EurJIC
European Journal of Inorganic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: Eur. J. Inorg. Chem. 10.1002/ejic.201601227

Link to VoR: https://doi.org/10.1002/ejic.201601227

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Synthesis and photophysical properties of triazolyl Ir(III)-nucleosides

Johan Passays,[a]† Christophe Rubay,[a] Lionel Marcélis,[a] and Benjamin Elias*[a]

Abstract: DNA-based nanomaterials are the subject of numerous researches. A series of modified nucleobases were synthesized, either to construct a double-helix where natural H-bonded bases are replaced by metal-coordinated liganosides, or to introduce a punctual modification inside a natural DNA structure. Thanks to their photophysical and photochemical properties, Iridium(III) complexes receive a growing interest for the development of sensors and photoreactants for biochemical applications. In this view, we previously demonstrated that some Ir(III) complexes are able to photoreact with DNA via photo-induced electron transfer. In this study, we report the synthesis and the characterization of nucleosides bearing Iridium complexes with unaltered properties compared to parent complexes.

Introduction

The first example of a “click-reaction” dates back to the sixties when Huisgen described the 1,3-dipolar cycloaddition between alkynes and azide leading to 1,2,3-triazoles [1,2]. The concept of “Click chemistry” itself has emerged thanks to its description by Sharpless *et al* [3,4], but its use has been more and more attractive since the development of the copper catalyzed version of the Huisgen’s [3+2] azide-alkyne cycloaddition, namely the CuAAC reaction [5]. This reaction presents many advantages, mainly due to its mild conditions of use. “Click chemistry” is now used in diverse fields of research such as bio-conjugation, materials science or drug discovery [6]. Its popularity for these applications is due to the large variety of “clickable” azides and alkynes reagents available [7], and because it can proceed readily in water, allowing the use of sensitive biomolecules like DNA [8,9].

DNA-based nanomaterials are more and more developed; new structures have emerged where the Watson-Crick base pairs have been replaced by nucleoside analogues called *ligandosides*, featuring metal-binding ligands in place of classical nucleobases [10,11,12]. These ligand-like nucleobases can for example be used to obtain DNA-like multichromophore systems [13] or to perform titration of metal ions in solutions when 2,2’bipyridine is incorporated as ligandoside [14,15]. Artificial helical-DNA structures were successfully obtained and described, where hydrogen bonds between nucleobases are replaced by coordinative bonds to metal ions [16]. The use of bipyridine ligandoside in classic DNA helix placed in front of an abasic site was also shown to stabilize the DNA-structure by favorable π-stacking interactions [17,18].

Many examples of β-nucleosides derivatives containing a triazole moiety at position 1’ were reported in literature [19,20,21,22,23]. Some examples present biological activities as antiviral HIV agents [24], for treating HCV infection (as Ribavirin analogues) [25], for antiviral and antitumor potential activity (as Eicar analogues), for anti-mycobacterial activity (as DPA analogues) [26], or for treatment of chronic myelogenous leukemia (as Tiazofurin analogues) [27].

Thanks to their photophysical and photochemical properties, Iridium(III) complexes receive a growing interest for the development of sensors [28,29] and photoreactants towards DNA. In this later case, we recently demonstrated that a Ir(III) terpy (2,2′:6′,2″-terpyridine) derivative is able to photo-oxidize purine bases of DNA [30]. Another cyclometalated Ir(III) complex was shown to be able to photo-oxidize guanine and photo-reduce cytosine [31]. Iridium(III) complexes are thus excellent candidates to study charge transfer processes involving DNA and polynucleotides.

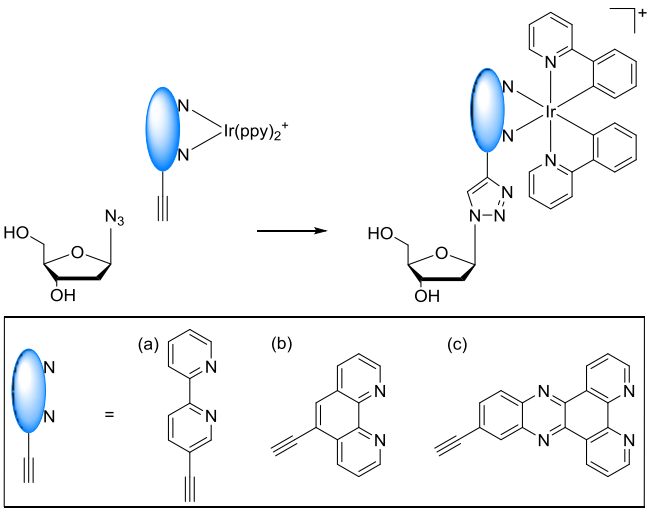

Figure 1. Synthetic scheme of the Ir(III) nucleosides (target molecules). Insert: modified ethynyl ligands (a) 5-ethynyl-2,2’-bipyridine **9**; (b) 5-ethynyl-1,10-phenanthroline **12**; (c) 11-ethynyldipyrido[3,2-a:2’,3’-c]phenazine.

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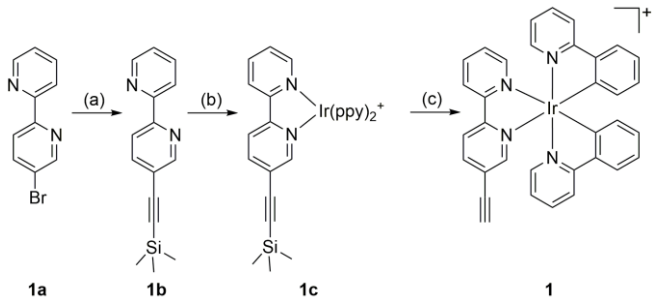
In this context, we report the design, synthesis and photophysical characterization of original iridium (III) complexes with functionalized bpy (2,2'-bipyridyne), phen (1,10-phenanthroline) and dppz (dipyrido[3,2-a;2',3'-c]phenazine) ligands at position 1' to a 2'-deoxyribose structure *via* a triazolyl linker formed by Huisgen click reaction (Figure 1). The goal of this research is (i) to develop a facile synthesis of Ir-nucleoside conjugates using mild conditions, and (b) to obtain such Ir-nucleoside conjugate having unaltered photophysical and photochemical properties compared to their parent complexes.

