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The Use of Factorial Planning in the Investigation of Structural Electronics Property for the Rational Design of Benzophenone Derivatives

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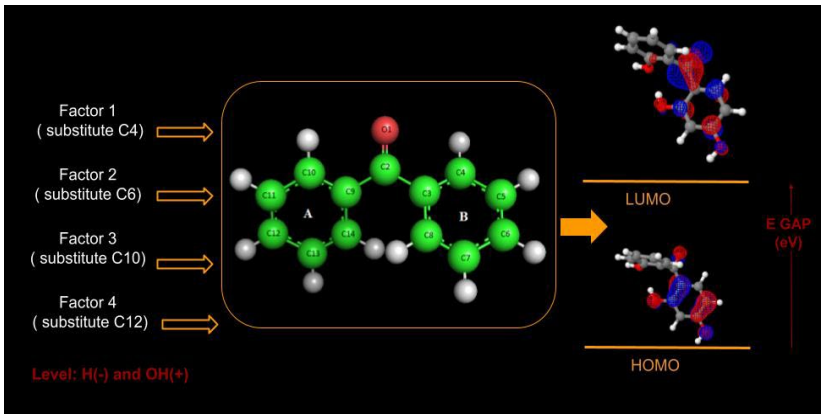
Human exposure to ultraviolet (UV) radiation leads photochemical excitation processes in the skin, causing problems to human health. The use of photoprotectors helps to minimize these intrinsic hazards. Benzophenone molecules stand out for the absorption of energy in the UVA and UVB range and structural changes in these, it is an area of interest to obtain safer and more effective molecules. This work applied the full factorial design methodology 2^4 in an investigation by molecular modeling using semi-empirical method PM7, in order to evaluate the impact generated on the decrease of the energy GAP with the insertion of OH (level +) and H (level –-). The results showed unfavorable and favorable contributions between interactions and in the main effect, and the compounds disubstituted in ortho and para position for the same aromatic ring showed a better percentage of contribution, indicating that these conditions are relevant for greater reactivity compared to the others. Thus, we conclude that the use of the experimental planning methodology is an ally in obtaining information for planning new protective filtersmore stable and safe.

Graphical abstract



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1. Introduction

Currently, computational design of active molecules and drugs is one of the most important components of medicinal chemistry [1]. As it involves an interactive process, it usually starts with a synthetic or natural prototype that has a certain

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biological profile and proceeds to optimize the activity and the route of synthesis of the compound [2, 3] However, this Research and Development process is costly, time consuming, and risky, since there is a high probability of failure [4]. In this sense, using computational and statistical tools for rational drug planning is a strategic and useful alternative in development processes, both in academia and in the chemical and pharmaceutical industries

Molecular modeling consists of a set of computational tools that reproduce the theoretical behavior of simple or complex molecules in specific environments, generating results of great quality, high speed and precision, graphic resources and low cost. There are different methods of calculations and the strategy to be used depends on the complexity of the systems and the objective to be achieved [2, 5].

Basically, computational methods are distinguished by the study of a set of energy functions and associated parameters, and are subdivided into Molecular Mechanics (MM) and Quantum Mechanics (QM). MM treats the molecule as spheres and springs representing the nucleus and bonds, respectively [2]. The calculations use the principles of classical Newtonian physics and take into account the set of force field of the nuclear positions, ignoring the movements of the electrons. The force field is usually constituted by the sum of terms of potential energy functions, related to the equilibrium positions of the system (bond distances, bond angles, torsion angles, electrostatic interactions, Van Der Waals interactions and repulsions), to which energy sanctions can be associated [3]. The great advantage of this method is in the speed when evaluating the most complex molecular systems, however, the results are limited by the quality and scope of parameters.

Quantum mechanics methods, on the other hand, allow for greater precision, but implies a higher computational cost (processing time and memory capacity). The method explicitly considers the interactions between nucleus and electrons, based on solutions of the Schrödinger equation. Developed by including the wave behavior of electrons in the energy calculation of the systems [6]. They provide good results of the electronic behavior of the molecule.

