Medicinal Chemistry
ISSN: 2161-0444

Manjubhargavi and Santosh, Med Chem (Los Angeles) 2018, 8:6
DOI: 10.4172/2161-0444.1000506

Research Article Open Access

Synthesis Characterization of New Polynucleating Ligands and their Biological Studies

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Abstract

This article summarizes synthesis of three new poly-nucleating ligands successfully in alcoholic medium. The ligands synthesized are characterized quantitatively and qualitatively by using NMR, IR Spectroscopy and UV-visible. The further biological activity are made like anti-cancer, anti-inflammatory and anti-microbial, these activities revealed that ligands I to III are showing positive results.

Keywords: Polynucleating ligands; NMR; IR; UV-visible spectra; Anticancer; Anti-microbial; Anti-inflammatory; Drug designing

Introduction

In the context of d-metal chemistry, the term complex means a central metal atom or ion surrounded by a set of ligands. The modern study of coordination compounds began with two men, Alfred Werner and Sophus Mads Jorgenson. 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. 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. Coordination chemistry plays a most important role in biological systems. For example, haemoglobin an iron-porphyrin complex of human blood plays a vital role in oxygen transport mechanism [1]. Chlorophyll, magnesium containing porphyrin complex plays a role in plant photosynthesis. Molybdenum cofactor of nitrogenase enzyme is essential for nitrogen fixation [2]. Vitamin B12 (cyanocobalamin) is a cobalt containing complex plays an important role in carbohydrate, fat and protein metabolism. Vitamin B12 deficiency causes pernicious anaemia in human beings. At the start of the 20th century, inorganic chemistry was not a prominent field until Werner studied the metal-amine complexes such as $[Co(NH_3)_6Cl_3]$. Werner recognized the existence of several forms of cobalt-ammonia chloride. These compounds have different colour and other characteristics. The chemical formula has three chloride ions per mole, but the number of chloride ions that precipitate with Ag^+ ions per formula is not always three. He thought only ionized chloride ions will form precipitate with silver ion. To distinguish ionized chloride from the coordinated chloride, Werner formulated the complex formula and explained structure of the cobalt complexes [3]. Coordination compounds have posed many challenges to the inorganic chemists. It is the chemistry of metals and its complexes/compounds with other organic/ inorganic groups called ligands. Coordination compounds are formed by almost all transition metals, lanthanide series metals and some of the non-metals like silicon etc. 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). 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 $Ni(ClO_4)_2$ 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.

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

The Lewis bases attached to the metal ion in such compounds are called ligands. These may be simple ions such as Cl^-, small molecules such as H_2O or NH_3, larger molecules such as $H_2NCH_2CH_2NH_2$ or $N(CH_2CH_2NH_2)_3$, or even macromolecules, such as proteins. The atom in the Lewis base ligand that forms the bond to the central atom is called the donor atom, because it donates the electrons for bond formation. The nature of a bond between metal ion and a donor atom in an coordination compound depends upon various factors like the nature of the metal ion, oxidation state of metal ions, nature of donor atoms, structure of the ligands, steric factors and metal ligand orbital interaction. The majority of ligands are either neutral or anionic. Those which coordinate to a metal ion through a single atom are described as mono-dentate or uni-dentate. Examples of such ligands include water, ammonia, chloride etc. Where two donor atoms can be used to bind to a metal ion, as with $H_2NCH_2CH_2NH_2$, the ligand is said to be bidentate and where several donor atoms are present in a single ligand as with $N(CH_2CH_2NH_2)_3$, the ligand is said to be polydentate. When a bi- or polydentate ligand uses two or more donor atoms to bind to a single metal ion, it is said to form a chelate complex (from the Greek for claw) [4]. A huge variety of ligands appear in coordination complexes. A variety of elements function as donor atoms towards metal ions, but the most commonly encountered are probably nitrogen, phosphorus, oxygen, sulfurand the halides. In addition, a large number of compounds are known which contain carbon donor atoms; these are known as organometallic compounds. Bidentate ligands may be classified according to the number of atoms in the ligand which separate the donor atoms and hence the size of the chelate ring formed with the metal ion. Thus 1,1-ligands form a four-membered chelate ring when bound to a metal ion, 1,2-ligands a five membered ring, and so on. Cyclic compounds which contain donor atoms oriented so that they can bind to a metal ion and which are large enough to encircle it are known as macro cyclic pro-ligands. Bicyclic pro-ligands are also known which can completely encapsulate a metal ion. Some of these systems have given the names cryptand or sepulchrate, which reflect their ability to wrap up and entomb the metal ion [5]. Sometimes

