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SYNTHESIS AND ANALGESIC ACTIVITY OF DIFFERENT 2-CHLORO-3-ARYLAMINO-1,4-NAPHTHOQUINONES & THEIR METAL CHELATES

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Keywords:

analgesic activity, tail flick, Eddy's hot plate.

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ABSTRACT

Different 2-chloro-3-arylamino-1,4-naphthoquinones and their Zinc chelates were synthesized. All the synthesized compounds have been screened for their analgesic activity by tail flick and Eddy's hot plate method. Among the compounds tested 2-Chloro-3-(4-fluorophenylamino)-naphthalen-1,4-dione and its Zinc chelate shows better analgesic activity as compared with standard Diclofenac sodium.

INTRODUCTION

Nowadays life of human being is in danger because of he is suffering from many upsetting diseases like, tuberculosis, arthritis, cancer, AIDS, and the diseases caused by several bacterial infections. In market some medicines are available to overcome these diseases, but there is need to synthesize a new chemical entity [NCE] to overcome the adverse effect and resistance of the current drug.

Literature survey reveals that, Lapachol, a yellow coloring matter obtained from *Tabebuia avellanedae* have the structure of an amylene hydroxynaphthoquinone used as an analgesic, anti-inflammatory, antineoplastic and diuretic¹ by the local people in Brazil.

Metal chelates of Lawsone oxime found to possess considerable anti-microbial activity². One of the hydroxyl derivative of 1,4-Naphthoquinone, i.e. Lawsone (2-

MATERIALS AND METHODS

Experimental:

Scheme of Synthesis:-

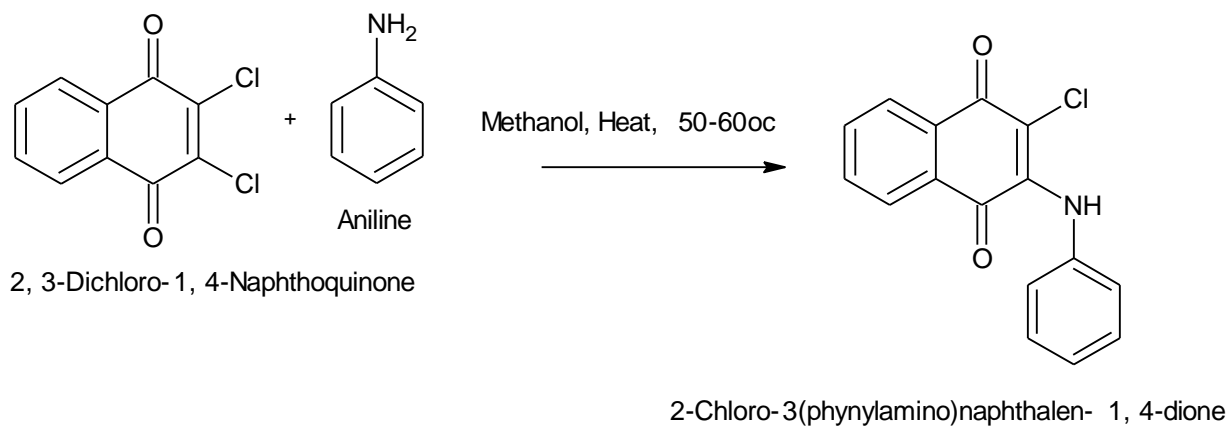
Hydroxy-1,4-naphthoquinone, III) is a monohydroxy naphthoquinone pigment of henna³ plant possessing various biological properties, including antitumor activity. It is also an effective chelator of divalent and trivalent metal ions due to its juxtaposed phenolic hydroxyl and keto groups. Some hydroxynaphthoquinone metal complexes shows good analgesic and antitumor activity.