In general, two types of QM treatment are employed in molecular modeling, semi-empirical methods, which use minimal bases in calculations, considering only the valence electrons combined with theoretical and experimental information, which aim to increase the speed in the calculations; and the *ab initio* methods that treat all the electrons of the chemical system, as far as possible without approximations, and with more precise wave functions for the orbitals [2, 6].

Semi-empirical methods are also known as molecular orbital methods. Although they have lower accuracy than *ab initio*, numerous studies bring success in calculations of equilibrium geometry, enthalpy of formation, dipole moment, ionization potential, interatomic distance, electrostatic potential map, electronic density contour, energy and coefficients of the boundary orbitals HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital), lipophilicity, among others [7, 11]. Thus, making use of such tools as, for example, semi-empirical PM-7 methods (Parametric Method-7) [12], in the prediction of structural-electronic parameters of a series of molecules is an excellent alternative, to guide in the process of rational planning of molecules.

In our previous studies, molecular modeling has demonstrated to be a useful tool for the design of new sunscreens active, reproducing the experimental UV absorption spectra of benzophenone [13], triazine and benzotriazole [14, 15] derivatives, which are some of the important compounds classes of current organic UV filters, and plants biophenols, such as resveratrol and oleuropein [16].

Currently, photoprotective molecules have a key relevance in the cosmetic industry, once they help to minimize the dangers intrinsic to the exposure of human skin to ultraviolet radiation, which promotes photochemical excitations in dermal structures and can lead to harmful damage such as: erythema, damage to the peripheral vascular system, photoaging, burning, immune suppression, and skin cancer [17-20].

The products with photoprotection contain organic and inorganic UV filters as actives in the formulation. Each filter has a spectrum of UV radiation protection in specific wavelength ranges [19,20], to expand the protection against UV radiation some of these substances are associated [21] sometimes result in increased risk of photostability and phototoxicity [22].The well-known organic UV filters has on their the chemical structure and the presence of chromophore functional groups, usually represented by conjugated double bonds and the presence of aromatic rings in the molecule that can absorb of high frequency radiation energetic UVA (400-320 nm) and UVB (320-280 nm) by photochemical process [19-21].These wave frequencies correspond to a photon of energy that upon being absorbed is able to promote electronic excitation from a lower energy state to one of higher energy within the molecule. Thus, in photochemical absorption occurs the transfer of electrons from the HOMO (occupied orbital of higher energy) to the LUMO (empty orbital of lower energy) and, when returning to the ground state, release the excess energy. This energy will now be lower than the incident energy, and as the wavelength is inversely proportional, the process starts to emanate a higher wave vibrational frequency, less aggressive to the skin, in the form of heat [19,20]. However this absorbed energy can be dissipated or via chemical reaction, giving rise to photoproducts and/or intermediates that are potentially reactive with other molecules, including various biomolecules [22], generating phototoxicity.The energy absorbed in this process is the energy difference between HOMO-LUMO, also known as the GAP energy (E gap). This property brings relevant information as a measure of the excitability of molecules. The lower the GAP energy, the easier the electronic excitation is, that is, the greater the ease in the electronic transition from a lower energy state to a higher energy state [13, 23].

High value in GAP energy indicates high stability of a molecule, that is, low reactivity in chemical reactions, while molecules with low GAP value are generally more reactive. Thus, photochemical processes of energy absorption increase with decreasing GAP energy between the ground and excited state [19]. Thus, evaluating Egap provides a measure of the photoreactive potential of chemicals [22-24], an auxiliary tool for phototoxicity studies [25]. Other than that chemicals with a packet of larger Egap absorb smaller wavelengths (greater energy) and may exhibit lower reactivity [25].

Organic photoprotective molecules are essentially aromatic compounds with carboxylic groups, which have an electron donor group, such as an amine or a methoxyl group, in the ortho position of the aromatic ring [19]. Among these molecules, the benzophenone derivatives stand out. Formed by two aromatic rings linked by a carbonyl (ketone function)

they present a π→π* and n→π* transition and absorb two energy peaks in the UV range, usually one UVA and the other UVB. For this reason they are classified as broad spectrum filters [13, 19, 20].

