Biological Activity of Complexes of Some Amino Acid: Review

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Abstract

Schiff bases (SBs) based on amino acid derivative stand for multipurpose ligands that formed by condensing amino acids with carbonyl groups. They are significant in pharmaceutical and medical areas due to their widespread biological actions such as antiseptic, antifungal, along with antitumor actions. Transition metallic complexes resulting from SB ligands with biological activity were extensively experimented in the literature. In this article, we review, in details, about synthesizing and biological performances of SBs along with its complexes.

Keywords: *Schiff bases (SBs), Amino acid, Metal complexes, antimicrobial activity, and antitumor activity.*

Introduction

Compounds having an azomethine cluster (-CH=N-), termed as Schiff bases (SBs) has typically synthesized as a result of condensing primary amine with a carbonyl compound.(1) SBs of aliphatic aldehydes have been somewhat unstable and freely polymerizable. On the other hand, SBs with aromatic aldehydes, including an in effect conjugation system, have been in higher degree of stability (2). SBs have, in general, particular preparation use, detection, applications, identification and determining of aldehydes or ketones, carbonyl or amino compounds purification, or protecting the groups throughout complex or sensitive reacting. (3) They correspondingly create elementary units in specified dyes. SBs usually stand for bi-or tri- dentate ligands able to produce highly stable complexes with transitional metals (4). Several of them can be employed as liquid crystals. SB reactions have been advantageous in creating carbon-nitrogen bonds in organic synthesis (5). SBs act as an imperative intermediary in a quantity of enzymatic reacting containing interacted enzyme with the amino or a carbonyl collection of the substrate. The most essential categories of catalytic process is the biochemical activity that includes condensed primary amine in the enzyme with usual lysine residue and carbonyl cluster of the substrate for forming an imine and SB.(6) Stereo chemical analysis based on molecular model has depicted that the formed SB concerning methylglyoxal as well as amino group of lysine side chains of proteins can be headed for number of atom of peptide groups in which the charge transfer can arise among oxygen atoms of SBs and these groups .(7) The pyridoxal SBs resulting from amino and pyridoxal acids had made and examined based on biological viewpoint. Enzyme models based on transition metal complexes of these ligands are very imperative in biochemical scopes. (8) The speedy expansion of these ligands have caused enhanced research activity for coordination chemistry with highly remarkable deductions.(9) In the current paper, we focusses on the formation and biological actions of several primary amines derivative SBs as well as its complexes.

Part one: SB of Amino Acid

Metal chelates of prepared SB as a result of uniting salicylaldehyde along with amino acids are effectually employed in realizing the process of transamination reacting. These can be biomimetic species. The present research paper is concentrated on the characterization, complexation , syntheses, behaviour and antimicrobial analyses of several formed new SBs from salicylaldehyde with 3-amino benzoic acid besides Glycine and Alanine

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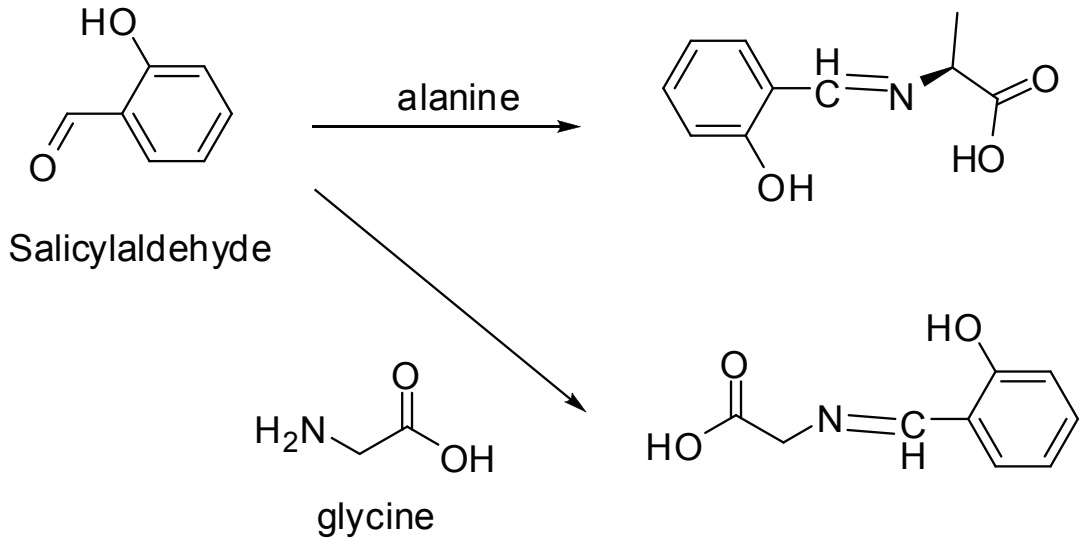
employing sodium hydroxide as a catalyst. The formed SB ligands were efficaciously complexed with Zn (II) metal and examined based on their spectral data. Morphological analyses have implemented by means of SEM. The complexation impact on the antimicrobial action of SBs besides its Zn (II) complexes is as well investigated.[10]



