Reymbayeva Tutiniso Egambergenovna
PhD student at the S.Y. Yunusov Institute of Chemistry
e-mail: reymbayevaniso@gmail.com *tel: +998977353534*
Valentina Ivanovna Vinogradova
Senior Researcher, PhD in Chemistry, S.Y. Yunusov Institute of Chemistry
e-mail**:** vinogradova@gmail.ru
Sadikov Alimdzhan Zairovich
Senior Researcher, DsC in Chemistry, S.Y. Yunusov Institute of Chemistry

SYNTHESIS OF LYCORINE ALKALOID ESTERS

Abstract. *This study describes the synthesis of lycorine esters, an alkaloid isolated from Ungernia victoris belonging to the family Amaryllidaceae. Based on experimental results and data reported in the literature, the synthetic processes, employed reagents, and reaction conditions were analyzed. By comparing the yields and isolation efficiency of the esters synthesized under different conditions, the optimal parameters for the synthesis were determined.*

Keywords: *lycorine, mono-, 1,2-di-O-acetyllycorine, mono-, 1,2-O-dibenzoyllycorine, 2-O-p-nitrobenzoyllycorine.*

Реймбаева Тутинсо Эгамбергеновна
Аспирант базовой докторантуры ИХРВ имени С.Ю. Юнусова
e-mail: reymbayevaniso@gmail.com *tel: +998977353534*
Валентина Ивановна Виноградова
ИХРВ имени С.Ю. Юнусова, старший научный сотрудник, кандидат химических наук
e-mail: vinogradova@gmail.ru
Садиков Алимджан Заирович
ИХРВ имени С.Ю. Юнусова, старший научный сотрудник, доктор химических наук

СИНТЕЗ СЛОЖНЫХ ЭФИРОВ АЛКАЛОИДОВ ЛИКОРИНА

Аннотация: В данной научной работе описан синтез сложных эфиров ликорина — алкалоида, выделенного из растения Ungernia victoris, относящегося к семейству Amaryllidaceae. На основе полученных экспериментальных данных и опубликованных в литературе были проанализированы процессы синтеза, использованные реагенты и условия проведения реакций. Сравнением выходов и эффективностью выделения полученных сложных эфиров, синтезированных в различных условиях, определены оптимальные параметры синтеза.

Ключевые слова: ликорин, моно-, 1,2-ди-О-ацетилликорин, моно-, 1,2-О-дибензоилликорин и 2-О-п-нитробензоилликорин

Reymbayeva To‘tiniso Egambergenovna
S.Y. Yunusovich nomidagi O‘MKI tayanch doktoranti
e-mail:*reymbayevaniso@gmail.com tel: +998977353534*
Valentina Ivanovna Vinogradova
S.Y. Yunusov nomidagi O‘MKI, kat.i.x, k.f.n.
e-mail:*vinogradova@gmail.ru*
Sadikov Alimdjan Zairovich
S.Y. Yunusov nomidagi O‘MKI, kat.i.x, k.f.d.

LIKORIN ALKALOIDINING MURAKKAB EFIRLARI SINTEZI

Annotatsiya. *Mazkur ilmiy ishda Amaryllidaceae oilasiga mansub Ungernia victoris o‘simligidan ajratib olingan alkaloid — likorinning murakkab efirlari sintezi yoritilgan. Eksperimental natijalar va ilmiy adabiyotlarda keltirilgan ma’lumotlar asosida sintez jarayonlari, qo‘llanilgan reagentlar hamda reaksiya sharoitlari tahlil qilindi. Turli sharoitlarda olingan murakkab efirlarning chiqishi va ajratib olish samaradorligi qiyosiy o‘rganilib, sintezning optimal parametrlari belgilandi.*

Kalit so‘zlar: *likorin, mono-, 1,2-di-O-atsetillikorin, mono-, 1,2-O-dibenzoyllikorin, 2-O-p-nitrobenzoyllikorin.*

Introduction

The family Amaryllidaceae includes about 70–80 genera and more than 2000 species of plants, making it one of the largest in its class. This family is distributed across all continents. The genus *Ungernia* (Amaryllidaceae) comprises about 10–11 species, found in Western Asia and Central Asia. In particular, within the flora of Uzbekistan and neighboring countries, 8 species of *Ungernia* occur. All of these species contain lycorine [1].

