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Full Paper

Antimicrobial Properties of Mono- and Di-*fac*-rhenium Tricarbonyl 2-Pyridyl-1,2,3-triazole Complexes[†]

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A family of mono- and di-*fac*-rhenium tricarbonyl 2-pyridyl-1,2,3-triazole complexes with different aliphatic and aromatic substituents was synthesized in good-to-excellent yields (46–99 %). The complexes were characterized by ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, electronic (UV-visible) spectroscopy, high-resolution electrospray mass spectrometry, and elemental analyses. In four examples, the solid-state structures of the rhenium(I) complexes were confirmed by X-ray crystallography. The family of the mono- and di-rhenium(I) complexes and the corresponding 2-pyridyl-1,2,3-triazole was tested for antimicrobial activity in vitro against both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) microorganisms. Agar-based disk diffusion assays indicated that most of the rhenium(I) complexes were active against *Staphylococcus aureus* and that the cationic rhenium(I) complexes were more active than the related neutral systems. However, in all cases, the minimum inhibitory concentrations for all the complexes were modest (i.e. 16–1024 μg mL^{-1}).

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Introduction

Bacteria have built up resistance to a wide variety of organic antibacterial agents that are commonly used to kill such pathogenic microbes.[1] This is in part due to the widespread overuse of antibacterial agents.[2] Additionally, there has been a lack of interest in the development of new antibacterial drugs.[3] These factors have led to the assertion by the World Health Organization (WHO) in 2014 that the human race is on the verge of a 'post-antibiotic era'.[4] As such, there is an urgent need for the development of new antimicrobial agents that display novel modes of biological activity.

In 1952, Dwyer and coworkers showed that hydrophobic cationic metal complexes of the formula $[M(phen/bipy)_3]^{2+}$ (where M = Ni^{2+}, Fe^{2+}, Ru^{2+}, Os^{2+}, phen = 1,10-phenanthroline, and bipy = 2,2′-bipyridine) displayed antibacterial activity against Gram-positive, Gram-negative, and acid-fast bacterial strains.[5] Inert hydrophobic complexes containing the $[Ru(phen)_3]^{2+}$ unit (**1a**, Fig. 1) proved to be the most effective.[5] Six decades after this landmark discovery, interest in these types of systems has re-emerged, in the hope that metal-based antimicrobial agents will have different modes of action compared with traditional organic systems and provide new weapons to fight resistant bacteria.[6] A wide range of cationic mono-[7] and di-metallic[8] complexes display promising antibacterial properties against different bacterial strains including methicillin-resistant *Staphylococcus aureus* (MRSA). However, inspired by Dwyer and coworkers,[5] considerable effort has focussed on systems containing inert hydrophobic cations of the type $[Ru(phen)_2(N–N)]^{2+}$ (where N–N = diimine ligand).[9] Though these mono-metallic complexes have proved effective against resistant bacterial strains such as MRSA, Keene and coworkers have shown that related di-metallic systems linked by alkyl spacer units (**2a**, Fig. 1) display improved activity.[9b] Subsequent studies[10] by the same group have suggested that the antibacterial activity of these inert di-metallic ruthenium(II) complexes is related to the cellular uptake. Complexes having longer alkyl chain spacers exhibited the greatest cellular accumulation and activity. Thus, it appears that the lipophilicity of complexes is an important parameter for activity. Furthermore, Keene and coworkers have shown that a subtle interplay among the overall charge on the complex, spacing between the charges, and lipophilicity leads to high activity. Mono- and di-iridium(III) complexes (**1b** and **2b**, Fig. 1) that are structurally analogous to the active ruthenium(II) complexes but display a higher 3+ charge at the metal centres are not active antimicrobial agents.[10d,10e] Additionally, related tri- and tetra-ruthenium(II) complexes that have the same or a higher overall charge than the iridium(III) complexes are active, presumably because the charge distribution in these systems is different. Though the exact biological mode of action for these systems is still not well defined, the above results suggest that inert hydrophobic cationic metal complexes hold great potential as antibacterial agents.

[†]This paper is dedicated to Prof. Brice Bosnich (FRS, 1936–2015), a gifted scientist and a superb mentor.

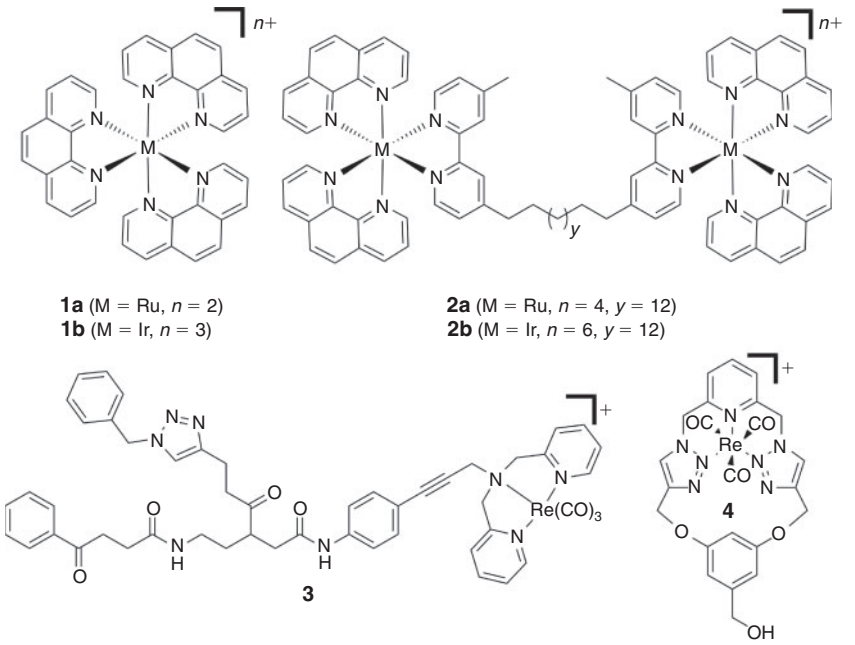


Fig. 1. Selected inert metal complexes that display antimicrobial activity.

