# A study on tailor made ruthenium sulphoxide complexes: Synthesis, characterization and application

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*Abstract*: In this study, a dinucleating spacer incorporating two 2-aminopyridine units was used to prepare seven novel dinuclear compounds. These molecules were characterized by elemental analyses, conductivity measurements, magnetic susceptibility, FT-IR, FAB-Mass, electronic, $^1$H-NMR and $^{13}$C{$^1$H}--NMR spectral studies. The complex [{*trans,mer*-RuCl$_2$(DMSO)$_3$}$_2$($\mu$-5,5′--methylenebis(2-aminopyridine))]·2DMSO (**2**) was also characterized through $^1$H-$^1$H COSY NMR. There are mainly three different formulations, [{*cis,fac*-RuCl$_2$(SO)$_3$}$_2$($\mu$-MBAP)]·2SO; [{*trans,mer*-RuCl$_2$(SO)$_3$}$_2$($\mu$-MBAP)]·2SO and [{*trans*-RuCl$_4$(SO)}$_2$($\mu$-MBAP)]$^{2-}$ [X]$_2$$^+$; where SO = DMSO / TMSO; MBAP = 5,5′-methylenebis(2-pyridinamine) and [X]$^+$ = [(DMSO)$_2$H]$^+$, Na$^+$ or [(TMSO)H]$^+$. The coordination was found through cyclic nitrogen of the pyridine ring in an octahedral environment for both metal centres. The chemical behaviour of [{*cis,fac*-RuCl$_2$(DMSO)$_3$}$_2$($\mu$-5,5′-methylenebis(2-pyridinamine))]·2DMSO (**1**) and (**2**) in aqueous solution with respect to time was observed by conductivity measurements and UV–Vis spectrophotometry. All complexes were found to possess prominent antibacterial activity against *Escherichia coli* in comparison to chloramphenicol and gatifloxacin.

*Keywords*: 2-aminopyridine; antibacterial; dinuclear; ruthenium; spacer; sulphoxide.

## INTRODUCTION

Metal complexes were found valuable for the design and development of synthetic restriction enzymes and new drugs because of their ability to bind with DNA.[1] In the past decade, ruthenium complexes have generated interest due to their potential application as chemotherapeutic agents.[2] Several ruthenium compounds were proven to have antitumour activity.[3–6] After introduction of two

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ruthenium compounds [indH] *trans*-[RuCl$_4$(ind)$_2$] (ind = indazole, KP1019) and [imH] *trans*-[RuCl$_4$(DMSO-*S*)(im)] (im = imidazole, NAMI-A), into clinical trials,[7,8] substantial attraction explored this field and a number of mononuclear analogue with different *N*-containing heterocyclic ligands were synthesized and tested for their *in vitro* antimicrobial and antitumour activity.[9–12]

As well as mononuclear analogues, dinuclear compounds have also been recognized with increased size, variety of molecular shapes and consisting of two discrete metal centres connected *via* a spacer of various lengths, type and composition.[13–18] The rational design and synthesis of new compounds with an organized molecular framework and functional feature is the major goal of a researcher. 2-Aminopyridine, functionally closed in biological systems and also able to form self-complementary intermolecular interactions, was chosen. The compounds bearing two 2-aminopyridyl moieties separated by linkers of different shapes and lengths (devoid any other functionality) might give a new look to synthesized molecules.[19] These findings suggested the preparation of 5,5′-methylenebis(2-aminopyridine) [MBAP],[20] with the anticipation of some noteworthy contribution. Thus, the aim of the present study was to synthesize and characterize dinuclear ruthenium sulphoxide complexes with the anticipation of a better pharmacological conclusion.

## EXPERIMENTAL

RuCl$_3$·3H$_2$O (Merck), 2-aminopyridine (Himedia, India), tetramethylenesulphoxide (TMSO, Lancaster, UK) and Muller Hinton agar (Himedia) were used as received. Analytical grade dimethyl sulphoxide (DMSO, Merck), formaldehyde (Merck) and routine solvents were used for synthetic purposes without further purification.

