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ORIGINAL ARTICLE / ÖZGÜN MAKALE

IMIDAZOLINONE-BASED SULFONAMIDE DERIVATIVES: SYNTHESIS, CHARACTERIZATION, AND INHIBITORY PROPERTY AGAINST SOME METABOLIC ENZYMES

İMİDAZOLİNON BAZLI SÜLFONAMİD TÜREVLERİ: SENTEZ, KARAKTERİZASYON VE BAZI METABOLİK ENZİMLERE KARŞI İNHİBİTÖR ÖZELLİKLERİ

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ABSTRACT

Objective: *The purpose of the work was to investigate new synthetic compounds of imidazolinone-based sulfonamide derivatives as potent and selective enyzme inhibitors. A number of compounds synthesized and their inhibitory action against acetylcholine esterase (AChE), and human (h) carbonic anhydrase (CA) isoforms I and II were investigated.*
Material and Method: *The identity of the compounds has been confirmed by HRMS, ^{1}H NMR, and ^{13}C NMR. The pharmacological potential of the compounds has been determined by in vitro enzyme-based assays.*

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Result and Discussion: *In this study, a series of imidazolinone-based sulfonamide derivatives were synthesized from 4-(2,4-dimethoxybenzylidene)-2-phenyloxazol-5(4H)-one, sodium acetate, glacial acetic acid, and suitable sulfonamide derivatives such as sulfaguanidine (3), sulfanilamide (4), sulfadiazine (5). These compounds showed potent inhibitory action against acetylcholine esterase (AChE), and human (h) carbonic anhydrase (CA) isoforms I and II. Compound 4 (Ki=19.53±1.23 nM) was a potent and selective inhibitor against hCA I while compound 3 (Ki=16.49±2.20 nM) was found to be potent inhibitor against hCA II. Compound 5 with Ki of 11.68±1.45 nM showed a potent inhibitory effect against the AChE enzyme. Imidazolinone-based sulfonamides can be used in the design of selective CAs inhibitors and anti-Alzheimer's compounds for further studies.*
Keywords: *Imidazolinone, synthesis, acetylcholinesterase, carbonic anhydrase, Alzheimer's disease*

ÖZ

Amaç: *Çalışmanın amacı, güçlü ve seçici enzim inhibitörleri olarak imidazolinon bazlı sülfonamid türevlerinin yeni sentetik bileşiklerini araştırmaktır. Sentezlenen bir dizi bileşik ve bunların asetilkolin esteraz (AChE) ve insan (h) karbonik anhidraz (CA) izoformları I ve II'ye karşı inhibe edici etkileri araştırılmıştır.*
Gereç ve Yöntem: *Bileşiklerin yapısı HRMS, ^{1}H ve ^{13}C NMR ile doğrulanmıştır. Bileşiklerin farmakolojik potansiyeli, in vitro enzim bazlı analizler ile belirlenmiştir.*
Sonuç ve Tartışma: *Bu çalışmada, imidazolinon bazlı sülfonamit bileşikleri serisi 4-(2,4-dimetoksibenziliden)-2-feniloksazol-5(4H)-on, sodyum asetat, buzlu asetik asit ve sulfaguanidin (3), sulfanilamid (4), sulfadiazin (5) gibi uygun sülfonamid türevlerinden hareketle sentezlendi. Bu bileşikler, asetilkolin esteraz (AChE) ve insan (h) karbonik anhidraz (CA) izoformları I ve II'ye karşı güçlü inhibe edici etki gösterdi. Bileşik 4 (Ki= 19.53±1.23 nM), hCA I'e karşı güçlü ve seçici bir inhibitör iken, bileşik 3'ün (Ki=16.49±2.20 nM) hCA II'ye karşı güçlü inhibitör olduğu bulundu. 11.68±1.45 nM Ki'ye sahip bileşik 5, AChE enzimine karşı güçlü bir inhibitör etki gösterdi. İmidazolinon bazlı sülfonamidler, seçici CA inhibitörleri ve anti-Alzheimer bileşiklerinin tasarımında ileriki çalışmalarda kullanılabilirler.*
Anahtar Kelimeler: *İmidazolin, sentez, asetilkolinesteraz, karbonik anhidraz, Alzheimer hastalığı*

INTRODUCTION

Heteroatoms comprise a very prevalent part of a number of active pharmaceutical materials [1]. Statistics indicate that greater than 85 % of all biologically active chemical components have a heterocyclic structure [1]. Using heterocycles to modify the ADME-Tox (absorption, distribution, metabolism, and excretion – toxicity) properties of the compounds is advantageous to obtain drug candidates having favorable pharmacokinetics [2]. An essential and original class of medicinal chemistry comprises nitrogen-based compounds [3-5]. These types of molecules continue to be the focus of increasing attention in recent research in the pharmaceutical sciences [6-8]. Vitamins, nucleic acids, pharmaceuticals, antibiotics, and agrochemicals which has *N*-heterocyclic structure are mainly distributed in nature and exhibit physiological and pharmacological properties [9-11].

