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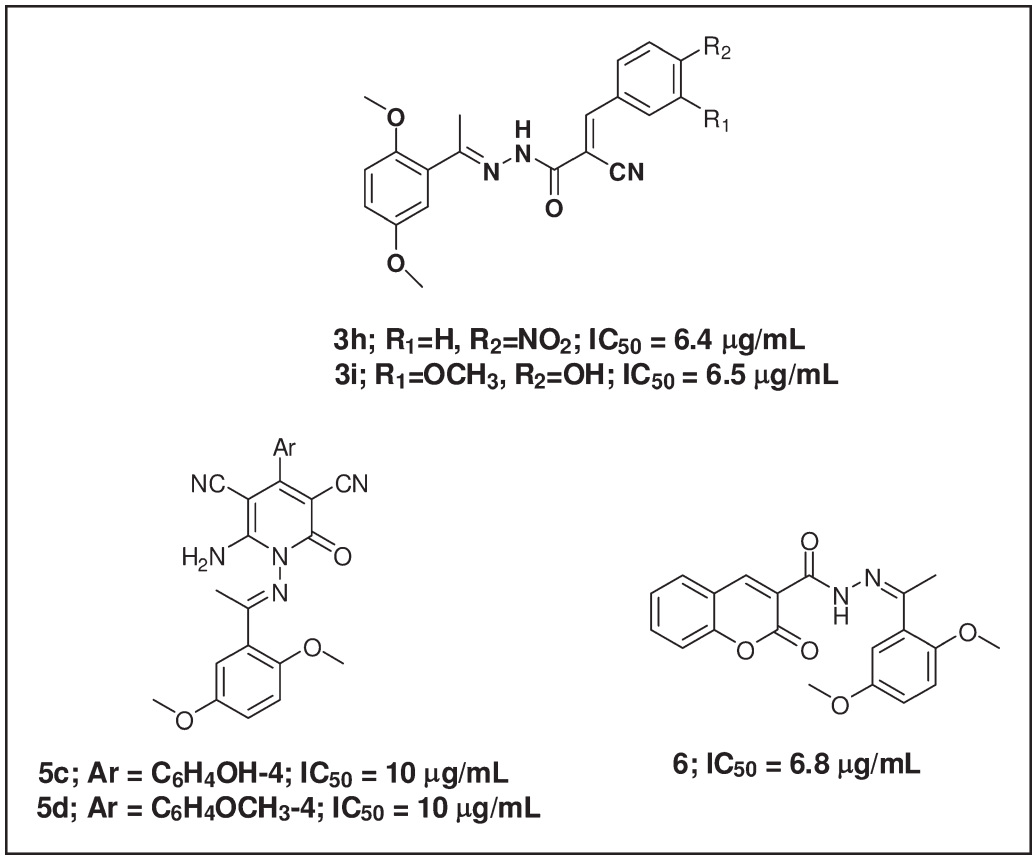

2-Cyano-N′-[1-(substitutedphenyl)ethylidene]acetohydrazide **2a–c** were obtained via reaction of acetophenone derivatives **1a–c** with cyanoacetic acid hydrazide. The hydrazidehydrazone derivative **2a** underwent a novel series of heterocyclization reactions via its reaction with aromatic aldehydes and/or arylidenemalononitriles to produce arylidene and dihydropyridine derivatives **3,5a–l**, respectively. Structures of the newly synthesized compounds were confirmed by elemental analyses, IR, ^{13}C-NMR, ^{1}H-NMR and mass spectral data. All the newly synthesized compounds were evaluated for their *in-vitro* antitumor activity against Ehrlich Ascities Carcinoma (EAC) cells. Some of them showed interesting cytotoxic activity compared with Doxorubicin (CAS 23214-92-8) as a reference drug.

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INTRODUCTION

Cancer is one of the difficult diseases to be cured, and very few effective drugs are available. The development of novel, efficient, and less toxic anticancer agents remains an important and challenging goal in medicinal chemistry. Understanding the molecular mechanism involved in cancers will lead to identification of novel anticancer agents. Changes in DNA, RNA, and protein levels due to mutations have been analyzed in many cancers, including leukemia and lymphoma [1–4]. From the literature survey, it was found that the hydrazide hydrazone group plays an important role for the anticancer activity [5–9]. On the other hand, a number of dihydropyridine derivatives claimed to possess interesting anticancer activity [10–13]. Also, the importance of the pyridine ring in the chemistry of biological system

has greatly realized because of their presence as substructure in many natural products of therapeutic importance, involved in oxidation-reduction process. The potent biological activity of various vitamins and drugs [14–17] is primarily contributed by the presence of pyridine ring in their molecular make-up. In addition, compounds having chromene ring are reported for their anticancer and antileukemic activities [18–20]. In the light of these facts, and as a continuation of our efforts towards synthesizing biologically active heterocyclic compounds especially antitumor activity [21–29], we planned to prepare a new derivatives of hydrazide, 1,2-dihydropyridine, chromene and benzochromene derivatives in the hope that new antitumor agents might be discovered.

RESULTS AND DISCUSSION

Several hydrazide-hydrazones, dihydropyridines, chromene and benzochro-mene were designed with the aim of exploring their antitumor activity (Schemes 1 and 2). This work reports the possible utility of cyanoacetic acid hydrazide in the synthesis of 2-cyano-N′-[1-(2,5-substitutedphenyl)ethylidene]acetohydrazide **2a–c**. The hydrazide-hydrazone derivatives **2a–c** were obtained via reaction of 2,5-dimethoxyacetophenone **1a,** or 2,5-dichloroacetophenone **1b** or 2-bromo-4-chloroacetophenone **1c** with cyanoacetic acid hydrazide. The structure of compounds **2a–c** was established on the basis of analytical and spectral data. IR spectrum of **2a** showed bands at 3209 cm^{-1} (NH), 2258 cm^{-1} (C≡N), 1683 cm^{-1} (C=O). ^{1}H-NMR spectrum of **2a** in (DMSO-d_6) revealed signals at δ 2.2 ppm corresponding to CH_3 group, group, 3.7 and 3.8 ppm for the two methoxy groups, a singlet at 4.1 ppm for CH_2 group, a multiplet at 6.9–7.1 ppm for the aromatic protons and a singlet at 10.9 ppm for an NH group. Mass spectrum of **2a** showed a molecular ion peak *m/z* at 261 [M^+] (21.3), with a base peak *m/z* at 163 (100). IR spectrum of **2b** revealed bands at 3210 cm^{-1} (NH), 2266 cm^{-1} (C≡N), 1694 cm^{-1} (C=O), 737 cm^{-1} C—Cl. Mass spectrum of **2b** exhibited a molecular ion peak *m/z* 270 [M^+] (1.94), with a base peak *m/z* at 167 (100). IR spectrum of **2c** revealed bands at 3377 cm^{-1} (NH), 2217 cm^{-1} (C≡N), 1695 cm^{-1} (C=O), 724 cm^{-1} C—Cl.

