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RESEARCH PAPER

Binding studies of ruthenium complexes with antithyroid drug

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Abstract: Medicinal substances are essential to our daily existence. A prudent approach to metal complexation with already available medications may result in more stylish, intelligent, and effective drug compositions. Thus, the binding of $[Ru(NN)_3]^{2+}$ (NN = 2,2ˈ-bipyridine, 1,10-phenanthroline) with the antithyroid medication thyronorm has been studied in the current attempt. The use of absorption and emission spectrum techniques allowed researchers to examine the complexes' interactions with antithyroid medications. Studies of absorption and emission spectra show that the complex and medication interact through coordinated ligand hydrophobic and hydrogen bonding interactions.Analysis has also been done on the binding of the antithyroid medication Thyronorm to ruthenium complexes. The Benesi-Hildebrand plot was used to determine the binding constants of the drug complexes. Current research indicates that the Thyronorm pill has good affinity with $[Ru(phen)_3]^{2+}$complex.

Keywords: *hormones, drug, antithyroid, Benesi-Hildebrand plot, Thyronorm, emission*

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INTRODUCTION

For many years, metals have been crucial to medicine. In varied amounts, many are necessary in human diets. Many manmade and natural substances function as highly potent medications. These substances are all biologically active in a variety of ways, including anti-bacterial, anti-fungal, anti-cancer, Apart from metallo antibiotics, some medications and prospective therapeutic agents also have metal-binding or metal-recognition sites. These sites have the ability to bind or interact with metal ions, hence possibly influencing their bioactivities by increasing or decreasing them. anti-tumorigenic, anti-viral, anti-inflammatory, anti-neoplastic, anti-HIV, and so forth. Certain metal ions that are harmful at greater concentrations can also be helpful for sustaining biological functions at lower quantities, and they can even be used to change some well-known medication molecules for the better.

Due to the various ways in which these medications affect the human body, they are frequently given. But these medications are also overused, which leads to an excessive concentration of them in the body, which is frequently unwanted. Metal ion complexation may have a beneficial or unfavorable impact on these substances' pharmacological action [1].

In addition to the metallo antibiotics, several medications and prospective pharmacological agents have metal-binding or metal-recognition sites that have the ability to interact or bind with metal ions to change (raise or reduce) the bioactivities of those ions. At lower concentrations, various metal ions that are poisonous at greater concentrations can also be helpful for sustaining life processes. They can even be used to change some well-known medication compounds for improved efficacy. Additionally, through their nutrition or various environmental conditions, humans are exposed to various metal ions. While some are hazardous in excess of

specific amounts, others are absolutely necessary for human health.

There are numerous pharmaceutical medicines that include metal ions that are now used in clinical settings, and new applications are being developed at a rapid pace [2]. A few of these are employed in biotransformation and targeting. The toxicity of the medication may be decreased if it is administered directly to the tissues, cells, and receptors where they are needed. The degree of ligand substitution and redox reactions that many metal complexes exhibit determines the complex's activity and potential for biotransformation. The more successful usage of metal compounds as medications will result from the identification of these active species. The relationship between metal ions and antibiotics has drawn special attention when discussing drug-metal ion interactions in biological systems. Numerous medications have altered pharmacological and toxicological characteristics when given as metallic complexes. In this regard, transition cations are perhaps the ones that have been investigated the most [3-6].

The medical benefits of naturally occurring compounds like chromones, flavonoids, and coumarins have long been recognized. These benefits include treating diabetes mellitus, preventing heavy metal poisoning, β-thalassemia, Friedreich ataxia, HIV, viral infections, spasmolytic disorders, Wilson's disease, Menkes' disease, lymphocytic leukemia, and HL-60 promyeocytic leukemia cell lines. They have anti-inflammatory, anti-allergenic, anti-thrombotic, antiviral, antibacterial, and anti-carcinogenic properties. These coumarins, flavonoids, and chromones all have strong chelation affinity for iron (III) and copper (II). Plants include non-nutritive substances called flavonoids, which have a wide range of pharmacological effects. One of the most prevalent naturally occurring flavonoids, quercetin (3', 3, 4', 5, 7-flavine), can be found in a variety of fruits and vegetables.

