A Green Method for Synthesis of 7H-thiazolo[3,2-b][1,2, 4]-triazin-7-one Derivatives as AChE Inhibitors

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ABSTRACT: The authors study an efficient and green approach for the synthesis of 7H-thiazolo [3, 2-b][1,2,4]triazin-7-one derivatives as AChE inhibitors. The 7H-thiazolo[3,2-b][1,2,4]triazin-7-ones were designed by molecular docking, and readily prepared via a one-pot reaction in morpholine hydrosulfate ([Hnhm]HSO4) Ionic liquid as the catalyst and solvent. The study of AChE inhibitory activity was carried out through using the Ellman colorimetric assay. The 7H-thiazolo[3,2-b][1,2,4]triazin-7-ones had been successfully synthesized by green catalyst. Most of the target compounds exhibited more than 50% inhibition at 10μM.

Keywords: 7H-thiazolo[3,2-b][1,2,4]triazin-7-ones; Ionic liquid; AChE inhibitor; synthesize

1   INTRODUCTION

The green chemistry movement began more than two decades ago. Specifically, the challenge in chemistry is to develop new products, processes, and services that achieve the societal, economic, and environmental benefits that are required now and tomorrow, and the need for alternative solvents for reactions has been one of the major issues we have faced[1]. Owing to their unique properties such as good solvating ability, negligible vapor pressure, variable polarity, nonflammability, and recyclability, ionic liquids have been widely used as catalysts and reaction media [2].

The global population has reached seven billion on Monday, October 31, 2011, accompanied by an aging society [3]. What will life in an aging society be maybe dramatically increased the age-related diseases. Alzheimer's disease (AD) is the most common single cause of dementia in the aging society, and it can be diagnosed in people over 65 years of age though the less-prevalent early-onset Alzheimer's can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050[4].

In our previous work, 7H-thiazolo[3,2-b]- 1,2,4-triazin-7-one derivatives were designed and synthesized, which exhibited inhibitory activity against acetylcholinesterase (AChE), and the molecular docking exhibited 7H-thiazolo [3,2-b]-1,2,4-triazin-7-one derivatives interacted with the catalytic active site (CAS) and the peripheral anionic site (PAS) of AChE[5-7]. AChE is a hydrolase that catalyzes the hydrolysis of neurotransmitter acetylcholine and it is presented in the most prominent constituents of central cholinergic pathways. AChE plays a crucial role in central and peripheral nervous systems [8]. Reduction in the activity of the cholinergic neurons is a well-known feature of AD. AChE inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh which is caused by the death of cholinergic neurons[9].

In continuation of our interest in developing new environmentally friendly methods and studying the the structure-AChE inhibitory activity relationships of 7H-thiazolo[3,2-b] -1,2,4-triazin-7-one derivatives, we utilized the acidic ionic liquid Morpholine hydrosulfate ([Hnhm]HSO$_4$) as catalyst and solvent for the synthesis of a new series of 7H-thiazolo[3,2-b][1,2,4]triazin-7-one derivatives. The inhibitory activity against AChE was evaluated.

2   RESULTS AND DISCUSSION

2.1   *Chemistry*

In the course of this study, we developed green chemistry by one-pot syntheses of target molecules in the absence of [Hnhm]HSO$_4$. The reaction scheme was shown in Figure 1. Various substituted arylpyruvic acids **1**, thiosemicarbazide **2**, and α-bromo acetophenone **3** are converted into 7H- thiazolo[3,2-b]-1,2,4-triazin-7-ones **4** in the presence of [Hnhm]HSO$_4$.

