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FULL PAPER

Synthesis of β-amino acid derivatives and their inhibitory profiles against some metabolic enzymes

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Abstract

Sulfamate and its derivatives have a range of biological activities. One-pot cyclocondensation of alkenes (**1a–i**) with chlorosulfonyl isocyanate generates β-lactams. β-Amino acid derivatives (**2a–i**) from β-lactams were synthesized. Then, these highly reactive compounds were opened with MeOH to produce the corresponding sulfamate derivatives in good yields. The inhibitory effects of the novel sulfamate derivatives were tested on human carbonic anhydrase I and II isoenzymes (hCA I and hCA II), acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and α-glycosidase (α-Gly). Novel sulfamate derivatives showed K_i values in the range of 23.81–42.97 nM against hCA I, 8.95–52.23 nM against hCA II, 8.10–45.51 nM against AChE, 23.16–81.84 nM against BChE, and 14.02–48.68 nM against α-Gly. As a result, the novel sulfamate derivatives had potent inhibitory effects against both isoenzymes. Overall, due to the inhibitory effects of the novel sulfamate derivatives on the tested metabolic enzymes, they are promising drug candidates for the treatment of diseases like glaucoma, epilepsy, leukemia, Alzheimer's disease, and type 2 diabetes mellitus, which are associated with high enzymatic activity of the indicated metabolic enzymes.

KEYWORDS
acetylcholinesterase, carbonic anhydrase, enzyme inhibition, α-glycosidase, β-amino acid

1 | INTRODUCTION

Pharmaceutical companies and organic chemists have shown interest in the potential biological activity of sulfamate and derivatives and their use in organic chemistry.[1,2] Effective methods for the synthesis of sulfamate and their derivatives have always been valuable for organic synthesis and drug discovery. Natural products that include primary sulfamate compounds in their structure are known. A number of sulfamate and its derivatives have been synthesized as potent CA I and II isoenzymes.[3] The primary sulfamate, especially five-ring containing sulfamate-natural products fits according to dictionary of natural products.[4] First, sulfamates were isolated from *Streptomyces* species, which were discovered in the soil microbe *Streptomyces calvus*.[5]

A lot of sulfamate derivatives exhibit strong inhibition of isoleucine and valyl transfer RNA. In this study, we have performed experiments using an equivalent amount of chlorosulfonyl isocyanate; β-amino acid derivatives can be one-pot synthesized from alkenes with high efficiency without any catalysts or additives. We have studied the ideal reaction conditions (Table 1) with high yields of β-amino acid derivatives resulting from reaction of commercially available alkenes with chlorosulfonyl isocyanate (CSI) in dichloromethane at 0°C. Conversion of β-lactams (**A**) to sulfamates **2a–i** required condition for the ring-opening step reaction media. Use of methanol afforded racemic sulfamates (Scheme 1).

The creation of sulfamates with CSI and three pathways has to be noted. The one-step (2+2) cycloaddition of alkene and CSI in similar β-lactam results in a good yield. The two-step process is ring-opening

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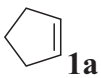
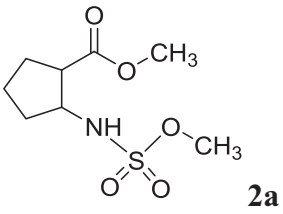
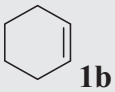
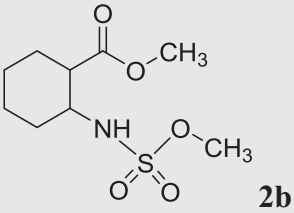
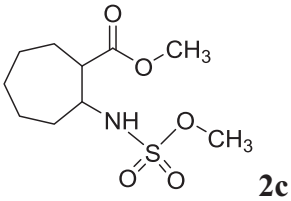
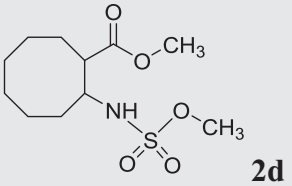
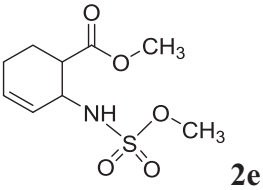
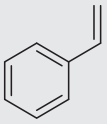
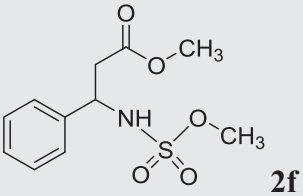
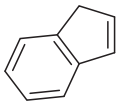
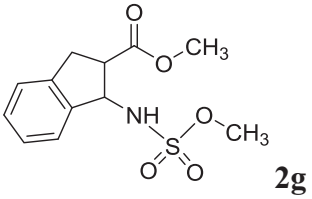
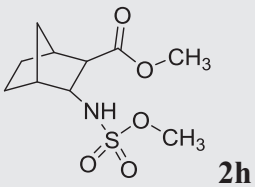
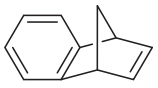
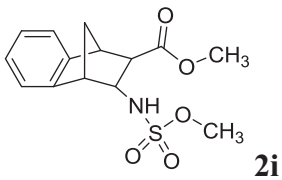
TABLE 1 One-pot synthesis of β-amino acid derivatives (**2a–i**) from alkenes (**1a–i**)

Entry	Substrate	Product	Yield (%)[a]
1	 **1a**	 **2a**	76
2	 **1b**	 **2b**	81
3	 **1c**	 **2c**	80
4	 **1d**	 **2d**	74
5	 **1e**	 **2e**	79
6	 **1f**	 **2f**	88
7	 **1g**	 **2g**	85
8	 **1h**		73

(Continues)

TABLE 1 (Continued)

Entry	Substrate	Product	Yield (%)[a]
		 **2h**	
9	 **1i**	 **2i**	75

[a]Isolated yield of pure materials.

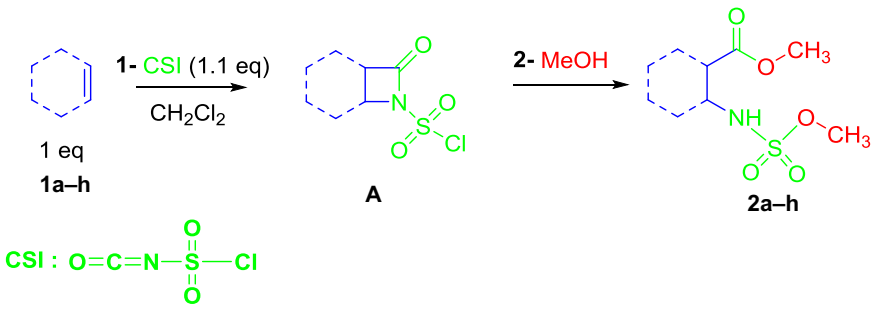
with methanol as a nucleophile and the three operate substitution reaction of sulfamoyl chloride with methanol.

