Virtual screening of Osimertinib and Dacomitinib Analogues with potential activity on EGFR (T790M and l858R Mutations) for non-small cell lung cancer treatment

Cribado virtual de Análogos de Osimertinib y Dacomitinib con actividad potencial sobre el receptor de factor de crecimiento epidérmico EGFR (MUTACIONES T790M Y L858R) para el tratamiento del cáncer de pulmón no microcítico

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ABSTRACT

Introduction: Tyrosine kinase inhibitors (TKIs) drugs act on epidermal growth factor (EGFR) receptors to treat Non-small cell lung cancer (NSCLC). However, mutations on EGFR receptors T790M and L858R allow just a global response rate (GRR) of 80% with Osimertinib, while Erlotinib and Gefitinib only 10%.

Objective: To identify promising molecules analogues to tyrosine kinase inhibitor (TKIs) drugs with the potential capacity to bind the native and mutated EGFR receptor (T790M and L858R) to avoid mutational resistance in NSCLC.

Methods: Virtual screening by molecular docking between analogues of Osimertinib (DB09330) and Dacomitinib (DB11963) drugs retrieved of DRUGBANK database and receptors of native EGFR and mutated on L585R and T790M obtained of Protein Data Bank was performed, using PyRx software. Finally, toxicological prediction was made using GUSAR.

Results: Analogues studied, DB03878, DB04739, DB07280 and DB06876 achieved significant affinity (-9,1 y -8,3 Kcal/mol) on mutated T790M EGFR compared with osimertinib (-7,6 Kcal/mol). Similarly, DB08091, DB08730, DB07220 and DB06920 achieved significant affinity (between 9.4 and -8.9 Kcal/mol) on L858R EGFR mutated compared with dacomitinib (-7.0 Kcal/mol). Overall, there were predominance of Van der Waals forces and links π-alkyl. Also, two analogues were safe with category IV according to predictions, DB08730 and DB03878.

Conclusions: Eight TKI analogues showed superior binding energy over EGFR compared to reference drugs. According to toxicological predictions only 2

analogues were selected as promising TKI-type safe candidates for the treatment of resistant NSCLC.

Keywords: EGFR; Osimertinib; Dacomitinib; Docking; Tyrosine kinase.

RESUMEN

Introducción: Los fármacos inhibidores de la tirosina quinasa (TKI) actúan sobre receptores del factor de crecimiento epidérmico (EGFR) para tratar el cáncer de pulmón no microcítico (CPNM). Sin embargo, las mutaciones del EGFR T790M y L858R sólo permiten una tasa de respuesta global (GRR) del 80% con Osimertinib, mientras que Erlotinib y Gefitinib sólo 10%.

Objetivo: Identificar moléculas prometedoras análogas a los fármacos inhibidores de la tirosina quinasa (TKIs) con capacidad potencial de unirse al EGFR nativo y mutado (T790M y L858R) para evitar la resistencia mutacional en el CPNM.

Métodos: Se realizó un cribado virtual mediante acoplamiento molecular entre análogos de Osimertinib (DB09330) y Dacomitinib (DB11963) obtenidos de la base de datos DRUGBANK y receptores de EGFR nativos y mutados (L585R y T790M) obtenidos del Protein Data Bank, para esto se utilizó el software PyRx. Por último, se realizó predicción toxicológica utilizando GUSTAR.

Resultados: Los análogos DB03878, DB04739, DB07280 y DB06876 alcanzaron una afinidad significativa (-9,1 y -8,3 Kcal/mol) sobre el EGFR mutado T790M en comparación con osimertinib (-7,6 Kcal/mol). Del mismo modo, DB08091, DB08730, DB07220 y DB06920 alcanzaron una afinidad significativa (entre 9,4 y -8,9 Kcal/mol) sobre el EGFR mutado L858R en comparación con dacomitinib (-7,0 Kcal/mol). En general, las fuerzas de Van der Waals y de los enlaces π-alquilo perdominaron. Además, DB08730 y DB03878 fueron seguros con categoría IV según las predicciones toxicológicas.

Conclusión: Ocho análogos de TKI mostraron una energía de unión superior sobre el EGFR en comparación con los fármacos de referencia. De acuerdo con las predicciones toxicológicas, sólo 2 análogos fueron seleccionados como candidatos seguros de tipo TKI prometedores para el tratamiento del CPNM resistente.

Palabras Clave: EGFR; Osimertinib; Dacomitinib; Acoplamiento molecular; Tirosina quinasa.

