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A convenient and simple synthesis of *N*-arylpirrolopyrimidines using boronic acids and promoted by copper (II) acetate

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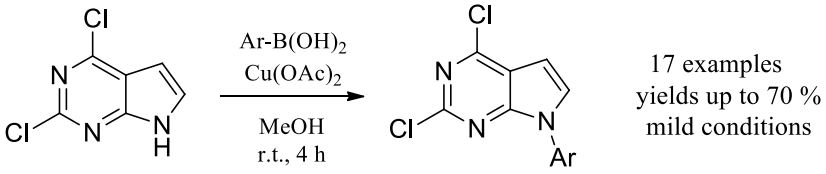
Abstract

A convenient and simple synthesis of novel *N*-arylated 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine using several aryl boronic acids and copper (II) acetate is described. The yields obtained for all derivatives are in the range of 45-70 % and this synthetic approach is extensible to other heterocycles such as 1*H*-indazoles.



Keywords: Heterocycles, *N*-arylation, pirrolopyrimidines, indazoles, boronic acids

Introduction

Nitrogen-containing heterocycles compounds are present in abundance in nature or as a scaffold in pharmaceuticals. Specifically, purine analogues pyrrolo[2,3-*d*]pyrimidines display significant anti-inflammatory, anti-cancer, antimicrobial and antiviral activities. [1-5] In fact, compound **I** was designed as an Aurora-A kinase inhibitor inducing cell death in cancer cells, while compound **II** is a strong and broad-spectrum antiproliferative agent, compound **III** acts as a phosphatidylinositol 4-kinase IIIβ inhibitor and derivative **IV** as a non-nucleoside hepatitis C virus NS5B polymerase inhibitor (Fig. 1). [6-10] Therefore, it is crucial to develop methods for the efficient synthesis and/or chemical modification of this kind of compounds. Most of them involve *N*-arylation reaction as the pivotal step. After the first reported *N*-arylation of heterocycles, which involved a Cu-catalyzed Ullmann procedure, [11-12] many synthetic methods for the construction of an aryl-nitrogen bond have been reported. The most interesting was a palladium-catalyzed approach, the Buchwald-Hartwig procedure being the most suitable variant.[13-14]

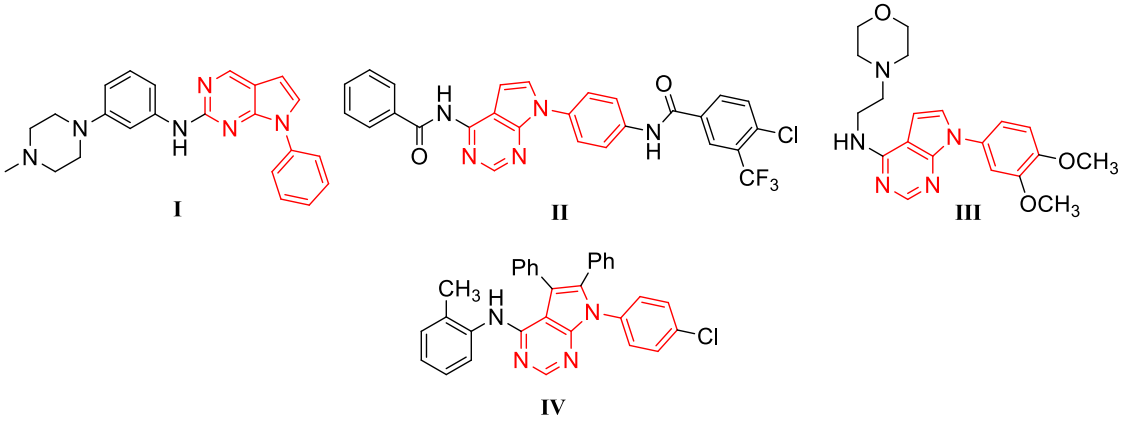


Figure 1. Structures of *N*-aryl-pyrrolo[2,3-*d*]pyrimidines with biological activities.