Corrêa at all (2012) [13] performed a molecular modeling study of a series of benzophenone derivatives with electron-donating substituents (hydroxy, methoxy, ethoxy and amino derivatives), correlating the electronic structural properties to the UV spectrum, revealing that the insertion of ortho-substituted electron donor groups decreases the transition force, also known as oscillator strength, and relates to spectral absorption in the UVA range, while the para-substituted ones influence the increase of the transition strength revealing a relationship with absorption in the UVB range.

The chemical structure of benzophenones (Figure 1) allows the insertion of a multitude of substituents that can provide useful properties for the study of new sunscreens photostable. In this context, employing factor planning methodology for the study of a system with many variables, can help in choosing the best conditions and propositions to be studied, allowing a more detailed understanding of the answers.

Factorial planning is a statistical approach, which involves the construction of a combination of factors, chosen from among the parameters to be studied, to investigate the optimization of one or more variables under study [26]. Thus, it allows to obtain useful information, simultaneously evaluating the effect of a large number of variables in a reduced number of experiments.

There are different ways of building factor planning. Among the initial steps is the definition of the manipulable factors, which, in general, are the variables that are intended to be controlled; and the responses, which are the output variables of the system, and which will or will not be affected by the changes caused by the manipulable factors [27]. There are different ways to construct the factorial design, the simplest case is that in which each factor k is present in only two levels. In conducting an experiment with k factors on two levels, 2 x 2 x ... x 2 (k times) = 2^k observations of the response variable are made, and therefore this planning is termed complete factorial 2^k. This representation shows that, if two different levels are chosen for 3 factors (2^3), the number of different experiments to be performed will be 8 [28, 29].

The present work seeks to present the application of the methodology of factorial planning of the type 2^4, in an investigation by molecular modeling. Analyzing the impact generated in the difference in energy HOMO and LUMO (GAP) in molecules derived from benzophenone (BZF), which underwent structural change with the insertion of the hydroxyl group in different ortho and para positions of the molecule. Showing that the use of the experimental planning methodology allows to evaluate in advance the best conditions for the development of photoprotective molecules, minimizing still more computational costs and working time

2. Material and Methods

The structure of Benzophenone (BZF) was built in AVOGADRO ® program [30] followed by classical optimization employing different force fields: TRIPOS 5. 2, UFF (Universal force field), MMFF94 (Merck Molecular Force Field) and GAFF (General AMBER force field), in order to identify the conformational structure with global minimum of best RMSD (Root Mean Square deviation) compared to the crystallographic structure obtained by pubchem under CCDC code 118986 (BPHEN 011), using the alignment command in the PYMOL® program [31]. The selection of the appropriate force field for the investigation aids in the success of the conformational analysis, since the other calculated results will be dependent on the success of this process.

Once the force field was determined, we built the structures of the derivatives with the GHEMICAL® program [32], followed by optimization and random conformational analysis. The structures were subsequently optimized using the semi-empirical PM7 method, implemented in the MOPAC 2016 ® package [12], which conferred the structural-electronic properties. Parameters of the HOMO Energy (EHOMO) and LUMO Energy (ELUMO) were extracted and the data were submitted to Equation 1, which gives the values of the difference in HOMO-LUMO energy, or energy GAP (EGAP).

$$EGAP = EHOMO - ELUMO \qquad \text{Eq. 1}$$

The Fig 1 illustrates the Benzophenone molecule and the numbering system of the atoms that underwent substitutions in this study.

