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FULL PAPER

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Novel sulfamate derivatives of menthol: Synthesis, characterization, and cholinesterases and carbonic anhydrase enzymes inhibition properties

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Abstract

Sulfamates have a large spectrum of biological activities including enzyme inhibition. Eight sulfamates derived from menthol (**2a–h**) were synthesized. Also, in the other section of this study, novel sulfamate derivatives of menthol were tested against some metabolic enzymes including acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and carbonic anhydrase I and II enzymes (hCAs I and II). The newly synthesized novel menthol sulfamate and menthol carbonyl sulfamate derivatives showed K_i values in the range of 34.37 ± 8.17 to 53.40 ± 10.61 nM against hCA I, 12.91 ± 4.57 to 38.67 ± 6.22 nM against hCA II, 111.17 ± 52.36 to 522.86 ± 120.08 nM against AChE, and 50.01 ± 11.73 to 109.63 ± 50.08 nM against BChE. As a result, the novel menthol sulfamate and menthol carbonyl sulfamate derivatives can be promising Alzheimer's disease drug candidates and novel hCA I and hCA II enzymes inhibitors.

KEYWORDS
acetylcholinesterase, butyrylcholinesterase, carbonic anhydrase, enzyme inhibition, sulfamate

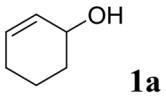
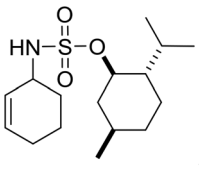
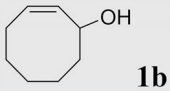
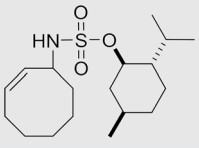
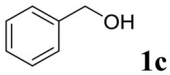
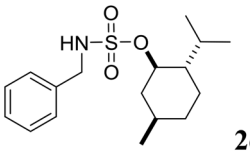
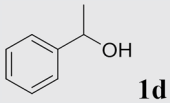
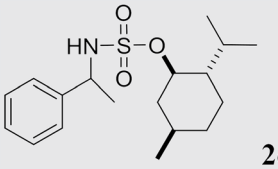
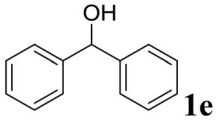
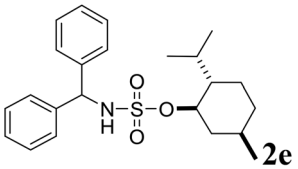
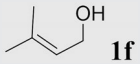
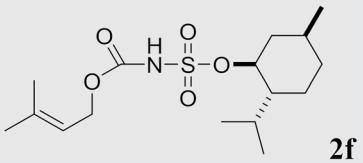
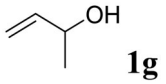
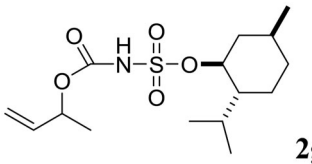
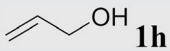
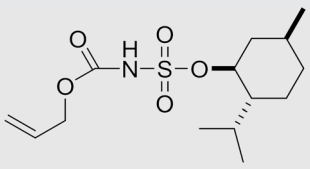
1 | INTRODUCTION

Sulfamates are commonly known biologically active compounds. Most medicines contain these functional groups. Sulfamates are widely used as therapeutic agents in medical chemistry. The sophistication of sulphamoyl chloride as advances sulfamate derivatives has been widely used for the synthesis of novel classes of such compounds.[1,2] In recent years, the improvement of an efficient strategy for the amination of allylic or benzylic alcohols has attracted considerable interest to organic chemists and pharmacists. The conversion of alcohols to amines using mercury acetate was reported in 2009. The use of metal in the reaction is discussed as green chemistry. It has been also achieved the allylic amination of allylic alcohols with sodium sulfate and sodium carbonate.[3] Menthol is known to chemically trigger transient receptor potential of cation channel subfamily M member eight receptors the cold-sensitive present in the skin when it is applied to the skin or inhaled.[4] Menthol is commonly used as an antibacterial agent toward various lactobacilli and streptococci in dental care.[5]

In our work, we have realized that the equivalent amount of chlorosulphonyl isocyanate (CSI), allylic or benzyl sulfamate menthol derivatives can be synthesized from alcohols with high efficiency without using any additives or catalysts. We have studied the reaction (Table 1) with high yields of mentholic sulfamate compounds resulting from reaction of commercially available allylic or benzylic alcohols with CSI in dichloromethane.

