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Synthesis and antimicrobial evaluation of new 2-pyridinone and 2-iminochromene derivatives containing morpholine moiety

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Abstract

As trail to overcome on the antimicrobial drug-resistance problems, new functionalized 2-pyridinone and 2-iminochromene derivatives bearing morpholine moiety were designed and synthesized. The 2-pyridinone derivatives were obtained through the cyclization of cyanoacetohydrazone of 4-morpholinylacetophenone with 1,3-dicarbonyl compounds, α,β-unsaturated nitriles or 2-(arylidene) malononitriles. The 2-iminochromene derivatives were synthesized through the ring closure of cyanoacetohydrazonewith salicylaldehyde derivatives. The antibacterial and antifungal activities for the synthesized 2-pyridinone and 2-iminochromene derivatives were investigated. Most of the tested compounds showed moderate activity against *P. vulgaris*. Compounds **4a,b** and **5a,b** showed moderate activity against G −ve bacteria. All iminochromene derivatives showed moderate activity against *C. albicans*. Compound **8c** was the most active compound.

1 | INTRODUCTION

Due to the widespread use, inaccurate diagnosis and misuse of antimicrobial agents, many observation for drug-resistant microbes have been reported [1,2]. For immunocompromised patients, treatment of drug-resistant microbes represent major hindrance [3]. According to the latest WHO's survey, about 500,000 people are antibiotic-resistant among the total infected patients across 22 countries. To accomplish this problem, some strategies were applied such as creation of novel pharmacophore. To get powerful synergistic effect; researches were directed to combine different pharmacophores in one structure [4–10]. Morpholine moiety is a simple heterocyclic ring which has great medicinal applications [11–13]. Many morpholine derivatives possess diverse pharmacological activities. Morpholine derivatives have great attention to design novel broad-spectra antimicrobial agents because they have unique mechanism of action. Morpholine nucleus is found in commercially available drugs. For example, Linezolid as antibiotic is used to fight gram-positive bacteria which are resistant to other drugs [14]. Amorolfine is used as antifungal drug for treatment of the toe fungal infection and finger nails [15]. Also, fenpropimorph is used in agriculture as fungicide. Large numbers of compounds which contain pyridine moiety are known in medicinal chemistry world as important compounds. The cyanopyridone derivatives have shown

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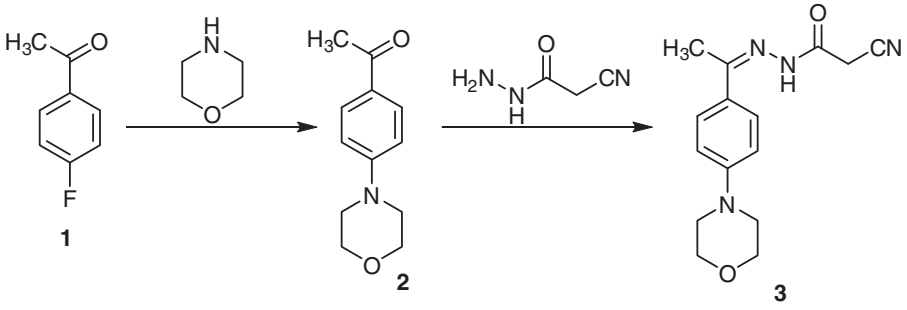
to possess promising biological activities [16–20]. Pyridine nucleus is found in commercially available antimicrobial drugs. For example, Isoniazid is used as a tuberculostatic drug. Moreover, the ciclopiroxis a synthetic antifungal drug that is used for treatment of skin for superficial mycoses. It is especially effective in treating Tinea versicolor. Chromene nucleus are of great interest for their various biological and medicinal activities as well as their therapeutical applications [21–25]. Chromene nucleus is naturally occurring and they are found in commercially available antimicrobial drugs. For example, novobiocin is an antibiotic drug. Also, clorobiocin is an aminocoumarin antibiotic.

Depending upon the above facts, it was aimed to synthesize new 2-pyridinone and 2-iminochromene derivatives containing morpholine moiety. These combination was suggested; wish to discover new structures that may have significant antimicrobial activity.

