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Article

One-Pot Synthesis of 4*H*-Chromene and Dihydropyrano[3,2-*c*]chromene Derivatives in Hydroalcoholic Media

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4*H*-Cromenos e diidropirano[3,2-*c*]cromenos são obtidos em rendimentos bons a excelentes através de um procedimento simples, brando e eficiente usando poli(*N*,*N*´-dibromo-*N*-etil-benzeno-1,3-dissulfonamida) [PBBS] e *N*,*N*,*N*´,*N*´-tetrabromobenzeno-1,3-dissulfonamida [TBBDA] como catalisadores.

4*H*-Chromenes and dihydropyrano[3,2-*c*]chromenes are obtained in good to excellent yields by a simple, mild and efficient procedure using poly(*N,N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide [TBBDA] as catalysts.

Keywords: 4*H*-chromenes, dihydropyrano[3,2-*c*]chromenes, TBBDA, PBBS

Introduction

The development of multi-component reactions (MCRs) has attracted much attention from the vantage point of combinatorial and medicinal chemistry.[1] Many important heterocycle syntheses are multi-component reactions. Recently, the synthesis of 4*H*-chromenes and dihydropyrano[3,2-*c*]chromenes derivatives have attracted great interest to their biological and pharmacological activities. The 4*H*-chromene derivatives show various pharmacological properties such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities.[2] Substituted 4*H*-chromenes are particularly versatile compounds that bind Bcl-2 protein (B-cell lymphoma 2) and induce apoptosis in tumor cells. Specifically, Bcl-2 can contribute to neoplastic cell expansion by preventing normal cell turnover caused by physiological cell death mechanisms. High levels of the Bcl-2 gene expressions are found in a wide variety of human cancers and can lead to tumor cell resistance to conventional chemotherapy and radiotherapy. Thus, Bcl-2 protein binding compounds provide a promising lead for the development of potential anticancer agents and direct methods for their synthesis are highly desirable.[3-5] Dihydropyrano[3,2-*c*]chromenes are a class of important heterocycles that have been used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus.[6] In addition, aminochromene derivatives exhibit a wide spectrum of biological activities including antihypertensive and anti-ischemic behavior.[7-9] Also, a number of 2-amino-4*H*-pyrans are useful as photoactive materials.[10]

4*H*-Chromenes have been prepared from salicylaldehydes and cyanoacetates in heterogeneous liquid phase catalysis using Al_2O_3[4,11] and molecular sieves.[5] They are also synthesized in the presence of $Zr(KPO_4)_2$[12] and Amberlyst A21®.[13] Despite their importance from pharmacological, industrial and synthetic point of views, comparatively few methods for accessing pyrano[3,2-*c*]chromene derivatives have been reported.[14-16] 2-Amino-4-aryl-5-oxo-4*H*, 5*H*-pyrano-[3,2-*c*]chromene-3-carbonitriles have already been prepared in the presence of organic bases like piperidine or pyridine in an organic solvent, i.e., ethanol and pyridine.[14] They are also obtained in the presence of diammonium hydrogen phosphate,[15] $H_6P_2W_{18}O_{62}\cdot 18H_2O$,[16] DBU[17] and K_2CO_3 under microwave irradiation.[18]

However, some of these protocols require long reaction times, multi-step reactions, complex synthetic pathways and afford products with only modest yields. Therefore, the introduction of milder, faster and more ecofriendly methods, accompanied with higher yields is needed.

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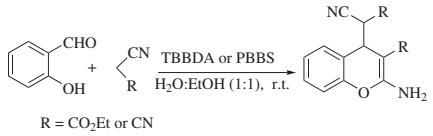
Results and Discussion

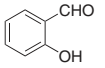
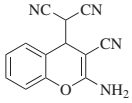
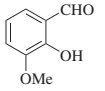
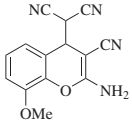
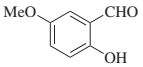
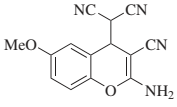
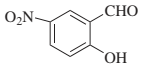
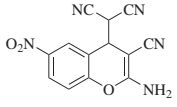
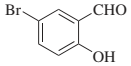
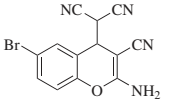
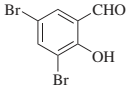
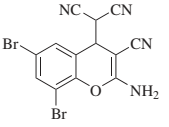
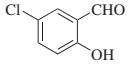
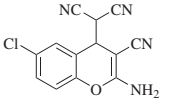
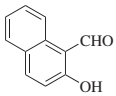
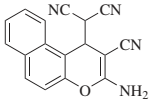
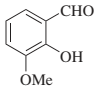
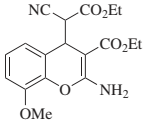
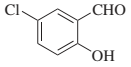
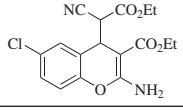
In continuation of our interest in the application of *N*,*N*,*N*',*N*'-tetrabromo benzene-1,3-disulfonamide [TBBDA] and poly(*N*,*N*'-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS][19-22] in organic synthesis, we report here a convenient method for the preparation of 4*H*-chromenes from salicylaldehydes and malononitrile or ethyl cyanoacetate in aqueous ethanol (H_2O:EtOH, (1:1)) at room temperature (Scheme 1 and Table 1).



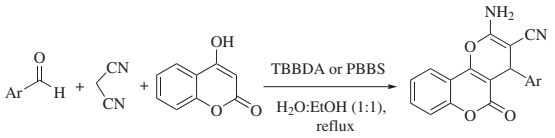
Scheme 1.

Also the synthesis of dihydropyrano[3,2-*c*]chromenes was achieved by the three-component condensation of an aromatic aldehyde, malononitrile and 4-hydroxycoumarin in the presence of the catalysts. The reaction was carried out in aqueous ethanol at reflux using TBBDA and PBBS as catalysts to give products in good to high yields (Scheme 2 and Table 2).

