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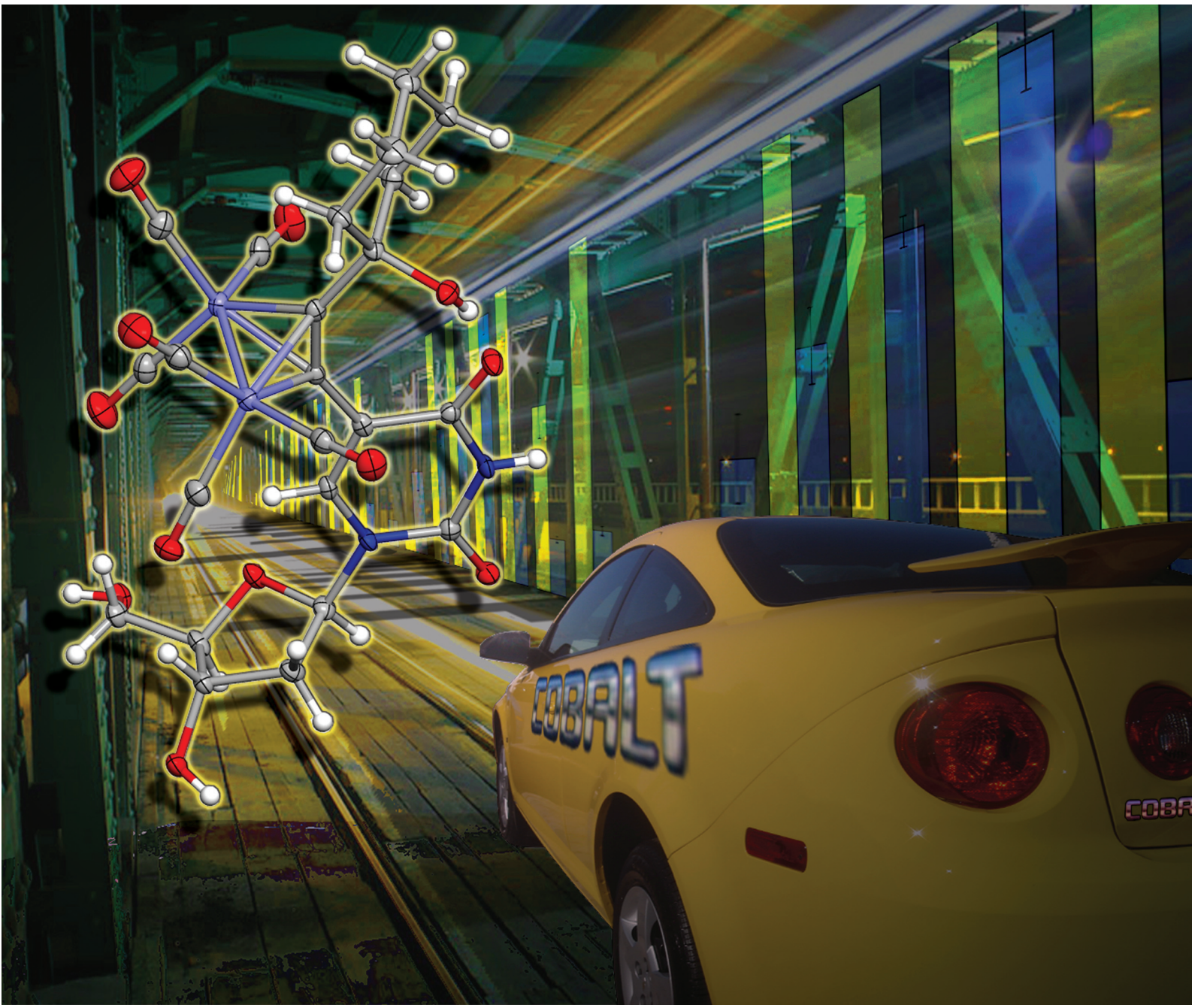

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FULL PAPER

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Metallo-nucleosides: synthesis and biological evaluation of hexacarbonyl dicobalt 5-alkynyl-2′-deoxyuridines†‡

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Reactions of 5-alkynyl-2′-deoxyuridines with dicobalt octacarbonyl $Co_2(CO)_8$ in THF at room temperature gave hexacarbonyl dicobalt nucleoside complexes (77–93%). The metallo-nucleosides were characterized, including an X-ray structure of a 1-cyclohexanol derivative. In crystalline form, the Co–Co bond is perpendicular to the plane of the uracil base, which is found in the *anti* position. The level of growth inhibition of MCF-7 and MDA-MB-231 human breast cancer cell lines was examined and compared to results obtained with the alkynyl nucleoside precursors. The cobalt compounds displayed good antiproliferative activities with IC_{50} values in the range of 5–50 μM. Interestingly, the coordination of the dicobalt carbonyl moiety to 5-alkynyl-2′-deoxyuridines led to a significant increase in the cytotoxic potency for alkyl/aryl substituents at the non-nucleoside side of the alkyne, but in the case of hydrogen (terminal alkyne) or a silyl group, a decrease of the cytotoxic effect was observed. As demonstrated using examples for an active and a low active target compound, the cytotoxicity was significantly influenced by the uptake into the tumor cells and the biodistribution into the nuclei.

Introduction

Bioorganometallic chemistry provides new tools for control of biological interactions.[1–8] In particular, organometallic compounds may offer innovative solutions for medicinal chemistry. Traditionally, platinum compounds have forged a path in this area, principally for cancer treatment. Yet, more recently, attention has encircled other transition metals and their carbonyl derivatives. For example, rhenium and technetium complexes (**1**, Fig. 1) show potential for breast cancer imaging and radiodiagnostics.[9,10] Biological assays contrived with the aid of organometallic bioconjugates and IR spectroscopy (carbonyl metalloimmunoassay) have been elaborated.[11] One current exciting development includes protein kinase inhibition by ruthenium complexes (such as **2**, Fig. 1).[12] The medicinal potential of metal carbonyl derivatives has been reviewed not long ago;[3,13] their antitumor activity has also been noted.[8] An example includes a triosmium cluster (**3**, Fig. 1), which exhibits anti-telomerase activity on semi-purified enzymes in a cell-free assay but is inactive towards the breast cancer MCF-7 cell line.[14] Recently, a nucleoside–iron carbonyl complex (**4**, Fig. 1) has been reported as bestowing a significant apoptosis-inducing activity against BJAB tumor cells.[15,16]