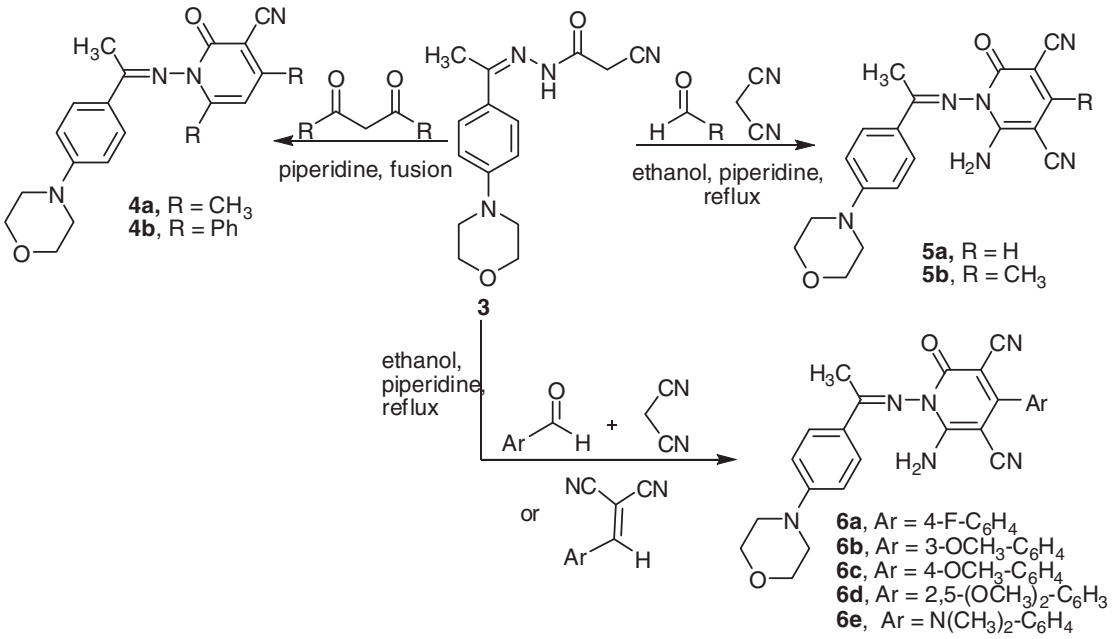
2 | RESULTS AND DISCUSSION

The cyanoacetohydrazone **3** as starting material was prepared as illustrated in Scheme 1. At first, 4-morpholinylacetophenone **2** was prepared via the nucleophilic replacement of fluorine atom at 4-fluoracetophenone **1** by morpholine ring [26]. Cyanoacetohydrazone of 4-morpholinylacetophenone was prepared through the condensation of 4-morpholinylacetophenone **2** with cyanoacetohydrazide.

It is well known that the reaction of cyanoacetamide derivatives with either 1,3-dicarbonyl compounds or α,β-unsaturated nitriles is easy and effective method for creation derivatives of 2-pyridones [17,18]. Thus, cyclocondensation of cyanoacetohydrazide **3** with acetyl acetone or 1,3-diphenylpropane-1,3-dione under fusion condition afforded the 2-pyridinone derivatives **4a,b** (Scheme 2). The structures of 2-pyridinones **4a,b** were proved by analytical and spectroscopic data. ^{1}H NMR spectrum of pyridinone **4a** was characteristic by the presence of three singlet signals at δ = 2.05, 2.21 and 2.37 ppm assignable for $3CH_3$ protons, two singlet signals at δ = 3.26 and 3.75 ppm formorpholine protons, singlet signal at δ = 6.43 ppm for pyridine-H5. In addition, two doublet signals with two protons integral value at δ = 7.03 and 7.90 ppm for phenylene AB protons were assigned. One-pot multi-component reactions of malononitrile, aliphatic aldehyde (namely, formaldehyde or acetaldehyde) and the derivative of cyanoacetamide **3** in one molar ratio in ethanolic piperidine under reflux condition afforded the 2-pyridinone derivatives **5a** and **5b**, respectively.^{1}H NMR spectrum of pyridine-2-one derivative **5b** showed at δ = 2.08 and 2.40 ppm two aliphatic singlet signals with three protons integral value assignable to two methyl protons. Two singlet signals with four protons integral value were displayed at δ = 3.22 and 3.75 ppm for morpholine protons. The two doublet signals with two protons integral value at δ = 6.99 and 7.93 ppm for phenylene AB protons were assigned. Broad exchangeable signal at δ = 8.06 ppm was assigned for the amino protons. Similarly, to the above reaction, one-pot, multi-component reaction of malononitrile, aromatic aldehydes and cyanoacetamide **3** in one molar ratio, in ethanolic piperidine gave the 1,2-dihydropyridine-2-one derivatives **6a-d**. Additionally, the 1,2-dihydropyridine-2-ones **6a-d** can be synthesized by heating cyanoacetamide **3** with the corresponding 2-(arylidene)-malononitrile in ethanolic piperidine under reflux. ^{1}H NMR spectrum of pyridine-2-one **6c**, as representative example, showed at δ = 3.24–3.31 and 3.70–3.80 ppm two multiplet signals with four protons integral value for morpholine protons. Two aliphatic signals at δ = 2.16 and 3.85 ppm with three protons integral value were assigned to methyl and methoxy protons, respectively. The four doublet signals with two protons integral value at δ = 7.04, 7.12, 7.52 and 7.97 ppm were assigned for two phenylene AB protons. The broad exchangeable signal at δ = 8.14 ppm was assigned for the amino protons. The creation of **6** is proposed to create though the Michael addition of the methyl function group of **3** to the activate olefinicbond of 2-(arylidene)malononitrile to form Michael adduct that was subjected to cyclize and loss of hydrogen molecule to yield **6** (Scheme 2).

