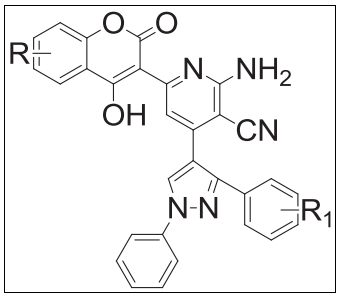
An Efficient Microwave-Assisted Synthesis and Antimicrobial Activity of Novel 2-Amino 3-Cyano Pyridine Derivatives using Two Reusable Solid Acids as Catalysts

Shailesh Thakrar, Abhay Bavishi, Ashish Radadiya, Hardevsinh Vala, Shrey Parekh, Dhairya Bhavsar, Ravi Chaniyara, and Anamik Shah*

Department of Chemistry, Saurashtra University, Rajkot 360005, India
*E-mail: anamik_shah@hotmail.com
Received September 9, 2011
DOI 10.1002/jhet.1641
Published online 00 Month 2013 in Wiley Online Library (wileyonlinelibrary.com).



Two solid acids, Fe^{3+} K-10 montmorillonite clay and HY-zeolite, have been employed efficiently for synthesis of 2-amino 3-cyano pyridines **4a–x** by multicomponent reaction of 3-acetyl 4-hydroxy coumarin **1a–c**, 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **2a–h**, malononitrile **3**, and ammonium acetate. Both the catalysts are recoverable and recyclable. The main significant of this procedure is short reaction time, high yields, easy workup procedure, and being environmentally friendly. The structures of all the compounds have been well characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. All the synthesized compounds were screened for their antimicrobial and antifungal activities.

J. Heterocyclic Chem., **00**, 00 (2013).

INTRODUCTION

Among a wide variety of heterocycles, cyanopyridines [1] and triazolopyridines [2] have played an important role in medicinal chemistry. They possess a broad spectrum of biological activity such as potential cardiovascular agents, antiviral [3,4], CNS depressant [5], bactericidal [6], ulcer inhibitors [7], and so on. Furthermore, researchers have also revealed that cyanopyridine derivatives constitute an important class of compounds possessing diverse type of biological properties such as antiparasitic [8], antiparkinsonian [9], anticonvulsant [10], and antihistaminic [11] as well as antihelmintic [12] properties. Many naturally occurring and synthetic compounds bearing pyridine scaffold possess interesting biological properties [13]. 2-Amino-3-cyanopyridine derivatives have been identified as IKK-β inhibitors [14,15]. Coumarin is a biologically active substance, with numerous metabolites, and is widespread in nature [16]. Coumarin derivatives constitute an important class of heterocyclic compounds that has attracted significant attention in recent years [17]. Moreover, the pyrazole framework containing compounds are known for its antibacterial, anti-HIV, anticancer, anti-inflammatory, analgesic, and hypoglycemic activities [18]. Pyrazoles are used as insecticides and pesticides because of their herbicidal and fungicidal activity [19]. Recently, pyrazoles containing aryl substituted emerged as p38 kinase inhibitors, antiparasitic activities [20]. Various routes for the synthesis of 2-amino-3-cyanopyridine derivatives have been reported using two-component as well as three-component reactions [21–25]. Feng Shi and coworkers [21] have reported a microwave-assisted facile synthesis of 2-amino 3-cyanopyridine derivatives in a one-pot reaction by using aromatic aldehyde, methyl ketone, malononitrile, and ammonium acetate. However, the protocols give comparatively lower yields and longer reaction time. Therefore, the synthesis of 2-amino 3-cyanopyridine derivatives continues to attract much interest in organic chemistry [26].

Different Lewis acids are used as catalyst for such reactions under microwave condition [27]. However, many of these Lewis acids are not easily available or expensive, nonreusable, and afford the unsatisfactory yields. Recently, we have reported the synthesis of various biologically active heterocycles by using various methods [28]. These finding prompted us to synthesize pyrazole and coumarin containing 2-amino 3-cyano pyridine derivatives for biological interest using cheap, reusable, and easily available catalyst.

RESULT AND DISCUSSION

Initially, 3-acetyl 4-hydroxy coumarin **1a–c** and pyrazole aldehydes **2a–h** were synthesized by reported methods [29,30]. To optimize the reaction condition for

Table 1

Yield optimization for **4a** and **4b**.

Entry	Condition	Fe^{+3} K-10[a] time (min)	HY-zeolite[b] time (min)	Yield[a] (%)	Yield[b] (%)
4a	100	16.0	17.0	71	65
4b	100	18.0	19.0	73	69
4a	200	9.0	12.0	82	79
4b	200	11.0	14.0	77	73
4a	400	4.0	6.0	94	92
4b	400	5.0	7.0	92	90

[a]Isolated yields in Fe+3 K-10 clay after purification
[b]Isolated yields in HY-zeolite after purification.
Reagents and conditions: 3-acetyl 4-hydroxy coumarin **1a** and **b** (0.01 mol), pyrazole aldehydes **2a** and **b** (0.01 mol), malononitrile **3** (0.01 mol), ammonium acetate (0.08 mol), HY-zeolite/Fe^{+3} montmorillonite k-10, MW 400 W.

Scheme 1

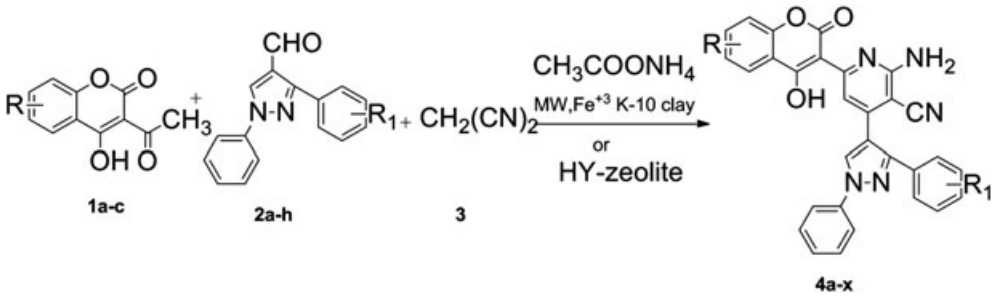


Table 2

Physical data.

Entry	Substitution R_1	Substitution R	Fe^{+3} K-10 time (min)	HY-zeolite[b] time (min)	Yield[a] (%)	Yield[b] (%)
4a	4-Cl	H	4.0	6.0	94	92
4b	4-CH_3	H	5.0	7.0	92	90
4c	H	H	5.0	6.0	91	88
4d	4-NO_2	H	4.0	8.0	89	86
4e	2-OH	H	5.0	6.0	90	82
4f	2-OCH_3	H	6.0	7.0	91	89
4g	3-NO_2	H	5.0	8.0	86	84
4h	4-F	H	6.0	7.0	87	78
4i	H	8-CH_3	5.0	8.0	88	79
4j	4-CH_3	8-CH_3	5.0	7.0	90	81
4k	4-Cl	8-CH_3	7.0	9.0	87	83
4l	4-NO_2	8-CH_3	6.0	8.0	91	87
4m	2-OH	8-CH_3	5.0	7.0	86	82
4n	2-OCH_3	8-CH_3	6.0	8.0	89	84
4o	3-NO_2	8-CH_3	5.0	9.0	89	79
4p	4-F	8-CH_3	5.0	7.0	88	91
4q	H	5,8-di CH_3	5.0	9.0	86	84
4r	4-CH_3	5,8-di CH_3	6.0	8.0	89	79
4s	4-Cl	5,8-di CH_3	4.0	7.0	86	81
4t	4-NO_2	5,8-di CH_3	4.0	6.0	89	80
4u	2-OH	5,8-di CH_3	6.0	8.0	87	82
4v	2-OCH_3	5,8-di CH_3	5.0	7.0	88	81
4w	3-NO_2	5,8-di CH_3	6.0	9.0	89	88
4x	4-F	5,8-di CH_3	5.0	9.0	94	92