Hexacarbonyl dicobalt complexes of acetylenes,[17] in addition to material science, inorganic/organometallic or synthetic chemistry, are employed in medicinal-related investigations.[11,18] A biochemical study of a cobalt derivative of 17α-ethynyltestosterone (**5**, Fig. 1) showed that the compound is still recognized by the androgen receptor even when the relative binding affinity is quite low (0.5%).[19] The cytotoxicity of dicobalt hexacarbonyl complexes has also been reported.[20–24] In particular, an aspirin cobalt carbonyl derivative (**6**, Fig. 1) was discovered to be antitumor active *in vitro* against MCF-7 and MDA-MB-231 human mammary tumor cells.[22,23] In cell culture experiments hexacarbonyl[2-acetoxy-(2-propynyl)benzoate]dicobalt **6** has been found to be more active than cisplatin at each tested concentration. It has been demonstrated that the presence of the cobalt carbonyl is essential to achieve the cytotoxic effect, as the alkynyl precursor does not exhibit any activity. More systematic structure–activity relationship studies confirmed the aspirin derivative **6** as the lead compound and suggested a mode of action in which cyclooxygenase inhibition plays a major role.[24]

Modified nucleosides have already acquired an important role as therapeutic agents.[25–29] Cytotoxic nucleoside analogues were among the first chemotherapeutic agents to be introduced for the medical treatment of cancer. This family of compounds has grown to include a variety of purine and pyrimidine nucleoside derivatives with activity in both solid tumors and hematological malignancies. These agents behave as antimetabolites, compete with physiologic nucleosides, and consequently, interact with a large number of intracellular targets to induce cytotoxicity.[25] Potent biological properties have arisen by substitution at the 5-position of the uracil base.

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† Electronic supplementary information (ESI) available: Tables of comparison of ^1H and ^{13}C NMR signals for compounds **8a–h**. ^1H and ^{13}C NMR spectra for compounds **8a–c, e–h**. Crystal and refinement data, and packing diagrams for compound **8c**. See DOI: 10.1039/b713371e

‡ CCDC reference number 646479. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b713371e

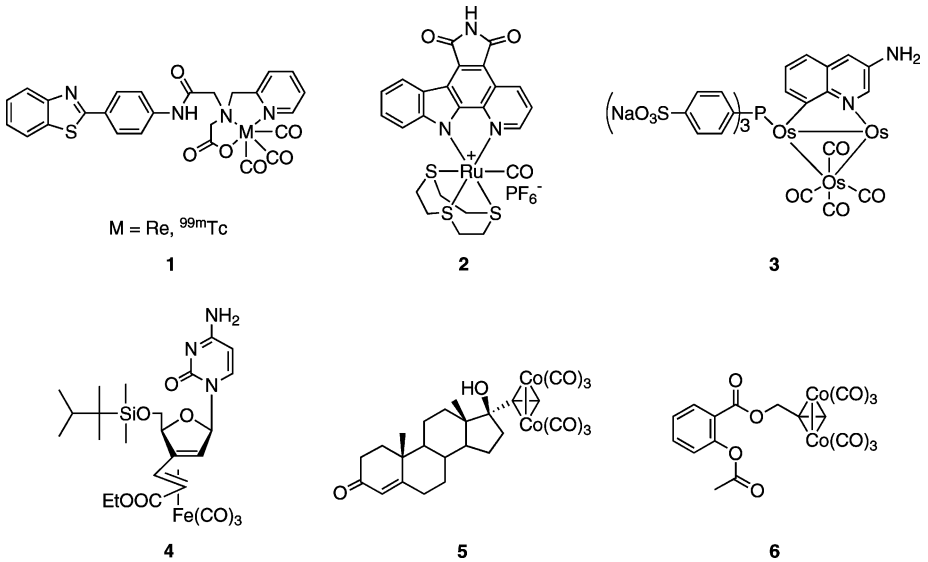


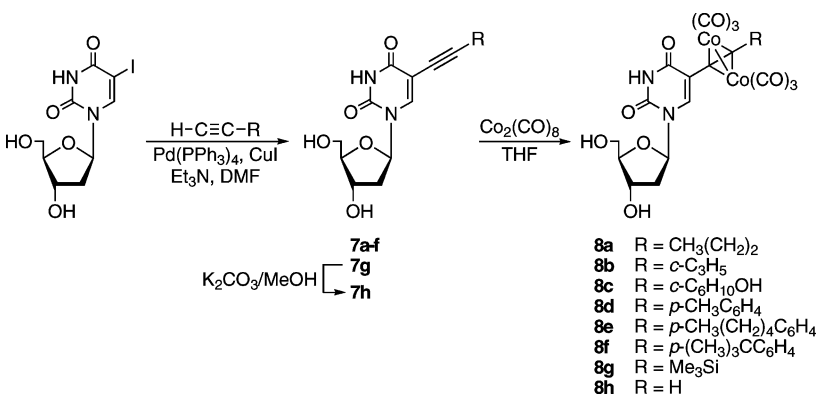
Fig. 1 Structures of representative metal–carbonyl complexes investigated for medicinal potential.

Interest in the use of the ethynyl (acetylenic) fragment for modification of nucleoside bases has resulted in a great number of applications for 5-alkynyl uridines.[30,31] Considering the antitumor activity of 5-alkynyl-2′-deoxyuridines (**7**)[30] and the high activity of hexacarbonyl dicobalt species,[20–24] a combination of both structural features in new target compounds was pursued. This strategy was further motivated by the significant apoptosis inducing properties of iron nucleoside analogues.[15] Similar to the results obtained with aspirin-derived cobalt carbonyl complexes, the activity depends on the presence of the iron carbonyl moiety suggesting that metal carbonyls are useful functional groups for the modification or inducement of biological activity.

However, up to this date only one alkynyl nucleoside has been converted into its hexacarbonyl dicobalt complex, and its biological evaluation has not been pursued.[32] In our ongoing interest in synthetic transformations of alkynyl-modified nucleosides[33] we have communicated a conversion of 5-(*p*-tolylethynyl)-2′-deoxyuridine (**7d**) into its hexacarbonyl dicobalt derivative (**8d**).[32] Here, this methodology was extended to a series of 5-alkynyl-2′-deoxyuridines, for which significant antiproliferative properties have been recently reported.[30] The preparation and structural characterization of the corresponding $Co_2(CO)_6$ complexes is described as well as the biological evaluation concerning cytotoxicity and uptake into the tumor cells and nuclei.

