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Synthesis of antibacterial and antifungal cobalt(II), copper(II), nickel(II) and zinc(II) complexes with bis-(1,1′-disubstituted ferrocenyl)thiocarbohydrazone and bis-(1,1′-disubstituted ferrocenyl)carbohydrazone

Zahid H. Chohan[1]*, Khalid M. Khan[2] and Claudiu T. Supuran[3]

[1]Department of Chemistry, Bahauddin Zakariya University, Multan, Pakistan
[2]HEJ Research Institute of Chemistry, International Centre for Chemical Sciences, University of Karachi, Karachi-75270, Pakistan
[3]University of Florence, Dipartmento di Chimica, Laboratorio di Chimica Bioinorganica, Polo Scientifico, Sesto Florentino, Florence, Italy

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The condensation reaction of 1,1′-diacetylferrocene with thiocarbohydrazide and carbohydrazide to form bis-(1,1′-disubstituted ferrocenyl)thiocarbohydrazone and bis-(1,1′-disubstituted ferrocenyl)carbohydrazone has been studied. The compounds obtained have been further used as ligands for their ligand and antimicrobial properties with cobalt(II), copper(II), nickel(II) and zinc(II) metal ions. The compounds synthesized have been characterized by physical, spectral and analytical methods and have been screened for antibacterial activity against *Escherichia coli*, *Bacillus subtillis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhi*, and for antifungal activity against *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani* and *Candida glaberata* using the agar well-diffusion method. All the compounds synthesized have shown good affinity as antibacterial and antifungal agents, which increased in most of the cases on complexation with the metal ions.

KEYWORDS: bis(1,1′-disubstituted ferrocenyl)hydrazones; metal complexes; antibacterial; antifungal

INTRODUCTION

Metal complexes with organometallic ligands that include a ferrocenyl group are of current interest[1–4] since antitumor activity in platinum and gold complexes of 1,1′-bis-(diphenylphosphino)ferrocene has been reported.[5,6] Enhanced antibacterial activity of penicillin and cephalosporine has also been observed by replacing aromatic groups with the ferrocenyl moiety.[7] Most of the antibiotics used in clinical practice share a common mechanism of action, acting as inhibitors of the bacterial cell wall biosynthesis or affecting protein synthesis on ribosomes but not intervening in more fundamental metabolic processes of the pathogen.[8–12] Other significant processes, such as colonization and evasion of host immune defenses, acquisition of nutrients for growth and proliferation, facilitation of dissemination, or tissue damage during infection are greatly affected by indiscriminate use of such classical antibiotics.[8–12] As a consequence, drug resistance to the presently available classes of antibiotics is becoming a worldwide medical problem. The process of chelation via metal complexes and its correlation with biological activity constitutes one emerging possibility for the design of novel antibiotics.[11] The application of ferrocene-containing systems in medicinal chemistry has not been well explored. However, the enzyme inhibiting properties of different hydrazone ligands have been extensively studied[13–17] and their condensation products with carbonyl compounds (aldehydes/ketones) are known to be less toxic than the parent hydrazides or hydrazines, which is probably due to the blocking of the free amino groups. These considerations attracted our attention[17–23] in designing and studying a new area of organometallic-based antibacterial and antifungal compounds and their enhancement on chelation with metal ions.

*Correspondence to: Zahid H. Chohan, Department of Chemistry, Bahauddin Zakariya University, Multan, Pakistan.
E-mail: zchohan@mul.paknet.com.pk

Acylferrocene undergoes an easy derivatization with aromatic/heteroaromatic amines. In an attempt to investigate such transformations of 1,1′-diacetylferrocene, we wish to report a new class of bis-(1,1′-disubstituted ferrocenyl) derivatives (Fig. 1) and their use as potential ligands in the preparation of cobalt(II), copper(II), nickel(II) and zinc(II) complexes. All these synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Bacillus subtillis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhi*, and for antifungal activity against *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani* and *Candida glaberata* using the agar well-diffusion method. The ligands showed varied antibacterial and antifungal activity and this activity enhanced respectively on coordination and chelation.

