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Syntheses and anti-inflammatory activity of Diphenylamine-2,2′-dicarboxylic acid and its metal complexes

GOVIND MOHAN[1], RAJESH NAGAR[1,†], S.C. AGARWAL[1,‡], KM. ANUGYA MEHTA[1,¶], & C. SHESHAGIRI RAO[2]

[1]*Department of Pharmacology, S.N. Medical College, Agra-282 002, India, and* [2]*Dr. Reddy's Research Foundation, Miyapur, Hyderabad, India*

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Abstract

Diphenylamine-2,2′-dicarboxylic acid and its Cu(II), Ni(II), Co(II) and Zn(II) complexes have been synthesized and characterized by their elemental analyses, molecular weight determination, molar conductance, infrared and electronic spectra and magnetic measurements. The Zinc complex was tested by different methods for its anti-inflammatory activity and found to be equipotent to naproxen and ibuprofen, though at higher doses.

Keywords: *Metal complex, NSAID'S, prostaglandins, anti-inflammatory agent*

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Introduction

Inflammation is a tissue response, involving physiological, morphological and biochemical changes. Several highly bioactive chemical mediators like histamine, 5-HT (serotonin), kinins, interleukin-1, hydrolytic enzymes and prostaglandins are released during the dynamic process, making the process complicated [1]. Unfortunately, none of the nonsteroidal antiinflammatory drugs (NSAIDs) is devoid of a high incidence of gastric ulceration and side effects on kidney, liver, bone marrow and skin. The discovery of ibuprofen [2-(4-isophenyl) propionic acid] in the early sixties, triggered a new trend in the research for non-steroid substituted aryl carboxylic acid derivatives. Though they were less gastric irritant than other NSAID'S their long term use did lead to undesirable side effects. The selective COX-2 inhibitors like celecoxib, rofecoxib and valdecoxib were good NSAIDs with less gastric irritation but clinical experience of their anti-inflammatory action is not excellent [2]. Therefore, there is still a need for a NSAID which is effective in rheumatoid arthritis, osteoarthitis, gout and other related disorders. The discovery that N-aryl anthranilic acid derivatives exhibit potent oral anti-inflammatory activity in the UV erythema assay further stimulated interest in this area.

Copper is known to suppress inflammation and to possess antiulcer properties [3,4]. Lower levels of zinc have been found in patient with rheumatoid arthritis. They respond to zinc supplementation [5] and zinc also possesses antiulcer activity [6]. Gold salts are well known to alter the course of rheumatoid arthritis and metals like iron, manganese, zinc and copper also have been shown to be concerned with the synthesis of procollagen, proelastin, mucopolysaccharide etc. which are necessary for healing, following tissue damage. Zinc is required for humoral and cellular immunity and stimulates plasma lipid peroxides [7]. Transition metal acetylsalicylates and their anti-inflammatory activity have also been reported.[8]

In the quest for better tolerated NSAIDs, we synthesized diphenylamine-2,2′-dicarboxylic acid

Correspondence: G. Mohan, Department of Pharmacology, S.N. Medical College, Agra-282 002, India. E-mail: rohit210477@rediffmail.com
[†]Present address: Superintendent of Salt, Regional Office, Government of India, Ministry of Industry and Commerce, Ajanta Commercial Centre, 4th Floor, B Block, Ashram Road, Ahmedabad (India).
[‡]Department of Chemistry, Agra College, Agra-282 002(India).
[¶]Department of Biotechnology, School of Studies in Biochemistry, Jiwaji University, Gwalior-474 011, India.

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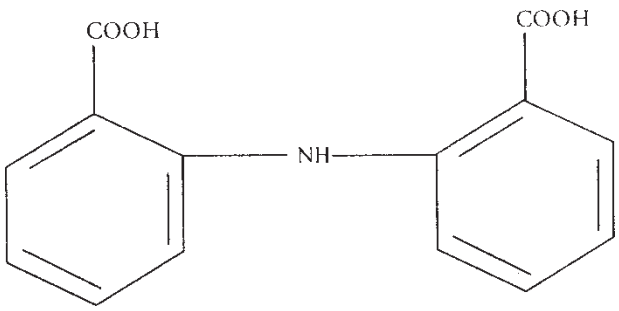

Figure 1. Diphenylamine-2,2′-dicarboxylic acid.