Aromatic heterocyclic ring system with five members $C_3N_2H_4$ is an imidazole ring structure with three carbon and two nitrogen atoms. Because of the presence of non-adjacent nitrogen in the ring structure, a diazole is an aromatic heterocyclic ring. The scientific community refers to this group of keto dihydroimidazoles as oxoimidazolines or imidazolinones. They are made up of an imidazoline derivative with carbon-nitrogen double bonds at positions 1 and 3 and carbon-oxygen double bonds at positions 2, 4 or 5 (Figure 1) [12].

Imidazolinones offer a variety of therapeutic properties, including anticonvulsant, antidepressant, antibacterial, anti-inflammatory, MAO inhibitory, anti-Parkinson, antihypertensive, anti carbonic anhydrase, and [13] acetylcholine esterase inhibitory, among others [14]. Kagthara et al. synthesized new imidazolidinone derivatives (Figure 2, compound 3 derivatives) incorporating benzimidazole and tested them *in vitro* for anti-microbial activity against bacteria like *S. citrus*, *E. coli*, and *S. typhi*, and these compounds were compared to standard drugs like ampicillin, norfloxacin, and chloramphenicol. They discovered that the majority of active molecules included imidazolinone ring [15].

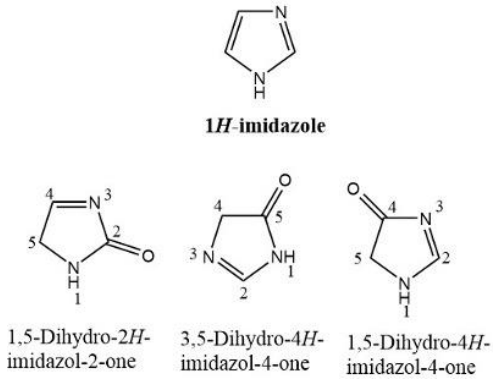


Figure 1. Different imidazolinones' chemical structures

A series of imidazolinone bearing compounds (Figure 2, compound 25 derivatives) were tested for their ability to reduce inflammation and bacterial development. Compound 25's derivatives, 25a, 25b, and 25c, demonstrated significant activity. The existence imidazolinone, styryl, and dipeptidyl moieties affected anti-bacterial activity [16].In another study, some 1,2,4-trisubstituted imidazolin-5-one derivatives were synthesized and tested for their ability to inhibit carbonic anhydrase (CA) enzymes. Compound 4a showed the best inhibitory efficacy with Ki values of 95.0, 0.83, 6.90, and 12.4 nM, respectively, against all the carbonic anhydrase isoforms tested (CA I, II, IV, and IX) when compared to acetazolamide (Figure 2) [17].

