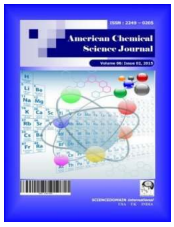

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The Synthesis of Atomoxetine-containing Carboxamides - Potential Human Carbonic Anhydrase Inhibitors

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Authors' contributions

This work was carried out in collaboration between all authors. Author AAS designed the study, participated in the interpretation of the spectral data and wrote the first draft of the manuscript. Authors ATO and AVS performed the laboratory experiments, acquired and interpreted the spectral data and managed the analyses of the study. Author MVD managed the literature searches and participated in editing the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The method of synthesis of Atomoxetine is developed, including enzyme-catalyzed stereospecific reduction 3-chloro-1-phenyl-propan-1-one and Mitsunobu condensation with a chiral alcohol, and *o*-cresol. New potential human carbonic anhydrase inhibitors were obtained via reaction Atomoxetine with carboxylic derivatives of benzene and thiophene containing primary sulfonamide moiety.

Keywords: Atomoxetine; sulfonamides; amide formation; biologically-active compounds; carbonic anhydrase inhibitor.

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1. INTRODUCTION

Sympathomimetic Atomoxetine is a widely used drug for the treatment of attention deficit/ hyperactivity disorder in children, included in the list of vital and essential medicines [1]. The active ingredient of the medicine is (3*R*)-*N*-methyl-3-(2-methylphenoxy)-3-phenyl-propan-1-amine hydrochloride. In a previous work [2] we have proposed a new method for producing the title compound using genetically engineered enzymes - ketoreductase and conditions enabling for the scaling process.

Due to the little scrutiny of Atomoxetine derivatives, an interest to the perspective directions for the further functionalization 3(*R*)-*N*-methyl-3-(2-methylphenoxy)-3-phenyl-propan-1-amine arose.

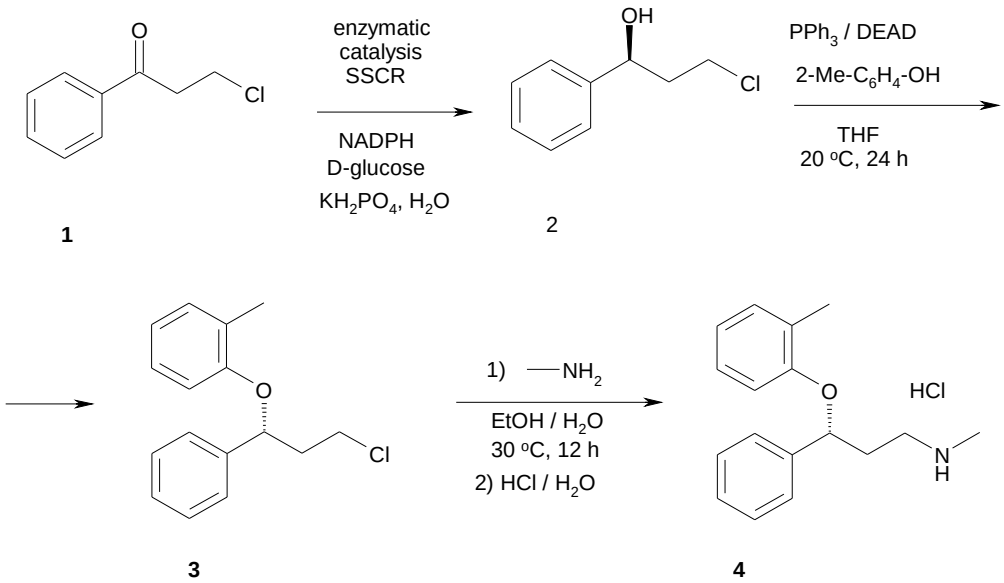
2. MATERIALS AND METHODS

2.1 General

Laboratory grade chemicals and solvents available commercially in high purity were used. Yields reported are isolated yields unless indicated otherwise. Control over the reaction process and the individuality of the obtained compounds realized by thin layer chromatography (TLC) on Silufol UV-254 plates, eluent - individual organic solvents (chloroform, methanol, hexane, ethyl acetate, petroleum ether), their mixtures in various proportions, the developer - UV radiation. The $_1$H NMR spectra were recorded on «Bruker MSL-400» spectrometer in DMSO-d_6, standard - residual signals of the solvent. Chemical shifts are given in ppm (δ-scale). Mass spectra are recorded on MX-1321 electron impact spectrometer with the direct input of the sample at 100-150℃ and ionizing voltage of 70 eV. Elemental analyses of the obtained compounds were performed for C, H, N on Perkin Elmer 2400 instrument.