[a]Isolated yields in Fe+3 K-10 clay after purification.
[b]Isolated yields in HY-zeolite after purification.
Reagents and conditions: 3-acetyl 4-hydroxy coumarin **1a-c** (0.01 mol), pyrazole aldehydes **2a–h** (0.01 mol), malononitrile **3** (0.01 mol), ammonium acetate (0.08 mol), HY-zeolite/Fe^{+3} montmorillonite k-10, MW 400 W.

Table 3

Antimicrobial and antifungal activities of compounds **4a–x**.

Compound	MIC value (μg/mL)			
	S. typhi MTCC-98	*V. cholera* TCC-3906	*S. pyogenus* MTCC-442	*C. albicans* MTCC-227
4a	**100**	**100**	250	1000
4b	250	250	1000	1000
4c	250	250	250	250
4d	**60.5**	200	250	1000
4e	200	200	500	**500**
4f	**100**	500	250	250
4g	**58.9**	250	250	**500**
4h	**69.4**	250	500	250
4i	500	250	500	**500**
4j	500	200	250	250
4k	250	**100**	**100**	250
4l	**62.7**	250	500	**500**
4m	250	250	250	250
4n	**61.5**	**100**	250	1000
4o	200	200	200	**100**
4p	200	250	500	**500**
4q	250	250	200	1000
4r	250	250	250	1000
4s	250	500	250	1000
4t	500	250	250	**500**
4u	500	200	500	**500**
4v	250	200	200	1000
4w	200	250	250	**500**
4x	500	200	500	**100**
Ampicillin	100	100	100	—
Chloramphenicol	50	50	50	—
Nystatin	—	—	—	100
Greseofulvin	—	—	—	500

4a and **4b**, we undertook a model reaction of **1a** and **b**, **2a** and **b**, ammonium acetate, and malononitrile 3 with Fe^{3+} K-10 montmorillonite clay as contrast to HY-zeolite by using different microwave irradiation powers. It was found that the reaction gives good yields in short reaction time at 400 wt. The results are shown in Table 1.

Further, the reaction of **1a–c**, malononitrile, **2a–h**, and ammonium acetate with Fe^{3+} K-10 montmorillonite clay/HY-zeolite under microwave irradiation gives title molecule **4a–x** (Scheme 1) in high yield (Table 2).

Antimicrobial and antifungal activities of compounds 4a–x. The newly synthesized 2-amino 3-cyano compounds **4a–x** have been screened for antimicrobial activity against *Staphylococcus Typhi*, *S. pyogenus* and *Vibrio cholera* and antifungal activity against *Candida albicans* by broth dilution method [31,32]. Ampicillin, chloramphenicol, nystatin, and greseofulvin were used as standards for comparison of antimicrobial and antifungal activities. The result shows that some of these compounds were active aligned with all the four organisms. The results of antimicrobial and antifungal activity are cited in Table 3.

Structure–activity relationship. A structure–activity relationship (SAR) study shows that 2-amino 3-cyano pyridines can be further modified to enhance the potency. Compounds **4c**, **4g**, **4h**, **4m**, **4k**, and **4o** can be optimized for the broad spectrum of antibacterial activity, whereas compounds **4a**, **4d**, **4f**, **4h**, **4l**, and **4n** can be optimized against *S. typhi*. Herein, electron-withdrawing group induces the potency (compounds **4a**, **4g**, **4h**, and **4l**), whereas hydrophobic group attached to coumarin ring lowers the potency. All compounds possess less potency against *C. albicans*, although compound **4o** can be further optimized for its potency. Furthermore, we will modify the compounds with bulkier electron-withdrawing group to increase the potency against broad-spectrum antibacterial species including *C. albicans*.

CONCLUSION

We have developed a new method for novel 2-amino 3-cyano derivatives that is rapid and high yielding. During the reaction procedure, it was observed that the time taken for reaction at higher temperature is less with high yield as compared with lower temperature. The antimicrobial and antifungal activities of these compounds were evaluated against various bacteria and fungi. Some of the compounds show good activity, and many of them showed moderate antimicrobial activity.

Structure–activity relationship studies give some insights for enhancing the potency of designed molecules. For detailed SAR, more diversity of the molecules will be generated by synthesizing diverse set of 2-amino 3-cyano pyridines. Thus, our current research is focused for development of diverse molecules. Herein, molecules **4a, 4g**, **4h**, and **4l** have the electron-withdrawing groups, so other electron-withdrawing groups such as $–CF_3$, –CN, and –COOH will be substituted at various positions to identifying the detailed SAR. Among the synthesized compounds, **4a, 4d, 4f, 4k, 4l, 4n**, and **4o** were found to be active against all microorganisms employed both for antimicrobial and antifungal activities. With this, we are now in a position to investigate the manifold biological activities of these molecules.

EXPERIMENTAL

All the melting points are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness, and spots were located by iodine and UV. All the reactions were carried out in Q-Pro-M microwave synthesizer. The IR spectra were recorded on a Shimadzu FTIR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/DMSO solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Elemental Vario EL III Carlo Erba 1108 model, and the results are in agreements with the structures assigned.

Synthesis of 2-amino 3-cyano pyridine derivatives (3a–c). A mixture of 3-acetyl 4-hydroxy coumarin **1a–c** (0.01 mol), pyrazole aldehydes **2a–h** (0.01 mol), malononitrile (0.01 mol), and ammonium acetate (0.08 mol) HY-zeolite/Fe^{+3} montmorillonite k-10 were taken in 100-mL microwave flask. The reaction mixture was irradiated under microwave irradiation by using Q-Pro-M microwave synthesizer for the desired time at 400 W. The progress and the completion of the reaction were checked at interval of every 1 min by using silica gel-G F_{254} thin layer chromatographic plates using hexane:ethyl acetate (2:3) as a mobile phase. The reaction mixture was allowed to cool at room temperature and resulting product extracted into $CHCl_3$. The solid HY-zeolite/Fe^{+3} montmorillonite k-10 were filtered off and the solvent removed by rotary evaporator. The solid clay portion was washed with methanol and dried at 110°C for 4–5 h to be reused in the next reaction. It can be used for more than three times.