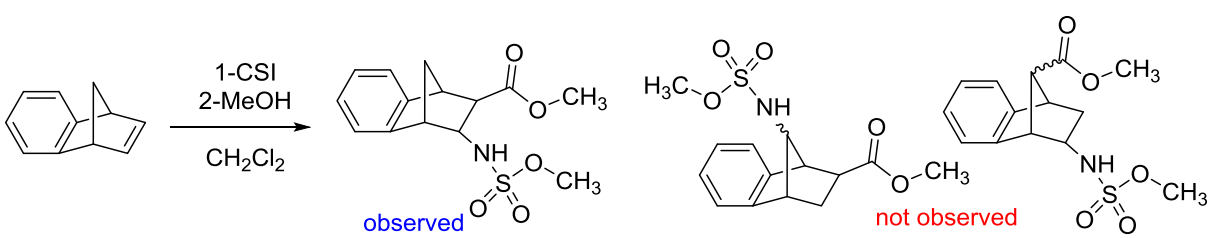
The formation of sulfamate **2i** has a wide range of examples in bicyclic alkene addition of CSI—especially, bicyclic alkene reaction of CSI, which was expected as the nonclassical carbocation rearrangement product. No rearrangement product was observed (Scheme 2).

The sulfamate ($R–OSO_2NH_2$) group is the closest congener and bioisostere to the primary sulfonamide group ($R–SO_2NH_2$).[6] The CA inhibitory properties of sulfamate derivatives are well known.[7] It was reported small molecule CA inhibitors incorporate a primary sulfamate ($–OSO_2NH_2$) as a zinc-binding functional group that blocks enzyme activity by coordinating with catalytic zinc. The most obvious bioisosteres of this group are sulfamates, in which an additional electron-withdrawing atom/group (O or NH, respectively) is directly attached to the sulfamoyl function, generating compounds with the general formula $R–O–SO_2NH_2$.[8] Nowadays, there are a large number of aromatic, heterocyclic, aliphatic and sugar-based sulfamates, which are shown to possess highly effective inhibitory properties against all known mammalian CA isoforms.[9]

Enzymes play a key role in the regulation of the metabolism of all organisms.[10,11] Carbonic anhydrases (CAs; E.C.4.2.1.1) catalyze carbon dioxide (CO_2) and reversibly convert them to bicarbonates (HCO_3^-) and protons (H^+).[12–14] This reaction has a crucial role in some vital physiologic functions linked to the metabolic pathways involved in CO_2. CAs are found in eukaryotic and prokaryotic cells. They are encoded by seven distinct gene families, α-, β-, γ-, δ-, ζ-, η- and θ-CAs.[15–17] Only the α-CA family is found in mammals. In mammals, when CO_2 in the blood plasma passes into red blood cells by diffusion, it is rapidly converted to

SCHEME 1 General procedure synthesis of β-amino acid derivatives





SCHEME 2 Synthesis of methyl-3-((methoxysulfonyl)amino)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylate (**2i**)

carbonic acid by CA enzyme.[18–22] To date, 16 different α-CA isoenzymes have been characterized in mammals by means of their amino acid sequence, catalytic activity, biochemical properties, subcellular localization, and sensitivity to inhibitors and activators. They are responsible for numerous processes in vivo and localized in different tissues.[23] These isoenzymes are grouped as cytoplasmic CAs (CAs I, II, III, VII, and XIII), membrane bound CAs (CAs IV, IX, XII, XIV, and XV), mitochondrial CAs (CA V), secretory CAs (CA VI), and CA-related proteins (CA-RPs: CAs VIII, X, and XI). CA-RPs have not performed CO_2 hydration activity and physiological function.[24,25] Due to these important physiological functions, numerous studies have been carried out on CAs. CAs I and II are the most-studied isoenzymes.[26,27] CA I is expressed in erythrocytes and the gastrointestinal tract, whereas CA II is expressed in almost all tissues. CAs I and II are involved in important metabolic functions such as gas exchange, and ion transport.[28,29] CA inhibitors (CAIs) are mainly used in therapy as diuretics and antiglaucoma agents but some of them also show marked anticonvulsant, antitumor and antiobesity effects.[30] For this purpose, development of novel CAIs is very important.

α-Glycosidase (E.C.3.2.1.20) is released from intestine cells and hydrolyzes oligosaccharides and polysaccharide to monosaccharide units including glucose and fructose in small intestine.[31,32] α-Glycosidase inhibitors (α-GIs) have great importance for controlling of type 2 diabetes mellitus (T2DM) and hyperglycemia in humans.[33,34] α-GIs can reduce the uptake of dietary carbohydrates and repress postprandial hyperglycemia and T2DM. Thus, these α-GIs are endowed with sugar molecules such as compete and moieties with the oligosaccharides for binding to the active site of the enzyme, hence effectively reducing the postprandial glucose levels in T2DM.[35,36]

Alzheimer's disease (AD) is a significant problem for old people worldwide. This disease can affect many aspects of a person's life. Also, there is no cure for AD, but several drugs are employed for the cure.[37,38] For the treatment of AD, one of the most successful methods developed so far is acetylcholinesterase (AChE; E.C.3.1.1.7) inhibition. AChE inhibitors (AChEIs) have been developed as an impact of the cholinergic assumption of cognitive decline.[39] Also, the effectiveness of these treatments has been investigated in a large number of randomized controlled tests between cognitive, global, neuropsychiatric domains, and functional.[40] AChEIs are employed for the treatment of mild-to-moderate AD. These compounds inhibit AChE, which is responsible for the separation of acetylcholine (ACh), a neurotransmitter molecule related to memory function.[41]

In the light of this information, in this study, we investigated the effects of novel sulfamate derivatives (**2a–i**) on hCA I and II isoenzymes, acetylcholinesterase, butyrylcholinesterase, and α-glycosidase enzymes. Also, their inhibition profiles were compared to acetazolamide as a clinically used inhibitor.

2 | RESULTS AND DISCUSSION

The cyclocondensation of alkenes with CSI was efficiently carried out and β-lactams at low temperature were provided without using any additives or catalysts. Then, the reaction mixture was added to methanol (MeOH). MeOH attacks nucleophiles. So, we synthesized β-amino acid derivatives (**2a–i**) with high efficiency (Scheme 3).

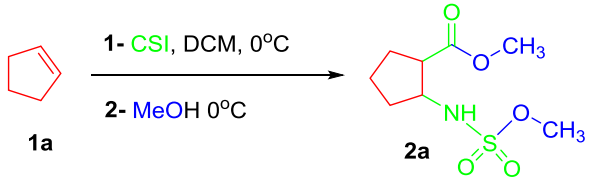
Initially, we examined cyclocondensation of cyclopentene (**1a**) with CSI at 0°C, which afforded the corresponding β-lactams. After this, methyl 2-((methoxysulfonyl)amino)cyclopentane-1-carboxylate (**2a**) yielded β-lactams as intermediate products by the nucleophilic reaction of MeOH in Scheme 2 and in a good yield, as shown in Entry 1, Table 1.