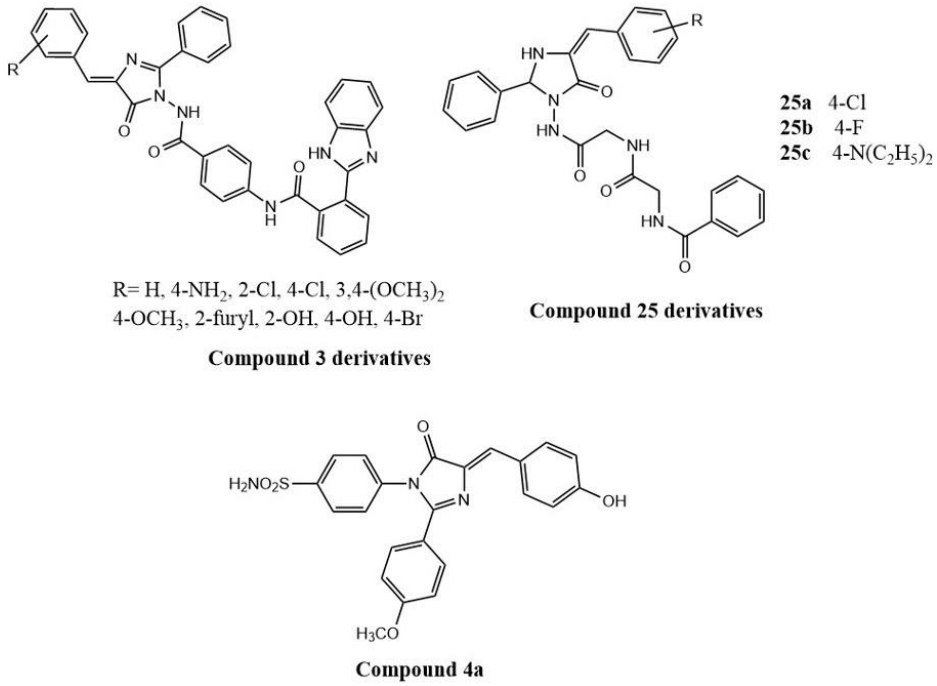
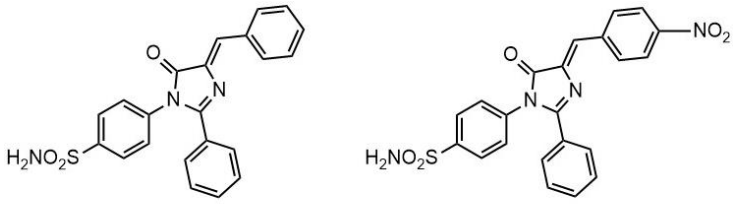


Figure 2. Chemical structures of bioactive imidazolinone derivatives

Sulfonamides contain the SO_2NH_2 moiety in their structure [18]. They are popular in drug design due to significant biological activities including antibacterial [19], antidiabetic [20], carbonic anhydrase inhibitory [21, 22], anti-inflammatory [23], antitumor [24], antioxidant [25], and anticancer [26] agent.

In a study, our research group generated a series of imidazolidinone derivative compounds (Figure 3). Following spectral confirmation of their structures, the compounds were tested against carbonic anhydrase (CA) and acetylcholinesterase (AChE) enzymes. Series 4 were found more potent CAs

inhibitors than series 3. Nitro-containing compounds in series 4 were 3.3-4.8 times more selective inhibitors than their series 3. Compounds 3c and 4c having the lowest Ki values, which contain the benzenesulfonamide moiety, were considered as the leaders in terms of AChE inhibition, [27].

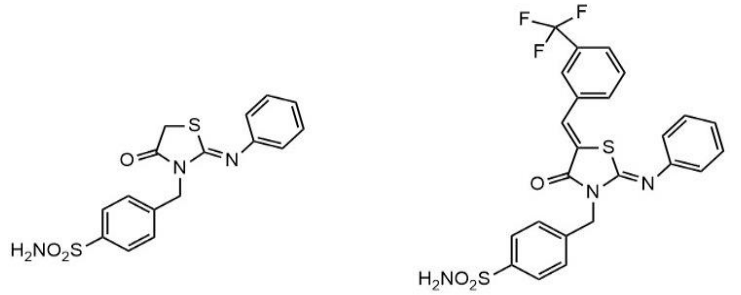


Compound 3c **Compound 4c**

Figure 3. Chemical structures of imidazolinone derivatives reported our research group

Carbonic anhydrase is a metalloenzyme that contains zinc (Zn^{2+}) ions in its active site and catalyzes the slow transformation of CO_2 to HCO_3^- and H^+. They have a role in a variety of physiological and pathological processes [28, 29]. The structures that represent the main inhibitory group of carbonic anhydrases are sulfonamide/sulfamate groups [30-32]. Carbonic anhydrase inhibitors (CAIs) have been used to treat glaucoma [33], diuretics [34], obesity [35], and cancer [36].

Zhang et al. synthesized compounds containing benzenesulfonamide residue and then tested their efficacy against the carbonic anhydrase enzymes. The profiles of the enzyme inhibition assays against *h*CA II were as good as the positive controls. Compounds 2 and 7 (Figure 4) efficiently bind in the active site cavity of an enzyme by generating adequate contacts with active site residues, according to docking studies [37].



Compound 2 **Compound 7**

Figure 4. Compounds with sulfonamide residues as CA inhibitors

The hydrolysis of acetylcholine (ACh) to choline and acetic acid by cholinesterases (ChEs) is a basic process for cholinergic neurotransmission [38]. At the presynaptic level, ACh molecules are produced from choline. Both the peripheral and central nervous systems (CNS) require them for cholinergic neurotransmission [38]. Alzheimer's disease (AD) is a neurodegenerative disease marked by cognitive decline, memory loss, and dementia [39]. In general, AD is treated with rivastigmine, tacrine, and donepezil acting as ChE inhibitors [40].

