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Design, synthesis and biological evaluation of acridone glycosides as selective BChE inhibitors

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ABSTRACT

Based on structure analyses of butyrylcholinesterase (BChE), a series of 21 acridone glycosides were designed, synthesized and evaluated *in vitro* for their BChE and acetylcholinesterase (AChE) inhibitory activities. D-ribose derivative **6f** exhibited the greatest inhibitory activity on BChE (IC_{50} = 6.95 μM), and was the most selective inhibitor of BChE with the IC_{50} ratio of AChE/BChE was 20.59. D-glucose and D-galactose derivatives **6a** and **6b** showed inhibitory activities against both AChE and BChE. Moreover, compounds **6a**, **6b**, **6f** and **5t** were found nontoxic on SHSY5Y neuroblastoma and HepG2 cell and exhibited remarkable neuroprotective activity. Besides, compound **6f** showed mixed-type inhibition against BChE (K_i = 1.76 μM), which renders **6f** a potential agent for the treatment of Alzheimer's disease. These novel acridone hybrids might be used as efficient probes to reveal the relationship between ligands and BChE and pave the way for developing selective BChE inhibitors to further study the pathogenesis of alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) [1,2], an age-related progressive neurodegenerative disease, is the main cause of dementia in elderly people affecting cognitive characteristics including intelligence, memory and language. According to the World Alzheimer Report 2018 [3], if an efficient treatment isn't developed by 2050, the number of patients with AD will rise to 152 million. The impact of this disease on the patients and their families is tremendous. Over the last hundred years, the pathogenesis of AD has not been fully studied. The hallmarks of histopathology such as amyloid β (Aβ) aggregates formation, tau-protein aggregation, increased oxidative stress, and low levels of the acetylcholine (ACh) [4,5] have been considered the key pathological features of AD. Based on the cholinergic hypothesis, low levels of ACh [6–8] is a key pathological hallmark of Alzheimer's disease. Currently, the main therapy of AD is the enhancement of the concentration of ACh in the synaptic cleft by inhibiting cholinesterase (ChE) [9], such as AChE inhibitors donepezil [10,11], galantamine [12] and the dual cholinesterase inhibitor rivastigmine [13]. However, recent research discovered that the levels of AChE is dramatically low in advanced AD, and the levels of BChE still very high. It suggested that ACh hydrolysis may occur by BChE catalysis [14–16] to a large extent. The influence of BChE in brain [17] on the symptoms and progression of cognitive impairments facilitated a better understanding of the role of BChE on AD progression and promoted BChE as an effective therapeutic strategy for Alzheimer disease. Therefore, it is of crucial importance to develop selective and effective BChE inhibitors. Although there are a series of scaffolds with selectively BChE inhibition [18–20], finding new BChE inhibitors remains a difficult and worthy task.

Tetrahydroacridine derivatives tacrine was the first drug for the treatment of AD approved by FDA. But due to its hepatotoxicity, it has been withdrawn from the market. Since then, researchers want to develop novel acridine based agents to reduce the side effects [21–23]. The naturally occurring acridone with a planar structure can be considered as 10-aza-analogs of anthrones [24] or xanthones [25]. A wide range of acridone-based derivatives have been discovered and shown various valuable biological properties including anti-cancer [26–28], anti-malarial [29,30], anti-microbial antibacterial [31,32], anti-viral

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[33,34] and modulation of multi-drug resistance [35–37].

Recently, naturally occurring acridone alkaloids [32] and synthetic acridone derivatives [38–40] have been found as selective cholinesterase inhibitors which makes promising the use of the acridone scaffold to obtain drugs for the therapy of neurodegenerative diseases. For examples, T. Akbarzadeh and coworkers synthesized a series of acridone linked to 1,2,3-triazole derivatives and some of the synthesized derivatives showed powerful activities in anti-AChE [39]. In addition, acridone-1,2,4-oxadiazole-1,2,3-triazole hybrids were synthesized and showed good acetylcholinesterase inhibitory activity (IC_{50} = 11.55 μM) [40].

On the other hand, carbohydrates were one of the most abundant natural compounds and key participants in many biological processes [41–43]. There have been many reports about compounds containing carbohydrate scaffolds possessed potent anticholinesterase activity. Flavanonol glucosides, isolated from the aerial parts of *Agrimonia pilosa* Ledeb., had moderate acetylcholinesterase inhibitory effects with IC50 values ranging from 76.59 to 97.53 μM [44]. Then Mughal and coworkers [45] synthesized a series of varyingly substituted 3-O-flavonol glucosides and some of the derivatives were potent inhibitors of acetylcholinesterase and butyrylcholinesterase with varying degree of IC_{50} values. However, there is poor selectivity for the two cholinesterases. Tacrine linked to carbohydrate-based moieties were synthesized by L. E. Dardenne and coworkers [46]. All compounds were potent inhibitors of both acetylcholinesterase and butyrylcholinesterase. Oxo-/thioxo-pyrimidines and tetrazoles linked to furanoses or pyranose [47] displayed acetylcholinesterase inhibition ranged from 20% to 80% for the concentration of 100 μg/mL.

Many BChE inhibitors by linking two aryl or other bicycle or tricycle groups with different length linker had been reported [48–50]. Structure analyses of BChE indicated that besides aryl residues TRP-82, PHE-329, TYR-332, HIS-438 in the bottom of the active site cavity, there are polar residues ASN-68, GLN-71, GLN-119, THR-120, GLU-197, SER-198, GLU-276, THR-284, SER-287, ASN-289 in middle or upper of the active site cavity (Fig. S1). In consideration of the potential of reported acridone-based molecules in the search of new cholinesterase inhibitors [42,43], we designed new BChE inhibitors by introducing polar pharmacophores, such as pyranose or furanose with different length linkers onto aryl pharmacophore acridone. The polar pharmacophores are expected to form hydrogen bond interaction with polar residues in the upper of the active site cavity, to strengthen their BChE affinity [51].

These newly designed compounds connected acridone nucleus with sugar derivatives such as D-glucose, D-mannose, D-galactose, *N*-acetyl-D-glucosamine, D-ribose, 2-Deoxy-d-ribose and lactose via 1,2,3-triazole (Fig. 1). Until now, selective AChE inhibitors or difunctional inhibitors have been widely reported, selective BChE inhibitors have been relatively few targeted. Our interesting is to develop selective BChE inhibitors combining the advantages of carbohydrates, by exploring the effects of the lengths of the linker and the types of sugar on the activities of cholinesterases to provide candidate molecules for studying the

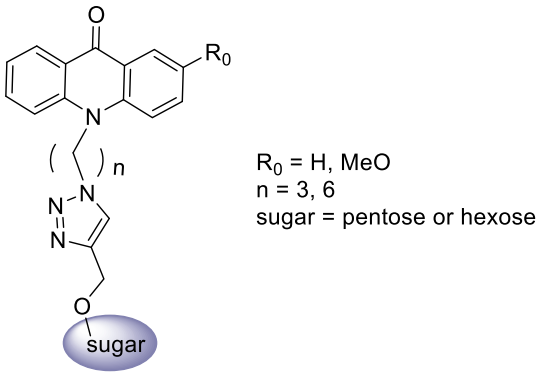


Fig. 1. Structures of newly designed acridone glycosides.

pathogenesis of alzheimer's disease. The inhibitory activities were determined by Ellman's assays using AChE and BChE, aiming to find efficient and selective BChE inhibitors. Besides, a preliminary screening of the acute cytotoxicity and neuroprotective effect of these compounds completed the biological studies.

2. Results and discussion

2.1. Computational modeling

To predict their BChE binding affinity, molecular docking was carried out with Surflex-Dock in SYBYL-X software (Tripos Inc., St. Louis, MO, USA). The docking results indicated that TotalScore of the newly designed BChE inhibitors is higher than or near to rivastigmine, which means they might have stronger BChE affinity. And **6a**, **6b**, **6f**, **6g**, **6k**, **6r**, **5s** and **5t** are predicted binding with BChE stronger than other inhibitors (Table S1). Detailed structure analyses and hydrogen bond interactions of these newly designed inhibitors were showed in Fig. 2.

Structure analyses indicated that the newly designed molecules occupied the active site of BChE by forming π … π interaction with TRP-82 or TYR-332, and the H-bond interaction between ASN-68, SER-287, GLU-276, ASN-289, GLN-119, ALA-277, ALA-199, GLY-116, GLY-117 or SER-198, and the sugar part of newly designed molecules strengthened their binding interaction. To verify the prediction, we synthesized these newly designed BChE inhibitors and evaluated their bioactivity.

2.2. Chemistry

The synthetic route for the synthesis of acridone derivative precursors is depicted in Scheme 1. Acridone derivatives **1** reacted with different dibromides using NaH in DMF at room temperature to afford three acridone derivatives **2a-c** with 66–78% yields, which were treated with excess NaN_3 in DMF to give azido-functionalized acridone derivatives **3a-3c** with two steps in 56–70% yields [52].

Subsequently, the synthetic route towards sugar-derived alkynes **4a-4g** is depicted in Scheme 2. The sugar-derived alkynes were prepared by the literature procedures [53–56]. The peracetylated sugar and propargyl alcohol were catalyzed by boron trifluoride diethyl etherate to afford propargyl-attached carbohydrates **4a-4f** with 76–89% yields. Treatment of the unprotected sugars 2-deoxy-d-ribose with propargyl alcohol *via* boron trifluoride diethyl etherate-promoted glycosylation could afford **4g** with 48% yield.

Finally, with prepared glycosyl alkynes and acridone derivatives in hand, the coupling reaction is shown in Scheme 3. Propargyl-attached carbohydrates moieties **4** were introduced onto acridone derivatives **3** *via* copper(I)-catalyzed click reactions to afford **5** with 70–99% yields. After global deacetylation under Zemplén condition in NaOMe/MeOH, the desired **6a-6r** was obtained in a quantitative yield.

2.3. AChE and BChE inhibition evaluation

The *in vitro* inhibitory activity against AChE and BChE was evaluated by Ellman's method [57] and rivastigmine as the reference drug. The IC_{50} values of 21 new acridone hybrids with sugar derivatives for AChE and BChE inhibition are summarized in Table 1. IC_{50} ratio of AChE/BChE was used to estimate the selectivity of BChE. All the data were presented as mean ± SD (Standard Deviation) of three independent experiments.

The results revealed that some of the synthesized compounds showed different inhibitory activities towards AChE and BChE with their IC_{50} values in the range of micromolar concentrations (IC_{50} AChE values of 38.15–223.13 μM and BChE values 6.95–175.28 μM). According to the biological activity results, the pentose such as D-ribose and d-2′-deoxyribose derivatives exhibited BChE selectivity. Compounds **6f**, **6l**, **5t**, and **5u** exhibited more active against BChE than

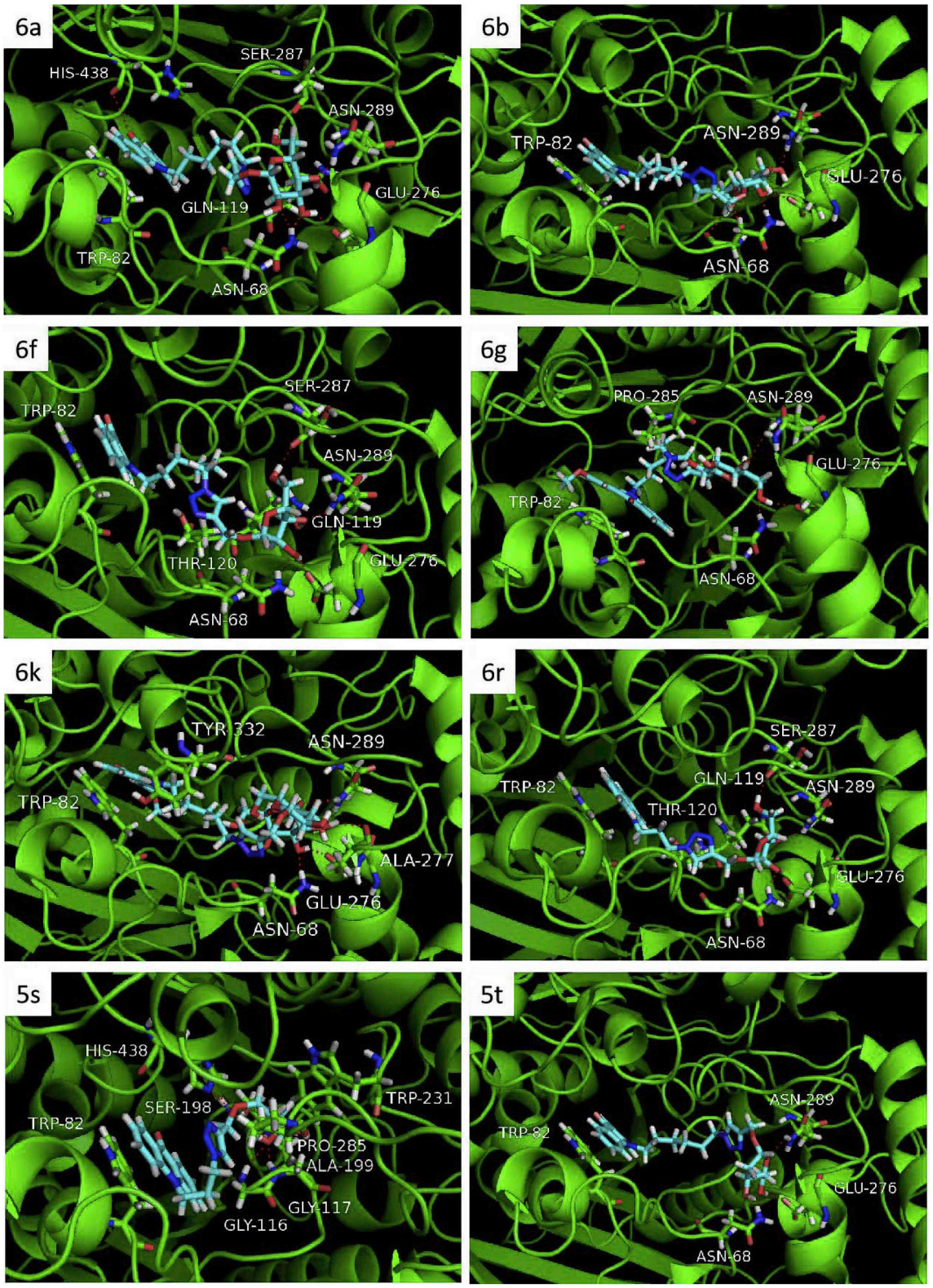
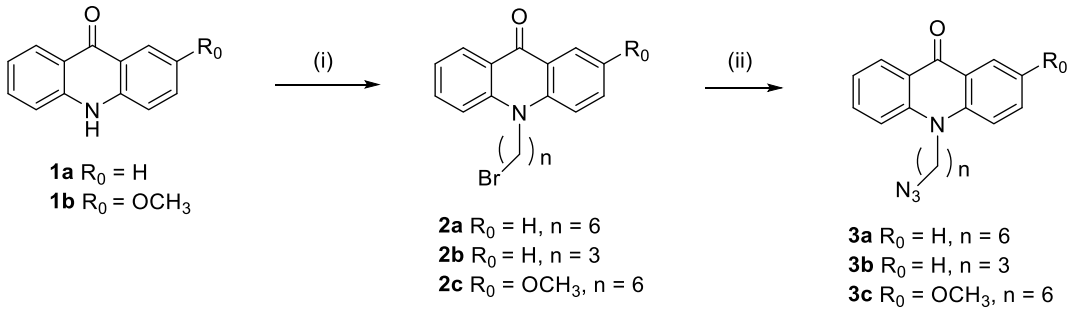


Fig. 2. The structures of BChE (green cartoon) and newly designed inhibitors (cyan). The hydrogen bond interactions were labeled in red dash line. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

AChE, and IC_{50} ratios of AChE/BChE were 20.59, 2.33, 3.91, and 2.40 respectively. Especially compound **6f** was the most selective for BChE, which exhibited the greatest inhibitory activity on BChE (IC_{50} = 6.95 μM) yet did not exhibit effective AChE inhibitory activity with IC_{50} values more than 100 μM. Besides, Structure analyses indicated that **6f** was binding with AChE and BChE in a similar way, while the TRP-286 of AChE hindered the interaction of polar residues and sugar head of **6f** (Fig. S99). In hexose derivatives, the D-glucose and D-galactose derivatives **6a** and **6b** showed inhibitory activities against both AChE (IC_{50} = 38.15 ± 1.22, 44.74 ± 0.29 μM) and BChE



Scheme 1. Preparation of acridone derivative precursors **3a-3c**. Reagents and conditions: (i) $Br(CH_2)_nBr$, NaH, DMF, r.t.; (ii) NaN_3, DMF, 85 °C. PPA, polyphosphoric acid.

(IC_{50} = 29.28 ± 2.99, 38.33 ± 0.62 μM). However, *N*-acetyl-d-glucosamine (**6d**, **6j**, **6p**) and mannose (**6c**, **6i**, **6o**) derivatives did not show significant inhibitory activity towards AChE and BChE. Moreover, maybe due to the steric hindrance, the disaccharide lactose derivatives (**6e**, **6k**, **6q**) shows no obvious inhibitory activity towards AChE and BChE.

