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Computational study on anti-inflammatory and anti-hypertensive drug molecules interaction with base pairs

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) and anti-hypertensive drugs have been in use for a long time for the treatment of inflammation, pain, hypertension. Besides these functions, they also show different types of other activities. Many of them exhibit critical side effects in different types of cancer such as colon, lung, and breast cancer. In the present study, we computationally investigated the interactions of some nonsteroidal anti-inflammatory and anti-hypertensive drugs (acebutolol, naproxen, diflunisal, bisoprolol) with nucleobases and interaction of drugs with nucleobase pairs by optimized at the B3LYP/6-31+G (d), B3LYP-D2/6-31+G (d) and ωB97X-D /6-31+G (d) levels of DFT. The main purpose of this study is was to determine the strengths of drug-DNA-base interactions and drug-DNA-base pair interactions that can provide insights about the side effects of the drugs. The calculations were produced the following results. Acebutolol has the highest interaction between adenine in single base-drug complexes. However, acebutolol has the strongest interaction between the guanine-cytosine base pair. The ωB97X-D method, which accounts for dispersion interaction properly, gives better results than the B3LYP and B3LYP-D2 methods.

Keywords: NSAIDs; beta blockers; nucleobase ; nucleobase pairs; binding energies; DFT methods.

1 Introduction

The DNA - drug interaction has a major role in pharmacology and this interaction has a vital feature for the determination of the mechanisms of drug action. Non-covalent interactions are important for biological systems (Toupkanloo and Rahmani 2 018). Non-covalent DNA- interacting agents can cause a conformational change in DNA. Non-covalent interactions are weaker than a chemical bond and they have a vital role in controling the structure and function of DNA and RNA in understanding of replication and origin of life (Ghosh et al. 2010). Therefore, interactions between drugs and nucleobases play an critical role in determining side effects (Abbas 2017-Kennard 1993). Non-steroidal anti-inflammatory drugs (NSAIDs) are a significant class of compounds to reduce inflammation and pain associated with infection or injury. Nevertheless, when NSAIDs are used for a long time, they cause various side-effects such as kidney failure, gastrointestinal problems, colon, lung, and breast cancer (Azam F et al. 2018). The ß-blockers belong to the antihypertensives class of medications and they are mainly used to manage high blood pressure (hypertension), treat arrhythmia and decrease the risk of heart complications after a heart attack.

The studies performed in the past few years aimed to provide an understanding of the fact that how drugs interact with the nucleobases of DNA/RNA. In 2003, Baik et al. studied how two possible hydrolysis products of cis-platinum complexes bind to adenine and guanine nucleobases. Their findings indicate that guanine is the preferred reactant for platination, and guanine is more suitable both thermodynamically and kinetically. In 2018, Toupkanloo and Rahmani investigated some bicyclic fragments, which may have possible genotoxic effects, interacting with nucleobases. Hence, they focused on the π-π stacking interactions and this interaction leads to both an increase and a decrease in hydrogen bond lengths in the drug-nucleobase interactions. The main objective of this study is to quantitatively determine and scale the interactions of some nonsteroidal anti-inflammatory and anti-hypertensive drugs with nucleobases with quantum chemical methods, especially with DFT methods.

2 Materials and Method

This study consists of two main parts: a) interaction of drugs with nucleobases b) interaction of drugs with nucleobase pairs. All structures have been optimized at the B3LYP/6-31+G (d), B3LYP-D2/6-31+G (d) and ωB97X-D /6-31+G (d) levels of DFT. That each optimized geometry corresponds to a local minimum on the potential energy surface was identified via harmonic vibrational analyses. The effect of implicit water solvation on complex formation was calculated by employing integral equation formalism of the Polarized Continuum Model (IEF-PCM). All calculations were performed using the Gaussian09 program (https://gaussian.com/g09citation/)

3 Results and Discussion

3.1 Binding Enthalpies of Drugs to Nucleobases

In this part, we scrutinized the effects of each drug on a single nucleobase. In order to determine drug-nucleobase interactions, all drugs-nucleobase complexes were optimized at the B3LYP/6-31 G(d), B3LYP-D2/6-31 G(d) and ωB97X-D/6-31 G(d) levels of DFT. The binding energies were calculated exploiting the following equation.

$$\Delta H_{bind} = H_{298}(complex) - \left(H_{298}(drug) + H_{298}(base)\right) \quad (1)$$

Table 1 Binding enthalpy (kcal/mol) values of the drug–nucleobase complexes optimized with the B3LYP, B3LYP-D2 and ωB97X-D methods.