Further evidence for the structure of compounds **2a–c** was obtained through studying their chemical reactivity via some chemical reactions. Thus, interaction of compound **2a** with aromatic aldehydes yielded the arylidene derivatives **3a–l**, respectively. The analytical and spectral data in agreement with the proposed structures.

The reactivity of hydrazide-hydrazone derivative **2a** toward arylidene-malononitriles was studied. Thus, the reaction of compound **2a** with arylidene- malononitriles furnished the corresponding 6-amino-1-[1-(2,5-dimethoxy-phenyl)ethylideneamino)-2-oxo-4-substituted-1,2-dihydropyridine-3,5-dicarbo-nitriles **5a–l**. The formation of compounds **5a–l** was proceed via intermediates **4a–l**, followed by intramolecular cyclization to give **5a–l**. The structure of compounds **5a–l** was proved based on analytical and spectral data. IR spectra of compounds **5a–l** exhibited bands at 3414–3208 cm^{-1} due to (NH_2) groups, 2219–2188 cm^{-1} (C≡N) groups, 1707–1654 cm^{-1} (C=O) groups, ^{1}H-NMR spectra of compounds **5a–l** revealed signals at 1.7–2.2 ppm corresponding to protons of the methyl groups; 3.7 ppm due to protons of methoxy groups and 6.4–6.9 ppm assigned to protons of (NH_2) groups.

Further confirmation for the structure of **5a–l** were obtained through their synthesis via another reaction root. Thus, interaction of compounds **3a–l** with malononitrile in dioxane containing triethylamine as catalyst yielded the same dihydropyridine derivatives **5a–l** (m.p., and mixed m.p.).

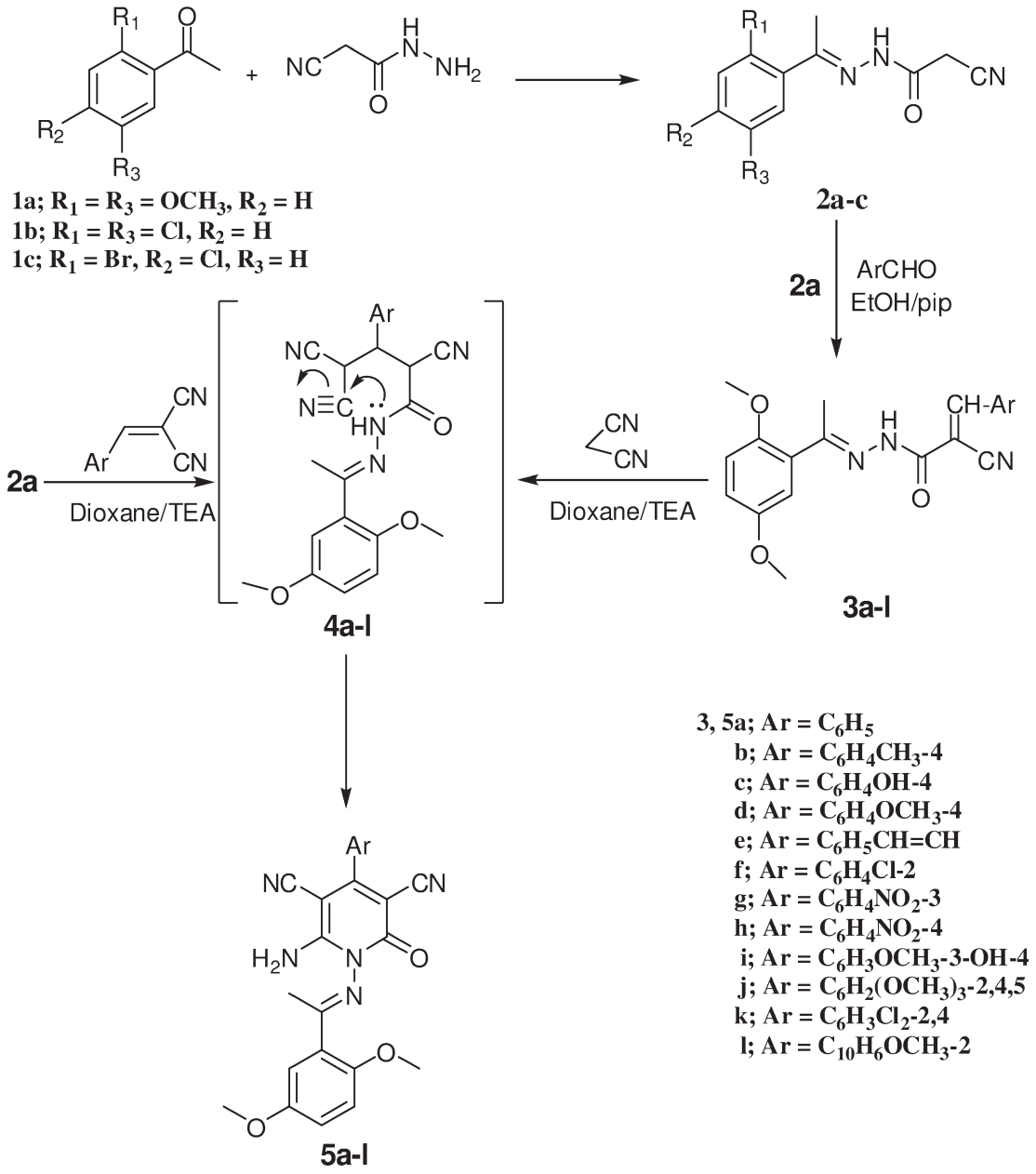
On the other hand, when compound **2a** reacted with salicyldehyde or 2-hydroxy-1-naphthaldehyde the chromene **6** and benzochromene **7** were obtained, respectively in good yield. The reaction goes in analogy with the reported literature [30,31].

The IR spectrum of compound **6** revealed the absence of (C≡N) band and presence of bands at 3420 cm^{-1} (NH), 1670, 1647 cm^{-1} (2 C=O), 1622 (C=N), its mass spectrum exhibited a molecular ion peak *m/z* at 366 [M^+] (5.9), with a base peak *m/z* at 62 (100). IR spectrum of compound **7** showed the absence of (C≡N) band and presence of bands at 3273 (NH), 1734 (2 C=O). Mass spectrum of **7** revealed a molecular ion peak *m/z* at 416 [M^+] (0.93), with a base peak *m/z* at 221 (100).