MATERIAL AND METHODS

Solvents used were analytical grades; all the metal(II) salts used were as chloride salts. IR spectra were recorded on a Philips Analytical PU 9800 FTIR spectrophotometer. NMR spectra were recorded on a Perkin–Elmer 283B spectrometer. UV–visible spectra were obtained in dimethylformamide (DMF) on a Hitachi U-2000 double-beam spectrophotometer. Butterworth Laboratories Ltd (UK) carried out carbon, hydrogen and nitrogen analyses. Conductance of the metal complexes was determined in DMF on a Hitachi (Japan) YSI-32 model conductivity meter. Magnetic measurements were carried out on solid complexes using the Gouy method. Melting points were recorded on a Gallenkamp (UK) apparatus and are not corrected. The complexes were analyzed for their metal contents by EDTA titration. Antibacterial and antifungal screening was done at HEJ Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Pakistan.

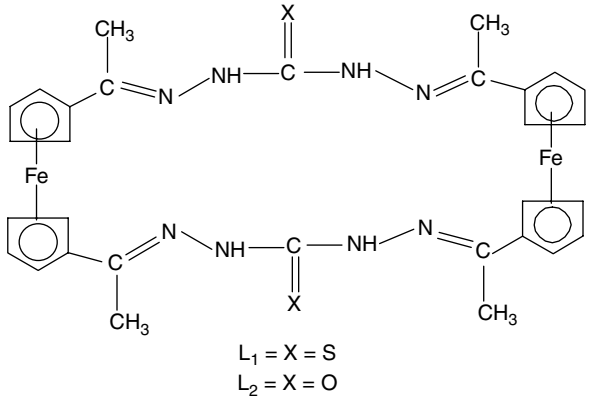

Figure 1. Structure of the ligands synthesized in the present study.

Synthesis of ligand (L^1)

For the preparation of ligand (L^1), a solution of 1,1′-diacetylferrocene (1.0 g, 0.0037 mol) in ethanol (20 cm^3) was added into a magnetically stirred solution of thiocarbohydrazide (0.4 g, 0.0037 mol) in hot ethanol (20 cm^3). The mixture was refluxed for 4 h. After allowing the solution to cool to room temperature, the solvent was evaporated to give an orange solid product. The orange crystalline solid thus obtained was recrystallized from a 70 : 30 mixture of dichloromethane : ethanol. Thin-layer chromatography of the recrystallized solid thus obtained showed a single spot of the desired product. A similar method was used for the preparation of the other ligand, L^2.

Synthesis of the metal(II) complexes

To a magnetically stirred and warmed (40 °C) solution of the ligand (0.001 mol) in ethanol (30 cm^3) was added a solution of the respective metal(II) chloride (0.001 mol) in ethanol (20 cm^3). The mixture was refluxed for 2 h. During this time, a complex was precipitated; upon cooling, this was filtered, washed several times with ethanol, then with diethyl ether and dried over anhydrous $CaCl_2$. All other complexes were prepared similarly.

Biological activity

The synthesized ligands (L^1 and L^2) and their corresponding metal(II) complexes (**1**–**8**) were screened *in vitro* for their antibacterial activity against *E. coli*, *B. subtillis*, *S. aureus*, *P. aeruginosa* and *S. typhi*, and for antifungal activity against *T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani* and *C. glaberata* using the agar well-diffusion method.[23,24] Bacterial inocula at 2–8 h old, containing approximately 10^4–10^6 cfu ml^{-1} (CFU: colony forming units), were used in these assays. The wells were dug in the media with the help of a sterile metallic borer with centers of at least 24 mm. The recommended concentration (100 µl) of the test sample (1 mg ml^{-1} in dimethylsulfoxide (DMSO)) was introduced in the corresponding wells. Other wells supplemented with DMSO and reference antibacterial drugs served as negative and positive controls respectively. The plates were incubated immediately at 37 °C for 20 h. Activity was determined by measuring the diameter (millimeters) of zones showing complete inhibition. Imipenum was used as a standard drug for antibacterial activity and, Miconazole and Amphotericin B for antifungal activity.

