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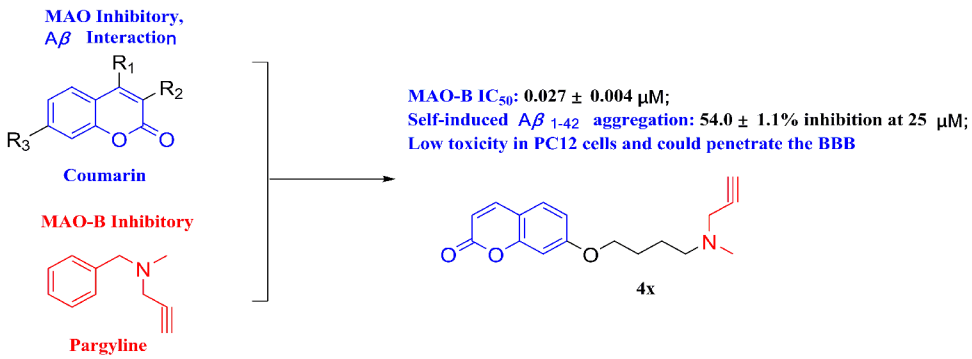

Design, synthesis and evaluation of coumarin-pargyline hybrids as novel dual inhibitors of monoamine oxidases and amyloid-*β* aggregation for the treatment of Alzheimer's disease

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Abstract

A series of coumarin-pargyline hybrids (**4a-x**) have been designed, synthesized and evaluated as novel dual inhibitors of Alzheimer's disease (AD). Most of the compounds exhibited a potent ability to inhibit amyloid-β (Aβ) aggregation and monoamine oxidases. In particular, compound **4x** exhibited remarkable inhibitory activities against monoamine oxidases (IC_{50}, 0.027±0.004 μM for MAO-B; 3.275±0.040 μM for MAO-A) and A$\beta_{1\text{-}42}$ aggregation (54.0±1.1%, 25 μM). Moreover, compound **4x** showed low toxicity according to *in vitro* cell toxicity test. The results of the parallel artificial membrane permeability assay for blood-brain barrier indicated that compound **4x** would be potent to cross the blood-brain barrier. Collectively, these findings demonstrate that compound **4x** was an effective and promising candidate for AD therapy.

Keywords: Alzheimer's disease, Coumarin, Pargyline, Monoamine oxidases, A$\beta_{1\text{-}42}$ aggregation.

1. Introduction

Alzheimer's disease (AD), the most ordinary form of dementia in the elderly, is an age-related progressive neurodegenerative disorder characterized by memory loss, decline in language skills and other cognitive impairments [1]. As reported by WHO, more than 30 million people are suffering from AD worldwide, and the incidence of AD will significantly rise to 100 million by 2050 [2]. Due to complex nature and multitude of factors potentially involved in pathogenesis, many aspects of AD are not yet fully known. Accordingly, some factors, such as low levels of neurotransmitter acetylcholine (ACh), the aggregation of β-amyloid peptide, dyshomeostasis of biometals, hyperphosphorylation of tau protein, and oxidative stress, are suggested to play key roles in the pathogenesis of AD [3, 4]. Thus, the multi-target-directed ligand (MTDL) strategy, aiming to this multifaceted disease, has drawn much attention as a promising therapeutic approach [5, 6].

Monoamine oxidases (MAOs), FAD-dependent enzymes responsible for the regulation and metabolism of major monoamine neurotransmitters, were drawn much attention in recent years [7-9]. By *in vivo* two-photon imaging, close correlation of monoamine oxidase activity with progress of AD in mice was reported in 2016 [10]. MAOs exist as two isoforms, MAO-A and MAO-B, which exhibit different substrate and inhibitor specificities. MAO-A, preferentially degrading serotonin, adrenaline and noradrenaline, has a close correlation with depression, whereas MAO-B is specifically responsible for the neurodegenerative disease such as AD [11]. High expression level of MAO-B in neuronal tissue relates to the level of hydrogen peroxide, resulting in oxidative damage and apoptotic signaling events [12, 13]. Thus, MAO-B inhibitors are considered as potential candidates for anti-Alzheimer drugs.

Among the multiple factors that induce AD, Aβ plays a crucial role. The aggregation of Aβ, especially A$\beta_{1\text{-}42}$ in brain leads to the formation of senile plaques, associated with neurodegeneration [14]. Recently, a study on amyloid-β oligomers and plaques provided solid evidence for the view that the accumulation of Aβ is an important mechanism underlying AD [15]. Therefore, inhibition of A$\beta_{1\text{-}42}$ aggregation is a potential therapeutic strategy for AD treatment.

Many efforts have been addressed toward the design of MTDLs targeting cholinesterase (ChE) inhibition, MAO inhibition, Aβ deposit inhibition, antioxidative and metal chelating properties [5, 16-18]. In this study, a series of coumarin-pargyline hybrids were designed, synthesized and evaluated for their biological activity, including MAO-B inhibitory activity, inhibition of A$\beta_{1\text{-}42}$ aggregation properties, and ability to cross the blood–brain barrier (BBB). Meanwhile, computational studies were performed to predict their binding modes in active pocket and illustrate their exceedingly high affinities.

2. Results and discussion

2.1. Design and synthesis of the target coumarin-pargyline hybrids

Coumarins are widely present in many plant species and have attracted considerable attention in recent years because they display a wide range of

biological properties associated with neurological disorders, especially for AD [18-20]. Previous studies have shown that coumarin analogs exhibited potent MAO-B inhibitory activity, especially for the 3-, 4-, and 7-substituted coumarin analogs [21, 22]. Besides its MAO-B inhibition, quite a few studies reported that coumarin analogs also exhibited Aβ anti-aggregation potency by functionalization of their aromatic center [22, 23]. These results indicate that coumarin is a noteworthy scaffold for the discovery and development of multifunctional drugs for the treatment of AD.

Pargyline is an irreversible selective MAO-B inhibitor drug (IC_{50} for MAO-A is 0.01152 μmol/L and for MAO-B is 0.00820 μmol/L) [24, 25]. The propargylamine moiety derived from selective MAO-B inhibitor plays an important role in neuroprotective properties [26, 27].

Considering the above mentioned, the privileged natural product coumarin and the drug fragment of pargyline were combined to design and synthesize a series of coumarin-pargyline hybrids which are expected to be selective MAO-B inhibitors, as well as inhibitors of A$\beta_{1\text{-}42}$ aggregation (**Figure. 1**).

The synthetic pathways of target compounds **4a-x** with 7-hydroxy-2*H*-chromen-2-one **1** as staring material were summarized in **Scheme 1**. Compounds **2a-c** were obtained by alkylation of **1** with different α, ω-dibromoalkanes in the presence of potassium carbonate. The obtained compounds **2a-c** reacted with commercially available secondary amines in refluxing CH_3CN for 10 h to give the key intermediates **3a-u**. Finally, the reaction of compounds **3a-u** with 3-bromopropyne under basic conditions provided target compounds **4a-u**. It should be noted that the propargylation of amines had to be performed by monitoring the reaction course at 65°C against the formation of dipropargylated products at high temperature [28]. To explore the superiority of *N*-benzylpropargylamine and *N*-methylpropargylamine moieties from pargyline, target compounds **4v-x** were synthesized by direct reaction of compounds **2a-c** with *N*-methylpropargylamine at the optimized conditions.

2.2. MAOs inhibitory activities of the target compounds

The *h*MAO-A and *h*MAO-B inhibitory activities of coumarin-pargyline hybrids were measured by a previously described fluorescence-based Amplex Red assay using pargyline as reference compound [29]. The corresponding IC_{50} values and selectivity index (SI) values are shown in **Table 1**. For compounds **4a-u**, the substituents in the phenoxy ring have no significant effect on *h*MAO-B inhibitory. Comparing the IC_{50} values of **4a-u** and **4v-x**, compounds with *N*-methylpropargylamine moiety performed much better activities than that with *N*-benzylpropargylamine moiety in *h*MAO-B inhibition. Besides, the linker length between coumarin and propargylamine moiety played a significant role in determining the inhibitory activity for *h*MAO-B inhibitory. Among them, **4x** with a four-carbon spacer (*h*MAO-B, IC_{50}=0.027±0.004 μM; SI, 121.3) showed the most potent inhibitory activity and selectivity for *h*MAO-B, which was stronger than the reference compound pargyline (*h*MAO-B, IC_{50}=0.194±0.030 μM; SI, 18.15).

The molecular modeling study based on MAO-B (PDB code: 2V60) was performed using docking program, AutoDock 4.2 package with Discovery Studio 2.0. As shown in the **Figure 2**, the size of compound **4x** with a four-carbon spacer is better suited to fill the binding cavity in *h*MAO-B.

2.3. Reversibility study of *h*MAO-B inhibition

The most promising compound **4x** with a nanomolar *h*MAO-B inhibitory activity was selected for further studies. To evaluate whether the target compound **4x** is a reversible *h*MAO-B inhibitor or not, a time-dependent inhibition assay was carried out [30]. The irreversible inhibitor pargyline was tested as the reference compound. As shown in **Figure 3**, **4x** was an irreversible inhibitor of *h*MAO-B as evidenced by a significant time-dependent increase of inhibitory activity. This result was consistent with irreversible inhibitor pargyline. According to the studies, propargylamino group present in the compound **4x** may lead to the irreversible inhibition of the enzyme [28, 31].

2.4. A$\beta_{1\text{-}42}$ self-aggregation inhibitory activity of the target compounds

With the above studies on the *h*MAO-B inhibitory activities of all the target compounds, **4o-x** presented a potential to inhibit *h*MAO-B, while the others had weak

activity. From the view of MTDLs targeting both *h*MAO and A$\beta_{1\text{-}42}$, hybrids **4o-x** with favorable *h*MAO-B inhibitory activities were chosen for their further bioassay to inhibit self-induced A$\beta_{1\text{-}42}$ aggregation by thioflavin-T based fluorescence assay [32, 33]. Curcumin and resveratrol were used as reference compounds [30, 33-34]. Inhibitory activities as inhibition ratios at a test concentration of 25 μM were displayed in **Figure 4**. The result showed that hybrids **4o-x** exhibited moderate-to-good potencies (30.6-59.3% at 25 μM) compared to that of curcumin (47.7% at 25 μM) and resveratrol (61.3% at 25 μM). The hybrids **4o** and **4w-x** had better performance on anti-β-amyloid aggregation property.

A structure-activity relationship analysis indicated that the property and locality of substituents in the phenoxy ring had significant impacts on A$\beta_{1\text{-}42}$ inhibitory activity. The F-substituted hybrid **4u** (30.6% at 25 μM) exhibited lower inhibitory activities than the corresponding CH_3-substituted hybird **4p** (50.0% at 25 μM). The *para*-substituted compound **4r** (49.1% at 25 μM) exhibited much higher inhibitory activities than *meta*-substituted compound **4s** (38.2% at 25 μM). From inhibition ratios of compounds **4v-x** (36.4%, 59.3%, 54.0% at 25 μM, respectively), **4w** with a three-carbon spacer and **4x** with a four-carbon spacer had more potent inhibition of self-induced A$\beta_{1\text{-}42}$ aggregation than **4v** with a three- carbon spacer.

The potent inhibitor **4x** was selected with X-ray crystal structure of the protein A$\beta_{1\text{-}42}$ structure (PDB code 1IYT) for molecular docking studies because of its total performance regarding *h*MAO-B inhibition and self-induced A$\beta_{1\text{-}42}$ aggregation inhibition. As shown in Figures **5A** and **5B,** the coumarin ring of compound **4x** interacted with the residue Phe20 via π-π stacking interaction. A hydrogen bond interaction was formed between carbonyl group of compound **4x** and the residue Lys16. These results indicated that the π-π stacking interaction and hydrogen bond interactions played important roles in the stability of the **4x**-Aβ complex.

2.5. In vitro blood-brain barrier permeation assay

The blood-brain barrier (BBB) protects the brain from harmful chemicals, and makes it difficult for drugs to reach the target cells. Thus, it is important to cross the blood-brain barrier (BBB) for the drugs targeting central nervous system (CNS). On

this basis, the parallel artificial membrane permeation assay (PAMPA)-BBB method was used to evaluate the brain penetration ability of compound **4x** [35]. **Table 2** showed the permeability values of eight reference drugs with known CNS penetration and compound **4x**. The experimental and reported permeability values of eight reference drugs provided a good linear correlation: P_e (exp) = 0.6022 P_e (Bibl) + 0.8073 (R^2 =0.9749). From this equation and considering the limits established by Di et al. for BBB permeation, we established that compound with P_e value above 3.22×10^{-6} cm s^{-1}could penetrate into the CNS. Compound **4x** showed a P_e value of 8.92×10^{-6} cm s^{-1}, indicating that it could easily cross the BBB.

2.6. Cell toxicity

The safety is extraordinary important for the CNS drugs, so the potential toxicity effect of **4x** was investigated on **4x**-treated PC12 cells. The cells were exposed to compound **4x** for 24 h and the cell viability was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay [36, 37]. As shown in **Figure 6**, compound **4x** showed little effect on the cell viability at 0-100 μM. The data showed that compound **4x** was nontoxic to PC12 and might be used to develop promising drug candidates for the therapy of treating AD.

2.7. Acute Toxicity.

Fifteen KM mice (KM mice, which are common closed colony mice and most widely used in biomedical research in China) were randomly allocated into 3 groups, and the compound **4x**, pargyline were given in a single oral dose of 2.4 mmol/kg respectively. After administration of compounds, mice were monitored continuously for the first 4 h for any abnormal behavior and mortality changes, intermittently for the next 24 h, and occasionally thereafter for 14 days to monitor the onset of any delayed effects. During the experimental period, no acute toxicity, such as mortality, or significant abnormal changes in water or food consumption or body weight were observed. Furthermore, all mice were sacrificed on the 14th day after drug administration, and no damage to the heart, liver, or kidneys was macroscopically detected.

Besides, the orbital blood was collected before decapitation, and the levels of

aspartate aminotranferase (AST) and alanine aminotranferase (ALT) were evaluated (**Figure. 7**) [38]. Compared with the control group, compound **4x** and pargyline did not significantly alter these parameters.

