*Chemistry of Natural Compounds, Vol. 38, No. 2, 2002*

# STRUCTURE-ACTIVITY RELATIONSHIP FOR HEMOSTATIC LAGOCHILIN DITERPENOIDS

**U. N. Zainutdinov,[1] R. Islamov,[1] D. N. Dalimov,[2] T. R. Abdurakhmanov,[2] O. D. Matchanov,[1] and N. L. Vypova[2]**

UDC 547.914.6+547.996.02

*The structure-hemostatic activity relationship of lagochilin and its natural and synthetic derivatives was investigated.*

**Key words:** *Lagochilus*, diterpenoids, 9,13-epoxylabdane, lagochilin, lagoden, lagochirsine, hemostatic activity.

Plants of the *Lagochilus* genus (Lamiaceae) comprise 44 species worldwide, 34 of which grow in the CIS republics; 25, in Central Asia; 17, in Uzbekistan [1]. Despite their wide application in folk and traditional medicine, the chemistry of these plants is poorly studied.

We investigated 12 species of *Lagochilus* [2-7] growing in Central Asia and isolated from these 25 diterpenoids with the 9,13-epoxylabdane skeleton. Of these, 20 were new. Known hydrocarbons, steroids, flavonoids, and iridoid glycosides accompanied the diterpenoids. Flavonoids and iridoids are observed in almost all studied species of these plants.

The diterpenoids and their synthetic derivatives can be subdivided by structure into three groups: I) lagochilin and its isopropylidene and acetyl derivatives (**1**-**16**), II) anhydrolagochilins (**17**, **18**), III) diterpenoid lactones and lagoden (**19**-**23**, **24**).

3,18-O-Isopropylidenelagochilin (**2**), di-O-isopropylidenelagochilin (**3**), 3,18-O-isopropylidenelagochilin-15,16-diacetate (**4**), and 3,18-O-isopropylidenelagochilin-15-acetate (**5**) were isolated from only one species, *L. pubescens*. However, lagochilin (**1**) and 11 isomeric acetyl derivatives of lagochilin (**6**-**16**) were found in *L. inebrians* and *L. pubescens*. Lagochilin (**1**) and the diterpenoid lactones lagochirsine (**19**), lagochirsine 3-acetate (**20**), lagochirsine 18-acetate (**21**), lagochirsine 3,18-diacetate (**22**), and lagochirsidine (**23**) were found in three species: *L. hirsutissimus*, *L. setulosus*, and *L. gupsaceus*. These diterpenoids and their synthetic derivatives (**17**, **18**, and **24**) were studied as hemostatics.

The sodium salt of 3,16,18-trihydroxy-9,13-epoxylabdan-15-oic acid (lagoden **24**) was used as a reference preparation with 100% hemostatic activity (Table 1).

It has been interesting to determine to what extent the hemostatic activity depends on the degree of shielding of the hydroxyls by acetyls and isopropyls in lagochilin, anhydrolagochilin, lagochirsine.

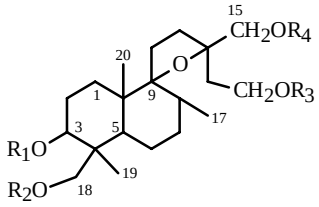
The hemostatic activity of the C-3 and C-8 isopropylidene derivative (**2**) of lagochilin (Table 1) decreases by 50%. Replacing the hydroxyls on C-15 and C-16 by O-isopropylidenes further reduces the activity to 33% (**3**). Compounds **4** and **5**, where the OH groups on C-3 and C-18 are shielded by isopropyl and the OH on C-15 and C-16 by one or two acetyls, have similar activities.

The lagochilin hydroxyls in **6**-**16** are shielded by acetyls to various extents. Aqueous solutions (0.5%) of these compounds, except the tetraacetyl derivative, exhibit 81-84% hemostatic activity. It should be noted that lagochilin is insoluble in water. Therefore, it was not studied as a hemostatic. However, lagochilin in peach oil (0.5%) exhibits 67% activity compared with the reference. Like for lagochilin, lagochilin tetraacetate is insoluble in water (to 0.5%) and exhibits 67% hemostatic activity in peach oil. Whereas anhydrolagochilin exhibits weak hemostatic activity (17%), shielding the C-3 and C-18 hydroxyls causes complete loss of activity (the hemostatic activity of aqueous-alcohol solutions of **17** and **18** was determined). Shielding the C-13 and C-18 hydroxyls in lagochirsine by acetyls (**19**-**22**) causes no particular change in their hemostatic activity (67%).

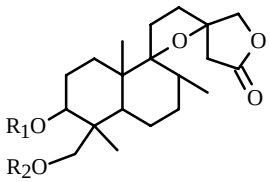
1) Mirzo Ulugbek National University of Uzbekistan, fax (99871) 46 24 72; 2) A. S. Sadykov Institute of Bioorganic Chemistry, fax (99871) 169 03 24. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 135-136, March-April, 2002. Original article submitted May 14, 2001; revision submitted April 14, 2002.

