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The Synthesis of Various 2-Imino-2H-chromene-3-carbonitrile Derivatives †

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Abstract: One-pot and stepwise reactions of salicylic aldehydes (salicylic, 5-bromsalicylic) and different equivalents of malononitrile and their mutual transformations were investigated. Various derivatives of 2-imino-2H-chromene-3-carbonitrile were isolated. This work reports the synthesis of novel 2-(4-amino-9-R-1-cyano-5-imino-3,5-dihydro-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitriles. The influence of reaction parameters, such as ultrasound activation conditions, solvent type, and the presence or absence of a catalyst, was studied in this work. The structures of the synthesized compounds were established using spectroscopic data (IR, NMR).

Keywords: 2-imino-2H-chromene-3-carbonitriles; 2-(2-amino-3-cyano-4H-chromen-4-yl)malononitriles; chromeno[3,4-c]pyridines; ultrasound activation; catalyst-free conditions

1. Introduction

Heterocyclic-fused derivatives of imino(amino)chromenes of natural and synthetic origin exhibit a wide variety of biological properties including antimicrobial, antiviral, anticancer, antioxidant, and anti-inflammatory activities [1–3]. Also, imino(amino)chromene derivatives have great interest in the fundamental research of organic chemistry.

It is known that reactions of salicylic aldehyde and malononitrile can lead to derivatives of 2-imino-2H-chromene-3-carbonitrile **1**—such as 2-(2-amino-3-cyano-4H-chromen-4-yl)malononitrile **2** and 2-(4,5-diamino-1-cyano-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile **3** [4–9].

2. Results and Discussion

In this work, we investigated the mutual transformations of imino(amino)cyanochromenes 1 and 2, as well as the accompanying reactions leading to previously unknown compounds. It has been shown that reactions of salicylic aldehyde and malononitrile with a 1:1 ratio in various solvents (IPA, EtOH, THF, dioxane, PEG-400) under thermal and ultrasound activation conditions, or with stirring at room temperature, can lead to the formation of **1**, **2**, **3** and **4** (Scheme 1). These reactions can occur with the presence of basic catalysts or under catalyst-free conditions.

The formation of 2-(4,5-diamino-1-cyano-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitriles **3** proceeds according to the following scheme. Some molecules of 2-(2-amino-3-cyano-4H-chromen-4-yl)malononitrile **2** undergo a retro Michael reaction. The eliminated molecule of malononitrile attacks the nitrile carbon of another molecule of aminochromene **2**. Subsequently, intramolecular cyclization occurs, followed by an isomerization to form the tautomeric mixture **3** and **3′** at a ratio of 1:3 (Scheme 2).

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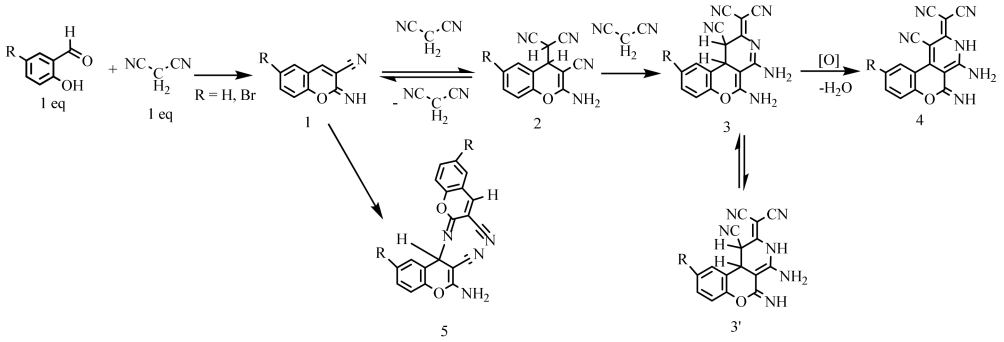
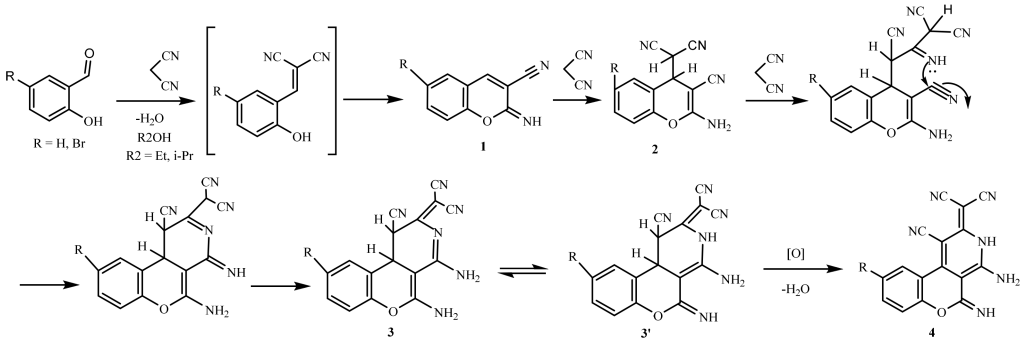


