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Synthesis, Characterization, and Biological Activity of Transition Metals Complexes with Mefenamic Acid (NSAIDs)[1]

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Abstract—A new series of transition metal complexes have been synthesized with [(2,3-dimethylphenyl)-amino]benzoic acid (Mefenamic acid) in 1 : 1/1 : 2 M : L ratio. The complexes have been characterized by elemental analysis, FT-IR and UV–Vis spectroscopy. Antifungal, antibacterial, antitumor, antioxidant (DPPH, H_2O_2 induced DNA damage) activity of the complexes and DNA interaction with the complexes were studied. The results revealed that the ligand and most of synthesized compounds did not demonstrate significant antibacterial activity unlike [Ni(Mef)(H_2O)Cl] that exhibited pronounced activity against *F. Solani*. Antitumor activity of the products was higher than that of the free ligand.

Keywords: mefenamic acid, transition metals, complexes, IR, UV–Vis, conductance, antibacterial, antifungal, antitumor, antioxidant activity, DNA interaction

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INTRODUCTION

According to numerous investigations binding of a drug to a metal enhances its activity [1, 2]. Cationic metal centers actively bind to negatively charged biomolecules including proteins and nucleic acids. Metal complexes demonstrate high pharmaceutical potential [3, 4].

[2-(2,3-Dimethylphenyl)amino]benzoic acid (mefenamic acid) is anthranilic acid derivative that demonstrates non-steroidal anti-inflammatory, antipyretic, and analgesic activity [5, 6]. It inhibits proliferation and triggers apoptotic cell death of several human cancer cell lines [7–9], acts as a neuro-protection in Alzheimer disease [10] and demonstrates many other biological sites of action [11, 12].

Pharmacological importance of mefenamic acid initiated our study of synthesis and biological activity of its metal complexes (Fig. 1).

EXPERIMENTAL

Chemicals and instrumentation. Most chemicals used were of analytical grade purchased from Merck. Mefenamic acid was provided by Ferozsons Ltd. (Lahore). The solvents were purified according to the conventional methods [13]. Melting points were measured in open capillary tubes by Mitamura Rikero Kogyo (Japan). IR spectra were recorded as KBr discs in the range of 4000–400 cm^{-1} on a Perkin-Elmer Spectrum-1000 FT-IR Spectrophotometer. CHN analysis was carried out with a Perkin-Elmer 2400 Series II instrument. Electronic spectra were recorded on a Lambda 2S Perkin Elmer spectrophotometer. Conductance was measured by Metrohm 712 conductometer.

Synthesis of potassium salt of mefenamic acid. 10 mL of KOH (1 mmol) solution were added

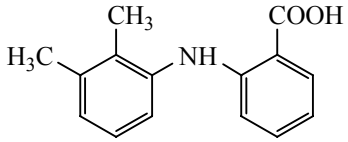

Fig. 1. 2-[(2,3-dimethylphenyl)amino]benzoic acid (Mefenamic acid).

[1] The text was submitted by the authors in English.

dropwise upon stirring to the solution of mefenamic acid (1 mmol) in ethanol (100 mL). The mixture was stirred for 1 h at room temperature. The solvent was removed in a rotary evaporator under reduced pressure. The solid product was recrystallized in chloroform : *n*-hexane (1 : 1).

Synthesis of transition metal complexes I–VIII. Potassium salt of mefenamic acid (1 mmol/2 mmol) was dissolved in ethanol (100 mL) at room temperature. The transition metal chloride (1 mmol) dissolved in ethanol (50 mL) was added drop wise to the above solution upon constant stirring. The reaction mixture was refluxed for 6 h with continuous stirring. KCl was filtered off and the solvent was evaporated in rotary evaporator under reduced pressure. The solid residue was recrystallized in chloroform *:* *n*-hexane mixture (4 : 1).

$$n\text{R-COOK} + \text{MCl}_x \cdot m\text{H}_2\text{O} \xrightarrow{\text{EtOH, Reflux 6 h}} \text{M(RCOOO)}_n\text{Cl}_x \cdot m\text{H}_2\text{O} + \text{KCl},$$

n = 1, 2; x = 2, 3; m = 2, 4, 6; M = Cr(III), Fe(III), Ni(II), Cu(II).

