Bioorganic Chemistry 104 (2020) 104279

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Synthesis of N-phenylsulfonamide derivatives and investigation of some esterase enzymes inhibiting properties

ARTICLE INFO

Keywords:
4-Phenyl-sulfonamide
Carbonic anhydrase
Aniline
Cholinesterase
Enzyme inhibition

ABSTRACT

In this study, synthesis of nine N-phenylsulfonamide derivatives was designed by starting from aniline, which is the simplest aromatic amine. These compounds were obtained in yields between 69 and 95%. Inhibitory properties of synthesized compounds on carbonic anhydrase I (CA I), CA II isoenzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes were investigated. Inhibitors of CA isoenzymes are important therapeutic targets, particularly due to their preventive/activation potential in the treatment of diseases such as edema, glaucoma, cancer and osteoporosis. Cholinesterase inhibitors are valuable compounds that can be used in many different therapeutic applications, including Alzheimer's disease. The compound **8** for CA I, AChE and BChE, **2** for CA II showed a very active inhibition profile (K_I 45.7 ± 0.46 for CA I, 33.5 ± 0.38 nM for CA II, 31.5 ± 0.33 nM for AChE and 24.4 ± 0.29 nM for BChE). The results indicate that these N-phenyl-sulfonamide derivatives are potent CA and cholinesterases and new potential drugs.

1. Introduction

Carbonic anhydrases (EC 4.2.1.1, CAs) are a family of enzymes that both have physiological hydratase and also esterase activity. CA isoenzymes are found in many tissues involved in many different important biological processes [1–5].

Sulfonamides are being used as CA inhibitors or activators and they have broad biological activities such as anticancer, antifungal, antiobesity, antibacterial, antidiuretic, antiglaucoma, and antiepileptic [2,6]. Generally, acetazolamide is used as an antiglaucoma agent, sulfadiazine is used as an antibiotic and sulfapyridine, a sulfonamide consisting of pyridine, is used against bacterial infections [7]. The other sulfonamide derivative is nimesulide, which has anticancer activity, is mainly used for designing novel sulfonamide derivatives [8] (see Fig. 1).

In some studies conducted recently by our group, we investigated the inhibition of carbonic anhydrase isoenzymes obtained from different organisms with different substances. These inhibitors were substances such as sulfonamides, pyrazole derivatives, phthalocyanine derivatives and some natural molecules [9–16].

Alzheimer's disease (AD) is defined as a neurodegenerative condition characterized by abnormal behaviours and intellectual reductions. This disease has become one of the leading public health problems due to the elderly increasing population especially in developed countries [17–20]. Inhibition of AChE and BuChE enzymes that hydrolyze acetylcholine (ACh) and butyrylcholine (BCh) neurotransmitters have become a treatment option for AD [21].

Therefore, many researchers have tried to identify novel inhibitors of these enzymes for the treatment of AD. The physiological activity of the AChE enzyme is the hydrolysis of ACh. Increasing ACh concentration is a treatment strategy due to the loss of cholinergic neurons in Alzheimer's patients. Drugs such as neostigmine, galantamine and rivastigmine are AChE enzyme inhibitors. These drugs act by increasing the amount of ACh by preventing the hydrolysis of ACh [21].

In the last 160 years, aniline has become one of the most used facial building blocks in the chemical industry. Aniline is a raw material used in several fields to produce functional products in many different application areas, such as the production of rubber processing chemicals, agrochemicals, paints and pigments and pharmaceuticals. In pharmaceutical chemistry, although it is a stable and small output molecule, aniline is mainly used for the preparation of analgesics, antipyretics, antiallergics and vitamins [22].

Sulfonamides, especially aromatic or heteroaromatic ones, are the well known inhibitors of CA isoenzymes and numerous literature has been reported in this area [23]. Nevertheless, sulfonamide derivatives of aniline has not yet been investigated. In this paper we focused on N-phenyl-sulfonamide derivatives that contain methanosulfonamide, 4-methoxybenzenesulfonamide, 3-(trifluoromethyl) benzenesulfonamid, 4-fluorobenzenesulfonamide, 3-fluorobenzenesulfonamide, 3-pyridinesulfonamide, 8-quinolinesulfonamide, 2-naphthalenesulfonamide, 2-thiophenesulfonamide. Sulfonamides were synthesized in yields from 69 to 95% and spectral data was taken from ^{1}H NMR. The ^{1}H NMR spectra of compounds was compatible with known molecular structures [24–27].

