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N–Acylation and *N*–Alkylation of Bis(benzo)aza–14–Crown–4 Ethers. Novel Hybrid Compound – Bis(furanyl)triazinethiolazacrown Ether

Truong H. Hieu,[a] Alexandra I. Komarova,[b] Alexander N. Levov,[b] Anatoly T. Soldatenkov,[b] Elena I. Polyakova,[b] Tuyen V. Nguyen,[a,d] Dang T. T. Anh,[a,d] Dat T. Nguyen,[c] Tran T. T. Van,[c] and Le Tuan Anh[c@]

[a]*Institute of Chemistry, Vietnam Academy of Science and Technology, 100000 Hanoi, Vietnam*
[b]*Department of Chemistry, Peoples' Friendship University of Russia, 117198 Moscow, Russia*
[c]*Faculty of Chemistry, VNU University of Science, 100000 Hanoi, Vietnam*
[d]*Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 100000 Hanoi, Vietnam*
[@]*Corresponding author E-mail: huschemical.lab@gmail.com*

*Macroheterocycles containing aza-14-crown-4 ether subunit were synthesized by one-step domino reaction. They are interesting objects for study of physicochemical properties and types of transformation. The N-acylated and N-alkylated aza-14-crown-4 ethers were obtained in good yields. The new hybrid compound – bis(furanyl)triazinethiolazacrown ether – was formed by S-alkylation of N-chloroacyl derivative (**3**). According to the PASS program, these substances can be inhibitors of the permeability of cell membrane and act also as a CYP2H substrate.*

Keywords: Azacrown ether, acylation, *S*-alkylation, multicomponent condensation reaction, hybrid compound.

N–ацилирование и *N*–алкилирование бис(бензо)аза–14–краун–4–эфиров. Новое гибридное соединение – бис(фуранил) триазинтиолазакраун–эфир

Т. Х. Хиеу,[a] А. И. Комарова,[b] А. Н. Левов,[b] А. Т. Солдатенков,[b] Е. И. Полякова,[b] Т. В. Нгуен,[a,d] Д. Т. Т. Ань,[a,d] Д. Т. Нгуен,[c] Т. Т. Т. Ван,[c] Л. Т. Ань[c@]

[a]*Институт химии, Вьетнамская академия наук и технологий, 100000 Ханой, Вьетнам*
[b]*Кафедра химии, Российский университет дружбы народов, 117198 Москва, Россия*
[c]*Факультет химии, Ханойский университет науки, 100000 Ханой, Вьетнам*
[d]*Высший университет науки и технологий, Вьетнамская академия наук и технологий, 100000 Ханой, Вьетнам*
[@]*E-mail: huschemical.lab@gmail.com*

*Одностадийной домино-реакцией были синтезированы макрогетероциклы, содержащие фрагмент аза-14-краун-4-эфира. Они являются интересными объектами для изучения физико-химических свойств и типов превращений. N-Ацилированные и N-алкилированные аза-14-краун-4-эфиры были получены с хорошими выходами. Новое гибридное соединение – бис(фуранил)триазинтиолазакраун-эфир – было синтезировано S-алкилированием N-хлорацил производного (**3**). В соответствии с результатами программы PASS, эти вещества могут быть ингибиторами проницаемости клеточной мембраны и действовать также как субстрат CYP2H.*

Keywords: Азакраун-эфир, ацилирование, *S*-алкилирование, многокомпонентная реакция конденсации, гибридное соединение.

Introduction

In the past ten years, supramolecular (such as azacrown ethers/their complexes)[1-4] and the one-step multicomponent condensation reaction (such as Hantzsch reaction, Petrenko–Kritchenko reaction)[5-7] have intensively attracted attention over the world. We have recently reported several methods of the synthesis of azacrown ethers containing piperidone, diazine, triazine and pyridine subunits by multicomponent condensation reaction.[8-10] It was found that these macrocyclic compounds have high cytotoxicity against Hep-G2, RD, FL, Lu1, MCF7, PC3, thus they could be promising potential anticancer agents.[11-13] However, there are several types of new azacrown ethers that were already obtained, but chemical properties and a ways of conversion of these azacrown systems have not been studied enough. In our previous work,[14] it was shown that NH-piperidine fragment of an azacrown (**2**) is easily acetylated by acetic anhydride to give the corresponding *N*-acetyl derivative (Scheme 1).