Table 1. Synthesis of various 4*H*-chromenes using TBBDA and PBBS at room temperature

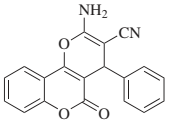
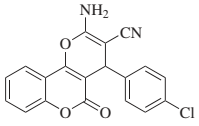
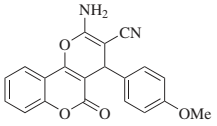
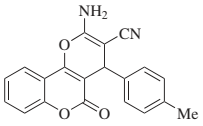
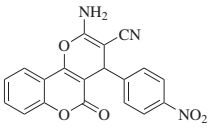
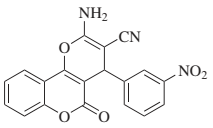
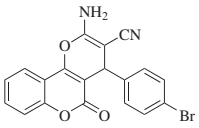
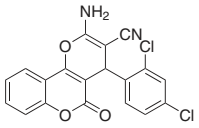
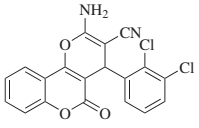
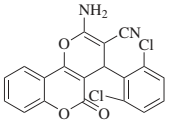
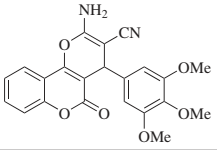
Entry	Aldehyde	R	Product[a]	TBBDA		PBBS		Ref.
				time/min	Yield/(%)	time/min	Yield/(%)	
1		CN		45(180)[b]	92(55)[b]	70	90	13
2		CN		120	92	150	92	13
3		CN		135	72	180	99	-
4		CN		30(180)[b]	85(55)[b]	65	96	13
5		CN		300	83	270	97	13
6		CN		90	98	15	94	13
7		CN		240	95	210	88	-
8		CN		420	76	60	82	13
9		CO_2Et		180	82	210	85	12
10		CO_2Et		270	92	260	88	12

[a]Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods. [b]Without using the catalysts.



Scheme 2.

Table 2. Synthesis of various dihydropyrano[3,2-*c*]chromenes using TBBDA and PBBS under refluxing H_2O:EtOH (1:1)

Entry	ArCHO	Product[a]	TBBDA		PBBS		Ref.
			time/min	Yield/(%)	time/min	Yield/(%)	
1	PhCHO		150	88	120	75	15
2	4-Cl-C_6H_4CHO		195	89	180	90	15
3	4-OMe-C_6H_4CHO		75	81	150	73	15
4	4-Me-C_6H_4CHO		50	72	200	79	17
5	4-NO_2-C_6H_4CHO		170(240)[b]	91(40)[b]	150	90	15
6	3-NO_2-C_6H_4CHO		180	97	240	83	15
7	4-Br-C_6H_4CHO		120	92	90	82	15
8	2,4-Cl_2-C_6H_4CHO		75	76	25	80	15
9	2,3-Cl_2-C_6H_4CHO		60	88	20	82	15
10	2,6-Cl_2-C_6H_4CHO		90	90	30	94	5
11	3,4,5-$(OMe)_3$-C_6H_4CHO		300	89	330	92	-

[a]Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods. [b]Without using the catalysts.

The advantages of PBBS and TBBDA are: (*i*) ease of preparation; (*ii*) reagent stability under atmospheric conditions for two months; (*iii*) possibility of re-use.

In conclusion, we have developed an efficient procedure for the synthesis of 4*H*-chromenes and dihydropyrano[3,2-*c*]chromenes derivatives in aqueous media using [TBBDA] and [PBBS]. This method offers several advantages such as inexpensive catalysts, easy synthetic procedure, high yields, simple work-up procedure and easy product isolation.

Experimental

All commercially available chemicals were obtained from Merck and Fluka, and used without further purifications unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol 90 MHz and a Bruker 300 MHz FT NMR spectrometers using TMS as internal standard and chemical shifts in δ (ppm). Infrared (IR) spectra were acquired on a Perkin Elmer GX FT-IR spectrometer. All yields refer to isolated products.

General procedure for the preparation of 4H-chromenes

A mixture of salicylaldehyde (5 mmol), malononitrile (1.2 mmol) and TBBDA (0.18 mmol) or PBBS (0.1 g) in H_2O (5 mL) and EtOH (5 mL) was stirred at room temperature for the appropriate time. After completion of the reaction, which was monitored by TLC, the solid product was collected by filtration, washed with water and aqueous ethanol and purified by recrystallization from ethanol.

General procedure for the preparation of 2-amino-5-oxo-dihydropyrano[3,2-c]chromenes

A mixture of aldehyde (10 mmol), malononitrile (1.2 mmol), 4-hydroxycoumarin (10 mmol) and TBBDA (0.18 mmol) or PBBS (0.1 g) in H_2O (5 mL) and EtOH (5 mL) was stirred under reflux for the appropriate time. After completion of the reaction, which was monitored by TLC, the mixture was monitored by TLC, the mixture was cooled to room temperature. The solid product was collected by filtration, washed with water and aqueous ethanol and purified by recrystallization from ethanol.

Recycling of the catalysts

The catalysts were recovered by evaporation of the solvent and washing of the solid with dichloromethane.

Supplementary Information

Supplementary characterization data and ^{1}H NMR spectra are available, free of charge at http://jbcs.sbq.org.br as a PDF file.

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Supplementary Information

One-Pot Synthesis of 4*H*-Chromene and Dihydropyrano[3,2-*c*]chromene Derivatives in Hydroalcoholic Media

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Analytical data for selected compounds

2-Amino-3-cyano-4-(1,1-dicyanomethyl)-4H-chromene (Table 1, entry 1)

mp 147-148 ºC; IR (KBr) ν_{max}/cm^{-1}: 3486, 3386, 3181, 2201, 1643, 1600, 1568, 1408, 1236, 754, ^{1}H NMR (DMSO, 90 MHz), δ 4.82 (d, 1H, *J* 3.5 Hz, CH), 4.95 (d, 1H, *J* 3.60 Hz, CH), 6.69 (s, 2H, NH_2), 7.38 (m, 4H, aromatic).

