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C-Functionalization of 9-deazapurines by cross-coupling reactions

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Abstract—C-Functionalization of pyrrolo[3,2-*d*]pyrimidine scaffold in positions 2, 4, and 7 using cross-coupling reactions was performed. Thus, 2-(5-(benzyloxymethyl)-2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)ethanol, a versatile synthetic precursor for 9-deazapurines and 4,6-diazaindoles, was prepared by vinylation of the corresponding iodide followed by hydroboration of the double bond. A synthesis of 9-(1,2-dihydroxyethyl)-9-deazaadenine, a 9-deaza-1′-nor congener to antiviral DHPA, was developed. In addition, an abnormal regioselectivity in methylalumination of the terminal triple bond in position 7 of the pyrrolo[3,2-*d*]pyrimidine scaffold leading to a transformation into (*Z*)-prop-1-enyl was observed.

1. Introduction

In recent years, *C*-substituted purines have become an intensively investigated group of compounds, resulting in some promising findings of biological activity.[1–9] The usual synthetic approach employing cross-coupling reactions allowed routine introduction of *C*-substituents into positions 6, 2, and 8. On the other hand, on 9-deazapurines (pyrrolo-[3,2-*d*]pyrimidines), cross-coupling reactions were used rarely. Only a few examples of Suzuki reaction in position 4 and Sonogashira coupling in position 7 were recently described.[10,11] However, applying the cross-coupling based methodology to pyrrolo[3,2-*d*]pyrimidine scaffold is of high interest, as many 7-*C*-substituted pyrrolo[3,2-d]pyrimidines are potent inhibitors of purine nucleoside phosphorylase (PNP) or exhibit other biological activities.[12–15] Moreover, it could open the route to a construction of 9-deaza congeners of some biologically active 9-substituted purines and 4,6-diaza congeners of 3-substituted indole containing biomolecules. For the preparation of 7-*C*-substituted pyrrolo-[3,2-*d*]pyrimidines, the traditional approach introduced by Klein and co-workers based on pyrimidine ring construction on suitably substituted pyrroles is used predominantly.[16] There are also some more recent methods—reductive cyclization of 6-cyanomethyl-5-nitropyrimidines,[15,17] addition of an electrophile to a carbanion[18] generated by metalation in position 7, modified Fisher indole synthesis[19] as well as Friedel–Crafts reaction in hot trifluoromethanesulfonic acid.[20] However, the approaches are either based on multiple syntheses or are limited only to a very narrow category of compatible substituents. Therefore, our aim is to assess the possibilities of routine C-functionalization of pyrrolo[3,2-*d*]-pyrimidines by cross-coupling reactions. Our special interest lies in an effective introduction of a 2-hydroxyethyl group into position 7, which could enable the construction of 9-deaza congeners of acyclic nucleoside phosphonates of PME type.[21]

2. Results and discussion

2,4-Dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine[22,23] (2,6-dichloro-9-deazapurine, **1**), easily available from 6-methyluracil, is an ideal synthetic precursor for the C-functionalization reaction (Scheme 1). On reaction with 1 equiv of phenylboronic acid at 100 °C it gave the phenyl derivative **2** with high regioselectivity. To assign the position of the substituent unequivocally, the remaining chlorine atom was removed by reduction with RedAl to form compound **3**. The position of the introduced hydrogen atom was determined from proton coupled ^{13}C NMR spectrum, in which the spin–spin interaction between H-2 and C-7a is present whereas no signal splitting corresponding to the interaction between H-4 and C-4a was observed. It suggests that the phenyl substituent is in position 4 and cannot be in position 2. Treatment of compound **2** with a further equivalent of phenylboronic acid gave the diphenyl derivative **4**, with 2-naphthylboronic acid gave the 2-(2-naphthyl) derivative **5**, and with $AlMe_3$ gave the 2-methyl derivative **6**. Reactions of compound **1** with tributyl(thiophen-2-yl)stannane and benzylzinc(II) bromide, respectively, are highly regioselective as well. The products are 4-*C*-substituted pyrrolo[3,2-*d*]pyrimidines **7** and **8**. The position of the substituents was assigned using

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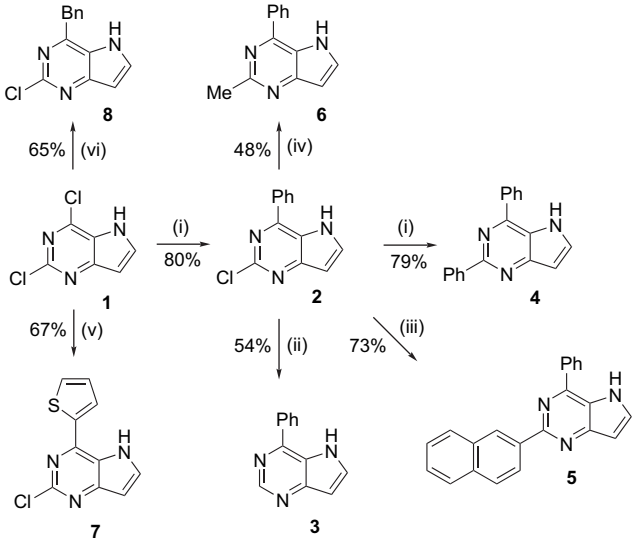
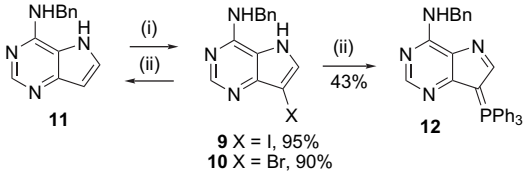
H,C-HMBC, wherein cross-peaks between *H*-3-thiophene (8.26 ppm) and C-4a (120.2) in **7**, and CH_2 (4.35 ppm) and C-4a (124.9 ppm) in **8** were observed. With the exception of boronic acids, all the agents were used in 100% excess. Under these conditions, the reactions were fully compatible with the free pyrrole NH group.



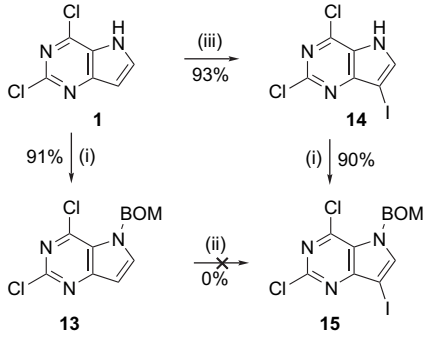
Scheme 1. (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, 100 °C, 5 h; (ii) RedAl, toluene, 100 °C, 1 h; (iii) 2-naphthylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene, 100 °C, 5 h; (iv) Me_3Al, $Pd(PPh_3)_4$, THF, reflux, 8 h; (v) tributyl(thiophen-2-yl)stannane, $Pd(PPh_3)_4$, toluene, reflux, 4 h; (vi) BnZnBr, $Pd(PPh_3)_4$, toluene, reflux, 8 h.

Initial experiments on cross-coupling reactions in position 7 were performed on *N*-benzyl-7-iodo-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (**9**) and its bromo congener **10** (Scheme 2). However, treatment with the same agents as above did not lead to products of C-substitution even if large excess was used. Mostly, the product of reductive dehalogenation **11** was isolated besides the unreacted starting compounds.[24] In the case of boronic acids, a small amount of the stable ylide **12** was obtained as well. Regardless of the additional NH group attached to position 4, the formation of the ylide **12** as well as of the dehalogenated compound **11** indicates that the tautomerization in the pyrrole ring, if not prevented, interferes with the formation of *C*-substituted product. Therefore, it was decided to protect the 5-NH group in further experiments.



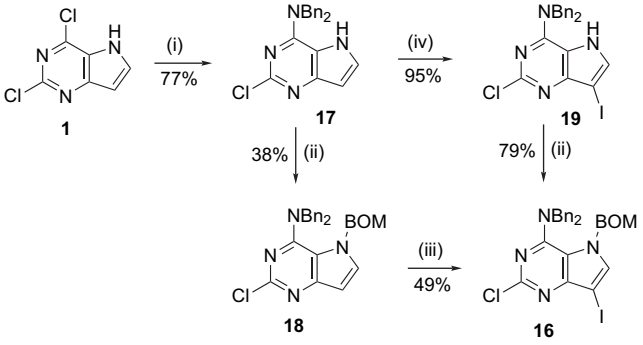
Scheme 2. (i) NIS or NBS, THF, 1 h; (ii) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, 80 °C, 8 h.

A construction of the protected precursor for the cross-coupling in position 7 from compound **1** is very attractive due to the possibility of an easy potential nucleophilic replacement of the chlorine atoms. As protecting group, benzyloxymethyl was chosen, because it is stable under alkaline conditions in cross-coupling reactions. Thus, by the treatment of compound **1** with benzyl chloromethyl ether and sodium hydride the protected derivative **13** was easily obtained (Scheme 3). However, further reaction with *N*-iodosuccinimide (NIS) did not give any product, even when the reaction time was prolonged to several days. In contrast, the inverse arrangement of those two steps led to a satisfactory result. The reaction of unprotected compound **1** with NIS proceeded smoothly affording the 7-iodo derivative **14** in high yield. Compound **14** was then protected by the formation of the benzyloxymethyl derivative **15**.



Scheme 3. (i) BOM–Cl, NaH, THF, rt; (ii) NIS, THF, rt, 7 days; (iii) NIS, THF, rt, 1 h.

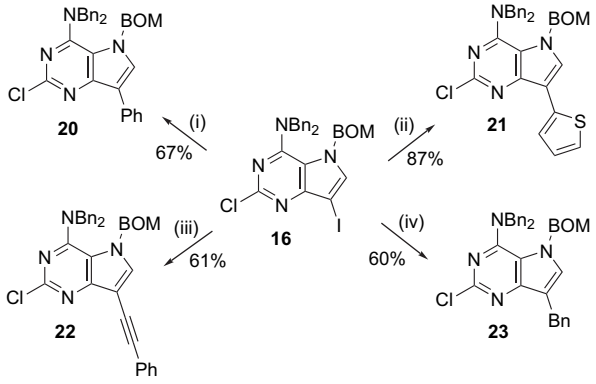
As a further substrate for the cross-coupling reactions, the 4-dibenzylamino derivative **16** was designed (Scheme 4). The reason was to increase the solubility in less polar solvents and remove the chlorine atom in position 4, which could compete with the iodine in position 7. Treatment of compound **1** with dibenzylamine in refluxing ethanol gave the 4-substituted derivative **17**, whose free NH group was then protected by the formation of benzyloxymethyl derivative **18**. The following reaction with NIS proceeded with difficulty. Despite using a large excess of the reagent and prolonged reaction time, the yield of compound **16** did not exceed 50%. As in the previous case, reversing the order of the reaction steps (via iodide **19**) resulted in high overall yield.



Scheme 4. (i) Bn_2NH, EtOH, reflux, 4 h; (ii) BOM–Cl, NaH, THF, rt, overnight; (iii) NIS, THF, rt, 7 days; (iv) NIS, THF, rt, 2 h.

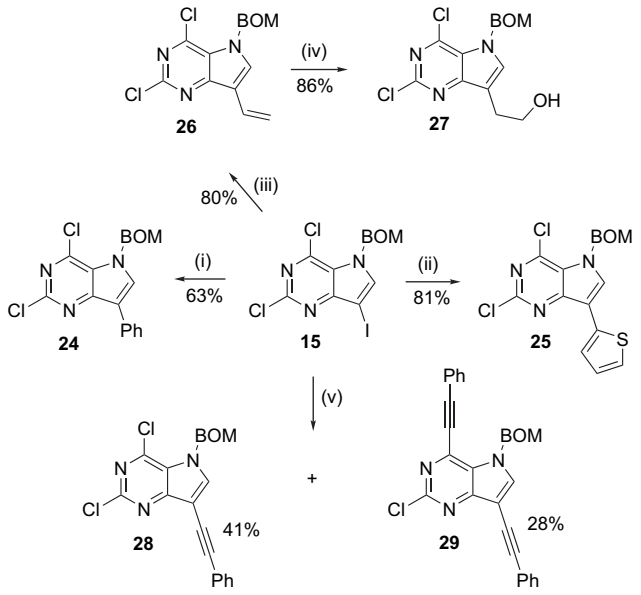
Reactivity of compound **16** in common cross-coupling reactions, such as Suzuki, Stille, Sonogashira, and Negishi, was assessed. Thus, treatment of iodide **16** with phenylboronic acid, tributyl(thiophen-2-yl)stannane, ethynylbenzene, and benzylzinc(II) bromide, respectively, resulted in the formation of 7-*C*-substituted products **20**–**23** in high

yields (Scheme 5). The chlorine atom in position 2 was quite inert. Again, the position of the *C*-substituents was confirmed (in addition to other evidence) by H,C-HMBC, wherein a correlation between H-6 and substituent carbon bound to C-7 was observed.



