ЕҢБЕК ҚЫЗЫЛ ТУ ОРДЕНДІ
«Ә. Б. БЕКТҰРОВ АТЫНДАҒЫ
ХИМИЯ ҒЫЛЫМДАРЫ ИНСТИТУТЫ»
АКЦИОНЕРЛІК ҚОҒАМЫ

ҚАЗАҚСТАННЫҢ ХИМИЯ ЖУРНАЛЫ

ХИМИЧЕСКИЙ ЖУРНАЛ КАЗАХСТАНА

CHEMICAL JOURNAL of KAZAKHSTAN

АКЦИОНЕРНОЕ ОБЩЕСТВО
ОРДЕНА ТРУДОВОГО КРАСНОГО ЗНАМЕНИ
«ИНСТИТУТ ХИМИЧЕСКИХ НАУК
им. А. Б. БЕКТУРОВА»

4 (72)

ОКТЯБРЬ – ДЕКАБРЬ 2020 г.

ИЗДАЕТСЯ С ОКТЯБРЯ 2003 ГОДА

ВЫХОДИТ 4 РАЗА В ГОД

АЛМАТЫ
2020

UDC 547.314+543.422+547.918

B. S. TEMIRGAZIEV[1,2], L. K. ABULYAISSOVA[1], A. M. KOZHANOVA[2], U. B. TULEUOV[1], A. K. DAYROV[2], P. K. KUDABAYEVA[2],YE. V, MINAYEVA[1], T. M. SEILKHANOV[3], B. I. TULEUOV[2], S. M. ADEKENOV[2]

[1]Y.A. Buketov Karaganda State University, Karaganda, Republic of Kazakhstan;
[2]International Research and Production Holding "Phytochemistry", Karaganda, Republic of Kazakhstan;
[3]Sh. Ualikhanov Kokshetau State University, Kokshetau, Republic of Kazakhstan

QUANTUM-CHEMICAL DFT-APPROACH TO THE STUDY OF SYNTHONS – 2-DEOXYECDYSONE, 2-DEOXYECDYSTERONE AND ECDYSTERONE AND THEIR VIRTUAL BIOSCREENING

Abstract. The geometric, energy and electronic parameters of 2-deoxyecdysterone were calculated by the quantum-chemical density functional method DFT/B3LYP/6-31G. A comparative analysis of the physical-chemical properties of the molecules of 2-deoxyecdysone, 2-deoxyecdysterone and ecdysterone that aresynthons for regioselective modifications was performed. A virtual bioscreening of the phytoecdysteroidsindicated was performed.

Keywords: phytoecdysteroids, 2-deoxyecdysone, 2-deoxyecdysterone, ecdysterone, structure, reactivity, quantum-chemical calculations, virtual screening.

Introduction. Ecdysteroids are hormones of molting and metamorphosis of insects and crustaceans. They are an extensive group of polyhydroxylated sterols. To date, more than 300 ecdysteroids of various structure and natural origin have been isolated and identified [1]. It is known that they have various biologically active properties that are useful for medicine and agriculture [2].

The need for chemical transformations of technologically available phytoecdysteroids is due to obtaining new analogues to study the relationship of their structure and physiological properties, for bindingwith the ecdysones receptor and for investigation of the mechanism of action, as well as for obtaining new derivatives for use as adaptogenic, anabolic and tonic drugs and preventive medicine remedies of new generation [3].

EXPERIMENTAL PART

We have previously isolated the most common phytoecdysteroid, ecdysterone (20-hydroxyecdysone) **3,** and low-polar steroids 2-deoxyecdysone (2-deoxy-α-ecdysone) **1** and 2-deoxyecdysterone **2** from the aboveground part of *Silenefruticulosa* (Pall.) Schischk. with high yields [4, 5].

In this regard, the purpose of this work is a quantum-chemical study of the reactivity of the abovementioned molecules for their further use as technologically available synthons and carrying out virtual bioscreening. The results of optimization of the geometric parameters of molecules **1**, **3** were obtained by us earlier [6].

The density functional theory method [7] was applied in the 6-31G valence-split basis in the framework of the GAUSSIAN09 program [8] for quantum-chemical calculations of the spatial and electronic structure of molecule **2** (figure 1). Structure **2** was modeled using a chemical editor, the ChemOffice program (ChemBio 3D Ultra subprogramme), the initial optimization using the molecular mechanics method, the final optimization using the GAUSSIAN program. As a result of the complete optimization of the geometrical parameters of molecule **2**, the optimal values of the chemical bond lengths, valence and torsion angles corresponding to the minimum energy of the molecule were determined. Accounting for the local symmetry of methylene and methyl groups was not carried out due to the asymmetry of the molecule as a whole.

