

Recent Advances in Acetaminophen (Paracetamol) Metal Complexes: Structural Chemistry and Potential Therapeutic Applications

Dr. Wei Zhang^{1*}

¹Peking University Health Science Center, Department of Pharmaceutical Chemistry and Biomedical Research, Beijing, China

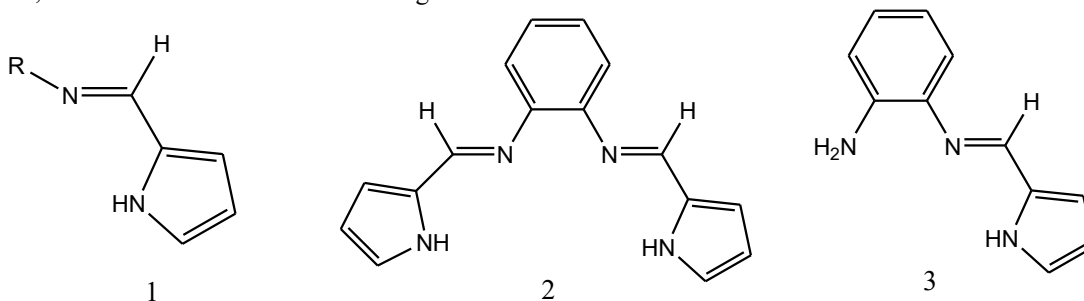
ABSTRACT

A concise overview is projects for bidentate ligand (PCM) with different metal and on their applications in various chemical transformations. Since the nature of ligand can be changed in a variety of ways, appealing routes for designing and preparing novel metal complexes can be foreseen in the future. This review critically summarizes the applications PCM drug as ligand for formation complex and its importance also offers a review of recent work on synthesis, in situ characterization, and applications of metal complex with the general formula $[M(L)_2] \cdot nH_2O \cdot X_2$ where M is transition metal. compounds derived from Co, Zn, Fe, Cu and Ni.

Key Words: Schiff bases, Metal complexes, Paracetamol, Ligands.

I. INTRODUCTION

Due to their rising potential as flexible catalysts for organic synthesis and Inorganic chemistry, metal complexes witnessed a spectacular growth during the last decade [1-26]. Several families of traction metal compounds have been prepared and extensively used in a variety of chemical transformations such as enol-ester synthesis, hydration, hydrogenation[26-29], oxidation[30-33] isomerization[34-35.], decarbonylation[36-37], epoxidation[38-39], cyclopropanation[40-42], Diels–Alder reaction[43-45], Kharasch addition [46], olefin metathesis[47-51]. The resultant imines ($R_1HC=N-R_2$) participate in binding with metal ions via nitrogen lone pair electrons. Like aldehydes, the ketones are also able to form ligands.



The mono-(**1**), di-(**2**), tri-(**3**) and multi-dentate chelating Schiff base ligands were design according to the binding environments of metal ions. The metal complexes of chiral ligands showed stereoselectivity in organic transformation, hence the synthesis of chiral complexes become an important area of current research in coordination chemistry.

Amudat Lawal and Joshua A. Obaleye gave novel complexes of Co (II), Ni (II) and Fe (III) with aspirin and paracetamol have synthesized and characterized using spectral, melting point and conductivity measurements. The two ligands have been found to act as bidentate chelating agents. Aspirin complexes coordinate through the carbonyl oxygen of the carboxyl and the ester groups, while paracetamol complexes coordinate through the oxygen of the hydroxyl and the amide groups[52].

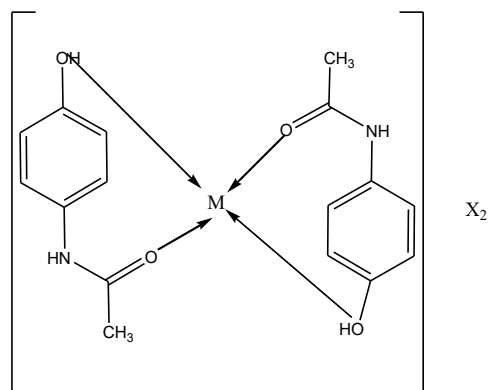


Figure 1: Structure of Paracetamol Meta Complex

A. Lawal, *et al* studied synthesizing copper(II) and zinc(II) complexes of mixed ascorbic acid and nicotinamide and physiochemically characterize by solubility test, melting point, conductivity test, infrared, electronic and proton nuclear magnetic resonance techniques[53].