Scheme 5. (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, 100 °C, 5 h; (ii) tributyl(thiophen-2-yl)stannane, $Pd_2(dba)_3$, CuI, $AsPh_3$, DMF, 70 °C, 1 h; (iii) PhC≡CH, $Pd(PPh_3)_4$, CuI, $(i\text{-}Pr)_2NEt$, THF, 50 °C, 2 h; (iv) BnZnBr, $Pd(PPh_3)_4$, DMF, 75 °C, 1 h.

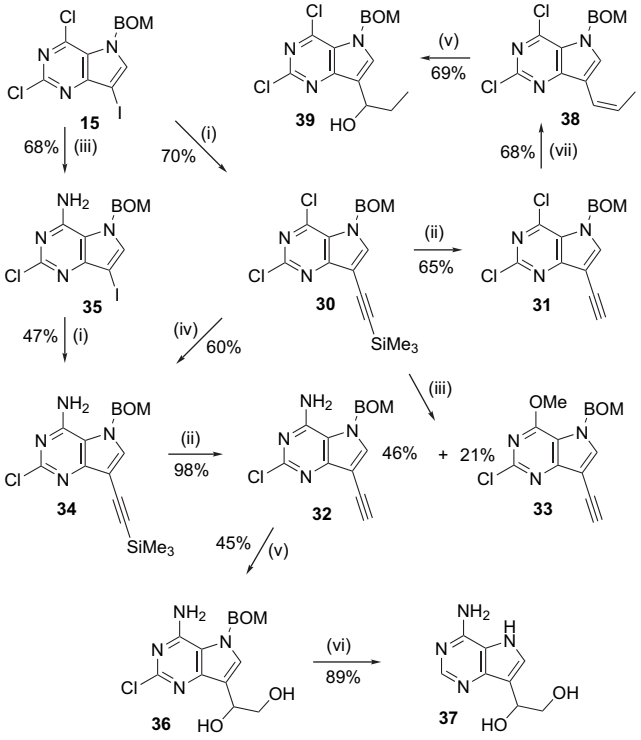
Precursor **15** bears three potential reaction centers for cross-coupling reactions. In comparison to compound **16**, it has a relatively reactive chlorine atom in position 4, which can compete with the iodine in position 7. Additionally, the chlorine in position 2 is more reactive than that in **16**, due to the absence of the electron donating dibenzylamino group in position 4. Hence, the question was whether the cross-coupling reactions are selective enough to give the 7-substituted products even in this case. Thus, the reaction of compound **15** with phenylboronic acid and tributyl(thiophen-2-yl)stannane, respectively, under the analogous conditions as above gave the 7-*C*-substituted products **24** and **25** (Scheme 6). As



Scheme 6. (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, 95 °C, 4 h; (ii) tributyl(thiophen-2-yl)stannane, $Pd_2(dba)_3$, $AsPh_3$, CuI, DMF, 50 °C, 2 h; (iii) tributyl(vinyl)stannane, $Pd_2(dba)_3$, $AsPh_3$, CuI, DMF, 75 °C, 2 h; (iv) (1) 9-BBN, THF, 0 °C to rt, 2 h; (2) $NaBO_3$, H_2O, rt, 2 h; (v) PhC≡CH, $Pd(PPh_3)_4$, CuI, Et_3N, THF, 50 °C, 2 h.

it was mentioned in Section 1, our special interest lays in functionalization of position 7 with 2-hydroxyethyl group. Therefore, we employed the regioselectivity of the Stille reaction for the preparation of vinyl derivative **26** by reaction with tributyl(vinyl)stannane. Hydroboration of compound **26** followed by oxidation with sodium perborate afforded the desired 2-hydroxyethyl derivative **27**. On the other hand, the reaction of the iodide **15** with ethynylbenzene was not selective enough giving an unseparable mixture of monosubstituted product **28** and disubstituted product **29**, which, however, could be identified by NMR spectroscopy. In the case of the reaction with benzylzinc(II) bromide, an unseparable mixture of products was obtained as well.

In contrast to ethynylbenzene, ethynyltrimethylsilane reacted with the iodide **15** regioselectively during the formation of the 7-*C*-substituted product **30** (Scheme 7). The trimethysilyl group was removed by tetrabutylammonium fluoride to give the acetylene **31**. Removal of the protecting group by methanolic ammonia at 120 °C led to the formation of amine **32** and a small amount of 4-methoxy derivative **33**. Using ethanolic ammonia at the same temperature prevented the formation of a 4-alkoxy derivative, however, it did not lead to the removal of the trimethylsilyl group as well, giving the unprotected amine **34**. Compound **34** was also prepared alternatively by the treatment of the iodide **15** with methanolic ammonia followed by a reaction of the resulting amine **35** with ethynyltrimethylsilane. The trimethylsilyl group of amine **34** was removed by tetrabutylammonium fluoride to give the unprotected acetylene **32**. Upon treatment with borane–dimethyl sulfide complex, compound **32** did not



Scheme 7. (i) $Me_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, rt, 2 h; (ii) TBAF, THF, rt, 10 min; (iii) NH_3 in MeOH, 120 °C, 12 h; (iv) NH_3 in EtOH, 120 °C, 12 h; (v) (1) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt, 2 h; (2) $NaBO_3$, H_2O, 2 h; (vi) H_2/Pd, MeOH, rt, overnight; (vii) $AlMe_3$, Cp_2ZrCl_2, CH_2Cl_2, 0 °C to rt, 2 h.

react unless more than 3 equiv of the reagent were added. After oxidation with sodium perborate, a product of double addition of borane—the diol **36** was obtained. The removal of the protecting group and chlorine atom in position 2 by hydrogenation led to the formation of compound **37**, which can be considered as a racemic 9-deaza-1′-nor congener of antiviral 9-(2,3-dihydroxypropyl)adenine (DHPA).[25,26] However, the tests on antiviral and antiproliferative activities were negative.

Once having the acetylene **31**, the conversion of the ethynyl group to isopropyl was also of interest as it could open the route to 9-deaza congeners of biologically active 9-isopropylpurines, e.g., myoseverin or purvalanol A. Upon treatment of compound **31** with trimethylaluminum in the presence of bis(cyclopentadienyl)zirconium dichloride, the addition of the methyl group should, according to literature precedent,[27] take place in the α-position to the heterocycle by a cis-mechanism. In fact, however, the methyl group was attached to the terminal carbon of the triple bond during the formation of the *cis*-olefin **38** (according J_{cis}(H,H)= 11.4 Hz), which is a product of trans-addition. The trans-mechanism as well as the opposite regioselectivity could be explainable by a chelation-controlled isomerization[28] proceeding via an aluminated intermediate, in which nitrogen atom in position 1 is coordinated to aluminum. Hydroboration of the *cis*-olefin **38** proceeded regioselectively during the formation of the racemic α-hydroxy derivative **39**.

3. Conclusion

To summarize, cross-coupling reactions were proven as a very good tool for C-functionalization of pyrrolo[3,2-*d*]-pyrimidine scaffold in positions 4, 2, and 7. Compound **15**, due to the widely different reactivities of its halogen atoms, is predestined to be employed in the synthesis of 9-deaza-purine and 4,6-diazaindole congeners of biomolecules. The facility of introduction of the (2-hydroxy)ethyl substituent into position 7 opens the route for the construction of 9-deaza congeners of acyclic nucleoside phosphonates of PME type with various substituents in positions 4 and 2. Finally, the abnormal carboalumination of compound **31** leading to the attachment of the methyl group to the terminal carbon of the triple bond by trans-mechanism is a remarkable finding, which is worth further investigating.

4. Experimental

4.1. General

Melting points were determined on a Kofler block and are uncorrected. Analytical TLC was performed on silica gel pre-coated aluminum plates with fluorescent indicator (Merck 5554, 60 F_{254}). Spots were visualized with UV light (254 nm) or by spraying with ninhydrin (1% solution in ethanol) followed by a short heating to 300–400 °C. Column chromatography was carried out on silica gel (Sigma S-0507, 40–63 μm). Mass spectra were measured on a ZAB-EQ (Micromass, Manchester, UK) spectrometer using the EI (electron energy 70 eV) or FAB (ionization with Xe, accelerating voltage 8 kV, thioglycerol–glycerol 3:1 mixture or bis(2-hydroxyethyl) disulfide were used as matrix). ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 (^{1}H at 400 MHz and ^{13}C at 100.6 MHz), Varian Unity 500, and Bruker Avance 500 instruments (^{1}H at 500 MHz and ^{13}C at 125.7 MHz) in $CDCl_3$ (referenced to TMS as an internal standard) or in DMSO-d_6 (referenced to the solvent signal δ=2.50 and 39.70 ppm, respectively). Complete assignment is based on heteronuclear correlation experiments HSQC and H,C-HMBC. Chemical shifts are in parts per million and coupling constants (*J*) in hertz. UV spectra were taken on a Beckman DU-65 spectrophotometer in methanol solution. IR spectra were obtained on an FTIR Bruker Equinox IFS 55 spectrometer in chloroform or KBr pellets. Elemental analyses were carried out on a Perkin–Elmer CHN Analyser 2400, Series II Sys (Perkin–Elmer, Norwolk, CT, USA).

4.1.1. 2-Chloro-4-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (2). Compound **1** (940 mg, 5 mmol), phenylboronic acid (760 mg, 6.3 mmol), potassium carbonate (900 mg, 6.5 mmol), and $Pd(PPh_3)_4$ (400 mg, 0.35 mmol) in toluene (40 mL) were heated under argon to 100 °C for 5 h. Then the reaction mixture was taken into ethyl acetate, washed with brine, and evaporated. Chromatography on a silica gel column (hexanes/ethyl acetate, 4:1) followed by crystallization (hexanes/ethyl acetate, 3:1) afforded compound **2** (920 mg, 80%, white crystals, mp 203–204 °C). MS (FAB) *m*/*z* (rel intensity): 232 (37, M[^{37}Cl]+H), 230 (100, M[^{35}Cl]+H), 196 (22, M−Cl+2H), 194 (9, M−Cl). HRMS (FAB) *m*/*z* calcd for $C_{12}H_9{}^{37}ClN_3$ (M+H): 232.0455, found: 232.0496; calcd for $C_{12}H_9{}^{35}ClN_3$ (M+H): 230.0485, found: 230.0452. MS (EI) *m*/*z* (rel intensity): 231 (34, M[^{37}Cl]), 229 (100, M[^{35}Cl]), 194 (35, M−Cl), 154 (4, M[^{37}Cl]−Ph), 152 (10, M[^{35}Cl]−Ph), 77 (23, Ph). ^{1}H NMR (500 MHz, DMSO-d_6): 12.26 (br s, 1H, NH-5), 8.05–8.07 (m, 2H, Ph), 8.02 (t, 1H, *J*=2.8, H-6), 7.61–7.63 (m, 3H, Ph), 6.69 (d, 1H, *J*=2.7, H-7). ^{13}C NMR (125.7 MHz, DMSO-d_6): 153.9 (ddd, *J*=2.9, 6.8, and 9.8, C-7a), 151.2 (s, C-2), 150.0 (t, *J*=3.9, C-4), 136.6 (br dd, *J*=9.8 and 188.5, C-6), 134.9 (dd, *J*=5.9 and 7.8, Ph), 131.0 (dt, *J*=2×7.8 and 161.1, Ph), 129.2 (ddd, *J*=3.9, 4.9, and 162.1, Ph), 128.9 (ddd, *J*=5.9, 7.8, and 161.1, Ph), 122.9 (br dt, *J*=2×4.4 and 7.8, C-4a), 101.5 (ddd, *J*=2.9, 7.8, and 178.7, C-7). IR ($CHCl_3$): 3465, 2997, 1609, 1600, 1539, 1421, 1369, 1257, 1173, 893, 864 cm^{-1}. UV (MeOH): 296 (11.00), 249 (12.10). Anal. Calcd for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; Cl, 15.44; N, 18.30. Found: C, 61.63; H, 3.44; Cl, 15.70; N, 18.32.

4.1.2. 4-Phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (3). To a solution of compound **2** (230 mg, 1 mmol) in toluene (40 mL) RedAl (65% solution in toluene, 2.5 mL, 8.3 mmol) was added and the reaction mixture was heated to 100 °C for 1 h. Water was added, the reaction mixture was taken into toluene, and washed with water. Chromatography on a silica gel column (chloroform/methanol, 97:3) followed by crystallization (hexanes/ethyl acetate, 1:1) afforded compound **3** (105 mg, 54%, white crystals, mp 171–173 °C). MS (EI) *m*/*z* (rel intensity): 195 (100, M), 168 (26), 149 (44), 140 (29), 118 (70, M−Ph+H), 104 (18), 89 (73), 77 (85, Ph). ^{1}H NMR (500 MHz, DMSO-d_6): 11.99 (br s, 1H, NH-5), 8.91 (s, 1H, H-2), 8.09–8.11 (m, 2H, Ph), 7.90 (br t, 1H, *J*=2.6, H-6), 7.56–7.63 (m, 3H, Ph), 6.71 (d, 1H, *J*=6.71,

H-7). ^{13}C NMR (125.7 MHz, DMSO-d_6): 151.3–151.6 (m, C-7a), 150.3 (d, J=200.2, C-2), 147.6 (dt, J=2×2.9 and 10.8, C-4), 136.3 (t, J=6.8, Ph), 134.1 (dd, J=8.8 and 185.5, C-6), 130.2 (dt, J=2×6.8 and 161.1, Ph), 129.1 (dd, 2C, J=6.8 and 161.1, Ph), 128.7 (dt, 2C, J=2×6.8 and 160.2, Ph), 123.7 (ddd, J=2.9, 5.8, and 6.8, C-4a), 101.8 (ddd, J=3.9, 7.8, and 176.8, C-7). IR ($CHCl_3$): 3467, 2978, 1609, 1599, 1543, 1490, 1417, 1373, 1364, 1249, 888 cm^{-1}. UV (MeOH): 289 (10.76), 245 (12.26). Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.96; H, 4.80; N, 21.34.