Scheme 1. Reactions between salicylaldehyde and malononitrile for the synthesis of imino(amino)cyanochromenes derivatives.



Scheme 2. Proposed mechanism for the reaction between salicylaldehyde and malononitrile for the synthesis of 2-amino-4H-chromene.

The structure of the tautomeric mixture of ylidene aminochromenes 2-(4,5-diamino-1-cyano-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile **3** and 2-(4-amino-1-cyano-5-imino-1,3,5,10b-tetrahydro-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile **3′** was confirmed by IR and NMR spectroscopy data.

The ^{1}H NMR spectra of the tautomers **3b** and **3b′** (R = Br) showed characteristic signals of doublets at 4.8–4.9 ppm for the vicinal protons H^{1}-H^{10b} (**3b** and **3b′**) and singlets at 7.1, 6.72 (**3**), 6.53, and 6.34 ppm (**3′**) for the amino groups and at 3.65 ppm (3′) for the imino group. The two-dimensional ^{1}H/^{13}C HSQC spectrum of **3b** and **3b′** displayed correlations between the vicinal protons H^{1} and H^{10b} and the sp3-hybridized carbon atoms C^{1} and C^{10b}, respectively: 4.9/34.89 (H^{1}/C^{1}), 4.88/30.82 (H^{10b}/C^{10b}). The two-dimensional ^{1}H/^{13}C HMBC spectrum contains cross peaks showing the main correlations for the two tautomers **3b** and **3b′** (R = Br) 4.89/30.85 (H^{1}/C^{10b}), 4.88/34.89 (H^{10b}/C^{1}), 4.89/113.23 (H^{1}/-CN), 4.89/83.54 (H^{1}/C^{4a}), (**3b**): 7.10/71.09 ($-NH_2/=C(CN)_2$), 7.10/83.57 ($-NH_2/C^{4a}$), 6.72/71.09 ($-NH_2/=C(CN)_2$), and (**3b′**) 3.65/85.5 ($=NH/C^{4a}$).

The novel 2-(4-amino-9-R-1-cyano-5-imino-3,5-dihydro-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitriles (**4a**,**b** R = H, Br) were obtained by increasing the reaction time with 2-(2-amino-6-R-3-cyano-4H-chromen-4-yl)malononitriles **2**. 2-(4,5-diamino-1-cyano-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitriles **3** can be oxidized to the novel 2-(4-amino-9-R-1-cyano-5-imino-3,5-dihydro-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitriles (**4a**,**b** R = H, Br) by atmospheric oxygen. The ^{1}H NMR spectra of the (2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile **4b**(R = Br) showed characteristic signals at 3.66, 6.20, and 6.50 ppm for the amino and the imino groups. Also, there are no signals of the vicinal protons in the ^{1}H NMR spectra of the compound **4b** (R = Br) (Figure 1). The main correlations in the ^{1}H/^{13}C HMBC spectrum are 3.66/85.56 57 ($=NH/C^{1}$), 6.32/70.70 ($=NH/C^{4a}$), 6.50/70.70 ($-NH_2$/C4a), and 6.50/85.56 ($-NH_2/C^{1}$).

