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ORIGINAL ARTICLE

Design and synthesis of benzodiazepine-1,2,3-triazole hybrid derivatives as selective butyrylcholinesterase inhibitors

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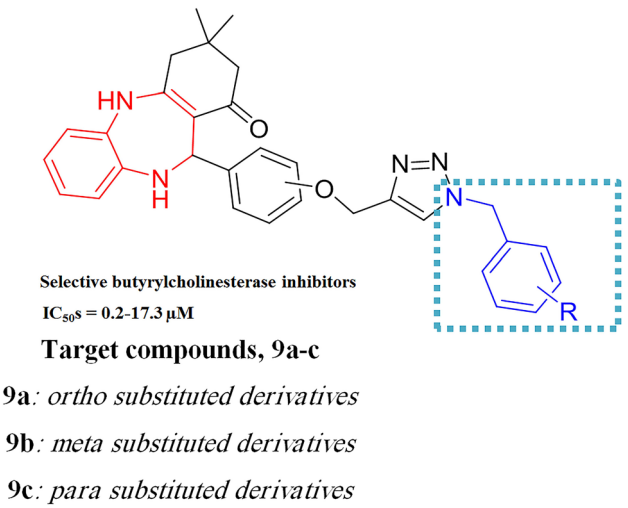
Abstract

A new series of compounds based on benzodiazepine-1,2,3-triazole were synthesized and evaluated as cholinesterase inhibitors by Ellman's method. The compounds proved to be selective inhibitors of butyrylcholinesterase (BuChE) over acetylcholinesterase. The most potent compound was 3,3-dimethyl-11-(3-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one, identified as a submicromolar inhibitor of BuChE with IC_{50} value of 0.2 µM. In addition, the amyloid-β self-aggregation evaluation studies for selected compounds showed potent inhibitory effects compared to donepezil. The docking and cell viability studies supported the potential of compound **9b-6** as significant BuChE inhibitor.

Graphic abstract



Keywords Alzheimer's disease · Benzodiazepine · 1,2,3-Triazole · Butyrylcholinesterase inhibitor · Click chemistry

Introduction

Dementia is one of the most widespread illnesses, affecting the lives of millions of people around the world [1–3]. Alzheimer's disease (AD) is a neurodegenerative, chronic, and progressive disease, associated with losses of mental capabilities in terms of memory and learning. These disabilities gradually lead to the tragic isolation of an individual

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due to the inability of communication with other people and the world. AD accounts for nearly 70% of dementia cases in people 65 years of age or older and classified as the apparent consequence of brain cells death especially pyramidal cells [4]. The tremendous impact on abilities of people with this disease has urged the needs for persistent care by family members and (un)paid caregivers along with expensive therapies. Accordingly, to both reduce economic consequences of the disease on society and increase the life expectancy in an old population, a growing budget should be applied to develop novel treatment approaches [5, 6].

There are different hypotheses about the causes of this destruction process including: protein aggregation, ROS production, oxidative stress, mitochondrial dysfunction, neuroinflammation, and cholinergic depletion. Protein aggregation is the biochemical process which led to the formation of abnormal protein within and outside of the brain cells including senile plaques and neurofibrillary tangles. The plaques come to existence because of the breakdown of the amyloid precursor protein (APP) to an insoluble β-amyloid peptide (Aβ) [7–9]. These pathological characters lead to the loss of neuronal synapses and pyramidal neurons by which the devastating effects of the disease occur [10, 11]. Oxidative stress and mitochondrial dysfunction are also increased by protein aggregation, resulting in the generation of ample reactive oxygen and nitrogen species and consequently neuronal damage.

The first proposed theory to explain AD, the cholinergic hypothesis, deals with the decline in cholinergic activity of some areas of brain which are vital in memory and cognitive activities. The main idea of this theory is based on utilizing cholinergic agonists [12] and acetylcholinesterase inhibitors (AChEIs), efficiently providing the promising improvement in cognitive functions by increasing acetylcholine level (ACh). Acetylcholine hydrolysis occurs by two cholinesterase forms, acetyl- (AChE, EC 3.1.1.7) and butyrylcholinesterase (BuChE, EC3.1.1.8). The level of AChE declines as AD progresses, so BuChE handles its function and becomes important in advanced levels of the disease [13, 14]. In recent years, the specific inhibition of BuChE, expressed in those parts of brain which are involved in cognition, has opened new horizons in the treatment of neurodegenerative disease. By considering all these facts and similarities between these enzymes in terms of amino acid sequence, overall structure, and mechanism, we can conclude that a promising approach for AD treatment could be the inhibition of ChE and thus keeping the synaptic level of ACh at its proper quantity [15]. As a result, the development of drugs capable of preventing the acetylcholine hydrolysis is a challenge which should be approached by developing new bioactive compounds as cholinesterase inhibitors.

Benzodiazepines have become widespread in the drug market, related to their effectiveness, safety, and low side effects of those molecules containing this heterocyclic core [16]. This special chemical structure has introduced unique derivatives from which a wide range of bioactivities such as anticonvulsant, antifungal, antibacterial and anti-inflammatory activities are observed [17]. On the basis of recent reports, some compounds containing benzodiazepine core exhibited anticholinesterase effects including: diazepam and cyclopenin [18, 19]. Therefore, the structure of benzodiazepine can be proposed as the scaffold for the production of bioactive compounds with anticholinesterase effects [20].

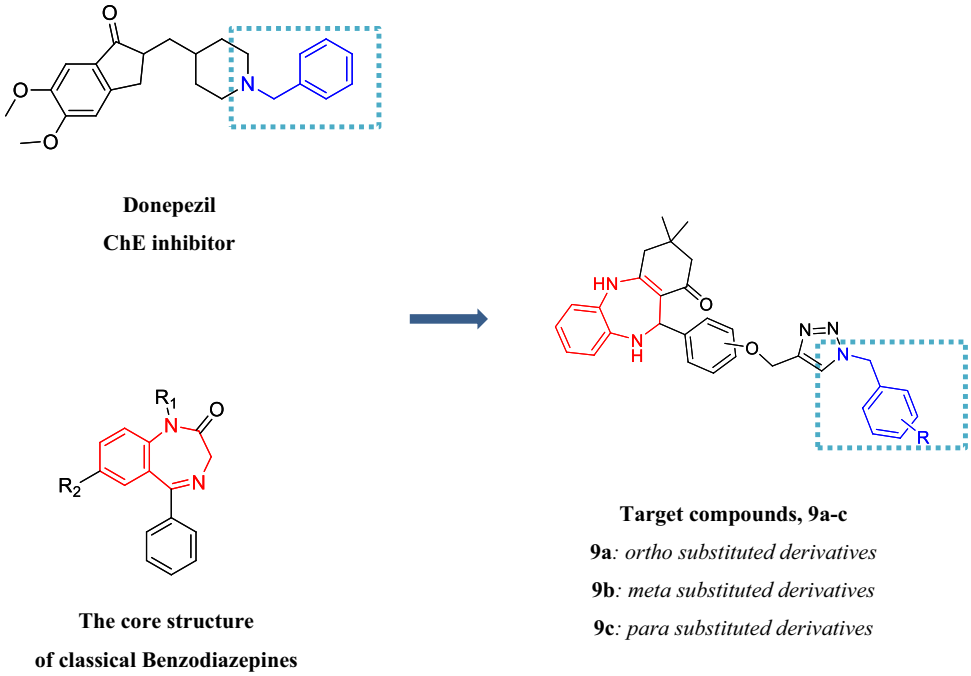
1,2,3-Triazoles are key structural motif in different areas of science from bioactive compounds to material sciences [21–23]. The presence of two H-bond acceptors, capable of forming significant interactions with the biomolecular targets through H-bonding, π–π stacking, and dipole interactions and the unique chemical stability of this core in biological environments, results in improved pharmacokinetic and toxicity properties of compounds with this core. Moreover, the highly efficient preparation method, click reaction, has confirmed the interest of organic and medicinal chemists towards the development of highly desirable and green approaches for the construction of triazole-containing molecules [24–28]. The presence of triazole ring in different systems enhanced the anti-AChE activity in various synthesized compounds [29–32]. Our look in the design strategy was focused on the structure of donepezil and our tries devoted to mimic the aromatic moiety of the donepezil with another aromatic group. Donepezil is a synthetic and reversible acetylcholinesterase inhibitor, exhibiting improvements in cognition and memory in AD patients. Based on the abovementioned points and our previous expertise in the synthesis of cholinesterase inhibitors [33–37], in this paper, we designed and synthesized some new anticholinesterase agents by hybridization of small molecules, benzodiazepine and triazole, to target pathological routes with AD [38] (Fig. 1).

Results and discussion

Chemistry

As outlined in Scheme 1, the reaction between benzene 1,2-diamine and 5,5-dimethylcyclohexane-1,3-dione (dimedone) in refluxing toluene afforded compound **3** [39, 40], which was cyclized upon the reaction with propargylated aromatic aldehydes **6a–c**. The propargylated derivatives were obtained from the reaction of differently substituted hydroxyl benzaldehydes **4a–c** and propargyl bromide in the presence of K_2CO_3 in DMF at 90 °C [41–43]. In the last step, the target compounds were prepared from the click reaction of **7a–c**, benzyl halide derivatives and sodium azide in H_2O/*t*-BuOH (Scheme 1). By utilizing different *ortho*-,

Fig. 1 Design strategy



meta- and *para*-substituted aromatic aldehydes, three series of compounds were synthesized and evaluated as cholinesterase inhibitors.

