Synthesis and properties of new biologically active analogues of Kazcaine

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The study focuses on the synthesis and pharmacological evaluation of novel structural analogs of the anesthetic and antiarrhythmic Kazcaine. Two new derivatives were synthesized by acylation of propylacetylene alcohol 1-(2-ethoxyethyl)-4-oxopiperidine with fluorobenzoyl chlorides. Their complexes with cyclodextrin were obtained for biological screening. The evaluation of the myelostimulating activity of these complexes revealed that one of them, specifically the 3-fluorobenzoyloxy derivative, demonstrated a pronounced myelostimulating effect, particularly with regard to the stimulation of leukopoiesis and thrombopoiesis. The compound, in complex with β-cyclodextrin, showed significant stimulation of leukocyte and platelet proliferation, with a noticeable increase in the total number of leukocytes and improvement in granulocyte and lymphocyte recovery. These results indicate that the synthesized compounds have significant potential for pharmacological use, especially for stimulating hematopoiesis and protecting against myelosuppression. In addition, quantum chemical calculations of the reactions showed that *ortho*- and *meta*-fluorobenzoyl chloride have higher reactivity, which is confirmed by the high yields of the products (94% and 89%) obtained as a result of the synthesis.

Keywords: analogues of Kazcaine; 1-(2-ethoxyethyl)-4-oxopiperidine; propylacetylene alcohol; myelostimulating activity; quantum-chemical calculations.

Казкаинның жаңа биологиялық белсенді аналогтарының синтезі және олардың қасиеттері

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Зерттеу анестетикалық және антиаритмиялық Казкайн препаратының жаңа құрылымдық аналогтарын синтездеуге және фармакологиялық бағалауға бағытталған. 1-(2-Этоксиэтил)-4-оксопиперидин негізіндегі пропилацетилен спиртін фторбензоилхлоридтермен ацилдеу арқылы оның негізінде 2 жаңа туынды синтезделді. Биологиялық скрининг жүргізу мақсатында бұл қосылыстардың циклодекстринмен кешендері алынды. Аталған кешендердің миелостимуляциялық белсенділігін зерттеу нәтижесінде олардың бірі — атап айтқанда, 3-фторбензоилокси туындысы жоғары миелостимуляциялық әсерді көрсетті, әсіресе лейкопоэз мен тромбопоэзді ынталандыруға қатысты. Бұл β-циклодекстринмен кешен қосылыс лейкоциттер мен тромбоциттер пролиферациясының айтарлықтай стимуляциясы жалпы лейкоциттер санының айтарлықтай жоғарылауымен және гранулоцитар мен лимфоциттердің қалпына келуі жақсарғанын көрсетті. Бұл нәтижелер синтезделген қосылыстардың фармакологиялық қолдану үшін, әсіресе гемопоэзді ынталандыру және миелосупрессиядан қорғау үшін маңызды әлеуеті бар екенін көрсетеді. Сонымен қатар кванттық-химиялық есептеулері *орто*- және *мета*-фторбензоилхлоридтердің реакцияға қабілеттілігі жоғары екенін жүргізілген реакциялардың синтез нәтижесінде алынған өнімдердің жоғары шығымдылығымен (94% және 89%) расталғанын көрсетті.

Түйін сөздер: Казкаин аналогтары; 1-(2-этоксиэтил)-4-оксопиперидин; пропилацетилен спирті; миелоынталандырғыш белсенділігі; кванттық химиялық есептеулер.