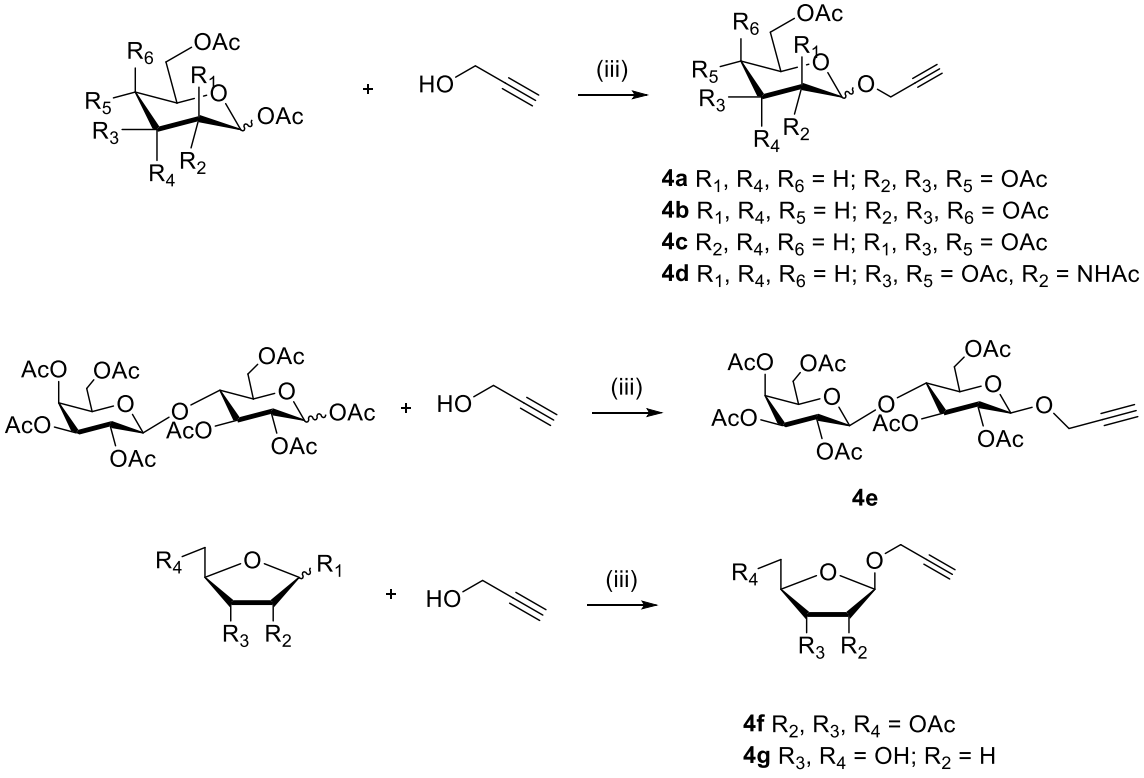
In general, the presence of OMe instead of hydrogen on the 2-substituted acridone moieties had no influence on potential interaction with BChE even led to the decrease of inhibitory activity on BChE and it is demonstrated in compounds **6g-6l**. Among the 2-substituted acridone derivatives, D-galactose derived **6h** was found to be the most selective AChE inhibitor, exhibiting an IC_{50} of 44.73 ± 0.23 μM against AChE and of 65.61 ± 3.08 μM against BChE. And D-ribose derived **6l** was found to have selective BChE inhibitor with an IC_{50} of 35.06 ± 0.88 μM. On the other hand, compared with longer linker (n = 6) derivatives, short linker (n = 3) derivatives (**6m-6r** and **5s**) exhibited less inhibition activity on both AChE and BChE. An increase of AChE and BChE inhibition could be ascribed to additional aliphatic interactions with cholinesterases introduced by the elongation of the linker chain [18,58].

2.4. Cytotoxicity assays

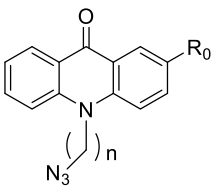
Before evaluating the neuroprotective properties of these newly designed compounds, we tested whether compounds exert cytotoxicity. The compound **6a**, **6b**, **6f** and **5t** were selected for the MTT assay in SH-SY5Y neuroblastoma and HepG2 cell lines at the concentrations of 50 and 100 μM, respectively. As shown in Fig. 3, all compounds showed no obvious effect on cell viability at concentrations of 50 μM and relative cell viabilities of SH-SY5Y neuroblastoma and HepG2 cells were all greater than 90%. Even when the concentration reaches 100 μM, the relative cell viabilities were still more than 75%, which indicated that these compounds had no obvious cytotoxicity.

2.5. Neuroprotective effect

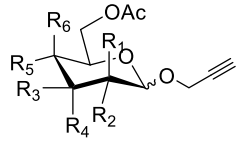
The neuroprotective activity of compounds **6a**, **6b**, **6f** and **5t** against H_2O_2, which caused oxidative stress-induced cell death, was evaluated in SH-SY5Y neuroblastoma cells using MTT method [59]. The results obtained were presented in Fig. 4. The relative cell viability of the positive control (hydrogen peroxide) was about 50% and the cell viability of compounds **6a**, **6b**, **6f** and **5t** was 78%, 81%, 73% and 75%,



Scheme 2. Preparation of sugar-derived alkynes precursors **4a-4g**. Reagents and conditions: (iii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C-r.t.

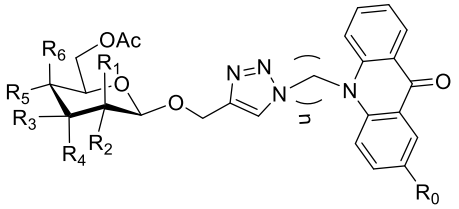


3a R_0 = H, n = 6
3b R_0 = H, n = 3
3c R_0 = OCH_3, n = 6



4a R_1, R_4, R_6 = H; R_2, R_3, R_5 = OAc
4b R_1, R_4, R_5 = H; R_2, R_3, R_6 = OAc
4c R_2, R_4, R_6 = H; R_1, R_3, R_5 = OAc
4d R_1, R_4, R_6 = H; R_3, R_5 = OAc, R_2 = NHAc

(iv)

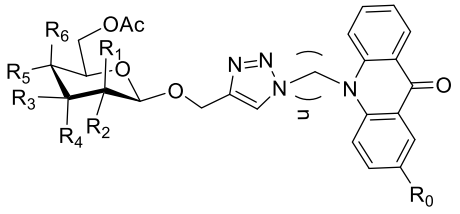


5a R_0 = H; n = 6; R_1, R_4, R_6 = H; R_2, R_3, R_5 = OAc
5b R_0 = H; n = 6; R_1, R_4, R_5 = H; R_2, R_3, R_6 = OAc
5c R_0 = H; n = 6; R_2, R_4, R_6 = H; R_1, R_3, R_5 = OAc
5d R_0 = H; n = 6; R_1, R_4, R_6 = H; R_3, R_5 = OAc, R_2 = NHAc

5g R_0 = OCH_3, n = 6; R_1, R_4, R_6 = H; R_2, R_3, R_5 = OAc
5h R_0 = OCH_3, n = 6; R_1, R_4, R_5 = H; R_2, R_3, R_6 = OAc
5i R_0 = OCH_3, n = 6; R_2, R_4, R_6 = H; R_1, R_3, R_5 = OAc
5j R_0 = OCH_3, n = 6; R_1, R_4, R_6 = H; R_3, R_5 = OAc, R_2 = NHAc

5m R_0 = H, n = 3; R_1, R_4, R_6 = H; R_2, R_3, R_5 = OAc
5n R_0 = H, n = 3; R_1, R_4, R_5 = H; R_2, R_3, R_6 = OAc
5o R_0 = H, n = 3; R_2, R_4, R_6 = H; R_1, R_3, R_5 = OAc
5p R_0 = H, n = 3; R_1, R_4, R_6 = H; R_3, R_5 = OAc, R_2 = NHAc

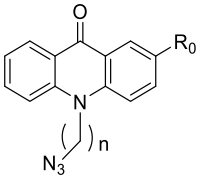
(v)



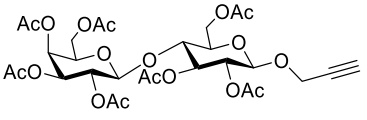
6a R_0 = H; n = 6; R_1, R_4, R_6 = H; R_2, R_3, R_5 = OH
6b R_0 = H; n = 6; R_1, R_4, R_5 = H; R_2, R_3, R_6 = OH
6c R_0 = H; n = 6; R_2, R_4, R_6 = H; R_1, R_3, R_5 = OH
6d R_0 = H; n = 6;R_1, R_4, R_6 = H; R_3, R_5 = OH, R_2 = NHAc

6g R_0 = OCH_3, n = 6; R_1, R_4, R_6 = H; R_2, R_3, R_5 = OH
6h R_0 = OCH_3, n = 6; R_1, R_4, R_5 = H; R_2, R_3, R_6 = OH
6i R_0 = OCH_3, n = 6; R_2, R_4, R_6 = H; R_1, R_3, R_5 = OH
6j R_0 = OCH_3, n = 6; R_1, R_4, R_6 = H; R_3, R_5 = OH, R_2 = NHAc

6m R_0 = H, n = 3; R_1, R_4, R_6 = H; R_2, R_3, R_5 = OH
6n R_0 = H, n = 3; R_1, R_4, R_5 = H; R_2, R_3, R_6 = OH
6o R_0 = H, n = 3; R_2, R_4, R_6 = H; R_1, R_3, R_5 = OH
6p R_0 = H, n = 3; R_1, R_4, R_6 = H; R_3, R_5 = OH, R_2 = NHAc

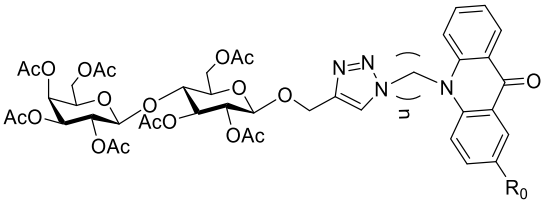


3a R_0 = H, n = 6
3b R_0 = H, n = 3
3c R_0 = OCH_3, n = 6



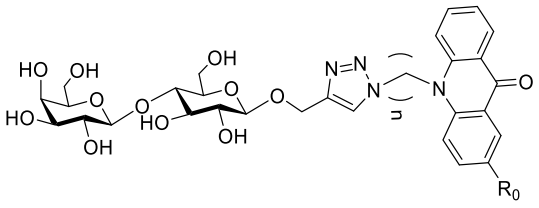
4e

(iv)



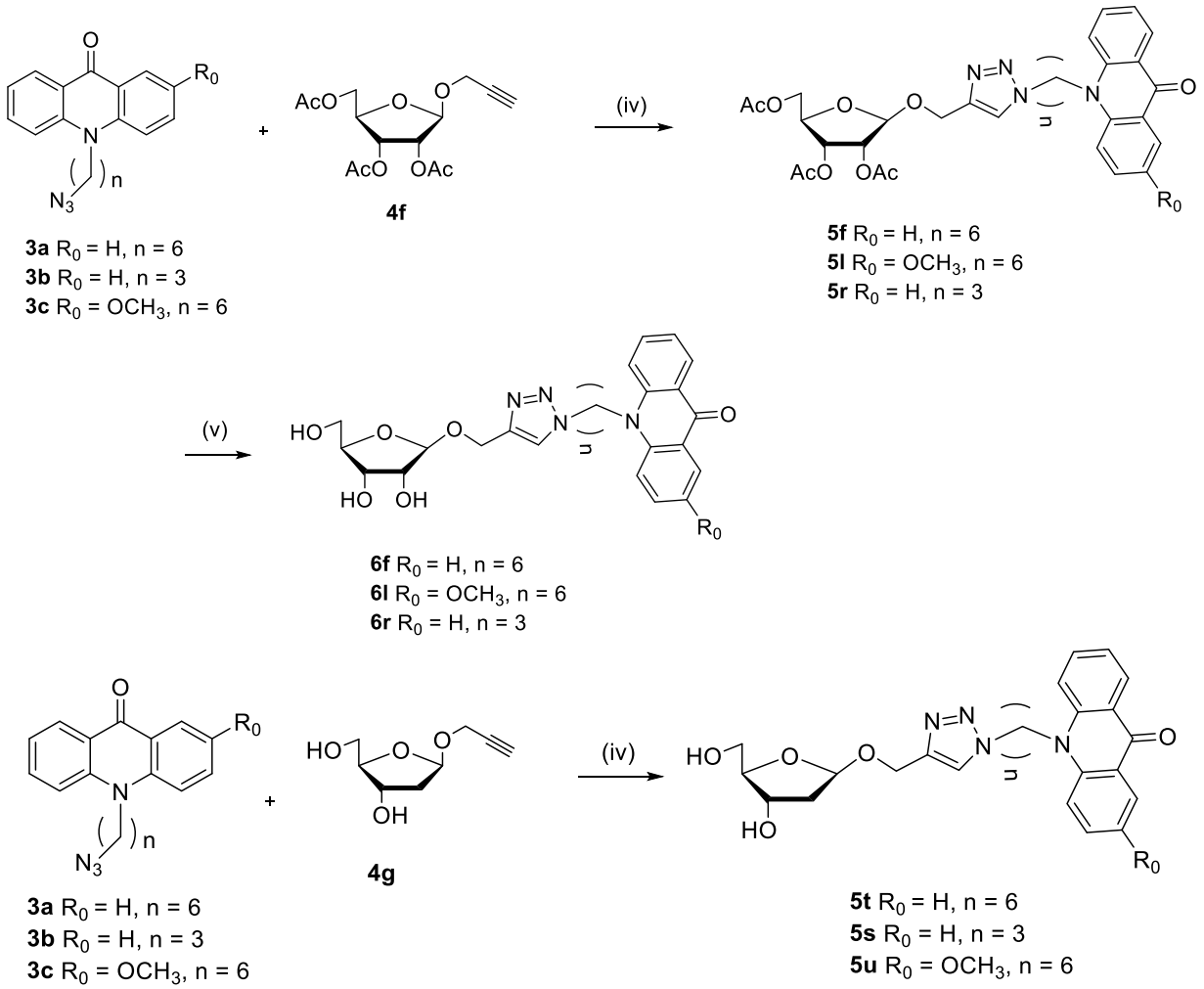
5e R_0 = H, n = 6
5k R_0 = OCH_3, n = 6
5q R_0 = H, n = 3

(v)



6e R_0 = H, n = 6
6k R_0 = OCH_3, n = 6
6q R_0 = H, n = 3

Scheme 3. Synthesis of acridone-(carbohydrate-derived) hybrids. Reagents and conditions: (iv) $CuSO_4$, THF/H_2O = 1/1, 65 °C (v) NaOMe, MeOH, r.t.



Scheme 3. (*continued*)

respectively. The compounds produced approximately 30% decrease in cell death induced by H_2O_2. Compared to the positive control (hydrogen peroxide), compounds **6a**, **6b**, **6f** and **5t** exhibited effective neuroprotective activity against oxidative stress.

2.6. Log P assessment

Log P (octanol-water partition coefficient) is the most important physicochemical parameter for evaluating the drug's ability to cross the blood-brain barrier (BBB). The optimal lop P value for penetrating the central nervous system is around 2.0 ± 0.7 [19]. The log P values of active compounds **6a**, **6b**, **6f** were 2.14, 2.14 and 2.68, respectively. The results showed that the active compounds **6a**, **6b** and **6f** had enough lipophilicity to pass through BBB *in vivo*.

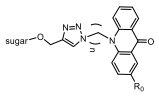
2.7. Kinetic study of BChE inhibition

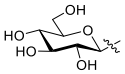
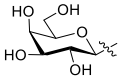
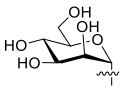
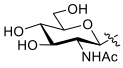
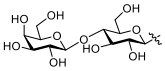
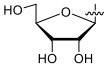
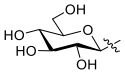
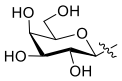
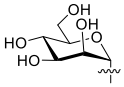
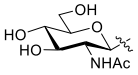
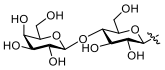
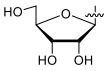
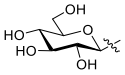
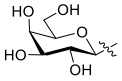
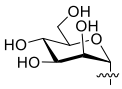
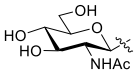
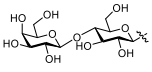
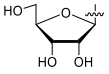
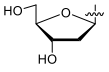
To determine the mechanism of BChE inhibition of the most potent compound **6f**, a kinetic study [19] was carried out. As shown in Fig. 5, with the increased of compound concentration, both apparent V_{max} and K_m values changed as well. It revealed that the type of inhibition is mixed. Furthermore, using the plot of the slope versus inhibitor concentration, the inhibition constant K_i for compound **6f** was calculated (K_i = 1.76 μM for BChE).

3. Conclusions

In this work, several BChE inhibitors were designed and synthesized from simple starting materials in just a few steps with good yields and showed high inhibitory potency against AChE and BChE at the micromolar range. Among them, D-ribose derivatives **6f** was the most selective inhibitor of BChE, which exhibited the greatest inhibitory activity on BChE (IC_{50} = 6.95 μM, IC_{50} ratio of AChE/BChE was 20.59). Different from other reports, the newly designed inhibitors enhanced BChE inhibition activity by forming H-bond interactions with poly residues ASN-289, ASN-68, SER-287, GLN-119 or GLU-276. Compared with short-chain inhibitors, the inhibitors with long chain had relatively higher BChE affinity, probably due to their flexibility. Besides, the structure-activity relationship (SAR) analysis showed that (1) the site of OH in sugar ring is of great importance for BChE inhibitory. BChE inhibitory activity of the pentose acridone derivatives is higher than that of the hexose acridone derivatives. (2) The steric hindrance of the disaccharide acridone derivative had an influence for BChE inhibitory. (3) The OMe on the 2-substituted acridone hybrids with carbohydrate derivatives led to the decrease of inhibitory activity of BChE. These active compounds were found to be nontoxic to SH-SY5Y neuroblastoma and HepG2 cells at their effective concentrations, and also had remarkable neuroprotective activity. Meanwhile, they also had sufficient lipophilicity to cross the BBB *in vivo*. Kinetic studies revealed that the type of inhibition is mixed for **6f** (K_i = 1.76 μM). These results open new promising perspectives for the search for new selective BChE

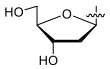
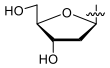
Table 1
The IC_{50} values of the compounds against AChE and BChE[a].



