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Synthesis of 1,2,3,4-tetrahydroacridine based 1,2,3-triazole derivatives and their biological evaluation as dual cholinesterase and α-glucosidase inhibitors†

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A series of new 1,2,3-triazole-linked tacrine derivatives were synthesized *via* Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) of C4-functionalized 9-azido-1,2,3,4-tetrahydroacridines and various phenyl acetylenes including tacrine-based terminal alkynes. All the compounds were obtained in good yields and evaluated for their *in vitro* cholinesterase (AChE and BChE) and α-glucosidase inhibitory activities. Several compounds exhibited potent dual enzyme inhibition for cholinesterase (AChE and BChE) and also α-glucosidase. *In silico* docking studies were in good agreement with *in vitro* results, confirming the dual binding inhibitory activity of the compounds.

Introduction

Alzheimer's disease (AD), a prevalent chronic neurodegenerative syndrome, causes progressive decline of cognitive abilities such as memory, language skills, and intelligence.[1] The precise etiology of Alzheimer's disease remains elusive, with a multitude of factors implicated in the pathogenesis, including genetic factors, amyloid aggregation, hyperphosphorylation of tau protein (neurofibrillary tangles), cholinergic hypofunction, oxidative stress, *etc.*[2] The predominant therapeutic strategy for the treatment of AD patients is to increase cholinergic activity in cholinergic clefts through inhibiting acetylcholinesterase[3] and inducing the interaction of acetylcholinesterase inhibitors with β-amyloid to inhibit AChE.[4] The four acetylcholinesterase inhibitors approved by the FDA are tacrine, donepezil, rivastigmine, and galantamine.[5] Despite showing therapeutic potential, tacrine was discontinued due to severe hepatic toxicity.[6]

The structure of AChE consists of a catalytic binding site (CS) and a peripheral anionic binding site (PAS), which are responsible for its enzymatic function. AChE inhibitors block the AChE by interacting with amino acid residues in the CS (competitive inhibitors) and PAS (non-competitive inhibitors).[7] According to the literature, tacrine acts as a specific inhibitor at the catalytic anionic site (CAS) within the CS of AChE.[8] The inhibitors that facilitate the dual interaction with the catalytic binding site and the peripheral anionic binding site show significantly better inhibitory efficiency.[9] Additionally, recent studies demonstrated that the PAS of AChE plays a significant role in the formation of Aβ-aggregates. A BChE knockout animal model also demonstrated that the BChE deficiency reduces the Aβ deposition in Alzheimer's disease.[10] In this respect, a great deal of attention has been paid to the development of dual binding sites (AChE and BChE inhibitors) to increase inhibitory activity through the enhancement of the number of drug–target interactions and prevent Aβ-aggregation. Thus, several dual-binding inhibitors have been synthesized and evaluated for anti-cholinesterase activity with special emphasis on tacrine derivatives towards elimination of the side effects of tacrine.[11] Some of these examples include the hybrids linked with either a heterocyclic moiety or a synthetic analogue/a biologically active molecule through a 1,2,3-triazole linker (Fig. 1).[7,8,11,12]

The 1,2,3-triazole ring is one of the important scaffolds in medicinal chemistry. This moiety can serve as a bioisostere for many functional groups like –COOH, –COOR, –$CONH_2$, *etc.* and has therefore attracted much attention in drug discovery.[13a] 1,2,3-Triazole compounds can be conveniently synthesised *via* Cu(I) catalysed azide–alkyne 1,3-dipolar cycloaddition (CuAAC), *i.e.* a click reaction.[13b,c] Triazole core embedded heterocycles have been shown to exhibit a wide range of biological activities such as anticancer,[14] antimicrobial,[15] anti-HIV,[16] *etc.* Triazole-containing derivatives were also evaluated for Alzheimer's

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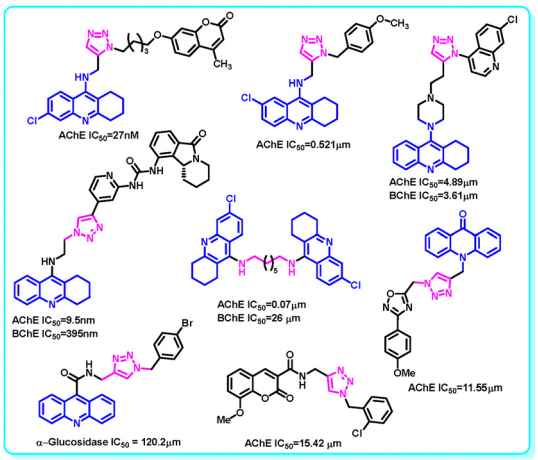


Fig. 1 Tacrine and 1,2,3-triazole containing cholinesterase and glucosidase inhibitors.