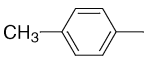
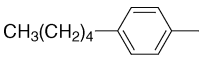
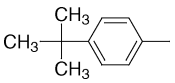
Chemistry

The series of 5-alkynyl-2′-deoxyuridines **7a–h** (with the following groups: an alkyl, a cycloalkyl, a cycloalkanol, three alkylphenyls, a trialkylsilyl, and a terminal alkyne) was synthesized, starting from 5-iodo-2′-deoxyuridine. Isolation in good yields (76–94%) was carried out according to an improved, frequently chromatography-free, larger scale protocol.[30,34] Conversion to the respective cobalt carbonyl derivatives **8** came next. As illustrated in Scheme 1, the alkynyl nucleosides **7a–h** were treated with $Co_2(CO)_8$ (1.2 equiv.) in THF at room temperature (22 °C) for approx. 1 h. Quantitative formation of **8** was observed by ^{1}H NMR or TLC. Isolation was accomplished by open-air standard silica gel column chromatography and gave brown or dark red nucleosides **8a–h** in high yield (77–93%). The functional groups of these nucleosides did not require any protection. The presence of a branched carbon next to the carbon–carbon triple bond did not affect the yield of **8c** significantly (77%). This was not surprising, since synthesis of simple cobalt complexes with a 1-ethynylcyclohexan-1-ol motif



Scheme 1 Synthesis of dicobalt hexacarbonyl 5-alkynyl-2′-deoxyuridines **8**.

Table 1 Preparation and cytotoxic activity of hexacarbonyl dicobalt 5-alkynyl-2′-deoxyuridines **8a–h** (IC_{50} values were obtained in two separate experiments, each $n = 6$)

Compound	R	Yield (%)	IC_{50}/μM	
			MCF-7	MDA-MB-231
8a	$CH_3CH_2CH_2-$	87	19.5 (±3.5)	29.1 (±3.6)
8b		93	12.6 (±1.4)	36.9 (±1.3)
8c		77	32.2 (±4.0)	47.3 (±3.3)
8d		92	13.3 (±0.2)	22.4 (±0.6)
8e		80	8.5 (±3.0)	8.6 (±0.5)
8f		86	6.8 (±1.0)	10.6 (±0.6)
8g	$(CH_3)_3Si-$	84[a]	10.9 (±2.0)	6.8 (±3.2)
8h	H–	87	6.7 (±4.6)	19.4 (±4.5)
Cisplatin[b]	—	—	2.0 (±0.3)	4.0 (±1.5)
5-Fluorouracil[b]	—	—	4.8 (±0.6)	9.6 (±0.3)

[a] Forms $CHCl_3$ solvate. [b] Ref. 24.

have been reported with comparable yields.[35] Structures for **8a–h** are depicted in Table 1.

The dicobalt complexes were characterized by ^1H and ^{13}C NMR, IR, and MS. The characteristic NMR (acetone-d_6) chemical shifts for **8a–h** include the ^1H signal of H-6 (8.29–8.57 ppm) and ^{13}C signals of C-5 (111.9–113.7, which reflects a downfield shift as compared to the alkynyl precursors at 97.5–99.6), C≡C (76.6–112.6), and CoCO (200.5–201.1 ppm).[36] Tables comparing all ^1H and ^{13}C NMR chemical shifts for **8a–h** are provided in the ESI† whereas a detailed characterization and similar comparison for **7a–h** is available in our earlier report.[30] IR spectra showed a CO stretching vibrational pattern characteristic for dicobalt hexacarbonyl alkynes (2096–2091, 2056–2050, and 2027–2021 cm^{-1}). Absorptions attributable to the nucleoside core were also observed (usually three bands between 1702–1603 cm^{-1}). Mass spectra for **8a–h** exhibited intense molecular ions and a sequential fragmentation with a loss of consecutive carbonyl groups.[37] Complexes **8** are obtained as an amorphous powder that can be stored for months in the freezer (−10 °C) under a nitrogen atmosphere without noticeable decomposition, as confirmed by ^1H NMR. They are more susceptible to degradation, while in organic solvents in an ambient atmosphere for an extended time (weeks), however, no significant decomposition was noticed by ^1H NMR when an acetone-d_6 solution of **8f** was stored in the freezer for 6 months.

A molecular structure of a representative nucleoside was confirmed by X-ray crystallography.‡ Efforts to obtain diffraction quality crystals have only been successful in the case of **8c** so far, by evaporation of a methanol–chloroform solution. Fig. 2 illustrates the molecular structure of the cyclohexanol-substituted nucleoside cobalt complex. It should first be noted that formation of a cobalt complex changes the position of the R group relative to the base since C–C≡C angles in cobalt complexes are of approximately 140–150° with the carbon atoms of the C–C≡C–C unit located in one plane. The C2 carbonyl group of **8c** adopted an *anti*

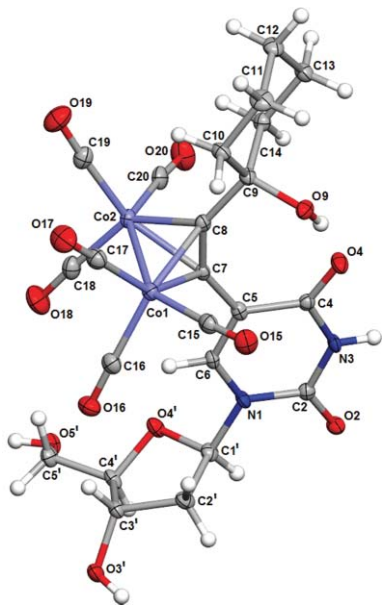


Fig. 2 An ORTEP view of the **8c** with the atom-labeling scheme. Thermal ellipsoids at the 50% probability level. Selected interatomic distances [Å]: C(5)–C(7) 1.456(4); C(7)–C(8) 1.347(4); C(8)–C(9) 1.520(4); Co(1)–Co(2) 2.4682(5); O(4)···H–O(9) 2.720(3). Key angles [deg]: C(5)–C(7)–C(8) 146.6(3); C(7)–C(8)–C(9) 141.3(2).

orientation towards the ribose ring in the crystalline form: the glycosidic bond torsion angle χ (O4′–C1′–N1–C2) is −126.7(2)°. The dihedral angle C(5)–C(7)–C(8)–C(9) of −4.21(7)° confirmed coplanarity of the alkyne and attached carbons. The dicobalt carbonyl unit is located *syn* to the ribose ring, with the Co–Co bond perpendicular to the uracil plane. The cyclohexanol ring adopted a staggered conformation across the C(8)–C(9) bond with O(9) of the hydroxyl group *anti* to the O(4′) of the ribose. In

relation to the cyclohexanol ring, the $Co_2(CO)_6$ unit in **8c** occupies the equatorial location. However, it is likely that the alkyne of non-coordinated **7c** prefers an axial position in the chair conformation, which has been changed (with a ring flip) after incorporation of cobalt carbonyl, similar to observations during conformational studies of 1-ethynylcyclohexanols.[35]

We also noticed a hydrogen bond between pyrimidine O(4) and cyclohexanol O(9), which is specific for compound **8c**. Unlike the structure reported for 5-ethynylferrocenyl-2′-deoxycytidine,[38] **8c** lacks Watson–Crick hydrogen bond motifs. This is due in part to the intramolecular O(4)···H–O(9) contact and non-covalent contacts between the sugar and base portions of **8c**. Base N(3) and each of the sugar OH groups participate in hydrogen bonds that contribute to the organization of **8c**. Packing diagrams are available in the ESI.†

Cytotoxicity

After completion of synthesis and characterization, the compounds were investigated for their antitumor activity *in vitro* against two different human breast cancer cultures MCF-7 and MDA-MB-231. The results are summarized in Table 1 and illustrated in comparison with the non-coordinated alkynyl nucleosides **7a–h**[30] in Fig. 3.