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Received May 26, 2018; **Accepted** June 11, 2018; **Published** June 16, 2018

Citation: Manjubhargavi OJ, Santosh MS (2018) Synthesis Characterization of New Polynucleating Ligands and their Biological Studies. Med Chem (Los Angeles) 8: 147-153. doi: 10.4172/2161-0444.1000506

ligands can bind to more than one metal ion in a bridging arrangement. Certain polydentate ligands are particularly good at linking together several metal ions and are referred to as poly-nucleating ligands [6]. Transition metal atoms have one *s*, three *p*, and five *d* orbitals that possess geometrical and energetic features suitable for bonding with the ligands [7]. In certain cases these nine orbitals permit the formation of bonds with nine ligands.

Scope and Objective of the Proposed Work

Objectives

The biological activity of the synthesized metallic complexes will lead to the development of new drugs. The results of research may be useful in understanding the structure and activity relationship of synthesized metallic complexes and their applications in various medicinal applications. The main objectives of the proposed research plan are as follows.

- To synthesize new polynucleating ligands.
- To study specific activities of synthesized ligands.
- To synthesize series of transition metal complexes.
- Structural characterization of new ligands and the complexes by micro analysis, infrared spectra, electronic spectra, NMR spectra, magnetic susceptibility measurements, molar conductance measurements and thermo gravimetric analysis.
- To study the preliminary biological activities of the synthesized ligands and complexes.

Materials and Methods

All the chemicals used were of analytical grade. Solvents were purified and dried according to standard procedure (Vogel 1989). 2-hydroxyacetophenone, benzaldehyde derivatives and boron triflouride etherate were purchased from Sigma Aldrich.

Physical measurements

Electronic spectra were measured on a GBC UV-Vis double beam spectrophotometer in dichloromethane solution in the 200-800 nm range. FT-IR spectra were recorded on a Thermo Nicolet Avatar FT-IR spectrometer as KBr powder in the frequency range 400-4000 cm^{-1}. The C, H and N contents were determined by Thermo flash EA1112 series elemental analyzer. ^{1}H NMR and ^{19}F NMR spectra were recorded in Bruker AV 400 instrument. 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.

General procedure for synthesis of ligands (1L-3L)

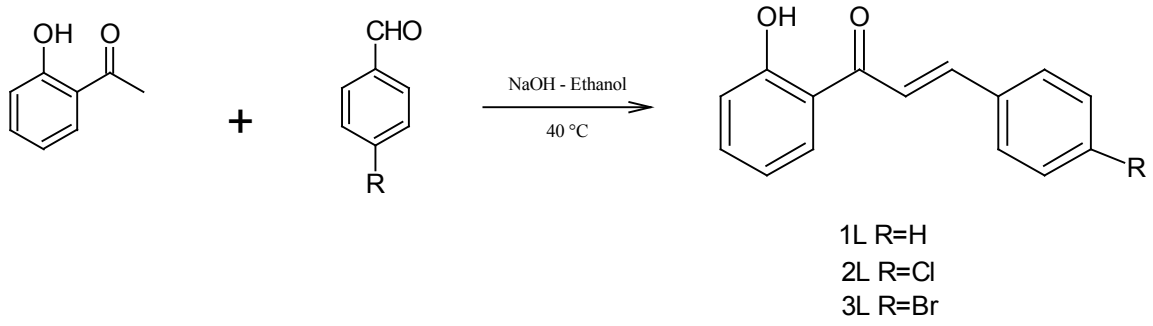
Ligands (**1L-3L**) were prepared by adding sodium hydroxide to the 2-hydroxyacetophenone and benzaldehyde derivatives in ethanol at 40°C. The mixture was stirred for 20 min and cooled to room temperature. The precipitate that formed was dissolved in water. The solution was made slightly acidic using dilute hydrochloric acid. The precipitate formed was filtered, washed with ice cold ethanol, and dried over calcium chloride to obtain crude ligands**.** These were purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (Scheme 1).

1 (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 3.20 g (23.5 mmol), the mixture was stirred for 20 minutes. To this solution 2.50 g (23.5 mmol) of benzaldehyde in 20 ml of ethanol was added at 40°C. The mixture was stirred for 2 hrs 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%.

