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Preliminary communication / Communication

Molecular docking investigation of cytotoxic phenanthrene derivatives

Etude de l’amarrage moléculaire de dérivés phénanthréniques cytotoxiques

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Abstract. Our previous experimental work indicated that the presence of ester functionality in phenanthrene derivatives $D-1$ and $D-2$ leads to potent cytotoxicity against the Caco-2 cell line. The present work is based on this experimental result. First, we optimized the structures of the studied molecules using the density functional theory method. Then we performed a study about their potential biological importance by evaluating the binding mode and exploring their intermolecular interactions with appropriate proteins using molecular docking calculations. Consequently, we confirmed the results obtained from experimental studies. In particular, our study indicated that many promising proteins are able to bind and interact with the phenanthrene skeleton from the binding site. Methyl 8-methyl-9,10-phenanthrenequinone-3-carboxylate $D-1$ and methyl 8-methylbenzo[a,c]phenazine-3-carboxylate $D-2$ displayed strong cytotoxicity. However, the best affinity is noted for B-Raf proto-oncogene serine/threonine-protein kinase (-9.8 Kcal/mol for molecule $D-1$ and -11.1 Kcal/mol for molecule $D-2$), which is higher than that of any other protein used. Especially, this protein is involved in sending signals inside cells that are involved in directing cell growth and is found to be a significant target in both types of studied cancers.

Résumé. Nos travaux expérimentaux antérieurs ont indiqué que la présence de la fonction ester sur les dérivés phénanthréniques $D-1$ et $D-2$ a montré une cytotoxicité puissante contre la lignée cellulaire Caco-2. Dans ce présent travail, nous nous basons sur ces résultats obtenus expérimentalement. Tout d’abord, nous avons optimisé à l’aide de la méthode DFT les structures des molécules étudiées, puis nous avons mené l’étude de leur importance biologique en évaluant le mode de liaison et en explorant...
leurs interactions intermoléculaires avec des protéines appropriées à l’aide des calculs d’amarrage moléculaire. Par conséquent, nous avons confirmé les résultats obtenus suite aux études expérimentales. En particulier, notre étude a indiqué que de nombreuses protéines prometteuses sont capables de se lier et d’interagir avec le squelette phénanthrénique à partir du site de liaison. Le 8-méthyl-9,10-phénanthrènequinone-3-carboxylate de méthyle D-1 et le 8-méthyldibenzo[a,c]phénazine-3-carboxylate de méthyle D-2 ont montré une forte cytotoxicité. La meilleure affinité est observée avec la protéine B-Raf proto-oncogène sérine/théronine kinase (-9.8 Kcal/mol pour la molécule D-1 et -11.1 Kcal/mol pour la molécule D-2) qui est plus importante que celle de toute autre protéine utilisée. Ajoutons que, cette protéine est impliquée dans l’envoi de signaux à l’intérieur des cellules qui participent à la direction de la croissance cellu-lulaire et se révèle être une cible significative dans les deux types de cancers étudiés.

**Keywords.** Phenanthrene, Cytotoxicity, DFT calculations, Molecular modeling, Docking, Proteins.

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1. **Introduction**

Polycyclic compounds based on aromatic hydrocarbons are considered attractive targets for synthesizing medicinal units since they exhibit favorable properties such as stability and ease of synthesis and possess high biological responses, particularly anticancer activity [1]. As a result, many researchers around the world have become interested in the preparation and development of new cytotoxic molecules [2–4]. In this context, H. Guédouar and co-workers [2] worked on the synthesis of a fairly large number of new phenanthrene skeletons, using a simple procedure, with the aim of preparing promising active compounds for the development of anticancer agents. In fact, they prepared a variety of tricyclic compounds by modifying the central structure of phenanthrene. The compounds were evaluated for their in vitro cytotoxic activity against two tumor cell lines. Interestingly, the analysis of the IC50 values suggests that most compounds exert cytotoxic effects with selectivity. Among them, methyl 8-methyl-9,10-phenanthrenequinone-3-carboxylate D-1 (IC50 = 0.97 µg/mL) and methyl 8-methyldibenzo[a,c]phenazine-3-carboxylate D-2 (IC50 = 1.09 µg/mL) are interesting substrates due to their highest potency against the Caco-2 cancer cell (Figure 1).