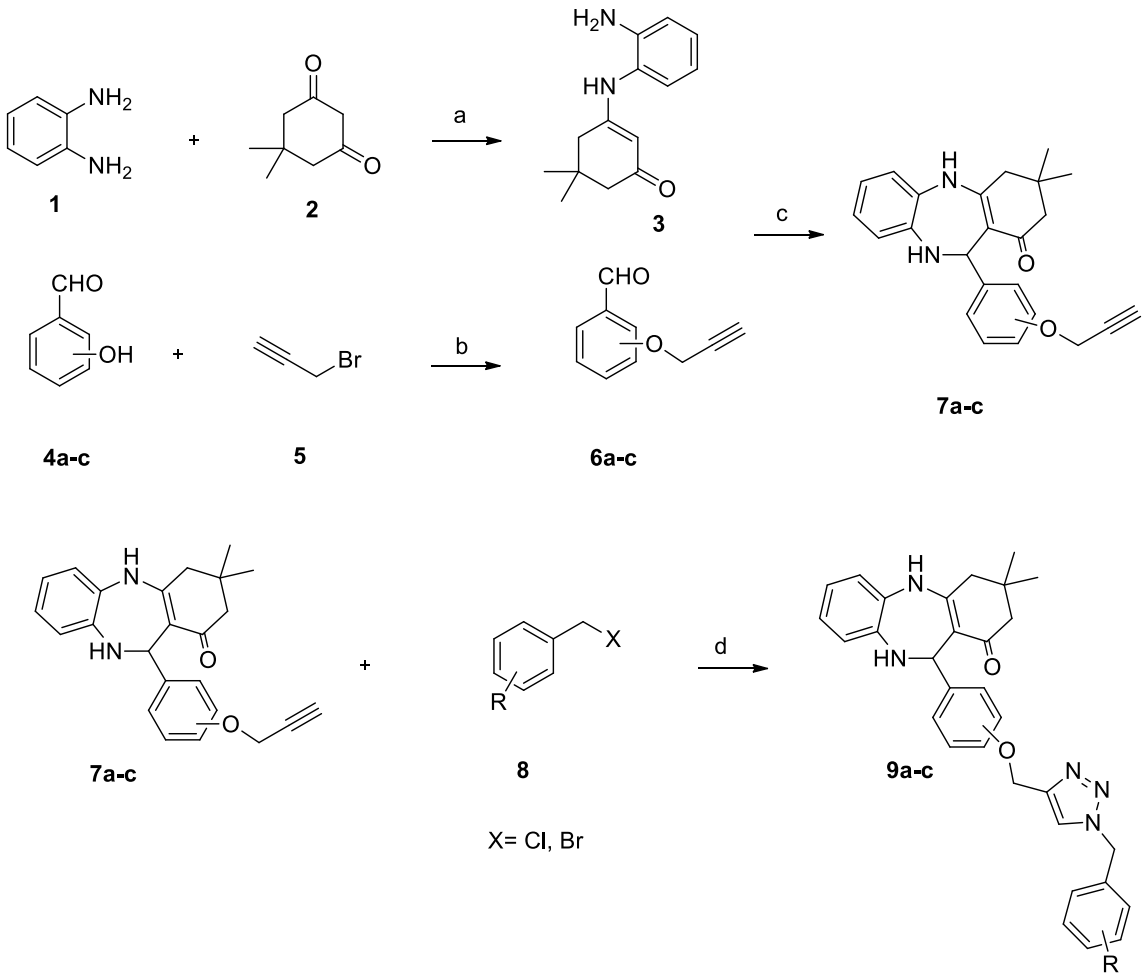
Cholinesterase activity evaluation

The activity of three series of compounds against AChE and BuChE was evaluated by modified Ellman's method, and the following results are obtained [44]. The results are shown as IC_{50s} and the percent of inhibition in Table 1. None of the target compounds is active against AChE, while most of them are potent and selective BuChE inhibitors at micromolar and sub-micro molar ranges. Among the synthesized compounds, **9a-4** and **9b-6** showed IC_{50} values of 0.4 µM and 0.2 µM, respectively, which are 17–34 times more potent than donepezil with IC_{50} value of 6.9 µM. Generally, among three series of compounds, **9a** and **9b** series showed better AChE and BuChE inhibitory effects compared to **9c**. In other words, *meta*-substituted derivatives were better butyrylcholinesterase inhibitors compared to *ortho*-substituted derivatives, except **9b-1** and **9b-3**. In all series, those derivatives containing chlorine at *ortho*-position showed better or same activities compared to fluorine-containing ones. Among different groups at *meta*-position, the presence of nitro group led to the weak or the same activities compared to fluorine-/chlorine-containing counterparts. Comparing the R groups at *para*-position revealed that the compound containing methyl group showed almost better inhibitory activity compared to other derivatives in all series. A decrease in the inhibitory activity was observed for electron-withdrawing containing compounds meaning nitro and fluorine groups at *para*-position. In *para*-substituted fluorine-, chlorine- and bromine-containing derivatives, those compounds that containing the most electronegative atom, fluorine, possessed the worst inhibitory activities. Conversely, the presence of fluorine at *meta*-position led to the better or same activities compared to chlorine-containing derivatives. Therefore, moving the fluorine atom from *ortho*-position to *meta*-position increased the activity, while the reduced activity was observed in *para*-fluorine-containing derivatives compared to *meta*-fluorine-containing analogues. The same pattern was observed by moving nitro group from *meta* to *para*-position (Table 1).

Docking studies

Docking studies were conducted to predict the binding sites and interactions of compounds **9b-3** and **9b-6** as the most potent compounds into the active site of acetylcholinesterase and butyrylcholinesterase enzymes, respectively [45, 46]. Docking studies were validated by re-docking tacrine and donepezil into the binding site. The root-mean-square distance (RMSD) of co-crystallized and re-docked ligands for tacrine and donepezil was obtained 0.62 Å and 1.12 Å, respectively, which showed high reliability of docking protocol (Fig. 2).

Considering the obtained docking results, we can conclude that these structures can be ideal inhibitors of this enzyme due to the establishment of multiple interactions with different sites of the active site of the enzyme, including the peripheral anionic site (PAS). As shown in Fig. 3, the dimethyl group of compound **9b-3** involved in the π-alkyl



Scheme 1 **a** Toluene, reflux, 7 h; **b** K_2CO_3, DMF, 90 °C, 3–4 h; **c** EtOH, acetic acid, r.t., 24 h; **d** NaN_3, H_2O/*t*-BuOH, Et_3N, r.t., 1 h; $CuSO_4{\cdot}5H_2O$, sodium ascorbate, **7a–c**, r.t., 18 h

interaction with Trp286, which is an aromatic residue of the peripheral anionic site. The π-anion interaction between Asp 74 and phenyl ring of this core stabilized this compound in the active site of AChE. 3-Fluoro-substituted benzyl ring displayed π–π stacking with the indole ring of the Trp86 and hydrogen bonds with Trp 133 and Ala 127. The nitrogen of triazole ring also made a hydrogen bond with both Ser203 and His447. The binding interaction energy of compound **9b-3** was − 6.6 kcal/mol, which stated that **9b-3** is less potent than donepezil (-8.4 kcal/mol) towards AChE inhibition.

The molecular docking of compound **9b-6** (Fig. 4) represented that the ligand was well inserted into the active site of enzyme with the best score energy (− 8.6 kcal/mol) and the oxygen atom of the OCH_2 linker in this compound established a hydrogen bonding with Ser198 and His438. The phenyl group attached to this linker involved in π–π interaction with Trp82 and π-anion interaction with negatively charged oxygen of Glu197. Moreover, 4-methyl-substituted phenyl ring established another π–π stacking interaction with Phe329 and Tyr332.

Inhibitory effects on the amyloid-$\beta_{(1-42)}$ self-aggregation

The potent compounds of each series were selected and evaluated for the determination of self-induced amyloid-β self-aggregation by thioflavin T (ThT) fluorescence assay (Table 2) [47]. Interestingly, all these compounds have significant effects on amyloid-β self-aggregation in comparison with donepezil as the reference compound. Compounds **9c-7** and **9c-9** exhibited 4–5 times superior anti-aggregation activity compared with donepezil.

Toxicity of some synthesized compounds on PC12 cells was measured according to the previous reports (Fig. 5) [48]. The PC12 cells were incubated with varying concentrations (0.01–100 μM) of the test compounds for 24 h. The results are displayed in Fig. 5, and the average of cell viability

Table 1 Cholinesterase inhibitory activities of target compounds **9a–9c** series

Compound	R	AChE Inhibition (%)[a]	IC_{50} (μM) BuChE
9a-1	2-F	30.3	1.3 ± 0.01
9a-2	2-Cl	30.9	1.3 ± 0.02
9a-3	3-CH_3	30.5	2.9 ± 0.06
9a-4	3-F	28.2	**0.4 ± 0.008**
9a-5	3-Cl	25.3	1.7 ± 0.07
9a-6	3-NO_2	25.3	5.3 ± 0.09
9a-7	4-CH_3	26.5	2.3 ± 0.07
9a-8	4-F	24.5	8.5 ± 0.2
9a-9	4-Cl	24.6	2.7 ± 0.06
9a-10	4-Br	20.8	2.2 ± 0.08
9a-11	4-NO_2	23.6	12.9 ± 0.4
9b-1	2-F	26.2	1.7 ± 0.02
9b-2	2-Cl	22.2	0.6 ± 0.007
9b-3	3-F	31.7	0.8 ± 0.003
9b-4	3-Cl	18.3	0.7 ± 0.008
9b-5	3-NO_2	31.4	0.7 ± 0.002
9b-6	4-CH_3	12.9	**0.2** ± 0.002
9b-7	4-F	29.3	1.1 ± 0.03
9b-8	4-Cl	16.7	0.6 ± 0.05
9b-9	4-Br	10.7	0.6 ± 0.08
9b-10	4-NO_2	16.7	0.9 ± 0.06
9c-1	2-F	7.1	7.5 ± 0.1
9c-2	2-Cl	14.3	1.5 ± 0.02
9c-3	3-CH_3	13.7	2.8 ± 0.03
9c-4	3-F	8.1	5.1 ± 0.09
9c-5	3-Cl	12.3	6.1 ± 0.07
9c-6	3-NO_2	16.2	9.6 ± 0.08
9c-7	4-CH_3	4.7	1.2 ± 0.02
9c-8	4-F	12.6	17.3 ± 0.2
9c-9	4-Cl	4.3	0.9 ± 0.07
9c-10	4-Br	2.1	10.8 ± 0.1
9c-11	4-NO_2	10.9	N/A
Donepezil	–	99.2	6.9 ± 0.1

The most potent compound was written in bold

[a]IC_{50} (μM) or inhibition % at 30 μM concentration. Values were the means of three replicates ± standard deviation (SD)

percentage for compounds **9b-2**, **9c-9** and donepezil was 87.2 ± 2.9, 88.5 ± 2.6, and 99.5 ± 4.7, respectively.

Conclusion

The present study described the synthesis and evaluation of benzodiazepine-triazole hybrid systems as cholinesterase inhibitors. The target compounds showed significant inhibitory activity against both BuChE and self-induced Aβ1–42 aggregation compared to donepezil. The docking results revealed the useful interactions of ligands with the active site of enzymes confirming the anticholinesterase activities of target compounds. Our studies led to the identification of the selective butyrylcholinesterase inhibitors with a potential application in the treatment of age-related neurodegenerative disorder, AD.

Materials and methods

Chemistry

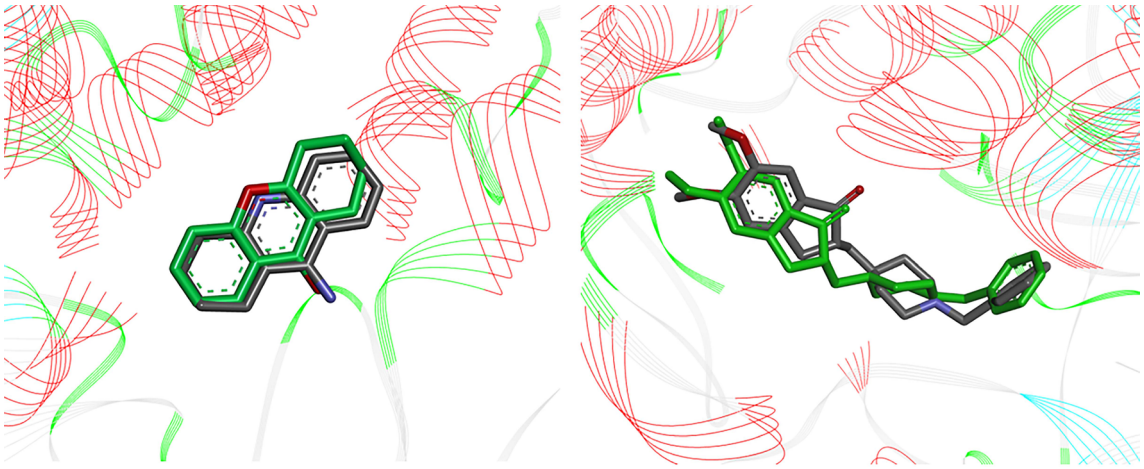
All the materials were prepared from Fluka, Sigma and Merck companies or in the laboratory. The melting points of the products were measured with a Kofler hot-stage apparatus. The nuclear magnetic resonance spectra were taken with the Bruker 500 MHz device. To record the ^1H NMR spectra and ^{13}C NMR, deuterated dimethyl sulfoxide (DMSO-d_6) and chloroform ($CDCl_3$) solvents were used and the chemical shift was measured relative to the tetramethyl silane (TMS) as standard. The IR spectra were recorded with the Nicolet FT-IR Magna 550 spectrometer. Also, the percentage of carbon, hydrogen and nitrogen elements was obtained using the LECO 600 CHN Elemental Analyzer. Agilent LC–MS6410 QQQHPLC Series 1200 (Santa Clara, USA) was used for LC-MS analysis. Positive ESI–MS mass spectra were recorded on an Agilent 6410 triple quadrupole mass spectrometer.

