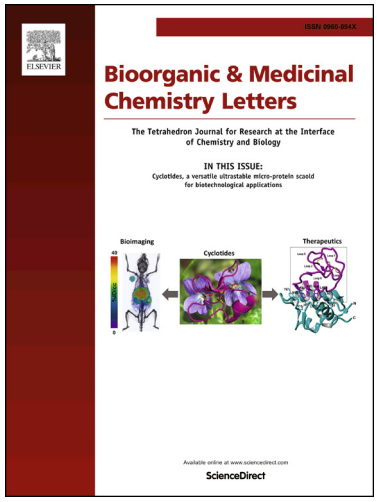
Accepted Manuscript



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PII: S0960-894X(18)30258-0
DOI: https://doi.org/10.1016/j.bmcl.2018.03.063
Reference: BMCL 25717

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 13 February 2018
Accepted Date: 22 March 2018

Please cite this article as: Marzag, H., Zerhouni, M., Tachallait, H., Demange, L., Robert, G., Bougrin, K., Auberger, P., Benhida, R., Modular synthesis of new *C*-aryl-nucleosides and their anti-CML activity, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.03.063

Modular synthesis of new *C*-aryl-nucleosides and their anti-CML activity

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# Equal contribution of the authors HM and MZ

ABSTRACT

The *C*-aryl-ribosyles are of utmost interest for the development of antiviral and anticancer agents. Even if several synthetic pathways have been disclosed for the preparation of these nucleosides, a direct, few steps and modular approaches are still lacking. In line with our previous efforts, we report herein a one step - eco-friendly β-ribosylation of aryles and heteroaryles through a direct Friedel-Craft ribosylation mediated by bismuth triflate, $Bi(OTf)_3$. The resulting carbohydrates have been functionalized by cross-coupling reactions, leading to a series of new *C*-aryl-nucleosides (32 compounds). Among them, we observed that **5d** exerts promising anti-proliferative effects against two human Chronic Myeloid Leukemia (CML) cell lines, both sensitive (K562-S) or resistant (K562-R) to imatinib, the "gold standard of care" used in this pathology. Moreover, we demonstrated that **5d** kills CML cells by a non-conventional mechanism of cell death.

KEYWORDS

Nucleoside analogues;

Modular syntheses;

Green chemistry;

Anti-CML agents.

Nucleosides have been considered for a long time as ideal pharmacophores in medicinal chemistry, since several nucleoside analogues are routinely used in antiviral and anticancer chemotherapies. For example, *N*-ribonucleosides have been used in antiviral chemotherapy as reverse transcriptase inhibitors against either DNA- and RNA-viruses.[1] Among them, the ribavirin is routinely used for the treatment of hepatitis C virus (HCV), in monotherapy or in combination with interferon.[2] Very recently, Sofosbuvir (Solvadi®), another nucleoside analogue, has revolutionized the treatment of HCV in curing this disease. Several anticancer nucleosides such as 5-azacytidine and decitabine,[3] have been recently approved for the treatment of myelodysplastic syndromes and acute myeloid leukemia. Another relevant bioactive ribonucleoside is AICAR (acadesine), an anti-proliferative agent exhibiting an interesting mode of action involving a pure autophagy cell death.[4]

While the *N*-nucleosides are relatively less stable to enzymatic and chemical degradation, by cleavage of the *C-N* glycosidic bond, their *C*-analogues featuring a carbon-carbon bond are much more stable.[5] Moreover, several *C*-nucleoside analogues have been reported for their therapeutic applications such as thiazofurin, a potent inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH).[6] BCX-4430 was recently reported for its strong activity against aggressive viruses such as Ebola, Marburg and Zika virus (Figure 1).[7] Therefore, a large number of synthetic approaches to *C*-nucleosides have been recently reported.[8] However, synthetic difficulties in terms of the required steps, yield and/or stereoselectivity have been frequently encountered.[9]

