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SYNTHESIS OF A 1,2,3-TRIAZOLE-CONTAINING MACROCYCLE BASED ON THE "CLICK CHEMISTRY" REACTION AND ANALYSIS OF ITS PLANAR CHIRALITY USING NMR AND DFT CALCULATIONS

Macrocycles represent previously unexplored promising drug candidates, that can be useful for treating protein-protein interactions. Atropoisomerism is an inherent feature of the natural macrocyclic peptides that is significant for their activity and selectivity, and, therefore, should be introduced into newly synthesized macrocycles. Synthesis of the libraries of artificial macrocycles faces many challenges due to their structure and size. Herein we report on the preparation of a 16-membered macrocycle containing 1,2,3-triazole ring, spiro-piperidine, and phenyl moieties, as well as a chiral carbon atom. Our approach to the macrocycle was inspired by the "build/couple/pair" (B/C/P) strategy, a part of diversity-oriented synthesis methodology. We have employed readily accessible starting materials and robust synthetic procedures which allowed us to obtain the target macrocycle in a high yield. Standard methods of amide bond formation were used for the coupling of macrocycle building blocks. Click chemistry azide-alkyne cycloaddition was exploited at the final ring closure step. The assignment of signals in ^{1}H and ^{13}C NMR spectra of the macrocycle was performed using a series of 2D NMR techniques. The macrocycle displayed planar chirality, which, in a combination with a stereocenter with the known configuration, was sufficient to propose possible structures of diastereomers. The diastereomers could differ by the relative position of triazole ring. Their racemization could occur through a "rope skipping" motion involving the cyclic chain crossing the plane of 1,2,3-triazole ring. The supposed structures of diastereomers were corroborated by means of a various NMR spectroscopy techniques and DFT calculations. Analysis of the amide NH chemical shift temperature coefficients coupled with the data on optimized geometries obtained by DFT convincingly demonstrated that the intramolecular hydrogen bonds play a major role in stabilization of the diastereomer structures. According to the variable temperature NMR experiment, the interconversion of two diastereomers did not occur even at heating up to 70 °C.

Keywords: macrocycle, click chemistry, planar chirality, NMR, DFT calculations.

Introduction. With the constantly ongoing evolution of bacteria strains and emergence of antibiotic-resistant ones, the search for new drug molecules is facing increasing challenges. This urges reconsideration of the existing criteria of compound drug-likeness and widening the scope of the compounds viewed as the prospective drug candidates. Thus, relatively large molecules were not considered in the scope of medicinal chemistry earlier because of failure to comply with the drug-likeness criteria, such as Lipinski or Veber rules. Nowadays such compounds, as macrocycles, are emerging in the drug discovery investigations [1–4]. They proved to be useful tools for targeting proteins that do not possess distinct ligand-binding site, for example protein-protein interactions [5–7].

However, involvement of macrocycles in the design of new drugs is hindered due to the difficulty of their synthesis and modification. One of the promising strategies of synthesis of macrocycle libraries is diversity-oriented synthesis (DOS) [8]. Classical "build/couple/pair" (B/C/P) strategy allows for a synthesis of large and diverse macrocycle libraries using a limited number of well-established procedures [9–11]. Quick and robust click chemistry approaches proved to be very useful in the preparation of macrocycles [12].

Planar chirality is an inherent feature of the natural macrocyclic peptides and plays a big role in their activity and selectivity. Apparently, atropoisomerism can be of paramount importance for the artificial macrocycles [13].

In this work we report on the synthesis of a new 16-membered macrocycle containing a 1,2,3-triazole core and a spiro-piperidine fragment. We investigate the structure and planar chirality of this compound based on NMR spectroscopy and quantum-chemical calculations.

Materials and methods. The solvents were purified according to the standard procedures [14]. All starting materials were available from Enamine Ltd. or purchased from other commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (atmospheric pressure ionization-electrospray (API-ES)).

1-*tert*-Butyl 4-ethyl 4-(2-chloroethyl)piperidine-1,4-dicarboxylate (2). Lithium diisopropyl amide (10.9 g, 102 mmol) was added dropwise to a solution of 1-*tert*-butyl 4-ethyl piperidine-1,4-dicarboxylate **1** (17.5 g, 68.0 mmol) in THF at –78 °C. The reaction mixture was stirred for 1 h. Then 1-bromo-2-chloroethane (13.6 g, 95.2 mmol) was added and the mixture was stirred overnight at room temperature. Then the mixture was cooled with ice and the saturated NH_4Cl solution was added. Resulting mixture was evaporated. Then EtOAc was added, the mixture was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography. Yield 24.5 g (99 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.0 Hz, 2H), 3.84 (br. s, 2H), 3.42 (t, *J* = 8.2 Hz, 2H), 2.85 (br. s, 2H), 2.08 (d, *J* = 13.2 Hz, 2H), 2.00 (t, *J* = 8.2 Hz, 2H), 1.41 (s, 9H), 1.38 – 1.31 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 3H). LC/MS(API-ES): *m/z* = 320 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{26}ClNO_4$: C 56.33; H 8.19; Cl 11.09; N 4.38; Found: C 56.10; H 8.16; Cl 11.05; N 4.49.

