Inorg. Chem. **2005**, *44*, 2198–2209

Rhenium Tricarbonyl Core Complexes of Thymidine and Uridine Derivatives

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Received December 3, 2004

Thymidine and uridine were modified at the C2′ and C5′ ribose positions to form amine analogues of the nucleosides (**1** and **4**). Direct amination with $NaBH(OAc)_3$ in DCE with the appropriate aldehydes yielded 1-{5-[(bis(pyridin-2-ylmethyl)amino)methyl]-4-hydroxytetrahydrofuran-2-yl}-5-methyl-1*H*-pyrimidine-2,4-dione (**L1**), 1-{5-[(bis(quinolin-2-ylmethyl)amino)methyl]-4-hydroxytetrahydrofuran-2-yl}-5-methyl-1*H*-pyrimidine-2,4-dione (**L2**), and 1-[3-(bis(pyridin-2-ylmethyl)amino)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1*H*-pyrimidine-2,4-dione (**L5**), while standard coupling procedures of **1** and **4** with 5-(bis(pyridin-2-ylmethyl)amino)pentanoic acid (**2**) and 5-(bis(quinolin-2-ylmethyl)-amino)pentanoic acid (**3**) in the presence of HOBT-EDCI in DMF provided a second novel series of bifunctional chelators: 5-(bis(pyridin-2-ylmethyl)amino)pentanoic acid [(3-hydroxy-5-(5-methyl-4-oxo-3,4-dihydro-2*H*-pyrimidin-1-yl)tetrahydrofuran-2-yl)methyl] amide (**L3**), 5-(bis(quinolin-2-ylmethyl)amino)pentanoic acid [(3-hydroxy-5-(5-methyl-4-oxo-3,4-dihydro-2*H*-pyrimidin-1-yl)tetrahydrofuran-2-yl)methyl] amide (**L4**), 5-(bis(pyridin-2-ylmethyl)amino)pentanoic acid [2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl] amide (**L6**), and 5-(bis(quinolin-2-ylmethyl)amino)pentanoic acid [2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-4-hydroxy-5-(hydroxy-methyl)tetrahydrofuran-3-yl] amide (**L7**). The rhenium tricarbonyl complexes of **L1**–**L4**, **L6**, and **L7**, $[Re(CO)_3(LX)]$-Br (X = **1**–**4**, **6**, **7**: compounds **5**–**10**, respectively), have been prepared by reacting the appropriate ligand with $[NEt_4][Re(CO)_3Br_3]$ in methanol. The ligands and their rhenium complexes were obtained in good yields and characterized by common spectroscopic techniques including 1D and 2D NMR, HRMS, IR, cyclic voltammetry, UV, and luminescence spectroscopy and X-ray crystallography. The crystal structure of complex **6**·0.5$NaPF_6$ displays a facial geometry of the carbonyl ligands. The nitrogen donors of the tridentate ligand complete the distorted octahedral spheres of the complex. Crystal data: monoclinic, *C*2, $a = 24.618(3)$ Å, $b = 11.4787(11)$ Å, $c = 15.5902(15)$ Å, $\beta = 112.422(4)°$, $Z = 4$, $D_{calc} = 1.562$ g/cm^3.

Introduction

Natural and unnatural modified nucleosides and nucleoside analogues play important roles in biology and medicine and as biomedical research tools.[1,2] Radiolabeled nucleosides and nucleoside analogues have been studied as potential inhibitors for nucleoside kinases and probes for monitoring tumor cell proliferation. In the field of positron emission tomography (PET), several proliferation markers have been developed. Thymidine labeled with ^{11}C was one of the first endeavors. A catabolism-resistant and DNA-incorporable thymidine analogue, 2′-fluoro-5-[^{11}C]methyl-1-*b*-D-arabinofuranosyl-uracil ([^{11}C]FMAU), overcame to a certain extent the cumbersome kinetic modeling process associated with [^{11}C]-thymidine imaging.[3] The short physical half-life of ^{11}C excludes any opportunity for a later observation of the DNA incorporation and clearance of radioactive metabolites. With a substitution at 3′ position, [^{18}F]FLT is not incorporated into DNA. Its accumulation is the result of metabolic trapping of its phosphate, similar to the trapping mechanism of FDG. Recently, a catabolism-resisting ^{76}Br-labeled thymidine

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10.1021/ic048301n CCC: $30.25
Published on Web 02/25/2005

analogue was developed (FBAU).[4] Similar to [^{11}C]FMAU with a 2′ fluoro substitution, this compound greatly enhances in vivo stability.

Technetium-99m is extensively used in diagnostic medicine because of its ideal nuclear properties (E_γ = 140 keV, $t_{1/2}$ = 6 h), low cost, and convenient availability from commercial generator columns.[5] The radionuclides of rhenium, the group 7 congener of Tc, are suitable for radiotherapeutic applications due to their favorable β-emitting properties (^{188}Re, $E_{\beta(max)}$ = 2.12 MeV, $t_{1/2}$ = 17 h; ^{186}Re, $E_{\beta(max)}$ = 1.07 MeV, $t_{1/2}$ = 3.7 d).[6] Complexes of nonradioactive isotopes of rhenium also serve as model compounds for the chemically related technetium compounds.

Despite their potential importance, radiopharmaceuticals based on technetium- and rhenium-labeled nucleosides and nucleoside analogues have not been extensively explored.[7,8] Our interest focused on nucleoside derivatives incorporating the metal−tricarbonyl cores, $\{Tc(CO)_3\}^+$ and $\{Re(CO)_3\}^+$, as the $\{M(CO)_3\}^+$ core is chemically robust, low-spin d^6, providing a convenient platform for drug development. A convenient synthesis for the $[Tc(CO)_3(H_2O)_3]^+$ core has been described by Alberto and colleagues, who have also extensively explored the core for the development of target-specific radiopharmaceuticals.[9,10]

We have recently reported on a series of bifunctional single amino acid chelates (SAAC) for labeling biomolecules with the $\{Tc(CO)_3\}^+$ and $\{Re(CO)_3\}^+$ cores.[11] Such amino acid analogues provide a tridentate donor set for chelation and an amino acid functionality for attachment to biomolecules and can be readily incorporated into peptides via solid-phase synthesis techniques.[12,13] In this work, we have coupled the amino acid chelators with nucleoside derivatives to provide novel potential inhibitors for nucleoside kinases and thymidine analogues. Furthermore, we also developed nucleoside−quinoline derivatives to provide fluorescent probes allowing the localization of the bioconjugate at the cellular level or with imaging small animals.[14−17] This can provide an optimal system in which the fluorescent and radioactive prosthetic groups are isostructural. These characteristics render these reagents ideal candidates for radiopharmaceuticals and fluorescent probes based upon the $\{M(CO)_3\}^+$ (M = Tc, Re) core.

Thymidine and uridine have been functionalized at the C2′ and C5′ ribose positions, and a series of tridentate chelators and their rhenium tricarbonyl complexes have been prepared. The representative complex $[Re(CO)_3(\mathbf{L2})]Br\cdot 0.5NaPF_6$ (**L2** = 1-{5-[(bis(quinolin-2-ylmethyl)amino)methyl]-4-hydroxytetrahydrofuran-2-yl}-5-methyl-1*H*-pyrimidine-2,4-dione) has been characterized by X-ray crystallography.

Experimental Section

General Methods. All reagents and organic solvents used in this study were reagent grade and were used without further purification. $[NEt_4]_2[ReBr_3(CO)_3]$[18] was prepared according to the literature method. Acetonitrile used for electrochemical experiments was dried by passing through an alumina column just prior to the experiments. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer; all peak positions are relative to TMS. IR spectra were recorded as KBr pellets with a Perkin-Elmer Series 1600 FT-IR spectrometer in the region of 400−4000 cm^{-1} with polystyrene as reference. High-resolution mass spectra were obtained on a Kratos MS-890 mass spectrometer under electron impact ionization conditions. Electrochemical measurements were performed on a BAS potentiostat (model CV-27) equipped with

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data-collecting and -analyzing capabilities. Dry acetonitrile, deoxygenated under nitrogen atmosphere, was used as the solvent with 0.1 M tetra-*n*-butylammonium hexafluorophosphate ($[NBu_4]PF_6$, TBAH) as supporting electrolyte. A three-compartment glass cell, with a platinum bead working electrode, a platinum wire counter electrode, and a silver wire reference electrode, was used for all experiments. Potential values were recorded without junction correction. Ferrocene was used as an internal standard. Under our experimental conditions, with a scan rate of 50 mV/s, the ferrocenium/ferrocene couple occurred at $E_{1/2} = +0.442$ V. Carbon, hydrogen, and nitrogen analyses were carried out by Oneida Research Services, Whitesboro, NY. Electronic absorption spectra were recorded on a Varian Cary 50 Bio UV−visible spectrophotometer. Measurement were performed with baseline correction using matched quartz cuvettes. Steady-state excitation and emission spectra and lifetime measurement were obtained on a PTI (Photon Technology International) spectrofluorometer. XenoFlash pulsed light was the excitation source for emission lifetime measurements. Luminescence quantum yields were measured by the optical dilute method[19] using an aerated aqueous solution of $[Ru(bpy)_3]Cl_2$ ($\Phi = 0.028$)[20] as the standard solution.

Ligand Syntheses. 1-(5-(Aminomethyl)-4-hydroxytetrahydrofuran-2-yl)-5-methyl-1*H*-pyrimidine-2,4-dione (1). Compound **1** was prepared according to the literature procedure[21] with minor modifications. Thymidine was transformed to 5′-azido-5′-deoxythymidine in 86% yield via the phosphonium salt and reaction with sodium azide. Hydrogenation of the azidothymidine by Pd/C in ethanol led to compound **1** in 90% yield.