The above detailed literature survey, encourage us to synthesize Zn, & Cd metal chelates of 2-Hydroxy-3-bromo-1,4-naphthoquinone, 2-Methoxy-3-bromo-1,4-Naphthoquinone, 2-Hydroxy-3-chloro-1,4-naphthoquinone and 2-Ethylcarboxamido-3-chloro-1,4-Naphthoquinone to evaluate their analgesic activities by Tail flick & Eddy's Hot Plate method on albino mice. The experimental results shows a good analgesic activity as compared to standard Diclofenac sodium.

Synthesis of Different 2-chloro-3-arylamino-1,4-naphthoquinones and their Zn chelates.

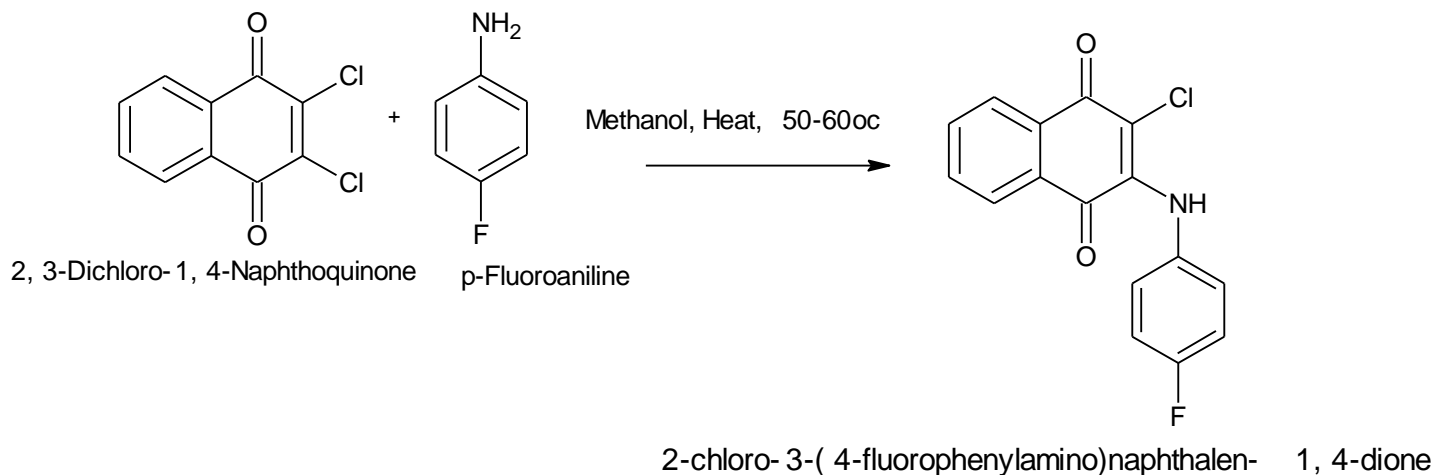
1. Synthesis of 2-Chloro-3-(phenylamino)-naphthalen-1,4-dione.:

Synthesis of 2-Chloro-3(phenylamino)naphthalen- 1, 4-dione



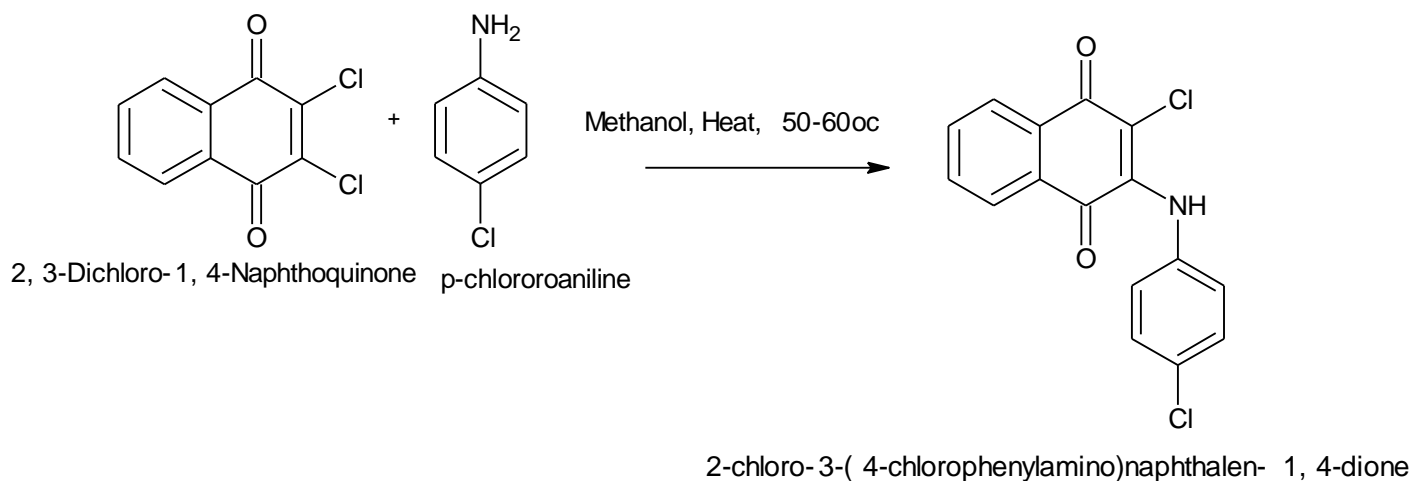
2. Synthesis of 2-Chloro-3-(4-fluorophenylamino)-naphthalen-1,4-dione.

Synthesis of 2-chloro-3-(4-fluorophenylamino)naphthalen- 1, 4-dione



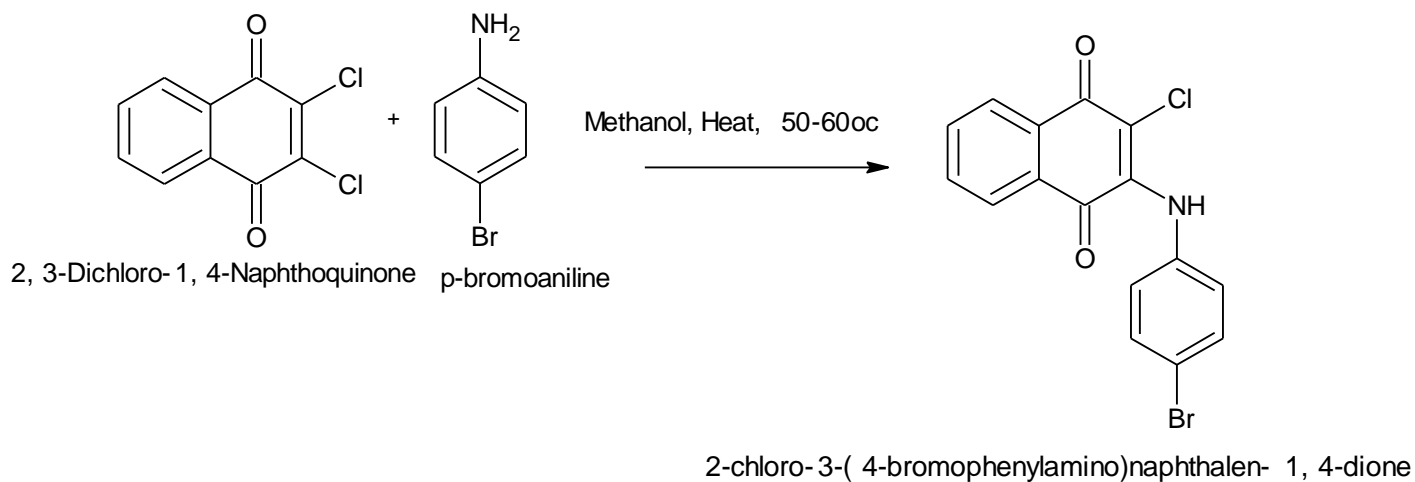
3. Synthesis of 2-Chloro-3-(4-chlorophenylamino)-naphthalen-1,4-dione.