2-Amino-8-methoxy-3-cyano-4-(1,1-dicyanomethyl)-4H-chromene (Table 1, entry 2)

mp 188-189 ºC; IR (KBr) ν_{max}/cm^{-1}: 3464, 3356, 2910, 2192, 1642, 1613, 1552, 1488, 1420, 1218, 750, ^{1}H NMR (DMSO, 90 MHz), δ 3.83 (s, 3H, CH_3), 4.53 (d, 1H, *J* 3.8 Hz, CH), 5.01 (d, 1H, *J* 3.90 Hz, CH), 7.07 (m, 3H, aromatic), 7.52 (s, 2H, NH_2).

2-Amino-6-methoxy-3-cyano-4-(1,1-dicyanomethyl)-4H-chromene (Table 1, entry 3)

mp 184-185 ºC; IR (KBr) ν_{max}/cm^{-1}: 3402, 3342, 3218, 2185, 1659, 1587, 1426, 1217, 1037, 820, ^{1}H NMR (DMSO, 90 MHz), δ 3.73 (s, 3H, CH_3), 4.54 (s, 1H, CH), 5.09 (s, 1H, CH), 7.02 (s, 3H, aromatic), 7.41 (s, 2H, NH_2). ^{13}C NMR [DMSO-d_6, 300 MHz]: δ 164.1, 156.3, 144.0, 120.0, 119.1, 118.4, 117.7, 116.3, 113.6, 113.4, 113.4, 56.0, 48.79, 38.0. Anal. Calc. C, 63.15; H, 3.79; N, 21.04%. Found: C, 62.90; H, 3.51; N, 20.65%. *m/z* 266.

2-Amino-6-nitro-3-cyano-4-(1,1-dicyanomethyl)-4H-chromene (Table 1, entry 4)

mp 180-181 ºC; IR (KBr) ν_{max}/cm^{-1}: 3408, 3319, 3074, 2199, 1659, 1608, 1526, 1352, 1262, 748, ^{1}H NMR (DMSO, 90 MHz), δ 4.76 (d, 2H, *J* 3.7 Hz, CH), 5.18 (d, 2H, *J* 3.7 Hz, CH), 7.32-7.42 (m, 1H, aromatic), 7.77 (s, 2H, NH_2), 8.23-8.50 (m, 2H, aromatic).

2-Amino-6-bromo-3-cyano-4-(1,1-dicyanomethyl)-4H-chromene (Table 1, entry 5)

mp 163-164 ºC; IR (KBr) ν_{max}/cm^{-1}: 3471, 3349, 2885, 2189, 1635, 1597, 1596, 1426, 1228, 817, ^{1}H NMR (DMSO, 90 MHz), δ 4.76 (d, 2H, *J* 3.5 Hz, CH), 5.19 (d, 2H, *J* 3.5 Hz, CH), 7.72-7.96 (m, 5H, aromatic and NH_2).

2-Amino-6, 8-dibromo-3-cyano-4-(1,1-dicyanomethyl)-4H-chromene (Table 1, entry 6)

mp 182-183 ºC; IR (KBr) ν_{max}/cm^{-1}: 3414, 3332, 2885, 2197, 1655, 1600, 1562, 1457, 1433, 871, ^{1}H NMR (DMSO, 90 MHz), δ 4.76 (d, 2H, *J* 3.6 Hz, CH), 5.17 (d, 2H, *J* 3.6 Hz, CH), 7.74-7.96 (m, 4H, aromatic and NH_2).

2-Amino-6-chloro-3-cyano-4-(1,1-dicyanomethyl)-4H-chromene (Table 1, entry 7)

mp 151-154 ºC; IR (KBr) ν_{max}/cm^{-1}: 3445, 3337, 2862, 2194, 1644, 1600, 1572, 1457, 1483, 819, ^{1}H NMR (DMSO, 90 MHz), δ 4.62 (d, 1H, *J* 3.8 Hz, CH), 5.14 (d, 1H, *J* 3.8 Hz, CH), 7.10-7.57 (m, 5H, aromatic and NH_2), ^{13}C NMR [DMSO-d6, 300 MHz]: δ 163.7, 149.0, 130.5, 129.0, 128.9, 120.3, 119.6, 119.2, 118.8, 113.4, 113.2, 48.9, 37.3. Anal. Calc. C, 57.69; H, 2.61; N, 20.07%. Found: C, 57.53; H, 2.36; N, 19.94%. *m/z* 270.

2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 1)

mp 260-264 ºC; IR (KBr) ν_{max}/cm^{-1}: 3379, 3305, 2196, 1713, 1676, 1637, ^{1}H NMR (DMSO, 90 MHz), δ 4.45 (s, 1H, CH), 7.28-7.86 (m, 11H, aromatic and NH_2).

2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 2)

mp 265-267 ºC; IR (KBr) ν_{max}/cm^{-1}: 3380, 3291, 3189, 2191, 1713, 1676, ^{1}H NMR (DMSO, 90 MHz), δ 4.72 (s, 1H, CH), 7.40-8.13 (m, 10H, aromatic and NH_2).

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2-Amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 3)

mp 246-249 ºC; IR (KBr) ν_{max}/cm^{-1}: 3500, 3450, 3350, 2208, 1647,1174, ^{1}H NMR (DMSO, 90 MHz), δ 3.71 (s, 3H, CH_3), 4.39 (s, 1H, CH), 6.81-7.85 (m, 10H, aromatic and NH_2).

2-Amino-5-oxo-4-p-tolyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 4)

mp 252-254 ºC; IR (KBr) ν_{max}/cm^{-1}: 3388, 3311, 3189, 2194, 1713, 1676, 1637, ^{1}H NMR (DMSO, 90 MHz), δ 2.25 (s, 3H, CH_3), 4.40 (s, 1H, CH), 7.12-7.93 (m, 10H, aromatic and NH_2).

