Journal of Molecular Structure 1220 (2020) 128657

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Synthesis, characterization and biological activity evaluation of novel naphthalenylmethylen hydrazine derivatives as carbonic anhydrase inhibitors

Hanif Shirinzadeh [a, *], Esra Dilek [b]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Erzincan Binali Yildirim University, Yalnizbag, Erzincan, Turkey
[b] Department of Biochemistry, Faculty of Pharmacy, Erzincan Binali Yildirim University, Yalnizbag, Erzincan, Turkey

ARTICLE INFO

Article history:
Received 6 March 2020
Received in revised form
8 June 2020
Accepted 8 June 2020
Available online 15 June 2020

Keywords:
Carbonic anhydrase
Enzyme inhibition
Naphthalenylmethylen hydrazine
Synthesis

ABSTRACT

In the current study some derivatives of naphthalenylmethylen hydrazine were synthesized and possible in vitro hCA I and II enzymes inhibition effects were investigated. The designed compounds were synthesized by condensation of phenylhydrazine with 1-naphthaldehyde or 6-methoxy-2-naphthaldehyde and eight compounds (1a-h) were obtained. The novel Schiff bases derivatives (compounds 1a-1h) were effective inhibitors of the cytosolic carbonic anhydrase I and II isoforms (hCA I and II) with Ki values in the range of 80.60 ± 17.90 to 492.53 ± 95.23 nM for hCA I, 102.88 ± 18.44 to 461.09 ± 102.50 nM for hCA II. 1f compound shows a remarkable inhibitory effect of hCA I and hCA II isoenzymes among the new synthesized compounds. The new derivatives of naphthalenylmethylen hydrazine can be a potent inhibitor of both cytosolic CA isoenzymes which are commonly used in the pharmaceutical industries and medical areas.

1. Introduction

Metalloenzymes are a combination of a metal ion or several metal ions in which the metal ion is strongly held in a protein. Using the enzyme as a scaffold for transition metal complexes, it becomes possible to carry out chemical transformations with selectivity. It should be well known which metal ions bind strongly to proteins. Knowing which metal ions are bound to proteins will contribute greatly to enzymatic analysis [1,2]. Metalloenzymes are central to a wide range of essential biological activities, including detoxification, nucleic acid modification, protein degradation, and many others [2,3]. The role of metalloenzymes in these processes also makes them central for the progression of many diseases and, as such, makes metalloenzymes attractive targets for therapeutic intervention [3].

Human carbonic anhydrase enzyme (hCA; Carbonate hydrolyses, EC 4.2.1.1) is a member of metalloenzyme family which are contain sixteen isoenzymes in mammals (CAI-CAXVI). Since most carbonic anhydrase enzymes contain zinc ions, they are classified as metalloenzymes. Human carbonic anhydrase enzymes are catalyzed the reversible hydration of carbon dioxide (CO2), which generates a proton (H+) and bicarbonate anion (HCO3−) lead to expressed as pH regulating enzyme in most tissues, especially in erythrocytes [4–9]. Many such CA isozymes which make these functions are important therapeutic targets with the potential to be inhibited/activated for the treatment of diseases such as glaucoma, edema, obesity, osteoporosis, epilepsy and cancer [5–11]. CA inhibitors (CAIs) such as acetazolamide (AZA), zonisamide (ZNS), methazolamide (MZA) and topiramate (TPM) are utilized in clinic as diuretics and factors for glaucoma-relevant intraocular hypertension [12,13].

Inhibitory effects of different phenols [14], anions [15], metal ions [16], sulfonamides [17], schiff bases and their amines [18], 1H-indazole molecules [19], amides [20], some chalcones [21], pyrimidine-thiones [22], some aminomethyl derivatives [23] which are specific inhibitors have been investigated against many CAs up to now. CA II inhibitors are used for various objectives like treatment of epilepsy, glucoma, antitumor agents/diagnostic tools or diuretics [8,24–26].

Nowadays, scientists are interested in discovery of novel CA

* Corresponding author. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Erzincan Binali Yildirim University, 24100, Yalnizbag, Erzincan, Turkey. Tel.: +00990(446)2245344-40201, fax: 0090(446)2245343.
E-mail addresses: hshirinzade@erzincan.edu.tr (H. Shirinzadeh), edilek@erzincan.edu.tr (E. Dilek).

https://doi.org/10.1016/j.molstruc.2020.128657
0022-2860/

inhibitors [8,14,24–27]. Recent studies are demonstrated that various derivatives of phenols [8,14], salicylic acid derivatives [28], different benzenes and bisphenols which have antioxidant properties and their various derivatives [29,30] are potential inhibitor of CA I and II isozymes.

In the current study, naphthalene ring which substituted with formation of imine were synthesized. All synthesized schiff bases compounds except 1e [31] were new compounds. Furthermore, the compounds 1c and 1d have CAS registry numbers, but no information exist in the literature related to the biological activity of 1c and 1d. The synthesized compounds were characterized on the basis of ^{1}H and ^{13}C NMR, mass spectra and elemental analyses. The CA inhibitory effect of the new synthesized compounds on CA I and II isoenzymes which isolated from human erythrocytes was performed by two different values, IC_{50} and Ki. IC_{50} values were calculated by determining percent activity at various inhibitor concentrations, with substrate concentrations kept constant, and then determining the concentration of inhibitor causing 50% inhibition graphically. The results were compared with acetazolamide (AZA).

