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BENZOYLATED BISPIDONE: SYNTHESIS AND INVESTIGATION OF BIOLOGICAL EFFECTS

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Abstract. *Introduction.* Local anaesthetics work by blocking voltage-gated sodium channels, which causes a temporary loss of sensation, a property used in many medical procedures. While novocaine, lidocaine, and trimecaine are effective, they have drawbacks such as short duration, possible toxicity, and tolerability problems. This study set out to create a complex of benzoylated 3-(3-butoxypropyl)-7-cyclopropanemethyl-substituted bispidone with β-cyclodextrin (LAC-5) and to compare its local anaesthetic effects with medicals using standard preclinical tests. LAC-5 was synthesised using Mannich condensation, oximation, *O*-benzoylation, and β-cyclodextrin complexation. Its structure was confirmed by methods such as infrared and nuclear magnetic resonance spectroscopies. Tests showed that LAC-5 has strong local anaesthetic effects, performing better than trimecaine, lidocaine, and novocaine in both infiltration and conduction anaesthesia models. In infiltration anaesthesia, LAC-5 achieved the maximum measurable depth of anaesthesia (index 36.0) at a 0.25% concentration, with a duration of complete anaesthesia of 56.66 min and a total duration of action of 76.66 min, exceeding the reference medications by up to 5.66- and 2.6-fold, respectively ($p < 0.001$). In conduction anaesthesia, LAC-5 produced a total duration of action of 160.0 ± 4.7 min, surpassing reference medications. Based on the results obtained, LAC-5 is recommended for comprehensive preclinical pharmacological evaluation, including assessment of acute toxicity, safety profile, and mechanism of action.

Keywords: benzoylated bispidone; β-cyclodextrin complex; biological activity; infiltration anaesthesia; conduction anaesthesia.

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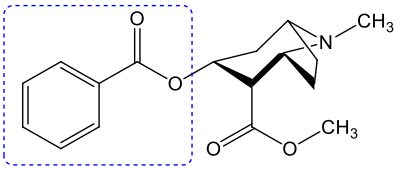
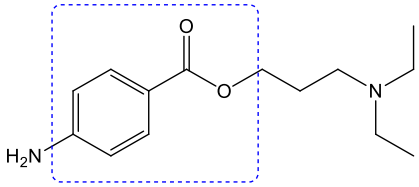
1. Introduction

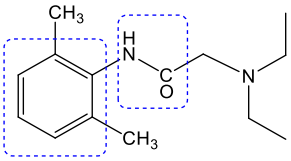
Local anaesthetics are widely used in surgery, dentistry, and many other medical procedures worldwide. Local anaesthetics work by temporarily stopping nerve signals. They do this by blocking voltage-gated sodium channels in nerve cell membranes. After crossing the nerve membrane, the non-ionised form of the anaesthetic enters the axon, picks up a proton inside the cell, and then attaches to sodium channels. This blocks sodium from entering the cell and stops action potentials from starting or spreading. As a result, sensory signals like pain do not reach the central nervous system, so you temporarily lose sensation [1,2]. After cocaine was isolated in the late XIX century and synthetic options like procaine (Novocaine), lidocaine, and bupivacaine were developed, researchers have continued to look for new local anaesthetics that work better, act faster, last longer, and have fewer side effects [3].



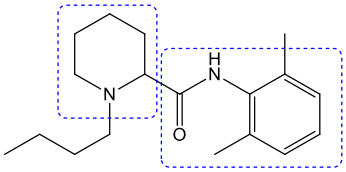
Lead compound (A)
Cocaine, 1884



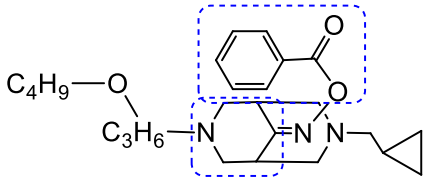
Lead compound (B)
Novocaine, 1905



Lead compound (C)
Lidocaine. 1948



Lead compound (D)
Bupivacaine, 1963



Target compound
Benzoylated 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone

Amino amides and amino esters are the two basic types of local anaesthetics. In contrast to amino esters, which have an ester connection between the intermediate chain and the aromatic end, amino amides contain an amide link. Amino amides and amino esters are different in several ways. While amino amides are broken down in the liver, amino esters are broken down in plasma by pseudocholinesterase. While amino amides are quite stable in solution, amino esters are unstable. Compared to amino amides, amino esters are far more prone to trigger allergic hypersensitivity reactions (Table 1) [4].