2.2 Synthesis of Atomoxetine Hydrochloride

(*R*)-*N*-methyl-(3-phenyl-3-*o*-tolyloxy)propan)-1-amine hydrochloride (atomoxetine hydrochloride) (4) obtained by the method [2]. R/S > 99/1 (by chiral HPLC). Mp. - 158-160℃ (diethyl ether). D -43.1° (5.9, MeOH). ^{1}H NMR (DMSO-d_6: 2.31 (s, 3H), 2.4-2.6 (m, 2H), 2.63 (s, 3H), 3.10 (m, 2H , J= 7,6 Hz), 5.35 (dd, 1H, J_1= 7.6 Hz, J_2= 4.5 Hz), 6.62 (d, 1H, J= 8,2 Hz), 6.78 (dd, 1H, J_1= 7,6 Hz, J_2= 7.0 Hz), 6.95 (dd, 1H, J_1= 8.0 Hz, J_2= 7.0 Hz), 7.12 (d, 1H, J= 7,6 Hz), 7.25-7.40 (m, 5H), 9.74 (s, 2H). ^{13}C NMR (DMSO-d_6): 16.5; 32.9; 34.6; 46.3; 77.1; 113.2; 120.9; 125.74; 126.7; 126.9; 128.1; 128.90; 130.85; 140.3; 155.4. Mass spectrum (EI, *m/z I* $_{rel}$, %): 255 (95) [M^+] 312 (5) 44 (100). Found for $C_{17}H_{22}ClNO$, %: C 69.77; H 7.62; N 4.75. Calculated, %: C 69.98; H 7.55; N 4.8.



1 2 **3** **4**

Scheme 1. The synthesis of Atomoxethine using of genetically engineered enzymes

2.3 General Procedure

Synthesis of carboxamides by (*R*)-*N*-methyl-(3-phenyl-3-*o*-tolyloxy) propan)-1-amine

N-[3-(dimethylamino)propyl]-*N*'-ethylcarbodiimide hydrochloride (1mmol) was added to the stirred solution of acid **5** in anhydrous *N, N*-dimethylacetamide. The solution was stirred for 30 min and then added successively 0.95 mmol of 1-*H*-1,2,3-benzotriazol-1-ol and 2.1 mmol of *N*-methylmorpholine. The reaction mixture stirred for 30 min, and then added Atomoxetine hydrochloride (1mmol) and the solution was stirred for the additional 12 hours. The reaction mixture is precipitated in water. The resulting solid was filtered and was purified by column chromatography on silica using the appropriate gradient of CH_2Cl_2 / methanol (95/5).

<u>*N*-methyl-*N*-(3-phenyl-3-(*o*-tolyloxy)propyl)-4-sulfamoylbenzamide (6a)</u>

Yield: 73%. ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H), 2,4-2,6 (m, 2H), 2.63 (s, 3H), 3.10 (t , 2H, J= 7.6 Hz), 5.35 (dd, 1H, J_1= 7.5 Hz, J_2= 5.0 Hz), 6.65 (d, 1H, J= 8.2 Hz), 6.76 (dd, 1H, J_1= 7.6 Гц, J_2= 7.0 Hz), 6.97 (dd, 1H, J_1= 8,0 Hz, J_2= 7,0 Hz), 7.12 (d, 1H, J= 7.6 Hz), 7.25-7.40 (m, 5H), 7.91 (d, 2H, J= 7.5 Hz), 8.31 (d, 2H, J= 7,5 Hz). ^{13}C NMR (DMSO-d_6: 15.4; 29.6; 36.5; 46.1; 82.1; 112.3; 120.2; 125.9; 126.3; 126.7; 127.1; 128.8; 128.9; 138.5; 144.4; 155.4. Mass-spectrum (EPCI, *m/z, I_{rel}*, %): 439 (100) [M+H$^+$]. Found for $C_{24}H_{26}N_2O_4S$, %: C 65.45; H 5.97; N 6.41. Calculated, %: C, 65.73; H, 5.98; N, 6.39.