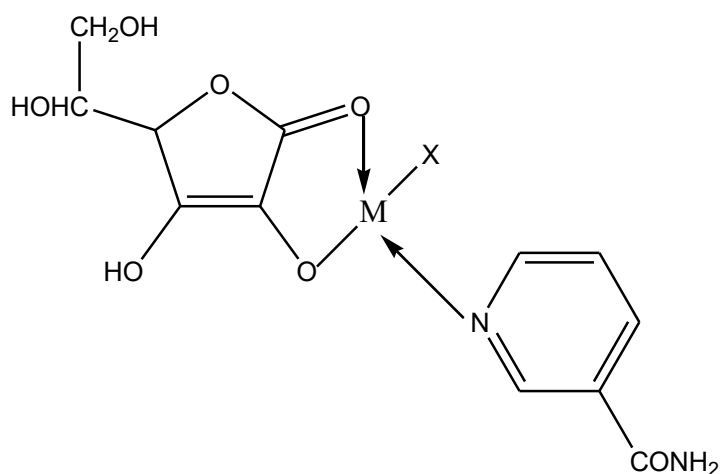


Figure 2: Structure for mixed Ascorbic acid- Nicotinamide metal Complexes

Ionut Ledeti *et al* studied Zn(II)-ACPH coordinative compound and synthesized and characterized by elemental analysis, FTIR spectroscopy and TG-DTG-HF technique. It was proven that the formation of complex occurs by both $-OH$ and $-C=O$ groups from ACPH.[54].

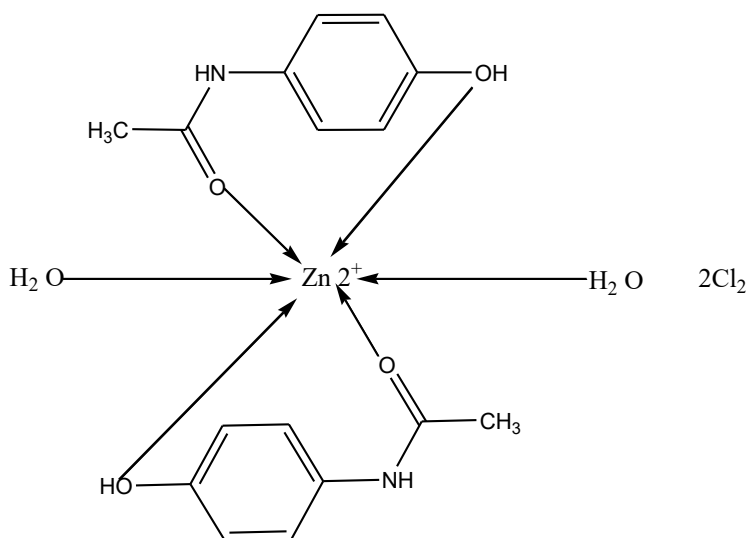


Figure: 3 The Structure of $[Zn(PCM)_2(OH)_2]^{2+} 2Cl^-$ Complex

Aderoju A. Osowole *et al* studied Heteroleptic metal(II) complexes of Paracetamol (HL) and Vanillin (HL1) mostly analyzed as $[M(L)(HL1)(H_2O)X]$, where $X = Cl/NO_3$; $M = Mn, Co, Ni, Cu$ and Zn based on percentage metal and conductance measurements. Infrared and electronic spectroscopies, with room temperature magnetic moments indicated a monomeric, 6-coordinate octahedral geometry for all the complexes with the exception of the $Cu(II)$ complex, which was dimeric[55]

Vanillin (4-hydroxy-3-methoxyphenol) is the largest use flavouring agent in foods and medicines. In addition, vanillin has very good antibacterial activity, which is exploited in perfumes and cleaning products [56-57.]. Detailed literature search shows that mixed drug metal complexes of *o*-vanillin and 4-methylthiosemicarbazone; Aspirin and Paracetamol; Paracetamol and Ibuprofen; Aspirin, Paracetamol and Naproxen have been reported [58-60].