In this research a number of sulphonamide derivatives were prepared by reaction of aniline with aromatic and aliphatic sulphonamides. The reaction of aniline with a series of sulfonyl chloride afforded the target compounds. Protocols for mesylation of amines offer simplicity, short reaction time and mild conditions. The reaction transform a broad range of substrates with excellent yield.

In this study, novel N-phenylsulfonamide derivatives were synthesized in order to discover some novel inhibitors of the esterase enzyme (both for CAs and cholinesterases). Two CA isoenzymes (hCA I and hCAII) from human erythrocytes were purified and the inhibitory effects of the indicated substances on hCA I, II, AChE and BChE were investigated.

https://doi.org/10.1016/j.bioorg.2020.104279
Received 13 March 2020; Received in revised form 11 August 2020; Accepted 11 September 2020
Available online 17 September 2020

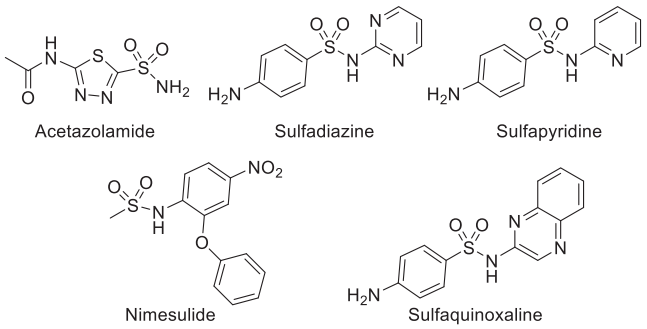

Fig. 1. Sulfonamides with extensive biological activity.

2. Experimental and methods

2.1. Chemistry

2.1.1. General information

Commercially available reagents utilized in this study were used directly without any additional purification. The reactions were carried out under a nitrogen atmosphere, unless otherwise stated. Anhydrous solvents were distilled over appropriate drying agents prior to use.

^{1}H NMR Spectra: Bruker 400 spectrometers. Melting points were determined in open glass capillary using a Stuart melting point SMP30 apparatus. The chromatographic purifications were performed by column chromatography employing silica gel (230–400 mesh, 40–63 μm), and eluting with hexane or hexane/EtOAc mixtures of increasing polarity. The progress of the reactions was monitored by thin layer chromatography. For detection of the spots, the TLC plates were exposed to UV light (254 and 365 nm).

2.1.2. General procedure for preparation of compounds 1–9

Appropriate sulfonyl chloride derivative (1.1 eq) was added to a stirred solution of the aniline (1 eq) in CH_2Cl_2 at room temperature. The resulting mixture was cooled down to 0 °C before Et_3N (2.17 eq) was slowly added. The resulting mixture was warmed to room temperature and stirred for 24 h before it was quenched with NH_4Cl (sat. aq.). The layers were separated and the organic layer was extracted with water and CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The remaining residue purified via column chromatography over silica gel using gradient elution with EtOAc and hexanes to yield sulfonamides **1–9**.

N-phenylmethanesulfonamide (1): The above procedure was followed with aniline and sulfonyl chloride (**10**) to yield **1** as a light yellow solid (85% yield) [24].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 7.9 Hz, 2H), 7.26–7.17 (m, 3H), 6.89 (s, 1H), 3.02 (s, 3H).

4-Methoxy-N-phenylbenzenesulfonamide (2): The above procedure was followed with aniline and sulfonyl chloride (**11**) to yield **2** as a white solid (78% yield) [24]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H), 7.29–7.20 (m, 2H), 7.15–6.95 (m, 3H), 6.92–6.80 (m, 2H), 3.82 (s, 3H)

N-phenyl-3-(trifluoromethyl)benzenesulfonamide (3): The above procedure was followed with aniline and sulfonyl chloride (**12**) to yield **3** as a white solid (84% yield) [25]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.30–7.25 (m, 2H), 7.20–7.15 (m, 1H), 7.10–7.05 (m, 2H), 6.90 (s, 1H).