Overall, compound **4x** was nontoxic and well tolerated at doses up to 2.4 mmol/kg.

3. Conclusions

In this study, a series of coumarin-pargyline hybrids were designed, synthesized and evaluated as dual inhibitors of amyloid-β aggregation and monoamine oxidases for the treatment of AD. Among the synthesized compounds, compound **4x** exhibited the most potent *h*MAO-B inhibitor activity, high selectivity for *h*MAO-B over *h*MAO-A, as well as significant inhibition of A$\beta_{1\text{-}42}$ aggregation. Meanwhile, compound **4x** could penetrate the blood-brain barrier (BBB) and showed low toxicity according to *in vitro* cell toxicity test and *in vivo* acute toxicity test. In summary, these results suggested that compound **4x** is an effective and promising candidate for AD therapy.

4. Methods

4.1. Chemistry

All chemicals (reagent grade) used were purchased from Sino pharm Chemical Reagent Co., Ltd. (China). Reaction progress was monitored using analytical thin layer chromatography (TLC) on precoated silica gel GF254 (Qingdao Haiyang Chemical Plant, Qing-Dao, China) plates and the spots were detected under UV light (254 nm). Column chromatography was performed on silica gel (90-150 μm; Qingdao Marine Chemical Inc.). ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker ACF-500 spectrometer at 25°C and referenced to TMS. Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra were obtained on a MS Agilent 1100 Series LC/MSD Trap mass spectrometer (ESI-MS) and a Mariner ESI-TOF spectrometer (HRESIMS), respectively.

*4.1.1.General procedures for the preparation of compounds **2a-c**.*

To a solution of 7-hydroxy-2*H*-chromen-2-one **1** (4 mmol) and powdered K_2CO_3 (8 mmol) in acetone (20 mL), corresponding α,ω-dibromoalkane (24 mmol) was added. The reaction mixture was refluxed for 10-12 h. Upon completion, K_2CO_3 was removed by filtration and the solvent was concentrated under vacuum, the residue was purified on silica gel chromatography with petroleum ether/ethyl acetate (7:1, v/v) as elution solvent to give the desired product **2a-c** [18, 38].

*4.1.1.1. 7-(2-bromoethoxy)-2H-chromen-2-one (**2a**).*

The general procedure described for **2a-c** was used, starting from **1**, 1,2-dibromoethane and powdered K_2CO_3, and **2a** was obtained as a White solid (yield 75%); ^{1}H NMR (500 MHz, DMSO) δ 8.00 (d, J = 9.5 Hz, 1H, H4-coumarin), 7.65 (d, J = 8.6 Hz, 1H, H5-coumarin), 7.03 (d, J = 2.4 Hz, 1H, H8-coumarin), 6.99 (dd, J = 8.6, 2.5 Hz, 1H, H7-coumarin), 6.31 (d, J = 9.5 Hz, 1H, H3-coumarin), 4.45 (t, J = 5.3 Hz, 2H,O-CH_2-), 3.84 (t, J = 5.3 Hz, 2H, CH_2Br). Analytical data of **2a** were conform to the literature [18, 38].

*4.1.1.2. 7-(3-Bromopropoxy)-2H-chromen-2-one (**2b**).*

The general procedure described for **2a-c** was used, starting from **1**, 1,3-dibromopropane and powdered K_2CO_3, and **2b** was obtained as a White solid (yield 79%); ^{1}H NMR (500 MHz, DMSO-d6) δ 7.98 (d, J = 9.5 Hz, 1H, H4-coumarin), 7.62 (d, J = 8.7 Hz, 1H, H5-coumarin), 7.00 (d, J = 2.5 Hz, 1H, H8-coumarin), 6.96 (dd, J = 8.6, 2.5 Hz, 1H, H7-coumarin), 6.29 (d, J = 9.5 Hz, 1H, H3-coumarin), 4.18 (s, 2H, O-CH_2-), 3.67 (t, J = 6.6 Hz, 2H, CH_2Br), 2.27 (t, J = 6.3 Hz, 2H, OCH_2-$\underline{CH_2}$). Analytical data of **2b** were conform to the literature [18, 38].

*4.1.1.3. 7-(4-Bromobutoxy)-2H-chromen-2-one (**2c**).*

The general procedure described for **2a-c** was used, starting from **1**, 1,4-dibrombutan and powdered K_2CO_3, and **2c** was obtained as a White solid (yield 83%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.4 Hz, 1H, H4-coumarin), 7.61 (d, J = 8.5 Hz, 1H, H5-coumarin), 6.98 (d, J = 2.3 Hz, 1H, H8-coumarin), 6.94 (d, J = 8.7 Hz, 1H, H7-coumarin), 6.27 (d, J = 9.5 Hz, 1H, H3-coumarin), 4.11 (s, 2H, O-CH_2-), 3.61 (s, 2H, CH_2Br), 1.97 (dd, J = 8.5, 6.2 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$), 1.86 (dd,

J = 8.6, 5.9 Hz, 2H, OCH_2-$\underline{CH_2}$). Analytical data of **2c** were conform to the literature [18, 38].

*4.1.2. General procedures for the preparation of compounds **3a-u**.*

A mixture of compound **2a-c** (1 mmol), benzylamine derivatives (3 mmol), powdered K_2CO_3 (5 mmol) and a catalytic amount of KI in acetonitrile (20 mL) was stirred at reflux for 10 hours. K_2CO_3 was removed by filtration and the solvent was concentrated under vacuum, the residue was purified on silica gel chromatography with DCM/MeOH (100:1, v/v) as elution solvent to give the desired product **3a-u** [18, 38].

*4.1.2.1. 7-[2-(benzylamino)ethoxy]-2H-chromen-2-one (**3a**).*

The general procedure described for **3a-u** was used, starting from **2a**, benzylamine, powdered K_2CO_3 and KI, and **3a** was obtained as a Yellow oil (yield 91%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.6 Hz, 1H, H4-coumarin), 7.62 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.32 (dt, *J* = 15.1, 7.5 Hz, 4H, Ph-H), 7.24 (m, 1H, Ph-H), 6.99 (d, *J* = 2.5 Hz, 1H, H8-coumarin), 6.95 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.14 (t, *J* = 5.6 Hz, 2H, O-CH_2-), 3.76 (s, 2H, CH_2Ph), 2.87 (t, *J* = 5.6 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{18}H_{17}NO_3$ $[M + H]^+$ 296.1208, found 296.1281.

*4.1.2.2. 7-{2-[(4-methylbenzyl)amino]ethoxy}-2H-chromen-2-one (**3b**)*

The general procedure described for **3a-u** was used, starting from **2a**, 4-methylbenzylamine, powdered K_2CO_3 and KI, and **3b** was obtained as a Yellow oil (yield 89%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.4 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.21 (d, *J* = 7.8 Hz, 2H, Ph-H), 7.10 (d, *J* = 7.7 Hz, 2H, Ph-H), 6.97 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.94 (d, *J* = 8.6 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.13 (t, *J* = 5.6 Hz, 2H, O-CH_2-), 3.71 (s, 2H, CH_2Ph), 2.85 (s, 2H, OCH_2-$\underline{CH_2}$), 2.26 (s, 3H, CH_3). HRMS: calcd for $C_{19}H_{19}NO_3$ $[M + H]^+$ 310.1365 , found 310.1438.

*4.1.2.3. 7-{2-[(4-isopropylbenzyl)amino]ethoxy}-2H-chromen-2-one (**3c**)*

The general procedure described for **3a-u** was used, starting from **2a**, 4-isopropylbenzylamine, powdered K_2CO_3 and KI, and **3c** was obtained as a Yellow

oil (yield 88%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, J = 8.6 Hz, 1H, H5-coumarin), 7.24 (d, J = 7.8 Hz, 2H, Ph-H), 7.16 (d, J = 7.8 Hz, 2H, Ph-H), 6.98 (d, J = 2.3 Hz, 1H, H8-coumarin), 6.94 (d, J = 8.6 Hz, 1H, H7-coumarin), 6.28 (d, J = 9.4 Hz, 1H, H3-coumarin), 4.13 (t, J = 5.6 Hz, 2H, O-CH_2-), 3.72 (s, 2H, CH_2Ph), 2.87 (t, J = 5.6 Hz, 2H, OCH_2-$\underline{CH_2}$), 2.85-2.80 (m, 1H, CH), 1.18 (d, J = 6.9 Hz, 6H, 2×CH_3). HRMS: calcd for $C_{21}H_{23}NO_3$ $[M + H]^+$ 338.1678, found 338.1751.

*4.1.2.4. 7-{2-[(4-methoxybenzyl)amino]ethoxy}-2H-chromen-2-one (**3d**)*

The general procedure described for **3a-u** was used, starting from **2a**, 4-methoxybenzylamine, powdered K_2CO_3 and KI, and **3d** was obtained as a Yellow oil (yield 80%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, J = 8.6 Hz, 1H, H5-coumarin), 7.25 (d, J = 8.2 Hz, 2H, Ph-H), 6.98 (d, J = 2.4 Hz, 1H, H8-coumarin), 6.94 (dd, J = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.86 (d, J = 8.5 Hz, 2H, Ph-H), 6.28 (d, J = 9.4 Hz, 1H, H3-coumarin), 4.13 (t, J = 5.7 Hz, 2H, O-CH_2-), 3.72 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2Ph), 2.85 (s, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{19}H_{19}NO_4$ $[M + H]^+$ 326.1314, found 326.1387.

*4.1.2.5. 7-{2-[(3-methoxybenzyl)amino]ethoxy}-2H-chromen-2-one (**3e**)*

The general procedure described for **3a-u** was used, starting from **2a**, 3-methoxybenzylamine, powdered K_2CO_3 and KI, and **3e** was obtained as a Yellow oil (yield 81%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.5 Hz, 1H, H4-coumarin), 7.62 (d, J = 8.6 Hz, 1H, H5-coumarin), 7.22 (t, J = 7.8 Hz, 1H, Ph-H), 6.99 (d, J = 2.4 Hz, 1H, H8-coumarin), 6.97-6.93 (m, 2H, Ph-H), 6.91 (d, J = 7.6 Hz, 1H, Ph-H), 6.78 (dd, J = 8.2, 2.6 Hz, 1H, H7-coumarin), 6.28 (d, J = 9.4 Hz, 1H, H3-coumarin), 4.14 (t, J = 5.6 Hz, 2H, O-CH_2-), 3.73 (d, J = 4.2 Hz, 5H, CH_2Ph+ OCH_3), 2.87 (t, J = 5.6 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{19}H_{19}NO_4$ $[M + H]^+$ 326.1314, found 326.1387.

*4.1.2.6. 7-{2-[(3-fluorobenzyl)amino]ethoxy}-2H-chromen-2-one (**3f**)*

The general procedure described for **3a-u** was used, starting from **2a**, 3-fluorobenzylamine, powdered K_2CO_3 and KI, and **3f** was obtained as a Yellow oil (yield 75%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.5 Hz, 1H, H4-coumarin),

7.62 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.34 (td, *J* = 8.0, 6.1 Hz, 1H, Ph-H), 7.26-7.10 (m, 2H, Ph-H), 7.03 (td, *J* = 8.0, 7.4, 2.2 Hz, 1H, Ph-H), 6.99 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.95 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.14 (s, 2H, O-CH_2-), 3.79 (s, 2H, CH_2Ph), 2.87 (s, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{18}H_{16}FNO_3$ $[M + H]^+$ 314.1114, found 314.1187.

*4.1.2.7. 7-{2-[(3,4-difluorobenzyl)amino]ethoxy}-2H-chromen-2-one (**3g**)*

The general procedure described for **3a-u** was used, starting from **2a**, 3,4-difluorobenzylamine, powdered K_2CO_3 and KI, and **3g** was obtained as a Yellow oil (yield 78%); ^{1}H NMR (500 MHz, DMSO-d6) δ 7.97 (d, *J* = 9.6 Hz, 1H, H4-coumarin), 7.60 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.46-7.25 (m, 2H, Ph-H), 7.18 (dd, *J* = 4.3, 2.1 Hz, 1H, Ph-H), 7.05-6.86 (m, 2H, H8+ H7-coumarin), 6.27 (d, *J* = 9.6 Hz, 1H, H3-coumarin), 4.13 (t, *J* = 5.6 Hz, 2H, O-CH_2-), 3.75 (s, 2H, CH_2Ph), 2.85 (t, *J* = 5.6 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{18}H_{15}F_2NO_3$ $[M + H]^+$ 332.1020, found 332.1093.

*4.1.2.8. 7-[3-(benzylamino)propoxy]-2H-chromen-2-one (**3h**)*

The general procedure described for **3a-u** was used, starting from **2b**, benzylamine, powdered K_2CO_3 and KI, and **3h** was obtained as a Yellow oil (yield 91%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.33-7.27 (m, 4H, Ph-H), 7.21 (d, *J* = 6.8 Hz, 1H, Ph-H), 6.97 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.93 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.15 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.70 (s, 2H, CH_2Ph), 2.64 (t, *J* = 6.9 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$), 1.89 (p, *J* = 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{19}H_{19}NO_3$ $[M + H]^+$ 310.1365, found 310.1438.

*4.1.2.9. 7-{3-[(4-methylbenzyl)amino]propoxy}-2H-chromen-2-one **(3i)***

The general procedure described for **3a-u** was used, starting from **2b**, 4-methylbenzylamine, powdered K_2CO_3 and KI, and **3i** was obtained as a Yellow oil (yield 89%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.20 (d, *J* = 7.7 Hz, 2H, Ph-H), 7.09 (d, *J* = 7.7 Hz, 2H, Ph-H), 6.96 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz,

1H, H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.14 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.65 (s, 2H, CH_2Ph), 2.63 (t, *J* = 6.8 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 2.26 (s, 3H, CH_3), 1.88 (p, *J* = 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{20}H_{21}NO_3$ $[M + H]^+$ 324.1521, found 324.1594.

