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Synthesis and antibacterial activity of Cu (II) complex of some novel 5-nitroimidazole derivatives

D. G. Desai[1*], B. R. Prajapati[2], A. K. Seth[1] and D. K. Sureja[1]

[1]Department of Pharmacy, Sumandeep Vidyapeeth, Po - Piparia, Ta - Waghodia, Vadodara - 391760, Gujarat, India
[2]Department of Pharmaceutical Chemistry, L. M. College of Pharmacy, Navrangpura, Ahmedabad-380009, Gujarat, India

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ABSTRACT

The Cu (II) complex of novel 2-(1-substituted-5-nitro-1H-imidazol-2-yl)-1-substitutedethanone derivatives have been designed, synthesized and characterized by UV, IR, ^{1}HNMR, Mass and conductivity measurements. 2-substituted 5-nitroimidazole acts as a bidentate ligand through the N-3 of imidazole ring and carbonyl group, which coordinate the copper ion to form 4-coordinate tetrahedral Cu (II) complex. Synthesized compounds then evaluated in-vitro for their antibacterial activity using cup plate method. Some of the metal complexes were found to be moderately active against Gram-positive bacteria, B. pumilus ATCC 14884 and S. aureus ATCC 29737.

Keywords: Copper (II) complex;5-nitroimidazole; Antibacterial activity.

INTRODUCTION

5-nitroimidazoles, especially tinidazole is a therapeutic agent of choice for treatment of amoebiasis and also used in combination with other antimicrobial drugs e.g., as part of combination therapy for *Helicobacter pylori* eradication protocols[1]. Under anaerobic conditions inside the cell, it reduces to cytotoxic free nitro radical and binds nonspecifically to DNA, causing DNA damage and leading to cell death.

Metal complexes of various drugs have played an important role in the development of coordination chemistry. It is well-known that coordination of metal ion has a positive effect on drug efficacy due to their ability to enhance cellular radiation damage both *in-vitro* and *in-vivo*[2].Many metal complexes have powerful antifungal activities and are already in common day to day use such silver and zinc complex of sulfadiazine[3].

Cu (II) ion is well known to modify the radiation response in both mammalian and bacterial cells[4,5]. The radio sensitizing mechanism in mammalian cells may involve reduction of Cu (II) to Cu (I)[4].More recently, it has been found thatcopper complexes can bind with double-helical DNA and promote DNA damage[6,7].

Cu(II) complex of many drugs shows potential antibacterial, antitumor, antioxidant and antifungal activity[8,9]. Literature survey shows that Cu(II) complex of azole drugs are more active antifungal agents than the metal-free azole drugs[10,11]. The enhancing effect of metals, particularly Cu(II), on the antibacterial and antifungal activity has also been found in studies on a number of other drugs[12-14]. Hence, investigation of Cu (II) complexes of2-substituted 5-nitroimidazole derivatives is of importance in the search for more effective drugs. The aim of the present work was to design and synthesize novel 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone ligands, complex the ligands to Cu (II) and then screen the metal complexes *in vitro* for their antibacterial activity. Herewith, we are reporting the synthesis and antibacterial activity of Cu (II) complex of some novel 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone derivatives.

EXPERIMENTAL SECTION

Chemicals and reagents

All the chemicals and solvents used for the syntheses, obtained commercially from Loba company, were of reagent grade and used without further purification.

Physical measurements

All the melting points were determined in open capillaries and are uncorrected. The UV spectra of the synthesized compounds were recorded using Shimandzu 1800 UV-Vis spectrophotometer. IR spectra were recorded in KBr on Shimandzu Fourier Transform Infrared 8400S spectrophotometer. Nuclear Magnetic Resonance spectra (^{1}H NMR) were recorded in DMSO-d_6 on Bruker advance II at 400 MHz and the chemical shift are given in parts per million, downfield from Tetramethylsilane (TMS). Mass spectra were recorded on Micromass Q-T, TOF MS ES+4.73e^3. Molar conductivity was measured on Conductivity Bridge, Systronics.