Table 1 - Comparison of the pharmacological characteristics of representative local anaesthetics

Class	**Local anaesthetics**	**Duration of action**	Metabolism	**Stability**	**Clinical use**
Ester group	Novocaine	Short	Hydrolysed in plasma by pseudocholinesterases	Less stable in solution	Limited use today; infiltration anaesthesia and diagnostic procedures
Amide type	Lidocaine	Intermediate	Primarily metabolised in the liver by cytochrome P450 enzymes	More chemically stable	Most widely used for infiltration, nerve block, epidural, spinal, and topical anaesthesia.
	Bupivacaine	Long	Metabolised primarily in the liver		Long-duration regional anaesthesia, epidural anaesthesia, peripheral nerve blocks, and postoperative pain management

Despite the current medications being clinically effective, problems such as cardiotoxicity, neurotoxicity, and allergic reactions continue to drive the search for new chemical entities with improved safety profiles [5]. Since 2008, human exposures with less severe consequences have dropped by 2.48% annually, whereas those with more severe consequences (moderate, major, or death) have increased by 4.44% annually since 2000. Approximately 3200 single exposures to additional or unknown local and/or topical anaesthetics and 1410 single exposures to lidocaine were recorded in the US in 2017. Additionally, 197 lidocaine exposures had a minor effect, 71 had a moderate outcome, 13 had a serious event, and one fatality was documented [6].

Azaheterocyclic systems are of considerable value in the development of new local anaesthetics owing to their structural rigidity, favourable lipophilicity,

and resemblance to naturally occurring alkaloids. Among these, 3,7-diazabicyclo[3.3.1]nonan-9-one (bispidone) is readily accessible synthetically and amenable to structural modification at both nitrogen atoms. Bispidone derivatives have been reported to exhibit antiarrhythmic, analgesic, and antimicrobial activities, and certain compounds of this class have been shown to interact with voltage-gated sodium channels - the primary molecular targets of local anaesthetics [7-13].

Adding a benzoyloxy group to bispidone can change its electronic properties and stability. These changes are important for how local anaesthetics work. Adding a benzoyloxy group can make the compound more lipophilic and create an ester bond that can be broken down in the body, releasing the original oxime [14-16].

In this study, we synthesised an oxime ether derivative of bispidone by reacting a bicyclic ketone precursor with hydroxylamine, followed by benzoylation. By combining the rigid bispidone structure with the *O*-benzoyloxime group and changing the substituents on the nitrogen atoms, we were able to study how these changes affect anaesthetic strength. The results help to understand bispidone-based compounds better and support the design of better local anaesthetics.

2. Experimental part

Chemical experimental part

Al_2O_3 with second-degree activity was used in TLC to monitor reaction progress and in column chromatography for purification. IR spectra were recorded using an FT-IR spectrometer Nicolet 5700, and NMR spectra were recorded using a JEOL JNM-ECA 400 spectrometer using $CDCl_3$ at frequencies of 399.78. Dry solvents and an inert gas environment were used for oxygen- or moisture-sensitive syntheses.

Benzoylated 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone was synthesised using a method previously reported [17,18].

3-(3-Butoxypropyl)-7-cyclopropanemethyl substituted bispidone (2), pale yellow oil; 92%. Calculated for $C_{18}H_{32}N_2O_2$: C 70.09; H 10.46; N 9.08. Found: C 70.16; H 10.42. IR (KBr) (ν_{max}/ cm^{-1}): 1734 (C=O), 1114 (C–O–C). ^{13}C NMR ($CDCl_3$, δ, ppm): 46.9 ($C_{1,5}$), 58.3, 58.7 ($C_{2,4,6,8}$), 215.4 (C_9).

Oxime of 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone (3), pale yellow oil; 85%. Calculated for $C_{18}H_{33}N_3O_2$: C 66.83; H 10.28; N 12.99. Found: C 70.01; H 10.20 IR (KBr) (ν_{max}/ cm^{-1}): 3133 (OH), 1670 (C=N). ^{13}C NMR ($CDCl_3$, δ, ppm): 30.7, 32.1 ($C_{1,5}$), 56.4, 56.3, 58.6, 58.1 ($C_{2,4,6,8}$), 161.2 (C_9).

