UDC 547.314

N.Merkhatuly[1], P.Vojtíšek[2], S.B.Abeuova[1], A.T.Omarova[1], A.N.Iskanderov[1]

[1]Ye.A.Buketov Karaganda State University;
[2]Charles University, Prague, Czech Republic
(E-mail: merhatuly@ya.ru)

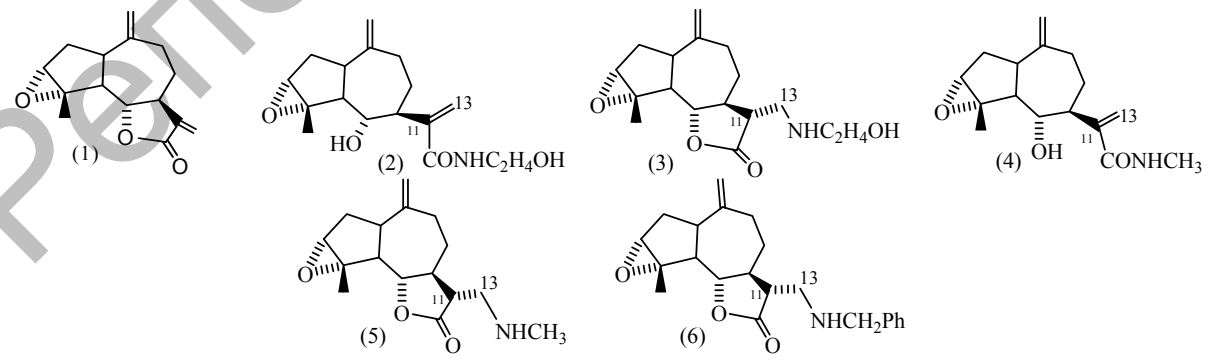
Synthesis and biological activity of nitrogen-containing derivatives of estafiatin

The reactions of guaianolide of estafiatin with various amines were investigated. It was shown that the aminolysis reactions of γ-lactone ring of estafiatin or reactions of Michael-type conjugate addition or tandem conversions of Michael and Knoevenagel-type were carried out depending on the nature of amines. The regularity of proceeding of estafiatin reactions with secondary aliphatic and aliphatic-aromatic amines was detected. It lies in the fact that the reactions proceed exclusively by Michael reaction and they are completely regio- and stereoselective. It was revealed that synthetic nitrogen-containing derivatives of estafiatin had antibacterial and antioxidant activity.

Key words: guaianolide, estafiatin, aminolysis, aliphatic amines, Michael reaction, tandem reaction, antibacterial and antioxidant activity.

Estafiatin (1), a guaiane sesquiterpene γ-lactone (guaianolide), induces interest for study of nucleophilic addition reactions of amines and synthesis of new potentially biologically active nitrogen-containing derivatives [1–3].

In this article the reactions of estafiatin (1) with various aliphatic and aliphatic-aromatic amines were investigated. Interaction of estafiatin (1) with primary amines as monoethanolamine, methylamine in ethanol medium at temperature 25–30 ºC leads to the formation of products of the aminolysis reaction of γ-lactone ring — hydroxy amides (2) (65 % yield) and (4) (53 % yield), respectively and of products of the Michael-type conjugated addition — adducts (3) (20 % yield) and (5) (30 % yield), respectively. The reaction of estafiatin (1) with benzylamine leads only to Michael adduct (6) with 96 % quantitative yield. ^{1}H-NMR spectrum data of obtained compounds are shown in Table 1.



Joining of primary aliphatic amines by Michael-type occurs stereoselectively and leads to the formation of stereoisomers with α-oriented C-13 carbon atom.