Based on this method, there have been several studies that aimed for this synthetic step (Fig. 2). Tumkevicius et al, considered the use of the catalytic system CuI/trans-1,2-diaminocyclohexane/K_3PO_4 to obtain pyrrolo[2,3-*d*]pyrimidines with extended π-systems. [15-16] On the other hand, Jung et al, reported the synthesis of *N*-aryl-pyrrolo[2,3-*d*]pyrimidine derivatives, as antiproliferative agents over melanoma cells, using CuI/L-proline/K_2CO_3 and DMSO as solvent. [17] Unfortunately these methods have several limitations and in an attempt to overcome their limitations (long reaction times, using harsh conditions and solvents that are not eco-friendly), [18-21] Lam-Chan developed a protocol based on the use of copper (II) acetate and boronic acids. [22-23] It takes advantage of the convenient, well-known properties of arylboronic acids: stability, structural diversity and lower toxicity. [24]

This article reports studies on the *N*-arylation of 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (Table 1), using a simple modified Lam-Chan conditions. The substrate of this reaction was choose due that is an interesting intermediate in the synthesis of substituted-purine derivatives with biological properties (Fig. 1). Modifications of Lam-Chan conditions were the absence of nitrogenous ligand, a polar solvent and shorter time reactions. The results of this methodology are shown in the following paragraphs.

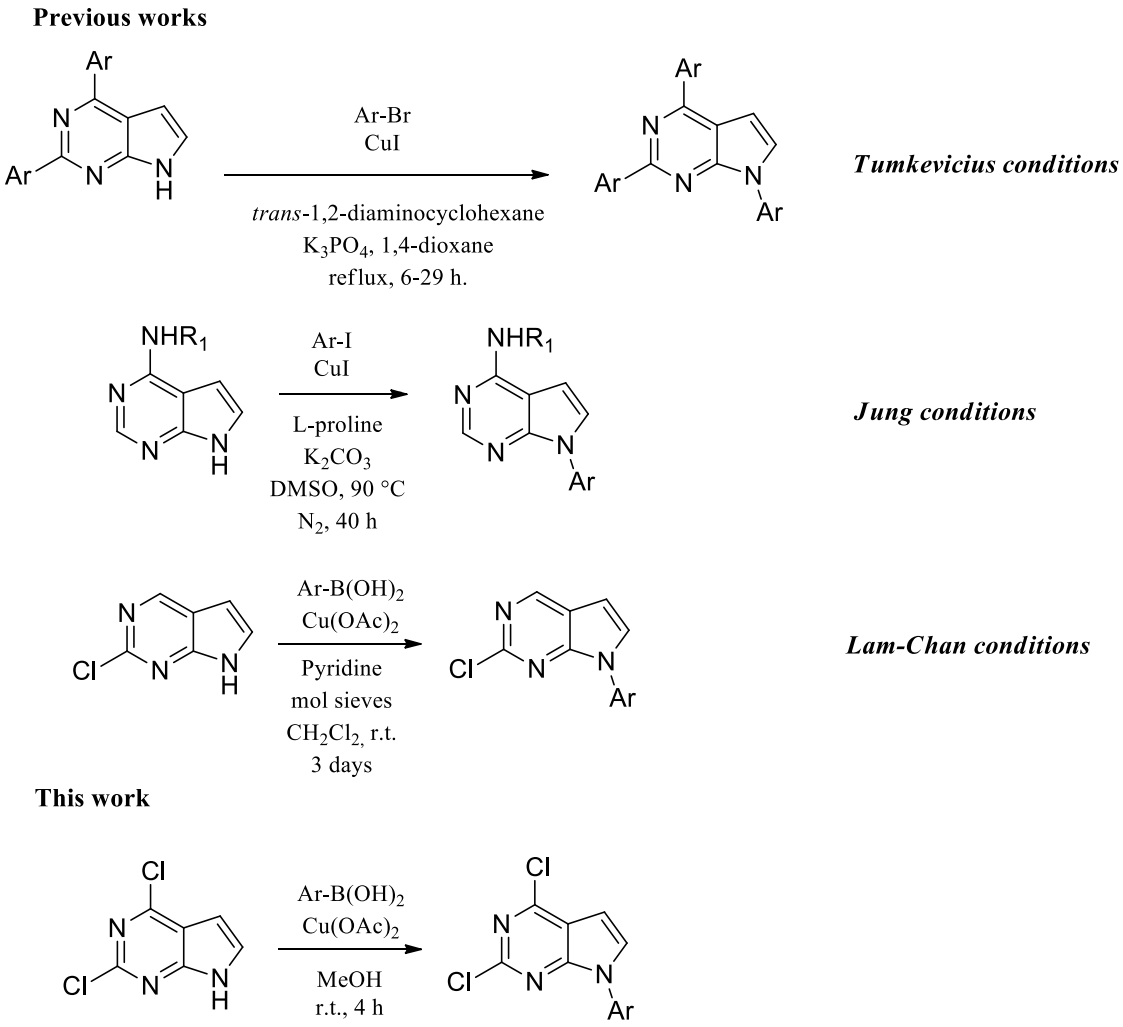
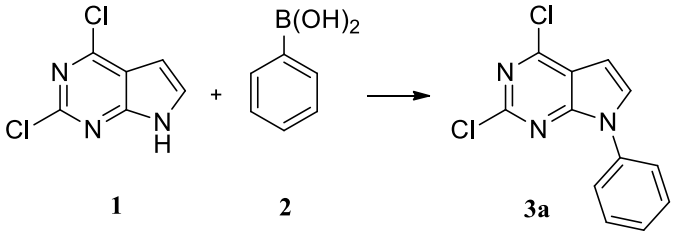