2. Material and methods

This study was designed to synthesize, characterize and investigate the possible in vitro CA I and II enzyme inhibitory effect of new naphthalenylmethylen hydrazine derivatives. The designed compound was synthesized by condensation of phenylhydrazine with 1-naphthaldehyde or 6-methoxy-2-naphthaldehyde. All new imines were obtained by using a methodology similar to that in a previous study [32] (Fig. 1). Two series of new compounds were synthesized (Table 1). First group are 1-substituted phenyl-2-(naphthalen-1-yl methylene)hydrazine and second group are 1-substituted phenyl-2-(6-methoxynaphthalen-1-yl methylene)hydrazine. Substituted naphthalene ring in second group help us to evaluate the effect of substituents in the naphthalene rings.

2.1. Chemistry – experimental and instruments

Uncorrected melting points were determined with a Stuart melting point SMP30 apparatus. The ^{1}H and ^{13}C NMR spectra were measured with a Varian 400 MHz spectrometer device (Palo Alto, CA) using TMS as an internal standard and DMSO-d_6 as solvent. ESI mass spectra were determined by a Waters Micromass ZQ device. Elemental analyses were performed using a CHNS-932 instrument (Leco Corporation, St. Joseph, MI). All spectral analyses were performed at the Central Laboratory of the Faculty of Pharmacy at Ankara University. Chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Sepharose-4B, indozole molecules, and chemical substances used for electrophoresis were obtained from Sigma-Aldrich. L-tyrosine was obtained E. Merck. The chemical reagents that were used in synthesis and other chemical substances were purchased from Sigma (Germany) and Aldrich (USA).

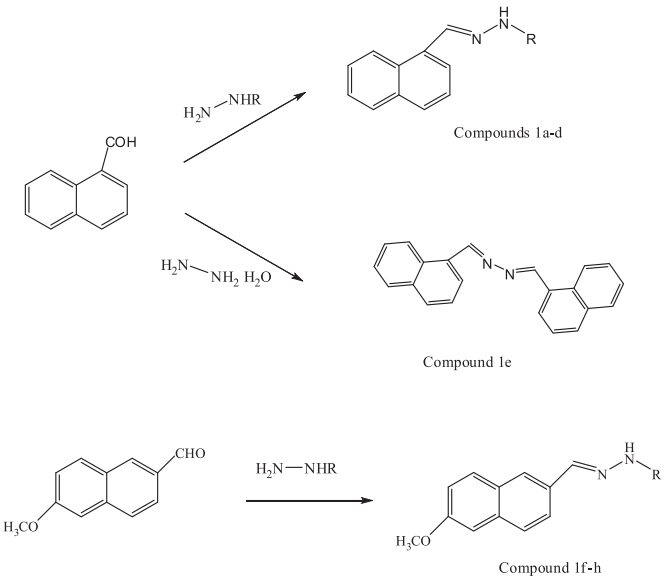


Fig. 1. Synthetic route to obtain new naphthalenylmethylen hydrazine derivatives.

2.2. General procedure for synthesis of compounds 1a-h

1 mmol of 1-naphthaldehyde or 6-Methoxy-2-naphthaldehyde and 1.2 mmol of phenyl hydrazine hydrochloride or its derivatives were dissolved in absolute ethanol (20 mL) and heated for 60 min on a hot water bath in the presence of CH_3COONa (0.4 g). After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitate was collected, washed with cold EtOH and recrystallized from EtOH to achieve 1a-1h (except 1e) with 70.79%–94% yield. For synthesis of 1e compound, the solution of 1-naphthaldehyde (2 mmol) and hydrazine hydrate (1 mmol) in EtOH (25 mL) was heated for 4 h on a hot water bath. After cooling, the precipitate was collected then washed with cold EtOH to give 1,2-bis(naphthalen-1-ylmethylene)hydrazine (1e) in 40.90% yield.

2.2.1. 1-(2-bromophenyl)-2-(naphthalen-1-ylmethylene)hydrazine (1a)

Yield 84.76%, m.p. 154–155 °C; ^{1}H NMR: δ 6.75–8.67 (m, 11H ArH); 9.12 (s, 1H, HC=N); 9.80 (s, 1H, NH); ^{13}C NMR: δ 106.02, 114.34, 120.38, 123.60, 124.91, 125.67, 125.67, 126.01, 126.79, 128.71, 128.88, 130.09, 130.67, 132.63, 133.56, 139.85,142.30 (C=N): MSI MS *m/z* 325 (M^+, 100%). Anal. calcd. for C17H13BrN2: C, 62.79%; H, 4.03%; N, 8.61%. Found: C,62.48%; H, 4.11%; N, 8.72%.

2.2.2. 1-(3-bromophenyl)-2-(naphthalen-1-ylmethylene) hydrazine(1b)

Yield 70.79%, m.p. 101–102 °C; ^{1}H NMR: δ 6.90–8.68 (m, 11H ArH); 8.55 (s, 1H, HC=N); 10.65 (s, 1H, NH); ^{13}C NMR: δ 111.08, 114.15, 121.16, 122.48, 122.48, 123.75, 125.55, 125.65, 126.01, 126.83, 128.72, 129.76, 130.54, 131.16, 133.59, 137.48, 146.77 (C=N): MSI MS *m/z* 325 (M^+, 100%), 327 (M+2, 97%). Anal. calcd. for C17H13BrN2: C, 62.79%; H, 4.03%; N, 8.61%. Found: C,62.42%; H, 3.96%; N, 8.61%.