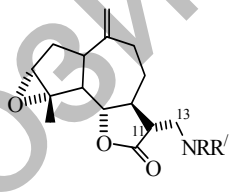
Table 1

^{1}H-NMR spectrum data

Protons	Compounds					
	(1)	(2)	(3)	(4)	(5)	(6)
Me-4	1,53 singlet	1,56 singlet	1,50 singlet	1,53 singlet	1,56 singlet	1,53 singlet
H-3	3,28 broad singlet	3,28 broad singlet	3,75 broad singlet	2,84 broad singlet	2,90 broad singlet	2,84 broad singlet
H-6	4,01 quintet (10,5;9)	4,0 triplet (10)	3,95 triplet (10)	3,34 triplet (10)	3,18 triplet (10)	3,03 broad triplet (9)
H-13a	5,42 doublet (3,5)	5,40 doublet (2,5)	2,67 multiplet	5,41 doublet (3)	2,50 doublet (3)	2,53 multiplet
H-13b	6,12 doublet (3,5)	6,1 doublet (2,5)	2,67 multiplet	6,21 doublet (3)	2,50 multiplet	2,53 multiplet
H-14a	4,78 broad singlet	4,78 broad singlet	4,75 broad singlet	4,53 broad singlet	4,56 broad singlet	4,50 broad singlet
H-14b	4,78 broad singlet	4,90 broad singlet	4,82 broad doublet	4,45 broad singlet	4,64 broad singlet	4,56 broad singlet
Other protons	–	$CONH(CH_2)_2OH$; 2,14 broad triplet (1H), (7,5) 2,17 broad singlet (4H)	$HN(CH_2)_2H$ 3,50 broad singlet (1H), 2,10 broad singlet (4H)	$CONHCH_3$; 2,52 broad singlet (1H), 1,84 singlet (3H)	$HNCH_3$; 2,70 broad singlet (1H), 1,90 singlet (3H)	NCH_2Ph -3,43 singlet (1H), 7,09 broad singlet (5H)

By analogy with primary amines we expected the competing attack by benzylamine to occur with the assistance of more reactive carbonyl group of estafiatin (1). However only a product of conjugate addition was obtained. It's the adduct (6) with 96 % quantitative yield. In this case, the Michael reaction completely occurs regio- and stereoselectively, giving the product (6) with α-oriented C-13-atom.

Considering that secondary aliphatic amines are the most basic and more reactive nucleophilic reagents than the primary we expected the regioselective addition to the carbonyl group of estafiatin to occur with the formation of products of aminolysis. However, the reactions of estafiatin (1) with diethanolamine, diethanolamine, diethylamine, piperidine and morpholine in ethanol medium at temperature 25–30 °C occur with the assistance of activated double bond C_{11}–C_{13} (Michael reaction) and lead to aminoadducts (7–11) (85–95 % high yields) with α-oriented C-13-atom (^{1}H-NMR spectrum data are shown in Table 2).



(7) $RR^/$=-CH_3
(8) =-C_2H_5
(9) =-$(CH_2)_2O(CH_2)_2$-
(10) $RR^/$=-$(CH_2)_5$-
(11) =-C_2H_4OH

Probably in reactions of estafiatin (1) with primary aliphatic-aromatic and secondary aliphatic amines, the regiospecific nucleophilic addition by Michael-type is also controlled by the nature of the amines, namely of hard and soft basic properties. So this regularity can be explained by the theory of HSAB. Obviously, these amines are boundary bases such as aniline, pyridine, etc. So, under these conditions, these amines like soft bases interact with soft electrophilic C13-carbon atom (1). They form only conjugate addition products.

The biological activity of the synthesized nitrogen-containing derivatives of estafiatin (1) was studied. It was found that morpholinamine (9) and benzylamine of estafiatin (6) had antibacterial activity against 16 strains of gram-positive bacteria (Staphylococcus aureus, St.epidermidis et al.), gram-negative bacteria (Salmonella spp., Klebsiella spp. et al.) and gram positive nonspore-forming anaerobic bacteria (Propionibakterium spp., Eubacterium spp.) and coccus (Reptococeus spp.) and also had fungicidal action against fungal strains of the genus Candida albicans and Mucor.

Furthermore, it was found that amino adducts (6), (9) and (10) had antioxidant activity. The relationship between their structure and biological activity was identified (Table 3).