disease (*in vitro* and *in vivo* activities) and have attracted great interest in searching for new inhibitors against Alzheimer's disease.[17] The triazole moiety is capable of interacting with biomolecular targets through H-bonding, π–π stacking and dipole interactions. Besides this, the triazole moiety offers better chemical stability in a physiological environment and helps in improving the pharmacokinetics and toxicity properties.[18]

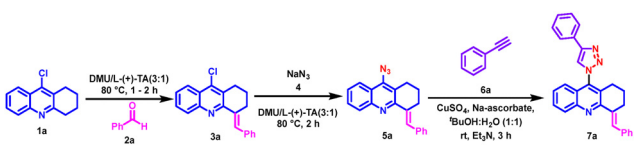
In this direction, our group has reported C4-functionalized tacrines, C4-functionalized tacrine amines and C4-functionalized Pfitzinger acid derivatives as potential cholinesterase and α-glucosidase inhibitors.[19] In all these cases, we have observed that the modification at the C4 and C9 positions of tacrine helps to enhance the inhibitory activity towards cholinesterase and α-glucosidase enzymes. Also, there have been no reports on the rigid 1,2,3-triazole at the C9 position of tacrine in the literature. Thus, in continuation of our interest and searching for better tacrine-based molecules for the inhibition of cholinesterase and α-glucosidase enzymes, in the present study, we endeavoured to substitute the tacrine $-NH_2$ by a 1,2,3-triazole moiety as a rigid unit.

Results and discussion

Towards achieving the objectives, the desired compound **7a** was obtained *via* the reaction illustrated in Scheme 1. Initially, 9-chloro-1,2,3,4-tetrahydroacridine **1a** (1.0 mmol) was treated with benzaldehyde **2a** (1.0 mmol) in a deep eutectic solvent [*i.e.* *N*,*N*′-dimethylurea and L-(+)-tartaric acid (3 : 1)] at 80 °C[20] to obtain the C(sp^3)–H functionalised derivative **3a**. To the same reaction pot, NaN_3 (5.0 equiv.) was added to afford the 9-azido-1,2,3,4-tetrahydroacridine derivative **5a** (in 2 h at 80 °C). Compound **5a** was filtered and recrystallised. Then compound **5a** (1.0 mmol) was treated with phenylacetylene **6a** (1.0 mmol) under click reaction conditions, *i.e.* in the presence of Et_3N, $CuSO_4$, and sodium ascorbate in H_2O : ^{t}BuOH (1 : 1) at room temperature for 3 h to give **7a** in 90% yield. The structure of **7a** was confirmed using ^{1}H- and ^{13}C-NMR and HRMS spectroscopy.

After confirming the structure of compound **7a**, we then studied the substrate scope of the reaction with various substituted C(sp^3)–H activated 1,2,3,4-tetrahydroacridine derivatives (**5b–5h**) and phenylacetylenes (**6a–6c**) to afford 1,2,3-triazole containing tacrine derivatives (**7a–7n**) with good to excellent yields (Fig. 2). All the C4-functionalized C9-azides reacted well with phenyl acetylenes, except the substrate (**7g**; 84%) with $-NO_2$ substitution at the *para* position of the aromatic system at the C4 position. In contrast, the $-NO_2$ functional group at the C6 position was well tolerated, giving the desired products in 95% (**7c**) and 96% (**7k**), respectively. There was not much impact observed from the substitution on the phenylacetylene part (though–Cl is relatively electron withdrawing).

As per the reports from the literature, dimeric tacrine[11] derivatives linked by a spacer show more potent inhibitory activity than tacrine as a single molecule (though there is no synergistic effect). Based on this, we attempted to synthesise similar structures (type **10**) with triazole as a rigid linker and two 1,2,3,4-tetrahydro acridine units by adopting click chemistry conditions. Towards this, 9-azido-1,2,3,4-tetrahydroacridines (**8a–8c**; synthesized from 9-chloro-1,2,3,4-tetrahydroacridines



Scheme 1 Synthesis of the 1,2,3-triazole containing tacrine derivative **7a** *via* a click reaction of azide (**5a**) with phenylacetylene (**6a**).

