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SYNTHESIS OF POTENTIAL ANTICONVULSANTS BASED ON CHLORAL HYDRATE AND CARBAMAZEPINE: THEIR SPECTRAL CHARACTERISTICS AND *IN SILICO* ADME PROFILING

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This paper reports the synthesis of a new potential anticonvulsant, *N*-(2,2,2-trichloro-1-hydroxyethyl)-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide. Its synthesis is based on condensing the anticonvulsant drug carbamazepine with chloral hydrate used in medical practice. The reaction was carried out in a melt or by boiling in dry benzene with the removal of the resulting water from the reaction medium. The product was obtained with yields of 88 and 79%, respectively. Replacing the hydroxyl group in the resulting condensation product with an amino group led to the formation of *N*-(1-amino-2,2,2-trichloroethyl)-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide. This synthesis was carried out in two stages. Initially, the hydroxy derivative was chlorinated with thionyl chloride. Then, by treating the resulting chlorine derivative with an aqueous solution of ammonia (25%) in MTBE medium, the target product was obtained. The structure of the obtained compounds was proven by ^{1}H NMR and IR spectroscopy data. The SwissADME online platform showed that the synthesized compounds should have high bioavailability as well as moderate solubility in water and be able to penetrate the blood-brain barrier.

Keywords: carbamazepine, chloral hydrate, condensation, in silico, ADME, anticonvulsant.

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Introduction

Epilepsy is a chronic, non-infectious, common neurological disease that is characterized by repeated, unprovoked seizures throughout the body or in any part of it and, sometimes, accompanied by loss of consciousness [1–3]. This disease affects about 50 million people worldwide [1]. It affects both sexes of all age groups and is one of the most common neurological diseases worldwide. Epilepsy has heavy consequences for the patient's health and socialization. This disease significantly reduces the patient's life expectancy, can lead to accidents involving him(her), decreases his(her) labor productivity, limits the choice of a possible field of activity, and complicates social relationships [1,4,5]. Seizures are caused by excessive electrical discharges in a group of brain cells. They can arise in various areas of the brain, and their consequences are manifested by muscle spasms or minor memory lapses and, in some cases by severe and prolonged convulsions [5].

Currently, practical medicine has several very effective anticonvulsants. However, in approximately 30% of patients, epilepsy is characterized by drug resistance and is difficult to treat with existing drugs [6]. In this regard, the search for new potential anticonvulsants is a task of extreme importance. Carboxylic acid amide derivatives are most widely used as anticonvulsants. This group of drugs includes drugs such as Carbamazepine, Valpromide, Valrocemide, Ameltolide, Lacosamide, Levetiracetam, Rufinamide, Retigabine, and some of their analogs [7]. Recently, a series of *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamides, condensation products of carboxylic acid amides, and chloral hydrate have been shown to have potential anticonvulsant activity [8]. As is known, chloral hydrate itself has a certain anticonvulsant activity, but it is more often used in experimental and diagnostic medicine, rather than to

eliminate seizures themselves [9]. In this work, we report the synthesis of new potential anticonvulsants based on carbamazepine and chloral hydrate.

Materials and methods

Chemistry

IR spectra were recorded in KBr pellets using a Spectrum BX II spectrometer. ^{1}H NMR spectra (400 MHz) were measured for solutions in DMSO-d_6 using a Varian VXR-400 spectrometer. Residual solvent signals were used as standards. Elemental analysis was performed on a LECO CHNS-900 instrument. The reaction and purity of the compounds were monitored by the TLC method on Silufol UV-254 plates. A mixture of chloroform and acetone in a ratio of 3:1 was used as an eluent. The melting point was determined in open capillaries and was not corrected.