*Instrumentation*

The electronic absorption spectra were recorded with a Shimadzu-1700 UV–Vis spectrophotometer equipped with a PC. Conductivity measurements were realised at 25 °C using an EI-181 conductivity bridge with a dipping type cell. The FT-IR spectra were recorded in KBr pellets on a Shimadzu-8400 PC, FT-IR spectrophotometer in the 4000–400 cm$^{-1}$ range and the far-IR spectra of the complexes were recorded using polyethylene pellets in the 500–100 cm$^{-1}$ region on a Nicolet Mega-550 FT-IR instrument. The $^1$H-, $^{13}$C- and $^1$H––$^1$H COSY NMR spectra were recorded in D$_2$O on a Bruker Avance-400 NMR spectrometer. The Gouy's method was employed for the measurements of magnetic susceptibility. Hg[Co(NCS)$_4$] was used as a standard. Diamagnetic correction was made using the Pascal constant. Elemental analyses (CHN) were performed on an Elementra Vario EL III elemental analyzer. FAB-MS spectra were recorded on Jeol SX-102 mass spectrometer.

*Preparation of the complexes*

Appropriate quantities of precursor ([*cis,fac*-RuCl$_2$(*S*-DMSO)$_3$(*O*-DMSO)]  (**1a**),[21] [*trans*-RuCl$_2$(DMSO-*S*)$_4$] (**2a**),[4] [(DMSO)$_2$H]$^+$ [*trans*-Ru(DMSO-*S*)$_2$Cl$_4$]$^-$ (**3a**)[5] or Na$^+$[*trans*--Ru(DMSO-*S*)$_2$Cl$_4$]$^-$ (**4a**)[5] was dissolved in the minimum volume (≈ 0.2 mL) of DMSO, or [*cis*-RuCl$_2$(TMSO-*S*)$_4$] (**5a**),[22] [*trans*-RuCl$_2$(TMSO-*S*)$_4$] (**6a**)[22] or [(TMSO)H]$^+$ [*trans*--Ru(TMSO-*S*)$_2$Cl$_4$]$^-$ (**7a**)[22] in TMSO (≈0.2 mL) and was mixed with a solution of MBAP in

acetone (10 mL) in a 1:1 ratio. The reaction mixture was stirred at room temperature for 3 h, followed by the addition of another mole of precursor (dissolved in ≈0.2 mL DMSO/TMSO). The reaction mixture was kept under reflux for 3–12 h. The volatile fraction was allowed to evaporate under vacuum and the obtained solids were washed with acetone / diethyl ether (1:2, *V/V*) solvent mixture. The impure product was re-crystallized by vapour diffusion of diethyl ether into a DCM solution at room temperature to afford yellow solids. The products were isolated by filtration, washed with diethyl ether and vacuum dried.

In vitro *antibacterial activity*

The complexes **1**–**7**, their precursors **1a**–**7a** and MBAP were screened for antibacterial properties against *Escherichia coli* MTCC 1304 at a concentration 2.5 µg mL$^{-1}$ in water by the agar well diffusion method as described by Mehrotra *et al.*[23] In brief, overnight grown bacterial cells ($\approx 10^5$ colony forming unit) were spread on Mueller–Hinton (MH) agar plates using a sterile cotton swab. Uniform wells (diameter of 6.0 mm) were created in the agar slab by using a cork borer. 50 µL of test and control solutions were placed in respective wells. Solutions, 0.25 µg mL$^{-1}$ of chloramphenicol (CM) and gatifloxacin (GT) were used as positive controls and MBAP in water as the negative control. All plates were incubated at 37 °C for 48 h followed by 4 °C incubation for 20 min. All plates were observed for the zone of inhibition.

*Minimum inhibitory concentration (*MIC*) determination*

The *MIC* values for complexes **1**–**7** were determined against *E. coli*. The successive dilution method reported by Mehrotra *et al.*[24] was used for *MIC* evaluation. In brief, the complexes were serially diluted to 25.0–0.0 µg mL$^{-1}$ in MH broth. The 5.7log (number of cells) were inoculated in respective dilutions. All the tubes were incubated at 37 °C for 24 h. The *MIC* was considered as concentrations of higher dilution tube in which bacterial growth was absent.

