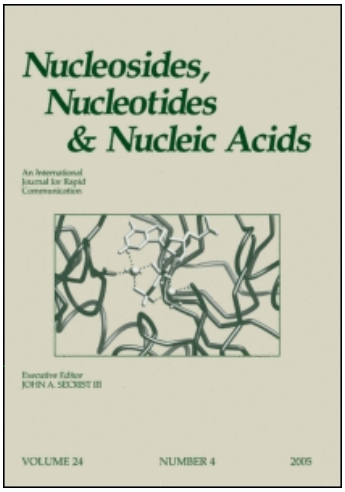

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF NEW CARBAACYCLONUCLEOSIDES AND 1'-OXAACYCLONUCLEOSIDES RELATED TO CLITOCINE

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Abstract :

We describe the synthesis of two series of acyclonucleosides : carbaacyclonucleosides and 1'-oxaacyclonucleosides which possess the same aglycone as clitocine **3** which is a natural nucleoside exhibiting interesting biological properties. These compounds have been obtained by condensation of 4-aminobutanol or 3-silyloxypropoxyamine with 4,6-dichloro-5-nitropyrimidine. Structural modifications have been made on the heterocyclic base and the side chain to enhance their potential activity.

All these compounds have been tested against different viruses : HIV-1, HSV-1, HSV-2, CMV, VZV, EBV. The carbaacyclonucleoside **10** was associated with an anti-EBV activity (EC_{50} = 0.86 μg/mL).

Introduction :

Following the discovery of antiherpetic properties of acyclovir (Figure 1), the structure-activity relationship for this class of compounds has been extensively studied. The studies include the modification of the heterocyclic base and/or the acyclic side chain.[1,2] Among them, HBG, 9-(4-hydroxybutyl)guanine **4**, is an antiviral agent and can be defined as a carbo analog of acyclovir. HBG was found to be a good inhibitor of herpes virus multiplication[3,4] and is the only active compound in the series with homologous hydroxy alkyl side chains. The isoster of acyclovir, 9-(3-hydroxypropoxy)guanine **2**, with oxygen bound directly to the N^9 position of purine, is 2 to 3 times more active than acyclovir against HSV-1 and HSV-2 and 4 to 5 times more active against VZV.[5-8] A significant activity against Epstein-Barr virus (EBV) has been also reported.[5,6,8]

Clitocine **3** is a natural exocyclic nucleoside isolated from the mushroom *Clitocybe Inversa*. It has been shown to possess strong insecticidal activity and potent cytostatic effects against several leukemia cell lines through inhibition of adenosine kinase.[9,10]

The biological properties of clitocine prompted us to prepare new acyclic nucleoside analogs : carba and 1'-oxaacyclonucleosides which possess the same aglycone as clitocine and the same side chain as HBG **4** and the isoster of acyclovir **2**. Structural modifications of the side chain and pyrimidine ring have been performed.

Some phosphonomethoxyalkyl derivatives of heterocyclic bases exhibit significant antiviral properties *in vivo*. The well-known compounds, such as PMEA[11,12], PMPA[13,14], HPMPC [15] were found to strongly inhibit DNA viruses and retroviruses.[16-20] The structure-activity of these compounds showed that the presence of an amino group on the purine moiety is necessary for the antiviral activity.[21] However, high antiviral activity has been described against herpesviruses in the series of N^6-mono and disubstituted adenine and 2,6-diaminopurine derivatives[22-24] which bear at the N^9 position either 2-phosphonomethoxyethyl or 2-phosphonomethoxypropyl residues. Among them, N-imidazolyl and N-cyclopropylamino derivatives were synthesized and several still exert certain activity against strains of VZV, HSV and MSV viruses. In the series of carbocyclic compounds, carbovir bearing N^6-cyclopropylamino (abacavir)[25] maximized anti-HIV potency and improved oral bioavailability.

In order to study the role of the amino function in the antiviral activity for this class of compounds the carbaanalogues bearing N^6-cyclopropylamino and N^6-(2'-imidazolyl) function were prepared. Among the carbocyclic series prepared in our laboratory, protection of hydroxymethyl group by *tert*-butyldimethylsilyl chloride or trityl chloride enhanced antiviral

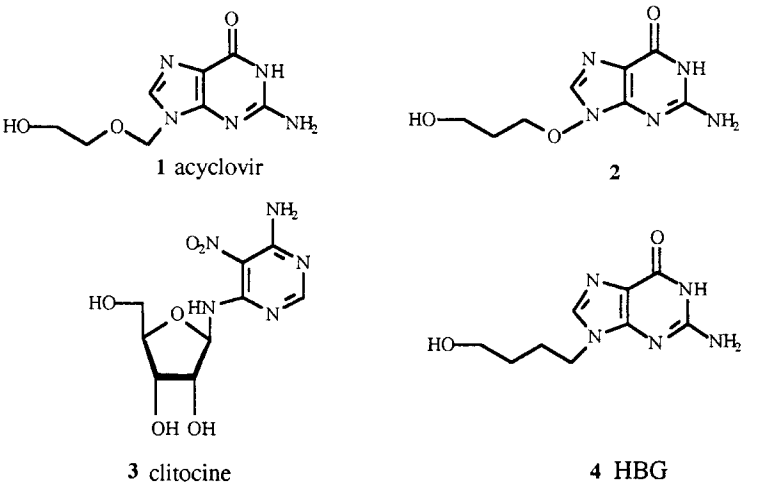


Figure 1 : Structure of acyclonucleosides and clitocine.

activity against strains of HCMV viruses.[26] The synthesis of pivaloyl derivatives was based on the bis(POM)PMEA[27] prodrugs.

Results and Discussion

Synthesis of N-hydroxybutylaminepyrimidine derivatives

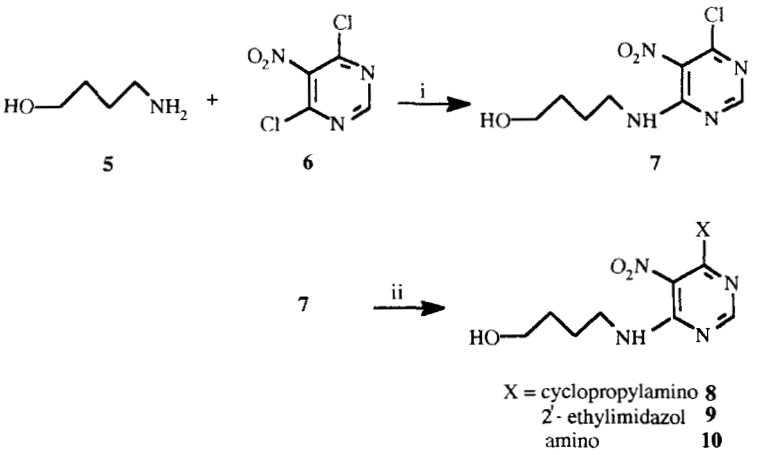
The 4-aminobutanol side chain was condensed with 4,6-dichloro-5-nitropyrimidine in the presence of triethylamine in 40% yield.[28]

Other compounds which were used in this study comprise structural alterations at the heterocyclic base, in order to increase their antiviral activity : N^6-cyclopropylamino and N^6-(2'-ethylimidazolyl) derivatives of pyrimidine (scheme 1). Alkylation of 6-chloropyrimidine **7** with 5 equivalents of cyclopropylamine[29,30] or 2-ethylimidazol,[31] afforded compounds **8** and **9** in 70% and 50% yield, respectively. Treatment of **7** with methanolic ammonia gave the aminopyrimidine **10** (80%).

Reaction of the hydroxyl group of the chlorocompound **7** with silyl, trityl or pivaloyl chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) gave **11-13** in 70-95% yield (scheme 2). These derivatives were then converted into N^6-derivatives **14-22** in 50-80% yield.

