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Chapter

Chiral Mono- and α-Diimines and Their Pd(II) Complexes with Anticancer Activity

Guadalupe Hernández, Daniela Gutiérrez, Gloria E. Moreno, Oscar Portillo, René Gutiérrez and Eduardo Brambila

Abstract

The aim of this review is to provide mainly an outlook of the synthesis and characterization of chiral mono- and α-diimines ligands and their Pd(II) complexes carried out in our group in the last few years. Some other issues with simple chiral imines synthesized in our lab are also outlined. The report includes details about their versatile coordination patterns, biological activity in cancer cell lines, and engaging properties in different fields, such as materials science.

Keywords: chiral imines, Pd complexes, solvent-free reactions, anticancer activity

1. Introduction

The importance of Schiff bases resides in their structural variety as well as their ability to form a wide range of appealing structural arrangements depending of the constituents parent molecules with transition metals by acting as *N*-donor ligands, affording mono-, bi- and polynuclear complexes [1–3]. Accordingly, Schiff bases display a broad range of useful biological activities such as, *inter alia*, antibacterial, antifungal, antidiabetic, anti-inflammatory, and anticancer agents generating a huge interest in the medicine field [4–8]. The proper choice of the ligands in metal complex synthesis is essential for the activity that they could present since they determine some aspects like reactivity and lipophilicity.

We have focused our attention on the synthesis of chiral compounds since chirality is almost omnipresent in a broad range of organic molecules in the human body such as proteins, enzymes, amino acids, carbohydrates, and nucleosides. The body acts like a chiral selector metabolizing enantiomers by separate pathways and generating different pharmacological activities. For that reason, the current approach is to target specific molecules by designing more selective drugs, especially in chemotherapy where the distinction between cancerous and normal cells is essential for the success of the treatment and the reduction of the toxicity.

Likewise, the search of more eco-friendly procedures in the synthesis of organic molecules is one of the goals of our research group. Green Chemistry techniques like the use of microwave irradiation and solvent-free reactions display numerous advantages such as shorter reaction times, minimum waste, operational simplicity as well as reduction of thermal degradative byproducts along with cleaner work-up and generally higher yields [9, 10].

On the other hand, the discovery of anticancer activity of the cisplatin was a key event for the introduction of metal-based compounds to medicine, and the interest on these kind of compounds increased significantly in the last decades due to their ability to coordinate ligands in a three-dimensional configuration and bind to specific cell targets. Platinum-based drugs, particularly cisplatin, are widely use in the treatment of different types of cancer, but the toxicity and high resistance that they present limits their use. Therefore, the major challenge for chemists is the design of new drugs with less side effects. Efforts have been made to consider other metal-based complexes with cytotoxic properties, such as palladium complexes. They are known to show structural and thermodynamic analogy in regard to Pt(II) complexes, and display versatile coordination behavior and interesting properties. Palladium complexes of various donor-atom ligands have been found to possess engaging anti-tumor activity, as well as anti-inflammatory, anti-microbial, antiviral and antifungal properties [11, 12].

2. Chiral Pd(II) complexes

The incorporation of optically pure aromatic amines into α-dicarbonylic compounds bearing aromatic rings such as benzil in a 1/1 ratio generating enantiopure α-ketoimines was the first step for our investigations, considering that a flexible X═C▬C═N (X = O, N) skeleton could lead to diverse coordination modes [13]. Then, the chiral mono-imine derived from (*S*)-(−)-1-phenylethylamine and benzyl under microwave radiation in solvent-free conditions led to the formation of the *N*-donor ligand (*S*)-(−)-(1-phenylethylimino)benzylphenylketone **1** which was allowed to react with K_2PdCl_4 giving two Pd complexes: a mono- **2** and a dinuclear Pd(II) **3** complexes (**Figure 1**).

On the other hand, *in vitro* assays are essential to determine the capacity of the compounds to modify basic cellular functions on different cancer cells. We have

