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Synthesis, Characterization of Metal Complexes and their Biological Studies

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ABSTRACT

A Total of 5 new novel metal complexes have been prepared successfully in alcoholic medium. The complexes synthesized are purified from column chromatography then characterized quantitatively and qualitatively by using NMR, IR Spectroscopy. The further biological activities are made like Anti-cancer activity, Anti-inflammatory, Anti-microbial, Anti-cholesterol, these activities revealed that the complexes are showing positive results, these results shown that the prepared complexes can be finding the place in the drug synthesis as an anticancer drugs.

Graphical Abstract

Synthesis of Ligands ↓ Synthesis of Complex with Ligands in Alcoholic Media ↓ Purified from Column Chromatography and Characterized by NMR and IR ↓ Further Done Biological Studies ↓ The Final Study Shows Positive Results for Anti-microbial, Anti-cancer, Anti-fungal,

Anti-neural, Anti-inflammatory and Anti-cholesterol.

Keywords: NMR, IR, Anticancer, Anti- Cholesterol, Anti-Fungal, Ant-microbial, Anti-inflammatory, Anti-neural, Drug synthesis.

INTRODUCTION

The modern study of coordination compounds began with two men, Alfred Werner and Sophus Mads Jorgenson, in the context of d-metal chemistry, the term complex means a central metal atom or ion surrounded by a set of ligands [1]. The pioneering contribution of Werner to the study of coordination chemistry fetched him the Nobel Prize in Chemistry in 1913 and incidentally he is the first inorganic chemist to win the coveted distinction. It is the chemistry of metals and its complexes/compounds with other organic/ inorganic groups called ligands [2]. Coordination compounds are formed by almost all transition metals, lanthanide series metals and some of the non-metals like silicon. The synthesis and study of coordination compounds have gained interest due to the role of the coordination compounds in the field of catalysis and its role in biochemistry [3]. Coordination

chemistry plays a most important role in biological systems. For example, haemoglobin an ironporphyrin complex of human blood plays a vital role in oxygen transport mechanism. Chlorophyll, magnesium containing porphyrin complex plays a role in plant photosynthesis [4].

Coordination compounds play an important role in fields like medicine, polymers, pesticides, fungicides, biochemical reactions, petrochemicals etc. A complex is a combination of Lewis acid (the central metal atom) with a number of Lewis bases (the ligands) [5]. A Lewis acid is an electron pair acceptor and a Lewis base is an electron pair donor. Thus the interaction of the Lewis acid metal centre in Ni(ClO₄)₂ with the Lewis base ammonia to form a complex, according to the equation given below provides an example of the formation of a coordination compound.

 $Ni(ClO_4)_2 + 6NH_3 \rightarrow [Ni(NH_3)_6](ClO_4)_2$

MATERIALS AND METHODS

All the chemicals used were of purely analytical grade. Solvents were purified and dried according to standard procedure [10]. Some important chemicals like, 2-hydroxyacetophenone, benzaldehyde derivatives and boron tri-flouride etherate were purchased from Sigma Aldrich laboratories.

Physical measurements: The Electronic spectra were measured by using GBC UV-Vis double beam spectrophotometer in dichloro-methane solution in the 200-800 nm range. The FT-IR spectra were recorded on a Thermo Nicolet Avatar FT–IR spectrometer as Potassium Bromide powder in the frequency range 400–4000 cm⁻¹. The C, H and N contents were determined by Thermo-flash EA1112 series elemental analyzer. ¹H NMR and ¹⁹F NMR spectra were recorded in Bruker AV 400 instrument. The NLO measurements was done using Q-switched Nd:YAG laser (Continuum, MiniLite) provided with the second harmonic option with laser pulses of 5 nanoseconds width at the wavelength of 532 nm.

Synthesis of ligands (1L-5L)

General procedure for synthesis of ligands (1L-5L): The Ligands (**1L-5L**) were prepared by adding sodium hydroxide to the 2-hydroxyacetophenoneand benzaldehyde derivatives in ethanol at 40°C. The mixture was stirred for20 min and cooled to room temperature. The precipitate that formed was dissolved in water. The solution was made slightly acidic using dilute hydrochloric acid. The precipitate formed was filtered, washed with ice cold ethanol, and dried over calcium chloride to obtain crude chalcones. These were purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (Scheme 1).



Scheme 1. Synthesis of ligands (1L-5L).