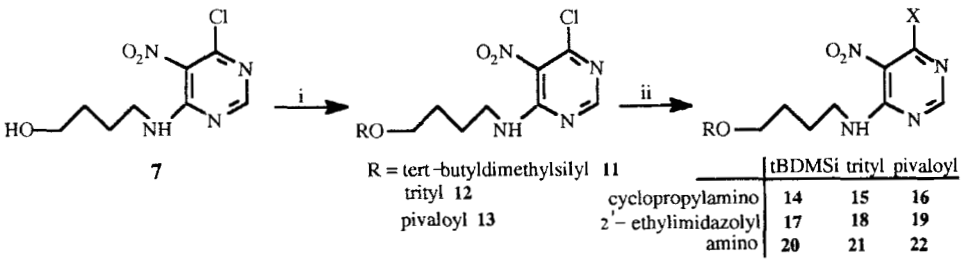
Synthesis of 3-hydroxypropoxyaminepyrimidine derivatives

The 6-propoxy derivative of pyrimidine **24** was obtained in 40% yield by the condensation with 3-[(*tert*-butyldimethylsilyl)oxy]propoxyamine[6] **23** and 4,6-dichloro-5-nitropyrimidine **7** in the presence of N-methylmorpholine (scheme 3). The use of other bases



i) CH_2Cl_2, Et_3N, r.t., 4 h ; ii) CH_2Cl_2, XH, r.t.

Scheme 1 : Synthesis of carbaacyclonucleosides.



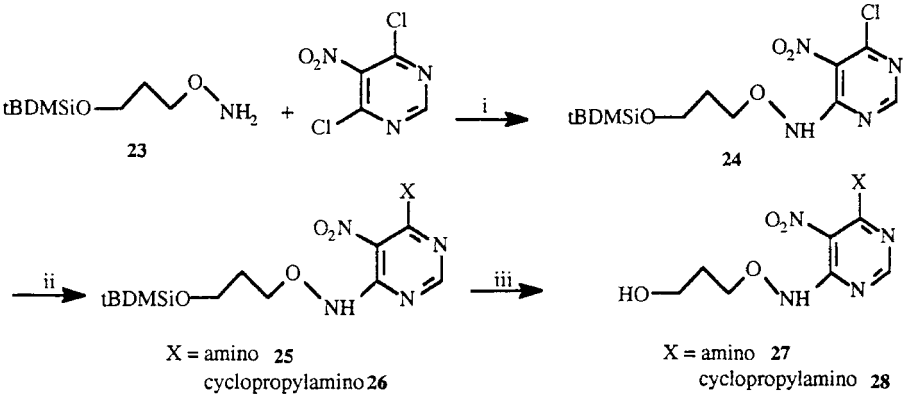
i) TBDMSiCl or TrtCl, CH_2Cl_2, Et_3N, DMAP or PivCl, CH_2Cl_2, Et_3N ; ii) XH, CH_2Cl_2.

Scheme 2 : Synthesis of protected carba acyclonucleosides.

such as Et_3N induced a lot of byproducts. The acyclonucleoside was then converted to its amino and cyclopropylamino form, in 50 and 61% yield respectively. Removal of the silyl group by acid hydrolysis provided quantitative yields of compounds **27** and **28**[32].

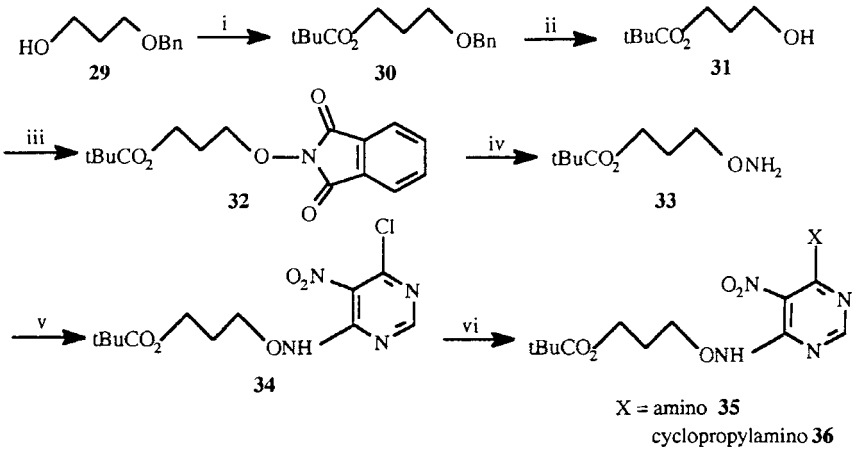
Synthesis of 3'-pivaloyloxypropoxypyrimidine derivatives

3-Benzyloxypropanol **29** was converted by reaction with pivaloylchloride and triethylamine to its acyl derivatives **30** in 60% yield (scheme 4). The catalytic hydrogenation of **30** over Pd/C 10% afforded **31** in 75% yield. Reaction of the alcohol **31** with N-hydroxyphtalimide under Mitsunobu conditions, followed by cleavage of the resultant N-



i) NMM, CH_2Cl_2 ; ii) MeOH/NH_3 or cyclopropylamine, CH_2Cl_2 ; iii) EtOH/HCl 1%

Scheme 3 : Synthesis of 1'-oxa acyclonucleosides.



.i) PivCl, Et_3N, CH_2Cl_2 ; ii) H_2, Pd/C, MeOH ; iii) PPh_3, DEAD, N-hydroxyphtalimide ; iv) NH_2NH_2, EtOH ; v) NMM, CH_2Cl_2, 4,6-dichloro-5-nitropyrimidine; vi) MeOH/NH_3 or cyclopropylamine, CH_2Cl_2

Scheme 4 : Synthesis of 3'-pivaloyloxaacyclonucleosides.

alkoxyphtalimide **32** with hydrazine monohydrate in ethanol at reflux temperature gave alkoxyamine **33** in 90% yield. A reaction of **33** with 4,6-dichloro-5-nitropyrimidine, in the presence of NMM, in dichloromethane afforded **34** in 30% yield. Amination of **34** with methanolic ammonia and cyclopropylamine in dichloromethane then gave **35** and **36** in 50% and 70% yield, respectively.

Biological results :

Acyclonucleosides **7-22** prepared in this study were evaluated against viruses HCMV, VZV, HSV-1, HSV-2, EBV, HIV *in vitro,* using different cell lines. The activity of the compounds against HSV-1, HSV-2, VZV and HCMV was determined in plaque reduction assays[33] and HIV-1 following a colorimetric assay.[34] Human Foreskin Fibroblast (HFF) cells were used for HSV, HCMV, VZV ; Daudi cells were used for EBV (activity is determined by expressing Viral Capsid Antigen) ; and human T4 cell line infected with HTLV-1 (MT4) were used for HIV. None of the compounds showed any anti-HIV activity. The trityl and N^6-imidazolyl derivatives were found to be inactive against HIV, herpes viruses and found to be very toxic. Compounds **8, 10, 16** showed anti-EBV activity : EC_{50} = 0.86 μg/mL (CC_{50} > 50 μg/mL), EC_{50} = 6.6 μg/mL (CC_{50} > 50 μg/mL), EC_{50} = 6.4 μg/mL (CC_{50} > 50 μg/mL) respectively (EC_{50} = 0.8-1 μg/mL for acyclovir). None of the modifications at the heterocyclic base and the side chain had enhanced antiviral activity of the compound **10**.

The second series of compounds, has been tested against HCMV, VZV, HSV-1, HSV-2, EBV, HIV-1 under the same conditions as for the carbaacyclonucleosides. All of them are found to be inactive.

Experimental section :

General Chemical Procedure : Solvents and chemicals were reagent grade and were used without further purification. Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured on a Brücker 200 NMR spectrometer in $CDCl_3$; all values are reported in parts per million (δ) from $(CH_3)_4Si$ unless otherwise stated. Mass measurements were carried out on INCOS 500 E FINNIGAN MAT (EI, 70eV, direct introduction) and TSQ 7000 FINNIGAN MAT (ESI / MS) instruments. Analytical thin-layer chromatography (TLC) was carried out with Merck silica gel 60 F-254 glass backed plates. All chromatographic purifications were carried out on Merck silica gel 60. High-performance liquid chromatography (HPLC) was performed on a Merck gradient liquid chromatograph with an UV wavelength detector set at 254 nm. Reactions were routinely monitored by TLC, ^1H NMR and purities were determined using a Merck HPLC and a C-18 reverse phase column (Lichrospher, 250x4 mm). Elemental analyses were performed by CNRS, Vernaison-France.