Figure 2. Previous *N*-arylation reports and our proposal.

Results and Discussion

We first attempted the *N*-arylation of 1 under the Lam-Chan conditions (Table 1, entry 1), but a low yield was achieved, probably due to the low solubility of the starting material in DCM, which is observed for the permanent presence of substrate until 48 h of reaction. This was confirmed when the reaction was carried out in methanol, the reaction time was 4 hours and a 58 % yield (Table 1, entry 2). Several attempts aimed at improve this yield were unsatisfactory. Thus, when catalytic amounts of $Cu(OAc)_2$ were used, the yields where substantially lower (Table 1, entries 3 and 4).

Table 1. Reaction parameters optimization to obtain **3a**



1 **2** **3a**

Entry	Copper source	Solvent	Time (h)	Yield (%)
1[a]	$Cu(OAc)_2$ (1.0 equiv.)	DCM	48	12
2[b]	$Cu(OAc)_2$ (0.2 equiv.)	MeOH	4	26
3[b]	$Cu(OAc)_2$ (0.5 equiv.)	MeOH	4	35
4[b]	**$Cu(OAc)_2$ (1.0 equiv.)**	**MeOH**	**4**	**58**
5[b]	Cu(OAc)2 (1.0 equiv.)	MeOH	24	55
6[c]	$Cu(OAc)_2$ (1.0 equiv.)	MeOH	4	21
7[b]	$Cu(OAc)_2$ (1.0 equiv.)	DMF	24	52
8[b]	$Cu(OAc)_2$ (1.0 equiv.)	THF	24	10
9[b]	$Cu(OAc)_2$ (1.0 equiv.)	CH_3CN	24	traces
10[b]	Cu_2O (1.0 equiv.)	MeOH	4	n.r.
11[b]	CuO (1.0 equiv.)	MeOH	4	traces
12[b]	$CuCO_3$ (1.0 equiv.)	MeOH	4	8
13[b]	CuCl (1.0 equiv.)	MeOH	4	n.r.

