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Ru(II) coordination compounds of N-N bidentate chelators with 1,2,3 triazole and isoquinoline subunits: Synthesis, spectroscopy and antimicrobial properties

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Abstract

Bidentate chelators 1-(1-benzyl-1,2,3-triazol-4-yl)isoquinoline and 3-(1-benzyl-1,2,3-triazol-4-yl)isoquinoline were prepared from benzyl bromide and trimethylsilylethynylisoquinoline precursors using a tandem deprotection/substitution/CuAAC synthetic approach. Each chelator is capable of forming a stable 3:1 Ru(II) coordination compound, which forms as a geometric isomer mixture. These Ru(II) complexes possess unique MLCT absorbance signatures at 450/472 nm (1-isomer) and 367 nm (3-isomer) relative to their constituent chelating units. Minimum inhibitory concentration values as low as 0.4 μ M are observed for Ru(II) complexes against representative Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus epidermidis*. Comparing the MIC values of these isoquinoline compounds with analogous 2-(1-benzyl-1,2,3-triazol-4-yl)pyridine compounds shows a 2.5- to 40-fold improvement in potency. This study establishes that increased hydrophobicity introduced at the central chelating units of Ru(II) coordination compounds can be a useful means by which to optimize antimicrobial activity that is complimentary to the variation of peripheral substituent identity at the chelator's N1 triazole position.

Graphical Abstract

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Isoquinoline-containing bidentate chelators with varying 1- and 3-connectivity prepared from tandem CuAAC methods are capable of forming stable 3:1 Ru(II) coordination compounds. Isoquinoline connectivity influences the spectroscopic properties of these complexes, while isoquinoline incorporation can significantly improve antibacterial properties relative to analogous complexes with pyridine-containing chelators.

Keywords

Antibacterial; Bidentate chelator; Coordination compound; Tandem synthesis; 1,2,3-Triazole

1. Introduction

The investigation of coordination compounds comprised of multidentate chelators containing 1,2,3-triazole subunits has amplified greatly since the establishment of Sharpless-Meldal copper-catalyzed azide alkyne cycloaddition (CuAAC) methodology as an efficient means by which to prepare 1,4-disubstituted-1,2,3-triazoles.[1–3] Bidentate and tridentate neutral N-donor chelators 2-(1-substituted-1,2,3-triazol-4-yl)pyridine (**pytz**) and 2,6-bis(1-substituted-1,2,3-triazol-4-yl)pyridine (**tzpytz**) have been shown to form stable complexes with a wide range of metal cations, and are now popular chelating motifs to engineer desired properties due to the ease in which peripheral substituents can be varied by CuAAC synthetic approaches.[4–7] While applications exploiting the optoelectronic and catalytic properties of such coordination compounds have been extensively reported,[8–14] studies probing their antimicrobial activity are significantly more limited.[12,15–18]

Because antibiotic resistant pathogens are a significant threat to global health, the discovery and development of new classes of antimicrobial compounds are urgently important.[19–22] Ru(II) coordination compounds comprised of polypyridyl N-N bidentate chelators have long been known to display a range of biological activity, including antimicrobial properties.[23,24] Recently, octahedral 3:1 Ru(II) complexes of **pytz** were reported to display potent antibacterial properties in a substituent-dependent manner.[17] In this study it was determined that an ideal balance of hydrophobicity and charge was needed for optimal potency, which could be engineered via modular variation of peripheral substituents on the 1,2,3-triazole subunits using CuAAC methodology. Such straightforward ability to synthetically tune bioactivity is an important tool for combating antibiotic resistance.

The aim of this study was to exploit the modularity of the CuAAC reaction to prepare bidentate chelators where the 2-pyridyl subunit of **pytz** was replaced with 1- and 3-isoquinolinyl subunits (Figure 2). Reports describing coordination compounds comprised of 1-(1-substituted-1,2,3-triazol-4-yl)isoquinolines (**1-iqtz**) are limited,[25,26] while those of 3-(1-substituted-1,2,3-triazol-4-yl)isoquinolines (**3-iqtz**) are entirely lacking. By examining octahedral Ru(II) complexes of these chelating motifs, the influence of isoquinoline incorporation (an expanded arene with increased hydrophobicity relative to pyridine) on both physical and biological properties can be defined. Described herein is the synthesis, spectroscopic structure-property relationship profiling and antimicrobial structure-activity relationship profiling of such isoquinoline-containing N-N bidentate chelators and their 3:1 Ru(II) coordination compounds.

