Synthesis, Characterization and Antimicrobial Evaluation of Zinc (II) Complexes of 4-((2-substitutedphenyl)imino)-2-(4-subsitutedphenyl)-4H-chromen-3-ol

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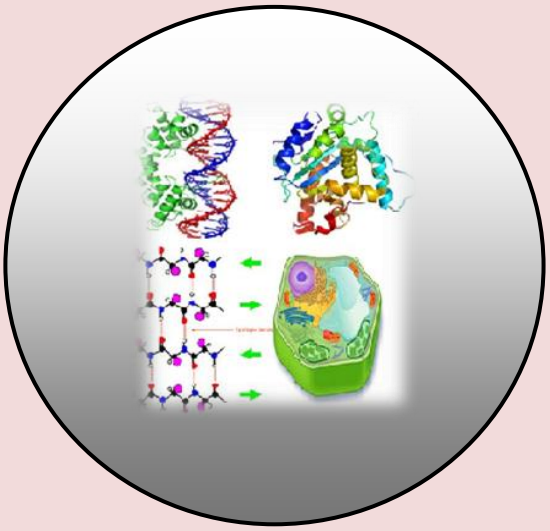

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RESEARCH PAPER

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Synthesis, Characterization and Antimicrobial Evaluation of Zinc (II) Complexes of 4-((2-substitutedphenyl)imino)-2-(4-subsitutedphenyl)-4H-chromen-3-ol

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ABSTRACT

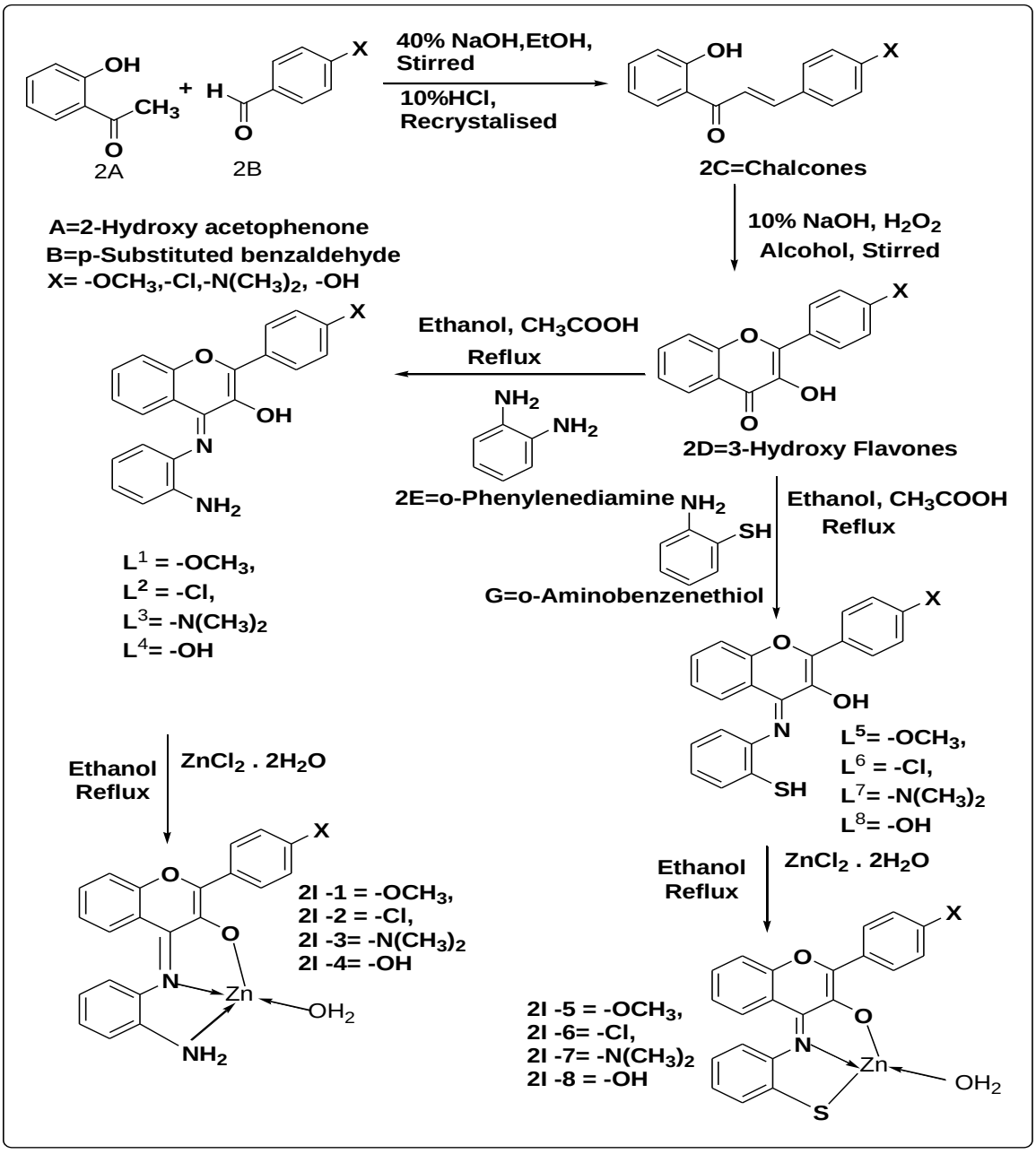
The synthesis of two series of eight new Zn(II) complexes [$ZnL^{1-8}.H_2O$] (2I-1 to 2I-8)incorporating the ligands (E)-4-((2-aminophenyl)imino)-2-(4-subsitutedphenyl)-4H-chromen-3-ol [L^1 to L^4] (A-series, 2I-1 to 2I-4) and (E)-4-((2-mercaptophenyl)imino)-2-(4-subsitutedphenyl)-4H-chromen-3-ol [L^5 to L^8] (B-series, 2I-5 to 2I-8) have been synthesized. The new synthesized complexes have been characterized by elemental analysis, IR, ^1H NMR, ^{13}C NMR spectroscopy, UV-vis. and ESI-MS spectrophotometry. Antimicrobial activity of complexes and their ligands were carried out against a panel of microorganism (antibacterial against Staphylococcus aureus, Escherichia coli, Salmonella typhi, and antifungal against Candida albicans and Aspergillus flavus) by using micro dilution method. The antimicrobial evaluation reveals that compound 2I-4 and 2I-8 exhibited moderate to good antibacterial and antifungal activity depending upon concentration.
Key words: Zinc complexes, Antifungal, Antibacterial Activity and Spectral Analysis.