Thus, we achieved one-pot synthesis of β-amino acid derivatives from various alkenes in mild condition without any catalysts or additives by using CSI (Table 1). As reported in the literature,[42] cyclocondensations were regioselective, and formed selective single-regioisomer products (**2e–g**). β-Amino acid derivatives are transformations of β-lactams in the one-pot with MeOH.

2.1 | Biochemical studies

Human CA inhibition has been the subject by investigations since the discovery of the biological importance of CA in living organisms.[43] In recent years, many novel compounds and their derivatives have been arising as main classes of hCA inhibitors, including hCA I and II isoenzymes.[44–46] Considering the fact that novel sulfamate derivatives (**2a–i**) are found to be effective CA inhibitors, we synthesized novel sulfamate derivatives (**2a–i**) to explore their possible hCAs I and II, AChE, BChE, and α-glycosidase inhibition effects. The inhibition data are summarized in Table 2. For evaluation of the effect of novel sulfamate derivatives (**2a–i**) on the indicated metabolic enzymes, the following results have been depicted.

The physiologically relevant hCA I is found at the highest level in erythrocytes and is also expressed in normal colorectal mucosa.[47] As for CA I, novel sulfamate derivatives (**2a–i**) showed K_i values in the low nanomolar range. K_i constant refers to the binding affinity of the inhibitor to the enzyme. Small K_i value indicates that the inhibitor is bound to the enzyme with strong affinity.[48] To determine the inhibition types and K_i constants of novel sulfamate derivatives (**2a–i**), Lineweaver–Burk graphs were drawn.[49] Novel sulfamate derivatives (**2a–i**) demonstrated low nanomolar inhibition levels on CA I isoenzyme. The K_i values of novel sulfamate derivatives (**2a–i**) were found between 23.81 and 42.97 nM for hCA I (Table 2). Also, methyl 2-((methoxysulfonyl)amino)cyclopentane-1-carboxylate (**2a**), which contains cyclopentene moiety, had a strong inhibition effect against hCA I isoenzyme (K_i: 23.81 ± 8.43 nM). On the contrary, acetazolamide (AZA), which is used as a reference inhibitor, had K_i values 141.02 ± 50.84 for hCA I isoenzyme. AZA, as a sulfonamide-based drug, is widely used as an excellent inhibitor of CA II isoenzyme. It



SCHEME 3 Synthesis of methyl 2-((methoxysulfonyl)amino)-cyclopentane-1-carboxylate (**2a**)

TABLE 2 IC_{50} and K_i values of novel sulfamate derivatives (**2a–i**) against hCAs I and II, α-glycosidase, AChE, and BChE enzymes

Compound	IC_{50} (nM)								K_i (nM)							
	hCA I	r^2	hCA II	r^2	AChE	r^2	BChE	r^2	α-Gly	r^2	hCA I	hCA II	AChE	BChE	α-Gly
2a	43.86	0.9667	12.72	0.9954	18.48	0.9859	21.86	0.9633	74.36	0.9974	23.81 ± 8.43	11.42 ± 2.01	22.55 ± 8.67	23.16 ± 7.72	16.48 ± 3.83
2b	40.53	0.9798	28.52	0.9666	23.98	0.9824	52.11	0.9817	29.36	0.9836	42.97 ± 14.58	17.35 ± 2.30	45.51 ± 2.01	30.84 ± 2.54	14.02 ± 3.73
2c	56.34	0.9765	24.23	0.9871	28.99	0.9756	42.78	0.9815	25.20	0.9628	25.25 ± 8.73	15.01 ± 4.18	42.94 ± 2.23	62.88 ± 3.45	16.46 ± 1.43
2d	55.88	0.9746	18.09	0.9715	19.09	0.9758	50.22	0.9693	28.99	0.9597	28.35 ± 8.12	8.95 ± 0.49	26.54 ± 6.63	56.45 ± 11.76	48.68 ± 0.24
2e	40.29	0.9763	30.13	0.9882	33.97	0.9635	44.71	0.9537	24.93	0.9803	41.55 ± 10.69	15.12 ± 5.72	14.74 ± 2.41	72.84 ± 24.21	30.47 ± 5.64
2f	41.01	0.9873	47.14	0.9678	33.48	0.9745	34.14	0.9864	17.91	0.9827	42.91 ± 2.11	12.99 ± 3.15	14.43 ± 2.24	28.35 ± 0.87	19.10 ± 7.75
2g	46.20	0.9884	35.18	0.9672	25.02	0.9681	45.00	0.9648	23.81	0.9626	25.56 ± 2.32	16.91 ± 0.71	11.28 ± 2.26	61.40 ± 4.31	14.19 ± 1.81
2h	35.54	0.9896	22.35	0.9814	29.74	0.9706	52.11	0.9625	20.38	0.9825	32.68 ± 9.47	52.23 ± 15.48	15.98 ± 3.82	81.84 ± 24.12	21.42 ± 7.66
2i	36.67	0.9824	22.43	0.9916	23.18	0.9724	35.18	0.9863	24.75	0.9714	37.13 ± 13.87	18.80 ± 3.41	8.10 ± 0.97	47.10 ± 14.04	17.33 ± 0.93
AZA[a]	113.79	0.9932	31.79	0.9816	–	–	–	–	–	–	141.02 ± 50.84	22.17 ± 0.65	–	–	–
TAC[b]	–	–	5.97	0.9706	8.37	0.9846	–	–	–	–	5.99 ± 1.79	2.43 ± 0.92	–	–	–

Abbreviations: AChE, acetylcholinesterase; AZA, acetazolamide; BChE, butyrylcholinesterase; hCA I, human carbonic anhydrase I isoenzyme; hCA II, human carbonic anhydrase II isoenzyme; TAC, tacrine; α-Gly, α-glycosidase.

[a]AZA was used as a standard inhibitor for both hCA I and II isoenzymes.

[b]TAC was used as a standard inhibitor for AChE and BChE enzymes.

exhibits minimal toxicity and provides good pharmacokinetic properties. However, this drug still exhibits a number of undesired side effects. It causes an increase in the volume of urine, finally leading to an increased release of sodium and potassium ions[50]; its application might lead to fatigue or a numbness of extremities.[23,51,52] All of these undesired side effects are a result of the nonspecific inhibition of CAs. These results clearly showed that the novel sulfamate derivatives (**2a–i**) had a stronger inhibitory effect than AZA against hCA I isoenzyme (Table 2). Also, the selectivity index values of the novel sulfamate derivatives (**2a–i**) are given in Table 3. Recently, it was proved that eight sulfamates, derived from menthol, inhibited hCA I isoenzyme in the range of 34.37 ± 8.17 to 53.40 ± 10.61 nM.[53] In previous studies, it was found that some novel Tris-chalcones (K_i: 9.9–39.5 nM),[54] new phenolic Mannich bases with piperazines (K_i: 0.209–0.484 nM),[55] bromophenol derivatives (K_i: 7.8–58.3 nM),[56] and novel pyrazoline derivatives (K_i: 17.4–40.7 nM)[57] had powerful inhibition effects against hCA I isoenzyme, which were found to be at the highest level in erythrocytes.