Biological activity. All products were tested for antibacterial, antifungal antioxidants, and potato disc tumor activity.

Antibacterial assay. The free ligand and metal complexes were tested for antibacterial activity against bacterial strains: gram positive *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6633) and *Micrococcus luteus* (ATCC 10240); and gram negative *Escherichia coli* (ATCC 15224) and *Enterobacter aerogenes* (ATCC 13048) by using agar well diffusion method [14]. Broth culture (0.75 mL) containing approximately 10^6 colony forming units (CFU/mL) of test strain was added to nutrient agar medium (75 mL) at 45ºC, mixed well, and poured into a 14 cm sterile petri plates. The medium was allowed to solidify and 8 mm wells were dug with a sterile metallic borer. One hundred μL of the test sample (1 mg/mL in DMSO) was poured in respective wells. In each plate DMSO served as negative control and standard antibacterial drugs Roxithromycin (1 mg/mL) and Cefexime (1 mg/mL) served as a positive control. Triplicate plates of each bacterial strain were prepared. The plates were incubated at 37ºC for 24 h. Antibacterial activity was determined by measuring the diameter of zones with complete inhibition (mm). Growth inhibition was calculated with reference to positive control.

Antifungal assay. Antifungal activity of free ligand and metal complexes was studied against fungal strains (*Mucor species*, *Aspergillus flavus, Aspergillus fumigatus* and *Fusarium solani*) by using agar tube dilution method [15]. Screw caped test tubes containing Sabouraud dextrose agar (SDA) medium (4 mL) were autoclaved at 121ºC for 15 min. Test tubes were allowed to cool down to 50ºC and non solidified SDA was loaded with 66.6 μL of the test compound from the stock solution (12 mg/mL in DMSO) to make final concentration 200 μL/mL. Test tubes content was then allowed to solidify in slanting position at room temperature. Each test tube containing solidified media and test compound were then inoculated with 4 mm diameter piece of inoculum from a seven days old culture. The media supplemented with DMSO and Terbinafine (200 μL/mL) were used as negative and positive controls, respectively. Test tubes were incubated at 28ºC for seven days and fungal growth was determined by measuring linear growth (mm). Growth inhibition was calculated with reference to the negative control.

Antitumor assay. To detect antitumor activity of the test compounds, potato disc antitumor assay was performed [15]. The 48 h old culture of AT-10 strain of *Agrobacterium tumefaciens* was used. Inoculums of five concentrations (0.01, 0.1, 10, 100, 1000 ppm) of each test sample containing bacterial culture were prepared. Red skinned potatoes were surface sterilized in 0.1% mercuric chloride solution and then under complete aseptic conditions. Potato discs (0.5 cm thickness) were obtained from these potatoes by using sterile metallic cork borer. The potato discs were placed in petri plates each containing 25 mL of 1.5% autoclaved agar solution. The inoculum (50 μL) was poured on each disc. The plates were sealed with parafilm and incubated at 28ºC for 21 days. Number of tumors was counted after staining with the lugol solution (10% KI and 5% I_2) with the help of dissecting microscope.

Antioxidant assay. Antioxidant and prooxidant effects of the synthesized compounds were studied *in vitro* by using DNA protection assay [16].

DPPH assay. Radical scavenging activity of compounds (conc. 100, 50, and 25 ppm) against stable free radical DPPH was determined spectrophotometrically [16]. Assay was carried out in triplicate. Reaction mixture was prepared by adding 100 μL of each test compound solution, 0.1 mM DPPH in ethanol