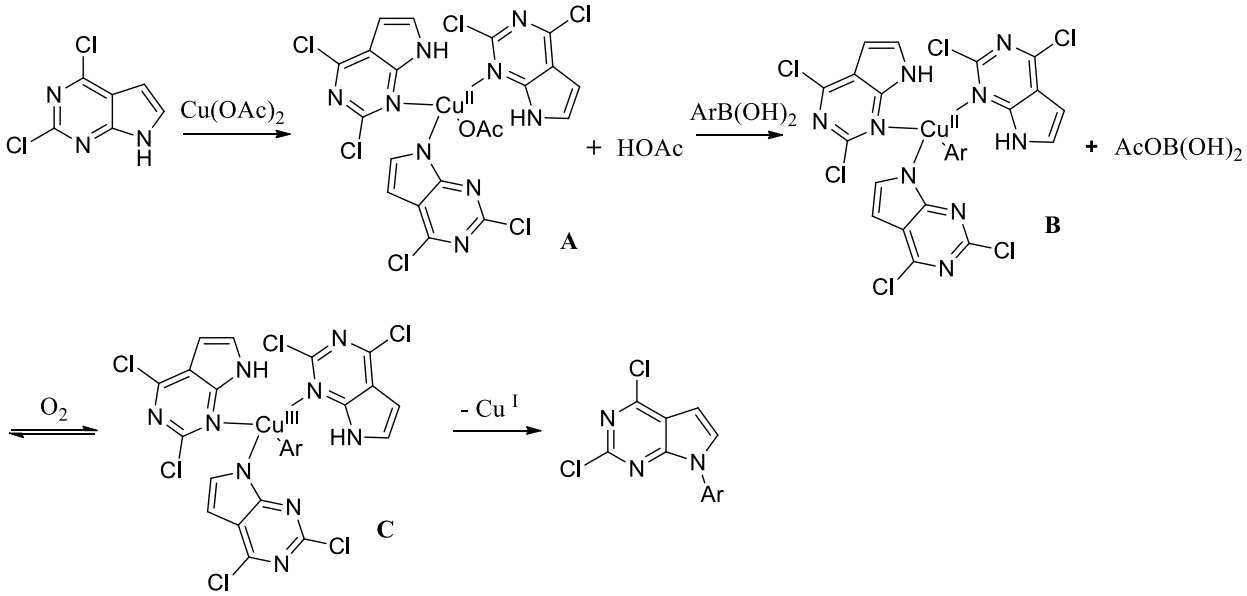
Reaction conditions: [a] **1** (0.5 mmol), **2** (1.0 mmol), pyridine (2.0 mmol), room temperature; [b] 1 (0.5 mmol), **2** (1.0 mmol), room temperature; [c] 1 (0.5 mmol), **2** (1.0 mmol), reflux temperature. n.r. = no reaction.

Moreover, when a longer reaction time was used the yield practically did not change (Table 1, entry 5) and it was substantially lower when the reaction was carried out under reflux conditions (Table 1, entry 6). On the other hand, the reaction was substantially slower when the solvent was DMF: 24 h were required from completion and the yield was lower than with MeOH (Table 1, entry 7). To complete the effect of the solvent in the *N*-arylation of **1**, non-protic polar solvents were used. When THF was used the yield of **3a** was very low (Table 1, entry 8), while with acetonitrile, only traces of the product was observed (Table1, entry 9). This results is probably due to the copper coordination toward nitrile moiety.

Finally, various copper salts other than $Cu(OAc)_2$ were tested. When copper (I) salts were tried, no reaction was observed, (Table 1, entries 10 and 11), whereas when using copper (II) salts, the reaction proceed with very poor yields (Table 1, entry 12 and 13).

An explanation of these results, shown in Table 1, could be related with a plausible mechanism for our *N*-arylation (Scheme 1). This mechanism is based on a proposal by Lam et al.[25] Although the classical Lam-Chan *N*-arylation conditions require the presence of pyridine, interestingly, our *N*-arylation experiments were satisfactorily carried out in absence of this ligand. As proposed, in our case the starting material can play the role of pyridine, acting as the required ligand involved in intermediates **A**, **B** and **C**. On the other hand, as shown in Scheme 1, oxygen is required for oxidation of the low valence copper intermediate **B**. [26-27] This explain the low yield achieved when the reaction was assayed under reflux conditions (Table 1, entry 6), and finally, the highly unsatisfactory yields achieved with Cu salts other than $Cu(OAc)_2$ (Table 1, entry 10-13),

clearly indicate that the copper source, in terms of valence and counterion, is fundamental for promotion of the first step of the *N*-arylation mechanism.



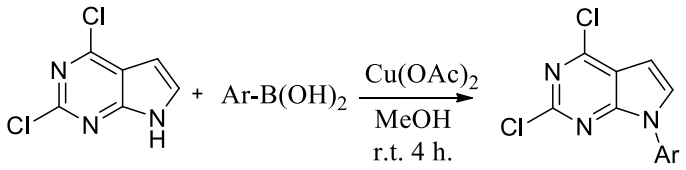
Scheme 1. Proposed mechanism for the *N*-arylation of **1**. Modified of reference.[25]

We next study the *N*-arylation of substrate **1** with substituted boronic acids, using the optimal conditions established for boronic acid itself. As shown in Table 2, fair to good yields were achieved. The better results correspond to boronic acids bearing a halogen atom at its para-position (compound **3d**, **3l** and **3n**) instead meta-position **3o**. This is probably due to that electron-withdrawing substituents would facilitate reductive elimination step involved in the *N*-arylation mechanism. An exception is compound **3m**, where the low yield achieved for this case is probably due to coordination of the Cu (II) with the cyano substituent. This is in accordance with the fact that boronic acids bearing electron-donating substituents (**3b-c** and **3e-k**), produce lower yields than unsubstituted boronic acids.

