Synthesis of Ruthenium Bipyridyl Linked with Steroidal Oxidative Quencher for Photo Redox Studies

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Abstract: Synthesis of ruthenium bipyridyl linked with steroid having oxidative quencher, viologens for study of photo redox properties were described.

Key words: Photoredox, Ruthenium bipyridyl, Steroids, Viologens, Oxidative Quencher

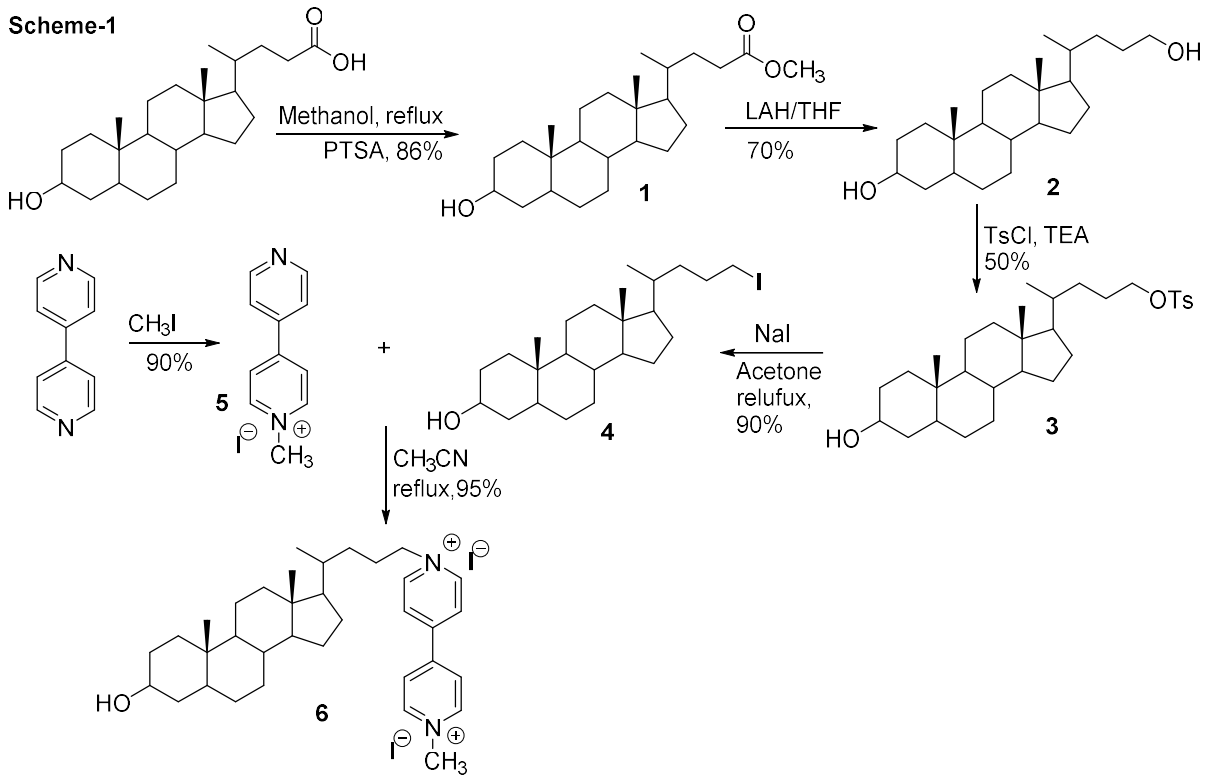
Introduction: Over the past decade, photoredox catalysis has risen to the forefront of synthetic organic chemistry as an indispensable tool for selective small-molecule activation and photoinduced chemical reactions[1-4]. This cutting-edge platform allows photosensitizers to convert visible light[5] into chemical energy[5,6], prompting generation of reactive radical intermediates[7]. The photochemical and thermal chelate exchange reactions involving $Ru(bpy)_3^{2+}$, where bpy is 2,2-bipyridine, and derivatives have been reported[8]. The extent of these photo reactions depends on these ligands under light conditions. A recent report[9] on the high yield synthesis of 4-carboxylic acid-2,2[1]-bipyridine-4[1]-methyl (MebpyCOOH) has paved a new avenue in the research of ruthenium polypyridyl complexes to biomolecules[10,11]. Only one acid group significantly simplifies the connection of this type of ruthenium complex to biological molecules with amine groups[12-14].