Table 1. Physical data of transition metal complexes of mefenamic acid

Comp. no.	Formula	M_W	mp, ºC	Yield, %	Elemental analysis data					
					C		H		N	
					found, %	calculated, %	found, %	calculated, %	found, %	calculated, %
HL	Mefenamic acid	241.2	230–231	–	–	–	–	–	–	–
I	$[Cr(Mef(H_2O)_2Cl_2]$	399.2	210–212	76	13.02	13.06	4.54	4.58	3.51	3.47
II	$[Cr(Mef)_2(H_2O)Cl]$	586.0	215–216	68	9.16	9.12	4.93	4.89	4.93	4.97
III	$[Fe(Mef)(H_2O)_3Cl]Cl$	421.1	205–206	78	13.26	13.21	4.79	4.74	3.33	3.37
IV	$[Fe(Mef)_2(H_2O)Cl]$	589.9	175–176	71	9.47	9.51	5.13	5.17	4.75	4.71
V	$[Ni(Mef)(H_2O)Cl]$	352.4	216–218	69	16.65	16.61	4.58	4.53	3.97	3.93
VI	$[Ni(Mef)_2]$	539.2	90–91	82	10.88	10.84	5.20	5.24	5.19	5.23
VII	$[Cu(Mef)(H_2O)_2]Cl$	375.3	204–206	77	16.93	16.97	4.83	4.88	3.73	3.77
VIII	$[Cu(Mef)_2]$	544.1	154–155	67	11.68	11.72	5.19	5.15	5.15	5.10

solution and 0.9 mL of 0.1 mM Tris-HCl in capped vials. DMSO was used as the negative control. Reaction mixture was incubated in darkness for 30 min at room temperature. Upon incubation absorbance of each reaction mixture was measured spectrophotometrically at 517 nm. Scavenging (%) of DPPH free radicals for each concentration of each compound was calculated.

H_2O_2 induced DNA damage assay. To determine the antioxidant/pro-oxidant potential of test compounds DNA protection assay was performed [17]. The reaction was conducted in eppendorf tubes at total volume of 15 μL containing 0.5 μg of pBR 322 DNA in 3 μL of 50 mM phosphate buffer (pH 7.4), 3 μL of 2 mM $FeSO_4$, and 5 μL of tested samples at various concentrations (10, 100, 1000 ppm). Then, 4 μL of 30% H_2O_2 were added. Similarly DNA samples of the reference containing the same content except the compounds were prepared. All reaction mixtures were incubated at 37ºC for 1 h. The mixtures were subjected to 1% agarose gel electrophoresis. DNA bands (supercoiled, linear and open circular) were stained with ethidium bromide. Gels were documented (Gel Doc, BioRad) and intensity of the bands was determined. DNA protection was calculated based on the DNA band corresponding to that of native in the presence and absence of different concentrations (10, 100, 1000 ppm) of test compounds. Evaluations of antioxidant or prooxidant effects on DNA were based on percent of increase or loss of supercoiled monomer compared to the control value. To avoid the effects of photoexcitation of samples, experiments were done in darkness.

DNA interaction studies. The DNA solution was made in distilled water which gave a ratio of UV absorbances at 260 and 280 nm of 1.72, indicating that the DNA was sufficiently free of proteins [18]. The DNA concentration was determined at 260 nm by using the formula: DNA conc. (μg/mL) = Absorbance at 260 nm × dil. Factor × 50 μg/mL × ratio. Standard ratio (1.8)

DNA solution of each compound was prepared in DMF of 1×10^{-3} concentration. Solvent mixture was prepared in the ratio water : DMF in which both the compound and DNA soluble.

Phosphate buffer (0.1 M) was prepared by adding 14.19 g of Na_2HPO_4 and 15.6 g of NaH_2PO_4 in 1 L of solvent mixture (BSM of pH 7.4). The assay was done on Agilent chemstation UV–Vis spectrophotometer. BSM was used as a blank and 50 μL of compound were added to 2950 μL of BSM. Change in absorbance upon addition of DNA was measured and spectra were recorded until we got the maximum interaction.

RESULTS AND DISCUSSION

The complexes were solids soluble in common organic solvents. Molar conductance of compounds was measured in 0.001M ethanol solution, μS cm^{-1}: 14.7 (Ligand), 40.1 (1), 27.6 (2), 29.9 (3), 25.9 (4), 18.2 (5), 55.3 (6), 25.9 (7), and 5.4 (8). Physical data are presented in Table 1.

