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Synthesis of Polymethoxy-Substituted Triazolobenzoxazepines

S. Yu. Bukhvalova, M. A. Ivanov, Yu. B. Malysheva, and A. Yu. Fedorov*

Lobachevsky State University of Nizhny Novgorod, pr. Gagarina 23, Nizhny Novgorod, 603950 Russia
**e-mail: afnn@rambler.ru*

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Abstract—A new approach has been proposed for the synthesis of polymethoxy-substituted [1,2,3]triazolo-[1,5-*a*][4,1]benzoxazepines starting from 2-bromo-4,5-dimethoxy- and 2-bromo-3,4,5-dimethoxybenzyl alcohols with thermal [3+2]-dipolar cycloaddition as the key stage.

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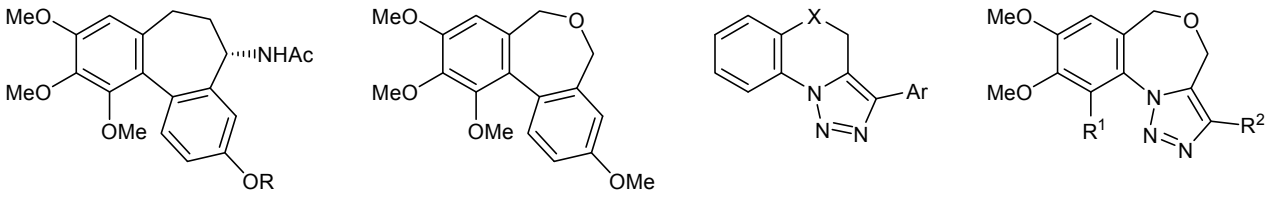
An important method for the treatment of oncological diseases is based on the use of medicinal agents suppressing vascularization of tumor tissues [1–6]. Among compounds possessing such properties, one of the most promising is ZD6126 (**1a**) which is a prodrug of *N*-acetylcolchinol (**1b**) [7–9]. This compound is now under clinical trials. Heterocyclic derivative **2** showed an analogous profile of antitumor activity [10–12]. It has recently been found that structurally related [1,2,3]triazolobenzoxazines, -benzoxazepines, and -benzodiazepines **3** are capable of acting as adenosine receptor antagonists and are therefore interesting from the viewpoint of treatment of not only oncological but also cardiovascular diseases [13]. The goal of the present study was to synthesize polymethoxy-substituted analogs of **2** and **3**, [1,2,3]triazolo[1,5-*a*]-[4,1]benzoxazepines **4**.

It has recently been proposed to synthesize compounds **3** by multicomponent reactions [13, 14]. However, derivatives containing donor aryl fragments were not obtained by these procedures, whereas polymethoxy-substituted benzene ring is considered to be the most important pharmacophore of colchicine analogs [15–17]. We analyzed two synthetic routes leading to compounds **4** (Scheme 1). Following pathway *a*, the target products can be obtained via annulation of triazoles **5**. The latter can be synthesized from aryl azides **7** by ruthenium-catalyzed dipolar cycloaddition with 1,5-regioselectivity [18–20], and aryl azides can be prepared from substituted bromobenzenes **8**. According to the second pathway (*b*), the tricyclic skeleton of triazolobenzoxazepines **4** may be constructed by the thermal Huisgen reaction [21] of propargyl ether **6** obtained from azide **7**.

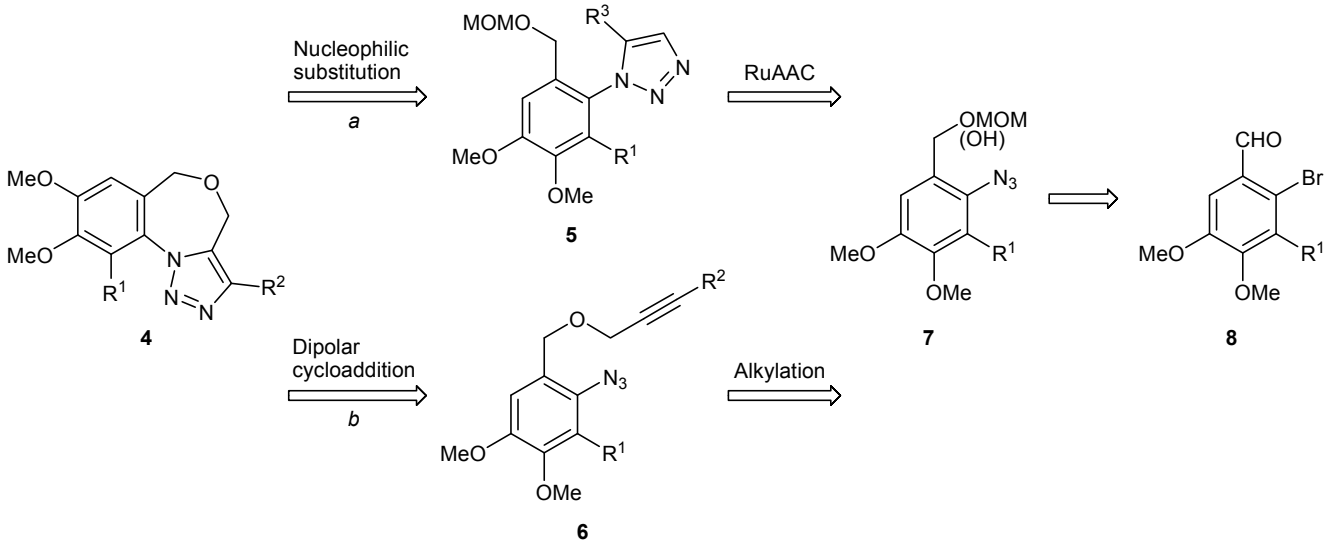
We synthesized aryltriazoles **5** starting from 2-bromobenzaldehyde **8a** which was converted to phenylboronic acid **9** (Scheme 2) [22]. The reaction of **9** with sodium azide [23–25] in the presence of $CuSO_4$ gave azide **10** in 92% yield. 1,3-Dipolar cycloaddition of **10** with terminal alkynes **11a** and **11b** in the presence of 6 mol % of Ru[Cp*(COD)Cl] in toluene at 90°C afforded mixtures of regioisomeric triazoles **5** and **12** at a ratio of 10:1. Aryltriazoles **12** were also synthesized following an alternative procedure. For this purpose, alkyne **11** and a 30% solution of sodium ascorbate were added to azide **10** (prepared by reaction of arylboronic acid **9** with sodium azide in the presence of $CuSO_4$) without isolation from the reaction mixture. Triazoles **12a** and **12b** were thus isolated in 59–70% yield.



