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SYNTHESIS OF 6-PYRIDYLAMINOPURINES

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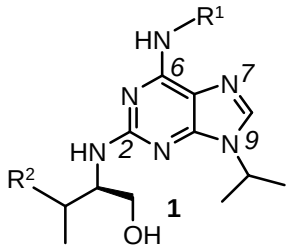
Abstract– An efficient synthesis of new 6-pyridinylaminopurines was developed based on Buchwald-Hartwig coupling reaction between aminopyridines and 2,6-dichloro-9-*iso*-propylpurine. The reaction was best carried out in the presence of a limited load of palladium acetate (4 %) as catalyst, racemic 2,2'-bis(diphenylphosphanyl)-1,1'-binaphtyl (8 %) as ligand and potassium *tert*-butoxide as base. Rising the load of catalyst, or using other catalysts and bases led to the development of side reactions.

INTRODUCTION

The purine scaffold, a structure with versatile binding properties, is widely used in medicinal chemistry. Functionalized purines are potent and selective ligands for a range of different biological targets[1-4] Our interest in the field of purine chemistry is focused on the development of new cyclin-dependent kinases inhibitors (CDKIs). Cyclin-dependent kinases (CDKs) are a class of serine-threonine kinases which play key functions in the regulation of cell cycle or apoptosis.[5] Their deregulation, and the subsequent abnormal progression of the cell cycle are observed in numerous diseases like cancer[6] or Alzheimer's disease.[7] Among the most advanced CDKIs, (*R*)-roscovitine,[8] (CYC202, or Seliciclib), a 2,6,9-trisubstitued purine (Figure 1) developed by *Cyclacel Pharmaceuticals*, is undergoing phase 2 clinical trials against non-small cell lung cancer and in pre-clinical evaluation against diabete.[9] Numerous roscovitine analogues have been described. In particular, purvalanol A, a purine bearing an aniline moiety in position 6 was found to be a highly potent CDKI.[10]



roscovitine : R^1 = benzyl; R^2 = H
purvalanol A : R^1 = 3-chlorophenyl R^2 =Me
azaroscovitine : R^1 = 3-pyridylmethyl; R^2 = H
6 : R^1 = pyridyl; R^2 = H

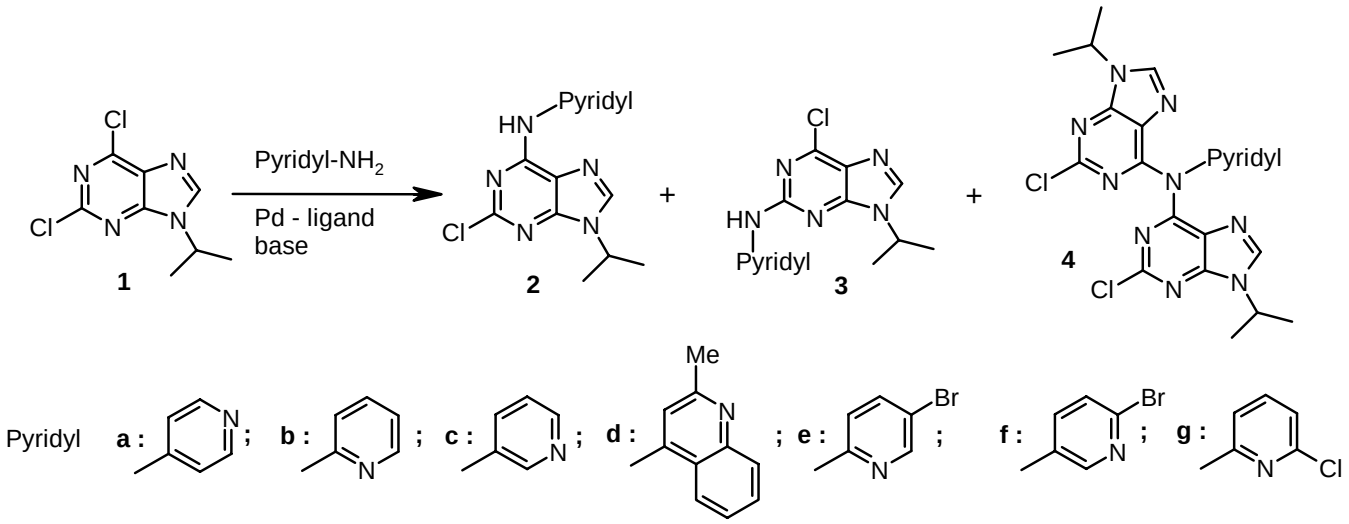
Figure 1. CDKIs and target compound **6**.