Синтез и свойства новых биологически активных аналогов Казкаина

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Исследование сосредоточено на синтезе и фармакологической оценке новых структурных аналогов анестетика и антиаритмика Казкаина. Ацилированием пропилацетиленового спирта 1-(2-этоксиэтил)-4-оксопиперидина фторбензоилхлоридами синтезировано 2 новых производных на его основе. Для биологического скрининга получены их комплексы с циклодекстрином. Исследование миелостимулирующей активности данных комплексов показало, что одно из них, а именно 3-фторбензоилокси-производное, проявило высокий миелостимулирующий эффект, особенно в отношении стимуляции лейкопоэза и тромбопоэза. Соединение в комплексе с β-циклодекстрином показало значительную стимуляцию пролиферации лейкоцитов и тромбоцитов с заметным увеличением общего числа лейкоцитов и улучшением восстановления гранулоцитов и лимфоцитов. Эти результаты свидетельствуют о том, что синтезированные соединения обладают значительным потенциалом для фармакологического применения, особенно для стимуляции кроветворения и защиты от миелосупрессии. Кроме того, проведенные квантово-химические расчеты проведенных реакций показали, что *орто*- и *мета*-фторбензоилхлорид обладают более высокой реакционной способностью, что и подтверждено высокими выходами продуктов (94% и 89%), полученных в результате синтеза.

Ключевые слова: аналоги Казкаина; 1-(2-этоксиэтил)-4-оксопиперидин; пропилацетиленовый спирт; миелостимулирующая активность; квантово-химические расчеты.

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Article

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1. Introduction

Over the years of research, the Laboratory of Synthetic and Natural Medicinal Compounds Chemistry at the Bekturov Institute of Chemical Sciences has identified several leading compounds, the further optimization of which has made it possible to obtain a number of new biologically active derivatives [1-7]. One of them is 1-(2-ethoxyethyl)-4-oxopiperidine (Figure 1), a synthon for many pharmacologically active compounds with high drug potential in medicine and agriculture. Notable examples include Prosidol, a non-narcotic synthetic alternative to morphine [1]; Kazcaine, a local anesthetic and antiarrhythmic that outperforms commonly used agents in infiltration and conduction anesthesia [2]; and the plant growth stimulator Kaz-6 [3]. Additionally, various derivatives have shown myelostimulating, antidiabetic, hepatoprotective, immunomodulatory, and antibacterial activities [4-7].

Despite of the large number of biologically active derivatives already obtained, the synthetic potential of this leading molecule has not yet been exhausted, so it seems advisable to obtain and study novel compounds based on it. Of particular interest are new analogues of Kazcaine, since the presence of a triple carbon-carbon bond and a benzoyl group in its structure makes it promising for the development of molecules with higher biological activity and selectivity toward molecular targets.

2. Experiment

The IR spectra were recorded on a Bruker Alpha-P ATR FTIR (diamond crystal) spectrometer (Bruker, Billerica, MA, USA). The ^{1}H and ^{13}C NMR spectra were recorded using a JNM-ECA 400 (JEOL, Tokyo, Japan) spectrometer, operating at frequencies of 399.78 MHz for ^{1}H and 100.53 MHz for ^{13}C, in $CDCl_3$.

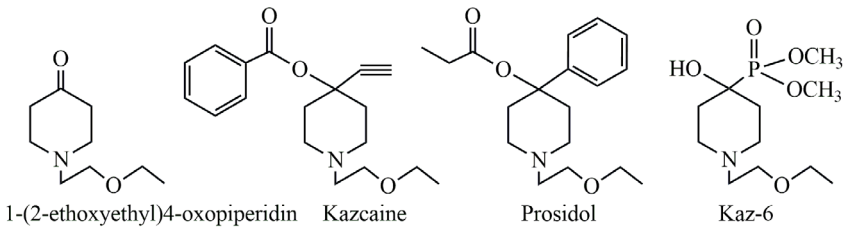

Figure 1 – 1-(2-Ethoxyethyl)-4-oxopiperidine and its derivatives

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General procedure for the preparation of 1-(2-ethoxyethyl)-4-(pentyn-1-yl)-4-(fluorobenzoyloxy)-piperidines (**3, 4**). 0.86 g (0.0054 mol) of the corresponding fluorobenzoyl chloride are added dropwise to 1.3 g (0.0054 mol) of 1-(2-ethoxyethyl)-4-(pentyn-1-yl)piperidin-4-ol (**2**). The mixture was stirred at room temperature for 24 hours. After the reaction is complete (TLC control), water is added to the reaction mixture and it is treated with potassium carbonate. The organic portion is extracted with benzene, the extract is dried over anhydrous $MgSO_4$, and the solvent is evaporated. Products **3, 4** are obtained as a yellow oil with 94% and 89% yields, respectively (individual characteristics are presented in Table 1).