General procedure for the synthesis of ligand:

To a mixture of 1-substituted-2-methyl-5-nitro-1*H*-imidazole (20 mM) and triethylamine (80 mM) in toluene (17.5 mL), various substituted benzoyl chloride (0.55 M) was added drop wise with occasional cooling. The mixture then stirred at room temperature for 22 h, diluted with 10 mL ether and chilled at 0°C. The precipitates thus formed was filtered and washed with 3*10 mL ether and then with 4*10 mL water. The whole crude product then dissolved in a mixture of water (10 mL), ethanol (15 mL) and conc. hydrochloric acid (10 mL) and refluxed for 2-4 h. After the completion of reaction, mixture was chilled and poured on to crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from ethanol to give desired ligand.

2-(1-(2-(ethylsulfonyl)ethyl)-5-nitro-1*H*-imidazol-2-yl)-1-phenylethanone(NIMP):
Yellow crystals; Yield: 80%; m.p.146-148 °C;R_f: 0.67 (Toluene: acetonitrile (4:1)); IR (KBr, cm^{-1}): 2977, 2800, 1720, 1560, 1365; ^{1}H NMR (DMSO-d_6, δ): 1.28 (t, 3H, -$SO_2CH_2\underline{CH_3}$), 3.15 (q, 2H, -$SO_2\underline{CH_2}CH_3$), 3.89 (t, 2H, -$CH_2\underline{CH_2}SO_2C_2H_5$), 4.26 (s, 2H, N=C-$\underline{CH_2}$-COAr), 4.96 (t, 2H, N-$\underline{CH_2}CH_2SO_2C_2H_5$), 7.56-7.94 (m, 5H, Ar-$\underline{H}$), 7.81 (s, 1H, C-4 of imidazole); MF: $C_{15}H_{17}N_3O_5S$ (351.38);MS: *m/z*351 (M^+).

1-(4-chlorophenyl)-2-(1-(2-(ethylsulfonyl)ethyl)-5-nitro-1*H*-imidazol-2-yl)ethanone(NIMPCl):
Light yellow crystals; Yield: 72%; m.p.152-154 °C;R_f: 0.69 (Toluene: acetonitrile (4:1)); IR (KBr, cm^{-1}): 2977, 2800, 1720, 1560, 1365; ^{1}H NMR (DMSO-d_6, δ): 1.28 (t, 3H, -$SO_2CH_2\underline{CH_3}$), 3.15 (q, 2H, -$SO_2\underline{CH_2}CH_3$), 3.66 (t, 2H, -$CH_2\underline{CH_2}SO_2C_2H_5$), 4.26 (s, 2H, N=C-$\underline{CH_2}$-COAr), 4.96 (t, 2H, N-$\underline{CH_2}CH_2SO_2C_2H_5$), 7.60-7.84 (m, 4H, Ar-$\underline{H}$), 7.87 (s,1H, C-4 of imidazole); MF: $C_{15}H_{16}ClN_3O_5S$ (385.82); MS: *m/z*385 (M^+), 387 (M^{+2}).

1-(3-chlorophenyl)-2-(1-(2-(ethylsulfonyl)ethyl)-5-nitro-1*H*-imidazol-2-yl)ethanone (NIMMCl):
Yellow crystals; Yield: 65%; m.p. 156-158°C;R_f: 0.62 (Toluene: acetonitrile (4:1)); IR (KBr, cm^{-1}): 2977, 2800, 1720, 1560, 1365; ^{1}H NMR (DMSO-d_6, δ): 1.28 (t, 3H, -$SO_2CH_2\underline{CH_3}$), 3.15 (q, 2H, -$SO_2\underline{CH_2}CH_3$), 3.66 (t, 2H, -$CH_2\underline{CH_2}SO_2C_2H_5$), 4.26 (s, 2H, N=C-$\underline{CH_2}$-COAr), 4.96 (t, 2H, N-$\underline{CH_2}CH_2SO_2C_2H_5$), 7.50-7.86 (m, 4H, Ar-$\underline{H}$), 7.87 (s,1H, C-4 of imidazole); MF: $C_{15}H_{16}ClN_3O_5S$ (385.82); MS: *m/z*385 (M^+), 387 (M^{+2}).