The effects of synthetic temperature, catalyst, and reaction time on the product yield were discussed. The reaction of 4-chlorophenylpyruvicacid, thiosemicarbazide, and α-bromoacetophenone was selected as a model reaction to optimize the reaction temperature for the synthesis of **4a** in [Hnhm]HSO$_4$ (1 equiv.). The results are summarized in Table 1. Based on the experimental results, with temperature increasing, the reaction rate was accelerated and the yield was increased. The highest yield was obtained at 80 °C. By repeated tests, a proper amount of catalyst loading for the model reaction is fixed. The amount of [Hnhm]HSO$_4$ was increased from 0.1 to 0.9 equivalents. The results are summarized in Table 2. What's
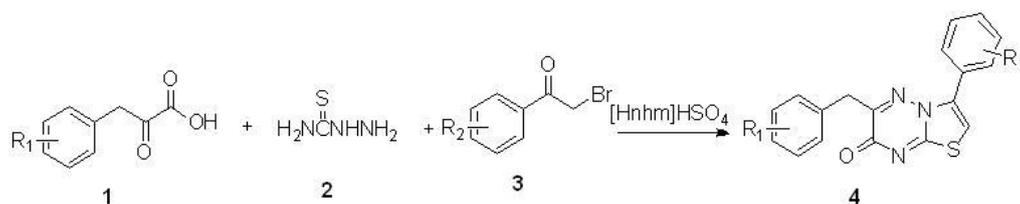
Figure 1. Synthetic route of 7H-thiazolo[3,2-b]-1,2,4 -triazin-7-ones

more, the results also indicated that the yield of **4a** may not be obviously increased with the increasing amount of [Hnhm]HSO$_4$ from 0.5 to 0.9 equiv. Thus, we chose 0.5 equiv. as the optimal amount of catalyst for further experiments.

Table 1. Effects of the reaction temperature on the synthesis of **4a** in [Hnhm]HSO$_4$

No.	Temp/^{o}C	Time/h	Yield/%
1	20	3	32
2	40	3	45
3	60	3	78
4	80	3	93
5	100	3	85

Table 2. Effects of the amount of [Hnhm]HSO$_4$ on the synthesis of **4a** at 80 ^{o}C

No.	[Hnhm]HSO$_4$/equiv.	Time/h	Yield/%
1	0.1	3	31
2	0.3	3	68
3	0.5	3	91
4	0.7	3	92
5	0.9	3	93

The recyclability of the catalyst was investigated through using the same reaction and scale. Upon the completion of the reaction, the product was readily isolated by filtration, washed with water, and dried under vacuum without further separation, whereas the filtrate containing [Hnhm]HSO$_4$ was dried to remove water at 60 ^{o}C under vacuum. The recovered ionic liquid was reused in the subsequent reactions. As shown in Table 3, for the preparation of **4a**, the ionic liquid [Hnmp]HSO$_4$ could be recycled three times without considerable decrease of activity.

Table 3. Recycling performance of 0.5 equiv. [Hnhm]HSO$_4$

No.	Temp/^{o}C	Time/h	Yield/%
1	80	3	91
2	80	3	87
3	80	3	85
4	80	3	83

Under this optimal condition, 7H-thiazolo[3,2-b][1,2,4]triazin-7-one derivatives was synthesized. As indicated in Table 4, the reaction efficiently proceeds with all of them.

Table 4. Synthesis of 7H-thiazolo[3,2-b][1,2,4] triazin-7-ones in 0.5 equiv. [Hnhm]HSO$_4$ at 80 ^{o}C

No.	R$_1$	R$_2$	Product	Yield/%
1	4-Cl	4-Cl	4a	91
2	4-OCH$_3$	2-OH	4b	90
3	3-OCH$_3$	4-Br	4c	92
4	3-OCH$_3$	4-Cl	4d	92
5	3-OCH$_3$	2-OH	4e	91
6	4-OH	4-CH$_3$	4f	90
7	4-OCH$_3$	4-OH	4g	89
8	4-OCH$_3$	4-OCH$_3$	4h	90

2.2 Inhibition of AChE

Inhibitory activities of target compounds on AChE were determined in comparison with the huperzine-A and the results data were reported in Table 5. All compounds are properly showed to good hAChE inhibitory activities with inhibition values ranging from 40.58% to 64.36%. **4b** exhibited the best inhibitory activity to AChE with the mean inhibition value of 64.36%. The compounds 4b, 4e and 4f showed better activity, and it is probably due to the presence of hydroxy group, which would be able to form hydrogen bond with AChE receptor.

