



One-pot reaction of amide functionalized Re(I) based dinuclear metallacycles: Synthesis, characterization and evaluation for anticancer potential

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ABSTRACT

A series of self-assembled dinuclear metallacycles featuring *fac*-Re(CO)₃ core as metal corners have been prepared in a facile one-pot reaction via a coordination driven self-assembly strategy. Self-assembly of Re(CO)₅Br and amide based flexible linkers (L1–L4) in a 1:1 ratio resulted in the formation of rhenium based dinuclear metallacycles with the general formula [Re(CO)₃(μ-N-L-N)Br]₂ (**1–4**). The metallacycles **1–4** were characterized based on elemental analysis, IR, UV–Vis, NMR and ESI-mass spectroscopic techniques. The molecular structures of compounds **1** and **2** were obtained using single-crystal X-ray diffraction methods. The anticancer activities of metallacycles **1–4** on five different cancer cells revealed that the metallacycles selectively inhibit certain cancer cells.

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1. Introduction

Recent literature has evinced that chemists and their compounds are contributing greatly to the stunning progress in the field of medicine [1,2]. Therapeutics based on organometallic compounds are the developing class of drugs in anticancer research [3,4]. Additionally, they provide ample opportunities in disease treatment where the current drugs are no longer effective due to resistance [5–8]. Notably, very few drugs/drug candidates containing transition metals other than platinum exist. In recent times, interest in non-platinum based metal complexes has grown enormously due to their versatility in biological functions [9]. On the other hand, the marriage of metal coordination chemistry and supramolecular self-assembly has resulted in the generation of an extraordinary range of metal-containing assemblies, often displaying unusual properties with interesting topologies. The primary interest in this field is driven by their potential in applications, such as sensors, catalysts, host–guest chemistry and model compounds that mimic natural systems.

Among the various self-assembly strategies, metal–ligand coordination driven self-assembly has proven to be attractive and effective because of the diverse structural motifs accessible via the coordination chemistry of transition metals. This has led to

the generation of macromolecules of unprecedented shapes, sizes and functionalities [10–24]. In particular, ligands containing the amide functionality have been shown to be versatile in the self-assembly processes through hydrogen bonding interactions and the assembled products have recognizable relevance to the natural systems [25]. Thus, incorporation of organic linkers containing an amide functional group in the formation of a metallacyclic architecture is fascinating with reference to the biological significance [26–28]. As part of our broad interest in *fac*-Re(CO)₃ core based metallasupramolecular chemistry, we have been designing and exploring metallacycles of diverse topologies with specific functional groups, such as amide and ester groups, owing to their interesting photophysical properties, potential applications in anion/cation sensing and biomedical fields [29–33]. Furthermore, incorporation of flexible units into the metallacycles might lead to materials that could structurally respond to an external stimulus [34–42]. Also, in comparison with some intensively investigated organometallic complexes, such as those based on ruthenium [43], relatively few examples of tricarbonylrhenium(I) complexes have been evaluated for their cytotoxic and antiproliferative activity against various cancer cell lines [44–48].

Moreover, several rhenium(I) carbonyl complexes have been employed in the study of energy transfer, chemiluminescent and electroluminescent systems [49–52]. Indeed, rhenium(I) based organometallic complexes display several intrinsic properties and advantages towards the development of novel anticancer agents

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[53–55]. Looking at the current state of affairs, we presume that there is still a long way to go for the accomplishment of better anticancer drug molecules. Hence, we have tried to link the versatility of the *fac*-Re(CO)₃ moiety with the coordinative functionality of flexible amide derivatives to design and synthesize a new series of compounds and have evaluated their anticancer activities. Herein, we presented the self-assembly of Re(I)-based amide functionalized dinuclear metallacycles of the general formula [Re(CO)₃(μ-N-L-N)Br]₂ (**1–4**), where N-L-N is an amide functionalized ditopic ligand. In this study, we have introduced the amide functionality along with hydrophobic moieties in the metallacyclic frameworks. The metallacycles **1–4** were characterized based on elemental analysis, IR, UV-Vis, emission, NMR and ESI-mass spectroscopic techniques, and the molecular structures of **1** and **2** were obtained using single-crystal X-ray diffraction methods. The anticancer activities of metallacycles **1–4** were tested on five different cancer cell lines and the studies revealed that the amide functionalized rhenium(I) based metallacycles selectively inhibit certain cancer cells.