(2-Hydroxyphenyl)-3-phenyl-2-propen-1-one (1L): Sodium hydroxide, 3.85 g (96.36 mmol), in 10 mL water, was added to the ethanolic solution (30 mL) of 2-hydroxyacetophenone 3.20g (23.5 mmol), the mixture was stirred for 20 min. To this solution 2.50g (23.5 mmol) of benzaldehyde in 20 mL of ethanol was added at 40°C. The mixture was stirred for2h and cooled to room temperature. The precipitate that formed was dissolved in 100 mL of water. The solution was made slightly acidic using dilute hydrochloric acid (50% 20 mL). The precipitate formed was filtered, purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (1:9), Yield 80%.

(2-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one (2L): The compound 2L was prepared following the same procedure used for 1L. Sodium hydroxide, 3.61 g (90.34 mmol), in 10 mL water, was added to the ethanolic solution (30 mL) of 2-hydroxyacetophenone 3.00g (22.03 mmol), the mixture was stirred for 20 min. To this solution 4.02g (28.64 mmol) of 4-chlorobenzaldehyde in 20 mL of ethanol was added at 40°C. The mixture was stirred for2hrs and cooled to room temperature. The precipitate that formed was dissolved in 100 mL of water. The solution was made slightly acidic using dilute hydrochloric acid (50% 20 mL). The precipitate formed was filtered, washed with ice cold ethanol, and dried over calcium chloride to obtain crude chalcone. It was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (1:9), Yield 75%.

(2-Hydroxyphenyl)-3-(4-bromophenyl)-2-propen-1-one (3L): The compound 3L was prepared following the same procedure used for 1L. Sodium hydroxide, 1.77 g (44.3 mmol), in 8 mL water, was added to the ethanolic solution (20 mL) of 2-hydroxyacetophenone 1.47g (10.8 mmol), the mixture was stirred for 20 min. To this solution 2.0g (10.8 mmol) of 4-bromobenzaldehyde in 20 mL of ethanol was added at 40°C. The mixture was stirred for2h and cooled to room temperature. The precipitate that formed was dissolved in 100 mL of water. The solution was made slightly acidic using dilute hydrochloric acid (50% 20 mL). The precipitate formed was filtered, washed with ice cold ethanol, and dried over calcium chloride to obtain crude chalcone. It was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (1:9), Yield 75%.

(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (4L): The compound 4L was prepared following the same procedure used for 1L. Sodium hydroxide, 2.40g (60.2 mmol), in 8 mL water, was added to the ethanolic solution (20 mL) of 2-hydroxyacetophenone 2.0g (14.68 mmol), the mixture was stirred for 20 min. To this solution 2.0g (14.68 mmol) of 4-methoxybenzaldehyde in 20 mL of ethanol was added at 40°C. The mixture was stirred for2h and cooled to room temperature. The precipitate that formed was dissolved in 100 mL of water. The solution was made slightly acidic using dilute hydrochloric acid (50% 20 mL). The precipitate formed was filtered, washed with ice cold ethanol, and dried over calcium chloride to obtain crude chalcone. It was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (1:9), Yield 75%.

(2-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one (5L): The compound 5L was prepared following the same procedure used for 1L. Sodium hydroxide, 2.73g (68.32 mmol), in 8 mL water, was added to the ethanolic solution (20 mL) of 2-hydroxyacetophenone 2.26g (16.66 mmol), the mixture was stirred for 20 min. To this solution 2.0g (16.66 mmol) of 4-methylbenzaldehyde in 20 mL of ethanol was added at 40°C. The mixture was stirred for2hrs and cooled to room temperature. The precipitate that formed was dissolved in 100 mL of water. The solution was made slightly acidic using dilute hydrochloric acid (50% 20 mL). The precipitate formed was filtered, washed with ice cold ethanol, and dried over calcium chloride to obtain crude chalcone. It was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (1:9), Yield 75%.

Synthesis of boron chalcone complexes

General method for the preparation of 2,2-difluorodioxaborinates (1C-5C): Equimolecular quantities of the 2'-hydroxychalcone (1L-5L) and boron trifluoride etherate were stirred at room

temperature on magnetic stirrer for 4h in dry benzene to give a solid which was filtered and washed with dry benzene (Scheme 2).



Scheme 2. synthesis of complexes 1C-5C.

Borondifluoro[1-(2-hydroxyphenyl)-3-phenyl-2-propeno-1-ato-O,O'] (1C): Compound 1C was prepared from 0.3g (1.00 mmol) of 2'-hydroxychalcone (1L) and 0.20 mL (1.20 mmol) of boron trifluoride in dry benzene to give yellow powder with 85 % yield, mp 247-251°C.