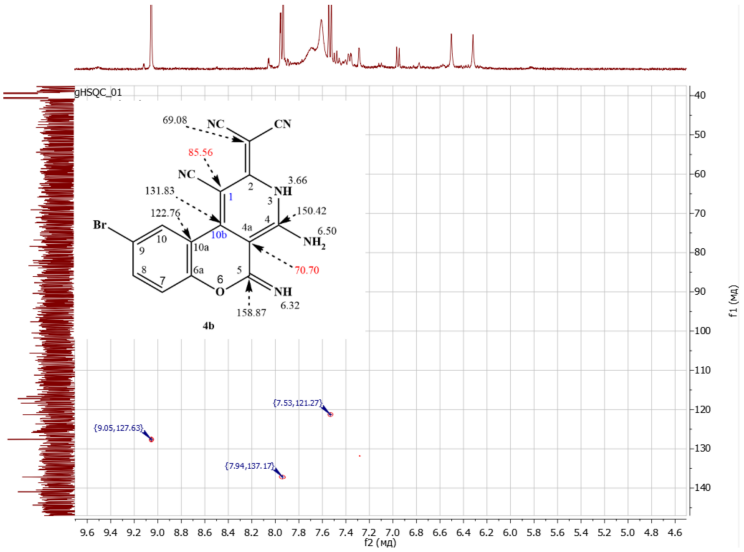
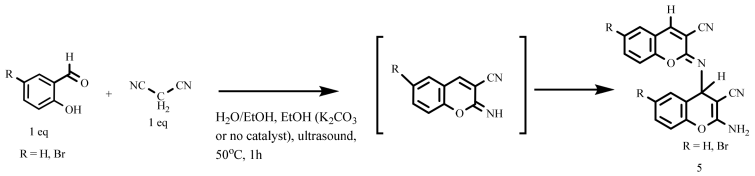


Figure 1. NMR HSQC 1H/13C spectrum and main correlations in the NMR HSQC 1H/13C and HMBC 1H/13C spectrum of **4b**.

Previously, compounds **2** and **3** were obtained using a 1:2 or 1:3 ratio of salicylic aldehydes and malononitrile, without taking into account the retro-Michael reaction, the possibility of the elimination of the malononitrile molecule from already formed molecules of aminochromene 2 [6–8].

Our study also showed that the reactions of equimolar amounts of salicylic aldehydes and malononitrile under ultrasound activation conditions without a catalyst led to the formation of 2-amino-6-R-4-((6-R-3-cyano-2H-chromen-2-ylidene)amino)-4H-chromene-3-carbonitriles **5a**,**b** (R = H, Br), which are the dimers of 2-iminochromene **1** (Scheme 3). The subject dimers have been synthesized previously [4] via stirring in methanol and water, in the presence of triethylamine at room temperature for 6–20 h. We observed the formation of these dimers under catalyst-free conditions in higher yields within a shorter reaction time. A dimeric compound **5b** (R = Br) was synthesized for the first time.



Scheme 3. The synthesis of 2-iminochromene **1** dimers: 2-amino-6-R-4-((6-R-3-cyano-2H-chromen-2-ylidene)amino)-4H-chromene-3-carbonitriles **5a**,**b**.