Synthesis of N-(2,2,2-trichloro-1-hydroxyethyl)-5H-dibenzo[b,f]azepine-5-carboxamide (3)

Method A

A thoroughly ground mixture of 11 mmol (1.82 g) of chloral hydrate (**2**) and 10 mmol (2.36 g) of Carbamazepine (**1**) was poured into a porcelain container heated in a sand bath to 250^{0}C. The resulting transparent melt was heated with stirring until it began to thicken. Then the heating was stopped and stirring continued for another 15–20 minutes until a colorless powdery product was obtained. The resulting product was dried for 48 hours and purified by recrystallization from acetonitrile.

Method B

A mixture of 11 mmol (1.82 g) of chloral hydrate (**2**) and 10 mmol (2.36 g) of Carbamazepine (**1**) was loaded into a round-bottom flask, filled with 25 mL of dry benzene and boiled with a Dean-Stark nozzle until the distillation of water stopped completely (approximately 6–7 hours). The reaction mixture was left for 12 hours, then filtered and dried for 24 hours. The product was purified by recrystallization from acetonitrile.

White crystals; yield method A: 88% (3.38 g), method B: 79% (3.03 g); mp 178–180^{0}C (MeCN); R_f=0.49. IR: ν_{max} 3468, 3426, 3368 (OH+NH), 3058, 3024, 2967, 2925, 2853, 2789 (CH), 1665 (C=O), 1595, 1504, 1489, 1435, 1354, 1297, 1271, 1228, 1155, 1128, 1083, 1050, 1009, 958, 884, 826, 800, 772, 738, 665,599, 566, 526, 465 cm^{-1}. ^{1}H NMR: δ 7.52–7.42 (m, 9H, 8H$_{arom.}$+OH), 7.03 (s, 2H, azepine), 5.53 (dd, *J*=8.8, 7.3 Hz, 1H, CH), 5.23 (d, *J*=8.8 Hz, 1H, NH). Anal. Calcd (%) for $C_{17}H_{13}Cl_3N_2O_2$ (383.65): C 53.22; H 3.42; N 7.30. Found: C 53.19; H 3.40; N 7.33.

Synthesis of N-(1-amino-2,2,2-trichloroethyl)-5H-dibenzo[b,f]azepine-5-carboxamide (4)

12 mmol of $SOCl_2$ was added to 10 mmol of *N*-(2,2,2-trichloro-1-hydroxyethyl)-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (**3**) in 25 mL CCl_4. The mixture was refluxed for 2 hours until the evolution of gaseous products completely ceased. The reaction mass was cooled and the solvent was evaporated on a rotary evaporator. The dry residue was treated with 10–12 mL of hexane, and the resulting suspension was filtered. The dry mass was filled with 15 mL of MTBE and 2 mL of aqueous ammonia solution (25%) was added. The mixture was stirred for 15 minutes and then left for half an hour. The ether layer was separated and evaporated on a rotary evaporator. The resulting product was purified by recrystallization from a mixture of benzene:hexane (1:1).

White crystals; yield 73% (2.79 g); mp 118–120^{0}C (MeCN); R_f=0.65. IR: ν_{max} 3348 (NH), 3052, 3018, 3006, 2930, 2832 (CH), 1686 (C=O), 1598, 1572, 1488, 1460, 1438, 1340, 1308, 1210, 1190, 1138, 1102, 1040, 1030, 994, 964, 952, 802, 792, 738, 672, 634, 568, 524, 474, 466, 442. 430 cm^{-1}. ^{1}H NMR: δ 7.56–7.40 (m, 8H, H$_{arom.}$), 7.06 (s, 2H, azepine), 5.35 (d, *J*=9.8, 1H, CH), 5.21 (d, *J*=9.8 Hz, 1H, NH), 3.38 (s, 2H, NH_2). Anal. Calcd (%) for $C_{17}H_{14}Cl_3N_3O$ (382.67): C 53.36; H 3.69; N 10.98. Found: C 53.39; H 3.66; N 11.02.

