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Original Article

Synthesis, characterization and in vitro cytotoxic activity of platinum(II) oxalato complexes involving 2-substitutedimidazole or 2-substitutedbenzimidazole derivatives as carrier ligands

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ABSTRACT

Background and Aims: Cisplatin is currently one of the most widely used anticancer drugs in the world. However, its clinical usefulness has frequently been limited by severe side effects, such as nephrotoxicity, ototoxicity and neurotoxicity. Therefore, platinum(II) oxalato complexes with substitute imidazole or benzimidazole carrier ligands were synthesized and their cytotoxic effects were investigated against non-small cell lung cancer (H1299) and human colon adenocarcinoma (CaCo-2), and mouse fibroblast cells lines (L929).

Methods: Four platinum(II) complexes, [Pt(**L1-L4**)$_2$(oxalate)] were synthesized and characterized by FT-IR, 1H NMR and elemental analyses. The MTT method was used to determine the potential antiproliferative effect of synthesized platinum(II) complexes and positive controls.

Results: In this study, the cytotoxic activity of platinum(II) complexes against tested cell lines was assessed, with moderate IC_{50} values. According to IC_{50} values, **Complex 5** with 2-ethylbenzimidazole ligand was found to be the most active complex against H1299 and CaCo-2 cell lines. In general, the compounds are also promising drug candidates for H1299 cell lines with very low activity against the CaCo-2 cell lines.

Conclusion: Further modification and development of **Complex 4** and **5** derivatives and *in vitro* cytotoxic activity studies against different cancer cell lines may lead to the emergence of new anticancer agents in the near future.

Keywords: Cytotoxic activity, 2-ethylbenzimidazole, 2-methylbenzimidazole, 2-phenylimidazole, platinum(II) complexes

INTRODUCTION

Cancer is characterized by uncontrolled cell division and can spread throughout the body via metastasis, which makes it a disease that causes the second-highest mortality rate in the world (Sung et al., 2021). In our clinic, cancer patients are currently treated with chemotherapeutic drugs alone or in combination with radiotherapy and surgery if necessary. In chemotherapeutic treatment, the immediate aim is to inhibit the growth of tumor tissue, avoid metastasis or trigger cytotoxic activity to eliminate the cancerous cells if possible (Dasari & Tchounwou, 2014). Since cancer comes in various forms and has widespread diagnosis and a high mortality rate, novel chemotherapeutic drugs are being throughly researched for the effective treatment of various types of cancer. (Diamond et al., 2015).

Cisplatin, the pioneer of platinum complex-based anticancer drug, has been used successfully for the treatment of many cancers. Although it is a highly effective and widely used chemotherapeutic agent against tumors, due to the development of resistance and side effects such as nephrotoxicity, neurotoxicity, ototoxicity and bone marrow toxicity, the development of new platinum complexes continues intensively (Peng, Liang, Liu, & Mao, 2021).

The need for cisplatin analogs with fewer toxic side effects and a broader spectrum of activity has led to the synthesis of numerous platinum(II) complexes over the last four decades. Second and third-generation platinum complexes are obtained by replacing the leaving groups with carboxylate groups, which are very slowly activated and significantly less toxic. These

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platinum-based compounds, namely cisplatin and its second or third-generation derivatives carboplatin and oxaliplatin, act as cytotoxic drugs through the formation of intrastrand or interstrand platinum-DNA adducts. These interactions are known to inhibit transcription and thus trigger apoptosis which eventually causes cell death (Ho, Woodward, & Coward, 2016; Deo et al., 2018).

Carboplatin is effective against cancers sensitive to cisplatin, but carboplatin has far fewer side effects. Similar to carboplatin, the less severe side effects of oxaliplatin compared to cisplatin are related to the cleavage of the dicarboxylate group, which again slows the production of reactive metabolites. Furthermore, the two ammine ligands in cisplatin were replaced by a single bidentate ligand (1R,2R)-cyclohexane1,2-diamine) in the oxaliplatin. Oxaliplatin is thought to overcome cisplatin resistance through different adducts formed with DNA (Burger et al., 2011; Perego & Robert, 2016).

The efficacy and broad range of activity of platinum(II) complexes can be changed through modifications to the carrier ligands, as is well known. The use of sterically demanding heterocyclic amines as carrier ligands for alternative compounds to cisplatin are slow or block repair enzymes (Deo et al., 2018).

