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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.

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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 acetylcholinesterase³ 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 A β -aggregates. A BChE knockout animal model also demonstrated that the BChE deficiency reduces the A β 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 A β -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, –CONH₂, *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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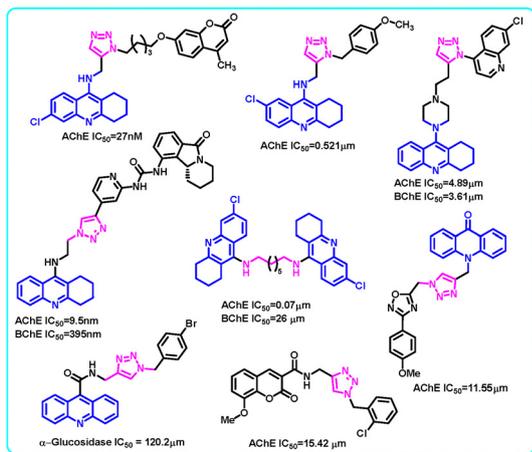


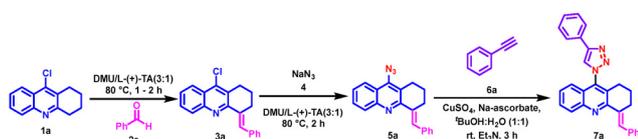
Fig. 1 Tacrine and 1,2,3-triazole containing cholinesterase and glucosidase inhibitors.

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 $-\text{NH}_2$ 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 °C²⁰ to



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

obtain the $\text{C}(\text{sp}^3)\text{-H}$ 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 $\text{H}_2\text{O}:\text{tBuOH}$ (1 : 1) at room temperature for 3 h to give **7a** in 90% yield. The structure of **7a** was confirmed using ^1H - 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 $\text{C}(\text{sp}^3)\text{-H}$ 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 $-\text{NO}_2$ substitution at the *para* position of the aromatic system at the C4 position. In contrast, the $-\text{NO}_2$ 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 $-\text{Cl}$ is relatively electron withdrawing).

As per the reports from the literature, dimeric tacrine¹¹ 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-tetrahydroacridine 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

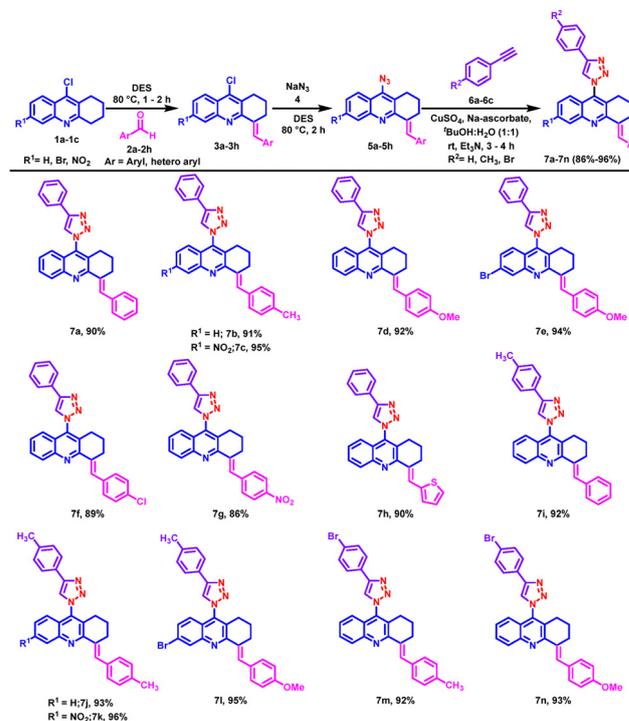
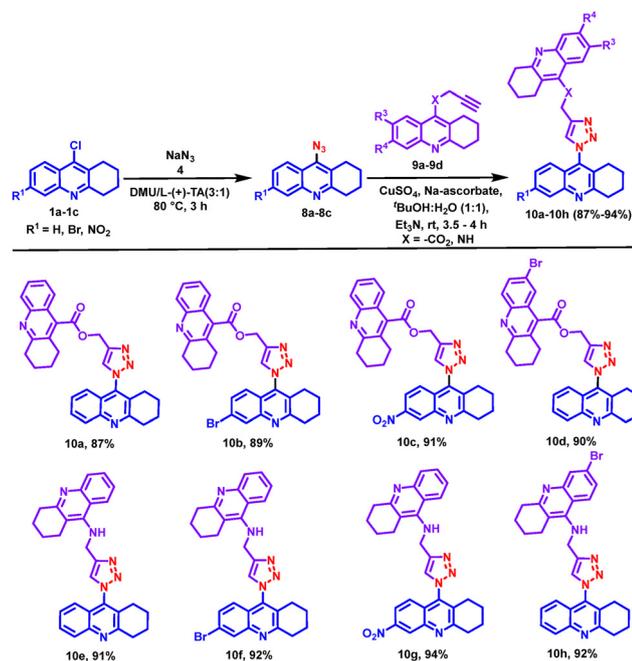


Fig. 2 Synthesis of 1,2,3-triazole containing tacrine derivatives (**7a–7n**).