***In vitro* antitumor activity.** Doxorubicin, the reference drug used in this study, is one of the most effective antitumor agents used to produce regressions in acute leukemias, Hodgkin's desease and other lymphomas. The relationship between survival ratio and drug concentration was plotted to obtain the survival curue of Ehrlich Ascites Carcinoma (EAC) cells. The response parameter calculated was IC_{50} value (Table 1), which corresponds to the compound concentration causing 50% mortality in net cells.

Structure activity relationship. The parent target molecules containing the corresponding hydrazide **3a–l**, 1,2-dihydropyridine **5a–l**, chromene **6** and benzochromene **7** derivatives were synthesized to study their structure-activity relationship. From these results in (Table 1) it was found that substitution with either 4-nitrophenyl

Scheme 1



Scheme 2

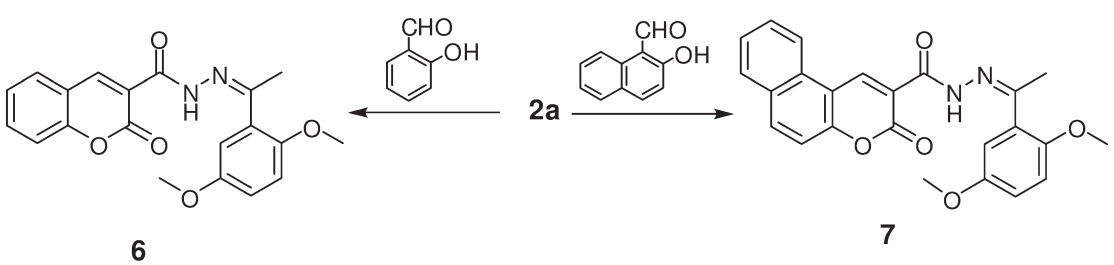


Table 1

In-vitro cytotoxic activity of the newly synthesized compounds **2a-7**.

	Nonviable cells (%)[a]					
	Concentration μg/mL					
Compd. no	100	50	25	10	IC_{50}[b] (μg/mL)	IC_{50} (μM)
Doxorubicin	100	60	39	20	37.5	68.99
2a	90	50	50	40	50	191.57
2b	80	50	40	40	50	185.18
2c	100	40	30	10	60	191.08
3a	50	30	20	10	100	286.53
3b	60	30	25	10	85	234.15
3c	90	70	50	30	25	68.49
3d	100	50	30	5	50	131.92
3e	30	10	10	10	>100[c]	-
3f	100	100	100	30	12.5	32.63
3g	100	70	40	30	33	83.75
3h	100	100	100	90	6.4	16.20
3i	100	80	70	60	6.5	16.45
3j	100	80	50	10	25	56.94
3k	60	40	20	5	75	179.42
3l	100	50	30	10	50	116.55
5a	50	30	30	5	100	242.13
5b	100	100	40	5	29	67.91
5c	100	80	60	50	10	23.31
5d	70	65	60	50	10	22.57
5e	100	60	20	10	31	70.61
5f	50	50	30	20	50	111.85
5g	100	70	50	30	25	54.58
5h	50	20	5	5	100	218.34
5i	100	80	50	30	25	54.46
5j	100	70	50	30	25	49.70
5k	100	80	30	20	35	72.46
5l	100	100	50	5	25	50.70
6	100	100	100	70	6.8	18.57
7	100	100	50	5	25	60.09

[a] Mean of nonviable percentage of three repeated experiments.
[b] IC_{50} value: corresponds to the compound concentration causing 50% mortality in net cells.
[c] Compounds with $IC_{50} > 100$ μg/mL are considered to be inactive.

3h, 4-hydroxy-3-methoxyphenyl **3i**, 2-chlorophenyl **3f**, 2,4,5-trimethoxyphenyl **3j**, and 4-hydroxyphenyl **3c** with IC_{50} values (16.20, 16.45, 32.63, 56.94, 68.49 μM) showed a significant cytotoxic activity which was even higher than that of reference drug doxorubicin (CAS-23214–92–8) with IC_{50} value (68.99 μM) as positive control. The substitution in *para*-position was found to enhance the cytotoxic activity rather than in *meta*-position. These findings were clearly observed as the presence of 4-nitrophenyl **3h,** IC_{50} value (16.20 μM) is more active than compound **3g** bearing 3-nitrophenyl IC_{50} value (83.75 μM).

Also, the presence of 4-hydroxy-3-methoxyphenyl **3i** with IC_{50} value (16.45 μM) is more active than compound **3c** carrying 4-hydroxyphenyl at the same position IC_{50} value (68.49 μM).

On the other hand, it was found that 1,2-dihydropyridins **5d** having 4-methoxyphenyl, **5c** bearing 4-hydroxyphenyl, **5j** carrying 2,4,5-trimethoxyphenyl, **5l** with 2-methoxy-1-naphthalene, **5i** with 4-hydroxy-3-methoxyphenyl, **5g** with 3-nitrophenyl and **5b** with 4-tolyl enhances the cytotoxic activity with IC_{50} values (22.57, 23.31. 49.70, 50.70, 54.46, 54.58, 67.91 μM) rather than the reference drug doxorubicin.

It was very interesting to observe that the corresponding hydropyridine derivative **5d** carrying 4-methoxyphenyl at 4-position with IC_{50} value (22.57 μM) is more potent than the hydrazide derivative **3d** having the same moiety with IC_{50} value (131.92 μM), which may give an idea about the presence of 4-methoxyphenyl group in compound **3d** resulted in a drop in cytotoxic activity. On the other hand, the hydrazide derivative **3h** bearing 4-nitrophenyl with IC_{50} value (16.20 μM) showed higher activity than that of dihydropyridine derivative **5h** with IC_{50} value (218.34 μM) carrying the same moiety, which indicate that this moiety may be enhance the anticancer activity in compound **3h**.

In addition, chromene derivative **6** with IC_{50} value (18.57 μM) is more potent than the corresponding benzochromene **7** with IC_{50} value (60.09 μM), and they exhibited higher activity when compared with doxorubicin as positive control.

Finally, compounds **5e** and **5k** with IC_{50} values (70.61, 72.46 μM) are nearly as active as doxorubicin as positive control, whereas compounds **3g**, **5f,** and **3l** revealed a moderate activity.

CONCLUSIONS

We report here the synthesis of some new hydrazide, 1,2-dihydropyridine, chromene and benzochromene derivatives containing biologically active dimethoxyphenyl moiety, it was clearly observed that hydrazide with either 4-nitrophenyl **3h** or 4-hydroxyphenyl **3i** or 2-chlorophenyl **3f**, 1,2-dihytropyridine with 4-methoxyphenyl **5d**, 4-hydroxyphenyl **5c**, 2,4-dichlorophenyl **5j**, 2-methoxynaphthalin **5l**, 4-hydroxy-3-methoxyphenyl **5i**, 3-nitrophenyl **5g** and chromene **6** exhibited higher antitumor activity than the reference drug Doxorubicin. Also, compounds **5e** and **5k** are nearly as active as Doxorubicin, whereas compounds **3g, 5f,** and **3l** exhibited a moderate activity.

