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Microwave-assisted preparation of 4-amino-3-cyano-5-methoxycarbonyl-*N*-arylpyrazoles as building blocks for the diversity-oriented synthesis of pyrazole-based polycyclic scaffolds

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INTRODUCTION

N-arylpyrazoles represent a class of heterocyclic compounds of significant importance for the agrochemical and pharmaceutical industries.[1] As selected examples, Celecoxib,[2] Rimonabant,[3] Doramapimod[4] and PNU-32945[5] are marketed-drugs or drug-candidates (Figure 1). They interact with major therapeutical targets such as cyclooxygenase 2 (COX-2), cannabinoid receptor type 1 (CB_1), p38α MAP-kinase or HIV-reverse transcriptase, respectively.

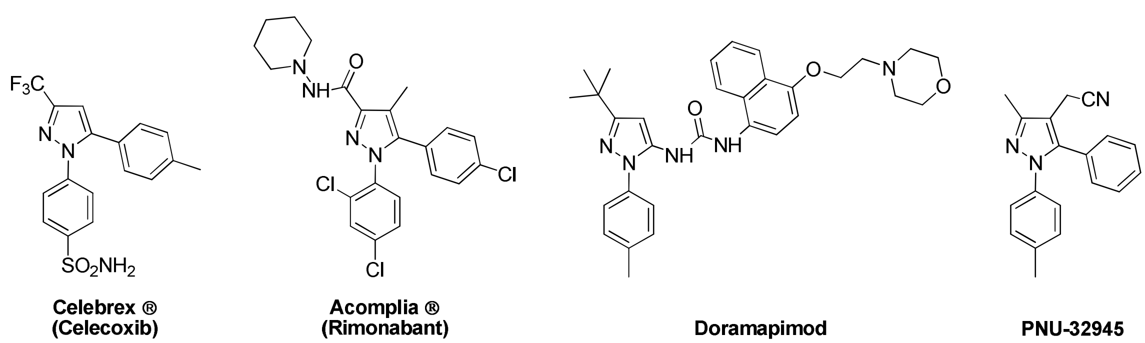
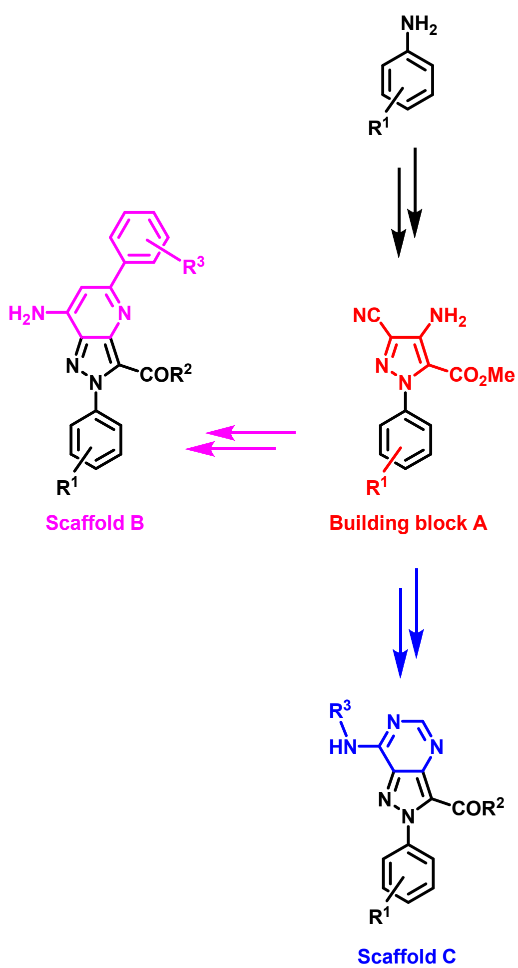


Figure 1. Selected examples of therapeutically relevant *N*-aryl-pyrazoles

From a synthetic point of view, aminopyrazole derivatives are also considered as extremely versatile building blocks to further elaborate bicyclic fused ring compounds, mostly [5.6] systems.[6] Much attention has been paid to the 3- or 5-amino-pyrazoles for the preparation of pyrazolo[1,5-*a*]pyrimidine or pyrazolo[3,4-*b*]pyridine due to their interesting biological activities, especially in the field of anticancer agents.[7-9]

In the course of our research program dedicated to the design of kinase inhibitors,[10-12] we became interested in developing series of bicyclic heteroaromatics bearing a 4-amino-*N*-arylpyrazole moiety for the sake of biological activity. Prompted by the desire of readily exploring the chemical space within the studied bioactive region, we turned our attention to a diversity-oriented synthesis strategy (Scheme 1). Since the introduction of the DOS concept in 2000, this kind of strategy is very attractive and efficient for drug discovery programs.[13, 14]

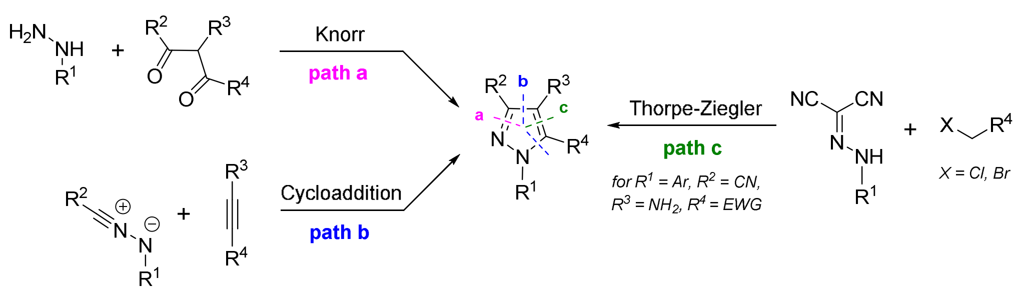


Scheme 1. Diversity-oriented synthesis of pyrazole-based scaffolds described herein

To this purpose, we focused on the synthesis of tetrasubstituted pyrazoles (TPs) bearing three different functionalities: nitrile, ester and amine. We thus report herein our results concerning the straightforward microwave activated synthesis of 4-amino-3-cyano-5-methoxycarbonyl-*N*-arylpyrazoles and the scope of their use for the diversity-oriented synthesis of various heterocyclic platforms.

RESULTS AND DISCUSSION

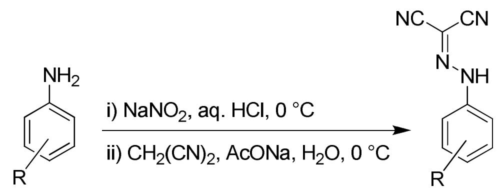
Several methods exist for the synthesis of TPs (Scheme 2).[15] Condensation of 1,3-diketone with hydrazine derivatives, known as Knorr reaction (path a, Scheme 2)[16-18] or 1,3-dipolar cycloaddition of nitrile imines with alkynes (path b, Scheme 2)[19-21] are the most popular methods. In the particular case of 4-amino-3-cyano-*N*-arylpyrazoles (R^2 = CN, R^3 = NH_2, R^4 = EWG), the access to the pyrazole ring involves a Thorpe-Ziegler cyclization[22] of dicyanohydrazone intermediates with activated methylene reagents (path c, Scheme 2).[23-26] Although this latter strategy appears highly attractive, very few examples were reported and, due to the poor yields observed, its scope has never been fully explored. Our first goal was therefore to re-investigate this Thorpe-Ziegler reaction in order to develop a general and efficient method allowing the access to the targeted 4-amino-3-cyano-*N*-arylpyrazoles.



Scheme 2. Main pathways for the synthesis of TPs

To start our study, a small library of dicyanohydrazones **2a-p** had to be prepared. Commercially available anilines **1a-o** bearing substituents such as benzyloxy, alkynyl, *tert*-butyl ester, bromide and nitro were chosen as substrates in order to allow subsequent functionalization. The 2,6-dichloro-3-methoxyaniline **1p** was prepared in 96% overall yield.[27] According to a standard procedure,[28] diazotization of the anilines **1a-p** with sodium nitrite in aqueous hydrochloric acid, followed by condensation with malononitrile in basic medium afforded the corresponding dicyanohydrazones **2a-p** in good to excellent yields (Table 1).

Table 1. Scope of the access to dicyanohydrazones



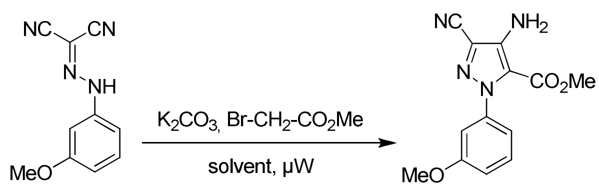
Entry	R	Product[a]	Yield[b] (%)
1	H	**2a**	99
2	2-OBn	**2b**	89
3	2-Br	**2c**	95
4	2-C≡CH	**2d**	60
5	2-NO_2	**2e**	88
6	3-OBn	**2f**	98
7	3-Br	**2g**	99[c]
8	3-CO_2*t*Bu	**2h**	92
9	3-C≡CH	**2i**	93
10	3-MeO	**2j**	91[c]
11	3-NO_2	**2k**	87
12	4-Br	**2l**	91
13	4-CO_2*t*Bu	**2m**	78
14	4-C≡CH	**2n**	86
15	4-NO_2	**2o**	98
16	2,6-di-Cl,3-OMe	**2p**	67

[a] Reaction conditions: ***i)*** aniline **1** (1 equiv.), 37% aq. HCl (11 equiv.), 1 M aq. $NaNO_2$ (1 equiv.), 0 °C, 30 min; ***ii)*** $CH_2(CN)_2$ (1.5 equiv.), AcONa (31 equiv.), H_2O, 0 °C, 2 h. [b] Yield of isolated product. [c] Versus 30% and 36% yield reported in the literature for **2g** and **2j** respectively.[24]

These experimental conditions proved to be highly efficient with both electron-withdrawing and electron-donating R substituents, either positioned in ortho, meta or para, leading to a library of 16 dicyanohydrazones with a half of original structures (entries 2, 4, 6, 8, 9, 13, 14 and 16, Table 1).

Having these dicyanohydrazones in hand, the study of the Thorpe-Ziegler reaction was undertaken using compound **2j** as a model substrate. According to previous reports, cyclization occurs with activated methylene reagents (ethyl or methyl bromoacetate, chloroacetonitrile) under basic conditions (K_2CO_3, TEA) in DMF at 90 °C within 6-7 h to give the corresponding aminopyrazole in 22-80% yield.[23-26] Recently, phase-transfer conditions were used to improve the yield and shorten the reaction time to 2-2.5 h.[29] With the same objective, we were wondering whether this Thorpe-Ziegler cyclization could be further optimized owing to microwave activation (Table 2). It is now well established that microwaves can greatly speed up reactions, thus lowering any possible degradation, and consequently improve the overall yield.[30, 31] As a blank experiment, compound **2j** was reacted under standard thermal conditions[24] at 100 °C with methyl bromoacetate (2.5 equiv.) and K_2CO_3 (2.7 equiv.) in DMF, affording after 5 h the desired cyclized product **3j** in a limited yield of 33% (entry 1, Table 2). Any attempt to optimize the reaction conditions by varying the base (DIPEA, Cs_2CO_3), the solvent (dioxane, MeCN, toluene), the temperature or the amount of bromoacetate failed to raise the yield. Microwave irradiation (open vessel mode, 90 W, 120 °C) was next studied, varying both the solvent and the amount of methyl bromoacetate (entries 2-9, Table 2).

Table 2. Optimization of the Thorpe-Ziegler cyclization[a]

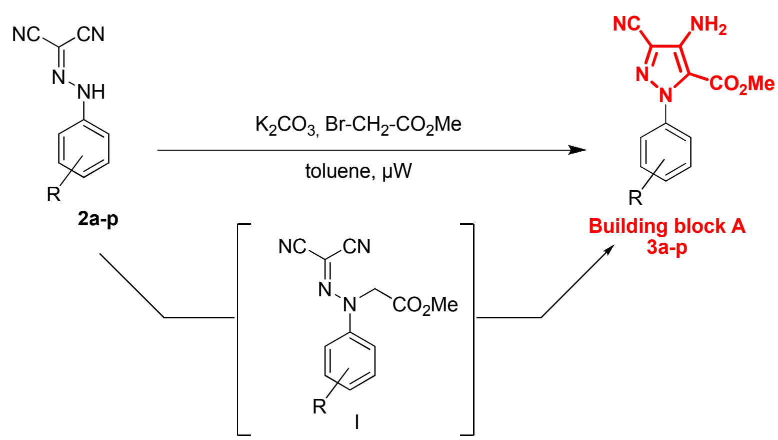


Entry	methyl bromoacetate (equiv.)	Solvent	Time	Yield[b] (%)
1	2.5	DMF	5 h	33[c]
2	2.5	DMF	10 min	53
3	5	DMF	10 min	25
4	1.5	toluene	1 h	41
5	5	toluene	30 min	32
6	7.5	toluene	10 min	80
7	8.5	toluene	10 min	80
8	5	dioxane	10 min	52
9	7.5	dioxane	10 min	67

[a] Reaction conditions: hydrazone **2j** (1 equiv.), K_2CO_3 (2.7 equiv.), Br-CH_2-CO_2Me, solvent, µW 90 W, 120 °C. [b] Yield of isolated product. [c] The reaction was performed at 110 °C without any µW activation.

The use of microwaves proved to be efficient, allowing the formation of the desired product **3j** in 53% yield within a reaction time of 10 min, leading to a 20% increase of the yield associated with a 24 fold decrease of the reaction time (entry 2 vs 1, Table 2). In DMF, using 5 equiv. of methyl bromoacetate led to sidereactions that lowered the yield of the desired product (25%, entry 3, Table 2). It was therefore decided to switch for apolar solvents such as toluene or dioxane which are known to be transparent to μW irradiation. In toluene, starting with 1.5 or 5 equiv. of methyl bromoacetate required much longer time to reach complete conversion (1 h and 30 min respectively, entries 4-5, Table 2). Nevertheless, raising its amount up to 7.5 or 8.5 equiv. afforded within 10 min the cyclized product **3j** in a very good 80% yield (entries 6-7, Table 2). In dioxane, repeating the trials with 5 and 7.5 equiv. resulted in a significant decrease of the yield (52% and 67% respectively, entries 8-9, Table 2). The best conditions appeared thus to be the use of 7.5 equiv. of bromoester in toluene (entry 6, Table 2) and consequently, they were selected to further examine the scope of the reaction.

