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Synthesis and anti-microbial activity of a new series of bis(diphosphine) rhenium(v) dioxo complexes†

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Rhenium-based metallodrugs have recently been highlighted as promising candidates for new antibiotics to combat multi-drug resistant (MDR) pathogens. A new class of rhenium(v) dioxo complexes were prepared from readily accessible diphosphine ligands, and have been shown to possess potent activity against *Staphylococcus aureus* (*S. aureus*) and *Candida albicans* (*C. albicans*) alongside low human cell toxicity.

Antibiotic resistance presents one of the gravest current threats to global health and food security.^{1,2} Bacterial resistance to many drugs derived from typical structural classes of organic molecules deployed as first-line antibiotics has led to the routine use of second- or third-line alternatives to combat common infections.^{3–5} Thus a rise in so-called multi-drug resistance (MDR) pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), has been highlighted by the WHO as a serious global health issue.^{6,7} Consequently, there is an urgent need to derive novel classes of medicinal compounds with the potential to combat these strains effectively.^{8,9}

Metal-based compounds have recently been highlighted as a promising alternative to traditional organic antibiotic classes.¹⁰ Their successful application as drugs in other fields of medicine, including oncology,^{11–14} and in neurodegenerative diseases,¹⁵ is well documented. However, to date, the application of metal complexes as antibiotics has been somewhat limited despite the advantages they offer: the potential for novel mechanisms of action which could avoid multi-drug resistant pathways;¹⁶ and their ability to more readily explore 3-dimensional structure–activity space (the so-called ‘escape

from flatland’).^{10,17,18} The potential of metal-based antibiotics has recently been reviewed by Frei *et al.*¹⁹

Over the last decade a range of transition metal complexes have been explored as potential antibiotics, including those derived from ruthenium,^{20–22} and others.¹⁹ Rhenium complexes, despite being of significant contemporary interest in anti-cancer applications,^{23–25} have been comparatively under-explored in this regard.

Metzler-Nolte, Bandow and co-workers have investigated a trimetallic peptide nucleic acid-derived complex containing a rhenium tricarbonyl unit chelated with a dipicolylamine derivative.²⁶ This unit was subsequently shown to be indispensable in the activity of the complex against MRSA (MIC = 2 μ M), and is the first evidence for a rhenium-dependent antibacterial mechanism of action.²⁷ Frei *et al.* have published the light-mediated activity of rhenium(i) bisquinoline complexes, which were shown to also possess a second light-independent mechanism of action.²⁸ Further Re(i) tricarbonyl complexes have been investigated in which the metal is coordinated with N-heterocyclic ligands,^{29,30} or various diimines.^{31,32} In a recent study, Zobi and co-workers identified two non-toxic cationic Re(i) tricarbonyl complexes bearing lipophilic diimine ligands as potent inhibitors of MRSA.³³ Such studies illustrate the efficacy of rhenium complexes in this regard, albeit with the all the complexes tested bearing a Re(i) carbonyl unit.²⁵ The antibacterial application of rhenium complexes in which the metal is in a different oxidation state to Re(i) are far rarer. To our knowledge, there are no examples of antimicrobial studies explicitly using Re(v) complexes, despite the prevalence of such complexes as isostructural analogues to Tc(v) used extensively in diagnostic nuclear medicine applications.³⁴

Our interest in the development of new phosphine-based chelators for the development of Tc(v) radiopharmaceuticals led us to explore the coordination chemistry of a class of N-centred N-functionalised diphosphine ligands.³⁵ A range of such ligands (NP₂^{Ph}X^R, X = functional group, R = alkyl, aryl linker) can be generated through a single-step phosphorus-based Mannich reaction (Fig. 1(a)).³⁶ This reaction has been

