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Tetrahedron
Tetrahedron 63 (2007) 12465–12470

2-Amino-6-iodo-4-tosyloxypyrimidine: a versatile key intermediate for regioselective functionalization of 2-aminopyrimidines in 4- and 6-positions

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Received 7 June 2007; revised 25 July 2007; accepted 26 July 2007
Available online 2 August 2007

Abstract—2-Amino-6-iodo-4-tosyloxypyrimidine, easily prepared from commercially available material, is a key intermediate for the preparation of differentially substituted 2-aminopyrimidines by means of sequenced Suzuki and/or Sonogashira reactions.

1. Introduction

Various polysubstituted 2-aminopyrimidines exhibit important pharmacological properties. For example, derivative **1** was reported as a $5HT_2$ receptor antagonist[1] whereas bicyclic compound **2** shows sorbitol dehydrogenase inhibition properties[2] (Fig. 1). Polysubstituted 2-aminopyrimidines also show purine receptor antagonist,[3] or antibacterial,[4] anticancer, and anti-inflammatory activities.[5]

In drug discovery, great importance is given to reducing the time needed for drug optimization. The most recent papers described relatively tedious methods for the preparation of 2-aminopyrimidine derivative **8** (Scheme 1). Pathway **A** initially requires preparation of the starting alkynones **3**,[6] or chalcone derivative **4** (X=NH or O),[7,8] which are cyclocondensed with guanidine. Pathway **B** involves a β-ketoester **5**, and yields the 2-amino-6-hydroxypyrimidine **6** after cyclization. After an activation step by means of $POCl_3$, the resulting iminochloride **7** could be subjected to various palladium cross-coupling reactions (PCCR) such as Suzuki[9,10] (R_2=Ar) or Sonogashira[11] (R_2=alkyne) with specific catalysts and reagents leading to the disubstituted compound **8**. Pathway **C** involves cyclocondensation of guanidine with diethylmalonate. The resulting 2-aminopyrimidine-4,6-dihydroxypyrimidine **9** constitutes a valuable

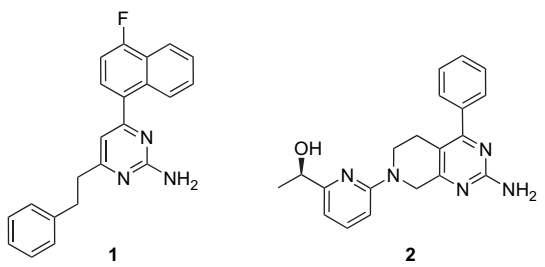
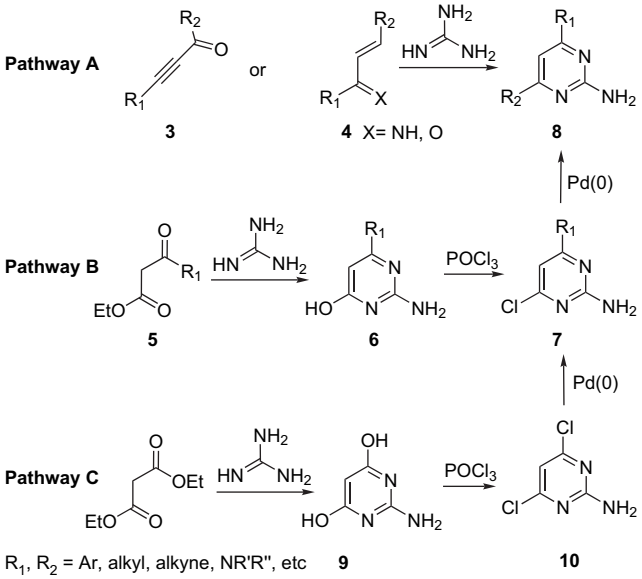


Figure 1. Examples of 2-aminopyrimidines with pharmacological activities.



Scheme 1. Alternative pathways leading to 4,6-disubstituted-2-aminopyrimidines.

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0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.100

synthon for introducing a high degree of structural diversity at both positions 4 and 6 via the dichloro derivative **10**.

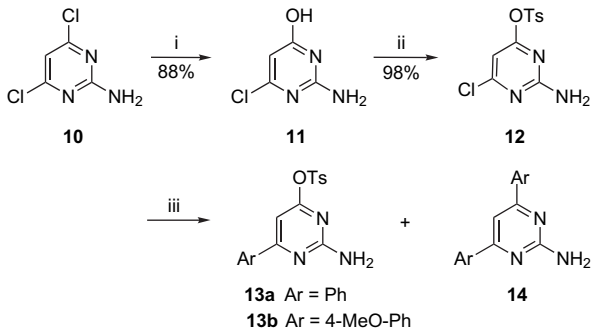
The aim of this communication is to investigate a pertinent strategy starting from readily available starting materials and leading to versatile functionalized scaffolds for building pyrimidine libraries in both mono and bicyclic series. The synthesis of unsymmetrical 4,6-pyrimidines was described recently.[12] However, the multistep sequences were applied only to the simple pyrimidine and it was not tried on more functionalized molecules such as 2-aminopyrimidines.

