Microwave-Assisted Synthesis of Substituted Pyrrolo[2,3-d]pyrimidines

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A new synthetic route to triaryl pyrrolo[2,3-d]pyrimidines from common 4,6-dichloropyrimidine has been developed. The triarylated compounds are synthesized by three crosscoupling reactions using three different catalysts. The introduction of a C-6 aryl group was achieved in a two-step process under Sonogashira conditions [Pd(dba)2/CuI] followed by intramolecular cyclization, and application of Suzuki–Miyaura conditions [Pd(PPh3)4; PdCl2(PPh3)2] led to C-4 and C-5 diarylation. This sequence allows a flexible synthetic approach to highly arylated pyrrolopyrimidines containing different aryl groups.

INTRODUCTION

Pyrrolo[2,3-d]pyrimidines (IUPAC numbering is used throughout the manuscript), also known as 7-deazapurines, are an important class of heterocyclic compound containing a pyrrole ring with pyrimidine fused at the α,β-position. The pyrrolo[2,3-d]pyrimidine core is found in a wide range of natural compounds, including nucleoside antibiotics such as toyocamycin, sangivamycin and tubercidin.[1] Its wide and versatile spectrum of biological activities has led to its incorporation in synthetic biologically active compounds such as neurogenesis inductors by GSK-3b inhibition (TWS119, Figure 1),[2] antitumor (ACK1 inhibitors with IC50 = 0.62 μm, Figure 1),[3] anti-inflammatory agents,[4] and analgesic derivatives.[5] In addition to these bioapplications, other structurally diverse substituted purines[6] and 7- deazapurines[7,8] have been studied for their photophysical properties as, for example, electronic material and blue-light emitters. In recent years, great efforts have been dedicated to the synthesis of this heterocyclic system and to the devel-opment and functionalization of biologically active compounds containing the pyrrolo[2,3-d]pyrimidine substructure.[9]

General methods for the preparation of pyrrolopyrimidines remain limited.[10] The majority of procedures provide C-4 monosubstituted or C-2, N-7 disubstituted compounds and there have been few general approaches to the functionalization of this heterocycle system.[11] In general, compounds possessing this nitrogenated scaffold can be prepared from alicyclic reagents in basic media.[12] A synthesis of pyrrolo[2,3-d]pyrimidines by the cyclization of appropriately substituted pyrrole was reported by Rashad et al.[13] and Hilmy et al.[14] The standard method entails the introduction of the pyrrole ring to bridge the pyrimidine at the C-4, C-5 positions. Other previously published synthetic approaches to pyrrolopyrimidines have used halogenated pyrimidines as the common intermediate, which are converted into the corresponding aminopyrimidines.[15] The crosscoupling reaction of aminopyrimidines with vinyl stannanes followed by cyclization furnishes the pyrrolopyrimidines without functionalization of the five-membered ring.[15] The reaction of 4-amino-5-bromopyrimidine through ketone α- arylation with acetophenone provides the 6-phenylpyrrolopyrimidine in 62% yield.[16] Recently, Kopecky and coworkers[3] reported a general route with which to access the bicyclic structure from 4,6-diamino-5-iodopyrimidine involving an intramolecular palladium-catalyzed Heck reaction. The cyclization reaction of 2-alkynylanilines constitutes an interesting procedure with which to obtain 2-substituted indoles, azaindoles or other heterocyclic cores including pyrrolopyrimidines.[17] However, this intramolecular cyclization requires a base and high temperatures (180–200 °C).[17,18]

Despite the wide range of methods available for the preparation of pyrrolopyrimidines, very few of them provide an efficient procedure with which to obtain the heterocyclic system with a range of substituents. To the best of our knowledge, the limited number of approaches available for the synthesis and functionalization of pyrrolo[2,3-d]pyrimidines do not include the preparation of 4,5,6-triarylpyrrolopyrimidines. Only 2,4,7-triarylpyrrolo[2,3-d]pyrimidines[19] and 2,6,8-triarylpurines,[20] possessing optical or adenosine antagonist properties, respectively, have been reported.

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RESULTS AND DISCUSSION

With the aim of developing an efficient route that is suitable for the triarylation of pyrrolopyrimidines, we designed the following general synthesis from the commercially available precursor 4,6-dichloropyrimidine (1; Scheme 1). This synthesis was performed in seven steps by using microwave irradiation under mild to moderate conditions from stable starting material.

The starting 5-alkynylpyrimidines 4 can be prepared easily by a Sonogashira type alkynylation[21] of 6-chloro-5-iodo-4-(methylamino)pyrimidine by using commercial alkynylbenzenes under microwave assistance. The use of microwave irradiation under palladium catalysis has been investigated and applied to organic synthesis in both academia and industry.[22] The Sonogashira reaction is chemoselective and the yield is not affected by the electronic properties of the 4-substituted aryl alkyne (Scheme 2). The 6-chloro-5-iodo-4-(methylamino)pyrimidine (3) used in this reaction was prepared by nucleophilic substitution of the 4,6-dichloropyrimidine with methylamine at C-4 followed by iodination under classical conditions.[17]

The intramolecular cyclization in the presence of base (Cs2CO3) and a catalytic amount of CuI (1 mol-%) under microwave irradiation afforded bicyclic heterocycle 5 in excellent yield with good tolerance of different substituent groups. These conditions allowed us to work at lower temperatures (100 °C) than those published by other authors (180–200 °C).[17,18] Applying the same conditions but performing the cyclization without CuI provided higher yields, showing that the reaction works even better without the copper catalyst (Scheme 3). The optimized protocol involved treating diarylalkyne with cesium carbonate in acetonitrile and heating at 100 °C for 30–90 min in a microwave system. Ring closure was achieved to give the desired product 5 in only one step from the common intermediate 4; the product was used in the next step without further purification.

In a preliminary study, the direct halogenation of 4-chloropyrrolopyrimidines 5 by using N-bromosuccinimide (NBS) or N-iodosuccinimide (NIS), under microwave assistance, provided the corresponding 5-bromopyrrolopyrimidines (87%) or 5-iodopyrrolopyrimidines (90%) (Scheme 4). Replacement of the bromo or iodo group attached at the C-5 position of the pyrrolopyrimidines by using the corresponding arylboronic acid provided the arylated compounds 9 in yields of 33 or 70%, from the bromo or iodo derivative, respectively.

In the following step, the isolated 4-chlorodiarylated pyrrolopyrimidines 9 were arylated by using aryl boronic acids and Suzuki–Miyaura catalysts in 83% yield. This synthetic procedure furnished triarylpyrrolopyrimidines 8 in seven steps with an overall yield of 12–32%.

With these results in hand, we attempted to generate triarylpyrrolopyrimidines from intermediate 5 by using an alternative route, reversing the order of arylation of the pyrrolopyrimidines so that arylation would first take place at C-4 and then at C-5. Thus, 4-arylderivatives 6 were obtained by treatment of 4-chloropyrrolopyrimidines 5 with arylboronic acids under Suzuki–Miyaura cross-coupling conditions[23] by using a microwave heat source.[24] The reaction yields were good to excellent (91–100%; Table 1), and the reaction incorporating the phenyl derivatives was found to be chemoselective. This method thus provides efficient access to diarylated compounds.

Direct arylation of C-5 was not achieved under a wide range of tested conditions. As a result, the diarylpyrrolopyrimidines were iodinated at the C-5 position by electrophilic substitution with N-iodosuccinimide[25] under microwave radiation at 100 °C with nearly quantitative conversion, very high yields, and sufficient purity as to obviate the need for a purification step (Table 2). Halogenation at C-5 was performed regioselectively. Interestingly, analysis of the iodo compounds by 1H NMR spectroscopy carried out at 30, 100, and 180 days after their preparation showed higher stability at room temperature when the compounds were stored without a solvent. Following this study, the iodo

compounds in chloroform solution showed complete stability after 30 days at room temperature. It should be emphasized that carrying out the C-4 arylation of the pyrrolopyrimidines before C-5 iodination avoided the Cl/I exchange that impedes the chemoselective arylation.

The third aryl group at the C-5 position of 4,6-diaryl-5-iodopyrrolo[2,3-d]pyrimidines 7 was introduced by treatment with arylboronic acids under Suzuki–Miyaura cross-coupling conditions. After workup, a new iodination process with NIS was carried out, which allowed some additional starting material to be recovered, separated, and reused. Microwave assistance enabled a rapid synthesis of a variety of triaryl pyrrolopyrimidines with different substituents. It was clear that meta and para substituents on the arylboronic acid (Ar2) were well-tolerated, whereas ortho substituents hampered the reaction as a result of steric hindrance (Table 3, entry 5). The ortho, meta or para substituents of the aryl groups attached at C-4 of the pyrrolopyrimidine core did not modify the arylation process (Table 3, entries 1, 6 and 9). Whereas the presence of a substituent of the aryl group linked to C-6 (Table 3, cf. entry 1 with entries 10 and 11) had a significant impact on the rate of the Suzuki–Miyaura reaction, the electron-donating or withdrawing nature of the substituents was not influential. Increasing the number of equivalents of the reactant, as well as the reaction time and temperature did not favor the reaction. The optimized procedure afforded the desired triaryl-substituted pyrrolopyrimidines in 35–50% overall yield in seven steps, which constitutes a significant improvement on the previously described route.

The molecular structure of the triaryl-substituted pyrrolo[2,3-d]pyrimidine 8k (Table 3, entry 11) was determined by means of X-ray diffraction studies, and the crystallographic data and structural refinement parameters have been deposited with the CCDC. Colorless crystals of 8k were obtained by slow diffusion of hexane over a saturated ethyl acetate solution. The compound crystallized in the prism space group C2/c. The crystallographic structure and atom numbering are given in Figure 2, which shows a perspective view of compound 8k. The crystallographic structure reveals the orientation of the three aryl substituents with respect to the pyrrolopyrimidine system.

CONCLUSIONS

The chemistry outlined here provides an efficient pathway for the synthesis of triarylated pyrrolo[2,3-d]pyrimidines through three cross-coupling reactions catalyzed by palladium under microwave irradiation. The high yields obtained in the different steps suggest that this process has considerable promise for the synthesis of pyrrolopyrimidines bearing three different (or equivalent) arylated substituents (overall yield 35–50%). This method allows arylation at C-4, C-5 and C-6 of pyrrolopyrimidines and should be of interest for the synthesis of medicinal and photoactive structures.