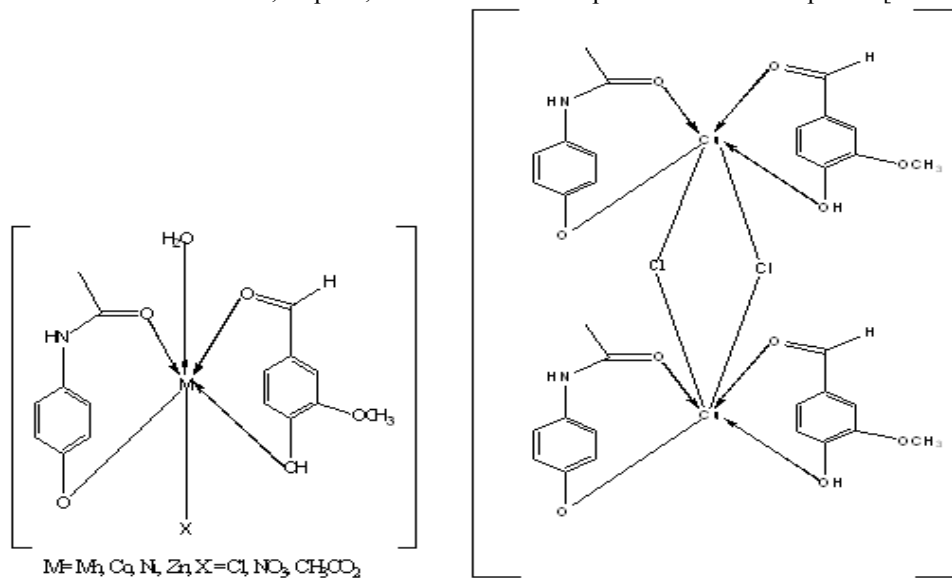


Figure 4: Propose structures for some of the Metal(II) complexes

Aderoju A *et al* in 2015 studied $Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II)$ mixed ligand complexes of Paracetamol (HL) and Benzoic acid (HL1) considering a six-coordinate octahedral geometry. The molar conductance measurements in DMSO solvent indicated that the metal(II) complexes were covalent. [61]

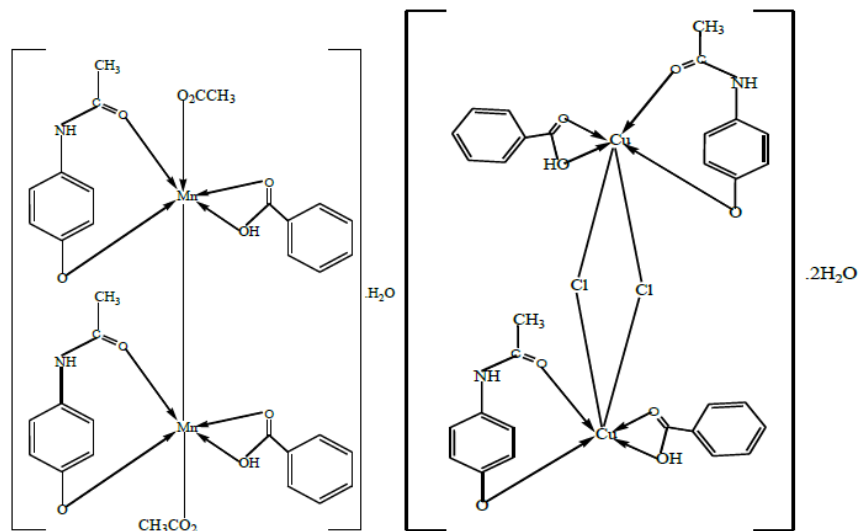


Figure 5: Structures for the Mn(II) and Cu(II) complexes

Organotin (IV) complex of paracetamol have been made in 2:1 ratio through azeotropic removal of H₂O. The spectral studies indicate tetrahedral geometry in metal ion in the paracetamol. In triorganotin complexes of Paracetamol trigonal bipyramidal geometry is observed by authors. They also investigated anti fungal activity of this complexes[62].

