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Synthesis of polyfunctionalized pyrroles via a tandem reaction of Michael addition and intramolecular cyanide-mediated nitrile-to-nitrile condensation

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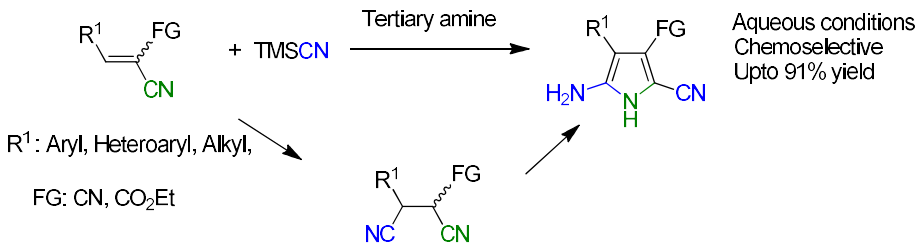


A new approach for synthesis of tetra-substituted/functionalized NH-pyrroles from *gem*-diactivated acrylonitriles and TMSCN has been developed. The strategy utilizes generation of *vic*-dinitrile via Michael addition and cyanide-mediated nitrile-to-nitrile cyclocondensation, which undergo in tandem guided by manifold roles of "CN". An extended application to production of fused-pyrrole has also been realized.

Pyrrole-class of compounds possess diverse biological and pharmaceutical properties.[1,2] Several drugs (e.g., Lipitor, Tolmetin, Ketorolac, Sunitinib, Pyrivinium) contain pyrrole core. In this family, 2-aminopyrrole is a privileged medicinal template. Compounds containing this scaffold exhibit versatile biological activities.[3] The motif is also present in several natural products, e.g., Rigidins, Storniamide A, Lamellarin O, and biologically active compounds.[3,4] In addition, reactivity of 2-aminopyrrole as an amidine functional motif is frequently applied to synthesis of various pyrrole-fused heterocycles.[5,6,7]

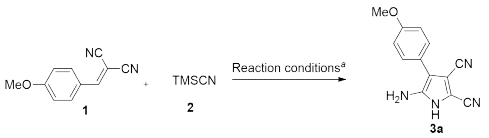
Conventional methods for synthesis of pyrroles are the Piloty-Robinson,[8] Knorr,[9] Paal–Knorr,[10] and Hantzsch[11] reactions. Significant development has been made in exploring different routes for construction of pyrrole skeleton.[12] For synthesis of *N*-substituted 2-aminopyrroles, various methods[13] including metal-catalyzed (Au, Au/Zn, Pd)[14] and isocyanide based reactions[15] have been reported. However, the synthesis of 2-aminopyrrole skeleton that possesses unsubstituted 2-amine as well as ring NH is rare.[16] On the other hand, these functionalities are important for further structural tune of compounds. 2-Amino-3*H*-pyrrole scaffold was prepared via a reaction of ketone and thiol with malononitrile as a source for dual role of 'CN'.[17] Obviously, a new direct approach for preparation of poly-substituted/functionalized 2-amino-NH-pyrrole core remains valuable.

The intramolecular cyclization via condensation of functional groups plays an excellent role in organic synthesis. For example, there are several popular conventional reactions for dicarbonyl-containing compounds. The important examples are cyclization of 1,4-dicarbonyl to form furan (Paal-Knorr),[10] reductive coupling to form alkene (McMurry),[18] pinacol coupling,[19] and acyloin[20] or benzoin condensation.[21] An intramolecular cyclization via [4+2]-cycloaddition based nitrile oxide dimerization to construct carbocyclic structure has been reported.[22]

Herein, we report a new approach for synthesis of 2-aminopyrroles via a strategic tandem process of the Michael addition to form *vic*-dinitrile and its intramolecular cyclization by a cyanide-mediated nitrile-to-nitrile condensation. The reaction constructs multiple C–C/N bonds and involves manifold C/N-nucleo- and electrophilic roles of nitrile. The compounds obtained are uniquely decorated with poly-substitutions/functionalities (amidine and 1,2-bis-nitrile). It is worth to mention that numerous drugs possess aromatic nitrile[23] and heterocyclic amidine that provides an interesting pattern of H-bond donor and acceptor interactions with enzyme or receptor and favourable physicochemical properties.[24]

We initiated investigation for a reaction of 2-(4-methoxybenzylidene)malononitrile with TMSCN.[25] Si-hypercoordination of TMSCN with a Lewis base generates a silicate intermediate that bears potential of releasing active cyanide nucleophile.[26] With this in mind, several organic and inorganic bases and other suitable agents as nucleophilic promoters for desilylation of TMSCN were evaluated (Table 1). Interestingly, our strategic reaction process provided the desired product in significant yields. Carbonates as effective promoters were previously reported.[27] In the present reaction, organic bases proved to be superior to inorganic bases

Table 1: Optimization study



#	Variable	Yield(%)[b]	#	Variable	Yield(%)[b]
	Base (2 equiv), Dioxane-H_2O[c], 95 °C				
1	Et_3N	54	8	Cs_2CO_3	46
2	DIPEA	55	9	TBAF	42
3	DMAP	48	10	KHF_2	40
4	DABCO	68	11	KF	55
5	DBU	90	12	K_3PO_4	45
6	Na_2CO_3	44	13	-	22
7	K_2CO_3	41			
	DBU (2 equiv), **Solvent**[c] (2 mL), 95 °C				
14[c]	Dioxane-H_2O	90	20	EtOH	38
15	Dioxane	68	21[c]	DMF-H_2O	83
16	Toluene	30	22[c]	MeCN-H_2O	88
17	DMF	58	23	H_2O	35
18	MeCN	62	24[c, d]	Dioxane-H_2O	85
19	^{t}BuOH	32	25[c,e]	Dioxane-H_2O	65

[a]Substrate, reagents and conditions: 2-(4-methoxybenzylidene)malononitrile **1** (1mmol), TMSCN (2 equiv); [b]yield for maximum conversion in optimum time; [c]organic solvent-H_2O (4:1; 1.6 and 0.4 mL) [d]DBU (1 equiv); [e]DBU (0.5 equiv).

