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Theoretical Investigation of 3,4-Dihydropyrimidin-2(*1H*)-Ones Derivatives and in-Silico Biological Analysis

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Abstract: 3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) are heterocyclic compounds with a pyrimidine moiety in the ring nucleus which, in recent decades, have aroused interest in medicinal chemistry due to their versatile biological activity. DHPMs possess a broad range of pharmacological activities and are widely used in pharmaceutical applications. The variety of pharmacological aspects associated with DHPM derivatives includes being potential anticancer, anti-inflammatory, antioxidant and antimicrobial agents as well as having antimalarial and antitubercular effects. The 3,4-dihydropyrimidin-2 (1H) -ones derivatives were synthesized by the Bigineli method, which consists of an easy reaction that is widely used in organic synthesis, which occurs in a single step to obtain multifunctional heterocycles. The geometry of all the products are optimized using density functional theory method at the B3LYP/6-311G(d,p) level of theory using gaussian09 suit of programs. Quantum chemical parameters have been determined and examined. Molecular electrostatic surface potential (MESP) plot analysis has simulated in order to determine the predominantly reactive sites of nucleophilic or electrophilic attacks. On the other hand, global reactivity descriptors are calculated in the framework of conceptual DFT, to shed light to the more reactive molecule. The in-silico biological properties of compounds have been calculated and discussed.

Keywords: 3,4-dihydropyrimidin-2(*1H*)-ones, DFT, ADMET properties, Drug likeness properties.

Introduction

3,4-dihydropyrimidine-2(1H)-ones have attracted considerable interest due to a wide range of biological activities, including antitumor (Matias et al., 2016), antioxidant (Stefani et al., 2006), antibacterial (Ashok et al., 2007), antifungal (Singh et al., 2008), anti-inflammatory (Bahekar & Shinde, 2004) and anti-hypertensive properties by acting as calcium channel blockers (Atwal et al., 1991). 3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) are heterocyclic compounds with a pyrimidine moiety in the ring nucleus which, in recent decades, have aroused interest in medicinal chemistry due to their versatile biological activity. DHPMs possess a broad range of pharmacological activities and are widely used in pharmaceutical applications.In view of the biological significance of 3,4-dihydropyrimidin-2(1H)-ones, we tended in this study to pre-evaluate the ADMET properties, in the regard of the phsyicochemical properties and pharmacokinetics properties of each one of the investigated derivative.