2. Experimental

2.1. Materials and methods

All reactions were carried out under a dry, oxygen-free, N₂ atmosphere using standard Schlenk techniques. The starting materials were purchased from Merck and Sigma-Aldrich Chemicals. Dirhenium decacarbonyl, isonicotinoyl chloride hydrochloride, 1,2-diaminoethane, 1,4-diaminobutane, 1,6-diaminohexane and 1,8-diaminooctane were used as received. According to the literature procedure, Re₂(CO)₁₀ was used to prepare Re(CO)₅Br [56]. The ditopic pyridyl ligands were synthesized as suggested by the literature procedure [57]. Toluene, ethanol, dichloromethane and other solvents were dried using the literature method prior to use [58]. IR spectra were recorded on a Nicolet iS10 FT-IR spectrometer. Electronic absorption spectra were obtained on a Shimadzu UV-2450 spectrophotometer. Emission spectra were recorded on a Fluoromax-4 spectrofluorometer. The ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer with TMS as the internal reference. Elemental analyses were performed in a Thermo Scientific Flash 2000 CHNS analyzer. ESI-mass spectra were taken on an Agilent 6530B Q-TOF mass spectrometer.

2.2. Synthesis of [Re(CO)₃(μ-bpce)Br]₂ (**1**)

A mixture of Re(CO)₅Br (41 mg, 0.1 mmol) and *N,N'*-bis(4-pyridinecarboxamide)-1,2-ethane (bpce) (27 mg, 0.1 mmol) was taken in a 50 mL Schlenk flask fitted with a reflux condenser and equipped with a magnetic stir bar. The system was evacuated and purged with N₂. To this was added a mixture of ethanol (21 mL) and toluene (7 mL), and the reaction mixture was stirred at 70 °C for 48 h. The color of the reaction mixture changed from colorless to yellow and the solvent was removed under vacuum. The product was washed with dichloromethane and dried under vacuum; a yellow solid of [Re(CO)₃(μ-bpce)Br]₂ (**1**) was isolated. Yield: 47 mg, 74% (based on Re(CO)₅Br). *Anal. Calc.* for C₃₄H₂₈N₈O₁₀Br₂Re₂: C, 32.91; H, 2.27; N, 9.03. Found: C, 32.42; H, 2.34; N, 9.22%. IR (THF, cm⁻¹): ν_(C=O) 2025 (s), 1925 (s), 1891 (s), ν_(amide C=O) 1670 (s). UV-Vis {λ_{max}^{ab} (THF, nm) (ε, dm³ mol⁻¹ cm⁻¹): 240 (28,248), 262 (25,360) (LIG), 313 (16,192) (MLCT)}. λ_{max}^{em} (THF, nm): 558. ¹H NMR (400 MHz, (CD₃)₂SO, δ, ppm): 9.00 (s, 4H, NH), 8.87 (m, 8H, H², py), 7.79 (m, 8H, H³, py), 3.46 (t, 8H, H¹, alkyl). ¹³C NMR (100 MHz, (CD₃)₂SO, δ, ppm): 195.7, 191.2 (2:1, CO), 164.2 (amide CO), 154.8 (C², py), 144.3 (C⁴, py), 124.0 (C³, py),

38.9 (NCH₂). HRMS for C₃₄H₂₉N₈O₁₀Br₂Re₂ [M+H]⁺ Calc.: 1240.9441, *m/z*; Found: 1240.9398, *m/z* (Fig. S1).

2.3. Synthesis of [Re(CO)₃(μ-bpcb)Br]₂ (**2**)

Compound **2** was prepared by the procedure adopted for **1**, using Re(CO)₅Br (41 mg, 0.1 mmol) and *N,N'*-bis(4-pyridinecarboxamide)-1,4-butane (bpcb) (29 mg, 0.1 mmol). The product [Re(CO)₃(μ-bpcb)Br]₂ (**2**) was isolated as a yellow solid. Yield: 41 mg, 63% (based on Re(CO)₅Br). *Anal. Calc.* for C₃₈H₃₆N₈O₁₀Br₂Re₂: C, 35.19; H, 2.80; N, 8.64. Found: C, 35.98; H, 2.75; N, 8.82%. IR (THF, cm⁻¹): ν_(C=O) 2025 (s), 1925 (s), 1893 (s), ν_(amide C=O) 1673 (s). UV-Vis {λ_{max}^{ab} (THF, nm) (ε, dm³ mol⁻¹ cm⁻¹): 244 (33,333), 264 (30,466) (LIG), 313 (19,367) (MLCT)}. λ_{max}^{em} (THF, nm): 549. ¹H NMR (400 MHz, (CD₃)₂SO, δ, ppm): 8.91 (s, 4H, NH), 8.82 (d, 8H, H², py), 8.07 (d, 8H, H³, py), 3.31 (t, 8H, H¹, alkyl), 1.54 (t, 8H, H², alkyl). ¹³C NMR (100 MHz, (CD₃)₂SO, δ, ppm): 195.8, 191.2 (2:1, CO), 163.4 (amide CO), 156.0 (C², py), 145.3 (C⁴, py), 124.4 (C³, py), 54.9 (NCH₂), 26.4 (CH₂). HRMS: for C₃₈H₃₇N₈O₁₀Br₂Re₂ [M+H]⁺ Calc.: 1297.0067, *m/z*; Found: 1297.0066, *m/z* (Fig. S2).

