# A Study of Anti-inflammatory and Analgesic Activity of New 2,3-Disubstituted 1,2-Dihydroquinazolin-4(3*H*)-one Derivative and Its Transition Metal Complexes

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**A new 2,3-disubstituted 1,2-dihydroquinazolin-4(3*H*)-one derivative namely 2-hydroxy-2-ethyl-(3-carboxylideneamino)-3-(2-(4-methyl-phenyl))-1,2-dihydroquinazolin-4(3*H*)-one (HECMDQ) is synthesized employing a modified method in higher yield and is complexed with Co(II), Ni(II), Cu(II) and Zn(II) metal ions in order to study its coordinating behavior. All the complexes were characterized by various physicochemical (analytical, IR, NMR, Electron Paramagnetic Resonance (EPR), mass, Thermogravimetric Analysis Differential Thermogravimetric Analysis (TGA-DTA)) methods. The molar conductivity measurements in *N*,*N*-dimethylformamide (DMF) solution indicate the non-electrolytic nature of complexes. IR spectral analysis reveal that coordination takes place through the deprotonated hydroxyl group, azomethine nitrogen and carbonyl oxygen. Four coordinated geometry was assigned to all the complexes on the basis of spectral studies. The anti-inflammatory activities of compounds are moderate. Co(II) complex exhibited highest activity among all the complexes. At lower dose level activity of Ni(II) and Cu(II) complexes is more compared to that of ligand. The analgesic activity of ligand has enhanced on complexation with Co(II), Ni(II) and Zn(II) metal ions. Among the compounds studied Co(II) complex has shown highest activity and is comparable with standard used.**

**Key words** 1,2-dihydroquinazolinone; metal complex; anti-inflammatory activity; analgesic activity

Quinazolinones and their derivatives have drawn much attention owing to their various pharmacological properties. They exhibit diverse biological properties like, antimicrobial,[1—3] antiviral,[4] anticancer,[5] anticonvulsant,[6] CNS depressant[7] and antihypertensive activity.[8] Amongst these, C-2 and N-3 disubstituted quinazolines with aryl and heteroaryl groups at N-3 position have shown enhanced anti-inflammatory activity as a result of their nitric oxide inhibitory activities.[9]

A good deal of research has been carried out on the coordinating behavior of 2,3-disubstituted quinazolin-4(3*H*)-ones which offer various potential donor sites.[10—15] In comparison, 2,3-disubstituted 1,2-dihydroquinazolinones and their metal complexes are not much explored. We have recently reported the synthesis of 1,2-dihydroquinazolinones by the condensation of 2-aminobenzoylhydrazide with aryl and heteroaryl aldehydes and their chelating behavior towards transition and inner transition metal ions.[16—22] Their antimicrobial potency is also tested against different bacterial and fungal strains. Our continued research in this perspective resulted in a new approach, in which 2-aminobenzoylhydrazide is converted to hydrazone in the first step. The reaction of this hydrazone with aromatic aldehydes results in the formation of biologically active 1,2-dihydroquinazolinones, with different substituent at C-2 and N-3 positions.

Aroylhydrazones of salicylaldehyde, which typically act as tridentate planar chelate coordinating through phenolic oxygen, amide oxygen and imine nitrogen (Chart 1a) are known for their interesting biological activities.[23] Keeping the framework of coordinating sites of aroylhydrazones intact, we have designed quinazoline analogue (Chart 1b) of aroylhydrazone of *o*-hydroxyacetophenone which is structurally similar with aroylhydrazones of salicylaldehyde. Recent investigation show that coordination of organic molecules and anti-inflammatory drugs with Co(II), Ni(II), Cu(II), Fe(II) and Zn(II) metal ions resulted in the enhancement of their activity.[24—26] Thus, the present article charts the progress of our methodology in the synthesis of new 1,2-dihydroquinazolin-4(3*H*)-one derivative *viz.*, 2-hydroxy-2-ethyl-(3-carboxylideneamino)-3-(2-(4-methyl-phenyl))-1,2-dihydroquinazolin-4(3*H*)-one (HECMDQ) (**C1**) with different substituent at C-2 and N-3 positions and its coordinating behavior towards Co(II), Ni(II), Cu(II) and Zn(II) ions. The results of analgesic activity are impressive and perhaps suggestive of future success.

