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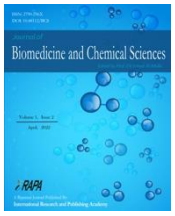

Design and Synthesis Ligands Tetradents Substituted with Halogenes in α- Position and Conjugation with Riboflavin (Bioconjugates):

Conjugate ligands Type TPA's with Flavonoids as un Electron Mediator

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ABSTRACT

In this article, we describe the process of binding riboflavin to a simple tetradents ligand substituted in α- position from TPAs types, by reacting bromotetraacetate riboflavin with α- substituted TPA with one of the pyridine rings by nitrile group and the two other pyridine rings by halogen atoms. This type of ligands showed very important properties for the activation and transfer of oxygen to a substrate in presence of iron salt. After the tetradents were obtained, the nitrile group was reduced to an amine group where it reacts with Boc group to protect one of the amine hydrogen and then bound to the bromotetraacetate through the amine group under special reactive conditions, to form the α-8-TPAs N- Ac4riboflavin ligands. This compound can be described as a molecular tweezers in which the flavin moiety acts as a potential electron mediator.

1. Introduction

In recent years, various iron(II) complexes with TPA-type ligands (chelates) have been intensively studied, and structural changes that make it possible to control the three-dimensional structure of the complex through many syntheses are to be carried out. Another example that is well studied in biological systems is tryptophan hydroxylase. It catalyzes important steps in serotonin biosynthesis and plays an important role in rhythms neurobiology (Malek et al., 2007; Malek et al., 2005). Recently, the complexes of these conjugates (or chelates) and their various functional derivatives have been examined, some of which have given functional analogues to some non-heme iron enzymes, which fall within the domain of activation of molecular oxygen, taking into account that in most cases hydrogen peroxide is used as an agent. Oxygen giver (Blackman, 2005; Malek et al., 2004; Malek & Labban, 2019). Also, during the last decade, iron(II) complexes with TPA-type ligands with multiple substituents have been extensively analysed (Tyeklar et al., 1993) despite the use of molecular oxygen but it should be noted that it only reacts with iron(II), which is bound to the substrate and plays a role in activating minerals such as catechols and thiols (Chuang, 1997; Offermann, 1980).

Attempting to mimic biological systems that carry out biomediated reactions to achieve chemical reactions under gentle conditions (Prévot-Halter et al., 1997) presents a major challenge to chemists. The process of designing, modifying and controlling biological systems was investigated in an attempt to imitate the natural heritage using the technique of assembling biomolecules and linking them to previously synthetic chemical molecules well, through organic synthesis reactions, which allowed chemists to make modifications to the structures of proteins and led to the design of synthetic enzymes . Some unexpected data resulting from these modifications in the structure of proteins allowed the discovery of new classes of enzymes.

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For example, flavin analogs are well known to mediate reactions such as the oxidation of tertiary amines, sulfides, and ketones, and hydroperoxide is generally used as an intermediate in oxidation (Romary et al., 1968; Harata et al., 1995). Also, some cases in which molecular oxygen is used have been observed (Chuang, 1997).

2. Materials and Methods

The aim of the present research is to activate one of the free sides present in riboflavin, which does not hinder its binding to molecule in an attempt to achieve the oxidation reaction of Dihydro Nicotineamide Figure 1the small protein (papain), which represents the biological.

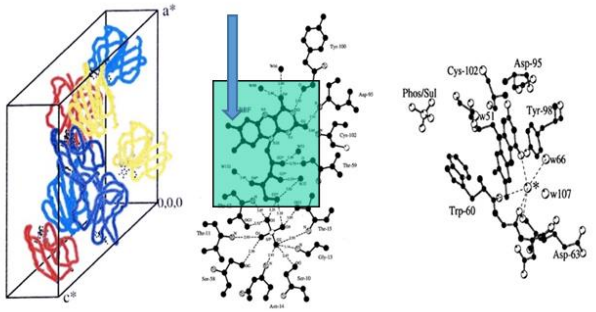


Fig. 1. X-ray steric structure of the apoflavodoxin/riboflavin complex

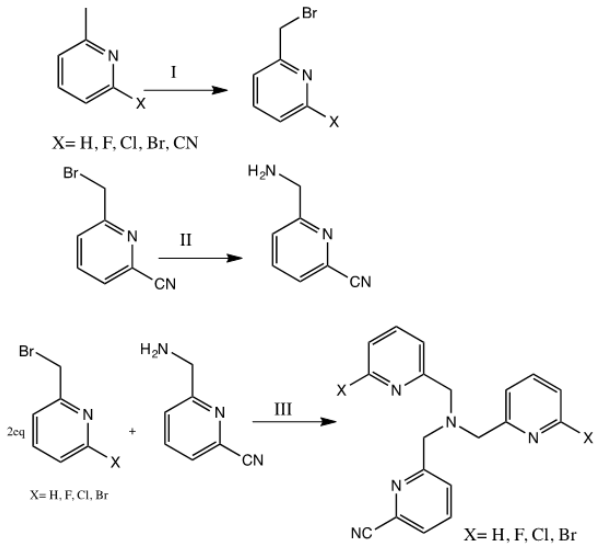
Figure 1 shows X-ray steric structure of the apoflavodoxin/riboflavin complex present in Desulfovibriovulgairs (Caprio & Mann, 1998), according to Hildenborough, which show a free methyl group (indicated by the arrow), which can form a binding point for the riboflavin metal complex by bromination of the methyl group to obtain bromoriboflavin and linked to the metal centre.

The subject of this study is the design of tetradents TPA's and their binding with riboflavin. These ligands replaced by the α- position have been well examined and two very important factors affecting the activity of these complexes in activating of oxygen molecular have been identified. The effect of these bonds on the metal center is summarized by two main factors: the first is a steric factor, where the size of the replaced groups at α- site helps determining the pentagonal or hexagonal coordination pattern, depending on the size of the functional groups replaced at α- site. As for the second factor, is the electronic factor through which it can be added electron-donating groups, or electron-withdrawing groups, this will raise in turn the Lewis acidity of the metal center according to the type of the substituted, which in this study are halogens, as it has an indirect steric effect depending on the size of the halogen atom substituted in the α-position (Shuman et al., 1990; Harata et al., 1995). The first example of this binding to the heme molecule was investigated shortly as an example of a semi-synthetic hydroxylase enzyme. Previously, the equivalence of binding between riboflavin and protoporphyrin IX was investigated in detail, allowing the reactive activation of molecular oxygen by artificial myoglobin (Offermann & Vögtle, 1980; Pueyo et al., 1996). In this example, the protein is bound to the porphyrin / flavin complex on the porphyrin side. Flavin derivatives can bind to proteins via flavin itself. The ability of flavins to bind to low-latency electron carriers such as flavin proteins to form stable complexes is well known in scientific libraries (Tyeklar, et al., 1993).

