Med Chem Res
DOI 10.1007/s00044-014-0943-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Cu(II) and Ni(II) complexes of coumarin derivatives with fourth generation flouroquinolone: synthesis, characterization, microbicidal and antioxidant assay

Jiten Patel · Hitesh Dholariya · Ketan Patel · Jaimin Bhatt · Kanuprasad Patel

Received: 16 September 2013 / Accepted: 7 February 2014

Abstract New Cu(II) and Ni(II) complexes of acetyl coumarin derivatives with gatifloxacin were synthesized. Characterization of the complexes was carried out by elemental analysis, FT-IR, FAB-MS, electronic spectra and magnetic measurement along with thermo gravimetric studies. Thermal study reveals the absence of coordinated water molecule in case of Cu(II) complexes. All the Cu(II) complexes were found more potent antibacterial activity compared to Ni(II) complexes. The antituberculosis data have shown that copper conjugation may be advantageous in designing highly effective drugs for antitubercular therapy. These complexes were also found to be potent antioxidizing agents comprising radical scavenging capability and ferric reducing abilities.

Keywords Antibacterial · Antitubercular · Radical scavenging activity · FRAP assay · Gatifloxacin

Introduction

Metal ions play a vital role in many biologically applications (Sigel *et al.,* 2006). Transition metal complexes are associated with various biomolecules related to essential physiological activities in human organism. Our effort is focused on these metal-ion complexes because of they are promising antibacterial, antitubercular and antioxidant agents (Beraldo and Gambinob, 2004; Sandbhor *et al.,* 2002; De Souza and De Giovani, 2004). Coumarin containing compounds have found important uses as ligand for the synthesis of coordination compounds (Kapoor *et al.,* 2012; Creaven *et al.,* 2006). We were particularly attracted to the transition metal complexes of coumarin derivatives because such compounds have been reported to function as not only superior thermal stability and optical properties, but also they have the promising biological and medical applications including anti-inflammatory, antitubercular, chemotherapeutic, anticoagulant, antibacterial, cycotoxicity and antioxidant (Fylaktakidou *et al.,* 2004; Egan *et al.,* 1997; Finn *et al.,* 2002; Appendino *et al.,* 2004; Patonay *et al.,* 1984; Lin *et al.,* 2008; Koshy *et al.,* 2000; Kidane *et al.,* 2004). There has been a tremendous growth of drugs from flouroquinolone family, since the exponential growth of this family has produced thousands of analogues (Da Silva *et al.,* 2003; De Souza, 2005). The coordination compounds of these drugs with metal ions of biological and pharmaceutical importance are of considerable interest. There have been several reports about the synthesis, crystal structure and biological evaluation of metal complexes with flouroquinolones (Sadeek and El-Shwiniy, 2010; Turel *et al.,* 2003; Sousa *et al.,* 2012). Fluoroquinolones generally act as bidentate ligands binding to the metallic ion through the carboxylate and carbonyl oxygens. Usually, distorted octahedral geometry was preferred for most trantisition metal complexes (Chulvi *et al.,* 1991). Coordination of the fluoroquinolones with metal ions having geometry other then octahedral is much less common. Gatifloxacin (GTF) is a novel 6-fluoro- 8-methoxy quinolone with important structural modification which expands their spectrum of activity beyond its antibacterial organisms, and reduced adverse effects as compared with earlier fluoroquinolones (Blondeau *et al.,* 2000; Bauernfeind, 1997).

Electronic supplementary material The online version of this article (doi:10.1007/s00044-014-0943-y) contains supplementary material, which is available to authorized users.

J. Patel · H. Dholariya · K. Patel · J. Bhatt · K. Patel (✉)
V. P. & R. P. T. P. Science College, Sardar Patel University, Vallabh Vidyanagar 388 120, Gujarat, India
e-mail: drkdpatel64@yahoo.co.in

J. Patel
e-mail: jitenpatel87@gmail.com

Published online: 27 February 2014

Oxidation is highly imperative for many living organisms to produce their metabolic energy by using biological processes. Atherosclerosis, diabetes, cancer etc. may be related to oxidative damage, that are continuously produced in cell result death and tissue damage (Gomes *et al.,* 2001; Kang *et al.,* 2003; Babbs, 1990). The coumarins were found as potent ROS scavengers, and they were also effective inhibitors against XO's reduction (Kontogiorgis *et al.,* 2006; Lien *et al.,* 1999). As transition metal ions play a vital role in the initiation of free radical processes, metal chelating compounds of coumarins extensively considered as potent antioxidant agents. The interaction of coumarins with metal ions may increase the antioxidant properties and some other biological effects (Ji and Zhang, 2004; Datta *et al.,* 2011), besides this some marketed drugs also found beneficial as antitubercular and antioxidant agent (Vincenzi and Thomas, 1999; Ahirrao, 2008).

Our interest in the activity of transition metals complexes with combination of pharmacophores having two diverse biologically active compounds. On this backdrop, we synthesized series of transition metal complexes of GTF with acetyl coumarin derivatives. The characterization of complexes are carried out on the basis of FT-IR, ESI–MS, elemental, TG, electronic spectral analysis and magnetic measurement. Also the diverse biological applications including antibacterial, antifungal, antituberculosis and antioxidant are carried out.

Experimental

Material

All chemicals were purchased from the following commercial sources: Spectrochem Pvt. Ltd., Mumbai, E. Merck Pvt. Ltd., Mumbai, s.d. fine-chem Ltd., Mumbai. All chemicals were of reagent grade and solvents of analytical grade were distilled, purified and dried using appropriate methods. All reactions were monitored by thin-layer chromatography (TLC on alluminium plates coated with silica gel 60 F_{254}, 0.25 mm thickness, Merck) and detection of the components were done under UV light or explore in iodine chamber. The metal nitrates were used in hydrated form.

Physical measurement

Elemental analysis (C, H, N) was performed using the PerkinElmer, USA 2400-II CHN analyzer. The melting point of all metal complexes was measured using open capillary tube method. FT-IR spectra (4,000–400 cm^{-1}) were recorded with Spectrum GX-PerkinElmer spectrophotometer using KBr pellets. The FAB-Mass spectrum of the complexes was recorded at SAIF, CDRI, Lucknow with JEOL SX-102/DA-6000 mass spectrometer at room temperature using Argon/Xenon as the FAB gas. The electronic spectra (200–1,200 nm) were collected using LAMBDA 19 UV/Vis/NIR spectrophotometer. Thermal stability and decomposition of the complexes were determined using a model 5000/2960 SDT, TA instrument, U.S.A. The experiments were performed in N_2 atmosphere at a heating rate of 20 °C min^{-1} in the temperature range 20–800 °C. The magnetic susceptibility measurement were obtained by the Gouy's method using mercury tetrathiocyanato cobaltate(II) as a calibrant ($\chi = 16.44 \times 10^{-6}$ c.g.s. units at 20 °C). Diamagnetic corrections were made using Pascal's constant.