*Statistical analysis*

Statistical analysis was performed by one-way analysis of variance (ANOVA) using GraphPad Prism 6 (version 6.04 (Trial) for Windows; GraphPad Software, Inc., CA). Differences were considered statistically significant at *P* values < 0.05.

RESULTS AND DISCUSSION

*Synthesis and physiochemical characterization*

The complexes **1**–**7** were obtained through tailored synthesis. The reaction was planned with selected Ru(II/III) sulphoxide precursors and MBAP (spacer), in acetone medium. The desired products were isolated as solids and purified through vapour diffusion of Et$_2$O into a DCM solution at room temperature. The attempts to obtain crystals failed and the obtained solid was only a precipitate. All complexes were stable in air at room temperature and soluble in water, chloroform, acetone, MeCN, DCM and DMSO.

The physical, analytical and spectral data for complexes **1**–**7** are given in the Supplementary material to this paper.

Empirical formulas for **1**–**7** were in good agreement with elemental data. The determined molecular weights were supported by FAB-MS spectra. The molar conductivities for complexes **1**, **2**, **5** and **6**, observed between 52 and 68

$\Omega^{-1}$ mol$^{-1}$ dm$^3$ cm$^{-1}$ in water, were within the range suggested for non-electrolytes. However, for **3**, **4**, and **7**, the values were comparatively high (between 122 and 130 $\Omega^{-1}$ mol$^{-1}$ dm$^3$ cm$^{-1}$), indicating the ionic nature of these complexes.[5,25]

*Spectral studies*

*Infrared spectral study.* In FTIR spectrum of MBAP, the absorption band at 3487 cm$^{-1}$, assigned to $\nu$(N–H),[20] did not show any appreciable shift in the spectra of **1**–**7**, confirming the non-participation of the (N–H) nitrogen in the coordination. The bands between 1609 and 1430 cm$^{-1}$, assigned to cyclic C=C and C=N stretching mode in MBAP,[20] were found shifted (by 30–60 cm$^{-1}$) on the positive scale in the spectra of the complexes. These bands were also less intense, indicating that both metal centres were symmetrically coordinated to the cyclic nitrogen of MBAP (spacer).[18] The appearance of the $\nu$(Ru–N) band at 280 cm$^{-1}$ was further support of metal ligand binding.[16]

The bands appearing in the range 1090–1136 cm$^{-1}$ were assigned to $\nu$(SO). In the spectra of **1**–**3**, an additional band was observed at about 1055 cm$^{-1}$, due to uncoordinated DMSO. In the spectra of **5**–**7**, the strong band of free TMSO appeared near 1028 cm$^{-1}$.[25,26] The $\nu$(Ru–Cl) stretching mode was observed at around 330 cm$^{-1}$ and the $\nu$(Ru–S) mode at about 402 cm$^{-1}$. In complexes **3** and **7**, the broad signal registered at 730 cm$^{-1}$ along with another sharp signal at 1056 cm$^{-1}$ in DMSO and at 1029 cm$^{-1}$ in the TMSO analogue indicates the presence of hydrogen bonded DMSO/TMSO in these complexes.[5,25]

*Electronic spectral study*. Complexes **1**, **2**, **5** and **6** were diamagnetic (low spin d$^6$, $S = 0$), as expected for low spin Ru(II) compounds. Four bands appeared in the spectra. In the visible region, two weak absorption bands with low extinction coefficient were observed between 662 and 580 nm, and 480 and 390 nm. These bands were assigned to the transitions $^1A_1g \rightarrow {}^1T_1g$ and $^1A_1g \rightarrow {}^1T_2g$, respectively. The band at about 350 nm was probably due to a metal ligand charge transfer transition (MLCT). Moreover, the higher energy absorption band at around 300 nm was due to $\pi \rightarrow \pi^*$ intraligand transitions in the coordinated $\pi$-acidic imine ligand.[27,28]