(DPDC) and its metal complexes involving Cu(II), Ni(II), Co(II) and Zn(II) as metal ions. Their structures were established using different physicochemical methods. The ligand and chelates were subjected to primary screening using the carrageenan-induced rat paw oedema test. It was found that the zinc chelate was the most active among all the compounds and, it was further investigated here.

Materials and methods

All the chemicals used were of analytical reagent grade.

Synthesis of Diphenylamine-2,2′-dicarboxylic acid (DPDC):

Diphenylamine-2,2′-dicarboxylic acid (Figure 1) was synthesized by condensing equimolar amounts of 2-chlorobenzoic acid with anthranilic acid in the presence of copper oxide in slightly alkaline media. The compound was decolorized with activated charcoal on boiling, dried under vacuum and crystallized from ethyl alcohol.

Synthesis of metal complexes:

All the complexes were prepared by the improved method of Musumeci *et al* [9]. The isolated compounds (Figure 2) were tested for purity using TLC. The infrared spectra of DPDC and its metal complexes

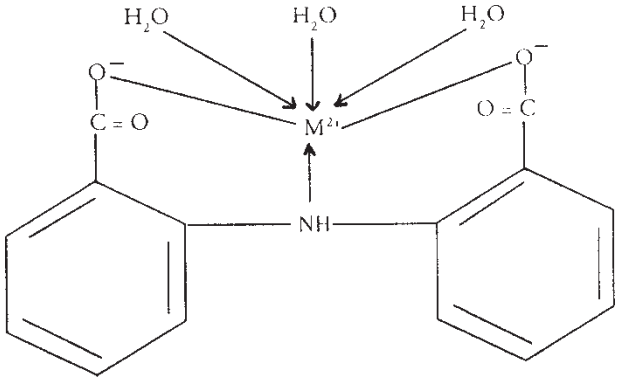

Figure 2. General structure of metal complex where M = Cu^{2+}, Ni^{2+}, Co^{2+} or Zn^{2+}.

were recorded on a Perkin Elmer 521 spectrophotometer. Magnetic susceptibility measurements were carried out at room temperature using Guoy's balance. The electronic spectra were recorded in dimethyl sulfoxide on a Shimadzu double beam spectrophotometer (UV-150-02 model). Molar conductance of the complexes was measured in DMSO solution using the Toshniwal Conductivity Bridge. The molecular weight of the compounds was determined by a cryoscopic method. Thermogravimetric analysis was carried out at the Regional Sophisticated Instrumentation Centre, Nagpur.

Pharmacology:

The standard drugs and zinc complex were administered subcutaneously as a suspension in saline containing 1.4% polyvinyl alcohol.

Carrageenan induced rat paw oedema test:

The anti-inflammatory action was assessed according to the method of Winter *et al* [10]. The standard drugs were naproxen and ibuprofen. Overnight-fasted rats (Wistar) of either sex weighing 140–160 gm, were arranged in group of six each. Oedema was induced by injecting 0.1 ml of 1% carrageenan (Marine colloids Inc., USA) suspension in normal saline into the plantar aponeurosis of the right paw. The paw volume was measured immediately and 4 h after the injection by a volume differential meter (M 7101, Ugo Basile, Milan, Italy). The percentage inhibition of swelling was calculated.

Carrageenan induced rat paw oedema in adrenalectomized rats:

Male Wistar rats (140–160 gm) were bilaterally adrenalectomized under light ether anesthesia by the method of Schultzer [11]. Water was replaced with normal saline for drinking purposes.

Two days after surgery the rats were divided into groups of six each. Oedema was induced by carrageenan and measured as in normal rats. The percentage inhibition of swelling was calculated.