Results and Discussion

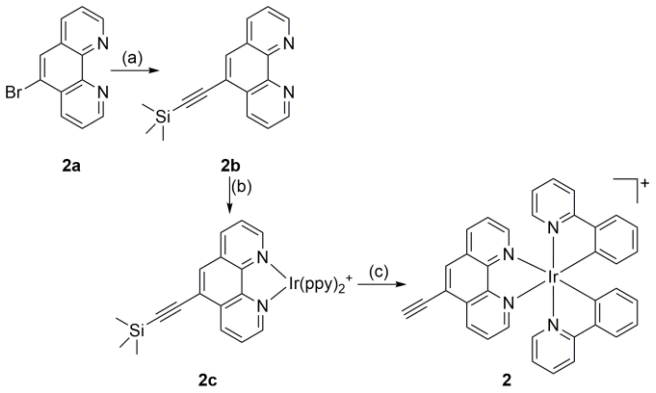
Towards the synthesis of ethynyl-Ir(III) polypyridyl complexes

Choi *et al*. recently report the synthesis of Iridium-nucleosides derivatives [32] and studied them as potential anti-cancer agents. Our Iridium nucleosides conjugates, presented in Figure 1, differentiate by the mode of anchoring of the complex on the sugar; in order to be able to vary more easily the nature of the complex tethered, we did not use the triazole ring as chelating moiety [32] in the Iridium complex but only as a linker. In this case, the tethering of the complex onto the nucleoside thus not affect the coordinating sphere around the Ir(III) and its photophysics remains unaltered.

The key precursors are designed to bear a single ethynyl functional group on one of the ligand chelated onto the Iridium center. We investigated three modified ligands based on bpy (2,2'-bipyridine), phen (1,10-phenanthroline) and dppz (dipyrido[3,2-a:2',3'-c]phenazine) ligands (see insert Figure 1).

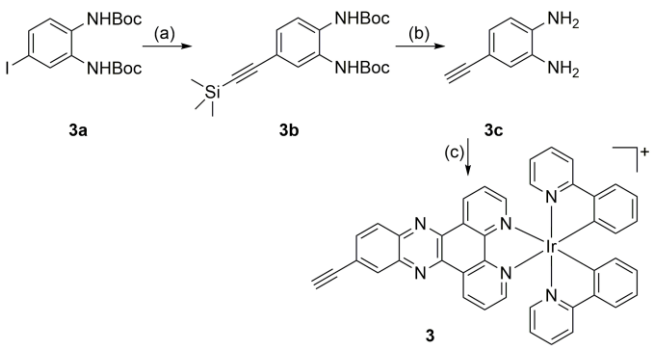


Scheme 1. Synthetic scheme for $[Ir(ppy)_2(Ethynyl\text{-}bpy)]^+$ **1**. *Reagents and conditions*: (a) Ethynyl-$SiMe_3$ (3.4 equiv.), $[Pd(PPh_3)_2Cl_2]$ (10mol%), CuI (16mol%), THF, i-Pr_2NH excess, rt, 48h, (79%); (b) $[Ir(ppy)_2Cl]_2$ (0.5 equiv.), CH_2Cl_2/MeOH 1:1, 65°C, 16h, (94%), (c) K_2CO_3 (2.3 equiv.), MeOH, rt, 16h, (71%).



Scheme 2. Synthetic scheme for $[Ir(ppy)_2(Ethynyl\text{-}phen)]^+$ **2**. *Reagents and conditions*: (a) Ethynyl-$SiMe_3$ (1.5 equiv.), $[Pd(PPh_3)_2Cl_2]$ (3mol%), CuI (10mol%), THF, i-Pr_2NH excess, rt, 24h, (85%); (b) $[Ir(ppy)_2Cl]_2$ (0.5 equiv.), CH_2Cl_2/MeOH 1:1, 65°C, 16h, (85%), (c) K_2CO_3 (1.4 equiv.), MeOH, rt, 24h, (72%).

For the bpy and phen based conjugates, the ethynyl-modified ligands are first synthesized and then chelated onto the Ir(III) (Scheme 1 and 2). 5-bromo-2,2'-bipyridine **1a** is obtained by a two steps procedure with stannylation of 2-bromopyridine followed by a $[Pd(PPh_3)_4]$ catalyzed Stille coupling reaction with 2,5-dibromopyridine [33]. Palladium catalyzed Sonogashira reaction with (trimethylsilyl)acetylene allowed us to obtain the protected ethynyl-bpy analogue **1b** [34,35]. 5-bromo-1,10-phenanthroline **2a** was prepared from 1,10-phenanthroline by reaction with bromine and oleum [36]. The (trimethylsilyl)acetylene moiety was introduced *via* Sonogashira reaction to obtain the intermediate **2b** [34]. TMS-protected bpy and phen ethynyl ligands were then individually reacted with $[Ir(ppy)_2Cl]_2$ dimer. Obtained complexes were afterwards deprotected under mild conditions upon treatment with K_2CO_3 in methanol to give respectively the desired ethynyl complexes **1** and **2** [37].



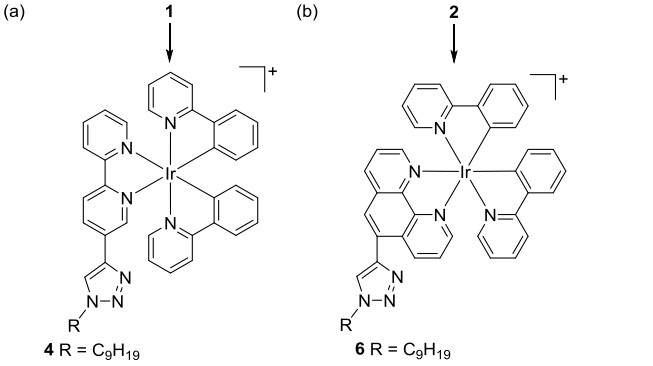
Scheme 3. Synthetic scheme for $[Ir(ppy)_2(Ethynyl\text{-}dppz)]^+$ **3**. *Reagents and conditions*: (a) Ethynyl-$SiMe_3$ (1.5 equiv.), $[Pd(PPh_3)_4]$ (7mol%), CuI (14mol%), THF, Et_3N excess, rt, 18h, (82%); (b) TFA (50 equiv.), CH_2Cl_2, 2h, rt; (c) $[Ir(ppy)_2(phendione)]^+$, CH_2Cl_2/MeOH 1:1, 65°C, 16h, (70%).

