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Macrocyclic zinc(II) Complexes with Tetradentate N_2O_2 Donor Schiff base Ligands Incorporating 1,3,4-thiadiazole Ring

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ABSTRACT

A new series of diazadioxa macrocyclic zinc(II) derivatives $[\{Zn(M)(H_2O)_2\}(OAc)_2]$ (M=macrocyclic ligands) prepared via template synthesis method, by the reaction of Schiff bases derived from bis-(2-hydrazino-1,3,4-thiadiazole-5-yl)arene/alkanes and 3,5-dichlorosalicyldehyde/2-hydroxy-1-naphthaldehyde with 1,4-dibromobutane in the presence of Zn(II) ion. The structures of all these complexes were established on the basis of elemental analyses, spectral data (IR and ^{1}H-NMR), PXRD, SEM techniques. Presence of coordinated water molecules in the Zn(II) complexes were confirmed by TGA analyses. The antimicrobial effects of all the synthesized complexes were evaluated against different species of pathogenic fungi (*A. niger, A. alternata*) and bacteria (*E. coli, B. subtilis*).

Keywords: Macrocyclic Zn(II), SEM, XRD, Antimicrobial activity.

INTRODUCTION

Thiadiazoles and its derivatives show interesting biological and pharmacological activities which may be due to the presence of C_2N_2S moiety and its high aromaticity.[1-3] Literature survey reveal that the molecule containing 1,3,4-thiadiazole ring have diverse therapeutic applications such as antimicrobial[4,5], analgesic[6], antiviral[7], anti-inflammatory[8], anticonvulsant[9,10], antidiabetic[11,12], anticancer[13,14], anti-tubercular activity[15]. Researchers have used medium to large sized cyclic compounds as a tool in discovery of drugs due to their significant biological and physic-chemical properties[16,17]. A number of macrocyclic polyether compounds incorporating a 1,3,4-thiadiazole moiety have been applied to inhibit corrosion of C38 carbon steel in acidic medium[18]. The creation of synthetic five to six-membered heterocyclic macrocyclic compounds has wide applications due to their remarkable properties in various fields[19]. Host-guest complexation relationships have been studied in such macrocycles depending upon side chain substitution pattern[20]. A number of macrocyclic metal complexes have been prepared via template synthesis method[21]. Biological and pharmacological properties of 1,3,4-thiadiazole make us confident to synthesize some more bis-Schiff base compounds. In this paper, synthesis, characterization and application of some diazadioxa macrocyclic Zn(II) derivatives prepared via template synthesis by the reaction of bis-(2-hydrazino-1,3,4-thiadiazole-5-yl)arene/alkanes (2-BHTA) and

3,5-dichlorosalicyldehyde (3,5-DCS)/2-hydroxy-1-naphthaldehyde (2-HN) with 1,4-dibromobutane (1,4-DBB) in presence of Zn(II) acetate salt have been discussed.

MATERIALS AND METHODS

Chemicals and Instrumentation

The chemicals were purchased from Merck and Aldrich. Elemental analysis was evaluated with a Vario EL III Carlo Erba 1105 CHN analyser. Melting points were determined by Buchi 530 apparatus. Shimadzu 8201 PC model spectrophotometer was used to record IR spectra in KBr; whereas NMR spectra were recorded by Bruker DRX-300 spectrometer in DMSO using tetramethylsilane (TMS) as standard. JOEL model JSM-6390LV scanning electron microscope was used to get SEM micrograph of the Zn(II) complexes. TGA data of the macrocyclic complexes were obtained using a Perkin Elmer-STA 6000 thermal instrument. Bruker AXS DB Advance diffractometer was used to record powder X-ray diffraction dimensions with CuKα radiation (λ=1.5406 Å).

