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Journal of Enzyme Inhibition and Medicinal Chemistry

ISSN: 1475-6366 (Print) 1475-6374 (Online) Journal homepage: informahealthcare.com/journals/ienz20

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To cite this article: Pramod B. Pansuriya, Pinakin Dhandhukia, Vasudev Thakkar & Mohan N. Patel (2007) Synthesis, spectroscopic and biological aspects of iron(II) complexes, Journal of Enzyme Inhibition and Medicinal Chemistry, 22:4, 477-487, DOI: 10.1080/14756360701228988

To link to this article: https://doi.org/10.1080/14756360701228988

Journal of Enzyme Inhibition and Medicinal Chemistry, August 2007; 22(4): 477–487

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Synthesis, spectroscopic and biological aspects of iron(II) complexes

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(Received 31 August 2006; in final form 10 December 2006)

Abstract

Five novel coordinated complexes of iron(II) with ciprofloxacin and neutral bidentate ligands have been prepared and characterized using elemental analyses, magnetic measurements, IR spectra, UV-VIS spectral, thermogravimetric analyses, ^{1}H-NMR and ^{13}C-NMR. The antimicrobial activity of the individual ligands, metal salt and metal complexes with respect to *Bacillus subtilis, Escherichia coli, Bacillus cereus, Staphylococcus aureus, Salmonella typhi, Serratia marcescens, Aspergillus niger, Aspergillus flavus and Lasiodiplodia theobromae* were evaluated by the agar-plate technique in comparison to reference standard drugs (ofloxacin, levofloxacin and fluconozole). Binding of the complexes to DNA was studied and is discussed.

Keywords: *Ciprofloxacin, quinolone-iron(II) complexes, Schiff bases, antimicrobial activity*

Introduction

Metal ions such as iron(II) and (III) are necessary for a number of vital functions in life sciences [1]. Iron complexes are known to be models for two stages of ferritin iron storage and biomineralization [2]. Iron is the central atom of the heme complex, which is made of photoporphyrin IX and iron(II) [3]. Apart from the porphyrins, a number of iron complexing ligands are found in aerobic microbial cells [4–5]. Discovery of quinolones was reported in 1962 and subsequently due to its mode of action, chemical design and potential antimicrobial activity more than 10000 compounds related to this fluoroquinolone group have been launched as clinical drugs. Quinolones antibiotics are complexing agents for a variety of metal ions including alkaline earth metal ions [6]. Many organic compounds used in medicine do not have a purely organic mode of action; some are activated or biotransformed by metal ions, others have a direct or indirect effect on metal ion metabolism [7]. Even though the quinolone family has been widely studied there is no evidence for a precise mechanism of its action. Some reports suggest that the drugs interacts directly with DNA, blocks the activity of the DNA-gyrase repair enzyme [8] or intercalate with the purine/pyrimidine bases of nucleic acids [9]. *d*-Block metals are also well known to cleave and to bind DNA as only metal or as their complexes with different ligands [10–12]. Several iron chelates have been reported for application in the treatment of thalassaemia, other transfusion-dependent diseases [13], and also used as MRI contrast agents [14]. Several iron complexes are well known for their antibacterial, antifungal and biomimetic activity [15–18] and here, five novel iron(II) complexes are examined for their antibacterial DNA-interactive activity.

Materials and methods

All the chemicals used were of analytical grade. 2,2′-Bipyridylamine (bipym), 1,8-diaminonaphthalene, and thiophene-*2*-carboxaldehyde were purchased from Lancaster (Morecambe, England). Ciprofloxacin

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ISSN 1475-6366 print/ISSN 1475-6374 online © 2007 Informa UK Ltd.
DOI: 10.1080/14756360701228988

hydrochloride was from Bayer AG (Wyppertal, Germany). 2-Aminopyridine, benzaldehyde, ethylenediamine, 3-chloro aniline, cyclohexanone, *o*-phenylenediamine, *p*-anisaldehyde and cupric nitrate were from E. Merck (India) Ltd. Mumbai, Luria broth and agar-agar were from SRL, India and Sperm herring DNA was from Sigma Chemical Co., India. The organic solvents were purified by standard methods [19].

Infrared spectra were recorded on a FT-IR Shimadzu spectrophotometer as KBr pellets in the range 4000–400 cm^{-1}. C, H and N elemental analyses were performed with a model 240 Perkin Elmer elemental analyzer. The reflectance spectra of the complexes were recorded in the range 1700–350 nm (as MgO discs) on a Beckman DK-2A spectrophotometer. The metal contents of the complexes were analyzed by EDTA titration [25] after decomposing the organic matter with a mixture of $HClO_4$, H_2SO_4, and HNO_3 (1:1.5:2.5). Thermogravimetric analyses studies were obtained with a model 5000/2960 SDTA, TA instrument (USA). The ^{1}H-NMR and ^{13}C-NMR was recorded on a Bruker Avance (400 MHz). The electronic spectra were recorded on a Shimadzu UV-VIS spectrophotometer. The magnetic moments were measured by Gouy's method using mercury tetrathiocyanatocobaltate(II) as the calibrant ($\chi_g = 16.44 \times 10^{-6}$ cgs units at 20°C), Citizen Balance. The diamagnetic correction was made using Pascal's constant [26].