1a, **1b** **2** **3** **4**

1, R = PO_3Na_2 (**a**), H (**b**); **3**, X = O, C(O)O, C(O)NH; **4**, R^1 = H, OMe; R^2 = H, Alk.

Scheme 1.

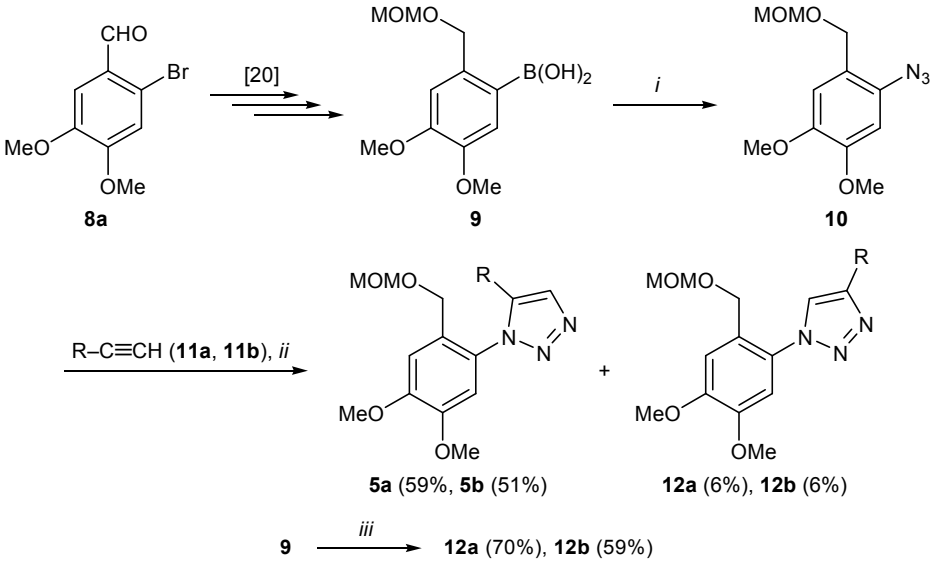


R^1 = H, OMe; R^2 = H, Alk; R^3 = CH_2OAc, $(CH_2)_2OH$.

It is known that removal of methoxymethyl protecting group from a benzylic position by the action of HCl in acetone [22] yields the corresponding benzyl alcohol or benzyl chloride **A**, depending on the concentration of HCl and temperature (Scheme 3). Analysis of published data [22, 26–30] allowed us to presume that the chloromethyl or hydroxymethyl group in intermediate **A** may be involved in intramolecular nucleophilic substitution in the R substituent [CH_2OAc, CH(Me)OH, $(CH_2)_2OH$] in position *5* of the triazole fragment, leading to target tricyclic structure **4**. Unfortunately, we failed to obtain compounds **4** by treatment of **5a** or **5b** with HCl–acetone at different HCl concentrations in the temperature range from 0 to 50°C. A probable reason is non-coplanar arrangement of the substituted aryl and triazole fragments in intermediate **A**.

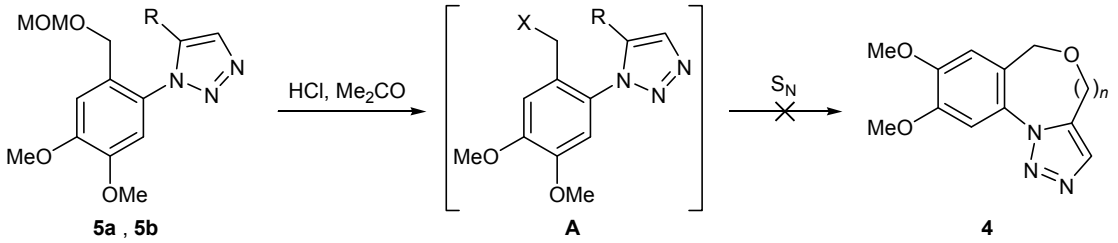
Therefore, we tried to synthesize triazolobenzoxazepines **4** according to path *b* (Scheme 1). In the first step, 2- bromobenzaldehydes **8a** and **8b** were converted into the corresponding arylboronic acids **13a** and **13b**. The latter were treated with sodium azide in

Scheme 2.



Reagents and conditions: *i*: NaN_3, $CuSO_4$, MeOH, 20°C, 5 h; *ii*: Ru[Cp*(COD)Cl] (6 mol %), toluene, 90°C, 5 h; *iii*: (1) NaN_3, $CuSO_4$, MeOH, 20°C, 5 h; (2) **11a**, **11b**, 30% AscNa, 20°C, 10 h.