RESULTS AND DISCUSSION

Figure 1 shows the optimized structure of molecule **2** with stereochemical-centers; figure 2 shows the numbering of atoms in the molecule.

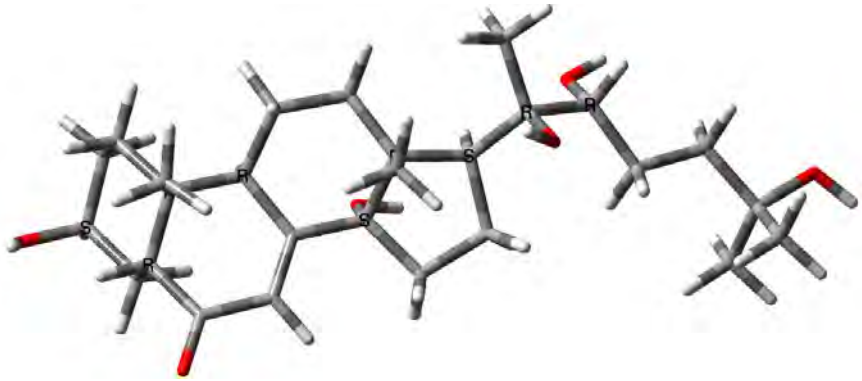


Figure 1 – Three-dimensional model of molecule **2** with an indication of chiral centers (B3LYP/6-31G method, oxygen atoms in red, hydrogen atoms in white, and carbon atoms in gray)

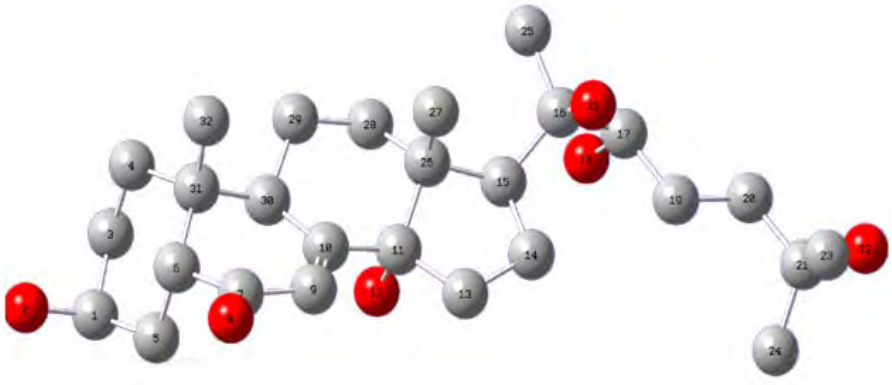


Figure 2 – The numbering of atoms in molecule **2** adopted in the calculations

Tables 1, 2 present the optimized geometrical parameters of molecule **2** calculated as a result of quantum chemical structure optimization. The theoretical values of the structural parameters of the molecule correspond to the standard values of the chemical bond lengths and valence angles. According to the results of the calculations, the **A**-ring of 5β-steroid, which is chair-shaped, is not distorted by the presence of a hydroxyl group. The sp^2-hybridized atom C7 flattens part of ring **B**. Cyclohexane ring **C** is chair-shaped, ring **D** is envelope-shaped:

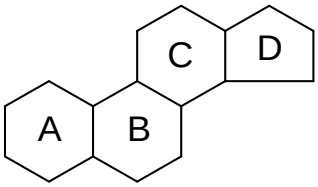


Table 1 – The bond lengths (R, Å), bond angles (α, grad) in molecule **2** according to calculations using the B3LYP/6-31G method