## Experimental

**Materials** Methylanthranilate (S.D. Fine Chemicals, India), hydrazine-hydrate (Spectrochem, India) *o*-hydroxyacetophenone (Himedia, India), *p*-methylbenzaldehyde (Spectrochem, India) and metal(II) chlorides used in the present study were of AR grade and used as supplied. All the solvents were distilled before use. *o*-Aminobenzoylhydrazide[27] and *o*-hydroxyacetophenone-*o*-aminobenzoylhydrazone[28] were prepared following the literature procedures.

**Physical Measurements** Metal content of the complexes was determined after wet ashing with HCl and $HClO_4$ by gravimetric methods for

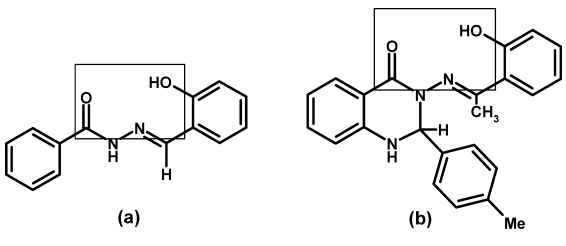


Chart 1

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cobalt, nickel and copper, while zinc was determined volumetrically. Chloride content is determined as silver chloride after decomposition with $HNO_3$.[29] The elemental analysis (C, H, N) was carried on a Thermoquest CHN analyser. Magentic susceptibility measurements were made at room temperature on Gouy balance using $Hg[Co(SCN)_4]$ as the calibrant. Diamagnetic corrections were made using Pascal's constants. Electronic spectra were recorded on a Carry-Bio-50Varian in *N*,*N*-dimethylformamide (DMF) solution in the range of 200—1000 nm. IR spectra were recorded in the region 400—4000 $cm^{-1}$ (KBr discs) on a Nicolet 170SX FT-IR spectrometer. $^1$H-NMR spectra of ligand and Zn(II) complex were obtained in $CDCl_3$ and DMSO-$d_6$ respectively using TMS as an internal reference on a Bruker Avance 300 MHz spectrometer operating at 300.13 MHz. Conductance measurements were recorded in DMF ($10^{-3}$ M) using an ELICO-CM-82 conductivity bridge with cell type CC-01 and cell constant 0.53. Thermogravimetric Analysis Differential Thermogravimetric Analysis (TG-DTA) studies were carried out in the 25—1000 °C temperature range using a TGA7 analyzer, Perkin-Elmer, U.S. with a heating rate of 10 °C per min in a $N_2$ atmosphere.

**Synthesis of HECMDQ (C1)** *o*-Hydroxyacetophenone-*o*-aminobezoylhydrazone (2.69 g, 10 mmol) and *p*-methylbenzaldehyde (1.18 ml, 10 mmol) were stirred for 2—3 h at room temperature in 50 ml ethanol (Chart 2). The colorless solid separated and was recrystallized from ethanol.

**C1**: White powder. Yield: 90%. mp 211—213 °C. $^1$H-NMR ($CDCl_3$) $\delta$ ppm: 12.09 (1H, s, O2H); 6.21 (1H, s, N1H); 2.36 (3H, s, $CH_3$ at C16); 2.31 (3H, s, $CH_3$ at C12); aromatic protons: 6.68—8.02. *Anal.* Calcd for $C_{23}H_{21}N_3O_2$: C, 74.39; H, 5.66; N, 11.32. Found: C, 74.56; H, 5.43; N, 11.09.

**Preparation of Complexes** The complexes were prepared by the addition of an ethanolic solution of metal(II) chloride (1 mmol) with constant stirring to the corresponding amount of ligand (0.371 g, 1 mmol) in the same solvent. The pH of the medium was maintained at 7 by adding 2—3 drops of ammonia and refluxed for 2 h. The complexes isolated were filtered, washed repeatedly with ethanol and air dried.