Cotton pellet granuloma test:

Inhibition of granuloma tissue formation was assessed by the method of Winter and Porter [12]. Sterile cotton pellets (50 ± 1 mg) were implanted subcutaneously on either side of the midline dorsally under light anesthesia in male Wistar rats. The zinc complex, naproxen and ibuprofen were administered each day for six days. On the 7th day the rats were sacrificed and the pellets were dissected out and dried to a constant weight at 80°C. The mean weight of granulation tissue

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formed around each pellet of the group was calculated.

Adjuvant arthritis (established):

Male Wistar rats (160 ± 20 gm) were injected with 0.1 ml of a fine suspension of Freunds adjuvant complete (Difco) into the plantar aponeurosis of the right paw and the paw was left untreated for 14 days [13]. On day 14, the rats which showed 45–55% oedema of the injected paw were grouped into 4 groups of 8 each. The naproxen and zinc complex were administered daily from the 14^{th} to the 28^{th} day. The paw volume of both injected and uninjected paw was measured every alternate day using a water plethysmometer (M 7150 Ugo Basile, Milan, Italy).

The percentage inhibition of swelling was calculated and data were assessed statistically using the student 't' test.

Secondary lesions were assessed in the ear, forelimbs, hind limbs and tail. The following scale was used depending upon the severity of the lesion: 0 = normal; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe;

Castor oil induced diarrhoea:

Effect of the zinc complex on castor oil (Amrutanjan Ltd., Hyderabad)-induced fluid loss was assessed by the method of Awouters *et al.*[14] Overnight fasted male rats (Charles Foster Strain) were used weighing 180 ± 20 gm. Vehicle/drug was administered s.c. 1/2 hour prior to 1 ml of castor oil orally. The treated rats were kept in groups of two in metabolic cages (Techniplast, Gazeda, Italy) for collection of castor oil-induced gastrointestinal evacuation. Paper sheets of uniform weight were kept beneath each metabolic cage for faecal collection and this was assessed at the end of 6 h. The percentage inhibition was calculated. The rats were again used after fifteen days in the cross over test.

Prostagladins (PG's) estimations:

Prostaglandins were extracted in the inflammatory exudate by the method of Higgs and Salman [15]. The exudate was transferred to a graduated tube, treated with 5.0 ml of absolute ice cold acetone, stirred and centrifuged at 0°C. The supernatant liquor, after addition of 2 volumes of n-hexane was stirred and centrifuged. The lower aqueous layer was acidified to pH 3.5 with citric acid and the PG's were extracted into ethyl acetate. The ethyl acetate layer was evaporated to dryness under reduced pressure and reconstituted in Kreb's solution for the bioassay. PG's were bio-assayed on the rat fundus strip [16]. PGE_2(Sigma) was used as a standard and the extracts were estimated by a matching assay.

Analgesic activity:

Analgesic activity was assessed in prescreened mice using acetic acid (BDH) [17] or Phenyl quinone (Sigma) [18]. The prescreened Swiss albino mice were divided into three groups. The mice were initially fasted for 16 h. The mice were given ibuprofen or zinc complex 1/2 hour before the injection of acetic acid (50 mg/kg) or phenylquinone (2 mg/kg) s.c. The data were reported as all or none i.e. number of writhing per minute for each mouse treated with vehicle or respective treatment groups. The number of writhing movements shown by each mice was counted for 20 min using a manually operated digital counter. The percentage inhibition of writhing was calculated.

Arachidonic acid-induced mortality in mice:

The test was conducted as by the method of Kohler *et al* [19]. Arachidonic acid (Sigma) solution was administered into the tail vein of Swiss albino mice in a volume of 10 ml/kg. To determining the inhibitory activity of the zinc complex or naproxen or vehicle, these were administered s.c. to groups of 5 mice, 1 h before the arachidonic acid challenge. The percentage mortality and percentage protection in each group was noted 24 h after the arachidonic acid challenge.

Ulcerogenic test:

Experiments were carried out in 24 hour-fasted male and female (non pregnant) rats (Charles Foster Strain) weighing between 140–175 gm. Phenylbutazone were used for comparison. Water was allowed *ad libitum* before and during the experiment. Diphenyl amine-2,2′-dicarboxylic acid or zinc complex or phenylbutazone was given orally as a suspension in saline containing 1.4% polyvinyl alcohol and the rats were sacrificed 6 h after the treatment. After opening the abdomen the stomach was removed, cut open along the greater curvature, washed and examined under a stereoscopic binocular microscope (Meopta) for scoring the lesions under blind conditions.[20] The lesions were scored as follows: 0 = No Lesion; 1 = Haemorrhagic effusion; 2 = Mucosal ulceration (< 2/3 area); 3 = Deep ulceration; 4 = Perforated ulcers.

