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Synthesis and evaluation of 6-methylcoumarin derivatives as potent and selective monoamine oxidase B inhibitors†

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A new series of 6-methyl-3-phenylcoumarins (**3a–c** and **5a–o**) and 6-methyl-3-heteroarylcoumarins (**5p–s**) have been designed, synthesized and evaluated as monoamine oxidase inhibitors. The results demonstrated that a large proportion of the synthesized compounds selectively inhibited monoamine oxidase B with IC_{50} values in the sub-micromolar range. Among them, compound **5n** (IC_{50} = 0.0601 μM) exhibited the most potent inhibitory activity and the highest selectivity for monoamine oxidase B (SI > 1664-fold). In addition, the possible binding model of the active compound **5n** was measured by docking it into the active site of the hMAO-B complex structure. The results showed that compound **5n** interacted with the well-known binding pocket of MAO-B, and a π–π interaction was found between the phenyl ring at position 3 of the coumarin and the phenyl ring of Tyr 326. Consequently, we supplied useful information about the interaction between the enzyme and inhibitor, and developed the 6-methyl-3-phenylcoumarin scaffold as an agent for multifaceted brain disorders.

Introduction

Monoamine oxidase (MAO) is an important enzyme containing flavin adenine dinucleotide (FAD) that regulates and metabolises most monoamine neurotransmitters, such as norepinephrine (NE), dopamine (DA), and 5-hydroxy-tryptamine (5-HT). MAO can modulate the concentrations of monoamine neurotransmitters in peripheral and central tissues.[1] MAO has two functional isozymic forms, namely MAO-A and MAO-B, which are differentiated by differences in their amino acid sequences, immunological properties, tissue distribution, inhibitor specificity, and substrate preference.[2–6] MAO-A is present in catecholaminergic neurons, while MAO-B is located predominantly in serotonergic glia and neurons.[7] Both enzymes can deaminate tyramine, DA and tryptamine by oxidation. However, MAO-A tends to metabolize epinephrine, 5-HT and NE, and is selectively inhibited by clorgyline. MAO-B preferentially deaminates β-phenethylamine and benzylamine, and is selectively inhibited by rasagiline and selegiline.[8,9] The MAOs have been used as drug targets for numerous decades and inhibitors of these enzymes are used primarily to treat neuropsychiatric syndromes. Selective MAO-B inhibitors are used to treat several neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease,[10] whereas inhibitors of MAO-A have been revealed to be effective antidepressants.[11] Based on these aspects, there is an intensive requirement for novel MAO inhibitors.

The crystal structures of the two MAO isoforms were described by Binda *et al.*, providing information about their pharmacophoric requirements and selective interactions to design potent and selective inhibitors.[12] The active site of monoamine oxidase is a lipophilic cage, largely filled with aromatic amino acids, surrounding the isoalloxazine moiety of the FAD cofactor. The diverse structure and shape of this active site in MAO-A and MAO-B results in the different affinities or selectivities for inhibitors and substrates.[13]

Coumarins are a wide family of compounds of both synthetic and natural origins. Due to their versatile synthetic methodologies and structural variability, they play a significant role not only in medicinal chemistry but also in organic chemistry.[14,15] Recently, coumarins or coumarin analogues have been utilized for the design of activity-based probes for MAO enzymes,[16–18] and differently substituted coumarins have been synthesized or isolated from natural sources and evaluated for their potential as MAO inhibitors (structures A–H in Fig. 1), showing selective inhibitory activities for either MAO-A or MAO-B isoforms in the micromolar to picomolar ranges.[19–28]

Discoveries reveal that expression levels of MAO in neuronal tissue increase 4-fold with age, leading to an increase in the production of hydrogen peroxide and metabolism of