*4.1.2.10. 7-{3-[(4-isopropylbenzyl)amino]propoxy}-2H-chromen-2-one (**3j**)*

The general procedure described for **3a-u** was used, starting from **2b**, 4-isopropylbenzylamine, powdered K_2CO_3 and KI, and **3j** was obtained as a Yellow oil (yield 88%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.4 Hz, 1H, H4-coumarin), 7.60 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.22 (d, *J* = 8.0 Hz, 2H，Ph-H), 7.14 (d, *J* = 7.8 Hz, 2H, Ph-H), 6.96 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.27 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.14 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.65 (s, 2H, CH_2Ph), 2.85-2.81 (m, 1H, CH), 2.63 (t, *J* = 6.8 Hz, 2H，O(CH_2)$_2$-$\underline{CH_2}$), 1.88 (p, *J* = 6.7 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.17 (d, *J* = 6.9 Hz, 6H, 2× CH_3). HRMS: calcd for $C_{22}H_{25}NO_3$ $[M + H]^+$ 352.1834, found 352.1907.

*4.1.2.11. 7-{3-[(4-methoxybenzyl)amino]propoxy}-2H-chromen-2-one (**3k**)*

The general procedure described for **3a-u** was used, starting from **2b**, 4-methoxybenzylamine, powdered K_2CO_3 and KI, and **3k** was obtained as a Yellow oil (yield 89%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.60 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.25-7.20 (m, 2H, Ph-H), 6.95 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.91 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.84 (d, *J* = 8.6 Hz, 2H, Ph-H), 6.27 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.13 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.71 (s, 3H, OCH_3), 3.62 (s, 2H, CH_2Ph), 2.61 (t, *J* = 6.8 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 1.90-1.82 (m, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{20}H_{21}NO_4$ $[M + H]^+$ 340.1471, found 340.1543.

*4.1.2.12. 7-{3-[(3-methoxybenzyl)amino]propoxy}-2H-chromen-2-one (**3l**)*

The general procedure described for **3a-u** was used, starting from **2b**, 3-methoxybenzylamine, powdered K_2CO_3 and KI, and **3l** was obtained as a Yellow oil (yield 82%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.19 (t, *J* = 7.8 Hz, 1H, Ph-H), 6.97 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.95-6.90 (m, 2H, Ph-H), 6.89 (d, *J* = 7.6 Hz,

1H, Ph-H), 6.77 (dd, *J* = 8.2, 2.6 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.15 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.72 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2Ph), 2.63 (t, *J* = 6.8 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$), 2.31 (s, 1H, NH), 1.89 (t, *J* = 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{20}H_{21}NO_4$ $[M + H]^+$ 340.1471, found 340.1543.

*4.1.2.13. 7-{3-[(3-fluorobenzyl)amino]propoxy}-2H-chromen-2-one (**3m**)*

The general procedure described for **3a-u** was used, starting from **2b**, 3-fluorobenzylamine, powdered K_2CO_3 and KI, and **3m** was obtained as a Yellow oil (yield 91%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.60 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.32 (q, *J* = 7.4 Hz, 1H, Ph-H), 7.19-7.12 (m, 2H, Ph-H), 7.01 (td, *J* = 8.9, 2.2 Hz, 1H, Ph-H), 6.96 (d, *J* = 2.3 Hz, 1H H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.27 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.14 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.71 (s, 2H, CH_2Ph), 2.62 (t, *J* = 6.7 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$), 2.32 (s, 1H, NH), 1.89 (p, *J* = 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{19}H_{18}FNO_3$ $[M + H]^+$ 328.1271, found 328.1343.

*4.1.2.14. 7-{3-[(3,4-difluorobenzyl)amino]propoxy}-2H-chromen-2-one (**3n**)*

The general procedure described for **3a-u** was used, starting from **2b**, 3,4-difluorobenzylamine, powdered K_2CO_3 and KI, and **3n** was obtained as a Yellow oil (yield 93%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.39-7.28 (m, 2H, Ph-H), 7.15 (dd, *J* = 8.3, 4.9 Hz, 1H, Ph-H), 6.96 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.91 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.27 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.14 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.68 (s, 2H, CH_2Ph), 2.61 (t, *J* = 6.8 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$), 2.31 (s, 1H, NH), 1.88 (t, *J* = 6.5 Hz, 2H, OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{19}H_{17}F_2NO_3$ $[M + H]^+$ 346.1176, found 346.1249.

*4.1.2.15. 7-[4-(benzylamino)butoxy]-2H-chromen-2-one (**3o**)*

The general procedure described for **3a-u** was used, starting from **2c**, benzylamine, powdered K_2CO_3 and KI, and **3o** was obtained as a Yellow oil (yield 95%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.34-7.26 (m, 4H, Ph-H), 7.23-7.17 (m, 1H, Ph-H), 6.96 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin),

6.27 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.07 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.68 (s, 2H, CH_2Ph), 2.53 (t, *J* = 7.0 Hz, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 2.12 (s, 1H, NH), 1.77 (p, *J* = 6.7 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.57 (p, *J* = 7.2 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{20}H_{21}NO_3$ $[M + H]^+$ 324.1521, found 324.1594.

*4.1.2.16. 7-{4-[(4-methylbenzyl)amino]butoxy}-2H-chromen-2-one (**3p**)*

The general procedure described for **3a-u** was used, starting from **2c**, 4-methylbenzylamine, powdered K_2CO_3 and KI, and **3p** was obtained as a Yellow oil (yield 94%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.19 (d, *J* = 7.7 Hz, 2H, Ph-H), 7.09 (d, *J* = 7.7 Hz, 2H, Ph-H), 6.95 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.27 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.06 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.63 (s, 2H, CH_2Ph), 2.52 (d, *J* = 7.0 Hz, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 2.26 (s, 3H, CH_3), 1.83-1.70 (m, 2H, OCH_2-$\underline{CH_2}$), 1.60-1.50 (m, 2H, O(CH_2)$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{21}H_{23}NO_3$ $[M + H]^+$ 338.1678, found 338.1751.

*4.1.2.17. 7-{4-[(4-isopropylbenzyl)amino]butoxy}-2H-chromen-2-one (**3q**)*

The general procedure described for **3a-u** was used, starting from **2c**, 4-isopropylbenzylamine, powdered K_2CO_3 and KI, and **3q** was obtained as a Yellow oil (yield 94%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.22 (d, *J* = 7.6 Hz, 2H, Ph-H), 7.14 (d, *J* = 7.9 Hz, 2H, Ph-H), 6.96 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.93 (s, 1H, H7-coumarin), 6.27 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.06 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.63 (s, 2H, CH_2Ph), 2.84 (d, *J* = 6.8 Hz, 1H, CH), 2.53 (t, *J* = 7.0 Hz, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 1.77 (p, *J* = 6.8 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.56 (q, *J* = 7.1 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 1.17 (d, *J* = 6.9 Hz, 6H, 2×CH_3). HRMS: calcd for $C_{23}H_{27}NO_3$ $[M + H]^+$ 366.1991, found 366.2064.

*4.1.2.18. 7-{4-[(4-methoxybenzyl)amino]butoxy}-2H-chromen-2-one (**3r**)*

The general procedure described for **3a-u** was used, starting from **2c**, 4-methoxybenzylamine, powdered K_2CO_3 and KI, and **3r** was obtained as a Yellow oil (yield 87%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.23 (d, *J* = 8.6 Hz, 2H, Ph-H),

6.96 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.85 (d, *J* = 8.6 Hz, 2H, Ph-H), 6.28 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.06 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.72 (s, 3H, OCH_3), 3.62 (s, 2H, CH_2Ph), 2.53 (d, *J* = 7.0 Hz, 2H, $O(CH_2)_3$-$\underline{CH_2}$), 1.77 (p, *J* = 6.7 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.57 (p, *J* = 7.1 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$). HRMS: calcd for $C_{21}H_{23}NO_4$ $[M + H]^+$ 354.1627, found 354.1700.

*4.1.2.19. 7-{4-[(3-methoxybenzyl)amino]butoxy}-2H-chromen-2-one (**3s**)*

The general procedure described for **3a-u** was used, starting from **2c**, 3-methoxybenzylamine, powdered K_2CO_3 and KI, and **3s** was obtained as a Yellow oil (yield 89%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.19 (t, *J* = 7.8 Hz, 1H, Ph-H), 6.95 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.94-6.89 (m, 2H, Ph-H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.76 (dd, *J* = 8.2, 2.6 Hz, 1H, H7-coumarin), 6.27 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.07 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.72 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2Ph), 2.53 (t, *J* = 7.0 Hz, 2H, $O(CH_2)_3$-$\underline{CH_2}$), 2.28 (s, 1H, NH), 1.77 (p, *J* = 6.7 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.57 (p, *J* = 7.2 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$). HRMS: calcd for $C_{21}H_{23}NO_4$ $[M + H]^+$ 354.1627, found 354.1700.

*4.1.2.20. 7-{4-[(3-fluorobenzyl)amino]butoxy}-2H-chromen-2-one (**3t**)*

The general procedure described for **3a-u** was used, starting from **2c**, 3-fluorobenzylamine, powdered K_2CO_3 and KI, and **3t** was obtained as a Yellow oil (yield 93%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.60 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.36-7.29 (m, 1H, Ph-H), 7.19-7.11 (m, 2H, Ph-H), 7.04-6.98 (m, 1H, Ph-H), 6.96 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.27 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.07 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.70 (s, 2H, CH_2Ph), 2.53 (t, *J* = 7.1 Hz, 2H, $O(CH_2)_3$-$\underline{CH_2}$), 2.32 (s, 1H, NH), 1.77 (p, *J* = 6.7 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.57 (p, *J* = 7.2 Hz, 2H，$O(CH_2)_2$-$\underline{CH_2}$). HRMS: calcd for $C_{20}H_{20}FNO_3$ $[M + H]^+$ 342.1427, found 342.1500.

*4.1.2.21. 7-{4-[(3,4-difluorobenzyl)amino]butoxy}-2H-chromen-2-one (**3u**)*

The general procedure described for **3a-u** was used, starting from **2c**, 3,4-difluorobenzylamine, powdered K_2CO_3 and KI, and **3u** was obtained as a Yellow

oil (yield 90%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.6 Hz, 1H，H4-coumarin), 7.61 (d, J = 8.6 Hz, 1H, H5-coumarin), 7.37-7.30 (m, 2H, Ph-H), 7.16 (s, 1H, Ph-H), 7.01-6.90 (m, 2H，H7+H8-coumarin), 6.28 (d, J = 9.4 Hz, 1H，H3-coumarin), 4.07 (t, J = 6.5 Hz, 2H, O-CH_2-), 3.67 (s, 2H, CH_2Ph), 2.52 (s, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 2.44 (s, 1H, NH), 1.78 (p, J = 6.7 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.57 (p, J = 7.1 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{20}H_{19}F_2NO_3$ $[M + H]^+$ 360.1333, found 360.1406.

*4.1.3. General procedures for the preparation of compounds **4a-u**.*

To a solution of compound **3a-u** (1 mmol), powdered K_2CO_3 (1.1 mmol) and a catalytic amount of KI in acetonitrile (15 mL), 3-bromopropyne (1.1 mmol) was added. The reaction mixture was heated for 1-2 hours at 65 °C. Upon completion, $K_2CO_3$was removed by filtration and the solvent was concentrated under vacuum, the residue was purified on silica gel chromatography with petroleum ether/ethyl acetate (10:1, v/v) as elution solvent to give the desired product **4a-u** [39].

*4.1.3.1. 7-{2-[benzyl(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one (**4a**)*

The general procedure described for **4a-u** was used, starting from **3a**, powdered K_2CO_3, 3-bromopropyne and KI, and **4a** was obtained as a Yellow solid (yield 56%); m.p. 102-104 °C; IR (KBr) v 3214, 2920, 1727, 1610, 1508, 1283, 1130, 1031, 845 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 9.5 Hz, 1H，H4-coumarin), 7.62 (d, J = 8.6 Hz, 1H, H5-coumarin), 7.36-7.29 (m, 4H, Ph-H), 7.29-7.20 (m, 1H, Ph-H), 7.00 (d, J = 2.3 Hz, 1H, H8-coumarin), 6.94 (d, J = 8.6 Hz, 1H, H7-coumarin), 6.29 (d, J = 9.5 Hz, 1H, H3-coumarin), 4.21 (t, J = 5.8 Hz, 2H, O-CH_2-), 3.70 (s, 2H, CH_2Ph), 3.40 (d, J = 2.4 Hz, 2H, CH_2-C≡), 3.22 (s, 1H, C≡CH), 2.88 (t, J = 5.8 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.08 (C2-coumarin), 160.77 (C7-coumarin), 155.84 (C8a-coumarin), 144.80 (C4-coumarin), 138.93 (C-Ph), 129.92 (C4a-coumarin), 129.19 (2×CH-Ph), 128.69 (2×CH-Ph), 127.55 (CH-Ph), 113.27 (C3-coumarin), 112.91 (C5-coumarin), 112.80 (C6-coumarin), 101.68 (C8-coumarin), 79.26 (-C≡), 76.61 (≡CH), 67.09 (O-CH_2-), 57.98 (N-CH_2-), 51.59 (OCH_2-$\underline{CH_2}$), 42.34 ($\underline{CH_2}$-C≡). HRMS: calcd for $C_{21}H_{19}NO_3$ $[M + H]^+$ 334.1365, found 334.1438.