Benzoylated 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone (4), pale yellow oil; 69%. Calculated for $C_{25}H_{37}N_3O_3$: C 70.22; H 8.72; N 9.83. Found: C 70.17; H 8.65. IR (KBr) (ν_{max}/ cm^{-1}): 1742 (C=O), 1641 (C=N).

β-Cyclodextrin complex of benzoylated 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone (5), cream-colored amorphous powder. Calculated for $C_{67}H_{107}N_3O_{38}$: C 51.50; H 6.90; N 2.69. Found: C 51.89; H 6.83.

Biological activity study

The β-cyclodextrin complex of benzoylated 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone (5), designated as LAC-5, was evaluated for its local anaesthetic activity. Data were compared with those of the reference drugs trimecaine, lidocaine, and novocaine. Results are summarised in Tables 2 and 3.

Infiltration anaesthetic activity

Infiltration anaesthetic activity was evaluated in male guinea pigs (200-250 g) using the Bülbring-Wade method. Following shaving of the animals' backs, 0.2 mL of isotonic solutions of the test compound and medications were injected into 4 sites arranged in a 3-cm square.

Each concentration was tested for local anaesthetic activity 6-8 times. Sensitivity was assessed by pressing a blunted injection needle 6 consecutive times at intervals of 3 to 4 sec. This process was repeated every five minutes for thirty minutes.

The anaesthesia index, which was computed as the average of 6 studies and had a maximum possible value of 36, was used to measure the depth of anaesthesia. The reference medications trimecaine, lidocaine, and novocaine at comparable concentrations were used to compare the test compound's action.

Conduction anaesthetic activity

Using basic screening techniques suggested by the Guidelines for Experimental Preclinical Studies of New Pharmacological Substances and the Pharmacological Committee of the Republic of Kazakhstan, local anaesthetic activity under conduction anaesthesia was assessed [19,20].

The tail-flick method was used to examine the activity of the test chemical and the comparative medicines in rats.

The following criteria were used to compare the chemical with the reference medications:

- Duration of complete anaesthesia induced;
- Total duration of action.

Non-anesthetised outbred white rats of both sexes were used, with 6 animals in each experimental and control group. One per cent aqueous solutions of the compounds were tested.

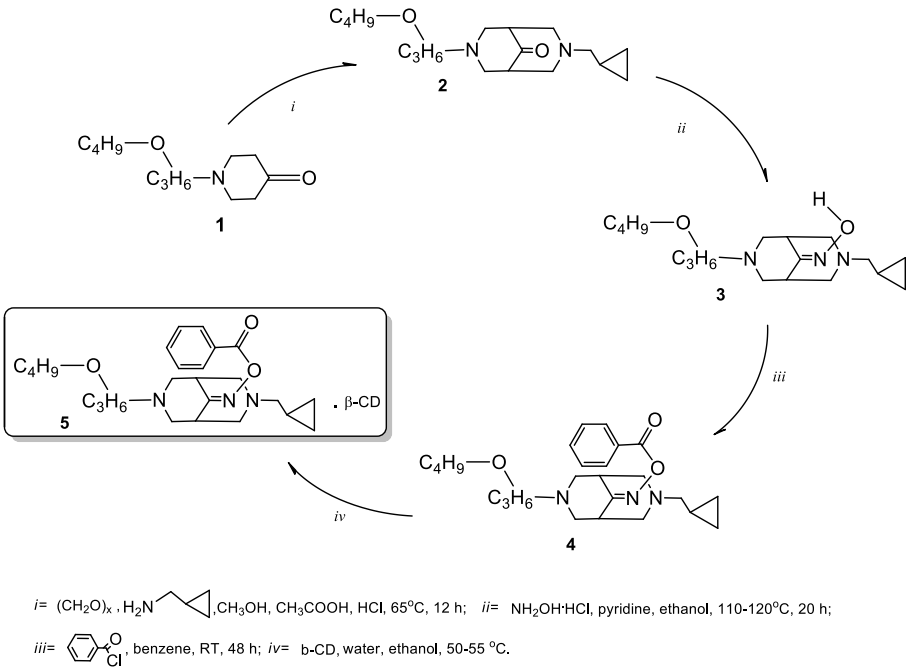
Statistical analysis

Data are presented as mean ± standard error of the mean (M±m). Statistical analysis was performed using Student's t-test. Differences were considered

statistically significant at $p < 0.05$. Data processing was carried out using GraphPad Prism 9.0 (GraphPad Software, USA).