Preparation of Schiff bases

Maffi et al method[22] was used to synthesize bis-(2-hydrazino-1,3,4-thiadiazole-5-yl) arene/alkanes. Schiff base was synthesized by the condensation reaction of 2-BHTA and 2-HN/3,5-DCS in 1:2 ratio in absolute ethanol containing concentrated HCl and the mixture was refluxed for 8-9 hours. Precipitate thus formed, was filtered and washed with ethanol and ether and recrystallized from alcohol.

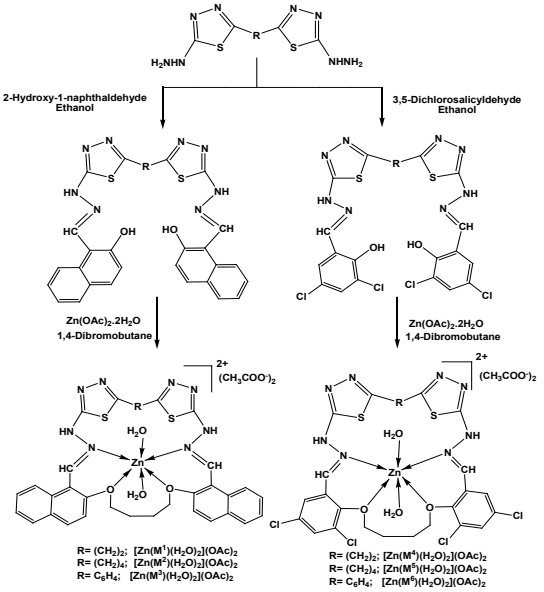

Fig. 1. Reaction route for the synthesis of MZ-II derivatives

Preparation of macrocyclic zinc(II) derivatives

Macrocyclic zinc(II) (MZ-II) complexes was synthesized via template synthesis method for which $Zn(CH_3COO)_2.2H_2O$ (0.02 mol) and 1,4-DBB (0.02 mol) was simultaneously added to the alcoholic solution (30 cm^3) of appropriate Schiff base (0.02 mol) and resultant content was refluxed for 11-14 hours. The resulting Yellow/brown substances was filtered, washed with ethanol and dried in vacuo. The general reaction scheme is given in Fig. 1 and the analytical data of the synthesized complexes is listed in Table 1.

Table 1: Analytical data of MZ-II derivatives

Compound	Molecular formula	% Yield% Analysis Found (Calc.)						
		C	H	N	S	Cl	Zn	
$[Zn(M_1)(H_2O)_2](OAc)_2$	$C_{36}H_{38}N_8O_8S_2Zn$	65	51.31	4.51	13.29	7.49	-	7.68
			(51.46)	(4.56)	(13.36)	(7.63)		(7.78)
$[Zn(M_2)(H_2O)_2](OAc)_2$	$C_{38}H_{42}N_8O_8S_2Zn$	56	52.49	4.85	12.81	7.31	-	7.46
			(52.56)	(4.88)	(12.91)	(7.39)		(7.53)
$[Zn(M_3)(H_2O)_2](OAc)_2$	$C_{40}H_{38}N_8O_8S_2Zn$	75	53.98	4.24	12.51	7.10	-	7.27
			(54.09)	(4.31)	(12.62)	(7.22)		(7.36)
$[Zn(M_4)(H_2O)_2](OAc)_2$	$C_{28}H_{30}N_8O_8S_2Cl_4Zn$	71	38.26	3.41	12.69	7.22	16.01	7.34
			(38.31)	(3.44)	(12.76)	(7.31)	(16.15)	(7.45)
$[Zn(M_5)(H_2O)_2](OAc)_2$	$C_{30}H_{34}N_8O_8S_2Cl_4Zn$	69	39.67	3.72	12.30	7.01	15.59	7.10
			(39.77)	(3.78)	(12.37)	(7.08)	(15.65)	(7.22)
$[Zn(M_6)(H_2O)_2](OAc)_2$	$C_{32}H_{30}N_8O_8S_2Cl_4Zn$	78	41.46	3.21	12.02	6.84	15.21	6.93
			(41.5)	(3.27)	(12.10)	(6.93)	(15.32)	(7.06)