In this study, molecular docking was performed on the two most active O-linked molecules D-1 and D-2, previously prepared by H. Guédouar and co-workers to identify the key structural features required to design new potent candidates of this class. Thus, the results extracted from this study might be useful to design potent antitumor drugs. Before performing the molecular docking, the studied molecules were optimized using the density functional theory (DFT) method. In recent years, the DFT has become the most popular quantum chemical method for computing several molecular properties such as those exhibited by chemical, physical, and biological systems [5–7]. The reported quantum chemical calculations were performed at the B3LYP/6-31G(d,p) level of theory [8–10]. The geometry optimization in the gas phases was carried out using the Gaussian 09 suite of programs [11].

2. **Molecular docking study**

Molecular docking analysis is a reliable method for the evaluation of binding affinity and the prediction of intermolecular interactions of novel compounds containing potential receptors [12,13]. We performed molecular docking studies for eight vital cancer targets (Table 1). Our research was based on the crystal structures of receptors with bound ligand molecules. This structure was obtained from X-ray crystal data of RCSB Protein Data Bank (PDB) [14–16].

In the majority of selected structures, co-crystallized ligand molecules are known drugs with proven action. Thus they were utilized to predict the binding site location [17] as well as to serve as references in our analysis. As previously demonstrated [2], molecules D-1 and D-2, whose 3D-QSAR structures are shown in Figure 2, are the most active. Docking studies of both compounds were carried out to analyze their ability to interact with each target for which the binding site locations are shown in Table 2.

Each enzyme does not necessarily contain a single active site. We chose the active site of interest...
Figure 1. Chemical structures of the studied phenanthrenes D-1 and D-2.

Table 1. Protein database used for docking study and their native ligands

| PDB code | Name                                              | Native ligand                     | Chain |
|----------|---------------------------------------------------|-----------------------------------|-------|
| 2HYY     | Human Proto-oncogene tyrosine-protein kinase ABL1 | Imatinib                          | A     |
| 3C4C     | B-Raf proto-oncogene serine/threonine-protein kinase | PLX4720                          | A     |
| 3EWH     | Vascular endothelial growth factor receptor 2     | Pyridyl-pyrimidine benzimidazole  | A     |
| 3RCD     | Receptor tyrosine-protein kinase erbB-2           | TAK-285                           | A     |
| 3W2S     | Epidermal growth factor receptor                  | W2R                              | A     |
| 4JT5     | Serine/threonine-protein kinase mTOR              | Torkinib (PP242)                 | A     |
| 4U5J     | Proto-oncogene tyrosine-protein kinase Src        | Ruxolitinib                       | A     |
| 6N2J     | GTPase KRas                                       | Tetrahydropyridopyrimidines      | A     |

Table 2. Binding site location for each target

| PDB code | X       | Y       | Z       |
|----------|---------|---------|---------|
| 2HYY     | 14.251  | 15.282  | 17.632  |
| 3C4C     | 0.478   | −2.111  | −19.745 |
| 3EWH     | 15.131  | −5.231  | 10.046  |
| 3RCD     | 13.047  | 1.810   | 28.168  |
| 3W2S     | 5.726   | 0.748   | 12.742  |
| 4JT5     | 51.856  | −0.015  | −49.145 |
| 4U5J     | −8.382  | 26.909  | 5.045   |
| 6N2J     | 22.52   | 2.591   | −22.481 |

With the aim of confirming the potential cytotoxicity of our phenanthrene derivatives D-1 and D-2, we evaluated the binding mode and explored their intermolecular interactions with appropriate proteins. The docking results are summarized in Table 3. The binding affinity was evaluated by the binding free energy (Kcal/mol). In fact, all the studied targets can establish binding with the two studied ligands. The tricyclic compound D-1 exhibited binding energies ranging from −9.8 to −8.3 kcal/mol. The molecular docking study with molecule D-2 revealed a binding energy ranging from −11.1 to −9.2 kcal/mol. This slight difference in energy is probably due to the size of the studied molecules. Indeed, molecule D-1 is tricyclic while D-2 is composed of five cycles, one of which is heterocyclic.
In addition, the data shown in Table 3 indicate that both molecules show a very high affinity to and stability with all the studied targets. In particular, the highest affinity is noted for the protein B-Raf proto-oncogene serine/threonine-protein kinase (PDB code 3C4C) [18,19]. In fact, the affinity between molecule D-1 and 3C4C is found to be about $-9.8 \text{ Kcal/mol}$. The affinity between 3C4C and molecule D-2 is about $-11.1 \text{ Kcal/mol}$. We can conclude from these results that the B-Raf protein is the most likely target for this molecule. Thus, it is worth noting that this protein is involved in sending signals inside cells that are involved in directing cell growth. It regulates cell proliferation and growth, cell survival, cell mobility, protein biosynthesis, and transcription, which suggests that it is the most targeted protein by our tricyclic molecule.