As an attempt to test our optimized, modified Lam-Chan *N*-arylation conditions to substrates other than 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **1**, we consider the case of 1*H*-indazole (**4**, Table 3). We choose this heterocyclic ring because is present as core in several compounds with pharmacological properties.[28-29]

To achieve this C–N bond forming reactions of this substrate were previously carried out using the palladium or copper-catalysed Buchwald–Hartwig type and Lam–Chan type reactions. [30] As shown in Table 3, a naphtyl- and ten phenylboronic acids were coupled to indazole **4**. In this case, the effect of the substituents of the boronic acid was unclear over the yield of reaction. Inseparable mixtures of the N^1-aryl (major) and N^2-aryl (minor) regioisomers 5 and 5′ were always obtained with global yields lower than for the *N*-arylation of pyrrolo[2,3-*d*]pyrimidine **1**. The ratio (N^1/N^2) of was established from the relative intensity of their H-3 signals in the ^{1}H NMR of the heterocyclic ring. For all derivatives, the N^1-aryl-1*H*-indazole isomer was obtained in greater proportion (> 72 %) than N^2-aryl-1*H*-indazole, therefore this synthetic method was considered regioselective. The low yields obtained for arylation of **4**, could be explained for the less ability to the nitrogen atom (N^2) to act as ligand, according to de mechanism proposed in Scheme 1.

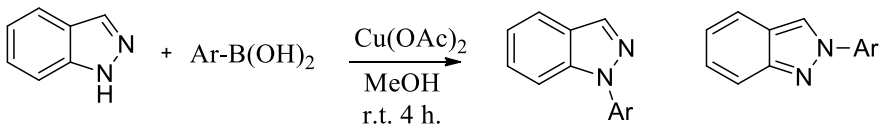
Table 2. Synthesis of *N*-Substituted pyrrole-pyrimidine derivatives **3b-q**[a]



Compound	Ar	Yield (%)
3b	4-Hydroxyphenyl	41
3c	2-Naphtyl	47
3d	4-Chlorophenyl	64
3e	4-Methoxyphenyl	48
3f	4-Isopropoxyphenyl	48
3g	4-Butylphenyl	53
3h	4-*tert*-Butylphenyl	51
3i	4-Phenoxyphenyl	50
3j	4-trifluromethylphenyl	46
3k	4-Methylphenyl	48
3l	4-Bromophenyl	59
3m	4-Cianophenyl	29
3n	4-Fluorophenyl	70
3o	3-Chlorophenyl	32
3p	4-Chloro-2-fluorophenyl	45
3q	3-Chloro-2-fluorophenyl	46

[a] Reaction conditions: **1** (0.5 mmol), arylboronic acid (0.6 mmol), $Cu(OAc)_2$ (0.5 mmol), MeOH (5 mL), room temperature, 4 h. [b] Isolated yields.

Table 3. Synthesis of *N*-Substituted indazole derivatives **5a-k** and **5a'-k'**



4 **5a-5k** **5a'-5k'**

Compound	Ar	Yield (%)[a]	Ratio (N^1/N^2)[b]
5a	Phenyl	30	84/16
5b	2-Naphtyl	34	72/28
5c	4-Chlorophenyl	37	91/9
5d	4-Methoxyphenyl	37	96/4
5e	4-Isopropoxyphenyl	50	81/19
5f	4-Butylphenyl	38	80/20
5g	4-*tert*-Butylphenyl	36	88/12
5h	4-Phenoxyphenyl	36	90/10
5i	4-Trifluromethylphenyl	32	87/13
5j	4-Methylphenyl	37	74/26
5k	4-Bromophenyl	53	88/12

[a] Yields of isolated mixture of both regioisomers. [b] Determined by ^{1}H NMR.

