Study Of Anti-Inflammatory Activity Of Different 1,4-Naphthoquinone Derivatives And Their Metal Chelates: Synthesis, Characterization, Elemental Analysis

Shivani, Research Scholar (Chemistry), SunRise University, Alwar (Raj.)
Dr. Parveen Kumar, Associate Professor, Department of Chemistry,Sunrise University Alwar (Raj.)

ABSTRACT

The aim of this work is to synthesize, characterize, elemental analysis and study of anti-inflammatory activity of 1,4-naphthoquinone derivatives and their metal chelates. Continuing our work with another derivatives of 1,4-naphthoquinone ligands, this work had been constructed for synthesis of new ligands derived from 1,4-naphthoquinone. which characterized on the basis of elemental analysis, electronic, IR, H- NMR spectral data. The synthesized ligands have been carried out to achieve the coordination behavior towards bi-valent metal ions like cobalt, zinc and copper. The solid chelates of the different ligands were prepared and subjected to analytical techniques such as elemental analyses, spectroscopic techniques including H-NMR, and IR spectroscopy, and thermal analyses techniques. The chelates were found to have octahedral geometry. The pharmacological activity of the prepared ligands and their binary metals complexes were also screened.

Keywords: 1,4-Naphthoquinone, Metal Complexes, Analgesic Acivity, NMR Spectroscopy

INTRODUCTION

During the beginning of nineteenth century some chemists like Berthelot started to put together the organic molecules which have some importance. Due to lesser understanding about molecular structure made the mid nineteenth century chemists confusion of synthetic organic molecules. Hofmann worked on some chemicals obtained from coal tar and suggested it can be possible to synthesize quinine like anti-malarial drug from chemicals obtained from coal tar that would help to independent on the European supply of natural quinine from plants. Later on Perkin tried at his small home laboratory for the synthesis of the quinine molecule but he failed to synthesize the quinine molecule from the available starting material. He failed to prepare the quinine molecule the one of the major reason for this was that at that time the molecular structure of the quinine was incomplete. But during the trial basis Perkin achieved some other things greater. During the vacation period Perkin decided to synthesis some synthetic dyes. After hard work of six months he succeeded to prepare a dye called Aniline purple. This dye at that time became more popular and then he founded a huge synthetic dye industry. After this the natural dyes started to duplicate in the laboratory. In 1867, Baeyer achieved success in the synthesis of dye indigo, alizarin which is also important naturally occurring dyes.

Naphthoquinone and their derivatives:

Most of Naphthoquinone are mainly obtained from natural source. The naphthoquinone are having different biological activities. Chemically naphthoquinone are the class of organic compounds derived from Naphthalene. Normally these exist in three isomeric forms. i.e.

1] 1,2-Naphthoquinone
2] 1,4-Naphthoquinone
3] 2,6-Naphthoquinone.

Transition metal chelates and co-ordination compounds.

A complex co-ordinate compound with polydentate ligand involving ring structure with metal is called metal chelate. Different naphthoquinones acts as multidentate ligand and are able to form metal chelates with different transition metals.

Transition metals possess characteristics property off undergoing complex formation. Due to this remarkable tendency, they form a large number of coordination compounds. Coordination compounds are not only formed by transition elements but also formed by several other non-transition metals although the tendency is much less. The subdivision of the subject chemistry involve the detailed study of Coordination compounds are great extently allotted in minerals, plants and animals and supposed to have played various

significant biofunctions. The process of photosynthesis in plants involve chlorophyll which is nothing but a coordination compound of Mg. The main red colored component of blood hemoglobin responsible for regulation of respiration process in animal world is a coordination compound of iron. A variety of metallurgical process catalyst and analytical reagents make use of coordination compounds. Therefore the study of coordination compounds is highly significant from biological , industrial and analytical point of view.