Chemistry

Preparation of Schiff bases

Benzylidene-2-aminopyridine (A^2=bap). 2-Aminopyridine (0.94 g, 10 mmol) in ethanol was added slowly to benzaldehyde (1.06 g, 10 mmol) in ethanol (~100 mL) and the mixture refluxed on a bath for 6 h, the solution concentrated to half volume and kept overnight under vacuum over P_2O_5. The separated ligand was washed with n-hexane and air-dried. Yield: 58%, m.p.: 142°C, Found %: C, 78.93; H, 5.47; N, 15.15. $C_{12}H_{10}N_2$ (182.22) requires %: C, 79.10; H, 5.53; N, 15.37.

Thiophene-2-carboxaldeneaniline (A^3=tca). Thiophene-*o*-carboxaldeneaniline was synthesized by the reported procedure [20].

Bis(benzylidene)-1,8-diaminonaphthalene (A^4=bendan). Bis(benzylidene)-1,8-diaminonaphthalene was synthesized by the reported procedure [21].

Bis(benzylidene)ethylenediamine (A^5=benen). Bis (benzylidene)-ethylenediamine(benen) was synthesized according to the published procedure [22].

N,N′-Bis-(4-methoxybenzylidene)-benzene-1,2-diamine (A^6=bmbbd). *p*-Anisaldehyde (2.72 g, 20 mmol) in ethanol was added drop wise to an ethanolic solution of *o*-phenylenediamine (1.08 g, 10 mmol) and refluxed on a water bath for 8 h. Fine yellow crystalline particles were obtained on filtration, which were further crystallized in ethanol, washed with n-hexane and air-dried. Yield: 45%, m.p.: 210°C, Found %: C, 76.72; H, 5.81; N, 8.09. $C_{22}H_{20}N_2O_2$ (344.41) requires %: C, 76.72; H, 5.85; N, 8.13%.

N,N′-Bis-(3-chlorophenyl)-1,2-diphenylethane-1,2-diimine(A^7=bcpded). An ethanolic solution of benzil (2.10 g, 10 mmol) and 3-chloroaniline (2.54 g, 20 mmol) was refluxed on a water bath for 24 h, concentrated to one third volume and kept overnight over sulfuric acid in a desiccator. The fine crystalline particles obtained on filtration were washed with ether : hexane (1:1) and air-dried. Yield: 56%, m.p.: 230°C, Found %: C, 72.93; H, 4.47; N, 16.15. $C_{26}H_{18}Cl_2N_2$ (429.34) requires %: C, 72.73; H, 4.23; N, 16.51%.

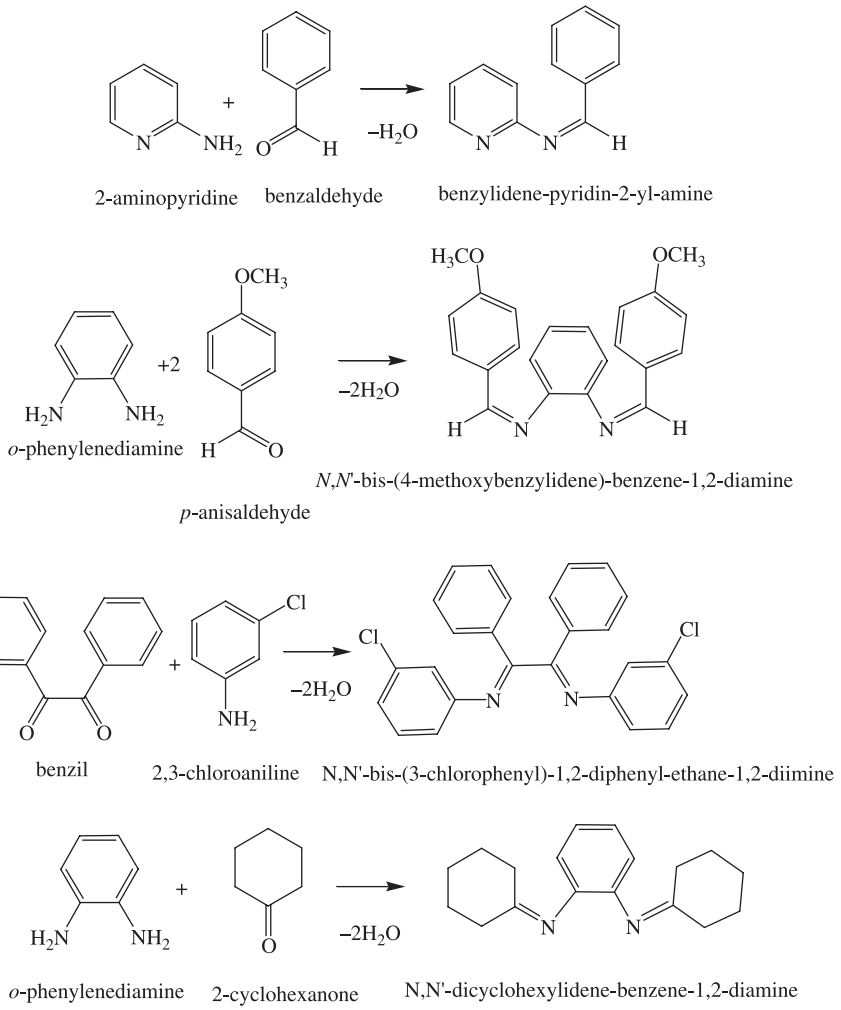
N,N′-Dicyclohexylidenebenzene-1,2-diamine (A^8=dcbd). An ethanolic solution of cyclohexanone (1.96 g, 20 mmol) was added to *o*-phenylenediamine (1.08 g, 10 mmol) in ethanol. The mixture was stirred continuously for 4 h when fine yellow crystalline particles were obtained which were washed with n-hexane and air-dried. Yield: 68%, m.p.:135°C, Found %: C, 80.47; H, 8.93; N, 10.40. $C_{18}H_{24}N_2$ (268.40) requires %: C, 80.55; H, 9.01; N, 10.44%. The reaction schemes for the preparation of the ligands are shown in Scheme 1.