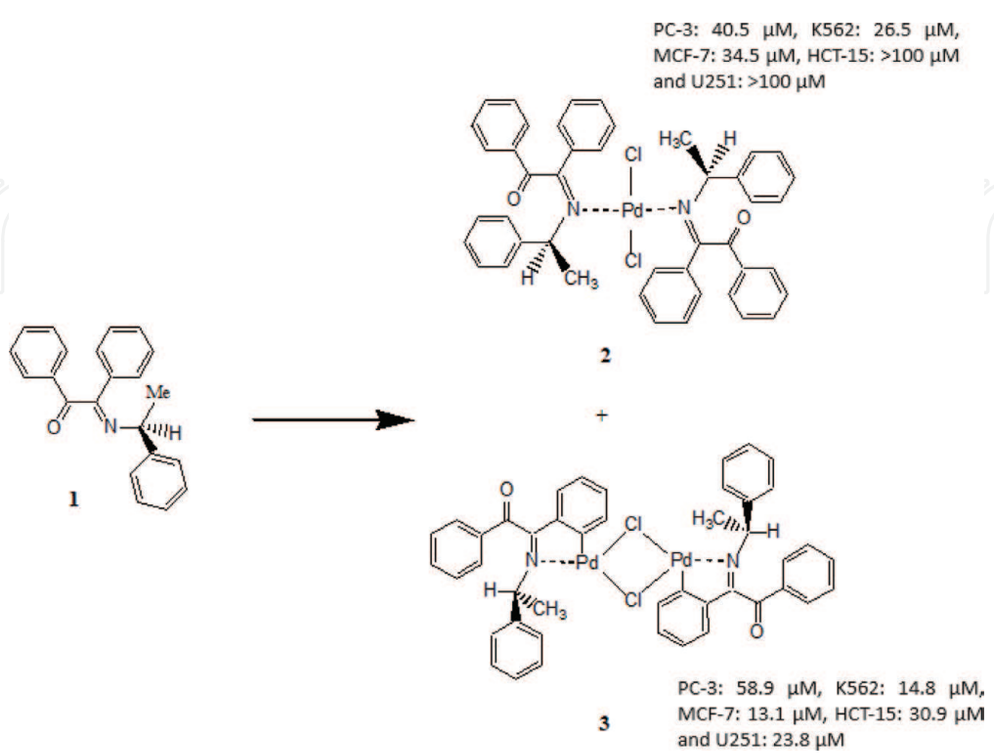


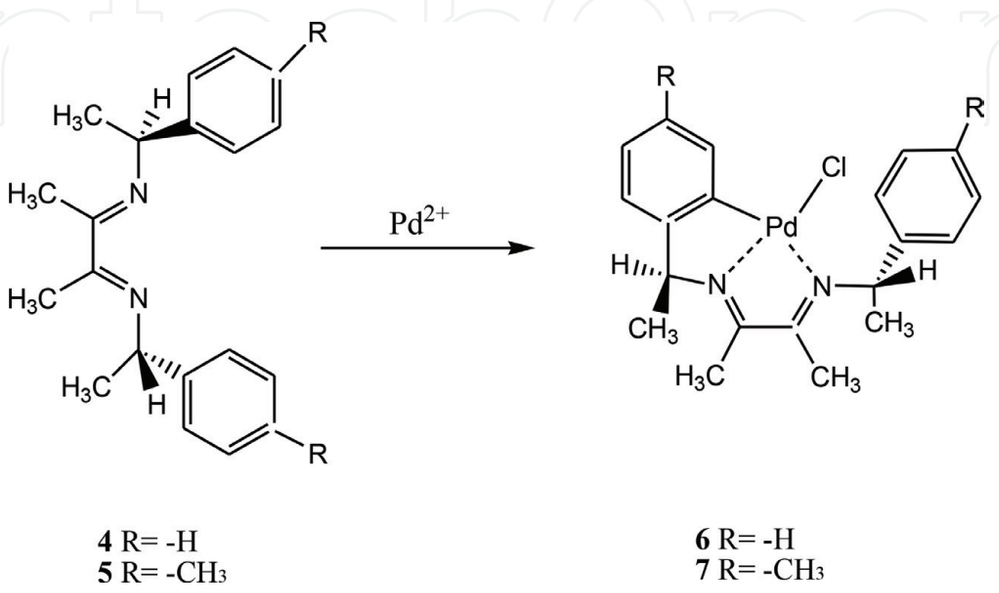
Figure 1.
Mono- and dinuclear chiral Pd(II) complexes **2** *and* **3** *with their respective* IC_{50} *values.*

employed sulforhodamine B staining to determine the cytotoxicity of our complexes, given the ease and high reproducibility of this method. By keeping constant the panel of human cancer cell lines (U251: central nervous system, PC-3: prostate cancer, K562: leukemia, HCT: colon cancer and MCF-7: breast cancer) we are able to compare the effects of the compounds in each cell and determine how the variations on the structure affect the activity. Those cell lines represent the most common types of cancer [14].

Complex **2** presented a common square planar geometry at the metal center with two Cl atoms *trans* and two ligands bonded through the N atoms N8 and N58 in a *trans* configuration while complex **3** is a dinuclear Pd(II) complex with one molecule in the asymmetric unit. For the binuclear complex, the coordination is carried through the N atoms (N8 and N58), like complex **2**, and the C atoms of the phenyl rings of the imino functions (C14 and C64). The low level of electronic delocalization in the ligand induced a high level of flexibility in the formation of complex **3**, producing a major distortion, due to the bite angles Cl-Pd-Cl and N-Pd-Cl.

