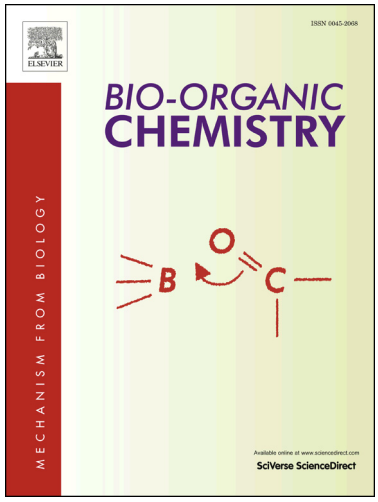

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Design and synthesis of novel anti-Alzheimer's agents: acridine-chromenone and quinoline-chromenone hybrids

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Key words: Acridine-Chromenone, Alzheimer's disease, Anti-Cholinesterase, Docking study, Neuroprotective activity, Quinoline-Chromenone, β-Secretase inhibitor.

Abstract: A novel series of acridine-chromenone and quinoline-chromenone hybrids were designed, synthesized, and evaluated as anti-Alzheimer's agents. All synthesized compounds were evaluated as cholinesterases (ChEs) inhibitors and among them, 7-(4-(6-chloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-9-ylamino)phenoxy)-4-methyl-2*H*-chromen-2-one (**8e**) exhibited the most potent anti-acetylcholinesterase (AChE) inhibitory activity (IC_{50} = 16.17 µM) comparing with rivastigmine (IC_{50} = 11.07 µM) as the reference drug. Also, compound **8e** was assessed for its β-secretase (BACE1) inhibitory and neuroprotective activities which demonstrated satisfactory results. It should be noted that both kinetic study on the inhibition of AChE and molecular modeling revealed that compound **8e** interacted simultaneously with both the catalytic active site (CAS) and peripheral anionic site (PAS) of AChE.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia which is characterized by the progressive cognitive impairment in the elderly people. The classic characteristics found in the brains of AD patients confirmed that the following factors are involved in the disease: *i*) loss of cholinergic neurons in areas of the brain associated with memory and cognition, *ii*) accumulation of the β-amyloid peptide (βA), and *iii*) formation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein [1-2]. Moreover, other factors such as mitochondrial dysfunction, hormone imbalance, inflammation, mitotic dysfunction, calcium mishandling, and genetic components play important roles in the development of disease [3]. Among factors involved in AD, the cholinergic hypothesis is related to the low concentration of acetylcholine (ACh) in hippocampus and cortex which are associated with learning and memory functions [4]. ACh is rapidly hydrolyzed by acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes into choline and acetic acid leading to the termination of neurotransmission signal. AChE has shown a very high catalytic efficiency for ACh hydrolysis and it is widely found in cholinergic synapses. However, BChE has exhibited low activity in the hydrolysis reaction and it is mainly distributed in plasma and tissues playing an supplementary role in synaptic transmission [5]. It should be considered that in patients with AD, the activity of AChE decreases or does not change but the activity of BChE gradually increases leading to imbalance between AChE and BChE [6]. It sees that both AChE and BChE are probably to be involved in the regulation of the ACh level [7] and ChE inhibitors increase ACh levels in cholinergic neurons which can be considered as an efficient strategy for the treatment of AD symptoms [8-9].

Deposition of βA (amyloid plaques) in the brain has emerged as one of the most important origin of AD. Consequently, development of compounds possessing both AChE and βA

aggregation inhibitory activities, provides additional advantages in AD therapeutic approach [10]. In this respect, one of the versatile routes for the inhibition of βA aggregation is prevention the hydrolysis of amyloid precursor protein (APP) *via* inhibition of β-secretase (BACE1) [11]. Also, it has been reported that development of amyloid plaques and neurofibrillary (NFT) tangles in the brain may be accelerated by oxidative damages [12]. Accordingly, neuroprotective agents can be helpful in the treatment of AD by inhibiting the formation of free radicals or protecting against oxidative stress [13].

AChE possesses two binding sites including catalytic site (CS which involves catalytic anionic site (CAS) and catalytic triad) and the peripheral anionic site (PAS) mainly characterized by two tryptophan residues, Trp84 at the active site and Trp279 at the mouth of the gorge [14]. In this respect, several dual-binding inhibitors have been synthesized and evaluated for anti-AChE activity [15-18]. Tacrine, donepezil, rivastigmine, and galantamine are well-known AChE inhibitors. Tacrine is the first cholinesterase inhibitor which was approved by the FDA in 1993. However, it soon showed hepatotoxicity and was subsequently abandoned [19, 20]. In this respect, lots of efforts were made to design and synthesize tacrine-based agents with low side effects and better pharmacokinetics properties. Also, tacrine hybrids such as tacrine-4-aminoquinoline, tacrine-huperzine A, tacrine-ferulic acid, tacrine-phenylphenanthridinium, tacrine-indole were efficiently developed [21-25]. To establish further tacrine-based inhibitors, we also focused on the anti-ChE activity of chromenones (**A**-**D**) (Fig. 1) [26-30], and in continuation of our research program on the synthesis of anti-ChE agents [31], novel series of acridine-chromenone and quinoline-chromenone hybrids **8** (Fig. 2) were designed, synthesized, and evaluated for their anti-Alzheimer's activities.

2. Results and Discussion

2.1. Chemistry

Synthetic route for the preparation of acridine-chromenone and quinoline-chromenone hybrids **8a–q** is depicted in Scheme 1. Initially, two required starting materials, compounds **4** and **7** were synthesized. For this purpose, compounds **3** were prepared through the reaction of 7-hydroxycoumarins (**1**) and 1-fluoro-4-nitrobenzene (**2**) in the presence of anhydrous K_2CO_3 in DMF at 80 °C overnight. Then, the latter compound **3** tolerated reduction reaction using Zn/NH_4Cl in H_2O/EtOH at room temperature for 3 h to obtain the corresponding amine **4**. Compounds **7** including 9-chloro-1*H*,2*H*,3*H*-cyclopenta[*b*]quinolines **7a-c**, 9-chloro-1,2,3,4-tetrahydroacridines **7d-f**, 11-chloro-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]quinolines **7g-i** were prepared by condensation of commercially available anthranilic acids **5a-c** and appropriate cycloketones **6a-c** in the presence of $POCl_3$ under reflux [32]. Finally, compounds **7a-i** reacted with amines **4a-b** in the presence of KI in refluxing *n*-propanol for 12–24 h affording target compounds **8a-q** in good yields (60–80%).

2.2. *Biological activity*

*2.2.1. The anti-AChE activity of compounds **8a-q***

In vitro anti-AChE and anti-BChE activities of the synthesized compounds **8a-q** were evaluated according to the modified Ellman's method [31, 33] comparing with rivastigmine as the reference drug. All results are presented in Table 1. Based on the IC_{50} values, compounds **8a**, **8c-g**, **8j-l**, and **8o-q** showed anti-AChE activity in the range of micromolar concentrations (IC_{50} = 16.17-83.10 µM) in comparison to rivastigmine (IC_{50} = 11.07 µM). As can be seen in Table 1, compounds **8a-q** can be divided into three categories, **8a-f**, **8g-l**, **8m-q** (Fig. 2) according to the cycloalkyl fused to quinolone moiety. Among the synthesized compounds,

compound **8e** possessing methyl and chlorine groups at 4-position of chromenone and 6-position of cyclopenta[*b*]quinoline moieties, showed the most potent inhibitory activity with IC_{50} = 16.17 μM. Replacing five-membered ring (in compound **8e**) by six-membered ring leading to the formation of tetrahydroacridine scaffold (compound **8k**), reduced inhibitory activity (IC_{50} = 18.03 μM). Further replacement by seven-membered ring (compound **8p**) led to decrease of inhibitory activity (IC_{50} = 31.81 μM).

Compound **8g** with tetrahydroacridine moiety and no other substituents showed IC_{50} = 19.07 μM. Introduction of methyl group into the 4-position of chromenone moiety in compound **8j** afforded lower anti-AChE activity (IC_{50} = 22.10 μM) in comparison to its counterpart **8g**. Also, our results revealed that introduction of chlorine into 7-position of tetrahydroacridine core (compound **8l**) reduced activity (IC_{50} = 30.80 μM) comparing with **8j** and **8k**. It seems that chlorine and its position on the tetrahydroacridine moiety plays important role since the following order was observed in the inhibitory activity of compounds **8k**>**8j**>**8l**. These results are in good agreement with those obtained for compounds **8e** (IC_{50} = 16.17 μM) and **8f** (IC_{50} = 36.65 μM) as well as literature describing that 6-chlorotacrine has shown more potent activity comparing with tacrine [34, 35]. Moreover, it was perceived that in the case of similar substituents on the chromenone and quinoline moieties, fused five-membered ring induced more activity comparing with six-membered ring since **8e** was more potent than **8k**.

Another instructive point is related to compounds **8p** (IC_{50} = 31.81 μM) having seven-membered ring fused to quinoline moiety. It showed lower activity comparing with its counterpart, **8e** and **8k** (IC_{50} = 16.17, 18.03 μM, respectively).

Compounds **8f** and **8c** both having five-membered ring showed IC_{50}s = 36.65 and 38.50 µM, respectively. It is clear that the introduction of methyl to 4-position of coumarin moiety did not significantly affect inhibitory activity. Compound **8d** showed the inhibitory activity with IC_{50} = 45.27 µM. Deletion of chlorine in this compound led to the reduction of activity and it was less active than its compartments **8e** and **8f**.

Compound **8q** having chlorine at 2-position of cyclohepta[*b*]quinoline (IC_{50} = 54.12 µM) was less active than **8p** having chlorine at 3-position of cyclohepta[*b*]quinoline (IC_{50} = 31.81 µM), the same results were observed for **8e**/**8f** and **8k**/**8l** pairs. Also, it was found that the presence of seven-membered in compound **8q** induced less activity in comparison to its compartments **8f** and **8l** as obtained for **8e**>**8k**>**8p**. The result obtained for compound **8o** (IC_{50} = 64.42 µM) confirmed that deletion of chlorine reduced activity comparing with **8p** and **8q**.

Most of synthesized compounds exhibited no activity against BChE and compounds **8b**, **8g**, **8j**, and **8k** showed IC_{50} = 11.65-38.63 µM. Among them, **8b** lacking methyl group at 4-position of chromenone and having chlorine at 6-position of cyclopenta[*b*]quinolone moiety was the most potent compound (IC_{50} = 11.65) comparing with rivastigmine as the reference drug (IC_{50} = 7.72 µM). The remained three active compounds were belonged to the tetrahydroacridine group. Compound **8g** showed IC_{50} = 28.67 µM and insertion of methyl group into 4-position of chromenone moiety led to reduction of inhibitory activity in compounds **8j** and **8k**.

