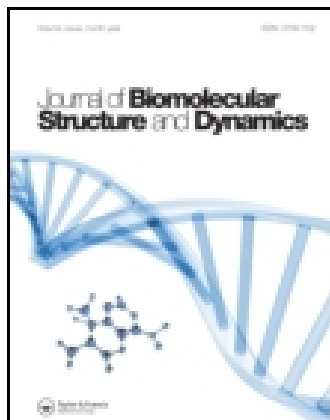


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Using Computer-aided Drug Design and Medicinal Chemistry Strategies in the Fight Against Diabetes

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Using Computer-aided Drug Design and Medicinal Chemistry Strategies in the Fight Against Diabetes

<http://www.jbsdonline.com>

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Abstract

The aim of this work is to present a simple, practical and efficient protocol for drug design, in particular Diabetes, which includes selection of the illness, good choice of a target as well as a bioactive ligand and then usage of various computer aided drug design and medicinal chemistry tools to design novel potential drug candidates in different diseases. We have selected the validated target dipeptidyl peptidase IV (DPP-IV), whose inhibition contributes to reduce glucose levels in type 2 diabetes patients. The most active inhibitor with complex X-ray structure reported was initially extracted from the BindingDB database. By using molecular modification strategies widely used in medicinal chemistry, besides current state-of-the-art tools in drug design (including flexible docking, virtual screening, molecular interaction fields, molecular dynamics, ADME and toxicity predictions), we have proposed 4 novel potential DPP-IV inhibitors with drug properties for Diabetes control, which have been supported and validated by all the computational tools used herewith.

Key words: Diabetes; Drug design; DPP-IV inhibitors.

Introduction

Diabetes is one of the most important diseases of our time, with an increasing reported worldwide incidence (1-3). The most important incretin hormones identified are the gastric inhibitory polypeptide (GIP) and the glucagon-like peptide-1 (GLP-1), which are quickly inactivated in circulation by the enzyme dipeptidyl peptidase IV (DPP-IV), a serine peptidase (4-7). Inhibition of DPP-IV prevents GLP-1 and GIP degradation and can reduce glucose levels in diabetics. DPP-IV is involved in intracellular signaling, metabolism and activation of peptides, including GIP, insulin-like growth factors, endomorphin, enterostatin. Most of the DPP-IV protein is extracellular, with a hydrophobic transmembrane sequence (amino acids 7-28) anchoring the protein in the cell membrane. The catalytic region encompasses amino acids 511-576. The wide tissue distribution of DPP-IV on numerous cell types and vascular beds as well as its presence as a soluble active enzyme in the circulation ensures that DPP-IV-mediated proteolysis is a common event in most tissue compartments. Thus, DPP-IV inhibition has been proposed as a new treatment of type 2 diabetes (8, 9), and after the discovery of GLP-1, DPP-IV inhibition became a major research target. An increasing number of theoretical research have recently investigated diseases such as cancer, AIDS and others, emphasizing therapeutic targets as well as inhibitors (10-12). The aim of this work is to present a practical sequence of steps or protocol toward a rational design of novel DPP-IV inhibitors for Diabetes therapy.

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The BindingDB database (13) was used to search for DPP-IV inhibitors. Among 447 inhibitors, the most active inhibitor with a complex X-ray structure solved was selected (PDB code 1RWQ), with IC_{50} of 0.1 nM (14).

By using the GOLD 4.2 software (15), a flexible docking procedure was employed with such DPP-IV structure and potential inhibitors to suggest binding modes for the proposed compounds. GOLD performs flexible docking using a genetic algorithm, which was originally optimized from a set of 305 complexes structures with coordinates deposited in PDB. Docking simulations were performed inside a sphere of 8 Å radius centered at the oxygen atom (hydroxyl group) of Y547 of DPP-IV, using default parameters of the genetic algorithm: populations of 100 conformers, 100000 operations, 95 mutations and 95 crossovers.

Molecular interaction fields (MIF) were calculated inside the DPP-IV active site region, using the GRID v.22 software (16). The electrostatic and van der Waals potentials were computed for interaction energy between chemical probes and atoms of a selected region of DPP-IV, a conservative box where the Poisson equation is solved. Two prototypical probe groups were used: aromatic carbon and NH of amide (a hydrogen bond donor), which were placed in a 0.33 Å spacing grid covering the overall binding site.