Results and Discussion

The starting compound, benzoylated 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone (2), was synthesised through a one-pot Mannich condensation of 1-(3-butoxypropyl)piperidin-4-one (1), paraformaldehyde, and cyclopropanemethylamine in acidified acetic acid-methanol solution, achieving a yield of 92%.



The reaction of 3-(3-butoxypropyl)-7-cyclopropanemethyl substituted bispidone (2) with hydroxylamine hydrochloride yielded the corresponding oxime (3), which was then acylated with benzoyl chloride to obtain the *O*-benzoyl derivative (4). The β-cyclodextrin complex (5) was synthesised by combining the *O*-benzoyloxime (4) with an equimolar amount of β-cyclodextrin. The structures and identities of these compounds were verified using elemental analysis, TLC, IR spectroscopy, and NMR spectroscopy. The IR spectrum of compound ***2*** showed a band at 1734 cm^{-1}, corresponding to the C=O stretching vibration of a ketone carbonyl within the bispidone ring. A band at 1114 cm^{-1}, assigned to C–O–C stretching, confirmed the presence of the butoxy ether group and further supported the proposed structure. In the ^{13}C NMR spectrum, C1 and C5 signals appeared at 46.9 ppm, which was attributed to the diazabicyclic core. In comparison, the cluster of resonances at 58.3 and 58.7 ppm accounted for the

methylene carbons C_2, C_4, C_6, and C_8 within the bispidone framework. A signal of an aliphatic ketone carbonyl C_9 appeared at 215.4 ppm, providing unambiguous evidence for the formation of a new ketone. In the oxime IR spectrum, a broad absorption at 3133 cm^{-1} was characteristic of the O–H stretch belonging to the newly introduced hydroxyl group. Meanwhile, the strong carbonyl band at 1734 cm^{-1} that had defined compound ***2*** was completely absent — replaced by a new band at 1670 cm^{-1}, right where C=N stretching would be expected. This pattern of disappearance and emergence provided straightforward, unambiguous evidence for oxime formation.

The ^{13}C NMR data C_1 and C_5 resonated at 30.7 and 32.1 ppm, shifted noticeably upfield from their positions in compound ***2*** - a natural consequence of the change in electronic environment when a ketone gives way to an oxime. The methylene carbons C_2, C_4, C_6, and C_8 in the bicyclic ring were identified at 56.3, 56.4, 58.1, and 58.6 ppm, respectively. The clinching evidence, though, came from the carbonyl region: the ketone signal at 215.4 ppm had disappeared without a trace, and in its place stood a new resonance at 161.2 ppm - exactly where an oxime carbon (C=N) is known to appear. Altogether, the spectroscopic data made a compelling case that compound ***2*** had been cleanly and successfully transformed into oxime ***3***.

The IR spectrum of compound ***4*** was fully consistent with the successful *O*-benzoylation of oxime ***3***. The broad O–H stretching band at 3133 cm^{-1}, clearly seen in compound ***3***, was no longer present in compound ***4***, which indicates that the hydroxyl group of the oxime was acylated. A new signal at 1742 cm^{-1} was assigned to the C=O stretching of the aryl ester group. The C=N stretching band shifted from 1670 cm^{-1} in oxime (3) to 1641 cm^{-1} in benzoylated bispidone (4). This shift is due to the change in electron density at the C=N bond after *O*-benzoylation. The fact that this band remained confirmed that the oxime group remained intact. These spectral results support the structure of compound ***4*** as the O-benzoylated oxime derivative.

According to the data presented in Table 1, compound LAC-5 demonstrated a pronounced local anaesthetic effect, with an anaesthesia index of 35.6.

6 animals were used for each concentration test. The average response values collected over 30 minutes were used to calculate the anaesthesia index. LAC-5 reached the highest level of anaesthesia that this method can measure, with an anaesthesia index of 36 (Table 2).

At a 0.25% concentration, it was statistically more potent than all reference medications, showing 1.1 times the activity of trimecaine, 1.55 times that of lidocaine, and 1.44 times that of novocaine.