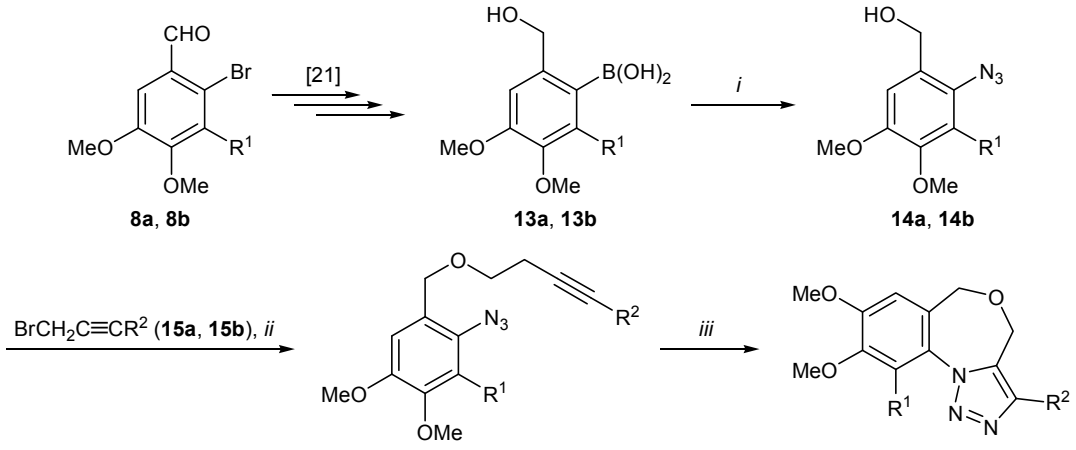
Scheme 3.



5a , **5b**

5, R = CH_2OAc (**a**), $(CH_2)_2OH$ (**b**); X = OH, Cl; **4**, *n* = 1, 2.

Scheme 4.



8a, **8b** **13a**, **13b** **14a**, **14b**

6a–6f **4a–4f**

Reagents and conditions: *i*: NaN_3,$CuSO_4$, MeOH, 20°C, 5 h; *ii*: NaH, THF, 24 h, 0 to 20°C; *iii*: toluene, 110°C, 24 h.
8, R^1 = H (**a**), OMe (**b**); **13**, X = $B(OH)_2$, R^1 = H (**a**), OMe (**b**); **14**, X = N_3, R^1 = H (**a**), OMe (**b**); **15**, R^2 = H (**a**), Me (**b**), Et (**c**); **4**, **6**, R^1 = R^2 = H (**a**); R^1 = H, R^2 = Me (**b**), Et (**c**); R^1 = OMe, R^2 = H (**d**), Me (**e**), Et (**f**).

the presence of copper catalyst to obtain aryl azides **14a** and **14b** in 52 and 45% yield, respectively. The alkylation of **14a** and **14b** with alkynyl bromides **15a**–**15c** afforded ethers **6a**–**6f** in good yield, and heating of **6a**–**6f** in toluene at 110°C led to the formation of target benzoxazepines **4a**–**4f** in 54–72% yield (Scheme 4).

Thus, we have proposed a synthetic approach to polymethoxy-substituted triazolobenzoxazepines which may be interesting as medicinal agents for the treatment of oncological and cardiovascular diseases.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on Agilent DD2 400 (400 and 101 MHz, respectively) and Bruker ARX 200 spectrometers (200 and 50 MHz, respectively). The chemical shifts were determined relative to tetramethylsilane. Column chromatography was performed on Silicagel 60 (70–230 mesh, Alfa Aesar). Commercially available reagents (from Aldrich, Alfa Aesar, Acros Organics) were used without preliminary purification. Solvent were dried and purified according to standard procedures; petroleum ether boiling in the range from 40 to 70°C was used.

Benzyl alcohols. Aldehyde **8a** or **8b** was dissolved in THF, methanol and 0.5 equiv of $NaBH_4$ were added, and the mixture was stirred for 20 min at room temperature. The mixture was diluted with water, the organic solvents were removed under reduced pressure, and the aqueous phase was extracted with diethyl ether. The extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, and the residue was recrystallized from chloroform–petroleum ether.

(2-Bromo-4,5-dimethoxyphenyl)metanol was synthesized from 0.53 g (3.2 mmol) of aldehyde **8a** using 0.06 g (1.6 mmol) of $NaBH_4$, 7 mL of THF, and 7 mL of methanol. Yield 0.51 g (97%), white crystals, mp 143°C [22].

(2-Bromo-3,4,5-trimethoxyphenyl)methanol was synthesized from 7 g (25.4 mmol) of aldehyde **8b**

using 0.48 g (12.7 mmol) of $NaBH_4$, 20 mL of THF, and 20 mL of methanol. Yield 6.3 g (90%), white crystals, mp 55°C [31].

1-Bromo-4,5-dimethoxy-2-[(methoxymethoxy)-methyl]benzene. A solution of 0.53 g (1.43 mmol) of 2-bromo-4,5-dimethoxybenzyl alcohol in 15 mL of anhydrous THF was cooled to 0°C, and 0.04 g (1.58 mmol) of sodium hydride was added under argon. The mixture was stirred for 15 min, 0.12 g (1.43 mmol) of methoxymethyl chloride in 5 mL of anhydrous THF was added dropwise, and the mixture was stirred for 2 h at room temperature and for 2 h at 60°C and left overnight at room temperature. The solvent was removed under reduced pressure, the viscous residue was dissolved in 30 mL of methylene chloride, and the solution was washed with water (3×7 mL). The product was isolated by column chromatography using ethyl acetate–petroleum ether (1:4) as eluent. Yield 263 mg (63%), oily material. ^{1}H NMR spectrum (200 MHz), δ, ppm: 3.40 s (3H, MeO), 3.83 s (3H, MeO), 3.85 s (3H, MeO), 4.57 s (2H, CH_2), 4.71 s (2H, CH_2), 6.96 s (1H, CH), 6.97 s (1H, CH). ^{13}C NMR spectrum (50 MHz), δ_C, ppm: 55.5, 56.0, 56.2, 68.7, 96.0, 112.3, 113.2, 115.4, 129.2, 148.4, 149.0.