The complexes **2** and **3** were tested by sulforhodamine B assays against U251, PC-3, K562, HCT and MCF-7 human cancer cell lines. Both compounds displayed cytotoxic activity, especially toward K562 (IC_{50}: 26.5 ± 0.4 and 14.8 ± 1.1 μM for complex **2** and **3**, respectively) and MCF-7 (IC_{50}: 34.5 ± 2.5and 13.1 ± 1.0 μM for complex **2** and **3**, respectively). In general, the binuclear complex was slightly better for all cell lines exhibiting lower IC_{50} values, while complex **2** surpassed the dose of 100 μM in U251 and HCT-15 cell lines [14].

Also, we have reported the synthesis of cyclopalladated compounds. Considering that our previous compounds displayed attractive properties, we decided to vary the substituents, replacing the aromatic rings in the α-dicarbonylic compounds by aliphatic substituents, such as two methyl groups and attaching also two chiral entities, i.e., to prepare α-diimines, as such kind of compounds have also a flexible N═C─C═N skeleton, displaying outstanding electron donor and acceptor properties and can potentially act in a variety of coordination modes. Then, the chiral diimines **4–5** were synthesized under solvent-free conditions starting from (*S*)-(−)-1-phenylethylamine and (*S*)-(−)-1-(4-methylphenyl) ethylamine with 2,3-butanedione, respectively. The reaction between Na_2PdCl_4 and each of the ligands **4–5** in a MeOH solution at ambient temperature led to the formation of the complexes **6** and 7 (**Figure 2**) [15]. In this case, the complex **6** is mononuclear



4 R= -H
5 R= -CH3

6 R= -H
7 R= -CH3

Figure 2.
Synthesis of chiral Pd complexes **6–7**.

with the Pd(II) center adopting a distorted square planar Pd[N_2CCl] coordination geometry where one benzene group is bonded to the metal center while the other is free of coordination. The steric hindrance produced by the benzene group and the formation of a Pd-C bound apparently blocked the dimerization of the complex. The solid obtained from complex **7** was not able to crystallize.

Both complexes **6** and **7** exhibited cytotoxic activity toward the panel of cultured cell lines previously mentioned, mainly against U251 and K562 cancer cells with IC_{50} values of 19.8 and 22.5 μM for complex **7**, and 23.6 and 25.44 μM for **6**, respectively. According to the data, **6** cannot be considered a good candidate as an anticancer agent since its IC_{50} values are too high for PC-3 and HCT-15, exceeding the dose of 100 μM. These compounds offer a better activity against U251 cell line compounds than the α-ketoimine complexes previously mentioned.

Thereafter, we carried out the synthesis of new unsymmetrical α-diimines by replacing one methyl group with a hydrogen atom and enlarging the number of chiral amines. A different method was used with the aim to improve the yields. Then, methylglyoxal and optically active aromatic and alicyclic primary amines were stirred in diethyl ether with Na_2SO_4 for 24 hours at room temperature leading to the formation of the ligands **8–11** (**Figure 3**). Solutions of the ligands **8–11** in benzene were treated this time with dichloro(1,5-cyclooctadiene) palladium (II) and stirred at room temperature under argon atmosphere to form complexes **12–15** (**Figure 4**). Worth-mentioning is that the coordination of the ligands took place in two different modes: chelating (σ, σ, N, N′) and monodentate (σ-N) [16].

Complexes **12** and **13** expose a *s-cis* chelate system and although they are chemically similar they crystallize in different way, in two distinct space groups. We believe that the crystal symmetry modification is a consequence of the crystallization rather than small conformational variations. The complex **15** displays two diimine ligands which are coordinated to the metal center in a *trans* square planar geometry, and the same behavior is observed in complex **14**. The importance of the *trans*-geometry around the Pd center has been attributed to the comparatively higher cytotoxicity values as those for *cis*-isomers.

It seems that the small substituents on the imine N atoms facilitates the orientation toward σ, σ, N, N′ coordination mode, stabilizing the complex through the chelate effect, while the monodentate (σ-N) coordination mode is favored by sterically hindered systems.

The results of the cytotoxic assay showed that Pd complexes with monodentate (σ-N) coordination mode (**14** and **15**) displayed IC_{50} values >100 μM; these complexes were dismissed for further assays because the doses required to inhibit cell

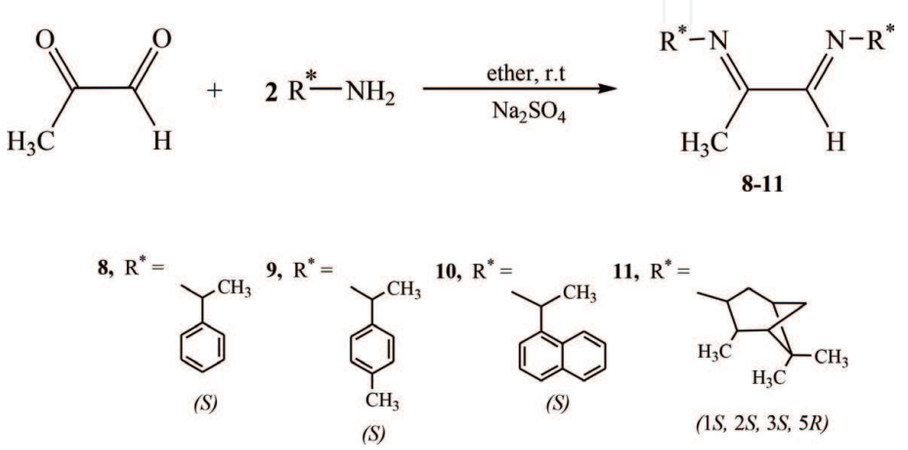


Figure 3.
Synthesis of chiral α-diimine ligands **8–11**.