Toxicity evaluation and ADME (absorption, distribution, metabolism and elimination) predictions were performed for our 4 proposals, respectively using the knowledge-based system DEREK(17) and the web server ADME/TOX WEB (<http://pharma-algorithms.com/webboxes/>).

Molecular dynamics simulation has been widely applied to investigate the intimate details of the structure and motion in diverse biological system as can be seen from the several recent publications in this *Journal* (18-52). It is very useful particularly to determine the stability of the binding of various drug candidates at the binding pocket of a receptor protein, and this will become clear towards the end of the present paper.

Molecular Dynamics (MD) were performed using the discover module of the Insight II package (53). Previously, the energies of the four complexes were minimized using 1000 steps of a combined steepest-descent/conjugate gradient algorithm and the Discover/CVFF force field of Insight II. Explicit solvent conditions filling the overall DPP-IV active site were employed. No constraints were made during any optimization procedure. Subsequently, 1500 ps MD simulations were carried out for each complex, with an equilibration phase of 80 ps, at 298 K.

Results and Discussion

In order to find novel DPP-IV inhibitors using computer-aided drug design and Medicinal Chemistry strategies, an initial search in the BindingDB database was done. There are 747 DPP-IV inhibitors with biological activity data reported. Among these, there are few compounds containing structures solved in complex with the enzyme in the PDB (Protein Data Bank). We have selected the most active inhibitor with a complex X-ray structure solved ((5-aminomethyl-6-(2,4-dichlorophenyl)-2-(3,5-dimethoxy-phenyl)-pyrimidin-4-ylamine in complex with human DPP-IV, PDB code 1RWQ), with IC_{50} of 0.1 nM.

Various series of DPP-IV inhibitors have been published as potential new drugs. Jens *et al.* (14) identified the 6-methylenedioxyphenyl-aminomethylpyrimidine compound (Figure 1A) as a weak inhibitor (lead compound) and also proposed analogues with increased potency, such as the inhibitor of the complex PDB coded

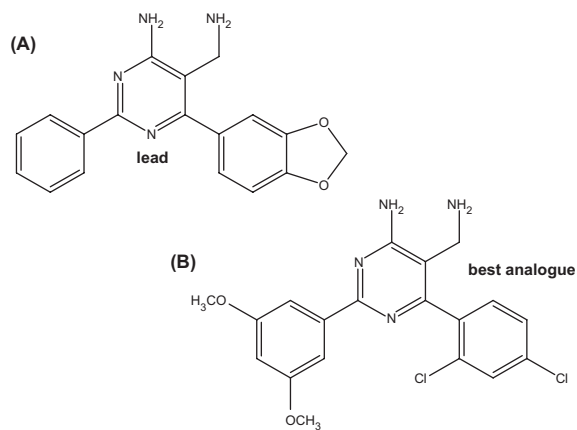


Figure 1: In (A), the lead compound (6-methylenedioxyphenyl-amino-methylpyrimidine) which was optimized to yield (B), the best analogue (5-aminomethyl-6-(2,4-dichloro-phenyl)-2-(3,5-dimethoxy-phenyl)-pyrimidin-4-ylamine) (14).

1RWQ (Figure 1B). Considering the structures of these two compounds, as well as the main interactions in the active sites of DPP-IV, we have employed three usual molecular modification strategies in Medicinal Chemistry (bioisosterism, molecular hybridization and simplification) to propose novel inhibitors, which could maintain (or enhance) the biological activity of the lead compound and improve its pharmacokinetic properties as well. We describe thus a simple and practical protocol for *in silico* design and evaluation of novel drug-like inhibitors of a selected therapeutic target.