4.1.3. 2,4-Diphenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (4). A mixture of compound **1** (280 mg, 1.5 mmol), phenylboronic acid (730 mg, 6 mmol), potassium carbonate (830 mg, 6 mmol), and $Pd(PPh_3)_4$ (350 mg, 0.3 mmol) in toluene (40 mL) was heated to 100 °C under argon for 5 h, then was taken into ethyl acetate, washed with water, and evaporated. Chromatography on a silica gel column (chloroform) followed by crystallization (petroleum ether/ethyl acetate, 3:1) afforded compound **4** (320 mg, 79%) as white crystals, mp 206–207 °C. MS (FAB) *m*/*z* (rel intensity): 272 (100, M+H), 185 (7), 93 (21). HRMS (FAB) calcd for $C_{18}H_{14}N_3$ (M+H): 272.1188, found: 272.1155. ^{1}H NMR (500 MHz, DMSO-d_6): 12.00 (br s, 1H, NH-5), 8.55 (dt, 2H, J=2×1.4 and 7.1, Ph), 8.23 (dt, 2H, J=2×1.4 and 6.7, Ph), 7.93 (d, 1H, J=3.1, H-6), 7.66 (tt, 2H, J=1.6 and 7.3, Ph), 7.61 (tt, 1H, J=1.6 and 7.2, Ph), 7.52 (tt, 2H, J=1.5 and 7.1, Ph), 7.45 (tt, 1H, J=1.6 and 7.3), 6.77 (d, 1H, J=3.1, H-7). ^{13}C NMR (125.7 MHz, DMSO-d_6): 155.6 (t, J=3.9, C-2), 152.6 (dd, J=2.9 and 8.8, C-7a), 147.5 (t, J=3.9), 139.2 (t, J=6.8, Ph), 136.5 (t, J=6.8, Ph), 134.6 (dd, J=8.8 and 185.5, C-6), 130.3 (dt, J=2×7.8 and 161.1, Ph), 129.4 (dt, J=2×7.8 and 160.1, Ph), 129.1 (dd, 2C, J=7.8 and 161.1, Ph), 128.8 (dt, 2C, J=2×7.8 and 161.2, Ph), 128.6 (dd, 2C, J=7.8 and 160.1, Ph), 127.6 (dt, 2C, J=2×7.8 and 160.2, Ph), 122.7 (dd, J=5.8 and 6.8, C-4a), 102.2 (dd, J=7.8 and 176.8, C-7). IR ($CHCl_3$): 3469, 2977, 1606, 1597, 1544, 1490, 1485, 1416, 1377, 1252, 1026, 891 cm^{-1}. UV (MeOH): 257 (8.94). Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83, N, 15.49. Found: C, 79.36, H, 4.87, N, 15.17.

4.1.4. 2-(Naphthalen-2-yl)-4-phenyl-5*H*-pyrrolo[3,2-*d*]-pyrimidine (5). A mixture of compound **2** (210 mg, 0.9 mmol), 2-naphthylboronic acid (310 mg, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol), and $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) in toluene (20 mL) was heated to 100 °C under argon for 5 h, then was taken into ethyl acetate, washed with water, and evaporated. Chromatography on a silica gel column (methanol/chloroform, 1:99) followed by crystallization (petroleum ether/ethyl acetate, 5:1) afforded compound **5** (210 mg, 73%) as white crystals, mp 174–175 °C. MS (EI) *m*/*z* (rel intensity): 321 (100, M), 244 (8, M−Ph), 217 (9), 190 (6), 168 (6), 160 (10), 158 (10), 140 (7), 127 (21, naphthyl). HRMS (EI) calcd for $C_{22}H_{15}N_3$ (M): 321.1266, found: 321.1280. ^{1}H NMR (500 MHz, DMSO-d_6): 12.04 (br s, 1H, NH-5), 9.10 (br s, 1H, arom.), 8.72 (dd, 1H, J=1.7 and 8.7, arom.), 8.28 (dt, 2H, J=1.5 and 6.9, arom.), 8.12–8.14 (m, 1H, arom.), 8.02 (d, 1H, J=8.8, arom.), 7.96–7.98 (m, 1H, arom.), 7.96 (d, 1H, J=3.2, H-6), 7.68 (tt, 2H, J=1.4 and 7.0, arom.), 7.63 (tt, 1H, J=1.3 and 7.2, arom.), 7.54–7.57 (m, 2H, arom.), 6.82 (d, 1H, J=3.2, H-7). ^{13}C NMR (125.7 MHz, DMSO-d_6): 155.6 (t, J=4.9, C-2), 152.6 (ddd, J=2.9, 6.8, and 9.8), 147.7 (t, J=4.9, C-4), 136.7 (arom.), 136.6 (arom.), 134.8 (dd, J=7.8 and 185.6, C-6), 133.7 (arom.), 133.2 (arom.), 130.3 (arom.), 129.1 (3C, arom.), 128.9 (arom.), 128.9 (3C, arom.), 128.0 (arom.), 127.7 (arom.), 126.7 (arom.), 126.4 (arom.), 122.8 (dt, J=3.9 and 2×6.8, C-4a), 102.2 (dd, J=7.8 and 176.8, C-7). IR ($CHCl_3$): 3468, 2977, 1608, 1597, 1544, 1508, 1416, 1378, 1306, 1254 cm^{-1}. UV (MeOH): 285 (10.92), 259 (29.34), 223 (15.50). Anal. Calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 81.78; H, 4.83; N, 12.94.

4.1.5. 2-Methyl-4-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (6). To a mixture of compound **2** (230 mg, 1 mmol) and $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) in THF (10 mL) trimethylaluminum solution in toluene (2 M, 1 mL) was added under argon and the reaction mixture was heated to 75 °C for 8 h. Methanol (3 mL) followed by water (10 mL) was added and the reaction mixture was evaporated. Chromatography on a silica gel column (methanol/chloroform, 2:98) followed by crystallization (petroleum ether/ethyl acetate, 2:1) afforded compound **6** (100 mg, 48%) as yellowish crystals, mp 188–191 °C. MS (EI) *m*/*z* (rel intensity): 209 (100, M), 168 (5), 140 (5), 132 (14, M−Ph), 106 (16), 89 (12), 77 (7, Ph). HRMS (EI) calcd for $C_{13}H_{11}N_3$ (M): 209.0953, found: 209.0951. ^{1}H NMR (500 MHz, DMSO-d_6): 11.80 (br s, 1H, NH-5), 8.06 (d, 2H, Ph), 7.86 (t, 1H, J=3.0, H-6), 7.58 (m, 3H, Ph), 6.58 (dd, 1H, J=1.7 and 3.1, H-7), 2.69 (s, 3H, CH_3). ^{13}C NMR (125.7 MHz, DMSO-d_6): 158.4 (q, J=6.8, C-2), 152.2 (ddd, J=2.9, 6.8, and 8.8, C-7a), 147.4 (t, J=4.9, C-4), 136.5 (t, J=7.8, Ph), 133.9 (ddd, J=2.9, 8.8, and 185.6, C-6), 130.1 (dt, J=2×7.8 and 162.1, Ph), 129.0 (dd, 2C, J=7.8 and 160.2, Ph), 128.7 (dt, 2C, J=2×7.8 and 160.2, Ph), 122.1 (ddd, J=4.9, 5.9, and 6.8, C-4a), 101.2 (ddd, J=4.9, 7.8, and 175.8, C-7), 25.8 (q, J=127.0, CH_3). IR ($CHCl_3$): 3469, 2966, 1611, 1599, 1543, 1418, 1371, 1245, 871 cm^{-1}. UV (MeOH): 291 (9.50), 242 (11.60). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.95; H, 5.16; N, 19.68.

4.1.6. 2-Chloro-4-(thiophen-2-yl)-5*H*-pyrrolo[3,2-*d*]-pyrimidine (7). A mixture of compound **1** (225 mg, 1.2 mmol), $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), and tributyl-(thiophen-2-yl)stannane (0.9 mg, 2.4 mmol) in toluene (15 mL) was refluxed under argon for 4 h and then the solvent was evaporated. Chromatography on a silica gel column (chloroform) followed by crystallization (petroleum ether/ethyl acetate, 3:1) afforded compound **7** (190 mg, 67%) as white crystals, mp 173–175 °C. MS (EI) *m*/*z* (rel intensity): 237 (37, M[^{37}Cl or ^{34}S]), 235 (100, M[^{35}Cl]), 200 (41, M−Cl). ^{1}H NMR (500 MHz, DMSO-d_6): 12.21 (br s, 1H, NH), 8.26 (dd, 1H, J=3.8 and 1.1, H-3′), 8.03 (d, 1H, J=3.1, H-6), 7.93 (dd, 1H, J=5.0 and 1.1, H-5′), 7.36 (dd, 1H, J=5.0 and 3.8, H-4′), 6.66 (d, 1H, J=3.1, H-7). ^{13}C NMR (125.7 MHz, DMSO-d_6): 154.1 (C-7a), 150.6 (C-2), 144.1 (C-4), 139.4 (C-2′), 136.3 (C-6), 131.8 (C-5′), 130.4 (C-3′), 129.3 (C-4′), 120.2 (C-4a), 101.8 (C-7). IR ($CHCl_3$): 3459, 2999, 1602, 1539, 1528, 1422, 1369, 1257, 1172, 947 cm^{-1}. UV (MeOH): 333 (16.40), 267 (7.80), 233 (13.80). Anal. Calcd for $C_{10}H_6ClN_3S$: C, 50.96; H, 2.57; Cl, 15.04; N, 17.83; S, 13.60. Found: C, 51.07; H, 2.80; Cl, 14.88; N, 17.71; S, 13.84.

4.1.7. 4-Benzyl-2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (8). Benzylzinc(II) bromide (solution in THF, 0.5 M, 6 mL) was added under argon to a mixture of compound **1** (280 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) in toluene (20 mL), and the reaction mixture was refluxed for 8 h. Methanol (3 mL) followed by water (10 mL) was added, the reaction mixture was taken into ethyl acetate, washed with water, and evaporated. Chromatography on a silica gel column (methanol/chloroform, 99:1) afforded compound **8** (230 mg, 65%) as an amorphous solid. MS (EI) *m/z* (rel intensity): 245 (33, M[^{37}Cl]), 244 (43), 243 (100, M[^{35}Cl]), 242 (86, M[^{35}Cl]−H), 208 (19, M−Cl), 206 (16). HRMS (EI) *m/z* calcd for $C_{13}H_{10}N_3{}^{37}Cl$ (M[^{37}Cl]): 245.0534, found: 245.0538; calcd for $C_{13}H_{10}N_3{}^{35}Cl$ (M[^{35}Cl]): 243.0563, found: 243.0514. ^{1}H NMR (500 MHz, DMSO-d_6): 12.40 (br s, 1H, NH), 8.04 (t, 1H, *J*=2.9, H-6), 7.60 (m, 1H, Ph), 7.40–7.15 (m, 4H, Ph), 6.60 (dd, 1H, *J*=2.9 and 1.3, H-7), 4.35 (s, 2H, CH_2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 154.1 (C-4), 152.3 (C-7a), 151.0 (C-2), 137.7 (Ph), 135.5 (C-6), 129.1 (2C, Ph), 128.7 (2C, Ph), 126.8 (Ph), 124.9 (C-4a), 101.3 (C-7), 38.8 (CH_2). IR ($CHCl_3$): 3451, 2995, 1607, 1539, 1498, 1455, 1421, 1370, 1242, 925, 704 cm^{-1}. UV (MeOH): 280 (6.70). Anal. Calcd for $C_{13}H_{11}N_3$: C, 64.07; H, 4.14; Cl, 14.55; N, 17.24. Found: C, 64.25; H, 4.16; Cl, 14.37; N, 17.11.

