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O-ALKYLATION OF 4-HYDROXYBENZOLSULFONAMIDE BY *N*-SUBSTITUTED 2-CHLOROACETAMIDES AND 5-(CHLOROMETHYL)-3-ARYL-1,2,4-OXADIAZOLES

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Abstract. *The paper presents a method for the synthesis of new representatives of the primary benzenesulfonamides class. They are promising agents for the treatment of open-angle glaucoma and neurodegenerative diseases. The authors have developed a mechanism for the O-alkylation of 4-hydroxybenzene sulfonamide with alkylating agents of different nature. The method provides mild conditions and selectivity of the process. The paper shows the necessity of activation of N-substituted 2-chloroacetamides and 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles by catalytic addition of potassium iodide in O-alkylation reactions of phenols. The authors demonstrated the applicability of the developed methodology on 12 examples of O-alkyl derivatives of 4-hydroxybenzene sulfonamide obtained in yields from 28 to 86%. The research proved the purity and structure of the new compounds by the combined methods of ^{1}H NMR, ^{13}C NMR, and elemental analysis.*

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Introduction

The primary sulfonamide pharmacophore is part of a wide range of drugs aimed at treating infectious diseases [1], pain syndrome [2], targeting and adjuvant cancer therapy [3-5]. According to the recent studies, benzenesulfonamide-containing pharmacological agents can

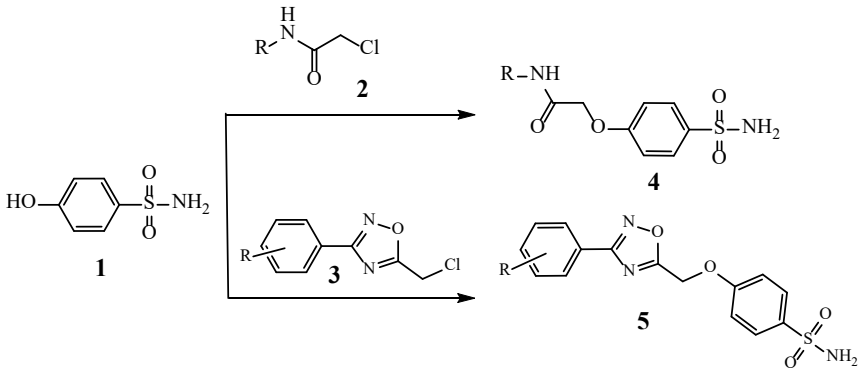
be successfully used to reduce intraocular pressure in glaucoma. Moreover, they can normalise dopamine levels in the synoptic cleft of the brain for Parkinson's disease [6-9].

Therefore, the search for rational ways to synthesise new primary benzenesulfonamide derivatives is an urgent task of organic synthesis.

There are many ways of sulfonamide fragment introduction as a result of direct sulfochlorination of aromatic substrates with chlorosulfonic acid followed by treatment of the resulting sulfochloride with ammonia [10]. A route for the preparation of primary sulfonamides by diazotisation reaction has been described [11, 12]. Nevertheless, such approaches are often non-selective, requiring the use of harsh reaction conditions and aggressive media, usually incompatible with poorly stable drug-like molecular frameworks. It is much more convenient to synthetically perform the introduction of the sulfonamide moiety. In this case, a convergent approach is applied using ready-made polyfunctional benzenesulfonamide bilding blocks as reagents. 4-hydroxybenzene sulfonamide is one of such commercially available reagents. It contains, in addition to the sulfonamide moiety, another nucleophilic centre – a hydroxy group suitable for functionalisation.