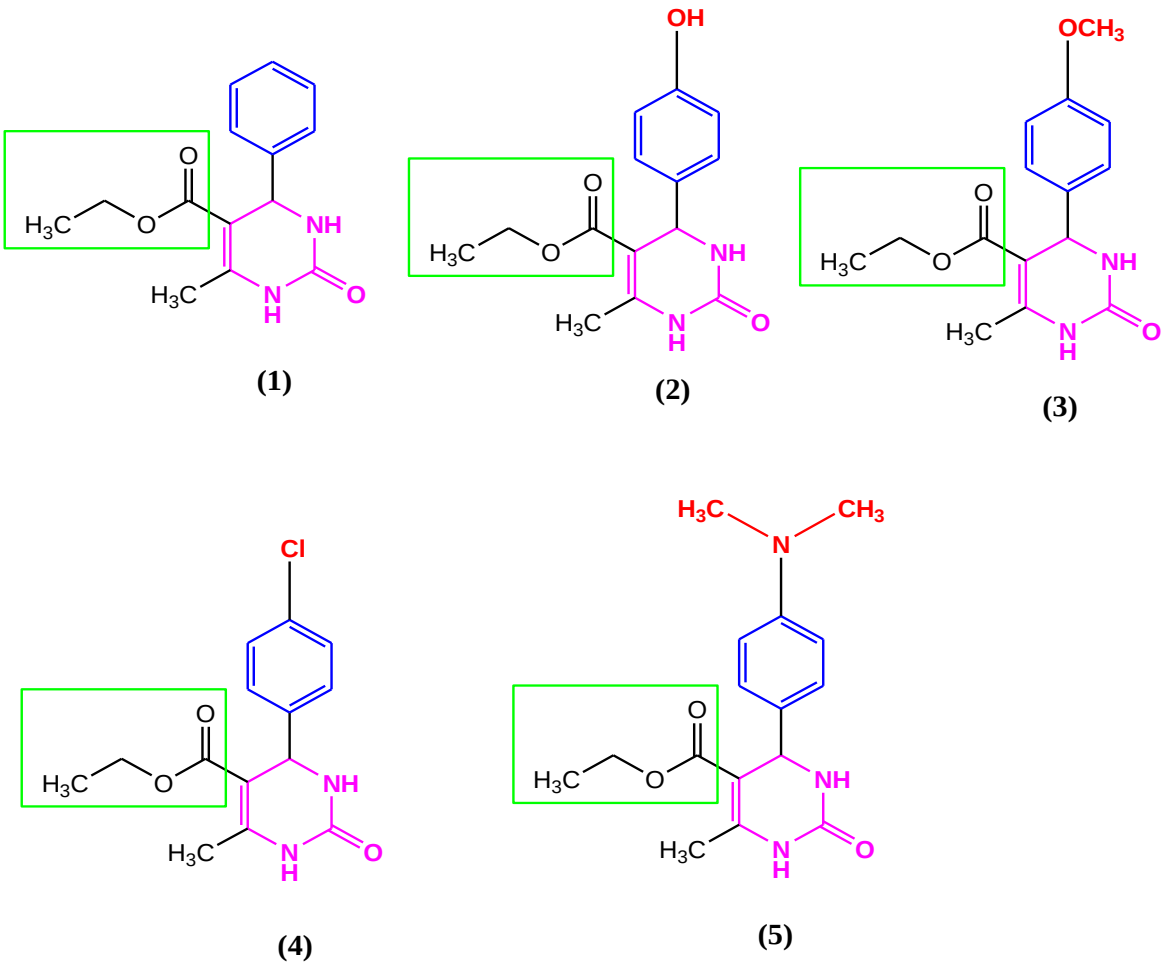

Figure 1. Strucrures under study.

Method

Computational Details

All the calculations were carried out using Gaussian 09 (Frisch, 2009) software package. The molecular geometry of the studied compounds were optimized using the density functional theory, within B3LYP (Becke, 1994) functional and the standard 6–31+G* basis set. Next, vibrational frequency are calculated on the obtained optimized geometries, to verify that no imaginary frequencies are present. GaussView (Hratchian, 2009) was used to visualize the optimized structure and to simulate the molecular electrostatic potential is surfaces.

ADMET Prediction

Phsyicochemical properties and Pharmacokinetics Properies such as Absorption, Distribution, Metabolism, Excretion and Toxicity of the molecular structure of 3,4-dihydropyrimidine-2(1H)-ones were studied via admetSAR (Yang et al., 2019) .

Results and Discussion

Optimized Geometries

The B3LYP/6-31G* optimized geometries of the 1-5 compounds are displayed in figure 2.