N-phenylquinoline-8-sulfonamide (4): The above procedure was followed with aniline and sulfonyl chloride (**13**) to yield **4** as a white solid (95% yield) [26]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, J = 4.3, 1.6 Hz, 1H), 8.63 (s, 1H), 8.37–8.32 (m, 2H), 8.04 (dd, J = 8.2, 1.0 Hz, 1H), 7.65 (dd, J = 8.3, 4.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.15–7.08 (m, 2H), 7.07–6.98 (m, 3H).

4-Fluoro-N-phenylbenzenesulfonamide (5): The above procedure was followed with aniline and sulfonyl chloride (**14**) to yield **5** as a white solid (70% yield) [24]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.76 (m, 2H), 7.28–7.24 (m, 2H), 7.18–7.05 (m, 5H).

3-Fluoro-N-phenylbenzenesulfonamide (6): The above procedure was followed with aniline and sulfonyl chloride (**15**) to yield **6** as a white solid (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.55 (m, 1H), 7.55–7.48 (m, 1H), 7.48–7.41 (m, 1H), 7.31–7.22 (m, 3H), 7.20–7.13 (m, 1H), 7.14–7.07 (m, 2H).

N-phenylpyridine-3-sulfonamide (7): The above procedure was followed with aniline and sulfonyl chloride (**16**) to yield **7** as a white solid (92% yield) [27]. ^{1}H NMR (400 MHz, DMSO) δ 10.51 (s, 1H), 8.87 (d, J = 2.1 Hz, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.12 (ddd, J = 8.1, 2.3, 1.5 Hz, 1H), 7.60 (dd, J = 8.1, 4.8 Hz, 1H), 7.25 (t, J = 7.9 Hz, 2H), 7.15–7.02 (m, 3H).

N-phenylnaphthalene-2-sulfonamide (8): The above procedure was followed with aniline and sulfonyl chloride (**17**) to yield **8** as a white solid (83% yield) [24]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.89 (dd, J = 9.3, 8.5 Hz, 3H), 7.80 (dd, J = 8.7, 1.6 Hz, 1H), 7.61 (dtd, J = 8.0, 6.9, 3.3 Hz, 2H), 7.30–7.18 (m, 2H), 7.18–7.06 (m, 4H).

N-phenylthiophene-2-sulfonamide (9): The above procedure was followed with aniline and sulfonyl chloride (**18**) to yield **9** as a light yellow solid (69% yield) [24]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (ddd, J = 5.0, 4.4, 1.3 Hz, 1H), 7.33–7.26 (m, 3H), 7.18–7.12 (m, 3H), 7.02 (dd, J = 5.0, 3.8 Hz, 1H).

2.2. Purification of hCA I and II isozymes

Human CA I and CA II isoenzymes were purified from fresh human erythrocytes using affinity chromatography. The purification method used in this study was described in previous studies in detail [15–17].

2.3. Esterase activity test for carbonic anhydrase isoenzymes

Inhibition kinetics studies for CA I and CA II isoenzymes have been performed with minor changes in the esterase method. In this part of our study, the inhibition effects of N-phenylsulfonamide derivatives **1–9** were determined. All trials were examined three times. Trials in different concentration ranges were performed for all inhibitors [15,28]. In the absence of the inhibitor in the measuring medium, the control cuvette activity was considered as 100%. K_I values were found by Lineweaver and Burk's curves [12–17] (Table1).

2.4. Activity test for cholinesterase enzymes

Inhibition activities of N-phenylsulfonamide derivatives (**1–9**) on cholinergic enzymes (AChE and BuChE) were determined using the Ellman method [29]. For this analyze neostigmine drug, an AChE inhibitor, was used as a reference molecule. K_I values obtained for N-phenylsulfonamide derivatives (**1–9**) are summarized in Table 1.

Table 1
hCA I, hCA II, AChE and BChE inhibition data some compounds.