4.1.8. *N*-Benzyl-7-iodo-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (9). Compound **11** (325 mg, 1.25 mmol) and *N*-iodosuccinimide (340 mg, 1.5 mmol) were stirred in THF (10 mL) for 1 h and the solvent was evaporated. Chromatography on a silica gel column (methanol/chloroform, 2:98) followed by crystallization (petroleum ether/ethyl acetate, 3:1) afforded compound **9** (115 mg, 95%) as white crystals, mp 219–220 °C. MS (EI) *m/z* (rel intensity): 350 (59, M), 333 (7), 245 (16, M−BnNH+H), 224 (27, M−I+H), 119 (17), 106 (100, BnNH), 91 (52, Bn). HRMS (EI) calcd for $C_{13}H_{11}N_4I$ (M): 350.0028, found: 350.0017. ^{1}H NMR (500 MHz, DMSO-d_6): 8.46 (br t, 1H, *J*=5.6, NH), 8.36 (s, 1H, H-2), 7.79 (s, 1H, H-6), 7.36 (d, 2H, *J*=7.5, Ph), 7.33 (t, 2H, *J*=7.5, Ph), 7.26 (t, 1H, *J*=7.5, Ph), 4.78 (d, 2H, *J*=5.6, CH_2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 149.9 (dq, *J*=3×3.9 and 10.7, C-4), 149.6 (d, *J*=201.2, C-2), 143.6 (t, *J*=8.8, C-7a), 138.9–139.1 (m, Ph), 132.6 (d, *J*=192.4, C-6), 128.6 (dd, 2C, *J*=7.8 and 160.2, Ph), 127.5 (dtt, 2C, *J*=2×3.9, 2×7.8, and 157.2, Ph), 127.3 (dt, *J*=2×7.8 and 161.1, Ph), 114.2 (d, *J*=6.8, C-4a), 55.6 (d, *J*=6.8, C-7), 43.7 (tt, *J*=3.9 and 138.7, CH_2). IR (KBr): 3303, 3087, 1627, 1533, 1441, 1402, 1340, 1017, 693, 655 cm^{-1}. UV (MeOH): 286 (12.78), 277 (13.30), 243 (20.74). Anal. Calcd for $C_{13}H_{11}IN_4$: C, 44.59; H, 3.17; I, 36.24; N, 16.00. Found: C, 44.43; H, 3.11; I, 36.40; N, 15.82.

4.1.9. *N*-Benzyl-7-bromo-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (10). Compound **11** (725 mg, 2.8 mmol) and *N*-bromosuccinimide (570 mg, 3.2 mmol) were stirred in THF (30 mL) for 1 h and the solvent was evaporated. Chromatography on a silica gel column (methanol/chloroform, 2:98) followed by crystallization (petroleum ether/ethyl acetate, 3:1) afforded compound **10** (755 mg, 90%) as white crystals, mp 257–260 °C. MS (EI) *m/z* (rel intensity): 304 (18, M[^{81}Br]), 302 (20, M[^{79}Br]), 199 (9, M[^{81}Br]−BnN), 198 (7), 197 (8, M[^{79}Br]−BnN), 196 (7), 172 (7), 144 (7), 131 (8), 117 (26, M−BnNH−Br), 106 (69, BnNH), 91 (100, Bn), 77 (54, Ph). ^{1}H NMR (500 MHz, DMSO-d_6): 11.28 (br s, 1H, NH-5), 8.27 (s, 1H, H-2), 7.69 (d, 1H, *J*=2.8, H-6), 7.60 (t, 1H, *J*=5.6, NH), 7.39 (d, 2H, *J*=7.4, Ph), 7.34 (t, 2H, *J*=7.8, Ph), 7.26 (t, 1H, *J*=7.2, Ph), 4.75 (d, 2H, *J*=5.6, CH_2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 151.1 (d, *J*=197.3, C-2), 149.6 (dq, *J*=3×3.9 and 10.7, C-4), 143.6 (ddd, *J*=5.8, 7.8, and 10.7, C-7a), 139.6–139.8 (m, Ph), 128.6 (dd, 2C, *J*=7.8 and 160.2, Ph), 127.8 (dm, 2C, *J*=157.2 and Σ*J*=21.5, Ph), 160.2 (dt, *J*=2×7.8 and 160.2, Ph),127.1 (dd, *J*=3.9 and 191.4, C-6), 113.9 (br d, *J*=6.8, C-4a), 89.5 (dd, *J*=4.9 and 6.8, C-7), 43.6 (tt, *J*=2.9 and 138.7, CH_2). IR (KBr): 3324, 3062, 1629, 1537, 1453, 1405, 1342, 1026, 893, 693 cm^{-1}. UV (MeOH): 286 (12.64), 277 (12.50), 241 (20.16). Anal. Calcd for $C_{13}H_{11}BrN_4$: C, 51.50; H, 3.66; Br, 26.36; N, 18.48. Found: C, 51.32; H, 3.67; Br, 26.32; N, 18.30.

4.1.10. *N*-Benzyl-7-(triphenylphosphoranylidene)-7*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (12). A mixture of compound **9** (200 mg, 0.5 mmol), phenylboronic acid (180 mg, 1.5 mmol), potassium carbonate (210 mg, 1.5 mmol), and $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) in dioxane/water mixture (4:1, 10 mL) was heated to 80 °C under argon for 8 h and the solvent was evaporated. Chromatography on a silica gel column (methanol/chloroform, 1:20) followed by crystallization (petroleum ether/ethyl acetate, 2:1) afforded unstable compound **12** (105 mg, 43%) as white crystals, mp 220–230 °C, which decomposes spontaneously (completely within several days) to *N*-benzyl-5*H*-pyrrolo[3,2-*d*]-pyrimidin-4-amine and triphenylphosphine. MS (EI) *m/z* (rel intensity): 484 (31, M), 407 (5, M−Ph), 393 (3, M−Bn), 379 (7, M−BnNH+H), 351 (13), 275 (18), 262 (4, PPh_3), 217 (4), 183 (20), 129 (10), 108 (13, PPh), 91 (31, Bn), 73 (29), 55 (53), 43 (100). HRMS (EI) calcd for $C_{31}H_{25}N_4P$ (M): 484.1817, found: 484.1736. ^{1}H NMR (500 MHz, $CDCl_3$): 8.37 (s, 1H, H-2), 7.68–7.76 (m, 9H, Ph), 7.57–7.60 (m, 6H, Ph), 7.47 (d, 2H, *J*=5.0, Ph), 7.30 (t, 2H, *J*=4.5, Ph), 7.22 (t, 1H, *J*=4.5, Ph), 7.18 (d, 1H, *J*=1.6, H-6), 6.96 (br, 1H, NH), 4.88 (d, 2H, *J*=5.7, CH_2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 153.1 (C-4), 151.3 (C-2), 150.5 (d, J_{CP}=8.3, C-7a), 144.6 (br d, J_{CP}=15.1, C-6), 139.4 (Ph), 133.8 (d, J_{CP}=10.7, PPh_3), 133.8 (d, J_{CP}=4.9, PPh_3), 129.6 (d, J_{CP}=13.2, PPh_3), 128.4 (2C, Ph), 127.7 (2C, arom.), 126.9 (Ph), 122.5 (d, J_{CP}=92.3, PPh_3), 58.8 (d, J_{CP}=125.3, C-7), 44.3 (CH_2). ^{31}P NMR (80.98 MHz, $CDCl_3$): 18.12 (s). IR (KBr): 3430, 1626, 1603, 1438, 1188, 1110, 703 cm^{-1}.

4.1.11. 5-(Benzyloxymethyl)-2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (13). Sodium hydride (60% dispersion in mineral oil, 150 mg, 3.75 mmol) was added to compound **1** (600 mg, 3.2 mmol) in THF (15 mL) and the mixture was sonicated for 1 h. Benzyl chloromethyl ether (1 mL, 5.7 mmol) was added, the reaction mixture was stirred for 24 h and the solvent was evaporated. Chromatography on a silica gel column (chloroform) afforded compound **13** (900 mg, 91%) as a colorless oil. MS (EI) *m/z* (rel intensity): 309 (12, M[^{37}Cl, ^{35}Cl]), 307 (18, M[^{35}Cl, ^{35}Cl]), 279 (8), 277 (15), 203 (16, M[^{37}Cl, ^{35}Cl]−BnO+H), 201 (22, M[^{35}Cl, ^{35}Cl]−BnO+H), 108 (44, BnOH), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.60 (d, 1H, *J*=3.3, H-6), 7.37–7.20 (m, 5H, Ph), 6.65 (d, 1H, *J*=3.3, H-7), 5.79 (s, 2H, N–CH_2–O), 4.51 (s, 2H, CH_2–O). ^{13}C NMR (100.6 MHz,

$CDCl_3$): 155.0 (C-7a), 150.8 (C-2), 143.3 (C-4), 138.5 (CH-6), 135.9 (C–*i*-Ph), 128.5, 128.1, 127.6 (CH–Ph), 122.9 (C-4a), 103.3 (CH-7), 76.6 (N–CH_2–O), 70.4 (CH_2–O). IR ($CHCl_3$): 3139, 3112, 3090, 3068, 1591, 1524, 1455, 1384, 1096. UV (MeOH): 282 (4.30). Anal. Calcd for $C_{14}H_{11}Cl_2N_3O$: C, 54.57; H, 3.60; N, 13.64, Cl, 23.01. Found: C, 54.64; H, 3.65; N, 13.23; Cl, 22.91.

4.1.12. 2,4-Dichloro-7-iodo-5*H*-pyrrolo[3,2-*d*]pyrimidine (14). Compound **1** (250 mg, 1.3 mmol) and *N*-iodosuccinimide (340 mg, 1.5 mmol) were stirred in THF (15 mL) for 1 h and the solvent was evaporated. Chromatography on a silica gel column (methanol/chloroform, 1:99) followed by crystallization (ethyl acetate/hexanes, 1:4) afforded compound **14** (390 mg, 93%) as yellowish crystals, mp 231–233 °C. MS (EI) *m/z* (rel intensity): 317 (10, M[^{37}Cl, ^{37}Cl]), 315 (65, M[^{37}Cl, ^{35}Cl]), 313 (100, M[^{35}Cl, ^{35}Cl]), 280 (10, M[^{37}Cl, ^{35}Cl]−^{35}Cl), 278 (33, M[^{35}Cl, ^{35}Cl]−^{35}Cl), 243 (31, M−2Cl). ^{1}H NMR (500 MHz, DMSO-d_6): 13.18 (br s, 1H, NH), 8.28 (s, 1H, H-6). ^{13}C NMR (125.7 MHz, DMSO-d_6): 153.1 (C-7a), 149.5 (C-2), 143.1 (C-4), 140.6 (CH-6), 124.1 (C-4a), 57.9 (C-7). IR (KBr): 3108, 3081, 3030, 1613, 1518, 1487, 1378, 1269, 910, 878. UV (MeOH): 282 (6.75), 239 (20.70). Anal. Calcd for $C_6H_2N_3Cl_2I$: C, 22.96; H, 0.64; N, 13.39; Cl, 22.59. Found: C, 23.25; H, 0.71; N, 13.16; Cl, 21.79.

4.1.13. 5-(Benzyloxymethyl)-2,4-dichloro-7-iodo-5*H*-pyrrolo[3,2-*d*]pyrimidine (15). Sodium hydride (60% dispersion in mineral oil, 800 mg, 20 mmol) was added to compound **14** (5 g, 16 mmol) in THF/DMF mixture (1:1, 80 mL) and the mixture was sonicated for 1 h. Benzyl chloromethyl ether (2.8 mL, 20 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (ethyl acetate/hexanes, 1:4) followed by crystallization (ethyl acetate/hexanes, 1:9) afforded compound **15** (6.2 g, 90%) as white crystals, mp 116–118 °C. MS (EI) *m/z* (rel intensity): 435 (16, M[^{37}Cl, ^{35}Cl]), 433 (25, M[^{35}Cl, ^{35}Cl]), 405 (15, M[^{37}Cl, ^{35}Cl]−CH_2O), 403 (25, M[^{35}Cl, ^{35}Cl]−CH_2O), 329 (24, M[^{37}Cl, ^{35}Cl]−BnO), 327 (36, M[^{35}Cl, ^{35}Cl]−BnO), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (s, 1H, H-6), 7.38–7.19 (m, 5H, Ph), 5.80 (s, 2H, N–CH_2–O), 4.55 (s, 2H, CH_2–O). ^{13}C NMR (100.6 MHz, $CDCl_3$): 155.2 (C-7a), 151.9 (C-2), 143.7 (C-4), 141.7 (CH-6), 135.7 (C–*i*-Ph), 128.6, 128.4, 127.6 (CH–Ph), 123.3 (C-4a), 77.0 (N–CH_2–O), 70.6 (CH_2–O), 58.4 (C-7). IR ($CHCl_3$): 3122, 3090, 3069, 1586, 1518, 1498, 1455, 1380, 1094. UV (MeOH): 321 (2.00), 285 (3.85), 243 (12.90). Anal. Calcd for $C_{14}H_{10}Cl_2IN_3O$: C, 38.74; H, 2.32; Cl, 16.34; N, 9.68. Found: C, 39.02; H, 2.52; Cl, 16.05; N, 9.47.

4.1.14. *N*,*N*-Dibenzyl-5-(benzyloxymethyl)-2-chloro-7-iodo-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (16).