8,9-Dimethoxy-4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]-benzoxazepine (4a). A solution of 60 mg (0.25 mmol) of aryl azide **6a** in 4 mL of toluene was heated for 24 h at 110°C. The mixture was evaporated under reduced pressure, and the product was isolated by silica gel column chromatography using petroleum ether–ethyl acetate (1:1) as eluent. Yield 45 mg (72%), light brown crystals, mp 197°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 3.95 s (3H, MeO), 3.98 s (3H, MeO), 4.47 s (2H, CH_2), 4.68 s (2H, CH_2), 6.90 s (1H, CH), 7.53 s (1H, CH), 7.76 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 56.41, 56.53, 58.17, 68.00, 105.68, 112.45, 121.49, 130.06, 132.82, 134.23, 149.46, 150.42. Found, %: C 56.94; H 5.37; N 17.11; O 20.58. $C_{12}H_{13}N_3O_3$. Calculated, %: C 58.29; H 5.30; N 17.00; O 19.47.

Compounds **4b**–**4f** were synthesized in a similar way.

8,9-Dimethoxy-3-methyl-4*H*,6*H*-[1,2,3]triazolo-[1,5-*a*][4,1]benzoxazepine (4b) was synthesized from 78 mg (0.30 mmol) of **6b** in 4 mL of toluene. Yield 51 mg (64%), brown crystals, mp 164°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.40 s (3H, CH_3), 3.94 s (3H, MeO), 3.97 s (3H, MeO), 4.44 s (2H, CH_2), 4.59 s (2H, CH_2), 6.89 s (1H, CH), 7.49 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 10.31, 56.38, 56.50, 57.72, 67.83, 105.52, 112.49, 121.34, 130.41, 130.81, 141.34, 149.28, 150.37. Found, %: C 59.55; H 5.92; N 16.12; O 18.41. $C_{13}H_{15}N_3O_3$. Calculated, %: C 59.76; H 5.79; N 16.09; O 18.36.

3-Ethyl-8,9-dimethoxy-4*H*,6*H*-[1,2,3]triazolo-[1,5-*a*][4,1]benzoxazepine (4c) was synthesized from 50 mg (0.20 mmol) of **6c** in 3 mL of toluene. Yield 34 mg (60%), light brown crystals, mp 193°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.35 t (3H, CH_3, J = 7.6 Hz), 2.79 q (2H, CH_2, J = 7.6 Hz), 3.95 s (3H, MeO), 3.98 s (3H, MeO), 4.45 s (2H, CH_2), 4.60 s (2H, CH_2), 6.90 s (1H, CH), 7.50 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 14.43, 18.55, 56.41, 56.52, 57.60, 67.82, 105.64, 112.51, 121.35, 130.50, 147.09, 149.29, 150.39. Found, %: C 61.72; H 6.55; N 14.19; O 17.54. $C_{14}H_{17}N_3O_3$. Calculated, %: C 61.08; H 6.22; N 15.27; O 17.43.

8,9,10-Trimethoxy-4*H*,6*H*-[1,2,3]triazolo[1,5-*a*]-[4,1]benzoxazepine (4d) was synthesized from 55 mg (0.2 mmol) of **6d** in 4 mL of toluene. The product was isolated using petroleum ether–ethyl acetate (3:1) as eluent. Yield 34.6 mg (63%), dark brown crystals, mp 167–170°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 3.94 s (3H, MeO), 3.96 s (3H, MeO), 4.02 s (3H, MeO), 4.27 s (2H, CH_2), 4.58 s (2H, CH_2), 6.77 s (1H, CH), 7.80 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 56.41, 56.59, 61.26, 62.72, 67.17, 108.73, 123.81, 126.13, 132.04, 140.56, 144.21, 147.89, 154.32. Found, %: C 57.38; H 5.47; N 15.02; O 22.13. $C_{13}H_{15}N_3O_4$. Calculated, %: C 56.31; H 5.45; N 15.11; O 23.13.

8,9,10-Trimethoxy-3-methyl-4*H*,6*H*-[1,2,3]tri-azolo[1,5-*a*][4,1]benzoxazepine (4e) was synthesized from 15 mg (0.05 mmol) of **6e** in 2 mL of toluene. Yield 9 mg (61%), light brown crystals, mp 131°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.45 s (3H, CH_3), 3.94 s (3H, MeO), 3.96 s (3H, MeO), 4.01 s (3H, MeO), 4.27 s (2H, CH_2), 4.52 s (2H, CH_2), 6.76 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 10.29, 56.16, 56.43, 61.31, 62.70, 67.17, 108.72, 124.17, 126.11, 131.00, 140.46, 144.19, 147.88, 154.21. Found, %: C 58.34; H 5.64; N 14.43; O 21.59. $C_{14}H_{17}N_3O_4$. Calculated, %: C 57.72; H 5.88; N 14.43; O 21.99.

3-Ethyl-8,9,10-trimethoxy-4*H*,6*H*-[1,2,3]triazolo-[1,5-*a*][4,1]benzoxazepine (4f) was synthesized from 20 mg (0.06 mmol) of **6f** in 2 mL of toluene. Yield 10.8 mg (54%), light brown crystals, mp 135°C.