<u>2-Methoxy-*N*-methyl-*N*-(3-phenyl-3-(*o*-tolyloxy)propyl)-4-sulfamoylbenzamide (6b)</u>

Yield: 80%. ^{1}H NMR (DMSO-d_6): 2.14 (s, 3H); 2.24-2.5 (m, 2H); 2.63 (s, 3H); 3.10 (m , 2H, J= 7.6 Hz); 3.67 (s, 3H); 5.15 (dd, 1H, J_1= 7.3 Hz, J_2= 5.0 Hz); 6.25 (d, 1H, J= 8.2 Hz); 6.59 (dd, 1H, J_1= 5.0 Hz, J_2= 4,9 Hz); 6.79 (dd, 1H, J_1= 6.0 Hz, J_2= 6.2 Hz); 7.10 (d , 1H, J= 7.6 Hz); 7.25-7.40 (m, 5H); 7.25 (s, 2H); 7.77 (d, 1H, J= 3 Hz); 7.81 (d, 1H, J= 3 Hz); 7.86 (s, 1H). ^{13}C NMR (DMSO-d_6): 15.3; 29.2; 36.7; 46.1; 55.4; 81.5; 111.0; 112.7; 120.4; 122.7; 125.9; 126.7; 127.8; 128.5; 128.9; 131.5; 146.4, 155.4; 158.2. MS (EPCI, m / z, I_{rel}, %): 469, 1 (100) [M+H$^+$]. Found for $C_{25}H_{28}N_2O_5S$, %: C 63.91; H 6.02; N 5.98. Calculated, %: C, 64.08; H, 6.02; N, 5.98.

<u>N-methyl-N-(3-phenyl-3-(*o*-tolyloxy)propyl)-3-sulfamoylbenzamide (6c)</u>

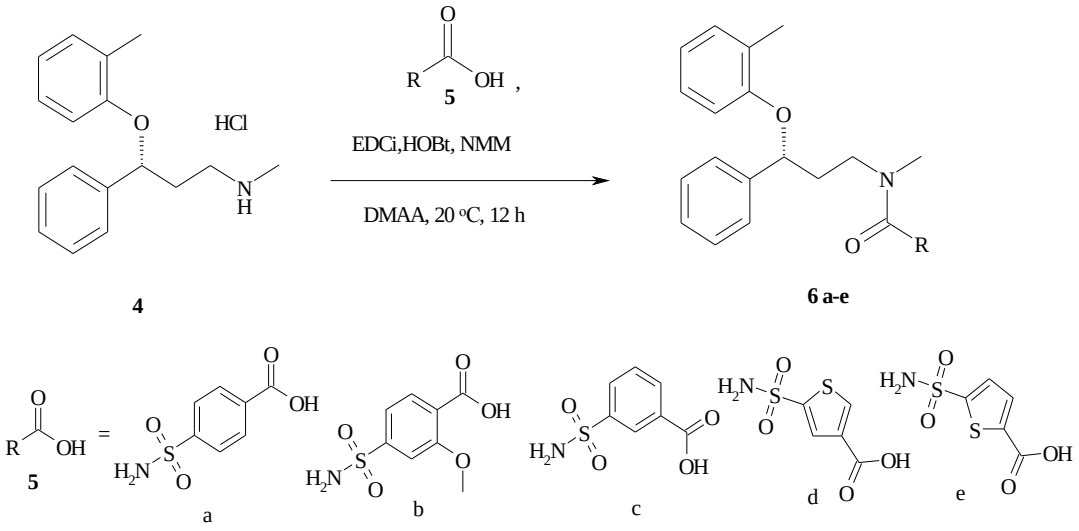
Yield: 77%. ^{1}H NMR (DMSO-d_6): 2.34 (s, 3H); 2.4-2.6 (m, 2H); 2.62 (s, 3H); 3.13 (m, 2H, J= 7.6 Hz); 5.33 (dd, 1H, J_1= 7.6 Hz, J_2= 4.5 Hz); 6.64 (d, 1H, J = 8.2 Hz); 6.79 (dd, 1H, J_1= 7.6 Hz, J_2= 7.1 Hz); 6.98 (dd, 1H, J_1= 8.0 Hz, J_2= 7.0 Hz); 7.18 (d, 1H, J= 7.6 Hz); 7.25-7.40 (m, 5H); 8.01 (d, 1H, J= 6 Hz); 8.17 (d, 1H, J= 6 Hz); 8.31 (2H, d, J= 7.5 Hz); 8,40 (s, 1H). ^{13}C NMR (DMSO-d_6): 15.4; 29.4; 36.8; 45.5; 80.8; 114.3; 121.7; 124.0; 127.4; 127.8; 128.5; 129.1; 138.5; 144.4; 155.3. MS (EPCI, m / z, I_{rel}, %): 438.5 (100) [M + H$^+$]. Found for $C_{24}H_{26}N_2O_4S$, %: C 65.75; H 5.99; N 6.40. Calculated, %: C, 65.73; H, 5.98; N, 6.39; S, 7.31.