4.1.14.1. Method A. Sodium hydride (60% dispersion in mineral oil, 170 mg, 3.8 mmol) was added to compound **19** (1.5 g, 3.2 mmol) in THF (18 mL) and the mixture was sonicated for 1 h. Benzyl chloromethyl ether (0.7 mL, 4.0 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (ethyl acetate/hexanes, 1:4) followed by crystallization (ethyl acetate/hexanes, 1:9) afforded compound **16** (1.5 g, 79%) as yellowish crystals, mp 114–116 °C. MS (FAB) *m/z* (rel intensity): 597 (6, M[^{37}Cl]+H), 595 (18, M[^{35}Cl]+H), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (s, 1H, H-6), 7.31–7.04 (m, 15H, 3Ph); 5.60 (s, 2H, N–CH_2–O), 4.51 (s, 4H, CH_2–N), 4.28 (s, 2H, CH_2–O). ^{13}C NMR (100.6 MHz, $CDCl_3$): 155.4 (C-4), 154.7 (C-7a), 152.7 (C-2), 138.9 (CH-6), 136.2, 135.9 (C–*i*-Ph), 128.6, 128.5, 128.5, 128.3, 127.7, 127.5 (CH–Ph), 117.6 (C-4a), 77.0 (N–CH_2–O), 71.0 (CH_2–O), 60.5 (C-7), 53.2 (CH_2–N). IR ($CHCl_3$): 3089, 3012, 2929, 1587, 1571, 1527, 1497, 1455, 1332, 1029, 907. UV (MeOH): 305 (10.50), 260 (8.65). Anal. Calcd for $C_{28}H_{24}ClIN_4O$: C, 56.53; H, 4.07; Cl, 5.96; N, 9.42. Found: C, 57.02; H, 4.17; Cl, 5.92; N, 9.64.

4.1.14.2. Method B. Compound **18** (890 mg, 1.5 mmol) and *N*-iodosuccinimide (1.0 g, 4.45 mmol) were stirred in THF (10 mL) for 7 days and the solvent was evaporated. Chromatography on a silica gel column (ethyl acetate/hexanes, 1:4) followed by crystallization (ethyl acetate/hexanes, 9:1) afforded compound **16** (560 mg, 49%) as yellowish crystals, mp 114–116 °C.

4.1.15. *N*,*N*-Dibenzyl-2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (17). Compound **1** (380 mg, 2 mmol) and dibenzylamine (1.25 mL, 6.5 mmol) were refluxed in ethanol (15 mL) for 4 h and the reaction mixture was evaporated. Chromatography on a silica gel column (methanol/chloroform, 1:99) followed by crystallization (petroleum ether/ethyl acetate, 5:1) afforded compound **16** (540 mg, 77%) as white crystals, mp 138–139 °C. MS (EI) *m/z* (rel intensity): 350 (1.6, M[^{37}Cl]), 348 (4, M[^{35}Cl]), 259 (37, M[^{37}Cl]−Bn), 257 (100, M[^{35}Cl]−Bn), 221 (6), 194 (5), 154 (7, M[^{37}Cl]−Bn_2N), 152 (18, M[^{35}Cl]−Bn_2N), 118 (15, M−Bn_2N−Cl+H), 91 (79, Bn), 77 (8, Ph). HRMS (EI) calcd for $C_{20}H_{17}{}^{35}ClN_4$ (M): 348.1142, found: 348.1155. ^{1}H NMR (400 MHz, DMSO-d_6): 11.35 (br s, 1H, NH-5), 7.53 (d, 1H, J=2.9, H-6), 7.31–7.34 (m, 4H, Ph), 3.25–7.28 (m, 6H, Ph), 6.41 (d, 1H, J=2.9, H-7), 4.92 (s, 4H, CH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6): 151.8–151.9 (m, C-7a), 151.3 (p, J=2.9, C-4a), 150.4 (s, C-2), 137.5 (m, 2C, Ph), 130.4 (dd, J=7.8 and 185.6, C-6), 128.7 (dd, 4C, J=7.8 and 160.2, Ph), 127.5 (dm, 4C, J=161.1, Ph), 127.4 (dt, 2C, J=2×7.8 and 161.1, Ph), 111.6 (t, J=6.8, C-4a), 101.5 (dd, J=7.8 and 176.7, C-7), 50.0 (tp, 2C, J=4×3.9 and 2×138.7, CH_2). IR (KBr): 3435, 1593, 1584, 1530, 1352, 941, 700 cm^{-1}. UV (MeOH): 293 (13.54), 242 (16.04). Anal. Calcd for $C_{20}H_{17}ClN_4$: C, 68.86; H, 4.91; Cl, 10.16; N, 16.06. Found: C, 69.08; H, 4.99; Cl, 10.32; N, 15.55.

4.1.16. *N*,*N*-Dibenzyl-5-(benzyloxymethyl)-2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (18). Sodium hydride (60% dispersion in mineral oil, 400 mg, 10.0 mmol) was added to compound **17** (1.8 g, 5 mmol) in THF (15 mL) and the mixture was sonicated for 1 h. Benzyl chloromethyl ether (1.6 mL, 9.0 mmol) was added, the reaction mixture was stirred for 24 h, and the solvent was evaporated. Chromatography on a silica gel column (ethyl acetate/hexanes, 1:9) followed by crystallization (ethyl acetate/hexanes, 4:1) afforded compound **18** (890 mg, 38%) as white crystals,

mp 84–86 °C. MS (EI) *m/z* (rel intensity): 469 (4, M[^{35}Cl]+H), 409 (5), 407 (12), 379 (35, M[^{37}Cl]−Bn), 378 (25), 377 (100, M[^{35}Cl]−Bn), 349 (8, M[^{37}Cl]−CH_2OBn), 347 (22, M[^{35}Cl]−CH_2OBn), 271 (9), 269 (23), 91 (95, Bn). ^{1}H NMR (500 MHz, $CDCl_3$): 7.45 (d, 1H, *J*=3.3, H-6), 7.06–7.36 (m, 15H, 3Ph), 6.65 (d, 1H, *J*=3.3, H-7), 5.62 (s, 2H, N–CH_2–O), 4.52 (s, 4H, CH_2–N), 4.25 (s, 2H, CH_2–O). ^{13}C NMR (125.7 MHz, $CDCl_3$): 155.3 (C-4), 154.8 (C-7a), 151.8 (C-2), 136.6, 136.5, 136.2 (C–*i*-Ph), 135.5 (CH-6), 128.5, 128.5, 128.2, 127.6, 127.5 (CH–Ph), 117.5 (C-4a), 104.9 (C-7), 76.7 (N–CH_2–O), 70.5 (CH_2–O), 53.1 (CH_2–N). IR ($CHCl_3$): 3090, 3033, 3012, 2962, 1600, 1575, 1497, 1455, 1387, 1070. UV (MeOH): 303 (7.10). Anal. Calcd for $C_{28}H_{25}ClN_4O$: C, 71.71; H, 5.37; N, 11.95; Cl, 7.56. Found: C, 71.55; H, 5.32; N, 11.78; Cl, 7.43.

4.1.17. *N*,*N*-Dibenzyl-2-chloro-7-iodo-5*H*-pyrrolo[3,2-*d*]-pyrimidin-4-amine (19). Compound **17** (2.5 g, 7.2 mmol) and *N*-iodosuccinimide (1.8 g, 7.9 mmol) were stirred in THF (20 mL) for 2 h and the solvent was evaporated. Chromatography on a silica gel column (chloroform) followed by crystallization (ethyl acetate/hexanes, 1:6) afforded compound **19** (3.2 g, 95%) as white crystals, mp 216–218 °C. MS (EI) *m/z* (rel intensity): 474 (7, M[^{35}Cl]), 385 (24, M[^{37}Cl]−Bn), 383 (78, M[^{35}Cl]−Bn), 259 (18, M[^{37}Cl]−Bn−I), 257 (55, M[^{35}Cl]−Bn−I), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 11.79 (br s, 1H, NH-5), 7.73 (s, 1H, H-6), 7.35–7.22 (m, 10H, 2Ph), 4.91 (s, 4H, CH_2–N). ^{13}C NMR (125.7 MHz, DMSO-d_6): 151.7 (C-7a), 151.5 (C-4), 151.2 (C-2), 137.3 (C–*i*-Ph), 134.6 (CH-6), 128.8, 127.5, 127.5 (CH–Ph), 112.2 (C-4a), 57.8 (C-7), 51.2 (CH_2–N). IR (KBr): 3268, 3029, 1590, 1582, 1530, 1451, 1203, 1132, 954, 906. UV (MeOH): 298 (12.10), 251 (14.30). Anal. Calcd for $C_{20}H_{16}ClIN_4$: C, 50.60; H, 3.40; Cl, 7.47; N, 11.80. Found: C, 50.67; H, 3.55; Cl, 7.49; N, 11.32.

4.1.18. *N*,*N*-Dibenzyl-5-(benzyloxymethyl)-2-chloro-7-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (20). A mixture of compound **16** (340 mg, 0.6 mmol), phenylboronic acid (290 mg, 2.4 mmol), potassium carbonate (330 mg, 2.4 mmol), and $Pd(PPh_3)_4$ (140 mg, 0.1 mmol) in toluene (30 mL) was heated to 100 °C under argon for 5 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform) followed by crystallization (hexanes/ethyl acetate, 3:1) afforded compound **20** (210 mg, 67%) as white crystals, mp 143–145 °C. MS (FAB) *m/z* (rel intensity): 547 (41, M[^{37}Cl]+H), 546 (40), 545 (100, M[^{35}Cl]+H), 91 (83, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (m, 2H, *o*-H–Ph-7), 7.70 (s, 1H, H-6), 7.45 (m, 2H, *m*-H–Ph-7), 7.34–7.23 (m, 11H, 2Ph+*p*-H–Ph-7), 7.15–7.06 (m, 5H, Ph), 5.68 (s, 2H, N–CH_2–O), 4.52 (s, 4H, CH_2–N), 4.30 (s, 2H, CH_2–O). ^{13}C NMR (100.6 MHz, $CDCl_3$): 155.5 (C-4), 152.2 (C-7a), 152.0 (C-2), 136.5, 136.2 (C–*i*-Ph), 132.0 (CH-6), 128.7, 128.6, 128.6, 128.5, 128.2, 127.6, 127.6, 126.9, 126.9 (CH–Ph), 118.7 (C-7), 118.4 (C-4a), 76.8 (N–CH_2–O), 70.8 (CH_2–O), 53.2 (CH_2–N). IR ($CHCl_3$): 3089, 3067, 3033, 1589, 1551, 1523, 1496, 1415, 1382, 1102, 949. UV (MeOH): 303 (4.40), 258 (8.50). Anal. Calcd for $C_{34}H_{29}ClN_4O$: C, 74.92; H, 5.36; Cl, 6.50; N, 10.28. Found: C, 74.79; H, 5.49; Cl, 6.77; N, 9.91.

4.1.19. *N*,*N*-Dibenzyl-5-(benzyloxymethyl)-2-chloro-7-(thiophen-2-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (21). Tributyl(thiophen-2-yl)stannane (0.1 mL, 0.3 mmol) was added under argon to a mixture of compound **16** (150 mg, 0.25 mmol), triphenylarsine (9.2 mg, 0.03 mmol), copper(I) iodide (5.7 mg, 0.03 mmol), and $Pd_2(dba)_3$ (7.8 mg, 0.0075 mmol) in DMF (2 mL). The reaction mixture was heated to 70 °C for 1 h, solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 4:1) followed by crystallization (hexanes/ethyl acetate, 9:1) afforded compound **21** (120 mg, 87%) as white crystals, mp 148–150 °C. MS (EI) *m/z* (rel intensity): 552 (16, M[^{37}Cl]), 551 (15), 550 (33, M[^{35}Cl]), 461 (23, M[^{37}Cl]−Bn), 459 (58, M[^{35}Cl]−Bn), 431 (32, M[^{37}Cl]−BnOMe), 429 (76, M[^{35}Cl]−BnOMe), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (dd, 1H, *J*=3.6 and 1.2, H-3′), 7.62 (s, 1H, H-6), 7.35–7.22 (m, 11H, 2Ph+H5′), 7.16–7.05 (m, 6H, Ph+H4′), 5.64 (s, 2H, N–CH_2–O), 4.51 (s, 4H, CH_2–N), 4.29 (s, 2H, CH_2–O). ^{13}C NMR (100.6 MHz, $CDCl_3$): 155.4 (C-4), 152.2 (C-2), 151.4 (C-7a), 136.4 (C–*i*-NBn), 136.0 (C–*i*-OBn), 133.3 (C-2′), 130.9 (CH-6), 128.6, 128.5, 128.5, 127.7, 127.6 (CH–Ph+CH-4′), 124.7 (CH-3′), 123.4 (CH-5′), 118.1 (C-4a), 113.8 (C-7), 76.8 (N–CH_2–O), 70.8 (CH_2–O), 53.1 (CH_2–N). IR ($CHCl_3$): 3089, 3067, 3033, 1597, 1564, 1527, 1496, 1380, 1103, 933. UV (MeOH): 281 (6.10). Anal. Calcd for $C_{32}H_{27}ClN_4OS$: C, 69.74; H, 4.94; N, 10.70; Cl, 6.43. Found: C, 69.68; H, 4.83; N, 10.77; Cl, 6.57.