Main body

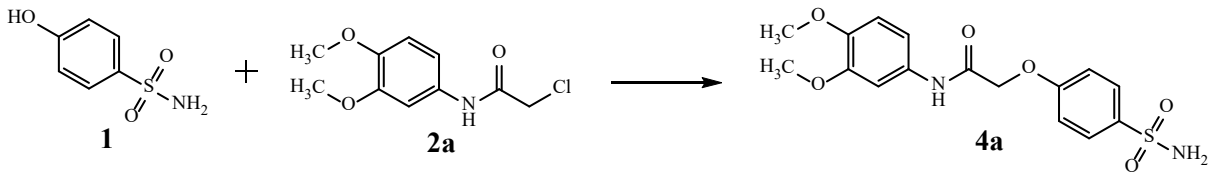
The present study investigates the regioselective *O*-alkylation of 4-hydroxybenzolsulfonamide by *N*-substituted 2-chloroacetamides and 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles. This provides an extension of the range of available primary benzenesulfonamides as potential inhibitors of human monoamine oxidase and carboanhydrase (Scheme 1).



Scheme 1. *O*-Alkylation of 4-hydroxybenzene sulfonamide with 2-chloroacetamides (**2**) and 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles (**3**)

Indeed, the interaction of phenols with various alkylating agents is performed in various systems: K_2CO_3/DMF, K_2CO_3/acetonitrile, K_2CO_3/KI/DMF, KOH/DMF [13]. The use of alkylating agents of medium strength (halogenacetoamides) and weakly activated chloromethanes requires the reaction to be conducted in a strongly basic - ionising environment and at increased temperature. Simultaneously, the presence of the second nitrogen-containing nucleophilic centre in the molecule of 4-hydroxybenzene sulfonamide imposes limitations on the use of strong bases in the synthesis of *O*-alkyl derivatives. In order to obtain preparative yields of the target products, it was necessary to find compromise conditions providing selectivity and acceptable process speed.

We selected the reaction conditions for the interaction of 4-hydroxybenzene sulfonamide with 2-chloro-*N*-(3,4-dimethoxyphenyl)acetamide as an example (Scheme 2). Table 1 presents the results of the interaction.



Scheme 2. Model reaction of 4-hydroxybenzene sulfonamide with 2-chloro-N-(3,4-dimethoxyphenyl)acetamide

Table 1. Selection of optimal conditions for the interaction of 4-hydroxybenzene sulfonamide with 2-chloro-N-(3,4-dimethoxyphenyl)acetamide (**2a**)

№	2a, eq	K_2CO_3 (eq)	KI (eq)	Solvent	Temperature, °C	Yield, %
1	1	1	-	Acetonitrile	20	-
2	1.2	2	-	Acetonitrile	50	-
3	1	2	-	DMF	20	-
4	1.2	2.5	-	DMF	50	-
5	1	2	0.25	DMF	20	60
6	1.2	2	0.25	DMF	20	58
7	1.2	2	0.25	DMF	50	32

However, the reaction of *O*-alkylation does not proceed in the absence of catalysis by potassium iodide. The interaction of 4-hydroxybenzene sulfanilamide with 2-chloro-*N*-(3,4-dimethoxyphenyl)acetamide proceeds only under conditions close to the Filkenstein reaction [14, 15]. Heating of the reaction mixture causes the formation of a mixture of by-products and hinders the separation of *O*-alkyl derivatives. Moreover, the increase in the process duration, as well as the use of excess alkylating agent does not increase the yield of the target product.

This study showed that the following conditions are optimal for *O*-alkylation of 4-hydroxybenzolsulfonamide: *N*-substituted 2-chloroacetamide: 4-hydroxybenzolsulfonamide: K_2CO_3 : KI : DMF (*N*, *N*-dimethylformamide) in the ratio 1:1:2:0.25; reaction temperature is 20-25 °C; reaction time is 10 - 12 hours. The conditions of alkylation of 4-hydroxybenzene sulfonamide described above also allow ones to synthesise the target products of the interaction of the above phenol with 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles obtained according to the methods of [16, 17]. We synthesised a series of new benzenesulfonamide derivatives in moderate to good yields of 28-86 % under these conditions (Fig. 1).

