


## Synthesis, carbonic anhydrase I and II inhibition studies of the 1,3,5-trisubstituted-pyrazolines

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### ABSTRACT

4-(3-(4-Substituted-phenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) benzenesulfonamides (**9–16**) were successfully synthesized and their chemical structures were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS spectra. Carbonic anhydrase I and II inhibitory effects of the compounds were investigated.  $K_i$  values of the compounds were in the range of  $316.7 \pm 9.6$ – $533.1 \pm 187.8$  nM towards hCA I and  $412.5 \pm 115.4$ – $624.6 \pm 168.2$  nM towards hCA II isoenzymes. While  $K_i$  values of the reference compound Acetazolamide were  $278.8 \pm 44.3$  nM and  $293.4 \pm 46.4$  nM towards hCA I and hCA II isoenzymes, respectively. Compound **14** with bromine and compound **13** with fluorine substituents can be considered as the leader compounds of the series because of the lowest  $K_i$  values in series to make further detailed carbonic anhydrase inhibition studies.

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### KEYWORDS

Carbonic anhydrase; enzyme; pyrazoline; sulfonamide

### Introduction

Carbonic anhydrases (CAs) are a ubiquitous metalloenzyme catalyzing the reversible conversion of carbon dioxide to bicarbonate. CAs are present in prokaryote and eukaryote life forms. The enzyme is found in many tissues such as gastrointestinal tract, nervous system, kidneys, lungs, skin, and eyes. CAs play key roles in a number of physiological and pathological processes such as ions and gas exchanges, pH regulation, photosynthesis, calcification, and biosynthetic reactions such as gluconeogenesis, lipogenesis, and ureagenesis<sup>1</sup>. The mammalian enzymes belonging to  $\alpha$ -CA family consist of 16 active members, in which several are cytosolic (CA I–III, CA VII, and CA XIII), five are membrane-bound (CA IV, CA IX, CA XII, CA XIV, and CA XV), two are mitochondrial (CA VA and VB), and one (CA VI) is secreted in saliva and milk. Out of 16 different isoforms of  $\alpha$ -class of human-associated CAs, hCA I is found together with hCA II in erythrocytes. hCA II is the most widely distributed isoform in the eye, kidney, central nervous system, and inner ear, and is a drug target for clinically used diuretics, anti-glaucoma drugs, and anticonvulsants. Targeting a particular CA is often associated with treatment of particular diseases such as CA II, IV, and XII are the targets for anti-glaucoma agents; CA VA and VB for antiobesity agents; CA IX and XII for antitumour agents or diagnostic tools for imaging hypoxic tumours<sup>2–5</sup>.

The sulfonamides are an important class of the pharmaceutical compounds with a wide spectrum of biological activities such as anticancer<sup>6,7</sup>, CA inhibitory<sup>8,9</sup>, antibacterial<sup>10</sup>, antihypertensive<sup>11</sup>, antiinflammatory<sup>12</sup>, and antiprotozoal<sup>13</sup> activities among others.





On one hand, Acetazolamide (5-amino-1,3,4-thiadiazole-2-sulfonamide, AZA), which is used systematically to reduce intraocular pressure by lowering the humor formation in the eye, has sulfonamide moiety<sup>14</sup>. Although AZA is in clinical use, it has several side

effects such as numbness and tingling in the fingers and toes, taste alterations, blurred vision, kidney stones, and an increase in urination<sup>14</sup>.

On the other hand, pyrazole derivatives were registered in literature with several biological activities including antiepileptic, antidepressant, antiinflammatory, antimicrobial, antitubercular, anticancer, antibacterial, antioxidant, and CA inhibitory activities<sup>7,9,15–17</sup>. In addition, several 2-pyrazoline derivatives are known with a broad range of pharmacological activities such as analgesic and antipyretic (Phenazone/Amidopyrene/Methampyrone), antiinflammatory (Azolid/Tandearil), insecticidal (Indoxacarb), and uricosuric (Anturane)<sup>18</sup>.