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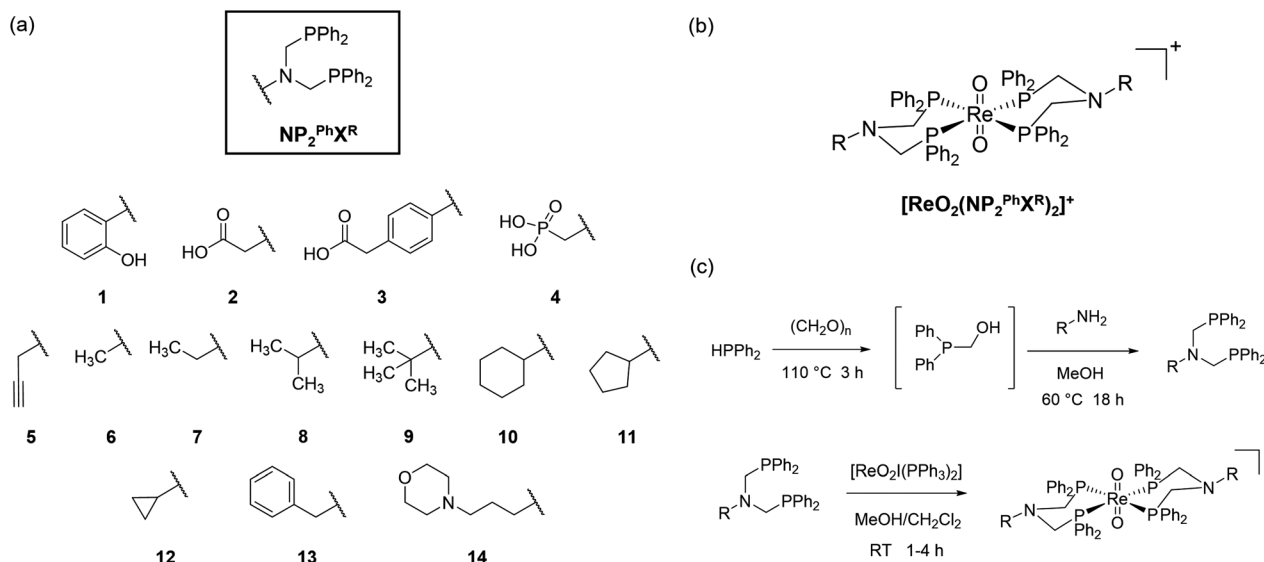


Fig. 1 (a) $\text{NP}_2^{\text{PhXR}}$ derivatives synthesised in this study. (b) General structure of $(\text{Re}^{\text{VO}_2})^+$ complexes of such ligands. (c) Synthetic scheme to $\text{NP}_2^{\text{PhXR}}$ ligands using a phosphorus-based Mannich reaction. Room temperature ligand substitution reaction to $[\text{Re}^{\text{VO}_2}(\text{NP}_2^{\text{PhXR}})_2]^+$ complexes.

employed by our group, and others, for the facile synthesis of numerous hetero-functionalised di- (and tri-) phosphines from parent primary amines or ammonia.^{37–40} Upon addition to a solution of a $\text{Re}(\text{v})$ precursor, the rapid formation of monocationic bis(diphosphine) complexes containing a *trans*-dioxo unit $\{\text{Re}^{\text{VO}_2}\}^+$ was observed (Fig. 1(b)).

Here, we report the synthesis and characterisation of fourteen novel $\{\text{Re}^{\text{VO}_2}\}^+$ complexes bearing N-functionalised diphosphines and their subsequent antimicrobial activity against Gram-positive and Gram-negative bacteria, and the *C. albicans* fungal strain. These easily accessible $\{\text{Re}^{\text{VO}_2}\}^+$ complexes have been shown to exhibit a range of antimicrobial/antifungal activities and toxicities dependent on the chemical nature of the group introduced through the primary amine, and are promising candidates for further studies. The antimicrobial inhibition study was facilitated through the Community for Open Antimicrobial Drug Discovery (CO-ADD).^{41,42}

A series of $\text{NP}_2^{\text{PhXR}}$ ligands were synthesised through a phosphorus-based Mannich reaction from HPPH_2 and paraformaldehyde, followed by addition of a primary amine (or hydrochloride salt thereof) (Fig. 1(c)).⁴³ The range of ligands was selected from published derivatives with both acidic and alkyl substituents, alongside new derivatives to complement known species by further varying their lipophilicity. Fig. 1(a) depicts all the ligands synthesised for this study. Novel ligands synthesised for this study include the phosphonic acid derivative $\text{NP}_2^{\text{PhPO}_3\text{H}_2\text{Me}}$ (4), the propargyl-functionalised derivative $\text{NP}_2^{\text{PhPrg}}$ (5), the ethyl- derivative $\text{NP}_2^{\text{PhEt}}$ (7), the cyclopentyl- and cyclopropyl-derivatives $\text{NP}_2^{\text{PhCyp}}$ (11) and $\text{NP}_2^{\text{PhCypr}}$ (12), and the morpholino-functionalised derivative $\text{NP}_2^{\text{PhMor}^{\text{Pr}}}$ (14). Other derivatives are known but have been prepared here using our modified synthetic route (see ESI†). An alternative synthesis for the novel ligand 5 was conducted through isolation of the dihydroxymethylphosphonium chloride salt

$[\text{Ph}_2\text{P}(\text{CH}_2\text{OH})_2]\text{Cl}$, and subsequent reaction with the primary amine in the presence of DIPEA.⁴⁴ Ligands 1–4, and 12 were isolated as off-white solids following precipitation from CH_2Cl_2 with hexane. Ligands 5–11, 13 and 14 could not be isolated as easily-handled solids but instead formed oily residues upon this step. Consequently, these ligands were re-dissolved in MeOH (10 mL) and stored under N_2 at -10°C . Such solutions of the $\text{NP}_2^{\text{PhXR}}$ derivatives were shown to be stable towards oxidation and decomposition for upwards of a year by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy (see ESI†) or could be used directly in complexation reactions.

