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Synthesis, characterization and biological activity of new complexes from Manniche base ligands derived from amoxicillin

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***Abstract*---**The importance of Manniche bases increased in pharmaceutical research, especially those prepared from pharmaceutical compounds. The study aims for an alternative design of a Manniche base of amoxicillin from sodium saccharin and benzaldehyde and ensures their consistency with some salts of transition elements Co (II), Ni (II), Cu (II), and Mn(II). They determined the expected stereo isometries of the resulting complexes Where the prepared complexes took the form of octahedral by diagnosing them by appropriate spectral and physical methods, infrared spectra (FT-IR), nuclear magnetic resonance spectroscopy (1H-NMR), accurate analysis of elements (C.H.N.S), Molar conductivity and measurement of melting points. The biological efficacy of all prepared compounds was studied, and two types of bacteria (Staphylococcus Aurous) and (Escherichia coli) were selected. Inhibition of bacteria at concentration (10-3) were studied.

***Keywords*---**Mannich base, complexes, organic ligands, amoxicillin, Staphylococcus Aurous.

Introduction

A Manniche base is a chemical compound obtained by condensing aldehyde with a mixture containing hydrogen (acid) and a primary or secondary amine or sometimes ammonia through a Manniche reaction (1-4). The name of this type of interaction was associated with the name of the first scientist concerned with its study, C. Manniche (5). Manniche's rules have been classified as popular compounds for a long time, and interest in these compounds continues due to their effectiveness in the pharmaceutical fields (6,7) and their industrial applications, such as polymers used in coatings and coatings as their applications in various areas. Manniche bases have been used in soil chemistry, where Manniche base compounds regulate plant growth (8), and as auxiliary and bonding materials in polymer chemistry (9).

The complexes of Manniche bases have an essential role in the development of coordinated chemistry, as they occupy a vast area in the preparation of new compounds (10-12), where the Manniche bases (Celite) contain the amide group as an influential group that can form complexes, which have a tremendous vital role, as it has many biological activities, including antibacterial effectiveness (13), antifungal (14), antimicrobial (15,16), anti-inflammatory and painkiller. (17) and anti-some types of cancer (18,19), as well as used as cofactors for the preparation of many biological compounds such as peptides, nucleotides and antibiotics (20).

Materials and Methods

Synthesis of compound(A1)

6-(2-(((1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)(phenyl)methyl)amino)-2-(4-hydroxyphenyl)acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicycloheptane-2-carboxylic acid

Mix (0.01mol, 3.65g)Amoxicillin dissolved in (30ml) Ethanol Absolut with (0.01mol, 2.06g) Sodium saccharin dissolved in (7ml) Ethanol Absolut at a temperature of (70-80)°C with continuous stirring and after half an hour add to the mixture benzaldehyde (1.02ml) Stir the mixture for two hours, and it has been observed to change the color of the mix from colorless to yellow, evaporation of the solvent at room temperature and the formation of a yellow precipitate recrystallized by ethanol, Its melting point is 170-172 °C, and its percentage is 85%.

Synthesis of Manniche Bases Complexes[A2-A5]

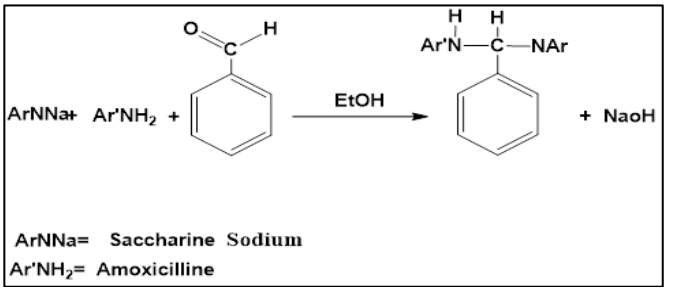
Add a (0.01mol) Manniche base (A1) solution dissolved in absolute ethanol (5 ml) to the metal salt solution (0.01 mol) dissolved in absolute ethanol (3 ml) and stir for (3-4 h) at room temperature. Then reflux, (2 h). vaporize the solvent at room temperature. The colored powdery products were recrystallized from ethanol absolute.