In general a coordination compound contains a central metal ion or atom surrounded by number of oppositely charged ions or neutral molecules. The bond between metal atom and these ions or molecules is coordinate bond.

e.g. $[Cu(NH_3)_4]^{2+}$ In these complex copper is the central metal ion while ammonia is the neutral molecule.

First time the chelate name was used by Greek chemist G.T.Morgan & Drew[5]The basis for metal chelates is the Werner's theory of coordination compounds.

The Werner has given some postulates in his theory, they are as given below,

1. Most of the metallic components possess 2 kinds of valance.
2. principal valence and secondary valence.
3. Every metal tends to satisfy both of its primary and secondary valence.
4. Every metal has a fixed number of secondary valence..
5. The secondary valence is always directed towards fixed positions in space.

The principal valence is also known as primary valence or ionisable valence designated by solid line. In modern term it corresponds to the oxidation state of the metal ion. The secondary valence also called as auxilary valence or subsidiary valence or residual or non-ionisable valence, designated by dotted line. In recent terms , it corresponds to the coordination number of the metal ion. Thus according to Werner there are two spheres of attraction around the metal ion in a complex. Inner sphere is the coordination sphere while outer sphere is the ionization sphere. Groups present in the inner sphere are rather firmly attached to the metal ion and therefore cannot be separated easily. On the other hand, the group present in the ionization sphere are loosely bound and therefore they can be separated as ions on dissolving the complex in suitable solvent.

The primary valences are those which a metal ion exercises towards the negative groups so that normal charge is satisfied by the formation of simple salts. Every element is characterized by its fixed secondary valence. For example, Fe(II), Co(II) and Pt(II) have coordination number 6,4 and 2 respectively.

Ligands:

The ligands are neutral molecules or ions and these are coordinated to the central metal ion or atom. These are also donor groups.

e.g. In $K_4[Fe(CN)_6]$ the six cyanide ions are coordinated to Fe2+ are the ligands. Similarly, in $[CoCl_2(NH3)_4]Cl$ the four ammonia molecules and the two chloride ions are the ligands.

Classification of Ligands.

Ligands can be classified into the following types depending upon total count of atoms that can be donated in the ligand i.e. denticity.

1).Unidentate ligand: The ligands having only one donor or one site of attachment and can coordinate to the central metal atom or ion at the only one place in the complex can be termed as monodentate ligand.

2) Multidentate ligands: The donor groups or neutral molecule which is having more than two sites of attachment and bind to the central metal atom or ion to form complex is regarded as polydentate ligands.

Polydentate ligands are further classified into bi, tri, tetra…. Hexa dentate depending upon the number of points of attachment with the ligand. It the chelate ligand has two points of attachments or donor groups. It is called bidentate, if three it is called tridentate and so on. e.g. Ethylene diamine(en) i.e. $H_2N\text{-}CH_2\text{-}CH_2\text{-}NH_2$, has two points of attachments with a metal ion, where each nitrogen atom donates a pair of electrons.

3) Ambidentate ligands: If ligand has two or more donor atoms, however while a complex is formed only one donor atom is attached to the metal then it is called ambidentate ligand. e.g. $NO2^-$ group has the donor atoms (N and O) . Out of the two only one donor atom is linked to the metal as M-NO_2 or M-ONO. The ligands like L_2X_4 ligand, Which has characteristics of the four negative ions and two neutral donating places should be categorized into L_2X ligand.