Scheme1- Preparation of amino acid based Schiff bases

In platinum (II) complexes having lessened amino acid ester SBs have interacting with salmon sperm DNA has been examined by dint of circular dichroism and ultraviolet spectroscopies. The potential antitumor performance of each compound has been *investigated in vitro* on HeLa and A549 tumor cell lines. Practically, each complex had superior cytotoxic action as compared to cisplatin in contradiction of these cell lines. [11]

Synthesizing new SB compound can be resulting from s-allyl cystiene and methionine. A new formed compound, 2-((2-((2-(allylthio)-1-carboxyethyl) imino)ethylidene)amino)-4-(methylthio)butanoic acid (ACEMB) has been categorized. ACEMB has shown potent *in vitro* antioxidant[12].

On the other hand, 3 integrated ligand Cu(II) complexes [Cu(o-vanillin-L-tryptophan Schiff base)(diimine)] (diimine =2,2′-bipyridine (1), 1,10-phenanthroline (2) in addition to 5,6-dimethyl-1,10-phenanthroline(3)) have been formed and categorized based on spectral and analytical approaches. In the gas phase for B3LYP/LanL2DZ levels, the 1–3 molecular structures have been boosted by means of density functional theory (DFT). [13]

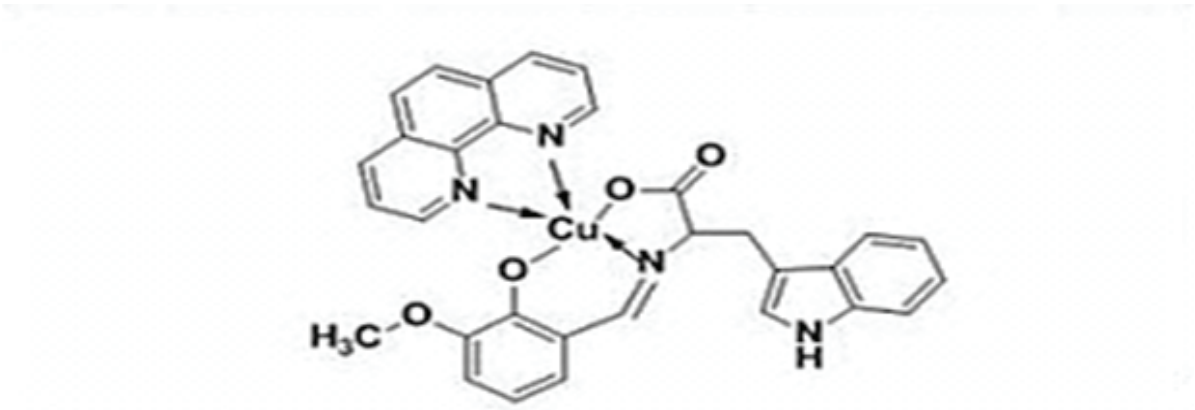
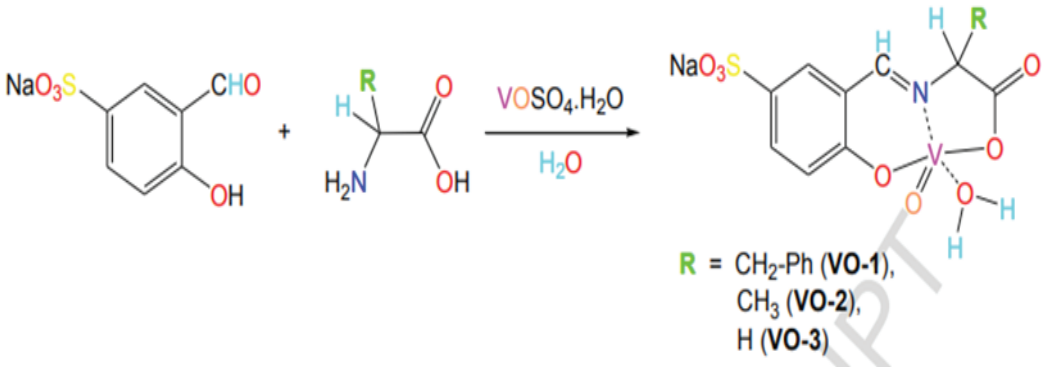