Drug name	Base	B3LYP	B3LYP-D2	ωB97X-D
Bisoprolol	A	2.02	8.3	-8.17
	T	1.7	3.33	-11.33
	G	-2.39	5.72	-11.78
	C	0.17	5.25	-7.22
Acebutolol	A	1.44	9.03	-12.56
	T	1.02	7.74	-7.9
	G	1.57	8.29	-9.51
	C	-2.83	*	-8.32
Naproxen	A	0.91	6.24	-9.7
	T	1.03	7.07	-8.45
	G	*	3.86	-11.11
Naproxen	C	0.94	7.36	-8.37
Diflunisal	A	-5.4	7.62	-7.45
	T	-6.05	7.22	-8.28
	G	-8.59	6.15	-7.59
	C	*	6.37	-6.91

* Calculations did not converge to a stable geometry.

Table 1 shows the binding enthalpy values of the drug–nucleobase complexes optimized with the B3LYP, B3LYP-D2 and ωB97X-D methods.

As seen from the table, the most negative binding energy is between adenine and acebutolol while the lowest one is between diflunisal and guanine. The ωB97X-D method predicted that all drug-nucleobase complexes are rather stable. Our expectation was that the B3LYP-D2 method would produce similar results since the D2 part includes the contribution of dispersion interactions that are not incorporated in the B3LYP method. However, this is not the case. Although the B3LYP methods produce somewhat reasonable results, the D2 correction made them worse. Hence, it can be said that the ωB97X-D method gives more reasonable results than the B3LYP-based methods.

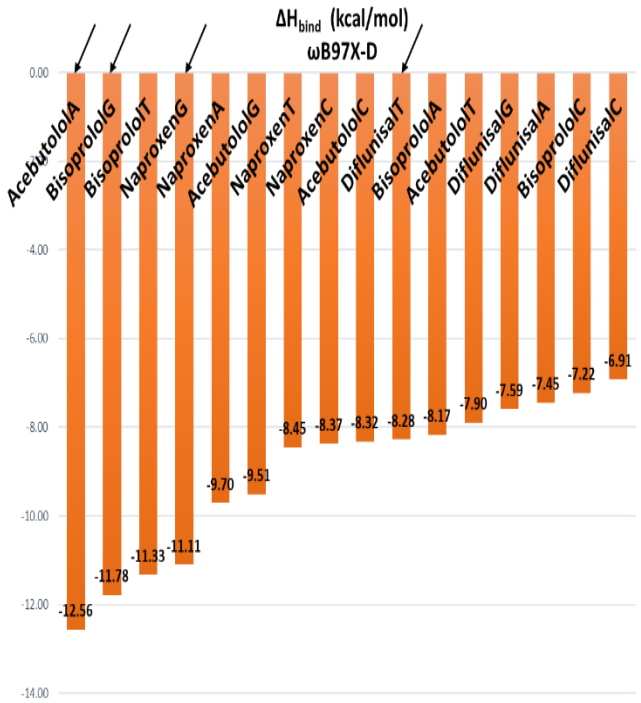

Figure 1 Highly interacting drug-base structures

The figure shows the highly-interacting-drug-nucleobase structures obtained with the ωB97X-D method. As previously stated, it is more likely that this method gives better results than the other two since it includes long-range interactions and it is claimed to give good results in the weakly interacting systems. Therefore, the ranking obtained with this method is presented here. Accordingly, acebutolol and adenine have the most negative binding energy among all single nucleobase–drug complexes. The second most interacting complex is the bisprolol-guanine complex. The next two complexes are naproxen-guanine and diflunisal-thymine complexes, too.