Transition metal ions are shows an key role in biological processes in the human body, for example, Nickel (II), Copper (II) and Zinc (II) ions are the most seen transition metals in humans. They are found either at the active sites or as structural components of a good number of enzymes. Metal complexes have been found to be particularly useful because of their potential to bind DNA via a multitude of interactions and to cleave the duplex by their intrinsic chemical, electrochemical and photochemical reactivity. Mixed ligand-metal complexes of Paracetamol and Ascorbic acid were synthesized using FeCl₂.4H₂O, CuCl₂.2H₂O, NiCl₂.6H₂O, CoCl₂.6H₂O and ZnSO₄ salts based on two concentrations (3mmol and 5mmol). The complexes were characterized[63]

Antibiotic resistance by microorganisms has triggered the need to discover new antibiotics to replace the old ones. The study was designed to prepare copper-paracetamol complexes which will serve as lead compounds towards the discovery of novel antibiotics. Copper sulphate was reacted with paracetamol in the presence of sodium nitrate in borate buffer to give products which were separated into three layers when extracted with a set of organic solvents[64] and Heterocyclic compounds[65-68]. Authors follows the synthesis of copper paracetamol complex A 0.2 M borate buffer of p^H 8.2 was prepared and used to dissolve exactly 3.19, 1.38 and 3.02 g of CuSO₄, NaNO₂ and paracetamol in different beakers. All the mixtures were transferred into a dark conical flask and top up to 100 ml. The reaction was stirred at room temperature without heat for 2 h

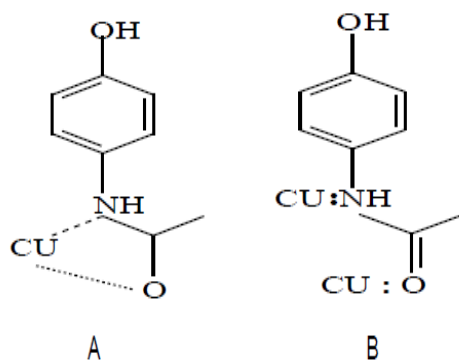


Figure 6. The possible constituents of copper paracetamol products in the yellow extract

II. CONCLUSION

The present paper offers a review of recent work on synthesis, in situ characterization, and applications of metal complex with the general formula $[M(L)_2] \cdot nH_2O \cdot X_2$ where M is transition metal. compounds derived from Co, Zn, Fe, Cu and Ni with general introduction followed by synthesis, These types of ligands (PCM) have been widely utilized applications. However, the biological activity of this class of compounds deserves further investigation.

III. ACKNOWLEDGEMENTS

The authors are greatly thankful to Principal and Head, Department of Chemistry JET's Z.B. Patil College, Dhule for providing the laboratory facilities for this work.