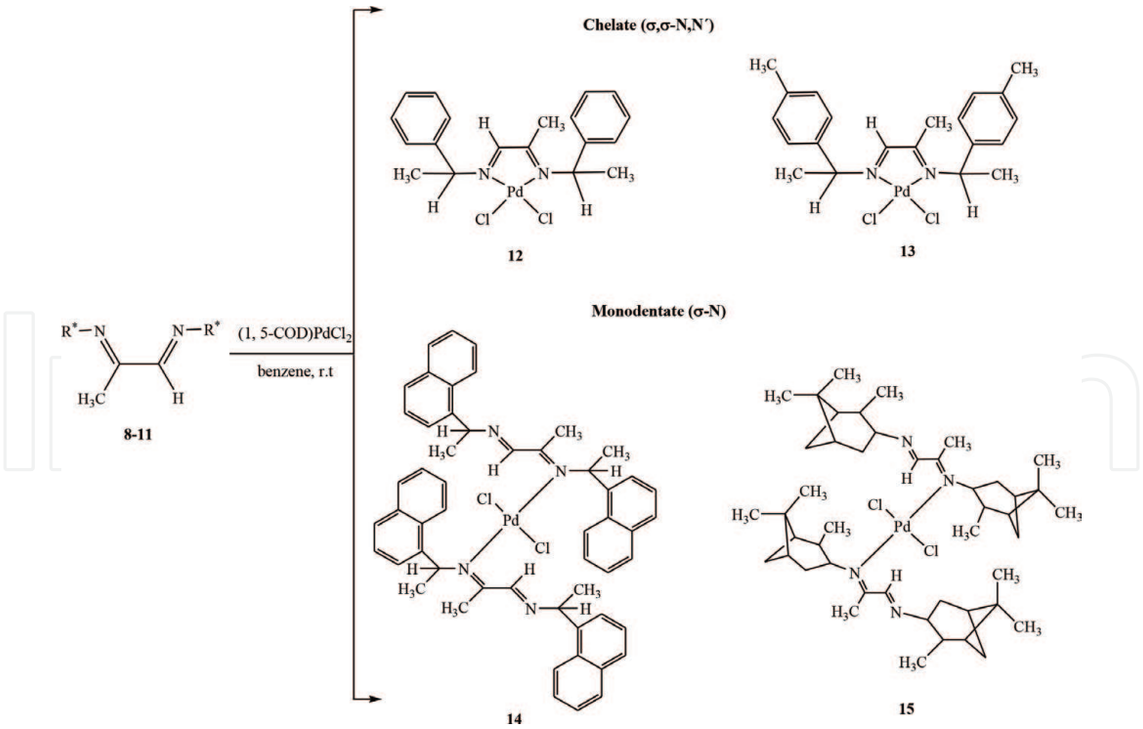


Figure 4.
Synthesis of chiral Pd(II) complexes **12–15.**

growth were too high. Complexes **12** and **13** also possessed cytotoxic activity against U251, PC-3, K562, HCT and MCF-7 cell lines, where IC_{50} ranged from 66 to 91 μM.

As such results were unpromising, we reconsidered the α-dicarbonylic compounds bearing aromatic rings, but this time with heterocyclic entities. By using the method previously used (microwave irradiation in solvent-free conditions), the chiral α-ketoimines **16–17** were synthesized from (S)-(−)-1-phenylethylamine and (S)-(−)-1-(4-methylphenyl) ethylamine with 2,2′-pyridil, respectively (**Figure 5**).

Complexes **18–19** (**Figure 6**) were synthesized by the reaction between $Pd(COD)Cl_2$ and each ligand **16-17** in a solution of benzene. It was not possible to obtain a monocrystal of complex **19**, however the crystal data of **18** showed that α-ketoimine **16** is a bidentate ligand and Pd(II) displayed a square-planar coordination geometry. In the case of **16**, the conjugation of imine and carbonyl double bonds with the aromatic systems and the substitution of vicinal C1 and C2 by pyridil rings implied that the ligand adopted a *gauche* conformation [17].

