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Carbonic anhydrase inhibitory properties of novel sulfonamide derivatives of aminoindanes and aminotetralins

Yusuf Akbaba[1], Akın Akıncıoğlu[1], Hülya Göçer[1,2], Süleyman Göksu[1], İlhami Gülçin[1], and Claudiu T. Supuran[3]

[1]*Faculty of Science, Department of Chemistry, Atatürk University, Erzurum, Turkey,* [2]*Agri Ibrahim Cecen University, Central Researching Laboratory, Agri, Turkey, and* [3]*Universita degli Studi di Firenze, Polo Scientifico, Laboratorio di Chimica Bioinorganica, Via della Lastruccia, Sesto Fiorentino (Florence), Italy*

Abstract

Six sulfonamides derived from indanes and tetralines were synthesized. The human carbonic anhydrase isozymes hCA I and hCA II inhibition effects of the synthesized sulfonamides were determined. From these compounds, while *N*-(5,6-dimethoxy-2,3-dihydro-1H-inden-2-yl) methane sulfonamide showed the most potent inhibitory effect against hCA I ($K_i = 46 \pm 5.4\,\mu M$, $r^2 = 0.978$), *N*-(1,2,3,4-tetrahydronaphthalene-2-yl)methanesulfonamide was found to have the best inhibitory effect against hCA II ($K_i = 94 \pm 7.6\,\mu M$, $r^2 = 0.982$).

Keywords

Aminoindane, aminotetralin, carbonic anhydrase, enzyme inhibition, sulfonamide

History

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Introduction

Sulfonamides are prominent biologically active compounds. Most drugs contain this functional group in their structures[1]. A carbonic anhydrase (CA) inhibitor drug acetazolamide (diamox, **1**) is used to treat glaucoma[2] and idiopathic intracranial hypertension[3]. A sulfonamide drug sultiame (sulthiame, **2**) is an anticonvulsant that reported to be used in the treatment of epilepsy and West syndrome[4]. A CA inhibitor diuretic ethoxzolamide (**3**) can be used in the treatment of glaucoma and duodenal ulcers[5] (Figure 1).

The CAs (E.C: 4.2.1.1) form a family of enzymes that catalyze the rapid interconversion of carbon dioxide (CO_2) and water to bicarbonate (HCO_3^-) and protons (H^+), a reversible reaction that occurs rather slowly in the absence of a catalyst. The reaction catalyzed by CA is:

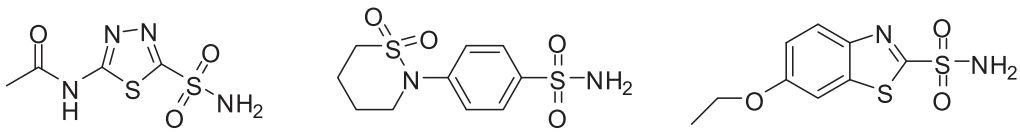
$$CO_2 + H_2O \Longleftrightarrow H_2CO_3 \Longleftrightarrow HCO_3^- + H^+$$

In the hydration direction, the first step is the nucleophilic attack of a Zn^{2+}-bound hydroxide ion on CO_2 with consequent formation of HCO_3^-, which is then displaced from the active site by a water molecule. Finally, it regenerates the catalytically active Zn^{2+}-bound hydroxide ion through a proton transfer reaction from the Zn^{2+}-bound water molecule to an exogenous proton acceptor or to an active site residue. Sulfonamides are the most important CA inhibitors, bind in a tetrahedral geometry of the Zn^{2+} ions, in deprotonated state[6].

Scheme 1 clearly shows that the deprotonated sulfonamide is coordinated to the Zn^{2+} ion of the CA isoenzymes, and its NH moiety participates in hydrogen bond with Thr 199, which in turn is engaged in another hydrogen bond to the carboxylate group of Glu 106, whereas one of the oxygen atoms of the sulfonamide moiety also participated in hydrogen bond with backbone-NH moiety of Thr 199[7]. These structures provide close insight into why the sulfonamide group appears to have unique properties for CA inhibition.

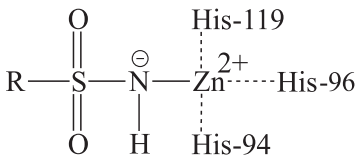
CAs are ubiquitous zinc enzymes and present in Archaea, prokaryotes and eukaryotes, encoded by three distinct and evolutionarily unrelated gene families: the α-CAs present in vertebrates, eubacteria, algae and cytoplasm of green plants. The β-CAs are predominantly in eubacteria, algae and chloroplasts of both mono- as well as dicotyledons. The γ-CAs are mainly in Archaea and some eubacteria[1,8]. Up to now, in higher vertebrates, including humans, 16 different CA isozymes or CA-related proteins have been described, which possess different subcellular localization and tissue distribution[1,7]. Among CA isozymes are the cytosolic ones (CA I, CA II, CA III, CA VII); CA-I is found together with CA-II in erythrocytes. CA-II is the most widely distributed CA in the eye, kidney, central nervous system (CNS) and inner ear. There are also membrane-bound (CA IV, CA IX, CA XII, CA XIV), mitochondrial (CA V), secretory forms (CA VI) and several acatalytic forms (CA VIII, CA X, CA XI)[9,10]. Other CA isoforms are found in a variety of tissues where they participate in several important biologic processes[11–14]. These enzymes catalyze a very simple physiological reaction, the interconversion between CO_2 and HCO_3^-, and are involved in crucial physiological processes connected with respiration and transport of CO_2/HCO_3^- between metabolizing tissues and the lungs, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues or organs, biosynthetic reactions such as gluconeogenesis, lipogenesis, and ureagenesis, bone resorption, calcification, tumorigenicity, and many other physiologic or pathologic processes. Thus, it is not surprising that many of these isozymes have been discovered as important targets for inhibitors with clinical applications[1,7,8,15]. Almost all of the most potent inhibitors of CAs contain a terminal sulfonamide as the anchoring group to coordinate the catalytic zinc[16,17]. These sulfonamides are widely used clinically, mainly as

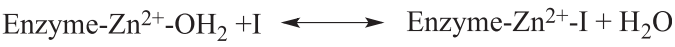
Address for correspondence: Süleyman Göksu, Department of Chemistry, Faculty of Science, Atatürk University, 25240 Erzurum, Turkey. Tel: +90 4422314389. Fax: +904422360948. E-mail: sgoksu@atauni.edu.tr



1 **2** **3**

Figure 1. Some sulfonamide drugs.





Scheme 1. Putative CA inhibition mechanism by sulfonamide inhibitors.

antiglaucoma agents but also for the therapy of other diseases such as increased intracranial pressure, various neurological/neuromuscular pathologies such as epilepsy, genetic hemiplegic migraine, and ataxia, tardive dyskinesia, hypokalemic periodic paralysis, essential tremor and Parkinson's disease, and mountain sickness. Accordingly, drugs of this pharmacological class are under constant development[1,8,13,14].

Because of the important biological activities of sulfonamides, the synthesis and CA inhibitory properties of novel sulfonamides **28**–**33** will be useful for further synthetic and biological purposes. In this context, here we report the first synthesis of sulfonamides **28**, **30**–**33**. We also evaluate CA isoenzymes (hCA I and hCA II) inhibitory affects of compounds **28**–**33**.

