Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry. This journal is © The Royal Society of Chemistry 2022

Synthesis of novel *C*-nucleoside analogues, bearing an anomeric cyano and a 1,2,3-triazole nucleobase, as potential antiviral agents

Pierre Sierocki^a, Krystal Gaillard^a, Ruben Arturo Arellano Reyes^a, Chloé Donnart^a, Emilie Lambert^b, Sandrine Grosse^c, Laurence Arzel^a, Arnaud Tessier^a, Jérôme Guillemont^{b,d}, Monique Mathé-Allainmat^{a*} and Jacques Lebreton^{a*}

^a Université de Nantes, CNRS, Laboratoire CEISAM–UMR 6230, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France.

^b Janssen-Cilag, Campus de Maigremont BP615, F-27106 Val de Reuil, Cedex, France

^c Janssen Research & Development, Turnhoutseweg 30, 2340 Beerse, Belgium

^d Present address : NovAliX on-site Janssen-Cilag. Centre de recherche Pharma, Campus de Maigremont. BP615, 27106 Val-de-Reuil Cedex ,France

Table of contents

Synthesis and XRD for 1'-α-carbamoyl compound 5'b	S2-S3
¹ H and ¹³ C NMR spectra of precursors 6, 8-9, 11, 14	S 4-S15
¹ H, ¹³ C and ¹⁹ F NMR and NOESY spectra of compounds 12-13	S16-S36
^{1}H , ^{13}C and ^{19}F NMR spectra of final ribofuranose compounds 5	S37-S46

Synthesis and X-ray crystallographic data for carbamoyl analogue of 5b, compound 5'b.

Following a two-steps procedure close to that described for compound **5b**, starting from **12b**, an hydrolysed form of **5b**, the α -carbamoyl compound **5'b** was isolated which DRX data could so confirmed the stereoselectivity of the cyanation step giving α -CN anomer.

(2S, 3R, 4S, 5R)-3,4-Dihydroxy-5-(hydroxymethyl)-2-(5-iodo-2H-1,2,3-triazol-4-yl)tetrahydrofuran-2-carboxamide (**5'b**)

NaOH (2.7 mL of a 1 M aqueous solution, 4.40 mmol, 2 eq) was added to a stirring solution of **12b** (0.1 g, 1.36 mmol, 1 eq) in MeOH (5.5 mL, 0.25 M) at 0°C and the resulting mixture was stirred 1h at RT. It was neutralized with a 1 M HCl aqueous solution and extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the expected *N*-triazole deprotected intermediate as a mixture of tautomers : HRMS (ESI⁺): calcd for $[M+Na]^+$ C₂₉H₂₇N₄O₄NaI = 368.9696; found 368.9695. This latter was dissolved in dry DCM (5.4 mL, 0.1 M) and the resulting solution cooled to 0°C. BCl₃ (3.38 mL of a 1 M solution in DCM, 3.38 mmol, 5 eq) was added and the reaction mixture was stirred for 2h at this temperature. It was then quenched with cold MeOH and warmed to RT. The resulting mixture was kept stirring for 30 additional min. Volatiles were removed under reduced pressure and the obtained residue was dissolved in MeOH. It was evaporated to dryness again, and the procedure was repeated three times. Finally the obtained residue was purified by flash column chromatography on silica gel [DCM/MeOH, 8:2] to afford **5b** and **5'b** (130 mg, 0.35 mmol, 26% yield). ¹H NMR (300 MHz, DMSO-*d*₆, 298 K): δ (ppm) 14.9 (br, 1H, NH), 7.46 (d, *J*_{gem} = 1.9, 1H, CONH₂), 7.25 $(d, J_{gem} = 1.9, 1H, CONH_2), 5.41 (d, {}^{3}J_{OH-2'} = 5.4, 1H, OH_{2'}), 4.86 (d, {}^{3}J_{OH-3'} = 8.3, 1H, OH_{3'}), 4.81$ $(dd, {}^{3}J_{2'-OH} = 5.4, {}^{3}J_{2'-3'} = 4.1, 1H, H_{2'}), 4.02 (ddd, {}^{3}J_{4'-3'} = 8.5, {}^{3}J_{4'-5'} = 5.3, {}^{3}J_{4'-5'} = 3.2, 1H, H_{4'}),$ $3.88 \text{ (m, 1H, H_{3'})}, 3.47 \text{ (dd, } J_{\text{gem}} = 11.6, {}^{3}J_{5'-4'} = 3.2, 1\text{H}, \text{H}_{5'}), 3.25 \text{ (dd, } J_{\text{gem}} = 11.6, {}^{3}J_{5'-4'} = 5.3, 1\text{H},$ H_{5'}. ¹³C NMR (100 MHz, CD₃OD, 303 K): δ (ppm) 174.3 (CO), 148.6 (C₄) 87.9 (C₅), 86.8 (C₁), 85.4 (C_{4'}), 76.8 (C_{2'}), 73.2 (C_{3'}), 63.7 (C_{5'}). HRMS (ESI-): calcd for $[M+Na]^+$ C₈H₁₀N₄O₅I = 368.9696; found 368.9695.