Borondifluoro[1-(2-hydroxyphenyl)-3-(4-chlorophenyl)-2-propenoato-O,O'](2C): Compound 2C was prepared from 0.2g (0.77 mmol) of 2'-hydroxychalcone (2L) and 0.11 mL (0.92 mmol) of boron trifluoride in dry benzene to give orange precipitate with 85 % yield, mp 247-251 °C.

Borondifluoro[1-(2-hydroxyphenyl)-3-(4-bromophenyl)-2-propenoato-O,O'](3C): Compound 3C was prepared from 0.4g (1.31 mmol) of 2'-hydroxychalcone (3L) and 0.199 mL (1.58 mmol) of boron trifluoride in dry benzene to give orange precipitate with 85 % yield, mp 247-251 °C.

Borondifluoro[1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propenoato-O,O'](4C):Compound 4C was prepared from 0.4g (1.57 mmol) of 2'-hydroxychalcone (4L) and 0.23 mL (1.88 mmol) of boron trifluoride in dry benzene to give orange precipitate with 85 % yield, mp 247-251°C.

Borondifluoro[1-(2-hydroxyphenyl)-3-(4-methylphenyl)-2-propenoato-O,O'](5C):Compound 5C was prepared from 0.4g (1.67 mmol) of 2'-hydroxychalcone and 0.25 mL (2.01 mmol) of boron trifluoride in dry benzene to give orange precipitate with 85 % yield, mp 247-251 °C.

Biological Studies

In silico analysis of target protein based on lead molecule activity: The microbial, cancer, cholesterol esterase, fungal and inflammatory protein receptor structures were directly used for molecular docking. The 3D structure of the protein with the above origin were taken from RCSB PDB database; viz, 4B3Z with cancerous origin, 2LAO with cholesterol esterase origin, 2E5B with inflammatory origin, 2BRX with microbial origin, 4FPR with fungal origin and 2YTR with neuronal origin were taken for this work.

Molecular docking studies: The docking simulation technique was considered as direct study on 3D structures of known functional characteristic proteins, which is a detailed study of intermolecular interaction with the ligands. The different functional characteristic of inflammatory, microbial and cancerous receptor-proteins was performed using PATCHDOCK server. The energy values are given in the following table.

RESULTS AND DISCUSSION

2-Hydroxyphenyl)-3-phenyl-2-propen-1-one (1L):¹H NMR (400 MHz, CDCl₃), [δ , ppm]: 12.79 (1H, s), 7.94-7.90 (3H, m), 7.68-7.64 (4H, m), 7.52-7.48 (1H, m), 7.45-7.42 (2H, m), 7.04-7.02 (1H, dd) and 6.96-6.92 (1H, m) (Figure 1). IR (KBr, cm⁻¹): 1635.5, 1565.8, 1199.4, 734.2 (Figure 2).Anal calcd for C₁₅H₁₂O₂, C 80.33%, H 5.35%. Found C 80.20 %, H 5.23%. UV-Vis: λ_{max} /nm (DCM) 317.48.



Figure 1.¹H NMR spectra of ligand **1L**.

Figure 2. IR spectra of ligand 1L.

2-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one (**2L**):¹H NMR (400 MHz, CDCl₃), [δ , ppm]: 12.72 (1H, s), 7.92-7.88 (1H, m), 7.84 (1H, s), 7.64 (1H, s), 7.61-7.58 (2H, m), 7.53-7.49 (1H, m), 7.43-7.40 (2H, m), 7.05-7.02 (1H, m) and 6.97-6.93 (1H, m) (figure 3). IR (KBr, cm⁻¹): 1636.9, 1561.8, 1201.6, 754.0 (figure 4). Anal calcd for C₁₅H₁₁ClO₂, C 69.63%, H 4.25%. Found C 69.43 %, H 4.18%. UV-Vis: λ_{max} /nm (DCM) 322.3.



Figure 3. 1H NMR spectra of ligand 2L.

Figure 4. IR spectra of ligand 2L.

(2-Hydroxyphenyl)-3-(4-bromophenyl)-2-propen-1-one (3L)¹H NMR (400 MHz, CDCl₃), [δ , ppm]: 12.72 (1H, s), 7.91-7.89 (1H, dd), 7.87-7.83 (1H, d), 7.66-6.62 (1H, d), 7.59-7.49 (5H, m), 7.04-7.02 (1H, dd) and 6.97-6.93 (1H, m) (figure 5). IR (KBr, cm⁻¹): 1639.3, 1561.6, 1201.8, 750.1 (figure 6). Anal calcd for C₁₅H₁₁BrO₂, C 59.42%, H 3.62%. Found C 59.23 %, H 3.40%. UV-Vis: λ_{max} /nm (DCM) 361.95.

