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Biopotential insights and structural chemistry of some zirconocene incorporated heterocyclic β-diketones and flexible N-protected α/β- amino acids

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The interaction of zirconocene dichloride with the heterocyclic β-diketones (LH) and flexible N-protected α/ β-amino acids (AH) in the presence of triethylamine in 1:1:1:2 molar ratio in refluxing dry THF has been resulted in the formation of zirconocene complexes of the general formula $[ZrCp_2(RCOC{:}C(O)N(C_6H_5)N{:}CCH_3)(O_2CCHR'NC(O)C_6H_4C(O))]$(where R= -$CH_3$, -$CH_2CH_3$, p-$ClC_6H_4$-, -$C_6H_5$ and CHR' = -$CH_2CH_2$and R' = $CH(CH_3)_2$). These newly generated zirconocene incorporated organic-inorganic hybrid products have been characterized by FTIR, NMR (^{1}H and ^{13}C) and mass spectrometry. Some of these complexes and their corresponding ligands have been tested for their antimicrobial activity to examine the biopotential activity-structure relationship.

Keywords: Heterocyclic β-diketones, N-protected α/ β-amino acids, Zirconocene complexes, Antimicrobial activity

The identity of organic ligands and experimental conditions play an important role in the reactions of zirconocene dichloride with various potential organic ligands. This interaction results in the formation of zirconocene complexes of variable compositions[1,2]. The chemistry of zirconocene complexes has developed towards an exquisite level with the emergence of widespread applications of these complexes in various fields such as pharmaceuticals[3,4], agrochemicals[5], as reagents in organic synthesis[6,7] for the development of electronic materials, catalysts[8,9] and find applications as metal based anticancer drugs[10,11]. The steric factors of the ligands may have significant effects on the reactivity of zirconocene dichloride. Heterocyclic β-diketones and N-protected α/β-amino acids are potential chelating ligands and the metal complexes derived from these ligands demonstrate significant biopotency[12-14]. It was considered relevant to incorporate zirconocene into heterocyclic β-diketones and N-protected α/β-amino acids. The newly generated zirconocene incorporated products were screened for their antimicrobial activity. The structure-biopotency relationship of these complexes was examined in terms of the presence of -CH_3, -CH_2CH_3, -C_6H_5, p-ClC_6H_4-, six-membered and four-membered chelate rings, $(C_5H_5)_2Zr$ group and N-protected β-amino acids in these products.

Experimental Details

The experimental work was carried out under stringent anhydrous conditions. The ligands were synthesized by reported methods[15,16]. Zirconocene dichloride was commercially available. IR spectra of zirconocene complexes were recorded on Perkin Elmer spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra of zirconocene complexes were recorded on a JEOL ECS 400 DELTA2_NMR spectrometer. Mass spectra of some representative zirconocene complexes were recorded on WATERS_G2S_QTOF_YDA200 mass spectrometer. The synthesis of one representative complex is described in detail and analytical data of other analogous complexes are summarized in Table 1.

Synthesis of $[ZrCp_2(CH_3COC{:}C(O)N(C_6H_5)N{:}CCH_3)(C(O)C_6H_4C(O)NCH_2CH_2COO)]$, $(C_5H_5)_2ZrL_{(1)}A_{(1)}$, (Complex 1)

The heterocyclic β-diketones ($L_{(1)}H$= 4-acetyl-2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-one) (0.45 g, 2.11 mmol) and N-protected amino acid ($A_{(1)}H$= 1,3-dihydro-1,3-dioxo-2H-isoindole-2-propionic acid) (0.46 g, 2.11 mmol) were dissolved in dry THF and then, this solution of the two organic ligands was added to a dry THF solution of zirconocene dichloride, Cp_2ZrCl_2 (0.61 g, 2.11 mmol). After this, triethylamine (0.42 g, 4.22 mmol) was added to this mixture immediately. The reaction mixture was