The ulcerogenic index (UI) was calculated as follows;

$$\text{Ulcerogenic index (UI)} = \frac{\text{ADU X \% RU}}{100}$$

where ADU - Average degree of ulceration%; RU - % of rats with ulcer.

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Table I. Effect of the zinc complex on carrageenan-induced rat paw oedema.

Pretreatment (Dose mg/kg s.c.)	Paw volume Mean ± SE	Percentage inhibition
Vehicle	1.03 ± 0.05	–
Naproxen (0.5)	0.60 ± 0.04	41.75
(1.0)	0.46 ± 0.06	55.33
(2.0)	0.44 ± 0.04	57.28
(4.0)	0.38 ± 0.03	63.10
(8.0)	0.25 ± 0.04	75.72
Vehicle	1.27 ± 0.05	–
Zinc complex (12.5)	0.76 ± 0.02	40.15
(25.0)	0.68 ± 0.03	46.45
(50.0)	0.76 ± 0.05	47.24
(100.0)	0.61 ± 0.04	51.96

n = 6 in each group.

Result and discussions

Chemistry:

Elemental analysis, molecular weight determination and conductance studies:. Elemental analysis and molecular weight of the compounds has been determined and found in agreement with the theoretical values. This data shows the presence of three water molecules in the complexes. Thermal dehydration and infrared spectra of the complexes further confirmed the presence of water molecules. The low conductance value ($0.9–1.8\,ohm^{-1}\,cm^2\,mol^{-1}$) indicated their non-electrolytic nature due to the charge neutralization of the metal ion by the ligand.

Electronic spectra and magnetic measurements:. The magnetic moments of the Cu(II), Ni(II) AND Co(II) complexes, calculated from the corrected magnetic susceptibility, and electronic spectra are discussed.

Copper complex:. The magnetic moment value of the Copper complex (1.86 B.M.) indicates octahedral geometry.[21] This was further confirmed by the electronic spectra. It shows only one band in the region $13793\,cm^{-1}$ due to the $^2E_g \rightarrow {}^3T_{2g}$ transition suggesting a distorted octahedral geometry [22].

Table III. Effect of the zinc complex on cotton pellet granuloma in rats.

Pretreatment (Dose mg/kg s.c. × 7 days)	Weight of dry granuloma Mean mg. ± SE	% inhibition
Control	250.4 ± 5.60	–
Zinc complex (50)	218.0 ± 5.60	13.00
Naproxen (25)	205.3 ± 4.00	18.00
Ibuprofen (50)	203.8 ± 5.30	18.61

n = 8 in each group.

Nickel complex:. The effective magnetic moment of the nickel complex (3.11 B.M.) suggests an octahedral geometry of the complex. The geometry was further supported by the electronic spectrum. The bands observed at $10190\,cm^{-1}$, $17200\,cm^{-1}$ and $26000\,cm^{-1}$ were probably due to the three spin allowed transitions from $^3A_{2g} \rightarrow {}^3T_{2g}$ (F), $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) and $^3A_{2g} \rightarrow {}^3T_{1g}$ (P) respectively in an octahedral environment.[22]

Cobalt complex:. The cobalt complex was expected to have an octahedral geometry as confirmed by its magnetic moment value (4.87 B.M.). Three bands observed in the electronic spectrum of the Cobalt complex at $7400\,cm^{-1}$, $17760\,cm^{-1}$ and $20150\,cm^{-1}$ respectively could be due to the three $^4T_{1g} \rightarrow {}^4T_{2g}$ (F), $^4T_{1g} \rightarrow {}^4A_{2g}$ (F) and $^4T_{1g} \rightarrow {}^4T_{1g}$ (P) transitions respectively [22].

