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Electrophilic alkylation of arenes with 5-bromopyrimidine en route to 4-aryl-5-alkynylpyrimidines†

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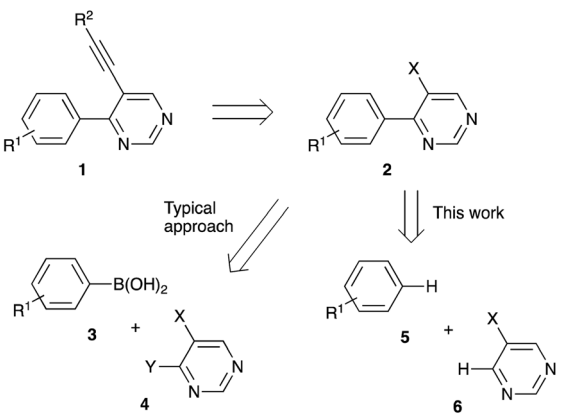
A new synthetic protocol for preparation of medicinally important 4-aryl-5-alkynylpyrimidines is described. The featured approach involves a sequence of chemo- and regioselective Brønsted acid-catalyzed electrophilic alkylation of arenes with 5-bromopyrimidine, followed by oxidative re-aromatization of the formed dihydropyrimidine ring. Finally, palladium-catalyzed Sonogashira cross-coupling reaction provided an end-game strategy.

Introduction

4-Arylpyrimidines **1** bearing acetylene substituents at C-5 (Scheme 1) were investigated as promising non-nucleoside-type adenosine kinase,[1,2] tyrosine kinase,[3,4] or lysine-specific demethylase[5] inhibitors. These molecules were also tested as potential anti-proliferative agents[6,7] or non-toxic selective herbicides,[8] or used as a synthetic platform for further derivatization en route to medicinally relevant structures.[9] Conveniently, structures of this type are accessible *via* Pd-catalyzed cross-coupling reaction involving terminal alkynes and hetaryl halides or sulfonates **2** (Scheme 1).[10,11] Alternatively, a decarboxylative cross-coupling of alkynyl halides with hetarylcarboxylic acids can be employed.[12] Although the synthetic route involving **2** as an electrophilic component in the Sonogashira reaction seems very straightforward, access to these starting materials typically relies on another transition metal-catalyzed cross-coupling step, usually chemoselective Suzuki reaction between arylboronic acid **3** and hetaryl dihalide **4** (Scheme 1).[13–18] Since this conventional approach lacks any atom-economy appeal, we wondered, if an alternative synthetic strategy could be designed, utilizing a formal oxidative functionalization of two C–H bonds in arene **5** and pyrimidine **6** (Scheme 1). In perspective, this would allow for an easier assembly of **2** from more affordable precursors, while generating less chemical waste. Herein we wish to report on our synthetic studies towards this goal.

Results and discussion

In recent years, our group was interested in designing novel acid-mediated multistep cascade transformations targeting material science and medicinal chemistry applications.[19–23] In particular, an unusual annulation reaction was demonstrated, involving perimidines **7** and pyrimidines **8** and leading to the formation of 1,3-diazapyrenes **9** (Scheme 2).[24] It was also shown that unlike most other pyrimidines, 5-bromopyrimidine **10** did not react according to this general scheme, forming monoalkylation products **11** instead (Scheme 2).[24,25] Apparently, this process is related to a Friedel–Crafts type S_EAr alkylation reaction, in which pyrimidine in protonated form serves as an



Scheme 1 Synthetic approaches towards 4-arylpyrimidines.

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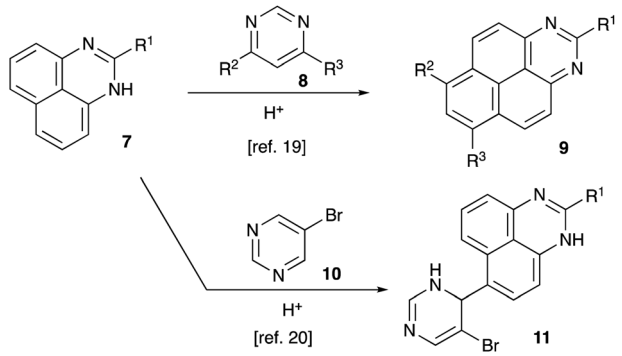
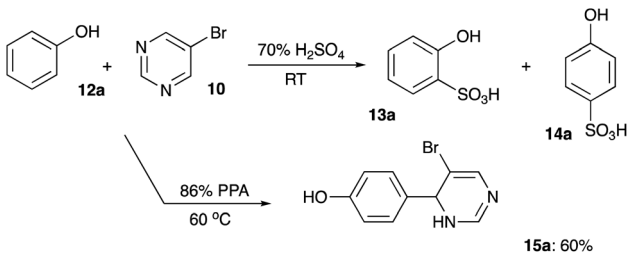


Scheme 2 Acid-assisted reactions of perimidines with pyrimidines.

