Preparation Characterization and Biological Evaluation of Schiff-Base of Some Drug Substances

Abdulbaset A. Elgellal
Misurata Univeristy/ChemistryDepartment, Misurata, Libya
AM_Elgellal@yahoo.com

Ahmed M. Alshadly
Tripoli University/Chemistry Department, Tripoli, Libya
lAA19662yahoo.com

***Abstract*—The work presented in this thesis concerns the preparation, characterization and biological evaluation of Schiff bases derived from amoxycillin, cephalexin, sulphamethoxazole and trimethoprim, and 2, 5-hydroxybenzaldehyde. In these complexes an amino group available in the drug substances was allowed to react with 2, 5-hydroxybenzaldehyde, separately, to obtain Schiff bases which were, subsequently,The Schiff bases prepared were: 2, 5-hydroxybensalideneamoxycillin, 2, 5-hydroxybenzalidenecephalexin, 2, 5-hydroxybenzalidenesulphamethoxazole, 2, 5-hydroxybenzalidenetrimetho-prim, The Schiff base ligands were characterized by microanalytical, thermogravimetric, magnetic and spectroscopic data. All the compounds under investigation possess antibacterial activity.The antibacterial activity showed the following trend: Schiff base ligands > parent drugs. The Schiff bases derived from cephalexin showed substantially enhanced activity against P. aeruginosa as compared with the parent drug. All Schiff Base were also found to be active against kaolin paw oedema whereas the parent drugs were inactive.**

***Index Terms*—amoxicillin, cephalexin, ligands,untibacteria, schiff bases**

I. INTRODUCTION

Compounds containing an azornethine group (–CH=N–) are known as Schiff bases. They are usually formed by condensation of a primary amine with a carbonyl compound [1] where R may be an aliphatic Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable [2]-[4] while those of aromatic aldehydes, having an effective conjugation system, are more stable [5]-[8]. Condensation of amines with aldehydes and ketones has numerous applicationswhich include preparative use, identification, detection and determination of aldehydes or ketones. Schiff bases obtained from aromatic amines are known as anils. In chemistry, Schiff bases find a versatile use [9]-[11]; some of them are the basic unit certain dyes, whereas, some are used as liquid crystals. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds. Schiff bases appear to be important intermediates in a number of enzymatic Reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate [12]. One of the most prevalent types of catalytic mechanisms in biochemical processes involves condensation of a primary amine in an enzyme, usually that of a lysine residue, with a carbonyl group of the substrate to form an imine. Stereo chemical investigations [13] carried out with the aid of molecular models showed that Schiff bases formed between inethylglyoxal and the amino groups of the lysine side chains of proteins can bend back in such a way towards the N atoms of peptidegroups that a charge transfer can occur between these groups and the oxygen atoms of the Schiff bases. In this respect, 2-hydroxybenzaldehyde Schiff bases derived from amino acids have been prepared and studied [14]. Schiff bases derived from pyridoxal and amino acids are considered very important ligands from the biological point of view. The rapid development of these ligands resulted in an enhanced research activity in the field of coordination chemistry leading to very interesting conclusions.Certain polymeric Schiff bases have been reported which possess antitumor activity [15]. The Schiff bases have the highest degree of hydrolysis at pH 5 and the solubility in water is also highest at this pH. The antitumor activity of the base towards ascitic tumours increases considerably with a slight increase in water solubility. Another important role of Schiff base structure is in transmination [16]. Tranaminases are found in mitochondria and cytosal of eukaryotic cells. All the tranaminases appear to have the same prosthetic group, i.e., pyridoxal phosphate, which is non-covalently linked to the enzyme protein. The biosynthesis of porphyrin, for which glycine is a precursor, is another important pathway, which involves the intermediate formation of Schiff base between keto group of one molecule of 6-amino levulinic acid and 6-amino groupof lysine residue of an enzyme.