Figure 1- structure of cu complexes

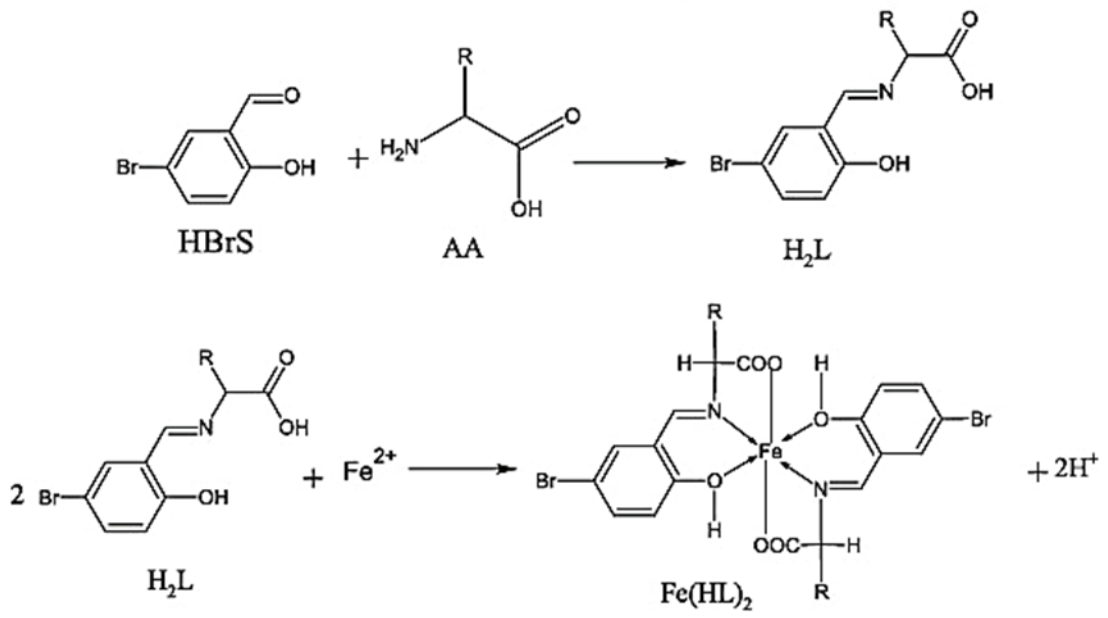
Critical investigation of thirteen crystallographic configurations of several Ni(II) complexes of amino acid SBs has performed. The foremost conclusion of [14] ha been the consequence of a parallel displaced category of aromatic interacting among Pro *N*-benzyl rings and *o*-amino-benzophenone. The aromatic interactions quality has revealed to be as controlled steric environment nearby amino acid side-chain, interpreting substituted Ni(II) complexes under dissimilar thermodynamic stabilities. [14]

