biology and life sciences forum

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Proceeding Paper

Getting into Structure-Activity Relationships of Ecdysteroids for Plant Protection Strategies against Insect Pests †

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† Presented at the 2nd International Electronic Conference on Plant Sciences—10th Anniversary of Journal Plants, 1–15 December 2021; Available online: https://iecps2021.sciforum.net/.

Abstract: The transformations of insects, and typical invertebrates, during the larval states (metamorphosis) in their life's cycle is an example of the chemical signals system in the cell-internal control mechanisms. The ecdysone, following the classic steroids action mechanism, controls the morphogenesis and metamorphosis and its chemical reactivity, as a quantitative term, depends of optimum geometric, electronic and chemical properties. Ecdysteroid activity of several naturally occurring and synthetic steroidal derivatives, have been studied previously and some results have been achieved. This communication intends: 1-Quantitative determining which are the key structural points of the ecdysone molecule and analogues that trigger the bio-functional action, starting from the structure-activity relationship and the analysis of electronic properties, using a very simple protocol, and, 2-Propitiating a mathematical-statistic tool that allows to discriminate most active molecules from the less active ones, optimizing the synthesis of steroidal analogs with defined ecdysteroid action, useful for applying in field conditions for controlling insect pests which affect the crop yields.

Keywords: ecdysteroids; structure-activity relationship; synthesis; plant protection; steroids

Citation: Tacoronte Morales, J.E., Quiñonez, R., Bedoya Flores, M., Espinal Santana, N., Cruel Sigüenza, J. Getting into Structure-Activity Relationships of Ecdysteroids for Plant Protection Strategies against Insect Pests. *Biol. Life Sci. Forum* **2021**, *1*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Antonella Vitti

Published: 30 November 2021

1. Introduction

The evolution of the organisms is a result of a complex and changing interactions (*geno* and *pheno*) with environment at a global planetary scale and population level. The cell, biological unit formed by a "powerful and extraordinary efficient chemical machinery" for providing it with energy, self-maintenance, exchange of materials with the exterior and amazing chemical signal system for communication (intra and inter), is not autonomous completely in its functions, even, in unicellular organisms. The multicellularity concept is necessary to guarantee a successful cell operation, which allows a more efficient specialization of the plasma in continuously changing environmental conditions During the development's process three fundamental points define, evolutionarily, the success of it: **1**. the cell-internal control mechanisms, **2**. external control of the cell, and **3**. links between the environment and genes. This "social control" is a guarantee of homogenous development of entire organism [1,2].

The transformations during development of insects, and typical invertebrates, during the larval states (metamorphosis) in their life's cycle is an example of the chemical signals system and mentioned above point 1. The ecdysone, the so-called "moulting and metamorphosis" hormone, following the classic steroids action mechanism [3], is produced by the prothoracic glands, after activation induced by neuropeptides [4]. This compound (and its derivatives) controls the morphogenesis and metamorphosis, jointly with juvenile hormones [5].

In biological systems where target-compound interactions define the physiological functionality, the chemical reactivity is a quantitative term, and it depends of optimum geometric and physic-chemical properties. Ecdysteroid activity of several (>300) naturally occurring and synthetic steroidal derivatives, starting from ecdysone, have been studied in the past 20 years [6]. However, the structural elements required for the hormonal activity are not clear. Therefore, this communication intends as objectives: 1-Quantitative determining which are the structural key points of the ecdysone and analogues molecule that trigger the action of the biological machinery, starting from the relationship structure-activity and of the analysis of electronic properties, using a very simple protocol, and, 2-Propitiating a mathematical-statistic tool that allows to discriminate against the most active molecules from the less active ones, optimizing the synthesis of steroidal analogs with defined ecdysteroid action, useful for applying in field conditions for controlling insect pests which affect the crop yields.

2. Materials y Methods

The study of the ecdysteroid molecules was carried out starting from elaborated designs in HYPERCHEM software, being carried out a first geometry optimization with molecular mechanics (MM3). The quantum calculations were made at semi-empirical level using PM3 formalism with MOPAC 6 program. And scheme mentioned before, first, the geometric structure of ecdysone was optimized and later functional groups were added or rest depending on the wished analogue and optimized again. HYPERCHEM 5.02 was used for illustrating the molecular orbitals as well, with ZINDO/S option.