RESULTS AND DISCUSSION

Chemistry

The condensation of thiocarbohydrazide and carbohydrazide with 1,1′-acetylferrocene (1 : 1 molar ratio) in methanol yielded the new ferrocenyl hydrazones, bis-(1,1′-disubstituted ferrocenyl)thiocarbohydrazone and bis-(1,1′-disubstituted ferrocenyl)carbohydrazone (L^1 and L^2) respectively (Fig. 1). The ligands are all soluble in methanol and

Table 1. Physical, spectral and analytical data of the ligands and complexes

Ligand/complex	M.P. (°C)	IR (cm^{-1})	Calc. (Found) (%) C	H	N	λ_{max} (cm^{-1})	Yield (%)
$L^1C_{30}H_{32}Fe_2N_8S_2$	193–195	1525, 1580 (N–NH), 1635 (C═N), 1175, 1065, 955	53.9 (54.2)	4.7 (4.5)	16.5 (16.9)	—	58
$L^2C_{30}H_{32}Fe_2N_8O_2$	198–200	1525, 1580 (N–NH), 1635 (C═N), 1175, 1065, 955	55.6 (55.9)	4.9 (5.3)	17.3 (17.0)	—	55
1 $[Co(L^1)Cl_2]C_{30}H_{32}Fe_2CoN_8O_2Cl_2$	220–222	1620, 1580, 385, 310	44.5 (44.6)	3.9 (3.6)	13.8 (14.2)	8725, 17 420, 2990	60
2 $[Cu(L^1)]Cl_2C_{30}H_{32}Fe_2CuN_8O_2Cl_2$	228–230	1620, 1580, 385	44.2 (44.5)	3.9 (3.5)	13.8 (13.5)	15 295, 19 465, 30 240	62
3 $[Ni(L^1)Cl_2]C_{30}H_{32}Fe_2NiN_8O_2Cl_2$	235–238	1620, 1580, 385, 310	44.5 (44.9)	3.9 (4.3)	13.8 (13.5)	10 245, 16 265, 29 380	61
4 $[Zn(L^1)Cl_2]C_{30}H_{32}Fe_2ZnN_8O_2Cl_2$	214–216	1620, 1580, 385, 310	44.1 (44.5)	3.9 (3.4)	13.7 (13.9)	28 235	59
5 $[Co(L^2)Cl_2]C_{30}H_{32}Fe_2CoN_8O_2Cl_2$	227–229	1625, 1580, 390, 310	50.9 (50.5)	4.5 (4.7)	15.9 (16.3)	8795, 17 655, 30 110	62
6 $[Cu(L^2)]Cl_2C_{30}H_{32}Fe_2CuN_8O_2Cl_2$	224–226	1625, 1580, 390	50.6 (50.4)	4.5 (4.8)	15.8 (15.5)	15 235, 19 590, 30 315	61
7 $[Ni(L^2)Cl_2]C_{30}H_{32}Fe_2NiN_8O_2Cl_2$	232–235	1625, 1580, 390, 310	51.0 (51.2)	4.5 (4.8)	15.9 (15.7)	10 395, 16 320, 29 395	57
8 $[Zn(L^2)Cl_2]C_{30}H_{32}Fe_2ZnN_8O_2Cl_2$	222–224	1625, 1580, 390, 310	50.5 (50.7)	4.5 (4.2)	15.7 (15.4)	28 280	62

Table 2. ^{1}H NMR and ^{13}C NMR data for the Ligands and zinc(II) complexes (**4** and **8**)