Table 2 - Efficacy of LAC-5 and medications in infiltration anaesthesia

Compound / Reference Drug	0.25%					
	Anesthesia Index M±m		Complete Anaesthesia Duration, min		Total Duration of Action, min	
LAC-5	36.0±0	p_1<0.001 p_2<0.001 p_3<0.001	56.66±1.05	p_1<0.001 p_2<0.001 p_3<0.001	76.66±1.05	p_1<0.001 p_2<0.001 p_3<0.001
Trimecaine	33.6±0.33		20,0±1.7		38.3±1.05	
Lidocaine	23.1±0.9		14.2±0.8		30.8±0.8	
Novocaine	25.0±1.0		10.0±1.2		29.1±1.5	

Note: p_1, compared with trimecaine; p_2, compared with lidocaine; p_3, compared with novocaine.

Comparison of duration parameters, including both the duration of complete anaesthesia and the total duration of action, showed that the compound outperformed the reference medications in these parameters.

The duration of complete anaesthesia induced by LAC-5 was 56.66 minutes, which was 2.83, 3.9, and 5.66 times longer than that of each medication, respectively. The total duration of the LAC-5 effect was 76.66 minutes. In comparison, the total anaesthesia duration for the reference medications was shorter: 38.3 minutes for trimecaine, 30.8 minutes for lidocaine, and 29.1 minutes for novocaine. Thus, the effect of LAC-5 was 2.0-, 2.4-, and 2.6-fold longer than that of the comparison medications, respectively.

The results of the conduction anaesthesia study for LAC-5 are presented in Table 3.

Table 3 - Activity of LAC-5 and medications in conduction anesthesia

Compound / Reference Drug	Duration of Action, min	
LAC-5	160.0±4.7	p_1 <0.02 p_2 <0.01 p_3 <0.001
Trimecaine	56.9±12.8	
Lidocaine	90.8±18.4	
Novocaine	42.3±13.6	

Note: p_1, compared with trimecaine; p_2, compared with lidocaine; p_3, compared with novocaine.

LAC-5 provided anaesthesia for 160 minutes, lasting 2.8, 1.8, and 3.8 times longer than the comparison medications. LAC-5 demonstrated a pronounced effect in infiltration anaesthesia, exceeding the performance of all reference medications across all measured parameters. Consequently, LAC-5 is recommended for further comprehensive pharmacological evaluation.

Conclusion

A study of LAC-5 showed that this compound has strong local anaesthetic effects that are better than those of the commonly used medications trimecaine, lidocaine, and novocaine. For infiltration anaesthesia, LAC-5 reached the

maximum depth of anaesthesia (index 36.0 ± 0) at a concentration of 0.25%, outperforming all reference medications. The complete anaesthesia lasted 56.66 minutes, which is 2.83, 3.9, and 5.66 times longer than the medications, respectively. The total duration of action was 76.66 minutes, 2.0 to 2.6 times longer than the reference medications ($p < 0.001$ for all comparisons). In conduction anaesthesia, LAC-5 provided anaesthesia for 160 minutes. All these differences were statistically significant.

Overall, these results show that LAC-5 is a very effective local anaesthetic, with greater strength and a much longer duration of action than those of medications currently in use.

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Conflict of interest: The authors report no conflicts of interest related to this article.