In a study, benzenesulfonamide derivatives were reported as acetylcholinesterase (AChE) enzyme inhibitors. The results revealed that the synthesized sulfonamide derivatives have potential inhibition properties for AChE with Ki constants ranging from 2.54±0.22–299.60±8.73 μM. The derivatives (S1, S1i, S3, and S3i) appeared a competitive inhibition effect, whereas others (S2, S2i, S4, and S4i) appeared mixed-type inhibition [41].

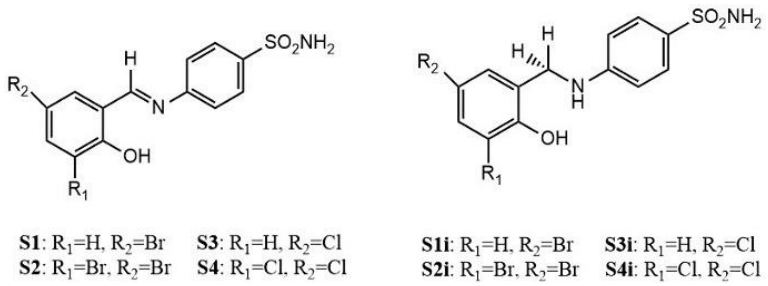
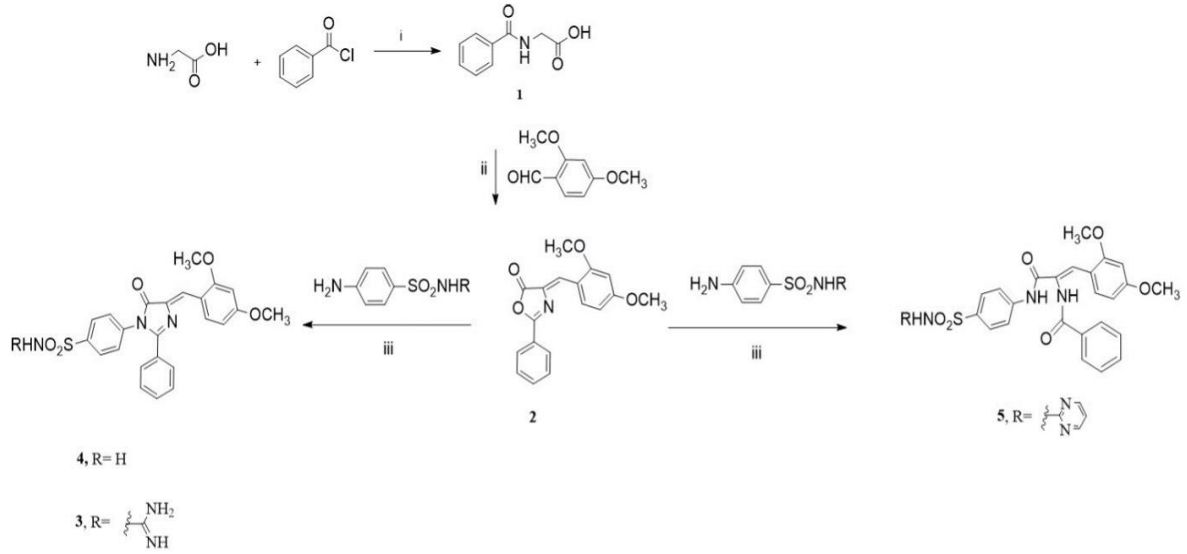


Figure 5. Chemical structures of the compounds (S1,S1i, S2, S2i, S3, S3i, S4, S4i)

Imidazolinone-based sulfonamide derivatives were designed and synthesized in this study (Scheme 1). Spectrometric methods (^{1}H, ^{13}C NMR, and HRMS) were used to characterize the chemical structures of the synthesized compounds. Compounds were investigated for their inhibitory effects on AChE, CA II, and CA I enzymes.