Table 3. Scope of the microwave-assisted cyclization: access to building block A



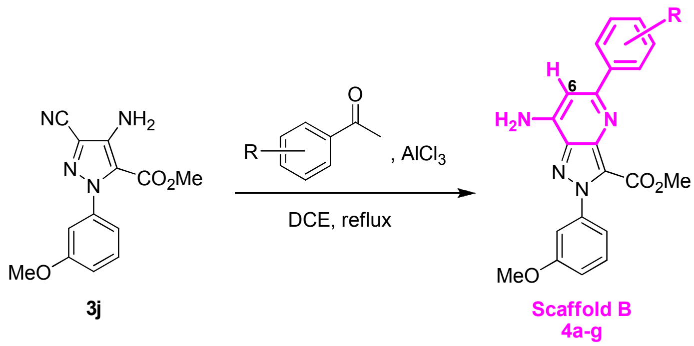
Entry	R	Time (min)	Product[a]	Yield[b] (%)
1	H	12	**3a**	70
2	2-OBn	10	**3b**	58[c]
3	2-Br	15	**3c**	40[c]
4	2-C≡CH	30	**3d**	0
5	2-NO_2	45	**3e**	43[c]
6	3-OBn	8	**3f**	79[c]
7	3-Br	10	**3g**	57
8	3-CO_2*t*Bu	10	**3h**	74
9	3-C≡CH	15	**3i**	83
10	3-MeO	10	**3j**	80
11	3-NO_2	30	**3k**	55[c]
12	4-Br	10	**3l**	48
13	4-CO_2*t*Bu	10	**3m**	54
14	4-C≡CH	10	**3n**	51
15	4-NO_2	15	**3o**	16[c]
16	2,6-di-Cl,3-OMe	40	**3p**	79[c]

[a] Reaction conditions: hydrazone **2** (1 equiv.), K_2CO_3 (2.7 equiv.), Br-CH_2-CO_2Me (7.5 equiv.), toluene, µW 90 W, 120 °C. [b] Yield of isolated product. [c] The reaction was performed in dioxane instead of toluene.

The reaction proved to tolerate electron-poor as well as electron-rich substrates, allowing the preparation of fifteen original TPs (Table 3). Their structure was confirmed by ^{1}H NMR spectrum in which the signal corresponding to the NH of the starting material (10-13 ppm) was replaced by a broad singlet around 4.5-5 ppm assigned to the aminopyrazole NH_2 group. Most of the desired compounds were obtained in moderate to good yields ranging from 43 to 83%. When the reaction failed, or was found to be not enough efficient in toluene, the solvent was advantageously replaced by dioxane (entries 2, 3, 5, 6, 11, 15 and 16, Table 3). The only limitations were the complete lack of reactivity of the 2-alkynyl substrate **2d** (entry 4, Table 3) and the modest yield obtained for the 4-nitro derivative **3o** (16%, entry 15, Table 3). Of note, in the particular case of **3p**, running the reaction for 20 min allowed to isolate the intermediate **I** (39% estimated NMR yield). This supports the mechanism proposed by Desai *et al*[29] which starts with the *N*-alkylation of the aminopyrazole prior to the nucleophilic attack of the nitrile function.

With these building blocks in hand, we next sought to develop a new diversity-oriented synthetic pathway allowing the access to various pyrazole-based polycyclic scaffolds. We first turned our attention to the possible annulation between the amine and the nitrile functional groups. For analogous 3-amino-2-cyanoselenophenes,[32] 4-amino-3-cyanopyrroles,[33] or 4-amino-5-cyanopyrazoles,[34] the formation of a pyridine ring can be achieved by condensation with acetophenone in the presence of aluminium chloride. This reaction is supposed to proceed *via* a Friedländer mechanism.[35] Starting from our 4-amino-3-cyano-pyrazoles, this methodology should open a new route to the pyrazolo[4,3-*b*]pyridine scaffold **B**. This hypothesis was nicely validated running the reaction with our model substrate **3j** and various acetophenones (Table 4).

Table 4. Access to pyrazolo[4,3-*b*]pyridine scaffold B



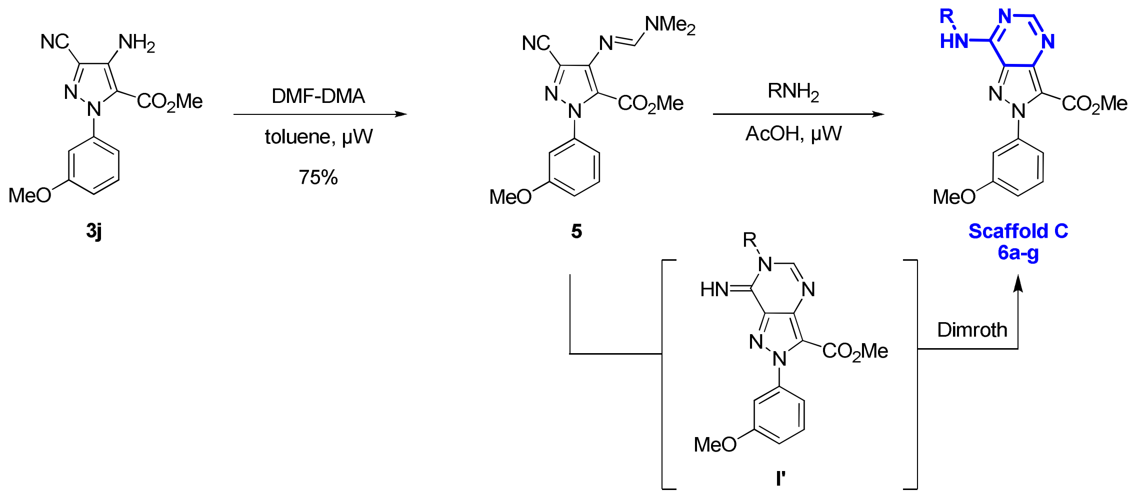
Entry	R	Product[a]	Yield[b] (%)
1	H	**4a**	75
2	2-NO_2	**4b**	30
3	2-OMe	**4c**	0
4	3-NO_2	**4d**	80
5	3-OMe	**4e**	71
6	4-NO_2	**4f**	77
7	4-OMe	**4g**	75

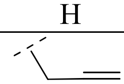
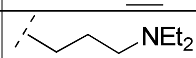
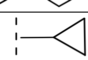
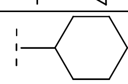
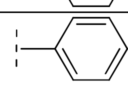
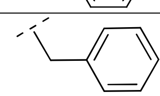
[a] Reaction conditions: pyrazole **3j** (1 equiv.), acetophenone (5 equiv.), $AlCl_3$ (3 equiv.), DCE, reflux, 12 h. [b] Yield of isolated product.

A short optimization of the reaction conditions showed that 5 equiv. of ketone, 3 equiv. of Lewis acid and 12 h refluxing in DCE are required to reach completion, affording **4a** in 75% isolated yield (entry 1, Table 4). Other acetophenones, bearing either electron-withdrawing or electron-donating groups, were then reacted in the same conditions. Meta and para-substituted acetophenones were well tolerated, leading to the desired pyridines **4d-g** in good to very good yields, ranging from 71 to 80% (entries 4-7, Table 4). Their structure was unambiguously assigned by ^1H NMR spectrum which shows a characteristic singlet around 7 ppm corresponding to the aromatic proton in position 6. Unsurprisingly, ortho-substituted acetophenones were found to be less reactive, as exemplified by the 2-NO_2 derivative **4b** (30% yield, entry 2, Table 4). Moreover, the 2-OMe derivative completely failed to afford the cyclized product **4c** (entry 3, Table 4), not only because of its low reactivity but also due to its light sensitivity. Nevertheless, our optimized conditions represent a new route towards the pyrazolo[4,3-*b*]pyridine scaffold **B**.

Ring closure between the amine and the nitrile functional groups of our TPs could also be achieved through a two-step sequence in order to furnish pyrazolo[4,3-*d*]pyrimidines **C**. According to previous studies carried out with 3-amino-2-cyanothiophenes,[36] anthranilonitriles,[37] or 2-amino-3-cyanofuranes,[38] the pyrimidine ring can be obtained by microwave-assisted condensation of a formamidine intermediate with amines. As reported by Besson *et al.*, this cyclization step is supposed to proceed *via* a Dimroth rearrangement.[37] We thus investigated the possible extension of these conditions to 4-amino-3-cyano-pyrazole **3j** (Table 5).

Table 5. Access to pyrazolo[4,3-*d*]pyrimidine scaffold C



Entry	R	Product[a]	Yield[b] (%)
1	H	**6a**	30
2		**6b**	34
3		**6c**	71
4		**6d**	87[c]
5		**6e**	57
6		**6f**	76
7		**6g**	82

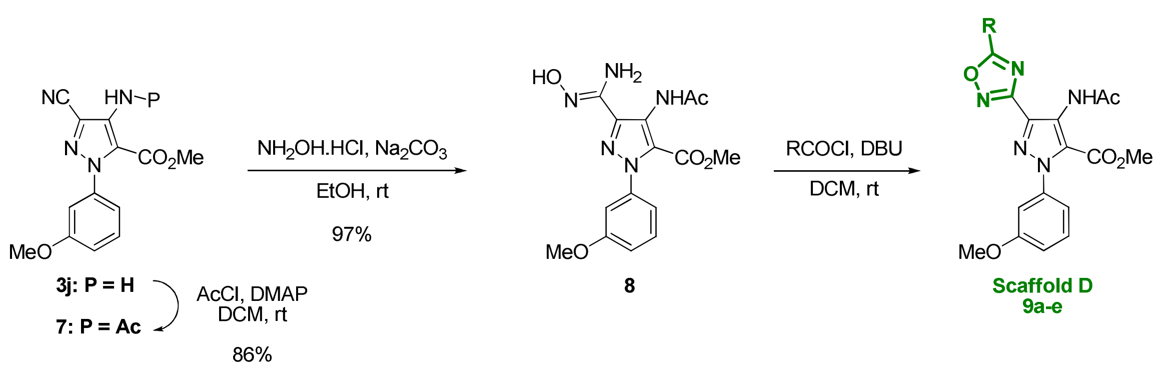
[a] Reaction conditions: formamidine **5** (1 equiv.), RNH_2 (1.5 equiv.), AcOH, μW 90 W, 120 °C, 15 min. [b] Yield of isolated product.

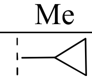
[c] The reaction was performed at 60 °C instead of 120 °C.

The formamidine **5**[39] was prepared in 75% yield by condensation with DMF-DMA (1.5 equiv.) in toluene under microwave activation. This key derivative was then reacted in acetic acid with various primary amines, except for the case of the unsubstituted aminopyrimidine **6a** which was obtained using ammonium acetate.[40] The reaction proved to tolerate both aliphatic and aromatic amines, leading to the desired pyrimidines in yields ranging from 57 to 87% (entries 3-7, Table 5). Specific ^{1}H-^{1}H correlations found in 2D COSY spectra unambiguously showed that the structure of the products corresponds to the aminopyrimidine form **C** and not to the supposed imino intermediate **I'** (see for example **6e** in the supporting information). In agreement with the proposed mechanism, acidic conditions were found to be necessary for the cyclization since the reaction did not take place when dioxane was used instead of acetic acid. Limitations were observed using ammonium acetate and propargylamine, inducing a 2 fold decrease in yield (30% and 34% respectively, entries 1-2, Table 5). Anyhow, these reaction conditions afford a straightforward access to *N*-substituted pyrazolo[4,3-*d*]pyrimidines **C**.

We finally explored the potentiality of converting the nitrile function into an oxadiazole ring, raising the access to pyrazolo-oxadiazoles **D**. As previously reported for analogous 3-cyanopyrazoles, oxadiazole synthesis requires a two-step sequence: prior transformation of the nitrile into a *N*-hydroxyamidine intermediate, followed by the *O*-acylation/*N*-cyclization tandem process that leads to the desired oxadiazole ring closure.[41] In the case of our TPs, this strategy requires the protection of the amino group to circumvent any competitive *N*- versus *O*-acylation. The oxadiazole synthesis was therefore planned starting from the *N*-protected aminopyrazole **7** (Table 6). Our model substrate **3j** was *N*-acylated under standard conditions and then reacted with hydroxylamine hydrochloride (5 equiv.) in basic medium to afford the key hydroxyamidine **8** in a nearly quantitative yield.[40] Upon treatment with various acyl chlorides in the presence of DBU,[41] the expected *O*-acylation/*N*-cyclization process easily took place, leading to the desired oxadiazoles **9a-e** in good yields ranging from 64 to 83% (entries 1-5, Table 6).

Table 6. Access to pyrazolo-oxadiazole scaffold D



Entry	R	Product D[a]	Yield[b] (%)
1	Me	**9a**	71
2		**9b**	77[c]
3	Ph	**9c**	64

4	4-MeOPh	**9d**	81
5	4-NO_2Ph	**9e**	83[c]

[a] Reaction conditions: *N*-hydroxyamidine **8** (1 equiv.), RCOCl (1.1 equiv.), DBU (2 equiv.), DCM, rt, 16 h. [b] Yield of isolated product. [c] Completion of the reaction was reached after 4 h.

Interestingly, the outcome of the reaction is not depending on the nature of the acyl chloride as it proved to tolerate both aliphatic (entries 1-2, Tables 6) and aromatic (entries 3-5, Tables 6) reagents. Moreover, in the case of benzoyl chlorides, the yield is unaffected by the presence of electron-donating or electron-withdrawing groups such as 4-OMe and 4-NO_2 (81% and 83% respectively, entry 4-5, Table 6). However the cyclization is faster with electron poor substrates since completion of the reaction was reached after 4 h for the 4-NO_2 derivative (entry 5, Table 6).

CONCLUSION

In the first part of this work, we have described an efficient two-step synthesis of 4-amino-3-cyano-*N*-arylpyrazoles **A**. The key step is a Thorpe-Ziegler cyclization that has been optimized thanks to the use of microwave activation. This method provides a useful contribution in the field of pyrazole chemistry since references to the synthesis of 4-amino-3-cyano-*N*-arylpyrazoles are scarce.