2.2.2. Kinetic studies

In order to obtain insight into the inhibition mode of AChE by the most potent compound **8e**, a kinetics study was carried out using the modified Ellman's method [31, 33]. As can be seen in Fig. 3, graphical analysis of the Lineweaver-Burk reciprocal plots confirmed a mixed type of

inhibition suggesting that compound **8e** can bind to the both free enzyme and enzyme-substrate complex. It seems that compound **8e** interacts with the both peripheral anionic site (PAS) and the catalytic anionic site (CAS) of enzyme. The inhibition constant (K_i = 34 µM) was calculated using secondary replots of the slope versus concentrations of compound **8e**.

2.2.3. BACE1 enzyme inhibitory activity of compound 8e

BACE-1 inhibitory activity of the most potent anti-AChE compound **8e** was evaluated *via* a fluorescence resonance energy transfer (FRET) based BACE-1 kit including BACE-1 enzyme and specific APP based peptide substrate (Rh-EVNLDAEFK-quencher). Experiments were repeated for three times and compared with the reference compound OM99-2. Results are shown in Table 2 indicating that compound **8e** possesses good inhibitory activity with IC_{50} = 7.99 µM in comparison to OM99-2 (IC_{50} = 0.014 µM). It is worth mentioning that non-peptide structure of compound **8e** is desired and acts as dual inhibitor of AChE and BACE1.

*2.2.4. Neuroprotective effect of compound **8e** against H_2O_2-induced cell death in PC12 neurons*

The PC12 cell line is a useful model for studying neuronal differentiation [36]. Consequently, differentiated PC12 cells and H_2O_2 were selected as *in vitro* model and oxidative agent, respectively [37]. Neuroprotective activity of the most potent compound **8e** against AChE was assessed by subjecting PC12 cells to H_2O_2-induced damage. As depicted in Fig. 4, the percent of cell viability was calculated in comparison to control group. Compound **8e** demonstrated remarkable neuroprotective activity at 50 and 100 µM (cell viability = 80.03 and 80.07 %, respectively and P <0.001 vs. H_2O_2 treatment alone). However, compound **8e** showed

moderate neuroprotective activity at 10 μM (cell viability = 66.15 % and P <0.05 vs. H_2O_2 treatment alone).

2.2.3. 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity

Compounds **8b**, **8e**, **8i**, **8l**, **8n** and **8q** were evaluated for their 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity (DPPH) according to the method described in the literature [38]. The test compounds were evaluated at 33, 167, 350, 700 μg/mL. All results are shown in Table 3. The inhibition percentage values were compared to butylated hydroxyanisole (BHA) as a standard antioxidant. All the tested compounds showed no remarkable antioxidant activities.

2.2.4. Docking studies

To understand a possible binding mode of the most active compound **8e**, a molecular modeling study was performed with Torpedo Californica AChE (PDB code: 2CMF) using the docking program, AutoDock 4.2 package with Discovery Studio 4.0 Client. Docking result showed that 100 GA runs for compound **8e** were categorized in 8 clusters and the mean binding energy scored by Autodock ranged from -11.82 to -14.58 (in kcal/mol). The lowest energy conformation of the highest populated cluster was selected for analysis (first cluster).

Docking results indicated that the most active compound **8e** is located in the binding site of AChE as the same as bis-(5)-tacrine. Also, it was clear that compound **8e** bound to both the CAS and the PAS. It has occupied the mid-gorge site between these two active sites of enzyme (Fig. 5 and Fig. 6). As it is shown in Fig. 6, there are two π-π interactions between quinoline moiety and Trp84 and Phe330 residues (in the CAS). Another one is hydrophobic interaction of chlorine at 6-position of compound **8e** with Ile439, Met436, Tyr442 and Trp432 residues (in the CAS). The phenoxy group has also occupied the mid-gorge making π-anion interaction

with Asp72 and π-π interaction with Phe330. Moreover, the 4-methylchromenone moiety established π-π and hydrophobic interaction with Trp279 (in the PAS).

2.2.5. Virtual calculation of pharmacokinetic properties

To qualify compound **8e** as drug candidate, some pharmacokinetics aspects, physicochemical and topological properties such as octanol-water partition coefficient (Clog P), number of H-bond donors (HBD), number of H-bond acceptors (HBA), rotatable bonds count (RBC), and topological polar surface area (tPSA) were calculated (Table 4). According to the Lipinski's rule-of-five including MW≤ 500, HBD ≤ 5, HBA ≤ 10, and Clog P ≤ 5 [39, 40] and as the compounds had rotatable bonds ≤ 10 and polar surface area ≤ 140 $Å^2$, it seems that these compounds are relatively orally active drugs in humans. The obtained results revealed that compound **8e** had 1 H-bond donor and 4 H-bond acceptors and it possessed tPSA 60.45 $Å^2$ and 3 RBC. Compound **8e** had molecular weight 468.9.93 Da with Clog P value of 8.23.

3. Conclusion

In summary, new acridine-chromenone and quinoline-chromenone hybrids were designed, synthesized and evaluated as novel anti-alzheimer's agents. Most of these compounds showed moderate potency for inhibition of AChE and compound **8e** indicated the most anti-AChE activity (IC_{50} = 16.17 µM). This compound contained a 4-methylchromenone moiety as a peripheral site interacting unit and quinoline moiety as a catalytic site binding unit. The kinetic studies and molecular modeling showed that compound **8e** had enough length to bind to both the CAS and the PAS of AChE as a dual binding inhibitor. The quinoline moiety of compound **8e** showed parallel π–π stacking with Trp84 at the gorge's bottom in the CAS, while the 4-

methylchromenone moiety of compound **8e** depicted parallel π–π stacking with Trp279 at the gorge's mouth in the PAS. Also, compound **8e** was evaluated for its neuroprotective and BACE1 inhibitory activities. The neuroprotective effect was moderate in comparison with quercetin. It should be noted that compound **8e** showed good BACE1 inhibitory activity (IC_{50} = 7.99 μM) which can be considered as a non-peptide agent. Our study presented advantageous results for AD drug discovery focusing on the novel acridine-chromenone, quinoline-chromenone hybrids and dual AChE/BACE1 inhibitors.

4. Methods and Materials

4.1. General chemistry

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra as well as 2D HSQC experiment were recorded on a Bruker FT-500, using TMS as an internal standard. IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (KBr disks). Elemental analysis was performed on an Elementar Analysensystem GmbH VarioEL CHNS mode. All chemical were obtained from Merck and Aldrich. 4-Methyl-7-hydroxycoumarin was prepared by Pechmann reaction via the condensation of resorcinol and ethylacetoacetate in the presence of concentrated sulfuric acid [41].

*4.2. General procedure for the synthesis of compounds **3***

K_2CO_3 (6 mmol) was added to a mixture of coumarin derivative **1** (10 mmol) and 1-fluoro-4-nitrobenzene (10 mmol) in DMF and heated at 80 °C overnight. After completion of reaction, the reaction mixture was cooled down to room temperature, poured into ice water; the precipitates were filtered off and washed with water to afford products **3** as cream solids.

*4.3. General procedure for the synthesis of compounds **4***

Zinc powder (10 mmol) was gradually added to a suspension of compound **3** (5 mmol) and NH_4Cl (10 mmol) in H_2O/EtOH (20 mL, 1:1). Then, the mixture was stirred at room temperature for 3 h. Upon completion of the reaction (checked by TLC), the mixture was diluted with H_2O, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pure compounds **4** as off-cream solids.

*4.4. General procedure for the synthesis of compounds **7***

$POCl_3$ (25 mL) was added to a mixture of anthranilic acid derivative **5** (23 mmol) and cycloketones derivative **6** (25 mmol) in an ice bath. The mixture was heated at reflux for 3 h. Then, it was cooled to room temperature and concentrated to give slurry. The residue was diluted with ethyl acetate, neutralized with aqueous K_2CO_3, the organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum affording a pale brown solid which was purified by flash chromatography on silica gel using petroleum ether/ ethyl acetate (9:1) to give **7** in 80-90 % yield.

*4.5. General procedure for the synthesis of compounds **8***

KI (50 mg) was added to a mixture of compound **7** (1.1 mmol) and compound **4** (1 mmol) in *n*-propanol. The mixture was heated at 100 $^{\circ}$C for 12-24 h. Next, it was cooled room temperature; the mixture was dissolved in 10% NaOH, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. Finally, the residue was purified by column chromatography on silica gel using petroleum ether/ethyl

acetate (1:9) to give **8** in 60-85 % yield. The structure of all compounds **8** was elucidated using ^{1}H and ^{13}C NMR as well as elemental analysis. Also, 2D HSQC experiment was performed for compound **8i** to describe chemical shift correlation between directly-bonded ^{1}H and ^{13}C (Table 5).

*4.5.1. 7-(4-((2,3-dihydro-1H-cyclopenta[b]quinolin-9-yl)amino)phenoxy)-2H-chromen-2-one (**8a**).* Yellow solid; yield: 68%, mp 212-214 °C. IR (KBr): 3391, 3065, 2953, 2922, 2840, 1726, 1616 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 8.02 (d, *J* = 8.0 Hz, 2H, $H_{5'}$, $H_{8'}$), 7.67 (d, *J* = 9.5 Hz, 1H, H_4), 7.61 (t, *J* = 8.0 Hz, 1H, $H_{6'}$), 7.44-7.42 (m, 2H, H_5, $H_{7'}$), 7.04 (d, *J* = 8.7 Hz, 2H, OC_6H_4), 6.99 (d, *J* = 8.7 Hz, 2H, OC_6H_4), 6.94 (dd, *J* = 8.5, 2.1 Hz, 1H, H_6), 6.83 (s, 1H, H_8), 6.30 (d, *J* = 9.5 Hz, 1H, H_3), 3.15 (t, *J* = 7.0 Hz, 2H, CH_2), 2.57 (t, *J* = 7.0 Hz, 2H, CH_2), 2.12 (quin, *J* = 7.0 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): 168.2 ($C_{3'a}$), 161.1 (C=O), 159.7 (C_7), 154.9 (C_{8a}), 150.5 ($C_{4'a}$), 148.3 (C-O), 143.9 (C_4), 141.5 ($C_{9'}$), 140.0 (C-NH), 129.8 ($C_{6'}$), 128.2 ($C_{5'}$), 128.1 (C_5), 126.6 ($C_{7'}$), 124.1 ($C_{8'}$), 122.7 ($C_{8'a}$), 121.4 ($C_{9'a}$), 120.5 (2C, OC_6H_4), 120.4 (2C, OC_6H_4), 113.7 (C_{4a}), 113.3 (C_6), 113.6 (C_3), 103.8 (C_8), 34.2 ($C_{3'}$), 30.4 ($C_{1'}$), 22.9 ($C_{2'}$). Anal. Calcd for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 77.31; H, 4.96; N, 6.82.