Following a Cartesian thinking, one simple and initial idea is to propose novel molecules with similar physical chemical characteristics of the aminomethylpyrimidine ring, which is present in both lead and analogue compounds (Figure 1). In principle, a bioisosteric replacement for 8-arylmethyl-9H-purin-6-amine ring could maintain the main interactions inside the DPP-IV active site, such as observed in the crystal complex structure (14). The aminomethylpyrimidine ring of the inhibitor forms an important and symmetrical hydrogen bonding network with Y662, N710 and two glutamic acid residues (E205, E206) of DPP-IV (Figure 2). We investigated molecular hybrids containing the methylenedioxy (present in the lead compound) or trimethoxy phenyl ring (present in some of the active compounds of the BindingDB database). In Figure 3, we show our proposals of novel DPP-IV inhibitor candidates.

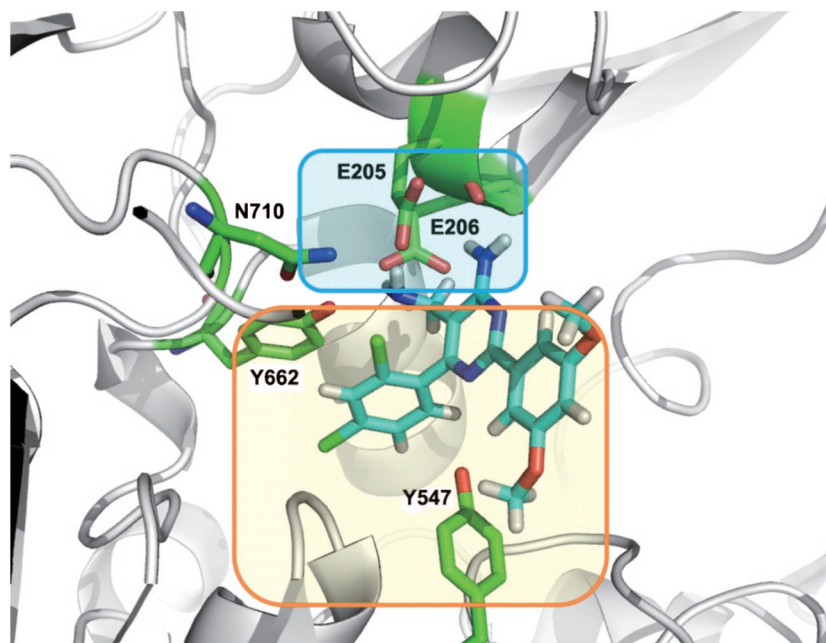


Figure 2: Selected residues and the main interactions between DPP-IV and the best analogue inhibitor (PDB code 1RWQ) are shown: hydrogen bonds (blue rectangle) and van der Waals (yellow rectangle).

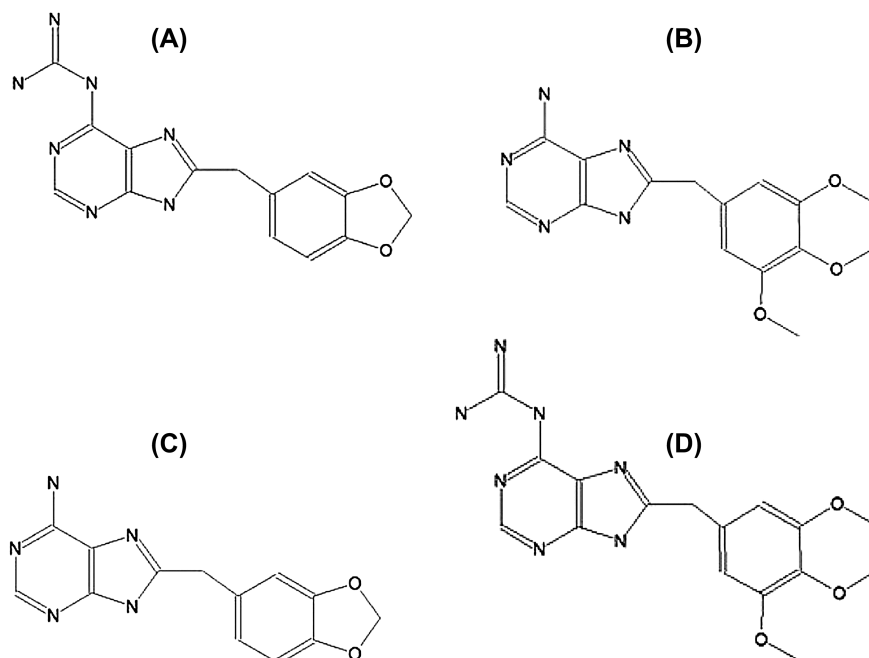


Figure 3: Structures of the novel potential DPP-IV inhibitors: Proposal 1 (A), Proposal 2 (B), Proposal 3 (C) and Proposal 4 (D).