Inhibitor	K_I (nM)*			
	hCA I	hCA II	AChE	BChE
1	103.1 ± 0.97	83.3 ± 0.78	41.0 ± 0.42	37.9 ± 0.41
2	49.5 ± 0.55	33.5 ± 0.38	40.3 ± 0.38	33.2 ± 0.38
3	47.3 ± 0.53	38.1 ± 0.36	61.9 ± 0.57	38.7 ± 0.40
4	46.4 ± 0.52	36.3 ± 0.37	35.7 ± 0.34	46.7 ± 0.49
5	69.1 ± 0.73	57.6 ± 0.45	54.2 ± 0.46	43.1 ± 0.45
6	61.2 ± 0.63	44.2 ± 0.43	36.9 ± 0.37	34.5 ± 0.38
7	78.4 ± 0.69	61.8 ± 0.57	72.3 ± 0.69	39.3 ± 0.40
8	45.7 ± 0.46	35.5 ± 0.36	31.5 ± 0.33	24.4 ± 0.29
9	65.3 ± 0.67	48.4 ± 0.49	52.5 ± 0.56	35.8 ± 0.36
AZA**	487.3 ± 3.92	224.9 ± 2.33	–	–
Neostigmine***	–	–	55.5 ± 0.46	33.3 ± 0.32

* Mean from at least three determinations.
** Acetazolamide (AZA) was used as a control for CA I and CA II.
*** Neostigmine was used as a control for AChE and BChE.

Stock solutions of derivatives **1–9** used in this study were prepared by dissolving them in dimethyl sulfoxide to the concentration of 1 mg / mL. The prepared stock solution was then diluted ten thousand times with distilled water. In order to determine the inhibition activities of derivatives **1–9** with these enzymes, measurements were performed in seven different concentrations. The method used in this study has been explained in previous studies in detail [17,30,31].

3. Results

3.1. Chemistry

In this research, a number of N-phenylsulfonamide derivatives were synthesized by using a facile and efficient sulfonation method of amines. Compounds were prepared by the reaction of aniline with aromatic and aliphatic sulphonamides. The reaction of aniline with a number of sulfonyl chlorides afforded the target compounds. Protocols for mesylation of amines offer simplicity, short reaction time and mild conditions. The reaction transformed a broad range of substrates in excellent yield.

The reaction has been performed in DCM as the solvent, in the presence of Et_3N as base, in accordance with the procedure previously reported by our group [6b]. Compounds **1–9** were characterized by standard chemical and physical methods that confirm their structure and were assayed for the inhibition of these esterase enzymes.

3.2. Biochemical studies

In this study, N-phenylsulfonamide derivatives **1–9** were synthesized and their inhibition effects on some esterase enzymes (CA I, CA II, AChE and BChE) were determined.

Many previous studies have shown that cholinesterase enzymes (AChE and BChE) have very important functions on cognition and memory. These enzymes catalyze the hydrolysis of ACh and BCh, which leads to reduced neural communication between nerve cells. This fact slows down brain functions of individuals with subnormal ACh levels and finally leads to AD. Therefore, the treatment of AH is to some extent dependent on the rebalancing of the ACh level [32–35]. Many studies have targeted cholinesterase inhibitors (ChEIs) for the treatment of cognitive disorders. Due to the disadvantages of existing AD drugs such as gastrointestinal disorders and bioavailability, many studies across the world are constantly investigating new ChEIs. Therefore, in this study, derivatives **1–9** were also screened for their inhibitory activities on cholinesterase enzymes.

(i) In inhibition studies of hCA I isoenzyme, N-phenylsulfonamide derivatives **1–9** showed good inhibitor activities, with K_I values in the range of 45.7–103.1 nM, similar to structurally related compounds 4-Amino-N-(pyridin-2-yl) benzenesulfonamide (Sulfapyridine) (K_I of 26.19 μM). Compounds **2**, **3**, **4**, and **8** exhibited much stronger hCA I inhibition effect compared to the other synthesized compounds. It has been determined that natural phenolic compounds, sulfonamides, uracil derivatives, pesticides and many different chemicals was shown to provide similar results with these compounds [6–12,36–41].

(ii) N-phenylsulfonamide derivatives **1–9** were found to inhibit the hCA II isoenzyme more strongly than the hCA I isoenzyme (Table 1). The structure–activity relationship (SAR) analyze for **1–9** compounds is as follows: The bulky group containing compounds **2**, **3**, **4**, **6**, and **8** are more effective than other derivatives. The best hCA II inhibitor among the derivatives **1–9** is the number **2,** containing the *p*-methoxybenzene group, with the K_I value of 33.5 nM. For hCA II isoenzyme, **3, 4**, **6**, and **8** yielded very close to each other with a range between 35.5 and 44.2 nM.