Table (1)
The physical properties of compounds(A2-A5)

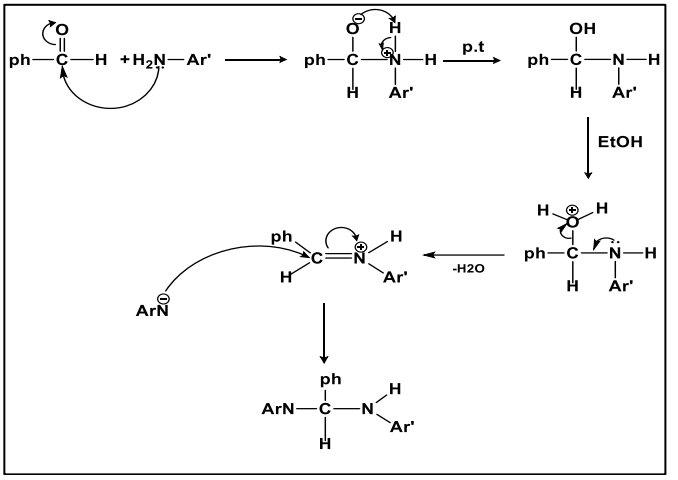
NO	Complexes	Color	C° m. p.	Yield %	Cond.Λm (Ω^{-1} cm^2 mol-1)
A2	Co(A1) $(H_2O)_2$ $(Cl)_2$	Dark Brown	125-127	84	8.4
A3	Ni(A1) $(H_2O)_2$ $(Cl)_2$	brown	200-202	87	6.2
A4	Cu(A1) $(H_2O)_2$ $(Cl)_2$	Dark green	178-180	78	3.2
A5	Mn(A1) $(H_2O)_2$ $(Cl)_2$	Yellowish white	156-159	83	2.5

Results and Discussions

The Manniche base was prepared from the reaction of Equimolar ratio of benzaldehyde, sodium saccharin and amoxicillin using absolute ethanol as solvent, as in the following equation.



The reaction mechanism mentioned in the literature [21] has been adopted as follows:



Infrared and nuclear resonance spectroscopy were used to diagnose this compound. Where the infrared spectrum of the compound (A1) showed a beam at the frequency (3402) cm-1 due to the riding frequency of the bond (O-H), and the appearance of two beams at the frequency (3350) cm-1 and frequency (3284) cm-1 due to the riding frequency of the two bonds (N-H), and we note the appearance of a beam at the frequency (1764) cm-1 due to the riding frequency of carbonyl (C = O) quadruple ring amides, and the formation of an intense beam at the frequency (1734) cm-1 due to the riding frequency of carbonyl (C = O) carboxyl group, In addition to the appearance of a beam at the frequency (1664) cm-1 which is due to the riding frequency of the carbonyl bond (C = O) open-chain amides, and the appearance of beams from the frequency (1595) cm-1 to the frequency (1496) cm-1 due to the riding frequency of the bond (C = C) in the aromatic rings, and the appearance of a beam at the frequency (1460) cm-1 due to the riding frequency of the bond (C-N), and the appearance of two beams belonging to the first SO2 group for the asymmetric riding frequency at the

frequency (1338) cm-1 and the second due to the symmetric riding frequency at (1182) cm-1

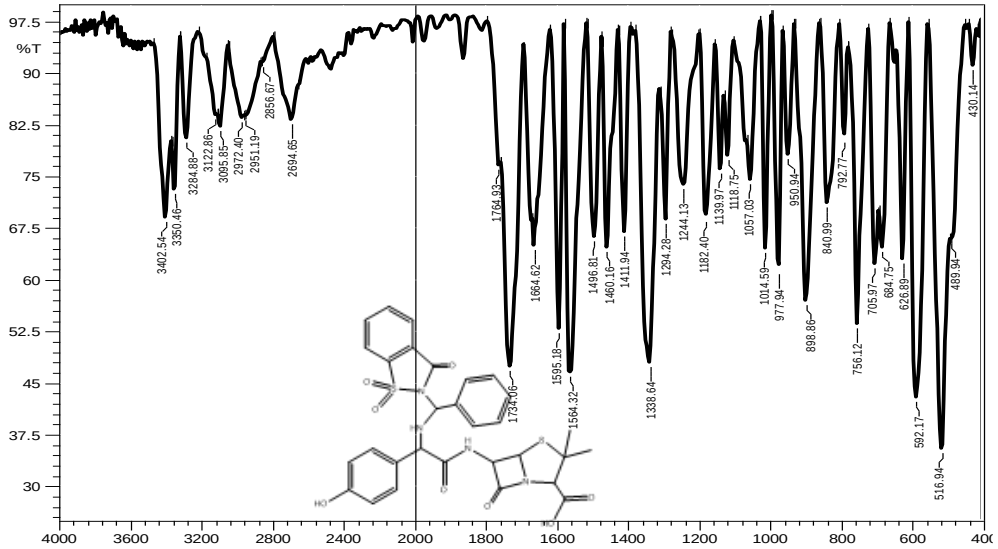


Figure (1) IR spectrum of compound (A1)

