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Synthesis and biological evaluation of novel quinazoline-triazole hybrid compounds with potential use in Alzheimer's disease

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ABSTRACT

A library of twelve quinazoline-triazole hybrid compounds were designed, synthesized and evaluated as a novel class of acetylcholinesterase inhibitors to treat Alzheimer's disease (AD). The biological assay results demonstrated the ability of several hybrid compounds to inhibit AChE enzyme (IC_{50} range = 0.2-83.9 μM). To understand the high potential activity of these compounds, molecular docking simulations were performed to get better insights into the mechanism of binding of quinazoline-triazole hybrid compounds. As expected, compounds **8a** and **9a-b** bind to both catalytic anionic site (CAS) and peripheral anionic site (PAS) in the active site of AChE enzyme, which implicates that these compounds could act as dual binding site inhibitors. These compounds were not cytotoxic and they also displayed appropriated physicochemical as well as pharmacokinetic profile to be developed as novel anti-AD drug candidates.

Keywords: Azheimer's disease, acetylcholinesterase inhibitor, click chemistry, quinazoline, triazole, hybridization

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder and one of the most common forms of dementia in the elderly. AD causes a progressive damage on the central nervous system, including memory loss, decline in language, cognitive dysfunction and behavioral disorders.[1-3] A wide ranges of factors have been considered as the main causes of AD, including formation of toxic amyloid beta (Aβ) protein in the brain,[4] tau protein hyperphosphorylation and aggregation,[5] biometals dysfunction (ions; copper, iron, and zinc),[6,7] alteration of calcium homeostasis, inflammation and oxidative stress due to generation of reactive oxygen species (ROS),[8] and deficits in the cholinergic transmission.[9] The complexity and heterogeneous etiology of AD play an important role in new drug development to avoid the progress of this disease. Nowadays, most of theurapeutic treatments for AD has focused on the inhibition of acetylcholinesterase (AChE) to increase the level of acetylcholine (ACh) in cholinergic synaptic clefts.[10] Acetylcholinesterase (AChE) has catalytic anionic site (CAS) and peripheral anionic site (PAS) which are selectively accepting ACh.[11,12] AChE can be inhibited by AChE inhibitors (AChEI) through the interaction of the

inhibitor and amino acid residues in the CS (competitive inhibitors) and PAS (non-competitive inhibitors). To date, only four cholinesterase inhibitors (AChEIs) including tacrine,[13] donepezil,[14] rivastigmine,[15] and galantamine[16] were approved for commercial use in the treatment of AD. However, tacrine was removed from the pharmaceutical market owing to severe adverse effects associated with hepatotoxicity.[17] Therefore, new safer cholinesterase inhibitors with [illegible] are urgently needed.

Nitrogen-containing heterocycles are key structural units in natural and synthetic bioactive agents. In the library of six-membered heterocyclic frameworks, quinazolines represent a privileged structure which has been widely utilized to design therapeutic drugs due to their diversity of the biological and pharmacological activities such as anti-cancer, anti-microbial etc.[18,19] Quinazoline derivatives have also attracted lots of attention as anti-AD agents.[3,20-25] They have been found as a crucial scaffold for the optimal AChEI activity interacting with the CAS and PS of AChE.[22] Recently, the study reported by Rao P. et al. has evidently hightlighted cholinesterase activities of 2,4-disubstituted quinazolines containing various primary amine groups at position C4 of quinazoline framework.[24] Apart from quinazolines, triazole-containing derivatives have been also considered as versatile anti-AChE agents.[2,26-28] The triazole moiety plays a crucial role for improving the AChE inhibitory activity. Study by Shaprless et al. demonstrated that 1,2,3-triazole-linked tacrine and phenanthridinium derivatives possessed remarkable AChEI activity by incorporation of 1,2,3-triazole ring.[26] Moreover, the conjugation of 1,2,3-triazole moiety with different heterocyclic systems such as chromenones,[27,28] quinolines,[29,30] isoxazoles,[31] or piperidines[32] indicated their potencies in the design and synthesis of novel anti-Alzheimer agents.