Conclusions and recommendations

The authors have developed a mechanism for the *O*-alkylation of 4-hydroxybenzene sulfonamide with alkylating agents of different nature. The method provides mild conditions and selectivity of the process. We have shown the necessity of activation of *N*-substituted 2-chloroacetamides and 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles by catalytic addition of potassium iodide in *O*-alkylation reactions of phenols.

Experimental part

Reagents and solvents (Aldrich, Acros) are commercially available and were used without prior purification. We monitored the reaction progress by thin layer chromatography (TLC) on silica gel on Silufol UV aluminium plates using the following eluent - toluene : acetone : petroleum ether in the volume ratio of 3:5:5. We performed elemental analysis on a PerkinElmer 2400. We determined the melting temperature using a Büchi M-560 melting point and boiling point apparatus. We recorded NMR spectra on a Varian XL-400 instrument for solutions in DMSO-d_6 and $CDCl_3$ at 25 °C. We chose the signals of the residual solvent-DMSO residual protons in ^1H NMR (δH 2.50 ppm) or ^{13}C NMR (δC 39.5 ppm) as a reference for counting chemical shifts. We used the tetramethylsilane signal as a marker; the shape of the signals is s for singlet, d for doublet, t for triplet, dd for doublet duplet, td for triplet doublet, and m for multiplet.