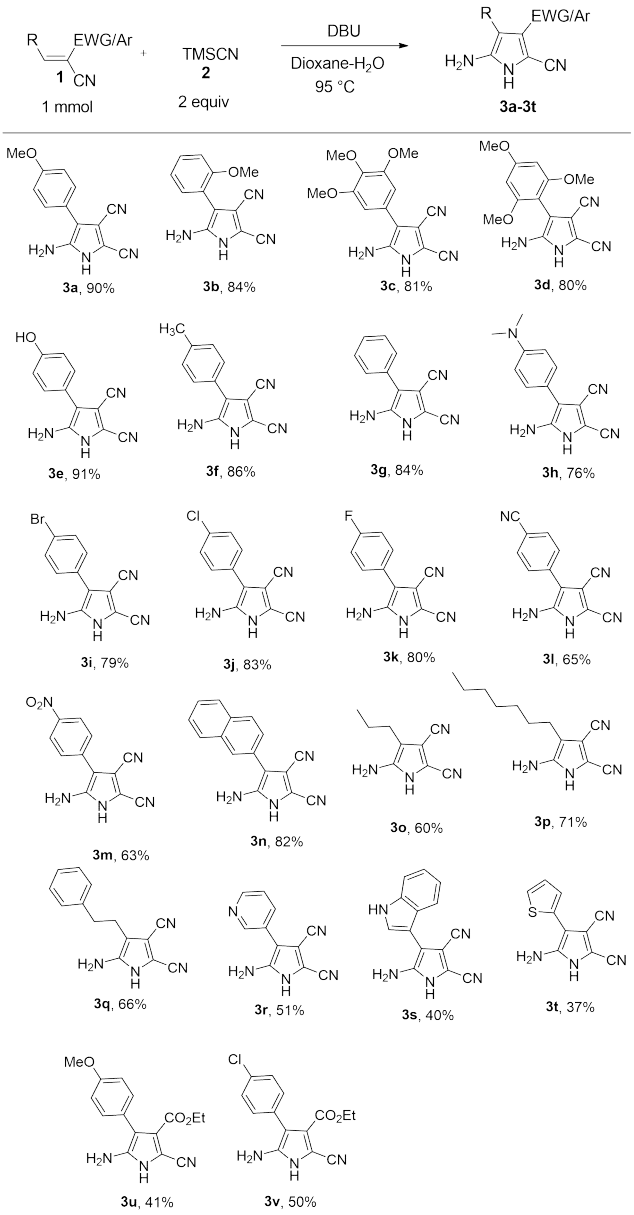
including carbonates. DBU was found to be most efficient providing product in 90% yield. DBU also accelerated the reaction rate. The reaction without base provided 20% yield of product. The efficient role of DBU in the reaction can be attributed to the unique silicon-philicity of its tertiary amidine-amine motif that possibly promotes effective release of cyanide ion from TMSCN.[27]

Various solvents were investigated. Dioxane, DMF and MeCN provided higher yields.[27] Dioxane-water was found to be most effective. Water plausibly acts as proton source[28] and induces H-bond-driven activation of functionalities.[29] Variation in volumetric ratio of dioxane and water solvents indicated that dioxane-water (4:1) was best. The use of water as exclusive solvent was detrimental for the reaction. Although highest yield (90%) was obtained with 2 equiv of DBU, the reaction with 1 equiv. DBU underwent smoothly without significant loss in yield (85%; entries 14 vs 24). Use of 0.5 equiv. DBU provided 65% yield (entry 25). These indicate a catalytic role of DBU involved in the present reaction.

We investigated also the efficiency of commonly used several other metal and non-metallic cyanating agents.[23,30] The reactions either did not undergo or were trace-to-moderate yielding; CuCN (0%), $Zn(CN)_2$ (0%), $K_4[Fe(CN)_6]$ (trace), pyruvonitrile (50%), benzoyl cyanide (10%), and ethyl cyanoformate (45%). These imply that TMSCN not only acts as cyanide-source but also plays additional role in the present reaction. Plausibly, silyl by-product generated from TMSCN acted as Lewis acid in electrophilic activation of substrate and intermediate.[25,26,28] The use of TMSCN as "CN" group-transfer reagent is well-known in numerous transformations, for example, cyanosilylation reactions of carbonyl,[31] imine (Strecker[32] and Reissert reaction),[33] aziridine,[34] oxirane,[35] and nitrone.[36] In the present reaction, TMSCN provides eventual multiple C–C/N bonds construction and produces poly-functionalized pyrroles. X-ray crystallography confirmed the molecular constitution of the product (See Fig S1, SI) identified by spectroscopies.