Carbonic anhydrase (CA) isoforms are metalloenzymes that participate in the conservation of pH homeostasis in the cells by catalyzing the reversible hydration of carbon dioxide (CO_2) and water to protons (H^+) and bicarbonate ions (HCO_3^-).[6–8] The CO_2/HCO_3^- buffer method predominantly controls maintenance of an

TABLE 1 Amination of allylic and benzylic alcohols (**1a–h**) formation of menthol sulfamates (**2a–e**) and menthol carbonyl sulfamates (**2f–h**)[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **2a**	78
2	 **1b**	 **2b**	70
3	 **1c**	 **2c**	65
4	 **1d**	 **2d**	68
5	 **1e**	 **2e**	70
6	 **1f**	 **2f**	72
7	 **1g**	 **2g**	73
8	 **1h**	 **2h**	68

[a]The reactions were carried out in dichloromethane at 1 eq. CSI and room temperature.
[b]Isolated yield of pure materials.

appropriate pH in the brain cells, and CA isoforms actively control this equilibrium by hydrolyzing the interconversion of two compounds/ions.[9,10] Hence, CA isoforms are promising aims to control seizures as some of the clinically good antiepileptic drugs have shown efficient CA inhibitory activity.[11] In the brain cells, various CA isoenzymes exist and are actively involved in diverse neurophysiologic or neuropathophysiologic mechanisms. CA II isoform is mostly expressed in the choroid plexus, astrocytes, oligodendrocytes, myelin sheaths, and myelinated tracts and overexpressed in multiple central nervous system disturbances including epilepsy.[12,13]

Alzheimer's disease (AD) is accompanied by an increase of acetylcholinesterase (AChE) activity that leads to run out of cholinergic neurotransmission in the brain areas related to memory and learning.[14,15] Amyloid beta-protein plaques, the major pathological sign in the brain of AD patients, are a degradation product of cholinesterase (ChE) enzyme. Currently, there are several approved drugs as AChE inhibitors (AChEIs) including donepezil, rivastigmine, and galantamine for the treatment of AD.[16,17] These drugs increase acetylcholine (ACh) level in the central nervous system to enhance cholinergic neurotransmission.[18] The inhibition of both hydrolysis products of ACh had crucial importance in AD. Both cholinergic enzymes are essential for successful treatment of AD because recent studies in AD patients reported that while the AChE activity is significantly reduced in specific regions of the brain, BChE activity can increase.[19,20] Adverse effects of some synthetic AChEIs used for the treatment of AD such as tacrine and donepezil led us to find innocent and most potent derivatives of that drugs.[21,22] Therefore, it is very important to find new substances, more efficient and less expensive than the currently used drugs, is urgently needed.

In this study, we aimed to investigate the inhibitory effects of newly synthesized menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives against hCA I, hCA II, BChE, and AChE enzymes.

2 | RESULTS AND DISCUSSION

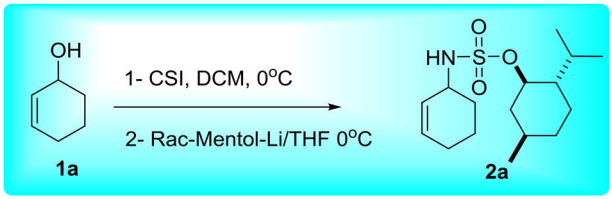
2.1 | Chemistry

Our research group has previously carried out the reaction of the sulfamoyl chlorides with the alcohols and amines.[23] The amination of allylic or benzylic alcohols with CSI was efficiently carried out and sulfamoyl chloride at low temperature was provided without any catalyst or additives. Fresh menthol–Li mixture was added to flask, which contains sulfamoyl chloride as an intermediate product. However, when menthol is added to the reaction mixture, the yield is about 10%. We treated the hydroxyl group of menthol with lithium to make it more nucleophilic. So we synthesized the menthol sulfamates (**2a–h**) with high efficiency.

Initially, we examined allylic amination of 2-cyclohexene-1-ol (**1a**) with CSI at 0°C, which afforded the corresponding sulfamoyl chloride. This reaction was performed. Following, 2-isopropyl-5-methylcyclohexyl cyclohex-2-en-1-ylsulfamate (**2a**) was obtained by the nucleophilic reaction of rac-menthol-Li with sulfamoyl chloride as shown in Scheme 1 and good yields were obtained as shown in Table 1.

However, when same reaction conditions were applied to the acyclic 3-methylbut-2-en-1-ol (**1f**), 3-buten-2-ol (**1g**), and prop-2-en-1-ol (**1h**), expected amination product was not formed. Instead of this, unexpected menthol carbonyl sulfamates (**2f–h**) were observed (Scheme 2).

