Asian Journal of Chemistry; Vol. 33, No. 1 (2021), 190-194

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2021.22982

Synthesis, Characterization of Ceftibuten-Copper(II) Complex and Prediction of Its Biological Activity

SHUCHISMITA DEY[1], MD. ZAKIR SULTAN[2] and MD. ABDUS SALAM[1,*]

[1]Department of Chemistry, University of Dhaka, Dhaka-1000, Bangladesh
[2]Centre for Advanced Research in Sciences (CARS), University of Dhaka, Dhaka-1000, Bangladesh

*Corresponding author: E-mail: masalam@du.ac.bd

Received: 2 September 2020; *Accepted*: 27 October 2020; *Published online*: 10 December 2020; AJC-20197

Ceftibuten dihydrate, one of the third-generation cephalosporin antibiotic is effectively used in curing several infectious diseases. The complexation of drug with metal may enhance the antibacterial activity. In this work, a new complex of ceftibuten dihydrate with Cu(II) was synthesized, characterized and antibacterial activity is reported. The *in vitro* test showed that the antibacterial activity of complex of ceftibuten was greatly enhanced against *Staphylococcus aureus* and *Salmonella typhi*.

Keywords: Ceftibuten, Copper(II) complex, Biological activity.

INTRODUCTION

The drug ceftibuten dihydrate belongs to third generation cephalosporins, a class of β-lactam antibiotic having structure similar to that of penicillin. Its chemical name is (+)-(6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazoyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid dihydrate [1]. Its molecular formula is $C_{15}H_{14}N_4O_6S_2{\cdot}2H_2O$ with a molecular weight 446.45 as dihydrate. As an orally-taken drug, ceftibuten is used to cure various bacterial infections including otitis media, bronchitis, pneumonia, tonsillitis, bladder infection, pharyngitis and bacteremia [2]. It has a broad spectrum of activity including both Gram-positive and Gram-negative aerobes [3,4]. Like other cephalosporins, ceftibuten inhibits the synthesis of bacterial cell wall through the binding of essential target proteins of bacterial cell wall *via* β-lactam ring. This binding finally causes cell lysis [5,6].

The metal coordination compounds show a great diversity in biological action [7]. Thus, complexation can be used to enhance the activity of biologically active molecules [8]. At present, metal complexation is an important area of research because of increasing effectiveness against bacteria upon chelation with the transition metal ions [9-12] as well as reducing toxicity of drugs [13]. In addition, many antibiotics of the Universe have become resistant to human body because of abuses of those drugs, which create threats to public health worldwide [14]. Therefore, the development of more potent antimicrobial agents is an urgent need to eradicate infections caused by drug resistant bacteria.

Copper(II) is used in this work because its complexes of various drugs can be used for the treatment of patients who suffer from many life threatening diseases like cancers [15]. Moreover, copper and its alloys are naturally abundant antimicrobial materials. The antimicrobial properties of copper are well known even before the concept of microbe became understood in the nineteenth century [16]. It is proved that many drugs upon chelation with metals like copper, silver, gold, platinum exhibit enhanced biological activity and reduced toxicity and also play an important role in detecting diseases [17,18].

As per literature survey, there is no report available about the synthesis, characterization and biological studies on ceftibuten-metal complex. So study of new metal complexes of ceftibuten and other antibiotics with metals can be applicable for specific treatment against various diseases [19]. In this regard, copper(II) complex of ceftibuten has been synthesized and characterized. The formation of new metal complex is confirmed by FT-IR, DSC and TGA analyses. Moreover, the biological activity of ceftibuten and its copper(II) complex were examined *in vitro* against Gram-positive and Gram-negative organisms.

EXPERIMENTAL

Ceftibuten dihydrate (potency 98.6%) was gift from Incepta Pharmaceuticals Ltd., Dhaka, Bangladesh. Copper sulphate ($CuSO_4 \cdot 5H_2O$) was used as the metal source. All other chemicals and solvents were of analytical grade and purchased from Merck. They were used without further purification.