After that, molecular properties such as: Ionization potential; energy of frontier orbitals (HOMO and LUMO), and contiguous orbital from HOMO-1 to −5, and from LUMO +1 to 3; atoms of higher contribution to these molecular orbitals; oxygen atoms with contribution to the HOMO-3 y HOMO–4 orbitals; spatial distribution of HOMO, LUMO and HOMO-3 orbitals; distances between intermolecular atoms, valence and torsion angles (τ) among all ring's atoms in the molecules; charge of each of atoms, were calculated. At the end of calculus, 167 variables per molecule were fruitfully available [7].

A statistical analysis on the analogues and ecdysone (Figure 1), mean statistical characterization from geometrical, and quantum point of view, was done. Therefore, try to discriminate the variables implicated on biological activity. The statistical analysis was carried out with descriptive and decisional techniques like cluster analysis, discrimination analysis with Lambda of Wilks methods, and T test (everything was made with SPSS statistical package). Every computer calculus was done on IBM-PC Dual Pentium II, 750 MHz, 1 Giga of RAM memory.

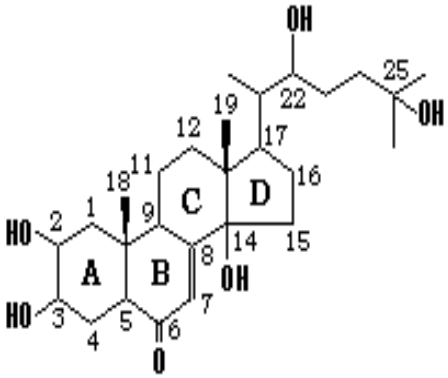

Figure 1. Ecdyzone and structural core with atom numeration used.

3. Results and Discussion

The analysis of presence/absence of OH groups and others functional groups was the first step. The existence of OH in the position C22 (Figure 2) and the functional

relationship of the OH in the position C5 and C14 are of hardly importance for making a discrimination between active and no active molecules. However, these variables do not guarantee of a strong discrimination. It seems to be that the existence, or not, of functional groups (generally OH) do not contribute a total explanation of a functional dependence between the structural properties and the biological activity [8].

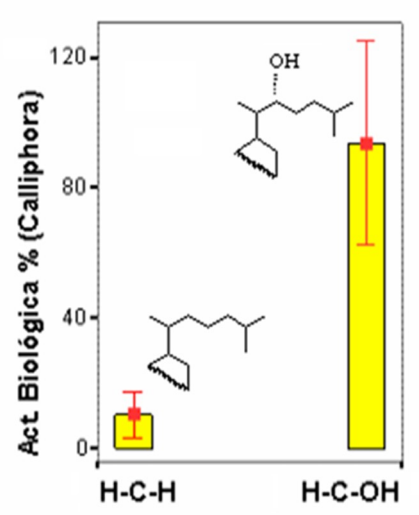

Figure 2. Biological activity with or without α OH in C22 (t = 0.04517).

By this way let to demonstrate which functional groups are fundamental cause of increment in the biological activity of a given molecule. However, is obligatory to make analysis where other properties refer to the whole molecule are included; therefore, the remaining causes for quantifying the relation structure-function could be solved.

Simple, and quick, research on computational chemistry was necessary for getting into geometric and quantum descriptors. Hence, a rigorous chemical-biological functional analysis through statistical and mathematical methods was begun.

Using a discriminate analysis were determinated structurally important variables for the functional dependence between ecdysteroids and their biological activity:

*-Distance O3-O22; O22-HOMO3;
*-Ang 2,3,4; Ang 8,9,10;
*-Distance C2-C3;
*-O3 atom with mayor contribution to HOMO-3;
*-Charge (q) at C16.

Later, a regression equation [F = 0.00461009; R^2 = 0.873467] was found in order to make an approximation of free energy of ligand-receptor binding [ΔG^0_{bind}] [9,10], resulting in a general equation:

$$\textbf{Log (Y-0.5)} = -46.184 + 1.356\ (\text{O22-HOMO3}) + 0.483\ (\text{O3-HOMO3}) + 0.398\ (\textit{Dist}.\ \text{O3-O22}) + 21.902\ (\textit{Dist}.\ \text{C2-C3}) - 0.258\ (\textit{Ang}.\ 2,3,4) + 2.229\ (\textit{Ang}.\ 8,9,10) - 94.714\ (q16)$$

If:
Dist. O3-O22 is x; *Dist*. C2-C3 is y; *Ang*. 2,3,4 is z; *Ang*. 8,9,10 is v and q 16 is w
The equation becomes in:

$$Y = 10^{-46.184+1.356\ (\text{O22 HOMO3})+0.483\ (\text{O3 HOMO3})+0.398x+21.902y-0.258z+0.229v-94.714w}$$

The derivatives analyzed are typical polyhydroxy compounds and are characterized by their capacity to generate H-bonds (3 Kcal/mol). Such bonds can, via stereochemical orientation of the OH groups, determine some functional properties as specific enzyme

activities [11]. A little view of this equation is enough for recognizing very precise and coincident properties, regions and atoms on these molecules (Figure 3).