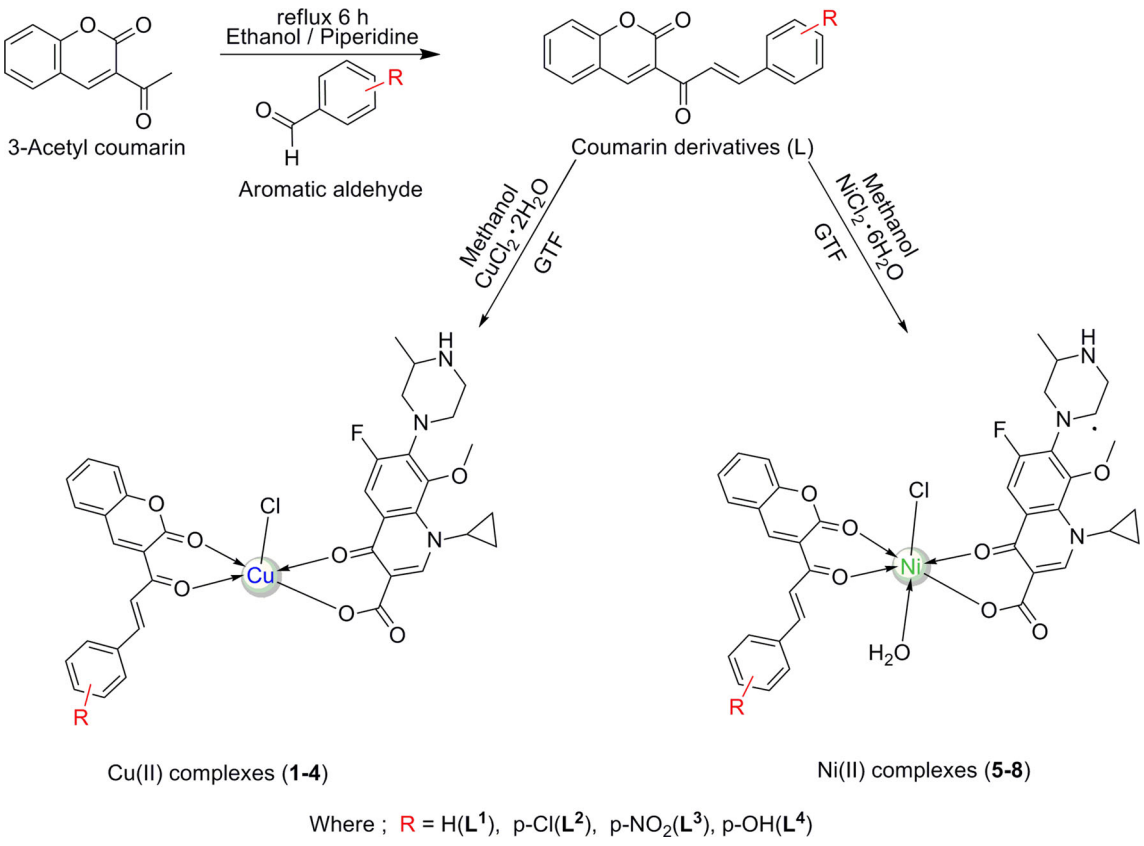
Preparation of ligands

All the neutral bidentate ligands were synthesized from reaction of 3-acetyl coumarin and various substituted aromatic aldehydes by Claisen-Schmidt condensation using reported method (Lin *et al.,* 2008). An ethanolic (50 mL) solution of 3-acetyl coumarin (0.01 M) and appropriate aromatic aldehyde (0.01 M) were taken in 3-neck round bottom flask, catalytic amount of piperidine (1.0 mL) was added in reaction mass and it was stirred for 10 min at room temperature. After a clear solution was obtained reaction mixture was refluxed in water bath for 6 h. The completion of reaction was monitored by TLC using mobile phase ethyl acetate:hexane (7:3). After the completion of reaction mixture was allowed to come at room temperature. A solid product separated out was filtered off, washed with cold ethanol and dried in air. It was recrystallized from ethanol.

General procedure for synthesis of ligands is shown in Scheme 1.

*3-(3-phenyl-acryloyl)-2H-chromen-2-one (**L**^{1})*

3-(3-phenyl-acryloyl)-2*H*-chromen-2-one was synthesized by reported method (Lin *et al.,* 2008) using 3-acetyl coumarin and benzaldehyde; $C_{18}H_{12}O_3$; Yield, 77 %; m.p. 142–146 °C; FTIR (KBr. cm^{-1}): 1610, *ν*(C=O, *α, β*-unsaturated ketone); 1740, *ν*(C=O, lactone carbonyl of coumarin); 1530, *ν*(C=C, aromatic stretching); 3028, *ν*(C–H, aromatic stretching); ^{1}H NMR (DMSO-d_6 400 MHz): δ 6.80 (1H, m, C_6-H), δ 7.11–7.63 (8H, m, aromatic protons), δ 7.77 (1H, *d*, $J = 7.6$, CH=CH– protons), δ 7.83 (1H, *d*, $J = 7.6$ CH=CH– protons), δ 8.49 (1H, *s*, C_4-H).; ^{13}C NMR (DMSO-d_6 100 MHz): δ 113.6 (C-4a), 117.1 (C-8), 118.9 (C-10, –CO–CH =), 124.7, 125.3, 126.0, 127.4, 128.8, 129.7, 133.6, 134.2 (8, Ar–C(C-3,C-5,C-6,C-7, C-12,C-13,17,C-14,16,C-15)), 146.9(C-11, –CH=CH–), 147.3(C-4), 152.2(C-8a), 159.3 (C=O, lactone carbonyl of



Scheme 1 General synthetic route of complexes (**1–8**)

coumarin(C-2)), 189.5 (C=O, *α, β*-unsaturated ketone(C-9)) ESI–MS (m/z): 276.7 [M] + . Found (%); C, 78.20, H, 4.32. calculated: C, 78.25, H, 4.38.

*3-(3-(3-hydroxyphenyl)acryloyl)-2H-chromen-2-one (**L²**)*

3-(3-(3-hydroxyphenyl)acryloyl)-2*H*-chromen-2-one was synthesized by same method as L^1 using 3-acetyl coumarin and 3- hydroxybenzaldehyde; $C_{18}H_{12}O_4$; Yield, 70 %; m.p. 201–205 °C; FTIR (KBr. cm^{-1}): 3479, *ν*(O–H, stretching); 1615, *ν*(C=O, *α, β*-unsaturated ketone); 1735, *ν*(C=O, lactone carbonyl of coumarin); 1555, *ν*(C=C, aromatic stretching); 3040, *ν*(C–H, aromatic stretching); ^{1}H NMR (DMSO-d_6 400 MHz): δ 6.87 (1H, m, C_6-H), δ 7.20–7.86 (7H, m, aromatic protons), δ 7.94 (1H, *d*, $J = 7.8$, CH=CH– protons), δ 8.04 (1H, *d*, $J = 8.0$ CH=CH– protons), δ 8.48 (1H, *s*, C_4-H). 9.48 (1H, s, –OH); ^{13}C NMR (DMSO-d_6 100 MHz): δ 114.8 (C-4a), 116.9 (C-8), 118.6 (C-10, –CO–CH =), 119.9, 120.0, 124.2, 124.8, 126.9, 127.6, 129.7, 130.0, 133.9 (9, Ar–C(C-3,C-5,C-6,C-7,C-12,C-13,C-15,C-16,C-17)), 146.6 (C-11, –CH=CH–), 147.2 (C-4), 152.8 (C-14, carbon attached to phenolic OH), 155.7 (C-8a), 159.6 (C=O, lactone carbonyl of coumarin(C-2)), 188.8 (C=O, *α, β*-unsaturated ketone(C-9)); ESI–MS (m/z): 292.4 [M] + . Found (%); C, 73.86, H, 4.05. calculated: C, 73.97, H, 4.14.

*3-(3-(4-hydroxyphenyl)acryloyl)-2H-chromen-2-one (**L³**)*

3-(3-(4-hydroxyphenyl)acryloyl)-2*H*-chromen-2-one was synthesized by same method as L^1 using 3-acetyl coumarin and 4- hydroxybenzaldehyde; $C_{18}H_{12}O_4$; Yield, 72 %; m.p. 210–212 °C; FTIR (KBr. cm^{-1}): 3484, *ν*(O–H, stretching); 1622, *ν*(C=O, *α, β*-unsaturated ketone); 1745, *ν*(C=O, lactone carbonyl of coumarin); 1484, *ν*(C=C, aromatic stretching); 3018, *ν*(C–H, aromatic stretching); ^{1}H NMR (DMSO-d_6 400 MHz): δ 6.86 (2H, d, $J = 7.8$, p-substituted phenyl ring), δ 6.88 (1H, d, $J = 16$, CH=CH– protons), δ 7.23 (1H, m, aromatic protons), δ 7.40 (2H, d, $J = 7.8$, p-substituted phenyl ring), δ 7.63–7.74 (3H, m, three aromatic protons), δ 7.90 (1H, d, $J = 16$, CH=CH– protons), δ 8.53 (1H, s, C_4-H), δ 9.58 (1H, s, –OH); ^{13}C NMR (DMSO-d_6 100 MHz): δ 114.4 (C-4a), 116.7 (C-8), 118.3 (C-10, –CO–CH =), 124.5, 125.0, 127.0, 127.5, 129.9, 130.2, 134.4 (7, Ar–C(C-3,C-5,C-6,C-7,C-12,C-13,17,C-14,16)), 147.1 (C-11, –CH=CH–), 147.5 (C-4), 151.7 (C-15, carbon attach to phenolic OH), 155.3 (C-8a), 159.2 (C=O, lactone carbonyl of coumarin(C-2)), 190.8

(C=O, α, β-unsaturated ketone(C-9)); ESI–MS (m/z); 292.7[M]+. Found (%): C, 73.90, H, 4.02. calculated: C, 73.97, H, 4.14.