2-Amino-4-(3-(4-chlorophneyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)nicotinonitrile (4a). IR (cm^{-1}): 3645, 3562, 3475, 3400, 3317, 3082, 3014, 2974, 2901, 2829, 2424, 2322, 1768, 1560, 1429, 1381, 1253, 1159, 762, 715. ^{1}H NMR (DMSO-d_6) δ ppm: 7.21–7.23 (d, 1H), 7.26–7.30 (t, 1H), 7.34–7.36 (d, 2H, J = 8.0 Hz), 7.38–7.40 (d, 1H), 7.51 (d, 1H), 7.55–7.60 (t, 4H), 7.85–7.87 (d, 2H, J = 8.0 Hz), 7.96 (s, 2H), 8.03–8.05 (d, 1H), 8.27 (s, 1H), 8.50 (s, 1H), 18.35 (s, 1H). ^{13}C NMR: 38.96, 39.19, 39.39, 39.60, 39.81, 40.05, 40.25, 78.15, 78.33, 79.83, 88.69, 97.20, 102.65, 105.99, 113.04, 117.05, 119.95, 124.09, 125.07, 127.73, 129.45, 129.73, 131.75, 132.96, 134.51, 135.57, 142.82, 145.22, 153.65, 155.86, 159.65, 161.52, 166.23. MS: m/z = 531 (M^{+2}); 533 (M + 2); *Anal*. Calcd for $C_{30}H_{18}ClN_5O_3$: C, 67.74; H, 3.41; N, 13.17; O, 9.02; found: C, 77.46; H, 3.36; N, 13.08; O, 9.09 (%).

2-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)nicotinonitrile (4b). IR (cm^{-1}): 3626, 3568, 3421, 3392, 3275, 3189, 3086, 2908, 2891, 2424, 2333, 1782, 1668, 1618, 1554, 1379, 1165, 790, 717. ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H), 7.16–7.18 (d, 2H), 7.20 (d, 1H), 7.25–7.27 (t, 1H), 7.34–7.38 (t, 1H), 7.44–7.46 (d, 2H), 7.50–7.52 (d, 2H, J = 8.0 Hz), 7.59–7.77 (t, 1H), 7.86–7.88 (d, 2H, J = 8.0 Hz), 7.92 (s, 2H), 7.92 (s, 2H), 8.02–8.05 (d, 2H), 8.25 (s, 1H), 8.30 (s, 1H), 8.50 (s, 1H), 18.30 (s, 1H). ^{13}C NMR: 18.58, 32.18, 36.97, 38.18, 39.19, 39.80, 39.88, 40.11, 40.42, 88.18, 97.39, 101.14, 103.55, 113.45, 116.09, 117.07, 119.83, 120.45, 125.73, 126.85, 127.46, 128.91, 130.67, 131.72, 143.32, 144.55, 145.76, 152.68 159.23, 161.25, 166.29. MS: m/z = 511.16; *Anal*. Calcd for $C_{31}H_{21}N_5O_3$: C, 72.79; H, 4.14; N, 13.69; O, 9.38; found: C, 72.81; H, 4.10; N, 13.48; O, 9.21 (%).

2-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)nicotinonitrile (4c). IR (cm^{-1}): 3635, 3542, 3465, 3401, 3032, 3024, 2984, 2823, 2332, 1778, 1570, 1428, 1382, 1263, 1158, 793, 716. ^{1}H NMR (DMSO-d_6) δ ppm: 7.18–7.20 (d, 1H), 7.25–7.28 (t, 1H), 7.36–7.38 (t, 4H), 7.51–7.57 (m, 5H), 7.87–7.89 (d, 2H), 8.02–8.04 (d, 3H), 8.24 (s, 1H), 8.55 (s, 1H), 18.32 (s, 1H). ^{13}C NMR: 32.18, 36.97, 38.18, 38.39, 40.60, 40.81, 98.18, 101.13, 103.45, 113.14, 116.25, 119.55, 120.19, 123.07, 125.63, 127.55, 126.73, 127.75, 129.06, 129.61, 130.67, 131.22, 133.23, 144.05, 146.76, 158.65, 159.51, 161.65. MS: m/z = 497.50; *Anal*. Calcd for $C_{30}H_{19}N_5O_3$: C, 72.43; H, 3.85; N, 14.08; O, 9.65; found: C, 72.34; H, 3.75; N, 14.00; O, 9.59 (%).

2-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-yl)nicotinonitrile (4d). IR (cm^{-1}): 3552, 3450, 3417, 3062, 3034, 2984, 2901, 2839, 2332, 1767, 1562, 1560, 1439, 1382, 1263, 1160, 794, 717. ^{1}H NMR (DMSO-d_6) δ ppm: 7.23–7.26 (d, 1H), 7.25–7.31 (t, 1H), 7.35–7.37 (d, 2H, J = 8.0 Hz), 7.39–7.42 (d, 1H), 7.52 (d, 1H), 7.57–7.65 (t, 4H), 7.77–7.89 (d, 2H, J = 8.0 Hz), 7.98 (s, 2H), 8.08–8.010 (d, 1H), 8.29 (s, 2H), 8.51 (s, 1H), 18.25 (s, 1H). ^{13}C NMR: 30.48, 32.87, 38.08, 39.39, 39.62, 40.31, 79.38, 97.68, 101.29, 103.25, 119.14, 119.95, 123.19, 125.87, 126.83, 129.55, 12.93, 131.67, 138.22, 143.02, 145.55, 146.76, 152.23, 159.85, 161.75, 155.65. MS: m/z = 542.50; *Anal*. Calcd for $C_{30}H_{18}N_6O_5$: C, 66.42; H, 3.34; N, 15.49; O,14.75; found: C, 66.40; H, 3.29; N, 15.33; O, 14.73 (%).

2-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4e). IR (cm^{-1}): 3602, 3451, 3427, 3032, 3014, 2974, 2961, 2838, 2342, 1769, 1572, 1438, 1381, 1262, 1161, 795, 716. ^{1}H NMR (DMSO-d_6) δ ppm: 6.84–6.87 (t, 2H), 7.19–7.21 (t, 2H), 7.27 (t, 1H), 7.37–7.41 (q, 2H), 7.52–7.58 (m, 3H), 7.79–7.91 (d, 2H, J = 8.0 Hz), 8.00–8.02 (s, 2H), 8.15 (s, 1H), 8.23 (s, 2H), 8.77 (s, 1H), 18.12 (s, 1H). ^{13}C NMR: 30.28, 36.87, 38.08, 39.49, 39.80, 88.19, 101.27, 103.85, 104.97, 113.14, 116.15, 118.65, 120.09, 121.17, 123.74, 126.85, 128.63, 130.85, 131.82, 141.45, 143.76, 152.82, 155.22, 160.45, 161.52. MS: m/z = 513.14; *Anal*. Calcd for $C_{30}H_{19}N_5O_4$: C, 70.17; H, 3.73; N, 13.64; O, 12.46; found: C, 70.13; H, 3.69; N, 13.53; O, 12.43 (%).

2-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4f). IR (cm^{-1}): 3562, 3456, 3427, 3072, 3024, 2983, 2911, 2849, 2342, 1768, 1552, 1449, 1372, 1262, 1161, 792, 715. ^{1}H NMR (DMSO-d_6) δ ppm: 2.39 (s, 3H), 7.29–7.33 (d, 2H), 7.38–7.41 (d, 1H), 7.47 (t, 1H), 7.52 (d, 1H), 7.59–7.65 (t, 4H), 7.78–7.81

(d, 2H), 8.03–8.07 (t, 1H), 8.12 (s, 1H), 8.19 (s, 2H), 8.29 (s, 1H), 8.40 (s, 1H), 18.13 (s, 1H). ^{13}C NMR: 31.19, 38.87, 39.08, 39.29, 39.62, 39.91, 56.22, 81.18, 82.79, 99.86, 101.23, 103.75, 111.25, 113.42, 115.74, 117.19, 118.54, 121.45, 124.09, 125.17, 129.83, 130.45, 130.67, 139.02, 143.15, 151.86, 152.65, 154.75, 160.74. MS: *m/z* = 527.50; *Anal*. Calcd for $C_{31}H_{21}N_5O_4$: C, 70.58; H, 4.01; N, 13.28; O, 12.13; found: C, 70.51; H, 3.99; N, 13.15; O, 12.06 (%).