In silico ADME evaluation

The bioavailability of Carbamazepine (**1**) and synthesized compounds **3** and **4** was assessed using the SwissADME online platform [10]. Before analysis, the structures of the investigated compounds were pre-converted into the SMILE format using the OpenBabel 2.3.1 software. To assess drug similarity, the following calculated physicochemical characteristics were used as lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), saturation (INSATU), and flexibility (FLEX) of the molecule. The values of these parameters were assessed visually using bioavailability radars. The Brain or IntestinaL Estimate D permeation (BOILED-Egg) method [11] implemented on the SwissADME platform was used to predict the ability of synthesized compounds to penetrate the blood-brain barrier. The solubility of the synthesized compounds in water (LogS) was also assessed. For this purpose, the ESOL [12] and Ali [13] methods were used. Both QSAR models were implemented in SwissADME.

Results and discussion

The condensation of Carbamazepine (**1**) with chloral hydrate (**2**) was carried out in two ways (Scheme 1). The first approach was based on a previously developed method of the condensation of chloral hydrate with carboxamides in the melt [14]. This method eliminated the use of expensive,

flammable, and toxic solvents and allowed us to obtain the target compound **3** in 88% yield. The second approach was based on the method of condensation of chloral hydrate with carboxamides by boiling in an anhydrous toluene or benzene environment. Using this method made it possible to obtain compound **3** with a slightly lower yield than the first method but with a greater degree of purity.

Amino derivative **4** was obtained through the stage of chlorination of compound **3** with thionyl chloride, followed by treatment of the resulting chlorinated derivative with an aqueous solution of ammonia (25%) in an MTBE medium by analogy with a previously developed procedure [15].

The structure of the obtained compounds was proven by ^{1}H NMR and IR spectroscopy data. In the ^{1}H NMR spectrum of compound **3** at 5.53 and 5.23 ppm, doublet-doublet and doublet signals of CH and NH protons are observed, respectively. For compound **4**, the signals of these protons are slightly shifted to the high field region, and both appear as doublets at 5.35 and 5.21 ppm. In the case of compound **3**, the signal of the OH proton is superimposed with eight signals of two benzene rings, which leads to the formation of a multiplet in the region of 7.52–7.42 ppm. In the ^{1}H NMR spectrum of compound **4**, the OH proton signal is absent, but a singlet signal of the NH_2 group is observed at 3.38 ppm. The signals of eight protons of two benzene rings for compound **4** appear in the region of 7.56–7.40 ppm. The two remaining protons of the azepine ring for compounds **3** and **4** appear as singlets at 7.03 and 7.06 ppm, respectively. In the IR spectra of compounds **3** and **4**, absorption bands are observed in the region of 3470–3370 cm^{-1}, corresponding to vibrations of the OH, NH_2, and NH groups, as well as an intense absorption band at 1686–1665 cm^{-1}, corresponding to vibrations of the C=O group.

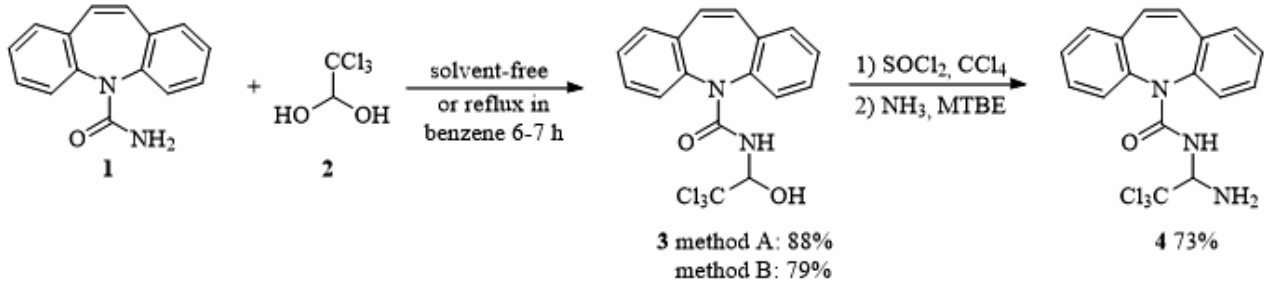
The resulting compounds are undoubtedly of interest as potential anticonvulsants. Before conducting further investigations to assess the biological activity of compounds **3** and **4** in animals, we decided to conduct an *in silico* assessment of their ADME properties. We used the SwissADME online server for this purpose [10]. We assessed such physicochemical properties as lipophilicity, size, polarity, solubility, flexibility, and saturation of the molecule. It can be seen from the bioavailability radars presented for Carbamazepine and compounds **3** and **4** in Fig. 1 that the resulting compounds have a high degree of drug similarity and should have high bioavailability.

