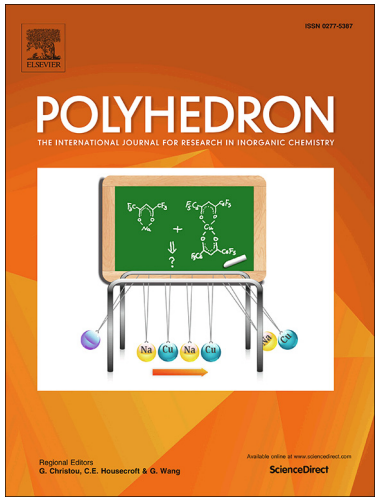


Ru(II) coordination compounds of N-N bidentate chelators with 1,2,3 triazole and isoquinoline subunits: Synthesis, spectroscopy and antimicrobial properties

Nicholas W. Kreofsky, Maxwell D. Dillenburg, Eric M. Villa, James T. Fletcher

PII: S0277-5387(19)30704-1
DOI: https://doi.org/10.1016/j.poly.2019.114259
Reference: POLY 114259

To appear in: *Polyhedron*

Received Date: 29 August 2019
Revised Date: 13 November 2019
Accepted Date: 4 December 2019

Please cite this article as: N.W. Kreofsky, M.D. Dillenburg, E.M. Villa, J.T. Fletcher, Ru(II) coordination compounds of N-N bidentate chelators with 1,2,3 triazole and isoquinoline subunits: Synthesis, spectroscopy and antimicrobial properties, *Polyhedron* (2019), doi: https://doi.org/10.1016/j.poly.2019.114259

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

Nicholas W. Kreofsky, Maxwell D. Dillenburg, Eric M. Villa and James T. Fletcher*

Address: Department of Chemistry, Creighton University, 2500 California Plaza, Omaha, NE 68178, U.S.A.

Email: James T. Fletcher - jamesfletcher@creighton.edu

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 μM 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.

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]

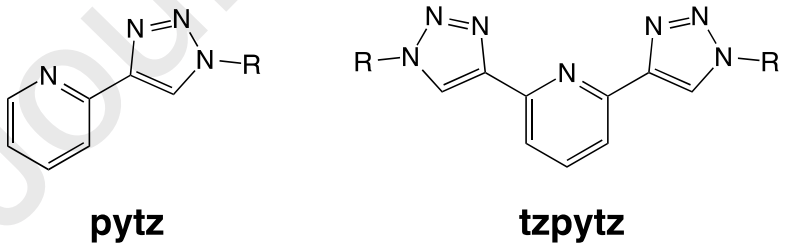


Figure 1. Structures of 2-(1-substituted-1,2,3-triazol-4-yl)pyridine (**pytz**) and 2,6-bis(1-substituted-1,2,3-triazol-4-yl)pyridine (**tzpytz**) chelators.

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.

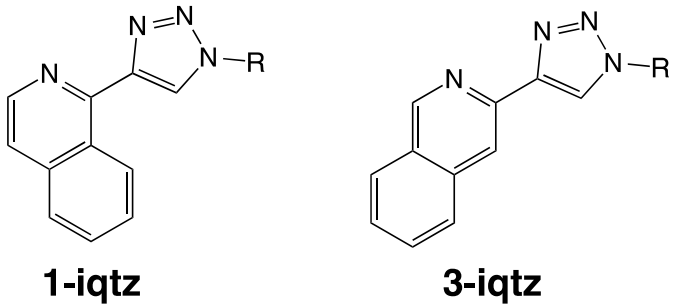


Figure 2. Structures of 1-(1-substituted-1,2,3-triazol-4-yl)isoquinoline (**1-iqtz**) and 3-(1-substituted-1,2,3-triazol-4-yl)isoquinoline (**3-iqtz**) chelators.

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 subtilus* (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 λ_{max} = 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-disubstuted-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% 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 $[RuL_3]Cl_2$ 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 ^oC 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-iqtz**). Prepared by tandem method. Tan solid, 88% yield, mp 115-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{18}N_4H_{14}Na$ $[M+Na]^+$ 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-iqtz**). Prepared by tandem method. White solid, 76% yield, mp 169-170°C; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{24}N_4H_{18}Na$ $[M+Na]^+$ 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-iqtz**). Prepared by tandem method. Tan solid, 71% yield, mp 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{18}N_4H_{14}Na$ $[M+Na]^+$ 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-iqtz**). Prepared by tandem method. White solid, 76% yield, mp 186-187°C; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{24}N_4H_{18}Na$ $[M+Na]^+$ 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-pytz**). Prepared by tandem method. Brown solid, 81% yield, mp 111-114 °C; ^{1}H 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 $C_{14}N_4H_{12}Na$ $[M+Na]^+$ 259.0960, found 259.0962; UV-vis (MeOH): λ = 279 (4.10).