*4.5.2. 7-(4-((6-Chloro-2,3-dihydro-1H-cyclopenta[b]quinolin-9-yl)amino)phenoxy)-2H-chromen-2-one (**8b**).* Cream solid; yield: 75%, mp 217-219 °C. IR (KBr): 3343, 3071, 2944, 2855, 1719, 1615, 1561 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 7.99 (d, *J* = 2.0 Hz, 1H, $H_{5'}$), 7.88 (d, *J* = 8.9 Hz, 1H, $H_{8'}$), 7.67 (d, *J* = 9.4 Hz, 1H, H_4), 7.44 (d, *J* = 8.5 Hz, 1H, H_5), 7.32 (dd, *J* = 8.9, 2.0 Hz, 1H, $H_{7'}$), 7.03 (d, *J* = 8.8 Hz, 2H, OC_6H_4), 6.96-6.93 (m, 3H, OC_6H_4, H_6), 6.79 (d, *J* = 2.3 Hz, 1H, H_8), 6.29 (d, *J* = 9.4 Hz, 1H, H_3), 3.12 (t, *J* = 7.5 Hz, 2H, CH_2), 2.63 (t, *J* = 7.5

Hz, 2H, CH_2), 2.14 (quin, *J* = 7.5 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 169.9 ($C_{3'a}$), 161.6 (C=O), 160.8 (C_7), 155.5 (C_{8a}), 149.9 ($C_{4'a}$), 148.7 (C-O), 143.2 (C_4), 141.9 ($C_{9'}$), 139.3 (C-NH), 134.6 ($C_{6'}$), 129.0 (C_5), 127.3 ($C_{5'}$), 125.5 ($C_{8'}$), 123.4 ($C_{7'}$), 122.5 ($C_{8'a}$), 121.4 (2C, OC_6H_4), 121.2 (2C, OC_6H_4), 119.7 ($C_{9'a}$), 114.2 (C_6), 114.0 (C_3), 113.8 (C_{4a}), 104.5 (C_8), 34.8 ($C_{3'}$), 30.4 ($C_{1'}$), 23.2 ($C_{2'}$). Anal. Calcd for $C_{27}H_{19}ClN_2O_3$: C, 71.29; H, 4.21; N, 6.16. Found: C, 77.45; H, 4.40; N, 6.32.

*4.5.3. 7-(4-((7-Chloro-2,3-dihydro-1H-cyclopenta[b]quinolin-9-yl)amino)phenoxy)-2H-chromen-2-one (**8c**).* Cream solid; yield: 79%, mp 234-236 °C. IR (KBr): 3342, 2941, 2901, 2852, 1720, 1619, 1503 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 7.96 (d, *J* = 8. 9, 1H, $H_{5'}$), 7.95 (s, 1H, $H_{8'}$), 7.67 (d, *J* = 9.0 Hz, 1H, H_4), 7.39 (dd, *J* = 8.7, 2.0 Hz, 1H, $H_{6'}$), 7.43 (d, *J* = 8.5, 1H, H_5), 7.04 (d, *J* = 8.6 Hz, 2H, OC_6H_4), 6.95 (d, *J* = 8.6 Hz, 2H, OC_6H_4), 6.93 (d, *J* = 8.5, 1H, H_6), 6.82 (d, *J* = 2.2, 1H, H_8), 6.67 (bs, 1H, NH), 6.30 (d, *J* = 9.0 Hz, 1H, H_3), 3.14 (t, *J* = 7.5 Hz, 2H, CH_2), 2.63 (t, *J* = 7.5 Hz, 2H, CH_2), 2.14 (quin, *J* = 7.5 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 169.1 ($C_{3'a}$), 161.6 (C=O), 160.8 (C_7), 155.5 (C_{8a}), 149.9 ($C_{4'a}$), 146.4 (C-O), 143.1 (C_4), 140.9 ($C_{9'}$), 139.2 (C-NH), 130.7 ($C_{7'}$), 130.0 ($C_{6'}$), 129.5 ($C_{5'}$), 129.0 (C_5), 123.3 ($C_{8'}$), 122.2 ($C_{8'a}$), 121.2 (2C, OC_6H_4), 121.0 (2C, OC_6H_4), 119.1 ($C_{9'a}$), 114.2 (C_6), 114.0 (C_3), 113.8 (C_{4a}), 104.5 (C_8), 34.8 ($C_{3'}$), 30.5 ($C_{1'}$), 23.3 ($C_{2'}$). Anal. Calcd for $C_{27}H_{19}ClN_2O_3$: C, 71.29; H, 4.21; N, 6.16. Found: C, 71.11; H, 4.38; N, 6.29.

*4.5.4. 7-(4-((2,3-Dihydro-1H-cyclopenta[b]quinolin-9-yl)amino)phenoxy)-4-methyl-2H-chromen-2-one (**8d**).* Off-green solid; yield: 60%, mp 161-163 °C. IR (KBr): 3360, 3037, 2969, 2923, 1723, 1621, 1498 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.74 (s, 1H, NH), 8.18 (d, *J* = 8.0 Hz, 1H, $H_{5'}$), 7.85 (d, *J* = 8.0 Hz, 1H, $H_{8'}$), 7.74 (d, *J* = 9.0 Hz, 1H, H_5), 7.61 (t, *J* = 8.0 Hz, 1H, $H_{H6'}$), 7.44 (t, *J* = 8.0 Hz, 1H, $H_{7'}$), 7.06 (d, *J* = 8.9 Hz, 2H, OC_6H_4), 6.95-6.94 (m, 3H, H_6,

OC_6H_4), 6.84 (J = 2.0 Hz, 1H, H_8), 6.24 (s, 1H, H_3), 2.98 (t, J = 7.2 Hz, 2H, CH_2), 2.54 (t, J = 7.2 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.02 (quin, J = 7.2 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): 168.4 ($C_{3'a}$), 161.1 (C=O), 159.8 (C_7), 154.4 (C_{8a}), 153.1 ($C_{4'a}$), 148.3 (C-O), 148.2 (C_4), 141.5 ($C_{9'}$), 140.0 (C-NH), 128.4 ($C_{6'}$), 128.3 ($C_{5'}$), 127.0 (C_5), 124.2 ($C_{7'}$), 122.9 ($C_{8'}$), 121.4 ($C_{8'a}$), 121.3 ($C_{9'a}$), 120.7 (2C, OC_6H_4), 120.5 (2C, OC_6H_4), 114.6 (C_{4a}), 113.3 (C_6), 112.0 (C_3), 103.9 (C_8), 34.3 ($C_{3'}$), 30.7 ($C_{1'}$), 23.1($C_{2'}$), 18.1 (Me). Anal. Calcd for $C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45. Found: C, 77.65; H, 5.21; N, 6.59.

*4.5.5 7-(4-((6-Chloro-2,3-dihydro-1H-cyclopenta[b]quinolin-9-yl)amino)phenoxy)-4-methyl-2H-chromen-2-one (**8e**).* Cream solid; yield: 75%, mp 217-219 °C. IR (KBr): 3355, 2961, 1737, 1610, 1581, 1539 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.85 (s, 1H, NH), 8.19 (d, J = 9.0 Hz, 1H, $H_{8'}$), 7.85 (d, J = 2.0 Hz, 1H, $H_{5'}$), 7.75 (d, J = 8.5 Hz, 1H, H_5), 7.46 (dd, J = 9.0, 2.0 Hz, 1H, $H_{7'}$), 7.08 (d, J = 8.8 Hz, 2H, OC_6H_4), 6.97-6.94 (m,3H, H_6, OC_6H_4), 6.85 (d, J = 2.5 Hz, 1H, H_8), 6.25 (s, 1H, H_3), 2.97 (t, J = 7.5 Hz, 2H, CH_2), 2.50 (t, J = 7.5 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.01 (quin, J = 7.5 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): 170.2 ($C_{3'a}$), 161.0 (C=O), 159.8 (C_7), 154.4 (C_{8a}), 153.1 ($C_{4'a}$), 149.1 (C-O), 148.6 (C_4), 141.6 ($C_{9'}$), 139.6 (C-NH), 132.8 ($C_{6'}$), 127.5 ($C_{5'}$), 127.0 (C_5), 124.9 ($C_{8'}$), 124.4 ($C_{7'}$), 121.4 ($C_{8'a}$), 120.9 (2C, OC_6H_4), 120.6 (2C, OC_6H_4), 120.0 ($C_{9'a}$), 114.6 (C_{4a}), 113.4 (C_6), 112.0 (C_3), 104.0 (C_8), 34.4 ($C_{3'}$), 30.7 ($C_{1'}$), 23.0 ($C_{2'}$), 18.1 (Me). Anal. Calcd for $C_{28}H_{21}ClN_2O_3$: 77.72; H, 4.51; N, 5.97. Found: C, 77.85; H, 4.35; N, 6.12.

*4.5.6. 7-(4-((7-Chloro-2,3-dihydro-1H-cyclopenta[b]quinolin-9-yl)amino)phenoxy)-4-methyl-2H-chromen-2-one (**8f**).* Cream solid; yield: 74%, mp 133-135 °C. IR (KBr): 3351, 2953, 2911, 1718, 1610, 1563, 1508 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.91 (s, 1H, NH), 8.27 (d, J = 2.2 Hz, 1H, $H_{8'}$), 7.86 (d, J = 8.9 Hz, 1H, $H_{5'}$), 7.77 (d, J = 8.8 Hz, 1H, H_5), 7.63 (dd, J =

8.9, 2.2 Hz, 1H, $H_{6'}$), 7.10 (d, *J* = 8.8 Hz, 2H, OC_6H_4), 6.96 (m, 3H, H_6, OC_6H_4), 6.87 (d, *J* = 2.4 Hz, 1H, H_8), 6.28 (s, 1H, H_3), 2.97 (t, *J* = 7.5 Hz, 2H, CH_2), 2.50 (t, *J* = 7.5 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.03 (quin, *J* = 7.5 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): 169.4 ($C_{3'a}$), 161.1 (C=O), 159.8 (C_7), 154.4 (C_{8a}), 153.2 ($C_{4'a}$), 148.6 (C-O), 146.9 (C_4), 140.7 ($C_{9'}$), 139.5 (C-NH), 130.5 ($C_{7'}$), 128.7 ($C_{6'}$), 128.6 (C_5), 127.1 ($C_{5'}$), 122.3 ($C_{8'}$), 121.9 ($C_{8'a}$), 121.8 ($C_{9'a}$), 120.9 (2C, OC_6H_4), 120.7 (2C, OC_6H_4), 114.6 (C_{4a}), 113.4 (C_6), 112.0 (C_3), 104.0 (C_8), 34.4 ($C_{3'}$), 30.9 ($C_{1'}$), 23.1 ($C_{2'}$), 18.1 (Me). Anal. Calcd for $C_{28}H_{21}ClN_2O_3$: C, 72.72; H, 4.51; N, 5.97. Found: C, 72.88; H, 4.70; N, 6.18.