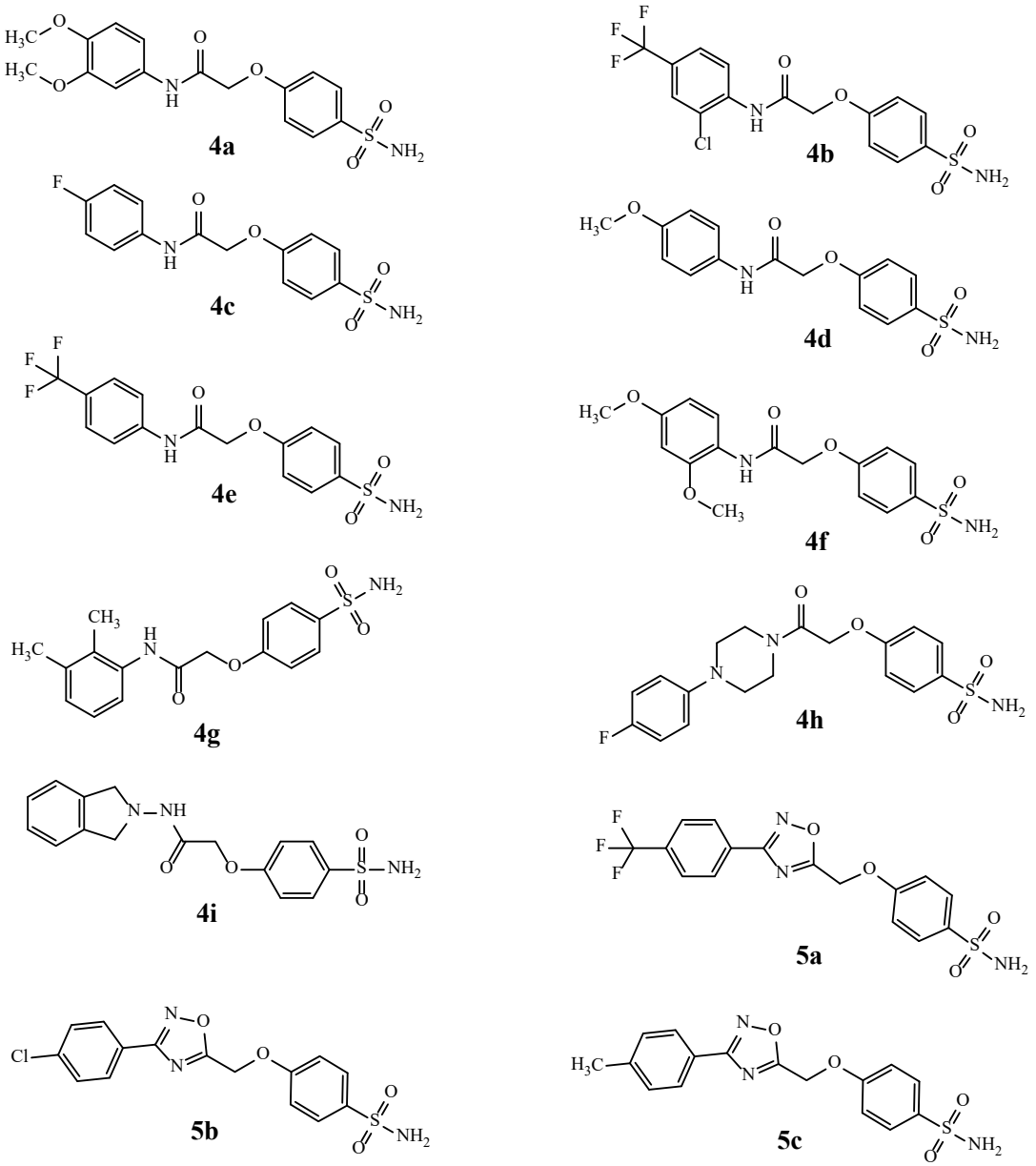


Fig. 1 Examples of synthesised compounds

General procedure for the O-alkylation of 4-hydroxybenzene sulfanylmide

We dissolved 0.002 mol of N-substituted 2-chloroacetamide in 4 mL of DMF, added 0.004 mol of K_2CO_3 and 0.0005 mol of KI. We stirred the mixture for 10 minutes, then sprinkled 0.002 mol of 4-hydroxybenzene sulphanilamide. We conducted the reaction at room temperature for 10-12 hours. We monitored the completeness of the reaction by TLC. We completed the reaction by depletion of 4-hydroxybenzene sulfonamide. We poured the reaction mixture into ten times volume of water under vigorous stirring. We filtered the precipitates and purified them by recrystallisation of acetonitrile.

N-(3,4-dimethoxyphenyl)-2-(4-sulfamoylphenoxy)acetamide (4a) Yield is 47%. Precipitate of grey colour, T.melt. is 201 - 203 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 9.95 (s, 1H), 7.82 – 7.73 (m, 2H), 7.32 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 9.3 Hz, 2H), 7.17 – 7.11 (m, 3H), 6.90 (d, *J* = 8.7 Hz, 1H), 4.77 (s, 2H), 3.73 (s, 6H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 166.19, 160.89, 149.19, 145.85, 137.45, 132.52, 128.31, 115.43, 112.65, 112.32, 105.50, 67.77, 56.38, 56.06. Found, %: C 52.53; H 4.91; N 7.69. $C_{16}H_{18}N_2O_6S$. Calculated, %: C 52.45; H 4.95; N 7.65.

N-(2-chloro-5-(trifluoromethyl)phenyl)-2-(4-sulfamoylphenoxy)acetamide (4b) Yield is 41%. Beige-coloured powder, T.melt. is 220 - 221 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 8.25 (d, *J* = 2.3 Hz, 1H), 8.07 (s, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.74 (m, 4H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 4.92 (s, 2H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 167.72, 160.65, 138.80, 137.64, 136.31, 132.01, 131.44, 130.94, 128.96, 128.63, 128.35, 127.38, 123.29, 122.24, 115.47, 67.67, 52.82. Found, %: C 44.12; H 2.94; N 6.90. $C_{15}H_{12}ClF_3N_2O_4S$. Calculated, %: C 44.07; H 2.96; N 6.85.