Complexes **3**, **4** and **7** were paramagnetic with magnetic moments of 1.87––1.89 $\mu_B$ per ruthenium centre, (low spin d$^5$, $S = 1/2$) as expected for low spin Ru(III) complexes. In the spectra, three bands were registered between 482 and 472, 446 and 430, and 302 and 301 nm. The intense absorption band around 430 nm coupled with a less intense transition at 470 nm was ascribed to a charge transfer transition from chloride to the Ru(III) ion. This is a typical identification for the RuCl$_4^-$ unit.[29] In complexes **3** and **7**, the weak absorption band at 300 nm was due to the protonated sulphoxide cation.[27,28]

*NMR spectral studies* The NMR study for **1**–**7** was found not very helpful since only small swings in the chemical shift were reported. However, in the ^{1}H--NMR spectra of **1**, **2**, **5** and **6**, broad signals for four $NH_2$ protons were observed between $\delta$ 5.49–5.43 ppm, and at almost the same position as observed in MBAP,[20] confirming the non-involvement of the $NH_2$ group in the coordination. A sharp signal for two methylenic protons appeared in the range $\delta$ 2.99–2.73 ppm and for six heteroaromatic protons observed between $\delta$ 7.94–6.93 ppm. In the ^{13}C{^{1}H}NMR spectra, signals for the methylenic carbon were observed between $\delta$ 40.3–39.4 ppm and for Ar-C between $\delta$ 149.9–110.1 ppm.[30]

Three singlets (intensity ratio 1:1:1) observed in the ^{1}H-NMR spectrum of **1**, (Fig. S-1 of the Supplementary material to this paper) indicated three different environments for the methyl protons of DMSO. The signals at $\delta$ 3.50 and 3.48 ppm were both assigned to twelve $CH_3$ protons of DMSO *trans* to Cl, and were in the diastereotopic arrangement to each other.[17] However, the signal centred at $\delta$ 3.40 ppm was assigned to twelve DMSO protons *trans* to the pyridine nitrogen.[25,31,32] The appearance of three signals at $\delta$ 45.7, 45.3 and 44.3 ppm in the ^{13}C-NMR spectrum of **1** (Fig. S-2 of the Supplementary material) supported the ^{1}H-NMR data. The signals at $\delta$ 45.7 and 45.3 ppm were assigned to the methyl carbon *trans* to Cl and at $\delta$ 44.3 ppm to the methyl carbon of DMSO *trans* to the pyridine nitrogen.

In ^{1}H-NMR spectra of **5**, four sets of signals were registered. The multiplet centered at $\delta$ 4.01 and 3.98 ppm (for eight protons each) were assigned to the S–$CH_2$ protons of TMSO *trans* to Cl and diastereotopic to each other.[17,25] The multiplet centred at $\delta$ 3.57 ppm (for eight protons) were assigned to two S–$CH_2$ protons situated *trans* to the pyridine nitrogen for both metal centres. However, the multiplet at $\delta$ 2.30 ppm was assigned to twenty-four protons of S–C–$CH_2$ groups. The relative intensity of these four signals was 1:1:1:3.[17,33] Similar conclusions were drawn from the ^{13}C-NMR data of **5**. The signals at $\delta$ 57.8 and 57.7 ppm were assigned to the (S–C) carbon of TMSO *trans* to Cl, and at $\delta$ 55.6 ppm *trans* to the pyridine nitrogen. The signals observed at $\delta$ 27.1, 26.9 and 25.7 ppm were assigned to the (S–C–C) carbons of TMSO.[33]

In the ^{1}H-NMR spectrum of **2**, two singlets appeared with an intensity ratio of 1:2, indicating two different environments for the $CH_3$ protons. The singlet at $\delta$ 3.49 ppm was assigned to twelve DMSO protons *trans* to the pyridine nitrogen and at $\delta$ 3.37 ppm to twenty-four DMSO protons *trans* to each other. In the ^{1}H––^{1}H COSY NMR spectrum of **2** (Fig. S-3 of the Supplementary material), no cross peaks were noticed in the sulphoxide region, indicating there was no connectivity between the methyl carbons of DMSO. Similar conclusions were derived from the ^{13}C-NMR results for **2**, (Fig. S-4 of the Supplementary material), in which two signals for the (S–C) carbon of DMSO were observed at $\delta$ 46.7 and 44.9 ppm.[32,33]