Moreover, it is believed that the remarkable activity of molecules D-1 and D-2 is related to their stability, which is explained by the numbers and types of bonds established with the studied potential targets. These descriptors are mentioned in Table 4, and the details of the interactions are presented in Table 5. In this regard, the amino acids VAL 471, PHE 583, LYS 483, ALA 481, and TRP 531 are found to be important for the antiproliferative activity of our molecules since they form bonds in both cases. As expected for 3C4C, it appears that the hydrogen bond formed with the amino acid ASP 594 increases affinity to the target, which in turn increases the activity of both molecules.

The positioning of each molecule in the active site and the binding pocket are shown in Table 6. Based on affinity, stability, and the study of different interactions, we can ensure that B-Raf proto-oncogene serine/threonine-protein kinase is the
Table 4. Modes and types of bonds between the studied molecules and their potential target

| PDB code | D-1       | D-2       |
|----------|-----------|-----------|
| 2HYY     |           |           |
| 3C4C     | VAL A:289 |           |
|          | ILE A:293 |           |
|          | ALA A:380 |           |
| 3EWH     | VAL A:1047|           |
|          | LEU A:840 |           |
|          | LEU A:866 |           |
|          | PHE A:1047|           |
|          | TRP A:531 |           |
|          | ALA A:481 |           |
|          | CYS A:532 |           |

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Table 4. (continued)

| PDB code | D-1 | D-2 |
|----------|-----|-----|
| 3RCD     | ![Diagram](image1) | ![Diagram](image2) |
| 3W2S     | ![Diagram](image3) | ![Diagram](image4) |
| 4JT5     | ![Diagram](image5) | ![Diagram](image6) |

(continued on next page)
Table 4. (continued)

| PDB code | D-1 | D-2 |
|-----------|-----|-----|
| 4U5J      | ![Diagram 1] | ![Diagram 2] |
| 6N2J      | ![Diagram 3] | ![Diagram 4] |

**Interactions**

- Green: Conventional Hydrogen Bond
- Orange: \(\pi\)-Anion, \(\pi\)-Cation
- Blue: Carbon Hydrogen Bond
- Light blue: \(\pi\)-Donor Hydrogen Bond
- Purple: \(\pi\-\sigma\)
- Magenta: \(\pi\-\pi\) T-shaped
- Pink: Alkyl
- Light pink: \(\pi\)-Alkyl

*C. R. Chimie, 2020, 23, no 4-5, 329-342*
Figure 4. Interactions between the protein B-Raf proto-oncogene serine/threonine-protein kinase and molecule D-1 (a), molecule D-2 (b), and the native ligand PLX4720 (c).
### Table 5. Details of the different interactions