Imidazole and benzimidazole are bioactive heteroaromatic compounds that exhibit different pharmacological activities. They involve biologically important histamine, histidine amino acid, iron-heme system, various metalloproteins and vitamin B12 derivatives (Iakovidis & Hadjiliadis, 1994; Sundberg & Martin, 1974). Furthermore, in organisms, histidine residue is involved in metal-binding regions to bind metal atoms in the active sites of many different enzymes (Živković, Rajković, & Djuran, 2008; Szulmanowicz, Zawartka, Gniewek, & Trzeciak, 2010). Also, as a biologically recognized heteroaromatic ring system, imidazole and benzimidazole possess ligand properties for various transition metals. Because of their low toxicity, high stability, interactions with metals, and electronic or steric properties, these two heteroaromatic rings are crucial for medicinal chemists (Salahuddin, Shaharyar & Mazumder, 2017; Ali, Lone, & Aboul-Enein, 2017).

Platinum compounds containing N-donor ligands such as substituted imidazole or benzimidazole derivatives show better biological activity with less toxicity. According to data in the literature, bulky or lipophilic substituted benz(imidazole)s at the C2 position have activity in various cancer cell types (Gümüş et al., 2003; Gümüş et al., 2009; Boğatarkan, Utku, & Acik, 2015). In our previous studies, with the consideration that variations in the chemical structure of the ammine groups of cisplatin might have a significant effect on the cytotoxic activity of platinum complexes and for the purpose of determining the role of the substituents on position 2 of the benzimidazole carrier ligands of platinum(II) complexes on cytotoxic properties, we synthesized some Pt(II) complexes with 2-substituted imidazole and 2-substituted benzimidazole carrier, thus leaving chloride and oxalate ligands (Figure 1) (Boğatarkan, Utku, & Acik, 2015; Gümüş et al., 2003; Gözelle et al., 2019; Özçelik et al., 2012; Utku et al., 2014; Utku, Topal, Döğen, & Serin, 2010). Based on in vitro cytotoxic tests against HeLa, MCF-7 and MDA-MB 231 cell lines, it was found that several of these [Pt(carrierligands)$_2$X (X=Cl$_2$ or oxalate] complexes possessed cytotoxic activity comparable to cisplatin or oxaliplatin.

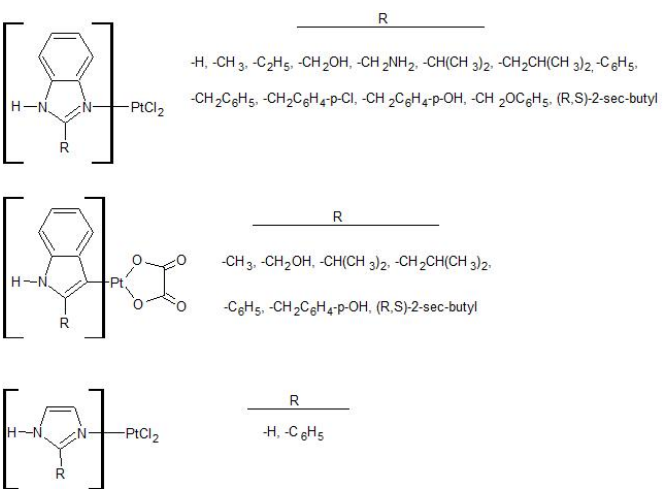

Figure 1. Platinum compounds bearing 2-substituted imidazole and benzimidazole ligands.

In this study, as an extension of our investigation on the probable anticancer activity of platinum complexes with 2-substituted imidazole or benzimidazole ligands, four platinum(II) complexes with bulky or/and planar carrier ligands, including imidazole **(L1)**, 2-phenylimidazole **(L2)**, 2-methylbenzimidazole **(L3)** and 2-methylbenzimidazole **(L4)**, were evaluated for their in vitro cytotoxic activities against H1299 and CaCo-2 cell lines using the MTT method.

MATERIAL AND METHODS

Chemistry

The starting materials were provided by Sigma-Aldrich. The elemental (C, H, N) analyses were run on a Leco-932 Elemental Analyzer. The IR spectra of **L1-L4** and **Complex 1-5** were obtained using Perkin Elmer Spectrum FT-IR/NIR Spectrometer between 4000-600 cm^{-1}. ^{1}H NMR spectra of carrier ligands **L1-L4** and **Complex 2-5** were recorded on a Varian 400 MHz FT NMR Spectrometer using a deuterium dimethyl sulfoxide (DMSO−d$_6$) solution.