In the second part of our study, we have demonstrated the usefulness of these pyrazoles as building blocks in a diversity-oriented strategy. Borrowing one or two-step reactions from classical heterocyclic chemistry, we developed new routes to access three distinct families of bicyclic heteroaromatic scaffolds: pyrazolo[4,3-*b*]pyridine **B**, pyrazolo[4,3-*d*]pyrimidine **C** and pyrazolo-oxadiazole **D**.

Interestingly, all these platforms display reactive sites allowing further modulations that could be designed depending on the biological target to readily achieve SAR studies. Our team keeps on investigating these functionalizations to develop new kinase inhibitors. Synthesis and biological evaluations of these compounds are in progress and will be reported elsewhere in due course.

EXPERIMENTAL SECTION

General experimental methods:

Microwave assisted reactions (µW) were performed with a commercially available single-mode focused microwave reactor (model CEM Discover Benchmate) in open vessel mode. The reaction mixture temperature was monitored with the external surface sensor. Heating time was included in the measurement of reaction time. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F-254). Flash chromatography was performed with silica gel 60 (40–63 µm). The solvent systems are given as v/v. Melting points were measured on a hot bench. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded at 300 K in DMSO unless indicated. Chemical shifts (*δ*) are reported in ppm relative to the solvent resonance, and coupling constants (*J*) are given in Hertz. Abbreviations used for peak multiplicity are: s (singlet), d (doublet), m (multiplet), br (broad). For each compound detailed peak assignments have been made according to COSY, HSQC and HMBC spectra. The numbering of molecules is indicated in the Supporting Information file. IR spectra were recorded on a FT-IR spectrophotometer, and the wavelentghts are reported in cm^{-1}. Low resolution mass spectra (LRMS) were recorded with an ion trap mass analyzer under electrospray ionization (ESI). High resolution mass spectra (HRMS) were recorded with a TOF mass analyzer.

General procedure I for the synthesis of the aryl-hydrazones 2a-p

To an ice-cooled solution of the aniline **1** (1 equiv.) in water (5 mL/mmol) were successively added dropwise 37% aq. HCl (11 equiv.) and 1 M aq. $NaNO_2$ (1 equiv.). The mixture was stirred 30 min and then dropwise added to a solution of malononitrile (1.5 equiv.) and sodium acetate (31 equiv.) in water (8.5 mL/mmol of aniline) with continous stirring and cooling to 0 °C. After 2 h, the insoluble hydrazone was filtered off and washed with water. The precipitate was dissolved with EtOAc and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired hydrazone which was used without purification (unless indicated).

General procedure II for the synthesis of the pyrazoles A

A mixture of hydrazone **2** (1 equiv.), potassium carbonate (7.5 equiv.), methyl bromoacetate (2.7 equiv.) in anhydrous solvent (3 mL/mmol) was irradiated at 120 °C (power imput: 90 W) for 8 to 45 min. The reaction mixture was cooled to rt and concentrated *in vacuo*. The resulting residue was dissolved in DCM and washed with brine. The organic layer was dried ($MgSO_4$) then concentrated *in vacuo*. Flash chromatography afforded the desired pyrazole.

General procedure III for the synthesis of the pyrazolo[4,3-*b*]pyridines B

To a solution of the pyrazole **3j** (1 equiv.) and acetophenone (5 equiv.) in DCE (22 mL/mmol) was added aluminium chloride (3 equiv.). The mixture was refluxed for 12 h, cooled to rt and quenched with 10% aq. NaOH (22 mL/mmol of **3j**). After 30 min, the mixture was diluted with DCM. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography afforded the desired pyrazolo[4,3-*b*]pyridine.

General procedure IV for the synthesis of the pyrazolo[4,3-*d*]pyrimidines C

A suspension of the formamidine **5** (1 equiv.) and the amine (1.5 equiv.) in AcOH (5.5 mL/mmol) was irradiated at 120 °C (power imput: 90 W) for 15 min. The reaction mixture was cooled to rt, poured into satd. aq. $NaHCO_3$ (150 mL/mmol) and extracted with DCM/MeOH 95:5 (2 x 300 mL/mmol). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography afforded the desired pyrazolo[4,3-*d*]pyrimidine.

General procedure (V) for the synthesis of the pyrazolo-oxadiazoles D

To an ice-cooled solution of the *N*-hydroxyamidine **8** (1 equiv.) in DCM (11.5 mL/mmol) were added DBU (2 equiv.) and acyl chloride (1.1 equiv.). The reaction mixture was stirred at rt for 4-16 h, diluted with DCM (140 mL/mmol), and the pH was adjusted to 2 with 1 M aq. HCl. The organic layer was washed with satd.

aq. $NaHCO_3$ until pH 8, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography afforded the desired pyrazolo-oxadiazole.

2-(Phenyl-hydrazono)-malononitrile (2a)

According to the general procedure I, hydrazone **2a** was synthesized from aniline (1.0 g, 10.73 mmol) and obtained as an orange solid (1.81 g, 99%): Mp 136-138 °C (EtOH); R_f 0.54 (cyclohexane/EtOAc 4:1); ^{1}H NMR δ 13.00 (br s, 1H, NH), 7.49-7.45 (m, 2H, H-2, H-6), 7.45-7.39 (m, 2H, H-3, H-5), 7.26-7.18 (m, 1H, H-4); ^{13}C NMR δ 141.3 (C-1), 129.5 (C-3, C-5), 125.8 (C-4), 116.4 (C-2, C-6), 114.3, 109.9 (2 C≡N), 84.5 (C=N); IR υ 3197 (NH), 2234, 2212 (C≡N), 1604, 1547, 1474, 1441, 1282; MS (ESI) *m/z* 169 $[M{-}H]^-$. Mp, IR and ^{1}H NMR spectral data are in agreement with literature.[44]

2-[(2-Benzyloxy-phenyl)-hydrazono]-malononitrile (2b)

According to the general procedure I, hydrazone **2b** was synthesized from 2-benzyloxyaniline (1.3 g, 6.52 mmol) and obtained as an orange solid (1.59 g, 89%): Mp 114-116 °C (EtOH); R_f 0.47 (cyclohexane/EtOAc 3:1); ^{1}H NMR (acetone-d_6) δ 10.62 (br s, 1H, NH), 7.58-7.51 (m, 3H, H_{Ar}), 7.44-7.33 (m, 3H, H_{Ar}), 7.30-7.21 (m, 2H, H-5, H-3), 7.13-7.07 (m, 1H, H-6), 5.32 (s, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ 148.1 (C-2), 137.4 (C-1'), 130.7 (C-1), 129.6 (CH), 129.1 (CH), 128.5 (CH), 127.6 (CH), 122.9 (CH), 116.9 (CH), 114.6 (CH), 113.9, 109.4 (2 C≡N), 88.2 (C=N), 71.9 (CH_2); IR υ 3275 (NH), 2223, 2205 (C≡N), 1609, 1594, 1530, 1485, 1461, 1441, 1278, 1162, 1107; MS (ESI) *m/z* 275 $[M{-}H]^-$; HRMS (ESI) *m/z* $[M{-}H]^-$ Calcd for $C_{16}H_{11}N_4O$ 275.0933, Found 275.0937.

2-[(2-Bromo-phenyl)-hydrazono]-malononitrile (2c)

According to the general procedure I, hydrazone **2c** was synthesized from 2-bromoaniline (1.0 g, 5.8 mmol) and obtained as an orange solid (1.38 g, 95%): R_f 0.57 (cyclohexane/EtOAc 4:1); ^{1}H NMR (250 MHz, acetone-d_6) δ 10.53 (br s, 1H, NH), 7.79-7.60 (m, 2H, H-3, H-6), 7.58-7.41 (m, 1H, H-5), 7.30-7.15 (m, 1H, H-4); ^{13}C NMR (63 MHz, DMSO-d_6) δ 139.1 (C-1), 133.3 (C-3), 129.0 (C-5), 128.1 (C-4), 121.1 (C-6), 113.9 (C≡N), 113.2 (C-2), 109.4 (C≡N), 87.0 (C=N); IR υ 3245 (NH), 2232, 2213 (C≡N), 1594, 1530, 1485, 1448, 1272; MS (ESI) *m/z* 247, 249 $[M{-}H]^-$.

2-[(2-Ethynyl-phenyl)-hydrazono]-malononitrile (2d)

According to the general procedure I, hydrazone **2d** was synthesized from 2-ethynylaniline (1.0 g, 8.54 mmol) and obtained as an orange solid (0.97 g, 60%): ^{1}H NMR (acetone-d_6) δ 10.60 (br s, 1H, NH), 7.70-7.47 (m, 3H, H_{Ar}), 7.35-7.22 (m, 1H, H-4), 4.43 (s, 1H, C≡C*H*); ^{13}C NMR (acetone- d_6) δ 141.8 (C-1), 133.7 (C-3), 131.8 (C-5), 126.7 (C-4), 116.4 (C-6), 113.4 (C≡N), 110.9 (C-2), 109.0 (C≡N), 89.8 (C=N), 88.6 (C≡*C*H), 77.8 (*C*≡CH); IR υ 3255 (NH), 2230, 2213 (C≡N), 1610, 1583, 1529, 1485, 1446, 1283; MS (ESI) *m/z* 193 $[M{-}H]^-$; HRMS (ESI) *m/z* $[M\text{-}H]^-$ Calcd for $C_{11}H_5N_4$ 193.0520, Found 193.0515.

2-[(2-Nitro-phenyl)-hydrazono]-malononitrile (2e)

According to the general procedure I, hydrazone **2e** was synthesized from 2-nitroaniline (1.0 g, 7.24 mmol) and obtained as a brown solid (1.37 g, 88%): R_f 0.50 (cyclohexane/EtOAc 2:1); ^{1}H NMR (250 MHz, acetone-d_6) δ 12.90 (br s, 1H, NH), 8.85-8.70 (m, 1H, H-3), 8.53-8.30 (m, 2H, H-6, H-5), 8.02-7.85 (m, 1H, H-4); ^{13}C NMR (63 MHz, DMSO-d_6) δ 137.6 (C-1), 136.1 (C-2), 135.7 (C-5), 125.8, 125.7 (C-3, C-4), 119.0 (C-6), 113.6, 109.3 (2 C≡N), 89.5 (C=N); IR υ 3201 (NH), 2231, 2219 (C≡N), 1610, 1515, 1504 (NO_2), 1338 (NO_2), 1244, 1140; MS (ESI) *m/z* 214 $[M{-}H]^-$. ^{1}H NMR spectral data is in agreement with literature.[45]

2-[(3-Benzyloxy-phenyl)-hydrazono]-malononitrile (2f)

According to the general procedure I, hydrazone **2f** was synthesized from 3-benzyloxyaniline (5.0 g, 25.1 mmol) and obtained as an orange solid (6.79 g, 98%): R_f 0.67 (cyclohexane/EtOAc 2:1); ^{1}H NMR δ 12.95 (br s, 1H, NH), 7.47-7.43 (m, 2H, H_{Bn}), 7.42-7.37 (m, 2H, H_{Bn}), 7.36-7.30 (m, 2H, H_{Bn}, H-5), 7.13-7.10 (m, 1H, H-2), 7.08-7.04 (m, 1H, H-4), 6.89-6.84 (m, 1H, H-6), 5.12 (s, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ 160.9 (C-3), 145.6 (C-1), 138.2 (C-1'), 131.3 (C-5), 129.4, 128.8, 128.5 (5 CH_{Bn}), 115.8 (C≡N), 113.3 (C-6), 111.2 (C≡N), 110.4 (C-4), 104.1 (C-2), 85.0 (C=N), 70.7 (CH_2); IR *υ* 3181 (NH), 2233, 2213 (C≡N), 1607, 1547, 1498, 1456, 1384, 1285 (C-O), 1144 (C-O), 1033; MS (ESI) *m/z* 275 $[M–H]^-$; HRMS (ESI) m/z $[M-H]^-$ Calcd for C16H11N4O 275.0938, Found 275.0937.

2-[(3-Bromo-phenyl)-hydrazono]-malononitrile (2g)

According to the general procedure I, hydrazone **2g** was synthesized from 3-bromoaniline (1.0 g, 5.81 mmol) and obtained as a brown solid (1.42 g, 99%): R_f 0.31 (cyclohexane/EtOAc 2:1); ^{1}H NMR δ 12.97 (br s, 1H, NH), 7.60-7.31 (m, 4H, H_{Ar}); ^{13}C NMR δ 145.8 (C-1), 131.3 (C-5), 127.6 (C-4), 122.2 (C-3), 119.3 (C-2), 116.3 (C-6), 115.8, 111.3 (2 C≡N), 83.3 (C=N); IR *υ* 3226 (NH); 2229 (C≡N), 1594, 1541, 1461, 1275. ^{1}H NMR spectral data is in agreement with literature.[24]

2-[(3-*tert*-butyl ester)-hydrazono]-malononitrile (2h)

According to the general procedure I, hydrazone **2h** was synthesized from 3-*tert*-butyl ester aniline (1.0 g, 5.17 mmol) and obtained as a yellow solid (1.28 g, 92%): R_f 0.67 (cyclohexane/EtOAc 2:1); ^{1}H NMR δ 13.13 (br s, 1H, NH), 8.02-7.96 (m, 1H, H-2), 7.74-7.71 (m, 1H, H-4), 7.71-7.67 (m, 1H, H-6), 7.54 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H, H-5), 1.53 (s, 9H, *t*Bu); ^{13}C NMR (63 MHz) δ 164.2 (CO), 141.7 (C-1), 132.5 (C-3), 129.9 (C-5), 126.0 (C-6), 120.3 (C-4), 116.9 (C-2), 114.2, 109.7 (2 C≡N), 85.4 (C=N), 81.2 (CMe_3), 27.8 (CMe_3); IR *υ* 3226 (NH), 2229, 2213 (C≡N), 1715 (C=O), 1595, 1550, 1489, 1466, 1369, 1307 (C-O), 1156 (C-O); MS (ESI) *m/z* 269 $[M–H]^-$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{15}N_4O_2$ 271.1195, Found 271.1187.