1-(2-chlorophenyl)-2-(1-(2-(ethylsulfonyl)ethyl)-5-nitro-1*H*-imidazol-2-yl)ethanone(NIMOCl):
Yellow crystals; Yield: 45%; m.p.180-182°C;R_f: 0.60 (Toluene: acetonitrile (4:1)); IR (KBr, cm^{-1}): 2977, 2800, 1720, 1560, 1365; ^{1}H NMR (DMSO-d_6, δ): 1.28 (t, 3H, -$SO_2CH_2\underline{CH_3}$), 3.15 (q, 2H, -$SO_2\underline{CH_2}CH_3$), 3.66 (t, 2H, -$CH_2\underline{CH_2}SO_2C_2H_5$), 4.26 (s, 2H, N=C-$\underline{CH_2}$-COAr), 4.96 (t, 2H, N-$\underline{CH_2}CH_2SO_2C_2H_5$), 7.44-7.88 (m, 4H, Ar-$\underline{H}$), 7.87 (s,1H, C-4 of imidazole); MF: $C_{15}H_{16}ClN_3O_5S$ (385.82); MS: *m/z*385 (M^+), 387 (M^{+2}).

2-(1-(2-(ethylsulfonyl)ethyl)-5-nitro-1*H*-imidazol-2-yl)-1-(furan-2-yl)ethanone(NIMF):
Yellow crystals; Yield: 75%; m.p. 165-166 °C;R_f: 0.56 (Toluene: acetonitrile (4:1)); IR (KBr, cm^{-1}): 2977, 2800, 1720, 1560, 1365; ^{1}H NMR (DMSO-d_6, δ): 1.30 (t, 3H, -$SO_2CH_2\underline{CH_3}$), 3.15 (q, 2H, -$SO_2\underline{CH_2}CH_3$), 3.66 (t, 2H, -$CH_2\underline{CH_2}SO_2C_2H_5$), 4.26 (s, 2H, N=C-$\underline{CH_2}$-COAr), 4.96 (t, 2H, N-$\underline{CH_2}CH_2SO_2C_2H_5$), 6.54 (d, 1H, C-4 of furan), 6.76 (d, 1H, C-3 of furan), 7.59(s, 1H, C-5 of furan), 7.87 (s,1H, C-4 of imidazole); MF: $C_{13}H_{15}N_3O_6S$ (341.34); MS: *m/z*341 (M^+).

1-(furan-2-yl)-2-(1-methyl-5-nitro-1*H*-imidazol-2-yl)ethanone(NIMDF):
Yellow crystals; Yield: 78%; m.p. 130-132°C;R_f: 0.50 (Toluene: acetonitrile (4:1)); IR (KBr, cm^{-1}): 2977, 2800, 1720, 1560, 1365; ^{1}H NMR (DMSO-d_6, δ): 3.79 (s, 3H, N-$\underline{CH_3}$), 4.26 (s, 2H, N=C-$\underline{CH_2}$-COAr), 6.54 (d, 1H, C-4 of furan), 6.76 (d, 1H, C-3 of furan), 7.59 (s, 1H, C-5 of furan), 7.87 (s,1H, C-4 of imidazole); MF: $C_{10}H_9N_3O_4$ (235.20); MS: *m/z*235 (M^+).

2-(1-methyl-5-nitro-1H-imidazol-2-yl)-1-phenylethanone (NIMDP):
Yellow crystals; Yield: 80%; m.p.136-138°C;R_f: 0.60(Toluene: acetonitrile (4:1)); IR (KBr, cm^{-1}): 2977, 2800, 1720, 1560, 1365; ^{1}H NMR (DMSO-d_6, δ): 3.79 (s, 3H, N-$\underline{CH_3}$), 4.26 (s, 2H, N=C-$\underline{CH_2}$-COAr), 7.50-7.86 (m, 5H, Ar-$\underline{H}$), 7.87 (s,1H, C-4 of imidazole); MF: $C_{12}H_{11}N_3O_3$ (245.23); MS: *m/z*245 (M^+).