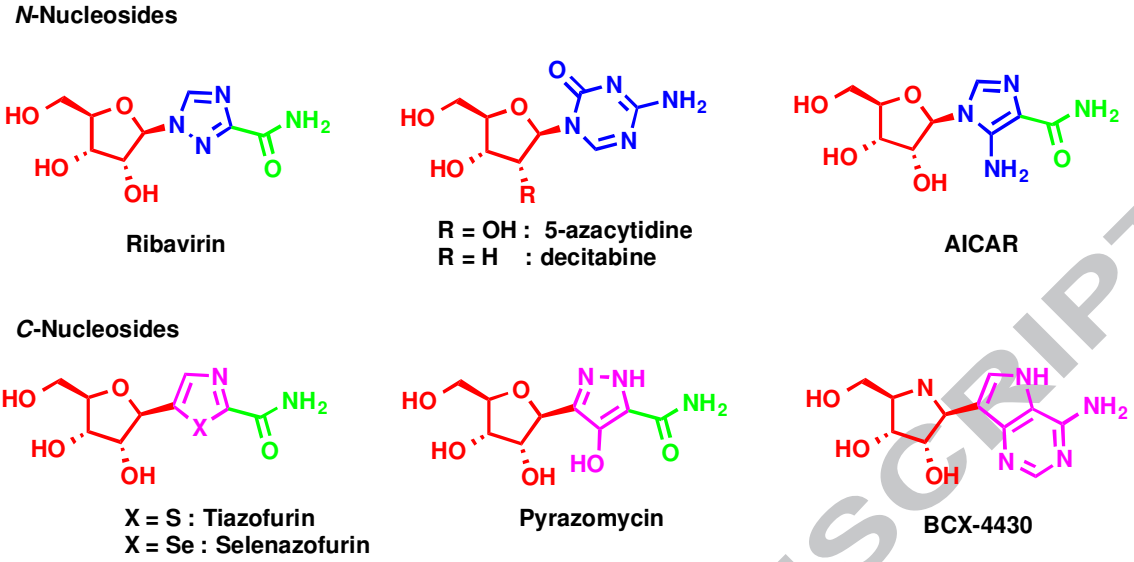


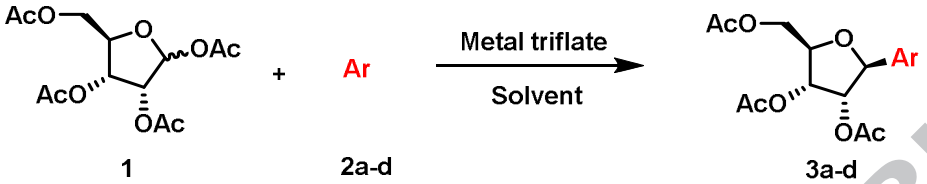
Figure 1. Relevant examples of bioactive *N*- and *C*-nucleosides analogues with antiviral of anticancer activity.

In continuation of our studies directed at the development of efficient synthetic routes to *C*-nucleosides,[10] we report herein a one-step modular Friedel-Craft ribosylation of aryles and heteroaryles using metal-triflates and particularly $Bi(OTf)_3$ as the most efficient catalyst for the *C*-*C* ribosylation reaction.

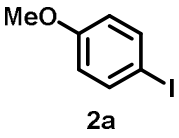
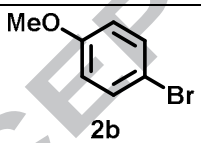
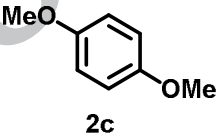
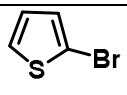
Our strategy was based on the preparation of a common halogenated intermediate, iodo-methoxy-phenyl nucleoside **3a**, for further post-synthetic transformations. In our first attempt, we used the rare-earth salts $Sc(OTf)_3$ and $Yb(OTf)_3$ (Table 1, entries 2-3), known to efficiently catalyze Friedel-Craft reactions between alcohol or acetate and various hetero-aromatic rings due to their strong Lewis acidity.[11] However, in our case, the expected *C*-aryl-nucleoside (**3a**) was obtained in very low yields (31 % and 15 %, respectively) even under hard conditions (100°C, 12h). We next focused on the other metal triflates $Mg(OTf)_2$, $Zn(OTf)_2$, $Cu(OTf)_2$ and $Al(OTf)_3$ (Table 1, entries 4-7).[12] Unfortunately, only poor conversion rates and yields were obtained, with $Al(OTf)_3$ being the best (30%, entry 7). Interestingly, the use of eco-friendly catalyst $Bi(OTf)_3$,[13] 5% molar in nitromethane at 50°C afforded **3a** in 64% yield (Table 1, entry 9). Moreover, by heating the reaction in refluxing nitromethane, the reaction time was decreased gradually to 10 min, and the yield was increased to 68% (Table 1, entry 10). The efficiency of $Bi(OTf)_3$ over the other metals may be explained by its remarkable acidity and the weak shielding effect of its *4f* electrons.[14]

Furthermore, the use of increased amount of catalyst led to decreased ribosylation yields (Table 1, entries 11-12).

Table 1. Survey of the ribosylation reaction conditions.



1 2a-d 3a-d

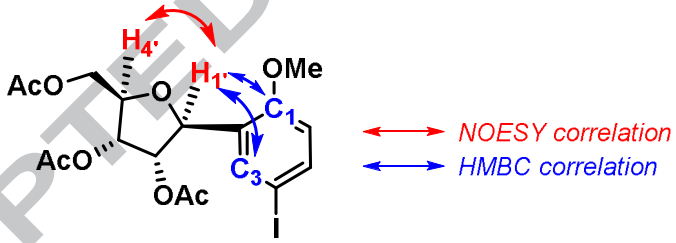
Entry	Ar	Catalyst	Solvent	Conditions	Yield
1	 2a	$SnCl_4$ (1.1 eq.)	CH_2Cl_2	0°C to rt, 16h	72 %
2		$Sc(OTf)_3$ (5%)	CH_3NO_2	50°C, 12h	31 %
3		$Yb(OTf)_3$ (5%)	CH_3NO_2	50°C, 12h	15 %
4		$Mg(OTf)_2$ (5 %)	CH_3NO_2	50°C, 12h	-
5		$Zn(OTf)_2$ (5 %)	CH_3NO_2	50°C, 12h	Traces
6		$Cu(OTf)_2$ (5 %)	CH_3NO_2	50°C, 12h	10 %
7		$Al(OTf)_3$ (5 %)	CH_3NO_2	50°C, 12h	30 %
8		$Bi(OTf)_3$ (5 %)	CH_3NO_2	rt, 12h	56 %
9		$Bi(OTf)_3$ (5 %)	CH_3NO_2	50°C, 3h	64 %
10		**$Bi(OTf)_3$ (5 %)**	**CH_3NO_2**	**Reflux, 10 min**	**68 %**
11		$Bi(OTf)_3$ (10 %)	CH_3NO_2	Reflux, 10 min	56 %
12		$Bi(OTf)_3$ (20 %)	CH_3NO_2	Reflux, 10 min	35 %
13		$Bi(OTf)_3$ (5 %)	CH_3CN	50°C, 24h	_
14		$Bi(OTf)_3$ (5 %)	CH_2Cl_2	rt, 24h	Traces
15		$Bi(OTf)_3$ (5 %)	C_6H_5Cl	50°C, 24h	Traces
16		$Bi(OTf)_3$ (5 %)	Xylene	50°C, 24h	_
17		$Bi(OTf)_3$ (5 %)	THF	50°C, 24h	Traces
18		$Bi(OTf)_3$ (5 %)	DMF	50°C, 24h	Traces
19	 2b	$Bi(OTf)_3$ (5 %)	CH_3NO_2	Reflux, 10 min	58 %
20	 2c	$Bi(OTf)_3$ (5 %)	CH_3NO_2	Reflux, 10 min	52 %
21	 2d	$Bi(OTf)_3$ (5 %)	CH_3NO_2	Reflux, 10 min	56 %