Experimental

Melting points were determined in open capillary tubes on a digital Stuart SMP3 apparatus. Elemental analysis was conducted on Euro Vector EA-3000 analyzer. IR spectra were recorded in KBr disks on an Infralum FT-801 spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ solution at 25 °C, using a BRUKER 500 MHz spectrometer and TMS as internal standard. Mass spectra were obtained on instruments Finnigan MAT 95 XL (EI, ionizing energy 70 eV).

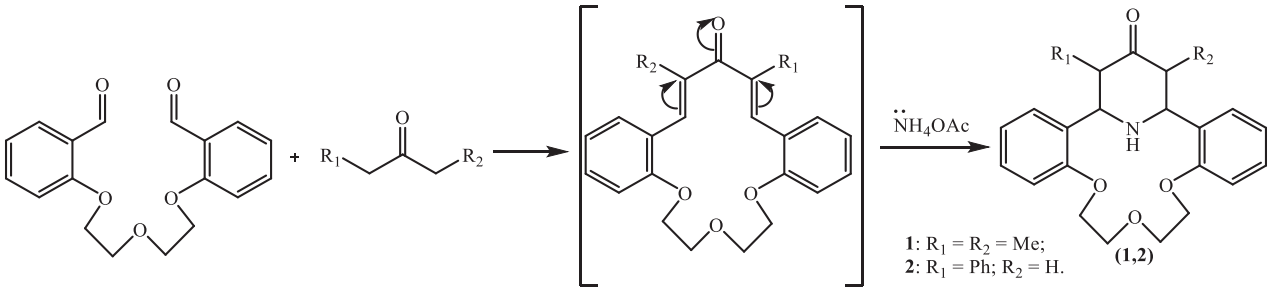
*22-Phenyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}] pentacosa-2,4,6,15(20),16,18-hexaen-23-one (**1**)* and *22,24-dimethyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexaen-23-one (**2**)* were synthesized by general methods.[9]

*25-N-(2'-Chloroacetyl)-22,24-dimethyl-8,11,14-trioxa-25-azatetracyclo-[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexaen-23-one (**3**).* To a mixture of 2.0 g (5.25 mmol) of piperidone, 1.0 g of K_2CO_3 in 30 ml of acetonitrile, 0.85 ml (10.5 mmol) of chloroacetyl chloride were slowly added dropwise. The reaction was monitored by TLC. The reaction mixture was poured into water, the precipitate formed was filtered off, washed with water, dried and recrystallized from ethyl acetate-alcohol. Crystals of white color were isolated, yield 1.22 g (51 %). $T_{m.p.}$ 218–220 °C. R_f=0.52 (sulphol, ethyl acetate). Found, %: C 65.51, H 5.98, Cl 7.69, N 2.95. $C_{25}H_{28}ClNO_5$. Calculated, %: C 65.57, H 6.16, Cl 7.74, N 3.06. *m/z* (I, %): 457 $[M]^+$ (28), 422 (30), 404 (7), 394 (31), 380 (60), 364 (50), 352 (29), 336 (12), 296 (3), 234 (9), 216 (8), 190 (17), 176 (26), 159 (33), 146 (38), 131 (68), 119 (40), 115 (40), 105 (50), 91 (93), 77 (69), 55 (24), 43 (100). IR (KBr) ν_{max} cm^{-1}: 1701 (C=O), 1646 (NC=O). ^{1}H NMR ($CDCl_3$) δ_H ppm: 1.04 and 1.43 (both d, each 3H, *J*=7.0 and 6.7 Hz, respectively, CH_3), 3.20–4.37 (m, 10H, OCH_2CH_2O, H^{22,24}), 4.43 and 5.13 (both d, each 1H, *J*=11.8 Hz, H^{1,21}), 5.28 (br.s, 2H, $NCOCH_2Cl$), 6.15–7.10 (m, 8H, H^{arom}).