(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (4L):¹H NMR (400 MHz, CDCl₃), [δ, ppm]: 12.91 (1H, s), 7.93-7.88 (2H, m), 7.65-7.61 (2H, m), 7.56-7.52 (1H, d), 7.50-7.46 (1H, m), 7.03-7.01 (1H, m), 6.97-6.91 (3H, m) and 3.86 (3H, s) (Figure 7). IR (KBr, cm⁻¹): 1634.3, 1558.2,

1203.4, 757.3 (Figure 8). Anal calcd for C₁₅H₁₄O₃, C 75.57%, H 5.50%. Found C 75.32 %, H 5.22%. UV-Vis: λ_{max} /nm (DCM) 365.91.



Figure 7.¹H NMR spectra of ligand **4L**.

Figure 8.IR spectra of ligand 4L.

(2-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one (5L):¹H NMR (400 MHz, CDCl₃), [δ , ppm]: 12.85 (1H, s), 7.93-7.89 (2H, m), 7.64-7.60 (1H, d), 7.57-7.56 (2H, m), 7.51-7.47 (1H, m), 7.25-7.23 (2H, d), 7.03-7.01 (1H, s), 6.96-6.92 (1H, s) and 2.40 (3H, s) (Figure 9). IR (KBr, cm⁻¹):1631.8, 1558.8, 1195.6, 738.4 (Figure 10). Anal calcd for C₁₅H₁₄O₂, C 80.64%, H 5.87%. Found C 80.62%, H 5.02%. UV-Vis: λ_{max} /nm (DCM) 331.0.



Figure 9.¹H NMR spectra of ligand **5**L

Figure 10.IR spectra of ligand 5L.

Boron chalcone complexes

Borondifluoro[1-(2-hydroxyphenyl)-3-phenyl-2-propeno-1-ato-O,O'] (1C): ¹H NMR (400 MHz, CDCl₃), [δ , ppm]: 8.53-8.49 (1H, d), 7.96-7.94 (1H, dd), 7.8-7.77 (2H, m), 7.76-7.66 (2H, d), 7.63-7.56 (1H, m), 7.52-7.5 (2H, m), 7.18-7.16 (1H, dd) and 7.06-7.04 (1H, m) (Figure 11). ¹⁹F NMR (400 MHz, CDCl₃), [δ , ppm]:142.49 (Figure 12). IR (KBr, cm⁻¹): 1617.6, 1560.6, 1035.7, 666.2 (Figure 13). Anal calcd for C₁₅H₁₁BF₂O₂, C 66.21%, H 4.04%. Found C 66.15 %, H 4.02 %. UV-Vis: λ_{max} /nm (DCM) 375.5.



Figure 11.¹H NMR spectra of complex 1C.

Figure 12.¹⁹F NMR spectra of complex 1C.



Figure 13. IR spectra of complex 1C.

Borondifluoro[1-(2-hydroxyphenyl)-3-(4-chlorophenyl)-2-propenoato-O,O'](2C): ¹H NMR (400 MHz, CDCl₃), [δ, ppm]: 8.46-8.43 (1H, d), 7.95-7.92 (1H, dd), 7.80-7.76 (1H, m), 7.72-7.70 (2H, m), 7.62-7.58 (1H, d), 7.51-7.49 (2H, m), 7.18-7.16 (1H, d) and 7.08-7.04 (1H, m) (Figure 14). ¹⁹F NMR (400 MHz, CDCl₃), [δ, ppm]:142.28 (Figure 15). IR (KBr, cm⁻¹): 1618.5, 1556.2, 1037.4, 646.7 (Fgure16). Anal calcd for $C_{15}H_{10}BF_2ClO_2$, C 59.21%, H 3.26%. Found C 59.15 %, H 3.18 %. UV-Vis: λ_{max} /nm (DCM) 366.34.

Borondifluoro[1-(2-hydroxyphenyl)-3-(4-bromophenyl)-2-propenoato-O,O'](3C): ¹HNMR (400 MHz, CDCl₃), [δ, ppm]: 8.44-8.41 (1H, d), 7.94-7.92 (1H, dd), 7.80-7.76 (1H, m), 7.68-7.54 (5H, m), 7.18-7.16 (1H, dd) and 7.08-7.04 (1H, m) (Figure17). 19F NMR (400 MHz, CDCl₃). ¹⁹F NMR (400 MHz, CDCl₃), [δ, ppm]:142.23 (Figure 18). IR (KBr, cm⁻¹): 1616.2, 1555.6, 1033.8, 634.2 (Figure 19). Anal calcd for C₁₅H₁₀BF₂BrO₂, C 55.33 %, H 2.84 %. Found C 55.20 %, H 2.60 %. UV-Vis: λ_{max} /nm (DCM) 377.54,