INTRODUCTION

Flavone derivatives are interesting bioactive heterocycles because they are present in many naturally occurring products and various drugs. They show an important pharmacophore in modern drug discovery and continue to be the most versatile class of compounds possessing different pharmacological activities such as antioxidant [Tair et al., 2014], antitumor [Güzel et al., 2018, Çimen et al., 2014, Jiang et al., 2013], antiulcer [Rodriguez-Morgade et al., 2013, Kupcewicz et al., 2011], antifungal [Budzisz et al., 2014, Budzisz et al., 2014], antibacterial [Budzisz et al., 2007, Uivarosi et al., 2013, Vetschera et al., 2009], anthelmintic [Leonarduzzi et al., 2010], anti-inflammatory [Valentová et al., 2018, Habala et al., 2016, Singh et al., 2012], anticonvulsant [Al-Resayes et al., 2012], antitubercular [Kaushal et al., 2018, Hickey and Donnelly, 2010, Quiruga and Ranninger, 2004], antidepressant [Lobana, 2015], antihypertensive [Abdul et al., 2019, Raman et al., 2009], anticoagulant [Hussain et al., 2010] and antiviral [Vogel, 1989]. The interaction of transition metal ions with flavones and its derivatives showed enhanced biological activities against different microorganism causing various infectious diseases. Also transition metals coordinated with drugs increase its sensitivity and specificity [Souza et al., 1985, Vogel, 1989, Meyer et al., 1991]. The Zn (II), most prominent trace metal in human body after iron, is essential for growth and development of various biological systems.

The bioactive drugs of Zinc is preferred due to redox inertness, low toxicity, hard Lewis acid properties, bioavailability of Zn(II) and least strained tetrahedral structure of its complexes. Biologically active flavones derivatives with N, O, S potent donor atom increase the stability of metal complexes and increase the potential of metal based drugs against microorganisms [Zgoda and Porter, 2001].

In view of the above observations, we have synthesized Zn(II) complexes of (E)-4-((2-aminophenyl)imino)-2-(4-subsitutedphenyl)-4H-chromen-3-ol and (E)-4-((2-mercaptophenyl)imino)-2-(4-subsitutedphenyl)-4H-chromen-3-ol. It has found that these complexes showed significant antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Salmonella typhi, Candida albicans* and *Aspergillus flavus* and comparedby using standard drugs ciprofloxacin and fluconazole respectively.



Scheme: Synthesis of ligands and their metal complexes.

EXPERIMENTAL SECTION

MATERIALS AND METHODS

All the chemicals used were purchased from sigma Aldrich. The solvents used were purified by reported method [Zgoda and Porter 2001]. Double distilled water has been used where ever necessary. The purity of the compound was monitored by TLC ($CHCl_3/CH_3OH$, 9:1), using silica gel plate (Merck). Melting points were determined with SSU melting point apparatus. Euro Vector E 3000 Elemental Analyser was used for elemental analysis. UV visible spectra were recorded on a double beam UV -Vis near IR Labtronics LT-2900 instrument. IR spectra (KBr discs) were recorded on Agilent Cary 360 FTIR spectrometer. ^1H NMR, ^{13}CNMR spectra were recorded on Brucker Advance 400 MHz FT NMR spectrometer. ESI mass spectrum was recorded on Waters UPLC-TQD Mass spectrometer. Molecular weight of the complexes determined by cryoscopic method in DMSO.

Biological evaluation

The organisms were used in this study are *Staphylococcus aureus, Escherichia coli, Salmonella typhi*(bacteria), *Candida albicans* and *Aspergillus flavus* (fungi). All the synthesized complexes 2I (1-8) were screened for their *in vitro* antibacterial and antifungal activities against various strains of microorganism to determine minimum inhibitory concentrations (MICs) in µg/mL by micro dilution method. 100 ml of a pure organism culture was added to 75 ml of an appropriate medium and a fresh organism culture was grown on a shaker under specific conditions. The pure cultures were diluted with sterile water to give the NCCLS (National Committee for Clinical Laboratory Standards) recommended MIC values of the control complexes. The number of colony forming units (CFU) per single well on the 96-well plate was determined for each organism. The cultures were then grown and diluted exactly under the same conditions each time an experiment was performed. Ciprofloxacin and Fluconazole are used as standard drugs.

Antibacterial activity

The *in vitro* antibacterial activities of all the synthesized Complexes 2I (1-8) were screened against Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*). Among the tested compounds, two compounds have shown approximately good antimicrobial activities compare to the reference drugs ciprofloxacin, while others among the screened compounds found to be less potent to the standard drugs. The experimentally observed MIC values of all screened compounds with respect to standard drugs were summarized in Table-1, Figure 1.

Antifungal activity

In order to enhance the antimicrobial activities, the antifungal screening was also done, which revealed that the synthesized compounds 2I(1-8) showed good inhibition against various tested fungal strains viz., *Aspergillus flavus,*and *Candida albicans.* Here, Fluconazole was used as standard drug. The results indicate that among all the screened compounds, compound 2I-4 and 2I-8 exhibited maximum inhibition activity (6.25µg/mL) against *C. albicans.* However, other substituted compounds such as 2I-1, 2I-2, 2I-3, 2I-5, 2I-6 and 2I-7 against *A. flavus,* and *Candida* did not show any activity even at maximum concentration (200µg/mL). The experimentally observed MIC values of all screened compounds with respect to standard drugs have been presented in Table 2, Figure 2.

