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## Chapter

# Some Aromatic Schiff Bases and Their Metal Complexes

*Mirjana M. Radanović and Berta Barta Holló*

## Abstract

Schiff bases represent a widely studied group of compounds, interesting from the synthetic and structural, but also applicational point of view. Among these, aromatic Schiff bases stand out due to their stability and possible application as safer therapeutic agents. Since the presence of the phenolic group and the heteroatom in the benzene ring seems to be of interest for the biological activity of Schiff bases, imine derivatives of some dihydroxybenzaldehydes, 2-acetylpyridine, and 2,6-diacetylpyridine are chosen to be described here. The syntheses, structural features, as well as investigations of possible application of Schiff bases themselves, but also their metal complexes are described. The Cambridge Structural Database has been searched to obtain a better knowledge of the structures of these Schiff bases and their metal complexes, structural changes upon coordination, and the most common and interesting modes of coordination. The main accent is given to those compounds that are promising candidates for medicinal and pharmaceutical use, but some of the described complexes are good as catalysts, optical materials, sensors, analytical reagents, etc.

**Keywords:** dihydroxybenzaldehydes, 2-acetylpyridine, 2,6-diacetylpyridine, imine derivative, metal complexes, synthesis, crystal structure, CSD search

## 1. Introduction

Nowadays, one of the greatest imperatives is the synthesis and characterization of new drugs with enhanced activity and safer application [1]. One of the promising groups of compounds in this field is undoubtedly Schiff bases and their metal complexes, due to the ease of synthesis, interesting coordination properties, and wide range of possible applications [2–4]. Research has shown that aromatic carbonyl compounds form stable Schiff bases, while those with aliphatic compounds are prone to polymerization. Also, aromatic derivatives of some therapeutic agents were shown to be safer to use [5].

Having in mind the bond between biological activity and complexation ability [2], thorough examinations have been done to explore the possibilities of syntheses of metal complexes with aromatic Schiff bases, as well as the properties of the obtained compounds. The overview, synthesis, and comparison of some structural features of all so far known metal complexes with selected Schiff bases of some dihydroxybenzaldehydes, 2-acetylpyridine, and 2,6-diacetylpyridine are presented.

## 2. Schiff bases of dihydroxybenzaldehydes

In this part, the significance, structure, and potential application of the Schiff bases of 2,3-; 2,4-; and 2,5-dihydroxybenzaldehyde (**Figure 1**) and their metal complexes will be presented.

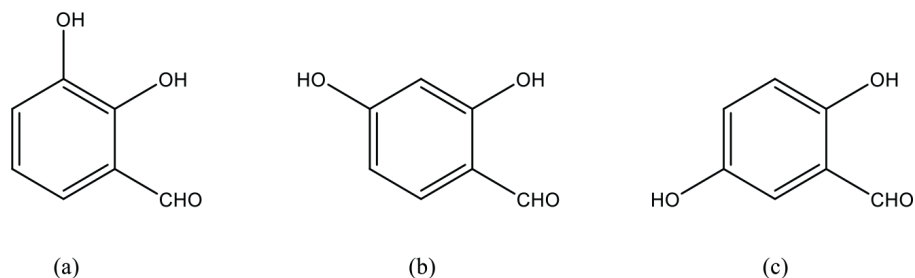
Since the knowledge about the structure of compounds leads to better insight into the mechanism of their activities, thus the prediction of improvements, the search of Cambridge Structural Database (CSD) [6] about the number and structural features of these Schiff bases and their metal complexes has been made. The comparative analysis of structural properties of free Schiff bases and coordinated ones is very important for their future applications.

Imine derivatives of 2,3-; 2,4-; and 2,5-dihydroxybenzaldehyde are part of the larger group of *o*-hydroxy Schiff bases. These compounds are interesting from the structural point of view, due to their ability to form intramolecular H-bonds. Also, metal complexes with Schiff bases containing phenol group through which the coordination is realized are considered models for important biological reactions, which mimic catalytic behavior of metalloenzymes [7]. Macrocyclic derivatives of these Schiff bases are the basis for the investigation of many biological processes, such as photosynthesis and oxygen metabolism [8].

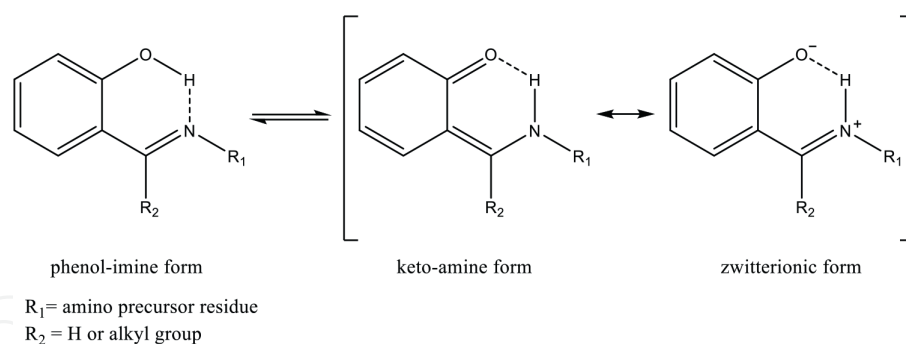
However, their existence in two different tautomeric forms, that is, phenol-imines and keto-amines (**Figure 2**), is one of the crucial factors in the determination of their photochromic and thermochromic properties [9]. Based on the tautomeric form, two types of intramolecular H-bonds could be formed: O–H···N in phenol-imines and N–H···O in keto-amines [9–11]. Another form of Schiff bases is zwitterionic tautomer, which is rather rare compared with the previously described [12]. This is in accordance with our findings based on the search of CSD.

Another interesting feature of dihydroxybenzaldehydes is the presence of another OH-group, which enables the formation of more H-bonds, but also the additional coordination *via* another oxygen atom (*vide infra*).

The CSD search has shown that 75 mono-condensed, 18 bi-condensed, two tri-condensed, and two tetra-condensed Schiff bases of 2,3-dihydroxybenzaldehyde have been structurally characterized. The number of structures of the Schiff bases with 2,4-dihydroxybenzaldehyde is similar (79 mono-condensed and 8 bi-condensed), while the number of imine derivatives of 2,5-dihydroxybenzaldehyde is significantly lower—27 structures of mono-condensed and only one structure of bi-condensed Schiff bases. In all of those structures, dihydroxybenzaldehyde fragment is present in its neutral form. As it is said before, the zwitterionic form is rare—29 structures of Schiff bases of 2,3-DHBA, but only 9 and 4 structures of Schiff bases of 2,4- and 2,5-DHBA, respectively. However, there is a certain number of structures in which



**Figure 1.** Structural formulas of 2,3- (a), 2,4- (b), and 2,5-DHBA (c).



**Figure 2.**  
Tautomerism in *o*-hydroxy Schiff bases.

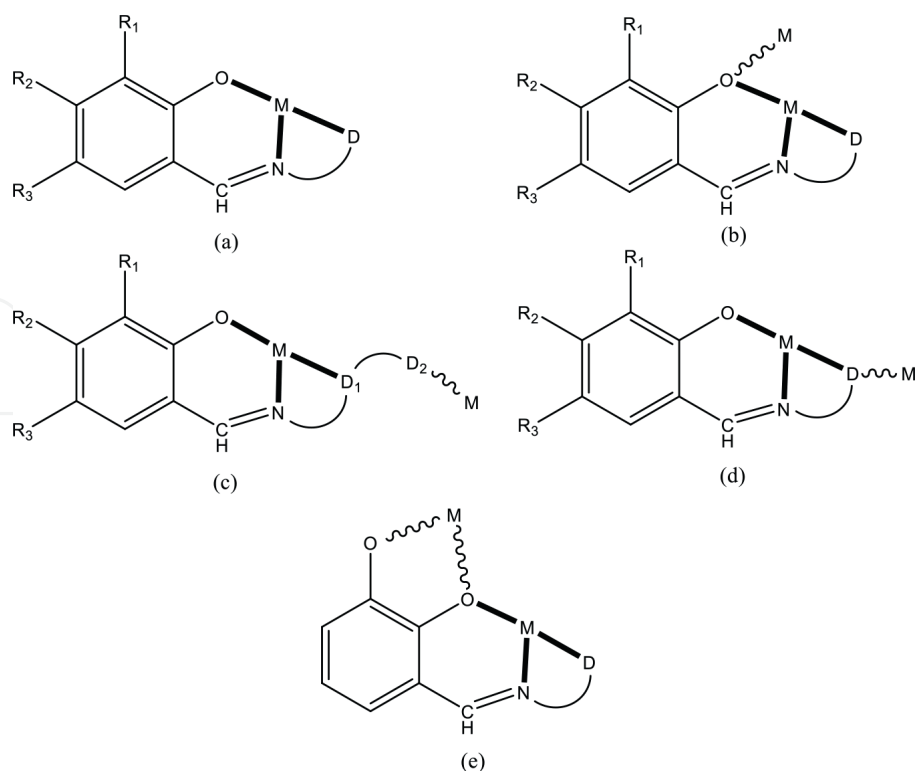
two dihydroxybenzaldehyde moieties are present, that is, one in neutral form and the other one in its monodeprotonated form. In the latter, the migration of H-atom from hydroxy-group in position 2 to azomethine nitrogen atom takes place and results in the formation of zwitterion of the Schiff base. This leads to changes in bond lengths, that is, the shortening of the C–O bond for ca. 0.06–0.07 Å, and the elongation of the C–N bond for ca. 0.02 Å.