*4.5.7 7-(4-((1,2,3,4-Tetrahydroacridin-9-yl)amino)phenoxy)-2H-chromen-2-one (**8g**).* Off-cream solid; yield: 71%, mp 130-132 °C. IR (KBr): 3251, 3080, 2931, 2864, 1716, 1615 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 8.02 (d, *J* = 8.2 Hz, 1H, $H_{8'}$), 7.81 (d, *J* = 8.2 Hz, 1H, $H_{5'}$), 7.64 (d, *J* = 9.0 Hz, 1H, H_4), 7.60 (t, *J* = 8.2 Hz, 1H, $H_{7'}$), 7.39 (d, *J* = 8.5 Hz, 1H, H_5), 7.36 (t, *J* = 8.2, 1H, $H_{7'}$), 6.93 (d, *J* = 8.7 Hz, 2H, OC_6H_4), 6.90 (d, *J* = 8.5 Hz, 1H, H_6), 6.77 (d, *J* = 2.3 Hz, 1H, H_8), 6.75 (d, *J* = 8.7 Hz, 2H, OC_6H_4), 6.26 (d, *J* = 9.0 Hz, 1H, H_3), 3.16 (t, *J* = 6.0 Hz, 2H, CH_2), 2.63 (t, *J* = 6.0 Hz, 2H, CH_2), 1.97 (quin, *J* = 6.0 Hz, 2H, CH_2), 1.87 (quin, *J* = 6.0 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 162.1 ($C_{4'a}$), 160.9 (C=O), 159.6 (C_7), 155.5 (C_{8a}), 148.4 ($C_{10'a}$), 146.6 (C-O), 143.7 (C_4), 143.2 ($C_{9'}$), 141.8 (C-NH), 129.0 ($C_{6'}$), 128.1 (C_5), 125.2 ($C_{5'}$), 123.16 ($C_{7'}$), 123.10 ($C_{8'}$), 122.7 ($C_{8'a}$), 122.5 ($C_{9'a}$), 121.5 (2C, OC_6H_4), 118.1 (2C, OC_6H_4), 114.1 (C_6), 113.7 (C_3), 113.6 (C_{4a}), 104.2 (C_8), 33.5 ($C_{4'}$), 25.3 ($C_{1'}$), 22.6 ($C_{2'}$), 22.6 ($C_{3'}$). Anal. Calcd for $C_{28}H_{22}N_2O_3$: C, 77.40; H, 5.10; N, 6.45. Found: C, 77.29; H, 5.26; N, 6.60.

*4.5.8. 7-(4-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)phenoxy)-2H-chromen-2-one (**8h***

Off-orange solid; yield: 85%, mp 134-136 °C. IR (KBr): 3524, 3245, 3085, 2933, 2864, 1718,

1613, 1558 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (s, 1H, $H_{5'}$), 7.74 (d, *J* = 9.0 Hz, 1H, $H_{8'}$), 7.66 (d, *J* = 9.5 Hz, 1H, H_4), 7.42 (d, *J* = 8.5 Hz, 1H, H_5), 7.30 (d, *J* = 9.0 Hz, 1H, $H_{7'}$), 6.96 (d, *J* = 8.8 Hz, 2H, OC_6H_4), 6.93 (dd, , *J* = 8.5, 2.3 Hz, 1H, H_6), 6.78 (m, 3H, H_8, OC_6H_4), 6.29 (d, *J* = 9.5 Hz, 1H, H_3), 3.12 (t, *J* = 6.0 Hz, 2H, CH_2), 2.63 (t, *J* = 6.0 Hz, 2H, CH_2), 1.97 (quin, *J* = 6.0 Hz, 2H, CH_2), 1.91 (quin, *J* = 6.0 Hz, 2H, CH_2) . ^{13}C NMR (125 MHz, $CDCl_3$): 161.9 ($C_{4'a}$), 160.9 (C=O), 160.8 (C_7), 155.5 (C_{8a}), 148.7 ($C_{10'a}$), 147.3 (C-O), 143.7 ($C_{9'}$), 143.2 (C_4), 141.5 (C-NH), 134.7 ($C_{6'}$), 128.9 ($C_{5'}$), 127.3 (C_5), 125.9 ($C_{8'}$), 124.7 ($C_{7'}$), 123.0 ($C_{8'a}$), 121.6 (2C, OC_6H_4), 120.9 ($C_{9'a}$), 118.3 (2C, OC_6H_4), 114.1 (C_6), 113.8 (C_3), 113.6 (C_{4a}), 104.5 (C_8), 33.7 ($C_{4'}$), 25.2 ($C_{1'}$), 22.5 ($C_{2'}$, $C_{3'}$). Anal. Calcd for $C_{28}H_{21}ClN_2O_3$: C, 71.72; H, 4.51; N, 5.97. Found: C, 71.51; H, 4.60; N, 6.05.

*4.5.9. 7-(4-((7-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)phenoxy)-2H-chromen-2-one (**8i**).* Cream solid; yield: 65%, mp 228-230 °C. IR (KBr): 3357, 3047, 2925, 2858, 1718, 1611, 1554 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 7.98 (d, *J* = 9.0 Hz, 1H, $H_{5'}$), 7.76 (d, *J* = 2.0 Hz, 1H, $H_{8'}$), 7.65 (d, *J* = 9.5 Hz, 1H, H_4), 7.51 (dd, *J*= 9.0, 2.0 Hz, 1H, $H_{6'}$), 7.40 (d, *J* = 8.5 Hz, 1H, H_5), 6.97 (d, *J* = 8.8 Hz, 2H, OC_6H_4), 6.90 (dd, *J* = 8.5, 2.3 Hz, 1H, H_6), 6.80 (d, *J* = 2.3 Hz, 1H, H_8), 6.78 (d, *J* = 8.8 Hz, 1H, OC_6H_4), 6.28 (d, *J* = 9.5 Hz, 1H, H_3), 3.15 (t, *J* = 6.2 Hz, 2H, CH_2), 2.68 (t, *J* = 6.2 Hz, 2H, CH_2), 1.93 (quin, *J* = 6.2 Hz, 2H, CH_2), 1.86 (quin, *J* = 6.2 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 161.9 ($C_{3'a}$), 161.0 (C=O), 159.7 (C_7), 155.5 (C_{8a}), 149.1 ($C_{4'a}$), 144.2 (C-O), 143.8 ($C_{9'}$), 143.3 (C_4), 141.0 (C-NH), 131.0 ($C_{7'}$), 130.1 ($C_{6'}$), 129.0 ($C_{5'}$, C_5), 123.4 ($C_{8'a}$), 123.4 ($C_{9'a}$), 123.1 ($C_{8'}$), 121.7 (2C, OC_6H_4), 118.9 (2C, OC_6H_4), 114.1 (C_6), 113.9 (C_3), 113.7 (C_{4a}), 104.4 (C_8), 32.8 ($C_{4'}$), 25.5 ($C_{1'}$), 22.3 ($C_{2'}$, $C_{3'}$). Anal. Calcd for $C_{28}H_{21}ClN_2O_3$: C, 71.72; H, 4.51; N, 5.97. Found: C, 71.53; H, 4.46; N, 6.08.

*4.5.10. 4-Methyl-7-(4-((1,2,3,4-tetrahydroacridin-9-yl)amino)phenoxy)-2H-chromen-2-one (**8j**).* Cream solid; yield: 77%, mp 202-204 °C. IR (KBr): 3343, 3054, 2934, 2859, 1692, 1602, 1558 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 8.29 (s, 1H, NH), 7.91 (d, J = 8.0 Hz, 1H, $H_{8'}$), 7.86 (d, J = 8.0 Hz, 1H, $H_{5'}$), 7.72 (d, J = 8.8 Hz, 1H, H_5), 7.60 (t, J = 8.0 Hz, 1H, $H_{H6'}$) 7.41 (t, J = 8.0 Hz, 1H, $H_{7'}$), 6.97 (d, J = 8.9 Hz, 2H, OC_6H_4), 6.91 (dd, J = 8.8, 2.5 Hz, 1H, H_6), 6.79 (d, J = 2.5 Hz, 1H, H_8), 6.68 (d, J = 8.9 Hz, 2H, OC_6H_4), 6.67 (d, J = 1.2 Hz, 1H, H_3), 3.02 (t, J = 6.3 Hz, 2H, CH_2), 2.69 (t, J = 6.3 Hz, 2H, CH_2), 2.38 (d, J = 1.2 Hz, 3H, CH_3), 1.87 (quin, J = 6.3 Hz, 2H, CH_2), 1.76 (quin, J = 6.3 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): 161.4 ($C_{4'a}$), 159.8 (C=O), 159.5 (C_7), 154.3 (C_{8a}), 153.1 ($C_{10'a}$), 146.9 (C-O), 146.6 ($C_{9'}$), 143.0 (C_4), 142.6 (C-NH), 128.4 ($C_{6'}$), 128.3 ($C_{5'}$), 126.9 (C_5), 124.6 ($C_{7'}$), 124.06 ($C_{8'a}$), 123.4 ($C_{8'}$), 123.2 ($C_{9'a}$), 121.1 (2C, OC_6H_4), 116.5 (2C, OC_6H_4), 114.3(C_{4a}), 113.1 (C_6), 111.8 (C_3), 103.6 (C_8), 33.4 ($C_{4'}$), 25.3 ($C_{1'}$), 22.3 ($C_{2'}$), 22.1 ($C_{3'}$), 18.0 (Me). Anal. Calcd for $C_{29}H_{24}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.78; H, 5.21; N, 6.42.