1-{5-[(Bis(pyridin-2-ylmethyl)amino)methyl]-4-hydroxytetrahydrofuran-2-yl}-5-methyl-1*H*-pyrimidine-2,4-dione (L1). 1 (0.1164 g, 0. 485 mmol) and 2-pyridinecarboxaldehyde (0.1039 g, 0.97 mmol) were mixed in 1,2-dichloroethane. Sodium triacetoxyborohydride (0.3084 g, 1.455 mmol) was then added. The suspension was stirred at ambient temperature under an argon atmosphere for 4 h. The reaction mixture was quenched by adding saturated sodium bicarbonate solution and extracted with dichloromethane. Concentrating the dichloromethane layer under vacuum gave **L1**. Yield: 0.204 g (quantitative). ^{1}H NMR (δ (ppm), $CDCl_3$): 8.52 (d, $J = 4.5$ Hz, 2H, Py), 7.58 (t, $J = 7.8$ Hz, 2H, Py), 7.26 (d, $J = 7.5$ Hz, 2H, Py), 7.14 (t, $J = 5.1$ Hz, 2H, Py), 6.87 (s, 1H, 6), 6.19 (t, $J = 6.6$ Hz, 1H, 1′), 4.09 (m, 1H, 3′), 3.96 (m, 1H, 4′), 3.91 (d, $J = 14.1$ Hz, 2H, Py-CH_2), 3.75(d, $J = 14.1$ Hz, 2H, Py-CH_2), 3.12 (m, 1H, 5′), 2.72 (m, 1H, 5′), 2.38 (m, 1H, 2′), 2.16 (m, 1H, 2′), 1.78 (s, 3H, 5-CH_3). ^{13}C NMR (δ (ppm), $CDCl_3$): 164.23, 158.63, 150.60, 149,03, 136.84, 135.22, 123.71, 122.55, 111.08, 83.89, 82.78, 73.47, 60.47, 56.62, 39.53, 12.70. IR (KBr, ν/cm^{-1}): 3378 (b), 1674 (ν_{as}(C═O)), 1450, 1264, 1052, 760. HRMS: calcd for $C_{22}H_{25}N_5O_4Na$ (M + Na^+), 446.179 873; found, 446.178 578.

1-{5-[(Bis(quinolin-2-ylmethyl)amino)methyl]-4-hydroxytetrahydrofuran-2-yl}-5-methyl-1*H*-pyrimidine-2,4-dione (L2). The ligand was prepared by a procedure similar to that described for **L1**, except that 2-quinolinecarboxaldehyde was used instead of 2-pyridinecarboxaldehyde. The crude product was purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (5/95) to give **L2**. Yield: 90%. ^{1}H NMR (δ (ppm), $CDCl_3$): 8.35 (bs, 1H, NH), 8.05−8.14 (m, 4H, Qu), 7.71−7.80 (m, 4H, Qu), 7.46−7.57 (m, 4H, Qu), 6.73 (s, 1H, 6), 6.21 (m, 1H, 1′), 4.18 (d, $J = 14.1$ Hz, 2H, Qu-CH_2), 4.02 (d, $J = 14.1$ Hz, 2H, Qu-CH_2), 4.02−4.18 (m, 2H, 3′, 4′), 3.33 (m, 1H, 5′), 2.82 (m, 1H, 5′), 2.47 (m, 1H, 2′), 2.23 (m, 1H, 2′), 1.53 (s, 3H, 5-CH_3). ^{13}C NMR (δ (ppm), $CDCl_3$): 163.66, 159.33, 150.27, 147.60, 136.97, 135.19, 130.09, 128.82, 127.76, 127.58, 126.78, 121.68, 111.25, 83.93, 82.55, 74.05, 61.73, 56.62, 39.65, 12.42. IR (KBr, ν/cm^{-1}): 3360 (b), 1676 (ν_{as}(C═O)), 1466, 1268, 1044, 828, 762. Mass spectrum (HRMS): calcd for $C_{30}H_{29}N_5O_4Na$ (M + Na^+), 546.211 173; found, 523.582 36.

5-(Bis(pyridin-2-ylmethyl)amino)pentanoic Acid (2). Compound **2** was synthesized by direct reductive amination procedure developed by our group.[22] 2-Pyridinecarboxaldehyde (19.6275 g, 183.24 mmol) and sodium triacetoxyborohydride (58.2558 g, 274.86 mmol) in DCE were added to a solution of 5-aminopentanoic acid (10.7336 g, 91.62 mmol) in 1,2-dichloroethane (DCE). The suspension was stirred at room temperature under argon atmosphere for 2 h. The reaction mixture was washed with saturated sodium bicarbonate solution and extracted with chloroform. The separated organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (6/94) as eluant to provide compound **2**. Yield: 23.29 g (77.88 mmol, 85%). ^{1}H NMR (δ (ppm), $CDCl_3$): 11.84 (bs, 1H, COOH), 8.47 (d, 2H, Py), 7.61 (t, 2H, Py), 7.49 (d, 2H, Py), 7.09 (t, 2H, Py), 3.76 (s, 4H, PyCH_2), 2.51 (t, 2H), 2.23 (t, 2H), 1.15 (m, 4H). ^{13}C NMR (δ (ppm), $CDCl_3$): 176.68 (COOH), 159.35 (2C, Py), 148.28 (2C, Py), 137.09 (2C, Py), 123.24 (2C, Py), 122.25 (2C, Py), 59.72 (2C, PyCH_2), 54.06, 34.32, 22.79, 18.37.

5-(Bis(quinolin-2-ylmethyl)amino)pentanoic Acid (3). Compound **3** was prepared by a procedure similar to that described for **2**, except that 2-quinolinecarboxaldehyde was used instead of 2-pyridinecarboxaldehyde. Yield: 80%. ^{1}H NMR (δ (ppm), $CDCl_3$): 11.06 (bs, 1H, COOH), 8.06 (t, 4H, Qu), 7.68 (t, 4H, Qu), 7.59 (t, 2H, Qu), 7.39 (t, 2H, Qu), 4.03 (s, 4H, QuCH_2), 2.65 (t, 2H), 2.29 (t, 2H), 1.65 (m, 4H). ^{13}C NMR (δ (ppm), $CDCl_3$): 176.99 (COOH), 160.22, 146.98, 136.82, 129.60, 128.24, 127.51, 127.34, 126.28, 121.18, 60.58, 54.28, 34.27, 26.51, 22.71.

5-(Bis(pyridin-2-ylmethyl)amino)pentanoic Acid [(3-Hydroxy-5-(5-methyl-4-oxo-3,4-dihydro-2*H*-pyrimidin-1-yl)tetrahydrofuran-2-yl)methyl] Amide (L3). Compound 2 (0.2542 g, 0.850 mmol) was dissolved in DMF. 1-Hydroxybenzotriazole (HOBT) (0.1264 g, 0.935 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (0.1793 g, 0.935 mmol), and triethylamine (0.4 mL, 2.87 mmol) were added. The mixture was stirred at room temperature for 2 h. The formation of the active ester was monitored by TLC and NMR. 5′-Amino-5′-deoxythymidine (1) (0.2040 g, 0.850 mmol) was added, and the reaction mixture was stirred at room temperature for 1 day. The solvent was removed under vacuum, and the residue was purified by alumina column using CH_3OH/CH_2Cl_2 (10/90) as eluant to give pure product as yellow oil. Yield: 0.337 g (0.646 mmol, 76%). ^{1}H NMR (δ (ppm), $CDCl_3$): 10.42 (bs, 1H, 3-NH), 8.49 (d, $J = 4.5$ Hz, 2H, Py), 7.63 (t, $J = 7.5$ Hz, 2H, Py), 7.50 (m, 1H, CONH), 7.46 (d, $J = 7.8$ Hz, 2H, Py), 7.15 (m, 3H, Py, 6), 6.05 (t, $J = 6.6$ Hz, 1H, 1′), 4.37 (m, 1H, 3′), 3.97 (m, 1H, 4′), 3.81 (s, 4H, Py-CH_2), 3.51 (m, 2H, 5′), 2.55 (t, 2H, d), 2.33 (m, 2H, 2′), 2.16 (t, 2H, a), 1.86 (s, 3H, 5-CH_3), 1.56 (m, 4H, b + c). ^{13}C NMR (δ (ppm), $CDCl_3$): 174.52, 164.36, 159.43, 150.87, 148.83, 137.07, 136.92, 123.52, 122.40, 111.27, 87.22, 85.34, 71.69, 59.93, 53.59, 41.23, 39.22, 36.05, 25.31, 23.65, 12.60. IR (KBr, ν/cm^{-1}): 3384 (b), 1668 (ν_{as}(C═O)), 1430, 1266, 1044, 760. HRMS: calcd for $C_{27}H_{34}N_6O_5Na^+$ (M + Na^+), 545.248 287; found, 545.250 939.

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ran-2-yl)methyl] Amide (L4). Ligand L4 was prepared by a procedure similar to that described for L3, except that 3 was used instead of 2. Yield: 70%. ^{1}H NMR (δ (ppm), $CDCl_3$): 8.11 (d, J = 8.4 Hz, 2H, Qu), 8.03 (d, J = 8.4 Hz, 2H, Qu), 7.76 (d, J = 8.1 Hz, 2H, Qu), 7.66 (m, 4H, Qu), 7.51−7.43 (m, 3H, Qu, CONH), 7.07 (s, 1H, 6), 6.02 (t, J = 6.6 Hz, 1H, 1′), 4.38 (m, 1H, 3′), 3.98 (bs, 5H, Qu-CH_2 + 4′), 3.52 (m, 2H, 5′), 2.60 (t, 2H, d), 2.32 (m, 2H, 2′), 2.14 (t, 2H, a), 1.81 (s, 3H, 5-CH_3), 1.58 (m, 4H, b + c). ^{13}C NMR (δ (ppm), $CDCl_3$): 174.47, 164.42, 160.50, 159.57, 150.80, 147.20, 136.75, 129.64, 128.45, 127.65, 127.37, 126.33, 121.32, 111.10, 86.39, 85.21, 71.73, 60.74, 53.83, 44.74, 41.35, 39.09, 35.87, 25.34, 23.43, 12.42. IR (KBr, ν/cm^{-1}): 3308 (b), 1668 (ν_{as}(C═O)), 1424, 1266, 1050, 828, 756. HRMS: calcd for $C_{35}H_{38}N_6O_5Na^+$ (M + Na^+), 645.279 587; found, 645.278 64.

1-(3-Amino-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (4). Compound **4** was prepared in five steps from uridine according to the published procedure[23] with minor modifications.