4-Chloro-6-[*N*-(4'-hydroxybutyl)amino]-5-nitropyrimidine (7) 783 mg (4.04 mmol) of 4,6-dichloro-5-nitropyrimidine were dissolved in 10 mL of anhydrous dichloromethane, 0.46 mL (4.04 mmol) of triethylamine were added at 0°C then 300 mg (3.36 mmol) of 4-

aminobutanol were added. The mixture was stirred for 5h, filtered over celite and the filtrate was dried under reduced pressure without heating. The residue was purified by column chromatography (n-hexane-EtOAc, 0-30%) to give 500 mg of **7** as a yellow solid (60.4%). Recrystallization from dichloromethane-n-hexane mixture gave the pure compound.
mp 82°C - 83°C, Rf 0.26 (n-hexane-EtOAc, 6 : 4), ^{1}H NMR δ ($CDCl_3$) : 8.32 (s, 1H, 2-**H**) ; 7.69 (broad s, 1H, N**H**) ; 4.45 (1H, O**H**, D_2O exchangeable) ; 3.71-3.55 (m, 4H, 1'-CH_2, 4'-CH_2) ; 1.75-1.57 (m, 4H, 2'-CH_2, 3'-CH_2), ^{13}C NMR δ ($CDCl_3$) : 160.0 (C_2) ; 62.3 ($C_{4'}$) ; 41.9 ($C_{1'}$) ; 29.6 ($C_{3'}$) ; 27.7 ($C_{2'}$) ; MS (ESI+) (m/z) 247 $(M+H)^+$, HPLC: Rt = 10.10 min (0.5 mL/min, CH_3CN-H_2O, 30 : 70).

4-(Cyclopropylamino)-6-[*N*-(4'-hydroxybutyl)amino]-5-nitropyrimidine (8) 50 mg (0.20 mmol) of 7 were dissolved in 3 mL of dichloromethane, cyclopropylamine (1.01 mmol) was then added at 0°C. The mixture was stirred at room temperature for 3h. Removal of the cyclopropylamine and the solvent followed by column chromatography of the residue (EtOAc) gave the compound in 70% yield (40 mg). Recrystallization from CH_2Cl_2-n-hexane mixture gave the analytical compound **8**. mp 74°C - 75°C, Rf 0.4 (EtOAc), ^{1}H NMR : δ ($CDCl_3$) : 9.32 (broad s, 1H, N**H**) ; 9.19 (broad s, 1H, N**H**) ; 8.12 (s, 1H, 2-H) ; 4.51 (1H, O**H**, D_2O exchangeable) ; 3.70-3.55 (m, 4H, 1'-CH_2, 4'-CH_2) ; 3.06-3.01 (m, 1H, C**H** cyclopropyl) ; 1.70-1.59 (m, 4H, 2'-CH_2, 3'- CH_2) ; 1.06-0.96 (m, 2H, 2 x C**H** cyclopropyl) ; 0.77-0.71 (m, 2H, 2 x C**H** cyclopropyl) ; ^{13}C NMR, δ ($CDCl_3$) : 160.0 (C_2) ; 62.5 ($C_{4'}$) ; 41.4 ($C_{1'}$) ; 29.8 ($C_{3'}$) ; 26.0 ($C_{2'}$) ; 24.8 (CH cyclopropyl) ; 7.5 (2 x CH_2 cyclopropyl) ; MS (ESI+) (m/z)268 (M+H)+ ; HPLC: Rt = 26.8 min (0.5 mL/min ; CH_3CN-H_2O, 20 :80) and Rt = 9.72 min (0.5 mL/min ; CH_3CN-H_2O, 30 : 70). Anal. Calcd. for ($C_{11}H_{17}O_3N_5$) : C 49.44%, H 6.37%, N 26.22%, found : C 49.30%, H 6.45%, N 26.74%.

4-(2'-Ethylimidazolyl)-6-[*N*-(4'-hydroxybutyl)amino]-nitropyrimidine (9) A mixture of 100 mg (0.4 mmol) of 7 and 194 mg (2.02 mmol) of 2-ethylimidazole in 5 mL of dichloromethane was stirred at room temperature for 48 h. The solution was then concentrated under reduced pressure and the analytical compound was obtained after purification by column chromatography (EtOAc) in 50% yield and recrystallisation from diethylether. mp 95-96°C ; Rf 0.36 (AcOEt) ; ^{1}H NMR : ($CDCl_3$) : 8.50 (s, 1H, 2-H) ; 7.89 (broad s, 1H, N**H**) ; 6.99-6.98 (d, 1H, C**H** EtIm ethylenic, ^3J = 1.72 Hz) ; 6.81-6.80 (d, 1H, C**H** EtIm ethylenic, ^3J = 1.72 Hz) ; 4.85 (1H, OH, D_2O exchangeable) ; 3.71-3.61 (m, 4H, 1'-CH_2, 4'-CH_2) ; 2.76-2.64 (q, 2H, CH_2CH_3 EtIM, ^3J = 7.63 Hz) ; 1.76-1.60 (m, 4H, 2'-CH_2, 3'-CH_2) ; 1.26-1.18 (t, 3H, CH_2CH_3, ^3J = 7.5 Hz) ;^{13}C NMR : δ ($CDCl_3$) : 172.9 (C, EtIm) ; 159.4 (C_2) ; 129.4 (C

ethylenic) ; 118.5 (C ethylenic) ; 62.3 ($C_{4'}$) ; 42.1 ($C_{1'}$) ; 29.8 ($C_{3'}$) ; 25.9 ($C_{2'}$) ; 21.1 (CH_3CH_2) ; 12.1 (CH_3CH_2) ; MS (ESI+) (m/z) 307 $(M+H)^+$, HPLC: Rt = 8.65 min (0.5 mL/min ; CH_3CN-H_2O, 30 : 70). Anal. Calcd. for ($C_{13}H_{18}O_3N_6$) : C 50.98%, H 5.88%, N 27.47%, found : C 50.61%, H 5.75%, N 27.30%.

4-Amino-6-[*N*-(4'-hydroxybutyl)amino]-5-nitropyrimidine (10) A solution of 100 mg (0.4 mmol) of **7** and NH_3-MeOH 2.0 M (0.8 mmol) in anhydrous MeOH was stirred under N_2 at room temperature for 18 h. The solution was then concentrated under reduced pressure and the residue purified by column chromatography (MeOH in EtOAc 0-2%) to give 70 mg of **10**, (77% yield) as a white powder. Recrystallization from MeOH gave the analytical product. mp 153-154 °C, Rf 0.29 (EtOAc), ^{1}H NMR : δ ($DMSOd_6$) : 9.41-9.35 (broad t, 1H, N**H**-CH_2, *J* = 5.4 Hz) ; 8.64-8.58 (broad d, 2H, 2 N**H**$_2$) ; 8.03 (s, 1H, 2-H) ; 4.52-4.47 (t, 1H, O**H**, *J* = 5.15 Hz, D_2O exchangeable) ; 3.64-3.54 (q, 2H, 4'-C**H**$_2$, *J* = 6.56 Hz) ; 3.51-3.43 (q, 2H, 1'-C**H**$_2$, *J* = 5.69 Hz) ; 1.70-1.59 (q, 2H, 3'-C**H**$_2$, *J* = 7.22 Hz) ; 1.57-1.43 (q, 2H, 2'-C**H**$_2$, *J* = 6.62 Hz) ; ^{13}C NMR δ (DMSO) : 159.16 (C_2) ; 60.11 ($C_{4'}$) ; 40.43 ($C_{1'}$) ; 29.49 ($C_{3'}$) ; 25.20 ($C_{2'}$) ; MS (ESI+) (m/z) 228 $(M+H)^+$; HPLC: Rt = 14.48 min (0.4 mL/min, MeOH-H_2O, 30 :70). Anal. Calcd. for ($C_8H_{13}O_3N_5$) : C 42.29%, H 5.73%, N 30.84%, found : C 42.21%, H 5.71%, N 30.53%.

4-Chloro-6-[*N*-(4'-*tert*-butyldimethylsilyloxybutyl)amino]-5-nitropyrimidine (11)
A solution of 200 mg (0.81 mmol) of **7** and 146.5 mg (0.97 mmol) of *tert*-butyldimethylsilyl chloride in anhydrous CH_2Cl_2 was stirred at 0°C. 0.3 mL (0.97 mmol) of triethylamine was then added with 4 mg (0.032 mmol) of DMAP. The mixture was stirred at room temperature for 8h. The mixture was worked up in the usual way, the residue was purified by column chromatography (CH_2Cl_2) to give 225 mg of **11** (77%) as a brown oil. Rf 0.29 (CH_2Cl_2) ; ^{1}H NMR : δ ($CDCl_3$) : 8.32 (s, 1H, 2-H) ; 7.57 (broad s, 1H, N**H**) ; 3.65-3.55 (m, 4H, 1'-C**H**$_2$, 4'-C**H**$_2$) ; 1.76-1.61 (m, 2H, 3'-C**H**$_2$) ; 1.60-1.48 (m, 2H, 2'-C**H**$_2$) ; 0.83 (s, 9H, tBu) ; ^{13}C NMR ($CDCl_3$) : 158.1 (C_2) ; 62.6 ($C_{4'}$) ; 42.0 ($C_{1'}$) ; 29.9 ($C_{3'}$) ; 26.0 (3 x **C**H_3, tBu) ; 25.9 ($C_{2'}$) ; -5.3 ($Si(CH_3)_2$) ; MS (ESI-) (m/z) 359 $(M-H)^-$; HPLC: Rt = 19.64 min (0.5 mL/min, CH_3CN-H_2O, 80 : 20).