(iii) Compound **7** (K_I = 72.3 nM) showed the weakest inhibitory effect among the agents **1–9** against the AChE enzyme. However, number **8** (31.5 nM), which is the only derivative having naphthalene group, showed a better inhibitory profile than other eight N-phenylsulfonamide derivatives. The most obvious difference between other compounds and this derivative is the larger volume of the derivative number **8.** Compared to others, the derivative **4** provided the closest result to derivative **8**. The fact that derivatives **4** and **8** bearing this two-ring sterically bulky functional group have stronger inhibition profiles may indicate that, geometry of these two compounds make them stronger to be able to interact with the active site of the AChE enzyme. According to the observed results for derivatives **1–9** and AChE, the presence of electronegative groups in functional groups may indicate a significant effect on the inhibition value. In addition, it can be concluded that hydrophobic and sterically larger molecules are more effective. The derivative **7,** which is determined to be the weakest inhibitor, contains pyridine as the functional group. Although the position of the F atom changes only in derivatives **5** and **6**, 1.47 times of activity variation was detected between them. In addition, the values obtained for the AChE enzyme in this study (31.5–72.3 nM) were compared with the reference molecule neostigmine (55.5 nM). While four of these synthesized derivatives showed approximate values to neostigmine, the other five molecules exhibited better results.

(iv) In inhibition studies of BChE enzyme with derivatives **1–9**, derivative **4** (K_I = 46.7 nM) was found to have the weakest inhibitory effect. Among the N-phenylsulfonamide derivatives we tested, the most effective BChE inhibitor was determined to be the naphthalene-containing derivative **8** (K_I = 24.4 nM). In addition, K_I values obtained for the BChE enzyme (24.4–46.7 nM) were compared with the reference molecule neostigmine (33.3 nM). According to these values, eight of these synthesized derivatives showed approximate values to neostigmine, while one molecule (**8**) provided better results.

Considering the results obtained for CA isoenzymes, all tested compounds **1–9** (Table 1) were capable of inhibiting CA II isoenzyme at lower doses. High selectivity for CA II proves the potential utilization of these compounds in the treatment of glaucoma. Inhibition values of cholinesterase, which is a useful and specific inhibitor, were obtained close to those of neostigmine; indicating that this series of substances are likely to be used in the treatment of neurodegenerative diseases such as neostigmine.

Sulfonamides are well known CA inhibitors, but recent studies have shown that their molecules containing different functional groups have

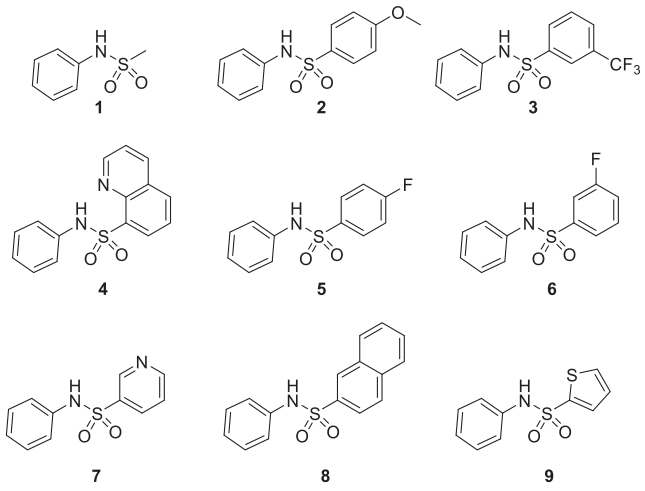

Fig. 2. Structure of tested compounds.

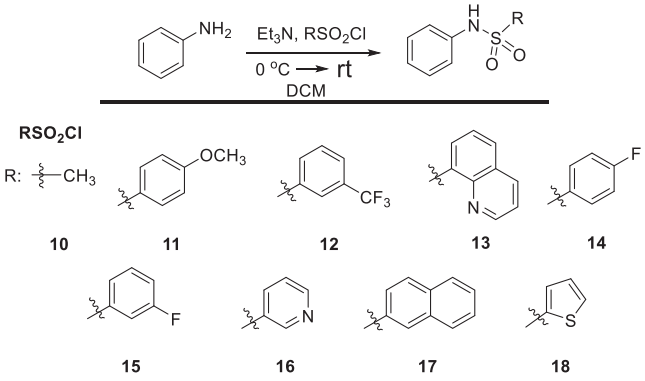

Fig. 3. Sulfonyl chlorides used in the synthesis of sulfonamide derivatives.