3. Results & Discussion

The biggest challenge lies in the design and manufacture of the ligands and adding modifications to the structure that allow controlling the steric geometry of the complexes in terms of determining the five or hexagonal chelation pattern, and controlling the multiple properties of the ligands (linkers) in terms of controlling the acidic properties of the mineral centre (Lewis acid) in terms of increasing or decreasing acidity, which allowed By activating molecular oxygen by biomimetic methods in biological mechanisms by activating the metal center of the complex (Thallaj et al., 2007-2008; Machkour et al., 2004; Murray et al., 2003). Studies have shown the clear effect of halogen substitution, which increases the reactivity of the metal centre with molecular oxygen, since the halogen atoms represent electron-withdrawing groups, which increases the acidity of the metal centre (Machkour et al., 2004; Thallaj, 2021), which represents the electronic action to activate this type of interaction, while The presence of groups with a stereotyped or electron-donating action leads to the slowing down of this type of interaction (Walker et al., 1972; Walsh et al., 1998). The redox potential of the synthesized ligands were measured using voltammetry and all the synthesized compounds were studied by 1H and 13C, 19F NMR spectroscopy and analyzed by elemental analysis and used mass spectrometry when necessary.

The ligands substituted at the α- position for the hydrogen atom are prepared by obtaining the bromine derivative, followed by converting the bromine derivative containing the nitrel group substituted on the α- position to the corresponding amine by synthesizing Gabriel and then reacting the product with two equivalents of the bromine derivative of the group of compounds The halogens (fluorine, chlorine, bromine) are substituted at α- position as shown in Scheme 1.

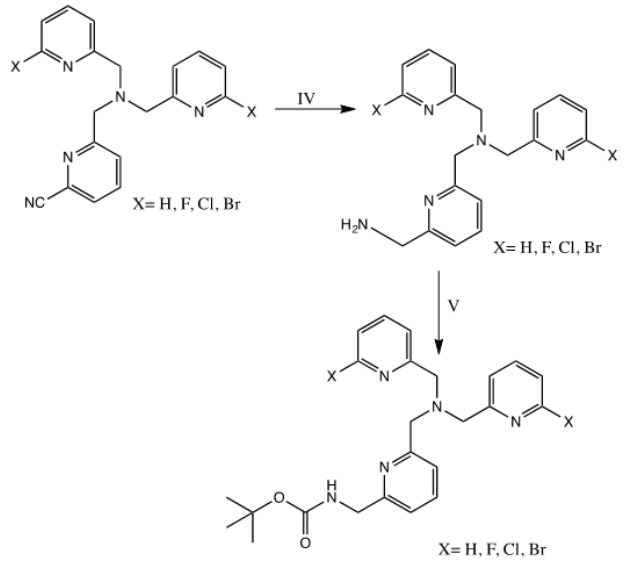


Scheme. 1. Preparation of the ligands manufactured in this study starting from the raw materials

I: Reaction in carbon tetra chloried, NBS, dibenzoylperoxyde, reflux,80 oC, 4h.

II: a) Potasum phtalamid, $NaHCO_3$, reflux, 6h, b) HBr (48%), reflux, 15h.

III: Reaction in ethanol, Na_2CO_3, reflux, 90 °C, 16h.

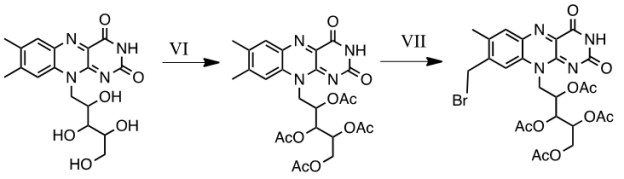


Scheme. 2. The process of reducing the nitrile group to a primary amine and then the process of protecting the amine group by using the appropriate protection group for this case (Boc).

IV:Reaction in ether (diethyl ether)$LiAlH_4$, r.t,24h.

V: $(Boc)_2O$, NaOH , H_2O, 25°C,30min.

After the ligands were synthesized and protecting one hydrogen from the amine group, we now prepare riboflavin for the process of linking it with these ligands, where we protect the goliath groups in riboflavin by reacting with acetic acid to form riboflavin acetate, and then we do the bromination reaction methylation to form bromo-riboflavin acetate according to Scheme 3.

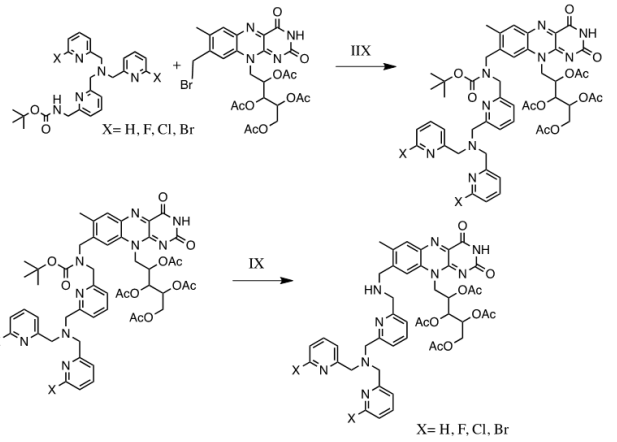


Scheme. 3. Preparation of riboflavin to binded with ligands prepared from TPAs.

VI: Reaction in AcOH, (Ac)2O, $HClO_4$, 1h.

VII: Reaction in deoxan, dibenzoylperoxid, Br2 in CCl4, relux.20min

Scheme 4 shows the process of binding of TPAs with riboflavin to form the ligand complex (TPAs/riboflavin) (Thallaj et al., 2007; Walker et al., 1972) where this reaction took place using TPAs with 8 α- bromo tetraacetate riboflavin (Mandon et al., 2002) in a solvent is dry DMF for 24 hours as the process used in the preparation reaction of 8 α- N imidazolyl riboflavin has been acclimatized (Machkour et al., 2004). The solution was evaporated and orange-brown compounds were obtained by re-deposition process from a mixture of carbon dioxide with diethyl ether (CH2Cl2/ Et2O). We get these compounds with yields ranging from 50-55%.



Scheme. 4. Binding of ligands (linkers) with 8 α- bromotetraacetate riboflavin IIX: Reaction in DMF, NaH,1h r.t, then ligands added. IX: (Cleavage) HCl 3N in EtOAc 25°C, 30 min.

It is worth mentioning here that to decode the protection groups, which here are four acetate groups, we use the traditional method i.e. we use potassium carbonate K2CO3 in a medium of dry ethanol for 48 hours with stirring and we modify the medium using ion exchange resin (sulfonated polystyrene), which is of the type Amberlite IR- 120 exchange resin, which allows us to loosen the protective group on the amine protected by a (Boc) group if we want to keep the protective group to the end, as shown in Scheme 4, the resulting compounds are brown in color with most of the organic solutions, but here in this study we chose to keep the Protection groups and we will not break these groups unless we want to bind with the protein, which we will do in the near future.