The commercially-available $\text{Re}(\text{v})$ precursor $[\text{ReO}_2\text{I}(\text{PPh}_3)_2]$ was selected for the synthesis of the $\{\text{Re}^{\text{VO}_2}\}^+$ complexes due to the presence of a dioxo unit in the coordination sphere of the metal. Four phosphine donors are known to favour formation of the $\{\text{Re}^{\text{VO}_2}\}^+$ unit over mono-oxo variants.⁴⁵ Addition of two equivalents of the ligand in MeOH to a solution of $[\text{ReO}_2\text{I}(\text{PPh}_3)_2]$ in CH_2Cl_2 at room temperature resulted in a rapid colour change from violet to brown to orange over the course of less than an hour. The reaction mixture was left stirring for several hours to ensure complete conversion. Removal of the displaced PPh_3 was achieved through trituration of the crude residue with hexane. Silica column chromatography (95 : 5 v : v $\text{DCM} : \text{MeOH}$) then yielded the pure monocationic $[\text{ReO}_2(\text{NP}_2^{\text{PhXR}})_2]^+$ complexes in a range of yields (32–94%).

These $\text{Re}(\text{v})$ complexes are pseudo-octahedral diamagnetic low-spin d^6 complexes and can be effectively characterised by ^1H , $^{31}\text{P}\{^1\text{H}\}$ and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy. Notable consistent features in the ^1H NMR spectrum include a singlet for the methylene environment of the bridging ligand arms, with negligible splitting due to small $^2J_{\text{PH}}$ coupling constants. This is contrary to the case of mono-oxo analogues in which complicated second-order lineshapes are observed through the presence of magnetically inequivalent hydrogen environments.³⁵



The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra contain lone singlet resonances corresponding to the four equivalent phosphorus atoms of the centrosymmetric complexes, with a higher frequency chemical shift (~ 12 ppm) relative to the free ligand. The molecular ion peak of each complex was observed by high-resolution mass spectrometry with minimal fragmentation. The $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were successfully obtained for all complexes.

Confirmation of the structures of complexes **Re-1**, **Re-3** and **Re-4** was achieved by single crystal X-ray diffraction despite appreciable disorder arising from the location of iodide counterions and solvent molecules in the crystallised lattice. Metathesis reactions to exchange the iodide counterion for tetrafluoroborate did not lead to an improvement in this regard. Nevertheless, the structure of the cation could be determined unambiguously and confirmed the centrosymmetric nature of the $\{\text{Re}^{\text{V}}\text{O}_2(\text{NP}_2^{\text{Ph}}\text{R})_2\}^+$ molecular ion, and the *pseudo*-chair conformations of the six-membered chelate rings (see ESI†).

Complexes **Re-1–Re-14** were tested in high-throughput bacterial broth microdilution minimal inhibition concentration (MIC) assays against a range of Gram-positive and Gram-negative bacteria and the fungal strain *C. albicans* according to the CO-ADD protocol (see ESI†). **Re-2–Re-7** were initially screened at $32\ \mu\text{g mL}^{-1}$ for %-inhibition, before being tested again in a dose-responsive manner to determine more accurate MICs. **Re-4** was neglected in this second screening due to minimal %-inhibition in the first instance. **Re-1** and **Re-8–Re-14** were directly screened by the dose-response method. Table 1 displays the MICs measured to a minimum of $0.25\ \mu\text{g mL}^{-1}$ against *S. aureus* and the fungal strain *C. albicans*. Whereas none of the complexes showed appreciable activity against Gram-negative bacterial strains (see ESI†), a range of complexes displayed significant activity towards the inhibition of

both Gram-positive *S. aureus* and *C. albicans* without displaying cytotoxicity towards human embryonic kidney cells (HEK-293) (or haemolysis) namely; **Re-6**, **Re-7**, **Re-8**, **Re-11** and **Re-14** (Fig. 2). Some general observations about how the nature of the amine component affects the antimicrobial properties of the complexes can be drawn from this data. The compounds **Re-1–Re-4**, with acidic functionalities, show reduced activity towards both *S. aureus* and *C. albicans* but also minimal toxicity. On the other hand, complexes with neutral components and overall monocationic charge exhibit greater activity towards both *S. aureus* and *C. albicans* but also a larger range of toxicity. Experiments with ruthenium complexes have shown the correlation between higher positive charge and enhanced antimicrobial activity.²⁰ Of particular note is the high activity and low toxicity of **Re-14** which contains a terminal morpholine unit. Morpholine units have been shown to promote subcellular lysosome localisation in Re(i) tricarbonyl complexes.⁴⁶