Similarly, complex **6** exhibited three sets of multiplets centred at $\delta$ 3.54, 3.51 and 2.32 ppm. The signals centred at $\delta$ 3.54 and 3.51 ppm were assigned to S–CH$_2$ protons and that at $\delta$ 2.32 ppm to S–C–CH$_2$ protons of TMSO. The intensity ratios for these three signals were 1:2:3. Therefore, it could be concluded that one TMSO unit was *trans* to the pyridine nitrogen and other two were *trans* to each other, in an octahedral environment for both metal centres.[33,34] This conclusion was further supported by the $^{13}$C-NMR spectral study. The signal centred at $\delta$ 57.2 ppm was assigned to the (S–C) carbon of TMSO *trans* to pyridine nitrogen and the signal for S–C carbon *trans* to each other was observed at $\delta$ 56.3 ppm. Moreover, for the S–C–C of TMSO, the signals appeared at $\delta$ 27.4 and 26.8 ppm.[33,34]

In $^1$H-NMR spectra of **1** and **2**, an additional singlet observed at about $\delta$ 2.75 ppm was due to free S–CH$_3$, while in **5** and **6**, the signals for the free S–CH$_2$ and S–C–CH$_2$ groups were centred at $\delta$ 2.54 and 2.21 ppm, respectively. This conclusion was further supported by $^{13}$C{$^1$H}NMR data, where in **1** and **2**, the signal at about $\delta$ 37.6 ppm was due to free (S–C) carbons of DMSO; while in **5** and **6**, the presence of free TMSO was evidenced by signals at $\delta$ 54.4 and 24.1 ppm.[14,22] Thus, the NMR results were in support the IR data and confirmed the presence of uncoordinated DMSO/TMSO in the Ru(II) complexes. Moreover, this feature was also in confirmation with elemental results and mass spectral studies. Thus, based on spectroscopic and elemental studies, the most plausible structure of the Ru(II) complexes **1**, **2**, **5** and **6** are presented in Fig. 1.
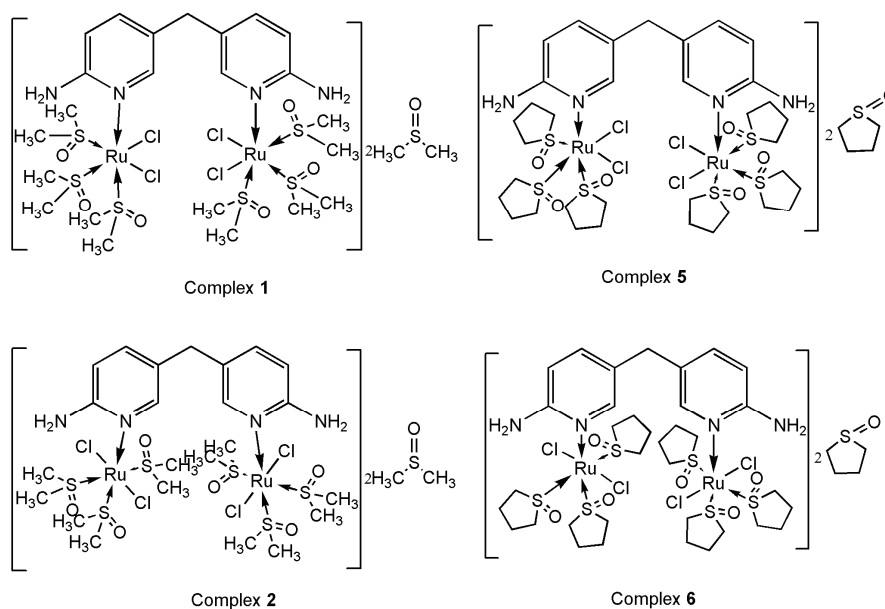


Fig. 1. Structures of Ru(II) complexes **1**, **2**, **5** and **6**.