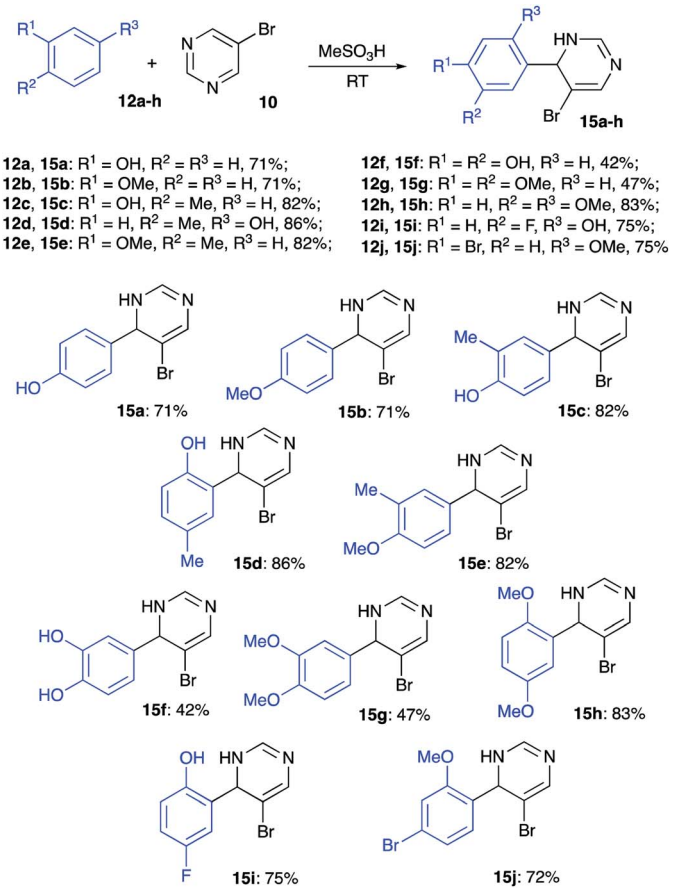


Scheme 3 Reactions of phenol **12a** with pyrimidine **15** in the presence of acids.

electrophile. We considered that an extension of the latter reaction to other nucleophilic arenes would help us to pursue our stated goal of installing an aryl substituent at C-4 of 5-bromopyrimidine ring.

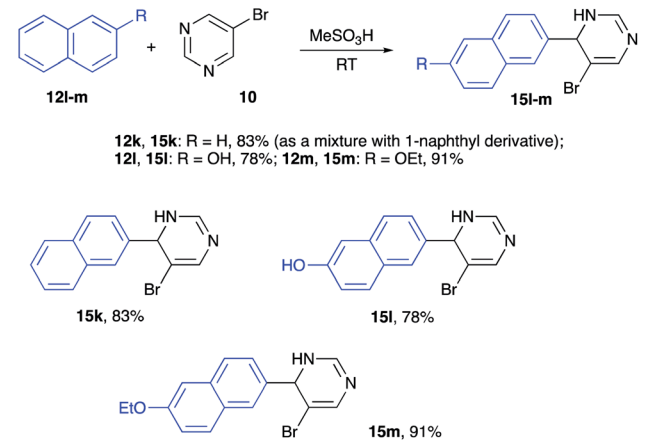
To test this idea, we carried out the reaction between phenol (**12a**) (as an example of electron rich nucleophilic arene) and 5-bromopyrimidine (**10**) in 70% aqueous sulfuric acid. Regrettably, this reaction led to the formation of a mixture of two sulfonic acids **13a** and **14a**, but the desired product **15a** did not form under these conditions (Scheme 3). Next, we tried to carry out the same transformation in 86% polyphosphoric acid (PPA). We were pleased to find that in this case **15a** was formed smoothly, and we managed to isolate it in 60% yield (Scheme 3). The same reaction carried out at room temperature in the presence of methanesulfonic acid afforded **15a** in 71% yield (Scheme 4).

Inspired by these results, we examined the reactivity of other electron rich arenes. To our delight, anisole (**12b**), *o*- and *p*-cresols (**12c** and **12d**, respectively), and *o*-methylanisole (**12e**) reacted smoothly providing the corresponding alkylated products **15b–e** in high yields (Scheme 4). Reactions of catechol (**12f**) and veratrole (**12g**) also proceeded smoothly, but isolation *via* extraction was accompanied with notable loss of products **15f** and **15g**, which proved to be quite water-soluble (Scheme 4). In contrast, reaction and isolation of 1,4-dimethoxybenzene (**12h**) proceeded uneventfully, leading to formation of **15h** in high yield (Scheme 4). Next, we tested the reactivity of halogenated phenol derivatives. Remarkably, both *p*-fluorophenol (**12i**) and *m*-bromoanisole (**12j**) afforded the corresponding coupling products **15i, j** very efficiently (Scheme 4).



Scheme 4 Alkylation of different electron-rich benzenes with 5-bromopyrimidine.

Reactions of naphthalenes with electrophilically activated 5-bromopyrimidine under the same conditions were also tested. Non-substituted naphthalene (**12k**) reacted very efficiently, but the regioselectivity was poor, and the 2 : 1 mixture of inseparable 2-naphthyl- (**15k**) and 1-naphthyl-regioisomeric products was isolated in 83% combined yield (Scheme 5). Alkylation of 2-



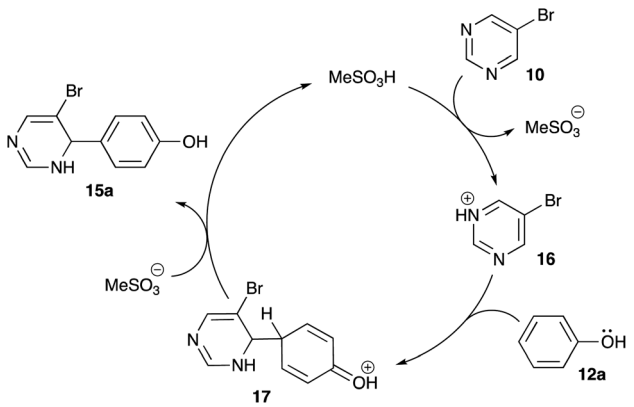
Scheme 5 Alkylation of different electron-rich naphthalenes with 5-bromopyrimidine.

naphthol (**12l**) and 2-ethoxynaphthalene (**12m**) proceeded regioselectively and the corresponding structures **15l** and **15m** were obtained as sole products isolated in high yields (Scheme 5).