1-*tert*-Butyl 4-ethyl 4-(2-azidoethyl)piperidine-1,4-dicarboxylate (3). Sodium azide (5.98 g, 91.9 mmol) was added to a solution of 1-*tert*-butyl 4-ethyl 4-(2-chloroethyl)piperidine-1,4-dicarboxylate **2** (24.5 g, 76.6 mmol) in DMF (250 mL). The reaction mixture was stirred at 90 °C for 12 h. Then the mixture was allowed to cool to r.t. and was poured into water. The obtained mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Yield 21.0 g (84%). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.86 (br. s, 2H), 3.26 (t, *J* = 7.5 Hz, 2H), 2.91 (br. s, 2H), 2.11 (d, *J* = 13.4 Hz, 2H), 1.81 (t, *J* = 7.5 Hz, 2H), 1.44 (s, 9H), 1.43 – 1.27 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). LC/MS(API-ES): *m/z* = 327 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{26}N_4O_4$: C 55.20; H 8.03; N 17.17; Found: C 54.97; H 8.01; N 17.43.

4-(2-Azidoethyl)-1-[(tert-butoxy)carbonyl]piperidine-4-carboxylic acid (4). Sodium hydroxide (3.09 g, 77.2 mmol) was added to a solution of 1-*tert*-butyl 4-ethyl 4-(2-azidoethyl)piperidine-1,4-dicarboxylate **3** (21.0 g, 64.3 mmol) in MeOH/H_2O (75/25, v/v). The reaction mixture was stirred overnight at 80 °C, then evaporated *in vacuo*, acidified to pH 2–3 and extracted with EtOAc. The extract obtained was dried over Na_2SO_4 and evaporated *in vacuo*. Yield 18.5 g (96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 1H), 5.23 – 5.08 (m, 2H), 4.60 – 4.49 (m, 1H), 4.49 – 4.36 (m, 1H), 4.36 – 4.21 (m, 2H), 3.88 – 3.79 (m, 1H), 3.45 – 3.29 (m, 2H), 2.31 – 2.11 (m, 3H), 1.44 (s, 9H). LC/MS(API-ES): *m/z* = 299 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{22}N_4O_4$: C 52.34; H 7.43; N 18.78; Found: C 52.52; H 7.43; N 18.54.

Methyl 2-(prop-2-yn-1-yloxy)benzoate (6). Potassium carbonate (20.0 g, 145 mmol) and 3-bromoprop-1-yne (17.2 g, 145 mmol) were added to a solution of methyl 2-hydroxybenzoate **5** (20.0 g, 131 mmol) in CH_3CN (200 mL). The reaction mixture was refluxed for 24 h, then allowed to cool to r.t. and filtered off. The solution obtained was evaporated *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. Yield 24.5 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.02 (t, *J* = 8.2, 1.2 Hz, 1H), 4.80 – 4.74 (m, 2H), 3.87 (s, 3H), 2.55 – 2.49 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.0, 156.0, 133.2, 130.7, 121.0, 120.8, 114.2, 78.9, 78.6, 56.1, 52.0. LC/MS(API-ES): *m/z* = 191 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{10}O_3$: C 69.46; H 5.30; Found: C 69.45; H 5.57.

2-(Prop-2-yn-1-yloxy)benzoic acid (7). Methyl 2-(prop-2-yn-1-yloxy)benzoate **6** (24.5 g, 129 mmol) and lithium hydroxide monohydrate (7.03 g, 167 mmol) were suspended in a mixture of MeOH (180 mL) and H_2O (60 mL) 20 °C. The resulting solution was concentrated under reduced pressure and acidified to pH 1 with $NaHSO_4$. The product was extracted with EtOAc, the extract was washed with water (3×75 mL), and then evaporated *in vacuo* at 60 °C. Yield 22.0 g (97%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.69 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 4.86 (s, 2H), 3.58 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) 167.2, 155.9, 132.7, 130.7, 122.1, 120.9, 114.1, 79.1, 78.6, 56.2. LC/MS(API-ES): *m/z* = 177 $[M+H]^+$. Anal. Calcd. for $C_{10}H_8O_3$: C 68.18; H 4.58; Found: C 68.41; H 4.61.