General synthesis of carrier ligands (L3, L4)

2-substituted benzimidazole derivatives **L3** and **L4** used as carrier ligands were prepared according to the Phillips method (Phillips, 1928).

2-Methylbenzimidazole (L3)

Yield 44.66 %, mp: 174°C (175-176 °C), ^{1}H NMR (400 MHz, DMSO−d$_6$): δ 12.12 (s, 1H, N-H), 7.44-7.40 (m, 2H, ArH),

7.10-7.06 (m, 2H, ArH), 2.46 (s, 3H, -CH_3); IR (υ cm^{-1}, KBr): 3176-2536 (N-H, =C-H, -C-H), 1622-1270 (C=N, C=C, C-H), 731 (substituted benzene =C-H) (Rabiger & Joullié, 1964).

2-Ethylbenzimidazole (L4)

Yield 46.71%, mp: 174°C (172-173°C); ^{1}H NMR (400 MHz, DMSO−d_6): δ 12.14 (s, 1H, N-H), 7.46-7.43 (m, 2H, ArH), 7.12-7.08 (m, 2H, ArH), 2.84-2.79 (q, 2H, -CH_2-), 1.33-1.29 (t, 3H, -CH_3); IR (υ cm^1, KBr): 3152-2632 (N-H, =C-H, -C-H), 1621-1270 (C=N and C=C and C-H), 738 (substituted benzene =C-H) (Rabiger & Joullié, 1964).

Synthesis of potassium bis(oxalato)platinate(II) dihydrate K_2[Pt(oxalate)$_2$].2H_2O (Complex 1)

Complex 1 was obtained similarly to a previously published approach as follows: 12 mmol potassium oxalate monohydrate was added to a solution of 2.41 mmol potassium tetrachloroplatinate in 10 mL of hot distilled water. The mixture was heated at 70 °C for 3 days. The light green product was filtered and washed in hot and then in cold water, and finally recrystallized from hot water. Green needle-like crystals of K_2[Pt(oxalate)$_2$].2H_2O which formed were filtered off and washed with cold water and ethanol. Yield 74.35%, IR (υ cm^{-1}, KBr): 3559 and 3476 (O-H, (H_2O)), 1696 and 1668 (C=O), 1234 (C-O), 565 (Pt-O)

General synthesis of platinum(II) complexes

To a solution of **L1-L4** (0.90 mmol) in ethanol/isopropanol at 50-60 °C, a solution of **Complex 1** (0.5 mmol) in distilled water at 50-60 °C was added dropwise and stirred for 4-6 days at 50-60 °C until complexation was finished. The precipitate was filtered and the crude product was washed with hot water, cold water, hot ethanol and cold ethanol.

Oxalato-di(imidazole)platinum(II) 0.5 H_2O (Complex 2)

Yield 53.64%, mp: >400°C. ^1H NMR (400 MHz, DMSO−d_6): 8.06 (s, 2H, 2x imidazole H), 7.32 (s, 2H, 2x imidazole H), 6.93 (s, 2H, 2x imidazole H); IR (υ cm^{-1}, KBr): 3135-2821 (N-H, =C-H and O-H), 1699 (C=O) 1653-1490 (C=N, C=C and C-O), 560 (Pt-O). Anal. Calcd. for [$C_8H_8N_4O_4$Pt. H_2O]: C, 21.97; H, 2.31; N, 12.81%; Found: C, 21.18; H, 2.44; N, 13.35%.

Oxalato-di(2-phenylimidazole)platinum(II) (Complex 3)

Yield 81.4 %, mp: > 400 C. ^1H NMR (400 MHz, DMSO−d_6): 8.67-8.56 (m, 2H, ArH), 8.29-8.16 (m, 2H, ArH), 7.55-7.46 (m, 4H, 2x ArH), 7.40-7.33 (m, 2H, 2x ArH and 4H 2x imidazole H); IR (υ cm^{-1}, KBr): 3140-2757 (N-H, =C-H), 1696 (C=O), 1651-1472 (C=N, C=C and C-O), 535 (Pt-O). Anal. Calcd. for [$C_{20}H_{16}N_4O_4$Pt]: C, 42.04; H, 2.82; N, 9.80%; Found: C, 42.16; H, 3.19; N, 10.25%.

