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SYNTHESIS OF NEW 1,4-BENZODIOXANE DERIVATIVES CONTAINING SUBSTITUTED 1,2,4-TRIAZOLES

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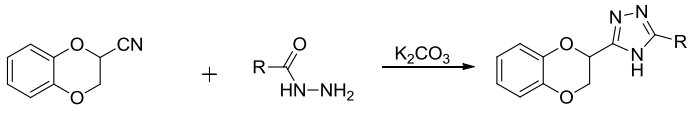
The synthesis of new derivatives of 1,4-benzodioxane containing a substituted 1,2,4-triazole ring was carried out. The interaction of various hydrazides and 1,4-benzodioxane-2-carboxylic acid nitrile in the presence of dry potash have been studied. It has been shown that the best results are achieved with the ratio of these components 1:2:3. In this case, butanol was used as a solvent, since the reaction in ethanol ends with the formation of an intermediate linear product, the structure of which, like all synthesized compounds, was proved by NMR spectroscopic analysis and thin layer chromatography.

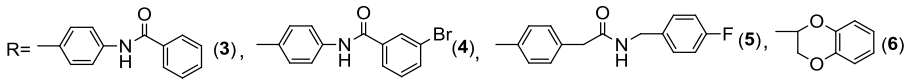
References 7.

Bicyclic compounds containing a 1,4-benzodioxane cycle are interesting in terms of identifying new highly active drugs [1–3], at the same time, five-membered rings with one, two and three heteroatoms play an important role in the manifestation of certain pharmacological properties. In particular, the 1,2,4-triazole ring is a component of numerous preparations widely used in practical medicine [4]. It is for this reason that we synthesized compounds combining 1,4-benzodioxane and 1,2,4-triazole heterocyclic fragments. In the structure of these compounds the substituents at the nitrogen atom in the 4th position of the triazole ring were varied: compounds with a hydrogen atom, phenyl and amine groups were obtained. In these compounds, substituted mercapto fragments were present in the 3rd position. The compounds synthesized by us exhibited moderate antihypoxic and antibacterial activity [5, 6]. In continuation of these studies, we have syn-

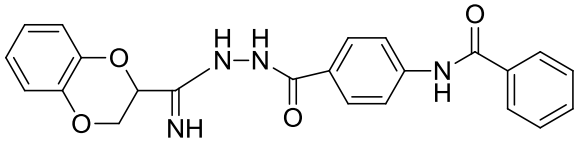
thesized new 3-aryl- and 3-heterylsubstituted derivatives of triazolobenzodioxanes by reacting 1,4-benzodioxane-2-carboxylic acid nitrile **(1)** in the presence of dry potash with hydrazides **2** obtained by condensation of ethyl esters of various acids with hydrazine hydrate. Target compounds **3-6** are white crystalline substances.



1 **2** **3-6**



The conditions for carrying out of this reaction have been studied. Thus, it has been shown that shortening the heating time of the reaction mixture, for example, in the case of unsubstituted arylhydrazide **2**, leads to the formation of intermediate linear compound **7**, which confirms that this reaction is a two-stage process.



7

This compound of a linear structure was also isolated during the reaction in absolute ethanol, while in butanol, after an hour of heating, crystals were formed, which, upon further heating, disappear, passing into the target cyclic product. As a result, it has been found that the best yields of triazolobenzodioxanes **3-6** are obtained by using per 1 *mol* of the corresponding hydrazide, 2 *moles* of nitrile 1 and 3 *moles* of dry potash. The reaction mixture was boiled in butanol for 4-5 *h*.

The structure and purity of all synthesized compounds were confirmed by physicochemical methods and thin layer chromatography.

Experimental part

IR spectra of the compounds were taken on a Nicolet Avatar 330 FT-IR spectrometer in vaseline oil, ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 instrument in DMSO-d_6, internal standard was TMS. Melting points were determined on a Boetius microheater. TLC was carried out on "Silufol UV-254" plates (eluent - benzene-acetone, 3:1, developer - iodine vapor).