Synthesis of ceftibuten-Cu(II) complex: The process of complexation of ceftibuten with copper(II) was carried out in an oil bath at 90 ºC. Hot aqueous solution of ligand (2.24×10^{-5} mol) was taken with $CuSO_4 \cdot 5H_2O$ (1.11×10^{-5} mol) in a round bottom flask maintaining the ratio of 2:1 [20]. pH was found (4.3) at that time. Heating was continued for about 3.5 to 4.0 h with continuous stirring. The reaction mixture was kept overnight. After that evaporation was done to reduce the volume and a precipitated complex was obtained, which was then filtered off (**Scheme-I**). The precipitated complex was purified by washing several times with distilled water, methonal followed by dry ether and then dried in a desiccator at room temperature (Yield: 70%, m.p.: 272 ºC decomp.). An obtained coloured complex was found to be soluble in hot water (90 ºC) and DMSO and insoluble in *n*-hexane, diethyl ether, methanol, ethanol, acetone and acetonitrile.

Characterization: FT-IR analysis was carried out using Shimadzu (Japan) FTIR 8400S model spectrophotometer as KBr pellets scanning in the range 4000-400 cm^{-1}. Spectra were recorded for both of ligand and metal complex. DSC instrument (model: DSC131 EVO, SETARAM Instrumentation, France) was used to record the thermograms. The thermograms of parent drug and its copper(II) complex were taken in aluminium pan at the temperature range of 20-700 ºC. Heating rate was 10 ºC/min and 20 mL/min flow rate of N_2 gas was maintained during recording the thermogram. The thermogravimetric studies of parent drug and its Cu(II) complex were carried out using TGA 50H, Shimadzu (Japan). Aluminium pan was used to record the thermograms at the temperature range of 25-800 ºC with 5 min holding time. Heating rate was 10 ºC/min and 10 mL/min flow rate of nitrogen gas was maintained during recording the thermogram.

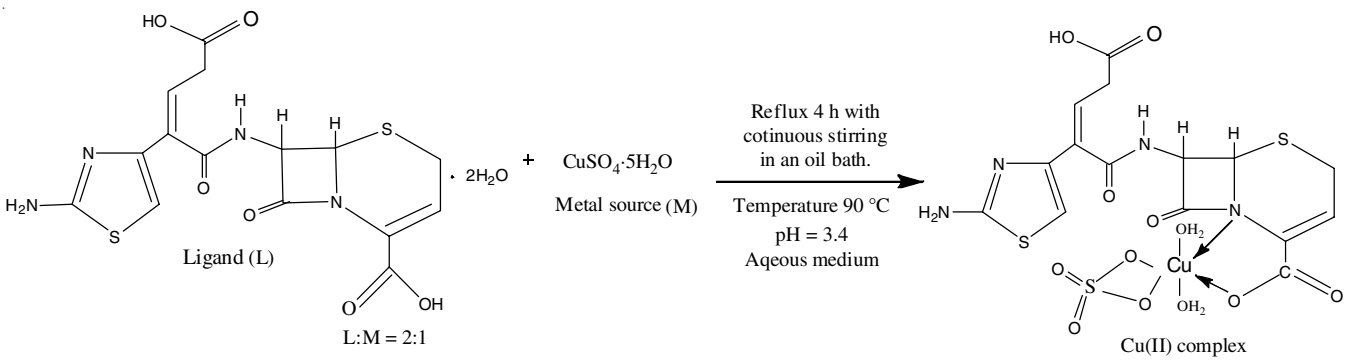
Biological activity: Biological screening was carried out for the ligand and its Cu(II) chelates against four bacterial strains, *Staphylococcus aureus, Escherichia coli, Salmonella typhi* and *Bacillus subtilis*. Agar well diffusion method was used to study the antibacterial activity [21-24]. DMSO (solvent) was used as negative control and reference antibacterial drug (rifampicin) was used as positive controls, respectively.