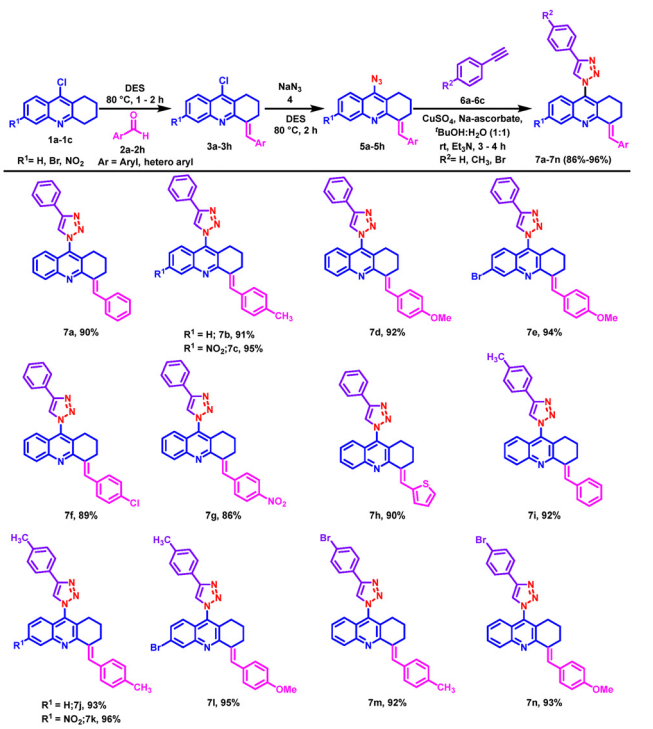
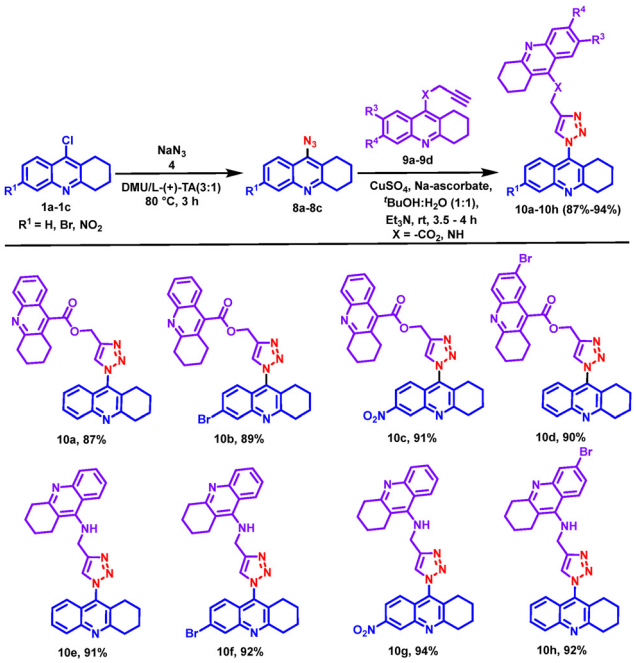


Fig. 2 Synthesis of 1,2,3-triazole containing tacrine derivatives (**7a–7n**).



Scheme 2 Synthesis of dimerized 1,2,3,4-tetrahydroacridine derivatives (**10a–10h**) with triazole as a linker.

1a–1c) were reacted with 1,2,3,4-tetrahydroacridine-based terminal alkynes (**9a–9d**; synthesized by independent propargylation of Pfitzinger acids and tacrine) under click reaction conditions to give the desired 1,2,3,4-tetrahydroacridine derivatives **10a–10h** with a triazole linker in good to excellent yields (87–92%) (Scheme 2). All the products were characterized by complementary spectroscopic data.

Biological assay

Having successfully synthesized the tacrine-1,2,3-triazole-based hybrids by replacing C9-NH_2 with a 1,2,3-triazole moiety, the next task was to evaluate them for acetyl/butyrylcholinesterase and α-glucosidase inhibition. Accordingly, all the *in silico* and *in vitro* studies were performed for all the resulting products (both **7** and **10** series) for acetyl/butyrylcholinesterase and α-glucosidase inhibition. Table 1 shows that many of the compounds tested here show good activity compared to standard drugs, tacrine (for acetyl/butyrylcholinesterase inhibition) and acarbose (for α-glucosidase inhibition), and the 2D and 3D binding interactions of potent compounds are shown in Fig. 3–5. The structure activity relationship (SAR) analysis indicating that the compounds with that. Among the synthesised compounds, compounds **7g**, **7h**, **7i**, **7j**, and **7m** show better activity for both acetyl- and butyrylcholinesterase with a simple aryl moiety as part of the C4 position of the 1*H*-1,2,3-triazole moiety. Strangely, **7b** and **7d** behaved differently for acetylcholinesterase (loss of activity). There was not much difference observed in the activity of the compounds with substitution at C6 (**7e** and **7k**).

The docking images of all these compounds show the involvement/interaction of the hydrophobic aromatic moiety with multiple amino acids. Similarly, among the dimer type molecules, **10c**, **10d**, **10e**, **10f** and **10h** show better inhibitory activity for both acetyl- and butyrylcholinesterase. The molecular docking studies revealed that the tested compounds **7j**, **7g**, **7i**, **10h**, and **10e** interact with the target protein *via* hydrogen bonding and π–π stacking interactions. The interactions are between hydrophobic amino acids present in the active site/pocket of both AChE and BChE, the 1,2,3,4-tetrahydroacridine

Table 1 *In vitro* and *in silico* molecular docking studies of the synthesised compounds

