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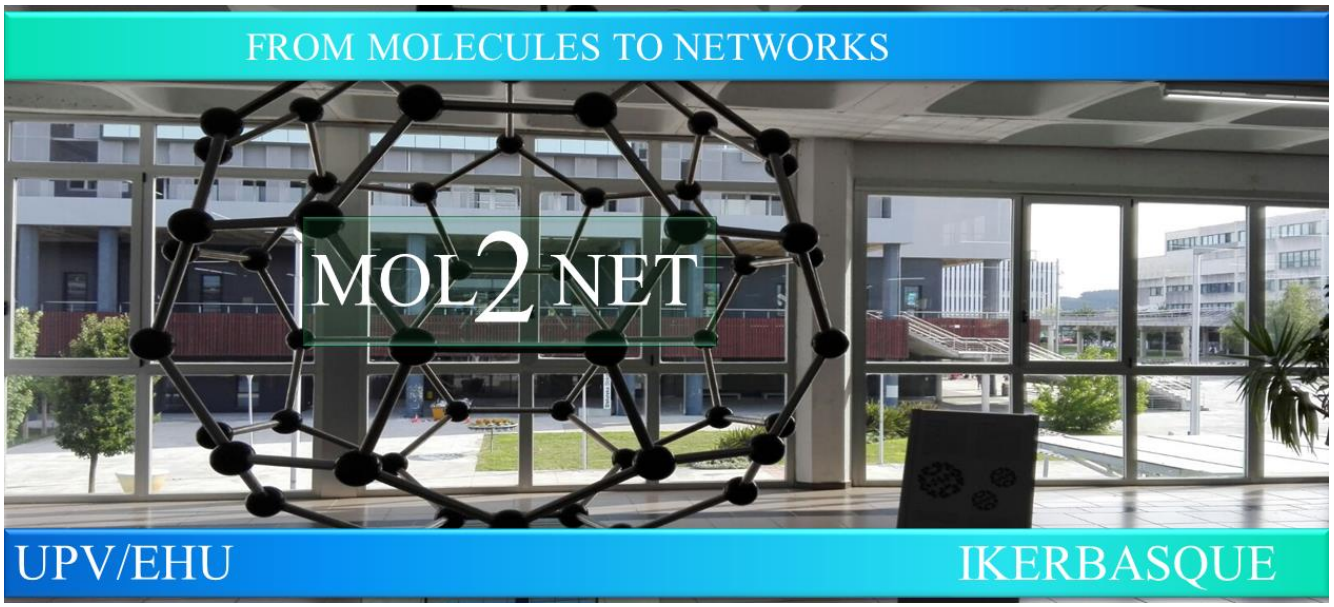

In silico study of anticancer platinum complexes

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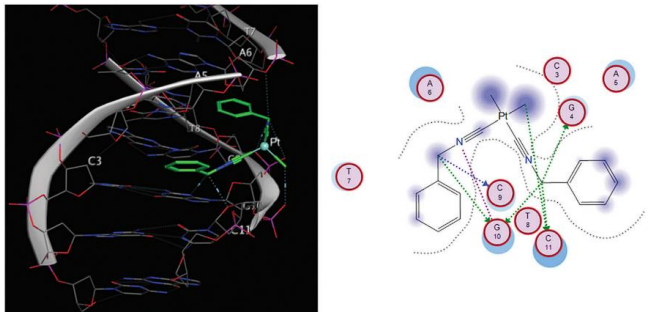
Graphical Abstract



Abstract

The works presented describe studies of new anticancer platinum complexes, which depart their syntheses and analyzes by molecular docking tool