2. Materials and Methods

2.1 Materials and instrumentation

Trimethylsilylacetylene (GFS Chemicals), benzyl bromide and isoquinoline reactants (Oakwood Chemical), Ru and Pd compounds (Oakwood), all other reactants (Aldrich), reaction solvents (Fisher Scientific), and NMR solvents (Cambridge Isotopes) were used as purchased. 1- and 3-isoquinolinyl triflates[27,28] and 1- and 3-trimethylsilylethynylisoquinolines[29,30] were prepared as previously described. Microorganisms were prepared from freeze-dried samples purchased from ATCC (*Bacillus subtilis* (ATCC 6051), *Staphylococcus epidermidis* (ATCC 14990), *Escherichia coli* (ATCC 25922), *Enterobacter aerogenes* (ATCC 13048), *Candida albicans* (ATCC 90028). Mueller-Hinton broth and YM broth were purchased from Fisher Scientific and prepared as instructed.

NMR analyses were obtained on a 400 MHz Bruker Ascend system. HRMS analyses were acquired on a Bruker micrOTOF-Q III system using an elution of 0.1% formic acid in methanol. UV-visible absorbance measurements were acquired on a Agilent 8453 spectrophotometer, and data are reported as $\lambda_{\text{max}} = \text{nm}$ (log ϵ). Crystals were run on a Rigaku SCX-Mini single-crystal x-ray diffractometer.

2.2 Synthetic methods

Synthesis of 1,4-disubstituted-1,2,3-triazoles by tandem CuAAC method—

Alkyne (1.0 mmol), benzyl bromide (1.0 mmol), sodium azide (1.0 mmol), K_2CO_3 (1.0 mmol), CuSO_4 (0.2 mmol), sodium ascorbate (0.4 mmol), *tert*-butanol (5 ml) and water (5 mL) were added to a 20 mL reaction vial and stirred rapidly at room temperature for 24 h. The reaction mixture was extracted with CH_2Cl_2 and 5% NH_4OH (aq), and the organic layer separated and dried over MgSO_4 . Following gravity filtration, volatiles were removed via rotary evaporation and the residue air dried to give the desired triazole product.

Synthesis of 1,4-disubstituted-1,2,3-triazoles by direct CuAAC method—Organic azide (1.0 mmol), alkyne (1.0 mmol), CuSO_4 (0.2 mmol), sodium ascorbate (0.4 mmol), *tert*-butanol (5 ml) and water (5 mL) were added to a 20 mL reaction vial and stirred rapidly at room temperature for 24 h. The reaction mixture was extracted with CH_2Cl_2 and 5%

NH₄OH (aq), and the organic layer separated and dried over MgSO₄. Following gravity filtration, volatiles were removed via rotary evaporation and the residue air dried to give the desired triazole product.

Synthesis of [RuL₃]Cl₂ coordination compounds—Triazole chelator (0.33 mmol), ruthenium chloride dihydrate (0.10 mmol), ethanol (20 ml) and water (5 ml) were added to a 40 ml reaction vial and stirred rapidly at 70 °C for 24 h. The reaction solvents were removed by rotary evaporation and the crude residue was purified by size exclusion chromatography using Sephadex LH-20 with methanol eluent. The isolated product band was dried by rotary evaporation to give the desired 3:1 octahedral Ru(II) complex.

2.3 Syntheses

1-(1-benzyl-1,2,3-triazol-4-yl)isoquinoline (Bz-1-igtz)—Prepared by tandem method. Tan solid, 88% yield, mp 115–117 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.50 (m, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 8.21 (s, 1H), 7.84 (dd, *J*₁ = 7.6 Hz, *J*₂ = 2.4 Hz, 1H), 7.70 (m, 2H), 7.61 (d, *J* = 5.2 Hz, 1H), 7.39 (m, 5H), 5.64 (s, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 150.0, 149.7, 141.9, 137.1, 134.5, 130.4, 129.4, 129.0, 128.5, 128.3, 128.1, 126.9, 124.9, 121.0, 54.5; HRMS (ESI) *m/z*: Calcd for C₁₈N₄H₁₄Na [M+Na]⁺ 309.1116, found 309.1119; UV-vis (MeOH): λ = 283 (3.96), 325 (3.96).