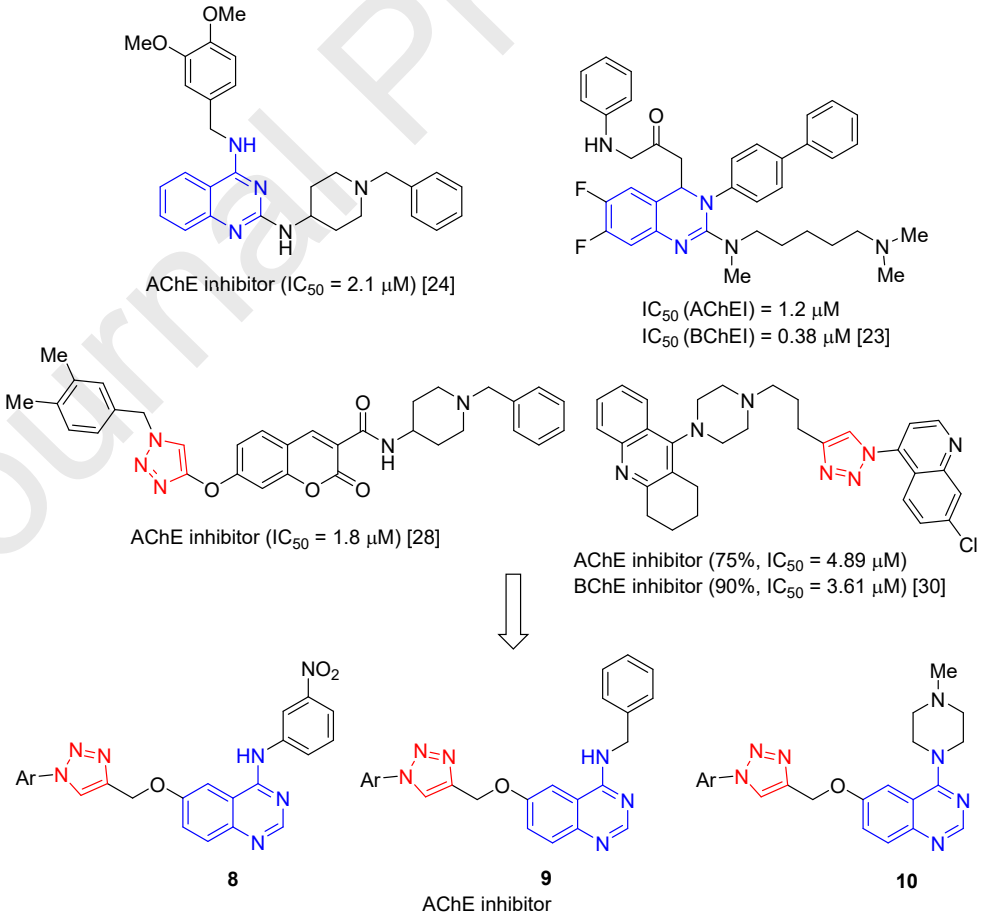
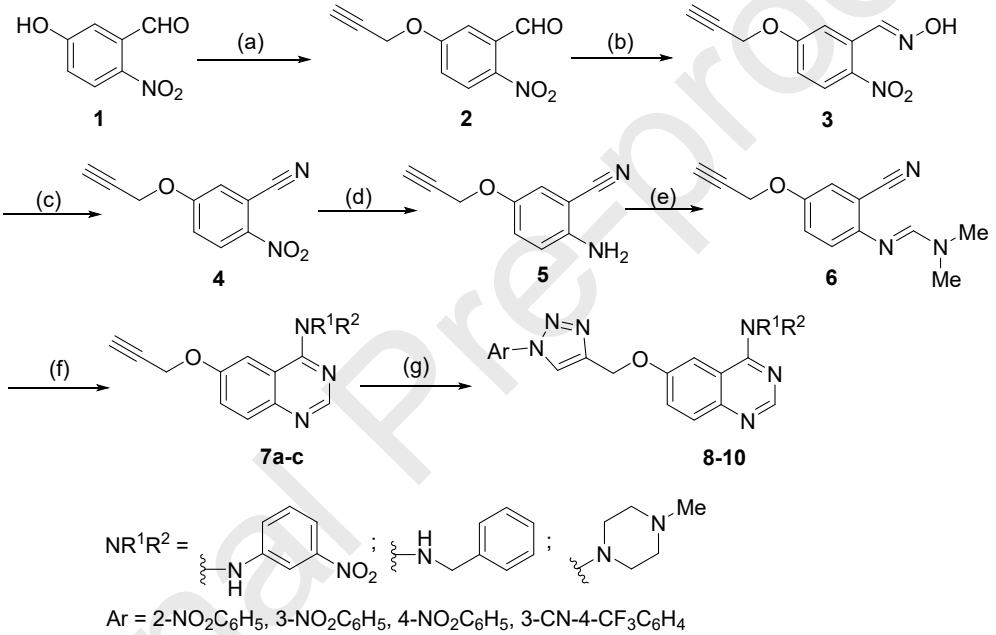


