

## Inhibitory Properties of Aniline, Aminophenol Compounds and their *N*-acetylated Derivatives on Carbonic Anhydrase

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### Abstract

Carbonic anhydrases (CAs) are a group of metalloenzymes responsible for speeding up the conversion of carbon dioxide and water to a bicarbonate ion and a proton. CAs is divided into seven well-defined classes, namely, alpha, beta, gamma, delta, zeta, eta and theta. The alpha class of CAs is found in animal systems and is involved in various physiological and pathological processes. In some cases CA inhibition is required to treat certain disorders. Over the years metal complexing anions and sulfonamide compounds have been used extensively for this purpose. This paper investigated the potential inhibitory properties of aminophenol (AP) compounds and their acetylated derivatives against human cytosolic carbonic anhydrase (hCA) isozymes I and II.

**Keywords:** Carbonic anhydrase, aminophenol, inhibitory, esterase activity

### Introduction

Carbonic anhydrases (CAs) are essential for life, they are found in all living organisms and are divided into seven well-defined classes named alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ), delta ( $\delta$ ), zeta ( $\zeta$ ), eta ( $\eta$ ) and theta ( $\theta$ )

CAs (DE SIMONE et al. 2015; DEL PRETE et al. 2014; OZENSOY GULER et al. 2016 and SUPURAN et al. 2017).  $\alpha$ -CAs has been identified in animal systems,  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ - and  $\theta$ -CAs has been identified in algae and plants,  $\alpha$ - and  $\beta$ -CAs has been identified in fungi and  $\alpha$ -,  $\beta$ -,  $\gamma$ -CAs has been identified in bacteria (SUPURAN et al. 2017; CAPASSO et al. 2016 and CAPASSO et al. 2015). CAs catalyze a simple but pivotal reversible reaction, the hydration of CO<sub>2</sub> by H<sub>2</sub>O to HCO<sub>3</sub><sup>-</sup> and H<sup>+</sup>, by means of a metal (zinc, cadmium, iron or cobalt) ion (SUPURAN et al. 2017; SUPURAN 2008 and SUPURAN 2017). The CAs are crucial components in various physiological and pathological processes, including respiration, pH and CO<sub>2</sub> homeostasis, bone resorption, calcification, tumorigenesis, biosynthetic processes, electrolyte secretion in tissues and organs, photosynthesis and CO<sub>2</sub> fixation (SUPURAN 2008; SUPURAN et al. 2017). In humans 16 diverse isoforms ( $\alpha$ -CA isozymes) are produced in various tissues, differing in their cellular localization, catalytic activity, sites of expression and biophysical properties (SUPURAN 2008). The human  $\alpha$ -CA isozymes are categorized as follow: five cytosolic (CA I, CA II, CA III, CA VII and CA XIII), five membrane-bound (CA IV, CA IX, CA XII, CA XIV and CA XV), two mitochondrial (CA VA and CA VB), one secreted (CA VI) and three non-catalytic enzymes named as carbonic anhydrase related proteins (CA VIII, CA X and CA XI). The current research focused on CA I and CA II. CA I is found in erythrocytes and GI tract and is involved in functions including antireflux defense, gas exchange and ion transport. CA II, the most catalytically active enzyme, is found in almost all cells and is involved in functions including hydration/dehydration of CO<sub>2</sub> and

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water, acid-base balance, antireflux defence, bone resorption, sperm motility, urine acidification and cerebrospinal fluid secretion (SLY et al. 1983 and HASSAN et al. 2013). CAs are drug targets for inhibitors and activators (not covered in this article). Inhibition of CAs restrain the activity of CA and leads to the treatment of a wide range of disorders and diseases, including glaucoma, obesity, cancer, edema, epilepsy and osteoporosis (SUPURAN 2017, SCOZZAFAVA et al. 2006; VULLO et al. 2005 and KRUNGKRAI 2005). Many carbonic anhydrase inhibitors (CAIs) have been marketed and many potential CAIs have been reported in the literature (SPLENDIANI et al. 2006; MINCIONE et al. 2007; SUGRUE 2000; PICARD 2000; VULLO et al. 2003 and RIIHONEN et al. 2007). CAI marketed over the years includes and are not limited to Acetazolamide (a mild diuretic), Methazolamide (antiglaucoma agent), Topiramate (anti-epileptic) and Dorzolamide (antiglaucoma agent). Although these drugs have been clinically used for decades, there is a pressing need for the identification and discovery of new molecules as starting points for drug development. Cost effective and green friendly routes to produce drugs with fewer side effects are also goals of these studies.