4.1.20. *N*,*N*-Dibenzyl-5-(benzyloxymethyl)-2-chloro-7-(phenylethynyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (22). A mixture of compound **16** (250 mg, 0.42 mmol), ethynylbenzene (50 mg, 0.5 mmol), diisopropylethylamine (1.7 mL), copper(I) iodide (8 mg, 0.042 mmol), and $Pd(PPh_3)_4$ (50 mg, 0.042 mmol) in THF (5 mL) was heated under argon to 50 °C for 2 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 92:8) afforded compound **22** (146 mg, 61%) as colorless oil. MS (EI) *m/z* (rel intensity): 568 (8, M[^{35}Cl]), 550 (16), 504 (10), 469 (15, M[^{37}Cl]−PhC≡C), 467 (40, M[^{35}Cl]−PhC≡C), 431 (28), 429 (60), 361 (23), 359 (40), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.68 (s, 1H, H-6), 7.62–7.56, 7.38–7.22, 7.17–7.11, 7.09–7.03 (4 m, 20H, 4Ph), 5.62 (s, 2H, N–CH_2O), 4.50 (s, 4H, CH_2N), 4.29 (s, 2H, CH_2O). ^{13}C NMR (100.6 MHz, $CDCl_3$): 155.5 (C-4), 154.1 (C-7a), 152.8 (C-2), 137.7 (CH-6), 136.2 (C–*i*-NBn), 135.9 (C–*i*-OBn), 131.7, 128.6, 128.5, 128.3, 128.2, 128.2, 127.7, 127.6 (CH–Ph), 123.3 (C–*i*-Ph), 117.2 (C-4a), 101.6 (C-7), 93.1 (–C≡*C*–Ph), 79.3 (–*C*≡C–Ph), 76.9 (N–CH_2–O), 70.8 (CH_2–O), 53.2 (CH_2–N). IR ($CHCl_3$): 3089, 3067, 3033, 1581, 1547, 1527, 1496, 1380, 1101, 962. UV (MeOH): 293 (32.20), 276 (30.50). Anal. Calcd for $C_{36}H_{29}ClN_4O$: C, 75.98; H, 5.14; Cl, 6.23; N, 9.84. Found: C, 75.78; H, 5.26; Cl, 5.97; N, 9.59.

4.1.21. *N*,*N*-7-Tribenzyl-5-(benzyloxymethyl)-2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (23). Benzylzinc(II) bromide (0.65 mL, 0.33 mmol, 0.5 M solution in THF) was added to a mixture of compound **16** (150 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) in DMF (4 mL) and

the reaction mixture was heated under argon to 75 °C for 1 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 93:7) followed by crystallization (hexanes/ethyl acetate, 9:1) afforded compound **23** (85 mg, 60%) as white crystals, mp 85–87 °C. MS (EI) *m/z* (rel intensity): 560 (7, M[^{37}Cl], 558 (19, M[^{35}Cl]), 469 (17, M[^{37}Cl]−Bn), 467 (48, M[^{35}Cl]−Bn), 439 (13, M[^{37}Cl]−BnOMe), 437 (32, M[^{35}Cl]−BnOMe), 461 (20), 359 (40), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.37–7.21, 7.12–7.01 (2 m, 20H, 4Ph), 6.97 (t, 1H, J=1.1, H-6), 5.51 (s, 2H, N–CH_2–O), 4.51 (s, 4H, CH_2–N), 4.17 (s, 2H, CH_2–O), 4.09 (d, 2H, J=1.1, CH_2-7). ^{13}C NMR (100.6 MHz, $CDCl_3$): 155.2 (C-4), 153.6 (C-7a), 151.6 (C-2), 140.1 (C–*i*-Bn-7), 136.7 (C–*i*-NBn), 136.3 (C–*i*-OBn), 133.8 (CH-6), 129.0, 128.6, 128.5, 128.5, 128.4, 128.1, 127.6, 127.5, 126.2 (CH–Ph), 119.1 (C-7), 117.8 (C-4a), 76.5 (N–CH_2–O), 70.5 (CH_2–O), 53.1 (CH_2–N), 29.8 (CH_2-7). IR ($CHCl_3$): 3088, 3067, 3032, 1593, 1550, 1524, 1496, 1454, 1102, 962. UV (MeOH): 304 (9.00), 257 (8.90). Anal. Calcd for $C_{35}H_{31}ClN_4O$: C, 75.19; H, 5.59; N, 10.02; Cl, 6.34. Found: C, 75.25; H, 5.58; N, 9.98; Cl, 6.41.

4.1.22. 5-(Benzyloxymethyl)-2,4-dichloro-7-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (24). A mixture of compound **15** (220 mg, 0.5 mmol), phenylboronic acid (80 mg, 0.65 mmol), potassium carbonate (90 mg, 0.65 mmol), and $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) in toluene (12 mL) was heated under argon to 95 °C for 4 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 9:1) followed by crystallization (hexanes/ethyl acetate, 9:1) afforded compound **24** (120 mg, 63%) as white crystals, mp 101–103 °C. MS (EI) *m/z* (rel intensity): 385 (29, M[^{37}Cl, ^{35}Cl]), 383 (42, M[^{35}Cl, ^{35}Cl]), 355 (27, M[^{37}Cl, ^{35}Cl]−CH_2O), 353 (40, M[^{35}Cl, ^{35}Cl]−CH_2O), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (m, 2H, H–*o*-Ph-7), 7.79 (s, 1H, H-6), 7.45 (m, 2H, H–*m*-Ph-7), 7.35–7.22 (m, 6H, H–*p*-Ph-7+Ph), 5.85 (s, 2H, N–CH_2–O), 4.56 (s, 2H, CH_2O). ^{13}C NMR (100.6 MHz, $CDCl_3$): 152.2 (C-7a), 151.1 (C-2), 143.5 (C-4), 136.0 (C–*i*-Bn), 134.9 (CH-6), 130.8 (C–*i*-Ph-7), 128.9 (CH–*m*-Ph-7), 128.6 (CH–*m*-Bn), 128.3 (CH–*p*-Bn), 127.7 (CH–*o*-Ph-7), 127.5 (CH–*p*-Ph-7), 126.9 (CH–*o*-Bn), 123.7 (C-4a), 117.4 (C-7), 76.8 (N–CH_2–O), 70.8 (CH_2–O). IR ($CHCl_3$): 3085, 3068, 3034, 1596, 1551, 1510, 1489, 1423, 1358, 1087, 1030. UV (MeOH): 255 (22.65). Anal. Calcd for $C_{20}H_{15}Cl_2N_3O$: C, 62.51; H, 3.93; N, 10.94; Cl, 18.45. Found: C, 62.14; H, 3.73; N, 10.54; Cl, 18.28.

4.1.23. 5-(Benzyloxymethyl)-2,4-dichloro-7-(thiophen-2-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (25). Tributyl(thiophen-2-yl)stannane (0.23 mL, 0.73 mmol) was added under argon to a mixture of compound **15** (250 mg, 0.6 mmol), triphenylarsine (21.3 mg, 0.07 mmol), copper(I) iodide (13.3 mg, 0.07 mmol), and $Pd_2(dba)_3$ (18 mg, 0.017 mmol) in DMF (4 ml) and the reaction mixture was heated to 50 °C for 2 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 94:6) followed by crystallization (hexanes/ethyl acetate, 5:1) afforded compound **25** (180 mg, 81%) as white crystals, mp 103–106 °C. MS (EI) *m/z* (rel intensity): 391 (38, M[^{37}Cl, ^{35}Cl]), 389 (54, M[^{35}Cl, ^{35}Cl]), 361 (32, M[^{37}Cl, ^{35}Cl]−CH_2O), 359 (46, M[^{35}Cl, ^{35}Cl]−CH_2O), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.71 (dd, 1H, J=3.6 and 1.2, H-3′), 7.70 (s, 1H, H-6), 7.36–7.22 (m, 6H, H-5′+Ph), 7.11 (dd, J=3.6 and 5.1, H-4′), 5.81 (s, 2H, N–CH_2–O), 4.55 (s, 2H, CH_2–O). ^{13}C NMR (100.6 MHz, $CDCl_3$): 151.3 (C-7a), 151.3 (C-2), 143.5 (C-4), 135.9 (C–*i*-Ph), 133.8 (CH-6), 131.9 (C-2′), 128.6 (*o*-CH–Ph), 128.5 (CH-4′), 127.8 (CH–*p*-Ph), 127.7 (CH–*m*-Ph), 125.2 (CH-3′), 124.0 (CH-5′), 123.4 (C-4a), 112.5 (C-7), 76.7 (N–CH_2–O), 70.8 (CH_2–O). IR ($CHCl_3$): 3090, 3069, 3035, 1603, 1512, 1456, 1417, 1380, 1337, 1087. UV (MeOH): 278 (16.25), 272 (15.90). Anal. Calcd for $C_{18}H_{13}Cl_2N_3OS$: C, 55.39; H, 3.36; N, 10.77; Cl, 18.17. Found: C, 55.56; H, 3.73; N, 10.67; Cl, 18.50.

4.1.24. 5-(Benzyloxymethyl)-2,4-dichloro-7-vinyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (26). Tributyl(vinyl)stannane (3.2 mL, 11 mmol) was added under argon to a mixture of compound **15** (4.3 g, 10 mmol), $Pd_2(dba)_3$ (180 mg, 0.2 mmol), triphenylarsine (250 mg, 0.8 mmol), and copper(I) iodide (2.25 g, 12 mmol) in DMF (30 mL) and the reaction mixture was heated to 75 °C for 2 h. The solvent was evaporated, the residue was taken into ethyl acetate and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 92:8) followed by crystallization (hexanes/ethyl acetate, 5:1) afforded compound **26** (2.7 g, 80%) as white crystals, mp 92–95 °C. MS (EI) *m/z* (rel intensity): 335 (25, M[^{37}Cl, ^{35}Cl]), 333 (35, M[^{35}Cl, ^{35}Cl]), 305 (44, M[^{37}Cl, ^{35}Cl]−CH_2O), 303 (48, M[^{35}Cl, ^{35}Cl]−CH_2O), 247 (18), 91 (100, Bn). ^{1}H NMR (500 MHz, $CDCl_3$): 7.55 (s, 1H, H-6), 7.35–7.22 (m, 5H, Ph), 6.75 (dd, 1H, J_{trans}=17.7, J_{cis}=11.3, –C*H*=CH_2), 6.21 (dd, 1H, J_{trans}=17.7, J_{gem}=1.5, –CH=C*Ha*Hb), 5.78 (s, 2H, N–CH_2–O), 5.40 (dd, 1H, J_{cis}=11.3, J_{gem}=1.5, –CH=Ha*Hb*), 4.52 (s, 2H, CH_2–O). ^{13}C NMR (125.7 MHz, $CDCl_3$): 152.6 (C-7a), 151.1 (C-2), 143.30 (C-4), 136.0 (C–*i*-Ph), 135.6 (CH-6), 128.6 (CH–*m*-Ph), 128.3 (CH–*p*-Ph), 127.7 (CH–*o*-Ph), 124.7 (*C*H=CH_2), 123.6 (C-4a), 116.6 (CH=*C*H_2), 115.9 (C-7), 76.6 (N–CH_2–O), 70.6 (CH_2–O). IR ($CHCl_3$): 3069, 3034, 3011, 1637, 1594, 1511, 1417, 1352, 1087. UV (MeOH): 330 (2.90), 279 (5.30), 249 (26.65). Anal. Calcd for $C_{16}H_{13}Cl_2N_3O$: C, 57.50; H, 3.92; N, 12.57; Cl, 21.22. Found: C, 57.20; H, 3.97; N, 12.47; Cl, 21.39.

