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Computational Quantum Chemical Study, Drug-Likeness and In Silico Cytotoxicity Evaluation of Some Steroidal Anti-Inflammatory Drugs

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ABSTRACT

This paper contains a theoretical study of ten Anti-inflammatory steroids (AIS) on the understanding of the relationship between the structure and activity of the drug, the pharmacokinetic parameters responsible for bioavailability and bioactivity and finally the toxicity evaluation. DFT calculations with B3LYP/6-31G (d, p) level have been used to analyze the electronic and geometric characteristics deduced for the stable structure of the compounds. Moreover, using the Frontier Molecular orbital (FMO) energies, MEP surface visualizations and the density-based descriptors such as chemical potential (**μ**), electronegativity (**χ**), hardness (**η**) and softness (**σ**), the chemical stability were determined. Furthermore, in silico, studies showed that Lipinski rules are applied, which means that these (AIS) are expected to have a high probability of good oral bioavailability. On the other side, the bioinformatic Osiris/Molinspiration analyses of the relative cytotoxicity of these derivatives are reported in comparison to Cortisol. In fact, it has been showed that almost of these compounds are non-toxics except for Mometasone that presents a great risk of tumorigenicity during reproduction with a slightly mutagenic structure due to the two chloride atoms. from all results obtained, we can conclude that fluticasone has the best physico-chemical properties which explains its high efficiency.

Keywords: Anti-inflammatory steroids, DFT, Lipinski rules, Tumorigenicity.

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INTRODUCTION

Corticosteroids are a group of structurally related molecules that include natural hormones secreted by the hypothalamic-pituitary-adrenal axis and synthetic drugs [1]. The endogenous corticosteroids have the function of regulating the physiological immune and metabolic mechanisms, in particular glucido-protein and phosphocalcic [2]. for therapeutic purposes, Corticosteroids are thus commonly used for their fantastic anti-inflammatory properties, but also for their cytostatic effects, which explain their effectiveness in inflammatory, immunoallergic and hematological malignancies [3]. Furthermore, Corticosteroids have the originality of exerting their actions through essentially genomic effects by acting on the transcription of DNA into RNA and on the post-transcriptional regulation of messenger RNA. Being less well known, corticosteroids can also have non-genomic effects, especially when used in high doses [4-6]. However, corticosteroids have side effects that should not be underestimated, especially during long-term treatments. First, metabolic disorders, such as sodium retention, hypokalemia, a diabetogenic effect and an increase in protein catabolism. Second, endocrine disorders in the event of an incorrectly administered dose of cortisone such as a braking of the cortico-adrenal axis. Finally, an increased risk of infection and possible digestive disorders (lower than AINS) [7].

The discovery of new molecules that could be more effective with fewer unwanted side effects is a constant concern of the pharmaceutical industry. So, it is moving towards new research methods, which consist in predicting the properties and activities of molecules even before they are synthesized [8]. The significant development of computer science as well as theoretical studies of quantum chemistry allow researchers to obtain more precise physicochemical and quantum parameters of compounds in a shorter time. It is moving towards the synthesis of a very large number of molecules simultaneously and to test their actions on therapeutic targets. This is the main objective of the QSPR property structure quantitative relationships. These studies are essentially based on the search for similarities between molecules in large databases of existing molecules whose activities or properties are known [9]. The relationships between the structures of molecules and their activities or properties are generally established using molecular

modeling methods and statistical methods. The usual techniques are based on the characterization of molecules by a set of descriptors, real numbers measured or calculated from molecular structures. It is then possible to establish a relationship between these descriptors and the modeled quantity [10].

This study aims to understand the relationship between the drug structure and its activity of ten chosen gluco-corticoids illustrated in **Fig 1.** using density functional theory (DFT) in order to clarify the properties responsible for the drugs efficiency. On the other hand, Toxicity risks and physico-chemical properties of all compounds were calculated by the methodology developed by Osiris and Molinspiration.