Scheme 1. Synthetic pathway of the target compounds **1-5 (**i: 10% NaOH, HCl, ii: acetic anhydride, sodium acetate, 100°C, iii: glacial acetic acid, sodium acetate, 100°C)

MATERIAL AND METHOD

Spectral techniques for ^{1}H and ^{13}C NMR (Varian, California, U.S.A), as well as HRMS (Shimadzu, Kyoto, Japan), were utilized for structural investigation. Coupling constants (*J*) are stated in hertz (Hz), and chemical shifts are reported in ppm. Electrothermal 9100/IA9100 (Bibby Scientific Limited in Staffordshire, U.K.) was used to determine melting points. To monitor the reaction process, silica gel 60 HF254 thin layer chromatography (TLC) was utilized. TLC solvent systems included a combination of chloroform and methanol (4.8:0.2).

Synthesis of 2-Benzamidoacetic Acid (1)

After 1 mmol of glycine was dissolved in sodium hydroxide solution (25 ml, 10%), benzoyl chloride (1 mmol) were added to the solution. Until the liquid is acidic (pH=4-5), strong hydrochloric acid was gently added to the mixture until pH=4-5. Then, benzoyl glycine was filtered and rinsed with ice-cold water. The solid was heated in carbon tetrachloride (100 ml, 10 min) to remove any benzoic acid. Then, cooled mixture was filtered and washed using carbon tetrachloride [27]. The following are the spectral and experimental results: White colour solid, mp: 192-193°C, yield 90%. ^{1}H NMR (DMSO-

d_6, ppm, 400 MHz), δ 8.76 (d, *J*= 5.3 Hz, 1H, Ar-H), 7.88 (d, *J*= 7.9 Hz, 2H, Ar-H), 7.57–7.46 (m, 3H, Ar-H, NH),3.94 (s, 2H, -CH_2); ^{13}C NMR (DMSO-d_6, ppm, 100 MHz) δ 171.3, 166.4, 133.8, 131.4, 128.3, 127.2, 41.2.

The General Method of Synthesis of 4-(2,4-Dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (2)

Dry sodium acetate, acetic anhydride, 2,4-dimethoxybenzaldehyde, and 4-benzoyl glycine were heated for one hour over a water bath. The resulting combination was let to stand at room temperature overnight. The solid was filtered and washed by cold water and dried at 60°C. The crude compound 2 was recrystallized using ethanol [27].

4-(2,4-Dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (2)

Cream colour solid, mp: 169-170°C, yield 76%. ^{1}H NMR (DMSO-d_6, ppm, 400 MHz) , δ 8.77-8.73 (m, 1H, Ar-H), 8.05 (t, *J*= 6.8 Hz, 2H, Ar-H), 7.69–7.57 (m, 3H, Ar-H, =CH-), 7.48 (d, 1H, *J*= 6.6 Hz, Ar-H), 6.74-6.71 (m, 1H, Ar-H), 6.64-6.61 (m, 1H, Ar-H), 3.91 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, ppm, 100 MHz) δ 167.2, 164.1, 161.3, 160.8, 133.6, 133.1, 129.5, 129.2, 127.5, 125.3, 124.2, 114.7, 97.7, 56.03, 55.6.

General Synthesis Method of the 3, 4 and 5

Sodium acetate (15 mmol), a suitable sulfonamide derivative (12 mmol) [sulfaguanidine (3), sulfanilamide (4), and sulfadiazine (5)], and compound 2 were refluxed in gl. acetic acid (10 ml) for 17-19 hours at 100°C. The crude was removed, washed with water, and dried. DMF/C_2H_5OH/H_2O mixture was used for crystallization. The isolated open-chain product 5 compound's spectral and experimental data are given below [17,27].

***N*-Carbamimidoyl-4-(4-(2,4-dimethoxybenzylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)benzenesulfonamide (3)**

White colour solid, mp: 294-296°C, yield 55%. ^{1}H NMR (DMSO-d_6, ppm, 400 MHz) , δ 8.95–8.92 (m, 1H, Ar-H), 7.82–7.80 (m, 2H, Ar-H), 7.56 (s, 1H, =CH-), 7.50–7.48 (m, 3H, Ar-H), 7.43–7.36 (m, 4H, Ar-H, NH), 6.77–6.74 (m, 4H, Ar-H, NH), 6.69 (bs, 2H, NH_2), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C NMR (DMSO- d_6, ppm, 100 MHz) δ 169.2, 163.5, 160.7, 158.3, 158.1, 143.9, 136.8, 135.3, 133.9, 131.2, 128.8, 128.6, 128.4, 127.8, 126.5, 121.6, 115.4, 107.1, 97.8, 55.9, 55.6; HRMS (ESI-MS) $C_{25}H_{23}N_5O_5S$, Calculated $[M+H]^+$: 506.1493; Found $[M+H]^+$: 506.1493.