БЕНЗОИЛДЕНГЕН БИСПИДОН: СИНТЕЗІ ЖӘНЕ БИОЛОГИЯЛЫҚ ӘСЕРІН ЗЕРТТЕУ

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Түйіндеме. *Кіріспе.* Жергілікті анестетиктер кернеуге тәуелді натрий арналарының белсенділігін қайтымды түрде бөгеп, хирургияда, стоматологияда және медициналық тәжірибедегі әртүрлі процедураларда қажетті сезімталдықтың уақытша жойылуын қамтамасыз етеді. Новокаин, лидокаин және тримекаиннің тиімділігіне қарамастан, олардың әсер ету ұзақтығы, уыттылығы және көтере алуға байланысты шектеулері анағұрлым жетілдірілген препараттарды іздеуді талап етеді. *Зерттеудің мақсаты* – бензоилденген 3-(3-бутоксипропил)-7-циклопропанметил орынбасқан биспидонның β-циклодекстриндік кешенін (LAC-5) синтездеу және оның жергілікті анестезиялық белсенділігін стандартты клиникаға дейінгі скрининг әдістерін пайдалана отырып, салыстырмалы препараттар - тримекаин, лидокаин және новокаинмен салыстыру. *Нәтижелер және талқылау.* LAC-5 Манних реакциясы, оксимдеу, *О*-бензоилдеу және β-циклодекстринмен кешен түзу арқылы синтезделді; барлық қосылыстардың құрылымы инфрақызыл және ядролық магниттік резананс спектроскопия зерттеу әдістері расталды. *Қорытынды.* Биологиялық бағалау нәтижелері LAC-5-тің инфильтрациялық және өткізгіштік анестезия модельдерінде клиникалық тәжірибеде қолданылатын салыстырмалы препараттар - тримекаин, лидокаин және новокаиннен жоғары айқын жергілікті анестезиялық қасиеттерге ие екенін көрсетті. Инфильтрациялық анестезия кезінде LAC-5 0.25 % концентрацияда анестезияның ең жоғары өлшенетін тереңдігіне (индекс 36.0 ± 0) жетіп, толық анестезия ұзақтығы 56.66 мин және жалпы әсер ету ұзақтығы 76.66 мин болды, бұл көрсеткіштер салыстырмалы препараттардан сәйкесінше 5.66 және 2.6 есеге дейін жоғары болды ($p < 0.001$). Өткізгіштік анестезия жағдайында LAC-5 жалпы әсер ету ұзақтығы салыстыру препараттарынан асып түсіп 160.0 ± 4.7 мин құрады. Алынған нәтижелер негізінде LAC-5 қосылысы жедел уыттылықты, қауіпсіздік бейінін және әсер ету механизмін бағалауды қамтитын кешенді клиникаға дейінгі фармакологиялық зерттеулерге ұсынылады.

Түйінді сөздер: бензоилденген биспидон; β-циклодекстрин кешені; биологиялық белсенділік; инфильтрациялық анестезия; өткізгіштік анестезия.

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БЕНЗОИЛИРОВАННЫЙ БИСПИДОН: СИНТЕЗ И ИССЛЕДОВАНИЕ БИОЛОГИЧЕСКИХ ЭФФЕКТОВ

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Резюме. *Введение.* Местные анестетики обратимо блокируют потенциалзависимые натриевые каналы, вызывая временную потерю чувствительности, необходимую в хирургии, стоматологии и других медицинских процедурах. Несмотря на эффективность новокаина, лидокаина и тримекаина, их ограничения, связанные с продолжительностью действия, токсичностью и переносимостью, обусловливают необходимость поиска более совершенных препаратов. *Цель исследования* синтезировать β-циклодекстриновый комплекс бензоилированного 3-(3-бутоксипропил)-7-циклопропанметил замещенного бисидона (LAC-5) и оценить его местноанестезирующую активность в сравнении с препаратами с использованием стандартных методов доклинического скрининга. *Результаты и обсуждение.* LAC-5 был получен посредством реакции Манниха, оксимирования, *О*-бензоилирования и комплексообразования с β-циклодекстрином; структуры полученных производных подтверждены методами инфракрасной и ядерной магнитно-резонансной спектроскопии. *Заключение.* Биологическая оценка показала, что LAC-5 обладает выраженными местноанестезирующими свойствами, превосходящими клинически применяемые препараты сравнения - тримекаин, лидокаин и новокаин - как в моделях инфильтрационной, так и проводниковой анестезии. При инфильтрационной анестезии LAC-5 достиг максимальной измеряемой глубины анестезии (индекс 36.0 ± 0) при концентрации 0.25 %, при длительности полной анестезии 56.66 мин и общей продолжительности действия 76.66 мин, превышая показатели препаратов сравнения соответственно до 5.66 и 2.6 раза ($p < 0.001$). В условиях проводниковой анестезии LAC-5 обеспечивал общую продолжительность действия 160.0 ± 4.7 мин, превосходя препараты сравнения. На основании полученных результатов LAC-5 рекомендуется для углублённого доклинического фармакологического исследования, включая оценку острой токсичности, профиля безопасности и механизма действия.

Ключевые слова: бензоилированный биспидон; β-циклодекстриновый комплекс; биологическая активность; инфильтрационная анестезия; проводниковая анестезия.

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