A different approach was considered for the synthesis of the complex $[Ir(ppy)_2(Ethynyl\text{-}dppz)]^+$ **3** (Scheme 3). The synthesis of the di-tert-butyl(4-iodo-1,2-phenylene)dicarbamate **3a** was performed from 5-iodo-2-nitroaniline by reduction of the nitro group and double protection of the diamine intermediate with Boc protecting groups, as described in literature [31]. A Sonogashira coupling reaction with (trimethylsilyl)acetylene was then realized, followed by a one-step total deprotection to obtain the 4-ethynylbenzene-1,2-diamine **3c**. Condensation of this diamine intermediate was then carried out with $[Ir(ppy)_2(phendione)]^+$, previously prepared from an iridium dichloro-bridged precursor and 1,10-phenanthroline-5,6-dione, to obtain the desired $[Ir(ppy)_2(Ethynyl\text{-}dppz)]^+$ **3** complex.

Synthesis of triazolyl Ir(III)-nucleosides

Triazolyl Ir(III)-nucleosides synthesis was performed from the Ethynyl-Iridium complexes and the 1'(α)-azido-(2')-deoxyribose (commercial) by classical click reaction (**5** and **7**, Scheme 4). In order to investigate the photophysical influence of triazolyl moiety in the Ir(III)-nucleosides, triazolyl Ir(III)-nonyl derivatives **4** and **6** were prepared as control analogs (Scheme 4). Briefly, 1-azidononane ($C_9H_{19}N_3$) was obtained quantitatively following a straightforward procedure of nonyl-bromide and NaN_3 in 10 minutes in DMF under microwave irradiation at 100°C [38]. Nonyl conjugates were obtained by click reaction from their respective Ethynyl-Iridium complexes.

It should be noted that despite our synthetic efforts, the reaction with $[Ir(ppy)_2(Ethynyl\text{-}dppz)]^+$ did not yield the desired Ir(III)-nucleosides conjugates or the triazolyl Ir(III)-nonyl. In this case, we faced solubility issues that should be responsible for the inefficiency of the click reaction between the modified complex **3** and the azido substrates.



Scheme 4. Structure of the triazolyl Ir(III) derivatives: (a) the nonyl-bpy $[Ir(ppy)_2(nonyl\text{-}tl\text{-}bpy)]^+$ **4** and the nucleoside conjugate $[Ir(ppy)_2((3',5'\text{-}toluoyl,1'\text{-}tl\text{-}bpy)deoxynucleoside)]^+$ **5** and (b) their phen counterparts $[Ir(ppy)_2(nonyl\text{-}tl\text{-}phen)]^+$ **6** and $[Ir(ppy)_2((3',5'\text{-}toluoyl,1'\text{-}tl\text{-}phen)deoxynucleoside)]^+$ **7**. *General procedure for coupling reaction*: azide (1.5 equiv.), sodium ascorbate (1.0 equiv.), $CuSO_4$ (1.0 equiv.), DMF/H_2O 1:1, argon, rt, overnight.

Table 1. Photophysical and electrochemical properties of Iridium complexes and conjugates.

Complex	Absorption[a]	Emission[b]	τ_0[c]	Φ_{Em}[d]	E_{ox}[e]	E_{red}[e]
$[Ir(ppy)_2(bpy)]^+$ [39]	265, 310 (3.6), 335 (1.6), 375, 410 (0.5), 455 (0.3), 465 (0.06)	606	337	0.093	1.32 [40]	-1.4 [40]
$[Ir(ppy)_2(Ethynyl\text{-}bpy)]^+$ **1**	265 (4.2), 310[f] (2.3), 383[f] (0.5)	621	280	0.024	1.19	-1.06
$[Ir(ppy)_2(nonyl\text{-}tl\text{-}bpy)]^+$ **4**	250 (2.6), 263[f] (2.5), 287[f] (2.1), 317[f] (1.7), 330 (1.6), 378[f] (0.4)	599	290	0.091	1.19	-1.19
$[Ir(ppy)_2((2',5'\text{-}toluyl,1'\text{-}tl\text{-}bpy)deoxynucleoside)]^+$ **5**	243 (5.5), 264[f] (3.8), 288[f] (3.1), 316 (2.4), 330[f] (2.3), 380[f] (0.5)	600	282	0.077	1.20	-1.16
$[Ir(ppy)_2(phen)]^+$	266 (4.8), 376 (0.6) [41]	590 [42]	360 [42]	0.27 [42]	1.22 [43]	-1.48 [43]
$[Ir(ppy)_2(Ethynyl\text{-}phen)]^+$ **2**	242 (5.1), 265 (4.7), 367[f] (0.7)	596	566	0.092	1.18	-1.11
$[Ir(ppy)_2(nonyl\text{-}tl\text{-}phen)]^+$ **6**	249 (4.4), 264[f] (3.6), 278[f] (3.2), 328[f] (1.2), 375[f] (0.6)	587	720	0.199	1.19	-1.16
$[Ir(ppy)_2((2',5'\text{-}toluyl,1'\text{-}tl\text{-}phen)deoxynucleoside)]^+$ **7**	241 (7.0), 264[f] (4.6), 279[f] (3.9), 332[f] (1.4), 376 (0.7)	584	311	0.192	1.19	-1.15
$[Ir(ppy)_2(dppz)]^+$ [31,44]	270 (7.12), 360 (1.86), 382 (1.81)	630	77	0.002	1.25	-0.94
$[Ir(ppy)_2(Ethynyl\text{-}dppz)]^+$ **3**	278 (7.5), 366[f] (1.5), 387 (1.4)	-[g]	-[g]	-[g]	1.18	-0.68

[a] λ_{max} in acetonitrile in nm ($\varepsilon x10^{-4} L.mol^{-1}.cm^{-1}$). [b] λ_{max} in acetonitrile in nm under argon at 298K; excitation wavelength = 375nm. [c] Luminescence lifetime in ns in acetonitrile under argon. [d] Quantum yield of luminescence in acetonitrile under argon at 298K. Measure relative to $[Ru(bpy)_3]^{3+}$ in aerated aqueous solution (Φ_{ref} = 0.028). [e] Oxidation and first reduction potential measured in dry MeCN (oxidation) or dry DMF (reduction) with 0.1 M tetrabutylammonium perchlorate. All

potentials are reported in V/SCE. [f] shoulder. [g] not emissive upon excitation at 375 nm.