Fig. 1. Design of compounds **8-10**

In the light of the potential AChE inhibitory of quinazolines and 1,2,3-triazole ring mentioned above, herein we designed and synthesized a series of quinazoline-triazole hybrid compounds with the aim of obtaining new leads in AChE inhibitors. It was demonstrated that the success of the dual-binding CAS and PAS sites strategy is evidence by the large increase in AChE inhibitory potency of dimers or hybrids compared to the parent compounds from which they have been designed.[33] Therefore, the hybridization of anti-AD potential quinazoline and triazole scaffolds led to the reasonable synthesis of the targeted compounds **8-10** (Fig. 1). Moreover, the introduction of a triazole moiety in the targeted molecules could facilitate H-bond interactions between the backbone and the catalytic aspartate, and provide suitable linkage for the attachment of a wide range of hetero/aromatic pendant groups. Hence, in the present work, several 4,6-disubstituted quinazolines containing propynyloxyl group at C6 position were synthesized, followed hybridization with different azide derivatives to give the targeted quinazoline-triazole hybrid compounds. The obtained compounds were then evaluated for their AChE inhibitory to investigate their potential use for treating AD.



Scheme 1: Preparation of anilinoquinazoline–substituted triazole hybrid compounds **8-10**. (a) propargyl bromide, Cs_2CO_3, acetonitrile, rt, 12 h, 97%; (b) $NH_2OH.HCl$, NaOH, MeOH, H_2O, rt, 30 min, 95%; (c) Ac_2O, reflux, 8 h, 85%; (d) $Na_2S_2O_4$, H_2O, 50-65°C, 4 h, 85%; (e) DMF-DMA, acetic acid, toluene, reflux, 4 h, 80%; (f) amine, acetic acid, toluene, 60°C-110°C, 4 h, 63-70%; (g) azide, DIPEA, CuI, THF, rt, 1-2 days, 65-91%.

The synthetic route to targeted hybrid compounds **8-10** is represented in Scheme 1. First, the starting material 2-nitro-5hydroxybenzaldehyde **1** reacted with propargyl bromide in basic conditions to give 2-nitro-5-(prop-2-yn-1-yloxy)benzaldehyde **2**, which was converted to aldoxime **3** by treatment with hydroxyamine. Aldoxime **3** was next subjected to intramolecular dehydration with anhydride acetic to afford the benzonitrile **4**. Reduction of the nitro group of compound **4** using sodium dithionite in acidic solution gave the corresponding amine **5**. The latter was treated with DMF-DMA to furnish the formamidine intermediate **6**, which was then subjected to cyclization with different amine to afford the 6-(prop-2-yn-1-yloxy)quinazolin-4-amines **7a-c** in moderate yields. In the final step, the hybridization of quinazolines **7a-c** with various arylazide derivatives was accomplished using catalyst CuI in the presence of DIPEA in THF at room temperature to afford quinazoline-triazole hybrid compounds **8-10** in 60-91% yields. The chemical structures of synthesized

compounds **7a-c, 8-10** were determined by IR, NMR and MS spectra. In the ^{1}H NMR spectra of compounds **8-10** a single peak corresponding to triazolyl proton was observed in the downfield (8.80-9.40 ppm). While proton NH of compounds **8a-d** appeared as singlet peak at 9.94-9.96 ppm, and those of compounds **9a-d** resonanced as triplet peak at 8.64-8.66 ppm.