4-(4-(2,4-Dimethoxybenzylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)benzenesulfonamide (4)

Dark cream colour solid, mp: 295-296°C, yield 65%. ^{1}H NMR (DMSO-d_6, ppm, 400 MHz) , δ 8.95-8.92 (m, 1H, Ar-H), 7.88 (d, *J*= 8.5 Hz, 2H, Ar-H), 7.57 (s, 1H, =CH-), 7.51-7.40 (m, 7H, Ar-H), 6.76 (d, *J*= 8.8 Hz, 2H, Ar-H), 6.68 (s, 2H, NH_2); 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C NMR (DMSO- d_6, ppm, 100 MHz) δ 169.2, 163.5, 160.8, 158.3, 143.4, 137.4, 135.3, 133.9, 131.2, 128.8, 128.6, 128.5, 128.1, 126.6, 121.7, 115.3, 107.2, 97.8, 56.0, 55.6; HRMS (ESI-MS) $C_{24}H_{21}N_3O_5S$, Calculated $[M+H]^+$: 464.1275; Found $[M+H]^+$: 464.1274.

***N*-(1-(2,4-dimethoxyphenyl)-3-oxo-3-((4-*(N*-(pyrimidin-2-yl)sulfamoyl)phenyl)amino)prop-1-en-1-yl)benzamide (5)**

Light cream colour solid, mp: 228-229°C, yield 65%. ^{1}H NMR (DMSO-d_6, ppm, 400 MHz), δ 10.43 (s, 1H, NH), 9.98 (s, 1H, NH), 8.51-8.49 (m, 2H, Ar-H), 8.00 (d, *J*= 7.5 Hz, 2H, Ar-H), 7.94–7.88 (m, 4H, Ar-H), 7.57–7.49 (m, 4H, Ar-H), 7.28 (s, 1H, =CH-), 7.04–7.01 (m, 1H, Ar-H), 6.63 (s, 1H, NH), 6.54 (d, *J*= 8.6 Hz, 1H, Ar-H), 3.83 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, ppm, 100 MHz) δ 166.4, 165.5, 161.9, 159.1, 158.8, 157.5, 157.3, 143.8, 134.6, 133.9, 132.2, 130.3, 129.1, 129.0, 128.8, 128.3, 123.8, 119.7, 115.6, 105.9, 98.7, 56.2, 55.8; HRMS (ESI-MS) $C_{28}H_{25}N_5O_6S$, Calculated $[M+H]^+$: 560.1598; Found $[M+H]^+$: 560.1602.

Pharmacological/Biological Assays

AChE and *h*CAs Inhibition Assay

Human erythrocytes' CA isoenzymes (I and II) were purified in accordance with published studies [42,43]. The *p*-nitrophenylacetate is utilized as a substrate and converted to the *p*-nitrophenolate ion by both isoforms [44,45]. Acetylthiocholine iodide and 5,5-Dithiobis(2-nitrobenzoic) acid were used as the substrates and inhibitory effects of the novel imidazolinone-based sulfonamide derivatives (**1**-**5**). The AChE activity of the compounds (**1**–**5**) tested was measured at 412 nm spectrophotometrically [46-48].

AChE *and h*CAs Kinetic Assay

At least five distinct inhibitor concentrations were used to test the inhibitory effects of the new compounds (**1-5**) on *h*CAs and AChE. According to other studies [27,49], the IC_{50}s of the synthesized derivatives were determined from Activity (%) [Derivative] graphs for each derivative. Lineweaver - Burk's curves were graphed to identify the types [50] of inhibition and Ki values [51].

Table 1. The inhibitory effects of the compounds **1-5** on CAs and AChE enzymes

	IC_{50} (nM)						K_i (nM)		
Compd	***h*CA I**	**r^2**	***h*CA II**	**r^2**	**AChE**	**r^2**	***h*CA I**	***h*CA II**	**AChE**
1	49.50	0.9891	63.00	0.9771	31.50	0.9858	40.97±7.06	83.50±14.27	30.15±1.62
2	34.65	0.9818	49.50	0.9824	30.13	0.9941	50.64±12.15	31.56±1.96	27.34±4.03
3	27.72	0.9812	22.35	0.9832	24.75	0.9915	23.61±2.34	16.49±2.20	20.14±1.21
4	26.65	0.9769	28.87	0.9803	23.10	0.9823	19.53±1.23	25.30±1.47	21.71±4.04
5	29.85	0.9842	30.13	0.9945	23.90	0.9819	20.27±3.44	20.85±2.33	11.68±1.45
AZA	46.75	0.9932	38.25	0.9890	-	-	30.74±3.52	22.27±1.56	-
TAC	-	-	-	-	25.78	0.9878	-	-	18.45±2.12