*4.1.3.2. 7-{2-[(4-methylbenzyl)(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one (**4b**)*

The general procedure described for **4a-u** was used, starting from **3b**, powdered K_2CO_3, 3-bromopropyne and KI, and **4b** was obtained as a Yellow solid (yield 84%); m.p. 71-73 °C; IR (KBr) *v* 3281, 2921, 1726, 1626, 1510, 1294, 1129, 1043, 829 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.00 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.62 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.25-7.09 (m, 4H, Ph-H), 6.99 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.94 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.30 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.20 (t, *J* = 5.9 Hz, 2H, O-CH_2-), 3.65 (s, 2H, CH_2Ph), 3.40 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.20 (t, *J* = 2.3 Hz, 1H, C≡CH), 2.87 (t, *J* = 5.9 Hz, 2H, OCH_2-$\underline{CH_2}$), 2.28 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.07 (C2-coumarin), 160.77 (C7-coumarin), 155.84(C8a-coumarin), 144.81(C4-coumarin), 136.59 (C-Ph), 135.79 (C-Ph), 129.91 (C4a-coumarin), 129.25 (2×CH-Ph), 129.18 (2×CH-Ph), 113.29 (C3-coumarin), 112.90 (C5-coumarin), 112.79 (C6-coumarin), 101.67 (C8-coumarin), 79.30 (-C≡), 76.57 (≡CH), 67.08 (O-CH_2-), 57.71 (N-CH_2-), 51.45 (OCH_2-$\underline{CH_2}$), 42.26 ($\underline{CH_2}$-C≡), 21.17 (CH_3). HRMS: calcd for $C_{22}H_{21}NO_3$ $[M + H]^+$ 348.1521, found 348.1594.

*4.1.3.3. 7-{2-[(4-isopropylbenzyl)(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one (**4c**)*

The general procedure described for **4a-u** was used, starting from **3c**, powdered K_2CO_3, 3-bromopropyne and KI, and **4c** was obtained as a Yellow solid (yield 51%); m.p. 58-59 °C; IR (KBr) *v* 3246, 2959, 1706, 1626, 1509, 1298, 1133, 1030, 829 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.26-7.12 (m, 4H, Ph-H), 6.98 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.93 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.19 (t, *J* = 5.8 Hz, 2H, O-CH_2-), 3.65 (s, 2H, CH_2Ph), 3.40 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.19 (s, 1H, C≡CH), 2.91-2.79 (m, 3H, OCH_2-$\underline{CH_2}$+CH), 1.17 (d, *J* = 6.9 Hz, 6H, 2×CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.06 (C2-coumarin), 160.76 (C7-coumarin), 155.83 (C8a-coumarin), 147.59 (C-Ph), 144.81(C4-coumarin), 136.25 (C-Ph), 129.91 (C4a-coumarin), 129.12 (2×CH-Ph), 126.56 (2×CH-Ph), 113.30 (C3-coumarin), 112.89 (C5-coumarin), 112.79 (C6-coumarin), 101.67

(C8-coumarin), 79.31 (-C≡), 76.59 (≡CH), 67.05 (O-CH_2-), 57.77 (N-CH_2-), 51.47 (OCH_2-$\underline{CH_2}$), 42.39 ($\underline{CH_2}$-C≡), 33.55 (CH), 24.37 (2×CH_3). HRMS: calcd for $C_{24}H_{25}NO_3$ $[M + H]^+$ 376.1834, found 376.1907.

4.1.3.4. 7-{2-[(4-methoxybenzyl)(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one ***(4d)***

The general procedure described for **4a-u** was used, starting from **3d**, powdered K_2CO_3, 3-bromopropyne and KI, and **4d** was obtained as a Light yellow solid (yield 49%); m.p. 79-81 °C; IR (KBr) *v* 3307, 2836, 1721, 1615, 1510, 1240, 1127, 1035, 835 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.22 (d, *J* = 8.5 Hz, 2H, Ph-H), 6.99 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.93 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.87 (d, *J* = 8.6 Hz, 2H, Ph-H), 6.29 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.19 (t, *J* = 5.9 Hz, 2H, O-CH_2-), 3.72 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2Ph), 3.38 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.19 (s, 1H, C≡CH), 2.86 (t, *J* = 5.9 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.07 (C2-coumarin), 160.77 (C7-coumarin), 158.81 (C-Ph), 155.84 (C8a-coumarin), 144.81(C4-coumarin), 130.65 (C-Ph), 130.41 (2×CH-Ph), 129.91 (C4a-coumarin), 114.06 (2×CH-Ph), 113.28 (C3-coumarin), 112.90 (C5-coumarin), 112.79 (C6-coumarin), 101.69 (C8-coumarin), 79.32 (-C≡), 76.56 (≡CH), 67.10 (O-CH_2-), 57.35 (N-CH_2-), 55.45 (OCH_3), 51.37 (OCH_2-$\underline{CH_2}$), 42.16 ($\underline{CH_2}$-C≡). HRMS: calcd for $C_{22}H_{21}NO_4$ $[M + H]^+$ 364.1471, found 364.1543.

4.1.3.5. 7-{2-[(3-methoxybenzyl)(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one ***(4e)***

The general procedure described for **4a-u** was used, starting from **3e**, powdered K_2CO_3, 3-bromopropyne and KI, and **4e** was obtained as a Light yellow solid (yield 62%); m.p. 73-74 °C; IR (KBr) *v* 3251, 2954, 1713, 1602, 1485, 1272, 1131, 1038, 837 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.4 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.22 (dd, *J* = 8.6, 7.1 Hz, 1H, Ph-H), 6.99 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.94 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.92-6.86 (m, 2H, Ph-H), 6.81 (dt, *J* = 8.2, 2.0 Hz, 1H, Ph-H), 6.29 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.20 (t, *J* = 5.8 Hz, 2H, O-CH_2-), 3.72 (s, 3H, OCH_3), 3.67 (s, 2H,

CH_2Ph), 3.42 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.20 (s, 1H, C≡CH), 2.88 (t, *J* = 5.8 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.09 (C2-coumarin), 160.77 (C7-coumarin), 159.72 (C-Ph), 155.84 (C8a-coumarin), 144.81 (C4-coumarin), 140.62 (C-Ph), 129.92 (C4a-coumarin), 129.71 (CH-Ph), 121.31 (CH-Ph), 114.58 (CH-Ph), 113.25 (C3-coumarin), 112.94 (CH-Ph), 112.91 (C5-coumarin), 112.80 (C6-coumarin), 101.69 (C8-coumarin), 79.31 (-C≡), 76.62 (≡CH), 67.07 (O-CH_2-), 57.98 (N-CH_2-), 55.37 (OCH_3), 51.54 (OCH_2-$\underline{CH_2}$), 42.47 ($\underline{CH_2}$-C≡). HRMS: calcd for $C_{22}H_{21}NO_4$ $[M + H]^+$ 364.1471, found 364.1543.

*4.1.3.6. 7-{2-[(3-fluorobenzyl)(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one (**4f**)*

The general procedure described for **4a-u** was used, starting from **3f**, powdered K_2CO_3, 3-bromopropyne and KI, and **4f** was obtained as a Light yellow solid (yield 55%); m.p. 58-59 °C; IR (KBr) *v* 3267, 2927, 1713, 1625, 1509, 1292, 1133, 1044, 831 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.4 Hz, 1H, H4-coumarin), 7.62 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.35 (td, *J* = 7.9, 6.2 Hz, 1H, Ph-H), 7.22-7.11 (m, 2H, Ph-H), 7.11-7.02 (m, 1H, Ph-H), 6.99 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.94 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.29 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.21 (t, *J* = 5.7 Hz, 2H, O-CH_2-), 3.72 (s, 2H, CH_2Ph), 3.44 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.22 (s, 1H, C≡CH), 2.88 (t, *J* = 5.7 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.51 (C-Ph), 162.06 (C2-coumarin), 161.90 (C-Ph), 160.77 (C7-coumarin), 155.84 (C8a-coumarin), 144.81 (C4-coumarin), 142.20 (CH-Ph), 130.59 (CH-Ph), 129.92 (C4a-coumarin), 125.01 (CH-Ph), 115.61 (CH-Ph), 114.37 (C6-coumarin), 113.24(C3-coumarin), 112.91 (C5-coumarin), 101.67 (C8-coumarin), 79.24 (-C≡), 76.67 (≡CH), 66.94 (O-CH_2-), 57.40 (N-CH_2-), 51.58 (OCH_2-$\underline{CH_2}$), 42.51 ($\underline{CH_2}$-C≡). HRMS: calcd for $C_{21}H_{18}FNO_3$ $[M + H]^+$ 352.1271, found 352.1343.

4.1.3.7.

*7-{2-[(3,4-difluorobenzyl)(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one(**4g**)*

The general procedure described for **4a-u** was used, starting from **3g**, powdered K_2CO_3, 3-bromopropyne and KI, and **4g** was obtained as a Light yellow solid (yield 61%); m.p. 75-76 °C; IR (KBr) *v* 3297, 2827, 1721, 1612, 1516, 1284, 1131, 1027, 839 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin),

7.62 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.40-7.30 (m, 2H, Ph-H), 7.18 (d, *J* = 4.2 Hz, 1H, Ph-H), 6.98 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.94 (d, *J* = 8.6 Hz, 1H, H7-coumarin), 6.29 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.21 (t, *J* = 5.7 Hz, 2H, O-CH_2-), 3.70 (s, 2H, CH_2Ph), 3.45 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.22 (s, 1H, C≡CH), 2.89 (t, *J* = 5.7 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.01 (C2-coumarin), 160.75 (C7-coumarin), 155.81 (C8a-coumarin), 150.61 (C-Ph), 149.77 (C-Ph), 148.99 (CH-Ph), 148.15 (CH-Ph), 144.76 (C4-coumarin), 137.02 (C-Ph), 129.88 (C4a-coumarin), 125.52 (CH-Ph), 117.58 (C6-coumarin), 113.20 (C3-coumarin), 112.89 (C5-coumarin), 101.64 (C8-coumarin), 79.21 (-C≡), 76.64 (≡CH), 66.85 (O-CH_2-), 56.86 (N-CH_2-), 51.44 (OCH_2-$\underline{CH_2}$), 42.49 ($\underline{CH_2}$-C≡). HRMS: calcd for $C_{21}H_{17}F_2NO_3$ $[M + H]^+$ 370.1176, found 370.1249.

*4.1.3.8. 7-{3-[benzyl(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one (**4h**)*

The general procedure described for **4a-u** was used, starting from **3h**, powdered K_2CO_3, 3-bromopropyne and KI, and **4h** was obtained as a Light yellow solid (yield 78%); m.p. 80-82 °C; IR (KBr) *v* 3240, 2919, 1721, 1611, 1465, 1281, 1119, 1048, 842 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.31-7.25 (m, 4H, Ph-H), 7.23 (s, 1H, Ph-H), 6.94 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.89 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.29 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.11 (t, *J* = 6.2 Hz, 2H, O-CH_2-), 3.60 (s, 2H, CH_2Ph), 3.32 (d, *J* = 2.4 Hz, 2H，CH_2-C≡), 3.17 (t, *J* = 2.3 Hz, 1H, C≡CH), 2.63 (t, *J* = 6.9 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 1.91 (t, *J* = 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.29 (C2-coumarin), 160.79 (C7-coumarin), 155.85 (C8a-coumarin), 144.83 (C4-coumarin), 139.11 (C-Ph), 129.92 (C4a-coumarin), 129.11 (2×CH-Ph), 128.65 (2×CH-Ph), 127.45 (CH-Ph), 113.16 (C3-coumarin), 112.85 (C5-coumarin), 112.73 (C6-coumarin), 101.59 (C8-coumarin), 79.09 (-C≡), 76.50 (≡CH), 66.86 (O-CH_2-), 57.77 (N-CH_2-), 49.36 (O(CH_2)$_2$-$\underline{CH_2}$), 41.59 ($\underline{CH_2}$-C≡), 26.91 (OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{22}H_{21}NO_3$ $[M + H]^+$ 348.1521, found 348.1594.

*4.1.3.9. 7-{3-[(4-methylbenzyl)(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one (**4i**)*

The general procedure described for **4a-u** was used, starting from **3i**, powdered K_2CO_3, 3-bromopropyne and KI, and **4i** was obtained as a Light yellow solid (yield 72%); m.p. 71-73 °C; IR (KBr) *v* 3263, 2918, 1707, 1627, 1511, 1299, 1140, 1049, 837 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.15 (d, *J* = 7.7 Hz, 2H, Ph-H), 7.05 (d, *J* = 7.7 Hz, 2H, Ph-H), 6.90 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.88 (d, *J* = 8.6 Hz, 1H, H3-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H，H7-coumarin), 4.08 (t, *J* = 6.3 Hz, 2H, O-CH_2-), 3.54 (s, 2H, CH_2Ph), 3.30 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.15 (s, 1H, C≡CH), 2.59 (d, *J* = 6.8 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 2.23 (s, 3H, CH_3), 1.89 (t, *J* = 6.5 Hz, 2H, OCH$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.30 (C2-coumarin), 160.79 (C7-coumarin), 155.84 (C8a-coumarin), 144.84 (C4-coumarin), 136.44 (C-Ph), 135.99 (C-Ph), 129.88 (C4a-coumarin), 129.20 (2×CH-Ph), 129.11 (2×CH-Ph), 113.12 (C3-coumarin), 112.83 (C5-coumarin), 112.70 (C6-coumarin), 101.59 (C8-coumarin), 79.18 (-C≡), 76.41 (≡CH), 66.81 (O-CH_2-), 57.53 (N-CH_2-), 49.14 (O(CH_2)$_2$-$\underline{CH_2}$), 41.59 ($\underline{CH_2}$-C≡), 26.90 (OCH$_2$-$\underline{CH_2}$), 21.15 (CH_3). HRMS: calcd for $C_{23}H_{23}NO_3$ $[M + H]^+$ 362.1678, found 362.1751.

4.1.3.10.