Experimental

All chemicals and solvents are commercially available. All solvents were distilled and dried according to standard procedures. Silica gel (SiO_2, 60 mesh; Merck, Darmstadt, Germany) was used for column chromatography (CC). In this study, 1 mm of SiO_2 60 PF (Merck) on glass plates was used for preparative thick layer chromatography. The m.p. of all compounds was determined with cap. melting-point apparatus (BUCHI 530; Flawil, Switzerland); uncorrected. IR spectra were recorded as solutions in 0.1 mm cells with a Mattson 1000 FT-IR spectrophotometer (Cambridge, England). ^{1}H- and ^{13}C-NMR spectra were recorded on 400 (100)-MHz Varian spectrometer (Danbury, CT) in deuterated solvents ($CDCl_3$ and D_2O) with tetramethylsilane (TMS, $SiMe_4$) as an internal standard for protons and solvent signals as internal standard for carbon spectra. Chemical shift values were mentioned δ in ppm. Elemental analyses were recorded on Leco CHNS-932 apparatus (Saint Joseph, MI). CA inhibitory properties of samples were determined on a spectrophotometer (UV-1208, Shimadzu, Japan).

Synthesis

Synthesis of alcohols **7**[18], **8**[19] and **9**[20], compound **16**[21], amine hydrochloride salt **21**[22] and amine **22**[23] has been described in the literature.

*Standard procedure for the synthesis of azides: 1-azido-5,6-dimethoxyindane (**10**)*

Alcohol **7** (4.47 g, 23.16 mmol) was dissolved in dry THF (100 ml). To this solution, diphenylphosphoryl azide (DPPA; 7.62 , 27.68 mmol) and DBU (4.19 g, 27.68 mmol) were added at 0 °C under Ar(g). The mixture was stirred for 2 h at the same temperature, then at 25 °C for 12 h. After the solvent was evaporated, CH_2Cl_2 (80 ml) and 10%HCl (30 ml) were added to the residue. Organic phase was separated and washed with 10%HCl (2×20 ml). Drying of the organic layer over Na_2SO_4, evaporation of the solvent and the CC of the residue on silica gel (30 g) with 10% EtOAc–hexane afforded azide **10** (3.60 g, 71% yield).

*1-Azido-5,6-dimethoxyindane (**10**)*

Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 4.79 (dd, 1H, CH-N_3, $J = 4.2$ and $J = 7.1$ Hz), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.02 (A part of AB, m, 1H, Ha of CH_2), 2.80 (B part of AB, ddd, 1H, Hb of CH_2, $J = 4.8$, $J = 8.4$ and $J = 15.4$ Hz), 2.50–2.41 (m, 1H, H of CH_2), 2.17–2.10 (m, 1H, H of CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.3 (C), 148.7 (C), 136.0 (C), 132.4 (C), 107.7 (CH), 107.4 (CH), 66.7 (CH–N_3), 56.3 (OCH_3), 56.2 (OCH_3), 33.1 (CH_2), 30.7 (CH_2). IR (CH_2Cl_2, cm^{-1}): 3070, 2999, 2938, 2857, 2833, 2092, 1607, 1505, 1465, 1413, 1339, 1311, 1260, 1223, 1188, 1092. Anal. Calcd for ($C_{11}H_{13}N_3O_2$): C 60.26, H 5.98 and N 19.17; Found C 60.30, H 5.97 and N 19.13.

*1-Azidoindane (**11**)*

A yellowish oily azide **11** was synthesized from **8** by applying the standard procedure described above for the synthesis of azides (87% yield). ^{1}H- and ^{13}C-NMR data of **11** are in good agreement with data given in the literature[24].

*1-Azido-5-methoxy-1,2,3,4-tetrahydronaphthalene (**12**)*

Compound **12** was synthesized from **9** as described in ''Standard Procedure for the synthesis of azides: 1-azido-5,6-dimethoxyindane (**10**)'' section, 80% yield, oily. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (t, 1H, Ar-H, $J = 8.1$ Hz), 6.95 (d, 1H, Ar-H, $J = 8.1$ Hz), 6.82 (d, 1H, Ar-H, $J = 8.1$ Hz), 4.58–4.57 (m, 1H, CH–N_3), 3.95 (s, 3H, OCH_3), 2.96–2.79 (m, 1H, H of CH_2), 2.60–2.54 (m, 1H, H of CH_2) and 2.02–1.83 (m, 4H, $2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.5 (C), 135.0 (C), 126.7 (CH), 126.6 (C), 121.4 (CH), 109.5 (CH), 59.7 (CH–N_3), 55.7 (OCH_3), 28.9 (CH_2), 22.9 (CH_2) and 18.5 (CH_2). IR (CH_2Cl_2, cm^{-1}): 2940, 2937, 2098, 1587, 1470, 1438, 1331, 1253, 1102 and 1065. Anal. Calcd for ($C_{11}H_{13}N_3O$): C 65.01, H 6.45 and N 20.68; Found C 65.04, H 6.49 and N 20.60.

*Standard procedure for the synthesis of amine hydrochlorides: 1-amino-5,6-dimethoxyindane hydrochloride (**13**)*

Pd-C (50 mg) and azide **10** (2.00 g, 12 mmol) in MeOH (50 ml) and $CHCl_3$ (4 ml) were placed in a 100-ml flask. A balloon filled with H_2 gas (3 L) was fitted to the flask. The mixture was deoxygenated by flushing with H_2 and then hydrogenated at RT for 20 h. The catalyst was removed by filtration. Recrystallization of the residue from MeOH–Et_2O gave 1-amino-5,6-dimethoxyindan hydrochloride (**13**) (1.98 g, 94% yield).

*1-Amino-5,6-dimethoxyindane hydrochloride (**13**)*

Colorless crystal. M.p.: 247–249 °C. ^{1}H-NMR (400 MHz, D_2O) δ 6.91 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 4.64–4.58 (m, 4H, CH–N, NH_3 and H_2O), 3.67 (s, 6H, $2OCH_3$), 2.95–2.87 (A part of AB, m, 1H, Ha of CH_2), 2.77–2.69 (B part of AB, m, 1H, Hb of CH_2), 2.42–2.35 (m, 1H, H of CH_2) and 2.00–1.93 (m, 1H, H of CH_2). ^{13}C-NMR (100 MHz, D_2O) δ 149.7 (C), 147.6 (C), 137.6 (C), 130.0 (C), 108.3 (CH), 107.6 (CH), 56.2 (OCH_3), 56.0 (OCH_3), 55.8 (CH–N), 30.4 (CH_2) and 29.7 (CH_2).

*1-Aminoindane hydrochloride (**14**)*

Standard procedure described in ''Standard procedure for the synthesis of amine hydrochlorides: 1-amino-5,6-dimethoxyindane hydrochloride (**13**)'' section was applied to azide **11** to give **14**, 91% yield, white solid. M.p.: 207–209 °C (literature[25] m.p.: 207–208 °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 1H, Ar-H, $J = 7.5$ Hz), 7.24–7.15 (m, 3H, Ar-H), 4.69–4.59 (m, 4H, CH–N, NH_3 and H_2O), 3.00–2.93 (A part of AB, m, 1H, H of CH_2), 2.82 (B part of AB, ddd, 1H, H of CH_2, $J = 5.7$, $J = 8.7$ and $J = 16.0$ Hz), 2.46–2.37 (m, 1H, H of CH_2), 1.98–1.90 (m, 1H, H of CH_2). ^{13}C-NMR (100 MHz, D_2O) δ 144.6 (C), 138.1 (C), 129.8 (CH), 127.2 (CH), 125.5 (CH), 124.5 (CH), 55.8 (CH-N), 30.2 (CH_2) and 29.7 (CH_2).