S. no.	Compound	*In vitro* AChE – IC_{50} (nM)	*In silico* docking score	*In vitro* BChE – IC_{50} (nM)	*In silico* docking score	*In vitro* glucosidase – IC_{50} (nM)	*In silico* docking score
1	**7a**	153.12	−8.03	149.32	−7.98	37 490	−6.98
2	**7b**	212.21	−7.1	165.32	−7.87	38 930	−6.39
3	**7c**	141.98	−8.01	134.05	−8.03	33 100	−7.21
4	**7d**	223.1	−7.2	156.35	−7.98	36 460	−6.76
5	**7e**	140.25	−9.8	142.65	−9.3	38 650	−6.82
6	**7f**	189.32	−7.34	196.35	−7.36	31 700	−7.3
7	**7g**	121.02	−11.1	132.75	−10.6	37 050	−6.93
8	**7h**	135.2	−10.7	130.45	−10.3	50 350	−6.05
9	**7i**	**130.54**	**−10.7**	**130.21**	**−10.1**	42 310	−6.22
10	**7j**	**120.67**	**−11.2**	**132.05**	**−10.6**	40 650	−6.31
11	**7k**	138.02	−10.2	140.24	−9.8	47 310	−6.54
12	**7l**	132.45	−10	147.03	−9.7	45 260	−6.12
13	**7m**	134.25	−10.5	131.08	−10.2	44 650	−6.47
14	**7n**	132.54	−10	143.05	−9.6	41 950	−6.3
15	**10a**	169.51	−7.61	160.53	−7.65	28 480	−7.62
16	**10b**	163.54	−7.71	156.67	−7.73	**22 390**	**−7.47**
17	**10c**	128.54	−12.9	133.54	−11.65	29 450	−7.31
18	**10d**	**129.26**	**−12.3**	**130.15**	**−11.54**	29 170	−7.59
19	**10e**	**131.65**	**−7.95**	**124.94**	**−7.92**	26 570	−7.41
20	**10f**	131.25	−11.6	131.58	−12.6	28 450	−7.68
21	**10g**	135.64	−11.4	136.57	−11.5	26 070	7.64
22	**10h**	**128.12**	**−12.6**	**129.45**	**−11.8**	27 980	−7.05
23	Tacrine	201.05	−7.76	202.14	−7.71	—	—
24	Acarbose	—	—		—	23 100	−7.89

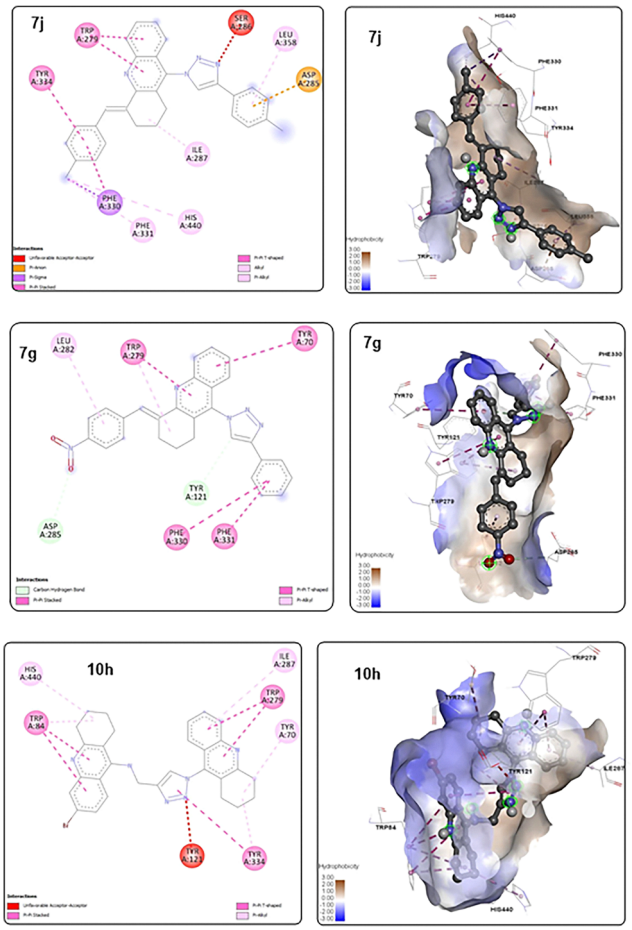


Fig. 3 **2D** and **3D** docking interactions of compounds **7j**, **7g,** and **10h** with protein **1DX6**.

