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Synthesis and Acylation of Novel Azacrownophanes Containing Fused Piperidin-4-one Subunit

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Azacrownophanes containing fused piperidin-4-one fragment were successfully prepared through the modification of Petrenko-Kritschenko condensation or nucleophilic addition of the corresponding piperidone derivative with aryl aldehyde followed by further cyclization. Acylation reaction of the synthesized azacrownophanes was performed under reflux leading to the formation of target compounds with high yield. Acetic anhydride was used in excess as solvent and acylated agent. All new compounds were structurally confirmed by the physical-chemical methods including IR, ^{1}H NMR, MS and elemental analysis which contributed greatly to the library of crown ether class.

Keywords: Azacrownophanes, Petrenko-Kritschenko condensation, fused piperidin-4-one, acylation.

Синтез и ацилирование новых азакраунофанов, содержащих аннелированный пиперидин-4-он

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Азакраунофаны, содержащие конденсированный фрагмент пиперидин-4-она, были получены по модифицированной методике конденсации Петренко-Крищенко или путем нуклеофильного присоединения соответствующего производного пиперидона арилальдегидом с последующей циклизацией. Реакцию ацилирования синтезированных азакраунофанов проводили при нагревании, что приводило к образованию целевых соединений с высоким выходом. Уксусный ангидрид использовали в избытке в качестве растворителя и ацилирующего агента. Все новые соединения были структурно подтверждены физико-химическими методами, включая ИК, ^{1}Н ЯМР, масс-спектральный и элементный анализ.

Ключевые слова: Азакраунофаны, конденсация Петренко-Криченко, пиперидин-4-он, ацилирование.

Introduction

Piperidone and their analogues play a vital role in organic chemistry. The presence of active centers such as carbonyl and amine groups make it be used as building blocks for the synthesis of larger molecules with wider range of application.[1] For example, their oxime, thiosemicarbazone and tetrahydropyridine derivatives exhibit significant analgesic and local anesthetic activity as well as anti-fungal activity.[2-4] Transformation of piperidone into piperidine spirooxadiazole derivatives makes it as α7-nicotinic receptor antagonists.[5] Therefore, the develop-

ment of novel piperidone derivatives and study of their chemical and biological properties greatly attract the attention of scientists around the world.

Multicomponent reactions (MCRs) offer remarkable advantages such as shorter reaction times, minimization of the requisite reagents as well as purification steps, energy and so on.[6-9] Nowadays, it becomes a power tool to assist the synthesis of organic compounds with diversity in structure and thereby generates chemical libraries of organic compounds.[10-12] Therefore, the synthesis of novel heterocycles from simple and readily available reagents based on MCRs is friendly and effective way.

A well-known method for the synthesis of piperidones is the Petrenko-Kritschenko reaction which concerns the condensation of alkyl-1,3-acetonedicarboxylate with benzaldehyde and an amine.[13] A lot of the modifications of Petrenko-Kritschenko reaction was generated to produce a library of new piperidone derivatives.[14-17] They are not only potential candidates for drug discovery,[15,17] but also good intermediates for other important transformations such as substitution reaction including N-alkylation,[18] N-acylation,[19,20] O-acylation;[19] electrophilic addition reaction with some agents such as hydroxylamine,[21] thiosemicarbazide;[22] reduction reaction[4,23] and so on. As a part of our ongoing research, this study presents the synthesis of azacrownophane containing fused piperidin-4-one subunit and its first acylation study. The structure of the new compounds was determined by the physical-chemical methods including IR, ^{1}H NMR, MS and elemental analysis.

Experimental

All reagents were purchased from Sigma Aldrich, Merck and were used without any additional purification. Dialdehyde **2** and azacrownophane **4'** derivatives were prepared according to the known procedures.[24,25] Melting point of the synthetic molecule was determined in capillary tubes on a digital Stuart SMP3 apparatus. Elemental analysis was conducted on Euro Vector EA-3000 analyzer. IR spectra were recorded in KBr pellets on an Infralum FT-801 spectrometer. The ^{1}H NMR spectra were recorded on a Bruker WP-400 instrument in $CDCl_3$, TMS as internal standard. The LC/MS analysis was performed using an Agilent 1100 series chromatograph equipped with Agilent 1100 series DAD (wavelength 254±4 nm was used for detection), Sedex 75 ELSD and Agilent LC/MSD VL mass spectrometer (ionization in ESI mode), Finnigan MAT 95 XL (EI, ionization energy 70 eV). TLC analysis was performed on commercially prepared silica gel plates (Merck, F254) and observed under UV lamp (λ = 254 nm).

