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Synthesis and Characterization of Cu(II) Complex with NSAIDs (Naproxen and Nimesulide) and Tetramethylethylenediamin

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Abstract:
Two monomeric ternary complexes of (+) -(S)-2-(6-Methoxynaphthalen-2-yl) propanoic acid (Naproxen) and N-(4-Nitro-2-phenoxy phenyl) methanesulfonamide (nimesulide) were prepared by the reaction of $CuCl_2 \cdot 2H_2O$ and N,N,N′,N′-tetramethylethylenediamine (tmen) in the presence of sodium hydroxide. Both complexes were characterized by the elemental combustion analysis, UV-visible and FT–IR spectroscopy, thermal analysis, and single-crystal X-ray diffraction. From the crystal structure of complexes, it is evident that each copper (II) ion is six-coordinate and is bonded to chelating tmen. The complexes of copper (II) and TMEDA with Naproxen and Nimesulide were in the ratio 1:2:1. The Complexes were blue in color and their melting points were recorded as 196 °C and 220 °C respectively. UV- Visible spectra of complexes exhibited three absorptions. The intense absorption band at higher energy was 250 nm and 300nm for both complexes respectively. Both complexes were found to possess antibacterial properties against four strains, including *Staphylococcus aureus*, *Bacillus spizizenii*, *Escherichia coli*, and *Klebsiella pneumonia*.
Keywords: Synthesis, Cu(II) complexes, Naproxen & Nimesulide, TMEDA.

INTRODUCTION

Copper is a chemical element with symbol Cu (from Latin Cuprum). It belongs to group 11 and 4th period of the periodic table. Its electron configuration is [Ar] $3d^{10}4s^{1}$. In the first transition, series copper has 3d series (Batool *et al.*, 2019). Copper occurs mostly in the form of ores. The most common ores are chalcopyrite $CuFeS_2$, chalcocites CuS_2, and copper carbonates $CuCO_3.Cu(OH)_2$. The concentration of copper ion is 50% in the earth's crust and 1ppm in humans (Clarke, 2015; Sharma and Kumar, 2018).

Copper is a key constituent of respiratory enzymes complex cytochrome c oxidase. Due to the remarkable significance of copper, its complexes are used in antimicrobial, antiviral, anti-tumor and anti-inflammatory compounds as enzymes inhibitors (Naysmith *et al.*, 2017). The concentration of copper in ores is 0.6% and copper is extracted from ores by the forth-floatation and bioleaching process (Destro *et al.*, 2018; Sharma *et al.*, 2016).

Copper is used in everyday life. Most copper use in electrical equipment such as electrical wires, motors and industrial machinery such as heat exchanger. Copper is used in paints, corrosion resistance, jewelry and power distribution (Noël, 2009).

Due to its higher oxidation state, copper is less reactive. Copper has a positive E value (0.34) and below from hydrogen in electro chemical series (Kumar *et al.*, 2018).

$$Cu^{2+} + 2e^{-} \rightarrow Cu_{(s)} \qquad E_o = 0.34$$

When copper react with conc. sulphuric acid and nitric acid, copper oxidized as Cu^{2+}.

$$Cu + 4HNO_3 \rightarrow 2NO_2 + Cu(NO_3)_2 + 2H_2$$

$$Cu + H_2SO_4 \rightarrow Cu^{2+} + SO_4^{2-} + H_2$$

Copper(II) like the other biometals, such as nickel(II), manganese(II), cobalt(II), and zinc(II), can be regarded as a trace element necessary for life. Since it is a bio-relevant element, copper forms a crucial part of many metalloproteins and metalloenzymes. Its presence in the active sites of many enzymes further emphasizes its role in biological systems. Copper is a part of Cu–Zn SOD which is a superoxide dismutase that reduces the effects of reactive oxygen species (Batool *et al.*, 2019).

Copper alloys are formulated with important metals such as zinc, brass, and bronze used in carat gold, carat solder and hardening and softening the colors (Jastrząb *et al.*, 2016). Cu-65 and Cu-63 are used for metabolism and gastrointestinal disease study. For the production of medical radioisotopes, Cu-63 used while Cu-64 and Zn-62 used for the diagnosis and treatment of cancer (O'Connor *et al.*, 2012). Cu-65 is used for the production of Cu-64 (Kaur *et al.*, 2017).