| Target | D-1 | D-2 | Target | D-1 | D-2 |
|--------|-----|-----|--------|-----|-----|
| 2HYY   | ASP 381 NH–O ligand | ALA 380 C–O ligand | 3W2S  | MET 793 NH–O ligand | LYS 745 NH–O ligand |
|        | ALA 330 C–O ligand  | VAL 299 C–O ligand  |        | THR 854 OH–O ligand  | LEU 718 C–π ligand  |
|        | ASP 381 O–π ligand  | ASP 381 O–π ligand  |        | LYS 745 C–O ligand  | VAL 726 C–π ligand  |
|        | ASP 381 O–π ligand  | ASP 381 O–π ligand  |        | GLY 796 C–O ligand  | VAL 726 C–π ligand  |
|        | ASP 381 O–π ligand  | ASP 381 O–π ligand  |        | LEU 718 C–π ligand  | LEU 844 C–π ligand  |
|        | VAL 289 C–π ligand  | VAL 289 C–π ligand  |        | LEU 844 C–π ligand  | ALA 743 C–π ligand  |
|        | VAL 289 π–C ligand  | VAL 289 C–π ligand  |        | VAL 726 π–π ligand  | VAL 726 π–π ligand  |
|        | ILE 293 π–π ligand  | MET 290 π–π ligand  |        | VAL 726 π–π ligand  | VAL 726 π–π ligand  |
|        |                  | VAL 289 π–π ligand  |        | VAL 726 π–π ligand  | VAL 726 π–π ligand  |
| 3C4C   | LYS 483 NH–O ligand | ASP 594 NH–O ligand | 4JT5   | LEU 2185 C–π ligand | LYS 2187 NH–N ligand |
|        | TRP 531 π–π ligand  | VAL 471 C–π ligand  |        | MET 2345 C–π ligand | ASP 2357 N–π ligand  |
|        | PHE 583 π–π ligand  | VAL 471 C–π ligand  |        | ILE 2356 C–π ligand | ILE 2237 C–π ligand  |
|        | PHE 583 π–π ligand  | TRP 531 π–π ligand  |        | TRP 2239 π–π ligand | ILE 2356 C–π ligand  |
|        | PHE 583 π–π ligand  | PHE 583 π–π ligand  |        | TYR 2225 π–π ligand | ILE 2356 C–π ligand  |
|        | TRP 531 π–C ligand  | PHE 583 π–π ligand  |        | TYR 2225 π–π ligand | ILE 2356 C–π ligand  |
|        | VAL 471 π–π ligand  | PHE 583 π–π ligand  |        | MET 2345 π–C ligand | ILE 2356 C–π ligand  |
|        | LYS 483 π–π ligand  | PHE 583 π–π ligand  |        | ILE 2356 π–π ligand | MET 2345 π–C ligand  |
|        | VAL 471 π–π ligand  | VAL 471 π–π ligand  |        | LEU 2285 π–π ligand | TRP 2239 π–C ligand  |
|        | VAL 471 π–π ligand  | VAL 471 π–π ligand  |        | ILE 2237 π–π ligand | ILE 2356 π–π ligand  |
|        | ALA 481 π–π ligand  | VAL 471 π–π ligand  |        | LEU 2185 π–π ligand | LEU 2185 π–π ligand  |
|        | LEU 514 π–π ligand  | VAL 471 π–π ligand  |        | ALA 481 π–π ligand  | LEU 2185 π–π ligand  |
|        | CYS 532 π–π ligand  | LYS 483 π–π ligand  |        | CYS 532 π–π ligand  | MET 2345 π–π ligand  |
|        |                  | ALA 481 π–π ligand  |        |                  |                  |
| 3EWH   | THR 916 OH–O ligand | LEU 840 C–π ligand  | 4U5J   | THR 338 OH–O ligand | LYS 295 NH–O ligand |
|        | CYS 919 NH–O ligand | VAL 848 C–π ligand  |        | MET 341 NH–O ligand | LEU 273 C–π ligand  |
|        | VAL 848 C–π ligand  | VAL 848 C–π ligand  |        | ASC 348 OH–C ligand | VAL 281 C–π ligand  |
|        | PHE 918 π–π ligand  | LEU 1035 C–π ligand |        | LEU 273 C–π ligand  | VAL 281 C–π ligand  |
|        | PHE 1074 π–π ligand | PHE 1047 π–π ligand |        | VAL 281 C–π ligand  | LEU 393 C–π ligand  |
|        | LEU 840 π–π ligand  | PHE 1047 π–π ligand |        | LEU 393 C–π ligand  | ALA 293 C–π ligand  |
|        | LEU 1035 π–π ligand | ALA 866 π–C ligand  |        | LYS 295 π–C ligand  | MET 341 π–C ligand  |
|        | LEU 1035 π–π ligand | LEU 840 π–π ligand  |        | VAL 323 π–C ligand  | LEU 393 π–C ligand  |
|        | LEU 840 π–π ligand  | ALA 866 π–π ligand  |        | LEU 393 π–π ligand  | TYR 340 C–π ligand  |