*4.5.11. 7-(4-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)phenoxy)-4-methyl-2H-chromen-2-one (**8k**).* Off-cream solid; yield: 68%, mp 193-195 °C. IR (KBr): 3367, 2933, 1727, 1610, 1556 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 8.43 (s, 1H, NH), 7.93 (d, J = 9.0 Hz, 1H, $H_{8'}$), 7.89 (s, 1H, $H_{5'}$), 7.72 (d, J = 8.8 Hz, 1H, H_5), 7.44 (d, J = 9.0 Hz, 1H, $H_{7'}$), 6.99 (d, J = 8.5 Hz, 2H, OC_6H_4), 6.91 (dd, J = 8.8, 2.2 Hz, 1H, H_6), 6.80 (d, J = 2.2 Hz, 1H, H_8), 6.73 (d, J = 8.5 Hz, 2H, OC_6H_4), 6.25 (s, 1H, H_3), 3.02 (t, J = 6.0 Hz, 2H, CH_2), 2.66 (t, J = 6.0 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 1.87 (quin, J = 6.0 Hz, 2H, CH_2), 1.76 (quin, J = 6.0 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): 161.3 ($C_{4'a}$), 161.1 (C=O), 159.8 (C_7), 154.4 (C_{8a}), 153.1 ($C_{10'a}$), 147.3 (C-O), 147.1 ($C_{9'}$), 143.5 (C_4), 142.2 (C-NH), 133.0 ($C_{6'}$), 127.2 ($C_{5'}$), 126.9 (C_5), 125.7 ($C_{8'}$), 125.1 ($C_{7'}$), 124.08 ($C_{8'a}$), 121.6 ($C_{9'a}$), 121.2 (2C, OC_6H_4), 117.1 (2C, OC_6H_4), 114.4

(C_{4a}), 113.2 (C_6), 111.9 (C_3), 103.6 (C_8), 33.4 ($C_{4'}$), 25.4 ($C_{1'}$), 22.2 ($C_{2'}$), 22.0 ($C_{3'}$), 18.1. Anal. Calcd for $C_{29}H_{23}ClN_2O_3$: C, 72.12; H, 4.80; N, 5.80. Found: C, 71.91; H, 4.93; N, 5.61.

*4.5.12. 7-(4-((7-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)phenoxy)-4-methyl-2H-chromen-2-one (**8l**).* Orange solid; yield: 85%, mp 258-260 °C. IR (KBr): 3355, 2934, 2857, 1713, 1607, 1555, 1493cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.44 (s, 1H, NH), 7.97 (s, 1H, $H_{8'}$), 7.86 (d, *J* = 8.9 Hz, 1H, $H_{5'}$), 7.73 (d, *J* = 8.8 Hz, 1H, H_5), 7.48 (d, *J* = 8.9 Hz, 1H, $H_{6'}$), 7.01 (d, *J* = 8.7 Hz, 2H, OC_6H_4), 6.93 (dd, *J* = 8.8, 2.3 Hz, 1H, H_6), 6.82 (d, *J* = 2.3 Hz, 1H, H_8), 6.72 (d, *J* = 8.7 Hz, 2H, OC_6H_4), 6.26 (s, 1H, H_3), 3.02 (t, *J* = 6.0 Hz, 2H, CH_2), 2.96 (t, *J* = 6.0 Hz, 2H, CH_2), 2.63 (s, 3H, CH_3), 1.88 (quin, *J* = 6.0 Hz, 2H, CH_2), 1.76 (quin, *J* = 6.0 Hz, 2H, CH_2) . ^{13}C NMR (125 MHz, DMSO-d_6): 161.4 ($C_{4'a}$), 160.3 (C=O), 159.8 (C_7), 154.4 (C_{8a}), 153.2 ($C_{10'a}$), 147.1 (C-O), 145.4 ($C_{9'}$), 142.5 (C_4), 142.0 (C-NH), 130.6 ($C_{7'}$), 129.2 ($C_{6'}$), 128.9 ($C_{5'}$), 127.0 (C_5), 124.6 ($C_{8'a}$), 123.8 ($C_{9'a}$), 122.2 ($C_{8'}$), 121.2 (2C, OC_6H_4), 117.2 (2C, OC_6H_4), 114.4 (C_{4a}), 113.2 (C_6), 111.9 (C_3), 103.7 (C_8), 33.3 ($C_{4'}$), 25.6 ($C_{1'}$), 22.3 ($C_{2'}$), 22.0 ($C_{3'}$), 18.1 (Me). Anal. Calcd for $C_{29}H_{23}ClN_2O_3$: C, 72.12; H, 4.80; N, 5.80. Found: C, 72.30; H, 4.64; N, 6.10.

*4.5.13. 7-(4-((7,8,9,10-Tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)phenoxy)-2H-chromen-2-one (**8m**).* Off-cream solid; yield: 77%, mp 204-206 °C. IR (KBr): 3264, 2965, 2912, 2864, 1743, 1617, 1559 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.29 (s, 1H, NH), 8.00 (d, *J* = 9.5 Hz, 1H, H_4), 7.92 (d, *J* = 8.1 Hz, 1H, $H_{1'}$), 7.89 (d, *J* = 8.1 Hz, 1H, $H_{4'}$), 7.65 (d, *J* = 8.6 Hz, 1H, H_5) 7.60 (t, *J* = 8.1 Hz, 1H, $H_{3'}$), 7.45 (t, *J* = 8.1 Hz, 1H, $H_{2'}$), 6.96 (d, *J* = 8.8 Hz, 2H, OC_6H_4), 6.89 (dd, *J* = 8.6, 2.3 Hz, 1H, H_6), 6.77 (d, *J* = 2.3 Hz, 1H, H_8), 6.66 (d, *J* = 8.8 Hz, 2H, OC_6H_4), 6.32 (d, *J* = 9.5 Hz, 1H, H_3), 3.17 (bs, 2H, CH_2), 2.89 (bs, 2H, CH_2), 1.80 (bs, 2H, CH_2), 1.71 (bs, 2H, CH_2), 1.57 (bs, 2H, CH_2). ^{13}C NMR (125 MHz, $CHCl_3$): 166.0 ($C_{5'a}$), 162.3 (C=O), 160.8 (C_7), 155.6 (C_{8a}), 147.6 ($C_{4'a}$), 147.3 (C-O), 143.5 ($C_{11'}$), 143.1 (C_4), 141.4 (C-

NH), 131.4 ($C_{4'}$), 129.2 ($C_{3'}$), 128.9 (C_5), 128.7 ($C_{2'}$), 125.9 ($C_{1'}$), 124.5 ($C_{1'a}$), 122.9 ($C_{10'a}$), 121.7 (2C, OC_6H_4), 116.3 (2C, OC_6H_4), 114.0 (C_6), 113.7 (C_3), 113.5 (C_{4a}), 104.2 (C_8), 40.4 ($C_{6'}$), 31.9 ($C_{10'}$), 28.1 ($C_{7'}$), 28.0 ($C_{9'}$), 26.9 ($C_{8'}$). Anal. Calcd for $C_{29}H_{24}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.51; H, 5.74; N, 6.02.

*4.5.14. 7-(4-((3-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)phenoxy)-2H-chromen-2-one (**8n**).* Cream solid; yield: 73%, mp 183-185 °C. IR (KBr): 3227, 2917, 2849, 1742, 1616, 1557cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.37 (s, 1H, NH), 8.00 (d, J = 9.5 Hz, 1H, H_4), 7.93 (d, J = 9.0 Hz, 1H, $H_{1'}$), 7.93 (s, 1H, $H_{4'}$), 7.66 (d, J = 8.6 Hz, 1H, H_5), 7.48 (d, J = 9.0 Hz, 1H, $H_{2'}$), 6.96 (d, J = 8.5 Hz, 2H, OC_6H_4), 6.89 (d, J = 8.6 Hz, 1H, H_6), 6.77 (s, 1H, H_8), 6.66 (d, J = 8.5 Hz, 2H, OC_6H_4), 6.32 (d, J = 9.5 Hz, 1H, H_3), 3.16 (bs, 2H, CH_2), 2.88 (bs, 2H, CH_2), 1.80 (bs, 2H, CH_2), 1.70 (bs, 2H, CH_2), 1.56 (bs, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 167.1 ($C_{5'a}$), 161.5 (C=O), 159.9 (C_7), 154.9 (C_{8a}), 147.1 ($C_{4'a}$), 146.3 (C-O), 144.0 ($C_{11'}$), 143.8 (C_4), 142.2 (C-NH), 132.9 ($C_{3'}$), 131.3 ($C_{4'}$), 129.8 (C_5), 127.1 ($C_{1'}$), 125.8 ($C_{1'a}$),, 125.7 ($C_{2'}$), 122.8 ($C_{10'a}$), 121.3 (2C, OC_6H_4), 115.6 (2C, OC_6H_4), 113.5 (C_{4a}), 113.3 (C_6), 113.2 (C_3), 103.4 (C_8), 39.8 ($C_{6'}$), 31.2 ($C_{10'}$), 27.5 ($C_{7'}$), 27.4 ($C_{9'}$), 26.4 ($C_{8'}$). Anal. Calcd for $C_{29}H_{23}ClN_2O_3$: C, 71.12; H, 4.80; N, 5.80. Found: C, 71.35; H, 4.69; N, 5.62.

*4.5.15. 4-Methyl-7-(4-((7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)phenoxy)-2H-chromen-2-one (**8o**).* Cream solid; yield: 69%, mp 226-228 °C. IR (KBr): 3335, 2925, 2848, 1721, 1608, 1561, 1498 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.29 (s, 1H, NH), 7.92 (d, J = 8.1 Hz, 1H, $H_{1'}$), 7.89 (d, J = 8.1 Hz, 1H, $H_{4'}$), 7.71 (d, J = 8.8 Hz, 1H, H_5), 7.62 (t, J = 8.1 Hz, 1H, $H_{2'}$) 7.45 (t, J = 8.1 Hz, 1H, $H_{3'}$), 6.94 (d, J = 8.7 Hz, 2H, OC_6H_4), 6.91 (dd, J = 8.8, 2.3 Hz, 1H, H_6), 6.76 (d, J = 2.3 Hz, 1H, H_8), 6.24 (d, J = 8.7 Hz, 2H, OC_6H_4), 6.24 (s, 1H, H_3), 3.17 (bs, 2H, CH_2), 2.89 (bs, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.81 (bs, 2H, CH_2), 1.72 (bs,

2H, CH_2), 1.57 (bs, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 166.0 ($C_{5'a}$), 162.1 (C=O), 160.9 (C_7), 155.0 (C_{8a}), 152.2 ($C_{4'a}$), 147.7 (C-O), 147.3 ($C_{11'}$), 143.1 (C_4), 141.6 (C-NH), 131.4 ($C_{3'}$), 129.2 ($C_{4'}$), 128.6 (C_5), 125.8 ($C_{2'}$), 125.6 ($C_{1'}$), 124.5 ($C_{1'a}$), 123.0 ($C_{10'a}$), 121.7 (2C, OC_6H_4), 116.3 (2C, OC_6H_4), 114.6 (C_{4a}), 113.7 (C_6), 112.5 (C_3), 104.2 (C_8), 40.4 ($C_{6'}$), 31.9 ($C_{10'}$), 28.1($C_{7'}$), 28.0 ($C_{9'}$), 26.9 ($C_{8'}$), 18.4 (Me). Anal. Calcd for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.06. Found: C, 77.78; H, 5.89; N, 5.89.