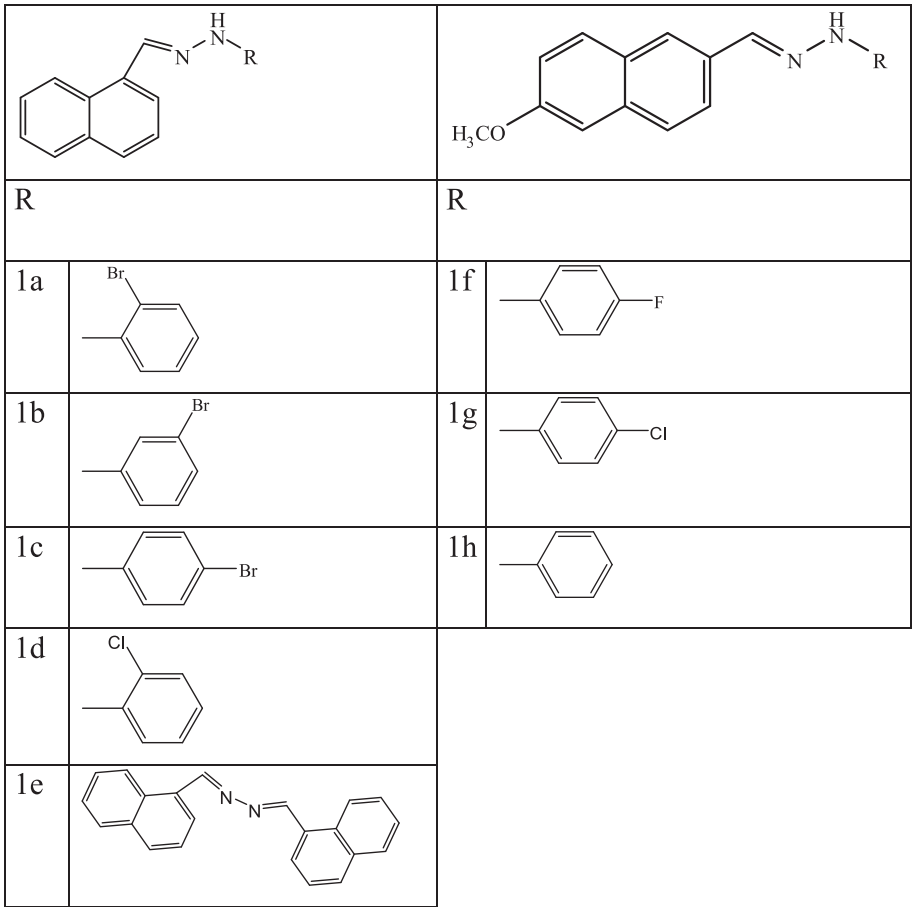
2.2.3. 1-(4-bromophenyl)-2-(naphthalen-1-ylmethylene) hydrazine(1c)

Yield 86.79%, m.p. 138–139 °C; ^{1}H NMR: δ 7.05–8.71 (m, 11H ArH); 8.53 (s, 1H, HC=N); 10.60 (s, 1H, NH); ^{13}C NMR: δ 109.65, 113.04, 123.87, 125.51, 125.62, 126.00, 126.83, 128.56, 128.70, 128.38, 129.70, 130.67, 131.83, 133.61, 137.04,144.50 (C=N): MSI MS *m/z* 325 (M^+, 100%), 327 (M+2, 80%). Anal. calcd. for C17H13BrN2: C, 62.79%; H, 4.03%; N, 8.61%. Found: C,62.74%; H, 3.96%; N, 8.67%.

2.2.4. 1-(2-chlorophenyl)-2-(naphthalen-1-ylmethylene)hydrazine (1d)

Yield 89.14%, m.p. 132–133 °C; ^{1}H NMR: δ 6.78–8.65 (m, 11H, Ar–H), 9.06 (s, 1H, HC=N), 9.99 (s, 1H, NH); ^{13}C NMR: δ 113.88, 116.16, 119.69, 123.59, 124.99, 125.67, 126.02, 126.82, 128.17, 128.72, 128.87, 129.41, 130.05, 130.66, 133.57, 139.74, 141.28 (C=N); MSI MS *m/z* 281 (M + H, 100%), 283 (M^++2, 35%). Anal. calcd. for C17H13ClN2: C, 72.73%; H, 4.67%; N, 9.98%. Found: C,72.94%; H, 4.84%; N, 9.99%.

Table 1
Chemical structures of newly synthesized compounds.



2.2.5. 1,2-bis(naphthalen-1-ylmethylene)hydrazine (1e)

Yield 40.90%, m.p. 153–154 °C; ^{1}H NMR: δ 7.61–9.18 (m, 14H ArH); 9.42 (s, 2H, HC=N); ^{13}C NMR: δ 125.06, 125.54, 126.44, 127.60, 128.77, 129.19, 130.36, 131.93, 133.55, 161.98 (C=N): MSI MS *m/z* 309 (M + H, 100%), 308 (M^{+}, 55%). Anal. calcd. for C22H16N2: C, 85.69%; H, 5.23%; N, 9.08%. Found: C,85.10%; H, 5.27%; N, 9.02%.