General procedure for the synthesis of metal complexes:
A solution of $CuCl_2.2H_2O$ (5 mM) in hot methanol (50 mL) was added to solution of appropriate ligand(10 mM) in 50 mL methanol. The pH of the mixture was adjusted to 8-10 using conc. ammonia. The greenish yellow colored solution thus formed, refluxed for 4-5 hand then kept at room temperature to get crystalline compounds. The product then filtered, washed with cooled absolute ethanol, recrystallized from acetonitrile or methanol and dried under vacuum.

$Cu(NIMP)_2$:
Yellow crystals; Yield: 78%; m.p.242-244 °C;UV (λmax, nm): 240,330, 444;IR (KBr, cm^{-1}): 3747, 3600, 2977, 2800, 2110, 1546,1338, 472; MF: $C_{30}H_{34}CuN_6O_{10}S_2$(766.30); MS: *m/z*766($M^+$); Λm ($\Omega^{-1}cm^2mol^{-1}$): 0.50.

$Cu(NIMPCl)_2$:
Yellow crystals; Yield: 76%; m.p.213-215 °C;UV (λmax, nm): 240,280,454;IR (KBr, cm^{-1}): 3750, 3660, 2980, 2850, 1990, 1542,1365, 550; MF: $C_{30}H_{32}Cl_2CuN_6O_{10}S_2$(835.19);Λm ($\Omega^{-1}cm^2mol^{-1}$): 0.60.

$Cu(NIMMCl)_2$:
Greenish yellow crystals; Yield: 76%; m.p.224-226 °C;UV (λmax, nm): 240,310,460;IR (KBr, cm^{-1}): 3650, 3450, 2900, 2850, 1950, 1550,1345, 520; MF: $C_{30}H_{32}Cl_2CuN_6O_{10}S_2$ (835.19); MS: *m/z*835 (M^+), 837 (M^{+2}), 839(M^{+4}); Λm ($\Omega^{-1}cm^2mol^{-1}$): 1.25.

$Cu(NIMOCl)_2$:
Red crystals; Yield: 68%; m.p.237-240 °C;UV (λmax, nm): 240,340,445;IR (KBr, cm^{-1}): 3610, 3500, 2900, 2850, 2000, 1556,1345, 516; ^{1}H NMR (DMSO-d_6, δ): 1.28 (t, 6H, -$SO_2CH_2\underline{CH_3}$), 3.20 (q, 4H, -$SO_2\underline{CH_2}CH_3$), 3.72 (t, 4H, -$CH_2\underline{CH_2}SO_2C_2H_5$), 4.30 (s, 4H, N=C-$\underline{CH_2}$-COAr), 4.90 (t, 4H, N-$\underline{CH_2}CH_2SO_2C_2H_5$), 7.60-7.84 (m, 8H, Ar-$\underline{H}$), 7.87 (s, 2H, C-4 of imidazole); MF: $C_{30}H_{32}Cl_2CuN_6O_{10}S_2$ (835.19);Λm ($\Omega^{-1}cm^2mol^{-1}$): 1.10.

$Cu(NIMF)_2$:
Greenish yellow crystals; Yield: 75%; m.p.232-235 °C;UV (λmax, nm): 240,335,455;IR (KBr, cm^{-1}): 3630, 3430, 2980, 2900, 1970, 1545,1360, 510; ^{1}H NMR (DMSO-d_6, δ): 1.40 (t, 6H, -$SO_2CH_2\underline{CH_3}$), 3.15 (q, 4H, -$SO_2\underline{CH_2}CH_3$), 3.66 (t, 4H, -$CH_2\underline{CH_2}SO_2C_2H_5$), 4.26 (s, 4H, N=C-$\underline{CH_2}$-COAr), 4.96 (t, 4H, N-$\underline{CH_2}CH_2SO_2C_2H_5$), 6.54 (d, 2H, C-4 of furan), 6.75 (d, 2H, C-3 of furan), 7.59 (s, 2H, C-5 of furan), 8.10 (s, 2H, C-4 of imidazole); MF: $C_{26}H_{30}CuN_6O_{12}S_2$ (746.23); Λm ($\Omega^{-1}cm^2mol^{-1}$): 2.00.