2.4. Synthesis of [Re(CO)₃(μ-bpch)Br]₂ (**3**)

Compound **3** was prepared by the procedure adopted for **1**, using Re(CO)₅Br (41 mg, 0.1 mmol) and *N,N'*-bis(4-pyridinecarboxamide)-1,6-hexane (bpch) (31 mg, 0.1 mmol). The product [Re(CO)₃(μ-bpch)Br]₂ (**3**) was isolated as a yellow solid. Yield: 49 mg, 72% (based on Re(CO)₅Br). *Anal. Calc.* for C₄₂H₄₄N₈O₁₀Br₂Re₂: C, 37.28; H, 3.28; N, 8.28. Found: C, 37.68; H, 3.39; N, 8.12%. IR (THF, cm⁻¹): ν_(C=O) 2025 (s), 1925 (s), 1893 (s), ν_(amide C=O) 1674 (s). UV-Vis {λ_{max}^{ab} (THF, nm) (ε, dm³ mol⁻¹ cm⁻¹): 244 (33,333), 263 (31,408) (LIG), 312 (20,297) (MLCT)}. λ_{max}^{em} (THF, nm): 548. ¹H NMR (400 MHz, (CD₃)₂SO, δ, ppm): 8.91 (s, 4H, NH), 8.84 (m, 8H, H², py), 7.85 (m, 8H, H³, py), 3.27 (m, 8H, H¹, alkyl), 1.51 (t, 8H, H², alkyl), 1.32 (m, 8H, H³, alkyl). ¹³C NMR (100 MHz, (CD₃)₂SO, δ, ppm): 197.0, 192.5 (2:1, CO), 164.4 (amide CO), 156.0 (C², py), 145.3 (C⁴, py), 124.4 (C³, py), 55.2 (NCH₂), 40.4 (CH₂), 27.0 (CH₂). HRMS: for C₄₂H₄₅N₈O₁₀Br₂Re₂ [M+H]⁺ Calc.: 1353.0693, *m/z*; Found: 1353.0635, *m/z* (Fig. S3).

2.5. Synthesis of [Re(CO)₃(μ-bpco)Br]₂ (**4**)

Compound **4** was prepared by the procedure adopted for **1**, using Re(CO)₅Br (41 mg, 0.1 mmol) and *N,N'*-bis(4-pyridinecarboxamide)-1,8-octane (bpco) (33 mg, 0.1 mmol). The product [Re(CO)₃(μ-bpco)Br]₂ (**4**) was isolated as a yellow solid. Yield: 52 mg, 73% (based on Re(CO)₅Br). *Anal. Calc.* for C₄₆H₅₂N₈O₁₀Br₂Re₂: C, 39.21; H, 3.72; N, 7.95. Found: C, 39.95; H, 3.78; N, 7.82%. IR (THF, cm⁻¹): ν_(C=O) 2027 (s), 1915 (s), 1894 (s), ν_(amide C=O) 1650 (s). UV-Vis {λ_{max}^{ab} (THF, nm) (ε, dm³ mol⁻¹ cm⁻¹): 241 (32,500), 263 (30,015) (LIG), 310 (19,330) (MLCT)}. λ_{max}^{em} (THF, nm): 544. ¹H NMR (400 MHz, (CD₃)₂SO, δ, ppm): 8.89 (s, 4H, NH), 8.84 (m, 8H, H², py), 7.85 (m, 8H, H³, py), 3.25 (s, 8H, H¹, alkyl), 1.49 (s, 8H, H², alkyl), 1.27 (m, 16H, H^{3&4}, alkyl). HRMS: for C₄₆H₅₃N₈O₁₀Br₂Re₂ [M+H]⁺ Calc.: 1409.1319, *m/z*; Found: 1409.1330, *m/z* (Fig. S4).

2.6. Crystal structure determination

Good quality crystals of **1** and **2** suitable for single-crystal X-ray diffraction studies were obtained by slow evaporation of concentrated solutions of the compounds in acetone at 28 °C. Single-crystal X-ray structural studies were performed on an Oxford Diffraction XCALIBUR-EOS CCD equipped diffractometer with an Oxford Instruments low temperature attachment. Crystal data were collected at 293(2)K using graphite-monochromated Mo Kα radiation (λ_α = 0.71073 Å). The strategy for the data collection

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