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 used 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 K₂PdCl₄ 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 IC₅₀ values.](image-url)
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 (IC50: 26.5 ± 0.4 and 14.8 ± 1.1 μM for complex 2 and 3, respectively) and MCF-7 (IC50: 34.5 ± 2.5 and 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 IC50 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 Na2PdCl4 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.

![Figure 2. Synthesis of chiral Pd complexes 6–7.](image-url)
with the Pd(II)中心采用一个失配的正方形平面Pd[N₂CCI]配位几何结构，其中一个苯环组键于金属中心而另一个则是自由的。苯环的立体阻碍产生的配位效应导致了金属中心的单键，从而阻止了配合物的二聚化。从配合物7中获得的固体无法结晶。

两种配合物6和7都展示了对先前提到的培养细胞系的细胞毒性，主要针对U251和K562癌细胞，IC₅₀值分别为19.8和22.5 μM，对于7，和23.6和25.44 μM，对于6。根据数据，6不能被考虑为一个好的抗癌药物候选，因为它的IC₅₀值对于PC-3和HCT-15超出了100 μM的剂量。这些化合物比α-酮肟配合物提供更好的活性，对U251细胞系的化合物比α-酮肟配合物提供更好的活性。

此后，我们合成了新的非对称α-二胺，通过用一个氢原子取代一个甲基单元和扩大手性胺的数目。使用了不同的方法来提高产率。我们以甲基乙二醛和手性芳香和环状伯胺在二乙醚中与Na₂SO₄混合24小时在室温下得到配体8–11（图3）。溶液8–11在苯中这次用二氯化(1,5-环辛二烯)钯(II)并用氩气搅拌形成配合物12–15（图4）。值得注意的是配体的配位采取了两种不同的模式：配离子(σ, σ, N, N')和单齿(σ-N) [16]

复杂12和13暴露了一个s-cis配离子系统，尽管它们在化学上是相似的，但由于几种不同的空间群，它们以不同的方式结晶。我们相信，晶体对称性变化是由于晶体化而非较小的构象变化的结果。配合物15显示了两个二胺配体，它们被配对到金属中心在一个trans正方形平面几何，而且这种行为在复杂14中被观察到。trans-几何在Pd中心的附近体现了更高的细胞毒性值，因为cis-异构体。它似乎在于，当小的取代基在胺N原子上时，它会促进σ, σ, N, N'配离子模式，通过配离子效应稳定了配合物，而单齿(σ-N)配离子模式则由立体性受阻的系统所偏爱。

结果的细胞毒性试验显示Pd配合物与单齿(σ-N)配离子模式(14和15)展示了IC₅₀值>100 μM;这些配合物被排除在进一步的试验中，因为所需的剂量来抑制细胞

![Figure 3.](image-url)  Synthesis of chiral α-diimine ligands 8–11.
growth were too high. Complexes 12 and 13 also possessed cytotoxic activity against U251, PC-3, K562, HCT and MCF-7 cell lines, where IC₅₀ 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)Cl₂ 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
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).
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-methoxyphenyl) 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...
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
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: \(-\text{F} < \text{Cl} < \text{Br}\), 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-naphthaldehyde but with the halogen atoms in the \(\text{para}\)-position of the benzene ring of the amines replaced by other functional groups, such as \(-\text{CH}_3\), \(-\text{OCH}_3\) 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.

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Conflict of interest

The authors declare no conflict of interest.

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