Synthesis of Ligands and Zinc (II) complexes

3-Hydoxy flavones derivatives and their Zn complexes were prepared by reported procedure. To the 10 mmol. solution of 3-hydroxy-4'-substituted flavone derivative(Sub.= 0.268g (-OCH_3), 0.254g (-OH), 0.364g (-Cl), 0.281g (-$N(CH_3)_2$), in methanol and o-Phenylenediamine (0.108g ,10mmol, A-series) or o-Aminothiophenol (0.125g, 10mmol, B-series) dissolved in methanol (20 mL) were placed in a round bottom flask and few drops of glacial acetic acid were added. Then the reaction mixture was refluxed for 7 hours at 70-80 °C. The resulting solution was cooled to room temperature, and then poured into ice with constant stirring. The precipitate thus obtained was filtered and washed with ethanol and diethyl ether. Further, the ligand was crystallized with hot ethanol and dried in vacuo over anhydrous $CaCl_2$. Furthermore, the metal complexes were synthesized by using these Ligands. To the 1mmol of the ligand (L^1(0.358g), L^2(0.345g), L^3(0.363g), L^4(0.372g), L^5(0.376g), L^6(0.362g), L^7(0.380g), L^8(0.389g), 1mmol) in ethanol (10mL) and zinc chloride(0.173g , 1mmol) in 2ml ethanol was dissolved separately and then mixed with continuous stirring. Further, the reaction mixture was refluxed for 6 hours and cooled at room temperature.

The solution was kept for overnight, thus the precipitate was obtained and filtered. The precipitated complex was washed several times with 10% cold ethanol, ether and then dried in vacuo over anhydrous $CaCl_2$. The complex was recrystallized in ethanol.

(E)-4-((2-aminophenyl)imino)-2-(4-methoxyphenyl)-4H-chromen-3-ol (L^1)

Yield: 78% (0.281g), Colour: Brown, m.p. 113°C IR (KBr, νcm^{-1}): 3513 (OH), 3412 (NH), 2812 (CH), 1565 (C=N), 1582 (C=C), 1236(C-O). ^{1}H NMR(400MHz, DMSO-d6): δ(ppm) 3.47 (3H, s), 6.26(2H,d, *J*=8.28), 6.39(2H, d, *J*=8.28Hz), 6.69-6.84(4H,m), 7.02-7.19 (4H, m,), 7.75 (2H, d, *J* = 8.68 Hz), 9.56(1H,s) ^{13}C (100MHz, DMSO-d6)NMR δ (ppm): 69.11, 69.11,114.24, 114.24, 115.32, 116.22, 119.48, 120.58, 120.58, 127.56, 132.99, 132.99, 137.21, 137.21, 137.87, 146.11, 146.11, 150.97, 150.97, 150.97, 152.92 Elemental analysis (%) Calc.: C, 73.73, H, 5.06, N, 7.82. Observed C, 73.75, H, 5.12, N, 7.85 ESI-MS: $[M+1]^+$ 359.39 (Observed) 358.39 (Calculated). M. F. $C_{22}H_{18}N_2O_3$ UV-vis.λ_{max}in nm(in DMSO, 2×10^{-4}M), 256, (π -π*transition), 360(n- π* transition).

(E)-4-((2-aminophenyl)imino)-2-(4-hydroxyphenyl)-4H-chromen-3-ol (L^2)

Yield: 62% (0.22g), Colour: Reddish brown, m.p. 210°C IR (KBr, νcm^{-1}): 3623 (OH & NH), 2906(CH), 1539 (C=N), 1573 (C=C), 1196(C-O). ^{1}H NMR (400MHz, DMSO-*d6*): δ (ppm) 6.98 (2H, d, *J* = 8.3, Hz), 7.06 (2H, d, *J* = 8.3, Hz), 7.28 (4H, m), 7.19-7.29 (4H, m), 7.11 (2H,s), 7.16 (2H,brs). ^{13}C (100MHz, DMSO-*d6*) NMR δ (ppm):113.74, 115.10, 115.72, 115.72, 118.65, 120.53, 123.79, 124.24, 124.77, 128.10, 129.27, 131.34, 131.42, 131.43, 136.23, 137.87, 154.36, 155.69, 155.82, 157.84,159.61 Elemental analysis (%) Calc. C, 73.24; H, 4.68; N, 8.13,Observed C, 73.76, H, 5.02, N, 8.85 ESI-MS: $[M+1]^+$ 345.36 (Observed) 344.36 (Calculated). M. F.$C_{21}H_{16}N_2O_3$, UV-vis.λ_{max}in nm(in DMSO,2×10^{-4}M),271,(π -π* transitions), 410(n- π* transition).

(E)-4-((2-aminophenyl) imino)-2-(4-chlorophenyl)-4H-chromen-3-ol (L^3)

Yield: 68% (0.25g), Colour: Brownish black, m.p. 121°C, IR (KBr, νcm^{-1}): 3569 (OH & NH), 2869(CH), 1553 (C=N), 1564(C=C), 723(C-Cl). ^{1}H NMR (400MHz, DMSO-*d6*): δ 7.03 (2H, d, *J* = 8.5, Hz), 7.19 (2H, d, *J* = 8.4Hz), 7.14 (4H, m), 7.00-7.10 (4H,m), 7.29 (2H,s), 7.51 (1H,brs). ^{13}C (100MHz, DMSO-*d6*) NMR δ (ppm): 113.74, 115.13, 118.66, 120.53, 123.79, 124.24, 124.75, 126.68, 126.70, 128.10, 128.96, 128.97, 129.25, 131.35, 135.65, 136.20, 137.87, 154.36, 155.64, 155.80, 159.59, Elemental analysis (%) Calc. C, 69.52; H, 4.17; N, 7.72 Observed C, 70.12, H, 4.42, N, 7.85 ESI-MS: $[M+1]^+$ 363.81 (Observed) 362.81 (Calculated). M. F. $C_{21}H_{15}ClN_2O_2$ UV-vis.λ_{max}in nm(in DMSO,2×10^{-4}M), 262(π -π* transitions), 385(n- π* transition).