The results of assessing the solubility of compounds 3 and 4 in water, which was carried out using two different methods, ESOL [12] and Ali [13], indicated their moderate solubility. The LogS value ranged from −4.99 to −4.96 and from −4.85 to −4.79 for compound 3 and 4, respectively.

However, to exhibit anticonvulsant activity, the substance must not only have high bioavailability but also effectively penetrate the blood-brain barrier. This ability was assessed using the BOILED-Egg method [11] implemented on the SwissADME platform [10]. According to the results of *in silico* analysis, compounds **3** and **4** are able, along with Carbamazepine, to penetrate the blood-brain barrier (Fig. 2). In addition, according to the analysis results, compound **3** is not a potential inhibitor of P-glycoprotein (P-gp, PGP). This makes it an attractive candidate for investigating its potential use in combination with other drugs.

Conclusions

A new potential anticonvulsant, *N*-(2,2,2-trichloro-1-hydroxyethyl)-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide, has been obtained by condensing Carbamazepine with chloral hydrate. Replacing the hydroxyl group in the resulting compound with an amino group has led to the formation of another potential anticonvulsant agent, *N*-(1-amino-2,2,2-trichloroethyl)-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide. The structure of the obtained compounds has been proven by ^{1}H NMR and IR spectroscopy data. The synthesized compounds have successfully passed the *in silico* stage of testing their bioavailability



Scheme 1. Synthesis of *N*-(2,2,2-trichloro-1-hydroxyethyl)-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (3) and *N*-(1-amino-2,2,2-trichloroethyl)-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (4)

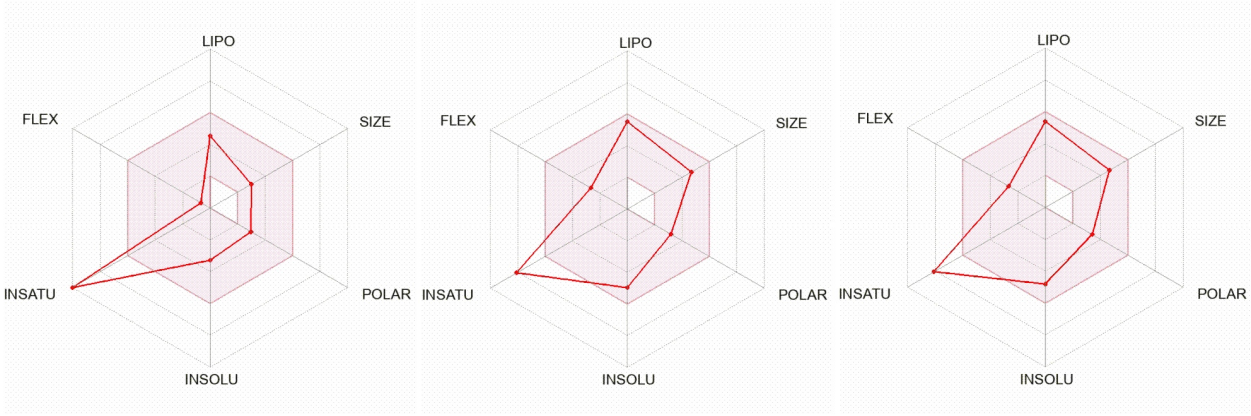


Fig. 1. Bioavailability radars for Carbamazepine (1), as well as compounds 3 (2) and 4 (3) allow assessing the similarity of these molecules to the drug according to such parameters as lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), saturation (INSATU) and flexibility (FLEX) of the molecule