The possible reaction mechanism is shown in Scheme 3. The first attack on CSI the carbonyl group in the alcohol oxygen is the resulting oxonium ion (**I**). It is then converted to the cyclobutane ring intermediate product (**II**) by the SNi mechanism. We estimated that



SCHEME 1 Synthesis of 2-isopropyl-5-methylcyclohexyl cyclohex-2-en-1-ylsulfamate (**2a**)

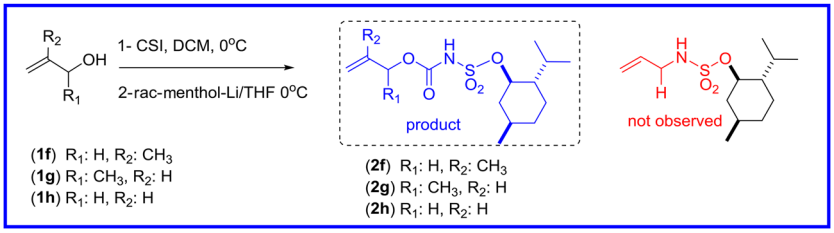
the menthol sulfamates associated with the substitution of sulfamoyl chlorides with rac-menthol-Li (**4**) with decarboxylation at the opening of the cyclobutane ring (Scheme 3). Thus, we achieved the synthesis of menthol sulfamate derivatives from acyclic or cyclic benzylic and allylic alcohols without any additive or catalyst by using CSI (Table 1).

2.2 | Biological activities

In this study, all the synthesized compounds (novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives) were tested to investigate their inhibitory activity toward the hCA I, the rapid cytosolic hCA II, AChE, and BChE enzymes. The chemical formula and reactions of novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives are given in Schemes 1–3. Their enzymes inhibition data are summarized in Table 2. Many CA isoforms are of therapeutic purposes to fight some disturbances like epilepsy, obesity, cancer, oedema, and glaucoma.[24,25] Sulfonamide compounds are the most significant class of CA inhibitors (CAIs), with various compounds such as acetazolamide (AZA), valdecoxib, sulthiame, dorzolamide, topiramate, dichlorophenamide, brinzolamide, methazolamideethoxzolamide, zonisamide, celecoxib, and sulpiride, which are available in the drug market for the therapy of glaucoma.[26,27]

AD is started with short-term memory loss and progresses progressively with signs like confusion, impaired communication, poor judgment, disorientation, behavior changes, and difficulty walking, speaking, and swallowing.[28,29] In 3–7 years after diagnosis of this disease, AD ends in death. At subcellular and cellular levels, AD happens as overproduction of β-amyloid peptides, further extracellular organization of plaques, synaptic degeneration, intracellular agglomeration of hyperphosphorylated τ protein forming neurofibrillary tangles, and neuronal cell death.[30,31] The death of neurons forcefully reduces the amounts of ACh in cholinergic brain synapses. By inhibition of the AChE, which hydrolyzes ACh molecule, the amounts of ACh are raised and the cholinergic transportation is improved. At present, the AChEIs, such as donepezil, rivastigmine, and galantamine, are the principal drugs approved for the treatment of AD.[32,33]

The hCA I isoform is discovered in many mammalian tissues and occurs in high concentrations in the gastrointestinal tract and blood cells.[34] It is involved in cerebral edema and retinal, and also the inhibition of this enzyme can be an important factor for fighting these situations or diseases.[35] For hCA I isoform, the K_i values were determined in range of 34.37 ± 8.17 to 53.40 ± 10.61 nM. In



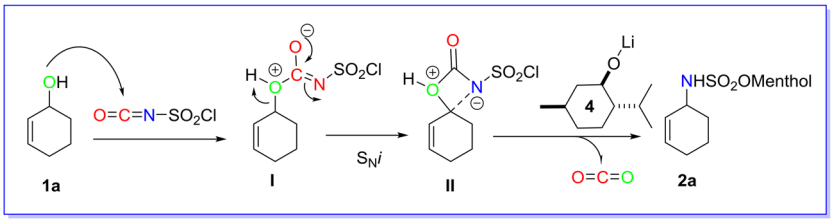
SCHEME 2 Synthesis of menthol carbonyl sulfamates (**2f–h**) from acyclic allylic alcohols

comparison, the K_i for the standard CA inhibitor AZA, a definitive hCA I inhibitor, was 136.57 ± 19.02 nmol/L against hCA I (Table 2). All novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives had effective inhibition effects than that of AZA. Also, among these compounds, 2-isopropyl-5-methylcyclohexyl ((but-3-en-2-yloxy)carbonyl)sulfamate (**2g**), which had 2-isopropyl-5-methylcyclohexyl, was the best hCA I inhibitor (K_i 34.37 ± 8.17 nM, Figure 1). It is well known that compounds containing carbonyl (—CO) and halogen groups are effective CAIs. As shown in Table 1, IC_{50} values are in the range of 37.97–53.55 nM toward hCA I and 15.97–29.96 nM for hCA II.