*25-N-{2'-[(5'',6''-Di(furan-2-yl)-1'',2'',4''-triazin-3''-yl) thio]acetyl}-22,24-dimethyl-8,11,14-trioxa-25-azatetracyclo-[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexaen-23-one (**4**).* A mixture of 0.54 g (2.2 mmol) of 3-mercapto-5,6-di(2-furyl)-1,2,4-triazine and 0.09 g (2.2 mmol) of NaOH in 30 ml of acetonitrile was heated until complete dissolution. 1.0 g (2.2 mmol) of the *N*-chloroacyl derivative (**3**) was added. The reaction was monitored by TLC. The acetonitrile was distilled off, the residue was separated by column chromatography on an alumina gel, eluting with a 1:1 mixture of ethyl acetate and hexane. 1.0 g (68 %) of the compound (**4**) was isolated. $T_{m.p.}$ 204–206 °C. R_f=0.59 (sulphol, ethyl acetate). Found, %: C 64.75, H 5.21, N 8.22. $C_{36}H_{34}N_4O_7S$. Calculated, %: C 64.85, H 5.44, N 8.40. *m/z* (LSMS) (I, %): 666 $[M]^+$ (8), 421 (1), 406 (1), 380 (6), 353 (1), 324 (2), 297 (4), 286 (6), 245 (1), 229 (23), 214 (60), 176 (10), 158 (40), 146 (18), 131 (35), 118 (27), 115 (27), 102 (100), 91 (70), 77 (38), 55 (19), 43 (60). ^{1}H NMR ($CDCl_3$) δ_H ppm: 1.4 and 1.5 (both br.s, each 3H, CH_3), 3.30–4.29 (m, 12H, OCH_2CH_2O, H^{1,21,22,24}), 5.14 and 5.66 (both br.s, each 1H, $NCOCH_2S$), 6.33, 6.49 and 6.80 (three br.s, 4H in total, H^{arom}), 6.51 (dd, 1H, *J*=3.6 and 1.8 Hz, H^{4} (Fu)), 6.61 (dd, 1H, *J*=3.6 and 1.8 Hz, H$^{4'}$ (Fu')), 6.81 (d, 2H, *J*=3.6 Hz, H^{3}, (Fu)), 6.98 (d, 2H, *J*=1.8 Hz, H^{5}, (Fu)), 6.88 (t, 2H, *J*=8.2 Hz, H^{arom}), 7.60 (d, 2H, *J*=8.2 Hz, H^{arom}).

*2-[22,24-Dimethyl-23-oxo-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]-pentacosa-2,4,6,15(20),16,18-hexaen-25-yl] acetonitrile (**5a**).* The solution was heated under reflux with 2.0 g (5.25 mmol) of (**2**), 1.2 g (16 mmol) of chloroacetonitrile, 2.2 g (16 mmol) of K_2CO_3, 0.3 g of TEBAC in 30 ml of acetonitrile for 3 hours. The acetonitrile was distilled off, 30 ml of water were added and extracted with chloroform (3×50 ml). The extract was dried with magnesium sulfate, the chloroform was distilled off, the residue was separated by column chromatography on silica gel, eluting with a 1:1 mixture of ethylacetate and hexane. The isolated fraction was purified by recrystallization from ethyl acetate to give the product as colorless crystals in 1.05 g (48 %) of the compound (**5a**). $T_{m.p.}$ 224–226 °C. R_f=0.75 (sulphol, ethyl acetate). Found, %: C 71.32, H 6.65, N 6.68.$C_{22}H_{28}N_2O_4$. Calculated, %: C 71.41, H 6.71, N 6.66. *m/z* (I, %): 420 $[M]^+$ (8), 380 (5), 324 (10), 310 (11), 297 (8), 204 (5), 187 (29), 173 (9), 160 (31), 145 (24), 131 (87), 119 (57), 105 (57), 91 (100), 77 (65), 67 (32), 55 (35), 43 (60). IR (KBr) ν_{max} cm^{-1}: 2225 (C≡N), 1725 (C=O). ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.79 (d, 6H, *J*=6.4 Hz, CH_3), 1.54 (br.m, 2H, H^{22,24}), 3.1 (s, 2H, NCH_2CN), 3.36 (d, 2H, *J*=10.7 Hz, H^{1,21}), 3.78–4.11 (m, 8H, OCH_2CH_2O), 6.82, 6.90, 7.24 and 7.28 (ABCD-system, 8H, *J*=8.04, 7.40, 1.69 and 0.9 Hz, H^{arom}).

*2-[22-Phenyl-23-oxo-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]-pentacosa-2,4,6,15(20),16,18-hexaen-25-yl] acetonitrile (**5b**).* 2.0 g (4.66 mmol) of piperidone (**1**), 1.1 g (14 mmol) of chloroacetonitrile, 1.9 g (14 mmol) of K_2CO_3, 0.3 g of TEBAC in 30 ml of acetonitrile were refrigerated for 3 hours. The acetonitrile was distilled off, 30 ml of water were added and extracted



Scheme 1. Synthesis of piperidonoaza-14-crown-4 ether (**1**, **2**) by Petrenko-Kritchenko reaction.