General procedure for the preparation of 3-((2-aminophenyl) amino)-5,5-dimethylcyclohex-2-enone

A mixture of benzene-1,2-diamine (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (1 mmol) in toluene (15 mL) was refluxed for 7 h. After this time, the mixture was allowed to come to the room temperature and the precipitate was collected and recrystallized from ethyl acetate/petroleum ether (2/8).

General procedure for the preparation of (prop-2-yn-1-yloxy) benzaldehydes; ortho-, meta- and para-substituted derivatives

A mixture of *ortho*-, *meta*- and *para*-substituted hydroxy-substituted benzaldehydes (1 mmol), propargyl bromide (1 mmol) and K_2CO_3 (1 mmol) in DMF (10 mL) was heated at 90 °C for 3–4 h. After completion, the mixture was poured into ice water (approx. 200 mL) and the resultant solid was filtered and used without further purification.



a **b**

Fig. 2 Validation of the docking methodology. **a** Superimposition of the docking best pose for tacrine (grey) with the crystallographic structure of 4BDS complexed with tacrine (green), **b** Superimposition of the docking best pose for donepezil (grey) with the crystallographic structure of 4EY7 complexed with donepezil (green). (Color figure online)

Fig. 3 interactions of the best pose of **9b-3** in the active site of AChE

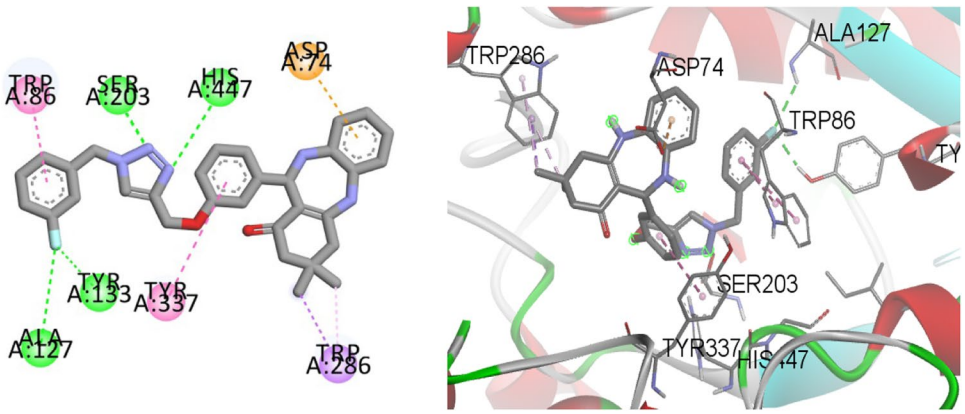


Fig. 4 interactions of the best pose of **9b-6** in the active site of BuChE

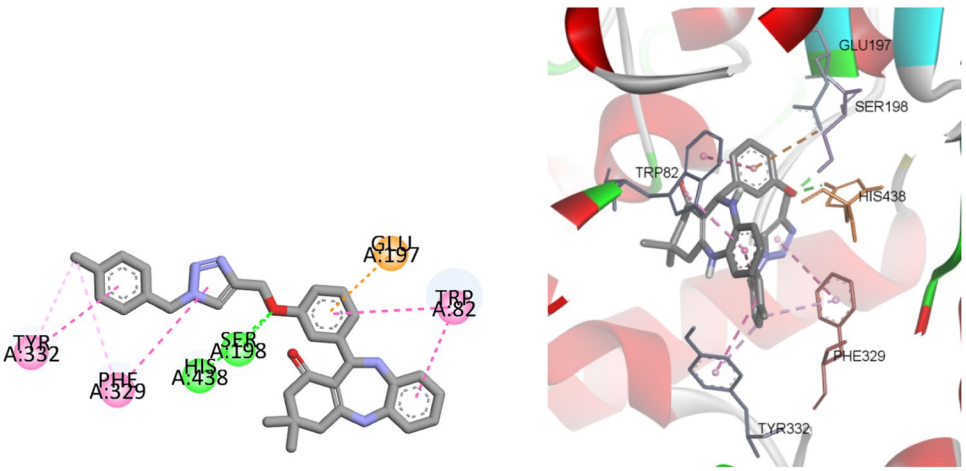


Table 2 Inhibitory effects on $A\beta_{(1-42)}$ self-aggregation

Samples	% Aggregation inhibition[a]
9a-1	55.6 ± 2.4
9a-4	52.9 ± 2.2
9b-2	47.4 ± 1.7
9b-6	49.6 ± 2.5
9c-2	63.9 ± 1.8
9c-7	72.4 ± 1.9
9c-9	68.4 ± 2.9
Donepezil	14.9 ± 2.5 (10 μM)

[a]Inhibition of self-induced $A\beta_{(1-42)}$ aggregation (10 μM) produced by the tested compound at 100 μM concentration. Values are expressed as mean ± SEM of three experiments

General procedure for the preparation of 7a–c

To a mixture of **3** (0.7 mmol) and **6a–c** (0.7 mmol) in ethanol (10 mL), 3–4 drops of glacial acetic acid was added and the mixture was stirred at room temperature for 24 h. Afterwards, the mixture was added to ice water (approx. 200 mL) and the precipitated solid was filtered and used without further purification.

General procedure for the preparation of target compounds 9a–c

A mixture of benzyl chloride/bromide derivatives **8** (0.5 mmol), Et_3N (0.5 mmol) and NaN_3 (0.5 mmol) in H_2O/*t*-BuOH (4 mL, 1:1) was stirred at room temperature for 1 h. Then, **7a–c** (0.5 mmol), sodium ascorbate (0.05 mmol) were added, followed by $CuSO_4{\cdot}5H_2O$ (0.005 mmol). The reaction was continued at room temperature for 18 h. After this time, the mixture was poured into ice water and stirred. The precipitate was collected and crystallized from ethyl acetate and petroleum ether (different ratios) to yield target compounds.

11-(2-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-1)

White solid; Yield: 0.175 g (67%); mp 201–202 °C; IR (KBr, cm^{-1}): 3299, 3239, 1596, 1535. ^1H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH**$_3$)$_2$), 1.07 (s, 3H, C(**CH**$_3$)$_2$), 2.07 (d, $J = 15.9$ Hz, 1H, H-4), 2.16 (d, $J = 15.9$ Hz, 1H, H-4), 2.61–2.66 (m, 2H, H-2), 5.20 (d, $J = 11.9$ Hz, 1H, OCH_2), 5.32–5.36 (m, 2H, H-11 and OCH_2), 5.77 (s, 2H,

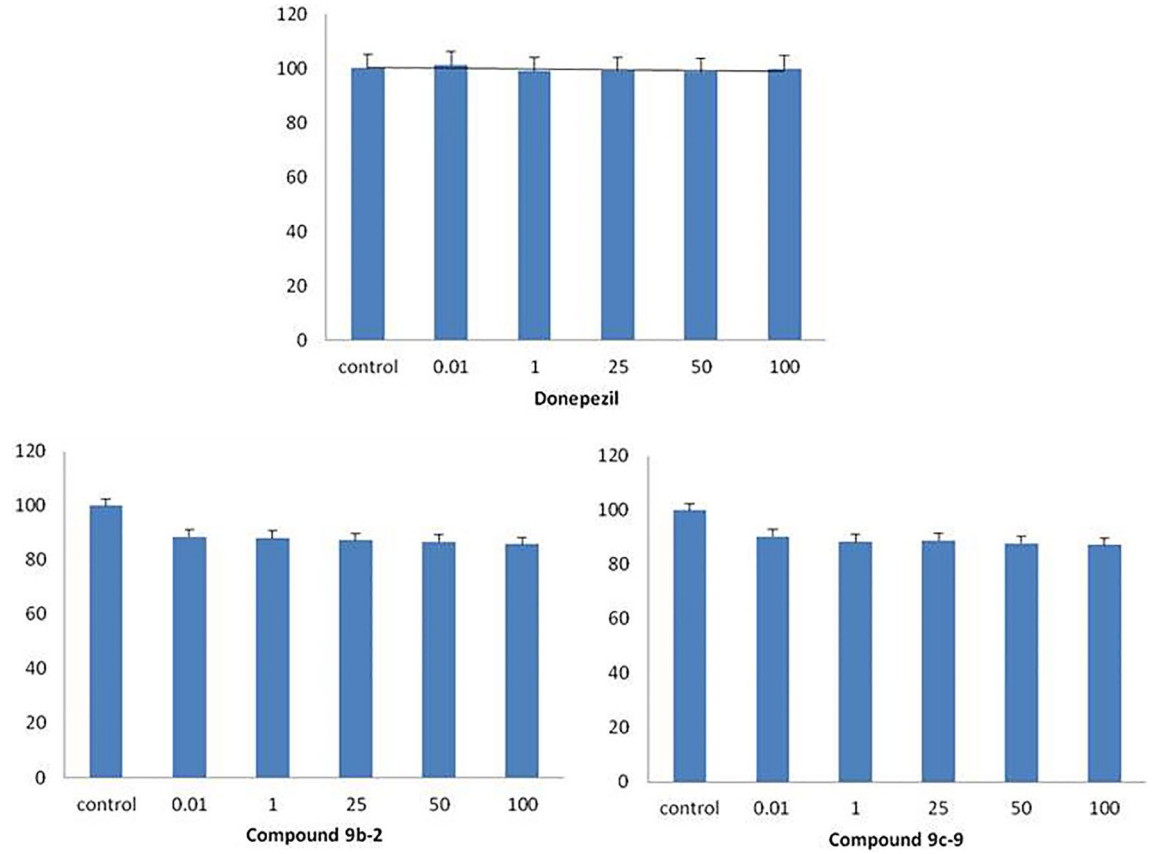


Fig. 5 Cytotoxicity in PC12 cells, MTT Assay

NCH_2), 5.89 (d, $J = 5.1$ Hz, 1H, **NH**CH), 6.46 (d, $J = 7.4$ Hz, 1H, H-9), 6.51 (t, $J = 7.0$ Hz, 1H, H-8), 6.56 (t, $J = 7.0$ Hz, 1H, H-7), 6.59–6.61 (m, 2H, H-6 and H-4′), 6.91 (d, $J = 7.6$ Hz, 1H, H-3′), 7.00–7.03 (m, 1H, H-5′), 7.07 (d, $J = 7.9$ Hz, 1H, H-6′), 7.21–7.29 (m, 2H, H-5″ and H-6″), 7.37–7.43 (m, 2H, H-3″ and H-4″), 8.44 (s, 1H, H-4, triazole), 8.83 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 32.8, 33.4, 36.9, 49.2, 52.1, 54.6, 57.5, 66.6, 113.8, 117.0, 120.8 (d, $J_{C\text{-}F} = 20.0$ Hz), 125.0, 125.2, 125.4, 127.8, 127.9, 128.0, 129.8, 130.0, 131.7, 132.9, 135.9 (d, $J_{C\text{-}F} = 3.8$ Hz), 136.0, 136.2, 136.7, 143.5, 148.4, 160.6, 161.0, 165.3 (d, $J_{C\text{-}F} = 245.2$ Hz), 197.2. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.47; H, 5.55; N, 13.05%. ESI–MS *m/z*: 524 $[M + H]^+$.