In order to propose binding modes for all the proposals inside the DPP-IV active site, we used a flexible docking procedure with GOLD 4.2. Previously, we have validated the docking methodology used, selecting the crystallographic complex (PDB code 1RWQ) and comparing the resultant 5 best-ranked docking solutions obtained for the inhibitor with the crystallographic orientation (Figure 4). Agreement between experimental and theoretical orientations was obtained for the DPP-IV-inhibitor system with a (RMSD of 2.07 Å). We note that the docked conformation was maintained, with a slight displacement of the original (crystallographic) orientation.

Five orientations of highest score for each proposed compound were selected using the GoldScore function and then analyzed. In Figure 5 we show the top-ranked solution obtained with GOLD for Proposal 1, where the main interactions discussed above for the crystallographic complex are maintained, but with an additional cation- π interaction between the guanidinium group of this proposal and the DPP-IV Y547 residue.

In order to support such docking result, a supplementary study of molecular interaction fields (MIF) was performed inside the DPP-IV active site region. Results obtained using the two probes agree with the orientations suggested by docking for aromatic ring and hydrogen bond acceptor groups, where the respective MIF can be visualized in Figure 6 for Proposal 1 (aromatic carbon, energy contoured at -3 kcal/mol, and NH of amide, energy contoured at -10 kcal/mol).

Another important issue in drug design is the toxicity, which is a frequent reason of failure in drug development projects. For all the proposals, DEREK suggests no apparent toxicity. However, it is noteworthy that this software indicates end points common to similar scaffolds found in its database. Using such expert system, similar end points have been reported for proposals 2-4, which are described below.

For Proposal 1, carcinogenicity plausible in mammals is indicated, and it is due to substituted pyrimidines. The Pyrimidine derivatives shown to have carcinogenic potential include uracil and thymine, which induce bladder carcinogenesis in rats

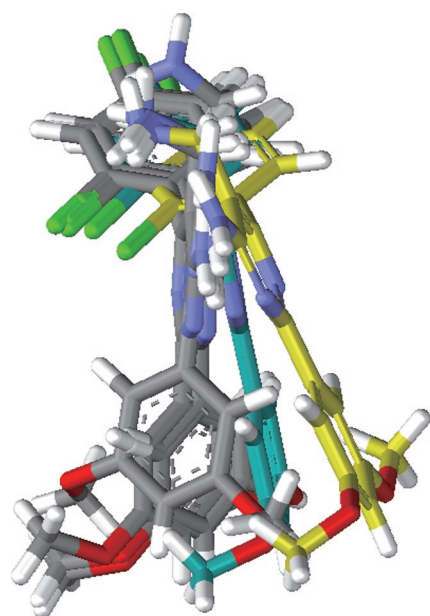


Figure 4: Superposition of the 5 best-ranked docking solutions and the crystallographic orientation of the 5-aminomethyl-6-(2,4-dichloro-phenyl)-2-(3,5-dimethoxy-phenyl)-pyrimidin-4-ylamine inhibitor regarding the DPP-IV active site: crystallographic (carbon atoms in yellow), top-ranked docking solution (carbon atoms in cyan) and the other 4 best-ranked solutions (carbon atoms in grey).