1,4-Benzodioxane-2-carboxylic acid nitrile (**1**) was obtained according by the method [7].

Benzodioxanyl-1,2,4-triazoles 3-6. General method. A mixture of 3.2 *g* (0.02 *mol*) of 1,4-benzodioxane-2-carboxylic acid nitrile (**1**), 0.01 *mol* of the corresponding hydrazide **2** and 4.1 *g* (0.03 *mol*) of dry potash is boiled in 50*ml* of butanol for 4-5 *h*. Water is added to the reaction mixture, the organic layer is separated and washed with water. The solvent is distilled off, ethanol is added to the residue, unreacted hydrazide is filtered off. Ethanol is distilled off, the residue is crystallized with diethylether and recrystallized from ethanol.

N-(4-(5-(1,4-Benzodioxan-2-yl)-4*H*-1,2,4-triazol-3-yl)phenyl)benzamide (3). Yield 1.7 *g* (43%), mp. 235-236 °C, R_f 0.41. IR spectrum, ν, cm^{-1}: 1658 (NC=O). ^{1}H NMR spectrum, δ, ppm, Hz: 4.44 d.d (1*H*, *J*=11.5, 8.1, CH_2), 4.52 d.d (1*H*, *J*=11.5, 2.7, CH_2), 5.29 d.d (1*H*, J=8.1, 2.7, CH), 6.77 – 6.92 m (4*H*, C_6H_4), 7.43–7.55 m (3*H*, H-3, 3',4 , C_6H_5), 7.90–8.07 m (6*H*, H-2, 2', C_6H_5 and C_6H_4N), 10.18 br.s (1*H*, CONH), 14.20 br.s (1*H*, NH).^{13}C NMR spectrum, δ, ppm: 65.8 (CH_2), 68.7(CH), 116.5 (CH), 116.8 (CH), 119.8 (2CH), 120.8 (2CH), 126.2 (2CH), 127.5 (2CH), 127.6 (2CH), 130.7 (CH), 134.8, 140.6, 142.6, 142.8, 164.9, 166.8. Found, %: C 69.15; H 4.69; N 14.28. $C_{23}H_{18}N_4O_3$. Calculated, %: C 69.34; H 4.55; N 14.06.

3-Bromo-N-(4-(5-(1,4-benzodioxan-2-yl)-4*H*-1,2,4-triazol-3-yl)phenyl)benzamide (4). Yield 2.1 *g* (44%), mp. 228-230 °C, R_f 0.36. IR spectrum, ν, cm^{-1}: 1661 (NC=O). ^{1}H NMR spectrum, δ, ppm, Hz: : 4.44 d.d (1*H*, *J*=11.4, 8.1, CH_2), 4.52 br.d (1*H*, *J* =11.4, CH_2), 5.28 br.d (1*H* , *J* =8.1, CH), 6.77 – 6.93 m (4H, C_6H_4), 7.42 t (1*H*, *J*=7.9, H-5 C_6H_4Br), 7.67 d.d.d (1H, *J*=7.9, 1.9, 0.9, H-4 C_6H_4Br), 7.88 -7.94 m (2H, C_6H_4N), 7.96 – 8.02 m (3*H*, C_6H_4N and H-6 C_6H_4Br), 8.19 d .d (1*H*, *J*=1.9, 1.5, H-2 C_6H_4Br), 10.29 br.s (1*H*, CONH), 14.24 br.s (1*H*, NH). Found, %: C 58.03; H 3.72; N 11.95. $C_{23}H_{17}BrN_4O_3$. Calculated, %: C 57.88; H 3.59; N 11.74