The most extensively made modifications on 2-pyrazolines were diaryl/hetroaryl group substitutions at 3 and/or 5 positions. Celecoxib and Valdecoxib, which are in clinical use, were developed as cyclooxygenase-2 (COX-2) specific inhibitors. They are also known with their potent CA inhibitory activities<sup>19</sup>. Both compounds possess a benzenesulfonamide group linked to a five-membered substituted heterocyclic ring. The presence of the  $-\text{SO}_2\text{NH}_2$  moiety seems not to be necessary for COX-2 inhibition but it is essential for the CA inhibition<sup>19</sup>. These two drugs have shown interesting isoform selective CA inhibitory effects. Their X-ray crystal structures were in a complex form with hCA II<sup>19</sup>.

Recently, our research group focused on the synthesis of the compounds having 2-pyrazoline and sulfonamide pharmacophores in a single molecule and investigated their several bioactivities such as cytotoxic and/or CA inhibitory activities based on the results of previous studies<sup>7–9,17</sup>. In the present study, it was aimed to synthesize 4-[3-(4-substitutedphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl] benzenesulfonamides to investigate their carbonic anhydrase inhibitory effects on hCA I and II isoenzymes.

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## Experimental

### Materials and methods

$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) spectra were obtained using a Varian Mercury Plus spectrometer (Varian Inc., Palo Alto, CA). Chemical shifts ( $\delta$ ) were reported in parts per million (ppm). HRMS spectra of the compounds were taken by liquid chromatography ion trap-time of flight tandem mass spectrometer (Shimadzu, Kyoto, Japan) equipped with an electrospray ionization (ESI) source, operating in both positive and negative ionization mode. Shimadzu's LCMS Solution software (Shimadzu, Kyoto, Japan) was used for data analysis. Melting points were determined on Buchi 530 (Buchi Labortechnik AG, Flawil, Switzerland).

### General procedure for the synthesis of chalcones (1–8, Scheme 1)

An aqueous solution of NaOH (10%, 10 mL) was added into the ethanol (6 mL) solution of benzaldehyde (20.0 mmol) and a suitable acetophenone (20.0 mmol). The mixture was stirred overnight at room temperature and it was then poured on ice-water (100 mL). The mixture was neutralized with a solution of HCl (10%). The colored precipitate formed was filtered and crystallized from methanol-water (1–8). The yields of the chalcones were in the range of 34–82% [1 (39%), 2 (57%), 3 (82%), 4 (79%), 5 (71%), 6 (42%), 7 (34%), 8 (37%)]<sup>7,9,17,20–22</sup>.

### General procedure for the synthesis of pyrazolines (9–16, Scheme 1)

The mixture of a suitable chalcone (1.0 mmol) and 4-hydrazinobenzenesulfonamide hydrochloride (1.1 mmol) was dissolved in ethanol, and then catalytic amount of glacial acetic acid was added<sup>7,9,17</sup>. The mixture was refluxed for 12 h. Reactions were followed by thin layer chromatography (TLC). After the reaction was stopped, some of the solvent was removed under vacuum and the mixture was stirred for 12 h at room temperature. The obtained solid was filtered, dried at room temperature and crystallized from methanol–ether.

### 4-(3,5-Diphenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (9)

Mp 202–204 °C. 2.81 g (78%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 7.77 (d, 2H,  $J$  = 8.1 Hz), 7.57 (d, 2H,  $J$  = 8.1 Hz), 7.45–7.31

(m, 5H), 7.25–7.22 (m, 3H), 7.06 (d, 2H,  $J$  = 8.4 Hz), 7.00 (s, 2H, NH<sub>2</sub>), 5.63 (dd, 1H,  $J$  = 12.1, 5.1 Hz), 3.96 (dd, 1H,  $J$  = 17.8, 12.1 Hz), 3.16 (dd, 1H,  $J$  = 17.8, 5.1 Hz);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 150.3, 146.6, 142.3, 133.7, 132.4, 130.0, 129.8, 129.4, 128.3, 127.8, 126.8, 126.4, 112.7, 63.0, 43.7; HRMS (ESI-MS): calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 378.1271; found 378.1265.