Synthesis of metal complexes

[Fe_2(Cip)$_2$(bipym)$_2$(pip)]·5H_2O (I). A methanolic solution of $FeSO_4 \cdot 7H_2O$ (2.78 g, 10 mmol) was added to bipym (1.71 g, 10 mmol) in methanol, followed by addition of a previously prepared solution of Cpf·HCl (3.67 g, 10 mmol) in water and the pH was adjusted to 4.5 ~ 6.0 pH with dilute HNO_3 or NaOH solution. During reaction the piperazine ring of ciprofloxacin was substituted by chloride ion in the presence of NaOH solution [23]. The resulting red solution was refluxed for 5 h, heated on a steam bath for 3–4 h, and then was kept overnight at room temperature. A fine colored crystalline product was obtained which was washed with ether and dried in a vacuum desiccator. Yield: 75%, m.p.: 352°C, Found %: C, 50.29; H, 4.31; N, 11.83; Fe, 9.40. $C_{50}H_{52}Cl_2F_2Fe_2N_{10}O_{11}$ (1189.60) requires %: C, 50.48; H, 4.41; N, 11.77; Fe, 9.39%.

The proposed reaction scheme for the preparation of the complex is shown in Scheme 2.

[Fe_2(Cip)$_2$(bap)$_2$(pip)]5H_2O (II). Prepared from bap (1.82 g, 10 mmol). Yield: 65%, m.p.: 210°C,



Scheme 1. Synthesis of ligands.

Found %: C, 53.48; H, 4.51; N, 9.19; Fe, 9.20. $C_{54}H_{54}Cl_2F_2Fe_2N_8O_{11}$ (1211.65) requires %: C, 53.53; H, 4.49; N, 9.25; Fe, 9.22.

[Fe_2(Cip)$_2$(tca)$_2$(pip)]·5H_2O (III). Prepared from tca (1.87 g, 10 mmol). Yield: 60%, m.p.: >360°C, Found %: C, 51.07; H, 4.18; N, 6.91; Fe, 9.15. $C_{52}H_{52}Cl_2F_2Fe_2N_6O_{11}S_2$ (1221.73) requires %: C, 51.12; H, 4.29; N, 6.88; Fe, 9.14.

[Fe_2(Cip)$_2$(bendan)$_2$(pip)]·5H_2O (IV). Prepared from bendan (3.34 g, 10 mmol). Yield: 57%, m.p.: 305°C, Found %: C, 61.70; H, 4.62; N, 7.44; Fe, 7.35. $C_{78}H_{70}Cl_2F_2Fe_2N_8O_{11}$ (1516.03) requires %: C, 61.80; H, 4.65; N, 7.39; Fe, 7.37.

[Fe_2(Cip)$_2$(benen)$_2$(pip)]·5H_2O (V). Prepared from benen (2.36 g, 10 mmol). Yield: 56%, m.p.: 303°C, Found %: C, 56.46; H, 4.98; N, 8.45; Fe, 8.49. $C_{62}H_{66}Cl_2F_2Fe_2N_8O_{11}$ (1319.83) requires %: C, 56.42; H, 5.04; N, 8.49; Fe, 8.46.

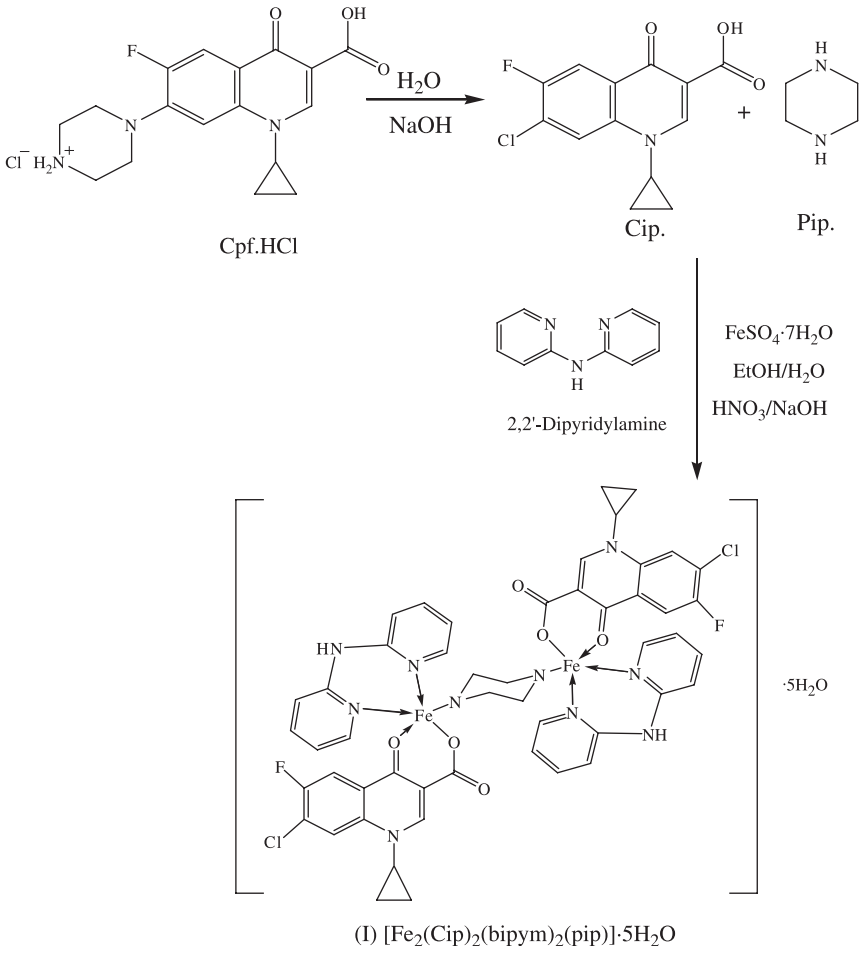
[Fe_2(Cip)$_2$(bmbbd)$_2$(pip)]·5H_2O (VI). Prepared from bmbbd (3.44 g, 10 mmol). Yield: 59%, m.p.: 230°C, Found %: C, 57.77; H, 4.90; N, 7.34; Fe, 7.21. $C_{74}H_{74}Cl_2F_2Fe_2N_8O_{15}$ (1536.02) requires %: C, 57.86; H, 4.86; N, 7.30; Fe, 7.27.