4-Chloro-6-[*N*-(4'-triphenylmethyloxybutyl)amino]-5-nitropyrimidine (12) A solution of 200 mg (0.81 mmol) of **7** and 340 mg (1.22 mmol) of triphenylmethyl chloride, in anhydrous CH_2Cl_2 was stirred at 0°C. 0.3 mL (2 mmol) of triethylamine and 4 mg (0.03 mmol) of DMAP were then added and stirred at room temperature for 18h. After the usual work up, a

column chromatography (n-hexane-CH_2Cl_2, 2 : 8) gave **12** which was recrystallized from the mixture of CH_3CN-H_2O to give the analytical compound. mp 112-113°C ; Rf 0.56 (CH_2Cl_2) ; ^{1}H NMR, δ ($CDCl_3$) : 8.27 (s, 1H, 2-H) ; 7.50 (broad s, 1H, N**H**) ; 7.38-7.15 (m, 15H, trityl) ; 3.64-3.54 (q, 2H, 4'-C**H**$_2$, ^3J = 6.43 Hz) ; 3.16-3.10 (t, 2H, 1'-C**H**$_2$, ^3J = 5.82 Hz) ; 1.93-1.64 (m, 4H, 2'-C**H**$_2$, 3'-C**H**$_2$) ; ^{13}C NMR : δ ($CDCl_3$) : 158.1 (C_2) ; 144.3 (**C** quat, trityl) ; 128.7 (C meta, trityl) ; 127.8 (**C** ortho, trityl) ; 127.1 (**C** para, trityl) ; 62.9 ($C_{4'}$) ; 42.00 ($C_{1'}$) ; 27.3 ($C_{3'}$) ; 26.2 ($C_{2'}$) ; MS (ESI-) (m/z) 487 $(M-H)^-$; HPLC: Rt = 22.88 min (0.5 mL/min ; CH_3CN-H_2O, 80 : 20).

4-Chloro-6-[*N*-(4'-trimethylacetyloxybutyl)amino]-5-nitropyrimidine (13) 200 mg (0.81 mmol) of **31** were dissolved in 5 mL of CH_2Cl_2 at 0°C. 0.3 mL (2 mmol) of triethylamine and 0.2 mL (1.6 mmol) of pivaloyl chloride were then added. The mixture was stirred for 2 h and after usual treatment purified by column chromatography (n-hexane-EtOAc 9 : 1) to yield **13** as an oil in 75-95% yield. Rf 0.71 (n-hexane-EtOAc, 6 : 4) ; ^{1}H NMR, δ ($CDCl_3$): 8.32 (s, 1H, 2-H) ; 7.56 (broad s, 1H, N**H**) ; 4.07-4.01 (broad t, 2H, 4'-C**H**$_2$, ^3J = 5.93 Hz) ; 3.64-3.55 (broad q, 2H, 1'-C**H**$_2$, ^3J = 6.48 Hz) ; 1.71-1.64 (m, 4H, 2'-C**H**$_2$, 3'-C**H**$_2$) ; 1.13 (s, 9H, tBu) ; ^{13}C NMR, δ ($CDCl_3$) : 172.9 (**C**=O) ; 158.2 (C_2) ; 63.7 ($C_{4'}$) ; 41.79 ($C_{1'}$) ; 27.3 (3 x **C**H$_3$, tBu) ; 26.2 ($C_{3'}$) ; 25.9 ($C_{2'}$) ; HPLC: Rt = 11.74 min (0.7 mL/min ; CH_3CN-H_2O, 60 : 40).

4-(Cyclopropylamino)-6-[*N*-(4'-*tert*-butyldimethylsilyloxybutyl)amino]-5-nitro pyrimidine (14) 100 mg (0.28 mmol) of **11** were dissolved in 5 mL of dichloromethane. 0.1 mL (1.51 mmol) of cyclopropylamine was then added at 0°C. The mixture was stirred at room temperature for 3h. Removal of the cyclopropylamine and the solvent followed by column chromatography (n-hexane-EtOAc, 9 : 1) gave compound **14** in 60% yield as an amorphous solid. Rf 0.59 (n-hexane/EtOAc, 6 : 4) ; ^{1}H NMR δ ($CDCl_3$) : 9.22 (broad d, 2H, N**H**$_2$) ; 8.14 (s, 1H, 2-H), 3.63-3.54 (m, 4H, 1'-C**H**$_2$,4'-C**H**$_2$) ; 3.11-2.98 (m, 1H, C**H** cyclopropyl) ; 1.73-1.52 (m, 4H, 2'-C**H**$_2$, 3'-C**H**$_2$) ; 0.96-0.82 (m, 2H, 2 x C**H** cyclopropyl) ; 0.66-0.58 (m, 2H, 2 x C**H** cyclopropyl) ; 0.86 (s, 9H, tBu) ; ^{13}C NMR, δ ($CDCl_3$) : 159.9 (C_2) ; 62.7 ($C_{4'}$) ; 41.6 ($C_{1'}$) ; 30.2 ($C_{3'}$) ; 26.1 (3 x **C**H$_3$, tBu) ; 26.0 ($C_{2'}$) ; 7.4 (2 x **C**H$_2$ cyclopropyl) ; 24.7 (**C**H cyclopropyl) ; MS (ESI+) (m/z) 382 $(M+H)^+$; HPLC: Rt = 10.43 min (1 mL/min ; CH_3CN-H_2O, 80 : 20). Anal. Calcd. for ($C_{17}H_{31}O_3N_5Si$) : C 53.54%, H 8.14%, N 18.37%, found : C 53.43%, H 8.09%, N 18.25%.

4-(Cyclopropylamino)-6-[*N*-(4'-triphenylmethyloxybutyl)amino]-5-nitropyrimidine (15) 100 mg (0.2 mmol) of **12** were dissolved in 5 mL of acetonitrile. 70 µL (1.02 mmol) of

cyclopropylamine were then added at 0°C. The mixture was stirred at room temperature for 3h. Removal of the cyclopropylamine and the solvent followed by column chromatography of the residue (CH_2Cl_2) gave compound **15**. Recrystallization from the mixture diethylether-n-hexane gave the analytical compound in 50% yield. mp 134-135°C ; Rf 0.36 (CH_2Cl_2) ; ^{1}H NMR, δ ($CDCl_3$) : 9.20 (broad d, 2H, 2 x N**H**) ; 8.10 (s, 1H, 2-**H**) ; 7.39-7.14 (m, 15H, trityl) ; 3.56-3.47 (q, 2H, 4'-C**H**$_2$, ^3J = 5.89 Hz) ; 3.10-3.06 (m, 3H, 1'-C**H**$_2$, C**H** cyclopropyl) ; 1.65 (m, 4H, 2'-C**H**$_2$, 3'-C**H**$_2$) ; 0.93-0.85 (q, 2H, 2 x C**H** cyclopropyl, ^3J = 5.89 Hz) ; 0.64-0.57 (t broad, 2H, 2 x C**H** cyclopropyl) ; ^{13}C NMR, δ ($CDCl_3$) : 159.9 (C_2) ; 144.5 (**C** quat., trityl) ; 128.8 (6 x **C** ortho, trityl) ; 127.9 (6 x **C** meta, trityl) ; 127.1 (3 x **C** para, trityl) ; 62.9 ($C_{4'}$) ; 41.6 ($C_{1'}$) ; 27.5 ($C_{3'}$) ; 26.3 ($C_{2'}$) ; 24.7 (**C**H cyclopropyl) ; 7.4 (2 x **C**H cyclopropyl); MS (ESI+) (m/z) 510 $(M+H)^+$; HPLC: Rt = 15.62 min (0.5 mL/min, CH_3CN-H_2O, 85 :15). Anal. Calcd. for ($C_{30}H_{31}O_3N_5$) : C 70.73%, H 6.09%, N 13.75%, found : C 70.95%, H 6.46%, N 13.43%.