Table 5. Inhibition of human AChE Activities by the targets at 10 μM (n=2)

No.	Inhibition(100%)	No.	Inhibition(100%)
4a	59.75	4e	63.32
4b	64.36	4f	62.98
4c	56.96	4g	62.43
4d	40.58	4h	48.56
Huperzine-A			100

2.3 Docking studies

Solution of the 3D structure of Torpedo californica acetylcholinesterase in 1991 opened up new horizons in research on an enzyme that had already been the subject of intensive investigation [10]. One of the striking structural features of the AChE revealed from the X-ray analysis is the presence of a narrow, long, hydrophobic gorge which is approximately 20Å deep [11]. The AChE aromatic gorge includes the following loci [12]: At the bottom of the gorge a catalytic triad (Ser200, His440 and Glu327) lies in catalytic active

site (CAS). The second binding is referred to as the peripheral anionic site (PAS), including Tyr70, Asp72, Tyr121, Glu278, Trp279 and Tyr334; it is known to be located at the gorge mouth around 18 Å away from the active site. Furthermore, in the middle of the gorge, Trp84, Tyr130, Phe330 and Tyr442 form an anionic binding site, a binding site for the quaternary nitrogen of their substrates and some ligands. The crystal structure of human AChE had been reported in 2000[13]. Comparison of the three-dimensional structures of TcAChE (1EVE) and hAChE (1B41) revealed a high degree of similarity, especially with regard to the active sites. The most significant difference between the active sites of TcAChE and hAChE is that the Phe330 of TcAChE was replaced with a Tyr337 of hAChE. Another difference is that the sequence number of some protein residues. For example, Ser200 of TcAChE was replaced by Ser203 of hAChE. The result was shown in Table 6:

Table 6. Differences in the protein residues of TcAChE and hAChE

Active Site	TcAChE	hAChE
catalytic active site (CAS)	Ser200	Ser203
	Glu327	Glu334
	His440	His447
anionic binding site	Trp84	Trp86
	Tyr130	Tyr133
	Phe330	Tyr337
	Tyr442	Tyr449
peripheral anionic site (PAS)	Tyr70	Tyr72
	Asp72	Asp74
	Tyr121	Tyr124
	Glu278	Glu285
	Trp279	Trp286
	Tyr334	Tyr341

To investigate the binding mode of the series of 7H-thiazolo[3,2-b]-1,2,4-triazin-7-one derivatives, docking simulations were performed with AUTO-DOCK 4 software. The model of the receptor was based on the crystal structure of hAChE complex with donepezil (PDB ID: 4EY7). The cocrystal natural substrate was taken out of the active site and docked again. The top three docking configurations were taken into consideration to validate the results, and the RMSD was calculated for each configuration in comparison with the co-crystallized ligand, donepezil. The acceptable results indicated that the docked configurations have similar binding positions and orientations within the binding site and they are similar to the co-crystal structure, which illustrates the fact that the used docking protocols could successfully generate the crystal donepezil-AChE complex precisely. The proposed binding model of donepezil with the key residues in the gorge site is shown in Figure 2. The binding model suggests that donepezil is bound near the bottom of the gorge, and it shows parallel π-π stacking against the six-membered ring of Trp86 in-

dole, while the indanone ring stacks against Trp286 in the PAS. The piperidinic nitrogen of the ligand contains a positive charge and complexes by cation-π interaction with the phenyl group of Tyr341 of the enzymatic cavity. And Donepezil interacts with key amino acid residues such as Ser203, His447 at the CAS and Tyr72, Asp74, and Trp286 at PAS.
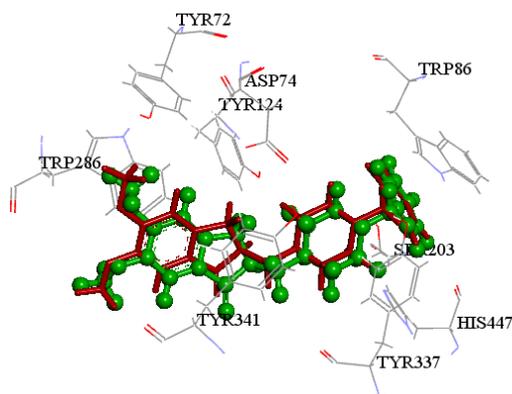