2-(1-(4-phenylbenzyl)-1,2,3-triazol-4-yl)pyridine (**Pbz-pytz**). Prepared by tandem method. Brown solid, 84% yield, mp 140-142°C; ^{1}H 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 $C_{20}N_4H_{16}Na$ $[M+Na]^+$ 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-pytz**). Prepared by direct method. Tan solid, 74% yield, mp 56.5-57.4°C; ^{1}H 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 $C_{13}N_4H_{19}$ $[M+H]^+$ 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; ^{1}H 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 $C_{17}N_4H_{21}$ $[M+H]^+$ 281.1766, found 281.1754; UV-vis (MeOH): λ = 280 (4.18), 327 (4.11).

*[Ru(**Bz-1-iqtz**)$_3$]Cl$_2$*. Dark brown solid, 72% yield; ^{1}H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.1:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*: Calcd for $C_{54}N_{12}H_{42}Ru$ $[M-2Cl]^{2+}$ 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**)$_3$]Cl$_2$*. Dark brown solid, 88% yield; ^{1}H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.0:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*: Calcd for $C_{72}N_{12}H_{54}Ru$ $[M-2Cl]^{2+}$ 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**)$_3$]Cl$_2$*. Yellow-green solid, 76% yield; ^{1}H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.5:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*: Calcd for

$C_{54}N_{12}H_{42}Ru$ $[M\text{-}2Cl]^{2+}$ 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**)$_3$]Cl_2*. Yellow solid, 80% yield; ^{1}H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.5:1 *mer:fac* isomers; HRMS (ESI) *m/z*: Calcd for $C_{72}N_{12}H_{54}Ru$ $[M\text{-}2Cl]^{2+}$ 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-pytz**)$_3$]Cl_2*. Green solid, 78% yield; ^{1}H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.1:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*: Calcd for $C_{42}N_{12}H_{36}Ru$ $[M\text{-}2Cl]^{2+}$ 405.1109, found 405.1114; UV-vis (MeOH): λ = 269 (4.87), 378 (4.24).

*[Ru(**Pbz-pytz**)$_3$]Cl_2*. Dark yellow solid, 72% yield; ^{1}H NMR (400 MHz, CD_3OD): δ (see Supplementary Data) 2.2:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z*: Calcd for $C_{60}N_{12}H_{48}Ru$ $[M\text{-}2Cl]^{2+}$ 519.1579, found 519.1599; UV-vis (MeOH): λ = 268 (4.88), 379 (3.99).

*[Ru(**Hex-pytz**)$_3$]Cl_2*. Yellow solid, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (see Supplementary Data) 0.8:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z* Calcd for $C_{39}N_{12}H_{54}Ru$ $[M\text{-}2Cl]^{2+}$ 396.1814, found 396.1809; UV-vis (MeOH): λ = 268 (4.88), 381 (4.33).

*[Ru(**Hex-1-iqtz**)$_3$]Cl_2*. Dark yellow solid, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (see Supplementary Data) 1.8:1 *mer:fac* isomer ratio observed; HRMS (ESI) *m/z* Calcd for $C_{51}N_{12}H_{60}Ru$ $[M\text{-}2Cl]^{2+}$ 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^{O}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 CH_2Cl_2 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

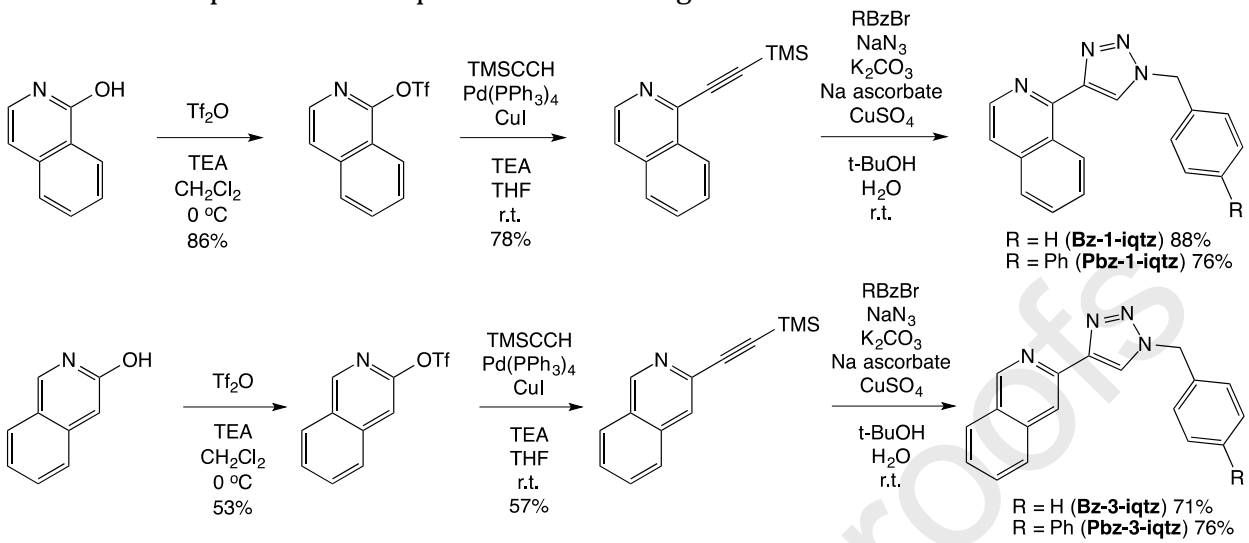
correction.[34] The structures were refined using SHELXT Intrinsic Phasing[35] and SHELXL.[36] Olex2 was used as a graphical interface.[37] Images for the above compounds generated using CrystalMaker® version 10.4.3: a crystal and molecular structures program for Mac and Windows (CrystalMaker Software Ltd, Oxford, England, www.crystalmaker.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 K_2CO_3 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).