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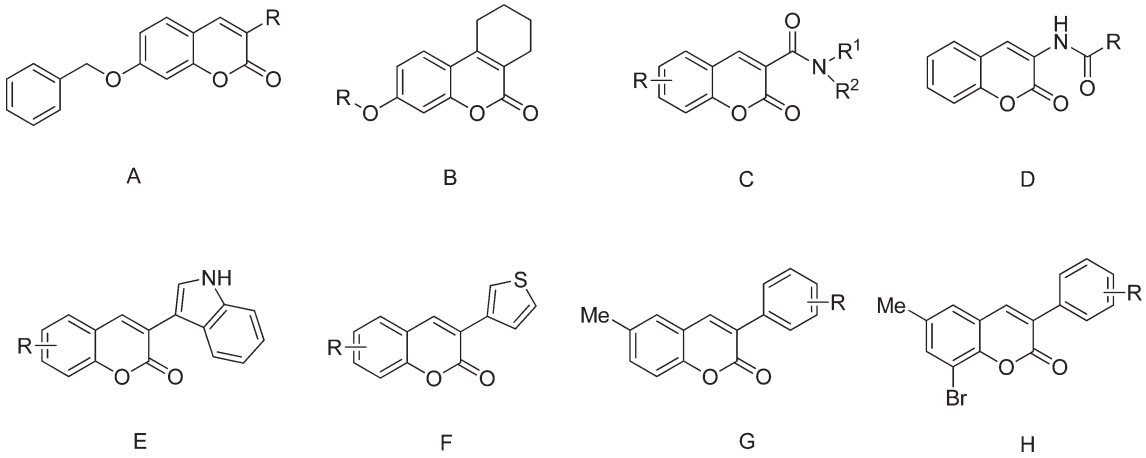


Fig. 1 Structures of known coumarin-based MAO inhibitors.

dopamine, which causes oxidative stress and might occur in neurodegenerative diseases.[29] Therefore, MAO-B inhibitors could be used to treat some neurodegenerative diseases. For example, it has been stated that neuronal cells are protected from oxidative stress by selegiline in patients suffering from neurodegenerative diseases.[30] Therefore, the search for novel, efficient and selective MAO-B inhibitors has significantly intensified over the past few years.

Recent studies of structure–activity relationships show that MAO-B inhibitory activity is modulated by substitution at position 3 of the coumarin nucleus.[21–23] Among the different inhibitors that exist, 6-methyl-3-phenylcoumarin derivatives have been deeply studied,[24–27] and all of the studied 6-methyl-3-phenylcoumarins show very high MAO-B selectivity. In particular, 6-methyl-3-(3-methoxyphenyl)coumarin was found to be the best MAO-B inhibitor (IC_{50} = 0.80 nM).[28] On the basis of previous studies, the methoxy group was substituted with other groups to gain more selective and potent MAO-B inhibitors.[27] Some coumarin derivatives substituted at the 3-position with different heterocyclic rings were also synthesized.[28] On account of these, we designed, synthesized and tested some new 6-methyl-coumarin derivatives as selective MAO-B inhibitors.

Results and discussion

Chemistry

The coumarin derivatives were synthesized according to Schemes 1 and 2. The general reaction conditions and the compound characterization are described in the experimental section.