Table 1 — Analytical data of zirconocene complexes of the type Cp_2ZrLA

Complex no.	Complex formula (Empirical formula)	Amount of reagents in g (mmol)				$Et_3N.HCl$ Found (Calc.)	% Yield (colour)	% Zr Found (Calc.)
		Et_3N	LH	AH	Cp_2ZrCl_2			
1	$Cp_2ZrL_{(1)}A_{(1)}$ ($C_{33}H_{29}N_3O_6Zr$)	0.42 (4.22)	0.45 (2.11)	0.46 (2.11)	0.61 (2.11)	0.57 (0.58)	52 (yellow)	13.92 (13.94)
2	$Cp_2ZrL_{(2)}A_{(1)}$ ($C_{34}H_{31}N_3O_6Zr$)	0.42 (4.16)	0.47 (2.08)	0.45 (2.08)	0.60 (2.08)	0.56 (0.57)	55 (orange yellow)	13.64 (13.65)
3	$Cp_2ZrL_{(3)}A_{(1)}$ ($C_{38}H_{30}N_3O_6ClZr$)	0.54 (5.36)	0.83 (2.68)	0.58 (2.68)	0.78 (2.68)	0.72 (0.73)	58 (yellow)	12.14 (12.15)
4	$Cp_2ZrL_{(4)}A_{(1)}$ ($C_{38}H_{31}N_3O_6Zr$)	0.59 (5.92)	0.82 (2.96)	0.64 (2.96)	0.86 (2.96)	0.80 (0.81)	59 (yellow)	12.72 (12.73)
5	$Cp_2ZrL_{(1)}A_{(2)}$ ($C_{35}H_{33}N_3O_6Zr$)	0.37 (3.72)	0.40 (1.86)	0.46 (1.86)	0.54 (1.86)	0.49 (0.51)	57 (yellow)	13.35 (13.37)
6	$Cp_2ZrL_{(2)}A_{(2)}$ ($C_{36}H_{35}N_3O_6Zr$)	0.37 (3.73)	0.42 (1.86)	0.46 (1.86)	0.54 (1.86)	0.50 (0.51)	54 (orange yellow)	13.08 (13.10)
7	$Cp_2ZrL_{(3)}A_{(2)}$ ($C_{40}H_{34}ClN_3O_6Zr$)	0.35 (3.47)	0.54 (1.73)	0.42 (1.73)	0.50 (1.73)	0.45 (0.47)	58 (yellow)	11.70 (11.71)
8	$Cp_2ZrL_{(4)}A_{(2)}$ ($C_{40}H_{35}N_3O_6Zr$)	0.36 (3.64)	0.50 (1.82)	0.45 (1.82)	0.53 (1.82)	0.48 (0.50)	53 (yellow)	12.24 (12.25)

refluxed for ~8 h. After completion of the reaction, triethylamine hydrochloride was filtered out. The excess solvent was removed in vacuo. A coloured solid product was isolated. This product was purified by recrystallization from benzene n-hexane mixture. (Yield= ~52%)

Antimicrobial activity

S. aureus, *E. coli*, *A. niger* and *C. albicans* were obtained from SMS Medical College, Jaipur, India.

Antibacterial assay

In vitro antibacterial activity of the complexes $(C_5H_5)_2ZrL_{(1)}A_{(1)}$ (Complex 1),$(C_5H_5)_2ZrL_{(2)}A_{(1)}$ (Complex 2), $(C_5H_5)_2ZrL_{(3)}A_{(1)}$ (Complex 3) and $(C_5H_5)_2ZrL_{(4)}A_{(1)}$ (Complex 4) and the ligands, heterocyclic β-diketones $L_{(1)}H$, $L_{(2)}H$, $L_{(3)}H$ and $L_{(4)}H$ and N-protected amino acid $A_{(1)}H$ were investigated against gram positive and gram negative bacterial strains by the agar well diffusion method[17].

Antifungal assay

Antifungal activity of the complexes 1-4 and the ligands, heterocyclic β-diketones $L_{(1)}H$, $L_{(2)}H$, $L_{(3)}H$, $L_{(4)}H$ and N-protected amino acid $A_{(1)}H$ was studied by agar well diffusion method[17].

