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Exploring the Anesthetic Potential of γ-Hydroxybutyric Acid Derivatives: Synthesis and Biological Evaluation of New Local Anesthetics

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Abstract

This research investigates the therapeutic potential of aqueous *Chlorophytum comosum* extract in managing bilirubin metabolism disturbances in laboratory animals with experimentally induced toxic hepatitis. The study compared the efficacy of three treatment approaches: *Chlorophytum comosum* extract monotherapy, standard vitamin therapy (including vitamins B_1, B_2, B_6, B_{12}, PP, E, and C), and a combination of both treatments. The experiment involved four groups of Chinchilla breed rabbits, with toxic hepatitis induced by a single subcutaneous injection of carbon tetrachloride (CCl_4). Blood samples were collected daily to measure total and direct bilirubin levels using the «Lakhema» test method. Key findings revealed that CCl_4 intoxication significantly increased bilirubin levels, primarily affecting direct bilirubin. The highest bilirubin concentrations were observed on the 4th day in untreated rabbits. Notably, the combination therapy group demonstrated the most effective reduction in bilirubin levels by the 10th day of the study. With efficacy comparable to that of regular vitamin therapy and additive benefits when combined, the study underlines the potential of Chlorophytum comosum extract as a promising hepatoprotective drug. According to these results, extract from Chlorophytum comosum may be a useful supplement in the treatment of toxic liver damage, providing a safe and natural substitute for traditional therapies. The study emphasizes the importance of further research into the hepatoprotective properties of plant-based remedies, particularly in addressing liver damage caused by environmental toxins and industrial pollutants. The results contribute to the growing body of evidence supporting the therapeutic potential of natural compounds in liver disease management.

Keywords: *Chlorophytum comosum* extract, Acute toxic hepatitis, Bilirubin fractions, γ-Hydroxybutyric

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Introduction

Cardiovascular diseases represent one of the most significant threats to modern human health, being the leading risk factor among “diseases of civilization” (Baklanov *et al*., 2020; Bułdak, 2022; Lavie, 2022). This alarming trend necessitates the development of new pharmacological agents with multifaceted therapeutic effects (Pelevin *et al*., 2018). Among various pharmacological approaches, special attention is drawn to heterofunctional γ-hydroxybutyric (4-hydroxybutanoic) acid (GHB) derivatives, which have shown promising results in cardiovascular therapy (Felmlee *et al*., 2021; Jung *et al*., 2021).

Previous studies have demonstrated that GHB derivatives exhibit multiple beneficial effects, including coronary tropism, anti-anginal activity, anti-necrotic properties, and cardioprotective effects (Logge *et al*., 2022; Gao *et al*., 2022; Jung *et al*., 2023). These therapeutic potentials are not limited to GHB derivatives alone; similar activities have been observed in structurally related compounds (Rodriguez-Cruz & Morris, 2021; Rodriguez-Cruz *et al*., 2021).

Particularly noteworthy are the findings regarding additive salts of 4-hydroxy-3-alkylamino-*N*-alkylbutanamide, especially 4-hydroxy-3-benzylamino-*N*-benzylbutanamide. These compounds have exhibited remarkable multidimensional pharmacological activity, including antiarrhythmic effects in conditions of myocardial ischemia in animal models (Avidan & Kushida, 2020; Di Trana *et al*., 2021). Additionally, they have demonstrated significant plant growth-regulating properties with antistress effects (Cuypers *et al*., 2024a).

Current local anesthetics, represented by well-known pharmaceuticals such as novocaine, trimecaine, lidocaine, and dicaine, while effective in clinical practice, possess several

limitations. These include a relatively narrow therapeutic window, potential tissue irritation, comparatively high toxicity levels, and a limited spectrum of application (Useinovic & Jevtovic-Todorovic, 2022; Habte *et al*., 2024; Hou *et al*., 2025).

This research focuses on addressing these limitations through the synthesis of novel GHB derivatives based on *N*-alkylamides of 3-(*N*-alkylamino)-4-hydroxybutanoic acid. The key structural fragment present in all synthesized compounds plays a crucial role in their anesthetic activity. This pharmacophore has been preserved in the design of new derivatives to maximize their therapeutic potential (Ishikawa *et al*., 2021; Coetzee & Absalom, 2023).