*7-{3-[(4-isopropylbenzyl)(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one (**4j**)*

The general procedure described for **4a-u** was used, starting from **3j**, powdered K_2CO_3, 3-bromopropyne and KI, and **4j** was obtained as a Yellow solid (yield 69%); m.p. 77-78 °C; IR (KBr) *v* 3258, 2960, 1720, 1624, 1511, 1296, 1139, 1047, 838 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.19 (d, *J* = 7.9 Hz, 2H, Ph-H), 7.12 (d, *J* = 7.9 Hz, 2H, Ph-H), 6.92 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.89 (dd, *J* = 8.5, 2.4 Hz, 1H, H3-coumarin), 6.29 (d, *J* = 9.5 Hz, 1H, H7-coumarin), 4.10 (t, *J* = 6.2 Hz, 2H, O-CH_2-), 3.56 (s, 2H, CH_2Ph), 3.32 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.15 (s, 1H，C≡CH), 2.82 (p, *J* = 6.9 Hz, 1H, CH), 2.62 (t, *J* = 6.8 Hz, 2H， O(CH_2)$_2$-$\underline{CH_2}$), 1.91 (p, *J* = 6.5 Hz, 2H， OCH$_2$-$\underline{CH_2}$), 1.16 (d, *J* = 6.9 Hz, 6H, 2×CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.30 (C2-coumarin), 160.77 (C7-coumarin), 155.84 (C8a-coumarin), 147.45 (C-Ph), 144.80 (C4-coumarin), 136.40 (C-Ph), 129.88 (C4a-coumarin), 129.07

(2×CH-Ph), 126.51 (2×CH-Ph), 113.08 (C3-coumarin), 112.83 (C5-coumarin), 112.71 (C6-coumarin), 101.59 (C8-coumarin), 79.13 (-C≡), 76.43 (≡CH), 66.77 (O-CH_2-), 57.54 (N-CH_2-), 49.13 (O(CH_2)$_2$-$\underline{CH_2}$), 41.57 ($\underline{CH_2}$-C≡), 33.52(CH), 26.88 (OCH$_2$-$\underline{CH_2}$), 24.33 (2×CH_3). HRMS: calcd for $C_{25}H_{27}NO_3$ $[M + H]^+$ 390.1991, found 390.2064.

4.1.3.11.

*7-{3-[(4-methoxybenzyl)(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one (**4k**)*

The general procedure described for **4a-u** was used, starting from **3k**, powdered K_2CO_3, 3-bromopropyne and KI, and **4k** was obtained as a Yellow solid (yield 75%); m.p. 82-84 °C; IR (KBr) *v* 3258, 2949, 1710, 1631, 1510, 1301, 1147, 1031, 836 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.19 (d, *J* = 8.5 Hz, 2H, Ph-H), 6.91 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.89 (d, *J* = 8.5 Hz, 1H, H7-coumarin), 6.82 (d, *J* = 8.5 Hz, 2H, Ph-H), 6.29 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.09 (t, *J* = 6.2 Hz, 2H, O-CH_2-), 3.70 (s, 3H, OCH_3), 3.53 (s, 2H, CH_2Ph), 3.30 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.15 (d, *J* = 2.3 Hz, 1H, C≡CH), 2.61 (t, *J* = 6.8 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 1.90 (p, *J* = 6.6 Hz, 2H, OCH$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.29 (C2-coumarin), 160.79 (C7-coumarin), 158.72 (C-Ph), 155.83 (C8a-coumarin), 144.80 (C4-coumarin), 130.84 (C-Ph), 130.32 (2×CH-Ph), 129.86 (C4a-coumarin), 113.97 (2×CH-Ph), 113.08 (C3-coumarin), 112.82 (C5-coumarin), 112.71 (C6-coumarin), 101.56 (C8-coumarin), 79.19 (-C≡), 76.37 (≡CH), 66.80 (O-CH_2-), 57.16 (N-CH_2-), 55.36 (OCH_3), 49.04 (O(CH_2)$_2$-$\underline{CH_2}$), 41.47 ($\underline{CH_2}$-C≡), 26.91 (OCH$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{23}H_{23}NO_4$ $[M + H]^+$ 378.1627, found 378.1700.

4.1.3.12.

*7-{3-[(3-methoxybenzyl)(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one (**4l**)*

The general procedure described for **4a-u** was used, starting from **3l**, powdered K_2CO_3, 3-bromopropyne and KI, and **4l** was obtained as a Light yellow solid (yield 83%); m.p. 65-67 °C; IR (KBr) *v* 3264, 2941, 1707, 1629, 1487, 1296, 1140, 1042, 840 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.60 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.19 (t, *J* = 7.8 Hz, 1H, Ph-H), 6.92 (d, *J* = 2.4

Hz, 1H, H8-coumarin), 6.90 – 6.82 (m, 3H, Ph-H), 6.78 (dd, *J* = 8.2, 2.5 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.10 (t, *J* = 6.2 Hz, 2H, O-CH_2-), 3.69 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2Ph), 3.34 (d, *J* = 2.5 Hz, 2H，CH_2-C≡), 3.16 (s, 1H，C≡CH), 2.63 (t, *J* = 6.9 Hz, 2H，$O(CH_2)_2$-$\underline{CH_2}$), 1.91 (p, *J* = 6.6 Hz, 2H，OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.29 (C2-coumarin), 160.78 (C7-coumarin), 159.68 (C-Ph), 155.84 (C8a-coumarin), 144.80 (C4-coumarin), 140.80 (C-Ph), 129.89 (C4a-coumarin), 129.65 (CH-Ph), 121.25(CH-Ph), 114.49 (CH-Ph), 113.10 (C3-coumarin), 112.86 (CH-Ph), 112.83 (C5-coumarin), 112.72 (C6-coumarin), 101.55 (C8-coumarin), 79.15 (-C≡), 76.46 (≡CH), 66.85 (O-CH_2-), 57.84 (N-CH_2-), 55.27 (OCH_3), 49.23 ($O(CH_2)_2$-$\underline{CH_2}$), 41.69 ($\underline{CH_2}$-C≡), 26.88 (OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{23}H_{23}NO_4$ $[M + H]^+$ 378.1627, found 378.1700.

4.1.3.13. 7-{3-[(3-fluorobenzyl)(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one ***(4m)***

The general procedure described for **4a-u** was used, starting from **3m**, powdered K_2CO_3, 3-bromopropyne and KI, and **4m** was obtained as a Light yellow solid (yield 69%); m.p. 46-48 °C; IR (KBr) *v* 3269, 2920, 1708, 1629, 1486, 1297, 1139, 1050, 840 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.31 (q, *J* = 7.6 Hz, 1H, Ph-H), 7.13 (d, *J* = 7.6 Hz, 1H, Ph-H), 7.08 (d, *J* = 10.1 Hz, 1H, Ph-H), 7.03 (td, *J* = 8.7, 2.6 Hz, 1H, Ph-H), 6.93 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.88 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.29 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.11 (t, *J* = 6.2 Hz, 2H, O-CH_2-), 3.63 (s, 2H, CH_2Ph), 3.35 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.19 (s, 1H, C≡CH), 2.63 (t, *J* = 6.8 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$), 1.91 (p, *J* = 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.48 (C-Ph), 162.27 (C2-coumarin), 161.87 (C-Ph), 160.79 (C7-coumarin), 155.85 (C8a-coumarin), 144.82 (C4-coumarin), 142.38 (CH-Ph), 130.55 (CH-Ph), 129.90 (C4a-coumarin), 124.97 (CH-Ph), 115.54 (CH-Ph), 114.30 (C6-coumarin), 113.11 (C3-coumarin), 112.84 (C5-coumarin), 101.56 (C8-coumarin), 79.03 (-C≡), 76.57 (≡CH), 66.77 (O-CH_2-), 57.31 (N-CH_2-), 49.23 ($O(CH_2)_2$-$\underline{CH_2}$), 41.76 ($\underline{CH_2}$-C≡), 26.84 (OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{22}H_{20}FNO_3$ $[M + H]^+$ 366.1427, found 366.1500.

4.1.3.14.

*7-{3-[(3,4-difluorobenzyl)(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one (**4n**)*

The general procedure described for **4a-u** was used, starting from **3n**, powdered K_2CO_3, 3-bromopropyne and KI, and **4n** was obtained as a White solid (yield 70%); m.p. 64-65°C; IR (KBr) *v* 3253, 2950, 1704, 1625, 1517, 1296, 1138, 1048, 841 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.35-7.20 (m, 2H, Ph-H), 7.12 (s, 1H, Ph-H), 6.91 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.86 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.29 (d, *J* = 9.4 Hz, 1H，H3-coumarin), 4.09 (t, *J* = 6.1 Hz, 2H, O-CH_2-), 3.59 (s, 2H, CH_2Ph), 3.37 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.19 (s, 1H, C≡CH), 2.62 (t, *J* = 6.8 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 1.90 (p, *J* = 6.5 Hz, 2H, OCH$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.23 (C2-coumarin), 160.79 (C7-coumarin), 155.83 (C8a-coumarin), 150.59 (C-Ph), 149.72 (C-Ph), 148.96 (CH-Ph), 148.10 (CH-Ph), 144.80 (C4-coumarin), 137.19 (C-Ph), 129.85 (C4a-coumarin), 125.57 (CH-Ph), 117.61 (C6-coumarin), 113.01 (C3-coumarin), 112.81 (C5-coumarin), 101.48 (C8-coumarin), 79.05 (-C≡), 76.54 (≡CH), 66.60 (O-CH_2-), 56.86 (N-CH_2-), 48.83 (O(CH_2)$_2$-$\underline{CH_2}$), 41.77 ($\underline{CH_2}$-C≡), 26.77 (OCH$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{22}H_{19}F_2NO_3$ $[M + H]^+$ 384.1333, found 384.1406.

*4.1.3.15. 7-{4-[benzyl(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one (**4o**)*

The general procedure described for **4a-u** was used, starting from **3o**, powdered K_2CO_3, 3-bromopropyne and KI, and **4o** was obtained as a White solid (yield 81%); m.p. 49-51°C; IR (KBr) *v* 3198, 2955, 1711, 1621, 1508, 1284, 1132, 1019, 833 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.30 (d, *J* = 6.6 Hz, 4H, Ph-H), 7.24 (dt, *J* = 6.5, 2.8 Hz, 1H, Ph-H), 6.95 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.5, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.06 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.58 (s, 2H, CH_2Ph), 3.28 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.14 (t, *J* = 2.3 Hz, 1H, C≡CH), 2.53 (d, *J* = 6.9 Hz, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 1.76 (p, *J* = 6.6 Hz, 2H, OCH$_2$-$\underline{CH_2}$), 1.60 (p, *J* = 6.6, 6.1 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.29 (C2-coumarin), 160.79 (C7-coumarin), 155.87 (C8a-coumarin),

144.83 (C4-coumarin), 139.21 (C-Ph), 129.93 (C4a-coumarin), 129.14 (2×CH-Ph), 128.68 (2×CH-Ph), 127.46 (CH-Ph), 113.21 (C3-coumarin), 112.83 (C5-coumarin), 112.70 (C6-coumarin), 101.58 (C8-coumarin), 79.11 (-C≡), 76.41 (≡CH), 68.53 (O-CH_2-), 57.62 (N-CH_2-), 52.30 (O(CH_2)$_3$-$\underline{CH_2}$), 41.34 ($\underline{CH_2}$-C≡), 26.57 (OCH_2-$\underline{CH_2}$), 23.55 (O(CH_2)$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{23}H_{23}NO_3$ $[M + H]^+$ 362.1678, found 362.1751.

4.1.3.16. 7-{4-[(4-methylbenzyl)(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one ***(4p)***

The general procedure described for **4a-u** was used, starting from **3p**, powdered K_2CO_3, 3-bromopropyne and KI, and **4p** was obtained as a Light yellow solid (yield 76%); m.p. 69-70 °C; IR (KBr) *v* 3213, 2954, 1711, 1621, 1509, 1285, 1131, 1020, 835 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.17 (d, *J* = 7.8 Hz, 2H, Ph-H), 7.10 (d, *J* = 7.7 Hz, 2H, Ph-H), 6.95-6.90 (m, 2H, H8+H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.04 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.52 (s, 2H, CH_2Ph), 3.27 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.13 (s, 1H, C≡CH), 2.53-2.50 (m, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 2.26 (s, 3H, CH_3), 1.75 (p, *J* = 6.5 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.59 (p, *J* = 7.1 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.30 (C2-coumarin), 160.78 (C7-coumarin), 155.87 (C8a-coumarin), 144.82 (C4-coumarin), 136.47 (C-Ph), 136.08 (C-Ph), 129.91 (C4a-coumarin), 129.25 (2×CH-Ph), 129.12 (2×CH-Ph), 113.21 (C3-coumarin), 112.82 (C5-coumarin), 112.69 (C6-coumarin), 101.56 (C8-coumarin), 79.16 (-C≡), 76.35 (≡CH), 68.48 (O-CH_2-), 57.36 (N-CH_2-), 52.09 (O(CH_2)$_3$-$\underline{CH_2}$), 41.28 ($\underline{CH_2}$-C≡), 26.52 (OCH_2-$\underline{CH_2}$), 23.49 (O(CH_2)$_2$-$\underline{CH_2}$), 21.16 (CH_3). HRMS: calcd for $C_{24}H_{25}NO_3$ $[M + H]^+$ 376.1834, found 376.1907.

4.1.3.17. 7-{4-[(4-isopropylbenzyl)(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one ***(4q)***

The general procedure described for **4a-u** was used, starting from **3q**, powdered K_2CO_3, 3-bromopropyne and KI, and **4q** was obtained as a Yellow solid (yield 84%); IR (KBr) *v* 3262, 2957, 1711, 1620, 1509, 1285, 1130, 1019, 834 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H,

H5-coumarin), 7.19 (d, *J* = 8.0 Hz, 2H, (2×CH-Ph)), 7.15 (d, *J* = 7.8 Hz, 2H, (2× CH-Ph)), 6.95 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.06 (t, *J* = 6.6 Hz, 2H, O-CH_2-), 3.53 (s, 2H, CH_2Ph), 3.27 (d, *J* = 2.3 Hz, 2H, CH_2-C≡), 3.13 (t, *J* = 2.3 Hz, 1H, C≡CH), 2.84 (p, *J* = 6.9 Hz, 1H, CH), 2.52 (s, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 1.77 (p, *J* = 6.5 Hz, 2H, OCH$_2$-$\underline{CH_2}$), 1.60 (p, *J* = 7.1 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 1.17 (d, *J* = 7.0 Hz, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.30 (C2-coumarin), 160.77 (C7-coumarin), 155.88 (C8a-coumarin), 147.49 (C-Ph), 144.81 (C4-coumarin), 136.50 (C-Ph), 129.91 (C4a-coumarin), 129.09 (2×CH-Ph), 126.55 (2×CH-Ph), 113.23 (C3-coumarin), 112.82 (C5-coumarin), 112.69 (C6-coumarin), 101.55 (C8-coumarin), 79.14 (-C≡), 76.36 (≡CH), 68.48 (O-CH_2-), 57.33 (N-CH_2-), 52.16 (O(CH_2)$_3$-$\underline{CH_2}$), 41.31 ($\underline{CH_2}$-C≡), 33.54 (CH), 26.52 (OCH$_2$-$\underline{CH_2}$), 24.35 (O(CH_2)$_2$-$\underline{CH_2}$), 23.48 (2×CH_3). HRMS: calcd for $C_{26}H_{29}NO_3$ $[M + H]^+$ 404.2147, found 404.2220.