One of the main areas of possible applications of Schiff bases, in general, is medicine or pharmacology. From this point of view, the most important characteristic of Schiff bases and an essential structural requirement for biological activity is their ability to cleave DNA [13]. The condensation of 2,3-, and 2,4-DHBA with tert-butyl-amine described in [14] gave two types of compounds. The analysis of the binding of these two ligands to human serum albumin (HSA) indicates the dominance of the latter. H-bonds stabilize the albumin-ligand system and have the main role in this type of binding.

Almost half a century ago, attempts for finding a cure for sickle cell anemia included the investigation of Schiff bases formed by amino groups of intracellular hemoglobin with aromatic aldehydes, such as 2,3-DHBA. Hydroxyl group as a substituent can lead 2,3-DHBA to specific hemoglobin sites, important for oxy-deoxy equilibrium. In this way, the affinity of sickle cells toward oxygen is increased, thus can lead to the mitigation of the effects of this disease [15].

The search of CSD revealed 136 structures of complex compounds with Schiff bases of 2,3-DHBA with 3d-, 4d-, 4f-, and s-metals, as well as uranium and organotin compounds. In the largest number of these complexes, Schiff bases have the role of tridentate (33 structures) (**Figure 3a**) and tetradentate ligand (**Figure 4a** and **b**) (20 structures). Significantly less common are bidentate (9 structures), pentadentate (2 structures), and hexadentate (2 structures) coordination of a chelating ligand. Due to the existence of two neighboring hydroxy groups, the coordination modes of these ligands could be described as versatile. In ca. 50 structures, additional bridging coordination of oxygen atom of one or both hydroxy groups is found (**Figure 3e**). Structures of numerous mixed complexes with these ligands containing 4f-metal centers are determined. A series of four mixed complexes with palladium and 4f-metals stands out. In these complexes besides the tetradentate ONNO coordination of the Schiff base, four oxygen donors of the neighboring OH-groups are coordinated to another metal center (**Figure 4d**). Also, one organometallic compound of palladium(II) is structurally characterized [16].

Complexes of 2,4-DHBA Schiff bases containing 3d-, 4d-metals, organotin compounds, lead and uranium are structurally characterized. The most common

**Figure 3.**

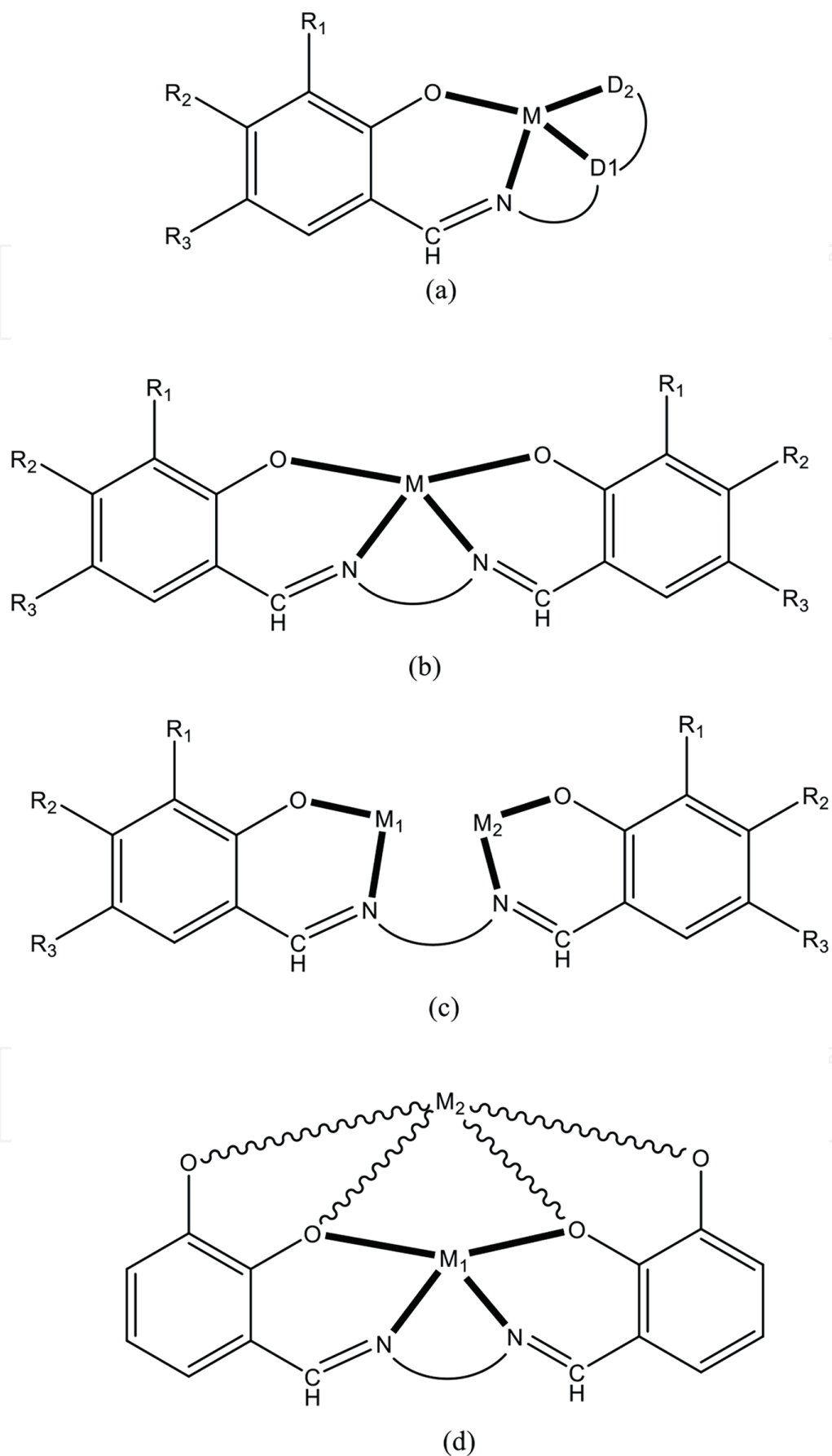
The most common modes of tridentate (a) and additional bridging coordination (b-e) of Schiff bases of 2,3-DHBA ( $R_1 = \text{OH}$ ,  $R_2 = R_3 = \text{H}$ ), 2,4-DHBA ( $R_2 = \text{OH}$ ,  $R_1 = R_3 = \text{H}$ ), and 2,5-DHBA ( $R_3 = \text{OH}$ ,  $R_1 = R_2 = \text{H}$ ).

coordination modes are ONX (X = O, N, S) tridentate (43 structures) (**Figure 3a**) and ONNO, ONNN, and ONOO tetradentate (42 structures). Unlike those, there are only 11 and 14 structures with bidentate and hexadentate coordination of these ligands, respectively. In a certain number of structures, bridging coordination of these Schiff bases is found, that is, in 8 structures besides the three donor atoms, an additional coordination bond is realized through some atom of the imine residue (**Figure 3c** and **d**), while in the other 8 structures, the bridging atom is deprotonated phenolic oxygen from the position 2 (**Figure 3b**). In the other 8 structures, both of those bridging coordination modes are proven. Finally, there are 5 structures with tetradentate and additional bridging coordination of another donor atom, as well as two structures with bidentate coordinated Schiff base and bridging of an oxygen atom from position 2 of the 2,4-DHBA moiety.

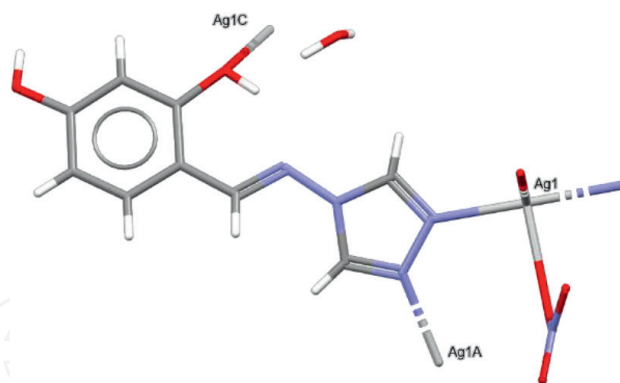
On the contrary, there are far fewer structures of the complexes with Schiff bases of 2,5-DHBA—only 12 complexes with 3d-metals and organotin. Nevertheless, the coordination modes of these ligands are numerous—in two structures bidentate coordination mode is found, in three structures—tridentate, in four structures—tetradentate, and in three structures additional bridging coordination of phenolic oxygen atom and/or another donor atom of imine residue (**Figure 3c–e**).