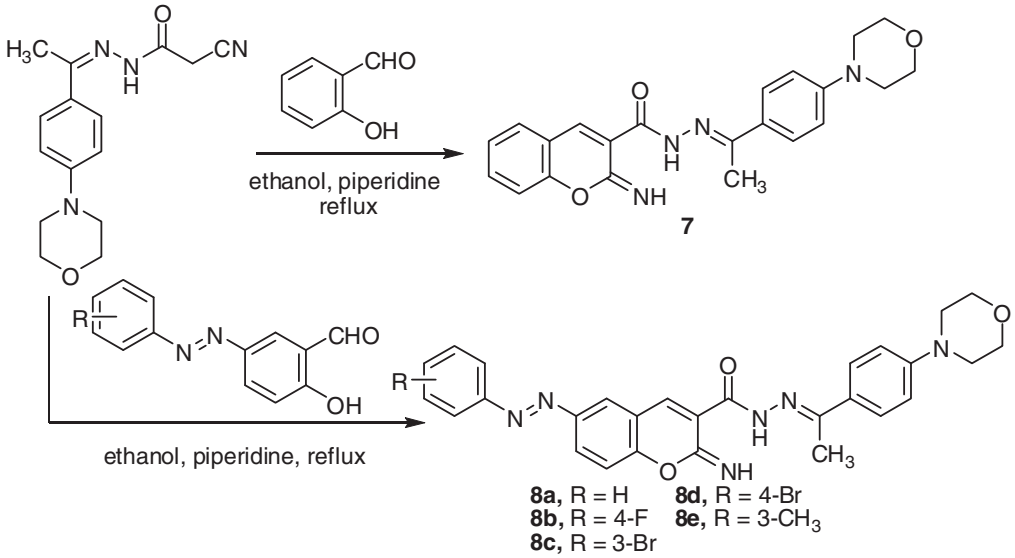


SCHEME 1 Synthesis of the starting material cyanoacetohydrazide **3**



SCHEME 2 Synthesis of 2-pyridinone derivatives **4-6**

SCHEME 3 Synthesis of 2-iminochromene derivatives **7** and **8a-e**



Here, the authors were aimed to synthesis chromene scaffold bearing morpholine moiety hoping to add some significant biological active compounds. Thus, cyclocondensation of cyanoacetamide **3** by salicylaldehyde afforded high yield of 2-iminochromene **7** as colored solid (Scheme 3). ^{1}H NMR spectrum of iminochromene derivative **7** was characteristic by found three singlet signals at δ = 8.54, 9.22 and 13.42 ppm assignable for chromene-H and 2NH protons, respectively.

Several diazenyl derivatives have been synthesized and evaluated for antimicrobial potentials. The majority of them have shown promising antimicrobial activities [27]. Thus, the present work was described the preparation of chromene nucleus containing aryldiazo group. Thus, cyclization of cyanoacetamide **3** with 5-aryldiazosalicylaldehydes in the presence of piperidine afforded 5-aryldiazo-2-iminochromene derivatives **8a-d** in reasonably good yields.