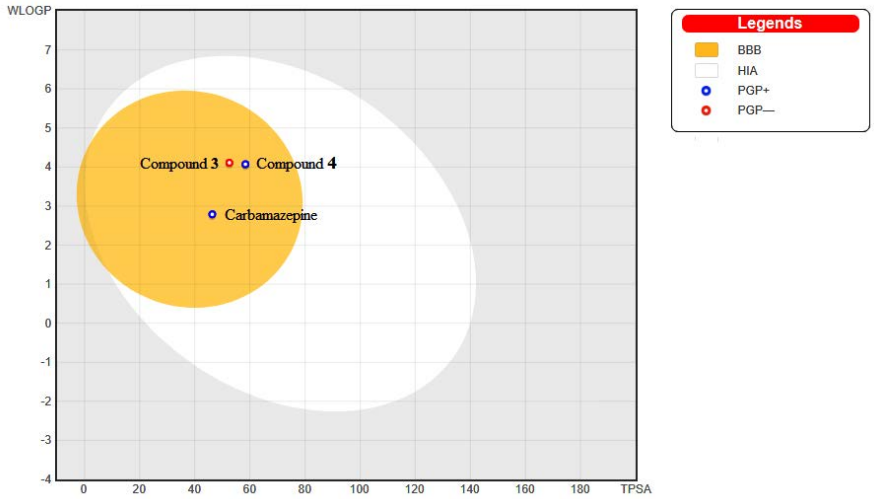


Fig. 2. Results of *in silico* assessment of the ability of Carbamazepine, as well as compounds 3 and 4 to penetrate the blood-brain barrier

and ability to penetrate the blood-brain barrier. They can be recommended for further investigations of their anticonvulsant and other types of biological activity.

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СИНТЕЗ ПОТЕНЦІЙНИХ ПРОТИСУДОМНИХ ЗАСОБІВ НА ОСНОВІ ХЛОРАЛГІДРАТУ ТА КАРБАМАЗЕПІНУ: ЇХ СПЕКТРАЛЬНІ ХАРАКТЕРИСТИКИ ТА *IN SILICO* ADME ПРОФІЛЮВАННЯ

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У даній роботі повідомляється про синтез нового потенційного протисудомного засобу –N-(2,2,2-трихлор-1-гідроксіетил)-5H-дибензо[b,f]азепін-5-карбоксаміду. Його синтез заснований на конденсації протисудомного препарату, що використовується в медичній практиці – Карбамазепіну з хлоральгідратом. Реакцію проводили в розплаві або при кип'ятінні в сухому бензолі з видаленням з реакційного середовища води, що утворювалась. Продукт було одержано з виходом 88 і 79%, відповідно. Заміна гідроксильної групи, в одержаному продукті конденсації, на аміногрупу призводила до утворення N-(1-аміно-2,2,2-трихлоретил)-5H-дибензо[b,f]азепін-5-карбоксаміду. Цей синтез було проведено в дві стадії. Спочатку гідроксипохідне хлорували тіонілхлоридом. Потім, шляхом обробки одержаного хлорпохідного водним розчином аміаку (25%) у середовищі МТБЕ одержували цільовий продукт. Будову одержаних сполук доведено даними ЯМР ^{1}H та ІЧ спектроскопії. З використанням онлайн платформи SwissADME було показано, що синтезовані сполуки повинні володіти високою біодоступністю, помірною розчинністю у воді і здатні проникати через гематоенцефалічний бар'єр.

Ключові слова: карбамазепін, хлоральгідрат, конденсація, in silico, ADME, протисудомний засіб.

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