2-Amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 5)

mp 255-258 ºC; IR (KBr) ν_{max}/cm^{-1}: 3482, 3370, 3071, 2196, 1718, 1673, 1606, 1505,1373, 1348, 766. ^{1}H NMR (DMSO, 90 MHz), δ 4.66 (s, 1H, CH), 7.47-8.21 (m, 10H, aromatic and NH_2).

2-Amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 6)

mp 256-259 ºC; IR (KBr) ν_{max}/cm^{-1}: 3408, 3324, 3192, 2194, 1710, 1677, 1608, 1528,1380, 1347, 764. ^{1}H NMR (DMSO, 90 MHz), δ 4.72 (s, 1H, CH), 7.54-8.12 (m, 10H, aromatic and NH_2).

2-Amino-4-(4-bromophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 7)

mp 255-257 ºC; IR (KBr) ν_{max}/cm^{-1}: 3387, 3309, 3188, 2181, 1710, 1677, 1602, 1577,1062, 758. ^{1}H NMR (DMSO, 90 MHz), δ 4.46 (s, 1H, CH), 7.19-7.84 (m, 10H, aromatic and NH_2).

2-Amino-4-(2,4-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 8)

mp 255-258 ºC; IR (KBr) ν_{max}/cm^{-1}: 3459, 3290, 3163, 2199, 1716, 1673, 1630, 1589,1061, 761. ^{1}H NMR (DMSO, 90 MHz), δ 4.94 (s, 1H, CH), 7.34-7.92 (m, 9H, aromatic and NH_2).

2-Amino-4-(2,3-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 9)

mp 273-276 ºC; IR (KBr) ν_{max}/cm^{-1}: 3405, 3305, 3181, 2199, 1711, 1674, 1602, 1492,1062, 764. ^{1}H NMR (DMSO, 90 MHz), δ 5.07 (s, 1H, CH), 7.33-7.96 (m, 9H, aromatic and NH_2).

2-Amino-4-(2,6-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 10)

mp 274-277 ºC; IR (KBr) ν_{max}/cm^{-1}: 3419, 3277, 3173, 2200, 1707, 1673, 1633, 1599,1379, 758. ^{1}H NMR (DMSO, 90 MHz), δ 5.51 (s, 1H, CH), 7.35-7.92 (m, 9H, aromatic and NH_2).

2-Amino-5-oxo-4-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 2, entry 11)

mp 224-226 ºC; IR (KBr) ν_{max}/cm^{-1}: 3425, 3321, 2191, 1672, 1595, 1375, 1154, ^{1}H NMR (DMSO, 90 MHz), δ 3.63 (s, 3H, CH_3), 3.71 (s, 6H, CH_3), 4.43(s, 1H, H), 6.52 (s, 2H, NH_2), 7.36-7.93 (m, 6H, aromatic), ^{13}C NMR [DMSO-d6, 300 MHz]: δ 160.1, 158.5, 154.0, 153.3, 152.6, 139.4, 137.1, 133.3, 125.1, 123.0, 119.7, 117.0, 113.6, 105.4, 104.1, 60.4, 58., 56., 37.7. Anal. Calc. C, 65.02; H, 4.46; N, 6.89%. Found: C, 65.0; H, 4.27; N, 6.93%. *m/z* 404.

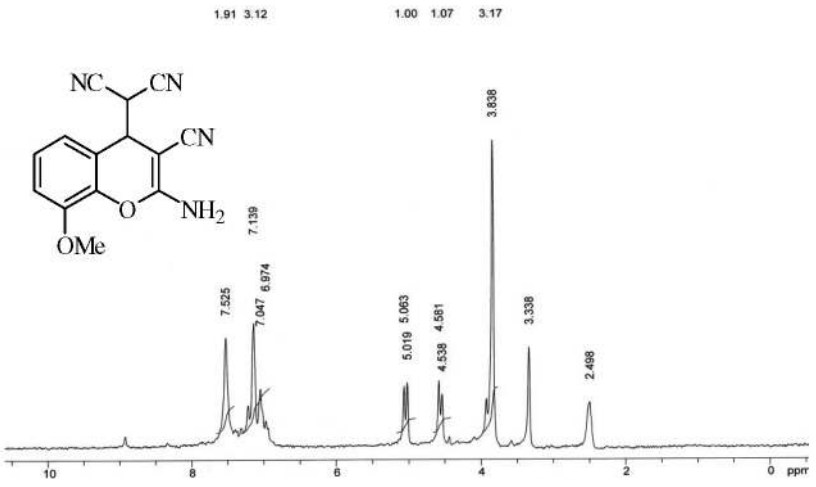

Figure S1. ^{1}H NMR (DMSO) 2-amino-8-methoxy-3-cyano-4-(1,1-dicyanomethyl)-4*H*-chromene (Table 1, entry 2).

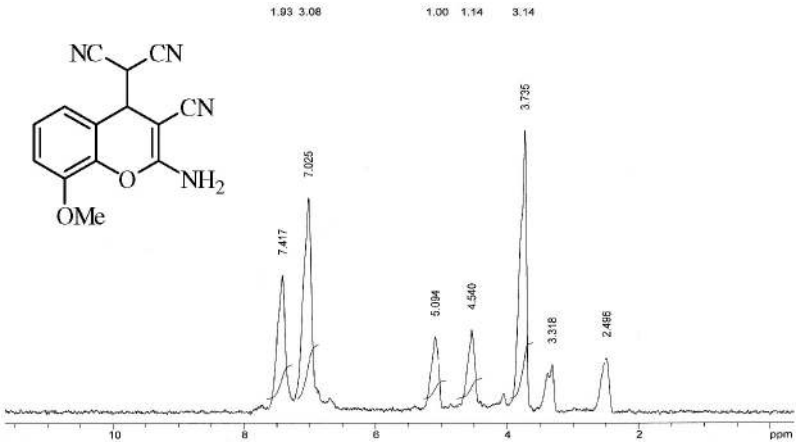

Figure S2. [1]H NMR (DMSO) 2-amino-6-methoxy-3-cyano-4-(1,1-dicyanomethyl)-4*H*-chromene (Table 1, entry 3).