In the second section of this work, the anti-AChE and anticancer activities of the synthezied compounds were evaluated. In vitro anti-AChE activity of quinazolines **7a-c** and 1,2,3-triazole-quinazoline hybrid compounds **8-10** was conducted based on modified Ellman's method[34,35] (Table 1). All data were presented as mean ± SEM of three independent experiments. The synthesized compounds **7-10** can be generally divided into three catagories based on the different amine moiety connected to C-4 position of quinazoline scaffold, 3-nitrophenylamine (**7a**, **8a-d**), benzylamine (**7b**, **9a-d**), and *N*-methylpiperazyl groups (**7c**, **10a-d**).

Substituation by different amine group on the C-4 position of quinazoline skeleton affected the AChE inhibition differently. Compound **7b** having benzylamine group displayed moderate activity (IC_{50} = 47.73 μM), whereas compound **7c** having *N*-methylpiperazyl group showed lower activity (IC_{50} = 83.90 μM), and compound **7a** having 3-nitrophenylamine group was not active toward AChE with IC_{50} > 200 μM. These results agreed with the work of Mohamed T. that the benzylamines at C-4 position of quinazoline framework has significant effect on AChEI activity.[24] It was hypothesized that the presence of benzylamine would enhance the C-4 group's flexibility and allow for more favorable binding within the ChE enzyme.

The coupling of substituted 1,2,3-triazolyl groups with targeted quinazolines **7a-c** at the C-6 side chain was found to differently affect the AChEI activity of the resulting hybrid compounds **8-10**. Some of them exhibited potent inhibitory activity against AChE with IC_{50} values ranging from microlar concentrations. As can be seen in Table 1, the best AChEI activity was obtained by compound **9a** (IC_{50} = 0.23 μM) in comparison to donepezil as the reference drug (IC_{50} = 0.12 μM). This compound **9a** possessed benzylamine moiety connected to C-4 position of quinazoline framework and 2-nitrophenyl connected to 1,2,3-triazole ring. Changing nitro group to *meta*-position led to a brief reduction of AChEI activity of compound **9b** with IC_{50} = 1.10 μM, however, compound **9c** having nitro group at *para*-position lost AChEI activity (IC_{50} > 200 μM).

The introduction of *N*-methylpiperazyl moiety instead of benzylamine led to different results. Generally, *N*-methylpiperazyl derivatives **10a-b** depicted lower activity than compounds **9a-b** (IC_{50} = 37.38 and 15.79 μM, respectively) and inversely 3-nitrophenyltriazole derivative **10b** was more active than 2-nitrophenyltriazole **10a** by two times. Compound **10c** showed no activity as compound **9c**, demonstrating that compounds containing 4-nitrophenyl linked to 1,2,3-triazole ring deteriorated inhibitory activity toward AChE. Besides that, a series of compounds **8a-d** possessing 3-nitrophenylamine moiety except **8a** showed no activity. However, compound **8a** showed potential AChEI activity with IC_{50} = 2.06 μM. These results indicated that the nature of amine groups linked to C-4 position of quinazoline scaffold played an important role in inducing anti-AChE activity of their hybrid compounds.

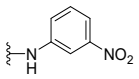
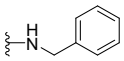
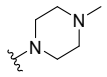
On the other hand, the AChEI activity of the synthesized hybrid compounds was also completely influenced by the electronic properties of substituents on the aromatic ring connected to 1,2,3-triazole. It seems that nitro group on the aryl ring connected to 1,2,3-triazole induced better anti-AChE activity compared that with 3-trifluoromethyl-4-nitrile

group. In fact, the replacement of nitrophenyl moiety by 3-nitrile-4-trifluoromethylphenyl led to a significant reduction of anti-AChE activity in compounds **8d**, **9d** and **10d**. The low inhibitory activity of these compounds suggests a lack flexibility caused by substituted fused aromatic moieties.

To conclude, comparing the most potent hybrid compounds **8a-b, 9a-b** and **10a-b** with separate quinazoline compounds **7a-c** on AChEI activity revealed that the valuable hybridization of merging 1,2,3-triazole and quinazoline into single hybrid compounds.