*General method for synthesis of azacrownophanes **3** containing fused piperidin-4-one subunit.*

*Method A (compounds **3a-3d**).* A mixture of dialdehyde (**2**) (7.0 g, 22.3 mmol), 4-piperidone derivatives (**1a** or **1b, 1c, 1d**) and ammonium acetate (3.43 g, 44.6 mmol) was placed in round bottom flash. To this mixture, 2 mL of AcOH and 50 mL of EtOH as a solvent for compound **1a** and **1c, 1d** or 50 mL of xylene for compound **1b** were added. The mixture was stirred at 20 °C for 5 days. After the reaction finished, solvent was removed partially under *vacuo*. The rest solution was neutralized with 50 mL of saturated solution of Na_2CO_3 and extracted with chloroform (3 × 70 mL). The organic phases were combined and dried over anhydrous $MgSO_4$. A solid residue obtained after evaporation of solvent *in vacuo* was purified by aluminium column chromatography using ethylacetate : hexane = 1:1 (v/v) as eluent. The precipitates were collected and recrystallized from ethanol affording white crystals.

*24-Methyl-8,11,14-trioxa-24,27-diazapentacyclo[19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20),16,18-hexaen-28-one (**3a**):* 0.4 g (4%). M.p. 223-224 °C, R_f = 0.39 (SiO_2, ethylacetate). Found, %: C 70.26, H 6.89, N 6.86 %. $C_{24}H_{28}N_2O_4$. Calculated, %: C 70.57; H 6.91; N 6.86. MS (EI), *m/z* (I, %): 408 $[M]^+$ (89), 378 (15), 365 (11), 336 (5), 324 (22), 310 (27), 297 (98), 260 (10), 244 (15), 215 (12), 200 (20), 183 (33), 173 (16), 163 (27), 148 (40), 131 (100), 121 (50), 110 (50), 91 (70), 77 (65), 55 (91), 44 (65). IR (KBr) ν_{max} cm^{-1}: 3294 (NH), 1719 (C=O). ^{1}H NMR (400 MHz, $CHCl_3$, TMS) δ_H ppm: 2.37 (3H, s, CH_3), 2.39 (2H, d, *J* = 10.7 Hz, H^{23,25}), 2.53 (2H, br.s, H^{22,26}), 2.92 (1H, t, *J* = 13.0 Hz, NH), 3.01 (2H, d, *J* = 10.7 Hz, H^{23,25}), 3.79-4.07 (8H, m, OCH_2CH_2O), 4.49 (2H, dd, *J* = 13.0 and 3.3 Hz, H^{1,21}), 6.84 (2H, t.t, *J* = 7.3, and 0.9 Hz H^{4,18}), 6.89 (2H, d, *J* = 7.9 Hz, H^{6,16}), 7.19-7.27 (4H, m, H^{3,5,17,19}).

*24-Benzyl-8,11,14-trioxa-24,27-diazapentacyclo[19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20),16,18-hexaen-28-one (**3b**):* 1.93 g (18%), M.p. 201-202 °C, R_f = 0.52 (SiO_2, ethylacetate). Found, %: C 74.20, H 6.57, N 5.70 %. $C_{30}H_{32}N_2O_4$. Calculated, %: C 74.36, H 6.66, N 5.78. MS (EI), *m/z* (I, %): 484 $[M]^+$ (4), 393 (6), 297 (25), 131 (15), 105 (7), 91 (100), 77 (12), 55 (18), 44 (8). IR (KBr) ν_{max} cm^{-1}: 3304 (NH), 1720 (C=O). ^{1}H NMR (400 MHz, $CHCl_3$, TMS) δ_H ppm: 2.45 (2H, d, *J* = 10.8 Hz, H^{23,25}), 2.53 (2H, br.s, H^{22,26}), 2.92 (1H, t, *J* = 12.9 Hz, NH), 3.01 (2H, d, *J* = 10.8 Hz, H^{23,25}), 3.68 (2H, s, C*H*$_2$Ph), 3.78-4.06 (8H, m, OCH_2CH_2O), 4.53 (2H, d.d, *J* = 12.9 and 2.9 Hz, H^{1,21}), 6.81 (2H, t, *J* = 7.4 Hz, H^{4,18}), 6.88 (2H, d, *J* = 8.1 Hz, H^{6,16}), 7.11 (2H, d.d, *J* = 7.3 and 1.4 Hz, H^{3,19}), 7.20 (2H, t.t, *J* = 8.1 and 1.4 Hz, H^{5,17}).