The Amaryllidaceae alkaloids are a distinctive chemotaxonomic feature of the Amaryllidoideae subfamily. Since the isolation of lycorine from *Narcissus pseudonarcissus* in 1877 by Gerrard,>600 alkaloids had been reported for this plant family up to the end of December 2018 [2]. The main regions of growth of *Ungernia* (industrial collection) in the world are shown in Table 1. [3].

Table 1

Geographical distribution of the genus *Ungernia*

Species	**Distribution**	**Phenology**	**Habitat**
Ungernia badghysi Botsch.	Turkmenistan (Badkhyz)	Blooms in July – September, Fruit set occurs in,september. October	Occurs on gypsum screes
Ungernia flava (Boiss. et Ilaussk.)	Iran	Blooms in August	
Ungernia ferganica Vved.	Central Asia, Tien Shan (Fergana Range). Endemic.	Blooms in August	On rocky (and fine-soil) slopes in the montane belt
Ungernia oligostroma Popov & Vved.	Uzbekistan Samarkand Region (Turkestan Range).	Blooms in July, Fruit set occurs in September.	On rocky slopes in the montane belt
Ungernia sewerzowii	Central Asia (Western	Blooms in July, Fruit	On rocky and

(Regel) B. Fedtsch.	Tien Shan), Uzbekistan, Tashkent Region (Parkent District).	set occurs in august.	gravelly slopes in the montane belt
Ungernia tadshikorum Vved.	Tajikistan	Blooms in July, Fruit set occurs in august.	On fine-soil or gravelly sparsely vegetated sites, among ephemerals or in shrubs
Ungernia victoris Vved. ex Artjush.	Afghanistan, Iran, Turkmenistan Uzbekistan	Blooms in august, Fruit set occurs in, september.	On clayey slopes in the montane belt

Ungernia sewertzowii (US) and *U. victoris* (UV) are medicinal plants and sources of biologically active compounds for pharmaceutical needs. The leaves of US contain 0.29–0.81% sum of alkaloids with a predominance of lycorine, which is 0.04–0.46% in leaves and 0.15–0.38% in bulbs. Lycorine is used to treat acute and chronic bronchitis. The leaves of UV contain 0.27–0.71% sum of alkaloids with a predominance of galanthamine 0.13–1.15% [4].

Lycorine is a colorless crystalline compound with a melting point of 260–262°C. It is insoluble in water, Me_2CO, Et_2O as well as in CHCl3 and alcohol. The biological activity of lycorine is closely related to its molecular structure. For example, its antitumor effect is directly associated with structural features, and even minor modifications within the molecule may significantly reduce or completely abolish its activity [5].

Background: asthma is one of the most prevalent, complex, and severe respiratory disorders, with rising rates of occurrence and death in both children and adults. An alkaloid derived from plants, lycorine possesses several pharmacological effects, primarily anti-inflammatory and antioxidative properties [6].

Liver fibrosis is a foremost medical concern worldwide. In Saudi Arabia, numerous risk factors contribute to its high rates. Lycorine a natural alkaloid has

antioxidant, antiinflammatory, and antitumor activates. It has been reported to inhibit STAT3 in cancer. Therefore, this study aimed at investigating the possible antifibrotic effect of lycorine against thioacetamide (TAA)-induced liver fibrosis in rats and at elucidating the possible mechanisms. Liver fibrosis was induced by TAA [7].