[Co(HECMDQ)Cl] (**C2**): Dark green powder. Yield 50%. mp >300 °C. *Anal.* Calcd for $[Co(C_{23}H_{20}N_3O_2)Cl]$: C, 59.42; H, 4.30; N, 9.04; Co, 12.68; Cl, 7.64. Found: C, 59.59; H, 4.70; N, 8.85; Co, 12.79; Cl, 7.91.

[Ni(HECMDQ)Cl] (**C3**): Orange powder. Yield 60%. mp >300 °C. *Anal.* Calcd for $[Ni(C_{23}H_{20}N_3O_2)Cl]$: C, 59.45; H, 4.31; N, 9.04; Co, 12.64; Cl, 7.65. Found: C, 59.41; H, 4.50; N, 9.17; Ni, 12.84; Cl, 7.92.

[Cu(HECMDQ)Cl] (**C4**): Green powder. Yield 70%. mp >300 °C. *Anal.* Calcd for $[Cu(C_{23}H_{20}N_3O_2)Cl]$: C, 58.84; H, 4.26; N, 8.95; Cu, 13.56; Cl, 7.56. Found: C, 58.50; H, 4.32; N, 8.75; Cu, 13.85; Cl, 7.77.

[Zn(HECMDQ)Cl] (**C5**): Colourless. Yield 45%. mp >300 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$ ppm:, 6.21 (1H, s, N1H); 2.48 (3H, s, $C16H_3$);, 2.31 (3H, s, $C13H_3$); aromatic protons: 6.66—8.00. *Anal.* Calcd for $[Zn(C_{23}H_{20}N_3O_2)Cl]$: C, 58.61; H, 4.24; N, 8.91; Cu, 13.88; Cl, 7.53. Found: C, 58.48; H, 4.39; N, 8.70; Zn, 13.55; Cl, 7.70.

**Pharmacology** All the synthesized compounds were screened for analgesic and anti-inflammatory activity in rats and mice. Wistar rats (230—250 g) and Swiss albino mice (25—30 g) were used and the animals were kept at 26±2 °C with relative humidity 44—56%, with 12 h light/12 h dark cycle. All the animals were fed with standard diet and water *ad libitum*. The approval for experimental protocol was obtained from Institutional Animal Ethics Committee (IAEC/2008/01-11/HSK) and the same was carried at H. S. K. College of Pharmacy, Baglkot, India. 18—24 h fasted animals were used for the experiments. Experimental groups were divided into 12, each containing 6 animals. The test compounds were suspended in 0.5% sodium carboxy methyl cellulose (Na-CMC) and administered at dose of 3 and 10 mg/kg of body weight (b.w.) and 10 mg/kg, b.w. of Indomethacin and Aspirin were administered as a reference standard drug for anti-inflammatory and analgesic activity respectively. The control group received 0.5% Na-CMC in distilled water.

**Anti-inflammatory Activity** The anti-inflammatory activity of the test compounds was evaluated as described by Winter *et al.*[30] and Diwan *et al.*[31] method. One hour after the administration of test compounds, rats in all groups were challenged with carrageenan (1% prepared in 0.4% NaCl) in the sub-plantar region of right hind paw. The paw volume was measured at different intervals of time (0.5, 1, 2, 3, 5 h) using digital plethysmometer (UGO Basil, Italy) and zero hour reading, before administration of the carrageenan was taken. The percentage inhibition of paw volume for each test group is calculated using following equation. Percentage of inhibition (%)=[1−volume in ml (test compound)/volume in ml (control)]×100.