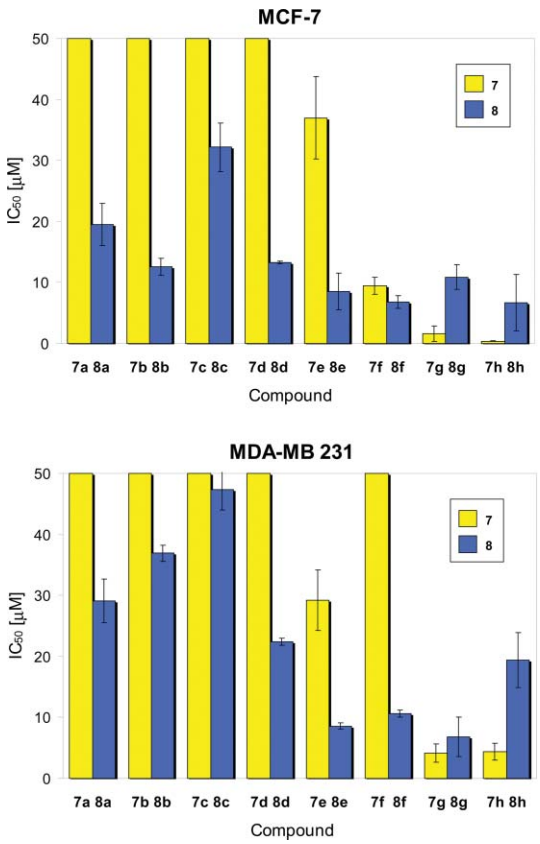


Fig. 3 Effect of the substituents of cobalt complexes **8** and their alkynyl precursors **7** for the proliferation of MCF-7 (top) and MDA-MB-231 (bottom) human breast cancer cell lines.[39]

All target compounds displayed significant antiproliferative effects with IC_{50} values in the range of 6.7 µM (**8h** in MCF-7 cells) to 47.3 µM (**8c** in MDA-MB-231 cells). Thus, the potency of the more active target compounds is well within the range of established anticancer drugs such as 5-fluorouracil and cisplatin or the lead compound for cytotoxic hexacarbonyldicobalt complexes **6** (IC_{50} values in the range of 1–10 µM in this assay).[24] With the exception of **8g**, MCF-7 cells were more sensitive towards the action of metallo-nucleosides, which is in good agreement with the results obtained with the non-coordinated alkynyl deoxyuridines **7a–h**. Interestingly, **7a–d** were inactive (IC_{50} values above 50 µM) whereas their cobalt carbonyl derivatives **8a–d** displayed activity in both tumor cell cultures investigated (Fig. 3). The alkynyl deoxyuridine **7f** had shown significant selectivity towards MCF-7 cells and was inactive in MDA-MB-231 cells. This selectivity almost disappeared for the corresponding $Co_2(CO)_6$ derivative **8f** as good antiproliferative effects could be noted in MDA-MB-231 cells. Concerning the alkyne precursors, derivatives with a hydrogen or silyl group at one end of the alkyne moiety were most active (IC_{50} values lower than 5 µM in all experiments with **7g** and **7h**). For the respective cobalt carbonyl species **8g** and **8h** the antiproliferative activity was decreased (IC_{50} values 6.7 to 19.4 µM).

Obviously, the coordination of alkynes to $Co_2(CO)_6$ has a strong influence on the biological activity of the respective alkyne compounds. In general, the coordination process led to a significant increase in the cytotoxic potency for alkyl/aryl substituents at the non-nucleoside side of the alkyne, but in the case of hydrogen (terminal alkyne) or a silyl group, a decrease of the cytotoxic effect was observed.

Uptake into cells and nuclei

Previous experiments proved that the hexacarbonyl dicobalt structure strongly increases the lipophilicity of alkyne species.[24] Thus, derivatization of deoxyuridines as cobalt carbonyl derivatives will alter their cellular uptake, intracellular distribution and interaction with biomolecules such as DNA, which can be considered the main target for novel nucleoside analogues. HPLC experiments using a reversed phase stationary phase were carried out for the selected alkyne/cobalt alkyne pairs **7g/8g** and **7h/8h**, and confirmed the lipophilicity increase associated with addition of the dicobalt hexacarbonyl unit (as indicated by the higher retention times of the complexes compared to the free ligands, see ESI for more details†).

One of the least active (**8c**) and one of the most active (**8f**) target compounds were selected for further studies on the uptake of the complexes into the tumor cells and into the nuclei of the cells. For this purpose, an established analytical method based on atomic absorption spectroscopy was applied. Fig. 4 shows the time dependent uptake of **8c** and **8f** into MCF-7 and MDA-MB-231 tumor cells. In general, the cellular levels were significantly higher for **8f** than for **8c**, which is in good agreement with the results from the cytotoxicity studies. Complex **8f** reached the highest levels after 6 h exposure while **8c** accumulated faster (maxima after 2 h incubation). During 24 h the cellular cobalt contents decreased for both complexes. This trend was less striking in the MCF-7 cell line and probably contributes to the higher overall sensitivity of MCF-7 compared to MDA-MB-231 cells. Altogether these results indicate that cellular uptake plays an important role for the bioactivity of cobalt carbonyl nucleosides. It can be assumed that the hydroxyl group positioned on the cyclohexanol moiety of

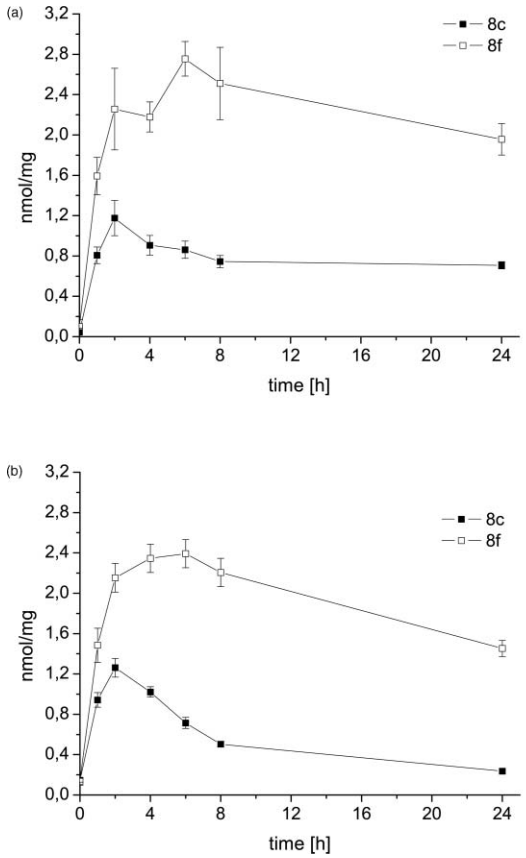


Fig. 4 Cellular uptake of complexes **8c** and **8f** into MCF-7 (top) and MDA-MB-231 (bottom); results are expressed as nmol compound per mg cellular protein ($n = 6$).