2.2.6. 1-(4-fluorophenyl)-2-((6-methoxynaphthalen-2-yl) methylene)hydrazine (1f)

Yield 85.03%, m.p. 206–207 °C; ^{1}H NMR: δ 3.85 (s, 3H, O CH_3), 7.03–7.92 (m, 10H, Ar- H), 7.96 (s, 1H, HC=N), 10.32 (s, 1H, NH); ^{13}C NMR: δ 55.20 (OCH_3), 106.31, 112.85, 115.48, 115.70, 118.83, 123.01, 125.72, 127.15, 128.46, 129.39, 131.31, 134.17, 136.88, 142.08 (C=N), 154.65, 156.97, 157.49 (O–C); MSI MS *m/z* 295 (M + H, 100%), 296 (M^{+}+1, 28%). Anal. calcd. for C18H15FN2O: C, 73.45%; H, 5.14%; N, 9.52%. Found: C,73.63%; H, 5.32%; N, 9.61%.

2.2.7. 1-(4-chlorophenyl)-2-((6-methoxynaphthalen-2-yl) methylene)hydrazine(1g)

Yield 83.87%, m.p. 220–221 °C; ^{1}H NMR: δ 3.86 (s, 3H, OCH_3); 7.07–7.92 (m, 10H ArH); 7.97 (s, 1H, HC=N); 10.46 (s, 1H, NH); ^{13}C NMR: δ 55.21 (OCH_3), 106.32, 113.34, 118.86, 121.79, 123.01, 126.00, 127.17, 128.42, 128.88, 129.44, 131.09, 134.28, 137.67, 144.28 (C=N), 157.57 (O–C): MSI MS *m/z* 311 (M + H, 100%), 312 (M+1, 32%). Anal. calcd. for C18H15ClN2O: C, 69.56%; H, 4.86%; N, 9.01%. Found: C,69.61%; H, 5.08%; N, 9.13%.

2.2.8. 1-((6-Methoxynaphthalen-2-yl)methylene)-2-phenylhydrazine(1h)

Yield 90.68%, m.p. 229–230 °C; ^{1}H NMR: δ 3.86 (s, 3H, OCH_3); 6.72–7.93 (m, 11H ArH); 7.97 (s, 1H, HC=N); 10.29 (s, 1H, NH); ^{13}C NMR: δ 55.20 (OCH_3), 106.31, 111.94, 118.60, 118.82, 123.03, 125.69, 127.15, 128.46, 129.10, 129.40, 131.38, 134.16, 136.79, 145.40 (C=N), 157.47(O–C): MSI MS *m/z* 277 (M + H, 100%). Anal. calcd. for C18H16N2O: C, 78.24%; H, 4.5.84%; N, 10.14%. Found: C,60.78%; H, 4.37%; N, 8.04%.

3. Experimental – biochemical activity

3.1. Purification of carbonic anhydrase isoenzymes and inhibition studies

The whole purification procedure was performed according to our previous studies [28–30]. Briefly, red blood cells which were isolated from fresh blood were hemolyzed and the pH of the obtained hemolysate was adjusted to 8.7 with solid Tris at 4 °C. Human erythrocyte hemolysate was applied to the Sepharose 4BL-tyrosine-sulfanilamide affinity column. The human carbonic anhydrase isozymes (hCA-I and hCA-II) were eluted with 1.0 M NaCl/25mMNa2HPO4 (pH 6.3) and 0.1M NaCH3COO/0.5M NaClO4 (pH 5.6), respectively. For purity of both isoenzymes sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) was applied and obtained single band (Fig. 2). The protein determination in the effluents showing activity were evaluated

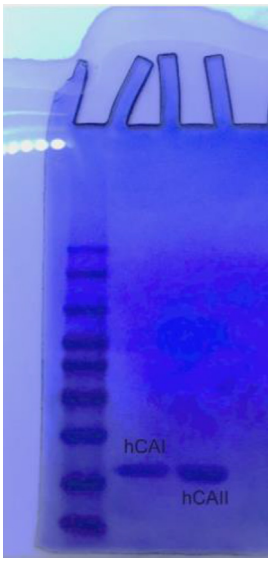


Fig. 2. PAGE of the purified CA isozymes. Lane 1: Standard proteins (24.5–116 kDa), lane 2: CA I, lane 3: CA II.

spectrophotometrically at 595 nm using the Bradford method [33]. CA isoenzymes activities were obtained in conforming to the procedure of Verpoorte et al. [34]. The increase in absorbance of the reaction medium was spectrophotometrically obtained at 348 nm. The esterase activity procedure was utilized for ascertaining the inhibition agents by the Lineweaver–Burk procedure [35] CA activity (%) versus inhibitory concentration and 1/V versus 1/[S] graphs were drawn.

Bovine serum albumin was used as standard protein as given previously in details [28–30]. For the designation of the inhibition efficacy of each novel naphthalenylmethylen hydrazine derivatives (la-h) on both hCA isoenzymes, a percent activity versus inhibitor (naphthalenylmethylen hydrazine) concentration graph was drawn. The IC50 values were obtained from these graphs. For the calculation of Ki values, three different novel naphthalenylmethylen hydrazine concentrations were used. In this study, they were given graphs which are drawn for the compound showing the most effective inhibition (Fig. 3).