Oxalato-di(2-methylbenzimidazole)platinum(II) (Complex 4)

Yield 26.56%, mp: > 400 °C. ^1H NMR (400 MHz, DMSO−d_6): δ 7.76-7.74 (m, 2H, 2x ArH), 7.46-7.44 (m, 2H, 2x ArH), 7.24-7.21 (m, 4H, 2x ArH), 2.69 (s, 6H, 2x -CH_3); IR (υ cm^{-1}, KBr): 3188-2781 (N-H, =C-H, -C-H), 1700 (C=O), 1645-1284 (C=N, C=C, C-H and C-O), 565 (Pt-O). Anal. Calcd. for $C_{18}H_{16}N_4O_4$Pt: C, 39.49; H, 2.95; N, 10.23 %; Found: C, 39.69; H, 2.52; N, 10.47% (Gözelle et al., 2019).

Oxalato-di(2-ethylbenzimidazole)platinum(II).H_2O (Complex 5)

Yield 25.13%, mp: > 400 °C. ^1H NMR (400 MHz, DMSO−d_6) δ 13.41 (s, 2H, 2x N-H), 7.92-7.90 (m, 2H, 2x ArH), 7.52-7.50 (m, 2H, 2x ArH), 7.33-7.29 (m, 4H, 2x ArH), 3.14-3.10 (q, 4H, 2x -CH2-), 1.33-1.31 (t, 6H, 2x -CH_3); IR (υ cm^{-1}, KBr): 3118-2744 (N-H, =C-H, -C-H), 1694 (C=O), 1645-1278 (C=N and C=C and C-H), 747 (substituted benzene =C-H). Anal. Calcd. for $C_{20}H_{20}N_4O_4$Pt.H2O: C, 40.47; H, 3.74; N, 9.44; Found: C, 40.59; H, 3.43; N, 9.56

MTT cell viability assay

H1299 (non-small-cell lung cancer), CaCo-2 (An1/human adenocarcinoma) and L929 (mouse fibroblast, An2 Mouse C3), cell lines were obtained from the Foot and Mouth Disease Institute (Ankara, Turkiye). L929 and H1299 cells in 10% bovine serum, 100 IU/mL penicillin/streptomycin with 4 μM glutamine DMEM liquid broth and CaCo-2 cells in 10% bovine serum, 100 IU/mL penicillin/streptomycin with 4 μM glutamine EMEM broth were incubated in an atmosphere containing 5% CO_2 at 37°C. 1.0 x 10^4 cells were seeded into each well of a 96-well cell culture plate and incubated for 24 h at 37°C and 5% CO_2 in a humidified incubator. **Complex 2-5** were then added to the cells at seven different concentrations. After 48 h incubation, 50 μl MTT (1 mg/mL) was added to each well and after an incubation period of 2 h at 37 °C, 100 μl isopropanol was added to the wells (Wang, Wang, Tao, & Cheng, 2012). A cell viability assay was run in a 96-well plate with measuring absorbance at 570 nm. Each compound was studied in three independent experiments. The amount of DMSO used as solvent did not exceed 1%. Cisplatin and oxaliplatin were used as positive controls and cell broth was used as blank.

RESULTS AND DISCUSSION

Chemistry

Complex 1, a yellow-colored compound with needle-like crystals, was determined via IR through its OH vibration from H_2O between 3559-3476 cm^{-1} and Pt-O vibration at 565 cm^{-1}. The spectral data and physical properties found in the literature are in agreement with our analyses (Štarha, Trávníček, & Popa, 2010).

Complex 2-5 were synthesized through the addition of L_1−L_4 solutions in ethanol/isopropanol into the aqueous solution of Complex1 (Figure 1).

Structural analyses of **Complex 2-5** were elucidated using elemental analysis, FT-IR and ^{1}H NMR spectra. Elemental analysis of **Complex 2-5** shows that monodentate **L1-L4** ligands react with **Complex 1** with a ratio of 1:2 metal:ligand (Grimmett, 1970; Manocha, Wakode, Kaur, Anand, & Kumar, 2016; Wright, 1951).