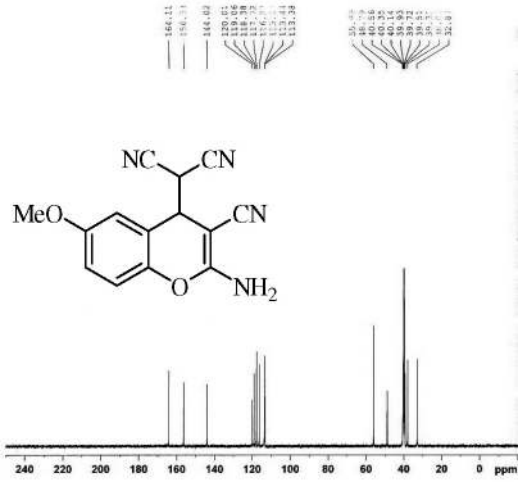

Figure S3. [13]C NMR (DMSO) 2-amino-6-methoxy-3-cyano-4-(1,1-dicyanomethyl)-4*H*-chromene (Table 1, entry 3).

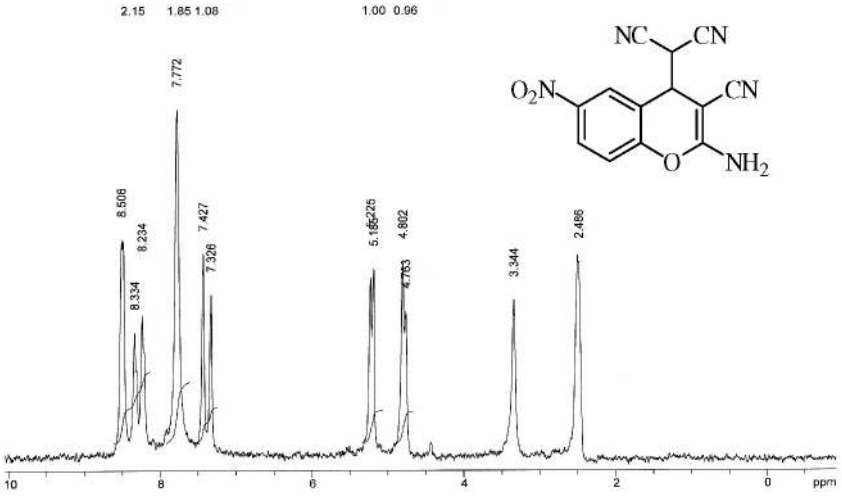

Figure S4. [1]H NMR (DMSO) 2-amino-6-nitro-3-cyano-4-(1,1-dicyanomethyl)-4*H*-chromene (Table 1, entry 4).

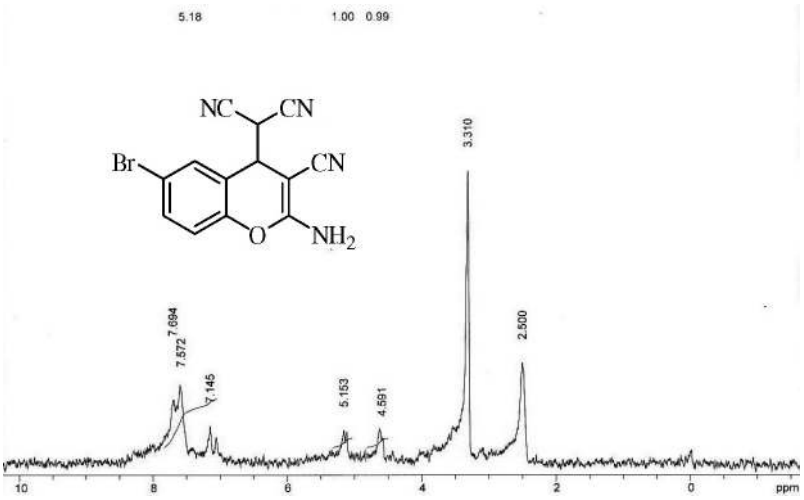

Figure S5. [1]H NMR (DMSO) 2-amino-6-bromo-3-cyano-4-(1,1-dicyanomethyl)-4*H*-chromene (Table 1, entry 5).

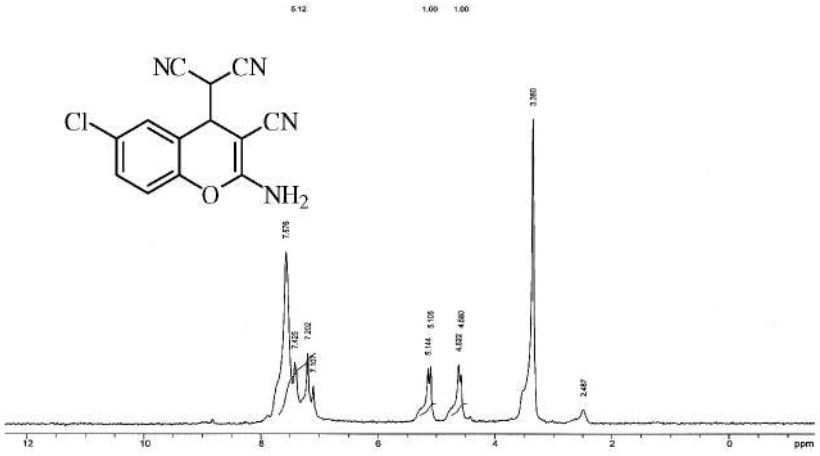

Figure S6. [1]H NMR (DMSO) 2-amino-6-chloro-3-cyano-4-(1,1-dicyanomethyl)-4*H*-chromene (Table 1, entry 7).