FT-IR spectroscopy. The NH band of mefenamic acid at 3340 cm^{-1} did not exhibit significant shift upon

Table 2. IR data (cm^{-1}) for the transition metals complexes of mefenamic acid

Comp. no.	ν(N–H)	ν(C=O)	ν(COO)		Δν	ν(M–O)
			ν_{as}(COO)	ν_s(COO)		
HL	3340	1730	1673	1422	251	–
I	3344	1730	1612	1421	191	486
II	3343	1756	1603	1490	113	470
III	3332	1759	1609	1486	123	468
IV	3334	1729	1610	1448	162	462
V	3345	1722	1576	1451	125	449
VI	3339	1734	1608	1413	195	468
VII	3350	1710	1566	1436	130	496
VIII	3343	1723	1617	1452	165	497

Table 3. UV–Vis data of transition metal complexes of mefenamic acid

Comp. no.	λ, cm^{-1} (nm)	Electronic transition	Geometry
I	17452 (573) 21673 (461) 34030 (294)	$^4A_{2g} \rightarrow {}^4T_{2g}$ $^4A_{2g} \rightarrow {}^4T_{1g}$ (F) $^4A_{2g} \rightarrow {}^4T_{1g}$ (P)	Octahedral
II	16125 (620) 21009 (476) 36122 (277)	$^4A_{2g} \rightarrow {}^4T_{2g}$ $^4A_{2g} \rightarrow {}^4T_{1g}$ (F) $^4A_{2g} \rightarrow {}^4T_{1g}$ (P)	Octahedral
III	16579 (603) 22124 (452)	$^6A_{1g} \rightarrow {}^5T_{1g}$ $^6A_{1g} \rightarrow {}^4T_{2g}$ (G)	Octahedral
IV	16560 (604) 21746 (460)	$^6A_{1g} \rightarrow {}^5T_{1g}$ $^6A_{1g} \rightarrow {}^4T_{2g}$ (G)	Octahedral
V	19987 (500) 25125 (398)	$^3A_{2g} \rightarrow {}^3T_{1g}$ (F) $^3A_{2g} \rightarrow {}^3T_{1g}$ (P)	Square planner
VI	19550 (512) 24991 (400)	$^3A_{2g} \rightarrow {}^3T_{1g}$ (F) $^3A_{2g} \rightarrow {}^3T_{1g}$ (P)	Square planner
VII	23678 (422)	$^2E_g \rightarrow {}^2B_{1g}$	Square planner [21]
VIII	24598 (406)	$^2E_g \rightarrow {}^2B_{1g}$	Square planner

complexation indicating no participation of the group in the process (Table 2).

IR data of the complexes demonstrated the separation value (Δν) between ν_{as}(COO) and ν_s(COO) to be < 200 cm^{-1} in the spectra of ligands suggesting bidentate bonding for the transition metals carboxylates [19, 20]. The new band in the range of 486–449 cm^{-1} in the spectra of products was assigned to (M–O) bond formation.

UV–Vis **spectra.** UV–Vis absorption pattern of the synthesized compounds was recorded in the region 200–800 nm (Table 3). Some bands in the spectra of complexes **I–VIII** were typical for interligand and charge transfer or $n \rightarrow \pi^*$ transitions and had decreased intensities. Sharp bands observed in the range 240–270 nm could be assigned to charge transfer L→M or $n \rightarrow \pi^*$ transition [21].

Antimicrobial activity. The ligand and compounds **I–VIII** did not demonstrate any activity against all five bacterial strains tested [22–24]. Only compound **V** demonstrated significant antifungal activity against s*F. solani* [25–27] (Table 4).

Antitumor assay. All products exhibited significant level of tumor inhibition as compared to the reference drug (Vincristine) and the ligand (Table 5) [28–30].

