Research Article

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Synthesis, Enzyme Inhibition, and Acid Dissociation Constant of 1,4-Naphthoquinone Thiazole Hybrid

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ABSTRACT

In this study, *N*-((Z)-4-((3r,5r,7r)-adamantan-1-yl)-3-(3-amino-1,4-dioxo-1,4-dihydronaphthalen-2-yl)thiazol-2(3H)-ylidene)-2,6-difluorobenzamide **3** was synthesized as a new 1,4-naphthoquinone thiazole hybrid compound by reaction of naphthoquinone acyl thiourea compound **2** with 1-((3r,5r,7r)-adamantan-1-yl)-2-bromoethan-1-one in 74% yield and its molecular structure was characterized by various analytical techniques such as $^{1}H/^{13}C$ NMR, FT-IR, and HRMS. The inhibition effect of the synthesized compound on butyrylcholinesterase (BChE), acetylcholinesterase (AChE), and human carbonic anhydrase isoenzymes (hCA I and hCA II) was investigated. The product **3** showed varying degrees of inhibition 89.92 ± 10.47 nM (against hCA I), 51.60 ± 5.37 nM (against hCA II), 68.11 ± 6.58 nM (against AChE), and 126.90 ± 10.99 (against BChE). Although 1,4-naphthoquinone thiazole hybrid **3** showed significant enzyme activity against the enzymes tested, it showed a higher inhibition activity against the AChE enzyme than the standard drug Tacrine. Three acid dissociation constants (pK_a) values (pK_{a1}= 2.75±0.02, pK_{a2}= 6.79±0.02, pK_{a3}= 10.85±0.02) of the product were determined potentiometrically in 0.1 M NaCl ionic strength at 25.0±0.1 ºC in 25% (v/v) DMSO:water hydro-organic medium.

Keywords: 1,4-Naphthoquinone, Acid dissociation constant, Enzyme inhibition, Thiazole

1. Introduction

A ubiquitous family of zinc metalloenzymes known as carbonic anhydrases (CAs), features a metal ion within their active site [1,2]. Present across various living organisms, CA enzymes primarily facilitate the reversible transformation of water and carbon dioxide into carbonate and a proton [3,4]. These ions play a fundamental role in maintaining the acid-base equilibrium within living cells. Furthermore, they are crucial for processes such as bone resorption, calcification, and electrolyte secretion, [5]. Consequently, the inhibition of CAs emerges as a significant category of therapeutic agents with the potential to address diverse physiological disorders. This includes conditions such as cancer, epilepsy, edema, obesity glaucoma and osteoporosis [6-8].

Alzheimer's disease (AD) is a persistent neurological disorder marked by behavioral disturbances, cognitive dysfunction, and memory impairment limitations in daily activities. AD has been linked to a cholinergic deficit in post-mortem brain tissue, marked by a substantial reduction in the levels of acetylcholine (ACh) [7,8]. The challenge of AD has escalated, especially in developed nations, as the elderly population with a longer life expectancy continues to grow. ACh, a neurotransmitter crucial in the pathology of AD, is primarily regulated by acetylcholinesterase (AChE) and, to a lesser extent, by butyrylcholinesterase (BChE) [9,10]. Both BChE and AChE enzymes are present in the brain, and they are identified within neuritic plaques and neurofibrillary tangles [11]. The cause of AD remains unknown; however, increasing ACh levels through the inhibition of AChE has been acknowledged as the most effective treatment strategy for AD. Consequently, AChE and BChE inhibitors have emerged as notable alternatives in AD treatment [12]. However, existing drugs like Donepezil, Rivastigmine, Galanthamine and Tacrine, which exhibit AChE inhibitory activity, have associated adverse impacts and are effective primarily against the mild form of AD. Notably, there is currently no marketed drug with BChE inhibitory effect [13,14].

The thiazole scaffold is among the most studied groups of pharmacophores in pharmaceutical chemistry, and many drug molecules containing the thiazole core are known today [15]. It is known to compounds bearing thiazole core exhibit antimicrobial [16,17], anticancer [18], antioxidant [19], DNA Cleavage [20] etc. as well as CAs [21, 22], AChE [21], α-glucosidase [23], BChE [24,25], and α-amylase [26] enzyme inhibitory activity.