Zinc complex:. On the basis of elemental analyses, thermal analyses, infrared spectra, molar conductance and molecular weight determination data the zinc complex was proposed to have an octahedral geometry.

Infrared spectra:. For the sake of brevity, only shifted or altogether new peaks appearing in the spectra of metal chelates are discussed. Diphenyl amine-2,2′-dicarboxylic acid shows a band around $3250\,cm^{-1}$ which is shifted to the lower frequency region in the case of their complexes, suggesting coordination through N of —NH group. The infrared spectra a showing a band at $1680\,cm^{-1}$ which is shifted to the lower frequency region in the metal complexes, confirm the coordination of the ligand to the metal

Table II. Effect of the zinc complex in normal and adrenalectomized rats against carrageenan-induced raw paw oedema.

Pretreatment	Normal rats		Adrenalectomized rats	
(Dose mg/kg s.c.)	Paw volume in ml. Mean ± SE	% Inhibition	Paw volume in ml. Mean ± SE	% inhibition
Vehicle	1.30 ± 0.40	–	1.02 ± 0.20	–
Zinc complex (50)	0.60 ± 0.03	53.84	0.60 ± 0.25	41.20
Ibuprofen (50)	0.62 ± 0.04	52.30	0.58 ± 0.40	43.20

n = 6 in each group.

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Table IV. Effect of the zinc complex on adjuvant arthritis (established) test in rats.

	Days							
Pretreatment (mg/kg s.c.)	0 14^{th}	2 16^{th}	4 18^{th}	6 20^{th}	8 22^{nd}	10 24^{th}	12 26^{th}	14 28^{th}
Control	1.41 ± 0.12	1.89 ± 0.15	1.85 ± 0.12	1.89 ± 0.09	1.84 ± 0.12	1.87 ± 0.12	1.82 ± 0.17	1.70 ± 0.16
Zinc complex (25)	1.40 ± 0.11	1.72 ± 0.15	1.64 ± 0.12	1.49 ± 0.13	1.37 ± 0.13	1.65 ± 0.15	1.38 ± 0.15	1.33 ± 0.16
p	–	*	*	*	*	*	*	*
% inhibition			9.00	11.30	18.10	25.50	11.80	24.20
Naproxen (4)	1.39 ± 0.12	1.32 ± 0.12	1.07 ± 0.09	0.98 ± 0.07	0.95 ± 0.08	0.77 ± 0.06	0.86 ± 0.08	0.87 ± 0.07
p		**	***	***	***	***	***	***
% inhibition	–	–	30.14	42.20	46.10	48.40	58.80	42.70
Naproxen (8)	1.32 ± 0.12	1.20 ± 0.14	1.03 ± 0.08	0.95 ± 0.06	0.85 ± 0.08	0.70 ± 0.08	0.73 ± 0.07	0.73 ± 0.10
p	–	**	***	***	***	***	***	***
% inhibition	–	–	36.50	44.30	47.80	53.80	62.60	59.90

n = 8 in each group; p = *** < 0.001, ** < 0.001, * < 0.005.

Table V. Effect of the zinc complex on castor oil-induced diarrhoea in rats.

Pretreatment (Dose mg/kg s.c.)	Mean evacuation in gm ± SE in 6 h	Percentage inhibition
Control	6.10 ± 0.16	–
Zinc complex (50)	4.62 ± 0.32	25

n = 15 in both groups.

Table VI. Effect of the zinc complex on PGE_2-like substances in the inflammatory exudate.

Pretreatment (Dose mg/kg s.c. × 3 days)	PGE_2 like substance mg/kg ± SE	Percentage
Control	40.80 ± 0.35	–
Zinc complex(50)	28.40 ± 0.37	30.40
Naproxen(25)	15.50 ± 0.28	62.00

n = 8 in each group.

Table VII. Effect of the zinc complex on 0.5% acetic acid-induced writhing in mice.

Pretreatment (Dose mg/kg s.c.)	Writhing Mean ± SE	% Protection
Control n = 6	11.00 ± 1.60	–
Ibuprofen (50) n = 5	8.20 ± 1.50	25
Zinc complex (50) n = 6 for each group.	11.33 ± 0.91	nil

Table VIII. Effect of the zinc complex on 0.02% phenylquinone-induced writhing test in mice.