Reaction conditions: 1'-β-ribofuranose-1',2',3',5'-tetraacetate (1.0 eq.), (hetero)aryle (2.0 aq.), catalyst (0.05 to 1.1 eq.), solvent (10 ml/mmol), heating at 50°C. After work up, crude material is purified by silica gel column chromatography (see supporting information for details).

Interestingly, the use of other solvents such as acetonitrile, dichloromethane, xylene, THF and DMF completely hampered the reaction (entries 13-18), which could be ascribed to solubility and solvation issues. Finally, this methodology was tested with three other aromatic compounds (*p*-iodoanisole **2b**, *p*-dimethoxybenzene **2c** and 2-bromothiophene **2d**, Table 1 entries 19-21). By applying the same reaction conditions, the corresponding *C*-aryl-nucleosides **3b**, **3c** and **3d** were isolated in 52% - 58% non-optimized yields.

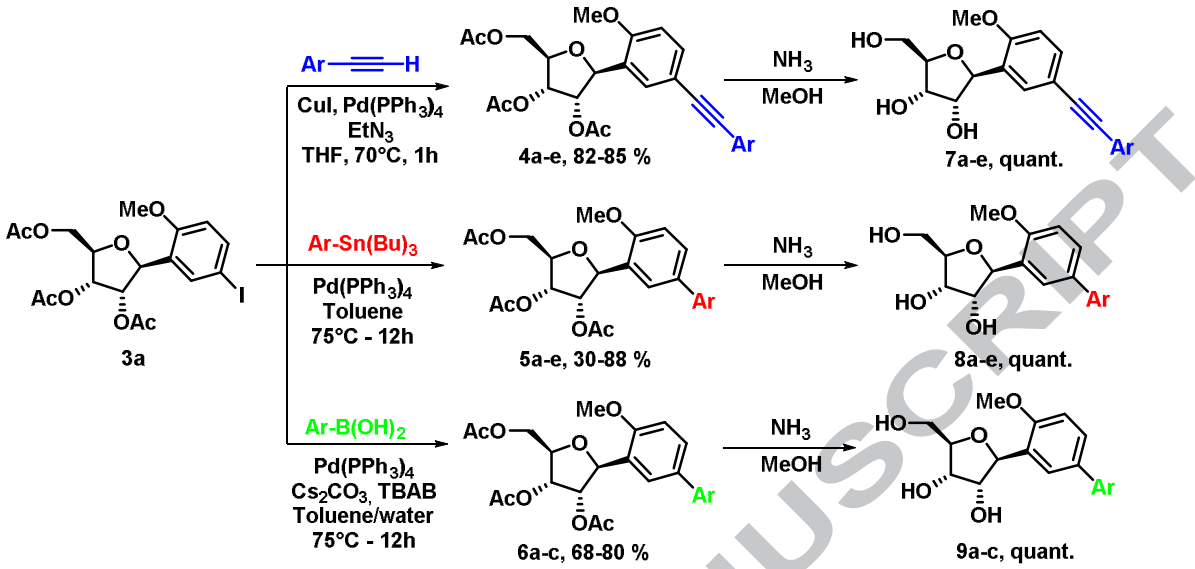
Importantly, we observed that the ribosylation reaction is stereoselective in favor of the β-anomer.[15] This stereoselectivity is probably due to a β-stereofacial addition of aryl nucleophile on the oxonium intermediate, which is stabilized by the acetate group at *C*-2 position of the ribose (anchimeric assistance).[16] Moreover, we do not observe any racemization at the anomeric position. For example, in the case of compound **3a**, we observed in the 2D NMR spectra a clear NOESY correlations between H_1' and H_4' and HMBC correlations between H_1'-C_1 and H_1'-C_3 unambiguously attesting for a β configuration (Figure 2).

Figure 2. Significant 2D NMR correlations (NOESY and HMBC experiments).