Antioxidant assay. In the assay majority of the products exhibited antioxidant concentration dependent activity (Table 6). Most of the products enhanced the

Table 4. Antifungal activity of transition metals complexes of mefenamic acid

Comp. no.	Percentage growth inhibition			
	A. fumigatus	*A. flavus*	*F. solani*	*Mucor* sp.
I	38.06452	59.85401	66.66667	14.28571
II	41.29032	27.0073	60.95238	13.60544
III	50.32258	42.33577	74.28571	23.80952
IV	32.25806	30.65693	57.14286	16.32653
V	37.41935	39.41606	71.42857	22.44898
VI	44.51613	37.22628	55.2381	27.89116
VII	43.22581	41.60584	33.33333	4.081633
VIII	38.06452	35.76642	57.14286	25.85034

Table 5. Antitumor activity of transition metal complexes of mefenamic acid

Comp. no.	Percentage age tumor inhibition at concentrations, ppm					IC_{50}, μg/mL
	1000	100	10	0.1	0.01	
I	100	100.00	100.00	75.98	68.99	BDR
II	100	76.54	62.12	51.51	30.30	0.281
III	100	100.00	63.56	58.13	5.42	BDR
IV	100	90.15	89.39	70.45	60.60	BDR
V	100	100.00	96.89	77.51	56.58	BDR
VI	100	66.47	56.60	40.03	33.33	0.661
VII	100	49.11	48.71	44.37	44.37	0.935
VIII	100	72.78	65.28	57.39	49.50	0.024

Table 6. DPPH free radical scavenging activity of transition metals complexes of mefenamic acid

Comp. no.	Percentage scavenging, ppm			IC_{50}, μg/mL	Remarks
	100	50	25		
I	–36.2347	–11.1518	–5.72943	BDR	Pro-oxidant
II	–35.6227	–16.2084	–3.41025	BDR	Pro-oxidant
III	–10.8427	1.195779	6.837513	BDR	Pro-oxidant
IV	–11.6815	1.230694	5.395298	BDR	Pro-oxidant
V	6.68587	1.413886	–1.42537	BDR	Pro-oxidant
VI	–31.9296	21.98066	39.45954	BDR	Pro-oxidant
VII	8.833381	11.17964	13.8137	>100	Antioxidant
VIII	62.71571	48.33388	40.24352	48.691	Antioxidant

DNA damage [31] at concentration 1000 ppm (Table 7). The compounds **II–IV** and **VI** protected plasmid DNA at all concentrations.

Interaction with DNA. Absorbance of the complex **IV** was DNA concentration dependent (Figs. 2, 3). The hypochromic effect was due to the interaction between electronic states of chromophores with DNA bases and indicated close proximity of the complex molecules to DNA bases.

Binding constant, *K*, was calculated on the basis of variations in the absorbance spectra of complexes upon binding to DNA according to the equation reported

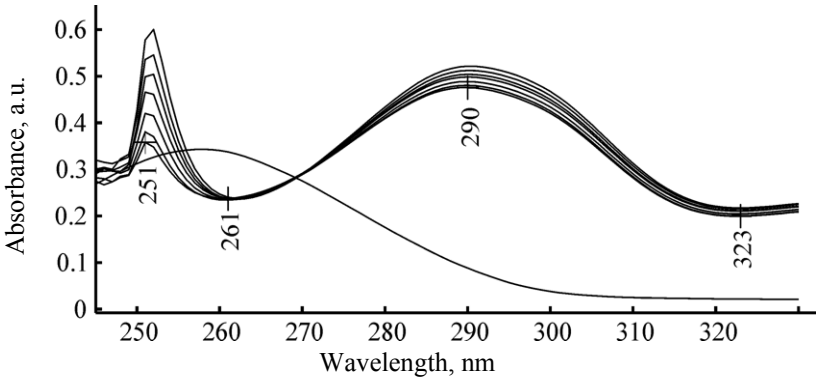

Fig. 2. Absorption spectra of mefenamic acid at different concentrations of DNA.