***tert*-Butyl *N*-[(2*S*)-1-amino-4-methylpentan-2-yl] carbamate (9).** *tert*-Butyl *N*-[(2*S*)-1-azido-4-methylpentan-2-yl]carbamate **9** (5.0 g, 20.6 mmol) was dissolved in methanol (200 mL), and Pd/C (110 mg, 1.03 mmol) was added. The resulting mixture was hydrogenated at ambient pressure and ambient temperature until the reaction was complete (monitored by TLC). Then the catalyst was filtered off and the filtrate was evaporated *in vacuo*. Yield 4.40 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (br. s, 1H), 3.62 (br. s, 1H), 2.76 (br. d, *J* = 13.1 Hz, 1H), 2.59 (dd, *J* = 13.1, 6.6 Hz, 1H), 1.70 – 1.60 (m, 1H), 1.55 (s, 2H) 1.44 (s, 9H), 1.30 – 1.21 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 6H). LC/MS(API-ES): *m/z* = 217 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{24}N_2O_2$: C 61.07; H 11.18; N 12.95; Found: C 61.4; H 11.37; N 12.69.

***N*-[(2*S*)-2-Amino-4-methylpentyl]-2-(prop-2-yn-1-yloxy)benzamide hydrochloride (11).** *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (4.78 g, 24.9 mmol), 1-hydroxybenzotriazole (3.37 g, 24.9 mmol), *i*Pr_2NEt (6.45 g, 49.9 mmol), and *tert*-butyl *N*-[(2*S*)-1-amino-4-methylpentan-2-yl]carbamate **9** (4.36 g, 20.2 mmol) were added to a solution of 2-(prop-2-yn-1-yloxy)benzoic acid **7** (3.38 g, 19.2 mmol) in THF (5 mL) at −10 °C. The resulting mixture was stirred at r.t. overnight. Then the mixture was evaporated, dissolved in EtOAc (25 mL), and washed with saturated aqueous $NaHCO_3$ solution (3×25 mL), 10% citric acid solution (3×25 mL) and brine (3×25 mL). The mixture was dried over Na_2SO_4 and evaporated under reduced pressure. Obtained residue was dissolved in CH_2Cl_2 (2 mL), then 4 M HCl in 1,4-dioxane (2 mL) was added and the resulting solution was stirred for 12 h at 25 °C. The reaction progress was monitored by TLC and ^{1}H NMR and upon its completion the reaction mixture was concentrated under reduced pressure. The product was collected by filtration, washed with CH_2Cl_2 (3×10 mL), and then dried in vacuo at 40 °C. Yield 3.80 g (60 %). 1H NMR (500 MHz, DMSO-d_6) δ 8.42 (t, J = 5.9 Hz, 1H), 8.13 (br. s, 3H), 7.74 (d, J = 7.7 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 7.07 (t, J = 7.7 Hz, 1H), 4.96 (s, 2H), 3.64 (s, 1H), 3.50 (t, J = 5.9 Hz, 2H), 3.32 – 3.27 (m, 1H), 1.84 – 1.74 (m, 1H), 1.46 (t, J = 7.2 Hz, 2H), 0.89 (dd, J = 11.0, 6.6 Hz, 6H). LC/MS(API-ES): *m/z* = 275 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{23}ClN_2O_2$: C 61.83; H 7.46; Cl 11.41; N 9.01; Found: C 61.89; H 7.42; Cl 11.49; N 9.14.

***tert*-Butyl-(2-azidoethyl)-4-{[(2*S*)-4-methyl-1-{[2-(prop-2-yn-1-yloxy)phenyl]formamido}pentan-2-yl]carbamoyl} piperidine-1-carboxylate (12).** [(Dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylidene]dimethyl-azanium hexafluorophosphate (5.14 g, 13.5 mmol), *i*Pr_2NEt (4.95 g, 38.3 mmol), 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol (1.84 g, 13.5 mmol), and *N*-[(2*S*)-2-amino-4-methylpentyl]-2-(prop-2-yn-1-yloxy)benzamide hydrochloride **11** (3.5 g, 11.3 mmol) were added to a solution of 4-(2-azidoethyl)-1-[(*tert*-butoxy)carbonyl]piperidine-4-carboxylic acid **4** (4.03 g, 13.5 mmol) in DMF (5 mL) at −10 °C. The resulting mixture was stirred at r.t. overnight. Upon completion of the reaction (monitored by LCMS), the reaction mixture was evaporated, dissolved in EtOAc (15 mL), washed with saturated aqueous $NaHCO_3$ solution (3×20 mL), 10% citric acid solution (3×20 mL)