Unlike OH-group from position 3 in 2,3-DHBA residue, in Schiff bases of 2,4-DHBA and 2,5-DHBA additional hydroxy groups (from positions 4 and 5, respectively) do not take part in coordination.

In the silver(I) complex (Ref. code MICVUS) [17] the organic ligand is coordinated in an exotridentate manner to three metal ions (**Figure 5**). It is interesting to note that the protonated hydroxy group of 2,4-DHBA residue is involved in coordination.



**Figure 4.** The most common modes of tetradentate (a-c) and additional bridging coordination (d) of Schiff bases of 2,3-DHBA ( $R_1 = \text{OH}$ ,  $R_2 = R_3 = \text{H}$ ), 2,4-DHBA ( $R_2 = \text{OH}$ ,  $R_1 = R_3 = \text{H}$ ), and 2,5-DHBA ( $R_3 = \text{OH}$ ,  $R_1 = R_2 = \text{H}$ ).



**Figure 5.**  
Molecular structure of Ag(I) complex with the Schiff base of 2,4-DHBA.

Dihydroxybenzaldehyde residue does not take part in coordination in two ferrocene derivatives (Ref. codes OWUXUB [18] and RUTYIP [19]), as well as in three Cu(I) complexes (Ref. codes VAHHUL, VAHJIB, and VAHKIC) [20] and one silicone complex (Ref. code XOSMOJ) in which the coordination is realized through the residue of the imine ligand precursor [21].

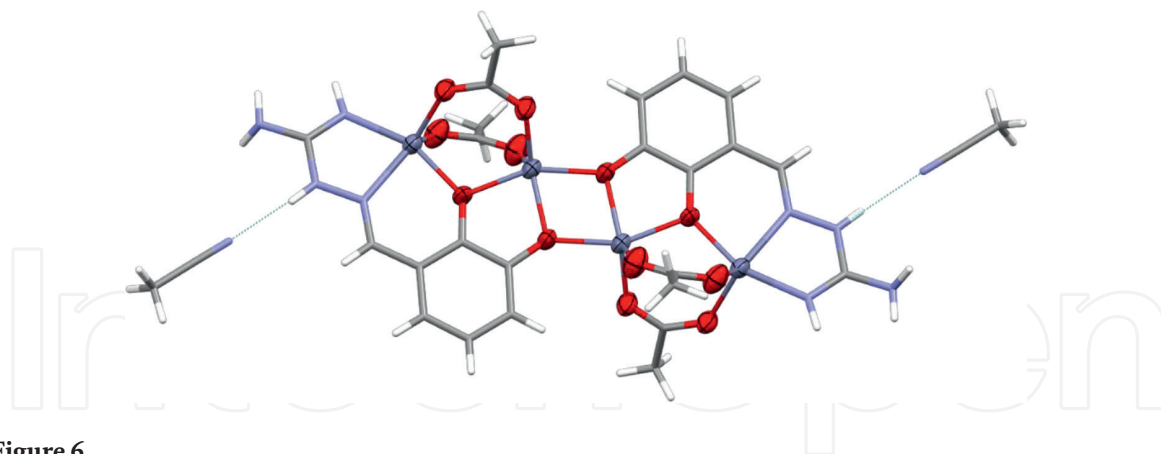
Besides, in one cadmium(II) complex (Ref. code QEWFUW) [22], the Schiff base of 2,4-DHBA is present in its neutral form but is not involved in coordination. Also, in two complexes of potassium and calcium (Ref. codes MAVNEE and MAVNII) [23] coordination is accomplished *via* sulfonato oxygen atoms, without the involvement of a 2,4-DHBA fragment. This is a good example of Pearson's theory of hard and soft acids and bases.

Schiff bases of 2,3-DHBA and their metal complexes showed to be important in the area of supramolecular chemistry, as precursors for obtaining octanuclear cluster compounds of zinc(II) [24], and some of them show significant photoluminescence [25]. Bidentate Schiff base of 2,3-DHBA and alkylamines is reported to be a good chelating ligand with significant selectivity and sensitivity for Co(II), Cu(II), and Fe(II) ions [26]. The asymmetric Schiff base obtained by condensation of allylamine has good antimicrobe activity, even better than its complex with Mo(VI) [27].

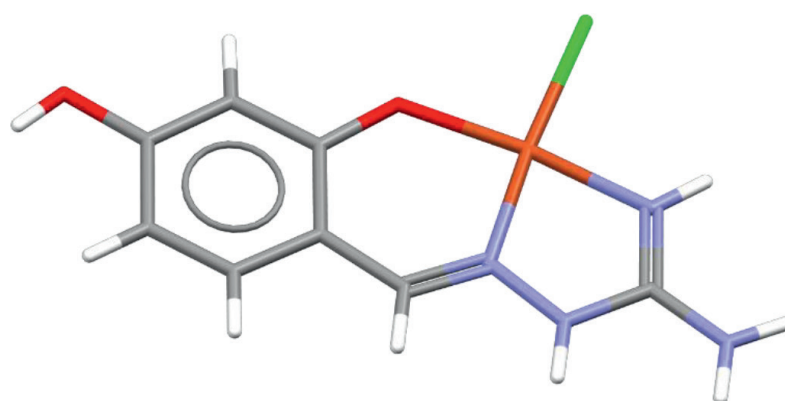
Octahedral complexes of chromium(III) with Schiff bases of metformin and 2,3-DHBA, 2,4-DHBA, 2,5-DHBA, and 3,4-DHBA are obtained by template reactions. For the complex with 2,4-DHBA Schiff base,  $[\text{CrLCl}(\text{H}_2\text{O})_2] \cdot 3\text{H}_2\text{O}$ , the research revealed the potential effect in lowering blood glucose levels [28].

A structurally interesting compound is the complex of zinc(II) with the Schiff base of 2,3-DHBA and aminoguanidine, of the formula  $[\text{Zn}_2\text{L}(\text{CH}_3\text{COO})_2]_2 \cdot 2\text{MeCN}$  (**Figure 6**). The asymmetric unit consists of the dianion of the chelating ligand, which is in an ONN tridentate manner coordinated to one metal center, and in a monodentate manner (*via* the oxygen atom of the deprotonated hydroxy group from position 3) to another zinc(II) ion, two acetate ions that have a bridging role, and one solvent molecule [29].

The research has shown that the tridentate Schiff base of 2,4-DHBA and aminoguanidine expresses antioxidative and antiglycation effects, similar to the Schiff base of pyridoxal and aminoguanidine. However, the Schiff base with 2,4-DHBA had a better *in vivo* antithrombic effect and thus could be useful in the treatment of diabetic complications [30]. One square-planar complex of copper(II) with this Schiff base has been synthesized and structurally characterized (**Figure 7**). In this complex, the chelating ligand is coordinated through the oxygen atom of the deprotonated hydroxy



**Figure 6.**  
Molecular structure of  $[Zn_2L(CH_3COO)_2]_2 \cdot 2MeCN$ .



**Figure 7.**  
Molecular structure of the complex  $[Cu(L-H)Cl] \cdot nH_2O$  ( $n = 4$ ) (water molecules are not shown).

group from position 2, the nitrogen atom of the azomethine group, and the nitrogen atom of the imine group of the aminoguanidine fragment [31].

### 3. Schiff bases of 2-acetylpyridine

#### 3.1 Significance and application

Schiff bases containing N donors and their metal complexes showed to be promising candidates for fighting against drug resistance, which many microorganisms have developed toward the drugs used [32, 33]. One of the good precursors for the synthesis of potentially biologically active imine derivatives is 2-acetylpyridine. Besides the potential for medicinal application, Schiff bases of this ketone have a wide range of other uses, such as fluorescent and luminescent probes [34, 35], optical sensors for determination of cadmium(II) in natural water and art-paint samples [36], effective catalysts [37], etc. The research has shown that imine derivatives of 2-acetylpyridine and their metal complexes express substantial *in vitro* activity against various human tumor lines [38, 39] and significant cytotoxicity against some solid tumors and leukemia cells [40].

Some cobalt(III) complexes with cytotoxic 2-acetylpyridine-derived hydrazones can release the bioactive ligand upon reduction. Also, these complexes interacted with HSA, indicating that they could be transported by this protein [40].