*24-Acetyl-8,11,14-trioxa-24,27-diazapentacyclo[19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20),16,18-hexaen-28-one (**3c**)* was prepared according to the known procedure:[26] 1.27 g (58 %), M.p.= 227–229 °C. Found, %: C, 69.03; H, 6.52; N, 6.43. Calculated, %: C, 68.79; H, 6.47; N, 6.42. IR (KBr) ν_{max} cm^{-1}: 1603, 1649, 1713, 3405, 3460. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ_H ppm: 2.37 (3H, s, CH_3 C=O), 2.91 (3H, m, H^{22,26,27}), 3.47 and 4.98 (1H each, both d.d, *J* = 7.3 and 1.1, H^{1,21}), 3.92–4.10 (12H, m, $OCH_2CH_2OCH_2CH_2O$, 2×H^{23} and 2×H^{25}), 6.75–6.95 (3H, m, H^{arom}), 7.21–7.36 (5H, m, H^{arom}).

*28-Oxo-24-propyl-8,11,14-trioxa-24,27-diazapentacyclo [19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20),16,18-hexaene (**3d**)* was prepared according to the known procedure:[27] 1.8 g (72%), M.p. =217–219 °C. Found: C, 67.54; H, 7.42; N, 5.41. Calculated, %: C, 67.72; H, 7.31; N, 5.64. IR (KBr) ν_{max} cm^{-1}: 1602, 1728, 3263, 3463. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ_H ppm: 1.08 (3H, t, *J* = 6.7, CH_3), 1.25 (2H, m, $CH_2CH_2CH_3$), 1.61 (2H, m, NCH_2CH_2), 1.83 (3H, s, CH_3COO^-), 2.49 (4H, m, 2×H^{23} and 2×H^{25}), 2.76 (2H, m, H^{22,26}), 3.12 (1H, br.m, NH), 3.86–4.10 (8H, m, $OCH_2CH_2OCH_2CH_2O$), 4.83 (2H, m, H^{1,21}), 6.78–6.86 (4H, m, H^{arom}), 7.25–7.41 (4H, m, H^{arom}). ^{13}C NMR ($CDCl_3$, 80 MHz, 300 K) δ_C ppm: 12.3 (CH_3), 21.2 (CH_2), 22.6 (CH_2), 54.4 (CH_2), 57.7 (CH_2), 60.5 (CH_2), 64.3 (CH_2), 67.0 (CH), 79.1 (CH), 111.5 (C^{arom}), 121.1 (C^{arom}), 129.1 (C^{arom}), 131.8 (C^{arom}), 175.7 (C=O).

*Method B. 23,25-Bis(2-hydroxyphenyl)-8,11,14-trioxa-24,27-diazapentancyclo[19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20),16,18-hexaen-28-one (**3e**).* In a round bottom flash, a mixture of azacrownophane **4** (2.0 g, 5.7 mmol), 2-hydroxybenzaldehyde (1.39 g, 11.4 mmol), ammonium acetate (0.87 g, 11.4 mmol), 2 mL of CH_3COOH and 30 mL of EtOH was placed. The mixture was stirred for 5 days at 20 °C. After the reaction completed, 2/3 volume of ethanol was removed under reduced pressure and the rest was neutralized with saturated solution of Na_2CO_3 following by extraction with chloroform (3×20 mL). Organic phases were combined and dried over anhydrous $MgSO_4$. Evaporation of organic solvent followed by silica gel column chromatography (ethyl acetate : hexane = 1:1) afforded white crystals, 0.3 g (9 %), M.p. >220°C (decomposed), R_f = 0.36 (SiO_2, ethylacetate-ethanol = 1:1). Found, %: C 72.42, H 5.88, N 4.52. $C_{35}H_{34}N_2O_6$. Calcu-

lated, %: C 72.65; H 5.92; N 4.84. LC/MS (ESI), *m/z* (%): 579 (100) $[(M+H)]^+$. IR (KBr) ν_{max} cm^{-1}: 3437 (br. signal OH, NH), 1732 and 1629 (C=O). ^{1}H NMR (400 MHz, $CHCl_3$, TMS) δ_H ppm: 2.69 (1H, t, *J* = 12.0, NH), 3.03-4.25 (14H, m, $H^{aliphatic}$), 6.62-7.23 (16H, m, H^{arom}), 7.83 (1H, s, OH).

