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A New, One-Pot, Multicomponent Synthesis of Bioactive *N*-Pyrazolylformamidines under Microwave Irradiation

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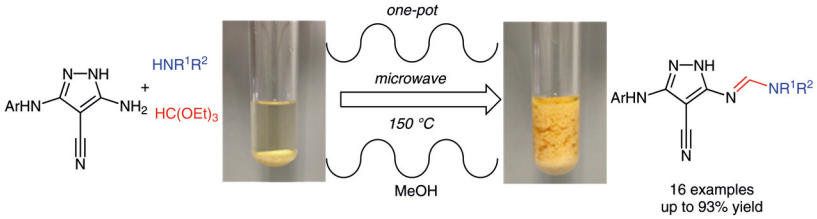

Dedicated to Professor Viktor E. Kolla on the occasion of his 90th birthday

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Abstract A one-pot, three-component, microwave-assisted reaction of polysubstituted 5-aminopyrazoles, triethyl orthoformate, and a series of cyclic secondary amines was developed and successfully employed for the synthesis of novel *N*-pyrazolylformamidines. Under catalyst-free conditions, the reaction proceeded in a chemo- and regioselective manner, resulting in the formation of unsymmetric formamidines, which were isolated in high yields and purity. Some of the prepared compounds were found to inhibit interleukin-17 secretion in phenotypic *in vitro* assays.

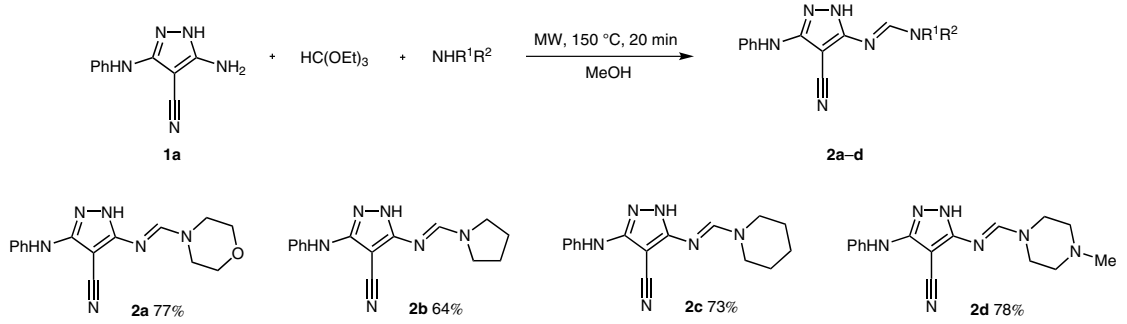
Key words formamidines, pyrazoles, orthoesters, multicomponent reaction, microwave-assisted synthesis

Formamidines are well known as useful building blocks in organic synthesis.[1] They are also a common feature in a variety of biologically active compounds. It has been demonstrated that transformation of primary amino groups of some anticancer[2] and antiviral[3] drugs by linking them to cyclic amines via a formamidine moiety resulted in enhancement of their therapeutic properties. Construction of these and other non-symmetric formamidines typically involves functionalisation of the primary amino group to an imidate, followed by its reaction with other amines.[4] Another approach exploits initial formation of *N*,*N*-dimethylformamidines in the reaction of primary amines with *N*,*N*-dimethylformamide dimethylacetal, followed by trans-amidination using an excess of other amines.[5] Several one-pot strategies have been developed based on reactions of primary amines with *N*,*N*-disubstituted formamides in the presence of coupling reagents such as sulfonyl chlorides,[6] phenyl chloroformate,[7] or trifluoroacetic anhydride and sodium hydride.[8]

N-Pyrazolylformamidines have been reported to possess anticancer activity.[9] In this group of compounds, particular attention was devoted to binucleine 2, a nitrile-substituted *N*-pyrazolylformamidine, which was found to be a potent and selective inhibitor of Aurora B kinase.[10] Construction of more complex heterocyclic systems using *N*-pyrazolylformamidines as synthons has also proved to be an efficient methodology, substantiating the special place of these compounds in the chemistry of fused pyrazoles.[11]

It was demonstrated that *N*-pyrazolylformamidines could be synthesised by reaction of aminopyrazoles, *N*,*N*-disubstituted formamides, and trifluoroacetic anhydride in the presence of sodium hydride.[8] *N*-Pyrazolylformamidines were also prepared when the corresponding aminopyrazoles were treated with *N*,*N*-disubstituted formamides and phosphorous oxychloride under microwave irradiation.[9,12] However, applications of these reagents are limited due to possible formylation of the pyrazole ring and lability of other functional groups.[13]