Figure 2. Binding orientation of redocked co-crystal donepezil with ball and stick (green) and original donepezil with stick (red)
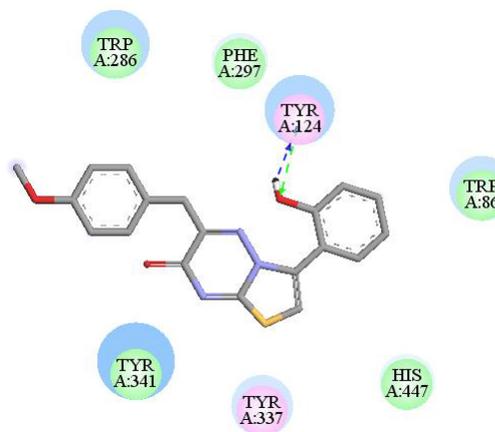

Figure 3. Docking model of compound 4b in the active sites of hAChE

The docking simulations reveal all target compounds exhibited multiple binding modes with the human AChE. For example, the compound 4b occupies the peripheral anionic site, the mid interaction site and the catalytic active site through hydrophobic interactions with Trp86, Trp286, Tyr341 and His447 (see Figure 3). The compound 4e formed hydrophobic interactions with Tyr72, Asp74, Tyr124, Trp286, Tyr341, Tyr337 and His447. The thiazolo[3,2-b]-1,2,4-triazin-7-one ring can establish a π-π interaction with the aromatic ring of Trp86 (see Figure 4). For

another example, the phenyl group of the compound **4f** can establish a π-π interaction with the aromatic ring of Tyr341, and at the same time, it forms hydrophobic interactions with Asp74, Trp86, Trp286 and Tyr337. The thiazolo[3,2-b]-1,2,4-triazin ring can form hydrophobic interaction with His447 in CAS (see Figure 5). Additionally significant H-bond interactions were also observed among the -OH group of compound **4b** with Tyr124, the -OH group of compound **4e** with Ser203 and the -OH group of compound **4f** with Tyr72, which might be the reason for their increased potency.
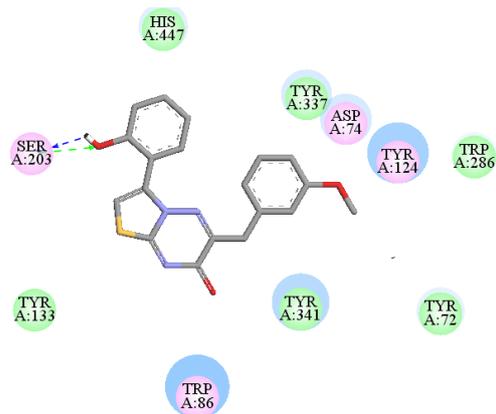

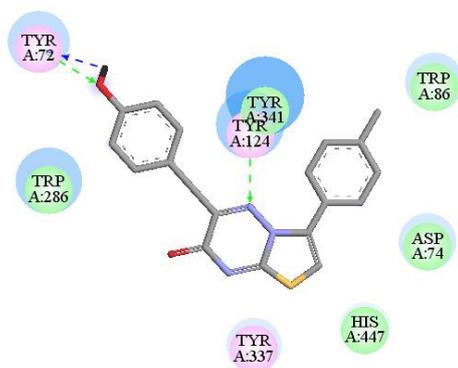Figure 4. Docking model of compound 4e in the active sites of hAChE

Figure 5. Docking model of compound 4f in the active sites of hAChE

3 EXPERIMENTAL SECTION

3.1 *Chemistry*

Reagents and solvents were purchased from common commercial suppliers and were used without further purification. All melting points were taken in open capillary tubes and are uncorrected. Nuclear magnetic resonance spectra were recorded in CDCl$_3$ or DMSO solutions through using Bruker 300 MHz spectrometers or 600 MHz spectrometers. The mass spectra (MS) were obtained by electronic impact (EI) at 70 eV in an Agilent spectrometer (with direct insertion probe) or by electrospray (ESI) in a Waters spectrometer. The IR spectra were obtained through using a PerkineElmer 298 spectrometer (PerkineElmer, Norwalk, CT, USA).