INTRODUCTION

Lung cancer is divided into two groups: small cell lung cancer and non-small cell lung cancer (NSCLC), the latter being the most common subtype in the population, accounting for approximately 85% of all lung tumors (1).

There are different options of NSCLC treatment, such as radiation, surgery, and chemotherapy, depending of disease stage. Another current therapeutic strategy is molecular treatments aimed at inhibiting activated epidermal growth factor receptors (EGFR) (1).

Nevertheless, despite having various treatment options, mutations are present in almost 50% of patients with NSCLC, these mutations predict sensitivity to first- and second-generation tyrosine kinase inhibitors (TKI), such as erlotinib, gefitinib or afatinib, intended primarily for patients with the L858R mutation in exon 21 (2). By the other hand, the mutations on EGFR receptors T790M in exon 20 is sensitivity by third generation tyrosine kinase inhibitors as Osimertinib.

However, acquired drug resistance generally "gatekeeper T790M mutation" occurs after 9–14 months of gefitinb or erlotinib clinical therapy (Kobayashi et al., 2005). The clinical application of the second-generation irreversible inhibitors afatinib and dacomitinib is also limited due to their poor therapeutic window.

Therefore, aim study was to identify promising molecules analogues to tyrosine kinase inhibitor (TKIs) drugs with the potential capacity to bind the native and mutated EGFR in exon 20 and 21, using molecular docking methodology to identify interaction protein-ligand and affinities.

METHODS

Search and selection of ligands.

A search of two drugs used as first-line treatment against NSCLC was realized in DrugBank database, obtaining the Molfile files for each drug. Subsequently, Bioinf online server of Johannes Kepler University (http://shiny.ml.jku.at/Analoging/) was entered, which allowed determining the analogues to be used at similarity greater 0.95. Obtaining a total of 23 analogues for osimertinib and 30 for dacomitinib.

Obtaining native and mutated EGFR

The structures of L858R and L858R/T790M mutant receptors were obtained from the Protein Data Bank database, identified by accession codes 4I20 and 4LL0. Afterward, the receptors were downloaded in PDB format. Previously, native receptor was obtained by modifying the respective residues using USFC Chimera bioinformatics tool. Also, proteins in PDB format were prepared by methodology of Contreras-Puentes et al. (3).

Molecular docking

Molecular docking was performed using AutoDock Vina 4.2.117, employed PyRx 0.8 software working interface (4). Molecules analogues of osimertinib and dacomitinib were configured on a grid space of x = 25 Å, y = 25 Å, z = 25 Å using a universal force field (UFF).

Subsequently, each simulation used a single analogues molecule for each drug, selected the top nine conformations with its respective free binding energy, which were organized according to the energy of each conformation. The structures with HER1 complex were obtained in pdbqt format, and finally converted to pdb employed Pymol and visualized by Discovery Studio 2.5 software (5).

Pharmacokinetic and drug-likeness prediction

A search was made for the structures in Simplified Molecular Input Line Entry System (SMILES) representation in the DrugBank database. Subsequently, the SMILES list was entered into the SwissADME online server, generating a prediction of parameters such as gastrointestinal absorption, brain penetration, CYP inhibition and bioavailability score. Likewise, a prediction of drug-likeness was made based on compliance of the Lipinski and Veber rules.

Toxicological prediction

Additionally, the molecules docked against the mutated EGFR were subjected to in silico prediction of toxicological profiles. So, the GUSAR-Online server was used; which the predictions of the lethal dose 50 values (LD50) in rats using intravenous (IV) and oral administration were calculated, classified through acute toxicity in rodents to chemical products condensed in OECD Project.

RESULTS

The interactions of osimertinib and dacomitinib are observed in Figure 1, which showed binding energies of -7.6 and -7.0 Kcal/mol, respectively.