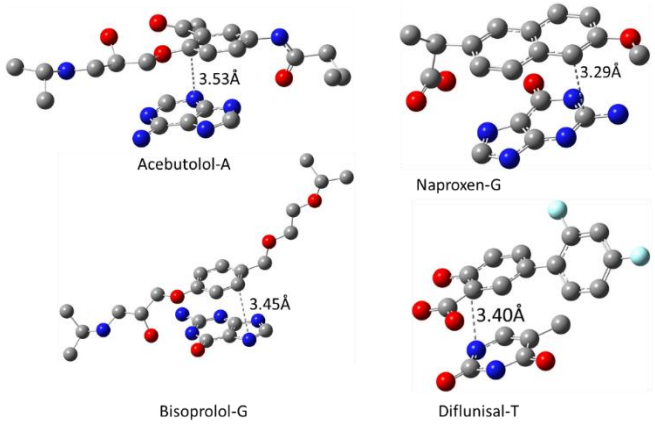

Figure 2 ωB97X-D optimized structures of drug–nucleobase complexes

3.2 Drug-Nucleobase-pair Binding Enthalpies

In this part, we investigated the effects of each drug on nucleobase -pairs. To determine these interactions, all drugs-nucleobase pair complexes were optimized at the B3LYP/6-31G(d), and ωB97X-D/6-31G(d) levels of theory. The binding energies were calculated using equation (1) as in the previous section.

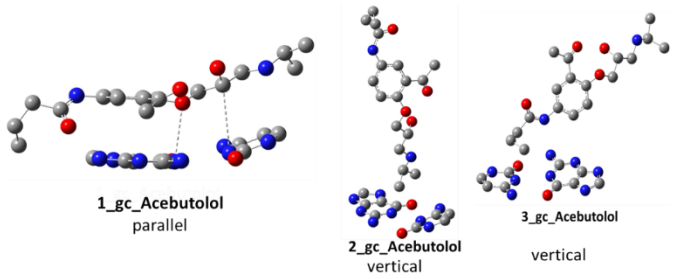

Figure 3 Orientations of drug–nucleobase pair complexes optimized by ωB97X-D

Drug molecules were interacted with nucleobase pairs in the orientations shown in Figure 3, and Table 2 shows the binding enthalpy values for all drugs that interact with the nucleobase pairs in these three orientations. The calculations predict that mostly the parallel oriented drug complexes have more negative interaction interaction than the vertical interacted ones.

As seen from the table, the strongest interaction is between Acebutolol and the G-C base pair. The ωB97X-D method predicted that all drug-nucleobase complexes be more stable than the ones predicted with B3LYP. However, in only one case, the B3LYP method predicts the π-π stacking interaction of the acebutolol drug with the A-T base pair approximately four times stronger than the one predicted by ωB97X-D. This is most probably spurious stability originating from the inability of the B3LYP method in this calculation. Because this high binding energy (-45 kcal/mol) is larger than the covalent bond in the F_2 molecule whose bond dissociation energy is about 37 kcal/mol [Ref F2_BDE]. This clearly shows that B3LYP does not work for this particular case. Figure 4 displays the binding enthalpy order of the drug-nucleobases pairs calculated with the ωB97X-D method.

Table 2 ΔH_{bind} (kcal/mol) values of B3LYP and ωB97X-D optimized drug–nucleobase pair complexes

Interreaction Site	Drug Name	Basepair	B3LYP	ωB97X-D
1_gc	Bisoprolol	G-C	1.26	-13.8
2_gc			1.74	-4.67
3_gc			1.66	-4.82
1_at	Bisoprolol	A-T	*	-13.38
2_at			1.67	-4.56
3_at			1.68	-4.66
1_gc	Acebutolol	G-C	0.63	-17.56
2_gc			0.59	-3.73
3_gc			1.13	-9.62
1_at	Acebutolol	A-T	-45.02	-11.87
2_at			-44.59	-3.67
3_at			-45.34	-6.63
1_gc	Naproxen	G-C	0.19	-9.99
2_gc			0.85	-12.79
3_gc			-1.83	-12.69
1_at	Naproxen	A-T	0.74	-10.31
2_at			1.02	-11.3
3_at			-2.29	-12.97
1_gc	Diflunisal	G-C	-6.15	-14.56
2_gc			-5.9	-11.52
3_gc			*	*
1_at	Diflunisal	A-T	-6.74	-14
2_at			-5.9	-14.76
3_at			-5.87	-10.94

* Calculations did not converge to a stable geometry.