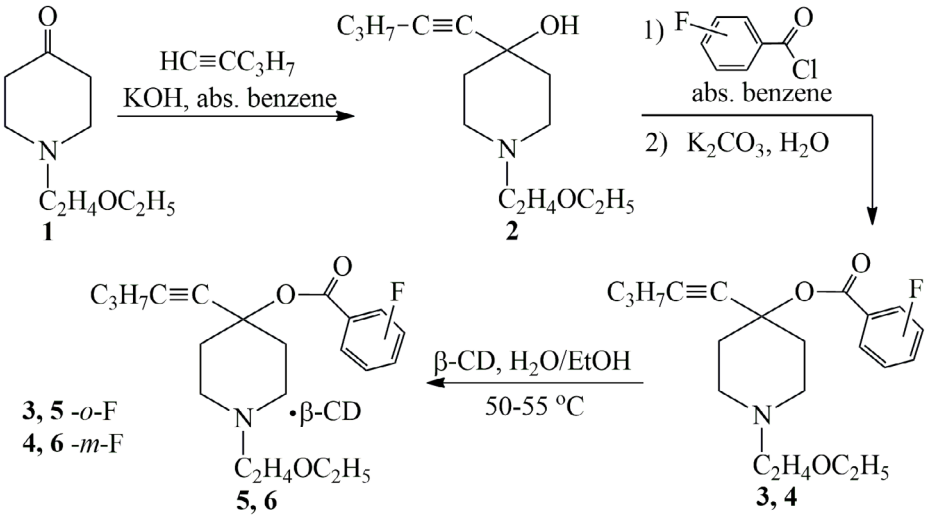
*General procedure for obtaining inclusion complexes with β-cyclodextrin (**5, 6**).* Mix solutions of 0.0022 mol of compounds **3** or **4** in 40 mL of ethyl a ethanol and 0.0022 mol of β-cyclodextrin in 70 mL of distilled water. Evaporate ethanol and water at 50-55 °C in a drying cabinet. Obtain inclusion complexes **5, 6** as a white powder with a melting point above 250°C.

Studies on myelostimulating (erythropoiesis-, leukopoiesis- and thrombocytopoiesis-stimulating) activity are carried out on healthy sexually mature animals - white laboratory female rats, 12-16 weeks old, weighing 210-280 g. Blood analysis is performed on a hematological analyzer “Abacus junior vet” (manufactured by Diatron, Denmark). The blood leukogram is controlled by microscopic examination of a smear stained according to Romanovsky-Giemsa on an SA3300C microscope under immersion (magnification 7x100) with 500 cells on each smear. Myelosuppression is induced by the injection of the cytostatic cyclophosphamide at a dose of 30 mg/kg animal body weight. Then, on the 6th, 8th, and 10th days of observation, the following solution is injected intramuscularly once a day: in group 1 and group 2, the test compounds **5** and **6** at a dose of 5 mg/kg in a volume of 0.5 mL; in group 3, the comparison drug methyluracil at a dose of 0.4 mg/kg in a volume of 0.5 mL; in group 4, a placebo (saline solution) in a volume of 0.5 mL; and group 5 is intact.

Complete optimization of the molecular geometry and calculations were performed using DFT/B3LYP/6-31G(d,p) method which is often used to calculate electronic properties (HOMO, LUMO, electrophilicity, nucleophilicity) and thermodynamic characteristics (**Δ**G, **Δ**H) [8]. The Gibbs free energy (**Δ**G) was computed by incorporating thermodynamic corrections. To account for the effect of the solvent (benzene), the IEFPCM method was employed. HOMO-LUMO energy gap (**Δ**E), electrophilic index (**ω**), electronegativity (**χ**), chemical softness (**σ**), polarizability (**α**) etc. were calculated according to the methods given in the article [9].