4.1.3.18. 7-{4-[(4-methoxybenzyl)(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one ***(4r)***

The general procedure described for **4a-u** was used, starting from **3r**, powdered K_2CO_3, 3-bromopropyne and KI, and **4r** was obtained as a Light yellow solid (yield 81%); m.p. 60-61°C; IR (KBr) *v* 3191, 2921, 1711, 1615, 1512, 1249, 1131, 1036, 833 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.19 (d, *J* = 8.6 Hz, 2H, Ph-H), 6.94 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.86 (d, *J* = 8.6 Hz, 2H, Ph-H), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.05 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.71 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2Ph), 3.25 (s, 2H, CH_2-C≡), 3.12 (s, 1H, C≡CH), 2.51 (s, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 1.75 (p, *J* = 6.4 Hz, 2H, OCH$_2$-$\underline{CH_2}$), 1.59 (p, *J* = 7.2 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.29 (C2-coumarin), 160.79 (C7-coumarin), 158.74 (C8a-coumarin), 155.88 (C-Ph), 144.83 (C4-coumarin), 130.93 (C-Ph), 130.35 (2×CH-Ph), 129.92 (C4a-coumarin), 114.03 (2×CH-Ph), 113.22 (C3-coumarin), 112.82 (C5-coumarin), 112.69 (C6-coumarin), 101.56 (C8-coumarin), 79.18 (-C≡), 76.33 (≡CH), 68.49 (O-CH_2-), 56.97 (N-CH_2-), 55.42

(OCH_3), 52.03 ($O(CH_2)_3$-$\underline{CH_2}$), 41.16 ($\underline{CH_2}$-C≡), 26.54 (OCH_2-$\underline{CH_2}$), 23.49 ($O(CH_2)_2$-$\underline{CH_2}$) . HRMS: calcd for $C_{24}H_{25}NO_4$ $[M + H]^+$ 392.1784, found 392.1856.

4.1.3.19. 7-{4-[(3-methoxybenzyl)(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one ***(4s)***

The general procedure described for **4a-u** was used, starting from **3s**, powdered K_2CO_3, 3-bromopropyne and KI, and **4s** was obtained as a Yellow oil (yield 77%); IR (KBr) *v* 3288, 2833, 1733, 1614, 1509, 1281, 1123, 1047, 836 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.4 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.5 Hz, 1H, H5-coumarin), 7.22 (t, *J* = 7.8 Hz, 1H, Ph-H), 6.94 (d, *J* = 2.3 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.88 – 6.84 (m, 2H, Ph-H), 6.80 (dd, *J* = 8.1, 2.5 Hz, 1H, Ph-H), 6.28 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 4.06 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.72 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2Ph), 3.30 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.14 (d, *J* = 2.3 Hz, 1H, C≡CH), 2.53 (s, 2H, $O(CH_2)_3$-$\underline{CH_2}$), 1.76 (p, *J* = 7.0, 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.60 (p, *J* = 6.6, 6.2 Hz, 2H, $O(CH_2)_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.29 (C2-coumarin), 160.78 (C7-coumarin), 159.69 (C8a-coumarin), 155.87 (C-Ph), 144.81 (C4-coumarin), 140.91 (C-Ph), 129.91 (C4a-coumarin), 129.70 (CH-Ph), 121.26 (CH-Ph), 114.54 (CH-Ph), 113.19 (C3-coumarin), 112.83 (C5-coumarin), 112.79 (CH-Ph), 112.69 (C6-coumarin), 101.56 (C8-coumarin), 79.16 (-C≡), 76.39 (≡CH), 68.52 (O-CH_2-), 57.66 (N-CH_2-), 55.33 (OCH_3), 52.21 ($O(CH_2)_3$-$\underline{CH_2}$), 41.46 ($\underline{CH_2}$-C≡), 26.57 (OCH_2-$\underline{CH_2}$), 23.54 ($O(CH_2)_2$-$\underline{CH_2}$). HRMS: calcd for $C_{24}H_{25}NO_4$ $[M + H]^+$ 392.1784, found 392.1856.

4.1.3.20. 7-{4-[(3-fluorobenzyl)(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one ***(4t)***

The general procedure described for **4a-u** was used, starting from **3t**, powdered K_2CO_3, 3-bromopropyne and KI, and **4t** was obtained as a Light yellow solid (yield 69%); m.p. 45-46 °C; IR (KBr) *v* 3196, 2957, 1711, 1620, 1508, 1285, 1131, 1019, 832 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 7.35 (q, *J* = 7.7 Hz, 1H, Ph-H), 7.14 (d, *J* = 7.6 Hz, 1H, Ph-H), 7.08 (t, *J* = 8.8 Hz, 2H, Ph-H), 6.95 (d, *J* = 2.2 Hz, 1H, H8-coumarin), 6.92 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.4 Hz, 1H,

H3-coumarin), 4.07 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.60 (s, 2H, CH_2Ph), 3.31 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.16 (d, *J* = 2.4 Hz, 1H, C≡CH), 2.53 (s, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 1.76 (p, 2H, OCH$_2$-$\underline{CH_2}$), 1.60 (p, *J* = 5.7, 4.3 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.50 (C-Ph), 162.28 (C2-coumarin), 161.88 (C-Ph), 160.79 (C7-coumarin), 155.87 (C8a-coumarin), 144.81 (C4-coumarin), 142.49 (CH-Ph), 130.61 (CH-Ph), 129.92 (C4a-coumarin), 125.00 (CH-Ph), 115.54 (CH-Ph), 114.32 (C6-coumarin), 113.18 (C3-coumarin), 112.83 (C5-coumarin), 101.56 (C8-coumarin), 79.03 (-C≡), 76.49 (≡CH), 68.52 (O-CH_2-), 57.10 (N-CH_2-), 52.34 (O(CH_2)$_3$-$\underline{CH_2}$), 41.50 ($\underline{CH_2}$-C≡), 26.55 (OCH$_2$-$\underline{CH_2}$), 23.56 (O(CH_2)$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{23}H_{22}FNO_3$ $[M + H]^+$ 380.1584, found 380.1656.

4.1.3.21.

*7-{4-[(3,4-difluorobenzyl)(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one (**4u**)*

The general procedure described for **4a-u** was used, starting from **3u**, powdered K_2CO_3, 3-bromopropyne and KI, and **4u** was obtained as a Light yellow solid (yield 75%); m.p. 66-67 °C; IR (KBr) *v* 3191, 2959, 1711, 1622, 1517, 1285, 1118, 1019, 834 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.4 Hz, 1H, H4-coumarin), 7.61 (d, *J* = 8.4 Hz, 1H, H5-coumarin), 7.40-7.25 (m, 2H, Ph-H), 7.15 (s, 1H，Ph-H), 6.98 – 6.88 (m, 2H, H8+H7-coumarin), 6.29 (d, *J* = 9.4 Hz, 1H, H3-coumarin), 4.07 (t, *J* = 6.4 Hz, 2H, O-CH_2-), 3.58 (s, 2H, CH_2Ph), 3.32 (s, 2H, CH_2-C≡), 3.16 (s, 1H, C≡CH), 2.53 (s, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 1.77 (p, *J* = 6.8 Hz, 2H, OCH$_2$-$\underline{CH_2}$), 1.60 (p, *J* = 7.2 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.25 (C2-coumarin), 160.76 (C7-coumarin), 155.86 (C8a-coumarin), 150.61 (C-Ph), 149.74 (C-Ph), 148.99 (CH-Ph), 148.12 (CH-Ph), 144.76 (C4-coumarin), 137.23 (C-Ph), 129.87 (C4a-coumarin), 125.48 (CH-Ph), 117.55 (C6-coumarin), 113.13 (C3-coumarin), 112.81 (C5-coumarin), 101.52 (C8-coumarin), 78.97 (-C≡), 76.48 (≡CH), 68.50 (O-CH_2-), 56.56 (N-CH_2-), 52.22 (O(CH_2)$_3$-$\underline{CH_2}$), 41.44 ($\underline{CH_2}$-C≡), 26.51 (OCH$_2$-$\underline{CH_2}$), 23.55 (O(CH_2)$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{23}H_{21}F_2NO_3$ $[M + H]^+$ 398.1489, found 398.1562.

*4.1.4. General procedures for the preparation of compounds **4v-x**.*

A mixture of compound **2a-c** (1 mmol), *N*-methylpropargylamine (1.1 mmol),

powdered K_2CO_3 (1.1 mmol) and a catalytic amount of KI in acetonitrile (15 mL) was stirred for 1-2 hours at 65 °C. K_2CO_3 was removed by filtration and the solvent was concentrated under vacuum, the residue was purified on silica gel chromatography with petroleum ether/ethyl acetate (3:1, v/v) as elution solvent to give the desired product **4v-x** [18, 38].

*4.1.4.1. 7-{2-[methyl(prop-2-yn-1-yl)amino]ethoxy}-2H-chromen-2-one (**4v**)*

The general procedure described for **4v-x** was used, starting from **2a**, powdered K_2CO_3, *N*-methylpropargylamine and KI, and **4v** was obtained as a Light yellow solid (yield 80%); m.p. 62-63 °C; IR (KBr) *v* 3237, 2946, 1706, 1615, 1278, 1127, 1028, 835 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 9.5 Hz, 1H, H4-coumarin), 7.62 (d, J = 8.7 Hz, 1H, H5-coumarin), 7.01 (d, J = 2.4 Hz, 1H, H8-coumarin), 6.95 (dd, J = 8.6, 2.5 Hz, 1H, H7-coumarin), 6.29 (d, J = 9.5 Hz, 1H, H3-coumarin), 4.16 (t, J = 5.8 Hz, 2H, O-CH_2-), 3.39 (d, J = 2.4 Hz, 2H, CH_2-C≡), 3.15 (t, J = 2.4 Hz, 1H, C≡CH), 2.77 (t, J = 5.7 Hz, 2H, OCH_2-$\underline{CH_2}$), 2.29 (s, 3H, N-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.10 (C2-coumarin), 160.77 (C7-coumarin), 155.84 (C8a-coumarin), 144.80 (C4-coumarin), 129.93 (C4a-coumarin), 113.24 (C3-coumarin), 112.92 (C5-coumarin), 112.79 (C6-coumarin), 101.64 (C8-coumarin), 79.42 (-C≡), 76.41 (≡CH), 66.90 (O-CH_2-), 54.10 (OCH_2-$\underline{CH_2}$), 45.81 ($\underline{CH_2}$-C≡), 42.08 (N-CH_3). HRMS: calcd for $C_{15}H_{15}NO_3$ $[M + H]^+$ 258.1052, found 258.1125.

*4.1.4.2. 7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}-2H-chromen-2-one (**4w**)*

The general procedure described for **4v-x** was used, starting from **2b**, powdered K_2CO_3, *N*-methylpropargylamine and KI, and **4w** was obtained as a White solid (yield 89%); m.p. 101-102 °C; IR (KBr) *v* 3209, 2938, 1724, 1610, 1282, 1121, 1025, 837 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.4 Hz, 1H, H4-coumarin), 7.62 (d, J = 8.5 Hz, 1H, H5-coumarin), 6.96 (d, J = 2.4 Hz, 1H, H8-coumarin), 6.94 (dd, J = 8.5, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, J = 9.5 Hz, 1H, H3-coumarin), 4.10 (t, J = 6.4 Hz, 2H, O-CH_2-), 3.32 (d, J = 2.4 Hz, 2H, CH_2-C≡), 3.11 (d, J = 2.4 Hz, 1H, C≡CH), 2.51 (s, 2H, O(CH_2)$_2$-$\underline{CH_2}$), 2.22 (s, 3H, N-CH_3), 1.87 (p, J = 6.7 Hz, 2H, OCH_2-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.29 (C2-coumarin), 160.77 (C7-coumarin), 155.85 (C8a-coumarin), 144.80 (C4-coumarin), 129.95

(C4a-coumarin), 113.14 (C3-coumarin), 112.87 (C5-coumarin), 112.74 (C6-coumarin), 101.61 (C8-coumarin), 79.42 (-C≡), 76.25 (≡CH), 67.00 (O-CH_2-), 51.96 (O(CH_2)$_2$-$\underline{CH_2}$), 45.46 ($\underline{CH_2}$-C≡), 41.73 (N-CH_3), 27.02 (OCH_2-$\underline{CH_2}$). HRMS: calcd for $C_{16}H_{17}NO_3$ $[M + H]^+$ 272.1208, found 272.1281.