Naproxen which is an NSAID (non-steroidal anti-inflammatory drug), used for the treatment of pain, inflammation, fever, and stiffness caused by osteoarthritis conditions, psoriatic arthritis, rheumatoid arthritis, gout, injury (fractures), ankylosing spondylitis, tendonitis, menstrual spondylitis, bursitis and for the treatment of dysmenorrhea (Sharma *et al.*, 2016).

Nimesulide is also an NSAID (non-steroidal anti-inflammatory drug) that used for the treatment of acute pain in other countries. Nimesulide also linked with transient serum low rate elevations enzyme in therapy. Nimesulide also linked with many clinically apparent instances of acute liver disease/injury that may result in liver failure, transplantation, and death (Sharma and Kumar, 2018).

Copper-based NSAIDs are reported to manifest not only an improved anti-inflammatory activity but also a condensed gastrointestinal (GI) toxicity when likened with parent NSAID. Copper(II)–NSAID complexes have also been reported for their good affinity for DNA and catechol oxidase mimetic activity, albumin serum binding, SOD mimetic activities, inhibition of

polymorphonuclear leukocyte oxidative metabolism (Kovala-Demertzi *et al.*, 2009).

The design and synthesis of metal-organic frameworks depend on many factors which include physical and chemical properties of both metal and ligands to be attached. Factors such as temperature, pH, nature of solvents, etc. also play an important role (Batool *et al.*, 2016).

Naproxen and Nimesulide are capable of coordinating with metal ions in the variability of coordination modes (monodentate, bidentate, and chelating bridging). The main objective of our study was to synthesis, structural characterization, and antibacterial studies of the ternary mononuclear CU(II) complex of Naproxen and TMEDA and Cu(II) complexes with Nimesulide and TMEDA.

MATERIALS AND METHODS

All chemicals & reagents, glassware, and machinery equipment used good quality manufacturing. Copper Chloride dihydrate $CuCl_2.2H_2O$ (Merck 99%), NaOH (0.1 Molar solution), Methanol (Fisher 99.8%), N, N, N′, N′-Tetramethylethylenediamine (Merck 99.5%), NSAIDs (Nimesulide, Naproxen, Merck 98%) and Distilled water. 100 ml beaker, magnetic hot plate, digital weighing balance, 10 ml graduated pipettes, spatula, filter Paper, Oven, digital freezing point, Thermo Nicolet FT/IR-200, and DB-20 UV-VIS spectrophotometer.

A solution of $CuCl_2.2H_2O$ (1 mmol= 0.17g) in 5 $cm^3$of methanol was taken in a 100 cm^3 beaker. In another beaker 0.46 g (2 mmol) of (+) -(S)-2-(6-Methoxynaphthalen-2-yl)propanoic acid (Naproxen) was dissolved in 15cm^3 of methanol, while stirring, then added 5 drops of 0.1 M NaOH in a dropwise manner. The green solution was then refluxed, with stirring at 50-60 °C for one hour.

The resulting green solution was cooled to nearly 5-10 °C and then added 4 mmol of TMEDA in a dropwise way while stirring in the cold state. A clear dark blue solution was obtained. The resulting blue solution was kept undisturbed for one week in the open air. A blue crystalline product which was air-stable separated out after partial concentration of the solution. The product was washed with cold methanol and was kept for analysis.

A solution of $CuCl_2.2H_2O$ (1mmol= 0.170) in 5cm^3 of methanol was taken in a 100 cm^3 beaker. In another beaker 0.64 g (2 mmol) of nimesulide dissolved in 15cm^3 of methanol and 15cm^3 of distilled water in copper chloride while stirring; then added 5 drops of 0.1 M NaOH in a dropwise manner at then reflux the solution with stirring at 50-60 °C for one hour. A light green solution was obtained.

The resulting solution was cool to nearly 5-10 °C and then added 4 mmol of TMEDA in a dropwise manner while stirring in the cold state. A clear blue solution was gained. The resulting blue solution was kept undisturbed for one week in the open air. A blue crystalline product which was air-stable separated out after partial concentration of the solution. The product was washed with cold methanol and was kept for analysis.

The antimicrobial activity of prepared complexes was checked by the method of agar well diffusion. Different strains were used as ATCC No: 25923 for *S. aureus*, ATCC No: 6633 for *B. spizizenii*, ATCC No: 8739 for *E. coli* and ATCC No: 13882 for *K. pneumonia*.