Results and Discussion

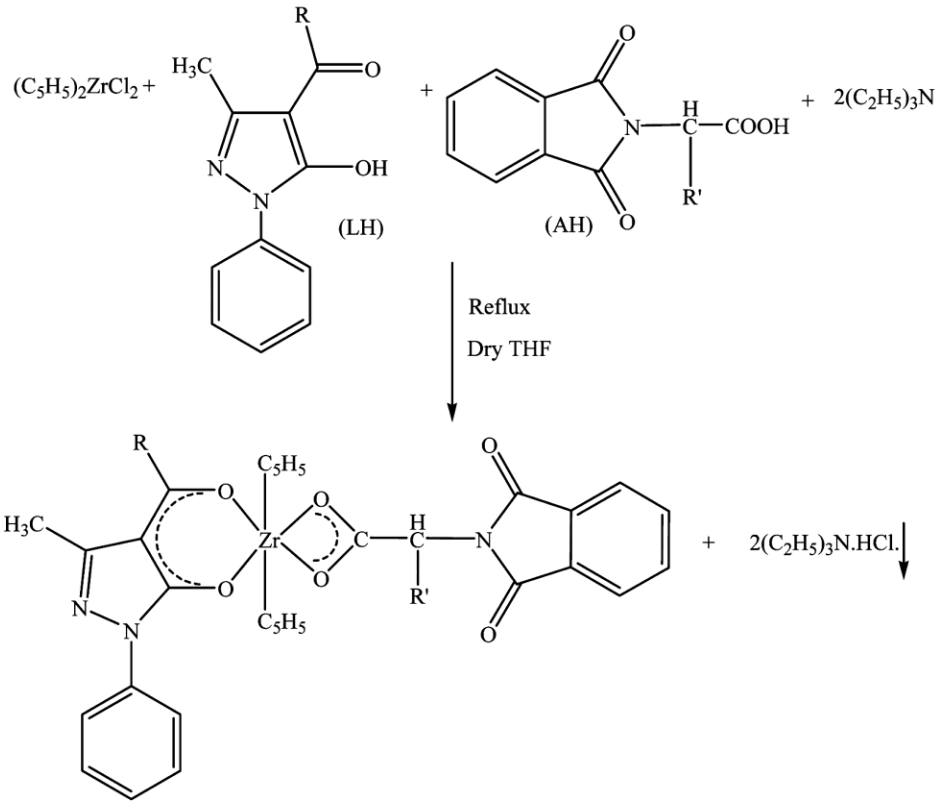
The interaction of $(C_5H_5)_2ZrCl_2$ with heterocyclic β-diketones (LH) and flexible N-protected α/ β-amino acids (AH) in the presence of triethylamine in 1:1:1:2 molar ratio in refluxing dry THF yielded zirconocene complexes of the general formula $[Cp_2ZrLA]$ (where LH= $(RCOC{:}C(OH)N(C_6H_5)N{:}CCH_3)$ and AH= $(C(O)C_6H_4C(O)NCH(R)COOH)$ where R= $-CH_3(L_{(1)}H)$, $-CH_2CH_3(L_{(2)}H)$, p-ClC_6H_4- $(L_{(3)}H)$, $-C_6H_5(L_{(4)}H)$ and CHR' = $-CH_2CH_2(A_{(1)}H)$ and R' = $CH(CH_3)_2(A_{(2)}H)$) (Scheme 1).

Triethylamine hydrochloride formed in these reactions was filtered out. The coloured solid products were obtained after removing the excess THF in vacuo. These zirconocene incorporated products were purified by recrystallization from benzene hexane mixture in 52-59% yield. These products were characterized with the aid of mass and spectroscopic studies.