*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 azacrown ether **4'** (1.0 g, 2.4 mmol) and 10 mL of 6M HCl was refluxed on water bath for 3 h. After the reaction finished, mixture was cooled until room temperature and neutralized by dilute solution of Na_2CO_3. The solution was then extracted with $CHCl_3$ (3×50 mL). The organic phases were combined and dried over $MgSO_4$. Removing solvent under *vacuo* afforded white crystals which were recrystallized in ethanol. Yield 72 % (0.6 g), M.p. 189-190 °C, R_f = 0.34. (SiO_2, ethylacetate). Found, %: C 71.22; H 6.49; N 3.77; $C_{21}H_{23}NO_4$. Calculated, %: C 71.37; H 6.56; N 3.96. EI, *m/z* (%): 353$[M]^+$ (50), 323 (22), 265 (18), 237 (22), 178 (14), 162 (14), 148 (42), 134 (47), 121 (93), 119 (68), 103 (25), 91 (100), 77 (80), 65 (33), 51 (18), 43 (70). IR (KBr) ν_{max} cm^{-1}: 3322 (NH), 1496 (C=O), 3322 (NH). ^{1}H NMR (400 MHz, $CHCl_3$, TMS) δ_H ppm: 2.54 (2H, d.d, ^2J = 13.9 and ^3J = 1.9 Hz, $H^{22,24}$), 3.23 (2H, br.t, *J* = 13.9 Hz, $H^{22,24}$), 3.86-3.99 (5H, m, H^{aliph}, $H^{1,21}$), 4.07 (1H, br.s, NH), 4.11 (6H, m, OCH_2CH_2O), 6.80 (2H, br.d, *J* = 8.2 Hz, $H^{6,16}$), 6.88 (2H, t.t, *J* = 7.5 and 0.8 Hz, $H^{4,18}$), 7.18-7.23 (4H, m, H^{arom}).

*General procedure for the synthesis of N-acyl derivatives (compounds **5a, 5b**).* A mixture of azacrownophane (**3b, 3e**) (0.5 g) and 3 mL of acetic anhydride was reluxed for 3 h. After completion of the reaction (controlled by TLC), the mixture was neutralized with saturated solution of Na_2CO_3 and extracted with chloroform (3×30 mL). The organic phases were combined and dried over anhydrous $MgSO_4$. Evaporation of organic solvent *in vacuo* afforded the residue which was crystallized from ethanol to give white precipitates.

*25-Acetyl-8,11,14-trioxa-33-azapentacyclo[19.11.1.1^{22,32}.0^{2,7} 0^{15,20}]-tetratriaconta-2,4,6,15(20)16,18-haxaen-34-one (**5a**):* 0.35 g (65%), m.p. 210-212°C, R_f = 0.66 (SiO_2, ethylacetate). Found, %: C 72.89, H 6.40, N 5.02. $C_{32}H_{34}N_2O_5$. Calculated, %: C 72.98; H 6.51; N 5.32. MS(EI), *m/z* (I, %): 526 $[M]^+$ (12), 483 (8), 350 (7), 186 (21), 146 (13), 134 (21), 103 (5), 91 (100), 77 (4), 55 (7), 43 (40). IR (KBr) ν_{max} cm^{-1}: 1635 (NC=O), 1718 (C=O). ^{1}H NMR (400 MHz, $CHCl_3$, TMS) δ_H ppm: 2.46 (3H, s, CH_3), 2.53 and 2.75 (1H each, d, *J* = 12.5 and 12.0 Hz, $H^{23,25}$), 2.91 and 3.06 (1H each, both s, $H^{22,26}$), 3.32-4.29 (12H, m, OCH_2CH_2O, CH_2Ph, $H^{23,25}$), 5.80 and 6.79 (1H each, br.s, $H^{1,21}$), 6.27, 6.39, 6.49, 6.62 (4H, ABCD-system, *J* = 7.8, 7.5, 6.4 Hz, $H^{aromatic}$), 6.78-6.82 (3H, m, $H^{aromatic}$), 7.03 (1H, d, *J* = 7.4 Hz, $H^{aromatic}$), 7.27-7.37 (5H, m, CH_2Ph).