CA II belongs to one of the most important enzyme groups of the human body. It is a well-studied isozyme from the CA family. CA II isoenzyme is also involved in the primary transport mechanism of Na into the eye. As a consequence of this transport, it is responsible for the regulation of the intraocular pressure (IOP).[58] Thus, inhibition of CA II decreases an elevated IOP usually accompanying glaucoma. This high IOP damages the eye's optic nerve. The treatment of glaucoma was a major reason to have a closer look at CA II inhibitors.[59] Also, another important pharmaceutical application of CA II inhibitors is their usage for the treatment of bone loss, which is most often observed during postmenopausal osteoporosis.[60] Most of the inhibitors for CA II are sulfamates that bind directly to the metal center in the active site of hCA II, which is the physiologically dominant and highly active cytosolic isoform.[9,26,34] As shown in Table 2, the inhibition profile of the considered novel sulfamate derivatives (**2a–i**) against cytosolic dominant hCA II revealed to be quite similar to that shown toward CA II. They demonstrated K_i values between 8.95 ± 0.49 and 52.23 ± 15.48 nM. On the contrary, AZA, which is used to treat glaucoma, altitude sickness, epilepsy, periodic paralysis, heart failure, and idiopathic intracranial hypertension,[61] has a K_i value of 22.17 ± 0.65 nM against hCA II. In our recent studies, it was found that eight sulfamates derived from menthol inhibited hCA II isoenzyme in the range of 12.91 ± 4.57 to 38.67 ± 6.22 nM.[26] Recently, it was found that some novel Tris-chalcones (K_i: 3.1–20.1 nM),[54] new phenolic Mannich bases with piperazines (K_i: 0.342–0.526 nM),[55] bromophenol derivatives (K_i: 43.1–150.2 nM),[56] and novel pyrazoline derivatives (K_i: 16.1–55.2 nM)[57] had marked inhibitory effects against hCA II isoenzyme, which is responsible for the regulation of IOP.

AChE and BChE inhibition properties of the novel sulfamate derivatives (**2a–i**) were recorded according to the procedure of Ellman et al.[62] as described previously.[63] Novel sulfamate derivatives (**2a–i**) had K_i values ranging from 8.10 ± 0.97 to 45.51 ± 2.01 nM for AChE and 23.16 ± 7.72 to 881.84 ± 24.12 nM for BChE. On the contrary, tacrine had K_i values of 5.99 ± 1.79 and 2.43 ± 0.92 nM toward both cholinergic

AChE and BChE, respectively. All evaluated novel sulfamate derivatives (**2a–i**) showed effective inhibition against both cholinergic enzymes, but methyl-3-((methoxysulfonyl)amino)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylate (**2i**), which had (1*R*,4*S*)1,4-dihydro-1,4-methanonaphthalene, showed perfect inhibition effect against AChE (K_i: 8.10 ± 0.97 nM). Also, selectivity index values of novel sulfamate derivatives (**2a–i**) are given in Table 3. On the contrary, methyl 2-((methoxysulfonyl)amino)cyclopentane-1-carboxylate (**2a**), which contains cyclopentene moiety, demonstrated the best inhibition effect against BChE (K_i: 23.16 ± 7.72 nM) enzymes (Table 2). Also, it was found that some novel Tris-chalcones (K_i: 3.1–20.1 nM on AChE, and 4.9–14.7 nM on BChE),[54] novel Tris-chalcones (K_i: 9.9–39.5 nM),[55] bromophenol derivatives (K_i: 159.6–924.2 nM against AChE),[56] and novel pyrazoline derivatives (K_i: 48.2–84.1 nM on AChE)[57] effectively inhibited both cholinergic enzymes.

Finally, for the α-glycosidase, which is present on cells lining the intestine, hydrolyzing monosaccharides are absorbed through the intestine, and novel sulfamate derivatives (**2a–i**) exhibit K_i values between 14.02 ± 3.73 and 48.68 ± 0.24 nM (Table 2). The results obtained from α-glycosidase assay showed that all novel sulfamate derivatives (**2a–i**) had effective α-glycosidase inhibition effects than that of acarbose (IC_{50}: 22.800 mM) as a standard α-glycosidase inhibitor.[64] Also, highly effective K_i values were obtained for methyl 2-((methoxysulfonyl)amino)cyclohexane-1-carboxylate (**2b**) bearing cyclohexene moiety (K_i value of 14.02 ± 3.73 nM). The inhibition of α-glycosidase had great importance in treating and preventing diabetes, postprandial glucose amounts, and hyperglycemia.[65–68] In a recent study, it was reported that some novel Tris-chalcones had effective inhibition profiles against α-glycosidase, with hydrolysis of glycosidic bonds in complex sugars, with K_i values in the range of 3.9–22.4 nM.[54]

3 | CONCLUSION

In summary, starting from the appropriate reagents, the new β-amino acid derivatives (**2a–i**) were synthesized. One-pot synthesized β-amino acid derivatives may be important for organic synthesis and biological purposes. The inhibitory effects of some sulfonamides on hCA I and II isoenzymes, AChE, BChE, and α-glycosidase were evaluated together. The sulfonamides we used in our study showed inhibition effects on hCA I and II isoenzymes, AChE, BChE and α-glycosidase activities at low concentrations. We believe that these results may be useful in the synthesis of new CA isoenzyme inhibitors and in the development of drugs for the treatment of some diseases. Especially, the new β-amino acid derivatives (**2a–i**) can be candidates for anticholinergic, antiepileptic, antiglaucoma, and antidiabetic applications. Furthermore, it is thought that there will be a need for clinical studies before application is recommended.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General remarks

All chemicals and solvents are commercially available. Infrared (IR) spectra are obtained from solutions in 0.1-mm cells and in dichloromethane (DCM) with a Perkin–Elmer spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra (see the Supporting Information) are recorded on Bruker and Varian spectrometers at 400 and 100 MHz, respectively, and NMR shifts are presented as δ in ppm. Elemental analyses are performed on LECO CHNS-932 apparatus. All column chromatography is performed on silica gel (60-mesh; Merck).

The InChI codes of the investigated compounds are provided as Supporting Information.