Table 2 Nuclear uptake of complexes **8c** and **8f** into MCF-7 and MDA-MB-231 cells after exposure for 24 h; results are expressed as nmol compound per mg nuclear protein ($n = 2$)

	Nuclear uptake/nmol mg^{-1}	
Cell line	**8c**	**8f**
MCF-7	0.051 (±0.020)	0.217 (±0.096)
MDA-MB-231	0.043 (±0.014)	0.321 (±0.159)

8c has a negative effect on cellular drug accumulation (due to a decrease of lipophilicity) and influences excretion or metabolism.

In order to evaluate if the target compounds reached the cellular location of their biological target DNA, the nuclei were isolated and the drug amount was quantified after exposure for 24 h (Table 2). The uptake into the nuclei increased in the same order as the cytotoxicity and cellular uptake (**8c** < **8h**). Thus, it can be concluded that both the intracellular distribution into the nuclei and the cellular uptake determine the antiproliferative properties of the investigated target compounds.

Conclusions

The present study shows that the concept of $Co_2(CO)_6$ derivatization can be used to change the potency of bioactive nucleoside compounds but a critical selection of the alkyne ligand remains an important issue. As summarized in Fig. 3, the $Co_2(CO)_6$ moiety may be a useful tool to convert inactive nucleosides into active ones but does not necessarily improve the cytotoxicity of already strong antiproliferative active derivatives. Explanations for this discrepancy may be found by the investigation of the molecular interactions with potential biological targets such as DNA or DNA related enzymes, which is the subject of ongoing studies.

In general, the presented results are in line with the former investigation of derivatives of benzoic acids, which showed that small structural modifications of the ligand structure can cause significant changes in the biological activity.[24] Moreover, the crystallographic data presented in this report underlined the impact of $Co_2(CO)_6$ coordination on the three dimensional structure of the nucleoside ligand. As demonstrated by means of an active and a poorly active complex, the uptake into the cells and intracellular biodistribution into the nuclei—parameters that are strongly influenced by the presence of the cobalt carbonyl complex—play an important role in the bioactivity of cobalt metallo-nucleosides.

Previous studies on **6** showed a high chemical stability of the $Co_2(CO)_6$-alkyne moiety,[23] as well as an extremely low cellular uptake of the precursor compound $Co_2(CO)_8$.[24] Therefore, it can be assumed that only intact complexes are accumulated inside the cells where they supposedly interact with biological targets and/or are transformed to active metabolites. The fate of the complexes inside the cells remains to be elucidated in detail. However, as indicated by evaluation of the cobalt content of the nuclei, some amounts of the complexes reach the main location of the most probable primary target DNA.

As an overall result, our studies showed that the alkyne cobalt carbonyl organometallic fragment is a useful tool in medicinal chemistry research concerning the modulation of the properties of known drugs or bioactive compounds.

Experimental section

General

Commercial chemicals were treated as follows: THF distilled from Na–benzophenone. $Co_2(CO)_8$ (Acros or Strem), silica gel (J. T. Baker, 60–200 mesh), TLC plates Analtech GF, cat. number 2521 or Merck 60, cat. number 5715 used as received. 5-Alkynyl-2′-deoxyuridines **7** were obtained as described.[30,40] Other materials not listed were used as received.

IR spectra were recorded on a Bio-Rad FTS-175C spectrometer. NMR spectra were obtained on a Bruker Avance DPX-200 spectrometer (^{1}H of 200 MHz and ^{13}C of 50 MHz). Chemical shift values (δ) are in ppm and coupling constant values (J) are in Hz. Mass spectra were recorded on a Micromass ZQ instrument; m/z indicates the most intense peak of the isotope envelope. Microanalyses were conducted by Atlantic Microlab.

Synthesis of hexacarbonyl dicobalt 5-alkynyl-2′-deoxyuridines (8). General procedure:

A Schlenk flask was charged under a nitrogen atmosphere with $Co_2(CO)_8$ (typically 0.36–0.46 mmol, 1.2 equiv.), THF (typically 4–6 mL), and **7** (typically 0.30–0.38 mmol). The mixture was stirred for *ca.* 1 h at room temperature (22 °C). The solvent was removed by rotary evaporation and the residue was dried by oil pump

vacuum for 1 h. The solid was dissolved in a minimum amount of $CHCl_3$ (*ca.* 1 mL). Silica gel column chromatography (typically 25 × 2.5 cm; $CHCl_3$–CH_3OH 100 : 0 → 90 : 10) gave a red-brown fraction. Solvent was removed by rotary evaporation and the residue was dried by an oil pump vacuum to give the dicobalt hexacarbonyl compounds **8a–h** as a brown or dark red powder that were stored, under a nitrogen atmosphere, in a freezer at −10 °C.

Hexacarbonyl dicobalt 5-pent-1-yn-1-yl-2′-deoxyuridine (8a)

From **7a** (0.0997 g, 0.339 mmol) and $Co_2(CO)_8$ (0.1390 g, 0.4065 mmol), in THF (6 mL). Dark brown solid of **8a** (0.1711 g, 0.2949 mmol, 87%). Anal. ($C_{20}H_{18}Co_2N_2O_{11}$) C, H: calcd, 41.40, 3.13; found, 41.40, 3.32%. IR (cm^{-1}, KBr) ν_{CoCO} 2091 s, 2050 vs, 2021 vs; 1702 s, 1686 s, 1638 w. MS (ES+, AcOK, MeOH) 619 ((M + K)$^+$, 15%), 591 ((M − CO + K)$^+$, 8%), 563 ((M − 2CO + K)$^+$, 6%), 535 ((M − 3CO + K)$^+$, 8%), 507 ((M − 4CO + K)$^+$, 6%), 333 ((M − $Co_2(CO)_6$ + K)$^+$, 100%). NMR (acetone-d_6):[36] ^{1}H 10.28 (s, 1H, N-3), 8.37 (s, 1H, H-6), 6.39 (dd, J = 7.7, 6.2, 1H, H-1′), 4.58–4.48 (m, 1H, OH-5′), 4.43 (d, J = 3.7, 1H, OH-3′), 4.32 (t, J = 4.8, 1H, H-3′), 4.04 (q, J = 2.2, 1H, H-4′), 3.90–3.75 (m, 2H, H-5′), 3.09 (t, 2H, J = 7.9, H-1″), 2.36–2.25 (m, 2H, H-2′), 1.71 (sextet, 2H, J = 7.7, H-2″), 1.06 (t, 3H, J = 7.3, H-3″); ^{13}C{^{1}H} 201.0 (CoCO), 161.5 (C-4), 150.8 (C-2), 140.2 (C-6), 113.3 (C-5), 104.8 (dU–C≡*C*), 89.3 (C-4′), 86.6 (C-1′), 85.6 (dU-*C*≡C), 73.0 (C-3′), 63.3 (C-5′), 41.9 (C-2′), 37.4 (C-1″), 26.0 (C-2″), 14.4 (C-3″).