Table 2

^{1}H-NMR spectrum data

Protons	Compounds					
	(1)	(7)	(8)	(9)	(10)	(11)
Me-4	1,53 singlet	1,56 singlet	1,56 singlet	1,59 singlet	1,56 singlet	1,20 doublet
H-3	3,28 broad singlet	2,09 broad singlet	3,31 broad singlet	2,89 broad singlet	2,87 broad singlet	–
H-6	4,01 quintet (10,5;9)	3,12 triplet (10)	4,0 broad triplet (10)	3,12 triplet (10)	3,12 triplet (10)	3,18 triplet (10)
H-13a	5,42 doublet (3,5)	2,37 doublet of doublets (8;9)	2,43 multiplet	2,01 multiplet	2,50 broad doublet (2,5)	3,87 broad singlet
H-13b	6,12 doublet (3,5)	2,65 doublet of doublets (8;9)	2,43 multiplet	2,01 multiplet	2,65 broad doublet (2,5)	3,87 broad singlet
H-14a	4,78 broad singlet	4,53 doublet (3)	4,87 broad singlet	4,39 doublet (2,5)	4,53 doublet (2,5)	4,65 doublet (2,5)
H-14b	4,78 broad singlet	4,53 doublet (3)	4,87 broad singlet	4,39 doublet (2,5)	4,53 doublet (2,5)	4,65 doublet (2,5)
Other protons	–	$N(CH_3)_2$; 1,89 singlet (6H),	$N(CH_2CH_3)_2$; 2,18 multiplet (4H), 0,93 triplet (6H, 9)	$N(CH_2)_2O(CH_2)_2$; 3,37 broad triplet (8H, 4)	$-N(CH_2)_5$; 2,78 broad singlet (10H)	$N(CH_2CH_2OH)_2$; -3,51 broad singlet (4H)

Table 3

Antioxidant activity of estafiatin (1) and its derivatives (parameters of initiated chemiluminescence of lipids in the presence of synthesized compounds)

N/N	Code and the number of compounds	H	τ	tg α	H, arbitrary units
1	T-1 (1)	2,11±0,08 arbitrary units	2,9±0,14 min	3,2±0,19	7,6±0,61
2	T-M (9)	5,5±0,5 arbitrary units	1,57±0,07 min	7,0±0,28	32,5±2,15
3	T-P (10)	5,75±0,6 arbitrary units	1,8±0,09 min	4,5±0,29	16,25±1,5
4	T-BA (6)	5,41±0,4 arbitrary units	1,7±0,11 min	5,6±0,22	17,5±1,4
5	Ionol	2,17±0,13 arbitrary units	7,64±0,15 min	2,69±0,13	6,34±0,51
6	Control	2,6±0,1 arbitrary units	2,0±0,09 min	3,5±0,29	7,1±0,55

For example, benzylamine (6), morpholine (9) and piperidine (10) lose the antioxidant activity of the estafiatin (1). The value of the latent period is decreased by 1.6 times or greater at transition from estafiatin (1) to its three derivatives (6), (9) and (10). It is explained by the absence of mobile hydrogen atoms of exomethylene group of γ-lactone ring (1) inhibiting free radical oxidation (FRO). Adequate change of parameters of initiated chemiluminescence of lipids was found for all mentioned derivatives of estafiatin. Derivative of morpholine (9) has an obvious pro-oxidant effect.

Thus, synthesized biologically active nitrogen-containing derivatives of guaianolide of estafiatin (1) are interesting for investigating their pharmacological activity and creating effective new drugs.

References

1 *Haimaya K., Inayama S.* Structure activity relationships of pseudoquaianolides isolated from Gaillardia pulchella and their derivatives // Heterocycles. — 1990. — Vol. 30, № 2. — P. 993–1008.

2 *Талжанов Н.А., Атажанова Г.А., Адекенов С.М.* Диеноновые гваянолиды: выделение из растений, особенности строения молекул и синтезы на их основе // Хим. журнал Казахстана. — 2005. — № 3. — С. 97–125.