*4.5.16. 7-(4-((3-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-yl)amino)phenoxy)-4-methyl-2H-chromen-2-one (**8p**).* Cream solid; yield: 64%, mp 198-200 °C. IR (KBr): 3257, 3053, 2918, 1736, 1619, 1559, 1499 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.40 (s, 1H, NH), 7.94 (d, J = 9.1 Hz, 1H, $H_{1'}$), 7.93 (s, 1H, $H_{4'}$), 7.73 (d, J = 8.7 Hz, 1H, H_5), 7.50 (d, J = 9.1 Hz, 1H, $H_{2'}$), 6.96 (d, J = 8.6 Hz, 2H, OC_6H_4), 7.92 (d, J = 8.7 Hz, 1H, H_6), 6.78 (s, 1H, H_8), 6.67 (d, J = 8.6 Hz, 2H, OC_6H_4), 6.25 (s, 1H, H_3), 3.18 (bs, 2H, CH_2), 2.89 (bs, 2H, CH_2), 2.39 (s, 2H, CH_3), 1.82 (bs, 2H, CH_2), 1.72 (bs, 2H, CH_2), 1.57 (bs, 2H, CH_2). ^{13}C NMR (125 MHz, $CHCl_3$): 167.3 ($C_{5'a}$), 162.0 (C=O), 160.9 (C_7), 155.0 (C_{8a}), 152.2 ($C_{4'a}$), 148.0 (C-O), 147.7 ($C_{11'}$), 143.2 (C_4), 141.6 (C-NH), 134.5 ($C_{3'}$), 131.5 ($C_{4'}$), 128.2 (C_5), 126.6 ($C_{2'}$), 125.7 ($C_{1'}$), 124.7 ($C_{1'a}$), 124.7 ($C_{10'a}$), 121.7 (2C, OC_6H_4), 116.5 (2C, OC_6H_4), 114.6 (C_{4a}), 113.7 (C_6), 112.5 (C_3), 104.2 (C_8), 40.3 ($C_{6'}$), 31.8 ($C_{10'}$), 27.9 ($C_{7'}$), 27.8 ($C_{9'}$), 26.8 ($C_{8'}$), 18.7 (Me). Anal. Calcd for $C_{30}H_{25}ClN_2O_3$: C, 72.50; H, 5.07; N, 5.64. Found: C, 72.73; H, 4.85; N, 5.49.

*4.5.17. 7-(4-(2-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-11-ylamino)phenoxy)-4-methyl-2H-chromen-2-one (**8q**).* Cream solid; yield: 71%, mp 262-264 °C. IR (KBr): 3338, 3062, 2916, 2854, 1721, 1608, 1558, 1501 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 8.35 (s, 1H, NH), 7.95 (s, 1H, $H_{1'}$), 7.90 (d, J = 8.9 Hz, 1H, $H_{4'}$), 7.72 (d, J = 8.8 Hz, 1H, H_5), 7.48 (d, J = 8.9 Hz, 1H, $H_{3'}$), 6.91 (d, J = 8.5 Hz, 2H, OC_6H_4), 6.90 (dd, J = 8.8, 2.2 Hz, 1H, H_6), 6.78 (d, J

= 2.2 Hz, 1H, H_8), 6.68 (d, *J* = 8.5 Hz, 2H, OC_6H_4), 6.24 (s, 1H, H_3), 3.16 (bs, 2H, CH_2), 2.86 (bs, 2H, CH_2), 2.38 (bs, 3H, CH_3), 1.80 (bs, 2H, CH_2), 1.71 (bs, 2H, CH_2), 1.71 (bs, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): 166.2 ($C_{5'a}$), 161.5 (C=O), 159.8 (C_7), 154.4 (C_{8a}), 153.1 ($C_{4'a}$), 146.5 (C-O), 145.2 ($C_{11'}$), 143.7 (C_4), 141.4 (C-NH), 131.9 ($C_{2'}$), 130.8 ($C_{4'}$), 129.9 ($C_{3'}$), 128.9 (C_5), 126.9 ($C_{1'}$), 125.0 ($C_{1'a}$), 122.4 ($C_{10'a}$), 121.3 (2C, OC_6H_4), 115.8 (2C, OC_6H_4), 114.3 (C_{4a}), 113.1 (C_6), 111.9 (C_3), 103.5 (C_8), 39.8 ($C_{6'}$), 31.3 ($C_{10'}$), 27.7 ($C_{7'}$), 27.5 ($C_{9'}$), 26.5 ($C_{8'}$), 18.1 (Me). Anal. Calcd for $C_{30}H_{25}ClN_2O_3$: C, 72.50; H, 5.07; N, 5.64. Found: C, 72.78; H, 4.88; N, 5.52.

4.6. AChE and BChE inhibition assay

Acetylcholinesterase (AChE, E.C. 3.1.1.7, Type V-S, lyophilized powder, from electric eel, 1000 unit), butylcholinesterase (BChE, E.C. 3.1.1.8, from equine serum), acetylthiocholine iodide (ATCI), and 5,5-dithiobis-(2-nitrobenzoic acid) (DTNB) were obtained from Sigma-Aldrich. Potassium dihydrogen phosphate, dipotassium hydrogen phosphate, potassium hydroxide, and sodium hydrogen carbonate were purchased from Fluka. *In vitro* AChEI activity was performed based on the modified Ellman's method [31, 33] as previously reported by our group using a 96-well plate reader (BioTek ELx808). For this purpose, compounds **8** were dissolve in a mixture of DMSO (5 mL) and methanol (5 mL) and diluted in 0.1 M KH_2PO_4/K_2HPO_4 buffer (pH 8.0). Each well contained 50 µL potassium phosphate buffer (KH_2PO_4/ K_2HPO_4, 0.1 M, pH 8), 25µL prepared sample as described above, 25µL enzyme with final concentration of 0.22 U/mL in buffer. They were preincubated for 15 min at rt, and then 125 µL DTNB (3 mM in buffer) was added. Characterization of the hydrolysis of ATCI catalyzed by AChE was performed spectrometrically at 405 nm followed by the addition of substrate (ATCI 3 mM in water). The change in absorbance was measured at 405 nm after 15

min. The IC_{50} values were determined graphically from inhibition curves (log inhibitor concentration vs. percent of inhibition). A control experiment was performed under the same conditions without inhibitor and the blank contained buffer, water, DTNB, and substrate. The described method was also used for BChE inhibition assay. For all compounds, four different concentrations were tested for each compound in triplicate to obtain the range of 20%-80% inhibition for AChE.

4.7. Kinetic studies of AChE inhibition

Estimates of the inhibition model and inhibition constant Ki, reciprocal plots of 1/V versus 1/[S] were obtained using different concentrations of the substrate (0.33–5.33 mM) acetylthiocholine. For this purpose, experiments were performed similar to enzyme inhibition assay [31-33]. The rate of enzymatic reaction was obtained with different concentrations of inhibitor (5, 10, and 15 μM) and in the absence of inhibitor. For each experiment, reaction was started by adding substrate (acetylthiocholine) and progress curves were recorded at 412 nm over 2 min. Next, double reciprocal plots (1/v vs. 1/[s]) were made using the slopes of progress curves to obtain the type of inhibition. Slopes of these reciprocal plots were then plotted against the concentration of compound **8e** in a weighted analysis, and Ki was determined as the intercept on the negative x-axis. All rate measurements were performed in triplicate and data analysis was performed with Microsoft Excel 2003.

4.8. *BACE1 enzymatic assay*

A FRET-based BACE1 enzyme assay kit was purchased from Invitrogen (former Pan Vera Corporation, Madison, WI) and the assay was carried out according to the manufacturers' instructions (Invitrogen. http://tools.invitrogen.com/content/sfs/manuals/L0724.pdf). Stock

solution of compound **8e** was prepared in DMSO. It was further diluted in assay buffer to prepare a 3X concentration of the test compounds. Ten µL of BACE1 substrate (3X concentration) was added to 10 µL of 3X concentration of the test compound in separate wells of a black 96-well microplate and gently mixed. Ten µL of 3X BACE1 enzyme was added to each well to start the reaction. Plates were incubated for 90 minutes at room temperature in the dark. Then, ten µL stop buffer (sodium acetate) was added to each well to stop the reaction. Finally, fluorescence measurements were performed with a multimode microplate reader (BMG Labtech) at excitation and emission wavelength of 545 nm and 585 nm, respectively. Experiments were repeated three to five times and mean percent of enzyme inhibitory activities at 10 and 50 µM concentrations of the test compounds were calculated.

4.8. Neuroprotection assay

Rat differentiated PC12 cells were provided as described in the literature [42]. Differentiated PC12 cells were incubated with different concentrations of the compound **8e** for 3 h before treatment with H_2O_2 (300 mM). Cell death by apoptosis was established after staining with DAPI, and cell viability was measured after 24 h by using the MTT assay. Briefly, 10 mL of MTT solution (5 mg/mL, Sigma) was added to the cell culture media (150 mL) and incubated in a CO_2 incubator for 3.5 h. Then, medium was removed and DMSO (150 mL) was added into the each well and the formazan precipitates were dissolved by shaking the plate for 10 min at speed of 120 rpm. Finally, optical density (OD) was determined at 560 nm on the microplate reader (BioTek synergy HT). Results were adjusted considering OD measured in the blank.

4.9. DPPH radical scavenging activity (DPPH)

Antioxidant activity of compounds **8b**, **8e**, **8i**, **8l**, **8n**, and **8q** were determined using DPPH (1,1-diphenyl-2-picrylhydrazyl) [38]. Several concentrations of the above mentioned compounds (33, 167, 350, 700 µg/mL) in DMSO were prepared. The compound solution (0.5 mL) was added to the methanolic DPPH solution (1.0 mL, 0.1 mM), and the mixture was kept in the dark for 30 min. Then, the absorbance at 517 nm was measured by an UV/visible spectrophotometer. The percent scavenging activity was calculated: (%) = 100× [($Abs_{control}$ − Abs_{sample})/ $Abs_{control}$] since $Abs_{control}$ = Abs_{DPPH} + $Abs_{solvent.}$

4.10. Molecular docking study

The crystallographic structure of tacrine was retrieved from RCSB protein data bank (PDB code: 2CMF). Molecular docking studies were carried out with AUTODOCK 4.2 software (http://autodock.scripps.edu/). Additionally, the program Cygwin (version 1.7. http://www.cygwin.com) was used to properly run the Autogrid and Autodock applications. To prepare AChE template, after eliminating the original inhibitors and water molecules, all polar hydrogens were added and Kollman charges were assigned using Autodock Tools (ADT, version 1.5.4). The structure of **8e** was built and converted to 3D using MarvineSketch 5.10.4, 2012, ChemAxon (http://www.chemaxon.com). To prepare the compound **8e** for docking purpose, all hydrogens were added and Gasteiger charges were assigned. The AutoDockTools (ADT) was used to merge nonpolar hydrogens and define which bonds should be rotatable. The scoring grid box for Autodock was approximately centered between the CAS and PAS (x-center: 3.381, y-center: 65.434, z-center: 63.34). The grid size was set to 60 × 60 × 60 points with a spacing value of 0.375 Å. The prepared compound was docked to the AChE template using a Lamarckian genetic algorithm of an initial population of 150 randomly placed individuals, the maximum number of 2.5 × 10^6 energy evaluations, the maximum number of

27,000 generations and the number of 100 GA runs. A cluster analysis was performed on the docking results using a root mean square (RMS) tolerance of 2.0 and the lowest energy conformation of the highest populated cluster was selected for analysis. Graphic visualizations were done by Discovery Studio 4.0 client software.