*1-amino-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride (**15**)*

Applying the procedure described in ''1-Azido-5-methoxy-1,2,3,4-tetrahydronaphthalene (**12**)'' section to azide **12** gave white solid **15** with 93% yield. M.p.: 248–250 °C (literature[26] m.p.: >250 °C). ^{1}H-NMR (400 MHz, D_2O) δ 7.08 (t, 1H, Ar-H, $J = 8.1$ Hz), 6.79 (d, 1H, Ar-H, $J = 8.1$ Hz), 6.78 (d, 1H, Ar-H, $J = 8.1$ Hz), 4.64 (bs, 1H of NH_3 and H of H_2O), 4.32 (dd, 1H, CH–N, $J = 5.0$ and $J = 9.9$ Hz), 3.61 (s, 3H, OCH_3), 2.54 (dt, 1H, H of CH_2, $J = 5.5$ and $J = 17.8$ Hz), 2.33 (dt, 1H, H of CH_2, $J = 7.3$ and $J = 17.8$ Hz), 1.92–1.74 (m, 2H, CH_2), 1.72–1.60 (m, 2H, CH_2). ^{13}C-NMR (100 MHz, D_2O) δ 157.0 (C), 132.4 (C), 127.3 (CH), 126.8 (C), 120.6 (CH), 111.0 (CH), 55.6 (OCH_3), 49.0 (CH–N), 26.7 (CH_2), 22.0 (CH_2) and 17.0 (CH_2).

*Methyl 5,6-dimethoxyindane-2-carboxylate (**17**)*

Et_3SiH (7.43, 63.94 mmol) was added to a solution of **16** (4.00 g, 15.98 mmol) in TFA (15 ml) under N_2 at room temperature. After the reaction mixture was refluxed for 2.5 h, TFA was evaporated. EtOAc (80 ml) and a concentrated solution of Na_2CO_3 in H_2O (50 ml) were added to the residue. Organic phase was separated and again washed with a solution concentration Na_2CO_3 in H_2O (50 ml). The organic phase was dried over Na_2SO_4 and solvent was evaporated. Chromatography of the residue on silica gel (25 g) column with 20% EtOAc–hexane yielded yellowish oily **17** (3.02 g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 2H, Ar-H), 3.70 (s, 3H, OCH_3), 3.696 (s, 3H, OCH_3), 3.692 (s, 3H, OCH_3), 3.35–3.32 (m, 1H, CH–CO), 3.21–3.09 (m, 4H, $2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.0 (CO), 148.4 (2C), 133.2 (2C), 107.7 (2CH), 56.2 ($2OCH_3$), 52.1 (OCH_3), 44.0 (CH-CO) and 36.4 ($2CH_2$).

*5,6-Dimethoxy-indane-2-carboxylic acid (**18**)*

Compound **17** (2.50 g, 10.58 mmol) was dissolved in MeOH (60 ml) and to this solution, 4 M NaOH (10 ml) was added at room temperature. The reaction mixture was stirred at room temperature for 20 h. After most of MeOH was evaporated, CH_2Cl_2 (20 ml) and H_2O (20 ml) were added to the residue. Organic layer was dispatched and the aqueous phase was acidified with 37% HCl (pH < 2). EtOAc (40 ml) was added to this acidified solution and organic layer was separated. H_2O phase was extracted with EtOAc (2×50 ml) and combined organic layers were dried over Na_2SO_4. After evaporation of the solvent and crystallization of the residue with CH_2Cl_2–hexane, acid **18** was obtained (2.25 g, 96%). M.p.: 124–126 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.4 (bs, 1, OH), 6.74 (s, 2H, Ar-H), 3.85 (s, 6H, $2OCH_3$), 3.41–3.25 (m, 1H, CH–CO), 3.23–3.14 (m, 4H, $2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 182.1 (CO), 148.6 (2C), 133.0 (2C), 107.7 (2CH), 56.3 ($2OCH_3$), 43.9 (CH-CO) and 36.2 ($2CH_2$).

*Benzyl 5,6-dimethoxyindane-2-ylcarbamate (**19**)*

To a stirred solution of **18** (2.10 g, 9.45 mmol) in anhydrous benzene (60 ml), DPPA (3.12 g, 11.33 mmol) and Et_3N (1.15 g, 11.33 mmol) were added. The mixture was heated at reflux temperature for 4 h. Then, benzyl alcohol (3.07 g, 28.48 mmol) was added, and refluxing of the mixture was continued for 30 h. The mixture was cooled to room temperature, the solvent was evaporated. Purifying of the resulting residue by CC on silica gel (20 g) with 20% EtOAc–hexane afforded 2.45 g (79%) of **19**, white solid. M.p.: 126–128 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (bs, 5H, Ph-H), 6.73 (s, 2H, Ar-H), 5.08 (s, 2H, OCH_2), 4.52 (bs, 1H, NH), 3.88–3.79 (m, 7H, H of CH–N and 6H of $2OCH_3$), 3.23 (A part of AB, dd, 2H, 2Ha-CH, $J = 6.6$ and $J = 15.5$ Hz), 2.73 (B part of AB, dd, 2H, 2Hb-CH, $J = 4.1$ and $J = 15.5$ Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.2 (CO), 148.6 (2C), 136.7 (C), 132.5 (2C), 128.8 (2CH), 128.4 (2CH), 108.2 (3CH), 66.9 (OCH_2), 56.3 ($2OCH_3$), 52.9 (CH–N) and 40.5 ($2CH_2$). IR (CH_2Cl_2, cm^{-1}): 3339, 3063, 3033, 2997, 2939, 2834, 1697, 1610, 1530, 1504, 1465, 1454, 1313, 1259, 1227, 1188, 1100 and 1044. Anal. Calcd for ($C_{19}H_{21}NO_4$): C 69.71, H 6.47 and N 4.28; Found C 69.68, H 6.48 and N 4.28.

*2-Amino-5,6-dimethoxyindane hydrocloride (**20**)*

The hydrogenolysis reaction of carbamate **19** was performed by the similar procedure described above for the reduction of azides to amine hydrochlorides in ''1-Azido-5-methoxy-1,2,3,4-tetrahydronaphthalene (**12**)'' section. But, here instead of azides, carbamate **19** was used to give **20** (95%) as colorless crystals m.p. 287–289 °C (literature[22] m.p. 287–289 °C). ^{1}H- and ^{13}C-NMR data are in agreement with data given previously[22].

*Standard procedure for hydrolysis of amine hydrochloride salts to amines: 1-amino-5,6-dimethoxyindane (**23**)*

Amine hydrochloride salt **13** (1.98 g, 12.00 mmol) was dissolved in MeOH (40 ml) and cooled to 0 °C. To this solution, solution of 10% NaOH (20 ml) was added. The reaction mixture was stirred at room temperature for 3 h. After most of MeOH was evaporated, CH_2Cl_2 (50 ml) and H_2O (20 ml) were added to the residue. Organic layer was separated and H_2O layer was extracted with CH_2Cl_2 (2×30 ml). Combined organic layers were dried over Na_2SO_4 and CH_2Cl_2 was evaporated. Oily aminoindane **23** (1.45 g, 94%) was synthesized and used without further purification in the next step. Amines **24**–**27** were synthesized from their corresponding salts **14**, **15**, **20** and **21** by the same procedure with yields of 92%, 95%, 95% and 94%, respectively.