^{1}H NMR spectrum (400 MHz), δ, ppm: 1.38 t (3H, CH_3, J = 7.0 Hz), 2.82 q (2H, CH_2, J = 7.3 Hz), 3.94 s (3H, MeO), 3.97 s (3H, MeO), 4.04 s (2H, CH_2), 4.27 s (2H, CH_2), 6.76 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 12.62, 13.91, 56.26, 58.45, 58.64, 61.85, 67.27, 107.83, 108.04, 108.94, 125.18, 132.97, 142.32, 150.74, 152.92. Found, %: C 58.11; H 6.75; N 13.87; O 21.27. $C_{15}H_{19}N_3O_4$. Calculated, %: C 59.01; H 6.27; N 13.77; O 20.98.

Triazoles 5a and 5b (*general procedure***).** A two-necked flask was charged under argon with 0.06 equiv of Ru[Cp*(COD)Cl] and 2 mL of toluene, a solution of 3 equiv of azide **10** and 1.5 equiv of alkyne **11** in 3 mL of toluene was then added under argon, and the mixture was stirred for 8–10 h at 90°C (TLC). The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography using petroleum ether–ethyl acetate (3:2) as eluent to obtain a mixture of triazoles **5** and **12** at a ratio of 10:1 (according to the NMR data). Compound **5** was isolated by reprecipitation from chloroform–diethyl ether–petroleum ether.

(1-{4,5-Dimethoxy-2-[(methoxymethoxy)methyl]-phenyl}-1*H*-1,2,3-triazol-5-yl)methyl acetate (5a) was synthesized from 93 mg (0.329 mmol) of azide **10** and 16.1 mg (0.1645 mmol) of alkyne **11a** using 2.5 mg (0.00658 mmol) of Ru[Cp*(COD)Cl]. Yield 56 mg (65%), yellow oily material. ^{1}H NMR spectrum (200 MHz), δ, ppm: 2.00 s [3H, $CH_3C(O)$], 3.23 s (3H, MeO), 3.86 s (3H, MeO), 3.96 s (3H, MeO), 4.19 s (2H, CH_2), 4.48 s (2H, CH_2), 4.99 s (2H, CH_2), 6.80 s (1H, CH), 7.07 s (1H, CH), 7.82 s (1H, CH). ^{13}C NMR spectrum (50 MHz), δ_C, ppm: 20.5, 54.0, 55.3, 56.1, 56.2, 64.6, 95.9, 110.4, 111.8, 126.2, 128.1, 133.9, 134.2, 148.6, 150.5, 169.9. Found, %: C 54.60; H 6.04; N 11.98; O 27.38. $C_{16}H_{21}N_3O_6$. Calculated, %: C 54.70; H 6.02; N 11.93; O 27.35.

(1-{4,5-Dimethoxy-2-[(methoxymethoxy)methyl]-phenyl}-1*H*-1,2,3-triazol-5-yl)ethan-1-ol (5b) was synthesized from 104 mg (0.367 mmol) of **10** and 12.85 mg (0.183 mmol) of **11b** using 2.79 mg (0.0073 mmol) of Ru[Cp*(COD)Cl]. Yield 75.5 mg (57%), yellow oily material. ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.83 t (2H, CH_2, J = 4.1 Hz), 2.77 t (2H, CH_2, J = 4.1 Hz), 3.23 s (3H, MeO), 3.81 s (3H, MeO), 3.95 s (3H, MeO), 4.22 s (2H, CH_2), 4.47 s (2H, CH_2), 6.82 s (1H, CH), 7.05 s (1H, CH), 7.64 s (1H, CH). ^{13}C NMR spectrum (50 MHz), δ_C, ppm: 26.8, 55.4, 56.1, 56.2, 60.2, 64.9, 95.9, 110.5, 112.0, 127.0, 127.8, 132.4, 136.9, 148.8, 150.2. Found, %: C 55.83; H 6.75; N 12.89; O 24.53. $C_{15}H_{21}N_3O_5$. Calculated, %: C 55.72; H 6.55; N 12.96; O 24.77.

Alkylation of 2-(hydroxymethyl)phenyl azides 14a and 14b (*general procedure***).** Aryl azide **14a** or **14b** was dissolved in anhydrous THF under argon, the solution was cooled to 0°C, sodium hydride was added, and the mixture was stirred for 1 h at room temperature. The mixture was cooled to 0°C, alkyne **15a**–**15c** was added, and the mixture was stirred for 24 h at room temperature. The product was isolated by silica gel column chromatography.

1-Azido-4,5-dimethoxy-2-[(prop-2-yn-1-yloxy)-methyl]benzene (6a) was synthesized from 227 mg (1.08 mmol) of **14a** and 167 μL (1.4 mmol) of propargyl bromide in 4 mL of anhydrous THF using 65 mg (1.62 mmol) of NaH. The product was isolated using petroleum ether–ethyl acetate (6:1) as eluent. Yield 203 mg (76%), light yellow crystals, mp 60°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.48 s (1H, CH), 3.87 s (3H, MeO), 3.91 s (3H, MeO), 4.19 d (2H, CH_2, J = 2.4 Hz), 4.52 s (2H, CH_2), 6.65 s (1H, CH), 6.92 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 56.31, 56.35, 57.55, 66.78, 74.83, 79.76, 101.94, 113.15, 120.67, 130.48, 146.55, 149.85. Found, %: C 57.13; H 5.71; N 16.89; O 20.27. $C_{12}H_{13}N_3O_3$. Calculated, %: C 58.29; H 5.30; N 17.00; O 19.47.