EXPERIMENTAL SECTION

General: Microwave-assisted reactions were carried out with a Biotage Initiator Microwave synthesis instrument and the internal temperature was measured by an IR sensor. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Column chromatography was performed with silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp) were obtained with a melting point apparatus with a digital thermometer in open capillary tubes and are reported without correction. IR spectra were obtained with an FTIR Infrared Spectrophotometer. 1H and 13C NMR spectra were recorded at 250 MHz (13C, 63 MHz), 300 (13C, 75.5 MHz), or 400 MHz (13C, 100 MHz). Chemical shifts (δ) (multiplicity, coupling constants and integration) are reported in parts per million (ppm) relative to the central peak of the solvent: CDCl3 [δ = 7.26 (H) and 77.16 (C) ppm], CD3OD [δ = 3.31 (H) and 49.45 (C) ppm], [D6]DMSO [δ = 2.49 (H) and 39.51 (C) ppm] as internal standards. The following abbreviations are used for the proton spectra multiplicities: s singlet, d doublet, t triplet, q quadruplet, m multiplet, dd doublet of doublets, dt doublet of triplets and br. broad signal. Coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded with a time-of-flight mass spectrometer fitted with either an electrospray (ESI) or atmospheric pressure ionization (APCI). All reagents were of high quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures.

6-Chloro-N-methylpyrimidin-4-amine (2): To a solution of 4,6-dichloropyrimidine (1; 200 mg, 1.34 mmol) in 2-propanol (1.3 mL), triethylamine (0.22 mL, 1.61 mmol) and MeNH2·HCl (108.8 mg, 1.61 mmol) were added. The reaction was stirred and heated to the reflux temperature of 2-propanol until complete consumption of the starting material as determined by TLC analysis (4 h). After cooling, the solvent was removed under vacuo. Water (15 mL) was added and the mixture was extracted with ethyl acetate (3 15 mL). The combined organic layers were washed with NH4Cl (10 mL). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 6:4) to afford 2 (150.7 mg, 1.05 mmol, 78%) as a white solid, m.p. 136–138 °C (EtOAc) [136–138 °C (hexane)].[26] Rf = 0.22 (CH2Cl2/ethyl acetate, 6:4). IR (ATR diamond): ν˜ = 3246, 3083, 2967, 1619, 1568, 1429, 1384, 1329, 1227, 1143, 1092, 976, 887, 834, 741, 708 cm–1. 1H NMR (400 MHz, CDCl3): δ = 2.92 (d, J = 4.3 Hz, 3 H), 5.87 (s, 1 H), 6.33 (s, 1 H), 8.31 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 28.3, 99.9, 158.2, 159.8, 164.0 ppm. HRMS (ESI): calcd. For C5H7ClN3 [M + H]+ 144.0323; found 144.0322.

6-Chloro-5-iodo-N-methylpyrimidin-4-amine (3): A solution of pyrimidine 2 (2 g, 13.9 mmol) in acetonitrile (30 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven twice at 100 °C for 15 min with previous addition of NIS (9.4 g, 41.7 mmol). The progress of the reaction was monitored by TLC (CH2Cl2/ethyl acetate, 6:4). After cooling, the solvent was removed, then CH2Cl2 (50 mL) was added and the organic layer was washed with aqueous saturated Na2S2O3 (2 50 mL), and NaOH (10%, 2 50 mL). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by recrystallization from ethanol (20 mL) to afford 3 (3.27 g, 12.1 mmol, 87%) as paleyellow crystals; m.p. 146–148 °C (EtOH). Rf = 0.50 (CH2Cl2/ethyl acetate, 6:4). IR (ATR diamond): ν˜ = 3292, 2936, 1557, 1499, 1389, 1326, 1263, 1237, 1179, 1122, 1080, 1001, 888, 762 cm–1. 1H NMR (250 MHz, CDCl3): δ = 3.06 (d, J = 4.9 Hz, 3 H), 5.64 (s, 1 H), 8.24 (s, 1 H) ppm. 13C NMR (63 MHz, CDCl3): δ = 29.45, 79.6, 157.3, 162.2, 163.0 ppm. HRMS (ESI): calcd. for C5H6ClIN3 [M + H]+ 269.9289; found 269.9291.

General Procedure A (Sonogashira Coupling): A mixture containing 3 (1.0 mmol), alkyne (2.0 mmol), Pd(dba)2 (0.03 mmol), tri(2-furyl) phosphine (0.06 mmol), and CuI (0.04 mmol) in anhydrous THF (1 mL) and anhydrous triethylamine (3.5 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven at 100 °C for 30 min. The progress of the reaction was monitored by TLC. After cooling, the mixture was diluted with aqueous saturated NH4Cl (15 mL) and the aqueous

phase was extracted with ethyl acetate (3 20 mL). The combined organic phases were dried with MgSO4 and filtered through Celite. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

6-Chloro-N-methyl-5-(2-phenylethynyl)pyrimidin-4-amine (4a); General Procedure A: The reaction was carried out by following general procedure A starting from the iodinated pyrimidine 3 (1 g, 3.71 mmol) and phenylacetylene (0.82 mL, 7.42 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/CH2Cl2/acetone, 8:1:1) followed by recrystallization (CH2Cl2/pentane) to afford 4a (842.2 mg, 3.46 mmol, 93%) as a white solid; m.p. 113–115 °C (pentane). Rf = 0.28 (petroleum ether/ CH2Cl2/acetone, 8:1:1). IR (ATR diamond): ν˜ = 3397, 1564, 1490.1392, 1274, 1230, 1138, 1088, 906, 848, 749, 684 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.12 (d, J = 5.0 Hz, 3 H), 5.76 (s, 1 H), 7.34–7.44 (m, 3 H), 7.51–7.60 (m, 2 H), 8.35 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 28.6, 79.6, 101.0, 102.3, 122.0, 128.7, 129.5, 131.8, 156.2, 159.2, 163.0 ppm. HRMS (ESI): calcd. For C13H11ClN3 [M + H]+ 244.0636; found 244.0637.

6-Chloro-5-[2-(4-methoxyphenyl)ethynyl]-N-methylpyrimidin-4-amine (4b): The reaction was carried out by following general procedure A starting from the iodinated pyrimidine 3 (150 mg, 0.56 mmol) and 1-ethynyl-4-methoxybenzene (147.1 mg, 1.11 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/CH2Cl2/acetone, 70:15:15) followed by recrystallization (CH2Cl2/pentane) to afford 4b (143.8 mg, 0.53 mmol, 94%) as a white solid; m.p. 131–133 °C (pentane). Rf = 0.30 (petroleum ether/CH2Cl2/acetone, 70:15:15). IR (ATR diamond): ν˜ = 3312, 2927, 2202, 1564, 1504, 1460, 1388, 1352, 1278, 1251, 1170, 1137.1086, 1031, 902, 831, 779, 731 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.11 (d, J = 5.0 Hz, 3 H), 3.84 (s, 3 H), 5.75 (s, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 7.48 (d, J = 8.7 Hz, 2 H), 8.33 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 28.5, 55.5, 78.3, 101.3, 102.5, 114.0, 114.3, 133.3, 156.0, 158.9, 160.6, 162.9 ppm. HRMS (ESI): calcd. for C14H13ClN3O [M + H]+274.0742; found 274.0743.

6-Chloro-N-methyl-5-{2-[4-(trifluoromethyl)phenyl]ethynyl}-pyrimidin-4-amine (4c): The reaction was carried out by following general procedure A starting from the iodinated pyrimidine 3 (150 mg, 0.56 mmol) and 1-ethynyl-4-(trifluoromethylbenzene) (0.2 mL, 1.11 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/CH2Cl2/acetone, 8:1:1) followed by recrystallization (CH2Cl2/pentane) to afford 4c (172.7 mg, 0.55 mmol, 99%) as a pale-yellow solid; m.p. 107–109 °C (pentane). Rf = 0.17 (petroleum ether/CH2Cl2/acetone, 8:1:1). IR (ATR diamond): ν˜ = 3360, 2925, 1562.1509, 1396, 1322, 1276, 1228, 1167, 1090, 1064, 903, 836, 781, 736 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.13 (d, J = 5.0 Hz, 3 H), 5.73 (s, 1 H), 7.64 (s, 4 H), 8.37 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 28.6, 81.9, 100.3, 100.6, 123.9 (J = 272 Hz), 125.6 (J = 4 Hz), 125.8 (J = 1 Hz), 131.1 (J = 33 Hz), 132.0, 156.7, 159.8, 163.0 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.94 (CF3) ppm. HRMS (ESI): calcd. for C14H10ClF3N3 [M + H]+ 312.0510; found 312.0511.

General Procedure B (Cyclization): A solution of alkyne 4a–c (1.0 mmol) and cesium carbonate (1.0 mmol) in acetonitrile (4.5 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven at 100 °C for the required time. The progress of the reaction was monitored by TLC. After cooling, the solvent was removed under vacuo. Water (20 mL) was added to the mixture and the crude material was extracted with ethyl acetate (3 15 mL). The combined organic phases were washed with aqueous saturated Na2CO3 (15 mL) and brine (15 mL). Purification was performed by column chromatography on silica gel to give the corresponding pure product 5.

4-Chloro-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (5a): The reaction was carried out by following general procedure B starting from the alkyne 4a (800 mg, 3.28 mmol) and microwave irradiation was applied for 30 min. The crude product was purified by silica gel column chromatography (petroleum ether/CH2Cl2/acetone, 8:1:1) followed by recrystallization (CH2Cl2/pentane) to afford 5a (795.2 mg, 3.26 mmol, 99%) as a pale-yellow solid; m.p. 151–153 °C (pentane). Rf = 0.18 (petroleum ether/CH2Cl2/acetone, 8:1:1). IR (ATR diamond): ν˜ = 3741, 2946, 1585, 1541, 1485, 1432, 1405, 1347, 1237, 1184, 1127, 1013, 938, 855, 755, 702 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.85 (s, 3 H), 6.62 (s, 1 H), 7.44–7.58 (m, 5 H), 8.64 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 30.5, 98.8,

117.7, 129.0, 129.3, 129.4, 130.9, 143.4, 150.6, 151.4, 152.7 ppm. HRMS (ESI): calcd. for C13H11ClN3 [M + H]+244.0636; found 244.0637.

4-Chloro-6-(4-methoxyphenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (5b): The reaction was carried out by following general procedure B starting from the alkyne 4b (267.6 mg, 0.98 mmol) and microwave irradiation was applied for 90 min. The crude product was purified by silica gel column chromatography (petroleum ether/ CH2Cl2/acetone, 8:1:1) followed by recrystallization (CH2Cl2/pentane) to afford 5b (254.2 mg, 0.93 mmol, 95%) as a pale-yellow solid; m.p. 134–136 °C (pentane). Rf = 0.24 (petroleum ether/CH2Cl2/acetone, 8:1:1). IR (ATR diamond): ν˜ = 3838, 3744, 2950, 1613, 1590, 1544, 1492, 1348, 1291, 1244, 1174, 1133, 1034, 940, 839, 805, 772, 741, 706 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.83 (s, 3 H), 3.88 (s, 3 H), 6.56 (s, 1 H), 7.00–7.07 (m, 2 H), 7.43–7.50 (m, 2 H), 8.63 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 30.5, 55.6, 98.1, 114.5, 117.8, 123.2, 130.7, 143.4, 150.3, 151.1, 152.7, 160.6 ppm. HRMS (ESI): calcd. for C14H13ClN3O [M + H]+ 274.0742; found 274.0744.