11-(2-((1-(2-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-2)

White solid; Yield: 0.175 g (65%); mp 208–209 °C; IR (KBr, cm^{-1}): 3287, 3236, 1599, 1517. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, $J = 15.9$ Hz, 1H, H-4), 2.16 (d, $J = 15.9$ Hz, 1H, H-4), 2.61–2.63 (m, 2H, H-2), 5.19 (d, $J = 11.95$ Hz, 1H, OCH_2), 5.33–5.35 (m, 2H, H-11 and OCH_2), 5.73 (s, 2H, NCH_2), 5.89 (d, $J = 5$ Hz, 1H, **NH**CH), 6.45 (d, $J = 7.5$ Hz, 1H, H-9), 6.50 (t, $J = 7.0$ Hz, 1H, H-8), 6.56 (t, $J = 7.0$ Hz, 1H, H-7), 6.59–6.61 (m, 2H, H-6 and H-4′), 6.91 (d, $J = 7.8$ Hz, 1H, H-3′), 7.00–7.03 (m, 1H, H-5′), 7.07 (d, $J = 7.9$ Hz, 1H, H-6′), 7.21–7.29 (m, 2H, H-5″ and H-6″), 7.37–7.43 (m, 2H, H-3″ and H-4″), 8.44 (s, 1H, H-4, triazole), 8.83 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.7, 28.4, 31.8, 49.5, 50.8, 52.4, 57.3, 61.5, 108.7, 112.0, 119.9, 120.1, 121.3, 122.7 (2C), 125.0, 126.6, 127.8, 128.4, 129.7, 130.3, 130.6, 131.1, 131.5, 132.7, 133.3, 138.4, 143.2, 155.6, 155.9, 192.1. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.65; H, 5.43; N, 13.23%. ESI–MS *m/z*: 541 $[M + H]^+$.

3,3-Dimethyl-11-(2-((1-(3-methylbenzyl)-1*H*-1,2,3 -triazol-4-yl)methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-3)

White solid; Yield: 0.158 g (61%); mp 184–185 °C; IR (KBr, cm^{-1}): 3294, 3239, 1597, 1535. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, $J = 15.3$ Hz, 1H, H-4), 2.16 (d, $J = 15.3$ Hz, 1H, H-4), 2.18 (s, 3H, CH_3), 2.58–2.66 (m, 2H, H-2), 5.20 (d, $J = 11.9$ Hz, 1H, OCH_2), 5.33–5.35 (m, 2H, H-11 and OCH_2), 5.61 (s, 2H, NCH_2), 5.87 (d, $J = 5.5$ Hz, 1H, **NH**CH), 6.45 (d, $J = 7.5$ Hz, 1H, H-9), 6.49 (t, $J = 7.1$ Hz, 1H, H-8), 6.56 (t, $J = 7.1$ Hz, 1H, H-7), 6.57–6.60 (m, 2H, H-6 and H-4′), 6.91 (d, $J = 7.7$ Hz, 1H, H-3′), 7.02–7.06 (m, 2H, H-5′ and H-6′), 7.14–7.16 (m, 3H, H-2″, H-4″ and H-6″), 7.69 (t, $J = 7.9$ Hz, 1H, H-5″), 8.42 (s, 1H, H-4, triazole), 8.84 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 21.0, 27.7, 28.3, 31.9, 44.1, 49.5, 52.4, 52.9, 61.5, 108.7, 111.9, 119.9, 120.1, 120.3, 122.7, 124.5, 125.1, 126.5, 127.8, 128.5, 128.7, 128.8, 129.7, 131.0, 131.6, 135.9, 138.1, 138.4, 143.4, 155.6, 155.8, 192.1. Anal. Calcd. For $C_{32}H_{33}N_5O_2$: C, 73.96; H, 6.40; N, 13.48%. Found: C, 74.25; H, 6.16; N, 13.23%. ESI–MS *m/z*: 520 $[M + H]^+$.

11-(2-((1-(3-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-4)

White solid; Yield: 0.178 g (68%); mp 173–174 °C; IR (KBr, cm^{-1}): 3299, 3242, 1596, 1534. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, $J = 15.8$ Hz, 1H, H-4), 2.16 (d, $J = 15.8$ Hz, 1H, H-4), 2.58–2.66 (m, 2H, H-2), 5.21 (d, $J = 11.9$ Hz, 1H, OCH_2), 5.33–5.36 (m, 2H, H-11 and OCH_2), 5.69 (s, 2H, NCH_2), 5.88 (d, $J = 5.5$ Hz, 1H, **NH**CH), 6.44 (d, $J = 7.4$ Hz, 1H, H-9), 6.50 (t, $J = 7.2$ Hz, 1H, H-8), 6.56 (t, $J = 7.2$ Hz, 1H, H-7), 6.59–6.61 (m, 2H, H-6 and H-4′), 6.91 (d, $J = 7.7$ Hz, 1H, H-3′), 7.01–7.03 (m, 1H, H-5′), 7.07 (d, $J = 8.0$ Hz, 1H, H-6′), 7.16–7.22 (m, 3H, H-2″, H-4″ and H-6″), 7.42–7.43 (m, 1H, H-5″), 8.47 (s, 1H, H-4, triazole), 8.83 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.7, 28.3, 31.8, 44.2, 49.5, 52.3, 52.4, 61.5, 108.7, 111.9, 114.8, 115.0, 115.2, 119.9, 120.1, 120.3, 122.7, 124.1, 124.6, 126.6, 127.8, 131.0 (2C), 131.1, 131.6, 138.4, 138.7, 143.5, 155.6, 155.8, 165.5 (d, $J_{C\text{-}F} = 248.9$ Hz), 192.1. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.35; H, 5.54; N, 13.05%. ESI–MS *m/z*: 524 $[M + H]^+$.

11-(2-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-5)

White solid; Yield: 0.172 g (64%); mp 207–208 °C; IR (KBr, cm^{-1}): 3296, 3240, 1597, 1533. ^{1}H NMR (500 MHz, DMSO-d_6): 1.07 (s, 6H, C(**CH$_3$**)$_2$), 2.08 (d, $J = 15.9$ Hz, 1H, H-4), 2.17 (d, $J = 15.9$ Hz, 1H, H-4), 2.58–2.63 (m, 2H, H-2), 5.20 (d, $J = 11.9$ Hz, 1H, OCH_2), 5.34–5.37 (m, 2H, H-11 and OCH_2), 5.70 (s, 2H, NCH_2), 5.89 (brs, 1H, **NH**CH), 6.45 (d, $J = 7.5$ Hz, 1H, H-9), 6.51–6.61 (m, 4H, H-6, H-7, H-8 and H-4′), 6.92 (d, $J = 7.75$ Hz, 1H, H-3′), 7.03–7.07 (m, 2H, H-5′ and H-6′), 7.31 (m, 1H, H-6″), 7.42–7.46 (m, 3H, H-2″, H-4″ and H-5″), 8.47 (s, 1H, H-4, triazole), 8.84 (s, 1H, NH). Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.67; H, 5.32; N, 13.32%. ESI–MS *m/z*: 541 $[M + H]^+$.

3,3-Dimethyl-11-(2-((1-(3-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*] [1,4]diazepin-1-one (9a-6)

Yellow solid; Yield: 0.187 g (68%); mp 184–185 °C; IR (KBr, cm^{-1}): 3291, 3237, 1581, 1530. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, J = 15.9 Hz, 1H, H-4), 2.16 (d, J = 15.9 Hz, 1H, H-4), 2.58–2.66 (m, 2H, H-2), 5.21 (d, J = 12.1 Hz, 1H, OCH_2), 5.32–5.37 (m, 2H, H-11 and OCH_2), 5.85 (s, 2H, NCH_2), 5.87 (d, J = 5.5 Hz, 1H, **NH**CH), 6.44 (d, J = 7.5 Hz, 1H, H-9), 6.50 (t, J = 7.2 Hz, 1H, H-8), 6.56 (t, J = 7.2 Hz, 1H, H-7), 6.59- 6.61 (m, 2H, H-6 and H-4′), 6.91 (d, J = 7.7 Hz, 1H, H-3′), 7.01–7.03 (m, 1H, H-5′), 7.07 (d, J = 8.0 Hz, 1H, H-6′), 7.69 (t, J = 7.9 Hz, 1H, H-5″), 7.80 (d, J = 7.9 Hz, 1H, H-6″), 8.21 (d, J = 7.9 Hz, 1H, H-4″), 8.29 (s, 1H, H-2″), 8.53 (s, 1H, H-4, triazole), 8.85 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.7, 28.3, 31.9, 44.3, 49.5, 51.9, 52.4, 61.5, 108.7, 111.9, 119.9, 120.1, 120.3, 122.8, 123.0, 123.2, 124.8, 126.6, 127.8, 130.5, 131.0, 131.5, 134.9, 135.5, 138.1, 138.4, 143.6, 147.9, 155.6, 155.8, 192.1. Anal. Calcd. For $C_{31}H_{30}N_6O_4$: C, 67.62; H, 5.49; N, 15.26%. Found: C, 67.38; H, 5.13; N, 15.54%. ESI–MS *m/z*: 551 $[M+H]^+$.

11-(2-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-8)

White solid; Yield: 0.170 g (65%); mp 201–202 °C; IR (KBr, cm^{-1}): 3309, 3240, 1603, 1529. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, J = 15.9 Hz, 1H, H-4), 2.17 (d, J = 15.9 Hz, 1H, H-4), 2.58–2.65 (m, 2H, H-2), 5.20 (d, J = 12.0 Hz, 1H, OCH_2), 5.32–5.35 (m, 2H, H-11 and OCH_2), 5.65 (s, 2H, NCH_2), 5.88 (d, J = 5.5 Hz, 1H, **NH**CH), 6.45 (d, J = 7.6 Hz, 1H, H-9), 6.50 (t, J = 7.5 Hz, 1H, H-8), 6.57–6.61 (m, 3H, H-7, H-6 and H-4′), 6.91 (d, J = 7.8 Hz, 1H, H-3′), 7.03–7.06 (m, 2H, H-5′ and H-6′), 7.31–7.34 (m, 2H, H-3″ and H-5″), 7.58 (m, 2H, H-2″ and H-6″), 8.43 (s, 1H, H-4, triazole), 8.83 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 32.8, 33.4, 36.9, 48.8, 54.6, 57.2, 57.5, 66.6, 113.8, 117.0, 117.1, 120.7, 120.9, 125.0, 125.2, 125.4, 127.8, 129.5, 130.9, 131.7, 132.9, 135.4, 135.5, 136.2, 136.7, 137.4, 143.5, 148.5, 160.7, 160.9, 197.2. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.44; H, 5.96; N, 13.13%. ESI–MS *m/z*: 524 $[M+H]^+$.

11-(2-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-9)

White solid; Yield: 0.178 g (66%); mp 188–189 °C; IR (KBr, cm^{-1}): 3297, 3240, 1599, 1536. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.08 (d, J = 16.0 Hz, 1H, H-4), 2.16 (d, J = 16.0 Hz, 1H, H-4), 2.58–2.66 (m, 2H, H-2), 5.20 (d, J = 12 Hz, 1H, OCH_2), 5.33–5.35 (m, 2H, H-11 and OCH_2), 5.67 (s, 2H, NCH_2), 5.88 (d, J = 4.9 Hz, 1H, **NH**CH), 6.44 (d, J = 7.5 Hz, 1H, H-9), 6.49 (t, J = 7.2 Hz, 1H, H-8), 6.56 (t, J = 7.2 Hz, 1H, H-7), 6.59–6.61 (m, 2H, H-6 and H-4′), 6.91 (d, J = 7.7 Hz, 1H, H-3′), 7.02–7.03 (m, 1H, H-5′), 7.07 (d, J = 7.9 Hz, 1H, H-6′), 7.37 (d, J = 7.8 Hz, 2H, H-3″ and H-5″), 7.45 (d, J = 7.8 Hz, 2H, H-2″ and H-6″), 8.44 (s, 1H, H-4, triazole), 8.83 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.7, 28.3, 31.8, 44.9, 49.5, 52.1, 52.4, 61.5, 108.8, 111.9, 119.9, 120.1, 120.3, 122.7, 124.6, 126.2, 127.8, 128.8, 130.0, 131.1, 131.6, 132.9, 134.1, 135.0, 138.4, 143.4, 155.6, 155.8, 192.1. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.71; H, 5.37; N, 12.63%. ESI–MS *m/z*: 541 $[M+H]^+$.