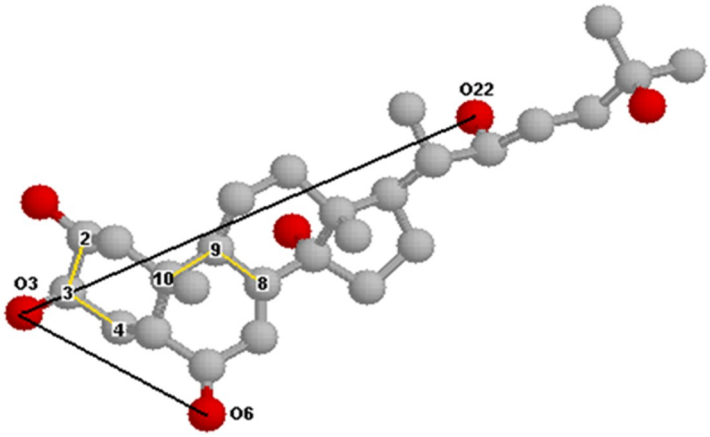

Figure 3. Spatial representation of the main molecular variables in ecdysteroids related with their biological activity. Interatomic distances (represented by black lines), angles (represented by yellow lines), the atoms O3 y O22 are key contributors to HOMO-3 orbital and the O6 is the major key contributor to HOMO.

From the results is inferred that for making a prediction of biological activity from the molecular structure: 1-Some functional groups, and sub-structural units, are indispensable as part of the molecule. 2-Whenever, the spatial distributions of them are important to carry out any biological reaction (interaction target receptor-ecdysteroid compound). Additionally, 3-these selected functional groups should contribute to properties of the whole molecule (e.g., the contribution of the atoms O3 and O22 to molecular orbital HOMO-3). Necessarily, the regularities of different kind of reaction between ligand and receptor should be take into account.

In fact, there is coincidence with [12] as well, oxygen atoms are important but, from the spatial point of view, not all of them. It is not necessary a space orientation of all oxygen atoms to carry out a reaction with the enzyme or receptor. The ligand, a plane molecule of steroid, won't need more than two bindings with the receptor for not spending unnecessary energy in bonds.

If the hydroxyls (-OH) perform a function on electronic structure of the molecules [13], then, we should not reduce the influence from these atoms to simple spatial disposition. Once bond the molecule by O22 position a distance restriction respect from this point will be necessary, and O3 bond is more probably, chemically.

Finally, using a very simple computational protocol, and taking in consideration the data reported, the process of ecdysteroid molecule binding to receptor is develop in the following way: ***Side Chain binding/A, B-ring acting***, similar to other steroids [14]. The results, derived from this research, currently, are applied in the synthesis of polyhydroxy- and keto spiro-steroidal derivatives, starting from steroidal sapogenins, with quite remarkable ecdysteroid activity and applicability in eco-sustainable conditions, for controlling insect pests and vectors. The synthetic protocol and evaluation of ecdysteroid activity, will be published soon.

Author Contributions: Conceptualization J.E.T.M. and J.C.S.; methodology, J.C.S. and J.E.T.M.; software, M.B.F.; validation J.C.S., J.E.T.M. and R.Q.; investigation and resources, J.E.T.M., N.E.S.; writing—original draft preparation, review and editing R.Q. and J.E.T.M.; visualization and supervision, M.B.F. and N.E.S.; project administration J.E.T.M. and J.C.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Sincere and profound thanks are extended to Noel Ferro for his invaluable considerations and pioneering research, more than 20 years ago, in this fascinating field of research in structure-activity relationship of bioactive compounds. The authors would like to thank Technical University of Esmeraldas, Ecuador, for its logistical support.

Conflicts of Interest: The authors declare no conflict of interest. The Technical University of Esmeraldas, Ecuador, had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. Authors declare that the research done is for pedagogical purposes only, and for comprehension of significance of computational chemistry, and its implementation, as a tool for designing new molecular entities.

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