International Journal of Multidisciplinary and Current Educational Research (IJMCER)
ISSN: 2581-7027 ||Volume|| 3 ||Issue|| 2 ||Pages 23-30 ||2021||

Synthesis and characterization of Mixed 2,2-Bipyridine and penicillin G metal (II) complexes

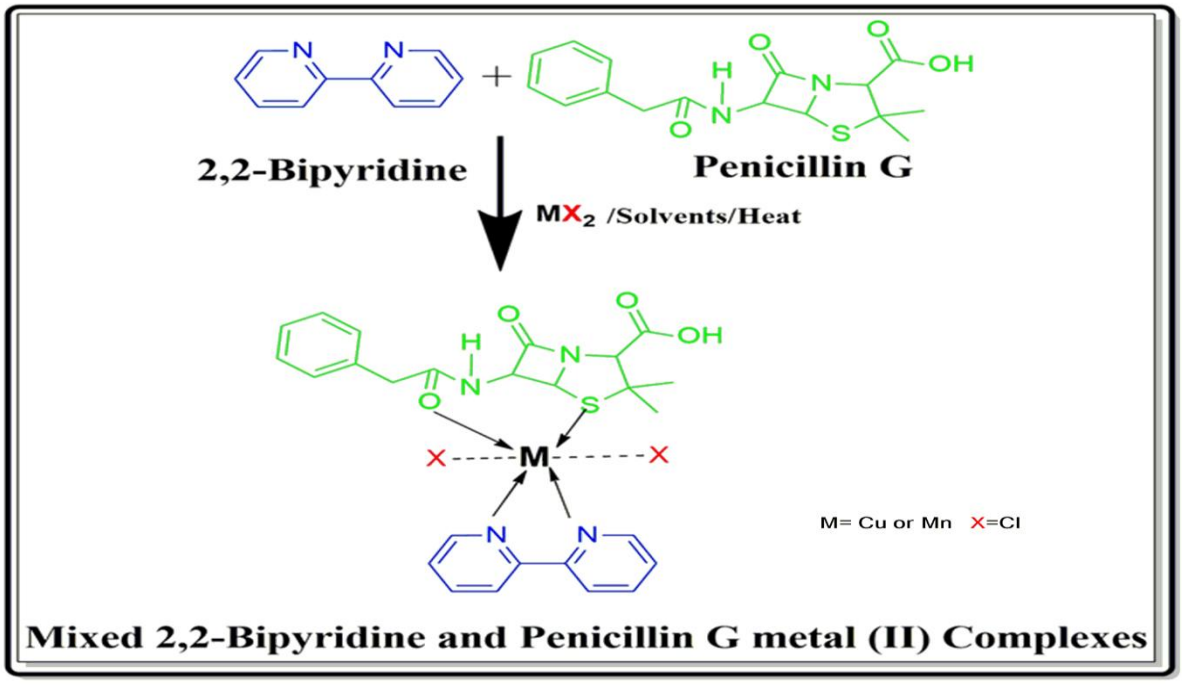
Egbele,R.O.[a],Ohwofosirai, A.[b],Ugbune U.[a], Kpomah, B.[a],Yerima,I.B[c] Osakwe, S.A.[d]&Nwajei, G.E.[d]

[a]Department ofChemisty Delta State College of Physical Education, Mosogar, Delta state, Nigeria.
[b]Department of Physics Delta State College of Physical Education, Mosogar, Delta state, Nigeria.
[c]Chemistry Department, Gombe State University ,PMB 127, Tudun Wada, Gombe, Gombe State,Nigeria.
[d]Department of chemistry Delta State University, Abraka, Delta State, Nigeria.