Scheme 1. Preparation of isoquinoline-containing N-N bidentate chelators



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).

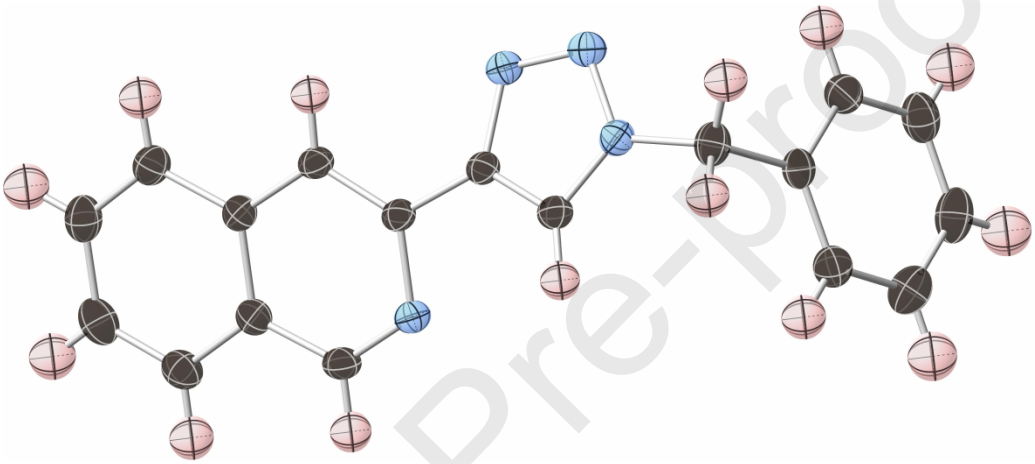


Figure 3. Thermal ellipsoid plot of **Bz-3-iqtz** shown at 25% probability.

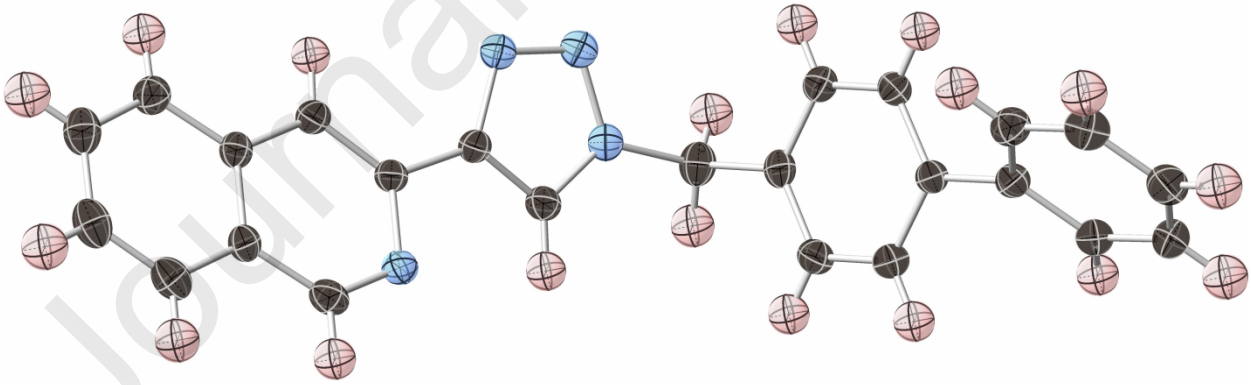


Figure 4. Thermal ellipsoid plot of **Pbz-3-iqtz** shown at 25% probability.