2-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4g). IR (cm^{-1}): 3552, 3450, 3417, 3062, 3034, 2984, 2901, 2839, 2332, 1767, 1562, 1565, 1439, 1382, 1263, 1154, 794, 717 702. ^{1}H NMR (DMSO-d_6) δ ppm: 7.28–7.31 (d, 2H), 7.37–7.40 (d, 1H), 7.45 (t, 1H), 7.51 (d, 1H), 7.58–7.65 (t, 4H), 7.77–7.81 (d, 2H), 8.02–8.05 (t, 1H), 8.10 (s, 1H), 8.18 (s, 2H), 8.28 (s, 1H), 8.39 (s, 1H), 18.12 (s, 1H). ^{13}C NMR: 31.08, 37.97, 38.18, 39.19, 39.68, 39.71, 40.11, 40.20, 79.83, 81.69, 88.91, 97.12, 101.55, 103.61, 113.13, 115.17, 119.43, 121.23, 123.34, 126.09, 127.07, 128.45, 130.57, 132.92, 141.32, 143.71, 143.67, 145.86, 155.65, 159.08, 161.56. MS: *m/z* = 542.0; *Anal*. Calcd for $C_{30}H_{18}N_6O_5$: C, 66.42; H, 3.34; N, 15.49; O, 14.75; found: C, 66.34; H, 3.16; N, 15.31; O, 14.62 (%).

2-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)nicotinonitrile (4h). IR (cm^{-1}): 3602, 3430, 3407, 3061, 3024, 2994, 2911, 2849, 2339, 1777, 1560, 1449, 1389, 1253, 1169, 790, 710. ^{1}H NMR (DMSO-d_6) δ ppm: 7.24–7.27 (d, 1H), 7.26–7.31 (t, 1H), 7.44–7.46 (d, 2H, *J* = 8.0 Hz), 7.48–7.50 (d, 1H), 7.55 (d, 1H), 7.57–7.61 (t, 4H), 7.86–7.88 (d, 2H, *J* = 8.0 Hz), 7.98 (s, 2H), 8.13–8.15 (d, 1H), 8.37 (s, 1H), 8.52 (s, 1H), 18.25 (s, 1H). ^{13}C NMR: 32.19, 39.87, 39.98, 40.01, 40.11, 83.79, 99.90, 101.78, 103.76, 113.52, 115.21, 117.56, 120.04, 123.43, 124.89, 126.07, 127.73, 128.59, 131.57, 141.32, 143.65, 145.86, 155.65, 159.81, 161.76. MS: *m/z* = 515 (M$^+$), 517 (M + 2); *Anal*. Calcd for $C_{30}H_{18}FN_5O_3$: C, 69.90; H, 3.52; N, 13.54; O, 9.31; found: C, 69.80; H, 3.41; N, 13.33; O, 9.25 (%).

2-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)nicotinonitrile (4i). IR (cm^{-1}): 3562, 3421, 3402, 3042, 3014, 2984, 2819, 2232, 1760, 1572, 1429, 1372, 1269, 1161, 792, 707. ^{1}H NMR (DMSO-d_6) δ ppm: 2.39 (s, 3H), 7.22–7.25 (d, 1H), 7.29–7.33 (t, 1H), 7.37–7.41 (t, 4H), 7.47–7.55 (m, 5H), 7.59–7.64 (d, 2H), 8.29 (s, 1H), 8.45 (s, 2H), 8.55 (s, 1H), 17.25 (s, 1H). ^{13}C NMR: 17.68, 20.98, 38.97, 39.18, 39.38, 39.59, 39.80, 40.01, 40.22, 78.10, 78.43, 78.75, 99.49, 112.52, 118.09, 124.27, 125.43, 126.71, 127.14, 128.42, 127.67, 127.93, 127.97, 128.55, 128.96, 132.62, 139.49, 141.84, 150.63. MS: *m/z* = 511.53; *Anal*. Calcd for $C_{31}H_{21}N_5O_3$: C, 72.79; H, 4.14; N, 13.69; O, 9.38; found: C, 72.83; H, 4.11; N,13.59; O, 9.39 (%).

2-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)nicotinonitrile (4j). IR (cm^{-1}): 3602, 3431, 3407, 3012, 2981, 2829, 2331, 1768, 1572, 1419, 1381, 1261, 1161, 764, 727. ^{1}H NMR (DMSO-d_6) δ ppm: 2.34 (s, 6H), 7.17–7.20 (m, 3H), 7.35–7.39 (t, 1H), 7.44–7.46 (d, 2H, *J* = 8.0 Hz), 7.52–7.56 (t, 2H), 7.84–7.85 (d, 1H), 7.96–7.98 (d, 2H, *J* = 8.0 Hz), 8.17–8.19 (d, 2H, *J* = 8.0 Hz), 8.37 (s, 2H), 8.88 (s, 1H), 17.72 (s, 1H). ^{13}C NMR: 15.12, 20.92, 38.92, 39.13, 39.34, 39.55, 39.76, 39.97, 40.18, 78.40, 78.73, 79.06, 91.45, 117.43, 118.51, 119.05, 124.88, 127.30, 129.04, 129.40, 137.58, 138.93, 150.04, 151.16, 153.32. MS: *m/z* = 525 (M$^+$); *Anal*. Calcd for $C_{32}H_{23}N_5O_3$: C, 73.13; H, 4.41; N, 13.33; O, 9.13; found: C, 73.03; H, 4.31; N, 13.17; O, 9.10 (%).

2-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-'(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)nicotinonitrile (4k). IR (cm^{-1}): 35562, 3420, 3069, 2991, 2849, 2342, 1777, 1582, 1429, 1372, 1273, 1140, 758, 719. ^{1}H NMR (DMSO-d_6) δ ppm: 2.47 (s, 3H), 7.20–7.23 (d, 1H), 7.25–7.30 (t, 1H), 7.34–7.36 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 1H), 7.59–7.66 (t, 4H), 7.80–7.82 (d, 2H, *J* = 8.0 Hz), 7.99 (s, 2H), 8.14–8.17 (d, 1H), 8.39 (s, 1H), 8.48 (s, 1H), 18.25 (s, 1H). ^{13}C NMR: 17.98, 31.78, 38.87, 39.08, 39.39, 39.61, 39.71, 88.18, 99.01, 101.89, 104.54, 113.15, 117.04, 120.48, 125.19, 126.17, 127.83, 128.55, 129.71, 131.51, 132.92, 141.32, 143.05, 145.76, 147.65, 151.56, 155.65, 161.75. MS: *m/z* = 545 (M$^+$), 547 (M + 2); *Anal*. Calcd for $C_{31}H_{20}ClN_5O_3$: C, 68.20; H, 3.69; N, 12.83; O, 8.79; found: C, 68.23; H, 3.51; N, 12.71; O, 8.89 (%).