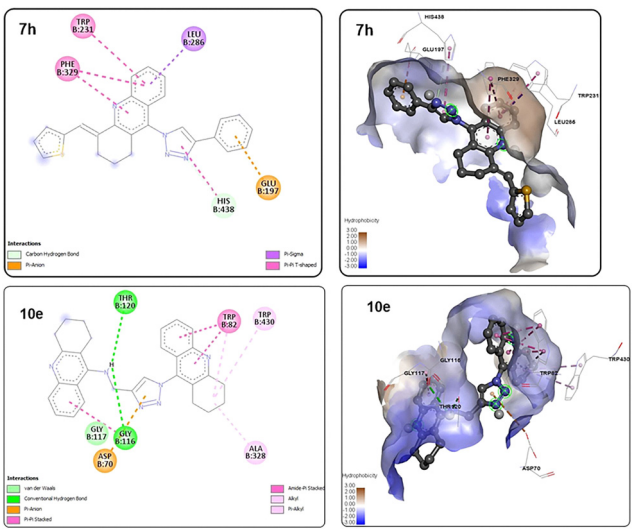


Fig. 4 **2D** and **3D** docking interactions of compounds **7i**, **7h**, and **10e** with protein **6EMI**.

moiety, the C4 aryl moiety, and the triazole-attached aryl moiety with a CH_3 substituent at the R^2 position in compounds **7j** and **7i.**

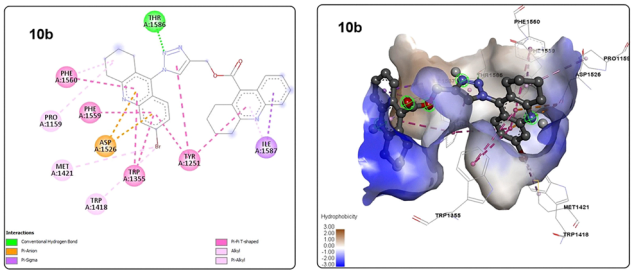


Fig. 5 **2D** and **3D** docking interactions of compound **10b** with protein **3TOP**.

Compound **10e** shows hydrogen bonding interactions through the NH moiety with the BChE active site. The compound having more π–π interactions showed a better docking score with good IC_{50} values. Compound **10b** showed good inhibitory activity against α-D-glucosidase. The 1,2,3,4-tetrahydroacridine moieties of compound **10b** showed π–π interactions with hydrophobic amino acids at the enzyme active site, and one of the nitrogens of 1,2,3-triazole showed hydrogen bonding. Furthermore, the *in silico* docking scores (−7.1 to −12.9 in the case of AChE and −7.3 to −11.8 in the case of BChE) are within the range of acceptance for the objectives set. Similar docking scores were observed for α-D-glucosidase ranging from −6.05 to −7.68.

Blood–brain barrier prediction

The ability to penetrate the blood–brain barrier (BBB) is a crucial characteristic for compounds designed for Alzheimer's disease treatment or any drug targeting the central nervous system. According to the predicted data from the BBB predictor module of ALzPlatform, all the tested compounds selected based on their *in vitro* inhibitory activity against AChE and BChE were determined to be BBB+. This indicates that these molecules possess BBB permeability and can traverse the blood–brain barrier. The predicted properties are shown in Table 2.

Prediction of drug-like properties

Drug-like properties were predicted based on Lipinski's Rule of Five, and the properties of the drug were predicted based on

Table 2 BBB prediction of ligands using ALzPlatform

Compound	SVM_MACCSFP BBB score	BBB permeability
7i	0.101	BBB+
7j	0.093	BBB+
7h	0.098	BBB+
7m	0.073	BBB+
7g	0.116	BBB+
10b	0.051	BBB+
10e	0.101	BBB+
10c	0.054	BBB+
10d	0.051	BBB+
10f	0.072	BBB+
10h	0.072	BBB+
Tacrine	0.120	BBB+

Table 3 Drug-likeness and *in silico* ADME properties

Compound	Molecular mass (g mol^{-1})	Lipophilicity (Log$P_{o/w}$)	Hydrogen bond donors	Hydrogen bond acceptors	Molecular refractivity	TPSA
7i	428.53	5.79	0	3	134.9	43.6
7j	442.55	6.11	0	3	139.86	43.6
7h	420.53	5.44	0	3	127.81	71.84
7m	507.42	6.39	0	3	142.6	43.6
7g	459.5	4.72	0	5	138.75	89.42
10b	568.46	5.66	0	6	150.29	82.79
10e	460.57	5.06	1	4	140.62	68.52
10c	534.57	4.31	0	8	151.41	128.61
10d	568.46	5.65	0	6	150.29	82.79
10f	539.47	5.61	1	4	148.32	68.52
10h	539.47	5.67	1	4	148.32	68.52

the molecular mass of the compounds less than 500 Dalton, lipophilicity (based on Log*P* less than 5), hydrogen bond donors (less than 5), hydrogen bond acceptors (less than 10), and molar refractivity in the range 40–150. The drug-likeness prediction was carried out using the SwissADME tool. Based on the analysis, it was observed that the compounds showed better inhibitory activity for α-glucosidase, AChE, and BChE, having drug-like properties (Table 3).