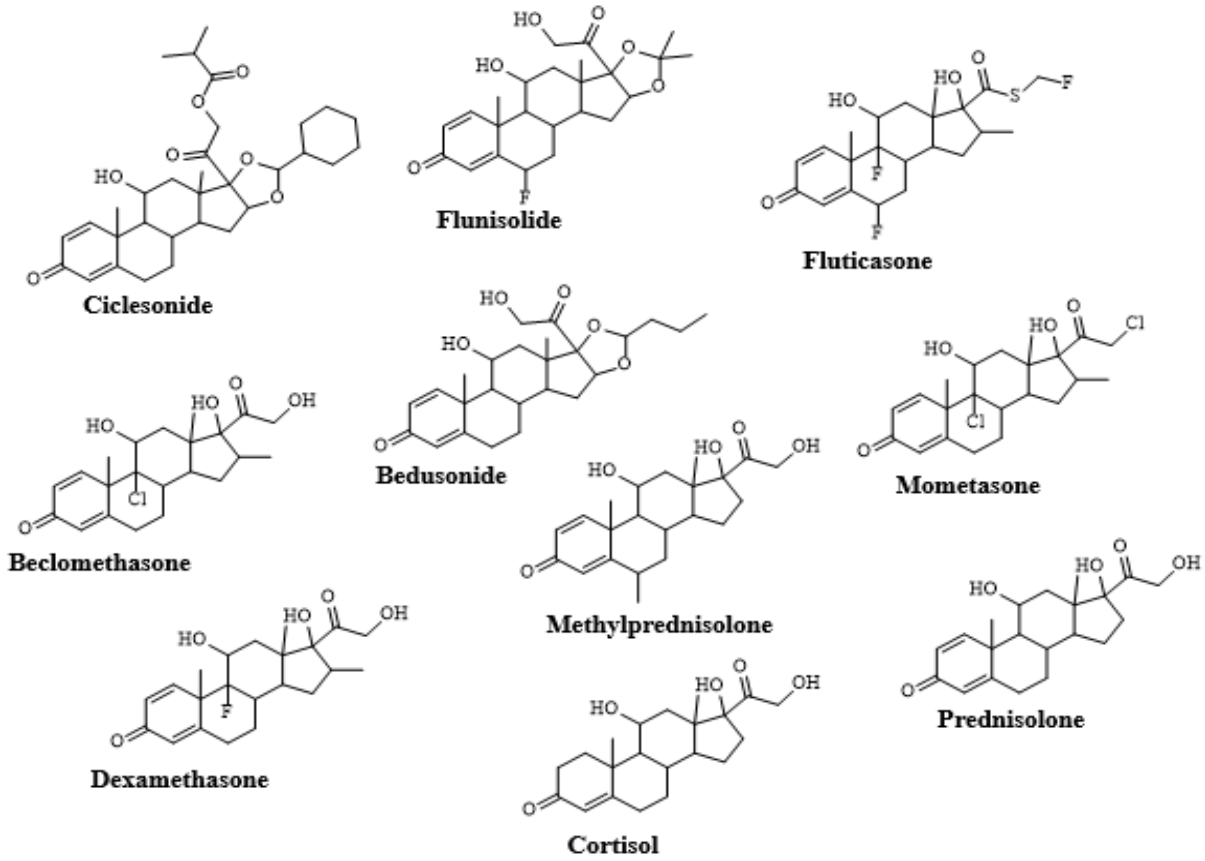

Figure 1: Chemical structures of some glucocorticoid's compounds.

COMPUTATIONAL STUDIES

The molecules under investigation have been analyzed with density functional theory (DFT), employing Becke's three parameter hybrid exchange functional [11] with Lee-Yang-Parr correlation functional (B3LYP) [12]. All the quantum chemical calculations in this study were performed using the Gaussian 09 program. Drawing the structure of the optimized geometry and visualization of the HOMO and LUMO calculations have been done by gausView 5.0.8 program [13]. The chemical reactivity descriptors were calculated using DFT. These are very important physical parameters to understand chemical and biological activities of these compounds. The calculated HOMO-LUMO orbital energies can be used to estimate the ionization energy, electron affinity, electronegativity, electronic chemical potential, molecular hardness, molecular softness, and electrophilicity index [14].

Using Molinspiration cheminformatic (https://www.molinspiration.com) , all pharmacokinetic parameters were performed to predict the bioactivity of compounds while The Osiris software analyses give information about the relative cytotoxicity of these derivatives witch are reported in comparison to Cortisol.