1-(1-(4-phenylbenzyl)-1,2,3-triazol-4-yl)isoquinoline (Pbz-1-igtz)—Prepared by tandem method. White solid, 76% yield, mp 169–170 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.52 (m, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 8.26 (s, 1H), 7.85 (dd, *J*₁ = 6.0 Hz, *J*₂ = 2.4 Hz, 1H), 7.71 (m, 2H), 7.60 (m, 5H), 7.45 (m, 4H), 7.36 (m, 1H), 5.69 (s, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 150.1, 149.7, 142.1, 141.9, 140.4, 137.2, 133.3, 130.4, 129.0, 129.0, 128.2, 128.1, 128.1, 127.8, 127.3, 126.9, 126.6, 124.9, 121.0, 54.2; HRMS (ESI) *m/z*: Calcd for C₂₄N₄H₁₈Na [M+Na]⁺ 385.1429, found 385.1439; UV-vis (MeOH): λ = 252 (4.56), 327 (3.97).

3-(1-benzyl-1,2,3-triazol-4-yl)isoquinoline (Bz-3-igtz)—Prepared by tandem method. Tan solid, 71% yield, mp 156–158 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.18 (s, 1H), 8.54 (s, 1H), 8.11 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.70 (m, 1H), 7.58 (m, 1H), 7.38 (m, 5H), 5.61 (s, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 152.5, 149.2, 143.9, 136.6, 134.6, 131.0, 129.3, 129.0, 128.5, 128.4, 127.8, 127.4, 127.3, 122.0, 116.3, 54.6; HRMS (ESI) *m/z*: Calcd for C₁₈N₄H₁₄Na [M+Na]⁺ 309.1116, found 309.1117; UV-vis (MeOH): λ = 285 (4.26), 297 (4.21).

3-(1-(4-phenylbenzyl)-1,2,3-triazol-4-yl)isoquinoline (Pbz-3-igtz)—Prepared by tandem method. White solid, 76% yield, mp 186–187 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.19 (s, 1H), 8.55 (s, 1H), 8.15 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.70 (m, 1H), 7.60 (m, 5H), 7.45 (m, 4H), 7.36 (m, 1H), 5.66 (s, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 152.5, 149.3, 143.9, 142.1, 140.5, 136.6, 133.5, 130.9, 129.0, 128.4, 128.1, 127.8, 127.8, 127.4, 127.3 (overlap), 127.3, 122.0, 116.3, 54.3; HRMS (ESI) *m/z*: Calcd for C₂₄N₄H₁₈Na [M+Na]⁺ 385.1429, found 385.1436; UV-vis (MeOH): λ = 250 (4.83), 284 (4.32), 297 (4.21).

2-(1-benzyl-1,2,3-triazol-4-yl)pyridine (Bz-pyztz)—Prepared by tandem method.

Brown solid, 81% yield, mp 111–114 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.53 (d, J = 4.24 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.76 (m, 1H), 7.35 (m, 5H), 7.21 (m, 1H), 5.58 (s, 2H); ^{13}C NMR (400 MHz, CDCl_3): δ 150.4, 149.5, 148.9, 137.0, 134.5, 129.3, 129.0, 128.5, 123.0, 122.0, 120.4, 54.5; HRMS (ESI) m/z : Calcd for $\text{C}_{14}\text{N}_4\text{H}_{12}\text{Na}$ $[\text{M}+\text{Na}]^+$ 259.0960, found 259.0962; UV-vis (MeOH): λ = 279 (4.10).

2-(1-(4-phenylbenzyl)-1,2,3-triazol-4-yl)pyridine (Pbz-pyztz)—Prepared by tandem method.

Brown solid, 84% yield, mp 140–142 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.55 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.09 (s, 1H), 7.77 (m, 1H), 7.58 (m, 4H), 7.43 (m, 5H), 7.22 (s, 1H), 5.63 (s, 2H); ^{13}C NMR (400 MHz, CDCl_3): δ 150.3, 149.4, 148.9, 142.0, 140.4, 137.0, 133.3, 129.0, 128.9, 128.0, 127.8, 127.2, 123.0, 122.0, 120.4, 54.2; HRMS (ESI) m/z : Calcd for $\text{C}_{20}\text{N}_4\text{H}_{16}\text{Na}$ $[\text{M}+\text{Na}]^+$ 335.1267, found 335.1260; UV-vis (MeOH): λ = 251 (4.35), 274 (sh) (4.10).

2-(1-hexyl-1,2,3-triazol-4-yl)pyridine (Hex-pyztz)—Prepared by direct method.