The structures of the compounds **5a**,**b** were established using spectroscopic data (IR, NMR). The ^{1}H NMR spectra of the dimer 2-amino-6-bromo-4-((6-R-3-cyano-2H-chromen-2-ylidene)amino)-4H-chromene-3-carbonitrile **5b** (R = Br) showed characteristic signals of singlet at 5.81 ppm for the methyn proton H^{4}, singlet at 7.22 ppm for the amino group, and the singlets at 7.53, 7.83, and 8.29 for the aromatic protons H^{5},$H^{5'}$,$H^{4'}$, respectively (Figure 2). The main correlations in the ^{1}H/^{13}C HSQC spectrum of **5b** are 5.81/48.62 (H^{4}/C^{4}), 7.53/132.10 (H^{5}/C^{5}), 7.83/131.80 ($H^{5'}/C^{5'}$), and 8.29/145.45 ($H^{4'}/C^{4'}$). The ^{1}H/^{13}C HMBC spectrum displayed the following main correlations between the methyn proton with the carbon atoms of both chromene scaffolds: 5.81/54.90 (H^{4}/C^{3}), 5.81/120.47 (H^{4}/-CN), and 5.81/146.4 ($H^{4}/C^{2'}$).

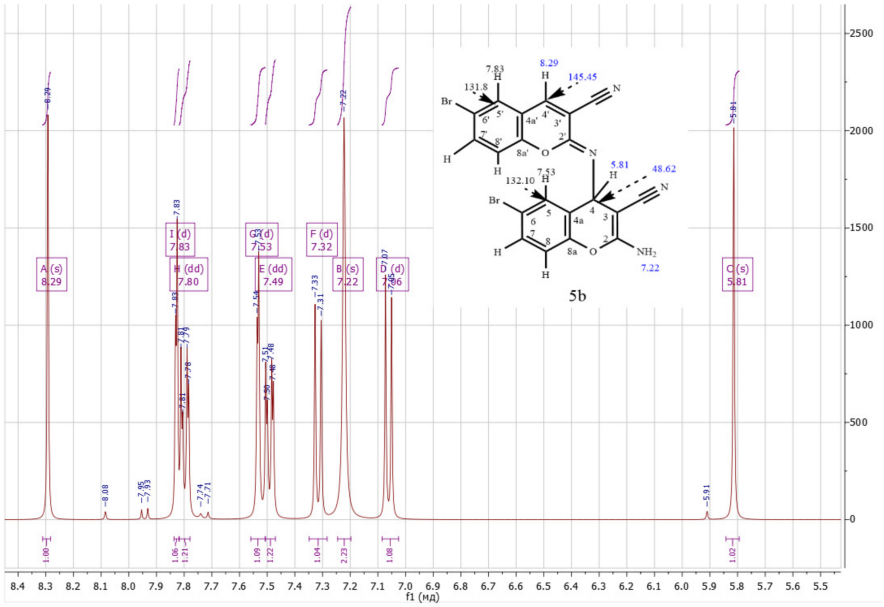


Figure 2. ^{1}H NMR spectrum of compound **5b**.

The authors of references [4–13] described how the domino reactions of salicylic aldehydes with one, two, and three molecules of malononitrile led to the formation of 2-iminochromene **1** derivatives depending on the reaction conditions and reaction time. We have shown the formation of dimers during one-pot reactions of salicylic aldehydes with molecule of malononitrile.

Thus, salicylic aldehydes and malononitrile undergo a wide range of transformations, among which the most important are the retro-Michael reaction, oxidation processes, and dimerization processes.

3. Experimental

3.1. General Information, Instrumentation, and Chemicals

The IR spectra were recorded on an FSM 1201Fourier spectrometer in KBr pellets. The ^{1}H, ^{13}C, ^{1}H/^{13}C HSQC, ^{1}H/^{1}H COSY, and ^{1}H/^{13}C HMBC spectra were recorded on a Varian 400 MHz spectrometer at 400 MHz (1H), the ^{13}C spectra were recorded at 100 MHz. NMR spectra were recorded in $CDCl_3$, $(CD_3)_2CO$, and DMSO-d6, internal standard TMS. Elemental analysis was performed on a Vario MICRO Cube automatic CHNS analyzer. The melting points were determined in an open capillary. The reaction progress was monitored by TLC on Fluka Silicagel/TLC-cards, eluent hexane–ethyl acetate–chloroform (2:2:1), and visualized by exposure to UV light and iodine vapor. Ultrasonic synthesis was performed in a Sapphire TTC ultrasonic bath (2.8 L, heated).