4-(Cyclopropylamino)-6-[*N*-(3'-trimethylacetyloxybutyl)amino]-5-nitropyrimidine (16) 100 mg (0.3 mmol) of **13** were dissolved in 5 mL of dichloromethane. 0.1 mL (1.51 mmol) of cyclopropylamine was then added at 0°C. The mixture was stirred at room temperature for 3h. Removal of the cyclopropylamine and the solvent followed by column chromatography of the residue (n-hexane/EtOAc, 8 : 2) gave compound **16** in 50% yield as an amorphous solid. Rf 0.46 (hexane-EtOAc, 6 : 4) ; ^{1}H NMR, δ ($CDCl_3$) : 9.26 (broad s, 1H, N**H**) ; 9.17 (broad s, 1H, N**H**) ; 8.11 (s, 1H, 2-H) ; 6.34 (broad s, 1H, N**H**-CH_2) ; 4.06-3.99 (t, 2H, 4'-C**H**$_2$, ^3J = 6.28 Hz) ; 3.61-3.54 (q, 2H, 1'-C**H**$_2$, ^3J = 6.28 Hz) ; 3.10-2.97 (m, 1H, C**H** cyclopropyl) ; 1.97-1.64 (m, 4H, 2'-C**H**$_2$, 3'-C**H**$_2$) ; 0.91-0.84 (m, 2H, 2 x C**H** cyclopropyl) ; 0.62-0.59 (m, 2H, 2 x C**H** cyclopropyl) ; ^{13}C NMR, δ ($CDCl_3$) : 172.9 (**C**=O) ; 159.9 (C_2) ; 63.8 (4'-C**H**$_2$) ; 41.3 (1'-C**H**$_2$) ; 27.3 (3 x C**H**$_3$, tBu) ; 26.3 (3'-C**H**$_2$) ; 26.1 (2'-C**H**$_2$) ; 24.8 (**C**H cyclopropyl) ; 7.4 (2 x C**H**$_2$ cyclopropyl) ; MS (ESI+) (m/z) 352 $(M+H)^+$; HPLC : Rt = 10.59 min (0.6 mL /min ; CH_3CN-H_2O, 50 : 50). Anal. Calcd. for($C_{16}H_{25}O_4N_5$) : C 54.70%, H 7.12%, N 19.94%, found : C 54.85%, H 7.20%, N 19.56%.

6-[*N*-(4'-*tert*-Butyldimethylsilyloxybutyl)amino]-4-(2'-ethylimidazolyl)-5-nitropyrimidine (17) A mixture of 100 mg (0.27 mmol) of **11** and 132 mg (1.38 mmol) of 2-ethylimidazole in 10 mL of dichloromethane was stirred at room temperature for 48 h. The solution was then concentrated under reduced pressure and the analytical compound was obtained after purification by column chromatography (n-hexane-EtOAc, 6:4) in 52% yield as an amorphous solid. Rf 0.67 (EtOAc) ; ^{1}H NMR, δ ($CDCl_3$) : 8.50 (s, 1H, 2-H) ; 7.55 (broad t,

1H, N**H**) ; 6.99 (d, 1H, C**H** ethylenic, ^3J = 1.62 Hz) ; 6.81 (d, 1H, C**H** ethylenic, ^3J = 1.62 Hz) ; 3.67-3.59 (m, 4H, 1'-C**H**$_2$, 4'-C**H**$_2$) ; 2.76-2.65 (q, 2H, C**H**$_2$CH$_3$, ^3J = 7.49 Hz) ; 1.72-1.65 (q, 2H, 3'-C**H**$_2$, ^3J = 7.28 Hz) ; 1.63-1.53 (q, 2H, 2'-C**H**$_2$, ^3J = 7.27 Hz) ; 1.27-1.19 (t, 3H, CH$_2$C**H**$_3$, ^3J = 7.49 Hz) ; 0.83 (s, 9H, tBu) ; ^{13}C NMR, δ ($CDCl_3$) : 172.8 (C., EtIm) ; 159.36 (C_2) ; 129.5 (C ethylenic) ; 118.5 (C ethylenic) ; 62.7 ($C_{4'}$) ; 42.11 ($C_{1'}$) ; 30.0 ($C_{3'}$) ; 26.1 (3 x C**H**$_3$, tBu) ; 26.0 ($C_{2'}$) ; 21.1 (C**H**$_2$CH$_3$) ; 12.1 (CH$_2$C**H**$_3$); MS (ESI+) (m/z) 421 $(M+H)^+$; HPLC: Rt = 6.25 min (1 mL/min, CH_3CN-H_2O, 80 : 20). Anal. Calcd. for ($C_{19}H_{32}O_3N_6Si$) : C 54.28%, H 7.62%, N 20.00%, found : C 54.21%, H 7.58%, N 19.74%.

4-(2'-Ethylimidazolyl)-6-[*N*-(4'-triphenylmethyloxybutyl)amino]-5-nitropyrimidine (18)

A mixture of 100 mg (0.2 mmol) of **12** and 98 mg (1.02 mmol) of 2-ethylimidazole in 10 mL of dichloromethane was stirred at room temperature for 48 h. The solution was then concentrated under reduced pressure and the analytical compound was obtained after purification by column chromatography (n-hexane/EtOAc, 8 : 2) in 60% yield as an oil. Rf 0.24 (n-hexane-EtOAc, 6 : 4) ; ^{1}H NMR, δ ($CDCl_3$) : 8.47 (s, 1H, 2-H) ; 7.68 (broad s, 1H, N**H**) ; 7.39-7.16 (m, 15H, trityl) ; 6.99-7.00 (d, 2H, H ethylenic, ^3J = 1.48 Hz) ; 6.80-6.79 (d, 2H, H ethylenic ^3J = 1.48 Hz) ; 3.63-3.53 (q, 2H, 4'-C**H**$_2$, ^3J = 6.47 Hz) ; 3.11-3.05 (t, 2H, 1'-C**H**$_2$, ^3J = 5.82 Hz) ; 2.75-2.64 (q, 2H, CH$_3$C**H**$_2$, ^3J = 1.49 Hz) ; 1.80-1.59 (m, 4H, 2'-C**H**$_2$, 3'-C**H**$_2$) ; 1.26-1.18 (t, 3H, C**H**$_3$CH$_2$, ^3J = 7.5 Hz) ; ^{13}C NMR, δ ($CDCl_3$) : 159.9 (C_2) ; 144.4 (Cquat., trityl) ; 128.8 (6 x **C** ortho, trityl) ; 127.9 (6 x **C** meta, trityl) ; 127.2 (3 x **C** para, trityl) ; 63.0 ($C_{4'}$) ; 42.2 ($C_{1'}$) ; 27.4 ($C_{3'}$) ; 26.3 ($C_{2'}$) ; 21.1 (CH$_3$CH$_2$) ; 12.1 (CH$_3$CH$_2$); MS (ESI+) (m/z) 549 $(M+H)^+$; HPLC: Rt = 21.59 min (0.5 mL/min; CH_3CN-H_2O, 70 : 30) . Anal. Calcd. for ($C_{32}H_{32}O_3N_6$) : C 70.07%, H 6.28%, N 15.33%, found : C 70.15%, H 6.35%, N 15.25%.