and brine (3×20 mL). Then the mixture was dried over Na_2SO_4 and evaporated under reduced pressure. The product was purified by column chromatography (eluent EtOAc – hexanes, 1:3 v/v). Yield 3.00 g (59 %). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (t, *J* = 5.5 Hz, 1H), 7.73 (dd, *J* = 8.1 Hz, 1H), 7.54 – 7.42 (m, 2H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 4.93 (s, 2H), 4.14 (br. s, 1H), 3.62 (s, 1H), 3.60 – 3.56 (m, 2H), 3.33 – 3.29 (m, 2H), 3.15 (q, *J* = 8.0 Hz, 2H), 2.82 (br. s, 3H), 2.00 (t, *J* = 14.6 Hz, 2H), 1.73 (t, *J* = 8.0 Hz, 2H), 1.63 – 1.44 (m, 2H), 1.36 (s, 9H), 1.29 – 1.25 (m, 2H), 0.87 (dd, *J* = 17.8, 6.4 Hz, 6H). LC/MS(API-ES): *m/z* = 555 $[M+H]^+$. Anal. Calcd. for $C_{29}H_{42}N_6O_5$: C 62.79; H 7.63; N 15.15; Found: C 62.86; H 7.62; N 15.26.

(13'*S*)-13'-(2-methylpropyl)-3'-oxa-11',14',19',20',21'-pentaazaspiro[piperidine-4,16'-tricyclo[17.2.1.04,9]docosane]-1'(22'),4'(9'),5',7',20'-pentaene-10',15'-dione hydrochloride (14). Sodium ascorbate (0.198 g, 0.001 mol) and $CuSO_4$ $5H_2O$ (0.050 g, 0.0002 mol) were added to a solution of compound **12** (0.550 g, 0.001 mol) in the mixture of *t*BuOH (166 mL) and H_2O (83 mL). The reaction mixture was stirred for 24 h and monitored by HPLC. Upon completion of the reaction, the mixture was evaporated *in vacuo*, dissolved in EtOAc (15 mL) and washed with brine (3×50 mL). The extract was then dried over Na_2SO_4 and evaporated under reduced pressure. Then the product was dissolved in CH_2Cl_2 (10 mL), and 4 M HCl in 1,4-dioxane (10 mL) was added at 0 °C. The reaction mixture was stirred for 3 h and evaporated *in vacuo* to obtain the product as the HCl salt. Yield 0.413 g (84 %). Major diastereomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (br. s, 2H), 7.98 – 7.90 (m, 2H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 6.5 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 5.35 – 5.24 (m, 2H), 4.53 – 4.42 (m, 1H), 4.42 – 4.32 (m, 1H), 3.93 – 3.85 (m, 1H), 3.57 – 3.39 (m, 2H), 3.24 – 3.08 (m, 2H), 2.79 – 2.74 (m, 1H), 2.28 – 2.25 (m, 1H), 2.25 – 2.13 (m, 2H), 2.10 – 2.01 (m, 1H), 1.91 – 1.82 (m, 1H), 1.65 – 1.41 (m, 3H), 1.41 – 1.33 (m, 1H), 1.22 – 1.11 (m, 1H), 0.84 (dd, *J* = 15.4, 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 165.3, 155.7, 143.0, 132.1, 130.3, 124.6, 124.3, 121.4, 114.5, 63.7, 57.4, 48.6, 45.1, 42.8, 42.2, 41.7, 41.0, 40.3, 30.0, 29.8, 24.3, 22.4, 22.4. LC/MS(API-ES): *m/z* = 455 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{34}N_6O_3$: C 58.70; H 7.18; N 17.12; Cl 7.22; Found: C 58.34; H 6.90; N 17.30; Cl 7.20.

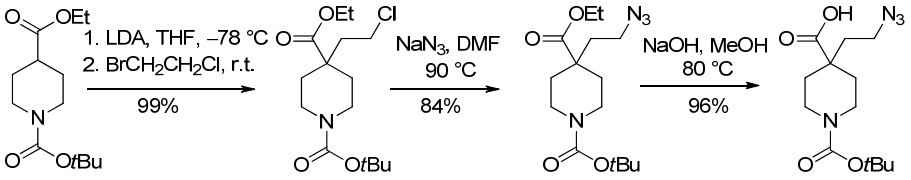
Calculation details. All the structures corresponding to the energy local minima were fully optimized without symmetry constraints using the TURBOMOLE program package (version 6.4) [15, 16]. The RI-BP86/TZVP method [17, 18] was used for geometry optimization. Our choice was determined by a highly efficient combination of the BP86 functional with the Resolution of the Identity (RI) approximation [19–22] within the TURBOMOLE set of programs. The TZVP basis sets were the TZV triple-zeta basis sets [23] extended by adding polarization functions. The fine SCF convergence criterion (SCFConv= 1.0×10^{-8} Hartree) and converge maximum norm of Cartesian gradients up to 10^{-5} a.u. were used for the geometry optimization. The finest grids were used for all calculations (grid=5). The molecular vibrations were derived analytically. These calculations yielded no imaginary vibrations for the local minima structures.