HCA II inhibition reduces HCO_3^- production and finally aqueous humor secretion, which leads to reduced pressure in the eye.[36] Indeed, hCA II has key role in diseases such as glaucoma disease. Indeed, HCO_3^- generation serves as a strategy to transport sodium ions (Na^+) into the eye along with the influx of water leading to an increase in intraocular pressure.[37] Novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives synthesized in this paper significantly inhibited hCA II with K_i in the low nanomolar range. K_i values were calculated between 12.91 ± 4.57 and 38.67 ± 6.22 nM (Table 2). On the other hand, 2-isopropyl-5-methylcyclohexyl benzhydrylsulfamate (**2e**), which contains two benzene rings (Figure 1 and Table 1) is in fact the best inhibitor in this molecules, being 6.33 times a better hCA II inhibitor compared to the clinical candidate drug (K_i of AZA: 81.80 ± 12.33 nM). These compounds are also an effective hCA II inhibitor, being almost four times more effective than AZA in inhibiting hCA II isoform.

In this work, AChE was also extremely inhibited by novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives at the low nanomolar inhibition with K_i values in range of 111.17 ± 52.36 to 522.86 ± 120.08 nM (Table 2). These results nicely determined that new-synthesized bromophenols had effective AChE inhibition properties. However, the most powerful AChE inhibition was recorded by novel compound **2e** with a K_i value of 111.17 ± 52.36 nM (Figure 1). Also, all the remaining newly synthesized compounds reported here were highly efficient inhibition constants against AChE. On the other hand, tacrine (1,2,3,4-tetrahydroacridin-9-amine), had K_i value of 605.46 ± 53.27 nM against cholinergic AChE. Finally, novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives inhibited BChE with K_i values in range of 50.01 ± 11.73 to 109.63 ± 50.08 nM (Table 2). The K_i values of novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives for BChE and AChE were obtained from Lineweaver–Burk plots. On the other hand, tacrine, which was the first ChE inhibitor to be discovered for the management of AD symptoms in 1993, had K_i value of 201.51 ± 40.30 nM. Furthermore, it was considered that donepezil hydrochloride compound, which is used for the therapy of mild-to-moderate AD and diverse other memory impairments, had been shown to lower AChE inhibition activity (IC_{50}: 55.0 nM). As seen in Table 2, IC_{50} values are in the range of 206.31–924.01 nM toward AChE, for BChE are in the range of 91.41–246.26 nM.

Evaluation of the effects of novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives on AChE, BChE, and hCA I and II enzymes was the important purpose of this paper, and inhibition results are present in Table 2 and Figure 1. For hCA I and II isoforms, their excellent inhibitors were 2-isopropyl-5-methylcyclohexyl ((but-3-en-2-yloxy)carbonyl)sulfamate (**2g**), 2-isopropyl-5-methylcyclohexyl (((3-methylbut-2-en-1-yl)oxy)carbonyl)sulfamate (**2f**), and 2-isopropyl-5-methylcyclohexyl ((*Z*)-cyclooct-2-en-1-yl) sulfamate (**2b**). 2-Isopropyl-5-methylcyclohexyl (1-phenylethyl) sulfamate (**2d**) compound is a weak inhibitor compared to other compounds for this isoenzymes. For AChE, their excellent inhibitors were 2-isopropyl-5-methylcyclohexyl benzhydrylsulfamate (**2e**) and



SCHEME 3 The possible general reaction mechanism synthesis of menthol sulfamate

TABLE 2 Human carbonic anhydrase I and II (hCA I and II) isoenzymes, acetylcholinesterase (AChE), and butyrylcholinesterase (BChE) enzymes inhibition effects of novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives

	IC_{50} (nM)							K_i (nM)			
Compounds	hCA I	r^2	hCA II	r^2	AChE	r^2	BChE	r^2	hCA I	hCA II	AChE	BChE
2a	53.55	0.9929	26.40	0.9844	430.16	0.9962	176.65	0.9753	40.43 ± 10.83	23.42 ± 4.62	269.40 ± 49.18	72.23 ± 11.86
2b	42.62	0.9876	23.52	0.9843	606.83	0.9857	227.51	0.9839	37.97 ± 3.67	18.81 ± 5.92	495.35 ± 70.60	109.63 ± 50.08
2c	53.26	0.9824	19.47	0.9882	529.41	0.9919	195.43	0.9718	50.27 ± 11.77	21.26 ± 3.47	522.86 ± 120.08	69.69 ± 31.10
2d	47.70	0.9912	24.11	0.9900	389.98	0.9872	150.62	0.9890	53.40 ± 10.61	18.75 ± 3.76	198.33 ± 54.44	69.07 ± 15.97
2e	44.05	0.9838	15.97	0.9843	206.31	0.9963	246.26	0.9974	48.71 ± 8.42	12.91 ± 4.57	111.17 ± 52.36	90.15 ± 23.37
2f	37.97	0.9757	29.96	0.9829	515.62	0.9938	91.41	0.9811	36.18 ± 5.30	27.28 ± 2.42	510.67 ± 50.76	50.01 ± 11.73
2g	45.60	0.9713	29.15	0.9848	924.01	0.9811	141.57	0.9792	34.37 ± 8.17	38.67 ± 6.22	369.81 ± 35.76	60.92 ± 18.94
2h	41.82	0.9984	19.34	0.9792	535.54	0.9736	128.35	0.9693	40.92 ± 6.58	20.31 ± 7.35	260.01 ± 17.33	58.26 ± 16.43
AZA[a]	174.78	0.9578	105.78	0.9786	–	–	–	–	136.57 ± 19.02	81.80 ± 12.33	–	–
TAC[b]	–	–	–	–	938.53	0.9679	306.30	0.9748	–	–	605.46 ± 53.27	201.51 ± 40.30

[a]Acetazolamide (AZA) was used as a standard inhibitor for both carbonic anhydrase I and II (hCA I and II) isoenzymes.
[b]Tacrine (TAC) was used as a standard inhibitor for acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes.

2-isopropyl-5-methylcyclohexyl (1-phenylethyl)sulfamate (**2d**). 2-Isopropyl-5-methylcyclohexyl benzylsulfamate (**2c**) compound is a weak inhibitor compared to other molecules of AChE. For BChE, their excellent inhibitors were 2-isopropyl-5-methylcyclohexyl (((3-methylbut-2-en-1-yl)oxy)carbonyl)sulfamate (**2f**) and 2-isopropyl-5-methylcyclohexyl ((allyloxy)carbonyl)sulfamate (**2h**). Also, for hCA II, their excellent inhibitors were 2-isopropyl-5-methylcyclohexyl benzhydrylsulfamate (**2e**) and 2-isopropyl-5-methylcyclohexyl (1-phenylethyl)sulfamate (**2d**).

3 | CONCLUSION

In summary, starting from the appropriate reagents, the novel **1b–8b** menthol derivative sulfamates were synthesized. The synthesized menthol derivative sulfamates may be important for biological and synthetic purposes. In this study, newly synthesized racemic menthol derivative sulfamates (**1b–8b**) were evaluated against cytosolic hCA I, hCA II, AChE, and BChE enzymes. All menthol derivative sulfamates have shown low nanomolar inhibition against used metabolic enzymes.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All solvents and chemicals are commercially available. IR spectra were obtained from solutions in 0.1 mm cells and in CH_2Cl_2 with a Perkin-Elmer spectrophotometer. ^1H and ^{13}C NMR spectrums were recorded on Varian and Bruker spectrometers at 400 and 100 MHz, respectively, and NMR shifts are presented. Elemental analyses were performed on LECO CHNS-932 apparatus. All column chromatography was performed on silica gel (60-mesh, Merck).

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | General procedure for the synthesis of menthol sulfamates

Allyl or benzyl alcohol (1.0 eq) was dissolved in 20 mL DCM. The reaction mixture was cooled to 0°C and CSI (1.1 eq) was added and resulting solution was stirred for 1 h (Scheme 4). Then, in a separate flask, menthol-Li (**3**) was prepared in THF with lithium (1.1 mol). Fresh menthol-Li (**4**) was added to the reaction mixture and stirred for 0.5 h. The reaction mixture was extracted with dichloromethane. The organic phase was dried over sodium sulfate and concentrated. Purification was performed through column chromatography on silica gel.