N-(4-fluorophenyl)-2-(4-sulfamoylphenoxy)acetamide (4c) Yield is 28%. White coloured powder, T.melt. is 185 - 187 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 10.16 (s, 1H), 7.77 (s, 2H), 7.64 (s, 2H), 7.19 (s, 2H), 7.15 (s, 4H), 4.79 (s, 2H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 166.63, 160.86, 160.19, 157.80, 137.50, 135.32, 128.33, 122.33, 122.25, 116.11, 115.89, 115.44, 67.75, 41.09. Found, %: C 51.93; H 4.01; N 8.62. $C_{14}H_{13}FN_2O_4S$. Calculated, %: C 51.85; H 4.04; N 8.64.

N-(4-methoxyphenyl)-2-(4-sulfamoylphenoxy)acetamide (4d) Yield is 86 %. White colour powder, T.melt. is 190 - 192 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 10.00 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.53 (dd, *J* = 8.8, 4.0 Hz, 2H), 7.22 (s, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.76 (s, 2H), 3.72 (s, 3H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 166.17, 160.91, 156.28, 137.47, 132.04, 128.32, 122.04, 121.46, 115.44, 114.56, 67.83, 55.87. Found, %: C 53.63; H 4.75; N 8.37. $C_{15}H_{16}N_2O_5S$. Calculated, %: C 53.56; H 4.79; N 8.33.

N-(4-(trifluoromethyl)phenyl)-2-(4-sulfamoylphenoxy)acetamide (4e) Yield is 78%. White colour powder, T.melt. is 185 - 186 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 10.52 (s, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.23 (s, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.86 (s, 2H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 167.37, 160.82, 142.59, 137.54, 128.34, 126.76, 120.24, 115.43, 67.69, 41.08, 26.12. Found, %: C 48.23; H 3.54; N 7.54. $C_{15}H_{13}F_3N_2O_4S$. Calculated, %: C 48.13; H 3.50; N 7.48.

N-(2,4-dimethoxyphenyl)-2-(4-sulfamoylphenoxy)acetamide (4f) Yield is 57%. Grey powder, Tmelt. is 218 - 220 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 9.17 (s, 1H), 7.81 – 7.73 (m, 3H), 7.24 (s, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.66 – 6.61 (m, 1H), 6.50 (d, *J* = 8.9 Hz, 1H), 4.81 (s, 2H), 3.82 (s, 3H), 3.74 (s, 3H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 166.22, 160.64, 157.74, 151.88, 137.64, 128.34, 123.66, 120.21, 115.50, 104.88, 99.59, 67.79, 56.54, 56.01. Found, %: C 52.51; H 4.98; N 7.71. $C_{16}H_{18}N_2O_6S$. Calculated, %: C 52.45; H 4.95; N 7.65.

N-(isoindolin-2-yl)-2-(4-sulfamoylphenoxy)acetamide (4g) Yield is 52%. Beige-coloured powder, T.melt. is 202 - 204 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 8.00 (d, *J* = 8.0 Hz, 1H), 7.82 – 7.70 (m, 2H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 13.9 Hz, 2H), 7.14 (dd, *J* = 8.0, 5.6 Hz, 3H), 7.06 – 6.98 (m, 1H), 5.05 (s, 2H), 4.16 (t, *J* = 8.4 Hz, 2H), 3.20 (t, *J* = 8.5 Hz, 2H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm.: 166.00, 161.19, 143.35, 137.10, 132.19, 128.15, 127.74, 125.58, 124.34, 116.48, 115.34, 66.66, 46.37, 28.34. Found, %: C 55.38; H 4.9; N 12.16. $C_{16}H_{17}N_3O_4S$. Calculated, %: C 55.32; H 4.93; N 12.10.