Synthesis of 2-chloro-3-(4-chlorophenylamino)naphthalen- 1, 4-dione



4. Synthesis of 2-Chloro-3-(4-bromophenylamino)-naphthalen-1,4-dione.

Synthesis of 2-chloro-3-(4-bromophenylamino)naphthalen- 1, 4-dione



Experimental Procedure:**1 Synthesis of 2-Chloro-3-(phenylamino)-naphthalen-1,4-dione.**

To a solution of 2,3-dichloro-1,4-naphthoquinone (1mmol) in absolute methanol was added aniline (1mmol). The reaction mixture was warmed to 50-60 oC and monitored by TCL. The solution was then allowed to cool to 0 oC. The solid material was collected by vacuum filtration. Recrystallization from CHCl₃ - methanol (3 : 1) provided **5a-f** 2-Chloro-3-(phenylamino)naphthalen-1,4-dione (100mg, 35%) ; red crystal solid ; mp 218-221 oC ;

2. Synthesis of 2-Chloro-3-(4-fluorophenylamino)-naphthalen-1,4-dione.

To a solution of 2,3-dichloro-1,4-naphthoquinone (1mmol) in absolute methanol was added 4-fluoroaniline (1mmol). The reaction mixture was warmed to 50-60 oC and monitored by TCL. The solution was then allowed to cool to 0 oC. The solid material was collected by vacuum filtration. Recrystallization from CHCl₃ - methanol (3 : 1)

2-Chloro-3-(4-fluorophenylamino)naphthalen-1,4-dione (**5b**) (100mg, 33%) ; red crystals solid; mp 237-239 oC ;

3. Synthesis of 2-Chloro-3-(4-chlorophenylamino)-naphthalen-1,4-dione.

To a solution of 2,3-dichloro-1,4-naphthoquinone (1mmol) in absolute methanol was added 4-chlororoaniline (1mmol). The reaction mixture was warmed to 50-60 oC and monitored by TCL. The solution was then allowed to cool to 0 oC. The solid material was collected by vacuum filtration. Recrystallization from CHCl₃ - methanol (3 : 1) to give 2-Chloro-3-(4-chlorophenylamino)naphthalen-1,4-dione (**5c**) (200mg, 55%) ; red crystals solid ; mp 263-265oC;

4. Synthesis of 2-Chloro-3-(4-bromophenylamino)-naphthalen-1,4-dione.

To a solution of 2,3-dichloro-1,4-naphthoquinone (1mmol) in absolute methanol was added 4-bromoaniline (1mmol). The reaction mixture was warmed to 50-60 oC and monitored by TCL. The solution was then allowed to cool to 0 oC. The solid material was collected by vacuum filtration. Recrystallization from CHCl₃ - methanol (3 : 1)

2-Chloro-3-(4-bromophenylamino)naphthalen-1,4-dione (**5d**): (190mg, 53%) ; red crystals solid ; mp 237-239 oC ;

Preparation of Metal Chelates of Different 2-chloro-3-arylamino-1,4-naphthoquinones

Preparation of Ligand Solutions:-

The ligands were weighed appropriately to obtain their accurate 2×10^{-3} M solutions. The weighed ligands were dissolved in sufficient amount of methanol to dissolve the ligand completely. In case of each experiment, clear solution of the ligand was obtained.

Preparation of the Metal salt Solution:

Aqueous solution of the metal ions like Zn[II] & Cd[II] corresponding to 1×10^{-3} M were prepared by dissolving the appropriate amounts of metal acetates in distilled water. Aqueous Ammonia solution [10%] was prepared in distilled water and was used to adjust the pH of reaction mixture.