2-(4-(5-(1,4-Benzodioxan-2-yl)-4*H*-1,2,4-triazol-3-yl)phenyl)-N-(4-fluorobenzyl)acetamide (5). Yield 1.7 *g* (38%), m.p. 136-138 °C, R_f 0.45. IR spectrum, ν, cm^{-1}: 1675 (NC=O). ^{1}H NMR spectrum, δ, ppm, Hz: 3.68 br.s (2H, CH_2), 4.31 br.d (2*H*, *J*=5.2, CH_2NH), 4.31 – 4.50 m (2*H*, OCH_2), 5.20 br. s (1*H*, OCH), 6.73–6.89 m (4*H*), 6.95–7.04 m (2*H*) and 7.25–7.34 m (2*H*, Ar), 8.55 br.s (1*H*, $\underline{NH}CH_2$), 13.78 br.s.(1*H*, NH). Found, %: C 67.78; H 4.93; N 12.85. $C_{25}H_{21}FN_4O_3$. Calculated, %: C 67.56; H 4.76; N 12.61.

3,5-Bis(1,4-benzodioxan-2-yl)-4*H*-1,2,4-triazole (6). Yield 1.4*g* (41.5%), m.p. 149-150 °C, R_f 0. 32. ^{1}H NMR spectrum, δ, ppm, Hz: 4.38 d.d.d (2*H*, *J*=11.5, 8.1, 0.6, CH_2), 4.51 d.d (2*H*, *J* =11.5, 2.6, CH_2), 5.32 d.d (2*H*, *J*= 8.1, 2.6, 2CH), 6.77–6.92 m (8*H*, $2C_6H_4$), 14.15 br. s (1*H*, NH). ^{13}C NMR spectrum, δ, ppm: 65.5(CH_2), 68.2(CH), 116.6(CH), 116.8(CH), 120.8(CH), 120.9(CH), 142.5(2C), 155.3(2C) . Found, %: C 64.28; H 4.67; N 12.78. $C_{18}H_{15}N_3O_4$ Calculated, %: C 64.09; H 4.48; N 12.46.

N-(4-(2-((1,4-Benzodioxan-2-yl)(imino)methyl)hydrazinocarbonyl)phenyl)benzamide (7). Yield 1.9*g* (46%), m.p. 255-257℃, R_f 0.49. ^{1}H NMR spectrum, δ, ppm, Hz: 4.23 d.d (1*H*, *J*=11.0, 8.5, CH_2), 4.49 d.d (1H, J =11.0, 4.0, CH_2), 4.72 d.d (1*H*, *J* =8.5, 4.0, CH), 6.36 br.s (2H, NH_2), 6.77–6.95 m (4*H*, C_6H_4), 7.43–7.55 m (3*H*, C_6H_5), 7.80–7.90 m (4*H*, C_6H_4- para), 7.96 -8.01 m (2*H*, C_6H_5), 9.81 br.s (1*H*, NH), 10.21 br.s (1*H*, NH). Found, %: C 66.28; H 5.12; N 13.69. $C_{23}H_{20}N_4O_4$. Calculated, %: C 66.34; H 4.84; N 13.45.

ՏԵՂԱԿԱԼՎԱԾ 1,2,4-ՏՐԻԱԶՈԼ ՊԱՐՈՒՆԱԿՈՂ 1,4-ԲԵՆԶՈԴԻՕՔՍԱՆԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶ

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Իրականացվել է տեղակալված 1,2,4-տրիազոլային օղակ պարունակող 1,4-բենզոդիօքսանի նոր ածանցյալների սինթեզ: Ուսումնասիրվել է զանազան հիդրազիդների և 1,4-բենզոդիօքսան-2-կարբոնաթթվի նիտրիլի փոխազդեցությունը չոր պոտաշի առկայությամբ: Յույց է տրվել, որ լավագույն ելքերը ստացվել են նշված կոմպոնենտների 1:2:3 հարաբերակցության ժամանակ: Ընդ որում որպես լուծիչ օգտագործվել է բութանոլ, քանի որ էթանոլում ռեակցիան ավարտվում է միջանկյալ գծային պրոդուկտի առաջացմամբ, որի, ինչպես նաև բոլոր սինթեզված միացությունների կառուցվածքը ապացուցվել է ՄՄՌ-սպեկտրոսկոպիկ և նրբաշերտ քրոմատոգրաֆիայի ուսումնասիրության արդյունքում:

СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ 1,4-БЕНЗОДИОКСАНА, СОДЕРЖАЩИХ ЗАМЕЩЕННЫЕ 1,2,4-ТРИАЗОЛЫ

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Осуществлен синтез новых производных 1,4-бензодиоксана, содержащих замещенное 1,2,4-триазольное кольцо. Исследовано взаимодействие различных гидразидов и нитрила 1,4-бензодиоксан-2-карбоновой кислоты в присутствии сухого поташа. Показано, что наилучшие результаты достигаются при соотношении указанных компонентов 1:2:3. При этом в качестве растворителя использовали бутанол, так как реакция в этаноле заканчивается образованием промежуточного линейного продукта, строение которого, как и всех синтезированных соединений, доказано в результате ЯМР- спектроскопического анализа и тонкослойной хроматографии.

References

[1] The use of stems in the selection of International Nonprietary Names (INN) for pharmaceutical substances 2018, WHO.

[2] *Straniero V., Casiraghi A., Fumagalli L., Valoti E.* - How do reaction conditions affect the enantiopure synthesis of 2-substituted-1, 4-benzodioxane derivatives? // Chirality, 2018, v.30, (7), p.p. 943 -950. doi.org/10.1002/chir.22968

[3] *Xuguang Yin, Yi Huang Ziyi Chen, Yang Hu, Lin Tao, Qingyang Zhao, Xiu-Qin Dong, and Xumu Zhang* - Enantioselective access to chiral 2-substituted 2,3- dihydro benzo[1,4]dioxane derivatives through Rh-catalyzed asymmetric hydrogenation // Org.Lett., 2018, v. 20, p.p. 4173-4177. doi.org/10.1021/acs.orglett.8b01469

[4] *Kumari, M., Tahlan, S., Narasimhan, B., Ramasamy K., Lim S.M., Shah S.A.A., Mani V., Kakkar S.* - Synthesis and biological evaluation of heterocyclic 1,2,4-triazole scaffolds as romising pharmacological agents. // BMC Chemistry, 2021, 15:5. doi.org/10.1186/s13065-020-00717-y

[5] *Авакян А.С., Вартанян С.О., Саргсян А.Б.*. Некоторые успехи органической и фармацевтической химии , Сборник трудов. Изд. НТЦ ОФХ НАН РА, Ереван, 2017, с.49-58.

[6] *Вартанян С. О., Авакян А. С., Агекян А. А., Саргсян А. Б., Арутюнян С. А., Гаспарян Г. В.* - Синтез и некоторые превращения 5-(1,4-бензодиоксан-2-ил)-4-фенил-4Н-1,2,4-триазол-3-тиола. // ЖОрХ, 2020, v. 56, (3), с.430-434.[*S. O. Vartanyan, A. S. Avakyan, A. A. Aghekyan, A. B. Sargsyan, S. A. Harutyunyan, and G. V. Gasparyan*. Russ. J. Org. Chem., 2020, Vol. 56, No. 3, pp. 436–439.] doi.org/10.1134/S1070428020030112

[7] *Вартанян С.О., Авакян А.С., Саргсян А.Б., Арутюнян С. А., Норавян О.С., Цатинян А.С.* - Синтез и биологические свойства новых производных тиазолилбензодиоксана.// ЖОрХ., 2016, т.52, №2, с. 244- 248. [*Vartanyan S.O., Avakyan A.S., Sargsyan A.B, Arutyunyan S.A., Noravyan O.S., Tsatinyan A.S.*, Russ. J. Org. Chem., 2016, 52(2), 244]. doi.org/10.1134/S107042801602