2-[(3-Ethynyl-phenyl)-hydrazono]-malononitrile (2i)

According to the general procedure I, hydrazone **2i** was synthesized from 3-ethynylaniline (1.0 g, 8.54 mmol) and obtained as a brown solid (1.54 g, 93%): R_f 0.61 (cyclohexane/EtOAc 2:1); ^{1}H NMRδ 12.99 (br s, 1H, NH), 7.53-7.46 (m, 2H, H-2, H-6), 7.42 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, H-5), 7.33-7.27 (m, 1H, H-4), 3.77 (s, 1H, C≡CH); ^{13}C NMR δ 141.6 (C-1), 130.0 (C-5), 128.8 (C-6), 122.8 (C-3), 119.2 (C-2), 117.0 (C-4), 114.0, 109.7 (2 C≡N), 85.5 (C=N) 82.6 (C≡*C*H), 81.5 (*C*≡CH); IR υ 3265 (≡C-H), 3205 (NH), 2233, 2217 (C≡N), 1589, 1551, 1485, 1460, 1283; MS (ESI) *m/z* 193 $[M-H]^-$; HRMS (ESI) *m/z* $[M-H]^-$ Calcd for $C_{11}H_5N_4$ 193.0520, Found 193.0509.

2-[(3-Methoxy-phenyl)-hydrazono]-malononitrile (2j)

According to the general procedure I, hydrazone **2j** was synthesized from 3-methoxyaniline (15.0 g, 121.8 mmol) and obtained as a yellow solid (22.2 g, 91%): R_f 0.41 (cyclohexane/EtOAc 7:3); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.61 (br s, 1H, NH), 7.30 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H, H-5), 6.91-6.73 (m, 3H, H-2, H-4, H-6), 3.83 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 161.3 (C-3), 141.2 (C-1), 130.9 (C-5), 113.1 (C-4), 112.5 (C≡N), 108.7 (C-6), 108.6 (C≡N), 101.8 (C-2), 86.6 (C=N), 55.8 (OCH_3); MS (ESI) *m/z* 199 $[M-H]^-$. ^{1}H NMR spectral data is in agreement with literature.[24]

2-[(3-Nitro-phenyl)-hydrazono]-malononitrile (2k)

According to the general procedure I, hydrazone **2k** was synthesized from 3-nitroaniline (1.0 g, 7.24 mmol) and obtained as a brown solid (1.39 g, 87%): R_f 0.31 (cyclohexane/EtOAc 2:1); ^{1}H NMR δ 8.26-8.22 (m, 1H, H-2), 8.04-7.99 (m, 1H, H-4), 7.88-7.83 (m, 1H, H-6), 7.69 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5); ^{13}C NMR δ 148.3 (C-3), 142.8 (C-1), 130.9 (C-5), 122.2 (C-6), 119.6 (C-4), 113.9 (C≡N), 110.9 (C-2), 109.6 (C≡N), 86.1 (C=N); IR υ 3226 (NH), 2233, 2201 (C≡N), 1604, 1530, 1504 (NO_2), 1469, 1352 (NO_2), 1283, 1268; MS (ESI) *m/z* 214 $[M-H]^-$.

2-[(4-Bromo-phenyl)-hydrazono]-malononitrile (2l)

According to the general procedure I, hydrazone **2l** was synthesized from 4-bromoaniline (1.0 g, 5.81 mmol) and obtained as an orange solid (1.31 g, 91%): R_f 0.49 (cyclohexane/EtOAc 3:1); ^{1}H NMR δ 13.04 (br s, 1H, NH), 7.62-7.58 (m, 2H, H-3, H-5), 7.43-7.39 (m, 2H, H-2, H-6); ^{13}C NMR δ 140.7 (C-1), 132.3 (C-3, C-5), 118.3 (C-2, C-6), 117.9 114.1, 109.7 (2 C≡N, C-4), 85.3 (C=N); IR υ 3215 (NH), 2228, 2219 (C≡N), 1599, 1542, 1467, 1271. ^{1}H NMR, ^{13}C NMR and IR spectral data are in agreement with literature.[46]

2-[(4-*tert*-butyl ester)-hydrazono]-malononitrile (2m)

According to the general procedure I, hydrazone **2m** was synthesized from 4-*tert*-butyl ester aniline (1.0 g, 5.17 mmol) and obtained as a yellow solid (1.09 g, 78%): R_f 0.67 (cyclohexane/EtOAc 2:1); ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.10 (br s, 1H, NH), 8.03-7.40 (m, 4H, H_{Ar}), 1.53 (s, 9H, *t*Bu); ^{13}C NMR (63 MHz, DMSO-d_6) δ 164.3 (C=O), 144.9 (C-1), 130.6 (2C, C-3, C-5), 127.9 (C-4), 116.1 (C-2, C-6), 114.1, 109.7 (2 C≡N), 86.5 (C=N), 80.7 (*C*Me$_3$), 27.8 (C*Me*$_3$); IR υ 3235 (NH), 2228, 2218 (C≡N), 1693 (C=O), 1607, 1542, 1476, 1307 (C-O), 1275, 1157 (C-O), 1120; MS (ESI) *m/z* 269 [M–H]$^-$; HRMS (ESI) *m/z* [M-H]$^-$ Calcd for $C_{14}H_{13}N_4O_2$ 269.1044, Found 269.1039.

2-[(4-Ethynyl-phenyl)-hydrazono]-malononitrile (2n)

According to the general procedure I, hydrazone **2n** was synthesized from 4-ethynylaniline (1.0 g, 8.54 mmol) and obtained as a brown solid (1.42 g, 86%): Mp dec.; R_f 0.67 (cyclohexane/EtOAc 2:1); ^{1}H NMR δ 13.07 (br s, 1H, NH), 7.53-7.50 (m, 2H, H-3, H-5), 7.48-7.44 (m, 2H, H-2, H-6), 4.21 (s, 1H, C≡CH); ^{13}C NMR δ 141.5 (C-1), 133.0 (C-3, C-5), 118.7 (C-4), 116.5 (C-2, C-6), 114.1, 109.7 (2 C≡N), 85.7 (C=N), 83.0, 81.3 (2 C≡*C*H); IR υ 3234 (≡C-H), 2228, 2218 (C≡N), 1693, 1551, 1485, 1460, 1283; MS (ESI) *m/z* 193 [M–H]$^-$; HRMS (ESI) *m/z* [M+H]$^+$ Calcd for $C_{11}H_7N_4$ 195.0672, Found 195.0671.

2-[(4-Nitro-phenyl)-hydrazono]-malononitrile (2o)

According to the general procedure I, hydrazone **2o** was synthesized from 4-nitroaniline (1.0 g, 7.24 mmol) and obtained as a brown solid (1.53 g, 98%): ^{1}H NMR δ 8.46-8.08 (m, 2H, H-2, H-6), 7.82-7.43 (m, 2H, H-3, H-5); ^{13}C NMR δ 146.6 (C-1), 143.9 (C-4), 125.4 (C-3, C-5), 116.6 (C-2, C-6), 113.7, 109.3 (2 C≡N), 88.5 (C=N); IR υ 3220 (NH), 2232 (C≡N), 1621, 1593, 1562, 1513 (NO_2), 1467, 1342 (NO_2), 1280, 1109; MS (ESI) *m/z* 286 [M–H]$^-$; HRMS (ESI) *m/z* [M–H]$^-$ Calcd for $C_{12}H_8N_5O_4$ 286.0576, Found 286.0545. ^{1}H NMR, ^{13}C NMR and IR spectral data are in agreement with literature.[46]

2-[(2,6-dichloro-3-methoxyphenyl) hydrazono]-malononitrile (2p)

According to the general procedure I, hydrazone **2p** was synthesized from 2,6-dichloro-3-methoxyaniline[25] (3.09 g, 16.11 mmol) and after flash chromatography (EtOAc/cyclohexane 1:3) followed by recrystallisation in Et_2O/pentane, and obtained as a yellow solid (2.91 g, 67%): Mp 152-154 °C (Et_2O/pentane); ^1H NMR (CD_3CN) δ 10.21 (s, 1H, NH), 7.51-7.45 (m, 1H, H-5), 7.15-7.10 (m, 1H, H-4), 3.92 (s, 3H, OCH_3); ^{13}C NMR (CD_3CN) δ 156.2 (C-3), 135.8 (C-1), 129.9 (C-5), 123.1 (Cq), 121.2 (Cq), 114.2 (C-4), 113.6, 109.1 (2 C≡N), 90.3 (C=N), 57.8 (OCH_3); IR υ 3225 (NH), 2233, 2213 (C≡N), 1590, 1535, 1513, 1476, 1436, 1399, 1300, 1258, 1075, 957, 843, 801, 709; MS (ESI) *m/z* 286 $[M–H]^-$; HRMS (ESI) *m/z* $[M–H]^-$ Calcd for $C_{12}H_8N_5O_4$ 286.0576, Found 286.0545.

Methyl 4-amino-3-cyano-1-phenyl-1*H*-pyrazole-5-carboxylate (3a)

According to the general procedure II, pyrazole **3a** was synthesized from the hydrazone **2a** (1.2 g, 7.08 mmol). The reaction was performed in toluene (20 mL) and the mixture was irradiated for 12 min. Flash chromatography (cyclohexane/EtOAc 8:2) afforded **3a** as a yellow solid (1.2 g, 70%): Mp 132-134 °C (EtOH); R_f 0.59 (cyclohexane/EtOAc 1:1); ^1H NMR ($CDCl_3$) δ 7.46-7.41 (m, 3H, H-3’, H-4’, H-5’), 7.37-7.32 (m, 2H, H-2’, H-6’), 4.79 (br s, 2H, NH_2), 3.74 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 159.5 (CO_2CH_3), 142.4 (Cq), 140.1 (C-1’), 129.5 (CH), 128.8 (CH), 125.9 (CH), 117.4 (Cq), 114.4 (Cq), 112.6 (Cq), 52.0 (CO_2CH_3); IR υ 3474, 3367, 2231, 1725, 1618, 1500, 1352, 1294, 1139; MS (ESI) *m/z* 243 $[M+H]^+$, HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{11}N_4O_2$ 243.0878, Found 243.0878.

Methyl 4-amino-1-(2-(benzyloxy)phenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3b)

According to the general procedure II, pyrazole **3b** was synthesized from the hydrazone **2b** (111 mg, 0.36 mmol). The reaction was performed in dioxane (1.1 mL) and the mixture was irradiated for 10 min. Flash chromatography (cyclohexane/EtOAc 8:2) afforded **3b** as a beige solid (73 mg, 58 %): Mp 100-102 °C (EtOH); R_f 0.32 (cyclohexane/EtOAc 7:3); ^1H NMR ($CDCl_3$) δ 7.41-7.36 (m, 1H, H-4’), 7.34-7.25 (m, 4H, H-6’, H-3”, H-5”, H-4”), 7.21-7.16 (m, 2H, H-2”, H-6”), 7.07-7.00 (m, 2H, H-5’, H-3’), 5.02 (s, 2H, OCH_2), 4.57 (br s, 2H, NH_2), 3.64 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 159.4 (CO_2CH_3), 153.8 (C-2’), 141.3

(C_{pyr}), 136.4 (C-1”), 131.1 (C-4’), 130.1 (C-1’), 128.7 (2C, C-3”, C-5”), 128.2 (C-4”), 127.8 (C-6’), 127.0 (2C, C-2”, C-6”), 121.2 (C-5’), 119.1 (C_{pyr}), 114.4 (C_{pyr}), 113.7 (C-3’), 112.8 (C≡N), 70.9 (OCH_2), 51.8 ($CO_2\mathit{C}H_3$); IR *υ* 3444, 3356 (NH_2), 2231 (C≡N), 1688 (C=O), 1628, 1553 (C=C, C=N), 1502 (CH_3), 1451, 1435, 1405 (C-N), 1302 (C-O), 1266, 1238; MS (ESI) *m/z* 349 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{19}H_{16}N_4O_3$ $[M+H]^+$ 349.1301, Found 349.1295.

Methyl 4-amino-1-(2-bromophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3c)

According to the general procedure II, pyrazole **3c** was synthesized from the hydrazone **2c** (50 mg, 0.2 mmol). The reaction was performed in dioxane (0.6 mL) and the mixture was irradiated for 15 min. Flash chromatography (cyclohexane/EtOAc 8:2) afforded **3c** as a yellow foam (26 mg, 40 %): Mp 186-188 °C (EtOH); R_f 0.25 (cyclohexane/EtOAc 7:3); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76-7.59 (m, 1H, H-3’), 7.52-7.28 (m, 3H, H-4’, H-5’, H-6’), 4.74 (br s, 2H, NH_2), 3.71 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 159.2 ($\mathit{C}O_2CH_3$), 141.5 (C-1’), 139.8 (C_{pyr}), 133.2 (C-3’), 131.4 (C-4’), 129.0 (C-5’), 128.2 (C-6’), 121.6 (C-2’), 118.6 (C_{pyr}), 115.0 (C_{pyr}), 112.4 (C≡N), 52.2 ($CO_2\mathit{C}H_3$); IR *υ* 3465, 3365 (NH_2), 2958, 2918, 2859 (C-H), 2233 (C≡N), 1724 (C=O), 1619, 1560 (C=C, C=N), 1483 (CH_3), 1437, 1354 (C-N), 1304 (C-O), 1139; MS (ESI) *m/z* 321, 323 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{10}{}^{79}BrN_4O_2$ 320.9987, Found 321.0001.