4-Chloro-7-methyl-6-[4-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]-pyrimidine (5c): The reaction was carried out by following general procedure B starting from the alkyne 4c (296.6 mg, 0.95 mmol) and microwave irradiation was applied for 30 min. The crude product was purified by silica gel column chromatography (petroleum ether/CH2Cl2/acetone, 8:1:1) followed by recrystallization (CH2Cl2/pentane) to afford 5c (98%, 290.6 mg, 0.93 mmol) as a yellow solid; m.p. 167–169 °C (pentane). Rf = 0.27 (petroleum ether/CH2Cl2/ acetone, 8:1:1). IR (ATR diamond): ν˜ = 3743, 2927, 1583, 1544, 1502, 1475, 1447, 1411, 1319, 1262, 1235, 1168, 1119, 1065, 1013, 944, 859, 804, 774, 745, 713 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.87 (s, 3 H), 6.70 (s, 1 H), 7.68 (d, J = 8.2 Hz, 2 H), 7.79 (d, J = 8.2 Hz, 2 H), 8.68 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 30.6, 99.9, 117.6, 124.0 (J = 272 Hz), 126.1 (J = 4 Hz), 129.6, 131.4 (J = 33 Hz), 134.5 (J = 1 Hz), 141.5, 152.0, 152.9 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.80 (CF3) ppm. HRMS (ESI): calcd. for C14H10ClF3N3 [M + H]+ 312.0510; found 312.0513.

General Procedure C (Suzuki–Miyaura Coupling at C-4): Under argon, a mixture of compound 5a–c (1.0 mmol), boronic acid (1.05 mmol), sodium carbonate (2.0 mmol), and tetrakis(triphenylphosphine) palladium (0.02 mmol) in a degassed solvent mixture of DME (3.8 mL) and H2O (0.6 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven at 100 °C for 60 min. The progress of the reaction was monitored by TLC. After cooling, the mixture was diluted with a mixture of brine and water (1:1, 20 mL) and the aqueous solution was extracted with ethyl acetate (3 20 mL). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

7-Methyl-6-phenyl-4-(3-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (6a): The reaction was carried out by following general procedure C starting from 4-chloropyrimidine 5a (450 mg, 1.85 mmol) and 3-tolylboronic acid (263.6 mg, 1.94 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 7:3) to afford 6a (507.4 mg, 1.69 mmol, 91%) as a pale-yellow solid. Rf = 0.32 (CH2Cl2/ethyl acetate, 6:4); m.p. 109–111 °C (ethyl acetate). IR (ATR diamond): ν˜ = 3836, 3741, 2922, 1698, 1560, 1490, 1468, 1396, 1343, 1268, 1217, 1078, 1014, 892, 814, 772, 745 cm–1. 1H NMR (400 MHz, CDCl3): δ = 2.47 (s, 3 H), 3.89 (s, 3 H), 6.86 (s, 1 H), 7.30–7.32 (m, 1 H), 7.40–7.58 (m, 6 H), 7.91–8.01 (m, 2 H), 8.99 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 21.5, 29.9, 99.8, 115.8, 125.9, 128.5, 128.7, 128.8, 129.1, 129.2, 130.6, 138.2, 138.4, 142.7, 151.3, 153.3, 156.8 ppm. HRMS (ESI): calcd. For C20H18N3 [M + H]+ 300.1495; found 300.1498.

7-Methyl-6-phenyl-4-(2-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (6b): The reaction was carried out by following general procedure C starting from 4-chloropyrimidine 5a (150 mg, 0.62 mmol) and 2-tolylboronic acid (87.9 mg, 0.65 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 8:2) to afford 6b (181.7 mg, 0.61 mmol, 99%) as a white solid. Rf = 0.45 (CH2Cl2/ethyl acetate, 8:2); m.p. 104–106 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2919,

2849, 1738, 1567, 1541, 1491, 1443, 1404, 1370, 1340, 1320, 1261, 1218, 1135, 1011, 935, 865, 787, 757, 748, 727, 699 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.39 (s, 3 H), 3.91 (s, 3 H), 6.47 (s, 1 H), 7.27–7.40 (m, 3 H), 7.44–7.56 (m, 6 H), 8.99 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 20.3, 30.1, 99.9, 117.8, 125.8, 128.9, 129.0, 129.1, 129.2, 129.8, 131.1, 131.4, 136.6, 137.5, 142.8, 151.1, 152.9, 159.3 ppm. HRMS (ESI): calcd. for C20H18N3 [M + H]+ 300.1495; found 300.1498.

7-Methyl-6-phenyl-4-(4-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (6c): The reaction was carried out by following general procedure C starting from 4-chloropyrimidine 5a (150 mg, 0.62 mmol) and 4-tolylboronic acid (87.9 mg, 0.65 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 8:2) to afford 6c (178.4 mg, 0.60 mmol, 96%) as a white solid. Rf = 0.48 (CH2Cl2/ethyl acetate, 8:2); m.p. 94–96 °C (ethyl acetate). IR (ATR diamond): ν˜ = 3052, 2921, 2855, 1732, 1609, 1554, 1443, 1331, 1261, 1180, 1017, 938, 834, 785, 759, 698 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.42 (s, 3 H), 3.85 (s, 3 H), 6.84 (s, 1 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.48–7.51 (m, 5 H), 8.06 (d, J = 8.0 Hz, 2 H), 8.96 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 21.6, 30.2, 100.1, 115.8, 128.9, 128.9, 129.0, 129.3, 129.6, 131.5, 135.6, 140.3, 142.8, 151.4, 153.5, 156.8 ppm. HRMS (ESI): calcd. For C20H18N3 [M + H]+ 300.1495; found 300.1500.

4-(4-Methoxyphenyl)-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (6d): The reaction was carried out by following general procedure C starting from 4-chloropyrimidine 5a (150 mg, 0.62 mmol) and 4-methoxyphenylboronic acid (98.2 mg, 0.65 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 6:4) to afford 6d (194.5 mg, 0.62 mmol, 100%) as a yellow solid. Rf = 0.48 (CH2Cl2/ethyl acetate, 8:2); m.p. 174–176 °C (ethyl acetate). IR (ATR diamond): ν˜ = 3054, 2921, 2845, 1550, 1512, 1439, 1328, 1247, 1172, 1021, 937, 851, 756 cm–1. 1H NMR (300 MHz, CDCl3): δ = 3.89 (s, 3 H), 3.90 (s, 3 H), 6.87 (s, 1 H), 7.07 (d, J = 8.2 Hz, 2 H), 7.47–7.59 (m, 5 H), 8.17 (d, J = 8.2 Hz, 2 H), 8.96 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 30.1, 55.8, 100.0, 114.3, 115.4, 128.9, 129.0, 129.3, 130.4, 131.0, 131.6, 142.6, 151.4, 153.4, 160.6, 161.3 ppm. HRMS (ESI): calcd. for C20H18N3O [M + H]+ 316.1444; found 316.1447.

7-Methyl-6-phenyl-4-[4-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]-pyrimidine (6e): The reaction was carried out by following general procedure C starting from 4-chloropyrimidine 5a (150 mg, 0.62 mmol) and 4-(trifluoromethyl)phenylboronic acid (122.8 mg, 0.65 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 8:2) to afford 6e (213.7 mg, 0.60 mmol, 98%) as a beige solid. Rf = 0.57 (CH2Cl2/ethyl acetate, 8:2); m.p. 137–139 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2960, 2920, 2849, 1736, 1620, 1555, 1493, 1466, 1400, 1327, 1307, 1265, 1219, 1185, 1165, 1103, 1064, 1014, 936, 850, 808, 783, 753, 730, 699 cm–1. 1H NMR (300 MHz, CDCl3): δ = 3.92 (s, 3 H), 6.85 (s, 1 H), 7.49–7.57 (m, 5 H), 7.81 (d, J = 8.0 Hz, 2 H), 8.28 (d, J = 8.0 Hz, 2 H), 9.02 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 30.3, 99.4, 116.2, 124.2 (J = 271 Hz), 125.8 (J = 4 Hz), 129.0, 129.2, 129.3, 129.4, 131.2, 131.7 (J = 32 Hz), 141.8, 143.8, 151.4, 153.7, 154.9 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.68 (CF3) ppm. HRMS (ESI): calcd. for C20H15N3F3 [M + H]+ 354.1213; found 354.1214.

6-(4-Methoxyphenyl)-7-methyl-4-(3-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (6f): The reaction was carried out by following general procedure C starting from 4-chloropyrimidine 5b (150 mg, 0.55 mmol) and 3-tolylboronic acid (78.2 mg, 0.58 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 8:2) to afford 6f (173.9 mg, 0.53 mmol, 96%) as an offwhite solid; m.p. 95–97 °C (ethyl acetate). Rf = 0.38 (CH2Cl2/ethyl acetate, 8:2). IR (ATR diamond): ν˜ = 2921, 2855, 2153, 1968, 1615, 1558, 1497, 1442, 1339, 1295, 1252, 1173, 1013, 893, 826, 786, 763, 700 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.59 (s, 3 H), 3.97 (s, 3 H), 3.98 (s, 3 H), 6.92 (s, 1 H), 7.14 (d, J = 8.8 Hz, 2 H), 7.42 (d, J = 7.5 Hz, 1 H), 7.54 (t, J = 7.5 Hz, 1 H), 7.59 (d, J = 8.8 Hz, 2 H), 8.04–8.14 (m, 2 H), 9.11 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 21.7, 30.1, 55.5, 99.3, 114.4, 116.0, 123.8, 126.1, 128.7, 129.4, 130.6, 130.8, 138.4, 138.9, 142.9, 151.2, 153.3, 156.6, 160.3 ppm. HRMS (ESI): calcd. for C21H20N3O [M + H]+330.1601; found 330.1602.

7-Methyl-4-(3-tolyl)-6-[4-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]-pyrimidine (6g): The reaction was carried out by following genera procedure C starting from 4-chloropyrimidine 5c (150 mg, 0.48

mmol) and 3-tolylboronic acid (68.7 mg, 0.51 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/ethyl acetate, 8:2) to afford 6g (169.4 mg, 0.46 mmol, 96%) as an off-white solid. Rf = 0.43 (CH2Cl2/ethyl acetate, 8:2); m.p. 109–111 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2921, 2849, 1615, 1551, 1440, 1322, 1160, 1114, 1068, 894, 847, 767, 702 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.45 (s, 3 H), 3.87 (s, 3 H), 6.89 (s, 1 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.67 (d, J = 8.2 Hz, 2 H), 7.75 (d, J = 8.2 Hz, 2 H), 7.91 (d, J = 7.6 Hz, 1 H), 7.95 (s, 1 H), 8.99 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 21.7, 30.3, 101.2, 115.8, 124.0 (J = 271 Hz), 125.9 (J = 4 Hz), 126.1, 128.8, 129.5, 129.6, 131.0 (J = 32 Hz), 131.1, 135.1, 138.1, 138.8, 141.1, 151.9, 153.6, 157.6 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.73 (CF3) ppm. HRMS (ESI): calcd. for C21H17N3F3 [M + H]+ 368.1369; found 368.1371.