Compound	^{1}H NMR (DMSO-d_6) (ppm)	^{13}C NMR (DMSO-d_6) (ppm)
L^1	2.3 (s, 12H, CH_3), 4.1–4.3 (m, 4H, ferrocenyl), 4.5–4.6 (m, 4H, ferrocenyl), 4.7–4.8 (m, 4H, ferrocenyl), 5.2–5.4 (m, 4H, ferrocenyl), 10.8 (s, 2H, NH)	22.6 (CH_3), 68.6, 69.6, 83.7 (ferrocenyl), 142.4 (C═N), 178.1 (C═S)
L^2	2.5 (s, 12H, CH_3), 4.2–4.3 (m, 4H, ferrocenyl), 4.4–4.5 (m, 4H, ferrocenyl), 4.6–4.7 (m, 4H, ferrocenyl), 5.3–5.5 (m, 4H, ferrocenyl), 11.1 (s, 2H, NH).	22.8 (CH_3), 68.6, 69.8, 83.8 (ferrocenyl), 142.7 (C═N), 205.5 (C═O)
4	2.5 (s, 12H, CH_3), 4.2–4.3 (m, 4H, ferrocenyl), 4.4–4.6 (m, 4H, ferrocenyl), 4.8–4.9 (m, 4H, ferrocenyl), 5.2–5.4 (m, 4H, ferrocenyl), 11.2 (s, 2H, NH).	22.9 (CH_3), 68.6, 69.7, 83.7 (ferrocenyl), 142.8 (C═N), 178.2 (C═S)
8	2.8 (s, 12H, CH_3), 4.2–4.3 (m, 4H, ferrocenyl), 4.5–4.6 (m, 4H, ferrocenyl), 4.7–4.8 (m, 4H, ferrocenyl), 5.3–5.5 (m, 4H, ferrocenyl), 11.4 (s, 2H, NH)	23.1 (CH_3), 68.6, 69.9, 83.7 (ferrocenyl), 142.9 (C═N), 205.5 (C═O)

ethanol. The structures of the ligands synthesized were established with the help of their IR, NMR and microanalytical data (Table 1). All the metal complexes (**1**–**8**; Table 2) of these ligands were prepared by the stoichiometric reaction of the corresponding ligand with the respective metal salt as chloride in a molar ratio M : L of 1 : 1. The metal complexes dissolve in DMF and DMSO. All of them are amorphous solids. Molar conductance values of the cobalt(II), nickel(II) and zinc(II) complexes (14–17 Ω cm^2 mol^{-1}) in DMF showed them to be non-electrolytes, and the copper(II) complexes (104–106 Ω cm^2 mol^{-1}) were electrolytic in nature.[26] The elemental analyses data agree with the proposed formulae for the ligands and also confirmed the $[M(L)Cl_2]$ composition for the cobalt(II), nickel(II) and zinc(II) complexes in an octahedral environment, and $[M(L)]Cl_2$ for the copper(II) complexes in a square-planar environment. Only microcrystalline powders of these compounds could be obtained, which were unsuitable use for X-ray structural determinations.

IR spectra

The IR spectra of the ligands and the metal complexes were recorded in KBr and are shown in Table 1 with some proposed assignments of important characteristic bands. IR spectra of the ligands are almost identical in the region 670–1550 cm^{-1} to those of the metal complexes. The ligands show the absence of bands at ~1710 cm^{-1} and 3420 cm^{-1} due to characteristic carbonyl ν(C═O) and $\nu(NH_2)$ stretching vibrations of the respective starting materials. Instead, the appearance of a new band in the spectra of the free ligands at 1635 cm^{-1} assigned to the azomethine ν(C═N) linkage suggested[27,28] the formation of the proposed ligands. Shifting of this band to the lower frequency side (10–15 cm^{-1}) in the complexes was observed. This lowering is due to coordination of azomethine nitrogen to the metal ion, although a few examples for the increase of this band due to coordination have been reported. Also, a sharp band in the vicinity of 1580 cm^{-1} was observed in the complexes, which can be attributed to the stretching mode of chromospheres ν(C═N–NH). The characteristic bands for the ferrocenyl groups appearing in the ligands remained almost unchanged in the complexes. In the far-IR region, a band at ~385–390 cm^{-1} attributed[29] to ν(M–N) was observed for all the complexes (Table 2), which was not found in the spectra of the free ligands. Also, a weak band at 310 cm^{-1} due to the ν(M–Cl) mode was observed only in the spectra of the cobalt(II), nickel(II) and zinc(II) complexes, strongly suggesting[30] their octahedral geometry (Fig. 2a). This band, however, was not found in the spectra of the copper(II) complexes, thus suggesting a four-coordinated square-planar geometry for the copper(II) complexes (Fig. 2b).