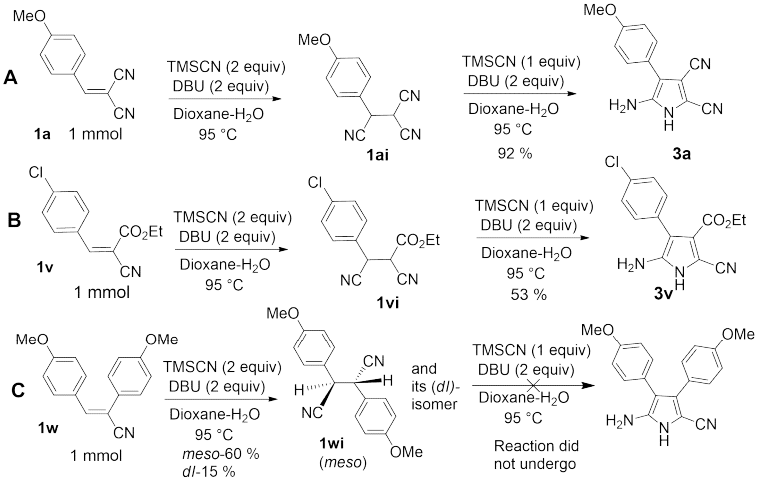
We next set out to explore the substrate scope of the developed method towards preparation of versatile tetrasubstituted 2-amino-NH-pyrroles. Alkylidene malononitrile substrates possessing various aryls, heteroaryls, alkyls and functionalities underwent the reaction with TMSCN (Table 2). The aryls with different electronic (electron-donating and withdrawing) and steric properties were compatible, though electron-withdrawing functionalities provided relatively low yields compared to electron-donating groups.

Table 2. Substrates scope: Synthesis of tetrasubstituted 2-amino-NH-pyrrole-nitriles [a,b]



[a]Substrate, reagents and conditions: *gem*-diactivated olefin 1(1 mmol), TMSCN (2 equiv), DBU (2 equiv), 1,4-Dioxane-H_2O (4:1; 1.6 and 0.4 mL), 95 °C, 1-3 h. [b]Isolated yield for maximum conversion in optimum time.

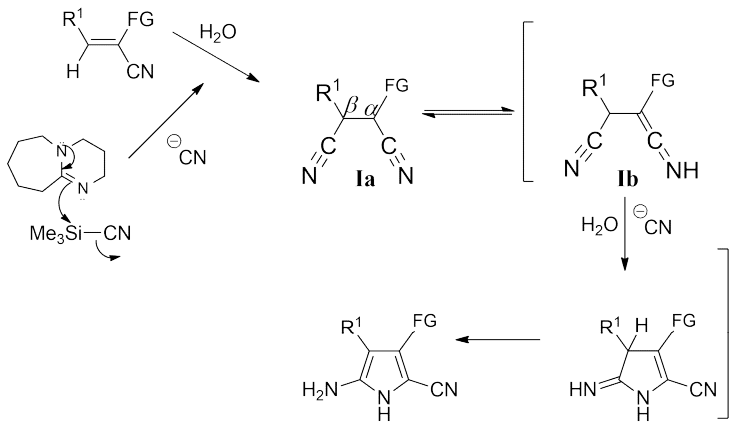
However, an enhanced conjugated benzylidenemalononitrile, derived from cinnamaldehyde and malononitrile, produced multiple non-isolable products. We investigated also other *gem*-diactivated olefins such as the olefins derived from cyanoacetate (**3u**-**3v**). The corresponding 2-amino-NH-pyrroles were obtained. Interestingly, the pyrrole-producing process occurred chemoselectively in the presence of ester functionality which is more reactive than nitrile.



Scheme 1. Isolation of *vic*-dinitrile intermediate and its use as substrate in the reaction

Performing the reaction at gram scale (6 mmol) did not cause significant decrease in yield (**3a**, 82%) of the product.

We were then interested to identify the possible mechanism. In the course of reaction of substrate **1a**, a product was isolated from the mixture obtained at intermediate time and found to be 2-(4-methoxyphenyl)ethane-1,1,2-tricarbonitrile (intermediate **1ai**, Scheme 1, See SI for data). The use of isolated intermediate (**1ai**) as substrate in the reaction with TMSCN (1 equiv) under identical conditions provided similar yield (92%) of the 2-aminopyrrole product **3a**. For substrate **1v** that possesses dissimilar functionality, an intermediate product was isolated and found to be *vic*-dinitrile **1vi (**Scheme 1). Use of intermediate **1vi** as substrate in separate reaction afforded product **3v** in similar yield (53%). The reaction of diarylacrylonitrile **1w** afforded the intermediates (**1wi** *meso* and *dl* isomers) (Scheme 1). However, further reaction of intermediates **1wi** as substrates towards formation of product did not undergo plausibly due to significant stability of the

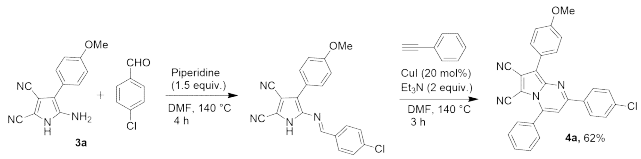


Scheme 2. Plausible mechanism

intermediates. Only interconversion between *meso* and *dl* isomers was observed.[37] These clearly indicate that the reaction undergoes via a pathway involving formation of the *vic*-dinitrile intermediate. A test by picric acid strip (color changed from yellow to brown) detected the presence of cyanide anion in the mixture during course of the reaction.[38] For the reaction of substrate **1a** to produce 2-aminopyrrole **3a**, separate experiments using TMSCN of 1 and 2 equiv. provided the product in 44% and 90% yields, respectively. This indicates that the reaction pathway is associated with involvement of 2 equiv. TMSCN. Based on all these results and incongruent to the literature,[26] a plausible mechanism has been proposed (Scheme 2). It involves DBU-promoted cyano release from TMSCN, Michael addition to acrylonitrile, intramolecular cyclization via cyanide-mediated condensation of nitriles, and aromatization-driven 1,3-prototropic shift. High regioselectivity obtained in this protocol can be attributed to relative higher acidity of α-hydrogen than β-hydrogen, which provides regioselectively ketenimine **1b.** An additional controlled experiment revealed interesting observation. The reaction of Michael adduct intermediate **1ai** with DBU in the absence of TMSCN results in formation of product 2-amino-5-cyanopyrrole **3a**, but in much lowered yield (11%). Interestingly, substrate **1a** was also produced in 10% yield in the reaction. On the other hand, the reaction of the intermediate **1ai** in presence of both DBU and TMSCN (identical conditions to optimized method) produces desired 2-amino-5-cyanopyrrole **3a** in 92% yield, which is similar to yield (90%, Table 2) obtained in optimized method and, moreover, substrate **1a** was not produced. These clearly indicate that an alternate pathway takes place for the conversion of intermediate **1ai** to product **3a** in the absence of TMSCN (See details in SI, Scheme-S1). It is worth to note that the reaction pathway of the established approach provides a unique feature of incorporating in the product skeleton a ring-amidine and an aromatic nitrile which is generally accomplished by transition-metal-catalyzed cyanation.