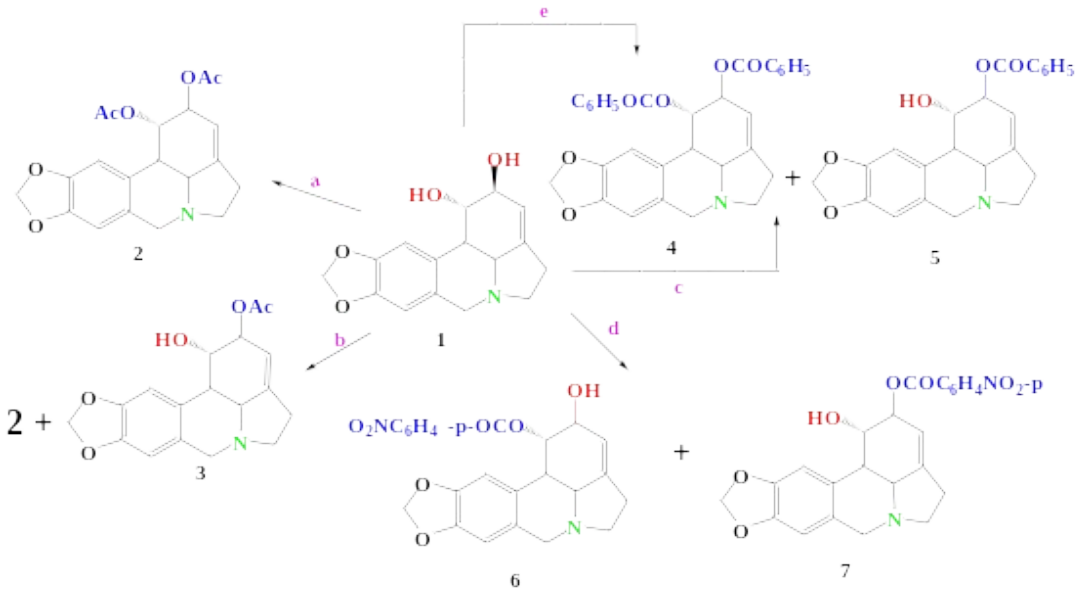
Cancer remains a major global health challenge, neces sitating the continual search for novel therapeutic agents. Chemical structures and anticancer mechanisms of lycorine and lycorine hydrochloride. The two chemical structures represent lycorine and lycorine hydrochloride, respectively. Anticancer mechanisms of lycorine and lycorine hydrochloride include inducing cell cycle arrest, triggering cellular senescence, regulating programmed cell death, suppressing migration and invasion, inhibiting angiogenesis, and modulating immune system [8].

1,2-O-Diatsetillikorin **(2**) were examined to determine their effects on HCV replication. Such as **2** exhibited reduced cytotoxicity while possessing levels of anti-HCV activity similar to that of lycorine [9].

Therefore, it was necessary to investigate the methods for obtaining acyl derivatives and compare them with literature data.

Research Methodology.

Six lycorine derivatives were prepared, character ized, and evaluated for their *in vitro* anti-*Trichomonas vaginalis* activity. Compounds bearing an acetyl (2), benzoyl (4 and 5), and p nitrobenzoyl (6 and 7) groups were synthesized. Preliminary structure–activity relationship points that unpro tected OH group at C-1 and C-2 is not necessary to the antiparasitic activity, and none of the deriva tive was less active than lycorine. This result is an important contribution with our ongoing studies regarding the mechanism of action of the Amaryllidaceae alkaloids on *T. vaginalis* cell death opening a new perspective to opti mize this innovative pharmacological potential [10].



Scheme 1: Reagents and conditions **(a)** Ac_2O, DMAP, Py, r.t, 24h 62% [10]; (**b**) CH_3COCl, Et_3N, C_6H_6, reflux, 8h **(2,** 40%), (**3**, (45%); **(c)** C_6H_5COCl, DMAP, dichlorometane, Py, r.t, 24h, **(4,**.47%), **(5**.23%) [10]; **(d)** p-$NO_2C_6H_4COCl$, DMAP, dichlorometane, Py. (**6,** 0.016 mmol, 7 mg, 17%) and (**7,** 0.017 mmol, 8 mg, 18%) [10]; **(e)** C_6H_5COCl, Et_3N, C_6H_6, reflux, 6h **(4,** 41%), (**5,** 33%).