**Analgesic Activity** The Eddy and Leimback hot plate test[32,33] was carried out in mice for evaluating analgesic activity. Swiss albino mice of either sex were divided into 12 groups, containing 6 animals each. Animals were administered with control (0.4% NaCl), test compounds (3, 10 mg/kg) and Aspirin (10 mg/kg) as an aqueous suspension of 1% sodium carboxy methyl cellulose. One hour after the administration of compounds, mice were kept on hot plate pre-heated to 50 °C for 15 s. Reaction time between the moment when the mouse reached hot plate and that when animal licked its hind paw was noted. The cut off time was fixed for 15 s to prevent injury to paw. The time taken to lick the hind paw was recorded at 60, 120 and 180 min. Increase in reaction time (time interval taken by animal to lick paw) was considered as proportional to analgesic activity.

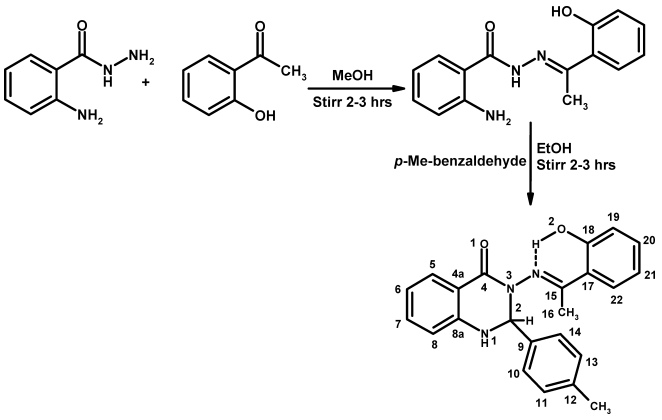


Chart 2. Synthetic Route for the Preparation of **C1**

## Results and Discussion

**Chemistry** In our previous communications the preparation of 1,2-dihydroquinazolinones by treating *o*-aminobenzoylhydrazide with aromatic aldehydes leading to similar substituents at C-2 and N-3 positions has been described earlier.[16—22] Our modified approach involves the isolation of hydrazone derived from the condensation of 2-aminobenzoylhydrazide with aromatic ketones with $-NH_2$ group attached to phenyl ring of hydrazide fragment free in the first step[34] and treatment of this hydrazone with aromatic aldehyde to give 1,2-dihydroquinazolinones in the second step (Chart 2). This method is an important modification of earlier methods and has the advantage of attaching different substituents at C-2 and N-3 positions. The transition metal complexes of the ligand were synthesized by treating ethanolic solution of ligand with corresponding solution of metal chlorides in equimolar quantities at pH 7.

The ligand is amorphous solid and soluble in most of the common organic solvents at a slightly higher temperature *ca.* 50 °C. The complexes **C2**—**C5** are colored while Zn(II) complex **C5** is colorless. All the complexes are stable in air, non-hygroscopic and melts above 300 °C. Elemental analyses of the complexes reveal 1 : 1 metal to ligand stoichiometry. Complexes are soluble in DMF and dimethyl sulfoxide (DMSO). The molar conductance of the complexes fall in the range of 1—10 $\Omega^{-1}cm^2mol^{-1}$ suggesting non-electrolytic nature[35] of the complexes.

**Infrared Spectral Studies** The IR spectrum of the ligand (**C1**) (Table 1) has a strong band at 3312 $cm^{-1}$ and a broad band at 3028 $cm^{-1}$ assigned to $\nu$(NH) of quinazoline ring and $\nu$(OH) of phenolic OH. The broadness of $\nu$(OH) stretching indicates that phenolic OH is involved in the intramolecular hydrogen bonding with azomethine nitrogen (Chart 2). The $\nu$(C=O) and $\nu$(C=N) stretching frequencies were observed at 1643 and 1609 $cm^{-1}$ respectively. In the IR spectra of complexes, the carbonyl and azomethine stretching

frequencies have shifted to lower wave number by 24—39 and 3—28 $cm^{-1}$ respectively indicating the coordination through carbonyl oxygen and azomehtine nitrogen. The absence of $\nu$(OH) in the IR spectra of all the complexes is indicative of coordination of phenolic oxygen by the loss of a proton.