4-(2'-Ethylimidazolyl)-6-[*N*-(4'-trimethylacetyloxybutyl)amino]-5-nitropyrimidine (19)

A mixture of 130 mg (0.39 mmol) of **13** and 188 mg (1.95 mmol) of 2-ethylimidazole in 10 mL of dichloromethane was stirred at room temperature for 48 h. The solution was then concentrated under reduced pressure and the analytical compound was obtained after purification by column chromatography (n-hexane-EtOAc 6 : 4) in 63% yield as an oil. Rf 0.32 (EtOAc) ; ^{1}H NMR, δ ($CDCl_3$) : 8.50 (s, 1H, 2-C**H**) ; (broad t, 1H, N**H**) ; 6.99-6.98 (d, 2H, H ethylenic ^3J = 1.54 Hz) ; 6.81-6.80 (d, 2H, H ethylenic ^3J = 1.47 Hz); 4.09-4.03 (broad t, 2H, 4'-C**H**$_2$, ^3J = 5.95 Hz) ; 3.69-3.60 (broad q, 2H, 1'-C**H**$_2$, ^3J = 6.49 Hz) ; 2.76-2.65 (q, 2H, C**H**$_2$CH$_3$, EtIm, ^3J = 7.49 Hz); 1.72-1.69 (m, 4H, 2'-C**H**$_2$, 3'-C**H**$_2$); 1.26-1.18 (t, 3H, CH$_2$C**H**$_3$ ^3J = 7.5 Hz) ; 1.14 (s, 9H, tBu) ; ^{13}C NMR, δ ($CDCl_3$) : 159.4 (C_2) ; 150.1 (Cquat) ;

129.5 (CH ethylenic); 118.5 (CH ethylenic) ; 63.7 ($C_{4'}$); 41.84 ($C_{1'}$) ; 38.9 (Cquat, tBu) ; 27.3 (3 x CH_3, tBu) ; 26.2 ($C_{3'}$) ; 25.9 ($C_{2'}$) ; 21.1 (CH_2CH_3) ; 12.1 (CH_2CH_3); MS (ESI+) (m/z) 91 $(M+H)^+$; HPLC: Rt = 9.00 min (0.7 mL/min; CH_3CN-H_2O, 55 : 45). Anal. Calcd. ($C_{18}H_{26}O_4N_6$) : C 55.38%, H 6.66%, O 16.41%, N 21.54%, found : C 55.29%, H 6.55%, N 21.75%.

4-Amino-6-[*N*-(4'-*tert*-butyldimethylsilyloxybutyl)amino]-5-nitropyrimidine (20) A solution of 130 mg (0.37 mmol) of **11** and 0.44 mL (0.74 mmol) of NH_3-MeOH 2.0 M in anhydrous methanol was stirred under N_2 at room temperature for 18h. The solution was then concentrated under reduced pressure and the residue purified by column chromatography (n-hexane-EtOAc, 6 : 4) to give 70 mg of **20** (60% yield) as a white powder. Recrystallization from MeOH gave the analytical product. mp 123°C, Rf 0.22 (CH_2Cl_2) ; ^{1}H NMR δ ($CDCl_3$) : 9.15 (broad s, 1H, NH) ; 8.52 (broad s, 1H, NH) ; 7.98 (s, 1H, 2-CH) ; 6.45 (broad s, 1H, NH) ; 3.64-3.54 (m, 4H, 1'-CH_2, 4'-CH_2) ; 1.73-1.52 (m, 4H, 2'-CH_2, 3'-CH_2) 0.84 (s, 9H, tBu) ; ^{13}C NMR, δ ($CDCl_3$) : 159.9 (C_2) ; 62.7 ($C_{4'}$) ; 41.6 ($C_{1'}$) ; 30.2 ($C_{3'}$) ; 26.1 (3 x CH_3, tBu) ; 26.1 ($C_{2'}$) ; 18.4 (C quat, tBu) ; -5.2 ($Si(CH_3)_2$) ; MS (ESI+) (m/z) 342 $(M+H)^+$; HPLC: Rt = 18.16 min (0.5 mL/min, CH_3CN-H_2O, 70 : 30). Anal. Calcd. for ($C_{14}H_{27}O_3N_5Si$) : C 49.27%, H 7.92%, N 20.53%, found C 49.15%, H 7.85%, N 20.48%.

4-Amino-6-[N-(4'-triphenylmethyloxybutyl)amino]-5-nitropyrimidine (21) A solution of 100 mg (0.2 mmol) of **12** and 0.24 mL (0.4 mmol) of NH_3-MeOH 2.0 M in anhydrous methanol was stirred under N_2 at room temperature for 18h. The solution was then concentrated under reduced pressure and the residue purified by column chromatography (CH_2Cl_2-EtOAc, 7 : 3) to give **21** in 35% yield as a white powder. Recrystallization from MeOH gave the analytical product. mp 164°C - 165 °C ; Rf 0.21 (CH_2Cl_2) ; ^{1}H NMR, δ ($CDCl_3$) : 9.09 (broad s, 1H, NH) ; 8.48 (broad s, 1H, NH) ; 7.93 (s, 1H, 2-H) ; 7.38-7.14 (m, 15H, trityl) ; 6.53 (broad s, 1H, NH) ; 4.09-3.99 (q, 2H, 4'-CH_2, ^3J = 6.28 Hz) ; 3.07-3.02 (t, 2H, 1'-CH_2, ^3J = 5.83 Hz) ; 1.71-1.64 (m, 4H, 2'-CH_2, 3'-CH_2) ; MS (ESI+) (m/z) 470 $(M+H)^+$; HPLC: Rt = 21.55 min, (0.5 mL/min ; CH_3CN-H_2O, 70 : 30). Anal. Calcd. for ($C_{27}H_{27}O_3N_5$) : C 69.08%, H 5.76%, N 14.92%, found : C 69.17%, H 5.90%, N 15.02%.

4-Amino-6-[N-(4'-trimethylacetyloxybutyl)amino]-5-nitropyrimidine (22) A solution of 120 mg (0.36 mmol) of **13** and 0.4 mL (0.72 mmol) of NH_3/MeOH 2.0 M in anhydrous methanol was stirred under N_2 at room temperature for 18h. The solution was then concentrated under reduced pressure and the residue purified by column chromatography (n-

hexane-EtOAc, 6 : 4) to give **22** in 54% yield as a white powder. Recrystallization from MeOH gave the analytical product. mp 109-110°C, Rf 0.24 (EtOAc) ; ^{1}H NMR, δ ($CDCl_3$) : 9.12 (broad s, 1H, N**H**) ; 8.49 (broad s, 1H, N**H**) ; 7.96 (s, 1H, 2-H) ; 6.34 (broad s, 1H, N**H**-CH_2) ; 4.07-4.01 (broad t, 2H, 4'-CH_2, ^{3}J = 5.78 Hz) ; 3.63-3.54 (broad q, 2H, 1'-CH_2, ^{3}J = 6.64 Hz) ; 1.71-1.65 (quint, 4H, 2'-CH_2, 3'-CH_2) ; ^{13}C NMR, δ ($CDCl_3$) : 172.9 (**C**=O) ; 160.0 (C_2) ; 63.84 ($C_{4'}$) ; 41.3 ($C_{1'}$) ; 27.3 (3 x CH_3, tBu) ; 26.3 ($C_{3'}$) ; 26.1 ($C_{2'}$) ; MS (ESI+) (m/z) 312 $(M+H)^+$; HPLC : Rt = 9.73 min (0.6 mL/min ; CH_3CN-H_2O, 50 : 50). Anal. Calcd. for ($C_{13}H_{21}O_4N_5$) : C 50.16%, H 6.75%, N 22.51%, found : C 50.45%, H 6.95%, N 22.46%.

6-[*N*-(3'-*tert*-Butyldimethylsilyloxypropoxy)amino]-4-chloro-5-nitropyrimidine (24)

0.16 mL (1.46 mmol) of 4-methylmorpholine (NMM) was added to a suspension of 284 mg (1.46 mmol) of 4,6-dichloro-5-nitropyrimidine in 7 mL of CH_2Cl_2. 250 mg (1.22 mmol) of propoxyamine **23** were then added at 0°C. The mixture was stirred at room temperature for 4h. The organic solution was washed with an aqueous solution of citric acid (10%), dried over Na_2SO_4 and evaporated to dryness wihout heating under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2). The reaction proceed in 41% yield. **24** was recrystallized from n-hexane. Rf 0.26 (CH_2Cl_2) ; ^{1}H NMR, δ ($CDCl_3$) : 9.58 (broad s, 1H, ON**H**) ; 8.40 (s, 1H, 2-C**H**) ; 4.04-3.98 (t, 2H, C**H**$_2$ONH, ^3J = 6.18 Hz); 3.72-3.67 (t, 2H, C**H**$_2$OSi, ^3J = 5.67 Hz); 1.88-1.76 (quint, 2H, C**H**$_2$, ^3J = 5.93 Hz); 0.82 (s, 9H, tBu); ^{13}C NMR, δ ($CDCl_3$) : 158.2 (C_2); 75.1 (**C**H_2ONH); 60.2 (**C**H_2OSi); 31.2 (**C**H_2); 26.1 (3 x CH_3, tBu); -5.0 (Si(**C**H_3)$_2$) ; HPLC : Rt = 9.80 min (1.5 mL/min; CH_3CN-H_2O, 85 : 15).