We present a new class of Re(v) complex, obtained through a facile synthetic route, which are the first examples of Re(v) complexes with appreciable anti-microbial activity. The preliminary data presented here are highly encouraging towards further exploration of this class of compound, including elucidation of a mechanism of action. Additionally, a particular advantage of rhenium-based antibiotics over other transition metals are their potential to form isostructural technetium-99m ($^{99\text{m}}\text{Tc}$) derivatives for tandem whole-body SPECT imaging of infection. This could be used to obtain biodistribution and pharmacokinetic data for promising candidates of this class due to the ease of access of the $[\text{Re}^{\text{V}}\text{O}_2(\text{NP}_2^{\text{Ph}}\text{R})_2]^+$ core.⁴⁷ Further work in our group is focused on the synthesis of $[\text{Re}^{\text{V}}\text{O}_2(\text{NP}_2^{\text{Ph}}\text{R})_2]^+$ derivatives bearing charged groups on the

Table 1 Reported MIC values ($\mu\text{g mL}^{-1}$) against *S. aureus* and *C. albicans* for all the complexes and controls used in this study

| Cmpd | <i>S. aureus</i> ATCC 43300 | <i>C. albicans</i> ATCC 90028 | Toxicity ^c CC ₅₀ ^d | Haem ^e HC ₁₀ ^f |
|--------------------------|--------------------------------|----------------------------------|--|--|
| Re-1 | >32 | >32 | >32 | 4.878 |
| Re-2 | 32 | >32 | >32 | >32 |
| Re-3^g | 16 | >32 | 27.55 | >32 |
| Re-4 | n.d. | n.d. | n.d. | — |
| Re-5^g | 4 | 16 | 6.724 | 0.952 |
| Re-6^h | 2 | 2 | >32 | >32 |
| Re-7^h | ≤ 0.25 | ≤ 0.25 | >32 | >32 |
| Re-8^h | ≤ 0.25 | ≤ 0.25 | >32 | >32 |
| Re-9^g | ≤ 0.25 | ≤ 0.25 | ≤ 0.25 | >32 |
| Re-10^g | ≤ 0.25 | ≤ 0.25 | ≤ 0.25 | >32 |
| Re-11^h | ≤ 0.25 | ≤ 0.25 | >32 | >32 |
| Re-12^g | ≤ 0.25 | ≤ 0.25 | ≤ 0.25 | >32 |
| Re-13^g | ≤ 0.25 | ≤ 0.25 | ≤ 0.25 | >32 |
| Re-14^h | ≤ 0.25 | 8 | >32 | >32 |
| Van^a | 1 | — | — | — |
| FCZ^b | — | 2 | — | — |

^a Vancomycin. ^b Fluconazole. ^c Against Human Embryonic Kidney Cells ATCC CRL 1573. ^d Concentration at 50% cytotoxicity. ^e Haemolysis against Human Red Blood Cells. ^f Concentration at 10% haemolysis. ^g Active. ^h Active and non-toxic.

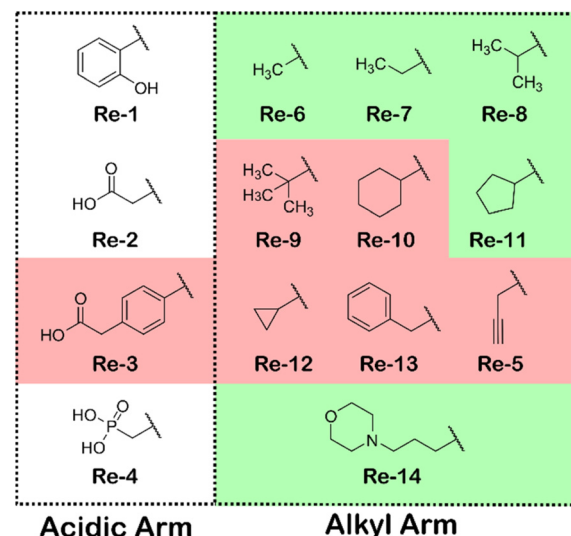


Fig. 2 *S. aureus* activity and toxicity of $[\text{ReO}_2(\text{NP}_2^{\text{Ph}}\text{R})_2]^+$ complexes as related to the chemical nature of the amine component. Groups highlighted in white were inactive, red were active but toxic, whereas those in green were active and non-toxic. Active defined as MIC $\leq 32\ \mu\text{g mL}^{-1}$ and non-toxic as CC₅₀ $> 32\ \mu\text{g mL}^{-1}$.

amine component to further elucidate the relationship between overall complex charge and anti-microbial activity. Such an approach should also help to improve the aqueous solubility of these complexes for further application in imaging and therapy.

Conflicts of interest

There are no conflicts of interest to declare.

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