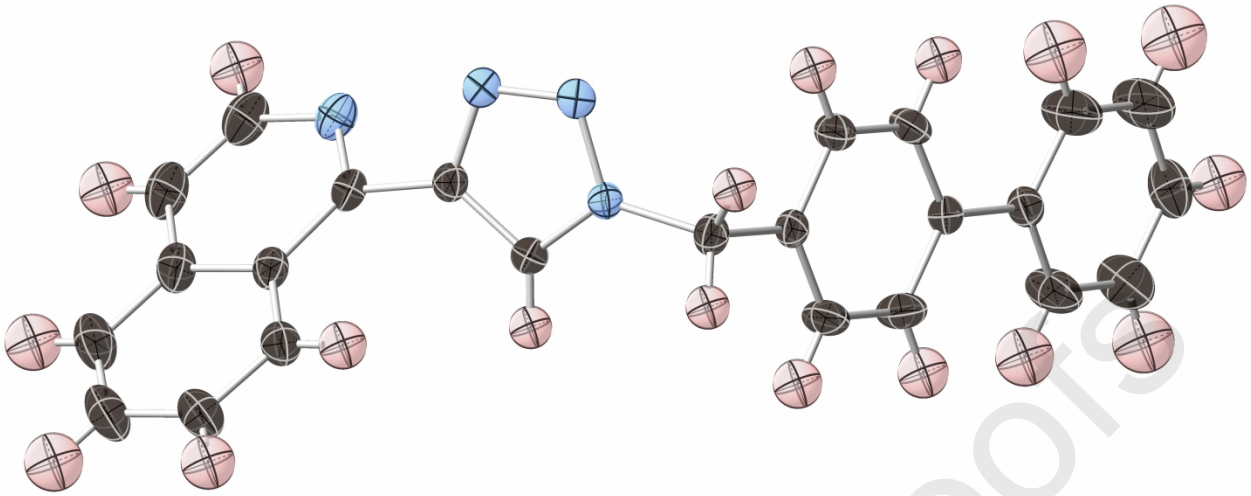


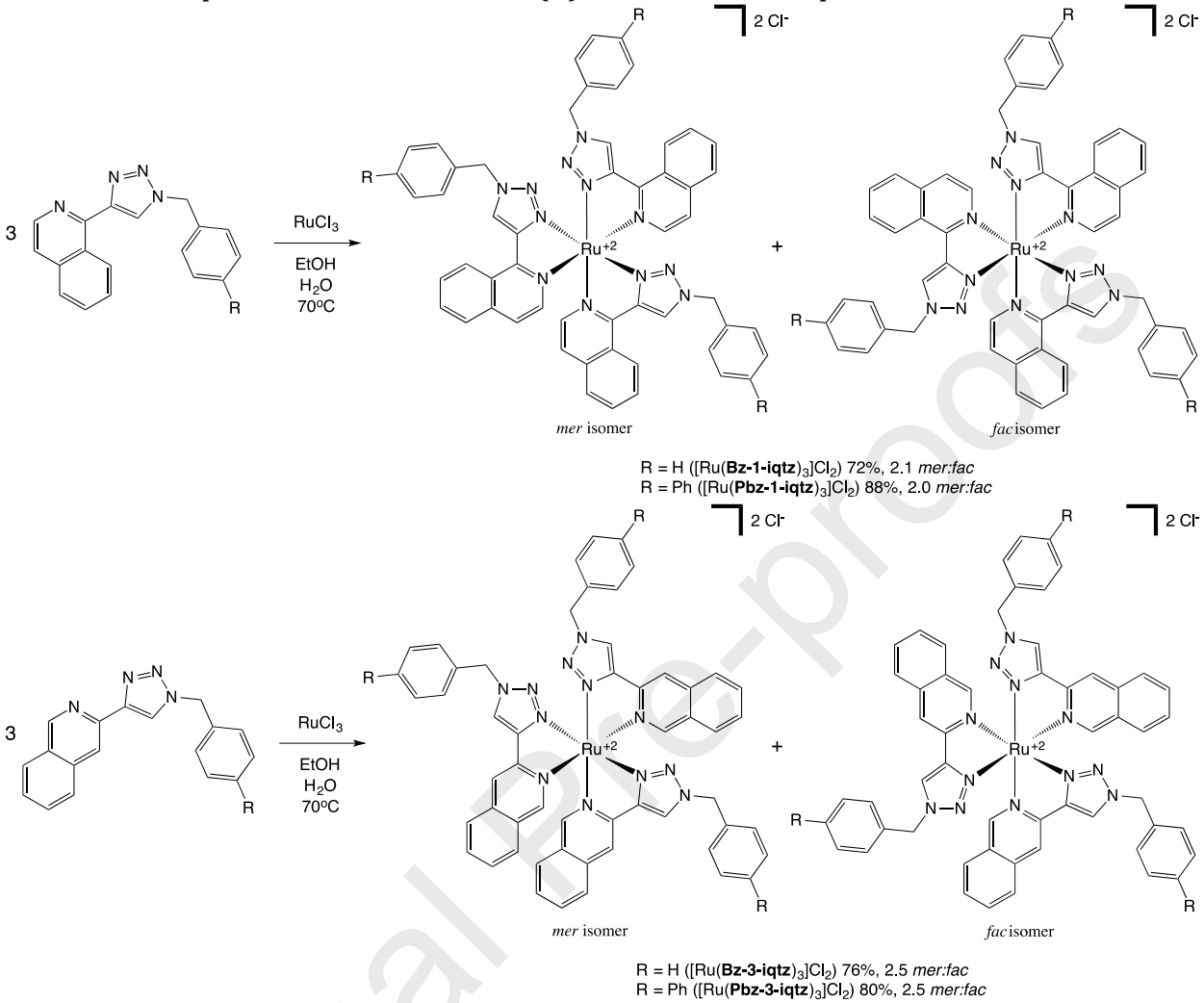
Figure 5. Thermal ellipsoid plot of **Pbz-1-iqtz** shown at 25% probability.