4-Amino-6-[*N*-(3'-*tert*-butyldimethylsilyloxypropoxy)amino]-5-nitropyrimidine (25)

A solution of 100 mg (0.27 mmol) of **24** and 0.3 mL (0.55 mmol) of NH_3-MeOH 2.0 M in anhydrous methanol was stirred under N_2 at room temperature for 18h. The solution was then concentrated under reduced pressure and the residue purified by column chromatography (n-hexane-EtOAc, 1 : 1) to give **25** in 50% yield as a white powder. Recrystallization from MeOH gave the analytical product. Rf 0.28 (n-hexane/EtOAc, 6 : 4) ; ^{1}H NMR, δ ($CDCl_3$) : 10.88 (s, 1H, ON**H**) ; 8.46 (broad s, 1H, NH**H'**); 8.09 (s, 1H, 2-C**H**) ; 6.48 (broad s, 1H, NH**H'**) ; 4.15-4.09 (t, 2H, C**H**$_2$ONH, ^3J = 6.39 Hz) ; 3.75-3.69 (t, 2H, C**H**$_2$OSi, ^3J = 5.90 Hz) ; 1.95-1.83 (quint, 2H, C**H**$_2$, ^3J = 6.14 Hz) ; 0.83 (s, 9H, tBu) ; ^{13}C NMR , δ ($CDCl_3$) : 160.7 (C_2) ; 74.7 (**C**H_2ONH) ; 59.8 (**C**H_2OSi) ; 31.2 (**C**H_2) ; 26.0 (3 x CH_3, tBu) ; -5.0 (Si(**C**H_3)$_2$) ; MS (ESI+) (m/z) 344 $(M+H)^+$. Anal. Calcd. for ($C_{13}H_{25}O_4N_5Si$) : C 45.48%, H 7.28%, N 20.41%, found C 45.20%, H 7.23%, N 19.95%.

6-[*N*-(3'-*tert*-Butyldimethylsilyloxypropoxy)amino]-4-(cyclopropylamino)-5-nitro pyrimidine (26) 100 mg (0.27 mmol) of **24** were dissolved in 5 mL of dichloromethane. 0.1 mL (1.51 mmol) of cyclopropylamine was then added at 0°C. The mixture was stirred at room temperature for 3h. Removal of the cyclopropylamine and the solvent followed by column chromatography of the residue (n-hexane-EOAct, 6 : 4) gave compound **26** in 61% yield as an amorphous solid. Rf 0.5 (n-hexane-EtOAc, 6 : 4) ; ^{1}H NMR δ ($CDCl_3$) : 10.95 (s, 1H, ONH) ; 9.09 (broad s, 1H, NH) ; 8.24 (s, 1H, 2-H) ; 4.15-4.08 (t, 2H, CH_2ONH, ^3J = 6.37 Hz) ; 3.75-3.69 (t, 2H, CH_2OSi), ^3J = 5.88 Hz) ; 3.12-2.99 (m, 1H, CH cyclopropyl) ; 1.94-1.82 (quint, 2H, CH_2, ^3J = 6.11 Hz) ; 0.95-0.77 (s + m, 11H, tBu, 2 x CH cyclopropyl) ; 0.65-0.57 (m, 2H, 2 x CH cyclopropyl) ; ^{13}C NMR, δ ($CDCl_3$) : 160.7 (C_2) ; 74.6 (CH_2ONH) ; 59.8 (CH_2OSi) ; 31.2 (CH_2) ; 26.0 (3 x CH_3, tBu) ; 24.8 (CH cyclopropyl) ; 7.5 (2 x CH_2 cyclopropyl) ; -5.0 (Si(CH_3)$_2$) ; MS (ESI+) (m/z) 384 $(M+H)^+$; HPLC : Rt = 11.47 min (1.5 mL/min ; CH_3CN-H_2O, 80 :20). Anal. Calcd. ($C_{16}H_{29}O_4N_5Si$) : C 50.13%, H 7.57%, N 18.27%, found C 49.63%, H 7.52%, N 18.77%.

4-Amino-6-[*N*-(3'-hydroxypropoxy)amino]-5-nitropyrimidine (27) A mixture of 50 mg (0.20 mmol) of the silyl derivative **25** in 2.0 mL of a solution of 1% HCl in aqueous ethanol was stirred at room temperature for 5 min. The solvent was evaporated under reduced pressure and the residue was purified by a column chromatography (EtOAc-MeOH, 8 : 2) to give an amorphous orange solid, in quantitative yield. Rf 0.47 (EtOAc-MeOH, 9 : 1) ; ^{1}H NMR, δ (CD_3OD) : 7.89 (s, 1H, 2-H) ; 4.17-4.11 (t, 2H, CH_2O, ^3J = 6.11 Hz) ; 3.75-3.69 (t, 2H, CH_2O, ^3J = 6.05 Hz) ; 1.97-1.85 (quint, 2H, CH_2, ^3J = 6.08 Hz) ; MS (ESI-) (m/z) 228 $(M-H)^-$; HPLC : Rt = 4.95 min (1.5 mL/min ; CH_3CN-H_2O, 55 :45). Anal. Calcd. for ($C_7H_{11}O_4N_5$) : C 36.68%, H 4.80%, N 30.57%, found : C 36.27%, H 4.77%, N 30.10%.

4-(Cyclopropylamino)-6-[*N*-(3'-hydroxypropoxy)amino]-5-nitropyrimidine (28) A mixture of 50 mg (0.20 mmol) of the silyl derivative **25** in 2.0 mL of a solution of 1% HCl in aqueous ethanol was stirred at room temperature for 5 min. The solvent was evaporated under reduced pressure and the residue was purified by a column chromatography EtOAc-MeOH, (9 : 1) to give an amorphous orange solid, in quantitative yield. Rf 0.28 (AcOEt) ; ^{1}H NMR, δ ($CDCl_3$) : 11.00 (broad s, 1H, ONH) ; 9.12 (broad s, 1H, NH) ; 8.21 (s, 1H, 2-H) ; 4.18-4.12 (t, 2H, CH_2O, ^3J = 5.54 Hz) ; 3.85-3.79 (t, 2H, CH_2, ^3J = 5.52 Hz) ; 3.13-3.04 (m, 1H, CH cyclopropyl) ; 1.89-1.79 (quint, 2H, CH_2, ^3J = 5.5 Hz) ; 0.97-0.87 (q, 2H, 2 x CH cyclopropyl, ^3J = 7.2 Hz) ; 0.67-0.58 (m, 2H, 2 x CH cyclopropyl) ; ^{13}C NMR, δ ($CDCl_3$) : 159.9 (C_2) ; 59.91 (CH_2OH), 30.3 (2'-CH_2), 25.0 (CH cyclopropyl), 7.5 (2 x CH_2 cyclopropyl) ; MS

(ESI+) (m/z) 268 (M+H)+ ; HPLC : Rt = 5.14 min (1.5 mL/min ; CH_3CN-H_2O, H_2O, 60 : 40). Anal. Calcd. for ($C_{10}H_{15}O_4N_5$) : C 44.61%, H 5.57%, N 26.02%, found : C 44.11%, H 5.58%, N 25.96%.

Benzyloxy-3-trimethylacetyloxypropane (30) 700 mg (4.22 mmol) of compound **29** were treated with pivaloylchloride and triethylamine in dichloromethane at room temperature for 2 hours. The solvent was removed and the residue purified by column chromatography eluting with dichloromethane-n-hexane mixture (0-30%) to afford **30** (320 mg, 60%) as an oil. Rf 0.30 (n-hexane-CH_2Cl_2, 2 : 8) ; ^{1}H NMR, δ ($CDCl_3$) : 7.27-7.22 (m, 5H, H-aromatic) ; 4.43 (s, 2H, C**H**$_2$, benzyl) ; 4.13-4.07 (t, 2H, C**H**$_2$O pivaloyl, ^3J = 6.36 Hz) ; 3.50-3.43 (t, 2H, C**H**$_2$O benzyl, ^3J = 6.25 Hz) ; 1.92-1.80 (quint, 2H, C**H**$_2$, ^3J = 6.3 Hz) ; 1.09 (s, 9H, tBu).