ABSTRACT : The harmonization of the metal-organic framework through the incorporation of metal ions into organic ligands has introduced a synergistic effect for novel applications in the biological system, in coordination chemistry, mostly, when heteroatom such as nitrogen and oxygen with lone pair of electrons are involved. This study focuses on the synthesis of mixed ligand metal complexes of the form $[M.(l)(L).Cl_2]$, where M represents Cu (II) and Mn (II) while L stands for 2,2-bipyridine and penicillin G (3,3-dimethyl-7-oxo-6-[(2-phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2carboxylic acid).The synthesized complexes were characterized. The functional groups of the synthesized complexes were determined using Infrared spectroscopy (FTIR). The FTIR result shows that all the functional groups observed in the ligands were also present in the complexes. The optical study was investigated using UV-Visible (UV). The UV-Visible result shows the formation of the complexes, with the indication of blue shift (d-d) transition and the present of ligand metal charge transfer (L^1MCT) in the complexes. Metal composition analysis was carried out using Atomic Absorption spectroscopy which reveals the metal present in the complexes. Conductivity, solubility, and melting point were also determined. Structures were proposed based on the analytical data obtained. The present of the oxygen and nitrogen donor sites make for their potential application as anticancer, antifungal, and antibacterial.

KEYWORDS: Synthesis, **2**,2-Bipyridine, Penicillin G, Metal, Complexes

Graphical Abstract



I. INTRODUCTION

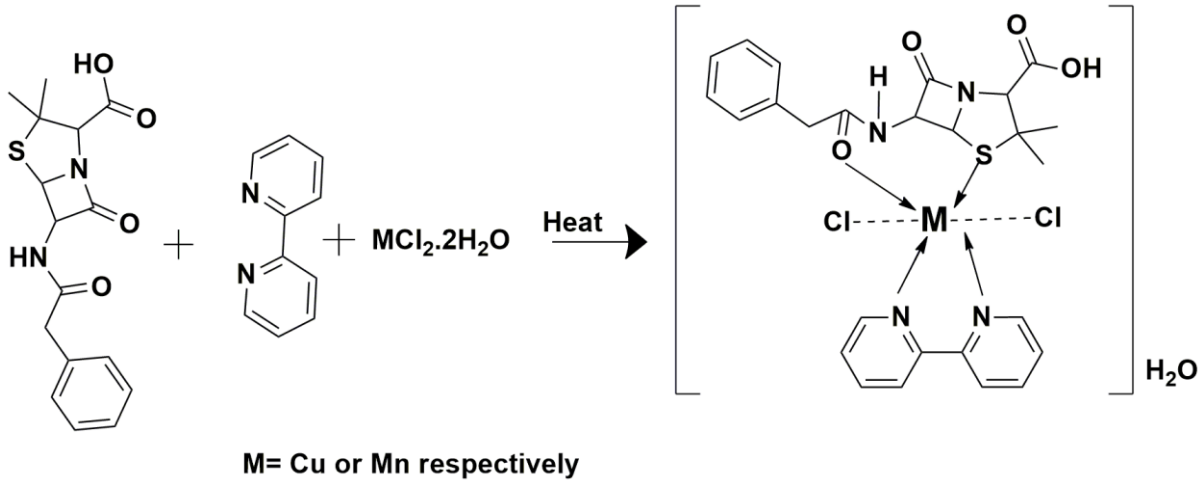
Coordinating metals to bioactive molecules can be employed as a strategy to improve their activity and overcome resistance[2].The structure and nature of bonding between metal ligands complexes and their coordination geometries account for their uniqueness in shape compared to single organic molecules[3]. These bonds determine the available coordination sites but depend on the metal oxidation state. The coordination of these metals'centers to theactive sites of organic drugs has been reported to enhance the activity and diversification of application in drug delivery [1,4-10].Metal complexes can deliver their bioactive functionto the respective site through a particular mechanism and still retain the drugs' therapeutic effectiveness [11]. Thus, improve the activity of the parent drug. Another challenging situation with orally taken drugs is the low solubility, making them less permeable [12]. Nevertheless, the coordination of metal centers to drugs improves drug solubility and permeability and enhances biological activity [3,5]. The permeable metal center is due to the chelating effect from the electron density in the bioactive ligand site. At the same time, the enhanced solubility is attributed to the hydrophilic nature of metals [13-15]. Also, oral bioavailability can be improved by coordinating them to metal and the metal functioning as the delivery system [16-18]. Besides, toxicity has been suppressed by metal coordinated drugs [19,20]. . Metal coordinated drugs has been in market with tremendous impact [21]. Bipyridine forms complexes with several transition metals with actibacterial property, while penicillin(Penicillin G)is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms.The name "penicillin" can either refer to several variants of penicillin available, or to the group of antibiotics derived from the penicillins. Penicillin G has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of penicillin G results from the inhibition of cell wall synthesis and is mediated through penicillin G binding to penicillin binding proteins (PBPs). Penicillin G is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases.