Hexacarbonyl dicobalt 5-(cyclopropylethynyl)-2′-deoxyuridine (8b)

From **7b** (0.1012 g, 0.3462 mmol) and $Co_2(CO)_8$ (0.1421 g, 0.4155 mmol), in THF (6 mL). Dark brown solid of **8b** (0.1851 g, 0.3201 mmol, 93%). Anal. ($C_{20}H_{16}Co_2N_2O_{11}$) C, H: calcd, 41.54, 2.79; found, 41.01, 2.90%. IR (cm^{-1}, KBr) ν_{CoCO} 2091 s, 2051 vs, 2022 vs; 1702 s, 1686 s, 1637 w. MS (ES+, AcOK, MeOH) 617 ((M + K)$^+$, 30%), 589 ((M − CO + K)$^+$, 11%), 561 ((M − 2CO + K)$^+$, 6%), 533 ((M − 3CO + K)$^+$, 13%), 505 ((M − 4CO + K)$^+$, 10%), 331 ((M − $Co_2(CO)_6$ + K)$^+$, 100%). NMR (acetone-d_6):[36] ^{1}H 10.27 (s, 1H, N-3), 8.35 (s, 1H, H-6), 6.39 (dd, J = 7.6, 6.3, 1H, H-1′), 4.59–4.47 (m, 1H, OH-5′), 4.43 (d, J = 3.6, 1H, OH-3′), 4.31 (t, J = 4.6, 1H, H-3′), 4.08–3.98 (m, 1H, H-4′), 3.90–3.65 (m, 2H, H-5′), 2.62–2.41 (m, 1H, H-1″), 2.38–2.21 (m, 2H, H-2′), 1.24–1.06 and 0.95–0.65 (2 m, 2 × 2H, H-2″ and H-3″); ^{13}C{^{1}H} 200.8 (CoCO), 161.3 (C-4), 150.8 (C-2), 139.6 (C-6), 113.2 (C-5), 109.2 (dU–C≡*C*), 89.2 (C-4′), 86.4 (C-1′), 85.0 (dU–*C*≡C), 73.0 (C-3′), 63.2 (C-5′), 41.8 (C-2′), 16.3 (C-1″), 13.1 and 12.9 (C-2″ and C-3″).

Hexacarbonyl dicobalt 5-[(1-hydroxycyclohexyl)ethynyl]-2′-deoxyuridine (8c)

From **7c** (0.1332 g, 0.3802 mmol) and $Co_2(CO)_8$ (0.1560 g, 0.4562 mmol), in THF (6 mL). Dark brown solid of **8c** (0.1850 g, 0.2912 mmol, 77%). Anal. ($C_{23}H_{22}Co_2N_2O_{12}$) C, H: calcd, 43.42, 3.49; found, 43.41, 3.77%. IR (cm^{-1}, KBr) ν_{CoCO} 2093 s, 2054 vs, 2025 vs; 1702 s, 1670 s, 1637 w. MS (ES+, AcOK, MeOH) 1311 ((2 M + K)$^+$, 12%), 675 ((M + K)$^+$, 53%), 647 ((M + K − CO)$^+$, 35%), 619 ((M − 2CO + K)$^+$, 8%), 591 ((M − 3CO + K)$^+$, 21%), 389 ((M − $Co_2(CO)_6$ + K)$^+$, 100%). NMR (acetone-d_6):[36] ^{1}H 10.60 (s, 1H, N-3), 8.47 (s, 1H, H-6), 6.38 (dd, J = 7.9, 5.9, 1H, H-1′), 5.59 (s, 1H, *H*O–C_6H_{10}), 4.53 (br s, 1H, OH-5′), 4.45 (br s, 1H, OH-3′), 4.34 (br s, 1H, H-3′), 4.11–4.01 (m, 1H, H-4′), 3.92–3.70 (m, 2H, H-5′), 2.45–2.15 (m, 2H, H-2′), 2.00–1.45 (m, 9H, c-C_6H_{10}), 1.35–1.10 (m, 1H, c-C_6H_{10}); ^{13}C 200.8 (CoCO), 162.9 (d, J = 9.6, C-4), 150.3 (d, J = 8.0, C-2), 142.2 (d, J = 183.5, C-6), 113.1 (s, C-5), 112.6 (dU–C≡*C*), 89.4 (d, J = 149.4, C-4′), 86.7 (d, J = 170.4, C-1′), 84.4 (d, J = 3.5, dU–*C*≡C), 73.2 (s, C-1″), 73.0 (d, J = 149.1, C-3′), 63.1 (d, J = 139.9, C-5′), 42.0 (t, J = 133.2, C-2′), 40.6 and 40.4 (2t, J = 132.1, C-2″), 26.5 (t, J = 125.0, C-4″), 23.9 and 22.8 (2t, J = 129.1, C-3″).