Herein, we report a new, selective, one-pot, multicomponent synthesis of bioactive formamidines constructed on the 5-amino-3-anilinopyrazole-4-carbonitrile scaffold. The synthesis of simple symmetric formamidines by using a multicomponent reaction of anilines and triethyl orthoformate has been well documented in the literature since the report of a general methodology by Taylor et al.[14] This reaction has been well explored and was found to proceed effectively under catalysis by cerium(IV) ammonium nitrate,[15] β-cyclodextrin,[16] sulphated zirconia,[17] and γ-Fe_2O_3@SiO_2-HA.[18] Good results were also obtained when hexafluoroisopropanol[19] or deep eutectic mixtures [tin(II) chloride–choline chloride][20] were used as solvents. Ultrasound irradiation was also reported to expedite a multicomponent synthesis of symmetric formamidines.[21] However, synthesis of complex unsymmetric formamidines by using a multicompo-



Scheme 1 Transformation of 5-amino-3-(phenylamino)pyrazole-4-carbonitrile (**1a**) into *N*-pyrazolylformamidines **2a–d**

nent approach has remained unexplored. Selectivity of the reaction appears to be the main problem for this approach due to competition with the formation of symmetric *N*,*N*′-bis(pyrazolyl)formamidines.[22] We anticipated that this problem could be solved by using focused microwave irradiation and careful selection of the reagent ratio, particularly by applying an excess of orthoformate and cyclic amine.[23]

5-Amino-3-(arylamino)pyrazole-4-carbonitriles **1** were prepared by using previously reported methods, viz. reaction of 3,3,-bis(methylsulfanyl)-2-cyanoacrylonitrile[24] with anilines and subsequent treatment of the resulting 3-anilino-3-methylsulfanyl-2-cyanoacrilonitrile with hydrazine.[25] The three-component reaction of 5-amino-3-(phenylamino)pyrazole-4-carbonitrile (**1a**) with triethyl orthoformate and morpholine was conducted first under reflux in methanol for 24 hours. Only traces of product (**2a**) were detected in the reaction mixture. However, the three-component reaction under microwave irradiation (150 °C, 20 min) in methanol by using the same reagents was found to afford selective formation of 5-[(morpholinomethylene)amino]-3-(phenylamino)-1*H*-pyrazole-4-carbonitrile (**2a**) in good yield (Scheme 1).

The structure of product **2a** was confirmed by spectroscopic data indicating the presence of the formamidine moiety (signal of methine proton at δ = 8.18 ppm in the ^{1}H NMR spectrum and signal of corresponding carbon atom at δ = 155 ppm in the ^{13}C NMR spectrum). A band at 2201 cm^{-1} in the IR spectrum and a signal at δ = 115.6 ppm in the ^{13}C NMR spectrum confirmed that the cyano group remained intact in the product. A singlet of the secondary amino group at δ = 8.46 ppm and a broad signal of the tautomerisable endocyclic proton on the pyrazole at δ = 12.07 ppm indicated that these groups did not participate in the reaction.

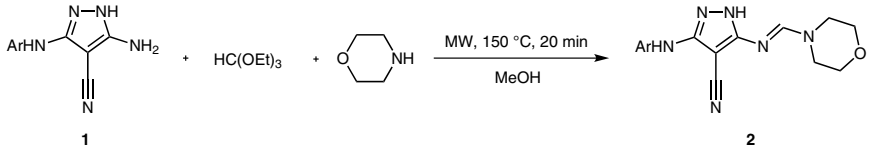
In similar reactions, by replacing morpholine with other cyclic amines, such as pyrrolidine, piperidine, and 4-methylpiperazine, the corresponding *N*-pyrazolylformamidines **2b**, **2c**, and **2d** were successfully obtained (Scheme 1).

Improvement in some properties of several anticancer drugs has been achieved through the conversion of amino groups to morpholine-based formamidines.[2] Therefore, we further applied our method to the preparation of an extended library of substituted pyrazoles with this moiety for biological testing. Under microwave irradiation, this reaction was effectively employed for the synthesis of a series of **2** containing various arylamino substituents (Table 1). It should be noted that the developed process was catalyst-free and involved very simple isolation of the highly pure products by simple filtration.