Spectroscopic and electrochemical investigation of triazolyl Ir(III)-nucleosides conjugates

Oxidation and reduction potentials of Ethynyl-Iridium complexes and their conjugates were determined by cyclic voltammetry. The potentials are gathered in Table 1 and compared with reference complexes. By comparison with their parent complexes, a small cathodic shift in the reduction potentials is observed when ethynyl group (**1**-**3**) or triazole moieties (**4**-**7**) are introduced on the bpy, phen or dppz ligand. This cathodic shift in reduction can be rationalized by the extended delocalization induced by the introduction of the alkyne or triazole moiety on the modified ligand. Similarly, a small decrease of the oxidation potential is also noticed. The absorption and emission spectra of the two nucleoside conjugates are presented in Figure 2 and the spectroscopic data for all complexes are gathered in Table 1.

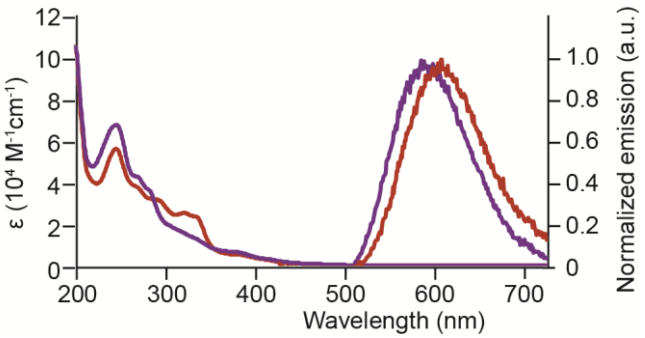


Figure 2 Absorption and normalized luminescence (excitation wavelength = 375nm) spectra of the nucleoside conjugates **5** (red line) and **7** (purple line) in acetonitrile at room temperature under air.

In absorption, no clear-cut modification of the absorption spectra can be noticed in the MLLCT (Metal-Ligand to Ligand Charge Transfer) bands around 380 nm between parent complexes and conjugates; shifts in the UV-region, corresponding to LC (Ligand Centered) transitions, are related to the modification of the structure of the ligand and the extended delocalization of the ligand orbitals. In steady-state emission, the wavelength of the luminescence maximum is shifted bathochromically upon introduction of the alkyne function on bpy or phen for complexes **1** and **2** respectively, while the Ethynyl-dppz complex **3** appears to be non-luminescent, although the parent complex $[Ir(ppy)_2(dppz)]^+$ is emissive in acetonitrile, and slightly emissive in water [31]. Interestingly, after the click reaction and formation of the triazole moiety, the luminescence of complexes **4**-**7** is almost unaffected in comparison with the parent complexes.

Luminescence lifetimes were measured for the bpy- and phen-based complexes. Upon modification of bpy ligand with the introduction of the ethynyl group (**1**) or the triazole moiety (**4**), the luminescence lifetime of the resulting complexes is slightly reduced. In contrast, a small enhancement of the luminescence lifetime for complexes **2** and **6** is observed compared to $[Ir(ppy)_2(phen)]^+$. These alteration of the luminescence lifetimes cannot be correlated to a displacement of the emission, *i.e.* a modification of the energy of the excited state, and could then be related to modification of the non-radiative decay via the dissipation of energy through the solvent; the different structures could affect the solvation of the complex and thus the ability of the solvent molecules to dissipate the energy.

Concerning the nucleoside conjugates **5** and **7**, their luminescence lifetime is similar to the one of the parent complexes $[Ir(ppy)_2(bpy)]^+$ and $[Ir(ppy)_2(phen)]^+$ respectively. This similarity demonstrates that no intramolecular quenching processes are at stake in these conjugates. Indeed, if a moderate shortening of the luminescence lifetime is noticed, consistent with the slight decrease of the quantum yield of emission, this behavior is attributed to a more efficient non-radiative decay via the dissipation of energy through the solvent; we could expect that this non-radiative decay will also be sensitive to the incorporation of the Ir(III)-nucleoside into a DNA sequence. In conclusion, based on the steady-state and time-resolved spectroscopic data, we can safely assert that the photophysical characteristics of Ir(III)-nucleoside complexes are similar to their parent complexes and that the photophysical properties of the iridium complexes are thus conserved when conjugated to a nucleoside moiety.

Conclusions

In this work, we reported the synthesis of Ir(III)-nucleosides using click reaction. In contrast to previous studies, our synthetic scheme allows the introduction of Iridium complexes that retain their coordination core, and thus do not alter the photophysical and photophysical properties. Despite our efforts, one of the targeted conjugates could not be successfully obtained. Nevertheless, the characterization of the phen- and bpy- Ir(III) conjugates demonstrated that the anchoring of Ir(III) complexes onto nucleosides via the triazoyl linker does not alter the properties of these complexes. This tethering method paves the way to the incorporation of photoreactive Ir(III) complexes in a DNA structure, and a new way to study DNA charge transfer process by using a photoreactive complex directly embeded within the DNA base stack.

Experimental Section

Materials and Instrumentation

Hoffer's chlorosugar was purchased from Carbosynth. 5-bromo-2,2'-bipyridine **(1a)** [33], 5-bromo-1,10-phenanthroline **(2a)** [36], di-tert-butyl (4-iodo-1,2-phenylene)dicarbamate **(3a)** [31], $[Ir(ppy)_2(phendione)]^+.Cl^-$ [45] and nonyl azide [38] were synthesized according to the literature methods. The other chemicals were obtained from commercial sources and used without further purification.

^{1}H NMR experiments were performed on a Bruker AC-300 Avance II (300 MHz) or on a Bruker AM-500 (500 MHz). The chemical shifts (given in ppm) were measured versus the residual peak of the solvent as the internal standard. High-resolution mass spectrometry (HRMS) were recorded on a Q-Extractive orbitrap from ThermoFisher. Samples were ionized by electrospray ionization (ESI; capillary temperature = 250 °C, vaporizer temperature = 250 °C, sheath gas flow rate = 20). UV–vis absorption spectra were recorded on a Shimadzu UV-1700. Room temperature fluorescence spectra were recorded on a Varian Cary Eclipse instrument. Emission quantum yields were determined by integrating the corrected emission spectra over the frequencies. $[Ru(bpy)_3]^{2+}$ in water under air was chosen as the standard luminophore (Φ_{Em} = 0.028); $\phi_X = \phi_{Ref}\left(A_{Ref}/A_X\right)\left(\int I_X \mathrm{d}\nu / \int I_{Ref}\mathrm{d}\nu\right)\left(\eta_X^2/\eta_{Ref}^2\right)$. Luminescence lifetimes were measured with a modified Applied Photophysics laser kinetic spectrometer by exciting the samples at 355 nm with a Nd:YAG pulsed laser (Continuum NY 61-10). Emitted light as a function of time was detected with a R-928 Hamamatsu photomultiplier tube whose output was applied to a digital oscilloscope (Hewlett-Packard HP 54200A) interfaced with a Dell Dimension DE051 computer. Signals were averaged over at least 16 shots and corrected for baseline. *Igor 6.1* (Wavemetrics) software was used for decay analyses. Cyclic voltammetry was carried out in a one-compartment cell, using a glassy carbon disk working electrode (approximate area = 0.03 cm^2), a platinum wire counter electrode and an Ag/AgCl reference electrode. The potential of the working electrode was controlled by an Autolab PGSTAT 100 potentiostat through a PC interface. For the sake of clarity, potentials are converted to V vs SCE. The cyclic voltammograms were recorded with a sweep rate of 100 mV s^{-1}, either in dry acetonitrile (Acros, HPLC grade) or in dry *N*,*N*-dimethylformamide (DMF; Sigma-Aldrich, HPLC grade) for reduction. Tetrabutylammonium perchlorate (0.1 M) was used as the supporting electrolyte and the samples were purged by argon before each measurement.