According to reports, organic ligands with nitrogen, oxygen, or sulfur exhibit a variety of biological activities. This could be because these ligands are involved in the donor sites of bioactive medicines. It is well known that acid hydrazides with nitrogen and oxygen donor sites have antibacterial, anti-tubercular, and anti-inflammatory properties.

One of the biggest challenges in the production of medicinal medicines is typically poor water solubility. Using co-solvents is one method frequently employed to improve the solubility of poorly soluble medications [7-8]. Other factors like selection of salt form [9-10], increase of specific surface area by reduction of particle size [11], complex formation with excipients such as hydrophilic polymers and cyclodextrins [12-13], change of crystal form (polymorphism/amorphism)affect the production of a drug.

Ruthenium coordination and organometallic chemistry have seen tremendous expansion and assessment in recent years. Ruthenium-based compounds and their applications in medicine, catalysis, nanoscience, redox, and photoactive materials have been the subject of several publications in recent years. Since the last 30 years, ruthenium polypyridyl complexes have been the subject of extensive research because of their exceptional photophysical and stability characteristics.After Paris and Brandt discovered the luminescence of $[Ru(bpy)_3]^{2+}$(bpy-bipyridyl) in 1959, a great deal of effort was done. These complexes may find use in the advancement of solar energy conversion, luminescence, and electron and energy transfer. These luminescent complexes are used as photocatalyst [14-15], sensors for biomolecular [16-19], phototherapeutic agents [20-21].They are used in chemotherapy [22]

Thyronorm is a basic polyol substance. It is a thick, colorless, odorless, sweet-tasting, and non-toxic liquid. It is extensively utilized in FDA-approved wound and burn therapies because of its antibacterial and antiviral qualities. It is also a useful marker for assessing liver disease. It is also frequently employed in medicinal formulations as a humectant and as a sweetener in the food sector. Thyronorm is hydroscopic by nature and somewhat miscible with water. The synthesis of Ruthenium(II) complexes with the ligands 1,10-phenanthroline and 2,2ˈ-bipyridine is the focus of this work. The complexes' photophysical characteristics were examined. Binding of these metal complexes with antithyroid drug Thyronorm were studied and the efficiency of binding of drug with the metal complexes were calculated using binding constants both by absorption and emission spectrophotometric methods

MATERIALS AND METHODS

Materials

Sigma Aldrich provided the ligands 1,10-phenanthroline and 2,2ˈ-bipyridine. We bought the medication Thyronorm from East West

Pharma, India, Pvt Ltd. Double-distilled deionized water was used for the binding experiments. Reagent-grade chemicals and solvents were utilized exactly as supplied.

Synthesis *of Tris (2,2'-bipyridine) Ruthenium (II) Chloride, $[Ru(bpy)_3]Cl_2$*

After dissolving 0.5g of $RuCl_3$ $3H_2O$ and 0.6g of 2, 2-bipyridine in 25 mL of ethanol, the mixture was refluxed for 20 hours.The orange-red complex that was produced as a result stayed in the ethanol solution. Using n-propanol as the eluent, the crude product was purified on a silica gel column. Following further evaporation, the pure complex was obtained [23].

Synthesis of Tris(1,10-phenanthroline) Ruthenium (II) Chloride, [Ru(phen)3]Cl2

After dissolving $RuCl_3.3H_2O$ (0.6 g, 3 mmol) in 50 mL of ethanol with a single drop of HCl, 1.6 g, 9 mmol) of phenanthroline was added gradually while stirring. For forty hours, the mixture was refluxed. After the mixture is filtered, 10 mL of 6N HCl is added to the heated, filtered solution dropwise while stirring. The volume of the solution is lowered by evaporation until a crystal forms if no solid has yet formed. Using hot water, the crude product was recrystallized. $\lambda^{ab}{}_{max}$ = 446 nm and $\lambda^{em}{}_{max}$ = 576 nm are the values of the absorption and emission maxima.

Equipment

SYSTRONICS 2203 Double beam spectrophotometer was used for the absorption spectral measurements of the $[Ru(bpy)_3]^{2+}$ and $[Ru(phen)_3]^{2+}$ complexes as well as the binding studies of the produced complexes with antithyroid medicine thyronorm. Each and every spectral measurement was done at ambient temperature. The FP-8200 Spectrofluorometer from JASCO was used to record the emission readings.