We investigated also to find further an exemplary extended synthetic utility of our developed approach. The product **3a** in a reaction[39] with aldehyde and alkyne produces pyrrole-fused

pyrimidine scaffold **4a** that contains multiple substitutions/functionalities (Scheme 3). Remarkably, the synthesis of pyrrole-fused pyrimidines is important. The compounds containing this skeleton have been found to display various biological activities.[40]



Scheme 3. Extended application: Synthesis of pyrrole-fused pyrimidine skeleton

In conclusion, we have discovered the synthesis of tetra-substituted/functionalized 2-amino-NH-pyrroles via a new reaction of *gem*-diactivated acrylonitrile with TMSCN. The approach involves a strategic utilization of Michael addition and an unprecedented cyanide-mediated nitrile-to-nitrile condensation, which construct amidine and aromatic nitrile in the product skeleton. The developed protocol is chemoselective, provides moderate to excellent yields of products, and uses easily accessible starting materials. The pyrrole-products possess multiple functional motifs and have potential in applications to numerous structural tunes.

EXPERIMENTAL SECTION

General Information: Infrared (IR) spectra were recorded on a Perkin Elmer FTIR with ATR & IR Microscope spectrometer. ^{1}H NMR spectra were measured on a Bruker Avance III-400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$/CD_3OD/DMSO-d_6/D_2O integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, td = triplet of doublet, dt = doublet of triplet, br = broad), and coupling constants (Hz). ^{13}C NMR spectra were measured on a Bruker Avance III-400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-resolution mass spectra (HRMS) were performed on Bruker maxis Q-TOF. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel

60 GF254, 0.25 mm) were used. The products were purified by column chromatography silica gel 100-200 (Merck, silica gel 100-200 mesh, neutral, spherical).

All commercially obtained reagents were used as received.

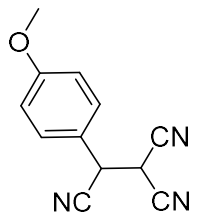
gem-diactivated olefins were prepared following the literature known methods.[41]

Representative experimental procedure for synthesis of 2-Amino-3-(4-methoxyphenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3a, Table 2): To 2-(4-methoxybenzylidene)malononitrile (1 mmol, 184 mg), taken in a sealed tube were added solvent Dioxane-H_2O (1.6 mL and 0.4 mL, respectively) and DBU (1 mmol, 0.3 mL). The mixture was cooled to 0°C and TMSCN (1 mmol, 0.25 mL) was added. The tube was sealed. The reaction mixture was then stirred at 95 °C. The progress of the reaction was monitored by TLC. After completion of the reaction conversion, the resultant mixture was then concentrated by rotary evapourator under vacuum. The column chromatographic purification of crude mass was performed on silica gel (mesh 100-200) partially deacidified by passing triethylamine (1-2 mL) using EtOAc-hexane (50%) as eluting solvent. The product 2-Amino-3-(4-methoxyphenyl)-1*H*-pyrrole-4,5-dicarbonitrile (**3a**) was isolated (214 mg, 90% yield).

Other products (**3b-v**, Table 2) were also prepared following this representative procedure.

Characterization Data for Intermediates (1ai, 1vi, 1wi, Scheme 1)

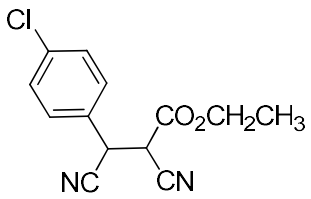
2-(4-methoxyphenyl)ethane-1,1,2-tricarbonitrile (1ai, Scheme 1)



Off white solid, 89 mg, 42%, m.p. 90-92 °C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 5.77 (d, J = 6.2 Hz, 1H) 5.46 (d, J = 6.16 Hz, 1H), 3.79 (s, 3H) ^{13}C{^{1}H}NMR

(100 MHz, DMSO-d_6): δ 160.3, 129.6, 121.6, 117.0, 114.8, 111.8, 55.3, 36.0, 28.9; IR: υ_{max} 3434, 2943, 2168, 2103, 1650, 1325, 693 cm^{-1}; MS (ESI) *m/z*: calcd. for $C_{12}H_9N_3ONa$ $[M+Na]^+$ 238.0, found: 234.0.

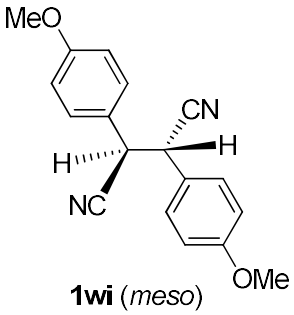
(erythro+threo) Ethyl 3-(4-chlorophenyl)-2,3-dicyanopropanoate (1vi, Scheme 1):



Pale yellow liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 8H), 4.60 (d, J = 5.1 Hz, 1H), 4.55 (d, J = 6.4 Hz, 1H), 4.41-4.29 (m, 4H), 4.12 (d, J = 6.4 Hz, 1H), 3.89 (d, J = 5.1 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, CDCl3): δ 162.4, 162.3, 136.4, 136.2, 129.9, 129.8, 129.8, 129.3, 128.9, 128.3, 116.6, 115.9, 112.6, 112.6, 64.4, 64.4, 43.6, 42.9, 37.1, 35.4, 13.9, 13.9 ppm; IR: υmax 3468, 2939, 2252, 1745, 1494, 1016, 835 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{11}ClN_2O_2Na$ $[M+Na]^+$ 285.0407, found:285.0398.