It is most attractive feature if ruthenium connected to through a non-conjugate bridge biomolecules having oxidative quencher, such as Viologens[15]. because ruthenium and oxidative quencher viologens have their spectroscopic versatility. Both the donor (Ru(bpy)3 2+*) and acceptor groups can be probed by a variety of different spectroscopic methods. Cholic acid[16] is one of the primary steroids, it has three hydroxyls groups oriented at positions of C3α, C7α and C12α on the polar concave side of the molecule, which is defined as hydrophilic α-face. Its hydrophobic steroidal backbone is defined as β-face. The facial amphiphiles of cholic acid can lead to self-aggregation in solution or aggregation with other specific supramolecular arrangement. Therefore, cholic acid has been widely used as the building block in supramolecular chemistry to transport ions and polar molecules through various membranes. In addition, cholic acid can be potentially used as an adjuvant of liver-specific drugs and absorption enhancers. Similarly, viologens are a well-studied species exhibiting three reversible redox states, possessing valuable electrochromic and electron-accepting properties. because of its properties, viologens have become of great interest as functional materials in a wide array of applications; a few to name include electrochromic devices, molecular machines, and organic batteries[17]. In the combined molecules, if reduction of the biomolecule is desired, a directly photoinduced electron transfer from ruthenium polypyridyl complexes through the bridging ligand, Mebpy-COOH, can be performed.[18] If oxidation of the biomolecule is desired, a flash-quench method can be employed[19,20]. In the flash-quench method, the excited ruthenium polypyridyl complexes have to be quenched from the non-bridged ligands first, followed by the ET through a bridging ligand[21].

Present work: In our lab, after synthesizing the Fluorescence Probe[22] to investigate cytochrome *c* folding kinetics, herein we disclosed the synthesis of a complex molecules having photoredox ruthenium bipyridyl were linked with biomolecules having oxidative quencher, viologen. Herein we used lithocholic acid instead of cholic acid to simplify the synthetic route.

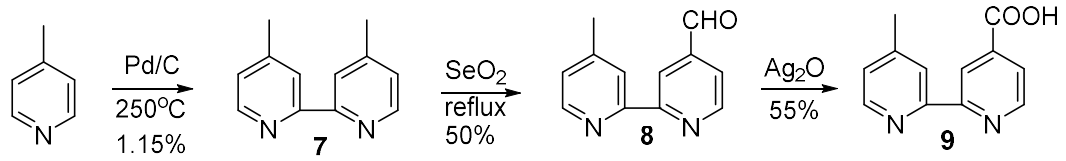
Synthesis Part: Commercially available lithocholic acid was esterified in presence of PTSA to obtained ester **1**, in 90% yield, which on reduction by using LAH to get the diol, **2** in 85% yield. Selective mono tosylation by using tosyl chloride in presence of base, TEA for 72 h at 4°C, isolated the mono-tosylated product **3**, which successfully converted to iodo product[23] **4** in 70% yield, under reflux condition with sodium Iodide in acetone. The mono viologen[24] **5**, is obtained 88 yield by following the modified procedure. Treating the mono viologen **5** with iodo compound **4** in presence of DCC reagent[25] to obtain the salt, which was characterized by NMR and Mass. (Scheme-1).

Scheme-1



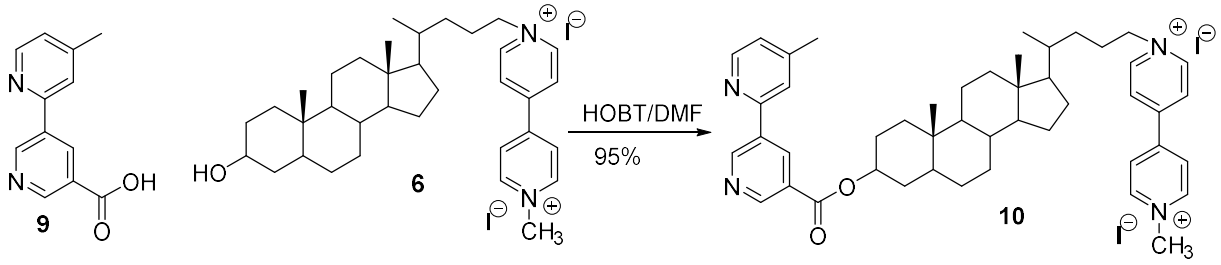
4-Picoline was treated with palladium under reflux conditions obtained the bipyridyl[26] **7**, in 20% yield. Selectively oxidation of **7** to mono-aldehyde **8** by using selenium dioxide[12], which on further oxidized using freshly prepared silver oxide[27]to obtained acid **9** in 55% yield. (scheme-2)