4.1.2 | General procedure for the synthesis of β-amino acid derivatives

Alkene (1 eq) was dissolved in 20 ml dichloromethane. The reaction mixture was cooled to 0°C and CSI (1.1 eq) was added, and resulting solution was stirred for 2 hr. Then, the reaction mixture was added to MeOH and stirred for 1 hr. The reaction mixture was extracted with

TABLE 3 Selectivity index values of novel sulfamate derivatives (**2a–i**)

Compound	K_i(hCA II)/K_i(hCA I)	K_i(AZA)/K_i(hCA I)	K_i(AZA)/K_i(hCA II)	K_i(AChE II)/K_i(BChE)	K_i(TAC)/K_i(AChE)	K_i(TAC)/K_i(BChE)
2a	0.479	5.922	1.941	0.973	0.265	0.105
2b	0.403	2.281	1.277	1.475	0.131	0.079
2c	0.595	5.584	1.477	0.682	0.139	0.038
2d	0.316	4.973	2.478	0.470	0.225	0.043
2e	0.364	3.393	1.466	0.202	0.406	0.033
2f	0.302	3.285	1.706	0.508	0.415	0.086
2g	0.612	5.516	1.311	0.183	0.531	0.040
2h	1.598	4.314	0.424	0.195	0.374	0.029
2i	0.506	3.797	1.179	0.172	0.740	0.520

Abbreviations: AChE, acetylcholinesterase; AZA, acetazolamide; BChE, butyrylcholinesterase; hCA I, human carbonic anhydrase I isoenzyme; hCA II, human carbonic anhydrase II isoenzyme; TAC, tacrine.

DCM. The organic phase was dried over sodium sulfate and concentrated. Purification was performed through thin layer and column chromatography on silica gel.

*Methyl 2-((methoxysulfonyl)amino)cyclopentane-1-carboxylate (**2a**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.47 (bd, 1H, *J*: 8.4 Hz), 3.86–3.92 (m, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.05–2.99 (m, 1H), and 2.06–1.55 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 175.1, 57.0, 56.4, 52.2, 46.3, 32,1, 28.3, and 21.8; IR (CH_2Cl_2, cm^{-1}): 3,559, 3,291, 2,956, 1,716, 1,438, 1,362, 1,176, and 998; Elemental analysis: C, 40.50; H, 6.37; N, 5.90; S, 13.51. Found: 40.58; H, 6.42; N, 5.54; S, 13.28.

*Methyl 2-((methoxysulfonyl)amino)cyclohexane-1-carboxylate (**2b**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.62 (bs, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.55–3.53 (m, 1H), 2.95–2.93 (m, 1H), and 2.16–1.20 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.5, 53.7, 52.1, 44.9, 29.9, 29.7, 27.6, 24.3, and 22.5; IR (CH_2Cl_2, cm^{-1}): 3,606, 3,309, 2,951, 2,862, 1,731, 1,454, 1,367, 1,178, and 997; Elemental analysis: C, 43.02; H, 6.82; N, 5.57; S, 12.76. Found: 43.32; H, 6.51; N, 5.43; S, 12.48.

*Methyl 2-((methoxysulfonyl)amino)cycloheptane-1-carboxylate (**2c**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.27 (bd, 1H, *J*: 8.1 Hz) 3.81 (s, 3H), 3.73 (s, 3H), 3.65–3.63 (m, 1H), 3.07–3.05 (m, 1H), and 1.98–1.25 (m, 10H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.7, 56.9, 48.1, 33.4, 29.9, 27.0, 26.9, 24.8, and 24.4. IR (CH_2Cl_2, cm^{-1}): 3,542, 3,302, 2,924, 2,855, 1,723, 1,435, 1,360, 1,169, and 1,001; Elemental analysis: C, 45.27; H, 7.22; N, 5.28; S, 12.08. Found: 45.58; H, 7.40; N, 5.76; S, 12.23.

*Methyl 2-((methoxysulfonyl)amino)cyclooctane-1-carboxylate (**2d**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.21 (bs, 1H, *J*: 8.0 Hz), 3.86–3.83 (m, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 2.98–2.94 (m, 1H), and 1.98–1.54 (m, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.9, 54.3, 52.2, 52.1, 47.5, 32.4, 27.3, 26.4, 26.0, 25.1, and 24.7; IR (CH_2Cl_2, cm^{-1}): 3,428, 2,923, 2,854, 1,722, 1,643, 1,436, 1,358, 1,174, and 998; Elemental analysis: C, 47.30; H, 7.58; N, 5.01; S, 11.48. Found: 47.62; H, 7.66; N, 4.92; S, 11.25.

*Methyl 2-((methoxysulfonyl)amino)cyclohex-3-ene-1-carboxylate (**2e**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.87–5.83 (m, 1H, A part of AB system), 5.79–5.75 (m, 1H, B part of AB system), 5.36 (bd, 1H, *J*: 9.7 Hz), 4.27–4.23 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.02–2.97 (m, 1H), and 2.07–1.92 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 173.4, 130.4, 126.7, 56.4, 51.9, 50.8, 43.1, 22.8, and 22.5; IR (CH_2Cl_2, cm^{-1}): 3,509, 3,284, 2,954, 2,848, 1,726, 1,436, 1,359, 1,222, 1,179, and 996; Elemental analysis: C, 43.36; H, 6.07; N, 5.62; S, 12.86. Found: 43.18; H, 6.32; N, 5.34; S, 13.01.

*Methyl 3-((methoxysulfonyl)amino)-3-phenylpropanoate (**2f**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.29–7.39 (m, 5H), 5.79 (bd, 1H, NH, *J*: 6.7 Hz), 4.85 (dd, 2H, *J*: 15.8, 8.12 Hz), 3.66 (s, 3H), 3.64 (s, 3H), and 2.95 (dd, 1H, *J*: 2.2, 5.86 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.46, 139.5, 129.1, 128.5, 126.6, 56.7, 54.9, 52.3, and 40.6; IR (CH_2Cl_2, cm^{-1}): 3,428, 2,924, 2,853, 2,104, 1,644, 1,456, 1,365, 1,174, and 1,001; Elemental analysis: C, 48.34; H, 5.53; N, 5.13; S, 11.73. Found: 48.02; H, 5.42; N, 5.38; S, 11.96.

*Methyl 1-((methoxysulfonyl)amino)-2,3-dihydro-1H-indene-2-carboxylate (**2g**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.47–7.45 (m, 1H), 7.31–7.21 (m, 3H), 5.55 (bd, 1H, *J*: 9.5 Hz), 5.18–5.14 (m, 1H), 3.85 (s, 3H), 3.73 (s, 3H), and 3.68–3.60 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 173.7, 140.4, 140.3, 129.2, 127.8, 125.1, 124.5, 60.2, 52.4, 48.1, 34.5, and 29.9; IR (CH_2Cl_2, cm^{-1}): 3,418, 2,953, 2,848, 1,720, 1,644, 1,457, 1,364, 1,179, and 982; Elemental analysis: C, 50.52; H, 5.30; N, 4.91; S, 11.24. Found: 50.34; H, 5.28; N, 4.67; S, 11.28.