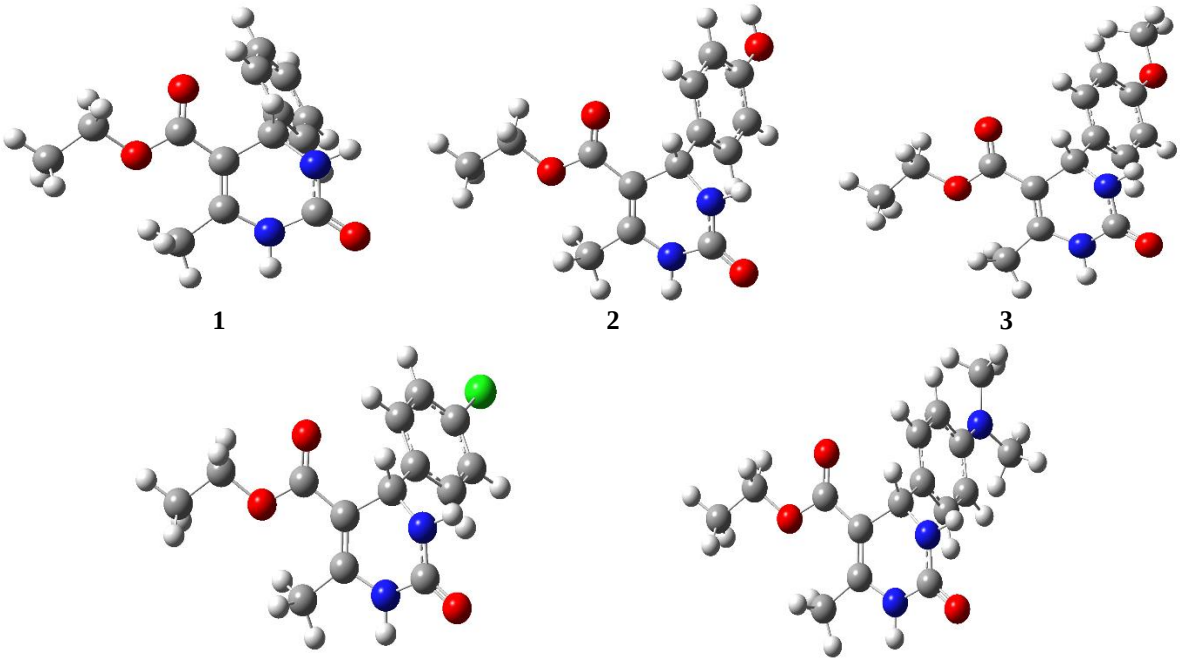

Figure 2. B3LYP/6-31G* optimized structure.

Molecular Electrostatic Potential Isosurfaces:

In order to check the regioselectivity of the studied compounds, simulated molecular electrostatic potential isosurfaces of the considered molecules are given in figure 2. The MEP is a graphical representation of the electrostatic potential as mapped on the surface of the electron density. The electrostatic potential indicates the progressive degradation of colors according to the scale: red < yellow < blue. According to the obtained results, the areas with the most positive electrostatic potential, is located around the hydrogen atoms of the pyrimidone, for all the studied compounds, representing the active sites for an nucleophilic attack. The red mapping surfaces reveal the predominantly negative nucleophilic zones, which is located mainly on the oxygen of the pyrimidone.

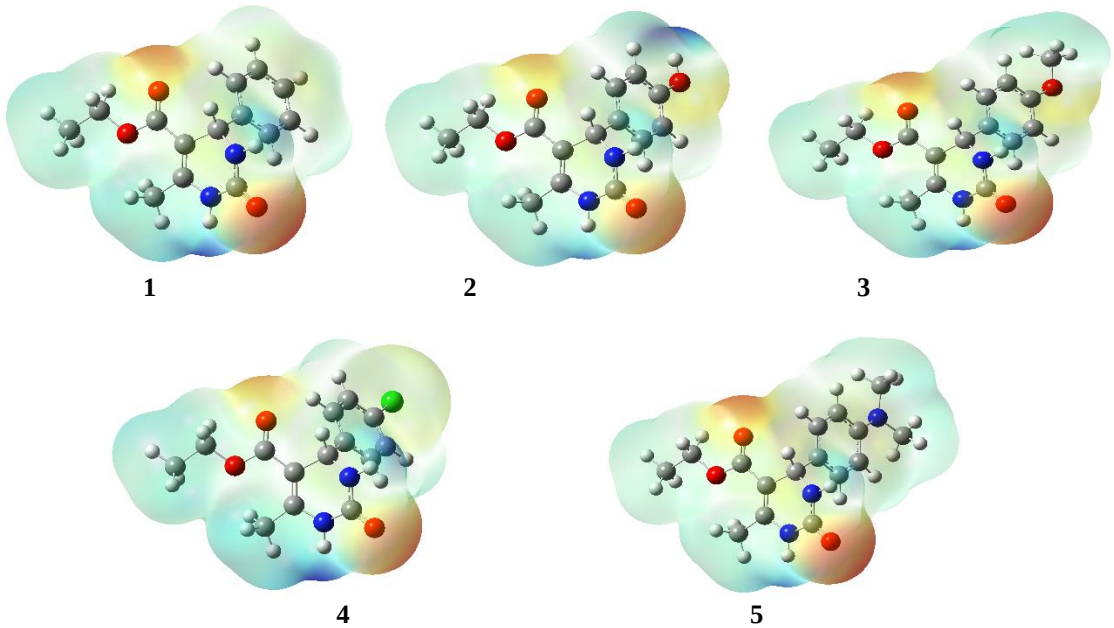

Figure 4. Molecular electrostatic potential isosurfaces of the studied compounds.The most negative potential corresponds to the areas coloured in bright red, while the regions with the most positive potential are indicated in blue.

HOMO-LUMO Energy

At the molecular level, the reactivity of a molecule is dominated by the HOMO and LUMO orbitals. A high HOMO-LUMO energy gap indicates that the molecular structure has lower chemical reactivity and high kinetic stability. On the contrary, lower HOMO-LUMO energy gap is a sign of higher chemical reactivity. The obtained HOMO-LUMO energy gap diagram is given in figure 3.