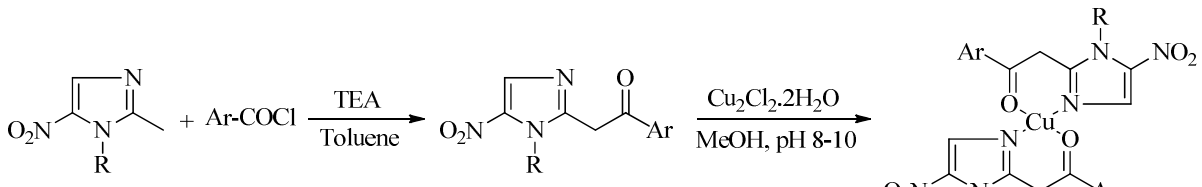
$Cu(NIMDF)_2$:
Greenish yellow crystals; Yield: 55%; m.p.210-212 °C;UV (λmax, nm): 240,332,440;IR (KBr, cm^{-1}): 3500, 3300, 2980, 2900, 2100, 1545,1360, 525; ^{1}H NMR (DMSO-d_6, δ): 3.82 (s, 6H, N-$\underline{CH_3}$), 4.30 (s, 4H, N=C-$\underline{CH_2}$-COAr), 6.54 (d, 2H, C-4 of furan), 6.75 (d, 2H, C-3 of furan), 7.59 (s, 2H, C-5 of furan), 7.98 (s, 2H, C-4 of imidazole); MF: $C_{20}H_{18}CuN_6O_8$ (533.94);MS: *m/z* 533 (M^+); Λm ($\Omega^{-1}cm^2mol^{-1}$): 1.85.

$Cu(NIMDP)_2$:
Greenish yellow crystals; Yield: 78%; m.p.218-222°C;UV (λmax, nm): 240,304,457;IR (KBr, cm^{-1}): 3500, 3400, 2980, 2900, 2010, 1555,1340, 512;^{1}H NMR (DMSO-d_6, δ): 3.79 (s, 6H, N-$\underline{CH_3}$), 4.30 (s, 4H, N=C-$\underline{CH_2}$-COAr), 7.40-7.78 (m, 10H, Ar-$\underline{H}$), 7.98 (s, 2H, C-4 of imidazole);MF: $C_{24}H_{22}CuN_6O_6$(554.01); Λm ($\Omega^{-1}cm^2mol^{-1}$): 1.20.

RESULTS AND DISCUSSION

Synthetic approach
2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone were obtainedin reasonably moderate to good yieldbythe reaction of 1-substituted-2-methyl-5-nitro-1*H*-imidazole with various substituted benzoyl chlorides in presence of catalytic amounts of triethylamine and toluene as solvent [15].

The metal complexes were obtained in good yield by *in situ* reaction ofrespective2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone with copper chloride dihydrate under reflux condition in basic medium. A synthetic route is depicted in scheme 1. The complexes are air-stable, crystalline solids, soluble in commonorganic solvents and insoluble in water.



Scheme 1 Synthetic route of ligand and metal complex

Characterization:

Thecharacterization of ligand and complexeshave been achieved by satisfactory physical methods and spectral (UV, IR, ^{1}H NMR, mass and conductance) studies.The UV spectra reveal three absorbance maxima for the ligand-metal complexes at 240,330 and 457 nm.

The first one may be assigned to intra-ligand π- π* transition, which is nearly unchanged on complexation, whereas the second and third bands may be assigned to the n-π* and charge transfer transition of the carbonyl group and nitrogen atom of the imidazole ring.

IR spectral data supports the formation of metal complexes from respective ligands. IRspectra of all metal complexes shows -CH stretchingat 3096-2980, -C=O stretching at 2100-1900, -NO_2 stretching at 1570-1540 (asymmetric) and 1366-1358 (symmetric) and M-O stretching at 600-480 cm^{-1}respectively. In order to study the binding mode of ligand to metal in the complexes, IR spectrum of the free ligand was compared with the spectra of the metal complexes.The frequencies for -CH and -NO_2stretching was identical in both spectrum. The C=O stretching gives very strong sharp bands which can be easily separated from the bands of other groups that may be present. The wave number of carbonyl group in a complex changed drastically compared to ligand, which confirmsthe formation of metal complex. The electron-richness of the metaland bonding of *d* orbitals of the metal and π* anti-bonding orbital of C-O (known as *backbonding*), weakens the C-O bond and lowers the wave number from 1720 to 2100-1900cm^{-1}. The nature of metal-ligand bonding is also confirmed by the newly formed band at 600-480 cm^{-1} in the spectra of the complexes which is tentatively due to M-O vibration.