^{1}H NMR spectrum of iminochromene derivative **8b** showed at δ = 3.20 and 3.75 ppm two singlet signals with four protons integral value for morpholine protons. A singlet signal at δ = 2.28 ppm with three protons integral value was assigned for methyl group. Four signals with two protons integral value were assigned at δ = 6.99, 7.45, 7.76 and 7.98 ppm for two phenylene AB protons.

The protons of benzopyran were assigned at $\delta = 7.48$, 8.07 and 8.40 as doublet, doublet and singlet signals with one proton integral value. Also, the singlet signal at $\delta = 8.73$ (one proton) was displayed for the chromene proton. The imine protonsignals were assigned at $\delta = 9.51$ and 13.36 ppm as two exchangeable signals.

The newly synthesized pyridinone andchromen-2-imine derivatives were screened for their expected antifungal and antibacterial activities. Three microbial groups were tested. Group one: G +ve bacteria; *Bacillus subtilis* (RCMB 015) and *Staphylococcus aureus* (ATCC 25923). Group two: Gram-ve bacteria; *Proteus vulgaris* (RCMB 004) and *Escherichia coli* (ATCC 25922). Group three: (Fungi): *Candida albicans* (RCMB 005003) and *Aspergillus fumigatus* (RCMB 002008). For probing the antibacterial properties, diffusion agar technique [5] was applied at 10 mg/mL concentration, well diameter 6.0 mm (100 μL). For comparison, gentamycin (antibacterial agent) and ketoconazole (antifungal agent) were chose as antimicrobial agents. The inhibition zone diameters were depicted in Table 1.

Regarding the antimicrobial activity of 2-pyridinone and 2-iminochromene derivatives, few compounds displayed weak activities toward some of the tested microorganisms. Most of tested compounds showed moderate activity against *Proteus vulgaris*. Compounds 4a,b and 5a,b showed moderate activity against G −ve bacteria. All 2-iminochromene derivatives showed moderate activity against *Candida albicans*. Compound 8c was the most active compound; it showed moderate activity against four tested organisms. The major compounds displayed no activities toward most of the tested microorganisms.

3 | CONCLUSION

Novel of nine 2-pyridinonesand six 2-iminochromenes containing morpholine moiety were synthesized. The 2-pyridinone derivatives were obtained through the cyclization of cyanoacetohydrazone of 4-morpholi nylacetophenone with 1,3-dicarbonyl compounds, α,β-unsaturated nitriles or 2-(arylidene)malononitriles. The 2-iminochromene derivatives were synthesized through the ring closure of cyanoacetohydrazone with salicylaldehyde derivatives. The antibacterial and antifungal properties for the synthesized 2-pyridinone and 2-iminochromene derivatives were investigated. The obtained results suggested that most of compounds do not possess significant antimicrobial activity. Most of tested compounds showed moderate activity against *P. vulgaris*. Compounds **4a,b** and **5a,b** showed moderate activity against G −ve bacteria. All iminochromene derivatives showed moderate activity against *C. albicans*. Compound **8c** was the most active compound; it showed

TABLE 1 The mean results of inhibition zone in mm

	G +ve bacteria		G −ve bacteria		Fungi	
Compd. No.	**B. s.**	**S. a.**	**P.v.**	**E. c.**	**C. a.**	**A. f.**
4a	NA	NA	12	10	NA	NA
4b	NA	NA	11	10	12	NA
5a	NA	10	16	8	13	NA
5b	NA	9	12	9	NA	NA
6a	NA	NA	18	NA	NA	NA
6b	NA	NA	NA	NA	NA	NA
6c	NA	NA	10	NA	NA	NA
6d	NA	NA	15	NA	NA	NA
6e	NA	9	16	NA	NA	NA
7	NA	NA	15	NA	13	NA
8a	NA	NA	16	NA	15	NA
8b	NA	NA	10	NA	12	NA
8c	10	NA	NA	11	13	18
8d	NA	NA	14	NA	10	NA
8e	NA	NA	12	NA	11	NA
Gent.	26	24	25	30	–	–
Ket.	–	–	–	–	20	17

Abbreviations: A. f., A. fumigates; B.s., B. subtilis; C. A., C. albicans; E. c., E. coli; Gent., Gentamycin; Ket., Ketoconazole; NA, no activity; P. V., P. vulgaris; S.a., S. aureus.

moderate activity against four tested organisms. The major compounds displayed no activities toward most of the tested microorganisms.