*Standard procedure for the synthesis of sulfonamides: N-(5,6-dimethoxyindane-1-yl)methanesulfonamide (**28**)*

Amine **23** (0.47 g, 2.44 mmol) was dissolved in CH_2Cl_2 (30 ml) and this solution was cooled to 0 °C. To this solution, Et_3N (0.23 g, 2.93 mmol) and $MeSO_2Cl$ (0.34 g, 2.93 mmol) were added. The reaction mixture was stirred at room temperature

for 15 h. After the solvent was evaporated, the residue was chromatographed on silica gel (30 g) column with 30% EtOAc–hexane. Sulfonamide **28** was synthesized as white solid (0.53 g, 80% yield).

*N-(5,6-dimethoxyindane-1-yl)methanesulfonamide (**28**)*

Melting point (m.p.): 144–146 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 4.93–4.88 (m, 1H, CH-N), 4.66 (bd, 1H, NH, $J = 9.2$ Hz), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.03 (s, 3H, CH_3), 2.94 (A part of AB, ddd, 1H, CH_2, $J = 3.9$, $J = 8.3$ and $J = 15.5$ Hz), 2.81–2.73 (B part of AB, m, 1H, CH_2), 2.61 (dddd, 1H, CH_2, $J = 4.0$, $J = 7.8$, $J = 12.1$ and $J = 16.8$ Hz), 1.96–1.87 (m, 1H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.9 (C), 148.9 (C), 134.9 (C), 133.5 (C), 107.7 (CH), 107.2 (CH), 59.4 (CH–N), 56.4 (OCH_3), 56.2 (OCH_3), 42.1 (CH_3), 35.5 (CH_2), 30.1 (CH_2). IR (CH_2Cl_2, cm^{-1}): 3284, 3002, 2935, 2857, 2834, 1608, 1504, 1465, 1412, 1309, 1264, 1221, 1188, 1148, 1097. Anal. Calcd for ($C_{12}H_{17}NO_4S$): C 53.12, H 6.32, N 5.16 and S 11.82; Found C 53.08, H 6.34, N 5.12 and S 11.80.

*N-(Indane-1-yl)methanesulfonamide (**29**)*

Yield 82%; m.p.: 93–95 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37–7.19 (m, 4H, Ar-H), 5.06 (bd, 1H, NH, $J = 9.0$ Hz), 4.89–4.83 (m, 1H, CH–N), 3.00–2.93 (m, 4H, 1H of CH_2 and CH_3), 2.84–2.76 (m, 1H of CH_2), 2.55 (dddd, 1H of CH_2, $J = 3.6$, $J = 7.8$, $J = 11.3$ and $J = 15.8$ Hz), 1.89 (dddd, 1H of CH_2, $J = 3.6$, $J = 8.1$, $J = 12.8$ and $J = 15.8$ Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.0 (C), 142.4 (C), 128.5 (CH), 127.1 (CH), 125.1 (CH), 124.5 (CH), 59.0 (CH-N), 41.9 (CH_3), 35.1 (CH_2), 30.2 (CH_2). Anal. Calcd for ($C_{10}H_{13}NO_2S$): C 56.85, H 6.20, N 6.63 and S 15.18; Found C 56.82, H 6.18, N 6.66 and S 15.21.

*N-(5-metoksi-1,2,3,4-tetrahydronaphthalene-1-yl)methanesulfonamide (**30**)*

Yield 83%; m.p.: 142–144 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, 1H, Ar-H, $J = 7.7$ and $J = 8.1$ Hz), 7.02 (d, 1H, Ar-H, $J = 7.7$ Hz), 6.75 (d, 1H, Ar-H, $J = 8.1$ Hz), 4.64 (ddd, 1H, CH–N, $J = 5.5$, $J = 7.7$ and $J = 13.0$ Hz), 4.50 (d, 1H, NH, $J = 7.7$ Hz), 3.82 (s, 3H, OCH_3), 3.07 (s, 3H, CH_3), 2.72 (A part of AB, dt, 1H, Ha of CH_2, $J = 6.1$ and $J = 18.0$ Hz), 2.57 (B part of AB, dt, 1H, Hb of CH_2, $J = 7.1$ and $J = 18.0$ Hz), 2.07–1.79 (m, 4H, $2CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.4 (C), 137.0 (C), 127.0 (CH), 126.9 (C), 120.8 (CH), 109.0 (CH), 55.6 (OCH_3), 52.5 (CH-N), 42.4 (CH_3), 31.1 (CH_2), 22.9 (CH_2) and 18.8 (CH_2). IR (CH_2Cl_2): 3647, 3280, 3008, 2935, 2862, 1587, 1470, 1438, 1408, 1319, 1252, 1149, 1101, 1078 cm^{-1}. Anal. Calcd for ($C_{12}H_{17}NO_3S$): C 56.45, H 6.71, N 5.49 and S 12.56; Found C 56.42, H 6.72, N 5.49 and S 12.57.

*N-(1,2,3,4-tetrahydronaphthalene -2-yl)methanesulfonamide (**31**)*

85% yield; m.p.: 126–128 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16–7.05 (m, 4H, Ar-H), 4.52 (d, 1H, NH, $J = 7.5$ Hz), 3.87–3.81 (m, 1H, CH–N), 3.17 (A part of AB, dd, 1H, Ha of CH_2, $J = 4.7$ and $J = 16.2$ Hz), 3.01 (s, 3H, CH_3) 2.92 (t, 2H, CH_2, $J = 6.6$ Hz), 2.77 (B part of AB, dd, 1H, Hb of CH_2, $J = 8.2$ and $J = 16.2$ Hz), 2.18–2.11 (m, 1H, CH_2), 1.90–1.81 (m, 1H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.2 (C), 133.5 (C), 129.6 (CH), 129.1 (CH), 126.7 (CH), 126.4 (CH), 50.0 (CH-N), 42.2 (CH_3), 37.2 (CH_2), 30.3 (CH_2) and 27.2 (CH_2). IR (CH_2Cl_2): 3647, 3272, 3020, 2928, 2852, 1494, 1439, 1316, 1150, 1113, 1072 cm^{-1}. Anal. Calcd for ($C_{11}H_{15}NO_2S$): C 58.64, H 6.71, N 6.22 and S 14.23; Found C 58.63, H 6.71, N 6.28 and S 14.25.

*N-(5,6-dimethoxy-2,3-dihydro-1H-inden-2-yl)methanesulfonamide (**32**)*

78% yield; mp.: 162–164 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 2H, Ar-H), 4.89 (bd, 1H, NH, $J = 8.4$ Hz), 4.31–4.22 (m, 1H, CH–N), 3.83 (s, 6H, $2OCH_3$), 3.24 (A part of AB, dd, 2H of CH_2, $J = 7.2$ and $J = 15.5$ Hz), 2.98 (s, 3H, CH_3), 2.83 (B part of AB, dd, 2H of CH_2, $J = 5.8$ and $J = 15.5$ Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.7 (2C), 131.8 (2C), 108.1 (2CH), 56.3 ($2OCH_3$), 55.3 (CH–N), 41.7 (CH_3) and 41.0 ($2CH_2$). IR (CH_2Cl_2): 3249, 2958, 2930, 2840, 1605, 1560, 1504, 1443, 1404, 1311, 1219, 1188, 1169, 1152, 1096 cm^{-1}. Anal. Calcd for ($C_{12}H_{17}NO_4S$): C 53.12, H 6.32, N 5.16 and S 11.82; Found C 53.10, H 6.31, N 5.18 and S 11.85.