The data from the sulforhodamine B assay evidenced that none of the compounds possess cytotoxicity toward K562, however they are able to inhibit cell

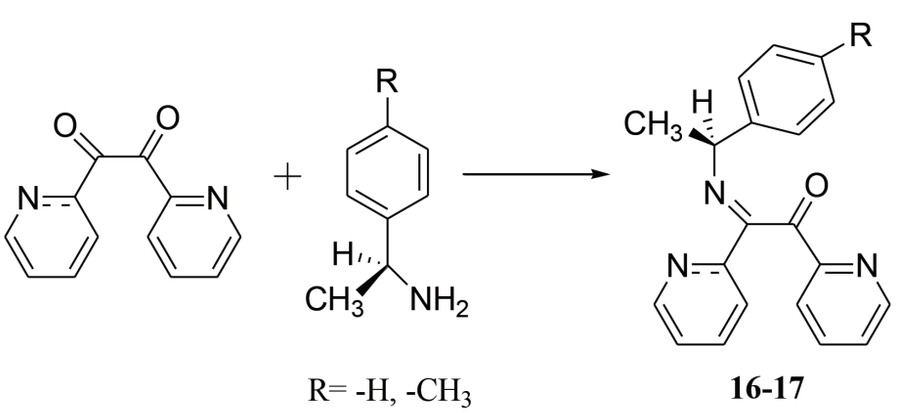


Figure 5.
Synthesis of chiral imines **16–17.**

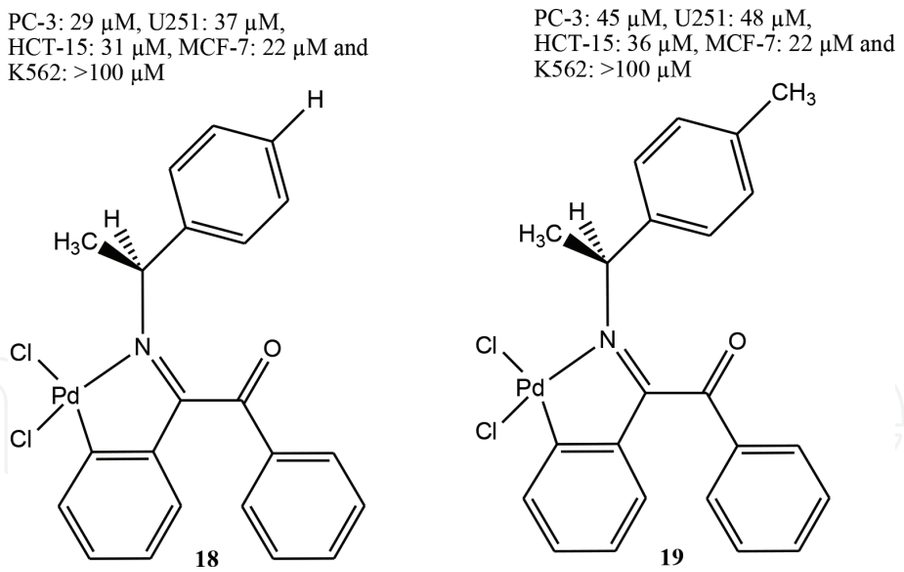


Figure 6.
Chiral Pd(II) complexes **18–19**.

growth in U251, PC-3, HCT-15 and MCF-7, being **18** slightly better than **19** for all cell lines. The studies suggest that the nature of the aromatic rings have an impact in the cytotoxicity and the coordination mode.

Such results were not particularly impressive (at least a factor of 10 poorer than cisplatin), but they certainly do show variations in activity as well in the other cases.

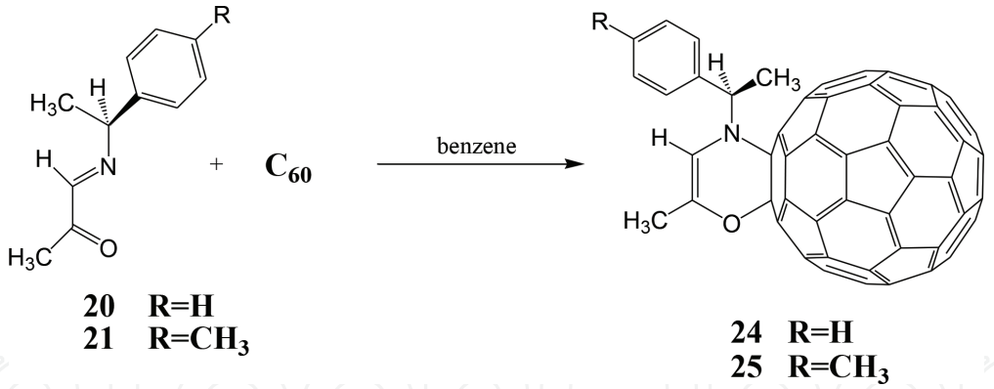
It must be pointed out that even when the Pd-Schiff Base-complexes displayed cell growth inhibition against different classes of cancer, the IC_{50} that they have showed are not comparable with cisplatin. In general, Pd(II) complexes are kinetically less stable than those of Pt(II), by losing their structural integrity in biological fluids in a short period of time due to their rapid exchange. More specific studies *in vitro* and *in vivo* need to be done to determine their toxicity and to understand in a better way the mechanisms of action since it will aid the development of more efficient palladium-based drugs.