2-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-'(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4l). IR (cm^{-1}): 3550, 3470, 3407, 3092, 2974, 2921, 2859, 2322, 1787, 1563, 1571, 1432, 1381, 1262, 1168, 751, 711. ^{1}H NMR (DMSO-d_6) δ ppm: 2.57 (s, 3H), 7.20–7.23 (d, 1H), 7.25–7.29 (t, 1H), 7.32–7.34 (d, 2H, *J* = 8.0 Hz), 7.52 (d, 1H), 7.55–7.61 (t, 4H), 7.70–7.72 (d, 2H, *J* = 8.0 Hz), 7.89 (s, 2H), 8.16–8.19 (d, 1H), 8.38 (s, 1H), 8.49 (s, 1H), 18.35 (s, 1H). ^{13}C NMR: 18.58, 30.19, 37.87, 38.08, 38.49, 39.61, 39.91, 83.79, 101.34, 103.90, 103.34, 113.19, 115.17, 118.14, 119.15, 124.19, 126.17, 127.73, 128.85, 131.58, 132.83, 140.21, 143.75, 146.86, 151.81, 153.65, 155.65, 161.76. MS: *m/z* = 556.15; *Anal*. Calcd for $C_{31}H_{20}N_6O_5$: C, 66.90; H, 3.62; N, 15.10; O, 14.37; found: C, 66.83; H, 3.61; N, 15.07; O, 14.49 (%).

2-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4m). IR (cm^{-1}): 3552, 3452, 3407, 3063, 3014, 2983, 2911, 2890, 2330, 1787, 1561, 1429, 1382, 1253, 1161, 761, 717. ^{1}H NMR (DMSO-d_6) δ ppm: 2.89 (s, 3H), 4.98 (s, 1H), 6.84–6.87 (d, 1H), 6.91–6.94 (s, 1H), 7.19–7.25 (t, 1H), 7.28 (t, 1H), 7.37–7.41 (t, 4H), 7.55–7.58 (t, 1H), 7.79–7.81 (d, 2H, *J* = 8.0 Hz), 8.03 (s, 1H), 8.14 (s, 1H), 8.24 (s, 2H), 8.78 (s, 1H), 18.12 (s, 1H). ^{13}C NMR: 17.98, 31.28, 37.97, 39.28, 39.19, 39.61, 39.91, 84.69, 99.89, 101.23, 103.34, 113.24, 118.14, 119.15, 119.49, 124.09, 126.17, 128.73, 129.45, 131.67, 132.92, 143.28, 145.75, 150.86, 152.34, 155.75, 159.09, 161.78, 166.87. MS: m/z = 527.16; *Anal*. Calcd for $C_{31}H_{21}N_5O_4$: C, 70.58; H, 4.01; N, 13.28; O, 12.13; found: C, 70.53; H, 4.01; N, 13.17; O, 12.11 (%).

2-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4n). IR (cm^{-1}): 3651, 3420, 3407, 3052, 3014, 2994, 2921, 2829, 2341, 1787, 1562, 1433, 1372, 1262, 1161, 764, 714. ^{1}H NMR (DMSO-d_6) δ ppm: 2.49 (s, 3H), 3.12 (s, 3H), 7.28–7.33 (d, 2H), 7.37–7.41 (d, 1H), 7.48 (t, 1H), 7.53 (d, 1H), 7.58–7.66 (t, 4H), 7.79–7.82 (d, 2H), 8.04–8.07 (t, 1H), 8.18 (s, 2H), 8.28 (s, 1H), 8.41 (s, 1H), 18.23 (s, 1H). ^{13}C NMR: 16.58, 30.88, 36.97, 39.18, 39.40, 56.72, 57.67, 88.08, 99.08, 101.25, 104.67, 111.90, 113.76, 118.14, 119.15, 119.49, 125.19, 126.09, 131.57, 132.92, 140.22, 141.65, 145.86, 155.65, 159.90, 164.67. MS: *m/z* = 541.56; *Anal*. Calcd for $C_{32}H_{23}N_5O_4$: C, 70.97; H, 4.28; N, 12.93; O, 11.82; found: C, 70.83; H, 4.21; N, 12.87; O, 11.75 (%).

2-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4o). IR (cm^{-1}): 3602, 3490, 3457, 3012, 3031, 2994, 2981, 2829, 2382, 1777, 1563, 1429, 1381, 1253, 1161, 755, 702. ^{1}H NMR (DMSO-d_6) δ ppm: 2.89(s, 3H), 7.26–7.30 (d, 1H), 7.37–7.40 (d, 2H), 7.43 (t, 1H), 7.53 (d, 1H), 7.59–7.66 (t, 4H), 7.78–7.81 (d, 2H), 8.09 (s, 1H), 8.17 (s, 2H), 8.29 (s, 1H), 8.37 (s, 1H),

18.22 (s, 1H). ^{13}C NMR: 16.98, 30.17, 37.87, 38.19, 39.49, 39.61, 39.71, 88.19, 97.81, 101.97, 102.79, 106.07, 113.14, 117.87, 119.21, 122.76, 123.45, 125.19, 127.07, 127.83, 129.45, 129.91, 131.50, 132.92, 133.49, 143.75, 145.36, 152.79, 155.35, 161.45. MS: *m/z* = 556.53; *Anal*. Calcd for $C_{31}H_{20}N_6O_5$: C, 66.90; H, 3.62; N, 15.10; O, 14.37; found: C, 66.91; H, 3.51; N, 15.07; O, 14.39 (%).

2-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)nicotinonitrile (4p). IR (cm^{-1}): 3552, 3450, 3417, 3062, 3034, 2984, 2901, 2839, 2332, 1767, 1562, 1439, 1382, 1263, 1160, 754, 717. ^{1}H NMR (DMSO-d_6) δ ppm: 2.48 (s, 3H), 7.21–7.24 (d, 1H), 7.29–7.32 (t, 1H), 7.34–7.36 (d, 2H, *J* = 8.0 Hz), 7.53 (d, 1H), 7.57–7.64 (t, 4H), 7.72–7.74 (d, 2H, *J* = 8.0 Hz), 7.88 (s, 2H), 8.18–8.21 (d, 1H), 8.39 (s, 1H), 8.50 (s, 1H), 18.45 (s, 1H). ^{13}C NMR: 15.11, 30.78, 35.88, 38.96, 39.17, 39.38, 39.59, 39.79, 40.00, 40.21, 78.07, 78.40, 78.73, 85.53, 91.43, 109.34, 115.01, 116.02, 117.94, 118.53, 118.78, 118.98, 122.63, 124.79, 126.72, 128.32, 129.32, 129.66, 134.11, 138.73, 149.02, 150.51, 151.12, 153.10, 153.23, 154.80, 160.69, 161.93, 178.01. MS: *m/z* = 529 (M$^+$), 531 (M + 2); *Anal*. Calcd for $C_{31}H_{20}FN_5O_3$: C, 70.31; H, 3.81; N, 13.23; O, 9.06; found: C, 70.21; H, 3.71; N, 13.21; O, 9.01 (%).