Results and discussion. B/C/P strategy implies three stages of macrocycle preparation: the "build" phase involves synthesis of starting building blocks, which are joined forming a backbone of the target molecule at the "couple" phase and the final ring closure occurs at the "pair" stage. Guided by this strategy, we started with the preparation of building blocks for the macrocycle.

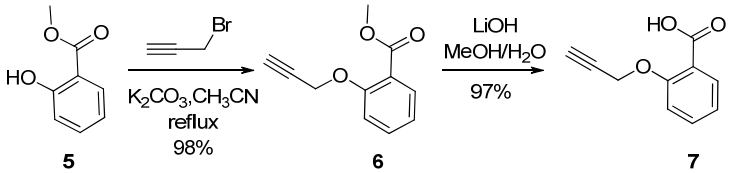
Thus, chloroalkylation of piperidine **1** with the further substitution of chlorine atom in **2** by azide group yielded ester **3**, that was further transformed to the free acid **4** (Scheme 1).

The second precursor, 2-(prop-2-yn-1-yloxy)benzoic acid **7**, was prepared by alkylation of methyl salicylate (**5**) with 3-bromoprop-1-yne and following ester hydrolysis (Scheme 2).

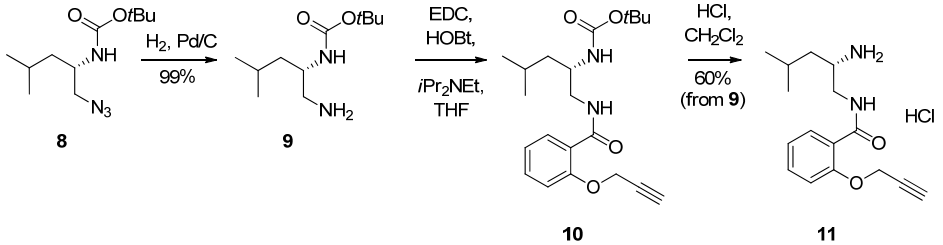
Monoprotected diamine building block **9** was synthesized by the reduction of azide group in the chiral precursor **8**. After that, **9** was coupled with benzoic acid derivative **7** using a standard acylation procedure involving EDC, HOBt, and *i*Pr_2NEt. The coupling product **10** was subsequently deprotected to give **11** (Scheme 3).



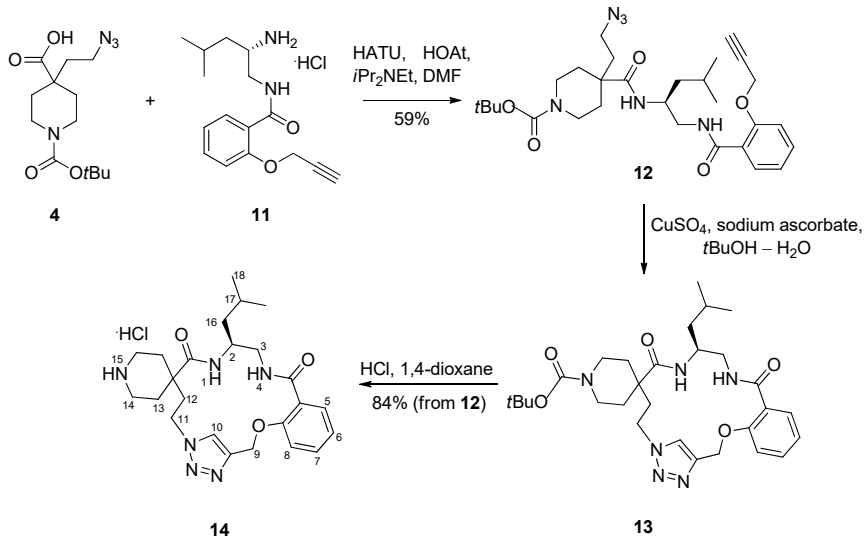
Scheme 1. Synthesis of piperidine building block 4