4 | EXPERIMENTAL SECTION

The nuclear magnetic resonance were carried out in deuterated dimethylsulfoxide (DMSO-d_6) by using Bruker spectrometers (^{1}H NMR 400 MHz; ^{13}C NMR 101 MHz) with chemical shift in δ from internal TMS.

4.1 | Synthesis of 4,6-disubstituted-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3-carbonitriles 4a,b

The mixture of cyanoacetohydrazone **3** (0.02 mol), acetylacetone or benzoylacetone (0.02 mol), 1 mL of piperidine was gently heated for 20 min at about 150°C. The products were triturated with ethanol and crystallized from THF.

4,6-Dimethyl-1-(1-(4-morpholinophenyl)ethyl-ideneamino)-2-oxo-1,2-dihydropyri-dine-3-carbonitrile (4a): Yield 80%; m.p. 237–238°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.06 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.27 (s, 4H, $2CH_2$), 3.75 (s, 4H, $2CH_2$), 6.44 (s, 1H, pyridone-H), 7.03 (d, 2H, J = 8.0 Hz, Ar-H), 7.90 (d, 9H, J = 7.9 Hz, Ar-H); ^{13}C NMR (101 MHz, DMSO): 16.4 (CH_3), 19.6 (CH_3), (CH_3), 20.8 (CH_3), 47.6 ($2CH_2$), 66.3 ($2CH_2$), 108.5 (C≡N), 114.1 (2CH), 116.6 (CH), 129.5 (2CH), 150.6 (C), 154.0 (C), 157.3 (C═O); MS, m/z (%): 350 (M^+; 66.3); Anal. Calcd. for $C_{20}H_{22}N_4O_2$ (350.41): C, 68.55; H, 6.33; N, 15.99; Found: C, 68.42; H, 6.30; N, 16.13%.

1-(1-(4-Morpholinophenyl)ethylideneamino)-2-oxo-4,-6-diphenyl-1,2-dihydropyri-dine-3-carbonitrile (4b): Yield 69%; m.p. 181–183°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.27 (s, 3H, CH_3), 3.20, 3.75 (2s, 8H, $4CH_2$), 6.97 (s, 1H, pyridone-H5), 7.35–8.73 (m, 14H, Ar-H); MS, m/z (%): 474 (M^+; 28.8); Anal. Calcd. for $C_{30}H_{26}N_4O_2$ (474.55): C, 75.93; H, 5.52; N, 11.81; Found: C, 75.89; H, 5.49; N, 11.76%.

4.2 | Synthesis of 6-amino-4-alkyl-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (5a,b)

The suspension of cyanoacetohydrazide **3** (0.015 mol), the appropriate aldehyde (namely formaldehyde or acetaldehyde) (0.015 mol), malononitrile (0.015 mol) and three drops of piperidinein 40 mL ethanol was heated for 3 h under reflux conditions. The obtained products were recrystallized from ethanol.

6-Amino-1-(1-(4-morpholinophenyl)ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (5a): Yield 65%; m.p. 223–225°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.27 (s, 3H, CH_3), 3.19, 3.75 (2s, 8H, $4CH_2$), 6.71–7.13 (m, 3H, Ar-H), 7.36–8.20 (m, 4H, 2Ar-H and NH_2); MS, m/z (%): 362 (M^+; 58.9); Anal. Calcd. for $C_{19}H_{18}N_6O_2$(362.39): C, 62.97; H, 5.01; N, 23.19; Found: C, 63.11; H, 5.01; N, 23.20%.

6-Amino-4-methyl-1-(1-(4-morpholinophenyl)ethyl-ideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (5b): Yield 75%; m.p. 293–295°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.08, 2.40 (2s, 6H, $2CH_3$), 3.22, 3.75 (2s, 8H, $4CH_2$), 6.99, 7.93 (2d, 4H, J = 8.1 Hz, Ar-H, AB), 8.06 (br, 2H, NH_2); ^{13}C NMR (101 MHz, DMSO): 16.8 (CH_3), 20.4 (CH_3), 47.6 ($2CH_2$), 48.6 (C), 66.3 ($2CH_2$), 75.6, 88.0, 113.7, 115.1, 116.9, 125.1, 126.3, 130.1, 153.6, 154.08, 155.4, 158.5, 178.9 (C═O); MS, m/z (%): 376 (M^+; 33.9); Anal. Calcd. for $C_{20}H_{20}N_6O_2$(376.41): C, 63.82; H, 5.36; N, 22.33; Found: C, 63.76; H, 5.34; N, 22.30%.