RESULTS AND DISCUSSION

Differential scanning calorimetry: An endothermic peak at 242.7 ºC was found in DSC thermogram of ceftibuten parent drug (Fig. 1a), suggesting the melting point of pure drug. The ceftibuten-Cu(II) metal complex showed an endothermic peak at 269.2 ºC (Fig. 1b). The endothermic peaks obtained for pure drug ceftibuten (242.7 ºC) and its complex (269.2 ºC) indicated the interaction between the drug and the metal.

Thermogravimetric analysis (TGA): The experimental results of thermogravimetric studies of ligand ceftibuten and its Cu(II) complex showed that the degradation occurred in different stages. The complex mass was decreased with increasing temperature and mass loss was continued up to 25 to 800 ºC. In TGA of ceftibuten (Fig. 2a), 9.77% mass loss was observed at 176.21 ºC, 55.78% mass loss at 396 ºC and finally 91.33% at 630 ºC. The drug metal complex, however, showed completely different degradation pattern. In Cu(II) complex of ceftibuten, mass loss was found 8.32, 34.73, 75.0 and finally 83.0% at 175, 312, 508 and 800 ºC, respectively (Fig. 2b). This pattern suggested a completely different substance, which indicated formation of a new drug-metal complex [25-27].

FT-IR analysis: The FT-IR spectrum of copper complex of ceftibuten exhibited the characteristic changes in the vibrational frequency as compared to pure drug. The vibrational frequency of characteristic groups like carbonyl group of β-lactam ring, carboxyl group, which are involved in forming chelates were taken into account for structure establishment. The strong band at 1770 and 1651 cm^{-1} in the spectrum of ceftibuten dihydrate (Fig. 3a) are assigned to lactam (C=O) and carboxyl (C=O) stretches. In the FT-IR spectrum of Cu(II) complex (Fig. 3b), the shifting of lactam (C=O) band was not significant. Appearing of two new peaks at 1629 and 1402 cm^{-1} for the chelate, which were assumed to asymmetric (ν_{asym}) and the symmetric (ν_{sym}) stretching vibrations of the carboxylate group. In this study, the IR spectrum of synthesized complex yielded $\Delta\nu > 200$ cm^{-1}, giving an evidence for monodentate coordination mode of carboxylate group [28]. Also there was a considerable shift in the frequency of *tert*.-N atom of the ring. The frequency of *tert*.-N atom in ligand appearing at 1361 cm^{-1} shifted to 1114 cm^{-1} in the complex [29,30]. A new band appea-



