VERSATILE THREE COMPONENT COUPLING FOR THE SYNTHESIS OF PYRAZOLOPYRIDINES AND OTHER PYRIDO FUSED SYSTEMS

Carmen Almansa, Marina Virgili, Elena Carceller, and Pedro Grima-Poveda

Innovation and Drug Discovery, Palau Pharma S. A. (Grupo Uriach). Av. Camí Reial, 51-57, E-08184, Palau-Solità i Plegamans, Spain

N. V. Organon, Molenstraat 110, 5340 BH Oss, The Netherlands
calmansa@palaupharma.com

Abstract - A new unexpected reaction of 1-(4-fluorophenyl)-2-(4-pyridyl)ethanone 2 with 3-aminopyrazole, involving loss of a 4-pyridylmethyl group, afforded 4,6-bis(4-fluorophenyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine 1 in good yields. Investigation of the features of this cyclization led to the development of a new three component coupling for the synthesis of pyrazolo[3,4-b]pyridines, from a ketone, an aldehyde and a 3-aminopyrazole in the presence of acid catalysis and a protic solvent. The study of the scope of this reaction showed its remarkable versatility and its usefulness in the preparation of other bicyclic systems, such as thieno[3,2-b]pyridines, pyrrolo[3,2-b]pyridines, imidazo[4,5-b]pyridines, furo[2,3-b]pyridines, isoxazolo[5,4-b]pyridines and, isothiazolo[5,4-b]pyridines. The three component nature of this reaction makes it suitable for the preparation of combinatorial libraries since scaffold decoration can be easily achieved in one step.

INTRODUCTION

In relation to a p38 MAP kinase program, we were interested in the synthesis of pyrazolopyrimidines such as A and other fused bicyclic compounds. Pyrazolopyrimidines are usually prepared by reaction of 1,3-dicarbonyl compounds and 3-aminopyrazoles under acidic conditions. However, when the dimethylaminomethylene derivative 3 was reacted with 3-aminopyrazole in the presence of c.HCl, the expected compound A was not produced and instead pyrazolopyridine 13 was isolated in very low yield (Scheme 1). Driven by the fact that 1 showed submicromolar p38 MAP kinase inhibition, we decided to investigate its preparation with the aim of explaining its formation, improving the yield and developing a method for the synthesis of analogues.
RESULTS AND DISCUSSION

The first hypothesis was that 1 arose from ketone 2 which could have been present in the reaction media. In fact, when the reaction was repeated in the same conditions (1 equivalent of 3-aminopyrazole and 1 equivalent of cHCl in EtOH) but using ketone 2 instead of its dimethylaminomethylene derivative, 1 was isolated in higher yield (15 %). In this case, the dihydro derivative 4 (Figure 1) was also isolated in similar yield and it was postulated that maybe by increasing the reaction temperature, in situ oxidation of 4 to 1 could be facilitated. It was indeed shown that using methoxyethanol as a solvent, the amount of 4 was reduced. Finally, the amount of HCl present in the reaction was varied from 1 to 0 equivalent at 0.1 intervals, which indicated that the optimal quantity was 0.3 equivalent and that in the absence of HCl the reaction did not take place. Thus, the best procedure developed provided 1 in 47 % yield together with 10 % of 5 as byproduct.

Besides the need of acid catalysis, it was shown that this process did not work when pyridine was replaced by other aromatic groups, such as phenyl or 4-fluorophenyl, and that the free pyrazole NH is needed, since 5-amino-1-methylpyrazole or 5-amino-2-methylpyrazole gave no reaction. Additionally, a cross coupling experiment starting from 0.5 equivalents of two different ketones, 2 and 1-phenyl-2-(4-pyridyl)ethanone, gave rise to the four possible isomers (1 and 6a-c) in similar amounts, as indicated by HPLC-MS of the mixture.
A possible mechanism that would explain all these findings is postulated in Scheme 2. Initial electrophilic substitution of the pyrazole ring would allow formation of intermediate B (isolated as byproduct 5), which on subsequent imine formation to give C and rearrangement would afford a cyclized derivative (D) upon which picoline elimination would take place. This hypothesis would justify the isolation of 5 as byproduct and the need of pyridine to be present, since the picolyl group is much better leaving group than benzyl. It would also agree with the observations of the required presence of pyrazole NH and with the isomeric mixture isolated in the crossing experiments previously mentioned.

Scheme 2

The new cyclization thus described was quite convenient for the synthesis of compounds with the same substituent at positions 4 and 6, and in fact, several of such derivatives were prepared in similar yields from the corresponding ketones (results not shown). However, from a medicinal chemistry point of view,
a process in which differently substituted derivatives could be obtained, was needed. The possibility of finding a suitable reagent that could react with ketone 2 and aminopyrazole in the conditions used for the preparation of 1 was then investigated. Initial trials with an acid chloride were unsuccessful but when 3,4-dichlorobenzaldehyde was used, the cyclization proceeded in good yield to afford 7. NOE experiments indicated (Figure 2) that the 3,4-dichlorophenyl ring was positioned vicinal to the pyrazole CH.