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 ^{1}H 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-iqtz** and **pytz** (Scheme S2) derivatives show a 2:1 preference for their *mer* isomers, while the **3-iqtz** derivatives show a slightly higher 2.5:1 *mer* isomeric excess. Interestingly, this ratio contrasts with previously reported alkyl substituted [Ru(**pytz**)$_3$]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-iqtz** 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-iqtz** and **3-iqtz** 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.

Scheme 2. Preparation of octahedral Ru(II) coordination compounds



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-iqtz** complex (367 nm) closely resembles that of the **pytz** complex (378 nm), the MLCT bands of the **1-iqtz** 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.

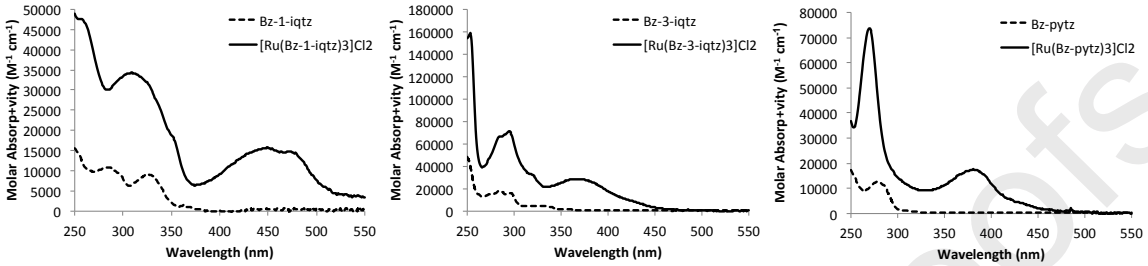


Figure 6. UV-Visible absorbance of benzyl-functionalized N-N bidentate chelators and their 3:1 Ru(II) complexes in methanol.

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 μM). 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 $[Ru(\mathbf{pytz})_3]Cl_2$ 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**)$_3$]Cl$_2$ 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**)$_3$]Cl$_2$ 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.

Table 1. Summary of bioactivity for [RuL$_3$]Cl$_2$ complexes.

		Minimum Inhibitory Concentration (μM)				
Entry	L =	*B.S.*	*S.E.*	*E.A.*	*E.C.*	*C.A.*
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).

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.

Acknowledgements

This publication was made possible by grants from the National Institute for General Medical Science (NIGMS) (5P20GM103427), a component of the National Institutes of Health (NIH), and its contents are the sole responsibility of the authors and do not necessarily represent the official views of NIGMS or NIH.

Appendix. Supplementary Data

Supplementary data related to this article can be found at _____. Experimental procedures, copies of ^{1}H 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-iqtz**, **Pbz-3-iqtz** and **Pbz-1-iqtz** are included. Crystallographic data for the structures presented in this paper have been deposited with the Cambridge Crystallographic Data Centre: **Bz-3-iqtz** as CCDC 1946238, **Pbz-3-iqtz** as 1946240 and **Pbz-1-iqtz** 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).

References

[1] V. V Rostovtsev, L.G. Green, V. V Fokin, K.B. Sharpless, A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes, Angew. Chemie Int. Ed. 41 (2002) 2596–2599. doi:10.1002/1521-3773.

[2] C.W. Tornøe, C. Christensen, M. Meldal, Peptidotriazoles on solid phase: [1,2,3]-Triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides, J. Org. Chem. 67 (2002) 3057–3064. doi:10.1021/jo011148j.