Scheme-I: Synthetic scheme of Cu(II) complex of ceftibuten dihydrate

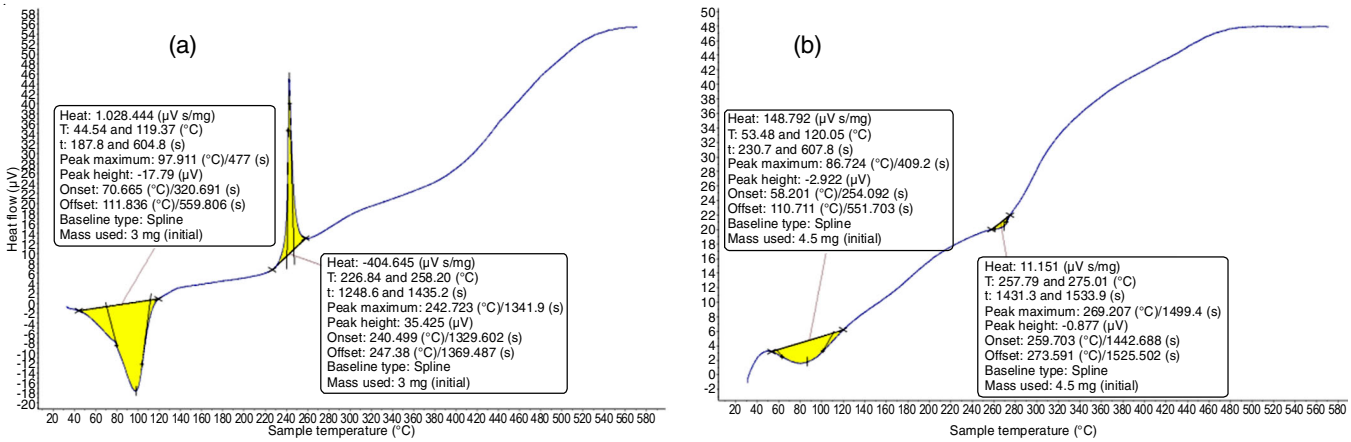


Fig. 1. DSC thermogram of (a) ceftibuten dihydrate and (b) ceftibuten-Cu(II) complex