*N-(Indane-2-yl)methanesulfonamide (**33**)*

80% yield; m.p.: 134–136 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23–7.17 (m, 4H, Ar-H), 4.64 (ddd, 1H, CH–N, $J = 5.5$, $J = 7.7$ and $J = 13.0$ Hz), 4.70 (bd, 1H, NH, $J = 7.7$ Hz), 4.31 (m, 1H, CH–N), 3.30 (A part of AB, dd, 2H, 2Ha of CH_2, $J = 7.1$ and $J = 15.7$ Hz), 3.01 (s, 3H, CH_3) 2.91 (B part of AB, dd, 2H, 2Hb of CH_2, $J = 5.9$ and $J = 15.7$ Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.15 (2C), 127.3 (2CH), 124.95 (2CH), 55.1 (CH–N), 41.81 ($2CH_2$) and 41.02 (CH_3). IR (CH_2Cl_2): 3230, 3064, 2964, 2930, 2901, 1459, 1436, 1306, 1228, 1135, 1103, 1018 cm^{-1}. Anal. Calcd for ($C_{10}H_{13}NO_2S$): C 56.85, H 6.20, N 6.63 and S 15.18; Found C 56.88, H 6.23, N 6.60 and S 15.21.

Purification of hCA I and hCA II by affinity chromatography

CA isoenzymes were purified affinity chromatography using a column packed with Sepharose 4B-L-Tyrosine sulphanilamide resin via a simple one-step method using Sepharose-4B-L tyrosine-sulphanilamide affinity gel chromatography; described previously[27,28].

Hydratase and esterase activity assays

The effect of novel sulfonamides **28–33** on HCA isozyme activity was determined colorimetrically using CO_2-hydration method of Wilbur and Anderson[29] described previously[9]. Esterase activity was determined according to the method described by Verpoorte et al[30].

Protein determination

The yield of protein during the purification steps was determined spectrophotometrically at 595 nm according to the Bradford method[31], explained previously using bovine serum albumin as the standard protein[32].

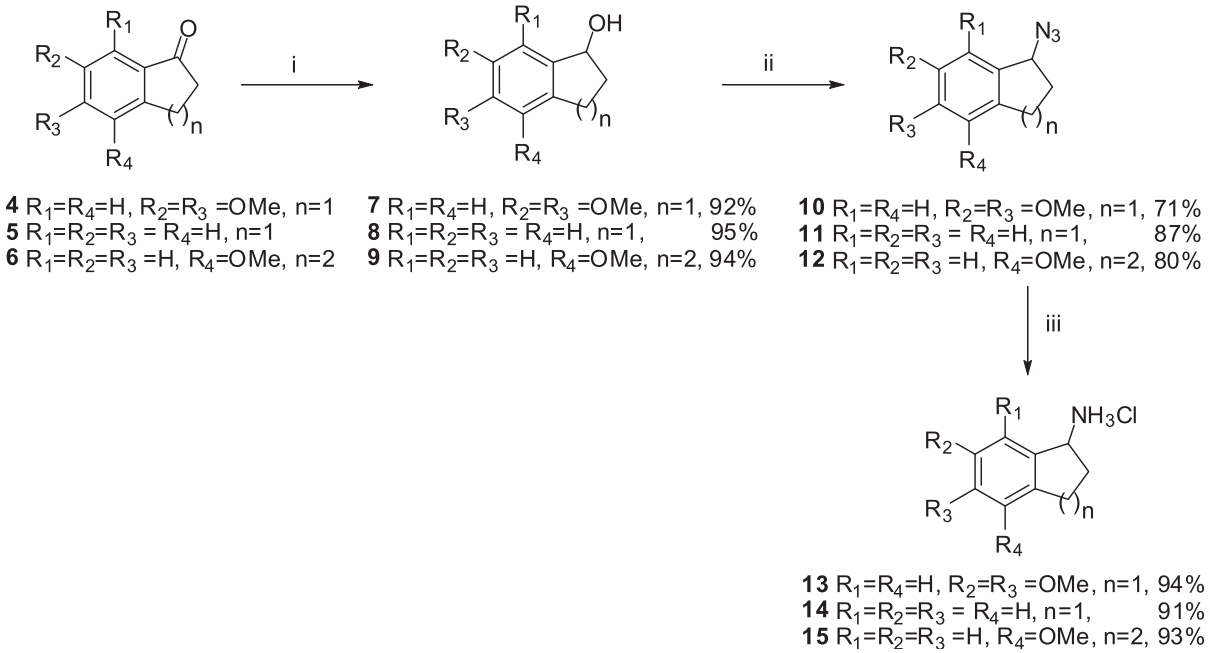
SDS polyacrylamide gel electrophoresis

SDS polyacrylamide gel electrophoresis (SDS-PAGE) by the method of Laemmli[33] was performed for determination of isoenzymes purity as described previously[34].

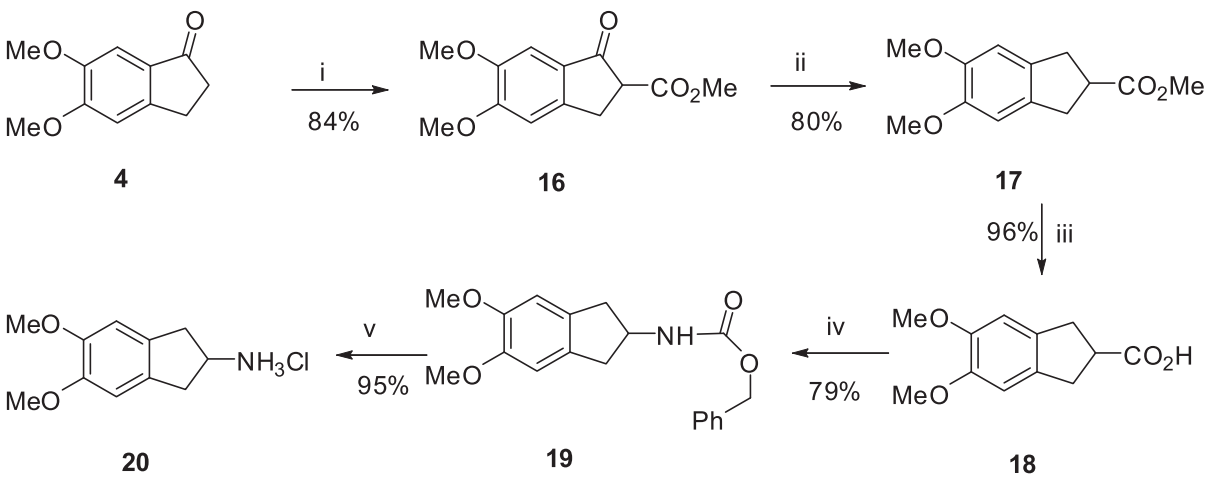
Results and discussion

Chemistry

Reduction of ketones **4–6** with $NaBH_4$ in MeOH at 0–25 °C gave corresponding alcohols **7**,[18] **8**[19] and **9**[20]. Mitsunobu reactions of *sec*-alcohols with HN_3 have been given in the literature clearly[35,36]. By applying this method to compounds **7–9**, we failed to synthesize azides **10–12**. In the literature, the synthesis of benzylazides from benzylalcohols has been managed with DPPA in the presence of DBU, which is known as an alternative



Scheme 2. Synthesis of benzylamine hydrochloride salts: (i) $NaBH_4$, MeOH, 0–25 °C, 3 h; (ii) DPPA/DBU, THF, 0 °C, 2 h, then 25 °C, 12 h, Ar(g); and (iii) H_2/Pd-C, $CHCl_3$–MeOH, 25 °C, 20 h.