EXPERIMENTAL

Chemistry. Melting points (°C, uncorrected) were determined in open capillaries on a Gallenkemp melting point apparatus (Sanyo Gallenkemp, Southborough, UK). Pre-coated silica gel plates (silica gel 0.25 mm, 60 G F 254; Merck, Germany) were used for thin layer chromatography, dichloromethane/methanol (9.5:0.5 ml) mixture was used as a developing solvent system and the spots were visualized by ultraviolet light and/or iodine. Infrared spectra were recorded in KBr discs using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). ^{13}C-NMR, ^{1}H-NMR spectra in (DMSO-d_6) were recorded on Bruker Ac-300 ultra shield NMR spectrometer (Bruker, Flawil, Switzerland, δ ppm) at 300 MHz, using TMS as internal standard. Electron impact Mass Spectra were recorded on a Shimadzu Gc-Ms-Qp 5000 instrument (Shimadzu, Tokyo, Japan). Elemental analyses were performed on Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany). All compounds were within ± 0.4% of the theoretical values.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]acetohydrazide, 2a, 2-cyano-N′-[1-(2,5-dichlorophenyl)ethylidene]acetohydrazide, 2b and N′-[1-(2-bromo-4-chloro-phenyl)ethylidene]-2-cyanoacetohydrazide, 2c. A mixture of 2-cyanoacetohydrazide (1 g, 0.01 mol) and either 2,5-dimethoxyacetophenone **1a** or 2,5-dichloroacetophenone **1b** or 2-bromo-4-chloroacetophenone **1c** (0.01 mol) in dioxane (20 mL) was refluxed for 2h. The reaction mixture was cooled and poured onto ice water. The solid obtained was crystallized from ethanol to give **2a–c**, respectively.

2a: Yield, 90%; m.p. 71–73°C; IR (KBr, cm^{-1}): 3209 (NH), 3038 (CH arom.), 2961, 2836 (CH aliph.), 2258 (C≡N), 1683 (C=O), 1634 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.21 [s, 3H, CH_3], 3.79, 3.81 [s, 6H, 2OCH_3], 4.12 [s, 2H, CH_2], 6.91–7.13 [m, 3H, Ar-H], 10.90 [s, 1H, NH]; ^{13}C-NMR (DMSO-d_6): 17.71, 24.82, 55.90 (2C), 113.24, 114.91, 115.91, 116.02, 119.54, 152.80, 154.91, 165.61, 198.41. MS (*m/z*): 261 [M$^+$] (21.3), 163 (100). Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.50; H, 5.40; N, 15.70.

2b: Yield, 89%; m.p. 166–168°C; IR (KBr, cm^{-1}): 3210 (NH), 3085 (CH arom.), 2964, 2924 (CH aliph.), 2226 (C≡N), 1694 (C=O), 1629 (C=N), 737 (C—Cl). ^{1}H NMR (DMSO-d_6) δ: 2.21 [s, 3H, CH_3], 4.12 [s, 2H, CH_2], 7.41–7.62 [m, 3H, Ar-H], 10.34 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 17.90, 24.51, 116.01, 130.81, 131.82, 132.41, 135.82 (2C), 140.03, 164.91, 198.72. MS (*m/z*): 270 [M$^+$] (1.94), 167 (100). Anal. Calcd for $C_{11}H_9Cl_2N_3O$: C, 48.91; H, 3.36; N, 15.56. Found: C, 48.60; H, 3.10; N, 15.20.

2c: Yield, 81%; m.p. > 300°C; IR (KBr, cm^{-1}): 3377 (NH), 3055 (CH arom.), 2953, 2860 (CH aliph.), 2217 (C≡N), 1695 (C=O), 1627 (C=N), 724 (C—Cl). ^{1}H NMR (DMSO-d_6) δ: 2.30 [s, 3H, CH_3], 4.71 [s, 2H, CH_2], 6.81–7.92 [m, 3H, Ar-H], 9.50 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 16.11, 26.72, 117.21, 124.62, 129.21, 131.20, 133.22, 135.41, 138.04, 163.92, 198.20. Anal. Calcd for $C_{11}H_9BrClN_3O$: C, 42.00; H, 2.88; N, 13.36. Found: C, 42.30; H, 2.50; N, 13.70.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-substitutedacrylohydrazide, 3a–l. *General procedure*. A mixture of **2a** (2.61 g, 0.01 mol) and aromatic aldehydes (0.01 mol) in dioxane (30 mL) containing piperidine (0.5 mL) was refluxed for 3h. The reaction mixture was left to cool then poured onto ice water containing few drops of HCl and the obtained solid was crystallized from dioxane to give **3a–l**, respectively.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-phenylacrylohydrazide, 3a. Yield, 79%; m.p. > 300°C; IR (KBr, cm^{-1}): 3364 (NH), 3094 (CH arom.), 2940, 2836 (CH aliph.), 2218 (C≡N), 1684 (C=O), 1610 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.58 [s, 3H, CH_3], 3.72 [s, 6H, 2OCH_3], 6.60–7.91 [m, 8H, Ar-H], 8.22 [s, 1H, CH], 9.90 [s, 1H, NH]. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.50; H, 5.20; N, 12.30.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-P-tolylacrylohydrazide, 3b. Yield, 72%; m.p. 210–212°C; IR (KBr, cm^{-1}): 3314 (NH), 3036 (CH arom.), 2938, 2860 (CH aliph.), 2205 (C≡N), 1702 (C=O), 1597 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.51 [s, 3H, CH_3 tolyl], 3.60 [s, 3H, CH_3], 3.81 [s, 6H, 2OCH_3], 6.71–7.92 [m, 7H, Ar-H], 8.10 [s, 1H, CH], 10.81 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 17.31, 24.81, 56.30 (2C), 100.31, 114.02, 115.32, 115.87 (2C), 116.88, 119.52, 126.71, 129.04, 130.51, 133.30, 149.21 (2C), 150.92, 158.51, 159.60, 161.91. MS *m/z* (%) 363 [M$^+$] (5.2), 63 (100). Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.10; H, 5.50; N, 11.20.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-(4-hydroxyphenyl)acrylohydra-zide, 3c. Yield 68; m.p. 254–256°C; IR (KBr, cm^{-1}): 3340 (OH), 3269 (NH), 3065 (CH arom.), 2940, 2860 (CH aliph.), 2213 (C≡N), 1661 (C=O), 1602 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.62 [s, 3H, CH_3], 3.71 [s, 6H, 2OCH_3], 6.70–8.01 [m, 7H, Ar-H], 8.31 [s, 1H, CH], 9.70 [s, 1H, OH], 10.61 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 16.41, 55.50 (2C), 100.31, 114.70 (2C), 115.91, 116.22 (2C), 117.94,