Scheme-2



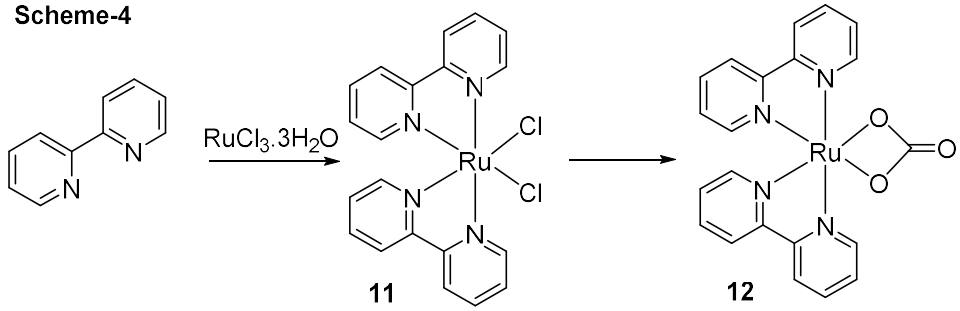
The bipyridyl acid **9** coupled with steroid linked with steroidal-viologen **6**, to obtained product[10,28,29]**10** in 95 yield. (scheme-3).

Scheme-3



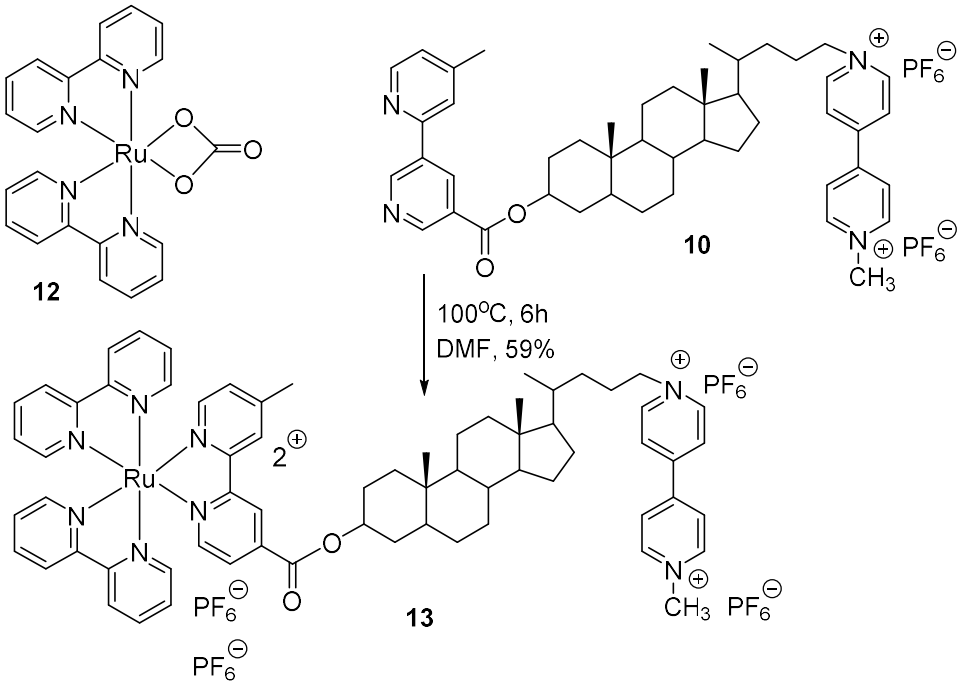
Ruthenium carbonate is prepared in two steps by treating 2,2-bipyridyl with ruthenium trichloride to obtained intermediate product[30] in 40% yield, which on treated with sodium carbonate under Argon atmosphere gives ruthenium carbonate[8] in 67% yield. (scheme-4)

Scheme-4



Ruthenium carbonate on treated with compounds 10 under heating condition. The product was separated by using the solubility differences of substrates to get 120 mg of pure product[31,32] in 59% yield. (scheme-5).