The procedure adopted was similar to the one previously reported (Batool *et al.*, 2019). One cm^3 of the respective broth cultures, each containing 10^6 CFU per cm^3 was poured into their respective sterile Petri dishes. Then, 20 cm^3 of nutrient agar was poured into each sterile Petri dish at 45 °C. The Petri dishes were kept at 5 °C and cooled for 1 h, to let them solidify completely. Afterward, the wells of 8 mm were dug in these media. 90 µl of solutions of three different concentrations (1000 µg/ml, 500 µg/ml,

and 250 µg/ml) of complex 1 in DMSO were placed into these wells separately.

The results were compared with cefixime and DMSO, which were applied as positive and negative standards, respectively. DMSO was used as a negative control and showed no activity. All concentrations were applied in sets of triplicates. Petri dishes containing bacterial cultures were incubated aerobically at 37 °C for 24 h. The activity of complexes as an antibacterial agent was measured (mm) based on the sizes of microbial growth inhibition zones in mm.

RESULTS AND DISCUSSION

Complexes are colored owing to d-d transition of transition metals which are given in table 1.

Melting points of complexes are given in table 2.

The results of solubility are shown in table 3. It depends upon the nature of the complex.

Table 1. Colors of ligands & complexes

Color of $CuCl_2.H_2O$	**Color of Naproxen**	**Color of TMEDA**	**Color of Complex(1)**	**Color of Nimesulide**	**Color of complex(II)**
Light bluish green	White	Colorless	Dark Blue crystal	Pale yellow	Bluish-green

Table 2. Melting Points of ligands & complexes

Compounds	**Melting Point**
Naproxen	153 °C
TMEDA	-55.1°C
$[Cu(Naproxen)_2(TMEDA)_2]$	196 °C
Nimesulide	143 °C
$[Cu(Nimesulide)_2(TMEDA)_2]$	220 °C

Table 3. The solubility of ligands & complexes

Complexes	**Solvent Used**			
	Water(H_2O)	**Methanol**	**Ethanol**	**DMSO**
NSAIDs (Naproxen, Nimesulide)	Partially Soluble	Partially soluble	Partially soluble	Partially soluble
TMEDA	Soluble	Soluble	Soluble	soluble
Cu(II)complex with Naproxen and Nimesulide with TMEDA	Soluble	soluble	Partially soluble	Soluble

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Complexes were characterized by a DB-VIS spectrophotometer. The electronic spectrum of Cu (II) complex of Naproxen and TMEDA was measured in the DMSO solution in the 200–1000 nm range as shown in figure 1. The complexes 1-2 exhibited three absorptions. The intense absorption band at higher energy is 250 nm and 300nm for the complex. A broad absorption band at 655 nm for the complex is due to the d-d transitions in square planar pyramidal complexes.

The electronic spectrum of Cu(II) complex N-(4-Nitro-2-henoxyphenyl)methanesulfonamide (Nimesulide) and TMEDA was measured in the DMSO solution in the 200–1000 nm range as showed in Figure 2. The intense absorption bands at higher energy, 244 nm, and 304 nm are assigned to the intra-ligand π→π* and n→π* transitions. A broad absorption band at 633 nm for complex (Roscales and Plumet, 2018) is due to the d-d transitions in square planar complexes. The visible absorption spectra also contain bands at 635 nm for, which are due to the copper(II) dxz;dyz→ dx_2-y_2 transitions in a square planar ligand field (Sharma, 2017).