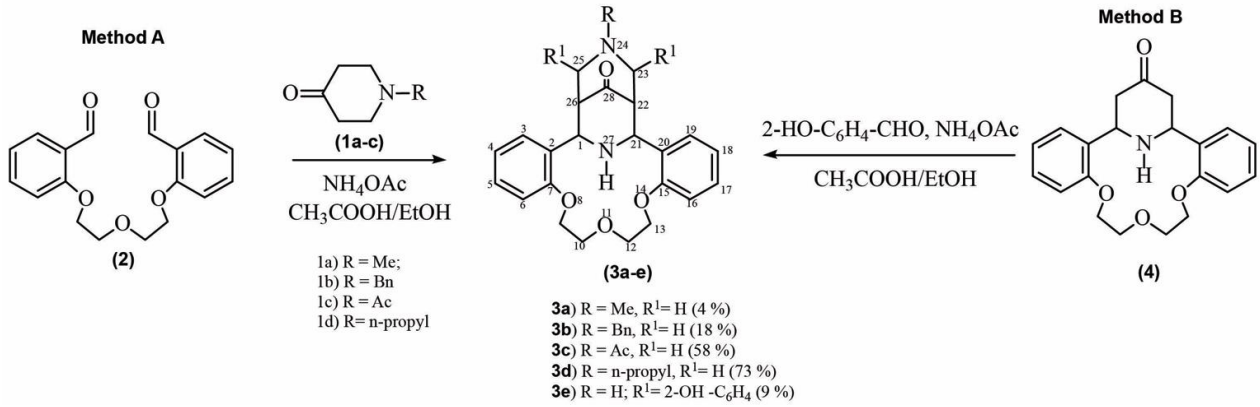
*23,25-Bis(2-acetyloxyphenyl)-24,27-diacetyl-8,11,14-trioxa-24,27-diazapentacyclo-[19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20), 16,18-hexaen-28-one (**5b**):* 0.45 g (70%), M.p. = 168-170 °C, R_f = 0.71 (SiO_2, ethylacetate : ethanol = 1:1). Found, %: C 68.96, H 5.58, N 3.73. $C_{43}H_{42}N_2O_{10}$. Calculated, %: C 69.16; H 5.67; N 3.75. LC/MS (ESI), *m/z* (%): 747(100) $[(M+H)^+]$. ^{1}H NMR (400 MHz, $CHCl_3$, TMS) δ_H ppm: 1.82, 1.99, 2.10 and 2.20 (3H each, all s, CH_3), 3.23 and 3.43 (1H each, both br.s, $H^{22,26}$), 3.57 - 4.16 (8H, m, OCH_2CH_2O), 6.03, 6.11, 6.51 and 6.87 (1H each, both t, *J* = 7.9 Hz, $H^{aromatic}$), 6.67, 6.75, 7.07 and 7.12 (1H each, all d, *J* = = 7.9 Hz, $H^{aromatic}$), 6.49, 6.79-6.89, 7.23-7.46 (10H, all m, $H^{aromatic}$).

Results and Discussion

Synthesis of azacrownophanes containing fused piperidin-4-one

It is well known that Petrenko-Kritschenko condensation reaction is always being used for preparation of piperidone derivatives. Therefore, *Method A* was designed by modification of this reaction. Three components selected from 4-piperidone derivatives **1a-c**, 1,5-bis(2-formylphenoxy)-3-oxapentane (**2**) and ammonium acetate were reacted and afforded the target compounds **3a-c**. Small amount of glacial acetic acid was used as a catalyst. The presence of a substituent attached on piperidone ring (**1a-c**) makes a great affection on the yield of product in which an electron withdrawing group will facilitate this reaction. So, compound **3c** was obtained in the highest yield followed by compounds **3b** and **3a** (Scheme 1).