RESULTS AND DISCUSSION

Frontier Molecular Orbital (FOM) Analysis

The Frontier Molecular orbital makes allows to predict the reactivity of the molecule whose active site can be demonstrated by the distribution of the orbital frontiers [15]. Indeed, The HOMO (Highest Occupied Molecular Orbital) is noted as a nucleophile that donates electrons, which behaves like an electron donor, while LUMO (Lowest Unoccupied Molecular Orbital) LUMO can be an electrophile it accepts electrons from nucleophile, which behaves like an electron acceptor [16]. several new chemical reactivity descriptors, such as the chemical potential, global hardness and electrophilicity, have been calculated to understand various aspects of pharmacological sciences including drug design and the possible eco-toxicological characteristics of the drug molecules. The global electrophilicity index is proposed as $\omega = \mu 2/2\eta$. It measures the stabilization in energy when the system accepted an additional electronic charge from the environment. Electrophilicity is considered to be a better descriptor of overall chemical reactivity encompassing both the ability of an electrophile to acquire an additional electronic charge and the resistance of the system to exchange an electronic charge with the environment. It provides information on electron transfer (chemical

potential) and stability (hardness). As shown in **Table 1.** The lowest value of the energy gap is about 0.1764 eV corresponding to the fluticasone molecule, which indicates that this molecule is the most stable and reactive one compared with the other cortisol derivatives. The same molecule has the biggest value of ionization potential **(I)** and electron affinity **(A)**, with 0.2363 and 0.0599 eV, respectively. Also, this compound is suggested to be a soft molecule. On the other hand, it can be observed that the commercialized derivatives show more stability and biological reactivity than the original cortisol molecule.

As known, molecules with high chemical hardness have a little intramolecular charge transfer.in our case, this result is corresponding to the flunisolide compound. The electronegativity is a measure of attraction of an atom for electrons in a covalent bond. When two unlike atoms are covalently bonded, the shared electrons will be more strongly attracted to the atom of greater electronegativity.

The global electrophilicity index is about 0.1234 eV for the third compound, which ensures strong energy transformation between HOMO and LUMO. The HOMO and LUMO orbitals of the best compound (Fluticasone) are illustrated in **Fig 2**.

Table 1: Calculated E_{HOMO}, E_{LUMO}, energy band gap (ΔE), ionization energy (I), electron affinity(A), global hardness (η), global softness (σ), Chemical potential (μ), Electronegativity (χ) and global electrophilicity index (**ω**).

Compounds	E_{HOMO}	E_{LUMO}	ΔE	I	A	η	σ	μ	χ	ω
Budesonide	-0.2316	-0.0521	0.1795	0.2316	0.0521	0.0897	5.5741	-0.1419	0.1419	0.1122
Beclomethasone	-0.2335	-0.0563	0.1772	0.2335	0.0563	0.0886	5.6433	-0.1449	0.1449	0.1185
Mometasone	-0.2356	-0.0584	0.1772	0.2356	0.0584	0.0886	5.6433	-0.1459	0.1469	0.1201
Ciclésonide	-0.2268	-0.0479	0.1789	0.2268	0.0479	0.0894	5.5928	-0.1373	0.1373	0.1054
Flunisolide	-0.2353	-0.0576	0.1777	0.2353	0.0576	0.0898	5.5679	-0.1464	0.1464	0.1193
Dexamethasone	-0.2336	-0.0563	0.1773	0.2336	0.0563	0.0886	5.6433	-0.1450	0.1460	0.1187
Prednisolone	-0.2297	-0.0510	0.1787	0.2297	0.0510	0.0894	5.5592	-0.1403	0.1403	0.1100
Methylprednisolone	-0.2303	-0.0517	0.1786	0.2303	0.0517	0.0893	5.5991	-0.1410	0.1410	0.1113
Fluticasone	-0.2363	-0.0599	0.1764	0.2363	0.0599	0.0882	5.6689	-0.1481	0.1481	0.1243
Cortisol	-0.2268	-0.0416	0.1852	0.2262	0.0416	0.0926	5.3995	-0.1339	0.1339	0.0967