Determination *of Association constants using absorption and emission techniques*

The association constants (K_a^{abs})of the $[Ru(NN)_3]^{2+}$ complexes with antithyroid drug in homogeneous medium were calculated using Benesi – Hildebrand method (eqn 1) [24].

$$\frac{1}{\Delta A}=\frac{1}{K_a^{abs}}\Delta\varepsilon[H]+\frac{1}{\Delta\varepsilon}[Q] \quad (1)$$

Here, [H] represents the host (sensitizer) concentration, [Q] the guest (thyronorm) concentration, and ∆A the change in [H] absorbance upon the addition of [G].The molar extinction coefficient is got by taking the difference of the free [H] and [H]-[G] complexes.∆. Plotting 1/ ∆A against 1/[G] values for all the guest molecules under investigation yields a good straight line that supports the creation of a 1:1 complex. The ratio of the Y-intercept to the straight line's slope yields the association constant

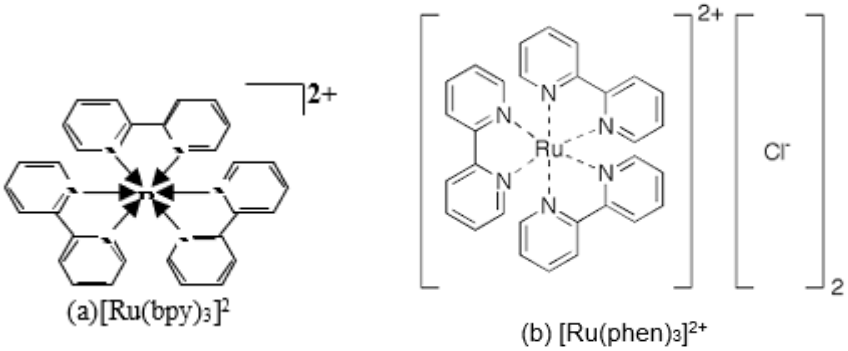
Using the luminescence intensity data, the association constant for the system were calculated by the following modified Stern - Volmer equation (eqn 2)

$$\log[(I_0- I) / [I]= n\log[G]- \log K_a^{em} \quad (2)$$

where Io, I, [Q], K_a^{em}, and n stand for the drug concentration, binding constant, stoichiometric ratio, emission intensity in the presence of the drug, and emission intensity in the absence of the drug, respectively.

RESULTS AND DISCUSSION

Fig. 1 depicts the structure of the synthetic complexes employed in this investigation.



(a)$[Ru(bpy)_3]^2$ (b) $[Ru(phen)_3]^{2+}$

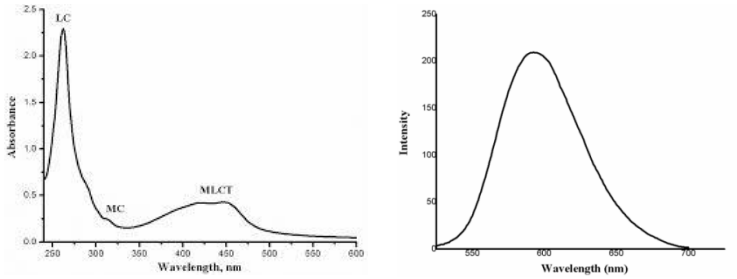
Figure.1 Structure of the Ruthenium complexes (a) $[Ru(bpy)_3]^{2+}$ (b) $[Ru(phen)_3]^{2+}$ used for the present study.

Measurement of absorption and emission spectrum

Because of its photophysical and excited state characteristics, ruthenium complexes are the most researched complexes. In an aqueous solution, $[Ru(bpy)_3]^{2+}$ exhibits an absorption maximum at 453 nm and an emission maximum at 596 nm. Triplet metal to ligand charge transfer state (^{3}MLCT) is the lowest excited state of $[Ru(bpy)_3]^{2+}$. Three closely spaced, equilibrium excited states that are discernible at 5K but in equilibrium at and above 77K combine to form the lowest ^{3}MLCT. In an aqueous solution, the maximal absorption and emission wavelengths for the $[Ru(phen)_3]^{2+}$ complex are 447 nm and 576 nm, respectively. The antithyroid medicine reaches its peak absorption at 232.4 nm.