2-Isopropyl-5-methylcyclohexyl cyclohex-2-en-1-ylsulfamate (2a)

Yield 78% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3238, 2952, 2926, 2868, 1742, 1720, 1457, 1383, 1289, 1232, 1174, 1049, 916;

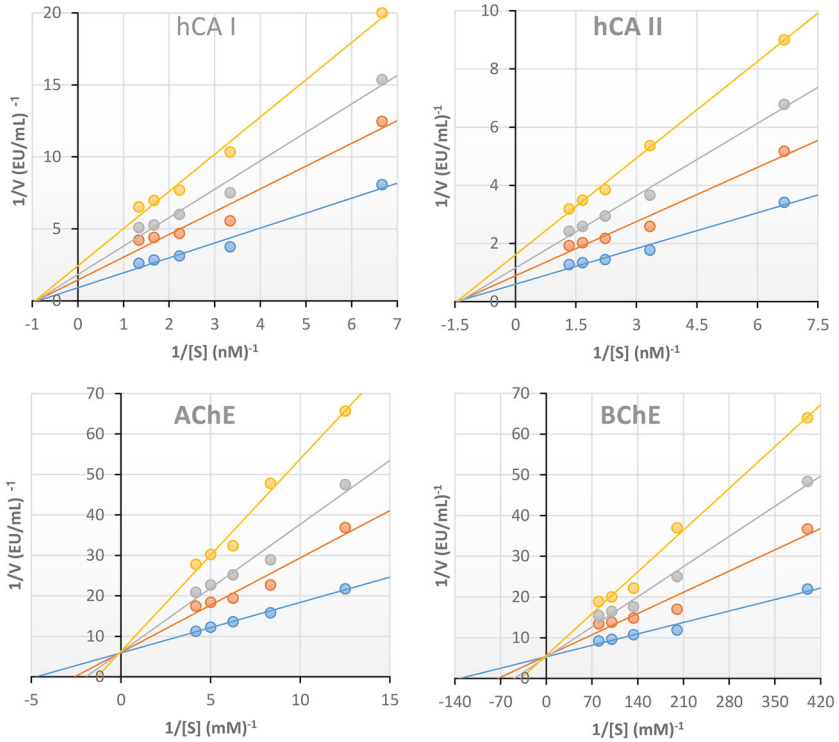


FIGURE 1 Determination of Lineweaver–Burk graphs for excellent inhibitors of human carbonic anhydrase I (**2g**) and II (**2e**) isoenzymes, acetylcholinesterase (AChE) (**2e**), and butyrylcholinesterase (BChE) (**2f**) enzymes

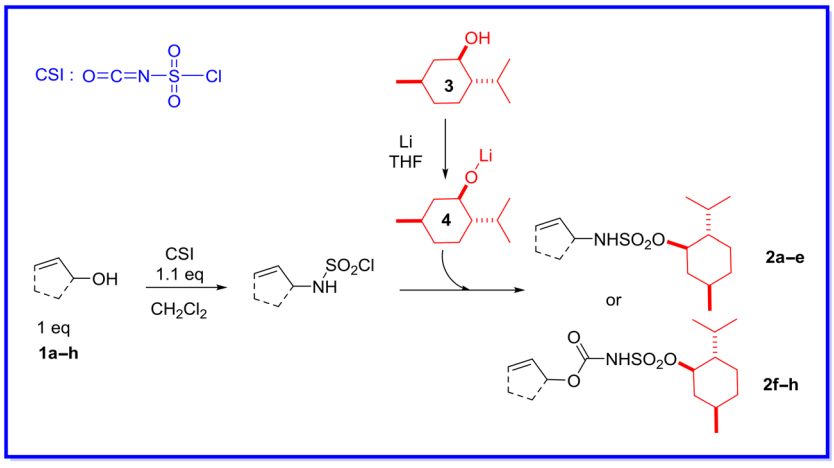
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22 (bs, 1H), 6.02 (m, 1H), 5.72–5.99 (m, 1H), 5.26 (m, 1H), 4.60 (td, J = 11.7, 21.6 Hz, 1H), 0.79–2.34 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 134.4, 124.5, 47.9, 41.4, 33.9, 31.9, 29.9, 28.3, 25.5, 25.0, 23.2, 22.1, 21.1, 18.6, 15.8, IR ($CHCl_3$, cm^{-1}): 3238, 2952, 2926, 1741, 1457, 1383, 1232, 916. Elemental analysis calcd. for C, 60.92; H, 9.27; N, 4.44; S, 10.16. Found: 60.58; H, 9.42; N, 4.44; S, 10.28.

2-Isopropyl-5-methylcyclohexyl ((*Z*)-cyclooct-2-en-1-yl) sulfamate (2b)

Yield 70% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3239, 2928, 2868, 1739, 1456, 1383, 1238, 1173, 1058, 918; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.32 (bs, 1H), 5.64–5.74 (m, 2H), 5.45–5.50 (m, 1H), 4.60 (m, 1H), 0.79–2.35 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 130.9, 129.4, 76.3, 47.9, 41.4, 35.2, 33.9, 31.9, 29.9, 28.9, 26.6, 25.9, 25.5, 23.4, 23.2, 22.1, 21.1, 15.8, IR ($CHCl_3$, cm^{-1}): 3239, 2928, 1739, 1456, 1383, 1238, 1173, 918. Elemental analysis calcd. for C, 62.93; H, 9.68; N, 4.08; S, 9.33. Found: C, 62.58; H, 9.73; N, 4.24; S, 9.48.