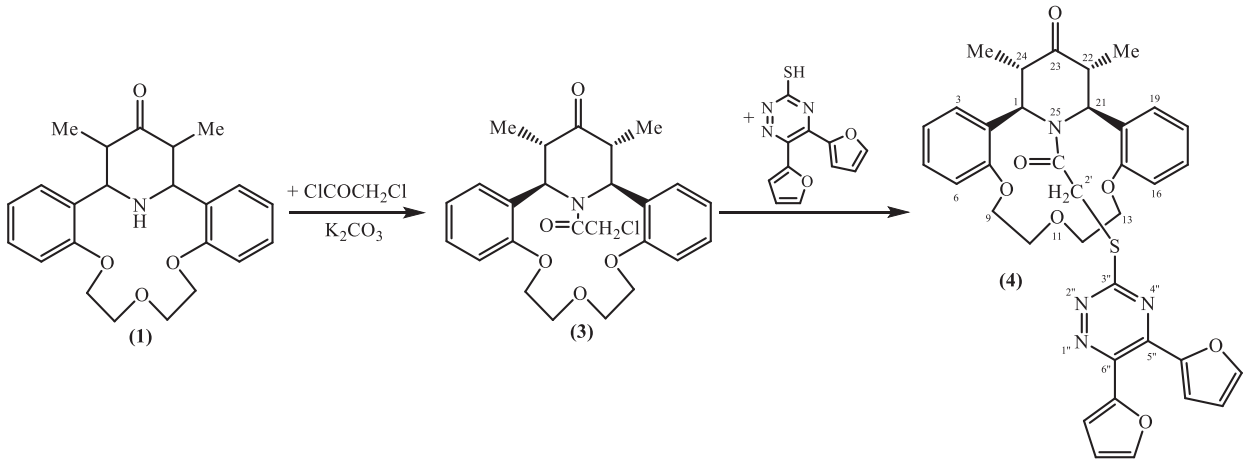
with chloroform (3×50 ml). The extract was dried with magnesium sulfate, the chloroform was distilled off, the residue was separated by column chromatography on silica gel, eluting with a 1:1 mixture of ethylacetate and hexane. The isolated fraction was purified by recrystallization from ethyl acetate to give the product as colorless crystals in 1.6 g (73 %) of compound (**5b**). $T_{m.p.}$ 229–231 °C. R_f=0.7 (sulphol, ethyl acetate). Found, %: C 74.41, H 6.15, N 5.66. $C_{29}H_{28}N_2O_4$. Calculated, %: C 74.34, H 6.02, N 5.98. *m/z* (I, %): 468 $[M]^+$ (4), 394 (4), 380 (8), 296 (2), 280 (3), 262 (22), 187 (36), 178 (7), 160 (20), 146 (21), 131 (52), 118 (100), 103 (19), 91 (95), 77 (47), 67 (26), 51 (19), 43 (51). IR (KBr) ν_{max} cm^{-1}: 2226 (C≡N), 1711 (C=O). ^{1}H NMR ($CDCl_3$) δ_H ppm: 1.25 (t, 1H, *J*=7.2 Hz, H^{24}), 1.55 (br.s, 1H, H^{24}), 3.6 (dd, 1H, *J*=12.4 and 1.3 Hz, H^{1}), 3.11 and 3.23 (AB-system, *J*=17.7 Hz, NCH_2CN), 3.91 (d, 1H, *J*=10.8 Hz, H^{21}), 3.87–4.23 (m, 8H, OCH_2CH_2O), 4.96 (d, 1H, *J*=10.8 Hz, H^{22}), 6.59–7.21 (m, 13H, H^{arom}).

Results and Discussion

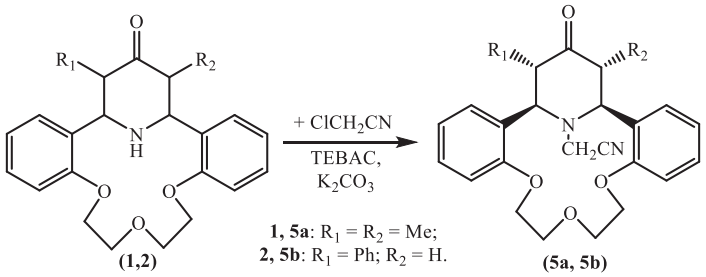
In this study, we attempted to carry out the *N*-acetylation and *N*-alkylation of these azacrown ethers with chloroacetyl chloride and 2-chloroacetonitril. Chloroacetyl chloride was chosen as the acylating agent for compound (**1**). At the same time, the presence of two chlorine atoms creates two reaction centers. The chlorine atom associated with the carbonyl group participates in the formation of a bond with the nitrogen atom of the piperidone fragment of compound (**1**). The chemical activity of the second chlorine atom is also high and can be replaced by nucleophiles. As a result of acylation transformation of compound (**1**), *N*-acyl derivative (**3**) was obtained in 51 % yield. Compound (**3**) is interesting in its chemical activity of chlorine atom which can be nucleophilically replaced by various nucleophiles (thiols, amines) in order to increase the potential of biological activity. On the basis of the condensation of the *N*-chloroacyl-aza-14-crown-4 ether (**3**) with 3-mercapto-5,6-di(2-furyl)-1,2,4-triazine, the hybrid compound (**4**) with the *N*-laureate moiety was synthesized and isolated chromatographically in 68 % yield (Scheme 2).