Scheme-5



Conclusion: A photoredox complex molecule with lithocholic acid groups as Lineker between Ruthenium bipyridyl and mono viologen was successfully synthesized by coupling reactions for the first time to study its photo redox, fluorescence, and electrochemical properties.

Experimental Part: All reagents were purchased from commercial sources and used without any further purification. Technical solvents were used unless otherwise stated. Anhydrous solvents were obtained by passing solvent through columns of molecular sieves in a solvent purification system. Flash chromatography employed 230-400 mesh silica gel. Solvents used for chromatography are quoted as volume/volume ratios. Analytical thin layer chromatography was performed using silica gel plates precoated with silica gel 60 F254 (0.2 mm) using UV light and 10% ethanolic solution phosphomolybdic acid dip to visualize the products. ^{1}H NMR spectra were recorded at 298 K unless otherwise stated using Varian VXR (200 MHz) spectrometers. Data is expressed in parts per million (ppm) downfield shift from tetramethyl

silane with residual solvent as an internal reference (δ 7.26 ppm for chloroform) and is reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet = multiplet), coupling constant (*J* in Hz) and integration (number of protons). ^{13}C NMR spectra were recorded at 298 K unless otherwise stated using Bruker Avance III 100 MHz spectrometers with complete proton decoupling. Data is expressed in parts per million (ppm) downfield shifts relative to the internal reference (δ 77.2 ppm for the central peak of deuterated chloroform) and is reported as position (δ in ppm). IR spectra were recorded on a Perkin Elmer 688 spectrometer. Mass spectra were obtained on a Shimadzu QP 1000 spectrometer. High resolution mass spectra (HRMS) were recorded using electrospray ionization on a Time of Flight (TOF) mass spectrometer at National Taiwan University.

Lithocholic acid methyl ester (1): Dissolved the lithocholic acid (5.0 g, 13.2 mmol) in methanol (150 mL) and added PTSA (455 mg, 2.65 mmol) and stir at RT for 24 h. Removed the solvent on rota evaporator, extracted with ethyl acetate (100 mL X 2) and washed with 10% $NaHCO_3$ solution, brine solution, dried over $MgSO_4$ and filter. Concentrated under reduced pressure on rota evaporator to give a residue which was purified by column chromatography by using 30% ethyl acetate in hexane, to obtained 4.5 g of the product in 86% yield. Melting point is 128-130^oC. ^1H NMR (200 MHz, $CDCl_3$): δ 3.65 (s, 3H), 2.41-2.10 (m, 2H), 2.00-0.81 (m, 20H), 0.63 (s, 3H) ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.8, 71.6, 56.3, 55.8, 51.3, 42.5, 41.9, 40.2, 40.0, 36.2, 35.6, 35.2, 34.4, 30.8, 30.8, 30.3, 28.0, 27.0, 26.2, 24.0, 23.2, 20.6, 18.0, 11.8. IR (KBr): 1748, 1540, 1320, 925, 750. Mass: (*m/z*): 390 (M+).

5β-Cholane-3α-24-Diol (2) Dissolved the lithocholic acid methyl ester (5.0 g, 12.8 mmol) in 50 mL of THF and cool to 0°C. Added Lithium aluminum hydride (970 mg, 25.6 mmol) portion-wise over a period of 10 minutes. Heated at reflux for 4 h. Cool to room temperature and remove the solvent on rota evaporator. Extracted with ethyl acetate (100 mL X 2) and washed with 10% $NaHCO_3$ solution, brine solution, dried over $MgSO_4$ and filter. Concentrated under reduced pressure on rota evaporator to give a residue which was purified by column chromatography by using 30% ethyl acetate in hexane, to obtained 3.24 g of product in 70% yield. Melting point is 174-176°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.65 (s, 3H), 2.01-0.87 (m, 20H), 0.64 (s, 3H). Mass: (*m/z*): 362 (M+).