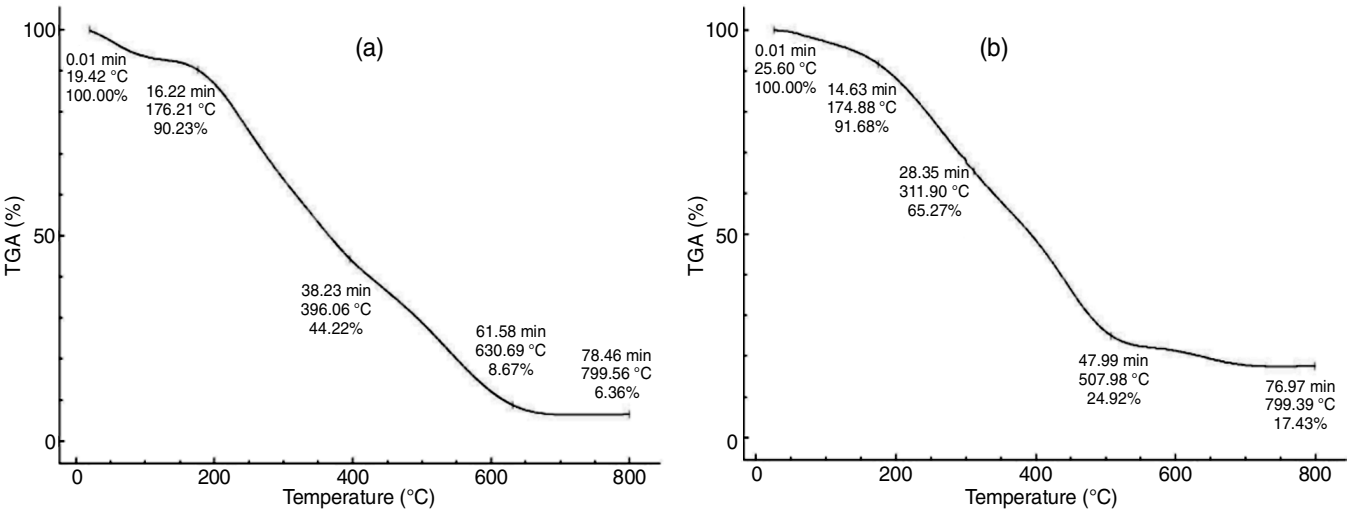


Fig. 2. TGA of (a) ceftibuten dihydrate and (b) ceftibuten-Cu(II) complex

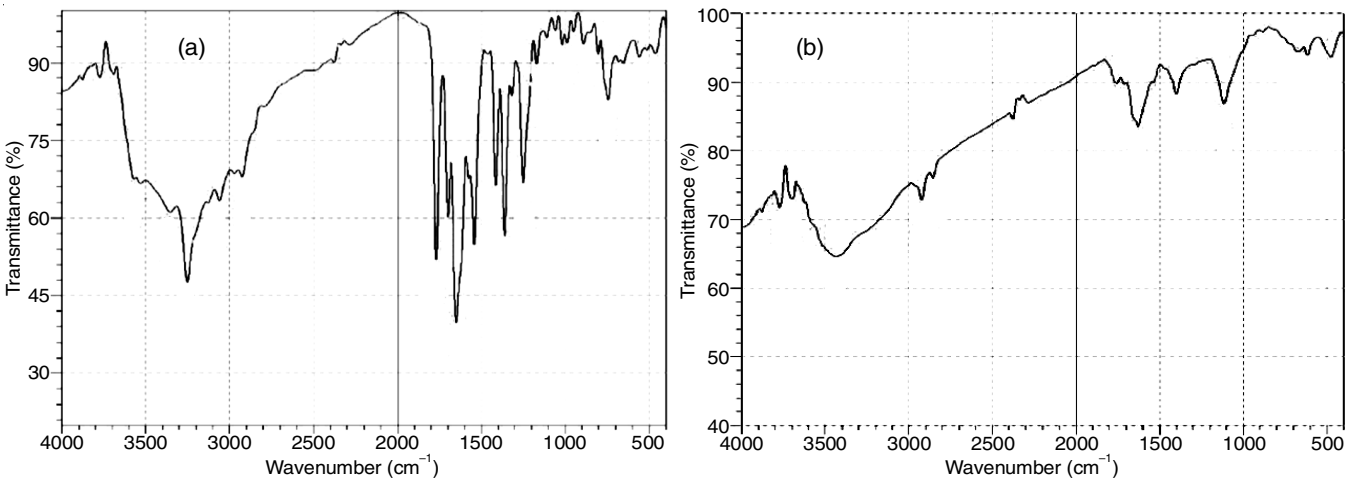


Fig. 3. IR spectrum of (a) ceftibuten dihydrate and (b) ceftibuten-Cu(II) complex

ring at 476 cm^{-1} in the metal complex (absent in the free ligand) is due to ν(Cu-N) stretching vibration also gave a strong evidence for the coordination of tertiary nitrogen atom with metal ion [31].

The analytical data stated above support the formation of new copper(II) complex. Many researchers [32-34] have studied complexes of several cephalosporin (β-lactam) antibiotics with transition and d^{10} metal ions and noticed the coordination chemistry with proper experimental evidence. Based on comparison of FT-IR spectral data of parent drug and its Cu(II) complex suggest the binding site of drug molecule with the metal ion. The tertiary nitrogen of the β-lactam ring and carboxylate ion are involved in metal coordination, forming a five membered

ring (**Scheme-I**). There is remarkable shift in the frequencies of tertiary nitrogen and of carboxylic group of the ring [11]. A new band appearing at 476 cm^{-1} in the present copper(II) complex also exhibited a strong evidence for the bonding of tertiary nitrogen atom β-lactam ring with metal ion [31].

Antibacterial activity: It has been suggested that when metal ion interacts with parent drug to form chelates through the formation of coordination bond between positively charged metal ion and donor groups of drug, the polarity of metal ion will be reduced. Moreover, it increases the delocalization of π-electron over the whole metal coordinated complex. As a result, the liposolubility of the metal complex is increased *via* chelation [35]. The activity of drug thus increased significantly due to enhanced permeation of the drug into the membrane of the microorganism cell wall. The respiration process of the cell is also interrupted by the chelate which can stop protein synthesis, causing cell lysis.

In the present study, both ligand and complex have been screened for investigation of bioactivity against both Gram-positive and Gram-negative bacteria. Significant antibacterial activities were observed as compared to standard drug. The results obtained revealed that on forming complex with copper the antibacterial activity of ligand ceftibuten was greatly enhanced against *S. aureus* and *S. typhi*. The copper(II) complex showed moderate activity against *B. subtilis* while it showed no activity against *E. coli*. An interesting point is that the metal complex showed very good activity against *S. aureus* being about 100% higher than parent drug, ceftibuten because ceftibuten did not show any activity against *S. aureus* (Table-1). Anacona and Silva [11] reported the similar results when studied the antibacterial activity of metal complexes of cefotaxime.