[Fe_2(Cip)$_2$(bcpded)$_2$(pip)]·5H_2O (VII). Prepared from bcpded (4.29 g, 10 mmol). Yield: 50%, m.p.: 300°C, Found %: C, 57.69; H, 4.05; N, 6.51; Fe, 6.48. $C_{82}H_{70}Cl_6F_2Fe_2N_8O_{11}$ (1705.88) requires %: C, 57.73; H, 4.14; N, 6.57; Fe, 6.55.

[Fe_2(Cip)$_2$(dcbd)$_2$(pip)]·5H_2O (VIII). Prepared from dcbd (2.68 g, 10 mmol). Yield: 58%, m.p.: 180°C, Found %: C, 57.14; H, 6.02; N, 8.07; Fe, 7.97. $C_{66}H_{82}Cl_2F_2Fe_2N_8O_{11}$ (1384.00) requires %: C, 57.28; H, 5.97; N, 8.10; Fe, 8.07.

In-vitro antimicrobial study

Preparation of stock solution. A stock solution of 2.5 ppm was made in 5% DMSO solution.



Scheme 2. Proposed reactions for the dimeric complex formation.

Determination of MIC value. The antimicrobial screening concentration to be used was estimated from the minimal inhibitory concentration (MIC). MIC was determined using the method of progressive double dilution in liquid media containing 1ppm to 50ppm of the compound being tested. All the compounds were more effective with MIC value at 2.5ppm $\approx$ 2.5μg/mL. Consequently the biological screening on solid media of all the compounds was carried out at this MIC (2.5μg/mL) and the results are expressed as zone of inhibition in mm. The antimicrobial activity using the Agar-Plate technique [24] of ofloxacin, levofloxacin, fluconozole, ligands, $FeSO_4 \cdot 7H_2O$, and the complexes were analyzed against various gram-negative and gram-positive microbial cultures of *Staphylococcus aureus, Bacillus subtilis, Bacillus cereus, Salmonella typhi, Escherichia coli and Serratia marcescens* and three fungi cultures namely *Aspergillus niger, Aspergillus flavus, Lasiodiplodia theobromae.*

Preparation of agar plates. The media was made up by dissolving bacteriological agar (20 gm) and Luria broth (20 gm) in 1 L distilled water. The mixture was autoclave for 15 minutes at 120 °C and then dispensed into sterilized petri dishes, allowed to solidify, and then inoculated.

Inoculation procedure. The target microorganism cultures were prepared separately in 15 mL of liquid LB medium. Inoculation was done with the help of a micropipette with sterilized tip; 100 μL of culture was placed onto the surface of an agar plate, and spread evenly over the surface by means of a sterile, bent glass rod. Then two wells (d = 10 mm) were based in each plate with a sterilized borer.

Application of discs. Sterilized stock solutions (2.5μg/mL) were applied on discs in the wells of the inoculated agar plates which were then incubated at 37 °C for 24 h. The zone of inhibition was then measured (in mm) around the disc and the results are shown in Table IV. Control experiments were performed with only equivalent volume of solvents without added test compounds. All experiments were performed in triplicate and ofloxacin, levofloxacin,

and fluconozole were used as a standard drug. The growth was compared with the control and is expressed as zone of inhibition.

Absorption titration

The DNA binding affinity study was performed on a UV-VIS spectrophotometer. Absorption titration of compounds in DMSO, and the whole system in buffer (phosphate, pH 7.2) was done by keeping fixed the amount of the iron complexes (where compound: I=11.89, II=12.11, III=12.21, IV=15.16, V=13.19, VI=15.36, VII=17.05, VIII=13.84 μgm) and varying the amount of DNA i.e. 3 − 7 μgm. Compound-DNA solutions were employed to record absorption spectra.

Results and discussion

Chemistry

The Schiff bases A^2–A^8 were prepared by condensation of the amine and aldehyde/ketone in ethanol. The structural characterizations of all Schiff bases have been done using IR spectra, ^{1}H- and ^{13}C-NMR spectra, and elemental analyses (Table I). The complexes under investigation have been characterized using IR spectra, magnetic measurements and electronic spectra and their data are presented in Tables II and III. All the complexes were insoluble in ether, hexane, chloroform, while partially soluble in water, methanol and dimethyl formamide, but were completely soluble in dimethyl sulphoxide.