1-[3-(Bis(pyridin-2-ylmethyl)amino)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1*H*-pyrimidine-2,4-dione (L5). Ligand **L5** was prepared by a procedure similar to that described for **L1**, except that **4** was used instead of **1**. Yield: 16%. ^{1}H NMR (δ (ppm), $CDCl_3$): 10.04 (bs, 1H, 3-NH), 8.67 (d, J = 4.5 Hz, 1H, Py), 8.34 (d, J = 4.2 Hz, 1H, Py), 7.76 (t, J = 7.5 Hz, 1H, Py), 7.62 (d, J = 7.8 Hz, 1H, Py), 7.50 (t, J = 7.5 Hz, 1H, Py), 7.35 (d, J = 8.1 Hz, 1H, 6), 7.32−7.21 (m, 2H, Py), 7.05 (t, J = 6.9 Hz, 1H, Py), 6.11 (d, J = 5.7 Hz, 1H, 1′), 5.59 (d, J = 7.8 Hz, 1H, 5), 5.11 (m, 1H, 3′), 4.34−4.28 (m, 2H, 2′ 4′), 3.99−3.83 (dd, J = 12 Hz, Py-CH_2), 3.76 (m, 2H, 5′). ^{13}C NMR (δ (ppm), $CDCl_3$): 163.54, 157.93, 156.39, 150.42, 140.44, 149.09, 141.89, 137.30, 136.75, 124.29, 123.24, 122.67, 122.54, 103.00, 95.01, 89.39, 85.00, 80.75, 69.83, 62.86, 53.46. HRMS: calcd for $C_{21}H_{23}N_5O_5Na^+$ (M + Na^+): 448.159 138; found, 448.163 105.

5-(Bis(pyridin-2-ylmethyl)amino)pentanoic acid [2-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-3-yl] amide (L6). Ligand L6 was prepared by a procedure similar to that described in for L3, except that 4 was used instead of 1. Yield: 78%. ^{1}H NMR (δ (ppm), CD_3OD): 8.40 (d, J = 5.1 Hz, 2H, Py), 7.99 (d, J = 8.1 Hz, 1H, 6), 7.74 (t, J = 7.5 Hz, 2H, Py), 7.56 (d, J = 7.8 Hz, 2H, Py), 7.22 (t, J = 6.3 Hz, 2H, Py), 6.04 (d, J = 8.1 Hz, 1H, 1′), 5.69 (d, J = 8.1 Hz, 1H, 5), 4.57 (m, 1H, 2′), 4.22 (m, 1H, 3′), 4.04 (m, 1H, 4′), 3.79−3.68 (m, 6H, 5′, Py-CH_2), 2.46 (m, 2H, d), 2.15 (m, 2H, a), 1.49 (m, 4H, b + c). ^{13}C NMR (δ (ppm), CD_3OD): 176.52 (CONH), 166.16, 160.83 (2C, Py), 152.70, 149.41 (2C, Py), 142.61 (C6), 138.79 (2C, Py), 125.06 (2C, Py), 123.82 (2C, Py), 103.37 (C5), 88.78 (C4′), 88.12 (C1′), 72.32 (C3′), 63.33 (C5′), 61.05 (2C, Py-CH_2), 56.98 (C2′), 55.38 (Cd), 36.51 (Ca), 27.28, 24.62 (Cb + Cc). IR (KBr, ν/cm^{-1}): 3348 (b), 1684 (ν_{as}(C═O)), 1440, 1262, 1088, 762. HRMS: calcd for $C_{26}H_{32}N_6O_6Na^+$ (M + Na^+), 547.227 552; found, 547.229 92.

5-(Bis(quinolin-2-ylmethyl)amino)pentanoic acid [2-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl] amide (L7). Ligand L7 was prepared by a procedure similar to that described for L4, except that 4 was used instead of 1. Yield: 73%. ^{1}H NMR (δ (ppm), CD_3OD): 8.23 (m, 2H, Qu), 7.98 (m, 3H, Qu+6), 7.72 (m, 6H, Qu), 7.52 (m, 2H, Qu), 6.05 (d, J = 8.4 Hz, 1′), 5.71 (d, J = 7.8 Hz, 5), 4.60 (m, 1H, 2′), 4.23 (m, 1H, 3′), 4.06 (m, 1H, 4′), 3.96 (s, 4H, Qu-CH_2), 3.76 (m, 2H, 5′), 2.59 (m, 2H, d), 1.16 (m, 2H, a), 1.56 (m, 4H, b + c). ^{13}C NMR (δ (ppm), CD_3OD): 176.58 (CONH), 166.19, 162.11 (Qu), 152.83, 148.27 (Qu), 142.69 (C6), 138.61 (Qu), 131.06 (Qu), 129.06 (Qu), 128.87 (Qu), 127.74 (Qu), 122.87 (Qu), 103.37 (C5), 88.81 (C4′), 88.21 (C1′), 72.34 (C3′), 63.35 (C5), 62.12 (Qu-CH_2), 56.98 (C2′), 55.93 (Cd), 36.54 (Ca), 27.54, 24.69 (Cb + Cc). IR (KBr, ν/cm^{-1}): 3320 (b), 1676 (ν_{as}(C═O)), 1458, 1258, 1086, 826, 766. HRMS: calcd for $C_{34}H_{36}N_6O_6Na^+$ (M + Na^+), 647.258 852; found, 647.259 41.

Syntheses of Rhenium Complexes of Ligands L1−L7. The complexes were prepared by similar procedures. A representative synthesis for the complex [Re(CO)$_3$(L1)]Br (**5**) is presented in detail.

[Re(CO)$_3$(L1)]Br (5). L1 (0.057 g, 0.136 mmol) in 2 mL of methanol was added to a stirred solution of $[NEt_4]_2[Re(CO)_3Br_3]$ (0.1044 g, 0.136 mmol) in 20 mL of methanol. The solution was stirred for 3 h. The reaction mixture was evaporated to dryness. The residue was purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (10/90) as eluant to give **5.** Yield: 80%. Anal. Calcd (found) for $C_{25}H_{25}BrN_5O_7Re$: C, 38.81 (38.62); H, 3.26 (3.45); N, 9.05 (8.89). ^{1}H NMR (δ (ppm), CD_3OD): 8.85 (m, 2H, Py), 7.93 (m, 2H, Py), 7.60 (d, 1H, 6), 7.58 (m, 2H, Py), 7.38 (m, 2H, Py), 6.31 (m, 1H, 1′), 5.13−4.88 (m, 4H, Py-CH_2), 4.43 (m, 2H, 3′, 5′), 4.23 (m, 2H, 4′, 5′), 2.53 (m, 1H, 2′), 2.34 (m, 1H, 2′), 1.90 (s, 3H, 5-CH_3). ^{13}C NMR (δ (ppm), CD_3OD): 197.26, 197.19, 196.40 (*fac*-Re(CO)$_3$), 166.42, 162.41, 162.01, 153.24, 153.14 (Py), 141.77, 141.73 (Py), 139.27 (C6), 127.08, 127.00 (Py), 124.94, 124.91 (Py), 112.22 (C5), 87.58 (C1′), 83.81 (C3′), 73.63 (C4′), 72.98 (C5′), 70.57, 68.88 (Py-CH_2), 39.23 (C2′), 12.49 (5-CH_3). IR (KBr, ν/ cm^{-1}): 3398 (b), 2030, 1922 (ν(*fac*-Re(CO)$_3$)), 1674 (ν_{as}(C═O)), 1444, 1272, 1074, 766. Mass spectrum (HRMS): calcd for $C_{25}H_{25}N_5O_7Re^+$ (M^+), 694.130 595; found, 694.132 62.

[Re(CO)$_3$(L2)]Br (6). Yield: 82%. Anal. Calcd (found) for $C_{33}H_{29}BrN_5O_7Re$: C, 45.36 (45.18); H, 3.35 (3.54); N, 8.02 (7.89). ^{1}H NMR (δ (ppm), CD_3OD): 8.52 (m, 4H, Qu), 8.02 (m, 2H, Qu), 7.87 (m, 2H, Qu), 7.70 (m, 2H, Qu), 7.61 (m, 2H Qu), 7.56 (d, 1H, 6), 6.27 (m, 1H, 1′), 5.41−5.17 (m, 4H, Qu-CH_2), 4.47 (m, 2H, 3′, 5′), 4.31 (m, 2H, 4′, 5′), 2.54 (m, 1H, 2′), 2.34 (m, 1H, 2′), 1.91 (s, 3H, 5-CH_3). ^{13}C NMR (δ (ppm), CD_3OD): 197.26, 195.50, 195.40 (*fac*-Re(CO)$_3$), 166.60, 166.51, 166.42, 152.34, 148.28, 148.22, 143.07, 143.01, 139.25,134.19, 134.15, 131.03, 129.96, 129.94, 129.68, 129.57, 121.19, 112.34, 87.78, 84.32, 73.88, 70.66, 39.07 (C2′), 12.50 (5-CH_3). IR (KBr, ν/cm^{-1}): 3382 (b), 2028, 1918, (ν(*fac*-Re(CO)$_3$)), 1684 (ν_{as}(C═O)), 1268, 1074, 780. Mass spectrum (HRMS): calcd for $C_{33}H_{29}N_5O_7Re^+$ (M^+), 794.161 895; found, 794.161 07.

[Re(CO)$_3$(L3)]Br (7). Yield: 75%. Anal. Calcd (found) for $C_{30}H_{34}BrN_6O_8Re$: C, 41.29 (41.12); H, 3.93 (4.08); N, 9.63 (9.46). ^{1}H NMR (δ (ppm), CD_3OD): 8.85 (d, J = 5.7 Hz, 2H, Py), 7.94 (t, J = 7.8 Hz, 2H, Py), 7.60 (s, 1H, 6), 7.56 (d, J = 6.3 Hz, 2H, Py), 7.38 (t, J = 6.3 Hz, 2H, Py), 6.22 (t, J = 6.6 Hz, 1H, 1′), 4.95−4.77 (dd, J = 16.8 Hz, 4H, Py-CH_2), 4.32 (m, 1H, 3′), 3.98 (m, 1H, 4′), 3.84 (m, 2H, a), 3.51 (m, 2H, 5′), 2.41 (t, J = 7.2 Hz, 2H, d), 2.27 (m, 2H, 2′), 1.99 (m, 2H, b), 1.92 (s, 3H, 5-CH_3), 1.77 (m, 2H, c). ^{13}C NMR (δ (ppm), CD_3OD): 197.37, 196.55 (*fac*-Re(CO)$_3$), 175.80 (CONH), 166.38 (thy-CO), 162.18 (2C, Py), 152.41 (2C, Py), 151.62 (thy-CO), 141.76 (2C, Py), 138.25 (C6), 127.03 (2C, Py), 124.83 (2C, Py), 111.99 (C5), 86.85 (C1′), 86.55 (C4′), 73.33 (C3′), 71.61 (Ca), 68.88 (2C, PyCH_2), 42.74 (C5′), 40.04 (C2′), 36.43 (Cd), 25.60 (Cb), 24.00 (Cc), 12.61 (5-CH_3). IR (KBr, ν/cm^{-1}): 3384, 2030, 1920, (ν(*fac*-Re(CO)$_3$)), 1666 (ν_{as}-(C═O)), 1448, 1266, 1056, 766. Mass spectrum (HRMS): calcd for $C_{30}H_{34}N_6O_8Re^+$ (M^+), 793.199 009; found: 793.196 90.