Azaroscovitine is also known and is more active than roscovitine.[11] This suggest that unknown 6-pyridylaminopurines (e.g. compound **6**, Figure 1) could display interesting biological activities. The classical amination of position 6 in 2,6-dichloropurines implies heating in *n*-butanol. Under these conditions, no reaction occurred, when 3-aminopyridine was reacted with 2,6-dichloro-9-*iso*-propylpurine **1**.

The Buchwald-Hartwig amination have seen widespread use in organic chemistry.[12-13] Conversely, very few reports are devoted to the reactivity of aryl dihalides.[14] We report the synthesis of 2-chloro-6-pyridylaminopurines using Pd catalysed amination of 2,6-dichloro-9-*iso*-propylpurine **1** and the extension of this methology to the regioselective introduction of some functionnalized aminopyridines.

RESULTS AND DISCUSSION

To test the feasibility of the proposed activation method, we first examined the propensivity of 4-aminopyridine, the less nucleophilic aminopyridine, to achieve nucleophilic substitution of the 6-chlorine in **1**. Taking into account the observation by Buchwald of the interest of palladium catalyst over copper based catalysts, with anilines,[15] a range of conditions, summarized in Table 1, were examined. Briefly, three different bases and three catalysts were experimented. The choice of the base had a significant effect on the regioselectivity of the reaction. When sodium *tert*-butoxide or Cs_2CO_3 were used, noticable amounts of the C-2 regioisomer : 6-chloro-9-*iso*propyl-2-pyridylaminopurine **3a** were formed. The combination of $Pd(OAc)_2$/BINAP catalyst system with potassium *tert*-butoxide as base was found to be the most effective (Entry 4). The use of two Pd(0) catalysts : tris(dibenzylideneacetone)dipalladium (Pd_2dba_3), and bis(dibenzylideneacetone)palladium ($Pddba_2$), instead of Pd(II) led to the formation of the triarylamine **4a**. The formation of dialkylation products have been previously reported with Pd(0) catalysts.[16] The methodology was extended to the synthesis of a range of 2-chloro-9-*iso*propyl-6-pyridylaminopurines (Entries 9-11). Interestingly, the reaction was tolerant of other halogens on the pyridine moiety (Entries 12-14). Having established a convenient protocol for coupling at the 6-position, we then turned our attention to the reactivity of some of the prepared 2-chloro-6-pyridylaminopurines.

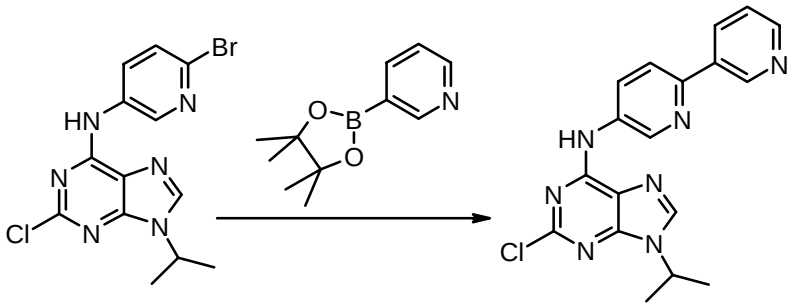


Scheme 1. Amination of dichloropurine **1**.

Table 1. Optimization studies, isolated yields are given except[a] determined by HPLC.