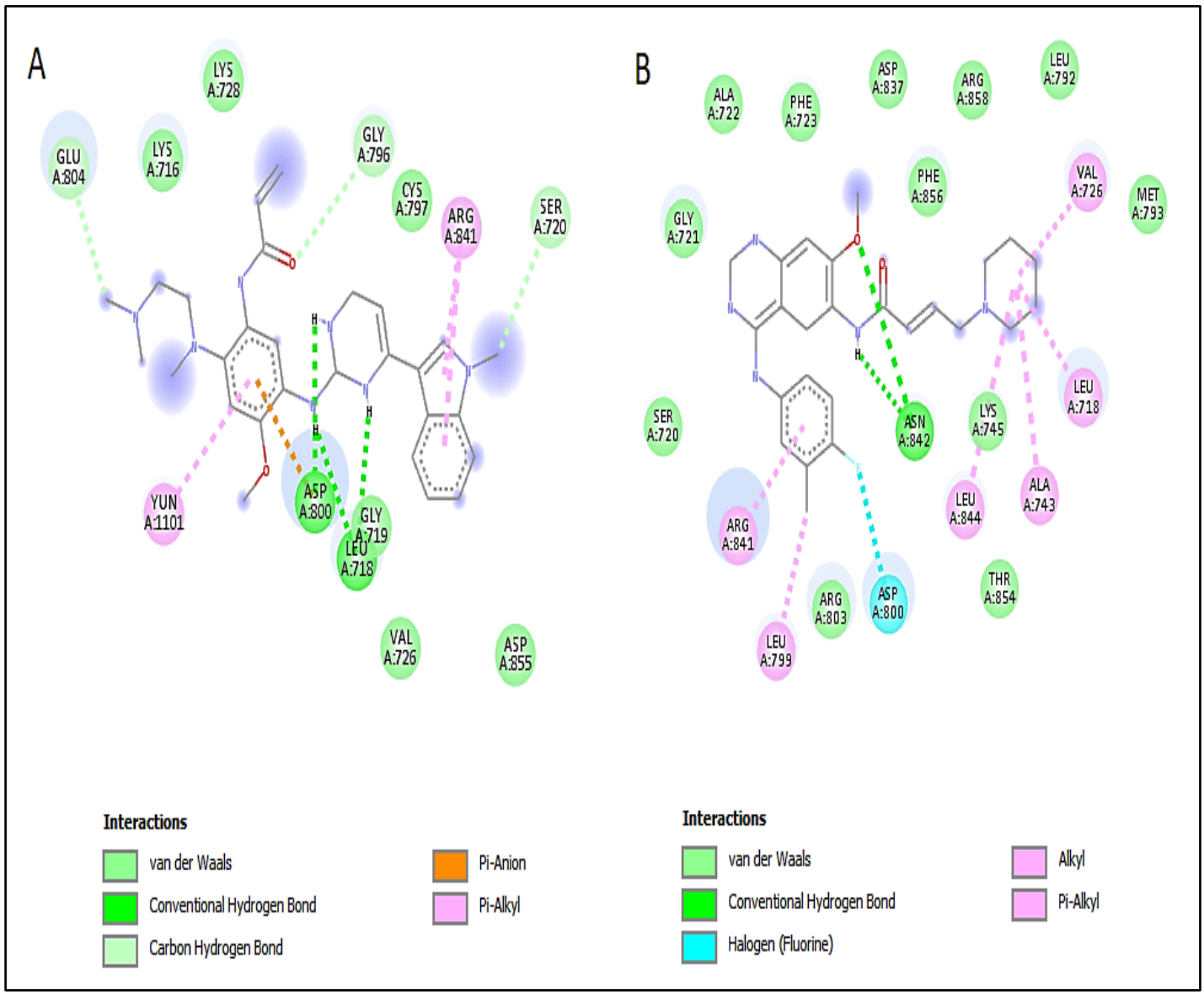

Figure 1. Molecular interaction of TKIs with mutated EGFR receptor. A. Dacomitinib-Mutation L858R. B. Osimertinib-Mutation L858R/T790M.

Likewise, molecular interactions between osimertinib and dacomitinib analogues and native EGFR, are shown in Figure 2 (Panels A–D). So, the molecules as DB07460, DB04739, DB04452, DB00246, DB07460, DB08730, DB08091 and DB02491 showed the highest energy affinity, indicating values between -9.4 and -8.6 Kcal/mol (Table 1) (Supplementary Material - Figure 1).

Otherwise, in Figure 3 (Panels A-D) can show interactions between the osimertinib and dacomitinib analogues with mutated EGFR, with values between -9.4, and -8.3 Kcal/mol, which corresponded to DB08091, DB08730, DB07220, DB06920, DB03878, DB04739, DB07280 and DB06876 (Table 2) (Supplementary Material - Figure 2).

The interactions observed in analogues and active site of the EGFR were H-bond (conventional and carbon), π-sigma, alkyl and π-alkyl and predominately Van der Waals forces.