*3-(3-(3-chlorophenyl)acryloyl)-2H-chromen-2-one (**L**^{4})*

3-(3-(3-chlorophenyl)acryloyl)-2*H*-chromen-2-one was synthesized by same method as L^1 using 3-acetyl coumarin and 3-cholorobenzaldehyde; $C_{18}H_{11}ClO_3$; Yield, 78 %; m.p. 215–217 °C; FTIR (KBr. cm^{-1}): 1615, *v*(C=O, α, β-unsaturated ketone); 1739, *v*(C=O, lactone carbonyl of coumarin); 1523, *v*(C=C, aromatic stretching); 3045, *v*(C–H, aromatic stretching); ^{1}H NMR (DMSO-d_6 400 MHz): δ 6.78 (1H, m, C_6-H), δ 7.18–7.65 (7H, m, aromatic protons), δ 7.72 (1H, *d*, *J* = 8.0, CH=CH– protons), δ 7.89 (1H, *d*, *J*=7.6 CH=CH– protons), δ 8.37 (1H, *s*, C_4-H); ^{13}C NMR (DMSO-d_6 100 MHz): δ 114.2 (C-4a), 116.5 (C-8), 118.2 (C-10, –CO–CH =), 124.7, 125.2, 126.9, 127.6, 128.4, 129.8, 130.4, 133.5, 134.0, 136.1 (10, Ar–C(C-3,C-5,C-6,C-7,C-12,C-13,C-14,C-15,C-16,C-17)), 146.8 (C-11, –CH=CH–), 147.7 (C-4), 155.7 (C-8a), 158.2 (C=O, lactone carbonyl of coumarin(C-2)), 187.6 (C=O, α, β-unsaturated ketone(C-9)); ESI–MS (m/z): 310.5, 312.7 [M]+; Found (%): C, 69.46, H, 3.57. calculated: C, 69.58, H, 3.49.

*3-(3-(4-chlorophenyl)acryloyl)-2H-chromen-2-one (**L**^{5})*

3-(3-(4-chlorophenyl)acryloyl)-2*H*-chromen-2-one was synthesized by same method as L^1 using 3-acetyl coumarin and 4- cholorobenzaldehyde; $C_{18}H_{11}ClO_3$; Yield, 70 %; m.p. 223–226 °C; FTIR (KBr. cm^{-1}): 1618, *v*(C=O, α, β-unsaturated ketone); 1742, *v*(C=O, lactone carbonyl of coumarin); 1591, *v*(C=C, aromatic stretching); 3062, *v*(C–H, aromatic stretching); ^{1}H NMR (DMSO-d_6 400 MHz): δ 6.86 (1H, m, C_6-H), δ 7.12 (2H, d, *J* = 7.2, p-substituted phenyl ring), δ 7.23 (1H, m, aromatic protons), δ 7.39 (2H, m, aromatic proton), δ 7.63 (2H, d, *J* = 7.2, p-substituted phenyl ring), δ 7.88 (1H, d, *J* = 7.8, CH=CH– protons), δ 7.90 (1H, d, *J* = 7.8, CH=CH– protons), δ 8.52 (1H, s, C_4-H); ^{13}C NMR (DMSO-d_6 100 MHz): δ 114.8 (C-4a), 116.5 (C-8), 118.6 (C-10, –CO–CH =), 124.2, 125.1, 126.2, 127.9, 129.8, 130.0, 133.5, 134.6 (8, Ar–C(C-3,C-5,C-6,C-7,C-12,C-13,17,C-14,16,C-15)), 147.1 (C-11, –CH=CH–), 147.6 (C-4), 151.5 (C-8a), 159.7 (C=O, lactone carbonyl of coumarin(C-2)), 190.2 (C=O, α, β-unsaturated ketone(C-9)); ESI–MS (m/z): 310.6, 312.7 [M]+; Found (%): C, 69.40, H, 3.66. calculated: C, 69.58, H, 3.57.

*3-(3-(3-nitrophenyl)acryloyl)-2H-chromen-2-one (**L**^{6})*

3-(3-(3-nitrophenyl)acryloyl)-2*H*-chromen-2-one was synthesized by same method as L^1 using 3-acetyl coumarin and 3- nitrobenzaldehyde; $C_{18}H_{11}NO_5$; Yield, 64 %; m.p. 178–182 °C; FTIR (KBr. cm^{-1}): 1610, *v*(C=O, α, β-unsaturated ketone); 1744, *v*(C=O, lactone carbonyl of coumarin); 1528 ($ArNO_2$, asymmetric); 1344 ($ArNO_2$, symmetric); 1535, *v*(C=C, aromatic stretching); 3034, *v*(C–H, aromatic stretching); ^{1}H NMR (DMSO-d_6 400 MHz):**:** δ 6.88 (1H, m, C_6-H), δ 7.23–7.71 (7H, m, aromatic protons), δ 7.79 (1H, *d*, *J* = 7.8, CH=CH– protons), δ 7.80 (1H, *d*, *J* = 7.8 CH=CH– protons), δ 8.52 (1H, *s*, C_4-H); ^{13}C NMR (DMSO-d_6 100 MHz): δ 113.8 (C-4a), 116.1 (C-8), 118.5 (C-10, –CO–CH =), 123.2, 124.4, 125.5, 127.1, 127.7, 128.4, 129.6, 130.5, 134.5 (9, Ar–C(C-3,C-5,C-6,C-7,C-12,C-13,C-15,C-16,C-17)), 147.2 (C-11, –CH=CH–), 147.9 (C-4), 149.7 (C-14, carbon attach to phenolic NO_2), 156.0 (C-8a), 159.7 (C=O, lactone carbonyl of coumarin(C-2)), 188.2 (C=O, α, β-unsaturated ketone(C-9)); ESI–MS (m/z): 321.2 [M]+; Found (%): C, 67.21, H, 3.27,N, 4.31. calculated: C, 67.34, H, 3.45, N, 4.39.

*3-(3-(4-nitrophenyl)acryloyl)-2H-chromen-2-one (**L**^{7})*

3-(3-(4-nitrophenyl)acryloyl)-2*H*-chromen-2-one was synthesized by same method as L^1 using 3-acetyl coumarin and 4-nitrobenzaldehyde; $C_{18}H_{11}NO_5$; Yield, 68 %; m.p. 171–175 °C; FTIR (KBr. cm^{-1}): 1614, *v*(C=O, α, β-unsaturated ketone); 1738, *v*(C=O, lactone carbonyl of coumarin); 1523 ($ArNO_2$, asymmetric); 1347 ($ArNO_2$, symmetric); 1543, *v*(C=C, aromatic stretching); 3037, *v*(C–H, aromatic stretching); ^{1}H NMR (DMSO-d_6 400 MHz): δ 6.90 (1H, m, C_6-H), δ 7.14 (2H, d, *J* = 7.2, p-substituted phenyl ring), δ 7.25 (1H, m, aromatic protons), δ 7.45 (2H, m, aromatic proton), δ 7.78 (2H, d, *J* = 7.2, p-substituted phenyl ring), δ 7.86 (1H, d, *J* = 7.2, CH=CH– protons), δ 7.91 (1H, d, *J* = 7.2, CH=CH– protons), δ 8.53 (1H, s, C_4-H); ^{13}C NMR (DMSO-d_6 100 MHz): δ 114.1 (C-4a), 116.3 (C-8), 118.5 (C-10, –CO–CH =), 124.9, 125.7, 126.9, 127.1, 129.5, 130.6, 134.8 (7, Ar–C(C-3,C-5,C-6,C-7,C-12,C-13,17,C-14,16)), 146.8 (C-11, –CH=CH–), 147.2 (C-4), 148.7 (C-15, carbon attach to phenolic NO_2), 154.7 (C-8a), 159.6 (C=O, lactone carbonyl of coumarin(C-2)), 189.7 (C=O, α, β-unsaturated ketone(C-9)); ESI–MS (m/z): 321.4 [M] + ; Found (%): C, 67.29, H, 3.37, N, 4.36. calculated: C, 67.34, H, 3.45, N, 4.39.