fac-Rhenium(I) tricarbonyl complexes are a well-studied class of inert hydrophobic metal complexes. Due to the inertness and photo-activity of these complexes, they have found use in biological systems as luminescent probes.[11] Additionally, it has been shown that some *fac*-rhenium(I) tricarbonyl complexes have potential as anticancer agents.[12] Despite these biological applications, there has been little interest in examining the antimicrobial activity of these inert lipophilic metal complexes. Very recently, Metzler-Nolte and coworkers reported that trimetallic complexes containing a *fac*-rhenium(I) tricarbonyl unit display potent bactericidal activity against MRSA.[13] Subsequent work showed that the *fac*-rhenium(I) tricarbonyl motif (**3**, Fig. 1) was essential for the activity.[14] We have shown that cationic *fac*-rhenium(I) tricarbonyl complexes of readily functionalized 'click' macrocycles (**4**, Fig. 1) display modest antimicrobial activity.[15]

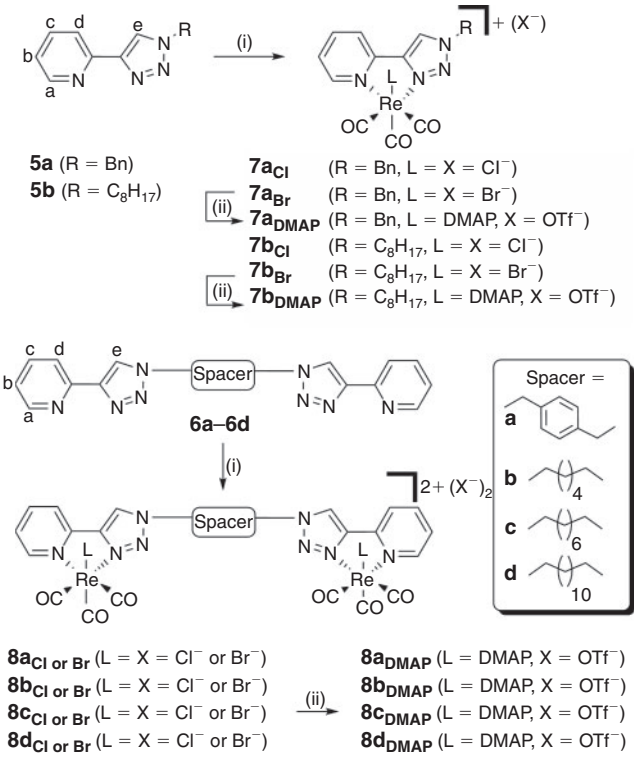
As part of our[16] interest in readily functionalized 2-pyridyl-1,2,3-triazole 'click' ligands,[17] generated using the functional group tolerant Cu(I)-catalyzed 1,3-cycloaddition of organic azides with terminal alkynes (the CuAAC reaction),[18] and biologically active metal complexes,[19] we herein report the syntheses and antibacterial properties of a series of mono- and di-*fac*-rhenium(I) complexes generated from mono- and di-2-pyridyl-1,2,3-triazole 'click' ligands.

Results and Discussion

Synthesis and Characterization of the 2-Pyridyl-1,2,3-triazole Ligands and Complexes

A small library of mono- (**5a** and **5b**) and di- (**6a** and **6b**) 2-pyridyl-1,2,3-triazole ligands substituted with aliphatic and aromatic spacer units were synthesized using our previously reported procedure (Supplementary Material).[16g] The procedure was slightly modified to generate the di-(2-pyridyl-1,2,3-triazole) ligands **6c** and **6d**. The dibromoalkyl precursor (either 1,6-dibromohexane or 1,8-dibromooctane; 1 equiv.) and sodium azide (3 equiv.) were dissolved in DMF/water (4 : 1), and the resulting solution was irradiated in a microwave reactor (200 W) at 125°C for 3 h. After cooling the reaction mixture to room temperature (RT), copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$; 0.4 equiv.), sodium ascorbate (0.5 equiv.) and 2-ethynylpyridine (2 equiv.) were added to the in situ generated diazides, and the resulting suspensions were stirred for 12 h, providing the new ligands (**6c** and **6d**) as colourless solids in good yields (79–85 %) after workup (Supplementary Material). The ^{1}H and ^{13}C NMR and high-resolution electrospray ionization mass spectra and elemental analysis data were all consistent with the expected formulation of the ligands.

We have reported the synthesis of *fac*-rhenium tricarbonyl 2-pyridyl-1,2,3-triazole chloride complexes (**7a$_{Cl}$** and **7b$_{Cl}$**) previously.[20] The mono-bromide (**7a$_{Br}$** and **7b$_{Br}$**) and the di-chloride and di-bromide (**8a$_{Cl}$**–**8d$_{Cl}$** and **8a$_{Br}$**–**8d$_{Br}$**) complexes were synthesized using similar procedures (Scheme 1).[20,21] One of the ligands (**5a**, **5b**, **6a**, **6b**, **6c** or **6d**) and either pentacarbonylrhenium(I) chloride [$Re(CO)_5Cl$] or pentacarbonylrhenium(I) bromide [$Re(CO)_5Br$] were suspended in ethanol, and the resulting mixture was refluxed for 24 h. The neutral chloride (**8a$_{Cl}$**–**8d$_{Cl}$**) and bromide (**7a$_{Br}$**, **7b$_{Br}$** and **8a$_{Br}$**–**8d$_{Br}$**) complexes were isolated as off-white solids in good-to-excellent yields (83–99 %). These neutral compounds were converted into the cationic 4-(*N*,*N*′-dimethylamino) pyridine (DMAP)[22] complexes (**7a$_{DMAP}$**, **7b$_{DMAP}$** and **8a$_{DMAP}$**–**8d$_{DMAP}$**) using a modification of the procedure developed by Benoist and coworkers (Scheme 1).[21b] One of the neutral rhenium bromide complexes (**7a$_{Br}$**, **7b$_{Br}$**, **8a$_{Br}$** or **8b$_{Br}$**; 1 equiv.) and silver triflate (AgOTf, 1 or 2 equiv.) were dissolved in dry dichloromethane and stirred at room temperature in the absence of light for 12 h. The silver bromide precipitate was removed and the in situ generated triflate complexes were added to DMAP (1 or 2 equiv.) in THF and irradiated for 1 h at 100°C in a pressurized microwave reactor. The monometallic complexes (**7a$_{DMAP}$** and **7b$_{DMAP}$**) were isolated in good yields (73–78 %), whereas the yields of the di-metallic systems (**8a$_{DMAP}$**–**8d$_{DMAP}$**) were more modest (46–53 %). Initial attempts to use the chloride complexes (**7a$_{Cl}$**, **7b$_{Cl}$**, **8a$_{Cl}$** and **8b$_{Cl}$**) as the synthetic precursors were not as successful.