11-(2-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9a-10)

White solid; Yield: 0.187 g (64%); mp 218–219 °C; IR (KBr, cm^{-1}): 3308, 3241, 1628, 1525. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, J = 15.9 Hz, 1H, H-4), 2.17 (d, J = 15.9 Hz, 1H, H-4), 2.58–2.66 (m, 2H, H-2), 5.20 (d, J = 12 Hz, 1H, OCH_2), 5.32–5.35 (m, 2H, H-11 and OCH_2), 5.65 (s, 2H, NCH_2), 5.88 (d, J = 5.5 Hz, 1H, **NH**CH), 6.43 (d, J = 7.6 Hz, 1H, H-9), 6.49 (t, J = 7.5 Hz, 1H, H-8), 6.56 (t, J = 7.5 Hz, 1H, H-7), 6.57–6.60 (m, 2H, H-6 and H-4′), 6.91 (d, J = 7.8 Hz, 1H, H-3′), 7.00–7.03 (m, 1H, H-5′), 7.07 (d, J = 8.0 Hz, 1H, H-6′), 7.30 (d, J = 8.1 Hz, 2H, H-3″ and H-5″), 7.58 (d, J = 8.1 Hz, 2H, H-2″ and H-6″), 8.44 (s, 1H, H-4, triazole), 8.83 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.2, 27.7, 31.3, 43.6, 49.0, 51.6, 51.8, 61.0, 108.2, 111.4, 119.3 (2C), 119.5, 119.7, 120.9, 122.1, 124.0, 126.0, 127.2, 129.7 (2C), 130.5, 131.1, 131.2 (2C), 134.8, 137.8, 142.9, 154.9, 155.3, 191.5. Anal. Calcd. For $C_{31}H_{30}BrN_5O_2$: C, 63.70; H, 5.17; N, 11.98%. Found: C, 63.56; H, 5.32; N, 11.77%. ESI–MS *m/z*: 585 $[M+H]^+$.

3,3-Dimethyl-11-(2-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*] [1,4]diazepin-1-one (9a-11)

Yellow solid; Yield: 0.18 g (69%); mp 180–181 °C; IR (KBr, cm^{-1}): 3341, 3292, 1631, 1527. ^{1}H NMR (500 MHz, DMSO-d_6): 1.06 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, J = 15.0 Hz, 1H, H-4), 2.16 (d, J = 15.0 Hz, 1H, H-4), 2.58–2.66 (m, 2H, H-2), 5.20 (d, J = 12.1 Hz, 1H, OCH_2), 5.23–5.35 (m, 2H, H-11 and OCH_2), 5.65 (s, 2H, NCH_2), 5.87 (d, J = 5.5 Hz, 1H, **NH**CH), 6.43 (d, J = 7.7 Hz, 1H, H-9), 6.49 (t, J = 7.5 Hz, 1H, H-8), 6.56 (t, J = 7.5 Hz, 1H, H-7), 6.59–6.62 (m, 2H, H-6 and H-4′), 6.91 (d, J = 7.85 Hz, 1H, H-3′), 7.00–7.03 (m, 1H, H-5′), 7.07 (d, J = 8.2 Hz, 1H, H-6′), 7.30 (d, J = 7.9 Hz, 2H, H-3″ and H-5″), 7.58 (d, J = 7.9 Hz, 2H, H-2″ and H-6″), 8.44 (s, 1H, H-4, triazole), 8.83 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.6, 28.6, 31.9, 44.2, 49.6, 51.9, 55.4, 61.0, 110.6, 113.8 (2C), 119.5, 120.0, 120.6, 122.7, 122.9, 123.2, 124.9, 128.4 (2C), 130.5, 131.2, 134.8, 137.3, 138.1, 138.7, 143.4, 148.0, 154.8, 156.2, 192.2. Anal. Calcd. For $C_{31}H_{30}N_6O_4$: C, 67.62; H, 5.49; N, 15.26%. Found: C, 67.45; H, 5.23; N, 15.39%. ESI–MS *m/z*: 551 $[M+H]^+$.

11-(3-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-1)

White solid; Yield: 0.183 g (70%); mp 113–114 °C; IR (KBr, cm^{-1}): 3332, 3281, 1642, 1531. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.08 (d, J = 15.9 Hz, 1H, H-4), 2.18 (d, J = 15.9 Hz, 1H, H-4), 2.57–2.60 (m, 2H, H-2), 4.95 (s, 2H, OCH_2), 5.65–5.72 (m, 3H, NCH_2 and H-11), 6.15 (brs, 1H, **NH**CH), 6.52–6.60 (m, 3H, H-7, H-8 and H-9), 6.67–6.68 (m, 2H, H-4′ and H-6′), 6.74 (s, 1H, H-2′), 6.90 (d, J = 7.4 Hz, 1H, H-6), 7.01 (t, J = 7.8 Hz, 1H, H-5′), 7.21–7.28 (m, 2H, H-5″ and H-6″), 7.34 (t, J = 7.15 Hz, 1H, H-3″), 7.42–7.43 (m, 1H, H-4″), 8.19 (s, 1H, H-4, triazole), 8.75 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.0, 27.8, 31.2, 43.5, 46.3, 48.9, 55.2, 60.2, 109.4, 111.2, 113.4, 115.0 (d, J = 20.0 Hz), 118.9, 119.4, 119.9, 122.1, 122.2, 124.1, 124.3, 128.0, 130.2, 130.2, 130.2, 130.4, 137.9, 142.3, 145.8, 154.2, 157.1, 159.5 (d, J = 245.0 Hz), 191.5. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.47; H, 5.51; N, 13.09%. ESI–MS *m/z*: 524 $[M+H]^+$.

11-(3-((1-(2-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-2)

White solid; Yield: 0.175 g (65%); mp 117–118 °C; IR (KBr, cm^{-1}): 3324, 3292, 1654, 1542. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.08 (d, J = 15.8 Hz, 1H, H-4), 2.17 (d, J = 15.8 Hz, 1H, H-4), 2.57–2.60 (m, 2H, H-2), 4.96 (s, 2H, OCH_2), 5.65 (d, J = 5 Hz, 1H, H-11), 5.70 (s, 2H, NCH_2), 6.16 (brs, 1H, **NH**CH), 6.52–6.60 (m, 3H, H-7, H-8 and H-9), 6.67–6.68 (m, 2H, H-4′ and H-6′), 6.75 (s, 1H, H-2′), 6.90 (d, J = 7.4 Hz, 1H, H-6), 7.01 (t, J = 7.7 Hz, 1H, H-5′), 7.21 (d, J = 7.1 Hz, 1H, H-6″), 7.35–7.42 (m, 2H, H-4″ and H-5″), 7.52 (d, J = 7.6 Hz, 1H, H-3″), 8.18 (s, 1H, H-4, triazole), 8.76 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.0, 27.8, 31.2, 43.5, 48.9, 50.0, 55.2, 60.2, 111.2, 113.5, 118.9, 119.4, 119.9, 122.1, 124.3, 127.2, 128.0, 129.0, 129.7 (2C), 129.9, 130.4 (2C), 132.0, 132.6, 137.9, 142.2, 145.8, 154.2, 157.1, 191.5. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.63; H, 5.37; N, 13.11%. ESI–MS *m/z*: 541 $[M+H]^+$.

11-(3-((1-(3-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-3)

White solid; Yield: 0.175 g (67%); mp 99–100 °C; IR (KBr, cm^{-1}): 3323, 3277, 1661, 1550. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.09 (d, J = 15.7 Hz, 1H, H-4), 2.18 (d, J = 15.7 Hz, 1H, H-4), 2.57–2.60 (m, 2H, H-2), 4.96 (s, 2H, OCH_2), 5.62 (s, 2H, NCH_2), 5.66 (d, J = 5.8 Hz, 1H, H-11), 6.17 (brs, 1H, **NH**CH), 6.54–6.60 (m, 3H, H-7, H-8 and H-9), 6.67–6.68 (m, 2H, H-4′ and H-6′), 6.75 (s, 1H, H-2′), 6.90 (d, J = 7.3 Hz, 1H, H-6), 7.02 (t, J = 7.3 Hz, 1H, H-5′), 7.13–7.18 (m, 3H, H-2″, H-4″ and H-6″), 7.42–7.43 (m, 1H, H-5″), 8.24 (s, 1H, H-4, triazole), 8.75 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.5, 28.4, 31.8, 44.0, 49.4, 52.1, 55.8, 60.7, 109.9, 111.7, 114.0, 114.8, 114.9, 115.1, 119.5, 120.0, 120.5, 122.6, 124.1 (2C), 124.7, 128.6, 130.8, 130.9, 131.0, 138.6, 143.0, 154.8, 157.7, 163.1 (d, J = 209 Hz), 192.1. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.47; H, 5.51; N, 13.69%. ESI–MS *m/z*: 524 $[M+H]^+$.

11-(3-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-4)

White solid; Yield: 0.170 g (63%); mp 118–119 °C; IR (KBr, cm^{-1}): 3340, 3198, 1656, 1548. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.08 (d, J = 16 Hz, 1H, H-4), 2.17 (d, J = 16 Hz, 1H, H-4), 2.57–2.60 (m, 2H, H-2), 4.96 (s, 2H, OCH_2), 5.62 (s, 2H, NCH_2), 5.65 (d, J = 5.6 Hz, 1H, H-11), 6.16 (d, J = 4.3 Hz, 1H, NH), 6.54–6.60 (m, 3H, H-7, H-8 and H-9), 6.67–6.68 (m, 2H, H-4′ and H-6′), 6.74 (s, 1H, H-2′), 6.90 (d, J = 7.0 Hz, 1H, H-6), 7.02 (t, J = 7.0 Hz, 1H, H-5′), 7.27

(s, 1H, H-6″), 7.41 (m, 3H, H-2″, H-4″ and H-5″), 8.25 (s, 1H, H-4, triazole), 8.75 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.5, 28.4, 31.8, 42.5, 49.4, 52.0, 55.8, 60.7, 109.9, 111.7, 113.9, 119.3, 119.5, 119.7, 119.9, 121.4, 122.6, 124.5, 128.6, 130.2, 130.8, 131.0, 131.7, 132.4, 135.4, 138.9, 143.0, 147.7, 154.8, 157.7, 192.1. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.69; H, 5.45; N, 13.20%. ESI–MS *m/z*: 541 $[M+H]^+$.