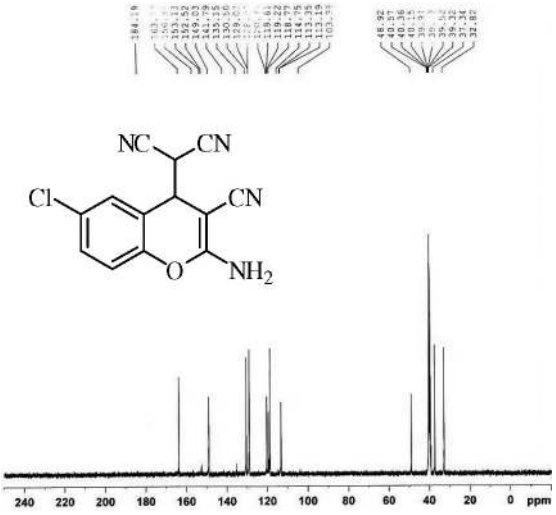

Figure S7. [13]C NMR (DMSO) 2-amino-6-chloro-3-cyano-4-(1,1-dicyanomethyl)-4*H*-chromene (Table 1, entry 7).

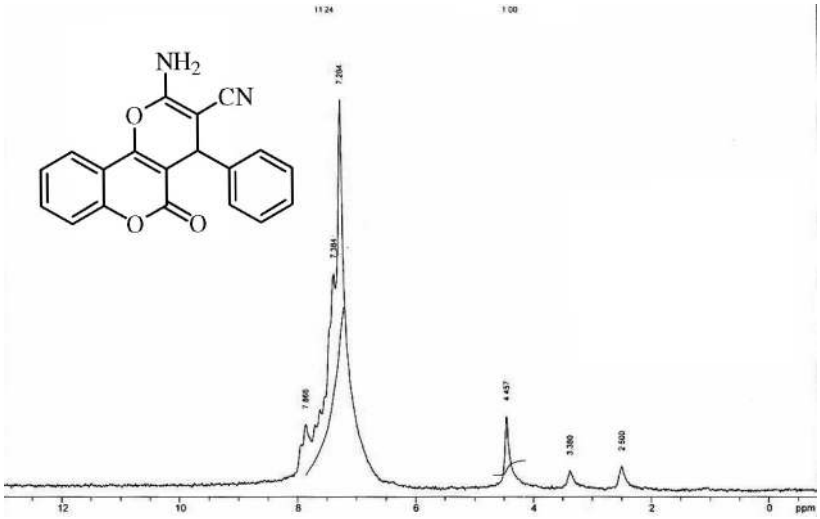

Figure S8. [1]H NMR (DMSO) 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 1).

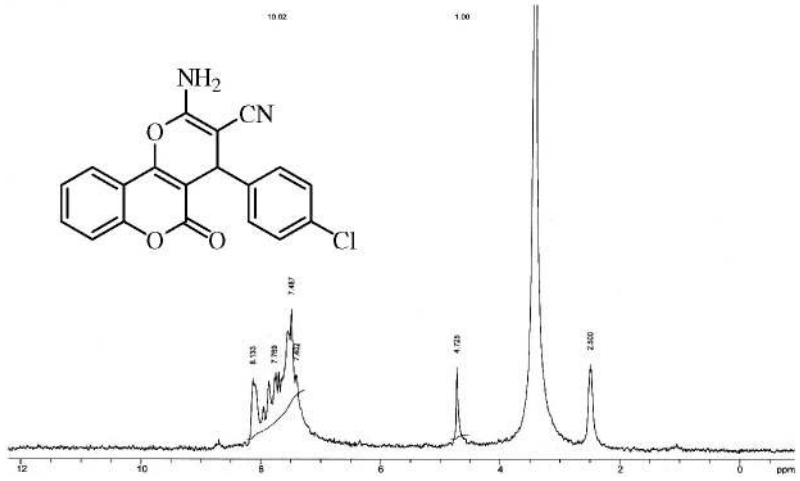

Figure S9. [1]H NMR (DMSO) 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 2).

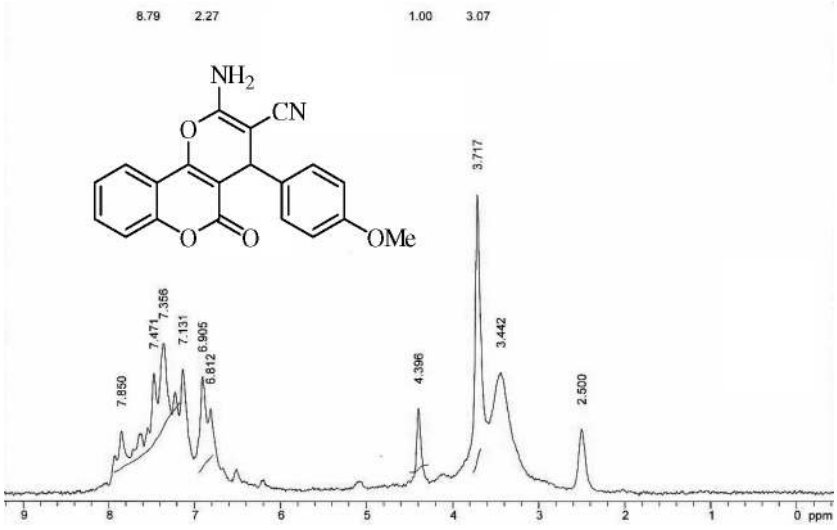

Figure S10. [1]H NMR (DMSO) 2-amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 3).

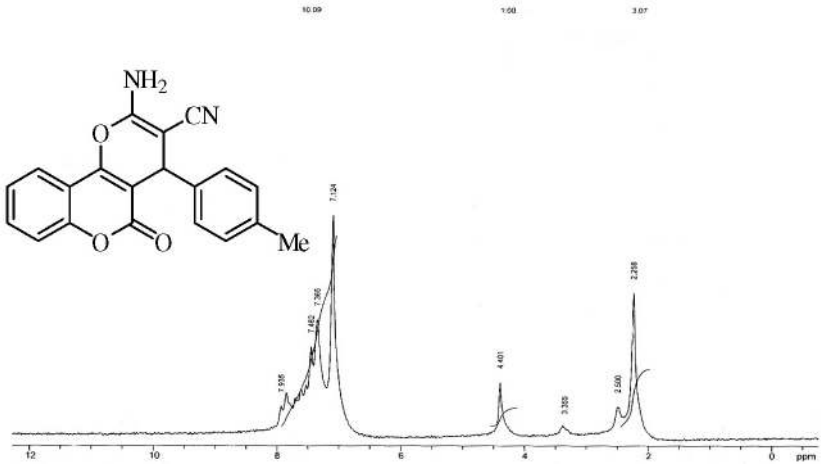

Figure S11. [1]H NMR (DMSO) 2-amino-5-oxo-4-p-tolyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 4).