Compound	R_0	n	Sugar	IC_{50} (μM) (or inhibition % at 50 μM)		IC_{50} ratio of AChE/BChE
				AChE[b]	BChE[c]	
6a	H	6		38.15 ± 1.22	29.28 ± 2.99	1.3
6b	H	6		44.74 ± 0.29	38.33 ± 0.62	1.16
6c	H	6		12.08 ± 3.01%	28.45 ± 1.27%	–
6d	H	6		15.82 ± 2.89%	35.27 ± 2.19%	–
6e	H	6		11.26 ± 1.63%	24.93 ± 1.85%	–
6f	H	6		143.11 ± 2.65	6.95 ± 0.71	20.59
6g	OCH_3	6		56.12 ± 1.13	82.35 ± 0.57	0.68
6h	OCH_3	6		44.73 ± 0.23	65.61 ± 3.08	0.68
6i	OCH_3	6		25.77 ± 2.34%	17.89 ± 4.59%	–
6j	OCH_3	6		40.11 ± 2.56%	12.80 ± 2.36%	–
6k	OCH_3	6		11.40 ± 3.61%	13.69 ± 1.19%	–
6l	OCH_3	6		81.83 ± 1.78	35.06 ± 0.88	2.33
6m	H	3		10.23 ± 2.58%	11.99 ± 3.64%	–
6n	H	3		9.45 ± 2.63%	10.03 ± 1.82%	–
6o	H	3		10.36 ± 4.52%	15.43 ± 4.52%	–
6p	H	3		9.37 ± 3.76%	12.71 ± 1.16%	–
6q	H	3		9.82 ± 5.63%	11.29 ± 4.83%	–
6r	H	3		18.52 ± 2.69%	33.81 ± 1.72%	–
5s	H	3		18.63 ± 2.33%	20.74 ± 3.52%	–

(*continued on next page*)

Table 1 (*continued*)

Compound	R_0	n	Sugar	IC_{50} (μM) (or inhibition % at 50 μM)		IC_{50} ratio of AChE/BChE
				AChE[b]	BChE[c]	
5t	H	6		167.36 ± 3.66	42.81 ± 0.71	3.91
5u	OCH_3	6		85.12 ± 1.04	35.43 ± 0.22	2.40
Rivastigmine				10.35 ± 1.32	4.88 ± 0.11	

[a] Each IC_{50} value was presented as mean ± SD of three independent experiments.
[b] AChE from electric eel.
[c] BChE from equine serum.

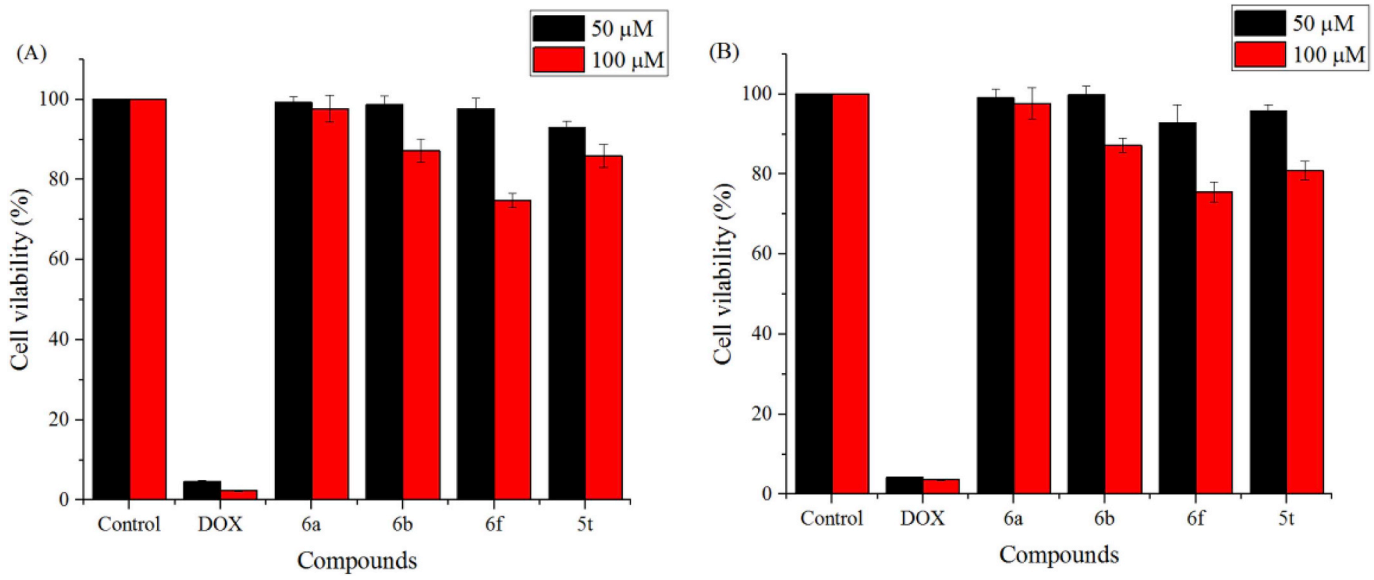


Fig. 3. The effect of compounds **6a**, **6b**, **6f**, **5t** on (A) SH-SY5Y cells and (B) HepG2 cells viabilities at two different concentrations.

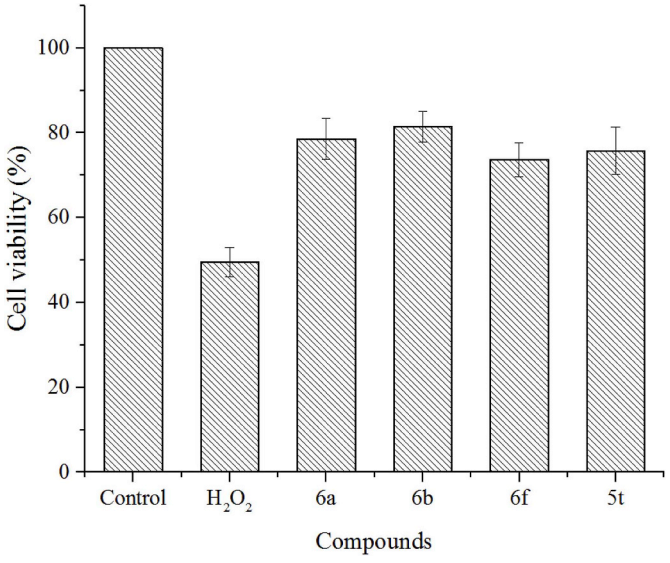


Fig. 4. Neuroprotective effect on SH-SY5Y cell lines of compounds **6a**, **6b**, **6f** and **5t** at 50 μM. Data were collected after 24 h incubation with H_2O_2 (5%, 300 μM). Untreated cells were used as control. Results were presented as mean ± S.E. of three independent experiments.

inhibitors against progressive neurodegenerative disorder based on acridone connected to carbohydrate fragments and provide the drug molecules for studying the mechanism of alzheimer's disease.

4. Materials and methods

4.1. Reagents and instrumentation

All the analytical grade reagents and solvents were obtained from commercial suppliers and used without further treatment unless indicated. Reactions were monitored by thin-layer chromatography with GF_{254} silica gel coated plates. Flash chromatography was carried out on silica gel (200–300 mesh). ^1H NMR and ^{13}C NMR spectra were obtained on Bruker Avance/600 spectrometer (^1H: 600 MHz, ^{13}C: 150 MHz at 25 °C) or Bruker Avance/400 spectrometer (^1H: 400 MHz, ^{13}C: 100 MHz at 25 °C). Chemical shifts of ^1H NMR spectra were given in ppm relative to a tetramethylsilane (TMS) internal standard to the residual solvent peak (abbreviation in spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). All high-resolution mass spectra (HRMS) were determined with a mass spectrometer by using electrospray ionization (ESI-oa-TOF), Melting points are measured on an XT4MP apparatus (Taike Corp., Beijing, China) and are not corrected.

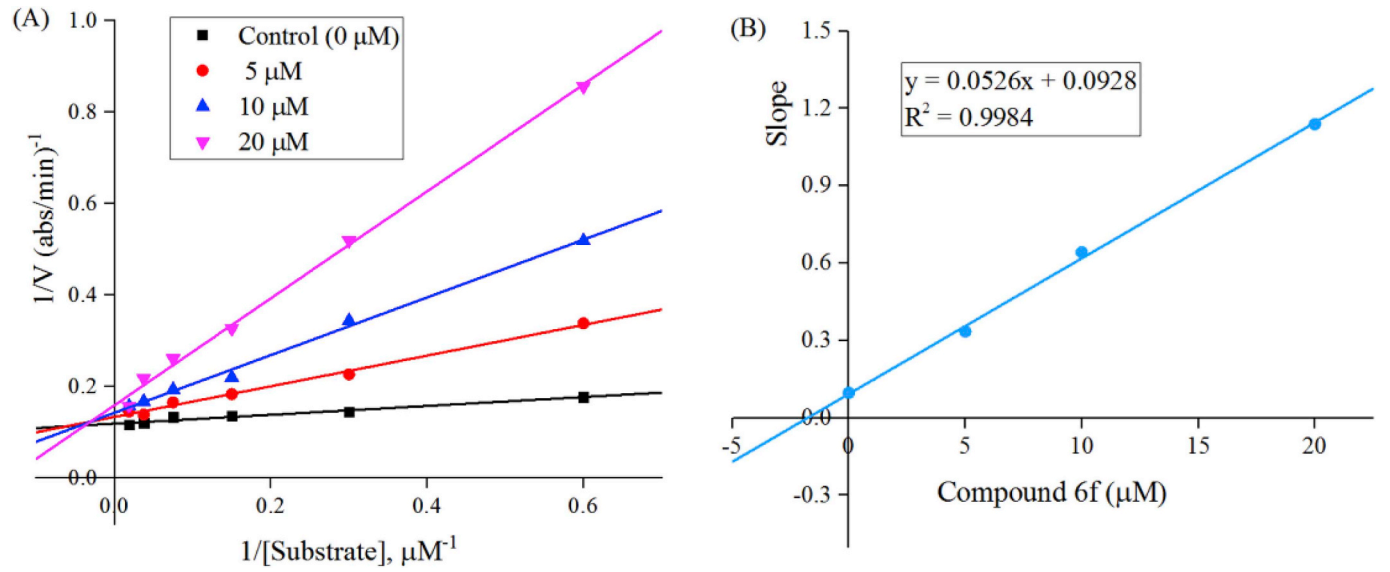


Fig. 5. (A) Lineweaver-Burk plots for the inhibition of BChE by compound **6f**. (B) Secondary plot for calculation of steady-state inhibition constant (K_i) of compound **6f**.

4.2. Computational details

To predict the BChE affinity of newly designed inhibitors, we mimicked their interaction with BChE with Surflex-Dock in SYBYL-X software (Tripos Inc., St. Louis, MO, USA). The structure of BChE was downloaded from Protein Data Bank (http://www.rcsb.org/, PDB code, 6EUL) [60], in which, the 198th residue was modified to be SER-198. The structure of Rivastigmine was derived from the extracted crystal structure ligand, and other designed inhibitors were drawn with Gaussview 5.08. The atomic charges of inhibitors were computed with Gasteiger-Huckel method. In the protein preparation, waters in the protein were removed, and hydrogen atoms were added, and the protein was loaded AMBER charges. Before docking, the protomol was generated with parameters Threshold 0.5 and Bloat 10.0 Å. Because the start conformation affected the docking results, we considered three conformations for each inhibitor by minimizing energy with the limit of Max Interactions 0, 100 and 1000 cycles or Gradient 0.05 kcal/(mol*Å). In the Surflex-Dock, the extracted ligand was used as a reference molecule, and other parameters used the default value. The highest TotalScore conformation of each ligand was used to further structural analysis.

4.3. General procedure for the synthesis of compounds 2a-2c [52]

To a solution of **1** (5.12 mmol) in dry THF (20 mL) was added sodium hydride (10.24 mmol, 60%) at 0 °C. After 1.5 h of stirring, dibromides (30.73 mmol) was added dropwise under the same condition. The reaction mixture was heated and kept refluxing for another 24 h and then allowed to cool to room temperature. The mixture was added water (15 mL), and then extracted by CH_2Cl_2. The organic phase was separated and dried overnight with $MgSO_4$. The solvent was removed by evaporation, and the residue was purified by a flash silica gel column chromatography to afford **2a-2c**.

4.3.1. 10-(6-Bromohexyl) acridin-9(10H)-one (2a)

The product was obtained as yellow solid in 78% yield. m.p. 232–235 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 7.6 Hz, 2H), 7.71 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 4.32 (t, J = 8.0 Hz, 2H), 3.44 (t, J = 6.4 Hz, 2H), 1.93 (s, 4H), 1.59 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 141.6, 133.9, 127.9, 122.4, 121.2, 114.4, 45.9, 33.6, 32.5, 27.8, 26.9, 26.0. HRMS (ESI), *m/z* calcd. for $C_{19}H_{20}BrNONa$ ([M + Na]$^+$) 380.0620, found: 380.0636.

4.3.2. 10-(3-Bromopropyl) acridin-9(10H)-one (2b)

The product was obtained as yellow solid in 66% yield. m.p. 225–227 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, J = 7.8 Hz, 2H), 7.68 (t, J = 7.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.8 Hz, 2H), 4.49 (t, J = 8.4 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 2.43–2.39 m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.0, 141.7, 134.1, 128.2, 122.6, 121.5, 114.2, 44.5, 30.2, 29.5. HRMS (ESI), *m/z* calcd. for $C_{16}H_{14}BrNNaO$ ([M + Na]$^+$) 338.0151, found: 338.0159.

4.3.3. 10-(6-Bromohexyl)-2-methoxyacridin-9(10H)-one (2c)

The product was obtained as yellow solid in 75% yield. m.p. 241–243 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.47 (t, J = 10.8 Hz, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 4.35 (t, J = 7.2 Hz, 2H), 3.95 (s, 3H), 3.44 (t, J = 6.6 Hz, 2H), 2.01–1.86 (m, 4H), 1.62–1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 154.4, 141.2, 136.6, 133.6, 128.0, 124.6, 123.2, 121.7, 120.9, 116.3, 114.3, 106.8, 55.8, 46.0, 33.5, 32.5, 27.8, 27.2, 26.1. HRMS (ESI), *m/z* calcd. for $C_{20}H_{22}BrNNaO_2$ ([M + Na]$^+$) 410.0726, found: 410.0727.

4.4. General procedure for the synthesis of compounds 3a-3c [52]

To a solution of bromide **2** (2.0 mmol) in anhydrous DMF (10 mL) was added NaN_3 (4.0 mmol) and NH_4Cl (3.0 mmol) at 85 °C. The reaction mixture was stirred overnight and then poured into water (50 mL). The product was extracted with EtOAc, and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed by evaporation, and the residue was purified by a flash silica gel column chromatography to afford **3a-3c**.

4.4.1. 10-(6-Azidohexyl) acridin-9(10H)-one (3a)

This product was obtained as yellow solid in 88% yield. m.p. 264–266 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 8.0 Hz, 2H), 7.71 (t, J = 8.4 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.27 (t, J = 7.2 Hz, 2H), 4.31 (t, J = 8.0 Hz, 2H), 3.31 (t, J = 6.4 Hz, 2H), 2.13–1.85 (m, 2H), 1.76–1.63 (m, 2H), 1.62–1.42 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 141.6, 133.8, 127.9, 122.4, 121.2, 114.4, 51.2, 45.9, 28.8, 27.0, 26.5, 26.4. HRMS (ESI), *m/z* calcd. for $C_{19}H_{20}N_4ONa$ ([M + Na]$^+$) 343.1529, found: 343.1523.

4.4.2. 10-(3-Azidopropyl) acridin-9(10H)-one (3b)

This product was obtained as yellow solid in 85% yield. m.p.

241–243 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, J = 8.4 Hz, 2H), 7.74 (t, J = 7.8 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 4.47 (t, J = 7.8 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 2.22–2.11 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 141.6, 134.1, 128.2, 122.5, 121.5, 114.2, 48.9, 43.1, 26.7. HRMS (ESI), *m/z* calcd. for $C_{16}H_{15}N_4O$ ([M + H]$^+$) 279.1240, found: 279.1239.

4.4.3. 10-(6-Azidohexyl)-2-methoxyacridin-9(10H)-one (3c)

This product was obtained as yellow solid in 86% yield. m.p. 270–273 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 8.0, 1H), 8.00 (d, J = 3.2 Hz, 1H), 7.73 (t, J = 8.4, 1H), 7.48 (t, J = 8.4, 2H), 7.39 (dd, J = 9.2, 2.8 Hz, 1H), 7.29 (t, J = 8.0, 1H), 4.37 (t, J = 8.4, 2H), 3.95 (s, 3H), 3.32 (t, J = 6.8 Hz, 2H), 1.99–1.91 (m, 2H), 1.77–1.63 (m, 2H), 1.56–1.51 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 154.4, 141.3, 136.6, 133.7, 128.1, 124.7, 123.2, 121.8, 120.9, 116.3, 114.3, 106.9, 55.8, 51.3, 46.1, 28.8, 27.3, 26.6, 26.5. HRMS (ESI), *m/z* calcd. for $C_{20}H_{22}N_4NaO_2$ ([M+Na]$^+$) 373.1635, found: 373.1636.

4.5. General procedure for the synthesis of compounds 4a-4g

Carbohydrate (2.0 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under N_2 atmosphere and cooled to 0 °C. Propargyl alcohol (3.0 mmol) was added, followed by drop-wise addition of boron trifluoride diethyl etherate (3.6 mmol). The reaction mixture was warmed to room temperature and stirred overnight. Potassium carbonate (200 mg) was added and stirred for 30 min to quench the reaction. After filtration, the mixture was washed with water and the filtrate was extracted with CH_2Cl_2. The combined organics were dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a flash silica gel column chromatography to afford **4a-4g**.

4.5.1. 2-Propargyl 2,3,4,6-tetra-O-acetyl-β-d-glucopyranoside (4a)

This product was obtained as white solid in 89% yield. m.p. 111–113 °C. $[\alpha]_D^{25}$ -42.6 (*c* 1.0, $CHCl_3$). Analytical data, $[\alpha]_D$ −39 (*c* 1.0, $CHCl_3$) [53]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (t, J = 9.6 Hz, 1H), 5.11 (t, J = 9.6 Hz, 1H), 5.02 (dd, J = 9.6, 8.0 Hz, 1H), 4.78 (d, J = 8.0 Hz, 1H), 4.37 (d, J = 2.4 Hz, 2H), 4.28 (dd, J = 12.4, 4.4 Hz, 1H), 4.14 (dd, J = 12.4, 2.4 Hz, 1H), 3.73 (m, 1H), 2.47 (t, J = 2.4 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{17}H_{22}NaO_{10}$ ([M+Na]$^+$) 409.1105, found: 409.1107. These data are consistent with literature [53].