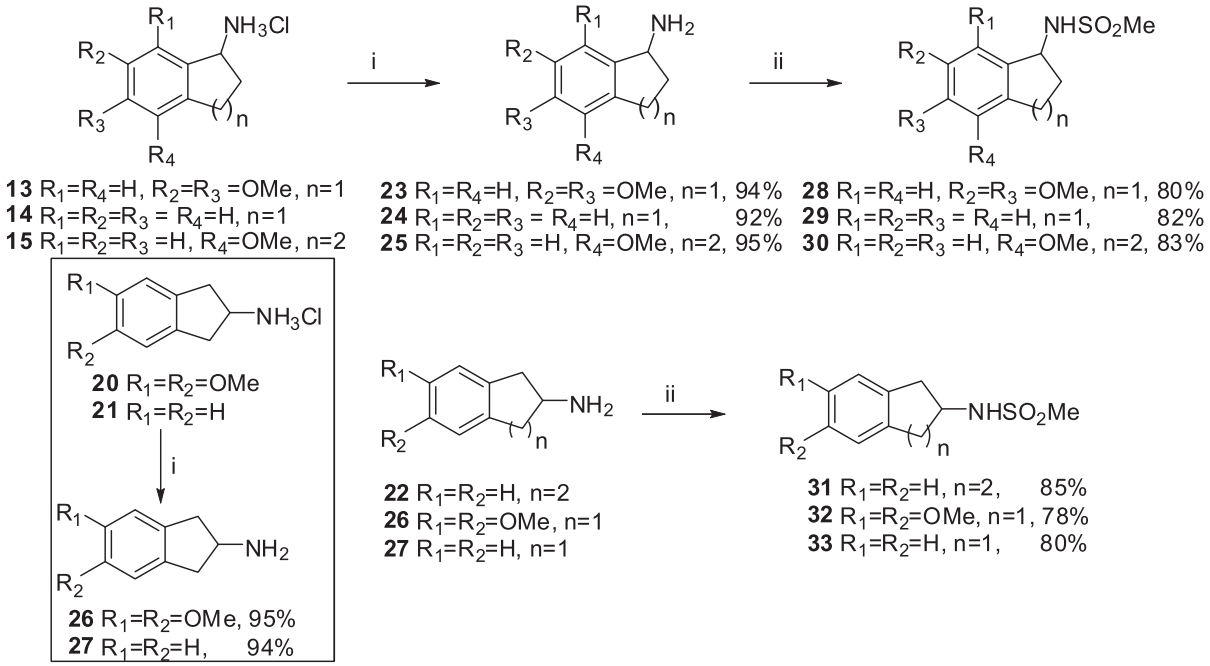


Scheme 3. Synthesis of 2-aminoindane hydrochloride **20**: (i) $(MeO)_2CO$/NaH, THF, 66 °C, 12 h; (ii) Et_3SiH, TFA, 72 °C, 2.5 h; (iii) a) 4 M NaOH solution, MeOH, 25 °C, 20 h; (b) 37% HCl; (iv) $(PhO)_2PON_3$, Et_3N, C_6H_6, reflux, 4 h then $PhCH_2OH$, reflux, 30 h; and (v) H_2/Pd-C, $CHCl_3$–MeOH, 25 °C, 20 h.

Mitsunobu reaction[37]. By a similar approach, the reaction of alcohols **7**–**9** with DPPA under mild conditions afforded azides **10**, **11**[24] and **12** in good yields. Reduction of azides to their corresponding amine hydrochloride salts via Pd-C catalyzed hydrogenation in MeOH–$CHCl_3$ has been reported.[22,38] Following the same synthetic methodology, we synthesized amine hydrochloride salts **13**, **14** and **15** (Scheme 2).

The reaction of **4** with $CO(OMe)_2$ in the presence of NaH in THF at reflux temperature afforded **16**. The reduction of ketone group of **16** with Et_3SiH in CF_3CO_2H gave **17**. Compound **18** was synthesized from the hydrolysis of **17** with aqueous NaOH in MeOH for 15 h then by acidification with concentrated HCl. The Curtius reactions of carboxylic acids with DPPA in benzene to alkyl isocyanates, the conversion of alkyl isocyanates to their corresponding carbamates and hydrogenolysis of carbamates to amine hydrochloride salts have been described previously.[39–41] By following this procedure, refluxing of acid **18** with DPPA in the presence of Et_3N in benzene for 6 h, then addition of $PhCH_2OH$ and hitting of the reaction mixture at the same temperature for 30 furnished a new carbamate **19**. Pd-C catalyzed hydrogenolysis of **19** in MeOH–$CHCl_3$ gave dopamine analogue **20**[24] (Scheme 3).

Compounds **21**[22] and **22**[23] were synthesized according to the literature procedure. Amine hydrochloride salts **13**–**15**, **20** and **21** were hydrolyzed to amines **23**–**27** with aqueous NaOH in MeOH. The synthesized amines **22**–**27** were used without further purification and characterization. All synthesized amines were converted to their sulfonamides **28**–**33** with $MeSO_2Cl$ in the presence of Et_3N in CH_2Cl_2 at 0–25 °C (Scheme 4). The structures of all synthesized compounds were characterized by ^{1}H- and ^{13}C-NMR. Azide functional groups were characterized by IR.



Scheme 4. Synthesis of sulfonamides: (i) 10% NaOH solution, MeOH, 0–25 °C, 3 h and (ii) $MeSO_2Cl/NEt_3$, CH_2Cl_2, 15 h.

CA isoenzyme inhibition studies

CA isoenzyme purification and activity assay

In order to remind CA inhibition mechanism by sulfonamide inhibitors (Scheme 1) should be noted that the active domain of CA isoenzymes contains an active zinc ion (Zn^{2+}) site; a strong Lewis acid that binds to, and activates a substrate H_2O molecule to catalyze the reversible hydration reaction of carbon dioxide. The metal ion is situated at the bottom of active site, being coordinated by three histidine residues (His 94, His 96 and His 119) and water molecule/hydroxide ion[42] (Scheme 1). Also, it was known that sulfonamides were the most important CA inhibitors, bind in a tetrahedral geometry of the Zn^{2+} ion, in deprotonated state[1,7] (Scheme 1).

In this study, CA isoenzymes I and II (hCA I and hCA II) were purified from human erythrocytes. The purification of both CA isozymes was performed using a simple one-step method with a Sepharose-4B-L-thyrosine-sulfanilamide affinity CC[43]. Human erythrocyte CA I isoenzyme was purified, 336.1-fold with a specific activity of 1445.2 EU mg^{-1} and overall yield of 62.4%; CA II isoenzyme was purified, 298.9-fold with a specific activity of 1285.4 EU mg^{-1} and an overall yield of 27.1%. We report here the first study on the inhibitory effects of novel sulfonamides **28–33** on the esterase activity of hCA I and hCA II. The inhibitor concentration that caused 50% inhibition (IC_{50}) was determined from activity versus (%)-(sulfonamides) plots and the average inhibition constant (K_i values) was calculated from Lineweaver–Burk plots (Table 1). The data of Table 1 show the following inhibition of hCA I and hCA II with novel sulfonamides **28–33**, by an esterase assay, with 4-NPA as substrate.