4.3 | Synthesis of 6-amino-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-4-aryl-1,2-dihydropyridine-3,5-dicarbonitrile (6a-d)

Method A: The suspension of cyanoacetohydrazone **3** (0.015 mol), the appropriate aldehyde (namely, 4-fluorobenzaldehyde, *m*-anisaldehyde, *p*-anisaldehyde, 2,5-dimethoxybenzaldehyde, *p*-dimetylaminobenzaldehyde; 0.015 mol), malononitrile (0.015 mol) and two drops of piperidine in 40 mL ethanol was heated for 3 hours under reflux conditions. The resulting products were separated by filtration and recrystallized from ethanol.

Method B: The suspension of equimolar amounts (0.015 mol) of cyanoacetohydrazone **3** and 2-(arylidene) malononitrile (2-(4-fluorobenzylidene)-malononitrile, 2-(3-methoxy-benzylidene)malononitrile, 2-(4-methoxy benzylidene)malononitrile, 2,5-dimethoxybenzylidene-malononitrile and *p*-dimetylaminobenzylidene-malononitrile) in 40 mL ethanol containing two drops of piperidine was heated for 3 h under reflux conditions.

6-Amino-4-(4-fluorophenyl)-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicar bonitrile (6a): Yield 75%; m.p. 271–272°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.15 (s, 3H, CH_3), 3.22–3.31, 3.69–3.81 (2m, 8H, $4CH_2$), 7.05 (d, 2H, J = 8.9 Hz,

Ar-H, AB), 7.43 (m, 2H,Ar-H), 7.64 (m, 2H,Ar-H), 7.98 (d, 2H, J = 8.9 Hz, Ar-H, AB), 8.22 (br, 2H, NH_2); MS, m/z (%): 456 (M^+; 28.3); Anal. Calcd. for $C_{25}H_{21}FN_6O_2$ (456.47): C, 65.78; H, 4.64; N, 18.41; Found: C, 65.82; H, 4.66; N, 18.38%.

6-Amino-4-(3-methoxyphenyl)-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (6b): Yield 70%; m.p. >300°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.17 (s, 3H, CH_3), 3.29, 3.72 (2m, 8H, $4CH_2$), 3.84 (s, 3H, OCH_3), 7.05 (d, 2H, J = 9.0 Hz, Ar-H, AB), 7.12 (m, 2H,Ar-H), 7.38–7.62 (m, 2H,Ar-H), 8.00 (d, 2H, J = 9.0 Hz, Ar-H, AB), 8.19 (br, 2H, NH_2); MS, m/z (%): 468 (M^+; 74.8); Anal. Calcd. for $C_{26}H_{24}N_6O_3$ (468.51): C, 66.65; H, 5.16; N, 17.94; Found: C, 66.71; H, 5.14; N, 18.03%.

6-Amino-4-(4-methoxyphenyl)-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (6c): Yield 80%; m.p. >300°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.15 (s, 3H, CH_3), 3.24–3.31, 3.70–3.80 (2m, 8H, $4CH_2$), 3.85 (s, 3H, OCH_3), 7.04, 7.12 (2d, 4H, J = 8.7 Hz, Ar-H, AB), 7.52 (d, 2H, J = 8.7 Hz, Ar-H, AB), 7.97 (d, 2H, J = 9.0 Hz, Ar-H, AB), 8.14 (br, 2H, NH_2); MS, m/z (%): 468 (M^+; 64.1); Anal. Calcd. for $C_{26}H_{24}N_6O_3$ (468.51): C, 66.65; H, 5.16; N, 17.94; Found: C, 66.69; H, 5.13; N, 18.07%.