Manuscript received August 14, 2013; revised October 15, 2013.

doi: 10.12720/jomb.3.3.187-189

II. Materials and Methods

A. Experimental Section General Procedure

All the reagents, solvents and catalyst are of analytical grade purchased from a commercial scours and used directly. All the Melting points were determined in a DBK programmed melting point apparatus and are uncorrected. The TLC of the compounds was performed on silica gel G coated glass plate with chloroform: ethanol (9:1) as solvent. Iodine vapour was used as detecting agent. The absorbance maxima (X max) were recorded on Shimadzu 2401 UV-Visible spectrophotometer. ^{1}H NMR was recorded on Bruker DRX-300 (300 MHz FT NMR), using DMSO, IR spectra was recorded on Shimadzu 8000S and Mass spectra were recorded on Joel SX-120 mass spectrophotometer.

B. General Procedure for Synthesis of Schiff Bases (A-D) Schem 1.

Drugs (2 mmol) dissolved in methanol (25 cm^3) was mixed with aldehyde (2, 5-dihydroxybenzaldehyde) (2 mmol, 0.2092 cm^3) dissolved in methanol (25 cm^3). To this NaOH (0.l% in methanol) was added to adjust the pH of the solution between 7-8 and the mixture was refluxed for 1h.,cooled at room temperature, filtered , washed, dried and recrystallized from suitable solvents *(schem 1).* Physical and micro analytical data of the Schiff base *(A-D)* were presented in Table I.

2, 5-dihydroxybenzalidenesulphamethoxazole (A) was prepared from sulphamethoxazole and 2, 5-dihydroxybenzaldehyde; Orange; m.p. 194 ^{o}C; 2.1 g (76 %) yield. IR (KBr, cm^{-1}) v 1580 (C=N), ^{1}HNMR (500 MHz, DMSO 8.3 (1H, -N=CH), 145,^{13}CNMR (1C, C=NH).

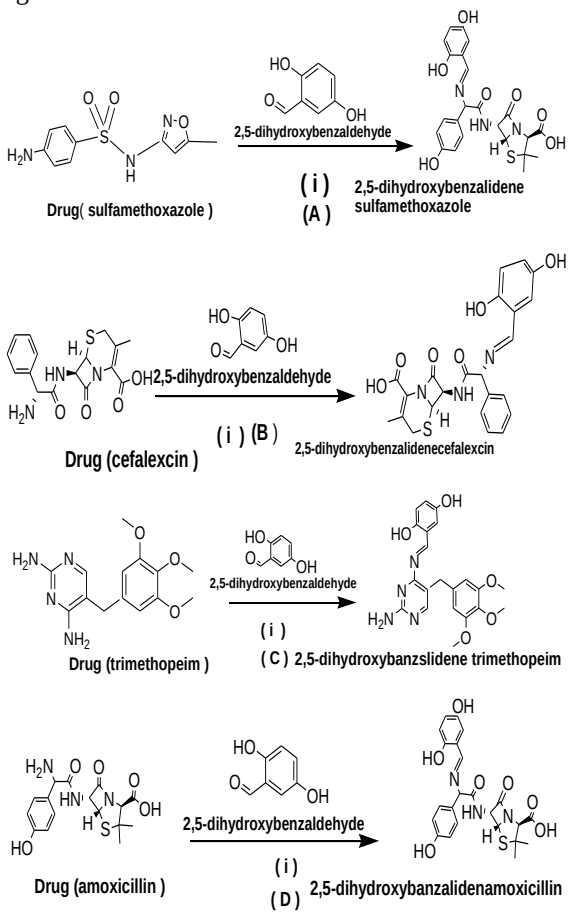
2, 5-dihydroxybenzalidenecephalexin (B) was prepared from cephalexin and 2, 5-dihydroxybenzaldehyde; yellow Orange; m.p. 193 ^{o}C; 2.1 g (77 %) yield. IR (KBr, cm^{-1}) v 1583 (C=N), ^{1}HNMR (500 MHz, DMSO 7.50 (1H, -N=CH), 155,^{13}CNMR (1C, C=NH).