2. Results and discussion

The commercially available 2-amino-4,6-dichloro-pyrimidine **10** seemed to be an useful starting material for a quick introduction to structural diversity in a monocyclic series including pyrimidines[13] by means of PCCR. However, as found with other symmetrical dichlorodiazines, in particular with pyridazines, the first PCCR performed on the 4,6-dichloropyrimidine **10** produced a mixture of mono and disubstituted-adducts.[14–16]

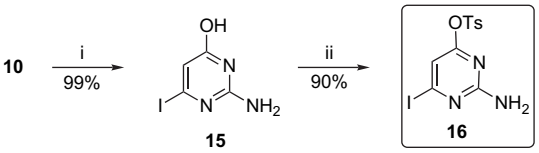
In order to differentiate the reactivities of both iminochlorides in 4,6-dichloropyrimidines, the authors attempted to replace one chlorine atom by iodine (by treatment with a mixture of HI and NaI), however a mixture of mono and disubstituted-iodo derivatives was obtained under these conditions.[17]

The differentiation of the two positions of substitution was investigated with the introduction of an *O*-tosyl group (Scheme 2), which is known to be less reactive in PCCR. Therefore, the 4,6-dichloropyrimidine **10** was firstly refluxed in an aqueous sodium hydroxide solution to give the 2-amino-6-chloro-4-hydroxypyrimidine **11** in 88% yield. Then the *O*-tosyl derivative **12** was obtained in nearly quantitative yield using tosylchloride and potassium carbonate in refluxing acetonitrile.[18] Although PCCR performed on the intermediate **12** did not allow to recover the monosubstituted adduct in good yield, it was determined that the substitution firstly occurred on the chlorine.



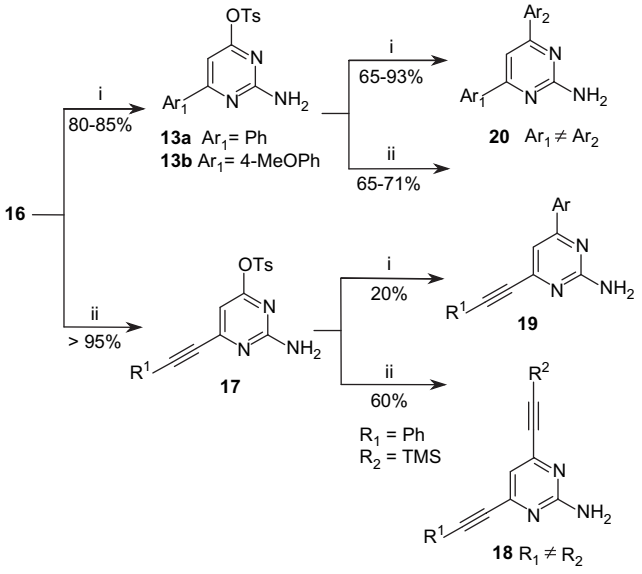
Scheme 2. Formation of 2-amino-4-chloro-6-tosyloxypyrimidine and attempt to perform monosubstitution. Reagents: (i) NaOH 1 M, reflux, 2 h; (ii) TsCl, K_2CO_3, CH_3CN, reflux, 3 h; (iii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DMF–H_2O, μ-waves.

In order to improve the regioselectivity of the substitution, we decided to replace the chlorine by a more reactive group. Therefore the 2-amino-6-iodo-4-tosyloxypyrimidine **16** was synthesized. By performing a Finkelstein reaction on the dichloropyrimidine **10** using NaI in a mixture of acetone and HI 55%, the 4-iodo-6-hydroxypyrimidine **15** was prepared in a quantitative yield. A further *O*-tosylation, performed as previously described, led to the key intermediate **16** with a 90% yield (Scheme 3).



Scheme 3. Synthesis of 2-amino-4-iodo-6-tosyloxypyrimidine. Reagents: (i) HI 55%, acetone, μ-waves, 100 °C, 5 min; (ii) TsCl, K_2CO_3, CH_3CN, reflux, 3 h.