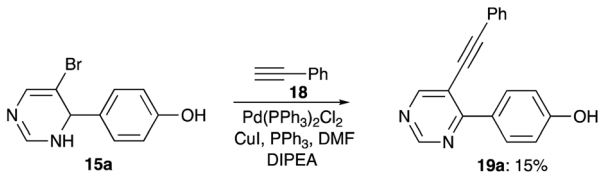
It is believed that this reaction proceeds *via* S_EAr mechanism. Indeed, protonation of one of the nitrogen atoms in pyrimidine **10** in the presence of strong Brønsted acid should afford highly electrophilic pyrimidinium species **16**, which could serve as an electrophile in Friedel–Crafts-like reaction involving electron-rich arenes (Scheme 6). To get an additional support to this mechanistic rationale we attempted to carry out this reaction employing electron deficient substrates: nitrobenzene, acetophenone, 2-hydroxyacetophenone, 2-acetonaphthone, 1-benzonaphthone, acetanilide, or 1,8-diaminonaphthalene (the latter upon protonation is converted in poorly nucleophilic ammonium form). Expectedly, the alkylation did not proceed with either of these substrates.

Next, we decided to investigate the possibility to use 5-bromo-3,4-dihydropyrimidin-4-yl arenes **15** in cross-coupling reaction with terminal alkynes. To this end, compound **15a** was treated with phenyl acetylene **18** under standard conditions for Sonogashira reaction. Unfortunately, reaction produced a complex mixture of products, among which we only were able to isolate minute amounts of pyrimidine **19a**, probably resulted from aerobic oxidation of the 3,4-dihydropyrimidine ring (Scheme 7).

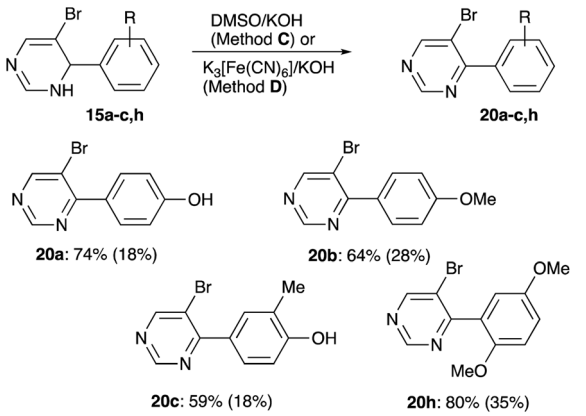
Since oxidation of dihydropyrimidine ring seemed to proceed spontaneously, it was decided to perform it first to achieve cleaner Sonogashira coupling at the next step. First, oxidation with DMSO was attempted (Method C), but this method was highly inefficient. Reaction of **19a** with DDQ also proceeded inefficiently, affording a mixture of three products,



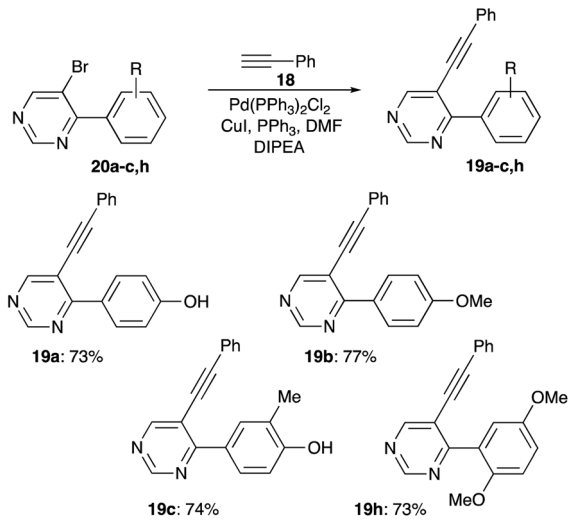
Scheme 6 Mechanism of electrophilic alkylation.



Scheme 7 Attempted Sonogashira coupling of dihydropyrimidine **15a**.



Scheme 8 Oxidative aromatization of dihydropyrimidines **15**. Yields for Method D and for Method C (in parentheses) are shown.



Scheme 9 Sonogashira cross-coupling reaction involving pyrimidines **20**.

none of which was identified as the desired product **20a**. However, we managed to obtain practical yields of aromatized products **20** in reactions with aqueous potassium ferricyanide (Method D, Scheme 8). Structure of compound **20a** was unambiguously confirmed by single crystal X-ray diffraction (CCDC #1983237).

Finally, acetylene substituent was installed into pyrimidine ring *via* Sonogashira coupling employing microwave irradiation. This allowed to obtain the target pyrimidylacetylenes **19** in good yields (Scheme 9).

Conclusion

In conclusion, a new synthetic protocol was developed, allowing for a facile assembly of 4-aryl-5-alkynylpyrimidines involving chemo- and regioselective acid catalyzed electrophilic alkylation of arenes with 5-bromopyrimidine, followed by oxidative aromatization of the formed dihydropyrimidine moieties, and subsequent Sonogashira cross-coupling reaction.