Table 1

Anti-acetylcholinesterase activity of synthesized compounds **7-10**

Entry	NR^1R^2	Ar	Compound	IC_{50} (AChE), μM
1		-	**7a**	> 200
2		2-$NO_2C_6H_5$	**8a**	**2.06 ± 0.19**
3		3-$NO_2C_6H_5$	**8b**	> 200
4		4-$NO_2C_6H_5$	**8c**	> 200
5		3-CN-4-$CF_3C_6H_4$	**8d**	> 200
6		-	**7b**	47.73 ± 0.81
7		2-$NO_2C_6H_5$	**9a**	**0.23 ± 0.15**
8		3-$NO_2C_6H_5$	**9b**	**1.10 ± 0.27**
9		4-$NO_2C_6H_5$	**9c**	> 200
10		3-CN-4-$CF_3C_6H_4$	**9d**	> 200
11		-	**7c**	83.90 ± 1.06
12		2-$NO_2C_6H_5$	**10a**	37.38 ± 2.01
13		3-$NO_2C_6H_5$	**10b**	15.79 ± 0.18
14		4-$NO_2C_6H_5$	**10c**	> 200
15		3-CN-4-$CF_3C_6H_4$	**10d**	> 200
16		Donepezil		0.12 ± 0.36

With the aim to evaluate the cytotoxic effects on human cancer cell lines, the most potent compounds **7b**, **7c**, **8a**, **9a**, **9b**, **10a** and **10b** were evaluated for their cytotoxicity against KB-CCL-17 (epidermoid carcinoma cancer), HepG2-HB-8065 (hepatoma carcinoma cancer) and SK-Lu-1 (non-small lung cancer) cancer cell lines through MTT assay (Table 2). Ellipticine were used as positive controls. As it is clear in Table 2, they showed no significant cytotoxic effect against these cancer cell lines.

Table 2

Cytotoxicity of the compounds **7b**, **7c**, **8a**, **9a**, **9b**, **10a** and **10b** against selected human cancer cell lines

Entry	Compound	IC_{50} (KB), μM	IC_{50} (HepG2), μM	IC_{50} (Lu), μM
1	**7b**	59.72 ± 2.30	> 200	> 200
2	**7c**	> 200	> 200	> 200
3	**8a**	> 200	> 200	> 200
4	**9a**	42.69 ± 3.40	> 200	> 200
5	**9b**	> 200	94.08 ± 1.35	> 200
6	**10a**	> 200	142.5 ± 1.07	> 200
7	**10b**	> 200	> 200	> 200
8	Ellipticine	1.10 ± 0.05	0.85 ± 0.04	1.30 ± 0.04

In this study, quinazoline-triazole hybrid analogues have been designed and synthesized. Some of them showed good inhibitory activities against AChE enzyme, such as **8a**, **9a**, **9b**, **10a** and **10b**. To better decipher the structure-activity relationships, the molecular docking simulations were performed using ICM-Pro Molsoft 3.8-7 to investigate the interactions between AChE enzyme and these compounds.[36] To do so, the crystal structure of recombinant human AChE in complex with Donepezil was retrieved from RCSB Protein Data bank (PDB ID: 4EY7).[37] Docking protocol was similar to those published previously. We firstly validated

the method by redocking co-crystal ligand into the active site of AChE, taking into account the root-mean square deviation (r.m.s.d.) and interaction paterns.[38]

As revealed from Fig. 2A, AChE has a deep and narrow gorge lined with aromatic amino acids, e.g. Tyr72, Tyr124, Trp286, Tyr341… which are important for the binding and orientation of inhibitors on their way from the PAS (peripheral anionic site) to the choline binding site (also named catalytic anionic site).[39] On the other site is the acyl binding pocket composed by Phe295 and Phe338, which could play a key role in the selective inhibition of AChE. The ligand, after being stabilized in the acyl and oxyanion hole, could interact with the catalytic triad of three residues Ser203, Glu334, and His447, those are important for the hydrolysis of acetylcholine.[37] From the Fig. 2B, the co-crystallized ligand and the redocked donepezil were highly overlapped with r.m.s.d. of 0.22Å and the docking score was -25.28 kCal/mol. All the interactions were highly conserved, including H-bonds between the 5,6-dimethoxy-1-indanone moiety of the drug and Phe295 as well as multiple π–π interactions with the residues at the PAS region and the choline binding site. The results obtained are similar to those previously published,[38] suggesting the validity of the docking method.