**NMR Studies** The numbering Chart 2 for the assignment of protons is given in Chart 2. $^1$H-NMR spectrum of ligand show singlets at 12.09, 6.21, 4.67 $\delta$ ppm assigned to phenolic O2H, N1H, C2H protons respectively and other singlets at 2.36 and 2.31 $\delta$ ppm are assigned to two methyl protons attached to C(15) and C(12) carbons respectively. The remaining aromatic protons were observed in the region 6.68—8.02 $\delta$ ppm. The signal at 12.09 $\delta$ ppm indicates hydrogen bonded hydroxy proton. The absence of this signal in the spectrum of Zn(II) complex confirms the complex formation *via* deprotonation. The C(16)$H_3$ protons have shifted to downfield which supports the complexation through azomethine nitrogen.

**Thermal Studies** Complex **C3** is taken as the representative of the series to study thermal behavior of the complexes. The complex is stable up to 360 °C. The sharp decomposition associated with loss of one chloride atom is observed at 380—410 °C and is followed by the loss of ligand molecule. The final product of decomposition above 700 °C resulted in the formation of stable NiO. The metal content calculated from this residue tallies with metal analysis.

**Magnetic Properties** The Co(II) complex (**C2**) exhibit $\mu_{eff}$ value of 4.2 BM expected for tetrahedral complexes.[36] The orange colored Ni(II) complex (**C3**) is found to be diamagnetic which is suggestive of square planar geometry around it.[36] The $\mu_{eff}$ value of 1.90 BM observed for Cu(II) complex (**C4**) is in accordance with distorted tetrahedral mononuclear complex.[37] The Zn(II) complex (**C5**) is diamagnetic.

**Electronic Spectra** The electronic spectrum of ligand exhibits an absorption at 325 nm assigned to $\pi\rightarrow\pi^*$. The electronic spectrum of green colored **C2** complex exhibits an absorption at 638 nm attributed to $^4A_2(F)\rightarrow{}^4T_1(P)$ transition indicating a tetrahedral geometry.[38] The band at 412 nm in the electronic spectrum of **C3** complex refers to the square-planar geometry.[39,40] The low intensities of the d–d bands compared to intra-ligand and metal to ligand charge transfer absorptions prevent an accurate assignment for the **C4** com-

Table 1. Diagnostic IR Bands for HECMDQ and Its Complexes

| Compound | Compound code | $\nu$(NH) | $\nu$(OH) Phenolic | $\nu$(C=O) | $\nu$(C=N) | $\nu$(C–O) |
|---|---|---|---|---|---|---|
| HECMDQ | **C1** | 3312s | 3028b | 1643s | 1609s | 1365m |
| [Co(HECMDQ)Cl] | **C2** | 3438s | n.o. | 1606s | 1606s | 1366m |
| [Ni(HECMDQ)Cl] | **C3** | 3283w | n.o. | 1604m | 1581m | 1438s |
| [Cu(HECMDQ)Cl] | **C4** | 3355s | n.o. | 1612m | 1587m | 1376s |
| [Zn(HECMDQ)Cl] | **C5** | 3264s | n.o. | 1612m | 1593s | 1378s |

b=broad, m=medium, s=strong, n.o.=not observed.