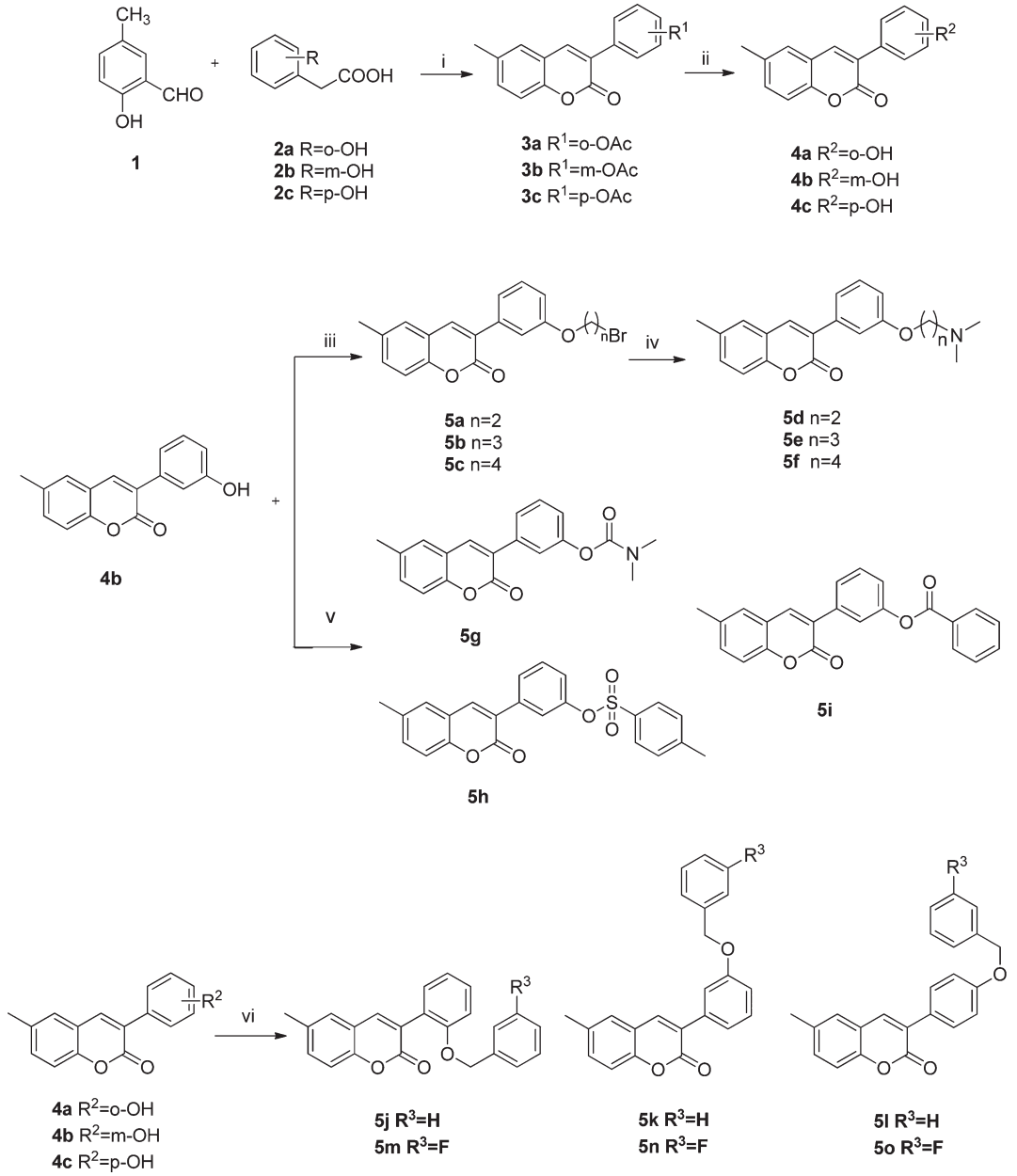
The synthetic routes for the 6-methyl-3-phenylcoumarins derivatives are presented (Scheme 1). The commercially available 5-methylsalicylaldehyde was reacted with *ortho*-hydroxylated benzaldehydes **2a–c** in the presence of triethylamine and acetic anhydride to provide compounds **3a–c**.[31] Hydrolysis of **3a–c** with 10% HCl/EtOH afforded phenolic products **4a–c**. Compound **4b** was reacted with different α,ω-dibromoalkanes in acetonitrile to produce compounds **5a–c** in 76–85% yields, and these compounds were treated with dimethylamine hydrochloride in the presence of potassium carbonate to give the key compounds **5d–f** in 75–89% yields. The treatment of **4a–c** and acyl chlorides/benzyl bromides with potassium carbonate in acetonitrile afforded compounds **5g–o**.

By condensation of the appropriately substituted acetic acids and 5-methylsalicylaldehyde with *N*, *N*′-dicyclohexylcarbodiimide (DCC) as a dehydrating agent, the 3-heteroarylcoumarin derivatives **5p–s** were synthesized *via* the classical Perkin reaction in moderate yields (Scheme 2).