In recent years, pharmacologists and organic chemists have done a lot of work in the modification and transformation of the lycorine. The modification of lycorine mainly concentrated in the following aspects: (1) Modifications hydroxyl at C1 and C2 positions; (2) Modification of A ring; (3) E ring opening and aromaticity of D ring; (3) oxidation of C2 position; (4) C7 position oxidation and reduc tion of the D ring; (5) oxidation of C7 position and the reduction of the double bond of D ring [11].

Analysis and Results:

(**1).** ^1H NMR ($CDCl_3$, 300 MHz): d 6.80 (1H, s, H-7); 6.57 (1H, s, H-10); 5.40 (1H, s, H-3); 5.90 (2H, s, OCH_2O); 4.37 (1H, s, H-1); 4.15 (1H, s, H-2); 4.10 (1H, d, J= 14.1 Hz, H-6); 3.30 (1H, d, J= 14.1 Hz, H-6); 3.25 (1H, m, H-12); 2.79 (1H, d, J= 10.2 Hz, H-4a); 2.65 (1H, d, J= 10.1 Hz, H-10b); 2.55 (2H, m, H-11); 2.35 (1H, m, H-12). ^{13}C NMR ($CDCl_3$, 75 MHz): d 149.7, 148.1, 137.9, 130.6, 125.7, 122.9, 108.8, 106.4, 102.8, 71.9, 70.1, 61.8, 54.2, 55.1, 38.2, 30.3. [10]

(a) Mixture lycorine (0.105 mmol) with acetic anhydride (0.53 mmol) in pyridine (3 mL) in the presence of catalytic amount of dimethylaminopyridine (DMAP) was stirred for 24h at room temperature. The solvent was evaporated and extracted with chloroform and water. The organic layer was evaporated under reduced pressure, and the residue was purified by column chromatography using dichlorometane:methanol as eluent furnishing (**2**) as a white crystal in 62% yield (25 mg, 0.065 mmol). m.p. 217–218.[10]

In 2017, Y.B. Ji Review on the Structure Modification of Lycorine. (**2)** Ac_2O, Py, 50^{o}C, 12h**,** 93%, (**3)**-59% [12]. In 2020, JACS Alkaloids of the Amaryllidaceae VI. (**2)** Ac_2O (3.0 eq) DMAP, py, r.t 8h, 78%. (**3)**, Ac_2O (1.0 eq), Py, r.t,2h 40% [13]. In 2012, NIH-PA Author Manuscript. Evdokimov et.al. (**2)-** Ac_2O, Py, 99% [14]. In 2014 CHEMMEDCHEM. Peng Wang, Lin-Feng L, (**2)-** Ac_2O, Py, 50^{o}C,12h, 93.3% [15].

(b) In our experience, a reaction between lycorine and acetyl chloride was carried out. Initially, 0.2 g (0.6 mmol) of lycorine, 0.082 g (1 mmol) of CH_3COCl, catalytic amount of Et_3N, and benzene as a solvent were used. The reaction was conducted at reflux 8 hours. The solvent was removed in vacuo, followed by the addition of $CHCl_3$ and water.The organic layer was washed with saturated aq $NaHCO_3$ and then brine and was dried over anhydrous $NaSO_4$ The resulting reaction products were separated by column chromatography ($CHCl_3$:CH_3OH 100:0 → 100:1). The isolated compounds were analyzed via mass spectrometry and identified as (1S,2S)-1-hydroxy-2,3a1,4,5,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de] phenanthridin-2-yl (**3**) acetate and (1S,2S)-2,3a1,4,5,7,12b-hexahydro-1H- [1,3] dioxolo[4,5-j]pyrrolo[3,2,1-de] phenanthridine-1,2-diyl (**2**) diacetate based on their molecular masses. White crystal in **(2)** 40%, (**3**) (45%) yield.