*Methyl 3-((methoxysulfonyl)amino)bicyclo[2.2.1]heptane-2-carboxylate (**2h**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 5.58 (bd, 1H, *J*: 8.4 Hz), 3.78 (s, 3H), 3.68 (s, 3H), 3.64–3.60 (m, 1H), 2.74 (d, 1H, *J*: 8.4 Hz), 2.43 (m, 1H), 2.37 (m, 1H), 1.86–1.83 (m, 1H), 1.60–1.52 (m, 2H), and 1.27–1.19 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.0, 59.2, 56.4, 52.2, 51.7, 42.7, 41.4, 34.5, 28.8, and 26.4; IR (CH_2Cl_2, cm^{-1}): 3,457, 3,289, 2,256, 2,129, 1,658, 1,360, 1,024, and 1,003; Elemental analysis: C, 45.62; H, 6.51; N, 5.32; S, 12.18. Found: 45.76; H, 6.45; N, 5.61; S, 12.01.

*Methyl 3-((methoxysulfonyl)amino)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylate (**2i**)*
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.29–7.25 (m, 1H), 7.19–7.11 (m, 3H), 5.76 (bd, 1H, NH, *J*: 9.4 Hz), 3.83 (s, 3H), 3.77 (s, 3H), 3.73–3.71 (m, 1H), 3.47 (s, 2H), 2.81 (d, 1H, *J*: 8.1 Hz), 2.30 (d, 1H, *J*: 9.8 Hz), and 1.94 (d, 1H, *J*: 9.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.3, 146.8, 145.1, 127.2, 127.0, 122.7, 121.2, 57.6, 52.7, 50.4, 50.3, 48.5, 48.3, 48.2, and 44.9; IR (CH_2Cl_2, cm^{-1}): 3,427, 3,267, 2,255, 2,128, 1,658, 1,456, 1,236, and 1,027; Elemental analysis: C, 54.01; H, 5.50; N, 4.50; S, 10.30. Found: C, 54.24; H, 5.73; N, 4.35; S, 10.04.

4.2 | Biochemical studies

4.2.1 | CA inhibition studies

In this study, both hCA I and II isoenzymes were purified by Sepharose-4B-L-tyrosine-sulfanilamide affinity chromatography.[69,70] It was used as an affinity matrix for selective retention of both hCA isoenzymes.[71] The activity of both hCA isoenzymes was spectrophotometrically determined according to Verpoorte et al.[72] as described previously in details.[73] *p*-Nitrophenylacetate (PNA) was used as a substrate and transformed to *p*-nitrophenolate ions.[74] One enzyme unit is accepted as the amount of CA, which had absorbance change at 348 nm of PNA to PNP (*p*-nitrophenolate) over a period of 3 min at 25°C.[75,76] The inhibition parameters of each sulfamate derivatives (**2a**–**i**) and an activity (%; novel sulfamate derivatives) graph was drawn. From these graphs, IC_{50} values for each sulfamate derivatives (**2a**–**i**) were determined. Also, for calculation of K_i values, three different novel sulfamate derivatives (**2a**–**i**) concentrations were used. Then, Lineweaver–Burk graphs were drawn according

to these measurement results. K_i values for novel sulfamate derivatives (**2a–i**) were determined from Lineweaver–Burk graphs[77] as described previously in details.[78,79]

Protein quantity during the purification stages was estimated according to the Bradford technique.[80] Bovine serum albumin was used as the standard protein.[81] Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used for visualizing both isoenzymes[82] and described in previous studies.[83,84]

4.2.2 | AChE/BChHE inhibition studies

The inhibitory effect of novel sulfamate derivatives (**2a–i**) on AChE/BChE activities was performed according to Ellman's method[62] as described previously.[85] Acetylthiocholine iodide/butrylcholine iodide (AChI/BChI) was used as substrate for both cholinergic reactions. In brief, an aliquot (100 μl) of Tris/HCl buffer (1.0 M, pH 8.0) and different concentration of sample solutions (10–30 μg/ml) were added to 50 μl of AChE/BChE enzymes solution (5.32×10^{-3} EU). The solutions were incubated at 20°C for 10 min. An aliquot (0.5 mM, 50 μl) of DTNB (5,5′-dithio-bis(2-nitro-benzoic) acid) and AChI/BChI were added to incubation mixture and enzymatic reactions were initiated. AChE/BChE activities were spectrophotometrically determined at 412 nm.[86]

4.2.3 | α-Glycosidase inhibition studies

α-Glycosidase's inhibition effect of novel sulfamate derivatives (**2a–i**) was evaluated according to the method of Tao et al.[64] First, phosphate buffer (pH 7.4, 75 μl) was mixed with 5 μl of the sample and α-glycosidase enzyme solution (20 μl), which was prepared in phosphate buffer (0.15 U/ml, pH 7.4). After preincubation, 50 μl of *p*-nitrophenyl-D-glycopyranoside (*p*-NPG) in phosphate buffer (5 mM, pH 7.4) was added, and the solution was reincubated at 37°C. The absorbance of mixtures was recorded at 405 nm. For the determination of K_i values, three different novel sulfamate derivatives (**2a–i**) concentrations were used. Then, the Lineweaver–Burk graphs were drawn.[77]