IR spectra

The IR spectra of these complexes demonstrated two new medium intensity bands in the regions 531.33-516.81 cm^{-1} and 659.55-609.85 cm^{-1} which may be due to Zr-O bonds. The carbonyl frequency υ (>C=O) of heterocyclic β-diketones was observed at 1545 cm^{-1} (Ref.18). In the IR spectra of the complexes, this band shifts to lower wave number in the region 1539.6-1526.9 cm^{-1}. This suggests the bidentate mode of bonding of the ligands

The $\upsilon(COO)_{sym}$ and the imido$\upsilon(CO)_{asym}$vibrations of N-protected amino acids ($A_{(1)}H$ and $A_{(2)}H$) appeared in the regions 1390-1380 cm^{-1} and 1770-



-R = -CH_3;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(1)}A_{(1)}$,	Complex 1
-R = -CH_2CH_3;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(2)}A_{(1)}$,	Complex 2
-R = p-ClC_6H_4;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(3)}A_{(1)}$,	Complex 3
-R = -C_6H_5;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(4)}A_{(1)}$,	Complex 4
-R = -CH_3;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(1)}A_{(2)}$,	Complex 5
-R = -CH_2CH_3;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(2)}A_{(2)}$,	Complex 6
-R = p-ClC_6H_4;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(3)}A_{(2)}$,	Complex 7
-R = -C_6H_5;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(4)}A_{(2)}$,	Complex 8

Scheme 1 — Synthesis of zirconocene complexes (Complex 1-8)

1760 cm^{-1}, respectively[19]. In the IR spectra of the complexes, $\upsilon(COO)_{sym}$ was observed in the region 1397.53-1378.92 cm^{-1} and $\upsilon(CO)_{asym}$ appeared in the region 1774.62-1771.56 cm^{-1}. In the IR spectra of the ligands ($A_{(1)}H$ and $A_{(2)}H$), the $\upsilon(COO)_{asym}$ and $\upsilon(CO)_{sym}$ bands were observed as a broad band in the region 1740-1690 cm^{-1} after their merger. In zirconocene complexes, this band splits into two bands. The $\upsilon(COO)_{asym}$ vibration appeared in the region 1629.10-1607.80 cm^{-1} whereas $\upsilon(CO)_{sym}$ vibration was observed in the region 1717.30-1709.16 cm^{-1}[(Ref. 20)]. The calculated values of $\Delta\upsilon$ [$\upsilon(COO)_{asym}$- $\upsilon(COO)_{sym}$] for these zirconocene complexes are in the range 210.27-248.91 cm^{-1}. These values suggest the chelating bidentate nature of these ligands in zirconocene complexes. In zirconocene complexes, absorption bands appeared in the regions 911.60-805.92 cm^{-1} and 1079.28-1007.76 cm^{-1} which may be assigned to υ(C-H) out of plane and υ(C-H) in plane vibrations, respectively.

^{1}H NMR spectra

In the ^{1}H NMR spectra of heterocyclic β-diketones $L_{(1)}H$, $L_{(3)}H$ and $L_{(4)}H$, the enolic -OH appeared as broad signals at 11.30, 10.20 and 11.82 ppm, respectively. The carboxylic -OH of N-protected amino acids, $A_{(1)}H$ and $A_{(2)}H$[(Ref.21)] are observed as broad singlets at 7.99 ppm and 8.90 ppm, respectively. These broad singlets disappeared from the ^{1}H NMR spectra of zirconocene complexes which clearly shows the deprotonation of the ligands $L_{(1)}H$, $L_{(3)}H$, $L_{(4)}H$, $A_{(1)}H$ and $A_{(2)}H$ and formation of Zr-O bonds. In the ^{1}H NMR spectra of zirconocene

complexes, the ring methyl proton signals are observed as singlets in the region 1.82-1.94 ppm. Aromatic proton signals of heterocyclic β-diketones and -C_6H_4 signals of N-protected amino acids are overlapping and appeared as a complex pattern in the region 7.02-7.74 ppm. The cyclopentadienyl ring protons signals were observed in the region 6.42-6.50 ppm. The peaks of other groups exhibited expected multiplicities (Table 2).