3.2. Synthesis and Characterization of the Compounds

- **2-(4,5-diamino-1-cyano-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile 3a and 2-(4-amino-1-cyano-5-imino-1,3,5,10b-tetrahydro-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile 3a′**

  (A) Equimolar amounts of malononitrile (0.13 g, 0.002 mol) and salicylic aldehyde (0.002 mol) were refluxed in dioxane for 6 h. The beige crystals that precipitated were filtered off, washed with hexane, and dried in desiccators. (B) 2a (0.3 g) was stirred in IPA at 60 °C for 1 h. The beige crystals that precipitated were filtered off, washed with hexane, and dried in desiccators. (C) 2a (0.3 g) was stirred in dioxane in an ultrasonic bath at room temperature for 1 h. The crystals that precipitated were filtered off, washed with hexane, and dried in desiccators.

  M.p. = 287–288 °C. Found, %; C, 62.37; H, 3.11; N, 27.46. $C_{16}H_{10}N_6O$. Calculated, %: C, 63.57; H, 3.33; N, 27.80; O, 5.29. beige crystals. ^{1}H NMR ($CDCl_3$), δ, ppm: (3a): 4.83

(H^1, d, 1H. J = 3.6 Hz), 4.91 (H^{10b}, d, 1H. J = 3.6 Hz), 6.69 (-NH_2, s, 2H), 7.08 (-NH_2, s, 2H), 7.20 (H^7, d, 1H. J = 8 Hz), 7.23–7.28 (H^8-H^{10}, m, 3H). (3a′): 4.58 (H^1, d, 1H. J = 3.6 Hz), 5.05 (H^{10b}, d, 1H. J = 3.6 Hz), 7.12 (H^7, d, 1H. J = 8 Hz), 7.41 (H^8-H^9, t, 2H. J = 8 Hz), 7.46 (H^{10}, d, 1H. J = 8 Hz), 7.51 (-NH_2, s, 2H), 8.37 (=NH, s, 1H), 8.85 (=NH, s, 1H). Yield: 70% (A), 86% (B), 87% (C).

- **2-(4,5-diamino-9-bromo-1-cyano-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile 3b and 2-(4-amino-9-bromo-1-cyano-5-imino-1,3,5,10b-tetrahydro-2H-chromeno[3,4-c] pyridin-2-ylidene)malononitrile 3b′**

  (A) Equimolar amounts of malononitrile (0.13 g, 0.002 mol) and salicylic aldehyde (0.002 mol) were refluxed in IPA in the presence of Et_3N (3 drops) for 6 h. The brown crystals that precipitated were filtered off, washed with hexane, and dried in desiccators. (B) 2b (0.35 g) in IPA was refluxed for 4 h. After cooling, the crystalline solid was filtered off, washed with hexane, and dried in desiccators. (C) 2b (0.3 g) was stirred in dioxane in ultrasonic bath at room temperature for 2 h. Brown crystals that precipitated were filtered off, washed with hexane, and dried in desiccators.
  M.p. = 280–282 °C. Brown crystals. Calculated, %: C, 50.41; H, 2.38; Br, 20.96; N, 22.05; O, 4.20. $C_{16}H_9BrN_6O$. Found, %: C, 50.47; H, 2.87; N, 22.52. ^{1}H NMR (DMSO-d6), δ, ppm: 4.8–4.9 (H^1-H^{10b}, dd, 2H. J = 4 Hz) (3b): 7.1 (=NH, s, 1H), 6.72 (-NH_2, s, 2H), 7.64–7.61 (H^8, d, 1H. J = 8 Hz), 7.5 (H^{10}, s, 1H), 7.21–7.19 (H^7, d, 1H. J = 8 Hz); (3b′): 3.65 (=NH, s, 1H), 6.34 (=NH, s, 1H), 6.53 (=NH, s, 1H), 6.97–6.95 (H^7, d, 1H. J = 8 Hz), 7.38–7.35 (H^8, d, 1H. J = 8 Hz), 7.29 (H^{10}, s, 1H). Yield: 76% (A), 78% (B), 85% (C).