Scheme 1. Synthesis of mono- and di-rhenium(I) tricarbonyl 2-pyridyl-1,2,3-triazole complexes. Reaction conditions: (i), either $[Re(CO)_5Cl]$ or $[Re(CO)_5Br]$, ethanol, reflux, 24 h; (ii) (a) silver triflate (AgOTf), CH_2Cl_2, RT, 12 h, (b) DMAP, THF, microwave irradiation (200 W), 100°C, 1 h.

Intractable mixtures containing very low yields of the desired DMAP complexes along with unreacted starting material and partially reacted mono-substituted complexes, in the case of the di-metallic systems, were obtained.

All complexes were characterized using a combination of ^1H and ^{13}C NMR, infrared (IR), and UV-visible spectroscopies, high-resolution electrospray mass spectrometry (HR-ESMS) and elemental analyses. IR spectra of the complexes (**7a$_{Cl}$**, **7b$_{Cl}$**, **7a$_{Br}$**, **7b$_{Br}$**, **7a$_{DMAP}$**, **7b$_{DMAP}$**, **8a$_{Cl}$**–**8d$_{Cl}$**, **8a$_{Br}$**–**8d$_{Br}$**, and **8a$_{DMAP}$**–**8d$_{DMAP}$**) displayed bands consistent with the presence of the aromatic units of the ligands (3100–2900 cm^{-1} and 1600–1400 cm^{-1}) and carbonyl ligands (three strong ν(CO) stretching bands in the range of 2020–1885 cm^{-1}), indicative of the presence of the *fac*-$[Re(CO)_3]^+$ core. The elemental analysis data were consistent with the expected formulation of the complexes and this was further supported by the HR-ESMS data. The mass spectra of the neutral mono-chloride and mono-bromide complexes (**7a$_{Cl}$**, **7b$_{Cl}$**, **7a$_{Br}$** and **7b$_{Br}$**) showed major ions due to $[(L)Re(CO)_3X + Na]^+$ (L = **5a** or **5b**, X = Br^- or Cl^-) and $[(L)Re(CO)_3]^+$, whereas the di-rhenium complexes (**8a$_{Cl}$**–**8d$_{Cl}$** and **8a$_{Br}$**–**8d$_{Br}$**) each displayed a prominent peak consistent with $[(L')Re_2(CO)_6X]^+$ (L′ = **6a** or **6b** or **6c** or **6d**, X = Br^- or Cl^-). Similarly, the mass spectra of the cationic DMAP complexes, **7a$_{DMAP}$** and **7b$_{DMAP}$** and **8a$_{DMAP}$**–**8d$_{DMAP}$**, showed major ions due to either $[(L)Re(CO)_3(DMAP)]^+$ or $[(L')Re_2(CO)_6(DMAP)_2]^{2+}$. All the mass spectra displayed the expected $^{185/187}Re$ isotope patterns (Supplementary Material).

The UV-visible spectra (recorded in DMF) of the neutral mono- and di-rhenium(I) complexes (**7a$_{Cl}$**, **7b$_{Cl}$**, **7a$_{Br}$** and **7b$_{Br}$**, **8a$_{Cl}$**–**8d$_{Cl}$**, and **8a$_{Br}$**–**8d$_{Br}$**) each display an intense shoulder at ~290 nm and a weaker band at 330 nm (Fig. 2 and

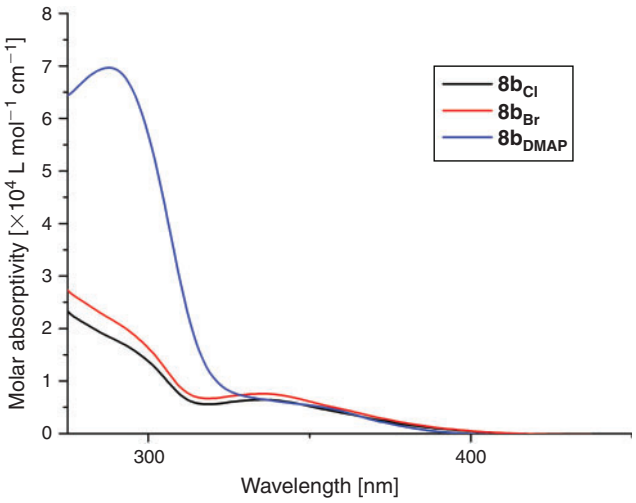


Fig. 2. Electronic absorption spectra (DMF, 10^{-5} M) of the neutral (**8b$_{Cl}$** and **8b$_{Br}$**) and cationic (**8b$_{DMAP}$**) di-rhenium(I) complexes.

Supplementary Material). The cationic mono- and di-rhenium (I) DMAP complexes are very similar, and each feature a well-defined peak at ~290 nm and a shoulder in the range of 330–340 nm (Fig. 2 and Supplementary Material). The higher energy, more intense absorptions are ascribed to intraligand π–π* transitions, whereas the lower energy bands are attributed to metal-to-ligand charge transfer transitions on the basis of previous density functional theory calculations.[20]

The ^1H NMR spectra (recorded in d_6-DMSO at 298 K) of the *fac*-rhenium(I) tricarbonyl complexes displayed large downfield shifts of pyridyl (H_a) and triazolyl (H_e) proton signals relative to the ligands, indicative of metal complexation (Fig. 3 and Supplementary Material). The ^1H NMR spectra of the cationic rhenium complexes (**7a$_{DMAP}$** and **7b$_{DMAP}$** and **8a$_{DMAP}$**–**8d$_{DMAP}$**) contained three additional resonances, two aromatic (between 7.70 and 6.40 ppm) and one alkyl (2.90 ppm), confirming the presence of the coordinated DMAP ligands to the rhenium ions (Fig. 3c and Supplementary Material).