119.53, 128.12, 151.87 (2C), 152.92, 153.52, 159.61 (2C), 160.01, 161.86. MS *m/z* (%) 365 [M^+] (3.2), 277 (100). Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.40; H, 5.50; N, 11.10.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-(4-methoxyphenyl)acrylohydra-zide, 3d. Yield, 72%; m.p. 186–188°C; IR (KBr, cm^{-1}): 3272 (NH), 3041 (CH arom.), 2934, 2837 (CH aliph.), 2208 (C≡N), 1678 (C=O), 1603 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.70, 3.81 [2s, 9H, $3OCH_3$], 6.91–8.02 [m, 7H, Ar-H], 8.40 [s, 1H, CH], 11.91 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 17.91, 56.12 (2C), 101.71, 113.02, 114.34, 114.80 (2C), 116.61, 117.12, 118.85 (2C), 126.52, 128.81, 150.70 (2C), 152.81, 153.10, 160.72, 161.01, 162.72. MS *m/z* (%) 379 [M^+] (0.7), 161 (100). Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.10; H, 5.20; N, 10.80.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-5-phenyl-penta-2,4-dienehydrazide, 3e. Yield, 64%; m.p. 102–104°C; IR (KBr, cm^{-1}): 3327 (NH), 3026 (CH arom.), 2937, 2834 (CH aliph.), 2210 (C≡N), 1684 (C=O), 1599 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.82 [s, 6H, $2OCH_3$], 6.60 [d, 1H, CH Ph, J = 7.1 Hz], 6.81 [m, 1H, CH], 7.01–7.64 [m, 8H, Ar-H], 7.92 [d, 1H, C=CH, J = 7.4 Hz], 10.21 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 14.61, 55.40, 96.32 (2C), 113.41, 113.94, 114.03, 119.51, 127.20 (2C), 128.02, 128.12, 128.44 (2C), 128.81, 130.04, 132.81, 152.72 (2C), 152.81, 168.10, 198.42. MS *m/z* (%) 375 [M^+] (3.6), 43 (100). Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.00; H, 5.40; N, 11.50.

3-(2-Chlorophenyl)-2-cyano-N′-[1-(2,5-dimethoxyphenyl)e-thylidene]acrylohydr-azide, 3f. Yield, 59%; m.p. 146–148°C; IR (KBr, cm^{-1}): 3329 (NH), 3056 (CH arom.), 2937, 2836 (CH aliph.), 2215 (C≡N), 1705 (C=O), 1589 (C=N), 751 (C—Cl). ^{1}H NMR (DMSO-d_6) δ: 3.60 [s, 3H, CH_3], 3.71 [s, 6H, $2OCH_3$], 6.80–7.94 [m, 7H, Ar-H], 8.41 [s, 1H, CH], 12.41 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 22.11, 55.41 (2C), 110.30, 114.02, 114.61, 115.14, 117.31, 119.52, 127.01, 127.62, 128.21, 129.72, 131.81, 134.03, 152.81, 153.02, 153.41, 164.10, 198.41. MS *m/z* (%) 383 [M^+] (4.2), 205 (100). Anal. Calcd for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; N, 10.95. Found: C, 62.20; H, 4.40; N, 10.70.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-(3-nitro-phenyl)acrylohydrazide, 3g. Yield, 76%; m.p. 132–134°C; IR (KBr, cm^{-1}): 3446 (NH), 3082 (CH arom.), 2934, 2834 (CH aliph.), 2190 (C≡N), 1653 (C=O), 1616 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.70 [s, 6H, $2OCH_3$], 6.91–8.12 [m, 7H, Ar-H], 8.51 [s, 1H, CH], 10.20 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 23.82, 55.91 (2C), 108.40, 113.70, 113.91, 116.31, 118.92, 119.34, 121.73, 124.42 (2C), 130.31, 135.02, 139.81, 148.21, 152.12, 152.94, 153.01, 163.62. MS *m/z* (%) 394 [M^+] (5.7), 50 (100). Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 60.60; H, 4.30; N, 14.50.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-(4-nitro-phenyl)acrylohydrazide, 3h. Yield, 81%; m.p. 136–138°C; IR (KBr, cm^{-1}): 3446 (NH), 2937, 2835 (CH aliph.), 2186 (C≡N), 1700 (C=O), 1598 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.72 [s, 6H, $2OCH_3$], 6.80–8.12 [m, 7H, Ar-H], 8.70 [s, 1H, CH], 11.62 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 22.13, 55.40, 104.81 (2C), 113.42, 114.43, 115.42, 119.50, 122.31, 123.70, 127.62 (2C), 143.14, 147.51, 151.87 (2C), 152.79, 153.10, 167.92, 198.41. MS *m/z* (%) 394 [M^+] (4.2), 176 (100). Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 60.70; H, 4.90; N, 14.00.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-(4-hydroxy-3-methoxyphenyl) acrylohydrazide, 3i. Yield, 77%; m.p. 144–146°C; IR (KBr, cm^{-1}): 3381 (NH), 2939, 2861 (CH aliph.), 2206 (C≡N), 1669 (C=O), 1589 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.60 [s, 3H, CH_3], 3.71, 3.92 [2s, 9H, $3OCH_3$], 6.61–8.12 [m, 6H, Ar-H], 8.31 [s, 1H, CH], 9.82 [s, 1H, OH], 11.62 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 21.40, 55.91 (2C), 56.22, 103.02, 108.41, 113.42, 114.02, 116.54, 118.31, 119.52, 120.04, 120.61, 123.82, 145.31, 152.84, 153.62, 155.41, 157.54, 166.20, 198.12. MS *m/z* (%) 395 [M^+] (33.9), 46 (100). Anal. Calcd for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.50; 5.00; N, 10.40.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-(2,4,5-tri-methoxyphenyl)-acrylohydrazide, 3j. Yield, 66%; m.p. 137–139°C; IR (KBr, cm^{-1}): 3196 (NH), 2941, 2839 (CH aliph.), 2207 (C≡N), 1670 (C=O), 1592 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.70, 3.80, 3.92 [3s, 15H, $5OCH_3$], 6.61–8.02 [m, 5H, Ar-H], 8.43 [s, 1H, CH], 11.81 [s, 1H, NH]. MS *m/z* (%) 439 [M^+] (19.1), 168 (100). Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 62.50; H, 5.40; N, 9.20.