### 4-(5-Phenyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (10)

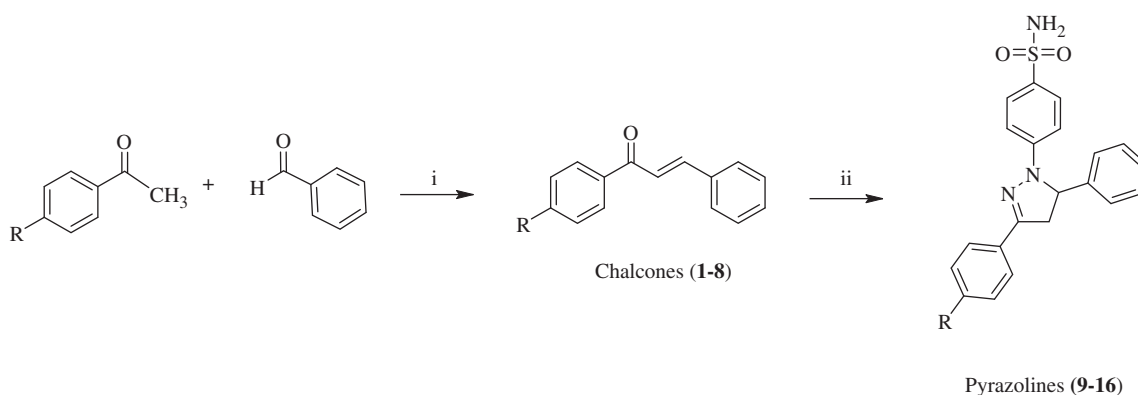
Mp 224–225 °C. 3.36 g (95%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 7.66 (d, 2H,  $J$  = 8.1 Hz), 7.56 (d, 2H,  $J$  = 9.1 Hz), 7.34–7.30 (m, 2H), 7.25–7.22 (m, 5H), 7.04 (d, 2H,  $J$  = 8.8 Hz), 6.99 (s, 2H, NH<sub>2</sub>), 5.59 (dd, 1H,  $J$  = 12.1, 5.1 Hz), 3.93 (dd, 1H,  $J$  = 17.6, 12.1 Hz), 3.14 (dd, 1H,  $J$  = 17.6, 5.1 Hz), 2.32 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 150.4, 146.6, 142.4, 139.8, 133.5, 130.0, 129.8, 129.7, 128.3, 127.8, 126.8, 126.4, 112.6, 62.9, 43.8, 21.7; HRMS (ESI-MS): calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 392.1427; found 392.1410.

### 4-(3-(4-Methoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (11)

Mp 204–206 °C. 2.91 g (85%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 7.71 (d, 2H,  $J$  = 8.8 Hz), 7.56 (d, 2H,  $J$  = 8.8 Hz), 7.34–7.30 (m, 2H), 7.25–7.22 (m, 3H), 7.03 (d, 2H,  $J$  = 8.8 Hz), 7.01–6.97 (m, 2H), 6.99 (s, 2H, NH<sub>2</sub>), 5.56 (dd, 1H,  $J$  = 12.1, 5.1 Hz), 3.92 (dd, 1H,  $J$  = 17.6, 12.1 Hz), 3.78 (s, 3H, OCH<sub>3</sub>), 3.13 (dd, 1H,  $J$  = 17.6, 5.1 Hz);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 160.9, 150.3, 146.8, 142.4, 133.3, 129.8, 128.4, 128.2, 127.8, 126.4, 125.0, 114.9, 112.4, 62.9, 55.9, 43.9; HRMS (ESI-MS): calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 408.1376; found 408.1370.