*4.1.4.3. 7-{4-[methyl(prop-2-yn-1-yl)amino]butoxy}-2H-chromen-2-one (**4x**)*

The general procedure described for **4v-x** was used, starting from **2c**, powdered K_2CO_3, *N*-methylpropargylamine and KI, and **4x** was obtained as a Light yellow solid (yield 73%); IR (KBr) *v* 3203, 2946, 1710, 1620, 1286, 1130, 1024, 829 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.5 Hz, 1H, H4-coumarin), 7.62 (d, *J* = 8.6 Hz, 1H, H5-coumarin), 6.98 (d, *J* = 2.4 Hz, 1H, H8-coumarin), 6.94 (dd, *J* = 8.6, 2.4 Hz, 1H, H7-coumarin), 6.28 (d, *J* = 9.5 Hz, 1H, H3-coumarin), 4.09 (t, *J* = 6.5 Hz, 2H, O-CH_2-), 3.30 (d, *J* = 2.4 Hz, 2H, CH_2-C≡), 3.10 (t, *J* = 2.4 Hz, 1H, C≡CH), 2.39 (t, *J* = 7.2 Hz, 2H, O(CH_2)$_3$-$\underline{CH_2}$), 2.19 (s, 3H, N-CH_3), 1.74 (p, *J* = 6.6 Hz, 2H, OCH_2-$\underline{CH_2}$), 1.54 (p, *J* = 7.2 Hz, 2H, O(CH_2)$_2$-$\underline{CH_2}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.31 (C2-coumarin), 160.78 (C7-coumarin), 155.88 (C8a-coumarin), 144.81 (C4-coumarin), 129.92 (C4a-coumarin), 113.19 (C3-coumarin), 112.82 (C5-coumarin), 112.69 (C6-coumarin), 101.57 (C8-coumarin), 79.50 (-C≡), 76.13 (≡CH), 68.58 (O-CH_2-), 54.84 (O(CH_2)$_3$-$\underline{CH_2}$), 45.33 ($\underline{CH_2}$-C≡), 41.64 (N-CH_3), 26.67 (OCH_2-$\underline{CH_2}$), 23.71 (O(CH_2)$_2$-$\underline{CH_2}$). HRMS: calcd for $C_{17}H_{19}NO_3$ $[M + H]^+$ 286.1365, found 286.1438.

4.2. Pharmacology

4.2.1. MAO inhibition assay

Human MAO-A and MAO-B were purchased from Sigma-Aldrich. The capacity of the test compounds to inhibit *h*MAO-A and *h*MAO-B activities was assessed by Amplex Red MAO assay [40, 41]. Firstly, MAOs activity were adjusted to obtain in our experimental conditions the same reaction velocity in the presence of both isoforms (i.e., to oxidize (in the control group) the same concentration of substrate: 165 pmol of *p*-tyramine/min(*h*MAO-A: 1.1μg protein; specific activity: 150 nmol of *p*-tyramine oxidized to *p*-hydroxyphenylacetaldehyde/min/mg protein; *h*MAO-B: 7.5μg protein; specific activity: 22 nmol of *p*-tyramine transformed/min/mg protein).

Then compounds were dissolved in DMSO (10 mM) and diluted in 0.05 M KH_2PO_4/K_2HPO_4 buffer (pH = 7.4) to the desired final concentration. All the compounds are soluble at the tested concentration. Test drugs (20 μL) and MAO (80 μL) were incubated at 37 °C for 15 min in a flat-black-bottom 96-well microtest plate in dark. The reaction was started by adding 200 μM Amplex Red reagent, 2 U/mL horseradish peroxidase, and 2 mM *p*-tyramine for *h*MAO at 37 °C for 20 min. The reaction was quantified in a multidetection microplate fluorescence reader based on the fluorescence generated (excitation, 545 nm; emission, 590 nm). The specific fluorescence emission was calculated after subtraction of the background activity, which was determined from vials containing all components except the *h*MAO isoforms, which were replaced by a sodium phosphate buffer solution. The percent inhibition was calculated by the following expression: (1 – IFi/IFc) × 100% in which IFi and IFc are the fluorescence intensities obtained for *h*MAO in the presence and absence of inhibitors after subtracting the respective background.

4.2.2. Reversibility of *h*MAO-B inhibition

To determine whether the inhibition of *h*MAO-B by the coumarin-pargyline hybrids were reversible or irreversible, the time-dependence of inhibition of the selected inhibitor **4x** and reference compound pargyline were examined [41]. Compound **4x** was allowed to preincubate with recombinant human MAO-B for various periods of time (0, 15, 30, 60 min) at 37 °C in potassium phosphate buffer (0.05 M, pH 7.4). These actions were subsequently diluted two-fold to yield a final enzyme concentration of 0.015 mg mL^{-1}. The final concentrations of compound **4x**, pargyline were 30 nM and 200 nM for the inhibition of *h*MAO-B, respectively. The reactions were incubated at 37 °C for a further 15 min. All measurements were carried out in triplicate and are expressed as mean ± SD.

4.2.3. Inhibition of self-induced A$\beta_{1\text{-}42}$ aggregation

Inhibition of A$\beta_{1\text{-}42}$ aggregation was measured using a thioflavin T (ThT)-binding assay [33]. Resveratrol and curcumin were used as reference compounds. A$\beta_{1\text{-}42}$ (Millipore, counterion: NaOH) was dissolved in ammonium hydroxide (1% v/v) to give a stock solution (2000 μM), which was aliquoted into

small samples and stored at −80 °C. For the experiment of self-mediated A$\beta_{1\text{-}42}$ aggregation inhibition, the Aβ stock solution was diluted with 50 mM phosphate buffer (pH 7.4) to 50 μM before use. A mixture of the peptide (10 μL, 25 μM, final concentration) with or without the tested compound (10 μL) was incubated at 37 °C for 48 h. Blanks using 50 mM phosphate buffer (pH 7.4) instead of Aβ with or without inhibitors were also carried out. The sample was diluted to a final volume of 200 μL with 50 mM glycine-NaOH buffer (pH 8.0) containing thioflavin T (5 μM). Then the fluorescence intensities were recorded 5 min later (excitation, 446 nm; emission, 490 nm). The percent inhibition of aggregation was calculated by the expression (1 − IFi/IFc) × 100%, in which IFi and IFc are the fluorescence intensities obtained for Aβ in the presence and absence of inhibitors after subtracting the background, respectively.

4.2.4. *In vitro* blood–brain barrier permeation assay

Brain penetration of compounds was evaluated using a parallel artificial membrane permeation assay (PAMPA). Commercial drugs were purchased from Sigma and Alfa Aesar. The porcine brain lipid (PBL) was obtained from Avanti Polar Lipids. The donor microplate (PVDF membrane, pore size 0.45 mm) and the acceptor microplate were both from Millipore. The 96-well UV plate (COSTAR$^{@}$) was from Corning Incorporated. The acceptor 96-well microplate was filled with 300 μL of PBS/EtOH (7:3), and the filter membrane was impregnated with 4 μL of PBL in dodecane (20 mg/mL). Compounds were dissolved in DMSO at 5 mg/mL and diluted 50-fold in PBS/EtOH (7:3) to achieve a concentration of 100 mg/mL, 200 μL of which was added to the donor wells. The acceptor filter plate was carefully placed on the donor plate to form a sandwich, which was left undisturbed for 16 h at 25 °C. After incubation, the donor plate was carefully removed and the concentration of compound in the acceptor wells was determined using a UV plate reader (Flexsta-tion$^{@}$ 3). Every sample was analyzed at five wavelengths, in four wells, in at least three independent runs, and the results are given as the mean ± standard deviation. In each experiment, 8 quality control standards of known BBB permeability were included to validate the analysis set.

4.2.5. Cell viability assay

The toxicity effect of compounds on the rat pheochromocytoma (PC12) cells was examined. The PC12 cells were routinely grown at 37 °C in a humidified incubator with 5% CO_2 in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% bovine calf serum, 100 units/mL penicillin, and 100 units/mL of streptomycin. Cells were subcultured in 96-well plates at a seeding density of 10,000 cells per well and allowed to adhere and grow. When cells reached the required confluence, they were placed into serum-free medium and treated with compound **4x**. Twenty-four hours later the survival of cells was determined by MTT assay. Briefly, after incubation with 20 μL of MTT at 37 °C for 4 h, living cells containing MTT formazan crystals were solubilized in 200 μL DMSO. The absorbance of each well was measured using a microculture plate reader with a test wavelength of 570 nm and a reference wavelength of 630 nm. Results are expressed as the mean ± SD of three independent experiments.

4.2.6. Acute Toxicity

A total of 15 KM mice (KM mice, which are common closed colony mice and most widely used in biomedical research in China; male, 22 days, 18−20 g) purchased from Comparative Medicine Center of Yangzhou University (Yangzhou, China) with eligibility certification NO. SCXK 2013-0006 were used to evaluate the acute toxicity of compound **4x** and pargyline. Mice were maintained with a 12 h light/dark cycle (light from 07:00 to 19:00) at 20-22 °C and 60-70% relative humidity. Sterile food and water were provided according to institutional guidelines. Prior to each experiment, mice were fasted overnight and allowed free access to water. Compounds were suspended in 0.5% carboxymethyl cellulose sodium (CMC-Na) salt solution (2.4 mmol/kg) and given via oral administration according to the divided experimental groups [33]. After administration of the compounds, the mice were observed continuously for the first 4 h for any abnormal behavior and mortality changes, intermittently for the next 24 h, and occasionally thereafter for 14 days for the onset of any delayed effects. All animals were sacrificed on the 14th day after drug administration and were macroscopically examined for possible damage to the heart,

liver, and kidneys.

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Table 1. Inhibition of human MAO-A and MAO-B activities of the synthesized compounds.

Compd	n	R	IC_{50} [a] (μM)		SI [b]
			*h*MAO-A	*h*MAO-B	
4a	2	H	89.50±1.42	8.298±0.441	10.79
4b	2	4-CH_3	56.41±0.91	5.643±0.251	10.00
4c	2	4-$CH(CH_3)_2$	70.02±1.33	6.958±0.273	10.06
4d	2	4-OCH_3	55.05±0.76	3.513±0.174	15..67
4e	2	3-OCH_3	72.06±1.18	7.014±0.382	10.27
4f	2	3-F	53.29±1.09	5.530±0.231	9.64
4g	2	3,4-F	40.78±0.84	9.625±0.465	4.24
4h	3	H	38.61±0.51	3.742±0.160	10.32
4i	3	4-CH_3	116.37±1.98	7.381±0.314	15.77
4j	3	4-$CH(CH_3)_2$	77.44±0.99	7.580±0.373	10.22
4k	3	4-OCH_3	59.99±0.65	6.078±0.288	9.87
4l	3	3-OCH_3	22.70±0.21	4.594±0.182	4.94
4m	3	3-F	29.26±0.19	4.437±0.177	6.59
4n	3	3,4-F	49.17±0.85	4.855±0.194	10.13
4o	4	H	89.35±1.86	0.978±0.032	91.36
4p	4	4-CH_3	94.53±2.10	1.676±0.058	56.40
4q	4	4-$CH(CH_3)_2$	35.40±0.49	3.495±0.159	10.13
4r	4	4-OCH_3	54.51±1.07	1.131±0.049	48.20
4s	4	3-OCH_3	78.56±1.66	2.339±0.128	33.59
4t	4	3-F	69.15±1.94	1.552±0.061	44.56
4u	4	3,4-F	93.24±2.21	2.369±0.159	39.36
4v	2	-	69.87±1.38	1.103±0.057	63.35
4w	3	-	36.87±0.62	1.085±0.080	33.98
4x	4	-	3.275±0.040	0.027±0.004	121.3
Pargyline [c]	-		3.521±0.069	0.194±0.030	18.15

[a] IC_{50}: 50% inhibitory concentration (means ± SD of three experiments).

[b] SI: IC_{50} (*h*MAO-A)/IC_{50} (*h*MAO-B).

[c] Pargyline was used as positive control.

Table 2. Permeability ($P_e \times 10^{-6}$ cm s^{-1}) in the PAMPA-BBB assay for 8 commercial drugs (used in the experiment validation) and compound **4x**.

Commercial drugs	Bibliography [a]	Experiment [b]
Testosterone	17	10.98 ± 1.14
Verapamil	16	10.11 ± 1.02
β-Estradiol	12	8.00 ± 0.85
Clonidine	5.3	4.80 ± 0.33
Corticosterone	5.1	4.92 ± 0.28
Piroxicam	2.5	1.51 ± 0.17
Hydrocortisone	1.9	1.77 ± 0.15
Lomefloxacin	1.1	1 .05 ± 0.09
4x	-	8.92 ± 0.93

[a] Taken from Ref [35].

[b] Data are the mean ± SD of three independent experiments.

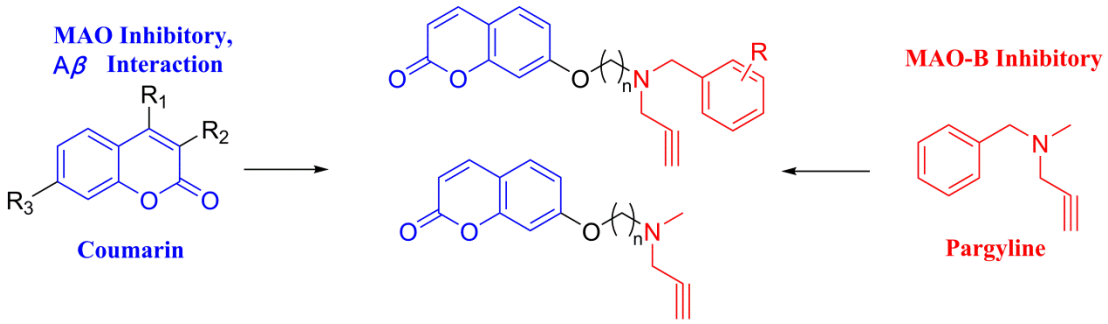


Figure 1. Design strategy for the coumarin-pargyline hybrids.