The molecular structures of the mono- (**7a$_{Br}$** and **7a$_{DMAP}$**) and di- (**8a$_{Cl}$** and **8a$_{DMAP}$**) rhenium(I) complexes (Fig. 4, Table 1, and Supplementary Material) were unambiguously confirmed by X-ray crystallography. X-ray-quality single crystals were obtained by vapour diffusion of either diethyl ether or diisopropyl ether into an acetonitrile (or DMF) solution of the complexes. The neutral rhenium(I) complexes (**7a$_{Br}$** and **8a$_{Cl}$**) crystallized in the orthorhombic space groups *Pbcn* and *Pbca*, respectively, whereas the cationic systems (**7a$_{DMAP}$** and **8a$_{DMAP}$**) were found to form in the triclinic space group $P\bar{1}$. As expected, the pyridyltriazole 'click' ligands are coordinated to the rhenium(I) ions in a bidentate fashion through the triazole (trz) and pyridyl (py) nitrogen atoms. The three carbonyl ligands are also bound to the rhenium ions in the expected facial array, leading to a distorted octahedral coordination environment at the metal centre. The final coordination site is occupied by either a chlorido, bromido, or DMAP ligand. The bidentate pyridyltriazole ligands form five-membered chelate rings and the bite angle of the ligands varies slightly in the complexes, ranging from 74.4(2)° to 74.9(1)°. In addition, the N_{py}–Re bonds (2.175 (7)–2.204(3) Å) are consistently longer than the N_{trz}–Re bonds (2.127(6)–2.153(9) Å), suggesting that the triazolyl nitrogens coordinate more strongly to the Re centre than the pyridyl nitrogens of the ligands; this behaviour has been observed in

other metal complexes of these 'click' ligands.[16] The Re–Br bond length (2.617(1) Å) of complex $\mathbf{7a_{Br}}$ is considerably longer than the Re–Cl distance (2.471(2) Å) reported for $\mathbf{7a_{Cl}}$,[21m] suggesting, as expected, that the Re–Br bond is weaker than the Re–Cl bond and providing a reason for the more facile activation of the bromido complexes. Somewhat surprisingly, the Re–DMAP bond distances (2.177(7) and 2.200(4) Å) are quite similar to the Re–py bond distance (2.201(3) Å) reported for $\mathbf{7a_{py}}$[21d] despite DMAP being a much more basic (electron-donating) ligand. The mono-rhenium complexes are chiral and crystallize as a racemic mixture of both the Λ and Δ enantiomers. The di-rhenium complexes can form either *syn* or *anti* stereoisomers (Supplementary Material). In the solid-state structures of $\mathbf{8a_{Cl}}$ and $\mathbf{8a_{DMAP}}$, the *syn* isomers are observed. This is consistent with the ^{1}H NMR spectra, which show only one set of resonances, suggesting the selective formation of a single diastereomer. However, we cannot rule out that a mixture of the *syn* and *anti* diastereomers (which display identical ^{1}H NMR spectra) are formed initially and then the *syn* complex selectively crystallizes from the mixture.[23]

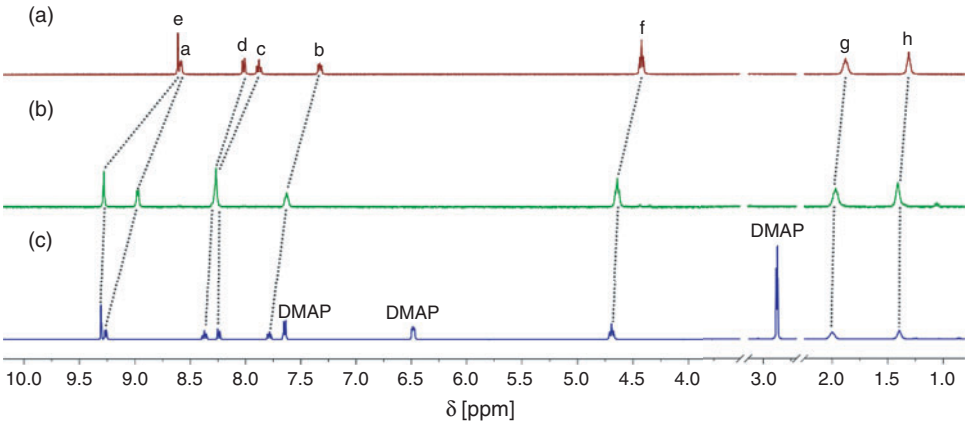


Fig. 3. Partial ^{1}H NMR spectra (400 MHz, d_6-DMSO, 298 K) of (a) ligand **6b**, (b) $\mathbf{8b_{Br}}$, and (c) $\mathbf{8b_{DMAP}}$. See Scheme 1 for peak labelling.