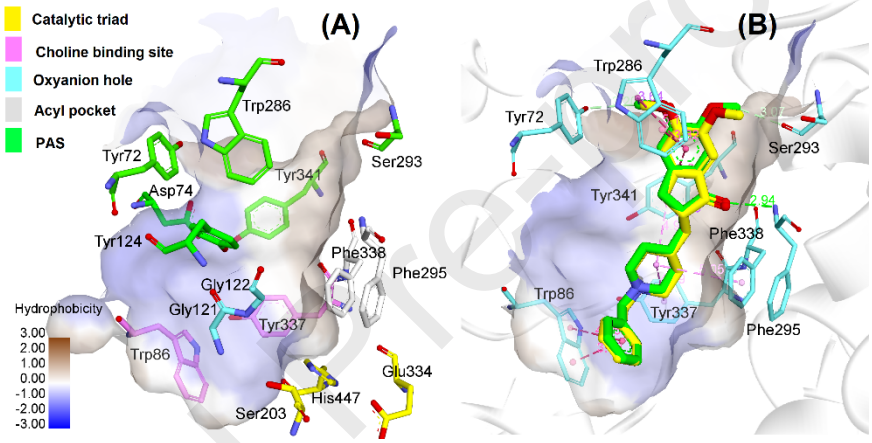


Figure 2. (A) Active site gorges of human AChE (chain A, PDB ID: 4EY7) and (B) superimposition of co-crystal (green) and redocked (yellow) Donepezil inside the active site of AChE.

Applying the docking method perviously validated, five derivatives were docked into the active site of human AChE. From **8a** to **10b**, there can be revealed some difference of binding modes (see Fig. 3). Compounds **8a**, **9a**, and **9b** showed strong interactions against Trp86 aromatic side chain of the choline binding region, meanwhile compounds **10a** and **10b** lacked of that stacking interactions. Compared to **9a** and **9b**, piperazyl moieties in **10a** and **10b** could favourably bind to the residues at PAS through stacking interactions with Trp286. In addition, the quinazoline systems appeared to be impotant for **8a**, **10a** and **10b** as they bound to Trp286 by multiple π–π interactions and H-bonds with Phe295 and/or Ser293 which is similar to donepezil. On the other hands, H-bonding played a significant role on the stabilization of **9a** and **9b** as they strongly interacted with Ser293 and Arg296 of the PAS site through the pyrimidine ring of quinazoline. All the compounds showed similar π–π interactions between triazoles towards Tyr341 and nitro-benzene rings with Tyr337. The docking scores estimated by ICM package for **8a**, **9a**, and **9b** ranked from -24.71 to -26.07 kCal/mol which are similar to that calculated for donepezil. Meanwhile docking scores of **10a** and **10b** were only -16.83

and -17.02 kCal/mol, suggesting a lower affinity of these compounds towards AChE compared to donepezil.