N-(2,3-dimethylphenyl)-2-(4-sulfamoylphenoxy)acetamide (4h) Yield is 46%. White colour powder, T.melt. is 197 - 198 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 9.62 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.23 (s, 2H), 7.20 – 7.12 (m, 3H), 7.11 – 7.01 (m, 2H), 4.82 (s, 2H), 2.25 (s, 3H), 2.05 (s, 3H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 166.83, 160.84, 137.70, 137.50, 135.93, 132.24, 128.30, 128.03, 125.93, 124.44, 115.46, 67.73, 20.80, 14.65. Found, %: C 57.49; H 5.46; N 8.42. $C_{16}H_{18}N_2O_4S$. Calculated, %: C 57.47; H 5.43; N 8.38.

4-(2-(4-(4-fluorophenyl)piperazin-1-yl)-2-oxoethoxy)benzolsulfonamide (4i) Yield is 42%. Beige-coloured powder, T.melt. is 222 - 225 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 7.73 (d, *J* = 8.8 Hz, 2H), 7.20 (s, 1H), 7.07 (dt, *J* = 8.6, 4.4 Hz, 5H), 6.99 (dd, *J* = 8.6, 5.3 Hz, 2H), 5.00 (s, 2H), 3.60 (t, *J* = 5.0 Hz, 4H), 3.14 (s, 2H), 3.06 (s, 2H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 166.02, 161.17, 148.34, 137.09, 128.16, 118.49, 118.41, 116.16, 115.94, 115.35, 66.42, 50.05, 49.71, 44.60, 41.80. Found, %: C 54.98; H 5.16; N 10.72. $C_{18}H_{20}FN_3O_4S$. Calculated, %: C 54.95; H 5.12; N 10.68.

4-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methoxy) benzenesulfonamide (5a) Yield is 45%. Beige-coloured powder, T.melt. is 188 - 189 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 8.24 (d, *J* = 8.1 Hz, 2H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 4H), 5.74 (s, 2H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 176.64, 167.55, 160.19, 138.26, 130.29, 128.70, 128.48, 127.03, 115.63, 61.80, 41.14, 21.70. Found, %: C 48.18; H 3.10; N 10.58. $C_{16}H_{12}F_3N_3O_4S$. Calculated, %: C 48.12; H 3.03; N 10.52.

4-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)benzenesulfonamide (5b) Yield is 57%. Brown coloured powder, T.melt. is 186-189 °C. NMR -spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 8.05 – 7.98 (m, 2H), 7.84 – 7.76 (m, 2H), 7.68 – 7.61 (m, 2H), 7.30 – 7.22 (m, 4H), 5.71 (s, 2H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 176.33, 167.69, 160.18, 138.22, 137.25, 130.23, 129.59, 128.47, 125.26, 115.60, 61.75. Found, %: C 49.311; H 3.35; N 11.52. $C_{15}H_{12}ClN_3O_4S$. Calculated, %: C 49.25; H 3.31; N 11.49.

4-((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methoxy)benzenesulfonamide (5c) Yield is 50%. Beige-coloured powder, T.melt. is 198 - 200 °C. NMR-spectrum ^{1}H (400 MHz, DMSO-d_6) δ, ppm: 7.94 – 7.87 (m, 2H), 7.83 – 7.76 (m, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 3.1 Hz,

2H), 7.26 – 7.22 (m, 2H), 5.69 (s, 2H), 2.38 (s, 3H). NMR-spectrum ^{13}C (101 MHz, DMSO-d_6) δ, ppm: 175.88, 168.42, 160.22, 142.51, 138.19, 130.58, 128.47, 127.71, 123.62, 115.60, 61.75, 21.77. Found, %: C 55.71; H 4.42; N 12.19. $C_{16}H_{15}N_3O_4S$. Calculated, %: C 55.64; H 4.38; N 12.17.

The study was performed within the framework of the State assignment of Yaroslavl State Pedagogical University named after K. D. Ushinsky for 2024 from the Ministry of Education of the Russian Federation on the topic "Development of a new drug for the treatment of neurodegenerative diseases based on a monoamine oxidase inhibitor" (registry entry number 720000F.99.1.BN62AAA12000).

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