Method A was performed in one-pot reaction with many advantages such as saving reaction time, energy, without separation of immediate products. Changing the R substituents of compound **1a-d** not only leads to the diversity of the obtained product but also affects on the yield of this reaction. Compound **3a** was obtained in a lower yield compared with compound **3b**. Compound **3c** was performed with higher yield from the reaction of 1-acetylpiperidin-4-one and podand (**2**) due to the presence of CH_3CO as an electronwithdrawing substituent that facilitates the formation of new bonds from the active methylene and CHO groups. Especially, compound **3d** was formed in the highest yield. Single X-ray diffraction revealed the complex **3d** with an acetic acid molecule by a strong intermolecular O—H···N hydrogen bond (Figure 1).[27] Therefore the equilibrium moves to the right according to Le Chatelier's principle.



Scheme 1. Two routes for the synthesis of azacrownophanes containing fused piperidin-4-one subunit.

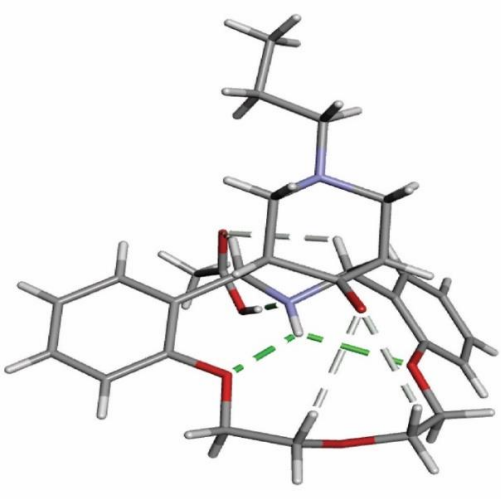


Figure 1a. The molecular structure of **3d**. Dashed lines indicate the intramolecular and intermolecular O—H···N hydrogen bonds.

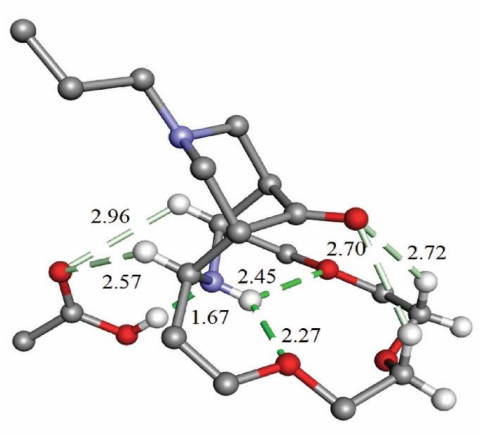


Figure 1b. The distance of hydrogen bonds and conformation of bicyclic and crown ether fragment in compound **3d**.

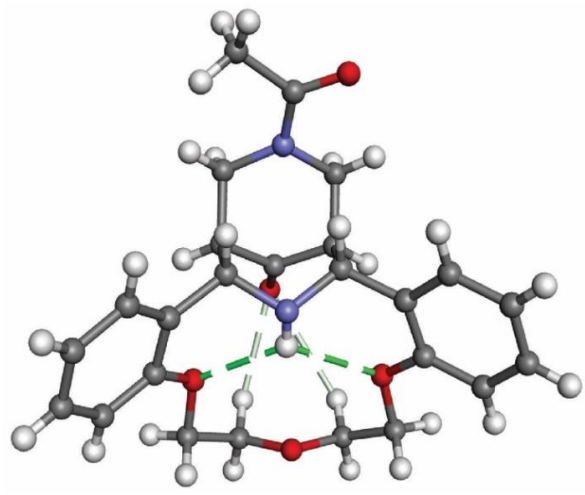


Figure 2a. H atoms are presented as small spheres and dashed lines indicate the intramolecular N–H···O and C-H···O hydrogen bonds in compound **3c**.