Keywords: molecular docking; anticancer; platinum; QSAR; Cheminformatics

Introduction

The study of bioactive compounds based on platinum is associated with the discovery of the inhibitory activity of cisplatin on the cell division of Escherichia Coli bacteria, in 1965 [1]. Its antimitotic activity was studied in malignant tumors, such as Kaposi 180, and its effectiveness was appreciated in low doses, being approved in 1978 by the Food and Drug Administration (FDA). Since the marketing approval, around 3000 platinum analogues have been synthesized, 185 of which have registered activity, but only five were approved, namely [2]. The mechanism of action of the cisplatin complex and its analogues begins with their entry into the cell through active diffusion, carried out by copper and organic cationic transporters. In the cytoplasm, it undergoes successive hydrolysis reactions, due to the low concentration of chloride anions. In sequence, platinum interacts with purines and triggers their cytotoxic action [2,3]. But the side effects related to his therapy resistance to inert cancers such as colon and non-small cell lung; or acquired, caused by biomolecules such as cysteine, methionine and GSH, it is necessary to study new compounds [3].

In silico approaches, despite having a smaller number of works, are increasing, as computational chemical methods at molecular, quantum or hybrid modeling levels (QM/MM) are providing relevant data to biological systems. In the field of molecular docking, methods are used to predict the preferred orientation of one molecule over a second when linked together to form a stable complex. In addition to providing descriptors for the study of the quantitative structure-activity relationship (QSAR). This is appreciated in the work by Chojnaki and team in which the electrostatic potentials at the DFT level describe cisplatin with greater interaction with serum sulfur atoms compared to transplatin [4]. The abstract describes two *in silico* studies that presented structure-activity data involving platinum antitumor agents, which provide promising data for the class.

The first article [5] describes the development of new platinum complexes, in which it proposes four medicinal compounds depending on the type of binder, as the first binder has anticancer efficacy, such as tamoxifen or methotrexate, and the second chemical compounds, such as curcumin or xanthine, were used as ligands that are bound to Pt^{+4} (prodrug). While the second [6] presents new Pt(II) complexes [R′2Pt(CNR)2] (1a–c; R′ = Me and 2a–c; R′ = p-tolyl) were synthesized by the reaction of the precursor complexes cis, cis-[$Me_2Pt(\mu\text{-}SMe_2)_2PtMe_2$], A, and cis-[$(p\text{-tolyl})_2Pt(SMe_2)_2$], B, with four and two equivalents of different types of isocyanide ligands (CNR; R = a; *t*-butyl, b; benzyl, and c; cyclohexyl isocyanide), respectively.

Materials and Methods

The first article, anchoring of the proposed drug compounds as anti-carcinogens was carried out in the active site of the oncogene protein using molecular modelling Environment (MOE) and iGemdock programs, in order to compare the results of each of the proposed drug compounds. The protein gap was discharged from the compounds and then the proposed compounds were anchored in the receptor protein gap as a fixed body and the free energy docking (G) for the proposed drug compounds were calculated with the protein gap. The structural structures of the used protein (Oncogene) were obtained from the Protein Database (PDB) (www.rcsb.org) and according to the code (PDB: 5p21). The pharmacokinetic properties were studied: absorption, distribution, metabolism, excretion as well as the toxicity (ADMET) of the pharmaceutical compounds selected as the best anti-cancer drugs according to the rules of the International Food and Drug Administration (FDA). Ras protein (H-RAS oncogene protein), which is responsible for cancerous tumors through its role in controlling cell division and reproduction where it was anchored inside the protein to find out the extent of the affinity of these compounds to inhibit the growth of the protein to eliminate cancer diseases. The analysis of the synthesized complexes was with high sensitivity electronic balance, Sartorius, infrared spectrophotometer, electronic spectroscopy, and nuclear magnetic resonance.