(E)-4-((2-aminophenyl) imino)-2-(4-(dimethylamino) phenyl)-4H-chromen-3-ol (L^4)

Yield: 73% (0.27g), Colour: Brown m.p. 135°C, IR (KBr, νcm^{-1}): 3469 (OH & NH), 2879(CH), 1562 (C=N), 1664(C=C), 623(C-N). ^{1}H NMR (400MHz, DMSO-*d6*): δ 2.88 (6H, s), 6.69 (2H, d, *J* = 8.3Hz), 6.93 (2H, d, *J* = 7.5 Hz), 6.99-7.17 (4H, m), 7.24 (4H, m), 7.19-7.26 (2H, s), 7.50 (1H, brs). ^{13}CNMR (100MHz, DMSO-*d6*): δ (ppm): 40.31, 40.32, 113.71, 113.83, 113.86, 115.10, 118.63, 120.53, 123.79, 124.24, 124.75, 126.40, 126.41, 129.26, 131.32, 136.24, 137.87, 151.44, 154.36, 155.64, 159.60 Elemental analysis (%) Calc. C, 74.37; H, 5.70; N, 11.31 Observed C, 75.10, H, 5.83, N, 11.86 ESI-MS: $[M+1]^+$ 372.43 (Observed) 371.43 (Calculated). M. F. $C_{23}H_{21}N_3O_2$ UV-vis.λ_{max}in nm(in DMSO,2×10^{-4}M), 265(π -π* transitions), 440(n- π* transition),

(E)-4-((2-mercaptophenyl) imino)-2-(4-methoxyphenyl)-4H-chromen-3-ol(L^5)

Yield: 73% (0.27g), Colour: Yellowish brown m.p. 121°C, IR (KBr, νcm^{-1}): 3530 (OH), 2850(CH), 1550 (C=N), 1524 (C=C), 2562 (SH), 1247 (C-S), 1220 (C-O). ^{1}H NMR(400MHz, DMSO-*d6*): δ (ppm) 2.92 (1H, s SH), 3.95 (3H, s), 6.89 (2H, d, *J* = 8.0Hz), 7.07 (2H, d *J* = 8.0,Hz), 7.10 (4H, m), 7.17 (4H, m), 9.8 (1H, s) ^{13}C NMR (100MHz, DMSO-*d6*): δ (ppm): 55.46, 111.82, 113.72, 118.68, 120.51, 124.79, 127.12, 127.49, 127.70, 128.09, 128.10, 131.72, 131.33, 131.75, 114.44, 114.42, 144.99, 154.35, 155.66, 155.80, 159.60, 160.41 Elemental analysis (%) Calc. C, 70.38; H, 4.56; N, 3.73; S, 8.54 Found C, 70.95, H, 4.83, N, 3.96; S, 8.72 ESI-MS: $[M+1]^+$ 376.44 (Observed) 375.44 (Calculated). M. F. $C_{22}H_{17}NO_3S$. UV-vis.λ_{max}in nm(in DMSO,2×10^{-4}M), 270(π -π* transitions), 430(n- π* transition),

(E)-2-(4-hydroxyphenyl)-4-((2-mercaptophenyl) imino)-4H-chromen-3-ol(L^6)

Yield: 76% (0.28g), Colour: Brown m.p. 186°C, IR (KBr, νcm^{-1}): 3480 (OH), 2950(CH), 1565 (C=N), 1530(C=C), 2580(SH), 1241 (C-S), 1243 (C-O). ^{1}H NMR(400MHz, DMSO-*d6*): δ (ppm) 6.97 (2H, d, *J* = 8.3, Hz),

7.03 (2H, d, *J* = 8.3, Hz), 7.11 (4H,m), 7.25 (4H, m,), 9.32(2H,s, OH),2.78(1H,s SH) ^{13}C (100MHz, DMSO-*d6*)NMR δ (ppm): 111.82, 113.74, 115.74, 115.75, 118.68, 120.55, 124.80, 127.13, 127.48, 127.70, 128.10, 128.10, 131.33, 131.38, 131.39, 144.96, 154.35, 155.67, 155.80, 157.82, 159.60, Elemental analysis (%) Calc. C, 69.79; H, 4.18; N, 3.88 S, 8.87 Observed C, 70.95, H, 4.63, N, 3.96 S, 8.98 ESI-MS: $[M+1]^+$ 362.41 (Observed) 361.41 (Calculated). M. F. $C_{21}H_{15}NO_3S$. UV-vis.λ_{max}in nm(in DMSO,2×10^{-4}M), 268(π -π* transitions), 365(n- π* transition),

(E)-2-(4-chlorophenyl)-4-((2-mercaptophenyl) imino)-4H-chromen-3-ol(L^7)

Yield: 68% (0.26g), Colour: Yellowish Brown m.p. 132°C IR (KBr, νcm^{-1}): 3480 (OH), 2950(CH), 1565 (C=N), 1530(C=C), 2580(SH), 1239 (C-S), 1243 (C-O).^{1}H NMR(400MHz, DMSO-*d6*): δ (ppm) 6.90 (2H, d, *J* = 7.9, Hz), 7.00 (2H, d, *J* = 8.3, Hz), 7.14 (4H, m,), 7.26 (4H,m), 9.57 (1H, s, OH), 3.00(1H,s, SH) ^{13}C (100MHz, DMSO-*d6*)NMR δ (ppm): 111.82, 113.72, 118.62, 120.51 124.78, 126.71, 126.72, 127.01, 127.49, 127.71, 128.10, 128.10, 128.96, 128.97, 131.34, 135.68, 144.98, 154.36, 155.66, 155.81, 159.60. Elemental analysis (%) Calc. C, 66.40, H, 3.71; N, 3.69,Cl, 9.33 S, 8.44 Observed C, 66.95, H, 3.83, N, 3.96 Cl, 9.47 S, 8.52ESI-MS: $[M+1]^+$ 380.86 (Observed) 379.86 (Calculated).M. F. $C_{21}H_{14}ClNO_2S$, UV-vis.λ_{max}in nm(in DMSO,2×10^{-4}M), 275(π -π* transitions), 355(n- π* transition)