^{1}H NMR and ^{13}C NMR spectra

^{1}H NMR and ^{13}C NMR spectra of the free ligands and their zinc(II) complexes have been recorded in DMSO-d_6 with tetramethylsilane as internal reference and are summarized in Table 2 with proposed assignments. ^{1}H NMR spectral data of the ligands display signals at δ 2.3–2.5, 4.1–5.5 and 10.8–11.1 ppm due to –C*H*$_3$, ferrocenyl and –N*H* protons.[31] The conclusions drawn from these studies lend further support to the mode of bonding discussed above in their IR spectra. In the spectra of their diamagnetic zinc(II) complexes (**4** and **8**) these protons shifted downfield as expected, due to the increased conjugation during coordination to the metal atoms. But there is no appreciable change in the chemical shifts of the ferrocenyl protons on coordination. There is agreement in number of protons calculated from the integration curves and those obtained from the values of the expected carbon, hydrogen and nitrogen analyses. In the ^{13}C NMR spectra, the ligand displays signals at δ 22.6–22.8 ppm, 68.6–83.7 ppm, 142.4–142.7 ppm, 178.1 ppm and 205.5 ppm, assigned respectively to –*C*H$_3$, ferrocenyl, *C*═N, *C*═S and *C*═O carbon atoms respectively. These signals appear downfield in comparison with the corresponding signals of the ligand, indicating[32] coordination and complexation with the central metal atom. It was observed that DMSO did not have any coordinating effect, either on the spectra of the ligands or on their metal complexes.

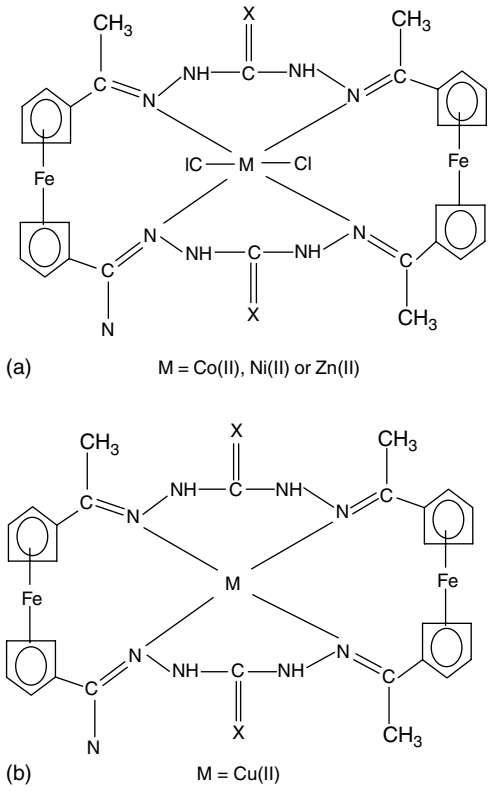

Figure 2. Proposed structure of the metal(II) complexes prepared in this study.

Electronic spectra and magnetic moments

The UV–visible spectral bands of the ligands and their complexes in DMSO are recorded in Table 1. The cobalt(II) complexes showed bands at 8725–8795 cm^{-1}, 17 420–17 655 cm^{-1} and 29 990–30 110 cm^{-1}. These may be assigned to the $^4T_{1g} \rightarrow {}^4T_{2g}(F)$, $^4T_{1g} \rightarrow {}^3A_{2g}(F)$ and $^4T_{1g} \rightarrow {}^4T_{1g}(P)$ transitions respectively and are suggestive[33] of octahedral geometry around the cobalt ions. The electronic spectra of the copper(II) complexes showed two low-energy week bands at 15 205–15 235 and 19 465–19 590 cm^{-1} and a strong high-energy band at 30 240–30 315 cm^{-1}. The low-energy bands in this region are typically expected for its square-planar configuration and may be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions respectively. The strong high-energy band, in turn, is assigned to a metal-to-ligand charge transfer. The nickel(II) complexes exhibited three spin-allowed bands, at 10 245–10 395, 16 265–16 310 and 29 380–29 395 cm^{-1}, assignable[34] respectively to the transitions $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)(\nu_1)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)(\nu_2)$ and $^3A_{2g}(F) \rightarrow {}^3T_{2g}(P)(\nu_3)$, which were characteristic of their octahedral geometry. The electronic spectra of the zinc(II) complexes showed only a high-intensity band at 28 235–28 280 cm^{-1} due to ligand-to-metal charge transfer in a distorted octahedral environment.[35]