2, 5-dihydroxybenzalidenetrimethoprim (C) was prepared from trimethoprim and 2, 5-dihydroxybenzaldehyde; pale yellowe; m.p. 197 ^{o}C; 2.1 g (87 %) yield. IR (KBr, cm^{-1}) v 1579(C=N), ^{1}HNMR (500 MHz, DMSO 7.85 (1H, -N=CH), 143,^{13}CNMR (1C, C=NH).

2, 5-dihydroxybenzalideneamoxicillin (D) was prepared from amoxicillin and 2, 5-dihydroxybenzaldehyde; yellow Green; m.p.190 ^{o}C; 2.1 g (84 %) yield. IR (KBr, cm^{-1}) v 1531 (C=N), ^{1}HNMR (500 MHz, DMSO 7.50 (1H,-N=CH), 158.4, ^{13}CNMR (1C, C=NH).

C. Antimicrobial Activity

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC-minimum inhibition concentration) in vitro by broth dilution method with two gram positive bacteria S. aureus and B. subtilis and gram negative bacteria E. coli, P. aeruginosa,and fungi species like C. albicans, A.niger organism taking .Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for test. DMSO was used as a dilute which not effected the growth of microbes.



Scheme 1. Synthesis of the Schiff bases of 2, 5-dihydroxybenzaldehyde with drug. (i): methanol, reflux

TABLE I. Physical and Micro Analytical Data of the Schiff Base

Schiff Bases	Color	MP (℃)	Elemental analysis %		
			C	**H**	**N**
A	Orange	194	58.10 (58.84)	5.18 (4.90)	8.76 (8.95)
B	Yellow Orange	193	60.90 (1.19)	4.99 (4.65L	9.19 (9.31)
C	Pale Yellow	197	57.10 (57.14)	4.30 (4.20)	11.12 (11.76)
D	Yellow Green	190	64.45 (63.95)	5.75 (5.58)	14.10 (14.21)

III. Results and Discussion

Substituted benzaldehyde underwent condensation with drugs, resulting in the formation of Schiff bases N=CH, which was confirmed by the IR, ^{1}H-NMR and ^{13}C-NMR spectra of compounds A-C. in the IR spectra, an absorption was found in range &1531-1584cm-1, while A strong signal appeared in the of 7.84-8,34 and 143-158.5 ppm in the ^{1}H-NMR and ^{13}C-NMR spectra of compounds *(a-c)*, respectively. These facts were also

supported by the disappearance of the signal for NH2, and the bands at 3325-3245 em^{-1} due to $–NH_2$ in the drug substances and at 2750-2830 cm^{-1} due to –HC=O group in 2, 5-benzlaldehyde present in ^{1}H-NMR, and IR spectrum.

A. Biological Study (Antibacterial)

The results of antibacterial study are given in Table II, 3. A cursory view of the data indicates the following trend in activity of the substances under investigation:

2, 5-dihydroxybenzalideneamoxicillin (D) was 3.26 times more active than amoxicillin, Schiff base against E. coli. 2, 5-dihydroxybenzalidenecephalexin (B) was 9.17times more active than cephalexin.2, 5-dihydroxybenzalidenesulphamethoxazole (A) was 3.04 times more active than sulphamethoxazole. 2,5dihydroxybenzalidenetrimethoprim (C) was 4.70 times more active than trimethoprim. 2, 5-dihydroxybenzalideneamoxicillin (D) was 1.1 times more active than amoxicillin Schiff base against S. aureus. 2, 5-dihydroxybenzalidenecephalexin (B) was 2.17 times more active than cephalexin. 2, 5-dihydroxybenzalidenesulphamethoxazole (A) was 4 times more active than sulphamethoxazole. 2, 5-dihydroxybenzalidenetrimethoprim (C) was 1 times more active than trimethoprim.All the Schiff base ligands under study were 1. 2-2 times more active than the parent drugs against E. coli and S. aureus.