The primary objectives of this study are to synthesize novel substituted GHB derivatives and investigate their biological activity profiles. Assessing their local anaesthetic qualities and determining structure-activity relationships are given special attention. The scientific novelty of this research lies in the unique structural modifications introduced, comprehensive biological activity screening, and detailed structure-activity analysis (Steuer *et al*., 2022; Cuypers *et al*., 2024b). The newly synthesized derivatives demonstrate several promising characteristics: enhanced therapeutic efficacy compared to existing anesthetics, improved safety profile with reduced toxicity, broadened spectrum of pharmacological activity, superior water solubility and stability, simplified synthesis procedures (Rodríguez-Nuévalos *et al*., 2021; Kim *et al*., 2022b). The development of novel local anesthetics is crucial for modern medicine, particularly considering the growing demand for more effective and safer analgesic agents (Küting *et al*., 2021; Cuypers *et al*., 2025). The proposed research direction addresses this need by exploring a new class of compounds with potentially superior properties.

This work represents a significant step towards developing next-generation local anesthetics with improved efficacy and safety profiles. The potential to create novel therapeutic agents based on these derivatives could revolutionize local anesthesia practices and contribute to overcoming the limitations of currently available medications. The successful implementation of this research could lead to the development of new pharmaceuticals that combine local anesthetic properties with additional therapeutic effects, opening new possibilities in clinical practice and improving patient care.

Materials and Methods

Chemical Synthesis and Characterization

All synthesized compounds were obtained primarily in water-soluble salt forms, which significantly facilitates experimental work and is highly desirable for pharmaceutical development. The main synthetic pathways for target products involved the following transformations **(Figure 1)**:

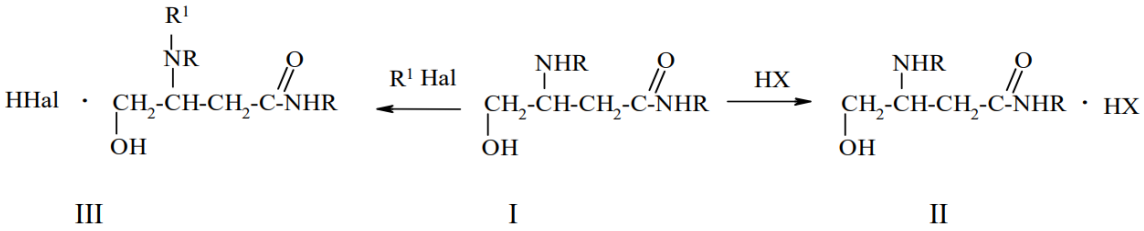

Figure 1. The main synthetic pathways for target products. Notes: R = $C_6H_5CH_2$, C_4H_9, C_2H_5, C_6H_{11}; R1 = $C_6H_5COCH_2$, $HOOCCHCH_2$ CH_3; X represents acid residues;
Hal=Cl, Br.

Substituted butyramides of series I were synthesized using optimized methods. Additive (ammonium) type salts II were obtained by reacting amides I with mineral and organic acids. The synthesis method for a wide range of individual compounds was optimized, and their physicochemical constants were established. In some cases, acidic and neutral salts were synthesized from dicarboxylic acids to compare their activity (Ha *et al*., 2022).

The hemisuccinate and hemiglutarate of 3-benzylamino-4-hydroxy-*N*-benzylbutanamide were prepared using established procedures. The hydrochloride of 3-benzylamino-4-hydroxy-*N*-benzylbutanamide was synthesized by adding 0.92 cm^3 of 34% hydrochloric acid to a solution of 2.98 g of 3-benzylamino-4-hydroxy-*N*-benzylbutanamide in 40 cm^3 of ethanol. After vacuum evaporation and washing with sulfur ether, 3.1 g (90%) of compound IIc was obtained with a melting point of 189‑190° C (Marabello *et al*., 2024).

Quaternary ammonium salts III were synthesized by alkylation of amides I. The hydrobromide of 4-hydroxy-3-*N*-(phenacyl)benzylamino-*N*-benzylbutanamide was prepared by heating 2.37 g of phenacyl bromide with 3.54 g of 3-benzylamino-4-hydroxy-*N*-benzylbutanamide in 50 cm^3 of ethyl acetate-chloroform mixture (2:1) (Fateh & Salehi-Najafabadi, 2022).