- **2-(4-amino-1-cyano-5-imino-3,5-dihydro-2H-chromeno[3,4-c]pyridin-2-ylidene) malononitrile 4a**

  (A) Equimolar amounts of malononitrile (0.13 g, 0.002 mol) and salicylic aldehyde (0.002 mol) were stirred in H_2O-PEG-400 solution at 40 °C for 4 h The orange-brown crystals that precipitated were filtered off, washed with hexane, and dried in air. (B) 2a (0.35 g) in IPA was refluxed for 4 h. After cooling, the crystalline solid was filtered off and dried in air.
  M.p. = 250–252 °C. Orange-brown crystals. Calculated, %: C, 64.00; H, 2.69; N, 27.99; O, 5.33. $C_{16}H_8N_6O$. Found, %: C, 63.76.00; H, 2.99; N, 28.05. ^{1}H NMR (DMSO-d6), δ, ppm: 3.65 (=NH, s, 1H), 6.31 (=NH, s, 2H), 6.50 (-NH_2, s, 2H), 6.98 (H^{10}, d, 1H. J = 8 Hz), 7.06 (H^9, t, 1H. J = 8 Hz), 7.54 (H^7, d, 1H. J = 8 Hz), 7.79 (H^8, t, 1H. J = 8 Hz). ^{1}H/^{13}C HSQC (DMSO-d6), δ, ppm: 6.98/116.74 (H^{10}/C^{10}), 7.06/124.23 (H^9/C^9), 7.54/125.79 (H^7/C^7), 7.79/134.80 (H^8/C^8). ^{1}H/^{13}C HMBC (DMSO-d6), δ, ppm: 3.65/86.05 (=NH/C^1), 3.65/119.48 (=NH/C^{10a}), 3.65/151.08 (=NH/C^4), 3.66/168.96 (=NH/C^5), 6.52/70.54 (-NH_2/C^{4a}), 6.52/86.05, (-NH_2/C^1),6.31/70.54 (=NH/C^{4a}). Yield: 84% (A), 75% (B).

- **2-(4-amino-9-bromo-1-cyano-5-imino-3,5-dihydro-2H-chromeno[3,4-c]pyridin-2-ylidene)malononitrile 4b**

  (A) Equimolar amounts of malononitrile (0.13 g, 0.002 mol) and 5-bromsalicylic aldehyde (0.002 mol) were refluxed in IPA for 6 h. After cooling, the crystalline solid was filtered off and dried in air. (B) 2b (0.35 g) in IPA was refluxed for 5 h. The crystalline solid was filtered off and dried in air. (C) 2b (0.35 g) was stirred in THF at 40 °C for 5 h. The crystalline solid was filtered off and dried in air.
  M.p. = 270–272 °C. Brown crystals. Calculated, %: C, 50.68; H, 1.86; Br, 21.07; N, 22.16; O, 4.22. $C_{16}H_7BrN_6O$. Found, C, %: 50,47; H, 2.05; N, 22.49. ^{1}H NMR (DMSO-d6), δ, ppm: 3.66 (=NH, s, 1H), 6.20 (=NH, s, 2H), 6.50 (-NH_2, s, 2H), 7.54 (H^7, d, 1H. J = 8 Hz), 7.94 (H^8, d, 1H. J = 8 Hz), 9.05 (H^{10}, s, 1H. J = 8 Hz). ^{1}H/^{13}C HSQC (DMSO-d6), δ, ppm: 7.53/121.27 (H^7/C^7), 7.94/137.17 (H^8/C^8), 9.05/127.63 (H^{10}/C^{10}). ^{1}H/^{13}C HMBC (DMSO-d6), δ, ppm: 3.66/85.56 57 (=NH/C^1). 3.66/122.76 (=NH/C^{10a}), 3.66/131.83 (=NH/C^{10b}), 3.66/150.42 (=NH/C^4), 3.66/158.87 (=NH/C^5), 6.32/70.70 (=NH/C^{4a}), 6.50/70.70 (-NH_2/C^{4a}), 6.50/85.56 (-NH_2/C^1). Yield: 70% (A), 75% (B), 86% (C).