The proton nuclear resonance spectroscopy (1H-NMR) of compound (A1) showed two single signals at the sites (δ=1.22ppm) and (δ=1.50ppm) belonging to the protons of the two terminal groups (CH3) in the amoxicillin compound, and a single signal appeared at the site (δ=3.70ppm) belonging to the (CH) group associated with the strong pulling carboxyl group, and the proton of the amine group (NH) appeared as a single signal at the site (δ=3.89ppm), and the proton of the two groups (CH) showed a quadruple ring double signal at the position (δ=4.91ppm). The CH group connecting the three compounds appeared as a single signal at the site (δ=6.75ppm), the phenolic (OH) group proton appeared as a monolithic signal at the site (δ=6.80ppm), multiple signs appeared within the range (δ=7.26-7.75ppm) attributable to the protons of the aromatic rings, the proton of the amide group (HN-CO) showed a single signal at the site (δ=8.46ppm). A sign appeared at the site (δ=10.08ppm) belonging to the acid carboxyl group proton.

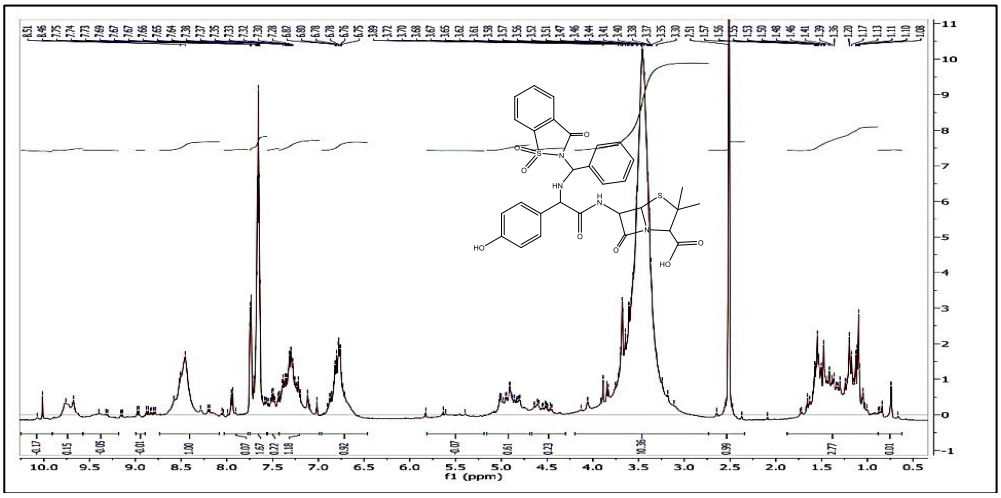
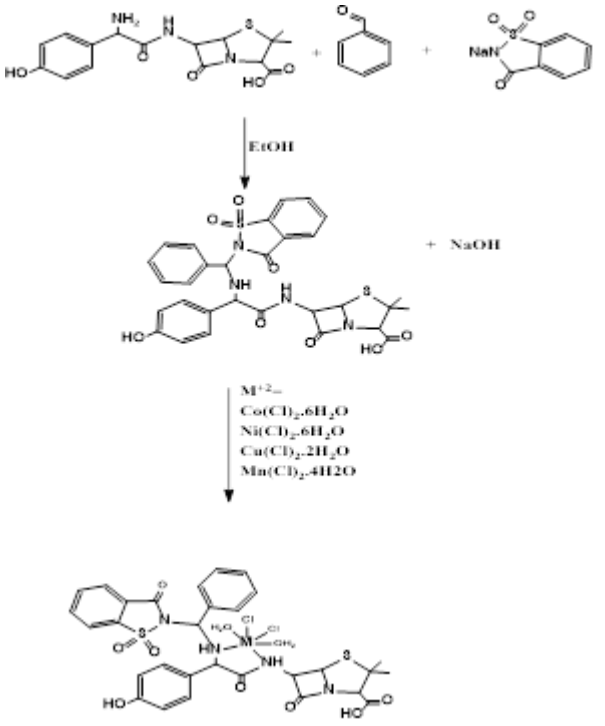


Figure (2) ^{1}H-NMR spectrum for Compound (A1)

The complexes were also prepared using equal moles of compound (A1), with some salts of transition elements Co(II), Ni(II), Cu(II), Mn(II), in absolute ethanol according to the following scheme.