The second paper has the known precursor complexes cis, cis-[$PtMe_2(m\text{-}SMe_2)_2PtMe_2$], A, and cis-[$(p\text{-tolyl})_2Pt(SMe_2)_2$], B, as starting points. Dimethyl sulfide is a good leaving group and can be easily replaced by monodentate isocyanide ligands under mild conditions. Treatment of A with 4 equivalents

or of B with 2 equivalents of different types of isocyanide ligands (CNR = a; *t*-butyl, b; benzyl, and C; cyclohexyl isocyanide) leads to the production of new platinum(II) complexes with the general formula [R'$_2$Pt(CNR)$_2$], (1a–c; R' = Me and 2a–c; R' = p-tolyl). All complexes were accurately characterized by HR ESI-mass, FTIR and NMR spectroscopy. To determine the binding ability of complexes to DNA, molecular modeling investigations were performed on the new Pt(II)–isocyanide complexes

Results and Discussion

Table 1: Molecular docking studies on DNA structures

Ligand/receptor	Docking binding energy[a] (kcal mol^{-1}) 1BNA[b]	1LU5[c]
1a	−4.31	−3.52
1b	−8.06	−5.33
1c	−4.13	−3.69
2a	−6.35	−6.25
2b	−5.76	−5.27
2c	−5.17	−4.89
Cocrystal-ligand	—	−4.78

Table 2: Molecular interactions study of the proposed drug compounds (platinum complexes) as anticancer with protein.

Table 8
Molecular interactions study of the proposed drug compounds (platinum complexes) as anticancer with protein.

NO.	Compounds	E-Doc*	NO.	Compounds	E-Doc*
1Pt	[Pt(methotrexate)(cur)]	**−16.87**	1 Ptx	[Pt(methotrexate)(xanthine)]	**−15.96**
2Pt	[Pt(vincristine)(cur)]	**−12.82**	2 Ptx	[Pt(vincristine)(xanthine)]	**−10.58**
3Pt	[Pt(vinblastine)(cur)]	**−15.54**	3 Ptx	[Pt(vinblastine)(xanthine)]	**−11.44**
4Pt	[Pt(amifostine)(cur)]	**−15.52**	4 Ptx	[Pt(amifostine)(xanthine)]	**−11.06**
5Pt	[Pt(amscarine)(cur)]	**−14.81**	5 Ptx	[Pt(amscarine)(xanthine)]	**−11.76**
6Pt	[Pt(azacitidine)(cur)]	**−16.32**	6 Ptx	[Pt(azacitidine)(xanthine)]	**−15.71**
7Pt	[Pt(busulfan)(cur)]	**−13.09**	7 Ptx	[Pt(busulfan)(xanthine)]	**−12.65**
8Pt	[Pt(carmustine)(cur)]	**−12.71**	8 Ptx	[Pt(carmustine)(xanthine)]	**−9.56**
9Pt	[Pt(podophyllotoxin)(cur)]	**−14.23**	9 Ptx	[Pt(podophyllotoxin)(xanthine)]	**−12.57**
10Pt	[Pt(cladribine)(cur)]	**−17.07**	10 Ptx	[Pt(cladribine)(xanthine)]	**−14.01**
11Pt	[Pt(dacarbazine)(cur)]	**−13.11**	11 Ptx	[Pt(dacarbazine)(xanthine)]	**−11.05**
12Pt	[Pt(doxorubicin)(cur)]	**−19.25**	12 Ptx	[Pt(doxorubicin)(xanthine)]	**−16.44**
13Pt	[Pt(fluorouracil)(cur)]	**−16.39**	13 Ptx	[Pt(fluorouracil)(xanthine)]	**−10.59**
14Pt	[Pt(flutamide)(cur)]	**−14.49**	14 Ptx	[Pt(flutamide)(xanthine)]	**−10.98**
15Pt	[Pt(Ifosfamide)(cur)]	**−15.08**	15 Ptx	[Pt(Ifosfamide)(xanthine)]	**−12.10**
16Pt	[Pt(mercaptopurine)(cur)]	**−14.87**	16 Ptx	[Pt(mercaptopurine)(xanthine)]	**−8.97**
17Pt	[Pt(mitotane)(cur)]	**−16.57**	17 Ptx	[Pt(mitotane)(xanthine)]	**−8.41**
18Pt	[Pt(pentostatin)(cur)]	**−12.66**	18 Ptx	[Pt(pentostatin)(xanthine)]	**−15.00**
19Pt	[Pt(tamoxifen)2(cur)]	**−16.41**	19 Ptx	[Pt(tamoxifen)2(xanthine)]	**−14.13**
20Pt	[Pt(etoposide)(cur)]	**−16.11**	20 Ptx	[Pt(etoposide)(xanthine)]	**−15.36**