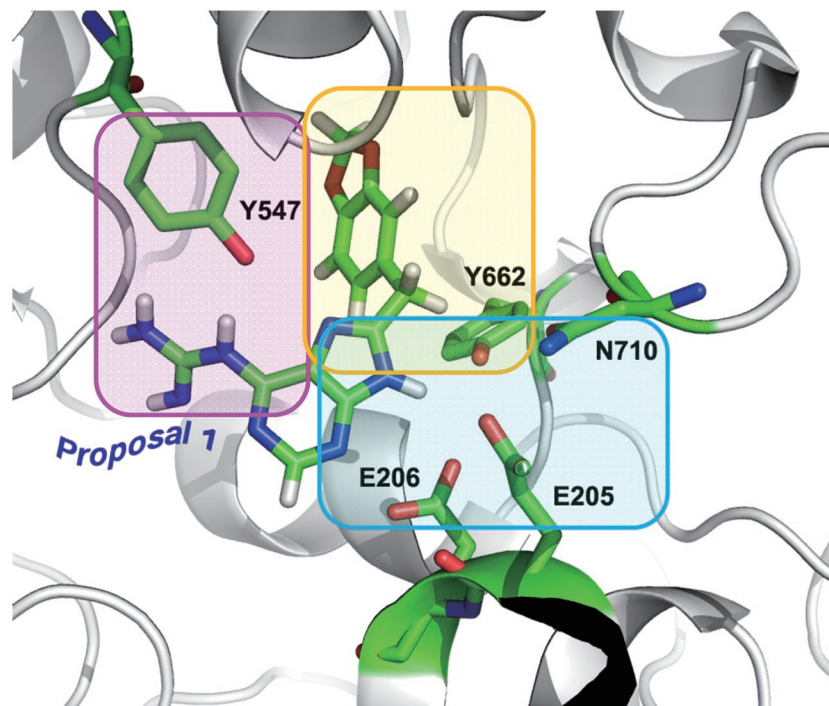


Figure 5: Selected residues and the main interactions between DPP-IV and the top-ranked docking solution of Proposal 1 are shown: hydrogen bonds (blue rectangle), van der Waals (yellow rectangle) and cation- π interaction (magenta rectangle).

and/or mice via calculi formation (54). Urinary calculi are formed when the urine becomes oversaturated with a compound. Large calculi then damage the urinary bladder epithelium mechanically and increase DNA synthesis in the cells resulting in tumour formation. In general, purines have displayed only trace or marginal carcinogenicity at most in some experiments (54, 55). In addition for such proposal, an alert of skin sensitization is also indicated as plausible in mammals, and it is due to aromatic primary or secondary amine. Whether or not the molecule will be a skin sensitizer will depend upon its percutaneous absorption. In general, small lipophilic molecules are more readily absorbed into the skin and are thus more likely to cause sensitization (56).

Analyzing the proposals regarding their pharmacotherapeutic profiles, we have initially estimated the oral bioavailability of the compounds from an absorption point of view, calculating the physicochemical properties of the Lipinski's Rule of Five-RO5 (57). None of the proposals violate the rule in two or more properties,

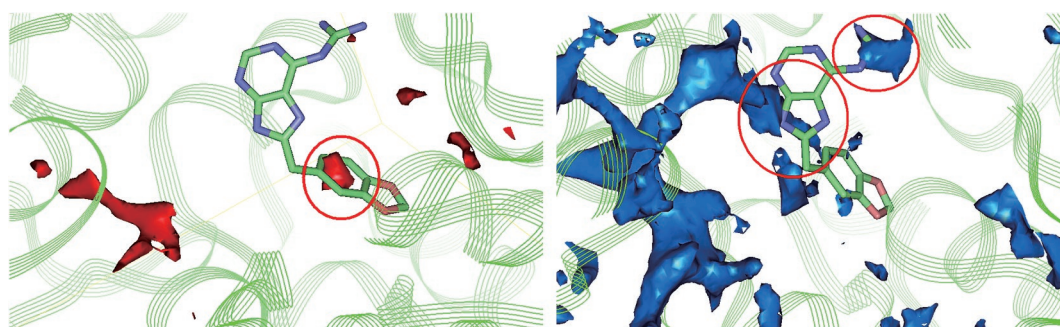


Figure 6: Molecular interaction fields (MIF) are shown inside the DPP-IV active site, in phase with the top-ranked docking solution for Proposal 1. For calculation, two prototypical chemical probes were used: aromatic carbon (map in red, energy contoured at -3 kcal/mol) and NH of amide - a hydrogen bond donor (map in blue, energy contoured at -10 kcal/mol). Red circles point out the agreement between docking and MIF results.

indicating theoretically good oral bioavailability profiles. Other selected pharmacokinetic properties were also Calculated using the web server ADME/TOX WEB (<http://pharma-algorithms.com/webboxes/>), with results summarized in Table 1.