The naphthoquinone scaffold is also a popular pharmacophore group in drug discovery studies. Furthermore, it is known to there are numerous pharmacologically important compounds bearing naphthoquinone core such as Doxorubicin and Psychorubrin [27,28]. Compounds bearing naphthoquinone core exhibit various pharmacologically activities like antimicrobial [29,30], anticancer [31], anti-inflammatory [32,33], DNA cleavage [34] activities as well as BChE [35,36], AChE [37,38], and CAs [21,38] enzyme inhibitory activity. While many drugs currently on the market, such as Avapritinib and Berotralstat, contain at least one fluorine atom in their molecular structure, drugs such as Relugolix and Pemigatinib contain a 2,6-fluorophenyl moiety in their molecular structure [39]. Furthermore, it is known that whether obtained from plants or synthesized, numerous compounds bearing adamantane, a highly symmetrical polycyclic structure, exhibit diverse pharmacological effects, and the adamantane moiety is frequently integrated into the molecular structure of the compounds to enhance their lipophilicity and improve their biological properties [40].

Herein, we report the synthesis of *N*-((Z)-4-((3r,5r,7r)-adamantan-1-yl)-3-(3-amino-1,4-dioxo-1,4-dihydronaphthalen-2-yl)thiazol-2(3H)-ylidene)-2,6-difluorobenzamide 3, and its enzyme inhibitory effect, and potentiometric determination of pK_a values.

2. Materials and Methods

2.1. Materials and Instrumentation

The reagents used were purchased high grade from commercial Merck or Aldrich, and commercially available solvents were used without further purification. Mattson 1000 FTIR spectrophotometer was used to record the Fourier transform infrared (FTIR) spectra. Bruker Ultrashield Plus Biospin GmbHt at 400 MHz was used to record the nuclear magnetic resonance (NMR) spectra. Chemical shifts were given in parts per million (δ) downfield from TMS as internal standard and spectra were determined in dimethyl sulfoxide-d_6 (DMSO-d_6). The following abbreviations were used; s = singlet, d = doublet, dd = doublet of doublets, and m = multiplet. Agilent

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Technologies 6224 TOF LC/MS was used to record the HRMS spectra. Mettler Toledo MP90 device was used to determine melting points. To perform pH-metric titrations, the Titroline 7000 automatic titrator with SI-Analytics combined with a glass pH electrode, which can be controlled by a computer and contains an automatic microburette, was used.

2.2. Synthesis of compound 2

Compound **2**, used as an intermediate in the synthesis of the product, was prepared as previously described [41] by reacting 2,3-diaminonaphthalene-1,4-dione **1** and 2,6-difluorobenzoyl isothiocyanate. A solution of 2,6-difluorobenzoyl chloride (2 mmol) in acetone (15 mL) was added to a stirred solution of the potassium thiocyanate (2 mmol) in acetone (10 mL), and the mixture was heated to the reflux temperature. After 1 hour, a solution of compound **1** (1 mmol) in acetone (25 mL) was added to the hot mixture and the mixture was heated for an additional 18 hours. After determining that the reaction was complete by thin layer chromatography, acetone was evaporated under reduced pressure using a rotary evaporator. The crude mixture was washed sequentially with deionized water and diethyl ether.