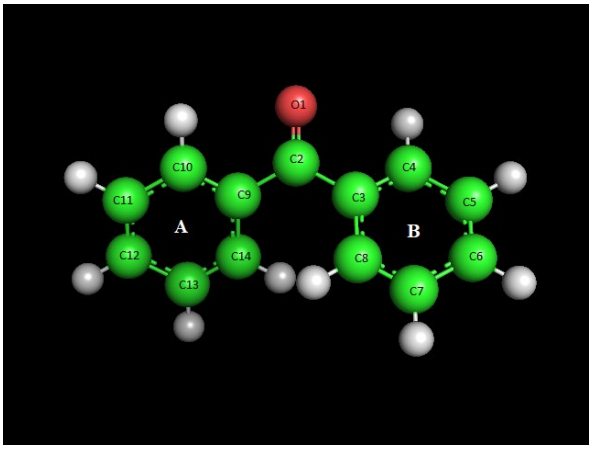


Fig. 1. Chemical structure of benzophenone (green spheres represent the carbon atom, red the oxygen and white the hydrogen atom).

2.2 Factorial Planning

The factorial design was obtained with the help of Excel® tools, using type 2^4 methodology, which consists of a minimum of 16 experimental trials with all possible combinations of factor levels of factors. The presence of hydroxyl (OH) substituents at the C4, C6, C10 and C12 positions of the benzophenone were determined as manipulable factors. The energy difference between HOMO and LUMO orbitals (EGAP (eV)) will be the responses, as shown in Table 1.

Table 1. Determination of factors, levels and response.

Factors		Level	
Factor 1	Substituint C4	H (-)	OH (+)
Factor 2	Substituint C6	H (-)	OH (+)
Factor 3	Substituint C10	H (-)	OH (+)
Factor 4	Substituint C12	H (-)	OH (+)
Response: EGAP (eV)			

The expected response of relevance in this study is in the impact generated by structural changes in the molecule with the insertion of the OH group (electron donor), here assigned to a level (+) and not replaced (H) level (-), in the contribution to the lower Egap.

Thus, it is expected that the lower the Egap, the greater the excitability of the proposed molecule, showing that the molecules can be more reactive to photochemical processes, alerting to a possible photoinstability with the insertion of the substituent. This feature may help to indicate the possibility of degradation of the molecule in the skin when exposed to UV radiation, compromising the safety of the UV filter.

3. Results and Discussion

The study of geometric optimization of the benzophenone molecule showed a variation in the RMDS of GAFF (RMDS = 2.502); UFF (RMDS = 2.498); MMFF4 (RMDS = 1.499) and TRIPOS 5.2 (RMDS = 1.482). Although all deviations are within acceptable values and and that there is no rigid rule to determine the best force field to be employed in research, we know that success in a computational analysis is dependent on accuracy in geometric calculations. Thus, we continue with the drawings and optimizations of the derivatives molecule by the computational package of Ghemical®, using the force field TRIPOS 5.2, which presented the lowest RMDS (Fig 2) in relation to the crystalline structure.

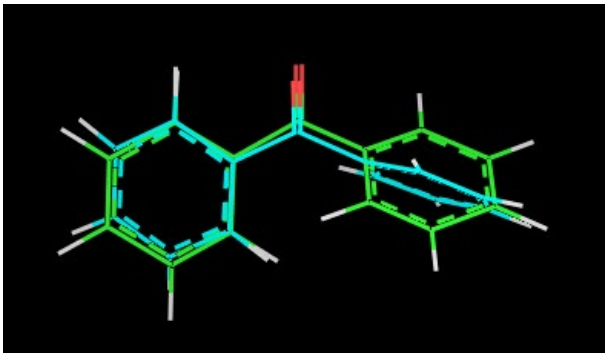


Fig. 2. Alignment of the crystallographic (blue) and optimized (green) structure of Benzophenone.

Factorial planning of type 2^4 followed the parameters stipulated in Table 1, in which the interest in discovering how Egap depends on the factors, which are the hydroxyl substitutions at the C4, C6, C10 and C12 position of BZF. To understand the effect of each factor on the given response we varied the levels and observed the results that this variation produces on the response. For a better understanding of the statistical calculations performed, we have the trials in the planning matrix in standard order, according to Table 2.

Table 2. Factorial planning matrix 2^4.