The geometry of the metal complexes has been further deduced from the magnetic moment data of the complexes. The room-temperature magnetic moment of the solid cobalt(II) complexes was 4.8 μ_B, indicative[36] of three unpaired electrons per cobalt(II) ion in an octahedral environment. The magnetic moment of the copper(II) complexes was found to be 1.7 μ_B, consistent[37] for square-planar geometry. The nickel(II) complexes showed μ_{eff} values of 3.6 μ_B, corresponding[36] to two unpaired electrons per nickel(II) ion for their six-coordinated configuration.

On the basis of the above observations, it is suggested that the cobalt(II), nickel(II) and zinc(II) complexes show octahedral geometry or distorted octahedral geometry and the copper(II) complexes show a square-planar geometry (Fig. 2b).

Antibacterial and antifungal properties

All the ligands and their complexes individually exhibited varying degrees of inhibitory effects on the growth of the bacterial/fungal strains tested. These results, presented in Tables 3 and 4, show that the newly synthesized ligands (L^1 and L^2) and their cobalt(II), copper(II), nickel(II) and zinc(II) complexes (**1**–**8**) possess good biological activity. New derivatives were screened for their antibacterial activity against *E. coli*, *B. subtillis*, *S. aureus*, *P. aeruginosa* and *S. typhi* and for their antifungal activity against *T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani* and *C. glaberata*. A marked enhancement of activity was exhibited on further coordination with the metal ions against all the bacterial/fungal strains tested. The compounds generally showed good antibacterial activity, but more significant antifungal activity was observed against most of the strains. It was evident from the data that the activity of the compounds synthesized was also increased on coordination. This enhancement in the activity can be rationalized on the basis of their structures possessing an additional C═N bond. Moreover, chelation/coordination reduces the polarity of the metal ion by partial sharing of its positive charge with the donor groups, and possibly π-electron delocalization within the whole chelate ring. This process thus increases the lipophilic nature of the central metal atom, which, in turn, favors its greater penetration through the bacterial wall of the microorganisms, thus killing them more effectively. It has also been observed[38–41] that the solubility, conductivity and dipole moment are also influenced by the presence of metal ions; these could be the significant factors responsible

Table 3. Antibacterial activity data for the ligands (L^1 and L^2) and complexes (**1**–**8**)

	Zones diameter showing complete growth inhibition[a] (mm)				
Compound	*E. coli*	*P. aeruginosa*	*B. subtillis*	*S. aureus*	*S. typhi*
L^1	11	10	10	10	11
L^2	10	12	12	10	10
1	13	14	13	13	12
2	14	15	12	14	13
3	14	14	15	16	12
4	15	15	13	14	13
5	12	15	12	14	14
6	11	14	13	13	14
7	13	15	14	15	12
8	15	16	13	16	15
Imipenum[b]	20	18	18	20	18

[a] 14–24 mm: significant activity; 7–13 mm: moderate activity; <7 mm: weak activity.
[b] Standard drug.

Table 4. Antifungal activity data for the ligands (L^1 and L^2) and complexes (**1**–**8**)

	Zones diameter showing complete growth inhibition[a] (mm)					
Compound	*T. longifusus*	*C. albicans*	*A. flavus*	*M. canis*	*F. solani*	*C. glaberata*
L^1	20	13	19	20	20	20
L^2	18	14	18	18	18	18
1	22	15	22	23	22	22
2	23	14	24	22	21	20
3	22	17	22	24	24	22
4	24	18	24	24	22	21
5	22	18	22	22	21	20
6	23	17	24	23	18	20
7	21	20	23	22	20	22
8	22	18	22	21	22	24
Miconazole[b]	25	20	25	25	25	25
Amphotericin B[b]	28	25	25	30	25	30

[a] 14–24 mm: significant activity; 7–13 mm: moderate activity; <7 mm: weak activity.
[b] Standard drug.

for increasing the hydrophobic character and liposolubility of the molecule, hence enhancing the biological utilization ratio and activity of the drug.

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