Inhibition of hMAO

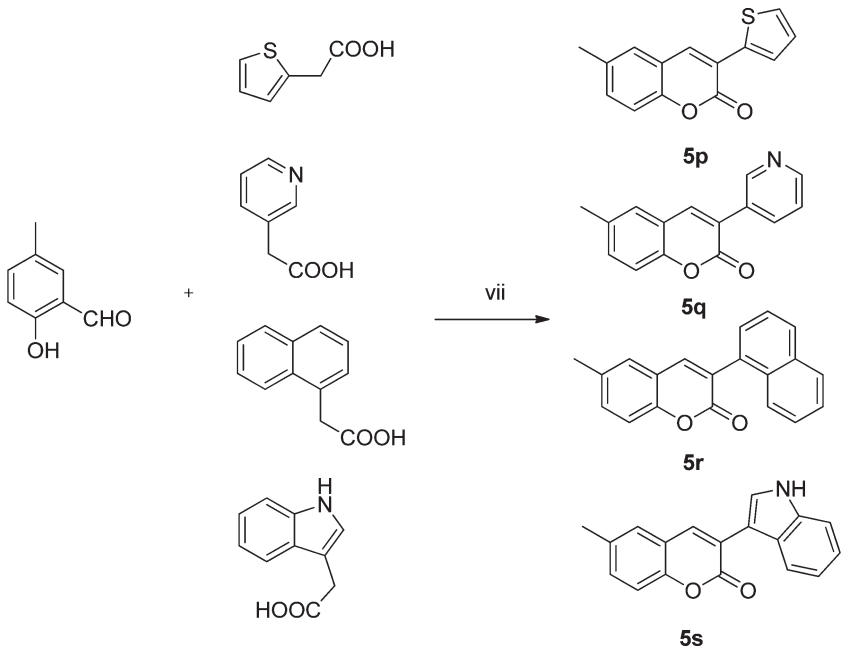
With iproniazid as a reference, the hMAO inhibitory activities were explored by using the Amplex Red MAO assay, according to the reported procedure.[32] The corresponding IC_{50} values and selectivity ratios for MAO-B are shown in Table 1. Based on the screening data, it can be seen that most of the tested compounds selectively inhibit MAO-B with IC_{50} values in the sub-micromolar range. Inhibition towards MAO-A was very weak and the structure–activity relationship was not apparent. Among the synthesized compounds, **5n** was the most potent and was a highly selective inhibitor against MAO-B (IC_{50} = 0.0601 μM), being about 130-fold more active than iproniazid.

To introduce groups with different properties to the 3-hydroxyphenyl ring of the coumarin moiety, compounds **3b**, **5a–i**, **5k** and **5n** were synthesized. Among **5a–c**, with the number of methylenes in the substituent on the 3-hydroxyphenyl ring varying from two to four, compound **5a** with a 2-carbon spacer gave the best inhibition for MAO-B (IC_{50} = 2.45 μM). Extending the chain length resulted in an apparent decrease in MAO-B inhibition, and a similar trend was observed for **5d–f**. On the other hand, **5d** (IC_{50} = 0.2180 μM) was a better inhibitor for MAO-B than **5a** (IC_{50} = 2.45 μM), and **5e** gave better results than **5b**. All of these results revealed that the length of the alkyl chain could affect the MAO-B inhibitory activity, and the inhibitory capacity was



Scheme 1 Synthesis of 6-methyl-3-phenylcoumarin derivatives. Reagents and conditions: (i) triethylamine, acetic anhydride, 120 °C, 8 h; (ii) 10% HCl/MeOH, 80 °C, 5–12 h; (iii) α,ω-dibromoalkanes, K_2CO_3, acetonitrile, 40 °C, 4 h; (iv) dimethylamine hydrochloride, K_2CO_3, acetonitrile, reflux, 8 h; (v) acyl chlorides, K_2CO_3, acetonitrile, r.t., 5 h; (vi) benzyl bromide or 3-fluorobenzyl bromide, K_2CO_3, acetonitrile, r.t., 4 h.

increased by introducing amino group side chains. Compounds **3b** and **5g–i** were obtained by treating **4b** with different acyl chlorides. Among them, compounds **3b**, **5h** and **5i** had MAO-B inhibitory activities in the sub-micromolar range, with **5h** (IC_{50} = 0.3052 μM) being the best. Compound **5k** was designed with the aim to explore the differences when the carboxyl group was deleted. Compared with **5i** (IC_{50} = 0.6511 μM), the inhibitory activity of **5k** (IC_{50} = 0.2010 μM) toward MAO-B was increased. On the basis of these results, compounds **5j** and **5l–o** were synthesized to explore the structure–activity relationship. **5j** and **5l** were *ortho* and *para* substituted on the hydroxyphenyl ring with a benzyl group, and compounds **5m–o** were produced by introducing 3-fluorobenzyl into **4a–c**. It is worth noting that compounds **5m–o** bearing a fluorine group exhibited slightly better inhibitory activities against MAO-B in comparation with **5j–l**, which revealed that an electron-withdrawing group seems to be crucial in MAO-B inhibitory activity. In addition, the activity data of the synthesized compounds pointed out that it seems to be unfavorable, in terms of the MAO inhibitory activity, to introduce substituents at the *ortho*-position of the 3-phenyl ring. For example, compounds **3a**, **5j** and **5m** showed decreased inhibitory activities compared with compounds bearing substituents at the *meta*- or *para*-positions.