Aminophenols (APs) are interesting compounds as they possess two nucleophilic centers which could be tweaked and transformed. They have been used for many years as intermediates and building blocks for the preparation of numerous compounds including various pharmaceutical compounds (SINGH et al. 2017; SHADYRO et al. 2008, GIURG et al. 2017 and GASICH et al. 2009). 4-Aminophenol and 2-aminophenol has been reported to have antioxidant and antibacterial activity (BARBER 1944 and BENDARY et al. 2013). In addition, 4-aminophenol is well-known since the acetylation of its amine group affords a renowned pain reliever named acetaminophen or more commonly known as paracetamol. The pharmacological properties of acetaminophen inspired us to screen a few aminophenol compounds and their corresponding *N*-acetylated derivatives as possible inhibitors of CA. In addition, we wanted to investigate compounds that are simple to prepare that can be used as drugs or building blocks for drugs. In this study we report a screening of amino phenol compounds, aniline and

their *N*-acetylated derivatives as potential inhibitors against hCA I and hCA II.

## Materials and Methods

### Chemicals

The compounds aniline, phenol, catechol, acetazolamide, 2-aminophenol, 2-amino-4-methylphenol and 2-amino-4-bromophenol were purchased from Sigma-Aldrich and used as received without further purification. All other chemicals and solvents were purchased from Merck (Darmstadt, Germany). All solvents were purified using standard methods and freshly distilled. Sepharose 4B, protein assay reagents and 4-nitrophenylacetate were obtained from Sigma-Aldrich.

### Experimental

**General Procedures.** Thin layer chromatography (tlc) was used to monitor reactions using aluminium-baked plates coated with Merck silica-gel F<sub>254</sub> in a suitable solvent system. Column chromatography was performed on Fluka Silica Gel 60. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian 400 spectrometer in deuterated chloroform or deuterated acetone. Chemical shifts are quoted using residual chloroform ( $\delta$  7.24 in <sup>1</sup>H NMR) as an internal standard. All chemical shifts are reported in ppm and all coupling constants are quoted in Hz.

**Reaction for the acetylation of aminophenols and aniline.** To a stirred solution of aminophenol (16 mmol) in 100 mL of CH<sub>2</sub>Cl<sub>2</sub>/acetone (80:20) was added imidazole (17 mmol) and cooled to 10 °C in an ice water bath. To the reaction mixture was added 10 mL acetyl chloride (17 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and the mixture was chromatographed on silica gel with hexane - ethyl acetate (3:2) as eluent to afford the corresponding acetanilides in high yields.

***N*-(2-Hydroxyphenyl) acetamide 2** (93 %) was obtained as a white solid.  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>): 2.10 (s, 3H, CH<sub>3</sub>), 6.76 (td, 1H, *J* = 7.9 and 1.0 Hz, Ar-CH), 6.85 (dd, 1H, *J* = 7.9 and 1.0 Hz, Ar-CH), 6.94 (td, 1H, *J* = 7.9 and 1.0 Hz, Ar-CH), 7.67 (dd, 1H, *J* =

7.9 and 1.0 Hz, Ar-CH), 9.31 (br. s, 1H, NH), 9.74 (s, 1H, OH).  $\delta_C$  (100 MHz,  $CDCl_3$ ): 23.5 ( $CH_3$ ), 115.9 (Ar-CH), 118.9 (Ar-CH), 122.3 (Ar-CH), 124.6 (Ar-CH), 126.4 (Ar-C), 147.8 (Ar-C), 168.9 (C=O) (JONCOUR et al. 2014).

***N*-(5-Bromo-2-Hydroxyphenyl) acetamide 6** (90 %) was obtained as a white solid.  $\delta_H$  (400 MHz,  $CDCl_3$ ): 2.10 (s, 3H,  $CH_3$ ), 6.81 (d, 1H,  $J = 8.4$  Hz, Ar-CH), 7.07 (d, 1H,  $J = 8.4$  Hz, Ar-CH), 8.07 (s, 1H, Ar-CH), 9.27 (br. s, 1H, NH), 10.15 (s, 1H, OH).  $\delta_C$  (100 MHz,  $CDCl_3$ ): 23.7 ( $CH_3$ ), 109.6 (Ar-CH), 116.9 (Ar-CH), 123.8 (Ar-CH), 126.4 (Ar-C), 128.1 (Ar-C), 146.7 (Ar-C), 169.0 (C=O) (ARMITAGE et al. 2012).