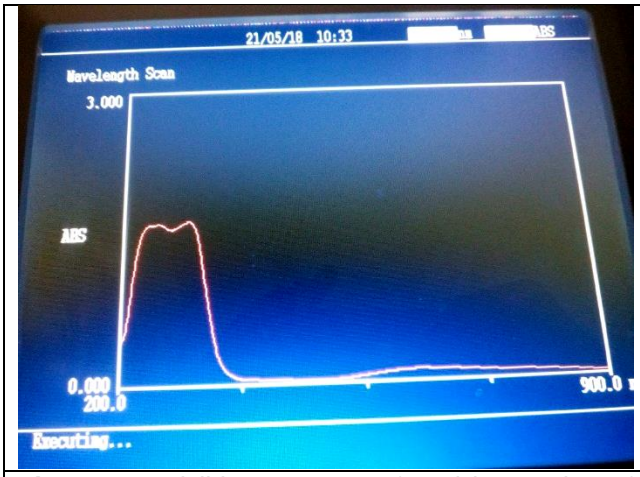

Fig. 1. UV-Visible spectrum of Cu(II) complex of Naproxen and TMEDA

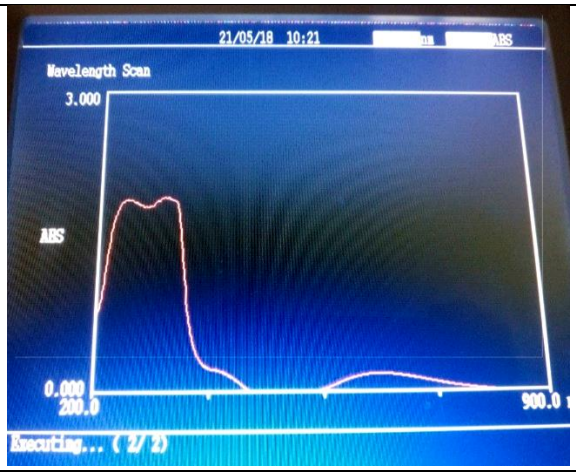

Fig. 2. UV-Visible spectrum of Cu(II) complex of Nimesulide and TMEDA

The peak exhibited as a sharp peak at 3031 cm^{-1}may be assigned to the $v(=C–H)_{Ar}$ stretch of the coordinated water molecule. The peaks at 2912 cm^{-1} and 2839 cm^{-1} are due to asymmetric and symmetric stretch of (CH_2) were obtained. The peaks at 1628 cm^{-1} and 1395 cm^{-1} are due to symmetric v_{as}(OCO) and asymmetric vs(OCO) respectively are stretches of carboxylate group of naproxen and the difference in v_{as}(OCO) and v_s(OCO) frequencies Δv is 233 cm^{-1}. The band around is due to the group of naproxen. The presence of v(C=N) of naproxen around 1125 cm-^{1}, may also indicate its coordination to the metal complexes. This clearly indicates that the coordination of both the ligands to the metal has been accomplished. The proposed structure of [Cu(TMEDA)$(Nap)_2(H_2O)$] is shown in figure 3.

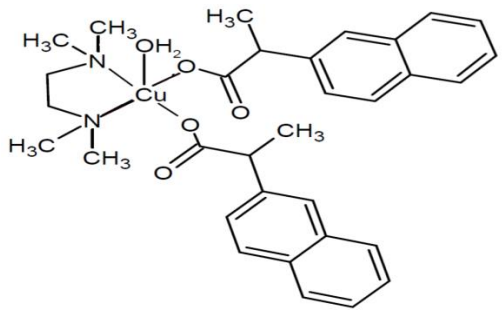

Fig. 3. Structure of [Cu$(nap)_2$(TMEDA)(H_2O)]

Table 4. Selected FT-IR frequencies of complexes, [Cu(nap)2tmeda]

FT-IR Assignments	TMEDA	Naproxen	Cu $(tmeda)_2(nap)_2$
v(=C–H) $_{Ar}$		3031	3031
v_{as}(C–H), CH_3	2970	2939	2987
v_{as}(C–H), CH_2	2943	2934	2912
v_s(C–H), CH_2	2860	2881	2839
v_{asym}(OC=O)		1623	1628
v_{sym}(OC=O)		1385	1395
v(C=C)		1564	1520
v(C–H)bent, CH_2	1467	1454	1468
v(=C-O)		1295	1294
v(C-O)		1226	1207
v(C-N)	1138		1125
v(Cu-O)			517
v(Cu-N)			446

The complex was prepared and its FT-IR spectrum shows different characteristics of peaks confirm the formation of complex II. FT-IR and its related peaks have been shown in table 4 & 5. Asymmetric and symmetric Stretches of the amino groups are 3383cm^{-1} and 3235$cm^{-1.}$ 3157 cm^{-1} are due to asymmetric aromatic stretch. The peaks at 1500 cm^{-1} and 1479 cm^{-1} are due to asymmetric and symmetric stretch of NO was obtained. The presence of v(C=N) of naproxen around 1385 cm $^{-1}$ and its asymmetric and symmetric stretch of SO_2 are 1216cm^{-1} and1185cm^{-1}. The Cu-N frequency at 445cm^{-1} may also indicate its coordination to the metal complex. This clearly indicates that the coordination of both the ligands to the metal has been accomplished.