4.1.25. 2-[5-(Benzyloxymethyl)-2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl]ethanol (27). Compound **26** (2.3 g, 6.9 mmol) in THF (10 mL) was added gradually under argon at 0 °C to a solution of 9-BBN (0.5 M in THF, 27 mL, 13.8 mmol) and the reaction mixture was stirred at 0 °C for 15 min and then 2 h at room temperature. Sodium perborate (tetrahydrate, 4.2 g, 27.5 mmol) in water (28 mL) was added and the reaction mixture was left to stand for additional 2 h. The solvent was evaporated, the residue was taken into ethyl acetate and washed with water. Chromatography on a silica gel column (chloroform/methanol, 98:2) afforded compound **27** (2.1 g, 86%) as colorless oil. MS (EI) *m/z* (rel intensity): 353 (4, M[^{37}Cl, ^{35}Cl]), 351 (6, M[^{35}Cl, ^{35}Cl]), 335 (8, M[^{37}Cl, ^{35}Cl]−H_2O), 333 (10, M[^{35}Cl, ^{35}Cl]−H_2O), 323 (51, M[^{37}Cl, ^{35}Cl]−CH_2O), 321 (78, M[^{35}Cl, ^{35}Cl]−CH_2O), 202 (30), 200 (40), 91 (100, Bn). ^{1}H NMR (400 MHz, DMSO-d_6): 8.10 (s, 1H, H-6),

7.29–7.18 (m, 5H, Ph), 5.84 (s, 2H, N–CH_2–O), 4.74 (t, 1H, J_{OH,CH_2}=5.4, OH), 4.53 (s, 2H, CH_2–O), 3.65 (td, 2H, J_{vic}=7.0, $J_{CH_2,OH}$=5.4, CH_2–OH), 2.80 (t, 2H, J_{vic}=7.0, CH_2–C7). ^{13}C NMR (100.6 Hz, DMSO-d_6): 154.0 (C-7a), 148.9 (C-2), 142.4 (C-4), 139.6 (CH-6), 137.4 (C–*i*-Ph), 128.3 (CH–*m*-Ph), 127.7 (CH–*p*-Ph), 127.6 (CH–*o*-Ph), 122.6 (C-4a), 113.3 (C-7), 76.9 (N–CH_2–O), 69.9 (CH_2–O), 60.5 (CH_2–OH), 26.9 (CH_2). IR ($CHCl_3$): 3390, 3091, 1601, 1515, 1455, 1384, 1234, 1108, 1075. UV (MeOH): 307 (4.60), 283 (7.30). Anal. Calcd for $C_{16}H_{15}Cl_2N_3O_2$: C, 54.56; H, 4.29; N, 11.93; Cl, 20.13. Found: C, 54.50; H, 4.62; N, 11.69; Cl, 19.92.

4.1.26. Mixture (3:2) of 5-(benzyloxymethyl)-2,4-dichloro-7-(phenylethynyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (28) and 5-(benzyloxymethyl)-2-chloro-4,7-bis(phenylethynyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (29). A mixture of compound **15** (430 mg, 1.0 mmol), ethynylbenzene (120 mg, 1.2 mmol), triethylamine (0.2 mL, 1.5 mmol), copper(I) iodide (11 mg, 0.06 mmol) and $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) in THF (6 mL) was heated under argon to 50 °C for 2 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 92:8) afforded an unseparable mixture (300 mg, 3:2) of compounds **28** and **29**. Compound **28**: MS (EI) *m*/*z*: 409 (33, M[^{37}Cl, ^{35}Cl]), 407 (48, M[^{35}Cl, ^{35}Cl]), 379 (36, M[^{37}Cl, ^{35}Cl]−CH_2O), 377 (55, M[^{35}Cl, ^{35}Cl]−CH_2O). ^{1}H NMR (500 MHz, $CDCl_3$): 7.78 (s, 1H, H-6), 7.59–7.25 (m, 10H, CH–Ph), 5.81 (s, 2H, N–CH_2–O), 4.55 (s, 2H, CH_2O). Compound **29**: MS (EI) *m*/*z*: 475 (4, M[^{37}Cl, ^{35}Cl]), 473 (10, M[^{35}Cl, ^{35}Cl]). ^{1}H NMR (500 MHz, $CDCl_3$): 7.81 (s, 1H, H-6), 7.59–7.25 (m, 15H, CH–Ph), 5.98 (s, 2H, N–CH_2–O), 4.58 (s, 2H, CH_2–O).

4.1.27. 5-(Benzyloxymethyl)-2,4-dichloro-7-[(trimethylsilyl)ethynyl]-5*H*-pyrrolo[3,2-*d*]pyrimidine (30). A mixture of compound **15** (10.9 g, 25 mmol), copper(I) iodide (290 mg, 1.5 mmol), triethylamine (5.2 mL, 37.5 mmol) and $PdCl_2(PPh_3)_2$ (530 mg, 0.75 mmol) in THF (40 mL) was stirred under argon for 10 min, ethynyltrimethylsilane (4 mL, 28.8 mmol) in THF (15 mL) was added gradually and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated, the residue was taken into ethyl acetate and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 92:8) followed by crystallization (hexanes/ethyl acetate, 9:1) afforded compound **30** (7.10 g, 70%) as white crystals, mp 76–78 °C. MS (FAB) *m*/*z* (rel intensity): 406 (42, M[^{37}Cl, ^{35}Cl]+H), 404 (42, M[^{35}Cl, ^{35}Cl]+H), 366 (60), 364 (84), 336 (30), 334 (32), 91 (100, Bn). ^{1}H NMR (500 MHz, $CDCl_3$): 7.78 (s, 1H, H-6), 7.37–7.29 (m, 3H, H–*m*,*p*-Ph), 7.26 (m, 2H, H–*o*-Ph), 5.79 (N–CH_2–O), 4.52 (CH_2O), 0.29 (s, 9H, Me_3Si). ^{13}C NMR (125.7 MHz, $CDCl_3$): 154.4 (C-7a), 152.0 (C-2), 144.0 (C-4), 141.2 (CH-6), 135.6 (C–*i*-Ph), 128.7 (CH–*m*-Ph), 128.4 (CH–*p*-Ph), 127.7 (CH–*o*-Ph), 122.4 (C-4a), 100.5 (C-7), 99.7 (*C*≡C–Si), 92.8 (C≡*C*–Si), 76.8 (N–CH_2–O), 70.7 (CH_2–O), −0.1 (Me_3Si). IR ($CHCl_3$): 3093, 3069, 3035, 2901, 2164, 1594, 1517, 1456, 1373, 1251, 1091. UV (MeOH): 319 (4.60), 278 (6.80), 248 (47.70). Anal. Calcd for $C_{19}H_{19}Cl_2N_3OSi$: C, 56.44; H, 4.74; N, 10.93; Cl, 17.54. Found: C, 56.27; H, 4.63; N, 10.85; Cl, 17.26.

4.1.28. 5-(Benzyloxymethyl)-2,4-dichloro-7-ethynyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (31). Tetrabutylammonium fluoride (1.1 M solution in THF, 17.5 mL, 19.4 mmol) was added to compound **30** (7.1 g, 17.5 mmol) and the reaction mixture was left to stand for 10 min. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (hexanes/ethyl acetate, 88:12) followed by crystallization (hexanes/ethyl acetate, 4:1) afforded compound **31** (3.8 g, 65%) as white crystals, mp 100–102 °C. MS (EI) *m*/*z* (rel intensity): 333 (18, M[^{37}Cl, ^{35}Cl]), 331 (20, M[^{35}Cl, ^{35}Cl]), 303 (16, M[^{37}Cl, ^{35}Cl]−CH_2O), 301 (20, M[^{35}Cl, ^{35}Cl]−CH_2O), 256 (68), 239 (25), 91 (100, Bn). ^{1}H NMR (500 MHz, $CDCl_3$): 7.75 (s, 1H, H-6), 7.35–7.27 (m, 3H, H–*m*,*p*-Ph), 7.24 (m, 2H, H–*o*-Ph), 5.79 (s, 2H, N–CH_2–O), 4.54 (s, 2H, CH_2–O), 3.30 (s, 1H, C≡CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 154.8 (C-7a), 152.1 (C-2), 144.1 (C-4), 140.9 (CH-6), 135.6 (C–*i*-Ph), 128.6 (CH–*m*-Ph), 128.4 (CH–*p*-Ph), 127.7 (CH–*o*-Ph), 122.6 (C-4a), 99.3 (C-7), 82.4 (C≡*C*H), 76.9 (N–CH_2–O), 72.3 (*C*≡CH), 70.9 (CH_2–O). IR ($CHCl_3$): 3306, 3105, 2123, 1594, 1517, 1421, 1357, 1236, 1092. UV (MeOH): 321 (2.00), 278 (2.75), 239 (14.90). Anal. Calcd for $C_{16}H_{11}Cl_2N_3O$: C, 57.85; H, 3.34; N, 12.65; Cl, 21.35. Found: C, 57.66; H, 3.28; N, 12.38; Cl, 21.21.

4.1.29. 5-(Benzyloxymethyl)-2-chloro-7-ethynyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (32).

4.1.29.1. Method A. Tetrabutylammonium fluoride (1.1 M in THF, 1.6 mL, 1.8 mmol) was added to a solution of compound **34** (620 mg, 1.6 mmol) in THF (10 mL) and left to stand for 10 min. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform/methanol, 98:2) followed by crystallization (hexanes/ethyl acetate, 4:1) afforded compound **32** (500 mg, 98%) as white crystals, mp 202–204 °C. MS (EI) *m*/*z* (rel intensity): 314 (26, M[^{37}Cl]), 312 (73, M[^{35}Cl]), 282 (28, M[^{35}Cl]−CH_2O), 277 (18, M−Cl), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.35 (m, 3H, H–*m*,*p*-Ph), 7.34 (s, 1H, H-6), 7.28 (m, 2H, H–*o*-Ph), 6.24 (br s, 2H, NH_2), 5.48 (s, 2H, N–CH_2–O), 4.58 (s, 2H, CH_2O), 3.24 (s, 1H, HC≡C). ^{13}C NMR (100.6 MHz, $CDCl_3$): 153.9 (C-2), 152.8 (C-7a), 152.1 (C-4), 135.6 (CH-6), 134.6 (C–*i*-Ph), 128.9 (CH–*p*-Ph), 128.9 (CH–*m*-Ph), 128.5 (CH–*o*-Ph), 113.2 (C-4a), 98.22 (C-7), 81.2 (C≡*C*H), 77.0 (N–CH_2–O), 73.7 (*C*≡CH), 70.4 (CH_2–O). IR (KBr): 3408, 3311, 3158, 2119, 1647, 1594, 1531, 1359, 1095. UV (MeOH): 293 (9.40), 240 (26.90). Anal. Calcd for $C_{16}H_{13}ClN_4O$: C, 61.44; H, 4.19; N, 17.91. Found: C, 61.65; H, 4.18; N, 17.80.

4.1.29.2. Method B. Compound **30** (700 mg, 1.7 mmol) was dissolved in methanolic ammonia (10 M, 40 mL) and heated to 120 °C in autoclave for 12 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform/methanol, 100:0 to 98:2) afforded compound **33** (120 mg, 21%), white crystals, mp 147–148 °C (hexanes/ethyl acetate, 9:1) and compound **32** (250 mg, 46%), white crystals, mp 202–204 °C (hexanes/ethyl acetate, 4:1).

4.1.30. 5-(Benzyloxymethyl)-2-chloro-7-ethynyl-4-methoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (33). The compound

was obtained as a side-product in the preparation of compound **32** (see Section 4.1.29.2). MS (EI) *m/z* (rel intensity): 329 (8, M[^{37}Cl]), 327 (26, M[^{35}Cl]), 299 (7, M[^{37}Cl]−CH_2O), 297 (22, M[^{35}Cl]−CH_2O), 223 (8, M[^{37}Cl]−BnO), 221 (28, M[^{35}Cl]−BnO), 91 (100, Bn). ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (s, 1H, H-6), 7.36–7.26 (m, 3H, H–*m*,*p*-Ph), 7.22 (m, 2H, H–*o*-Ph), 5.66 (s, 2H, N–CH_2–O), 4.47 (s, 2H, CH_2–O), 4.12 (s, 3H, MeO), 3.25 (s, 1H, HC≡C). ^{13}C NMR (100.6 MHz, $CDCl_3$): 156.9 (C-4), 152.9 (C-7a), 151.9 (C-2), 136.9 (CH-6), 136.2 (C–*i*-Ph), 128.5 (CH–*m*-Ph), 128.1 (CH–*p*-Ph), 127.6 (CH–*o*-Ph), 113.8 (C-4a), 99.1 (C-7), 81.3 (C≡*C*H), 77.1 (N–CH_2–O), 73.6 (*C*≡CH), 70.5 (CH_2–O), 54.6 (MeO). IR ($CHCl_3$): 3306, 3091, 2121, 1606, 1543, 1462, 1415, 1363, 1090. UV (MeOH): 289 (5.50), 263 (5.20). Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.80; Cl, 10.82. Found: C, 62.10; H, 4.34; N, 12.61; Cl, 11.07.

4.1.31. 5-(Benzyloxymethyl)-2-chloro-7-[(trimethylsilyl)-ethynyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (34).