3.2 *General procedure for synthesis of various substituted arylpyruvic acids 1*

A mixture of aromatic aldehyde (100 mmol), N-acylglycine(10.7 g, 120 mmol) and sodium acetate (51 g, 500 mmol) were mixed and heated at 120 °C for 7 h in acetic anhydride. After completion of the reaction, the resulting solution was kept in refrigerator overnight to obtain a solidified mass which was triturated with cold water and ethanol. The resulting yellow crystals were collected and dried to give 4-(arylmethylene)-2-methyl-5(4H) -oxazolone.

4-(Arylmethylene)-2-methyl-5(4H)-oxazolone(10.8 5 g, 50 mmol), acetone (85 mL), and H$_2$O (70 mL) were refluxed for 10 h. The solvent was evaporated to give 2-acetamido-3-arylacrylic acids as a residual solid.

2-Acetamido-3-arylacrylic acids (10 mmol) and 1 mol/L HCl aqueous solution (60 mL) were refluxed for 7 h. After that the resulting mixture was allowed to cool to room temperature. And the resulting precipitate was collected by filtration. The filtrate was extracted with ethyl acetate (3×20 mL). The organic extract was evaporated to give arylpyruvic acid which was combined with the filtered precipitate. The aryl pyruvic acid was dried under vacuum and was recrystallized form ethanol.

3.3 *General procedure for synthesis of 7H-thiazolo[3,2-b][1,2,4]triazin-7-ones (4a-4h)*

Arylpyruvic acid 1 (1 mmol) and thiosemicarbazide (2, 1.1 mmol) were mixed together in the presence of [Hnhm]HSO4, then they were stirred at 80 °C. An hour later, α-bromoacetophenone 3 (1.1 mmol) were added. Upon the completion of the reaction, the reaction mixture was poured into water and the precipitate of 7H-thiazolo-[3,2-b][1,2,4]triazin-7-one 4 was filtered, washed, and crystallized from ethanol. The residue solution containing [Hnhm]HSO4 was reused for subsequent reactions.

3.3.1 *6-(4-chlorobenzyl)-3-(4-chlorophenyl)-7H-thia zolo[3,2-b]-1,2,4-triazin-7-one (4a)*

Yellow crystal; mp: 230-232℃; ^{1}H-NMR (600 MHz, DMSO-d6): δ7.61 (2H, d, *J* = 9.0Hz), 7.58 (1H, s), 7.48 (2H, d, *J* = 8.4Hz), 7.37 (2H, d, *J* = 9.0Hz), 7.31 (2H, d, *J* = 8.4Hz), 3.98 (2H, s); ESI-MS (m/z): 387.9 (M+H)[+], 798.6 (2M+Na)[+]; IR (KBr): υ 3104, 1636, 1576, 1482, 1402, 1383, 1359, 1322, 1188, 1118,

1093, 1043, 1014, 878, 808, 755 cm⁻¹.

3.3.2 6-(4-methoxybenzyl)-3-(4-hydroxyphenyl)-7H-thiazolo[3,2-b]-1,2,4-triazin-7-one (4b)

White crystal; mp: 218-219℃; ¹H-NMR (300 MHz, DMSO-d6): δ 9.99 (1H, s), 7.37 (1H, s), 7.32-7.58 (2H, m), 7.18 (2H, d, *J* = 8.7Hz), 6.99 (1H, d), 6.89 (1H, t), 6.81 (2H, d, *J* = 8.7Hz), 3.80 (2H, s), 3.72 (3H, s); EI-MS (m/z): 51, 63, 77, 89, 104, 121, 132, 147, 159, 174, 192, 193, 218, 231, 282, 350, 365(M)⁺; IR (KBr): υ 3102, 2965, 1663, 1621, 1571, 1513, 1486, 1384, 1294, 1267, 1243, 1180, 1127, 1107, 1047, 1025, 943, 921, 879, 842, 803, 773 cm⁻¹.