![Figure 2](image)

The synthesis of 1 from ketone 2, 3-aminopyrazole and 4-fluorobenzaldehyde was used to further investigate the reaction conditions. Acid catalysis was shown to be necessary and the use of 0.3 equivalents of HCl was maintained. Regarding the solvent, it was shown that toluene did not provide any cyclized compound, while the use of methoxyethanol (method A) provided 1 in 68 % yield. Using ethanol (method B) 1 was obtained in 26 % yield together with 70 % of its dihydroderivative 4. Method A was preferred to method B in order to minimize formation of dihydro derivative, but as will be shown below, method B provided better yields in the case of unstable heterocyclic amines or when some functionality present in any of the reagents precluded the use of high temperatures.

The scope of the reaction was then further explored (Scheme 3). The reaction of ketone 2 with different aldehydes 9 was first investigated and as shown in Table 1 good yields of pyrazolopyridines 10a-g were obtained with several aromatic and aliphatic aldehydes.

![Scheme 3](image)
Table 1. Pyrazolopyridines 1, 7 and 10a-n.

<table>
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<tr>
<th>comp</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
<th>Method</th>
<th>Yield (%)</th>
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Other substituents were also introduced at positions 5 and 6 and good yields were obtained for the substituted pyridyl and pyrimidinyl derivatives 10h-i. In this case the presence of the pyridylmethyl leaving group was not required and the reaction proceeded, although in lower yields, when R₅ was fluorophenyl (10j), methyl (10k) or hydrogen (10l). When 1-phenyl-2-propanone was used, the two possible products 10m and 10n were obtained in 17 and 8 % yield respectively. The corresponding starting ketones 8 were commercially available or were prepared in a similar manner to that described in the experimental section for the preparation of 2.

Aminopyrazoles substituted at the 5 position could also be used. Hence, 3-amino-5-methylpyrazole provided 11 in 56 % yield, while 3-amino-5-phenylpyrazole gave the 3-phenyl derivative 12 in 60 % yield (Figure 2).
This reaction represents the first general 3 component coupling for the synthesis of 1(2)-unsubstituted pyrazolopyridines, which are commonly prepared by reaction of 3-cyano or 3-acetyl-2-halopyridines with hydrazine and subsequent functional group modification. The preparation of 1(2)-unsubstituted pyrazolopyridines from direct coupling of 1,3-dicarbonyl compounds or α-keto-olefins with 3-aminopyrazoles competes with the formation of the pyrazolopyrimidine framework, which is predominantly formed in many instances, as illustrated by Suzuki et al. (Figure 3). Only Quiroga et al. have reported two examples of direct preparation of 1(2)-unsubstituted pyrazolopyridines and they involve the reaction of α-cyanochalcones with 3-aryl-5-aminopyrazoles and the reaction of benzoylacetonitrile with 5-aminopyrazolone and aromatic aldehydes.

![Figure 3](image)

The three component cyclization no longer required the presence of the pyrazole NH, in contrast to the coupling in the absence of aldehyde. Thus, the 1-ethyl and 2-methyl derivatives 13 and 14 were isolated in 64 and 71% yield respectively, by reaction of 2 and 4-fluorobenzaldehyde with the corresponding pyrazoles (Figure 4).

![Figure 4](image)

Since the reaction worked with alkylated pyrazoles, the general applicability of this methodology for the preparation of other bicyclic systems was studied. Commercial availability of five-membered heterocyclic amines is limited, since many of these systems are highly unstable. One representative of each of the commercially available different chemotypes was selected and the results are shown in Table 2.
Table 2. Preparation of bicycles 16 from amines 15.

Best yields were obtained for the preparation of the thieno[3,2-b]pyridine (16d), pyrrolo[3,2-b]pyridine (16e) and imidazo[4,5-b]pyridine (16f) scaffolds. In this latter case a high proportion of decarboxylated derivative 16g was obtained using method A, but it was substantially reduced under the lower temperature used in method B. Other frameworks, such as the furo[2,3-b]pyridine (16c), isoxazolo[5,4-b]pyridine (16b) and isothiazolo[5,4-b]pyridine (16a) were obtained in moderate yields. Compound 16a could only be isolated under the milder conditions of method B, indicating that amine instability at higher temperatures could be the cause for the reaction not to work using methoxyethanol. This is probably also the cause for the 1H-pyrazolo[4,3-b]pyridine system (16h) to be isolated in only 5 % yield, since amine 15h is obtained by in situ hydrogenation of the corresponding commercially available nitro derivative and shows marked instability.
There is no precedent for the synthesis of any of the above mentioned bicyclic systems by a three component coupling, such as the one described here. Usual synthesis imply cyclization from conveniently functionalized pyridines and suitable reagents or reaction of the corresponding aromatic amines with 1,3-dicarbonyl derivatives to afford thieno[3,2-b]pyridines, pyrrolo[3,2-b]pyridines, imidazo[4,5-b]pyridines, furo[2,3-b]pyridines, isoxazolo[5,4-b]pyridines and isothiazolo[5,4-b]pyridines. Due to its simplicity, this reaction provides a useful addition to the existing arsenal of methodology for the preparation of said bicycles. Moreover its three component nature makes it attractive for the preparation of combinatorial libraries since scaffold decoration can be easily achieved in one step.