*3-(3-(4-hydroxy-3-methoxyphenyl)acryloyl)-2H-chromen-2-one (**L**^{8})*

3-(3-(4-hydroxy-3-methoxyphenyl)acryloyl)-2*H*-chromen-2-one was synthesized by same method as L^1 using 3-acetyl coumarin and 4-hydroxy-3-methoxybenzaldehyde; $C_{19}H_{14}O_5$; Yield, 79 %; m.p. 230–234 °C; FTIR (KBr. cm^{-1}): 3475, *v*(O–H, stretching); 1620, *v*(C=O, α, β-unsaturated ketone); 1743, *v*(C=O, lactone carbonyl of coumarin); 1241 (C–O–C, asymmetric); 1039 (C–O–C,

symmetric); ^{1}H NMR (DMSO-d_6 400 MHz):**):** δ 3.86 (3H, s, –OCH_3), δ 6.91(1H, m, C_6-H), 7.12–7.79 (6H, m, aromatic protons), δ 7.89 (1H, d, $J = 7.6$, CH=CH– protons), δ 7.93 (1H, d, $J = 7.6$, CH=CH– protons), δ 8.56 (1H, s, C_4-H), δ 9.67 (1H, s, -OH); ^{13}C NMR (DMSO-d_6 100 MHz):): δ 34.9 (C-18, OCH_3), 111.5 (C-13), 114.6 (C-16), 115.1 (C-4a), 116.4 (C-8), 118.0 (C-10, –CO–CH=), 124.2, 125.8, 127.6, 129.4, 130.4, 134.5 (6 different types of aromatic carbons(C-3,C-5,C-6,C-7,C-12,C-17)), 147.2 (C-11, –CH=CH–), 147.4 (C-4), 148.8 (C-14), 151.7 (C-15, carbon attach to phenolic OH), 155.6 (C-8a), 158.8 (C=O, lactone carbonyl of coumarin(C-2)), 190.4 (C=O, α, β-unsaturated ketone(C-9)); ESI–MS (m/z): 322.1 [M]+; Found (%): C, 78.77, H, 4.31. calculated: C, 78.80, H, 4.38.

Synthesis of complexes **(C_1–C_8)**

All the metal complexes (**1–8**) were synthesized according to (Scheme 1) using the following general method. An aqueous solution of appropriate divalent metals $CuCl_2.2H_2O$/$NiCl_2.6H_2O$ (10 mmol, 10 mL) was added to methanolic solution of appropriate ligand (L) (10 mmol, 50 mL) followed by addition of an ethanolic solution of GTF (10 mmol, 50 mL), the pH was adjusted to 6.0 with diluted CH_3ONa solution. The resulting solution was refluxed for 5–8 h and then heated over a steam bath to evaporate up to half of the volume. The reaction mixture was kept overnight at room temperature. A fine coloured powder was obtained was washed with ether and dried over vacuum desiccators. The analytical and physiochemical data of the ligands and complexes are summarized in (Table 1).

Method of antimicrobial assay

The biological activity of metal complexes were tested against variety of bacteria such as *B. subtilis*, *S. aureus*, *S. pneumonia* (Gram positive), *E. coli*, *P. aeruginosa*, *S. typhi* (Gram negative), because these microorganisms can get resistance to antibiotics and their metal complexes through biochemical and morphological modifications. The antibacterial activity was determined as minimum inhibitory concentration (MIC) by following method (Trommel and Marzilli, 2001). Antibacterial activity of complexes were compared with respect to second (CPF), third (LVF) and fourth (GTF) generation quinolones. The in vitro antibacterial activity of all the synthesized compounds was carried out against 24 h old cultures of microorganisms by broth dilution method. Serial broth micro dilution method was adopted as a reference method. 10 ml Luria broth solution was prepared in distilled water, while pH of the solution was adjusted to 7.4 ± 0.2 at room temperature and sterilized by autoclaving at 15 lb pressure for 20 min. The tested microorganism strains were made in the Luria broth and incubated at 37 °C for overnight. Sample and standard solutions were prepared in DMSO. Serial dilutions of test compounds were inoculated in broth; to this a standardized microorganism suspension was added. Each test tube incubated at 37 °C for 24 h. At the end of the incubation period tubes were examined for the turbidity. Turbidity in the test tubes indicated that microorganism growth has not inhibited by the antibiotic contained in the medium at the test concentration.

Antituberculosis activity

The activity of Cu (**1–4**) and Ni (**5–8**) complexes against Mycobacterium tuberculosis strain H37Rv (MTCC200) was determined by following method (Rattan, 2000). The resulted antituberculosis activity was expressed as minimal inhibition concentration (MIC) as well as % inhibition of growth was measured at MIC are summarized in concluding part. Isoniazid and Rifampicin were used as standard drugs for comparison purpose were as GTF used as control. All the synthesized complexes were examined for antituberculosis activity against Mycobacterium tuberculosis H37Rv strain using Lowenstein-Jensen medium method. Isoniazid and Rifampicin was used as the standard

Table 1 Analytical and physiochemical parameters of synthesized compounds

Compounds/Empirical formula	Elemental analyses, % found (required)				m.p. (°C)	Yield (%)	Molecular mass	μ_{eff}/ B.M.
	C	H	N	Cu(II)				
[Cu(GTF)(**L^1**)(Cl)]5H_2O $C_{37}H_{43}ClCuFN_3O_{12}$/(**1**)	52.88 (52.92)	5.14 (5.16)	4.97 (5.00)	7.55 (7.57)	>300	60	839.75	1.82
[Cu(GTF)(**L^2**)(Cl)]5H_2O $C_{37}H_{42}Cl_2CuFN_3O_{12}$/(**2**)	50.82 (50.84)	4.86 (4.84)	4.76 (4.81)	7.32 (7.27)	>300	62	874.19	1.78
[Cu(GTF)(**L^3**)(Cl)]5H_2O $C_{37}H_{42}ClCuFN_4O_{14}$/(**3**)	50.27 (50.23)	4.75 (4.78)	6.40 (6.33)	7.12 (7.18)	>300	58	884.75	1.75
[Cu(GTF)(**L^4**)(Cl)]5H_2O $C_{37}H_{43}ClCuFN_3O_{13}$/(**4**)	51.88 (51.93)	5.01 (5.06)	4.87 (4.91)	7.40 (7.43)	>300	65	855.75	1.80
[Ni(GTF)(**L^1**)(Cl)(H_2O)]3H_2O $C_{37}H_{41}ClFN_3NiO_{11}$/(**5**)	54.36 (54.40)	5.09 (5.06)	5.20 (5.14)	7.15 (7.19)	>300	48	816.88	3.10
[Ni(GTF)(**L^2**)(Cl)(H_2O)]3H_2O $C_{37}H_{40}Cl_2FN_3NiO_{11}$/(**6**)	52.14 (52.20)	4.72 (4.74)	4.91 (4.94)	6.92 (6.89)	>300	55	851.13	3.17
[Ni(GTF)(**L^3**)(Cl)(H_2O)]3H_2O $C_{37}H_{40}ClFN_4NiO_{13}$/(**7**)	51.50 (51.56)	4.63 (4.68)	6.45 (6.50)	6.78 (6.81)	>300	52	861.88	2.98
[Ni(GTF)(**L^4**)(Cl)(H_2O)]3H_2O $C_{37}H_{41}ClFN_3NiO_{12}$/(**8**)	53.39 (53.36)	4.91 (4.96)	4.99 (5.05)	7.01 (7.05)	>300	59	831.17	3.05

drug, whereas GTF used as control. The dilutions of standard drugs were prepared in DMSO to get different concentrations of 0.1–2 μg mL^{-1}. Stock solutions of synthesized compounds were prepared in DMSO. Further dilutions were prepared in DMSO to get different concentrations. 1.0 mL of each concentration was used for the study, to this 9.0 mL of Lowenstein- Jensen medium was added. A sweep from *M. tuberculosis* H37RV strain culture was discharged with the help of nichrome wire loop having 3 mm external diameter into a vial containing 4 mL of sterile distilled water. The vial was shaken for 5 min. The suspension was inoculated on the surface test compounds containing Lowenstein–Jensen medium. Further test media was incubated for 2 weeks at 37 °C. Readings were taken after incubation period of 2 weeks.