4. Results and discussion

As a result of inhibition studies on CA enzyme activity, it can be used in the treatment of glaucoma. In these inhibition studies, the catalytic mechanisms of CA enzyme have been tried to be elucidated. The distribution of the enzyme in tissues and their vital functions in these tissues has been revealed as a result of these studies. As a result of all these developments, studies of synthesizing inhibitors and activators of the enzyme have increased rapidly. Therefore, many types of enzyme inhibitors have been synthesized and used as primarily medicines for the treatment of glaucoma. As well as glaucoma, it is also currently used in clinics as antitumor, analgesic, epilepsy, antiulcer, diuretics, antibiotics and neurological disease drugs [36].

The new compounds based on Schiff bases were synthesized and the inhibition effect on CA enzyme was observed. Compounds with the structure of –C=N- (azomethine group) which are usually synthesized from the condensation of primary amines and active carbonyl groups are known as Schiff bases. Schiff bases and their derivatives were investigated in many studies and established to be associated with a variety of biological activities like anticonvulsant [37] antiproliferative [38], anticancer [39], cytotoxic [40] antifungal and other activities [41]. In this study we investigated, whether the inhibition effect of some naphthalenylmethylen hydrazine derivatives on CA I and II isoenzymes isolated from human erythrocytes. As part of our ongoing research, we were synthesized eight new compounds of naphthalenylmethylene hydrazine derivatives to investigate their possible in vitro CA I and II enzymes inhibitory effects.

In our study, the inhibitory effect of naphthalenylmethylen hydrazine derivatives was determined by two different values of IC50 and Ki. IC50 were calculated by determining percent activity at various inhibitor concentrations, with substrate concentrations kept constant, and then determining the concentration of inhibitor causing 50% inhibition graphically. For hCA-I, the obtained IC50 values are respectively 106.30, 116.60, 129.70, 160.27, 172.55, 201.57, 207.05, 248.71, 424.33 nM for 1f, 1g, 1h, 1c, 1b, 1a, 1d, 1e and AZA compounds. Also, the obtained IC50 values for hCA-II enzyme are respectively 79.50, 93.20, 113.37, 141.50, 142.05, 162.32, 167.53, 202.67, 232.48 nM for 1f, 1g, 1c, 1h, 1b, 1a, 1d, 1e and AZA compounds. Among the synthesized compounds, 1f demonstrated a potent inhibitory effect for both hCA I and hCAII (Table 2).

To determine the Ki constant, Lineweaver–Burk graphs were drawn, and Ki constants and inhibition types were determined from these graphs. The Ki constant is a value which indicates the binding affinity of the inhibitor to the enzyme. The cytosolic enzyme hCA I was inhibited by the novel naphthalenylmethylen hydrazine derivatives (1f, 1g, 1h, 1c, 1b, 1a, 1d, 1e), with Ki values ranging between 80.60 ± 17.90 and 492.5330 ± 95.23 nM. Ki values of newly molecules except 1e are better than those of the standard used drug AZA (Ki 446.83 ± 149.27 nM) (Table 2 and Fig. 3). Accordingly, 1f (Ki: 80.60 ± 17.90 nM) had a high binding affinity for hCA I.

The cytosolic enzyme hCA II was inhibited by the novel naphthalenylmethylen hydrazine derivatives (1f, 1g, 1h, 1c, 1b, 1a, 1d, 1e), with Ki values ranging between 126.70 ± 33.20 and 461.09 ± 102.50 nM. Accordingly, 1g (Ki: 126.70 ± 33.20 nM) had a high binding affinity for hCAII. The clinically and standard used drug acetazolamide (AZA) calculated a Ki value of 332.18 ± 78.44 nM. Thus, the evaluated novel naphthalenylmethylen hydrazine derivatives except 1e showed considerable inhibitory profiles when compared to the AZA molecule (Table 2 and Fig. 3).

5. Conclusion

The investigated compounds exhibited more effective inhibitory profiles compared to AZA used as standard drug. Therefore new compounds inhibited the hCA I and hCA II activities at more low concentrations. When the most effective compounds (1f and 1g) are assessed, two important properties of these compounds stand out. The first one is that naphthalene ring have methoxy group in sixth position and second one is the phenyl group on hydrazine molecule are para-halogenated. It is believed that, the oxygen in the methoxy group and the halogen in the para position of the phenyl ring may made hydrogen bond with CAs enzymes.

In the study of heterocyclic series of aromatic sulfonamides binding to CA, the halogenated benzene ring significantly enhanced the observed affinities as it increased the fraction of deprotonated ligand [42,43]. In this study, the derivatives with a halogenated benzene ring, particularly on the para-position demonstrated more activity. In addition, one of the sulfonamide oxygens which is making ionic interaction with existing zinc ion in the active site of the enzyme was reported in other studies [43,44]. In the present study, when the compound of 1f and 1g, whose activity is very high, was examined, it was observed that a naphthalene ring has a