Table 2. Effect of Prepared Compounds on Carrageenan-Induced Paw Edema in Rats

| Groups (dose) | Edema volume in ml (mean percent inhibition) [mean percent inhibition of corresponding metal chlorides] | | | | | |
|---|---|---|---|---|---|---|
| | 0 h | 0.5 h | 1 h | 2 h | 3 h | 5 h |
| Control | 1.743±0.058 | 1.848±0.024 | 1.923±0.030 | 2.013±0.052 | 2.083±0.028 | 2.110±0.013 |
| | — | — | — | — | — | — |
| Indomethacin (10 mg/kg) | 0.160±0.030** (90.08) | 0.200±0.019*** (89.18) | 0.290±0.036*** (84.91) | 0.380±0.090*** (82.01) | 0.310±0.069*** (85.11) | 0.220±0.560*** (89.57) |
| **C1** (3 mg/kg) | 1.743±0.080 (00.00) | 1.893±0.065 (00.00) | 1.785±0.067 (07.17) | 1.968±0.129 (02.23) | 2.220±0.063 (00.00) | 2.103±0.086 (00.33) |
| **C1** (10 mg/kg) | 1.785±0.013 (00.00) | 1.633±0.107 (13.16) | 1.625±0.030*** (15.40) | 1.658±0.075** (17.63) | 1.835±0.072 (11.90) | 1.825±0.066** (13.50) |
| **C2** (3 mg/kg) | 1.658±0.047 (04.80) [0.18] | 1.628±0.039 (11.90) [1.82] | 1.560±0.034*** (18.80) [1.90] | 1.690±0.047 (16.04) [2.0] | 1.930±0.015 (07.34) [1.77] | 1.878±0.117 (10.99) [1.86] |
| **C2** (10 mg/kg) | 1.678±0.076 (03.70) [0.19] | 1.595±0.077 (13.69) [0.08] | 1.475±0.066*** (23.29) [2.03] | 1.425±0.040*** (29.21) [3.08] | 1.808±0.048 (13.20) [2.15] | 1.905±0.050 (09.71) [1.24] |
| **C3** (3 mg/kg) | 1.665±0.043 (04.40) [1.27] | 1.540±0.104* (16.66) [1.14] | 1.568±0.040*** (18.46) [2.54] | 1.783±0.062 (11.42) [0.00] | 1.815±0.096* (12.86) [1.25] | 1.905±0.114 (09.71) [2.48] |
| **C3** (10 mg/kg) | 1.718±0.058 (01.40) [0.27] | 1.560±0.023* (15.58) [3.42] | 1.490±0.048*** (22.51) [1.09] | 1.788±0.068 (11.17) [1.05] | 1.893±0.075 (09.12) [1.25] | 1.998±0.049 (05.30) [1.34] |
| **C4** (3 mg/kg) | 1.568±0.042 (10.04) [0.18] | 1.703±0.074 (07.80) [2.66] | 1.585±0.075*** (17.57) [34.00] | 1.768±0.090 (16.04) [20.00] | 1.795±0.075* (13.82) [17.29] | 1.940±0.126 (08.05) [16.14] |
| **C4** (10 mg/kg) | 1.670±0.051 (04.10) [1.82] | 1.635±0.065 (11.52) [6.24] | 1.588±0.054*** (17.42) [32.00] | 1.723±0.063* (14.40) [15.00] | 1.773±0.048* (14.88) [23.20] | 1.885±0.078* (10.66) [18.63] |
| **C5** (3 mg/kg) | 1.798±0.067 (00.00) [1.27] | 1.728±0.051 (06.40) [1.90] | 1.708±0.045* (11.18) [2.54] | 1.995±0.133 (00.89) [0.00] | 2.155±0.079 (00.00) [0.00] | 1.988±0.065 (05.30) [3.72] |
| **C5** (10 mg/kg) | 1.813±0.051 (00.00) [0.00] | 1.728±0.051 (06.49) [1.89] | 1.648±0.027** (14.30) [1.09] | 1.748±0.067* (13.16) [2.38] | 1.810±0.137 (13.10) [3.77] | 1.728±0.047*** (18.10) [5.59] |

Results expressed in mean±S.E.M. ($n$=6). ANOVA followed by Dunnett's test. *** $p<0.001$, ** $p<0.01$, * $p<0.05$ when compared to control group. **C1**=HECMDQ; **C2**=[Co(HECMDQ)Cl]; **C3**=[Ni(HECMDQ)Cl]; **C4**=[Cu(HECMDQ)Cl]; **C5**=[Zn(HECMDQ)Cl].

plex. The Zn(II) complex has not shown any d–d absorptions.