With this optimized procedure in hand, we decided to take advantage of the aromatic iodine to perform post synthetic transformations by means of Pd-catalyzed cross-coupling reactions: Sonogashira, Buchwald-Hartwig and Stille cross-coupling reactions (Figure 3 and Table 2).

Figure 3. Post-functionalization of the *C*-aryl-nucleoside **3a**.



We first started by Pd-catalyzed Sonogashira coupling.[17,18] After several optimizations, the coupling of **3a** with various terminal alkynes at 75°C afforded the expected products **4a-e** in high yield (82-85%).

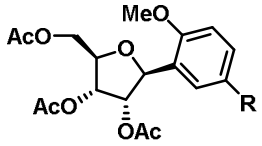
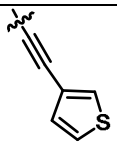
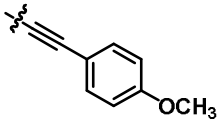
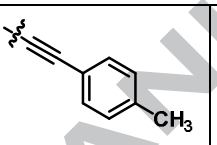
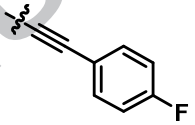
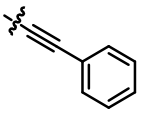
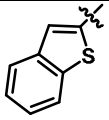
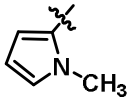
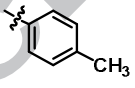
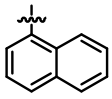
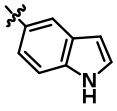
On the other hand, two series of *C*-biaryl-ribosyles have been synthesized through Stille and Suzuki cross coupling reactions.[19] First, a selection of aryl stannane derivatives have been coupled under argon atmosphere to compound **3a** in presence of $Pd(PPh_3)_4$ (5% mol) in toluene. After warming at 75°C for 12h, the expected biaryle *C*-nucleoside (**5a-e**) have been isolated in good yields, depending on the aryl group. We have obtained very good conversion rates when using tributyl(furan-2-yl)stannane (**5c**, 80%) and tributyl(thiophen-2-yl)stannane (**5b**, 88%); however, in the other cases, low yields were obtained (30-40%), due to the concomitant formation of the homocoupling products.

Next, compound **3a** was allowed to react with *p*-tolylboronic acid in presence of $Pd(PPh_3)_4$ and cesium carbonate. However, no coupling occurred after 12h in refluxing toluene. When water was used as co-solvent (toluene/water 4/1), the expected product **6a** was obtained in low yield (28%). Interestingly, the best conversion rates (80%) have been obtained when adding TBAF, as it combines solvation and basic properties.[20] Moreover, this catalytic system allowed the coupling of very bulky boronic acid, such as naphthalene-1-yl boronic acid. In this case, the corresponding coupling product **6b** has been isolated in 68 % yield.

Lastly, all the functionalized compounds (**4a-e**, **5a-e** and **6a-c**) have been deprotected under mild conditions (Na_2CO_3 in methanol), to quantitatively afford the corresponding unprotected *C*-nucleosides (Scheme 2, **7a-e**, **8a-e** and **9a-c**).

All these newly synthesized compounds have been characterized by NMR spectroscopies and the corresponding data are given in the supplementary material section.

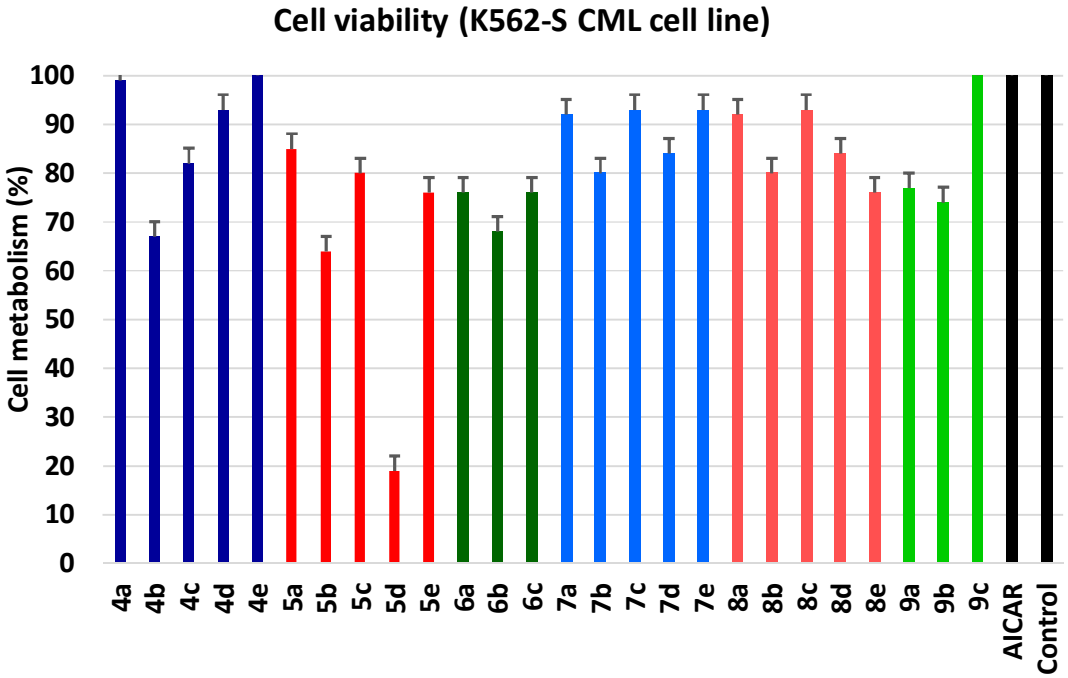
Table 2. List of the functionalized *C*-aryl-nucleosides synthesized.