1-Azido-2-[(but-2-yn-1-yloxy)methyl]-4,5-dimethoxybenzene (6b) was synthesized from 50 mg (0.24 mmol) of **14a** and 167 μL (0.36 mmol) of 1-bromobut-2-yne in 2 mL of anhydrous THF using 14 mg (0.36 mmol) of NaH. The product was isolated using petroleum ether–ethyl acetate (3:1) as eluent. Yield 38 mg (60%), light brown crystals, mp 47–49°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.87 t (3H, CH_3, J = 2.3 Hz), 3.86 s (3H, MeO), 3.89 (3H, MeO), 4.13 q (2H, CH_2, J = 2.3 Hz), 4.47 s (2H, CH_2), 6.63 s (1H, CH), 6.92 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 56.30, 58.18, 66.62, 75.13, 82.86, 101.89, 112.26, 113.04, 115.38, 121.07, 130.27, 146.49, 149.66. Found, %: C 59.97; H 5.85; N 16.12; O 18.06. $C_{13}H_{15}N_3O_3$. Calculated, %: C 59.76; H 5.79; N 16.09; O 18.36.

1-Azido-4,5-dimethoxy-2-[(pent-2-yn-1-yloxy)-methyl]benzene (6c) was synthesized from 50 mg (0.24 mmol) of **14a** and 167 μL (0.36 mmol) of 1-bromopent-2-yne in 2 mL of anhydrous THF using 14 mg (0.36 mmol) of NaH. The product was isolated as described above for **6b**. Yield 42 mg (64%), brown

crystals, mp 53–55°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.25 t (3H, CH_3, J = 7.1 Hz), 2.03 s (2H, CH_2), 3.86 s (3H, MeO), 3.89 s (3H, MeO), 4.15 s (2H, CH_2), 4.48 s (2H, CH_2), 6.63 s (1H, CH), 6.92 (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 12.62, 13.92, 56.28, 56.31, 58.15, 66.53, 75.25, 88.78, 101.90, 113.11, 121.09, 130.33, 146.50, 149.68. Found, %: C 61.74; H 6.43; N 15.11; O 16.72. $C_{14}H_{17}N_3O_3$. Calculated, %: C 61.08; H 6.22; N 15.27; O 17.43.

2-Azido-3,4,5-trimethoxy-1-[(prop-2-yn-1-yloxy)-methyl]benzene (6d) was synthesized from 130 mg (0.54 mmol) of **14b** and 72 μL (0.65 mmol) of propargyl bromide in 4 mL of anhydrous THF using 37 mg (0.92 mmol) of NaH. The product was isolated as described above for **6a**. Yield 150 mg (73%), dark yellow viscous oil. ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.48 t (1H, CH, J = 2.2 Hz), 3.84 s (3H, MeO), 3.87 s (3H, MeO), 3.95 s (3H, MeO), 4.21 d (2H, CH_2, J = 2.1 Hz), 4.52 s (2H, CH_2), 6.72 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 56.28, 57.83, 61.08, 61.87, 67.52, 74.89, 79.67, 107.86, 124.14, 124.73, 131.71, 142.46, 150.77. Found, %: C 57.41; H 5.29; N 15.21; O 22.09. $C_{13}H_{15}N_3O_4$. Calculated, %: C 56.31; H 5.45; N 15.11; O 23.13.

2-Azido-1-[(but-2-yn-1-yloxy)methyl]-3,4,5-trimethoxybenzene (6e) was synthesized from 170 mg (0.71 mmol) of **14b** and 73 μL (0.85 mmol) of 1-bromobut-2-yne in 4 mL of anhydrous THF using 57 mg (1.42 mmol) of NaH. The product was isolated as described above for **6b**. Yield 124 mg (60%), brown oil. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.88 t (3H, CH_3, J = 2.3 Hz), 3.85 s (3H, MeO), 3.87 s (3H, MeO), 3.95 s (3H, MeO), 4.17 q (2H, CH_2, J = 2.3 Hz), 4.49 s (2H, CH_2), 6.73 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 14.26, 22.79, 31.73, 56.30, 58.51, 61.09, 61.88, 67.40, 82.99, 107.79, 124.13, 125.19, 148.16, 150.77. Found, %: C 58.42; H 5.64; N 14.54; O 21.40. $C_{14}H_{17}N_3O_4$. Calculated, %: C 57.72; H 5.88; N 14.43; O 21.99.

2-Azido-3,4,5-trimethoxy-1-[(pent-2-yn-1-yloxy)-methyl]benzene (6f) was synthesized from 50 mg (0.21 mmol) of **14b** and 167 μL (0.36 mmol) of 1-bromopent-2-yne in 2 mL of anhydrous THF using 14 mg (0.36 mmol) of NaH. The product was siolated as described above for **6b**. Yield 65 mg (70%), light yellow oil. ^{1}H NMR spectrum (400 MHz), δ, ppm: 1.17 t (3H, CH_3, J = 7.0 Hz), 2.24 d (2H, CH_2, J = 6.7 Hz), 3.84 s (3H, MeO), 3.95 s (3H, MeO), 4.12 s (3H, MeO), 4.21 s (2H, CH_2), 4.49 s (2H, CH_2), 6.73 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 14.40, 18.50, 27.65, 29.85, 53.57, 56.42, 61.29, 62.82, 67.21, 108.76, 126.13, 144.23, 146.10, 147.89, 154.17. Found, %: C 59.72; H 6.75; N 13.84; O 19.69. $C_{15}H_{19}N_3O_4$. Calculated, %: C 59.01; H 6.27; N 13.77; O 20.98.