The signals in the NMR spectra of **3**, **4** and **7** were too broad due to intervention of the paramagnetic ion. Thus, it was not possible to use NMR as a diagnostic tool for the Ru(III) complexes.[16,25] Hence, the binding mode was concluded based on FT-IR, UV–Vis, CHN analyses and FAB-MS. The most probable structures are shown in Fig. 2.
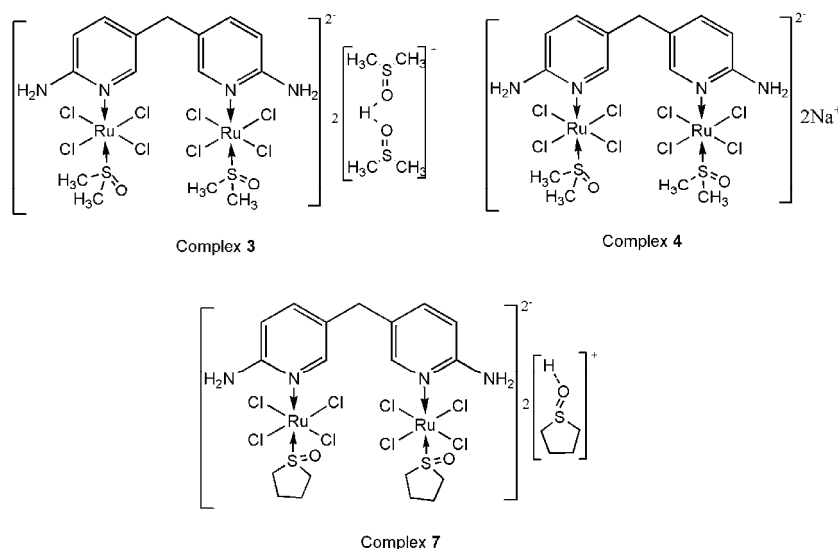


Complex **3**                                                            Complex **4**



Complex **7**

Fig. 2. Structures of Ru(III) complexes **3**, **4** and **7**.

*Chemical behaviour of complexes 1 and 2 in aqueous solution*

The chemical behaviours of complexes **1** and **2** in aqueous solution were studied by repetitive electronic absorption and conductivity measurements. The conductivity for light protected solutions of **1** ($10^{-3}$ M) slowly increased from a non electrolytic to a 1:1 electrolytic range (68 to 102 $\Omega^{-1}$ mol$^{-1}$ dm$^3$ cm$^{-1}$ at 25 °C) due to the release of Cl$^-$ over 12 h. The chloride dissociation step was confirmed spectrophometrically. In the electronic spectra of complex **1**, significant changes in the 300–440 nm range were registered with respect to time (Fig. 3A). The clear isosbestic points (324 and 362 nm) suggested the conversion of the parent complex to the corresponding aqua species.[35]

However, complex **2** once dissolved immediately released one of the *trans* DMSO (at each ruthenium centre) due to the strong trans influence that was followed by the slow release of Cl$^-$. The conductivity determined for **2** ($10^{-3}$ M) increased in time at a lower rate than that of **1**. The release of Cl$^-$ is in agreement with the lower *trans* effect of chloride with respect to DMSO.[4] A molar conductance of 108 $\Omega^{-1}$ mol$^{-1}$ dm$^3$ cm$^{-1}$ was obtained after 24 h at 25 °C, characteristic for a 1:1 electrolyte. This observation was in support of hydrolytic step and