24-para-Toluene-sulfoxy-5β-Cholane-3α-ol (3) Dissolved the 5β-cholane-3α-24-diol (2.5 g, 6.9 mmol) in THF (15 ml) and cool to 0°C. Added 1.8 mL (1.4 g, 13.8 mmol, 2.0 eq) of triethylamine and followed by 2.63 g (13.8 mmol) of 4-Methyl-benzenesulfonyl chloride. Stirred and maintain at 4°C for 72 h. Remove the solvent on rota evaporator. Extracted with ethyl acetate (100 mL X 2) and washed with 10% $NaHCO_3$ solution, brine solution, dried over $MgSO_4$ and filter. Concentrated under reduced pressure on rota evaporator to give a residue which was purified by column chromatography by using 30% ethyl acetate in hexane, to obtained 1.0 g of product in 50% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 3.93 (t, 2H, *J* = 6.2 Hz & 12.4 Hz), 3.55-3.42 (m, 1H), 2.82 (br-s, 1H, OH), 2.37 (s, 3H), 2.00-0.81 (m, 20H), 0.53 (s, 3H). NMR (50 MHz, $CDCl_3$): δ 144.4, 133.0, 129.6, 71.3, 71.0, 56.1, 55.6, 42.3, 41.7, 40.0, 39.8, 35.9, 35.4, 35.0, 34.8, 34.2, 31.0, 30.0, 27.8, 26.8, 26.1, 25.2, 23.8, 23.0, 21.3, 20.4, 18.0, 11.6. Mass: (*m/z*): 516 (M+).

24-Iodo-5β-Cholane-3α-ol (4) Dissolved the 24-p-toluene-sulfoxy-5β-cholane-3α-ol (0.2 g, 0.383 mmol) in acetone (10 mL) and added 115 mg (0.775 mmol) of sodium iodide. Heated at reflux for 4 h. cool to room temperature and remove the solvent on rota evaporator. **E**xtracted with ethyl acetate (100 mL X 2) and wash with 10% $NaHCO_3$ solution, brine solution, dried over $MgSO_4$ and filter. Concentrated under reduced pressure on rota evaporator to give a residue which was purified by column chromatography by using 10% ethyl acetate in hexane, to obtained 165 mg of the product in 90% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.67-3.58 (m, 1H), 3.22-3.02 (m, 2H), 2.00-0.89 (m, 20H), 0.63 (s, 3H). NMR (50 MHz, $CDCl_3$): δ 71.5, 56.3, 55.8, 42.5, 41.9, 40.2, 39.9, 36.6, 36.1, 35.6, 35.2, 34.8, 34.3, 30.2, 30.1, 28.1, 27.0, 26.2, 24.0, 23.2, 20.6, 18.5, 11.8, 07.6. Mass: (*m/z*): 472 (M+).

1-Methyl-[4,4']bipyridinium iodide (5) Dissolved 4,4-Bipyridine (5) (2.5 g, 16.0 mmol) in dichloromethane and added (1 mL, 2.25 g, 6.0 mmol) of methyl iodide. Stirred at room temperature for 12 h. Yellow precipitate is formed. Filter to obtained solid, the filtrate mainly contains unreacted starting material. The solid product on recrystallization in ethanol at hot condition, give yellow solid in 90% yield. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.14 (d, 2H, *J* = 6.6 Hz), 8.86 (d, 2H, *J* = 6 Hz), 8.62 (d, 2H, *J* = 6.2 Hz), 8.04 (d, 2H, *J* = 6.2 Hz), 4.38 (s, 3H). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 151.9, 151.2, 146.3, 140.9, 125.1, 122.0, 47.8. Mass: (*m/z*): 171 (M+).

4α,6α-Dimethyl-7-[1-methyl-4-(1'-methyl-[4,4'] bipyridinyl-1-yl)-butyl]-octadecahydro-chrysen-2-ol (6) Taken (0. 2 g, 0.673 mmol) of 1-Methyl-[4,4']bipyridinium iodide **(5)** and 24-iodo-5-β-cholane-3-α-ol **(4)** (350 mg, 0.74 mmol) in acetonitrile (10 mL) and heated at reflux for

48 h. Pout into water, extracted with ethyl acetate to remove iodo compound and filter the aqueous layer to get 490 mg of solid in 95% yield. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.41 (d, 2H, *J* = 5.4 Hz), 9.26 (d, 2H, *J* = 5.4 Hz), 8.78 (t, 4H, *J* = 4.6 & 7.8 Hz), 4.68-4.58 (m, 1H,), 4.42-4.32 (m, 2H), 2.46 (s, 3H), 2.00-0.81 (m, 20H), 0.63 (s, 3H). Mass: (*m/z*): 768 (M+) (with iodo), 516 (without iodo). FAB: 516.