Biological Testing Methodology

The evaluation of synthesized compounds was conducted using established standard methodologies, ensuring reliable and reproducible results. Comparative analysis with reference substances demonstrated that the investigated compounds exhibited superior efficacy in several cases compared to the control samples. Statistical analysis of the experimental data revealed a certain variability, which is represented as ($x \pm S_1$) to account for experimental dispersion.

The reference substances used in the study were:

- Dicaine (Tetracaine) – β-dimethylaminoethyl ester of p-butylaminobenzoic acid hydrochloride
- Lidocaine – (2-diethylamino)-N-(2,6-dimethylphenyl)acetamide
- Procaine (Novocaine) – diethylaminoethyl ester of p-aminobenzoic acid hydrochloride
- Trimecaine – α-diethylamino-2,4,6-trimethylacetanilide hydrochloride

The research methodology included several testing approaches. Firstly, surface (terminal) anesthesia was evaluated using the Renier method on rabbit corneas, providing valuable insights into the compounds' ocular effects (Freeman *et al*., 2024). The investigation of infiltration anesthesia for compounds IIa and IIb was performed on rats and guinea pigs using the intradermal method (Walker & Cios, 2021). All anesthetic solutions were prepared in a 0.7% sodium chloride solution to ensure consistent delivery.

The experimental data underwent thorough statistical processing to determine: mean effective concentrations (EC_{50}), relative activity coefficients, and therapeutic indices (LD_{50}/EC_{50}). This comprehensive approach allowed for a detailed evaluation of the synthesized compounds' anesthetic properties and their potential therapeutic applications (Lara-López *et al*., 2025). The results obtained provided valuable insights into the compounds' efficacy, safety profile, and comparative advantages over existing anesthetic agents.

Statistical Data Processing

Statistical data processing played a crucial role in ensuring the reliability and validity of the experimental findings. To examine the gathered data, the research team used extensive statistical techniques. The analysis involved determining mean effective concentrations (EC_{50}) using the method of least squares, calculating relative activity coefficients, and establishing therapeutic indices through the LD_{50}/EC_{50} ratio. The experimental variability was carefully accounted for by representing the data as ($x \pm S_1$), which allowed for a precise evaluation of the results' reliability. This approach provided a quantitative measure of the data dispersion and helped establish confidence intervals for the observed effects. Comparative evaluations across experimental groups were also incorporated into the statistical analysis, allowing researchers to make insightful inferences on the respective safety and efficacy profiles of the drugs under test. By applying these rigorous statistical methods, the study ensured that the observed effects were not due to random variation but represented genuine biological responses to the tested substances. The results of the statistical processing confirmed the superior efficacy of some synthesized compounds compared to reference substances, particularly in terms of therapeutic indices and duration of action. This comprehensive approach to data analysis strengthened the scientific rigor of the study and provided a solid foundation for further research and potential clinical applications.

Results and Discussion

Research into group II salts has demonstrated that certain substances within this group exhibit notable local anesthetic effects, significantly influenced by the composition of the counterion (acid residue). It has been established that middle salts of dibasic acids (hemisuccinates, hemimalates, hemiglutarates) show considerably higher physiological activity compared to acidic salts **(**Ahmed *et al*., 2022; Saravanakumar *et al*., 2022).

The data obtained from studying surface (terminal) anesthesia are presented in **Table 1**. The table presents the results of comparative evaluation of compounds Ia-Iv and IIIa against trimecaine, lidocaine, and dicaine used at 5% concentration during surface anesthesia experiments on rabbit corneas (drops administered into the conjunctival sac). Compound IIg, when used in solutions exceeding 1% concentration, forms unstable solutions that precipitate, thus limiting its study. For a 1% solution of compound IIg, the Renier index was determined to be 268.2 ± 27.7.

It is noteworthy that salts IIb and IIg, when used in 1‑5% solutions, similar to dicaine starting from a 2% concentration, cause conjunctival hyperemia and corneal epithelium desquamation. The study revealed that hemisuccinate 3-benzylamino-4-hydroxy-*N*-benzylbutanamide (IIa) and hemiglutarate 3-benzylamino-4-hydroxy-*N*-benzylbutanamide (IIb) exhibit significant local anesthetic effects (Pontell *et al*., 2023).