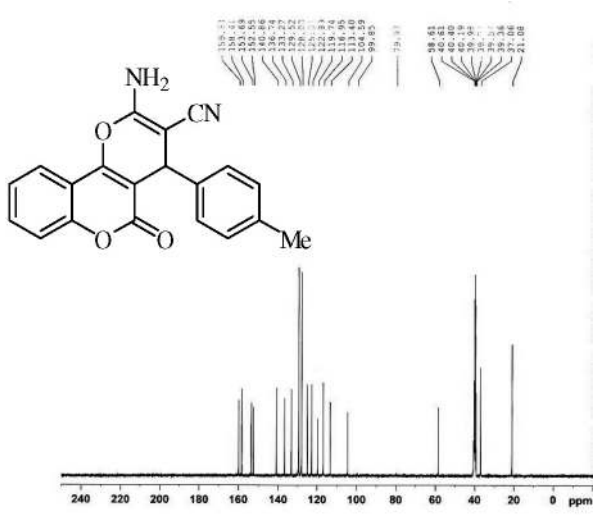

Figure S12. [13]C NMR (DMSO) 2-amino-5-oxo-4-p-tolyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 4).

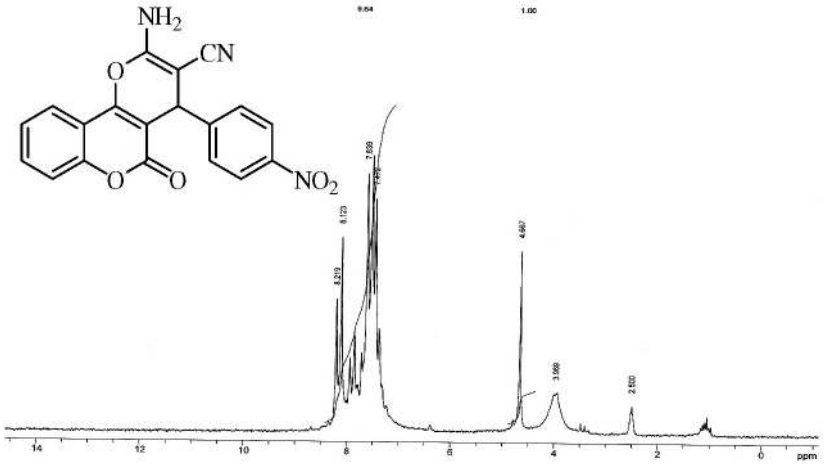

Figure S13. [1]H NMR (DMSO) 2-amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 5).

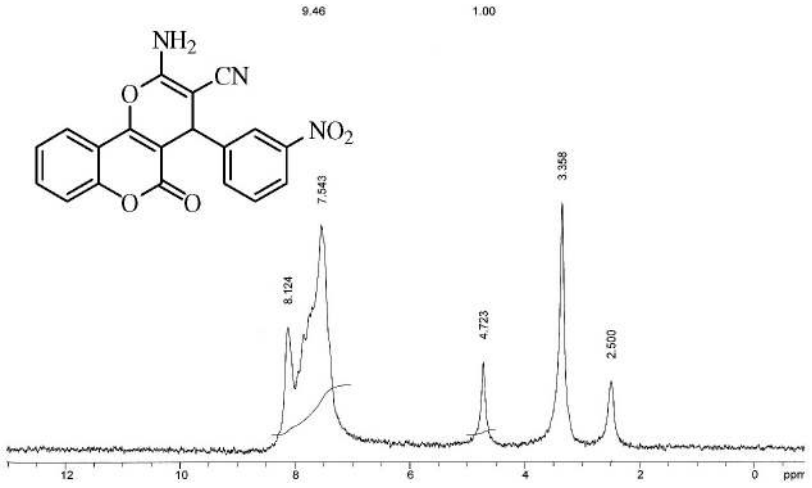

Figure S14. [1]H NMR (DMSO) 2-amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 6).

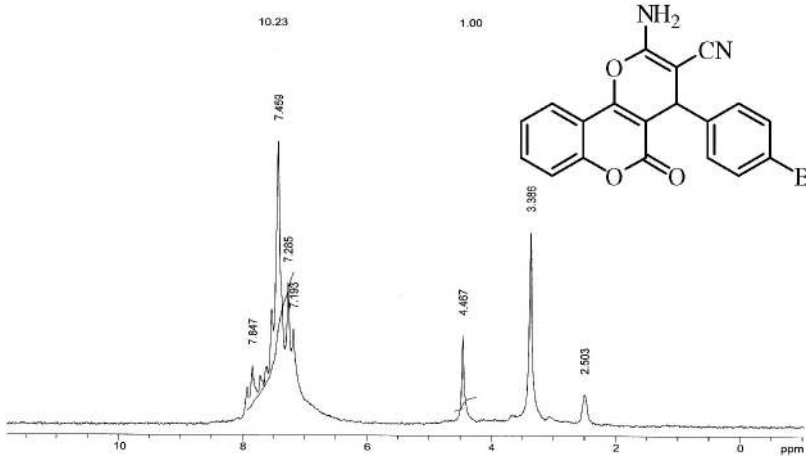

Figure S15. [1]H NMR (DMSO) 2-amino-4-(4-bromophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 7).