^{1}H NMR (400 MHz, $CDCl_3$), [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 1A). IR (KBr, cm^{-1}): 1635.5, 1565.8, 1199.4, 734.2 (Figure 1B). Anal calcd for $C_{15}H_{12}O_2$, C 80.33%, H 5.35%. Found C 80.20%, H 5.23%. UV-vis: λ_{max}/nm (DCM) 317.48.

Linear optical study: The electronic spectra of the ligand (**1L**) are shown in Figure 1C.

(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 3.00 g (22.03 mmol), the mixture was stirred for 20 minutes. To this solution 4.02 g (28.64 mmol) of 4-chlorobenzaldehyde in 20 ml of ethanol was added at 40°C. The mixture was stirred for 2 hrs 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%. ^{1}H NMR (400 MHz, $CDCl_3$), [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,



Scheme 1: Synthesis of ligands (**1L-3L**).

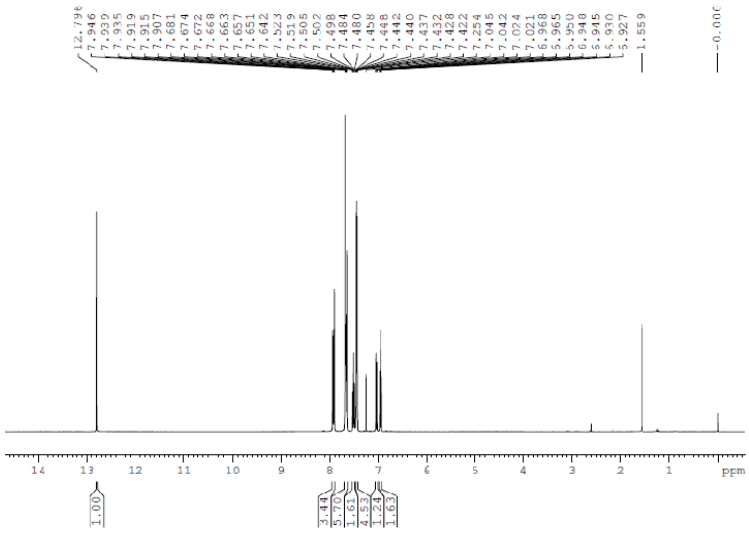


Figure 1A: ^{1}H NMR spectra of ligand **1L.**

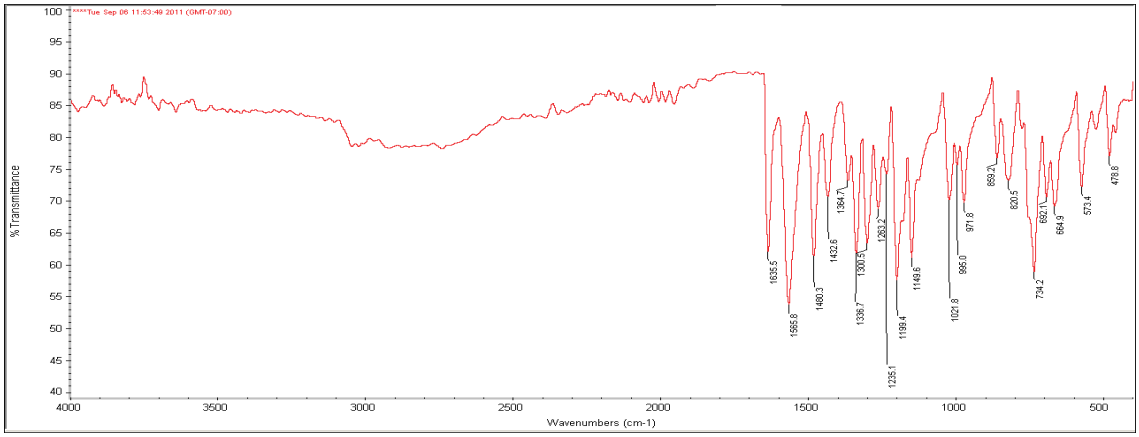


Figure 1B: IR spectra of ligand **1L.**

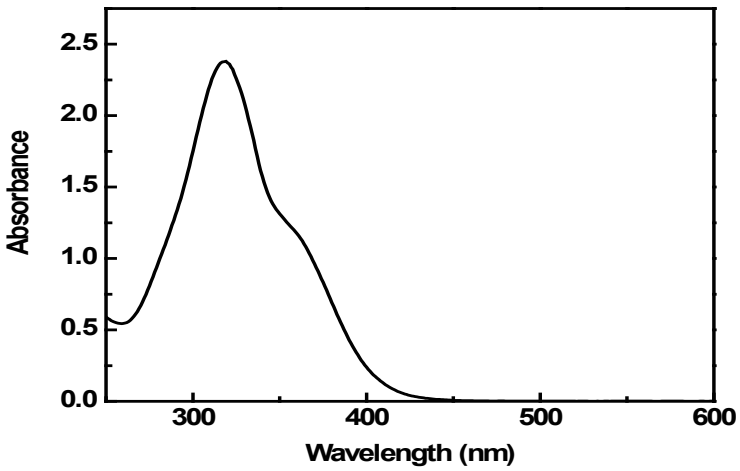


Figure 1C: UV-visible spectra of the ligand **1L.**

m) and 6.97-6.93 (1H, m) (Figure 2A). IR (KBr, cm^{-1}): 1636.9, 1561.8, 1201.6, 754.0 (Figure 2B). Anal calcd for $C_{15}H_{11}ClO_2$, C 69.63%, H 4.25%. Found C 69.43%, H 4.18%. UV-vis: λ_{max}/nm (DCM) 322.3.

Linear optical study: The electronic spectra of the ligand (**2L**) are shown in Figure 2C.