Study of the oxidation potentials of the ligands (linked) separately and of riboflavin:

All measurements were made with acetonitrile solution at room temperature, cell velocity 200mV/Sec. Electrolyte used is (TBAPF6 0.1M) electrodes made of platinum, ECS.

For each of these bonds, we get an irreversible wave responsible for the oxidation of the central amine in the bonds, knowing that we used ferrocene/ferrocenium as a reference for comparison, which gives a reversible wave at E1/2=0.382 as shown in Table 1. It is noted that with an increase in the electronegativity of a halogen atom, the oxidation potential increases For the central amine in the double-substituted bonds with two halogen atoms on the site α- with two pyridine rings, where the ligand replaced by two fluorine atoms has the highest oxidation potential, which corresponds to the use of these bonds, an increase in Lewis acidity on the metal center used, which is reflected in the complex's effectiveness on activating molecular oxygen, and transferring it to substrate.

Table 1
Values of oxidation potentials measured for tetradental ligands (tetradents) riboflavin tetraacetate shows a reversible return wave at E1/2 = –0.770 V, Using the same conditions as above.

	TPA	TPABr2	TPACl2	TPAF2
Ea (V/ECS)	1.118	1.206	1.221	1.236

The ligands were synthesized from the type of double-substituted TPA's at the α- position with two halogen atoms, and these ligands were previously studied, and the related

results have been published in terms of formation of complexes with different iron salts and the type of pentagonal or hexagonal support (Machkour et al., 2004; Miyaura et al., 1981). These studies have shown the important role of this type of binding in activating the mineral center according to the biological mechanism and not according to the mechanism of free radicals. Also, the activation of molecular oxygen and its transfer to a substrate of alkanes and the conversion of cyclohexane to cyclohexanone and cyclohexanol were studied (Thallaj et al., 2005), and thus this type of ligand and its complexes are effective towards the activation and transfer of molecular oxygen to the substrates. In many of these studied cases, we were able to restore the mineral center after the oxidation process by amalgamation of zinc and mercury. The flavin/flavodoxin complex can function as a single electron carrier within a domain close to the potential of the hydrogen pathways, allowing the structure of the riboflavin-bound moiety to be modified. Thus, we can add electron-withdrawing or electron-donating groups if we have established the steric factor and we have studied the electronic factor, and we can prove the electronic factor and modify the steric structure and then make modifications that allow the development of the electronic factor in accordance with the objectives of the studies to be applied to this type of industrial enzymes, and we can To do both operations at the same time.

A complex has been prepared in which the ligands are of the type (Tridents) DPA and its derivatives valence-linked with riboflavin, which plays an important role as an electron carrier for oxidation and reduction processes. The flavin/ligand model is a synthetic conductor, and to our knowledge there are only a few examples and an article was published in 2007 linking this type of ligand with biological conductors of the riboflavin type (Murray & Swenson, 2003).

3.1. Experimental Section

2-halogen-6-bromomethylpyridine : X= H, Br,Cl,Br,CN.

(57 mmol) commercially available 2-halo-6-methylpyridine (it is 6-methylpyridine in the absence of a halogen substitute) is dissolved in 200 mL CTC, then 10.14 g (56 mmol) of (N) is added. -bromo-succinimide, NBS) and an amount of bromination initiator which is benzoyl peroxide is added to the mixture, then the reaction mixture was placed by reflux for 5 hours at a temperature of 90 ° C. The mixture is cooled after the specified period has elapsed, then filtered to separate the solid from the solution and the solution is evaporated. The compounds are separated using column chromatography using silica (column dimensions are 4 cm in diameter and 45 cm in height). = 0.49), (for the chlorine derivative R_f = 0.43), (for the bromine derivative R_f = 0.39), (for the cyano derivative R_f = 0.45) Toluene is used as a carrier liquid in the separation column and in tracking the separation process by thin layer chromatography, by the end of the process we get 48% yield as a white solid the color..

fluoride derivative:

Elemental analysis:C_6H_5NBrF : :calculated %: C: 37.93; H: 2.65; N: 7.37.

Analysis results:%: C: 37.60; H: 2.21; N: 7.17.

^{1}H NMR : ($CDCl_3$, δ, ppm) : 7.78, 1H, dd, $^3J^{HH}$ = 8.05 Hz, $^3J^{HF}$= 7.05 Hz; 7.30, 1H, dd, $^3J^{HH}$= 7.32 Hz, $^5J^{HF}$ = 2.20 Hz; 6.85, 1H, dd, $^3J^{HH}$= 8.23 Hz, $^4J^{HF}$ = 2.74 Hz; 4.44, 2H,s.

^{19}F NMR : ($CDCl_3$, δ, ppm) : -66.88 ppm, $^3J^{FH}$ = 7.05 Hz.

Chloride derivative:

Elemental analysis: C_6H_5NBrCl : calculated %: C: 34.90; H: 2.44; N: 6.78.

Analysis results %: C: 34.80; H: 2.40; N: 6.73.

^{1}H NMR, : ($CDCl_3$, δ, ppm) : 7.66 (t, CH_γ, 1H), 7.38, (d, $CH_{\beta'}$,1H), 7.25 (d, CH_β, 1H); 4.48, (s, CH2, 2H).

bromide derivative:

Elemental analysis:C_6H_5NBrBr :calculated %: C: 28.72; H: 2.01; N: 5.58.

Analysis results %: C: 28.66; H: 1,98; N: 5.53.

^{1}H NMR : ($CDCl_3$, δ, ppm) : 7.7(t,1H,CH_γ) -7.35, (dd,1H,CH_β) 7.3, (dd,1H,$CH_{\beta'}$) H_{arom}, m; 4.41, 2H, s.

Nitrile derivative

Elemental analysis: $C_7H_5N_2Br$: calculated %: C: 42.67; H: 2.56; N: 14.22.

Analysis results %: C: 42.64; H: 2.53; N: 14.19.

^{1}H NMR, δ, ppm, $CDCl_3$: 7.86(t,1H,CH_γ); 7.69(dd,1H,$CH_{\beta'}$); 7.62(dd,1H,CH_β); 4.55(s,2H,CH_2).