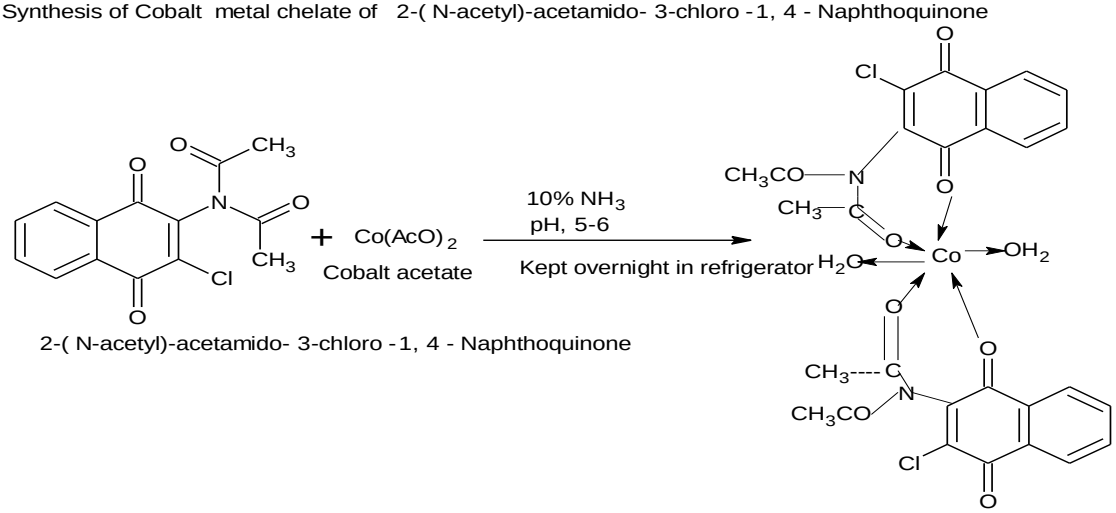
SYNTHESIS OF DIFFERENT 1,4-NAPHTHOQUINONE DERIVATIVES & THEIR METAL CHELATES

Synthesis of metal[Co,Cu,Zn&Cd] chelates of 2-(N-acetyl)-acetamido-3-chloro- 1,4-napthoquinone

A. Synthesis of Cobalt [Co] Metal Chelate of 2-(N-acetyl)-acetamido-3-Chloro-1,4-naphthoquinone:

Scheme of Synthesis

Synthesis of Cobalt metal chelate of 2-(N-acetyl)-acetamido- 3-chloro -1, 4 - Naphthoquinone

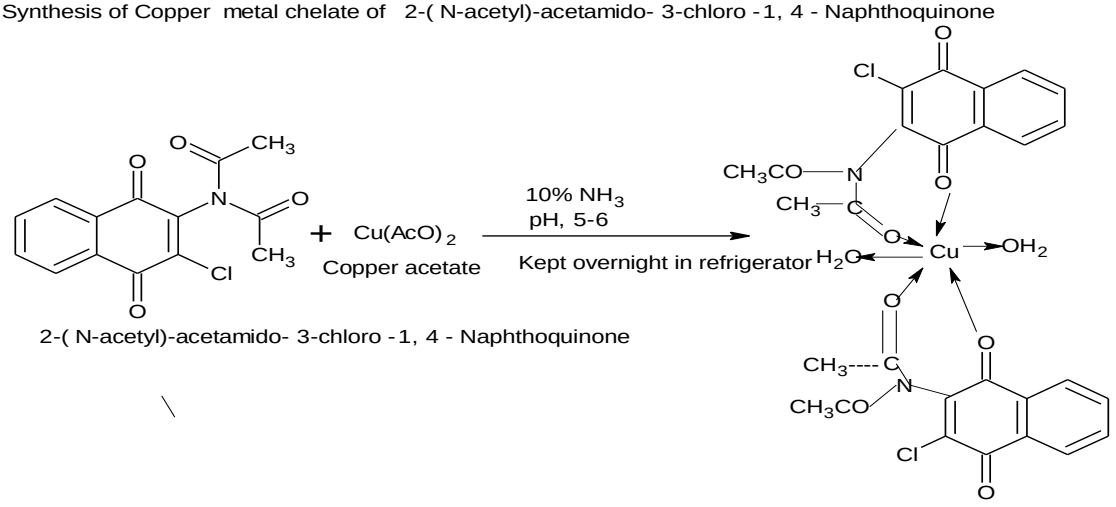


Cabalt chelate of 2-(N-acetyl)-acetamido- 3-chloro-1, 4- Naphthoquinone

B. Synthesis of the Copper Metal Chelate of 2-(N-acetyl)-acetamido-**3-Chloro-1,4-naphthoquinone Ligand Solution:**

Scheme of Synthesis

Synthesis of Copper metal chelate of 2-(N-acetyl)-acetamido- 3-chloro -1, 4 - Naphthoquinone