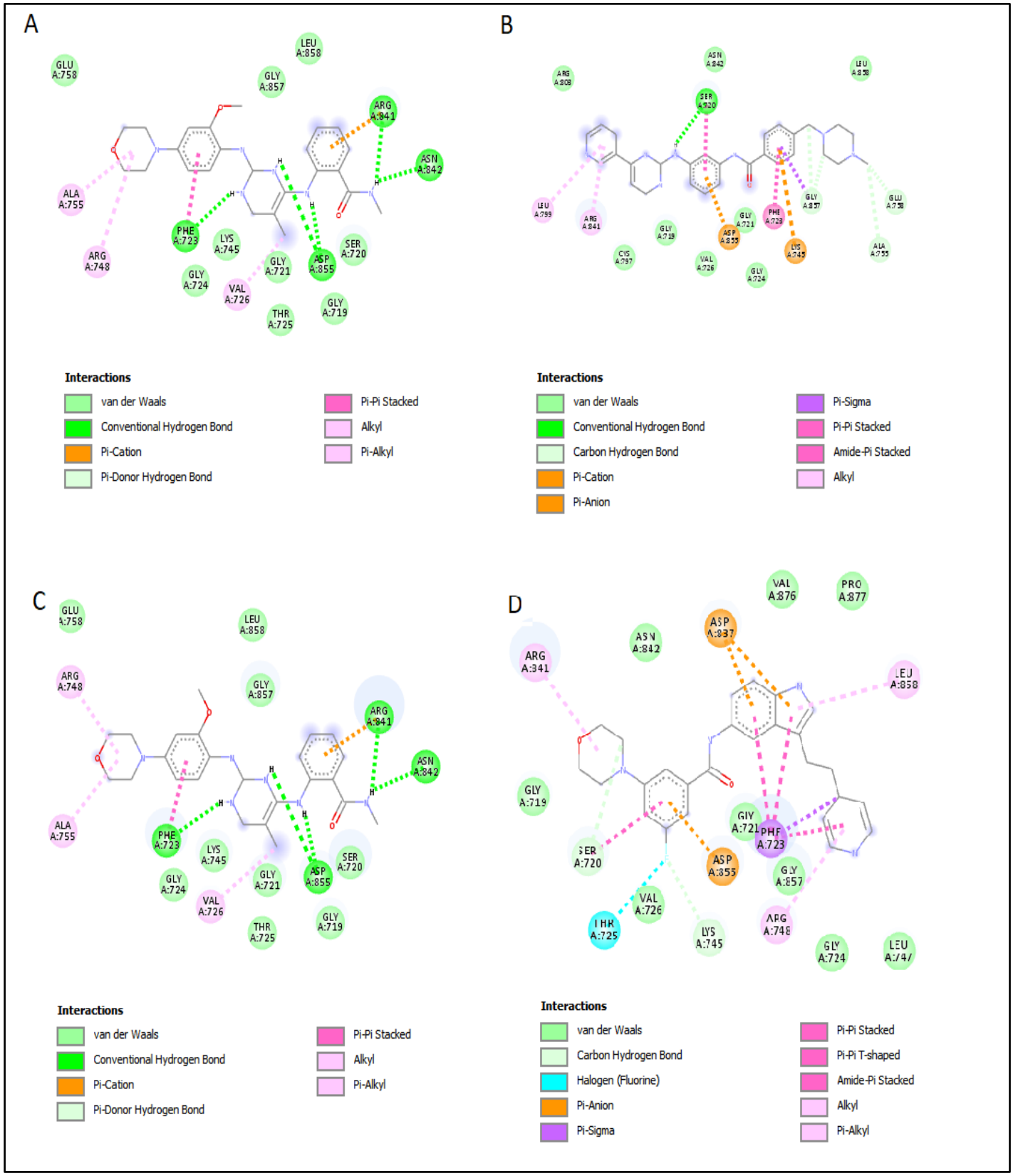

Figure 2. Molecular interaction of analogues with native HER1. A. DB07460 (Osimertinib analogue). B. DB04739 (Osimertinib analogue). C. DB07460 (Dacomitinib analogue). D.DB08730 (Dacomitinib analogue).