Experimental part

General information

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with a BBO probe in $CDCl_3$, DMSO-d_6, acetone-d_6 using TMS as an internal standard. High-resolution mass spectra were registered with a Bruker Maxis spectrometer (electrospray ionization, in MeCN solution, using HCO_2Na–HCO_2H for calibration). Melting points were measured with a Stuart smp30 apparatus. All reactions were performed in oven-dried 5 mL round-bottomed flasks equipped with reflux condensers. The reaction progress and purity of isolated compounds were controlled by TLC on Silufol UV-254 plates, with EtOAc as eluent. Polyphosphoric acids (86%) were obtained by dissolving of precise amount of P_2O_5 in 85% orthophosphoric acid according to the published protocols.[26,27] All reagents and solvents were purchased from commercial vendors and used as received.

Preparation of (5-bromo-3,4-dihydropyrimidin-4-yl)-benzenes (general procedure)

Method A (in methanesulfonic acid). A 10 mL round-bottomed flask equipped with magnetic stirring bar was charged with the corresponding substituted arene **4** (1.00 mmol), methanesulfonic acid (5 mL), and 5-bromopyridine 158 mg (1.00 mmol). The mixture was stirred at room temperature for 30 min (1 h for naphthalenes), then poured into cold water (50 mL), and aqueous ammonia was added dropwise to achieve a neutral reaction (pH 7–8). The formed precipitate was filtered, rinsed with small portions of cold water, and dried on air. This material was sufficiently pure for most application and did not require any additional purification.

Method A (in polyphosphoric acid). A 10 mL round-bottomed flask equipped with magnetic spin-bar was charged with the corresponding substituted arene **4** (1.00 mmol), 86% polyphosphoric acid (5 g), and 5-bromopyridine 158 mg (1.00 mmol). The mixture was stirred at 60 °C for 1 h. The subsequent quench, aqueous work up and isolation was identical to the one described for Method A. The formed precipitate was filtered, rinsed with small portions of cold water, and dried on air. This material was sufficiently pure for most application and did not require any additional purification.

4-(5-Bromo-3,4-dihydropyrimidin-4-yl)phenol (15a). Colorless solid, mp 183–185 °C. Yield 179 mg (0.71 mmol, 71% *via* Method A); 151 mg (0.60 mmol, 60% *via* Method B). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.22 (d, J = 8.5 Hz, 2H, 2,6H), 7.12 (s, 1H, 2H, 4-pyr), 6.82 (d, J = 8.5 Hz, 2H, 3,5H), 6.64 (s, 1H, 6H, 4-pyr), 5.20 (s, 1H, 4H, 4-pyr). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.1, 143.1, 134.6, 128.4 (2C), 124.9, 115.0 (2C), 106.5, 59.4. FT IR (ZnSe, cm^{-1}): 3244, 1601, 1575, 1241, 841, 650. HRMS (TOF-ES): calculated for $C_{10}H_{10}BrN_2O$ $(M + H)^+$ 252.9971, found 252.9968.

5-Bromo-6-(4-methoxyphenyl)-1,6-dihydropyrimidine (15b). Colorless solid, mp 125–127 °C. Yield 189 mg (0.71 mmol, 71% *via* Method A). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.31 (d, J = 8.7 Hz, 2H, 3,5H 4-methoxyphenyl), 7.13 (s, 1H, 2H), 6.92 (d, J = 8.7 Hz, 2H, 2,6H 4-methoxyphenyl), 6.64 (s, 1H, 4H), 5.23 (s, 1H, 6H), 3.79 (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 145.6, 133.1, 129.1 (2C), 126.5, 114.5 (2C), 105.6, 60.4, 55.5. FT IR (ZnSe, cm^{-1}): 2950, 1601, 1505, 1254, 1177, 1046, 761, 632. HRMS (TOF-ES): calculated for $C_{11}H_{12}BrN_2O$ $(M + H)^+$ 267.0127, found 267.0130.

4-(5-Bromo-3,4-dihydropyrimidin-4-yl)-2-methylphenol (15c). Colorless solid, mp 155–157 °C. Yield 218 mg (0.82 mmol, 82% *via* Method A). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.04 (s, 1H, 2H 4-pyr), 7.00 (s, 1H, 3H), 6.94 (d, J = 8.1 Hz, 1H, 5H), 6.74 (d, J = 8.1 Hz, 1H, 6H), 6.59 (s, 1H, 6H 4-pyr), 5.05 (s, 1H, 4H 4-pyr), 2.11 (s, 3H, –Me). ^{13}C NMR (101 MHz, DMSO) δ 155.2, 144.1, 134.4, 129.6, 127.4, 125.7, 123.7, 116.8, 114.4, 60.8, 16.1. FT IR (ZnSe, cm^{-1}): 3422, 1623, 1575, 1450, 1379, 1278, 1250, 830, 625. HRMS (TOF-ES): calculated for $C_{11}H_{12}BrN_2O$ $(M + H)^+$ 267.0127, found 267.0129.

2-(5-Bromo-3,4-dihydropyrimidin-4-yl)-4-methylphenol (15d). Colorless solid, mp 175–180 °C. Yield 229 mg (0.86 mmol, 86% *via* Method A); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.16–7.10 (m, 2H, 3H, 2H 2-pyr), 6.94 (d, J = 8.0 Hz, 1H, 6H), 6.79–6.71 (m, 2H, 5H, 6H 2-pyr), 5.68 (s, 1H, 4H 2-pyr), 2.24 (s, 3H, –Me). ^{13}C NMR (101 MHz, acetone-d_6) δ 153.4, 145.2, 132.4, 130.0, 129.5, 129.3 (2C), 116.5, 102.1, 57.1, 20.6. FT IR (ZnSe, cm^{-1}): 3310, 2500, 1873, 1745, 1590, 1267, 801. HRMS (TOF-ES): calculated for $C_{11}H_{12}BrN_2O$ $(M + H)^+$ 267.0127, found 267.0126.