Table 5. Selected FT-IR frequencies of complexes, [Cu(nimesulide)2(tmeda)2]

FTIR Assignments	TMEDA	Nimesulide	Cu tmeda(Nimesulide)
v_{as}(N–H)		3383	3450
v_s(N–H)		3235	3340
v_{as}(=C-H)Ar		3157	3088
v_{as}(C–H), CH_3	2970	2950	2943
v_{as}(C–H), CH_2	2943		2929
v_s(C–H), CH_2	2860		2865
v(C=C)		1650	1638
vas(NO)		1536	1500
v(NO)		1332	1479
v(C–H)bent, CH_2	1467	1446	1477
v(=C-N)	1138	1346	1385
v(=C-O)		1261	1250
v_{as} (SO_2)		1185	1207
v_s(SO_2)		1216	1115
v(Cu-N)			445

The complexes of copper(II) and TMEDA with Naproxen and Nimesulide were in the ratio 1:2:1. The Complexes are blue in colors and their melting points are recorded as 196^{0}C and 220 ^{0}C respectively. UV- Visible spectra of complexes 1-2 exhibited three absorptions. The intense absorption band at higher energy is 250 nm and 300nm for the complex. A broad absorption band at 655 nm for the complex is due to the d-d transitions in square planar complexes. The intense absorption bands at higher energy, 244 nm, and 304 nm are assigned to the intraligand π→π* and n→π* transitions. A broad absorption band at 633 nm for the complex is due to the d-d transitions in square planar pyramidal complexes. The visible absorption spectra also contain bands at 635 nm for, which are due to the copper(II) dxz;dyz→ dx-y2 transitions in the square planar field.

In complex (1-2), the peak exhibited as a sharp peak at 3031cm^{-1}and 3350cm^{-1}may be assigned to the $\nu(=C–H)_{Ar}$ stretch of a coordinated water molecule. The peaks at 2912 cm^{-1} and 2839 cm^{-1} are due to asymmetric and symmetric stretch of (CH_2) were obtained. The peaks at 1628 cm^{-1} and 1395 cm-^{1} are due to symmetric ν_{as}(OCO) and asymmetric vs(OCO) respectively are stretches of carboxylate group of naproxen and the difference in ν_{as}(OCO) and ν_s(OCO) frequencies Δv is 233 cm-1. The peak exhibited as a sharp peak at 3383 cm-^{1} may be assigned to the $\nu(=C–H)_{Ar}$ stretch of coordinated water molecule. The peaks at 1500 cm^{-1} and 1479 cm^{-1} are due to asymmetric and symmetric stretch of NO was obtained. This clearly indicates that the coordination of both types of ligands to the metal has been accomplished.

CONCLUSION

In summary, the synthesis of mononuclear complexes was carried out by the reaction of $CuCl_2{\cdot}2H_2O$ with a non-steroidal anti-inflammatory naproxen and nimesulide drug in the presence of sodium hydroxide, followed by the addition of tmen.

The structural characterization of complexes showed that both tmen and naproxen and nimesulide coordinate with copper(II) in a bidentate mode and complexes is six-coordinate, similar to the other reported copper naproxen and nimesulide complexes with N donors. Other physicochemical tests such as the elemental and thermal analyses and spectroscopic data (UV-visible, FT–IR) also supported the structure. Naproxen and nimesulide are coordinated to copper(II) ions in the bidentate mode via carboxylate oxygen atoms.

The six-coordinate environment was suggested by its UV-visible spectrum. However, the confirmation of the actual structure came from single-crystal X-ray diffraction studies. Furthermore, it is also interesting that the structure of complexes is not only similar to the predicted copper(II)-tmen- naproxen and nimesulide structure, but also shows certain properties of the said structure (Batool *et al.*, 2019).

The antimicrobial assay showed that the complexes are active against *S. aureus* and *B. spizizenii*, *E. coli* and *K. pneumonia*. Hence, complexes can be expected to possess similar biological activities as those of the mentioned copper(II)-tmen adduct with mef (Batool *et al.*, 2019).

CONFLICT OF INTEREST

All the authors have declared that no conflict of interest exists.

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