3-anionic oxide-vanadium SB *N*-salicylidene amino acid complexes have been resulting by reacting sodium salicylaldehyde-5-sulfonate with phenylalanine (VO^{-1}), alanine (VO^{-2}) or glycine (VO^{-3}), subsequently, and mixed with vanadyl sulfate monohydrate. Inhibiting consequence of VO^{-3}, VO^{-2}, in addition to VO^{-1} has examined for carbon steel corrosion in chloride acid solution. Based on electrochemical experiments and in an existence of 1.0 mm VO^{-1} inhibitor, VO-complexes preserve carbon steel corrosion, producing extreme inhibiting efficiency equal to 94.7%. Each VO-complex has mixed-type inhibitors.[15]



Scheme 5- The synthetic of the VO salicylediene amino acids complexes

By condensing 5-bromo-2-hydroxybenzaldehyde along with α-amino acids (L-alanine (ala), L-phenylalanine (phala), L-aspartic acid (aspa), L-histidine (his) and L-arginine (arg)), Novel chains of Fe(II) complexes and SB amino acids were proposed and formed by bioactive ligands. Infrared, ultraviolet–visible spectra, elemental analyses,, in addition to magnetic susceptibility and conductivity measurements have been employed to clarify the geometry of anew primed Fe(II) complexes. Additionally, the stability along with stoichiometry coefficients of the organized complexes was spectrophotometrically measured. The consequences put forward that the organized SB amino acid ligands perform as dibasic tridentate ONO ligands and have binding to Iron(II) in octahedral structure as stated by the typical formulary $[Fe(bs:aa)_2].nH_2O$. In the case of pH = 7.2 and based on electronic absorption spectra besides viscosity measurements, DNA interacting of these complexes has been examined. The investigational consequences specified that the examined complexes can be binded to DNA by means of intercalative mode and have shown a dissimilar DNA binding action based on this arrangement: bsari > bshi > bsali > bsasi > bsphali. Besides, the organized compounds have investigated for their *in vitro* antibacterial action in contradiction of 3 kinds of bacteria, *Bacillus cereus, Pseudomonas aeruginosa* as well as *Escherichia coli*. The consequences have given an indication that the metallic complexes have been in a greater reactivity concerning their resultant SB ligands [16].



Scheme 6- The formation of the investigated Schiff base amino acid

Ligands and their complexes

Synthesized novel metal complex of Co and Zn withamino acid-nucleobase hybrid ligand were accomplished through minimal chemical reacting of metal salt with amino acid L-histidine in addition to nucleobase adenine as ligands. The reactivity concerning BSA has shown that BSA fluorescence quenching by the dual complexes have been in static quenching, while as compared with the complex 2, complex 1 has the greater BSA-binding capability. The pharmacological action of the ligand in addition to the complexes has examined through antioxidant activity. They display implying influence in contradiction of radical DPPH. The consequences of the molecular docking investigations of reinforced thecomplexes.[17]

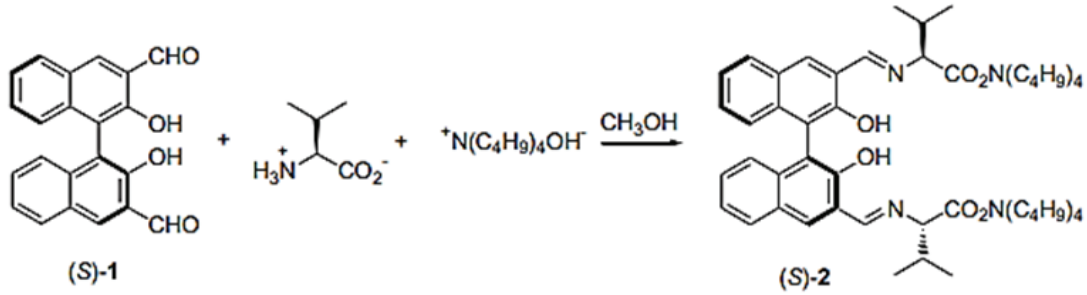
For amino acid SBs, formation and organizational categorization of cobalt (II) complexes has primed based on Salicylaldehyde and 3 amino acid in basic medium (Leucine, Valine , and Isoleucine) . The SBs and their metallic complexes have been initially scanned in contradiction of numerous microbes strains to investigate their biological influence. [18]