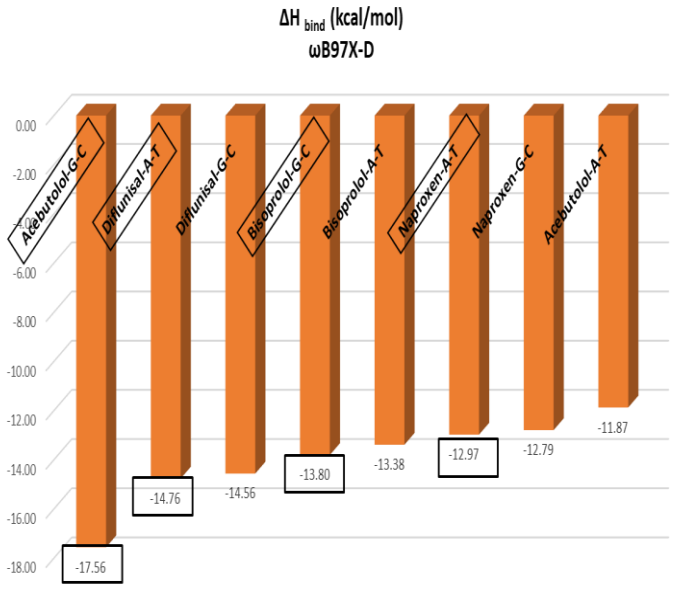

Figure 4 The highly interacting drug-base pair structures

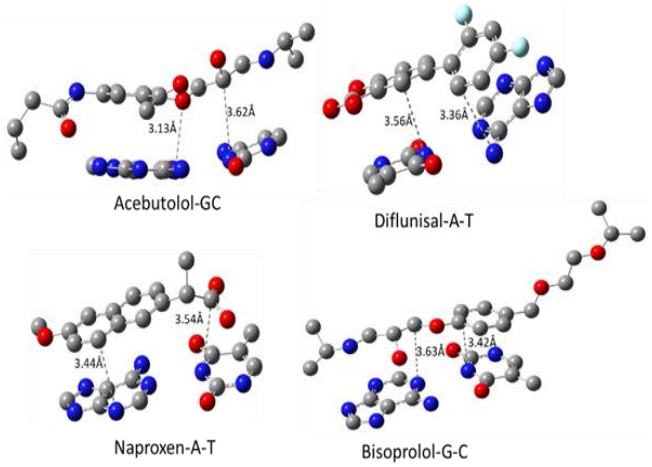

Figure 5 ωB97X-D optimized structures of drug–nucleobase pair complexes

Figure 5 shows the highly-interacting -drug-nucleobase structures obtained with the ωB97X-D method. Acebutolol and Bisoprolol, which are antihypertensive drugs, show the largest interaction with guanine-cytosine base pair. Besides, Diflunisal and Naproxen which are Non-steroidal anti-inflammatory drugs, give the largest interaction with the adenine-thymine base pair.

Table 3. ΔH_{bind} (kcal/mol) values of ωB97X-D and B3LYP, B3LYP-D2 optimized the parallel-oriented drug–nucleobase pair complexes

Interreaction site	B3LYP	B3LYP-D2	ωB97X-D
Bisoprolol-G-C	*	11.39	-13.8
Bisoprolol-A-T	1.26	11.77	-13.38
Acebutolol-A-T	-45.02	11.35	-11.87
Acebutolol-G-C	0.63	*	-17.56
Naproxen-A-T	-2.29	3.68	-12.97
Naproxen-G-C	0.85	13.29	-12.79
Diflunisal-A-T	-5.9	13.39	-14.76
Diflunisal-G-C	-6.15	12.6	-14.56

* Calculations did not converge to a stable geometry.