3.3.3 6-(3-methoxybenzyl)-3-(4-bromophenyl)-7H-thiazolo[3,2-b]-1,2,4-triazin-7-one (4c)

Yellow crystal; mp: 201-203℃; ¹H-NMR (600 MHz, DMSO-d6): δ 7.59-7.63 (5H, m), 7.22 (1H, t), 6.87 (1H, s), 6.85 (1H, d), 6.82 (1H, d), 6.77 (1H, s), 3.94 (2H, s), 3.71 (3H, s); ESI-MS (m/z): 428.1 ([M+ H]⁺), 450.3 ([M+Na]⁺);; IR (KBr): υ 3101, 2950, 1635, 1576, 1480, 1384, 1322, 1296, 1259, 1152, 1113, 1047, 1007, 818, 784, 754 cm⁻¹.

3.3.4 6-(3-methoxybenzyl)-3-(4-chlorophenyl)-7H-thiazolo[3,2-b]-1,2,4-triazin-7-one (4d)

Yellow crystal; mp: 213-214℃; ¹H-NMR (300 MHz, CDCl3): δ 7.48 (2H, d, *J* = 8.6Hz), 7.40 (2H, d, *J* = 8.6Hz), 7.22 (1H, t), 6.90 (2H, d), 6.82 (2H, d), 4.10 (2H, s), 3.77 (3H, s); ESI-MS(m/z): 284.2 ([M+H]⁺); IR (KBr): υ 3103, 2932, 1636, 1577, 1482, 1403, 1384, 1297, 1258, 1154, 1115, 1090, 1050, 1010, 846, 819, 785, 767, 756 cm⁻¹.

3.3.5 6-(3-methoxybenzyl)-3-(4-hydroxyphenyl)-7H-thiazolo[3,2-b]-1,2,4-triazin-7-one (4e)

Yellow crystal; mp: 200-203℃; ¹H-NMR (600 MHz, DMSO-*d6*): δ 9.94 (1H, s), 7.38 (1H, s), 7.32-7.36 (2H, m), 7.17 (1H, t), 6.97 (1H, d), 6.81-6.88 (3H, m), 6.77 (1H, d), 3.85 (2H, s), 3.75 (3H, s); EI-MS (m/z): 51, 65, 77, 90, 104, 121, 132, 150, 159, 175, 192, 218, 231, 334, 351, 365(M)⁺; IR (KBr): υ 3315, 2926, 1672, 1603, 1551, 1513, 1464, 1447, 1384, 1342, 1296, 1258, 1195, 1155, 1126, 1047, 841, 786, 753, 709 cm⁻¹.

3.3.6 6-(4-hydroxybenzyl)-3-(4-methylphenyl)-7H-thiazolo[3,2-b]-1,2,4-triazin-7-one (4f)

Yellow crystal; mp: 275-277℃; ¹H-NMR (300 MHz, DMSO-d6): δ 9.25 (1H, s), 7.54 (2H, d, *J* = 8.0Hz), 7.44 (1H, s), 7.25 (2H, d, *J* = 8.0Hz), 7.06 (2H, d, J = 8.4Hz), 6.76 (2H, d, *J* = 8.4Hz), 3.83 (2H, s), 2.35 (3H, s); ESI-MS (m/z): 350.0 (M+H)⁺, 720.9 (2M+Na)⁺; IR (KBr): υ 3109, 1643, 1580, 1515, 1481, 1414, 1384, 1363, 1319, 1265, 1213, 1172, 1114, 1042, 876, 816, 790, 765, 751 cm⁻¹.

3.3.7 6-(4-methoxybenzyl)-3-(4-hydroxyphenyl)-7H-thiazolo[3,2-b]-1,2,4-triazin-7-one (4g)

White crystal; mp: 188-189℃; ¹H-NMR (600 MHz, DMSO-d6): δ 10.0 (1H, s), 7.48 (2H, d, *J* = 8.4Hz), 7.33 (1H, s), 7.21 (2H, d, *J* = 8.4Hz), 6.87 (2H, d, *J* = 8.4Hz), 6.80 (2H, d, *J* = 8.4Hz), 3.91 (2H, s), 3.76 (3H, s); ESI-MS (m/z): 366.0 (M+H)⁺, 752.8 (2M+Na)⁺; IR (KBr): υ 3119, 1610, 1511, 1476, 1385, 1279, 1247, 1176, 1123, 1029, 838, 752 cm⁻¹.