**EXPERIMENTAL**

Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS silica gel Chromagel 60 ACC-(230-400 mesh). Melting points were determined with a Mettler FP 80 central processor melting point apparatus and are uncorrected. Structure identity was established with $^1$H-(300 MHz) NMR spectra, which were recorded on a Bruker Avance DPX-300 spectrometer and in three cases (4, 16a and 16h) with a $^1$H-(400 MHz) NMR spectra, which were recorded on a Bruker Avance DPX-400. They are reported in ppm on the $\delta$ scale, from the reference indicated. Additional peaks not attributable to the assigned structure are not observed in any of the spectra. Exact Mass determination was performed on a Waters Acquity UPLC system (Waters Corporation, Milford, USA) coupled to a Waters Micromass QTOF-Premier (Manchester, UK) equipped with an electrospray source operating in positive ion mode. The source was set at 120 °C with a desolvation gas temperature of 400 °C and a desolvation gas flow of 1000 L h$^{-1}$ was employed. The capillary voltage was set at 3.0 kV and the cone voltage to 20 V. Leucine enkephalin (conc. 500 pg/µL) was employed as the lock-mass [M+H]$^+$ = 556.2771 at a flow rate of 30 µL/min. Data was collected in centroid mode. Combustion analyses were performed with a EUROVECTOR EA 3000 analyzer.

**1-(4-Fluorophenyl)-2-(4-pyridyl)ethanone (2).**  

a) 4-Fluoro-N-methoxy-N-methylbenzamide. To a mixture of N,O-dimethylhydroxylamine hydrochloride (25.54 g, 261.8 mmol) and CH$_2$Cl$_2$ (443 mL) under an argon atmosphere at 0 °C, 4-fluorobenzoyl chloride (34.59 g, 218.2 mmol) was added followed by the slow addition of triethylamine (48.13 g, 475.6 mmol). The reaction was stirred for 30 min at 5 °C and allowed to reach rt. It was washed with 5% aqueous citric acid (180 mL) and with 5% aqueous NaHCO$_3$ (180 mL). The aqueous phase was extracted with CH$_2$Cl$_2$. The organic phase was dried over Na$_2$SO$_4$ and concentrated to dryness, to afford the desired compound (20.23 g, 88%).

b) To a solution of diisopropylamine (23.4 mL, 165.7 mmol) in THF (250 mL), cooled to –78 °C, BuLi (103.5 mL of a 1.6 M solution in hexane, 165.7 mmol) was added dropwise under an argon atmosphere.
After 5 minutes, a solution of 4-methylpyridine (10.28 g, 110.4 mmol) in THF (85 mL) was added over 20 min. The mixture was stirred at 0 °C for 15 min and a solution of 4-fluoro-N-methoxy-N-methylbenzamide in THF (85 mL) was added over a 30 min period. The reaction was allowed to reach room temperature. Water (100 mL) and EtOAc (100 mL) were added and the mixture was stirred for 30 min. The organic phase was separated, dried over Na₂SO₄ and concentrated to dryness, to afford 2 as a yellowish oil (24.32 g, 100 %). ¹H NMR (300 MHz, CDCl₃) δ (TMS): 4.29 (s, 2 H), 7.14 – 7.23 (complex signal, 4 H), 8.05 (m, 2 H), 8.59 (dd, J₀ = 1.6 Hz, Jₘ = 4.4 Hz, 2 H).

4,6-Bis(4-fluorophenyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (1).

Cyclization of ketone 2 and aminopyrazole. To a solution of 2 (23.56 g, 109.4 mmol) in 2-methoxyethanol (150 mL), a solution of 3-amino-2H-pyrazole (10.00 g, 120.3 mmol) in 2-methoxyethanol (170 mL) and 37 % HCl (3.23 g, 32.8 mmol) were added under argon. This was heated to reflux for 24 h. It was allowed to cool to rt and concentrated. The solid obtained was dissolved in CHCl₃ (400 mL) and MeOH (50 mL) and washed with 0.1 N HCl (300 mL) and 1 N NaOH (300 mL). The organic phase was dried over Na₂SO₄ and concentrated to dryness, to afford 1 in solid cream form (9.93 g, 47 %): mp > 300 °C; ¹H-NMR (300 MHz, CDCl₃ + CD₃OD) δ (TMS): 4.08 (s, NH + H₂O-CD₃OD), 6.80 - 7.01 (complex signal, 6 H), 7.21 (m, 2 H), 7.28 (m, 2 H), 7.95 (s, 1 H), 8.27 (dd, J₀ = 1.4 Hz, Jₘ = 4.6 Hz, 2 H); ¹³C-NMR (75 MHz, CDCl₃ + CD₃OD) δ (TMS): 118.12 (C), 118.82 (2CH, J = 22 Hz, C-F), 130.28 (2CH, J = 22 Hz, C-F), 127.30 (C), 129.26 (C), 130.05 (2CH), 134.92 (CH), 134.98 (2CH, J = 8 Hz, C-F), 135.34 (2CH, J = 8 Hz, C-F), 139.53 (C), 141.72 (C), 151.04 (C), 152.24 (CH, x2), 161.30 (C), 166.33 (2C, J = 248 Hz, C-F); HRMS for C₂₃H₁₄F₂N₄ (M+H⁺) requires 385.1265, found 385.1260; Anal. Calcd for C₂₃H₁₄F₂N₄·0.5H₂O: C, 70.82; H, 3.82; N, 14.10. Found: C, 70.59; H, 3.58; N, 14.12.