formation of aqua species, which was verified by UV–Vis spectrophotometer (Fig. 3B). However, on long-standing periods (4 days), the conductivity was found to increase at a very slow rate up to values characteristic for 2:1 electrolytes.
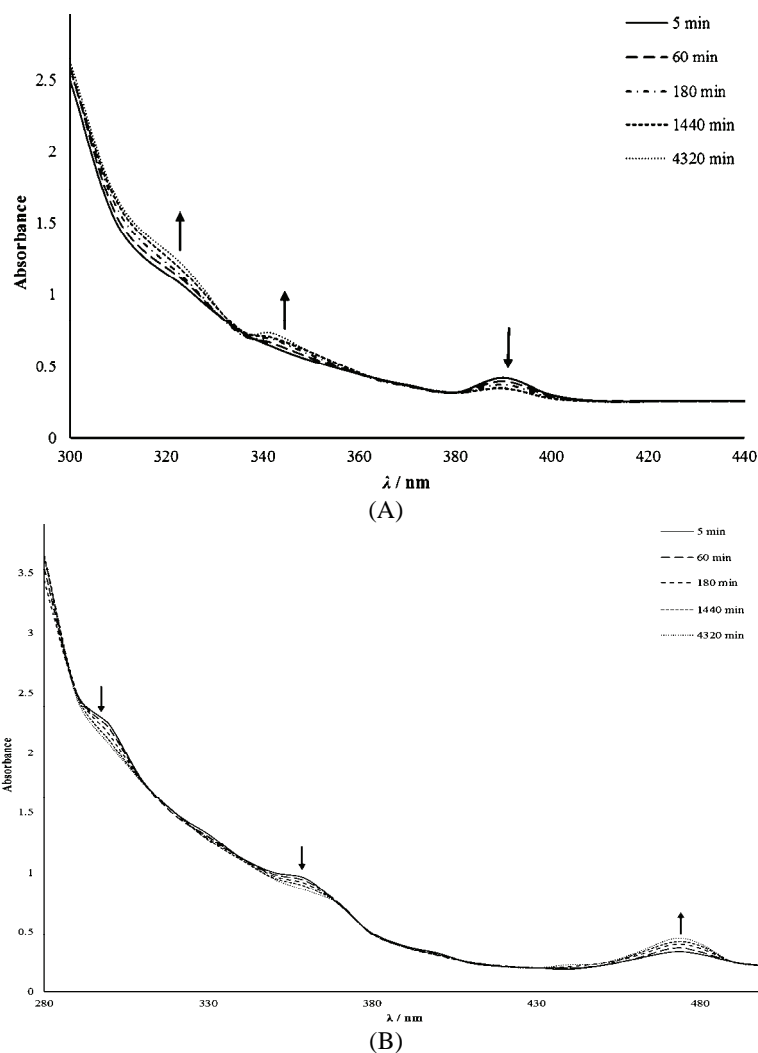


Fig. 3. Time evolution of the UV–Vis spectra of **1** (A) and **2** (B) in $H_2O$ at 25 °C.

The chemical behaviour of complexes **1** and **2** are presented in Figs. S-5 and S-6 of the Supplementary material, respectively.

*Antibacterial assay and determination of* MIC *values*

A significant increase ($P < 0.0001$) in the zone of inhibition (26 mm) was observed for **7** against *E. coli* as compared with GT (Fig. 4B). The zone of inhi-

bition for **4** was 17 mm ($P < 0.0001$); for **3**, 16 mm ($P < 0.05$); for **6**, 12 mm ($P < 0.05$); for **5**, 10 mm ($P < 0.0001$); for **2**, 8 mm ($P < 0.0001$) and for **1**, 6 mm ($P < 0.0015$). The enhanced antibacterial activities of **1**–**7** as compared to the control (MBAP in water) was probably due to the increased liphophilicity of the complexes causing permeability barrier breakdown and enzyme binding inhibition leading to cell death.[23]
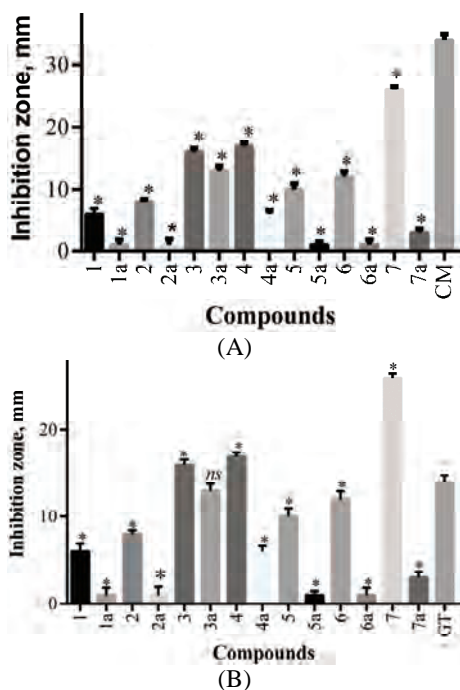


(A)

(B)

Fig. 4. Effect of the precursors **1a**–**7a** and **1**–**7** on the inhibition zone at a concentration 2.5 μg mL$^{-1}$ against *E. coli* in comparison to chloramphenicol, CM (A), and gatifloxacin, GT (B). The values of the zones of inhibition were obtained by subtracting control (MBAP in water). Statistics points are the average values of three independent experiments (mean ± standard deviation; $n = 3$). *: $P < 0.05$; *ns* = not significant.