^{13}C NMR spectra

The ^{13}C NMR spectra of zirconocene complexes demonstrate some shift in the positions of C_3, C_4 and C_6 carbon signals as compared to their positions in the free heterocyclic β-diketones[22]. This clearly shows bidentate mode of bonding of these ligands. The carboxylic carbon signal of N-phthaloyl valine ($A_{(2)}H$) was observed at 173.82 ppm. There is some downfield shift (1.64-2.83 ppm) in its position in the ^{13}C NMR spectra of zirconocene complexes. This clearly shows the bidentate nature of bonding of N-phthaloyl valine in these complexes. The cyclopentadienyl ring carbon signals appeared at 114.39 ppm, 116.60 ppm, 117.28 ppm and 116.95 ppm in Complexes 5, 6, 7, and 8, respectively. The aromatic carbon signals of the ligands and zirconocene complexes were observed in the region 120.4- 148.59 ppm. (Table 3)

Mass spectra

The mass spectra demonstrated many peaks which suggested the formation of various fragments due to loss of the ligands and the side-chains. Molecular ion peaks were observed in most of these complexes. On the basis of mass and other spectroscopic studies, the following plausible structure (Fig. 1) with a distorted octahedral geometry may be suggested for these zirconocene complexes.

Table 2 — ^{1}H NMR data of zirconocene complexes and the corresponding ligands in (δ) ppm

Ligand/ Complex	(RCOC:C(OH)N(C_6H_5)N:CCH$_3$) (LH)					(C(O)C_6H_4C(O)NCH(R')COOH) (AH)					
				Terminal groups							
	OH	Ring CH_3	Ring C_6H_5	p-Cl C_6H_4 /C_6H_5	CH_3	COOH	C_6H_4	CH_2	CH	CH_3	C_5H_5
$L_{(1)}H$	11.30 (bs)	2.41 (s)	7.24-7.81 (m)		2.43 (s)						
$L_{(3)}H$	10.20 (bs)	2.10 (s)	7.24-7.85 (m)	**							
$L_{(4)}H$	11.82 (bs)	2.12 (s)	7.29-7.87 (m)	**							
$A_{(1)}H$						7.99 (bs)	7.77-7.84 (m)	3.90,3.88,3.86(t) 2.65,2.63,2.61(t)			
$A_{(2)}H$[a]						8.90 (bs)	7.28-7.89 (m)		4.63(d) 2.76(m)	1.17(d) 0.90(d)	
$Cp_2ZrL_{(1)}A_{(1)}$ (Complex 1)	-	1.87 (s)	7.02-7.52 (m)		*	-	**	3.81,3.80,3.78(t) 2.66,2.65(t)(ur)			6.50 (bs) 6.45 (bs)
$Cp_2ZrL_{(3)}A_{(1)}$ (Complex 3)	-	1.94 (s)	7.02-7.52 (m)	**		-	**	3.84,3.82, 3.80 (t) 2.24,2.00 (t)(ur)			6.48 (bs)
$Cp_2ZrL_{(4)}A_{(1)}$ (Complex 4)	-	1.86 (bs)	7.24-7.60 (m)	**		-	**	3.79-3.85 (t)(ur) 2.66(t) (ur)			6.42 (bs)
$Cp_2ZrL_{(3)}A_{(2)}$ (Complex 7)	-	1.82 (bs)	7.24-7.69 (m)	**		-	**		4.40(d) 2.71(m)	1.28(d) 0.84(d)	6.46 (bs)
$Cp_2ZrL_{(4)}A_{(2)}$ (Complex 8)	-	1.83 (s)	7.24-7.74 (m)	**		-	**		4.36(d) 2.73(d)	1.01(d) 0.99(d)	6.48 (bs)

* merged with ring methyl, (bs)= broad singlet, ** merged with ring phenyl , s= singlet t = triplet ,d=doublet , m=multiplet, ur= unresolved