6-Amino-4-(2,5-dimethoxyphenyl)-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (6d): Yield 85%; m.p. >300°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.15 (d, 3H, CH_3), 3.28 (s, 4H, $2CH_2$), 3.77–3.81 (m, 10H, $2CH_2$ and $2OCH_3$), 6.85–7.20 (m, 5H, Ar-H), 7.97 (d, 2H, J = 8.6 Hz, Ar-H), 8.15 (br, 2H, NH_2); ^{13}C NMR (101 MHz, DMSO): 16.9 (CH_3), 47.7 ($2CH_2$), 48.5, 56.1 (OCH_3), 56.7 (OCH_3), 66.3 ($2CH_2$), 66.5, 76.3, 88.6, 113.8, 115.1, 115.3, 115.8, 116.7, 124.7, 125.1, 130.2, 150.1, 153.3, 153.7, 154.1, 155.6, 157.6, 179.1 (C=O); MS, m/z (%): 498 (M^+; 59.0); Anal. Calcd. for $C_{27}H_{26}N_6O_4$ (498.53): C, 65.05; H, 5.26; N, 16.86; Found: C, 64.96; H, 5.23; N, 16.90%.

6-Amino-4-(4-(dimethylamino)phenyl)-1-(1-(4-morpholinophenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (6e): Yield 68%; m.p. 243–245°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.27, 3.00, 3.08 (3s, 9H, $3CH_3$), 3.18–3.21, 3.73–3.75 (2m, 8H, $4CH_2$), 6.80–6.86 (m, 4H, Ar-H), 6.97, 7.36 (2d, 4H, J = 8.7 Hz, Ar-H), 8.28 (br, 2H, NH_2); MS, m/z (%): 481 (M^+; 65.3); Anal. Calcd. for $C_{27}H_{27}N_7O_2$ (481.55): C, 67.34; H, 5.65; N, 20.36; Found: C, 67.29; H, 5.61; N, 20.29%.

4.4 | Synthesis of 2-imino-*N*′-(1-(4-morpholinophenyl)ethylidene)-2H-chromene-3-carbohydrazide (7)

The suspension of equimolar amounts (0.015 mol) of cyanoacetohydrazide **3** and salicyaldehyde in 40 mL ethanol containing two drops of piperidine was heated for 1 h under reflux conditions. The solid product was filtrated and recrystallized from dioxane to afford **7**. Yield 75%; m.p. 219–220°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.22 (s, 3H, CH_3), 3.15, 3.71 (2s, 8H, $4CH_2$), 6.93–7.25 (m, 4H, Ar-H), 7.71–7.76 (m, 4H, Ar-H), 8.54 (s, 1H, Chromen-H), 9.22, 13.42 (2s, 2H, 2NH); ^{13}C NMR (101 MHz, DMSO): 16.8 (CH_3), 47.6 ($2CH_2$), 66.3 ($2CH_2$), 113.7, 115.1, 116.9, 125.1, 126.3, 130.1, 153.6, 154.1, 155.4, 158.5, 178.9, (C=N); MS, m/z (%): 390 (M^+; 47.4); Anal. Calcd. for $C_{22}H_{22}N_4O_3$(390.44): C, 67.68; H, 5.68; N, 14.35; Found: C, 67.73; H, 5.66; N, 14.31%.

4.5 | Synthesis of 2-imino-*N*′-(1-(4-morpholinophenyl)ethylidene)-6-(aryldiazenyl)-2*H*-chromene-3-carbohydrazides 8a-e

The suspension of equimolar amounts (0.015 mol) of cyanoacetohydrazide **3** and aryldiazosalicylaldehydes in 40 mL ethanol containing few drops of piperidine was heated for 0.5 h under reflux conditions. The created solid products were separated by filtration and crystallized from dioxane to afford **8a-e**.

2-Imino-N′-(1-(4-morpholinophenyl)ethylidene)-6-(phenyldiazenyl)-2H-chromene-3-carbohydrazide (8a): Yield 85%; m.p. 221–222°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.28 (s, 3H, CH_3), 3.21, 3.75 (2s, 8H, $4CH_2$), 6.99 (d, 2H, J = 7.9 Hz, Ar-H), 7.46 (d, 1H, J = 8.5 Hz, Ar-H), 7.61 (s, 2H, Ar-H), 7.77 (d, 2H, J = 7.8 Hz, Ar-H), 7.91 (d, 2H, J = 5.6 Hz, Ar-H), 8.09 (d, 1H, J = 7.1 Hz, Ar-H), 8.44 (s, 1H, Ar-H), 8.75 (s, 1H, Chromen-H), 9.52, 13.37 (2s, 2H, 2NH); MS, m/z (%): 494 (M^+; 64.7); Anal. Calcd. for $C_{28}H_{26}N_6O_3$ (494.54): C, 68.00; H, 5.30; N, 16.99; Found: C, 68.07; H, 5.28; N, 17.08%.