In the NMR spectra of all compounds of the prepared series, we observed magnetic non-equivalence of the morpholine signals of atoms located on the opposite sides of the ring. The delocalisation of the electron pair on the morpholine nitrogen atom to the formamidine moiety was further extended over the pyrazole ring and cyano group. This high level of delocalisation resulted in restricted rotation around the C–N formamidine bond, which was translated into two signals in the ^{13}C NMR spectra at δ = 42.5 and 48.8 ppm from carbon atoms adjacent to the morpholine nitrogen and two groups of signals from the corresponding methylene protons in the ^{1}H NMR spectra at δ = 3.46–3.55 and 3.60–3.68 ppm. Moreover, the observed anisotropic effect was further extended to carbon atoms adjacent to the morpholine oxygen, splitting their signals in the ^{13}C NMR spectra to δ = 65.4 and 66.5 ppm.

The prepared compounds were subjected to pharmacological screening in a series of *in vitro* assays under the Open Innovation Drug Discovery (OIDD) platform supported by Eli Lilly.[26] Some of compounds **2** were found to significantly affect secretion of interleukin-17 (IL-17), which plays an important role in many autoimmune diseases.[27] Stimulated memory T-cells by anti-CD3, anti-CD28 and IL-23 in human peripheral blood mononuclear cells (hPBMC) were used to identify inhibitors of IL-17 secretion by using ELISA assays. The most active compounds identified in the series were **2h** and **2k**, which inhibited secretion of IL-17 in hPBMC with IC_{50} values of 0.34 and 0.63 μM, respectively.

Table 1 Synthesis of 3-(Arylamino)-5-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitriles **2e**–**p**



1 **2**

Entry	Ar	Product	Yield (%)	Mp (°C)	Entry	Ar	Product	Yield (%)	Mp (°C)
1	4-FC_6H_4	**2e**	91	267–269[a]	7	4-EtC_6H_4	**2k**	86	268–270[c]
2	4-ClC_6H_4	**2f**	91	266–268[a]	8	2-$MeOC_6H_4$	**2l**	82	264–266[b]
3	3-BrC_6H_4	**2g**	92	285–287[b]	9	4-$MeOC_6H_4$	**2m**	88	224–226[b]
4	4-BrC_6H_4	**2h**	90	268–270[a]	10	2-$EtOC_6H_4$	**2n**	93	219–220[b]
5	3-MeC_6H_4	**2i**	87	253–255[b]	11	4-$EtOC_6H_4$	**2o**	85	231–233[b]
6	4-MeC_6H_4	**2j**	87	256–258[c]	12	3-$F_3CC_6H_4$	**2p**	78	235–237[b]

[a] Recrystallised from MeOH.
[b] Recrystallised from MeCN.
[c] Recrystallised from *i*-PrOH.

These compounds also demonstrated good selectivity over inhibition of IL-5 secretion and were found to possess a favourable cytotoxicity profile (EC_{50} > 30 μM) against hPBMC.

In conclusion, we have successfully developed a microwave-assisted, multicomponent, catalyst-free method for the synthesis of new bioactive *N*-pyrazolylformamidines **2** by using easily attainable reagents. The attractive practical aspects of this method also include short reaction times and simple isolation of the products obtained in good yields.

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz). ^{13}C NMR spectra and HMBC experiments used for the signal assignments were performed using a Bruker Fourier 300 spectrometer (300 MHz) and by using DMSO-d_6 as a solvent. TMS was used as an internal reference. IR spectra were recorded using ATR sample base plate diamond on a Spectrum Two (PerkinElmer) FT-IR spectrometer. Microwave-assisted reactions were carried out in the closed vessel focused single mode by using a CEM Discover microwave synthesizer. The reaction temperature was monitored by an equipped IR sensor.

N-Pyrazolylformamidines 2; General Procedure

A mixture of **1** (1 mmol), the appropriate amine (2.5 mmol), and $HC(OEt)_3$ (0.42 mL, 2.5 mmol) in MeOH (2 mL) was irradiated in a 10 mL seamless pressure vial by using the microwave system operating at maximal microwave power up to 150 W at 150 °C for 20 min. After cooling of the mixture, the precipitated product **2** was filtered, washed with cold MeOH, and recrystallised from a suitable solvent.

5(3)-[(Morpholinomethylene)amino]-3(5)-(phenylamino)-1*H*-pyrazole-4-carbonitrile (2a)

Yellow solid; yield: 227 mg (77%); mp 266–268 °C (MeOH).