LH= (RCOC:C(OH)N(C_6H_5)N:CCH$_3$) [Where R = -CH_3 ($L_{(1)}H$), R = p-ClC_6H_4 ($L_{(3)}H$), R=C_6H_5 ($L_{(4)}H$)]

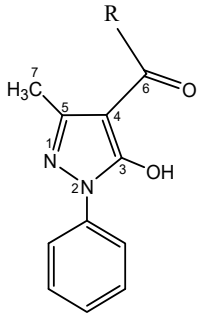
AH= (C(O)C_6H_4C(O)NCH(R')COOH) [Where CHR'= -CH_2CH_2- ($A_{(1)}H$), R'= -$CH(CH_3)_2$($A_{(2)}H$)]

a= ref. 21

Table 3 — ^{13}C-NMR data of zirconocene complexes and the corresponding ligands in (δ)ppm.

Ligand/ Complex	$(RCOC{:}C(OH)N(C_6H_5)N{:}CCH_3)_{(LH)}$									$A_{(2)}H=(C(O)C_6H_4C(O)NCH(CH(CH_3)_2)COOH$					
						Ring phenyl	Terminal groups								
	C_3	C_4	C_5	C_6	C_7		CH_2	CH_3	p-Cl C_6H_4 /C_6H_5	COOH	CO	CH_3	CH	C_6H_4	Zr-Cp
$L_{(1)}H^b$	160.4	104.1	137.1	196.2	15.4	147.0,129.2, 126.1,120.4		26.2							
$L_{(2)}H^b$	160.4	103.4	137.0	198.0	15.9	147.0,129.0, 126.4,120.8	32.6	8.4							
$L_{(3)}H^b$	161.1	103.5	138.1	190.9	15.8	147.6,129.1, 128.8,120.8			138.0, 136.2, 129.0, 126.8						
$L_{(4)}H^b$	161.5	103.6	137.5	191.5	15.7	147.9,128.9,12 6.5,120.6			131.7, 128.9, 128.3, 127.8						
$A_{(2)}H^a$										173.82	167.87	19.46, 20.94	28.42 57.49 (CH-N)	123.64 131.53 134.52	
$Cp_2ZrL_{(1)}A_{(2)}$ (5)	161.20	104.89	*	197.97	16.69			27.89	123.49-148.59	175.46	163.01	22.26, 23.59	27.89 56.64	*	114.39
$Cp_2ZrL_{(2)}A_{(2)}$ (6)	162.05	103.90	*	197.33	16.42		34.06	8.84	123.24-146.52	176.65	168.38	19.87, 21.51	28.76 58.01	*	116.60
$Cp_2ZrL_{(3)}A_{(2)}$ (7)	162.98	106.10	*	191.24	16.18	*			123.46-148.48	173.16	**	19.66, 21.13	27.86 58.90	*	117.28
$Cp_2ZrL_{(4)}A_{(2)}$ (8)	162.90	102.96	*	193.42	16.06	*			120.02-148.50	175.83	167.77	19.96, 20.83	28.84 59.73	*	116.95

*Merged with phenyl ring
** merged with C_3



LH= [Where R = -CH_3 ($L_{(1)}H$), R = p-ClC_6H_4 ($L_{(3)}H$), R=C_6H_5 ($L_{(4)}H$)]

$A_{(2)}H=(C(O)C_6H_4C(O)NCH(CH(CH_3)_2)COOH)$

a= ref. 21; b= ref. 22

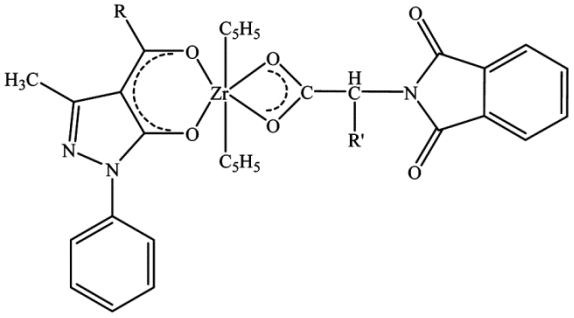
These zirconocene complexes possess one six-membered ring, one four-membered ring and two C_5H_5 rings attached to central zirconium atom. Hence, a distorted octahedral geometry may be assigned to these zirconocene complexes.