Compound 2: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.73 (1H, s, H-7); 6.56 (1H, s, H-10); 5.90 (2H, s, OCH_2O); 5.72 (1H, s, H-1); 5.52 (1H, s, H-3); 5.24 (1H, s, H-2); 4.17 (1H, d, J = 12.4 Hz, H-6); 3.53 (1H, d, J = 12.4 Hz, H-6); 3.36 (1H, m, H-12); 2.87 (1H, d, J = 10.3 Hz, H-10b); 2.79 (1H, d, J=10.3 Hz, H 4a); 2.64 (2H,

m, H-11); 2.41 (1H, m, H-12), 2.07 (3H, s, $OCOCH_3$); 1.94 (3H, s, $OCOCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 169.9, 146.6, 146.5, 146.1, 129.4, 126.7, 114.0, 107.5, 105.2, 101.1, 71.0, 69.4, 61.3, 56.9, 53.7, 40.5, 28.8, 21.3, 21.0 [10].

(c) 1,2-*O*-Dibenzoyllycorine (**4**) and 2- *O* -benzoyllycorine (**5**) were obtained by reaction of lycorine (0.105 mmol) with benzoyl chloride (0.21 mmol) in pyridine (2 mL) and in the presence of catalytic amount of DMAP. The reaction mixture was stirred for 2 days at room temperature. The solvent was evaporated under reduced pres sure followed by extraction with chloroform and saturated aqueous solution of sodium bicarbonate. The organic layer was concentrated, and the residue was purified by column chromatography using dichlorometane :methanol as eluent yielding compounds (**4**) (0.046 mmol, 23 mg, 47%) and (**5**) (0.023 mmol, 9 mg, 23%) [10].

(d) 2-*O*-*p*-Nitrobenzoyllycorine (**6**) and 1- *O*-*p* -nitrobenzoyllycorine (**7**) were obtained by reaction of lycorine (0.105 mmol) with *p*-nitro benzoyl chloride (0.30 mmol) in pyridine (2 mL) and in the presence of catalytic amount of DMAP. The reaction mixture was stirred for 4 days at room temperature. The solvent was evaporated under reduced pressure followed by extraction with chloroform and saturated aqueous solution of sodium bicarbonate. The organic layer was concentrated, and the residue was purified by column chromatography using dichlorometane:methanol as eluent yielding compounds (**6**, 0.016 mmol, 7 mg, 17%) and (**7**, 0.017 mmol, 8 mg, 18%) [10].

(e) In our experience, a reaction between lycorine and benzoylchloride was carried out. Initially, 0.2 g (0.6 mmol) of lycorine, 0.096 ml (0.8 mmol) of C_6H_5COCl, catalytic amount of Et_3N, and benzene as a solvent were used. The reaction was conducted at reflux for 6 hours. 0 The solvent was removed in vacuo, followed by the addition of $CHCl_3$ and water.The organic layer was washed with saturated aq $NaHCO_3$ and then brine and was dried over anhydrous $NaSO_4$. The resulting reaction products were separated by column chromatography ($CHCl_3$:CH_3OH 100:0 → 100:1). The isolated compounds **(4,** m.p 90-93°C, 71%). were analyzed via mass spectrometry**.**

In our experience, a reaction between lycorine and *m*-nitro benzoyl chloride was carried out. Initially, 0.2 g (0.6 mmol) of lycorine, 0.129 g (0.8 mmol) of *m*-nitro benzoyl chloride, catalytic amount of Et_3N, and benzene as a solvent were used. The reaction was conducted at reflux for 22 hours. In the reaction between lycorine and meta-nitrobenzoyl chloride, the expected result was not achieved.

Conclusion

In conclusion, it can be stated that considering the high biological and pharmacological activities of lycorine, an alkaloid from *Ungernia victoris*, the synthesis of its derivatives is considered a targeted and purposeful approach. The synthesis methods provided in the above-mentioned literature serve as practical guidance for the development of new lycorine-based compounds. Conditions for the simultaneous production of mono- and di-acetyl (1:1) lycorine and dibenzoyl lycorine derivatives with high yields were found.

The work was supported by the Budgetary Basic Scientific Research Program of the Academy of Sciences of the Republic of Uzbekistan.