### 4-(3-(4-Chlorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (12)

Mp 196–198 °C. 2.75 g (81%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 7.77 (d, 2H,  $J$  = 8.4 Hz), 7.58 (d, 2H,  $J$  = 9.0 Hz), 7.48 (d, 2H,  $J$  = 8.4 Hz), 7.34–7.31 (m, 2H), 7.25–7.22 (m, 3H), 7.07 (d, 2H,  $J$  = 9.0 Hz), 7.02 (s, 2H, NH<sub>2</sub>), 5.63 (dd, 1H,  $J$  = 12.1, 5.1 Hz), 3.94 (dd, 1H,  $J$  = 17.8, 12.1 Hz), 3.16 (dd, 1H,  $J$  = 17.8, 5.1 Hz);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ , ppm)  $\delta$  = 149.2, 146.4, 142.2, 134.4, 134.0, 131.4, 129.8, 129.4, 128.4, 128.3, 127.8, 126.4, 112.8, 63.2, 43.5; HRMS (ESI-MS): calcd. for C<sub>21</sub>H<sub>19</sub>ClN<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 412.0881; found 412.0873.



(i) NaOH 10% aq, EtOH, 0–5 °C, 12 h; (ii) 4-Hydrazinobenzenesulfonamide hydrochloride, EtOH/glacial acetic acid, reflux 12 h. R: H for 1, 9; CH<sub>3</sub> for 2, 10; CH<sub>3</sub>O for 3, 11; Cl for 4, 12; F for 5, 13; Br for 6, 14; NO<sub>2</sub> for 7, 15; OH for 8, 16.

Scheme 1. Synthetic pathway of the benzenesulfonamides, 9–16.

#### 4-(3-(4-Fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (13)

Mp 202–204 °C. 3.03 g (87%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 7.82 (dd, 2H, *J* = 8.8, 5.5 Hz), 7.57 (d, 2H, *J* = 9.1 Hz), 7.34–7.22 (m, 7H), 7.05 (d, 2H, *J* = 9.1 Hz), 6.99 (s, 2H, NH<sub>2</sub>), 5.62 (dd, 1H, *J* = 12.1, 5.1 Hz), 3.95 (dd, 1H, *J* = 17.9, 12.1 Hz), 3.17 (dd, 1H, *J* = 17.9, 5.1 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 163.4 (d, <sup>1</sup>*J* = 247 Hz), 149.5, 146.6, 142.3, 133.8, 129.8, 129.1 (d, <sup>4</sup>*J* = 3 Hz), 129.0 (d, <sup>3</sup>*J* = 9 Hz), 128.3, 127.8, 126.4, 116.4 (d, <sup>2</sup>*J* = 21 Hz), 112.7, 63.2, 43.8; HRMS (ESI-MS): calcd. for C<sub>21</sub>H<sub>19</sub>FN<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 396.1177; found 396.1166.

#### 4-(3-(4-Bromophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (14)

Mp 190–192 °C. 2.86 g (90%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 7.71 (d, 2H, *J* = 8.8 Hz), 7.62 (d, 2H, *J* = 8.8 Hz), 7.57 (d, 2H, *J* = 9.0 Hz), 7.34–7.31 (m, 2H), 7.25–7.22 (m, 3H), 7.06 (d, 2H, *J* = 9.0 Hz), 7.01 (s, 2H, NH<sub>2</sub>), 5.63 (dd, 1H, *J* = 12.2, 5.3 Hz), 3.94 (dd, 1H, *J* = 17.8, 12.2 Hz), 3.16 (dd, 1H, *J* = 17.8, 5.3 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 149.3, 146.4, 142.2, 134.0, 132.4, 131.7, 129.8, 128.7, 128.4, 127.8, 126.4, 123.1, 112.8, 63.2, 43.4; HRMS (ESI-MS): calcd. for C<sub>21</sub>H<sub>19</sub>BrN<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 456.0376; found 456.0364.