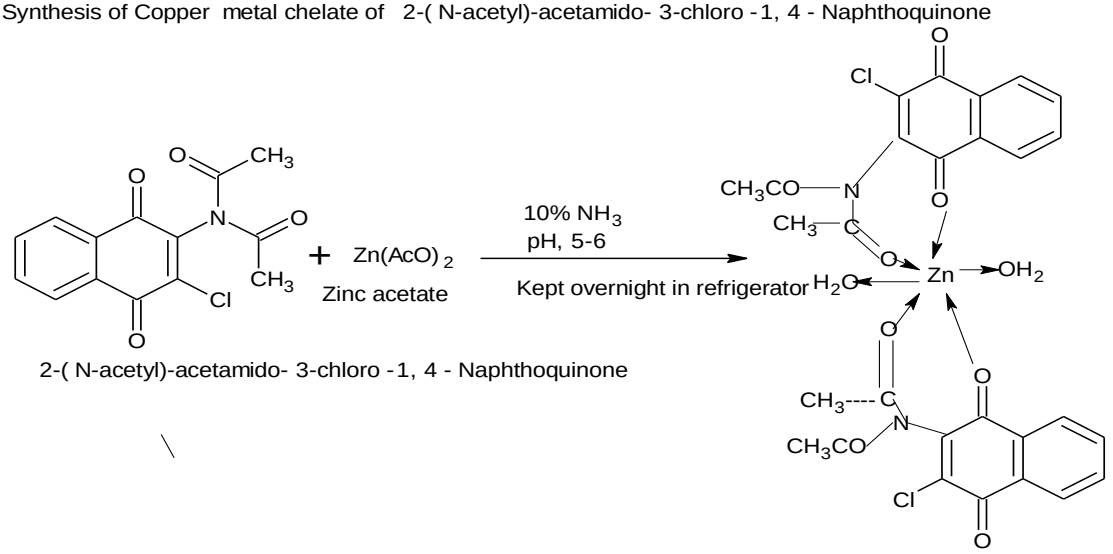


Copper chelate of 2-(N-acetyl)-acetamido- 3-chloro-1, 4- Naphthoquinone

C. Synthesis of Zinc[Zn] Metal Chelate of2-(N-acetyl)-acetamido-3-Chloro-1,4-naphthoquinone:

Scheme of Synthesis

Synthesis of Copper metal chelate of 2-(N-acetyl)-acetamido- 3-chloro -1, 4 - Naphthoquinone



2-(N-acetyl)-acetamido- 3-chloro -1, 4 - Naphthoquinone

Zinc chelate of 2-(N-acetyl)-acetamido- 3-chloro-1, 4- Naphthoquinone

CHARACTERIZATION OF 1,4-NAPHTHOQUINONE DERIVATIVES AND THEIR METAL CHELATES.

Different physical characters of metal chelates of 1,4-Naphthoquinone derivatives and their metal chelates described as,

1. Elemental Analysis
2. Physical Constant(M.P.) determination
3. IR Spectral Studies
4. NMR Spectral Studies.

Elemental Analysis of 1,4-Naphthoquinone Derivatives And Their Metal Chelates.:

All the compounds syntheisized were subjected for elemental analysis of C,H,O and N contents by Perkin Elmer Elemental analyser. The C.H, O & N contents of all compounds are shown in table.

Table 1: Elemental Analysis of Synthesized compounds.