2-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)nicotinonitrile (4q). IR (cm^{-1}): 3642, 3451, 3427, 3069, 3014, 2994, 2831, 2334, 1787, 1564, 1439, 1382, 1269, 1159, 759, 711. ^{1}H NMR (DMSO-d_6) δ ppm: 2.48 (s, 3H), 3.02 (s, 3H), 7.36–7.38 (d, 2H, *J* = 8.0 Hz), 7.36–7.41 (t, 4H), 7.53 (d, 1H), 7.55–7.61 (t, 4H), 7.77–7.79 (d, 2H, *J* = 8.0 Hz), 8.13–8.15 (d, 1H), 8.55 (s, 1H), 8.36 (s, 1H), 18.41 (s, 1H). ^{13}C NMR: 27.90, 33.99, 38.96, 39.17, 39.38, 39.59, 39.80, 40.01, 40.22, 78.01, 78.34, 78.67, 112.51, 118.10, 118.80, 124.24, 125.43, 125.71, 126.93, 127.08, 127.42, 127.67, 127.93, 127.97, 128.54, 128.94, 132.61, 137.77, 139.49, 141.83, 145.52, 150.67. MS: *m/z* = 525.56; *Anal*. Calcd for $C_{32}H_{23}N_5O_3$: C, 73.13; H, 4.41; N, 13.33; O, 9.13; found: C, 73.05; H, 4.31; N, 13.27; O, 9.08 (%).

2-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)nicotinonitrile (4r). IR (cm^{-1}): 3602, 3460, 3417, 3068, 3024, 2989, 2911, 2829, 2342, 1747, 1532, 1439, 1382, 1268, 1169, 748, 719. ^{1}H NMR (DMSO-d_6) δ ppm: 2.79 (s, 3H), 3.04 (s, 3H), 3.14 (s, 3H), 7.22–7.26 (d, 1H), 7.26–7.32 (t, 1H), 7.36–7.38 (d, 2H, *J* = 8.0 Hz), 7.52 (d, 1H), 7.56–7.60 (t, 4H), 7.83–7.85 (d, 2H, *J* = 8.0 Hz), 8.28 (s, 2H), 8.51 (s, 1H), 8.45 (s, 1H), 18.58 (s, 1H). ^{13}C NMR: 15.34, 20.91, 23.08, 35.87, 39.16, 39.37, 39.58, 39.79, 40.00, 78.12, 78.45, 78.78, 85.79, 99.49, 117.22, 117.51, 118.47, 122.70, 126.07, 127.25, 128.92, 129.02, 129.26, 137.50, 138.92, 149.32, 161.94. MS: *m/z* = 539.58; *Anal*. Calcd for $C_{33}H_{25}N_5O_3$: C, 73.46; H, 4.67; N, 12.98; O, 8.90; found: C, 73.33; H, 4.61; N, 12.97; O, 8.84 (%).

2-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)nicotinonitrile (4s). IR (cm^{-1}): 3552, 3450, 3417, 3061, 3031, 2974, 2911, 2839, 2332, 1767, 1561, 1438, 1381, 1262, 1162, 795, 717. ^{1}H NMR (DMSO-d_6) δ ppm: 2.89 (s, 3H), 3.14 (s, 3H), 7.24–7.27 (d, 1H), 7.26–7.31 (t, 1H), 7.38–7.40 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 1H), 7.57–7.64 (t, 4H), 7.88–7.90 (d, 2H, *J* = 8.0 Hz), 8.29 (s, 2H), 8.52 (s, 1H), 8.66 (s, 1H), 18.48 (s, 1H). ^{13}C NMR: 18.68, 22.75, 31.19, 38.87, 39.08, 39.19, 39.61, 39.91, 82.60, 98.90, 101.21, 103.44, 118.14, 119.55, 120.55, 123.19, 126.06, 128.63, 129.61, 131.58, 132.72, 143.69, 145.76, 147.76, 151.45, 155.75, 161.80. MS: *m/z* = 559 (M$^+$), 561 (M + 2); *Anal*. Calcd for $C_{32}H_{22}ClN_5O_3$: C, 68.63; H, 3.96; N, 12.51; O, 8.57; found: C, 68.53; H, 3.91; N, 12.41; O, 8.47 (%).

2-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4t). IR (cm^{-1}): 3556, 3456, 3467, 3162, 3024, 2994, 2981, 2829, 2331, 1768, 1562, 1560, 1429, 1392, 1253, 1161, 754, 707. ^{1}H NMR (DMSO-d_6) δ ppm: 2.99 (s, 3H), 3.24 (s, 3H), 7.26–7.29 (d, 1H), 7.32–7.35 (t, 1H), 7.37–7.39 (d, 2H, *J* = 8.0 Hz), 7.50 (d, 1H), 7.60–7.66 (t, 4H), 7.90–7.92 (d, 2H, *J* = 8.0 Hz), 8.20 (s, 2H), 8.54 (s, 1H), 8.68 (s, 1H), 18.18 (s, 1H). ^{13}C NMR: 17.98, 22.67, 30.19, 39.97, 82.89, 99.78, 101.56, 103.77, 113.23, 117.14, 119.15, 123.34, 124.54, 125.19, 126.17, 129.71, 131.67, 133.82, 143.75, 145.76, 151.25, 152.56, 155.65, 159.75, 161.25. MS: *m/z* = 570.55; *Anal*. Calcd for $C_{32}H_{22}N_6O_5$: C, 67.36; H, 3.89; N, 14.73; O, 14.02; found: C, 67.33; H, 3.81; N, 14.67; O, 14.06 (%).

2-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4u). IR (cm^{-1}): 3612, 3460, 3427, 3065, 3014, 2994, 2911, 2839, 2332, 1767, 1562, 1449, 1383, 1253, 1169, 759, 717. ^{1}H NMR (DMSO-d_6) δ ppm: 2.38 (s, 3H), 2.89 (s, 3H), 4.87 (s, 1H), 7.22–7.24 (d, 1H), 7.27–7.30 (t, 1H), 7.37–7.40 (d, 1H), 7.49 (d, 1H), 7.53 (d, 1H), 7.54–7.60 (t, 4H), 7.78–7.85 (d, 1H), 8.02–8.05 (d, 1H), 8.37 (d, 2H), 8.51 (s, 1H), 8.39 (s, 1H), 18.72 (s, 1H). ^{13}C NMR: 17.25, 23.46, 30.19, 37.87, 38.19, 39.38, 39.61, 39.91, 88.08, 99.90, 101.82, 103.87, 113.24, 117.65, 119.40, 121.35, 123.34, 125.19, 128.49, 128.79, 131.67, 132.80, 133.42, 143.75, 144.76, 150.32, 151.67, 155.85, 159.67, 161.98. MS: *m/z* = 541.56; *Anal*. Calcd for $C_{32}H_{23}N_5O_4$: C, 70.97; H, 4.28; N, 12.93; O, 11.82; found: C, 70.83; H, 4.17; N, 12.77; O, 11.74 (%).