The significance of this work is in understanding of electron transfer, mixed valence complexes, magnetic transition, covalent and non-covalent interaction in biological system. Ligands and metal selectivity, in terms of charges, shape, bonds, electronic structures and effect on bioactivity on the complex coordination structure [22].
Copper (Cu) is one of the bio essential metal ions that takes path in several biological processes. Cu is essential in cell formation, more so when Cu (II) are well-coordinated to the active sites of organic drugs. Such complexes may be effective antioxidants, antimicrobials, antibacterial and anticancer agents[23-26]. On the other hand, maganese metal complexes could react with oxygen easily ,and has been used as anti-leukemic agents [27]. Thus, mixed ligand metal is receiving significant attention. This study, synthesized and characterized some mixed ligands metal complexes by the use of mixed 2,2-bipyridine and penicillinprocraine, with Cu and Mn transition metal chlorides.

II. EXPERIMENTAL

Materials : The chemicals, drugs, and solvents were purchased from Sonitex Nigeria Enterprise, wer of high purity and used without further purification.

Synthesis of $[CuCl_2(Bipy)(pen)Cl_2]H_2O$: Metal preparation was carried out by following the method reported by Adeyemo et al [5], while the mixed ligands metal complexes were prepared following a literature procedure by El- Wahab et al [28]. Briefly, a solution of $CuCl_2.2H_2O$ (0.714g, 0.003mole) in distilled water (30mL) was added to a solution consisting of 2, 2- Bipyridine (0.468g, 0.003mole) in 30mL distilled water heated in a water bath for 5 minutes and pennicillinprocraine (0.55g, 0.003mole) also in 30mL distilled water. The resulting mixture was stirred and heated for 1hour until a Green coloured precipitate was formed. When there was complete precipitation the mixture was allow to cooled to room temperature. The green precipitate was filtered and dried at room temperature. The percentage yield is 62.37%. The same procedure was followed for Mn mixed ligand complex,however $CuCl_2.2H_2O$ was replaced with $MnCl_2.2H_2O$.The equation of the reactions is shown below:-



Scheme 1. Reaction scheme for mixed ligand (Penicillin G and 2,2-Bipyridine)metal(II) complex of Cu and Mn complexes respectively

III. RESULTS AND DISCUSSION

Table 1: Result of solubility determination for mixed 2, 2-Bipyridine, and penicillin procrainemetal complexes

COMPOUND	Dist. H_2O		Ethanol		Methanol		Acetone		Chloroform		DMSO	
	C	H	C	H	C	H	C	H	C	H	C	H
2, 2-Bipyridine	NS	S	SS	S	S	S	S	S	S	S	S	S
Penicilin G	S	S	S	S	S	S	SS	SS	NS	SS	S	S
Cu(Bipy)(Pen)Cl_2	SS	S	NS	-	NS	-	NS	-	-	-	-	-
Mn(Bipy)(Pen)Cl_2	SS	S	NS	SS	NS	SS	NS	SS	NS	NS	ScS	S

KEY: C – Cold, H – Hot, S – Soluble, SS – Slightly Soluble, NS – Not Soluble

From **Table 1** most of the complexes were soluble in the various solvents but showed variable solubility in their cooled solvents.