On the other hand, considering other alternatives to the flexible X═C▬C═N (X = O, N) skeleton, for example as a heterodiene, we have also reported the microwave-assisted Diels-Alder [4+2] cycloaddition reaction of the optically pure α-ketoimines **20–21** and α-diimines **22–23**, with fullerene C_{60}. The chiral α-ketoimines **20–21** were readily synthesized in quantitative yield under solvent-free conditions starting from (*S*)-(−)-1-phenylethylamine and (*S*)-(−)-1-(4-methylphenyl) ethylamine with pyruvaldehyde, respectively, and upon reaction of C_{60} under focused-microwave irradiation in benzene, after 20 min the formation of the adducts **24–25** was observed (**Figure 7**) [18].

With the chiral α-diimines **22–23**, which were also readily prepared from (*S*)-(−)-1-phenylethylamine and (*S*)-(−)-1-(4-methylphenyl) ethylamine with pyruvaldehyde, respectively, the adducts **26–27** were obtained (**Figure 8**).

In addition, extending our studies to include some other transition metals, we have reported the preparation of chiral Hg(II) complexes with simpler chiral imines **28–30** as they present some relevant crystallographic features along with antimicrobial activity. [19] Thus, the solvent-free reaction of 2-pyridylcarboxaldehyde with optically active aromatic and alicyclic primary amines afforded the chiral imines **28–30** in almost quantitative yields (see **Figure 9**).

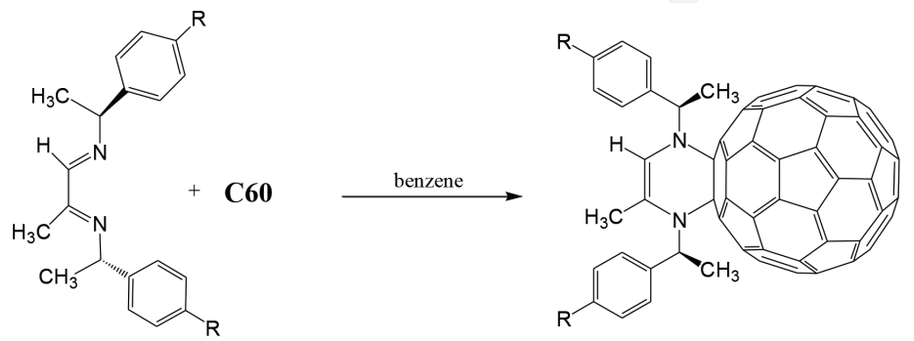
Solutions of the chiral imines **28–30** in methanol were treated with $HgCl_2$ with stirring at room temperature for 1 h, leading to the formation of complexes **31–33** (**Figure 10**).



20 R=H
21 R=CH_3

24 R=H
25 R=CH_3

Figure 7.
Adducts **24–25** *synthesized.*



22 R=H
23 R=CH_3

26 R=H
27 R=CH_3

Figure 8.
Adducts **26–27** *synthesized.*

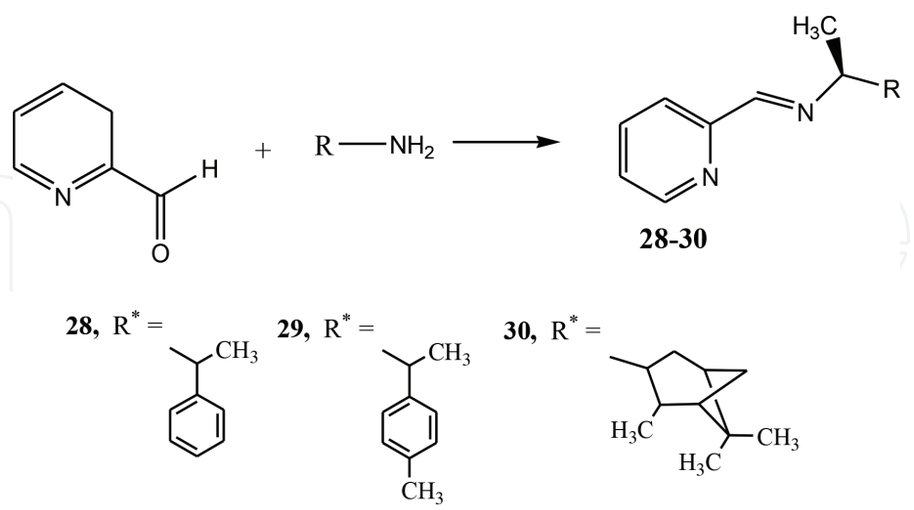


Figure 9.
Synthesis of chiral imines **28–30**.