2.3. General procedure for the synthesis of compound 3

To stirred solution of **2** (1 mmol, 0.39 g) in acetone (30 mL) at room temperature, a solution of 1-((3r,5r,7r)-adamantan-1-yl)-2-bromoethan-1-one (1.2 mmol, 0.31 g) in acetone (20 mL) was added dropwise, and reaction solution was heated to reflux temperature (Scheme 1). It was determined that the reaction was completed after 30 hours. The solvent was then evaporated under reduced pressure and the resulting crude mixture was washed sequentially with saturated $NaHCO_3$, water and methanol until the desired compound in pure form was obtained. The molecular structure of the compound **3** was characterized by various analytical techniques. Green powder. Yield, 0.42 g, 74%. m.p.: 291-293 ºC (decomp.). IR (cm^{-1}): υ_{max} 3439, 3289, 3252, 3143, 2912, 2850, 1685, 1647, 1619, 1585, 1551, 1460, 1436. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, 1H, J = 7.5 Hz, Ar-H), 8.00 (d, 1H, J = 7.5 Hz, Ar-H), 7.94 (s, 1H, NH), 7.91-7.88 (m, 1H, Ar-H), 7.83-7.79 (m, 1H, Ar-H), 7.71 (s, 1H, NH), 7.38-7.30 (m, 1H, Ar-H), 6.99-6.95 (m, 2H, Ar-H), 6.82 (s, 1H, thiazole C-H), 1.90-1.80 (m, 9H, C-H adamantane), 1.63-1.51 (m, 6H, C-H adamantane). ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.1 (C=O), 176.8 (C=O), 170.8 (C=O), 168.0, 159.4 (dd, J_{FC} = 250.7 Hz, 7.2 Hz, 2 x C-F), 147.7, 147.1, 135.7, 133.0, 132.1, 130.9 (dd, J_{FC} = 10.2 Hz, 9.8 Hz, C), 130.0, 126.4, 126.1, 117.9 (dd, J_{FC} = 19.3 Hz, 19.3 Hz, C), 113.6, 111.9 (dd, J_{FC} = 18.9 Hz, 6.0 Hz, 2 x C), 105.1, 40.1 (3 x C), 35.9 (3 x C), 35.7, 27.7 (3 x C). HRMS (ESI-TOF-MS): calcd. for $C_{30}H_{26}F_2N_3O_3S$ [M+H$^+$] 546.1657; found 546.1657.

2.4. Enzyme inhibition studies

The esterase activity of hCA I and II was assessed by employing Verpoorte's technique [42], which involves monitoring the alteration in absorbance at 348 nm to ascertain the inhibitory impacts of compound 3. The compound's *in vitro* effects on AChE and BChE activity were examined according to Ellman et al.'s approach [43], with spectrophotometric analysis conducted at 412 nm using acetylcholine iodate (AChI) and butyrylcholine iodate (BChI). Standard inhibitors such as Acetazolamide (AAZ) and Tacrine (TAC) were utilized. To explore the *in vitro* inhibitory mechanisms of compound **3**, kinetic assays were conducted with varying substrate and chemical concentrations. The resulting data were utilized to generate Lineweaver-Burk plots, enabling the determination of K_i constants and identification of different types of inhibition [44,45].

2.5. Determination of acid dissociation constants

The pK_a values of compound **3** were determined potentiometrically in 25% (*v*/*v*) DMSO:water hydro-organic medium at 25.0 ±0.1 ºC using a literature method [46]. A 1x10^{-3} M stock solution of compound 3 in DMSO was prepared. 0.025 M of NaOH, 0.1 M of HCl and 1 M of NaCl stock solutions in deionized water were prepared were also prepared. A computer-controlled automatic titrator was used to perform potentiometric titrations, and a thermostat was used to keep the temperature constant at 25.0 ± 0.1 °C using. 10 mL of product **3** stock solution was added to the titration cell, followed by DMSO (2.5 mL), 0.1 M HCl (1 mL), 1 M NaCl (5 mL) stock solutions, and deionized water (31.5 mL), respectively, and the titration cell lid was closed. Nitrogen gas was then passed through the solution and the solution was stirred at constant speed throughout the titration. pK_a values were calculated with the HYPERQUAD com-

puter program using the data obtained as a result of the titration.