General Procedure D (Aryl Iodination): A solution of 6a–g (1.0 mmol) and NIS (1.1 mmol) in acetonitrile (4.5 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven at 100 °C for 30 min. The progress of the reaction was monitored by TLC. After cooling, the solvent was removed under vacuo. Dichloromethane (20 mL) was added and the organic layer was washed with aqueous saturated Na2S2O3 (2 16 mL), and NaOH (10%, 2 16 mL). Evaporation of the solvent under reduced pressure gave the crude product, which did not require further purification.

5-Iodo-7-methyl-6-phenyl-4-(3-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (7a): The reaction was carried out by following general procedure D starting from diaryl pyrimidine 6a (500 mg, 1.67 mmol) to afford 7a (710.0 mg, 1.67 mmol, 100 %) as a yellow solid. Rf = 0.27 (CH2Cl2/ethyl acetate, 8:2); m.p. 188–190 °C (ethyl acetate). IR (ATR diamond): ν˜ = 3045, 2913, 1547, 1439, 1402, 1330, 1254, 1182, 1088, 1020, 958, 915, 783, 764, 708, 682 cm–1. 1H NMR (400 MHz, CDCl3): δ = 2.45 (s, 3 H), 3.77 (s, 3 H), 7.32 (d, J = 7.6 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.43–7.47 (m, 2 H), 7.49–7.61 (m, 5 H), 8.98 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 21.6, 30.9, 55.2, 117.3, 127.7, 128.2, 128.8, 129.7, 130.3, 130.9, 131.3, 131.8, 135.8, 137.3, 144.5, 151.1, 152.5, 160.5 ppm. HRMS (ESI): calcd. for C20H17IN3 [M + H]+ 426.0462; found 426.0463.

5-Iodo-7-methyl-6-phenyl-4-(2-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (7b): The reaction was carried out by following general procedure D starting from diaryl pyrimidine 6b (150 mg, 0.5 mmol) to afford 7b (211.5 mg, 0.50 mmol, 99 %) as a yellow solid. Rf = 0.51 (CH2Cl2/ethyl acetate, 8:2); m.p. 185–187 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2917, 2849, 1736, 1552, 1438, 1403, 1334, 1242, 1176, 1120, 1089, 951, 887, 796, 765, 725, 701 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.16 (s, 3 H), 3.79 (s, 3 H), 7.30–7.32 (m, 3 H), 7.37–7.41 (m, 1 H), 7.43–7.46 (m, 2 H), 7.50–7.54 (m, 3 H), 8.98 (s, 1 H) ppm. 13C NMR (63 MHz, CDCl3): δ = 20.3, 30.9, 54.9, 118.2, 125.3, 128.8, 129.7, 129.9, 130.0, 130.8, 130.9, 135.7, 136.6, 142.8, 136.9, 151.3, 152.0, 162.2 ppm. HRMS (ESI): calcd. for C20H17IN3 [M + H]+ 426.0462; found 426.0463.

5-Iodo-7-methyl-6-phenyl-4-(4-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (7c): The reaction was carried out by following general procedure D starting from diaryl pyrimidine 6c (150 mg, 0.50 mmol) to afford 7c (212.3 mg, 0.50 mmol, 100%) as an off-white solid. Rf = 0.29 (CH2Cl2/ethyl acetate, 8:2); m.p. 204–206 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2960, 2923, 2849, 1612, 1557, 1513, 1480, 1459, 1441, 1335, 1287, 1243, 1224, 1177, 1033, 953, 827, 764, 703 cm–1. 1H NMR (250 MHz, CDCl3): δ = 2.45 (s, 3 H), 3.77 (s, 3 H), 7.32 (d, J = 7.8 Hz, 2 H), 7.39–7.49 (m, 2 H), 7.52–7.55 (m, 3 H), 7.65 (d, J = 7.8 Hz, 1 H), 8.97 (s, 1 H) ppm. 13C NMR (63 MHz, CDCl3): δ = 21.7, 31.0, 55.2, 117.3, 128.5, 128.8, 129.7, 130.9, 131.1, 131.3, 133.2, 139.6, 144.4, 151.1, 152.5, 160.5 ppm. HRMS (ESI): calcd. for C20H17IN3 [M + H]+ 426.0462; found 426.0463.

5-Iodo-4-(4-methoxyphenyl)-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (7d): The reaction was carried out by following general procedure D starting from diaryl pyrimidine 6d (150 mg, 0.48 mmol) to afford 7d (209.1 mg, 0.48 mmol, 100%) as a yellow solid. Rf = 0.51 (CH2Cl2/ethyl acetate, 8:2); m.p. 196–198 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2921, 2849, 1608, 1556, 1513, 1439, 1321, 1293, 1243, 1174, 1025, 951, 885, 833, 797, 764, 739, 704 cm–1. 1H NMR (300 MHz, CDCl3): δ = 3.77 (s, 3 H), 3.89 (s, 3 H), 7.04 (d, J = 8.8 Hz, 2 H), 7.41–7.49 (m, 2 H), 7.50–7.58 (m, 3 H), 7.73 (d, J = 8.8 Hz, 2 H), 8.96 (s, 1 H) ppm. 13C NMR (63 MHz, CDCl3): δ = 31.0, 55.4, 55.5, 113.2, 117.2,

128.5, 128.8, 129.7, 130.9, 131.3, 132.7, 144.4, 151.1, 152.6, 160.0, 161.0 ppm. HRMS (ESI): calcd. for C20H17IN3O [M + H]+ 442.0411; found 442.0412.

5-Iodo-7-methyl-6-phenyl-4-[4-(trifluoromethyl)phenyl]-7H-pyrrolo-[2.3-d]pyrimidine (7e): The reaction was carried out by following general procedure D starting from diaryl pyrimidine 6e (150 mg, 0.42 mmol) to afford 7e (202.4 mg, 0.42 mmol, 99%) as a beige solid. Rf = 0.60 (CH2Cl2/ethyl acetate, 8:2); m.p. 198–200 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2922, 2852, 1733, 1557, 1476, 1440, 1400, 1325, 1244, 1155, 1117, 1107, 1062, 1017, 948, 885, 843, 799, 762.704 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.79 (s, 3 H), 7.41–7.48 (m, 2 H), 7.51–7.59 (m, 3 H), 7.78 (d, J = 8.4 Hz, 2 H), 7.86 (d, J = 8.4 Hz, 2 H), 8.99 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 30.9, 54.4, 117.4, 124.2 (J = 272 Hz), 124.6 (J = 4 Hz), 128.8, 129.8, 130.7, 130.8, 131.3, 131.4 (J = 32 Hz), 139.4 (J = 1 Hz), 145.0, 151.0, 152.5, 158.5 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.52 (CF3) ppm. HRMS (ESI): calcd. for C20H14F3IN3 [M + H]+ 480.0179; found 480.0180.

5-Iodo-6-(4-methoxyphenyl)-7-methyl-4-(3-tolyl)-7H-pyrrolo[2,3-d]-pyrimidine (7f): The reaction was carried out by following general procedure D starting from diaryl pyrimidine 6f (150 mg, 0.46 mmol) to afford 7f (100%, 207.3 mg, 0.46 mmol) as a yellow solid. Rf = 0.32 (CH2Cl2/acetone, 9:1); m.p. 179–181 °C (acetone). IR (ATR diamond): ν˜ = 2955, 2918, 2849, 1736, 1609, 1559, 1533, 1467, 1446, 1414, 1289, 1243, 1173, 1021, 954, 837, 782, 711 cm–1. 1H NMR (250 MHz, CDCl3): δ = 2.45 (s, 3 H), 3.77 (s, 3 H), 3.90 (s, 3 H), 7.05 (d, J = 8.8 Hz, 2 H), 7.28–7.34 (m, 1 H), 7.35–7.43 (m, 3 H), 7.52–7.55 (m, 2 H), 8.96 (s, 1 H) ppm. 13C NMR (63 MHz, CDCl3): δ = 21.6, 30.9, 55.2, 55.5, 114.2, 117.3, 123.2, 127.7, 128.2, 130.2, 131.8, 132.3, 135.9, 137.3, 144.5, 150.9, 152.5, 160.2, 160.6 ppm. HRMS (ESI): calcd. for C21H19IN3O [M + H]+456.0567; found 456.0566.

5-Iodo-7-methyl-4-(3-tolyl)-6-[4-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine (7g): The reaction was carried out by following general procedure D starting from diaryl pyrimidine 6g (150 mg, 0.41 mmol) to afford 7g (201.2 mg, 0.41 mmol, 100%) as a beige solid. Rf = 0.53 (CH2Cl2/ethyl acetate, 7:3); m.p. 137–139 °C (ethyl acetate). IR (ATR diamond): ν˜ = 2923, 2855, 1736, 1555, 1447, 1407, 1320, 1251, 1163, 1127, 1067, 1017, 964, 911, 855, 791, 709 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.46 (s, 3 H), 3.79 (s, 3 H), 7.31–7.36 (m, 1 H), 7.38–7.45 (m, 1 H), 7.51–7.57 (m, 2 H), 7.61 (d, J = 8.7 Hz, 2 H), 7.82 (d, J = 8.7 Hz, 2 H), 9.01 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 21.5, 30.9, 55.8, 117.1, 123.8 (J = 274 Hz), 125.7 (J = 4 Hz), 127.7, 128.0, 130.4, 131.4, 131.6, 131.7 (J = 33 Hz), 134.8 (J = 1 Hz), 135.3, 137.3, 142.7, 151.2, 152.5, 160.8 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.82 (CF3) ppm. HRMS (ESI): calcd. for C21H16F3IN3 [M + H]+494.0336; found 494.0335.

General Procedure E (Suzuki–Miyaura Coupling at C-5): Under argon, a mixture of compound 7a–g (1.0 mmol), boronic acid (1.05 mmol), sodium carbonate (2.0 mmol), and dichlorobis(triphenylphosphine) palladium (0.05 mmol) in a degassed solvent mixture of DME (3.8 mL) and H2O (0.6 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven at 100 °C for 60 min. The progress of the reaction was monitored by TLC. After cooling, the mixture was diluted with a mixture of brine and water (1:1, 20 mL), and the aqueous solution was extracted with ethyl acetate (3 20 mL). Evaporation of the solvent under reduced pressure gave the crude product. A solution of the previous residue and NIS (1.1 mmol) in acetonitrile (4.5 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven at 100 °C for 30 min. The progress of the reaction was monitored by TLC. After cooling, the solvent was removed, then dichloromethane (20 mL) was added and the organic layer was washed with aqueous saturated Na2S2O3 (2 16 mL) and NaOH (10%, 2 16 mL). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

5-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(3-tolyl)-7H-pyrrolo-[2,3-d]pyrimidine (8a): The reaction was carried out by following general procedure E starting from the iodo derivative 7a (100 mg, 0.24 mmol) and 4-methoxyphenylboronic acid (39.3 mg, 0.26 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 95:5) to afford 8a (83.9 mg, 0.21 mmol, 88%) as a white solid (8% starting material was also recovered). Rf = 0.11 (CH2Cl2/acetone, 95:5); m.p. 144–

146°C (acetone). IR (ATR diamond): ν˜ = 2954, 1614, 1552, 1535, 1514, 1466, 1438, 1413, 1349, 1322, 1287, 1238, 1176, 1134, 1108, 1036, 964, 919, 847, 816, 790, 762, 746 cm–1. 1H NMR (400 MHz, [D6]-DMSO): δ = 1.96 (s, 3 H), 3.64 (s, 3 H), 3.73 (s, 3 H), 6.52 (d, J = 8.8 Hz, 2 H), 6.68 (d, J = 8.8 Hz, 2 H), 6.88 (s, 1 H), 7.03–7.09 (m, 2 H), 7.21–7.27 (m, 1 H), 7.35–7.39 (m, 2 H), 7.39–7.43 (m, 3 H), 8.91 (s, 1 H) ppm. 13C NMR (100 MHz, [D6]DMSO): δ = 20.5, 29.6, 55.0, 112.9, 113.0, 114.2, 126.1, 126.2, 127.7, 128.3, 128.7, 129.1, 130.1, 130.8, 130.9, 131.6, 136.2, 137.0, 138.9, 150.6, 151.4, 157.6, 158.3 ppm. HRMS (ESI): calcd. for C27H24N3O [M + H]+406.1914; found 406.1915.