Infrared technology was used to diagnose the prepared complexes by comparing the spectrum of the compound (A1) with the spectra of the prepared complexes, and Table (2) shows the values of the Infrared absorptions bonds in the prepared complexes (A2-A5).

Table (2)
Infrared absorptions bands of the Manniche Bases Complexes[A2-A5]

NO.	Complexes	O-H	N-H	C=O	SO_2		M-Cl	M-N	M-O
					Asy.	Sym.			
A2	$[Co(A1)(H_2O)_2](Cl)_2$	3535	3373	1735	1290 1151		754	536	783
A3	$[Ni(A1)(H_2O)_2](Cl)_2$	3535	3373	1735	1292 1151		758	538	783
A4	$[Cu(A1)(H_2O)_2](Cl)_2$	3429	3329	1728	1292 1157		754	518	788
A5	$[Mn(A1)(H_2O)_2](Cl)_2$	3574	3244	1658	1288 1155		756	532	788

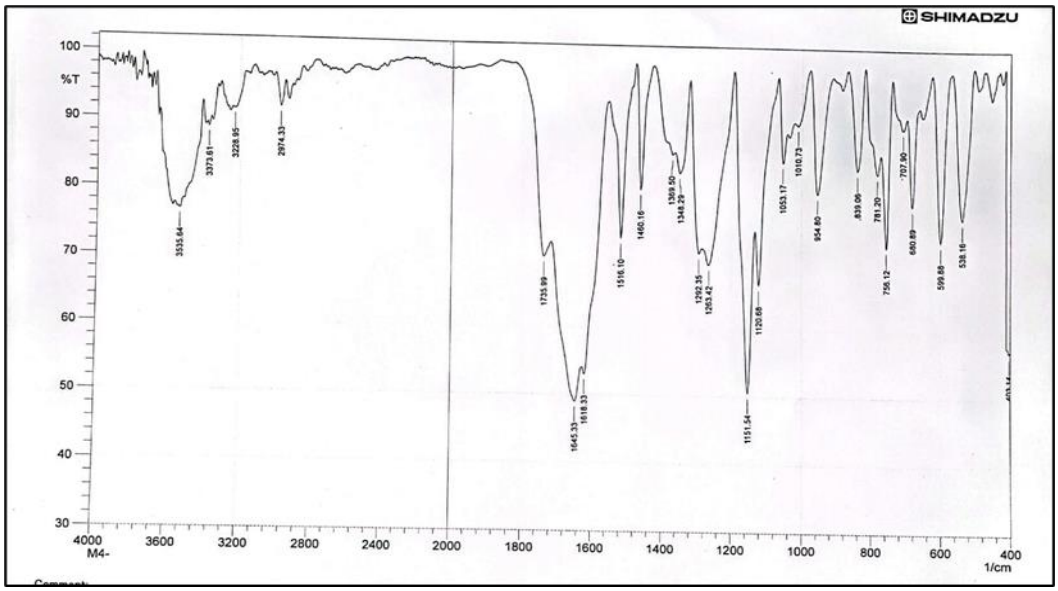


Figure (3) IR spectrum of compound (A3)

Conclusion

Element analysis (C.H.N.S)

The detailed analysis of the elements was measured to prove the validity of the prepared Manniche base's proposed molecular formulas and complexes. The practical results were close to the theoretically calculated values, and Table (3) shows the results of the accurate analysis of the elements of the prepared Manniche base and its complexes.

Table (3)
Elemental analysis of the compounds (A1_A5)

No.	Structure	Element analyses calc.(theory.) %			
		C	H	N	S
A1	C30H28N4O8S2	.51.65 (56.54)	73.4 (4.39)	75.8 (8.79)	9.95 (10.05)
A2	Co(A1)(H2O)2Cl2	44.71 (44.85)	3.46 (3.48)	6.89 (6.97)	7.93 (7.97)
A3	Ni(A1)(H2O)2(Cl)2	44.75 (44.8)	3.47 (3.48)	6.82 (6.97)	7.96 (7.97)
A4	Cu(A1)(H2O)2Cl)2	44.71 (44.72)	3.96 (3.97)	6.89 (6.95)	7.91 (7.95)
A5	$Mn(A1)(H_2O)_2Cl_2$	45.02 (45.12)	4.11 (4.04)	7.14 (7.02)	8.03 (8.11)