***N*-(5-Methyl-2-Hydroxyphenyl) acetamide 7** (85 %) was obtained as a white solid.  $\delta_H$  (400 MHz,  $CDCl_3$ ): 2.16 (s, 3H,  $CH_3$ ), 7.11 (m, 1H, Ar-CH), 7.32 (m, 2H, Ar-CH), 7.50 (m, 2H, Ar-CH).  $\delta_C$  (100 MHz,  $CDCl_3$ ): 24.6 ( $CH_3$ ), 119.9 (2 x Ar-CH), 124.3 (Ar-CH), 129.0 (2 x Ar-CH), 137.9 (Ar-C), 168.5 (C=O) (JADHAV et al. 2016).

***N*-phenylacetamide 9** (89 %) was obtained as a white solid.  $\delta_H$  (400 MHz,  $CDCl_3$ ): 2.19 (s, 3H,  $CH_3$ ), 2.20 (s, 3H,  $CH_3$ ), 6.81 (m, 2H, Ar-CH), 7.18 (s, 1H, Ar-CH), 9.10 (br. s, 1H, NH), 9.24 (br. s, 1H, OH).  $\delta_C$  (100 MHz,  $CDCl_3$ ): 19.8 ( $CH_3$ ), 22.8 ( $CH_3$ ), 118.2 (Ar-CH), 122.6 (Ar-CH), 126.5 (Ar-CH), 126.7 (Ar-C), 128.9 (Ar-C), 146.5 (Ar-C), 170.5 (C=O) (PISANESCHI et al. 2011).

#### ***Purification of Carbonic Anhydrase isozymes from human erythrocytes by affinity chromatography***

Fresh human blood obtained from the Blood Center at Ataturk University Research Hospital was used to obtain purified erythrocytes. The blood samples were centrifuged at 1500 rpm for 15 min and then the plasma and white blood cells were removed. The red blood cells (erythrocytes) were washed two times with saline (0.9 % NaCl) and homolyzed with ice-cold deionized water. The serum was isolated by centrifugation at 20,000 rpm for 30 min at 4 °C. The pH of the hemolysate was adjusted to 8.7 with solid Tris. The enzyme was purified with a prepared Sepharose 4B-aniline-sulfanylamide affinity column. The column was equilibrated with 25 mM Tris-HCl/0.1 M  $Na_2SO_4$ , pH 8.7. The hemolysate was

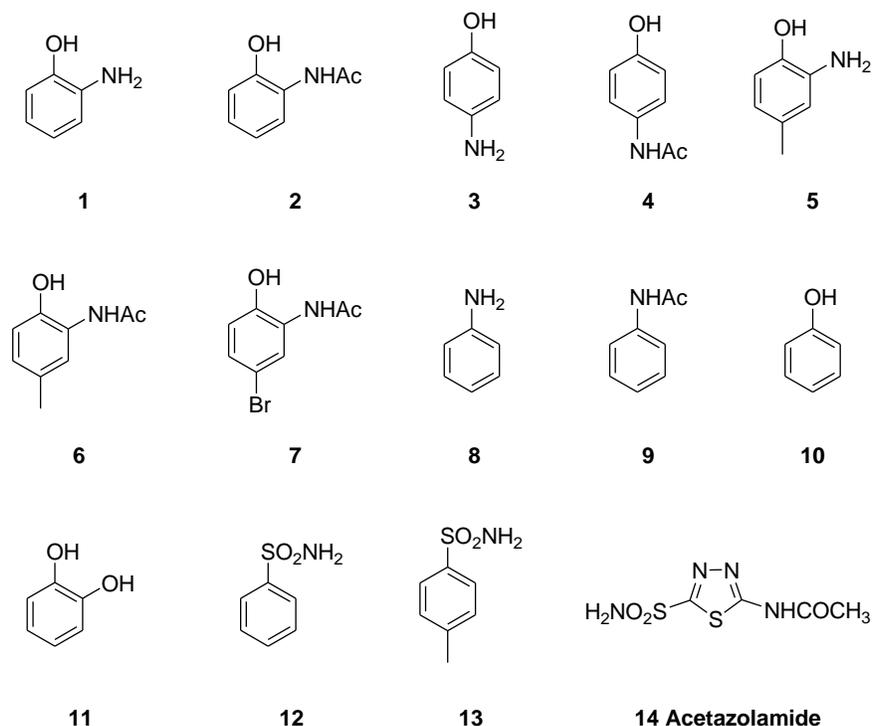
applied to the column and the column was washed with 25 mM Tris-HCl/22 mM  $Na_2SO_4$ , pH 8.7. The hCA I and hCA II isozymes were eluted with 1 M NaCl/25 mM  $Na_2HPO_4$ , pH 6.3 and 0.1 M  $CH_3COONa$ /0.5 M  $NaClO_4$ , pH 5.6, respectively (ALP et al. 2010).