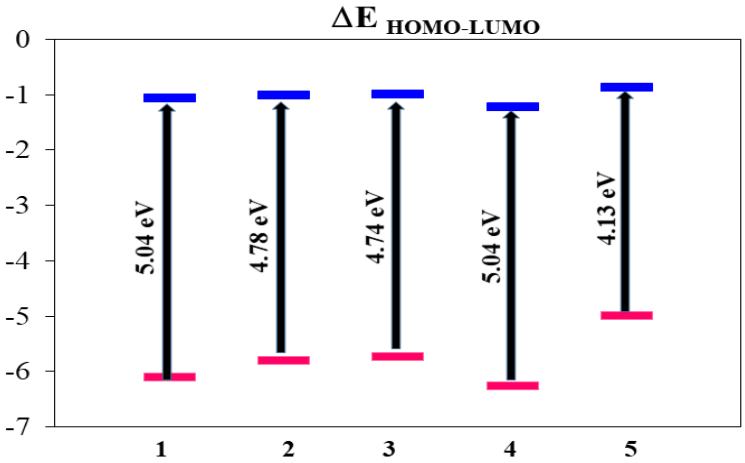

Figure 3. B3LYP/6-31G* calculated HOMO-LUMO energy gap.

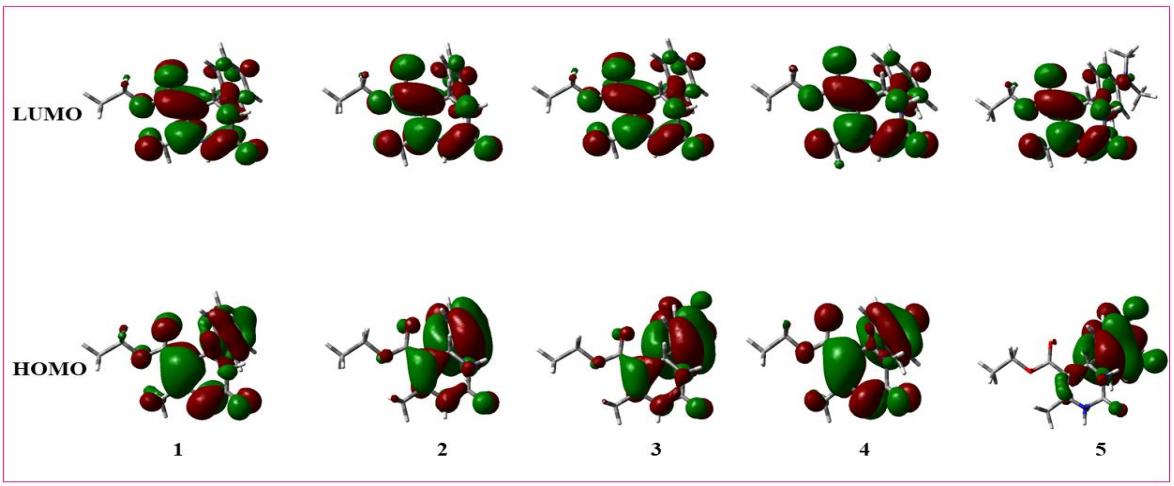

Figure 4. Frontiers molecular orbitals for the calculated molecules.

According to the calculated HOMO-LUMO energy gap of the studied molecules, it can be seen that the 5 compound have the less HOMO-LUMO energy gap (4.13 eV), it is the more reactive and the less stable due to the easy electron transfer from HOMO to LUMO. On the contrary, 1 and 4 present the higher H-L energy gap (5.04 eV), they are the less susceptible to electron transfer from HOMO to LUMO and thus less reactive and the more stable among the studied compounds.

Global Reactivity Descriptors

Global reactivity descriptors are crusial for describing the chemical reactivity of molecules. In this work we calculated chemical potential (μ), hardness (η), softness (σ) and electrophilic index (ω), (Manjeet, 2024; Khelifi and all, 2023) for the all the considered compounds at the B3LYP/6-31G* level (Table). Ionization potential (I) and electron affinity (A) are estimated as HOMO and LUMO proper values with negative energies.

Applying Koopmans' approximation, $A = -E_{LUMO}$; $I = -E_{HOMO}$.

