8, 119.4, 119.7, 120.6, 124.3, 139.2, 147.1, 163.0, 164.9 ppm.

*4.2.6. 2-(2-amino-3-cyano-8-ethoxy-4H-chromen-4-yl)-2-cyanoacetamide (**4f**)*

White solid (1.19 g, 80%); diastereomeric ratio 3:1; mp 167–169 °C; ν_{max} (KBr): 3434, 3322, 2936, 2190, 1678, 1654, 1580, 1426 cm^{-1}; HRMS (ESI): found *m/z* 321.0954; calcd for $C_{15}H_{14}N_4NaO_3$ $[M + Na]^+$ 321.0958; major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (t, $^3J_{H,H}$ = 6.9 Hz, 3H, CH_3), 3.91 (d, $^3J_{H,H}$ = 5.2 Hz, 1H, CH), 4.11 (q, $^3J_{H,H}$ = 6.9 Hz, 2H, CH_2), 4.22 (d, $^3J_{H,H}$ = 5.2 Hz, 1H, CH), 6.75–7.30 (m, 5H, Ar, NH_2), 7.57 (s, 1H, $CONH_2$), 7.82 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 37.1, 47.7, 51.4, 64.3, 113.4, 116.9, 119.7, 119.8, 120.4, 124.3, 139.5, 146.3, 163.0, 164.9 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (t, $^3J_{H,H}$ = 6.9 Hz, 3H, CH_3), 3.92 (d, $^3J_{H,H}$ = 4.7 Hz, 1H, CH), 4.11 (q, $^3J_{H,H}$ = 6.9 Hz, 2H, CH_2), 4.24 (d, $^3J_{H,H}$ = 4.7 Hz, 1H, CH), 6.75–7.30 (m, 5H, Ar, NH_2), 7.51 (s, 1H, $CONH_2$), 7.70 (s, 1H, $CONH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 37.0, 48.6, 49.9, 64.3, 113.0, 116.8, 119.4, 119.7, 121.9, 124.7, 139.4, 146.3, 163.0, 164.7 ppm.

*4.2.7. 2-amino-4-(1-cyano-2-oxo-2-pyrrolidin-1-ylethyl)-4H-chromen-3-carbonitrile (**6a**)*

White solid (1.26 g, 82%); diastereomeric ratio 8:1; mp 152–153 °C; ν_{max} (KBr): 3475, 2979, 2185, 1636, 1576, 1446, 1413 cm^{-1}; HRMS (ESI): found *m/z* 331.1167; calcd for $C_{17}H_{16}N_4NaO_2$ $[M + Na]^+$ 331.1165; major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55–1.95 (m, 4H, CH_2), 2.84–2.97 (m, 1H, CH_2), 3.19–3.41 (m, 2H, CH_2), 3.49–3.62 (m, 1H, CH_2), 4.20 (d, $^3J_{H,H}$ = 6.2 Hz, 1H, CH), 4.28 (d, $^3J_{H,H}$ = 6.2 Hz, 1H, CH), 7.04–7.40 (m, 6H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.6, 25.5, 36.9, 45.5, 46.1, 46.3, 50.5, 116.0, 116.8, 119.9, 120.5, 124.5, 128.3, 129.1, 150.0, 161.4, 163.1 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55–1.95 (m, 4H, CH_2), 2.84–2.97 (m, 1H, CH_2), 3.19–3.41 (m, 2H, CH_2), 3.49–3.62 (m, 1H, CH_2), 4.14 (d, $^3J_{H,H}$ = 6.3 Hz, 1H, CH), 4.25 (d, $^3J_{H,H}$ = 6.3 Hz, 1H, CH), 7.04–7.40 (m, 6H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.7, 25.4, 37.2, 45.8, 46.1, 46.6, 51.0, 115.5, 117.0, 119.4, 119.9, 124.3, 128.3, 129.3, 150.0, 161.6, 163.1 ppm.

*4.2.8. 2-amino-4-(1-cyano-2-morpholin-4-yl-2-oxoethyl)-4H-chromen-3-carbonitrile (**6b**)*

White solid (1.41 g, 87%); diastereomeric ratio 2:1; mp 145–147 °C; ν_{max} (KBr): 3335, 2929, 2204, 1648, 1581, 1442, 1419 cm^{-1}; HRMS (ESI): found *m/z* 347.1120; calcd for $C_{17}H_{16}N_4NaO_3$ $[M + Na]^+$ 347.1115; major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20–3.75 (m, 8H, $4CH_2$), 4.20 (d, $^3J_{H,H}$ = 5.7 Hz, 1H, CH), 4.66 (d, $^3J_{H,H}$ = 5.7 Hz, 1H, CH), 7.05–7.45 (m, 6H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.0, 42.2, 44.7, 46.1, 49.9, 65.7 ($2CH_2O$), 116.1, 116.8, 119.9, 120.3, 124.6, 129.2 (2CH), 149.9, 162.1, 163.1 ppm; minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20–3.75 (m, 8H, $4CH_2$), 4.11 (d, $^3J_{H,H}$ = 6.6 Hz, 1H, CH), 4.58 (d, $^3J_{H,H}$ = 6.6 Hz, 1H, CH), 7.05–7.45 (m, 6H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.5, 42.4, 43.2, 46.2, 50.7, 65.4 ($2CH_2O$), 116.0, 117.2, 119.7, 120.0, 124.5, 128.6 (2CH), 150.0, 162.4, 163.2 ppm.

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