(E)-2-(4-(dimethylamino)phenyl)-4-((2-mercaptophenyl)imino)-4H-chromen-3-ol(L^8)

Yield: 66% (0.26g), Colour: Reddish Brown m.p. 145°C IR (KBr, νcm^{-1}): 3464 (OH), 2897(CH), 1523 (C=N), 1578(C=C), 2571(SH), 1235 (C-S), 1206 (C-O), 1277(C-N). ^{1}H NMR (400MHz, DMSO-*d6*): δ (ppm) 2.89 (6H, s), 6.61 (2H, d, *J* = 8.8 Hz), 7.04 (2H, d, *J* = 7.5Hz), 7.40-7.56 (4H,m), 7.31 (4H,m)), 2.86 (1H, s, SH), 9.93 (1H, s, OH) ^{13}C (100MHz, DMSO-*d6*)NMR δ (ppm):40.31, 40.31, 111.78, 118.66, 113.77, 113.84, 113.84, 120.53, 124.75, 126.42, 126.44, 127.11, 127.49, 127.69, 128.09, 128.10, 131.34, 144.99, 151.40, 154.34, 155.68, 155.81, 159.59. Elemental analysis (%) Calc. C, 71.11; H, 5.19; N, 7.21 S, 8.25Observed C, 71.75, H, 5.63, N, 7.77; S, 8.68 ESI-MS: $[M+1]^+$ 389.48 (Observed) 388.48 (Calculated).M. F. $C_{23}H_{20}N_2O_2S$ UV-vis.λ_{max}in nm(in DMSO,2×10^{-4}M) 273(π -π* transitions), 347(n- π* transition).

(E)-((4-(2-Aminophenyl)imino)-2-(4-methoxyphenyl)-4H-chromen-3-yl)oxy)zinc hydrate(2I-1)

Colour: Yellow; Yield 65%, m. p. >230^{o}C. IR (KBr, vcm^{-1}): 3441(OH), 3418(OH), 3356 (NH) 2859(CH), 1557 (C=N), 1548 (C=C), 1298 (C-O). ^{1}H-NMR (DMSO-*d6*, 400 MHz, 25^{o}C, TMS): δ (ppm). 5.24 (s, 2H), 6.37-6.39(2H, d, *J*=8.86) 7.85(2H, d, *J*=8.86), 7.00-9.80 (m, Ar-H); Elemental analysis (%) Calc.: C, 59.95, H, 4.34, N, 6.36, Zn, 14.83. Observed C, 60.34, H, 4.72, N, 6.75, Zn, 14.83. ForESI-MS: $[M+1]^+$ 441.78 (Observed) 440.78 (Calculated). M. F. $C_{22}H_{19}N_2O_4ZnUV$-Vis.λ_{max}in nm(in DMSO,2×10^{-4}M), 260 (π -π*transition), 510(n- π* transition).

(E)-((4-((2-Aminophenyl)imino)-2-(4-hydroxyphenyl)-4H-chromen-3-yl)oxy)zinc hydrate (2I-2)

Colour: Light Yellow; Yield 60%, m. p. >360^{o}C. IR (KBr, vcm^{-1}): 3440(OH), 3419(OH), 2837(CH), 1563 (C=N), 1629 (C=C), 1302 (C-O). ^{1}H-NMR (DMSO-*d6*, 400 MHz, 25^{o}C, TMS): δ (ppm). 5.59 (s, 2H),6.38-7.02(2H, d, *J*=8.28) 6.86-8.96 (m, Ar-H); Elemental analysis (%) Calc.: C, 59.10, H, 4.02, N, 6.56, Zn, 15.32. Observed C, 60.34, H, 4.32, N, 6.75, Zn, 15.83. For ESI-MS: $[M+1]^+$427.75 (Observed) 426.75 (Calculated). M. F. $C_{21}H_{17}N_2O_4Zn$ UV-vis. λ_{max}in nm (in DMSO,10^{-3}M), 275,(π -π* transitions), 535(n- π* transition).

(E)-((4-((2-Aminophenyl)imino)-2-(4-chlorophenyl)-4H-chromen-3-yl)oxy)zinc hydrate (2I-3)

Colour: Yellowish brown; Yield 55%, m. p. >300^{o}C. IR (KBr, vcm^{-1}): 3486 (OH), 3033 (CH), 1585 (C=N), 1624 (C=C), 1314 (C-O). ^{1}H-NMR (DMSO-*d6*, 400 MHz, 25^{o}C, TMS): δ (ppm). 7.3 (s, 2H), 9.78 (s, OH), 7.46-9.23 (m, Ar-H); Elemental analysis (%) Calc.: C, 56.65, H, 3.62, N, 6.29,Cl, 7.96, Zn, 14.69. Observed C, 56.93, H, 3.95, N, 6.66, Zn, 15.03. For ESI-MS: $[M+1]^+$ 446.20 (Observed) 445.20 (Calculated). M. F. $C_{21}H_{16}ClN_2O_3ZnUV$-vis. (λ_{max} nm in DMSO,2×10^{-4}M), 271(π -π* transitions), 505(n- π* transition).