Table 1. Calculated global reactivity properties: chemical potential (μ), hardness (η), softness (σ), electrophilic index (ω), for the studied compounds from B3LYP/6-31G* level of theory.

Cpd.	HOMO	LUMO	μ	η	σ	ω
1	-6.12	-1.08	-3.6	2.52	0.20	2.57
2	-5.81	-1.03	-3.42	2.39	0.21	2.45
3	-5.74	-1	-3.37	2.37	0.21	2.40
4	-6.27	-1.23	-3.75	2.52	0.20	2.79
5	-5.01	-0.88	-2.95	2.07	0.24	2.10

Chemical Potential

Chemical potential indicates the affinity of an electron to flee, it can be calculated as:

$$\mu = \frac{E_{HOMO}+E_{LUMO}}{2}$$

As chemical potential (μ) becomes more negative, removing the electron becomes very hard and easier to gain one. According to our results, we can conclude that the compound 4 possesses the highest chemical potential with μ = -3.75 eV, it is the less reactive compared to the others compounds. On the contrary, compound 5 is the least stable and the most reactive among all the compounds due to the low value of μ (-2.95 eV).

Chemical Hardness

Chemical hardness (η) is a reactivity descriptor that quantifies the resistance of a system to electron transfer.

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

From Table 1, we can see that the compounds 1 and 4 are characterized by the highest hardness value of 2.52eV and A by the lowest one (2.07 e2.07). These results indicate that 1 and 4 are highly stable and least active molecules while 5 is the least stable and highly reactive among other compounds

Chemical Softness

Chemical softness (σ) is another reactivity descriptor that complements chemical hardness.

$$\sigma = \frac{1}{2\eta}$$

A higher softness value indicates a more reactive and less stable system, and a lower softness value characterize a relatively stable and less reactive system. For the studied compounds, it can be see that 1 et 5 compounds with σ = 0.20 eV complements the high hardness value, they are the less reactive compounds. On the other hand, 5 has the highest σ equal to 0.24 eV making it a highly reactive and least stable compound.

Elctrophilic Index:

The electrophilic index (ω) is a reactivity descriptor that measures the electrophilic character of a molecule, it is calculated as:

$$\omega = \frac{\mu^2}{2(\eta)}$$

The results show that compound 4 has a higher value of the electrophilic index , ω = 2.79 eV, traducing a stronger electrophilic character and a greater tendency to accept electrons, while 5 present the lower of electrophilic index , ω = 2.10eV, suggesting a weaker electrophilic character and a reduced ability to accept electrons.

Table 2. ADMET prediction results of the fives 3,4-dihydropyrimidine-2(1H)-ones derivatives

	Physicochemical properties	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**
Lipophilicity	Log P	2.44	2.04	2.99	2.57	2.75
	H-bond donors	1	2	0	1	1
Hydrogen bonds	H-bond acceptors	3	4	3	4	3
Molecular weight	MW ($g.mol^{-1}$)	259.3	275.3	292.7	275.3	302.3
Flexibility	Rotatable bonds	4	4	4	5	5
Polarity	TPSA ($Å^2$)	55.40	75.6	43.3	64.6	58.64
Solubility	Log S	-2.19	-2.17	-5.17	2.44	-4.43
Saturation	Fraction of C sp^3	0.33	0.33	0.38	0.33	0.41
Pharmacokinetics properties						
Absorption	GI absorption	High	High	High	High	High
	Caco-2	Yes	No	Yes	Yes	Yes
Distribution	BBB permeability	Yes	Yes	Yes	Yes	Yes
Metabolism	CYP2D6 inhibitor	No	No	No	No	No
	CYP2C19 inhibitor	Yes	No	Yes	Yes	No
Excretion	Oct-2 ihnibitor	No	No	No	No	No
	Carcinogenicity (binary)	No	No	No	No	No
	Ames mutagenesis	No	No	No	No	No
Toxicity	hERG K+ channel inhibitor	No	No	No	Yes	Yes
	Respiratory toxicity	Yes	Yes	No	Yes	Yes
	Hepatotoxicity	Yes	No	Yes	No	Yes

ADMET Prediction

To confirm a drug and its efficacy as a top candidate against any disease, ADMET is essential. The partition coefficient (cLogP), donor hydrogen bond and drug similarity were calculated using physicochemical methods. Pharmacokinetic studies were also conducted for clinical trials of these derivatives molecules. The results are presented in Table 2.