7-Methyl-6-phenyl-4-(3-tolyl)-5-[4-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine (8b): The reaction was carried out by following general procedure E starting from the iodo derivative 7a (100 mg, 0.24 mmol) and 4-trifluoromethylphenylboronic acid (49.1 mg, 0.26 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 97.5:2.5 to 9:1) to afford 8b (69.8 mg, 0.16 mmol, 67%) as a beige solid (29% of starting material was also recovered). Rf = 0.22 (CH2Cl2/acetone, 9:1); m.p. 199–201 °C (acetone). IR (ATR diamond): ν˜ = 3043, 2921, 2847, 1618, 1556, 1538, 1438, 1409, 1348, 1323, 1238, 1161, 1115, 1106, 1064, 1023, 962, 919, 856, 825, 789, 760, 711, 697 cm–1. 1H NMR (400 MHz, CDCl3): δ = 1.98 (s, 3 H), 3.84 (s, 3 H), 6.85 (d, J = 8.0 Hz, 2 H), 6.90 (s, 1 H), 7.04 (d, J = 6.5 Hz, 2 H), 7.16 (d, J = 8.0 Hz, 2 H), 7.22 (d, J = 6.5 Hz, 1 H), 7.24–7.28 (m, 2 H), 7.39–7.41 (m, 3 H), 9.04 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 20.9, 30.1, 113.2, 114.7, 124.2 (J = 4 Hz), 124.4 (J = 273 Hz), 126.4, 127.8, 128.1 (J = 32 Hz), 128.4, 128.8, 129.2, 129.8, 130.0, 130.9, 131.0, 131.1, 137.3, 138.1, 139.8, 151.5, 152.4, 159.6 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.55 (CF3) ppm. HRMS (ESI): calcd. for C27H21F3N3 [M + H]+ 444.1682; found 444.1683.

7-Methyl-6-phenyl-4-(3-tolyl)-5-(4-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (8c): The reaction was carried out by following general procedure E starting from the iodo derivative 7a (100 mg, 0.24 mmol) and p-tolylboronic acid (35.2 mg, 0.26 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 98:2 to 9:1) to afford 8c (64.8 mg, 0.17 mmol, 71%) as a darkbeige solid (26% of starting material was also recovered). Rf = 0.23 (CH2Cl2/acetone, 9:1); m.p. 204–206 °C (acetone). IR (ATR diamond): ν˜ = 3034, 2917, 2849, 1737, 1553, 1537, 1516, 1436, 1413, 1348, 1320, 1273, 1238, 1210, 1177, 1130, 1026, 962, 918, 892, 845, 816, 788, 763, 743, 710, 698 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.00 (s, 3 H), 2.21 (s, 3 H), 3.82 (s, 3 H), 6.64 (d, J = 8.0 Hz, 2 H), 6.73 (d, J = 8.0 Hz, 2 H), 6.92–7.08 (m, 3 H), 7.24–7.31 (m, 3 H), 7.33–7.40 (m, 3 H), 9.01 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 21.2, 21.4, 30.3, 114.8, 115.2, 126.8, 127.7, 128.3, 128.7, 128.8, 129.6, 130.9, 131.0, 131.2, 131.3, 131.4, 135.8, 137.1, 137.5, 139.2, 151.2, 152.5, 159.7 ppm. HRMS (ESI): calcd. For C27H24N3 [M + H]+ 390.1965; found 390.1964.

7-Methyl-6-phenyl-4,5-bis-(3-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (8d): The reaction was carried out by following general procedure E starting from the iodo derivative 7a (100 mg, 0.24 mmol) and m-tolylboronic acid (35.2 mg, 0.26 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 98:2 to 9:1) to afford 8d (69.6 mg, 0.18 mmol, 76%) as a white solid (22% of starting material was also recovered). Rf = 0.09 (CH2Cl2/acetone, 9:1); m.p. 151–153 °C (acetone). IR (ATR diamond): ν˜ = 3028, 2919, 2847, 1557, 1538, 1492, 1463, 1441, 1418, 1349, 1324, 1241, 1193, 1166, 1128, 1086, 1025, 1000, 969, 924, 901, 870, 839, 812, 788, 763, 748, 719, 703 cm–1. 1H NMR (300 MHz, CDCl3): δ = 1.93 (s, 3 H), 2.03 (s, 3 H), 3.82 (s, 3 H), 6.50 (s, 1 H), 6.60 (d, J = 7.1 Hz, 1 H), 6.78–6.86 (m, 2 H), 7.01–7.04 (m, 3 H), 7.21–7.23 (m, 1 H), 7.26–7.32 (m, 2 H), 7.34–7.39 (m, 3 H), 9.02 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 21.1, 30.0, 114.7, 115.0, 126.5, 126.8, 127.3, 127.4, 127.7, 128.5, 128.7, 129.4, 130.7, 130.9, 131.1, 132.3, 133.7, 136.9, 137.6, 139.0, 151.1, 152.3, 159.7 ppm. HRMS (ESI): calcd. for C27H24N3 [M + H]+ 390.1965; found 390.1967.

7-Methyl-6-phenyl-4-(3-tolyl)-5-(2-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (8e): The reaction was carried out by following general procedure E starting from the iodo derivative 7a (100 mg, 0.24 mmol, 1.0 equiv.) and p-tolylboronic acid (35.2 mg, 0.26 mmol, 1.1 equiv.). The product was purified by chromatography on silica gel (CH2Cl2/ acetone, 98:2 to 9:1) to afford starting material (82 %). Product 8e was not observed.

5-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(2-tolyl)-7H-pyrrolo-[2,3-d]pyrimidine (8f): The reaction was carried out by following general procedure E starting from the iodo derivative 7b (100 mg, 0.24 mmol) and 4-methoxyphenylboronic acid (39.3 mg, 0.26 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 98:2 to 9:1) to afford 8f (89.5 mg, 0.22 mmol, 94%) as a beige solid (5% of starting material was also recovered). Rf = 0.42 (CH2Cl2/acetone, 9:1); m.p. 186–188 °C (acetone). IR (ATR diamond): ν˜ = 3060, 2997, 2931, 1609, 1559, 1513, 1415, 1349, 1319, 1287, 1243, 1224, 1179, 1121, 1033, 953, 894, 837, 809, 774, 763, 729, 701 cm–1. 1H NMR (400 MHz, CDCl3): δ = 1.99 (s, 3 H), 3.65 (s, 3 H), 3.83 (s, 3 H), 6.34 (d, J = 8.6 Hz, 2 H), 6.55 (d, J = 8.6 Hz, 2 H), 6.94 (t, J = 7.4 Hz, 2 H), 7.01 (d, J = 7.4 Hz, 1 H), 7.09 (t, J = 7.4 Hz, 1 H), 7.26–7.28 (m, 2 H), 7.34–7.36 (m, 3 H), 9.00 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 19.8, 30.0, 55.2, 112.7, 114.4, 116.3, 125.1, 125.2, 128.3, 128.6, 128.7, 129.4, 129.7, 130.6, 131.1, 131.5, 135.8, 137.7, 138.9, 151.1, 151.8, 157.7, 160.1 ppm. HRMS (ESI): calcd. For C27H24N3O [M + H]+ 406.1914; found 406.1913.

5-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(4-tolyl)-7H-pyrrolo-[2,3-d]pyrimidine (8g): The reaction was carried out by following general procedure E starting from the iodo derivative 7c (100 mg, 0.24 mmol) and 4-methoxyphenylboronic acid (39.3 mg, 0.26 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 98:2 to 9:1) to afford 8g (61.9 mg, 0.15 mmol, 65%) as a beige solid (29% of starting material was also recovered). Rf = 0.21 (CH2Cl2/acetone, 8:2); m.p. 157–159 °C (acetone). IR (ATR diamond): ν˜ = 2917, 2849, 1550, 1532, 1510, 1462, 1440, 1418, 1346, 1321, 1290, 1237, 1174, 1132, 1110, 1035, 953, 892, 831, 800, 783, 767, 713, 704 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.27 (s, 3 H), 3.69 (s, 3 H), 3.81 (s, 3 H), 6.46 (d, J = 8.7 Hz, 2 H), 6.64 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.0 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.25–7.29 (m, 2 H), 7.32–7.45 (m, 3 H), 9.00 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 21.4, 29.9, 55.3, 113.0, 114.2, 115.0, 126.4, 128.0, 128.5, 128.6, 129.6, 130.7, 131.1, 131.9, 134.7, 138.5, 138.9, 151.0, 152.2, 158.0, 159.4 ppm. HRMS (ESI): calcd. for C27H24N3O [M + H]+406.1914; found 406.1916.

4,5-Bis(4-methoxyphenyl)-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (8h): The reaction was carried out by following general procedure E starting from the iodo derivative 7d (100 mg, 0.23 mmol) and 4-methoxyphenylboronic acid (37.9 mg, 0.25 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 98:2 to 9:1) to afford 8h (87.7 mg, 0.21 mmol, 92%) as an off-white solid (6% of starting material was also recovered). Rf = 0.39 (CH2Cl2/acetone, 8:2); m.p. 172–174 °C (acetone). IR (ATR diamond): ν˜ = 3039, 2923, 2832, 1605, 1552, 1532, 1510, 1455, 1435, 1416, 1347, 1322, 1301, 1289, 1246, 1235, 1173, 1130, 1108, 1034, 954, 927, 892, 842, 804, 783, 768, 704 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.71 (s, 3 H), 3.74 (s, 3 H), 3.81 (s, 3 H), 6.50 (d, J = 8.8 Hz, 2 H), 6.59 (d, J = 8.8 Hz, 2 H), 6.67 (d, J = 8.8 Hz, 2 H), 7.24–7.29 (m, 4 H), 7.34–7.39 (m, 3 H), 8.98 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 30.0, 55.3, 55.4, 112.9, 113.1, 114.2, 114.8, 126.6, 128.5, 128.6, 130.2, 130.8, 131.2, 131.3, 132.0, 138.8, 151.1, 152.3, 158.1, 159.0, 160.3 ppm. HRMS (ESI): calcd. for C27H24N3O2 [M + H]+ 422.1863; found 422.1864.