4.5.2. 2-Propargyl 2,3,4,6-tetra-O-acetyl-β-d-glactopyranoside (4b)

This product was obtained as white solid in 88% yield. m.p. 122–124 °C. $[\alpha]_D^{25}$ -25.3 (*c* 1.0, $CHCl_3$). Analytical data, $[\alpha]_D$ −23 (*c* 1.0, $CHCl_3$) [53]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (s, 1H), 5.22 (t, J = 9.2 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.74 (d, J = 8.4 Hz, 1H), 4.38 (s, 2H), 4.22–4.16 (m, 1H), 4.14–4.11 (m, 1H), 3.94 (t, J = 6.6 Hz, 1H), 2.46 (s, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{17}H_{23}O_{10}$ ([M+H]$^+$) 387.1286, found: 387.1290. These data are consistent with literature [53].

4.5.3. 2-Propargyl 2,3,4,6-tetra-O-acetyl-α-d-mannopyranoside (4c)

This product was obtained as colourless liquid in 85% yield. $[\alpha]_D^{25}$ +73.8 (*c* 0.1, MeOH). Analytical data, $[\alpha]_D^{22}$ +71 (*c* 0.1, MeOH) [54]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (dd, J = 9.6, 3.2 Hz, 1H), 5.29–5.26 (m, 2H), 5.02 (d, J = 1.2 Hz, 1H), 4.30–4.27 (m, 3H), 4.11 (dd, J = 12.4, 2.4 Hz, 1H), 4.05–3.98 (m, 1H), 2.47 (t, J = 2.4 Hz, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{17}H_{22}NaO_{10}$ ([M+Na]$^+$) 409.1105, found: 409.1108. These data are consistent with literature [54].

4.5.4. 2-Propargyl 3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-d-glucopyranoside (4d)

This product was obtained as white solid in 83% yield. m.p. 145–148 °C. $[\alpha]_D^{25}$ -41.6 (*c* 0.1, $CHCl_3$). Analytical data, $[\alpha]_D^{20}$ -39.0 (*c* 0.1, $CHCl_3$) [54]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.68 (d, J = 9.0 Hz, 1H), 5.27 (d, J = 9.6 Hz, 1H), 5.07 (t, J = 9.6 Hz, 1H), 4.84 (d, J = 8.4 Hz, 1H), 4.36 (s, 2H), 4.24 (dd, J = 12.6, 4.2 Hz, 1H), 4.13 (dd, J = 12.6, 2.4 Hz, 1H), 3.95–3.91 (m, 1H), 3.74–3.65 (m, 1H), 2.47 (t, J = 1.8, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.94 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{17}H_{24}NO_9$ ([M+H]$^+$) 386.1446, found: 386.1449. These data are consistent with literature [54].

4.5.5. 2-Propargyl 2,3,6–tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-d-galactopyranosyl)-β-d-glucopyranoside (4e)

This product was obtained as white solid in 85% yield. m.p. 140–142 °C. $[\alpha]_D^{25}$ -12.2 (*c* 1.0, $CHCl_3$). Analytical data, $[\alpha]_D$ −12.8 (*c* 1.0, $CHCl_3$) [53]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.34 (d, J = 3.0 Hz, 1H), 5.22 (t, J = 9.6 Hz, 1H), 5.10 (dd, J = 10.2, 7.8 Hz, 1H), 4.98–4.86 (m, 2H), 4.74 (d, J = 7.8 Hz, 1H), 4.49 (m, 2H), 4.33 (d, J = 1.8 Hz, 2H), 4.17–4.02 (m, 4H), 3.87 (t, J = 6.6 Hz, 1H), 3.81 (t, J = 9.6 Hz, 1H), 3.63 (dd, J = 9.6, 3.0 Hz, 1H), 2.45 (s, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 2.04 (s, 6H), 1.96 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{29}H_{39}O_{18}$ ([M+H]$^+$) 675.2131, found: 675.2135. These data are consistent with literature [53].

4.5.6. 2-Propargyl 2,3,5-tri-O-acetyl-β-d-ribofuranoside (4f)

This product was obtained as colourless liquid in 76% yield. $[\alpha]_D^{25}$ -30.2 (*c* 1.0, CH_2Cl_2). Analytical data, $[\alpha]_D^{20}$ -31.9 (*c* 1.069, CH_2Cl_2) [55]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.35–5.31 (m, 1H), 5.25 (d, J = 4.8 Hz, 1H), 5.17 (s, 1H), 4.33–4.26 (m, 2H), 4.25–4.23 (m, 1H), 4.23–4.20 (m, 1H), 4.09 (dd, J = 11.4, 4.8 Hz, 1H), 2.43 (t, J = 1.8 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H). HRMS (ESI), *m/z* calcd. for $C_{14}H_{18}NaO_8$ ([M+Na]$^+$) 337.0894, found: 337.0898. These data are consistent with literature [55].

4.5.7. 2-Propargyl 2-deoxy-β-d-ribofuranoside (4g)

This product was obtained as colourless liquid in 48% yield. $[\alpha]_D^{25}$ +220.3 (*c* 1.0, CD_3OD). Analytical data, $[\alpha]_D^{26}$ +216.4 (*c* 1.0, CD_3OD) [56]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (t, J = 2.8 Hz, 1H), 4.21 (qd, J = 16.0, 2.4 Hz, 2H), 4.10–4.03 (m, 1H), 3.87–3.82 (m, 2H), 3.74 (dd, J = 12.0, 2.4 Hz, 1H), 2.43 (t, J = 2.4 Hz, 1H), 2.37–2.34 (m, 1H), 2.16–2.14 (m, 1H), 1.95–1.92 (m, 2H). HRMS (ESI), *m/z* calcd. for $C_8H_{13}O_4$ ([M+H]$^+$) 173.0808, found: 173.0806. These data are consistent with literature [56].

4.6. General procedure for the synthesis of compounds 5a-5u

To a mixture of compound **3** (0.2 mmol) and compound 4 (0.3 mmol) in H_2O-THF (1:1, 10 mL) were added sodium ascorbate (0.2 mmol) and $CuSO_4$ (0.1 mmol). The reaction mixture was stirred in dark at 65 °C for 4 h. After removal of THF under reduced pressure, water (20 mL) was added, and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by a flash silica gel column chromatography to afford **5a-5u**.

4.6.1. 10-(6-(4-((2,3,4,6-Tetra-O-acetyl-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)acridin-9(10H)-one (5a)

This product was obtained as yellow liquid in 78% yield. $[\alpha]_D^{25}$ -30.5 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 8.0 Hz, 2H), 7.70 (t, J = 7.6 Hz, 2H), 7.54 (s, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.27 (t, J = 7.2, 2H), 5.19 (t, J = 9.6 Hz, 1H), 5.08 (t, J = 9.6 Hz, 1H), 5.03–4.89 (m, 2H), 4.81 (d, J = 12.4 Hz, 1H), 4.68 (d, J = 8.0 Hz, 1H), 4.37 (t, J = 7.2 Hz, 2H), 4.34–4.21 (m, 3H), 4.15–4.12 (m, 1H), 3.75–3.71 (m, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.95–1.81 (m, 4H), 1.58–1.53 (m, 2H), 1.48–1.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 170.6, 170.2, 169.5, 169.4, 144.2, 141.6, 134.0, 128.0, 122.8, 122.4, 121.3, 114.5, 100.1, 72.7, 71.9, 71.2, 68.3, 63.1, 61.8, 50.2, 45.8, 30.2, 27.0, 26.3, 26.3, 20.8, 20.7, 20.6. HRMS (ESI), *m/z* calcd. for $C_{36}H_{43}N_4O_{11}$ ([M+H]$^+$) 707.2923, found: 707.2920.

4.6.2. 10-(6-(4-((2,3,4,6-Tetra-O-acetyl-β-d-galactopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)acridin-9(10H)-one (5b)

This product was obtained as yellow liquid in 75% yield. $[\alpha]_D^{25}$ -33.1 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.0 Hz, 2H), 7.73 (t, J = 7.6 Hz, 2H), 7.52 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 5.41 (d, J = 3.2 Hz, 1H), 5.23 (dd, J = 10.4, 8.0 Hz, 1H), 5.03 (dd, J = 10.4, 3.2 Hz, 1H), 4.98 (d, J = 12.4 Hz, 1H), 4.81 (d, J = 12.4 Hz, 1H), 4.66 (d, J = 8.0 Hz, 1H), 4.43–4.30 (m, 4H), 4.21–4.11 (m, 2H), 3.96 (t, J = 6.4 Hz, 1H), 2.14 (s, 3H), 2.05 (s, 3H), 1.98 (s, 6H), 1.97–1.87 (m, 4H), 1.61–1.58 (m, 2H), 1.50–1.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 170.4, 170.1, 170.0, 169.5, 144.3, 141.6, 133.9, 128.0, 122.5, 122.4, 121.2, 114.4, 100.6, 70.8, 70.7, 68.8, 67.0, 63.1, 61.2, 50.1, 45.8, 30.2, 27.0, 26.3, 26.3, 20.7, 20.6, 20.6, 20.5. HRMS (ESI), *m/z* calcd. for $C_{36}H_{43}N_4O_{11}$ ($[M+H]^+$) 707.2923, found: 707.2912.

4.6.3. 10-(6-(4-((2,3,4,6-Tetra-O-acetyl-β-d-mannopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)acridin-9(10H)-one (5c)

This product was obtained as yellow liquid in 70% yield. $[\alpha]_D^{25}$ +29.6 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J = 8.0, 1.6 Hz, 2H), 7.71 (ddd, J = 8.8, 7.2, 1.6 Hz, 2H), 7.57 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.30–7.25 (m, 2H), 5.30–5.27 (m, 2H), 5.22 (dd, J = 2.8, 2.0 Hz, 1H), 4.94 (d, J = 1.6 Hz, 1H), 4.84 (d, J = 12.4 Hz, 1H), 4.66 (d, J = 12.4 Hz, 1H), 4.38 (t, J = 7.2 Hz, 2H), 4.33–4.26 (m, 3H), 4.12–4.04 (m, 2H), 2.12 (s, 3H), 2.10 (s, 3H), 2.01 (s, 3H), 1.99–1.97 (m, 2H), 1.96 (s, 3H), 1.94–1.90 (m, 2H), 1.63–1.55 (m, 2H), 1.51–1.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 170.6, 170.0, 169.9, 169.6, 143.6, 141.6, 133.9, 128.0, 122.7, 122.4, 121.2, 114.4, 96.8, 69.4, 69.0, 68.7, 66.0, 62.3, 61.1, 50.1, 45.8, 30.1, 27.0, 26.3, 20.8, 20.7, 20.6. HRMS (ESI), *m/z* calcd. for $C_{36}H_{43}N_4O_{11}$ ($[M+H]^+$) 707.2923, found: 707.2916.

4.6.4. 10-(6-(4-((3,4,6-Tri-O-acetyl-2-acetamido-2-deoxy-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)acridin-9(10H)-one (5d)

This product was obtained as yellow liquid in 76% yield. $[\alpha]_D^{25}$ -40.5 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (dd, J = 7.8, 1.2 Hz, 2H), 7.73–7.65 (m, 2H), 7.53 (s, 1H), 7.42 (d, J = 9.0 Hz, 2H), 7.26 (t, J = 7.2 Hz, 2H), 6.18 (d, J = 9.0 Hz, 1H), 5.23 (t, J = 9.0 Hz, 1H), 5.07 (t, J = 8.4 Hz, 1H), 4.93 (d, J = 12.6 Hz, 1H), 4.84 (d, J = 8.4 Hz, 1H), 4.76 (d, J = 12.6 Hz, 1H), 4.35–4.32 (m, 2H), 4.28 (t, J = 8.4 Hz, 2H), 4.24 (dd, J = 12.0, 4.8 Hz, 1H), 4.12 (dd, J = 12.6, 2.4 Hz, 1H), 3.98 (dd, J = 19.2, 8.4 Hz, 1H), 3.71 (m, 1H), 2.05 (s, 3H), 2.00 (s, 6H), 1.96–1.91 (m, 2H), 1.91–1.85 (m, 2H), 1.83 (s, 3H), 1.60–1.50 (m, 2H), 1.46–1.40 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 170.8, 170.6, 170.3, 169.3, 144.5, 141.6, 133.9, 127.9, 122.6, 122.3, 121.2, 114.4, 100.5, 72.5, 71.9, 68.5, 62.9, 62.0, 54.3, 50.0, 45.8, 30.1, 27.0, 26.3, 26.2, 23.2, 20.7, 20.6, 20.6. HRMS (ESI), *m/z* calcd. for $C_{36}H_{43}N_5NaO_{10}$ ($[M+Na]^+$) 728.2902, found: 728.2891.

4.6.5. 10-(6-(4-((2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-d-galactopyranosyl)-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)acridin-9(10H)-one (5e)

This product was obtained as yellow liquid in 79% yield. $[\alpha]_D^{25}$ -53.3 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (dd, J = 7.8, 1.2 Hz, 2H), 7.70–7.62 (m, 2H), 7.48 (s, 1H), 7.40 (d, J = 9.0 Hz, 2H), 7.23 (t, J = 7.8 Hz, 2H), 5.31 (d, J = 3.0 Hz, 1H), 5.14 (t, J = 9.0 Hz, 1H), 5.06 (dd, J = 10.2, 7.8 Hz, 1H), 4.93 (dd, J = 10.2, 3.6 Hz, 1H), 4.87–4.85 (m, 2H), 4.75 (d, J = 12.6 Hz, 1H), 4.59 (d, J = 7.8 Hz, 1H), 4.46–4.49 (m, 2H), 4.33 (t, J = 7.2 Hz, 2H), 4.26 (t, J = 8.4 Hz, 2H), 4.10–4.02 (m, 3H), 3.85 (t, J = 6.6 Hz, 1H), 3.77 (t, J = 9.6 Hz, 1H), 3.59 (m, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.99 (s, 6H), 1.96–1.91 (m, 8H), 1.89–1.83 (m, 2H), 1.56–1.51 (m, 2H), 1.44–1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 170.1, 169.9, 169.8, 169.5, 169.4, 168.9, 144.0, 141.5, 133.8, 127.7, 122.5, 122.2, 121.1, 114.3, 100.8, 99.6, 75.9, 72.6, 72.6, 71.4, 70.8, 70.5, 68.9, 66.5, 62.9, 61.6, 60.6, 60.2, 49.9, 45.6, 30.0, 26.8, 26.1, 20.7, 20.6, 20.5, 20.4, 20.3. HRMS (ESI), *m/z* calcd. for $C_{48}H_{59}N_4O_{19}$ ($[M+H]^+$) 995.3768, found: 995.3756.

4.6.6. 10-(6-(4-((2,3,5-Tri-O-acetyl-β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)acridin-9(10H)-one (5f)

This product was obtained as yellow liquid in 79% yield. $[\alpha]_D^{25}$ -10.2 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, J = 7.8 Hz, 2H), 7.71 (t, J = 7.2 Hz, 2H), 7.55 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 7.2 Hz, 2H), 5.34 (t, J = 3.6 Hz, 1H), 5.13 (d, J = 3.0 Hz, 1H), 5.03 (t, J = 3.0 Hz, 1H), 4.95 (d, J = 3.0 Hz, 1H), 4.86 (d, J = 12.6 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.37 (t, J = 7.2 Hz, 2H), 4.30 (t, J = 8.4 Hz, 2H), 4.04 (dd, J = 12.6, 2.4 Hz, 1H), 3.81 (dd, J = 12.6, 3.6 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.99–1.95 (m, 2H), 1.93–1.90 (m, 2H), 1.64–1.54 (m, 2H), 1.51–1.37 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 170.1, 169.9, 169.7, 143.9, 141.6, 133.9, 127.9, 122.6, 122.4, 121.2, 114.4, 97.6, 68.0, 66.7, 65.6, 61.5, 61.3, 50.1, 45.8, 30.1, 27.0, 26.3, 26.3, 20.9, 20.8, 20.6. HRMS (ESI), *m/z* calcd. for $C_{33}H_{39}N_4O_9$ ($[M+H]^+$) 635.2712, found: 635.2703.

4.6.7. 10-(6-(4-((2,3,4,6-Tetra-O-acetyl-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (5g)

This product was obtained as yellow liquid in 81% yield. $[\alpha]_D^{25}$ -35.3 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J = 8.0, 1.6 Hz, 1H), 7.99 (d, J = 3.2 Hz, 1H), 7.72 (m, 1H), 7.50 (s, 1H), 7.45 (dd, J = 8.4, 6.8 Hz, 2H), 7.38 (dd, J = 9.2, 3.2 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 5.20 (t, J = 9.2 Hz, 1H), 5.09 (t, J = 9.6 Hz, 1H), 5.01 (dd, J = 9.2, 7.6 Hz, 1H), 4.94 (d, J = 12.4 Hz, 1H), 4.81 (d, J = 12.4 Hz, 1H), 4.68 (d, J = 8.0 Hz, 1H), 4.42–4.31 (m, 4H), 4.26 (dd, J = 12.0, 4.8 Hz, 1H), 4.18–4.11 (m, 1H), 3.94 (s, 3H), 3.72 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 2.00–1.89 (m, 10H), 1.62–1.54 (m, 2H), 1.50–1.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 170.6, 170.2, 169.4, 169.4, 154.4, 144.3, 141.3, 136.6, 133.7, 128.1, 124.7, 123.2, 122.6, 121.8, 121.0, 116.3, 114.3, 106.9, 100.1, 72.7, 71.9, 71.3, 68.3, 63.2, 61.8, 55.8, 50.1, 45.9, 30.2, 27.3, 26.4, 26.3, 20.8, 20.7, 20.6. HRMS (ESI), *m/z* calcd. for $C_{37}H_{45}N_4O_{12}$ ($[M+H]^+$) 737.3028, found: 737.3023.