Entry	Conditions	**2** (Yield %)	**3** (Yield %)	**4** (Yield %)
1	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.04 equiv), *t*BuOK (1.5 equiv)	**2a**(17)		
2	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.04 equiv), *t*BuOK (4.5 equiv)	**2a** (18)	**3a** (12)	
3	$Pd(OAc)_2$ (0.08 equiv), BINAP (0.08 equiv), *t*BuONa (1.5 equiv)	**2a** (34)	**3a** (16)	
4	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2a** (73)		
5	$Pd(OAc)_2$ (0.08 equiv), BINAP (0.08 equiv), Cs_2CO_3 (1.5 equiv)	**2a** (20)	**3a** (10)	
6	Pd_2dba_3 (0.04 equiv), BINAP (0.08 equiv), *t*BuONa (1.5 equiv)	**2a** (12)		**4a** (32)
7	$Pddba_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuONa (1.5 equiv)	**2a** (5)[a]		**4a** (33)
8	Pd_2dba_3 (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2a** (3)[a]		**4a** (25)
9	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2b** (73)		
10	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2c** (76)		
11	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2d** (66)		
12	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2e** (48)		
13	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2f** (65)		
14	$Pd(OAc)_2$ (0.04 equiv), BINAP (0.08 equiv), *t*BuOK (1.5 equiv)	**2g** (42)		

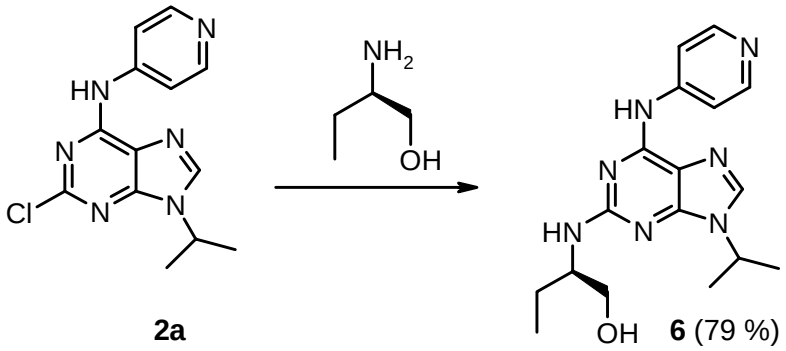
As we have observed that the bromine of 3-amino-5-bromopyridine did not interfered in the formation of **2e** it was of interest to examine, if after coupling to the purine, the halogen of **2e** was reactive. This experiment was also undertaken in view of the high antiproliferative potency observed with several biarylmethylaminopurines.[17] Therefore, the bromo derivative **2e** was reacted under Suzuki cross-coupling conditions and afforded the biarylaminopurine **5** (Scheme 2).



2e **5** (85%)

Scheme 2. *Reagents and conditions*: $Pd[P(C_6H_5)_3]_4$, Na_2CO_3, dioxane, 6 h 90 °C.

In a second experiment, the trisubstituted derivative **6** has been prepared under usual amination conditions (Scheme 3).



2a **6** (79 %)

Scheme 3. *Reagents and conditions*: NBu_3, 3 h 170 °C.

In a preliminary biological evaluation, compound **6**, was found approximatively ten-times more potent than roscovitine.

In conclusion, a convenient catalytic system for the synthesis of substituted 6-pyridylaminopurines is described. Regardless of interesting biological activity displayed by **6**, the first compound of the series,

this work describes optimized conditions which tolerated halo groups on the aminopyridine component opening the route to diversely functionnalized pyridines.

EXPERIMENTAL

Melting points were determined on a kofler hot-stage (Reichert) and are uncorrected. NMR spectra were recorded on a Bruker Avance 400 MHz (100 MHz for ^{13}C-NMR). Chemical shift are given in ppm downfield of tetramethylsilane (TMS). **2a** and **3a** were distinguished by 2D-NMR experiments (^{1}H-^{1}H Cosy**,** ^{1}H-^{1}H Noesy, ^{1}H-^{1}H Tocsy, ^{1}H-^{13}C HMQC, ^{1}H-^{13}C HSQC). Column chromatography were carried out on SDS Chromagel 60 ACC, 40-63 μm.