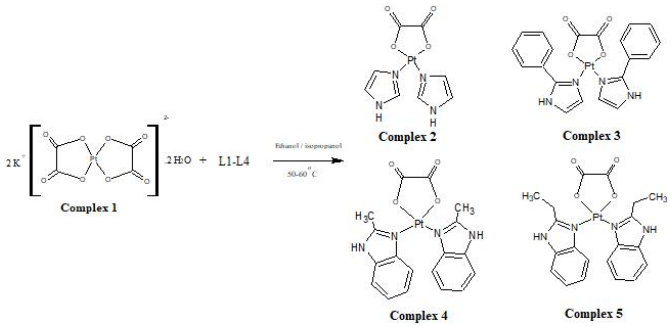

Figure 2. Synthesis of **Complexes 2-5**

The ^{1}H NMR spectra of **Complex 2-5** were obtained by dissolving in DMSO−d_6 due to the insolubility of complexes in other NMR solvents. In general, related to complexation, the aromatic or/and aliphatic proton peaks of **Complex 2-5** shifted to low areas compared to **L1-L4**. In addition, because of ½ spin-quant number and 33% isotope abundance of ^{195}Pt isotope, peak diversion was observed as a result of ^{195}Pt-^{1}H spin-spin coupling. Complexation-related ligand protons' peak shift to high ppm values is in agreement with the literature data (Navarro-Ranninger, Zamora, Alfonson Martínez-Cruz, Isea, & Masaguer, 1996).

Biological Evaluation

Complexes 2-5 were tested for their cytotoxic activity on H1299, CaCo-2, and L929 cell lines using the MTT method. The results of this experiment and IC_{50} values of compounds are presented in Table 1.

An evaluation of **Complex 2-5** using IC_{50} values revealed that cytotoxic activity enhances if substitution exists at position 2 or if the size of substitution is increased. **Complex 5** bearing 2-ethylimidazole is the most potent complex on H1299 and CaCo-2 cell lines compared to other complexes. Based on MTT results, IC_{50} values of tested complexes are less active compared to cisplatin and oxaliplatin.

Platinum(II) complexes bearing dicarboxylate or chloride leaving ligands have previously been tested for their cytotoxic activities on various cell lines. These tests revealed that depending on the substituent groups in the carrier ligands of these platinum(II) complexes, there are differences in the intracellular entry, their binding to DNA and also in their cytotoxic activity values (Gözelle et al., 2019; Özçelik et al., 2012; Özçelik, Gümüş, Sagkan, & Musabak, 2015; Özçelik, Kılıç Süloğlu, Selmanoğlu, & Gümüş, 2019; Tarı, Gümüş, Açık, & Aydın, 2017; Utku et al., 2014). In these studies, it was observed that the cytotoxicity of compounds increased as the substituent's size expanded. In this present study, **Complex 4** and **Complex 5** bearing methyl and ethyl substituents at position 2 of benzimidazole, respectively, were found to be the most potent compounds among the synthesized complexes. These results are in agreement with the literature (Spingler, Whittington, & Lippard, 2001; Wu et al., 2004; Todd & Lippard, 2009).

Table 1. IC_{50} (μM) values of **Complex 2-5**, cisplatin and oxaliplatin by using the MTT test in cancerous and healthy cells

Complexs No	H1299		CaCo-2		L-929
	IC_{50}[a]	SI[b]	IC_{50}[a]	SI[b]	IC_{50}[a]
2 [Pt(L1)$_2$oxalate]	168.84 ± 9.87	1.14	281.25 ± 4.37	0.68	192.90 ± 5.03
3 [Pt(L2)$_2$oxalate]	132.31 ± 8.89	1.05	273.75 ± 5.79	0.51	139.49 ± 6.14
4 [Pt(L3)$_2$oxalate]	110.48 ± 5.42	1.42	286.95 ± 7.14	0.55	157.78 ± 3.67
5 [Pt(L4)$_2$oxalate]	101.24 ± 6.47	1.44	270.36 ± 9.94	0.54	145.43 ± 7.48
Cisplatin	50.97 ± 7.55	1.25	64.51 ± 14.32	0.99	63.66 ± 9.37
Oxaliplatin	27.21 ± 12.78	2.10	53.58 ± 6.47	1.06	57.04 ± 5.36

[a] IC_{50} = 50% cytotoxic concentration against in vitro tested cells. Data are presented as mean ± SD.
[b] SI = Selectivity Index—IC_{50} value relative to a healthy cell.

CONCLUSION

In summary, this work is based on the synthesis, characterization and in vitro cytotoxic of oxalato platinum(II) complexes. **Complexes 2-5** were investigated for their potential anticancer activity against H1299 and CaCo-2 cell lines using the MTT method. Among all the synthesized complexes tested, Complex 4 and Complex 5, which have methyl and ethyl substituents at the second positions of the carrier ligand, were found to be the most effective platinum(II) complexes. It is also likely that novel molecules to be designed by development and modification of **Complex 4** and **Complex 5** derivatives will exhibit selective inhibitor activity against different cancer cell lines.

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Conflict of Interest: The authors have no conflict of interest to declare.

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