IR (ATR): 3329 (N-H), 3164 (N-H), 2907 (C-H), 2201 (C≡N), 1612, 1532, 1436, 1269, 1114 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.46–3.49 (m, 2 H, CH_2), 3.63–3.67 (m, 6 H, $(CH_2)_3$), 6.77 (t, ^3J = 7.9 Hz, 2 H, H-3′ and H-5′), 7.18 (t, ^3J = 7.3 Hz, 1 H, H-4′), 7.43 (br s, 2 H, H-2′ and H-6′), 8.18 (s, 1 H, CH), 8.46 (br s, 1 H, NH), 12.07 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.5 (CH_2), 48.8 (CH_2), 65.4 (CH_2), 66.5 (CH_2), 68.6 (C-4), 115.7 (C≡N), 116.1 (C-2′ and C-6′), 119.2 (C-4′), 128.5 (C-3′ and C-5′), 142.6 (C-1′), 151.6 (C-3), 155.0 (CH=N), 155.2 (C-5).

Anal. Calcd for $C_{15}H_{16}N_6O$: C, 60.80; H, 5.44; N, 28.36. Found: C, 60.77; H, 5.52; N, 28.27.

3(5)-(Phenylamino)-5(3)-[(pyrrolidinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2b)

Yellow solid; yield: 179 mg (64%); mp 297–299 °C (MeCN).

IR (ATR): 3305 (N-H), 3136 (N-H), 2955 (C-H), 2212 (C≡N), 1621, 1537, 1465, 1250, 1174 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.86–1.94 (m, 4 H, $(CH_2)_2$), 3.38–3.42 (m, 2 H, CH_2), 3.54–3.58 (m, 2 H, CH_2), 6.77 (t, ^3J = 7.3 Hz, 1 H, H-4′), 7.18 (t, ^3J = 7.9 Hz, 2 H, H-3′ and H-5′), 7.45 (d, ^3J = 7.2 Hz, 2 H, H-2′ and H-6′), 8.34 (s, 1 H, CH), 8.42 (br s, 1 H, NH), 12.00 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.0 (CH_2), 24.6 (CH_2), 45.3 (CH_2), 48.7 (CH_2), 67.9 (C-4), 116.0 (C≡N), 116.0 (C-2′ and C-6′), 119.1 (C-4′), 128.5 (C-3′ and C-5′), 142.7 (C-1′), 151.6 (C-3), 153.0 (CH=N), 155.6 (C-5).

Anal. Calcd for $C_{15}H_{16}N_6$: C, 64.27; H, 5.75; N, 29.98. Found: C, 64.08; H, 5.86; N, 29.79.

3(5)-(Phenylamino)-5(3)-[(1-piperidylmethylene)amino]-1*H*-pyrazole-4-carbonitrile (2c)

Yellow solid; yield: 215 mg (73%); mp 275–277 °C (MeCN).

IR (ATR): 3323 (N-H), 3054 (N-H), 2941 (C-H), 2201 (C≡N), 1614, 1532, 1440, 1250 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.56–1.60 (m, 4 H, $(CH_2)_2$), 1.62–1.66 (m, 2 H, CH_2), 3.39–3.42 (m, 2 H, CH_2), 3.57–3.60 (m, 2 H, CH_2), 6.77 (t, ^3J = 7.3 Hz, 1 H, H-4′), 7.18 (t, ^3J = 7.9 Hz, 2 H, H-3′ and H-5′), 7.45 (d, ^3J = 6.9 Hz, 2 H, H-2′ and H-6′), 8.13 (s, 1 H, CH), 8.43 (br s, 1 H, NH), 11.98 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.8 (CH_2), 24.6 (CH_2), 26.2 (CH_2), 42.4 (CH_2), 50.0 (CH_2), 68.2 (C-4), 115.8 (C≡N), 116.0 (C-2′ and C-6′), 119.1 (C-4′), 128.5 (C-3′ and C-5′), 142.7 (C-1′), 151.5 (C-3), 154.7 (CH=N), 155.7 (C-5).

Anal. Calcd for $C_{16}H_{18}N_6$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.20; H, 6.22; N, 28.47.

5(3)-[(4-Methylpiperazinylmethylene)amino]-3(5)-(phenylamino)-1*H*-pyrazole-4-carbonitrile (2d)

Yellow solid; yield: 241 mg (78%); mp 256–258 °C (MeCN).