Antimicrobial properties

Antifungal effect of MZ-II complexes were evaluated against two pathogenic fungal strains (*A. niger* and *A. alternata*) by agar plate technique method reported in litrature[23]; the outcomes were recorded as percentage of inhibtion and compared

with fluconazole which was used as standard drug. Antibacterial effect of MZ-II complexes were screened against *Gram-positive B. subtilis* and *Gram-negative E. coli* by agar well diffusion method[24] and the results were recorded by measuring zone of inhibition (mm) and compared with tetracyclin.

RESULTS AND DISCUSSION

The synthesized MZ-II complexes were air stable and soluble in DMSO and DMF solvents. The analytical analyses of the synthesized MZ-II complexes agree well with the proposed macrocyclic frame. The electrical conductance measurements have been evaluated in DMF which indicate that the MZ-II derivatives are electrolytic nature. The presence of acetate ion has also been confirmed by neutral $FeCl_3$ solution test which gives blood red color with the complexes. TGA studies confirm the presence of coordinated water molecules in the MZ-II complexes, as it shows weight loss in the range of 135-170°C.

Spectral Interpretation

Table 2 contains IR spectral data of the synthesized MZ-II derivatives. A band at ca. 3232-3192 cm^{-1} in the acyclic ligands and their corresponding MZ-II derivatives is due to υ(N-H). A medium band at ca. 1638 cm^{-1} is assignable to υ(C=N) group in acyclic ligands which appears at lower frequency (~15-25 cm^{-1}) in the related MZ-II complexes[25,26], and this change assures the involvement of azomethine nitrogen in bonding with zinc ion, which is also confirmed by a new band at ca. 418-462 cm^{-1} attributable to υ(Zn-N) in the MZ-II complexes. Spectra of acyclic ligands show intramolecular H-bonded phenolic –OH bands[27] at nearly 2900 cm^{-1} which vanishes in their respective MZ-II derivatives and a new band appears at ca. 509-528 cm^{-1} attributable to υ(Zn-O)[28]. Acyclic ligands show a band at ca. 1101 cm^{-1} because of υ(C-S-C) vibration, which remains unaltered in corresponding MZ-II derivatives, suggesting the non-involvement of thiadiazole ring sulphur. A broad band in the region ca. 3409-3452 cm^{-1} is attributable to coordinated water molecules[29] in the MZ-II complexes. Presence of acetate ions in the MZ-II complexes were confirmed by asymmetrical and symmetrical stretching band at ca. 1625-1640 and ca. 1420 cm^{-1} respectively[30].

Table 2: ^{1}H-NMR spectral data of MZ-II derivatives

Compound	^{1}H-NMR data (δ, ppm)						
	$-CH_2-$	$-O(CH_2)_4O-$	-NH	Aromatic rings	-HC=N-	$-OOCCH_3$	H_2O
$[Zn(M_1)(H_2O)_2](OAc)_2$	2.52 t	3.62 t,2.13 m	10.25 s	7.12-8.00 m	8.54 s	2.37 s	5.38 s
$[Zn(M_2)(H_2O)_2](OAc)_2$	2.77 t,1.91 m	3.57 t,2.11 m	10.16 s	6.94-7.85 m	8.48 s	2.35 s	5.31s
$[Zn(M_3)(H_2O)_2](OAc)_2$	-	3.65 t,2.18 m	10.31 s	7.18-8.05 m	8.61 s	2.39 s	5.49 s
$[Zn(M_4)(H_2O)_2](OAc)_2$	2.55 t	3.56 t,2.17 m	10.51 s	7.51, 7.75 s	8.72 s	2.41 s	5.47 s
$[Zn(M_5)(H_2O)_2](OAc)_2$	2.69 t,1.94 m	3.54 t,2.14 m	10.41 s	7.50, 7.75 s	8.65 s 8.78 s	2.38 s	5.42 s
$[Zn(M_6)(H_2O)_2](OAc)_2$	-	3.59 t,2.18 m	10.58 s	7.52 m, 7.56, 7.79 s		2.45 s	5.57 s