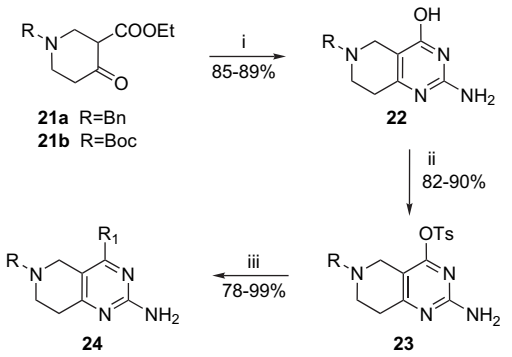
Suzuki or Sonogashira procedures were successfully applied to give the expected monosubstituted adduct (compounds **13** and **17**) in good yields (80–95%). Finally, by performing a second palladium cross-coupling reaction, the synthesis of 4,6-disubstituted 2-aminopyrimidines was carried out considering two different alkynes (compound **18**), an aryl and an alkyne (compound **19**), or two different aryl groups (compound **20**, Scheme 4).



Scheme 4. Use of 2-amino-4-iodo-6-tosyloxypyrimidine (**16**) for sequential discriminative approach to 4,6 disubstituted 2-aminopyrimidines. Reagents: (i) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DMF–H_2O, μ-waves; (ii) R–≡, CuI, $PdCl_2(PPh_3)_2$, NEt_3, μ-waves.

The bicyclic 2-amino-4-hydroxypyrimidine **22** is another example, which gave access to bicyclic compounds offering a single element of diversity at position 4 (Fig. 1). It was easily prepared by cyclocondensation of the ethyl 4-oxopiperidine-3-carboxylate **21** with guanidine (Scheme 5).[19] As described for the synthesis of **16**, the expected *O*-tosyl derivatives **23a** and **23b** were recovered in good yields (82–90%) and provided various derivatives by means of Suzuki and Sonogashira reactions (Table 1, compounds **24a–f**).

In summary, starting from a commercially available material, a two-step sequence allowed an easy access to the key



Scheme 5. Application of the tosylate activation for the synthesis of bicyclic aminopyrimidines. Reagents: (i) guanidine, Na, EtOH, 100 °C, 16 h; (ii) TsCl, K_2CO_3, MeCN, 3 h; (iii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DMF–H_2O, μ-waves; or R–≡, CuI, $PdCl_2(PPh_3)_2$, NEt_3, μ-waves.

Table 1. PCCR's with compound **24**

Entry	24	R	Reagent	Yield %
1	a	Bn	$PhB(OH)_2$	99
2	b	Boc	$PhB(OH)_2$	98
3	c	Boc	4-$ClPhB(OH)_2$	84
4	d	Boc	4-$OMePhB(OH)_2$	99
5	e	Boc	3,4-$OMePhB(OH)_2$	83
6	f	Boc	Ph—≡	78

intermediate **16** leading to various libraries of compounds with three different anchor points (R_1, R_2, NR). In a similar manner, activation of aminopyrimidinol by a tosylate also opens an interesting pathway for the preparation of bicyclic aminopyrimidines' libraries.

3. Experimental section

3.1. General

Chemicals and solvents were purchased puriss p.A. and used without purification. For thin-layer chromatography (TLC), silica gel plates Merck 60F254 were used and compounds were visualized by irradiation with UV light. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). Melting points were measured on a BUCHI B-450 apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on Bruker Avance Spectrometer. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in hertz. High-resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer. Microwave irradiation has been performed using Biotage Initiator EXP (http://www.biotage.com).

3.2. 2-Amino-6-iodo-4-hydroxypyrimidine (15)

4,6-Dichloro-2-aminopyrimidine **10** (1.0 g, 6.01 mmol), NaI (1.1 g, 7.32 mmol), 55% of HI (10 mL), and acetone (10 mL) were mixed in a process vial (25–30 mL) heated by microwaves to 100 °C for 5 min. The residue was dissolved in 20 mL of H_2O and the resulting solution was adjusted to pH 7.0 with a saturated solution of $NaHCO_3$. Finally a 10% $NaHSO_3$ solution (20 mL) was added and the precipitate was collected by suction filtration and dried in vacuo to give 2-amino-6-iodo-4-hydroxypyrimidine **15** as a light brown solid (1.44 g, 99%). Mp>250 °C; TLC R_f=0.46 (CH_2Cl_2–MeOH 9:1). ^{1}H NMR showed adequate purity for the next step. ^{1}H NMR (DMSO-d_6) δ: 6.05 (s, 1H, ArH), 6.91 (br s, 2H, NH_2), 11.11 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 112.6, 130.6, 154.9, 161.5. ESMS m/z: 253.9 (M−H).