Bond	R, Å	Angle	α, grad
C1-O2	1.534	C(1)-C(3)-C(4)	112.2
C1-C3	1.432	C(3)-C(1)-O(2)	117.8
C3-C4	1.527	C(5)-C(1)-C(3)	108.4
C1-C5	1.478	C(6)-C(5)-C(1)	109.1
C5-C6	1.530	C(7)-C(6)-C(5)	116.5
C6-C7	1.480	O(8)-C(7)-C(6)	121.3
C7-O8	1.212	C(9)-C(7)-O(8)	124.1
C7-C9	1.512	C(9)-C(10)-C(11)	113.0
C9-C10	1.363	C(10)-C(9)-C(7)	112.7
C10-C11	1.545	C(9)-C(10)-C(30)	111.4
C10-C30	1.540	C(10)-C(11)-C(13)	112.8
C11-C13	1.537	C(11)-C(13)-C(14)	113.4
C13-C14	1.575	O(12)-C(11)-C(13)	106.0
C14-C15	1.535	C(13)-C(14)-C(15)	111.8
C15-C16	1,542	C(14)-C(15)-C(26)	101,0
C16-C17	1,557	C(15)-C(26)-C(11)	104,5
C17-C19	1.544	C(16)-C(15)-C(14)	114.7
C20-C21	1.528	C(17)-C(16)-C(15)	108.1
C20-C19	1.575	O(18)-C(17)-C(16)	111.4
C21-O22	1.445	C(20)-C(19)-C(17)	112,5
C22-O22	1.443	C(23)-C(21)-O(22)	111.1
C21-C24	1.527	C(24)-C(21)-O(22)	108.3
C25-O25	1.451	O(22)-C(21)-C(20)	111.2

Table 2 – Torsion angles (φ, grad) in molecule **2** (B3LYP/6-31G)

Angle	φ, grad
C(1)-C(3)-C(4)-C(31)	54.1
C(6)-C(5)-C(1)-C(3)	50.2
C(15)-C(14)-C(13)-C(11)	7.0
C(17)-C(16)-C(15)-C(14)	75.3
O(18)-C(17)-C(16)-C(15)	50.8
C(19)-C(17)-C(16)-C(15)	-70.3
C(20)-C(19)-C(17)-C(16)	-160.3
C(21)-C(20)-C(19)-C(17)	-179.3
O(22)-C(21)-C(20)-C(19)	179.3
O(18)-C(17)-C(16)-C(15)	50.8
O(8)-C(7)-C(6)-C(5)	-98.1
O(2)-C(1)-C(3)-C(4)	73.9
O(8)-C(7)-C(9)-C(10)	-166.1
O(33)-C(16)-C(17)-C(19)	45.7

Physical-chemical parameters of the molecule obtained in the framework of the method B3LYP/6-31Gare given in table 3.

To determine the preferred sites of electrophilic and nucleophilic attacks, the reactivity indices of **2**, the boundary electron densities of the highest occupied (HOMO) and lowest unoccupied (LUMO) orbitals of the molecule, were calculated. The HOMO highest boundary density is observed for C9 and C10 atoms, which are favorable for an electrophilic attack. Indeed, under the influence of the π-conjugation of double bonds C7 = O8 and C9 = C10, the electron density of the latter must be shifted towards the carbon atom C9, which is consistent with a higher boundary (HOMO) density value of this atom. A nucleophilic attack should take place predominantly on the electron-depleted atoms. When analyzing deeper molecular orbitals, one can determine additional reaction centers of the molecule.

It was interesting to compare the physical-chemical properties of three related compounds – **1**, **2**, and **3** based on these calculations. The molecules of these steroids are based on the structure of a polycyclic saturated hydrocarbon estrane built from four condensed carbon rings (given above). They contain hydroxyl groups, as well as hydrocarbon side chains with two and three hydroxyl groups. The difference of molecules from each other is in hydroxyl groups number: **1** has 4 such groups, **2**–5, and **3**–6. An increase in the number of OH groups should affect the reactivity and physical properties of molecules.

Theoretical parameters calculated for structures of the title compounds by DFT/B3LYP method, for example, total energy, rotational constants and dipole moments are given in table 3. The molecular properties such as electronegativity

(χ), chemical hardness (η) and chemical softness (S) were calculatedby using HOMO (the highest occupied molecular orbital) and LUMO (the lowestlyingunoccupied molecular orbital) energy difference.