5-Bromo-6-(4-methoxy-3-methylphenyl)-1,6-dihydropyrimidine (15e). Light-brown oil. Yield 230 mg (0.82 mmol, 82%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.56 (s, 1H, 2H), 7.24–7.19 (m, 2H, 2H, 5H 6-(4-methoxy-3-methylphenyl)), 6.92 (d, J = 8.9 Hz, 1H, 6H 6-(4-methoxy-3-methylphenyl)), 6.74 (s, 1H, 4H), 5.31 (s, 1H, 6H), 3.84 (s, 3H, –OMe), 2.18 (s, 3H, 2-Me). ^{13}C NMR (101 MHz, acetone-d_6) δ 158.8, 145.9, 135.1, 130.6, 128.7, 127.3, 127.2, 110.7, 104.8, 61.6, 55.7, 16.4. FT IR (ZnSe, cm^{-1}): 2918, 1503, 1391, 1250, 1132, 1032, 776. HRMS (TOF-ES): calculated for $C_{12}H_{14}BrN_2O$ $(M + H)^+$ 281.0283, found 281.0280.

4-(5-Bromo-3,4-dihydropyrimidin-4-yl)benzene-1,2-diol (15f). Light-grey solid, mp 175–177 °C. Yield 113 mg (0.42 mmol, 42%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.23 (s, 1H, 2H 4-pyr), 6.98 (s, 1H, 3H), 6.76 (d, J = 8.0 Hz, 1H, 6H), 6.67 (m, 2H, 5H, 6H 4-pyr), 5.18 (s, 1H, 4H 4-pyr). ^{13}C NMR (101 MHz, acetone-d_6) δ 146.8, 146.5, 145.7, 136.1, 132.1, 119.5, 115.4, 115.0, 105.7, 61.9; FT IR (ZnSe, cm^{-1}): 3247, 2930, 1607, 1510, 1261, 1119, 827, 646. HRMS (TOF-ES): calculated for $C_{10}H_{10}BrN_2O_2$ $(M + H)^+$ 268.9920, found 268.9924.

5-Bromo-6-(3,4-dimethoxyphenyl)-1,6-dihydropyrimidine (15g). Colorless solid, mp 94–96 °C. Yield 139 mg (0.47 mmol, 47%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.16 (brs, 1H, 2H 6-(3,4-dimethoxyphenyl)), 7.00 (s, 1H, 2H), 6.93 (m, 2H, 5H, 6H 6-(3,4-dimethoxyphenyl)), 6.66 (s, 1H, 4H), 5.24 (s, 1H, 6H), 3.80 (s, 6H, OMe). ^{13}C NMR (101 MHz, acetone-d_6) δ 150.4, 150.2, 144.5, 137.4, 131.3, 120.6, 112.5, 112.3, 103.6, 62.8, 56.2, 56.1. FT IR (ZnSe, cm^{-1}): 2350, 1695, 1532, 1253, 1125, 1033, 763. HRMS (TOF-ES): calculated for $C_{12}H_{14}BrN_2O_2$ $(M + H)^+$ 297.0233, found 297.0235.

5-Bromo-6-(2,5-dimethoxyphenyl)-1,6-dihydropyrimidine (15h). Colorless solid, mp 115–117 °C. Yield 246 mg (0.83 mmol,

83%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.06 (s, 1H, 2H), 6.98 (s, 1H, 6H 6-(2,5-dimethoxyphenyl)), 6.94 (d, J = 8.9 Hz, 1H, 3H 6-(2,5-dimethoxyphenyl)), 6.85 (d, J = 8.9 Hz, 1H, 4H 6-(2,5-dimethoxyphenyl)), 6.74 (s, 1H, 4H), 5.70 (s, 1H, 6H), 3.79 (s, 3H, OMe), 3.74 (s, 3H, OMe). ^{13}C NMR (101 MHz, acetone-d_6) δ 150.4, 150.2, 144.5, 137.4, 131.3, 120.6, 112.5, 112.3, 103.6, 62.8, 56.2, 56.1. FT IR (ZnSe, cm^{-1}): 2350, 1695, 1532, 1253, 1125, 1033, 763. HRMS (TOF-ES): calculated for $C_{12}H_{14}BrN_2O_2$ $(M + H)^+$ 297.0233, found 297.0233.

2-(5-Bromo-3,4-dihydropyrimidin-4-yl)-4-fluorophenol (15i). Light-yellow solid, mp 173–175 °C. Yield 203 mg (0.75 mmol, 75%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.20 (s, 1H, 2H 2-pyr), 7.04 (dd, J = 9.3, 3.0 Hz, 1H, 5H), 6.94–6.76 (m, 3H, 6H 2-pyr, 3H, 6H), 5.71 (s, 1H, 4H 2-pyr). ^{13}C NMR (101 MHz, acetone-d_6) δ 157.4 (d, J = 234.5 Hz), 151.9, 145.1, 131.7 (d), 131.2, 117.7 (d), 115.8 (d), 115.2 (d), 99.4, 57.3. FT IR (ZnSe, cm^{-1}): 3287, 2400, 1635, 1576, 1447, 1356, 1254, 1179, 1024, 731. HRMS (TOF-ES): calculated for $C_{10}H_9BrFN_2O$ $(M + H)^+$ 270.9877, found 270.9879.