					
Sonogashira coupling reactions					
R =					
Cpd.	**4a**	**4b**	**4c**	**4d**	**4e**
Yield	83%	84%	85%	82%	82%
Stille coupling reactions					
R =					
Cpd.	**5a**	**5b**	**5c**	**5d**	**5e**
Yield	30%	88%	80%	41%	40%
Suzuki coupling reactions					
R =					
Cpd.	**6a**	**6b**	**6c**		
Yield	80%	68%	40%		

All the above-mentioned products have been first screened at the single dose of 10µM (except for compounds **3a-d**, which have been evaluated at 20 µM) against K562-S, a human myelogenous leukemia cell line sensitive to the kinase inhibitor imatinib (Gleevec®), the current drug used for the treatment of patients suffering this malignancy. The cell viability has

been evaluated through an XTT assay, performed after 48h of incubation, and compared to these measured with AICAR (Figure 4) and Imatinib (see table 3); results are reported Figure 2.[21]

Figure 4. Cytotoxicity of post-functionalized *C*-nucleosides. (CML K562-S cell line, measured by XTT assay, and after 48h. incubation with selected compounds at 10 µM).



First, except for **4a** and **4e**, all the post-functionalized compounds exert a biological activity stronger than those observed with the parent compounds **3a-d** (no effect on K562-S viability at 20 µM, see SI Table 1). Second, we found that these products are more efficient than AICAR, previously reported as a promising anti-CML agent particularly against imatinib-resistant cells (no cytotoxic effect at 10 µM on sensitive cells).[4c,22] Among these 32 newly synthesized molecules, four compounds (**4b**, **5b**, **5d**, **6b**) reduce by more than 30% the K562-S viability, which remains significant. Lastly, it is to note that the deacetylated compounds (**7a-e**, **8a-e** and **9a-c**) appear less active than the protected ones; this is particularly highlighted by comparison of **5d** *vs* **8d** (K536-S viability reduction at 10µM: 81 % *vs* 16%).

Furthermore, this screening pointed out the inhibitory effect of compound **5d**, substituted by a bulky biaryle group, since it kills more than 80% of the K562-S cells at 10 µM. Indeed, this

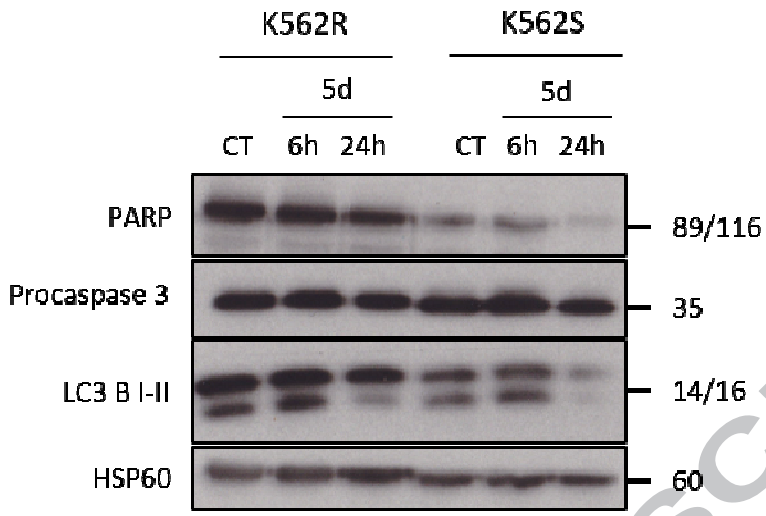
molecule reduces the K562-S viability in a dose dependent manner (IC_{50} = 4.0 ± 0.2 µM); it is thereby 200-fold more active than AICAR, and only 4-fold less cytotoxic than imatinib (IC_{50} = 1.1 µM). More interestingly, **5d** retains a similar cytotoxicity, when assayed against the K562-R cells (IC_{50} = 2.9 ± 0.2 µM), which are resistant to imatinib (Table 3).

Table 3. IC_{50} of compound **5d** compared to those of AICAR and imatinib (Gleevec©) in K562-S and K562-R cell lines.