FRAP assay and radical scavenging activity

Ferric reducing antioxidant power (FRAP) as well as 1,1-diphenyl-2-picryl-hydrazil (DPPH) radical scavenging activity of all compounds were determined according to the reported methods (Patel *et al.,* 2012a, b; Blois, 1958). In FRAP assay, reducing power of the TPTZ-Fe(III) complex to TPTZ-Fe(II) complex for the total antioxidant capacity of tested samples was measured. The total antioxidant capacities of a compound consider as a significant indicator of its potential antioxidant activity and compared to the standard antioxidant compound ascorbic acid. For DPPH radical activity, tests were run in triplicate for all compounds, and the results were obtained for fix concentration at which each compound showed approximately 50 % activity (IC_{50}). The DPPH free radical scavenging capability was determined by following formula, % activity $= [(A_0 - A_c)/A_0] \times 100$ where A_0 and A_c represent the absorbance in the absence and presence of the tested complex, respectively.

Results and discussion

Synthesis and structural determination

3-(3-phenyl-acryloyl)-2*H*-chromen-2-one ($\mathbf{L^1}$), 3-(3-(4-chlorophenyl)acryloyl)-2*H*-chromen-2-one ($\mathbf{L^2}$), 3-(3-(4-nitrophenyl)acryloyl)-2*H*-chromen-2-one ($\mathbf{L^3}$) and 3-(3-(4-hydroxyphenyl)acryloyl)-2*H*-chromen-2-one ($\mathbf{L^4}$) were used for the preparation of M (II) (M = Cu, Ni) complexes (Scheme 1). These neutral bidentate ligands using Claisen-Schmidt condensation method were previously reported by us (Patel *et al.,* 2012a, b). 3-acetyl coumarin is reacted with equimolar respective aromatic aldehyde in presence of piperidine catalyst. M (II) complexes were obtained by refluxing the equimolar reaction mass of two bidentate ligands and metal chloride solution. The metal content in the complex was determined spectrophotometrically. All the coloured metal complexes are stable in atmospheric conditions for extended periods and soluble in DMSO, while insoluble in water and in most organic solvents. Elemental data found by analysis (Table 1) were in good agreement with proposed structures as per (Scheme 1). The coordination was confirmed by FAB-Mass, electronic spectra, FT-IR spectra, thermal study and magnetic measurement.

IR spectra

The important infrared spectral bands and their assignments for compounds (Table 2) were showed that coumarin derivatives coordinate to the metal ions in a bidentate behaviour via the α, β-unsaturated ketone and the lactone carbonyl oxygens. IR spectral data of the coumarin derivatives shows 1,610–1,625 and 1,740–1,750 cm^{-1} bands corresponding to α, β-unsaturated ketone and lactone carbonyl ketone, respectively, on complexation these peaks shifted to a lower frequency 1,595–1,608 and 1,728–1,735 cm^{-1} due to complex formation which is good indication that coumarin is coordinated to the metal ions. Spectra of the mixed-ligand Ni(II) complexes reveals that a broad band in the region 3,300–3,450 cm^{-1} due to the OH stretching of the water molecule which indicates formation of complexes (Anacona and Toledo, 2001). Absent of this OH band indicates no coordinated water molecule present in case of Cu complexes. Besides this according to the elemental analysis and thermogravimetric studies, all the complexes contain water of crystallization. The IR spectra showed characteristic absorption bands around ~3,430, ~1,615, ~1,336 cm^{-1} were attributed to the stretching vibration ν(H–O), ν(COO)asym, ν(COO)-sym, respectively. These bands of carboxylic group of GTF have been replaced by two strong bands in the range 1,553–1,573 cm^{-1} [ν_{asym}(C=O)] and 1,360–1,370 cm^{-1} [ν_{sym}(C=O)] due to the coordination with metal ion (S. Jain *et al.,* 2002). The monodentate coordination mode of carboxylato ligand was characterized by *D* value falling in the range 192–212 cm^{-1} (Nakamoto, 1986; Deacon and Philips, 1980). The valence vibration of the carboxylic stretch for free GTF was found at ~1,730 cm^{-1} which disappears due to the complexation. Peak in range 1,615–1,630 cm^{-1} found in case of complexes were for pyridone ν(C=O) atom which appeared at ~1,720 cm^{-1} in GTF; this shift in band towards lower energy suggests coordination via pyridone oxygen atom (Turel *et al.,* 1997). The coordination is also supported by the appearance of IR bands due to ν(Cu–O) and ν(Ni–O) vibrations in the range 505–525 and 545–558 cm^{-1}, respectively (Kharadi and Patel, 2010; Singh *et al.,* 2012).

Table 2 FT-IR data of synthesized compounds in cm^{-1}

Complexes (**1–8**)	$\nu(O–H)^{br}$	α, β-unsaturated $\nu(C = O)^{s}$	lactone carbonyl $\nu(C = O)^{s}$	$\nu(C = O)$ of pyridone	$\nu(COO)$asym	$\nu(COO)$sym	$\nu(M–O)^{w}$
$[Cu(GTF)(L^1)(Cl)]5H_2O$/(**1**)	–	1,595	1,732	1,615	1,553	1,361	518
$[Cu(GTF)(L^2)(Cl)]5H_2O$/(**2**)	–	1,603	1,730	1,618	1,557	1,363	525
$[Cu(GTF)(L^3)(Cl)]5H_2O$/(**3**)	–	1,600	1,728	1,630	1,562	1,368	520
$[Cu(GTF)(L^4)(Cl)]5H_2O$/(**4**)	–	1,608	1,735	1,624	1,558	1,363	505
$[Ni(GTF)(L^1)(Cl)(H_2O)]3H_2O$/(**5**)	3,335	1,597	1,730	1,619	1,556	1,364	545
$[Ni(GTF)(L^2)(Cl)(H_2O)]3H_2O$/(**6**)	3,340	1,604	1,728	1,624	1,562	1,366	552
$[Ni(GTF)(L^3)(Cl)(H_2O)]3H_2O$/(**7**)	3,342	1,600	1,730	1,628	1,573	1,370	558
$[Ni(GTF)(L^4)(Cl)(H_2O)]3H_2O$/(**8**)	3,340	1,608	1,734	1,622	1,567	1,360	550

s strong, *w* weak, *br* broad

Electronic spectra and magnetic measurement

Electronic spectral data together with magnetic susceptibility measurements gave enough support to discover the geometry of metal complexes. Copper(II) complexes that is, d^9 system with a simple ligand at low temperature exhibit an absorption band with a large width make them very difficult to interpret. Cu(II) complexes with different coordination numbers resulted in different geometry. However, many copper compounds show temperature dependent geometric distortions, and single copper ions in a host lattice of regular symmetry may exhibit interesting spectroscopic properties (Weber *et al.,* 2009). In our case of copper(II) complexes, bands observed in the regions ~9,550(ν_1), ~13,500(ν_2) and ~18,800(ν_3) cm^{-1} have been ascribed to the transitions $2B_1 \rightarrow 2A_1$, $2B_1 \rightarrow 2B_2$ and $2B_1 \rightarrow 2E$, respectively, which was further ascertained by its magnetic moment of 1.75–1.82 BM falls within the range normally observed for square pyramidal Cu(II) complexes (**1–4**) (Figgis and Lewis, 1960; Carballo *et al.,* 2004). The absorption spectra of nickel complexes display three d–d transition bands with D_4h symmetry in the range ~10,800(ν_1), ~14,600(ν_2) and ~21,180(ν_3) cm^{-1}. The transitions correspond to the $3A_2g$ (F) $\rightarrow$ $3T_2g$ (F), $3A_2g$ (F) $\rightarrow$ $3T_1g$ (F) and $3A_2g$ (F) $\rightarrow$ $3T_2g$ (P), respectively. These transitions reveal that the Ni(II) complexes possess octahedral geometry, which was further supported by the observed magnetic moment values between 2.98 and 3.17 B.M. (Balhausen, 1962; Al-Resayes *et al.,* 2012).The observed magnetic moments of Ni(II) complexes are in the range expected for spin-free d^8 systems.