4,5-Dimethoxy-2-[(methoxymethoxy)methyl]-phenylboronic acid (9). A solution of 0.38 g (0.93 mmol) of 1-bromo-4,5-dimethoxy-2-[(methoxymethoxy)methyl]benzene in 5 mL of anhydrous THF was cooled to –78°C, and 0.6 mL of a solution of butyllithium in hexane (c = 1.6 M) was added dropwise under argon. The mixture was kept for 15 min at –78°C, 0.23 mL (0.98 mmol) of triisopropyl borate was added, and the mixture was kept for 1.5 h at –78°C, allowed to slowly warm up to room temperature, and stirred overnight. Water, 3 mL, was then added dropwise, and the mixture was evaporated under reduced pressure. The residue was dissolved in 30 mL of ethyl acetate, 10 mL of water was added, and the mixture was vigorously shaken for 10 min in a separatory funnel. The organic layer was separated and washed with water (2×10 mL), and the aqueous phase was extracted with ethyl acetate. The extracts were combined with the organic phase and evaporated under reduced pressure. The viscous residue was dissolved in chloroform, the solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure, and the residue was recrystallized from chloroform–petroleum ether. Yield 136 mg (55%), colorless crystals. ^{1}H NMR spectrum (200 MHz), δ, ppm: 3.43 s (3H, MeO), 3.91 s (3H, MeO), 3.93 s (3H, MeO), 4.66 s (2H, CH_2), 4.68 s (2H, CH_2), 6.81 s (1H, CH), 7.41 s (1H, CH). ^{13}C NMR spectrum (50 MHz), δ_C, ppm: 55.7, 55.8, 55.9, 69.8, 94.0, 113.9, 118.3, 134.0, 148.3, 150.2.

1-Azido-4,5-dimethoxy-2-[(methoxymethoxy)-methyl]benzene (10). A mixture of 0.2 g (0.78 mmol) of boronic acid **9**, 0.346 g (0.78 mmol) of lead tetraacetate, and 0.025 g (0.078 mmol) of mercury acetate was dissolved under argon in anhydrous chloroform, and the solution was heated for 2 h at 40°C. The mixture was cooled to room temperature and left to stand for 12 h. The solvent was removed under reduced pressure, 0.153 g (2.3 mmol) of sodium azide and 3 mL of DMSO were added, and the mixture was stirred for 10 h at room temperature. It was then diluted with water (50 mL) and extracted with chloroform, the extract was evaporated under reduced pressure, and the product was isolated by silica gel column chromatography using ethyl acetate–petroleum ether

(1:4) as eluent. Yield 0.18 g (92%), yellow oil. ^{1}H NMR spectrum (200 MHz), δ, ppm: 3.40 s (3H, MeO), 3.87 s (3H, MeO), 3.89 s (3H, MeO), 4.49 s (2H, CH_2), 4.68 s (2H, CH_2), 6.64 s (1H, CH), 6.89 s (1H, CH). ^{13}C NMR spectrum (50 MHz), δ_C, ppm: 55.3, 56.0, 56.1, 64.3, 95.4, 101.8, 113.0, 120.9, 130.2, 146.3, 149.5. Found, %: C 51.27; H 6.11; N 16.20; O 26.42. $C_{12}H_{17}N_3O_5$. Calculated, %: C 50.88; H 6.05; N 16.34; O 26.73.

Triazole derivatives 12a and 12b (*general procedure*). Azide **10**, 1 equiv, was dissolved in THF, 1.5 equiv of alkyne **11a** or **11b** was added, the mixture was diluted with an equal volume of water, a 30% solution of sodium ascorbate (0.3 equiv) was added under vigorous stirring, and a 0.1 M solution of copper(II) sulfate (0.07 equiv) was then added. The progress of the reaction was monitored by TLC.

{1-[4,5-Dimethoxy-2-(methoxymethoxymethyl)-phenyl]-1*H*-1,2,3-triazol-4-yl}methyl acetate (12a) was synthesized from 0.0464 g (0.18 mmol) of azide **10** and 26.46 mg (0.27 mmol) of alkyne **11a** using 2 mL of water and 2 mL of THF. The product was isolated by silica gel column chromatography using ethyl acetate–petroleum ether (1:1) as eluent. Yield 0.0305 g (47%), yellow oil. ^{1}H NMR spectrum (200 MHz), δ, ppm: 2.09 s (3H, CH_3CO), 3.32 s (3H, MeO), 3.88 s (3H, MeO), 3.95 s (3H, MeO), 4.34 s (2H, CH_2), 4.61 s (2H, CH_2), 5.28 s (2H, CH_2), 6.94 s (1H, CH), 7.04 s (1H, CH), 7.97 s (1H, CH). ^{13}C NMR spectrum (50 MHz), δ_C, ppm: 20.8, 55.5, 56.2, 56.2, 57.2, 64.9, 95.8, 109.2, 112.4, 124.9, 126.1, 128.8, 142.5, 148.9, 149.9, 170.8. Found, %: C 54.06; H 6.07; N 12.65; O 27.22. $C_{16}H_{21}N_3O_6$. Calculated, %: C 54.70; H 6.02; N 12.50; O 26.78.

2-{1-[4,5-Dimethoxy-2-(methoxymethoxymethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}ethanol (12b) was synthesized from 50 mg (0.1767 mmol) of azide **10** and 18.55 mg (0.265 mmol) of alkyne **11b** using 2 mL of water and 2 mL of THF. The product was isolated using ethyl acetate as eluent. Yield 24 mg (59%), yellow oil. ^{1}H NMR spectrum (200 MHz), δ, ppm: 2.58–3.19 m (4H, CH_2CH_2), 3.31 s (3H, MeO), 3.88 s (3H, MeO), 4.35 s (2H, CH_2), 4.59 s (2H, CH_2), 6.94 s (1H, CH), 7.03 s (1H, CH), 8.85 br.s (1H, CH). ^{13}C NMR spectrum (50 MHz), δ_C, ppm: 28.6, 55.5, 56.1, 56.2, 61.5, 64.8, 95.7, 109.2, 112.4, 124.9, 129.1, 129.2, 129.3, 148.9, 148.9, 149.8. Found, %: C 55.83; H 6.75; N 12.84; O 24.58. $C_{15}H_{21}N_3O_5$. Calculated, %: C 55.72; H 6.55; N 12.96; O 24.77.