5-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-[4-(trifluoromethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidine (8i): The reaction was carried out by following general procedure E starting from the iodo derivative 7e (100 mg, 0.21 mmol) and 4-methoxyphenylboronic acid (34.9 mg, 0.23 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 98:2 to 9:1) to afford 8i (71.4 mg, 0.16 mmol, 74%) as a fluorescent yellow solid (20% of starting material was also recovered). Rf = 0.5 (CH2Cl2/acetone, 8:2); m.p. 198–200 °C (acetone). IR (ATR diamond): ν˜ = 3038, 2935, 2832, 1612, 1557, 1513, 1484, 1470, 1442, 1406, 1349, 1318, 1290, 1246, 1232, 1172, 1158, 1119, 1104, 1064, 1037, 1017, 953, 926, 895, 846, 804, 780, 763, 748, 734, 703 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.67 (s, 3 H), 3.84 (s, 3 H), 6.45 (d, J = 8.7 Hz, 2 H), 6.60 (d, J = 8.7 Hz, 2 H), 7.27–7.34 (m, 4 H), 7.36–7.40 (m, 5 H), 9.03 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 30.1, 55.2, 113.2, 113.8, 115.6, 124.2 (J = 273 Hz), 124.2 (J = 4 Hz), 125.8, 128.6, 128.9, 129.9, 130.3, 130.4 (J = 32 Hz), 131.0, 131.8, 139.5, 141.1, 151.2, 152.3, 157.7, 158.4 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.70 (CF3) ppm. HRMS (ESI): calcd. for C27H21F3N3O [M + H]+ 460.1631; found 460.1632.

5,6-Bis(4-methoxyphenyl)-7-methyl-4-(3-tolyl)-7H-pyrrolo[2,3-d]pyrimidine (8j): The reaction was carried out by following general procedure E starting from the iodo derivative 7f (100 mg, 0.22 mmol) and 4-methoxyphenylboronic acid (36.7 mg, 0.24 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 98:2 to 8:2) to afford 8j (54.6 mg, 0.13 mmol, 57%) as a beige solid (40% of starting material was also recovered). Rf = 0.20 (CH2Cl2/acetone, 9:1); m.p. 195–197 °C (acetone). IR (ATR diamond): ν˜ = 3033, 2921, 2850, 1738, 1612, 1541, 1519, 1496, 1463, 1442, 1422, 1394, 1346, 1319, 1292, 1242, 1174, 1132, 1108, 1028, 961, 933, 917, 852, 835, 810, 798, 784, 741, 725, 709 cm–1. 1H NMR (300 MHz, CDCl3): δ = 2.04 (s, 3 H), 3.70 (s, 3 H), 3.81 (2s, 6 H), 6.48 (d, J = 8.9 Hz, 2 H), 6.66 (d, J = 8.9 Hz, 2 H), 6.89 (d, J = 8.9 Hz, 2 H), 7.00–7.06 (m, 3 H), 7.19 (d, J = 8.9 Hz, 2 H), 7.21–7.24 (m, 1 H), 8.99 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 21.1, 30.0, 55.3, 55.4, 113.0, 113.8, 114.0, 115.0, 122.7, 126.6, 126.7, 127.4, 129.3, 131.0, 131.9, 132.3, 137.0, 137.4, 138.9, 150.8, 152.2, 157.9, 159.1, 159.7 ppm. HRMS (ESI): calcd. for C28H26N3O2 [M + H]+ 436.2020; found 436.2020.

5-(4-Methoxyphenyl)-7-methyl-4-(3-tolyl)-6-[4-(trifluoromethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidine (8k): The reaction was carried out by following general procedure E starting from the iodo derivative 7g (150 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (50.8 mg, 0.36 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 95:5) to afford 8k (84.5 mg, 0.18 mmol, 59%) as a white solid (34% of starting material was also recovered). Rf = 0.39 (CH2Cl2/acetone, 7:3); m.p. 191–193 °C (acetone). IR (ATR diamond): ν˜ = 3055, 2955, 2923, 2854, 1708, 1557, 1539, 1514, 1438, 1416, 1349, 1319, 1287, 1243, 1224, 1179, 1120, 1086, 1033, 953, 894, 837, 809, 773, 763, 722, 701 cm–1. 1H NMR (400 MHz, CDCl3): δ = 2.05 (s, 3 H), 3.71 (s, 3 H), 3.83 (s, 3 H), 6.51 (d, J = 8.8 Hz, 2 H), 6.65 (d, J = 8.8 Hz, 2 H), 6.96–7.06 (m, 3 H), 7.21–7.25 (m, 1 H), 7.40 (d, J = 8.0 Hz, 2 H), 7.63 (d, J = 8.0Hz, 2 H), 9.02 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 21.1, 30.2, 55.3, 113.3, 115.0, 115.3, 124.0 (J = 274 Hz), 125.5 (J = 4 Hz), 125.9, 126.7, 127.5, 129.6, 130.4, 130.7, 131.0, 131.5, 131.9, 134.6 (J = 1 Hz), 137.1, 137.2, 151.6, 152.5, 158.3, 160.2 ppm. 19F NMR (376 MHz, CDCl3): δ = –62.73 (CF3) ppm. HRMS (ESI): calcd. for C28H23F3N3O [M + H]+474.1788; found 474.1787. CCDC-963176 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4-Chloro-5-(4-methoxyphenyl)-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]-pyrimidine (9): The reaction was carried out by following general procedure E starting from 10 (150 mg, 10a: 0.46mmol or 10b: 0.41 mmol) and 4-methoxyphenylboronic acid (10a: 77.5mg, 0.51 mmol or 10b: 68.4 mg, 0.45 mmol). The crude product was purified by silica gel column chromatography (CH2Cl2/acetone, 95:5) to afford 9 as a white solid in 33% (53.5 mg, 0.15 mmol from 10a) and 70% (99.2 mg, 0.28 mmol from 10b) yield. Rf = 0.35 (CH2Cl2/acetone, 95:5); m.p. 150–152 °C (acetone). IR (ATR diamond): ν˜ = 2931, 2836, 1541, 1515, 1479, 1445, 1414, 1286, 1247, 1234, 1220, 1178, 1155, 1124, 1028, 955, 892, 834, 750, 708, 700 cm–1. 1H NMR (250 MHz, CDCl3): δ = 3.81 (s, 3 H), 3.83 (s, 3 H), 6.83 (d, J = 8.8 Hz, 2 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.25–7.34 (m, 2 H), 7.36–7.45 (m, 3 H), 8.70 (s, 1 H) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 33.4, 55.3, 113.1, 113.9, 115.8, 124.6, 128.6, 128.9, 129.8, 130.8, 132.9, 140.0, 150.3, 151.7, 151.8, 158.7 ppm. HRMS (ESI): calcd. for C20H17ClN3O [M + H]+350.1055; found 350.1055.

5-Bromo-4-chloro-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (10a): A solution of 4-chloropyrimidine 5a (750 mg, 3.08 mmol) and NBS (639 mg, 3.59 mmol) in acetonitrile (5.5 mL) was transferred to a special microwave tube and irradiated in a microwave oven at 100 °C for 30 min. The progress of the reaction was monitored by TLC. After cooling, the solvent was removed under vacuo. Dichloromethane (20 mL) was added and the organic layer was washed with aqueous saturated Na2S2O3 (2 16 mL), and NaOH (10%, 2 16 mL). Evaporation of the solvent under reduced pressure gave the crude product 10a (874.6 mg, 2.71 mmol, 87%) as a yellow solid, which did not require further purification. Rf = 0.41 (CH2Cl2/ethyl acetate, 9:1); m.p. 168–170 °C (ethyl acetate). IR (ATR diamond): ν˜ = 3059, 2931, 1582, 1544, 1488, 1468, 1436, 1347, 1221, 1174, 1152, 1028, 962, 890, 780, 762, 701 cm–1. 1H NMR (250 MHz, CDCl3): δ = 3.75 (s, 3 H), 7.47–7.58 (m, 5 H), 8.66 (s, 1 H) ppm. 13C NMR (63 MHz, CDCl3): δ = 30.9, 87.3, 115.3, 128.7, 129.0, 130.0, 130.6, 140.8, 150.9, 151.3, 151.8 ppm. HRMS (ESI): calcd. for C13H10BrClN3 [M + H]+ 321.9741; found 321.9742.

4-Chloro-5-iodo-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (10b): The reaction was carried out by following general procedure D starting from 4-chloropyrimidine (5a) (300 mg, 1.23 mmol, 1.0 equiv.) to afford 10b (435.5 mg, 1.18 mmol, 96%) as a yellow solid. Rf = 0.34 (CH_2Cl_2/ethyl acetate, 95:5); m.p. 203–205 °C (ethyl acetate). IR (ATR diamond): $\tilde{\nu}$ = 3744, 3058, 2924, 2854, 1541, 1479, 1434, 1343, 1265, 1217, 1168, 1026, 952, 886, 765, 702 cm–1. 1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 7.41–7.47 (m, 2 H), 7.53–7.58 (m, 3 H), 8.64 (s, 1 H) ppm. 13C NMR (100 MHz, $CDCl_3$): δ = 31.4, 54.0, 117.5, 129.0, 130.1, 130.5, 130.8, 144.8, 150.6, 152.2, 152.4 ppm. HRMS (ESI): calcd. for $C_{13}H_{10}ClIN_3$ $[M + H]^+$ 369.9603; found 369.9604.

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Legends to figures

Figure 1. Purines and 7-deazapurines.

Scheme 1. Two synthetic routes to the triarylated pyrrolopyrimidines 8.