4.1.31.1. Method A. Ethynyltrimethylsilane (0.28 mL, 2 mmol) in THF (1.5 mL) was added gradually under argon to a mixture of compound **35** (570 mg, 1.5 mmol), copper(I) iodide (18 mg, 0.09 mmol), $PdCl_2(PPh_3)_2$ (32 mg, 0.045 mmol), and triethylamine (0.3 mL, 2.2 mmol) in THF (3 mL) and the reaction mixture was stirred for 2 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform) followed by crystallization (hexanes/ethyl acetate, 6:1) afforded compound **34** (260 mg, 47%) as white crystals, mp 90–92 °C. MS (FAB) *m/z* (rel intensity): 387 (6, M[^{37}Cl]+H), 385 (20, M[^{35}Cl]+H), 91 (35, Bn), 73 (100, $SiMe_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.41–7.36 (m, 3H, H–*m*,*p*-Ph), 7.35 (s, 1H, H-6), 7.27 (m, 2H, H–*o*-Ph), 6.47 (br s, 2H, NH_2), 5.47 (s, 2H, N–CH_2–O), 4.56 (s, 2H, CH_2–O), 0.26 (s, 9H, Me_3Si). ^{13}C NMR (100.6 MHz, $CDCl_3$): 153.7 (C-2), 152.2 (C-7a), 152.2 (C-4), 136.1 (CH-6), 134.7 (C–*i*-Ph), 128.9 (CH–*m*-Ph), 128.8 (CH–*p*-Ph), 128.4 (CH–*o*-Ph), 113.1 (C-4a), 99.4 (C-7), 98.0 (C≡*C*–Si), 94.5 (*C*≡C–Si), 77.1 (N–CH_2–O), 70.2 (CH_2–O), 0.1 (Me_3Si). IR ($CHCl_3$): 3479, 3360, 2902, 2159, 1626, 1594, 1533, 1424, 1356, 1251. UV (MeOH): 296 (8.00), 245 (31.70). Anal. Calcd for $C_{19}H_{21}ClN_4OSi$: C, 59.28; H, 5.50; N, 14.55; Cl, 9.21. Found: C, 59.02; H, 5.41; N, 14.33; Cl, 9.53.

4.1.31.2. Method B. Compound **30** (1.1 g, 3 mmol) was dissolved in ethanolic ammonia (2 M, 50 mL) and heated to 120 °C in autoclave for 12 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform) followed by crystallization (hexanes/ethyl acetate, 6:1) afforded compound **34** (620 mg, 60%) as white crystals, mp 90–92 °C.

4.1.32. 5-(Benzyloxymethyl)-2-chloro-7-iodo-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-amine (35). Compound **15** (2.0 g, 4.6 mmol) was dissolved in methanolic ammonia (10 M, 40 mL) and heated to 120 °C in autoclave for 12 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform) followed by crystallization (hexanes/ethyl acetate, 6:1) afforded compound **35** (1.2 g, 68%) as white crystals, mp 197–199 °C. MS (EI) *m/z* (rel intensity): 416 (20, M[^{37}Cl]), 414 (60, M[^{35}Cl]), 259 (14, M[^{37}Cl]−CH_2O−I), 257 (40, M[^{35}Cl]−CH_2O−I), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 7.90 (s, 1H, H-6), 7.35–7.16 (m, 7H, NH_2+Ph), 5.73 (s, 2H, N–CH_2–O), 4.49 (s, 2H, CH_2–O). ^{13}C NMR (125.7 MHz, DMSO-d_6): 152.5 (C-2), 152.4 (C-4), 151.9 (C-7a), 137.9 (CH-6), 136.9 (C–*i*-Ph), 128.4, 128.0, 127.9 (CH–Ph), 113.2 (C-4a), 77.7 (N–CH_2–O), 69.8 (CH_2–O), 57.4 (C-7). IR (KBr): 3480, 3361, 3031, 1625, 1585, 1536, 1417, 1354, 1072. UV (MeOH): 291 (6.90), 243 (16.30). Anal. Calcd for $C_{14}H_{12}ClIN_4O$: C, 40.55; H, 2.92; N, 13.51; Cl, 8.55. Found: C, 39.99; H, 2.86; N, 13.32; Cl, 8.88.

4.1.33. 1-[4-Amino-5-(benzyloxymethyl)-2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl]ethane-1,2-diol (36). A solution of compound **32** (500 mg, 1.6 mmol) in THF (4 mL) was added gradually under argon to a solution of borane–dimethyl sulfide complex (1 M solution in dichloromethane, 4.8 mL, 4.8 mmol) and the reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 2 h. Sodium perborate (tetrahydrate, 1.7 g, 11 mmol) in water (8 mL) was added and the reaction mixture was left to stand for additional 2 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform/methanol, 97:3) followed by crystallization (hexanes/ethyl acetate, 3:1) afforded compound **36** (250 mg, 45%) as white crystals, mp 176–178 °C. MS (EI) *m/z* (rel intensity): 332 (12, M[^{37}Cl]−H_2O), 331 (12), 330 (22, M[^{35}Cl]−H_2O), 319 (20), 318 (30, M[^{35}Cl]−CH_2O), 317 (52), 304 (9), 302 (28), 91 (100, Bn). ^{1}H NMR (500 MHz, DMSO-d_6): 7.58 (br s, 1H, H-6), 7.35–7.20 (m, 5H, Ph), 7.05 (br s, 2H, NH_2), 5.70 (br s, 2H, N–CH_2–O), 5.10 (br d, 1H, $J_{OH,CH}$=3.7, OH), 4.77 (br m, 1H, C*H*–OH), 4.75 (br t, 1H, J_{OH,CH_2}=5.9, OH), 4.45 (s, 2H, CH_2Ph), 3.70, 3.45 (2br dt, 2H, J_{gem}=11.1, J_{vic}=6.4, $J_{CH_2,OH}$=5.9, CH_2OH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 152.2 (C-4), 151.3 (C-2), 149.3 (C-7a), 137.1 (C–*i*-Ph), 132.6 (CH-6), 128.5 (CH–*m*-Ph), 128.0 (CH–*p*-Ph), 127.9 (CH–*o*-Ph), 117.2 (C-7), 112.8 (C-4a), 77.4 (N–CH_2–O), 69.5 (CH_2Ph), 66.9 (CH–OH), 66.3 (CH_2–OH). IR (KBr): 3401, 3295, 3120, 3035, 1647, 1604, 1529, 1435, 1363, 1088. UV (MeOH): 283 (7.05), 238 (18.90). Anal. Calcd for $C_{16}H_{17}ClN_4O_3$: C, 55.10; H, 4.91; N, 16.06. Found: C, 54.84; H, 4.91; N, 15.81.

4.1.34. 1-(4-Amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)-ethane-1,2-diol (37). Compound **36** (250 mg, 0.72 mmol) in methanol (100 mL) was acidified by the addition of methanolic hydrogen chloride (1 M, 3 mL) and hydrogenated under slight overpressure in the presence of Pd–C catalyst (10 wt%, 40 mg) overnight. The catalyst was filtered off through a Celite pad and the filtrate was evaporated. Chromatography on a silica gel column (chloroform/methanol, 97:3 to 90:10) followed by crystallization (ethyl acetate/methanol, 4:1) afforded compound **37** (125 mg, 89%) as white crystals, mp>300 °C. MS (EI) *m/z* (rel intensity): 178 (14, M−H_2O). ^{1}H NMR (500 MHz, DMSO-d_6): 12.79 (br s, 1H, NH), 8.94 (br s, 2H, NH_2), 8.43 (s, 1H, H-2), 7.74 (d, 1H, $J_{H6,NH}$=2.8, H-6), 5.49 (br s, 1H, OH), 4.85 (t, 1H, J_{vic}=5.9, CH–OH), 3.61, 3.56 (2 dd, 2H, J_{gem}=11.0, J_{vic}=5.9, CH_2–OH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 152.6 (C-4), 145.0 (CH-2), 132.5 (C-7a),

129.1 (CH-6), 114.0 (C-7), 112.8 (C-4a), 66.7 (CH–OH), 66.4 (CH_2–OH). IR (KBr): 3401, 3204, 2906, 1648, 1537, 1458, 1417, 1082, 1029. UV (MeOH): 272 (4.65). Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.72; H, 5.25; N, 28.45.

4.1.35. (*Z*)-5-(Benzyloxymethyl)-2,4-dichloro-7-(prop-1-enyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (38). Trimethylaluminum (2 M solution in toluene, 20 mL, 40 mmol) and a solution of compound **31** (3.4 g, 10.2 mmol) in dichloromethane (10 mL) were added under argon to a solution of Cp_2ZrCl_2 (3.0 g, 10.2 mmol) in dichloromethane and the reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 2 h. The reaction was quenched by pouring onto water with ice (100 mL), chloroform was added, the organic layer was washed with water, and evaporated. Chromatography on a silica gel column (hexanes/ethyl acetate, 92:8) followed by crystallization (hexanes/ethyl acetate, 5:1) afforded compound **38** (2.4 g, 68%) as white crystals, mp 127–129 °C. MS (EI) *m*/*z* (rel intensity): 349 (48, M[^{37}Cl, ^{35}Cl]), 347 (74, M[^{35}Cl, ^{35}Cl]), 319 (23, M[^{37}Cl, ^{35}Cl]−CH_2OH), 317 (34, M[^{35}Cl, ^{35}Cl]−CH_2OH), 228 (48, M[^{37}Cl, ^{35}Cl]−BnOMe), 226 (76, M[^{35}Cl, ^{35}Cl]−BnOMe), 91 (100, Bn). ^{1}H NMR (500 MHz, $CDCl_3$): 7.61 (s, 1H, H-6), 7.35–7.22 (m, 5H, Ph), 6.65 (dqd, 1H, J_{cis}=11.4, J_{CH,CH_3}=1.8, $J_{CH,H\text{-}6}$=0.8, C*H*=CH–CH_3), 5.92 (dq, 1H, J_{cis}=11.4, J_{CH,CH_3}=7.1, CH=C*H*–CH_3), 5.83 (s, 2H, N–CH_2–O), 4.54 (s, 2H, CH_2–O), 1.92 (dd, 3H, *J*=7.1 and 1.8, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): 153.7 (C-7a), 150.8 (C-2), 143.2 (C-4), 136.0 (C–*i*-Ph), 135.8 (CH-6), 128.6 (CH–*m*-Ph), 128.3 (CH–*p*-Ph), 127.7 (CH–*o*-Ph), 127.3 (CH=*C*H–CH_3), 122.7 (C-4a), 117.0 (*C*H=CH–CH_3), 114.7 (C-7), 76.6 (N–CH_2–O), 70.6 (CH_2–O), 15.6 (CH_3). IR ($CHCl_3$): 3068, 3034, 1626, 1594, 1511, 1416, 1381, 1357, 1089. UV (MeOH): 319 (3.05), 281 (6.35), 243 (29.60). Anal. Calcd for $C_{17}H_{15}Cl_2N_3O$: C, 58.63; H, 4.34; N, 12.07. Found: C, 58.75; H, 4.22; N, 11.83.

4.1.36. 1-[5-(Benzyloxymethyl)-2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl]propan-1-ol (39). Compound **38** (1.8 g, 5.2 mmol) in THF was added gradually under argon at 0 °C to a solution of borane–dimethyl sulfide complex (2 M in toluene, 7.5 mL, 15 mmol) and the reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 2 h. Then sodium perborate (tetrahydrate, 4.5 g, 30 mmol) in water (15 mL) was added and the reaction mixture was stirred for additional 2 h. The solvent was evaporated, the residue was taken into ethyl acetate, and washed with water. Chromatography on a silica gel column (chloroform) afforded compound **39** (1.3 g, 69%) as colorless oil. MS (EI) *m*/*z* (rel intensity): 367 (2, M[^{37}Cl, ^{35}Cl]), 365 (4, M[^{35}Cl, ^{35}Cl]), 349 (10), 347 (14, M[^{35}Cl, ^{35}Cl]−H_2O), 338 (54, M[^{37}Cl, ^{35}Cl]−CH_3CH_2), 336 (84, M[^{35}Cl, ^{35}Cl]−CH_3CH_2), 308 (24), 306 (36, M[^{35}Cl, ^{35}Cl]−$OCH_2CH_2CH_3$), 91 (100, Bn). ^{1}H NMR (400 MHz, DMSO-d_6): 8.15 (s, 1H, H-6), 7.29–7.18 (m, 5H, Ph), 5.87 (s, 2H, N–CH_2–O), 5.25 (br s, 1H, OH), 4.81 (dd, 1H, J_{vic}=7.2 and 5.0, C*H*–OH), 4.52 (s, 2H, CH_2–O), 1.88, 1.75 (2 m, 2H, CH_2), 0.86 (t, 3H, J_{vic}=7.4, CH_3). ^{13}C NMR (100.6 MHz, DMSO-d_6): 152.2 (C-7a), 148.9 (C-2), 142.5 (C-4), 138.6 (CH-6), 137.3 (C–*i*-Ph), 128.3 (CH–*m*-Ph), 127.7 (CH–*p*-Ph), 127.6 (CH–*o*-Ph), 122.8 (C-4a), 120.8 (C-7), 77.0 (N–CH_2–O), 69.9 (CH_2–O), 65.8 (CH–OH), 30.3 (CH_2), 10.0 (CH_3). IR ($CHCl_3$): 3607, 3445, 3031, 1600, 1513, 1455, 1383, 1088. UV (MeOH): 280 (4.05). Anal. Calcd for $C_{17}H_{17}Cl_2N_3O_2$: C, 55.75; H, 4.68; N, 11.47; Cl, 19.36. Found: C, 55.50; H, 4.37; N, 11.57; Cl, 19.46.

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