2,3-bis(4-Methoxyphenyl)buta-1,3-diene-1,4-diimine (1wi, Scheme 1):

***meso* form:**

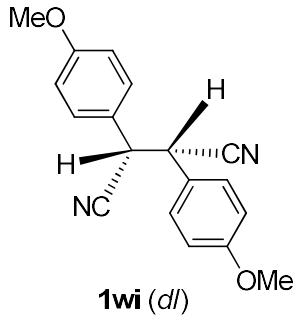


1wi (*meso*)

Peach solid, 175 mg, 60%, m.p. >200 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 7.30 (d, J = 8.0 Hz, 4H), 6.99 (d, J = 8.0 Hz, 4H), 5.01 (s, 2H), 3.77 (s, 6H) ppm; $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6): δ 160.0,

130.2, 124.6, 119.2, 114.7, 55.6 ppm; IR: υmax 3444, 2996, 2839, 2246, 1614, 1515, 1251, 1178, 1030, 821 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{16}N_2O_2Na$ $[M+Na]^+$ 315.1110, found: 315.1107.

***dl* Isomer:**

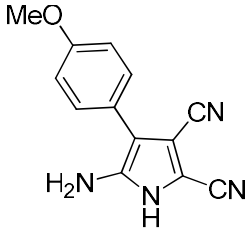


1wi (*dl*)

White solid, 44 mg, 15%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (d, J = 8.7 Hz, 4H), 7.30 (d, J = 8.6 Hz, 4H), 6.99 (d, J = 4.2 Hz, 8H), 6.97 (s, 4H), 5.01 (s, 2H), 5.00 (s, 2H), 3.77 (s, 6H), 3.76 (s, 6H) ppm; ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6): δ 160.0, 159.9, 130.2, 129.9, 124.6, 124.5, 119.2, 119.1, 114.7, 55.6, 41.1 ppm; IR: υmax 3398, 2969, 2839, 2245, 1614, 1515, 1250, 1032, 821 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{16}N_2O_2Na$ $[M+Na]^+$ 315.1110, found: 315.1102.

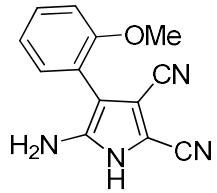
Characterization data for polysubstituted 2-aminopyrroles (Compound 3a-v, Table 2)

2-Amino-3-(4-methoxyphenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3a, Table 2):



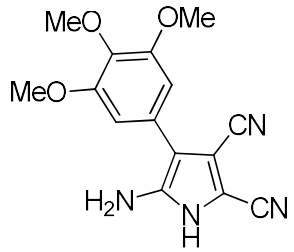
Dark brown solid, 214 mg, 90%, m.p. 184-186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 5.64 (s, 2H), 3.77 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.6, 141.3, 129.4, 124.1, 115.1, 114.9, 113.8, 107.1, 101.7, 97.4, 55.6 ppm; IR: υ_{max} 3350, 2208, 1634, 1247, 1177 cm-^{1}; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{10}N_4ONa$ $[M+Na]^+$ 261.0753, found: 261.0746.

2-Amino-3-(2-methoxyphenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3b, Table 2):



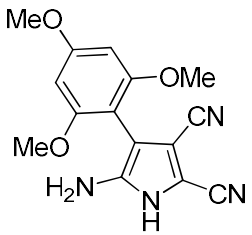
Brown solid, 200 mg, 84%, m.p. 144-146 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (dt, J = 8.1 Hz, J = 1.7 Hz, 1H), 7.24 (dd, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.09 (d, J = 7.9 Hz, 1H), 7.00 (dt, J = 7.4 Hz, J = 0.8 Hz, 1H), 5.42 (s, 2H), 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 142.4, 131.0, 129.3, 121.0, 120.3, 115.1, 114.2, 111.9, 104.3, 103.3, 97.9, 55.7 ppm; IR: υ_{max} 3408, 3334, 3235, 2231, 2206, 1260, 1015cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{11}N_4O$ $[M+H]^+$ 239.0933, found: 239.0925.

2-Amino-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3c, Table 2):



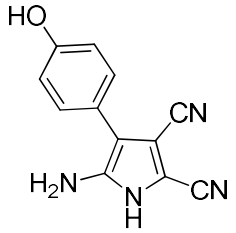
Dark brown solid, 241 mg, 81%, m.p. 85-87 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.69 (s, 2H), 3.80 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.5, 141.8, 136.7, 127.5, 115.2, 113.8, 107.0, 105.3, 101.7, 97.9, 60.5, 56.2 ppm; IR: υ_{max} 3338, 2209, 1598, 1128, 735 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{15}H_{15}N_4O_3$ $[M+H]^+$ 299.1144, found: 299.1141.