Syntheses

5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (1b): This product was prepared according to procedures described in literature [34,35]. 5-bromo-2,2'-bipyridine **(1a)** (300 mg, 1.28 mmol) was placed in a 50mL flask under argon and diluted with 22 mL of degassed anhydrous THF. Trimethylsilylacetylene (437 μL, 3.07 mmol), $[PdCl_2(PPh_3)_2]$ (10mol%) and copper iodide (16mol%) were then successively added. The reaction mixture was flushed with argon and diisopropylamine (4.5 mL) was added dropwise with a syringe. The reaction was stirred at room temperature during 48h. The solvent was removed under vacuum. The crude product was purified by silica gel flash column chromatography (hexane/AcOEt 95:5, gradient to pure AcOEt) to obtain 256 mg of the desired product as a white solid (79% yield). TLC: R_f (hexane/AcOEt, 80:20): 0.50. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 8.69 (dd, *J* = 2.1, 0.8 Hz, 1H, H_6), 8.59 (ddd, *J* = 4.8, 1.7, 0.8 Hz, 1H, $H_{6'}$), 8.35 – 8.27 (m, 2H, H_3, $H_{3'}$), 7.80 (dd, *J* = 8.2, 2.1 Hz, 1H, H_4), 7.71 (td, *J* = 7.8, 1.8 Hz, 1H, $H_{4'}$), 7.20 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H, $H_{5'}$), 0.23 (s, 9H, $SiMe_3$). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 155.32, 154.88, 151.97, 149.18, 139.71, 136.86, 123.87, 121.34, 120.13, 120.08, 101.90, 99.05, -0.12. MS (ESI): m/z = 253.34 [M+1].

$[Ir(ppy)_2(TMS\text{-}Ethynyl\text{-}bpy)]^+.Cl^-$ (1c): Adapted from *procedure for the preparation of the deprotected/PF_6 analog* [46]. 5-((trimethylsilyl)ethynyl)-2,2'-bipyridine **(1b)** (82.4 mg, 326 µmol) and $[Ir(ppy)_2Cl]_2$ (175 mg, 163 µmol) were placed in a 10mL flask with a condenser and diluted with 2 mL of anhydrous dichloromethane and 2 mL of anhydrous methanol. The reaction was stirred overnight at 65°C, during which time the color of the solution changed from yellow-orange to red. The solvent was then removed under vacuum. The crude product was purified by silica gel flash column chromatography (dichloromethane/methanol 99:1 with gradient to 85:15) to give the iridium complex as a red solid in 94% yield (242mg). TLC: R_f (dichloromethane/methanol, 90:10): 0.28. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 9.58 (d, *J* = 8.6 Hz, 1H), 9.48 (d, *J* = 8.2 Hz, 1H), 8.28 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.25 – 8.18 (m, 1H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 1.8 Hz, 2H), 7.85 (t, *J* = 7.8 Hz, 2H), 7.72 (dd, *J* = 7.7, 2.3 Hz, 2H), 7.49 (d, *J* = 6.4 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.06 (t, *J* = 6.4 Hz, 2H), 7.00 (q, *J* = 6.7 Hz, 2H), 6.96 – 6.85 (m, 2H), 6.33 (d, *J* = 7.4 Hz, 1H), 6.29 (d, *J* = 7.4 Hz, 1H), 5.30 (s, 1H), 0.24 (s, $SiMe_3$, 9H). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 167.36, 167.22, 154.87, 154.43, 151.86, 149.70, 149.38, 149.34, 147.87, 147.84, 143.09, 143.02, 142.26, 139.71, 138.12, 131.28, 131.12, 130.41, 127.89, 126.72, 125.95, 124.63, 124.55, 124.01, 123.02, 122.37, 122.32, 119.68, 119.59, 103.76, 98.70, 53.31, -0.83. HRMS (ESI): calcd. for $C_{37}H_{32}ClIrN_4Si$ 753.20200 [M-Cl]; found 753.20130.

$[Ir(ppy)_2(Ethynyl\text{-}bpy)]^+.Cl^-$ (1): $[Ir(ppy)_2(TMS\text{-}Ethynyl\text{-}bpy)]^+.Cl^-$ **(1c)** (242 mg, 307 µmol) and potassium carbonate (97.6 mg, 706 µmol) were placed in a 10mL flask and diluted with 5 mL anhydrous methanol. The reaction was stirred during 20h at room temperature. The solvent was then removed under vacuum. The crude product was purified by silica gel flash column chromatography (dichloromethane/methanol 99:1) to give the iridium complex as a red solid in 71% yield (155 mg). TLC: R_f (dichloromethane/methanol, 90:10): 0.28. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 9.47 (d, *J* = 8.3 Hz, 1H), 9.39 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.82 (dd, *J* = 7.9, 3.6 Hz, 2H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.76 (d, *J* = 4.9 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.32-7.29 (m, 3H), 6.90 (t, *J* = 6.5 Hz, 2H), 6.83 (t, *J* = 7.4 Hz, 2H), 6.75-6.71 (m, 2H), 6.14 (d, *J* = 7.5 Hz, 1H), 6.12 (d, *J* = 7.5 Hz, 1H), 3.42 (s, 1H). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 167.47, 167.35, 155.07, 154.93, 152.16, 149.85, 149.45, 149.40, 148.01, 143.14, 142.56, 139.90, 138.27, 131.37, 131.28, 130.64, 130.57, 128.12, 127.07, 126.22, 124.78, 124.69, 123.30, 123.18, 122.62, 122.53, 119.76, 119.71, 85.69, 77.85. HRMS (ESI): calcd. for $C_{34}H_{24}ClIrN_4$ 681.16247 [M-Cl]; found 681.16195.