The combined aqueous phase was concentrated to half the volume and it was saturated with NaCl. It was extracted with AcOEt and the organic phase was dried and concentrated to dryness, to afford 2 as a yellow solid: mp 176-178 °C; ¹H-NMR (300 MHz, CDCl₃) δ (TMS): 6.80 (d, J = 6 Hz, 2 H), 7.09 (m, 2 H), 7.15 (m, 1H), 7.28 (m, 3 H), 8.33 (d, J = 6 Hz, 2 H), 10.90 (s, 1H).

Method A: To a solution of 2 (0.30 g, 1.4 mmol) in 2-methoxyethanol (4 mL), 3-amino-2H-pyrazole (0.13 g, 1.5 mmol), 4-fluorobenzaldehyde (0.17 g, 1.4 mmol) and 37 % HCl (0.04 g, 0.4 mmol) were added under an argon atmosphere. The mixture was heated to reflux overnight. It was allowed to cool and concentrated. The solid obtained was dissolved in CHCl₃ and some drops of MeOH. Saturated aqueous NaHCO₃ was added and the aqueous phase was extracted 3 times with CHCl₃. The combined organic phases were dried over Na₂SO₄ and concentrated to dryness. The crude product was purified by chromatography on silica gel using hexane-EtOAc mixtures of increasing polarity as eluent to afford 1 (0.37 g, 68 %).
Method B: To a solution of 2 (9.73 g, 45 mmol) in EtOH (150 mL), 3-amino-2H-pyrazole (4.13 g, 50 mmol), 4-fluorobenzaldehyde (4.88 mL, 45 mmol) and 37 % HCl (1.13 g, 13 mmol) were added. The mixture was heated to reflux for 18 h. Then it was allowed to cool and a precipitate was formed. The solid was filtered, washed thoroughly with water and dried under vacuum to give 4.46 g of 1 (26 %).

The filtrate was concentrated and recrystallized from toluene/acetone. The solid thus obtained was filtered and dried to give 1 4 (2.26 g, 70 %) as a yellow solid. 1H-NMR (400 MHz, DMSO-d6) δ (TMS): 3.43 (brs, NH + H2O), 5.44 (s, 1 H), 7.06 (d, J = 6 Hz, 2 H), 7.11 (t, J = 8 Hz, 2 H), 7.29 (t, J = 8 Hz, 2 H), 7.42 (m, 3H), 7.52 (m, 2 H), 8.21 (d, J = 6 Hz, 2 H), 10.14 (s, NH).

The compounds described in the text were prepared following methods A or B as indicated in Tables 1-3.

3-Amino-4-[1-(4-fluorophenyl)-2-(pyridin-4-yl)ethenyl]pyrazole (5). Yellow solid; 1H-NMR (400 MHz, CD3OD) δ (TMS): 4.85 (s, 3 H + H2O), 6.76 (broad s, 1 H), 6.88 (d, J = 6 Hz, 2 H), 7.09 (s, 1 H), 7.11 (m, 2 H), 7.26 (m, 2 H), 8.15 (d, J = 6 Hz, 2 H).

4-(3,4-Dichlorophenyl)-6-(4-fluorophenyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (7). White solid; mp 284-286 ºC; 1H-NMR (300 MHz, CDCl3 + CD3OD) δ (TMS): 3.74 (s, 1 H, H1 + H2O), 6.86 (d, J = 6 Hz, 2 H, H7), 6.9 (m, 3 H, H5, H10), 7.23 (m, 2 H, H9), 7.32 (brs, 1 H, H4), 7.37 (d, J = 12 Hz, 1 H, H6), 7.92 (s, 1 H, H3), 8.40 (d, J = 6 Hz, 2 H, H8). 1H-NMR-NOESSY (300 MHz, CDCl3) δ (TMS): NOE is seen between H3 and H4. ESI-HRMS for C23H13Cl2FN4 (M+H+) requires 435.0580, found 435.0580; Anal. Calcd for C23H13Cl2FN4.0.5H2O: C, 62.16; H, 3.15; N, 12.61. Found: C, 62.02; H, 3.45; N, 12.10.