**Anti-inflammatory Activity** All the synthesized compounds (**C1**—**C5**) were screened for the anti-inflammatory activity by carrageenan induced rat paw edema model. Carrageenan is a pro-inflammatory agent, induces the inflammation by releasing inflammatory mediators such as histamine, serotonin and cytokines leads cascade inflammation reactions[41] in short period time and later (up to 6 h) further augmentation of inflammation reaction is mediated by prostaglandins (PGs) derived from arachidonic acid by the action of prostaglandin H synthase [also referred as cyclooxygenase (COX)]. The present study illustrate that the ligand and its complexes show dose dependent response (Table 2, Fig. 1). The ligand is active at 10 mg/kg dose with percentage inhibition of 17.63% and among all complexes **C2** complex has shown promising activity percentage inhibition of 29.21% at 2nd hour. Similarly **C3** complex at 10 mg/kg showed 22.51% percentage inhibition at 1st hour. The order of percentage protection by complexes is found to be **C2**>**C3**>**C4**>**C5**>**C1**. Thus the activity of ligand is enhanced on complexation with metal ions. These results suggest that the test compounds, exert their action may be through of inhibition of lecucocyte migration, reducing the cytokine production and prostaglandin synthesis by inhibiting the activity of cyclooxygenase enzyme.[42] The anti-inflammatory activity of the complexes is more as compared to corresponding metal chlorides except copper chloride which exhibited notable activity at as compared to corresponding complex.

**Analgesic Activity** Analgesic activity was performed by Eddy's hot plate method, which involves the use of heat as source to induce pain in mice. The increase in the reaction time (time interval) compared to basal is proportional to analgesic activity of the test compounds. The results are summarized in Table 3. The ligand **C1** showed dose dependent activity and significantly higher protection at 60 min which is comparable to the standard drug, it indicates that it

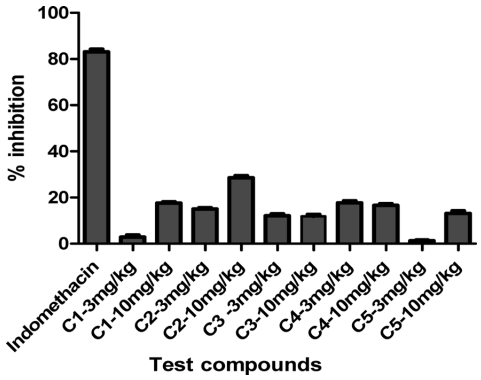


Fig. 1. Anti-inflammatory Activity (% Inhibition of Paw Edema) of **C1** and Its Transition Metal Complexes at 2nd Hour

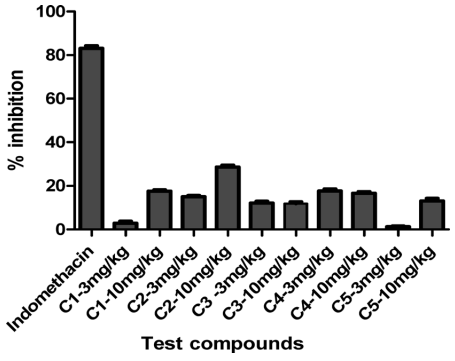


Fig. 2. Analgesic Activity of **C1** and Its Transition Metal Complexes at 180 min