2-Cyano-3-(2,4-dichlorophenyl)-N′-[1-(2,5-dimethoxyphenyl) ethylidene]acrylohyd-razide, 3k. Yield, 78%; m.p. 90–92°C; IR (KBr, cm^{-1}): 3446 (NH), 2936, 2836 (CH aliph.), 2210 (C≡N), 1700 (C=O), 1584 (C=N), 816 (C—Cl). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.72 [s, 6H, $2OCH_3$], 6.90–7.81 [m, 6H, Ar-H], 8.04 [s, 1H, CH], 10.41 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 22.40, 55.91, 109.71, 113.92, 114.04, 115.71, 119.10, 119.52, 127.83, 129.81, 131.04, 133.82, 134.81 (2C), 135.87, 152.71, 153.02, 153.21, 172.89, 198.41. MS *m/z* (%) 418 [M^+] (3.9), 177 (100). Anal. Calcd for $C_{20}H_{17}Cl_2N_3O_3$: C, 57.43; H, 4.10; N, 10.05. Found: C, 57.10; H, 3.80; N, 9.70.

2-Cyano-N′-[1-(2,5-dimethoxyphenyl)ethylidene]-3-(2-methox-ynaphthalen-1-yl]-acrylohydrazide, 3l. Yield, 65%; m.p. 199–201°C; IR (KBr, cm^{-1}): 3300 (NH), 3100 (CH arom.), 2939, 2840 (CH aliph.), 2217 (C≡N), 1670 (C=O), 1622 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.70, 3.81 [2s, 9H, $3OCH_3$], 6.91–8.02 [m, 9H, Ar-H], 8.72 [s, 1H, CH], 12.21 [s, 1H, NH]. ^{13}C-NMR (DMSO-d_6): 22.11, 55.42 (2C), 56.61, 106.90, 107.11, 113.42, 113.91, 114.40 (2C), 115.34, 119.54, 123.61, 125.80 (2C), 127.72, 128.71, 130.70, 133.12, 152.73, 152.78, 155.31, 157.89, 158.10, 198.44. MS *m/z* (%) 429 [M^+] (0.9), 169 (100). Anal. Calcd for $C_{25}H_{23}N_3O_4$: C, 69.92; H, 5.40; N, 9.78. Found: C, 69.60; H, 5.10; N, 10.10.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-2-oxo-4-substituted-1,2-dih-ydropyridine-3,5-dicarbonitriles, 5a–l. **Method (A):** A mixture of **2a** (2.61 g, 0.01 mol) and arylidene malononitriles (0.01 mol) in dioxane (30 mL) containing triethylamine (1 mL) was refluxed for 4 h. The reaction mixture was poured onto ice water and the solid obtained was crystallized from dioxane to give **5a–l**, respectively.

Method (B): A mixture of compounds **3a–l** (0.01 mol) and malononitrile (0.66 g, 0.01 mol) in dioxane (30 mL) containing triethylamine (0.5 mL) was refluxed for 5 h. The reaction mixture was cooled and poured onto ice water and the obtained solid was crystallized from dioxane to give **5a–l** (m.p and mixed m.p).

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-2-oxo-4-phenyl-1,2-dihy-dropyridine-3,5-dicarbonitrile, 5a. Yield, 68%; m.p. 85–87°C; IR (KBr, cm^{-1}): 3385, 3342 (NH_2), 3100 (CH arom.), 2959, 2853 (CH aliph.), 2217 (C≡N), 1654 (C=O), 1559 (C=N). ^{1}H NMR (DMSO-d_6) δ: 1.71 [s, 3H, CH_3], 3.72 [s, 6H, 2OCH_3], 6.82 [s, 2H, NH_2 exchangeable with D_2O], 6.91–7.60 [m, 8H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 20.41, 55.62 (2C), 80.71, 114.70, 115.33, 115.82 (2C), 116.11, 117.44, 119.51, 126.20, 127.81, 128.62 (2C), 133.41, 150.71, 152.12, 152.81, 161.20 (2C), 164.62, 198.41. MS *m/z* (%) 413 [M^+] (5.5), 44 (100). Anal. Calcd for $C_{23}H_{19}N_5O_3$: C, 66.82; H, 4.63; N, 16.94. Found: C, 66.50, H, 4.40; N, 16.70.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-2-oxo-4-P-tolyl-1,2-dihy-dropyridine-3,5-dicarbonitrile, 5b. Yield, 71%; m.p. 96–98°C; IR (KBr, cm^{-1}): 3334, 3212 (NH_2), 3094 (CH arom.), 2957, 2854 (CH aliph.), 2216 (C≡N), 1654 (C=O), 1599 (C=N). ^{1}H NMR (DMSO-d_6) δ: 1.81 [s, 3H, CH_3], 2.32 [s, 3H, CH_3 tolyl], 3.73 [s, 6H, 2OCH_3], 6.82 [s, 2H, NH_2 exchangeable with D_2O], 6.91–7.52 [m, 7H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 20.41, 24.32, 55.43 (2C), 74.93, 114.84 (2C), 115.32, 115.91, 116.30, 117.41, 119.51, 126.32, 128.02, 129.61, 137.10, 152.22 (2C), 154.52, 159.63, 160.44 (2C), 182.61, 198.42. MS *m/z* (%) 427 [M^+] (1.1), 47 (100). Anal. Calcd for $C_{24}H_{21}N_5O_3$: C, 67.44; H, 4.95; N, 16.38. Found: C, 67.10; H, 4.60; N, 16.70.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-4-(4-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5c. Yield, 65%; m.p. 128–130°C; IR (KBr, cm^{-1}): 3410 (OH), 3326, 3206 (NH_2), 3056 (CH arom.), 2942, 2836 (CH aliph.), 2216 (C≡N), 1653 (C=O), 1607 (C=N). ^{1}H NMR (DMSO-d_6) δ: 1.81 [s, 3H, CH_3], 3.72 [s, 6H, 2OCH_3], 6.63 [s, 2H, NH_2 exchangeable with D_2O], 6.71–7.92 [m, 7H, Ar-H], 10.71 [s, 1H, OH]. ^{13}C-NMR (DMSO-d_6): 20.41, 55.40 (2C), 80.62, 114.11, 115.02, 115.73, 116.21, 117.40, 119.52, 126.31 (2C), 128.12, 152.82 (2C), 153.53, 154.71, 159.44 (2C), 159.81, 160.41, 198.42 (2C). MS *m/z* (%) 429 [M^+] (6.8), 47 (100). Anal. Calcd for $C_{23}H_{19}N_5O_4$: C, 64.33; H, 4.46; N, 16.31. Found: C, 64.70; H, 4.10; N, 16.60.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5d. Yield, 76%; m.p. 120–122°C; IR (KBr, cm^{-1}): 3334, 3208 (NH_2), 3082 (CH arom.), 2957, 2837 (CH aliph.), 2215 (C≡N), 1662 (C=O), 1605 (C=N). ^{1}H NMR (DMSO-d_6) δ: 1.80 [s, 3H, CH_3], 3.72, 3.80 [2s, 9H, 3OCH_3], 6.64 [s, 2H, NH_2 exchangeable with D_2O], 6.71–7.52 [m, 7H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 20.40, 56.31 (2C), 74.92, 114.00, 114.91, 115.32 (2C), 115.63, 116.14 (2C), 117.44, 119.52, 125.31, 128.10, 152.24, 154.73, 158.91, 159.40 (2C), 160.14, 160.71 (2C), 160.82. MS *m/z* (%) 443 [M^+] (5.9), 44 (100). Anal. Calcd for $C_{24}H_{21}N_5O_4$: C, 65.00; H, 4.77; N, 15.79. Found: C, 65.30; H, 4.40; N, 15.50.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-2-oxo-4-styryl]-1,2-dihydro-pyridine-3,5-dicarbonitrile, 5e. Yield, 69%; m.p. 130–132°C; IR (KBr, cm^{-1}): 3380, 3348 (NH_2), 3067 (CH arom.), 2940, 2860 (CH aliph.), 2218 (C≡N), 1680 (C=O), 1636 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.11 [s, 3H, CH_3], 3.70 [s, 6H, 2OCH_3], 6.51 [s, 2H, NH_2 exchangeable with D_2O], 6.61, 6.70 [d, 2H, CH=CH, J = 7.7, Hz], 6.90–7.81 [m, 8H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 18.50, 55.41 (2C), 66.34, 95.32, 114.03, 115.81 (2C), 116.32, 117.40, 119.52, 126.41, 128.13, 128.64, 129.31 (2C), 137.52, 137.90 (2C), 152.71, 153.02, 160.44, 165.10, 178.61, 198.40. MS *m/z* (%) 439 [M^+] (5.2), 46 (100). Anal. Calcd for $C_{25}H_{21}N_5O_3$: C, 68.33; H, 4.82; N, 15.94. Found: C, 68.60; H, 4.50; N, 15.70.