[3] M. Meldal, C.W. Tornøe, Cu-Catalyzed Azide- Alkyne Cycloaddition, Chem. Rev. 108 (2008) 2952–3015. doi:10.1021/cr0783479.

[4] T.L. Mindt, C. Schweinsberg, L. Brans, A. Hagenbach, U. Abram, D. Tourwé, E. Garcia-Garayoa, R. Schibli, A click approach to structurally diverse conjugates containing a central di-1,2,3-triazole metal chelate, ChemMedChem. 4 (2009) 529–539. doi:10.1002/cmdc.200800418.

[5] H. Struthers, T.L. Mindt, R. Schibli, Metal chelating systems synthesized using the copper(i) catalyzed azide-alkynecycloaddition, Dalt. Trans. 39 (2010) 675–696. doi:10.1039/B912608B.

[6] J.D. Crowley, D.A. McMorran, "Click-Triazole" Coordination Chemistry: Exploiting 1,4-Disubstituted-1,2,3-Triazoles as Ligands, in: Top. Heterocycl. Chem., 2012: pp. 31–84. doi:10.1007/7081_2011_67.

[7] J.P. Byrne, J.A. Kitchen, T. Gunnlaugsson, The [2,6-bis(1,2,3-triazol-4-yl)pyridine] binding motif: a new versatile terdentate ligand for supramolecular and coordination chemistry., Chem. Soc. Rev. 43 (2014) 5302–25. doi:10.1039/c4cs00120f.

[8] Y.H. Lau, P.J. Rutledge, M. Watkinson, M.H. Todd, Chemical sensors that incorporate click-derived triazoles, Chem. Soc. Rev. 40 (2011) 2848. doi:10.1039/c0cs00143k.

[9] J.J. Bryant, U.H.F. Bunz, Click To Bind: Metal Sensors, Chem. - An Asian J. 8 (2013) 1354–1367. doi:10.1002/asia.201300260.

[10] H. Struthers, B. Spingler, T.L. Mindt, R. Schibli, "Click-to-chelate": Design and incorporation of triazole-containing metal-chelating systems into biomolecules of diagnostic and therapeutic interest, Chem. - A Eur. J. 14 (2008) 6173–6183. doi:10.1002/chem.200702024.

[11] B. Schulze, U.S. Schubert, Beyond click chemistry - supramolecular interactions of 1,2,3-triazoles., Chem. Soc. Rev. 43 (2014) 2522–2571. doi:10.1039/c3cs60386e.

[12] Q.V.C. van Hilst, N.R. Lagesse, D. Preston, J.D. Crowley, Functional metal complexes from CuAAC "click" bidentate and tridentate pyridyl-1,2,3-triazole ligands, Dalt. Trans. 47 (2018) 997–1002. doi:10.1039/C7DT04570K.

[13] P.A. Scattergood, A. Sinopoli, P.I.P. Elliott, Photophysics and photochemistry of 1,2,3-triazole-based complexes, Coord. Chem. Rev. 350 (2017) 136–154. doi:10.1016/j.ccr.2017.06.017.

[14] T.L. Mindt, C. Müller, F. Stuker, J.-F. Salazar, A. Hohn, T. Mueggler, M. Rudin, R. Schibli, A "Click Chemistry" Approach to the Efficient Synthesis of Multiple Imaging Probes Derived from a Single Precursor, Bioconjug. Chem. 20 (2009) 1940–1949. doi:10.1021/bc900276b.

[15] S. V. Kumar, W.K.C. Lo, H.J.L. Brooks, L.R. Hanton, J.D. Crowley, Antimicrobial Properties of Mono- and Di-fac-rhenium Tricarbonyl 2-Pyridyl-1,2,3-triazole Complexes, Aust. J. Chem. 69 (2016) 489. doi:10.1071/CH15433.

[16] S. V. Kumar, W.K.C. Lo, H.J.L. Brooks, J.D. Crowley, Synthesis, structure, stability and antimicrobial activity of a ruthenium(II) helicate derived from a bis-bidentate "click" pyridyl-1,2,3-triazole ligand, Inorganica Chim. Acta. 425 (2015) 1–6. doi:10.1016/j.ica.2014.10.011.

[17] S. V. Kumar, S.Ø. Scottwell, E. Waugh, C.J. McAdam, L.R. Hanton, H.J.L. Brooks, J.D. Crowley, Antimicrobial Properties of Tris(homoleptic) Ruthenium(II) 2-Pyridyl-1,2,3-triazole "Click" Complexes against Pathogenic Bacteria, Including Methicillin-Resistant Staphylococcus aureus (MRSA), Inorg. Chem. 55 (2016) 9767–9777. doi:10.1021/acs.inorgchem.6b01574.