Table 3 contains chemical shifts for MZ-II complexes protons which were recorded in dissimilar environments using deuterated DMSO solvent. A signal at ca. 11.58 ppm is observed in acyclic ligands due to phenolic protons which vanish in the corresponding MZ-II derivatives. Naphthyl and aromatic protons appear as a multiplet at ca. 6.99-7.85 ppm. Signals at ca. 10.16 and 8.28 ppm is because of hydrazino NH and azomethine protons correspondingly in Schiff bases. Among the two signals, first one remains unchanged whereas the second signal shifts downfield and observed at ca. 8.48 ppm in the corresponding MZ-II derivatives and it confirms the coordination of the azomethine nitrogen to the zinc(II) ion. A signal at ca. 2.35 ppm indicates the presence of acetate ion in the MZ-II complexes. The spectra of all MZ-II derivatives show a new signal at ca. 5.5 ppm assignable to water protons.

Table 3: ^{1}H-NMR spectral data of MZ-II derivatives

Compound	^{1}H-NMR data (δ, ppm)						
	$-CH_2-$	$-O(CH_2)_4O-$	-NH	Aromatic rings	-HC=N-	$-OOCCH_3$	H2O
$[Zn(M_1)(H_2O)_2](OAc)_2$	2.52 t	3.62 t,2.13 m	10.25 s	7.12-8.00 m	8.54 s	2.37 s	5.38 s
$[Zn(M_2)(H_2O)_2](OAc)_2$	2.77 t,1.91 m	3.57 t,2.11 m	10.16 s	6.94-7.85 m	8.48 s	2.35 s	5.31s
$[Zn(M_3)(H_2O)_2](OAc)_2$	-	3.65 t,2.18 m	10.31 s	7.18-8.05 m	8.61 s	2.39 s	5.49 s
$[Zn(M_4)(H_2O)_2](OAc)_2$	2.55 t	3.56 t,2.17 m	10.51 s	7.51, 7.75 s	8.72 s	2.41 s	5.47 s
$[Zn(M_5)(H_2O)_2](OAc)_2$	2.69 t,1.94 m	3.54 t,2.14 m	10.41 s	7.50, 7.75 s	8.65 s 8.78 s	2.38 s	5.42 s
$[Zn(M_6)(H_2O)_2](OAc)_2$	-	3.59 t,2.18 m	10.58 s	7.52 m, 7.56, 7.79 s		2.45 s	5.57 s

SEM

Surface morphology of one of the representative complex $[Zn(M_2)(H_2O)_2](OAc)_2$ was evaluated and the micrograph show irregular arrangement of nano-ranged particles with globular morphology (Figure 2).

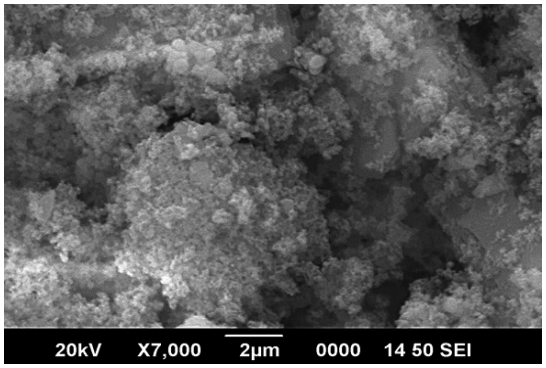

Fig. 2. SEM image of $[Zn(M_2)(H_2O)_2](OAc)_2$

X-Ray Diffraction

The XRD studies of one of the complex $[Zn(M_2)(H_2O)_2](OAc)_2$, indicates the nano-crystal (Fig. 3) formation. The particles size of the selected macrocyclic Zn(II) complex have been determined by Debye-Scherer formula[31] ($D=0.94\lambda/\beta Cos\theta$). Calculated particles size falls in range of 83.02-83.65 nm.