3.3. Typical procedure for sulfonation

TsCl (201 mg, 1.05 mmol) and K_2CO_3 (146 mg, 1.05 mmol) were added to a stirred solution of **15** or **22** (1.05 mmol) in CH_3CN (15 mL). The resulting mixture was heated to 100 °C for 3 h then cooled to room temperature. The slurry was concentrated under reduced pressure. The residue was dissolved with ethyl acetate (50 mL) and water (10 mL). The organic layer was washed with a saturated solution of $NaHCO_3$, followed by water, and brine. The combined organic layers were dried by addition of Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (CH_2Cl_2–MeOH 99:1) to yield pure aminopyrimidines **16**, **24a** or **24b**.

3.3.1. 2-Amino-6-iodopyrimidin-4-yl methyl benzenesulfonate (16). Starting from 2-amino-6-iodo-4-hydroxypyrimidine **15** and following the general procedure, 2-amino-6-iodopyrimidin-4-yl methyl benzenesulfonate **16** was obtained as a white solid (373 mg, 90%). Mp 176–178 °C; TLC R_f=0.57 (CH_2Cl_2–MeOH 98:2); ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 5.44 (br s, 2H, NH_2), 6.77 (s, 1H, ArH), 7.34 (d, 2H, J=8.3, ArH), 7.88 (d, 2H, J=8.3, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.2, 109.1, 129.4, 130.3, 131.3, 133.4, 146.4, 162.4, 163.2. (EI) m/z: 391.9582 ($MH^{+\bullet}$ $C_{11}H_{11}I_1N_3O_3S_1$ requires 391.9560).

3.3.2. 2-Amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl 4-methyl benzenesulfonate (23a). Starting from 2-amino-6-benzyl-5,6,7,8-tetrahydro[4,3-*d*]pyrimidin-4-ol **22a** and following the general procedure, 2-amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl 4-methybenzenesulfonate **23a** was obtained as a white solid (319 mg, 74%). Mp 149–151 °C; TLC R_f=0.37 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ: 2.50 (s, 3H, Me), 2.68 (t, J=5.50, 2H, CH_2), 2.78 (t, J=5.50, 2H, NCH_2), 3.50 (s, 2H, CH_2), 3.73 (s, 2H, CH_2), 4.87 (br s, 2H, NH_2), 7.25–7.50 (m, 7H, ArH), 7.89–8.10 (d, J=8.3, 2H, ArH). ESMS m/z: 411.3 (M+H).

3.3.3. *tert*-Butyl-2-amino-4-{[(4-methylphenyl)sulfonyl]oxy}-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (23b). Starting from *tert*-butyl-2-amino-4-hydroxy-7,8-dihydropyrido [4,3-*d*]pyrimidine-6(5*H*)-carboxylate **22b** and following the general procedure, *tert*-butyl-2-amino-4-{[4-methylphenyl)sulfonyl]-oxy}-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **23b** was obtained as a viscous oil (438 mg, 99%). TLC R_f=0.50 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ: 1.47 (s, 9H, $C(CH_3)_3$), 2.46 (s, 3H, Me), 2.59 (t, J=5.8, 2H, CH_2), 3.60 (t, J=5.8, 2H, NCH_2), 4.39 (s, 2H, CH_2), 5.09 (br s, 2H, NH_2), 7.37 (d, J=8.1, 2H, ArH), 7.96 (d, J=8.1, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ: 21.82, 22.19, 28.80, 41.15, 47.75, 80.87, 107.28, 129.23, 130.08, 134.31, 146.07, 154.81, 160.70, 163.35. ESMS m/z: 421.2 (M+H).

3.4. Typical procedure for microwave-assisted Suzuki reaction

A suspension of **13**, **16** or **23** (0.256 mmol), sodium carbonate (54 mg, 0.511 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol, 0.10 equiv), and the corresponding arylboronic (0.258 mmol, 1.01 equiv) in a 9:1 mixture of DMF–H_2O (4 mL) was flushed with argon for 2 min. The reaction mixture was then heated by microwaves. The resulting slurry was concentrated to dryness under reduced pressure. The resulting residue was extracted with AcOEt, washed with water, and brine. The organic layer was dried over Na_2SO_4, concentrated under vacuum, and then purified by column chromatography on silica gel to give the desired aminopyrimidine **13a**, **13b**, **20**, **24a**, **24b**, **24c**, **24d**, and **24e**.