4.11. Computational methods

The log P values, tPSA, HBD, and HBA were calculated by the means of MarvineSketch 5.8.3. RBC was calculated using Autodock Tools (ver.1.5.4).

4.12. Statistical analysis

Results for neuroprotective effects are expressed as the means ± SD value. The significant differences among various groups were compared by one-way analysis of variance (ANOVA) followed by Tukey's test using Graphpad prism software version 5. $P<0.05$ was considered to be statistically significant.

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Conflict of interest

The authors have declared no conflict of interest.

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tetracyclic tacrine analogs containing pyrano[2,3-c]pyrazole: Efficient synthesis, biological assessment and docking simulation study, Eur. J. Med. Chem. 89 (2015) 296-303.

Legends:

Fig. 1. Coumarin-tacrine hybrids as anti-AChE agents.

Fig. 2. Novel acridine-chromenone and quinoline-chromenone hybrids as anti-AChE.

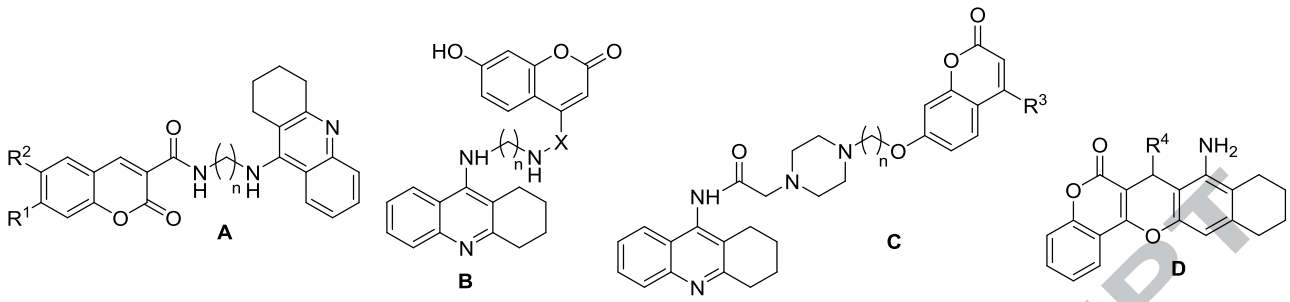
Fig. 3. Kinetic study of compound **8e** on the inhibition mechanism of EeAChE by Lineweaver-Burk plot.

Fig. 4. Neuroprotective effect of compound **8e** on cell viability of PC12 cells in H_2O_2-induced damage. Data are expressed as mean ± SD (n = 8) and one-way analysis of variance (ANOVA) followed by tukey's test was carried out to determine the level of significance. ###$P < 0.001$ vs. control, ***$P < 0.001$ vs. H_2O_2 and *$P < 0.05$ vs. H_2O_2.

Fig. 5. Superimposition of the most potent compound **8e** (green) and bis-(5)-tacrine (grey) in the active site of AChE.

Fig. 6. Representation of the binding mode of the most active compound **8e** in the active site of AChE.

Scheme 1. Synthesis of novel acridine-chromenone and quinoline-chromenone hybrids **8**. a) K_2CO_3/DMF/80 °C, b) Zn/NH_4Cl/H_2O/EtOH/ r.t, c) $POCl_3$/Reflux 3h, d) KI/n-Propanol/Reflux.



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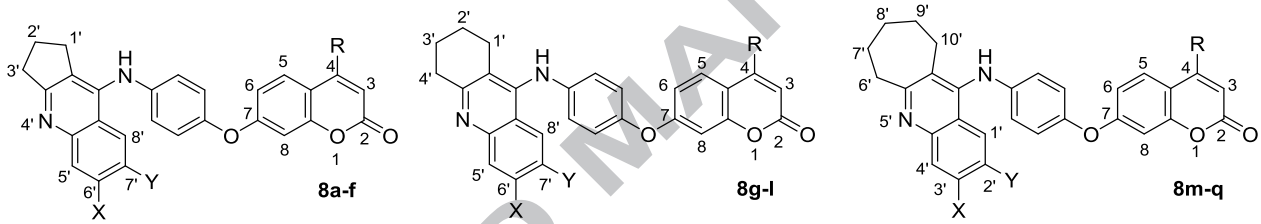

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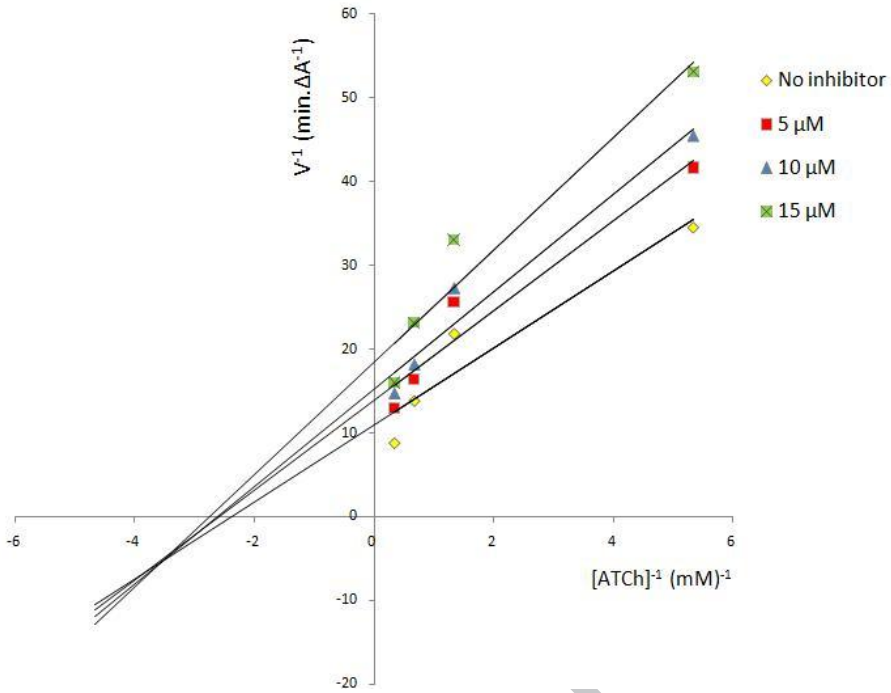

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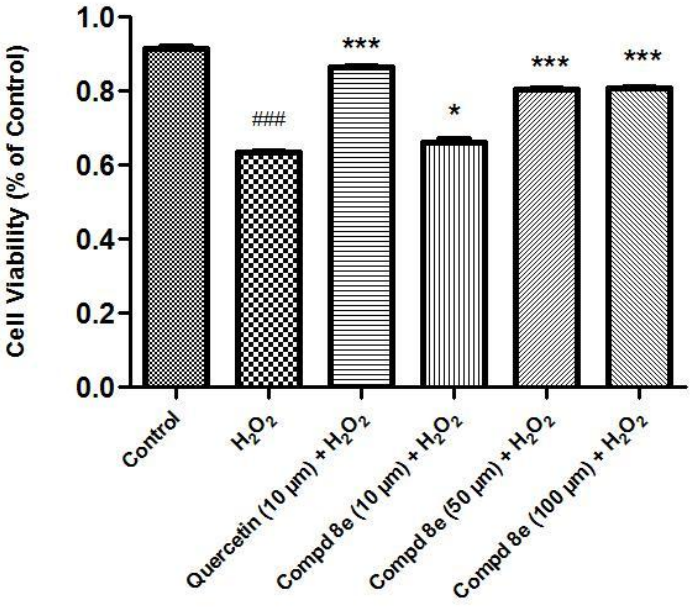

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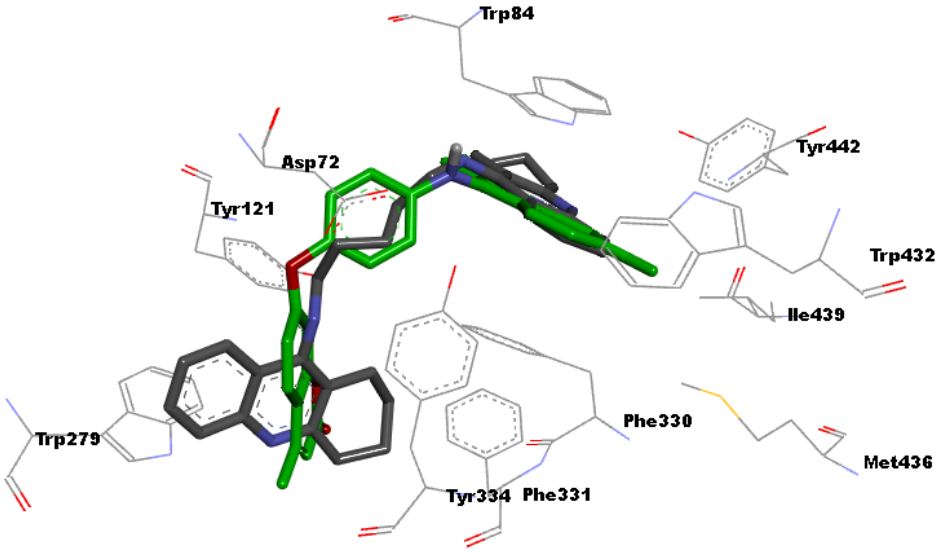

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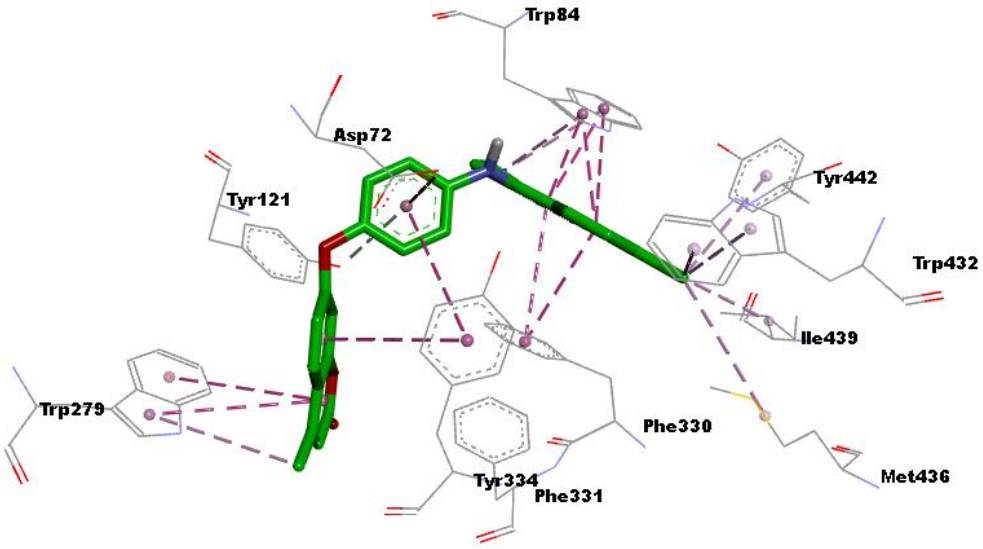