The Biological activity against Bacteria

A study was conducted to test the sensitivity of bacteria to Manniche bases and complexes prepared on two types of bacteria isolated in a pure and laboratory-diagnosed form, where the bacteria Staphylococcus aureus positive for the dye of the vine and the bacteria (Escherichia coli) negative for the shade of the vine were selected for causing many diseases affecting humans. In addition to using tetracycline as a reference antibiotic, the Agar-Well diffusion method was used in this study, and DMSO was used as a solvent. Table (4) shows the effect of Manniche bases and their prepared complexes on bacteria, where it was found that the prepared compounds have varying strength effectiveness in inhibiting the growth of the studied bacteria at a concentration of 0.001 M. It was noted that the inhibition of the development of bacteria type (Staphylococcus aureus) is higher than the growth inhibition of bacteria type (Escherichia coli), where the highest inhibition of bacteria (Staphylococcus aureus) is for complex (A4).

Table (4)
Antibacterial activity of Manniche base and their complexes

NO	Complexes	E-Coli.	Staphylo.
A1	C30H28N4O8S2	-	13mm
A2	Co(A1)(H2O)2 Cl2	mm6	12mm
A3	Ni(A1)(H2O)2Cl2	7mm	11mm
A4	Cu(A1)(H2O)2 Cl2	8mm	17mm
A5	Mn(A1)(H2O)2Cl2	5mm	10mm

It is possible to inhibit the growth of the two types of bacteria studied to the presence of active groups in the prepared derivatives. These groups interfere with the mechanism of cell division and work to stop bacterial growth.

References

1. Ahmed .A. Samir .M. El Rayes. ACS Omega , 6, 8,(2021)5244–5254
2. Ali, Rana A., and Suad M. Al-Araji. Baghdad Science Journal 9.1 (2012): 168-177.
3. Andraos,John.thealgebraof organic synthesis.green metrics, design strategy,route selection andoptimization, C.R.C. press 2016
4. Ayneni,A.O,Watkine,G.M.Bulletin oftheChemical Socity of Ethiopia,33(2)2019, 341-348
5. Deepak M. Nagrik and Umesh S. Shelke2020 J. Phys.: Conf. Ser. 1644 012018
6. Diaz-Oviedo.C,&Quevedo,R. Journal of Molecular Struture, , 127283 (2020) 1202
7. Fu.Yun, Yang.Y, Zhou,S, Y.Yanbin, International Journal of Oncology, 45 (2014) 2092-2100
8. Guo,H.EuopeanJournal ofmedicinal chemistry,164.(2019)678-688
9. H. Leqin,Q. Shenjun, C.Tao, S.Yuzhuang and Z.Jiquan, Int. Jour. Mol. Sci.,15, (2014). 8656-8666
10. Kalaivanan,C.Sankaranesh,M. Journal ofMolecularLiquids,320(2020)114423
11. M.Travnicek and M Potacek.Molecules.2(1999)238-244
12. Mohamed M. Ibrahim A.C.S. Omega 2021, 6, 8, 5244–5254
13. Rapacz,A.Rybka, S.Obniska,J Euopean Journal ofPharmcology869(2020) 172890.
14. S. M. Jo seph, Ph. D. Thesis, Stockholm University, (2005).
15. Seivearaj, S. David, R. Krishnaveni, and Dhanapal Tamilvendan. Material Today: Proceedings 33(2020): 4271-4279.
16. Shareef,T,H,M,A&Padusha,M,S,A.Int.J.Pharm.Sci6,(2014)466-472
17. Shehab, Omer H., and Ayaa S. Amer. activity. Journal of university of Anbar for Pure science 8.2(2014).
18. Sivakami.M.,Natarajan.B..M.,ChemicalScienceTransactions,3(3).(2014)1110-1114
19. Subramaniapillai, Selva Ganesan .''Mannich reaction :A versatile and convenient approach to bioactive skeletons.'' Journal of Chemical Sciences 125.3 (2013):467-482.
20. Tamer,A.A&Qassir,A,J.IraqiJouranalofpharmaceticalSciences,28(1)2019,124-130.
21. William J. Burke J. Org. Chem. 1964, 29, 2, 407–410