Table 3 shows the parallel-oriented drug-nucleobase pair complexes that were optimized at the B3LYP/6-31G(d), B3LYP-D2/6-31G(d) and ωB97X-D/6-31G(d) levels of DFT. All of these complexes are π-π stacking complexes. Here, it is seen that the B3LYP underestimates the stability of the complexes as expected except for acebutolol A-T as explained above. However, B3LYP-D2 results are very surprising. Although we performed D2 calculations to improve the results of B3LYP method, B3LYP-D2 made them worse as in the single base-drug interaction case.

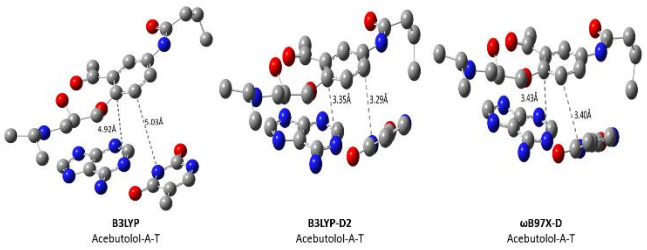

Figure 6 Optimized structures of drug–nucleobase pair complexes

Table 4 Distances between hydrogen bonds of ωB97X-D optimized drug–G-C basepair complexes

Angstrom	O-H	N-H	O-H	difference	difference	difference
G-C	1.840	1.906	1.858	0.000	0.000	0.000
G-C- Acebutolol	1.849	1.905	1.854	0.009	-0.001	-0.004
G-C-Bisoprolol	1.857	1.899	1.866	0.018	-0.007	0.009

Table 5 Distances between hydrogen bonds of ωB97X-D optimized drug– A-T basepair complexes

Angstrom	O-H	N-H	difference	difference
A-T	1.909	1.861	0.000	0.000
A-T-Diflunisal	1.967	1.857	0.058	-0.004
A-T-Naproxen	1.863	1.896	-0.045	0.034

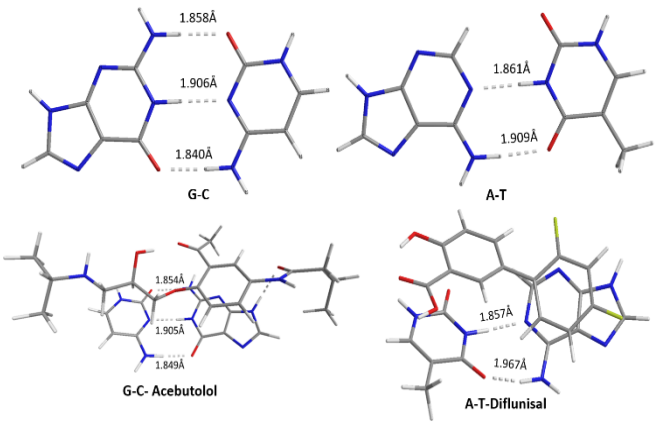

Figure 7 Intermolecular interaction of drug–nucleobase pair complexes

Table 4 shows that the acebutolol affects the bond lengths of the hydrogen bonds between the G-C base pair. On the other hand, the diflunisal affects the bond lengths of the hydrogen bonds between the adenine-thymine base pairs, shown in Table 5 Accordingly, it is likely that these drugs may cause DNA breakage in long-term usage.

4 Conclusion

In this study, we calculated drug-nucleobase and drug nucleobase base-pair interactions with various DFT methods, and we aimed to quantitatively determine the strengths of drug-DNA-base interactions that may improve our understandings about the side effects of the drugs. The most negative binding energy among the drug-single base complexes is between acebutolol and adenine. In the base pair drug complexes, however, acebutolol has the strongest attractive interaction between the guanine-cytosine base pair. Furthermore, we can conclude that the ωB97X-D method gives better results for such non-covalently interacting systems than both the B3LYP and B3LYP-D2 methods since this method accounts for dispersion interaction more accurately.

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