^{1}H- and ^{13}C-NMR spectra of Schiff bases. The ^{13}C-NMR spectra and ^{1}H-NMR spectra of the ligands were recorded in DMSO-d_6. The ^{13}C-NMR and ^{1}H-NMR spectral data are reported along with the possible assignment in Table I. In the ^{13}C-NMR, the spectra peaks observed at 114.5–136.4, 113.5–144.5, and 128.5–143.0 ppm were assigned to aromatic, pyridine, and thiophene carbons respectively. Peaks observed at 157.9–180.5, 155.3–161.2, 123.5–155.3 ppm were assigned to C=N, CH=N, and C–N carbons respectively. In the ^{1}H-NMR spectra of the ligands, peaks observed at 7.0–8.0 ppm were assigned to the aromatic protons and the singlet peak appearing at 7.8–9.1 ppm was assigned to the azomethine proton (–CH=N–).

IR spectra. The IR spectra of the ligands and complexes are shown in Table II. The peak observed at 3520 cm^{-1} in ciprofloxacin [27] is due to hydrogen bonding which contributed to the ionic resonance structure. This peak was absent in the spectra of the metal complexes signifying deprotonation of the carboxylic proton. This data is supported by ν(M–O) [28] band appearing at about 505 ~ 512 cm^{-1}. The ν(C=O) band appears at 1708 cm^{-1} in the spectra of ciprofloxacin; the complexes show this band at 1626–1633 cm^{-1}, a shift towards lower energy suggesting that coordination occurs through the carbonyl oxygen atom [29]. The frequency separation ($\Delta\nu = \nu\ COO_{asy} - \nu\ COO_{sym}$) in investigated complexes is greater than 200 cm^{-1}, suggesting a unidentate bonding nature for the carboxylate group [30–32]. In 2,2′ bipyridylamine the ν (C=N) band appears at 1585 cm^{-1}. This band shifts to a higher frequency at 1618 cm^{-1} [33] in the complexes indicating the bidentate N–N coordination of the ligand. Similarly for benzylidene-2-aminopyridine the two strong bands at 1615 and 1593 cm^{-1} are assigned to ν (C=N) of the azomethine and pyridine ring, respectively. On complexation these bands are shifted to 1565 cm^{-1} and 1620 cm^{-1}, respectively, suggesting the bidentate N–N involvement in coordination [34–35]. The ν (C=N) peak for the synthesized

Table I. ^{1}H NMR and ^{13}C NMR spectral data of Schiff bases[a].

Compounds	^{1}H NMR δ-ppm	^{13}C NMR δ-ppm
A^2	7.5–7.8 (5H, m, Ar-H), 7.1–8.5 (4H, m, Py-H), 9.1 (1H, s, CH=N)	128.8–132.1(Ar), 113.5–144.5(Py), 157.9(Py, C=N), 149.1(Py, C=N), 161.1(CH=N).
A^3	7.0–7.4 (4H, m, Ar-H), 7.1–7.7 (3H, m, Thiophene-H), 7.5 (1H, s, CH=N)	122.1–130.4 (Ar), 128.5–143.0(Thiophene), 150.2 (C–N), 155.3 (CH=N)
A^4	7.4–8.0 (16H, m, Ar-H), 8.7 (2H, s, CH=N)	114.5–135.7v(Ar), 150.8 (C–N), 160.0(CH=N)
A^5	7.5–7.8 (10H, m, Ar-H), 5.2 (4H, t, CH_2-aliphatic), 8.7 (1H, s, CH=N)	128.8–136.4 (Ar), 161.2 (CH=N), 54.1(C–N, aliphatic)
A^6	7.0–7.8 (12H, m, Ar-H), 3.8(6H, s, CH_3-aliphatic), 8.6 (2H, s, CH=N)	115.0–132.8 (Ar), 163.5 (C–O, Ar), 123.5 (C–N), 160.5 (C=N), 56.0(OCH_3)
A^7	7.4–7.9 (18H, m Ar-H)	120.5–133.7 (Ar), 165.8 (C=N), 155.3 (C–N)
A^8	7.3–7.4 (4H, m, Ar-H), 1.6(4H, m), 1.7 (4H, m), 2.35(2H,t)	124.2–130.7(Ar), 180.5(C=N), 140.0(C–N, Ar), 22.3, 25.8, 37.0

[a] A^2 (bap): Benzylidene-2-aminopyridine; A^3 (tca): Thiophene-2-carboxaldeneaniline; A^4 (bendan): Bis(benzylidene)-1,8-diaminonaphthalene; A^5 (benen): Bis(benzylidene)ethylenediamine; A^6 (bmbbd): N,N′-Bis-(4-methoxybenzylidene)benzene-1,2-diamine; A^7 (bcpded): N,N′-Bis-(3-Chlorophenyl)-1,2-Diphenyl-ethane-1,2-diimine; A^8 (dcbd): N,N′-Dicyclohexylidene-benzene-1,2-diamine.

Table II. Infrared spectral data of complexes[a].