[18] S. Vellas, J. Lewis, M. Shankar, A. Sagatova, J. Tyndall, B. Monk, C. Fitchett, L. Hanton, J. Crowley, [Fe2L3]4+ Cylinders Derived from Bis(bidentate) 2-Pyridyl-1,2,3-triazole "Click" Ligands: Synthesis, Structures and Exploration of Biological Activity, Molecules. 18 (2013) 6383–6407. doi:10.3390/molecules18066383.

[19] CDC, Antibiotic resistance threats in the United States, 2013, Centers for Disease Control and Prevention (2013).

[20] WHO, Antimicrobial resistance. Global report on surveillance, World Health Organization (2014).

[21] M. Bassetti, M. Merelli, C. Temperoni, A. Astilean, New antibiotics for bad bugs: where are we?, Ann. Clin. Microbiol. Antimicrob. 12 (2013) 22. doi:10.1186/1476-0711-12-22.

[22] D.R. Dodds, Antibiotic resistance: A current epilogue, Biochem. Pharmacol. 134 (2017) 139–146. doi:10.1016/j.bcp.2016.12.005.

[23] D.H. Simpson, P. Scott, Antimicrobial Metallodrugs, in: Inorg. Organomet. Transit.

Met. Complexes with Biol. Mol. Living Cells, 2017. doi:10.1016/B978-0-12-803814-7.00007-1.

[24] F. Li, J.G. Collins, F.R. Keene, Ruthenium complexes as antimicrobial agents, Chem. Soc. Rev. 44 (2015) 2529–2542. doi:10.1039/C4CS00343H.

[25] T.U. Connell, J.M. White, T.A. Smith, P.S. Donnelly, Luminescent Iridium(III) Cyclometalated Complexes with 1,2,3-Triazole "Click" Ligands, Inorg. Chem. 55 (2016) 2776–2790. doi:10.1021/acs.inorgchem.5b02607.

[26] C. Minozzi, A. Caron, J.-C. Grenier-Petel, J. Santandrea, S.K. Collins, Heteroleptic Copper(I)-Based Complexes for Photocatalysis: Combinatorial Assembly, Discovery, and Optimization, Angew. Chemie Int. Ed. 57 (2018) 5477–5481. doi:10.1002/anie.201800144.

[27] J. Wu, Y. Liu, C. Lu, Q. Shen, Palladium-catalyzed difluoromethylthiolation of heteroaryl bromides, iodides, triflates and aryl iodides, Chem. Sci. 7 (2016) 3757–3762. doi:10.1039/C6SC00082G.

[28] X. Pan, C. Yang, J.L. Cleveland, T.D. Bannister, Synthesis and Cytoxicity of Sempervirine and Analogues, J. Org. Chem. (2016). doi:10.1021/acs.joc.6b00022.

[29] T. Okita, M. Isobe, Palladium-catalyzed coupling of heteroaromatic triflates with acetylene and its application for a dynemicin a intermediate, Tetrahedron. 51 (1995) 3737–3744. doi:10.1016/0040-4020(95)00118-R.

[30] T. Sakamoto, M. Shiraiwa, Y. Kondo, H. Yamanaka, A Facile Synthesis of Ethynyl-Substituted Six-Membered N -Heteroaromatic Compounds, Synthesis (Stuttg). 1983 (1983) 312–314. doi:10.1055/s-1983-30319.

[31] CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow*

Aerobically - Tenth Edition. CLSI document M07-A10. Wayne, PA: Clinical and Laboratory Standards Insititute; 2015. Vol 35.; 2015.

[32] CLSI. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts: Approved Standard - Third Edition*. CLSI document M27-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.

[33] American Society for Microbiology, Manual of antimicrobial susceptibility testing, 2005. doi:10.1007/s13398-014-0173-7.2.

[34] Rigaku Oxford Diffraction, CrysAlis PRO (2015).

[35] G.M. Sheldrick, SHELXT – Integrated space-group and crystal-structure determination, Acta Crystallogr. Sect. A Found. Adv. 71 (2015) 3–8. doi:10.1107/S2053273314026370.

[36] G.M. Sheldrick, Crystal structure refinement with SHELXL, Acta Crystallogr. Sect. C Struct. Chem. 71 (2015) 3–8. doi:10.1107/S2053229614024218.

[37] O. V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, OLEX2 : a complete structure solution, refinement and analysis program, J. Appl. Crystallogr. 42 (2009) 339–341. doi:10.1107/S0021889808042726.

[38] I.S. David Palmer, Michael Conley, Louis Parsonson, Leila Rimmer, CrystalMaker, (2019).

[39] J.T. Fletcher, B.J. Bumgarner, N.D. Engels, D.A. Skoglund, Multidentate 1,2,3-Triazole-Containing Chelators from Tandem Deprotection/Click Reactions of (Trimethylsilyl)alkynes and Comparison of Their Ruthenium(II) Complexes, Organometallics. 27 (2008) 5430–5433. doi:10.1021/om800768k.