The topological polar surface area (TPSA) should be less than <140 Å2 for significant oral bioavailability, our results showed good values of TPSA ranging between 43.3 $Å^2$ and 75.6 $Å^2$. Furthermore, the results descibes that all compounds showed high GI adsorption and Caco-2 permeability. Moreover, most of the molecules can be metabolized by the major cytochromes, except molecule (1), and derivatives containing chlorine radical (molecule 3) and methoxy radical (molecule 4). Moreover, all the molecules are non oct-2 -inhibitors, indicating a good excretion.

A drug candidate must first pass a toxicity risk assessment to be considered for drug development. Low toxicity and side effects indicate a high therapeutic index of the drug. For this reason, a toxicity prediction analysis was performed, the results indicate that all the molecules are anticarcinogenic and are non-AMES toxic. However only derivatives that contain methoxy radical (molecule 4) and amino radical (molecule 5) are hERG ihnibitors which indicates that they act as K+ channel blockers, known as anti-hypertensives. Interinstegly, the derivatives that cointain hydroxy radical (molecule 2) and methoxy radical (molecule 3) are presenting an anti-hepatotoxicity. And finally, only the derivative that contains chlorine radical (molecule 3) presented a non-respiratory toxicity.

Additionnaly of being anticancer, antihypertensive and anti-hepatotoxic agents as shown from the results above, literature have already revealed that for a majority of the analogues of 3,4-dihydropyrimidine-2(1H)-ones derivatives, their biological activity is affected by the lipophilicity (logP) and the nature of the substituents; For instance, in *Tale et al* study (Tale et al., 2011), it has been found that derivative having chlorine or fluorine as radicals in the para-position on the benzene ring, are having high lipohilicity, and presenting active IL-6 inhibitory effect at concentration of 10 uM, and hence they are considered as anti-inflammatory agents. In this study, molecule 3 is the best candidate for being an anti-inflammatory agent, due to its its chlorine radical in the para-position, and highest lipophilicity compared to the other molecules (Table 2)

Concerning the antibacterial and antifongic activities, *Tale et al* study (Tale et al., 2011) have revealed that antibacterial and antifongic potency against gram-positive *Staphylococcus aureus, Bacillus subtilis and* gram-negative *Escherichia coli and Salmonella typhimurium* and also molds including *Candida albicans , Aspergillus niger, Fusarium solani, Aspergillus flavus* is higher when the derivatives are bearing oxy-radicals in the para-

position and having a high H-Bond acceptor number. In this study, molecule 2 and molecule 4 are expected to have the greatest antibacterial and antifongic activities, bearing hydroxy and methoxy radicals, respectively.

Conclusion

In conclusion, 3,4-Dihydropyrimidin-2(1*H*)-ones 1-5 compounds are theoreticcaly studied at the B3LYP/6-31G* level of theory. The regioselectivity of the studied compounds is investigated using simulated molecular electrostatic potential isosurfaces. The results indicates that the active sites for an nucleophilic attack is the hydrogen atoms of the pyrimidone, and negative nucleophilic zones is located mainly on the oxygen of the pyrimidone. According to calculated global reactivity descriptors, we conclude that the 5 compound is the more reactive and the less stable one, and compounds 1 and 4 are the less reactive and the more stable among the studied compounds. In addition, calculated electrophilic index show that compound 4 is has the high electrophilic character and a greater tendency to accept electrons, while 5 present the weaker electrophilic character and a reduced ability to accept electrons.

The ADMET prediction study showed optimal physicochemical, pharmacological, and bioavailability, with estimating the biological activity of each derivatives of the studied of 3,4-dihydropyrimidine-2(1H)-ones derivatives, including anticancer, antihypertensive and anti-hepatotoxic, anti-inflamatory, antibacterial and antifongic activities. It was found that amongst all the compounds screened, derivative 3, besides of its non-respiratory toxicity and anti-hepatotoxicity, showed a promising tendency to be anti-inflammatory active. Derivatives 4 and 5 showed a tendence of being anti-hypertensives, while derivative 4 exhibited also possible antibacterial and antifongic activities, along with derivative 2 that showed also an anti-hepatotoxicity. Globaly, the ADMET results showed that the investigated 3,4-dihydropyrimidine-2(1H)-ones derivatives could be pontent biological active compounds, however, an In-vitro study is necessary for further investigation.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

Acknowledgements or Notes

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