#### 4-(3-(4-Nitrophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (15)

Mp 216–218 °C. 2.74 g (82%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 8.25 (d, 2H, *J* = 8.6 Hz), 7.99 (d, 2H, *J* = 8.6 Hz), 7.61 (d, 2H, *J* = 8.8 Hz), 7.35–7.32 (m, 2H), 7.26–7.24 (m, 3H), 7.14 (d, 2H, *J* = 8.8 Hz), 7.06 (s, 2H, NH<sub>2</sub>), 5.74 (dd, 1H, *J* = 12.4, 5.3 Hz), 4.01 (dd, 1H, *J* = 17.8, 12.4 Hz), 3.24 (dd, 1H, *J* = 17.8, 5.3 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 148.3, 147.7, 145.8, 141.9, 138.8, 134.9, 129.9, 128.5, 127.8, 127.5, 126.4, 124.7, 113.4, 63.7, 43.1; HRMS (ESI-MS): calcd. for C<sub>21</sub>H<sub>19</sub>N<sub>4</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 423.1122; found 423.1120.

#### 4-(3-(4-Hydroxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (16)

Mp 184–186 °C. 0.77 g (22%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 9.86 (s, 1H, OH), 7.61 (d, 2H, *J* = 8.8 Hz), 7.54 (d, 2H, *J* = 8.8 Hz), 7.33–7.30 (m, 2H), 7.24–7.21 (m, 3H), 6.99 (d, 2H, *J* = 9.1 Hz), 6.97 (s, 2H, NH<sub>2</sub>), 6.81 (d, 2H, *J* = 8.8 Hz), 5.54 (dd, 1H, *J* = 11.7, 5.1 Hz), 3.89 (dd, 1H, *J* = 17.6, 11.7 Hz), 3.10 (dd, 1H, *J* = 17.6, 5.1 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, ppm) δ = 159.5, 150.6, 146.8, 142.5, 133.1, 129.8, 128.5, 128.2, 127.8, 126.4, 123.4, 116.2, 112.3, 62.7, 43.9; HRMS (ESI-MS): calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 394.1220; found 394.1206.

## Biological activity

### Carbonic anhydrase enzyme assay

The purification of cytosolic CA isoenzymes (CA I and II) were previously described with a simple one-step method by a Sepharose-4B-L tyrosine-sulfanilamide affinity chromatography<sup>23</sup>. The protein quantity in the column effluents was determined spectrophotometrically at 280 nm. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was applied with a Bio-Rad Mini Gel system (Mini-PROTEAN Tetra System, Guangdong, China) after purification of both CA isoenzymes<sup>24,25</sup>. Briefly, it was performed in acrylamide for the running (10%) and the stacking gel (3%)

contained SDS (0.1%), respectively. Activities of CA I and II isoenzymes were determined according to the esterase method by Verpoorte et al.<sup>26</sup>. The increase in absorbance of reaction medium was spectrophotometrically recorded at 348 nm (UV-VIS Spectrophotometer, Shimadzu, UVmini-1240, Kyoto, Japan). Also, the quantity of protein was determined at 595 nm according to Bradford method<sup>27</sup>. Bovine serum albumin was used as standard protein. The IC<sub>50</sub> values were obtained from activity (%) versus compounds plots. For calculation of *K<sub>i</sub>* values, three different concentrations were used. The Lineweaver–Burk curves were drawn and calculations were realised<sup>28</sup>.

## Results and discussion

The compounds designed were successfully synthesized. The chemical structures of the compounds were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS spectra. The CA inhibition effects of the compounds were evaluated towards hCA I and hCA II isoenzymes. The inhibition values are presented in Table 1. As shown in Table 1, IC<sub>50</sub> values were in the range of 402.9–554.8 nM towards hCA I, while they were in the range of 458.6–620.4 nM towards hCA II. The IC<sub>50</sub> values of the reference compound AZA towards hCA I and hCA II were 985.8 nM and 489.4 nM, respectively. All compounds had lower IC<sub>50</sub> value than AZA toward hCA I, while the compounds **11**, **14**, and **16** had lower IC<sub>50</sub> value than AZA towards hCA II. According to IC<sub>50</sub> values of the compounds, chlorine-bearing compound **12** and bromine-bearing compound **14** were the most effective compounds towards hCA I while it was hydroxy derivative **16** towards hCA II.