5-((trimethylsilyl)ethynyl)-1,10-phenanthroline (2b): Adapted from literature [37,47]. 5-bromo-1,10-phenanthroline **(2a)** (324 mg, 1.24 mmol) was placed in a 100mL flask and diluted with 38 mL of anhydrous THF. Diisopropylamine (13 mL) was added and the solution was degassed by freeze-thaw cycle and flushed with argon. $[PdCl_2(PPh_3)_2]$ (10mol%) and copper iodide (11mol%) were then successively added and the resulting mixture was degassed by bubbling with argon during 30 minutes. Trimethylsilylacetylene (267 μL, 1.87 mmol) was then added and the reaction was stirred at room temperature during 24h to obtain a black/brown mixture. The solvent was removed under vacuum and the crude product was dissolved in methanol (20mL). An aqueous solution (15mL) of EDTA was added and the solution was stirred for 30 minutes and extracted several times with dichloromethane. The organic phase was subsequently dried with Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by silica gel flash column chromatography (dichloromethane/methanol 99:1 with gradient until 97:3) to obtain 293mg of the desired product as a white solid (85% yield). TLC: R_f (dichloromethane/methanol, 99:1): 0.37. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 9.21 (dd, J = 4.3; 1.6 Hz, 1H, H_2 or H_9), 9.14 (dd, J = 4.3; 1.6 Hz, 1H, H_2 or H_9), 8.72 (dd, J = 8.3; 1.7 Hz, 1H, H_4 or H_7), 8.13 (dd, J = 8.1, 1.7 Hz, 1H, H_4 or H_7), 7.98 (s, 1H, H_6), 7.73 (dd, J = 8.2, 4.3 Hz, 1H, H_3 or H_8), 7.58 (dd, J = 8.1, 4.4 Hz, 1H, H_3 or H_8), 0.41 (s, 9H, $SiMe_3$). MS (APCI): m/z = 277.33 [M+1], 278.31 [M+2].

$[Ir(ppy)_2(TMS\text{-}Ethynyl\text{-}phen)]^+.Cl^-$ (2c): 5-((trimethylsilyl)ethynyl)-1,10-phenanthroline **(2b)** (55.3 mg, 200 µmol) and $[Ir(ppy)_2Cl]_2$ (107 mg, 100 µmol) were placed in a 10mL flask with a condenser and diluted with 1 mL of anhydrous dichloromethane and 1 mL of anhydrous methanol. The reaction was stirred overnight at 65°C, during which time the color of the solution changed from yellow-orange to red. The solvent was then

removed under vacuum. The crude product was purified by silica gel flash column chromatography (dichloromethane/methanol 99:1 with gradient to 85:15) to give the iridium complex as a red solid in 85% yield (139mg). TLC: R_f (dichloromethane/methanol, 95:5): 0.10. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 8.89 – 8.81 (m, 2H), 8.38 (s, 1H), 8.23 (dd, J = 5.0, 1.2 Hz, 1H), 8.14 (dd, J = 5.0, 1.2 Hz, 1H), 7.96-7.92 (m, 2H,), 7.85 (d, J = 8.2 Hz, 2H), 7.71 – 7.67 (m, 2H), 7.62 (dd, J = 4.4, 3.3 Hz, 2H), 7.20 (t, J = 5.3 Hz, 2H), 6.93 (t, J = 7.3 Hz, 2H), 6.89 – 6.79 (m, 4H), 6.28 (t, J = 6.2 Hz, 2H), 0.26 (s, 9H). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 167.7, 167.7, 151.3, 151.3, 149.2, 149.0, 148.3, 148.2, 146.6, 146.1, 143.6, 143.5, 139.4, 138.5, 138.4, 137.3, 132.6, 131.8, 131.8, 131.1, 130.9, 130.8, 127.8, 127.2, 124.9, 124.9, 123.5, 123.4, 122.9, 122.1, 119.8, 119.8, 105.3, 98.7, -0.2. HRMS (ESI): calcd. for $C_{39}H_{32}IrN_4Si$ 777.20200 [M-Cl]; found 777.20161.

[Ir(ppy)$_2$(Ethynyl-phen)]$^+$.Cl$^-$ (2): [Ir(ppy)$_2$(TMS-Ethynyl-phen)]$^+$.Cl$^-$ **(2c)** (140 mg, 172 µmol) and potassium carbonate (33.5 mg, 241 µmol) were placed in a 10mL flask and diluted with 5 mL anhydrous methanol. The reaction was stirred during 20h at room temperature. The solvent was then removed under vacuum. The crude product was purified by silica gel flash column chromatography (dichloromethane/methanol 95:5 with a gradient until 80:20) to give the iridium complex as a red solid in 72% yield (92 mg). TLC: R_f (dichloromethane/methanol, 90:10): 0.30. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 9.01 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.98 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.57 (s, 1H), 8.30 (dd, *J* = 5.0, 1.4 Hz, 1H), 8.25 (dd, *J* = 5.0, 1.3 Hz, 1H), 8.03 (dd, *J* = 7.9, 4.7 Hz, 1H), 8.01 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.92 (dd, *J* = 8.0, 4.6 Hz, 2H), 7.78 – 7.72 (m, 2H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.33 (dd, *J* = 5.8, 0.8 Hz, 1H), 7.29 (dd, *J* = 5.9, 0.7 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.98 – 6.88 (m, 4H), 6.36 (t, J = 8.0 Hz, 2H). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 167.89, 167.82, 151.70, 151.44, 149.35, 149.09, 148.62, 148.41, 146.71, 146.44, 143.69, 143.61, 139.68, 138.52, 138.49, 137.35, 133.59, 131.94, 131.91, 131.34, 131.02, 130.99, 130.96, 127.93, 127.39, 125.02, 123.62, 123.52, 123.06, 123.06, 121.29, 119.95, 119.87, 86.93, 78.11. HRMS (ESI): calcd. for $C_{36}H_{24}ClIrN_4$ 705.16247 [M-Cl]; found 705.16224.