Table 1. Molecular interactions of the active site of native HER1 with dacomitinib and osimertinib analogues

Ligand	Binding Energy Kcal/mol	Type of interaction	Receptor
DB07460	-9.4	Van der Waals, Hydrogen bond, π-alkyl, π-Cation, π-π Stacking	EGFR
DB04739	-9.4	Van der Waals, Hydrogen bond, π-alkyl, π-Cation, π-π Stacking	EGFR
DB04452	-9.5	Van der Waals, Hydrogen bond, π-alkyl, π-Cation, π-π Stacking	EGFR
DB00246	-9.4	Van der Waals, Hydrogen bond, π-alkyl, π-Cation, π-π Stacking	EGFR
DB07460	-8.2	Van der Waals, Hydrogen bond, π-alkyl, π-Cation, π-π Stacking	EGFR
DB08730	-8.9	Van der Waals, Hydrogen bond, π-alkyl, π-Cation, π-anion, Halogen (Fluorine), π-π T-shaped, π-sulfur	EGFR
DB08091	-8.5	Van der Waals, Hydrogen bond, π-alkyl, π-anion, Halogen (Fluorine), π-π T-shaped, π-sulfur	EGFR
DB02491	-8.6	Van der Waals, Hydrogen bond, π-alkyl, π-anion, Halogen (Fluorine), π-π T-shaped	EGFR

In the Table 2, the dacomitinib and osimertinib analogues shows some pharmacokinetics properties as high absorption, low permeation to blood brain barrier, CYP inhibitory effect and adequate bioavailability score. Like, non-violation of Lipinski and Veber rules associated to drug-likeness.

Finally, in the Table 3 shows the toxicological predictions made, which were considered moderately toxic (class III) and lightly toxic (Class IV). However, DB07220 presented a toxic category II.

DISCUSSION

EGFR have been established as valid therapeutic targets for treatment of NSCLC and increase its expression with point mutations such as L858R and T790M correlated with disease progression, hereby, the therapy with TKI directed against receptors can inhibit tumour growth at different stages, thus ensuring the specificity of treatment and selectivity. Leading to selection of TKIs as first, second and third generation to treat different stages of lung cancer depending each mutation (6).