Sr. No.	Compound	Molecular Formula	Mol.Wt gm./mole	Elemental Analysis					
				% C		% H		% O	
				Cal.	Found	Cal.	Found	Cal.	Found
1	G	$C_{12}H_8O_3Cl.N$	249.45	57.72	57.63	3.20	3.11	19.24	19.15
2	G-1	$Co[C_{12}H_8O_3Cl.N]_2.2H_2O$	594	48.48	48.39	3.37	3.28	21.55	21.47
3	G-2	$Cu[C_{12}H_8O_3Cl.N]_2.2H_2O$	598.5	48.12	48.07	3.34	3.26	21.38	21.29
4	G-3	$Zn[C_{12}H_8O_3Cl.N]_2.2H_2O$	600.4	47.97	47.88	3.33	3.26	21.32	21.25
5	G-4	$Cd[C_{12}H_8O_3Cl.N]_2.2H_2O$	647.4	44.48	44.39	3.08	3.01	19.77	19.69
6	H	$C_{16}H_9O_4Cl.N$	314.45	61.05	60.98	2.86	2.77	20.35	2026
7	H-1	$Co[C_{16}H_9O_4Cl.N]_2.2H_2O$	724	53.04	53.01	3.04	3.00	22.09	22.02
8	H-2	$Cu[C_{16}H_9O_4Cl.N]_2.2H_2O$	728.5	52.71	52.64	3.02	2.98	21.97	21.89
9	H-3	$Zn[C_{16}H_9O_4Cl.N]_2.2H_2O$	730.4	52.57	52.49	3.01	2.98	21.91	21.87
10	H-4	$Cd[C_{16}H_9O_4Cl.N]_2.2H_2O$	777.4	49.39	49.31	2.83	2.75	20.58	20.49
11	I	$C_{16}H_9O_4Cl.N$	314.45	61.05	60.98	2.86	2.75	20.35	20.26
12	I-1	$Co[C_{16}H_9O_4Cl.N]_2.2H_2O$	724	53.04	53.01	3.04	3.00	22.09	22.02
13	I-2	$Cu[C_{16}H_9O_4Cl.N]_2.2H_2O$	728.5	52.71	52.64	3.02	2.98	21.97	21.89
14	I-3	$Zn[C_{16}H_9O_4Cl.N]_2.2H_2O$	730.4	52.57	52.49	3.01	2.98	21.91	21.87
15	I-4	$Cd[C_{16}H_9O_4Cl.N]_2.2H_2O$	777.4	49.39	49.31	2.83	2.75	20.58	20.49
16	J	$C_{16}H_9O_4Cl.N$	314.45	61.05	60.98	2.86	2.79	20.35	2026
17	J-1	$Co[C_{16}H_9O_4Cl.N]_2.2H_2O$	724	53.04	53.01	3.04	3.00	22.09	22.02
18	J-2	$Cu[C_{16}H_9O_4Cl.N]_2.2H_2O$	728.5	52.71	52.64	3.02	2.98	21.97	21.89
19	J-3	$Zn[C_{16}H_9O_4Cl.N]_2.2H_2O$	730.4	52.57	52.49	3.01	2.98	21.91	21.87
20	J-4	$Cd[C_{16}H_9O_4Cl.N]_2.2H_2O$	777.4	49.39	49.31	2.83	2.75	20.58	20.49

Physical Constant(M.P.) determination of different 1,4-Naphthoquinone Derivatives and Their Metal Chelates:

The melting points of the compounds that were synthesized were determined with the help of digital melting point apparatus. The Melting point of various synthesized compounds are shown as in the following table.