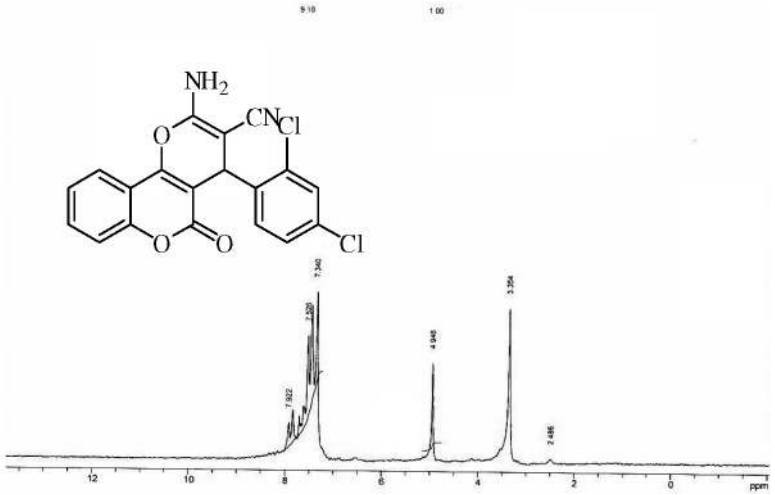

Figure S16. [1]H NMR (DMSO) 2-amino-4-(2,4-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 8).

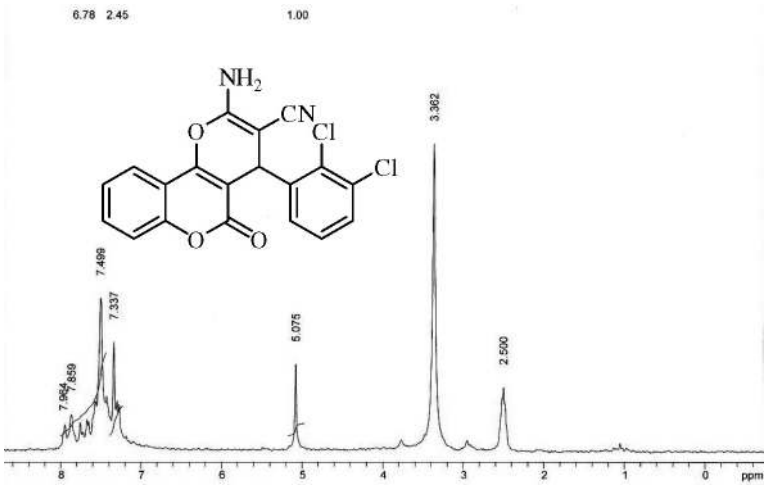

Figure S17. [1]H NMR (DMSO) 2-amino-4-(2,3-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 9).

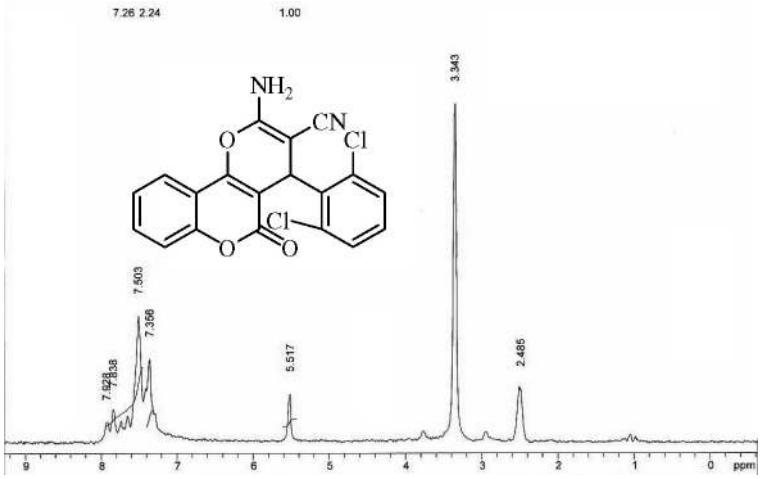

Figure S18. [1]H NMR (DMSO) 2-amino-4-(2,6-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 10).

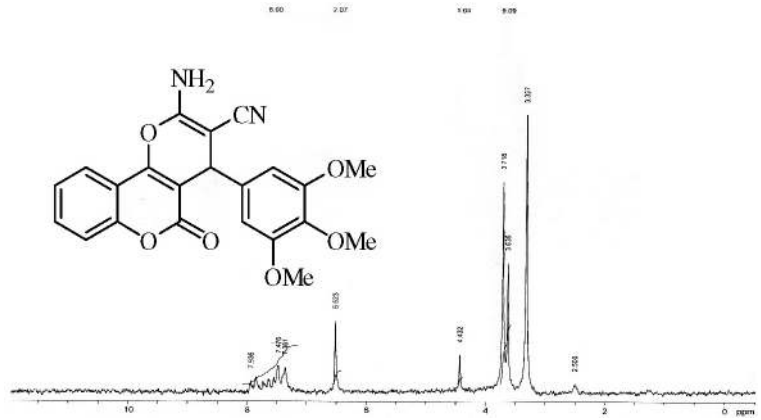

Figure S19. [1]H NMR (DMSO) 2-amino-5-oxo-4-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 11).

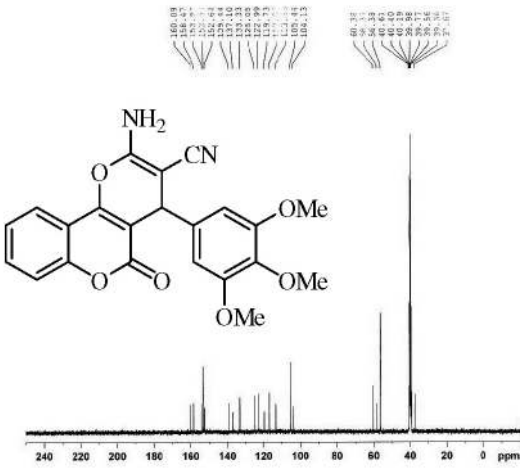

Figure S20. ^{13}C NMR (DMSO) 2-amino-5-oxo-4-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (Table 2, entry 11).