3.4.1. 2-Amino-6-phenylpyrimidin-4-yl 4-methyl benzenesulfonate (13a). Starting from 2-amino-6-iodopyrimidin-4-yl methyl benzenesulfonate **16** and following the general procedure in presence of phenylboronic acid (experimental conditions: 100 °C, 25 min), 2-amino-6-phenylpyrimidin-4-yl 4-methyl benzenesulfonate **13a** was obtained as a white solid (70 mg, 80%). Mp 167–169 °C; TLC R_f=0.78 (CH_2Cl_2–MeOH 99:1); ^{1}H NMR ($CDCl_3$) δ: 2.48 (s, 3H, CH_3), 5.20 (s, 2H, NH_2), 6.79 (s, 1H, ArH), 7.39 (d, 2H, J=8.3, ArH), 7.43–7.56 (m, 3H, ArH), 7.89–7.98 (m, 2H, ArH), 7.97 (d, 2H, J=8.3, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.1, 95.2, 127.5, 129.1, 129.3, 130.3, 131.4, 133.9, 137.0, 146.1, 162.2, 163.4, 165.9, 168.8. (EI) m/z: 341.0861 ($MH^{+\bullet}$ $C_{17}H_{16}I_1N_3O_3S_1$ requires 341.0834).

3.4.2. 2-Amino-6-(4-methoxyphenyl)-pyrimidin-4-yl 4-methyl benzenesulfonate (13b). Starting from 2-amino-6-iodopyrimidin-4-yl methyl benzenesulfonate **16** and following the general procedure in presence of 4-methoxyphenylboronic acid (experimental conditions: 100 °C, 25 min), 2-amino-6-(4-methoxyphenyl)-pyrimidin-4-yl 4-methyl benzenesulfonate **13b** was obtained as a white solid (80 mg, 82%). Mp 161–163 °C; TLC R_f=0.58 (AcOEt–heptane 1:1); ^{1}H NMR ($CDCl_3$) δ: 2.49 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 5.16 (s, 2H, NH_2), 6.75 (s, 1H, ArH), 6.99 (d, 2H, J=8.6, ArH), 7.39 (d, 2H, J=8.3, ArH), 7.94 (d, 2H, J=8.3, ArH), 7.98 (d, 2H, J=8.6, ArH); ^{13}C NMR ($CDCl_3$) δ: 21.7, 56.4, 100.1, 115.4, 126.3, 129.2, 129.5, 132.3, 139.4, 145.2, 152.3, 154.1, 162.2, 163.1. (EI) m/z: 372.1032 ($MH^{+\bullet}$ $C_{18}H_{18}I_1N_3O_4S_1$ requires 372.1013).

3.4.3. 4-Methoxyphenyl-6-phenylpyrimidin-2-amine (20). Starting from 2-amino-6-phenylpyrimidin-4-yl 4-methyl benzenesulfonate **13a** and following the general procedure in presence of 4-methoxy-phenylboronic acid (experimental conditions: 120 °C, 15 min), 4-methoxyphenyl-6-phenylpyrimidin-2-amine **20** was obtained as a white solid (66 mg, 93%). Starting from 2-amino-6-(4-methoxyphenyl)-pyrimidin-4-yl 4-methyl benzenesulfonate **13b** in presence of phenylboronic acid (experimental conditions: 140 °C, 20 min) **20** was obtained in 65% yield. Mp 160–161 °C; TLC R_f=0.58 (CH_2Cl_2–MeOH 99:1); ^{1}H NMR ($CDCl_3$) δ: 3.91 (s, 3H, CH_3), 5.34 (br s, 2H, NH_2), 7.04 (d, 2H, J=8.8, 2H, ArH), 7.29 (s, 1H, ArH), 7.49–7.62 (m, 3H, ArH), 8.07 (d, 2H, J=8.8, ArH); ^{13}C NMR ($CDCl_3$) δ: 55.82, 103.95, 114.51, 127.51, 129.05, 129.16, 130.51, 130.75, 138.35, 162.05, 164.02, 166.07, 166.41. (EI) m/z: 278.1295 ($MH^{+\bullet}$ $C_{17}H_{15}N_3O$ requires 278.1288).

3.4.4. 6-Benzyl-4-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]-pyrimidin-2-amine (24a). Starting from 2-amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl 4-methyl benzenesulfonate **23a** in presence of phenylboronic acid (experimental conditions: 100 °C, 10 min), 6-benzyl-4-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-2-amine **24a** was obtained as a light yellow solid (80 mg, 99%). Mp 106–107 °C; TLC R_f=0.38 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ: 2.67 (t, J=5.1, 2H, CH_2), 2.74 (t, J=5.1, 2H, NCH_2), 3.58 (s, 2H, NCH_2), 3.70 (s, 2H, CH_2), 5.08 (br s, 2H, NH_2), 7.23–7.63 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ: 26.74, 50.84, 58.43, 62.92, 115.58, 127.77, 128.72, 128.81, 129.48, 129.60, 137.87, 138.52, 161.31, 165.42, 166.82.