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REFERENCES

[1] J. Mittendorf, F. Kunisch., M. Matzke, H. C. Militzer, A. Schmidt, W. Schönfeld, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433.
[2] M. Nivsarkar, D. Thavaselvam, S. Prasanna, M. Sharma, M. P. Kaushik, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1371.
[3] F. Abbate, C. T. Supuran, A. Scozzafava, P. Orioli, M. T. Stubbs, G. Klebe, *J. Med. Chem.* **2002**, *45*, 3583.
[4] P. Mujumdar, S. A. Poulsen, *J. Nat. Prod.* **2015**, *78*, 1470.
[5] R. I. Hewitt, A. R. Gumble, L. H. Taylor, W. S. Wallace, *Antibiot. Annu.* **1957**, 722.
[6] F. Carta, C. T. Supuran, A. Scozzafava, *Fut. Med. Chem.* **2014**, *6*, 1149.
[7] A. Nocentini, D. Moi, G. Balboni, S. Salvadori, V. Onnis, C. T. Supuran, *Bioorg. Chem.* **2018**, *77*, 633.
[8] V. Alterio, A. Di Fiore, K. D'Ambrosio, C. T. Supuran, G. De Simone, *Chem. Rev.* **2012**, *112*, 4421.
[9] C. T. Supuran, *Nat. Rev. Drug Discov.* **2008**, *7*, 168.
[10] C. Caglayan, Y. Demir, S. Kucukler, P. Taslimi, F. M. Kandemir, İ. Gulçin, *J. Food Biochem.* **2019**, *43*, e12720.
[11] F. Turkan, A. Cetin, P. Taslimi, M. Karaman, İ. Gulçin, *Bioorg. Chem.* **2019**, *86*, 420.
[12] K. Kucukoglu, H. İ. Gul, P. Taslimi, İ. Gulcin, C. T. Supuran, *Bioorg. Chem.* **2019**, *86*, 316.
[13] F. Erdemir, D. B. Celepci, A. Aktaş, Y. Gök, R. Kaya, P. Taslimi, Y. Demir, İ. Gulçin, *Bioorg. Chem.* **2019**, *91*, 103134.
[14] S. Burmaoglu, A. O. Yilmaz, M. F. Polat, R. Kaya, İ. Gulcin, O. Algul, *Bioorg. Chem.* **2019**, *85*, 191.
[15] C. Bayrak, P. Taslimi, H. S. Karaman, İ. Gulcin, A. Menzek, *Bioorg. Chem.* **2019**, *85*, 128.
[16] Ş. Aras Hisar, O. Hisar, Ş. Beydemir, İ. Gülçin, T. Yanik, *Acta Vet. Hung.* **2004**, *52*, 413.
[17] D. Ozmen Ozgun, H. İ. Gul, C. Yamali, H. Sakagami, İ. Gulcin, M. Sukuroglu, C. T. Supuran, *Bioorg. Chem.* **2019**, *84*, 511.
[18] İ. Gülçin, Ş. Beydemir, M. E. Büyükokuroğlu, *Biol. Pharm. Bull.* **2004**, *27*, 613.
[19] S. Bayindir, C. Caglayan, M. Karaman, İ. Gülcin, *Bioorg. Chem.* **2019**, *90*, 103096.
[20] O. Hisar, Ş. Aras Hisar, T. Yanık, *Turk. J. Vet. Anim. Sci.* **2005**, *29*, 1081.
[21] I. Gülçin, Ş. Beydemir, M. E. Büyükokuroğlu, *Biol. Pharm. Bull.* **2004**, *27*, 613.
[22] O. Hisar, Ş. Beydemir, I. Gülçin, Ö. İ. Küfrevioğlu, C. T. Supuran, *J. Enzyme Inhib. Med. Chem.* **2008**, *20*, 35.
[23] C. T. Supuran, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3467.
[24] S. Ökten, M. Ekiz, Ü. M. Koçyiğit, A. Tutar, I. Çelik, M. Akkurt, F. Gökalp, P. Taslimi, I. Gülçin, *J. Mol. Struct.* **2019**, *1175*, 906.
[25] A. Biçer, P. Taslimi, G. Yakalı, I. Gülçin, M. Serdar Gültekin, G. Turgut Cin, *Bioorg. Chem.* **2019**, *82*, 393.
[26] S. Daryadel, U. Atmaca, P. Taslimi, I. Gülçin, M. Çelik, *Arch. Pharm. Chem. Life Sci.* **2018**, *351*, e1800209.
[27] T. A. Çoban, Ş. Beydemir, İ. Gülçin, D. Ekinci, *Biol. Pharm. Bull.* **2007**, *30*, 2257.
[28] F. Turkan, A. Cetin, P. Taslimi, İ. Gulçin, *Arch. Pharm. Chem. Life Sci.* **2018**, *351*, e1800200.
[29] M. Şentürk, İ. Gülçin, A. Daştan, Ö. İrfan Küfrevioğlu, C. T. Supuran, *Bioorg. Med. Chem.* **2009**, *17*, 3207.
[30] A. Scozzafava, M. Passaponti, C. T. Supuran, I. Gülçin, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 586.
[31] I. Gulçin, P. Taslimi, A. Aygün, N. Sadeghian, E. Bastem, O. I. Kufrevioglu, F. Turkan, F. Şen, *Int. J. Biol. Macromol.* **2018**, *119*, 741.
[32] P. Taslimi, H. E. Aslan, Y. Demir, N. Oztaskin, A. Maraş, I. Gulçin, S. Beydemir, S. Goksu, *Int. J. Bio. Macromol.* **2018**, *119*, 857.
[33] G. Gondolova, P. Taslimi, A. Medjidov, V. Farzaliyev, A. Sujayev, M. Huseynova, O. Şahin, B. Yalçın, F. Turkan, I. Gulçin, *J. Biochem. Mol. Toxicol.* **2018**, *32*, e22197.
[34] Y. Demir, P. Taslimi, M. S. Ozaslan, N. Oztaskin, Y. Çetinkaya, İ. Gulçin, Ş. Beydemir, S. Goksu, *Arch. Pharm. Chem. Life Sci.* **2018**, *351*, e1800263.
[35] G. Maharramova, P. Taslimi, A. Sujayev, V. Farzaliyev, L. Durmaz, İ. Gulçin, *J. Biochem. Mol. Toxicol.* **2018**, *32*, e22221.