(E)-((4-((2-Aminophenyl)imino)-2-(4-dimethylamino)phenyl)-4H-chromen-3-yl)oxy)zinc hydrate(2I-4)

Colour: Yellow; Yield 62%, m. p. >280^{o}C. . IR (KBr, vcm^{-1}): 3438(OH), 3420(OH), 3021 (CH), 1585 (C=N), 1654 (C=C), 1296 (C-O). ^{1}H-NMR (DMSO-*d6*, 400 MHz, 25^{o}C, TMS): δ (ppm). 2.68(s, 6H),6.02 (s, 2H), 7.16-9.86 (m, Ar-H); Elemental analysis (%) Calc.: C, 56.65, H, 4.89, N, 9.26, Zn, 14.41. Observed C, 56.74, H, 4.92, N, 9.35, Zn, 14.60. For ESI-MS: $[M+1]^+$ 454.82(Observed) 453.82 (Calculated). M. F. $C_{23}H_{22}N_3O_3Zn$(λ_{max} nm in DMSO,2×10^{-4}M), 272(π -π* transitions), 526(n- π* transition).

(E)-((4-((2-mercaptophenyl)imino)-2-(4-methoxyphenyl)-4H-chromen-3-yl)oxy)zinc hydrate(2I-5)
Colour: Yellow; Yield 66%, m. p. >360°C. IR (KBr, vcm^{-1}): 3441(OH), 3418(OH), 2890(CH), 1590 (C=N), 1564 (C=C), 1293 (C-S), 1297 (C-O). 1H-NMR (DMSO-*d6*, 400 MHz, 25°C, TMS): δ (ppm). 5.8 (1H, s) 10.42 (s, OH), 6.96-9.36 (m, Ar-H); Elemental analysis (%) Calc.: C, 59.10, H, 4.02, N, 6.56, Zn, 15.32. Observed C, 60.34, H, 4.32, N, 6.75, Zn, 15.83. For ESI-MS: $[M+1]^+$ 477.83 (Observed) 476.83 (Calculated). M. F. $C_{22}H_{21}NO_5SZn$ UV-vis. (λ_{max} nm in DMSO,2×10^{-4}M), 273(π -π* transitions), 516(n-π* transition).

(E)-((2-(4-Hydroxyphenyl)-4-((2-mercaptophenyl)imino)-4H-chromen-3-yl)oxy)zinc hydrate (2I-6)
Colour: Brown; Yield 67%, m. p. >290°C. IR (KBr, vcm^{-1}): 3440(OH), 3419(OH), 2990(CH), 1576 (C=N), 1614 (C=C), 1281 (C-S), 1307 (C-O). 1H-NMR (DMSO-d6, 400 MHz, 25°C, TMS): δ (ppm). 5.43 (1H, s) 9.78 (s, OH), 6.96-8.93 (m, Ar-H); Elemental analysis (%) Calc.: C, 57.84, H, 3.75, N, 3.07, Zn, 14.31. Observed C, 57.92, H, 3.82, N, 3.25, Zn, 14.44. For ESI-MS: $[M+1]^+$ 457.82 (Observed) 456.82 (Calculated). M. F. $C_{22}H_{17}NO_4SZn$ UV-vis. λ_{max}in nm (DMSO,2×10^{-4}M), 270(π -π* transitions), 503(n-π* transition).

(E)-((2-(4-(Chlorophenyl)-4-((2-mercaptophenyl)imino)-4H-chromen-3-yl)oxy)zinc hydrate (2I-7)
Colour: Light Yellow; Yield 57%, m. p. >320°C. IR (KBr, vcm^{-1}): 3439OH), 3419(OH), 2870(CH), 1570 (C=N), 1627 (C=C), 1274 (C-S), 1316 (C-O). 1H-NMR (DMSO-d6, 400 MHz, 25°C, TMS): δ (ppm). 4.43 (1H, s) 9.58 (s, OH), 6.72-8.82 (m, Ar-H); Elemental analysis (%) Calc.: C, 54.68, H, 3.06, N, 3.04,Cl, 7.69, Zn, 14.17. Observed C, 54.74, H, 3.22, N, 3.15, Zn, 14.23. For ESI-MS: $[M+1]^+$ 462.24 (Observed) 461.24 (Calculated). M. F. $C_{21}H_{14}ClNO_3SZn$, UV-vis. λ_{max}in nm(in DMSO,2×10^{-4}M), 277(π -π* transitions), 515(n-π* transition)

(E)-((2-(4-Dimethylamino)phenyl)-4-((2-mercaptophenyl)imino)-4H-chromen-3-yl)oxy)zinc hydrate (2I-8)
Colour: Brown; Yield 53%, m. p. >310°C. IR (KBr, vcm^{-1}): 3440(OH), 3419(OH), 2965(CH), 1562 (C=N), 1579 (C=C), 1263 (C-S), 1309 (C-O). 1H-NMR (DMSO-*d6*, 400 MHz, 25°C, TMS): δ (ppm). 3.31 (6H, s), 5.62 (1H, s) 10.28 (s, OH), 7.52-9.87 (m, Ar-H); Elemental analysis (%) Calc.: C, 58.79, H, 4.29, N, 5.96, S, 6.82, Zn, 13.91. Observed C, 58.84, H, 4.32, N, 6.03, Zn, 13.93. For ESI-MS: $[M+1]^+$ 470.86 (Observed) 469.86 (Calculated). M. F. $C_{23}H_{20}N_2O_3SZn$UV-vis.λ_{max}in nm (in DMSO,2×10^{-4}M) 274(π -π* transitions), 507(n-π* transition).

RESULT AND DISCUSSION

The analytical and spectroscopic data obtained for synthesized Zn(II)complexesshows that all are mononuclear tetrahedral of type [ZnLH$_2$O] (where L=L$^{1\text{-}8}$ tridentate3-hydroxy substituted flavone ligands). The analytical data obtained for new complexes (2I-1 to 2I-8) were agreed well with the proposed molecular formulae.