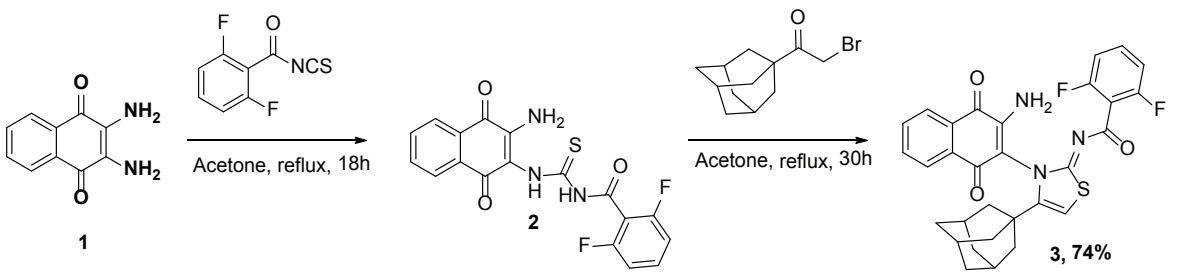
3. Results and Discussion

3.1. Synthesis and characterization

New naphthoquinone thiazole hybrid **3** was synthesized by the reacting naphthoquinone acylthiourea compound **2**, prepared from 2,3-diaminonaphthalene-1,4-dione **1** using a literature method [41], with 1-((3r,5r,7r)-adamantan-1-yl)-2-bromoethan-1-one in acetone at refluxing temperature in 74% yield (Scheme 1). The molecular structure of the desired product 3 was fully characterized by ^{1}H / ^{13}C NMR (Figures 1 and 2), FT-IR, and HRMS. ^{1}H NMR spectrum of **3** (Figure 1), the singlet peak at 6.82 ppm belongs to the thiazole proton and the singlet peaks at 7.94 ppm and 7.71 ppm belong to the NH_2 protons. Fifteen protons of the adamantane moiety appear as multiple peaks at 1.90-1.80 ppm and 1.63-1.51 ppm. In addition, ^{13}C NMR spectrum of **3** (Figure 2), the peaks of the three carbonyl carbons in the structure of the compound are seen at 181.1 ppm, 176.8 ppm, and 170.8 ppm.

3.2. Enzymes inhibition studies

We have synthesized compound **3** in search of anti-Alzheimer and anti-epileptic agents. Also, we evaluated their anticholinesterase and CAs activities. Com-



Scheme 1. Synthesis of compound 3.