3.4.5. *tert*-Butyl-2-amino-4-phenyl-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (24b). Starting from *tert*-butyl-2-amino-4-{[4-methylphenyl)sulfonyl]-oxy}-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **23b** in presence of phenylboronic acid (experimental conditions: 100 °C, 10 min), *tert*-butyl-2-amino-4-phenyl-7,8-dihydropyrido [4,3-*d*]pyrimidine-6(5*H*)-carboxylate **24b** was obtained as a white solid (82 mg, 98%). Mp 153–154 °C; TLC R_f=0.44 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ: 1.51 (s, 9H, $C(CH_3)_3$), 2.74 (t, J=5.1, 2H, CH_2), 3.58 (t, J=5.1, 2H, NCH_2), 4.57 (s, 2H, NCH_2), 5.51 (br s, 2H, NH_2), 7.41–7.68 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 26.57, 28.86, 44.27, 48.81, 80.72, 114.23, 115.43, 130.08, 130.66, 132.41, 154.92, 161.11, 161.16. (EI) m/z: 327.1833 ($MH^{+\bullet}$ $C_{18}H_{23}N_4O_2$ requires 327.1816).

3.4.6. *tert*-Butyl-2-amino-4-(4-chlorophenyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (24c). Starting from 2-amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl 4-methyl benzenesulfonate **23b** in presence of 4-chloro-phenylboronic acid (experimental conditions: 100 °C, 10 min), *tert*-butyl-2-amino-4-(4-chlorophenyl)-7,8-dihydro pyrido[4,3-*d*] pyrimidine-6(5*H*)-carboxylate **24c** was obtained as a white solid (78 mg, 84%). Mp 133–135 °C; TLC R_f=0.49 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ: 1.53 (s, 9H, $C(CH_3)_3$), 2.71 (t, J=5.5, 2H, CH_2), 3.59 (t, J=5.1, 2H, NCH_2), 4.54 (s, 2H, NCH_2), 5.25 (br s, 2H, NH_2), 7.45 (d, J=8.6, 2H, ArH), 7.52 (d, J=8.6, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 28.44, 28.85, 44.20, 48.73, 80.85, 118.80, 129.08, 130.42, 132.40, 136.16, 152.65, 154.87, 161.26, 164.56. (EI) m/z: 361.1444 ($MH^{+\bullet}$ $C_{18}H_{22}$ $Cl_1N_4O_2$ requires 361.1426).

3.4.7. *tert*-Butyl-2-amino-4-(4-methoxyphenyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (24d). Starting from 2-amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*] pyrimidin-4-yl 4-methyl benzenesulfonate **23b** in presence of 4-methoxy-phenylboronic acid (experimental conditions: 100 °C, 10 min), *tert*-butyl-2-amino-4-(4-methoxyphenyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **24d** was obtained as a white solid (90 mg, 99%). Mp 118–120 °C; TLC R_f=0.33 (CH_2Cl_2–MeOH 95:5). ^{1}H NMR ($CDCl_3$) δ: 1.53 (s, 9H, $C(CH_3)_3$), 2.75 (t, J=5.5, 2H, CH_2), 3.58 (t, J=5.5, 2H, NCH_2), 3.88 (s, 3H, OMe), 4.53 (s, 2H, NCH_2), 5.30 (br s, 2H, NH_2), 7.00 (d, J=8.6, 2H, ArH), 7.54 (d, J=8.6, 2H, ArH); ^{13}C NMR ($CDCl_3$)

δ: 26.57, 28.86, 44.27, 48.81, 55.80, 80.72, 114.23, 115.43, 130.08, 130.66, 136.16, 154.92, 161.15, 161.16, 162.9, 168.1. (EI) *m/z*: 357.1936 ($MH^{+\bullet}$ $C_{19}H_{25}N_4O_3$ requires 357.1921).

3.4.8. *tert*-Butyl-2-amino-4-(3,4-dimethoxyphenyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (24e). Starting from 2-amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl 4-methyl benzenesulfonate **23b** in presence of 3,4-dimethoxy-phenylboronic acid (experimental conditions: 100 °C, 10 min), *tert*-butyl-2-amino-4-(3,4-dimethoxyphenyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **24e** was obtained as a white solid (82 mg, 83%). Mp 168–170 °C; TLC R_f=0.32 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ: 1.52 (s, 9H, $C(CH_3)_3$), 2.76 (t, J=5.5, 2H, CH_2), 3.58 (t, J=5.5, 2H, NCH_2), 3.94 (s, 6H, OMe), 4.52 (s, 2H, NCH_2), 5.28 (br s, 2H, NH_2), 6.95 (s, 1H, ArH), 7.12 (s, 1H, ArH), 7.15 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ: 26.67, 28.86, 41.01, 48.61, 56.42, 80.73, 111.07, 112.27, 115.45, 122.12, 130.36, 149.34, 149.52, 150.62, 154.94, 161.27, 164.46. (EI) *m/z*: 387.2043 ($MH^{+\bullet}$ $C_{20}H_{27}N_4O_4$ requires 387.2027).