The metal-complexing anions and the sulfonamides with a terminal SO_2NH_2 group that coordinates to the Zn^{2+} ion. Simple anions such as HS-, CN-, NCO-, N_3-, HSO_3^-, I^- and $HCOO^-$ may bind with tetrahedral geometry or form trigonal–bipyramidal coordination[1,44], whereas the sulfonamides replace the water coordinated to zinc and the ''deep-water'' hydrogen-bonded to Thr199NH. Both waters are present in the uncomplexed state[45]. It had been shown that sulfamide and sulfamic acid act as moderate hCA II inhibitors, with inhibition constants of 1130 μM for sulfamide and 390 μM for sulfamic acid at the physiological pH (7.4), respectively. This contrasts remarkably to the strongly reduced affinity of the sulfate ion (1–2 M) toward hCA II[7].

Table 1. Human CA isoenzymes (hCA I and hCA II) inhibition data with some novel sulfonamides **28-33** by an esterase assay with 4-nitrophenylacetate as substrate.

	K_I (μM)			
Compounds	hCA-I	r^2	hCA-II	r^2
28	52 ± 9.2	0.982	215 ± 81.9	0.998
29	173 ± 47.7	0.972	211 ± 12.6	0.985
30	185 ± 15.4	0.968	112 ± 28.0	0.968
31	228 ± 64.3	0.954	94 ± 7.6	0.982
32	46 ± 5.4	0.978	372 ± 12.3	0.971
33	104 ± 32.1	0.952	170 ± 42.4	0.890

CA isoenzyme inhibition effects

hCA I and hCA II inhibitory effects of the novel sulfonamides **28–33** were tested under *in vitro* conditions and IC_{50} and K_i values were calculated and given in Table 1.

We report here the initial study on the inhibitory effects of synthesized novel sulfonamides **28–33** and on the hydratase activity of hCA I and hCA II. The data in Table 1 show the following regarding the inhibition of hCA I and hCA II activity by novel sulfonamides **28–33**. The strongest inhibitory activity has been observed with compound **32** ($IC_{50} = 266$ μM, $K_i = 46 \pm 5.4$ μM, $r^2 = 0.978$), investigated here for the inhibition of the rapid cytosolic isozymes hCA I. We speculated that two methyl groups of both molecules sterically facilitate the inhibition of hCA I. Similarly, the compound **28** ($IC_{50} = 487$ μM, $K_i = 52 \pm 05.4$, $r^2 = 0.982$) with the two methyl groups demonstrated same hCA I inhibitory activity. On the other hand, the most powerful hCA II isoenzyme inhibitory effect found in the compound **31** with K_i: 94 ± 7.6 μM ($IC_{50} = 338$ μM, $r^2 = 0.982$, Table 1). The half maximal inhibitory concentration (IC_{50}) is a measure of the

effectiveness of novel sulfonamides **28–33** in inhibiting CA isoenzyme function. A lower IC_{50} value reflects strong CA isoenzyme inhibition effect. Also, the remaining other sulfonamides were quite effective cytosolic isozyme hCA I inhibitors with IC_{50}s within the range of 52 ± 9.2–228 ± 6.43 μM and hCA II inhibitors with IC_{50}s in the range of 112 ± 28–372 ± 12.3 μM (Table 1). It is widely known that sulfonamides compounds are CA isoenzymes[46,47]. The results obtained from Table 1 clearly showed that the physiologically dominant cytosolic isozyme hCA I and hCA II were effectively inhibited by compounds **22–28**, with K_is within the range of 52 ± 9.2–372 ± 12.3 μM. The structure–activity relationship and inhibition properties of hCA II isoenzyme is particularly comparable to that what is outlined above for hCA I. Due to the two enzymes having a high sequence homology of amino acid present within the active site[48].

The synthesized novel sulfonamides **28–33** have one aromatic ring. These new synthesized compounds have been investigated as CA isoenzymes inhibitors in this study. The rationale of investigating these compounds as CA inhibitors exists in the fact that the compounds with aromatic rings have been shown to be the only competitive inhibitor with CO_2 as the substrate for the main isoform of CA, i.e. human CA I and II.

Conclusions

In summary, a series of novel **28**, **30–33** and a known sulfonamide **29** were synthesized starting from convenient reagents. The synthesized compounds may be important for further synthetic and biological purposes. In addition, CA inhibitory properties of the synthesized compounds **28–33** have also been evaluated. These compounds **28**, **30–33** are selective hCA I and hCA II inhibitors with selectivity ratios in the range of 52 ± 9.2–372 ± 12.3 μM.

Declaration of interest

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The authors report no conflicts of interest.