Table 2: Analytical data of mixed 2, 2-Bipyridine and penicillinprocraine metal complexes

Compound	Colour	Melting Point (°C)	% Yield	Conductivity(µs/cm)
2, 2- Bipyridine	White	90	-	01
Pennicillin G	White	158	-	17
Cu(Bipy)(Pen)Cl_2	Green	198	16.64	02
Mn(Bipy)(Pen)Cl_2	Clay	249	62.37	12

From **Table 2** all the complexes showed higher melting points compared to the individual ligands used in complex formation. They showed different colours. One of the ligands has shown a higher conductivity value than the complexes, while the others showed a lower conductivity than the complexes.

Table 3: Spectroscopic properties of mixed 2, 2-Bipyridine, and penicillinprocraine metal complexes

Compound	V(N-H)	V(C-N)	Aromatic substituted benzene V(C-H)	Aromatic V(C=C)	V(C-S)	V(M-L)	V(C-Cl)	V(C=O)	V(C=N)	Aromatic Ring	V(O-H)	V(C-O)	CH_3
2, 2-Bipyridine	3649.44 (w)	1338.64 (m,s)	3055.35 (s)	1597.11 (w)	-	-	-	-	1697.41 (w)	758.05 (s)	-	-	-
Penicilline G	3853.90 (w)	1361.79 (m)	3030.27 (s)	1556.61 (s)	1273.06 (m)	-	-	1782.29 (s)	1693.56 (s)	775.41	-	1273.06 (s)	1400.37 (m)
Cu(Bipy)(Pen)Cl_2	3248.23 (w)	1317.72 (s)	3061.13 (m)	1570.11 (m)	1176.62	418.57	852.56	1714.7 (w)	1647.26 (s)	769.62 (s)	3398.69 (w)	1271.13 (s)	1496.81 (m)
Mn(Bipy)($PenCl_2$	3524.06 (s)	1315.50 (s)	3115.14 (m)	-	1163.11 (s)	410.85 (s)	800.49 (s)	1788.07 (m)	1635.69 (w)	765.77 (s)	3450.77 (s)	1247.97 (s)	1477.52 (s)

KEY: s – sharp, w – weak, m – medium, b – broad

From **Table 3.** The IR spectra of 2, 2-Bipyridine and penicillin G procraine and those of their combination metal-complexes were compared. It was observed that the absorption band 1338.64 cm^{-1} due to V(C-N) vibration has shifted for all the complexes as compared with the 2, 2-Bipyridine ligands.In the same way, the band V(C=N) for 2, 2-Bipyridine 1697.41 cm^{-1} also shifted for the complexes.The (N-H) stretching frequency of the Penicillin molecule undergoes a shift in all the complexes. V(N-H) 3853.90 cm^{-1} for the complexes has shifted to various lower frequencies showing likely coordination site for the complexes – Cu (Bipy) (Pen) Cl_2 and Mn (Bipy) (Pen) Cl_2. the V(C-S) vibration band also shifted from 1273.06 cm^{-1} to lower frequencies of 1176.62 cm^{-1} and 1163.11 cm^{-1} indicating a coordination site.

Table 4: Uv-visible spectral of mixed 2, 2-Bipyridine, and Penicillin G procraine metal complexes and their ligands

Compound	Wavelength (nm)	Energies (KJ/mol)	Assignment
2, 2-Bipyridine	191.40	625.41	$\pi \rightarrow \pi^*$
	288.40	415.06	$n \rightarrow \pi^*$
Pennicilline	194.20	616.40	$\pi \rightarrow \pi^*$
	299.60	399.55	$n \rightarrow \pi^*$
Cu(Bipy)(Pen)Cl_2	200.50	597.03	$\pi \rightarrow \pi^*$
	311.50	384.28	$n \rightarrow \pi^*$
	470.00	254.69	LMCT
Mn(Bipy)(Pen)Cl_2	220.50	542.88	$\pi \rightarrow \pi^*$
	288.00	415.64	$n \rightarrow \pi^*$
	535.00	223.74	LMCT

From **Table 4**, 2, 2-Bipyridine shows two absorption bands at 191.40 nm (625.41 KJ/mol) and 288.40 nm (415.06 KJ/mol) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$. While penicilline G procraine also shows two bands; 194.20 nm (616.40 KJ/mol) and 299.60 nm (399.55 KJ/mol) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$. The bands have undergone both bathochromic and hypsochromic shift in its complexes due to complexation. LMCT was also observed in the complexes, indicating complexation.The selected Uv-visible spectroscopic data of the mixed 212-Bipyridine and penicilline metal complexes and their ligands are presented in the table.