<u>*N*-methyl-*N*-(3-phenyl-3-(*o*-tolyloxy)propyl)-5-sulfamoylthiophene-3-carboxamide (6e)</u>

Yield: 68 %. ^{1}H NMR (DMSO-d_6): 2.21 (s, 3H); 2,3-2,44 (m, 2H); 2.55 (s, 3H); 3.11 (m, 2H, J= 7.2 Hz); 5.35 (dd, 1H, J_1= 7.0 Hz, J_2= 3.0 Hz); 6.65 (d, 1H, J= 7.2 Hz); 6.76 (dd, 1H, J_1= 7.6 Hz, J_2= 7.0 Hz); 6.97 (dd , 1H, J_1= 8.0 Hz, J_2= 7.0 Hz); 7.12 (d, 1H, J= 7.6 Hz); 7.3-7.42 (m, 5H); 7.96 (s, 2H); 8.10 (s, 1H); 8.87 (s, 1H). ^{13}C NMR (DMSO-d_6): 15.2; 30.4; 36.5; 46.1; 82.1; 114.1; 120.0; 125.1; 126.3; 127.1; 127.4; 128.0; 128.4; 135.0; 141.1; 169.4. MS (EPCI, m / z, I_{rel}, %): 445.12 (100) [M+H$^+$]. Found for $C_{22}H_{24}N_2O_4S_2$, %: C 59.30; H 5.43; N 6.30. Calculated, %: C, 59.44; H, 5.44; N, 6.30.

<u>*N*-methyl-*N*-(3-phenyl-3-(*o*-tolyloxy)propyl)-5-sulfamoylthiophene-2-carboxamide (6d)</u>

Yield: 83%. ^{1}H NMR (DMSO-d_6): 2.20 (s, 3H); 2.3-2.42 (m, 2H); 2.49 (s, 3H); 3.01 (t, 2H, J_1= J_2= 6 Hz); 5.35-5.45 (m, 1H); 6.40 (d, 1H, J= 8.2 Hz); 6.76 (dd, 1H, J_1= 7.6 Hz, J_2= 7.0 Hz); 6.85 (dd, 1H, J_1= 8.0 Hz, J_2= 7.0 Hz); 7.10 (d, 1H, J= 7.6 Hz); 7.25-7.40 (m, 5H); 7.83 (s, 2H); 8.05 (s, 1H); 8.44 (s, 1H). ^{13}C NMR (DMSO-d_6): 15.2; 30.4; 36.5; 46.1; 82.1; 114.1; 120.0; 126.5; 126.9; 127.1; 127.4; 128.8; 128.9; 136.0; 140.5; 165.1. MS (EPCI, m / z, I_{rel}, %): [M+H$^+$] 445.5 (100). Found for $C_{22}H_{24}N_2O_4S_2$, %: C 59.19; H 5.44; N 6.31. Calculated, %: C, 59.44; H, 5.44; N, 6.30.



Scheme 2. Synthesis of Atomoxetine-containing carboxamides

3. RESULTS AND DISCUSSION

The main purpose of this work was to obtain the series of carboxamide Atomoxetine derivatives, containing primary sulfonamide group. By virtue of the fact that primary sulfonamide moiety is the ideal ligand for carbonic anhydrase, and of the presence of lipophilic Atomoxetine linker, facilitates the penetration of molecules through the blood-brain barrier, obtained derivatives are perspective candidates for the treatment of ophtalmological diseases and diseases of the nervous systems [3-7]. In addition, aromatic amide groups can also be important for carbonic anhydrase inhibition as reported in papers devoted to amide derivatives of Probenecid [8-10].

For the functionalisation of Atomoxetine molecule we have chosen the convergent way, which excludes the using of aggressive environments and reagents fraught with possible transformation of the configuration of a chiral center of the Atomoxetine molecule. Introduction of carboxamide and sulfonamide groups was realized via reaction of Atomoxetine amine with aromatic and heterocyclic carboxylic acids, containing a primary sulfonamide moiety by the action of the water-soluble carbodiimide EDCi as the dehydrating agent.

4. CONCLUSION

As the result of our work we have obtained the series of atomoxetine-containing sulfonamides, which are of interest for further bioscreening research of their interaction with human carbonic anhydrase.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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