Expansion of innovative drugs stands for important solution to oppose in effect antimicrobial resistance threat. SB and Cinnamaldehyde-amino acid compounds stand for anew detected compounds that show noble antibacterial action in contradiction of gram-negative and gram-positive bacteria. Quantitative structure–activity relationship (QSAR) approach has employed for exploring the relationship among compound structures and antibacterial activity. [19]

Amino acid derivative SB as formed by reacting leucine with salicyldehyde in basic medium. A SB has employed as a ligand that reacted with Mn, Co, Cd and Cu metals with the intention of forming stable complexes. Each compound with ligand and complexes have correspondingly involved with diverse bacterial (staphylococcus aureus, Bacillus subbtilis and Escheria coli) and fungous strains (Aspergillus flavus, Aspergillus niger and Alternaria alternate) with the aim of investigating inhibiting activities for titled compounds. The consequences have depicted that the metallic complexes possess larger antimicrobial actions as compared with ligand. [20]

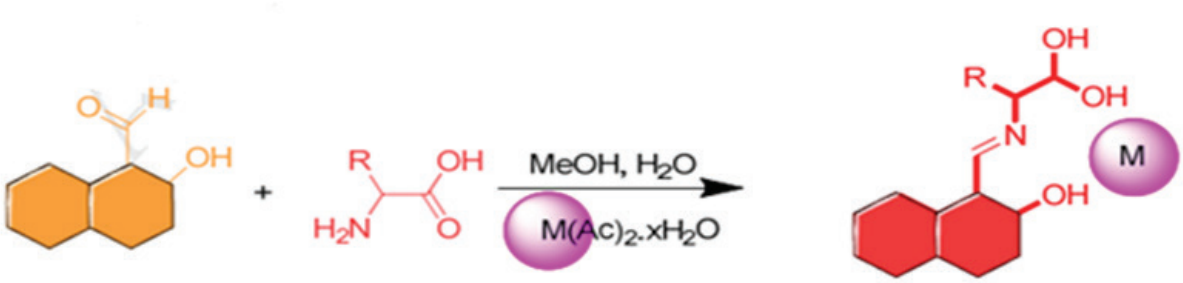
The amino-acid for SB (*S*)-**2** has organized based on condensing (*S*)-3,3′-diformyl BINOL (BINOL = 1,1′-bi-2-naphthol) with L-valine in an existence of tetrabutylammonium hydroxide in methanol. The compound shows off-on-off fluorescence reaction concerning Zn^{2+}. Spectroscopic investigations expose

(*S*)-**2**reacts with 1 equiv Zn^{2+} for forming the dimeric [2+2] complex with significantly improved fluorescence. Extra quantity of Zn^{2+} feasibly produces dissociated dimeric complex for giving significant diminished fluorescence. [21]



Scheme 10- Condensation of Schiff Base (S)-2

Resulting from 2-hydroxynaphthaldehyde with glycine and phenylalanine, Zinc (II), Cu (II), nickel (II), cobalt (II) and Iron (III) complexes of SB (LG, LP) have been testified. The LP, LG and their metallic complexes were partitioned for their antimicrobial actions in contradiction of 5 Gram-positive (Methicillin resistant Staphylococcus aureus (MRSA), Staphylococcus aureus, Streptococcus mutans, Enterococcus faecalis as well as Bacillus cereus) and 3 Gram-negative (Klebsiella pneumonia, Pseudomonas aeruginosa besides Escherichia coli) along with Candida albicans via broth microdilution methods. Resultant data have shown that ligands along with their metallic complexes have shown medium to good actions in contradiction of fungi and Grampositive bacteria. [22]



Scheme 11- The general synthesis procedure of ligands and complexes

The SB resulting from condensing tyrosine along with salicylaldehyde has been produced. In addition, its Pd(II), Pt(II) and Cu(II) complexes have primed. Antibacterial performance for the complexes has determined in vitro in contradiction of diverse bacterial strains as in Bacillus subtilis along with Pseudomonas aeruginosa using well-diffusion technique. Transition metal complexes possess noteworthy developed antibacterial activity as compared with parental drug. [23]