The results of antibacterial activity are in agreement with MIC evaluation. It was shown that Ru(III) compounds **3**, **4** and **7** were found to be more active to inhibit *E. coli* at *MIC* of 0.31 μg/mL (Table I) in comparison to respective precursors.

TABLE I. *MIC* evaluation (μg/mL) of **1**–**7** and market drugs against *E. coli*

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | Chloramphenicol (CM) | Gatifloxacin (GT) |
|------|------|------|------|------|------|------|------|------|
| 0.62 | 0.62 | 0.31 | 0.31 | 0.62 | 1.25 | 0.31 | 0.25 | 0.25 |

## CONCLUSIONS

Seven dinuclear Ru(II/III) complexes were synthesized by the reaction of a spacer, MBAP and the building block, ruthenium sulphoxide precursors. All compounds were characterized based on spectroscopic techniques and were found novel due to their specific structure and biological action against *E. coli*.

The use of ruthenium medicinal chemistry could be interesting as a potentially less toxic alternative to platinum. The results reported herein indicate that ruthenium complexes show potent antibacterial action. They may find importance in the future due to other aspects of biological activity in the age of superbugs. Their characterization, chemical reactivity and inherent activity give a new look to ruthenium-based pharmaceuticals.

## SUPPLEMENTARY MATERIAL

Physical, analytical and spectral data for the synthesised complexes are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

## ИСПИТИВАЊЕ НОВИХ РУТЕНИЈУМОВИХ СУЛФОКСИДНИХ КОМПЛЕКСА: СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И ПРИМЕНА

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У овом раду, једињење који садржи две 2-аминопиридинске јединице је коришћено као мосни лиганд за синтезу седам нових динуклеарних комплекса рутенијума(II/III). Ови комплекси су окарактерисани помоћу елементалне микроанализе, кондуктометриј-ских, магнетних, FT-IR, FAB-масених, електронских, $^1$H- и $^{13}$C{$^1$H}NMR мерења. Поред тога, [{*trans,mer*-RuCl$_2$(DMSO)$_3$}$_2$($\mu$-5,5′-метиленбис(2-пиридинамин-к$N^1$))]·2DMSO ком-плекс **2** је окарактерисан помоћу $^1$H–$^1$H COSY NMR спектроскопије. Нађено је да пос-тоје три различите комплексне врсте које се могу представити на следећи начин: [{*cis,fac*-RuCl$_2$(SO)$_3$}$_2$($\mu$-MBAP)]·2SO, [{*trans,mer*-RuCl$_2$(SO)$_3$}$_2$($\mu$-MBAP)]·2SO и [{*trans*--RuCl$_4$(SO)}$_2$($\mu$-MBAP)]$^{2-}$ [X]$_2^+$; где су SO = DMSO/TMSO, MBAP = 5,5'-метиленбис(2--аминопиридин) и [X]$^+$ = [(DMSO)$_2$H]$^+$, Na$^+$ или [(TMSO)H]$^+$. На основу кондуктомет-ријских мерења и UV–Vis спектрофотометрије испитиванао је хемијско понашање комплекса [{*cis,fac*-RuCl$_2$(DMSO)$_3$}$_2$($\mu$-5,5'-метиленбис(2- пиридинамин-к$N^1$))]·2DMSO (**1**) и комплекса **2** у раствору у току различитих временских интервала. Нађено је да сви испитивани комплекси показују значајну антибактеријску активност на *Escherichia coli* у односу на хлорамфеникол и гатифлоксацин.

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