6-(aminomethyl)picolinonitrile

Dissolve (29.7 mmol) of 2-cyano-6-bromomethylpyridine in 50 mL of DMF, add 11.8 g (63.9 mmol) of potassium phthalamide, and then add 6.38 g (73.7 mmol) of acidic sodium carbonate. The mixture is placed by reflux distillation for 3 hours, then it is left to reduce its temperature to room temperature, after which the mixture is filtered and the white solid compound is separated from the filtrate, which is taken and the solution is evaporated from it, then the distilled water is gradually added until a white precipitate is formed that is filtered and this precipitate is the phthalamide derivative of the required compound. To the white precipitate is added 150 ml of hydrogen bromine (48%) and the mixture is placed under reflux for 15 hours. After the distillation is completed, the mixture is cooled to room temperature, then the mixture is cooled to zero degrees Celsius, and we get a precipitate, phthalic acid, which is separated by filtration. The filtrate is taken and cooled to zero degrees Celsius by an ice bath, and a 10 molar solution of sodium hydroxide is gradually added to the filtrate with stirring until we reach an alkaline medium. The compound is extracted from the water phase by diethyl ether several times, then the organic phase (PH = 10) is dried by Anhydrous magnesium sulfate and then diethyl ether is evaporated, we get 3.04 g of (6-cyanopyrene-2-yl) methylamine and the yield is 58%.

Elemental analysis: $C_7H_7N_3$: :calculated %: C: 63.14; H: 5.30; N: 31.56.

Analysis results: %: C: 63.08; H: 5.22; N: 31.49.

^{1}H NMR: ($CDCl_3$,δ en ppm): 7.6 (dd,1H), 7.3-7.1 (m, 2H), 4.0 (s, 2H), 2.0 (br s, 2H, NH).

riboflavin tetra Acetae Müller[28]:

Dissolve 20 g of riboflavin (36.54 mmol) in 75 ml of 100% acetic acid and add to it an equal amount, i.e., 75 ml of acetic acid in a double-headed flask, stir the mixture and add to it dropwise 8 ml of thick perchloric acid, cooled to 0°C. The reaction mixture continues to be stirred after adding the medium for an hour, then 11 ml of cooled water is added to zero degrees Celsius, after which the product is extracted by carbon dioxide 3 times each time by 50 ml. The organic phase is dried by anhydrous magnesium sulfate, then the mixture is filtered and the filtrate is taken and the volume is reduced to 20 ml by a rotary evaporator. The precipitate was cooled and dry with diethyl ether three times each time 30 ml, and then the precipitate was dried using the cell, and we got a pale yellow precipitate with a yield of 90%.

Elemental analysis: $C_{17}H_{20}N_4O_6$: calculated %: C: 54.25.14; H: 5.36; N: 14.89.

Analysis results: %: C: 54.22.14; H: 5.31; N: 14.82.

1H NMR: δ, CDCl3, ppm: 8.5 (s, 1H, Ar δ δ; 8.02 (s, 1H, NH); 7.56 (s, 1H, Ar); 5.74-7.60 (1H, CH aliphatic); 5.50-5.35 (m, 2H, CH, aliphatic); 5.28 – 5.70 (Large , 2H, N-CH2); 4.50-4.37 (dd, 1H, aliphatic); 4.30-4.14 (dd, 2H, aliphatic); 2.56 (s, 3H, methyl); 2.44 (s, 3H, methyl); 2.28 (s, 3H, acetyl); 2.21 (s, 3H, acetyl); 2.07 (s, 3H, acetyl) ; 1.75 (s, 3H, acetyl).

^{13}C NMR δ, $CDCl_3$, ppm:170.68(C, of CO, acetyl);170.37(C, of CO, acetyl);169.90(C, of CO, acetyl):169.77(C, of CO, acetyl) ; 159(C, of CO, carbonyl, riboflavine); 155(C, of CO, carbonyl, riboflavine); 150(C, of riboflavine); 148(C, of riboflavine); 137(C,C-CH_3 of riboflavine) ;135(C,C-CH_3 of riboflavine) ; 134(C, of riboflavine) ; 132(C aromatic of,CH de riboflavine); 132(C, aromatic of,CH de riboflavine); 115(C, aliphatic of CH riboflavine) ; 70.63(C, aliphatic of CH riboflavine); 69.59(C, aliphatic of CH riboflavine) ; 69.37(C, aliphatic of CH riboflavine); 68.98(C, aliphatic of CH_2 riboflavine); 61.86(C, aliphatic of CH_2 riboflavine); 24.45 (C, of CH_3, acetyl) ; 21.04(C, of CH_3, carbonyl, acetyl); 20.80(C, of CH_3, acetyl,); 20.68(C, of CH_3, acetyl,); 20.32(C, of CH_3, riboflavine) ; 19.43(C, of CH_3, riboflavine).

Bromo-tetra Acetate riboflavine

The monobromotetraacetate riboflavin is obtained according to the method described in Walker et al.[29]

By dissolving 7 g (12.9 mmol) of the previously prepared riboflavin tetraacetate in 70 ml of dioxane and adding to it 60 mg of the initiator, dibenzoyl peroxide, and then adding 2.9 g (18 mmol) of bromine dissolved in 10 ml of carbon tetrachloride by drop with stirring. During 5 minutes, the mixture is placed by reflux for 20 minutes, the mixture is left to cool to room temperature, then the solution is evaporated by a rotary evaporator, and then the solid substance is re-dissolved in 70 ml of dichloromethane and washed with a buffer solution (pH = 7) of phosphate twice in succession and from Then it is washed with distilled water, the organic phase is dried by anhydrous magnesium sulfate, the mixture is filtered, the filtrate is taken and the volume is reduced to 20 ml by evaporation. The bromine derivative of tetra-riboflavin acetate is obtained by precipitation by adding 80 ml of dry and cold diethyl ether, we get a yellow solid substance that is dried by low pressure, and we get a yield of 75% of the bromine derivative of tetrariboflavin acetate.

Elemental analysis: $C_{17}H_{19}$ Br N_4O_6 : :calculated %: C: 44.85; H: 4.21; N: 12.31.

Analysis results: %: C: 44.79; H: 4.19; N: 12.28.

^{1}H NMR: δ, CDCl3, ppm: δ δ, CDCl3, ppm: 8.78 (s, 1H, NH); 8.02 (s, 1H, Ar□□; 7.80(s, 1H, Ar); 5.74-7.60 (1H, CH aliphatic); 5.50-5.35 (m, 2H, CH, aliphatic); 5.28 – 5.70 (Large , 2H, N-CH2); 4.67(s, 2H, CH2,of Br-CH2); 4.50-4.37 (dd, 1H, aliphatic); 4.30-4.14 (dd, 2H, aliphatic); 2.58 (s, 3H, methyl); 2.29 (s, 3H, acetyl); 2.24 (s, 3H, acetyl); 2.08 (s, 3H, acetyl) ; 1.75 (s, 3H, acetyl).^{13}C NMR δ, CDCl3, ppm:170.68(C, of CO, acetyl);170.37(C, de CO, acetyl);169.90(C, of CO, acetyl):169.77(C, of CO, acetyl) ; 159(C, of CO, carbonyl, riboflavine); 155(C, of CO, carbonyl, riboflavine); 150(C, of riboflavine); 148(C, of riboflavine); 137(C,C-CH3 of riboflavine) ;135(C,C-CH3 of riboflavine) ; 134(C, of riboflavine) ; 132(C aromatic of,CH of riboflavine); 132(C, aromatic of,CH of riboflavine); 115(C, aliphatic of CH riboflavine) ; 70.63(C, aliphatic of CH riboflavine); 69.59(C, aliphatic of CH riboflavine) ; 69.37(C, aliphatic of CH riboflavine); 68.98(C, aliphatic of CH2 riboflavine); 61.86(C, aliphatic of CH2 riboflavine); 30.8(C, of CH2-Br); 24.45 (C, of CH3, acetyl) ; 21.04(C, of CH3, carbonyl, acetyl); 20.80(C, of CH3, acetyl,); 20.68(C, of CH3, acetyl,); 20.32(C, ofCH3, riboflavine) ; 19.43(C, of CH3, riboflavine).