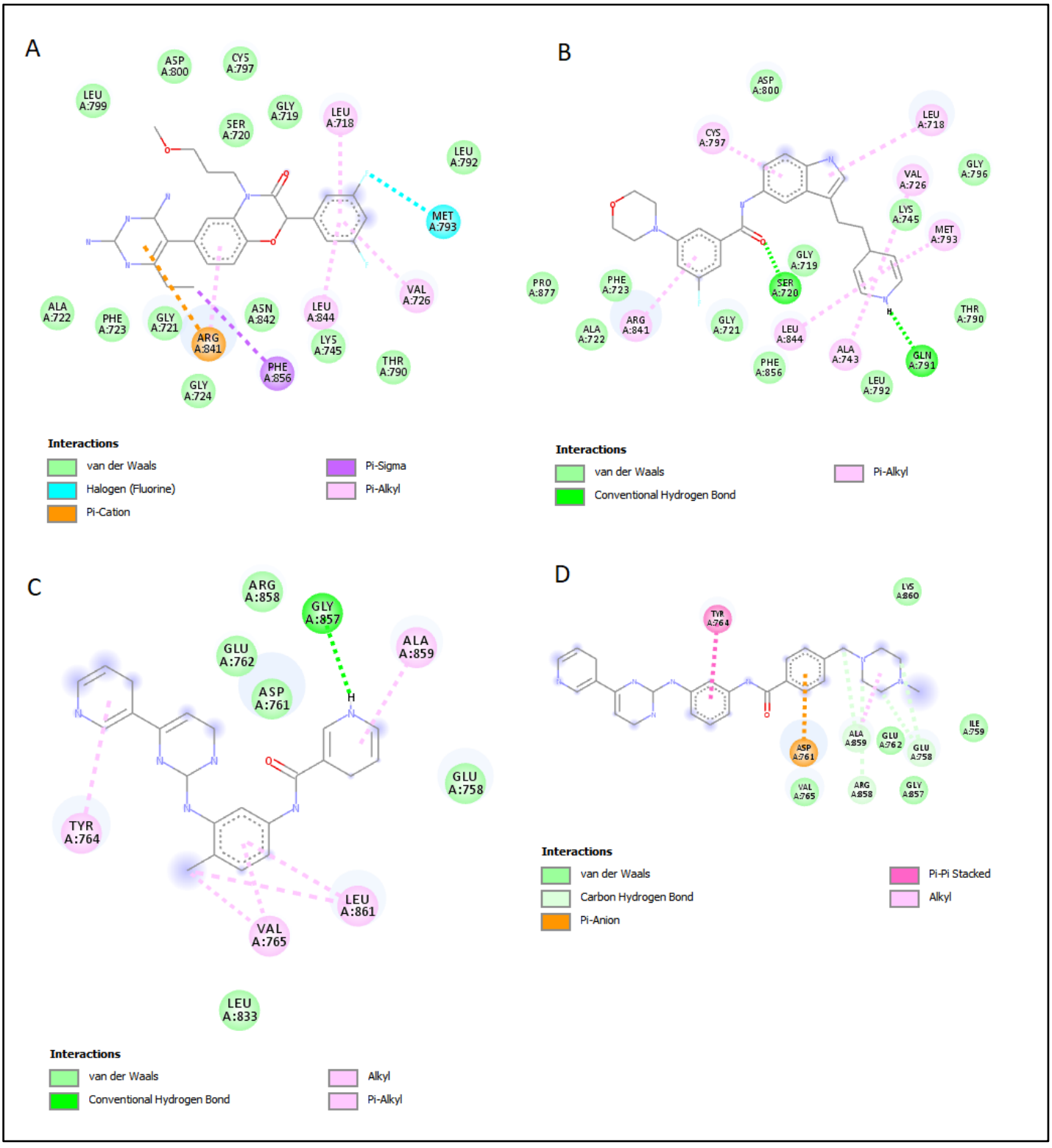

Figure 3. Molecular interaction of analogues with mutated EGFR. A. DB08091 (Dacomitinib Analogue). B. DB08730 (Dacomitinib analogue). C. DB03878 (Osimertinib analogue). D. DB04739 (Osimertinib analogue).

Table 2. Molecular interactions of the active site of mutated HER1 with dacomitinib and osimertinib analogues.

Tying	Energy of union Kcal/ mole	Type of interaction	Type of receptor (mutation)
Dacomitinib (Control)	-7.6	Van der Waals, Hydrogen bond, π-alkyl, Halogen (Fluorine)	L858R
DB08091	-9.4	π-Cation, π-σ, Van der Waals, π-alkyl, Halogen (Fluorine)	L858R
DB08730	-9.2	Van der Waals, Hydrogen bond, π-alkyl	L858R
DB07220	-9.4	Van der Waals, Hydrogen bond, π-alkyl, C-H bond, π-σ	L858R
DB06920	-8.9	Van der Waals, Hydrogen bond, π-alkyl, C-H bond, π-Anion	L858R
Osimertinib (Control)	-7.0	Van der Waals, Hydrogen bond, π-alkyl, C-H bond, π-Anion	L858R/T790M
DB03878	-9.1	Van der Waals, Hydrogen bond, π-alkyl, C-H bond	L858R/T790M
DB04739	-8.3	Van der Waals, Hydrogen bond, π-alkyl, C-H bond, π-cation, π-anion, π-σ, π-π-T-shaped	L858R/T790M
DB03916	-8.3	Van der Waals, Hydrogen bond, π-alkyl, C-H bond	L858R/T790M
DB06876	-8.3	Van der Waals, Hydrogen bond, π-alkyl, C-H bond, π-cation, π-anion	L858R/T790M

Table 3. Pharmacokinetic and drug-likeness prediction of dacomitinib and osimertinib analogues using SwissADME server.

Compounds	**Pharmacokinetic**						**Drug-likeness**		
	Absorption GI	Permeation BBB	P-gp	CYP1A2 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski	Veber	Bioavailability score
DB07460	High	NO	NO	YES	YES	YES	YES	YES	0.55
DB04739	High	NO	YES	YES	YES	YES	YES	YES	0.55
DB04452	High	NO	YES	YES	NO	YES	YES	YES	0.55
DB00246	High	YES	YES	YES	YES	YES	YES	YES	0.55
DB08730	High	YES	YES	YES	YES	YES	YES	YES	0.55
DB08091	High	YES	YES	YES	YES	YES	YES	YES	0.55
DB02491	High	NO	YES	YES	YES	YES	YES	YES	0.55
DB07220	High	NO	YES	NO	YES	YES	YES	YES	0.55
DB06920	High	NO	YES	NO	YES	YES	YES	YES	0.55
Dacomitinib	High	NO	NO	NO	YES	YES	YES	YES	0.55
Osimertinib	High	NO	YES	NO	YES	NO	YES	NO (1 viol)	0.55
DB03878	High	NO	YES	YES	YES	YES	YES	YES	0.55
DB03916	High	NO	YES	YES	YES	YES	YES	YES	0.55
DB06876	High	YES	YES	YES	YES	YES	YES	YES	0.55