Di-tert-butyl (4-((trimethylsilyl)ethynyl)-1,2-phenylene)dicarbamate (3b): Adapted from literature [31]. di-tert-butyl(4-iodo-1,2-phenylene)dicarbamate **(3a)** (200 mg, 460 µmol) was placed with [Pd(PPh$_3$)$_4$] (7mol%) and copper iodide (14mol%) in a dried 25mL flask under argon and diluted with 7 mL of degassed anhydrous THF. Anhydrous triethylamine (0.5 mL) was then added, followed by a dropwise addition of trimethylsilylacetylene (131 *µ*L, 921 µmol). The reaction mixture got dark and was stirred at room temperature during 18h to obtain a black/brown mixture. The solvent was removed under vacuum and the crude product was purified by silica gel flash column chromatography (hexane/AcOEt 95:5) to obtain 153mg of the desired product as a yellow solid (82% yield). TLC: R_f (hexane/AcOEt, 80:20): 0.62. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.65-7.40 (m, 2H, 2xNH), 7.20 (dd, J = 8.4; 1.7 Hz, 1H), 6.91 (br s, 1H), 6.75 (br s, 1H), 1.49 (s, 18H, 2x*t*-Bu), 0.22 (s, 9H, SiMe$_3$).

[Ir(ppy)$_2$(Ethynyl-dppz)]$^+$.Cl$^-$ (3): Adapted from literature [31,45]. Di-tert-butyl (4-((trimethylsilyl)ethynyl)-1,2-phenylene)dicarbamate **(3b)** (150 mg, 371 µmol) were placed in a 25mL flask under argon and dissolved with anhydrous dichloromethane (3.3 mL). TFA was then added dropwise with a syringe and the solution was stirred at room temperature during 2h. The solvent was then removed under vacuum, an aqueous solution of Na_2CO_3 was added, and the mixture was then extracted with AcOEt. The solvent was then removed under vacuum to obtain the **4-ethynylbenzene-1,2-diamine** intermediate **(3c)**. Thereafter, the latter was engaged in excess (1.7 equiv.) for the subsequent condensation reaction. This diamine and [Ir(ppy)$_2$(phendione)]$^+$.Cl$^-$ (166 mg, 222 µmol, 1.0 equiv.) were placed in a 25mL flask with a condenser and dissolved with absolute ethanol (2 mL) and methanol (1 mL). The reaction was refluxed overnight and the solvent was afterwards removed under vacuum. The crude product was purified by silica gel flash column chromatography (dichloromethane/methanol 95:5 with gradient to 85:15) to give the iridium complex as red solid in 70% yield over two steps (130mg). TLC: R_f (dichloromethane/methanol, 90:10): 0.40. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 9.76 (dd, *J* = 7.8, 1.1 Hz, 2H), 8.83 (d, *J* = 1.0 Hz, 1H), 8.38-8.25 (m, 4H), 8.10 (dd, *J* = 8.2, 5.2 Hz, 1H), 8.07 (dd, *J* = 8.2, 5.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.71 (t, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 5.7 Hz, 2H), 7.01-6.94 (m, 4H), 6.89 (t, *J* = 7.4 Hz, 2H), 6.35 (d, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 196.99, 167.51, 152.70, 152.57, 149.48, 149.19, 148.87, 148.73, 144.42, 143.57, 142.33, 140.74, 140.26, 138.87, 138.58, 136.27, 136.12, 131.78, 131.44, 130.84, 130.75, 130.19, 129.68, 128.72, 128.57, 124.91, 123.74, 122.98, 119.86. HRMS (ESI): calcd. for $C_{42}H_{28}O_1IrN_6$ 825.19484 [M-Cl+H_2O]; found 825.19434.

1-(β)-azido-3, 5-di-(O- p-toluoyl)-2-deoxy-D-ribose: A commercial 20% aqueous solution of LiN_3 (3 eq.) was added to 3 ml of DMF at 0°C. Commercial Hoffer's chlorosugar (300 mg, 772 µmol) was then added to the suspension. The mixture was stirred 1h at 0°C, then 1h at room temperature. It was diluted in Et_2O and consequently washed with 10% $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4 and the solvents evaporated by rotavapor and vacuum pump. The obtained mixture of isomers was then separated by silicagel column chromatography (hexane/AcOEt = 95:5) to isolate each anomer with a total yield of 70% (β 81 : 19 α) among which 226 mg of β-anomer. Adapted from literature [19] [45-46]. TLC: R_f (hexane/AcOEt, 90:10): 0.30 for β ; 0.20 for α. Analysis for β-anomer: ^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.98 (d, *J* = 8.2 Hz, 2H, $H_{2,6\ p\text{-Tol}}$), 7.90 (d, *J* = 8.2 Hz, 2H, $H_{2,6\ p\text{-Tol}}$), 7.25-7.23 (m, 4H, $H_{3,5\ p\text{-Tol}}$), 5.72 (t, *J* = 5.2 Hz, 1H, $H_{1'}$), 5.57 (td, *J* = 5.4, 2.8 Hz, 1H, $H_{3'}$), 4.60-4.52 (m, 3H, $H_{4'}$, $H_{5'}$), 2.42 (s, 3H, Me $_{p\text{-Tol}}$), 2.41 (s, 3H, Me $_{p\text{-Tol}}$), 2.43-2.41 (m, 2H, $H_{2'}$). MS (ESI): m/z **=** 418.22 [M+Na].

General procedure for the preparation of Iridium complexe/triazolyl/nucleosides (5) and (7) *via* azide-alkyne cycloaddition reaction: In a round-bottom flask fitted with a septum, **azide** (1.0 equiv) and **iridium-alkyne complex** (1.0 equiv) were dissolved in a solution THF:H_2O and degassed for 10 min with argon. After that, 20 mol% sodium ascorbate dissolved in a small quantity of water was added, and the solution was degassed for another 5 min. Then 10 mol% copper sulfate dissolved in a small quantity of water was added followed by degassing 5 min. The final ratio of THF to H_2O in the reaction mixture was maintained as 3:1. Finally, diisopropylethylamine (DIPEA) was added to the reaction mixture (1.5 equiv). The solution was refluxed at 65°C overnight with stirring. The red solution become yellow during the reaction. After full consumption of the starting azide, the reaction mixture was evaporated and partitioned between water and dichloromethane. The organic layer was then concentrated. The crude product was then separated by silicagel column chromatography (DCM-MeOH 95:5, gradient until 92:8) and characterized. Adapted from literature [48].