4-,4'-Dimethyl,2,2'-bipyridine (7): Charged 28 g of Pd/C into two neck-two-liter round bottom flask equipped with reflux condenser and pour 700 mL (665 g) of 4-picoline. Heated at reflux (250^{o}C) for 4 days and cool to 150^{o}C. Add 250 mL of benzene and heat at reflux (250^{o}C) for 1 h. Cool to 150^{o}C. Then filter through celite pad. The filtrate was distilled under vacuum on rota evaporator to get the residue (20 g). Dissolved the residue in 200 mL of acetone and added water (500 mL) to get precipitate. Filtered the precipitate and dry in vacuum to get 15 g of product in 1.15% yield. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.49 (d, 2H, *J* = 4.8 Hz), 8.20 (s, 2H), 7.24 (d, 2H, *J* = 4.8 Hz), 2.39 (s, 6H).

4'-Methyl-[2,2']bipyridinyl-4-carbaldehyde (8) Dissolved the 2.6 g (14 mmol**)** of 4,4'-Dimethyl,2,2'-bipyridine (**7**) in 1,4-dioxane (50 mL) and added 1.72 g (15.5 mol) of selenium dioxide. Heated at reflux for 24 h. Cool to 90^{o}C and filter the selenium dioxide to get the filterate-1. Cool the filterate-1 to room temperature and filtered to remove selenium dioxide and to get the fitlerate-2. The filterate-2 on concentration gives the residue. Dissolve the residue in ethyl acetate (250 mL) and filtered to get filterate-3. The filterate-3 was extracted with 1.0 M sodium carbonate (100 mL X 2) to remove the acid (side product), then washed with 0.3 M $Na_2S_2O_5$ (100 mL X 3). The aqueous layer was neutralized to pH = 10 by addition of solid,

sodium carbonate. Extracted with DCM (100 mL X 2) and wash with 10% $NaHCO_3$ solution, brine solution, dried over $MgSO_4$ and filtered. Concentrated under reduced pressure on rota evaporator to give 1.4 g of pure aldehyde in 50% yield. ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.20 (s, 1H), 8.91 (d, 1H, *J* = 5.0 Hz), 8.85 (s, 1H), 8.59 (d, 1H, *J* = 5.0 Hz), 8.29 (s, 1H), 7.74 (d, 1H, *J* = 5.0 Hz), 7.22 (d, 1H, *J* = 5.0 Hz), 2.47 (s, 3H). IR (nujol): 1736, 1690, 1665, 1630, 1595, 1556.

4'-Methyl-[2,2']bipyridinyl-4-carboxylic acid (9) Dissolved 1.4 g (7.0 mmol**)** of 4'- Methyl-[2,2']bipyridinyl-4-carbaldehyde **(8)** in ethanol (50 mL) and protect with aluminum foil. Added freshly prepared silver nitrate solution (1.4 g, 8.4 mol) in 10 ml of water). Added 570 mg (0.014 mol) of NaOH solution (in 10 mL of water) drop-wise over a period of 30 minutes. Stirred the reaction mixture in under dark place for 15 h, removed the ethanol and water from reaction mixture on rota evaporator to get residue. Dissolved the residue in 1.0 M NaOH solution (100 mL) and filtered to remove the silver oxide and metallic silver. Extracted with dichloromethane to remove unreacted aldehyde from aqueous layer. The aqueous layer on neutralized with 1:1 solution of 4N hydrochloric acid and acetic acid to get white gelatineous ppt. Stored in cool condition for overnight. Filtered the precipitate and dry under vacuum to get 840 mg of product in 55% yield. ^{1}H NMR (200 MHz, D_2O): δ 8.40 (d, 1H, *J* = 5.0 Hz), 8.16 (d, 1H, *J* = 5.0 Hz), 7.92 (s, 1H), 7.55 (d, 1H, *J* = 5.2 Hz), 7.43 (s, 1H), 7.04 (d, 1H, *J* = 4.8 Hz) 2.14 (s, 3H). Mass: (*m/z*): 215 (M+). IR (nujol): 1721, 1698, 1681, 1650, 1601, 1561.