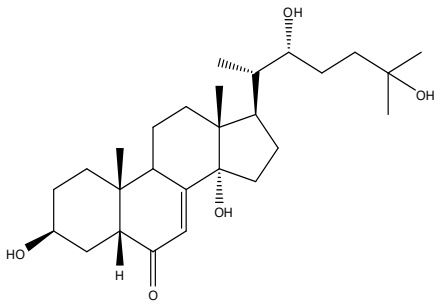
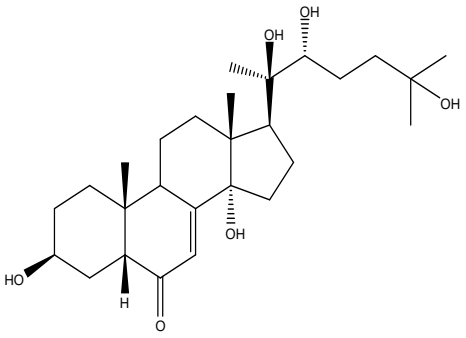
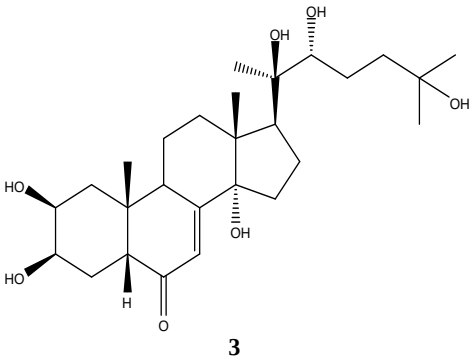
Table 3 – The physical-chemical parameters of the compounds (B3LYP/6-31G method)

Parameters	Compounds		
	1	**2**	**3**
Totalenergy (Hartree)	-1431.0520106	-1506.2419769	-1581.4320708
E_{HOMO} (a.u.)	-0.23296	-0.22923	-0.22869
E_{LUMO} (a.u.)	-0.04758	-0.04664	-0.04572
$\Delta E_{HOMO-LUMO}$ (eV)	5.044	4.968	4.979
I (eV)	6.339	6.238	6.223
A (eV)	1.295	1.269	1.244
χ(eV)	3.817	3.754	3.734
η(eV)	2.522	2.485	2.490
S (eV)	0.1983	0.2012	0.2008
Rotational constants (GHz)			
A	0.2960717	0.3185723	0.2941818
B	0.0542781	0.0510269	0.0474460
C	0.0524861	0.0495343	0.0462503
Dipole moment (Debye)			
μ_{total}	5.137	6.359	4.0811
μ_x	-4.628	5.639	-4.0781
μ_y	2.230	2.935	0.1196
μ_z	-0.043	0.127	0.0991

The following conclusions are done on the basis of the data of table 3. The values of the total electronic energy show their dependence from a number of electrons: **1**($C_{27}H_{44}O_5$) contains 246, **2** ($C_{27}H_{44}O_6$) – 254, and **3**($C_{27}H_{44}O_7$) - 262 electrons (when increasing the OH groups). HOMO and LUMO energies are considered as reaction capability indexes. The ability of electron giving is characterized by HOMO energy and the ability of electron accepting is characterized by LUMO energy. These arise from **1**to **3**and correspond to theionization potential (I) and the electron affinity (A), respectively: in the Hartree-Fock approximation, the ionization potential is equal to the orbital energy of the ionized molecule taken with the opposite sign, the electron affinity is defined by the same way. The values $E_{HOMO} < 0$correspond to the positive ionization potentials. The gap between HOMO and LUMO characterizes the molecular chemical stability [9] and decreases from **1**to **2** and **3**.

Some of the molecular properties were calculated theoretically using HOMO and LUMO energy difference, for example, electronegativity (χ), chemical hardness (η) and chemical softness (S) (Table 3).The absolute electronegativity was

Table 4 – Data of PASS-prediction of the spectrum of the biological activity of molecules **1**, **2** and **3**

Compounds	Type of proposed activity	Probability (P_a), %
 **1**	Anti-ischemic Hepatoprotective Antipsoriatic Dermatological Anti-osteoporotic Cytoprotective Anti-eczema Antitumor Immunostimulating Hypolipidemic Analeptic Antivirus Antihypercholesterolemic Anti-inflammatory Cardiotonic	91 80 79 76 73 70 69 68 66 64 58 56 53 52 51
 **2**	Anti-ischemic Anti-osteoporotic Antipsoriatic Immunostimulating Dermatological Cytoprotective Hypolipidemic Anti-inflammatory Hepatoprotective Analeptic Antivirus Antinociceptive	99 87 84 83 82 62 61 62 60 57 51 51
 **3**	Antinociceptive Anti-osteoporotic Immunostimulating Antipsoriatic Dermatological Anti-inflammatory Hepatoprotective Analeptic Antivirus Anti-eczema Cytoprotective	99 85 84 83 82 71 58 58 57 54 53