IV. RESULTS OF ATOMIC ABSORPTION SPECTROMETER(AAS) FOR METAL DETERMINATION.

Table 5: Results of Atomic Absorption Spectrometer (AAS) for metal determination

S/N	Metals Analysed	Concentration (µg/g)
1.	Copper	157.38
2.	Manganese	193.32

From **Table 5** the Atomic Absorption Spectrometer (AAS) of the mixed ligands metal complexes shows that the metals were present in the complexes with Cu having 157. 38 and Mn 193.323 From table 22 the Atomic Absorption Spectrometer (AAS) of the mixed ligands metal complexes shows that the metals were present in the complexes from the range of 96.14 µg/g to 214.63 µg/g.

Proposed structure for mixed 2, 2-Bipyridine and penicilline metal complexes.

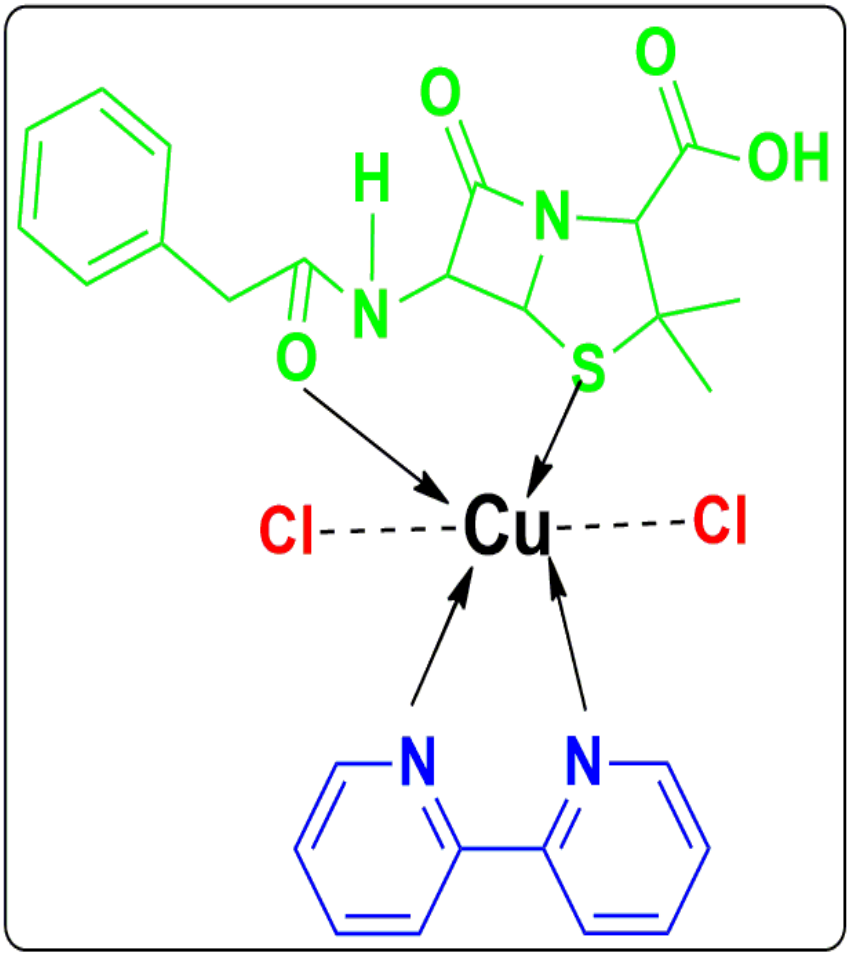


Figure. 1:Proposed Copper (II) Mixed ligand Complex structure**(Cu (Bipy) (Pen) Cl_2)**

Figure 1 is a proposed Copper (II) mixed ligand complex structure. The copper(II) ion coordinated to the penicillin G ligand through the nitrogen of the secondary amine and sulphur. While it coordinates to 2, 2-Bipyridinethrough the pyridine nitrogen. It also coordinated to two chloride ions.