[40] J.T. Fletcher, S.E. Walz, M.E. Keeney, Monosubstituted 1,2,3-triazoles from two-step

one-pot deprotection/click additions of trimethylsilylacetylene, Tetrahedron Lett. 49 (2008) 7030–7032. doi:10.1016/j.tetlet.2008.09.136.

[41] A. Indapurkar, B. Henriksen, J. Tolman, J. Fletcher, Evaluation of Triazole-Chelated Lanthanides as Chemically Stabile Bioimaging Agents, J. Pharm. Sci. 102 (2013) 2589–2598. doi:10.1002/jps.23616.

[42] J.D. Crowley, P.H. Bandeen, L.R. Hanton, A one pot multi-component CuAAC "click" approach to bidentate and tridentate pyridyl-1,2,3-triazole ligands: Synthesis, X-ray structures and copper(II) and silver(I) complexes, Polyhedron. 29 (2010) 70–83. doi:10.1016/j.poly.2009.06.010.

[43] R.M. Meudtner, M. Ostermeier, R. Goddard, C. Limberg, S. Hecht, Multifunctional "clickates" as versatile extended heteroaromatic building blocks: Efficient synthesis via click chemistry, conformational preferences, and metal coordination, Chem. - A Eur. J. 13 (2007) 9834–9840. doi:10.1002/chem.200701240.

[44] G.-P. Charbonneau, Y. Delugeard, Structural transition in polyphenyls. III. Crystal structure of biphenyl at 110 K, Acta Crystallogr. Sect. B Struct. Crystallogr. Cryst. Chem. (1976). doi:10.1107/s0567740876005487.

[45] K.P.C. Minbiole, M.C. Jennings, L.E. Ator, J.W. Black, M.C. Grenier, J.E. LaDow, K.L. Caran, K. Seifert, W.M. Wuest, From antimicrobial activity to mechanism of resistance: the multifaceted role of simple quaternary ammonium compounds in bacterial eradication, Tetrahedron. 72 (2016) 3559–3566. doi:10.1016/j.tet.2016.01.014.

[46] M.C. Jennings, K.P.C. Minbiole, W.M. Wuest, Quaternary Ammonium Compounds: An Antimicrobial Mainstay and Platform for Innovation to Address Bacterial Resistance,

ACS Infect. Dis. 1 (2016) 288–303. doi:10.1021/acsinfecdis.5b00047.

[47] J.P.S. Powers, R.E.W. Hancock, The relationship between peptide structure and antibacterial activity, Peptides. 24 (2003) 1681–1691. doi:10.1016/j.peptides.2003.08.023.

Declaration of interests

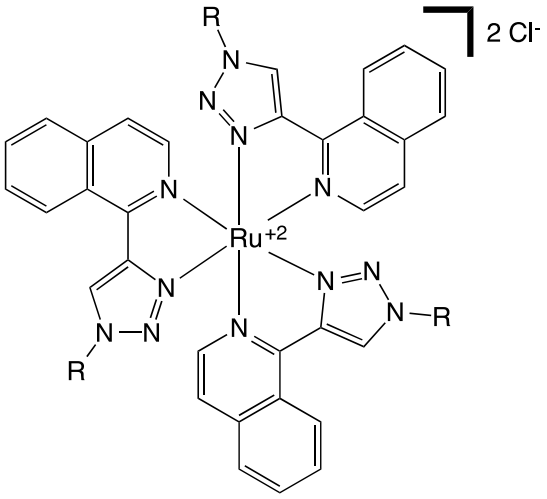
☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

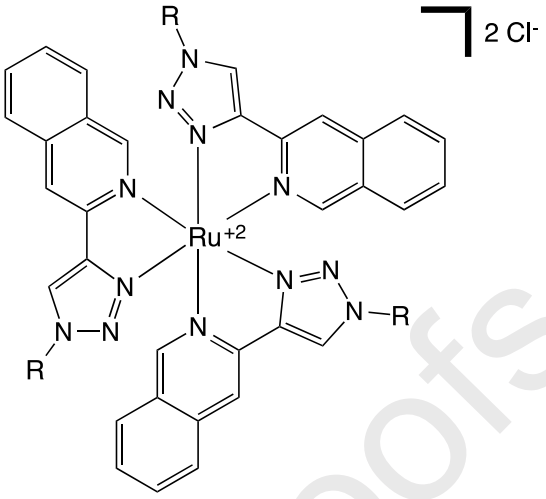
First option selected (could not get checkmark to appear in box of template file) = no competing interests.

James Fletcher

10/29/19



1-isomer



3-isomer

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.