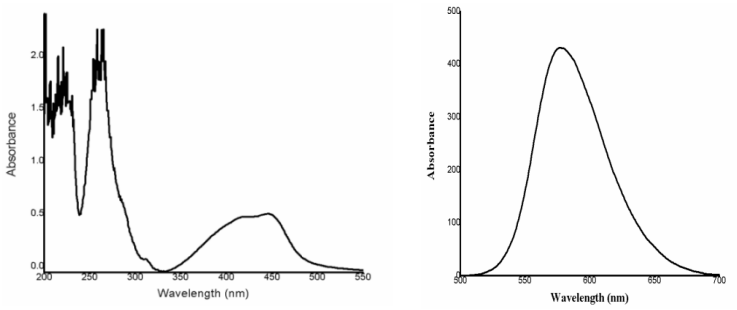
Table 1. Photophysical properties of $[Ru(NN)_3]^{2+}$ and Thyronorm in aqueous medium.

Complexes	Absorption maximum (nm)	Emission Maximum (nm)
$[Ru(bpy)_3]^{2+}$	453	596
$[Ru(phen)_3]^{2+}$	447	576
Thyronorm	246,491	519



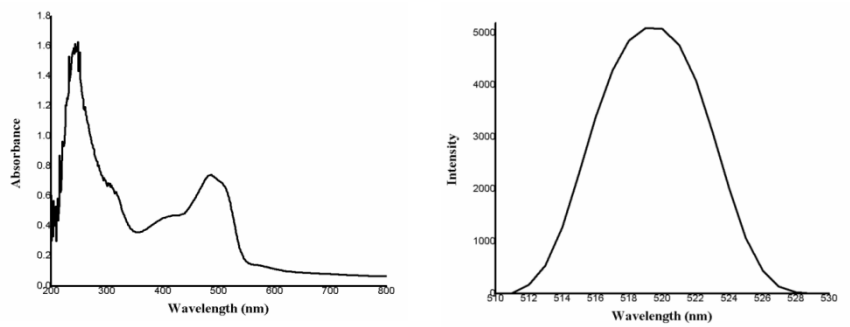
(a) (b)

Figure 2. (a) Absorption and (b) emission spectrum of $[Ru(bpy)_3]^{2+}$ complexes in aqueous medium



(a) (b)

Figure 3. (a) Absorption and (b) emission spectrum of $[Ru(phen)_3]^{2+}$ complex in aqueous medium



(a) (b)

Figure 4. (a) Absorption and (b) emission spectrum of Thyronorm

The Ru(II) complexes emission maximum arises from the dπ-π* ^{3}MLCT transition. The absorption and emission spectra of the room-temperature $[Ru(bpy)_3]^{2+}$ and $[Ru(phen)_3]^{2+}$ complexes in an aqueous solution are displayed in Figures 2 and 3.

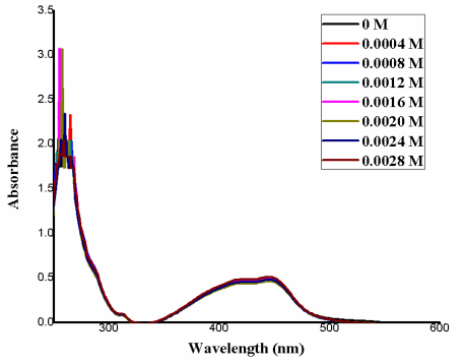
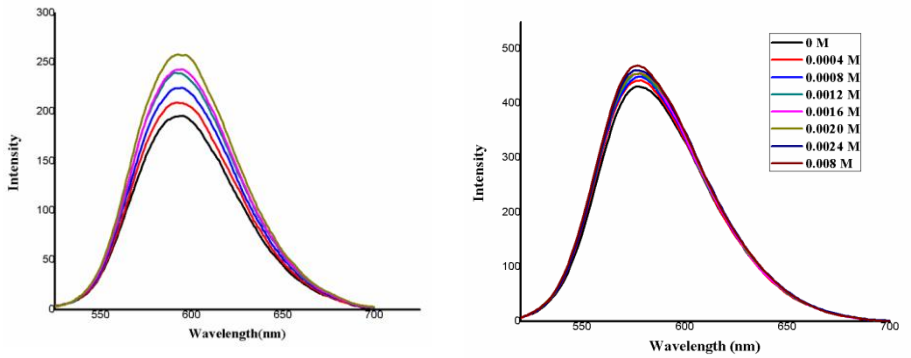


Figure 5. Absorption spectra of $[Ru(phen)_3]^{2+}$ complex with incremental concentration of the drug Thyronorm in aqueous medium at room temperature.