AZA: Acetazolamide, **TAC:** Tacrine

RESULT AND DISCUSSION

Synthesis

Scheme 1 shows the synthesis of imidazolinone-based sulfonamide derivatives (**3-5**). In the presence of glacial acetic acid, the reaction of 4-(2,4-dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one substituted with various sulfonamide derivatives and sodium acetate resulted in the desired novel compounds (**3–5**). Their chemical structures were validated using spectroscopies such as HRMS, ^{1}H, and ^{13}C NMR.

NMR data confirmed the ring closure of compound 2. The increase of proton integration in the aromatic area and aromatic carbons confirmed that compounds **3** and **4** were obtained starting from compound **2**. Interestingly, the targeted cyclic compound **5** could not be obtained under the same experimental conditions. The cyclic target product did not form in 18 hours when we utilized sulfadiazine by using starting compound **2**; instead, compound **5** was produced given in Scheme 1. According to NMR data, δ 10.43 (s, 1H, NH) and 9.98 (s, 1H, NH) peaks confirmed that the imidazolinone ring was not closed for the compound 5.

Biochemistry

AChE inhibition potential of the new compounds (**3-5**) synthesized in this study is given in Figure 6**E-F** and Table 1. Inhibition type and Ki parameters were defined using Lineweaver-Burk plots. The order of the Ki for compounds (**3-5**) was discovered to be between 11.68±1.45 and 21.71±4.04 nM against AChE (Table 1). Results clearly demonstrate that the Ki values of these compounds are rather close to one another. But the greatest inhibition was found in *N*-(1-(2,4-dimethoxyphenyl)-3-oxo-3-((4-(*N*-(pyrimidine-2-yl)sulfamoyl)phenyl)amino)prop-1-en-1-yl)benzamide (**5**) with low nanomolar Ki value of 11.68±1.45 nM. When compared to the reference compound (Tacrine Ki: 18.45±2.12 nM), compounds (**3-5**) demonstrated close inhibitory capacity based on their Ki values.

New imidazolinone compounds (3-5) were tested towards physiologically significant CA I and II isoforms. The inhibition results and graphs are shown in Figures 6A-6D and Table 1. CA isoenzymes are physiologically important enzymes. Dysfunction of the carbonic anhydrase isoenzyme is typically associated with many diseases such as cancer, glaucoma, epilepsy, osteoporosis, and so on. Therefore, the clinical use of CAIs is critical for treating these disorders. The cytosolic isoform *h*CA I was tested for imidazolinone derivatives (**3**–**5**) and Ki values were calculated in the range of 19.53±1.23–23.61±2.34 nM (Table 1). As a well-known *h*CA I inhibitor, AZA had a Ki of 30.74±3.52 nM. Among the compounds, **4** had the highest inhibition potency (Ki: 19.53±1.23 nM) towards the *h*CA I enzyme.

For *h*CA II, new imidazolinone derivatives (**3**–**5**) had Ki values in the range of 16.49±2.20–25.30±1.47 nM. Compound **3**, with a Ki value of 16.49±2.20 nM against cytosolic CA II, displayed the best inhibitory profile.-In addition, AZA exhibited inhibition potency at 22.27±1.56 nM.