COMPLEX-1 (10): Taken 70 mg (0.31 mmol) of 4'-Methyl-[2,2']bipyridinyl-4-carboxylic acid (9), HOBT (45 mg, 0.31 mmol), DCC (70 mg, 0.31 mmol) in DMF (5 mL) and stir under nitrogen

atmosphere for 6 h. Add 0.2 g (0.260 mmol) compound 6 and stir at room temperature for 24 h. During this time, precipitate is formed, and solution is turned to red in color. Removed the DMF solvent on rota evaporator to get residue and quenched the residue with water. Extracted with ethyl acetate to remove excess of reagents. Filtered the aqueous layer to remove urea side product formed and unreacted acid compound. To aqueous layer (contains essentially pure product) add ammonium hexafluoro phosphate to get precipitate, concentrated the aqueous layer to half of its volume and cool in freezer to and filtered to get 250 mg of solid product in 95% yield. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.38-9.28 (d, 2H, J = 20.0 Hz), 8.76-8.61 (m, 2H), 8.29 (s, 2H), 7.91 (s, 2H), 7.67 (s, 2H), 7.37 (s, 2H), 7.12 (s, 2H), 4.68-4.58 (m, 3H), 2.46 (s, 6H), 2.00-0.81 (m, 20 H), 0.63 (s, 3H). Mass m/z: 1000, 712 (M+), 647, 516 (100%), 495, 363, 251. IR (nujol): 1724, 1647, 1509, 1377, 1182, 834. $C_{47}H_{60}N_40_2$ $(PF_6)_2$ = 1000. **Solubility studies:** (a) Complex-1 soluble in water, DMF. Insoluble in ethyl acetate. (b) Acid soluble in DMF, insoluble in ethyl acetate, water. (c) DCC and HOBT soluble in ethyl acetate, DMF, and insoluble in water.

Ruthenium, bis(2,2'-bipyridine-kN1,kN1')dichloro (11): To a solution of 2.5 g (9.5 mmol,1.0 eq) of $RuCl_3.3H_2O$ and 2.75 g (61 mmol, 6.4 eq) of LiCl in 25 ml DMF was added 2.94 g (19 mmol, 2.0 eq) bipyridine at room temperature. Heated at reflux for 45 minutes, while continuously check the tlc for emission under uv lamp. Cool to RT. Poured into 100 mL of acetone. After cooling in freezer for 24 h, ppt is formed. Filtered and washed with water and acetone until pale color appeared. After 2 h dry in vacuum, obtained 1.9 g of product in 40% yield. Melting Point = 196-198^{o}C. Mass (m/z): 484 (M+).

Ruthenium, bis(2,2'-bipyridine-kN1,kN1')[carbonato(2-)-kO,kO']-, (OC-6-22) (12): charged 2.0 g (4.13 mmol) of compound **11** in 50 ml of water, heated at reflux under argon atmosphere for 15 minutes. Added 6.6 g (6.3 mmol) of sodium carbonate and heated at reflux for 45 minutes. Cool to RT and filtered, washed the solid with water and dry in vacuum for 2 h to obtained 1.3 g of product **12** in 67 yield. Mass: 474 (M+).

FINAL COMPLEX (13): Take Compound 10, (0.1 g, 0.1 mmol) and 52 mg (0.11 mg, 0.11 mmol) of ruthenium carbonate complex (12) in DMF (5 mL) and heat at 100°C for 6 h. Monitored by uv light. Clear solution is formed. Removed the solvent on rota evaporator to get residue. Dissolved the residue in water (clear solution is formed) and add ammonium hexafluoro phosphate to get precipitate. Filtered the precipitate and dry under vacuum to get 120 mg of the product. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.36 (m, 1H), 9.26 (m, 2H), 8.91 (m, 5H), 8.16 (m, 6H), 7.88 (m, 6H), 7.78 (s, 2H), 7.55 (s, 2H), 7.34 (s, 2H), 7.09 (s, 2H), 6.96 (s, 2H), 4.68-4.58 (m, 3H,), 2.46 (s, 6H), 2.00-0.81 (m, 20H), 0.63 (s, 3H). IR (nujol): 1734, 1685, 1647, 1508, 1376, 838, 720. Mass: (*m/z*): 1693, 1533, 1329, 1191, 1153 (M+), 1006, 860, 661, 561, 215, 145,117. FAB: 1190, 1173, 1056, 1005, 661, 154, 136. Solubility studies: Compound (10): soluble in DMF, DMSO, insoluble in methanol, ethanol, and sparingly soluble in acetonitrile. Ruthenium carbonate (12): water soluble, DMF sparingly soluble. Product (13): soluble in acetonitrile and DMSO. Insoluble in methanol, ethanol.

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■ Competing interests:

There is no Competing Interests pending

Reference:

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