3. Results and discussion

To obtain new homologues of Kazcaine, propylacetylene alcohol **2** was synthesized from the prepared 1-(2-ethoxyethyl)-4-oxopiperidine **1** using the method described in [10] with the solvent replaced by anhydrous benzene (Scheme 1). Compound **2** was then treated with fluorobenzoyl chloride, also in anhydrous benzene, at room temperature to obtain 1-(2-ethoxyethyl)-4-(pent-1-yn-1-yl)piperidin-4-yl *o-,m*-fluorobenzoates (**3**, **4**) in 95% and 89% yields, respectively. An attempt to obtain 1-(2-ethoxyethyl)-4-(pent-1-yn-1-yl) piperidine-4-yl *p*-fluorobenzoate under similar conditions, as well as in dioxane, was unsuccessful — the reaction did not proceed. In addition, water-soluble forms of compounds **3** and **4** were obtained as complexes with β-cyclodextrin **5**, **6** for further pharmacological screening.



Scheme 1 – The synthesis of 1-(2-ethoxyethyl)-4-(pent-1-yn-1-yl)piperidin-4-yl *o-,m*-fluorobenzoates **(3, 4)** and their β-cyclodextrin complexes **5**, **6**

Table 1 – Yields and physicochemical characteristics of compounds **3, 4**

№	Yield,%	n_D^{20}	*R_f	IR spectrum, cm^{-1}				
				C=O	C-O-C (ester)	C-O-C (ether)	C-F	Ph
3	95	1.4810	0.71	1720	1299	1108	1074	1612, 1454, 755
4	89	1.4817	0.69	1727	1270	1091	1065	1592, 1444, 754

Notes: * – Eluent: benzene:dioxane=10:1

The yields and physicochemical characteristics of compounds **3** and **4** are presented in Table 1.

In the IR spectrum of compounds **3** and **4**, absorption bands of the C=O group of the ester are observed at 1720 cm^{-1} and 1727 cm^{-1}, as well as absorption bands of the C-O-C group of the ester (1299 cm^{-1} and 1270 cm^{-1}) and ether (1108 cm^{-1} and 1091 cm^{-1}), respectively. Absorption bands of the C-F bond are observed at 1074 cm^{-1} and 1065 cm^{-1}. Phenyl substituents of compounds **3** and **4** give a signal in the region of 1612 cm^{-1} and 1592 cm^{-1}, 1454 cm^{-1} and 1444 cm^{-1}, as well as at 755 cm^{-1} and 754 cm^{-1}, respectively.

In the ^{1}H NMR spectrum of compounds **3** and **4**, the methyl protons are observed at 0.89-0.94, 0.86-0.89 ppm for the 4-(pentyn-1-yl)- and at 1.10-1.20, 1.01-1.05 ppm for the 1-(2-ethoxyethyl)-fragments, respectively, as three-proton multiplets. The methylene protons of 4-(pentyn-1-yl)-fragment are recorded as follows: one set appears as a two-proton multiplet at 1.45-1.51 ppm (**3**) and 1.37-1.42 ppm (**4**), while the second set appears as a six-proton multiplet together with the piperidine protons H3ax,5ax, H-3eq,5eq at 2.08-2.23 ppm (**3**) and 2.10-2.16 ppm (**4**). The piperidine protons H-2ax,6ax, H-2eq,6eq appear together with the methylene protons of the ethoxyethyl fragment in the region of 2.63-2.73 ppm (m.,6H) for compound **3** and in the region of 2.43-2.45 ppm (m.,4H), 2.57 ppm (s.,2H) for compound **4**. Additionally, the methylene protons of the ethoxyethyl fragment resonate as two-proton multiplets at 3.40-3.45 and 3.49-3.52 ppm (**3**), and as a four-proton multiplet at 3.31-3.43 ppm (**4**). The aromatic protons of the F-benzoyloxy group of compounds **3** and **4** appear as single-proton multiplets in the regions of 6.97-7.98 ppm and 7.41-7.74 ppm, respectively.