Thermal study

Thermal decomposition occurs in three steps for Cu(II) complex (**1**) (Psomas *et al.,* 1998). First weight loss occurs between 70 and 140 °C due to loss of five molecules of water (calc. 10.71 %, obs. 10.86 %), This low temperature loss confirms that the water molecules do not participate in coordination and considered as crystalline water. In second step, weight loss occurs between 180 and 390 °C due to decomposition of bidentate ligand (calc. 32.90 %, obs. 33.20 %) where as third weight loss between 430 and 650° corresponds to decomposition of GTF (calc. 44.67 %, obs. 42.90 %). Thermogravimetric curve of Ni(II) complex **(5)** provides similar three step decomposition as Cu(II) complex with varies in temperature and mass loses. First weight loss occurs between 50 and 120 °C due to loss of three crystalline water molecules (calc. 6.61 %, obs. 6.68 %), in second step between 160 and 410 °C corresponds to decomposition of bidentate ligand and one coordinated molecule of each (Cl and H_2O) (calc. 40.36 %, obs. 40.10 %) where as third loss between 440 and 690 °C corresponds to decomposition of GTF (calc. 45.93 %, obs. 44.86 %). Rest of the compound in both complexes considers as metal oxides e.g. CuO and NiO.

FAB-mass spectra

FAB-Mass spectra of all complexes were obtained using m-nitrobenzyl alcohol as matrix. Figure 1 represents the FAB-MS of complex $[Cu(GTF)(\mathbf{L^1})(Cl)]5H_2O$ (**1**) and $[Ni(GTF)(\mathbf{L^1})(Cl)(H_2O)]3H_2O$ (**5**). The $[M+2H]^+$ fragments without water of crystallization are observed at 748, 750 and 763, 761 m/z in case of complex **1** and complex **5**, respectively. There also exists a fragment of complex **1** (at m/z = 708) and **5** (at m/z = 713) indicates the presence of Cl atom in respective complexes. The peaks at 615 m/z and 610 m/z correspond to removal of piperazine ring, respectively, in complex **1** and **5**. Also, the peak at 743 m/z corresponds to loss of coordinated water molecule was found in case of complex **5**, apart from it several peaks found at 136, 137, 154, 289 and 307 m/z are due to usage of matrix in both the complexes.

Antibacterial activity

Activity data from (Table 3) indicate that all the Cu(II) complexes (**1**–**4**) found more potent then Ni(II) complexes (**5**–**8**), beyond which Cu(II) complex (**4**) with hydroxyl molecule at pera position found most potent against all the bacteria. The result indicates that substitution of the hydroxyl groups on the phenyl ring of the coumarin ligand play vital for improved the antibacterial activity of Cu(II) complexes. Comparison between the gram positive and gram negative strains indicates enhanced potency of all complexes (**1**–**8**) for gram positive bacteria, particularly *S. aureus* and *S. Pneumonia*. in gram negative bacteria. *aeruginosa* found to be more potent than other two bacteria *E. coli* and *S. typhi* along with it, *P. aeruginosa* was only the gram negative bacteria which found more potent then gram positive bacteria *B. subtilis*.

1. Gram positive bacteria

   B. subtilis: In this case, complex **4** is only compound, which found more potent than all the standard drugs and complexes **1** and **2** found more potent then GTF, where as complex **8** found equipotent compared to GTF.
   S. aureus: Complexes **2**, **4** and **8** are found active against all standard drug, beyond which **4** is found most potent, where as all the remaining complexes excluding **7** are found active against LVF and CPF.
   S. Pneumonia: In this case, all the complexes excluding **7** are found more potent against all standard drugs, beyond which **4** is found most potent.

2. Gram negative bacteria

   E. coli: In this case, none of the complex found more potent than any standard drug.
   P. aeruginosa: Complexes **2**, **4** and **8** are found active against all standard drug, beyond which 4 is found most potent, where as all the remaining complexes found less potent against all standard drugs.
   S. Pneumonia: In this case, only single complex i.e. **4** found equipotent with GTF, where as remaining complexes found less potent compare to standard drugs.

Reviewing the activity data, these rationales are considered for increased in activity of all complexes, (I) bidentate nature of the ligand (II) chelating affect in which bidentate coordination of quinolone with metal ion (III) on the basis of Overtone's and Tweed's chelation theory (IV) dinuclear centres are usually more active than mononuclear ones. In general, the in vitro evaluation of all complexes revealed improved therapeutic effectiveness of GTF when it binds with metal and bidentate ligands, as compared to the standard antibiotics including GTF itself. Further developmental studies to acquire more information about structure–activity relationships are in progress in our laboratories.

Antituberculosis activity

The encouraging results from the antibacterial studies prompted us to go for preliminary screening of complexes

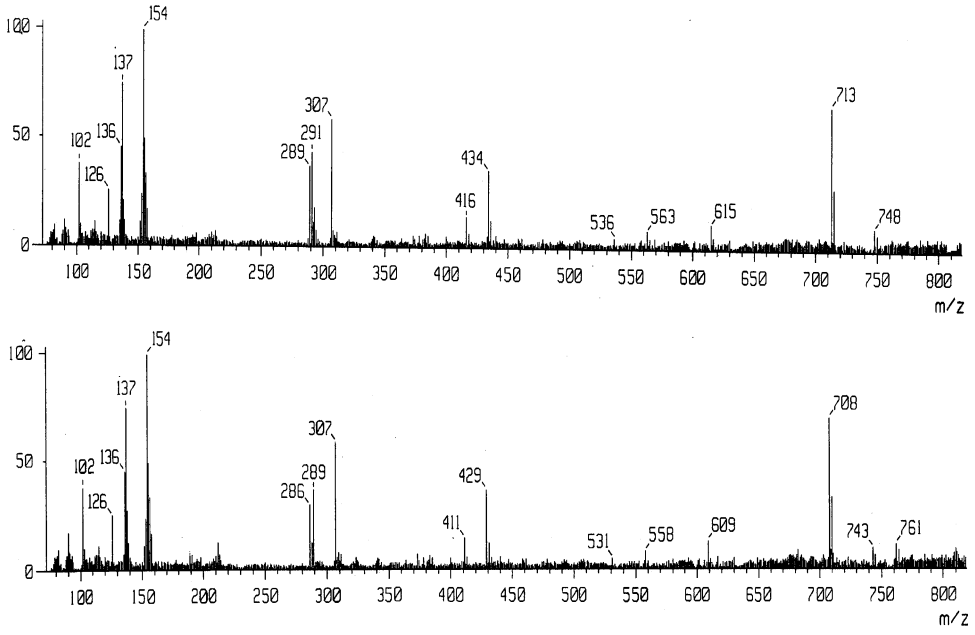


Fig. 1 FAB-Mass spectra of Cu(II) and Ni (II) complex

Table 3 Antibacterial activity of complexes

Compound	M	R	Minimum inhibitory concentration (μg/mL)					
			Gram positive bacteria			Gram negative bacteria		
			B. s. MTCC-441	*S. a.* MTCC-96	*S. pn.* MTCC-2672	*E. c.* MTCC-443	*P. a.* MTCC-1688	*S. ty.* MTCC-98
$CuCl_2{\cdot}2H_2O$			2620	2,510	2,550	2,890	2,430	2,760
1	Cu	H	3.0	2.1	1.5	15.0	3.8	7.0
2		Cl	2.8	0.9	0.6	10.0	1.5	10.0
3		NO_2	5.0	3.5	1.8	>20.0	4.8	>20.0
4		OH	1.2	0.6	0.3	6.8	1.0	4.5
$NiCl_2{\cdot}6H_2O$			3,450	3,040	2,920	3,680	3,150	3,290
5	Ni	H	5.2	3.0	1.5	15.0	4.6	10.0
6		Cl	5.0	2.5	0.9	15.0	4.2	10.0
7		NO_2	7.0	5.8	2.2	>20.0	6.8	>20.0
8		OH	3.5	1.4	0.6	8.0	2.0	7.0
Gatifloxacin			3.5	2.0	2.0	5.0	2.7	4.5
Levofloxacin			2.5	3.8	3.6	3.1	2.7	4.0
Ciprofloxacin			1.8	6.0	4.5	1.3	3.0	2.5

B.s.: *B. subtilis* (MTCC-441), *S.a.*: *S. aureus* (MTCC-96), *S. pn.*: *S. pneumonia* (MTCC-2672), *E.c.*: *E. coli* (MTCC-443), *P.a.*: *P. aeruginosa* (MTCC-1688), *S.ty.*: *S. typhi* (MTCC-98), *M* metal, *R* variables

for their in vitro antituberculosis activity. Antituberculosis activity data (Table 4) of the complexes clearly indicate that most complexes provide excellent % inhibition (≥90). Reviewing the MIC data, Both Cu(II) and Ni(II) complexes (**4** and **8**) with GTF containing hydroxyl group were most active within each series inhibiting bacterial growth at 0.25 and 0.35 mg/mL, respectively. On the other hand, the least active complexes (**3** and **7**) of the series were Cu(II) and Ni(II) complex with GTF containing nitro group which exhibited MIC value of 1.15 and 1.50 mg/mL, respectively. Rest of the complexes containing Cl and H has shown significant activity between 0.30 and 0.80. The activity data show advantages of copper coordination over nickel complexes. In general, all the complexes exhibited superior activity then marketed drug Rifampicin except complex **3** and **7**.