Methyl 4-amino-3-cyano-1-(2-nitrophenyl)-1*H*-pyrazole-5-carboxylate (3e)

According to the general procedure II, pyrazole **3e** was synthesized from the hydrazone **2e** (500 mg, 2.32 mmol). The reaction was performed in dioxane (7 mL) and the mixture was irradiated for 45 min. Flash chromatography (cyclohexane/EtOAc 7:3) afforded **3e** as a yellow solid (284 mg, 43%): Mp 176-178 °C (EtOH); R_f 0.16 (cyclohexane/EtOAc 7:3); ^{1}H NMR δ 8.23 (dd, J = 8.2 Hz, J = 1.3 Hz, 1H, H-3’), 7.94-7.88 (m, 1H, H_{Ar}), 7.86-7.80 (m, 1H, H_{Ar}), 7.47 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz, 1H, H-6’), 6.18 (br s, 2H, NH_2), 3.67 (s, 3H, CO_2CH_3); ^{13}C NMR δ 158.6 ($\mathit{C}O_2CH_3$), 144.6 (C-1’), 141.9 (C_{pyr}), 134.4 (C-5’), 132.8 (C-2’), 131.2 (C-4’), 130.1 (C-6’), 125.0 (C-3’), 116.9 (C_{pyr}), 114.1 (C_{pyr}), 112.7 (C≡N), 51.8 ($CO_2\mathit{C}H_3$); IR *υ* 3465, 3349 (NH_2), 2958, 2926, 2856 (C-H), 2238 (C≡N), 1724 (C=O), 1632, 1610, 1572 (C=C, C=N), 1521 (NO_2, CH_3), 1434 (C-N), 1349 (NO_2, C-N), 1296 (C-O), 1144; MS (ESI) *m/z* = 286 $[M-H]^-$; HRMS (ESI) *m/z* $[M-H]^-$ Calcd for $C_{12}H_8N_5O_4$ 286.0576, Found 286.0582.

Methyl 4-amino-1-(3-(benzyloxy)phenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3f)

According to the general procedure II, pyrazole **3f** was synthesized from the hydrazone **2f** (303 mg, 1.1 mmol). The reaction was performed in dioxane (3 mL) and the mixture was irradiated for 8 min. Flash chromatography (cyclohexane/EtOAc 9:1) afforded **3f** as a yellow solid (302 mg, 79%): Mp 106-108 °C (EtOH); R_f 0.31 (cyclohexane/EtOAc 7:3); ^{1}H NMR ($CDCl_3$) δ 7.43-7.29 (m, 6H, H_{Ph}, H-5’), 7.08-7.04 (m, 1H, H-4’), 7.00-6.97 (m, 1H, H-2’), 6.96-6.92 (m, 1H, H-6’), 5.07 (s, 2H, OCH_2), 4.75 (br s, 2H, NH_2), 3.73 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 159.4 ($\mathit{C}O_2CH_3$), 159.1 (C-3’), 142.4 (C_{pyr}), 141.1 (C-1’), 136.6 (C_{Ph}), 129.5 (C-5’), 128.9, 128.4, 127.7 (5 CH_{Ph}), 118.5 (C-6’), 117.4 (C_{pyr}), 116.3 (C-4’), 114.4 (C_{pyr}), 112.7 (C-2’), 112.6 (C≡N), 70.6 (OCH_2), 52.1 ($CO_2\mathit{C}H_3$); IR υ 3364 (NH_2), 2958, 2928, 2868 (C-H), 2223 (C≡N), 1764 (C=O), 1614, 1592 (C=C, C=N), 1495, 1300, 1249; MS (ESI) *m/z* 349 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{19}H_{17}N_4O_3$ 349.1301, Found 349.1295.

Methyl 4-amino-1-(3-bromophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3g)

According to the general procedure II, pyrazole **3g** was synthesized from the hydrazone **2g** (100 mg, 0.40 mmol). The reaction was performed in toluene (1.2 mL) and the mixture was irradiated for 10 min. Flash chromatography (cyclohexane/EtOAc 8:2) afforded **3g** as a yellow solid (73 mg, 57%): Mp 180-182 °C (EtOH); R_f 0.26 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$) δ 7.61-7.53 (m, 2H, H-4’, H-2’), 7.32-7.29 (m, 2H, H-5’, H-6’), 4.78 (br s, 2H, NH_2), 3.78 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 159.3 ($\mathit{C}O_2CH_3$), 142.6 (C_{pyr}), 141.0 (C-1’), 132.6 (C-4’), 130.0 (C-5’), 129.2 (C-2’), 124.7 (C-6’), 122.1 (C-3’), 117.1 (C_{pyr}), 115.1 (C_{pyr}), 112.3 (C≡N), 52.2 ($CO_2\mathit{C}H_3$); IR υ 3419, 3364 (NH_2), 2970, 2923 (C-H), 2229 (C≡N), 1732 (C=O), 1609 (C=C, C=N), 1478 (CH_3), 1435, 1355 (C-N), 1307, 1228 (C-O), 1144; MS (ESI) *m/z* 319, 321 $[M-H]^-$; HRMS (ESI) *m/z* $[M-H]^-$ Calcd for $C_{12}H_8{}^{79}BrN_4O_2$ 318.9831, Found 318.9845.

Methyl 4-amino-1-(3-(*tert*-butoxycarbonyl)phenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3h)

According to the general procedure II, pyrazole **3h** was synthesized from the hydrazone **2h** (2.7 g, 10 mmol). The reaction was performed in toluene (30 mL) and the mixture was irradiated for 10 min. Flash chromatography (cyclohexane/EtOAc 7:3) afforded **3h** as a yellow solid (2.53 g, 74%): Mp 194-196 °C (EtOH); R_f 0.27 (cyclohexane/EtOAc 7:3); ^{1}H NMR ($CDCl_3$) δ 8.09-8.04 (m, 1H, H-4'), 7.97-7.93 (m, 1H, H-2'), 7.53-7.47 (m, 2H, H-6', H-5'), 4.81 (br s, 2H, NH_2), 3.74 (s, 3H, CO_2CH_3), 1.57 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$) δ 164.5 ($\mathit{C}O_2t$Bu), 159.4 ($\mathit{C}O_2CH_3$), 142.6 (C_{pyr}), 140.1 (C-1'), 133.1 (C-3'), 130.4 (C-4'), 129.7 (C-6'), 128.7 (C-5'), 126.9 (C-2'), 117.4 114.9 (2 C_{pyr}), 112.4 (C≡N), 82.0 (*C*Me_3), 52.1 ($CO_2\mathit{C}H_3$), 28.4 (*t*Bu); IR υ 3424, 3315 (NH_2), 2982, 2963 (C-H), 2233 (C≡N), 1732, 1708 (2 C=O), 1605, 1587, 1562 (C=C, C=N), 1451, 1354 (C-N), 1281 (C-O), 1139; MS (ESI) *m/z* 343 $[M+H]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ Calcd for $C_{17}H_{18}N_4NaO_4$ 365.1226, Found 365.1240.

Methyl 4-amino-3-cyano-1-(3-ethynylphenyl)-1*H*-pyrazole-5-carboxylate (3i)

According to the general procedure II, pyrazole **3i** was synthesized from the hydrazone **2i** (1.33 g, 6.86 mmol). The reaction was performed in toluene (20 mL) and the mixture was irradiated for 15 min. Flash chromatography (cyclohexane/EtOAc 3:1) afforded **3i** as a yellow solid (1.51 g, 83%): Mp 190-192 °C (EtOH); R_f 0.24 (EtOAc/cyclohexane 2:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.60-7.53 (m, 1H, H-4'), 7.52-7.46 (m, 1H, H-2'), 7.45-7.30 (m, 2H, H-5', H-6'), 4.79 (br s, 2H, NH_2), 3.76 (s, 3H, CO_2CH_3), 3.11 (s, 1H, C≡CH); ^{13}C NMR ($CDCl_3$) δ 159.4 ($\mathit{C}O_2CH_3$), 142.6 (C_{pyr}), 140.1 (C-1'), 133.1 (C-4'), 129.6 (C-5'), 128.8 (C-2'), 126.4 (C-6'), 123.2 (C-3'), 117.4, 114.9 (2 C_{pyr}), 112.4 (C≡N), 82.3 (*C*≡CH), 78.9 (C≡*C*H), 52.2 ($CO_2\mathit{C}H_3$); IR υ 3426, 3305(NH_2), 3269 (C≡C-H), 2234 (C≡N), 1733 (C=O), 1630, 1560 (C=C, C=N), 1506, 1486 (CH_3), 1435, 1355 (C-N), 1310 (C-O), 1133, 1030; MS (ESI) *m/z* 267 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}N_4O_2$ 267.0882, Found 267.0891.

Methyl 4-amino-3-cyano-1-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (3j)

According to the general procedure II, pyrazole **3j** was synthesized from the hydrazone **2j** (2.0 g, 10.0 mmol). The reaction was performed in toluene (30 mL) and the mixture was irradiated for 10 min. Flash chromatography (cyclohexane/EtOAc 2:1) afforded **3j** as a yellow solid (2.17 g, 80%): Mp 142-144 °C (EtOH); R_f 0.29 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$) δ 7.31 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H, H-5'), 6.99-6.95 (m, 1H, H-4'), 6.93-6.87 (m, 2H, H-6', H-2'), 4.67 (br s, 2H, NH_2), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 159.8 (C-3'), 159.3 ($\mathit{C}O_2CH_3$), 142.4 (C_{pyr}), 141.0 (C-1'), 129.4 (C-5'), 118.2 (C-6'), 117.4 (C_{pyr}), 115.3 (C-4'), 114.3 (C_{pyr}), 112.6 (C≡N), 111.7 (C-2'), 55.7 (OCH_3), 52.0 ($CO_2\mathit{C}H_3$); IR υ 3456, 3357 (NH_2), 2932, 2855 (CH), 2233 (C≡N), 1735 (C=O), 1688, 1610 (C=C, C=N), 1493 (CH_3), 1437 (C-N), 1293 (C-O), 1225, 1130, 1044, 1011; MS (ESI) *m/z* 273 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{13}H_{13}N_4O_3$ 273.0988, Found 273.0994.

Methyl 4-amino-3-cyano-1-(3-nitrophenyl)-1*H*-pyrazole-5-carboxylate (3k)

According to the general procedure II, pyrazole **3k** was synthesized from the hydrazone **2k** (50 mg, 0.23 mmol). The reaction was performed in dioxane (0.7 mL) and the mixture was irradiated for 30 min. Flash chromatography (cyclohexane/EtOAc 9:1) afforded **3k** as a yellow solid (36 mg, 55%): Mp 202-204 °C (EtOH); R_f 0.18 (cyclohexane/EtOAc 2:1); ^{1}H NMR δ 8.40-8.37 (m, 1H, H-2'), 8.37-8.32 (m, 1H, H-4'), 8.02-7.97 (m, 1H, H-6'), 7.79 (dd, 1H, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 6.18 (br s, 2H, NH_2), 3.72 (s, 3H, CO_2CH_3); ^{13}C NMR δ 158.7 ($\mathit{C}O_2CH_3$), 147.4 (C-3'), 142.6 (C_{pyr}), 140.2 (C-1'), 132.3 (C-6'), 129.9 (C-5'), 123.7 (C-4'), 120.8 (C-2'), 116.4 (C_{pyr}), 114.1 (C_{pyr}), 112.9 (C≡N), 51.7 ($CO_2\mathit{C}H_3$); IR υ 3470, 3367 (NH_2), 2957, 2924, 2856 (C-H), 2242 (C≡N), 1717 (C=O), 1637 (C=C, C=N), 1533 (NO_2), 1485 (CH_3), 1436 (C-N), 1350 (NO_2, C-N), 1305 (C-O), 1222, 1142, 1021; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{10}N_5O_4$ 288.0733, Found 288.0739.

Methyl 4-amino-1-(4-bromophenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3l)

According to the general procedure II, pyrazole **3l** was synthesized from the hydrazone **2l** (100 mg, 0.40 mmol). The reaction was performed in toluene (1.2 mL) and the mixture was irradiated for 10 min. Flash chromatography (cyclohexane/EtOAc 4:1) followed by trituration in boiling Et_2O afforded **3l** as a white solid (62 mg, 48 %): Mp 246-248 °C (EtOH); R_f 0.21 (cyclohexane/EtOAc 2:1); ^{1}H NMR δ 7.74-7.63 (m, 2H, H-3', H-5'), 7.51-7.39 (m, 2H, H-2', H-6'), 6.09 (br s, 2H, NH_2), 3.71 (s, 3H, CO_2CH_3); ^{13}C NMR δ 158.7 ($\mathit{C}O_2CH_3$), 142.5 (C_{pyr}), 138.9 (C-1'), 131.4 (C-3', C-5'), 127.8 (C-2', C-6'), 122.0 (C-4'), 116.3, 113.4, 113.0 (C≡N, 2 C_{pyr}), 51.6 ($CO_2\mathit{C}H_3$); IR υ 3476, 3369 (NH_2), 2232 (C≡N), 1730 (C=O), 1617, 1565 (C=C, C=N), 1489 (CH_3), 1431, 1355 (C-N), 1297 (C-O), 1135, 1005; MS (ESI) *m/z* 321, 323 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{10}{}^{79}BrN_4O_2$ 320.9987, Found 320.9972.

Methyl 4-amino-1-(4-(*tert*-butoxycarbonyl)phenyl)-3-cyano-1*H*-pyrazole-5-carboxylate (3m)

According to the general procedure II, pyrazole **3m** was synthesized from the hydrazone **2m** (100 mg, 0.37 mmol). The reaction was performed in toluene (1.1 mL) and the mixture was irradiated for 10 min. Flash chromatography (cyclohexane/EtOAc 4:1) afforded **3m** as a white solid (68 mg, 54 %): Mp 136-138 °C (EtOH); R_f 0.33 (cyclohexane/EtOAc 7:3); ^{1}H NMR ($CDCl_3$) δ 8.10-8.00 (m, 2H, H-3', H-5'), 7.45-7.35 (m, 2H, H-2', H-6'), 4.81 (br s, 2H, NH_2), 3.75 (s, 3H, CO_2CH_3), 1.59 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$) δ 164.8 ($\mathit{C}O_2\mathit{t}Bu$), 159.4 ($\mathit{C}O_2CH_3$), 143.0 (C-1'), 142.7 ($C_{pyr}$), 132.9 (C-4'), 130.0 (C-3'), 125.6 (C-2'), 117.2 (C_{pyr}), 115.2 (C≡N), 112.4 (C_{pyr}), 81.9 (*C*Me_3), 52.2 ($CO_2\mathit{C}H_3$), 28.4 (*t*Bu); IR υ 3443, 3355 (NH_2), 2978, 2953, 2928 (C-H), 2239 (C≡N), 1715, 1692 (C=O), 1634, 1605, 1558 (C=C, C=N), 1511 (CH_3), 1440, 1367 (C-N), 1301 (C-O), 1254, 1166, 1120; MS (ESI) *m/z* 343 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{17}H_{19}N_4O_4$ 343.1406, Found 343.1423.