Tan solid, 74% yield, mp 56.5–57.4 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.58 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 8.13 (s, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 6.4 Hz, 1H), 4.41 (t, J = 6.8, 2H), 1.95 (m, 2H), 1.33 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 150.3, 149.3, 148.1, 136.7, 122.6, 121.6, 120.1, 50.4, 31.0, 30.1, 26.0, 22.3, 13.8; HRMS (ESI) m/z : Calcd for $\text{C}_{13}\text{N}_4\text{H}_{19}$ $[\text{M}+\text{H}]^+$ 231.1610, found 231.1610; UV-vis (MeOH): λ = 278 (4.34).

1-(1-hexyl-1,2,3-triazol-4-yl)isoquinoline (Hex-1-iqtz)—Prepared by direct method.

Dark amber oil, 85% yield; ^1H NMR (400 MHz, CDCl_3): δ 9.49 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 8.27 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.68 (m, 2H), 7.62 (s, 1H), 4.46 (t, J = 7.2 Hz, 2H), 1.99 (m, 2H), 1.32 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, CDCl_3): δ 149.7, 149.4, 141.8, 137.0, 130.3, 128.2, 127.9, 126.8, 126.4, 124.7, 120.8, 50.5, 31.2, 30.2, 26.2, 22.4, 14.0; HRMS (ESI) m/z : Calcd for $\text{C}_{17}\text{N}_4\text{H}_{21}$ $[\text{M}+\text{H}]^+$ 281.1766, found 281.1754; UV-vis (MeOH): λ = 280 (4.18), 327 (4.11).

[Ru(Bz-1-iqtz)₃]Cl₂—Dark brown solid, 72% yield; ^1H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.1:1 *mer:fac* isomer ratio observed; HRMS (ESI) m/z : Calcd for $\text{C}_{54}\text{N}_{12}\text{H}_{42}\text{Ru}$ $[\text{M}-2\text{Cl}]^{2+}$ 480.1344, found 480.1361; UV-vis (MeOH): λ = 253 (sh) (4.68), 309 (4.50), 450 (4.19), 472 (4.17).

[Ru(Pbz-1-iqtz)₃]Cl₂—Dark brown solid, 88% yield; ^1H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.0:1 *mer:fac* isomer ratio observed; HRMS (ESI) m/z : Calcd for $\text{C}_{72}\text{N}_{12}\text{H}_{54}\text{Ru}$ $[\text{M}-2\text{Cl}]^{2+}$ 594.1813, found 594.1838; UV-vis (MeOH): λ = 255 (5.02), 298 (4.55), 350 (sh) (4.26), 444 (4.19), 467 (4.13).

[Ru(Bz-3-iqtz)₃]Cl₂—Yellow-green solid, 76% yield; ^1H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.5:1 *mer:fac* isomer ratio observed; HRMS (ESI) m/z : Calcd for $\text{C}_{54}\text{N}_{12}\text{H}_{42}\text{Ru}$ $[\text{M}-2\text{Cl}]^{2+}$ 480.1344, found 480.1351; UV-vis (MeOH): λ = 253 (5.20), 286 (4.83), 294 (4.85), 316 (sh) (4.52), 367 (4.46).

[Ru(Pbz-3-*iqtz*)₃]Cl₂—Yellow solid, 80% yield; ¹H NMR (400 MHz, CD₃OD): δ (see Supplementary Data) 2.5:1 *mer:fac* isomers; HRMS (ESI) *m/z*. Calcd for C₇₂N₁₂H₅₄Ru [M-2Cl]²⁺ 594.1813, found 594.1818; UV-vis (MeOH): λ = 253 (5.32), 283 (4.93), 294 (4.89), 317 (sh) (4.53), 370 (4.41).

[Ru(Bz-pyztz)₃]Cl₂—Green solid, 78% yield; ¹H NMR (400 MHz, CD₃OD): δ (see Supplementary Data) 2.1:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*. Calcd for C₄₂N₁₂H₃₆Ru [M-2Cl]²⁺ 405.1109, found 405.1114; UV-vis (MeOH): λ = 269 (4.87), 378 (4.24).

[Ru(Pbz-pyztz)₃]Cl₂—Dark yellow solid, 72% yield; ¹H NMR (400 MHz, CD₃OD): δ (see Supplementary Data) 2.2:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*. Calcd for C₆₀N₁₂H₄₈Ru [M-2Cl]²⁺ 519.1579, found 519.1599; UV-vis (MeOH): λ = 268 (4.88), 379 (3.99).