2-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4v). IR (cm$^-$1): 3552, 3458, 3034, 2901, 2849, 2342, 1777, 1561, 1439, 1382, 1261, 1161, 758, 712. ^{1}H NMR (DMSO-d_6) δ ppm: 2.48 (s, 3H), 2.79 (s, 3H), 3.02 (s, 3H), 7.29–7.33 (d, 2H), 7.49 (s, 1H), 7.54 (d, 1H), 7.59–7.66 (t, 4H), 7.77–7.82 (d, 2H), 8.03–8.07 (t, 1H), 8.19 (s, 2H), 8.29 (s, 1H), 8.42 (s, 1H), 18.13 (s, 1H). ^{13}C NMR: 17.98, 22.32, 31.89, 37.96, 56.76, 83.79, 98.56, 102.45, 104.34, 111.04, 113.23, 117.25, 119.15, 119.46, 121.25, 123.43, 124.35, 126.17, 128.30, 129.73, 129.91, 130.67, 131.72, 133.32, 138.32, 143.66, 145.06, 150.23, 152.23, 157.65. MS: *m/z* = 555.19; *Anal*. Calcd for $C_{33}H_{25}N_5O_4$: C, 71.34; H, 4.54; N, 12.61; O, 11.52; found: C, 71.23; H, 4.41; N, 12.57; O, 11.41(%).

2-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)nicotinonitrile (4w). IR (cm^{-1}): 3612, 3455, 3447, 3062, 3014, 2974, 2849, 2334, 1769, 1569, 1561, 1449, 1384, 1264, 1164, 769, 719. ^{1}H NMR (DMSO-d_6) δ ppm: 2.99 (s, 3H), 3.24 (s, 3H), 7.27–7.30 (d, 2H), 7.36–7.38 (d, 2H, *J* = 8.0 Hz), 7.40 (t, 1H), 7.52 (d, 1H), 7.56–7.60 (t, 4H), 7.79–7.81 (d, 2H, *J* = 8.0 Hz), 8.04–8.07 (s, 1H), 8.26 (s, 1H), 8.36 (s, 1H), 18.32 (s, 1H). ^{13}C NMR: 17.78, 22.17, 30.98, 38.79, 39.08, 88.19, 98.12, 101.43, 103.23, 113.04, 117.15, 119.55, 122.09, 123.17, 128.73, 128.40, 128.83, 131.57, 132.92, 143.85, 145.76, 148.75, 152.23, 155.75, 159.32, 161.12. MS: *m/z* = 570.55; Anal. Calcd for $C_{32}H_{22}N_6O_5$: C, 67.36; H, 3.89; N, 14.73; O, 14.02; found: C, 67.23; H, 3.81; N, 14.67; O, 14.01 (%).

2-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)nicotinonitrile (4x). IR (cm^{-1}): 3562, 3456, 3427, 3092, 3084, 2901, 2899, 2342, 1787, 1563, 1449, 1342, 1264, 1164, 768, 707. ^{1}H NMR (DMSO-d_6) δ ppm: 2.89 (s, 3H), 3.14 (s, 3H), 7.27–7.30 (d, 1H),

7.34–7.38 (t, 1H), 7.47–7.49 (d, 2H, $J = 8.0$ Hz), 7.51 (d, 1H), 7.62–7.68 (t, 4H), 7.92–7.94 (d, 2H, $J = 8.0$ Hz), 8.31 (s, 2H), 8.64 (s, 1H), 8.78 (s, 1H), 18.17 (s, 1H). ^{13}C NMR: 17.68, 22.32, 32.28, 88.8, 97.56, 101.24, 103.43, 113.23, 116.32, 117.68, 118.02, 119.65, 123.43, 126.19, 129.61, 131.57, 133.92, 143.85, 145.76, 150.98, 152.23, 155.75, 159.67, 161.23. MS: $m/z = 543$ (M^+), 545 (M + 2); *Anal*. Calcd for $C_{32}H_{22}FN_5O_3$: C, 70.71; H, 4.08; N, 12.88; O, 8.83; found: C, 70.65; H, 4.02; N, 12.79; O, 8.72 (%).

Acknowledgments. The authors are thankful to FIST-DST and SAP-UGC for their generous financial and instrumentation support. Special thanks are due to "National Facility for Drug Discovery through New Chemical Entities (NCE's) Development and Instrumentation Support to Small Manufacturing Pharma Enterprises" Program under Drug and Pharma Research Support (DPRS) jointly funded by Department of Science and Technology, New Delhi, Government of Gujarat Industries Commissionerate and Saurashtra University, Rajkot.

REFERENCES AND NOTES

[1] (a) Klimesova, V.; Otcenaaek, M.; Waisser, K. Eur J Med Chem 1996, 31, 389. (b) Suloeva, E.; Yure, M.; Gudriniece, E.; Petrova, M.; Gutcaits, A. Chemistr Heterocycl Compounds 2001, 37, 872. (c) Quintela, J. M.; Peinador, C.; Botana, L.; Estevez, M.; Riguera, R. Bioorg Med Chem 1997, 5, 1543.

[2] (a) Abarca, B.; Ballesteros, R.; Elmasnaouy, M. Tetrahedron 1999, 55, 12881. (b) Abarca, B.; Ballesteros, R.; Elmasnaouy, M. Arkivoc 2002, 6, 146. (c) Abarca, B.; Ballesteros, R.; Elmasnaouy, M.; D'Ocón, P., Ivorra, M. D.; Valiente, M. Arkivoc 2002, 10, 9. (d) Abarca, B.; Ballesteros, R.; Chadlaoui, M. Arkivoc 2002, 10, 52. (e) Abarca, B.; Ballesteros, R.; Chadlaoui, M. Arkivoc 2004, 4, 42.

[3] Sanghavi, Y. S.; Larson, S. B.; Robinse, R. K.; Revenkar, G. R. J Med Chem 1989, 32, 945.

[4] Ddhlbom, R.; Ekstramd, T. Arch Intern Pharmacodynamics 1996, 159, 70.

[5] Paller, M.; Ponzio, K. Chem Abstr 1983, 99, 158406.

[6] Prakash, L.; Sharma, R.; Shukla, S.; Goval, R. D. Pharmazie 1993, 48, 221; Chem Abstr 1993, 119, 95456.

[7] Heichachiro, A.; Shinozaki, K.; Niwa, S.; Tomosho, A.; Masao, S.; Mitsui, S.; Shiggeru, U. Chem Abstr 1989, 110, 23891.

[8] Weil, C. S. Biometrics 1952, 8, 249.

[9] Harpen, B. N. J Am Med Assoc 1945, 129, 1219.

[10] Genzer, J. D.; Lewis, M. N.; McMillan, F. H.; King, J. A. J Am Chem Soc 1953, 75, 2206.

[11] Dushay, L. J. Rev Can Biol 1961, 20, 321.

[12] Douglass, J. R.; Baker, N. F.; Longwest, M. W. Am J Vet Res 1956, 17, 318.

[13] Temple, C.; Rener, Jr. G. A.; Raud, W. R.; Noker, P. E. J Med Chem 1992, 35, 3686.

[14] Murata, T.; Shimada, M.; Sakakibara, S.; Yoshino, T.; Kadono, H.; Masuda, T.; Shimazaki, M.; Shintani, T.; Fuchikami, K.; Sakai, K.; Inbe, H.; Takeshita, K.; Niki, T.; Umeda, M.; Bacon, K. B.; Ziegelbauer, K. B.; Lowinger, T. B. Bioorg Med Chem Lett 2003, 13, 913.