#### ***Esterase Activity Assay***

The esterase activity was determined spectrophotometrically (ThermoScientific Evolution 200 Series UV-VIS). The method by Verpoorte was followed by which the change in absorbance at 348 nm of 4-nitrophenylacetate (NPA - substrate) to 4-nitrophenylate ion over a period of 3 min at 25 °C was measured (VERPOORTE et al. 1976). Each inhibitor (1 mg) was dissolved in 1mL DMSO and then diluted to various concentrations with deionized water (six serial dilutions). All inhibitors were tested in triplicate at each concentration. The reaction system was prepared at room temperature in a quartz cuvette. The reaction system was composed of 1.4 mL of buffer (0.5 M, pH 7.4: Tris- $SO_4$  buffer), 1 mL 4-nitrophenylacetate (3 mM), 0.5 mL  $H_2O$  and 0.1 mL enzyme solution. A reference measurement was obtained by measuring the reaction solution without the enzyme. hCA I and hCA II enzyme activities of inhibitors **1**, **2**, **5**, **6**, **7**, **8** and **9** were measured. The control contained the reaction mixture without the inhibitor. For each inhibitor an Activity (%) – Inhibitor Concentration ( $\mu M$  or nM) graph was drawn. The results are reported as inhibitory constants ( $K_i$ ). To determine the  $K_i$  values, six different inhibitor concentrations were tested and Lineweaver-Burk curves were drawn (LINEWEAVER et al 1934).

#### ***Results and Discussion***

CAs are essential for many processes however they do have negative impacts on various systems including the human body. In these cases CAIs are used to reverse the unwanted effects. Clinically used CAIs includes diuretics, anticonvulsants, glaucoma drugs and anticancer agents. The search for new inhibitors has escalated over the years. New compounds are constantly being screened in the hope to find isozyme selective inhibitors with increased CA inhibition activity. In a search for new CAIs human CA isozymes I and II were purified and the



**Figure 1.** Structures of the compounds screened against CA.

inhibitory effects of APs and their *N*-acetylated derivatives (**1**, **2**, **5**, **6** and **7**) and aniline **8** and its acetylated derivative **9** were investigated (Figure 1). 4-Aminophenol **3**, its acetylated derivative acetaminophen **4**, phenol **10**, catechol **11**, benzenesulfonamide **12** and 4-methylbenzenesulfonamide **13** were also included in this study for comparison purposes. Compound **14**, acetazolamide, a clinically used CAI possessing a sulfonamide group was used as standard.

Classical CAIs includes sulfonamides and their derivatives, which were first reported in 1940 (MANN et al. 1940). Forty two years later phenol was discovered to be a CAI (SIMONSSON et al. 1982). Since then many studies have been reported relating to the CA inhibitory activity of phenolic compounds (INNOCENTI et al. 2008 and SARIKAYA et al. 2011). Sulfonamides (SO<sub>2</sub>NH<sub>2</sub>) bind to the zinc ion of the enzyme while phenols (OH) bind to the zinc-bound water/hydroxide ion of the enzyme and to the amide of Thr199 (an amino acid that plays a pivotal role in the catalytic cycle of

the enzymes) through hydrogen bonds (INNOCENTI et al. 2008). It was anticipated that APs could possess similar inhibitory activity to phenolic compounds since APs contain an OH group as well as a NH group. The NH group could bind in the same way as the OH group binds to the enzyme. In light of this, aniline and phenol were included in the study to determine the effect of a simple aromatic ring with either a NH or OH moiety compared to APs with both a NH and OH attached to the aromatic ring.

Inhibition data against CA I and II with compounds **1-14** are shown in Table 1. Acetazolamide (**AZA**) showed K<sub>i</sub> values of 0.2 μM and 0.01 μM for hCA I and hCA II respectively. A comparison of the K<sub>i</sub> values of the compounds **1-9** revealed that they possess good to moderate inhibitory activity against hCA I (K<sub>i</sub> values between 3.0 μM and 420.5 μM) and moderate to weak inhibitory activity against hCA II (K<sub>i</sub> values between 6.2 μM and 4030.0 μM). Comparing the K<sub>i</sub> values of the APs (**1**, **3** and **5**), aniline **8** and the simplest phenol **10** the following results were observed: (i) the APs were weaker