[Re(CO)$_3$(L4)]Br (8). Yield: 70%. Anal. Calcd (found) for $C_{38}H_{38}BrN_6O_8Re$: C, 46.91 (46.77); H, 3.94 (4.08); N, 8.64 (8.39).

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^{1}H NMR (δ (ppm), CD_3OD): 8.55 (d, J = 8.4 Hz, 2H,Qu), 8.50 (d, J = 8.7 Hz, 2H, Qu), 8.03 (d, J = 8.1 Hz, 2H, Qu), 7.87 (m, 2H, Qu), 7.74−7.66 (m, 4H, Qu), 7.55 (d, 1H, 6), 6.27 (t, J = 6.6 Hz, 1H, 1′), 5.24−5.11 (m, 4H, Qu-CH_2), 4.31 (m, 1H, 3′), 3.96 (m, 1H, 4′), 3.88 (m, 2H, a), 3.50 (m, 2H, 5′), 2.41 (t, J = 7.2 Hz, 2H, d), 2.26 (m, 2H, 2′), 2.08 (m, 2H, b), 1.93 (s, 3H, 5-CH_3), 1.83 (m, 2H, c). ^{13}C NMR (δ (ppm), CD_3OD): 195.65, 194.70 (*fac*-Re(CO)$_3$), 175.88, 166.69, 166.65, 166.45, 152.44, 148.11, 143.07, 138.27, 134.10, 131.06, 129.85, 121.21, 111.99, 86.76, 86.48, 73.27, 70.27, 69.29, 42.30, 39.97, 36.53, 26.68, 24.13, 12.63. IR (KBr, ν/cm^{-1}): 3386 (b), 2026, 1924, (ν(*fac*-Re(CO)$_3$)), 1678 (ν_{as}(C═O)), 1446, 1268, 1070, 778. Mass spectrum (HRMS): calcd for $C_{38}H_{38}N_6O_8Re^+$ (M^+), 893.230 309; found, 893.229 95.

[Re(CO)$_3$(L6)]Br (9). Yield: 82%. Anal. Calcd (found) for $C_{29}H_{32}BrN_6O_9Re$: C, 39.82 (39.77); H, 3.69 (3.86); N, 9.61 (9.39). ^{1}H NMR (δ (ppm), CD_3OD): 8.86 (d, J = 5.1 Hz, 2H, Py), 8.07 (d, J = 8.1 Hz, 1H, 6), 7.95 (t, J = 7.2 Hz, 2H, Py), 7.61 (d, J = 8.1 Hz, 2H, Py), 7.38 (t, J = 6.3 Hz, 2H, Py), 6.09 (d, J = 8.1 Hz, 1H, 1′), 5.75 (d, J = 8.1 Hz, 5), 4.95−4.75 (dd, J = 16.8 Hz, 4H, Py-CH_2), 4.60 (m, 1H, 2′), 4.29 (m, 1H, 3′), 4.10 (m, 1H, 4′), 3.83 (m, 2H, a), 3.79 (m, 2H, 5′), 2.41 (m, 2H, d), 1.92 (m, 2H, b), 1.70 (m, 2H, c). ^{13}C NMR (δ (ppm), CD_3OD): 197.40, 196.60 (*fac*-Re(CO)$_3$), 176.03 (CONH), 166.17 (uri-CO), 162.35 (2C, Py), 153.19 (2C, Py), 152.86 (uri-CO), 142.81(C6), 141.73 (2C, Py), 127.00 (2C, Py), 124.88 (2C, Py), 103.36 (C5), 88.93 (C4′), 88.53 (C1′), 72.42 (C3′), 71.73 (Ca), 68.90 (2C, PyCH_2), 63.31 (C5′), 57.34 (C2′), 35.88 (Cd), 25.19 (Cb), 23.75 (Cc). IR (KBr, ν/cm^{-1}): 3338 (b), 2028, 1916, (ν(*fac*-Re(CO)$_3$)), 1666 (ν_{as}(C═O)), 1458, 1262, 1086, 766. Mass spectrum (HRMS): calcd for $C_{29}H_{32}N_6O_9Re^+$ (M^+), 795.178 274; found, 795.177 57.

[Re(CO)$_3$(L7)]Br (10). Yield: 76%. Anal. Calcd (found) for $C_{37}H_{36}BrN_6O_9Re$: C, 45.59 (45.39); H, 3.72 (3.87); N, 8.62 (8.41). ^{1}H NMR (δ (ppm), CD_3OD): 8.57−8.49 (m, 4H, Qu), 8.08 (d, J = 8.1 Hz, 1H, 6), 8.02 (d, J = 8.1 Hz, 2H, Qu), 7.87 (m, 2H, Qu), 7.73−7.67 (m, 4H, Qu), 6.09 (d, J = 8.1 Hz, 1H, 1′), 5.75 (d, J = 8.1 Hz, 1H, 5), 5.31−5.06 (m, 4H, Qu-CH_2), 4.69 (m, 1H, 2′), 4.28 (m, 1H, 3′), 4.10 (m, 1H, 4′), 3.87 (m, 2H, a), 3.79 (m, 2H, 5′), 2.40 (m, 2H, d), 2.00 (m, 2H, b), 1.77 (m, 2H, c). ^{13}C NMR (δ (ppm), CD_3OD): 197.35, 195.66 (*fac*-Re(CO)$_3$), 176.05 (CONH), 166.70 (uri-CO), 166.21 (2C, Qu), 152.90 (uri-CO), 148.22 (2C, Qu), 143.05 (2C, Qu), 142.81 (C6), 134.15 (2C, Qu), 131.03 (2C, Qu), 129.94 (2C, Qu), 129.64 (2C, Qu), 129.55 (2C, Qu), 121.18 (2C, Qu), 103.38 (C5), 88.93 (C4′), 88.58 (C1′), 72.44 (C3′), 69.14 (Ca), 63.32 (C5′), 57.38 (C2′), 35.90 (Cd), 26.12 (Cb), 23.85 (Cc). IR (KBr, ν/cm^{-1}): 3390 (b), 2028, 1916 (ν(*fac*-Re(CO)$_3$)), 1676 (ν_{as}(C═O)), 1466, 1266, 1074, 780. Mass spectrum (HRMS): calcd for $C_{37}H_{36}N_6O_9Re^+$ (M^+), 895.210 12; found, 895.211 18.

X-ray Crystal Structure Determination of Complex 6. The crystal of the complex **6** was studied on a Bruker diffractometer equipped with the SMART CCD system,[24] using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). The data collection was carried out at 90(5) K. The data were corrected for Lorentz polarization effects, and absorption corrections were made using SADABS.[25] All calculations were performed using SHELXTL.[26] The structures were solved by direct methods, and all of the non-hydrogen atoms were located from the initial solution. After location of all the non-hydrogen atoms in the structure, the model was refined against F^2, initially using isotropic and later anisotropic thermal displacement parameters until the final value of Δ/σ_{max} was less than 0.001. At this point the hydrogen atoms were located from the electron density difference map and a final cycle of refinements was performed, until the final value of Δ/σ_{max} was again less than 0.001. No anomalies were encountered in the refinement of the structure. The relevant parameters for crystal data, data collection, structure solution, and refinement are summarized in Table 1, and important bond lengths and bond angles are presented in Table 2. A complete description of the details of the crystallographic methods is given in the Supporting Information.

Table 1. Crystal Data for the Structure Refinement for Complex **6**·0.5NaPF$_6$

formula	$C_{33}H_{29}BrF_3N_5Na_{0.50}O_9P_{0.50}Re$
fw	989.70
space group	*C*2
T, K	90(2)
a, Å	24.618(3)
b, Å	11.4787(11)
c, Å	15.5902(15)
β, deg	112.422(4)
V, Å^3	4072.5(7)
Z	4
D_{calc}, g cm^{-3}	1.614
μ, mm^{-1}	4.057
R1[a]	0.0579
wR2[a]	0.1370

[a] R1 = $\Sigma||F_o| - |F_c||/\Sigma|F_o|$; wR2 = $[\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for Complex **6**·0.5NaPF$_6$

Re(1)−C(2)	1.869(11)	Re(1)−N(2)	2.210(9)
Re(1)−C(1)	1.899(10)	Re(1)−N(3)	2.232(8)
Re(1)−C(3)	1.918(11)	Re(1)−N(1)	2.236(9)
C(2)−Re(1)−C(1)	85.3(4)	C(3)−Re(1)−N(3)	95.3(4)
C(2)−Re(1)−C(3)	89.5(4)	N(2)−Re(1)−N(3)	73.9(3)
C(1)−Re(1)−C(3)	83.0(5)	C(2)−Re(1)−N(1)	92.4(4)
C(2)−Re(1)−N(2)	172.4(4)	C(1)−Re(1)−N(1)	104.3(4)
C(1)−Re(1)−N(2)	101.3(4)	C(3)−Re(1)−N(1)	172.6(4)
C(3)−Re(1)−N(2)	87.8(4)	N(2)−Re(1)−N(1)	89.5(3)
C(2)−Re(1)−N(3)	99.4(4)	N(3)−Re(1)−N(1)	77.3(3)
C(1)−Re(1)−N(3)	175.1(4)		