3.5. Typical procedure for microwave-assisted Sonogashira reaction

A suspension of **13**, **16**, **17** or **23** (0.51 mmol), $PdCl_2(PPh_3)_2$ (27 mg, 0.05 mmol, 0.1 equiv), CuI (7.5 mg, 0.05 mmol, 0.1 equiv) in a 5:1 mixture of CH_3CN–NEt_3 (5 mL) was mixed in a process vial (2–5 mL) and flushed with argon for 2 min. The corresponding alkyne (0.56 mmol) was finally added. The reaction mixture was then heated by microwaves (excepted for compound **16**). The resulting suspension was concentrated to dryness under reduced pressure. The resulting residue was purified by column chromatography on silica gel to obtain the aminopyrimidine **17**, **18**, **19a**, **19b**, and **24f**.

3.5.1. 2-Amino-6-(phenylethynyl)pyrimidin-4-yl 4-methyl benzenesulfonate (17). Starting from 2-amino-6-iodopyrimidin-4-yl methyl benzenesulfonate **16** and following the general procedure (experimental conditions: RT, 30 min) in presence of phenylacetylene, 2-amino-6-(phenylethynyl)-pyrimidin-4-yl 4-methyl benzenesulfonate **17** was obtained as a yellow solid (137 mg, 98%). Mp 147–149 °C; TLC R_f=0.56 (AcOEt–heptane 1:1). ^{1}H NMR ($CDCl_3$) δ: 2.48 (s, 3H, CH_3), 5.42 (br s, 2H, NH_2), 6.58 (s, 1H, ArH), 7.33–7.49 (m, 5H, ArH), 7.59 (dd, J=8.28, 2H, ArH), 7.95 (d, J=8.28, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.18, 86.64, 93.96, 103.29, 121.31, 128.96, 129.15, 130.23, 130.42, 132.83, 133.63, 146.35, 154.32, 162.95, 165.28.

3.5.2. 4-(Phenylethynyl)-6-[(trimethylsilyl)ethynyl]pyrimidin-2-amine (18). Starting from 2-amino-6-(phenylethynyl) pyrimidin-4-yl 4-methyl benzenesulfonate **17** and following the general procedure (experimental conditions: 120 °C, 15 min) in presence of trimethylsilylacetylene, 4-(phenylethynyl)-6-[(trimethylsilyl)ethynyl]pyrimidin-2-amine **18** was obtained as an yellow solid (89 mg, 60%). Mp 80–82 °C; TLC R_f=0.56 (AcOEt–heptane 1:1). ^{1}H NMR ($CDCl_3$) δ: 0.29 (s, 9H; Me), 5.36 (br s, 2H, NH_2), 6.96 (s, 1H, ArH), 7.33–7.45 (m, 3H, ArH), 7.52–7.66 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ: 0.08, 93.43, 99.93, 101.91, 116.69, 121.62, 128.93, 130.22, 132.77, 152.34, 162.26, 163.32. (EI) *m/z*: 292.1257 ($MH^{+\bullet}$ $C_{17}H_{17}N_3Si$ requires 292.1265).

3.5.3. 4-Phenyl-6-(phenylethynyl)pyrimidin-2-amine (19a). Starting from 2-amino-6-phenylpyrimidin-4-yl 4-methyl benzenesulfonate **13a** and following the general procedure in presence of phenylacetylene (experimental conditions: 120 °C, 10 min), 4-phenyl-6-(phenylethynyl) pyrimidin-2-amine **19a** was obtained as an orange solid (90 mg, 65%). Mp 120–122 °C; TLC R_f=0.55 (CH_2Cl_2–MeOH 98:2). ^{1}H NMR ($CDCl_3$) δ: 5.38 (br s, 2H, NH_2), 7.27 (s, 1H, ArH), 7.45–7.55 (m, 6H, ArH), 7.56–7.68 (m, 2H, ArH), 7.95–8.05 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ: 87.83, 92.27, 110.80, 121.93, 127.52, 128.90, 129.22, 130.01, 131.26, 132.75, 137.21, 152.28, 163.65, 166.36.