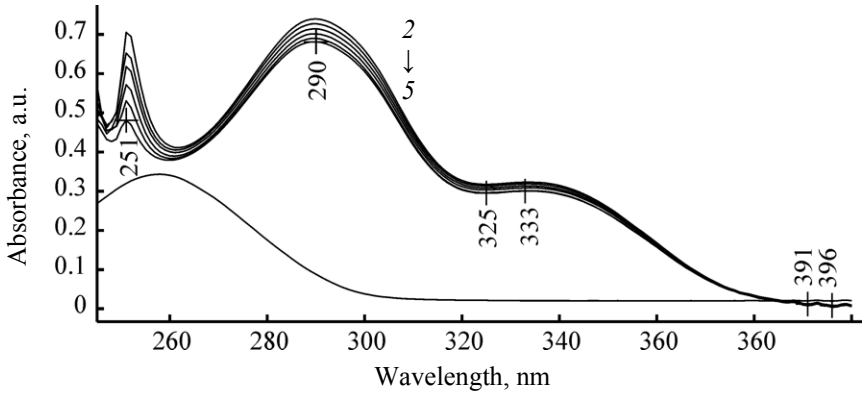

Fig. 3. Absorption spectra of (*1*) compound **IV** at different concentrations of DNA, M × 10^{-5}: (*2*) 1.64; (*3*) 3.23; (*4*) 4.76; and (*5*) 6.25.

Table 7. DNA protection of transition metals complexes of mefenamic acid[a]

Comp. no.	Concentration	Protection	Damage
I	1000	–	+++
	100	++	–
	10	++	–
II	1000	++	–
	100	++	–
	10	+	–
III	1000	++	–
	100	++	–
	10	++	–
IV	1000	++	–
	100	++	–
	10	++	–
V	1000	–	+++
	100	++	–
	10	++	–
VI	1000	++	–
	100	++	–
	10	++	-
VII	1000	–	+++
	100	++	–
	10	++	–
VIII	1000	–	+++
	100	–	++
	10	++	–

[a] (+) Weaklyeffective; (++) moderately effective; (+++) strongly effective.

earlier [32] (Table 8). The plot of $A_0/(A - A_0)$ vs. 1/[DNA] was contracted using the data. The intercept to slope ratio yielded the binding constant (Fig. 4). The accumulated data indicated high affinity of the products with DNA.

Table 8. Association constants and Gibbs free energies of transition metals complexes of mefenamic acid

Comp. no.	$(K/M)^{-1}$	$-\Delta G$, kJ/mol
HL	58.24×10^3	27.18
III	-57.75×10^3	–
IV	39.15×10^3	26.20
VII	13.51×10^3	23.56
VIII	48.48×10^3	26.73

CONCLUSIONS

FT-IR data indicated that mefenamic acid acted as the bidentate ligand. The products did not exhibit antibacterial activity against tested bacterial strains probably due to their low lipophilicity. Only [Ni(Mef)·(H_2O)Cl] (**V**) demonstrated significant antifungal activity against *F. solani*. All complexes were remarkably antitumor active against AT10. The compounds **II–IV** and **VI** protected the plasmid DNA at all concentrations. The hypochromic effect in UV–Vis spectra of products indicated the interaction among electronic sites of chromophores with DNA bases.

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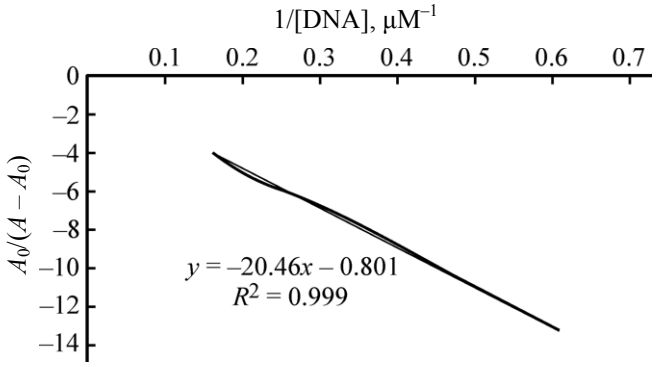

Fig. 4. Plot of $A_0/(A - A_0)$ vs. 1/[DNA] for determination of binding constant of complex **IV**–DNA adduct.

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