0009-3130/02/3802-0161$27.00 

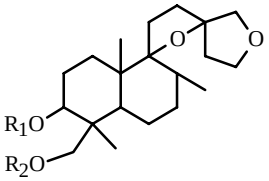
TABLE 1. Hemostatic Activity of Lagochilin and Its Derivatives (M ± m; n = 10)



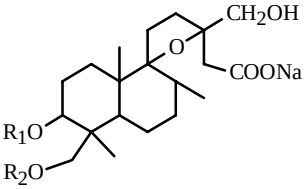

**1 - 16**



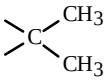

**17- 18**

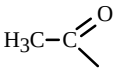



**19 - 23**




**24**

a 


b 


| Compound | Substituents | | | | Hemostatic activity | |
|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | s | % |
| **1** | H | H | H | H | 130±12.6 | 67 |
| **2** | a | | H | H | 147±14.8 | 50 |
| **3** | a | | a | | 163.7±14.8 | 33 |
| **4** | a | | b | b | 163.7±13.5 | 33 |
| **5** | a | | b | H | 165±14.7 | 32 |
| **6** | b | H | H | H | 115±11.4 | 83 |
| **7** | H | H | H | b | 116±10.8 | 82 |
| **8** | H | H | b | b | 115±10.5 | 86 |
| **9** | b | b | H | H | 114±10.6 | 84 |
| **10** | b | H | H | b | 115±10.6 | 83 |
| **11** | b | H | b | H | 115±11.0 | 83 |
| **12** | H | b | b | H | 115±11.0 | 83 |
| **13** | H | b | b | b | 117±10.6 | 81 |
| **14** | b | b | H | b | 115±11.2 | 83 |
| **15** | b | b | b | H | 117±10.5 | 81 |
| **16** | b | b | b | b | 130±13.0 | 67 |
| **17** | H | H | | | 179±16.5 | 17 |
| **18** | a | | | | 266±16.0 | 0 |
| **19** | H | H | | | 129±13.0 | 68 |
| **20** | b | H | | | 130±13.0 | 67 |
| **21** | H | b | | | 130±12.7 | 67 |
| **22** | b | b | | | 131±12.6 | 66 |
| **23** | a | | | | 140±13.0 | 51 |
| **24** | H | H | | | 98±10 | 100 |
| Control | | | | | 265±15.6 | |

$p < 0.05$.

Adding an isopropylidene to lagochirsine reduces the activity (51%) whereas opening the lactone ring by forming the corresponding sodium salt of 3,16,18-trihydroxy-9,13-epoxylabdan-15-oic acid (**24**) causes a sharp increase of hemostatic activity (100%). A comparison of the hemostatic activity of lagochilin, anhydrolagochilin, and lagochirsine using aqueous-alcohol solutions indicates that lagochirsine is the most active.

Thus, shielding three of the four lagochilin hydroxyls by acetyls has no effect on the hemostatic activity. Only complete shielding of the hydroxyls leads to loss of activity. Introducing isopropylidene groups has negative effects on the hemostatic activity. This may be due to increased hydrophobicity of lagochilin. Apparently the solubility of the lagochilin derivatives is

important for the manifestation of hemostatic activity because it ensures that they are readily available.

## EXPERIMENTAL

We used a published screening method [8]. Diterpenoids **1** and **16** were dissolved in oil; **2**-**5** and **17**-**23**, in aqueous-alcohol (50%); the others, in water.

Experiments were performed on white rats of 200-250 g mass with 10 rats in each group for each compound. The results were analyzed statistically according to the literature [9].

## REFERENCES


1. T. I. Tsukervanik, *Bot. Zh.*, **70**, 9, 1183 (1985).
2. U. N. Zainutdinov, Kh. A. Aslanov, and A. S. Sadykov, Fifth Soviet-Indian Symposium on the Chemistry of Natural Compounds [in Russian], Erevan (1978), 127.
3. Z. I. Mavlyankulova, U. N. Zainutdinov, and Kh. A. Aslanov, *Khim. Prir. Soedin.*, 46 (1977)
4. Z. I. Mavlyankulova, U. N. Zainutdinov, Kh. A. Aslanov, and F. G. Kamaev, *Khim. Prir. Soedin.*, 82 (1978).
5. R. Islamov, U. N. Zainutdinov, and Kh. A. Aslanov, *Khim. Prir. Soedin.*, 404 (1978).
6. R. Islamov, U. N. Zainutdinov, and Kh. A. Aslanov, *Khim. Prir. Soedin.*, 57 (1987).
7. U. N. Zainutdinov, Kh. A. Aslanov, M. P. Nurmatova, F. G. Kamaev, and A. S. Sadykov, Fifth Soviet-Indian Symposium on the Chemistry of Natural Compounds [in Russian], Erevan (1978), 127.
8. I. E. Akopov, M. V. Yadrova, and L. V. Murtazaeva, *Nauchn. Tr. Kuban. Med. Inst.*, **55**, 12 (1976).
9. M. L. Belen′kii, *Elements of Quantitative Evaluation of Pharmacologic Effects* [in Russian], Riga (1963), p. 81.