3-Trimethylacetyloxypropanol (31) To a solution of 620 mg (2.48 mmol) of **30** in anhydrous methanol (10 ml), 660 mg (0.62 mmol) of Pd/C 10% were added under N_2. The suspension was stirred under H_2 for 2h at room temperature, filtered over celite and the filtrate concentrated under reduced pressure to give 300 mg (75%) of **31** as an oil. ^{1}H NMR , δ (CD_3OD) : 4.23-4.17 (t, 2H, C**H**$_2$O pivaloyl, ^3J = 6.4 Hz) ; 3.71-3.65 (t, 2H, C**H**$_2$OH, ^3J = 6.4 Hz) ; 1.95-1.82 (quint, 2H, C**H**$_2$, ^3J = 6.3 Hz) ; 1.24 (s, 9H, tBu).

***N*-[3-Trimethylacetyloxypropoxy]phtalimide (32)** 0.63 mL (4mmol) of diethylazodicarboxylate was added to a solution of 426 mg (2.66 mmol) of **31**, 1 g (3.94 mmol) of triphenylphosphine and 651 mg (4 mmol) of N-hydroxyphtalimide in THF (30 mL). The solution was stirred at room temperature for 24 h and then the solvent was removed. The residue was purified by column chromatography (n-hexane-EtOAc, 6 : 4) to afford **32** (777 mg, 96%), as a viscous and colourless oil. Rf 0.47 (n-hexane-AcOEt, 6 : 4) ; ^{1}H NMR, δ ($CDCl_3$) : 7.80-7.66 (m, 4H, H aromatic) ; 4.27-4.20 (m, 2H, C**H**$_2$ON) ; 2.12-1.97 (quint, 2H, C**H**$_2$, ^3J = 6.2 Hz) ; 1.14 (s, 9H, tBu).

3-(Trimethylacetyloxy)propoxyamine (33) 0.12 mL (2.5 mmol) of hydrazine monohydrate was added to 770 mg (2.5 mmol) of **32** in ethanol (10 mL). The mixture was stirred for 1 h at reflux temperature. The residue was then allowed to cool to room temperature and the solvent was removed. An aqueous solution of Na_2CO_3 3% (10 ml) was then added and extracted with ether (3 x 20 ml). The organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give 300 mg (80%) of **33** as a colourless oil. ^{1}H NMR, δ ($CDCl_3$) : 5.24 (s broad, 2H, ON**H**$_2$) ; 4.09-4.03 (t, 2H, C**H**$_2$O pivaloyl, ^3J = 6.4 Hz) ; 3.69-3.63 (t, 2H, C**H**$_2$ONH$_2$, ^3J = 6.4 Hz) ; 1.91-1.78 (quint, 2H, C**H**$_2$, ^3J = 6.4 Hz) ; 1.12 (s, 9H, tBu).

4-Chloro-6-[*N*-(3'-trimethylacetyloxypropoxy)amino]-5-nitropyrimidine (34) 0.14 mL (1.03 mmol) of NMM was added to a suspension of 200 mg (1.03 mmol) of 4,6-dichloro-5-nitropyrimidine in 10 mL of dichloromethane. 150 mg (0.86 mmol) of propoxyamine **32** were added at 0°C. The mixture was stirred for 6h. After usual work up, the residue was purified by column chromatography (n-hexane-EtOAc, 8 : 2) to give 77 mg (30%) of **34** as an amorphous solid. Rf 0.29 (CH_2Cl_2) ; ^{1}H NMR δ ($CDCl_3$) : 9.45 (broad s, 1H, N**H**) ; 8.45 (s, 1H, 2-H) ; 4.20-4.14 (t, 2H, C**H**$_2$O pivaloyl, ^3J = 6.22 Hz) ; 4.06-3.99 (t, 2H, C**H**$_2$ONH, ^3J = 6.27 Hz) ; 2.03-1.90 (quint, 2H, C**H**$_2$, ^3J = 6.25 Hz) ; 1.14 (s, 9H, tBu) ; ^{13}C NMR, δ ($CDCl_3$) : 178.9 (**C**=O) ; 157.0 (C_2) ; 73.7 (**C**H$_2$ONH) ; 60.9 (**C**H$_2$O pivaloyl) ; 27.6 (**C**H$_2$) ; 27.2 (3 x **C**H$_3$, tBu) ; HPLC : Rt = 10.07 min (1.5 mL/min ; CH_3CN-H_2O, 80 : 20).

4-Amino-6-[*N*-(3'-trimethylacetyloxypropoxy)amino]-5-nitropyrimidine (35) A solution of 100 mg (0.3 mmol) of **34** and 0.3 mL (0.6 mmol) of NH_3-MeOH 2.0 M in anhydrous methanol was stirred under N_2 at room temperature for 18h. The solution was then concentrated under reduced pressure and the residue purified by column chromatography (n-hexane-EtOAc, 5 : 5) to give **25** in 50% yield as an amorphous white solid. Rf 0.14 (n-hexane-EtOAc, 6 : 4) ; ^{1}H NMR, δ ($CDCl_3$) : 10.85 (broad s, 1H, ON**H**) ; 8.45 (broad s, 1H, N**H**$_2$) ; 8.10 (s, 1H, 2-H) ; 6.49 (broad s, 1H, N**H**$_2$) ; 4.23-4.16 (t, 2H, C**H**$_2$ O pivaloyl, ^3J = 6.21 Hz) ; 4.13-4.03 (q, 2H, C**H**$_2$ONH, ^3J = 6.5 Hz) ; 2.08-1.97 (quint, 2H, C**H**$_2$, ^3J = 6.3 Hz) ; 1.14 (s, 9H, tBu) ; ^{13}C NMR, δ ($CDCl_3$) : 187.4 (**C**=O) ; 158.9 (C_2) ; 74.1 (**C**H$_2$ONH) ; 61.1 (**C**H$_2$O pivaloyl) ; 27.7 (CH$_2$) ; 27.3 (3 x **C**H$_3$, tBu) ; MS (ESI-) (m/z) 312 (M-H)$^-$; HPLC: Rt = 5.63 min (1.5 mL/min ; CH_3CN-H_2O , 80 :20). Anal. Calcd. for ($C_{12}H_{19}O_5N_5$) : C 46.01%, H 6.07%, N 22.36%, found : C 46.48%, H 6.10%, N 22.12%.

4-(Cyclopropylamino)-6-[*N*-(3'-trimethylacetyloxypropoxy)amino]-5-nitropyrimidine (36) 35 mg (0.01 mmol) of **34** were dissolved in 5 mL of dichloromethane. 40 µL (0.5 mmol) of cyclopropylamine was then added at 0°C. The mixture was stirred at room temperature for 3h. Removal of the cyclopropylamine and the solvent followed by column chromatography of the residue (n-hexane-AcOEt, 5 : 5) gave compound **36** in 70% yield as an amorphous solid. Rf 0.29 (n-hexane-EtOAc, 6 : 4) ; ^{1}H NMR, δ ($CDCl_3$) : 10.91 (broad s, 1H, ON**H**) ; 9.08 (broad s, 1H, N**H** cyclopropyl) ; 8.24 (s, 1H, 2-H) ; 4.22-4.16 (t, 2H, C**H**$_2$O pivaloyl, ^3J = 6.2 Hz) ; 4.13-4.06 (t, 2H, C**H**$_2$ONH, ^3J = 6.33 Hz) ; 3.11-3.02 (m, 1H, C**H** cyclopropyl) ; 2.08-1.95 (quint, 2H, C**H**$_2$, ^3J = 6.27 Hz) ; 1.14 (s, 9H, tBu) ; 0.95-0.86 (q, 2H, 2 x C**H**, cyclopropyl, ^3J = 7.23 Hz) ; 0.66-0.60 (m, 2H, 2 x C**H** cyclopropyl) ; ^{13}C NMR, δ ($CDCl_3$) : 160.9 (**C**H, base) ; 74.1 (**C**H$_2$ONH) ; 61.1 (**C**H$_2$O pivaloyl) ; 27.6 (**C**H$_2$) ; 27.3 (3 x **C**H$_3$,

tBu) ; 7.5 (2 x CH_2 cyclopropyl) ; MS (ESI-) (m/z) 352 $(M-H)^-$; HPLC : Rt = 6.59 min (1.5 mL/min ; CH_3CN-H_2O, 80 : 20). Anal. Calcd. for ($C_{15}H_{23}O_5N_5$) : C 50.99%, H 6.51%, N 19.83%, found : C 51.42%, H 6.55%, N 20.16%.

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