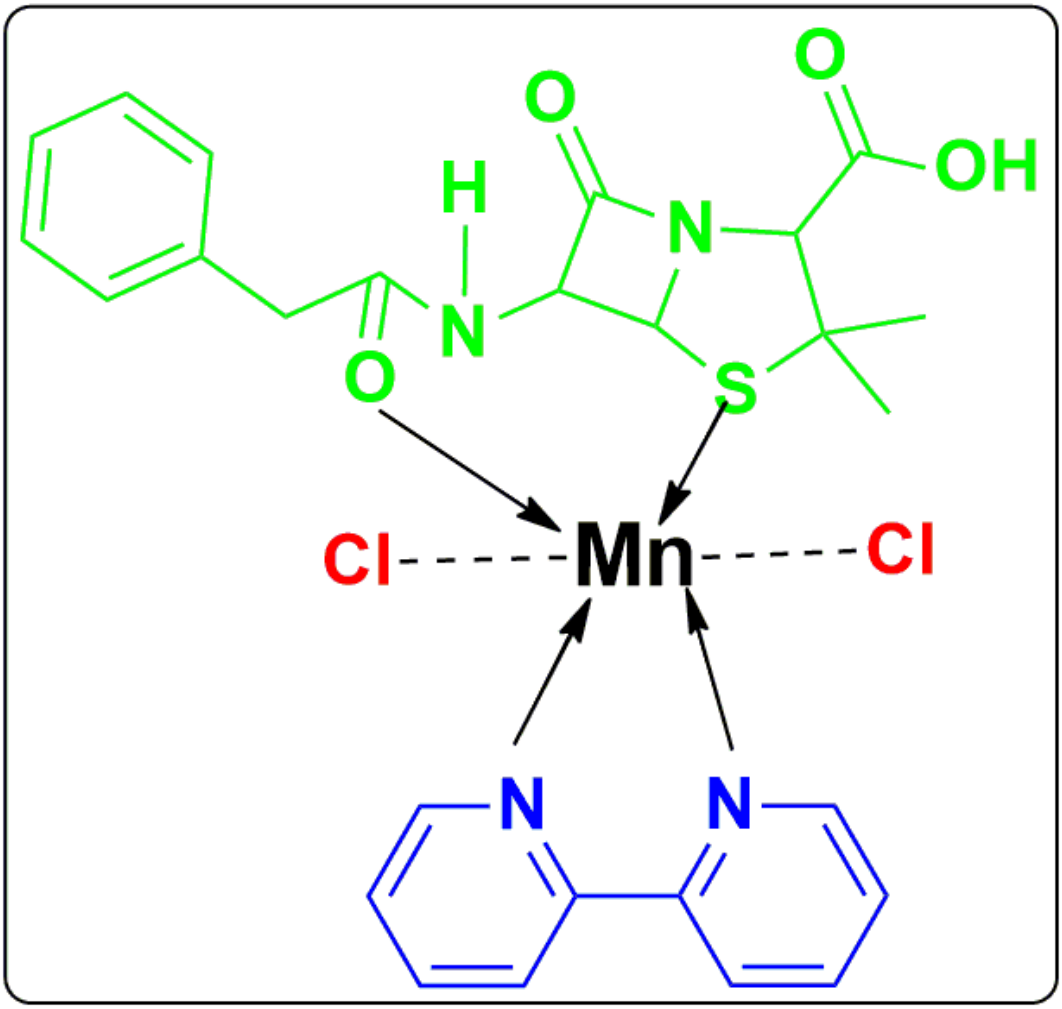


Figure2: Proposed Manganese (II) Mixed ligand Complex structure**(Mn(Bipy)(Pen)Cl$_2$)**

Figure 2 is a proposed Manganese (II) mixed ligand complex structure.The manganese ion coordinated to the penicillin ligand through the nitrogen of the secondary amine and sulphur. While it coordinates to 2, 2-Bipyridinethrough the pyridine Nitrogen. It also coordinated to two chloride ions.