6-Amino-4-(2-chlorophenyl)-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5f. Yield, 59%; m.p. 100–102°C; IR (KBr, cm^{-1}): 3334, 3260 (NH_2), 3067 (CH arom.), 2956, 2835 (CH aliph.), 2193 (C≡N), 1699 (C=O), 1646 (C=N), 755 (C—Cl). ^{1}H NMR (DMSO-d_6) δ: 2.10 [s, 3H, CH_3], 3.72 [s, 6H, 2OCH_3], 6.90 [s, 2H, NH_2 exchangeable with D_2O], 7.01–7.64 [m, 7H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 21.12, 55.51 (2C), 72.43, 112.70, 113.41 (2C), 113.71, 114.01, 115.014, 119.50, 127.54, 128.14, 128.43, 129.70, 133.41, 134.04, 152.71, 152.82, 158.62, 161.83, 166.74, 198.41. MS *m/z* (%) 447.5 [M^+] (2.8), 40 (100). Anal. Calcd for $C_{23}H_{18}ClN_5O_3$: C, 61.67; H, 4.02; N, 15.64. Found: C, 61.30; H, 4.40; N, 15.90.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-4-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5g. Yield, 61%; m.p. 135–137°C; IR (KBr, cm^{-1}): 3380, 3347 (NH_2), 3086 (CH arom.), 2935, 2837 (CH aliph.), 2189 (C≡N), 1656 (C=O), 1616 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.10 [s, 3H, CH_3], 3.71 [s, 6H, 2OCH_3], 6.80 [s, 2H, NH_2 exchangeable with D_2O], 7.01–8.02 [m, 7H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 17.70, 55.91 (2C), 66.32, 114.83, 115.54, 116.12, 116.61, 117.40, 119.42, 121.61, 124.23 (2C), 130.14, 134.81, 135.30, 148.22, 151.21, 152.74, 152.90, 167.81, 177.62, 198.43. Anal. Calcd for $C_{23}H_{18}N_6O_5$: C, 60.26; H, 3.96; N, 18.33. Found: C, 60.50; H, 3.60; N, 18.00.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5h. Yield, 66%; m.p. 170–172°C; IR (KBr, cm^{-1}): 3372, 3354 (NH_2), 3070 (CH arom.), 2942, 2870 (CH aliph.), 2219 (C≡N), 1689 (C=O), 1598 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.02 [s, 3H, CH_3], 3.70 [s, 6H, 2OCH_3], 6.81 [s, 2H, NH_2 exchangeable with D_2O], 6.92–8.31 [m, 7H, Ar-H]. MS *m/z* (%) 458 [M^+] (3.3), 40 (100). Anal. Calcd for $C_{23}H_{18}N_6O_5$: C, 60.26; H, 3.96; N, 18.33. Found: C, 60.50; H, 4.20; N, 18.60.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-4-(4-hydroxy-3-methoxy-phenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles, 5i. Yield, 56%; m.p. 96–98°C; IR (KBr, cm^{-1}): 3430 (OH), 3336, 3280 (NH_2), 3066 (CH arom.), 2940, 2837 (CH aliph.), 2214 (C≡N), 1654 (C=O), 1597 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.10 [s, 3H, CH_3], 3.71, 3.82 [2s, 9H, 3OCH_3], 6.50 [s, 2H, NH_2 exchangeable with D_2O], 6.81–7.72 [m, 6H, Ar-H], 9.80 [s, 1H, OH]. MS *m/z* (%) 459 [M^+] (4.9), 40 (100). Anal. Calcd for $C_{24}H_{21}N_5O_5$: C, 62.74; H, 4.61; N, 15.24. Found: C, 62.40; H, 4.90; N, 15.50.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-4-(2,4–5-trimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5j. Yield, 68%; m.p. 249–251°C; IR (KBr, cm^{-1}): 3384, 3341 (NH_2), 3067 (CH arom.), 2942, 2837 (CH aliph.), 2188 (C≡N), 1707 (C=O), 1639 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.11 [s, 3H, CH_3], 3.71, 3.82 [2s, 15H, 5OCH_3], 6.40 [s, 2H, NH_2 exchangeable with D_2O], 6.81–7.22 [m, 5H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 20.20, 55.64 (2C), 56.31, 56.72, 84.12, 107.31, 113.14, 113.40, 114.01, 115.02, 115.63, 116.13 (2C), 117.84, 119.52, 141.41, 151.50, 152.82, 153.74, 155.91 (2C), 159.63, 165.43, 188.64, 198.42. MS *m/z* (%) 503 [M^+] (2.6), 46 (100). Anal. Calcd for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91. Found: C, 62.40; H, 5.30; N, 13.60.