Spectroscopic Studies

FT-IR Spectra

The reaction of substituted 3-hydroxy flavone ligands (L) with Zn (II) metal ion produced new series of mononuclear tetrahedral metal complexes. The band of ligands was compared with those of complexes in order to infer the coordination mode. The spectrum of ligands was given in experimental section (L^1 to L^8& 2I-1 to 2I-8). The stretching frequency of eight ligands ν(O-H)phenolic, ν(N-H),ν(C=N), ν(C-O)phenolic, ν(C-S), ν(C-N)andν(S-H) were observed at 3500-3600 cm^{-1},3370-3450 cm^{-1}(5I-8I), 1600-1625cm^{-1}, 1250-1300cm^{-1}, 1230-1250cm^{-1}, 1175-1225cm^{-1} and 2500-2550cm^{-1} respectively. In all complexes, the νC=N band is shifted to lower frequency, 1550-1590 cm^{-1}, indicating coordination of ligands through azomethine N-atom. A strong band, observed at 1250-1300 in the free imino flavones is due to phenolic C-O stretching. In complexes, the C-Ostretching vibration appears at higher frequency 1290-1320 cm^{-1} inferred coordination occurs through the phenolic O-atom. Moreover, the absorption due to ν(C-S) of the ligand(L^5 to L^8) at 1230-1250 cm^{-1} shifted to 1260-1296 cm^{-1}(2I-5 to 2I-8) and the absorption due to ν(C-N) of the ligands (L^1 to L^4) at 1175-1225 cm^{-1} shifted to 1210-1260 cm^{-1} in the complexes indicates the coordination through phenolic S and N atom. The disappearance of absoption bands due to ν(O-H) andν(S-H) in the complexes occurred during co-ordination shows de-protonation of phenolic and thiophenolic protons.

The Zn (II) complexes exhibit a broad band around 3440 and 3419 cm^{-1} respectively, which can be assigned to ν(O-H) of water molecule co-ordinated with the metal ion. The new bands appeared in the metal complexesin the region 515-755 cm^{-1},410-578 $cm^{-1}$and 444-482 cm^{-1} are attributed to ν(M-N), ν(M-O) and ν(M-S) respectively. On the basis of vibrational bands it is inferred that the ligands are behaving as a monobasic (L^1 to L^4) and dibasic (L^5 to L^8) tridentate ligands.

^{1}HNMR Spectra

The ^{1}HNMR spectra of ligands and complexes were recorded in DMSO –*d6*.The protons of flavone derivatives appeared in the regionδ 6.90-9.98, δ 3.20-3.80, δ 2.2-2.9, δ 8.90-9.83,δ 3.0-5.0 and δ 2.5-3.5of Ar-H, -OCH_3(2F-1, 2H-1&2I-1, 2I-5), -NCH_3(2F-3, 2H-3 and 2I-3, 2I-8), -OH, and SH (2H-1 to 2H-4) respectively. In the complexes, aromatic protons shifted from δ 6.90-9.98 toδ 6.35-8.76. The phenolic and thiophenolic proton of the ligands disappeared in the complexes. This indicates the involvement of phenolic (-OH) group and (-SH) group in the bond formation moiety. The C-N-H protons shifted from δ3.0-5.0 to δ 2.6-4.5, indicate coordination of N of amino group with Zn (II) metal ion.

Electronic spectra

The UV–visible spectral bands of the ligands and their complexes were recorded in DMSO, 2×10^{-4}M solution. Ligands L^1-L^8 show absorption maxima (λ_{max}in nm) at 256, 271, 262, 265, 270, 268, 275 and 273 respectively due to π -π* transitions and band of lower energy at 360, 410, 385, 430,440, 365, 355 and 347 due to *n*- π* transition of azomethine linkage. These bands due to π -π* are almost unchanged in the spectra of the complex. The *n*-π* transition has shown bathochromic shift due to the donation of a lone pair of electron of azomethine N to the Zn(II). The shifts in ligands band are the evidence for coordination of azomethine. Further, the new absorption band in complexes at 503nm to 535 nm are attributed to charge transfer transition from ligand to Zn (L→M).Zn(II) complexes do not exhibit d-d electronic transition due to completely filled d-orbital. All four coordinated Zn(II) complexes would have tetrahedral geometry.

Table 1. *In vitro* antibacterial activity of Zinc complexes of flavone derivatives.

Minimum inhibitory concentration (MIC) in µg/mL					
Compounds	4-Substituent	Ligand	Gram Positive bacteria	Gram Negative bacteria	
			S. aureus	*E. coli*	*S. typhi*
2I-1	-OCH_3	L^1	>200	>100	100
2I-2	-OH	L^2	>100	>200	>200
2I-3	-$N(CH_3)_2$	L^3	75	50	25
2I-4	-Cl	L^4	**10.5**	100	**11.5**
2I-5	-OCH_3	L^5	50	75	50
2I-6	-OH	L^6	25	>100	25
2I-7	-$N(CH_3)_2$	L^7	50	25	75
2I-8	-Cl	L^8	100	**9.5**	100
Ciprofloxacin			12.5	12.5	12.5

Biological Evaluation

The antimicrobial screening of all synthesized Zinc complexes of flavone derivatives have exhibited moderate to good antimicrobial activities with respect to standard drugs. The screening results of these compounds are summarized in Table 1 and 2.The minimum inhibitory concentration of compound 2I-4 was 10.5 and 11.5 µg/mL against *S. aureus* and *S. typhi* and 2I-8 was 9.5µg/mL against *E.coli*. However, 2I-4 has 9.75 and 4.75 µg/mL against *C. albicans* and *2I-8* has 8.5and 3.75µg/mL against *A. Flavus*. The *in vitro* antimicrobial screened compounds, the 2I-4 and 2I-8 were displayed excellent antibacterial and antifungal activities as compared to standard drug ciprofloxacin and fluconazole. This may be due to chlorine group present at para position of phenyl ring in the complex. The antimicrobial studies of the substituted flavone derivatives and their complexes along with the standard drugs, indicates that the Zn(II)complexes exhibited higher antibacterial and antifungal activities.