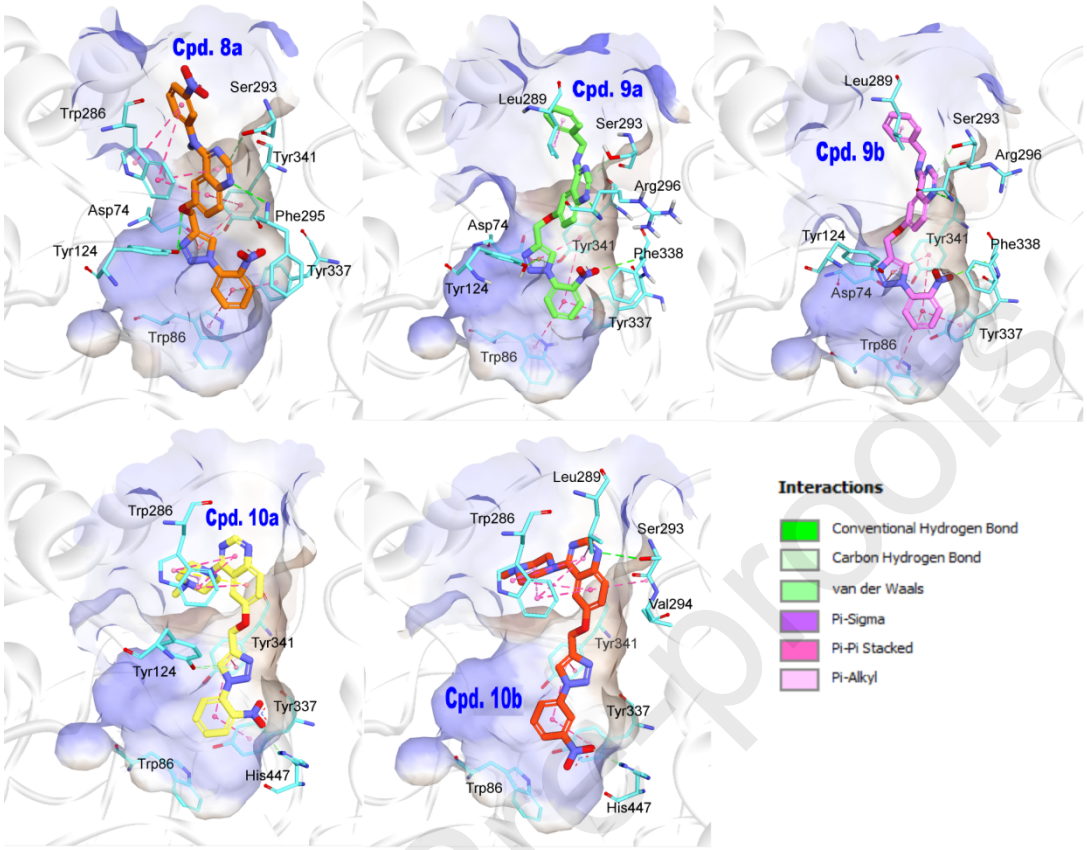


Figure 3. Conformations of the docked compounds **8a**, **9a-b**, and **10a-b** in the active site of human AChE.

Today early drug-likeness profiling has become pivotal in the drug discovery process.[40] We therefore decided to predict several physicochemical and pharmacokinetic properties of the AChE bioactive compounds **8a**, **9a**, **9b**, **10a** and **10b** using suitable approaches. The main results were shown in Table 3.

Table 3. Predicted pharmacokinetic properties of synthesized compounds

Cpd.	Ro5[1]	Tox. Rule[2]	Solubility[3] (mg/ml)	Caco-2 permeability class[4]	BBB[5] distribution	P-gp[6] substrate	Cytochrome P450[7]
8a	1	Low	1.97e-3	High	High	No	1A2, 3A4
9a	0	Moderate	2.27e-03	Moderate	Moderate	No	2C9, 2C19, 3A4
9b	0	Moderate	2.25e-03	Moderate	Moderate	No	2C9, 2C19, 3A4
10a	1	Low	2.26e-02	High	High	No	2C9, 3A4
10b	1	Low	2.24e-02	High	High	No	2C9, 3A4

[1]Number of Lipinski's Rule of Five violations[41]; [2]in vivo toxicological rule of Hughes et al[42]; [3]intrinsic solubility at 25°C calculated by ESOL equation of Delaney[43]; [4]Caco-2 cell permeability classification using 3Prule[44]: High class if $P_{app} \geq 16\times10^{6}$cm/s, Moderate class if $0.7\times10^{-6} \leq P_{app} < 16\times10^{-6}$cm/s; [5]Blood-Brain Barrier distribution classes based on Castillo-Garit et al[45]; [6]P-glycoprotein efflux inhibition state identified via online server http://pgp.biozyne.com/[46]; [7]metabolisms via CYP enzymes identified via admetSAR 1.0 approach.[47]

We first computed physicochemical properties involved into the Lipinski's rule of five (Ro5) and the toxicological rule proposed by Hughes et al. using Volsurf 1.0.4+ software.[41,42,48] The results showed that **8a**, **10a** and **10b** had > 10 H-bond acceptors in the structures with logP < 3 and PSA > 75Å^2 which could be translated into one violation of Ro5