Complexation of N(4)-tolyl-2-acetylpyridine-derived thiosemicarbazones to gold(III), platinum(II), and platinum(IV) enhanced cytotoxic activity of the Schiff base [41]. Research also showed that bismuth(III), antimony(III), gallium(III), palladium(II), platinum(II), and tin(IV) complexes with 2-acetylpyridine-N(4)-ortho-chlorophenylthiosemicarbazone express cytotoxic activity to some solid tumor cells and that gallium(III), bismuth(III) and rhenium(I) complexes with 2-acetylpyridine- and 2-benzoylpyridine-derived hydrazones express cytotoxic effects against solid tumor and leukemia cells [42].

Recently, some lanthanide(III) complexes with 2-acetylpyridine derivatives were suggested to have great potential in biomedical application, due to their ability to inhibit proliferation and induce apoptosis in human lung and gastric cancer cell lines, thus good antitumor activities [43].

Due to the possible biologic activity of Schiff bases of amino acids and their metal complexes, it is not surprising that they represent a very interesting field of investigation [44]. Some copper(II) complexes with Schiff base of 2-acetylpyridine and leucine showed significant analgesic and antirheumatic effects, while the Schiff base with L-tryptophan forms 3D coordination polymers with copper(II), zinc(II), and cadmium(II) that express antitumor activity toward breast cancer cells [45]. Interestingly, the most promising of those is the cadmium complex, which showed the highest antiproliferative activity and potential to inhibit proteasomal chymotrypsin-like activity and induce apoptosis of human breast cancer cell lines.

In [2] some 3d-metal complexes are described as potential antibacterial drugs that could be used to control some Gram+ bacteria nosocomial infections in the hospital. Another series of 3d-metal complexes of Schiff base of 2-acetylpyridine and 4,4-oxydianniline express not only antibacterial but also anticorrosion behavior [46].

Some 2-acetylpyridine derivatives and their gallium(III) complexes were proposed to be good antitumor drug candidates to treat brain tumors [47].

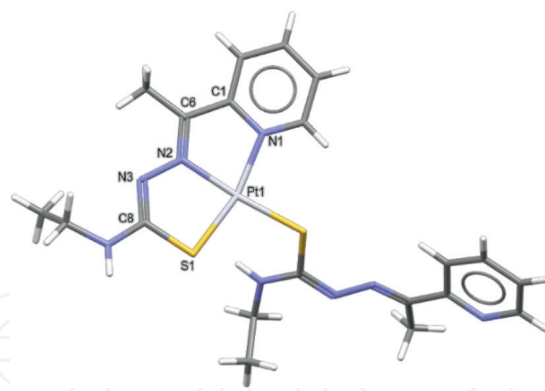
The most recent research [48] describes synthesis and structure of dinuclear silver(I) complex with selective anticancer activity. This compound inhibits the growth of cancer cells, while it does not make adverse effects on normal cells.

Since the biological activity is in the narrow bond with the structure of the compounds, some biologically active and, at the same time, structurally interesting complexes will be described in the following section.

### 3.2 Coordination behavior

The survey of CSD revealed 132 structures of free Schiff bases of 2-acetylpyridine. Most of these compounds are neutral, and only the sixth part of the total number has protonated pyridine nitrogen atom, thus exists in the form of salts or zwitterionic form. The number of complexes with 2-acetylpyridine imine derivatives is significantly larger, that is, almost 1400 structures. Analysis of these data leads to the conclusion that the denticity of those compounds varies from monodentate to heptadentate ligands. There are examples of structures in which pyridine or azomethine nitrogen atoms do not take part in coordination. However, monodentate mode always includes coordination of donor atom of amine precursor residue, usually sulfur.

It is interesting to mention that there are complexes in which two moieties of the Schiff base are coordinated differently. For example, in Pt(II) complex with 2-acetylpyridine-4 N-ethyl thiosemicarbazone (**Figure 8**, Ref. code ESAZIH) one ligand moiety is coordinated as NNS tridentate, while the other one achieves coordination *via* sulfur atom of thiosemicarbazide residue [49]. In this complex, the tridentate

**Figure 8.**

Molecular structure of Pt(II) complex with 2-acetylpyridine-4N-ethyl thiosemicarbazone.

ligand shows a Z, E, Z configuration about the C1–C6, C6–N2, and N3–C8 bonds for the two nitrogen and one sulfur donor atoms, while the monodentate ligand shows an E, E, Z configuration for the same atoms.

The described mode of coordination could be governed by many factors, such as rigid ligands, preferences of the metal toward the sulfur as softer base over nitrogen, stability of the tricyclic ring system, as well as preferences of Pt(II) to be in square-planar environments [49]. This complex is synthesized as a part of a series of Pt(II) and Pd(II) complexes, which showed to be promising candidates to overcome cisplatin resistance. The same coordination modes, as well as the same configuration of ligands, were found in other two Pd(II) complexes (Ref. codes MUSVOL, TEWZOK) with imine derivatives of 2-acetylpyridine, one of which was investigated as an antitumor agent [50]. The other example consists of two structures of Ag(I) (Ref. codes LAPCIR and YIMCAZ) and one structure of Cu(II) (Ref. code NEMCIR) in which one Schiff base moiety has the role of bidentate, while the other one acts as a tridentate ligand [51–53].

In two complexes – one complex of Cu(II) (Ref. code BABFET) and one of In(III) (Ref. code NAQFEQ) one Schiff base ligand is coordinated, while the other one has a role of counterion, with protonated pyridine nitrogen atom [54, 55].

Besides, there are four complexes in which Schiff base has exclusively the role of the counter ion—one complex of thorium(IV) (Ref. code BEQVAU) [56] and one complex of uranium(VI) (Ref. code MOYRIB) [57] with nitrates as ligands, and one complex of zinc(II) (Ref. code QELKOK) and one complex of cadmium(II) (Ref. code QELLAX) with chlorides as ligands [58]. Here, the synthetic routes should be mentioned, that is, in the presence of the deprotonating agent the coordination of the Schiff base will take place, whereas in the absence of an agent for deprotonation the Schiff base will be present in its protonated form and have a role of a counterion.

Recently, a series of copper(II) complexes with 2-acetylpyridine-aminoguanidine have been synthesized and structurally characterized and their interactions with the chemotherapeutic drug, cisplatin, were investigated [1, 59].

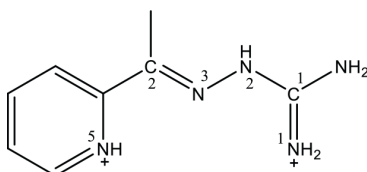
### 3.3 2-acetylpyridine-aminoguanidine as ligand

Synthesis of the titled Schiff base was described back in 1999 [60]. The reaction of aminoguanidine hydrogen carbonate and 2-acetylpyridine in acidic medium was refluxed to give microcrystals of the Schiff base. Recently, due to slight modification of the synthetic procedure, the chloride and sulfate salts (**Figure 9**) of this ligand

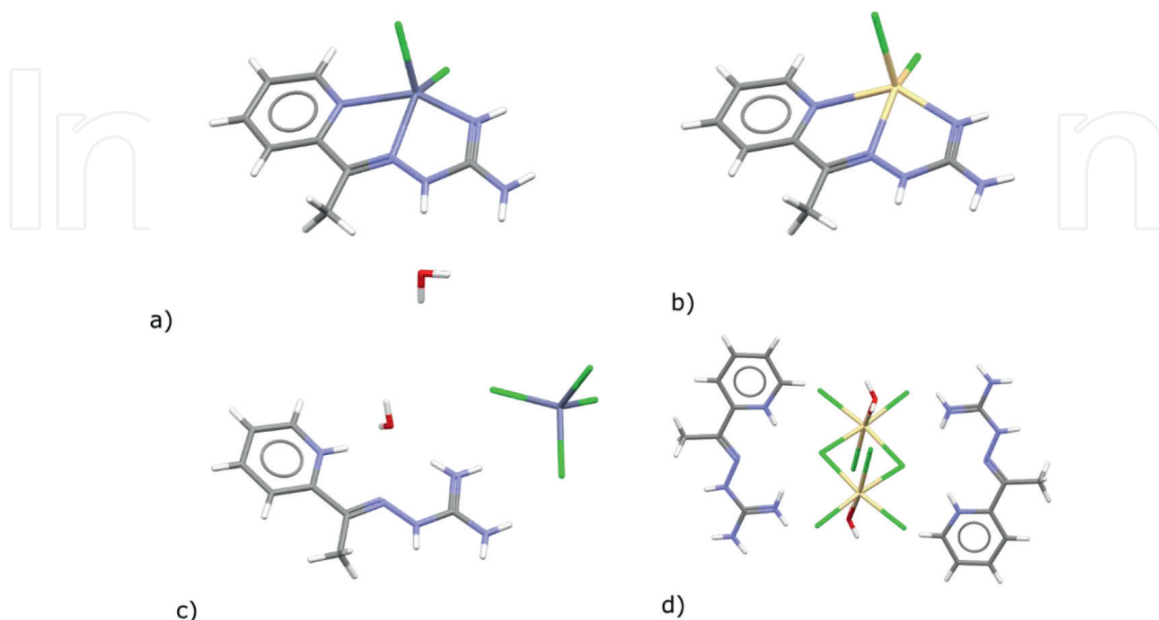
were obtained in the form of white prismatic single crystals [59]. Besides, the thiocyanate ligand salt was obtained by the reaction of chloride ligand salt with ammonium-thiocyanate [61]. In this double-protonated form of the Schiff base, both pyridine and imino nitrogen atoms of the aminoguanidine residue are protonated. These results enabled detailed structural comparison of the free ligand in its cationic form (**Figure 9**) and its coordinated forms.