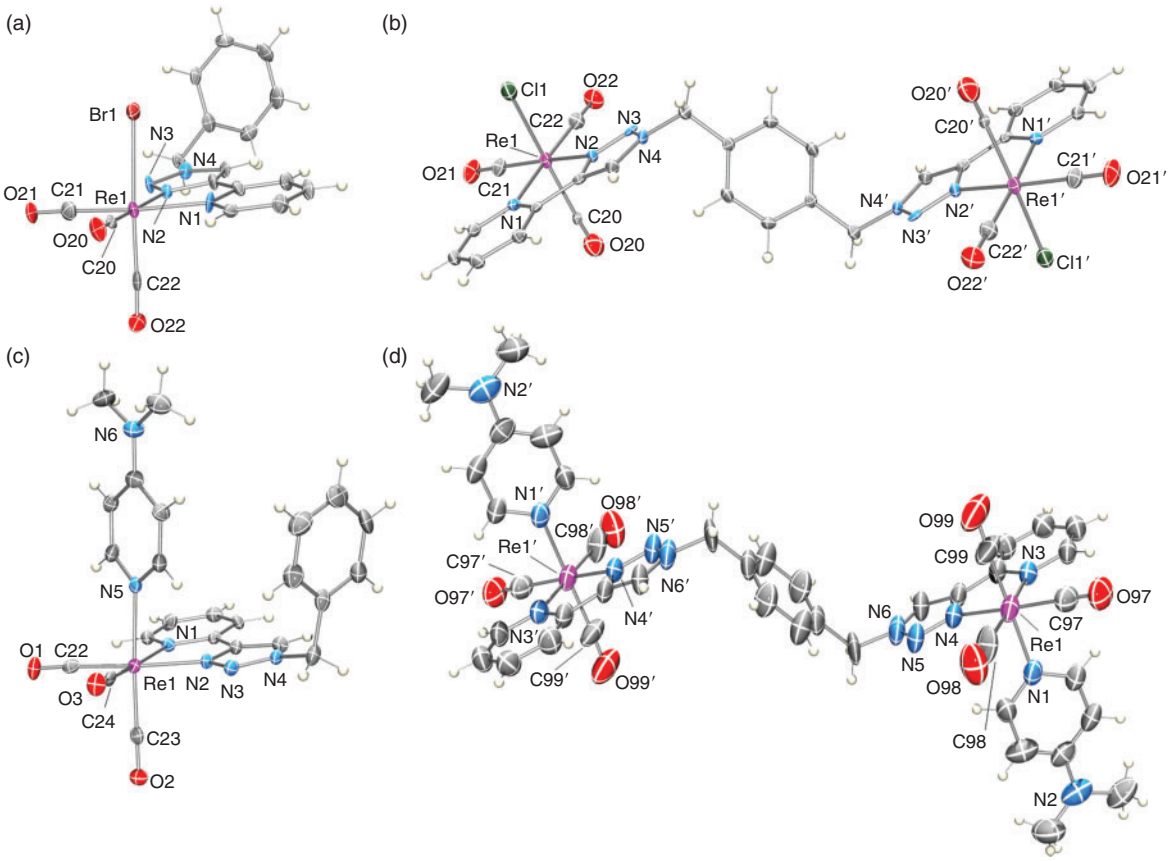


Fig. 4. *ORTEP*s[24] of the molecular structures of the *fac*-rhenium tricarbonyl 2-pyridyl-1,2,3-triazole complexes: (a) $\mathbf{7a_{Br}}$, (b) $\mathbf{8a_{Cl}}$, (c) $\mathbf{7a_{DMAP}}$, and (d) $\mathbf{8a_{DMAP}}$. The thermal ellipsoids are shown at the 50 % probability level. Solvent molecules and counter anions are omitted for clarity. Selected bond lengths (Å) and bond angles (°) for the rhenium complexes are listed in Table 1.

Competition Experiments to Evaluate the Kinetic Stability of the Rhenium(I) Complexes Versus Histidine

Before carrying out the antimicrobial testing, the kinetic stability of two of the di-rhenium(I) 2-pyridyl-1,2,3-triazole complexes (**8a$_{Cl}$** and **8c$_{DMAP}$**) was examined using histidine as a competitive ligand. One of the complexes (either **8a$_{Cl}$** or **8c$_{DMAP}$**) was dissolved in d_6-DMSO and DL-histidine (D- and L-histidine) hydrochloride monohydrate (6 equiv.) and $NaHCO_3$ (6 equiv.) were added. The resulting mixture was heated at 40°C, and the ^{1}H NMR spectra of the mixtures were recorded at specific intervals of time over a period of 24 h. Upon addition of DL-histidine hydrochloride monohydrate (6 equiv.) and $NaHCO_3$ (6 equiv.) to the rhenium(I) complexes, the triazole proton (H_e) signal of the complexes shifted downfield. We ascribe this shift to a hydrogen bonding interaction between histidine and the triazole unit. For the neutral complex **8a$_{Cl}$**, the downfield shift of the triazole proton signal (H_e), is the only change observed over a period of 24 h; no new signals related to the formation of free ligand or degradation products were observed (Supplementary Material), suggesting that the complex is kinetically stable in the presence of histidine over this time period. Conversely, over a similar time period, additional resonances appear in the ^{1}H NMR spectra of the cationic complex **8c$_{DMAP}$**. A new set of peaks begin to appear after approximately 7 h, and after 24 h, two sets of additional resonances are present (Fig. 5). One set of chemical shifts are consistent with the presence of the free ligand **6c** in the reaction mixture. We attribute the second set of new resonances to a mono-metallic complex where one of the *fac*-rhenium tricarbonyl units has been lost from the parent complex **8c$_{DMAP}$**. This postulate is supported by the mass spectral data of the reaction mixture after 24 h. The mass spectrum displayed peaks due to the intact **8c$_{DMAP}$** complex along with peaks at *m*/*z* 795.2577 and 425.2176, which correspond to $[Re(CO)_3(DMAP)(\mathbf{6c})]^+$ and $[\mathbf{6c} + Na]^+$ ions, respectively. It is noted that though two new species have formed over the 24 h period of the reaction, the major species (>85 %) in solution is the **8c$_{DMAP}$** complex. These observations were consistent with the stability studies carried out on analogous rhenium(I) complexes by Schubert and coworkers.[21c] Presumably, the cationic charge on the rhenium(I) complex **8c$_{DMAP}$** makes it more attractive to the histidine nucleophile, leading to the faster decomposition of the compound relative to the neutral **8a$_{Cl}$** complex.

Table 1. Selected bond lengths (Å) and angles (°) of the mono- (7a$_{Br}$ and 7a$_{DMAP}$) and di- (8a$_{Cl}$ and 8a$_{DMAP}$) rhenium(I) 'click' complexes

Compound	N_{py}–Re	N_{trz}–Re	N_{trz}–Re–N_{py}	X or L–Re[A]
7a$_{Br}$	2.193(9)	2.153(9)	74.6(3)	2.617(1)
7a$_{Cl}$[21m]	2.197(5)	2.127(6)	74.4(2)	2.471(2)
7a$_{DMAP}$	2.192(4)	2.133(4)	74.7(2)	2.200(4)
7a$_{py}$[21d]	2.204(3)	2.138(2)	74.43(9)	2.201(3)
8a$_{Cl}$	2.196(4)	2.153(4)	74.9(1)	2.459(1)
8a$_{DMAP}$	2.175(7)	2.141(7)	74.6(3)	2.177(7)

[A]X = Cl^- or Br^- and L = py or DMAP.

Antibacterial Activity of Rhenium(I) Complexes and Ligands

Having confirmed that the rhenium(I) complexes displayed good stability in the presence of biological nucleophiles, we evaluated their antibacterial activity against the Gram-positive bacterium *Staphylococcus aureus* (*S. aureus*) (ATCC 25923) and the Gram-negative bacterium *Escherichia coli* (*E. coli*) (ATCC 25922) using disk diffusion, disk dilution, and broth microdilution methods[25] (Tables 2 and 3). Initially, we examined the mono-metallic rhenium(I) complexes and their corresponding ligands (Table 2). None of the ligands or