X-ray single-crystal diffraction data were collected on a Rigaku Oxford Diffraction SuperNova diffractometer equipped with Atlas CCD detector and micro-focus Cu-K_{α} radiation ($\lambda = 1.54184$ Å). The structures were solved by dual-space algorithm, expanded and refined on F² by full matrix least-squares techniques using SHELX programs (G. M. Sheldrick, SHELXT 2018/2 and SHELXL 2018/3). All non-H atoms were refined anisotropically and multiscan empirical absorption was corrected using CrysAlisPro program (CrysAlisPro, Agilent Technologies, V1.171.38.46, 2015 for **5'b**. The H atoms were placed at calculated positions and refined using a riding model.

Crystallographic data for **5'b**:



 $C_{16}H_{26}I_2N_8O_{12}$, M = 776.25, T=294K, colorless needle, 0.072 x 0.035 x 0.016 mm³, monoclinic, space group *P*₂₁, a = 7.1449(9) Å, b = 15.429(3) Å, c = 11.890(2) Å, β = 99.95(1)°, V = 1291.0(4) Å³, Z = 2, pcalc = 1.997 g/cm³, μ = 19.813 mm⁻¹, F(000) = 760, θ min = 3.774°, θ max = 73.497°, 6796 reflections collected, 4304 unique (R_{int} = 0.0652), parameters / restraints = 349 / 1, R1 = 0.0641 and wR2 = 0.1486 using 2910 reflections with I>2 σ (I), R1 = 0.0904 and wR2 = 0.1763 using all data, absolute structure parameter = -0.02(2), GOF = 0.997, -1.336 < $\Delta \rho$ < 0.925 e.Å⁻³.



¹H and ¹³C NMR spectra of compound (6)



¹H and ¹³C NMR spectra of compound (9 α)



¹H and ¹³C NMR spectra of compound (9β)









¹H and ¹³C NMR spectra of compound (11b)







¹H, ¹⁹F and ¹³C NMR spectra of compound (11d)





¹H and ¹³C NMR spectra of compound (11h)

¹H and ¹³C NMR spectra of compound (14)





¹H and ¹³C NMR spectra of compound (11i)





¹H and ¹³C NMR spectra of compound (12a)







¹H and ¹³C NMR spectra of compound (12c)











¹H and ¹³C NMR spectra of compound (12e)



¹H and ¹³C NMR spectra of compound (12f)

¹H and ¹³C NMR spectra of compound (12g)







¹H and ¹³C NMR spectra of compound (12i)



¹H, ¹³C NMR and NOESY spectra of compound (13a)









¹H and ¹³C NMR spectra of compound (13c)



S29

¹H, ¹⁹F and ¹³C NMR spectra of compound (13d)