Biological activity results

MZ-II complexes are more toxic than the parent ligands. The cause behind the better toxicity of the MZ-II derivatives can be understood by chelation theory, which explains that chelation reduces the polarity of the metal ion, thus it allows the permeation of the compounds via cell membranes[32]. *In vitro* antifungal studies of all the compounds was evaluated against *A. niger* and *A. alternata*, using Fluconazole as standard drug and the results were noted at 10, 100 and 1000 ppm concentration. Antifungal results (Fig. 4 and Table 4) show that all MZ-II complexes were more active against *A. niger* while complexes 4, 5 and 6 were more toxic which may be due to chloro group.

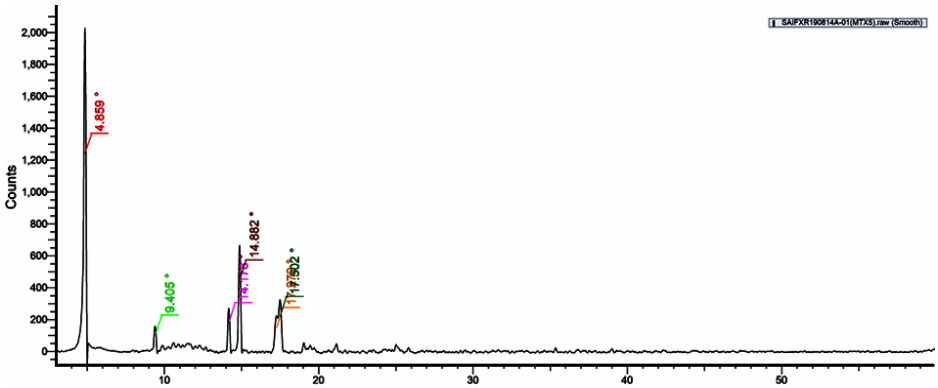

Fig. 3. XRD image of $[Zn(M_2)(H_2O)_2](OAc)_2$

Table 4: Antifungal screening data of MZ-II derivatives

Compound	Percentage Inhibition					
	A. niger			*A. alternata*		
	10	100	1000	10	100	1000
$[Zn(M_1)(H_2O)_2](OAc)_2$	31	48	62	-	24	39
$[Zn(M_2)(H_2O)_2](OAc)_2$	28	45	58	-	-	35
$[Zn(M_3)(H_2O)_2](OAc)_2$	45	51	65	21	42	51
$[Zn(M_4)(H_2O)_2](OAc)_2$	49	56	69	35	45	60
$[Zn(M_5)(H_2O)_2](OAc)_2$	45	51	65	31	42	58
$[Zn(M_6)(H_2O)_2](OAc)_2$	55	64	72	39	48	61
Fluconazole	100	100	100	100	100	100

The antibacterial activities of the compounds were studied against *E. coli* and *B. subtilis*, using Tetracyclin as standard and the results were listed by measuring the diameter complete inhibition zone (mm). The antibacterial studies (Fig. 5 and Table 5) reveal that MZ-II derivatives were more toxic to *B. substilis*, while complexes containing chloro group were more effective.