Scheme 2. Preparation of 2-(prop-2-yn-1-yloxy)benzoic acid 7



Scheme 3. Synthesis of chiral amine 11

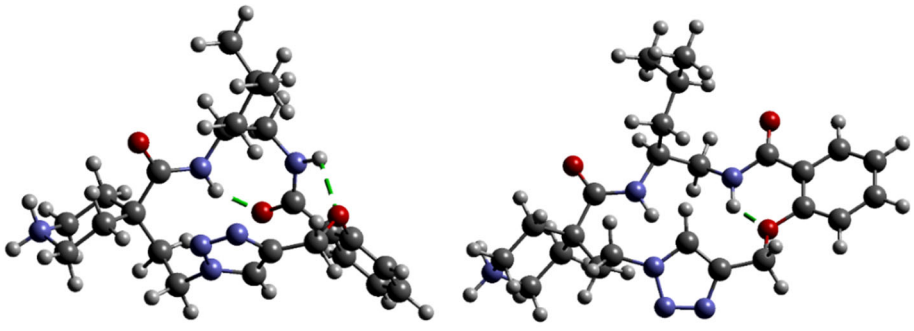


4 **11** **12** **13** **14**

Scheme 4. Preparation of macrocycle 14

Finally, amine **11** was coupled with piperidine **4** using the well-known amide bond formation method involving HATU, HOAt, *i*Pr$_2$NEt. The "pair" stage involved a "click chemistry" formation of 1,2,3-triazole core to give the target macrocycle **14**. This procedure allowed synthesis of the macrocycle in 24 % overall yield from the reagents **1**, **5** and **8**, which is a reasonably high value compared to the usual yields of the macrocycle syntheses [24]. The success of the described procedure is due to the simple well-developed approaches used for the preparation of building blocks and their coupling.

^{1}H NMR spectrum of the product obviously represented a mixture of two diastereomers at a ratio of ca. 3:1. We supposed that the two diastereomers emerged at the "pair" stage during the 1,2,3-triazole ring formation. It could undergo in two spatial arrangements resulting in triazole core being turned "up" or "down", so that the diastereomers would differ by the relative positions of the triazole ring and the isobutyl substituent (Fig. 1). In this way, the macrocycle planar chirality combined with the C-2 stereocenter could lead to the existence of two stereoisomeric pairs. As the configuration of the stereocenter was pre-defined due to the usage of enantiomerically pure azide **8**, only two diastereomers were obtained. Using a series of 2D NMR techniques (COSY, HMBC, HSQC, and ROESY) we have been able to assign the signals in ^{1}H and ^{13}C NMR spectra of the major diastereomer (Figure 2). Unfortunately, due to the slow conformational mobility and partial overlap of the signals of two diasteromers, it was virtually impossible to interpret the spectrum of the minor stereoisomer or to gain insights into its geometry. Therefore, we have turned to the quantum chemistry methods. We have optimized the structures of these two possible diastereomers at DFT approximation level (RI-BP86/TZVP, Fig. 1). The optimization yielded two distinct stereoisomers, of which **14-I** was 5.6 kcal/mol lower in Gibbs free energy than **14-II**.



14-I **14-II**

Fig. 1. Geometries of two diastereomers of macrocycle 14 based on DFT calculations. Hydrogen bonds rendered as dashed green lines

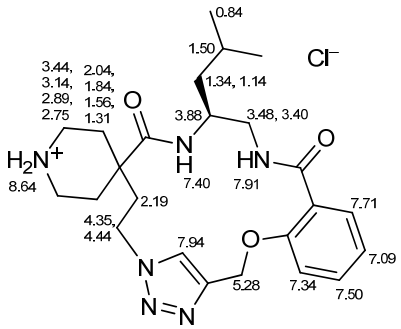


Fig. 2. ^{1}H NMR chemical shifts for the major diastereomer 14-I (DMSO-d_6)

The two diastereomers may convert into each other by the macrocycle rotation similarly to the reported interconversion pathway for imidazole-containing macrocycles [24]. To gain a deeper insight into the conformational equilibrium of the compound **14** we have recorded ^{1}H NMR spectra under heating up to 70 °C (Fig. 3). Interestingly, even at the highest temperature explored, the ratio of conformers is virtually unchanged compared to the ambient temperature. Apparently, disregards the relatively large size of the macrocycle, its rotation is sufficiently energetically demanding, so that it does not occur in the studied temperature range. Still we have observed the increased mobility of the ring at the elevated temperatures and corresponding signal changes. We first turned our attention to the amide NH chemical shift temperature coefficients $\Delta\delta/\Delta T$. It is known that these values can be used for the estimation of hydrogen bond presence [25, 26]: values higher than -4.6×10^{-3} ppm/K evidence that the NH group serves as the intramolecular hydrogen bond donor. The observed values for NH-1 and NH-4 were -1.25×10^{-3} and -1.75×10^{-3} ppm/K, respectively. These values show that both amide NH groups are involved in the intramolecular hydrogen bonds. These bonds are observed in the DFT optimized structure of diastereomer **14-I**, one between NH-4 proton and OPh oxygen, and the second one between NH-1 proton and the carbonyl oxygen of the second amide moiety, (Fig. 1). Two hydrogen bonds stabilize the diastereomer conformation **14-I** and may be responsible for its lower energy relatively to **14-II**.