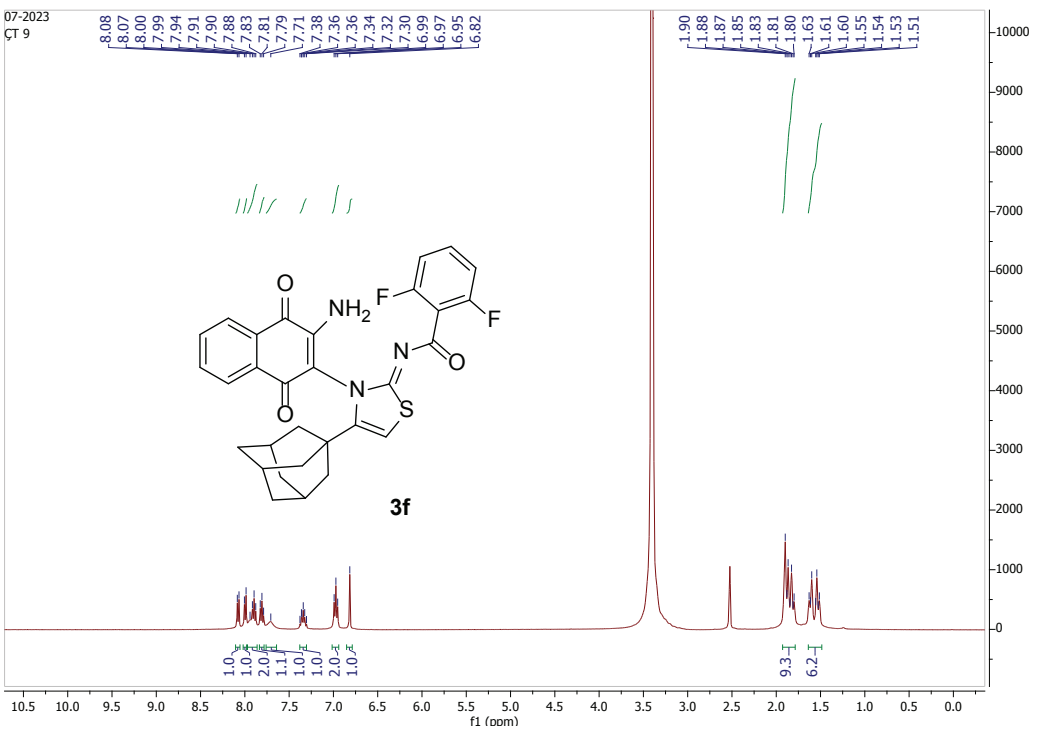


Figure 1. ^{1}H NMR Spectra of **3**

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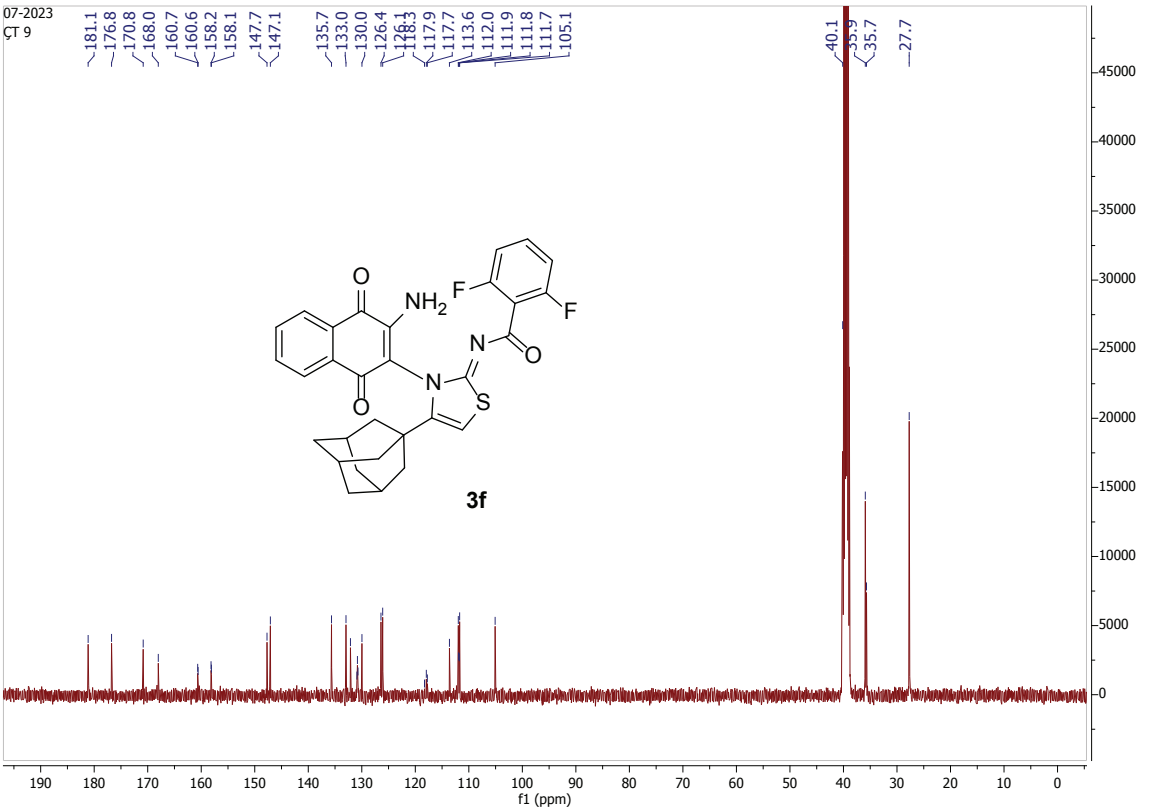

Figure 2. ^{13}C NMR Spectra of **3**

pound **3** showed varying degrees of inhibition 89.92 ± 10.47 nM (against hCA I), 51.60 ± 5.37 nM (against hCA II), 68.11 ± 6.58 nM (against AChE) and 126.90 ± 10.99 (against BChE) (Table 1, Figure 3).