IR (ATR): 3340 (N-H), 3057 (N-H), 2932 (C-H), 2202 (C≡N), 1617, 1540, 1438, 1250, 1140 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3 H, CH_3), 2.34–2.39 (m, 4 H, $(CH_2)_2$), 3.43–3.46 (m, 2 H, CH_2), 3.59–3.62 (m, 2 H, CH_2), 6.77 (t, ^3J = 7.3 Hz, 1 H, H-4′), 7.18 (t, ^3J = 7.9 Hz, 2 H, H-3′ and H-5′), 7.44 (d, ^3J = 6.3 Hz, 2 H, H-2′ and H-6′), 8.14 (s, 1 H, CH), 8.45 (br s, 1 H, NH), 12.03 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 41.7 (CH_3), 45.6 (CH_2), 48.6 (CH_2), 53.5 (CH_2), 54.8 (CH_2), 68.5 (C-4), 115.7 (C≡N), 116.0 (C-2′ and C-6′), 119.2 (C-4′), 128.5 (C-3′ and C-5′), 142.6 (C-1′), 151.5 (C-3), 154.8 (CH=N), 155.5 (C-5).

Anal. Calcd for $C_{16}H_{19}N_7$: C, 62.12; H, 6.19; N, 31.69. Found: C, 62.02; H, 6.33; N, 31.55.

3(5)-(4-Fluorophenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2e)

Yellow solid; yield: 287 mg (91%); mp 267–269 °C (MeOH).

IR (ATR): 3330 (N-H), 3155 (N-H), 2902 (C-H), 2202 (C≡N), 1617, 1537, 1450, 1272, 1110 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.46–3.50 (m, 2 H, CH_2), 3.62–3.67 (m, 6 H, $(CH_2)_3$), 7.02 (dd, ^3J = 8.9, $^3J_{H-F}$ = 8.9 Hz, 2 H, H-3′ and H-5′), 7.49 (br s, 2 H, H-2′ and H-6′), 8.18 (s, 1 H, CH), 8.51 (br s, 1 H, NH), 12.04 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.4 (CH_2), 48.8 (CH_2), 65.3 (CH_2), 66.4 (CH_2), 67.9 (C-4), 114.8 (d, $^2J_{C-F}$ = 22.0 Hz, C-3′ and C-5′), 115.6 (C≡N), 117.4 (d, $^3J_{C-F}$ = 7.2 Hz, C-2′ and C-6′), 138.9 (d, $^4J_{C-F}$ = 1.4 Hz, C-1′), 153.4 (d, $^1J_{C-F}$ = 261.2 Hz, C-4′), 154.2 (C-3), 155.0 (CH=N), 157.3 (C-5).

Anal. Calcd for $C_{15}H_{15}FN_6O$: C, 57.32; H, 4.81; N, 26.74. Found: C, 57.26; H, 4.88; N, 26.69.

3(5)-(4-Chlorophenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2f)

Yellow solid; yield: 301 mg (91%); mp 266–268 °C (MeOH).

IR (ATR): 3333 (N-H), 3144 (N-H) 2902 (C-H), 2199 (C≡N), 1615, 1532, 1450, 1272, 1115 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.47–3.52 (m, 2 H, CH_2), 3.63–3.67 (m, 6 H, $(CH_2)_3$), 7.22 (d, ^3J = 9.0 Hz, 2 H, H-3′ and H-5′), 7.49 (d, 2 H, ^3J = 8.2 Hz H-2′ and H-6′), 8.18 (s, 1 H, CH), 8.68 (br s, 1 H, NH), 12.12 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.4 (CH_2), 48.8 (CH_2), 65.3 (CH_2), 66.4 (CH_2), 68.3 (C-4), 115.4 (C≡N), 117.5 (C-2′ and C-6′), 122.4 (C-4′), 128.2 (C-3′ and C-5′), 141.4 (C-1′), 151.2 (C-3), 155.0 (CH=N), 155.2 (C-5).

Anal. Calcd for $C_{15}H_{15}ClN_6O$: C, 54.47; H, 4.57; N, 25.41. Found: C, 54.40; H, 4.62; N, 25.36.

3(5)-(3-Bromophenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2g)

Yellow solid; yield: 343 mg (92%); mp 285–287 °C (MeCN).

IR (ATR): 3324 (N-H), 3196 (N-H), 2914 (C-H), 2203 (C≡N), 1614, 1531, 1434, 1265, 1115 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.47–3.53 (m, 2 H, CH_2), 3.61–3.68 (m, 6 H, $(CH_2)_3$), 6.94 (ddd, ^4J = 0.8, ^4J = 1.86, ^3J = 7.86 Hz, 1 H, H-4′), 7.14 (t, ^3J = 8.1 Hz, 1 H, H-5′), 7.39 (d, ^3J = 8.0 Hz, 1 H H-6′), 7.82 (s, 1 H, H-2′), 8.19 (s, 1 H, CH), 8.79 (br s, 1 H, NH), 12.18 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.5 (CH_2), 48.9 (CH_2), 65.3 (CH_2), 66.5 (CH_2), 68.6 (C-4), 115.0 (C-6′), 115.4 (C≡N), 118.2 (C-2′), 121.6 (C-4′), 121.7 (C-3′), 130.4 (C-5′), 144.1 (C-1′), 151.0 (C-3), 155.1 (CH=N), 155.3 (C-5).