Hexacarbonyl dicobalt 5-[(4-methylphenyl)ethynyl]-2′-deoxyuridine (8d)

From **7d** (0.1016 g, 0.2968 mmol) and $Co_2(CO)_8$ (0.1218 g, 0.3561 mmol), in THF (5 mL). Dark brown solid of **8d** (0.1716 g, 0.2731 mmol, 92%). Anal. ($C_{24}H_{18}Co_2N_2O_{11}$) C, H: calcd, 45.88, 2.89; found, 45.66, 3.36%. IR (cm^{-1}, KBr) ν_{CoCO} 2092 s, 2055 vs, 2023 vs; 1690 s, 1603 w. MS[37] (ES+, KCl, MeOH) 1295 ((2 M + K)$^+$, 36%), 667 ((M + K)$^+$, 92%), 639 ((M + K − CO)$^+$, 100%), 629 ((M + H)$^+$, 12%). NMR (acetone-d_6):[36] ^{1}H 10.32 (s, 1H, N-3), 8.43 (s, 1H, H-6), 7.53 (d, J = 8.0, 2H, *o*-C_6H_4C≡C), 7.19 (d, J = 8.0, 2H, *m*-C_6H_4C≡C), 6.43 (t, J = 6.9, 1H, H-1′), 4.52 (br s, 1H, OH-5′), 4.43 (d, J = 2.7, 1H, OH-3′), 4.24 (t, J = 4.5, 1H, H-3′), 4.06–4.02 (m, 1H, H-4′), 3.83–3.68 (m, 2H, H-5′), 2.32 (s, 3H, CH_3), 2.40–2.25 (m, 2H, H-2′); ^{13}C{^{1}H} 200.5 (CoCO), 160.8 (C-4), 150.8 (C-2), 139.8 (C-6), 138.8 (*p*-C_6H_4C≡C), 136.3 (*i*-C_6H_4C≡C), 130.6 (*o*-C_6H_4C≡C), 130.2 (*m*-C_6H_4C≡C), 113.6 (C-5), 96.7 (dU-C≡*C*), 89.2 (C-4′), 86.4 (C-1′), 86.2 (dU–*C*≡C), 73.1 (C-3′), 63.3 (C-5′), 41.9 (C-2′), 21.4 (CH_3).

Hexacarbonyl dicobalt 5-[(4-pentylphenyl)ethynyl]-2′-deoxyuridine (8e)

From **7e** (0.1200 g, 0.3012 mmol) and $Co_2(CO)_8$ (0.1236 g, 0.3614 mmol), in THF (5 mL). Dark brown solid of **8e** (0.1643 g, 0.2402 mmol, 80%). Anal. ($C_{28}H_{26}Co_2N_2O_{11}$) C, H: calcd, 49.14, 3.83; found, 48.76, 3.93%. IR (cm^{-1}, KBr) ν_{CoCO} 2092 s, 2056 vs, 2024 vs; 1700 s, 1686 s, 1606 w. MS (ES+, KCl, MeOH) 721 ((M + K)$^+$, 65%), 693 ((M − CO + K)$^+$, 100%), 666 ((M − 2CO + K)$^+$, 32%), 638 ((M − 3CO + K)$^+$, 37%), 610 ((M − 4CO + K)$^+$, 64%), 582 ((M − 5CO + K)$^+$, 59%), 554 ((M − 6CO + K)$^+$, 42%), 436 ((M − $Co_2(CO)_6$ + K)$^+$, 25%). NMR (acetone-d_6):[36] ^{1}H 10.34 (s, 1H, N-3), 8.43 (s, 1H, H-6), 7.56 (d, J = 8.2, 2H, *o*-C_6H_4C≡C), 7.22 (d, J = 8.2, 2H, *m*-C_6H_4C≡C), 6.43 (dd, J = 7.9, 6.2, 1H, H-1′), 4.58–4.48 (m, 1H, OH-5′), 4.46 (d, J = 3.6, 1H, OH-3′), 4.26 (t, J = 4.6, 1H, H-3′), 4.11–4.00 (m, 1H, H-4′), 3.90–3.67 (m, 2H, H-5′), 2.61 (t, J = 7.3, 2H, H-1″), 2.42–2.18 (m, 2H, H-2′), 1.74–1.54 (m, 2H, H-2″), 1.43–1.25 (m, 4H, H-3″, H-4″), 0.89 (t, J = 6.6, 3H, H-5″); ^{13}C{^{1}H} 200.6 (CoCO), 160.8 (C-4), 150.8 (C-2), 143.8 (C-6), 139.8 (*p*-C_6H_4C≡C), 136.5 (*i*-C_6H_4C≡C), 130.6 (*o*-C_6H_4C≡C), 129.5 (*m*-C_6H_4C≡C), 113.6 (C-5), 96.7 (dU–C≡*C*), 89.2 (C-4′), 86.4 (C-1′), 86.2 (dU–*C*≡C), 73.1 (C-3′), 63.2 (C-5′), 41.8 (C-2′), 36.4 (C-1″), 32.3 (C-3″), 31.8 (C-2″), 23.2 (C-4″), 14.3 (C-5″).

Hexacarbonyl dicobalt 5-[(4-*tert*-butylphenyl)ethynyl]-2′-deoxyuridine (8f)

From **7f** (0.0622 g, 0.162 mmol) and $Co_2(CO)_8$ (0.0665 g, 0.194 mmol), in THF (4 mL). Dark brown solid of **8f** (0.0935 g, 0.140 mmol, 86%). Anal. ($C_{27}H_{24}Co_2N_2O_{11}$) C, H: calcd, 48.38,

3.61; found, 48.08, 3.63%. IR (cm^{-1}, KBr) ν_{CoCO} 2091 s, 2055 vs, 2025 vs; 1702 s, 1686 s, 1637 w. MS (ES+, AcOK, MeOH) 709 ((M + K)$^+$, 100%), 681 ((M + K − CO)$^+$, 71%), 653 ((M − 2CO + K)$^+$, 29%), 625 ((M − 3CO + K)$^+$, 22%), 597 ((M − 4CO + K)$^+$, 6%), 423 ((M − $Co_2(CO)_6$ + K)$^+$, 48%). NMR (acetone-d_6):[36] ^{1}H 10.33 (s, 1H, N-3), 8.44 (s, 1H, H-6), 7.60 (d, J = 8.2, 2H, *o*-$C_6H_4C{\equiv}C$), 7.44 (d, J = 8.2, 2H, *m*-$C_6H_4C{\equiv}C$), 6.44 (dd, J = 7.8, 6.2, 1H, H-1′), 4.58–4.47 (m, 1H, OH-5′), 4.43 (d, J = 3.7, 1H, OH-3′), 4.21 (t, J = 4.6, 1H, H-3′), 4.10–4.00 (m, 1H, H-4′), 3.90–3.65 (m, 2H, H-5′), 2.43–2.16 (m, 2H, H-2′), 1.35 (s, 9H, $C(CH_3)_3$); ^{13}C 200.5 (s, CoCO), 160.9 (d, J = 9.3, C-4), 151.8 (br s, *p*-$C_6H_4C{\equiv}C$), 151.0 (d, J = 7.4, C-2), 139.8 (d, J = 181.0, C-6), 136.3 (t, J = 7.8, *i*-$C_6H_4C{\equiv}C$), 130.4 (dd, J = 159.8, 6.0, *o*-$C_6H_4C{\equiv}C$), 126.5 (dd, J = 157.2, 6.6, *m*-$C_6H_4C{\equiv}C$), 113.6 (s, C-5), 96.5 (s, dU–C≡*C*), 89.2 (d, J = 147.3, C-4′), 86.4 (d, J = 169.6, C-1′), 86.2 (d, J = 4.8, dU–*C*≡C), 73.1 (d, J = 151.0, C-3′), 63.3 (t, J = 141.0, C-5′), 41.9 (t, J = 133.8, C-2′), 35.3 (s, *C*$(CH_3)_3$), 31.5 (qt, J = 126.0, 4.4, C(*C*$H_3)_3$).