Borondifluoro[1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propenoato-O,O'](4C): ¹H NMR (400 MHz, CDCl₃), [δ, ppm]: 8.51-8.48 (1H, d), 7.94-7.91 (1H, dd), 7.78-7.74 (2H, m), 7.73-7.70 (1H, m), 7.50-7.46 (1H, d), 7.16-7.14 (1H, dd), 7.05-7.01 (3H, m) and 3.92 (3H, s) (Figure 20). 19F NMR (400 MHz, CDCl₃), [δ, ppm]: 143.29 (Figure 21). IR (KBr, cm⁻¹): 1617.5, 1559.9, 1031.6, 659.4 (Figure 22). Anal calcd for $C_{15}H_{13}BF_2O_3$, C 63.61 %, H 4.30 %. Found C 63.15 %, H 4.20 %. UV-vis: λ_{max}/nm (DCM) 454.00.

Borondifluoro[1-(2-hydroxyphenyl)-3-(4-methylphenyl)-2-propenoato-O,O'](5C): ¹H NMR (400 MHz, CDCl₃), [δ, ppm]: 8.51-8.47 (1H, d), 7.95-7.93 (1H, dd), 7.77-7.73 (1H, m), 7.69-7.67 (2H, m), 7.61-7.57 (1H, d), 7.33-7.31 (2H, d), 7.17-7.14 (1H, dd), 7.06-7.02 (1H, m) and 2.49 (3H, s) (Figure 23). ¹⁹F NMR (400 MHz, CDCl₃), [δ, ppm]: 142.81 (Figure 24). IR (KBr, cm⁻¹): 1617.1, 1556.2, *www. joac.info* 1626

1032.2, 655.8 (Figure 25). Anal calcd for $C_{15}H_{13}BF_2O_2$, C 67.17 %, H 4.54%. Found C 67.02 %, H 4.34 %. UV-Vis: λ_{max}/nm (DCM) 382.0.





Figure 25. IR spectra of complex 5C.

Biological Studies

In silico analysis of target protein based on lead molecule activity: The selected protein structures are validated using Ramachandran Plot server at Uppsala University. Thus, stereo-chemical activity and quality were presented in table 1 [6]. The resultant overall modeled structures are potentially used for docking against the synthesized ligands [7].

Molecular docking studies: The different functional characteristic of inflammatory, microbial and cancerous receptor-proteins was performed using PATCHDOCK server [8]. The energy values are given in the above table 2.

RCSB, PDB Data bases	Residues in Ramachandran Plot checked	In core regions (plus signs)	Outlier
4B3Z	1709	1674	35
2LAO	217	212	5
2E5B	852	837	15
2BRX	387	374	13
4FPR	479	469	10
2YT8	1600	1533	67

Table 1.Ramachandran Plot Analysis

Molecular docking studies: The different functional characteristic of inflammatory, microbial and cancerous receptor-proteins was performed using PATCHDOCK server [9]. The energy values are given in the above table 2.

2LAO	Complexes	Docking Score (Kcal/mol)	2LAO	Complexes	Docking Score (Kcal/mol)
Cholesterol	1C	3962	I. 2E5B	1C	5010
Esterase	2C	4366	Inflammatory	2C	5136
	3C	4130		3C	4824
	4C	4378	II.	4C	5248
	5C	4334		5C	5086
III. 4B3Z	1C	4546	2YT8	1C	3782
Cancerous	2C	4854	IV. NEURONAL	2C	3850
	3C	4564		3C	3742
V.	4C	4836		4C	3970
	5C	4842	VI.	5C	3854
2BRX	1C	4322	VII. 4FPR	1C	4696
VIII. MICROBIAL	2C	4492	Fungal	2C	4866
	3C	4292		3C	4820
	4C	4650	IX.	4C	5194
Х.	5C	5238		5C	5000

Table 2. Docking analysis

APPLICATION

The synthesized novel metal complexes were playing an important role in medical field and drug synthesis. The biological study carried over on theses complexes shows positive results for anti-fungal, anti-neural, anti-inflammatory, anti-microbial, anti-cancer and anti-cholesterol activities. This present work is helpful in various new drug synthesis and reference for new complex formations in coordination chemistry.

CONCLUSION

The ligands and complexes synthesized are purified by column chromatography. The elementary analysis was done by NMR and IR, the biological activities are showing that, the five ligands and complexes are showing Anti-cancer, Anti- microbial and Anti-inflammatory

properties, Anti-fungal, Anti-cholesterol, Anti neural, the results are mentioned in the above tables.

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