3,3-Dimethyl-11-(3-((1-(3-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*] [1,4]diazepin-1-one (9b-5)

Yellow solid; Yield: 0.190 g (69%); mp 98–99 °C; IR (KBr, cm^{-1}): 3337, 3258, 1674, 1533. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.08 (d, *J* = 15.9 Hz, 1H, H-4), 2.17 (d, *J* = 15.9 Hz, 1H, H-4), 2.57–2.60 (m, 2H, H-2), 4.97 (s, 2H, OCH_2), 5.65 (d, *J* = 5.8 Hz, 1H, H-11), 5.78 (s, 2H, NCH_2), 6.15 (d, *J* = 4.3 Hz, 1H, **NH**CH), 6.52–6.61 (m, 3H, H-7, H-8 and H-9), 6.67–6.68 (m, 2H, H-4′ and H-6′), 6.74 (s, 1H, H-2′), 6.90 (d, *J* = 7.6 Hz, 1H, H-6), 7.02 (t, *J* = 7.8 Hz, 1H, H-5′), 7.69 (t, *J* = 7.7 Hz, 1H, H-5″), 7.77 (d, *J* = 7.7 Hz, 1H, H-6″), 8.21 (d, *J* = 7.7 Hz, 1H, H-4″), 8.24 (s, 1H, H-2″), 8.30 (s, 1H, H-4, triazole), 8.75 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.0, 27.8, 31.2, 43.5, 48.9, 51.2, 55.3, 60.2, 109.4, 111.2, 113.4, 119.0, 119.4, 119.5, 120.0, 122.1, 122.3, 122.6, 124.2, 128.1, 129.8, 130.5, 134.2, 137.4, 137.8, 142.6, 145.8, 147.3, 154.2, 157.1, 191.5. Anal. Calcd. For $C_{31}H_{30}N_6O_4$: C, 67.62; H, 5.49; N, 15.26%. Found: C, 67.94; H, 5.57; N, 15.14%. ESI–MS *m/z*: 551 $[M+H]^+$.

3,3-Dimethyl-11-(3-((1-(4-methylbenzyl)-1*H*-1,2,3 -triazol-4-yl)methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-6)

White solid; Yield: 0.158 (61%); mp 111–112 °C; IR (KBr, cm^{-1}): 3318, 3266, 1660, 1541. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.09 (d, *J* = 15.8 Hz, 1H, H-4), 2.17 (d, *J* = 15.8 Hz, 1H, H-4), 2.27 (s, 3H, CH_3), 2.56–2.58 (m, 2H, H-2), 4.93 (s, 2H, OCH_2), 5.53 (s, 2H, NCH_2), 5.65 (d, *J* = 5.2 Hz, 1H, H-11), 6.16 (d, *J* = 5.1 Hz, 1H, **NH**CH), 6.52–6.59 (m, 3H, H-7, H-8 and H-9), 6.66–6.67 (m, 2H, H-4′ and H-6′), 6.74 (s, 1H, H-2′), 6.90 (d, *J* = 7.3 Hz, 1H, H-6), 7.01 (t, *J* = 7.7 Hz, 1H, H-5′), 7.17 (d, *J* = 7.1, 2H, H-3″ and H-5″), 7.22 (d, *J* = 7.1, 2H, H-2″ and H-6″), 8.17 (s, 1H, H-4, triazole), 8.74 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 24.2, 25.3, 26.1, 29.5, 41.8, 47.2, 49.7, 53.6, 58.6, 110.6, 113.0, 115.6, 117.9, 120.0, 120.2, 122.5, 123.0, 123.8, 128.2 (2C), 128.8 (2C), 129.8, 134.3, 134.4, 136.9, 138.2, 143.8, 146.2, 153.0, 157.9, 197.2. Anal. Calcd. For $C_{32}H_{33}N_5O_2$: C, 73.96; H, 6.40; N, 13.48%. Found: C, 73.87; H, 6.49; N, 13.41%. ESI–MS *m/z*: 520 $[M+H]^+$.

11-(3-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-7)

White solid; Yield: 0.180 g (69%); mp 117–118 °C; IR (KBr, cm^{-1}): 3309, 3275, 1660, 1556. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.08 (d, *J* = 15.9 Hz, 1H, H-4), 2.18 (d, *J* = 15.9 Hz, 1H, H-4), 2.57–2.60 (m, 2H, H-2), 4.94 (s, 2H, OCH_2), 5.58 (s, 2H, NCH_2), 5.65 (d, *J* = 5.3 Hz, 1H, H-11), 6.15 (d, *J* = 5.5 Hz, 1H, **NH**CH), 6.52–6.60 (m, 3H, H-7, H-8 and H-9), 6.66–6.68 (m, 2H, H-4′ and H-6′), 6.74 (s, 1H, H-2′), 6.90 (d, *J* = 7.3 Hz, 1H, H-6), 7.01 (t, *J* = 7.7 Hz, 1H, H-5′), 7.21 (m, 2H, H-3″ and H-5″), 7.37–7.39 (m, 2H, H-2″ and H-6″), 8.20 (s, 1H, H-4, triazole), 8.73 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 26.0, 27.8, 32.5, 40.1, 42.4, 49.9, 52.2, 52.2, 58.0, 110.7, 113.0, 115.2 (d, *J* = 20.0 Hz, 2C), 115.6, 117.9, 120.0, 120.2, 122.5, 123.0, 123.8, 129.8, 130.2 (d, *J* = 7.5 Hz, 2C), 133.0, 134.3, 138.2, 143.8, 146.2, 153.0, 157.9, 162.1 (d, *J* = 252.5 Hz), 197.2. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.35; H, 5.91; N, 13.66%. ESI–MS *m/z*: 524 $[M+H]^+$.

11-(3-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-8)

White solid; Yield: 0.173 g (64%); mp 123–124 °C; IR (KBr, cm^{-1}): 3319, 3266, 1654, 1537. ^{1}H NMR (500 MHz, DMSO-d_6): 1.03 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.11 (d, *J* = 15.5 Hz, 1H, H-4), 2.18 (d, *J* = 15.5 Hz, 1H, H-4), 2.54 (d, *J* = 16.2 Hz, 1H, H-2), 2.59 (d, *J* = 16.2 Hz, 1H, H-2), 4.95 (s, 2H, OCH_2), 5.60 (s, 2H, NCH_2), 5.73 (s, 1H, H-11), 6.60–6.63 (m, 4H, **NH**CH, H-7, H-8 and H-9), 6.67–6.69 (m, 2H, H-4′ and H-6′), 6.76 (s, 1H, H-2′), 6.94–6.96 (m, 1H, H-6), 7.02 (t, *J* = 7.7 Hz, 1H, H-5′), 7.33 (d, *J* = 8.1 Hz, 2H, H-2″ and H-6″), 7.44 (d, *J* = 8.1 Hz, 2H, H-3″ and H-5″), 8.23 (s, 1H, H-4, triazole), 8.88 (brs, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.6, 28.3, 31.3, 31.8, 44.0, 49.3, 52.0, 60.7, 112.1, 114.0, 120.0, 120.1, 121.5, 122.7, 124.7, 125.4, 126.2, 128.8, 129.9, 130.4, 132.9, 134.9, 135.1, 136.6, 143.0, 154.9 (2C), 157.7, 192.1. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.67; H, 5.83; N, 12.69%. ESI–MS *m/z*: 541 $[M+H]^+$.

11-(3-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9b-9)

White solid; Yield: 0.184 g (63%); mp 118–119 °C; IR (KBr, cm^{-1}): 3328, 3273, 1645, 1587. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.08 (d, J = 15.9 Hz, 1H, H-4), 2.18 (d, J = 15.9 Hz, 1H, H-4), 2.57–2.60 (m, 2H, H-2), 4.95 (s, 2H, OCH_2), 5.58 (s, 2H, NCH_2), 5.66 (d, J = 5.0 Hz, 1H, H-11), 6.15 (d, J = 4.3 Hz, 1H, **NH**CH), 6.52–6.60 (m, 3H, H-7, H-8 and H-9), 6.67–6.68 (m, 2H, H-4′ and H-6′), 6.74 (s, 1H, H-2′), 6.90 (d, J = 7.5 Hz, 1H, H-6), 7.01 (t, J = 7.5 Hz, 1H, H-5′), 7.27 (d, J = 7.9 Hz, 2H, H-2″ and H-6″), 7.57 (d, J = 7.9 Hz, 2H, H-3″ and H-5″), 8.21 (s, 1H, H-4, triazole), 8.74 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.5, 28.4, 31.8, 49.5, 52.0, 55.8, 58.9, 62.2, 109.9, 111.7, 113.9, 119.5, 119.9, 120.5, 121.4, 122.6, 128.6, 130.2 (2C), 131.0, 131.7 (2C), 135.4, 138.5, 143.0, 146.4, 154.8, 157.7, 192.1. Anal. Calcd. For $C_{31}H_{30}BrN_5O_2$: C, 63.70; H, 5.17; N, 11.98%. Found: C, 63.46; H, 5.43; N, 11.64%. ESI–MS *m/z*: 585 $[M+H]^+$.

3,3-Dimethyl-11-(3-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*] [1,4]diazepin-1-one (9b-10)

Yellow solid; Yield: 0.187 g (68%); mp 118–119 °C; IR (KBr, cm^{-1}): 3325, 3271, 1671, 1542. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.85 (d, J = 14.6, 1H, H-4), 2.18 (d, J = 14.6 Hz, 1H, H-4), 2.55–2.59 (m, 2H, H-2), 4.98 (s, 2H, OCH_2), 5.65 (d, J = 5.6 Hz, 1H, H-11), 5.78 (s, 2H, NCH_2), 6.16 (d, J = 5.7 Hz, 1H, **NH**CH), 6.25–6.46 (m, 3H, H-7, H-8 and H-9), 6.67–6.68 (m, 2H, H-4′ and H-6′), 6.74 (s, 1H, H-2′), 6.9 (d, J = 7.5 Hz, 1H, H-6), 7.02 (t, J = 7.8 Hz, 1H, H-5′), 7.52 (d, J = 8.4 Hz, 2H, H-2″ and H-6″), 8.24 (d, J = 8.4 Hz, 2H, H-3″ and H-5″), 8.27 (s, 1H, H-4, triazole), 8.74 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.0, 27.8, 31.2, 43.5, 48.9, 51.4, 55.2, 60.3, 109.5, 111.2, 113.5, 118.9, 119.4, 119.9, 122.0, 123.3 (2C), 124.4, 128.0, 128.5 (2C), 130.4, 137.9, 142.6, 142.7, 145.8, 146.6, 151.4, 154.2, 157.1, 191.5. Anal. Calcd. For $C_{31}H_{30}N_6O_4$: C, 67.62; H, 5.49; N, 15.26%. Found: C, 67.48; H, 5.11; N, 15.09%. ESI–MS *m/z*: 551 $[M+H]^+$.

11-(4-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-1)

White solid; Yield: 0.186 g (71%); mp 133–134 °C; IR (KBr, cm^{-1}): 3333, 3240, 1653, 1571. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, J = 15.9 Hz, 1H, H-4), 2.17 (d, J = 15.9 Hz, 1H, H-4), 2.55–2.59 (m, 2H, H-2), 4.96 (s, 2H, OCH_2), 5.64 (s, 2H, NCH_2), 5.65 (d, J = 5.7 Hz, 1H, H-11), 6.13 (brs, 1H, **NH**CH), 6.51 (d, J = 7.3 Hz, 1H, H-9), 6.54–6.59 (m, 2H, H-7 and H-8), 6.74 (d, J = 8.1 Hz, 2H, H-3′ and H-5′), 6.90 (d, J = 7.5 Hz, 1H, H-6), 6.99 (d, J = 8.1 Hz, 2H, H-2′ and H-6′), 7.19–7.26 (m, 2H, H-5″ and H-6″), 7.31 (t, J = 7.4 Hz, 1H, H-3″), 7.40–7.41 (m, 1H, H-4″), 8.19 (s, 1H, H-4, triazole), 8.74 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 28.2, 29.2, 32.5, 44.8, 50.2, 52.7, 55.9, 61.6, 110.6, 115.2 (d, J = 20.0 Hz), 115.8 (2C), 117.9, 120.3, 122.5, 123.0, 123.4 (d, J = 20.0 Hz), 123.8, 124.7, 126.8 (2C), 128.9, 130.6, 134.3, 136.4, 138.2, 146.2, 153.0, 157.0, 160.7 (d, J = 251.1 Hz), 197.2. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.47; H, 5.44; N, 13.62%. ESI–MS *m/z*: 524 $[M+H]^+$.