Part 2: mixed ligand of several amino acids

The ternary complexes of Zn(II), Cu(II), Cd(II) along with Ni(II) with 2-aminomethylbenzimidazole (AMBI) and glycine. The secluded chelates were partitioned for their antibacterial and antifungal actions using disc diffusion technique. The compound cytotoxicity in contradiction of larynx (HEP2) and colon (HCT116) cancer cells thoroughly investigated. For ternary M-AMBI-Gly complexes, stability constants have evaluated in aqueous solution at I = 0.1 mol dm3 NaCl potentiometrically. [24]

The Ni(II) , Co (II), Zn(II) , Cu(II), Hg(II) and Cd(II) complexes of integrated amino acid (L-Proline) as well as Trimethoprim antibiotic have formed. The ligands and their metal complexeswere have for their antimicrobial performance in contradiction of 4 bacteria including gram positive besides gram negative types. [25]

Diverse ligand complexes of bivalent metal ions with Ni(II), Co(II), Zn(II), Cu(II), Cd (II), and Hg(II) for [M(Anth)2(TMP)] composition in 1:2:1 molar ratio, in which AnthrH= Anthranilic acid (C7H7NO2) and

Trimethoprime (TMP) = (C14H18N4O3) were formed and categorized. The dual ligands along with their metallic complexes were screened for their bacterial performance in contradiction of particular microbial strains gram positive and gram negative types. (26)

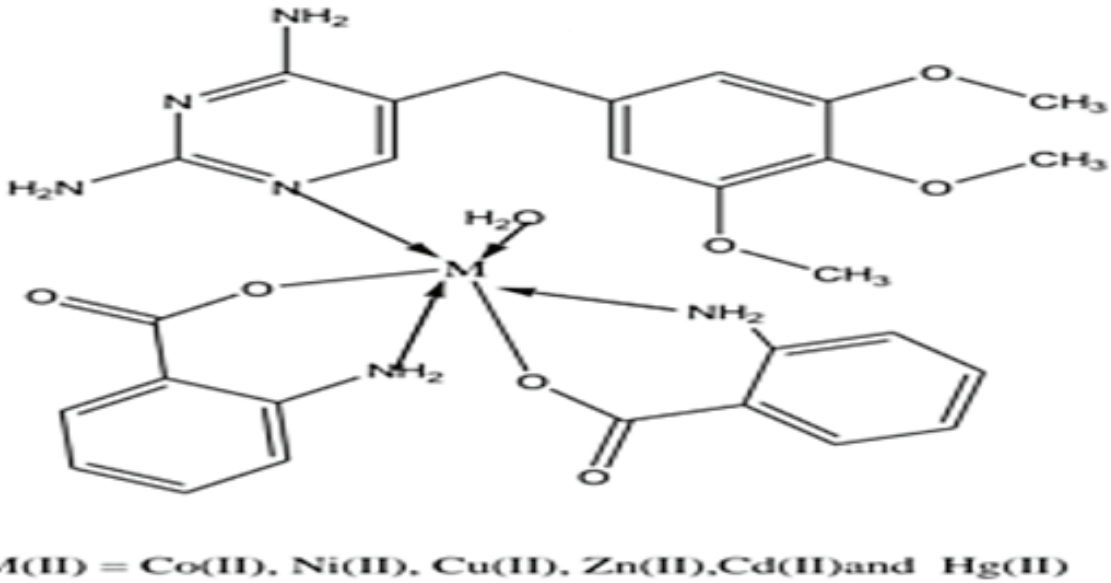


Figure5-preparation of the Complexes [M(Anth)2(TMP)]

Through condensing {3-amino-1-phenyl-2-pyrazolin-5-one (APO)} and o-phathalaldehyde and anthranillic acid (L2) accompanied by several transition metallic ions, mixed ligand complexes with SB derivative ligand (L1) were created. All these compounds were determined in contradiction of mirobial strains gram positive and gram negative types based on the analytical studies.(27)