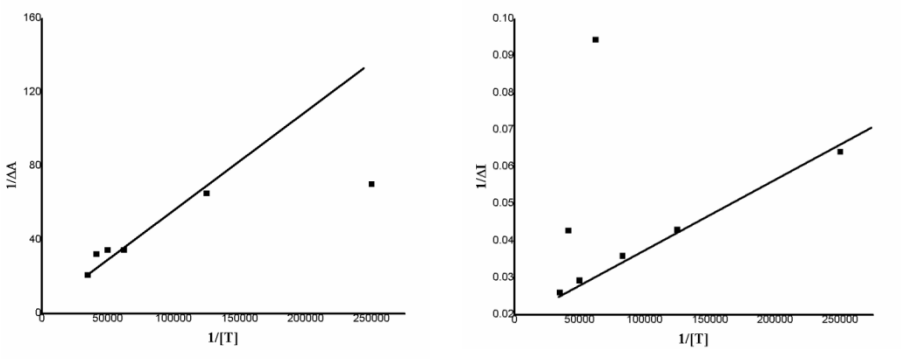
(a) (b)

Figure 6. Emission spectra of (a) $[Ru(bpy)_3]^{2+}$ and (b) $[Ru(phen)_3]^{2+}$ complexes with incremental concentration of the drug thyronorm in aqueous medium at room temperature.

Table 2. Absorption maximum of the [Ru(bpy)3]2+ complex(C1)with incremental addition of Thyroxine drug (T) in aqueous medium.

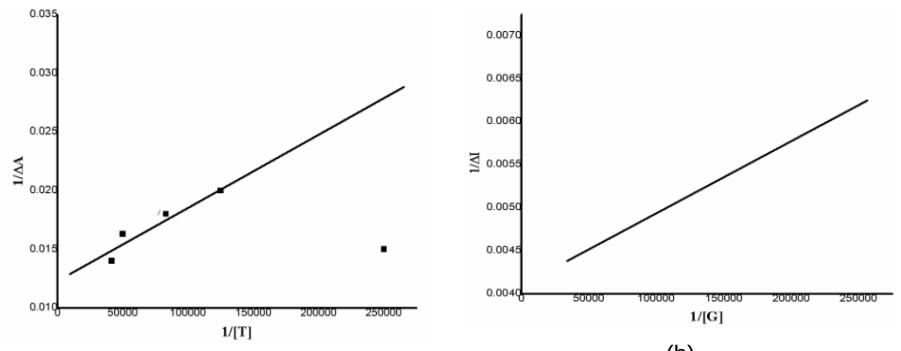
Name	[T] x10^{-5}	1/[T]	Absorbance	$\Delta A=A_0-A$	1/ΔA
C_1T_{11}	0		0.483		
C_1T_{12}	0.4	250000	0.506	0.005	200.00
C_1T_{13}	0.8	125000	0.507	0.005	200.00
C_1T_{14}	1.2	83000	0.481	0.006	166.66
C_1T_{15}	1.6	62500	0.507	0.029	34.482
C_1T_{16}	12.0	50000	0.464	0.029	34.482
C_1T_{17}	2.4	41600	0.483	0.031	32.258
C_1T_{18}	2.8	35714	0.512	0.048	20.833

Binding of the drugs with various metal complexes are calculated using these data got from absorption as well as emission spectral data. The concentration of the metal complex was kept fixed and the drug concentration was varied such that the total volume of the drug metal complex solution was kept as 5 mL. Measurements of absorption and emission were made for a range of complicated drug concentrations. The change in absorbance were calculated for the absorption measurements. For the emission spectral data, the change in emission intensity were also calculated. Using these calculations, the binding constant for the drug-metal interaction were found out. This is done using the Benesi-Hildebrand plot [25]. The Benesi-Hildebrand plot for the metal drug complex are shown using both the absorption as well as emission measurements. The binding constants for these plot were calculated by taking the ratio of the intercept and the slope. The data are shown in Table 3.This table shows that both absorption as well as emission binding studies were carried out. From the graph, both the slope and intercept were calculated.Their ratio gives the binding constant value.