General method of synthesis $TPAX_2CN$; X=H,Br,Cl,F

Dissolve (6 mmol) of 6-(aminomethyl)picolinonitrile 6-(aminomethyl)picolinonitrile in 200 ml of ethanol and add to it (12 mmol) of 2-halogen 6-bromomethylpyridine (2-halogen-6-bromomethylpyridine) and in In the simple case, 6-bromomethylpyridine (6-bromomethylpyridine) is added to it (24 mmol) of sodium carbonate (Na2CO3). The reaction mixture is placed by reflux distillation for 14 hours at a temperature of 950C. After the end of the mentioned period, the solution is completely evaporated. Distilled water is added to get rid of sodium carbonate, and carbon dioxide is added to dissolve the desired compound. The organic phase is separated, which contains the desired compound, and dried using anhydrous magnesium sulfate MgSO4. The mixture is filtered to separate the magnesium sulfate from the organic phase, the solution is evaporated, the product is recrystallized by using cold pentane (-200C) and the yield is: 80% in the simple unreplaced case, 59% in the case of fluorine replacement, 63% in the case of chlorine replacement, and 52 % in case of bromine replacement.

X=H:TPACN

Chemical Formula: $C_{19}H_{17}N_5$

Elemental analysis: calculated: C% :72.36 ;H%:5.43; N%:22.21.

Analysis results: C% :72.63; H%:5.08; N%:22.42.

^{1}H NMR, δ, ppm, $CDCl_3$: 8.53(m,2H,CH_α); 7.82(dd,1H,$CH_{\beta1}$); 7.77(t,1H,$CH_{\gamma1}$); 7.65 (td,2H,CH_γ); 7.54(dd,1H,$CH_{\beta1'}$); 7.51(dt,2H,$CH_{\beta'}$); 7.15(m,2H,CH_β); 3.92 (s,2H,CH_2); 3.88 (s,4H,CH_2).

^{13}C NMR : 162(1C,2') ; 159(2C,2) ; 149(2C,6) ; 137(1C,4') ; 136(1C,4) ; 132(1C,6') ; 127(1C,3') ; 126(1C,5') ; 123(2C,3) ; 122(2C,5) ; 117(1C,CN) ; 60(2C,CH_2) ; 59(1C,CH_2).

I.R.: $\nu_{(CN)}$=2539 cm^{-1}.

X=F: F_2(CN)TPA

Chemical Formula: $C_{19}H_{15}F_2N_5$

Elemental analysis: calculated: C% :64.95 ;H%:4.30; N%:19.93.

Analysis results: C% : 64.87 ;H%:4.22; N%:19.88.

^{1}H NMR ($CDCl_3$, δδ, ppm) : 7.82(dd,1H,$CH_{\beta1}$); 7.77(t,1H,$CH_{\gamma1}$); 7.54(dd,1H,$CH_{\beta1'}$); 7.48,(dd, 2H); 7.70,(dd 2H); 6.77,(dd 2H); 3.89,(s 4H) 3.92 (s,2H,CH_2).

I.R.: $\nu_{(CN)}$=2532 cm^{-1}.

X=Cl: Cl_2(CN)TPA

Chemical Formula: $C_{19}H_{15}Cl_2N_5$

Elemental Analysis: C, 59.39; H, 3.93; Cl, 18.45; N, 18.23

Elemental analysis: calculated: C% :59.39 ;H%:3.93; N%:18.23.

Analysis results: C% : :59.44 ;H%:3.97; N%:18.41.

^{1}H NMR ($CDCl_3$, δδ, ppm) , 7.80(dd,1H,$CH_{\beta1}$); 7.73(t,1H,$CH_{\gamma1}$); 7.68–7.54,(m, CHarom, 6H); 7.50(dd,1H,CHβ1');; 3.90 (s,2H,CH2); 3.87 (s,CH2, 4H).

I.R.: $\nu_{(CN)}$=2534 cm^{-1}.

X=Br: Br_2(CN)TPA

Chemical Formula: $C_{19}H_{15}Br_2N_5$

Elemental analysis: calculated: C% :48.23 ;H%:3.20; N%:14.80.

Analysis results: C% : 48.24 ;H%:3.26; N%:14.86.

^{1}H NMR (CDCl3, δδ, ppm): 7.82(dd,1H,CHβ1); 7.74(t,1H,CHγ1); 7.70–7.60,(m, CHarom, 6H); 7.52(dd,1H,CHβ1');; 3.90 (s,2H,CH2); 3.86 (s,CH2, 4H).

I.R.: ν(CN)=2529 cm-1.

(X_2)TPACH$_2$NH$_2$: X=H,F,Cl,Br.

An amount of (7.42 mmol) of TPAX2CN is placed in a reaction flask, 300 cm3 of freshly distilled diethyl ether is added to it, and (37.11 mmol) of LiAlH4 is added gradually to the solution. The reaction mixture is left by stirring at laboratory temperature (room temperature). For 24 hours, after the expiration of the period, 50 ml of distilled water is added to the mixture by slow drip and stirring. The product is filtered and the compound is extracted from the mixture with diethyl ether three times. We get the product in the form of a viscous oily liquid with a brown color, and the yield is up to 86%.

TPACH2NH2^{1}H NMR, *δ, ppm, $CDCl_3$* : 8.46(m,2H,CH_α) ; 7.63 (m,4H,$CH_{\beta'\text{-}\beta}$) ; 7.56 (m,1H,$CH_{\gamma1}$) ; 7.52 (m,1H,$CH_{\beta1'}$) ; 7.05 (m,3H,$CH_{\gamma\text{-}\ \beta1}$) ; 3.88 (s,2H,$CH_2$) ; 3.83 (s,4H,$CH_2$) ; 3.82 (s,2H,$CH_2NH_2$) ; 2.83 (s,2H,$NH_2$).

^{13}C NMR: 160 (1C,2') ; 159 (2C,2) ; 158 (1C,6') ; 149 (2C,6) ; 137 (1C,4') ; 136 (2C,4) ; 123 (2C,3) ; 121 (2C,5) ; 120 (1C,3') ; 119 (1C,5') ; 60 (3C,CH_2) ; 48 (1C,CH_2NH_2).