Conclusions

Modified Lam-Chan conditions were established for the *N*-arylation of 2,4-dichloro-7-aryl-7*H*-pyrrolo[2,3-*d*]pyrimidine with moderate to good yields, using boronic acids and promoted by copper (II) acetate. In this *N*-arylation do not requires the use of a nitrogen ligand and was achieved in a polar solvent and shorter reaction times were required. Although the yields of *N*-arylation of indazole derivatives were not excellent, this alternative offers a fast and inexpensive method to substitute heterocyclic compounds. Further efforts in the study of the scope of this reaction toward another heterocyclic systems, as well as, the elucidation of the mechanism of reaction involved, are currently ongoing in our laboratory.

Experimental Section

General. Melting points were determined on a Kofler Thermogerate apparatus and were uncorrected. Infrared spectra were recorded on a JASCO FT/IR-400 spectrophotometer. Nuclear magnetic resonance spectra were recorded, unless otherwise specified, on a Bruker AM-400 instrument using deuterochloroform or dimethylsulfoxide solutions containing tetramethylsilane as an internal standard. Mass spectra were obtained on a HP 5988A mass spectrometer. HRMS-ESI-MS experiments were done using a Thermo Scientific Exactive Plus Orbitrap spectrometer with a constant nebulizer temperature of 250 °C. The experiments were carried out in positive or negative ion mode, with a scan range of m/z 300.00-1510.40 with resolution 140 000. The samples were infused directly into the ESI source, via a syringe pump, at flow rates of 5 µL min-1, through the instrument's injection valve. Thin layer chromatography (tlc) was performed using Merck GF-254 type 60 silica gel. Column chromatography was carried out using Merck type 9385 silica gel. The purity of the compounds was determined by tlc and high-resolution mass spectrometry (HRMS).

General procedures for the synthesis of 3a-3q. 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.5 mmol), respective aryl boronic acid (0.6 mmol) and copper (II) acetate (0.5 mmol) in methanol (10 mL) was stirred at room temperature for 4 hours. Then, the reaction mixture was filtered over celite pad and the solvent was evaporated. The crude product was purified through flash column chromatography on a silica gel using dichloromethane as eluent to yield the respective products.

2,4-Dichloro-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (3a). White solid, mp 166-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* 7.9 Hz, 2H, H2´and H6´), 7.37-7.33 (m, 3H, H3´, H5´ and H6), 7.23 (t, *J* 7.4 Hz, 1H, H4´), 6.58 (d, *J* 3.7 Hz, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.16, 152.68, 151.56, 136.50, 129.85, 129.72 (2C), 127.93, 124.00 (2C), 117.28, 101.31. IR (KBr, cm^{-1}): 1579, 1513, 1386, 1261, 1241, 1175. HRMS for ($C_{12}H_8Cl_2N_3$ [M+H]$^+$). Calcd: 264.0090. Found: 264.0078.

2,4-Dichloro-7-(naphthalen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3c). White solid, mp 184-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, H2´), 7.96 (d, *J* 8.8 Hz, 1H, H7´), 7.87 (d, *J* 6.0 Hz, 2H, H3´and H6´), 7.74 (d, *J* 8.7 Hz, 1H, H8´), 7.58 (d, *J* 3.5 Hz, 1H, H6), 7.56 – 7.48 (m, 2H, H4´and H5´), 6.76 (d, *J* 3.4 Hz, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.17, 152.72, 151.73, 133.90, 133.36, 132.38, 130.08, 129.75, 128.08, 127.85, 127.19, 126.84, 122.29, 122.17, 117.30, 101.42. HRMS for ($C_{16}H_{10}Cl_2N_3$ [M+H]$^+$). Calcd: 314.0246. Found: 314.0232.

2,4-Dichloro-7-(4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3d). White solid, mp 178-180 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* 8.5 Hz, 2H, H3´and H5´), 7.49 (d, *J* 8.8 Hz, 2H, H2´ and H6´), 7.46 (d, *J* 3.8 Hz, 1H, H6), 6.75 (d, *J* 3.5 Hz, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.36, 152.86, 151.55, 134.96, 133.71, 129.89 (2C), 129.39, 125.14 (2C), 117.30, 101.71. HRMS for ($C_{12}H_7Cl_3N_3$ [M+H]$^+$). Calcd: 297.9700. Found: 298.2152.