2-Amino-3-(2,4,6-trimethoxyphenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3d, Table 2):



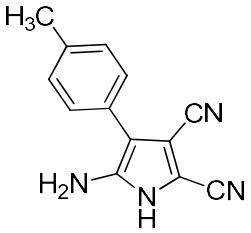
Dark brown solid, 238 mg, 80%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H), 6.29 (s, 2H), 5.14 (s, 2H), 3.82 (s, 3H), 3.73 (s, 6H) ppm; ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6): δ 161.5, 159.0, 142.4, 115.0, 114.1, 105.2, 100.5, 100.4, 96.1, 91.3, 55.9, 55.7 ppm; IR: υmax 3426, 3346, 2229, 2207, 1630, 1275, 1109 cm^{-1}. HRMS (ESI) *m/z*: calcd. for $C_{15}H_{15}N_4O_3$ $[M+H]^+$ 299.1144, found: 299.1146.

2-Amino-3-(4-hydroxyphenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3e, Table 2):



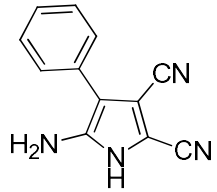
Red solid, 204 mg, 91%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.56 (s, 1H), 7.22 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.59 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 141.2, 129.4, 122.5, 116.2, 115.2, 113.9, 107.6, 101.6, 97.2 ppm; IR: υ_{max} 3390, 3350, 2209, 1627, 1249 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_9N_4O$ $[M+Na]^+$ 247.0596, found: 247.0583.

2-Amino-3-(p-tolyl)-1*H*-pyrrole-4,5-dicarbonitrile (3f, Table 2):



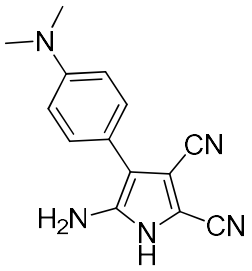
Brown solid, 191 mg, 86%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (s, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 5.75 (s, 2H), 2.33 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.5, 136.4, 129.9, 128.9, 127.9, 115.0, 113.7, 106.9, 101.7, 97.7, 21.2 ppm; IR: υ_{max} 3443, 3334, 3224, 2237, 2208, 1628, 1286 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{10}N_4Na$ $[M+Na]^+$ 245.0803, found: 245.0801.

2-Amino-3-phenyl-1*H*-pyrrole-4,5-dicarbonitrile (3g, Table 2):



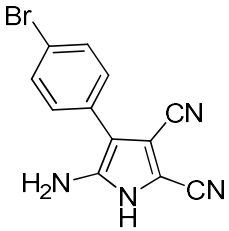
Brown solid, 175 mg, 84%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.22 (s, 1H), 7.44-7.31 (m, 5H), 5.82 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.6, 131.9, 129.3, 127.9, 127.1, 115.0, 113.6, 106.7, 101.7, 98.0 ppm; IR: υ_{max} 3404, 3330, 3248, 2229, 2215, 1638, 1276 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_8N_4Na$ $[M+Na]^+$ 231.0647, found: 231.0646.

2-Amino-3-(4-(dimethylamino)phenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3h, Table 2):



Dark brown solid, 191 mg, 76%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 5.55 (s, 2H), 2.92 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.9, 139.9, 128.3, 119.4, 114.1, 112.9, 112.5, 108.8, 101.6, 97.0, 39.4 ppm; IR: υ_{max} 3478, 3386, 3250, 2229, 2212, 1613 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{14}N_5$ $[M+H]^+$ 252.1249, found: 252.1249.

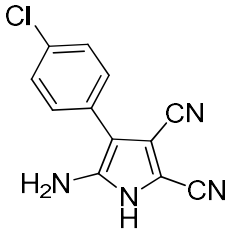
2-Amino-3-(4-bromophenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3i, Table 2):



Dark brown solid, 225 mg, 79%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 5.91 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.8,

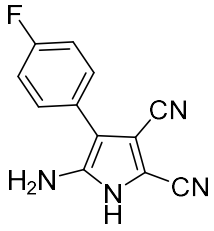
132.3, 131.2, 130.0, 120.0, 114.8, 113.5, 105.3, 101.6, 98.3 ppm; IR: υ_{max} 3468, 3379, 3241, 2233, 2208, 1618, 1267, 750 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_7BrN_4Na$ $[M+Na]^+$ 308.9752, found: 308.9749.

2-Amino-3-(4-chlorophenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3j, Table 2):



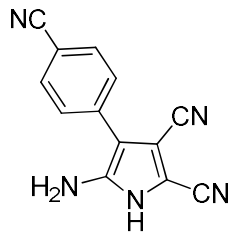
Dark red solid, 200 mg, 83%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 5.91 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.8, 131.5, 130.8, 129.7, 129.3, 114.8, 113.5, 105.3, 101.7, 98.3 ppm; IR: υ_{max} 3470, 3388, 3243, 2221, 2208, 1623, 1269, 827 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_7ClN_4Na$ $[M+Na]^+$ 265.0257, found: 265.0249.

2-Amino-3-(4-fluorophenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3k, Table 2):



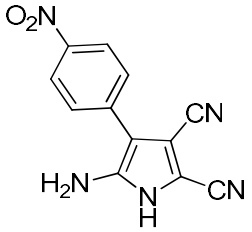
Light brown solid, 181 mg, 80%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.25 (s, 1H), 7.47-7.44 (m, 2H), 7.28 (dd, J = 8.8 Hz, J = 8.8 Hz, 2H), 5.82 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.3 (d, $J_{C\text{-}F}$ = 242 Hz), 141.6, 130.1 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8 Hz), 128.3 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3 Hz), 116.2 (d, $J_{C\text{-}C\text{-}F}$ = 22 Hz), 114.9, 113.5, 105.8, 101.8, 97.8 ppm; IR: υ_{max} 3450, 3353, 2215, 1624, 1217 cm^{-1}. HRMS (ESI) *m/z*: calcd. for $C_{12}H_8FN_4$ $[M+H]^+$ 227.0733, found: 227.0726

2-Amino-3-(4-cyanophenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3l, Table 2):



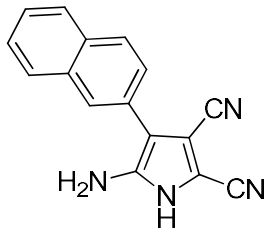
Dark brown solid, 151 mg, 65%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.92 (s, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 6.83 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.1, 135.7, 134.2, 133.4, 128.5, 119.0, 116.1, 114.8, 111.4, 91.4, 72.5 ppm; IR: υ_{max} 3437, 3348, 3226, 2208, 1636, 1247 cm^{-1}. HRMS (ESI) *m/z*: calcd. for $C_{13}H_8N_5$ $[M+H]^+$ 234.0780, found: 234.0787.