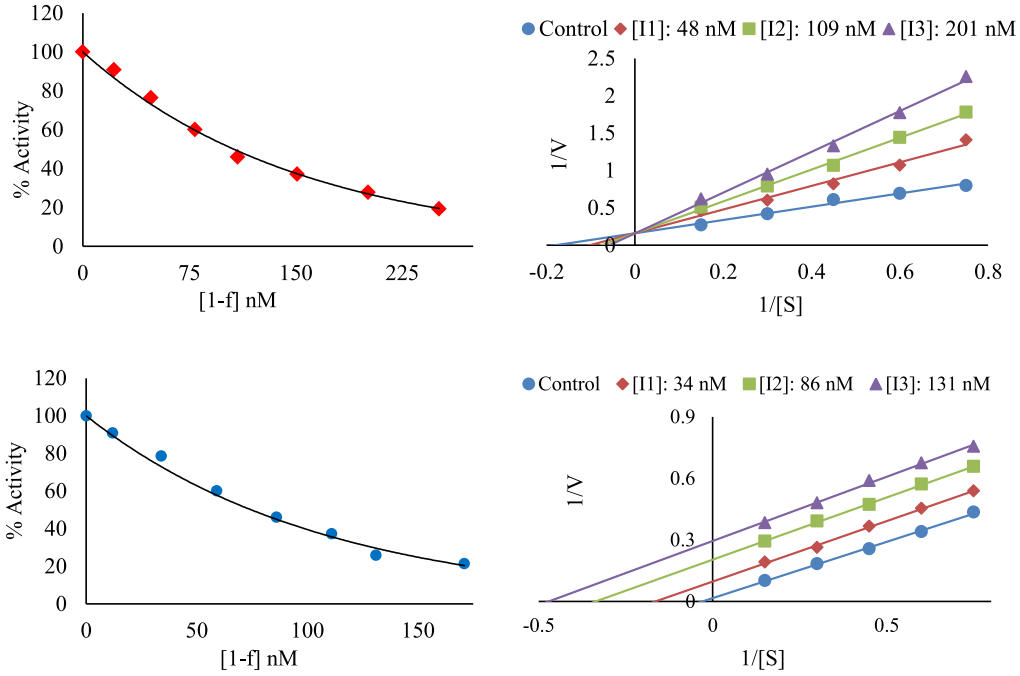


Fig. 3. Determination of % Activity/[1f] curve and Lineweaver–Burk graphs for excellent inhibitors of hCA I and hCA II isoenzymes.

Table 2
IC_{50} and K_i values of hCA I and hCA II with compounds and AZA, by an esterase assay.

Compounds	IC_{50} (nM)				K_i (nM)	
	hCA I	r^2	hCA II	r^2	hCA I	hCA II
1a	201,57	0.977	162,32	0.984	194.18 ± 51.30	136.17 ± 36.22
1b	172,55	0.992	142,05	0.995	201.29 ± 42.44	152.83 ± 51.22
1c	160,27	0.990	113,37	0.979	149.43 ± 30.03	102.88 ± 18.44
1d	207,05	0.988	167,53	0.994	232.18 ± 23.45	147.81 ± 23.48
1e	248,71	0.972	202,67	0.981	259.07 ± 28.01	217.45 ± 48.51
1f	106,30	0.996	79,50	0.987	80.60 ± 17.90	129.70 ± 29.10
1g	116,60	0.982	93,20	0.993	116.20 ± 22.50	126.70 ± 33.20
1h	129,70	0.990	141,50	0.986	148.80 ± 9.97	135.30 ± 7.16
Acetazolamide (AZA)	424,33	0.981	232,48	0.972	446.83 ± 149.27	332.18 ± 78.44

Mean from at least three determinations. Errors in the range of 3–5% of the reported value (data not shown).

methoxy group at the 6th position. Presumably, the oxygen's ionic bonding with zinc in the active site of the enzyme played an important role in making the compound much more effective than AZA.

Although our results are promising, in order to obtain a perfect and reliable hCA I and II enzyme inhibitor, we intend to undertake advanced studies to explain the cytotoxicity and action mechanism of these compounds. Thus, we believe that these novel naphthalenyl methylene hydrazine derivatives compounds are hopeful as leading compounds to improve as CA inhibitors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Hanif Shirinzadeh: Writing - review & editing, Funding acquisition, Methodology, Investigation, Formal analysis, Project administration, Resources, Supervision. **Esra Dilek:** Writing - review & editing, Methodology, Investigation, Validation, Visualization.

Acknowledgements

The authors appreciate the Scientific Research Council of Erzincan Binali Yildirim University for their support of the Project (Project No: SAG-A-240215-0120).

Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.molstruc.2020.128657. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

[1] B.A. Sandoval, T.K. Hyster, Emerging strategies for expanding the toolbox of enzymes in biocatalysis, Curr. Opin. Chem. Biol. 55 (2020) 45–51.
[2] T.C. Ramalho, A.A. de Castro, D.R. Silva, M.C. Silva, T.C. Franca, B.J. Bennion,