General procedure for amination of 1.

To a solution of 2,6-dichloro-9-*iso*-propylpurine **1**[18] (3.5 g, 15 mmol) in dry toluene (15 mL) under N_2 were added $Pd(OAc)_2$ (0.14 g, 0.6 mmol) and BINAP (0.74 g, 1.2 mmol). After 5 min stirring, *tert*-BuOK (2.50 g, 22 mmol) and aminopyridine (15 mmol) were added at 20 °C. The mixture was heated for 6 h at 100 °C, then, after cooling, diluted in CH_2Cl_2 and washed with H_2O. The organic layer was concentrated in vacuo. The residue was purified by chromatography on silica gel using AcOEt/cyclohexane 9:1 as eluent.

2-Chloro-6-(4-pyridylamino)-9-*iso*propyl-*9H*-purine (2a) : mp 164-166 °C; ^{1}H-NMR ($CDCl_3$) : δ 1.64 (d, 6H, *J* = 7.5 Hz, $(CH_3)_2CH$), 4.82 (hept, 1H, *J* = 7.5 Hz, $CH(CH_3)_2$), 7.79 (d, 2H, *J* = 8.0 Hz, H-3 pyridine), 7.94 (s, 1H, H-8), 7.97 (s, 1H, NH), 8.49 (d, 2H, *J* = 8.0 Hz, H-2 pyridine); ^{13}C-NMR: δ 23.22 ($CH(CH_3)_2$), 47.97 ($CH(CH_3)_2$), 114.08 (C-3 pyridine), 120.45 (C-5), 139.89 (C-8), 145.62 (C-4 pyridine), 151.28 (C-2 pyridine), 151.34 (C-4), 152.22 (C-6), 153.85 (C-2). ES – MS *m/z* (%) : 311 (100), 289 (82). Anal. Calcd for $C_{13}H_{13}ClN_6$: C, 54.08; H, 4.54; N, 29.11. Found: C, 53.80; H, 4.82; N, 29.34.

2-Chloro-6-(2-pyridylamino)-9-*iso*propyl-*9H*-purine (2b) : mp 160-162 °C; ^{1}H-NMR ($CDCl_3$) : δ 1.62 (d, 6H, *J* = 7 Hz, $(CH_3)_2CH$), 4.88 (hept, 1H, *J* = 7 Hz, $CH(CH_3)_2$), 7.05 (dd, 1H, *J* = 6.0, 4.0 Hz, H-3 pyridine), 7.79 (dt, 1H, *J* = 8.0, 3.0 Hz, H-5 pyridine), 7.94 (s, 1H, H-8), 8.34 (dd, 1H, *J* = 4.0, 3.0 Hz, H-4 pyridine), 8.54 (s, 1H, NH), 8.60 (d, 1H, *J* = 8.0 Hz, H-6 pyridine).^{13}C-NMR : δ 22.8, 47.3, 114.1, 119.1, 119.8, 138.3, 139.5, 148.1, 150.6, 151.4, 153.3. ES – MS m/z (%) : 313 (33), 311 (100), 289 (6). Anal. Calcd $C_{13}H_{13}ClN_6$: C, 54.08; H, 4.54; N, 29.11. Found: C, 53.77; H, 4.81; N, 28.90.