REFERENCE

1. T. Opstal, F. Verpoort, *Angew. Chem. Int. Ed.* 42 (2003) 2876
2. N. Dieltiens, C.V. Stevens, D. De Vos, B. Allaert, R. Drozdak, F. Verpoort, *Tetrahedron Lett.* 45 (2004) 8995.
3. M.I. Bruce, *Coord. Chem. Rev.* 248 (2004) 1603
4. M.I. Bruce, *Coord. Chem. Rev.* 166 (1997) 91
5. J.P. Selegue, *Coord. Chem. Rev.* 248 (2004) 1543
6. R.B. King, *Coord. Chem. Rev.* 248 (2004) 1531.
7. M.P. Doyle, D.C. Forbes, *Chem. Rev.* 98 (1998) 911
8. B.M. Trost, F.D. Toste, A.B. Pinkerton, *Chem. Rev.* 101 (2001) 2067
9. G. Maas, *Chem. Soc. Rev.* 23 (2004) 183
10. K. Utsumoniya, J.F. Harwig, *J. Am. Chem. Soc.* 126 (2004) 2702.
11. C. Bianchini, P. Barbaro, G. Scapacci, *J. Organometall. Chem.* 621 (2001) 26
12. C. Ciardi, G. Reginato, L. Gonsalvi, I. De los Rios, A. Romerosa, M. Peruzzini, *Organometallics* 23 (2004) 2020
13. M.C. Puerta, P. Valerga, *Coord. Chem. Rev.* 193/195 (1999) 977
14. W.W. Ellis, W. Odenkirk, B. Bosnich, *Chem. Commun.* 12 (1998) 1311
15. P.E. Ellis, J.E. Lyons, *Coord. Chem. Rev.* 105 (1990) 181.
16. V. Cadierno, M.P. Gamasa, J. Gimeno, *Coord. Chem. Rev.* 248 (2004) 1627
17. V. Cadierno, M.P. Gamasa, J. Gimeno, *Eur. J. Inorg. Chem.* (2001) 571
18. V. Cadierno, M.P. Gamasa, J. Gimeno, *J. Organometall. Chem.* 621 (2001) 39.
19. A. Dijkstra, J.W.C.E. Arends, R.A. Sheldon, *Platinum Met. Rev.* 45 (2001) 15
20. A. Dijkstra, A. Marino-Gonzales, A. Mairata, I. Payeras, J.W.C.E. Arends, R.A. Sheldon, *J. Am. Chem. Soc.* 123 (2001) 6826.
21. A. Srikanth, G. Nagendrappa, S. Chandrasekaran, *Tetrahedron* 59 (2003) 7761
22. A.A. Sauve, J.T. Groves, *J. Am. Chem. Soc.* 124 (2002) 4770
23. W. Tang, X. Hu, X. Zhang, *Tetrahedron Lett.* 43 (2002) 2078
24. S. Rajendran, D.C. Trivedi, *Synthesis* (1995) 153.
25. V. Dragutan, R. Streck, *Catalytic Polymerization of Cycloolefins*, Elsevier, Amsterdam, 2000.
26. S.E. Clapham, A. Hadzovic, R.H. Morris, *Coord. Chem. Rev.* 248 (2004) 2201.
27. P. Barbaro, C. Bianchini, A. Meli, M. Moreno, F. Vizza, *Organometallics* 21 (2002) 1430
28. J.P. Genet, *Acc. Chem. Res.* 36 (2003) 908
29. Y.-G. Zhou, W. Thang, W.-B. Wang, W. Li, X. Zhang, *J. Am. Chem. Soc.* 124 (2002) 4952
30. T. Kuwabara, T. Saito, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* 112 (1990) 7812
31. A. Miyata, M. Furukawa, R. Irie, T. Katsuki, *Tetrahedron Lett.* 43 (2002) 3481
32. A. Miyata, M. Murakami, R. Irie, T. Katsuki, *Tetrahedron Lett.* 42 (2001) 7097
33. a.R. Ramesh, *Inorg. Chem. Commun.* 7 (2004) 274; (b) S. Rajendran, D.C. Trivedi, *Synthesis* (1995) 153.
34. U. Matteoli, M. Bianchi, P. Frediani, G. Menchi, C. Boteghi, M. Marchetti, *J. Organometall. Chem.* 263 (1984) 243
35. R. Antonya, G.L. Tembea, M. Ravindranathana, R.N. Ramb, *Polymer* 39 (1998) 4327
36. U. Matteoli, M. Bianchi, P. Frediani, G. Menchi, C. Boteghi, M. Marchetti, *J. Organometall. Chem.* 263 (1984) 243