3.5.4. 4-(4-Methoxyphenyl)-6-(phenylethynyl)pyrimidin-2-amine (19b). Starting from 2-amino-6-(4-methoxyphenyl)-pyrimidin-4-yl 4-methyl benzenesulfonate **13b** and following the general procedure in presence of phenylacetylene (experimental conditions: 120 °C, 10 min), 4-(4-methoxyphenyl)-6-(phenylethynyl)pyrimidin-2-amine **19b** was obtained as an yellow solid (110 mg, 71%). Mp 98–99 °C; TLC R_f=0.48 (CH_2Cl_2–MeOH 98:2); ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 3H, CH_3), 5.23 (br s, 2H, NH_2), 6.99 (d, J=9.1, 2H, ArH), 7.22 (s, 1H, ArH), 7.32–7.46 (m, 3H, ArH), 7.55–7.70 (m, 2H, ArH), 8.01 (d, J=9.1 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ: 55.80, 87.99, 91.89, 110.07, 114.56, 122.03, 128.86, 129.08, 129.56, 129.90, 132.71, 151.99, 162.41, 163.58, 165.73. (EI) *m/z*: 302.1281 ($MH^{+\bullet}$ $C_{19}H_{15}N_3O$ requires 302.1288).

3.5.5. *tert*-Butyl-2-amino-4-(phenylethynyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (24f). Starting from *tert*-butyl-2-amino-4-{[4-methylphenyl)sulfonyl]-oxy}-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **24b** in presence of phenylacetylene (experimental conditions: 100 °C, 20 min), *tert*-butyl-2-amino-4-(phenylethynyl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **25f** was obtained in 78% yield. TLC R_f=0.53 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR ($CDCl_3$) δ: 1.48 (s, 9H, $C(CH_3)_3$), 2.85 (t, J=5.5, 2H, CH_2), 3.68 (t, J=5.5, 2H, NCH_2), 4.45 (s, 2H, NCH_2), 5.30 (br s, 2H, NH_2), 7.31–7.45 (m, 3H, ArH), 7.53–7.63 (m, 2H, ArH). (EI) *m/z*: 351.1835 ($MH^{+\bullet}$ $C_{20}H_{23}N_4O_2$ requires 351.1816).

3.6. Typical procedure for preparation of *N*-protected 2-amino-5,6,7,8-tetrahydro[4,3-*d*]pyrimidin-4-ol (22)

Sodium ethanolate was prepared from sodium (0.25 g) and 30 mL of anhydrous ethanol. Protected ethyl 4-oxopiperidin-4(3*H*)-one **21** (10.1 mmol, 1.0 equiv) and guanidine (2.18 g, 12.1 mmol, 1.2 equiv) were then added and the mixture was refluxed for 16 h. After cooling to room temperature the slurry was filtered and the solvent was evaporated. The residue was taken up in a minimum of 95% ethanol and water was added until precipitation. The white solid precipitate was collected and dried in vacuo to give the aminopyrimidines **22a** and **22b**.

3.6.1. 2-Amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]-pyrimidin-4-ol (22a). Starting from ethyl-1-benzyl-4-oxopiperidine-3-carboxylate **21a** and following the general

procedure, 2-amino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-ol **22a** was obtained as a white solid (2.3 g, 89%). Mp 190–195 °C; TLC R_f=0.38 (CH_2Cl_2–MeOH 9:1); ^{1}H NMR (DMSO-d_6) δ: 2.24 (CH_2, J=5.27), 2.54 (t, 2H, CH_2, J=5.27), 3.05 (s, 2H, CH_2Ar), 6.38 (br s, NH_2), 7.18–7.37 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6) δ: 21.9, 49.8, 56.7, 61.5, 106.3, 127.5, 128.6, 129.2, 138.2, 154.1, 162.5. ESMS *m*/*z*: 257 (M+H).

3.6.2. *tert*-Butyl-2-amino-4-hydroxy-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (22b). Starting from 1-*tert*-butyl-3-ethyl 4-oxopiperidine-1,3-dicarboxylate **21b** and following the general procedure, *tert*-butyl-2-amino-4-hydroxy-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **22b** was obtained as a yellow oil (2.33 g, 85%). TLC R_f=0.27 (CH_2Cl_2–MeOH 95:5); ^{1}H NMR (DMSO-d_6) δ: 1.41 (s, 9H, $C(CH_3)_3$), 2.25 (t, J=5.60, 2H, CH_2), 3.45 (t, J=5.6, 2H, NCH_2), 4.01 (s, 2H, NCH_2), 6.62 (br s, 2H, NH_2), 11.61 (br s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ: 21.98, 28.92, 42.22, 48.05, 79.84, 106.54, 154.63, 156.17, 158.52, 164.87. ESMS *m*/*z*: 272.3 (M+H).

Acknowledgements

Financial support from the Agence Nationale de Recherche et Technologie (ANRT) and Neuro3D is gratefully acknowledged. Financial support (Proc No. 0085057) of CAPES/Brazil to J.X.A.-Jr. and Cofecub are acknowledged. The authors thank Dr. Gilbert Schlewer for helpful discussions and encouragement.

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