The molecular docking revealed that selected analogues showed considerable affinity against mutated EGFR in exon 20. The osimertinib analogues with better binding energy were DB03878, DB04739, DB07280 and DB06876 with values of -9.1, -8.3, -8.3 and -8.3 Kcal/mol, respectively, while for osimertinib as reference ligand against the receptor with the T790M mutation it was -7.6 Kcal/mol. Additionally, it has been denoted that the osimertinib structures interact with R841 forming π-alkyl bond with indole group of the structure; likewise, the pyrimdin-2-yl ring establishes H-bond and C-H-bond interactions by D800, L718 and G719 residues, as well as, oxygen atom of carbonyl in propen-2-amide forming indicating H-bond bonds with G796. On the other hand, DB03878 is able to anchor into pocket protein through of hydrophobic residues as A743, V726, L844 and R841 binding to 3-pyridinyl. Thus, in the studies by Hanan et al., the role of pyrimidine-derived inhibitors was described, in which showed that residues such as V726 exhibited a structural disposition towards the side chain of the compounds evaluated, allowing lipophilic contacts with pyrimidine ring, and mainly influencing its arrangement in the lipophilic ribose pocket related to the active site, behavior that was similar to that described in this study, where it was able to interact not only with V726 but with three hydrophobic amino acids that induced a greater effect stabilizer with pyridinyl ring (7).

Also has been described the involvement of F856 and R841 which favor π-alkyl binding to 4-methyl-3 amino-phenyl; equally, the presence of H-bond linkage to 2-pyrimidinyl and L718, and Q791 linked to ring of 3-pyridinyl. Therefore, the importance of Q791 residues in the formation of hydrogen bonds has been corroborated, promising greater stability of the pyrimidinyl ring and allowing a more polar location; however, it is observed that the nitrogenous aromatic rings arranged in the pocket are associated with residues such as L745, M793, T790, which were described in previous studies and which are important for the recognition of inhibitors in the center of the active site (7,8).

Table 4. Prediction *in silico* of DL_{50} mg/Kg for Rats (IV and Oral) by Gusar on-line prediction

Tying	LD_{50} mg/Kg for rats (Oral)	LD_{50} mg/Kg for rats (IV)	Classification LD_{50} for rats (oral)
Dacomitinib (Control)	444.700	444.700	Class 4
DB08091	319.700	53.090	Class 4
DB08730	1166.000	42.150	Class 4
DB07220	0.000	0.000	Class 1
DB06920	745.200	110.600	Class 4
Osimertinib (Control)	368.200	22.140	Class 4
DB03878	1206.000	72.320	Class 4
DB04739	352.600	37.500	Class 4
DB03916	992.800	61.420	Class 4
DB06876	170.500	38.120	Class 3

LD_{50}: Lethal Doses 50; IV: Intravenous

For dacomitinib analogues, the compounds with major affinity energy were DB08091, DB08730, DB07220 and DB06920 with values of -9.4, -9.2, -9.4 and -8.9 Kcal/mol, respectively; while that dacomitinib was relatively lowest with -7.0 Kcal/mol. Likewise, from the structural point of

view DB08091 analogue shows very similar characteristics to the reference drug regarding the arrangement of the amino acids involved in the active site. However, the compound DB08091 has been determined to evolve polar groups such as the 5-morpholin nucleus proximal to the residues of F723 and P877 by attaching via van der Waals interactions. On the other hand, dacomitinib and DB08091 have piperidine and pyridin rings in their structure that maintain lipophilicity with the active site through V726, L718, A743 and L844, as well as the presence of R841, which has been defined as one of the important amino acids that define the active site and responsible for maintaining a hydrophobic character defining interactions with 3-fluorobenzamine rings for DB08091 and 3-chloro-4-fluorophenylamino (9,10). On the other hand, Arg841 residue, being present in the interactions observed for both cases through π-alkyl bonds, could be responsible for the binding of the ligand and drugs with the receptor. Various studies have documented the importance of π interactions in various biological processes and in the drug-receptor interaction (11). Inclusively, some polar interactions have been defined for the structural analogue with Q791 forming hydrogen bonds with the N of the pyridine ring. Comparatively, with the results obtained in this study, the presence of residue C797 has been observed, forming π-alkyl type junctions with indole ring of the analogues, which had similarities with what was proposed by Gajiwala et al, describe that dacomitinib tends to stable covalent inclination with this residue. Therefore, the authors establish that the covalent bond in C797 restricts the aliphatic region and maintains its proximity in the hinge region, which is consistent with the behavior employed on the indole ring present in the analogue studied (12).