2-Amino-3-(4-nitrophenyl)-1*H*-pyrrole-4,5-dicarbonitrile (3m, Table 2):



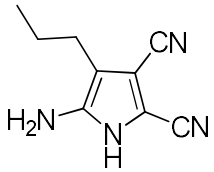
Red solid, 160 mg, 63%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.39 (d, J = 7.6 Hz, 2H), 7.99 (d, J = 7.6 Hz, 2H), 6.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.0, 147.6, 136.9, 134.8, 127.4, 124.9, 115.5, 114.3, 87.0, 81.3 ppm; IR: υ_{max} 3450, 3363, 3252, 2206, 1637, 1341, 1270 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{12}H_7N_5O_2Na$ $[M+Na]^+$ 276.0498, found: 276.0493.

2-Amino-3-(naphthalen-2-yl)-1*H*-pyrrole-4,5-dicarbonitrile (3n, Table 2):



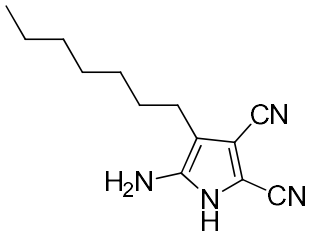
Buff solid, 211 mg, 82%, m.p. 145-147 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00-7.95 (m, 1H), 7.68-7.66 (m, 1H), 7.59-7.52 (m, 3H), 7.44 (dd, J = 7.0 Hz, J = 0.8 Hz, 1H), 5.46 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.4, 134.0, 131.9, 129.2, 128.9, 128.8, 126.9, 126.6, 126.2, 125.7, 114.7, 113.8, 105.4, 104.1, 97.5 ppm; IR: υ_{max} 3445, 3352, 3231, 2234, 2208, 1620, 1276 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{10}N_4Na$ $[M+Na]^+$ 281.0803, found: 281.0797.

2-Amino-3-propyl-1*H*-pyrrole-4,5-dicarbonitrile (3o, Table 2):



Dark brown solid, 104 mg, 60%, m.p. 163-165 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 4.06 (s, 2H), 2.34 (t, J = 7.3 Hz, 2H), 1.49-1.40 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.7, 114.7, 113.9, 107.2, 103.1, 94.9, 25.4, 23.1, 13.7 ppm; IR: υ_{max} 3449, 3360, 2238, 2202, 1624, 1274 cm^{-1}. HRMS (ESI) *m/z*: calcd. for $C_9H_{11}N_4$ $[M+H]^+$ 175.0984, found: 175.0980.

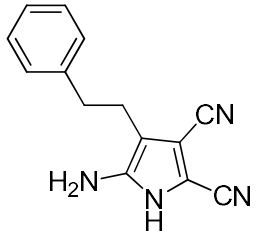
5-Amino-4-heptyl-1*H*-pyrrole-2,3-dicarbonitrile (3p, Table 2):



Dark brown solid, 164 mg, 71%, m.p. 112-114 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 11.90 (s,1H), 5.53 (s, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.46-1.41 (m, 2H), 1.24 (s, 8H), 0.85 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.9, 114.8, 114.1, 107.4, 103.0, 95.0, 31.7, 29.8, 28.9, 28.8, 23.4, 22.5, 14.4

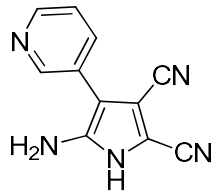
ppm; IR: υ_{max} 3350, 2924, 2206, 1595, 1496, 1275, 1082, 750 cm^{-1}. MS (ESI) calcd. for $C_{13}H_{19}N_4$ $[M+H]^+$ 231.1, found: 231.1.

5-Amino-4-phenethyl-1H-pyrrole-2,3-dicarbonitrile (3q, Table 2):



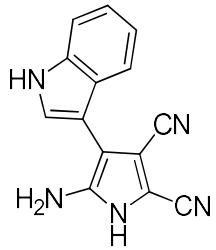
Light brown solid, 155 mg, 66%, m.p. 123-125 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 11.91 (s, 1H), 7.29-7.25(m, 2H), 7.21-7.18 (m, 3H) 5.62 (s, 2H), 2.74-2.70 (m, 2H), 2.67-2.63 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.0, 141.4, 128.8, 128.6, 126.4, 114.6, 114.0, 106.4, 103.2, 95.1, 35.7, 25.7 ppm; IR: υ_{max} 3347, 2209, 1626, 1500, 1416, 1287, 1080, 702 cm^{-1}. MS (ESI) calcd. for $C_{14}H_{12}N_4Na$ $[M+Na]^+$ 259.0, found: 259.0.