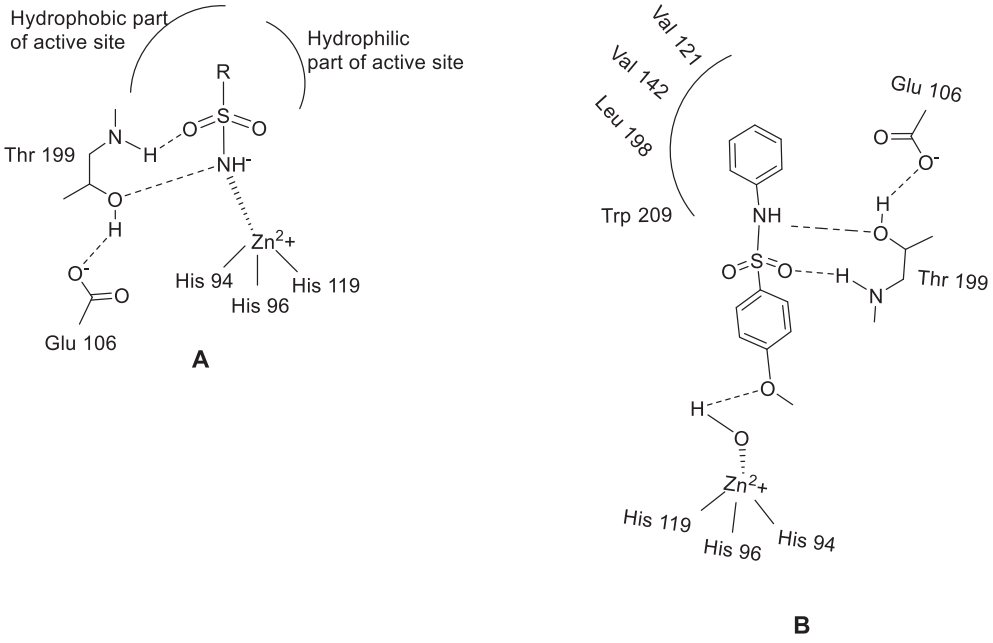

Fig. 4. The model of sulfonamides binding to the active site of the CA II isoenzyme (A) [12,41] and the estimated binding model of the derivative **2** to the active site in the CA II isoenzyme (B).

as good inhibitory effects as sulfonamides [6–17,36–44]. In addition, it has been determined in recent studies that the molecules which are effective on CA isoenzymes also have effects on another esterase enzyme group, AChE and BChE enzymes. These results indicate that N-phenylsulfonamide derivatives exhibit both hCA I, II and AChE/BChE inhibitory activity due to the presence of different functional groups.