4.6.8. 10-(6-(4-((2,3,4,6-Tetra-O-acetyl-β-d-galactopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (5 h)

This product was obtained as yellow liquid in 85% yield. $[\alpha]_D^{25}$ -29.2 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, J = 8.0, 1.6 Hz, 1H), 7.98 (d, J = 3.2 Hz, 1H), 7.71 (m, 1H), 7.50 (s, 1H), 7.45 (dd, J = 9.2, 6.0 Hz, 2H), 7.37 (dd, J = 9.2, 3.2 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 5.39 (dd, J = 3.2, 0.8 Hz, 1H), 5.22 (dd, J = 10.4, 8.0 Hz, 1H), 5.02 (dd, J = 10.4, 3.2 Hz, 1H), 4.97 (d, J = 12.4 Hz, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.65 (d, J = 8.0 Hz, 1H), 4.42–4.27 (m, 4H), 4.19–4.10 (m, 2H), 3.97–3.92 (m, 4H), 2.13 (s, 3H), 2.04 (s, 3H), 1.97 (s, 6H), 2.02–1.85 (m, 4H), 1.63–1.52 (m, 2H), 1.51–1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 170.4, 170.2, 170.1, 169.5, 154.4, 144.4, 141.2, 136.6, 133.7, 128.1, 124.7, 123.2, 122.5, 121.7, 121.0, 116.3, 114.3, 106.9, 100.6, 70.9, 70.8, 68.8, 67.0, 63.2, 61.3, 55.8, 50.1, 45.9, 30.2, 27.3, 26.4, 26.3, 20.8, 20.7, 20.6, 20.6. HRMS (ESI), *m/z* calcd. for $C_{37}H_{44}N_4NaO_{12}$ ($[M+Na]^+$) 759.2848, found: 759.2845.

4.6.9. 10-(6-(4-((2,3,4,6-Tetra-O-acetyl-β-d-mannopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (5i)

This product was obtained as yellow liquid in 79% yield. $[\alpha]_D^{25}$ +31.8 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J = 8.0, 1.6 Hz, 1H), 7.99 (d, J = 3.2 Hz, 1H), 7.72 (m, 1H), 7.57 (s, 1H), 7.46 (dd, J = 8.8, 6.8 Hz, 2H), 7.38 (dd, J = 9.2, 3.2 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 5.35–5.27 (m, 2H), 5.26–5.22 (m, 1H), 4.96 (d, J = 1.6 Hz, 1H), 4.86 (d, J = 12.4 Hz, 1H), 4.68 (d, J = 12.4 Hz, 1H), 4.45–4.24 (m, 5H), 4.16–4.05 (m, 2H), 3.95 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.07–2.04 (m, 1H), 2.02 (s, 3H), 2.01–1.99 (m, 1H), 1.98 (s, 3H), 1.94–1.90 (m, 2H),1.64–1.56 (m, 2H), 1.53–1.45 (m, 2H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 177.4, 170.7, 170.1, 170.0, 169.7, 154.4, 143.7, 141.3, 136.6, 133.7, 128.0, 124.7, 123.2, 122.7, 121.7, 121.0, 116.3, 114.3, 106.9, 96.9, 69.5, 69.0, 68.7, 66.1, 62.4, 61.2, 55.8, 50.2, 46.-, 30.2, 27.3, 26.4, 20.9, 20.8, 20.7. HRMS (ESI), *m/z* calcd. for $C_{37}H_{45}N_4O_{12}$ ($[M+H]^+$) 737.3028, found: 737.3030.

4.6.10. 10-(6-(4-((3,4,6-Tri-O-acetyl-2-acetamido-2-deoxy-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (5j)

This product was obtained as yellow liquid in 88% yield. $[\alpha]_D^{25}$ -42.6 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (dd, J = 7.8, 1.2 Hz, 1H), 7.93 (d, J = 3.0 Hz, 1H), 7.75–7.61 (m, 1H), 7.52 (s, 1H), 7.40 (dd, J = 11.4, 9.0 Hz, 2H), 7.33 (dd, J = 9.6, 3.0 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 6.18 (d, J = 9.0 Hz, 1H), 5.23 (t, J = 9.6 Hz, 1H), 5.06 (t, J = 9.6 Hz, 1H), 4.92 (d, J = 12.6 Hz, 1H), 4.84 (d, J = 8.4 Hz, 1H), 4.75 (d, J = 12.6 Hz, 1H), 4.35–4.31 (m, 2H), 4.28 (t, J = 7.8 Hz, 2H), 4.24 (dd, J = 12.0, 4.8 Hz, 1H), 4.12 (dd, J = 12.0, 2.4 Hz, 1H), 3.97 (dd, J = 19.2, 8.4 Hz, 1H), 3.90 (s, 3H), 3.71 (m, 1H), 2.05 (s, 3H), 1.99 (s, 6H), 1.96–1.89 (m, 2H), 1.90–1.83 (m, 2H), 1.83 (s, 3H), 1.54–1.50 (m, 2H), 1.43–1.40 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 170.7, 170.6, 170.3, 169.3, 154.3, 144.4, 141.1, 136.4, 133.6, 127.8, 124.6, 123.0, 122.6, 121.5, 120.9, 116.3, 114.3, 106.7, 100.5, 72.5, 71.8, 68.5, 62.9, 62.0, 55.7, 54.3, 50.0, 45.8, 30.1, 27.2, 26.2, 26.2, 23.2, 20.7, 20.6, 20.5. HRMS (ESI), *m/z* calcd. for $C_{37}H_{45}N_5NaO_{11}$ ($[M+Na]^+$) 758.3008, found: 758.3006.

4.6.11. 10-(6-(4-((2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-d-galactopyranosyl) -β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)-2-methoxyacridin-9(10H)-one (5k)

This product was obtained as yellow liquid in 82% yield. $[\alpha]_D^{25}$ -49.2 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J = 8.0, 1.6 Hz, 1H), 7.98 (d, J = 3.2 Hz, 1H), 7.72 (m, 1H), 7.49 (s, 1H), 7.46 (dd, J = 8.8, 6.8 Hz, 2H), 7.38 (dd, J = 9.2, 3.2 Hz, 1H), 7.29 (t, J = 7.6 Hz 1H), 5.34 (d, J = 2.4 Hz, 1H), 5.18 (t, J = 9.2 Hz, 1H), 5.10 (dd, J = 10.4, 8.0 Hz, 1H), 4.99–4.86 (m, 3H), 4.79 (d, J = 12.4 Hz, 1H), 4.62 (d, J = 8.0 Hz, 1H), 4.52 (dd, J = 12.0, 1.6 Hz, 1H), 4.47 (d, J = 8.0 Hz, 1H), 4.38–4.32 (m, 4H), 4.18–4.02 (m, 3H), 3.94 (s, 3H), 3.87 (t, J = 7.2 Hz, 1H), 3.79 (t, J = 9.6 Hz, 1H), 3.62 (m, 1H), 2.15 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00–1.91 (m, 10H), 1.62–1.54 (m, 2H), 1.49–1.43 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4, 170.3, 170.1, 170.1, 169.7, 169.6, 169.0, 154.4, 144.2, 141.2, 136.5, 133.7, 128.0, 124.7, 123.2, 122.6, 121.7, 120.9, 116.3, 114.3, 106.8, 101.0, 99.8, 76.1, 72.8, 72.7, 71.5, 70.9, 70.7, 69.1, 66.6, 63.2, 61.7, 60.7, 55.8, 50.1, 45.9, 30.2, 27.3, 26.4, 26.3, 20.9, 20.8, 20.7, 20.6, 20.5. HRMS (ESI), *m/z* calcd. for $C_{49}H_{60}N_4NaO_{20}$ ($[M+Na]^+$) 1047.3693, found: 1047.3691.

4.6.12. 10-(6-(4-((2,3,5-Tri-O-acetyl-β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (5l)

This product was obtained as yellow liquid in 77% yield. $[\alpha]_D^{25}$ -15.6 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (dd, J = 7.8, 1.2 Hz, 1H), 7.99 (d, J = 3.0 Hz, 1H), 7.74–7.70 (m, 1H), 7.54 (s, 1H), 7.46 (dd, J = 11.4, 9.0 Hz, 2H), 7.38 (dd, J = 9.6, 3.0 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 5.35 (t, J = 3.6 Hz, 1H), 5.15 (d, J = 3.0 Hz, 1H), 5.04 (t, J = 3.0 Hz, 1H), 4.96 (d, J = 3.0 Hz, 1H), 4.87 (d, J = 12.6 Hz, 1H), 4.69 (d, J = 12.6 Hz, 1H), 4.38 (t, J = 7.2 Hz, 2H), 4.36 (t, J = 7.8 Hz, 2H), 4.05 (dd, J = 12.6, 2.4 Hz, 1H), 3.94 (s, 3H), 3.83 (dd, J = 12.6, 3.6 Hz, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 2.03–1.97 (m, 2H), 1.97–1.89 (m, 2H), 1.61–1.56 (m, 2H), 1.49–1.44 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4, 170.2, 169.9, 169.8, 154.4, 144.1, 141.3, 136.6, 133.7, 128.1, 124.7, 123.2, 122.6, 121.7, 121.0, 116.3, 114.3, 106.9, 97.7, 68.1, 66.7, 65.6, 61.6, 61.4, 55.8, 50.2, 46.0, 30.2, 27.3, 26.4, 26.4, 21.0, 20.9, 20.7. HRMS (ESI), *m/z* calcd. for $C_{34}H_{41}N_4O_{10}$ ($[M+H]^+$) 665.2817, found: 665.2795.

4.6.13. 10-(3-(4-((2,3,4,6-Tetra-O-acetyl-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)propyl)acridin-9(10H)-one (5m)

This product was obtained as yellow liquid in 89% yield. $[\alpha]_D^{25}$ -26.6 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, J = 7.8 Hz, 2H), 7.71 (t, J = 7.8 Hz, 2H), 7.61 (s, 1H), 7.37 (d, J = 9.0 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 5.22 (t, J = 9.6 Hz, 1H), 5.11 (t, J = 9.6 Hz, 1H), 5.03 (t, J = 8.4 Hz, 1H), 4.98 (d, J = 12.6 Hz, 1H), 4.88 (d, J = 12.6 Hz, 1H), 4.71 (d, J = 7.8 Hz, 1H), 4.58 (t, J = 6.6 Hz, 2H), 4.53 (d, J = 7.8 Hz, 2H), 4.25 (dd, J = 12.0, 4.2 Hz, 1H), 4.19 (d, J = 12.0 Hz, 1H), 3.75 (d, J = 8.4 Hz, 1H), 2.59 (m, 2H), 2.06 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 170.6, 170.2, 169.4, 169.4, 144.8, 141.5, 134.2, 128.2, 123.3, 122.6, 121.6, 114.0, 100.3, 72.7, 72.0, 71.2, 68.3, 63.3, 61.7, 47.7, 43.0, 27.2, 20.7, 20.7, 20.6. HRMS (ESI), *m/z* calcd. for $C_{33}H_{36}N_4N_aO_{11}$ ($[M+Na]^+$) 687.2273, found: 687.2268.

4.6.14. 10-(3-(4-((2,3,4,6-Tetra-O-acetyl-β-d-galactopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)propyl)acridin-9(10H)-one (5n)

This product was obtained as yellow liquid in 85% yield. $[\alpha]_D^{25}$ -29.0 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, J = 7.8 Hz, 2H), 7.67 (t, J = 7.8 Hz, 2H), 7.62 (s, 1H), 7.33 (d, J = 9.0 Hz, 2H), 7.26 (t, J = 7.2 Hz, 2H), 5.40 (s, 1H), 5.23 (t, J = 9.6 Hz, 1H), 5.03 (t, J = 9.6 Hz, 2H), 4.85 (d, J = 12.6 Hz, 1H), 4.68 (d, J = 7.8 Hz, 1H), 4.56 (t, J = 6.0 Hz, 2H), 4.47 (t, J = 7.8 Hz, 2H), 4.23–4.16 (m, 1H), 4.15–4.10 (m, 1H), 3.96 (t, J = 6.0 Hz, 1H), 2.56–2.53 (m, 2H), 2.12 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8, 170.4, 170.2, 170.1, 169.6, 144.8, 141.4, 134.2, 128.1, 123.3, 122.5, 121.6, 114.1, 100.7, 70.9, 70.8, 68.8, 67.1, 63.1, 61.3, 47.7, 43.01, 27.2, 20.8, 20.7, 20.7, 20.6. HRMS (ESI), *m/z* calcd. for $C_{33}H_{36}N_4N_aO_{11}$ ($[M+Na]^+$) 687.2273, found: 687.2265.

4.6.15. 10-(3-(4-((2,3,4,6-Tetra-O-acetyl-β-d-mannopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)propyl)acridin-9(10H)-one (5o)

This product was obtained as yellow liquid in 77% yield. $[\alpha]_D^{25}$ +22.1 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J = 8.0, 1.6 Hz, 2H), 7.73–7.61 (m, 3H), 7.34 (d, J = 8.8 Hz, 2H), 7.25 (t, J = 7.6 Hz, 2H), 5.30–5.27 (m, 2H), 5.25–5.20 (m, 1H), 4.97 (d, J = 1.6 Hz, 1H), 4.88 (d, J = 12.4 Hz, 1H), 4.71 (d, J = 12.4 Hz, 1H), 4.57 (t, J = 6.4 Hz, 2H), 4.48 (t, J = 8.0 Hz, 2H), 4.28 (dd, J = 12.4, 5.2 Hz, 1H), 4.11–4.06 (m, 1H), 2.69–2.47 (m, 2H), 2.10 (s, 3H), 2.09 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 170.6, 170.0, 169.9, 169.6, 143.9, 141.4, 134.2, 128.0, 123.5, 122.4, 121.5, 114.1, 96.8, 69.4, 68.9, 68.7, 66.0, 62.3, 61.0, 47.7, 43.0, 27.1, 20.8, 20.7, 20.6. HRMS (ESI), *m/z* calcd. for $C_{33}H_{37}N_4O_{11}$ ($[M+H]^+$) 665.2453, found: 665.2449.

4.6.16. 10-(3-(4-((3,4,6-Tri-O-acetyl-2-acetamido-2-deoxy-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)propyl)acridin-9(10H)-one (5p)

This product was obtained as yellow liquid in 80% yield. $[\alpha]_D^{25}$ -43.3 (0.3, CHCl3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (dd, J = 7.8, 1.2 Hz, 2H), 7.66 (t, J = 7.2 Hz, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 6.17 (d, J = 9.0 Hz, 1H), 5.26 (t, J = 9.6 Hz, 1H), 5.09 (t, J = 9.6 Hz, 1H), 4.98 (d, J = 11.4 Hz, 1H), 4.88–4.83 (m, 2H), 4.55 (t, J = 6.0 Hz, 2H), 4.43 (t, J = 7.8 Hz, 2H), 4.25 (dd, J = 12.0, 4.2 Hz, 1H), 4.17 (dd, J = 12.6, 2.4 Hz, 1H), 3.99 (dd, J = 18.6, 9.0 Hz, 1H), 3.74 (m, 1H), 2.60–2.41 (m, 2H), 2.05 (s, 3H), 2.00 (s, 6H), 1.85 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8, 170.8, 170.6, 170.4, 169.4, 141.4, 134.2, 128.0, 122.4, 121.5, 114.1, 100.6, 72.4, 71.9, 68.5, 62.9, 61.9, 54.4, 47.7, 43.0, 27.1, 23.3, 20.7, 20.6, 20.6. HRMS (ESI), *m/z* calcd. for $C_{33}H_{37}N_5NaO_{10}$ ($[M+Na]^+$) 686.2433, found: 686.2425.

4.6.17. 10-(3-(4-((2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-d-galactopyranosyl)-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) propyl)acridin-9(10H)-one (5q)

This product was obtained as yellow liquid in 80% yield. $[\alpha]_D^{25}$ -30.3 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J = 8.0, 1.6 Hz, 2H), 7.69 (m, 2H), 7.61 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 5.34 (d, J = 3.2 Hz, 1H), 5.19 (t, J = 9.2 Hz, 1H), 5.10 (dd, J = 10.4, 7.6 Hz, 1H), 5.01–4.81 (m, 4H), 4.65 (d, J = 8.0 Hz, 1H), 4.61–4.53 (m, 3H), 4.50 (t, J = 7.6 Hz, 2H), 4.14–4.03 (m, 3H), 3.86 (t, J = 7.2 Hz, 1H), 3.81 (t, J = 9.2 Hz, 1H), 3.63 (m, 1H), 2.67–2.49 (m, 2H), 2.14 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 170.3, 170.1, 170.0, 169.7, 169.6, 169.0, 144.8, 141.4, 134.2, 128.1, 123.4, 122.5, 121.5, 114.1, 101.0, 100.2, 75.9, 72.9, 72.7, 71.5, 70.9, 70.7, 69.1, 66.6, 63.4, 61.5, 60.7, 47.6, 43.0, 27.2, 20.9, 20.7, 20.7, 20.6, 20.5. HRMS (ESI), *m/z* calcd. for $C_{45}H_{53}N_4O_{19}$ ($[M+H]^+$) 953.3299, found: 953.3294.

4.6.18. 10-(3-(4-((2,3,5-Tri-O-acetyl-β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl) propyl)acridin-9(10H)-one (5r)

This product was obtained as yellow liquid in 75% yield. $[\alpha]_D^{25}$ -10.9 (0.3, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 8.0, 1.6 Hz, 2H), 7.71 (m, 2H), 7.64 (s, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 5.37 (t, J = 3.6 Hz, 1H), 5.16 (dd, J = 6.4, 3.2 Hz, 1H), 5.05 (t, J = 3.2 Hz, 1H), 4.98 (d, J = 2.8 Hz, 1H), 4.93 (d, J = 12.4 Hz, 1H), 4.75 (d, J = 12.4 Hz, 1H), 4.58 (t, J = 6.4 Hz, 2H), 4.53 (t, J = 8 Hz, 2H), 4.07 (dd, J = 12.8, 2.8 Hz, 1H), 3.85 (dd, J = 12.8, 4.0 Hz, 1H), 2.67–2.55 (m, 2H), 2.12 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 170.1, 169.9, 169.7, 144.4, 141.5, 134.2, 128.2, 123.3, 122.5, 121.6, 114.1, 97.7, 68.1, 66.7, 65.6, 61.5, 61.4, 47.7, 43.0, 27.2, 20.9, 20.8, 20.6. HRMS (ESI), *m/z* calcd. for $C_{30}H_{32}N_4NaO_9$ ($[M+Na]^+$) 615.2061, found: 615.2059.