[Ru(Hex-pyztz)₃]Cl₂—Yellow solid, 94% yield; ¹H NMR (400 MHz, CDCl₃): δ (see Supplementary Data) 0.8:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*. Calcd for C₃₉N₁₂H₅₄Ru [M-2Cl]²⁺ 396.1814, found 396.1809; UV-vis (MeOH): λ = 268 (4.88), 381 (4.33).

[Ru(Hex-1-*iqtz*)₃]Cl₂—Dark yellow solid, 75% yield; ¹H NMR (400 MHz, CDCl₃): δ (see Supplementary Data) 1.8:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*. Calcd for C₅₁N₁₂H₆₀Ru [M-2Cl]²⁺ 471.2048, found 471.2054; UV-vis (MeOH): λ = 252 (4.71), 299 (4.58), 350 (sh) (4.27), 430 (4.31).

2.4 Minimum Inhibitory Concentration Assays

Inoculum were prepared following standard microdilution assay procedures[31–33] using Mueller-Hinton broth for all bacteria and YM broth for yeast. Each triazole and triazolium bromide compound was prepared as a 10 mM solution in DMSO. 10 μL of each DMSO stock solution was diluted into 190 μL broth and a 1:1 serial dilution was performed in a 96 well plate. Addition of 100 μL inoculum to each well resulted in a range of 250, 120, 62, 31, 16, 8, 4 and 2 μM concentrations for each MIC assay. Plates were incubated for 20 h (bacteria) and 24 h (yeast) at 37°C then examined by eye for cloudiness indicating microbial growth. The most dilute member within a serial dilution that remained transparent after 24 h was defined as the minimum inhibitory concentration (MIC) value for that compound/organism combination. Assays were performed in triplicate. Any compounds displaying activity at the minimum 2 μM concentration of the original assay were tested again at a 10-fold dilution using the same microdilution procedure with a 1 mM DMSO stock solution.

2.5 XRD Analysis

Crystals of **Bz-3-*iqtz***, **Pbz-3-*iqtz*** and **Pbz-1-*iqtz*** were grown from evaporation of CH₂Cl₂ solutions. Crystals were mounted on MiTeGen Microloop with non-drying immersion oil. The crystals were then optically aligned on the Rigaku SCX-Mini diffractometer using a digital camera. Initial matrix images were collected to determine the unit cell, validity and proper exposure time. Three hemispheres (where φ = 0.0, 120.0 and 240.0) of data were

collected with each consisting 180 images each with 1.00° widths and a 1.00° step. CrysAlis PRO 1.171.39.46 was used to integration, scaling and absorption correction.[34] The structures were refined using SHELXT Intrinsic Phasing[35] and SHELXL.[36] Olex2 was used as a graphical interface.[37] Images for the above compounds generated using CrystalMaker® version 10.4.3: a crystal and molecular structures program for Mac and Windows (CrystalMaker Software Ltd, Oxford, England, www.crystallmaker.com).[38] Crystallographic information for the three obtained structures are summarized in Supporting Information Table S1, followed by thermal ellipsoid plots and packing images for each (Figures S11–S17). Lastly, atomic coordinates and additional structural information are provided in Tables S2–S6.

3. Results and Discussion

3.1 Preparation of chelators

N1-benzyl- and phenylbenzyl-substituted analogs of chelators **1-iqtz** and **3-iqtz** were each prepared using a three step synthetic sequence (Scheme 1). Following triflation of commercially-available 1-hydroxyisoquinoline and isoquinolin-3(2H)-one precursors, [27,28] Sonogashira coupling was used to prepare 1- and 3-trimethylsilylethynylisoquinolines.[27–30] An efficient three-step one-pot transformation involving K₂CO₃ promoted TMS deprotection, benzylic azide substitution and CuAAC was used to prepare the desired chelators in 71–88% isolated yields.[39–42] In order to directly compare the influence of the isoquinoline subunits relative to the pyridine subunit on coordination, spectroscopic and antimicrobial properties, **pytz** chelators with identical N1-substituents were also similarly prepared (Scheme S1).