In ^{13}C NMR for compound **3,** the carbon signals of the 4-(pentyn-1-yl) fragment appear at 13.46, 22.18, 20.79, 79.44, 87.77 ppm, while for compound 4, they appear at 13.69, 22.28, 20.37, 80.06, and 87.86 ppm.The carbons of the 1-(2-ethoxyethyl) group are detected at 36.82 (C-3,5), 50.18 (C-2,6), 74.68 (C-4) ppm for compound **3**, and at 37.06 (C-3,5), 50.16 (C-2,6), 75.12 (C-4) for compound **4**. The carbon signals of the F-benzoyloxy group resonate at 162.50 ppm (C=O), 160.66 and 163.33 ppm (C-F), and in the region of 117.07-134.29 ppm (Ph) for compound **3**, while for compound **4**, they resonate at 163.07 ppm (C=O), 161.29 and 163.73 ppm (C-F), and in the region of 116.17-133.99 ppm (Ph).

Complexes **5** and **6** were studied for myelostimulating activity (stimulating effect, influencing the proliferative activity of erythropoiesis, thrombocytopoiesis and leukopoiesis) (Table 2).

The results of the studies showed that compound **5** did not exhibit the desired activity, while compound **6** demonstrated a pronounced stimulating effect on the proliferation of blood cells. Compound **6** restored leukocyte indices without changing the Harkavi index. The total leukocyte count in the compound **6** group was (21.61±7.46)·10^9/L of blood, which was 2.60 times higher than the intact group (11.08±0.80)·10^9/L ($p \leq 0.05$), 6.05 times higher than the control group (6.20±0.80)·10^9/L ($p \leq 0.001$), and 8.19 times higher than the placebo group (4.72±0.93)·10^9/L ($p \leq 0.001$). Compound **6** also stimulated granulocyte recovery: absolute granulocyte indices in the compound **6** group were (5.91±0.42)·10^9/L, which is 2.92 times higher than in the control group (2.02±0.91)·10^9/L ($p \leq 0.05$). Lymphocyte indices were also restored: the relative lymphocyte index in the compound **6** group was (70.15±4.35)%, which is similar to the intact group (69.72±1.10%). Absolute lymphocyte indices in the compound **6** group were (15.15±2.72)·10^9/L, which is 4.06 times higher than in the control group (3.73±0.30)·10^9/L ($p \leq 0.01$). Compound **6** showed moderate erythropoiesis-stimulating activity. The erythrocyte index was (7.68±0.33)·10^9/L, the hemoglobin level was (136.0±6.0) g/L, which corresponded to the values of the intact group. Compound **6** also showed high thrombopoiesis-stimulating activity, with a total platelet index of (892.00±55.33)·10^9/L, which is significantly higher than the indices of the intact (690.00±166.33)·10^9/L) and control group (521.00±135.33)·10^9/L). Thus, 1-(2-ethoxyethyl)-4-(pentyn-1-yl)-4-(3-fluorobenzoyloxy)-piperidine in complex with β-cyclodextrin (**6**) showed high leukopoiesis- and thrombopoiesis-stimulating activity, as well as moderate erythropoiesis-stimulating activity. It can be recommended for further studies as a myelostimulant. Based on the results of the high myelostimulating activity demonstrated by the compound, a patent for the invention was obtained [11].

Considering the high myelostimulating activity of compound **6** and its potential as a therapeutic agent, it is advisable to investigate the structural factors influencing the efficiency of synthesizing related compounds. Due to the inability to obtain a derivative with a p-fluorobenzoyloxy substituent, quantum-chemical calculations were conducted to evaluate the thermodynamic parameters of the acylation reaction of propylacetylene alcohol with fluorobenzoyl chlorides. The aim was to assess the thermodynamic favorability