Elemental analysis:

Chemical Formula: $C_{19}H_{21}N_5$

calculated: C% =71.47 H%=6.58 N%=21.94.

Analysis results: C% =71.60 H%=6.67 N%=21.82.

F_2TPACH$_2$NH$_2$

^{1}H NMR (300 MHz, CDCl3) : δ (ppm) 7,70 (m, 2H) 7,67 (m, 1H) ; 7,63 (m, 1H) ; 7,48 (m, 2H) ; 7,19 (m, 1H) ; 6,77 (m, 2H) ; 3,86 (s, 4H) ; 3,94 (s, 2H) ; 3.82 (s,2H,CH2NH2) ; 2.80 (s,2H,NH2).

Elemental analysis:

Chemical Formula: $C_{19}H_{19}F_2N_5$

Elemental Analysis: C, 64.21; H, 5.39; F, 10.69; N, 19.71

calculated: C% =64.21 H%=5.39 N%=19.71.

Analysis results: C% =64.18 H%=5.36 N%=19.67.

Cl_2TPACH$_2$NH$_2$

^{1}H NMR ($CDCl_3$, δ, ppm) , 7,68 (m, 2H) 7,65 (m, 1H) ; 7,60 (m, 1H) ; 7,43 (m, 2H) ; 7,16 (m, 1H) ; 6,75 (m, 2H) ; 3,83 (s, 4H) ; 3,91 (s, 2H) ; 3.82 (s,2H,CH_2NH_2) ; 2.81 (s,2H,NH_2).

Elemental analysis:

Chemical Formula: $C_{19}H_{19}Cl_2N_5$

Elemental Analysis: C, 58.77; H, 4.93; Cl, 18.26; N, 18.04

calculated: C% =58.77 H%=4.93 N%=18.04.

Analysis results: C% ==58.74 H%=4.87 N%=17.94.

Br_2TPACH$_2$NH$_2$

^{1}H NMR (300 MHz, CDCl3) : δ (ppm) 7,68 (m, 2H) 7,62 (m, 1H) ; 7,58 (m, 1H) ; 7,44 (m, 2H) ; 7,14 (m, 1H) ; 6,75 (m, 2H) ; 3,81 (s, 4H) ; 3,88 (s, 2H) ; 3.80 (s,2H,CH2NH2) ; 2.83 (s,2H,NH2).

Elemental analysis:

Chemical Formula: $C_{19}H_{19}Br_2N_5$

calculated: C% =47.82 H%=4.01 N%=14.68.

Analysis results: C% =47.78 H%=3.97 N%=14.65.

$(X_2)TPACH_2NHBoc$ X=H,F,Cl,Br.

(47.58 mmol) of (X2)TPACH2NH2 is dissolved in 50 mL of dichloromethane, added to the saline solution (128.3 mmol) of (tert-butyl dicarbonate), then 50 mL of a regular 7-sodium hydroxide solution is added to the reaction mixture. The mixture was stirred at laboratory temperature for 3 hours. After this stage, it is extracted by dichloromethane three times each time by 50 ml, the organic phase is dried by supersaturated sodium chloride solution and then by anhydrous magnesium sulfate, the mixture is filtered and the organic phase is taken and the solution is evaporated, and the solution is purified by column chromatography using alumina using a mixture of 70% carbon dioxide and 30% ethyl acetate. The required compounds are obtained as a dark orange solid with a yield of 68.5%.

$TPACH_2NHBoc$

^{1}H NMR *δ, ppm, CDCl$_3$* : 8.46(m,2H,CH_α) ; 7.63 (m,4H,$CH_{\beta'\text{-}\beta}$) ; 7.56 (m,1H,$CH_{\gamma 1}$) ; 7.52 (m,1H,$CH_{\beta 1'}$) ; 7.05 (m,3H,$CH_{\gamma\text{-}\ \beta 1}$) ; 3.88 (s,2H,$CH_2$) ; 3.83 (s,4H,$CH_2$) ; 3.82 (s,2H,$CH_2NH_2$) ; 2.90 (s,1H,$NH_2$) 1.35 (s, 9H).

Elemental analysis:

Chemical Formula: $C_{19}H_{21}N_5$

calculated: C% =71.47 H%=6.58 N%=21.94.

Analysis results: C% =71.60 H%=6.67 N%=21.82.

F_2TPACH_2NHBoc

^{1}H NMR (300 MHz, CDCl3) : δ (ppm) 7,70 (m, 2H) 7,67 (m, 1H) ; 7,63 (m, 1H) ; 7,48 (m, 2H) ; 7,19 (m, 1H) ; 6,77 (m, 2H) ; 3,86 (s, 4H) ; 3,94 (s, 2H) ; 3.82 (s,2H,CH2NH2) ; 2.90 (s,1H,NH2) 1.40 (s, 9H).

Elemental analysis:

Chemical Formula: $C_{19}H_{19}F_2N_5$

calculated: C% =64.21 H%=5.39 N%=19.71.

Analysis results: C% =64.18 H%=5.36 N%=19.67.

Cl_2TPACH_2NHBoc

^{1}H NMR ($CDCl_3$, δ, ppm) , 7,68 (m, 2H) 7,65 (m, 1H) ; 7,60 (m, 1H) ; 7,43 (m, 2H) ; 7,16 (m, 1H) ; 6,75 (m, 2H) ; 3,83 (s, 4H) ; 3,91 (s, 2H) ; 3.82 (s,2H,CH_2NH_2) ; 2.90 (s,1H,NH_2) 1.42 (s, 9H).

Elemental analysis:

Chemical Formula: $C_{19}H_{19}Cl_2N_5$

calculated: C% =58.77 H%=4.93 N%=18.04.

Analysis results: C% ==58.74 H%=4.87 N%=17.94.

Br_2TPACH_2NHBoc

^{1}H NMR (300 MHz, CDCl3) : δ (ppm) 7,68 (m, 2H) 7,62 (m, 1H) ; 7,58 (m, 1H) ; 7,44 (m, 2H) ; 7,14 (m, 1H) ; 6,75 (m, 2H) ; 3,81 (s, 4H) ; 3,88 (s, 2H) ; 3.80 (s,2H,CH2NH2) ; 2.90 (s,1H,NH2) 1.38 (s, 9H).

Elemental analysis:

Chemical Formula: $C_{19}H_{19}Br_2N_5$

calculated: C% =47.82 H%=4.01 N%=14.68.

Analysis results: C% =47.78 H%=3.97 N%=14.65.