Table 5: Antibacterial screening data of MZ-II derivatives

Compound	Zone of Inhibition	
	E. coli	B.subtilis
$[Zn(M_1)(H_2O)_2](OAc)_2$	-	-
$[Zn(M_2)(H_2O)_2](OAc)_2$	-	-
$[Zn(M_3)(H_2O)_2](OAc)_2$	13	15
$[Zn(M_4)(H_2O)_2](OAc)_2$	11	19
$[Zn(M_5)(H_2O)_2](OAc)_2$	10	18
$[Zn(M_6)(H_2O)_2](OAc)_2$	14	21
Tetracyclin	28	25

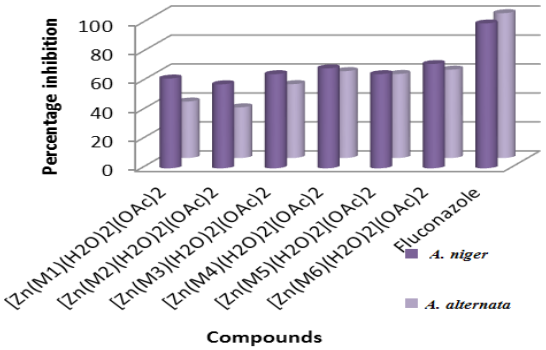

Fig. 4. Antifungal activities of MZ-II complexes at 1000 ppm

CONCLUSION

The tetradenatae N_2O_2 type ligands were used to prepare stable macrocyclic derivatives with Zn^{2+} ion and an octahedral geometry of MZ-II complexes has been estimated with the help of spectral data. The TG analysis study reveals the presence of water molecules that are coordinated to the Zn(II) ion in the MZ-II complexes. Nano-range structure of the MZ-II complexes was confirmed By XRD pattern, whereas SEM studies reveal irregular globular morphology of the MZ-II derivatives. Good antifungal and antibacterial behavior is shown by MZ-II derivatives which are due to chelation effect.

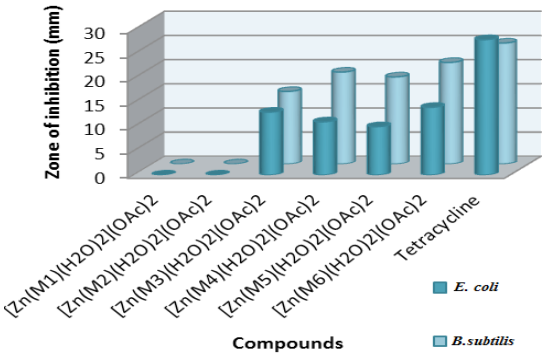

Fig. 5. Antibacterial activities of MZ-II complexes

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Conflict of interest

Authors declare no conflict of interest.

REFERENCES

1. Foks, D. P.-K. H.; Gobis, K.; *J. Heterocycl. Chem.*, **2014**, *51*, 507-512.
2. Hu, Y.; Li, C.-Y.; Wang, X.-M.; Yang, Y.-H.; Zhu, H.-L.; *Chem. Rev.*, **2014**, *114*(10), 5572-5610.
3. Shivakumara, N.; Krishna, P. M.; *J. Mol. Struc.,* **2020**, *1199*, 126999.
4. Kamal, M.; Shakya, A. K.; Jawaid, T.; *Int. J. Biomed. Res.,* **2011**, *2*(1), 41-61.
5. Serban, G.; Stanasel, O.; Serban, E.; Bota, S.; *Drug Des. Dev. Ther.*, **2018**, *12*, 1545-1566.
6. Mathew, V.; Keshavayya, J.; Vaidya, V.P.; Giles, D.; *Eur. J. Med. Chem.*, **2007**, *42*, 823-840.
7. Sidwell, R.W.; Robins, R.K.; Hillyard, I.W.; *Pharmacol. Ther. Drugs.*, **1978**, *6*, 123-146.
8. Mullican, M. D.; Wilson, M. W.; Conner, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D.; *J. Med. Chem.*, **1993**, *36*(8), 1090-1099.
9. Stillings, M. R.; Welbourn, A. P.; Walter, D. S.; *J. Med. Chem.*, **1986**, *29*(11), 2280-2284.
10. Yar, M. S.; Akhter, M.W.; *Acta Pol. Pharm.*, **2009**, *66*, 393-397.
11. Pattan, S. R.; Kittur, B. S.; Sastry, B. S.; Jaday, S. G.; Thakur, D. K.; Madamwar, S. A.; Shinde, H.V.; *Indian J. Chem.*, **2011**, *50B*, 615-618.
12. Datar, P.A.; Deokule, T.A.; *Med. Chem.,* **2014**, *4*(4), 390-399.
13. Gomha, S. M.; Edrees, M. M.; Muhammad, Z. A.; El-Reedy, A. AM.; *Drug Des. Dev. Ther.,* **2018**, *12*, 1511-1523.
14. Gomha, S.M.; Abdel-Aziz, H.M.; *Heterocycles.*, **2015**, *91*, 583-592.
15. Foroumadi, A.; Kargar, Z.; Sakhteman, A.; Sharifzadeh, Z.; Feyzmohammadi, R.; Kazemi, M.; Shafiee, A.; *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1164-1167.