37. R. Antonya, G.L. Tembea, M. Ravindranathana, R.N. Ramb, *Polymer* 39 (1998) 4327.
38. A. Shrikanth, G. Nagendrappa, S. Chandrasekaran, *Tetrahedron* 59 (2003) 7761
39. T.J. Groves, R. Quinn, *J. Am. Chem. Soc.* 107 (1985) 5790
40. H. Lebel, J.F. Marcoux, C. Molinaro, A.B. Charette, *Chem. Rev.* 103 (2003) 977;
41. A. Demonceau, E. Saive, Y. de Froidmont, A.F. Noels, A.J. Hubert, I.T. Chizhevsky, I.A. Lobanova, V.I. Bregadze, *Tetrahedron Lett.* 33 (1992) 2009
42. A. Demonceau, A.F. Noels, E. Saive, A.J. Hubert, *J. Mol. Catal.* 76 (1992) 123
43. H. Lebel, J.F. Marcoux, C. Molinaro, A.B. Charette, *Chem. Rev.* 103 (2003) 977;
44. A. Demonceau, E. Saive, Y. de Froidmont, A.F. Noels, A.J. Hubert, I.T. Chizhevsky, I.A. Lobanova, V.I. Bregadze, *Tetrahedron Lett.* 33 (1992) 2009
45. A. Demonceau, A.F. Noels, E. Saive, A.J. Hubert, *J. Mol. Catal.* 76 (1992) 123
46. B. De Clercq, F. Verpoort, *Adv. Synth. Catal.* 344 (2002) 639.
47. A. Furstner (Ed.), *Alkene Metathesis in Organic Synthesis*, Springer, Berlin, 1998;
48. A. Furstner, *Angew. Chem.* 112 (2000) 3140
49. A. Furstner, *Angew. Chem. Int. Ed.* 39 (2000) 3012
50. C. Pariya, K.N. Jayaprakash, A. Sarkar, *Coord. Chem. Rev.* 168 (1998) 1
51. V. Dragutan, I. Dragutan, A.T. Balaban, *Platinum Met. Rev.* 45 (2001) 155.
52. Amudat Lawal and Joshua A. Obaleye, *Synthesis, Characterization And Antibacterial Activity Of Aspirin And Paracetamolmetal Complexes Biokemistri*, 2007,19(1):9-15.
53. A. Lawal, S.A. Amolegbe, A. O. Rajee, H.F. Babamale, and M. T. Yunus-Issa, *Synthesis, Characterization And Antimicrobial Activity Of Mixed Ascorbic Acid - Nicotinamide Metal Complexes*, *Bayero Journal of Pure and Applied Sciences*, 8(1): 139 – 142
54. Ionut Ledeti, Georgeta Simu, Gabriela Vlase, Germaine Savoiu, Titus Vlase, Lenuta-Maria Suta, Calin Popoiu, Adriana Fulias, *REV. CHIM. (Bucharest)*, 2013,64 (10),1127-1130
55. Aderoju A. Osowole and Oluwatoosin Agbaje, *Synthesis, characterization and antibacterial properties of some heteroleptic metal(II) complexes of paracetamol and vanillin*, *Asian J Pharm Clin Res*, Vol 7, Issue 3, 2014, 145-149
56. Walton NJ, Mayer MJ, Narbad A. *Vanillin. Phytochemistry* 2003;63(5):505-15
57. Fitzgerald DJ, Stratford M, Gasson MJ, Ueckert J, Bos A, Narbad A. *Mode of antimicrobial action of vanillin against Escherichia coli, Lactobacillus plantarum and Listeria innocua. J Appl Microbiol.* 2004;97(1):104-13
58. Lawal A, Obaleye JA. *Synthesis, characterization and antibacterial activity of aspirin and paracetamol-metal complexes. Biokemistri* 2007;19(1):9-15
59. Obaleye JA, Orjiekwe CL, Famurewa O. *Effects of Some Novel Ascorbic Acid Metal Complexes on Selected Bacterial and Fungal Species. J. Sci. I.R. of Iran*, 1994;5(4):154-7
60. Nahas R, Moher M. *Complementary and alternative medicine for the treatment of type 2 diabetes (Review). Can. Fam. Physician*, 2009;55(6):591-6.
61. Aderoju A. Osowole and Oluwatoosin Agbaje, Sherifah Monilola Wakil, *International Journal of Applied Medical Sciences*, 1(2), 2015: 77-87
62. Harminder Kaur, Kanav Dhir, Jaspreet Kaur, Bharti Mittu and Ashish Chauhan, *American Journal of Drug Discovery and Development*, 2013, 3(1), 13-22
63. H. F. Babamale, A.Lawal, O. A. Rajee,; E. A. Oloyede, *J. Appl. Sci. Environ. Manage.*, 2016, 20 (4) 1157-1161
64. Samuel Mawuli Kwabena Sarfo, *Afr. J. Pure Appl. Chem.* 2016, 10(5), 56-62.
65. A. P. Rajput, D. V. Nagarale, *ihydropyridine-3,5-Diyl} Dimethylylidene} Dipropanedinitrile Using Green Catalyst L-Proline-Fe₃O₄ MNP*, *Journal of Applicable Chemistry*, 2018, 7 (6): 1592-1596.
66. A. P. Rajput, D. V., Nagarale, *Der Pharma Chemica*, 2016, 8(8):182-186.
67. A. P. Rajput, D. V. Nagarale, *IJPC* (2016) 06 (07), 181-185.
68. A. P. Rajput, D. V. Nagarale., *Chem Sci Trans.*, 2016, 5(4), 912-917.