A different mixed Iron (III) and Zinc (II) complexes along with iso nitroso acetophenone (HINAP) besides L-amino acids like, L-histidine, L-proline and L-phenylalanine, were formed and characterized. The antimicrobial performance has examined in contradiction of bacteria (bacillus subtilis, Staphylococcus aureus,, *Pseudomonas aeruginosa*, *Escherichia coli)* and *Candida albicans* fungi . The Fe and Zn complexes have been in a higher activity active in contradiction of Gram + than Gram - bacteria. They likewise exhibit significant growth inhibiting in contradiction of the tested fungi. In vitro antitumor activity has examined in contradiction of cancer cell lines of larynx or HEP2 type has shown significant ligands toxicity with their mixed complexes. (28)

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

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References

1. Dayagi S, Degani Y. Methods of formation of the carbon-nitrogen double bond. Carbon–Nitrogen Double Bonds (1970). 1970 Jan 1:61-147.
2. Hussain Z, Yousif E, Ahmed A, Altaie A. Synthesis and characterization of Schiff's bases of sulfamethoxazole. Organic and medicinal chemistry letters. 2014 Dec;4(1):1.
3. Gangani BJ, Parsania PH. Microwave-Irradiated and Classical Syntheses of Symmetric Double Schiff Bases of 1, 1′-Bis (4-aminophenyl) cyclohexane and their Physicochemical Characterization. Spectroscopy Letters. 2007 Mar 1;40(1):97-112.
4. Nishat N, Hasnain S, Ahmad T, Parveen A. Synthesis, characterization, and biological evaluation of new polyester containing Schiff base

metal complexes. Journal of thermal analysis and calorimetry. 2011 Sep 1;105(3):969-79.

5. Al-Noor TH, Karim LK, Ali FM. Schiff Base And Ligand Metal Complexes of Some Amino Acids and Drug. LAP LAMBERT Academic Publishing; 2016.
6. Kumar S, Dhar DN, Saxena PN. Applications of metal complexes of Schiff bases-A review. 2009; 68(03) : 181-187.
7. Arulmurugan S., Kavitha H.P. and Venkatraman B.R. (2010), Rasayan J. Chem., 3: 385-410.
8. Al-Obidi LK, Al-Noor TH. Synthesis, Spectral and Bacterial Studies of Mixed Ligand Complexes of Schiff Base Derived from Methyldopa and Anthranilic Acid with Some Metal Ions. Ibn AL-Haitham Journal For Pure and Applied Science. 2018 Apr 24:235-47.
9. Radhi IM, Mohammed YI, Himdan TA, Badri DH. Adsorption of Tetracycline on the Bauxite and Modified Bauxite at Different Temperatures. Ibn AL-Haitham Journal For Pure and Applied Science. 2017 Dec 28;30(3):150-7.
10. Antony A, Fasna F, Ajil PA, Varkey JT. Amino Acid based Schiff Bases and its Zn (II) Complexes. Res. Rev. J. Chem. 2016 Jul;5:37-44.
11. Yan QQ, Yuan Z, Liu GJ, Lv ZH, Fu B, Du JL, Li LJ. Synthesis, characterization and cytotoxicity of platinum (II) complexes containing reduced amino acid ester Schiff bases. Applied Organometallic Chemistry. 2017 Jun;31(6):e3689.
12. Ratha P, Chitra L, Ancy I, Kumaradhas P, Palvannan T. New amino acid-Schiff base derived from s-allyl cysteine and methionine alleviates carbon tetrachloride-induced liver dysfunction. Biochimie. 2017 Jul 1;138:70-81.
13. Sathiyendran M, Anitha K. Structural investigation and molecular docking studies of 2-amino-1H-benzimidazolium 2-hydroxybenzoate and 2-amino-1H-benzimidazolium pyridine 2-carboxylate single crystal. Materials Science and Engineering: C. 2018 Oct 1;91:103-14.
14. Nian Y, Wang J, Moriwaki H, Soloshonok VA, Liu H. Analysis of crystallographic structures of Ni (II) complexes of α-amino acid Schiff bases: elucidation of the substituent effect on stereochemical preferences. Dalton Transactions. 2017;46(13):4191-8.
15. Adam MS, El-Lateef HM, Soliman KA. Anionic oxide-vanadium Schiff base amino acid complexes as potent inhibitors and as effective catalysts for sulfides oxidation: Experimental studies complemented with quantum chemical calculations. Journal of Molecular Liquids. 2018 Jan 1;250:307-22.
16. Abdel-Rahman LH, El-Khatib RM, Nassr LA, Abu-Dief AM. DNA binding ability mode, spectroscopic studies, hydrophobicity, and in vitro antibacterial evaluation of some new Fe (II) complexes bearing ONO donors amino acid Schiff bases. Arabian Journal of Chemistry. 2017 May 1;10:S1835-46..
17. Dhayabaran VV, Prakash TD. Spectral And Theoretical Studies On The Impact Of M (II) Complexes Of Amino Acid-Nucleobase Hybrid Ligand On BSA Binding. International Journal of Engineering Technology Science and Research. 2017; 4 (9): 172-183.
18. Salama MM, Ahmed SG, Hassan SS. Synthesis, Characterizations, Biological, and Molecular Docking Studies of Some Amino Acid Schiff Bases with Their Cobalt (II) Complexes. Advances in Biological Chemistry. 2017 Sep 22;7(05):182.
19. Wang H, Jiang M, Sun F, Li S, Hse CY, Jin C. Screening, Synthesis, and QSAR Research on Cinnamaldehyde-Amino Acid Schiff Base Compounds as Antibacterial Agents. Molecules. 2018 Nov 20;23(11):3027..
20. Pervaiz M, Ahmad I, Yousaf M, Kirn S, Munawar A, Saeed Z, Adnan A, Gulzar T, Kamal T, Ahmad A, Rashid A. Synthesis, spectral and antimicrobial studies of amino acid derivative Schiff base metal (Co, Mn, Cu, and Cd) complexes. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2019 Jan 5;206:642-9.
21. Wang X, Shi D, Xu Y, Yu S, Zhao F, Wang Y, Hu L, Tian J, Yu X, Pu L. Reaction of Zn (II) with a BINOL-amino-acid Schiff base: An unusual Off-On-Off fluorescence response. Tetrahedron Letters. 2018 Jun 13;59(24):2332-4.
22. Sevgi F, Bagkesici U, Kursunlu AN, Guler E. Fe (III), Co (II), Ni (II), Cu (II) and Zn (II) complexes of Schiff bases based-on glycine and phenylalanine:

synthesis, magnetic/thermal properties and antimicrobial activity. Journal of Molecular Structure. 2018 Feb 15;1154:256-60.

23. Anjum R. Synthesis, Characterisation and Biological Activity of Schiff Base and its Cu (II), Pd (II), Pt (II) Complexes Derived from Tyrosine and Aromatic Aldehyde. Pakistan Journal of Scientific & Industrial Research Series A: Physical Sciences. 2018 Apr 26;61(1):1-7.
24. Aljahdali M. Synthesis, characterization and equilibrium studies of some potential antimicrobial and antitumor complexes of Cu (II), Ni (II), Zn (II) and Cd (II) ions involving 2-aminomethylbenzimidazole and glycine. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2013 Aug 1;112:364-76..
25. 26. Al-Noor TH, Karim LK. Synthesis , Characterization and Antibacterial Activities of Co(II),Ni(II),Cu(II),Zn(II),Cd(II)and Hg(II) Mixed-Ligand Complexes of L-Proline and Trimethoprim antibiotic, Chemistry and Materials Research.2015;7(3):32-39.
26. Al-Noor TH, Karim LK. synthetic, spectroscopic and antibacterial studies of Co (II), Ni (II), Cu (II), Zn (II), Cd (II) and Hg (II), mixed ligand complexes of trimethoprime antibiotic and anthranilic acid. TOFIQ Journal of Medical Sciences. 2016; 3(1):64-75.
27. Mahdi SH, Karem LK. Synthesis, Spectral and Biochemical Studies of New Complexes of Mixed Ligand Schiff Base and Anthranilic Acid. Oriental Journal of Chemistry. 2018 Jan 1;34(3):1565-72. Rahmouni NT, el Houda Bensiradj N, Megatli SA, Djebbar S, Baitich OB. New Mixed Amino Acids Complexes of Iron (III) and Zinc (II) with Isonitrosoacetophenone: Synthesis, Spectral Characterization, DFT Study and Anticancer Activity. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2019 Apr 15;213:235-48