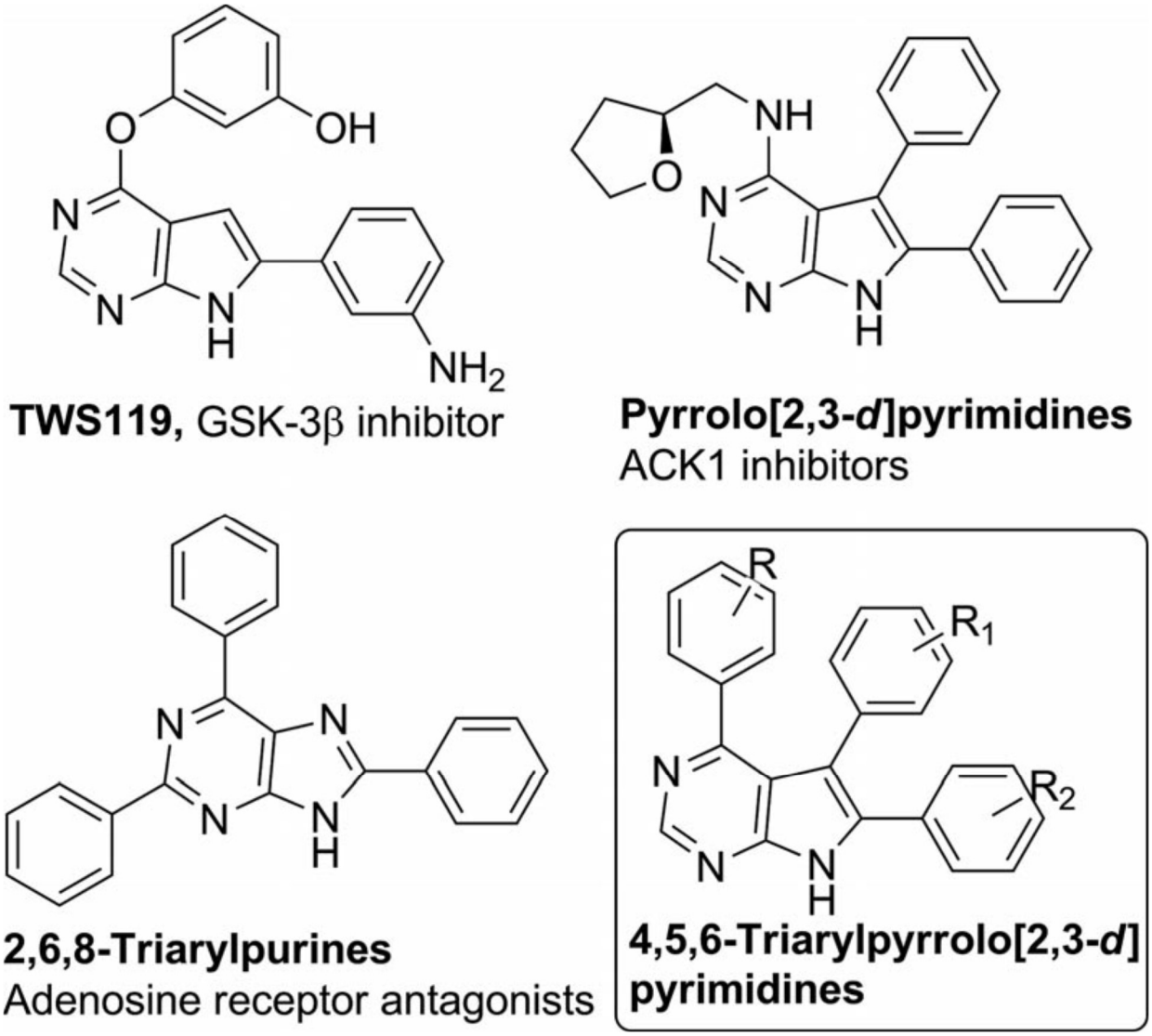
Scheme 2. Alkynylation of iodopyrimidines 3.

Scheme 3. Intramolecular cyclization of diarylalkynyl derivatives 4.

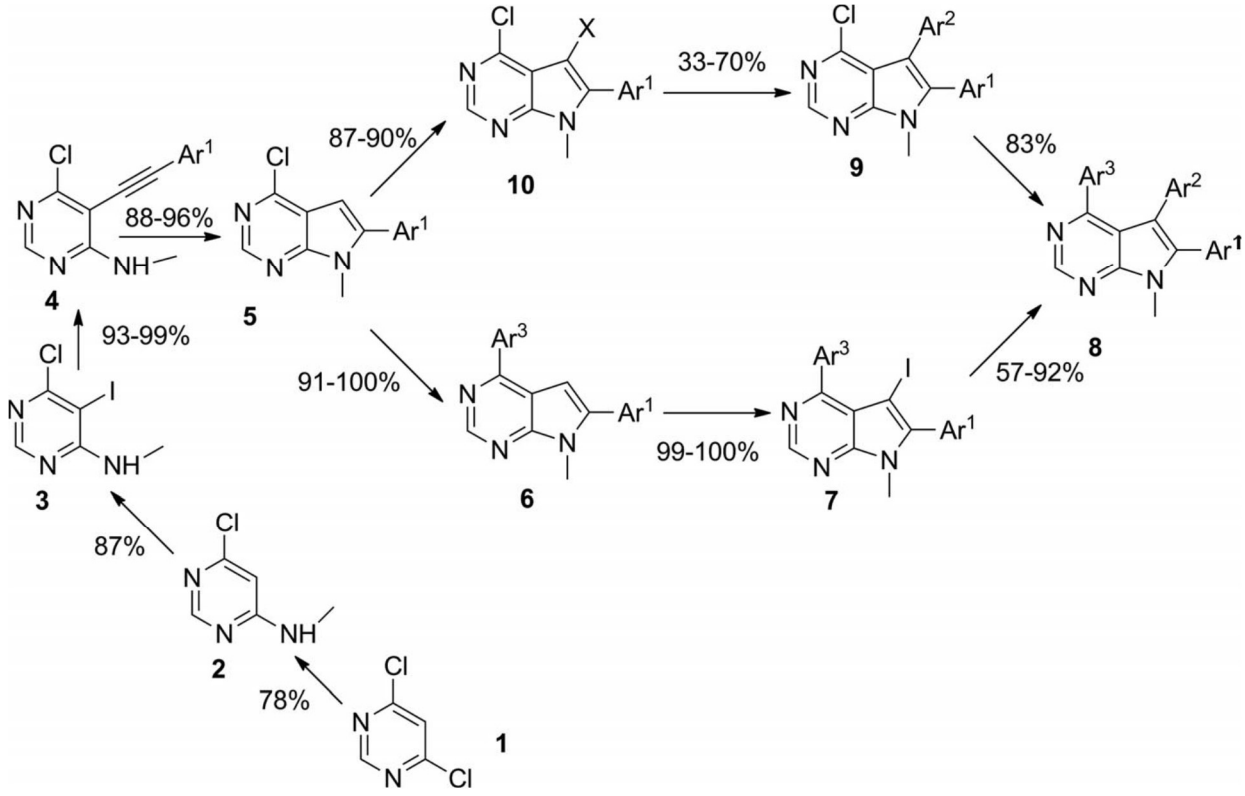
Scheme 4. Diarylation of pyrrolopyrimidines.

Figure 2. Molecular structure of 8k. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii.

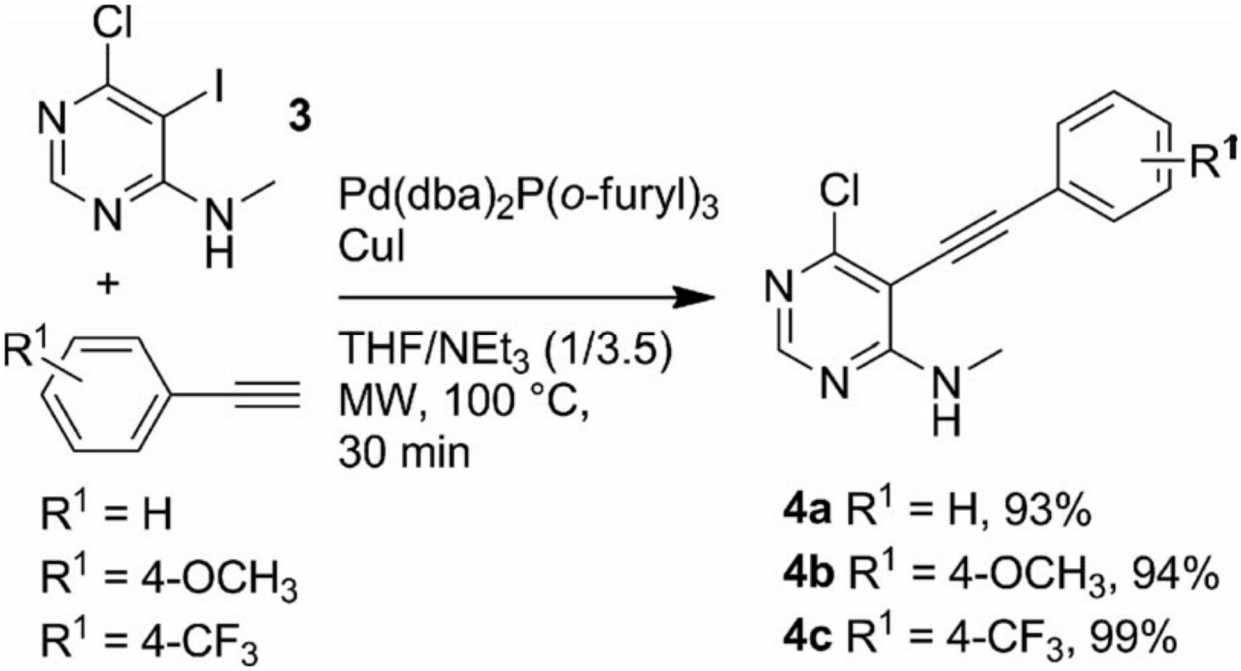
FIGURE 1


TWS119, GSK-3β inhibitor
Pyrrolo[2,3-d]pyrimidines
ACK1 inhibitors
2,6,8-Triarylpurines
Adenosine receptor antagonists
4,5,6-Triarylpyrrolo[2,3-d]
pyrimidines

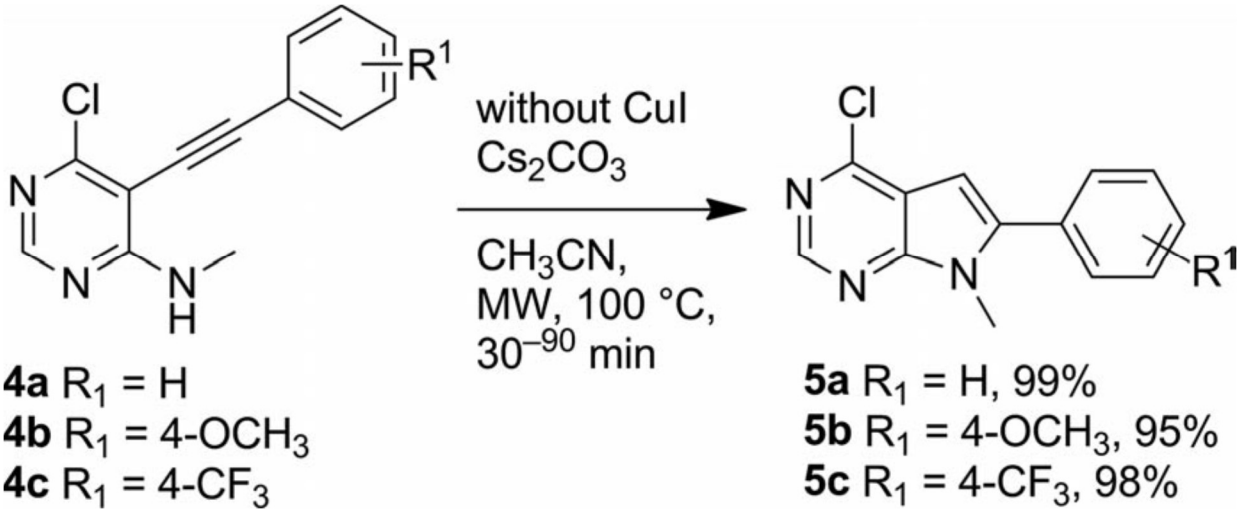
SCHEME 1


Cl
X
Ar1
N
N
10
33-70%
Cl
Ar2
Ar1
9
83%
Ar3
Ar2
Ar1
8
87-90%
Cl
Ar1
5
88-96%
Cl
Ar1
NH
4
93-99%
Cl
I
NH
3
91-100%
Ar3
Ar1
6
99-100%
Ar3
I
Ar1
7
57-92%
87%
Cl
NH
2
78%
Cl
Cl
1