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**Table 5.** (continued)

| Target                  | **D-1** | **D-2** | Target                  | **D-1** | **D-2** |
|-------------------------|---------|---------|-------------------------|---------|---------|
| ALA 866 $\pi-\pi$ ligand | LEU 1035 $\pi-\pi$ ligand | VAL 281 $\pi-\pi$ ligand | LEU 393 $\pi-\pi$ ligand |
| ALA 866 $\pi-\pi$ ligand | LEU 840 $\pi-\pi$ ligand | ALA 293 $\pi-\pi$ ligand | LEU 273 $\pi-\pi$ ligand |
| ALA 866 $\pi-\pi$ ligand | LYS 295 $\pi-\pi$ ligand | VAL 281 $\pi-\pi$ ligand | LEU 393 $\pi-\pi$ ligand |
| CYS 919 $\pi-\pi$ ligand | LEU 393 $\pi-\pi$ ligand | VAL 281 $\pi-\pi$ ligand | VAL 293 $\pi-\pi$ ligand |

**3RCD** THR 862 OH–O ligand  
ALA 751 OH–C ligand  
LEU 796 O–C ligand  
VAL 734 C–$\pi$ ligand  
LEU 852 C–$\pi$ ligand  
LEU 726 $\pi$–C ligand  
PHE 1004 $\pi$–C ligand  
VAL 734 $\pi$–$\pi$ ligand  
ALA 751 $\pi$–$\pi$ ligand  
LYS 753 $\pi$–$\pi$ ligand  
ALA 751 $\pi$–$\pi$ ligand  
LEU 852 $\pi$–$\pi$ ligand  
ALA 751 $\pi$–$\pi$ ligand  

**6N2J** THR 862 OH–O ligand  
ALA 571 O–C ligand  
LEU 796 O–C ligand  
VAL 734 C–$\pi$ ligand  
LEU 852 C–$\pi$ ligand  
LEU 726 $\pi$–C ligand  
PHE 1004 $\pi$–C ligand  
VAL 734 $\pi$–$\pi$ ligand  
ALA 751 $\pi$–$\pi$ ligand  
LYS 753 $\pi$–$\pi$ ligand  
ALA 751 $\pi$–$\pi$ ligand  
LEU 852 $\pi$–$\pi$ ligand  
ALA 751 $\pi$–$\pi$ ligand  

**potential target** for these molecules. To better confirm these results, we have compared the types and numbers of bonds of our molecules D-1 and D-2 with those of the native ligand PLX4720 (Figure 3).

It can be seen from the comparison of the interactions between the potential target and the studied molecules as well as the reference molecule that most of the amino acids that interact with the reference molecule also interact with our studied molecules. These interactions are essentially hydrophobic bonds, hydrogen bonds, and $\pi$-interactions (Figure 4).

### 3. Conclusion

Following the study of H. Guédouar and co-workers that evaluated the antiproliferative activity of phenanthrene derivatives against the *Caco-2* cancer cell line, this study proposed two molecules that exhibited the best activity against this cancerous cell. For understanding the mode of action of these molecules to propose a potential therapeutic target in the two types of studied cancers, we established molecular docking against eight vital cancer targets. As a result, molecular docking results confirmed that tricyclic molecules D-1 and D-2 show significant activity. Both of the studied compounds were found to display low binding energies and the best affinity is noted in the protein B-Raf proto-oncogene serine/threonine-protein kinase, which is an important target in both types of studied cancers. Moreover, the comparison of the types and the modes of interactions between these molecules and the reference ligand, which is an inhibitor of this protein,
Table 6. Positioning and the binding pocket of each molecule in the active site

| PDB code | D-1 | D-2 |
|----------|-----|-----|
| 2HYY     | ![Image](2HYY_D1.png) | ![Image](2HYY_D2.png) |
| 3C4C     | ![Image](3C4C_D1.png) | ![Image](3C4C_D2.png) |
| 3EWH     | ![Image](3EWH_D1.png) | ![Image](3EWH_D2.png) |

(continued on next page)
Table 6. (continued)

| PDB code | D-1 | D-2 |
|----------|-----|-----|
| 3RCD     |     |     |
| 3W2S     |     |     |
| 4JT5     |     |     |

shows remarkable similarity in the binding of amino acids in the types of interactions, which suggests that molecules D-1 and D-2 are ligands that can inhibit this protein.
Table 6. (continued)

| PDB code | D-1                  | D-2                  |
|----------|----------------------|----------------------|
| 4U5J     | ![Image](image1.png) | ![Image](image2.png) |
| 6N2J     | ![Image](image3.png) | ![Image](image4.png) |

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