Table2: Physical Constant (M.P.) determination of different 1,4-Naphthoquinone Derivatives And Their Metal Chelates

Sr. No.	Compound No.	Melting Point [0^0C]	% Yield
1	G	206-208	45
2	G-1	220-222	43
3	G-2	216-218	46
4	G-3	218-220	44
5	G-4	219-221	46
6	H	216-218	48
7	H-1	222-224	42
8	H-2	220-222	43
9	H-3	224-226	46
10	H-4	223-225	44
11	I	215-217	47
12	I-1	223-225	48
13	I-2	226-228	45
14	I-3	225-227	46
15	I-4	230-232	43
16	J	218-220	43
17	J-1	224-226	45
18	J-2	226-228	44
19	J-3	225-227	45
20	J-4	227-229	43

Infrared Spectral Studies:

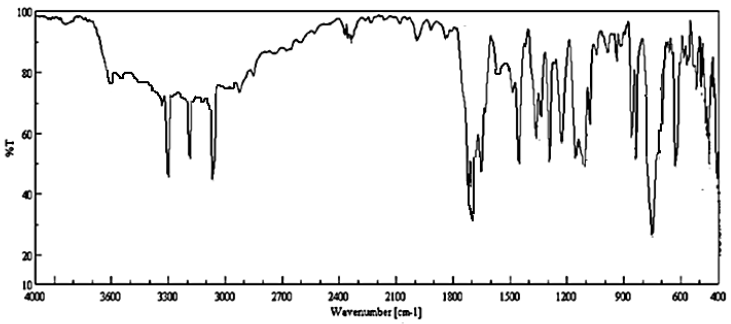


Fig 1: IR spectra of Compound- G

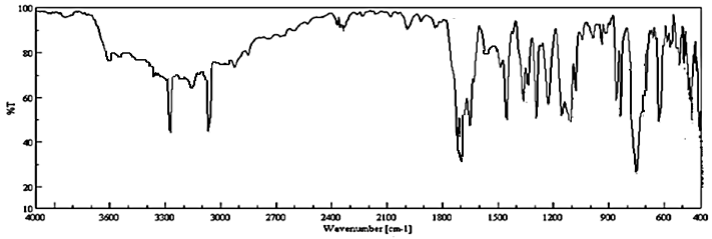


Fig 2: IR spectra of Compound- G-1

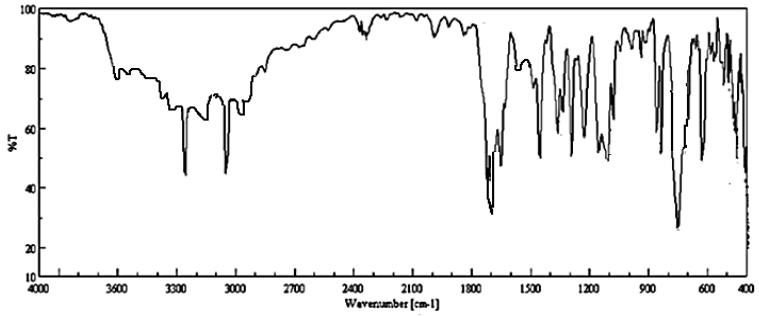


Fig 3: IR spectra of Compound- G-2.

EVALUATION OF ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS:

MATERIALS:

Carboxy methyl cellulose, Carrageenan , Indomethacin, plethysmometer, different 1,4-Naphthoquinone derivatives.Albino rats weighing in the range of 120g to 150g were purchased from Raj Biotech, Shirval, Taluka - khandala, District- Satara & were maintained in standard household condition and food and water is provided to them.

METHODS;

Acute Toxicity Studies:

The acute toxicity study, before analgesic activity was carried out by Karber's method[253], and the LD_{50} value of synthesized compounds were found to by 200mg/kg body weight of albino mice. Hence the ED_{50} was selected as 20mg/kg body weight of albimino mice for the present study.