6-Amino-4-(2,4-dichlorophenyl)-1-[1-(2,5-dimethoxyphenyl) ethylideneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5k. Yield, 71%; m.p. 110–112°C; IR (KBr, cm^{-1}): 3316, 3260 (NH_2), 3084 (CH arom.), 2939, 2835 (CH aliph.), 2218 (C≡N), 1675 (C=O), 1588 (C=N), 741 (C─Cl). ^{1}H NMR (DMSO-d_6) δ: 2.20 [s, 3H, CH_3], 3.71 [s, 6H, $2OCH_3$], 6.62 [s, 2H, NH_2 exchangeable with D_2O], 6.91–7.84 [m, 6H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 22.71, 55.62 (2C), 74.84, 114.71, 115.30, 115.92, 116.43, 117.54, 119.41, 126.10, 129.41, 131.14, 133.51, 134.52, 135.54, 151.81 (2C), 152.82, 156.10, 156.42, 158.84, 198.32. MS *m/z* (%) 482 [M^+] (1.43), 48 (100). Anal. Calcd for $C_{23}H_{17}Cl_2N_5O_3$: C, 57.27; H, 3.55; N, 14.52. Found: C, 57.50; H, 3.20; N, 14.20.

6-Amino-1-[1-(2,5-dimethoxyphenyl)ethylideneamino)-4-(2-methoxynaphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 5l. Yield, 69%; m.p. 94–96°C; IR (KBr, cm^{-1}): 3414, 3380 (NH_2), 3100 (CH arom.), 2940, 2838 (CH aliph.), 2218 (C≡N), 1669 (C=O), 1623 (C=N). ^{1}H NMR (DMSO-d_6) δ: 2.00 [s, 3H, CH_3], 3.71 [s, 9H, $3OCH_3$], 6.92 [s, 2H, NH_2 exchangeable with D_2O], 6.91–8.32 [m, 9H, Ar-H]. ^{13}C-NMR (DMSO-d_6): 18.31, 55.42 (2C), 56.84, 74.62, 113.43, 114.00, 114.81, 115.12, 115.31, 115.52, 116.41, 119.50, 123.44, 124.51, 126.92, 128.51, 129.70, 130.22, 132.41, 151.41 (2C), 152.90, 155.14, 155.62, 162.93, 163.21, 198.44. MS *m/z* (%) 493 [M^+] (1.32), 46 (100). Anal. Calcd for $C_{28}H_{23}N_5O_4$: C, 68.14; H, 4.70; N, 14.19. Found: C, 68.40; H, 4.30; N, 14.50.

N′[1-(2,5-dimethoxyphenyl)ethylidene)-2-oxo-2H-chromene-3-carbohydrazide, 6 and N′ [1-(2,5-dimethoxyphenyl)ethylidene)-3-oxo-3H-benzo[f]chromene-2-carbohydrazide, 7. A mixture of **2a** (2.61 g, 0.01 mol) and either salicyldehyde or 2-hydroxy-1-naphthaldehyde (0.01 mol) in dioxane (30 mL) containing piperidine (0.5 mL) was refluxed for 3 h. The reaction mixture was poured onto ice water containing few drops of HCl and the obtained solid was crystallized from dioxane to give **6** and **7**, respectively.

6: Yield, 82%; m.p. 114–116°C; IR (KBr, cm^{-1}): 3420 (NH), 3037 (CH arom.), 2940, 2837 (CH aliph.), 1670, 1647 (2 C=O), 1622 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.72 [s, 6H, $2OCH_3$], 6.90–7.72 [m, 7H, Ar-H], 8.91 [s, 1H, CH], 10.22 [s, 1H, NH exchangeable with D_2O]. ^{13}C-NMR (DMSO-d_6): 20.91, 55.30 (2C), 114.72, 115.33, 116.21, 118.70, 119.30, 119.51, 121.32, 124.63, 127.31, 129.52, 134.21, 151.64, 152.82, 154.10, 159.44, 167.71, 177.52. MS *m/z* (%) 366 [M^+] (5.9), 62 (100). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.20; H, 4.60; N, 7.30.

7: Yield, 69%; m.p. 293–295°C; IR (KBr, cm^{-1}): 3273 (NH), 3057 (CH arom.), 2940, 2860 (CH aliph.), 1734 (2 C=O), 1624 (C=N). ^{1}H NMR (DMSO-d_6) δ: 3.61 [s, 3H, CH_3], 3.70 [s, 6H, $2OCH_3$], 7.02–7.92 [m, 9H, Ar-H], 8.71 [s, 1H, CH], 12.81 [s, 1H, NH]. MS *m/z* (%): 416 [M^+] (0.93), 221 (100). Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.50; H, 4.60; N, 6.40.

Biological testing. ***Animals, chemicals and facilities.*** Ehrich ascites carcinoma (EAC) cells were maintained in female Swiss albino mice weighing 25–30 g (the holding company for biological products and vaccines. VACSERA, Cairo, Egypt) were housed at a constant temperature (24 ± 2°C) with alternating 12 h. light and dark cycles and fed standard laboratory food (Milad, Cairo, Egypt) and water *ad libitum*. All chemicals and reagents were of the highest grade commercially available. Facilities including animal house, biochemical equipments have been made available by the National Center for Radiation Research and Technology (NCRRT), Atomic Energy Authority (AEA), Cairo, Egypt. Animal care and handling was done according to the guidelines set by the world heath organization, Geneva, Switherland and approved from the committee for animals care at NCRRT, AEA.

In-vitro antitumor activity. EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice; under aseptic conditions [32]. Tumor cells suspension (2.5×10^6 per mL) was prepared in RPMI-1640 media. Tested compounds were prepared with various dilutions by dissolving: 100, 50, 25, 10 μg of the tested compounds in DMSO (1 mL).

In a set of sterile test tubes 0.8 mL RPMI-1640 media containing (glutamine, fetal calf serum as nutrient, streptomycin and penicillin), 0.1 mL of each of the tested compounds (corresponding to 100, 50, 25, 10 μg) were mixed then 0.1 mL of tumor cell suspension (2.5×10^5) was added. The test tubes were incubated at 37°C for 2h. Trypan blue exclusion test was carried out to calculate the percentage of nonviable cells after 2h of incubation [33,34].

$$\%\ \text{of non- viable cells} = \frac{\text{No. of non-viable cells}}{\text{Total No. of cells}} \times 100$$

The results of *in-vitro* cytotoxic activity experiments are presented in Table (1). Compounds producing more than 70% of nonviable cells were considered active [35].

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