Compounds	ν (O–H) cm^{-1}	ν (C=O) cm^{-1} Pyridone	ν (C–S) cm^{-1}	ν $(COO)_{asy}$ cm^{-1}	ν $(COO)_{sym}$ cm^{-1}	$\Delta\nu$ cm^{-1}	ν (C–Cl) cm^{-1}	ν (C=N) cm^{-1} Azo methine	ν (C=N) cm^{-1} Ring	ν (M–N) cm^{-1}	ν (M–O) cm^{-1}	ν (M–S) cm^{-1}
L	3520	1708	–	1624	1384	240	–	–	–	–	–	–
A^1	–	–	–	–	–	–	–	–	1585	–	–	–
A^2	–	–	–	–	–	–	–	1615	1593	–	–	–
A^3	–	–	765	–	–	–	–	1622	–	–	–	–
A^4	–	–	–	–	–	–	–	1629	–	–	–	–
A^5	–	–	–	–	–	–	–	1629	–	–	–	–
A^6	–	–	–	–	–	–	–	1608	–	–	–	–
A^7	–	–	–	–	–	–		1601	–	–	–	–
A^8	–	–	–	–	–	–	–	1602	–	–	–	–
I	–	1630	–	1582	1380	202	1130	–	1618	530	511	–
II	–	1629	–	1590	1383	208	1138	1565	1620	540	505	–
III	–	1629	752	1585	1382	203	1137	1580	–	540	506	420
IV	–	1633	–	1577	1365	215	1135	1593	–	535	510	–
V	–	1626	–	1584	1378	206	1145	1607	–	538	512	–
VI	–	1628	–	1591	1389	202	1149	1575	–	534	508	–
VII	–	1629	–	1590	1382	208	1117	1579	–	540	507	–
VIII	–	1632	–	1575	1364	211	1129	1570	–	536	509	–

[a] See Table I and A^1 (bipym): 2,2′-bipyridylamine; L(Cip): 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid; Pip: piperazine.

Table III. Electronic spectral data of the ligands and complexes[a].

Compounds	λ_{max} in DMSO			μ_{eff} BM
	$\pi-\pi^\star$ transition	d–d transition	MLCT	
I	262	520	721	4.99
II	263	580	750	5.08
III	264	539	758	4.84
IV	264	590	763	5.04
V	263	560	775	4.89
VI	262	540	777	4.73
VII	275	635	805	4.69
VIII	263	564	807	5.17

[a] see Table I.

Schiff bases A^3–A^8 is observed at 1602–1629 cm^{-1} and is shifted to 1570–1593 cm^{-1}, indicating the N–S or N–N bidentate coordination of ligand [36–39]. These data are further supported by ν (M–N) [40] which appears at about 530 ~ 540 cm^{-1}. In $[Fe_2(Cip)_2(tca)_2(pip)]\cdot 5H_2O$, the ν (C–S) band of the ligand (tca) observed at 765 cm^{-1} is shifted lower to 752 cm^{-1} in the spectra of the complex indicating the participation of the sulfur atom of thiophene ring. This data is further supported by a new band observed at 420 cm^{-1} which may be assigned to the ν (M–S) [41–43] mode.

Electronic spectra and magnetic properties. Electronic spectral data and magnetic moments are presented in Table III. Fe(II) complexes are an intense greenish brown in color, but the origin of this color is doubtful. The spectrophotometrically characterized five coordinated Fe(II) complexes are rarely reported [44]. The diffuse reflectance spectra of the diiron(II) complexes $[Fe_2(L)_2(A^n)_2(pip)]\cdot 5H_2O$ exhibited three band at about ~265 nm, ~550 nm, and ~700 nm[45,46]. These bands are assigned to different transitions of ~265 nm for $\pi \rightarrow \pi^\star$, ~550 nm for d–d, and ~700 nm for MLCT in the d^6-system of Fe(II) atom. The magnetic moments of all compounds was in the range 4.73–5.17 BM which is in good agreement for a five coordinated dinuclear Fe(II) mixed ligand system and consistent with the presence of four unpaired electrons [47,48] suggesting a paramagnetic nature. The magnetic moment and electronic spectra suggest that Fe(II) is in a distorted square pyramidal coordination environment.

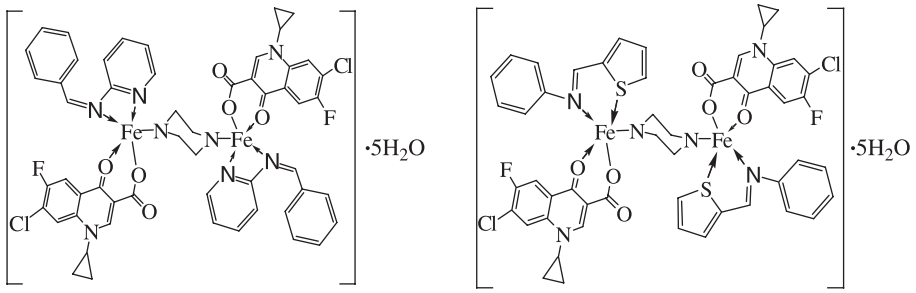
TGA. The thermal stability of the complexes was investigated using thermogravimetric analyses. The TGA curves obtained at a heating rate of 10°C/min in a N_2 atmosphere over the temperature range of 50–800°C showed that all the complexes had a loss in weight corresponding to five water molecules in the range of 50–100°C indicating that these water molecules are water of crystallization. In the temperature range 100–800°C the ligand molecules are lost. In all cases the final products were metal oxides. These results are in good agreement with the composition of the complexes. The suggested structures of the complexes are shown in Figure 1.

Antimicrobial activity

The increase in antimicrobial activity of the complexes over the ligands A^1–A^8 may be due to the effect of the metal coordination and as a consequence of their structures and additional > C═N– bond [49]. A possible explanation for the increase in antimicrobial activity may be considered in the light of Overtone's concept [50] and the Tweedy's chelation theory [51]. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid-soluble materials so that liposolubility is an important factor controlling the antimicrobial activity [52]. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups [53,54]. Further, the mode of action of the compounds may involve the formation of a hydrogen bond through the azomethine group with the active centre of cell constituents, resulting in interference with the normal cell process [55]. Comparative analysis showed a higher antimicrobial activity for the complexes than the free ligands, metal salt and the control (DMSO). The complexes exhibited higher activities as compared to the standard drugs ofloxacin, levofloxacin, and flucanozole for *B. subtilis* and *E. coli*, while for *S. aureus*, *B. cereus*, *S. typhi and S. marcescens* all the complexes possessed good activity (Table IV). With *A. niger, A. flavus and L. theobromae,* there was no significant antifungal activity.