Antimicrobial activity

The antimicrobial activity of some heterocyclic β-diketones, $L_{(1)}H$, $L_{(2)}H$, $L_{(3)}H$ and $L_{(4)}H$, N-protected amino acid $A_{(1)}H$ and newly synthesized zirconocene complexes 1-4 were investigated against two bacterial

strains *S. aureus*, *E. coli* and two fungal strains *A. niger* and *C. albicans* (Table 4).

The heterocyclic β-diketone $L_{(3)}H$ demonstrates highest activity and $L_{(1)}H$ is the least active in the series against *S. aureus* at 30 μL, 60 μL, 90 μL and 120 μL concentrations. The antimicrobial activity of the ligands and zirconocene complexes increases with the increase of concentration. In general, these complexes are more active than their parent ligands. In the case of *S. aureus*, at 30 μL, 60 μL, 90 μL and 120μL concentrations, Complex 3 demonstrates the highest activity as compared to the other complexes. This complex shows maximum activity at 120 μL concentration. The presence of two Cp rings directly attached to zirconium atom, chlorine, six-membered and four-membered chelate rings may be important contributors for antibacterial activity of this zirconocene complex. On the contrary, Complex 1 exhibits lowest activity in the series. This complex lacks chlorine atom in its structure. In the case of *E. coli*, at 30 μL, 60 μL, 90 μL and 120 μL concentrations, Complex 3 shows maximum activity whereas the Complex 2 exhibits minimum activity. These observations can be explained on the basis of the presence of chlorine atom in the complex structure. The Complex 3 possesses chlorine atom whereas the Complex 2 lacks chlorine atom.



-R = -CH_3;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(1)}A_{(1)}$,	Complex 1
-R = -CH_2CH_3;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(2)}A_{(1)}$,	Complex 2
-R = p-ClC_6H_4;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(3)}A_{(1)}$,	Complex 3
-R = -C_6H_5;	-CHR' = -CH_2CH_2,	$(C_5H_5)_2ZrL_{(4)}A_{(1)}$,	Complex 4
-R = -CH_3;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(1)}A_{(2)}$,	Complex 5
-R = -CH_2CH_3;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(2)}A_{(2)}$,	Complex 6
-R = p-ClC_6H_4;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(3)}A_{(2)}$,	Complex 7
-R = -C_6H_5;	-R' = -$CH(CH_3)_2$,	$(C_5H_5)_2ZrL_{(4)}A_{(2)}$,	Complex 8

Fig. 1 — Structure of the complex $[(C_5H_5)_2Zr(RCOC{:}C(O)N(C_6H_5)N{:}CCH_3)(O_2CCHR'NC(O)C_6H_4C(O))]$

Antifungal activity

In the case of *A. niger*, at 30 μL, 60 μL, 90 μL and 120 μL concentrations, $L_{(3)}H$ shows highest antifungal activity whereas $L_{(1)}H$ exhibits lowest activity in the series of heterocyclic β-diketones. The antifungal activity of the ligands and zirconocene complexes

Table 4 — Antibacterial activity of the zirconocene complexes and the corresponding ligands