V. CONCLUSION

Two mixed ligand of 2, 2- Bipyridine and penicillin G were successfully complexed with two metal (II) chloride of Cu and Mn respectively. The analytical data shows that 2, 2-Bipyridine is a bidentate ligand coordinating through the pyridinyl nitrogen. In comparison, penicillin G coordinated through the nitrogen of the secondary amine and sulphur. The tentative metal-ligand (M-L) assignments favours the six coordination studies. In summary, this work has provided additional results and data on mixed ligand metal complexes.

RECOMMENDATION

An antimicrobial and anticancer test is recommended for the newly synthesized mixed ligands metal (II)complexes to evaluate it potency or otherwise against pathogenic microbes and cancer cells.However toxicity test need to be carried out to ascertain its safety in a biological system..

REFERENCES

1 Begum, S., Hassan, Z., Bräse, S., Wöll, C. & Tsotsalas, M. Metal–Organic Framework-Templated Biomaterials: Recent Progress in Synthesis, Functionalization, and Applications. *Accounts of Chemical Research***52**, 1598-1610, doi:10.1021/acs.accounts.9b00039 (2019).

2 Khare, E., Holten-Andersen, N. & Buehler, M. J. Transition-metal coordinate bonds for bioinspired macromolecules with tunable mechanical properties. *Nature Reviews Materials*, doi:10.1038/s41578-020-00270-z (2021).

3 Lawson, H. D., Walton, S. P. & Chan, C. Metal–Organic Frameworks for Drug Delivery: A Design Perspective. *ACS Applied Materials & Interfaces*, doi:10.1021/acsami.1c01089 (2021).

4 Farooq, T. Triazoles in Coordination Complexes. *Advances in Triazole Chemistry*, 201 (2020).

5 Egbele, R. O. Synthesis and Characterization of Mixed 1, 10-Phenanthroline and Penicillin G Procaine Metal (II) Complexes.

6 Boros, E., Dyson, P. J. & Gasser, G. Classification of Metal-Based Drugs according to Their Mechanisms of Action. *Chem***6**, 41-60, doi:https://doi.org/10.1016/j.chempr.2019.10.013 (2020).

7 Ejima, H., Richardson, J. J. & Caruso, F. Metal-phenolic networks as a versatile platform to engineer nanomaterials and biointerfaces. *Nano Today***12**, 136-148, doi:https://doi.org/10.1016/j.nantod.2016.12.012 (2017).

8 Gershell, L. J. & Atkins, J. H. A brief history of novel drug discovery technologies. *Nature Reviews Drug Discovery***2**, 321-327, doi:10.1038/nrd1064 (2003).

9 Grindy, S. C. & Holten-Andersen, N. Bio-inspired metal-coordinate hydrogels with programmable viscoelastic material functions controlled by longwave UV light. *Soft Matter***13**, 4057-4065, doi:10.1039/C7SM00617A (2017).

10 Rojas, S., Devic, T. & Horcajada, P. Metal organic frameworks based on bioactive components. *Journal of Materials Chemistry B***5**, 2560-2573, doi:10.1039/C6TB03217F (2017).

11 Renfrew, A. K. Transition metal complexes with bioactive ligands: mechanisms for selective ligand release and applications for drug delivery. *Metallomics***6**, 1324-1335, doi:10.1039/c4mt00069b (2014).

12 Gupta, S., Kesarla, R. & Omri, A. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. *International Scholarly Research Notices***2013** (2013).

13 Johnson, T. J. & Hedge, D. D. Esomeprazole: A clinical review. *American Journal of Health-System Pharmacy***59**, 1333-1339, doi:10.1093/ajhp/59.14.1333 (2002).

14 Siddappa, K., Mane, S. B. & Manikprabhu, D. Spectral Characterization and 3D Molecular Modeling Studies of Metal Complexes Involving the O, N-Donor Environment of Quinazoline-4(3H)-one Schiff Base and Their Biological Studies. *The Scientific World Journal***2014**, 817365, doi:10.1155/2014/817365 (2014).