- **2-amino-6-R-4-((6-R-3-cyano-2H-chromen-2-ylidene)amino)-4H-chromene-3-carbonitriles 5b**

  (A) Equimolar amounts of malononitrile (0.13 g, 0.002 mol) and 5-bromsalicylic aldehyde (0.002 mol) were heated in ethanol in an ultrasonic bath at 55 °C for 1 h. The beige crystals that precipitated were filtered off, washed with hexane, and dried in a desiccator. (B) Equimolar amounts of malononitrile (0.13 g, 0.002 mol) and 5-bromsalicylic aldehyde (0.002 mol) were heated in aqueous–ethanolic medium (1:1) in the presence of potassium carbonate (3 mol %) in an ultrasonic bath at 55 °C for 1 h. The beige crystals were filtered off, washed with hexane, and dried in a desiccator.
  M.p. = 200–201 °C. Beige crystals. Calculated, %: C, 48.22; H, 2.02; Br, 32.08; N, 11.25; O, 6.42. $C_{20}H_{10}Br_2N_4O_2$. Found, %: C, 47.98; H, 2.07; N, 11.85. ^{1}H NMR (DMSO-d6), δ, ppm: 5.81 (H^4, s, 1H), 7.06 (H^8, d, 1H. J = 8 Hz), 7.22 (-NH_2, s, 2H), 7.31 ($H^{8'}$, d, 1H. J = 8 Hz), 7.49 (H^7, d, 1H. J = 8 Hz), 7.53 (H^5, s, 1H), 7.78–7.81 ($H^{7'}$, d, 1H. J = 8 Hz), 7.83 ($H^{5'}$, s, 1H), 8.29 ($H^{4'}$, s, 1H). ^{1}H/^{13}C HSQC (DMSO-d6), δ, ppm: 5.81/48.62 (H^4/C^4), 7.07/118.80 (H^8/C^8), 7.32/118.68 ($H^{8'}/C^{8'}$), 7.49/132.22 (H^7/C^7), 7.53/132.10 (H^5/C^5), 7.80/136.76 ($H^{7'}/C^{7'}$),7.83/131.80 ($H^{5'}/C^{5'}$), 8.29/145.45 ($H^{4'}/C^{4'}$). ^{1}H/^{13}C HMBC (DMSO-d6), δ, ppm: 5.81/54.90 (H^4/C^3), 5.81/120.47 (H^4/-CN), 5.81/124.94 (H^4/C^{4a}), 5.81/132.06 (H^4/C^5), 5.81/146.44 ($H^4/C^{2'}$), 5.81/148.48 (H^4/C^{8a}), 5.81/162.07 (H^4/C^2), 7.22/54.89 (-NH_2/C^3), 7.53/48.65 (H^5/C^4), 7.83/145.53 ($H^{5'}/C^{4'}$), 7.83/152.63 ($H^{5'}/C^{8a'}$), 8.29/115.16 ($H^{4'}$/-CN'), 8.29/131.75 ($H^{4'}/C^{5'}$), 8.29/146.43 ($H^{4'}/C^{2'}$), 8.29/152.62 ($H^{4'}/C^{8a'}$). Yield: 80% (A), 83% (B).

4. Conclusions

In addition to the condensation reaction, retro-Michael reactions, oxidation processes, and dimerization processes occur in the reaction of malononitrile and salicylic aldehydes, which leads to new compounds **4a**,**b**, and **5b**.

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