[36] A. Aktaş, D. Barut Celepci, R. Kaya, P. Taslimi, Y. Gök, M. Aygün, İ. Gülçin, *Polyhedron* **2019**, *159*, 345.
[37] N. Eruygur, U. M. Koçyiğit, P. Taslimi, M. Ataş, M. Tekin, İ. Gülçin, *S. Afr. J. Bot.* **2019**, *120*, 141.
[38] B. Kuzu, M. Tan, P. Taslimi, İ. Gülçin, M. Taşpınar, N. Menges, *Bioorg. Chem.* **2019**, *86*, 187.
[39] E. Bursal, A. Aras, Ö. Kılıç, P. Taslimi, A. C. Gören, İ. Gülçin, *J. Food Biochem.* **2019**, *43*, e12776.
[40] N. Öztaşkın, R. Kaya, A. Maraş, E. Şahin, İ. Gülcin, S. Göksu, *Bioorg. Chem.* **2019**, *87*, 91.
[41] F. Türkan, Z. Huyut, P. Taslimi, İ. Gülçin, *Arch. Physiol. Biochem.* **2019**, *125*, 12.
[42] E. Forró, F. Fülöp, *Tetrahedron: Asymmetry* **2004**, *15*, 2875.
[43] A. Scozzafava, M. Passaponti, C. T. Supuran, I. Gülçin, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 586.
[44] M. Boztaş, Y. Çetinkaya, M. Topal, İ. Gülçin, A. Menzek, E. Şahin, M. Tanc, C. T. Supuran, *J. Med. Chem.* **2015**, *58*, 640.
[45] A. Yıldırım, U. Atmaca, A. Keskin, M. Topal, M. Çelik, I. Gülçin, C. T. Supuran, *Bioorg. Med. Chem.* **2015**, *23*, 2598.
[46] B. Aydin, I. Gulcin, S. H. Alwasel, *Int. J. Food Prop.* **2015**, *18*, 2735.
[47] A. Akıncıoğlu, H. Akıncıoğlu, I. Gülçin, S. Durdagi, C. T. Supuran, S. Göksu, *Bioorg. Med. Chem.* **2015**, *23*, 3592.
[48] N. Öztaşkın, Y. Çetinkaya, P. Taslimi, S. Göksu, İ. Gülçin, *Bioorg. Chem.* **2015**, *60*, 49.
[49] A. Scozzafava, P. Kalın, C. T. Supuran, İ. Gülçin, S. H. Alwasel, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 941.
[50] G. Splendiani, S. Condo, G. Ital, *J. Ital. Nefrol.* **2006**, *23*, 74.
[51] B. Arabaci, I. Gulcin, S. Alwasel, *Molecules* **2014**, *19*, 10103.
[52] S. Göksu, A. Naderi, Y. Akbaba, P. Kalın, A. Akıncıoğlu, I. Gülçin, S. Durdagi, R. E. Salmas, *Bioorg. Chem.* **2014**, *56*, 75.
[53] H. Göçer, A. Akincioğlu, S. Göksu, I. Gülçin, C. T. Supuran, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 316.
[54] S. Burmaoğlu, A. O. Yılmaz, M. F. Polat, R. Kaya, İ. Gülçin, Ö. Algül, *Arch. Physiol. Biochem.* **2019**, *43*, e12908.
[55] H. İ. Gul, M. Tugrak, M. Gul, S. Mazlumoglu, H. Sakagami, İ. Gulcin, C. T. Supuran, *Bioorg. Chem.* **2019**, *90*, 103057.
[56] M. Boztas, P. Taslimi, M. A. Yavari, İ. Gulcin, E. Sahin, A. Menzek, *Bioorg. Chem.* **2019**, *89*, 103017.
[57] F. Turkan, A. Cetin, P. Taslimi, H. S. Karaman, İ. Gulçin, *Arch. Pharm Chem. Life Sci.* **2019**, *352*, e1800359.
[58] P. J. Wistrand, M. Schenholm, G. Lonnerholm, *Invest. Ophthalmol. Vis. Sci.* **1986**, *27*, 419.
[59] S. Schwarz, S. Sommerwerk, S. D. Lucas, L. Heller, R. Csuk, *Eur. J. Med. Chem.* **2014**, *86*, 95.
[60] A. D. Kenny, *SAAS Bull. Biochem. Biotechnol.* **1991**, *4*, 6.
[61] I. Gulçin, P. Taslimi, *Expert Opin. Ther. Pat.* **2018**, *28*, 541.
[62] G. L. Ellman, K. D. Courtney, V. Andres Jr, R. M. Featherstone, *Biochem. Pharmacol.* **1961**, *7*, 88.
[63] U. Atmaca, R. Kaya, H. S. Karaman, M. Çelik, İ. Gülçin, *Bioorg. Chem.* **2019**, *88*, 102980.
[64] Y. Tao, Y. Zhang, Y. Cheng, Y. Wang, *Biomed. Chromatogr.* **2013**, *27*, 148.
[65] H. Genç Bilgiçli, A. Kestane, P. Taslimi, O. Karabay, A. Bytyqi-Damoni, M. Zengin, İ. Gulçin, *Bioorg. Chem.* **2019**, *88*, 102931.
[66] R. Kaya, P. Taslimi, M. E. Naldan, İ. Gülçin, *Lett. Drug Des. Discov.* **2019**, *14*, 573.
[67] E. Güzel, Ü. M. Koçyiğit, B. S. Arslan, M. Ataş, P. Taslimi, F. Gökalp, M. Nebioğlu, İ. Şişman, İ. Gulçin, *Arch. Pharm. Chem. Life Sci.* **2019**, *352*, e1800292.
[68] A. Maharramov, R. Kaya, P. Taslimi, M. Kurbanova, A. Sadigova, V. Farzaliyev, A. Sujayev, İ. Gulçin, *Arch. Pharm. Chem. Life Sci.* **2019**, *352*, e1800317.
[69] A. Cetin, F. Türkan, P. Taslimi, İ. Gulçin, *J. Biochem. Mol. Toxicol.* **2019**, *33*, 22261.
[70] P. Taslimi, S. Osmanova, C. Caglayan, F. Turkan, S. Sardarova, V. Farzaliyev, A. Sujayev, N. Sadeghian, I. Gulçin, *J. Biochem. Mol. Toxicol.* **2018**, *32*, e22191.
[71] T. Abdülkadir Coban, Ş. Beydemir, İ. Gücin, D. Ekinci, A. Innocenti, D. Vullo, C. T. Supuran, *Bioorg. Med. Chem.* **2009**, *17*, 5791.
[72] J. A. Verpoorte, S. Mehta, J. T. Edsall, *J. Biol. Chem.* **1967**, *242*, 4221.
[73] S. Beyza Öztürk Sarıkaya, I. Gülçin, C. T. Supuran, *Chem. Biol. Drug Des.* **2010**, *75*, 515.
[74] A. Innocenti, S. Beyza Öztürk Sarıkaya, İ. Gülçin, C. T. Supuran, *Bioorg. Med. Chem.* **2010**, *18*, 2159.
[75] M. Şentürk, İ. Gülçin, Ş. Beydemir, Ö. İ. Küfrevioğlu, C. T. Supuran, *Chem. Biol. Drugs Des.* **2011**, *77*, 494.
[76] A. Innocenti, İ. Gülçin, A. Scozzafava, C. T. Supuran, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5050.
[77] H. Lineweaver, D. Burk, *J. Am. Chem. Soc.* **1934**, *56*, 658.
[78] M. Tugrak, H. Inci Gul, H. Sakagami, I. Gulcin, C. T. Supuran, *Bioorg. Chem.* **2018**, *81*, 433.
[79] S. B. Öztürk Sarikaya, F. Topal, M. Şentürk, İ. Gülçin, C. T. Supuran, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4259.
[80] M. M. Bradford, *Anal. Biochem.* **1976**, *72*, 248.
[81] K. Aksu, H. Akıncıoğlu, A. Akıncıoğlu, S. Göksu, F. Tümer, I. Gülçin, *Arch. Pharm. Chem. Life Sci.* **2018**, *351*, e1800150.
[82] M. Huseynova, P. Taslimi, A. Medjidov, V. Farzaliyev, M. Aliyeva, G. Gondolova, O. Şahin, B. Yalçın, A. Sujayev, E. B. Orman, A. R. Özkaya, I. Gulçin, *Polyhedron* **2018**, *155*, 25.
[83] M. Zengin, H. Genc, P. Taslimi, A. Kestane, E. Guclu, A. Ogutlu, O. Karabay, I. Gulçin, *Bioorg. Chem.* **2018**, *81*, 119.
[84] B. Yiğit, M. Yiğit, D. Barut Celepci, Y. Gök, A. Aktaş, M. Aygün, P. Taslimi, İ. Gülçin, *ChemistrySelect* **2018**, *3*, 7976.
[85] P. Taslimi, I. Gulçin, *J. Food Biochem.* **2018**, *42*, e12516.
[86] M. Rezai, C. Bayrak, P. Taslimi, I. Gulcin, A. Menzek, *Turk. J. Chem.* **2018**, *42*, 808.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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