The ^{1}HNMR (DMSO-d_6) spectra of metal complex, displays the triplet of methyl group (-$SO_2CH_2\underline{CH_3}$) at δ 1.28-1.40 ppm, quartet of methylene group (-$SO_2\underline{CH_2}CH_3$) at δ 3.15 ppm, triplet of methylene group (-$CH_2\underline{CH_2}SO_2C_2H_5$) at δ 3.66-3.89 ppm, singlet of methylene group (-N=C-$\underline{CH_2}$-CO-Ar) at δ 4.26-4.30, triplet of methylene group (N-$\underline{CH_2}CH_2SO_2C_2H_5$)at δ 4.96 ppm, multiplet of aromatic protons between δ 6.54-7.94ppm and the singlet for proton atC-4 of imidazole ring between δ 7.87-8.1 ppm respectively.

In mass spectra of ligand and ligand metal complexes, molecular ions corresponds to molecular weight were observed. The fragmentation routes primarily involved losses of NO (M-30), NO_2 (M-46) and HNO_2 (M-47) from the molecular ion. The higher molecular weight of the compound shows that the metal to ligand ratio is 1:2.

The molar conductance values of the synthesized mixed ligand complexes with the mentioned metal ions were determined in 10^{-3} M DMF and were in the range of 0.50-2.0 $\Omega^{-1}cm^2mol^{-1}$. The low molar conductance values reveal non-electrolytic nature of the complexes[16].

Antibacterial activity:

The metal complexes were dissolved in minimumamount of dimethylformamideand diluted with water. Agar medium suitable for testing the sensitivity of clinicallyimportant pathogens towards antibiotics, and nutrient broth were prepared according to thestandard preparatory techniques. All the synthesized metal complexes of 2-substituted5-nitroimidazole were screened*in vitro* for antibacterial activity against gram positive (*B. pumilus* and *S. aureus*) and gram negative (*S. aboney*) bacteriausingcup plate method according to Clinical Laboratory Standards Institute (CLSI 2006b, formerly National Committee for Clinical Laboratory Standards NCCLS) guidelines. Ciprofloxacin and Tinidazole were used as reference standards.The results wereexpressed inthe terms of zone of inhibition(mm) at 100 µg/mL concentration and are presented in Table 1.

Table 1 Antibacterial activity of metal-ligand complexes

Metal-Ligand Complex	*Zone of inhibition (mm)		
	Gram positive		Gram negative
	*B. pumilus*ATCC 14884	*S. aureus*ATCC 29737	*S. aboney*NCTC 6017
$Cu(NIMP)_2$	ND[#]	ND	ND
$Cu(NIMPCl)_2$	ND	ND	ND
$Cu(NIMMCl)_2$	ND	ND	ND
$Cu(NIMOCl)_2$	ND	ND	ND
$Cu(NIMF)_2$	12	08	ND
$Cu(NIMDF)_2$	08	22	ND
$Cu(NIMDP)_2$	08	20	ND
Tinidazole	ND	ND	ND
Ciprofloxacin	32	26	31

**Average of triplicate reading (conc. 100 µg/mL)*
[#]ND -Zone of inhibition not detected

CONCLUSION

Cu (II)complexes of 2-(1-substituted-5-nitro-1*H*-imidazol-2-yl)-1-substitutedethanone have been designed, synthesized and characterized. The characterization techniques confirm that ligands are bidentately coordinated to the metal through the N-3 of imidazole ring and carbonyl group 2-substituted 5-nitroimidazole to form 4-coordinate tetrahedral Cu (II) complex. The antibacterial screening results indicate that some of the compounds exhibited antibacterial activity against gram positive bacteria only. It can be noted that none of the Cu (II) complex showed inhibitory effect against gram negative bacteria.

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