References

1. Supuran CT, Scozzafava A. Carbonic anhydrase inhibitors and their therapeutic potential. Expert Opin Ther Pat 2000;10:575–601.
2. Kaur IP, Smitha R, Aggarwal D, Kapil M. Acetazolamide: future perspective in topical glaucoma therapeutics. Int J Pharm 2002; 248:1–14.
3. Celebisoy N, Gökçay F, Sirin H, Akyürekli O. Treatment of idiopathic intracranial hypertension: topiramate vs acetazolamide, an open-label study. Acta Neurol Scand 2007;116:322–7.
4. Debus OM, Kurlemann G. Sulthiame in the primary therapy of West syndrome: a randomized double-blind placebo-controlled add-on trial on baseline pyridoxine medication. Epilepsia 2004;45: 103–8.
5. Puscas I, Buzas G. Treatment of duodenal ulcers with ethoxzolamide, an inhibitor of gastric mucosa carbonic anhydrase. Int J Clin Pharmacol Ther Toxicol 1986;24:97–9.
6. Supuran CT, Scozzafava A, Casini A. Carbonic anhydrase inhibitors. Med Res Rev 2003;23:146–89.
7. Abbate F, Supuran CT, Scozzafava A, et al. Nonaromatic sulfonamide group as an ideal anchor for potent human carbonic anhydrase inhibitors: role of hydrogen-bonding networks in ligand binding and drug design. J Med Chem 2002;45:3583–7.
8. Şentürk M, Gülçin İ, Daştan A, et al. Carbonic anhydrase inhibitors: inhibition of human erythrocyte isozymes I and II with a series of antioxidant phenols. Bioorg Med Chem 2009;17:3207–11.
9. Gülçin İ, Beydemir Ş, Büyükokuroğlu ME. In vitro and in vivo effects of dantrolene on carbonic anhydrase enzyme activities. Biol Pharm Bull 2004;27:613–16.
10. Hisar O, Beydemir Ş, Gülçin İ, et al. The effect of melatonin hormone on carbonic anhydrase enzyme activity in rainbow trout (*Oncorhynchus mykiss*) erythrocytes in vitro and in vivo. Turk J Vet Anim Sci 2005;29:841–5.
11. Innocenti A, Gülçin İ, Scozzafava A, Supuran CT. Carbonic anhydrase inhibitors: antioxidant polyphenol natural products effectively inhibit mammalian isoforms I-XV. Bioorg Med Chem Lett 2010;20:5050–3.
12. Innocenti A, Öztürk Sarıkaya SB, Gülçin İ, Supuran CT. Carbonic anhydrase inhibitors: Inhibition of mammalian isoforms I-XIV with a series of natural product polyphenols and phenolic acids. Bioorg Med Chem 2010;18:2159–64.
13. Öztürk Sarikaya SB, Topal F, Şentürk M, et al. In vitro inhibition of α-carbonic anhydrase isozymes by some phenolic compounds. Bioorg Med Chem Lett 2011;21:4259–62.
14. Öztürk Sarikaya SB, Gülçin İ, Supuran CT. Carbonic anhydrase inhibitors: inhibition of human erythrocyte isozymes I and II with a series of phenolic acids. Chem Biol Drug Design 2010;75: 515–20.
15. Beydemir Ş, Gülçin İ. Effect of melatonin on carbonic anhydrase from human erythrocyte in vitro and from rat erythrocyte in vivo. J Enzyme Inhib Med Chem 2004;19:193–7.
16. Çoban TA, Beydemir Ş, Gülçin İ, Ekinci D. Morphine inhibits erythrocyte carbonic anhydrase in vitro and in vivo. Biol Pharm Bull 2007;30:2257–61.
17. Çoban TA, Beydemir Ş, Gülçin İ, Ekinci D. The inhibitory effect of ethanol on carbonic anhydrase isoenzymes: in vivo and in vitro studies. J Enzyme Inhib Med Chem 2008;23:266–70.
18. Fraga BM, Cabrera I. The dimerization of 5,6-dimethoxy-indene. J Chem Res 2003;35:252–3.
19. Siscovic E, Chaudhari PN, Rao AS. Synthesis of some optically active substituted indans. Ind J Chem 1968;6:400–1.
20. Penick MA, Mahindaratne MP, Gutierrez RD, et al. Tandem Friedel-Crafts annulation to novel perylene analogues. J Org Chem 2008;73:6378–81.
21. Pan C, Zeng X, Guan Y, et al. Design and synthesis of brazilin-like compounds. Synlett 2011;425–9.
22. Göksu S, Seçen H. Concise syntheses of 2-aminoindans via indan-2-ol. Tetrahedron 2005;61:6801–7.
23. Orsini F, Sello G, Travainia E, Gennaro PD. A chemoenzymic synthesis of (2R)-8-substituted 2-aminotetralins. Tetrahedron Asymm 2002;13:253–9.
24. Breton GW, Daus KA, Kropp PJ. Surface-mediated reactions 2. Addition of hydrazoic acid to alkenes. J Org Chem 1992;57:6646–9.
25. Drefahl G, Ponsold K. Amino alcohols. X. Addition of iodine isocyanate to unsymmetrical olefins. Chem Ber 1960;93:519–23.
26. Martin YC, Jarboe CH, Krause RA, et al. Potential anti-Parkinson drugs designed by receptor mapping. J Med Chem 1973;16:147–50.
27. Senturk M, Ekinci D, Göksu S, Supuran CT. Effects of dopaminergic compounds on carbonic anhydrase isozymes I, II, and VI. J Enzyme Inhib Med Chem 2012;27:365–9.
28. Atasaver A, Özdemir H, Gülçin İ, Küfrevioğlu Öİ. One-step purification of lactoperoxidase from bovine milk by affinity chromatography. Food Chem 2013;136:864–70.
29. Wilbur KM, Anderson NG. Electrometric and colorimetric determination of carbonic anhydrase. J Biol Chem 1948;176:147–54.
30. Verpoorte JA, Mehta S, Edsall JT. Esterase activities of human carbonic anhydrases B and C. J Biol Chem 1967;242:4221–9.
31. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein dye binding. Anal Biochem 1976;72:248–51.
32. Gülçin İ, Küfrevioğlu Öİ, Oktay M. Purification and characterization of polyphenol oxidase from nettle (*Urtica dioica* L.) and inhibition effects of some chemicals on the enzyme activity. J Enzyme Inhib Med Chem 2005;20:297–302.
33. Laemmli UK. Cleavage of structural proteins during assembly of the head of bacteriophage T4. Nature 1970;227:680–5.
34. Şentürk M, Gülçin İ, Çiftci M, Küfrevioğlu Öİ. Dantrolene inhibits human erythrocyte glutathione reductase. Biol Pharm Bull 2008;31:2036–9.
35. Göksu S, Seçen H, Sütbeyaz Y. One-pot and stereospecific synthesis of cis-1,2-diazides via Mitsunobu reaction of epoxides. Synthesis 2002;2373–8.

36. Göksu S, Özalp Ç, Seçen H, et al. Double Mitsunobu reactions of cis-cycloalk-2-ene-1,4-diols and 3,4-epoxycycloalkenes: rearrangements of allylic diazides. Synthesis 2004;2849–54.
37. Thompson AS, Humphrey GR, DeMarco AM, et al. Direct conversion of activated alcohols to azides using diphenyl phosphorazidate: a practical alternative to Mitsunobu conditions. J Org Chem 1993;58:5886–8.
38. Mete E, Maraş A, Seçen H. A short synthesis of 4-amino-3-hydroxybutyric acid (GABOB) via allyl cyanide. Russ Chem Bull 2003;52:1879–81.
39. Göksu S, Kazaz C, Sütbeyaz Y, Seçen H. A concise synthesis of 2-amino-1,2,3,4-tetrahydronaphthalene-6,7-diol ('6,7-ADTN') from naphthalene-2,3-diol. Helv Chim Acta 2003;86:3310–13.
40. Göksu S, Seçen H, Sütbeyaz Y. An alternative synthesis of the dopaminergic drug 2-amino-1,2,3,4- tetrahydronaphthalene-5,6-diol (5,6-ADTN). Helv Chim Acta 2006;89:270–3.
41. Öztaşkın N, Göksu S, Seçen H. Alternative and straightforward synthesis of dopaminergic 5-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine. Synth Commun 2011;41:2017–24.
42. Şentürk M, Gülçin İ, Beydemir Ş, et al. In vitro inhibition of human carbonic anhydrase I and II isozymes with natural phenolic compounds. Chem Biol Drug Design 2011;77:494–9.
43. Coban TA, Beydemir S, Gücin İ, et al. Sildenafil is a strong activator of mammalian carbonic anhydrase isoforms I-XIV. Bioorg Med Chem 2009;17:5791–5.
44. Guerri A, Briganti F, Scozzafava A, et al. Mechanism of cyanamide hydration catalyzed by carbonic anhydrase II suggested by cryogenic X-ray diffraction. Biochemistry 2000;39:12391–7.
45. Hakansson K, Carlsson M, Svensson AL, Liljas A. Structure of native and apo carbonic anhydrase II and structure of some of its anion-ligand complexes. J Mol Biol 1992;227:1192–204.
46. Supuran CT, Clare BW. Carbonic anhydrase inhibitors-part 57: quantum chemical QSAR of a group of 1,3,4-thiadiazole-and 1,3,4-thiadiazoline disulfonamides with carbonic anhydrase inhibitory properties. Eur J Med Chem 1999;34:41–50.
47. Agrawal VK, Bano S, Supuran CT, Khadikar PV. QSAR study on carbonic anhydrase inhibitors: aromatic/heterocyclic sulfonamides containing 8-quinoline-sulfonyl moieties, with topical activity as antiglaucoma agents. Eur J Med Chem 2004;39:593–600.
48. Xue Y, Liljas A, Jonsson BH, Lindskog S. Structural analysis of the zinc hydroxide-Thr 199-Glu 106 hydrogen-bond network in human carbonic anhydrase II. Proteins: Struct Funct Genet 1993;106:93–106.

Notice of Correction:
The iFirst version of this article published online ahead of print on 12 January 2013 contained an error on page 6. In Scheme 4 ''R_1'' should have read ''R_2''. The corrected version is shown in this issue.