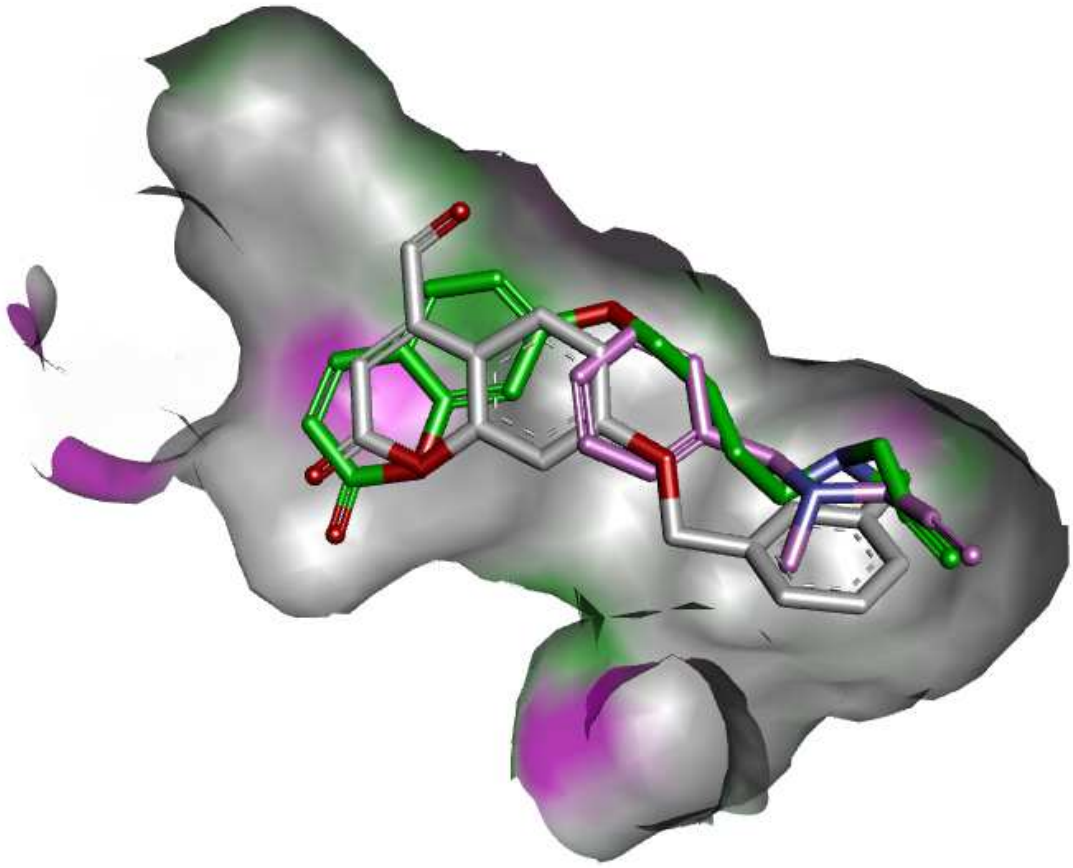


Figure 2. Docking studies of compound **4x**, pargyline and with *h*MAO-B (PDB code: 2V60). Atom colors: green-carbon atoms of compound **4x**, pink-carbon atoms of pargyline, silver-carbon atoms of ligand of *h*MAO-B, dark blue-nitrogen atoms, red-oxygen atoms.

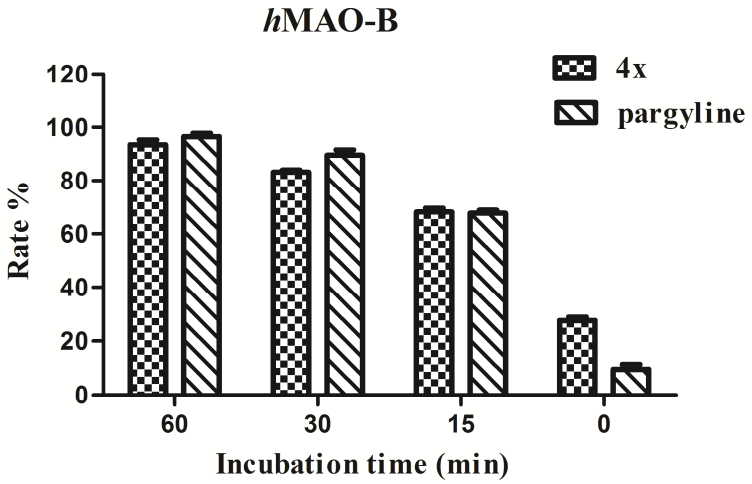


Figure 3. Reversibility study of *h*MAO-B inhibition by compound **4x** . The final concentrations of compound **4x**, pargyline were 30 nM and 200 nM for the inhibition of *h*MAO-B, respectively. The reactions were incubated at 37 °C for various periods of time (0-60 min). All measurements were carried out in triplicate and are expressed as mean ± SD.

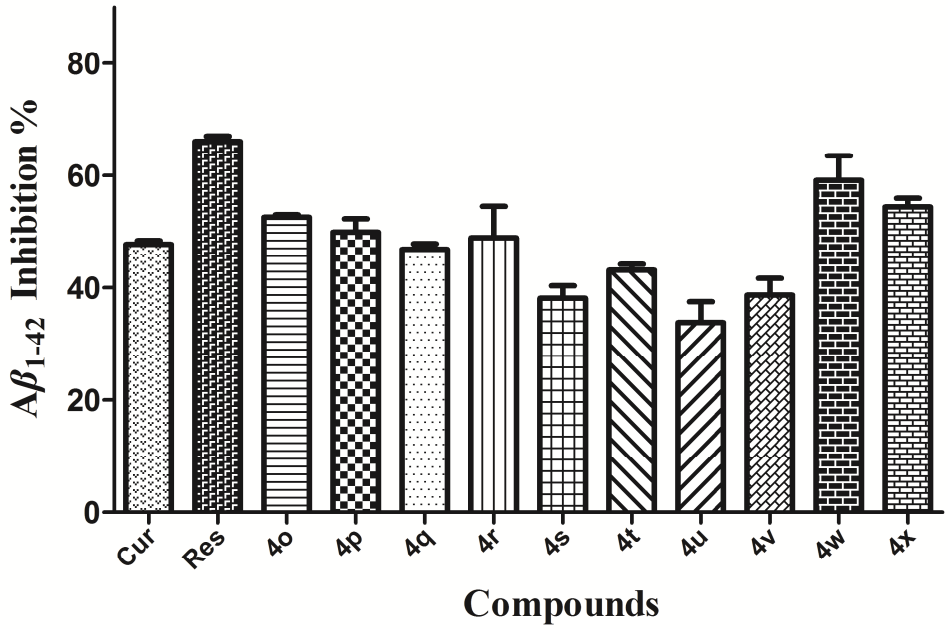


Figure 4. Inhibition of A$\beta_{1\text{-}42}$ self-induced aggregation by compounds **4a-x** comparing with those of curcumin (Cur) and resveratrol (Res). The thioflavin-T fluorescence method was used and the measurements were carried out in the presence of 25 μM test compound. The mean ± SD values from three independent experiments were shown.

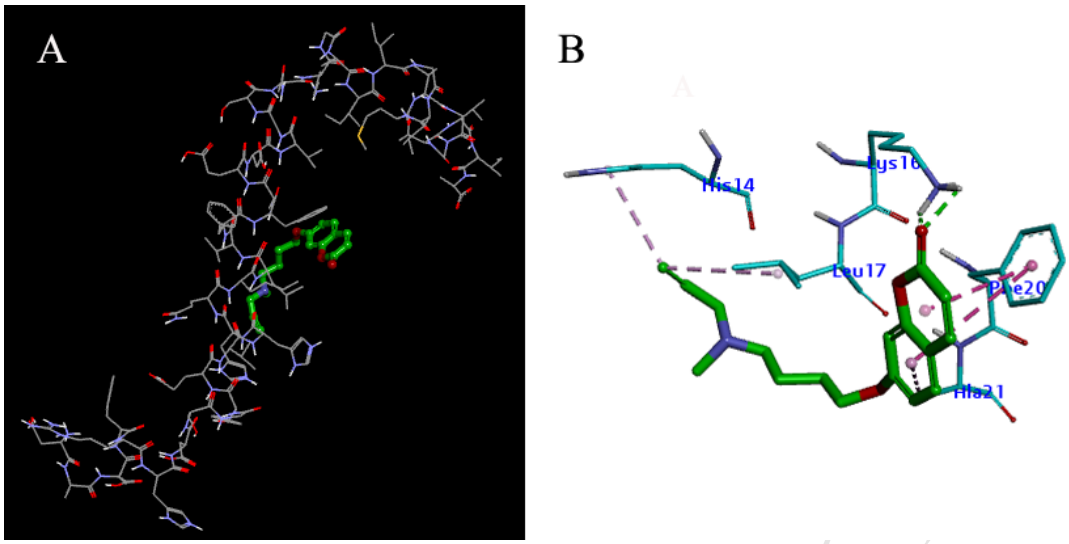


Figure 5. Docking study of compound **4x** (colored green) with A$\beta_{1\text{-}42}$ (PDB code 1IYT). (A) Cartoon representations of compound **4x** interacting with A$\beta_{1\text{-}42}$. (B) Association of **4x** (colored green) and the A$\beta_{1\text{-}42}$ obtained from docking calculations. The π-π stacking are depicted with purple dotted lines; H-bonds are represented by green dotted lines.

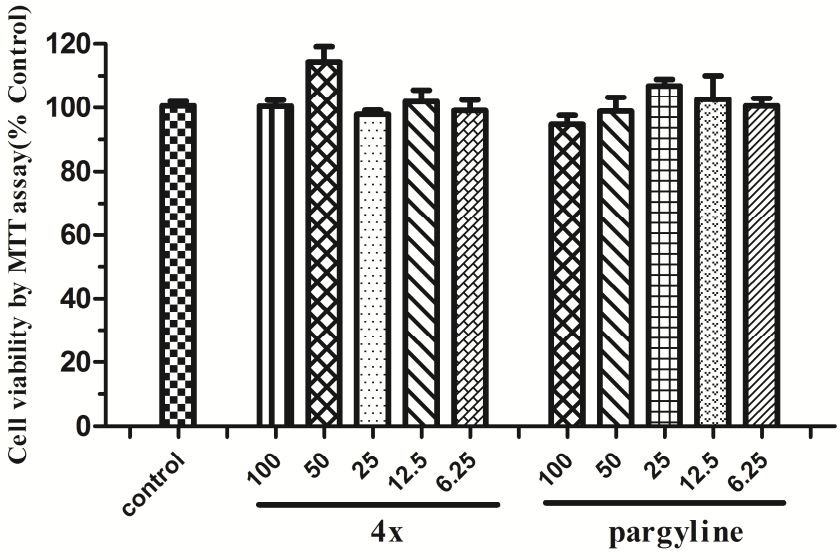


Figure 6. Effects of various concentrations of compound **4x** and pargyline on cell viability in PC 12 cells after treatment for 24 h. Cell viability was measured by MTT assay. Data were shown as mean ± SD of three independent experiments.

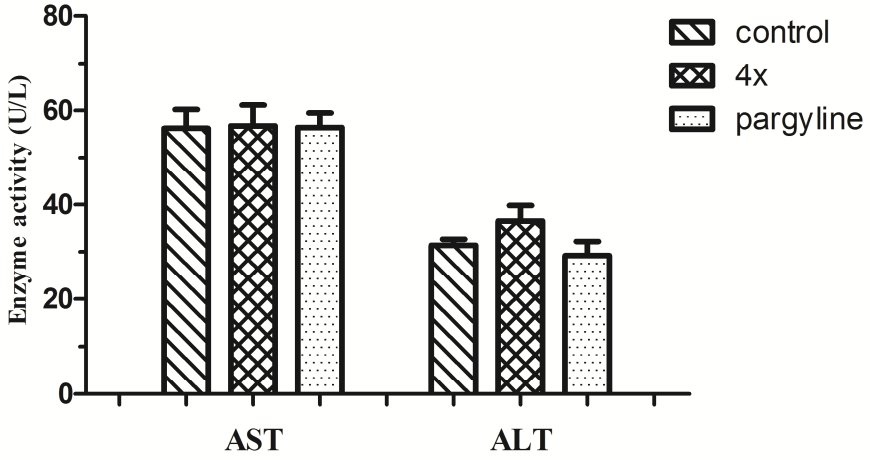
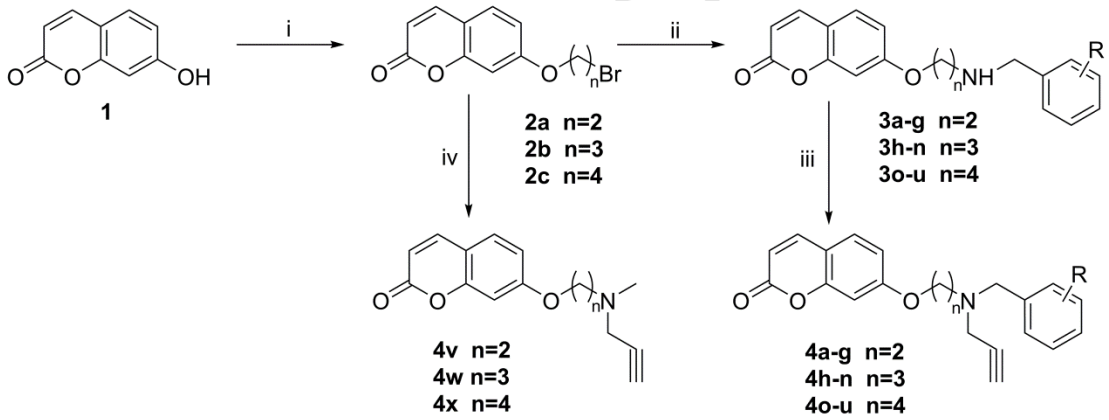


Figure 7. The AST and ALT activity on the 14th day after administration of a single oral dose (2.4 mmol/kg) of compound **4x** or pargyline. Results are expressed as mean ± SD of three independent experiments.



Scheme 1. Synthesis of coumarin-pargyline hybrids **4a-x**. Reagents and conditions: (i) α, ω-dibromoalkane, anhydrous K_2CO_3, acetone, reflux, 10-12h; (ii) appropriate benzylamine, anhydrous K_2CO_3, KI, CH_3CN, reflux, 10h; (iii) 3-bromopropyne, anhydrous K_2CO_3, KI, CH_3CN, 65°C, 1-2h; (iv) *N*-methylpropargylamine, anhydrous K_2CO_3, KI, CH_3CN, 65°C, 1-2h.

Highlights

- Novel multi-target-directed ligands for Alzheimer's disease were designed and synthesized.
- The new hybrids have been obtained by fusing coumarin with pargyline.
- Hybrid **4x** exhibited remarkable inhibitory activities against MAO-B and A$\beta_{1\text{-}42}$ aggregation.
- Hybrid **4x** showed a low neurotoxicity and potent BBB penetration