For all the proposals, the oral bioavailabilities (%F) were estimated between 30 and 70%, with a slight advantage for Proposal 3, for which the probability of %F > 30% is 72.2%. Solubility in water (S_w) is moderate to low for all the proposals, with better results for Proposal 2: $S_w = 0.2$ mg/mL (99% of probability). Most of such DPP-IV potential inhibitors also show theoretically good passive absorption across intestinal barrier (>70%), with maximum passive absorption of up to 100% for proposals 2 and 3, 85% for Proposal 1 and 51% for Proposal 4. No active transport is predicted for any DPP-IV inhibitor candidate.

For proposals 1-4, in general no significant first-pass metabolism in liver and/or intestine is predicted, and no high probabilities to bind plasmatic proteins were observed, *i.e.* %PPB between 26.9% (Proposal 4) to 77.6% (Proposal 3). Volumes of distribution (V_d) predicted for our proposals were moderate or high, with values between 1.36 (Proposal 4) and 1.96 L/kg (Proposal 3). Volume of distribution is a theoretical but relevant concept that connects the administered dose with the actual initial concentration present in the circulation, determining the half-life of a drug (22). The web server ADME/TOX WEB contains a predictive algorithm that generates a quantitative estimate of the apparent volume of distribution of a compound, based on charge state, lipophilicity, hydrogen bonding capacity and other parameters.

P-gp inhibitor probability calculated for Proposal 1 was very low (4.9%), thus classified as a non inhibitor. It was also classified as a non substrate of the glycoprotein, with a probability of 19.1%. For Proposal 2, the P-gp inhibitor probability calculated was similarly low (4.8%). It can also classify as a non substrate of glycoprotein, with a relatively low probability of 34.8%. Proposal 3 has a P-gp inhibitor probability calculated of 2.6% and it was also classified as a non substrate of glycoprotein (35.7% probability). However, for our Proposal 4, the P-gp inhibitor probability estimated was moderate (38.4%), with a substrate probability of 31.2%.

Analyzing the results estimated for our four candidates, proposals 1 and 2 have the best pharmacotherapeutic profiles, indicating good oral bioavailabilities as well as absorption profiles. The binding properties are computed from physicochemical properties (lipophilicity, ionization constants and hydrogen-bonding capacity) as well as structural descriptors of the compounds. In general, it is assumed that only free drug can cross membranes and bind to the intended molecular target (58), and for Proposal 1 the estimated fraction of drugs bound to plasma proteins is low.

Proposal 2 is also indicated as a soluble drug, with good characteristics of distribution and transport. For a compound crossing a membrane by purely passive

Table I
Pharmacokinetic properties calculated for proposals 1-4 of potential DPP-IV inhibitors.

Inhibitor	% F	% Maximum passive absorption	S_w (mg/mL)	% PPB	V_d (L/kg)	P-gp substrate probability (%)	P-gp inhibitor probability (%)
Proposal 1	30-70	85	0.09	28.0	1.81	19.1	4.9
Proposal 2	30-70	~100	0.20	76.6	1.45	34.8	4.8
Proposal 3	30-70	~100	0.11	77.6	1.96	35.7	2.6
Proposal 4	30-70	51	0.17	26.9	1.36	31.2	38.4

diffusion, a reasonable permeability estimate can be made using single molecular properties, such as partition and distribution coefficients or hydrogen-bonding capacity. Some compounds can also be affected by the influence of transporters and metabolism (58). Many drugs are substrates for transporter proteins, which can either promote or hinder permeability. In particular, P-glycoprotein is the most widely known efflux transporter, having a great effect on the success of drug discovery projects, and our proposals **1** and **2** contemplate this objective with low P-gp inhibitor probabilities.