Investigation of the coordination behavior of 2-acetylpyridine-aminoguanidine revealed that, due to the pronounced alkalinity of aminoguanidine residue nitrogen atoms, spontaneous deprotonation of the ligand is unlikely, thus the role of Schiff base in the formed complexes (ligand or counterion) should be defined by the presence (or the absence) of deprotonating agents. In the reaction of  $ZnCl_2$  or  $CdCl_2$  with chloride ligand salt, in the presence of LiOAc complexes of the formula  $[M(L)Cl_2] \cdot nH_2O$  ( $n = 0, 1$ ) are formed, while the same reactants in the absence of LiOAc give complexes in which coordination of Schiff base did not take place, thus it is double protonated and has a role of counterion (**Figure 10**) [58].

Upon coordination, the Schiff base retains a high degree of planarity and the same *E*-configuration at C2–N3 bond as observed for the protonated ligand. Deprotonation of the AG residue leads to shortening of the C1–N1 bond and elongation of the C1–N2 bond, while coordination of the ligand causes changes of the angles in aminoguanidine residue which bring N1 and N5 donors closer.



**Figure 9.**  
Structural formula of the cation of 2-acetylpyridine-aminoguanidine.



**Figure 10.**  
Molecular structures of the complexes  $[Zn(L)Cl_2] \cdot H_2O$  (a),  $[Cd(L)Cl_2]$  (b),  $[H_2L][ZnCl_4] \cdot H_2O$  (c), and  $[H_2L]_2[Cd_2Cl_8(H_2O)_2]$  (d).

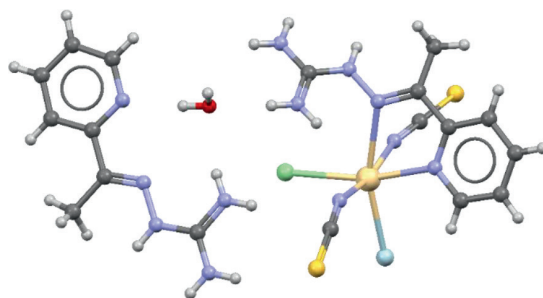
So far, with this ligand, five copper(II) complexes [59], three complexes of zinc(II) and cadmium(II) each [58, 61, 62], two complexes of iron(III) [63, 64], and one complex of cobalt(III) [63] were synthesized and structurally characterized.

In most of these complexes, Schiff base is coordinated in its neutral form, in the NNN tridentate manner, *via* pyridine, azomethine, and the nitrogen atom of the aminoguanidine residue. Monodeprotonated form of this ligand is realized by the deprotonation of the hydrazine nitrogen atom, and this form is achieved only in two iron(III) complexes.

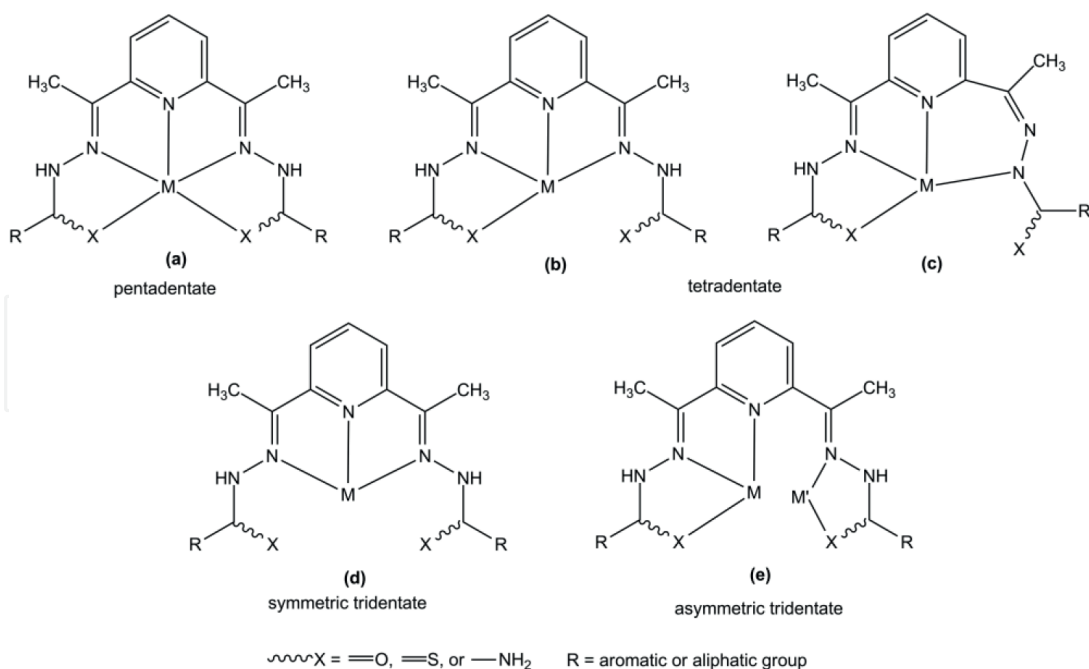
In four complexes Schiff base is fully protonated and acts as a counterion, while there is only one complex in which monocation of the Schiff base is coordinated in a bidentate manner, while another cation of the Schiff base is neutralizing the charge of the complex anion. This is an interesting structure as the Cd(II) is situated in distorted octahedral environments, with two axial sites occupied by NCS<sup>-</sup> ions, two equatorial sites occupied by bidentate coordinated organic ligand, and the remaining two equatorial sites (X, and Y) occupied by Cl<sup>-</sup>/Br<sup>-</sup> and Br<sup>-</sup>/SCN<sup>-</sup> ions, respectively. This means that the crystal structure contains four different anions: [Cd(HL)(NCS)<sub>2</sub>Br(SCN)]<sup>-</sup> (ca. 61%), [Cd(HL)(NCS)<sub>2</sub>Cl(SCN)]<sup>-</sup> (ca. 35%), [Cd(HL)(NCS)<sub>2</sub>Br<sub>2</sub>]<sup>-</sup> (ca. 3%), and [Cd(HL)(NCS)<sub>2</sub>ClBr]<sup>-</sup> (ca. 1%).

#### 4. Schiff bases of 2,6-diacetylpyridine

In this part, we will present the most common and interesting coordination modes, structural properties, and arrangement of Schiff bases of 2,6-diacetylpyridine (DAP) in their coordination complexes. The disubstituted pyridines show different properties, such as antimicrobial [65], anti-inflammatory, antitumor, analgetic [66], etc. activities. Some pyridine derivatives were used to prepare sensor membranes [67, 68], catalysts [69, 70], and ionophores for metal ion catching. Between them, a very important class is the 2,6-disubstituted pyridines, which are generally prepared by deriving DAP. The development of the one-pot-synthesis of DAP contributes to increase of its significance as a precursor for further syntheses [71]. Symmetrical disubstituted derivatives of DAP were obtained with different potential applicability, but mostly with significant biological activity [72]. The very important classes of DAPs are their thiosemicarbazones, hydrazones, and macrocyclic derivatives with promising biological activities. From the structural point of view, the symmetrically substituted DAPs can act as tri-, tetra-, or pentadentate ligands. On the other hand, the asymmetrical DAP derivatives characterize a smaller number of coordinative bonds. Both symmetrical and asymmetrical DAPs may coordinate as bridging or chelating ligands.



**Figure 11.** Molecular structure of [HL][Cd(HL)(NCS)<sub>2</sub>XY]·H<sub>2</sub>O, X = Cl<sup>-</sup>/Br<sup>-</sup> (teal ball), and Y = Br<sup>-</sup>/SCN<sup>-</sup> (green ball).

**Figure 12.**

Coordination modes of hydrazone-type Schiff bases of DAP - pentadentate (a), tetradentate (b and c), symmetric tridentate (d) and asymmetric tridentate (e).

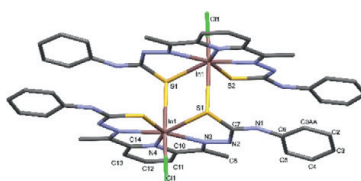
The first is more characteristic for asymmetrical, while the last one is for symmetrical DAPs. The most common coordination modes of symmetric DAP-type Schiff bases are presented in **Figure 12**. Since DAP thiosemicarbazones are the focus of numerous studies [73–76], they would be described in the first subclass of DAPs.