(a) (b)

Figure 7, Benesi-Hildebrand plots from the (a) absorption and (b) emission spectrum for the binding of $[Ru(bpy_3]^{2+}$ with incremental addition of thyronorm in aqueous medium



(a) (b)

Figure 8. Benesi-Hildebrand plots from the (a) absorption and (b) emission binding of $[Ru(phen)_3]^{2+}$ with incremental addition of Thyronorm in aqueous medium .

Figures 7 and 8 display Benesi-Hildebrand graphs made from the absorption and emission spectrum data for the $[Ru(bpy)_3]^{2+}$ and $[Ru(phen)_3]^{2+}$ complexes with the medication added incrementally in an aqueous medium.

Table 3. Binding constant, K_b (M^{-1}) from for the drugs with $[Ru(NN)_3]^{2+}$ complexes in aqueous medium using absorption spectral data.

Complex		**intercept**	**Slope**	**K_b (M^{-1})**
$[Ru(bpy)_3]^{2+}$	uv bind	17.577	13.5×10^{-4}	1.302×10^4
	Emission bind	0.0387	0.01×10^{-5}	3.860×10^5
$[Ru(phen)_3]^{2+}$	uv bind	0.0314	0.01×10^{-4}	1.853×10^4
	Emission bind	15.07	3.56×10^{-6}	4.223×10^6

Based on the integrated absorption and luminescence intensity emitted by the metal complexes in the presence of different drug concentrations, the binding constant (K_b) for the formation of adducts between the drug Thyronorm and photoexcited Ru(II)-complexes is given in Table 3. The binding constant K_b (M^{-1}) values obtained for the drugs with $[Ru(NN)^3]^{2+}$ complexes in aqueous medium are in the range of 10^4-10^6 M^{-1}.

These data show that the antithyroid tablet has more binding affinity for the $[Ru(phen)_3]^{2+}$ complex. These studies show that the bioavailability of the drugs can be enhanced by complexing them with metal complexes. Thus it is a boon to use these metal complexes to enhance their solubility of poorly soluble drug in water.

CONCLUSION

Medicinal substances are essential to our daily existence. With a few outliers, metal ion complexation has consistently demonstrated this. A prudent approach to metal complexation with already available medications may result in more stylish, intelligent, and effective drug compositions. The current review will motivate researchers in

pharmaceutical science to use novel metal complexes in order to improve therapeutic action creation. Ruthenium complexes containing 2,2'-bipyridine (bpy) and 1,10-phenanthroline (phen) have been the subject of much research because of their intriguing biological and physico-chemical characteristics. These complexes are utilized in the production of innovative chemotherapeutics and photochemical reagents, which serve as new diagnostic instruments. They act as oxidizing reagents and show high biological activity. Therefore in the present attempt, the binding of $[Ru(NN)_3]^{2+}$ (NN = 2,2ˈ-bipyridine, 1,10-phenanthroline) with antithyroid drug has been investigated. These complexes' photophysical and photochemical characteristics are examined, and specifics about the electronic absorption and emission spectrum measurements are provided. The binding of drug molecules Thyronorm with the Ruthenium(II) complexes have been studied. The details of the evaluation of binding constants are explained. The calculation of binding constants both by absorption and emission spectrophotometric methods were shown. Binding constants were evaluated by plotting Benesi-Hildebrand plot. So these studies reveal that poorly soluble drugs can be complexed with metal polypyridyl complexes and can be administered so that their solubility is quiet enhanced. Our present investigation show that the antithyroid tablet has a good affinity with $[Ru(phen)_3]^{2+}$ complex. So the Ruthenium polypyridyl complex can be used to bind with the drug,so that the bioavailability of the drug can be increased.Also these complexes are non-toxic and eco friendly.

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CONFLICT OF INTEREST

Conflicts of interest are not disclosed by the writers.

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