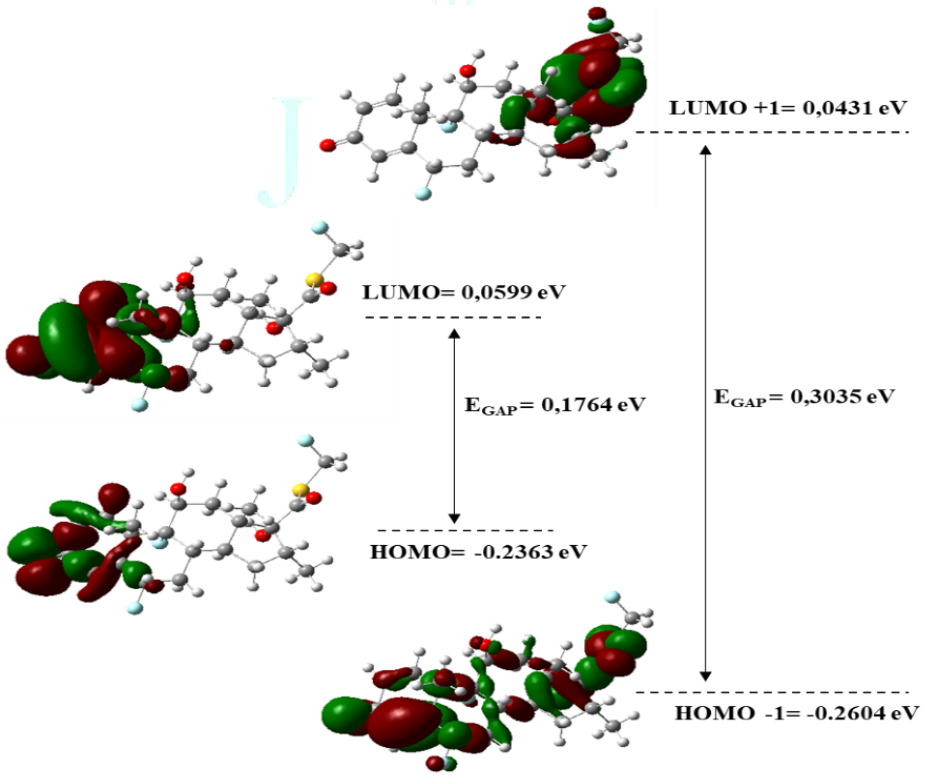

Figure 2: The frontier molecular orbitals density distributions for Fluticasone drug.

Molecular Electrostatic Potential

Molecular electrostatic potential (MEP) provides information on the molecular regions preferred or avoided by an electrophile or a nucleophile. indeed, any chemical system creates an electrostatic potential around it [17]. MEP has proven to be a very useful tool for studying the correlation between molecular structure and the physicochemical property relationship of molecules, including biomolecules and drugs [18]. When we take a hypothetical positive unit charge ' as a probe, it is 'volumeless' sed to feel the attractive or repulsive forces in regions where the electrostatic potential is negative or positive, respectively [19]. The different values of the MEP on the surface of the acids studied appear with the different colors [20]. Generally, the regions of the negatively charged molecule are colored in red while those with positive charge are colored in blue. The green color corresponds to an intermediate potential with zero charge located between the two extremes (red and dark blue) [15]. The yellow and light blue color divides the difference between the average color (green) and the extremes (red / dark blue) [21].

The MEP surface map of cortisol derivatives **Fig 3**, shows the two regions characterized by the color red (negative electrostatic potential) around the towing oxygen atoms which explain the capacity of an electrophilic attack on these positions, also, the blue color (positive electrostatic potential) around the three hydrogen atoms explains that these regions are susceptible to nucleophilic attack.

Finally, for the green color located between the red and blue regions, corresponds to the electrostatic neutral potential surface. The variation in the electrostatic potential produced by a molecule is largely responsible for the binding of a drug to its active sites (receptor) since the binding site in general should have opposite areas of electrostatic potential. As can be seen in **Fig 3.** the sulfur atom in the fluticasone molecule, presented with a yellow color, has a primary role in the interaction of the drug with the amino acids of the receptor sites.