QSAR analysis

For comparable structures, docking analyses were carried out to ascertain their biological importance. A QSAR model was developed, and the docking score acquired for a set of substances with comparable structural/functional groupings was used to determine their biological activity. Compounds with arylmethyl at the R^2 position and with aryl substitution at C4 exhibited good interactions with better inhibitory activity. A combination of Br at the R^1 position and aryl substitution at C4 positions in the substance showed a good correlation with the inhibitory effect. In addition, the compounds with Br at the R^2 position and a methyl-, methoxy-substituted aryl moiety at C4 also showed better inhibitory activity towards AChE. However, the compounds without substitutions at the R^2 position lacked inhibitory properties. In dimerized 1,2,3,4-tetrahydroacridine derivatives, the compounds with either Br or NO_2 substitution at R^3 or R^4 exhibit good interactions, showing better inhibition activity. According to the interactions obtained in docking studies and assumptions made by using the QSAR studies, it can be concluded that for AChE and BChE TRP231 was found to interact with the 1,2,3,4-tetrahydroacridine moiety (Table 4).

Table 4 Statistical parameters of the GA-LDA

Parameters	Training set	Test set
No. of compounds	45	15
Sensitivity (%)	68.83	73.9
Specificity (%)	69.32	74.5
Accuracy (%)	90.0	95.2
Precision (%)	75.5	76.3
MCC	0.548	0.541
AUROC	0.896	0.883

Conclusions

In conclusion, we have synthesized a series of tacrine-1,2,3-triazole hybrids under Cu(I) catalyzed click reaction conditions. The synthesized compounds were evaluated for inhibitory activities against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and α-glucosidase enzymes. Among the tested compounds, **7j**, **7g**, and **10h** demonstrated the most potent AChE inhibition, with IC_{50} values of 120.67 nM, 121.02 nM, and 128.12 nM, respectively. Compounds **7i**, **7h**, and **10e** exhibited strong BChE inhibitory activity, with IC_{50} values of 130.21 nM, 130.45 nM and 124.94 nM, respectively. In addition, compound **10b** showed notable α-glucosidase inhibition with an IC_{50} of 22390 nM. A QSAR model was developed, suggesting that the presence of the 1,2,3,4-tetrahydroacridine core and an arylmethyl at the R_2 position significantly contributes to enhanced inhibitory potency.

Conflicts of interest

There are no conflicts to declare.

Data availability

All the data (ESI†) of this manuscript have been submitted along with the article. This will be made available along with the manuscript as per the journals policy.

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Notes and references

1 X. Jiang, J. Zhou, Y. Wang, L. Chen, Y. Duan, J. Huang, C. Liu, Y. Chen, W. Liu, H. Sun, F. Feng and W. Qu, Rational design and biological evaluation of a new class of thiazolopyridyl tetrahydroacridines as cholinesterase and GSK-3

dual inhibitors for Alzheimer's disease, *Eur. J. Med. Chem.*, 2020, **207**, 112751.

2 (*a*) M. Mohammadi-Khanaposhtani, M. Saeedi, N. S. Zafarghandi, M. Mahdavi, R. Sabourian, E. K. Razkenari, H. Alinezhad, M. Khanavi, A. Foroumadi, A. Shafiee and T. Akbarzadeh, Potent acetylcholinesterase inhibitors: Design, synthesis, biological evaluation, and docking study of acridone linked to 1,2,3-triazole derivatives, *Eur. J. Med. Chem.*, 2015, **92**, 799–806; (*b*) M. Saeedi, S. Ansari, M. Mahdavi, R. Sabourian, T. Akbarzadeh, A. Foroumadi and A. Shafiee, Synthesis of Novel 1,2,3-Triazole-dihydro[3,2-*c*]chromenones as Acetylcholinesterase Inhibitors, *Synth. Commun.*, 2015, **45**(20), 2311–2318; (*c*) P. De Andrade, S. P. Mantoani, P. S. Gonçalves Nunes, C. R. Magadán, C. Pérez, D. J. Xavier, E. T. S. Hojo, N. E. Campillo, A. Martínez and I. Carvalho, Highly potent and selective aryl-1,2,3-triazolyl benzylpiperidine inhibitors toward butyrylcholinesterase in Alzheimer's disease, *Bioorg. Med. Chem.*, 2019, **27**(6), 931–943.

3 M. Saeedi, M. Safavi, E. Karimpour-Razkenari, M. Mahdavi, N. Edraki, F. H. Moghadam, M. Khanavi and T. Akbarzadeh, Synthesis of novel chromenones linked to 1,2,3-triazole ring system: Investigation of biological activities against Alzheimer's disease, *Bioorganic Chem.*, 2017, **70**, 86–93.

4 S.-S. Xie, X.-B. Wang, J.-Y. Li, L. Yang and L.-Y. Kong, Design, synthesis and evaluation of novel tacrine–coumarin hybrids as multifunctional cholinesterase inhibitors against Alzheimer's disease, *Eur. J. Med. Chem.*, 2013, **64**, 540–553.

5 R. J. Obaid, N. Naeem, E. U. Mughal, M. M. Al-Rooqi, A. Sadiq, R. S. Jassas, Z. Moussa and S. A. Ahmed, Inhibitory potential of nitrogen, oxygen and sulfur containing heterocyclic scaffolds against acetylcholinesterase and butyrylcholinesterase, *RSC Adv.*, 2022, **12**(31), 19764–19855.