Removal of methoxymethyl protecting group. Compound **5a** or **5b**, 75 mg (0.23 mmol), was dissolved in 3 mL of acetone, 6 drops of concentrated aqueous HCl were added, and the mixture was stirred for 2–3 h at 40°C. The progress of the reaction was monitored by TLC. The solvent was distilled off, the residue was treated with chloroform, the extract was washed with a solution of sodium hydrogen carbonate, and the product was isolated by silica gel column chromatography using ethyl acetate as eluent.

2-(Hydroxymethyl)phenylboronic acids 13a and 13b (*general procedure*). A solution of the corresponding 2-bromobenzyl alcohol in anhydrous THF was cooled to –78°C, a solution of butyllithium (3 equiv) in hexane was added dropwise under argon, the mixture was stirred for 15 min at –78°C, and 3 equiv of triisopropyl borate was added dropwise. The mixture was stirred for 1.5 h at –78°C, allowed to slowly warm up to room temperature, and stirred overnight, 5 mL of 10% aqueous HCl was added dropwise, and the mixture was evaporated under reduced pressure. Ethyl acetate, 15 mL, was added to the residue, the mixture was vigorously shaken for 10 min in a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure, and the residue was recrystallized from chloroform–petroleum ether.

2-(Hydroxymethyl)-4,5-dimethoxyphenylboronic acid (13a) was synthesized from 1 g (4 mmol) of (2-bromo-4,5-dimethoxyphenyl)methanol in 25 mL of anhydrous THF using 5.3 mL of a solution of butyllithium in hexane (c = 1.6 M) and 3.2 mL (14 mmol) of triisopropyl borate. Yield 398 mg (47%), white crystals. ^{1}H NMR spectrum (400 MHz), δ, ppm: 3.83 s (3H, MeO), 3.87 s (3H, MeO), 5.00 s (2H, CH_2), 6.80 s (1H, CH), 7.17 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 55.87, 55.91, 70.89, 103.64, 111.48, 147.47, 148.90, 152.38.

6-(Hydroxymethyl)-2,3,4-trimethoxyphenylboronic acid (13b) was synthesized from 1 g (3.6 mmol) of (2-bromo-3,4,5-trimethoxyphenyl)methanol in 25 mL of anhydrous THF using 6.7 mL of a solution of butyllithium in hexane (c = 1.6 M) and 3.2 mL (14 mmol) of triisopropyl borate. Yield 462 mg (53%), light yellow oil. ^{1}H NMR spectrum (400 MHz), δ, ppm: 3.72 s (3H, MeO), 3.78 s (6H, MeO), 4.88 s (2H, CH_2), 6.52 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 55.89, 55.92, 60.67, 65.56, 103.83, 135.43, 137.07, 153.12, 153.16.

Azidopolymethoxyphenylmethanols 14a and 14b (*general procedure*). A solution of boronic acid **13a** or **13b**, 2 equiv of sodium azide, and 0.2 equiv of copper(II) sulfate pentahydrate in methanol was stirred until the initial compound disappeared (TLC). The solvent was removed under reduced pressure, the dry residue was treated with water and extracted with ethyl acetate, the extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure, and the product was isolated by silica gel column chromatography.

(2-Azido-4,5-dimethoxyphenyl)methanol (14a) was synthesized from 600 mg (2.5 mmol) of **13a** using 322 mg (4.96 mmol) of sodium azide, 122 mg (0.5 mmol) of $CuSO_4 \cdot 5H_2O$, and 10 mL of methanol. The product was isolated using petroleum ether–ethyl acetate (3 : 1) as eluent. Yield 210 mg (40%), dark brown crystals, mp 91°C. ^{1}H NMR spectrum (400 MHz), δ, ppm: 3.79 s (3H, MeO), 3.84 s (3H, MeO), 4.49 s (2H, CH_2), 6.57 s (1H, CH), 6.84 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 14.08, 22.65, 56.12, 60.69, 101.81, 112.24, 129.42, 146.33, 149.28. Found, %: C 51.87; H 5.45; N 20.90; O 21.78. $C_9H_{11}N_3O_3$. Calculated, %: C 51.67; H 5.30; N 20.09; O 24.40.

(2-Azido-3,4,5-trimethoxyphenyl)methanol (14b) was synthesized from 100 mg (0.41 mmol) of **13b** using 54 mg (0.82 mmol) of sodium azide, 20.5 mg (0.082 mmol) of $CuSO_4 \cdot 5H_2O$, and 3 mL of methanol. The product was isolated using petroleum ether–ethyl acetate (1 : 1) as eluent. Yield 44 mg (45%), dark brown oil. ^{1}H NMR spectrum (400 MHz), δ, ppm: 3.84 s (3H, MeO), 3.87 s (3H, MeO), 3.96 s (3H, MeO), 4.58 s (2H, CH_2), 6.68 s (1H, CH). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 56.16, 60.95, 61.76, 62.00, 107.31, 123.44, 127.79, 142.16, 148.12, 150.63. Found, %: C 50.19; H 5.68; N 17.47; O 26.66. $C_{10}H_{13}N_3O_4$. Calculated, %: C 50.21; H 5.48; N 17.53; O 26.78.

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