inhibitors against hCA I compared to **8** and **10**; (ii) the APs were weaker inhibitors against hCA II compared to **10** but stronger inhibitors compared to **8** (see entry 1, 3, 5, 8 and 10). A simple aromatic ring possessing both OH and NH<sub>2</sub> functionalities did not increase the activity as anticipated although it should be noted that this was a screening of a small library of compounds, a broader study needs to be undertaken to conclude these results. Minor structural changes to **10** led to a loss of inhibitory activity, adding a NH<sub>2</sub> functional group to **10** in the ortho (**1**) or para (**3**)

position led to a decrease in activity by 3.8 and 15.6 times respectively for hCA I and 78.7 and 136.7 times respectively for hCA II (see entries 1, 3 and 10). Nair et al. showed that the phenyl component of phenol laid snugly within the hydrophobic part of the hCA II active site, which is one of the reasons for the good CA inhibition activity of phenol (NAIR et al. 1994). Additional studies will be initiated in order to understand the molecular features responsible for the change in activity noticed in these aminophenol compounds.

**Table 1.** Screening results of various compounds against hCA I and hCA II.

Entry	Tested Compounds	K <sub>i</sub> (μM) <sup>a</sup> hCA I	K <sub>i</sub> (μM) <sup>a</sup> hCA II
<b>1</b>	<b>1</b>	39.3	433.2
<b>2</b>	<b>2</b>	31.5	135.8
<b>3</b>	<b>3</b> *	159.0	752.0
<b>4</b>	<b>4</b> *	10.0	6.2
<b>5</b>	<b>5</b>	35.3	184.2
<b>6</b>	<b>6</b>	10.2	76.5
<b>7</b>	<b>7</b>	43.3	79.8
<b>8</b>	<b>8</b>	3.0	4030
<b>9</b>	<b>9</b>	420.5	130.0
<b>10</b>	Phenol ( <b>10</b> )*	10.2	5.5
<b>11</b>	Catechol ( <b>11</b> )*	4003	9.9
<b>12</b>	Benzenesulfonamide ( <b>12</b> ) <sup>+</sup>	23.4	5.9
<b>13</b>	4-Methylbenzenesulfonamide ( <b>13</b> ) <sup>+</sup>	78.5	0.3
<b>14</b>	Acetazolamide ( <b>14</b> )	0.2	0.01

<sup>a</sup> Mean from three different assays. Errors in the range of 2 % of the reported value (data not shown).

\* Innocenti 2008 and <sup>+</sup> Demirdağ 2013

An interesting trend was observed when comparing the APs to their *N*-acetylated derivatives. Supuran et al. showed that 4-aminophenol **3** (K<sub>i</sub> of 159.0 μM) was 16 times less active compared to its acetylated derivative acetaminophen **4** (K<sub>i</sub> of 10.0 μM) for hCA I. This was also observed for the hCA II study, **3** (K<sub>i</sub> of 752.0 μM) was 121 times less active compared to **4** (K<sub>i</sub> of 6.2 μM) (INNOCENTI et al. 2008). The same

trends were observed for the APs and their *N*-acetylated derivatives (**1**, **2**, **5**, **6**) synthesized in the current study for both hCA I and hCA II (see entries 1, 2, 5 and 6). An exception was found for aniline and acetanilide. Although the trend was observed between **8** and **9** (**8**: K<sub>i</sub> of 4030 μM and **9**: K<sub>i</sub> of 130.0 μM) for hCA II, the trend was not observed against hCA I for these compounds, **8** (K<sub>i</sub> of 3.0 μM) was more active

compared to its acetylated derivative **9** ( $K_i$  of 420.5  $\mu\text{M}$ ). It could be argued that **8** and **9** are not aminophenols and thus the discrepancy. In light of these findings, this study will be continued with a larger library of compounds.

AP **5** showed the highest inhibitory activity compared to the other APs tested against hCA I and hCA II,  $K_i$  values of 35.3  $\mu\text{M}$  and 184.2  $\mu\text{M}$  respectively. For the *N*-acetylated derivatives, **4** showed the strongest inhibitory activity for both hCA I and hCA II,  $K_i$  values of 10.0  $\mu\text{M}$  and 6.2  $\mu\text{M}$  respectively. The  $K_i$  values obtained for **4** are in the same range as the simple CAI phenol. However, both **4** and **5** were not stronger inhibitors compared to **AZA**.

### Conclusion

In conclusion, a screening of the binding activity of amino phenols, aniline and their *N*-acetylated derivatives to hCA I and II was investigated. The compounds inhibited both hCA I and II in the macromolar range however they were less moderate inhibitors compared to acetazolamide. The results indicate that aminophenols and their *N*-acetylated derivatives may be used as leads for designing compounds with much more potent inhibitory activity against CAs.

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