(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 1.47 g (10.8 mmol), the mixture was stirred for 20 minutes. To this solution 2.0 g (10.8 mmol) of 4-bromobenzaldehyde in 20 ml of ethanol was added at 40°C. The mixture was stirred for 2 hrs 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%. ^{1}H NMR (400 MHz, $CDCl_3$), [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 3A). IR (KBr, cm^{-1}): 1639.3, 1561.6, 1201.8, 750.1 (Figure 3B). Anal calcd for $C_{15}H_{11}BrO_2$, C 59.42%, H 3.62%. Found C 59.23%, H 3.40%. UV-vis: λ_{max}/nm (DCM) 361.95.

Linear optical study: The electronic spectra of the ligand (**3L**) are shown in Figure 3C.

Biological Study of the Ligands

In silico analysis of target protein based on lead molecule activity

The anti-microbial, anti-cancer, and anti-inflammatory protein receptor structures were directly used for molecular docking. The 3D structures 1MZC with cancerous origin, 2TOD with microbial origin and 4F2A with inflammatory origin were taken for this work. Proteins were taken from RCSB database.

The selected protein structures are validated using RAMPAGE Ramachandran Plot server. Thus, stereo-chemical activity and quality were presented in Table 1. The resultant overall modeled structures are potentially used for docking against the synthesized ligands [8-11].