4.6.19. 10-(3-(4-((2-Deoxy-β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl)propyl) acridin-9(10H)-one (5s)

This product was obtained as yellow foam solid in 99% yield. $[\alpha]_D^{25}$ -12.6 (0.5, MeOH). m.p. 203–207 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (dd, J = 8.0, 1.6 Hz, 2H), 8.09 (s, 1H), 7.83 (m, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.36 (m, 2H), 4.92 (d, J = 12.4 Hz, 1H), 4.76–4.66 (m, 4H), 4.64–4.57 (m, 2H), 3.93 (dd, J = 12.4, 4.4 Hz, 1H), 3.84–3.74 (m, 1H), 3.70–3.62 (m, 1H), 3.52 (dd, J = 12.4, 2.4 Hz, 1H), 2.55 (m, 2H), 1.94–1.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 176.5, 144.0, 141.4, 134.3, 126.8, 124.3, 121.6, 121.4, 115.5, 96.7, 67.3, 64.2, 63.5, 59.7, 46.8, 42.7, 34.0, 27.3. HRMS (ESI), *m/z* calcd. for $C_{24}H_{26}N_4NaO_5$ ($[M+Na]^+$) 473.1795, found: 473.1779.

4.6.20. 10-(6-(4-((2-Deoxy-β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl) acridin-9(10H)-one (5t)

This product was obtained as yellow foam solid in 99% yield. $[\alpha]_D^{25}$ -14.7 (0.5, MeOH). m.p. 204–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, J = 8.0, 1.6 Hz, 2H), 7.73 (m, 2H), 7.51 (s, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 5.00 (t, J = 3.2 Hz, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.59 (d, J = 12.4 Hz, 1H), 4.39–4.32 (m, 4H), 4.11–4.00 (m, 1H), 3.89 (dd, J = 12.4, 1.6 Hz, 1H), 3.82 (s, 1H), 3.75 (dd, J = 12.4, 3.2 Hz, 1H), 2.04–1.87 (m, 6H), 1.64–1.53 (m, 2H), 1.52–1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 144.6, 141.7, 134.0, 128.1, 122.5, 121.3, 114.4, 97.2, 68.0, 64.8, 62.9, 60.6, 50.1, 45.8, 33.7, 30.2, 27.1, 26.3. HRMS (ESI), *m/z* calcd. for $C_{27}H_{32}N_4NaO_5$ ($[M+Na]^+$) 515.2265, found: 515.2263.

4.6.21. 10-(6-(4-((2-Deoxy-β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (5u)

This product was obtained as yellow foam solid in 99% yield. $[\alpha]_D^{25}$ -10.2 (0.5, MeOH). m.p. 209–211 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.36 (d, J = 8.0 Hz, 1H), 8.10 (s, 1H), 7.88–7.80 (m, 3H), 7.77 (d, J = 3.2 Hz, 1H), 7.49 (dd, J = 9.2, 3.2 Hz, 1H), 7.31 (m, 1H), 4.88 (t, J = 3.2 Hz, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.53 (dd, J = 14.0, 4.4 Hz, 2H), 4.50–4.41 (m, 3H), 4.35 (t, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.78–3.73 (m, 1H), 3.68–3.60 (m, 1H), 3.54–3.49 (m, 2H), 2.00–1.69 (m, 6H), 1.56–1.49 (m, 2H), 1.36–1.32 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4, 154.4, 144.6, 141.2, 136.5, 133.7, 128.0, 124.7, 123.1, 122.5, 121.7, 121.0, 116.3, 114.3, 106.8, 97.2, 68.0, 64.8, 62.9, 60.6, 55.8, 50.1, 45.9, 33.7, 30.1, 27.3, 26.3. HRMS (ESI), *m/z* calcd. for $C_{28}H_{34}N_4NaO_6$ ($[M+Na]^+$) 545.2371, found: 545.2367.

4.7. General procedure for the synthesis of compounds 6a-6r

To a solution of compound **5a-5r** in anhydrous methanol (10 mL) was added 1 M solution of sodium methoxide in MeOH until pH 9–10 was reached. The reaction mixture was stirred at r.t. for 4 h. The reaction was neutralized with amberlite IR-120 (H^+) and filtered, the solvent was evaporated in vacuo. The residue was purified by a flash silica gel column chromatography to afford **6a-6r**.

4.7.1. 10-(6-(4-((β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)acridin-9(10H)-one (6a)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -39.4 (0.5, MeOH). m.p. 236–237 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (dd, J = 8.0, 1.6 Hz, 2H), 8.03 (s, 1H), 7.81 (m, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 4.97 (d, J = 12.4 Hz, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.44–4.39 (m, 5H), 3.90 (d, J = 12.0 Hz, 1H), 3.68 (dd, J = 12.0, 5.6 Hz, 1H), 3.38–3.35 (m, 1H), 3.33–3.32 (m, 1H), 3.31–3.29 (m, 1H), 3.23 (dd, J = 8.8, 7.6 Hz, 1H), 2.04–1.91 (m, 2H), 1.91–1.76 (m, 2H), 1.66–1.50 (m, 2H), 1.48–1.26 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.7, 145.7, 143.1, 135.7, 128.2, 125.3, 123.0, 122.6, 116.7, 103.7, 78.1, 78.0, 75.0, 71.6, 63.1, 62.8, 51.2, 46.8, 31.1, 28.1, 27.2, 27.0. HRMS (ESI), *m/z* calcd. for $C_{28}H_{35}N_4O_7$ ($[M+H]^+$) 539.2500, found: 539.2490.

4.7.2. 10-(6-(4-((β-d-galactopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)acridin-9(10H)-one (6b)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -36.6 (0.5, MeOH). m.p. 233–235 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.43 (d, J = 7.8 Hz, 2H), 8.03 (s, 1H), 7.81 (t, J = 7.8 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 4.98 (d, J = 12.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.43–4.39 (m, 4H), 4.36 (d, J = 7.8 Hz, 1H), 3.85 (d, J = 3.0 Hz, 1H), 3.81 (dd, J = 11.4, 7.2 Hz, 1H), 3.75 (dd, J = 11.4, 4.8 Hz, 1H), 3.62–3.53 (m, 2H), 3.48 (dd, J = 9.6, 3.0 Hz, 1H), 2.06–1.90 (m, 2H), 1.89–1.76 (m, 2H), 1.65–1.53 (m, 2H), 1.45–1.41 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.7, 145.8, 143.1, 135.7, 128.2, 125.3, 123.0, 122.6, 116.7, 104.3, 76.8, 74.9, 72.4, 70.3, 63.0, 62.6, 51.2, 46.8, 31.2, 28.1, 27.2, 27.0. HRMS (ESI), *m/z* calcd. for $C_{28}H_{34}N_4N_aO_7$ ($[M+Na]^+$) 561.2320, found: 561.2311.

4.7.3. 10-(6-(4-((β-d-mannopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)acridin-9(10H)-one (6c)

This product was obtained as yellow liquid in quantitative yield. $[\alpha]_D^{25}$ +48.8 (0.5, MeOH). ^{1}H NMR (600 MHz, CD_3OD) δ 8.41 (d, J = 7.8 Hz, 2H), 8.02 (s, 1H), 7.79 (t, J = 7.8 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 4.86 (s, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.6 Hz, 1H), 4.49–4.28 (m, 4H), 3.85 (d, J = 11.4 Hz, 1H), 3.78 (s, 1H), 3.71 (dd, J = 11.4, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 3.0 Hz, 1H), 3.61 (t, J = 9.6 Hz, 1H), 3.59–3.54 (m, 1H), 1.99–1.90 (m, 2H), 1.87–1.79 (m, 2H), 1.59–1.53 (m, 2H), 1.44–1.39 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.7, 143.1, 135.7, 128.2, 123.0, 122.6, 116.7, 100.8, 75.0, 72.5, 72.0, 68.6, 63.0, 60.7, 51.2, 46.8, 31.2, 28.1, 27.2, 27.0. HRMS (ESI), *m/z* calcd. for $C_{28}H_{35}N_4O_7$ ($[M+H]^+$) 539.2500, found: 539.2491.

4.7.4. 10-(6-(4-((2-Acetamido-2-deoxy-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)acridin-9(10H)-one (6d)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -68.3 (0.5, MeOH). m.p. 260–263 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.36 (dd, J = 7.8, 1.8 Hz, 2H), 7.91 (s, 1H), 7.74 (m, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.25 (t, J = 7.2 Hz, 2H), 4.87 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 12.6 Hz, 1H), 4.50 (d, J = 8.4 Hz, 1H), 4.40–4.28 (m, 4H), 3.87 (d, J = 12.0 Hz, 1H), 3.72–3.58 (m, 2H), 3.43 (dd, J = 10.2, 8.4 Hz, 1H), 3.28–3.25 (m, 2H), 1.90–1.87 (m, 2H), 1.87 (s, 3H), 1.82–1.69 (m, 2H), 1.61–1.44 (m, 2H), 1.47–1.27 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 179.7, 173.7, 145.7, 143.1, 135.7, 128.2, 125.3, 123.0, 122.6, 116.7, 101.9, 78.1, 76.0, 72.1, 62.8, 62.8, 57.3, 51.2, 46.8, 31.1, 28.1, 27.2, 27.0, 23.0. HRMS (ESI), *m/z* calcd. for $C_{30}H_{37}N_5NaO_7$ ($[M+Na]^+$) 602.2585, found: 602.2587.

4.7.5. 10-(6-(4-((4-O-(β-d-galactopyranosyl)-β-d-glucopyranosyl) methyl)-1H-1,2,3-triazol-1-yl)hexyl)acridin-9(10H)-one (6e)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -70.6 (0.5, MeOH). m.p. 220–221 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.42 (d, J = 7.8 Hz, 2H), 8.03 (s, 1H), 7.79 (t, J = 7.8 Hz, 2H), 7.66 (d, J = 9.0 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 4.97 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.50–4.33 (m, 6H), 3.95 (d, J = 12.0 Hz, 1H), 3.89–3.83 (m, 2H), 3.80 (dd, J = 11.4, 7.2 Hz, 1H), 3.72 (dd, J = 11.4, 4.2 Hz, 1H), 3.64–3.56 (m, 3H), 3.56–3.48 (m, 2H), 3.48–3.41 (m, 1H), 3.33–3.27 (m, 1H), 1.96–1.93 (m, 2H), 1.85–1.81 (m, 2H), 1.58–1.53 (m, 2H), 1.43–1.39 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.6, 145.7, 143.0, 135.7, 128.2, 125.3, 122.9, 122.6, 116.6, 105.1, 103.4, 80.5, 77.1, 76.5, 76.3, 74.8, 74.6, 72.5, 70.3, 63.1, 62.5, 61.9, 51.2, 46.8, 31.1, 28.1, 27.2, 26.9. HRMS (ESI), *m/z* calcd. for $C_{34}H_{44}N_4N_aO_{12}$ ($[M+Na]^+$) 723.2848, found: 723.2831.

4.7.6. 10-(6-(4-((β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl) acridin-9(10H)-one (6f)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -16.4 (0.5, MeOH). m.p. 228–229 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.40 (d, J = 7.8 Hz, 2H), 8.01 (s, 1H), 7.77 (t, J = 7.8 Hz, 2H), 7.64 (d, J = 9.0 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 4.85 (d, J = 3.6 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.42 (t, J = 7.2 Hz, 2H), 4.35 (t, J = 8.4 Hz, 2H), 3.86–3.80 (m, 2H), 3.77 (s, 1H), 3.71 (dd, J = 11.4, 4.8 Hz, 1H), 3.59 (t, J = 3.0 Hz, 1H), 1.98–1.90 (m, 2H), 1.86–1.75 (m, 2H), 1.61–1.48 (m, 2H), 1.46–1.34 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.6, 143.1, 135.7, 128.2, 125.2, 123.0, 122.6, 116.6, 101.6, 72.4, 70.6, 68.0, 65.1, 61.6, 51.2, 46.8, 31.2, 28.1, 27.2, 27.0. HRMS (ESI), *m/z* calcd. for $C_{27}H_{33}N_4O_6$ ($[M+H]^+$) 509.2395, found: 509.2399.

4.7.7. 10-(6-(4-((β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)-2-methoxyacridin-9(10H)-one (6g)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -52.0 (0.5, MeOH). m.p. 239–241 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.29 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 7.64 (t, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H), 7.29–7.23 (m, 1H), 7.18 (t, J = 7.8 Hz, 1H), 4.96 (d, J = 12.0 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 7.8 Hz, 1H), 4.35 (t, J = 6.6 Hz, 2H), 4.13 (t, J = 7.8 Hz, 2H), 3.90 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H), 3.69 (dd, J = 12.0, 4.2 Hz, 1H), 3.39 (t, J = 8.4 Hz, 1H), 3.35–3.32 (m, 2H), 3.24 (t, J = 8.4 Hz, 1H), 1.96–1.79 (m, 2H), 1.66–1.62 (s, 2H), 1.56–1.37 (m, 2H), 1.37–1.25 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.5, 155.7, 145.6, 142.2, 137.6, 135.2, 128.0, 126.0, 125.3, 123.4, 122.2, 122.0, 118.3, 116.3, 106.7, 103.6, 78.0, 77.9, 75.0, 71.6, 63.0, 62.8, 56.0, 51.1, 46.9, 31.1, 28.1, 27.1, 26.9. HRMS (ESI), *m/z* calcd. for $C_{29}H_{36}N_4N_aO_8$ ($[M+Na]^+$) 591.2425, found: 591.2429.

4.7.8. 10-(6-(4-((β-d-galactopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)-2-methoxyacridin-9(10H)-one (6 h)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -66.9 (0.5, MeOH). m.p. 241–243 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.46 (dd, J = 7.8, 1.8 Hz, 1H), 8.01 (s, 1H), 7.86 (d, J = 3.6 Hz, 1H), 7.82 (m, 1H), 7.74–7.72 (m, 2H), 7.48 (dd, J = 9.0, 3.0 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 4.96 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.48 (t, J = 8.4 Hz, 2H), 4.42 (t, J = 7.2 Hz, 2H), 4.33 (d, J = 7.8 Hz, 1H), 3.92 (s, 3H), 3.82 (d, J = 3.0 Hz, 1H), 3.78 (dd, J = 11.4, 7.2 Hz, 1H), 3.72 (dd, J = 11.4, 4.8 Hz, 1H), 3.55–3.51 (m, 2H), 3.45 (dd, J = 9.6, 3.0 Hz, 1H), 2.01–1.91 (m, 2H), 1.90–1.85 (m, 2H), 1.61–1.55 (m, 2H), 1.45–1.40 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 177.7, 154.8, 144.5, 141.3, 136.8, 134.0, 126.8, 125.0, 123.9, 122.4, 121.0, 120.9, 117.3, 115.2, 105.6, 102.9, 75.5, 73.5, 71.0, 68.9, 61.7, 61.2, 54.7, 49.8, 45.6, 29.8, 27.0, 25.9, 25.6. HRMS (ESI), *m/z* calcd. for $C_{29}H_{37}N_4O_8$ ($[M+H]^+$) 569.2606, found: 569.2604.

4.7.9. 10-(6-(4-((β-d-mannopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl) -2-methoxyacridin-9(10H)-one (6i)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ +29.2 (0.5, MeOH). m.p. 220–223 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (dd, J = 7.8, 1.6 Hz, 1H), 8.02 (s, 1H), 7.82 (d, J = 2.8 Hz, 1H), 7.78 (m, 1H), 7.67 (dd, J = 9.2, 4.0 Hz, 2H), 7.43 (dd, J = 9.2, 3.2 Hz, 1H), 7.37–7.23 (m, 1H), 4.84 (d, J = 1.6 Hz, 1H), 4.80 (d, J = 12.4 Hz, 1H), 4.64 (d, J = 12.4 Hz, 1H), 4.48–4.31 (m, 4H), 3.90 (s, 3H), 3.85 (dd, J = 11.6, 2.4 Hz, 1H), 3.78 (dd, J = 3.2, 1.6 Hz, 1H), 3.75–3.64 (m, 2H), 3.63–3.56 (m, 2H), 2.01–1.90 (m, 2H), 1.88–1.77 (m, 2H), 1.62–1.49 (m, 2H), 1.49–1.36 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.5, 155.7, 142.2, 137.6, 135.1, 128.0, 126.0, 123.4, 122.2, 122.0, 118.3, 116.3, 106.7, 100.8, 75.0, 72.5, 72.0, 68.6, 63.0, 60.7, 56.0, 51.2, 46.9, 31.1, 28.1, 27.1, 26.9. HRMS (ESI), *m/z* calcd. for $C_{29}H_{36}N_4N_aO_8$ ($[M+Na]^+$) 591.2425, found: 591.2432.

4.7.10. 10-(6-(4-((2-Acetamido-2-deoxy-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (6j)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -81.2 (0.5, MeOH). m.p. 250–252 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.39 (dd, J = 7.8, 1.2 Hz, 1H), 7.96 (s, 1H), 7.77 (d, J = 3.0 Hz, 1H), 7.75 (m, 1H), 7.62 (t, J = 9.6 Hz, 2H), 7.40 (dd, J = 9.6, 3.0 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.72 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 8.4 Hz, 1H), 4.40 (t, J = 7.2 Hz, 2H), 4.35 (t, J = 8.4 Hz, 2H), 3.91 (d, J = 12.0 Hz, 1H), 3.88 (s, 3H), 3.72–3.64 (m, 2H), 3.46 (dd, J = 10.2, 8.4 Hz, 1H), 3.35–3.32 (m, 2H), 1.96–1.92 (m, 2H), 1.91 (s, 3H), 1.83–1.73 (m, 2H), 1.54–1.50 (m, 2H), 1.41–1.37 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 176.9, 171.7, 154.0, 140.5, 135.9, 133.3, 126.1, 124.2, 123.4, 121.6, 120.3, 120.2, 116.5, 114.5, 104.9, 99.9, 76.1, 74.0, 70.1, 60.8, 60.8, 55.3, 54.1, 49.3, 45.0, 29.1, 26.3, 25.2, 25.0, 21.0. HRMS (ESI), *m/z* calcd. for $C_{31}H_{39}N_5NaO_8$ ($[M+Na]^+$) 632.2691, found: 632.2689.