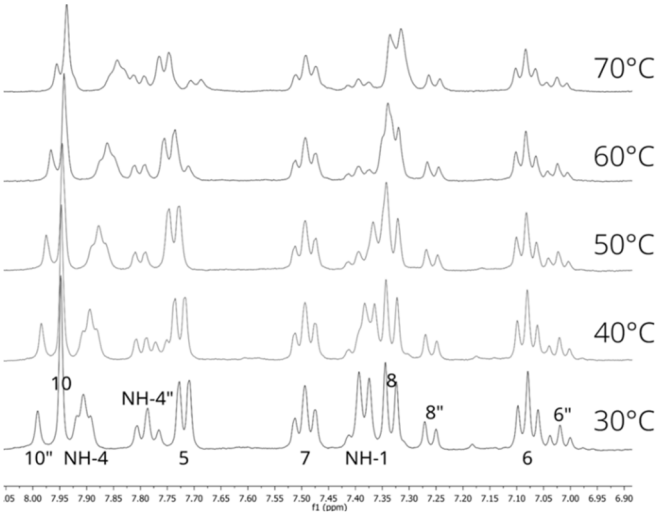


Fig. 3. A series of ^{1}H NMR spectra of 14 at elevated temperatures, aromatic region. Proton assignments are given as numbers above or below peaks. Protons denoted with double quotation mark belong to the minor diasteromer

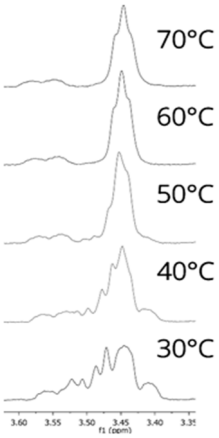


Fig. 4. CH_2-3 methylene group signals in ^{1}H NMR spectrum at the temperature variation

Another feature of the series of ^{1}H NMR spectra of **14** taken at different temperatures is the coalescence of some signals under heating, which is a common feature for the conformationally flexible compounds. It is especially pronounced for the CH_2-3 protons, which are displayed as a multiplet at 30 °C and gradually coalesce under heating to form triplet with J = 5.2 Hz (Fig. 4).

Conclusions. Using the methodology of diversity-oriented synthesis, we have prepared a 16-membered macrocycle containing a 1,2,3-triazole core and a spiro-piperidine moiety. A "click chemistry" formation of a triazole ring was applied at ring closure step. The macrocycle displayed planar chirality and a sterocenter with known configuration introduced in the molecule allowed us to study the formed diastereomers by means of NMR techniques. Quantum-chemical calculations afforded us to establish the geometry of diastereomers and estimate that intramolecular hydrogen bonds play a major role in the stabilization of a specific diastereomer. This work may serve as a quick and robust pathway to the synthesis of libraries of atropoisomeric macrocyclic compounds.

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СИНТЕЗ 1,2,3-ТРИАЗОЛОВМІСНОГО МАКРОЦИКЛУ З ВИКОРИСТАННЯМ РЕАКЦІЇ КЛІК-ХІМІЇ Й АНАЛІЗ ЙОГО ПЛАНАРНОЇ ХІРАЛЬНОСТІ ЗА ДОПОМОГОЮ ЯМР І РОЗРАХУНКІВ DFT

Синтезовано 16-членний макроцикл, що містить 1,2,3-триазольне кільце, спіро-піперидиновий фрагмент і хіральний атом вуглецю. Використаний підхід до отримання макроциклу був натхнений стратегією "будування/сполучення/з'єднання" (BCP) методології синтезу, орієнтованого на різноманітність (DOS). Використання легкодоступних реагентів і надійних синтетичних процедур, включаючи методи клік-хімії, дозволило отримати цільовий макроцикл із високим виходом. Віднесення сигналів у спектрах ЯМР ^{1}H і ^{13}C макроциклу проводили з використанням ряду двовимірних методів ЯМР. Оскільки макроциклу одночасно була притаманна планарна хіральність і присутній стереоцентр із наперед відомою конфігурацією, запропоновано можливі структури діастереомерів. Це припущення було підтверджене за допомогою ряду методів ЯМР-спектроскопії та розрахунків DFT. Обидва методи свідчать про те, що внутрішньомолекулярні водневі зв'язки відіграють важливу роль у стабілізації структур діастереомерів. Згідно з експериментом ЯМР із варіюванням температури, взаємоперетворення двох діастереомерів не відбулося навіть під час нагрівання до 70 °C.

Ключові слова: макроцикл, клік-хімія, планарна хіральність, ЯМР, розрахунки DFT.