Ligand/complexes	30 μL	60 μL	90 μL	120 μL	Organism
$L_{(1)}H$	12 mm	14 mm	16mm	18mm	
$L_{(2)}H$	13 mm	15 mm	17mm	20mm	
$L_{(3)}H$	15 mm	17 mm	19mm	22mm	*S. aureus*
$L_{(4)}H$	14 mm	16 mm	18mm	21mm	
$A_{(1)}H$	-	14 mm	16mm	18mm	
$Cp_2ZrL_{(1)}A_{(1)}$ (1)	14 mm	16 mm	17mm	19mm	
$Cp_2ZrL_{(2)}A_{(1)}$ (2)	15 mm	17 mm	19mm	21mm	
$Cp_2ZrL_{(3)}A_{(1)}$ (3)	17 mm	19 mm	21mm	24mm	
$Cp_2ZrL_{(4)}A_{(1)}$ (4)	16 mm	18 mm	20mm	23mm	
$L_{(1)}H$	-	-	16 mm	17 mm	
$L_{(2)}H$	-	-	17 mm	18 mm	
$L_{(3)}H$	21 mm	24 mm	26 mm	28 mm	
$L_{(4)}H$	20 mm	23 mm	25 mm	27 mm	
$A_{(1)}H$	-	-	15 mm	16 mm	*E. coli*
$Cp_2ZrL_{(1)}A_{(1)}$ (1)	-	20 mm	22mm	23 mm	
$Cp_2ZrL_{(2)}A_{(1)}$ (2)	-	-	18 mm	19 mm	
$Cp_2ZrL_{(3)}A_{(1)}$ (3)	23 mm	25 mm	27 mm	29 mm	
$Cp_2ZrL_{(4)}A_{(1)}$ (4)	22 mm	24 mm	26 mm	28 mm	

Table 5 — Antifungal activity of the zirconocene complexes and the corresponding ligands

Ligand/complexes	30 µL	60 µL	90 µL	120 µL	Organism
$L_{(1)}H$	-	10 mm	12 mm	14 mm	
$L_{(2)}H$	-	11mm	13 mm	15 mm	
$L_{(3)}H$	12 mm	14 mm	16 mm	19 mm	*A. niger*
$L_{(4)}H$	10 mm	12 mm	15 mm	18 mm	
$A_{(1)}H$	-	13 mm	16 mm	19 mm	
$Cp_2ZrL_{(1)}A_{(1)}$ (1)	-	14 mm	17 mm	20 mm	
$Cp_2ZrL_{(2)}A_{(1)}$ (2)	-	15 mm	18 mm	21 mm	
$Cp_2ZrL_{(3)}A_{(1)}$ (3)	13 mm	17 mm	19 mm	23 mm	
$Cp_2ZrL_{(4)}A_{(1)}$ (4)	12 mm	16 mm	18 mm	22 mm	
$L_{(1)}H$	-	15 mm	18 mm	21mm	
$L_{(2)}H$	-	17 mm	19 mm	23 mm	
$L_{(3)}H$	16 mm	20 mm	23 mm	25 mm	
$L_{(4)}H$	15 mm	19 mm	22 mm	24 mm	
$A_{(1)}H$	-	14 mm	18 mm	21 mm	*C.albicans*
$Cp_2ZrL_{(1)}A_{(1)}$ (1)	-	17 mm	20 mm	22 mm	
$Cp_2ZrL_{(2)}A_{(1)}$ (2)	16 mm	18 mm	20 mm	24 mm	
$Cp_2ZrL_{(3)}A_{(1)}$ (3)	18 mm	21 mm	24 mm	26 mm	
$Cp_2ZrL_{(4)}A_{(1)}$ (4)	17 mm	20 mm	23 mm	25 mm	

enhances with the increase of concentration (Table 5). In the case of *A. niger*, at 30 µL, 60 µL, 90 µL and 120 µL concentrations, Complex 3 shows highest antifungal activity whereas Complex 1 exhibits minimum antifungal activity in the series. The most probable reason for the highest activity of the complex Complex 3 may be the presence of chlorine atom. Similarly, in the case of *C. albicans*, at 30 µL, 60 µL, 90 µL and 120 µL concentrations, Complex 3 displays highest activity whereas Complex 1 was found to be least active in the series.

Conclusion

A new set of zirconocene complexes was synthesized by the interaction of zirconocene dichloride with heterocyclic β-diketones and N-protected amino acids in the presence of triethylamine. The tentative structures of these zirconocene incorporated organic-inorganic hybrid complexes were suggested using spectroscopic techniques. Some representative complexes and their corresponding ligands were screened for their antimicrobial activity in order to study and correlate the structure with their biopotential.

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