Methyl 4-amino-3-cyano-1-(4-ethynylphenyl)-1*H*-pyrazole-5-carboxylate (3n)

According to the general procedure II, pyrazole **3n** was synthesized from the hydrazone **2n** (101 mg, 0.52 mmol). The reaction was performed in toluene (1.6 mL) and the mixture was irradiated for 10 min. Flash chromatography (DCM) afforded **3n** as a white solid (71 mg, 51%): Mp dec.; R_f 0.28 (cyclohexane/EtOAc 3:1); ^{1}H NMR δ 7.61-7.55 (m, 2H, H-2', H-6'), 7.52-7.47 (m, 2H, H-3', H-5'), 6.11 (br s, 2H, NH_2), 4.33 (s, 1H, C≡CH), 3.71 (s, 3H, CO_2CH_3); ^{13}C NMR δ 158.7 ($\mathit{C}O_2CH_3$), 142.6 (C_{pyr}), 139.7 (C-1'), 131.8 (C-3', C-

5'), 125.9 (C-2', C-6'), 122.3 (C-4'), 116.2 (C_{pyr}), 113.5 (C≡N), 113.0 (C_{pyr}), 82.5 (*C*≡CH), 82.2 (C≡*C*H), 51.6 (CO_2CH_3); IR υ 3360, 3275 (C≡C-H), 2952, 2918, 2848 (C-H), 2228 (C≡N), 1720 (C=O), 1616, 1560 (C=C, C=N), 1506 (CH_3), 1426, 1352 (C-N), 1298 (C-O), 1219, 1134. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}N_4O_2$ 267.0877, Found 267.0868.

Methyl 4-amino-3-cyano-1-(4-nitrophenyl)-1*H*-pyrazole-5-carboxylate (3o)

According to the general procedure II, pyrazole **3o** was synthesized from the hydrazone **2o** (101 mg, 0.47 mmol). The reaction was performed in dioxane (1.4 mL) and the mixture was irradiated for 15 min. Flash chromatography (DCM) afforded **3o** as a yellow solid (21 mg, 16 %): Mp 260-262 °C (EtOH); R_f 0.35 (cyclohexane/EtOAc 1:1); ^{1}H NMR δ 8.36-8.27 (m, 2H, H-3', H-5'), 7.84-7.75 (m, 2H, H-2', H-6'), 6.20 (br s, 2H, NH_2), 3.73 (s, 3H, CO_2CH_3); ^{13}C NMR δ 158.7 (CO_2CH_3), 147.1, 144.2 (C-1', C-4'), 142.8 (C_{pyr}), 126.7 (C-3', C-5'), 123.9 (C-2', C-6'), 116.2 (C_{pyr}), 114.7 (C_{pyr}), 112.8 (C≡N), 51.8 (CO_2CH_3); IR υ 3484, 3380 (NH_2), 2958, 2923, 2853 (C-H), 2233 (C≡N), 1718 (C=O), 1629, 1597 (C=C, C=N), 1518 (NO_2), 1498 (CH_3), 1434 (C-N), 1350 (NO_2, C-N), 1296 (C-O), 1142; MS (ESI) *m/z* = 286 $[M-H]^-$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{10}N_5O_4$ 288.0733, Found 288.0739.

Methyl 4-amino-3-cyano-1-(2,6-dichloro-3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (3p)

According to the general procedure II, pyrazole **3p** was synthesized from the hydrazone **2p** (435 mg, 1.62 mmol). The reaction was performed in dioxane (1.4 mL) and the mixture was irradiated for 40 min. Flash chromatography (DCM) afforded **3p** as a yellow solid (436 mg, 79 %): Mp dec.; R_f 0.22 (EtOAc/cyclohexane 2:1); ^{1}H NMR δ 7.68-7.60 (m, 1H, H-5'), 7.43-7.38 (m, 1H, H-4'), 6.18 (br s, 2H, NH_2), 3.95 (s, 3H, OCH_3), 3.69 (s, 3H, CO_2CH_3); ^{13}C NMR δ 158.2 (CO_2CH_3), 154.2 (C-3'), 141.2 (C-1'), 135.8 (C-6'), 128.2 (C-5'), 123.4 (C_{pyr}), 121.6 (C-2'), 116.9 (C_{pyr}), 115.0 (C-4'), 114.4 (C_{pyr}), 112.6 (C≡N), 56.9 (OCH_3), 51.8 (CO_2CH_3); IR υ 3368 (NH_2), 2239 (C≡N), 1716, 1702 (C=O), 1629, 1586, 1561 (C=C, C=N), 1507, 1478, 1284 (C-O), 1229, 1190, 1125, 1082, 1012; MS (ESI) *m/z* 341, 343 $[M-H]^-$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{13}H_{11}{}^{35}Cl_2N_4O_3$ 341.0208, Found 341.0204.

Methyl 7-amino-2-(3-methoxyphenyl)-5-phenyl-2*H*-pyrazolo[4,3-*b*]pyridine-3 carboxylate (4a)

According to the general procedure III, pyridine **4a** was synthesized from the pyrazole **3j** (100 mg, 0.37 mmol) and acetophenone (220 µL, 1.85 mmol). Flash chromatography (cyclohexane/EtOAc 3:1) afforded **4a** as a yellow solid (104 mg, 75%): Mp 176-178 °C (EtOH); R_f 0.2 (cyclohexane/EtOAc 3:1); ^{1}H NMR ($CDCl_3$) δ 8.09-8.03 (m, 2H, H-2", H-6"), 7.48-7.42 (m, 2H, H-3", H-5"), 7.42-7.37 (m, 2H, H-4", H-5'), 7.10-7.03 (m, 3H, H-2', H-4', H-6'), 6.90 (s, 1H, H-6), 5.07 (br s, 2H, NH_2), 3.96 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 160.6 (C-5), 160.2 (C-3'), 160.0 ($\mathit{C}O_2CH_3$), 145.1 (C-7), 142.1 (C-1'), 140.4 (C-1"), 140.2 (C-3), 135.2 (C-7a), 129.7, 129.3 (C-4", C-5'), 128.7 (C-3", C-5"), 127.7 (C-2", C-6"), 125.5 (C-3a), 118.5 (C-6'), 115.5 (C-4'), 112.0 (C-2'), 100.1 (C-6), 55.7 (OCH_3), 52.6 ($CO_2\mathit{C}H_3$); IR υ 3205, 3144 (NH_2), 1714 (C=O), 1635, 1609 (C=N); MS (ESI) *m/z* 375 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{19}N_4O_3$ 375.1457, Found 375.1473.

Methyl 7-amino-2-(3-methoxyphenyl)-5-(2-nitrophenyl)-2*H*-pyrazolo[4,3-*b*]pyridine-3-carboxylate (4b)

According to the general procedure III, pyridine **4b** was synthesized from the pyrazole **3j** (100 mg, 0.37 mmol) and 2-nitroacetophenone (250 µL, 1.85 mmol). Flash chromatography (cyclohexane/EtOAc 3:1) afforded **4b** as a brown solid (45 mg, 30%): Mp 90-92 °C (EtOH); R_f 0.48 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$) δ 7.78-7.73 (m, 1H, H-3"), 7.67-7.62 (m, 1H, H-6"), 7.57-7.52 (m, 1H, H-5"), 7.47-7.42 (m, 1H, H-4"), 7.42-7.36 (m, 1H, H-5'), 7.09-7.01 (m, 3H, H-2', H-4', H-6'), 6.58 (s, 1H, H-6), 5.24 (br s, 2H, NH_2), 3.90 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 160.0 (C-3'), 159.9 ($\mathit{C}O_2CH_3$), 157.7 (C-5), 150.2 (C-2"), 145.5 (C-7), 141.9 (C-1'), 139.6 (C-3), 135.9 (C-1"), 134.7 (C-7a), 132.0 (C-5"), 131.1 (C-6"), 129.7 (C-5'), 129.3 (C-4"), 125.7 (C-3a), 124.2 (C-3"), 118.6 (C-6') 115.7 (C-4'), 112.0 (C-2'), 101.0 (C-6), 55.7 (OCH_3), 52.6 ($CO_2\mathit{C}H_3$); IR υ 3444, 3361 (NH_2), 2954, 2926, 2852 (C-H), 1718 (C=O), 1623, 1607, 1590, 1572 (C=N); MS (ESI) *m/z* 420 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{18}N_5O_5$ 420.1308, Found 420.1307.

Methyl 7-amino-2-(3-methoxyphenyl)-5-(3-nitrophenyl)-2*H*-pyrazolo[4,3-*b*]pyridine-3-carboxylate (4d)

According to the general procedure III, pyridine **4d** was synthesized from the pyrazole **3j** (200 mg, 0.73 mmol) and 3-nitroacetophenone (607 mg, 3.67 mmol). Flash chromatography (cyclohexane/EtOAc 3:1) afforded **4d** as a brown solid (254 mg, 80%): Mp 188-190 °C (EtOH); R_f 0.35 (cyclohexane/EtOAc 3:1); ^{1}H NMR (acetone-d_6) δ 9.04-9.00 (m, 1H, H-2''), 8.63-8.57 (m, 1H, H-6''), 8.34-8.25 (m, 1H, H-4''), 7.83-7.73 (m, 1H, H-5''), 7.54-7.45 (m, 1H, H-5'), 7.24-7.22 (m, 2H, H-2', H-6), 7.21-7.18 (m, 1H, H-4'), 7.16-7.13 (m, 1H, H-6'), 6.44 (br s, 2H, NH_2), 3.90 (s, 6H, CO_2CH_3, OCH_3); ^{13}C NMR (acetone-d_6) δ 160.9, 160.6 (C-3', $\mathit{C}O_2CH_3$), 157.2 (C-5), 149.8 (Cq), 147.8 (C-7), 143.3 (Cq, C-1'), 141,0 (C-3), 136.1 (C-7a), 134.1 (C-6''), 130.7 (C-5''), 130.4 (C-5'), 126.6 (C-3a), 124.2 (C-4''), 122.7 (C-2''), 119.2 (C-6'), 115.9 (C-4'), 112.9 (C-2'), 99.0 (C-6), 56.2 (OCH_3), 52.4 ($CO_2\mathit{C}H_3$); IR υ 3201, 3148 (NH_2), 1725 (C=O), 1650, 1619 (C=N); MS (ESI) *m/z* 420 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{18}N_5O_5$ 420.1308, Found 420.1301.

Methyl 7-amino-2,5-bis(3-methoxyphenyl)-2*H*-pyrazolo[4,3-*b*]pyridine-3-carboxylate (4e)

According to the general procedure III, pyridine **4e** was synthesized from the pyrazole **3j** (100 mg, 0.37 mmol) and 3-methoxyacetophenone (260 µL, 1.85 mmol). Flash chromatography (cyclohexane/EtOAc 3:1) afforded **4e** as a yellow solid (104 mg, 71%): Mp 118-120 °C (EtOH); R_f 0.15 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$) δ 7.71-7.66 (m, 1H, H-2''), 7.64-7.60 (m, 1H, H-6''), 7.44-7.39 (m, 1H, H-5'), 7.39-7.34 (m, 1H, H-5''), 7.10-7.03 (m, 3H, H-2', H-4', H-6'), 6.99-6.95 (m, 1H, H-4''), 6.94 (s, 1H, H-6), 5.01 (br s, 2H, NH_2), 3.97 (s, 3H, CO_2CH_3), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 160.4 (C-5), 160.2 ($\mathit{C}O_2CH_3$), 160.2 (C-3''), 160.1 (C-3'), 145.0 (C-7), 142.2 (C-1''), 142.0 (C-1'), 140.1 (C-3), 135.3 (C-7a), 129.8 (C-5'), 129.7 (C-5''), 125.7 (C-3a), 120.3 (C-6''), 118.6, 115.6, 112.1 (C-2', C-4', C-6'), 115.4 (C-4''), 113.1 (C-2''), 100.3 (C-6), 55.8, 55.6 (2 OCH_3), 52.6 ($CO_2\mathit{C}H_3$); IR υ 3468, 3369 (NH_2), 1717 (C=O), 1604 (C=N); MS (ESI) *m/z* 405 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{22}H_{21}N_4O_4$ 405.1563, Found 405.1552.

Methyl 7-amino-2-(3-methoxyphenyl)-5-(4-nitrophenyl)-2*H*-pyrazolo[4,3-*b*]pyridine-3-carboxylate (4f)

According to the general procedure III, pyridine **4f** was synthesized from the pyrazole **3j** (1.0 g, 3.70 mmol) and 4-nitroacetophenone (2.78 g, 18.50 mmol). Flash chromatography (cyclohexane/EtOAc 4:1) afforded **4f** as a yellow solid (1.20 g, 77%): Mp 222-224 °C (EtOH); R_f 0.43 (cyclohexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$) δ 8.33-8.27 (m, 2H, H-2”, H-6”), 8.27-8.20 (m, 2H, H-3”, H-5”), 7.47-7.38 (m, 1H, H-5’), 7.12-7.04 (m, 3H, H-2’, H-4’, H-6’), 6.95 (s, 1H, H-6), 5.15 (br s, 2H, NH_2), 3.97 (s, 3H, CO_2CH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 160.1 (C-3’), 160.0 ($\mathit{C}O_2CH_3$), 157.8 (C-5), 148.4 (C-4”), 146.5 (C-1”), 145.5 (C-7), 142.0 (C-1’), 140.2 (C-3), 135.1 (C-7a), 129.8 (C-5’), 128.6 (2C, C-3”, C-5”), 126.1 (C-3a), 124.0 (2C, C-2”, C-6”), 118.5, 115.7, 112.1 (C-2’, C-4’, C-6’), 100.0 (C-6), 55.8 (OCH_3), 52.8 ($CO_2\mathit{C}H_3$); IR υ 3306 (NH_2), 2926 (C-H), 1732 (C=O), 1623, 1570 (C=N); MS (ESI) *m/z* 420 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{18}N_5O_5$ 420.1308, Found 420.1320.