Current Data Parameters NAME P31-457-P1B-2D EXPRO P2 - Acquisition Parameters D2 - Acquisition Parameters D3 - 56 ms PAEBO BB- PULPECS softhiggn TD 131072 SOLVENT MeOD NS 14 D3 - 67567.550 Hz D1 0.0000000 see D1 0.000000 see D1 0.0000000 see D1 0.000000000 see D1 0.00000000000000000000000000000000000		4
$ \begin{array}{c} \text{LiME} & \text{PST-45V-PIE-20} & \text{O} \\ \text{LIZERO} & 1 & 1 \\ \text{PEOCNO} & 1 & 1 \\ \text{PEOCNO} & 1 & 1 \\ \end{array} \\ \begin{array}{c} \text{P2 - Acquisition Parameters} \\ \text{Date_} & 20190415 \\ \text{Time} & 18.58 \\ \text{IISTRUM} & \text{opect} \\ \text{PROBID 5 mm PABEO BB-} \\ \text{PULPROG sighting m} \\ \text{TD} & 131072 \\ \text{SOLVEIT} & \text{HeOD} \\ \text{HS} & 16 \\ \text{DS} & 16 \\ \text{SWR} & 67567.570 \text{ Hz} \\ \text{DS} & 1.4 \\ \text{OW} & 10.0000000 \text{ eve} \\ \text{DE} & 7.400 \text{ usec} \\ \text{DI} & 10.00000000 \text{ eve} \\ \text{D11} & 10.00000000 \text{ eve} \\ \text{D12} & 0.00002000 \text{ eve} \\ \text{D11} & 10.550 \text{ usec} \\ \text{F1} & 1.455 \text{ usec} \\ \text{F1} & 1.455 \text{ usec} \\ \text{F1} & 232.3761148 \text{ HHz} \\ \end{array} $	Current Data Parameters	
EXPNO 11 F2 - Acquisition Parameters Date_ 20190415 Time 18.58 INSTRM speet PTUPROG softhiggn TD 131072 SOLVENT MeoD HS 16 DS 4 STM 67567.570 Hz FIDEES 0.515500 Hz AQ 0.9699328 see RG 181 DW 7.400 usec DE 6.50 usec TE 2056 K D1 10.0000000 see D13 0.0000000 see D13 0.0000000 see D13 0.0000000 sec D13 0.0000000 sec D14 0.0000000 sec D13 0.0000000 sec D14 0.0000000 sec D15 0.000000 sec D15 0.0000000 sec D14 0.0000000 sec D15 0.000000 sec D15 0.0000000 sec D16 0.0000000 sec D17 0.0000000 sec D17 0.000000 sec D18 0.0000000 sec D19 0.0000000 sec D10 0.000000 sec D10 0.0000000 sec D10 0.0000000000000000000000000000000000	NAME PSI-457-F1B-2D	ίρ
PROFIDE 1 F2 - Acquisition Persenters Date_ 20190415 Time 18.58 INGTRUM opect PROEND 5 nm PABEO BB- PROEND 5 sgfliggn TD 131072 S01VEHT NoD HG 6567.570 H FUDES 0.515500 H AQ 0.9699328 see RG 1.81 WW 7.400 usee DE 6.50 usee DE 296.6 K D1 10.0000000 see D12 0.00002000 see D12 0.00002000 see D12 0.00002000 see D11 10.50 usee PI 14.50 usee PI 14.50 usee PI 12 3.50 dB PFO1 282.3761148 NHm	EXPNO 11	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	PROCNO 1	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	P2 - leggicition Revenetave	
There is a set of the	Date 20190415	F-\ N O
INCIDENT operation operation PROBED 5 mar PABEO BB- $opfhiggn$ PULPEROG $sofhiggn$ TD 131073 SOLVENT M=0D HS 16 DS 4 SWH 67667.57.61 H PULPES 0.515500 HE AQ 0.9699328 mec EG 151 DN 7.400 usec DE 6.50 usec TE 296.6 K D1 0.03000000 sec D11 0.03000000 sec D12 0.0002000 sec TD0 1 Image: CHAINEL f1 155 GF01 282.3761148 MHz	Time 18.58	
PROBUD 5 mm PABBO BB- PULPROG softhighn TD 131072 SOLVEINT HeOD HS 16 DS 4 SWR 67567.570 Hz FIDERS 0.51550 Hz AQ 0.9669328 see RS 181 DW 7.400 usee PE 296.6 K D1 10.0000000 see D11 0.0000000 see D12 0.000000 see D11 14.50 usee PL1 3.50 dB SFO1 282.3761148 MHz	INSTRUM spect	