A positive aspect is that the studied solutions of compounds IIa and IIb do not have an irritating effect on the conjunctiva of the eye. This finding is particularly important for clinical applications, as it indicates the potential safety and tolerability of these compounds when used in ophthalmological procedures (DeJoseph & Pou, 2020).

These results suggest that the structural modifications introduced into the molecules of these compounds significantly influence their pharmacological properties, particularly their local anesthetic activity and tissue compatibility (Narayanan *et al*., 2024; Blinov *et al*., 2025). Further research into these compounds could lead to the development of new, more effective local anesthetics with improved safety profiles.

Table 1. Comparative activity of compounds in surface (terminal) anesthesia. The data is represented as mean values with standard deviation ($x \pm S_1$), with sample size n = 6.

Compound	Number of Drops	Renier Index
Ia	1	562.5 ± 53.0
	2	337.0 ± 25.4
Ib	1	160.0 ± 11.8
	2	552.7 ± 31.8
Ic	1	406.0 ± 61.9
	2	787.5 ± 28.3
IIa	1	225.7 ± 25.4
	2	762.8 ± 24.4
Trimecaine	1	255.0 ± 61.9
	2	1300.0 ± 0.0
Lidocaine	–	443.5 ± 40.1

Dicaine	–	300.0 ± 0.0

The study of infiltration anesthesia focused on compounds IIa and IIb, which demonstrated higher activity among the tested substances (Savva *et al*., 2023; Thazha *et al*., 2023; Belaldavar & Angadi, 2024; Česaitis *et al*., 2024; Soman *et al*., 2024). These compounds were investigated in experiments using the intradermal method on rats and guinea pigs. The results of these experiments are presented in **Table 2**. Both studied substances showed superior local anesthetic activity and a broader therapeutic effect compared to trimecaine (Kim *et al*., 2022a).

Table 2. Comparative Local Anesthetic Activity of Compounds IIa, IIb, IIIa, and Trimecaine in Infiltration Anesthesia Experiments on Rats and Guinea Pigs. The results are shown as mean values with standard deviation (x ± S_1), sample size n = 6.

Compound	Local Anesthetic Activity			Toxicity of 0.5% Solution (IP administration in mice)*			Therapeutic Index	
	EC_{50}		Relative to Trimecaine	LD_{50}		Relative to Trimecaine	Absolute	Relative
	%	mM/L		%	mM/kg			
Guinea Pigs								
IIa	0,0254(0,0634) ** / 0,0230÷0,0296	0,71	4,25	154 / 140,0÷170,0	0,4314	1,48	6063,0	2,86
Trimecaine	0,0856(0,2140) / 0,0712÷0,1004	3,02	1	181,6 / 164,9÷198,4	0,6380	1	2121,5	1
Rats								
IIb	0,0500 (20) *** / 0,04÷0,07	1,18	2,72	129,0 (8) / 110,0÷150,0	0,388	0,7	16300	3,87
IIIa	0,06 (20) / 0,04÷0,08	1,22	2,59	558,0 (25) / 482,0÷634,0	1,1341	1,17	9300,0	2,21
Trimecaine	0,09(15) / 0,05÷0,15	3,16	1	379,1 / 337,4÷421,0	1,3325	1	4212,2	1

Notes:
* For rats, the toxicity of the 0.5% solution was determined via subcutaneous administration
** Values above the line (in parentheses) represent EC_{50} in mg, values below the line indicate confidence intervals at p = 0.05
*** Numbers in brackets for LD_{50} represent range values

Spinal anesthesia was studied in rat experiments, with procaine and trimecaine used as reference substances **(Table 3)**. The research demonstrated that the tested compounds induced clear spinal anesthesia in rats (Dehaghi *et al*., 2022; Huong *et al*., 2022; Istyagina-Eliseeva *et al*., 2022; Cahyaningsih *et al*., 2023; Khan *et al*., 2023; Yahyaeva *et al*., 2023; Doddapanen *et al*., 2024; Karthikeyan *et al*., 2024; Singar, 2024). Among them, hemiglutarate IIb exhibited the highest activity, surpassing trimecaine by a factor of 4.36 and procaine by a factor of 5.89 in a 2% solution. Increasing the dose of compound IIb to 15 mg/kg when administered into the spinal canal resulted in even longer-lasting anesthesia, although it caused respiratory depression in the animals (Röell *et al*., 2021).