Results and Discussions

Syntheses and Spectroscopic Properties. Examples of 2′-amino-2′-deoxy ribonucleosides are known to possess antibacterial, anticancer, and biosynthetic inhibitory effects.[27a,b] It has also been reported that Tc(V) and Re(V) complexes of 2′,3′-diamino-2′,3′-dideoxy nucleosides are potent inhibitors of ribonucleases.[27(c)] Frank and co-workers recently reported the synthesis of 5′-metalated thymidine derivatives which accommodate ruthenium moieties at the 5′ terminus of oligonucleotides with little structural and electronic perturbation to either the metal complexes or DNA.[28a] Furthermore, Martin and co-workers have described a series of carboxamide derivatives of 5′-amino-2′,5′-dideoxy-5-

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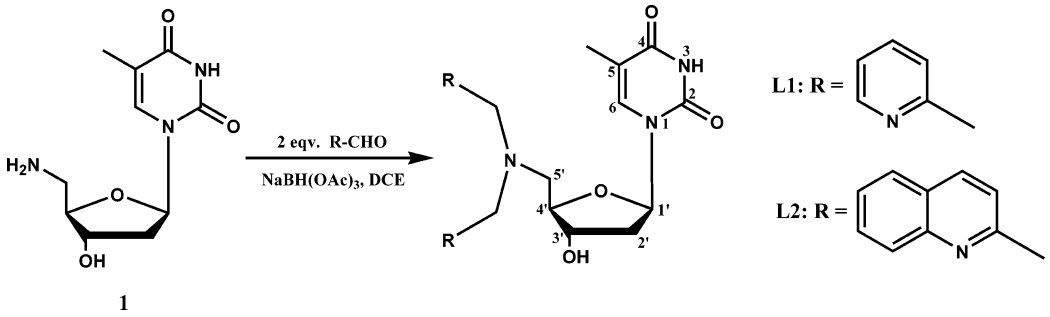
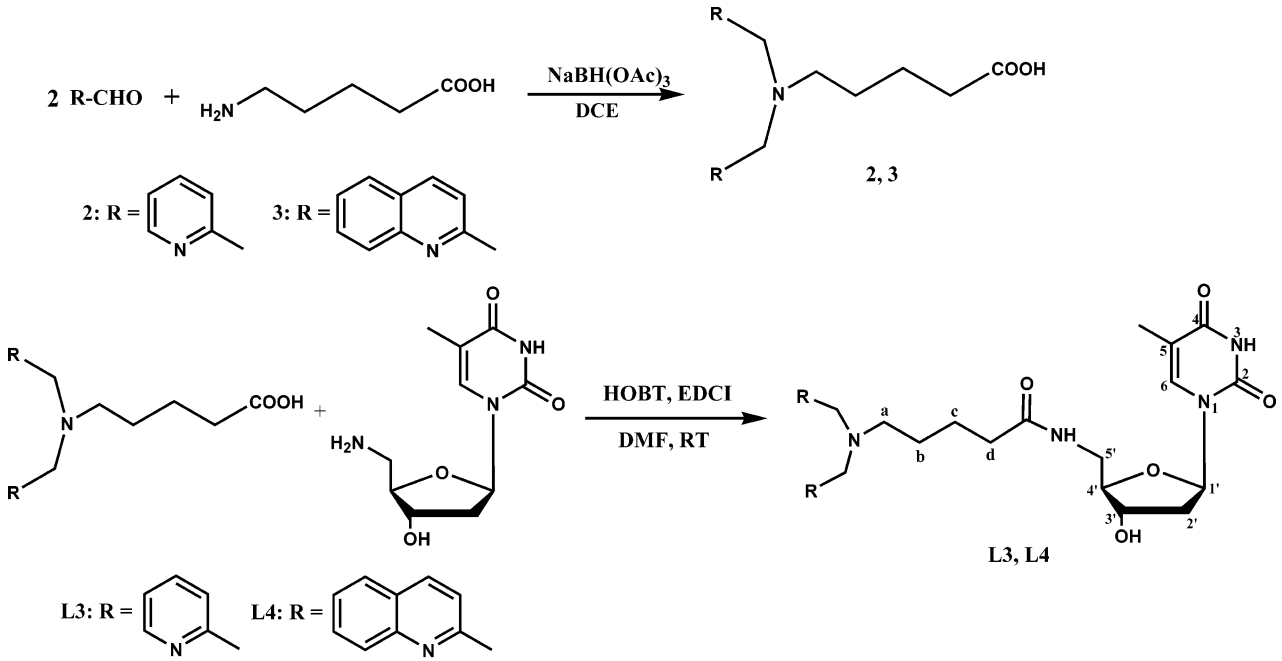
Scheme 1



1

Scheme 2



HOBT: 1-hydroxybenzotriazole
EDCI: 1-[3-dimethylamino)propyl]-3-ethyl-carbodiimide

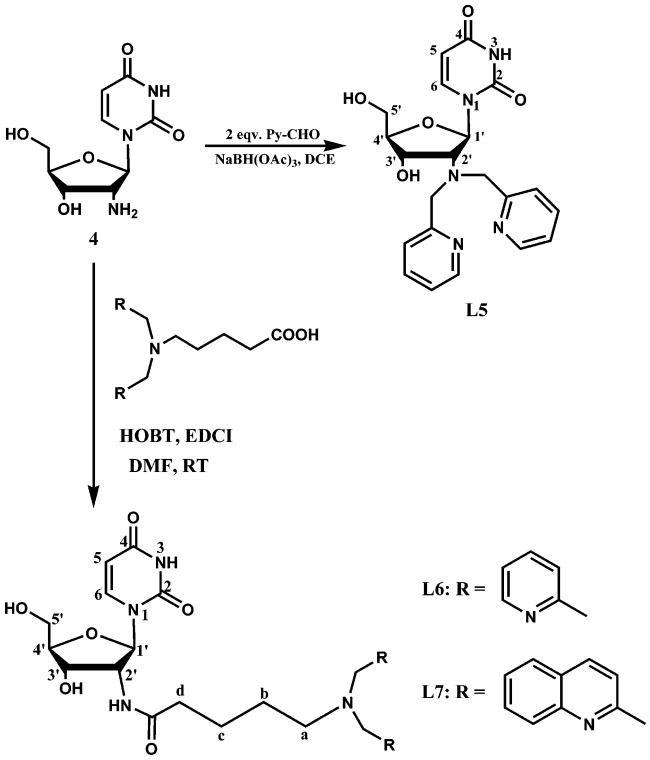
ethyluridine which are highly potent inhibitors of HSV1-TK and HSV2-TK.[28b] In view of these observations, we chose to modify thymidine and uridine at the 2′ and 5′ ribose positions.

The 5′-amine derivative of thymidine (compound **1**) was synthesized according to the published procedure with minor modifications.[21] Thymidine was converted to 5′-azido-5′-deoxythymidine via the phosphonium salt and reaction with sodium azide, followed by hydrogenation over Pd/C to give compound **1**. The 2′-amine analogue of uridine (compound **4**) was prepared in five steps from uridine by following the literature procedure[23] with some minor modification.

Ligands **L1** and **L2** were prepared by the direct reductive amination procedure developed by our group for the SAAC bifunctional chelators.[22] 5′-Amino-5′-deoxythymidine (**1**) was reacted with 2-pyridine carboxyaldehyde or 2-quinolinecarboxaldehyde in 1,2-dichloroethane (DCE) (Scheme 1) using sodium triacetoxyborohydride as a robust and effective reducing agent to form ligands **L1** and **L2** in quantitative and 90% yield, respectively. Following the same method, we attempted to make similar derivatives at 2′-position of uridine. However, the 2′-diquinolinyl derivative of uridine could not be prepared by this method. The 2′-dipicolyl derivative of uridine (**L5**) was prepared (Scheme 3) only in low yield (16%), presumably as a result of the steric hindrance at the 2′ position of uridine. Mannose triflate reacts with fluoride to make FDG, but the correct isomer cannot be made if you try to make the 2′-fluoro derivative of a nucleoside because of the base steric hindrance. Apparently, the significantly greater steric requirements of quinoline compared to pyridine are reflected in the inability to prepare the 2′-diquinolinyl derivative of uridine. It is noteworthy that the presence of the 5′-methylene group in thymidine results in reduced steric demands and consequently the 5′-derivatives of thymidine could be prepared in high yields.

The tethered analogues of dipyridyl and diquinolinyl derivatives (compounds **2** and **3**) were prepared by direct reductive amination of 2-pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde with 5-aminopentanoic acid using sodium triacetoxyborohydride as reducing agent in DCE (Scheme 2). The acid tails of compounds **2** and **3** were coupled with the amine analogues of thymidine and uridine (compounds **1** and **4**) by following the standard coupling procedure with 1-hydroxybenzotriazole (HOBT) and 1-[3-

Scheme 3



dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) in DMF (Schemes 2, 3). 5-(Bis(pyridin-2-ylmethyl)amino)pentanoic acid (**2**) or 5-(bis(quinolin-2-ylmethyl)amino)pentanoic acid (**3**) were reacted with HOBT, EDCI·HCl, and triethylamine for 2 h at room temperature to provide the active esters as confirmed by TLC and NMR. Subsequently, the active esters were reacted with the amine residues of the thymidine or uridine analogues to give ligands **L3**, **L4**, **L6**, and **L7** (Schemes 2, 3).

The rhenium complexes (complexes **5**−**10**) were prepared in excellent yields by reacting equivalent amounts of ligands **L1**−**L4**, **L6**, and **L7** with $(NEt_4)_2[Re(CO)_3Br_3]$ in methanol at room temperature for 3 h. All complexes are soluble in water and polar organic solvents, which is a prerequisite for radiopharmaceutical applications and in vitro biological studies. All ligands and rhenium complexes have been unambiguously characterized by elemental analysis, IR, high-resolution mass spectroscopy, and 1D and 2D-NMR spectroscopy.