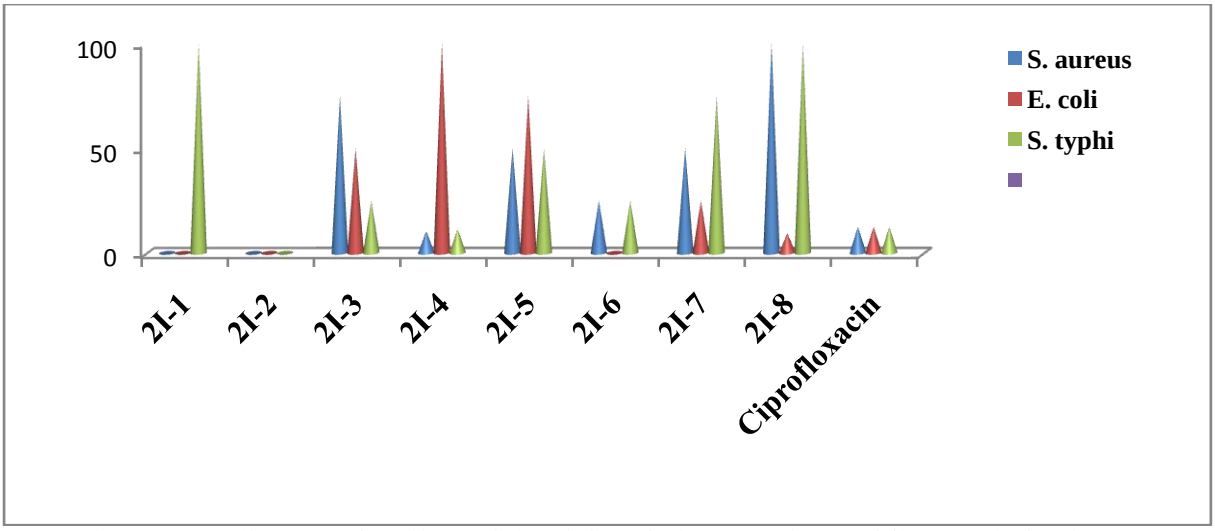


Figure 1. Bardiagram of antibacterial activity of Zinc complexes of flavone derivatives.

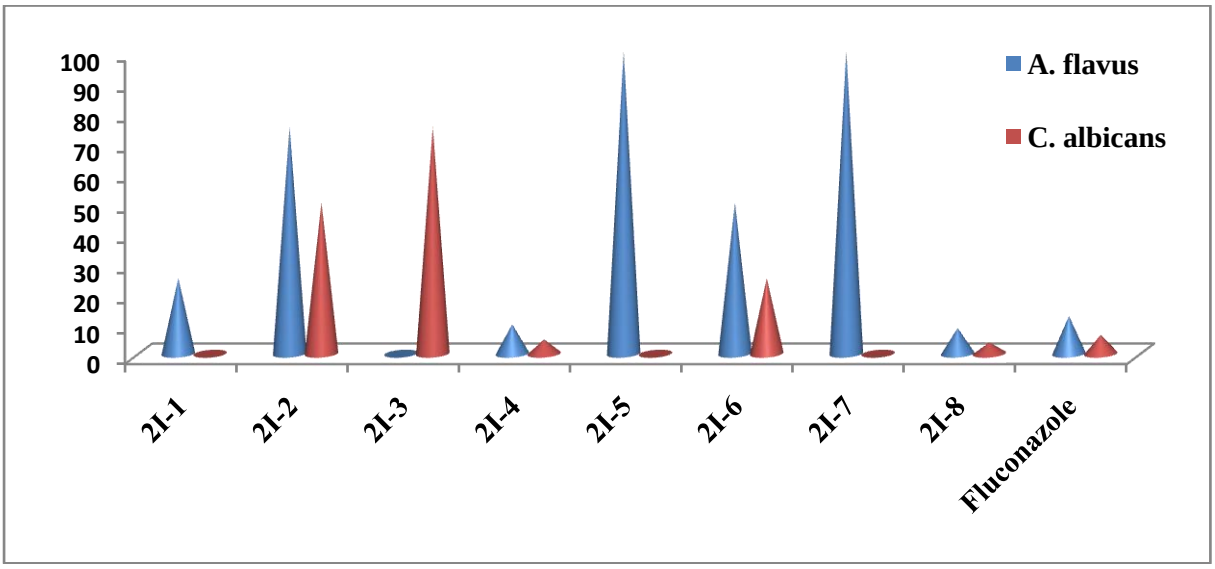


Figure 2. Bardiagram of antifungal activity of Zinc complexes of flavone derivatives.

Table 2. *In vitro* antifungal activity of Zinc complexes of flavone derivatives derivatives.

Minimum inhibitory concentration (MIC) in µg/mL				
Compounds	**X**	**Ligand**	***A. flavus***	***C. albicans***
2I-1	X = OCH_3	L^1	25	>100
2I-2	X = OH	L^2	75	50
2I-3	X = $N(CH_3)_2$	L^3	>100	75
2I-4	X =Cl	L^4	**9.75**	**4.75**
2I-5	X = OCH_3	L^5	100	>100
2I-6	X = OH	L^6	50	25
2I-7	X = $N(CH_3)_2$	L^7	100	>100
2I-8	X =Cl	L^8	**8.5**	**3.75**
Fluconazole			12.5	12.5

Thus, the increase in the antibacterial and antifungal activities of complexes was found on the basis of overlap of the ligand orbital and partial sharing of positive charges of metal ion with donorgroups. Further, the delocalization of electrons over the chelate ring enhanced the lipophillicity of the complexes. This increase lipophillicity enhanced the penetration of the complexes into lipid membrane and blocking the metal sites on enzymes of microorganism.

CONCLUSION

Tridentate flavone derivative ligands (L^1 to L^8) and their Zn(II) complexes (2I-1 to 2I-8) were synthesized and characterized by spectroscopic methods. The flavone derivative ligands and Zn(II) complexes were screened for the antibacterial and antifungal activities by the micro dilution method. The result of antimicrobial activities show that the Zn(II) complexes and the ligands exhibit antimicrobial properties and it is important to note that Zn(II) complexes show enhance activity compared with parent flavone derivative ligands.

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