On the other hand, *in silico* analysis of the pharmacokinetic properties of dacomitinib and osimertinib analogues, it indicates that predicted structures showed a high gastrointestinal absorption. Thus, as evidenced in clinical studies with dacomitinib and osimertinib, dacomitinib has low solubility (> 1 mg/mL) and considerable permeation. Additionally, *in vitro* studies indicate that its passively absorbed and constitutes a variable element as substrate for intestinal transporters associated with P-glycoproteins (P-gp) and BCRP protein. Then again, slow absorption processes have been indicated *in vivo* tests, however, at oral doses of 45 mg, the main bioavailability was around 80%(13); like, has been indicated at levels of 30 to 60 mg, obtaining a half-life within 59 to 85 h(14,15). Meanwhile, *in vitro* study using murine models has shown that osimertinib accomplishes plasmatic values of 4.5 h after oral administration(16). Its validated in *in vivo* studies with healthy volunteers, where osimertinib despite registering slow absorption and C_{max} within 5.9 - 8.9 h, with maximum peaks at 24 h(17). Else, in cohort studies osimertinib at dose of 80 mg has been reported half-life of 48.6 h(39.9–59.4)(18). Likewise, in comparative studies with oral formulations of osimertinib it was shown equivalence limits of 80 to 125% without significant differences and bioavailability values around of 70%(17,18). Despite, the authors indicate that slow absorption of TKI is an effect of the processes subsequent to dissolution, where it has been shown that the dissolution rate and solubility are not complete determinants(18).

Otherwise, TKIs are metabolized by CYP systems, conditioning the appearance of drug-drug interactions, and therefore the modification of areas under the curve (AUC) and maximum plasma concentration (Cmax). In the predictive analysis of possible interaction with enzymatic isoforms of CYP and of osimertinib and dacomitinib, it was mainly shown at inhibitory behavior, with the exception of DB04452 in relation to CYP2D6 and osimertinib with CYP3A4. Thus, some studies have corroborated that CYP3A4 is a weak enzymatic inducer of osimertinib(19,20), which has been associated in demethylation and hydroxylation reactions (DM-1, DM-2, OH-1 and OH-2). Osimertinib is a substrate and inducer of CYP1A1, which has demonstrated its role in the effective treatment with biological targets at the pulmonary level, in which CYP1A1 generated demethylated and hydroxylated products that are key to understanding the role in regulation of lung cancer(21). Alternatively, CYP2D6 is a dacomitinib

inhibitor and widespread in many EGFR-TKIs, associated with oxidative and conjugative metabolism, its active metabolism being generated by its form of O-desmethyl dacomitinib (PF-05199265), which is regulated by CYP2D6 and CYP2C9(22). Consequently, dacomitinib was shown in different studies to strongly inhibit the capacity of this enzyme complex(23). Additionally, it has been verified in phase I studies, using competitive inhibitors such as concomitant paroxetine with dacomitinib, evidencing a 37% increase in AUC and a reduction in PF-05199265, corroborating the substantial effect that this drug presents with the cytochrome isoform(24).

Additionally, the toxicological predictions have established in the case of the T790M/L858R mutation, that DB03878 would be a promising compound for pharmacological therapy since of the analysed analogues, it presented a class 4 toxicity with a value of LD50 of 1206 mg/Kg orally, a value that is well above that obtained with the reference drug which was 368,2 mg/Kg orally. No dose-related toxicities up to 240 mg daily have been detected in clinical trials with osimertinib and there is little experience regarding accidental overdoses (25). Finally, dacomitinib has an asymptomatic maximum dose in rats of 50 mg/Kg has been established; Dose-limiting and overdose toxicities include stomatitis, rash, palmar-plantar erythrodystesia syndrome, dehydration, paronychia, and diarrhea. Thus, the maximum tolerated dose for humans is 45 mg. However, after starting treatment, cases of grade III toxicity have been reported, requiring a reduction in the indicated dose (EMA (European Medicines Agency), 2019). This value as a reference, DB0891 could be a promising compound since it presented a value of 319,7 mg/Kg orally.

In conclussion, the computational tools have been great progress for identification of new therapeutic agents with potential pharmacological activity, due to speed and low cost in the processes, facilitating the arduous path to reach the clinical phase stage with clearer arguments in accordance with the theoretical results obtained. This group of osimertinib analogues (DB03878, DB04739, DB07280 and DB06876) and dacomitinib analogues (DB08091, DB08730, DB07220 and DB06920) identified had significant affinity by native and mutated EGFR. Therefore, are promising for the treatment of non-small cell lung cancer and its stages of progression, contributing to the problem of acquired resistance and safety profile with respect to current pharmacological treatment and constituting an advance of precision medicine from the computational approach in the treatment of lung cancer.

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