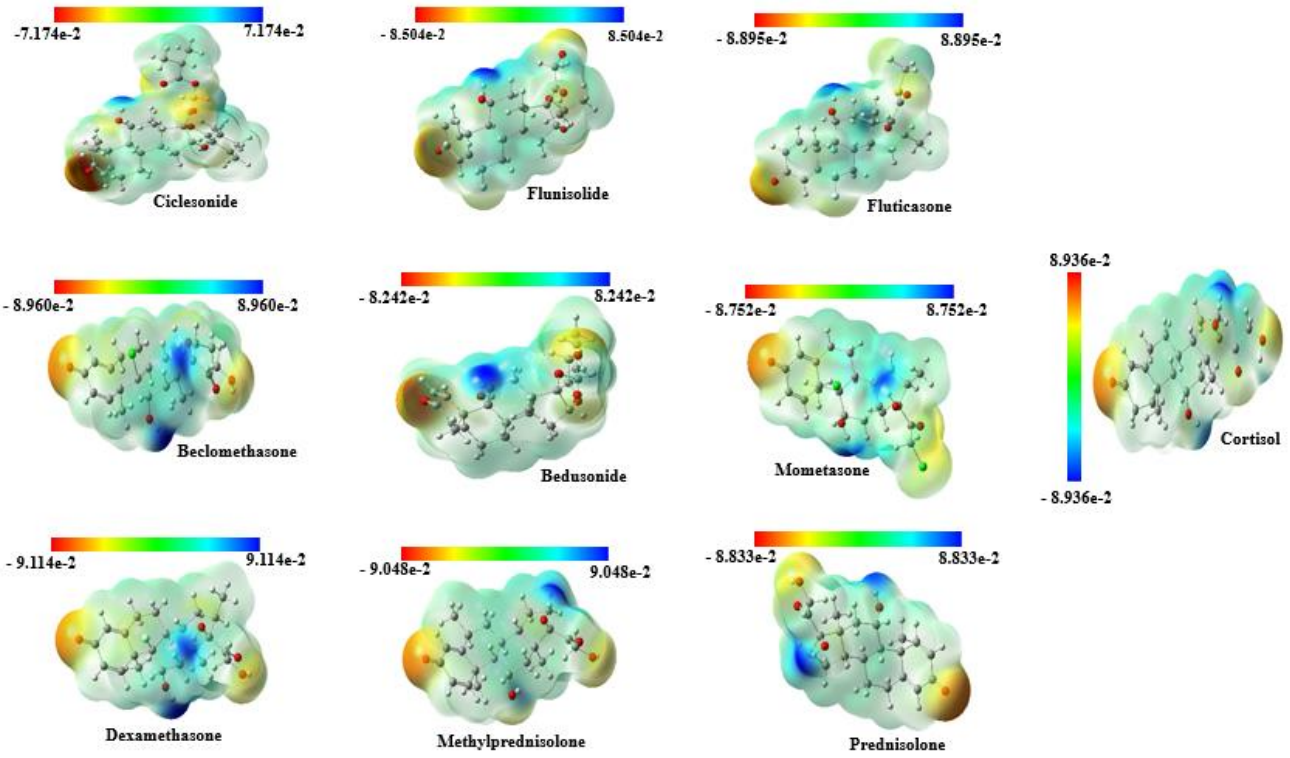

Fig 3. Representation of the molecular electrostatic potential MEP of the studied Steroidal Anti-Inflammatory Drugs. Parts of positive electrostatic potential are marked blue, and the negative electrostatic potential regions are red (**0.001 electron Bohr^{-3}/surface**).

Molinspirations Calculations

MiLogP (octanol / water partition coefficient) is a sum of contributions based on fragments and correction factors, this method, considered robust, can treat practically all organic molecules and most organometallic molecules. The TPSA molecular polar surface is calculated based on the methodology published by **Ertl et al**. as the sum of fragmentary contributions [22]. The polar fragments centered O and N are considered. PSA is a good descriptor used to characterize drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and penetration of the blood-brain barrier. The results for predicting the molecular properties of compounds 1-10 (TPSA, ligand GPCR and ICM) are evaluated and illustrated in **Table 2**. Also, to predict the bioavailability of drug molecules, Lipophilicity (logP value) and surface values polar (PSA) [22], were calculated for compounds 1 to 10 using Molinspirations software with a comparison with the values obtained for the standard drug. For all compounds, except for Ceclisonide, the calculated clogP values were approximately 1.41 - 3.54 (<5), which is the upper limit for drug penetration through biomembranes according to the rules of Lipinski. Thus, all these compounds have good bioavailability.