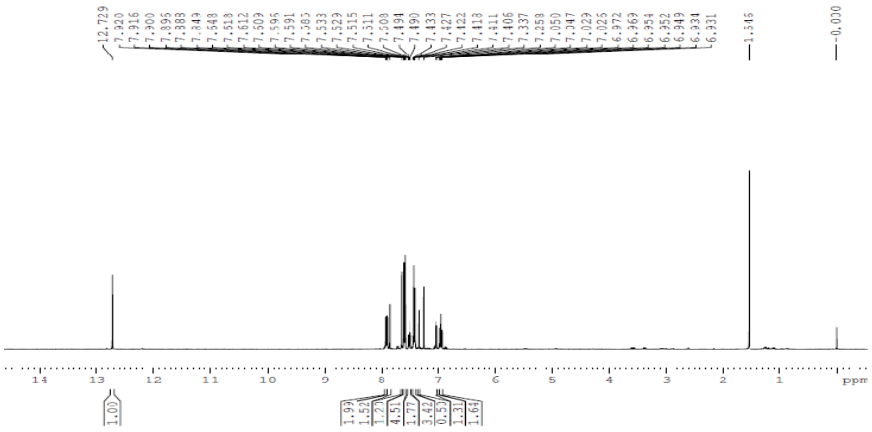


Figure 2A: ^{1}H NMR spectra of ligand **2L.**

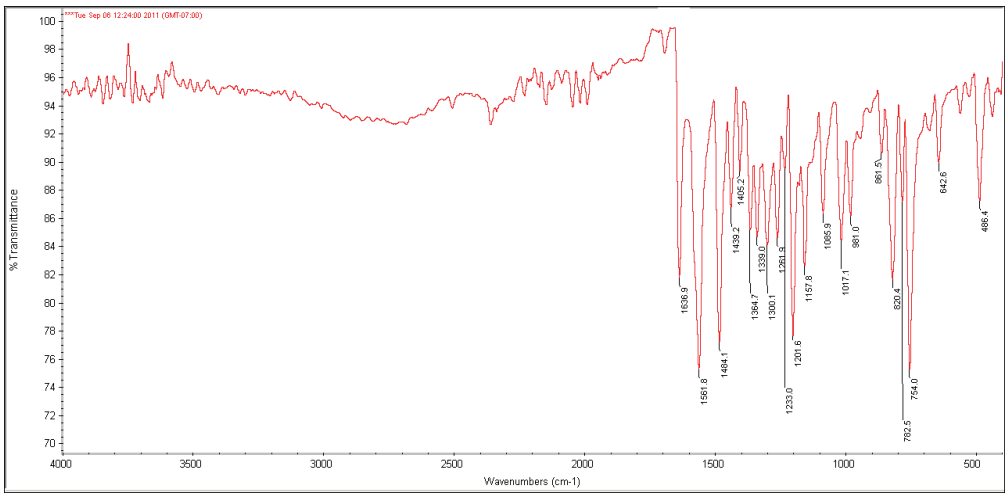


Figure 2B: IR spectra of ligand 2L.

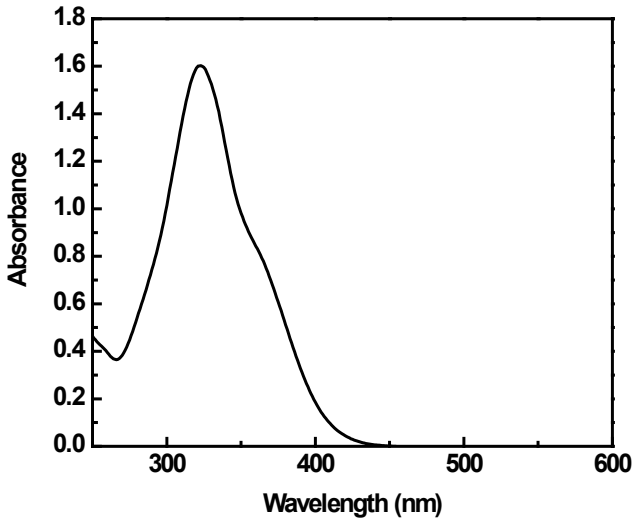


Figure 2C: UV-visible spectra of ligand 2L.

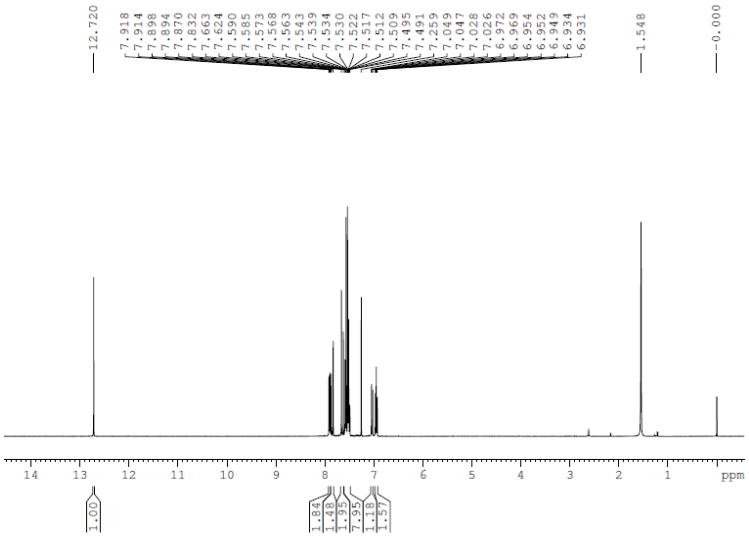


Figure 3A: ^{1}H NMR spectra of ligand 3L.

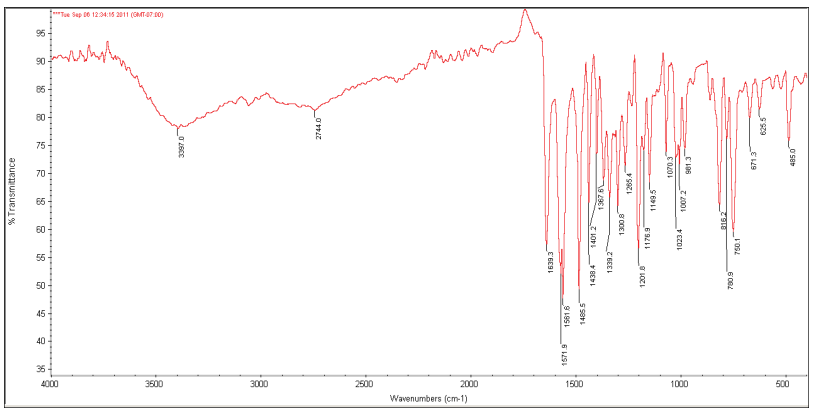


Figure 3B: IR spectra of ligand 3L.