K. Kuca, Computational enzymology and organophosphorus degrading enzymes: promising approaches toward remediation technologies of warfare agents and pesticides, Curr. Med. Chem. 23 (10) (2016) 1041–1061.
[3] A.Y. Chen, R.N. Adamek, B.L. Dick, C.V. Credille, C.N. Morrison, S.M. Cohen, Targeting metalloenzymes for therapeutic intervention, Chem. Rev. 119 (2) (2018) 1323–1455.
[4] M.I. Hassan, B. Shajee, A. Waheed, F. Ahmad, W.S. Sly, Structure, function and applications of carbonic anhydrase isozymes, Bioorg. Med. Chem. 21 (2013) 1570–1582.
[5] C.T. Supuran, D. Vullo, G. Manole, A. Casini, A. Scozzafava, Designing of novel carbonic anhydrase inhibitors and activators, Curr. Med. Chem. Cardiovasc. Hematol. Agents 2 (2004) 49–68.
[6] C.T. Supuran, A. Scozzafava, Carbonic anhydrases as targets for medicinal chemistry, Bioorg. Med. Chem. 15 (2007) 4336–4350.
[7] C.T. Supuran, Carbonic anhydrases: novel therapeutic applications for inhibitors and activators, Nat. Rev. Drug Discov. 7 (2008) 168–181.
[8] A. Innocenti, D. Vullo, A. Scozzafava, C.T. Supuran, Carbonic anhydrase inhibitors: interactions of phenols with the 12 catalytically active mammalian isoforms (CA I-XIV), Bioorg. Med. Chem. Lett 18 (2008) 1583–1587.
[9] S.B.O. Sarikaya, F. Topal, M. Senturk, I. Gulcin, C.T. Supuran, In vitro inhibition of α-carbonic anhydrase isozymes by some phenolic compounds, Bioorg. Med. Chem. Lett 21 (2011) 4259–4262.
[10] S.K. Nair, P.A. Ludwig, D.W. Christianson, Two-site binding of phenol in the active site of human carbonic anhydrase II: structural implications for substrate association, J. Am. Chem. Soc. 116 (1994) 3659.
[11] J.R. Casey, Why bicarbonate? Biochem. Cell. Biol. 84 (2006) 930–939.
[12] F. Özbey, P. Taslimi, İ. Gulcin, A. Maraş, S. Goksu, C.T. Supuran, Synthesis of diaryl ethers with acetylcholinesterase, butyrylcholinesterase and carbonic anhydrase inhibitory actions, J. Enzym. Inhib. Med. Chem. 31 (2016) 79–85.
[13] E. Garibov, P. Taslimi, A. Sujayev, Z. Bingöl, S. Çetinkaya, İ. Gulcin, S. Beydemir, V. Farzaliyev, S.H. Alwasel, C.T. Supuran, Synthesis of 4,5-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidines and investigation of their acetylcholinesterase, butyrylcholinesterase, carbonic anhydrase I/II inhibitory and antioxidant activities, J. Enzym. Inhib. Med. Chem. 31 (2016) 1–9.
[14] A. Innocenti, M. Hilvo, A. Scozzafava, S. Parkkila, C.T. Supuran, Carbonic anhydrase inhibitors: inhibition of the new membrane-associated isoform XV with phenols, Bioorg. Med. Chem. Lett 18 (2008) 3593–3596.
[15] A. Thiry, J.M. Dogne, C.T. Supuran, B. Masereel, Carbonic anhydrase inhibitors as anticonvulsant agents, Curr. Top. Med. Chem. 7 (2007) 855–864.
[16] D. Ekinci, S. Beydemir, O.I. Kufrevioglu, In vitro inhibitory effects of some heavy metals on human erythrocyte carbonic anhydrases, J. Enzym. Inhib. Med. Chem. 22 (2007) 745–750.
[17] C.T. Supuran, Diuretics: from classical carbonic anhydrase inhibitors to novel applications of the sulfonamides, Curr. Pharmaceut. Des. 14 (2008) 641–648.
[18] B. Yiğit, M. Yiğit, P. Taslimi, Y. Gök, İ. Gülçin, Schiff bases and their amines: synthesis and discovery of carbonic anhydrase and acetylcholinesterase enzymes inhibitors, Arch Pharm 351 (9) (2018) 1–9.
[19] Z. Alim, 1H-indazole molecules reduced the activity of human erythrocytes carbonic anhydrase I and II isoenzymes, J. Biochem. Mol. Toxicol. 32 (2018), e22194.
[20] P. Taslimi, S. Osmanova, I. Gulçin, S. Sardarova, V. Farzaliyev, A. Sujayev, R. Kaya, F. Koc, S. Beydemir, S.H. Alwasel, O.I. Kufrevioglu, Discovery of potent carbonic anhydrase, acetylcholinesterase, and butyrylcholinesterase enzymes inhibitors: the new amides and thiazolidine-4-ones synthesized on an acetophenone base, J. Biochem. Mol. Toxicol. (2017), e21931.
[21] H.E. Aslan, Y. Demir, M.S. Özaslan, F. Türkan, Beydemir Ş, Ö.I. Küfrevioğlu, The behavior of some chalcones on acetylcholinesterase and carbonic anhydrase activity, Drug Chem. Toxicol. (2018) 1–7.
[22] P. Taslimi, A. Sujayev, F. Turkan, E. Garibov, Z. Huyut, V. Farzaliyev, S. Mamedova, I. Gulçin, Synthesis and investigation of the conversion reactions of pyrimidine-thiones with nucleophilic reagent and evaluation of their acetylcholinesterase, carbonic anhydrase inhibition, and antioxidant activities, J. Biochem. Mol. Toxicol. 32 (2018), e22019.