4.7.11. 10-(6-(4-((4-O-(β-d-galactopyranosyl)-β-d-glucopyranosyl) methyl) -1H-1,2,3-triazol-1-yl)hexyl)-2-methoxyacridin-9(10H)-one (6k)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -78.2 (0.5, MeOH). m.p. 236–238 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.39 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.77–7.35 (m, 2H), 7.59 (dd, J = 12.0, 9.6 Hz, 2H), 7.39 (dd, J = 9.6, 3.0 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 4.96 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.50–4.35 (m, 4H), 4.31 (t, J = 7.8 Hz, 2H), 3.94 (d, J = 11.4 Hz, 1H), 3.88 (s, 3H), 3.86–3.83 (m, 2H), 3.80 (dd, J = 11.4, 7.2 Hz, 1H), 3.72 (dd, J = 11.4, 4.2 Hz, 1H), 3.64–3.56 (m, 3H), 3.55–3.49 (m, 2H), 3.44 (d, J = 9.6 Hz, 1H), 3.32–3.29 (m, 1H), 2.00–1.84 (m, 2H), 1.83–1.70 (m, 2H), 1.54–1.49 (m, 2H), 1.46–1.32 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.8, 155.9, 145.6, 142.4, 137.8, 135.3, 128.1, 126.2, 125.3, 123.5, 122.3, 122.1, 118.5, 116.4, 106.8, 105.1, 103.4, 80.5, 77.0, 76.5, 76.3, 74.8, 74.6, 72.5, 70.3, 63.1, 62.5, 61.9, 56.0, 51.2, 46.9, 31.1, 28.2, 27.1, 26.9. HRMS (ESI), *m/z* calcd. for $C_{35}H_{46}N_4N_aO_{13}$ ($[M+Na]^+$) 753.2954, found: 753.2933.

4.7.12. 10-(6-(4-((β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl) hexyl)-2-methoxyacridin-9(10H)-one (6l)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -20.8 (0.5, MeOH). m.p. 227–229 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.40 (d, J = 7.8 Hz, 1H), 8.01 (s, 1H), 7.78 (d, J = 3.0 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.61 (dd, J = 11.4, 9.0 Hz, 2H), 7.39 (dd, J = 9.6, 3.0 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 4.85 (d, J = 3.6 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.42 (t, J = 7.2 Hz, 2H), 4.33 (t, J = 8.4 Hz, 2H), 3.89 (s, 3H), 3.83–3.81 (m, 2H), 3.78–3.76 (m, 1H), 3.70 (dd, J = 11.4, 4.8 Hz, 1H), 3.59 (t, J = 3.0 Hz, 1H), 1.98–1.87 (m, 2H), 1.86–1.71 (m, 2H), 1.64–1.48 (m, 2H), 1.47–1.35 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.8, 156.0, 145.4, 142.4, 137.9, 135.3, 128.1, 126.2, 125.2, 123.6, 122.3, 122.2, 118.5, 116.5, 106.8, 101.6, 72.4, 70.6, 68.0, 65.1, 61.7, 56.0, 51.2, 46.9, 31.2, 28.3, 27.2, 26.9. HRMS (ESI), *m/z* calcd. for $C_{28}H_{35}N_4O_7$ ($[M+H]^+$) 539.2500, found: 539.2507.

4.7.13. 10-(3-(4-((β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) propyl)acridin-9(10H)-one (6 m)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -29.8 (0.5, MeOH). m.p. 235–236 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.41 (d, J = 7.8 Hz, 2H), 8.12 (s, 1H), 7.80 (t, J = 7.8 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 5.02 (d, J = 12.0 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.70 (t, J = 5.4 Hz, 2H), 4.55 (t, J = 7.2 Hz, 2H), 4.43 (d, J = 7.2 Hz, 1H), 3.90 (d, J = 12.0 Hz, 1H), 3.67 (dd, J = 11.4, 5.4 Hz, 1H), 3.37–3.32 (m, 2H), 3.29–3.23 (m, 2H), 2.54–2.49 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 179.8, 146.1, 143.0, 135.9, 128.3, 126.0, 123.1, 122.8, 116.3, 103.8, 78.1, 78.0, 75.1, 71.7, 63.1, 62.8, 48.7, 44.2, 28.4. HRMS (ESI), *m/z* calcd. for $C_{25}H_{28}N_4NaO_7$ ($[M+Na]^+$) 519.1850, found: 519.1845.

4.7.14. 10-(3-(4-((β-d-galactopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) propyl)acridin-9(10H)-one (6n)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -31.3 (0.5, MeOH). m.p. 240–244 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 (dd, J = 8.0, 1.6 Hz, 2H), 8.11 (s, 1H), 7.80 (m, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 5.03 (d, J = 12.4 Hz, 1H), 4.84 (d, J = 12.4 Hz, 1H), 4.69 (t, J = 6.4 Hz, 2H), 4.53 (t, J = 8.0 Hz, 2H), 4.38 (d, J = 8.0 Hz, 1H), 3.90–3.69 (m, 3H), 3.63–3.53 (m, 2H), 3.47 (dd, J = 9.6, 3.6 Hz, 1H), 2.75–2.25 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 178.3, 144.8, 141.6, 134.5, 126.9, 124.6, 121.7, 121.4, 114.9, 103.0, 75.5, 73.6, 71.1, 69.0, 61.7, 61.3, 47.3, 42.8, 27.0. HRMS (ESI), *m/z* calcd. for $C_{25}H_{28}N_4NaO_7$ ($[M+Na]^+$) 519.1850, found: 519.1840.

4.7.15. 10-(3-(4-((β-d-mannopyranosyl)methyl)-1H-1,2,3-triazol-1-yl) propyl)acridin-9(10H)-one (6°)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ +33.8 (0.5, MeOH). m.p. 219–220 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (dd, J = 8.0, 1.6 Hz, 2H), 8.11 (s, 1H), 7.77 (m, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.37–7.23 (m, 2H), 4.90 (d, J = 1.6 Hz, 1H), 4.85 (d, J = 12.0 Hz, 1H), 4.74–4.65 (m, 3H), 4.51 (t, J = 8.4 Hz, 2H), 3.88 (dd, J = 11.6, 1.6 Hz, 1H), 3.82 (dd, J = 3.2, 1.6 Hz, 1H), 3.77–3.67 (m, 2H), 3.63–3.61 (m, 2H), 2.65–2.32 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 179.6, 145.6, 142.9, 135.8, 128.2, 126.0, 123.0, 122.8, 116.2, 100.9, 75.1, 72.5, 72.0, 68.7, 63.0, 60.7, 48.7, 44.2, 28.3. HRMS (ESI), *m/z* calcd. for $C_{25}H_{28}N_4NaO_7$ ($[M+Na]^+$) 519.1850, found: 519.1843.

4.7.16. 10-(3-(4-((2-Acetamido-2-deoxy-β-d-glucopyranosyl)methyl)-1H-1,2,3-triazol-1-yl)propyl)acridin-9(10H)-one (6p)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -58.8 (0.5, MeOH). m.p. 249–252 °C. ^{1}H NMR (600 MHz, DMSO:$CDCl_3$ = 20:1) δ 8.35 (dd, J = 7.8, 1.8 Hz, 2H), 8.12 (s, 1H), 7.82 (m, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 9.0 Hz, 1H), 7.34 (t, J = 7.2 Hz, 2H), 4.98 (br s, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.68 (t, J = 7.2 Hz, 2H), 4.65 (d, J = 12.0 Hz, 1H), 4.55 (dd, J = 9.6, 7.2 Hz, 2H), 4.41 (d, J = 8.4 Hz, 1H), 3.72 (dd, J = 11.4, 1.8 Hz, 1H), 3.48–3.41 (m, 3H), 3.28 (dd, J = 10.2, 8.4 Hz, 2H), 3.14–3.11 (m, 1H), 3.10–3.03 (t, J = 9.0, 1H), 2.43–2.32 (m, 2H), 1.73 (s, 3H). ^{13}C NMR (150 MHz, DMSO:$CDCl_3$ = 20:1) δ 177.0, 169.5, 144.6, 141.9, 134.8, 127.3, 124.8, 122.1, 121.9, 116.0, 100.8, 77.6, 74.7, 71.1, 61.8, 61.6, 55.8, 47.2, 43.2, 27.8, 23.5. HRMS (ESI), *m/z* calcd. for $C_{27}H_{31}N_5NaO_7$ ($[M+Na]^+$) 560.2116, found: 560.2113.

4.7.17. 10-(3-(4-((4-O-(β-d-galactopyranosyl)-β-d-glucopyranosyl) methyl)-1H-1,2,3-triazol-1-yl)propyl)acridin-9(10H)-one (6q)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -35.6 (0.5, MeOH). m.p. 239–242 °C. ^{1}H NMR (600 MHz, CD_3OD) δ 8.43 (d, J = 7.8 Hz, 2H), 8.11 (s, 1H), 7.81 (t, J = 7.2 Hz, 2H), 7.61 (d, J = 9.0 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 5.01 (d, J = 12.0 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.70 (t, J = 6.0 Hz, 2H), 4.56 (t, J = 7.8 Hz, 2H), 4.47 (d, J = 7.8 Hz, 1H), 4.35 (d, J = 7.2 Hz, 1H), 3.94 (d, J = 12.0 Hz, 1H), 3.90–3.73 (m, 3H), 3.69 (d, J = 11.4 Hz, 1H), 3.63–3.41 (m, 6H), 3.33–3.31 (m, 1H), 2.57–2.48 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 179.4, 145.4, 142.8, 135.5, 128.0, 125.1, 122.7, 122.4, 116.4, 104.9, 103.2, 80.3, 76.9, 76.3, 76.1, 74.6, 74.4 72.3, 70.1, 62.9, 62.3, 61.7, 51.0, 46.6, 27.9. HRMS (ESI), *m/z* calcd. for $C_{31}H_{38}N_4NaO_{12}$ ($[M+Na]^+$) 681.2378, found: 681.2370.

4.7.18. 10-(3-(4-((β-d-ribofuranosyl)methyl)-1H-1,2,3-triazol-1-yl) propyl)acridin-9(10H)-one (6r)

This product was obtained as yellow foam solid in quantitative yield. $[\alpha]_D^{25}$ -19.9 (0.5, MeOH). m.p. 218–220 °C. ^{1}H NMR (600 MHz, CD_3OD:$CDCl_3$ = 4:1) δ 8.47 (d, J = 7.8 Hz, 2H), 8.03 (s, 1H), 7.81 (t, J = 7.8 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 4.89–4.85 (m, 2H), 4.71–4.68 (m, 3H), 4.62 (t, J = 8.4 Hz, 2H), 3.84 (d, J = 11.4 Hz, 2H), 3.78 (s, 1H), 3.73 (dd, J = 11.4, 3.6 Hz, 1H), 3.62 (s, 1H), 2.64–2.52 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 179.8, 145.8, 143.1, 135.9, 128.4, 125.8, 123.2, 122.9, 116.4, 101.7, 72.4, 70.6, 68.1, 65.2, 61.7, 49.6, 44.3, 28.4. HRMS (ESI), *m/z* calcd. for $C_{24}H_{26}N_4NaO_6$ ($[M+Na]^+$) 489.1745, found: 489.1750.

4.8. Inhibition assays on AChE and BChE in vitro

Inhibitory activity of the synthesized compounds against AChE and BChE *in vitro* was measured using the modified Ellman's method [56]. Acetylcholinesterase (AChE, E.C. 3.1.1.7, from electric eel, Type VI-S, lyophilized powder, 500 units) and butyrylcholinesterase (BChE, E.C. 3.1.1.8, from equine serum, 1200 unit) were purchased from Sigma-Aldrich. 5,5′-Dithiobis-(2-nitrobenzoic acid) (DTNB) and acetylthiocholine iodide (ATCI) were purchased from J&K. The compounds were dissolved in DMSO and diluted in phosphate-buffered solution (0.1 M, pH 7.4) to provide a final concentration range. To determine the IC_{50} value, five different concentrations of each compound were used to obtain enzyme activities between 20% and 80% of the control.

The analysis was run in 96-well plates, each well was added 50 μL phosphate-buffered, 25 μL different concentration of the tested compounds, 25 μL enzyme (final concentration 0.2 U/mL in buffer), 50 μL DTNB (3 mM in buffer) successively. They were preincubated for 5 min at room temperature, then 50 μL ATCI solution (3 mM in buffer) was added. The hydrolysis of acetylthiocholine catalyzed by AChE was monitored by the formation of the yellow 5-thio-2-nitrobenzoate anion. The absorbance change was measured at 405 nm. A control experiment was performed under the same conditions without inhibitor. Each experiment was done in triplicate. IC_{50} values were calculated as the concentration of compound with 50% inhibitory activity.

The described method was also used for BChE inhibition assay.

4.9. Kinetic studies of enzyme inhibition

The mechanism studies of the BChE inhibition was performed with the same test conditions through the modified Ellman's method and

determined by plotting Lineweaver-Burk curves [19]. Four different concentrations of **6f** (0, 5, 10 and 20 μM) and six different concentrations of butyrylcholine iodide (18.75, 37.5, 75, 150, 300, and 600 μM) were used as inhibitor and substrate, respectively. Correspondingly, a secondary plot was obtained using the plot of slope versus inhibitor concentration of **6f**, Ki was calculated as the intercept of the negative X-axis.

4.10. Cytotoxicity testing

The cell of SH-SY5Y neuroblastoma, HepG2 were selected for the *in vitro* cytotoxicity study using the MTT methods. The cells were seeded in 96-well plates at the density of 4000 cells per well. These cells were incubated at 37 °C in 100 μL DMEM culture medium containing 5% CO_2 for 24 h to allow cells adherence. Then the solutions of the synthesized compounds at 50 and 100 μM were prepared and added, the cells were incubated at 37 °C and 5% CO_2 atmosphere for another 24 h. Following the culture media were replaced with 100 μL fresh DMEM media containing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; 5 mg/mL) 20 μL and incubated for additional 4 h. Then the MTT solution was removed, and 100 μL of DMSO was added to dissolve the formazan crystals. The plate was shaken for 10 min to fully dissolve formazan. The absorbance was measured at a wavelength of 570 nm. Cells cultured with culture media were selected as controls, and their viabilities were defined as 100%. And the relative cell viability (%) was expressed as a percentage relative to the untreated control cells. DOX was used as a positive control.

4.11. Neuroprotective effect

The SH-SY5Y neuroblastoma cells and oxidative agent H_2O_2 were used as *in vitro* model to assess neuroprotective effect [59]. SH-SY5Y neuroblastoma cells were incubated with compounds **6a**, **6b**, **6f** and **5t** (50 μM) for 4 h before treatment with H_2O_2 (5%). Cell viability was measured after 24 h using MTT method described above. Hydrogen peroxide was used as positive control.

4.12. Log P

The log P values of the compound **6a**, **6b**, **6f** and **5t** were calculated using the ChemDraw Ultra 14.0 [61].

Declaration of competing interest

No potential conflict of interest was reported by the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2020.107977.