6 Y. Wang, Y. Yang, K. H. Hong, Y. Ning, P. Yu, J. Ren, M. Ji and J. Cai, Design, synthesis and evaluation of a novel metal chelator as multifunctional agents for the treatment of Alzheimer's disease, *Bioorganic Chem.*, 2019, **87**, 720–727.

7 Z. Najafi, M. Mahdavi, M. Saeedi, E. Karimpour-Razkenari, R. Asatouri, F. Vafadarnejad, F. H. Moghadam, M. Khanavi, M. Sharifzadeh and T. Akbarzadeh, Novel tacrine-1,2,3-triazole hybrids: *In vitro*, *in vivo* biological evaluation and docking study of cholinesterase inhibitors, *Eur. J. Med. Chem.*, 2017, **125**, 1200–1212.

8 Z. Najafia, M. Mahdavic, M. Saeedid, E. Karimpour-Razkenarie, N. Edrakif, M. Sharifzadehg, M. Khanavih and T. Akbarzadeha, Novel tacrine-coumarin hybrids linked to 1,2,3-triazole as anti-Alzheimer's compounds: *In vitro* and *in vivo* biological evaluation and docking study, *Bioorganic Chem.*, 2019, **83**, 303–316.

9 M. Mohammadi-Khanaposhtani, M. Mahdavi, M. Saeedi, R. Sabourian, M. Safavi, M. Khanavi, A. Foroumadi, A. Shafiee and T. Akbarzadeh, Design, Synthesis, Biological Evaluation, and Docking Study of Acetylcholinesterase Inhibitors: New Acridone-1,2,4-oxadiazole-1,2,3-triazole Hybrids, *Chem. Biol. Drug Des.*, 2015, **86**(6), 1425–1432.

10 N. C. Inestrosa, J. P. Sagal and M. Colombres, *Acetylcholinesterase Interaction with Alzheimer Amyloid* β, 2005, pp. 299–317.

11 (*a*) Y.-P. Pang, P. Quiram, T. Jelacic, F. Hong and S. Brimijoin, Highly Potent, Selective, and Low Cost Bis-tetrahydroaminacrine Inhibitors of Acetylcholinesterase, *J. Biol. Chem.*, 1996, **271**(39), 23646–23649; (*b*) M. I. Fernández-Bachiller, C. Pérez, G. C. González-Muñoz, S. Conde, M. G. López, M. Villarroya, A. G. García and M. I. Rodríguez-Franco, Novel Tacrine−8-Hydroxyquinoline Hybrids as Multifunctional Agents for the Treatment of Alzheimer's Disease, with Neuroprotective, Cholinergic, Antioxidant, and Copper-Complexing Properties, *J. Med. Chem.*, 2010, **53**(13), 4927–4937; (*c*) K. Oukoloff, N. Coquelle, M. Bartolini, M. Naldi, R. Le Guevel, S. Bach, B. Josselin, S. Ruchaud, M. Catto, L. Pisani, N. Denora, R. M. Iacobazzi, I. Silman, J. L. Sussman, F. Buron, J.-P. Colletier, L. Jean, S. Routier and P.-Y. Renard, Design, biological evaluation and X-ray crystallography of nanomolar multifunctional ligands targeting simultaneously acetylcholinesterase and glycogen synthase kinase-3, *Eur. J. Med. Chem.*, 2019, **168**, 58–77; (*d*) M.-K. Hu, L.-J. Wu, G. Hsiao and M.-H. Yen, Homodimeric Tacrine Congeners as Acetylcholinesterase Inhibitors, *J. Med. Chem.*, 2002, **45**(11), 2277–2282.

12 (*a*) C. J. Monceaux, C. Hirata-Fukae, P. C.-H. Lam, M. M. Totrov, Y. Matsuoka and P. R. Carlier, Triazole-linked reduced amide isosteres: An approach for the fragment-based drug discovery of anti-Alzheimer's BACE1 inhibitors, *Bioorg. Med. Chem. Lett.*, 2011, **21**(13), 3992–3996; (*b*) W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radić, P. R. Carlier, P. Taylor, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**(6), 1053–1057.

13 (*a*) E. Bonandi, M. S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli and D. Passarella, The 1,2,3-triazole ring as bioisostere in medicinal chemistry, *Drug Discovery Today*, 2017, **22**(10), 1572–1581; (*b*) K. Bozorov, J. Zhao and H. A. Aisa, 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview, *Bioorg. Med. Chem.*, 2019, **27**(16), 3511–3531; (*c*) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone and A. M. Almerico, 1,2,3-Triazole in Heterocyclic Compounds, Endowed with Biological Activity, through 1,3-Dipolar Cycloadditions, *Eur. J. Org. Chem.*, 2014, 3289–3306.