Table 4 Antituberculosis activity of complexes

Compound	MIC μg/mL *M. tuberculosis* (MTCC 200)	% Inhibition
1	0.78	85
2	0.31	95
3	1.15	60
4	0.25	99
5	0.69	90
6	0.40	98
7	1.50	45
8	0.35	98
Gatifloxacin	0.1	99
Isoniazid	0.20	98
Rifampicin	1.0	95

FRAP assay and radical scavenging activity

The FRAP assay data from Fig. 2 indicate that metal complexes exhibit higher antioxidant activity then its free ligands. The internal comparison of complexes clearly indicates the higher antioxidant potency of Cu(II) complexes. DPPH scavenging activity amongst the all compounds, the complexes (**1**–**4**) show higher antioxidant potency due to presence of Cu(II) ion as shown in Fig. 3. In particular, all the compounds have been found potent ferric

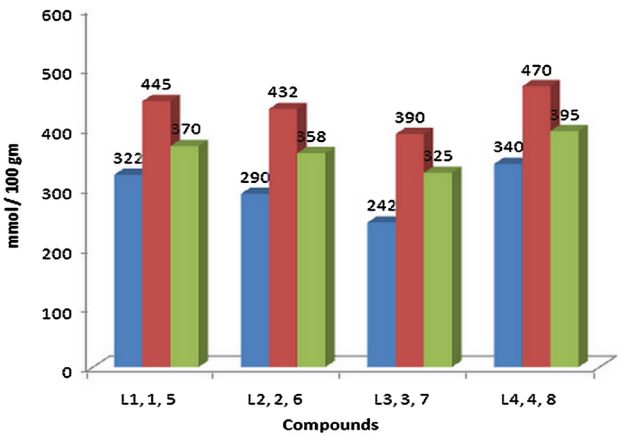


Fig. 2 Frap assay of compounds

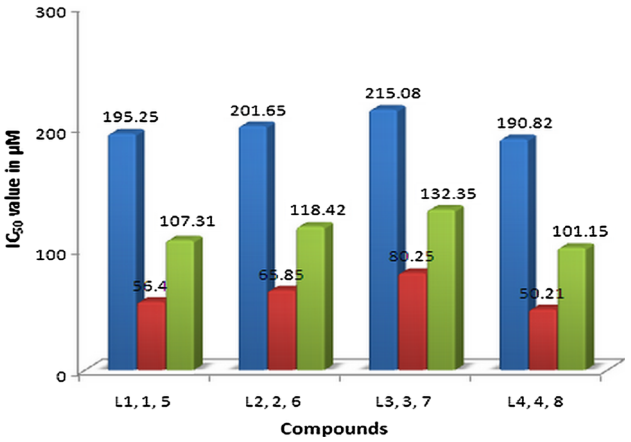


Fig. 3 DPPH radical scavenging activity of compounds

reducing capacity and radical scavenging capability compared to standard drug (ascorbic acid). The antioxidant activity of the ligand and its M(II) complexes (where M = Ni and Cu) against the DDPH radical and FRAP assay was found to increase in the order of L < Ni(II) < Cu(II).

Conclusion

The neutral bidentate ligands were prepared with 1:1 molar ratio of 3-acetyl coumarin and various aromatic aldehydes using piperidine as catalyst in ethanol. All the complexes (**C**) were obtained by the reaction of ligands and GTF with metal chloride having 1:1:1 molar ratio in ethanol and the yields were good to moderate. In all the metal–GTF complexes, metal ions coordinated by four oxygen atoms amongst which two from GTF and two ketone groups (lactone carbonyl oxygen and α,β-unsaturated carbonyl oxygen) from coumarin chalcone. GTF acts as a bidentate ligand through the ring carbonyl group at position-4 and through one of the oxygen atom of carboxylate group at position-3.The different geometry was assigned for Cu(II) and Ni(II)complexes on the basis of electronic, magnetic moment value and thermogravimetric analysis. Also, FAB-Mass fragments support the different coordinated molecules for Cu(II) and Ni(II) complexes. All the complexes found excellent antibacterial and antituberculosis activity. They have been also found as potent antioxidant agents comprising radical scavenging capability and ferric reducing abilities. In general, metal interaction with two distinct biological compounds is beneficial to prepare biologically potent agents against infectious diseases.

Acknowledgments We articulate our appreciation to authorities of V. P. & R. P. T. P. Science College, Sardar Patel University, Vallabh Vidyanagar, India for providing infrastructural & chemical facilities. We are greatful to Department of Science and Technology (DST) Delhi, India for providing financial support to one of the author (JDB) in the form of INSPIRE fellowship. We are thankful to the Director, SICART, Vallabh Vidyanagar for spectral analysis facility. Authors are also grateful to the Microcare laboratory, Surat for providing bio-analysis facility.

References

Ahirrao P (2008) Recent developments in antitubercular drug. Mini Rev Med Chem 8:1441–1451

Al-Resayes SI, Shakir M, Abbasi A, Amin KMY, Lateef A (2012) Synthesis, spectroscopic characterization and biological activities of N_4O_2 Schiff base ligand and its metal complexes of Co(II), Ni(II), Cu(II) and Zn(II), Spectrochim. Acta Part A 93:86–94

Anacona JR, Toledo C (2001) Synthesis and antitubercular activity of palladium and platinum complexes with fluoroquinolones. Trans Met Chem 26:228–231

Appendino G, Mercalli E, Fuzzati N, Arnoldi L, Stavri M, Gibbons S, Ballero M, Maxia A (2004) Chemical composition and in vitro activity of plant extracts from ferula communis and *Dittrichia viscosa* against postharvest fungi. J Nat Prod 67:2108–2110

Babbs CF (1990) Oxygen radicals in ulcerative colitis. Free Radic Biol Med 8:191–200

Balhausen CJ (1962) Introduction to ligand fields. McGraw Hill, New York

Bauernfeind A (1997) Comparison of the antibacterial activities of the quinolones Bay 12-8039, gatifloxacin (AM 1155), trovafloxacin, clinafloxacin, levofloxacin and ciprofloxacin. J Antimicrob Chemother 40:639–651

Beraldo H, Gambinob D (2004) The wide pharmacological versatility of semicarbazones, thiosemicarbazones and their metal complexes. Mini Rev Med Chem 4:31–39

Blois MS (1958) Antioxidant determinations by the use of stable free radical. Nature 26:1199–1200

Blondeau JM, Laskowski R, Bjarnason J, Stewart C (2000) Comparative in vitro activity of gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin and trovafloxacin against 4151 Gram-negative and Gram-positive organisms. Int J Antimicrob Agents 14:45–50

Carballo R, Castineiras A, Covelo B, Garcia-Martinez E, Niclos J, Vazquez-Lopez EM (2004) Solid state coordination chemistry of mononuclear mixed-ligand complexes of Ni (II), Cu (II) and Zn (II) with α-hydroxycarboxylic acids and imidazole. Polyhedron 23:1505–1518

Chulvi C, Munoz MC, Perello L, Ortiz R, Arriortua MI, Via J, Urtiaga K, Amigo JM, Ochando LE (1991) Coordination behavior of cinoxacine: synthesis and crystal structure of tris (cinoxacinate) cobaltate(II) of sodium hexahydrate (HC*x* = 1-ethyl-4(1*H*)-oxo-(1,3) dioxolo-(4,5g) cinnoline-3-carboxylic acid). J Inorg Biochem 42:133–138