Compound	IC_{50} (µM)	
	K562-S	**K562-R**
5d	4.0 ± 0.2	2.9 ± 0.2
AICAR	800	800
Imatinib	1.1	>50

This result prompted us to investigate the mechanism by which compound **5d** could kill K562 cells. Thus, we first analyzed by western blot the expression of procaspase 3, an essential executioner caspase and of one of its preferential substrate Poly ADP-Ribose Polymerase (PARP). Compound **5d** failed to induce caspase 3 and PARP cleavage after 6 and 24 h ruling out the possibility that it exerted its anti-leukemic effect in K562-S and K562-R cells by inducing apoptosis (Figure 5). We next analyzed the effect of compound **5d** on the lipidation and cleavage of microtubule-associated protein 1A/1B-light chain 3 (LC3). LC3-I cleavage into LC3-II represents a hallmark of autophagy induction. A high rate of autophagy was found in both K562-S and K562-R cells, as attested by an important accumulation of LC3-II in untreated cells. Of note, compound **5d** decreased LC3-II accumulation in both cell lines at 24 h, suggesting an inhibition of the autophagy rate. In K562 cells, induction of autophagy has been reported as a prosurvival mechanism.[21-23] Whether or not this inhibition in the autophagy rate mediated by compound **5d** is responsible for its anti-leukemic activity remains however to be established. Altogether, these results suggest a non-conventional mechanism of cell death by compound **5d** that may occur through a reduction of the high basal protective autophagy rate present in CML cell lines. [23] Nonetheless, this observation is of great interest for the development of future anti-cancer agents, able to overcome tumor resistance against conventional drugs.[24]

Figure 5. Immunobloting analysis of selected markers of apoptosis and autophagy mechanisms.

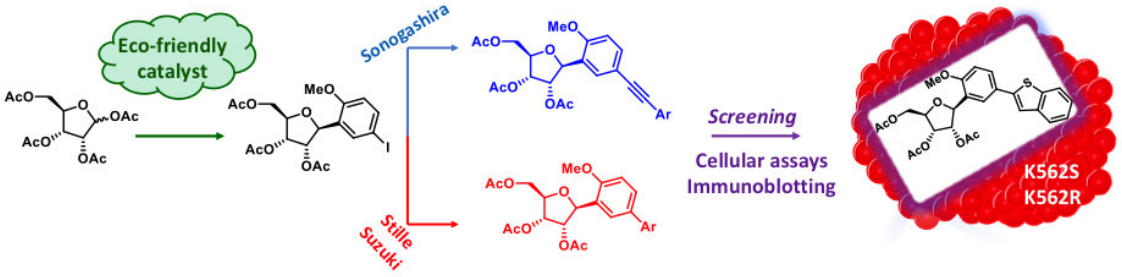


In summary, we report herein a 2-steps modular synthesis of *C*-nucleosides, consisting in: (i) an eco-friendly and stereoselective Friedel Craft ribosylation reaction catalyzed by $Bi(OTf)_3$, and (ii) a post-functionalization of iodo-aryl *C*-nucleoside through Sonogashira, Stille and Suzuki cross-coupling reactions. The expected products have been obtained in good yields and fully characterized. The cytotoxicity of the 32 newly synthesized *C*-nucleosides has been evaluated against two human CML cell lines, sensitive and resistant to Imatinib. This preliminary screening showed the potential of compound **5d** as an interesting hit for further structural optimizations, and particularly for the treatment of Imatinib-resistant patients. Lastly, our preliminary assays suggest that biological effect of **5d**, is due to its ability to induce a non-conventional mechanism of cell death in K562-S and K562-R cells.

ACKNOWLEDGMENTS

This work is supported by PHC Toubkal, CNRS, CNRST, the Institut National du Cancer INCa-PL2011-0249 and Canceropôle PACA. This article is based upon work form COST Action CA15135, supported by COST.

GRAPHICAL ABSTRACT



REFERENCES AND NOTES

1. a. Fonvielle M, Sakkas N, Iannazzo L, Le Fournis C, Patin D, Mengin-Lecreulx D, El-Sagheer A, Braud E, Cardon S, Brown T, Artur M, Etheve-Quelquejeu M. *Angewandte Chem. Ed. Int. Engl.* 2016;55:13553; b. Chen Y-L, Yokokawa F, Shi P-Y. *Antiviral Res.* 2015;122:12 ; c. Xia Y, Wang M, Beraldi E, Cong M, Zoubeidi A, Gleave M, Peng L. *Anticancer Agents Med Chem.* 2015;15(10):1333; d. Hamada M, Roy V, McBrayer TR, Whitaker T, Urbina-Blanco C, Nolan SP, Balzarini J, Snoeck R, Andrei G, Schinazi RF, Agrofoglio LA. *Eur J Med Chem.* 2013;67:398-408; e. Xia Y, Liu Y, Wan J, Wang M, Rocchi P, Qu F, Iovanna JL, Peng L. *J Med Chem.* 2009;52:6083.

2. Pecoraro V, Cariani E, Villa E, Trenti T. *Eur J Clin Invest.* 2016;46(8):737;

3. a. Ball B, Zeidan A, Gore S, Prebet T. *Leuk Lymphoma* 2017;58(5):1022-1036; b. Nieto M, Demolis P, Behanzin E, Moreau A, Hudson I, Flores B, Stemplewski H, Salmonson T, Gisselbrecht C, Bowen D, Pignatti F. *Oncologist* 2016;21:1; c. Scott LJ. *Drugs* 2016,76:889; d. Finelli C, Follo MY, Stanzani M, Parisi S, Clissa C, Mongiorgi S, Barraco M, Cocco L. *Curr Pharm Design.* 2016;22:2349; e. El Fakih RO, Champlin R, Oran B. *Expert Opin Orphan Drugs.* 2015;3(10):1197.