Table 2 – Blood hemogram indicators

Blood parameters	Compound 5	Compound 6	Control group	Placebo group	Intact group
WBC, $\cdot 10^9$/L	7.9±2.45	21.61±7.46	6.20±0.47	4.72±0.35	11.08±0.32
LYM, %	48.8±3.6	70.15±4.35	60.04±3.93	57.01±1.65	69.72±1.1
NEU, %	36.75±3.35	27.35±3.15	32.68 ± 1.6	36.05±9.3	30±0.8
MI, %	5.2±1.9	3.2±0.6	7.28±0.4	7.03±5.3	0.28±0.1
Lym, $\cdot 10^9$/L	2.98±1.16	15.15±2.72	3.73±0.30	2.69±0.87	7.72±1.03
Neu, $\cdot 10^9$/L	3.77±0.91	5.91±0.42	2.02±0.91	1.70±0.6	3.32±0.72
Mon, $\cdot 10^9$/L	0.36±0.02	0.69±0.74	0.45±0.00	0.33±0.00	0.03±0.00
RBC, $\cdot 10^{12}$/L	6.75±0.72	7.68±0.33	6.06±0.06	3.59±0.20	7.02±0.23
HGB, g/L	138.5±17.5	136±6	125±4.00	96±2.67	147±6.00
HCT, %	30.7±4.1	35.75±1.65	23.35±0.70	20.75±0.30	37.3±0.27
MCV, fl	45.2±001	47.0±2.23	54.45±0.43	41.8±0.07	82.6±0.23
MCH, pg	2.04±0.01	17.9±0.0	12.75±0.43	12.25±0.30	18.4±0.17
MCHC, g/L	448±1.02	381±1.23	428±9.33	363.6±5.00	406±4.00
RDW-CV, %	15.0±0.05	15.8±0.01	25.35±0.57	23±0.40	23.6±0.20
PLT, $\cdot 10^9$/L	591.5±168.5	892±55	521±135.33	422±41.33	690±166.33
PCT, %	0.49±0.13	0.74±0.06	0.2815±0.07	0.23±0.02	0.372±0.08
MPV, fl	8.2±0.02	8.4±0.01	6.1±0.47	5.5±0.13	7.4±0.30
PDW, %	18.2±1.02	16.2±1.01	12.25±0.57	11.25±0.23	11.4±0.43

Notes: WBC – total white blood cell count, LYM – absolute lymphocyte count, MON – absolute monocyte count, NEU – absolute neutrophil count, Lym – relative lymphocyte count, Mon - relative monocyte count, Neu – relative neutrophil count, RBC – total red blood cell count, HGB – hemoglobin, HCT – hematocrit, MCV – mean corpuscular volume, MCH – mean hemoglobin content, MCHC – mean corpuscular hemoglobin concentration, RDW-CV – red blood cell distribution width, RDW-SD – red blood cell distribution index, PLT – total platelet count, PCT – platelet crit count, MPV – mean platelet volume, PDW – platelet distribution width, P-LCR – large platelet ratio

of forming 1-(2-ethoxyethyl)-4-(pentyn-1-yl)-4-(2-fluorobenzoyloxy)-piperidine (**3**), 1-(2-ethoxyethyl)-4-(pentyn-1-yl)-4-(3-fluorobenzoyloxy)-piperidine (**4**), and 1-(2-ethoxyethyl)-4-(pentyn-1-yl)-4-(4-fluorobenzoyloxy)-piperidine (**7**), which differ in the position of the fluorine substituent on the benzene ring. Gibbs free energy (ΔG) values were calculated for each reaction to determine the relative thermodynamic stability of the products (3, 4, and 7) compared to the starting materials—compound 2 and the corresponding o-, m-, and p-fluorobenzoyl chlorides. The calculation results are presented in Table 3.

The reaction forming product **3** (*ortho* position) has the largest negative Δ*G* value (-37.2 kJ/mol), indicating that it is the most thermodynamically favorable compared to other reactions. This could be attributed to the position of the substituent on the benzene ring in this reaction results in the greatest stabilization of the product.

FMO analysis is another method widely used in the study of chemical stability and reactivity parameters of molecular structures, based on estimation of HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energies. The hydroxyl group is a nucleophile, so the reactivity of fluorobenzoyl chlorides will depend on how much the molecule can accept electrons (electrophilicity) or stabilize the transition state. The calculation results for the reactivity parameters are given in Table 4.