In experiments evaluating the inhibitory effects on CA enzymes, AAZ is utilized as a positive control and for on cholinergic enzymes, TAC is employed as a positive control. An enzymatic inhibition analysis revealed compound **3** inhibited hCA II enzyme more than other enzymes and showed the least effect against BChE. Looking at the results in Table 1, compound **3** did not exhibit an effective result on CAs enzymes compared to the standard (AAZ, K_i: 20.52±3.17 for hCA I and K_i: 23.77±4.01 for hCA II). It exhibited approximately 1.19 times more effective inhibition of the AChE enzyme than TAC (TAC, K_i: 81.21±10.45 for AChE). As with CA enzymes, it was not more effective on the BChE enzyme than the standard (TAC, K_i: 73.13±13.67 for BChE). Perhaps this is due to the inability of the amino acids in the active structure of the enzymes to interact due to steric hindrance caused by the structure of compound **3**.

3.3. Acid dissociation constants

The pK_a values of **3** calculated by HYPERQUAD computer program are given in Table 2. Titration curve and the distribution curve of **3** are given in Figures 4A and 4B, respectively. Three pK_a values for compound **3** could be determined, and the pK_{a1}, pK_{a2}, and pK_{a3} values were found as 2.75±0.02, 6.79±0.02, and 10.85±0.02, respectively (Table 2). Since 1,4-naphthoquinones behave like naphthalene-1,4-diol because of delocalization, the pK_a value in the DMSO:water hydro-organic medium is expected to be above 10 [33,34]. The pK_a value of the NH_2 group bonding to the naphthoquinone moiety was reported in the range of 5.25 ± 0.02-7.27 ± 0.02 by Nural et al. [34]. The pK_a of *N*-(thiazol-2-yl)methanimine moiety was reported in the range of 2.46-2.85 by Altun et al. [47]. In addition, the pK_a value of the nitrogen atom of the imino form of thiazoles was reported in the range of 4.16-3.36 by Öğretir et al. [48]. It can be said that the pK_{a1} (2.75±0.02), pK_{a2} (6.79±0.02), and pK_{a3} (10.85±0.02) may be related to protonated imino nitrogen, NH_2, and carbonyl oxygen of naphthoquinone moiety, respectively.

Table 1. The inhibition data of compound 3 for studied enzymes

Compound ID	hCA I		hCA II		AChE		BChE	
	K_i (nM)	R^2	K_i (nM)	R^2	K_i (nM)	R^2	K_i (nM)	R^2
3	89.92 ± 10.47	0.9815	51.60 ± 5.37	0.9864	68.11 ± 6.58	0.9823	126.90 ± 10.99	0.9861
AAZ [21] [a]	20.52±3.17	0.9812	23.77±4.01	0.9891	-	-	-	-
TAC [21] [b]	-	-	-	-	81.21±10.45	0.9788	73.13±13.67	0.9788

[a] Acetazolamide. [b] Tacrine.