3.2 X-ray crystallography

Single crystals of **Bz-3-iqtz**, **Pbz-3-iqtz** and **Pbz-1-iqtz** suitable for XRD structural analyses were grown from slow evaporation of dichloromethane solutions. The dihedral angles between isoquinoline and 1,2,3-triazole subunits differ greatly among the 1- and 3-isoquinoline isomers. In the 3-isoquinoline analogs, the N-C-C-N dihedral angle between the chelating subunits is 156° and 157°, respectively (Figures 3 and 4). This largely coplanar *anti* geometry is typically observed in such non-coordinated 1,2,3-triazole-containing bidentate and tridentate chelating systems, and has been attributed to favorable electrostatic interactions between heterocycles.[43] In contrast, the N-C-C-N dihedral angle between chelating subunits in the 1-isoquinoline isomer is 50° (Figure 5). This adaptation of a more *syn*-like geometry is attributed to the six-atom separation between N3 of the triazole and H8 of the isoquinoline (versus the analogous five-atom separation of the equivalent atoms in the 3-isoquinoline isomers), which introduces steric hindrance that precludes the electrostatic stabilization afforded by the nearly coplanar *anti* orientation.

The dihedral angles observed in the phenylbenzyl peripheral substituents also differ significantly. The 5° biphenyl dihedral angle observed in **Pbz-1-iqtz** closely resembles the largely coplanar geometry typically observed in crystalline biphenyl compounds,[44] while in **Pbz-3-iqtz** the biphenyl dihedral angle is twisted to 50°. This observed difference is likely due to differences in crystal packing forces between these two compounds (Figure S17).

3.3 Preparation of Ru(II) complexes

Preparation of target 3:1 Ru(II) coordination compounds comprised of these N-N bidentate chelators was accomplished by heating three equivalents of each analog with ruthenium trichloride hydrate salt in aqueous ethanol (Scheme 2).[39] Complexes were purified by size-exclusion chromatography using Sephadex gel eluted in methanol. Due to the unmatched pairs of heterocycles comprising these N-N bidentate chelators, the octahedral Ru(II) complexes formed as a mixture of meridional (*mer*) and facial (*fac*) geometric isomers, the relative abundance of which could be quantified by ^1H NMR. The singlet generated from the C5 position of the triazole ring experiences disparate chemical shifts between the two geometric isomers: each of the three chelating units in the *fac* isomer experience equivalent chemical environments revealed as one downfield-shifted singlet relative to the chelator itself, while each of the three chelating units in the *mer* isomer experience unique chemical environments resulting in three unique downfield-shifted singlets for this analogous triazole position (Figures S1–S8).

Both benzyl and phenylbenzyl analogs of **1-igtz** and **pytz** (Scheme S2) derivatives show a 2:1 preference for their *mer* isomers, while the **3-igtz** derivatives show a slightly higher 2.5:1 *mer* isomeric excess. Interestingly, this ratio contrasts with previously reported alkyl substituted $[\text{Ru}(\text{pytz})_3]\text{Cl}_2$ complexes[39] where statistical mixtures (1:1) of *fac:mer* isomers were observed. (Similarly, a 1.2:1 *fac:mer* ratio was observed for the alkyl analog in the present study.) N1-hexyl-substituted **1-igtz** showed a slightly diminished 1.8-fold preference for the *mer* isomer (Schemes S3–S5). This dataset illustrates that the identity of both the chelating subunit as well as the peripheral substituent can significantly influence the relative populations of geometric isomers, likely attributable to steric hindrance within the congested octahedral coordination environment. It was previously reported that *fac* and *mer* isomers do not display significant differences in either their electronic absorption or antimicrobial properties.[17] Therefore, while a partial separation of **1-igtz** and **3-igtz** isomers was achievable by meticulous use of size-exclusion chromatography (with the larger phenylbenzyl analogs displaying better resolution than the benzyl analogs), each of these coordination compounds was utilized as geometric isomer mixture for the duration of this investigation.

3.4 UV-visible spectroscopy

UV-visible spectroscopy shows that isoquinoline connectivity within the chelator significantly impacts the emergent electronic properties of their Ru(II) coordination compounds. Low energy absorbance signatures indicative of MLCT transitions[17,39] were observed for all Ru(II) complexes relative to their constituent chelating units (Figure 6). While the energy of this signature in the benzyl-substituted **3-igtz** complex (367 nm) closely resembles that of the **pytz** complex (378 nm), the MLCT bands of the **1-igtz** complex extend into the visible range of the electromagnetic spectrum (450 nm, 472 nm). Similar trends were observed for the phenylbenzyl and hexyl analogs (Figures S9–S10). None of the complexes studied displayed observable luminescence at room temperature.