$X_2TPACH_2N(Boc)$-tetra Acetate riboflavineGeneral method of synthesis

A solution of (10.93mmol) of the derivative protected by the protection group (Boc) prepared above (hydrogen, fluorine, chlorine, bromine) is prepared in 50 ml of absolute DMF, 262 mg (10.93mmol) NaH is added to this solution. With mineral oil at a concentration of 60% and thus we take an amount of 436 mg. The reaction mixture is placed at room temperature with continuous stirring in an atmosphere of inert argon gas for an hour until the solution is homogeneous. A 20ml solution of absolute DMF containing (10.93 mmol) of bromo-tetra acetate riboflavin is added to the mixture. The mixture is left by stirring for 24 hours at room temperature. At the end of the reaction, the solution is evaporated by low pressure. The remaining oily substance is dissolved after evaporation of the solution. 50 ml of dichloromethane and washed three times with distilled water each time using 50 ml, the organic phase is dried by anhydrous magnesium sulfate, then the mixture is filtered and the filtrate is taken and the volume of the solution is reduced to 20 ml. Filtered and dried by low pressure, and the product was a yellowish-brown solid with a yield of 58% in the four cases.

$TPACH_2N(Boc)$-tetra Acetate riboflavin

^{1}H NMR*: δ, CDCl$_3$, ppm*: 8.53 (s, 1H, NH); 8.46(m,2H,CH_α) 7.92 (s, 1H Ar); 7.63 (m,4H,$CH_{\beta'\text{-}\beta}$) ; 7.56 (m,1H,$CH_{\gamma 1}$) ; 7.52 (m,1H,$CH_{\beta 1'}$) ;; 7.49 (s, 1H, Ar); 7.05 (m,3H,$CH_{\gamma\text{-}\ \beta 1}$) 5.59 (d, 1H, ribityl CH); 5.46 (m, 2H, ribityl CH_2); 4.44-4.39 (dd, 1H, aliphatic); 4.31-4.23 (m, 1H, aliphatic); 4.15 (s,4H,-$CH_2N(Boc)$- CH_2)); 3.82 (s, 2H, CH_2-ribofl.); 3.88 (s,2H,CH_2) ; 3.83 (s,4H,CH_2) ;; 2.55 (s, 3H, methyl); 2.42 (s, 3H, acetyl); 2.32 (s, 3H, acetyl); 2.26 (s, 3H, acetyl); 2.19 (s, 3H, acetyl) 1.35 (s, 9H-methyl ofBoc).

^{13}C NMR *δ, CDCl$_3$, ppm*: 171-169.4 (4 acetyl C=O) ; 159.4 (flavin C=O); 157.8 (C_{quat}); 156.6 (C_{quat});155.6 (C=O Boc); 152.6 (flavin C=O); 150 (C_{quat} flavin); 148.6 (C_{quat}); 146.7 ($2CH_{pyridyl}$); 140. ($2C_{quat}$ flavin); 138.6($2CH_{pyridyl}$); 126.7($2CH_{pyridyl}$); 122.6($2CH_{pyridyl}$); 120.6($2CH_{pyridyl}$); 136.8 (C_{quat} flavin); 132.1. (C_{quat} flavin); 124.2 (C_{quat} flavin);115.5 ($2CH_{Ar}$);78.8 (C_{quat}, Boc); 70.4, 69.4, 69.1 (3CH); 65.6 ($2CH_{2pyridyl}$); 62.7

($2CH_{2pyridyl}$);61.9 (CH_2 ribofl); 27.0 ($3CH_3$ of Boc);21.4, 21.1, 21.0, 20.8, ($4CH_3$ of Ac);20.0 (CH_3 of flavin).

Chemical Formula: $C_{49}H_{55}N_9O_{12}$

Elemental analysis

calculated: C: 61.18; H:5.76; N: 13.10.

Analysis resultsل : : C: 61.14; H:5.70; N: 13.07.

Mass spectroscopy: ES^+, CH_3CN + 0.1% formic acid, m/z: 963 ($L+H^+$).

F_2TPACH_2N(Boc)-tetra Acetate riboflavine

^1H NMR*: δ, $CDCl_3$, ppm*:8.55 (s, 1H, NH); 7.92 (s, 1H Ar); 7,70 (m, 2H γ); 7,67 (m, 1H) ; 7,63 (m, 1H) ;7.56 (s, 1H, Ar); 7,48 (m, 2H) ; 7,19 (m, 1H) ; 6,77 (m, 2H) 5.59 (d, 1H, ribityl CH); 5.46 (m, 2H, ribityl CH_2); 5.3 – 5.1 (m, 2H, N-CH_2); 4.44-4.39 (dd, 1H, aliphatic); 4.31-4.23 (m, 1H, aliphatic); 4.15 (s,4H,-CH_2N(Boc)- CH_2)); 4,05 (s, 2H, CH_2); 3,90 (s, 4H CH_2); 3.82 (s, 2H, CH_2-ribofl.); 2.55 (s, 3H, methyl); 2.42 (s, 3H, acetyl); 2.32 (s, 3H, acetyl); 2.26 (s, 3H, acetyl); 2.19 (s, 3H, acetyl) 1.40 (s, 9H-methyl ofBoc).

^{13}C NMR *δ, $CDCl_3$, ppm*: 171-169.4 (4 acetyl C=O) ; 159.4 (flavin C=O); 157.8 (C_{quat}); 156.6 (C_{quat});155.6 (C=O Boc); 152.6 (flavin C=O); 150 (C_{quat} flavin); 148.6 (C_{quat}); 166.7 (2C-$F_{pyridyl}$); 140. ($2C_{quat}$ flavin); 139.6($2CH_{pyridyl}$); 128.7($2CH_{pyridyl}$); 126.6($2CH_{pyridyl}$); 120.6($2CH_{pyridyl}$); 136.8 (C_{quat} flavin); 132.1. (C_{quat} flavin); 124.2 (C_{quat} flavin);115.5 ($2CH_{Ar}$); 78.8 (C_{quat}, Boc); 70.4, 69.4, 69.1 (3CH); 65.6 ($2CH_{2pyridyl}$); 62.7 ($2CH_{2pyridyl}$);61.9 (CH_2 ribofl); 27.0 ($3CH_3$ of Boc);21.4, 21.1, 21.0, 20.8, ($4CH_3$ of Ac);20.0 (CH_3 of flavin).

Elemental analysis

Chemical Formula: $C_{49}H_{53}F_2N_9O_{12}$

Calculated: C: 58.97; H:5.35; N:12.36.

Analysis results: C: 58.99; H:5.38; N:12.39.

Mass spectroscopy: ES^+, CH_3CN + 0.1% formic acid, m/z: 999 ($L+H^+$).