2-Chloro-6-(3-pyridylamino)-9-isopropyl-*9H*-purine (2c) : mp 146-148 °C; ^{1}H-NMR ($CDCl_3$) : δ 1.63 (d, 6H, *J* = 7 Hz, $(CH_3)_2CH$), 4.88 (hept, 1H, *J* = 7 Hz, $CH(CH_3)_2$), 7.36 (dd, 1H, *J* = 8.0, 4.0 Hz, H-5

pyridine), 7.76 (s, 1H, NH), 7.92 (s, 1H, H-8), 8.38 (dd, 1H, *J* = 4.0, 2.0 Hz, H-4 pyridine), 8.44-8.48 (m, 1H, H-2 pyridine), 8.82 (m, 1H, H-6 pyridine). ^{13}C-NMR : δ 22.6, 47.1, 113.8, 115.6, 119.7, 139.7, 140.5, 148.8, 150.3, 150.8, 151.1, 153.1. ES – MS m/z (%): 311 (100). Anal. Calcd for $C_{13}H_{13}ClN_6$: C, 54.08; H, 4.54; N, 29.11. Found: C, 53.83; H, 4.71; N, 28.98.

2-Chloro-6-(4-quinaldylamino)-9-*iso*propyl-*9H*-purine (2d) : mp 182-187 °C; ^{1}H-NMR ($CDCl_3$) : δ 1.66 (d, 6H, *J* = 6.8 Hz, $(CH_3)_2CH$), 2,81 (s, 3H, CH_3), 4.91 (hept, 1H, *J* = 6.8 Hz, $CH(CH_3)_2$), 7.57 (t, 1H, *J* = 8.1 Hz, H-6 quinaldine), 7,73 (t, 1H, *J* = 8.1 Hz, H-7 quinaldine), 7,98 (s, 1H, H-8), 8-8.1 (m, 2H, H-5 and H-8 quinaldine), 8.42 (s, 1H, NH), 8.54 (s, 1H, H-2 quinaldine); ^{13}C-NMR : δ 22.7, 29.7, 47.5, 110.9, 118.8, 119.1, 120.5, 125.6, 129.5, 129.6, 139.4, 140.4, 145.0, 148.6, 151.9, 153.5, 160.0 ES – MS m/z (%): 377 (29); 375 (100). Anal. Calcd for $C_{18}H_{17}ClN_6$: C, 61.28; H, 4.86; N, 23.82. Found: C, 60.97; H, 4.71; N, 23.97.

6-(5-Bromo-2-pyridylamino)-2-chloro-9-*iso*propyl-*9H*-purine (2e) : mp 217-220 °C; ^{1}H NMR ($CDCl_3$) : δ 1.62 (d, 6H, *J* = 6.8 Hz, $(CH_3)_2CH$), 4.87 (s, 1H, *J* = 6.8 Hz $CH(CH_3)_2$), 7.52 (d, 1H, *J* = 8.5 Hz, H-3 pyridine), 7.92 (s, 1H, H-8 purine), 7.97 (s, 1H, NH), 8.35 (dd, 1H, *J* = 8.5, 2.8 Hz H-4 pyridine), 8,65 (d, 1H, *J* = 2.8 Hz, H-6 pyridine). ^{13}C-NMR : δ 22.7, 47.3, 113.9, 115.3, 139.3, 140.6, 148.8, 150.1, 150.7, 151.0. ES – MS m/z (%): 389 (95); 391 (100). Anal. Calcd for $C_{13}H_{12}BrClN_6$: C 42.47; H, 3.29; N, 22.86. Found C 42.32; H, 3.04; N, 22.71.

6-(6-Bromo-3-pyridylamino)-2-chloro-9-*iso*propyl-*9H*-purine (2f) : mp 167-169 °C; ^{1}H NMR ($CDCl_3$) : δ 1,62 (d, 6H, *J* = 6.8 Hz, $(CH_3)_2CH$), 4,87 (hept, 1H, *J* = 6.8 Hz, $CH(CH_3)_2$), 7.87 (dd, 1H, *J* = 8.8, 2.3 Hz, H-4 pyridine), 7.94 (s, 1H, *H*-8 purine), 8.37 (d, 1H, *J* = 2.3 Hz, H-2 pyridine), 8,48 (s, 1H, N*H*), 8,55 (d, 1H, *J* = 8.8 Hz, H-5 pyridine). ^{13}C-NMR : δ 22.8, 47.3, 113.9, 115.6, 119.7, 139.8, 140.6, 148.7, 150.2, 150.7, 151.2, 153.2. ES – MS m/z (%): 389 (84); 391 (100). Anal. Calcd for $C_{13}H_{12}BrClN_6$: C 42.47; H, 3.29; N, 22.86. Found C 42.29; H, 3.11; N, 22.65.