Preparation of the Metal Chelates:

All the chelates were prepared by following a general procedure as described below:

The ligand solution 2×10^{-3} M was taken in a 3 neck-flask. The metal ion solution 1×10^{-3} M was added drop by drop from a dropping funnel into the ligand solution, with constant stirring. After the addition of the metal solution aq. Ammonia solution [10%] was added dropwise to adjust pH 5-6. The flask containing the reaction

mixture was then kept overnight in refrigerator, after stirring the reaction mixture for about one hour. The products were then filtered under vacuum at room temperature, thoroughly washed with distilled water and then with little methanol. Finally they were dried in vacuum desiccator.

PHARMACOLOGICAL STUDIES:-

Material and methods:

Materials:-

Different Synthesized compounds, Diclofenac Sodium & carboxy methyl cellulose were used as received.

Acute Toxicity Studies:

The acute toxicity study, before analgesic activity was carried out by Karber's method⁴, and the LD₅₀ value of synthesized compounds were found to be by 200mg/kg body weight of albino mice. Hence the ED₅₀ was selected as 20mg/kg body weight of albino mice for the present study.

Study of Analgesic activity:-

1. Tail Flicking Method/ Heat Conduction Method⁵:

Swiss albino mice weighing 20-30gm of either sex were maintained under controlled condition of light (12 hr) and temperature $25 \pm 1^{\circ}\text{C}$. in the animal house. These animals were grouped into ten [10] groups of six animals each. Group-I received distilled water, which served as control group.

Group-II received Sodium Diclofenac (10 mg/kg. i.p) and served as standard group. Group-III-X received oral 20mg/kg body weight of synthesized compounds A, A₁,B,B₁,C,C₁,D&D₁. respectively. Sixty minutes after oral administration of synthesized compounds and 30 minutes after i.p. injection of Sodium Diclofenac, the tail tip of individual animals was dipped up to 5cm into hot water (maintained at 58⁰c) and the response/reaction time was noted as sudden withdrawl of the tail from the hot water. The cut off period of 12 seconds was maintained.

2. Eddy's Hot Plate Method⁶:

The animals were grouped into ten groups of six animals each. Group-I received distilled water, which served as control group. Group-II received Sodium Diclofenac (10 mg/kg. i.p) and served as standard group. Group-III-X received oral 20mg/kg body weight of synthesized

compounds A, A₁,B,B₁,C,C₁,D&D₁ respectively. Sixty minutes after oral administration of synthesized compounds and 30 minutes after i.p. injection of Sodium Diclofenac, animals were individually placed on the Hot plate(maintained at 55⁰C) and the responses such as paw licking or jump response, whichever appeared first were noted out. The cut off period of 15 sec. was maintained.

Statistical analysis: The data were statistically analyzed using one-way ANOVA followed by Dunnett's test for individual comparision of groups with control . "p" values below 0.001 were considered as singnificant. All values of statistical analysis are expressed as mean ± SEM.

RESULTS AND DISCUSSION**Table No.1 :**

Physicochemical data for Different 2-chloro-3-arylamino 1.4-Naphthoquinones and their metal chelates.

Sr.No.	Compd. Name.	Mol.formula	% Yield	Melting Point(0°C)
1	2-Chloro-3-(phenylamino)-naphthalen-1,4-dione [A]	C ₁₆ H ₁₀ O ₂ NCl	35%	218-221 ⁰ C.
2	Zn Chelate of 2-Chloro-3-(phenylamino)-naphthalen-1,4-dione [A ₁]	C ₁₆ H ₁₀ O ₂ NClZn	31%	226-228 ⁰ C.
3	2-Chloro-3-(4-fluorophenylamino)-naphthalen-1,4-dione [B]	C ₁₆ H ₁₀ O ₂ NF	33%	237-239 ⁰ C.
4	Zn chelate of 2-Chloro-3-(4-fluorophenylamino)-naphthalen-1,4-dione [B ₁]	C ₁₆ H ₁₀ O ₂ NFZn	29%	206-208 ⁰ C.
5	2-Chloro-3-(4-chlorophenylamino)-naphthalen-1,4-dione.[C]	C ₁₆ H ₁₀ O ₂ NCl ₂	55%	263-265 ⁰ C.
6	Zn chelate of 2-Chloro-3-(4-chlorophenylamino)-naphthalen-1,4-dione.[C ₁]	C ₁₆ H ₁₀ O ₂ NCl ₂ Zn	48%	272-274 ⁰ C.
7	2-Chloro-3-(4-bromophenylamino)-naphthalen-1,4-dione.[D]	C ₁₆ H ₁₀ O ₂ NBrCl	53%	237-239 ⁰ C.
8	Zn chelate of 2-Chloro-3-(4-bromophenylamino)-naphthalen-1,4-dione.[D ₁]	C ₁₆ H ₁₀ O ₂ NBrClZn	48%	246-248 ⁰ C.