Thiosemicarbazide (TSC) is known as a chemical precursor/intermediate during syntheses, reagent for ketones, and detection of certain metals [77–79]. Based on literature data, it was used in photography and as a rodenticide, herbicide, etc. [80]. The thiosemicarbazones of DAP (DAP-TSCs) may be synthesized easily by direct method or in the presence of a metal template. Numerous examples of DAP-TSCs with *d*-metals are given in the papers [76, 81–84]. In [76] a dimeric compound is presented. The ligand is a common DAP-TSC without additional substituents, formed from DAP and two TSCs in the presence of  $LaCl_3$ . In the dimeric complex, described in [76], DAP-TSC forms five coplanar coordinative bonds with zinc(II). Two additional axial coordination bonds are also determined with bromide or hydroxide, and with the sulfur of the nearby complex unit. The sulfur atom from one TSC fragment from each DAP-TSC ligand coordinates to both metal centers of the dimer forming a bridge between them. The central atoms and the sulfur bridges are in the same plane, which is not completely normal ( $85.61^\circ$ ) for the plane of the DAP-TSC ligand [76]. In another paper a complex of Pt(II) with 2,6-diacetylpyridine bis( $^4N$ -tolylthiosemicarbazone) (DAP-TTSC) is described [81]. Before the complexation reaction, DAP-TTSC was prepared by direct synthesis. In the coordination compound, the Pt(II) is placed in the center of a square planar coordination polyhedron. The ligand's donor atoms are the hydrazine N, the pyridine, and the azomethine N atoms. The fourth position in the square planar arrangement is occupied by the S atom of the TTSC arm. The free ligand is symmetric as can be expected. During the reaction with  $K_2PtCl_4$ , one of the two tolyl rings is reduced and became cyclohexyl [81]. In the continuation of this study, Pt(II) Pd(II) compounds with 2,6-diacetylpyridine bis( $^4N$ -tolylthiosemicarbazones) were characterized and tested against several cancer cell lines [84]. The

metal ions, Pt(II) and Pd(II) in these compounds are in a square-planar environment and the *p*-tolyl substituted DAP-TTSC ligand coordinates to them asymmetrically. Namely, besides the pyridine N atom, donor atoms are the azomethine N and the S atom from the same TTSC arm. The other TSC arm coordinates to the metal center only through the azomethine N atom. This way of coordination results in thiol formation on the second TTSC arm. The DAP-TSC type ligands usually coordinate through pyridine and azomethine N atoms [65, 76, 85–89]. The coordination through hydrazine N is less common but also found, mostly in asymmetric complex compounds [81, 82, 84]. Due to the generally good biological activity of thiosemicarbazones, several papers address syntheses, spectral, and magnetic characterization, and tests of biological activity. Usually, antimicrobial, antifungal, or antiproliferative activity is tested on different cell lines. Such an example is [90] in which the procedure of synthesis of 2,6-diacetylpyridine bis(thiocarbohydrazone), 4-amino substituted thiocarbazone, and its reaction with Mn(II), Co(II) and Cu(II) nitrates, and acetates is described. The compounds were characterized by spectroscopic techniques [90]. It is supposed that the described compounds coordinate in a pentadentate manner and gives a positively charged complex unit. The antifungal and antibacterial tests have proved that the complex compounds are more active than the free ligand but less active than the reference substances against fungi and bacteria. Between them, the highest antifungal and antibacterial impact were shown by Cu(II) compounds.

The slightly modified thiosemicarbazides with DAP give symmetric bis(thiosemicarbazone) 2,6-diacetylpyridines under mild conditions, as described in [91]. They synthesized three monoligand coordination complexes of indium(III) with pentadentate DAP-TSCs and one binuclear compound. The ligands were prepared by direct synthesis from mixtures of DAP and thiosemicarbazide (TSC); 4-methyl-3-thiosemicarbazide (MTSC); 4,4-dimethyl-3-thiosemicarbazide (DTSC); and 4-phenyl-3-thiosemicarbazide (PTSC). The first three thiosemicarbazone-type ligands coordinate as pentadentate with the SNNNS donor set. The coordination is realized through the S atom of thiosemicarbazide fragments, the azomethine N, and the N atom from the pyridine ring. The ligands even during coordination kept their planar structure and the In(III) ion in the obtained coordination complexes with DAP-TSC, DAP-MTSC, and DAP-DTSC is placed in the center of a pentagonal bipyramidal coordination polyhedron. The equatorial plane is occupied by the DAP-TSC moiety, while the axial positions are saturated by chlorides from the starting  $\text{InCl}_3$ . Differently, the DAP-PTSC coordinates as a hexadentate. Namely, it is bonded as a pentadentate to the central In(III) ion like in the previous compounds, but a sulfur atom of one of the two thiosemicarbazone moieties from the ligand coordinates to the neighbor indium(III) ion, too, and *vice versa*. This In-S-In-S plane is analog to Zn-S-Zn-S moiety presented in [76]. The DAP moiety of the ligand occupies the equatorial plane of the pentagonal bipyramidal coordination polyhedron. However, this plane is more distorted than in the monomeric complexes. The bridging S atom occupies one of the two axial positions of the next In(III) and only one axially bonded chloride is involved in the complex formation (**Figure 13**).

The bridging sulfur atoms with the In(III) ions define a plane that is almost normal to the equatorial planes of the compound. The angle between the two planes is  $85.50^\circ$ . The lipophilic character of the thiosemicarbazone fragments of the ligand determines its anticancer activity. Compounds with higher lipophilicity are more active (more toxic) against cancer cells [91]. Despite the voluminous 4-phenyl substituted thiosemicarbazides and dimeric structure of its complex (**Figure 13**), the most lipophilic compound is the complex of DAP-DTSC. Another group of



**Figure 13.**  
The structure of the dimeric complex with the In-S-In-S plane.

authors describes a structurally very intriguing Bi(III) compound with promising anticancer and antimicrobial properties [87]. For ligand preparation besides DAP, <sup>4</sup>N-methylthiosemicarbazide was used and 2,6-diacetylpyridine bis(4-methylthiosemicarbazone) (DAP-MTSC) was obtained. This ligand reacts with Bi(NO<sub>3</sub>)<sub>3</sub> under reflux for 1 h. The result of the reaction is a nine-coordinated Bi(III) compound. The DAP-MTSC ligand coordinates similarly to the complexes of indium (III) [91] in a pentadentate manner through its N<sub>3</sub>S<sub>2</sub> donor set. The relatively rigid ligand has a distorted planar geometry after the coordination to Bi(III). The planarity is disturbed by the repulsion between the two sulfur atoms, which are placed slightly above and below the ligands plane. The probably most interesting detail in this structure is the bidentate coordination of two nitrates. Despite the weak coordination ability, in this complex two nitrates give in summary four Bi–O coordination bonds. The Bi–N and Bi–S bonds are not equal in length as was expected. Due to the different bond lengths, the coordination polyhedron around Bi(III) is distorted with the largest distance between the two S donor atoms. The thiosemicarbazone-type ligand coordinates through azomethine-, and pyridine N atoms as well as by sulfur atoms.

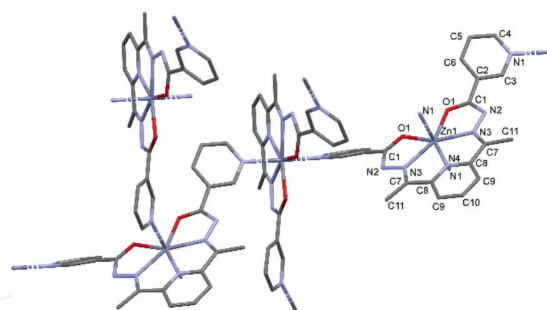
Due to the physiological significance and promising anticancer activity of Zn compounds and the significant biological activity of thiosemicarbazone-type Schiff bases, a series of Zn complexes with thiosemicarbazone-type ligands is synthesized to get a more potent multi-targeted anticancer drug [92]. The synthesis, structure, and mechanism of the anticancer effect of five Zn complexes with thiosemicarbazone moieties substituted differently in the <sup>4</sup>N position are given. Only one of the presented five complexes is monomeric with the 2,6-diacetylpyridine bis(4-phenylthiosemicarbazone) (DAP-PTSC) ligand. In this compound, the Schiff base ligand is coordinated as a pentadentate in a monodeprotonated form. The sixth coordination position is occupied by chloride. For Zn(II) ions the tetrahedral coordination geometry is the most favorable, but an octahedral arrangement is also acceptable. Since the ligand is pentadentate and relatively rigid, it cannot give a regular coordination polyhedron. Therefore, the compound presented in [92] is very distorted and fits neither in a tetragonal bipyramid (octahedron) nor in a pentagonal pyramid. The other four compounds with DAP-TSC type ligands prepared from thiosemicarbazide (TSC), N,N-diethylthiosemicarbazide (ETSC), N-methylthiosemicarbazide (MTSC), and N-tert(butyl)thiosemicarbazide (BTSC), are dimeric. In all complexes, one of the two thiosemicarbazone moieties of the ligand molecule is coordinated to one Zn(II), while the other moiety is coordinated to the other Zn(II) and *vice versa*. In the compound with DAP-TSC pyridine N atoms from both ligands are coordinated to the same Zn(II) ion, so that is hexacoordinated. To the other Zn(II) center only the TSC fragments in a tetrahedral arrangement are coordinated. The compound of DAP-ETSC is symmetrical and both Zn(II) centers are in a distorted trigonal bipyramidal environment with a coordinated NNS donor set from one of the DAP-ETSC ligands and an NS set from another one. The same coordination characteristics are observed in the case of the