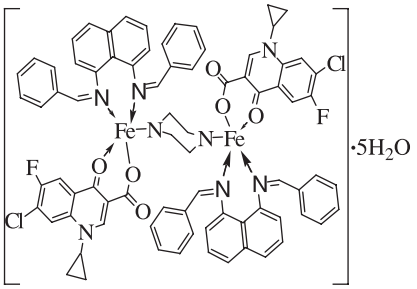
DNA binding

Absorption spectroscopy is extensively used to confirm the binding of complexes with the DNA

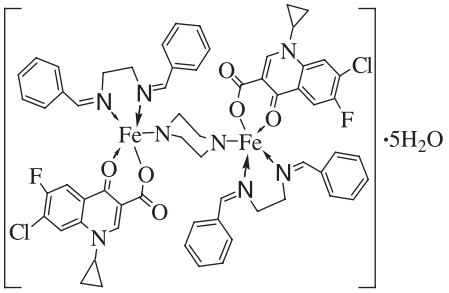


(II) $[Fe_2(Cip)_2(bap)_2(pip)]5H_2O$

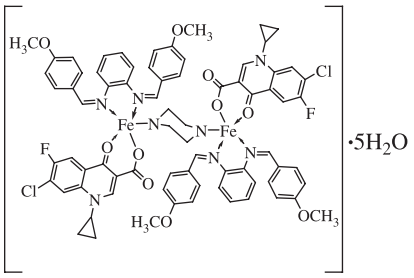
(III) $[Fe_2(Cip)_2(tca)_2(pip)]\cdot 5H_2O$



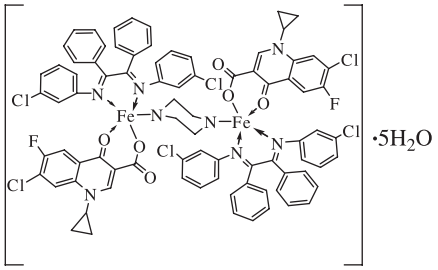
(IV) $[Fe_2(Cip)_2(bendan)_2(pip)]\cdot 5H_2O$



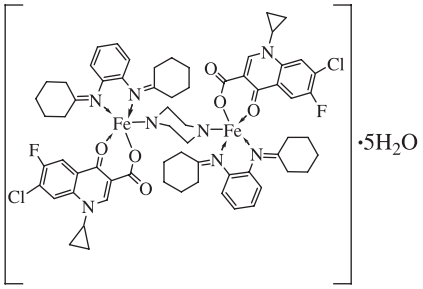
(V) $[Fe_2(Cip)_2(benen)_2(pip)]\cdot 5H_2O$



(VI) $[Fe_2(Cip)_2(bmbbd)_2(pip)]\cdot 5H_2O$



(VII) $[Fe_2(Cip)_2(bcpded)_2(pip)]\cdot 5H_2O$



(VIII) $[Fe_2(Cip)_2(dcbd)_2(pip)]\cdot 5H_2O$

Figure 1. Suggested structures of the complexes.

helix. Complexes bound to DNA through interaction result in a bathochromic (red) shift and hypochromic (blue) shift due to interaction between chromophores and the base pair of the DNA helix. The level of hypochromism is commonly consistent with the strength of the intercalative interaction [56–57]. The DNA binding data for the complexes are shown in Table V. The maxima at about 272 nm is observed in the spectrum of the complex in the absence of DNA, but this decreases as the amount of DNA increases and is observed at about 247 nm in the presence of 7μgm DNA. The absorption spectra of the complex $[Fe_2(Cip)_2(bipym)_2(pip)].5H_2O$ is shown in Figure 2.

Similarly for the variable ligands (A^1–A^8), $FeSO_4.7H_2O$, and ciprofloxacin the maxima was observed at c. 260 nm in the absence of DNA but in the presence of 7μgm DNA maxima was observed at

Table IV. Antimicrobial activity of compounds.

Compounds	Zone of Inhibition in mm					
	E. Coli	*B. Subtilis*	*S. aureus*	*S. typhi*	*B. cereus*	*S. marcescens*
Control	11	11	10	11	11	11
$FeSO_4 \cdot 3H_2O$	13	16	19	14	18	19
LH(Cpf. HCl)	28	34	40	32	31	37
Std. 1 (Ofl. HCl)	30	34	39	33	30	32
Std. 2 (Lef. HCl)	33	36	38	29	28	34
Std. 3 (fluconozole)	15	19	11	12	11	12
A^1	12	15	25	18	19	22
A^2	17	17	12	12	11	16
A^3	13	14	16	14	15	19
A^4	19	12	11	16	12	14
A^5	11	11	11	11	12	19
A^6	13	14	13	14	15	14
A^7	17	11	12	16	15	17
A^8	14	14	15	11	11	19
I	45	40	45	25	25	38
II	42	40	44	26	28	38
III	45	40	41	27	25	34
IV	44	38	39	28	29	22
V	46	43	41	29	31	35
VI	41	40	40	33	24	36
VII	45	40	43	26	26	35
VIII	42	39	40	26	28	40

Table V. DNA interaction data for the complexes.