3.3.8 6-(4-methoxybenzyl)-3-(4-methoxyphenyl)-7H-thiazolo[3,2-b]-1,2,4-triazin-7-one (4h)

Yellow crystal; mp: 205-206℃; ¹H-NMR (600 MHz, DMSO-d6): δ 7.57 (2H, d, *J* = 8.4Hz), 7.40 (1H, s), 7.20 (2H, d, *J* = 9.0Hz), 6.97 (2H, d, *J* = 9.0Hz), 6.87 (2H, d, *J* = 8.4Hz), 3.90 (2H, s), 3.81 (3H, s), 3.73 (3H, s); ESI-MS (m/z): 380.0 (M+H)⁺, 780.9 (2M+Na)⁺; IR (KBr): υ 3107, 2931, 2833, 1636, 1580, 1513, 1481, 1417, 1385, 1359, 1300, 1253, 1176, 1115, 1034, 876, 821, 785, 755 cm⁻¹.

3.4 Biology inhibition of AChE

The inhibitory potency against AChE was evaluated by means of Ellman's test [14]. AChE stock solution was prepared by dissolving human AChE 0.5 unit in 100 mM PBS buffer (pH 7.4). Tested target compounds (10 mM) were prepared in DMSO. The assay solution consisted of 100mMPBS buffer (pH 7.4) with the addition of 10mM 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB, Ellman's reagent), AChE (5 mL), drug (10 mL), and 12.5 mM acetylthiocholine iodide (ATCh) water solution. The final assay volume was 900 mL. Incubate the reaction at 37 °C for 15 min with continuous gentle shake. Add 50mL ATCh and 50 mL DTNB. Incubate at 37 °C for about 20 min with continuously gentle shake. Wait until the yellow color was developed and measure it at 412 nm. Calculate the specific inhibition rates.

3.5 Docking studies

To disclose a possible binding mode of compounds with hAChE enzyme's binding pockets, the docking simulation was performed through using the available crystallographic structure of enzyme (PDB ID: 4EY7) and AUTODOCK 4.0 (The Scripps Research Institute, LA Jolla, CA, USA). To obtain the better results from docking protocols, water molecules and other ligand (NAG) were excluded. The polar hydrogen atoms of the enzyme were added, the non-polar hydrogen atoms were merged, and Gasteiger charges were assigned. For all ligands, the non-polar hydrogen atoms were merged and the Gasteiger charges were assigned. The grid box dimensions were 60×60×60Å around the active site, and the grid spacing was set to 0.375 Å. Docking was performed through using the empirical free energy function together with the Lamarckian genetic algorithm (LGA). The LGA protocol was applied to 150 individuals, while 250000 energy evaluations were used for the 20 LGA runs. In addition, the maximum number of evaluations was set to 27000. In this study, the co-crystal natural substrate, donepezil, was taken out of the active site and docked

again, and it was used as the template for molecular alignment. The cluster analyses were computed with a cluster tolerance by< 1.5 Å in positional root-mean-square deviation. The Discovery Studio (DS) Visualizer 2.5 software was used for visualization of protein-ligand interactions.

4 CONCLUSION

7H-thiazolo[3,2-b]-1,2,4-triazin-7-one derivatives were designed and synthesized as dual binding site inhibitors of AChE. We have found a practical and green synthesis procedure for preparing 7H-thiazolo[3,2-b][1,2,4]triazin-7-ones by one-pot, three-component condensation of arylpyruvic acids, thiosemicarbazide, and 2-bromoacetophenones in the presence of ionic liquid [Hnhm]HSO$_4$. The main advantages of higher yields lack organic solvent and the easy synthetic procedure. All these derivatives have been investigated for their inhibitory activity in vitro through using Ellman's method. The results revealed that most compounds displayed moderate inhibitory activity. Among them, compounds 4b, 4e 4f, and 4g bearing hydroxy group exert the better potency. Molecular docking results revealed that 4b, 4e 4f, and 4g might be able to form hydrogen bond with AChE receptor. These studies suggest that 7H-thiazolo [3,2-b]-1,2,4-triazin-7-one derivatives may be a promising structural template for the development of novel AChE inhibitors in managing amnesic disorders including AD.

ACKNOWLEDGEMENT

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