References

1. Итоги исследования алкалоидоносных растений. – под ред. . Арипова Х. Н., “Фан”, Ташкент, 1993.

2. Strahil Berkova, Edison Osoriob, Francesc Viladomatc, Jaume Bastidac. Chemodiversity, chemotaxonomy and chemoecology of Amaryllidaceae alkaloids. // Sciencedirect –2020. –V. 83– P. 113-185

3. Zhamalova D., Kurbaniazova G. ФИЗИОЛОГИЯ И БИОХИМИЯ РАСТЕНИЙ //Главный редактор. – 2021. – P. 45.

4. Mustafina, F. U., Juraeva, H. K. K., Jamalova, D. N. K., Hazratov, A. T. O, Janabaeva, A. J, Kim, H. J., Abdinazarov, S. K. Conservation Potential Trough *In Vitro* Regeneration of Two Threatened Medicinal Plants *Ungernia sewertzowii* and *U. victoris* //Plants. – 2024. – V. 13. – №. 14. – P. 1966.

5. Roy M. Liang, L. Xiao, X., Feng. P., Ye. M., Liu J. Lycorine: A prospective natural lead for anticancer drug discovery //Biomedicine & Pharmacotherapy. – 2018. – V. 107. – P. 615-624.

6. Wang Y., Wu. Y., Alzahrani A. R., Seshadri V. D., Li F. Lycorine Attenuates Airway Inflammation in an OVA induced Allergic Asthma Model //Ind. J. Pharm. Ed. Res. – 2023. – V. 57. – №. 3. – P. 756-762.

7. Alkreathy H. M., Esmat A. Lycorine ameliorates thioacetamide-induced hepatic fibrosis in rats: Emphasis on antioxidant, anti-inflammatory, and STAT3 inhibition effects //Pharmaceuticals. – 2022. – V. 15. – №. 3. – P. 369.

8 Zhang Y. M. et al. Uncover the anticancer potential of lycorine //Chinese Med. – 2024. – V. 19. – №. 1. – P. 121.

9.Chen. D., Cai, J., Chen.J., Jing C., Yin J., Jiang J., Peng Z., Hao X., Design, synthesis and structure-activity relationship optimization of lycorine derivatives for HCV inhibition //Sci. rep. – 2015. – V. 5. – №. 1. – P. 14972.

10. Giordani R. B., Junior C. O., de Andrade J. P., Bastida J., Zuanazzi J. A., Tasca T., de Almeida M. V. Lycorine derivatives against *Trichomonas vaginalis* //Chem. Biol. Drug Design. – 2012. – V. 80. – №. 1. – P. 129-133.

11. Ji Y. B., Yang S. L., Zhang X. L., Liu Y. J. Review on the Structure Modification of Lycorine //IOP Conference Series: Earth and Environmental Science. – IOP Publishing, 2017. – V. 100. – №. 1. – P. l012052

12. Ji Y. B., Yang S. L., Zhang X. L., Liu Y. J. Review on the Structure Modification of Lycorine //IOP Conference Series: Earth and Environmental Science. – IOP Publishing, 2017. – V. 100. – №. 1. – P. 012052.

13. Ka S. Koirala, M. Mérindol, N. Desgagné-Penix, I. Biosynthesis and biological activities of newly discovered Amaryllidaceae alkaloids //Molecules. – 2020. – V. 25. – №. 21. – P. 4901.

14. Evdokimov N. M., Lamoral-Theys D., Mathieu V., Andolfi A., Frolova L. V., Pelly S.C, Kornienko A. In search of a cytostatic agent derived from the alkaloid lycorine: Synthesis and growth inhibitory properties of lycorine derivatives //Bioorg. Med. Chem. – 2011. – V. 19. – №. 23. – P. 7252-7261.

15. Wang P., Li L. F., Wang Q. Y., Shang L. Q., Shi P. Y., Yin Z. Anti-dengue-virus activity and structure–activity relationship studies of lycorine derivatives //ChemMedChem. – 2014. – V. 9. – №. 7. – P. 1522-1533.