14 G. Valdomir, M. D. L. Á. Fernández, I. Lagunes, J. I. Padrón, V. S. Martín, J. M. Padrón and D. Davyt, Oxa/thiazole-tetrahydropyran triazole-linked hybrids with selective antiproliferative activity against human tumour cells, *New J. Chem.*, 2018, **42**(16), 13784–13789.

15 S. M. M. Lopes, J. S. Novais, D. C. S. Costa, H. C. Castro, A. M. S. Figueiredo, V. F. Ferreira, T. M. V. D. Pinho, E. Melo and F. D. C. Da Silva, Hetero-Diels-Alder reactions of novel 3-triazolyl-nitrosoalkenes as an approach to functionalized 1,2,3-triazoles with antibacterial profile, *Eur. J. Med. Chem.*, 2018, **143**, 1010–1020.

16 F. D. C. Da Silva, M. C. B. V. De Souza, I. I. P. Frugulhetti, H. C. Castro, S. L. D. O. Souza, T. M. L. De Souza, D. Q. Rodrigues, A. M. T. Souza, P. A. Abreu and F. Passamani, Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1*H*-1,2,3-triazole derivatives of carbohydrates, *Eur. J. Med. Chem.*, 2009, **44**(1), 373–383.

17 (*a*) M. Xu, Y. Peng, L. Zhu, S. Wang, J. Ji and K. P. Rakesh, Triazole derivatives as inhibitors of Alzheimer's disease: Current developments and structure-activity relationships, *Eur. J. Med. Chem.*, 2019, **180**, 656–672; (*b*) A. Rastegari, H. Nadri, M. Mahdavi, A. Moradi, S. S. Mirfazli, N. Edraki, F. H. Moghadam, B. Larijani, T. Akbarzadeh and M. Saeedi, Design, synthesis and anti-Alzheimer's activity of novel 1,2,3-triazole-chromenone carboxamide derivatives, *Bioorg. Chem.*, 2019, **83**, 391–401.

18 (*a*) H. Kaur Gulati, S. Choudhary, N. Kumar, A. Ahmed, K. Bhagat, J. Vir Singh, A. Singh, A. Kumar, P. M. Singh Bedi, H. Singh and D. Mukherjee, Design, Synthesis, biological investigations and molecular interactions of triazole linked tacrine glycoconjugates as Acetylcholinesterase inhibitors with reduced hepatotoxicity, *Bioorg. Chem.*, 2022, **118**, 105479; (*b*) G. Wu, Y. Gao, D. Kang, B. Huang, Z. Huo, H. Liu, V. Poongavanam, P. Zhan and X. Liu, Design, synthesis and biological evaluation of tacrine-1,2,3-triazole derivatives as potent cholinesterase inhibitors, *MedChemComm*, 2018, **9**(1), 149–159.

19 (*a*) T. Shirisha, S. Majhi, K. Divakar and D. Kashinath, Synthesis of C4-functionalized 1,2,3,4-tetrahydroacridine-based Pfitzinger acid derivatives in deep eutectic solvents and their biological evaluation as dual cholinesterase and a-glucosidase inhibitors, *New J. Chem.*, 2025, **49**, 1072; (*b*) T. Shirisha, S. Majhi, K. Divakar and D. Kashinath, Metal-free synthesis of functionalized tacrine derivatives and their evaluation for acetyl/butyrylcholinesterase and α-glucosidase inhibition, *Org. Biomol. Chem.*, 2024, **22**, 790; (*c*) N. Satyanarayana, B. Ramya Sree, K. Sathish, S. Nagaraju, K. Divakar, R. Pawar, T. Shirisha and D. Kashinath, Synthesis of 2-styryl-quinazoline and 3-styryl-quinoxaline based sulfonate esters via sp3 C–H activation and their evaluation for α-glucosidase inhibition, *New J. Chem.*, 2022, **46**, 5162.

20 (*a*) N. Satyanarayana, K. Sathish, S. Nagaraju, R. Pawar, M. Faizan, M. Arumugavel, T. Shirisha and D. Kashinath, Metal-free, one-pot synthesis of 2-styrylquinolines via Friedlander annulation and sp3 C–H activation using 1,3-dimethylurea and L-tartaric acid (3 : 1) as a deep eutectic solvent, *New J. Chem.*, 2022, **46**, 1637; (*b*) T. Shirisha, S. Majhi, S. Balasubramanian and D. Kashinath, Metal-free C(sp3)–H functionalization (C–C and C–N bond formation) of 1,2,3,4-tetrahydroacridines using deep eutectic solvents as catalyst and reaction medium, *Org. Biomol. Chem.*, 2024, **22**, 1434; (*c*) T. Shirisha, S. Majhi and D. Kashinath, One-Pot Synthesis of Functionalized Carbazoles and β-Carbolines *via* Diethyl Azodicarboxylate Mediated Dehydrogenative Aromatization in Deep Eutectic Solvent, *ChemistrySelect*, 2024, **9**, e2024012.