6-(4-Fluorophenyl)-4-(4-hydroxyphenyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (10a). White solid; mp > 300 ºC; 1H-NMR (300 MHz, CDCl3 + CD3OD) δ (TMS): 4.08 (s, NH + OH + H2O-CD3OD), 6.68 (d, J = 6 Hz, 2 H, H7), 6.80 - 7.01 (complex signal, 4 H), 7.19 (m, 2 H), 7.35 (m, 2 H), 7.91 (s, 1 H), 8.19 (d, J = 6 Hz, 2 H). HRMS for C23H15FN4O [M+H] requires 382.122965, found 383.1315 [M+H +]; Anal. Calcd for C23H15FN4O.H2O: C, 69.17; H, 4.01; N, 14.03. Found: C, 69.54; H, 4.30; N, 13.74.

6-(4-Fluorophenyl)-4-(imidazol-5-yl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (10c). White solid; mp > 300 ºC; 1H-NMR (300 MHz, CDCl3) δ (TMS): 3.35 (s, 2 NH + H2O-DMSO), 5.43 (m, 1 H), 7.01 (m, 2 H), 7.08 (d, J = 6 Hz, 2 H), 7.23 (m, 2 H), 7.61 (m, 1 H), 8.34 (m, 3 H). HRMS for C20H13FN6 [M+H] requires 357.1152, found 357.1160. Anal. Calcd for C20H13FN6: C, 67.41; H, 3.68; N, 23.58. Found: C, 67.32; H, 3.44; N, 23.86.
6-(4-Fluorophenyl)-4-methyl-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (10d). White solid; mp 222-225 °C; \(^{1}\)H-NMR (300 MHz, CD\(_{3}\)OD) \(\delta\) (TMS): 2.40 (s, 3 H), 3.89 (s, NH + H\(_{2}\)O-CD\(_{3}\)OD), 6.82 (m, 2 H), 7.02 (d, \(J = 6\) Hz, 2 H), 7.12 (m, 2 H), 8.11 (s, 1 H), 8.39 (d, \(J = 6\) Hz, 2 H). HRMS for C\(_{18}\)H\(_{13}\)FN\(_{4}\) [M+H] requires 305.1202, found 305.1199; Anal. Calcd for C\(_{18}\)H\(_{13}\)FN\(_{4}\)0.25H\(_{2}\)O: C, 70.01; H, 4.38; N, 18.15. Found: C, 69.87; H, 4.40; N, 17.85.

6-(4-Fluorophenyl)-4-propyl-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (10e). White solid; mp 177-178 °C; \(^{1}\)H-NMR (300 MHz, CDCl\(_{3}\)) \(\delta\) (TMS): 0.88 (t, \(J = 8\) Hz, 3 H), 1.65 (m, 2 H), 2.80 (t, \(J = 8\) Hz, 2 H), 6.91 (m, 2 H), 7.06 (d, \(J = 6\) Hz, 2 H), 7.22 (m, 2 H), 8.19 (s, 1 H), 8.56 (d, \(J = 6\) Hz, 2 H); 10.75 (s, 1 H, NH). HRMS for C\(_{20}\)H\(_{17}\)FN\(_{4}\) [M+H] requires 333.1516, found 333.1519; Anal. Calcd for C\(_{20}\)H\(_{17}\)FN\(_{4}\): C, 72.27; H, 5.16; N, 16.86. Found: C, 72.32; H, 5.49; N, 16.88.

6-(4-Fluorophenyl)-4-(2-phenylethyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (10f). White solid; mp 261-262 °C; \(^{1}\)H-NMR (300 MHz, CDCl\(_{3}\)) \(\delta\) (TMS): 2.87 (t, \(J = 8\) Hz, 2 H), 3.12 (t, \(J = 8\) Hz, 2 H), 6.85 (m, 6 H), 7.21 (m, 5 H), 8.15 (s, 1 H), 8.52 (d, \(J = 6\) Hz, 2 H), 10.81 (s, 1 H). HRMS for C\(_{25}\)H\(_{19}\)FN\(_{4}\) [M+H] requires 395.1672, found 395.1681; Anal. Calcd for C\(_{25}\)H\(_{19}\)FN\(_{4}\).1.75H\(_{2}\)O: C, 70.50; H, 5.28; N, 13.16. Found: C, 70.61; H, 4.88; N, 12.95.

6-(4-Fluorophenyl)-4-(4-hydroxybutyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (10g). \(^{1}\)H-NMR (300 MHz, CDCl\(_{3}\)+CD\(_{3}\)OD) \(\delta\) (TMS): 1.60 (m, 4 H), 2.87 (t, \(J = 8\) Hz, 2 H), 3.35 (t, \(J = 8\) Hz, 2 H), 3.40 (s, NH + OH + H\(_{2}\)O-CD\(_{3}\)OD), 6.95 (m, 2 H), 7.11 (d, \(J = 6\) Hz, 2 H), 7.25 (m, 2 H), 8.20 (s, 1 H), 8.52 (d, \(J = 6\) Hz, 2 H). HRMS for C\(_{21}\)H\(_{19}\)FN\(_{4}\)O [M+H] requires 363.1321, found 363.1319; Anal. Calcd for C\(_{21}\)H\(_{19}\)FN\(_{4}\): C, 69.60; H, 5.28; N, 15.40. Found: C, 69.59; H, 5.58; N, 15.12.