5-Bromo-6-(4-bromo-2-methoxyphenyl)-1,6-dihydropyrimidine (15j). Colorless crystalline solid, mp 69–72 °C, Yield 248 mg (0.72 mmol, 72%). ^{1}H NMR (400 MHz, acetone-d_6) 7.48 (d, J = 8.6 Hz, 1H, 4H), 7.16–7.11 (m, 2H, 2H 4-pyr, 6H), 7.03 (dd, J = 8.6, 2.6 Hz, 1H, 3H), 6.74 (s, 1H 6H 2-pyr), 5.74 (s, 1H, 4H 2-pyr), 3.83 (s, 3H, –OMe). ^{13}C NMR (101 MHz, acetone) δ 160.7, 144.1, 135.4, 131.8 (2C), 123.4, 118.3, 115.4, 101.3, 61.8, 56.0. FT IR (ZnSe, cm^{-1}): 2820, 1589, 1485, 1225, 1029, 852. HRMS (TOF-ES): calculated for $C_{11}H_{11}Br_2N_2O$ $(M + H)^+$ 344.9233, found 344.9231.

5-Bromo-6-(naphthalene-1-yl)-1,6-dihydropyrimidine and 5-bromo-6-(naphthalene-2-yl)-1,6-dihydropyrimidine (15k). Pale-yellow solid, mp 110–115 °C. Yield 237 mg (0.83 mmol, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 7.9 Hz, 1H), 8.02–7.76 (m, 4H), 7.54 (d, J = 7.5 Hz, 5.5H), 7.18 (s, 0.5H), 7.06 (s, 1H), 6.83 (s, 1H), 6.71 (s, 0.5H), 6.07 (s, 1H), 5.41 (s, 0.5H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.5, 143.9, 141.5, 138.7, 134.1, 133.2, 133.1, 131.1, 129.0, 128.9, 128.6, 128.4, 128.0, 126.8, 126.7 (2C), 126.6, 126.3, 126.2 (2C), 126.1, 126.0, 124.4, 101.5, 99.7, 62.6, 59.6, 40.6. FT IR (ZnSe, cm^{-1}): 1631, 1510, 1352, 1257, 1010, 771, 646. HRMS (TOF-ES): calculated for $C_{14}H_{12}BrN_2$ $(M + H)^+$ 287.0178, found 287.0181.

6-(5-Bromo-3,4-dihydropyrimidin-4-yl)naphthalen-2-ol (15l). Pale-yellow solid, mp 150–152 °C. Yield 237 mg (0.78 mmol, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 8.7 Hz, 1H, 4H), 7.70 (d, J = 8.5 Hz, 1H,8H), 7.64 (s, 1H, 5H), 7.41 (d, J = 8.5 Hz, 1H, 7H), 7.18–7.05 (m, 3H, 1H, 3H, 2H 6-pyr), 6.68 (s, 1H, 6H 6-pyr), 5.31 (s, 1H, 4H 6-pyr). ^{13}C NMR (101 MHz, acetone-d_6) δ 156.5, 144.7, 139.1, 135.7, 131.3, 130.5, 128.9, 127.6, 126.8 (2C), 119.5, 109.7, 103,4, 63.4. FT IR (ZnSe, cm^{-1}): 3150, 2354, 1610, 1350, 1247, 1150, 1010, 854, 673. HRMS (TOF-ES): calculated for $C_{14}H_{12}BrN_2O$ $(M + H)^+$ 303.0128, found 303.0124.

5-Bromo-6-(6-ethoxynaphthalen-2-yl)-1,6-dihydropyrimidine (15m). Light-grey solid, mp 123–125 °C. Yield 303 mg (0.914 mmol, 91%). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.82 (d, J = 9.4 Hz, 2H, 4H, 8H), 7.76 (s, 1H, 5H), 7.56 (d, J = 9.4 Hz, 1H, 7H), 7.29 (s, 2H, 1H, 2H 6-pyr), 7.16 (d, J = 8.9 Hz, 1H, 3H), 6.73 (s, 1H, 4H 6-pyr), 5.46 (s, 1H, 6H 6-pyr), 4.17 (q, J = 7.0 Hz, 2H, –Et), 1.43 (t, J = 7.0 Hz, 3H, –Et). ^{13}C NMR (101 MHz, acetone-d_6) δ 158.9, 144.9, 139.4, 135.5, 130.6, 130.4, 129.4, 128.2, 126.9 (2C), 120.1, 107.3, 103.4, 64.1, 63.3, 15.1. FT IR (ZnSe, cm^{-1}): 2350, 1610, 1503, 1360, 1261, 1147, 1037, 803, 632. HRMS (TOF-ES): calculated for $C_{16}H_{16}BrN_2O$ $(M + H)^+$ 331.0441, found 331.0445.

Preparation of (5-bromo-3,4-pyrimidin-4-yl)-benzenes (general procedure)

Method C. A 10 mL round bottomed flask equipped with magnetic stirring bar was charged with DMSO (5 mL), potassium hydroxyde (112 mg, 2.00 mmol), and the corresponding (5-bromo-3,4-dihydropyrimidine-4-yl)benzene (1.00 mmol). The mixture was stirred for 4 h at 60 °C, then poured into cold water (10 mL). Formed precipitate is collected, washed on a filter with small portions of water and dried on air. Thus obtained crude material was purified by column chromatography eluting with a mixture of petroleum ether and ethyl acetate (1 : 1).