[23] I.M. Timur, U. Kocyigit, T. Dastan, S. Sanda, A.O. Ceribası, P. Taslimi, İ. Gulcin, M. Koparir, M. Karatepe, M. Çiftçi, In vitro cytotoxic and in vivo antitumoral activities of some aminomethyl derivatives of 2,4-dihydro-3H-1,2,4-triazole-3-thiones-Evaluation of their acetylcholinesterase and carbonic anhydrase enzymes inhibition profiles, J. Biochem. Mol. Toxicol. 33 (2019) e22239.
[24] C.T. Supuran, A. Scozzafava, Carbonic anhydrases as targets for medicinal chemistry, Bioorg. Med. Chem. 15 (2007) 4336–4350.
[25] W.S. Sly, P.Y. Hu, Human carbonic anhydrases and carbonic anhydrase deficiencies, Annu. Rev. Biochem. 64 (1995) 375–401.
[26] O. Ozensoy, O. Arslan, S.O. Sinan, A new method for purification of carbonic anhydrase isozymes by affinity chromatography, Biochemistry 69 (2004) 216–219.
[27] S. Pastorekova, S. Parkkila, J. Pastorek, C.T. Supuran, Carbonic anhydrases: current state of the art, therapeutic applications and future prospects, J. Enzym. Inhib. Med. Chem. 19 (2004) 199–229.
[28] E. Bayram, M. Senturk, O.I. Kufrevioglu, C.T. Supuran, In vitro inhibition of salicylic acid derivatives on human cytosolic carbonic anhydrase isozymes I and II, Bioorg. Med. Chem. 6 (2008) 9101–9105.
[29] S. Burmaoğlu, E. Dilek, A.O. Yılmaz, C.T. Supuran, Synthesis of two phloroglucinol derivatives with cinnamyl moieties as inhibitors of the carbonic anhydrase isozymes I and II: an in vitro study, J. Enzym. Inhib. Med. Chem. 13 (2016) 1–5.
[30] S. Caglar, E. Dilek, B. Caglar, E. Adigüzel, E. Temel, O. Buyukgungor, New metal complexes with diclofenac containing 2-pyridineethanol or 2-pyridinepropanol: synthesis, structural, spectroscopic, thermalproperties, catechol oxidase and carbonic anhydrase activities, J. Coord. Chem. 69 (2016) 3321–3335.
[31] M. Grigoras, C.O. Catanescu, G. Colotin, Poly(Schiff base)s containing 1,1'-binaphthyl moieties: synthesis and characterization, Macromol. Chem. Phys. 202 (11) (2001) 2262–2266.
[32] M. Kidwai, N. Negi, S.D. Gupta, Synthesis and antifertility activity of 1,5-diaryl-3 (3'-indolyl)formazans, Chem. Pharm. Bull. (Tokyo) 42 (1994) 2363–2364.
[33] M.M. Bradford, A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding, Anal. Biochem. 72 (1976) 248–254.
[34] J.A. Verpoorte, S. Mehta, J.T. Edsall, Esterase activities of human carbonic anhydrases B and C, J. Biol. Chem. 242 (1967) 4221–4229.
[35] H. Lineweaver, D. Burk, The determination of enzyme dissociation constants, J. Am. Chem. Soc. 56 (1934) 658–666.
[36] C.T. Supuran, A. Scozzafava, Carbonic anhydrase inhibitors, Curr. Med. Chem. 1 (2001) 61–97.
[37] I. Kucukguzel, S.G. Kucukguzel, S. Rollas, G.O. Sanis, O. Ozdemir, I. Bayrak, T. Altug, J.P. Stables, Synthesis of some 3-(arylalkylthio)-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazole derivatives and their anticonvulsant activity, Farmaco 59 (11) (2004) 893–901.
[38] P. Vicini, A. Geronikaki, M. Incerti, B. Busonera, G. Poni, C.A. Kabras, P.L. Colla, Synthesis and biological evaluation of benzo[d] isothiazole, benzothiazole and thiazole Schiff bases, Bioorg. Med. Chem. 11 (22) (2003) 4785–4789.
[39] R. Pignatello, A. Panico, P. Mazzane, M.R. Pinizzotto, A. Garozzo, P.M. Fumeri, Schiff bases of N-hydroxy-N′-aminoguanidines as antiviral, antibacterial and anticancer agents, Eur. J. Med. Chem. 29 (10) (1994) 781–785.
[40] M.T. Tarafder, A. Kasbollah, N. Saravan, K.A. Crouse, A.M. Ali, O.K. Tin, S-methyldithiocarbazate and its Schiff bases: evaluation of bondings and biological properties, J. Biochem. Mol. Biol. Biophys. 6 (2) (2002) 85–91.
[41] M.S. Karthikeyan, D.J. Prasad, B. Poojary, K. Subrahmanya Bhat, B.S. Holla, N.S. Kumari, Synthesis and biological activity of Schiff nad Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety, Bioorg. Med. Chem. 14 (22) (2006) 7482–7489.
[42] A. Zubriene, J. Smirnoviene, A. Smirnov, V. Morkūnaite, V. Michailoviene, J. Jachno, V. Juozapaitiene, P. Norvaisas, E. Manakova, S. Grazulis, D. Matulis, Intrinsic thermodynamics of 4-substituted-2,3,5,6-tetrafluorobenzenesulfonamide binding to carbonic anhydrases by isothermal titration calorimetry, Biophys. Chem. 205 (2015) 51–65.
[43] B.N. Saglik, U.A. Cevika, D. Osmaniye, S. Leventa, B. Kaya Cavusoglu, Y. Demir, S. Ilgind, Y. Ozkaya, A.S. Koparal, S. Beydemir, Z.A. Kaplancikli, Synthesis, molecular docking analysis and carbonic anhydrase I-II inhibitory evaluation of new sulfonamide derivatives, Bioorg. Chem. 91 (2019) 103153.
[44] M. Ahmed, m Abdul Qadir, A. Hameed, M.N. Arshad, M. Asiri A, M. Muddassar, Sulfonamides containing curcumin scaffold: synthesis, characterization, carbonic anhydrase inhibition and molecular docking studies, Bioorg. Chem. 76 (2018) 218–227.