Pretreatment (Dose mg/kg s.c.)	Writhing Mean ± S.E.	% Protection
Control n = 6	14.00 ± 1.20	–
Ibuprofen(50) n = 5	1.60 ± 0.20	80
Zinc complex(50) n = 5 for each group.	20.00 ± 4.60	nil

ion through a carboxylic acid moiety [23]. The presence of coordinated water molecules in the complexes is revealed by stretching modes occurring at 3500–3600 cm^{-1} and bending modes at 1580 cm^{-1}. The appearance of the band at 480–490 cm^{-1} (M–N) and 405–420 cm^{-1} (M–O) support coordination through the N and O donor sites of the ligand [24].

Pharmacology:

Anti inflammatory activity:. In a quest for safe, effective and better tolerated NSAIDs, we synthesized diphenyl amine-2,2′-dicarboxylic acid and its metal complexes. The compounds were primarily screened in an acute model of inflammation i.e. the carrageenan-induced rat paw oedema test. It was found that the zinc complex inhibited 40–52% oedema at a dose level of 12.5–100 mg/kg (Table I) and it was almost equipotent with ibuprofen in normal and adrenalectomized rats (Table II). However, it was approximately 28% less effective in the subacute cotton pellet granuloma test for inflammation (Table III) and was approximately 50% effective as compared to 4 mg/kg naproxen in the chronic

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Table IX. Effect of the zinc complex on arachidonic acid-induced mortality in mice.

Pretreatment (Dose mg/kg s.c.)	No. of mice dead	% mortality	% Protection
Control	5	100	–
Zinc complex (50)	4	80	20
Naproxen (25)	0	0	100

n = 5 in each group.

Table X. Ulcerogenic potential of diphenyl amine-2,2′-dicarboxylic acid and its zinc complex.

Pretreatment (Dose mg/kg PO)	ADU	% RU	UI
Vehicle	0	0	0
DPDC (100)	1.5	80	1.2
Zinc complex (100)	1.0	80	0.6
Oxyphenbutazone (50)	2.0	100	2.0
(100)	3.0	100	3.0

n = 10 in each group.

test of inflammation i.e. adjuvant arthritis established (Table IV).

It has been reported that inhibitors of prostaglandin synthesis are effective in inhibiting castor oil-induced diarrhea (Awouters *et al* [14]). Prostaglandins are synthesized throughout the gut to sustain peristaltic activity which is inhibited by NSAIDs [25]. The zinc complex also inhibited prostaglandin synthesis induced by ricinoleic acid, a major component of castor oil (Table V). This was further substantiated by the fact that the zinc complex inhibited (30.4%) prostaglandin E_2-like substances in the inflammatory exudate (Table VI). The zinc complex did not prevent acetic acid- or phenylquinone-induced writhing in mice as compared to 50 mg/kg ibuprofen which protected 25% and 80% writhing respectively (Tables VII and VIII), primarily indicating that the zinc complex did not have an analgesic activity. However, other methods to evaluate its analgesic activity are in progress. It has been observed that intravenous injection of arachidonic acid leads to formation of either prostaglandin's or thromboxane A_2 which induces platelet thrombi and constriction of pulmonary vessels [26]. The zinc complex at 50 mg/kg dose protected the mice (20%) against arachidonic acid-induced mortality (Table IX).

Gastrointestinal ulceration is a well known side effect of NSAIDs and is the common reason for rejecting an active anti-inflammatory compound. Therefore, it is necessary in the very early stages of a screening programme for new anti-inflammatory compound to assess the incidence and severity of gastric ulceration. The zinc complex has very a low ulcerogenic index and therefore can be said to have a low incidence of gastric irritation common to most of NSAID's (Table X).

On gross behavioural studies, it has been observed that the zinc complex showed a mild increase in spontaneous activity and respiration. It also induced passivity whereas the compound had no effect on piloerection, crouching gait, diuresis and body temperature. Further toxicological studies are in progress.

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