In order to functionalize the piperidone cycle of azacrowns (**1**, **2**), their interaction with chloroacetonitrile under conditions of phase-transfer catalysis (MPC) was studied. It was supposed that the reaction could proceed in two directions: 1) alkylation at the nitrogen atom and/or 2) formation of the oxirane ring by the Darzan reaction. The reaction was carried out using TEBAC, in boiling acetonitrile for three hours in the presence of a 50 % NaOH solution. It was found that the endocyclic nitrogen atom of the piperidone fragment in compounds (**1**) and (**2**) was fairly easily alkylated with chloroacetonitrile, and the Darzan reaction product was not formed, apparently because of the steric hindrance of the equatorial substituents at the α-position to the carbonyl group. Compounds (**5a**,**b**) were isolated in good yields (Scheme 3) and are interesting for the synthesis as a precursor of biologically active substances (for example, piperidol derivatives containing a glycine fragment as neuro- and nootropic substances of central action).[15]

The structures of compounds (**3**, **4**, **5a**,**b**) were determined by ^{1}H NMR, IR, MS spectrometry. For example, the ^{1}H NMR spectrum of the product (**3**) showed two doublet signals at δ=1.04 ppm (d, 3H) and δ=1.43 ppm (d,



Scheme 2. Acylation of azacrown ether (**1**) and hybrid compound containing polyether fragment.



Scheme 3. Alkylation of piperidonoaza-14-crown-4 ether (**1**, **2**).

Table 1. Prediction of several bioactivities of compounds (**3**, **4**, **5a**, **5b**) by PASS program (Pa>50 %).

Compound	Activities	P_a (%)
(**3**)	CYP2H substrate	84.3
(**4**)	Mcl-1 antagonist	80.7
	CYP2H substrate	69.1
	Neuropeptide Y2 antagonist	56.7
	Phosphatase inhibitor	56.4
(**5a**)	CYP2H substrate	85.7
	Membrane permeability inhibitor	66.8
	Spasmolytic, urinary	63.3
(**5b**)	Membrane permeability inhibitor	61.0
	Polarisation stimulant	58.3
	Spasmolytic, urinary	58.9

3H) with spin-spin coupling constant ^3J=7.0 and 6.7 Hz, respectively for six methyl protons of the piperidone ring (CH_3-CO-CH_3). Signals from the H^{22}, H^{24} and eight protons of polyether group (–CH_2O–) appeared as multiplets in the region δ=3.20–4.37 ppm. Other signals of piperidone protons (H^{1}, H^{21}) appeared at δ=4.43 and δ=5.13 ppm as doublets with ^3J=11.8 Hz in both cases to confirm the *trans*-positions of CH_3 and Ar substitutes in a piperidone subunit. The protons of *N*-chloroacyl fragment (N-CO-CH_2-Cl) were observed in the low field at δ=5.13 ppm as broad singlet. Analogously, in the ^{1}H NMR spectra of hybrid compound (**4**), these protons appeared separately in low field at δ=5.14 (1H) and δ=5.66 ppm (1H) as broad single both (N-CO-CH_2-S). Six protons of two furyl fragments of the corresponding multiplicity were observed in the 6.52–6.98 ppm region (^3J=3.6, 3.4 and 1.7 Hz).

The substances (**5a**,**b**) according to the data of the PASS program[16] with probability 66.8 and 61.0 % potentially can act as inhibitors of membrane permeability (Table 1). Azacrown ethers (**3**, **4**, **5a**) may act also as CYP2H substrate (84.3, 69.1 and 85.7 %, respectively).