Likewise, preliminary data have revealed that chiral imines **34–37** derived from 2-piridylcarboxaldehyde and the optically active aromatic amines (*S*)-(−)-1-(4-methylphenyl) ethylamine, (*S*)-(−)-1-(4-metoxyphenyl) ethylamine, (*S*)-(−)-1-(4-chlorophenyl) ethylamine and (*R*)-(+)-1-(4-fluorophenyl) ethylamine under solvent-free conditions (**Figure 11**) were allowed to react with $Zn(CLO)_4$ affording

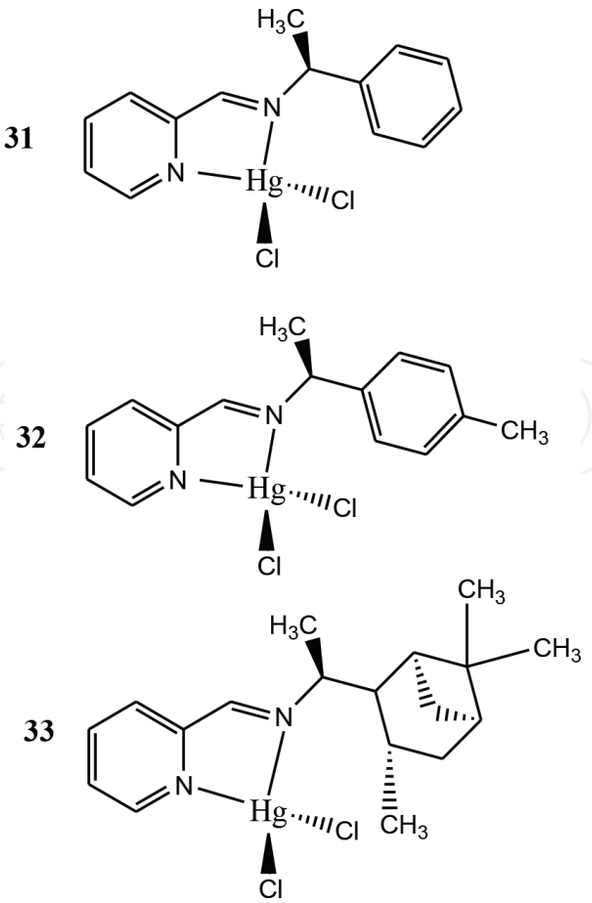


Figure 10.
Chiral Hg(II) complexes **31–33**.

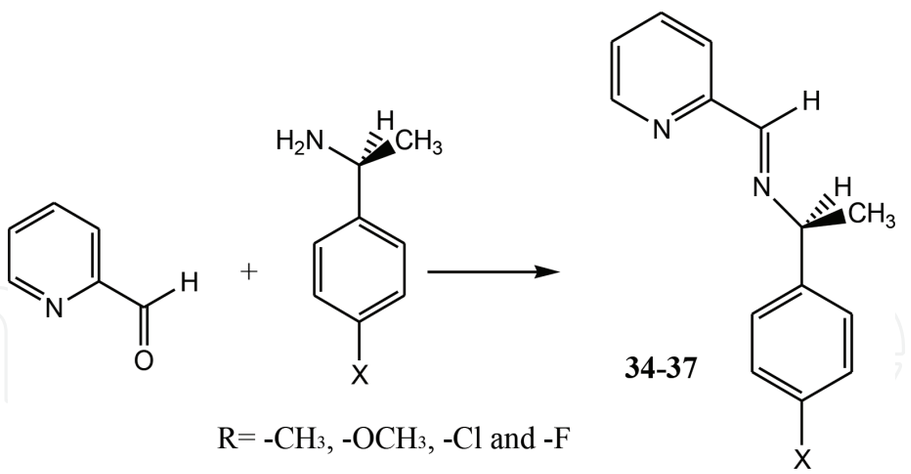


Figure 11.
Chiral imines **34–37**.

Zn complexes **38–41** (**Figure 12**) with cytotoxic activity against the aforementioned human cancer cell lines as well as low toxicity in brine shrimps, along with antibacterial activity against *P. aeruginosa*, *E. coli* and *S. aureus*. Such results will be reported in due time.

On the other hand, simpler chiral imines have triggered interest in some other fields, especially in materials science; where by changing the substituents in the chiral moiety can afford morphological, optical and structural changes resulting in photoluminescent properties, which are extremely interesting since the viewpoint of physicists. In this context, we have recently reported a series of halogenated