*All melting points are uncorrected.

Table-2 :

Analgesic activity of Halogenated derivatives of 1.4-Naphthoquinone derivative and their metal chelates. By Tail Flick Method.

Sr. No.	Groups	Dose [mg/kg]	Reaction Time (seconds)
1	Group-I (Control)	Distilled water	2.6±0.254
2	Group-II(Standard)	10	11.2±0.123
3	Group-III (Compd.A)	20	6.2±0.243
4	Group-IV(Compd.A ₁)	20	6.4±0.321
5	Group-V(Compd.B)	20	6.5±0.316
6	Group-VI(Compd.B ₁)	20	7.2±0.421
7	Group-VII(Compd.C)	20	6.8±0.324
8	Group-VIII(Compd.C ₁)	20	7.1±0.381
9	Group-IX(Compd.D)	20	8.1±0.354
10	Group-X (Compd. D ₁)	20	8.5±0.215

Values are expressed as mean ± SEM; n=6; p<0.001

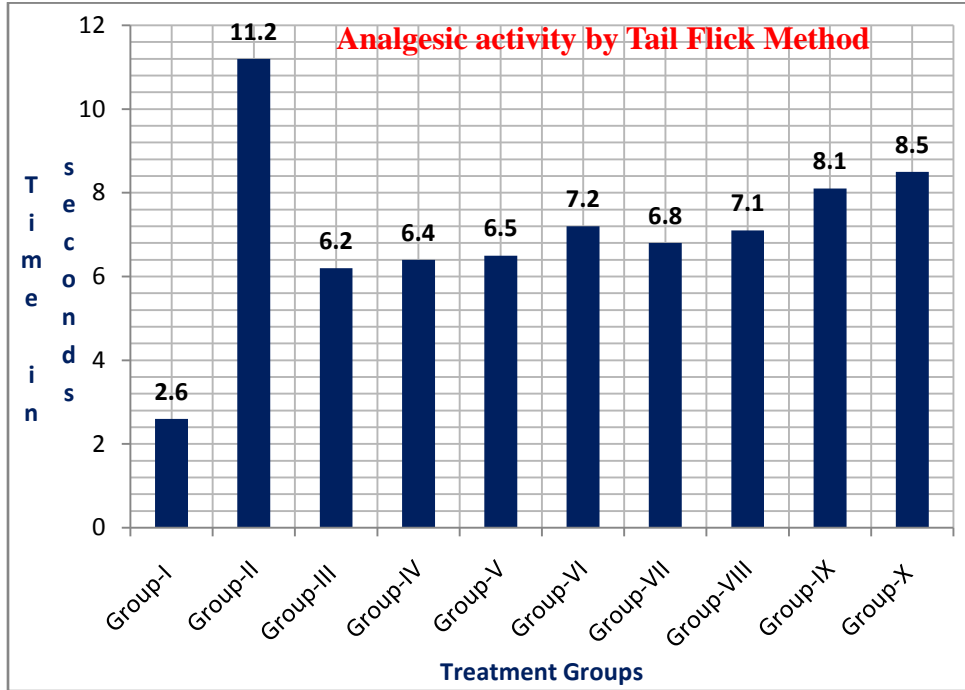
Table-3

Analgesic activity of Halogenated derivatives of 1.4-Naphthoquinone derivative and their metal chelates. By Eddy's Hot Plate Method.