2,4-dichloro-7-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3e). White solid, mp 135-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* 8.9 Hz, 2H, H2′ and H6′), 7.63 (d, *J* 3.7 Hz, 1H, H6), 7.22 (d, *J* 8.9 Hz, 2H, H3′ and H5′), 6.92 (d, *J* 3.6 Hz, 1H, H5), 4.04 (s, 1H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.20, 153.03, 152.56, 151.62, 130.23, 129.42, 125.56 (2C), 116.99, 114.86 (2C), 100.85, 55.64. HRMS for ($C_{13}H_{10}Cl_2N_3O$ $[M+H]^+$). Calcd: 294.0195. Found: 294.0182.

2,4-dichloro-7-(4-isopropoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3f). White solid, mp 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* 8.5 Hz, 2H, H2′ and H6′), 7.65 (d, *J* 3.3 Hz, 1H, H6), 7.22 (d, *J* 8.5 Hz, 2H, H3′ and H5′), 6.94 (d, *J* 3.3 Hz, 1H, H5), 4.80 (dt, *J* 11.9, 5.9 Hz, 1H, CH), 1.59 (s, 3H, CH_3), 1.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.60, 153.01, 152.52, 151.59, 130.30, 129.10, 125.54 (2C), 117.49, 116.59 (2C), 100.79, 70.40, 22.00 (2C). HRMS for ($C_{15}H_{14}Cl_2N_3O$ $[M+H]^+$). Calcd: 322.0508. Found: 322.0494.

7-(4-butylphenyl)-2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (3g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* 8.3 Hz, 2H, H2′ and H6′), 7.37 (d, *J* 3.7 Hz, 1H, H6), 7.22 (d, *J* 8.3 Hz, 2H, H3′ and H5′), 6.63 (d, *J* 3.7 Hz, 1H, H5), 2.59 – 2.52 (m, 2H, CH_2), 1.58 – 1.45 (m, 2H, CH_2), 1.34 – 1.20 (m, 2H, CH_2), 0.83 (t, *J* 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.06, 152.57, 151.53, 142.99, 134.12, 130.05, 129.62 (2C), 123.88 (2C), 117.18, 101.03, 35.23, 33.51, 22.34, 13.93. HRMS for ($C_{16}H_{16}Cl_2N_3$ $[M+H]^+$). Calcd: 320.0716. Found: 320.0702.

7-(4-(tert-Butyl)phenyl)-2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (3h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 4H, H2′, H3′, H5′ and H6′), 7.48 (d, *J* 3.6 Hz, 1H, H6), 6.73 (d, *J* 3.6 Hz, 1H, H5), 1.34 (s, 9H, 3 x CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.09, 152.59, 151.54, 151.15, 133.90, 130.02, 126.66 (2C), 123.60 (2C), 117.21, 101.07, 34.75, 31.31 (3C). HRMS for ($C_{16}H_{16}Cl_2N_3$ $[M+H]^+$). Calcd: 320.0716. Found: 320.0702.

2,4-Dichloro-7-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* 8.3 Hz, 2H, H2′ and H10′), 7.56 (d, *J* 3.6 Hz, 1H, H6), 7.47 (t, *J* 7.6 Hz, 1H, H5′ and H7′), 7.27-7.21 (m, 3H, H4′, H6′ and H8′), 7.16 (d, *J* 8.0 Hz, 2H, H3′ and H9′), 6.84 (d, *J* 3.6 Hz, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.23, 156.37, 153.18, 152.68, 151.59, 131.34, 130.00 (3C), 125.60 (2C), 124.12, 119.55 (2C), 119.26 (2C), 117.12, 101.17. HRMS for ($C_{18}H_{12}Cl_2N_3O$ $[M+H]^+$). Calcd: 356.0352. Found: 356.0336.

2,4-Dichloro-7-(4-(trifluoromethyl)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3j). White solid, mp 157-158 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 – 7.69 (m, 4H, H2′, H3′ H5′ and H6′), 7.50 (d, *J* 3.8 Hz, 1H, H6), 6.76 (d, *J* 3.8 Hz, 1H, H5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.55, 153.06, 151.65, 139.30, 138.85, 130.09, 129.43, 128.95, 126.96 (q, J_{CF} 3.7 Hz), 126.35-120.94 (d, J_{CF} 271.0 Hz), 123.82, 117.54, 102.27. HRMS for ($C_{13}H_7Cl_2F_3N_3$ $[M+H]^+$). Calcd: 331.9964. Found: 331.9949.