Anal. Calcd for $C_{15}H_{15}BrN_6O$: C, 48.01; H, 4.03; N, 22.40. Found: C, 47.87; H, 4.11; N, 22.32.

3(5)-(4-Bromophenylamino)-5(3)[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2h)

Yellow solid; yield: 339 mg (90%); mp 268–270 °C (MeOH).

IR (ATR): 3298 (N-H), 3129 (N-H), 2910 (C-H), 2219 (C≡N), 1614, 1540, 1416, 1235, 1112 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.47–3.52 (m, 2 H, CH_2), 3.63–3.67 (m, 6 H, $(CH_2)_3$), 7.34 (d, ^3J = 8.9 Hz, 2 H, H-3′ and H-5′), 7.44 (d, 2 H, ^3J = 8.4 Hz H-2′ and H-6′), 8.18 (s, 1 H, CH), 8.70 (br s, 1 H, NH), 12.13 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.5 (CH_2), 48.9 (CH_2), 65.4 (CH_2), 66.5 (CH_2), 68.5 (C-4), 110.3 (C-4′), 115.5 (C≡N), 118.1 (C-2′ and C-6′), 131.2 (C-3′ and C-5′), 141.9 (C-1′), 151.2 (C-3), 155.1 (CH=N), 155.4 (C-5).

Anal. Calcd for $C_{15}H_{15}BrN_6O$: C, 48.01; H, 4.03; N, 22.40. Found: C, 47.90; H, 4.14; N, 22.28.

3(5)-(3-Methylphenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2i)

Yellow solid; yield: 267 mg (87%); mp 253–255 °C (MeCN).

IR (ATR): 3332 (N-H), 3163 (N-H), 2912 (C-H), 2202 (C≡N), 1614, 1533, 1435, 1269, 1115 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3 H, CH_3), 3.46–3.49 (m, 2 H, CH_2), 3.62–3.67 (m, 6 H, $(CH_2)_3$), 6.60 (d, ^3J = 7.3 Hz, 1 H, H-4′), 7.06 (t, ^3J = 7.8 Hz, 1 H, H-5′), 7.20–7.29 (m, 2 H, H-2′ and H-6′), 8.17 (s, 1 H, CH), 8.37 (br s, 1 H, NH), 12.05 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.4 (CH_3), 42.5 (CH_2), 48.9 (CH_2), 65.4 (CH_2), 66.5 (CH_2), 68.6 (C-4), 113.4 (C-6′), 115.7 (C≡N), 116.6 (C-2′), 120.0 (C-4′), 128.4 (C-5′), 137.5 (C-3′), 142.6 (C-1′), 151.7 (C-3), 155.0 (CH=N), 155.2 (C-5).

Anal. Calcd for $C_{16}H_{18}N_6O$: C, 61.92; H, 5.85; N, 27.08. Found: C, 61.85; H, 5.91; N, 26.99.

3(5)-(4-Methylphenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2j)

Yellow solid; yield: 271 mg (87%); mp 256–258 °C (*i*-PrOH).

IR (ATR): 3302 (N-H), 3140 (N-H), 2917 (C-H), 2220 (C≡N), 1621, 1538, 1417, 1265, 1112 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.20 (s, 3 H, CH_3), 3.46–3.48 (m, 2 H, CH_2), 3.60–3.67 (m, 6 H, $(CH_2)_3$), 6.99 (d, ^3J = 8.3 Hz, 2 H, H-3′ and H-5′), 7.34 (br s, 2 H, H-2′ and H-6′), 8.17 (s, 1 H, CH), 8.33 (br s, 1 H, NH), 12.01 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.3 (CH_3), 42.5 (CH_2), 48.9 (CH_2), 65.4 (CH_2), 66.5 (CH_2), 68.2 (C-4), 115.8 (C≡N), 116.2 (C-2′ and C-6′), 127.7 (C-4′), 128.9 (C-3′ and C-5′), 140.2 (C-1′), 151.9 (C-3), 155.0 (CH=N), 155.2 (C-5).

Anal. Calcd for $C_{16}H_{18}N_6O$: C, 61.92; H, 5.85; N, 27.08. Found: C, 61.80; H, 5.98; N, 26.95.

3(5)-(4-Ethylphenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2k)

Yellow solid; yield: 278 mg (86%); mp 268–270 °C (*i*-PrOH).