FOLPROG argfhiggn HO // N TD 131072 HO // N SOLVENT NeOD HO HO DS 4 HO HO SWH 67567.570 Hz HO HO PIDPEE 0.515500 Hz HO HO AQ 0.9699326 sec E E EG 131 HO HO DW 7.400 usec E DE 6.50 usec E D1 10.0000000 sec D11 D11 0.0000000 sec D12 D12 0.00002000 sec E D13 0.5000000 sec D P1 14.50 usec P1 282.3761148 HHz	PROBHD 5 mm PABBO BB-	
ID 1910/2 ID HeDD HC 16 DS 4 SWH 67567.570 Hz FIDEES 0.515500 Hz AQ 0.98699328 sec EG 181 DW 7.400 usec DE 6.55 usec TE 296.6 K D1 0.03000000 sec D12 0.03000000 sec D12 0.0300000 sec D11 1.4550 usec P1 14.550 usec P1 14.550 usec SF01 282.3761148 MHz	PULPROG zgfhigqn	HO MAN AND AND AND AND AND AND AND AND AND A
No. 16 16 No. 16 16 No. 16 07 No. 0.9699328 see 16 No. 0.9699328 see 17 No. 0.9000200 see 1 Image: No. 1 16 No. 1 14 SPO1 282.3761148 MHz	SOLVENT M-OD	
DS 4 SWH 67567.570 Hz PIDDES 0.515500 Hz AQ 0.969328 see EG 181 DN 7.400 usec DE 6.50 usec TE 296.6 K D1 10.0000000 sec D12 0.0002000 sec D12 0.0002000 sec TD0 1	NS 16	no on
SNH 67567.570 HE FIDEES 0.15500 HE AQ 0.9669328 sec FG 181 DW 7.400 usec DE 6.50 usec TE 296.6 K D1 10.0000000 sec D11 0.0300000 sec D12 0.0000200 sec TD0 1	DS 4	
FIDEE: 0.515500 Hz AQ 0.9699328 sec PG 181 DW 7.400 usec DE 6.50 usec TE 296.6 K D11 10.0000000 sec D12 0.0002000 sec TD0 1	SWH 67567.570 Hz	
AQ 0.9699335 sec RG 181 DW 7.400 usec DE 6.50 usec TE 296.6 K D1 10.0000000 sec D11 0.0000000 sec D12 0.0000200 sec TD0 1 	FIDRES 0.515500 Hz	
100 7.401 usec D1 6.50 usec D1 10.000000 sec D12 0.0002000 sec D12 0.0002000 sec 10001 1 HUG1 14.50 usec P1 14.50 usec P1 282.3761148 MHz	AQ 0.9699328 sec	
DE 6.50 Wee TE 296.6 K D1 10.0000000 sec D12 0.0002000 sec TD0 1 CHAINEL f1 NUC1 19F F1 14.50 Wee FL1 3.50 dB SF01 282.3761148 MHz	DW 7.400 uses	
TE 296.6 K D1 10.0000000 sec D11 0.0300000 sec D12 0.0000200 sec TD0 1	DE 6.50 uper	
D1 10.0000000 sec D11 0.000000 sec D12 0.0000200 sec TD0 1 	TE 296.6 K	
D11 0.0300000 sec D12 0.000200 sec TD0 1 CHAINEL f1 NUC1 19F P1 14.50 usec P11 3.50 dB SF01 282.3761148 MHz	D1 10.0000000 sec	
D12 0.0000000 see TD0 1 CHAINEL f1 NUC1 14.50 upee Pl1 3.50 dB SFO1 282.3761148 MHm	D11 0.03000000 sec	
CHAINNEL f1 NUCL 19F P1 14.50 usec PLI 3.50 dB SFOI 282.3761148 MHz	TD0 0.00002000 see	
	120	
NUCL 19F P1 14.50 usec PLI 3.50 dB 3FOI 282.3761148 MHz	CHANNEL fl	
PI 14:50 upec PII 3:50 dB SFOI 282.3761148 MHz	NUC1 19F	
282.3761148 MHz	PI 14.50 used	
	SF01 282.3761148 MHz	
. الب		. II.

-30	-40	-50	-60	-70	-80	-90	-100	-110	-120	-130	-140	ppm



¹H and ¹³C NMR spectra of compound (13f)



S33

¹H and ¹³C NMR spectra of compound (13g)



S34

¹H and ¹³C NMR spectra of compound (13h)









¹H and ¹³C NMR spectra of compound (5a)

¹H and ¹³C NMR spectra of compound (5b)



S38

¹H and ¹³C NMR spectra of compound (5c)



¹H, ¹⁹F and ¹³C NMR spectra of compound (5d)





¹H and ¹³C NMR spectra of compound (5e)



¹H and ¹³C NMR spectra of compound (5f)



¹H and ¹³C NMR spectra of compound (5g)







¹H and ¹³C NMR spectra of compound (5i)