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СИНТЕЗ 1,2,3-ТРИАЗОЛСОДЕРЖАЩЕГО МАКРОЦИКЛА С ИСПОЛЬЗОВАНИЕМ РЕАКЦИИ КЛИК-ХИМИИ И АНАЛИЗ ЕГО ПЛАНАРНОЙ ХИРАЛЬНОСТИ С ПОМОЩЬЮ ЯМР И РАСЧЕТОВ DFT

Синтезирован 16-членный макроцикл, содержащий 1,2,3-триазольный цикл, спиро-пиперидиновый фрагмент и хиральный атом углерода. Использованный подход к получению макроцикла был вдохновлен стратегией "построение/соединение/замыкание" (B/C/P) методологии диверсифицированно-ориентированного синтеза (DOS). Использование легкодоступных реагентов и простых синтетических процедур, включая методы клик-химии, позволило получить целевой макроцикл с высоким выходом. Отнесение сигналов в спектрах ЯМР ^{1}H и ^{13}C макроцикла проводили с использованием ряда двумерных методов ЯМР. Поскольку макроциклу одновременно была присуща планарная хиральность, и в его структуре присутствовал стереоцентр с заранее известной конфигурацией, мы предложили возможные структуры диастереомеров. Это предположение было подтверждено с помощью ряда методов ЯМР-спектроскопии и расчетов DFT. Оба метода свидетельствовали о том, что внутримолекулярные водородные связи играют важную роль в стабилизации структур диастереомеров. Согласно экспериментам ЯМР с варьированием температуры, взаимопревращения двух диастереомеров не происходило даже при нагревании до 70 °C.

Ключевые слова: макроцикл, клик-химия, планарная хиральность, ЯМР, расчеты DFT.

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ОПТИЧНІ ТА ФОТОХІМІЧНІ ВЛАСТИВОСТІ ПОЛІМЕРІВ НА ОСНОВІ 2-(4-МЕТАКРИЛОКСИСТИРИЛ)ХІНОЛІНУ

Описано синтез 2-(4-метакрилоксистирил)хіноліну та 2-(4-метакрилоксистирил)-6-метоксихіноліну. Синтезовані полімери з діарилетиленовим фрагментом одержано за вільнорадикальним механізмом полімеризації. Полімеризацію проводили в розчині диметилформаміду, як ініціатор використовували азобісізобутиронітрил. Будову одержаних полімерів і дослідження їхніх фотохімічних властивостей проводили за допомогою ^{1}H ЯМР, УФ-спектроскопії. Температури склування визначені методом диференційної сканувальної калориметрії.

Ключові слова: стирилхінолін, фотоізомеризація, фотолюмінесценція, радикальна полімеризація

Вступ. В останні роки широкого розвитку набули методи синтезу й дослідження фотоактивних сполук для створення на їхній основі нових перспективних матеріалів [1–5]. Серед них особливу увагу дослідники фокусують на матеріалах, для яких опромінення світлом приводить до індукованого внутрішньомолекулярного фотохімічного процесу (фотоізомеризація, фотоциклізація), що дозволяє керовано впливати на зміни фізичних властивостей у досліджених сполуках [6–10]. Окрім цього, у процесі опромінення таких матеріалів може спостерігатися зміна забарвлення та перехід від менш кон'югованої непланарної конфігурації до більш спряженої планарної, а також зміни у спектрах поглинання, випромінювання флуоресценції, електропровідності, електрохімічних і магнітних властивостях, дипольних моментах, показниках заломлення, діелектричних константах і геометрії структур [11, 12]. Крім того, у полімерах спостерігаються зміни в конформаційних характеристиках, змочуваності поверхні, проникності мембран, pH, розчинності, температури золь-гель переходу і температури поділу фаз для полімерних сумішей. Зміни конформації в полімерних матеріалах, що досліджуються в розчині, можуть призвести до фазового поділу. Також слід відзначити, що в рідкокристалічних полімерних композитах можуть відбуватися фазові переходи. Саме тому світлочутливі матеріали відіграють важливу роль у широкому спектрі сфер використання, серед яких зберігання даних високої щільності, комутаційні елементи для мікроелектроніки, нелінійної оптики, датчиків, медицини й ін. [8, 9, 13–19].

Тим не менше, дизайн і синтез нових полімерних матеріалів із контрольованими та передбачуваними властивостями залишається актуальним і перспективним напрямом сучасних досліджень. Фотоактивний хромофор може бути включений у полімер шляхом уведення хромофорів у систему гість-господар, або введенням хромофорного фрагменту у структуру полімера в основний або бічний ланцюг. Хоча жоден із цих способів не є ідеальним, кожен має свої переваги й недоліки. Виявлено, що полімери, функціоналізовані хромофорами, більш ефективні й можуть знайти більш широке застосування завдяки можливості контролю концентрації введенного хромофору; зменшенню впливу орієнтаційних і релаксаційних процесів; відсутності поділу фаз, що зменшує внесок втрат під час розсіювання. Для таких полімерів можна використовувати такі техніки й методи: плазмове травлення, оптично індуковані зміни показника