Derived	Test	1	2	3	4	GAP (1)	GAP (2)	Average
BZF	1	-	-	-	-	9.370	9.370	**9.370**
4-OHBZF	2	+	-	-	-	8.917	8.917	**8.917**
6-OHBZF	3	-	+	-	-	8.896	8.895	**8.896**
4,6-OHBZF	4	+	+	-	-	8.990	8.990	**8.990**
10-OHBZF	5	-	-	+	-	8.917	8.917	**8.917**
4,10-OHBZF	6	+	-	+	-	8.807	8.806	**8.807**
6,10-OHBZF	7	-	+	+	-	8.735	8.735	**8.735**
4,6,10-OHBZF	8	+	+	+	-	8.868	8.868	**8.868**
12-OHBZF	9	-	-	-	+	8.896	8.895	**8.896**
4,12-OHBZF	10	+	-	-	+	8.735	8.735	**8.735**
6,12- OHBZF	11	-	+	-	+	8.878	8.878	**8.878**
4,6,12-OHBZF	12	+	+	-	+	8.752	8.759	**8.756**
10,12-OHBZ	13	-	-	+	+	8.990	8.990	**8.990**
4,10,12-OHBZF	14	+	-	+	+	8.868	8.868	**8.868**
6,10,12-OHBZF	15	-	+	+	+	8.752	8.759	**8.756**
4,6,10,12-OHBZF	16	+	+	+	+	8.885	8.885	**8.885**

From the planning matrix, we formed the table of contrast coefficients by multiplying the signs of the appropriate columns to obtain the columns corresponding to the interactions (Table 3). The last column contains the average Egap values obtained in the trials. Considering the contrast coefficients for factor 2^4 and the possession of the mean Egap values obtained in each of the trials, we calculated the 15 interaction effects and the overall average according to Table 4, with four main effects, six interactions of two factors, four interactions of three factors and an interaction of four factors.

Next, analysing the results, it is evident that they are statistically significant at a significance level of 0.05 defined in this study. According to Table 4, all the effects showed a very low p-value, which means that the changes made in the molecules generate effects that implicitly interfere in the variation of the GAP energy.

The results also showed that the combined estimation of test variance and effect variance respectively gave extremely low values of 3.156 E^{-06} and 3.945 E^{-07}, which expresses the excellent accuracy and repeatability of the tests by the method used for computational calculations, confirming the precision of the method. The estimate of error of the

interaction effects corresponds to 0.06%.

Table 3. Contrast coefficients for a factorial 2^4.

Test	Average	1	2	3	4	12	13	14	23	24	34	123	124	134	234	1234	$\bar{y}$
1	+	-	-	-	-	+	+	+	+	+	+	-	-	-	-	+	9.370
2	+	+	-	-	-	-	-	-	+	+	+	+	+	+	-	-	8.917
3	+	-	+	-	-	-	+	+	-	-	+	+	+	-	+	-	8.896
4	+	+	+	-	-	+	-	-	-	-	+	-	-	+	+	+	8.990
5	+	-	-	+	-	+	-	+	-	+	-	+	-	+	+	-	8.917
6	+	+	-	+	-	-	+	-	-	+	-	-	+	-	+	+	8.807
7	+	-	+	+	-	-	-	+	+	-	-	-	+	+	-	+	8.735
8	+	+	+	+	-	+	+	-	+	-	-	+	-	-	-	-	8.868
9	+	-	-	-	+	+	+	-	+	-	-	-	+	+	+	-	8.896
10	+	+	-	-	+	-	-	+	+	-	-	+	-	-	+	+	8.735
11	+	-	+	-	+	-	+	-	-	+	-	+	-	+	-	+	8.878
12	+	+	+	-	+	+	-	+	-	+	-	-	+	-	-	-	8.756
13	+	-	-	+	+	+	-	-	-	-	+	+	+	-	-	+	8.990
14	+	+	-	+	+	-	+	+	-	-	+	-	-	+	-	-	8.868
15	+	-	+	+	+	-	-	-	+	+	+	-	-	-	+	-	8.756
16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	8.885

Table 4. Statistical results of the tests.