6-Chloro-2-(6-chloro-2-pyridylamino)-9-*iso*propyl-*9H*-purine (2g) : mp 147-149 °C; ^{1}H NMR ($CDCl_3$) : δ 1,64 (d, 6H, *J* = 6.8 Hz, $(CH_3)_2CH$), 4,86 (hept, 1H, *J* = 6.8 Hz, C*H*$(CH_3)_2$), 7.1 (d, 1H, *J* = 8.1 Hz, H-3 pyridine), 7,74 (t, 1H, *J* = 8.1 Hz, H-4 pyridine), 8.14 (s, 1H, H-8), 8,5 (d, 1H, *J* = 8.1 Hz, H-5 pyridine). ^{13}C-NMR : 27.6, 47.4, 109.1; 112.3; 139.4; 140.5; 148.5; 150.3; 152.3; 159.1. ES – MS m/z (%): 345 (100). Anal. Calcd for $C_{13}H_{12}Cl_2N_6$: C, 48.31; H, 3.74; N, 26.00. Found: 48.11; H, 3.85; N, 25.75.

6-Chloro-2-(4-pyridylamino)-9-*iso*propyl-*9H*-purine (3a) : mp 132-136 °C; ^{1}H NMR ($CDCl_3$) : δ 1.65 (d, 6H, *J* = 8 Hz, $(CH_3)_2CH$), 4.79 (hept, 1H, *J* = 8 Hz, $CH(CH_3)_2$), 7.65 (d, 2H, *J* = 8 Hz, H-3 + H-5 pyridine), 7.81 (s, 1H, H-8), 8.47 (d, 2H, *J* = 8 Hz, H-2 and H-6 pyridine); ^{13}C NMR : δ 22.5, 47.2, 112.2, 138.1, 146.9, 150.2, 152.6, 154.2. ES – MS m/z (%) : 313 (22), 311 (100) Anal. Calcd for $C_{13}H_{13}ClN_6$: C, 54.08; H, 4.54; N, 29.11. Found: C, 53.77; H, 4.67; N, 29.44.

***N,N*-Di(2-chloro-9-*iso*propyl-*9H*-purin-6-yl)-4-aminopyridine(4a) :** Mp> 260 °C; ^{1}H NMR ($CDCl_3$) : δ 1.62 (d, 6H, *J* = 6.8 Hz, $(CH_3)_2CH$), 1.66 (d, 6H, *J* = 6.8 Hz, CH_3-CH_2-), 4.89 (hept, 1H, *J* = 8 Hz, -$CH(CH_3)_2$), 4.97 (hept, 1H, *J* = 8 Hz, $CH(CH_3)_2$), 7.17 (d, 2H, *J* = 8 Hz, *H*-3 and H-5 pyridine), 7.97(s, 1H, H-8), 8.14 (s, 1H, H-8), 9.26(d, 2H, *J* = 8 Hz, H-2 and H-6 pyridine); ^{13}C-NMR: δ 22.5, 22.7, 46.9, 48.1, 121.5, 125.8, 134.2, 139.9, 142.2, 147.8, 132.7, 152.9, 153.5, 155.3, 160.4. ES – MS m/z (%) : 521 (6), 507 (62), 505 (100), 485 (8), 483 (12). Anal. Calcd for $C_{21}H_{20}Cl_2N_{10}$: C, 52.18; H, 4.17; N, 28.98. Found: C, 52.03; H, 4.38; N; 28.67.