2-Isopropyl-5-methylcyclohexyl benzylsulfamate (2c)

Yield 65% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3465, 2955, 2869, 1630, 1455, 1387, 1290, 1167, 1105, 950; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.28–7.2 (m, 6H), 4.95–5 (m, 2H), 4.3–4.36 (m, 1H), 0.65–2.33 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 136.6, 128.6,



SCHEME 4 General procedure for the synthesis of menthol sulfamate compounds

128.4, 128.5, 128.0, 83.7, 68.7, 47.9, 41.6, 34.1, 31.6, 25.4, 23.2, 22.2, 21.2, 15.9. Elemental analysis calcd. for C, 62.74; H, 8.36; N, 4.30; S, 9.85. Found: C, 62.56; H, 8.42; N, 4.54; S, 9.76.

2-Isopropyl-5-methylcyclohexyl (1-phenylethyl)sulfamate (2d)

Yield 68% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3243, 2957, 2924, 2873, 1745, 1455, 1377, 1172, 914; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.63–7.64 (m, 1H), 7.28–7.37 (m, 4H), 5.88–5.91 (m, 1H), 4.52–4.59 (m, 1H), 0.7–2.27 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 128.9, 128.8, 128.7, 126.5, 126.4, 88.0, 76.3, 47.8, 41.3, 33.8, 31.8, 25.5, 23.1, 22.2, 22.1, 21.1, 15.6. Elemental analysis calcd. for C, 63.68; H, 8.61; N, 4.13; S, 9.44. Found: C, 63.74; H, 8.66; N, 4.22; S, 9.54.

2-Isopropyl-5-methylcyclohexyl benzhydrylsulfamate (2e)

Yield 70% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3247, 2966, 2934, 2855, 1767, 1476, 1367, 1178, 918; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22–737 (m, 10H), 5.71–5.73 (d, 1H), 4.93–4.95 (d, J = .02 Hz, 1H), 4.35–4.36 (m, 1H), 0.68–2.16 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 128.9, 128.8, 128.1, 127.7, 127.6, 84.3, 62.2, 47.7, 41.6, 33.4, 31.7, 29.9, 25.6, 23.2, 22.1, 21.1, 15.8. Elemental analysis calcd. for C, 68.79; H, 7.78; N, 3.49; S, 7.98. Found: C, 68.57; H, 7.65; N, 3.62; S, 7.64.

2-Isopropyl-5-methylcyclohexyl (((3-methylbut-2-en-1-yl)oxy)-carbonyl)sulfamate (2f)

Yield 72% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3432, 2952, 2924, 1741, 1638, 1459, 1173, 1093, 918; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.27 (bs, 1H), 5.32–5.36 (m, 1H), 4.67 (d, J = 8.8 Hz, 1H), 4.53–4.60 (m, 1H), 0.78–2.33 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 157.7, 141.0, 117.7, 87.7, 64.2, 47.8, 41.4, 33.9, 31.9, 26.0, 25.5, 23.3, 23.1, 22.1, 21.1, 15.7. Elemental analysis calcd. for C, 55.31; H, 8.41; N, 4.03; S, 9.23. Found: C, 55.24; H, 8.53; N, 4.41; S, 9.38.

2-Isopropyl-5-methylcyclohexyl ((but-3-en-2-yloxy)carbonyl)-sulfamate (2g)

Yield 73% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3484, 2952, 2927, 1738, 1647, 1460, 1376, 1289, 1174, 1174, 1039, 915; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.64 (bs, 1H), 5.79–5.87 (m, 1H), 5.18–5.37 (m, 2H), 4.56–4.62 (m, 1H), 0.77–2.33 (m, 22H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.6, 136.5, 117.5, 87.9, 75.0, 47.8, 41.4, 33.8, 31.9, 25.5, 23.2, 22.1, 21.1, 20.1, 15.8. Elemental analysis calcd. for C, 54.03; H, 8.16; N, 4.20; S, 9.61. Found: C, 54.32; H, 8.07; N, 4.43; S, 9.54.