31.Study of Anti-inflammatory activity of Compounds,

Anti-inflammatory activity of different 1,4-Naphthoquinone derivatives and their metal chelates was evaluated by induced hind paw oedema by carrageenin with the help of plethysmometer.[252-255]

Swiss albino rats of male or female were taken into 12 groups. Each group contains 6 animals. The Ist group was given orally a suspension of

Carboxy methyl cellulose with 2% weight/volume of 0.2ml and this group is served as control group. The IInd group was given Sodium diclofenac(10 mg/kg. i.p) & this is taken as group of standard. The remaining group 3^{rd} to 12^{th} was given an oral dose 20mg/kg body weight of synthesized compounds. After 0.5hr. 0.1mL of Carrageenan(1% w/v). After 30minutes the carrageen 0.1ml of 1% weight/volume inserted into the hind paw planter region by injecting rats. The measurement of volume of paw was taken with the help of Plethysmometer at interval of 0-3hrs. after the injection of carrageenan. The reduction in paw volume i.e. percentage inhibition was determined

with the help of formula, **Percentage of Inhibition = 100(1-Vt/Vo)** where Vt= increase paw volume after test compounds was administered and Vo= increase paw volume of control group.

Statistical analysis: The one-way ANOVA analysis test taken for the analysis of data. The ANOVA test is followed by test of Dunnet for purpose of separate individual comparative study with control grouped animals. The p value less than 0.001 was taken considered as significant value. The calculated all the values for statistical analysis are shown as mean ± SEM.

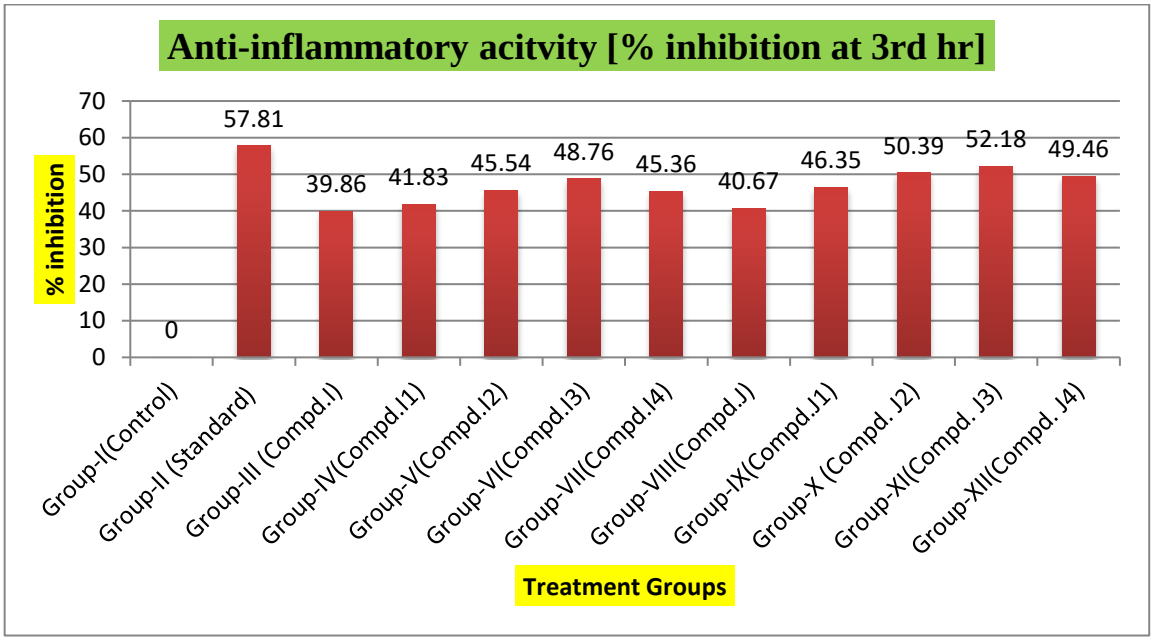


Fig. 6.10. Histogram showing anti-inflammatory(% inhibition) activity of Compounds [I,I_1,I_2,I_3,I_4,J,J_1,J_2,J_3&J_4]

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