Method D. 10 mL round bottomed flask equipped with magnetic stirring bar was charged with water (5 mL), potassium ferricyanide (658 mg, 2.00 mmol), and potassium hydroxyde (224 mg, 4.00 mmol). (5-Bromo-3,4-dihydropyrimidine-4-yl) benzene (1.00 mmol) was added to the formed solution, and the mixture was stirred at room temperature for 2 h. Aqueous work up, isolation and purification of the product was performed in the same way as described for Method C.

4-(5-Bromopyrimidin-4-yl)phenol (20a). Colorless solid, mp 120–121 °C. Rf 0.20 (EtOAc/hexanes, 1 : 1). Yield 44 mg (0.18 mmol, 18% *via* Method C); 138 mg (0.55 mmol, 55% *via* Method D). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H, –OH), 9.13 (s, 1H, 2H 4-pyr), 9.02 (s, 1H, 6H 4-pyr), 7.73 (d, J = 8.6 Hz, 2H, 3,5H), 6.90 (d, J = 8.7 Hz, 2H, 2,6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.9, 160.1, 159.6, 156.8, 131.2 (2C), 127.1, 118.1, 115.0 (2C). FT IR (ZnSe, cm^{-1}): 2923, 1701, 1558, 1436, 1390, 1150, 1028, 822. HRMS (TOF-ES): calculated for $C_{10}H_8BrN_2O$ $(M + H)^+$ 250.9815, found 250.9816.

5-Bromo-4-(4-methoxyphenyl)pyrimidine[28] (20b). Colorless solid, mp 99–101 °C. Rf 0.26 (EtOAc/hexanes, 1 : 1). Yield 73 mg (0.28 mmol, 28% *via* Method C); 169 mg (0.64 mmol, 64% *via* Method D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H, 2H), 8.87 (s, 1H, 6H), 7.87 (d, J = 8.8 Hz, 2H, 2,6H 4-(4-methoxyphenyl)), 7.01 (d, J = 8.8 Hz, 2H, 3,5H 4-(4-methoxyphenyl)), 3.88 (s, 3H, OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 161.5, 160.3, 156.9, 131.3 (2C), 129.1, 118.8, 113.8 (2C), 55.6. FT IR (ZnSe, cm^{-1}): 2955, 2325, 1895, 1726, 1607, 1554, 1431, 1259, 1154, 1023, 825, 776. HRMS (TOF-ES): calculated for $C_{11}H_{10}BrN_2O$ $(M + H)^+$ 264.9971, found 264.9974

4-(5-Bromopyrimidin-4-yl)-2-methylphenol (20c). Colorless solid, mp 160–165 °C. Rf 0.22 (EtOAc/hexanes, 1 : 1). Yield 46 mg (0.18 mmol, 18% *via* Method C); 155 mg (0.59 mmol, 59% *via* Method D). ^{1}H NMR (400 MHz, acetone-d_6) δ 9.07 (s, 1H, 2H 4-pyr), 8.92 (s, 1H, 6H 4-pyr), 8.88 (s, 1H, –OH), 7.70 (s, 1H, 5H), 7.65 (d, J = 8.3 Hz, 1H, 3H), 6.96 (d, J = 8.3 Hz, 1H, 2H), 2.28 (s, 3H, –Me). ^{13}C NMR (101 MHz, acetone-d_6) δ 164.3, 160.9, 158.4, 157.6, 133.2, 129.6, 128.9, 119.1, 115.0, 16.2. FT IR (ZnSe, cm^{-1}): 3049, 2358, 2217, 1565, 1485, 1401, 1279, 1116, 917, 788. HRMS (TOF-ES): calculated for $C_{11}H_{10}BrN_2O$ $(M + H)^+$ 264.9971, found 264.9968.

5-Bromo-4-(2,5-dimethoxyphenyl)pyrimidine (20h). Light-brown oil. Rf 0.25 (EtOAc/hexanes, 1 : 1). Yield 102 mg (0.35 mmol, 35% *via* Method C); 236 mg (0.80 mmol, 80% *via* Method D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H, 2H), 8.89 (s, 1H, 6H), 7.01 (d, J = 9.0 Hz, 1H, 3H 4-(2,5-dimethoxyphenyl)), 6.94 (d, J = 9.0 Hz, 1H, 4H 4-(2,5-dimethoxyphenyl)), 6.86 (s, 1H, 6H 4-(2,5-dimethoxyphenyl)), 3.80 (s, 3H, 2-MeO–), 3.78 (s, 3H, 5-MeO–). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 164.8, 158.7, 156.3, 153.7, 150.8, 126.9, 117.1, 115.1 (2C), 112.6, 56.2, 56.0. FT IR (ZnSe, cm^{-1}): 2947, 2322, 1723, 1554, 1506, 1435, 1221, 1019, 810. HRMS (TOF-ES): calculated for $C_{12}H_{14}BrN_2O_2$ (M + H)$^+$ 297.0233, found 297.0237.

Preparation of 4-(5-(phenylethynyl)pyrimidin-4-yl)benzenes *via* Sonogashira coupling (general procedure)

Pyrex microwave vessel was charged with phenylacetylene (102 mg, 1.00 mmol) and the corresponding substituted 4-(5-bromopyrimidin-4-yl)-2-benzene (1.00 mmol) in dry DMF (0.5 mL). Dry nitrogen was passed to the vessel for 50 min, then anhydrous DIPEA (1.5 mL, 1.11 g, 8.6 mmol), dry triphenylphosphine (23 mg, 0.087 mmol) were introduced, followed by bis(triphenylphosphine)palladium chloride ($Pd(PPh_3)Cl_2$, 15 mg, 0.021 mmol) and copper(I) iodide (CuI, 3.8 mg, 0.020 mmol). The vessel was sealed and microwaved at 115 °C for 25 min. Then the mixture was cooled down and extracted with ethyl acetate (2 × 50 mL). Combined organic extracts were consecutively washed with aqueous ammonium chloride solution (2 × 25 mL) and water (2 × 25 mL), and dried with sodium sulfate. Pure product was crystallized from concentrated solution obtained after evaporation of most solvent.