Compound	DNA μgm	Compound λ_{max} nm	A^n λ_{max} nm	L λ_{max} nm	Fe(II) λ_{max} nm
I $[Fe_2(L)_2(A^1)_2(pip)] \cdot 5H_2O$	0	275.0	260.4	260.0	268.4
	3	261.2	259.6	259.2	259.6
	5	260.4	258.6	258.8	258.0
	7	244.6	245.0	247.4	245.2
II $[Fe_2(L)_2(A^2)_2(pip)] \cdot 5H_2O$	0	270.6	260.6	260.0	268.4
	3	261.4	258.4	259.2	259.6
	5	258.4	258.0	258.8	258.0
	7	247.4	249.4	247.4	245.2
III $[Fe_2(L)_2(A^3)_2(pip)] \cdot 5H_2O$	0	271.5	260.0	260.0	268.4
	3	262.4	258.2	259.2	259.6
	5	260.4	257.8	258.8	258.0
	7	249.8	246.6	247.4	245.2
IV $[Fe_2(L)_2(A^4)_2(pip)] \cdot 5H_2O$	0	274.3	263.0	260.0	268.4
	3	260.0	259.2	259.2	259.6
	5	258.8	258.2	258.8	258.0
	7	246.6	244.2	247.4	245.2
V $[Fe_2(L)_2(A^5)_2(pip)] \cdot 5H_2O$	0	276.7	265.2	260.0	268.4
	3	261.4	259.2	259.2	259.6
	5	259.0	258.2	258.8	258.0
	7	248.0	246.6	247.4	245.2
VI $[Fe_2(L)_2(A^6)_2(pip)] \cdot 5H_2O$	0	273.0	261.7	260.0	268.4
	3	261.8	258.8	259.2	259.6
	5	258.6	258.0	258.8	258.0
	7	247.6	244.6	247.4	245.2
VII $[Fe_2(L)_2(A^7)_2(pip)] \cdot 5H_2O$	0	267.9	259.0	260.0	268.4
	3	260.8	258.4	259.2	259.6
	5	258.6	258.0	258.8	258.0
	7	247.0	245.4	247.4	245.2
VIII $[Fe_2(L)_2(A^8)_2(pip)] \cdot 5H_2O$	0	272.8	260.3	260.0	268.4
	3	261.2	259.4	259.2	259.6
	5	258.8	258.4	258.8	258.0
	7	247.4	247.4	247.4	245.2

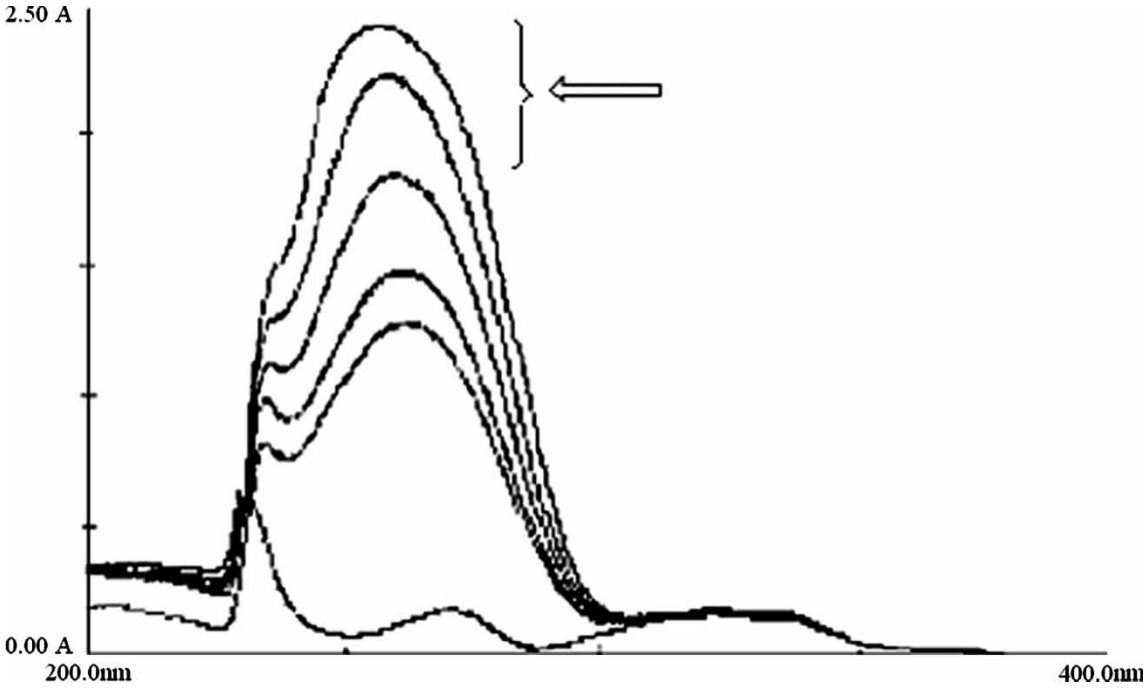


Figure 2. Absorption spectra of complex $[Fe_2(L)_2(A^1)_2(pip)]\cdot 5H_2O$ in absence and presence of DNA.

c. 245 nm. All data leads to the suggestion that in the presence of 7 μgm of DNA (maxima at about 245 nm) the whole complex dissociates, and free Fe(II), constant ligand(Cip), and variable ligands(A^1–A^8) bind with DNA.

Bathochromic wavelength shifts and hypochromic absorption are characteristic of the electronic spectra of many DNA bound groove binders and most if not all DNA–bound intercalators [58].

Acknowledgements

We thank Prof. J. S. Parmar, Head, Department of Chemistry, and Prof. D. Madammvar, Head, Department of Biosciences, Sardar Patel University, Vallabh Vidyanagar, Gujarat, India for providing the laboratory facilities.

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