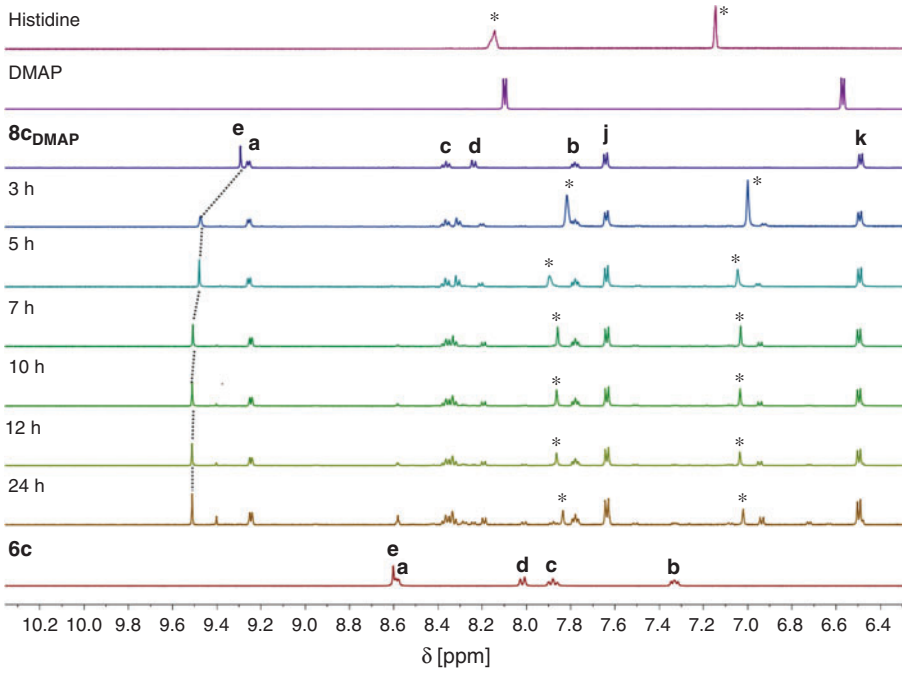


Fig. 5. Partial ^{1}H NMR spectra (500 MHz, d_6-DMSO, 313 K) of mixtures containing the rhenium complex (**8c$_{DMAP}$**) (1 equiv.), DL-histidine hydrochloride monohydrate (6 equiv.), and $NaHCO_3$ (6 equiv.) recorded over a 24 h period. For comparison, the partial ^{1}H NMR spectra of histidine, DMAP, and **6c** are also displayed. See Scheme 1 and the Supplementary Material for peak labelling.

Table 2. Antibacterial activity of the neutral and cationic mono-*fac*-rhenium tricarbonyl complexes against Gram-positive *S. aureus* and Gram-negative *E. coli* evaluated by disk diffusion, disk dilution and broth microdilution methods

Bacteria	*S. aureus* (ATCC 25923)		*E. coli* (ATCC 25922)	
Compound	Zone of inhibition [mm]	MIC [μg mL^{-1}]	Zone of inhibition [mm]	MIC [μg mL^{-1}]
5a	Nil	–	Nil	–
7a$_{Cl}$	Nil	–	Nil	–
7a$_{Br}$	10	512	Nil	–
7a$_{DMAP}$	21	128	Nil	–
5b	Nil	–	Nil	–
7b$_{Cl}$	12	64	Nil	–
7b$_{Br}$	11	64	Nil	–
7b$_{DMAP}$	16	16	Nil	–
Gentamicin	26	<0.5	23	<0.5

Nil = no zone of inhibition.

Table 3. Antibacterial activity of the neutral and cationic di-*fac*-rhenium tricarbonyl complexes against Gram-positive *S. aureus* and Gram-negative *E. coli* evaluated by disk diffusion, disk dilution and broth microdilution methods

Bacteria	*S. aureus* (ATCC 25923)		*E. coli* (ATCC 25922)	
Compound	Zone of inhibition [mm]	MIC [μg mL^{-1}]	Zone of inhibition [mm]	MIC [μg mL^{-1}]
6a	Nil	–	Nil	–
8a$_{Cl}$	Nil	–	Nil	–
8a$_{Br}$	Nil	–	Nil	–
8a$_{DMAP}$	12	64	Nil	–
6b	Nil	–	Nil	–
8b$_{Cl}$	10	128	Nil	–
8b$_{Br}$	Nil	–	Nil	–
8b$_{DMAP}$	12	16	Nil	–
6c	Nil	–	Nil	–
8c$_{Cl}$	Nil	–	Nil	–
8c$_{Br}$	Nil	–	Nil	–
8c$_{DMAP}$	15	16	15	32
6d	Nil	–	Nil	–
8d$_{Cl}$	Nil	–	Nil	–
8d$_{Br}$	Nil	–	Nil	–
8d$_{DMAP}$	11	256	9	1024
Gentamicin	26	<0.5	23	<0.5

Nil = no zone of inhibition.

complexes displayed activity against *E. coli*. Neither of the ligands (**5a** or **5b**) displayed activity against *S. aureus*. However, the neutral mononuclear rhenium(I) complexes, **7b$_{Cl}$**, **7a$_{Br}$** and **7b$_{Br}$**, were effective against *S. aureus* at higher concentrations (minimum inhibitory concentration (MIC) = 64–512 μg mL^{-1}). Furthermore, the cationic complexes **7a$_{DMAP}$** and **7b$_{DMAP}$** were found to display better activity (MIC = 16–128 μg mL^{-1}) than the neutral complexes. Additionally, the presumably more lipophilic octyl-substituted complexes were more active than the corresponding benzyl-substituted compounds. Though the activity of the cationic complexes was modest, the results were promising given that Keene and coworkers had previously demonstrated a significant increase in the antibacterial activity upon moving from mono-metallic to di-metallic ruthenium(II) polypyridyl complexes.[9b] Inspired by this, the antibacterial activity of the di-metallic rhenium(I) complexes **8a$_{Cl}$**–**8d$_{Cl}$**, **8a$_{Br}$**–**8d$_{Br}$**, and **8a$_{DMAP}$**–**8d$_{DMAP}$** were evaluated against *S. aureus* and *E. coli* using disk diffusion, disk dilution and broth microdilution methods (Table 3).