4,6-Bis(4-fluorophenyl)-5-(2-chloro-4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (10h). White solid; mp > 300 °C; \(^{1}\)H-NMR (300 MHz, CDCl\(_{3}\)) \(\delta\) (TMS): 6.76 (d, \(J = 4\) Hz, 1 H), 6.90 (s, 1 H), 7.0-7.3 (m, 8 H), 7.96 (s, 1 H), 8.12 (d, \(J = 4\) Hz, 1 H), 11.20 (s, 1 H). HRMS for C\(_{23}\)H\(_{13}\)ClF\(_{2}\)N\(_{4}\) [M+H] requires 419.0875, found 419.0884; Anal. Calcd for C\(_{23}\)H\(_{13}\)ClF\(_{2}\)N\(_{4}\): C, 65.87; H, 3.10; N, 13.37. Found: C, 65.68; H, 3.24; N, 13.09.

4,6-Bis(4-fluorophenyl)-5-(2-methylthio-4-pyrimidinyl)-1H-pyrazolo[3,4-b]pyridine (10i). White solid; mp 124-125 °C; \(^{1}\)H-NMR (300 MHz, CDCl\(_{3}\)) \(\delta\) (TMS): 2.23 (s, 3 H), 6.15 (d, \(J = 5\) Hz, 1 H), 6.9-7.1 (m, 4 H), 7.2-7.4 (m, 4 H), 7.98 (s, 1 H), 8.20 (d, \(J = 5\) Hz, 1 H), 10.90 (s, 1 H). HRMS for C\(_{23}\)H\(_{15}\)F\(_{2}\)N\(_{5}\)S [M+H] requires 432.1064, found 432.1098; Anal. Calcd for C\(_{23}\)H\(_{15}\)F\(_{2}\)N\(_{5}\)S.0.25H\(_{2}\)O: C, 63.37; H, 3.56; N, 16.07. Found: C, 63.32; H, 3.64; N, 15.67.

4,5-Bis(4-fluorophenyl)-6-phenyl-1H-pyrazolo[3,4-b]pyridine (10j). White solid; mp > 300 °C; \(^{1}\)H-NMR (300 MHz, CDCl\(_{3}\)) \(\delta\) (TMS): 6.8-7.3 (m, 13 H), 7.96 (s, 1 H), 11.20 (s, 1 H). HRMS for C\(_{24}\)H\(_{15}\)F\(_{3}\)N\(_{3}\) [M+H] requires 384.1312, found 384.1301; Anal. Calcd for C\(_{24}\)H\(_{15}\)F\(_{3}\)N\(_{3}.0.25\)H\(_{2}\)O: C, 74.32; H, 4.00; N, 10.84. Found: C, 74.49; H, 3.99; N, 10.86.
4-(4-Chlorophenyl)-6-(4-fluorophenyl)-5-methyl-1H-pyrazolo[3,4-b]pyridine (10k). White solid; mp 232-234 °C; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (TMS): 2.24 (s, 3 H), 7.20 (m, 2 H), 7.42 (d, \(J = 9\) Hz, 2 H), 7.53 (d, \(J = 9\) Hz, 2 H), 7.55 (m, 2 H), 7.79 (s, 1 H), 10.60 (s, 1 H). HRMS for C\(_{19}\)H\(_{13}\)ClFN\(_3\) [M+H] requires 338.0860, found 338.0854; Anal. Calcd for C\(_{19}\)H\(_{13}\)ClFN\(_3\): C, 67.56; H, 3.88; N, 12.44. Found: C, 67.87; H, 4.25; N, 12.55.

4,6-Bis(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine (10l). White solid; mp 204-221 °C; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (TMS): 7.2-7.4 (m, 4 H), 7.64 (s, 1 H), 7.82 (m, 2 H), 8.11 (m, 2 H), 8.22 (s, 1 H), 11.20 (s, 1 H). HRMS for C\(_{18}\)H\(_{11}\)F\(_2\)N\(_3\) [M+H] requires 308.0999, found 308.1006; Anal. Calcd for C\(_{18}\)H\(_{11}\)F\(_2\)N\(_3\).0.75H\(_2\)O: C, 67.39; H, 3.90; N, 13.10. Found: C, 67.71; H, 3.93; N, 13.33.

4-(4-Fluorophenyl)-6-methyl-5-phenyl-1H-pyrazolo[3,4-b]pyridine (10m). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (TMS): 2.51 (s, 3 H), 6.9 (m, 2 H), 7.05-7.3 (m, 7 H), 7.87 (s, 1 H), 11.20 (s, 1 H). HRMS for C\(_{19}\)H\(_{14}\)FN\(_3\) [M+H] requires 304.1250, found 304.1250; Anal. Calcd for C\(_{19}\)H\(_{14}\)FN\(_3\) 0.5H\(_2\)O: C, 73.07; H, 4.81; N, 13.46. Found: C, 72.80; H, 4.78; N, 13.06.