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-NH₂ 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	<i>In vitro</i> AChE – IC ₅₀ (nM)	<i>In silico</i> docking score	<i>In vitro</i> BChE – IC ₅₀ (nM)	<i>In silico</i> docking score	<i>In vitro</i> glucosidase – IC ₅₀ (nM)	<i>In silico</i> 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



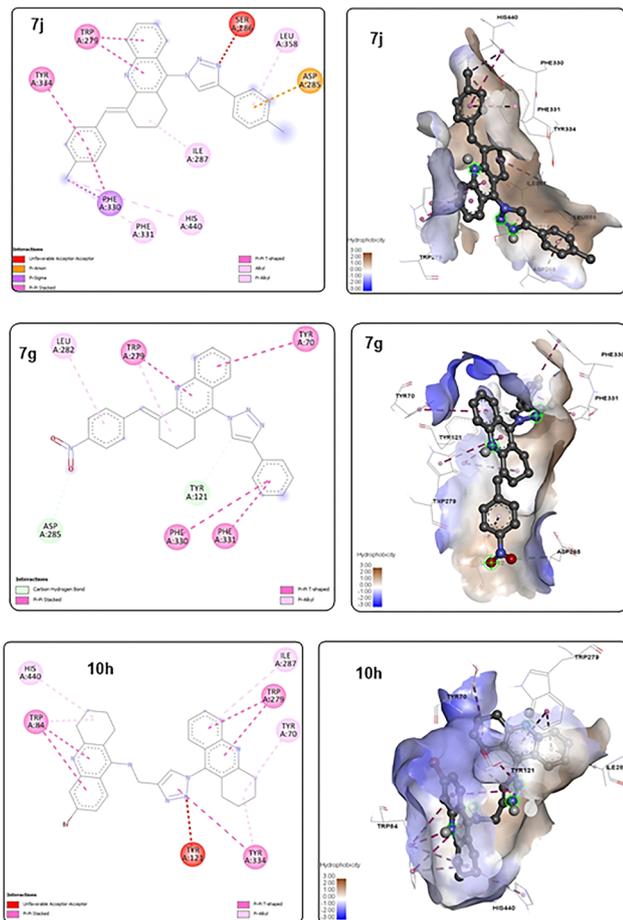


Fig. 3 2D and 3D docking interactions of compounds **7j**, **7g**, and **10h** with protein **1DX6**.

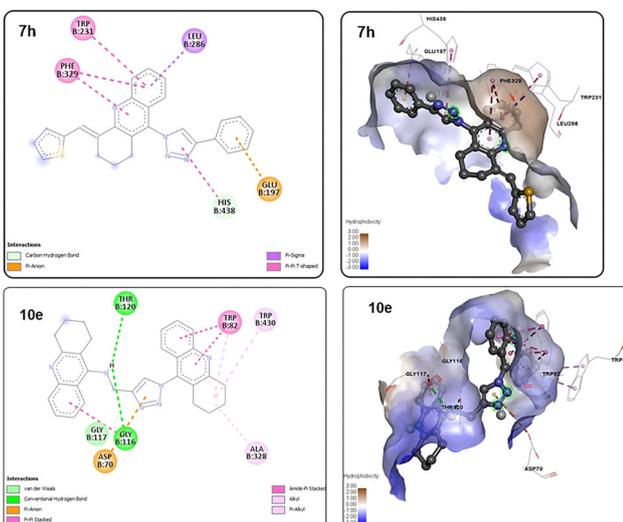


Fig. 4 2D and 3D docking interactions of compounds **7i**, **7h**, and **10e** with protein **6EMI**.

moiety, the C4 aryl moiety, and the triazole-attached aryl moiety with a CH₃ substituent at the R² position in compounds **7j** and **7i**.

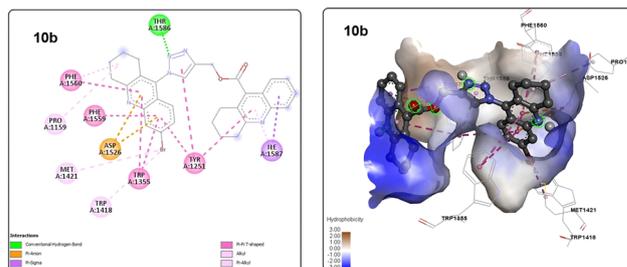


Fig. 5 2D and 3D docking interactions of compound **10b** with protein **3TOP**.

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 IC₅₀ 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 (LogP _{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 LogP 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 R² position and with aryl substitution at C4 exhibited good interactions with better inhibitory activity. A combination of Br at the R¹ 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 R² position and a methyl-, methoxy-substituted aryl moiety at C4 also showed better inhibitory activity towards AChE. However, the compounds without substitutions at the R² position lacked inhibitory properties. In dimerized 1,2,3,4-tetrahydroacridine derivatives, the compounds with either Br or NO₂ substitution at R³ or R⁴ 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 IC₅₀ values of 120.67 nM, 121.02 nM, and 128.12 nM, respectively. Compounds 7i, 7h, and 10e exhibited strong BChE inhibitory activity, with IC₅₀ values of 130.21 nM, 130.45 nM and 124.94 nM, respectively. In addition, compound 10b showed notable α -glucosidase inhibition with an IC₅₀ 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 R₂ 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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