2-Chloro-6-[6-(3-pyridyl)pyrid-3-ylamino]-9-*iso*propyl-*9H*-purine (5): To a solution **2e** (0.36 g, 0.98 mmol) in dioxane (8 mL) and Na_2CO_3 1M (4 mL) $Pd(PPh_3)_4$ (0.052 g, 0.048 mmol) was added, under N_2. After 5 min, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.20 g 1 mmol) was added. The mixture was heated 6 h at 90 °C, then concentrated in vacuo to half of its initial volume. After addition of H_2O (10 mL), the mixture was extracted with CH_2Cl_2. The organic layer was dried and evaporated. The residue was purified by chromatography on silica gel using a 96:4 CH_2Cl_2-CH_3OH eluent. Mp 205-210 °C; ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 6H, *J* = 7.1 Hz $(CH_3)_2CH$); 4.82 (hept, 1H, *J* = 7.1 Hz $CH(CH_3)_2$), 7.42 (d, 1H, *J* = 8 Hz, H-3'pyridine), 7.65 (s, 1H, H-8), 7.84(d, 1H, *J* = 8 Hz, H-5 pyridine), 8.14 (s, 1H, NH), 8,34 (m, 1H, H-4' pyridine), 8,85 (s, 1H, H-2 pyridine), 9.12 (d, 1H, *J* = 8 Hz, H-6' pyridine), 9.22 (s, 1H, H-2' pyridine); ^{13}C-NMR δ 23.06 ($CH(CH_3)_2$); 47.83 ($CH(CH_3)_2$); 120.08 (C-5); 120.93 (C-5 pyridine); 123.96(C-3' pyridine); 134.63 (C-5); 139.45 (C-8) 141.91(C-4 pyridine); 148.27 (C-2' pyridine) 149.84 (C-2 pyridine); 150.89 (C-4); 152.15 (C-2). ES – MS m/z (%) 368 (33); 366(100). Anal. Calcd for $C_{18}H_{16}ClN_7$: C, 59.10; H, 4.41; N, 26.80. Found: C, 59.36; H, 4.21; N 26.65.

(2R)-2-(1-Hydroxybut-2-ylamino)-6-(2-pyridylamino)-9-*iso*propyl-*9H*-purine (6). A solution of **2a** (0.144 g, 0.5 mmol) in tributylamine (0.5 mL) and (*R*)-2-aminobutan-1-ol (0.2 g, 2.2 mmol) was heated at 170 °C for 3 h. After cooling to rt, 5 mL H_2O were added and the mixture was extracted (CH_2Cl_2, 3x 5 mL) and concentrated in vacuo. The residue was purified by chromatography on silica gel using a 96:4 CH_2Cl_2-CH_3OH eluent. Compound **6** was washed with Et_2O and isolated as a white powder: mp

95-98 °C; ^{1}H-NMR ($CDCl_3$) : δ 1.07 (t, 3H, *J* = 5.7 Hz, CH_3CH_2), 1.58 (d, 6H, *J* = 7.5 Hz, $(CH_3)_2CH$), 1.63-1.80 (m, 2H, CH_3CH_2), 3.71 (m, 1H, CH_2OH), 3.87 (m, 1H, CH_2OH), 4.01 (m, 1H, CHNH), 4.66 (hept, 1H, *J* = 7.5 Hz, $CH(CH_3)_2$), 5.06 (d, 1H, *J* = 7.4 Hz, NHCH), 7.63 (s, 1H, H-8),7.73 (d, 2H, *J* = 6.0 Hz, H-3 and H-5 pyridine), 8.49 (d, 2H, *J* = 6.0 Hz, H-2 and H-6 pyridine); ^{13}C-NMR: δ (ppm) 10.9, 22.3, 24.9, 46.9, 55.7, 66.3, 113.4, 115.3, 135.8, 147.0, 149.3, 151.5, 159.2. ES – MS m/z (%): 342 (100). Anal. Calcd for $C_{17}H_{23}N_7O$: C, 59.81; H, 6.79; N, 28.72. Found: C, 59.67; H, 6.89; N, 28.57.

Evaluation of 6. IC_{50} determined[8b] for CDK1 and CDK5 were 50 nM and 22 nM compared to roscovitine : 500 nM and 160 nM respectively.

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