and low toxicological profile.[41,42] At the same time **9a** and **9b** fulfilled the Ro5 and show high-logP/high-PSA profiles. The aqueous solubility of the chemicals was predicted to be quite low (< 0.1 mg/ml) excepting **10a** and **10b**.[48] In addition, all compounds were predicted as moderate-to-high permeants across Caco-2 monolayer, a model of gastrointestinal membrane, according to the 3PRule developed by Pham-The et al.[44] Taking into consideration of the permeability and solubility classes, **8a**, **10a** and **10b** could be predicted as high intestinal absorption (fraction absorbed higher than 85%) meanwhile **9a** and **9b** could have varied absorption extents (30-85%).[49] According to the classification trees proposed by Castillo-Garit et al,[45] all compounds showed moderate-to-high blood-brain barrier distributions which are desirable to be developed as anti-AD agents. At last, the possible first pass metabolisms via P-glycoprotein (P-gp), an efflux membrane transporter, and multiple Cytochrome P450 enzymes were predicted by using cheminformatics approaches.[46,47] According to the support vector machine model proposed by Levatic et al.,[46] all compounds were predicted as non-substrates of P-gp. Nevertheless, the predictions of admetSAR webtool showed that the synthesized compounds are sensible to the enzymes such as CYP1A2, 2C9, 2C19 and 3A4.[47]

In summary, a series of quinazoline–triazole hybrid compounds were designed, synthesized and evaluated for their anti-AChE activity. Most of the synthesized compounds showed moderate to good AChEI activity and among them, compound *N*-benzyl-6-((1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)quinazolin-4-amine (**9a**) was found to be the most potent inhibitor with IC_{50} = 0.23 μM. Premilinary investigation of the structure-activity relationships (SARs) of these synthezied compounds **7-10** revealed that the nature of the amine linked to C4 of quinazoline scaffold and the aryl group which connected to the triazole influenced the anti-AChE activity remarkably. Our molecular docking study revealed that compounds **8a** and **9a-b** bind to both catalytic anionic site (CAS) and peripheral anionic site (PAS) in the active site of AChE enzyme, which implicates that these compounds could act as dual binding site inhibitors. Furthermore, compounds **8a**, **9a-b** and **10a-b** were not cytotoxic and they also displayed appropriated physicochemical as well as pharmacokinetic profile to be developed as novel anti-AD drug candidates. Considering these overall results, this study demonstrates how our strategy enable the discovery of novel promising and privileged structures. Finally, the results indicate that these new compounds could be considered as a new lead for further optimization.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2020.

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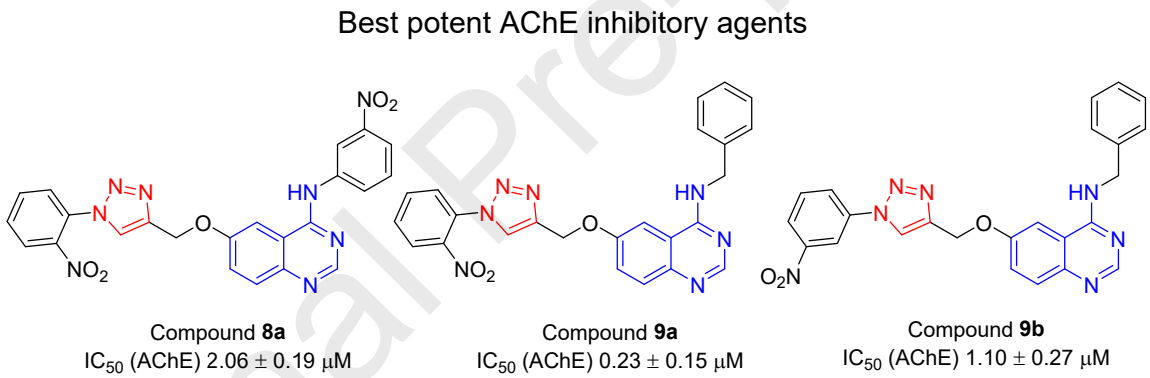
GRAPHICAL ABSTRACT

Synthesis and biological evaluation of novel quinazoline-triazole hybrid compounds with potential use in Alzheimer's disease



Synthesis and biological evaluation of novel quinazoline-triazole hybrid compounds with potential use in Alzheimer's disease

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- Twelve new quinazoline-triazole hybrid compounds were designed and synthesized.
- Their acetylcholinesterase inhibitory activity was evaluated.
- Compound **9a** was found to be the most promising anti-AChE agent with IC_{50} = 0.23 μM.
- Molecular modeling suggested a selective inhibition of hit compounds **8a, 9a**, and **9b** bind to both catalytic (CAS) and peripheral site (PS) in the active site of AChE.