References

[1] M. Goedert, M.G. Spillantini, A century of Alzheimer's disease, Science 314 (2006) 777–781, https://doi.org/10.1126/science.1132814.
[2] Alzheimer's association, Alzheimer's disease facts and figures, Alzheimers Dement 13 (2017) 325–373, https://doi.org/10.1016/j.jalz.2017.02.001 2017.
[3] R. Purgatorio, M. Candia, M. Catto, A. Carrieri, L. Pisani, A. Palma, M. Toma, O.A. Ivanova, L.G. Voskressensky, C.D. Altomare, Investigating 1,2,3,4,5,6-hexahydroazepino[4,3-*b*] indole as scaffold of butyrylcholinesterase-selective inhibitors with additional neuroprotective activities for Alzheimer's disease, Eur. J. Med. Chem. 177 (2019) 414–424, https://doi.org/10.1016/j.ejmech.2019.05.062.
[4] Y. Huang, L. Mucke, Alzheimer mechanisms and therapeutic strategies, Cell 148 (2012) 1204–1222, https://doi.org/10.1016/j.cell.2012.02.040.
[5] J.T. Coyle, D.L. Price, M.R. DeLong, Alzheimer's disease: a disorder of cortical cholinergic innervation, Science 219 (1983) 1184–1190, https://doi.org/10.1126/science.6338589.
[6] E.J. Mufson, S.E. Counts, S.E. Perez, S.D. Ginsberg, Cholinergic system during the progression of Alzheimer's disease: therapeutic implications, Expert Rev. Neurother. 8 (2008) 1703–1718, https://doi.org/10.1586/14737175.8.11.1703.
[7] A.V. Terry, J.J. Buccafusco, The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development, J. Pharmacol. Exp. Therapeut. 306 (2003) 821–827, https://doi.org/10.1124/jpet.102.041616.
[8] R.T. Bartus, R.L. Dean 3rd, B. Beer, A.S. Lippa, The cholinergic hypothesis of geriatric memory dysfunction, Science 217 (1982) 408–414, https://doi.org/10.1126/science.7046051.
[9] L.S. Schneider, A critical review of cholinesterase inhibitors as a treatment modality in Alzheimer's disease, Dialogues Clin. Neurosci. 2 (2000) 111–128 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181592/.
[10] J.T. Brewster, S. Dell'Acqua, D.Q. Thach, J.L. Sessler, Classics in chemical neuroscience: donepezil, ACS Chem. Neurosci. 10 (2019) 155–167, https://doi.org/10.1021/acschemneuro.8b00517.
[11] H. Sugimoto, Y. Yamanishi, Y. Iimura, Y. Kawakami, Donepezil hydrochloride (E2020) and other acetylcholinesterase inhibitors, Curr. Med. Chem. 7 (2000) 303–339, https://doi.org/10.2174/0929867003375191.
[12] V. Zarotsky, J.J. Sramek, N.R. Cutler, Galantamine hydrobromide: an agent for Alzheimer's disease, Am. J. Health Syst. Pharm. 60 (2003) 446–452, https://doi.org/10.1093/ajhp/60.5.446.
[13] M.W. Jann, Rivastigmine, a new-generation cholinesterase inhibitor for the treatment of Alzheimer's disease, Pharmacotherapy 20 (2000) 1–12, https://doi.org/10.1592/phco.20.1.1.34664.
[14] S. Darvesh, D.A. Hopkins, C. Geula, Neurobiology of butyrylcholinesterase, Nat. Rev. Neurosci. 4 (2003) 131–138, https://doi.org/10.1038/nrn1035.
[15] Q. Li, H. Yang, Y. Chen, H. Sun, Recent progress in the identification of selective butyrylcholinesterase inhibitors for Alzheimer's disease, Eur. J. Med. Chem. 132 (2017) 294–309, https://doi.org/10.1016/j.ejmech.2017.03.062.
[16] O. Lockridge, Review of human butyrylcholinesterase structure, function, genetic variants, history of use in the clinic, and potential therapeutic uses, Pharmacol. Ther. 148 (2015) 34–46, https://doi.org/10.1016/j.pharmthera.2014.11.011.
[17] A. Tasker, E.K. Perry, C.G. Ballard, Butyrylcholinesterase: impact on symptoms and progression of cognitive impairment, Expert Rev. Neurother. 5 (2005) 101–106, https://doi.org/10.1586/14737175.5.1.101.
[18] I. Łozińska, A. Świerczyńska, Z. Molęda, A.M. Hartman, A.K.H. Hirsch, Z. Czarnocki, Donepezil-melatonin hybrids as butyrylcholinesterase inhibitors: improving binding affinity through varying mode of linking fragments, Arch. Pharm. 351 (2018) e1800194, , https://doi.org/10.1002/ardp.201800194.
[19] G.L. Qiu, S.S. He, S.C. Chen, B. Li, H.H. Wu, J. Zhang, W.J. Tang, Design, synthesis and biological evaluation of tricyclic pyrazolo[1,5-*c*][1,3]benzoxazin-5(5*H*)-one scaffolds as selective BuChE inhibitors, J. Enzym. Inhib. Med. Chem. 33 (2018) 1506–1515, https://doi.org/10.1080/14756366.2018.1488696.
[20] A. Bosak, A. Ramić, T. Šmidlehner, T. Hrenar, I. Primožič, Z. Kovarik, Design and evaluation of selective butyrylcholinesterase inhibitors based on Cinchona alkaloid scaffold, PloS One 13 (2018) e0205193, , https://doi.org/10.1371/journal.pone.0205193.
[21] G. Wu, Y. Gao, D. Kang, B. Huang, Z. Huo, H. Liu, V. Poongavanam, P. Zhan, X. Liu, Design, synthesis and biological evaluation of tacrine-1,2,3-triazole derivatives as potent cholinesterase inhibitors, Medchemcomm 9 (2017) 149–159, https://doi.org/10.1039/C7MD00457E.
[22] P. Szymański, M. Markowicz, E. Mikiciuk-Olasik, Synthesis and biological activity of derivatives of tetrahydroacridine as acetylcholinesterase inhibitors, Bioorg. Chem. 39 (2011) 138–142, https://doi.org/10.1016/j.bioorg.2011.05.001.
[23] V. Tumiatti, A. Minarini, M.L. Bolognesi, A. Milelli, M. Rosini, C. Melchiorre, Tacrine derivatives and Alzheimer's disease, Curr. Med. Chem. 17 (2010) 1825–1838, https://doi.org/10.2174/092986710791111206.
[24] D. Cao, C. Gao, H. Meierd, A facile synthesis of homotriptycenes from anthranol derivatives, Synlett 20 (2005) 3166–3168, https://doi.org/10.1055/s-2005-921929.
[25] Y. Liu, L. Zou, L. Ma, W.H. Chen, B. Wang, Z.L. Xu, Synthesis and pharmacological activities of xanthone derivatives as alpha-glucosidase inhibitors, Bioorg. Med. Chem. 14 (2006) 5683–5690, https://doi.org/10.1016/j.bmc.2006.04.014.
[26] M. Murahari, P.S. Kharkar, N. Lonikar, Y.C. Mayur, Design, synthesis, biological evaluation, molecular docking and QSAR studies of 2,4-dimethylacridones as anticancer agents, Eur. J. Med. Chem. 130 (2017) 154–170, https://doi.org/10.1016/j.ejmech.2017.02.022.
[27] O.O. Fadeyi, S.T. Adamson, E.L. Myles, C.O. Okoro, Novel fluorinated acridone derivatives. Part 1: synthesis and evaluation as potential anticancer agents, Bioorg. Med. Chem. Lett 18 (2008) 4172–4176, https://doi.org/10.1016/j.bmcl.2008.05.078.
[28] B. Zhang, N. Wang, C. Zhang, C. Gao, W. Zhang, K. Chen, W. Wu, Y. Chen, C. Tan, F. Liu, Y. Jiang, Novel multi-substituted benzyl acridone derivatives as survivin inhibitors for hepatocellular carcinoma treatment, Eur. J. Med. Chem. 129 (2017)

337–348, https://doi.org/10.1016/j.ejmech.2017.02.027.
[29] J.X. Kelly, M.J. Smilkstein, R. Brun, S. Wittlin, R.A. Cooper, K.D. Lane, A. Janowsky, R.A. Johnson, R.A. Dodean, R. Winter, D.J. Hinrichs, M.K. Riscoe, Discovery of dual function acridones as a new antimalarial chemotype, Nature 459 (2009) 270–273, https://doi.org/10.1038/nature07937.
[30] R.W. Winter, J.X. Kelly, M.J. Smilkstein, R. Dodean, G.C. Bagby, R.K. Rathbun, J.I. Levin, D. Hinrichs, M.K. Riscoe, Evaluation and lead optimization of anti-malarial acridones, Exp. Parasitol. 114 (2006) 47–56, https://doi.org/10.1016/j.exppara.2006.03.014.
[31] V.N. Wouatsa, L. Misra, S. Kumar, O. Prakash, F. Khan, F. Tchoumbougnang, R.K. Venkatesh, Aromatase and glycosyl transferase inhibiting acridone alkaloids from fruits of Cameroonian Zanthoxylum species, Chem. Cent. J. 7 (2013) 125 http://journal.chemistrycentral.com/content/7/1/125.
[32] Y.Y. Yang, W. Yang, W.J. Zuo, Y.B. Zeng, S.B. Liu, W.L. Mei, H.F. Dai, Two new acridone alkaloids from the branch of Atalantia buxifolia and their biological activity, J. Asian Nat. Prod. Res. 15 (2013) 899–904, https://doi.org/10.1080/10286020.2013.803073.
[33] T.S. Wahyuni, A. Widyawaruyanti, M.I. Lusida, A. Fuad, Soetjipto, H. Fuchino, N. Kawahara, Y. Hayashi, C. Aoki, H. Hotta, Inhibition of hepatitis C virus replication by chalepin and pseudane IX isolated from Ruta angustifolia leaves, Fitoterapia 99 (2014) 276–283, https://doi.org/10.1016/j.fitote.2014.10.011.
[34] L.R. Daghigh, M. Pordel, A. Davoodnia, M. Jajarmi, Synthesis, antiviral, and cytotoxic investigation of imidazo[4,5-*a*]acridones, Med. Chem. Res. 24 (2015) 3912–3919, https://doi.org/10.1007/s00044-015-1438-1.
[35] Y.C. Mayur, Zaheeruddin, G.J. Peters, C. Lemos, I. Kathmann, V.V. Prasad, Synthesis of 2-fluoro N(10)-substituted acridones and their cytotoxicity studies in sensitive and resistant cancer cell lines and their DNA intercalation studies, Arch. Pharm. 342 (2009) 640–650, https://doi.org/10.1002/ardp.200900046.
[36] V.V. Rajendra Prasad, J. Venkat Rao, R.S. Giri, N.K. Sathish, S.M. Shanta Kumar, Y.C. Mayur, Chloro acridone derivatives as cytotoxic agents active on multidrug-resistant cell lines and their duplex DNA complex studies by electrospray ionization mass spectrometry, Chem. Biol. Interact. 176 (2008) 212–219, https://doi.org/10.1016/j.cbi.2008.06.007.
[37] P. Singh, J. Kaur, P. Kaur, S. Kaur, Search for MDR modulators: design, syntheses and evaluations of N-substituted acridones for interactions with p-glycoprotein and Mg^{2+}, Bioorg. Med. Chem. 17 (2009) 2423–2427, https://doi.org/10.1016/j.bmc.2009.02.002.
[38] M. Parveen, A. Aslam, S.A. Nami, A.M. Malla, M. Alam, D.U. Lee, S. Rehman, P.S. Silva, M.R. Silva, Potent acetylcholinesterase inhibitors: synthesis, biological assay and docking study of nitro acridone derivatives, J. Photochem. Photobiol., B 161 (2016) 304–311, https://doi.org/10.1016/j.jphotobiol.2016.05.028.
[39] M. Mohammadi-Khanaposhtani, M. Saeedi, N.S. Zafarghandi, M. Mahdavi, R. Sabourian, E.K. Razkenari, H. Alinezhad, M. Khanavi, A. Foroumadi, A. Shafiee, 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. 92 (2015) 799–806, https://doi.org/10.1016/j.ejmech.2015.01.044.
[40] M. Mohammadi-Khanaposhtani, M. Mahdavi, M. Saeedi, R. Sabourian, M. Safavi, M. Khanavi, A. Foroumadi, A. Shafiee, 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. 86 (2015) 1425–1432, https://doi.org/10.1111/cbdd.12609.
[41] X.P. He, Y.L. Zeng, Y. Zang, J. Li, R.A. Field, G.R. Chen, Carbohydrate CuAAC click chemistry for therapy and diagnosis, Carbohydr. Res. 429 (2016) 1–22, https://doi.org/10.1016/j.carres.2016.03.022.
[42] A.A. Belik, K.M. Tabakmakher, A.S. Silchenko, T.N. Makarieva, C.V. Minh, S.P. Ermakova, T.N. Zvyagintseva, Sulfated steroids of Halichondriidae family sponges–natural inhibitors of polysaccharide-degrading enzymes of bacterium Formosa algae, inhabiting brown alga Fucus evanescens, Carbohydr. Res. 484 (2019) 107776, https://doi.org/10.1016/j.carres.2019.107776.
[43] J.L. Sacoman, L.N. Badish, T.D. Sharkey, R.I. Hollingsworth, The metabolic and biochemical impact of glucose 6-sulfonate (sulfoquinovose), a dietary sugar, on carbohydrate metabolism, Carbohydr. Res. 362 (2012) 21–29, https://doi.org/10.1016/j.carres.2012.09.014.
[44] U.M. Seo, D.H. Nguyen, B.T. Zhao, B.S. Min, M.H. Woo, Flavanonol glucosides from the aerial parts of Agrimonia pilosa Ledeb. and their acetylcholinesterase inhibitory effects, Carbohydr. Res. 445 (2017) 75–79, https://doi.org/10.1016/j.carres.2017.01.007.
[45] E.U. Mughal, A. Javid, A. Sadiq, S. Murtaza, M.N. Zafar, B.A. Khan, S.H. Sumrra, M.N. Tahir, Kanwal, K.M. Khan, Synthesis, structure-activity relationship and molecular docking studies of 3-O-flavonol glycosides as cholinesterase inhibitors, Bioorg. Med. Chem. 26 (2018) 3696–3706, https://doi.org/10.1016/j.bmc.2018.05.050.
[46] J.P.B. Lopes, L. Silva, G. da Costa Franarin, M. Antonio Ceschi, D. Seibert Lüdtke, R. Ferreira Dantas, C.M.C. de Salles, F. Paes Silva- Jr., M. Roberto Senger, I. Alvim Guedes, L. Emmanuel Dardenne, Design, synthesis, cholinesterase inhibition and molecular modelling study of novel tacrine hybrids with carbohydrate derivatives, Bioorg. Med. Chem. 26 (2018) 5566–5577, https://doi.org/10.1016/j.bmc.2018.10.003.
[47] J.A. Figueiredo, M.I. Ismael, J.M. Pinheiro, A.M. Silva, J. Justino, F.V. Silva, M. Goulart, D. Mira, M.E. Araújo, R. Campoy, A.P. Rauter, Facile synthesis of oxo-/thioxopyrimidines and tetrazoles C-C linked to sugars as novel non-toxic anti-oxidant acetylcholinesterase inhibitors, Carbohydr. Res. 347 (2012) 47–54, https://doi.org/10.1016/j.carres.2011.11.006.
[48] C. Galdeano, N. Coquelle, M. Cieslikiewicz-Bouet, M. Bartolini, B. Pérez, M.V. Clos, I. Silman, L. Jean, J.P. Colletier, P.Y. Renard, D. Muñoz-Torrero, Increasing Polarity in Tacrine and Huprine Derivatives: Potent Anticholinesterase Agents for the Treatment of Myasthenia Gravis, Molecules vol. 23, (2018), https://doi.org/10.3390/molecules23030634 pii: E634.
[49] K. Chalupova, J. Korabecny, M. Bartolini, B. Monti, D. Lamba, R. Caliandro, A. Pesaresi, X. Brazzolotto, A.J. Gastellier, F. Nachon, J. Pejchal, M. Jarosova, V. Hepnarova, D. Jun, M. Hrabinova, R. Dolezal, J.Z. Karasova, M. Mzik, Z. Kristofikova, J. Misik, L. Muckova, P. Jost, O. Soukup, M. Benkova, V. Setnicka, L. Habartova, M. Chvojkova, L. Kleteckova, K. Vales, E. Mezeiova, E. Uliassi, M. Valis, E. Nepovimova, M.L. Bolognesi, K. Kuca, Novel tacrine-tryptophan hybrids: multi-target directed ligands as potential treatment for Alzheimer's disease, Eur. J. Med. Chem. 168 (2019) 491–514, https://doi.org/10.1016/j.ejmech.2019.02.021.
[50] 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, 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. 168 (2019) 58–77, https://doi.org/10.1016/j.ejmech.2018.12.063.
[51] M. Katalinić, G. Rusak, J.D. Barović, G. Šinko, D. Jelić, R. Antolović, Z. Kovarik, Structural aspects of flavonoids as inhibitors of human butyrylcholinesterase, Eur. J. Med. Chem. 45 (2010) 186–192, https://doi.org/10.1016/j.ejmech.2009.09.041.
[52] Q. Chen, B.H. Han, Prepolymerization and postpolymerization functionalization approaches to fluorescent conjugated carbazole-based glycopolymers via "click chemistry", J. Polym. Sci., Polym. Chem. Ed. 47 (2009) 2948–2957, https://doi.org/10.1002/pola.23372.
[53] H.B. Mereyala, S.R. Gurrala, A highly diastereoselective, practical synthesis of allyl, propargyl 2,3,4,6-tetra-O-acetyl-*β*-D-gluco, *β*-D-galactopyranosides and allyl, propargyl heptaacetyl-*β*-D-lactosides, Carbohydr. Res. 307 (1998) 351–354, https://doi.org/10.1016/S0008-6215(97)10104-5.
[54] R. Daly, G. Vaz, A.M. Davies, M.O. Senge, E.M. Scanlan, Synthesis and biological evaluation of a library of glycoporphyrin compounds, Chem. Eur J. 18 (2012) 14671–14679, https://doi.org/10.1002/chem.201202064.
[55] A.S. Rowan, N.I. Nicely, N. Cochrane, W.A. Wlassoff, A. Claiborne, C.J. Hamilton, Nucleoside triphosphate mimicry: a sugar triazolyl nucleoside as an ATP-competitive inhibitor of B. anthracis pantothenate kinase, Org. Biomol. Chem. 7 (2009) 4029–4036, https://doi.org/10.1039/b909729e.
[56] Y. Hari, M. Nakahara, S. Obika, Triplex-forming ability of oligonucleotides containing 1-aryl-1,2,3-triazole nucleobases linked via a two atom-length spacer, Bioorg. Med. Chem. 21 (2013) 5583–5588, https://doi.org/10.1016/j.bmc.2013.05.034.
[57] G.L. Ellman, K.D. Courtney, V. Andres, R.M. Featherstone, A new and rapid colorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol. 7 (1961) 88–95, https://doi.org/10.1016/0006-2952(61)90145-9.
[58] A. Bosak, D.M. Opsenica, G. Sinko, M. Zlatar, Z. Kovarik, Structural aspects of 4-aminoquinolines as reversible inhibitors of human acetylcholinesterase and butyrylcholinesterase, Chem. Biol. Interact. 308 (2019) 101–109, https://doi.org/10.1016/j.cbi.2019.05.024.
[59] O. Unsal-Tan, T.T. Küçükkılınç, B. Ayazgök, A. Balkan, K. Ozadali-Sari, Synthesis, molecular docking, and biological evaluation of novel 2-pyrazoline derivatives as multifunctional agents for the treatment of Alzheimer's disease, Medchemcomm 10 (2019) 1018–1026, https://doi.org/10.1039/C9MD00030E.
[60] S.N. Dighe, E. De la Mora, S. Chan, S. Kantham, G. McColl, J.A. Miles, S.K. Veliyath, B.Y. Sreenivas, Z.D. Nassar, I. Silman, J.L. Sussman, M. Weik, R.P. McGeary, M.O. Parat, X. Brazzolotto, B.P. Ross, Rivastigmine and metabolite analogues with putative Alzheimer's disease-modifying properties in a *Caenorhabditis elegans* model, Commun. Chem. 2 (2019) 35, https://doi.org/10.1038/s42004-019-0133-4.
[61] M.B. Tehrani, Z. Rezaei, M. Asadi, H. Behnammanesh, H. Nadri, F. Afsharirad, A. Moradi, B. Larijani, M. Mohammadi-Khanaposhtani, M. Mahdavi, Design, synthesis, and cholinesterase inhibition assay of coumarin-3-carboxamide-N-morpholine hybrids as new anti-Alzheimer agents, Chem. Biodivers. 16 (2019) e1900144, , https://doi.org/10.1002/cbdv.201900144.