SCHEME 2


Cl
I
N
N
N
H
3
+
R1
Pd(dba)2P(o-furyl)3
CuI
THF/NEt3 (1/3.5)
MW, 100 °C,
30 min
R1 = H
R1 = 4-OCH3
R1 = 4-CF3
Cl
N
N
N
H
R1
4a R1 = H, 93%
4b R1 = 4-OCH3, 94%
4c R1 = 4-CF3, 99%

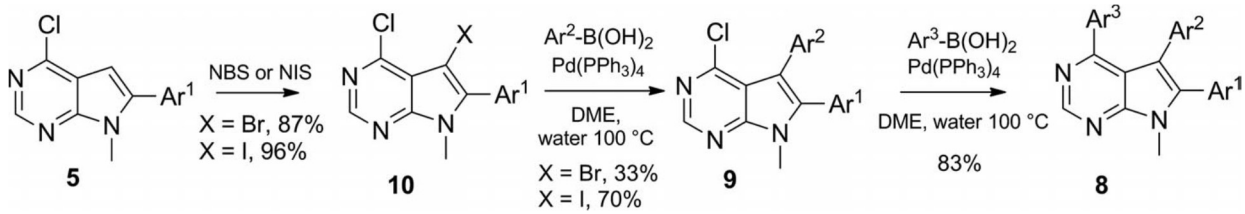
SCHEME 3


Cl
N
N
N
H
R1
without CuI
Cs2CO3
CH3CN,
MW, 100 °C,
30–90 min
Cl
N
N
N
R1
4a R1 = H
4b R1 = 4-OCH3
4c R1 = 4-CF3
5a R1 = H, 99%
5b R1 = 4-OCH3, 95%
5c R1 = 4-CF3, 98%

778 **SCHEME 4**

779

780



781

782

FIGURE 2

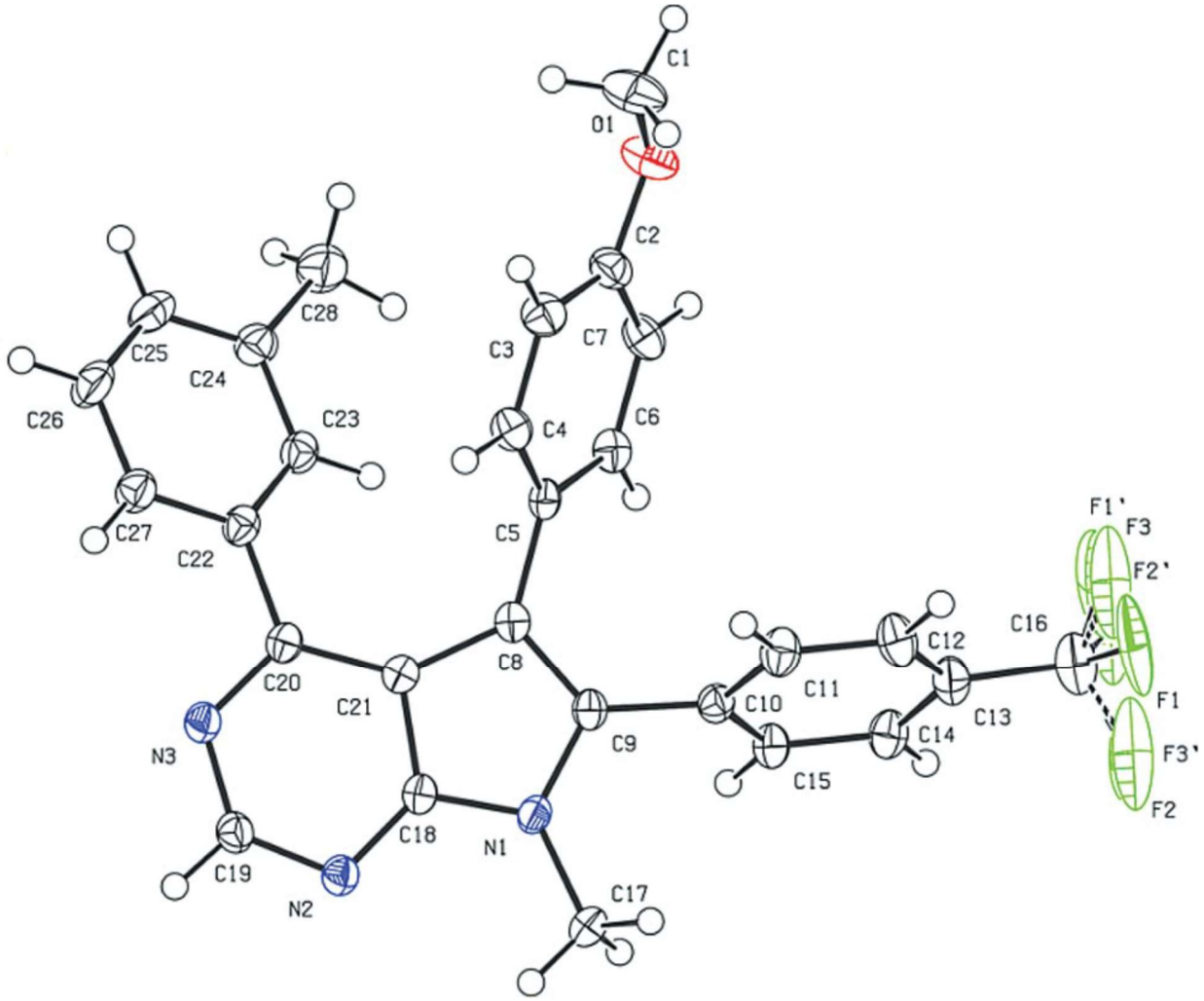
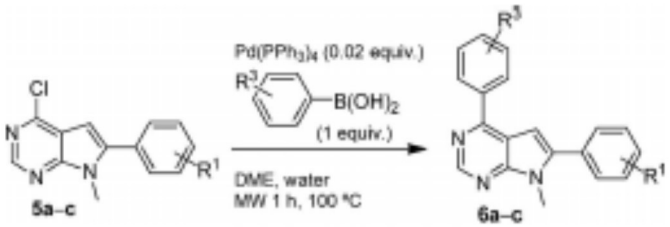
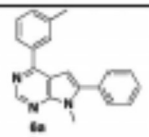
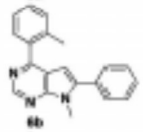
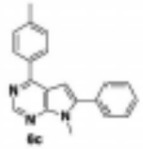
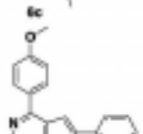
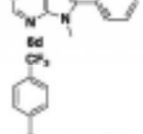
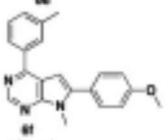
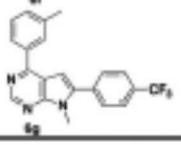

C1
O1
C2
C28
C25
C24
C3
C7
C26
C23
C4
C6
C27
C22
C5
F1'
F3
F2'
C16
C12
C20
C8
C11
F1
C21
C10
C13
N3
C9
C14
F3'
C15
F2
C18
N1
C19
N2
C17

Table 1. Suzuki–Miyaura cross-coupling reactions at the 4-position of heterocycle 5 leading to 4,6-disubstituted pyrrolopyrimidines 6.

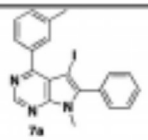
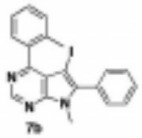
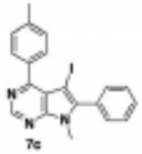
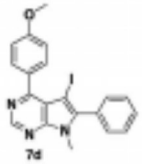
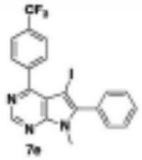
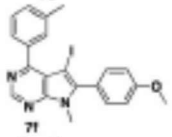
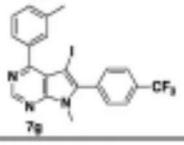


Entry	R^1	R^3	Product	Yield (%)[a]
1	H	3-Me		91
2	H	2-Me		99
3	H	4-Me		96
4	H	4-MeO		100
5	H	4-CF_3		98
6	4-MeO	3-Me		96
7	4-CF_3	3-Me		96

[a] Yield of isolated compound.

798 **Table 2.** Iodination of pyrrolopyrimidines 6.
799

6a–g 7a–g

Entry	R^1	R^3	Product	Yield (%)[a]
1	H	3-Me		100
2	H	2-Me		99
3	H	4-Me		100
4	H	4-MeO		100
5	H	CF_3		100
6	4-MeO	3-Me		100
7	4-CF_3	3-Me		100

[a] Yield of isolated compound.

800
801
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804

805 **Table 3.** Suzuki–Miyaura cross-coupling reaction at C-5 of pyrrolopyrimidines 7..
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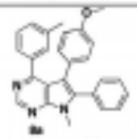
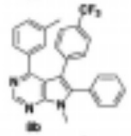
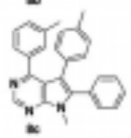
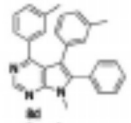
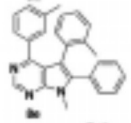
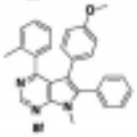
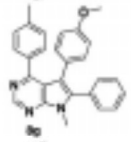
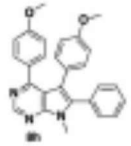
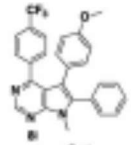
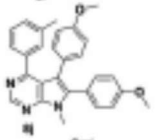
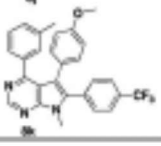
807

Entry	Compd.	R^1	R^2	R^3	Product	Yield[a]
1	7a	H	4-MeO	3-Me		88
2	-	H	4-CF_3	3-Me		67
3	-	H	4-Me	3-Me		71
4	-	H	3-Me	3-Me		76
5	-	H	2-Me	3-Me		traces
6	7b	H	4-MeO	2-Me		94
7	7c	H	4-MeO	4-Me		65
8	7d	H	4-MeO	4-MeO		92
9	7e	H	4-MeO	4-CF_3		74
10	7f	4-MeO	4-MeO	3-Me		57
11	7g	4-CF_3	4-MeO	3-Me		59

[a] Yield of isolated compound.