Table 3 – Calculated values Gibbs free energy и Δ*G* of reactions, kJ/mol

Reaction	Gibbs free energy, Hartree			Δ*G* of reaction, Hartree	Δ*G* of reaction, kJ/mol
	2	*o,m,p*-fluorobenzoyl chlorides	**3, 4, 7**		
3	-753.3779	-904.3596	-1657.7516	-0.0142	-37.20
4	-753.3779	-904.3653	-1657.7550	-0.0118	-31.10
7	-753.3779	-904.3673	-1657.7562	-0.0110	-28.95

Table 4 – Reactivity parameters of fluorobenzoyl chlorides

Reactivity parameters	Fluorobenzoyl chlorides		
	o-	*m*-	*p*-
HOMO energy (E_{HOMO}), eV	-7.30	-7.29	-7.42
LUMO energy (E_{LUMO}), eV	-2.16	-2.29	-2.13
Energy gap (ΔE), eV	5.14	5.00	5.28
Ionization potential (IP), eV	7.30	7.29	7.42
Electron affinity (EA), eV	2.16	2.29	2.13
Electronegativity (χ), eV	4.73	4.79	4.78
Chemical Hardness (η), eV	2.57	2.50	2.64
Chemical potential (μ), eV	-4.73	-4.79	-4.78
Electrophilicity (ω), eV	4.35	4.59	4.32
Softness (S), eV^{-1}	0.19	0.20	0.19
Nucleophilicity (N), eV	-1.83	-1.84	-1.71
Asymmetry Factor (A)	-0.54	-0.52	-0.55
Polarizability (α), a.u.	0.39	0.40	0.38
Global Electrophilic Donor Index (ω^-)	10.37	10.64	10.41
Global Electrophilic Acceptor Index (ω^+)	0.91	1.05	0.86
Electrophilic/Nucleophilic Rank (ω^+/ω)	0.09	0.10	0.08
Self-Energy Stabilization (SES), eV	-24.65	-23.18	-25.79

Below we will look at the reactivity parameters and their meanings to understand which compound will react more actively. The *meta* isomer has the smallest energy gap Δ*E* (5 eV), indicating the highest reactivity. The *meta* isomer has the highest ω^+ value (1.05), making it more prone to accepting electrons, which is important for interaction with the nucleophilic hydroxyl group. Thus, its higher reactivity than the *ortho* and *para* isomers is indicated by higher values of self-stabilization (SES), electrophilicity (*ω*), softness (*S*) and polarizability (α).

At first glance, this may contradict previous conclusions based on the free energy calculations of the reaction given above. Thermodynamic stability (Δ*G*) determines which product is more stable at equilibrium, while kinetic factors (e.g., lower HOMO-LUMO gap, higher electrophilicity) influence the reaction rates.

The reaction products of a *meta* isomer may be less stable than the reaction products of an *ortho* isomer. The Δ*G* of a reaction is higher for the *meta* isomer, this indicates that the reaction is less thermodynamically favorable than with the *ortho* isomer. However, the *meta* isomer may be more reactive (kinetically accessible) due to its electronic properties, such as lower chemical hardness and higher electrophilicity.

The *para* isomer has the largest energy gap (ΔE = 5.28 eV) among the isomers, indicating its relatively low reactivity. However, it has high chemical hardness (η = 2.64 eV) and moderate electrophilicity (ω = 4.32 eV), making it more stable and less prone to reactions with nucleophiles. The *para* isomer also exhibits the highest self-interaction stabilization (SES = -25.79 eV), emphasizing its stability at equilibrium. Visualization of the frontier molecular orbitals of *o,m,p*-fluorobenzoyl chlorides is shown in Figure 2.

The formation of compound **7** from the *para* isomer is less thermodynamically favorable than the formation of compounds **3** and **4**. The transition state for the formation of compound **7** would likely has a higher energy barrier, indicating that the reaction requires more energy to overcome the activation threshold. To achieve this transformation, the application of higher temperatures or the presence of a stronger electrophilic catalyst may be necessary to facilitate the reaction. However, despite these adjustments, the overall process remains less thermodynamically favorable, and the formation of compounds **3** and **4** remains more efficient under typical conditions, as confirmed by experimental data.