11-(4-((1-(2-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-2)

White solid; Yield: 0.181 g (67%); IR (KBr, cm^{-1}): 3342, 3227, 1641, 1555. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, J = 15.8 Hz, 1H, H-4), 2.17 (d, J = 15.8 Hz, 1H, H-4), 2.55–2.59 (m, 2H, H-2), 4.98 (s, 2H, OCH_2), 5.63 (d, J = 5.7 Hz, 1H, H-11), 5.68 (s, 2H, NCH_2), 6.12 (d, J = 5.6 Hz, 1H, **NH**CH), 6.51 (d, J = 7.4 Hz, 1H, H-9), 6.54–6.59 (m, 2H, H-7 and H-8), 6.75 (d, J = 8.4 Hz, 2H, H-3′ and H-5′), 6.90 (d, J = 7.4 Hz, 1H, H-6), 6.99 (d, J = 8.4 Hz, 2H, H-2′ and H-6′), 7.18 (d, J = 7.2 Hz, 1H, H-6″), 7.33–7.40 (m, 2H, H-5″ and H-3″), 7.51 (m, 1H, H-4″), 8.18 (s, 1H, H-4, triazole), 8.73 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 26.9, 27.9, 31.2, 43.5, 48.9, 50.0, 54.7, 60.2, 109.9, 113.2, 118.9, 119.4, 120.0, 122.0, 124.3, 127.1, 127.7 (2C), 129.0 (2C), 129.7, 129.9, 130.5, 132.0, 132.6, 136.6, 138.1, 142.4, 154.1, 155.5, 191.5. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.63; H, 5.77; N, 12.74%. ESI–MS *m/z*: 541 $[M+H]^+$.

3,3-Dimethyl-11-(4-((1-(3-methylbenzyl)-1*H*-1,2,3 -triazol-4-yl)methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-3)

White solid; Yield: 0.166 g (64%); mp 122–123 °C; IR (KBr, cm^{-1}): 3351, 3243, 1650, 1572. ^{1}H NMR (500 MHz, DMSO-d_6): 1.03 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, J = 15.8 Hz, 1H, H-4), 2.19 (d, J = 15.8 Hz, 1H, H-4), 2.27 (s, 3H, CH_3), 2.55–2.58 (m, 2H, H-2), 4.96 (s, 2H, OCH_2), 5.52 (s, 2H, NCH_2), 5.65 (d, J = 5.5 Hz, 1H, H-11), 6.11 (brs, 1H, **NH**CH), 6.51 (d, J = 7.5 Hz, 1H, H-9), 6.55–6.60 (m, 2H, H-7 and H-8), 6.75 (d, J = 8.5 Hz, 2H, H-3′ and H-5′), 6.90 (d, J = 7.4 Hz, 1H, H-6), 7.00 (d,

$J = 8.5$ Hz, 2H, H-2′ and H-6′), 7.07–7.13 (m, 3H, H-2″, H-4″ and H-5″), 7.22–7.24 (m, 1H, H-6″), 8.18 (s, 1H, H-4, triazole), 8.72 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 20.3, 26.9, 27.9, 31.2, 43.5, 48.9, 52.2, 54.6, 60.3, 110.0, 113.1, 118.8, 119.3, 119.9, 122.0, 123.9, 124.5, 127.7 (2C), 127.9, 128.1, 128.2 (2C), 130.5, 135.3, 136.6, 137.4, 138.1, 142.5, 154.0, 155.5, 191.4. Anal. Calcd. For $C_{32}H_{33}N_5O_2$: C, 73.96; H, 6.40; N, 13.48%. Found: C, 73.64; H, 6.77; N, 13.16%. ESI–MS *m/z*: 520 $[M+H]^+$.

11-(4-((1-(3-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-4)

White solid; Yield: 0.178 g (68%); mp 125–127 °C; IR (KBr, cm^{-1}): 3325, 3219, 1667, 1581. ^{1}H NMR (500 MHz, DMSO-d_6): 1.03 (s, 3H, C($\mathbf{CH_3}$)$_2$), 1.07 (s, 3H, C($\mathbf{CH_3}$)$_2$), 2.07 (d, $J = 15.8$ Hz, 1H, H-4), 2.18 (d, $J = 15.8$ Hz, 1H, H-4), 2.55–2.60 (m, 2H, H-2), 4.97 (s, 2H, OCH_2), 5.60 (s, 2H, NCH_2), 5.63 (d, $J = 5.7$ Hz, 1H, H-11), 6.11 (d, $J = 5.2$ Hz, 1H, **NH**CH), 6.51 (d, $J = 7.4$ Hz, 1H, H-9), 6.54–6.61 (m, 2H, H-7 and H-8), 6.75 (d, $J = 8.4$ Hz, 2H, H-3′ and H-5′), 6.90 (d, $J = 7.4$ Hz, 1H, H-6), 6.99 (d, $J = 8.4$ Hz, 2H, H-2′ and H-6′), 7.11 (d, $J = 7.7$ Hz, 1H, H-6″), 7.15–7.16 (m, 2H, H-2″ and H-4″), 7.39–7.43 (m, 1H, H-5″), 8.23 (s, 1H, H-4, triazole), 8.71 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.6, 28.7, 31.9, 44.3, 49.6, 50.8, 55.4, 60.9, 110.6, 114.6 (d, $J = 20.0$ Hz), 115.3 (d, $J = 20.0$ Hz), 115.8 (2C), 117.9, 120.2, 122.5, 123.0, 123.8, 124.3, 126.8 (2C), 130.1, 134.3, 136.4, 137.9, 138.2, 146.2, 153.0, 157.0, 162.8 (d, $J = 252.5$ Hz), 197.2. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.38; H, 5.51; N, 13.07%. ESI–MS *m/z*: 524 $[M+H]^+$.

11-(4-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-5)

White solid; Yield: 0.181 g (67%); mp 119–120 °C; IR (KBr, cm^{-1}): 3342, 3264, 1665, 1556. ^{1}H NMR (500 MHz, DMSO-d_6): 1.03 (s, 3H, C($\mathbf{CH_3}$)$_2$), 1.07 (s, 3H, C($\mathbf{CH_3}$)$_2$), 2.07 (d, $J = 15.9$ Hz, 1H, H-4), 2.17 (d, $J = 15.9$ Hz, 1H, H-4), 2.55–2.68 (m, 2H, H-2), 4.98 (s, 2H, OCH_2), 5.59 (s, 2H, NCH_2), 5.64 (d, $J = 5.6$ Hz, 1H, H-11), 6.10 (brs, 1H, **NH**CH), 6.51 (d, $J = 7.5$ Hz, 1H, H-9), 6.54–6.59 (m, 2H, H-7 and H-8), 6.75 (d, $J = 8.4$ Hz, 2H, H-3′ and H-5′), 6.90 (d, $J = 7.5$ Hz, 1H, H-6), 7.00 (d, $J = 8.4$ Hz, 2H, H-2′ and H-6′), 7.23–7.25 (m, 1H, H-4″), 7.37–7.39 (m, 3H, H-2″, H-5″ and H-6″), 8.23 (s, 1H, H-4, triazole), 8.71 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 25.8, 26.8, 30.1, 42.4, 47.8, 50.3, 53.5, 59.1, 110.0, 115.8 (2C), 117.9, 120.2, 122.5, 123.0, 123.8, 126.8 (2C), 127.2, 127.4, 128.4, 129.7, 134.0, 134.2, 136.4, 137.2, 138.2, 146.2, 149.7, 157.0, 193.1. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.62; H, 5.87; N, 12.74%. ESI–MS *m/z*: 541 $[M+H]^+$.

3,3-Dimethyl-11-(4-((1-(3-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*] [1,4]diazepin-1-one (9c-6)

Yellow solid; Yield: 0.192 g (70%); mp 132–133 °C; IR (KBr, cm^{-1}): 3347, 3223, 1647, 1569. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C($\mathbf{CH_3}$)$_2$), 1.07 (s, 3H, C($\mathbf{CH_3}$)$_2$), 2.07 (d, $J = 15.8$ Hz, 1H, H-4), 2.17 (d, $J = 15.8$ Hz, 1H, H-4), 2.55–2.58 (m, 2H, H-2), 4.98 (s, 2H, OCH_2), 5.63 (d, $J = 5.5$ Hz, 1H, H-11), 5.76 (s, 2H, NCH_2), 6.17 (brs, 1H, **NH**CH), 6.51 (d, $J = 7.2$ Hz, 1H, H-9), 6.55–6.59 (m, 2H, H-7 and H-8), 6.75 (d, $J = 8.3$ Hz, 2H, H-3′ and H-5′), 6.90 (d, $J = 7.5$ Hz, 1H, H-6), 6.99 (d, $J = 8.3$ Hz, 2H, H-2′ and H-6′), 7.67 (t, $J = 7.8$ Hz, 1H, H-5″), 7.74 (d, $J = 7.4$ Hz, 1H, H-6″), 8.19 (d, $J = 8.2$ Hz, 1H, H-4″), 8.22 (s, 1H H-2″), 8.28 (s, 1H, H-4, triazole), 8.73 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 26.9, 27.9, 31.2, 43.5, 48.9, 51.2, 54.7, 60.3, 109.9, 113.2, 118.9, 119.4, 120.0, 122.0, 122.2, 122.5, 124.2, 127.8 (2C), 129.8 (2C), 130.5, 134.1, 136.6, 137.4, 138.1, 142.7, 147.3, 154.1, 155.5, 191.5. Anal. Calcd. For $C_{31}H_{30}N_6O_4$: C, 67.62; H, 5.49; N, 15.26%. Found: C, 67.79; H, 5.63; N, 15.51%. ESI–MS *m/z*: 551 $[M+H]^+$.

3,3-Dimethyl-11-(4-((1-(4-methylbenzyl)-1*H*-1,2,3 -triazol-4-yl)methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-7)

White solid; Yield: 0.163 g (63%); mp 124–125 °C; IR (KBr, cm^{-1}): 3341, 3225, 1668, 1565. ^{1}H NMR (500 MHz, DMSO-d_6): 1.03 (s, 3H, C($\mathbf{CH_3}$)$_2$), 1.07 (s, 3H, C($\mathbf{CH_3}$)$_2$), 2.07 (d, $J = 15.9$ Hz, 1H, H-4), 2.19 (d, $J = 15.9$ Hz, 1H, H-4), 2.26 (s, 3H, CH_3), 2.54–2.58 (m, 2H, H-2), 4.96 (s, 2H, OCH_2), 5.51 (s, 2H, NCH_2), 5.65 (d, $J = 5.7$ Hz, 1H, H-11), 6.13 (d, $J = 5.7$ Hz, 1H, **NH**CH), 6.52 (d, $J = 7.5$ Hz, 1H, H-9), 6.52–6.60 (m, 2H, H-7 and H-8), 6.74 (d, $J = 8.4$ Hz, 2H, H-3′ and H-5′), 6.91 (d, $J = 7.5$ Hz, 1H, H-6), 7.00 (d, $J = 8.4$ Hz, 2H, H-2′ and H-6′), 7.16–7.20 (m, 4H, H-2″, H-3″, H-5″ and H-6″), 8.16 (s, 1H, H-4, triazole), 8.74 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): 20.7, 27.5, 28.5, 31.8, 44.1, 49.5, 52.6, 55.2, 60.3, 110.4, 113.7, 119.4, 119.9, 120.5, 122.6, 124.4, 128.0 (2C), 128.3, 129.3 (2C), 131.0, 133.0, 137.1, 137.5, 138.7, 143.0, 154.6, 156.1, 192.0. Anal. Calcd. For $C_{32}H_{33}N_5O_2$: C, 73.96; H, 6.40; N, 13.48%. Found: C, 73.79; H, 6.17; N, 13.24%. ESI–MS *m/z*: 520 $[M+H]^+$.