Note: Probability of manifestation of this type of activity in biological test systems *in vitro* and *in vivo*.

calculated as a half-sum of the ionization potential and the electron affinity, the absolute chemical hardness was identified as their half-difference. The chemical softness is the inverse of the hardness. **1** has the greatestionizationpotential, electronegativity, the positiveelectron affinity. The HOMO-LUMO gap value indicates a lower polarizability of the molecule**2**, which is consistent with the great value of its permanent dipole moment (table 3). Its highest moment is due to the presence of an odd number (5) of OH groups in molecule while two other molecules contain an even number of such groups whose dipole moments compensate each other.

The measure of resistance to change in the electronic configuration, the so-called hardness of the substance, is higher in the case of 2-deoxyecdyzone, and, respectively, its softness is lower than that of two molecules.All molecules are asymmetric tops due to the different rotational constants.

Prediction of the spectrum of biological activity of steroid molecules was carried out using the PASS online computer program (Prediction of Activity Spectra for Substances) [10]. The PASS online program (http://www.pharmaexpert.ru/passonline) allows you to select the most promising ones from the point of view of pharmacological properties from a variety of compounds based on the principle of "sliding control" of databases of chemical compounds. The accuracy of the prediction of biological activity is about 94% [11, 12].

The following results were obtained as a result of virtual bioscreening using the PASS online program (table 4).

It can be seen from the data in Table 4 that each compound tested has potentially a wide range of biological properties. Thus, the PASS online program predicts the presence of antiischemic, hepatoprotective, antiosteoporotic, immunostimulating, antiinflammatory, and antiviral activity for almost every compound.

In this case, anti-ischemic activity is predicted with a high probability of experimental confirmation for the tested compounds, in particular, for molecules **2** and **3** with a probability of 99%, and for **1** with a probability of 91%.

The hepatoprotective properties of steroid compounds are of particular interest. As can be seen from table 4, the presence of hepatoprotective properties is predicted for each of the compounds tested, however, a relatively high probability of experimental confirmation of this activity is predicted only for molecule **1** – 80%.

Based on the data predicted, it would be advisable to carry out in-depth studies of the anti-osteoporotic properties of all molecular samples in model systems *in vitro* and *in vivo*.

Conclusion. Thus, using quantum chemical calculations with the help of the DFT/B3LYP method, the physical-chemical parameters of three phytoecdysteroids, ecdysterone, 2-deoxyecdysone and 2-deoxyecdysterone, were predicted and their comparative analysis was performed.

According to the results of virtual bioscreening of steroid molecules using the PASS online computer program, it was shown that all the considered compounds were interesting for real in-depth study using biological test systems for the development of original drugs.

Acknowledgements. This work was fulfilled under the grant project of Scientific Committee of the Ministry of Education and Science of the Republic of Kazakhstan №AP05133718.

REFERENCES

[1] Levina I.S., Zavarzin I.V. Phytoecdysteroids: isolation, synthesis, and biological properties // Pharmaceutical Bulletin. 2015. N 3-4. P. 50-67.

[2] Tuleuov B.I. Steroid compounds of plants and medicinal preparations based on them. Search, chemical modification and practical aspects of the application. Karaganda: Glasir, 2009. 208 p.

[3] Tuleuov B.I. Phytosteroid medicines technology. Karaganda: Glasir, 2017. 112 p.

[4] Adekenov S.M., Almagambetov A.M., Gulyakevich O.V., Zhabinsky V.N., Kozhanova A.M., Tuleuov B.I., Khabdolda G., Khripach V.A. Composition and content of ecdysteroids in plants *Silenefruticulosa* (Pall.) Schischk // Proceedings of the NAS of Belarus. Ser. Chemical. 2014. N 1. P. 64-67.

[5] Kuatbayev O.U., Tuleuov B.I., Khripach V.A., Adekenov S.M. Chemical study of the aerial parts of *Silenefruticulosa* (Pall.) Schischk // Pharmaceutical Bulletin. 2015. N 3-4. P. 126-130.

[6] Abulyisova L.K., Isaiynova L.A., Kutzhanova K.Zh., Kenzhetaeva S.O., Zhumakaev A.M., Almagambetov A.M., Habdolda G., Tuleuov B.I., Adekenov S.M. Quantum and chemical research of reactionary ability and computer bio screening of a molecule 20-hydroxyecdyzone // Chemical journal of Kazakhstan. 2013. N 3. P. 135-145.