16. Veber, D. F.; Holly, F. W.; Nutt, R. F.; Bergstrand, S. J.; Brady, S. F.; Hirschmann, R.; Glitzer, M. S.; Saperstein, R.; *Nature*., **1979**, *280*, 512-514.
17. Abdelraheem, E. M. M.; Shaabani, S.; Domling, A.; *Drug Discovery Today: Tech.,* **2018**, *29*, 11-17.
18. Bentiss, F.; Lebrini, M.; Vezin, H.; Chai, F.; Traisnel, M.; Lagrené, M.; *Corrosion Science*., **2009**, *51*, 2165-2173.
19. Foroughifar, N.; Mobinikhaledi, A.; Ebrahimi, S.; Moghanian, H.; Fard, M. A. B.; Kalhor, M.; *Tetrahedron Lett.,* **2009**, *50*, 836-839.
20. Lv, J.; Liu, T.; Wang, Y.; *Eur. J. Med. Chem.,* **2008**, *43*, 19-24.
21. Beattie, J. W.; SantaLucia , D. J.; White, D. S.; Groysman, S.; *Inorg. Chim. Acta*., **2017**, *460*, 8-16.
22. Maffii, G.; Testa E.; Ettorre, R.; *Chem. Abstr.,* **1959**, *53*, 2211a.
23. Grower, R. K.; Moore, J. D.; *Phytopathology*., **1962**, *52*, 876-880.
24. Rahman, A. U.; Choudhary, M. I.; Thomsen, W. J.; Harwood Academic Publishers, The Netherlands., **2001**.
25. Foroughifar, N.; Mobinikhaledi, A.; Ebrahimi, S.; Moghanian, H.; Fard, M. A. B.; Kalhor, M.; *Tetrahedron Lett.,* **2009**, *50*, 836-839.
26. Gull, P.; Malik, M. A.; Dar, O. A.; Hashmi, A. A.; Microb. Pathogenesis, 2017, 104, 212-216.
27. Filarowski, A.; Koll, A.; Kochel, A.; Kalenik, J.; Hansen, P. E.; *J. Mol. Struc*., **2004**, *700*(1-3), 67-72.
28. Koch, A.; Phukan, A.; Chanu, O. B.; Kumar, A.; Lal, R. A.; *J. Mol. Struc.,* **2014**, *1060*, 119-130.
29. Shukla, P. R.; Singh, V. K.; Jaiswal, A. M.; Narain, J.; *J. Indian Chem. Soc*., **1983**, *60*, 321-324.
30. Ferrari, A.; Braibanti, A.; Bigliardi, G.; Lanfredi, A. M.; *Acta Crystallogr.,* **1965**, *19*(4), 548-555.
31. Langford, J. I.; Wilson, A. J. C.; *J. Appl. Cryst.,* **1978,** *11*, 102-113.
32. Mahiwal, K.; Kumar, P.; Narasimhan, B.; *Med. Chem. Res*., **2012**, *21*, 293-307.