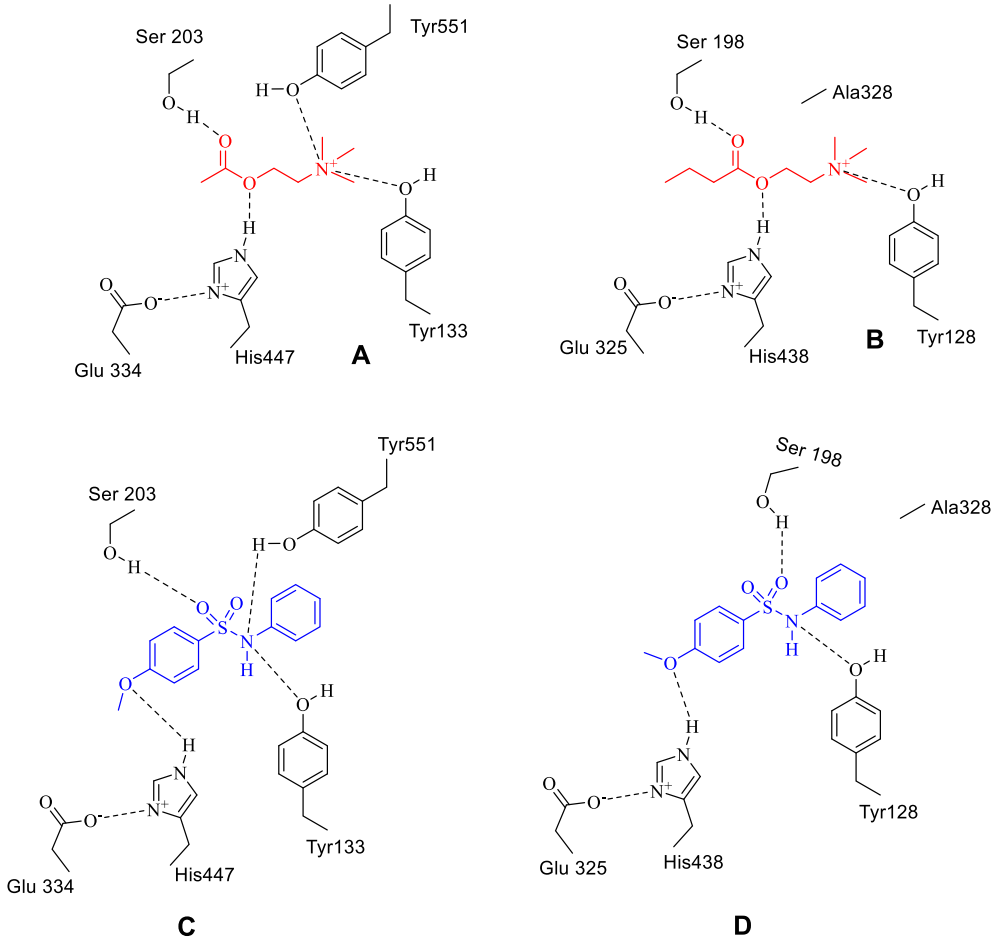

Fig. 5. A: The binding of acetylcholine with the active region of the hAChE enzyme (pdb: 4ey4) [4,42,43] **B:** The binding pattern of butyrylcholine with the active site of the hBChE enzyme (pdb: 1p0i) [4,42–44]. **C:** The estimated AChE binding form of 2, **D:** The predicted BChE binding pattern of 2.

The proposed mechanisms for enzyme inhibition are given in Figs. 4 and 5.

4. Discussion

The main goal of the present study was to synthesize and investigate the inhibition effects on the CA I, CA II, AChE and BChE enzymes due to the presence of different functional groups (-F, -CH_3, -OCH_3, -CF_3, naphthalene, pyridine, etc.) found in their molecular structures. The synthesis of the target compounds was performed according to the previously reported literature procedure as outlined in Fig. 3 [6]. Before the sulfonation reaction of the aniline, H's of aniline signals were observed at 7.20 (t, 2H, J = 7.5 Hz), 6.81 (t, 1H, J = 7.5 Hz), 6.71 (d, 2H, J = 7.5 Hz), 3.65 (br s, 2H, -NH_2) ppm at the ^{1}H NMR spectra. After sulfonamide formation, it was observed that there were changes in the peaks of benzylic aniline and disappear the broad singlet (2H, -NH_2) of aniline. All sulfonamide structures were confirmed by ^{1}H NMR in literature. [23–26]

N-phenylsulfonamide derivatives **1–9** used in this study showed different inhibition effects on CA I, CA II, AChE and BChE enzymes due to the presence of different functional groups (-F, -CH_3, -OCH_3, -CF_3, naphthalene, pyridine, etc.) found in their particular molecular structures. Results of this study show that synthesized compounds are highly effective on the tested esterase enzymes at nanomolar concentrations. The data obtained from this study exhibit the potential usage of these synthesized compounds for the production of strong CAIs or cholinesterase inhibitors that target other CA isoforms that have not yet been tested (Fig. 2).

The findings of this study provides multiple targets. Tested inhibitors of esterase enzymes are currently considered as effective drugs in the treatment of several diseases. Since these N-phenylsulfonamide derivatives (**1–9**) are effective cholinesterase inhibitors, they can be used in the treatment of Alzheimer's disease, as well as in the treatment of diseases such as glucoma, edema and cancer, since they are also effective CAIs. In addition to comparing the synthesized N-phenylsulfonamides with many other compounds, this study will expand targets to determine the structure–activity relationship for N-phenylsulfonamides **1–9**. Thus, the synthesized N-phenylsulfonamides can also be evaluated as drug precursors or building blocks in the preparation of more effective drug molecules.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by Kilis 7 Aralik University, Scientific Research Projects Coordinatorship (BAP 18-12191)

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