The infrared spectra of complexes **5**−**10** exhibit a sharp, strong band in the 2026−2030 cm^{-1} range and a broad, intense absorption in the 1916−1924 cm^{-1} range, attributed to ν(C−O) of the *fac*-{$Re(CO)_3$} unit.[29] The absorptions are significantly blue shifted compared to the starting material $[Re(CO)_3Br_3]^{2-}$ (2000, 1886 cm^{-1}). The complexes and the ligands show strong absorption peaks between 1666 cm^{-1} and 1684 cm^{-1}, corresponding to the asymmetric vibration of C═O groups of thymidine and uridine rings and the amide units. There are less intense bands in the regions 1258−1272 and 1044−1088 cm^{-1}, which can be assigned to the symmetric vibrations of the CONH moieties and the bending vibrations of the N−H bonds of the thymidine/uridine and amide groups.[30]

The high-resolution mass spectra of the complexes and the ligands are consistent with the formulations from the elemental analysis and from the spectroscopic evidence. For the rhenium complexes, the highest *m*/*z* values are assigned to the $[Re(CO)_3(L)]^+$ parent ions on the basis of the isotopic distribution of ^{185,187}Re. For the ligands, the most prominent *m*/*z* values correspond to $(M + Na)^+$ from NaCl added to the solution of the ligands in methanol to obtain the mass spectra.

NMR spectra provide additional evidence for the proposed composition and molecular structure of the ligands and the corresponding rhenium complexes. The assignment of all protons and carbons are based on intensity, spin−spin splitting structure, ^{1}H−^{1}H COSY, and ^{1}H−^{13}C HMQC spectroscopy and are presented in the Experimental Section and Supporting Information. Figures 1 and 2 show the ^{1}H NMR and ^{13}C NMR spectra of ligands **L1** and **L3** and complexes **5** and **7**. Figure 3 shows the COSY and HMQC NMR spectra of complex **9**.

The proton NMR spectrum of dipicolyl−thymidine derivative **L1** shows two sets of doublets in the range of 3.91−3.75 ppm with coupling constants (J = 14.1 Hz) consistent with geminal coupling. This AB spin pattern reflects the rigid structure of the dipicolyl-tertiary amine-C5′ moiety of ligand **L1**. The protons of the methylene groups adjacent to the pyridines are nonequivalent by virtue of their axial and equatorial positions. After ligand **L1** has been coordinated to rhenium, the splitting pattern of these methylene protons becomes more complicated, resulting in multiplets in the 5.13−4.88 ppm range. The two protons at the 5′-position of ligand **L1** exhibit two multiplets at 3.12 and 2.72 ppm. After complexation, these proton signals are shifted to 4.43 and 4.23 ppm (overlapping with the 3′- and 4′-protons) because of the proximity of the 5′-protons to the rhenium center. The pyridine proton signals also show an downfield shift. These features indicate the tridentate coordination mode of ligand **L1** via the tertiary amine and the two pyridine nitrogens.

The ^{13}C NMR spectrum of complex **5** shows three carbonyl peaks indicating that although the dipicolylamine coordination moiety possesses mirror symmetry, the molecule itself lacks mirror symmetry. The proximity of the peaks at 197.26 and 197.19 ppm allows their assignment to the two carbonyl groups adjacent to the two pyridine rings. Consequently, the peak at 196.40 ppm is assigned to the carbonyl group trans to the tertiary amine. The NMR spectra of ligand **L2** and of complex **6** exhibit patterns similar to those of ligand **L1** and complex **5**.

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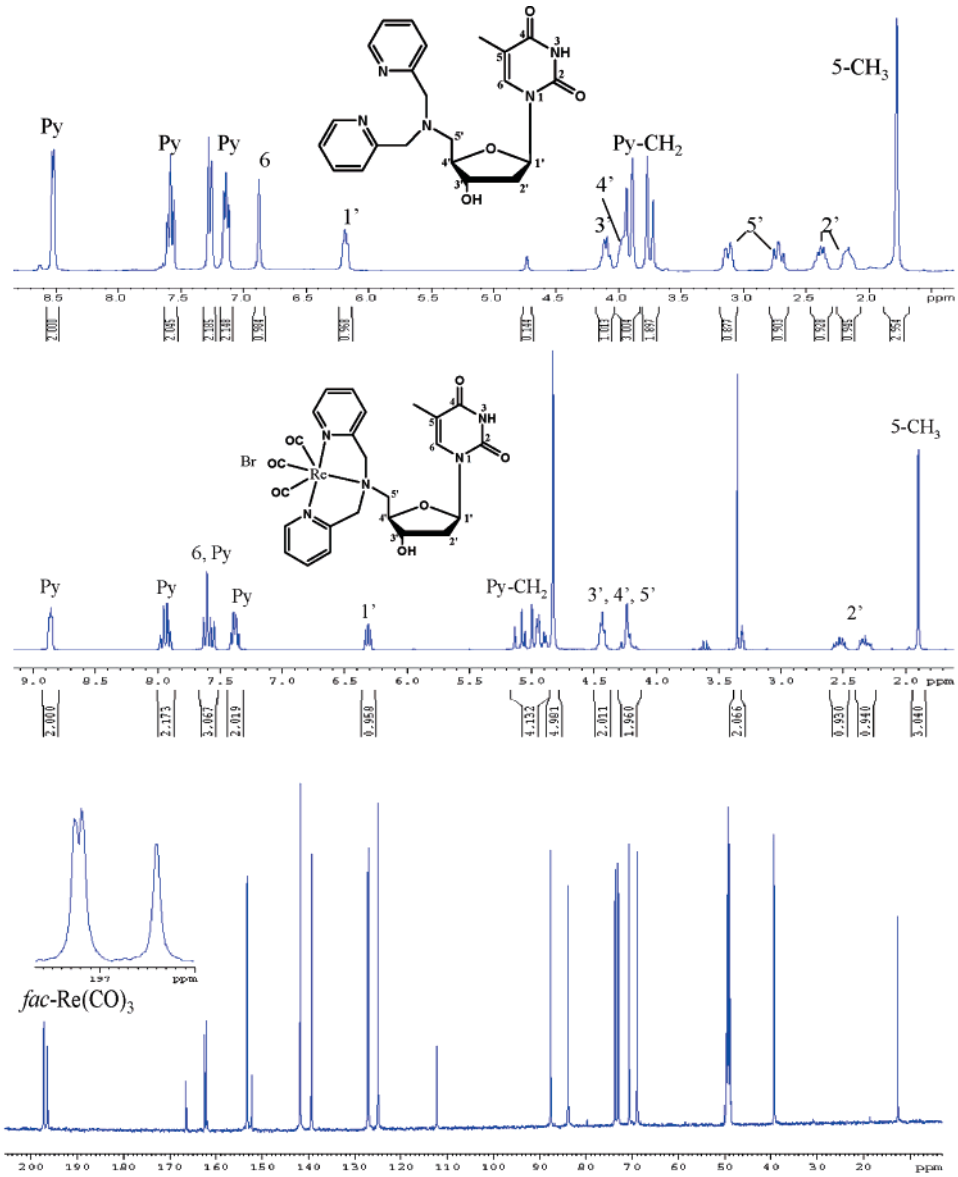

Figure 1. ^{1}H NMR spectrum of **L1** in $CDCl_3$ at room temperature and ^{1}H and ^{13}C NMR spectra of complex **5** in CD_3OD at room temperature.

In contrast to ligand **L1**, the structure of compound **L3** is considerably more flexible because of the expanded tether between the dipicolyl group and the thymidine group. The ^{1}H NMR spectrum shows one singlet for the four protons of the methylene groups adjacent to the pyridine rings. In the complex $[Re(CO)_3(L3)]Br$ (**7**), coordination to the metal center results in a more rigid environment which in turn produces nonequivalence of the methylene protons occupying axial and equatorial positions. This observation is reflected in the two sets of doublets (coupling constant $J = 16.8$ Hz) in the ^{1}H NMR spectrum of complex **7**. Similar spectroscopic features have been previously reported for the rhenium tricarbonyl complexes of the SAAC ligands[11,31] and the IDA-functionalized desoxyglucose and glucose derivatives.[10d]

The multiplet proton peaks of the methylene group adjacent to the tertiary amine are shifted from 2.16 ppm in ligand **L3** to 3.84 ppm in complex **7**, indicating that these protons are close to the rhenium site. In addition, after complexation, the multiplet (1.56 ppm) assigned to the middle two methylene groups of the spacer unit is split into two multiplets at 1.99 and 1.77 ppm. The ^{13}C NMR spectrum of complex **7** shows two Re−carbonyl peaks at 197.37 and 196.55 ppm with the characteristic 2:1 peak height. The two CO groups possess equivalent chemical environments as a result of the mirror plane along the axis of the Re and the third CO group. Similar NMR spectra are observed for the dipicolyl−uridine derivatives (**L6** and complex **9**) and the diquinolinyl−thymidine/uridine derivatives (**L4** and **L7** and complex **8** and **10**).

Finally, compared to the spectra of the free ligands, the ^{1}H and ^{13}C NMR spectra of all the complexes display no significant chemical shifts and splittings for the proton and carbon peaks at the base and ribose positions of thymidine and uridine, except for the C5′-position of thymidine in complexes **5** and **6**. This observation excluded the possibility