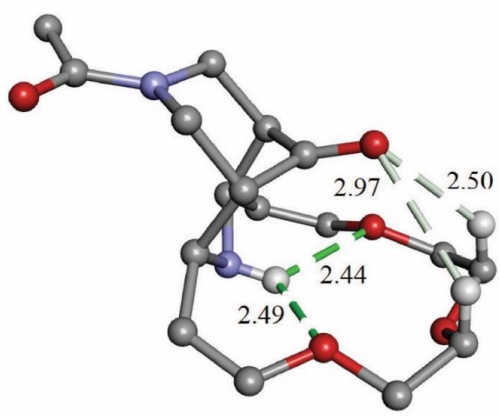
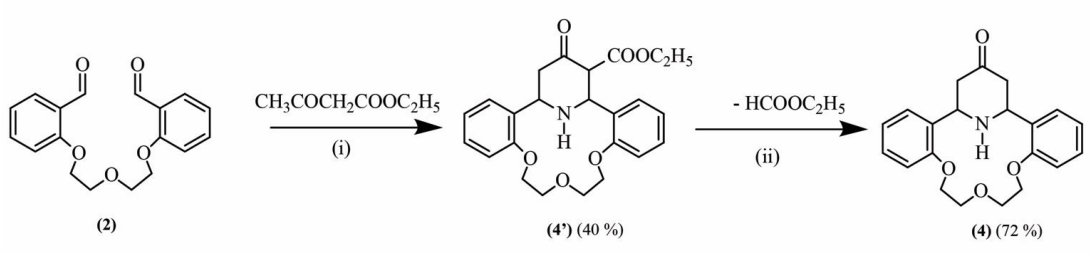


Figure 2b. The distance of hydrogen bonds and conformation of bicyclic and crown ether fragment in compound **3c.**

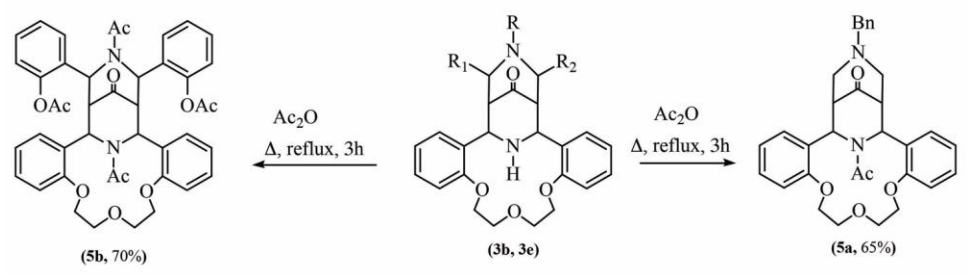
As we have mentioned above, *Method A* was used to synthesize a series of azacrownophane containing fused piperidin-4-one subunit with different substituents attached at N24 position. For making azacrownophane with different substituents at C25 and C23 positions, *Method B* was used.[25] Two molecules of aromatic aldehyde derivatives, one molecule of compound **4** and an excess amount of ammonium acetate react in the mixture of dry ethanol and glacial acetic acid to form compound **3e** in yield of 9 %. Indeed, compound **4** plays as an active methylene compound and participates into the nucleophilic addition reaction with aldehyde derivatives. Ammonium acetate contributes to supply nitrogen source. Experimental results showed that this reaction takes place with only aryl aldehyde due to its good electrophilic properties. A. I. Komarova and her co-workers also performed this reaction with 4-fluorobenzaldehyde and 3,4-dimethoxybenzaldehyde giving the corresponding azacrownophane with the yield of 15 and 11%, respectively.[25] However, *Method B* requires two steps to prepare compound **4**. The first step (i) concerns the domino reaction of podand **2** and β-keto esters, ammonium acetate to synthesize compound **4**' in the yield of 40%.[28] The second step (ii) is decarboxylation under inorganic acid media (Scheme 2).

Acylation of new azacrownophanes

Acylation of azacrownophanes **3b, 3e** produced the N-acyl derivatives **5a,b** (Scheme 3). This reaction is performed in pure acetic anhydride as a solvent and acylating agent. After stirring for 3 h under reflux, the corresponding compounds **5a,b** were obtained in high yield. The hydroxyl group attached to benzene ring also participated in acylation process (compound **5b**). Normally, in azacrownophanes containing single piperidone ring, the C=O group and the aza-14-crown-4-ether moiety are arranged in *trans* position to the the piperidine plane and the piperidine ring adopts an almost *ideal* chair conformation.[28] Therefore, prolongated heating of piperidone derivatives with the presence of a large excess of acetic anhydride led to their enolization with subsequent O-acylation.[4] However, in our azacrownophanes containing fused piperidin-4-one subunit, O-acylation process was restricted due to the steric hindrance.



Scheme 2. The synthesis of compound **4**: (i) NH_4OAc, CH_3COOH, C_2H_5OH, reflux, 5 h; (ii) 6 M HCl, reflux, 3 h.