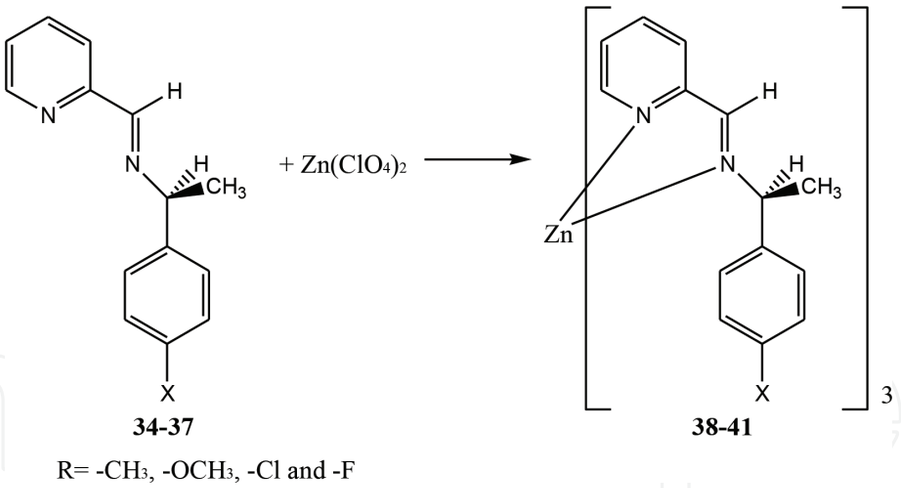


Figure 12.
Chiral Zn(II) complexes **38–41**.

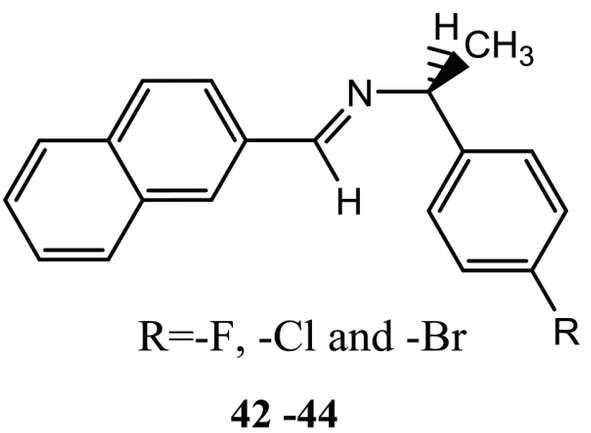


Figure 13.
Chiral halogenated imines **42–44**.

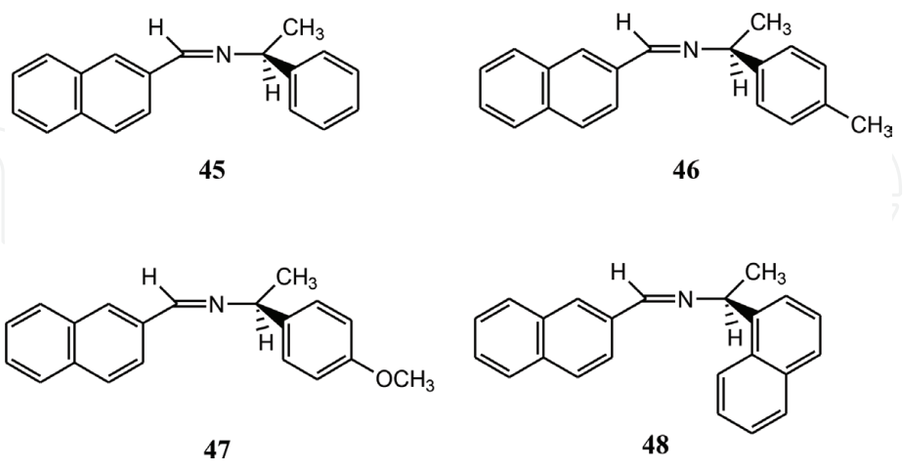


Figure 14.
Chiral imines **45–48**.

imines (**Figure 13**) derived from 2-naphtaldehyde and optically pure halogenated amines, under solvent-free conditions. As a result, imines **42–44** with a lamellar morphology exhibited photoluminescent properties. By changing the halogen atoms in the chiral moiety of the imines, the crystalline packing was modified. The bands observed in the visible region are caused by interstitial defects, vacancies,

grain boundaries and stacking faults in the crystals The intensity of the bands increased in the following order: —F < —Cl < —Br, according to the increase in atomic radii. These features result attractive because of their possible applications in organic electroluminescent devices, organic light- emitting diodes, etc. [20, 21].

Likewise, in a series of chiral imines derived from 2-naphtaldehyde but with the halogen atoms in the *para*-position of the benzene ring of the amines replaced by other functional groups, such as —CH_3, —OCH_3 and naphthyl groups, imines **45–48** (**Figure 14**) exhibited green luminescence. As the previous results, the variations on the functional group as well as the molecular packing determined the morphological changes and consequently the luminescent properties of the imines [22].

3. Conclusion

The chemistry of Schiff bases and their transition metal complexes, especially Pd, is a field that is being noticed not only for their remarkable biological properties but also for their extensive applications in other fields. This area requires further studies to be carried out, and improvements in the permeability and transport are some of the factors to take into account in the design of these metal-based complexes.

Acknowledgements

Support from VIEP-UAP is acknowledged.

Conflict of interest

The authors declare no conflict of interest.

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