6-Benzyl-4-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine (10n). White solid; mp 190-191 °C; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (TMS): 4.35 (s, 2 H), 7.1-7.4 (m, 4 H), 7.60 (d, \(J = 6\) Hz, 1 H), 6.9-7.2 (m, 6 H), 7.3 (m, 2 H), 8.30 (d, \(J = 6\) Hz, 2 H). HRMS for C\(_{29}\)H\(_{17}\)Cl\(_2\)FN\(_4\) [M+H] requires 511.0894, found 511.0892; Anal. Calcd for C\(_{29}\)H\(_{17}\)Cl\(_2\)FN\(_4\): C, 68.10; H, 3.33; N, 10.96. Found: C, 68.01; H, 3.63; N, 10.62.

4-(4-Chlorophenyl)-6-(4-fluorophenyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (12). White solid; mp >300 °C; \(^1\)H-NMR (300 MHz, CD\(_3\)OD) \(\delta\) (TMS): 3.57 (s, NH + MeOH), 6.60 (d, \(J = 6\) Hz, 1 H), 6.75-7.2 (m, 13 H), 8.17 (d, \(J = 6\) Hz, 2 H). HRMS for C\(_{29}\)H\(_{17}\)Cl\(_2\)FN\(_4\) [M+H] requires 511.0894, found 511.0892; Anal. Calcd for C\(_{29}\)H\(_{17}\)Cl\(_2\)FN\(_4\): C, 68.10; H, 3.33; N, 10.96. Found: C, 68.01; H, 3.63; N, 10.62.

1-Ethyl-4-(3,4-dichlorophenyl)-6-(4-fluorophenyl)-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (13). White solid; mp 143-144 °C; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (TMS): 1.58 (t, \(J = 7\) Hz, 3 H), 4.67 (q, \(J = 7\) Hz, 2 H), 6.83 (d, \(J = 6\) Hz, 2 H), 6.9 (m, 3 H), 7.3 (m, 2 H), 7.38 (m, 2 H), 7.87 (s, 1 H), 8.37 (d, \(J = 6\) Hz, 2 H). HRMS for C\(_{25}\)H\(_{17}\)Cl\(_2\)FN\(_4\) [M+H] requires 511.0894, found 511.0892; Anal. Calcd for C\(_{25}\)H\(_{17}\)Cl\(_2\)FN\(_4\): C, 68.10; H, 3.33; N, 10.96. Found: C, 68.01; H, 3.63; N, 10.62.

4,6-Bis-(4-fluorophenyl)-3-methyl-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (11). White solid; mp 258-262 °C; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (TMS): 2.05 (s, 3 H), 6.83 (d, \(J = 6\) Hz, 2 H), 6.9 (m, 3 H), 7.3 (m, 2 H), 8.30 (d, \(J = 6\) Hz, 2 H), 11.20 (s, 1 H). HRMS for C\(_{25}\)H\(_{17}\)Cl\(_2\)FN\(_4\) [M+H] requires 399.1421, found 399.1423; Anal. Calcd for C\(_{25}\)H\(_{17}\)Cl\(_2\)FN\(_4\): C, 72.35; H, 4.05; N, 13.65. Found: C, 72.26; H, 4.89; N, 13.65.

4,6-Bis(4-fluorophenyl)-2-methyl-5-(4-pyridyl)-1H-pyrazolo[3,4-b]pyridine (14). White solid; mp 122-126 °C; \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) (TMS): 4.27 (s, 3 H), 6.83 (d, \(J = 6\) Hz, 2 H), 6.90 (t, \(J = 8\) Hz, 2 H). HRMS for C\(_{25}\)H\(_{17}\)Cl\(_2\)FN\(_4\) [M+H] requires 511.0894, found 511.0892; Anal. Calcd for C\(_{25}\)H\(_{17}\)Cl\(_2\)FN\(_4\): C, 68.10; H, 3.70; N, 12.09. Found: C, 65.09; H, 4.08; N, 12.04.
4,6-Bis-(4-fluorophenyl)-3-methyl-5-(4-pyridyl)-isothiazolo[5,4-b]pyridine (16a). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ (TMS): 2.05 (s, 3 H), 6.80 (d, $J = 6$ Hz, 2 H), 6.95 (t, $J = 8$ Hz, 2 H), 7.05 (t, $J = 8$ Hz, 2 H), 7.12 (m, 2 H), 7.35 (m, 2 H), 8.32 (d, $J = 6$ Hz, 2 H). HRMS for C$_{24}$H$_{16}$F$_2$N$_4$ [M+H] requires 399.1421, found 399.1422; Anal. Calcd for C$_{24}$H$_{16}$F$_2$N$_4$·0.25H$_2$O: C, 71.55; H, 4.10; N, 13.91. Found: C, 71.58; H, 4.25; N, 13.87.

4,6-Bis-(4-fluorophenyl)-3-methyl-5-(4-pyridyl)-isoxazolo[5,4-b]pyridine (16b). White solid; mp 217-219 ºC; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (TMS): 2.06 (s, 3 H), 6.80 (d, $J = 6$ Hz, 2 H), 6.9 (m, 2 H), 7.3 (m, 2 H), 8.33 (d, $J = 6$ Hz, 2 H). HRMS for C$_{24}$H$_{15}$F$_2$N$_3$O [M+H] requires 416.1033, found 416.1043; Anal. Calcd for C$_{24}$H$_{15}$F$_2$N$_3$O: C, 72.17; H, 3.79; N, 10.52. Found: C, 72.16; H, 4.20; N, 10.86.