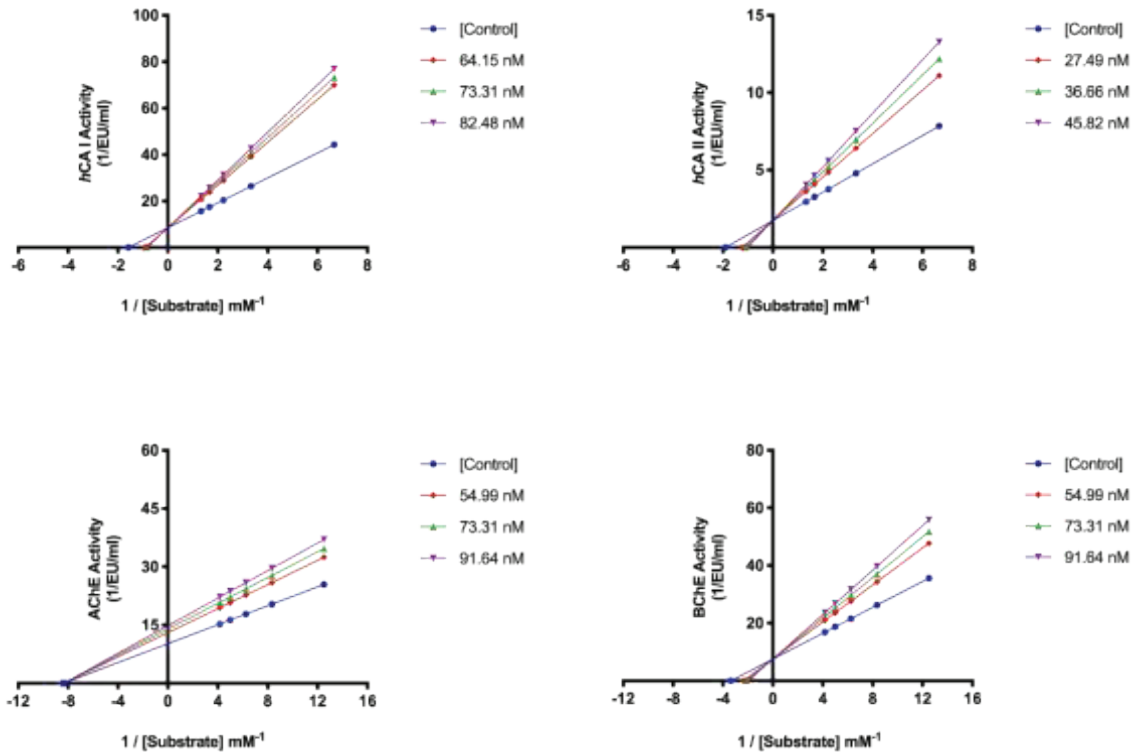

Figure 3. Lineweaver-Burk graphs of the compound **3**.

4. Conclusions

In summary, we have demonstrated the synthesis of new 1,4-naphthoquinone thiazole hybrid **3**, and its potentiometric determination of pK_a values in 25% (v/v) DMSO:water hydro-organic medium (I= 0.1 M NaCl) at 25.0±0.1 ºC. It is thought that the three determined pK_a values are related to the imino nitrogen, NH_2 and carbonyl oxygen of the naphthoquinone group. The research focused on assessing the inhibitory effects of compound **3** on hCA I, II isoenzymes, AChE, and BChE. The compound investigated in this study exhibited substantial inhibition of enzyme activities at low nanomolar concentrations. Except for the AChE enzyme, compound **3** did not exhibit more effective inhibition than the standards in other enzymes. Compared to this result, it can be used as a precursor agent in the treatment of AD by adding more effective groups.

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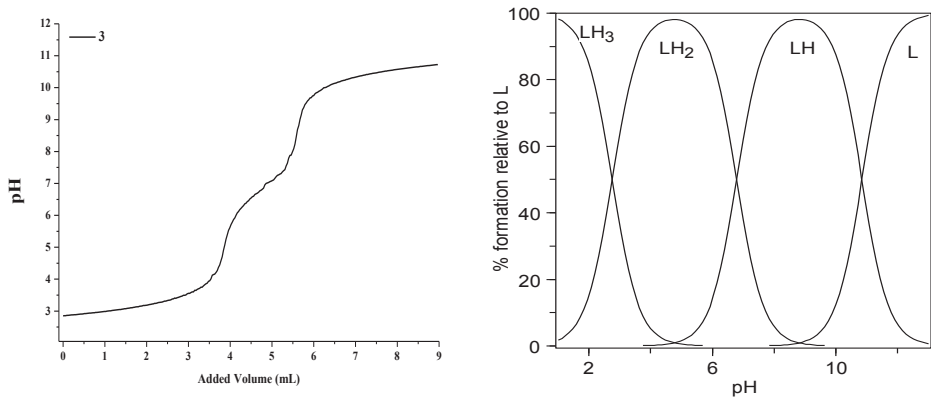
Table 2. pK_a values of **3** in DMSO:water hydro-organic medium, 25:75 (*v/v*), 25.0 ±0.1 ºC, *I*= 0.1 M NaCl

Ligand	pK_{a1}	pK_{a2}	pK_{a3}
3	2.75±0.02	6.79±0.02	10.85±0.02



A B

Figure 4. Titration curve (A) and Distribution curve (B) of **3** (25.0±0.1 °C, I= 0.1 M NaCl, DMSO:water hydro-organic medium 25:75 v/v)

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Conflict of Interest

The authors have no conflicts of interest, financial or otherwise, to declare.

Statement of Contribution of Researchers

Concept, Design, Supervision, Resources, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Search, Writing, and Critical Reviews – Y.N., Y.D.

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