2,4-Dichloro-7-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3k). White solid, mp 124-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 3H, H6, H2′ and H6′), 7.22 (d, *J* 8.1 Hz, 2H, H3′ and H5′), 6.63 (d, *J* 3.7 Hz, 1H, H5), 2.31 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.03, 152.56, 151.55, 138.02, 133.97, 130.23 (2C), 130.02, 123.91 (2C), 117.15, 101.02, 21.11. HRMS for ($C_{13}H_{10}Cl_2N_3$ $[M+H]^+$). Calcd: 278.0246. Found: 278.0236.

7-(4-Bromophenyl)-2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (3l). White solid, mp 122-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* 8.8 Hz, 2H, H3′ and H5′), 7.53 (d, *J* 8.8 Hz, 2H, H2′ and H6′), 7.46 (d, *J* 3.7 Hz, 1H, H6), 6.76 (d, *J* 3.7 Hz, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.37, 152.87, 151.52, 135.47, 132.86 (2C), 129.30, 125.40 (2C), 121.58, 117.34, 101.77. MS (EI, *m/z*): 343.8 $[M^+]$.

4-(2,4-Dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)benzonitrile (3m). White solid, mp 224-226 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* 8.8 Hz, 2H, H3′ and H5′), 7.83 (d, *J* 8.8 Hz, 2H, H2′ and H6′), 7.55 (d, *J* 3.8 Hz, 1H, H6), 6.83 (d, *J* 3.8 Hz, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 153.28, 151.72, 140.06, 133.77 (2C), 128.44, 123.84 (2C), 117.93, 117.75, 111.31, 102.85. MS (EI, *m/z*): 289.1 $[M^+]$.

2,4-Dichloro-7-(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3n). White solid, mp 156-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* 8.4, 4.7 Hz, 2H, H3′ and H5′), 7.46 (d, *J* 3.5 Hz, 1H, H6), 7.23 (t, *J* 8.3 Hz, 2H, H2′ and H6′), 6.76 (d, *J* 3.5 Hz, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.85 (d, J_{CF} = 248.5 Hz), 153.29, 152.79, 151.61,

132.52 (d, J_{CF} = 3.2 Hz), 129.79, 125.93 (d, J_{CF} = 8.6 Hz, 2C), 117.14, 116.68 (d, J_{CF} = 23.1 Hz, 2C), 101.41. HRMS for ($C_{12}H_7Cl_2FN_3$ $[M+H]^+$). Calcd: 281.9996. Found: 281.9984.

2,4-Dichloro-7-(3-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3o). White solid, mp 163-164 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 – 7.49 (m, 2H), 7.49 – 7.27 (m, 3H), 6.72 (d, *J* 3.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.39, 152.93, 151.58, 137.47, 135.35, 130.71, 129.31, 128.03, 124.05, 122.08, 117.35, 101.84.

2,4-Dichloro-7-(4-chloro-2-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3p). White solid, mp 83-85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H, H3´ and H5´), 7.26 – 7.20 (m, 3H, H5, H6 and H2´). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.54 (d, J_{CF} = 253.8 Hz), 135.29 – 135.09 (m), 132.06 (t, J_{CF} = 2.9 Hz, 2C), 124.69 (2C), 121.13 (dd, J_{CF} = 10.1, 4.8 Hz, 3C), 116.77 (dt, J_{CF} = 17.2, 9.4 Hz, 3C). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.99.

2,4-Dichloro-7-(3-chloro-2-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (3q). White solid, 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* 3.9 Hz, 1H, H6), 7.32 (br, 2H, H3´ and H4´), 7.23 (t, *J* 7.9 Hz, 2H, H5 and H2´). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.31 (d, J_{CF} = 251.1 Hz), 130.83 (3C), 129.73 (t, J_{CF} = 2.0 Hz, 2C), 124.54 (t, J_{CF} = 2.3 Hz, 2C), 124.23 (dd, J_{CF} = 10.1, 4.9 Hz, 2C), 121.82 (dd, J_{CF} = 12.9, 5.6 Hz, 2C). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.01.

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