Similar to the smaller 2-pyridyl-1,2,3-triazole ligands (**5a** and **5b**), none of the di-(2-pyridyl-1,2,3-triazole) ligands (**6a**–**6d**) showed activity against either the Gram-positive or Gram-negative bacteria. Disappointingly, in most cases, the neutral di-metallic rhenium(I) complexes were ineffective against either *S. aureus* or *E. coli*. Of the neutral di-metallic complexes, only **8b$_{Cl}$** (MIC = 128 μg mL^{-1} versus *S. aureus*) showed activity. More promisingly, all of the cationic rhenium(I) complexes **8a$_{DMAP}$**–**8d$_{DMAP}$** displayed activity against *S. aureus* and one complex (**8c$_{DMAP}$**, the octyl-substituted compound) was found to inhibit the growth of *E. coli* at an MIC of 32 μg mL^{-1}. However, the MICs against *S. aureus* proved to be modest (i.e. 16–128 μg mL^{-1}). This low activity suggests that it is unlikely that these rhenium(I) complexes will find use as antimicrobial agents, except possibly as topical agents (where high concentrations are achievable) for the treatment of localized, superficial infections such as occur in chronic wounds.[26] The results are consistent with the idea that the overall charge on the complex, spacing between the charges, and lipophilicity influence activity.[10] The more lipophilic, cationic di-rhenium (I) complexes displayed the highest antimicrobial activity. Though these rhenium(I) complexes are structurally similar to the related di-ruthenium(II) complexes (i.e. **2a**), they are not as active. Presumably, this lower activity is related to the lower charge on the rhenium(I) complexes and it suggests that complexes with a 2+ charge should be targeted to prepare more effective antimicrobial agents. However, the difference in the molecular shape of the [Re(pytri)(CO)$_3$L]$^+$ and [Ru(phen)(N–N)]$^{2+}$ units may also play a role in the biological activity.

Conclusion

A family of mono- and di-*fac*-rhenium tricarbonyl 2-pyridyl-1,2,3-triazole complexes with different aliphatic and aromatic substituents was synthesized in good-to-excellent yields (46–99 %). The complexes were characterized using a range of spectroscopy techniques, high-resolution electrospray mass spectrometry, and elemental analyses. In four examples, the solid-state structures of the rhenium(I) complexes were confirmed by X-ray crystallography. The mono- and di-rhenium(I) complexes and the corresponding 2-pyridyl-1,2,3-triazole compounds were tested for antimicrobial activity in vitro against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) microorganisms. Agar-based disk diffusion assays indicated that most of the rhenium(I) complexes were active against *S. aureus* and that the cationic rhenium(I) complexes were more active than the related neutral systems. However, disappointingly, in all cases, the MICs for all complexes were modest (i.e. 16–1024 μg mL^{-1}), indicating that these compounds are unlikely to find use as antimicrobial agents, except possibly in the more limited setting of topical application.

Experimental

General Experimental

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. A CEM S-class microwave reactor was used to carry out the microwave-enhanced reactions. ^{1}H and ^{13}C NMR spectra were recorded on either a 400 MHz Varian MR or 500 MHz Varian

AR spectrometer at 298 K. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual solvent peaks ($CDCl_3$: ^{1}H δ 7.26, ^{13}C δ 77.16 ppm; d_6-DMSO: ^{1}H δ 2.50 ppm, ^{13}C δ 39.50 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, q = quartet, p = pentet, ddd = doublet of doublet of doublets, dt = doublet of triplet, dd = doublet of doublet, t = triplet, d = doublet, and s = singlet. IR spectra were recorded on a Bruker ALPHA Fourier transform infrared spectrometer with an attached ALPHA-P measurement module. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago. HR-ESMS patterns were collected on a Bruker micrOTOF-Q spectrometer. UV-Visible absorption spectra were obtained on a PerkinElmer Lambda-950 spectrophotometer in DMF (10^{-5} M). Melting points were determined using a Leica VMHB melting bar. Bidentate 2-pyridyl-1,2,3-triazole ligands (**5a** and **5b**),[16f] di-(2-pyridyl-1,2,3-triazole) ligands (**6a** and **6b**),[16g] and rhenium complexes (**7a$_{Cl}$** and **7b$_{Cl}$**)[20] were prepared by previously reported procedures.

Safety Note: Though no problems were encountered during the course of this work, azide compounds are potentially explosive and appropriate precautions should be taken when working with them.

General Procedure for the Synthesis of the Ligands

A dibromoalkane (1 equiv.) and sodium azide (3 equiv.) were dissolved in 4 : 1 DMF/H_2O (15 mL). The mixture was irradiated in a CEM microwave reactor at 125°C (200 W, 200 psi) for 3 h. The reaction mixture was then cooled to room temperature, and 2-ethynylpyridine (2 equiv.), sodium ascorbate (0.5 equiv.), and $CuSO_4{\cdot}5H_2O$ (0.4 equiv.) were added to the reaction mixture. The mixture was stirred at room temperature for 12 h. The suspension was partitioned between aqueous 0.1 M NH_4OH/ethylenediaminetetraacetic acid (EDTA) (100 mL) and CH_2Cl_2 (100 mL), and the layers were separated. The organic phase was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to provide the ligands as off-white solids.

General Procedure for the Synthesis of the Neutral Rhenium(I) Complexes

Either pentacarbonylrhenium(I) chloride (1 or 2 equiv.) or pentacarbonylrhenium(I) bromide (1 or 2 equiv.) and a 2-pyridyl-1,2,3-triazole or a di-(2-pyridyl-1,2,3-triazole) ligand (1 equiv.) were dissolved in ethanol (15 mL). The resulting mixture was refluxed at 78°C for 24 h in the absence of light. The suspension was cooled to room temperature, and the solvent volume was reduced by half using rotary evaporation. Addition of diethyl ether led to the precipitation of the rhenium(I) complexes as yellow solids, which were collected by filtration, washed with diethyl ether and petroleum ether, and vacuum dried.

General Procedure for the Synthesis of the Cationic Rhenium(I) Complexes

One of the neutral mono- or di-rhenium bromide complexes and silver triflate (1.25 equiv. or 2.5 equiv.) were dissolved in dry CH_2Cl_2 (10 mL) and stirred overnight at room temperature in the absence of light. The reaction mixture was filtered through cotton wool, and the solvent was removed under reduced pressure. The resultant golden yellow oil was re-dissolved in dry THF (8 mL), after which DMAP (1 equiv. or 2 equiv.) was added. The mixture was then irradiated in a CEM microwave reactor at 100°C (200 W, 200 psi) for 1 h. Removal of the solvent under reduced pressure and subsequent purification by silica gel column chromatography (10 % methanol in CH_2Cl_2), followed by recrystallization afforded the complexes as pale yellow solids.

Histidine Competition Experiment for the Rhenium Complex *8a$_{Cl}$*

The rhenium complex **8a$_{Cl}$** (0.0080 g, 0.0079 mmol, 1 equiv.), DL-histidine hydrochloride monohydrate (0.0100 g, 0.048 mmol, 6 equiv.), and $NaHCO_3$ (0.0040 g, 0.048 mmol, 6 equiv.) were dissolved in d_6-DMSO, and the mixture was heated to 40°C. The ^{1}H NMR spectra of the solution were recorded at regular time intervals for 24 h.