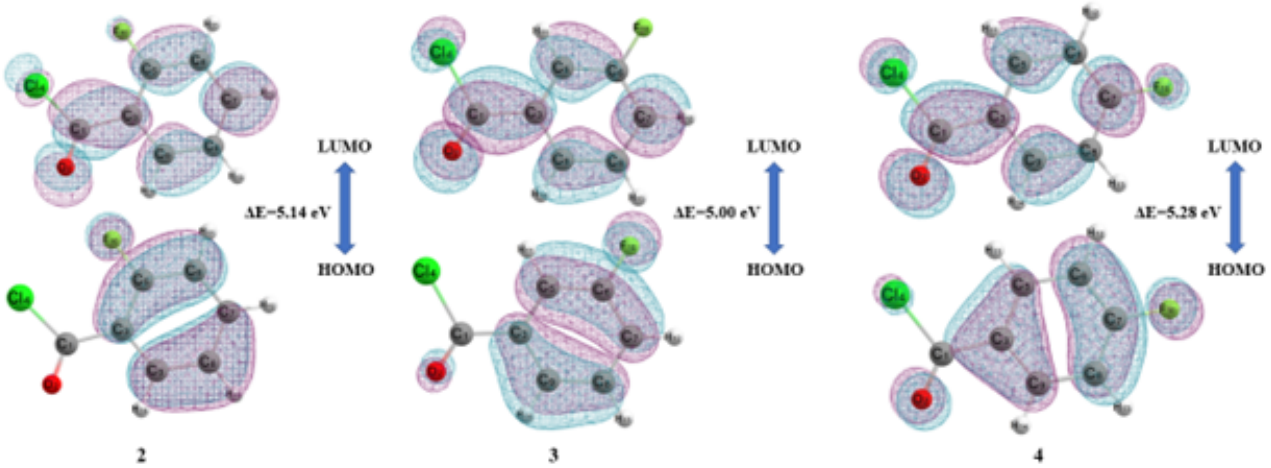


Figure 2 – Frontier molecular orbitals of *o,m,p*-fluorobenzoyl chlorides
Isovalue = 0.02

4. Conclusion

The research conducted demonstrated that the molecule 1-(2-ethoxyethyl)-4-oxopiperidine remains an important starting compound for the synthesis of novel biologically active derivatives with high pharmacological activity. One such product is 1-(2-ethoxyethyl)-4-(pent-1-enyl)-4-(4-fluoro-benzoyloxy)-piperidine, which exhibited significant myelostimulatory activity, particularly stimulating leukopoiesis and thrombopoiesis. Complex **6**, obtained with β-cyclodextrin, showed high leukopoietic activity, increasing the total leukocyte count 2.6 times compared to the control group, as well as stimulating the recovery of granulocytes and lymphocytes. Erythropoietic activity was moderate, but thrombopoiesis was significantly enhanced, indicating promising properties for this compound.

Furthermore, a theoretical study of the thermodynamic stability of the reaction between propylacetylene alcohol and fluorobenzoyl chlorides was conducted. The results confirmed that the reaction with o-fluorobenzoyl chloride is the most thermodynamically favorable, with the largest negative ΔG value (-37.2 kJ/mol). At the same time, FMO analysis showed that the acylating agent m-fluorobenzyl chloride has better reactivity parameters (higher values of self-stabilization, electrophilicity, softness, polarizability, smallest energy gap ΔE, and highest ω^+ value). This means that under the given conditions, reactions with *ortho* and *meta* isomers are more likely and preferable, in contrast to the para isomer, as confirmed by experimental data.

Based on these data, it can be concluded that the synthesized compounds, particularly complex **6**, possess significant biological potential and may be recommended for further research in the fields of pharmacology and medicine, particularly as agents for stimulating hematopoiesis and protecting the body from myelosuppression.

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Zhumakova S.S.: Writing - Original Draft, Investigation; Ten A.Yu.: Writing - Review & Editing Methodology; Yergaliyeva E.M.: Formal analysis; Zharkynbek T.Y.: Investigation; Bayazit S.: Investigation; Belyankova Y.O.: Writing – review & editing; Zazybin A.G.: Project administration, Resources, Funding acquisition; Sokolenko A.S.: Investigation; Shenderovich I.G.: Formal analysis; Yu V.K.: Supervision, Conceptualization.

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