When *K<sub>i</sub>* values of the compounds were considered, *K<sub>i</sub>* values of the compounds were in the range of 316.7 ± 9.6–533.1 ± 187.8 nM towards hCA I, while *K<sub>i</sub>* values were 412.5 ± 115.4–624.6 ± 168.2 nM towards hCA II. The *K<sub>i</sub>* values of reference compound AZA were 278.8 ± 44.3 nM and 293.4 ± 46.4 nM towards hCA I and hCA II, respectively. When *K<sub>i</sub>* values of the compounds were considered, **12** with chlorine, **14** with bromine, and **15** with nitro substituents, which have very close *K<sub>i</sub>* values, are the leader compounds of series towards hCA I, while **14** was the leader compound of the series towards hCA II because of the lowest *K<sub>i</sub>* values. All compounds were less effective than AZA on both hCA I and II isoenzymes, since *K<sub>i</sub>* value of the compound had higher values than AZA's.

Any substitution rather than hydrogen at the *para* position of phenyl ring decreased *K<sub>i</sub>* value of the substituted compound toward hCA I by comparing with **9**, which is non-substituted derivative. This means that substitution at the *para* position of phenyl ring was a useful modification to increase the effect of compound toward hCA I. Exception was **11**, which is a methoxy-

**Table 1.** Human CA isoenzymes (hCA I and II) inhibition value of the compounds (9–16) by the esterase method with 4-nitrophenyl acetate as substrate.

Compounds	IC <sub>50</sub> (nM)		<i>K<sub>i</sub></i> (nM)			
	hCA I	<i>r</i> <sup>2</sup>	hCA II	<i>r</i> <sup>2</sup>	hCA I	hCA II
<b>9</b>	554.8	0.9759	586.3	0.9723	506.3 ± 133.5	624.6 ± 168.2
<b>10</b>	491.8	0.9816	620.4	0.9565	476.5 ± 81.1	561.5 ± 133.9
<b>11</b>	483.9	0.9743	486.3	0.9688	533.1 ± 187.8	469.0 ± 63.0
<b>12</b>	402.9	0.9646	559.3	0.9814	377.6 ± 113.8	520.6 ± 131.8
<b>13</b>	493.2	0.9709	536.0	0.9737	462.2 ± 133.5	587.3 ± 188.5
<b>14</b>	404.8	0.9817	470.5	0.9602	316.7 ± 9.6	412.5 ± 115.4
<b>15</b>	416.5	0.9815	534.3	0.9631	325.8 ± 29.4	430.3 ± 87.3
<b>16</b>	528.2	0.9710	458.6	0.9772	472.0 ± 57.5	591.9 ± 134.5
AZA	985.8	0.9811	489.4	0.9972	278.8 ± 44.3	293.4 ± 46.4

Acetazolamide (AZA) was used as a standard inhibitor for all hCA isoenzymes. The results were expressed as nanomolar (nM).

substituted derivative. The effect of any substituent on phenyl ring to  $K_i$  value of substituted compound towards hCA II isoenzyme was similar to hCA I's. It means that any type of substituent on phenyl ring rather than hydrogen was a useful modification to increase the compounds effect on hCA II by lowering the  $K_i$  values without exception.


## Conclusion

In conclusion, the compounds **12**, **14**, and **15** towards hCA I and **14** towards hCA II seem to be the leader compounds of the series for further investigations.

## Disclosure statement

The authors report that they have no conflicts of interest and are responsible for the contents and writing of the paper. The authors H. I. G. and E. M. thank to Ataturk University for the financial support. This research work was supported by Ataturk University Research Found, Turkey (Project No: 2013/289).

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