Cl_2TPACH_2N(Boc)-tetra Acetate riboflavine

^1H NMR*: δ, $CDCl_3$, ppm*:8.55 (s, 1H, NH); 7.92 (s, 1H Ar); 7,70 (m, 2H γ); 7,67 (m, 1H) ; 7,63 (m, 1H) ;7.56 (s, 1H, Ar); 7,45 (m, 2H) ; 7,18 (m, 1H) ; 6,76 (m, 2H) 5.59 (d, 1H, ribityl CH); 5.46 (m, 2H, ribityl CH_2); 5.3 – 5.1 (m, 2H, N-CH_2); 4.44-4.39 (dd, 1H, aliphatic); 4.31-4.23 (m, 1H, aliphatic); 4.10 (s,4H,-CH_2N(Boc)- CH_2)); 3,95 (s, 2H, CH_2); 3,80 (s, 4H CH_2); 3.80 (s, 2H, CH_2-ribofl.); 2.55 (s, 3H, methyl); 2.42 (s, 3H, acetyl); 2.32 (s, 3H, acetyl); 2.26 (s, 3H, acetyl); 2.19 (s, 3H, acetyl) 1.40 (s, 9H-methyl ofBoc).

^{13}C NMR *δ, $CDCl_3$, ppm*: 171-169.4 (4 acetyl C=O) ; 159.4 (flavin C=O); 157.8 (C_{quat}); 156.6 (C_{quat});155.6 (C=O Boc); 152.6 (flavin C=O); 150 (C_{quat} flavin); 148.6 (C_{quat}); 163.2 (2C-$Cl_{pyridyl}$); 140. ($2C_{quat}$ flavin); 139.6($2CH_{pyridyl}$); 128.7($2CH_{pyridyl}$); 126.6($2CH_{pyridyl}$); 120.6($2CH_{pyridyl}$); 136.8 (C_{quat} flavin); 132.1. (C_{quat} flavin); 124.2 (C_{quat} flavin);115.5 ($2CH_{Ar}$); 78.8 (C_{quat}, Boc); 70.4, 69.4, 69.1 (3CH); 65.6 ($2CH_{2pyridyl}$); 62.7 ($2CH_{2pyridyl}$);61.9 (CH_2 ribofl); 27.0 ($3CH_3$ of Boc);21.4, 21.1, 21.0, 20.8, ($4CH_3$ of Ac);20.0 (CH_3 of flavin).

Elemental analysis:

Chemical Formula: $C_{49}H_{53}Cl_2N_9O_{12}$

calculated: C: 57.09; H:5.18; N: 12.23.

Analysis results: C: 57.11, H: 5.22, N: 12.25.

Mass spectroscopy: ES^+, CH_3CN + 0.1% formic acid, m/z: 1031 ($L+H^+$).

Br_2TPACH_2N(Boc)-tetra Acetate riboflavine

^1H NMR*: δ, $CDCl_3$, ppm*:8.55 (s, 1H, NH); 7.92 (s, 1H Ar); 7,68 (m, 2H γ); 7,62 (m, 1H) ; 7,58 (m, 1H) ;7.56 (s, 1H, Ar); 7,44-7.42 (m, 2H) ; 7,14 (m, 1H) ; 6,77 (m, 2H) 5.59 (d, 1H, ribityl CH); 5.46 (m, 2H, ribityl CH_2); 5.3 – 5.1 (m, 2H, N-CH_2); 4.44-4.39 (dd, 1H, aliphatic); 4.31-4.23 (m, 1H, aliphatic); 3.95 (s,4H,-CH_2N(Boc)- CH_2)); 3,90 (s, 2H, CH_2); 3,84 (s, 4H CH_2); 3.80 (s, 2H, CH_2-ribofl.); 2.55 (s, 3H, methyl); 2.42 (s, 3H, acetyl); 2.32 (s, 3H, acetyl); 2.26 (s, 3H, acetyl); 2.19 (s, 3H, acetyl) 1.38 (s, 9H-methyl ofBoc).

^{13}C NMR *δ, $CDCl_3$, ppm*: 171-169.4 (4 acetyl C=O) ; 159.4 (flavin C=O); 157.8 (C_{quat}); 156.6 (C_{quat});155.6 (C=O Boc); 152.6 (flavin C=O); 150 (C_{quat} flavin); 148.6 (C_{quat}); 161.2 (2C-$Br_{pyridyl}$); 140. ($2C_{quat}$ flavin); 139.6($2CH_{pyridyl}$); 128.7($2CH_{pyridyl}$); 126.6($2CH_{pyridyl}$); 120.6($2CH_{pyridyl}$); 136.8 (C_{quat} flavin); 132.1. (C_{quat} flavin); 124.2 (C_{quat} flavin);115.5 ($2CH_{Ar}$); 78.8 (C_{quat}, Boc); 70.4, 69.4, 69.1 (3CH); 65.6 ($2CH_{2pyridyl}$); 62.7 ($2CH_{2pyridyl}$);61.9 (CH_2 ribofl); 27.0 ($3CH_3$ of Boc);21.4, 21.1, 21.0, 20.8, ($4CH_3$ of Ac);20.0 (CH_3 of flavin). Elemental analysis

Chemical Formula: $C_{49}H_{53}Br_2N_9O_{12}$

calculated: C: 52.56; H:4.77; N: 11.26.

Analysis results: C: 52.60; H:4.80; N: 11.32.

Mass spectroscopy: ES^+, CH_3CN + 0.1% formic acid, m/z: 1121 ($L+H^+$).

4. Conclusions

The flavin moiety acts as the site on which the reaction takes place. Flavin and its derivatives in biological oxidation processes play the role of electron mediators, so this assembly of flavin derivatives needs electron-conducting systems. The fact that the flavin/flavodoxin complex can act as a single electron carrier in a field close to the potential of the hydrogen pathways as previously discussed (allowing modification of the structure of the riboflavin-bound segment), enables to add electron-withdrawing or electron-donating groups.

If we make stable the steric factor, with studying the electronic factor, and vice versa, we can modify the stereo structure and then make modifications allowing the development of the electronic factor in accordance with the objectives of the studies to be applied to this type of industrial enzymes, and we can do both processes at the same time. Complexes of iron dichloride with ligands containing substituents on the pyridine ring in the α-position have been extensively studied during the previous

years, many structural modifications have been achieved that enabled the control of the steric structure of the complex by synthesizing many ligands.

This study is a follow-up to previous studies regarding the synthesis of types of bonds (Tetradents) TPA and its halogen derivatives, and to prove the possibility of linking and measuring the potentials of the bonds and the electronic conductor, and thus the process of manufacturing new types of couplings within the field of electronic agent control by measuring potentials. In the future, and as an extension of this study, it can be supported by studies that help control the stereo factor and then mix both steric and electronic factors to reach the optimum steric and electronic conditions. It is also possible to link this type of bonds, which have proven their efficiency in advance, with nanoparticles that play the role of electronic carriers of the C60 type or nanotubes. In an attempt to employ the unique properties of nanoparticles in the process of forming homogeneous mediated ligands, they take the place of enzymatic reactions, with quality and advantages that surpass biological mediation in some respects.

Competing Interests

The authors have declared that no competing interests exist.

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