DAP-BTSC complex. DAP-MTSC ligand with Zn(II) gives two different molecules per asymmetric unit. Namely, in one of these two molecules both Zn(II) are in the same distorted trigonal bipyramidal environment with NNS and NS donor sets from the two ligand molecules. In the other dimeric unit, one of the zinc(II) ions is coordinated in a distorted octahedral manner. To this metal center, N atoms of both ligands are bonded. The other Zn center is surrounded by tetrahedrally arranged NS donors of the ligand molecules. However, the focus of the paper [92] is on the mechanism of its anticancer activity, but the examined compounds are interesting from a structural aspect also. An explicit relationship between structure and anticancer activity is also found. The dimeric complexes with two Zn centers per complex molecule are more active against tumor cells than the monomeric compound. Another example of thiosemicarbazone type Schiff base is given in the paper [74]. This compound expresses good antioxidant activity, and additionally, easily reacts with transition metal ions, such as Ni(II) and Cu(II). The spectral studies have shown that both Cu(II) and Ni(II) are in an octahedral environment. From these data it may be concluded that the Schiff base ligand is coordinated as a tetradentate and in the axial positions are the chlorides from the starting metal salts. The complexes unfortunately show only minor antioxidant activity.

In addition, some compounds with S-substituted thiosemicarbazones are also published. Due to good coordination abilities and tunable biological activity, the S-methylisothiosemicarbazides (ITSC) have been a longer in focus of coordination chemistry studies. They can easily condense with carbonyl groups and give Schiff bases. Such a condensate is 2,6-diacetylpyridine bis(S-methylisothiosemicarbazone) (DAP-ITSC). With this ligand syntheses and physicochemical characterization of Mn(II), Co(II), Ni(II), and Zn(II) compounds are described [93]. The composition and most probable coordination of the ligand is supposed. Based on elemental analysis, conductometric data, and IR spectra one can conclude that the metal templated synthesis of the ligand was successful and resulted in complex formation. The IR spectra of Mn(II), Co(II), and Zn(II) complexes suggest the pentadentate coordination of the ligand through the 5N donor set. The two axial positions are most probably occupied by iodide and/or methanol and the final geometry is pentagonal bipyramidal. Differently, the collected data suggest that the Ni(II) complexes are cationic with pentadentate DAP-ITSC ligand, which is arranged in a helical trigonal bipyramidal geometry around Ni(II) ion. Neither the  $I^-$  nor the  $NCS^-$  ion is coordinated to Ni(II). These anions are counter ions in the outer coordination sphere. In the paper [94], a Ni(II) compound with the previous ligand is described. In the presented complex the DAP-ITSC ligand coordinates asymmetrically through the pyridine N; amino N and azomethine N from one ITSC arm, and hydrazine N atom from the other ITSC arm (**Figure 12c**). In this way, 4 N tetradentate coordination is achieved. Besides, an iodide is coordinated to Ni(II) in the apical position. The S-methyl substituents disturb the planarity of DAP-ITSC and the overall geometry of the compound is distorted square-pyramidal. An analogous compound with pyridine-2,6-dicarbaldehyde and ITSC was synthesized and described in [95]. The dicarbaldehyde-type ligand coordinates like the analog DAP derivative. One of the ITSC arms is deprotonated and coordinated as a bidentate to Ni(II), while the amino group of the other one is protonated and this one is coordinated as a monodentate. Together with the pyridine N, the ligand is coordinated by the 4 N donor set. By comparing the planarity of the same ligand in two complexes with Ni(II) [94] and Fe(III) [96] it is clear that the same DAP-ITSC ligand with different metal ions and in the presence of different anions is arranged differently in the coordination polyhedron.



Besides the thiosemicarbazones of 2,6-diacetylpyridine different carbazones and hydrazones of DAP are also significant in structural and antimicrobial aspects. Hydrazones are usually obtained by condensation of different hydrazines with DAP. The condensation reaction is relatively simple and can be carried out easily. By the procedure described in [97], three 2,6-diacetylpyridine bis(benzoylhydrazones) (DAP-BH) with R = H, Cl, and NO<sub>2</sub> substituents in the *para* position on the ring of the benzoyl moiety were prepared [98]. The authors have found that coordination complexes of such DAP-BH Schiff bases with Sb(III) and Bi(III) show activity against selected bacteria and tumor cell lines. The bismuth(III) compounds are more potent antibacterial and anticancer agents than the Sb(III) analogs. The DAP-BH type ligand coordinates symmetrical as a pentadentate through its ONNNO donor set. The [2,6-diacetylpyridine bis(*p*-chlorobenzoylhydrazone)]chlorido-antimony(III) has a distorted pentagonal pyramidal structure. Interestingly the otherwise planar DAP-BH in the basal plane of this complex bends toward the chloride apex of the pyramid, like an umbrella. The authors explained it with the lone electron pair of Sb(III) [98]. The Bi(III) complex beside the DAP-BH ligand and chloride contains a coordinated dimethyl sulfoxide (DMSO) in the other apex of the pentagonal bipyramid. The coordination geometry of this compound is also distorted like that in Sb(III) complex. Compounds of Ag(I) with the previous DAP-BHs, which express promising antifungal activity, were prepared and investigated also [99]. The pentadentate DAP-BH type Schiff bases can coordinate with lanthanides, such as Gd(III), Tb(III), Dy(III), and Er(III), too, and give stable single molecule- and single chain magnets [100–102], which keep their magnetism even after removal of the external magnetic field. The cobalt(II) compounds of 2,6-diacetylpyridine bis(4-hydroxybenzoylhydrazone) have an analogous structure to the previous DAP-BH complexes. It is coordinated as a planar pentadentate ligand. In the reference [103], the structure of a [Co(DAP-BH)(NSC)<sub>2</sub>] is presented together with significant DNA binding and cleavage activity. The condensation of DAP with benzoyl or isonicotinoyl hydrazides can be carried out by direct synthesis. The condensation and hydrazone formation is also successful in the presence of Ni(II) ion. This metal-templated reaction gives positively charged complex ions [104]. These hydrazones depending on the extent of deprotonation can form mononuclear complexes in which they act as tri-, tetra-, or pentadentate ligands. They also can be at the same time chelating and bridging ligands that form binuclear dimeric coordination compounds [104]. The nicotinoyl- and isonicotinoyl hydrazone (DAP-NH and DAP-INH) analogs of previous benzoylhydrazone type Schiff bases are presented in [105]. The coordination of DAP-INH is analogous to the previous hydrazone type ligand with the ONNNO donor set. The apices of the coordination polyhedron are occupied by ethyl groups. This coordination complex is cationic with a 2+ charge. The anions necessary for electroneutrality are chlorides and a diethyltrichloridostanate(II) ion. Recently 2D coordination polymers were prepared from the same DAP-NH and DAP-INH ligands and Mn(II). The final composition as well as the discrete or polymeric structure of the compounds depends on reaction conditions [106]. By template synthesis in the presence of KNCS both MnCl<sub>2</sub> and Mn(NO<sub>3</sub>)<sub>2</sub>, give discrete coordination complexes. Differently, by direct solvothermal synthesis 2D polymers were obtained. In these polymeric chains, the DAP-NH and DAP-INH ligands are coordinated pentadentately as previously (in one plane), and the N atoms of the neighbor nicotinoyl/isonicotinoyl moieties coordinate to Mn(II) below and above the DAP-NH/DAP-INH plane, apically. By solvothermal method of synthesis, homo- and heterometallic coordination polymers with DAP-NH Schiff base were obtained and described [107]. The 2D coordination polymers presented in



**Figure 14.**  
Coordination modes of DAP-NH Schiff base in a 2D coordination polymer.

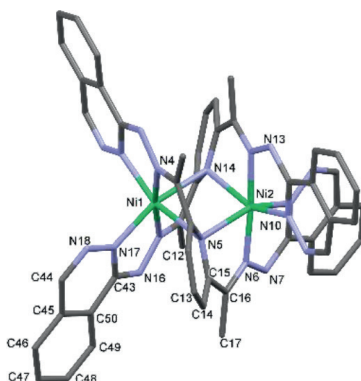
Ref. [107] due to the free space in their crystal lattices may adsorb solvent molecules and accommodate them until relatively high temperatures. In these polymers, the DAP-NH ligand is coordinated as a pentadentate for one metal center and at the same time is coordinated through one or both of its nicotinic N atoms to the neighbor metal ion/ions. The pentadentate DAP-hydrazone moiety gives the equatorial plane of the pentagonal bipyramid coordination polyhedron around the metal center. The nicotinoyl rings coordinate in the apical positions of the neighbor metal ions, forming chains in such a way (**Figure 14**).