IR (ATR): 3329 (N-H), 3132 (N-H), 2925 (C-H), 2202 (C≡N), 1618, 1534, 1420, 1269, 1115 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.14 (t, ^3J = 7.6 Hz, 3 H, CH_3), 2.50 (q, ^3J = 7.6 Hz, 2 H, CH_2), 3.46–3.48 (m, 2 H, CH_2), 3.60–3.67 (m, 6 H, $(CH_2)_3$), 7.02 (d, ^3J = 8.4 Hz, 2 H, H-3′ and H-5′), 7.36 (br s, 2 H, H-2′ and H-6′), 8.17 (s, 1 H, CH), 8.34 (br s, 1 H, NH), 12.01 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.9 (CH_3), 27.4 (CH_2), 42.4 (CH_2), 48.8 (CH_2), 65.3 (CH_2), 66.5 (CH_2), 68.2 (C-4), 115.7 (C≡N), 116.3 (C-2′ and C-6′), 127.7 (C-3′ and C-5′), 134.4 (C-4′), 140.4 (C-1′), 151.9 (C-3), 155.0 (CH=N), 155.1 (C-5).

Anal. Calcd for $C_{17}H_{20}N_6O$: C, 62.95; H, 6.21; N, 25.91. Found: C, 62.90; H, 6.24; N, 25.86.

3(5)-(2-Methoxyphenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2l)

Yellow solid; yield: 268 mg (82%); mp 264–266 °C (MeCN).

IR (ATR): 3419 (N-H), 3170 (N-H), 2915 (C-H), 2206 (C≡N), 1617, 1541, 1434, 1247, 1109 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.47–3.49 (m, 2 H, CH_2), 3.63–3.67 (m, 6 H, $(CH_2)_3$), 3.87 (s, 3 H, CH_3), 6.83 (td, ^4J = 1.9, ^3J = 7.1 Hz, 1 H, H-3′), 6.87 (td, ^4J = 1.8, ^3J = 7.1 Hz, 1 H, H-5′), 6.95 (br s, 1 H, H-4′), 6.98 (dd, ^4J = 1.9, ^3J = 7.5 Hz, H-6′), 7.82 (br s, 1 H, NH), 8.18 (s, 1 H, CH), 12.15 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.5 (CH_2), 48.9 (CH_2), 55.7 (OCH_3), 65.3 (CH_2), 66.4 (CH_2), 68.5 (C-4), 110.3 (C-3′), 115.2 (C≡N), 115.3 (C-6′), 119.8 (C-4′), 120.6 (C-5′), 130.9 (C-1′), 146.6 (C-2′), 151.4 (C-3), 154.8 (C-5), 155.1 (CH=N).

Anal. Calcd for $C_{16}H_{18}N_6O_2$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.76; H, 5.63; N, 25.67.

3(5)-(4-Methoxyphenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2m)

Yellow solid; yield: 286 mg (88%); mp 224–226 °C (MeCN).

IR (ATR): 3301 (N-H), 3140 (N-H), 2959 (C-H), 2216 (C≡N), 1619, 1538, 1463, 1227, 1109 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.46–3.50 (m, 2 H, CH_2), 3.62–3.66 (m, 6 H, $(CH_2)_3$), 3.67 (s, 3 H, CH_3), 6.79 (d, ^3J = 9.0 Hz, 2 H, H-3′ and H-5′), 7.40 (br s, 2 H, H-2′ and H-6′), 8.16 (s, 1 H, CH), 8.23 (br s, 1 H, NH), 11.93 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.4 (CH_2), 48.8 (CH_2), 55.1 (OCH_3), 65.3 (CH_2), 66.5 (CH_2), 67.7 (C-4), 113.8 (C-3′ and C-5′), 115.8 (C≡N), 117.7 (C-2′ and C-6′), 136.1 (C-1′), 152.3 (C-3), 152.7 (C-4′), 154.9 (CH=N), 155.1 (C-5).

Anal. Calcd for $C_{16}H_{18}N_6O_2$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.80; H, 5.62; N, 25.69.

3(5)-(2-Ethoxyphenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2n)

Yellow solid; yield: 316 mg (93%); mp 219–220 °C (MeCN).