TABLE 1
ANTIBACTERIAL ACTIVITY OF STANDARD DRUG, PARENT DRUG AND ITS Cu(II)-COMPLEX

Microbial species	Zone of inhibition (mm)		
	Ceftibuten dihydrate	Ceftibuten-Cu(II) complex	Rifampicin
B. subtilis	30	25	10
E. coli	23	0	9
S. aureus	0	15	19
S. typhi	9	15	13

Conclusion

A new complex of ceftibuten dihydrate with Cu(II) was synthesized and characterized. The biological activity of both of cefitibuten dihydrate and its complex with Cu(II) was also screened. The formation of new complex was confirmed by experimental results. DSC showed different endothermic peak of complex from its parent drug. In TGA different degradation pattern indicated formation of new complex. Finally, it was justified that newly formed complex possessed good antibacterial activity against *S. aureus* and *S. typhi*.

ACKNOWLEDGEMENTS

This paper is dedicated to Prof. Katsuyuki Aoki, Toyohashi University of Technology, Japan for celebration of his 75th birthday. The authors are grateful to Center for Advanced Research in Sciences (CARS) and Department of Chemistry, University of Dhaka, Bangladesh for their logistic support during this study. The authors are also grateful to Incepta Pharmaceuticals Ltd., Bangladesh for the gift of ceftibuten dihydrate. One of the authors, Shuchismita Dey is grateful to the authority of Southeast University, Dhaka, Bangladesh for approving study leave to pursue Doctoral studies in Dhaka University, Bangladesh.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. B.T. Hathiram, D.S. Grewal, P. Tankwal, N. Shah and R. Agarwal, *Indian J. Otolaryngol. HNS*, **51**, 104 (1999); https://doi.org/10.1007/BF02998005
2. R. Vijayalakshmi, P. Bhargavi, P.S. Kumari, P. Sruthi and M.D. Dhanaraju, *E-J. Chem.*, **7**, 551 (2010); https://doi.org/10.1155/2010/120417
3. A. Bauernfeind, *Diagn. Microbiol. Infect. Dis.*, **14**, 89 (1991); https://doi.org/10.1016/0732-8893(91)90095-W
4. R. Shawar, M. Larocco and T.G. Cleary, *Antimicrob. Agents Chemother.*, **33**, 781 (1989); https://doi.org/10.1128/AAC.33.5.781
5. M. Shahid, F. Sobia, A. Singh, A. Malik, H.M. Khan, D. Jonas and P.M. Hawkey, *Crtic. Rev. Microbiol.*, **35**, 81 (2009); https://doi.org/10.1080/10408410902733979
6. X. Zeng and J. Lin, *Front. Microbiol.*, **4**, 128 (2013); https://doi.org/10.3389/fmicb.2013.00128
7. M. Selevaganapathy and N. Raman, *J. Chem. Biol. Therap.*, **1**, 108 (2016); https://doi.org/10.4172/2572-0406.1000108
8. S, Ramotowska, M, Wysocka, J. Brzeski, A. Chylewska and M. Malowski, *TrAC-Trends Analyt. Chem.*, **123**, 115771 (2020); https://doi.org/10.1016/j.trac.2019.115771
9. Z.H. Chohan, C.T. Supuran and A. Scozzafava, *J. Enzyme Inhib. Med. Chem.*, **20**, 303 (2005); https://doi.org/10.1080/14756360310001624948
10. A.N. Mustapha, N.P. Ndahi, B.B. Paul and M.B. Fugu, *J. Chem. Pharm. Res.*, **6**, 588 (2014).
11. J.R. Anacona and G.D. Silva, *J. Chil. Chem. Soc.*, **50**, 447 (2005).
12. S.H. Auda, Y. Mrestani, M.I. Fetouh and R.H.H. Neubert, *Pharmazie*, **63**, 555 (2008).
13. D.C. Ware, P.J. Brothers, G.R. Clark, W.A. Denny, B.D. Palmer and W.R. Wilson, *J. Chem. Soc., Dalton Trans.*, 925 (2000); https://doi.org/10.1039/a909447d
14. M.S. Islam, K.Y. Sikdar, A.M. Hossain and A. Faroque, *Dhaka Univ. J. Pharm. Sci.*, **18**, 135 (2019); https://doi.org/10.3329/dujps.v18i2.43255
15. D.R. Williams, The Metals of Life: the Solution Chemistry of Metal Ions in Biological Systems, Van Nostrand Reinhold: London (1971).
16. H.H.A. Dollwet and J.R.J. Sorenson, *Trace Elem. Med.*, **2**, 80 (1985).
17. I. Neda, T. Kaukorat, R. Schmutzler, U. Niemeyer, B. Kutscher and J. Pohl, *Phosphorus Sulfur Silicon Rel. Elem.*, **162**, 81 (2000); https://doi.org/10.1080/10426500008045221
18. S.-A. Filimon, C.G. Hrib, S. Randoll, I. Neda, P.G. Jones and M. Tamm, *Z. Anorg. Allg. Chem.*, **636**, 691 (2010); https://doi.org/10.1002/zaac.200900485
19. S. Rafique, M. Idrees, A. Nasim, H. Akbar and A. Athar, *Biotechnol. Mol. Biol. Rev.*, **5**, 38 (2010).
20. M.S. Arayne, N. Sultana, S. Shamim and A. Naz, *Modern Chem. Appl.*, **2**, 133 (2014); https://doi.org/10.4172/2329-6798.1000127
21. A.W. Bauer, W.M.M. Kirby, J.C. Sherris and M. Turck, *Am. J. Clin. Pathol.*, **45(4_ts)**, 493 (1966); https://doi.org/10.1093/ajcp/45.4_ts.493