We have also performed Molecular Dynamics (MD) simulations to investigate the stability of the proposals inside the DPP-IV active site. In general, the low values of RMSD obtained in the MD simulations for our 4 proposals (less than 0.5 Å) indicate a tendency of small changes in respect to the conformations/orientations suggested by docking (Figure 7). Results thus indicate apparent stability for our candidates, in particular for proposals **1** and **2** (with low and stable values of root mean square deviation from the original coordinates, as well as the two lowest complex energies at the end of the simulations), although the RMSD vs. time plot indicates a slight and temporary conformational change at 300-700 ps for Proposal **1**. This change is mainly due to the charged guanidinium group, which establishes

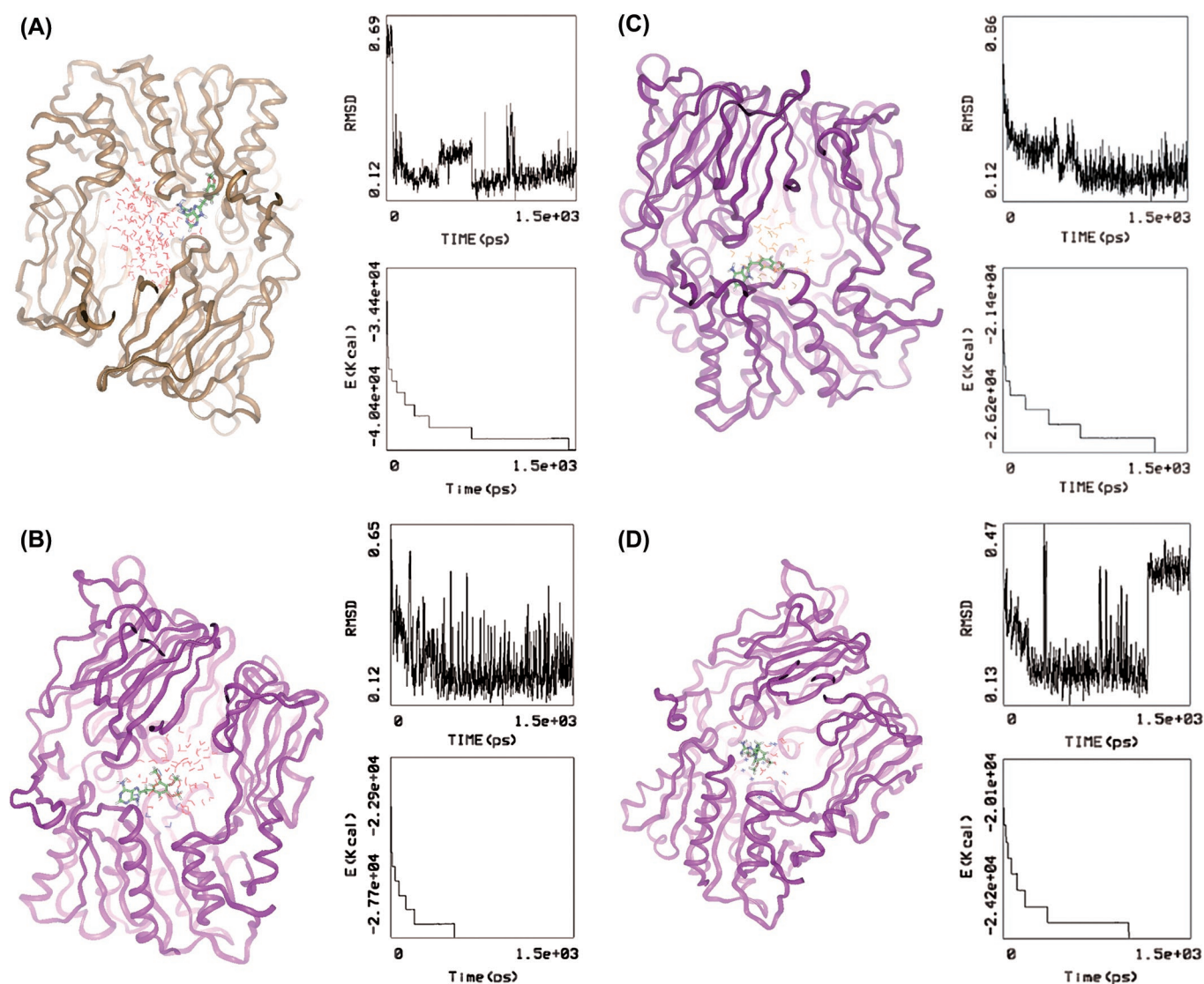


Figure 7: Results of Molecular Dynamics simulations with explicit solvation, performed with DPP-IV and the proposed novel inhibitors, are shown: Proposal **1** (A), Proposal **2** (B), Proposal **3** (C) and Proposal **4** (D). RMSD values are given in angstroms.