Methyl 7-amino-2,5-bis(4-methoxyphenyl)-2*H*-pyrazolo[4,3-*b*]pyridine-3-carboxylate (4g)

According to the general procedure III, pyridine **4g** was synthesized from the pyrazole **3j** (100 mg, 0.37 mmol) and 4-methoxyacetophenone (556 mg, 3.70 mmol). Flash chromatography (cyclohexane/EtOAc 3:1) afforded **4g** as a yellow solid (112 mg, 75%): Mp 190-192 °C (EtOH); R_f 0.15 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$) δ 8.04-7.98 (m, 2H, H-2”, H-6”), 7.43-7.36 (m, 1H, H-5’), 7.09-7.01 (m, 3H, H-2’, H-4’, H-6’), 6.98-6.93 (m, 2H, H-3”, H-5”), 6.87 (s, 1H, H-6), 5.14 (br s, 2H, NH_2), 3.95 (s, 3H, CO_2CH_3), 3.83 (s, 6H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 160.9 (C-4”), 160.2 ($\mathit{C}O_2CH_3$), 160.0 (C-3’), 160.0 (C-5), 145.2 (C-7), 142.1 (C-1’), 140.0 (C-3), 135.2 (C-7a), 132.8 (C-1”), 129.7 (C-5’), 129.0 (C-2”), 125.1 (C-3a), 118.6, 115.5, 112.0 (C-2’, C-4’, C-6’), 114.1 (C-3”), 99.6 (C-6), 55.7, 55.5 (2 OCH_3), 52.5 ($CO_2\mathit{C}H_3$); IR υ 3320, 3161 (NH_2), 1701 (C=O), 1604, 1599 (C=N); MS (ESI) *m/z* 405 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{22}H_{21}N_4O_4$ 405.1563, Found 405.1576.

Methyl 3-cyano-4-[(dimethylamino)methyleneamino]-1-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (5)

A suspension of the aminopyrazole **3j** (573 mg, 2.10 mmol) and dimethylformamide dimethyl acetal (0.42 mL, 3.16 mmol, 1.5 equiv.) in toluene (6 mL) was irradiated at 110 °C (power imput: 90 W) for 10 min. The reaction mixture was cooled to rt and concentrated *in vacuo*. Flash chromatography (cyclohexane/acetone 2:1) followed by recrystallization (acetone/pentane) afforded the formamidine **5** as a brown solid (524 mg, 76%): Mp dec.; R_f 0.42 (cyclohexane/acetone 2:1); ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H, HC=N), 7.31 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 7.00-6.85 (m, 3H, H-4', H-2', H-6'), 3.81 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 3.06 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$) δ 160.1 (C-3'), 159.6 (CO_2CH_3), 156.2 (HC=N), 144.8 (C_{pyr}), 141.5 (C-1'), 129.6 (C-5'), 124.1 (C_{pyr}), 120.2 (C_{pyr}), 117.5 (C-6'), 115.2 (C-4'), 113.7 (C≡N), 111.1 (C-2'), 55.7 (OCH_3), 52.2 (CO_2CH_3), 40.6, 34.5 (NMe_2); IR υ 2948, 2926 (CH), 2235 (C≡N), 1719 (C=O), 1631, 1608, 1593, 1536 (C=C, C=N), 1493, 1393, 1247, 1105, 1027; MS (ESI) *m/z* 328 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{16}H_{18}N_5O_3$ 328.1410, Found 328.1404.

Methyl 7-amino-2-(3-methoxyphenyl)-2*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate (6a)

According to the general procedure IV, pyrimidine **6a** was synthesized from the formamidine **5** (100 mg, 0.31 mmol) and ammonium acetate (36 mg, 0.46 mmol). Flash chromatography (DCM/MeOH 95:5) afforded **6a** as a yellow solid (27 mg, 30%): Mp 194-196 °C (EtOH); R_f 0.15 (DCM/MeOH 95:5); ^{1}H NMR (DMF-d_7) δ 8.37 (s, 1H, H-5), 8.30 (br s, 1H, NH), 7.98 (br s, 1H, NH), 7.54 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 7.36-7.30 (m, 1H, H-2'), 7.29-7.17 (m, 2H, H-4', H-6'), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, CO_2CH_3); ^{13}C NMR (DMF-d_7) δ 160.2 (C-3'), 159.6 (CO_2CH_3), 157.2 (C-7), 156.4 (C-5), 142.4 (C-1'), 140.5 (C-7a), 132.1 (C-3), 129.9 (C-5'), 125.3 (C-3a), 118.7 (C-6'), 115.4 (C-4'), 112.6 (C-2'), 55.7 (OCH_3), 51.9 (CO_2CH_3); IR υ 3469, 3414, 3320 (NH_2), 3087, 2972, 1720 (C=O), 1705, 1666, 1592, 1498, 1394, 1374, 1322, 1307, 1231, 1154, 1058; MS (ESI) *m/z* 300 $[M+H]^+$; HRMS (ESI) *m/z* $[M+Na]^+$ Calcd for $C_{14}H_{13}N_5NaO_3$ 322.0916, Found 322.0921.

Methyl 2-(3-methoxyphenyl)-7-(prop-2-ynylamino)-2*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate (6b)

According to the general procedure IV, pyrimidine **6b** was synthesized from the formamidine **5** (100 mg, 0.31 mmol) and propargylamine (30 µL, 0.46 mmol). Flash chromatography (gradient from EtOAc to

EtOAc/MeOH 98:2) afforded **6b** as a white solid (34 mg, 34%): Mp 198-200 °C (EtOH); R_f 0.35 (EtOAc); ^{1}H NMR δ 9.10-9.00 (m, 1H, NH), 8.43 (s, 1H, H-5), 7.46 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 7.25-7.21 (m, 1H, H-2'), 7.19-7.13 (m, 2H, H-4', H-6'), 4.33-4.27 (m, 1H, CH_2), 3.81 (s, 6H, OCH_3, CO_2CH_3), 3.10-3.07 (m, 1H, C≡CH); ^{13}C NMR δ 159.5 (C-3'), 158.7 (CO_2CH_3), 155.4 (C-5), 153.8 (C-7), 141.3 (C-1'), 139.2 (C-7a), 131.4 (C-3), 129.5 (C-5'), 124.9 (C-3a), 118.4 (C-6'), 115.4 (C-4'), 112.0 (C-2'), 80.8 (*C*≡CH), 72.8 (C≡*C*H), 55.6 (OCH_3), 52.0 (CO_2CH_3), 29.0 (CH_2); IR υ 3271 (NH_2), 1726 (C=O), 1564, 1493, 1460, 1390, 1356, 1336, 1302, 1263, 1250, 1222, 1186, 1152, 1109, 1072, 1041; MS (ESI) *m/z* 338 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{17}H_{16}N_5O_3$ 338.1253, Found 338.1240.

Methyl 7-(3-(diethylamino)propylamino)-2-(3-methoxyphenyl)-2*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate (6c)

According to the general procedure IV, pyrimidine **6c** was synthesized from the formamidine **5** (100 mg, 0.31 mmol) and *N,N*-diethylpropane-1,3-diamine (60 µL, 0.46 mmol). Flash chromatography (DCM/MeOH/Et_3N 90:10:0.5) afforded **6c** as a yellow solid (90 mg, 71%): R_f 0.10 (DCM/MeOH/Et_3N 90:10:0.5); ^{1}H NMR (acetone-d_6) δ 8.36 (s, 1H, H-5), 7.46 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, H-5'), 7.22-7.08 (m, 3H, H-2, H-4', H-6'), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, CO_2CH_3), 3.78-3.72 (m, 2H, H-a), 2.67-2.61 (m, 2H, H-c), 2.59-2.49 (m, 4H, CH_2CH_3), 1.93-1.83 (m, 2H, H-b), 1.08-1.00 (m, 6H, CH_2CH_3); ^{13}C NMR (63 MHz, acetone-d_6) δ 160.7 (C-3'), 160.1 (CO_2CH_3), 156.8 (C-5), 155.5 (C-7), 142.7 (C-1'), 140.6 (C-7a), 133.2 (C-3), 130.3 (C-5'), 126.1 (C-3a), 119.0 (C-6'), 116.0 (C-4'), 112.6 (C-2'), 56.1 (OCH_3), 53.1 (C-c), 52.4 (CO_2CH_3), 47.6 (2 CH_2CH_3), 41.1 (C-a), 26.4 (C-b), 12.3 (2 CH_2CH_3); IR υ 3245 (NH_2), 2957, 1715 (C=O), 1604, 1569, 1490, 1461, 1394, 1362, 1303, 1252, 1228, 1154, 1115; MS (ESI) *m/z* 413 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{29}N_6O_3$ 413.2301, Found 413.2308.

7-Cyclopropylamino-2-(3-methoxy-phenyl)-2*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid methyl ester (6d)

According to the general procedure IV, pyrimidine **6d** was synthesized from the formamidine **5** (100 mg, 0.31 mmol) and cyclopropylamine (32 µL, 0.46 mmol). Flash chromatography (DCM/MeOH 95:5) afforded

6d as a beige solid (90 mg, 87%): Mp dec.; R_f 0.19 (DCM/MeOH/Et_3N 95:5:0.5); ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H, H-5), 7.45-7.28 (m, 1H, H-5'), 7.10-6.88 (m, 3H, H-2', H-4', H-6'), 6.39 (br s, 1H, NH), 3.92 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 3.22-2.91 (m, 1H, H-a), 1.04-0.83 (m, 2H, H-b), 0.76-0.58 (m, 2H, H-b); ^{13}C NMR ($CDCl_3$) δ 160.0 (C-3'), 159.4 (CO_2CH_3), 156.8 (C-5), 156.1 (C-7), 141.5 (C-1'), 139.5 (C-7a), 132.1 (C-3), 129.8 (C-5'), 125.5 (C-3a), 118.4 (C-6'), 115.8 (C-4'), 112.0 (C-2'), 55.7 (OCH_3), 52.8 (CO_2CH_3), 23.7 (C-a), 7.3 (2 C-b); IR υ 3384 (NH_2), 1716 (C=O), 1610, 1587, 1496, 1473, 1402, 1304, 1252, 1162, 1151, 1125, 1055, 1021; MS (ESI) *m/z* 340 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{17}H_{18}N_5O_3$ 340.1410, Found 340.1408.

Methyl 7-(cyclohexylamino)-2-(3-methoxyphenyl)-2*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate (6e)

According to the general procedure IV, pyrimidine **6e** was synthesized from the formamidine **5** (100 mg, 0.31 mmol) and cyclohexylamine (54 µL, 0.46 mmol). Flash chromatography (EtOAc) afforded **6e** as a beige solid (66 mg, 57%): R_f 0.17 (EtOAc); ^{1}H NMR (acetone-d_6) δ 8.36 (s, 1H, H-5), 7.45 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 7.41-7.34 (m, 1H, NH), 7.19-7.09 (m, 3H, H-2', H-4', H-6'), 4.35-4.23 (m, 1H, CH_{cyc}), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, CO_2CH_3), 2.14-2.05 (m, 2H, CH_2), 1.86-1.77 (m, 2H, CH_2), 1.72-1.64 (m, 1H, CH_2), 1.57-1.38 (m, 4H, CH_2), 1.31-1.19 (m, 1H, CH_2); ^{13}C NMR (acetone-d_6) δ 160.8 (C-3'), 160.1 (CO_2CH_3), 156.8 (C-5), 155.0 (C-7), 142.9 (C-1'), 140.6 (C-7a), 133.0 (C-3), 130.3 (C-5'), 126.2 (C-3a), 119.3 (C-6'), 116.0 (C-4'), 113.0 (C-2'), 56.1 (OCH_3), 52.3 (CO_2CH_3), 50.3 (CH_{cyc}), 33.3 (2 CH_2), 26.4 (2 CH_2), 26.0 (2 CH_2); IR υ 2936, 1729 (C=O), 1617, 1608, 1566, 1490, 1399, 1358, 1302, 1251, 1203, 1111, 1083; MS (ESI) *m/z* 382 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{20}H_{24}N_5O_3$ 382.1879, Found 382.1863.

Methyl 2-(3-methoxyphenyl)-7-(phenylamino)-2*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate (6f)

According to the general procedure IV, pyrimidine **6f** was synthesized from the formamidine **5** (100 mg, 0.31 mmol) and aniline (42 µL, 0.46 mmol). Flash chromatography (EtOAc/cyclohexane 1:1) afforded **6f** as a yellow solid (82 mg, 76%): R_f 0.14 (EtOAc/cyclohexane 1:1); ^{1}H NMR (DMF-d_7) δ 10.71 (s, 1H, NH), 8.61 (s, 1H, H-5), 8.33-8.20 (m, 2H, H-2", H-6"), 7.63-7.55 (m, 1H, H-5'), 7.50-7.36 (m, 3H, H-3", H-5", H-2'), 7.34-7.12 (m, 3H, H-6', H-4', H-4"), 3.93 (s, 3H, OCH_3), 3.91 (s, 3H, CO_2CH_3); ^{13}C NMR (DMF-d_7) δ 161.0 (C-3'), 160.1 (CO_2CH_3), 156.0 (C-5), 153.7 (C-7), 142.9 (C-1'), 141.0 (C-7a), 140.6 (C-1"), 132.8 (C-3), 130.7 (C-5'), 129.5 (2C, C-3", C-5"), 126.6 (C-3a), 124.6 (C-4"), 122.4 (2C, C-2", C-6"), 119.5 (C-6'), 116.2 (C-4'), 113.4 (C-2'), 56.4 (OCH_3), 52.7 (CO_2CH_3); IR υ 3365, 1723 (C=O), 1624, 1591, 1565, 1509, 1491, 1400, 1322, 1235, 1179, 1113, 1044; MS (ESI) *m/z* 376 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{20}H_{18}N_5O_3$ 376.1410, Found 376.1392.