Creaven BS, Egan DA, Kavanagh K, McCann M, Noble A, Thati B, Walsh M (2006) Synthesis, characterization and antimicrobial activity of a series of substituted coumarin-3-carboxylatosilver(I) complexes. Inorg Chim Acta 359:3976–3984

Da Silva AD, De Almeida MV, De Souza MVN, Couri MRC (2003) Biological activity and synthetic metodologies for the preparation of fluoroquinolones, a class of potent antibacterial agents. Curr Med Chem 10:21–39

Datta P, Mukhopadhyay AP, Manna P, Tiekink ERT, Sil PC, Sinha CJ (2011) Structure, photophysics, electrochemistry, DFT calculation, and in vitro antioxidant activity of coumarin Schiff base complexes of Group 6 metal carbonyls. Inorg Biochem 105:577–588

De Souza MVN (2005) New fluoroquinolones: a class of potent antibiotics. Mini Rev Med Chem 5:1009–1017

De Souza RFV, De Giovani WF (2004) Antioxidant properties of complexes of flavonoids with metal ions. Redox Rep 9:97–104

Deacon GB, Philips RJ (1980) Carboxylate as the protonation site in (Peroxo)diiron(III) model complexes of soluble methane monooxygenase and related diiron proteins. Coord Chem Rev 33:227–250

Egan DA, James P, Cooke D, O'Kennedy R (1997) Cytotoxic activity of new acetoxycoumarin derivatives in cancer cell lines. Cancer Lett 118:201–211

Figgis BN, Lewis J (1960) Modern coordination chemistry. In: Lewis J, Wilkins RG (eds) Principles and methods. Interscience, New York

Finn GJ, Kenealy E, Creaven BS, Egan DA (2002) 7,8-Dihydroxycoumarin inhibits A549 human lung adenocarcinoma cell proliferation by inducing apoptosis via suppression of Akt/NF-κB signaling. Cancer Lett 183:61–68

Fylaktakidou KC, Hadjipavlou-Litina DJ, Litinas KE, Nicolaides DN (2004) Cytotoxic activity of new acetoxycoumarin derivatives in cancer cell lines. Curr Pharm Des 10:3813–3833

Gomes AJ, Lunardi CN, Gonzalez S, Tedesco AC (2001) The antioxidant action of *Polypodium leucotomos* extract and kojic acid: reactions with reactive oxygen species. Braz J Med Biol Res 34:1487–1494

Jain S, Jain NK, Pitre KS (2002) Bio-inorganic studies on the Fe(II) sparfloxacin complex. Met Based Drugs 9:1–8

Ji HF, Zhang HY (2004) A new strategy to combat Alzheimer's disease. Combining radical-scavenging potential with metal-protein-attenuating ability in one molecule. Chem Res Toxicol 17:471–475

Kang DG, Yun CK, Lee HSJ (2003) Identification and characterization of antioxidants from *Sophora flavescens*. Ethnopharmacol. 87:231–236

Kapoor P, Singh RV, Fahmi NJ (2012) Preparation, spectroscopic characterization and biological evaluation of metal complexes with schiff base derived from benzofuran and coumarin moieties. Coord Chem 65:262–277

Kharadi GJ, Patel KD (2010) In-vitro antimicrobial, thermal and spectral studies of mixed ligand Cu(II) heterochelates of clioquinol and coumarin derivatives. Appl Organomet Chem 24:332–337

Kidane AG, Salacinski H, Tiwari A, Bruckdorfer KR, Seifalian AM (2004) Anticoagulant and antiplatelet agents: their clinical and device application(s) together with usages to engineer surfaces. Biomacromolecules 5:798–813

Kontogiorgis CA, Savvoglou K, Hadjipavlou LDJ (2006) Evaluation of natural substances from *Evolvulus alsinoides* L. with the purpose of determining their antioxidant potency. J Enzyme Inhib Med Chem 21:21–29

Koshy J, Das VGK, Balabaskaran S, Ng SW, Wahab N (2000) High in-vitro antitumour activity of triphenyltin coumarin 3-carboxylate and its coordination complexes with monodentate oxygen donor ligands against the epstein barr virus (EBV)-DNA positive Raji and the P-388 murine leukaemia cell lines, and evidence for the suppression by organotin of the early antigen complex in the EBV lytic cycle. Met Based Drugs 7:245–251

Lien EJ, Ren S, Bui HH, Wang R (1999) Flavonoid B-ring chemistry and antioxidant activity: fast reaction kinetics. Free Radic Biol Med 14:285–294

Lin HC, Tsai SH, Chen CS, Chang YC, Lee CM, Lai ZY, Lin CM (2008) Structure-activity relationship of coumarin derivatives on xanthine oxidase-inhibiting and free radical-scavenging activities. Biochem Pharmacol 75:1416–1425

Nakamoto K (1986) Infrared and Raman spectra of inorganic and coordination compounds, 4th edn. Wiley Interscience, New York

Patel JC, Dholariya HR, Patel KS, Patel KD (2012a) Spectral, thermal, biological and multi-heating rate kinetic properties of Cu(II) complexes containing N_2O_2 donor ligands: 1,10-phenanthroline and acyl coumarins. Appl Organomet Chem 24:332–337

Patel KS, Patel JC, Dholariya HR, Patel KD (2012b) Multiple heating rate kinetic parameters, thermal, X-ray diffraction studies of newly synthesized octahedral copper complexes based on bromo-coumarins along with their antioxidant, anti-tubercular and antimicrobial activity evaluation, Spectrochim. Acta Part A 96:468–479

Patonay T, Litkei G, Bognar R, Eredi J, Miszti C (1984) Synthesis, antibacterial and antifungal activity of 4-hydroxycoumarin derivatives, analogues of novobiocin. Pharmazie 39:86–91

Psomas G, Dendrinou-Samara C, Philippakopoulos P, Tangoulis V, Raptopoulou CP, Samaras EL, Kessissoglou DP (1998) Cu^{II}-herbicide complexes: structure and bioactivity. Inorg Chim Acta 272:24–32

Rattan A (2000) In: Churchill BI (ed) Antimicrobials in laboratory medicine. Livingstone, New Delhi

Sadeek AS, El-Shwiniy WH (2010) Metal complexes of the fourth generation quinolone antimicrobial drug gatifloxacin: synthesis, structure and biological evaluation. J Mol Struct 977:243–253

Sandbhor U, Padhye S, Billington D, Rathbone D, Franzblau S, Anson CE, Powell AKJ (2002) Inorg Biochem 90:127–136

Sigel A, Sigel H, Sigel RKO (2006) Metal ions in life sciences. Wiley, Chichester

Singh K, Kumar Y, Puri P, Kumar M, Sharma C (2012) Cobalt, nickel, copper and zinc complexes with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde Schiff bases: antimicrobial, spectroscopic, thermal and fluorescence studies. Eur J Med Chem 52:313–321

Sousa I, Claro V, Pereira JL, Amaral AL, Silva LC, De Castro B, Feio MJ, Pereira E, Gameiro PJ (2012) Synthesis, characterization and antibacterial studies of a copper(II) levofloxacin ternary complex. Inorg Biochem 110:64–71

Trommel JS, Marzilli LG (2001) Synthesis and DNA Binding of novel water-soluble cationic methylcobalt porphyrins. Inorg Chem 40:4374–4384

Turel I, Leban I, Bukovec N (1997) Crystal structures and characterization of the Bismuth (III) compound with quinolone family member (Ciprofloxacin). Antibacterial study. J Inorg Biochem 66:241–245

Turel I, Golobic A, Klavzar A, Pihlar B, Buglyo P, Tolis E, Rehder D, Sepcic KJ (2003) Interactions of oxovanadium(IV) and the quinolone family member—ciprofloxacin. Inorg Biochem 95:199–207

Vincenzi FF, Thomas HR (1999) Stobadine: bellwether of a broader view of drug actions. Life Sci 65:1857–1864

Weber E, Marten J, Seichter W (2009) Synthesis and crystal structures of the chelating ligand 3-[(2,6-dimethylphenyl)hydrazono]-1,1,1-trifluoropentane-2,4-dione and its complex with copper(II). J Coord Chim 62:3401–3410