Histidine Competition Experiment for the Rhenium Complex *8c$_{DMAP}$*

The rhenium complex **8c$_{DMAP}$** (0.0020 g, 0.0013 mmol, 1 equiv.), DL-histidine hydrochloride monohydrate (0.0017 g, 0.0083 mmol, 6 equiv.), and $NaHCO_3$ (0.0010 g, 0.0083 mmol, 6 equiv.), were dissolved in d_6-DMSO, and the mixture was heated to 40°C. The ^{1}H NMR spectra of the solution were recorded at regular time intervals for 24 h.

X-Ray Crystallography

X-ray data for the rhenium complexes **7a$_{Br}$** and **8a$_{Cl}$** were collected at 89 K on a Bruker Kappa Apex II area detector diffractometer using graphite monochromated Mo Kα radiation (λ 0.71073 Å). Intensities were corrected for Lorentz polarization effects.[27] Absorption corrections were applied by semi-empirical methods (*SADABS*).[28] The structures were solved using *SIR-97*[29] or by direct methods using *SHELXS-97*[30] and refined against F^2 using all data by full-matrix least-squares procedures within *SHELXL-97*.[30] All non-hydrogen atoms (except where noted in the crystallographic information file) were refined with anisotropic thermal displacement parameters. The hydrogen atoms were placed in the calculated positions and refined using a riding model. In the crystal structure of **7a$_{Br}$**, the ISOR command was employed to restrain the atomic displacement parameters of C6, C7, and N3 atoms. In the crystal structure of **8a$_{Cl}$**, the ISOR command was employed to restrain the atomic displacement parameters of C20 atom.

X-ray data of the rhenium complexes **7a$_{DMAP}$** and **8a$_{DMAP}$** were collected at 100 K on an Agilent Technologies SuperNova diffractometer with Atlas detector using either Cu Kα (λ 1.54184 Å) or Mo Kα radiation (λ 0.71073 Å), and the data were treated using *CrysAlisPro* software.[31] The structures were solved by either *SIR-97*[29] or *SUPERFLIP*[32] and refined against F^2 using anisotropic thermal displacement parameters for all non-hydrogen atoms (except where noted in the crystallographic information file) using *SHELXL-97*[30] running within the *WinGX* program.[33] Hydrogen atoms were placed in calculated positions and refined using a riding model. The crystal lattice of **8a$_{DMAP}$** contained diffuse electron density that could not be appropriately modelled. The SQUEEZE routine within *PLATON*[34] was employed to resolve this problem, resulting in a void electron count of 241 that were assigned to one diisopropyl ether, two acetonitrile, and two triflate molecules (232 electrons in total, Supplementary Material).

Antibacterial Assays

The preliminary antibacterial activity of the neutral and cationic rhenium complexes was evaluated against *S. aureus* (ATCC 25923) as a representative Gram-positive bacterial strain and *E. coli* (ATCC 25922) as a representative Gram-negative bacterium. DMSO was used as a solvent to prepare stock solutions of these complexes. Each bacterial strain was inoculated into a separate cation-adjusted Mueller Hinton broth (MHB; BD, Auckland, New Zealand) and incubated at 35 ± 2°C for a period of 24 h. The bacterial suspensions were adjusted to a 0.5 Macfarland opacity standard (1–2 × 10^8 colony forming units CFU mL^{-1}) and spread onto cation-adjusted Mueller Hinton agar (BD, Auckland, New Zealand) plates before placing sterile paper disks (4 per plate, 6 mm diameter; BD, Auckland, New Zealand) equidistant on the plate. Stock solutions of the rhenium (I) complexes and the 2-pyridyl-1,2,3-triazole ligands were prepared by dissolving the compound (1 mg) in DMSO (1 mL). The compounds (20 µL) were then introduced onto the disks. The plates were incubated for a period of 24 h at 35 ± 2°C, after which the zones of inhibition were measured. The disk assays were performed using gentamicin (10 µg disks; BD, USA) as a positive control and DMSO (20 µL) as a negative control, and the experiments were done in duplicate.

Minimum Inhibitory Concentrations of the Neutral Rhenium Complexes (Disk Dilution Method)

The neutral rhenium complexes precipitated after the addition of MHB, preventing the determination of the MIC by the broth microdilution method. Stock solutions of the rhenium(I) complexes, which were found to be active according to the initial disk assays, were prepared by dissolution in DMSO, followed by sterilization using 0.25-µm pore size filters (Sartorius Stedim Biotech, Germany). Gentamicin, prepared by two-fold dilution in distilled water with concentrations ranging from 16 to 0.125 µg mL^{-1}, was used as the positive control, and DMSO (100 %) was used as the negative control. Mueller Hinton lawn plates with disks were prepared as described above. Different concentrations of these complexes ranging from 1024 to 1 µg mL^{-1} were prepared by two-fold serial dilutions and portions (20 µL) of these complexes were introduced onto the disks and incubated at 35 ± 2°C for 24 h. The lowest concentration at which bacterial growth was inhibited was recorded as the MIC. The assays were carried out in triplicate.

Minimum Inhibitory Concentrations of the Cationic Rhenium Complexes (Broth Microdilution Method)

The MICs for the cationic rhenium complexes were determined by the broth microdilution method using 96-well U-bottom tissue culture plates (Falcon, BD, USA). The bacterial suspensions were initially diluted with double-strength cation-adjusted MHB. Each well was inoculated with a known amount of the bacterial cells (100 µL) and diluted with the same volume of the rhenium complexes (in distilled water), leading to a concentration range of 256–0.5 µg mL^{-1} and a final bacterial concentration of 5 × 10^5 CFU mL^{-1} according to the CLSI guidelines.[35] Gentamicin was used as the positive control and the non-inoculated broth was used as the sterility control. The inoculated broth devoid of the rhenium complexes was used as the growth control. The plates were incubated at 35 ± 2°C for 24 h. The lowest concentration at which bacterial growth was inhibited was recorded as the MIC. The experiments were performed in triplicate.

Supplementary Material

Full synthetic procedures, ^{1}H NMR, UV-visible, and HR-ESMS spectra, molecular models, and crystallographic data are available on the Journal's website.

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