IR (ATR): 3427 (N-H), 3181 (N-H), 2974 (C-H), 2193 (C≡N), 1625, 1556, 1445, 1246, 1114 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.38 (t, ^3J = 6.9 Hz, 3 H, CH_3), 3.47–3.49 (m, 2 H, CH_2), 3.63–3.68 (m, 6 H, $(CH_2)_3$), 4.12 (q, ^3J = 7.0 Hz, 2 H, CH_2), 6.81 (td, ^4J = 1.8, ^3J = 7.7 Hz, 1 H, H-3′), 6.86 (td, ^4J = 1.5, ^3J = 7.6 Hz, 1 H, H-5′), 6.93 (br s, 1 H, H-4′), 6.97 (dd, ^4J = 1.6, ^3J = 7.8 Hz, 1 H, H-6′), 7.83 (br s, 1 H, NH), 8.18 (s, 1 H, CH), 12.15 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.7 (CH_3), 42.5 (CH_2), 48.9 (CH_2), 64.0 (OCH_2), 65.3 (CH_2), 66.4 (CH_2), 68.4 (C-4), 111.4 (C-3′), 115.2 (C≡N), 115.2 (C-6′), 119.8 (C-4′), 120.7 (C-5′), 131.0 (C-1′), 145.6 (C-2′), 151.5 (C-3), 154.7 (C-5), 155.1 (CH=N).

Anal. Calcd for $C_{17}H_{20}N_6O_2$: C, 59.99; H, 5.92; N, 24.69. Found: C, 59.93 H, 6.03; N, 24.62.

3(5)-(4-Ethoxyphenylamino)-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2o)

Greenish-yellow solid; yield: 290 mg (85%); mp 231–233 °C (MeCN).

IR (ATR): 3298 (N-H), 3098 (N-H), 2963 (C-H), 2218 (C≡N), 1622, 1538, 1422, 1233, 1112 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.29 (t, ^3J = 7.0 Hz, 3 H, CH_3), 3.46–3.48 (m, 2 H, CH_2), 3.62–3.67 (m, 6 H, $(CH_2)_3$), 3.94 (q, ^3J = 7.0 Hz, 2 H, CH_2), 6.78 (d, ^3J = 9.0 Hz, 2 H, H-3′ and H-5′), 7.38 (br s, 2 H, H-2′ and H-6′), 8.16 (s, 1 H, CH), 8.21 (br s, 1 H, NH), 11.92 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.7 (CH_3), 42.4 (CH_2), 48.7 (CH_2), 63.0 (OCH_2), 65.3 (CH_2), 66.4 (CH_2), 67.6 (C-4), 114.4 (C-3′ and C-5′), 115.7 (C≡N), 117.6 (C-2′ and C-6′), 135.9 (C-1′), 151.9 (C-3), 152.2 (C-4′), 154.8 (CH=N), 155.0 (C-5).

Anal. Calcd for $C_{17}H_{20}N_6O_2$: C, 59.99; H, 5.92; N, 24.69. Found: C, 59.86 H, 6.12; N, 24.54.

3(5)-[3-(Trifluoromethyl)phenylamino]-5(3)-[(morpholinomethylene)amino]-1*H*-pyrazole-4-carbonitrile (2p)

Yellow solid; yield: 285 mg (78%); mp 235–237 °C (MeCN).

IR (ATR): 3332 (N-H), 3113 (N-H), 2978 (C-H), 2205 (C≡N), 1610, 1537, 1434, 1235, 1100 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.48–3.55 (m, 2 H, CH_2), 3.64–3.68 (m, 6 H, $(CH_2)_3$), 7.11 (d, 1 H, $^3J_{H-F}$ = 7.6 Hz, H-4′), 7.42 (t, 1 H, $^3J_{H-F}$ = 8.0 Hz, H-5′), 7.71 (d, 1 H, $^3J_{H-F}$ = 8.1 Hz H-6′), 7.99 (s, 1 H, H-2′), 8.20 (s, 1 H, CH), 8.99 (br s, 1 H, NH), 12.22 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.5 (CH_2), 48.9 (CH_2), 65.3 (CH_2), 66.5 (CH_2), 68.5 (C-4), 112.0 (q, $^3J_{C-F}$ = 4.0 Hz, C-2′), 115.3 (C≡N), 115.3 (q, $^3J_{C-F}$ = 3.3 Hz, C-4′), 119.6 (C-6′), 124.4 (q, $^1J_{C-F}$ = 272.1 Hz, CF_3), 129.4 (q, $^2J_{C-F}$ = 31.1 Hz, C-3′), 129.5 (C-5′), 143.2 (C-1′), 151.1 (C-3), 155.1 (CH=N), 155.4 (C-5).

Anal. Calcd for $C_{16}H_{15}F_3N_6O$: C, 52.75; H, 4.15; N, 23.07. Found: C, 52.58; H, 4.24; N, 22.92.

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Supporting Information

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