Table 3. Comparative activity of compounds in spinal anesthesia experiments on rats. The results are shown as mean values with standard deviation (x ± S_1).

Compound	Solution Concentration (%)	Dose (mg/kg)	Number of Animals*	Duration of Anesthesia (min)	Percentage of Animals Without Anesthesia	Percentage of Fatalities**
IIa	2	10	10 (7)	42,60±6,05	20,0	10,0
IIb	2	10	10 (8)	71,90 ±6,63	10,0	10,0
IIIa	2	10	10(9)	46,9±2,98	-	10,0
Procaine	2	10	8 (4)	12,20±2,80	12,5	37,5
Trimecaine	2	10	10 (8)	16,50±1,33	10,0	10,0
IIa	5	10	11 (8)	51,70±5,70	-	27,3
IIb	5	10	10 (8)	102,50±7,29	-	20,0

IIIa	5	10	10(8)	79,1±7,56	-	20,0
Procaine	5	10	10 (6)	23,60±2,12	20,0	20,0
Trimecaine	5	10	7 (5)	33,80±3,00	-	28,6

Notes:
*Numbers in parentheses indicate the number of animals included in the calculation
**The cause of animal fatalities was not determined

Toxicity studies revealed the following LD50 values for white mice upon single intraperitoneal administration: 154 mg/kg for IIa, 129 mg/kg for IIb, 112 mg/kg for IIc, and 120 mg/kg for IId. The toxicity of hydrobromide IIIa was found to be 290 mg/kg (for procaine and trimecaine, the corresponding values were 206 mg/kg and 182 mg/kg).

Among the quaternary ammonium salts of series III, hydrobromide 4-hydroxy-3-[*N*-(phenacyl)benzylamino]-*N*-benzylbutanamide IIIa showed the highest activity in experiments. Its action was particularly effective under infiltration and spinal anesthesia conditions. This compound demonstrated local anesthetic activity and a therapeutic effect 2.59 and 2.21 times greater than trimecaine, respectively **(Table 2)**.

Under spinal anesthesia in rat experiments, it was found that hydrobromide IIIa (10 mg/kg) in 2% and 5% solutions surpassed trimecaine and procaine in terms of anesthesia duration **(Table 3)**. These findings indicate the significant potential of the synthesized compounds for developing new local anesthetic agents with improved efficacy and safety profiles (Doyno & White, 2021; Kwatra & Morris, 2021).

Conclusion

We have developed simple methods for producing groups of substituted γ-hydroxybutyric acid compounds - functionalized derivatives of N-alkylamides of 3-(N-alkylamino)-4-hydroxybutanoic acid. These compounds were obtained in the form of additives and quaternary ammonium salts, among which active substances with local anesthetic properties were found.

Among the studied additive salts of N-alkylamides of 3-(N-alkylamino)-4-hydroxybutanoic acid, the most effective were the hemisuccinate and hemiglutarate of benzamide of 3-benzylamino-4-hydroxybutanoic acid. These substances outperformed well-known anaesthetics in terms of efficacy. The research findings indicate the potential benefits of conducting more in-depth studies to explore the possibility of developing new local anesthetic drugs based on these compounds, particularly those exhibiting complex effects.

The salts of alkylamides of 3-dialkylamino-4-hydroxybutanoic acid from series III, particularly the hydrobromide of 4-hydroxy-3-[N-(phenacyl)benzylamino]-N-benzylbutanamide, exhibited more pronounced local anesthetic activity. This can be attributed to the lower permeability of these compounds through the blood-brain barrier and higher lipophilicity due to the pharmacophore substituent.

All studied compounds have several significant advantages: absence of irritating effects on the conjunctiva during terminal anesthesia; relatively simple synthesis process; good stability during storage; relatively low toxicity; good water solubility.

The conducted research demonstrates the potential of these compounds for developing new local anesthetics based on 4-hydroxybutanamides. To further investigate the medicinal potential of the substances under study, it is also advisable to broaden the scope of the research. These results pave the way for the creation of innovative local anaesthetics with enhanced safety and efficacy profiles.

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Conflict of interest: None

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Ethics statement: All studies were conducted in compliance with the ethical standards and principles of the Helsinki Declaration.

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