Scheme 3. Acylation of new azacrownophanes.

Indeed, the data from single crystal show that in azacrown ether containing fused piperidones, the existence of intramolecular N—H···O hydrogen bond leads to the conformation of the central piperidone ring as a boat, whereas the terminal piperidone ring adopts a chair conformation (Figures 1, 2).[27] Oxygen atom of CO group also forms intramolecular C—H···N hydrogen bond which hinders the attack of acetyl group on this atom and as a consequence, O-acylation is limited.

The structure of synthesized compounds was determined by the physical-chemical methods including IR, ^{1}H NMR, MS and elemental analysis. In IR spectra, the compounds **3a-d** show the vibration of amine group in range of 3200-3300 cm^{-1}, one vibration of C=O group is around 1700 cm^{-1} which characterizes the formation of fused piperidin-4-one subunit. ^{1}H NMR, MS and elemental analysis were used to firmly support the structure of target compounds. Moreover, structure of compounds **3c, 3d** was confirmed by single X-ray diffraction.[26] Its data provide reliable information about the crystal structures and atomic spacing of azacrownophanes containing fused piperidin-4-one.

N-Acyl derivatives differ from corresponding starting material by the disappearance of NH and OH signals in IR spectra as well as in ^{1}H NMR spectra. Vibration of N-C=O and C=O groups of N-acyl derivatives shows peaks at 1635 and 1718 cm^{-1} (compound **5a**), and 1629 and 1732 cm^{-1} (compound **5b**), respectively. The NMR spectra also reveal the signals of CH_3 group as singlet at 2.46 ppm (compound **5a**) whereas compound **5b** shows signals at 4 points: 1.82, 1.99, 2.10 and 2.20 ppm which proved the acylation of two NH groups and two OH groups of this compound.

The qualitative structure-anti-cancer activity relationships (QSAR) of azacrownophanes and its N-acyl derivatives was studied by physicochemical calculations using the SwissADME web server (*http://www.swissadme.ch/)*[29] and the Molsoft web server (*http://molsoft.com/mprop/*). The results are presented in Table 1. Except for compound **5b**, all compounds satisfy or have only one violation of Lipinski's rule, have the same bioavailability score of 0.55. The Blood-Brain Barrier (BBB) score is one of characters that inform the toxicities of drugs and its value should be less than 6.0. The BBB score of all synthetic compounds (**3a-d**, **5a-b**) are ranged from 0.68 to 4.0. The drug likeness scores (DLS) are in the range of 0.29 - 0.7. Acylation process tolerates N-acyl derivatives (**5a, 5b**) with increasing value of DSL in comparation with corresponding fused piperidones (**3b, 3e**). These calculated results primarily evaluate that the synthesized compounds are potent candidates for biological activities. Moreover, in our previous study, the biological assays were performed and shown the good prospects of N-acyl derivatives toward the analgesic properties and myorelaxant activity as well as a sedative effect.[4]

Conclusions

Azacrownophane derivatives containing fused piperidin-4-one fragment were successfully synthesized under mild conditions based on multicomponent reaction by different approaches. The obtained compounds have enough purity and can serve as a good material for biological and chemical studies. By doing acylation process of two azacrownophane derivatives containing fused piperidin-4-one with acetic anhydride, we found that piperidone derivatives can react very fast with acylated agent and afford N-acyl derivatives in high yield. Based on the ADME caculation, further biological assays of the synthesized compound will be explored in our ongoing research.

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Table 1. Physicochemical calculations of synthetic compounds.

Entry	MW	logP	Num. H-bond donors	Num. H-bond acceptors	logS	DSL	BBB Score	Bioavailability Score	Lipinski's rule
3a	408.49	2.9	1	6	-3.78	0.29	4.0	0.55	0
3b	484.24	3.63	1	6	-5.13	0.35	3.49	0.55	0
3c	436.20	2.19	1	6	-3.53	0.06	3.40	0.55	0
3d	578.67	3.31	4	8	-6.00	0.10	1.08	0.55	1 (MW)
3e	436.54	3.36	1	6	-4.36	0.69	4.0	0.55	
5a	526.52	3.54	0	6	-5.25	0.69	3.58	0.55	1 (MW)
5b	746.80	3.57	0	12	-6.60	0.7	0.68	0.17	2 (MW and Num. H-bond acceptors)

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