15 Singh, R. V., Dwivedi, R. & Joshi, S. C. Synthetic, magnetic, spectral, antimicrobial and antifertility studies of dioxomolybdenum(VI) unsymmetrical imine complexes having a N∩N donor system. *Transition Metal Chemistry***29**, 70-74, doi:10.1023/B:TMCH.0000014487.86754.93 (2004).

16 Baluom, M., Friedman, M. & Rubinstein, A. Improved intestinal absorption of sulpiride in rats with synchronized oral delivery systems. *Journal of Controlled Release***70**, 139-147, doi:https://doi.org/10.1016/S0168-3659(00)00337-0 (2001).

17 Loftsson, T. Drug solubilization by complexation. *International Journal of Pharmaceutics***531**, 276-280, doi:https://doi.org/10.1016/j.ijpharm.2017.08.087 (2017).

18 Yalkowsky, S. H. *Solubility and solubilization in aqueous media*. (American Chemical Society, 1999).

19 Agotegaray, M., Gumilar, F., Boeris, M., Toso, R. & Minetti, A. Enhanced Analgesic Properties and Reduced Ulcerogenic Effect of a Mononuclear Copper(II) Complex with Fenoprofen in Comparison to the Parent Drug: Promising Insights in the Treatment of Chronic Inflammatory Diseases. *BioMed Research International***2014**, 505987, doi:10.1155/2014/505987 (2014).

20 Bergamo, A., Gaiddon, C., Schellens, J. H. M., Beijnen, J. H. & Sava, G. Approaching tumour therapy beyond platinum drugs: Status of the art and perspectives of ruthenium drug candidates. *Journal of Inorganic Biochemistry***106**, 90-99, doi:https://doi.org/10.1016/j.jinorgbio.2011.09.030 (2012).

21 Haas, K. L. & Franz, K. J. Application of Metal Coordination Chemistry To Explore and Manipulate Cell Biology. *Chemical Reviews***109**, 4921-4960, doi:10.1021/cr900134a (2009).

22 Ren, Y. *et al.* Unraveling the coordination structure-performance relationship in Pt1/Fe2O3 single-atom catalyst. *Nature Communications***10**, 4500, doi:10.1038/s41467-019-12459-0 (2019).

23 Fan, C. *et al.* A novel copper complex of salicylaldehyde pyrazole hydrazone induces apoptosis through up-regulating integrin β4 in H322 lung carcinoma cells. *European Journal of Medicinal Chemistry***45**, 1438-1446, doi:https://doi.org/10.1016/j.ejmech.2009.12.048 (2010).

24 Ranford, J. D., Sadler, P. J. & Tocher, D. A. Cytotoxicity and antiviral activity of transition-metal salicylato complexes and crystal structure of Bis(diisopropylsalicylato)(1,10-phenanthroline)copper(II). *Journal of the Chemical Society, Dalton Transactions*, 3393-3399, doi:10.1039/DT9930003393 (1993).

25 Ng, C. H. *et al.* Synthesis, characterization, DNA-binding study and anticancer properties of ternary metal(ii) complexes of edda and an intercalating ligand. *Dalton Transactions*, 447-454, doi:10.1039/B709269E (2008).

26 Yoshida, D., Ikeda, Y. & Nakazawa, S. Quantitative analysis of copper, zinc and copper/zinc ratio in selected human brain tumors. *Journal of Neuro-Oncology***16**, 109-115, doi:10.1007/BF01324697 (1993).

27 Dash, S. K. *et al.* Antileukemic efficacy of monomeric manganese-based metal complex on KG-1A and K562 cell lines. *International Scholarly Research Notices***2013** (2013).

28 El-Wahab, Z. H. A. & El-Sarrag, M. R. Derivatives of phosphate Schiff base transition metal complexes: synthesis, studies and biological activity. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy***60**, 271-277, doi:https://doi.org/10.1016/S1386-1425(03)00216-6 (2004).