Methyl 7-(benzylamino)-2-(3-methoxyphenyl)-2*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate (6g)

According to the general procedure IV, pyrimidine **6g** was synthesized from the formamidine **5** (60 mg, 0.18 mmol) and benzylamine (30 µL, 0.27 mmol). Flash chromatography (DCM/MeOH 98:2) followed by recrystallisation in EtOH afforded **6g** as yellow solid (58 mg, 82%): R_f 0.35 (DCM/MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H, H-5), 7.43-7.26 m, 6H, H-5', H-2", H-3", H-4", H-5", H-6"), 7.08-6.96 (m, 3H, H-2', H-4', H-6'), 6.40-6.31 (m, 1H, NH), 4.92-4.81 (m, 2H, CH_2), 3.96 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 160.1 (C-3'), 159.5 (CO_2CH_3), 156.9 (C-5), 154.9 (C-7), 141.5 (C-1'), 139.7 (C-7a), 137.5 (C-1"), 132.2 (C-3), 129.8 (C-5'), 129.1 (C-3", C-5"), 128.3 (C-2", C-6"), 128.2 (C-4"), 125.6 (C-3a), 118.5 (C-6'), 115.9 (C-4'), 112.0 (C-2'), 55.8 (CO_2CH_3), 52.0 (OCH_3), 44.9 (CH_2); IR υ 3255 (NH), 2962, 2833, 1731 (CO_2), 1607, 1562, 1493, 1448, 1392, 1350, 1300, 1251, 1223, 1181, 1150, 1105, 1065; MS (ESI) *m/z* = 390 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{20}N_5O_3$ 390.1566, Found 390.1564.

Methyl 4-acetamido-3-cyano-1-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (7)

To an ice-cooled solution of the aminopyrazole **3j** (2 g, 7.35 mmol) in DCM (34 mL) were successively added DMAP (942 mg, 7.72 mmol, 1.05 equiv.) and acetyl chloride (530 µL, 7.42 mmol, 1 equiv.). The reaction mixture was stirred at rt for 18 h. After dilution with DCM (150 mL), the organic layer was successively washed with 0.5 N HCl (30 mL), satd. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (DCM/MeOH 98:2) afforded **7** as a grey solid (1.97 g, 86%): Mp 176-178 °C (EtOH); R_f 0.50 (DCM/MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ 8.52 (br s, 1H, NHAc), 7.35 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 7.04-7.00 (m, 1H, H-4'), 6.92-6.88 (m, 2H, H-6', H-2'), 3.83 (s, 3H, OCH_3), 3.74 (s, 3H, CO_2CH_3), 2.25 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 168.1 ($COCH_3$), 160.1 (C-3'), 159.3 (CO_2CH_3), 140.6 (C-1'), 129.9 (C_{pyr}), 129.7 (C-5'), 123.0 (C_{pyr}), 120.6 (C_{pyr}), 118.2 (C-6'), 115.9 (C-4'), 112.6 (C≡N), 111.8 (C-2'), 55.8 (OCH_3), 52.9 (CO_2CH_3), 23.7 ($COCH_3$); IR υ 3302 (NH), 2245 (C≡N), 1730 (C=O), 1686 (HNC=O), 1603, 1561 (C=C, C=N), 1461 (CH_3), 1260, 1246 (C-O), 1133, 1054, 1028; MS (ESI) *m/z* 337 $[M+Na]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{15}N_4O_4$ 315.1093, Found 315.1084.

Methyl 4-acetamido-3-(*N'*-hydroxycarbamimidoyl)-1-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (8)

A mixture of the aminopyrazole **7** (1.97 g, 6.27 mmol), hydroxylamine hydrochloride (2.19 g, 31.5 mmol, 5 equiv.) and Na_2CO_3 (1.68 g, 15.8 mmol, 2.5 equiv.) in EtOH (125 mL) was heated at 80 °C for 1 h. After cooling to rt, the solution was concentrated *in vacuo*. The resulting residue was dissolved in DCM (250 mL) and washed with brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the *N*-hydroxyamidine **8** as a yellow solid (2.10 g, 97%) which was used without further purification: Mp 178-180 °C; R_f 0.14 (DCM/MeOH 95:5); ^1H NMR ($CDCl_3$) δ 9.02 (br s, 1H, NHAc), 7.30 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 7.03-6.91 (m, 3H, H-2', H-4', H-6'), 5.32 (br s, 2H, NH_2), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, CO_2CH_3), 2.13 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 168.0 ($COCH_3$), 161.3 (CO_2CH_3), 160.3 (C-3'), 149.2 (C=N-OH), 141.0 (C-1'), 134.2 (C_{pyr}), 129.8 (C-5'), 128.2, 120.3 (2 C_{pyr}), 117.3 (C-6'), 115.1 (C-4'), 111.0 (C-2'), 55.8 (OCH_3), 52.6 (CO_2CH_3), 23.7 ($COCH_3$); IR υ 3255 (NH, OH), 1731 (2C=O), 1609, 1591, 1562, 1527 (C=C, C=N), 1495, 1349, 1306, 1251 (C-O); MS (ESI) *m/z* 348 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{18}N_5O_5$ 348.1308, Found 348.1296.

Methyl 4-acetamido-1-(3-methoxyphenyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)-1*H*-pyrazole-5-carboxylate (9a)

According to the general procedure (V), oxadiazole **9a** was synthesized from *N*-hydroxyamidine **8** (50 mg, 0.14 mmol) and acetyl chloride (12 µL, 0.16 mmol) within 16 h. Flash chromatography (EtOAc/cyclohexane 8:2) afforded **9a** as a white solid (31 mg, 71%): Mp dec.; R_f 0.13 (EtOAc/cyclohexane

7:3); ^{1}H NMR ($CDCl_3$) δ 8.32 (br s, 1H, NHAc), 7.31 (dd, J = 8.2 Hz, J = 8.2 Hz, 1H, H-5'), 7.08-6.99 (m, 2H, H-2', H-6'), 6.98-6.93 (m, 1H, H-4'), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, CO_2CH_3), 2.68 (s, 3H, N=C-CH_3), 2.22 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 177.0 (C-5''), 167.9 ($\mathit{C}OCH_3$), 163.2 (C-3''), 160.7, 160.1 (C-3', $\mathit{C}O_2CH_3$), 140.8 (C-1'), 132.2 (C_{pyr}), 129.6 (C-5'), 128.3 (C_{pyr}), 122.1 (C_{pyr}), 117.6 (C-6'), 115.5 (C-4'), 111.0 (C-2'), 55.8 (OCH_3), 52.7 ($CO_2\mathit{C}H_3$), 23.8 ($CO\mathit{C}H_3$), 12.5 (CH_3); IR υ 3260 (NH), 1728 (C=O), 1669 (HNC=O), 1560, 1550 (C=C, C=N), 1476 (CH), 1224 (C-O); MS (ESI) *m/z* 372 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{17}H_{18}N_5O_5$ 372.1308, Found 372.1286.

Methyl 4-acetamido-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-1-(3-methoxyphenyl)-1*H*-pyrazole-5-carboxylate (9b)

According to the general procedure V, oxadiazole **9b** was synthesized from *N*-hydroxyamidine **8** (50 mg, 0.14 mmol) and cyclopropanecarbonyl chloride (14 µL, 0.16 mmol) within 4 h. Flash chromatography (DCM/MeOH 98:2) afforded **9b** as a grey solid (44 mg, 77%): Mp 124-126 °C (EtOH); R_f 0.26 (EtOAc/cyclohexane 8:2); ^{1}H NMR δ 9.62 (br s, 1H, NHAc), 7.51-7.37 (m, 1H, H-5'), 7.19-6.92 (m, 3H, H-2', H-4', H-6'), 3.81 (s, 3H, OCH_3), 3.70 (s, 3H, CO_2CH_3), 2.50-2.36 (m, 1H, Hcyc), 2.03 (m, 3H, $COCH_3$), 1.36-1.10 (m, 4H, Hcyc); ^{13}C NMR δ 181.5 (C-5''), 168.5 ($\mathit{C}OCH_3$), 161.9 (C-3''), 158.7 (C-3', $\mathit{C}O_2CH_3$), 140.4 (C-1'), 135.2 (C_{pyr}), 129.8 (C-5'), 129.1 (C_{pyr}), 122.9 (C_{pyr}), 117.3 (C-6'), 114.9 (C-4'), 110.8 (C-2'), 55.5 (OCH_3), 52.3 ($CO_2\mathit{C}H_3$), 22.6 ($CO\mathit{C}H_3$), 10.2 (CH_2), 7.1 (2C, CH_2); IR υ 3215 (NH), 1735 (C=O), 1661 (HNC=O), 1577, 1550 (C=C, C=N), 1478 (CH), 1243 (C-O), 1127, 1023; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{19}H_{20}N_5O_5$ 398.1458, Found 398.1464.

Methyl 4-acetamido-1-(3-methoxyphenyl)-3-(5-phenyl-1,2,4-oxadiazol-3-yl)-1*H*-pyrazole-5-carboxylate (9c)

According to the general procedure (V), oxadiazole **9c** was synthesized from *N*-hydroxyamidine **8** (50 mg, 0.14 mmol) and benzoyl chloride (18 µL, 0.28 mmol) within 16 h. Flash chromatography (DCM/MeOH 98:2) afforded **9c** as a white solid (40 mg, 64%): Mp 186-188 °C (EtOH); R_f 0.31 (DCM/MeOH 98:2); ^{1}H NMR δ 9.81 (br s, 1H, NHAc), 8.24-8.15 (m, 2H, H-2''', H-6'''), 7.78-7.72 (m, 1H, H-4'''), 7.71-7.64 (m, 2H, H-3''', H-5'''), 7.50-7.42 (m, 1H, H-5'), 7.16-7.05 (m, 3H, H-2', H-4', H-6'), 3.83 (s, 3H, OCH_3), 3.73 (s, 3H, CO_2CH_3), 2.08 (s, 3H, $COCH_3$); ^{13}C NMR δ 175.0 (C-5''), 168.5 (*C*OCH_3), 162.7 (C-3''), 159.4 (C-3'), 158.7 (*C*O_2CH_3), 140.5 (C-1'), 135.0 (C_{pyr}), 133.5 (C-4'''), 129.8 (C-5'), 129.6 (C-3''', C-5'''), 129.2 (C_{pyr}), 127.9 (C-2''', C-6'''), 123.2, 123.1 (C-1''', C_{pyr}), 117.3 (C-6'), 114.9 (C-4'), 110.8 (C-2'), 55.5 (OCH_3), 52.3 (CO_2*C*H_3), 22.7 (CO*C*H_3); IR υ 3251 (NH), 1726 (C=O), 1671 (HNC=O), 1607, 1584, 1550 (C=C, C=N), 1493, 1468, 1453, 1476, 1369, 1248, 1224, 1127, 1048, 1031; MS (ESI) *m/z* 434 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{22}H_{20}N_5O_5$ 434.1459, Found 434.1455.

Methyl 4-acetamido-1-(3-methoxyphenyl)-3-(5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-1*H*-pyrazole-5-carboxylate (9d)

According to the general procedure (V), oxadiazole **9c** was synthesized from *N*-hydroxyamidine **8** (50 mg, 0.14 mmol) and 4-methoxybenzoyl chloride (22 µL, 0.16 mmol) within 16 h. Flash chromatography (DCM/MeOH 98:2) afforded **9c** as a beige solid (54 mg, 81%): Mp dec.; R_f 0.23 (DCM/MeOH 98:2); ^{1}H NMR δ 9.79 (br s, 1H, NHAc), 8.16-8.11 (m, 2H, H-2''', H-6'''), 7.49-7.43 (m, 1H, H-5'), 7.24-7.18 (m, 2H, H-3''', H-5'''), 7.14-7.05 (m, 3H, H-2', H-4', H-6'), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, CO_2CH_3), 3.72 (s, 3H, OCH_3), 2.08 (s, 3H, $COCH_3$); ^{13}C NMR δ 174.9 (C-5''), 168.5 (*C*OCH_3), 163.2 (C-4'''), 162.6 (C-3''), 159.5 (C-3'), 158.8 (*C*O_2CH_3), 140.5 (C-1'), 135.2 (C_{pyr}), 130.0 (C-2''', C-6'''), 129.8 (C-5'), 129.2 (C_{pyr}), 123.1 (C-4), 117.4 (C-6'), 115.5 (C-1'''), 115.1 (C-3''', C-5'''), 115.0 (C-4'), 110.9 (C-2'), 55.6 (OCH_3), 55.5 (OCH_3), 52.3 (CO_2*C*H_3), 22.7 (CO*C*H_3); IR υ 3284, 3259 (NH), 1728 (C=O), 1676 (HNC=O), 1609, 1585 (C=C, C=N), 1501 (CH), 1466, 1253 (C-O), 1172, 1050, 1021; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{23}H_{29}N_5O_6$ 464.1570, Found 464.1569.

Methyl 4-acetamido-1-(3-methoxyphenyl)-3-(5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl)-1*H*-pyrazole-5-carboxylate (9e)

According to the general procedure (V), oxadiazole **9e** was synthesized from *N*-hydroxyamidine **8** (50 mg, 0.14 mmol) and 4-nitrobenzoyl chloride (30 mg, 0.16 mmol) within 4 h. Flash chromatography (DCM/MeOH 98:2) afforded **9e** as a beige solid (57 mg, 83%): Mp 248-250 °C (EtOH); R_f 0.26

($CHCl_3$/MeOH 98:2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.53-8.38 (m, 4H, H-2''', H-3''', H-5''', H-6'''), 8.26 (br s, 1H, NHAc), 7.34 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, H-5'), 7.12-6.93 (m, 3H, H-2', H-4', H-6'), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, CO_2CH_3), 2.26 (s, 3H, $COCH_3$); ^{13}C NMR δ 173.4 (C-5''), 168.6 ($\mathit{C}OCH_3$), 163.0 (C-3''), 159.4 (C-3'), 158.7 ($\mathit{C}O_2CH_3$), 150.0 (C-4'''), 140.4 (C-1'), 134.8 (C_{pyr}), 129.8 (C-5'), 129.5 (C-2''', C-6'''), 129.2 (C_{pyr}), 128.4 (C-1'''), 124.6 (C-3''', C-5'''), 123.3 (C_{pyr}), 117.4 (C-6'), 115.0 (C-4'), 110.9 (C-2'), 55.5 (OCH_3), 52.3 ($CO_2\mathit{C}H_3$), 22.7 ($CO\mathit{C}H_3$); IR υ 3245 (NH), 1727 (C=O), 1676 (NHC=O), 1607, 1574, 1560 (C=C, C=N), 1529 (NO_2), 1495 (CH), 1347 (NO_2), 1242 (C-O), 1132, 1048, 1032; MS (ESI) *m/z* 479 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{22}H_{19}N_6O_7$ 479.1315, Found 479.1331.

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SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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