22. A.U. Rahman, M.I. Choudhary and W.J. Thomson, Bioassay Techniques for Drug Development, Harwood Academic Publishers: Netherland (2001).
23. M. Balouiri, M. Sadiki and S.K. Ibnsouda, *J. Pharm. Anal.*, **6**, 71 (2016); https://doi.org/10.1016/j.jpha.2015.11.005
24. M.H.U. Biswas, A.H.M.Z. Shaheed and A. Farooque, *Bangladesh Pharm. J.*, **12**, 43 (2002).
25. K. Seku, A.K. Yamala, M. Kancherla, K. Kumar and V. Badathala, *J. Anal. Sci. Technol.*, **9**, 14 (2018); https://doi.org/10.1186/s40543-018-0147-z
26. B. Vimala, S.R. Jayapradha and A. Selvan, *Asian J. Chem.*, **32**, 488 (2020); https://doi.org/10.14233/ajchem.2020.22362
27. F. Aktar, M.Z. Sultan and M.A. Rashid, *Dhaka Univ. J. Pharm. Sci.*, **18**, 271 (2019); https://doi.org/10.3329/dujps.v18i2.44467
28. G.B. Deacon and R.J. Philips, *Coord. Chem. Rev.*, **33**, 227 (1980); https://doi.org/10.1016/S0010-8545(00)80455-5
29. N. Sultana, M.S. Arayne and M. Afzal, *Pak. J. Pharm. Sci.*, **16**, 59 (2003).
30. N. Sultana, M.S. Arayne and M. Afzal, *Pak. J. Pharm. Sci.*, **18**, 36 (2005).
31. S.F. Tan, K.P. Ang and H.L. Jayachandran, *Transition Met. Chem.*, **9**, 390 (1984); https://doi.org/10.1007/BF00637026
32. J.R. Anacona and C. Toledo, *Transition Met. Chem.*, **26**, 228 (2001); https://doi.org/10.1023/A:1007154817081
33. J.R. Anacona and J. Serrano, *J. Coord. Chem.*, **56**, 313 (2003); https://doi.org/10.1080/0095897031000069085
34. J.R. Anacona, *J. Coord. Chem.*, **54**, 355 (2001); https://doi.org/10.1080/00958970108022648
35. M. Tümer, H. Köksal, M.K. Sener and S. Serin, *Transition Met. Chem.*, **24**, 414 (1999); https://doi.org/10.1023/A:1006973823926