Hexacarbonyl dicobalt 5-[(trimethylsilyl)ethynyl]-2′-deoxyuridine (8g)

From **7g** (0.1000 g, 0.3083 mmol) and $Co_2(CO)_8$ (0.1266 g, 0.3700 mmol), in THF (5 mL). Dark brown solid of **8g**·1/3($CHCl_3$) (0.1680 g, 0.2584 mmol, 84%). Anal. ($C_{20}H_{20}Co_2N_2O_{11}Si$)·1/3($CHCl_3$): C, H: calcd, 37.56, 3.15; found, 37.66, 3.63%. IR (cm^{-1}, KBr) ν_{CoCO} 2090 s, 2052 vs, 2021 vs; 1700 s, 1685 s, 1638 w. MS (ES+, KCl, MeOH) 648 ((M + K)$^+$, 76%), 620 ((M − CO + K)$^+$, 61%), 592 ((M − 2CO + K)$^+$, 37%), 564 ((M − 3CO + K)$^+$, 11%), 536 ((M − 4CO + K)$^+$, 65%), 508 ((M − 5CO + K)$^+$, 6%), 480 ((M − 6CO + K)$^+$, 51%), 409 ((M − 6CO − $Si(CH_3)_3$ + K)$^+$, 57%), 363 ((M − $Co_2(CO)_6$ + K)$^+$, 100%). NMR (acetone-d_6):[36] ^{1}H 10.38 (s, 1H, N-3), 8.29 (s, 1H, H-6), 6.38 (dd, J = 7.9, 5.9, 1H, H-1′), 4.65–4.47 (m, 1H, OH-5′), 4.44 (d, J = 3.6, 1H, OH-3′), 4.26 (t, J = 4.7, 1H, H-3′), 4.05 (q, J = 2.2, 1H, H-4′), 3.95–3.75 (m, 2H, H-5′), 2.45–2.15 (m, 2H, H-2′), 0.37 (s, 9H, $Si(CH_3)_3$); ^{13}C{^{1}H} 201.1 (CoCO), 160.8 (C-4), 150.6 (C-2), 140.7 (C-6), 113.7 (C-5), 98.1 (dU–C≡*C*), 89.2 (C-4′), 86.5 (C-1′), 85.7 (dU–*C*≡C), 73.0 (C-3′), 63.1 (C-5′), 41.7 (C-2′), 1.0 ($Si(CH_3)_3$).

Hexacarbonyl dicobalt 5-ethynyl-2′-deoxyuridine (8h)

From **7h** (0.0802 g, 0.318 mmol) and $Co_2(CO)_8$ (0.1305 g, 0.3816 mmol), in THF (6 mL). Dark brown solid of **8h** (0.1490 g, 0.2769 mmol, 87%). Anal. ($C_{17}H_{12}Co_2N_2O_{11}$) C, H: calcd, 37.94, 2.25; found, 38.04, 2.46%. IR (cm^{-1}, KBr) ν_{CoCO} 2096 s, 2055 vs, 2027 vs; 1702 s, 1686 s, 1638 w. MS (ES+, AcOK, MeOH) 577 ((M + K)$^+$, 58%), 549 ((M − CO + K)$^+$, 34%), 521 ((M − 2CO + K)$^+$, 6%), 493 ((M − 3CO + K)$^+$, 20%), 465 ((M − 4CO + K)$^+$, 20%), 291 ((M − $Co_2(CO)_6$ + K)$^+$, 100%). NMR (acetone-d_6):[36] ^{1}H 10.25 (s, 1H, N-3), 8.57 (s, 1H, H-6), 6.71 (s, 1H, C≡CH), 6.35 (t, J = 6.6, 1H, H-1′), 4.53 (br s, 1H, OH-5′), 4.44 (br s, 1H, OH-3′), 4.36 (t, J = 4.2, 1H, H-3′), 4.10–3.93 (m, 1H, H-4′), 3.93–3.72 (m, 2H, H-5′), 2.39–2.20 (m, 2H, H-2′); ^{13}C 200.9 (s, CoCO), 161.5 (d, J = 9.3, C-4), 150.8 (d, J = 8.0, C-2), 141.0 (d, J = 179.5, C-6), 111.9 (s, C-5), 89.2 (d, J = 148.9, C-4′), 86.6 (d, J = 170.5, C-1′), 83.1 (s, dU–*C*≡C), 76.6 (d, J = 224.4, dU–C≡*C*), 72.5 (d, J = 150.3, C-3′), 62.9 (t, J = 140.5, C-5′), 41.9 (t, J = 133.7, C-2′).

Crystallography

Light brown plates of **8c** were grown by evaporation of a $CHCl_3$–MeOH (1 : 1 v/v) solution during 14 days, placed over molecular sieves in a closed jar under a nitrogen atmosphere in a glove box. Data were collected as outlined in the ESI (Table S3).†

Biological evaluation

Experiments concerning cytotoxicity and uptake into the cells and nuclei were performed according to recently described procedures.[24]

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36 (*a*) We were not able to achieve an NMR spectral resolution comparable to that of the 5-alkynyl-2′-deoxyuridines.[30] This can likely be attributed to the presence of cobalt. Thus, more advancedtechniques that would help to facilitate complete assignments of signals were not pursued. Doublet/broad singlet and multiplet peaks (acetone-d_6) were assigned to 3′- and 5′-OH, respectively. For **7**, the 3′- and 5′-OH (also assigned based upon multiplicity; doublet and triplet, DMSO-d_6) exhibit reversed relative positions of chemical shifts; (*b*) Pairs of *o*- and *m*- of the phenyl rings ^{1}H and ^{13}C signals, C-1′ and C-4′, and C≡C signals were tentatively assigned following trends for **7**,[30] except the C≡C for **8h**, where we were able to observe $^{1}J_{C-H}$.
37 MS ES+ (positive) data are given. We observed that negative spectra also show consecutive fragmentations with a loss of CO. A representative ES− (negative) spectrum for **8d** is available in the supplementary materials of our earlier work[32].
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39 Corrected value for **7d**/MCF-7 from the one given in ref. 30.
40 The equivalents reported in the general procedure in ref. 30 apply to volatile alkynes. To produce **7c–f**, 1.2 equiv. of a less volatile alkyne may be used. For an alternate procedure utilizing volatile alkynes see: S. Ghilagaber, W. N. Hunter and R. Marquez, *Tetrahedron Lett.*, 2007, **48**, 483–486.