	Effects	Error	t(16)	*p*-value
Average	**8.8913**	±0.0003	28311.0	$5E^{-63}$
1	-0.0764	±0.0006	121.693	$4E^{-25}$
2	-0.0921	±0.0006	146.568	$2E^{-26}$
3	-0.0764	±0.0006	121.693	$4E^{-25}$
4	-0.0921	±0.0006	146.568	$2E^{-26}$
12	0.1351	±0.0006	215.027	$4E^{-29}$
13	0.0839	±0.0006	133.633	$8E^{-26}$
14	0.0076	±0.0006	12.0399	$2E^{-09}$
23	0.0076	±0.0006	12.0399	$2E^{-09}$
24	0.0384	±0.0006	61.1947	$2E^{-20}$
34	0.1351	±0.0006	215.027	$4E^{-29}$
123	-0.0113	±0.0006	18.0101	$5E^{-12}$
124	-0.0627	±0.0006	99.8022	$9E^{-24}$
134	-0.0113	±0.0006	18.0101	$5E^{-12}$
234	-0.0627	±0.0006	99.8022	$9E^{-24}$
1234	0.0647	±0.0006	102.986	$5E^{-24}$

Table 5 and Graph 1, demonstrate the distribution of the main effects and the interactions of the effects that describe the response. A response that disadvantages the decrease of GAP energy in relation to the global average was observed in all main effects and in the interactions with three factors. While the favorable effect of the GAP decrease was observed in the interactions between two and four factors. These data show that the response depends on the levels of the substituents as well as the positions at which the substitution occurs.

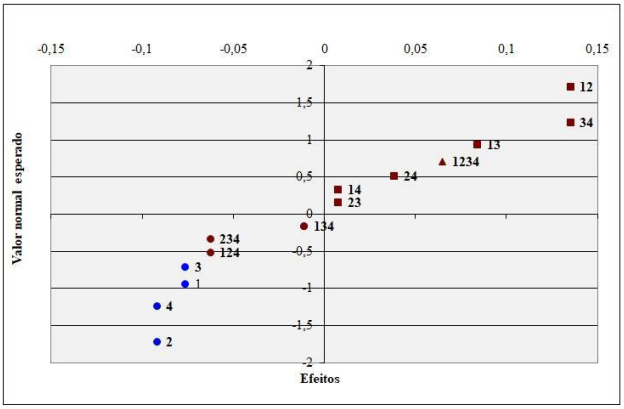
The factorial design shows that among the main effects, effect 2 and 4, which correspond respectively to the derivatives 6-OHBZF and 12-OHBZF (identical molecules), para-substituted showed a favorable contribution to increase the energy GAP by 9.21% ± 0.06. On the other hand, the main effects 1 and 3, referring to 4-OHBZF and 10-OH-BZF (identical

molecules), (ortho-substituted) confer an increase in energy GAP by 7.64% ± 0.06 in relation to the global average obtained. This corresponds to say that modifications with substituent OH (electron donor) in positions for makes the molecule more stable and less likely to absorb energy for transition from the fundamental to the excited state compared to the ORTO substituent.

Table 5. Main effects, interaction effects, and overall average.

Average Global: 8.886 ± 0,031%			
Main effects			
1	substitute OH- R1		**-0.0764 ± 0.0006**
2	substitute OH- R2		**-0.0921 ± 0.0006**
3	substitute OH- R3		**-0.0764 ± 0.0006**
4	substitute OH- R4		**-0.0921 ± 0.0006**
Interaction between two factors			
12	**0.1351± 0.0006**	**13**	**0.0839± 0.0006**
14	**0.0076 ± 0.0006**	**23**	**0.0076 ± 0.0006**
24	**0.1299 ± 0.0006**	**34**	**0.1351 ± 0.0006**
Interaction between three factors			
123	**-0.0113 ± 0.0006**	**124**	**-0.0627 ± 0.0006**
134	**-0.0113 ± 0.0006**	**234**	**-0.0627 ± 0.0006**
Interaction between four factors			
1234			**0.0647 ± 0.0006**

Graph 1. Distribution of main effects (blue) and interactions (red).