The lowest degree of lipophilicity among all the compounds was exhibited by compounds 1-10 indicating good solubility in water. The polar surface (PSA) is calculated from the surfaces which are occupied by the oxygen and nitrogen atoms and by the hydrogen atoms attached to them. Thus, PSA is closely linked to the hydrogen bonding potential of a

compound [23]. Molecules with PSA values of around 160 Å or more would show poor intestinal absorption [24]. indeed, all the compounds are within this limit. It should be noted that the log P and PSA values are not sufficient to predict the oral absorption of a drug [25]. To support this claim, note that all the compounds have respect the rule of 5, except for Ceclisonide which has two violations. As known, two or more violations of the rule of 5 suggest the likelihood of bioavailability problems [26]. The drug resemblance tabulated for compounds (**Table 2**) reflects a complex balance of various molecular properties and structural characteristics that determine whether a molecule is similar to known drugs. These properties, mainly hydrogen bonding characteristics, hydrophobicity, electronic distribution, flexibility, size of molecules and the presence of various characteristics of pharmacophores has an effect on the behavior of the molecule in a biological medium, including the bioavailability, reactivity, toxicity, protein affinity, metabolic stability, transport properties and many more. The activity of all standard compounds and drugs has been rigorously analyzed according to four criteria of successful drug activity known in the fields of the activity of the GPCR ligand, the modulation of ion channels, the activity of inhibition of kinase, nuclear receptor ligand, protease inhibitor and enzyme inhibitor. The results are presented for all the compounds in **Table 3**.

Table 2: Important pharmacokinetic parameters for good bioavailability of compounds [1-10]

Compounds.	Molinspirations calculations							
	Vol	TPSA	NROTB	HBA	HBD	LogP	MW	Lipinski's violations
Rule	_	_	_	**< 10**	**< 5**	**≤ 5**	**< 500**	**≤ 1**
Budesonide	403.00	93.07	4	6	2	3.19	430.54	0
Beclomethasone	366.68	94.83	2	5	3	2.36	408.92	0
Mometasone	372.19	74.60	2	4	2	2.92	427.37	0
Ciclésonide	512.74	99.14	6	7	1	5.65	540.70	2
Flunisolide	390.60	93.07	2	6	2	2.58	434.50	0
Dexamethasone	358.07	94.83	2	5	3	2.06	392.47	0
Prednisolone	331.01	91.67	2	5	2	1.41	358.43	0
Methylprednisolone	353.46	94.83	2	5	3	2.07	3.74.48	0
Fluticasone	378.07	74.60	3	2	4	3.54	441.51	0
Cortisol	343.36	94.83	2	5	3	1.62	362.47	0

Vol. volume; **TPSA.** Topological polar surface area; **NROTB.** number of rotatable bonds; **HBA**. number of hydrogen bond donors; **HBD**. number of hydrogen bond acceptors; **Log P**. logarithm of compound partition; **MW**. molecular weight.

Table 3: Bioactivity score of the compounds according to Molinspiration Cheminformatics software[1-10].

Compounds.	Drug-likeness					
	GPCRL	ICM	KI	NRL	PI	EI
Budesonide	0.21	-029	-0.64	1.27	0.27	0.67
Beclomethasone	-0.09	-0.40	-0.85	1.24	0.31	0.52
Mometasone	-0.17	-0.38	-0.80	1.24	0.25	0.45
Ciclésonide	-0.03	-0.53	-0.74	0.78	0.11	0.33
Flunisolide	0.08	-0.11	-0.48	1.49	0.45	0.70
Dexamethasone	0.03	-0.21	-0.81	1.59	0.76	0.78
Prednisolone	0.02	-0.12	-0.81	1.00	0.06	0.63
Methylprednisolone	0.07	-0.28	-0.72	1.22	0.30	0.71
Fluticasone	0.16	0.02	-0.65	2.00	1.04	0.90
Cortisol	-0.00	-0.29	-0.85	1.17	0.09	0.63