Table 3. Analgesic Activity of Prepared Compounds

| Compound | Dose (mg/kg) | Reaction time (X±S.E.) in seconds (difference in reaction time compared to basal value) | | | |
|---|---|---|---|---|---|
| | | Basal | 60 min | 120 min | 180 min |
| Control | | 4.75±0.48 | 9.50±2.90 | 9.50±2.53 | 10.50±2.06 |
| Aspirin | 10 | 4.93±2.33* | 11.21±2.16** | 14.68±2.42*** | 15.00±0.00*** |
| | | | (6.28±0.16) | (9.75±0.09) | (10.07±2.33) |
| **C1** | 3 | 7.75±1.89 | 13.25±0.85 | 13.75±1.25 | 13.25±1.75 |
| | | | (5.50±2.03) | (6.66±0.64) | (5.50±0.14) |
| **C1** | 10 | 08.50±2.26 | 14.50±0.50* | 15.00±0.00 | 14.75±0.25* |
| | | | (6.00±1.76) | (6.50±2.26) | (6.25±2.51) |
| **C2** | 3 | 3.75±0.25 | 8.75±2.18 | 11.00±2.27 | 13.75±1.25 |
| | | | (5.00±1.93) | (7.25±2.02) | (10.00±1.00) |
| **C2** | 10 | 5.00±1.73 | 10.25±2.06 | 14.25±0.48* | 14.75±0.25* |
| | | | (5.25±0.33) | (9.25±1.25) | (9.75±1.48) |
| **C3** | 3 | 7.50±1.56 | 11.75±1.18 | 13.25±0.75 | 13.50±1.25 |
| | | | (4.25±0.37) | (5.75±0.81) | (6.00±0.31) |
| **C3** | 10 | 6.32±1.65* | 10.50±1.19 | 12.75±1.11 | 14.25±0.48 |
| | | | (4.18±0.46) | (6.43±0.54) | (7.93±1.17) |
| **C4** | 3 | 8.28±1.85* | 12.50±0.87 | 12.75±1.65 | 13.50±1.19 |
| | | | (4.22±0.98) | (4.47±0.20) | (5.22±0.66) |
| **C4** | 10 | 7.84±1.25*** | 13.75±0.95 | 12.50±1.44 | 14.25±0.75 |
| | | | (5.91±0.30) | (4.66±0.19) | (6.41±0.50) |
| **C5** | 3 | 6. 75.±1.60 | 10.00±2.92 | 15.00±0.00 | 13.00±2.00 |
| | | | (3.25±1.31) | (8.25±1.60) | (6.25±0.40) |
| **C5** | 10 | 6.70±1.11** | 10.50±1.19 | 15.00±0.00** | 15.00±0.00** |
| | | | (3.80±0.08) | (8.30±1.11) | (8.30±1.11) |

Results expressed in mean±S.E.M. ($n$=6). Significance level $*p<0.5$, $**p<0.01$, $***p<0.001$. **C1**=HECMDQ; **C2**=[Co(HECMDQ)Cl]; **C3**=[Ni(HECMDQ)Cl]; **C4**=[Cu(HECMDQ)Cl]; **C5**=[Zn(HECMDQ)Cl].

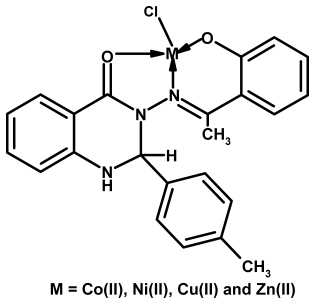


Fig. 3. Proposed Structure for the Complexes

may exert its action in a same manner as that of well established drug Aspirin. Complexes **C2**, **C3** and **C5** exhibit moderate analgesic activity and activity has increased at 120 min and reached the maximum peak at 180 min. Activity of **C4** (10 mg/kg) at 60 min is comparable with ligand and the standard drug. Among all complexes **C2** is found to exhibit significant analgesic activity at 120 min. The analgesic activity of metal(II) chlorides was found to be nil. These results indicate that **C1** and **C2** are more promising molecules and further studies are required to elucidation of exact mechanism of action for their therapeutic potential.

## Conclusion

A new quinazoline derivative has been synthesized by adapting a modified strategy which has the advantage of employing non-drastic reaction conditions to give high yields of 1,2-dihydroquinazolin-4(3*H*)-ones. At the same time, the starting materials are cheap and easily available. The quinazoline derivative is complexed with Co(II), Ni(II), Cu(II) and Zn(II) ions. Spectral and analytical data evidences the monobasic tridentate nature of the ligand coordinating through carbonyl oxygen, azomethine nitrogen and phenolic oxygen with the loss of proton. Four coordinate geometry was assigned to all the complexes on the basis of IR, $^1$H-NMR, electronic spectral studies and magnetic properties. The tentatively proposed structure for complexes is given in Fig. 3. The anti-inflammatory activity of the compounds is moderate, among the complexes reported here, Co(II) complex has shown highest percentage inhibition. The analgesic activities of all the compounds show promising results. The activity of the ligand is enhanced on complexation. Among the complexes, Co(II) complex has shown highest activity and is even more than the standard itself.

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