4. Gonzalez-Girones DM, Moncunill-Massaguer C, Iglesias-Serret D, Cosialls AM, Perez-Perarnau A, Palmeri CM, Rubio-Patino C, Villunger A, Pons G, Gil J. *Apoptosis.* 2013;18:4384; b. Daignan-Fornier B, Pinson B. *Metabolites* 2012;2:292; c. Robert G, Ben Sahra I, Puissant A, Colosetti P, Belhacene N, Gounon P, Hofman P, Bost F, Cassuto JP, Auberger P. *PLoS ONE.* 2009;4(11):e7889.

5. De Clercq E. *J Med Chem.* 2016;59:2301; Leclerc E., Pannecoucke X, Etheve-Quelquejeu M, Sollogoub M. *Chem Soc Rev*. 2013;42(10):4270.

6. a. Popsavin M, Kojic V, Torovic L, Svircev M, Spaic S, Jakimov D, Aleksic L, Bogdanovic G, Popsavin V. *Eur J Med Chem.* 2016;111:114; b. Rouf A, Tanyeli C. *Eur J Med Chem.* 2015;97:911.

7. a. Izawa K, Acena JL, Wang J, Soloshonok VA, Liu H. *Eur J Med Chem.* 2016;1:8; b. Warren TK, Wells J, Panchal RG, Stuthman KS, Garza NL, Van Tongeren SA, Dong L, Retterer CJ, Eaton BP, Pegoraro G, Honnold S, Bantia S, Kotian P, Chen X, Taubenheim BR, Welch LS, Minning DM, Babu YS, Sheridan WP, Bavari S. *Nature.* 2014;508(7496):402.

8. a. Lalitha K, Muthusamy K, Prasad YS, Vemula PK, Nagarajan S. *Carbohydr Res.* 2015;402 :158; b. Tokarenko A, Postova Slavetinska L, Klepetarova B, Hocek M. *Eur J Org Chem.* 2015;2015(36):7962; c. Kubelka, T, Slavetinska L, Eigner V, Hocek M. *Org Biomol Chem.* 2013;11(28):4702; d. Joubert N, Pohl R, Klepetarova B, Hocek M. *J Org Chem.* 2007;72:6797; e. Harusawa S, Matsuda C, Araki L, Kurihara T. Synthesis 2006;5:793; Taniguchi Y, Nakamura A, Senko Y, Nagatsugi F, Sasaki S. *J Org Chem.* 2006;71:2115; f. Zivkovic A, Engels JW. *Nucleosides Nucleotides and Nucleic Acids* 2005;24:1023; g. Hikishima S, Minakawa N, Kuramoto K, Fujisawa Y, Ogawa M, Matsuda A. *Angewandte Chem Ed Int Engl.* 2005;44:596; h. Sollogoub M, Fox KR, Powers VEC, Brown T. *Tetrahedron Lett.* 2002;43:3121; i. Guianvarc'h D, Fourrey JL, Tran Huu Dau ME, Guérineau, R. Benhida. *J Org Chem.* 2002;67:3724.

9. a. Yang Y, Yu B. *Chem Rev.* 2017;doi :10.1021/acs.chemrev.7b00234; b. Stambasky J, Hocek M, Kocovsky P. *Chem Rev.* 2009;109:6729.

10. a. Spadafora M, Mehiri M, Burger A, Benhida R. *Tetrahedron Lett.* 2008;49:3967; b. Jazouli M, Guianvarc'h D, Soufiaoui M, Bougrin K, Vierling P, Benhida R. *Tetrahedron Lett.* 2003;44(31):5807.

11. a. Song CE, Shim WH, Roh EJ, Choi JH. *Chem Commun.* 2002;1695; b. Sinha S, Mandal B, Chandrasekaran S. *Tetrahedron Lett.* 2000;41:9109; c. Kotsuki H, Ohishi T, Inoue M. Synlett. 1998;255; d. Tshuchimoto T, Hiyama T, Fukuzawa S. *Chem Commun.* 1996; 2345.

12. a. Poulsen TB, Jorgensen KA. *Chem Rev*. 2008;108 :2903; b. Esquivias J, Arrayas RG, Carretero J. *Angewandte Chem Ed Int Eng*. 2006;45:629; c. Lu SF, Du DM, Xu J. *Org Lett.* 2006;8(10):2115.

13. Salvador JAR, Figueiredo SAC, Pinto RMA, Silvestre SM. *Future Med Chem.* 2012;4(11):1495.

14. a. Tran PH, Phung HQ, Duong MN, Pham-Tran NN. *Tetrahedron Lett.* 2017;58:1558; b. Tran PH, Nguyen HT, Hansen PE, Le TN. *ChemistrySelect.* 2017;2:571; c. Ondet P, Lemière G, Dunach E. *Eur J Org Chem.* 2017;4(26) :761; d. Ollevier T. *Org Biomol Chem.* 2013;11 :2740; e. Répichet S, Le Roux C, Dubac J, Desmurs JR. *Eur J Org Chem.* 1998;12 :2743; f. Matsushita Y, Sugamoto K, Matsui T. *Tetrahedron Lett.* 2004;45:4723.

15. The β/α ratio has been evaluated by NMR analyses, and it is always up to 90/10.

16. a. Alaoui S, Driowya M, Demange L, Benhida R, Bougrin K. Ultrason Sonochem. 2018;40:289; b. Marzag H, Alaoui S, Amdouni H, Martin AR, Bougrin K, Benhida R. *New J Chem.* 2015;39(7):5437; c. Marzag H, Robert G, Dufies M, Bougrin K, Auberger P, Benhida R. Ultrason Sonochem. 2015;22:15.