The similar analysis for hybrid compound (**4**) revealed the possibility of manifesting Mcl-1 (80.7 %) and neuropeptide Y2 (56.7 %) antagonists. Especially, the PASS program has shown that substance (**4**) lost the activity of membrane permeability inhibitor.

Conclusions

The products of *N*-acylation (**3**) and *N*-alkylation (**5a**,**b**) of aza-14-crown-4 ethers (**1**, **2**) were successfully synthesized. Novel hybrid compound – bis(furanyl)triazinethiolazacrown ether (**4**) from *N*-chloroacyl derivative (**3**) and 5,6-di(furan-2-yl)-1,2,4-triazine-3-thiol was obtained by *S*-alkylation reaction. According to the PASS program, functionalization (acylation and alkylation) of aza-14-crown-4 ethers (**1**, **2**) should extend the potential and diversity of their biological activity.

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References

1. Mazur V.M., Kolyadina N.M., Sokol V.I., Soro S., Sergienko V.S., Davydov V.V. *Russ. J. Coord. Chem.* **2010**, *36*, 838–843.
2. Sokol V.I., Kolyadina N.M., Kvartalov V.B., Sergienko V.S., Soldatenkov A.T., Davydov V.V. *Russ. Chem. Bull., Int. Ed.* **2011**, *60*, 2124–2127.
3. Sokol V.I., Kvartalov V.B., Kolyadina N.M., Sergienko V.S., Soldatenkov A.T., Davydov V.V., Drogova G.M. *Russ. J. Inorg. Chem.* **2014**, *59*, 1094–1100.
4. Kolyadina N.M., Sokol V.I., Kvartalov V.B., Davydov V.V., Fomicheva E.A., Soldatenkov A.T., Sergienko V.S. *Russ. J. Inorg. Chem.* **2013**, *58*, 671–677.
5. Komarova A.I., Levov A.N., Soldatenkov A.T., Soldatova S.A. *Chem. Heterocycl. Compd.* **2008**, *44*, 624–645.
6. Le T.A., Truong H.H., Nguyen T.T.P., Tran T.T.V., Dao T.N., Soldatenkov A.T. *Vietnam Journal of Chemistry* **2015**, *53*(4e1), 141–144.
7. Tran T.T.V., Anh L.T., Nguyen H.H., Truong H.H., Soldatenkov A.T. *Acta Cryst. E Crystallogr. Commun.* **2016**, *E72*, 663–666.
8. Levov A.N., Strokina V.M., Komarova A.I., Anh L.T., Soldatenkov A.T. *Chem. Heterocycl. Compd.* **2006**, *42*, 125–126.
9. Levov A.N., Anh L.T., Komarova A.I., Strokina V.M., Soldatenkov A.T., Khrustalev V.N. *Russ. J. Org. Chem.* **2008**, *44*, 456–461.
10. Anh L.T., Levov A.N., Soldatenkov A.T., Gruzdev R.D., Hieu T.H. *Russ. J. Org. Chem.* **2008**, *44*, 462–464.
11. Le A.T., Truong H.H., Nguyen P.T.T., Pham H.T., Kotsuba V.E., Soldatenkov A.T., Khrustalev V.N., Wodajo A.T. *Macroheterocycles* **2014**, *7*, 386–390.
12. Le A.T., Truong H.H., Nguyen P.T.T., Thi N.D., To H.T., Thi H.P., Soldatenkov A.T. *Mendeleev Commun.* **2015**, *25*, 224–225.
13. Anh L.T., Phuong N.T.T., Hieu T.H., Soldatenkov A.T., Van B.T., Van T.T.T., Nhung D.T., Voskressensky L.G., Tung T.H., Khrustalev V.N. *Macroheterocycles* **2018**, *11*, 197–202.
14. Levov A.N., Anh L.T., Soldatenkov A.T., Khieu C.K., Khrustalev V.N. *Russ. J. Org. Chem.* **2008**, *44*, 612–616.
15. *Register of Medicines in Russia. Encyclopedia of Medicines*. The 15th issue. (Vyshkovsky G.L., Krylov Yu.F., Eds.). Moscow: RLS, **2006**. 1487 p. (in Russ.) [*Регистр лекарственных средств России. Энциклопедия лекарств.* 15-й вып. (Вышковский Г.Л., Крылов Ю.Ф., ред.). М.: РЛС, **2006**. 1487 с.].
16. Filimonov D.A., Lagunin A.A., Gloriozova T.A., Rudik A.V., Druzhilovskii D.S., Pogodin P.V., Poroikov V.V. *Chem. Heterocycl. Compd.* **2014**, *50*, 444–457.

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