a cation- π interaction with Y547. It's worth mentioning that this interaction can be additionally reinforced since Proposal 4 is the most buried inhibitor among the other proposals, thus revealed in the MD simulations carried out with explicit solvation (see Figure 7). Guanidinium is also present in Proposal 4, but a more pronounced conformational change was necessary for this fourth proposal in order to optimize interactions with DPP-IV, such as can be observed at the end of the MD simulation (Figure 7D).

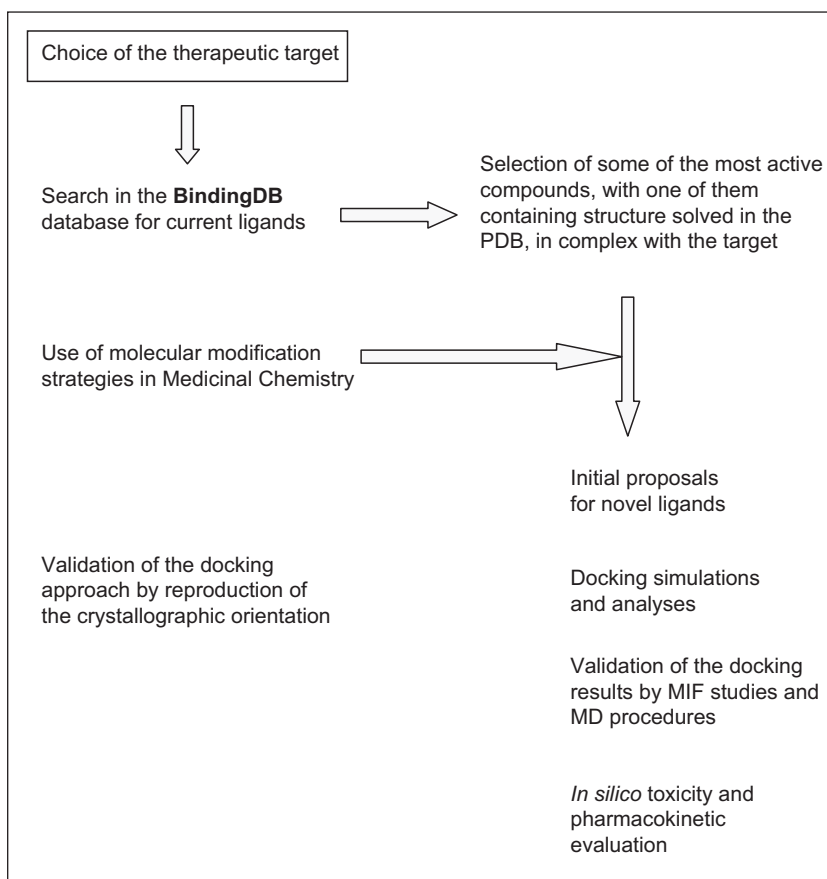
We thus indicate our Proposal 1 as the most promising DPP-IV inhibitor with drug-like properties. This proposal has the best docking score and most intense interactions (in agreement with the results obtained with molecular interaction fields studies), does not indicate toxicity effects, shows good pharmacotherapeutic profile and is one of the most stable inhibitors inside the DPP-IV active site as indicated by Molecular Dynamics procedures. Finally, the proposed protocol for drug design has been thus validated, and can be summarized in Scheme 1.

Conclusion

We thus try to show in this work, a simple and practical protocol for drug design, *i.e.* selection of the illness, good choice of a target as well as a bioactive ligand and then usage of selected computer-aided drug design methods and Medicinal Chemistry strategies to design novel potential drug candidates for different diseases, in particular Diabetes.

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Scheme 1: Flowchart of the protocol suggested for drug design.

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