6-((4-Fluorophenyl)diazenyl)-2-imino-N′-(1-(4-morpholinophenyl)ethylidene)-2H-chromene-3-carbohydrazide (8b): Yield 86%; m.p. 224–226°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.28 (s, 3H, CH_3), 3.19, 3.75 (2s, 8H, $4CH_2$), 6.99 (d, 2H, J = 8.5 Hz, Ar-H), 7.43–7.48 (m, 3H, Ar-H), 7.76 (d, 2H, J = 8.4 Hz, Ar-H), 7.93–8.04 (m, 2H, Ar-H), 8.07 (d, 1H, J = 8.7 Hz, Ar-H), 8.40 (s, 1H, Ar-H), 8.73 (s, 1H, Chromen-H), 9.51, 13.36 (2s, 2H, 2NH); MS, m/z (%): 512 (M^+; 47.1); Anal. Calcd. for $C_{28}H_{25}FN_6O_3$ (512.53): C, 65.61; H, 4.92; N, 16.40; Found: C, 65.56; H, 4.91; N, 16.36%.

6-((3-Bromophenyl)diazenyl)-2-imino-N′-(1-(4-morpholinophenyl)ethylidene)-2H-chromene-3-carbohydrazide (8c): Yield 88%; m.p. 240–242°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.29 (s, 3H, CH_3), 3.20, 3.76 (2s, 8H, $4CH_2$), 7.00 (m, 2H, Ar-H), 7.59 (m, 2H, Ar-H), 7.78 (m, 2H, Ar-H), 8.02 (s, 1H, Ar-H), 8.11 (d, 1H, Ar-H), 8.46 (s, 1H, Ar-H), 8.74 (s, 1H, Ar-H), 9.53, 13.36 (2s, 2H, 2NH); MS, m/z (%): 573 (M^+; 34.3); Anal. Calcd. for $C_{28}H_{25}BrN_6O_3$ (573.44): C, 58.65; H, 4.39; N, 14.66; Found: C, 58.63; H, 4.38; N, 14.69%.

6-((4-Bromophenyl)diazenyl)-2-imino-N′-(1-(4-morpholinophenyl)ethylidene)-2H-chromene-3-carbohydrazide (8d): Yield 86%; m.p. 244–245°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.27 (s, 3H, CH_3), 3.21, 3.75 (2s, 8H, $4CH_2$), 6.99 (d, 2H, J = 8.3 Hz, Ar-H), 7.45 (d, 1H, J = 9.1 Hz, Ar-H), 7.76–7.84 (m, 4H, Ar-H), 8.08 (d, 1H, Ar-H),8.43 (s, 1H, Ar-H), 8.73 (s, 1H, Chromen-H), 9.53, 13.35 (2s, 2H, 2NH); MS, m/z (%): 573 (M^+; 55.7); Anal. Calcd. for $C_{28}H_{25}BrN_6O_3$ (573.44): C, 58.65; H, 4.39; N, 14.66; Found: C, 58.68; H, 4.40; N, 14.70%.

2-Imino-N′-(1-(4-morpholinophenyl)ethylidene)-6-(m-tolyldiazenyl)-2H-chromene-3-carbohydrazide (8e): Yield 86%; m.p. 238–240°C; ^{1}H NMR (400 MHz, DMSO): δ = 2.26, 2.43 (2s, 6H, $2CH_3$), 3.20, 3.74 (2s, 8H, $4CH_2$), 6.97 (m, 2H, Ar-H), 7.38–7.57 (m, 3H, Ar-H), 7.67–7.86 (m, 4H, Ar-H), 8.07 (m, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 8.70 (s, 1H, Chromen-H), 9.48, 13.37 (2s, 2H, 2NH); MS, m/z (%): 508 (M^+; 28.3); Anal. Calcd. for $C_{29}H_{28}N_6O_3$ (508.57): C, 68.49; H, 5.55; N, 16.52; Found: C, 68.53; H, 5.53; N, 16.47%.

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DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

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