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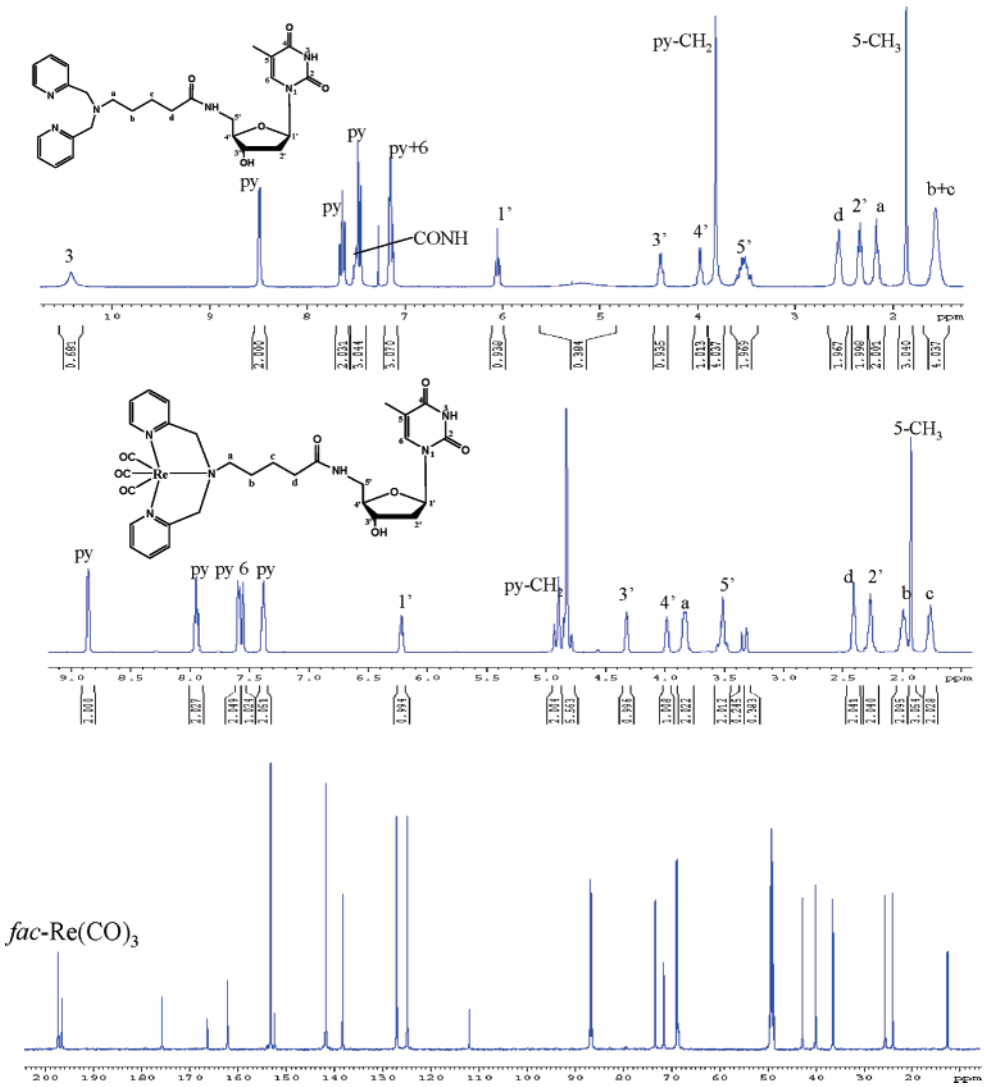

Figure 2. ^{1}H NMR spectrum of **L3** in $CDCl_3$ at room temperature and ^{1}H and ^{13}C NMR spectra of complex **7** in CD_3OD at room temperature.

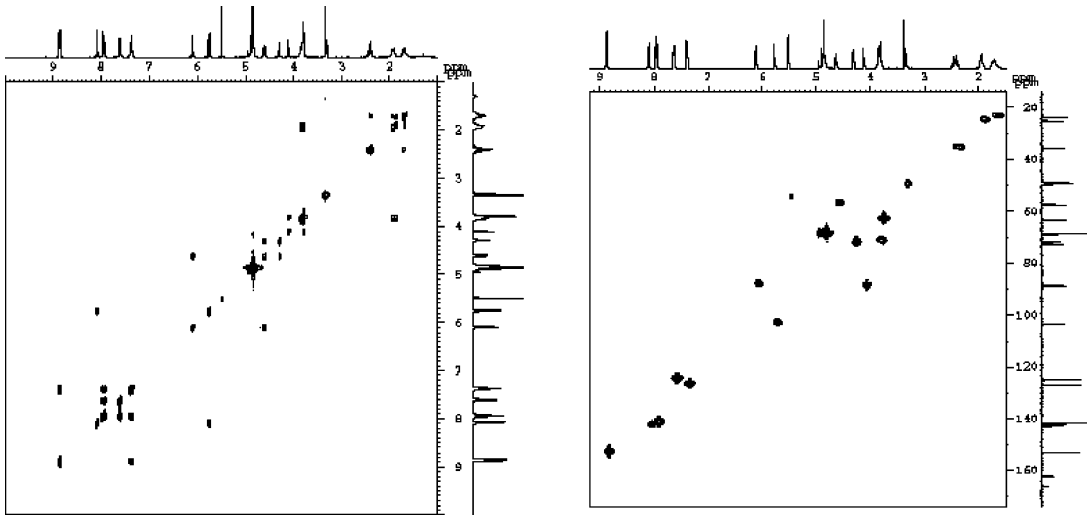

Figure 3. COSY and HMQC NMR spectra of complex **9** in CD_3OD at room temperature.

of nonspecific coordination or interaction of the metal centers with the functional groups of thymidine and uridine.

Crystallographic Studies. Single crystals of complex $[Re(CO)_3(L2)]Br\cdot 0.5NaPF_6$ (**6**·$0.5NaPF_6$) suitable for X-ray crystallography were obtained by slow diffusion of ether into a concentrated solution of complex **6** and $NaPF_6$ in methanol. The crystal structure of complex **6**·$0.5NaPF_6$ consists of discrete $[Re(CO)_3(L2)]^+$ cations, shown in Figure 4, discrete

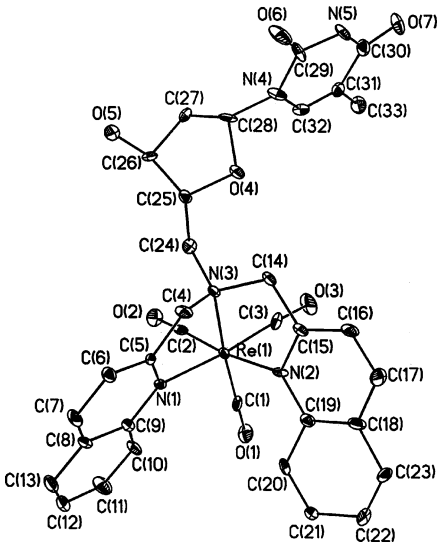

Figure 4. View of the structure of the molecular cation of [Re(CO)$_3$(L2)]-Br·0.5NaPF$_6$ (**6**·0.5NaPF$_6$).

Table 3. Electrochemical Data for Complexes **5**−**10**

complexes	oxidn $E_{1/2}$,[a] V		redn E_{pc},[b] V
5	0.702	0.990	−1.680
6	0.709	1.015	−1.249
7	0.750	0.992	−1.657
8	0.762	1.065	−1.261
9	0.758	1.020	−1.616
10	0.769	1.084	−1.258

[a] Quasi-reversible peak, $E_{1/2} = 1/2(E_{pa} + E_{pc})$, $\Delta E = E_{pa} - E_{pc} \approx 80$ mV. [b] Irreversible peak; E_{pc}, cathodic peak potential.

Br$^-$ anions, Na$^+$ cations, and PF$_6^-$ anions. The distorted octahedral environment of the Re(I) in the molecular cations is defined by the three facially bound CO groups, the tertiary amine, and the quinoline nitrogen donors of the ligand. The Re−carbonyl bond distances (1.864(11)−1.918(11) Å) are consistent with those found in other Re tricarbonyl complexes.[11,31,32] The Re−N3 distance of 2.233(8) Å is longer than the Re−N2 bond length of 2.210(9) Å, as anticipated for the sp^3 hybridization at N3 and sp^2 hybridization at the N2 sites. However, Re−N1 (sp^2 hybridized) bond length (2.236(9) Å) is longer than Re−N3 bond length. This unexpected behavior is likely related to the steric demands produced by two bulky quinoline groups, allowing a single quinoline group to bind tightly to the rhenium center, while the second adopts a longer bond distance to compensate for the crowding. The most significant angular distortions from the idealized octahedral geometry are a consequence of the constraints imposed by the tridentate chelate ligand, which forms five-membered rings with the rhenium center, resulting in N1−Re−N3 and N2−Re−N3 angles of 73.9(3) and 74.3(3)°, respectively. The steric requirements of the CO ligands are manifested in the C−Re−N cis angles of 96.8(1)° (average) and in the C−Re−N trans angles of 173.5(7)° (average). The thymidine group is directed away from the metal center, and consequently, no direct or indirect interaction of the thymidine moiety with the rhenium chelate unit was observed.

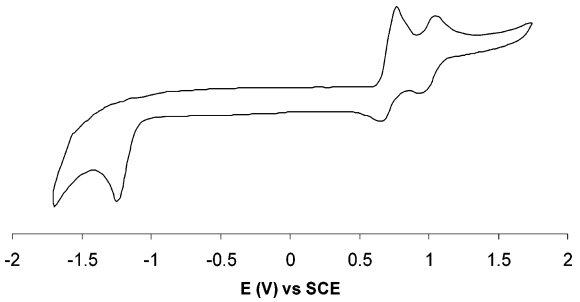

Figure 5. Cyclic voltammogram of complex **6** in acetonitrile at a platinum electrode (room temperature; scan rate, 50 mV/s).

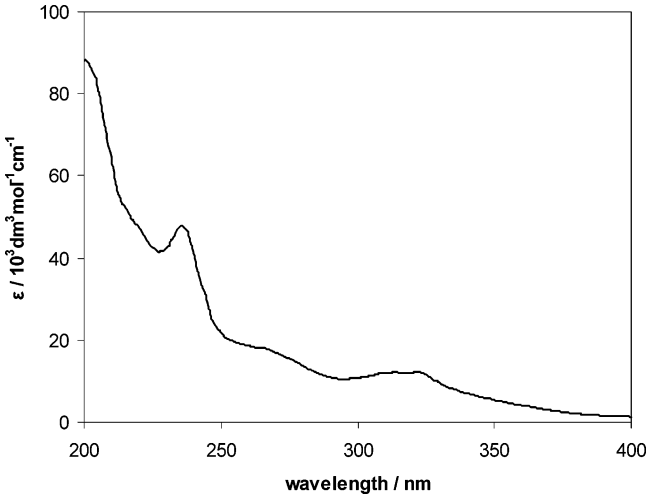

Figure 6. UV spectrum of **6** in acetonitrile at room temperature.

Electrochemistry. The electrochemistry of the rhenium complexes provides a convenient measurement of the chemical reactivity associated with the redox processes and, hence, provides a measure of the stability of the rhenium core and the ligands in the presence of redox active agents. The electrochemical behavior of complexes **5**−**10** was studied in acetonitrile solution under the conditions described in the Experimental Section. The cyclic voltammetry data are summarized in Table 3, and a representative cyclic voltammogram is presented in Figure 5.