3.5 Antimicrobial Assays

The antimicrobial properties of each N-N bidentate chelator and 3:1 Ru(II) coordination compound were evaluated using minimum inhibitory concentration (MIC) assays against exemplary BSL1 Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus epidermidis*, Gram-negative bacteria *Escherichia coli* and *Enterobacter aerogenes*, and yeast *Candida albicans*. [31,33] None of the chelators themselves showed inhibition at the concentrations surveyed (up to 250 μ M). In contrast, Ru(II) complexes prepared from these chelators showed MIC values that varied significantly as chelator and peripheral substituent identity was each varied systematically.

It was recently reported that MIC potency can be optimized in [Ru(**pytz**)₃]Cl₂ complexes by achieving an ideal balance of charge and hydrophobicity, accessible by synthetic variation of n-alkyl chain length at the N1 position of the triazole subunits. [17] Because the stereochemistry of these previously reported complexes was shown not to significantly influence antimicrobial properties, and because the balance of charge and hydrophobicity is commonly understood to play an important role in optimizing cytotoxicity in common antibiotics such as quaternary ammonium compounds, [45,46] it was hypothesized that hydrophobicity would play a prominent role in tuning the MIC values of the Ru(II) complexes reported herein. This study focused on evaluating three structure activity relationships: (1) varying hydrophobicity at the central chelating unit versus at the periphery, (2) varying aromatic versus aliphatic peripheral substituent identity, and (3) the impact of isoquinoline incorporation in chelators with aliphatic peripheral substitution.

Isoquinoline regiochemistry has no impact on antimicrobial properties (Table 1, entries 1–2 and 4–5), but isoquinoline incorporation itself does significantly alter MIC values relative to equivalent pyridine analogs (entries 3 and 6). For the benzyl complexes, the enhanced hydrophobicity of the isoquinoline groups increases potency towards both Gram-positive bacteria (20- to 40-fold) and Gram-negative bacteria (at least 8-fold). But for the phenylbenzyl complexes, isoquinoline incorporation decreases potency against all organisms tested (at least 15-fold). These comparisons exemplify the balance that is needed between charge and hydrophobicity for antimicrobial Ru(II) complexes. Isoquinoline incorporation in the benzyl analogs improves this balance, whereas in the more hydrophobic phenylbenzyl series it appears to reach an excessive amount of hydrophobicity detrimental to MIC potency. These observations indicate that variation of hydrophobicity at the chelating unit can be utilized in a complimentary manner to variation of peripheral group hydrophobicity in tuning antimicrobial potency.

In order to evaluate whether this observed synergy between central and peripheral aromatic group hydrophobicity might be generally applicable to recently reported aliphatic systems, Ru(II) complexes comprised of n-hexyl substituted **pytz** and **1-iqtz** chelators were also prepared and assayed (entries 7–8). [Ru(**Hex-1-pytz**)₃]Cl₂ was previously shown to possess optimal antibacterial properties among a series of analogs with varying lengths of n-alkyl substituents. [17] Under the assay conditions employed in the present study it similarly displays potent MIC values selectively against Gram-positive bacteria. Replacement of the pyridine N-N chelator subunit with isoquinoline [Ru(**Hex-1-iqtz**)₃]Cl₂ results in a 2.5 to 32-

fold improvement in MIC values against both Gram-positive and Gram-negative bacteria. This supports the general utility of varying hydrophobicity at the chelating unit as a tool for optimizing the antimicrobial properties of Ru(II) coordination compounds.

In general, relative to Gram-positive bacteria these Ru(II) complexes showed reduced bioactivity against Gram-negative bacteria. This is typically observed for amphiphilic antimicrobial compound due to the outer membrane of the Gram-negative bacteria serving as an additional barrier to cell wall permeation. MIC values measured against the yeast strain *Candida albicans* (a representative eukaryotic organism) were either very high or not observed for each analog in this study. This organismal selectivity whereupon the Ru(II) complexes are able to preferentially target prokaryotic organisms over eukaryotic organisms correlates with the low toxicity and hemolytic activity previously reported for N-N chelated Ru(II) compounds.[17] Such selectivity is attributed to the attraction of the cationic Ru(II) center to the negatively charged outer surfaces of prokaryotic organisms, and follows typical bioactivity observed for cationic amphiphiles such as quaternary ammonium compounds and antimicrobial peptides.[45–47]