[7]Foresman J.B., Frisch A. Exploring chemistry with electronic structure methods. Pittsburgh: Gaussian Inc., 1996. 304 p.

[8] Gaussian 09, revision A02. M Frisch, GW Trucks, HB Schlegel, GE Scuseria, MA Robb, etc. Inc., Wallingford, CT 200, 2009.

[9] Fleming I. Frontier Orbitals and Organic Chemical Reactions. London: Wiley, 1976. 249 p.

[10] Poroikov V., Filimonov D. Rational approaches to drug design // Prous Science. 2001. Vol. 16, N 11. P. 403-407.

[11] Filimonov D.A., Lagunin A.A., Gloriozova T.A., Rudik A.V., Druzhilovsky S.V., Pogodin P.V., Poroikov V.V. Prediction of the spectra of biological activity of organic compounds using the PASS online web resource // Chemistry of heterocyclic compounds. 2014. N 3. P. 483-499.

[12] Khan T., Dixit Sh., Ahmad R., Raza S., Azad I., Joshi S., Khan A.R. Molecular docking, PASS analysis, bioactivity score prediction, synthesis, characterization and biological activity evaluation of a functionalized 2-butanone thiosemicarbazone ligand and its complexes // Journal of Chemical Biology. 2017. Vol. 10, Issue 3. P. 91-104.

Резюме

Б. С. Темірғазиев, Л. Қ. Әбуләйісова, А. М. Қожанова,
У. Б. Төлеуов, А. К. Даиров, П. К. Құдабаева, Е. В. Минаева,
Т. М. Сейлханов, Б. И. Төлеуов, С. М. Әдекенов

2-ДЕЗОКСИЭКДИЗОН, 2-ДЕЗОКСИЭКДИСТЕРОНМЕН ЭКДИСТЕРОН – СИНТОНДАРЫН ЗЕРТТЕУДЕГІ КВАНТТЫҚ-ХИМИЯЛЫҚ DFT-ӘДІСІ ЖӘНЕ ВИРТУАЛДЫ БИОСКРИНИНГІ

Тығыздық функционалы теориясының кванттық-химиялық DFT/B3LYP/6-31G әдісімен 2-дезоксиэкдистеронның геометриялық, энергиялық және электрондық параметрлері есептелген. Региоселективті модификациялар үшін синтондар – 2-дезоксиэкдизон, 2-дезоксиэкдистерон мен экдистерон молеку-

лаларының физика-химиялық қасиеттерінің салыстырмалы талдауы орындалды. Аталған фитоэкдистероидтардың виртуалды биоскринингі жүргізілді.

Түйін сөздер: фитоэкдистероидтар, 2-дезоксиэкдизон, 2-дезоксиэкдистерон, экдистерон, құрылым, реакцияға қабілеттілік, кванттық-химиялық есептеулер, виртуалды биоскрининг.

Резюме

Б. С. Темиргазиев, Л. К. Абуляисова, А. М. Кожанова,
У. Б. Тулеуов, А. К. Даиров, П. К. Кудабаева, Е. В. Минаева,
Т. М. Сейлханов, Б. И. Тулеуов, С. М. Адекенов

КВАНТОВО-ХИМИЧЕСКИЙ DFT- ПОДХОД К ИЗУЧЕНИЮ СИНТОНОВ – 2-ДЕЗОКСИЭКДИЗОНА, 2-ДЕЗОКСИЭКДИСТЕРОНА И ЭКДИСТЕРОНА И ИХ ВИРТУАЛЬНЫЙ БИОСКРИНИНГ

Квантово-химическим методом функционала плотности DFT/B3LYP/6-31G рассчитаны геометрические, энергетические и электронные параметры 2-дезоксиэкдистерона. Выполнен сравнительный анализ физико-химических свойств молекул 2-дезоксиэкдизона, 2-дезоксиэкдистерона и экдистерона – синтонов для региоселективных модификаций. Проведен виртуальный биоскрининг указанных фитоэкдистероидов.

Ключевые слова: фитоэкдистероиды, 2-дезоксиэкдизон, 2-дезоксиэкдистерон, экдистерон, структура, реакционная способность, квантово-химические расчеты, виртуальный скрининг.