The complexes display a quasi-reversible (peak to peak separation of ca. 80 mV) one-electron oxidation processes in the range +0.990 to +1.084 V, which can be assigned to the Re^{II}/Re^{I} oxidation couple. The redox behavior is similar to that of previously reported examples of Re^{II}/Re^{I} couples for the {Re(CO)$_3$}$^+$ complexes.[31a,33−35] The $E_{1/2}$ values of

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Table 4. Electronic Absorption Spectral Data for Complexes **6**, **8**, and **10** at Room Temperature

complex	solvent	λ_{abs}, nm (ϵ, $dm^3 \cdot mol^{-1} \cdot cm^{-1}$)
6	ethylene glycol	238 (46 675), 272 sh (12 870), 313 sh (11 210), 324 (11 995)
	acetonitrile	235 (46 020), 268 sh (17 055), 311 sh (11 640), 322 (11 130)
8	ethylene glycol	237 (64 955), 272 sh (16 710), 313 sh (14 855), 323 (15 775)
	acetonitrile	236 (45 125), 271 sh (12 360), 312 sh (10 434), 322 (10 964)
10	ethylene glycol	236 (64 079), 271 sh (16 458), 312 sh (14 564), 322 (15 536)
	acetonitrile	235 (52 850), 270 sh (13 500), 311 sh (11 135), 322 (11 740)

Table 5. Photophysical Data for Complexes **6**, **8**, and **10** at Room Temperature

complex	medium		λ_{em},[a] nm	τ,[b] μs	Φ[c]
6	ethylene glycol	N_2 equilibrated	559	14.38 ± 0.05	0.0162
		air equilibrated	565		0.0056
	acetonitrile	N_2 equilibrated	554	16.01 ± 0.07	0.0125
		air equilibrated	552		0.0004
8	ethylene glycol	N_2 equilibrated	428, 557	18.64 ± 0.10	0.0234
		air equilibrated	429, 558		0.0085
	acetonitrile	N_2 equilibrated	424, 559	17.08 ± 0.12	0.0163
		air equilibrated	425		
10	ethylene glycol	N_2 equilibrated	427, 555	17.35 ± 0.10	0.0162
		air equilibrated	428, 554		0.0060
	acetonitrile	N_2 equilibrated	418, 554	15.84 ± 0.10	0.0146
		air equilibrated	421		

[a] 325 nm excitation. [b] Emission lifetimes measured at $\lambda_{em} = 555$ nm with $\lambda_{ex} = 325$ nm. [c] Quantum yields measured for the peaks in the 554−565 nm range.

complexes **6**, **8**, and **10** are more positive than those of complexes **5**, **7**, and **9**, an observation consistent with conjugation effects. The more extended conjugation by the quinolinyl group compared to that of the pyridyl group renders the rhenium(I) site less electron rich and, hence, decreases the ease of oxidation.

The complexes show an additional quasi-reversible oxidation couple in the +0.702 to +0.769 V range (peak to peak separation of ca. 80 mV) and an irreversible reduction peak in the range −1.249 to −1.261 V for bis(quinolinyl) complexes and −1.616 to −1.680 V for the bis(pyridyl) complexes. These peaks are tentatively assigned to ligand-centered oxidation and reduction since similar waves are observed for the uncoordinated ligands. The more positive oxidation potentials and the less negative reduction potentials of complexes **6**, **8**, and **10**, compared to complexes **5**, **7**, and **9**, are also related to the more extended conjugation by the quinolinyl group than by the pyridyl group.

UV and Luminescence Spectroscopy. Complexes **6**, **8**, and **10** exhibit very similar intense and structured absorption spectra, for which the data are summarized in Table 4. The absorption spectrum of complex **6** in acetonitrile at room temperature is shown in Figure 6 as a representative example. On the basis of previous spectroscopic studies of rhenium tricarbonyl polypyridine complexes,[19−22] we have tentatively assigned the absorption peaks. The intense absorptions at ca. 225−290 nm are related to intraligand (IL) transitions ($\pi-\pi^*$) since similar absorption bands are observed for the uncoordinated ligands. The less intense and lower energy absorptions at ca. 300−380 nm are related to the metal to ligand charge transfer (MLCT) [$d\pi(Re)-\pi^*$(ligand)] transitions. It is likely that these transitions have considerable IL character, given that the free ligands also absorb in this region.

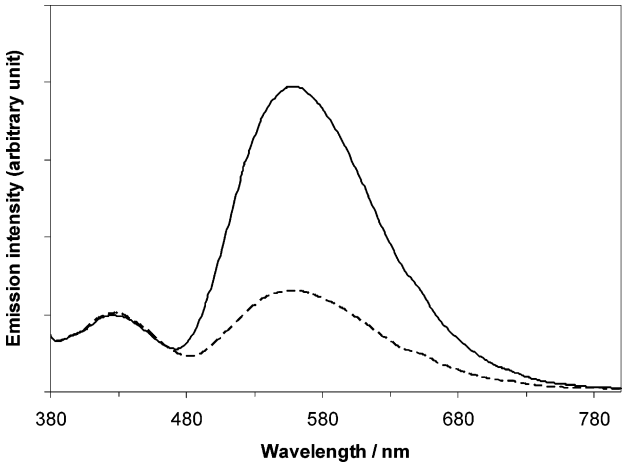

Figure 7. Emission spectra of **8** in ethylene glycol at room temperature: N_2 equilibrated (solid line); air equilibrated (dashed line).

The excitation spectra roughly closely correlate with the absorption spectra. The steady-state emission spectra were measured from 350 to 750 nm with an excitation wavelength of 325 nm in 1 nm step sizes with an integration time of 1 s and band-passes of 2 nm. The photophysical data of complexes **6**, **8**, and **10** are listed in Table 5. The emission spectra of complex **8** in nitrogen-equilibrated and air-equilibrated ethylene glycol are shown in Figure 7. The photophysical properties of complex **6** are quite similar to those of complexes **8** and **10**, indicating that the presence of the spacer between the bis(quinolinyl) group and the thymidine/uridine moiety does not significantly affect the absorption and emission properties of the complexes.

Excitation of complex **6** at 325 nm gives rise to emission peaks in the 552−565 nm range in different solvent environ-

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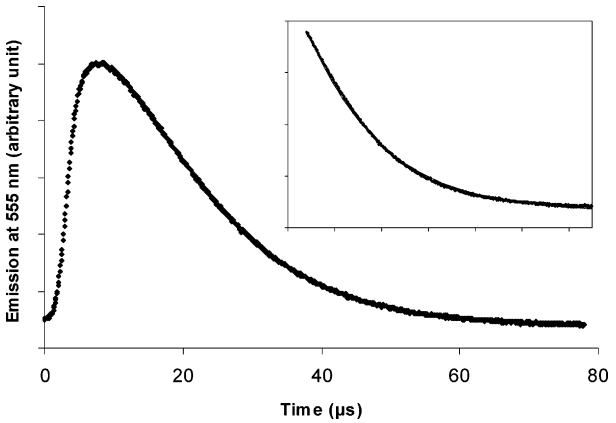

Figure 8. Emission decay trace, monitored at 555 nm in ethylene glycol, for **10** at room temperature, after 325 nm excitation. Inset: Monoexponential fit to emission decay at 555 nm with lifetime of $\tau = 17.4$ μs.

ments and in the presence or absence of air. Under the same experimental conditions, complexes **8** and **10** show two fluorescence peaks in the ranges of 418−429 and 554−559 nm. On the basis of previous spectroscopic studies on the rhenium(I) tricarbonyl complexes,[14−17] these two emission peaks are assigned to IL and metal to ligand charge transfer (MLCT) transitions, respectively. The quantum yields of the complexes, which range from 0.0004 to 0.0234, are comparable to those of previously reported transition-metal-based fluorescence probes.[14−17,27b,36−38] The quantum yields are solvent-dependent, and changing from the less polar solvent acetonitrile to the more polar solvent ethylene glycol results in an increase of the quantum yields. The quantum yields also depend on the degree of quenching due to the presence of dissolved oxygen in the samples. Equilibration of the samples in a nitrogen gas atmosphere dramatically increases the quantum yields of the rhenium complexes (Figure 7, Table 5). Curiously, the oxygen quenching is more effective in the less polar solvent acetonitrile than in the more polar ethylene glycol. In ethylene glycol, the quantum yields decrease by approximately 3-fold in the presence of oxygen, compared to N_2-saturated solution. In acetonitrile, this decrease is about 35-fold for complex **6**. For acetonitrile solutions of complexes **8** and **10**, no emissions were observed in the 550−565 nm range.

Lifetime measurements by phosphorescence decay were performed in degassed solutions with excitation and emission wavelength of 325 and 555 nm, respectively (20 nm bandpasses). The emission decay spectrum of complex **10** is shown in Figure 8. The complexes exhibit single-exponential decays with emission lifetimes of ca. 14.4−18.6 μs. There is no significant difference for the lifetimes in different solvents. The observation of long emission lifetimes (in the μs time scale), relatively high luminescence quantum yields, and large Stokes' shifts suggest that the Re(CO)$_3$−bis(quinolinyl)−nucleoside complexes are promising candidates for fluorescent probes for monitoring biological processes in vitro.

Conclusions

A series of tridentate ligands derived from the nucleosides thymidine and uridine has been developed, starting from the amine analogues. The ligands react cleanly and in high yields with $[NEt_4]_2[Re(CO)_3Br_3]$ to give complexes of the type [Re(CO)$_3$(ligand)]Br. The complexes provide novel potential inhibitors for nucleoside kinases as well as thymidine analogues, endowing them with suitable properties for therapeutic and diagnostic applications. The Re(CO)$_3$−nucleoside−bis(quinoline) derivatives display MLCT luminescence at ca. 550−565 nm with long emission lifetimes, relatively high quantum yields, and large Stokes' shifts suggesting that these complexes are ideal fluorescence probes for in vitro imaging studies. Syntheses and characterization of nucleosides at the base positions, the isolation and characterization of the ^{99m}Tc radioconjugates, and biodistribution studies are currently under investigation.

Acknowledgment. This work was supported by a grant from the National Institutes of Health, National Institute of Allergy and Infectious Diseases, STTR 1R41 A1044080-01.

Supporting Information Available: Tables listing crystal data, atomic positional parameters, anisotropic temperature factors, bond lengths and angles, torsion angles, and hydrogen-bonding distances for the structure of **6**·0.5NaPF$_6$ (CIF), ^{1}H, ^{13}C, COSY, and HMQC NMR spectra of selected ligands and complexes, and HRMS spectra of the complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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