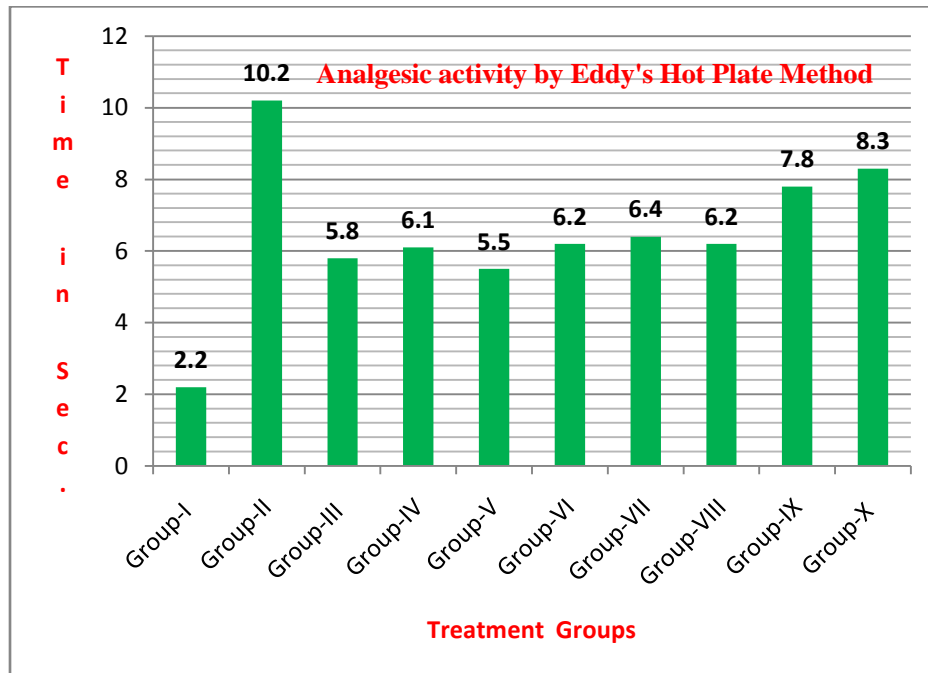
Sr. No.	Groups	Dose [mg/kg]	Reaction Time (seconds)
1	Group-I (Control)	Distilled water	2.2±0.142
2	Group-II(Na.Diclofenac)	10	10.2±0.223
3	Group-III (Compd.A)	20	5.8±0.143
4	Group-IV(Compd.A ₁)	20	6.1±0.224
5	Group-V(Compd.B)	20	5.5±0.413
6	Group-VI(Compd.B ₁)	20	6.2±0.323
7	Group-VII(Compd.C)	20	6.4±0.124
8	Group-VIII(Compd.C ₁)	20	6.2±0.152
9	Group-IX(Compd.D)	20	7.8±0.254
10	Group-X (Compd. D ₁)	20	8.3±0.114

Values are expressed as mean ± SEM; n=6; p<0.001

Histogram-1 Analgesic activity by Tail Flick Method.



Histogram-2 Analgesic activity by Eddy's Hot Plate Method.



Conclusion:-

Different 2-chloro-3-arylamino-1,4-naphthoquinones and their Zinc metal chelates were synthesized. The synthesized compounds Percentage yield and Physical constants were obtained and shown in table 1. Further the synthesized compounds and their metal chelates were screened for their Analgesic activities and shown in Table-3 and Table-4 and represented in Graph-I and Graph-II and found to possess moderately good Analgesic activity as compared to standard Sodium Diclofenac.

From this study it can be concluded that, the newly synthesized Different 2-chloro-3-arylamino-1,4-naphthoquinones and their Zinc metal chelates are stable and can be substituted for existing analgesic drugs to increase efficiency with less toxicity and side effects.

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