All the effects of the interactions of three factors also showed results that favor an increase in Egap. The effect observed in interactions 124 and 234, which corresponds to derivatives 4,6,12 OHBZF and 6,10,12 OH BZF was 6,27% ± 0,06 in relation to the global average, a contribution relatively close to the ortho-monosubstituted one. When comparing interactions 123 and 134, which express derivatives 4,6,10-OHBZF and 4,10,12-OHBZF, respectively, show a relatively small contribution to the increase in GAP energy (1.13% ± 0.06).

Finally, when replaced all the suggested positions 4,6,10,12-OHBZF by OH (1234 interaction), there was a decrease in the energy gap, at a favorable contribution of 6.47% with an error estimate of ± 0.06%, but did not show the best result.

The analysis of the contributions to the reduction of GAP energy were all observed in the interactions of two factors and four factors, showing that these input variables in the study are relevant to the expected response. We observed that the OH-di-substituted benzophenones in the para position of aromatic ring A and in the orto position of aromatic ring B (6,10-OHBZ and 4,12-OHBZF), interactions 14 and 23 have lesser effects in reducing GAP energy (0.76% ± 0.06), making these di-substituted molecules less reactive. The interaction 13, corresponding to the 4,10-OHBZF derivative that presents the substitution in the orto position of the A and B rings shows a favorable effect in reducing Egap of 8.39%.. When the disubstitution is present in the para position of the two rings (interaction 24) the contribution becomes more pronounced, with an effect of 12.99% ±0.06% in relation to the overall average. The best result presented for the reduction of energy GAP was observed in interaction 12 and 34, in which the di-substitution by the hydroxyl group was performed in the orto and para position of the same ring (4,6-OHBZF and 10,12 OH-BZF), with a favorable effect of 13.51% for Egap reduction in relation to the global average.

This already consolidated by organic chemists that the insertion of electron donor group in an aromatic structure, by inductive effect, increases the electronic density of the molecule, increasing its reactivity with decreasing the difference in energy HOMO and LUMO (GAP). The study in question showed that although all derivatives have a lower energy GAP than unsubstituted benzophenone (E gap = 9.370 eV), the main effects and interactions between factors (insertion of the hydroxyl group in the different ortho and para positions of the benzophenone) showed unfavorable and favorable contributions to the reduction of Egap, signaling that the interaction of two electron donating factors in ortho and para position of the same aromatic ring offers greater impact for the decrease in energy GAP, making the molecule more

unstable, more reactive and more susceptible to photochemical absorption processes.

From these data, we believe that the use of the statistical tool of factorial planning combined with molecular modeling studies of electronic structural characteristics can help in the prediction and rational design of new molecules with greater stability and less reactivity to photochemical effects assisting in *vitro* and *in vivo* research on phototoxicity.

4. Conclusions

In the present work, the factorial design showed that there is a significant impact of the substitution of the hydroxyl radical (proton donor) in the BZF molecule according to the level of the substituent, allowing to evaluate the best conditions when making changes in the structure. The most accentuated favorable contributions to the decrease in Egap were observed in the OH-disubstituted derivatives in ortho and para positions of the same aromatic ring of benzophenones, certainly the presence of electron donor groups in these positions favor the inductive effect and the participation in the electronic resonance in the structure of the molecule, providing faster excitability and reactivity of the molecule.

In this sense, we show that the use of statistical factorial planning tools help in proposing in silico future photoprotective compounds that are more stable to photochemical degradation reactions, suggesting less phototoxicity, ensuring effectiveness and safety in the development of new UV filters.

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Author Contributions

Fabiana Passamani - Conceptualization, Investigation, Methodology, Formal analysis and writing - Original draft preparation; Isadora Auróra Guerra - Investigation, Formal analysis and Methodology. Paulo Roberto Filgueiras, Bianca Aloise Maneira Corrêa Santos and Arlan da Silva Gonçalves – Supervision and Formal analysis. All authors contributed for the review and editing of the manuscript.

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