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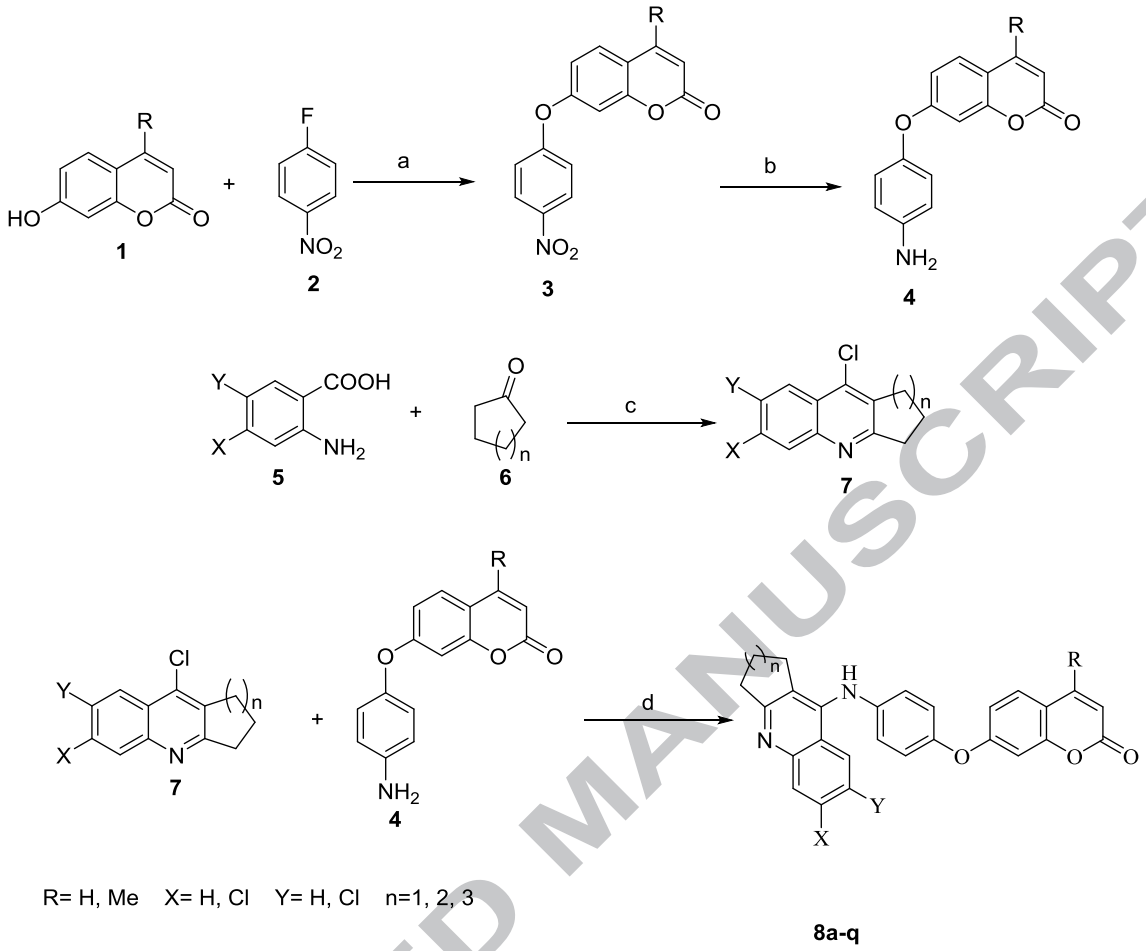

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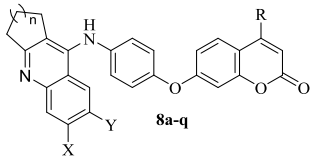
Table 1

The IC_{50} values of the compounds **8** against AChE and BChE[a]



8a-q

Entry	Compound **8**	n	R	X	Y	AChE inhibition [IC_{50} (μM)]	BChE inhibition [IC_{50} (μM)]
1	**8a**	1	H	H	H	83.10±0.01	≥100
2	**8b**	1	H	Cl	H	≥100	11.65±0.03
3	**8c**	1	H	H	Cl	38.50±0.03	≥100
4	**8d**	1	Me	H	H	45.27±0.05	≥100
5	**8e**	1	Me	Cl	H	16.17±0.02	≥100
6	**8f**	1	Me	H	Cl	36.65±0.04	≥100
7	**8g**	2	H	H	H	19.07±0.01	28.67±0.01
8	**8h**	2	H	Cl	H	≥100	≥100
9	**8i**	2	H	H	Cl	≥100	≥100
10	**8j**	2	Me	H	H	22.10±0.01	38.63±0.11
11	**8k**	2	Me	Cl	H	18.03±0.02	31.20±0.10
12	**8l**	2	Me	H	Cl	30.80±0.03	≥100
13	**8m**	3	H	H	H	≥100	≥100
14	**8n**	3	H	Cl	H	≥100	≥100
15	**8o**	3	Me	H	H	64.42±0.03	≥100

16	**8p**	3	Me	Cl	H	31.81±0.05	≥100
17	**8q**	3	Me	H	Cl	54.12±0.04	≥100
18	**Rivastigmine**					11.07±0.01	7.72±0.02

[a]Data are expressed as Mean ± SE (three independent experiments).

Table 2
The IC_{50} values of the compound **8e** against BACE1

Compd.	Inhibition at 50 μM[a] (%)	Inhibition at 10 μM[a] (%)	IC_{50} (μM)
8e	93.73	60.81	7.99±0.916
OM99-2	-	-	0.014±0.001

[a] Values represent means ± standard error (S.E.) of three independent experiments.
[b] OM99 was tested at 10, 1 and 0.1 nM.

Table 3

DPPH antioxidant activities of the compounds **8b**, **8e**, **8i**, **8l**, **8n**, and **8q**[a]

Entry	Compound **8**	Inhibition (%) (700μg/ml)[b]	EC_{50} (μg/ml)
1	**8b**	11.89±0.20	>700
2	**8e**	18.71±0.29	>700
3	**8i**	18.84±0.40	>700
4	**8l**	32.60±0.16	>700
5	**8n**	21.70±0.87	>700
6	**8q**	25.31±0.86	>700
7	**BHA**	95.70±0.53	1.19

[a]Data are expressed as Mean ± SE (three independent experiments).

[b]The highest concentration of the tested compounds.

Table 4

Molecular descriptors[a] of the compounds **8e**

Entry	Compound **8**	HBD	HBA	Clog P	tPSA [Å^2]	MW	RBC
9	**8e**	1	4	8.23	60.45	468.93	4

[a] HBD: H-bond donors, HBA: H-bond acceptors, Clog P: Calculated octanol-water partition coefficient, tPSA: topological polar surface area, RBC: Rotatable bond count.

Table 5

Chemical shifts of the compound **8i**

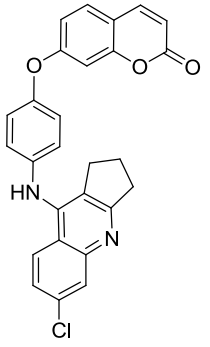
Atom number	Compound **8i**	
	^{1}H (δ ppm) $CDCl_3$, 500 MHz	^{13}C (δ ppm) $CDCl_3$, 125 MHz
2	-	161.0
3	6.28	113.9
4	7.65	143.3
4a	-	-
5	7.40	129.0
6	6.90	114.1
7	-	-
8	6.80	104.4
8a	-	
1'	2.68	25.5
2'	1.86	22.3
3'	1.93	22.3
4'	3.15	32.8
4'a	-	-
5'	7.98	129.0
6'	7.51	130.1
7'	-	-
8'	7.76	123.1
8'a	-	-
9'	-	-
9'a	-	-
10'	-	-
10'a	-	-
OC_6H_4	6.97	121.7
OC_6H_4	6.78	118.9
OC_6H_4	-	-

OC_6H_4	-	-

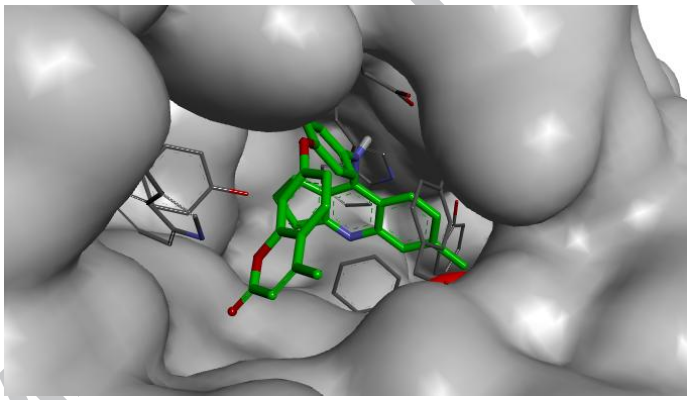
Graphical abstract

Design and synthesis of novel anti-Alzheimer's agents: acridine-chromenone and quinoline-chromenone hybrids

Zahra Najafi, Mina Saeedi, Mohammad Mahdavi, Reyhaneh Sabourian, Mahnaz Khanavi, Maliheh Barazandeh Tehrani, Farshad Homayouni Moghadam, Najmeh Edraki, Elahe Karimpor-Razkenari, Mohammad Sharifzadeh, Alireza Foroumadi, Abbas Shafiee Tahmineh Akbarzadeh



Anti-AChE agent
IC_{50} = 16.17 µM



Novel acridine-chromenone and quinoline-chromenone hybrids were designed, synthesized, andevaluated for their anti-Alzheimer's disease activity.

Highlights

- Seventeen novel acridine-chromenone and quinoline-chromenone hybrids were designed and synthesized.
  - All of them were evaluated for their acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activity.
  - Among them, 7-(4-(6-chloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-9-ylamino)phenoxy)-4-methyl-2H-chromen-2-one (**8e**) exhibited the most potent inhibitory activity: IC_{50} = 16.17 µM.
  - The most active compound was evaluated for β-secretase and neuroprotective activities.