Osiris Calculations

Nowadays, structure-based design is very common, but because of ADME-Tox responsibilities, many potential drugs do not reach the clinic. A very important class of enzymes responsible for many ADMET problems is the cytochromes P450. Inhibition of these or the production of unwanted metabolites can lead to many adverse drug reactions. Thanks to recent work on drug design by combining various pharmacophoric sites using a heterocyclic structure, it is now possible to predict activity and / or inhibition with increasing success on two targets (bacteria and HIV) [27]. The risks of toxicity (mutagenicity, tumorigenicity, irritation, reproduction) and the physicochemical properties (miLogP, solubility, drug likeness and drug score) of compounds 1-10 are calculated by the methodology developed by Osiris and illustrated in Table 4. The toxicity risk predictor locates fragments in a molecule, indicating a potential toxicity risk. these alerts indicate that the structure drawn can be harmful concerning the specified risk category. According to the data evaluated in table 4, five of the ten compounds (budesonide, flunisolide, dexamethasone, methyl prednisolone, fluticasone) have structures supposed to be non-mutagenic, non-irritant and without effects on reproduction during the execution of l of mutagenicity by comparison with the standard drug used (Hydrocortisone). except for Mometasone which presents a great risk of tumorigenicity during reproduction with a slightly mutagenic structure due to the two chloride atoms. The logP value of a compound, which is the logarithm of its partition coefficient between n-octanol and water, is a well-established measure of the hydrophilicity of the compound. Low hydrophilicity and therefore high logP values can lead to poor absorption or permeation. Compounds have been shown to have a reasonable probability of being well absorbed, their logP value should not be greater than 5.0. On this basis, all compounds 1 to 10 have logP values within the acceptable criteria. At the same time, the right compounds, which have shown good results in screening for anti-inflammatory steroids, have the best drug score values (DS = 0.62 - 0.83), compared to the other compounds in the series.

Table 4: Osiris calculations of compounds [1-10].

Compounds	Toxicity Risks				Osiris calculations			
	MUT	TUMO	IRRI	REP	CLP	S	DL	DS
Budesonide					2.04	-3.82	1.69	0.67
Beclomethasone					1.98	-3.46	4.55	0.46
Mometasone					3.14	-4.37	4.01	0.18
Ciclésonide					3.69	-5.44	0.98	0.22
Flunisolide					1.30	-3.71	0.79	0.62
Dexamethasone					1.28	-3.25	3.17	0.79
Prednisolone					1.14	-2.95	4.09	0.85
Methylprednisolone					1.41	-3.11	4.16	0.83
Fluticasone					1.79	-4.41	4.32	0.66
Cortisol					1.41	-3.18	3.31	0.49

: Not toxic; : Slightly toxic ; : Highly toxic ; MUT : mutagenic ; TUMO : tumorigenic ; IRRI: irritant ; REP: reproductive effective ; CLP: cLogP ; S: Solubility ; DL : Drug-likeness ;DS : Drug-Score.

CONCLUSION

The present work provided additional structure–activity and structure–cytotoxicity information for the series of ten Anti-inflammatory steroids (AIS). Using DFT methods, the ground state structure was calculated using the B3LYP/6–31G(d) level of theory. Indeed, the relative stabilities, HOMO–LUMO energy gap and implications of the electronic properties were calculated and discussed with all compounds that are potentially able to cross biological membranes and to have a good oral bioavailability. The FMO theory offers good information about the reactivity of these compounds that are found to be in agreement with the literature that gives information about the relationship between the drug structure and its efficiency, which allows us to design new molecules. in order to get information about positive (nucleophilic attack) and negative (electrophilic attack) regions, MESP surface visualizations were performed. generally, this study aims to illustrate how the electronic and geometric characteristics can be useful in identifying all possible bioactivity of organic compounds. Moreover, the bioinformatic Osiris/Molinspiration analyses of the relative cytotoxicity of these derivatives are reported in comparison to Cortisol. From the theoretical calculations of the studied compounds, it can be resolved that the molecular structure influences on the inhibition efficiency.

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