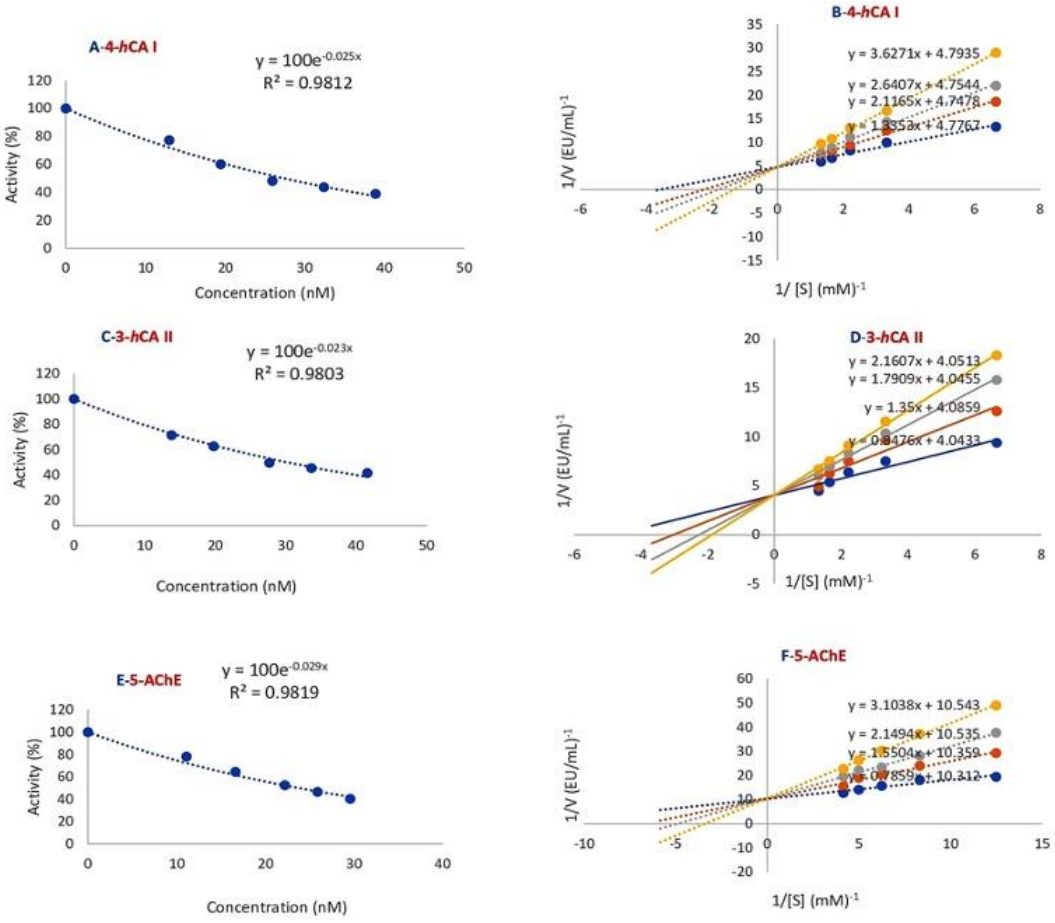


Figure 6. Lineweaver-Burk graphs for the compounds against CA I, II, and AChE enzymes

Lipinski's rule of five (RO5) is used to identify the drug-likeness characteristics of oral medicines [52]. Based on the analysis [53] (Table 2), the following values were determined: logP (lipophilicity, 2.35–3.16), number of H-bond donors (1–3), number of H-bond acceptors (7,8) and molecular weight (463.51–559.59). Lipinski's RO5 was shown to be compatible with compound 4. While the other two compounds (compounds **3** and **5**) were compatible with Lipinski's rule of 4, deviations in molecular weight were observed.

Table 2. Druglikeness properties of compounds **3-5** based on Lipinski's RO5

Compd No	Formula	Molecular Weight (g/mol)	H-bond acceptors	H-bond donors	TPSA	MLog P
3	$C_{25}H_{23}N_5O_5S$	505.55 g/mol	7	3	155.55 Å²	2.35
4	$C_{24}H_{21}N_3O_5S$	463.51 g/mol	7	1	119.67 Å²	2.76
5	$C_{28}H_{25}N_5O_6S$	559.59 g/mol	8	3	156.99 Å²	3.16

Lipinski filter: MW < 500, MlogP < 4.15, N or O <10, NH or OH <5 [52]

In conclusion, in the present research, the new imidazolinone derivatives (**3-5**) have shown effective inhibitory profiles against both *h*CA isoenzymes and the AChE enzyme. In this study, Ki and IC_{50} values were calculated for new compounds (**3-5**) against metabolic enzymes associated with some global disorders such as glaucoma, epilepsy, and Alzheimer's disease, among others. As a result, these substances (**3-5**) showed inhibitory potency in both *h*CA isoenzymes and the AChE enzyme in treating the aforementioned illnesses. Inhibition studies further demonstrated that compounds **4** and **3** have a strong inhibitory impact on *h*CA I and *h*CA II isoenzymes, respectively. In addition, compound **5** has a considerable inhibitory effect on the AChE enzyme. Based on Ki values, it could be concluded that the final compounds **3-5** have more favorable inhibitory potency than intermediates **1** and **2**. So, incorporating benzenesulfonamide moiety and imidazolinone ring in the structure increased inhibition against AChE and CA enzymes. Therefore, these benzenesulfonamide-based compounds could be used as lead compounds in future pharmaceutical research.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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