TABLE II. ANTIBACTERIAL ACTIVITY OF SCHIFF BASE

Schiff Bases	MICs (,u g m II^I)			
	E.coli	S.aureus	P .aeruginos	B. subtilis
•	96	12	>300	10
••	100	10	>300	9.5
•••	100	65	>300	9.5
••••	0.5	0.5	>300	10
D	70.0	8.5	> 300	60
B	50.5	5.0	> 300	50.5
A	75.5	45.0	> 300	65
C	0.35	0.4	> 300	60

•A moxicillin, ••Cephalexin Sodium, •••Sulphamethoxazole, ••••Trimethoprim

B. Antifungal Activity

Formed the screening results of (Table III) Schiff bases (A-D) showed very good activity against C. albicans and A. Niger and it is higher activity than the parent drugs. Rest of the Schiff bases show moderately active or less active against all fungal strain.

TABLE III. ANTIFUNGAL ACTIVITY OF SCHIFF BASE

Schiff Base	MICs (,u g m II^I)	
	A. Niger	C. lbicans
*	NA	NA
**	NA	NA
***	100	100
****	NA	NA
A	6.0	5.0
B	5.5	6.0
C	6.0	6.0
D	6.0	5.5

ACKNOWLEDGEMENT

The authors are thankful to the Department of Chemistry, Science Faculty, MisurataUniveresty, Libya and a lot thanks to Microbiology Department, Science Faculty, Tripoli Univeresty, Libya for antimicrobial screening.

REFERENCES

[1] S. C. Bell, G. L. Conklin, and S. J. Childress, *J. Am. Chem. Soc.*, vol. 85, pp. 2868, 1963.
[2] K. N. Campbell, H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.*, vol. 66, pp. 82, 1944.
[3] J. Hine and C. Y. Yeh, *J. Am. Chem. Soc.*, vol. 89, pp. 2669, 1967.
[4] I. A. Savich, A. K. Pikaev, 1. A. Lebedev, and V. I. Spitsyn, *Vestnik. Moskov. Univ.*, vol. 11, pp. 225, 1956.
[5] H. Tazoki and K. Miyano, *J. Chem. Soc.*, pp. 9769, 1959.
[6] D. N. Robertson, *U. S. Pat.*, vol. 2, no. 920, pp. 101, 1960.
[7] C. M. Brewster, *J. Am. Chem. Soc.*, vol. 46, pp. 2463, 1924.
[8] C. Munir, S. M. Yousaf, and N. Ahmad, *J. Chem. Soc. Pak*, vol. 7, no. 4, pp. 301, 1985.
[9] E. Brand and S. M. Berg, *Org. Synth. Coll.*, vol. 2, pp. 49, 1943.
[10] E. Dane, F. Drees, P. Konard, and T. Dockner, *Agnew Chem.*, vol. 74, pp. 873, 1962.
[11] J. C, Sheehan and V. J. Grenda, *J. Am. Chem. Soc.*, vol. 84, pp. 2417, 1962.
[12] A. L. Lehlinger, *Biochemistry*, 2nd ed., Worth Publisher, 1975, pp. 84, 85, 220, 563 and 564.
[13] P. Otto, J. Ladik, K. Laki, and A. Szent-Gyorgyi, *Proc. Natl. Acad. Sci.*, USA, vol. 75, no. 8, 1978, pp. 3548.
[14] D. T. Ming, *Biochem.*, vol. 17, no. 16, pp. 3183, 1978.
[15] Georgiev, *Dokl. Bolg. Akad. Nauk.*, vol. 34, no. 2, pp. 189, 1981.
[16] A. E. Braunstein, "Amino group transfer," in *Enzymes*, P. D. Boyer, Ed. Pt. B, Acad. Press, N. Y., vol. 9, 1973, pp. 379.

Abdulbaset M.Elgellal is working at Department of Chemistry, Faculty of Science, University of Misurata, Libya. He was an Assistant Professor in Chemistry 2012. He got his Doctor of Philosophy. Chif. Univ. 2007, M.Sc.in Chemistry, Department of Chemistry, Misurata University, 1997, and B.Sc. in Chemistry, Misurata University, Misurata Libya