3 *Adekenov S.M.* Synthesis of new derivatives of natural guaianolides // Chemistry of Natural Compounds. — 2013. — Vol. 48. — P. 988–995.

Н.Мерхатұлы, П.Войтичек, С.Б.Әбеуова, А.Т.Омарова, А.Н.Искандеров

Эстафиатиннің азотқұрамды туындыларының синтезі және биологиялық белсенділігі

Гваянолид эстафиатиннің әр түрлі аминдермен реакциялары зерттелді. Аминдердің табиғатына байланысты эстафиатиннің γ-лактонды циклінің аминолиз реакциясы, немесе Михаэль типі бойынша қосарланған қосылу реакциялары, немесе Михаэль және Кневенагель типтері бойынша тандемді реакциялары жүретіні көрсетілді. Эстафиатиннің екіншілік аминдермен және майлы ароматты аминдермен реакциялары Михаэль типі бойынша жүретіні мен бұл реакциялардың регио- және стереоселективті екені дәлелденді. Эстафиатиннің синтезделіп алынған азотқұрамды туындылары антиоксидантты және микробқа қарсы белсенділік көрсететіні анықталды.

Н.Мерхатулы, П.Войтичек, С.Б.Абеуова, А.Т.Омарова, А.Н.Искандеров

Синтез и биологическая активность азотсодержащих производных эстафиатина

Изучены реакции гваянолида эстафиатина с различными аминами. Показано, что, в зависимости от природы аминов осуществляются либо реакции аминолиза γ-лактонного цикла эстафиатина, либо реакции сопряженного присоединения по типу Михаэля, либо тандемные превращения по типу Михаэля и Кневенагеля. Выявлена закономерность протекания реакций эстафиатина с вторичными алифатическими и жирноароматическими аминами, заключающаяся в том, что они реализуются исключительно по реакции Михаэля и являются полностью регио- и стереоселективными. Установлено, что ряд синтезированных азотсодержащих производных эстафиатина обладает антиоксидантной и противомикробной активностью.

References

1 Haimaya K., Inayama S. *Heterocycles*, 1990, 30, 2, p. 993–1008.
2 Talzhanov N.A., Atazhanova G.A., Adekenov S.M. *Chem. Journal of Kazakhstan*, 2005, 3, p. 97–125.
3 Adekenov S.M. *Chemistry of Natural Compounds*, 2013, 48, p. 988–995.

Information about authors

Merkhatuly Nurlan — Head of Inorganic and Technical Chemistry Department, Doctor of chemical sciences, Professor, Ye.A.Buketov Karaganda State University.

Vojtíšek Pavel — RNDr., CSc, Ass. Professor of Department of Inorganic Chemistry, Faculty of Science, Charles University, Prague, Czech Republic.

Abeuova Saltanat B. — PhD student, Inorganic and Technical Chemistry Department, Ye.A.Buketov Karaganda State University.

Omarova Arailym Turssunovna — Teacher of Inorganic and Technical Chemistry Department, Master of chemical sciences, Ye.A. Buketov Karaganda State University.

Iskanderov Amantai Nurbaevich — Engineer of laboratory of Natural Compounds Chemistry, Inorganic and Technical chemistry Department, Ye.A.Buketov Karaganda State University.

Сведения об авторах

Мерхатулы Нурлан — профессор кафедры неорганической и технической химии д.х.н., Карагандинский государственный университет им. Е.А.Букетова.

Войтичек Павел — ассоциированный профессор кафедры неорганической химии, Карлов Университет в Праге, Чехия.

Абеуова Салтанат Б. — PhD студент кафедры неорганической и технической химии, Карагандинский государственный университет им. Е.А.Букетова.

Омарова Арайлым Турсыновна — преподаватель кафедры неорганической и технической химии магистр химических наук, Карагандинский государственный университет им. Е.А.Букетова.

Искандеров Амантай Нурбаевич — инженер лаборатории химии природных соединений, Карагандинский государственный университет им. Е.А.Букетова.