11-(4-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-8)

White solid; Yield: 0.177 g (68%); mp 120–121 °C; IR (KBr, cm^{-1}): 3345, 3223, 1624, 1542. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, *J* = 15.9 Hz, 1H, H-4), 2.19 (d, *J* = 15.9 Hz, 1H, H-4), 2.55–2.58 (m, 2H, H-2), 4.96 (s, 2H, OCH_2), 5.56 (s, 2H, NCH_2), 5.64 (d, *J* = 5.5 Hz, 1H, H-11), 6.13 (d, *J* = 5.4 Hz, 1H, **NH**CH), 6.51 (d, *J* = 7.4 Hz, 1H, H-9), 6.54–6.61 (m, 2H, H-7 and H-8), 6.74 (d, *J* = 8.3 Hz, 2H, H-3′ and H-5′), 6.90 (d, *J* = 7.5 Hz, 1H, H-6), 6.99 (d, *J* = 8.3 Hz, 2H, H-2′ and H-6′), 7.19–7.21 (m, 2H, H-2″ and H-6″), 7.37–7.40 (m, 2H, H-3″ and H-5″), 8.20 (s, 1H, H-4, triazole), 8.73 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 26.9, 27.9, 31.2, 43. 6, 48.9, 51.4, 54.7, 60.3, 110.0, 113.2 (2C), 115.1 (d, 2C, *J* = 21.2 Hz), 118.9, 119.4, 120.0, 122.4, 123.8, 127.7 (2C), 129.7 (d, 2C, *J* = 8.7 Hz), 130.5, 131.6, 136.6, 138.2, 142.6, 154.0, 155.5, 161.3 (d, *J* = 257.5 Hz), 191.4. Anal. Calcd. For $C_{31}H_{30}FN_5O_2$: C, 71.11; H, 5.78; N, 13.38%. Found: C, 71.21; H, 5.63; N, 13.15%. ESI–MS *m/z*: 524 $[M+H]^+$.

11-(4-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-9)

White solid; Yield: 0.175 g (65%); mp 121–122 °C; IR (KBr, cm^{-1}): 3358, 3222, 1649, 1537. ^{1}H NMR (500 MHz, DMSO-d_6): 1.03 (s, 3H, C(**CH$_3$**)$_2$), 1.08 (s, 3H, C(**CH$_3$**)$_2$), 2.09 (d, *J* = 15.9 Hz, 1H, H-4), 2.20 (d, *J* = 15.9 Hz, 1H, H-4), 2.55–2.63 (m, 2H, H-2), 4.97 (s, 2H, OCH_2), 5.61 (s, 2H, NCH_2), 5.67 (d, *J* = 5.5 Hz, 1H, H-11), 6.19 (d, *J* = 5.7 Hz, 1H, **NH**CH), 6.54–6.63 (m, 3H, H-7, H-8 and H-9), 6.69 (d, *J* = 8.4 Hz, 2H, H-3′ and H-5′), 6.76 (d, *J* = 7.5 Hz, 1H, H-6), 6.92 (d, *J* = 8.4 Hz, 2H, H-2′ and H-6′), 7.34 (d, *J* = 8.5 Hz, 2H, H-2″ and H-6″), 7.45 (d, *J* = 8.5 Hz, 2H, H-3″ and H-5″), 8.23 (s, 1H H-4, triazole), 8.77 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.0, 27.8, 31.2, 43.5, 48.9, 51.4, 55.2, 60.2, 109.4, 111.2, 113.4, 118.9, 119.4 (2C), 119.9, 122.1, 124.0 (2C), 128.2 (2C), 129.3 (2C), 130.4, 132.3, 134.3, 137.9, 142.5, 145.8, 154.2, 157.1, 191.5. Anal. Calcd. For $C_{31}H_{30}ClN_5O_2$: C, 68.94; H, 5.60; N, 12.97%. Found: C, 68.79; H, 5.37; N, 13.19%. ESI–MS *m/z*: 541 $[M+H]^+$.

11-(4-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-10)

White solid; Yield: 0.181 g (62%); mp 132–133 °C; IR (KBr, cm^{-1}): 3347, 3268, 1685, 1563. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, *J* = 15.8 Hz, 1H, H-4), 2.19 (d, *J* = 15.8 Hz, 1H, H-4), 2.55–2.58 (m, 2H, H-2), 4.97 (s, 2H, OCH_2), 5.56 (s, 2H, NCH_2), 5.63 (d, *J* = 5.5 Hz, 1H, H-11), 6.13 (brs, 1H, **NH**CH), 6.52 (d, *J* = 7.5 Hz, 1H, H-9), 6.54–6.61 (m, 2H, H-7 and H-8), 6.74 (d, *J* = 8.4 Hz, 2H, H-3′ and H-5′), 6.90 (d, *J* = 7.5 Hz, 1H, H-6), 6.99 (d, *J* = 8.4 Hz, 2H, H-2′ and H-6′), 7.24 (d, *J* = 8.5 Hz, 2H, H-2″ and H-6″), 7.56 (d, *J* = 8.5 Hz, 2H, H-3″ and H-5″), 8.20 (s, 1H, H-4, triazole), 8.73 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 28.2, 29.1, 32.5, 44.8, 50.1, 51.3, 56.5, 61.5, 110.0, 115.8 (2C), 118.0, 120.2, 121.8, 122.5, 123.0, 123.8, 126.8 (2C), 130.2 (2C), 131.5 (2C), 134.0, 135.3, 136.4, 138.2, 146.2, 149.67, 157.0, 193.1. Anal. Calcd. For $C_{31}H_{30}BrN_5O_2$: C, 63.70; H, 5.17; N, 11.98%. Found: C, 63.47; H, 5.34; N, 11.74%. ESI–MS *m/z*: 585 $[M+H]^+$.

3,3-Dimethyl-11-(4-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (9c-11)

Yellow solid; Yield: 0.190 g (69%); mp 142–143 °C; IR (KBr, cm^{-1}): 3344, 3215, 1667, 1524. ^{1}H NMR (500 MHz, DMSO-d_6): 1.02 (s, 3H, C(**CH$_3$**)$_2$), 1.07 (s, 3H, C(**CH$_3$**)$_2$), 2.07 (d, *J* = 15.9 Hz, 1H, H-4), 2.19 (d, *J* = 15.9 Hz, 1H, H-4), 2.55–2.58 (m, 2H, H-2), 4.99 (s, 2H, OCH_2), 5.63 (d, *J* = 5.6 Hz, 1H, H-11), 5.76 (s, 2H, NCH_2), 6.12 (d, *J* = 5.6 Hz, 1H, **NH**CH), 6.51 (d, *J* = 7.5 Hz, 1H, H-9), 6.55–6.59 (m, 2H, H-7 and H-8), 6.75 (d, *J* = 8.4 Hz, 2H, H-3′ and H-5′), 6.90 (d, *J* = 7.5 Hz, 1H, H-6), 7.00 (d, *J* = 8.4 Hz, 2H, H-2′ and H-6′), 7.51 (d, *J* = 8.5 Hz, 2H, H-2″ and H-6″), 8.23 (d, *J* = 8.5 Hz, 2H, H-3″ and H-5″), 8.27 (s, 1H, H-4, triazole), 8.73 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 27.4, 28.5, 31.8, 44.6, 49.6, 51.9, 55.4, 60.3, 109.4, 110.4, 113.7, 119.8, 120.3, 121.7, 123.9, 125.5, 128.3, 129.0, 131.0, 136.4, 137.1, 138.8, 143.4, 147.2, 154.7, 156.0, 192.1. Anal. Calcd. For $C_{31}H_{30}N_6O_4$: C, 67.62; H, 5.49; N, 15.26%. Found: C, 67.29; H, 5.27; N, 15.07%. ESI–MS *m/z*: 551 $[M+H]^+$.

Molecular modelling

Docking studies were performed with Autodock (ver. 4.2.6.) The 3D structure of acetylcholinesterase (PDB entry code (4EY7) in complex with donepezil) and butyrylcholinesterase (PDB entry code (4BDS) in complex with tacrine) was obtained from protein data bank. After editing the crystallographic structure which contains removing ligand and water molecules and adding hydrogen atoms, the prepared ligands (the ligands were sketched and optimized in MarvinSketch 15.8.1, 2015) were docked into the active site of protein. Upon completion of docking simulations, the superior docking poses were selected and their interactions with the receptor were drafted and viewed by Discovery Studio visualizer

4.5. To visualize the 3D and 2D diagram interactions, we open the ligand and receptor complex file created by Autodock with this programme.

Anticholinesterase assay

Biological tests were performed to determine the amount of inhibition of acetylcholinesterase enzyme by Ellman method. In this method, hydrolysis of acetylthiocholine and butyrylthiocholine by AChE and BuChE yields to the production of acetate or butyrate and thiocholine. Butyrylcholinesterase and acetylcholinesterase are obtained from equine serum and electrophorus electricus (AChE, eel), respectively. Each compound was tested in five different concentrations against the enzyme to achieve a range of inhibition between 20 and 80%. After 5-min incubation of a mixture containing phosphate buffer (0.1 M, pH = 8.0, 2 mL), acetylcholinesterase or butyrylcholinesterase (40 µL), 5,5-dithio-bis-2-nitrobenzoic acid (DTNB, 60 µL) and compounds solution (30 µL), acetylthiocholine iodide or butyrylthiocholine iodide (40 µL) was added as substrate and the change of absorbance was recorded at 412 nm for 2 min using a Synergy BioTech® multiplate reader. The stock solution was prepared by absolute ethanol. The absorption changes were measured in 2 min at 412 nm using the UV Unico Double Beam spectrophotometer. Their IC_{50} values were obtained from the logarithm of the concentration of inhibitor against the inhibitory percentages.

Determination of the inhibitory potency on $A\beta_{1-42}$ self-aggregation

In order to determinate the inhibitory properties of compounds on the $A\beta_{1-42}$ self-aggregation, a Thioflavin T (ThT)-based fluorometric assay was assessed. To prepare $A\beta_{1-42}$ peptide with final Aβ concentration of 50 µM, $A\beta_{1-42}$ peptide (Sigma-Aldrich) prepared was dissolved in NaCl phosphate buffer (pH 7.4) and incubated at 37 °C for 72 h. To performing the experiment, 10 µL $A\beta_{1-42}$ was added to phosphate buffer (pH 7.4) with and without inhibitor (100 µM) and then samples (100 µL) were incubated. After incubation, 50 µL of thioflavin-T with 200 µM concentration in 50 mM glycine–NaOH buffer (pH 8.5) was added into the samples to achieve final volume of 150 µL. The fluorescence intensity was carried out at 448 nm/490 nm using a SpectraMax® Microplate Reader. Donepezil (100 µM, Sigma D-6821) was also tested as reference agents. Self-aggregation was determined from the following calculation: $[(IF_i/IF_o) \times 100]$ where IF_i and IF_o are the fluorescence intensities obtained for Aβ in the presence and in the absence of inhibitors

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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