[Ir(ppy)$_2$((3',5'-toluoyl,1'-tl-bpy)deoxynucleoside)]$^+$.Cl$^-$ (5): The above procedure for azide-alkyne cycloaddition reaction was followed using 1-(β)-azido-3, 5-di-(O- p-toluoyl)-2-deoxy-D-ribose (16.5 mg, 42 µmol) and the complex [Ir(ppy)$_2$(Ethynyl-bpy)]$^+$.Cl$^-$ **(1)** to afford the desired product as a yellow/orange solid (41 mg, 88%). ^{1}H NMR (500 MHz; $CDCl_3$): δ = 9.24 (t, *J* = 8.4 Hz, 1H), 9.16 (dd, *J* = 14.0, 8.1 Hz, 1H), 8.72 (t, *J* = 8.8 Hz, 1H), 8.63 (d, *J* = 38.7 Hz, 1H), 8.49 (d, *J* = 20.3 Hz, 1H), 8.20 (brs, 1H), 7.94 – 7.90 (m, 4H), 7.88 (dd, *J* = 13.4, 5.2 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.74 (dd, *J* = 17.2, 7.9 Hz, 2H), 7.71-7.65 (m, 2H), 7.56 (t, *J* = 6.6 Hz, 1H), 7.47 (d, *J* = 5.5 Hz, 1H), 7.43-7.36 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.08-6.88 (m,

6H), 6.52 (dd, *J* = 13.3, 6.4 Hz, 1H, $H_{1'}$), 6.31 (t, *J* = 6.5 Hz, 2H), 5.81-5.75 (m, 1H, $H_{3'}$), 4.66-4.59 (m, 1H, $H_{4'}$), 4.59-4.46 (m, 2H, $H_{5'}$), 3.33-3.23 (m, 1H, $H_{2'}$), 2.87-2.75 (m, 1H, $H_{2'}$), 2.41 (s, 3H, Me $_{p\text{-Tol}}$), 2.36 (d, *J* = 5.8 Hz, 3H, Me $_{p\text{-Tol}}$). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 168.16, 167.89, 166.25, 165.92, 156.03, 154.51, 150.42, 150.12, 150.05, 148.77, 148.36, 146.97, 144.52, 144.13, 143.55, 143.35, 142.70, 140.06, 138.16, 136.92, 131.82, 131.38, 131.18, 130.90, 129.91, 129.86, 129.35, 129.31 , 127.82, 126.81, 126.54, 126.22, 125.16, 124.91, 123.42, 123.20, 122.72, 120.01, 119.72, 89.01 ($C_{1'}$), 83.77 ($C_{4'}$), 75.01 ($C_{3'}$), 64.26 ($C_{5'}$), 37.89 ($C_{2'}$), 21.83 (2xMe $_{p\text{-Tol}}$). HRMS (ESI): calcd. for $C_{55}H_{45}IrN_7O_5$ 1076.31059 [M-Cl]; found 1076.30998

[Ir(ppy)$_2$((3',5'-toluoyl,1'-tl-phen) deoxynucleoside)]$^+$.Cl$^-$ (7): The above procedure for azide-alkyne cycloaddition reaction was followed using 1-(β)-azido-3, 5-di-(O- p-toluoyl)-2-deoxy-D-ribose (10.7 mg, 27 µmol) and the complex [Ir(ppy)$_2$(Ethynyl-phen)]$^+$.Cl$^-$ **(2)** to afford the desired product as a yellow/orange solid (22 mg, 71%). ^{1}H NMR (500 MHz; $CDCl_3$): δ = 9.83 (br s, 1H), 9.79 (t, *J* = 8.7 Hz, 1H), 9.21 (br s, 1H), 9.05 (br s, 1H), 8.26 (d, *J* = 4.7 Hz, 1H), 8.21 (d, *J* = 4.8 Hz, 1H), 7.97-7.92 (m, 6H), 7.85 – 7.80 (m, 1H), 7.80 – 7.76 (m, 1H), 7.75 – 7.70 (m, 4H), 7.34 (dd, *J* = 11.8, 5.7 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 2H), 6.92 – 6.75 (m, 3H), 6.41 (d, *J* = 7.4 Hz, 2H), 5.94 (brs, 1H, $H_{3'}$), 4.74-4.60 (m, 3H, $H_{4'}$, $H_{5'}$), 3.63-3.52 (m, 1H, $H_{2'}$), 2.96-2.87 (m, 1H, $H_{2'}$), 2.42 (s, 3H, Me $_{p\text{-Tol}}$), 2.33 (s, 3H, Me $_{p\text{-Tol}}$). ^{13}C NMR (126 MHz; $CDCl_3$): δ = 168.04, 166.38, 166.03, 150.53, 150.12, 149.70, 148.58, 147.19, 146.25, 144.56, 144.36, 143.74, 143.69, 140.04, 138.97, 138.25, 132.01, 131.60, 131.01, 130.25, 130.00, 129.34, 129.19, 127.21, 127.13, 126.79, 126.69, 126.63, 125.00, 123.37, 122.96, 119.80, 89.01 ($C_{1'}$), 83.62 ($C_{4'}$), 75.30 ($C_{3'}$), 64.55 ($C_{5'}$), 37.71 ($C_{2'}$), 21.86 (Me $_{p\text{-Tol}}$), 21.78 (Me $_{p\text{-Tol}}$). HRMS (ESI): calcd. for $C_{57}H_{45}IrN_7O_5$ 1100,31059 [M-Cl]; found 1100.30995.

Acknowledgements

J.P., C.R., L.M. and B.E. gratefully acknowledge the Université catholique de Louvain, the Fonds National pour la Recherche Scientifique (F.R.S.-F.N.R.S.), the Région Wallonne and the Prix Pierre et Colette Bauchau for financial support.

Keywords: Iridium • nucleoside • click chemistry • DNA • polypyridyl complex

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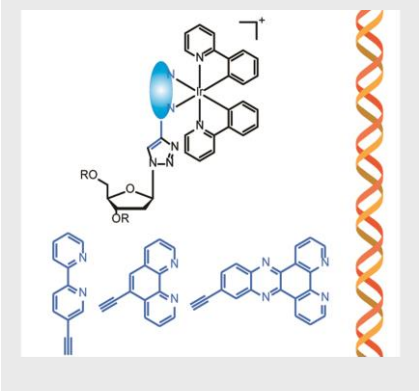

Iridium complexes*

*Johan Passays, Christophe Rubay, Lionel Marcélis, Benjamin Elias**

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Synthesis and photophysical properties of triazolyl Ir(III)-nucleosides

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