A characteristic hydrazide that easily can react with DAP is trimethylammonium acetohydrazide, known as Girard's T reagent. The preparation procedure of 2,6-diacetylpyridine bis(trimethylammoniumacetohydrazone) (DAP-GT) at first was published in a study by Main and Fritz [108]. Later this procedure was improved, and the same Schiff base somewhat easier and faster was got [109]. The structure of the coordination complex of DAP-GT with Mn(II) is pentagonal bipyramidal as the other 2,6-diacetylpyridine bis(hydrazones) with ONNNO donor set in the equatorial plane and the N ends of thiocyanates coordinated in axial positions. Beside Mn(II), with the same ligands were prepared coordination complexes of Co(II), Ni(II) [88], Zn(II), Cd(II) [110], and Fe(III) [111]. A group of 2,6-diacetylpyridine bis(benzenesulfonohydrazones) (DAP-BS) was synthesized by reflux of acidic reaction mixtures of DAP with benzenesulfonohydrazide (BS), 4-methylbenzenesulfonohydrazide (MBS), and 4-methoxybenzenesulfonohydrazide (OBS) [112]. The Cu(II) complexes of the DAP-BSs show significant inhibition of Methicillin-resistant strains of *Staphylococcus aureus*. From the prepared Schiff bases and copper(II) complexes, only one coordination complex was precipitated as a single crystal, with 2,6-diacetylpyridine bis(4-methoxybenzenesulfonohydrazone) (DAP-OBS). In this compound, the Schiff base ligand is coordinated as a tetradentate with an NNNO donor set (**Figure 12c**). Besides the pyridine and two azomethine N atoms, an O from one sulfonyl group is the fourth coordinating atom. Additionally, one pyridine is also coordinated and a distorted tetragonal pyramidal geometry is formed around Cu(II). Because of the geometry of sulfonyl groups, the benzene rings are displaced from the basal plane of the coordination polyhedron. Interestingly, the apical pyridine ligand and the ring of the coordinated benzenesulfonyl moiety are oriented similarly, very close to being parallel. In another paper of the same group, the molecular structure of unsubstituted DAP-BS and its Zn complex is determined [113]. In the Zn(II) compound, the Schiff base ligand is coordinated as a pentadentate through pyridine and two azomethine N atoms and oxygens from both benzenesulfonyl groups. Additionally, two DMSO molecules are coordinated to Zn(II) apically. The ligands together form a pentagonal bipyramidal surrounding of Zn(II). Recently the crystal

structure of 2,6-diacetylpyridine bis(phenylhydrazone) (DAP-PH) and its mixed-valence copper complex is published [114]. In the described compound two DAP-PH Schiff bases coordinate to Cu(II) and give a bis(ligand) complex cation. DAP-PH coordinates as a tridentate with the NNN donor set. The counter ion consists of two Cu(I) bridged by two bromides and with a terminal bromide bonded to each Cu(I).

An interesting group of DAP hydrazones is prepared from biologically active compounds. Copper(II) complex of condensed 2,3-diamino-1,4-naphthoquinone with DAP shows inhibition of *S. aureus* comparable with inhibition of penicillin [115]. With glucosamine and ethanolamine, DAP also may give adducts. The reaction is Fe(III)-templated [116]. The authors give data about the antibacterial and radical scavenging activity of the compounds. The crystal structures of transition metal complexes with the antihypertensive phtalazine-1-hydrazones, also known as hydralazine (HZ) were published in [117–119]. It was found that the Schiff base 2,6-diacetylpyridine bis(phtalazine-1-hydrazone) (DAP-HZ) is a good ligand for the formation of binuclear complexes [117]. Nickel(II) gives a binuclear compound with DAP-HZ in which the Schiff base DAP-HZ acts as a hexadentate bridging ligand. Namely, one of the arms of DAP-HZ coordinates through pyridine N, azomethine N, and N atom from the hydralazine moiety to the first Ni(II) center, while the other arm through the analogous atoms to the second Ni(II) center. The pyridine N atom is coordinated with both Ni(II) ions. The other DAP-HZ coordinates with these two Ni(II) in the same way and forms a binuclear coordination compound with octahedral coordination geometry around both nuclei (**Figure 15**).

About 20 years later the structures, detailed characterization, and antimicrobial activity of mononuclear transition metal (Co(III), Ni(II), and Cu(II)) complexes of DAP-HZ were described in Ref. [119]. In the discussed compounds DAP-HZ acts as a monodeprotonated tetradentate ligand with a 4 N donor set. It gives the equatorial or basal plane of the complexes. One of the hydralazine moieties is not coordinated and bends out of the plane of the rest of the molecule. The electroneutrality of the compounds is achieved with chlorides. Accordingly, Co(III) are bonded two chlorides in the axial positions, and an octahedral complex is formed. The square planar geometry, characteristic of Ni(II), is realized by coordination only of DAP-HZ. Since the Schiff base is 1– charged, the other necessary negative charge ensured the chloride as a counter ion. The Cu(II) is in a tetragonal pyramidal environment with the chloride coordinated to the Cu(II) center in the apical position. In the reaction with Zn(II), DAP-HZ is additionally deprotonated and as a bianionic ligand gives a neutral complex. The influence of these compounds and some other aromatic Schiff



**Figure 15.**  
Coordination mode of DAP-HZ in the binuclear Ni(II) compound.

bases on the anticancer activity of cisplatin is described in [1]. Another biologically active aromatic compound with a functional group analogous to HZ is 3-chloro-6-hydrazinopyridazine (HP). The corresponding pyridazone analog of DAP was prepared by direct synthesis. The coordination ability of obtained 2,6-diacetylpyridine bis(3-chloropyridazine-6-hydrazone) (DAP-HP) was investigated in reaction with Co(II), Ni(II), Cu(II), and Zn(II) [118]. DAP-HP deprotonates during complex formation and gives neutral coordination complexes with the metal ions. In the reaction of cobalt(II) acetate with DAP-HP, in the presence of methanol, Co(II) is oxidized to Co(III) and a binuclear compound is formed. One of the arms of DAP-HP coordinates as a tridentate to one Co(III) center through pyridine, azomethine, and pyridazine N atoms, while to the other Co(III) center as a bidentate through azomethine and pyridazine N atoms of the other arm. The other DAP-HP ligand coordinates in the opposite way. The sixth coordination position of both Co(III) centers is occupied by a peroxide bridge. Based on IR, Raman, molar conductivity, and thermal data, the Ni(II), Cu(II), and Zn(II) complexes are mononuclear with a square-planar arrangement of the tetradentate DAP-HP ligand.

Besides different carbazones and hydrazones, DAP can give Schiff base-type macrocyclic compounds. Some macrocyclic compounds show significant biological activity. Such compounds were described in [66]. The obtained semicarbazide pyridine derivative showed slight anticonvulsant and analgetic activity. Differently, 2,6-bis-[ $\beta$ -(2-thienyl)acryloylphenylsemicarbazide]-pyridine derivative showed activity comparable with referent drugs [66]. The macrocyclic compounds may also act as ligands for coordination compounds. The template synthesis of Mn(II), Zn(II), and Cd(II) complexes of a DAP derivative macrocyclic ligand is given in [120]. The Zn(II) compound is active against some bacteria and cell lines, while the antioxidant activity of the Mn(II) compound is similar to that of the reference substance. The macrocyclic ligands DAP moiety coordinates to the metal center similarly to the earlier compounds as a tridentate. The piperazine moiety forms two additional coordination bonds with the central atom through N atoms of the piperazine ring.

## 5. Conclusion

The significance, syntheses, structural properties, and potential or real application of the dihydroxybenzaldehyde, 2-acetylpyridine, and 2,6-diacetylpyridine Schiff bases are described. Besides, for the first two groups of compounds, the search for CSD was made and the number and the frequency of certain coordination modes were investigated. Some interesting examples with mostly biological activity are collected with an accent on their structure and the coordination modes of DAP in them. There are many more Schiff bases of these compounds, than those presented in this summary with different potential or real applications. This shows the importance of future research in the field of Schiff bases and their metal complexes.

## Acknowledgements

The authors acknowledge the financial support of the Ministry of Education, Science, and Technological Development of the Republic of Serbia (Grant No. 451-03-9/2021-2114/200125) and the Provincial Secretariat for Higher Education and Scientific Research (Grant No. 42-451-2197/2022).

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