4-(5-(Phenylethynyl)pyrimidin-4-yl)phenol (19a). Pale-yellow solid, mp 194–195 °C. Rf 0.38 (EtOAc/hexanes, 1 : 1). Yield 199 mg (0.73 mmol, 73%). ^{1}H NMR (400 MHz, acetone-d_6) δ 9.09 (s, 1H, 2H 4-pyr), 8.92 (s, 1H, 6H 4-pyr), 8.27 (d, J = 8.8 Hz, 2H, 2,6H), 7.63–7.53 (m, 2H, 2,6H 4-(5-(phenylethynyl)pyr)), 7.46 (m, 3H, 3-5H 4-(5-(phenylethynyl)pyr)), 7.04 (d, J = 8.8 Hz, 2H, 3,5H). ^{13}C NMR (101 MHz, acetone-d_6) δ 164.7, 161.9, 161.0, 157.6, 132.3 (2C), 132.1 (2C), 130.2, 129.6 (2C), 129.1, 123.2, 116.1 (2C), 115.7, 97.9, 85.7. FT IR (ZnSe, cm^{-1}): 3057, 2362, 2217, 1565, 1504, 1432, 1287, 1165, 845. HRMS (TOF-ES): calculated for $C_{18}H_{13}N_2O$ (M + H)$^+$ 273.1022, found 273.1025.

4-(4-Methoxyphenyl)-5-(phenylethynyl)pyrimidine (19b). Light brown solid, mp 80–83 °C. Rf 0.47 (EtOAc/hexanes, 1 : 1). Yield 220 mg (0.77 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H, 2H), 8.89 (s, 1H, 6H), 8.31 (d, J = 8.8 Hz, 2H, 3,5H 4-(4-methoxyphenyl)), 7.53–7.49 (m, 2H, 2,6H 5-(phenylethynyl)), 7.41–7.36 (m, 3H, 3-5H 5-(phenylethynyl)), 7.05 (d, J = 8.9 Hz, 2H, 2,6H 4-(4-methoxyphenyl)), 3.90 (s, 3H 4-MeO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 162.5, 159.7, 155.2, 131.7 (2C), 131.5 (2C), 129.5, 128.8, 128.7 (2C), 122.1, 115.8, 114.0 (2C), 98.5, 84.3, 55.6. FT IR (ZnSe, cm^{-1}): 2929, 2221, 1726, 1607, 1509, 1435, 1259, 1173, 1027, 783. HRMS (TOF-ES): calculated for $C_{19}H_{15}N_2O$ (M + H)$^+$ 287.1179, found 287.1180.

2-Methyl-4-(5-(phenylethynyl)pyrimidin-4-yl)phenol (19c). Light-brown solid, mp 168–170 °C. Rf 0.43 (EtOAc/hexanes, 1 : 1). Yield 210 mg (0.74 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H, 2H 4-pyr), 8.87 (s, 1H, 6H 4-pyr)), 8.12 (s, 1H, 5H), 8.07 (d, J = 8.4 Hz, 1H, 3H), 7.55–7.45 (m, 2H, 2,6H 4-(5-(phenylethynyl)pyr)), 7.41–7.35 (m, 3H, 3-5H 4-(5-(phenylethynyl)pyr), 6.94 (d, J = 8.4 Hz, 1H, 6H), 2.34 (s, 3H, –Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 160.6, 157.2, 156.1, 132.6, 131.7 (2C), 129.4, 129.0, 128.7 (2C), 124.3, 122.4 (2C), 115.8, 114.9, 98.0, 84.7, 16.2. FT IR (ZnSe, cm^{-1}): 3049, 2358, 2217, 1565, 1485, 1401, 1279, 1116, 917, 788. HRMS (TOF-ES): calculated for $C_{19}H_{15}N_2O$ (M + H)$^+$ 287.1179, found 287.1175.

4-(2,5-Dimethoxyphenyl)-5-(phenylethynyl)pyrimidine (19h). Light-brown oil. Rf 0.36 (EtOAc/hexanes, 1 : 1). Yield 220 mg (0.73 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H, 2H), 8.90 (s, 1H, 6H), 7.34–7.29 (m, 5H), 7.08–7.01 (m, 2H, 3,6H 4-(2,5-dimethoxyphenyl)), 6.97 (d, J = 8.6 Hz, 1H, 4H 4-(2,5-dimethoxyphenyl)), 3.82 (s, 3H, 2-MeO), 3.78 (s, 3H 4-MeO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 158.2, 154.1, 153.6, 151.7, 131.8 (2C), 129.6, 128.7 (2C), 125.6, 122.0, 120.3, 118.4, 115.6, 112.7, 98.8, 83.1, 56.3, 56.1. FT IR (ZnSe, cm^{-1}): 2943, 2831, 2217, 1726, 1498, 1431, 1397, 1274, 1221, 1034, 810. HRMS (TOF-ES): calculated for $C_{20}H_{17}N_2$ (M + H)$^+$ 317.1285, found 317.1286.

Conflicts of interest

There are no conflicts to declare.

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