Methyl 4,6-bis-(4-fluorophenyl)-5-(4-pyridyl)-furo[2,3-b]pyridine-2-carboxylate (16c). White solid; mp 194 ºC; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (TMS): 4.00 (s, 3 H), 6.80 (d, $J = 6$ Hz, 2 H), 6.84 (m, 2 H), 7.40 (s, 1 H), 8.37 (d, $J = 6$ Hz, 2 H). HRMS for C$_{26}$H$_{16}$F$_2$N$_2$O$_3$ [M+H] requires 443.1207, found 443.1201; Anal. Calcd for C$_{26}$H$_{16}$F$_2$N$_2$O$_3$: C, 70.59; H, 3.65; N, 6.33. Found: C, 70.62; H, 3.87; N, 6.49.

Methyl 5,7-bis-(4-fluorophenyl)-6-(4-pyridyl)-thieno[3,2-b]pyridine-3-carboxylate (16d). White solid; mp 150-151 ºC; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (TMS): 4.12 (s, 3 H), 6.85 (d, $J = 6$ Hz, 2 H), 6.95 (m, 2 H), 7.1 (m, 2 H), 7.4 (m, 2 H), 8.37 (d, $J = 6$ Hz, 2 H). HRMS for C$_{26}$H$_{16}$F$_2$N$_2$O$_3$ [M+H] requires 459.0979, found 459.0987; Anal. Calcd for C$_{26}$H$_{16}$F$_2$N$_2$O$_3$: C, 68.56; H, 2.88; N, 6.15. Found: C, 68.19; H, 2.73; N, 6.38.

Methyl 5,7-bis-(4-fluorophenyl)-1-methyl-6-(4-pyridyl)-pyrrolo[3,2-b]pyridine-2-carboxylate (16e). White solid; mp 195-199 ºC; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (TMS): 3.52 (s, 3 H), 3.95 (s, 3 H), 6.78 (d, $J = 6$ Hz, 2 H), 6.90 (m, 2 H), 7.0 (m, 2 H), 7.15 (m, 2 H), 7.20 (m, 2 H), 8.28 (d, $J = 6$ Hz, 2 H). HRMS for C$_{27}$H$_{20}$F$_2$N$_3$O$_2$ [M+H] requires 456.1524, found 456.1535; Anal. Calcd for C$_{27}$H$_{20}$F$_2$N$_3$O$_2$: C, 71.68; H, 3.56; N, 9.29. Found: C, 71.80; H, 3.49; N, 9.57.

Ethyl 5,7-bis-(4-fluorophenyl)-1-methyl-6-(4-pyridyl)-imidazo[4,5-b]pyridine-2-carboxylate (16f). White solid; mp 200-202 ºC; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (TMS): 1.50 (t, $J = 6$ Hz, 3 H), 3.61 (s, 3 H), 4.50 (q, $J = 6$ Hz, 2 H), 6.80 (d, $J = 6$ Hz, 2 H), 6.85 (m, 2 H), 7.0 (m, 2 H), 7.15 (m, 2 H), 7.25 (m, 2 H), 8.28 (d, $J = 6$ Hz, 2 H). HRMS for C$_{27}$H$_{20}$F$_2$N$_2$O$_2$ [M+H] requires 471.1633, found 471.1646; Anal. Calcd for C$_{27}$H$_{20}$F$_2$N$_2$O$_2$: C, 69.23; H, 3.87; N, 11.96. Found: C, 69.12; H, 4.26; N, 11.66.

5,7-Bis-(4-fluorophenyl)-1-methyl-6-(4-pyridyl)-imidazo[4,5-b]pyridine (16g). White solid; mp 264-268 ºC; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ (TMS): 3.31 (s, 3 H), 6.80 (d, $J = 6$ Hz, 2 H), 6.85 (m, 2 H), 7.0
Methyl 5,7-bis-(4-fluorophenyl)-6-(4-pyridyl)-1H-pyrazolo[4,3-b]pyridine-3-carboxylate (16h). $^1$H-NMR (400 MHz, DMSO-<d6>) $\delta$ (TMS): 3.40 (s, NH + H2O), 3.95 (s, 3 H), 7.09 (d, $J$ = 6 Hz, 2 H), 7.10 (t, $J$ = 8 Hz, 2 H), 7.23 (t, $J$ = 8 Hz, 2 H), 7.30 (m, 2 H), 7.35 (m, 2 H), 8.34 (d, $J$ = 6 Hz, 2 H). HRMS for C25H16F2N4O2 [M+H] requires 443.1320, found 443.1316; Anal. Calcd for C25H16F2N4O2: C, 67.72; H, 3.61; N, 12.64. Found: C, 67.35; H, 3.29; N, 12.31.

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