2-Isopropyl-5-methylcyclohexyl ((allyloxy)carbonyl)sulfamate (2h)

Yield 68% as a colorless liquid. IR (CH_2Cl_2, cm^{-1}): 3468, 2956, 2871, 1739, 1648, 1459, 1385, 1229, 1170, 912; ^1H NMR (400 MHz, $CDCl_3$, ppm): 5.86–5.96 (m, 1H), 5.38–5.4 (m, 1H), 5.27–5.36 (m, 1H), 4.67–4.68 (m, 2H), 4.55–4.62 (m, 1H), 0.78–2.35 (m, 19H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 150.1, 131.1, 119.9, 87.9, 67.9, 47.9, 41.4, 33.9, 31.9, 23.3, 23.2, 22.1, 21.1, 15.8. Elemental analysis calcd. for C, 52.64; H, 7.89; N, 4.39; S, 10.04. Found: C, 52.57; H, 7.97; N, 4.16; S, 10.23.

4.2 | Biochemical studies

4.2.1 | Cholinesterases activity tests

Inhibitory activities of tested novel compounds against AChE and BChE were measured by slightly modified spectrophotometric method, developed by Ellman et al.[38] as described previously.[39] Acetylthiocholine iodide and butyrylthiocholine iodide were used as substrates of the reaction and 5,5′-dithio-bis(2-nitro-benzoic)acid (DTNB) method was used for the measurement of the anti-ChE activity. One hundred thirty microliter of 100 mM sodium phosphate buffer (pH 8.0), test compound solutions and of solution of AChE or BChE were mixed and incubated for 15 min at 25°C, and 0.5 mM DTNB was added.[40] The reaction was then initiated by the addition of acetylthiocholine iodide (0.71 mM) or butyrylthiocholine chloride (0.2 mM). The hydrolysis of these substrates was monitored spectrophotometrically by the formation of yellow 5-thio-2-nitrobenzoate anion as a result of the reaction of DTNB with thiocholine, released by the enzymatic hydrolysis of acetylthiocholine iodide or butyrylthiocholine chloride, at a wavelength of 412 nm.[41–43] AChE enzyme obtained from *Electrophorus electricus* (C3389) and BChE enzyme obtained from *Equus caballus* (C4290) were supplied from market. Tacrine was used as standard compound. Percentage of inhibition of AChE or BChE was determined by a comparison of the rates of reaction of samples relative to blank sample (ethanol in phosphate buffer pH 8.0) using the following formula:

$$[(E - S)/E] \times 100$$

where E is the activity of enzyme without test sample, and S is the activity of enzyme with test sample.[44–46] The anti-ChE activity of the novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives were measured at different concentrations (from 10^{-8} to 200 μM) for calculation of the IC_{50} values. Each substance was tested three times in triplicate against AChE and BChE enzymes.[47,48]

4.2.2 | hCA isoenzyme purification and inhibition studies

For the investigation of inhibitory effects of novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivative on hCA isoformes, both hCA isoforms from human erythrocytes were purified via a simple single-step method by Sepharose-4B-L-tyrosine-sulfanilamide affinity gel chromatography.[49–52] For this purpose, the human erythrocyte samples were centrifuged at 13000 rpm for 25 min. Then the solution was filtered to remove precipitate.[53] Both hCA isoenzymes were isolated from the serum, which the pH was adjusted to 8.7 by adding solid Tris. Affinity column was equilibrated by buffer solution (25 mM Tris-HCl/0.1 M Na_2SO_4) at pH 8.7. The serum was loaded to affinity gel and washed with buffer solution (25 mM Tris-HCl/22 mM Na_2SO_4) at pH 8.7.[54,55] The hCA I isoenzyme was eluted by buffer solution (1.0 M NaCl/0.25 M sodium phosphate) at pH 6.3. On the other hand, hCA II isoenzyme was eluted by another buffer

solution (0.1 M sodium acetate/0.5 M $NaClO_4$) at pH 5.6.[56–59] Both isoenzymes were taken from the column in fractions of 2 mL. All works were realized at 4°C. The hCA isoenzymes activity was measured by following the change at absorbance a specific (348 nm) of *p*-nitrophenylacetate (PNA) to *p*-nitrophenolate ion over a period of 3 min at room temperature (25°C) using a spectrophotometer (Thermo Scientific, UV-Vis spectrophotometer) according to the method of Verpoorte et al.[60] as described previously.[61–63] There were 0.4 mL Tris-SO_4 buffer (0.05 M, pH 7.4), 0.3 mL of 3 mM PNA, 0.2 mL of H_2O, and 0.1 mL of enzyme solution in a test tube content of this reaction.[64–66] Esterase activity assays were identified from a series of experiments at three different novel menthol sulfamate (**2a–e**) and menthol carbonyl sulfamate (**2f–h**) derivatives.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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