17. a. Buchanan HS, Pauff SM, Kosmidis TD, Taladriz-Sender A, Rutherford OI, Hatit MZC, Fenner S, Watson AJB, Burley GA. *Org Lett.* 2017;19:3759; b. Yamauchi T, Takeda T, Yanagi M, Takahashi N, Suzuki A, Saito Y. *Tetrahedron Lett.* 2017;58(2):117; c. Chistov AA, Ivanov NM, Kutyakov SV, Ustinov AV, Glybin AV, Streshnev PP, Mikhura IV, Korshun VA. *Tetrahedron Lett.* 2016;57(43):4821.

18. a. Simonova A, Havran L, Pohl R, Fojta M, Hocek M. *Org Biomol Chem.* 2017;15(33):6984; b. Ramin MA, Baillet J, Benizri S, Latxague L, Barthélémy P. *New J Chem.* 2016;40(12):9903; c. Garg S, Shakya N, Srivastav NC, Agrawal B, Kunimoto DY, Kumar R. *Bioorg Med Chem Lett.* 2016;24(21):5521.

19. a. Ren H, An H, Hatala PJ, Stevens Jr. WC, Tao J, He B. *Beilstein J Org Chem* 2015;11:2509; b. James D, Escudier JM, Szlosek-Pinaud M, Fouquet E. *Molecules.* 2013;18(11):13654; c. Merino P, Torejo T, Marca E, Gomollon-Bel F, Delso I, Matute R. *Heterocycle.* 2012;86(2):791; d. Naus P, Perlikova P, Bourderioux A, Pohl R, Slavetinska L, Votruba I, Bahador G, Birkus G, Cihlar T, Hocek M. *Bioorg Med Chem* 2012;20(17):5202.

20. a. Joy MN, Bodke YD, Khader KKA, Sajith AM, Venkatesh T, Ajeesh AK. *J Fluor Chem.* 2016;182:109; b. Li JH, Deng CL, Xie YX. *Synth Commun*. 2007;37(14):2433; c. Miyashita K, Sakai T, Imanishi T. *Org Lett.* 2013;5(15):2683.

21. Cassuto O, Dufies M, Jacquel A, Robert G, Ginet C, Dubois A, Hamouda A, Puissant A, Luciano F, Karsenti JM, Legros L, Cassuto JP, Lenain P, Auberger P. *Oncotarget.* 2012;3 :1557.

22. Puissant A, Robert G, Auberger P. *Cell Cycle.* 2010;9(17):3470.

23. a. Alaoui S, Dufies M, Driowya M, Demange L, Bougrin K, Robert G, Auberger P, Pagès G, Benhida G. *Bioorg Med Chem Lett* 2017;27(9):1989; b. Amdouni H, Robert G, Driowya M, Furtoss N, Metier C, Dubois A, Dufies M, Zerhouni M, Orange F, Lacas-Gervais S, Bougrin K, Martin AR, Auberger P, Benhida R. *J Med Chem* 2017;60(4):1523; c. Ronco C, Millet A, Plaisant M, Abbe P, Hamouda-Tekaya N, Rocchi S, Benhida R. *Bioorg Med Chem Lett.* 2017;27(10):2192-2196; d. Millet A, Plaisant M, Ronco C, Cerezo M, Abbe P, Jaune E, Cavazza E, Rocchi S, Benhida R. *J Med Chem* 2016;59(18):8276; e. Cerezo M, Lehraiki A, Millet A, Rouaud F, Plaisant M, Jaune E, Botton Th, Ronco C, Abbe P, Amdouni H, Passeron Th, Hofman V, Mograbi B, Dabert-Gay A.-S, Debayle D, Alcor D, Rabhi N, Annicotte J.-S, Heliot L, Gonzalez-Pisfil M, Robert C, Morera S, Vigouroux A, Gual Ph, Ali MMU, Bertolotto C, Hofman P, Ballotti R, Benhida R, Rocchi S. *Cancer Cell.* 2016;29(6):805; f. Giuliano S, Cormerais Y, Dufies M, Grepin R, Colosetti P, Belaid A, Parola J, Martin A, Lacas-Gervais S, Mazure NM, Benhida R, Auberger P, Mograbi B, Pages G. *Autophagy.* 2015;11(10):1891.

24. a. Liu WQ, Lepelletier Y, Montes M, Borriello L, Jarray R, Grépin R, Leforban B, Loukaci A, Benhida R, Hermine O, Dufour S, Pagès G, Raynaud F, Hadj-Slimane R, Demange L. *Cancer Lett.* 2018;414:88; b. Ronco C, Martin AR, Demange L, Benhida R. *Med Chem Commun*. 2017;8(2):295; c. Martin AR, Ronco C, Demange L, Benhida R. *Med Chem Commun.* 2017;8(1):21; d. Borriello L, Montes M, Lepelletier Y, Leforban B, Liu WQ, Demange L, Delhomme B, Pavoni S, Jarray R, Boucher J.-L, Dufour S, Hermine O, Garbay C, Hadj-Slimane R, Raynaud F. *Cancer Lett.* 2014;349:120.