Table 1: [a]All the docking protocols were performed on validated structures with RMSD values below 2 Å. [b]Structure of a B-DNA dodecamer. c Asymmetric platinum complex [Pt(ammine)(cyclohexylamine)]$^{2+}$ bound to a dodecamer DNA duplex. Table 2: *E-Doc.: The energy of the interaction between the drug and the protein is expressed in kilocalories per mole (kcal/mol). Fig. 3. The interaction of)1Pt) with the cavity of H-RA.

Article one describes that more than 40 drug compounds proposed in drug design programs were studied through the association of pharmaceutical compounds approved as anticancer by the FDA with chemical compounds, specifically curcumin and xanthine, which preliminarily studies indicate its importance in the treatment of diseases cancerous as ligands by metallic elements (Pt). The values (Table 2) of interaction energies showed greater importance for the proposed drug complexes compared to drugs and chemical compounds used alone as a binder, and there was also a preference for curcumin complexes compared to to xanthine, which indicates the importance of curcumin as a anticancer greater than xanthine. We also note that the top three complexes were 1Pt, 10Pt and 12Pt which have the values of the calculated interaction energies -16.87, -17.07 and -19.25, respectively. From the practical study, it was found that the complexes that all appeared coloured and have a solid and stable nature in addition to the fact that some of them are amorphous, and have close melting points, do not have a solubility in water, but they are completely soluble in DMF and DMSO.

In the second paper, the dock binding energies of Pt(II) complexes synthesized with DNA (two different PDB DNA structures) are shown in Table 1. The highest nominal binding energies (kcal/mol 1) in the AutoDock were taken as the response in each run. As shown in Tables 1, 1b, one of our complexes that stands out in terms of cytotoxic activity shows increased anchorage binding energies (8.06 kcal/mol) when binding to 1BNA. Furthermore, 2a, another complex with high cytotoxic activity, showed stronger anchoring binding energies (6.25 kcal/mol) on binding to 1LU5 compared to other complexes. 1a and 1c showed weaker DNA binding energies. Complexes 1b and 2a-c had better docking binding energies compared to the cocrystal ligand (Pt(amine)(cyclohexylamine) $^{2+}$ of 1LU5. The nested model suggests that 1b interacts with the DNA minor groove (Fig. 5). The methyl groups attached to the platinum(II) are placed further away from the base pairs in the minor groove, and the benzyl groups that are attached to the isocyanide fit in the minor groove of the DNA. Complex 1b interacts through its CH_2 benzyl groups with base pairs C9, G10, G4, and C11. The interaction of the methyl group with C11 and isocyanide nitrogen with G10 was also observed.

Conclusions

In the first article the binding energy of twenty antitumor drugs compounds approved by the World Food and Drug Organization was calculated with the protein of the gene (Ras) that causes carcinogenicity, which gave different binding results in the strength of its binding to the receptor protein, as the best interaction energy value (-16.07) belongs to the compound (12A), while compound (16A) had the lowest binding energy (-6.49). In addition to which 40 drug compounds were proposed due to the association of the twenty compounds previously studied. Curcumin or xanthine platinum complexes showed better binding energies than the studied free ligands.

In the second paper, the strength of interaction of the presented complexes with DNA was evaluated by molecular modeling to study their binding site, binding modes and the best special geometry based on their binding energy to DNA. The nested model suggests that the complexes bind to DNA via a groove-binding mode. Consequently, the results indicate that 1b has significant potential for further development as an anticancer agent. According to results, 1b and 2a showed greater anti-proliferative activity, whereas other complexes exhibited less potency. Compared to cisplatin, 1b and 2a furnished higher in vitro cytotoxicity against the MCF-7 cell line.

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