4. Conclusion

A tandem CuAAC synthetic approach has been used to efficiently prepare a series of 1-(1-substituted-1,2,3-triazol-4-yl)isoquinoline and 3-(1-substituted-1,2,3-triazol-4-yl)isoquinoline compounds. N-N bidentate chelators **1-iqtz** and **3-iqtz** are demonstrated herein to be capable units for constructing stable 3:1 Ru(II) octahedral coordination compounds and expand the breadth of heterocyclic representation among reported 1,2,3-triazole-containing chelators deriving from CuAAC synthetic approaches. Isoquinoline subunit connectivity significantly influences the electronic absorbance spectra of such complexes, with the **1-iqtz** isomer producing compounds with MLCT absorbances in the visible electromagnetic spectrum unique from **3-iqtz** and **pytz** analogs. The *mer:fac* distribution of octahedral coordination geometry is also impacted by isoquinoline connectivity. The antimicrobial evaluation of these isoquinoline containing chelators relative to **pytz** analogs demonstrates that increasing central hydrophobicity within this class of 3:1 octahedral Ru(II) coordination compounds can be an effective means by which to optimize bioactivity that is complimentary to approaches varying peripheral substituent hydrophobicity. This establishes a new tool available for studies aiming to optimize biological activity via striking a proper balance of charge and hydrophobicity within coordination compounds, including the development of next-generation molecular approaches to combat antibiotic resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix. Supplementary Data

Experimental procedures, copies of ^1H and ^{13}C NMR spectra and UV-Visible spectra for all newly reported compounds, and crystallographic information for the SC-XRD analysis of compounds **Bz-3-igtz**, **Pbz-3-igtz** and **Pbz-1-igtz** are included. Crystallographic data for the structures presented in this paper have been deposited with the Cambridge Crystallographic Data Centre: **Bz-3-igtz** as CCDC 1946238, **Pbz-3-igtz** as 1946240 and **Pbz-1-igtz** as 1946239. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: despoit@ccdc.cam.ac.uk).

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Figure 1. Structures of 2-(1-substituted-1,2,3-triazol-4-yl)pyridine (**pytz**) and 2,6-bis(1-substituted-1,2,3-triazol-4-yl)pyridine (**tzpytz**) chelators.

Figure 2.
Structures of 1-(1-substituted-1,2,3-triazol-4-yl)isoquinoline (**1-iqtz**) and 3-(1-substituted-1,2,3-triazol-4-yl)isoquinoline (**3-iqtz**) chelators.

Figure 3.
Thermal ellipsoid plot of **Bz-3-iqtz** shown at 25% probability.

Figure 4.
Thermal ellipsoid plot of **Pbz-3-iqtz** shown at 25% probability.

Figure 5.
Thermal ellipsoid plot of **Pbz-1-iqtz** shown at 25% probability.

Figure 6.
UV-Visible absorbance of benzyl-functionalized N-N bidentate chelators and their 3:1 Ru(II) complexes in methanol.

Scheme 1.

Preparation of isoquinoline-containing N-N bidentate chelators

Scheme 2.

Preparation of octahedral Ru(II) coordination compounds

Table 1.Summary of bioactivity for [RuL₃]Cl₂ complexes.

Entry	L =	Minimum Inhibitory Concentration (μM)				
		<i>B.S.</i>	<i>S.E.</i>	<i>E.A.</i>	<i>E.C.</i>	<i>C.A.</i>
1	Bz-1-iqtz	0.8	0.4	31	31	250
2	Bz-3-iqtz	0.8	0.4	31	31	250
3	Bz-pytz	16	16	>250	>250	>250
4	Pbz-1-iqtz	>250	>250	>250	>250	>250
5	Pbz-3-iqtz	>250	>250	>250	>250	>250
6	Pbz-pytz	4	8	62	250	250
7	Hex-pytz	4	2	250	250	125
8	Hex-1-iqtz	0.8	0.8	31	8	>250

Concentrations surveyed: 250, 125, 62, 31, 16, 8, 4 and 2 μM. *B.S.* = *Bacillus subtilis* (ATCC 6051); *S.E.* = *Staphylococcus epidermidis* (ATCC 14990); *E.C.* = *Escherichia coli* (ATCC 25922); *E.A.* = *Enterobacter aerogenes* (ATCC 13048); *C.A.* = *Candida albicans* (ATCC 90028).