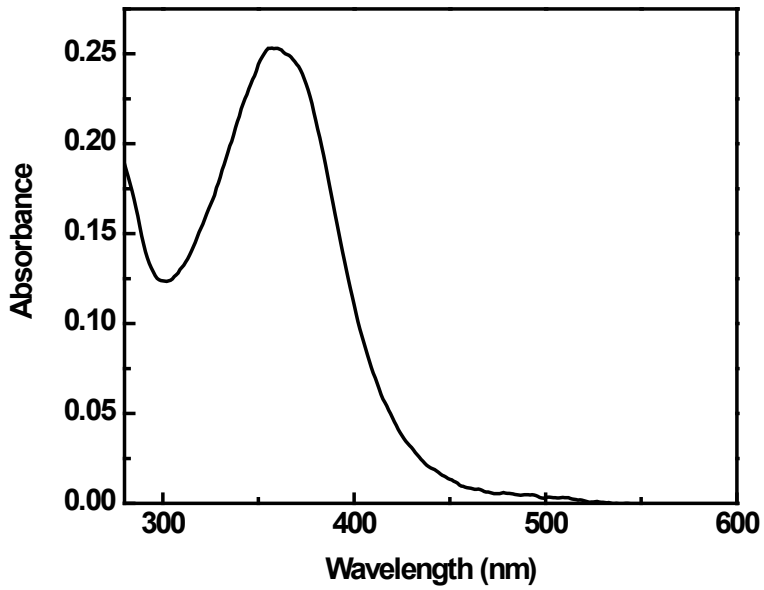


Figure 3C: UV-visible spectra of ligand 3L.

	Number of residues in favoured region (~98.0% expected)	Number of residues in allowed region (~2.0% expected)	Number of residues in outlier region
1MZC	697 (97.3%)	17 (2.4%)	2 (0.3%)
2TOD	1329 (95.8%)	52 (3.7%)	6 (0.4%)
4F2A	434 (92.3%)	34 (7.2%)	2 (0.4%)

Table 1: Ramachandran plot analysis.

1MZC		Docking Score (in Kcal/mol)
Anti-cancerous	1L	4470
	2L	5270
	3L	5530
2TOD		
Anti-microbial	1L	4140
	2L	4940
	3L	4594
4F2A		
Anti-inflammatory	1L	4206
	2L	5302
	3L	4540

Table 2: Docking analysis.

	miLogP	TPSA	natoms	MW	nON	nOHNH	nrotb	Volume	nviolations
1L	1.07	20.40	21	286.09	2	0	2	270.97	0
2L	4.20	37.30	18	238.29	2	1	3	226.43	0
3L	5.24	62.03	25	330.39	4	1	3	306.09	1

Legends: LogP: (octanol/water partition coefficient); TPSA: Molecular Polar Surface Area; natoms: number of atoms; MW: Molecular weight; nON: Number of ON; nOHNH: number of OHNH; Volume: Molecular volume, nrotb: Number of rotatable bonds; nviolations: number of violations.

Table 3: ADME studies.

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 anti-inflammatory, anti-microbial and anti-cancerous receptor-proteins was performed using PATCHDOCK server. The energy values are given in Table 2 [8-11].

In silico screening ADMET (Absorption, Distribution, Metabolism and Excretion) studies

There are many compounds with poor bioavailability shows less effective against disease. To solve this problem, predicting bioavailability properties will be great advantage for drug development. Hence using computer based methods like ADME the molecular descriptors and drug likeliness properties was studied. The pharmacokinetic properties are represented in Table 3.

From the overall results, it was predicted that test compounds (except **3L**) have good drug like, lead like and fragment like properties which are strongly accepts for pharmacokinetic and toxicity properties [8-11].

Conclusion

The proposed ligands are showing an importance in the field of medicinal chemistry, synthesized ligands are purified by column chromatography. The elementary analysis was done by NMR and IR, and UV, the biological activities shows that, the three ligands are showing anti-cancer, anti-microbial and anti-inflammatory properties, the results are mentioned in the above tables.

Acknowledgements

Our sincere thanks to Padmashree Institute of Management and Sciences, Bengaluru, India.

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