[15] (a) Shishoo, C. J.; Devani, M. B.; Bhadti, V. S.; Ananthan, S.; Ullas, G. V. Tetrahedron Lett 1983, 24, 4611. (b) Doe, K.; Avasthi, K.; Pratap, R.; Bakuni, D. S.; Joshi, M. N. Indian J Chem 1990, 29, 459.

[16] Kennedy, R.O.; Thornes, R.D. Coumarins: Biology, Applications and Mode of Actions; John Wiley: England, 1997; 333.

[17] Antigoni, K.; Ioannis, S.L.; Philip, A. H. Tetrahedron Lett 2007, 48, 7181.

[18] (a) Shin, K. D.; Lee, M. Y.; Shin, D. S.; Lee, S.; Son, K. H.; Koh, S.; Paik, Y. K.; Kwon, B. M.; Han, D. C. J. Biol Chem 2005, 280, 41439. (b) Demers, J.; Hageman, W.; Johnson, S.; Klaubert, D.; Look, R.; Moore J. Bioorg Med Chem Lett 1994, 4, 2451. (c) Simoni, D.; Roberti, M.; Paolo, I. F.; Rondanin, R.; Baruchello, R.; Malagutti, C.; Mazzali, A.; Rossi, M.; Grimaudo, S.; Capone, F.; Dusonchet, L.; Meli, M.; Raimondi, M. V.; Landino, M.; D'Alessandro, N.; Tolomeo, M.; Arindam, D.; Lu, S.; Benbrook, D. M. J Med Chem 2001, 44, 2308. (d) Liu, X. H.; Cui, P.; Song, B. A.; Bhadury, P. S.; Zhu, H. L.; Wang, S. F. Bioorg Med Chem 2008, 16, 4075. (e) Velaparthi, S.; Brunsteiner, M.; Uddin, R.; Wan, B.; Franzblau, S. G.; Petukhov, P. A. J Med Chem 2008, 51, 1999. (f) Magedov, I. V.; Manpadi, M.; Van Slambrouck, S.; Steelant, W. F. A.; Rozhkova, E.; Przheval'skii, N. M.; Rogelj, S.; Kornienko, A. J Med Chem 2007, 50, 5183.

[19] (a) Pinho, E. M.; Teresa, M. V. D. Curr Org Chem 2005, 9, 925. (b) Colliot, F.; Kukorowski, K. A.; Hawkins, D. W.; Roberts, D. A. Brighton Crop Prot Conf Pests Dis 1992, 1, 29. (c) Chen, H. S.; Li, Z. M.; Han, Y. F. J. Agric Food Chem 2000, 48, 5312. (d) Vicentini, C. B.; Romagnoli, C.; Reotti, E.; Mares, D. J Agric Food Chem 2007, 55, 10331. (e) Vicentini, C. B.; Mares, D.; Tartari, A.; Manfrini, M.; Forlani, G. J. J Agric Food Chem 2004, 52, 1898.

[20] (a) Graneto, M. J.; Kurumbail, R. G.; Vazquez, M. L.; Shieh, H. S.; Pawlitz, J. L.; Williams, J. M.; Stallings, W. C.; Geng, L.; Naraian, A. S.; Koszyk, F. J.; Stealey, M. A.; Xu, X. D.; Weier, R. M.; Hanson, G. J.; Mourey, R. J.; Compton, R. P.; Mnich, S. J.; Anderson, G. D.; Monahan, J. B.; Devraj, R. J Med Chem 2007, 50, 5712. (b) Kuettel, S.; Zambon, A.; Kaiser, M.; Brun, R.; Scapozza, L.; Perozzo, R. J Med Chem 2007, 50, 5833.

[21] Feng, S.; Shujiang, T.; Fang, F.; Tuanjie, L. Arkivoc 2005, 1, 137.

[22] Rafat, M. S.; Fathy, F. A. J Chem Re (S) 1997, 294.

[23] Vyas, D. H.; Tala, S. D.; Akbari, J. D.; Dhaduk, M. F.; Joshi, K. A. Indian J Chem 2009, 48, 833.

[24] Zhou, J. F.; Gong, G. X.; Zhu, F. X.; Zhi, S. J. Chin Chem Lett 2009, 20, 37.

[25] Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadere, B. Tetrahedron Lett 2004, 45, 6603.

[26] Paul, S.; Gupta, R.; Loupy, A. J Chem Res (S) 1998, 330.

[27] (a) Boger, D. L.; Weinreb, S. M. Hetero-Diels-Alder Methodology in Organic Synthesis; Academic Press: San Diego, 1987, Chap. 2 and 9. (b) Boger, D. L.; Weinreb, S. M. Hetero-Diels-Alder Methodology in Organic Synthesis; Academic Press: San Diego, 1987, Chap. 9. (c) Cabral, J.; Laszlo, P.; Montaufier, M. T. Tetrahedron Lett 1988, 29, 547. (d) Weinreb, S.M. In Comrehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, 401. (e) Babu, G.; Perumal, P. T. Tetrahedron Lett 1998, 39, 3225. (f) Yadav, J. S.; Reddy, B.V.S.; Srinivas, R.; Madhuri, Ch.; Ramalingam, T. Synlett 2001, 240.

[28] (a) Parekh, S.; Bhavsar, D.; Savant, M.; Thakrar, S.; Bavishi, A.; Parmar, M.; Vala, H.; Radadiya, A.; Pandya, N.; Serly, J.; Molnár, J.; Shah, A. Eur J Med Chem, 2011, 46(5), 1942. (b) Upadhyay, K.; Bavishi, A.; Thakrar, S.; Radadiya, A.; Vala, H.; Parekh, S.; Bhavsar, D.; Savant, M.; Parmar, M.; Adlakha, P.; Shah, A. Bioorg Med Chem Lett 2011, 21(8), 2547. (c) Bhavsar, D.; Trivedi, J.; Parekh, S.; Thakrar, S.; Bavishi, A.; Radadiya, A.; Roberta Loddo, Shah, K.; Bioorg Med Chem Lett 2011, 21(11), 3443. (d) Thakrar, S.; Bavishi, A.; Radadiya, A.; Parekh, S.; Bhavsar, D.; Vala, H.; Pandya, N.; Shah, A. J Heterocycl Chem 2013, 50, E73.

[29] Venkateshwara Rao V.; Sundaramurthy V. Proc Indian Acad Sci 1975, 81(3), 118.

[30] Liu, X. H.; Cui, P.; Song, B. A.; Bhadury, P. S.; Zhu, H. L.; Wang, S. F. Bioorg Med Chem 2008, 16, 4075. (e) Velaparthi, S.; Brunsteiner, M.; Uddin, R.; Wan, B.; Franzblau, S. G.; Petukhov, P. A. J Med Chem 2008, 51, 1999. (f) Magedov, I. V.; Manpadi, M.; Van slambrouck, S.; Steelant, W. F. A.; Rozhkova, E.; Przheval'skii, N. M.; Rogelj, S.; Kornienko, A. J Med Chem 2007, 50, 5183.

[31] Vishnupriya, V.; Mallika, J.; Surapaneni, K. M.; Saraswathi, P.; Chandra Sada Gopan, V. Int J Pharma Sci Res 2010, 1(8), 278.

[32] Lipipun, V.; Nantawanit, N.; Pongsamart, S.J.; Songklanakarin Sci Technol 2002, 24(1), 31.