2-Amino-3-(pyridin-3-yl)-1*H*-pyrrole-4,5-dicarbonitrile (3r, Table 2):



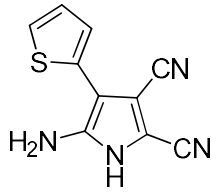
Pale white solid, 106 mg, 51%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.74 (d, J = 1.8 Hz, 1H), 8.62 (dd, J = 4.8 Hz, J = 1.4 Hz, 1H), 7.95 (dt, J = 4.9 Hz, J = 1.8 Hz), 7.55 (dd, J = 7.9 Hz, J = 4.8 Hz, 1H), 6.78 (s, 2H) ppm; ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6): δ 150.9, 149.9, 148.2, 135.4, 133.1, 127.3, 124.5, 116.2, 114.9, 91.1, 72.8 ppm; IR: υmax 3406, 3335, 3218, 2204, 1646, 1540, 1254 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{11}H_8N_5$ $[M+H]^+$ 210.0779, found: 210.0777.

2-Amino-3-(1*H*-indol-3-yl)-1*H*-pyrrole-4,5-dicarbonitrile (3s, Table 2):



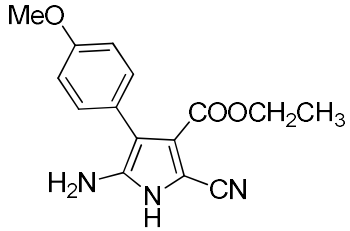
Black solid, 99 mg, 40%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (s, 1H), 7.48-7.41 (m, 3H), 7.14 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 7.9 Hz, 1H), 5.45 (s, 2H), 4.47 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.9, 136.6, 126.4, 124.9, 121.9, 119.8, 112.2, 105.1, 63.2 ppm; IR: υ_{max} 2924, 2215, 1713, 1462, 804 cm^{-1}.MS (ESI) *m/z*: calcd. for $C_{14}H_9N_5Na$ $[M+Na]^+$ 270.0, found: 270.0.

2-Amino-3-(thiophen-2-yl)-1*H*-pyrrole-4,5-dicarbonitrile (3t, Table 2):



Black solid, 79 mg, 37%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H), 7.61 (d, J = 5.0 Hz, 1H), 7.44 (d, J = 3.6 Hz, 1H), 7.16 (t, J = 3.9 Hz, 1H), 6.67 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.9, 132.1, 129.7, 128.4, 127.3, 126.5, 116.4, 115.2, 89.8, 72.1 ppm; IR: υ_{max} 3333, 2199, 1613 cm^{-1}. MS (ESI) calcd. for $C_{10}H_6N_4SNa$ $[M+Na]^+$ 237.0, found: 237.0.

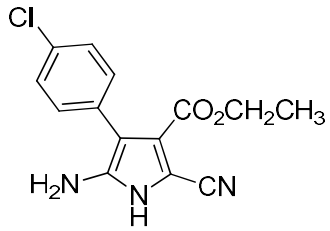
Ethyl 2-amino-5-cyano-3-(4-methoxyphenyl)-1*H*-pyrrole-4-carboxylate (3u, Table 2):



Light orange solid, 117 mg, 41%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.04 (s, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 1.10 (t,

7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8, 158.1, 141.4, 131.6, 125.6, 122.2, 115.3, 113.8, 106.1, 94.7, 60.2, 55.5, 14.3 ppm; IR: υ_{max} 3215, 2926, 2201, 1717, 1658, 1275, 1175 cm^{-1}. HRMS (ESI) *m/z*: calcd. for $C_{15}H_{16}N_3O_3$ $[M+H]^+$ 286.1192, found: 286.1188.

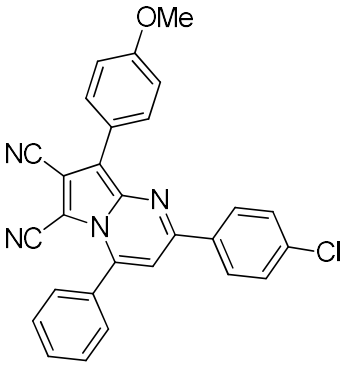
Ethyl 2-amino-3-(4-chlorophenyl)-5-cyano-1*H*-pyrrole-4-carboxylate (3v, Table 2):



Light orange solid, 115 mg, 40%, m.p. >200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.24 (s, 2H), 4.09 (q, J = 7.1, 2H), 1.11 (t, J = 7.1, 2H) ppm; ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6): δ 162.14, 141.26, 131.96, 131.76, 130.54, 127.71, 121.56, 114.57, 104.23, 94.89, 59.83, 13.71 ppm; IR: υmax 3475, 3377, 2211, 1663, 1614, 1508, 1310, 1220, 835, 701 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{12}ClN_3O_2Na$ $[M+Na]^+$ 312.0516, found: 312.0506.

Characterization Data for 2-(4-chlorophenyl)-8-(4-methoxyphenyl)-4-phenylpyrrolo[1,2-a]pyrimidine-6,7-dicarbonitrile (4a, Scheme 3)

2-(4-chlorophenyl)-8-(4-methoxyphenyl)-4-phenylpyrrolo[1,2-a]pyrimidine-6,7-dicarbonitrile (4a, Scheme 3)



Yellow solid, 142 mg, 62%, m.p. >200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.6 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H), 7.74 (dd, J = 7.3, 7.3 Hz, 1H), 7.67 (dd, J = 7.7, 7.3 Hz, 2H), 7.61 (d, J = 7.3 Hz,

2H), 7.52 (d, J = 8.6 Hz, 2H), 7.35 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 3.93(s, 3H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 154.3, 146.7, 139.8, 137.7, 134.2, 132.2, 130.2, 130.1, 129.5, 129.3, 129.1, 128.5, 122.3, 119.2, 114.4, 113.3, 109.8, 109.5, 108.3, 96.7, 55.4 ppm; IR: υ_{max} 2956, 2839, 2250, 2208, 1618, 1459, 1275, 1260, 750 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{28}H_{18}Cl^{35}N_4O$ $[M+H]^+$ 461.1169, found: 461.1184.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystal details for compound **3f** and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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