Scheme 2 Synthesis of 6-methyl-3-phenylcoumarin derivatives. Reagents and conditions: (vii) DCC, DMSO, 110 °C, 24–48 h.

It is notable that the replacement of the 3-phenyl group with heterocyclic groups in the same position resulted in compounds **5p–s**, which all showed a reduction in *anti*-MAO potency.

Table 1 MAO inhibitory activities of the synthesized compounds

Compounds	IC_{50} (μM)[a]		Selectivity index[b]
	MAO-A	MAO-B	
3a	N[c]	0.9384 ± 0.0089	>106.6
3b	N	0.7141 ± 0.0194	>140.0
3c	N	0.4013 ± 0.0120	>249.1
5a	20.75 ± 0.83	2.45 ± 0.12	8.47
5b	19.46 ± 0.76	3.67 ± 0.14	5.30
5c	40.58 ± 1.23	10.71 ± 0.37	3.79
5d	N	0.2180 ± 0.0101	>458.7
5e	34.89 ± 1.41	0.9046 ± 0.0178	38.57
5f	26.73 ± 0.97	1.13 ± 0.04	23.65
5g	N	4.43 ± 0.16	>22.57
5h	N	0.3052 ± 0.0045	>327.7
5i	15.77 ± 0.45	0.6511 ± 0.0203	24.22
5j	N	0.2564 ± 0.0082	>390.0
5k	N	0.2010 ± 0.0120	>497.6
5l	N	0.1056 ± 0.0044	>947.0
5m	N	0.2532 ± 0.0056	>394.9
5n	N	0.0601 ± 0.0024	>1663.9
5o	N	0.1748 ± 0.0031	>572.1
5p	8.09 ± 0.18	3.76 ± 0.14	2.16
5q	6.67 ± 0.09	2.58 ± 0.13	2.59
5r	55.47 ± 1.80	6.49 ± 0.31	8.55
5s	43.93 ± 1.76	5.67 ± 0.28	7.75
Iproniazid	6.58 ± 0.69	7.82 ± 0.41	0.84

[a] IC_{50}: 50% inhibitory concentration (mean ± SEM of three experiments). [b] Selectivity index = IC_{50} (MAO-A)/IC_{50} (MAO-B). [c] Inactive at 100 μM (highest concentration tested); at higher concentrations the compounds precipitate.

Molecular modeling studies

In order to carry out a detailed study of the MAO-B binding modes, molecular docking studies were performed. The crystallographic structure of MAO-B (PDB code 2V61) from the Protein Data Bank was used to dock the derivatives under study.[33] According to the inhibition results, compound **5n** was selected as a typical ligand. The 2D and 3D pictures of binding are illustrated in Fig. 2A and B. As shown in Fig. 2, compound **5n** interacted with the well-known binding pocket of the isoenzyme,[34] with the methyl substituent at C6 pointing towards the FAD cofactor, Tyr 188 and Tyr 435. The coumarin ring was at the bottom of the substrate cavity, interacting with Tyr 398 and Cys 172. There was a π–π interaction between the phenyl ring at position 3 of the coumarin and the phenyl ring of Tyr 326, with length of 3.23 Å. Finally, the substituted benzyl group occupied the entrance cavity, a hydrophobic subpocket existing only in the MAO-B isoform and is composed of Leu 164, Ile 199, Tyr 326, Leu 164, Trp 119, Leu 167 and Phe 168. This might be one reason for the MAO-B selectivity of our compounds.

Cell toxicity

Based on the screening results above, compound **5n**, the most potent and a highly selective inhibitor against MAO-B, was selected to further examine the potential toxicity effect on the normal cell line HUVEC, neural cell line PC12 and neural cell line SH-SY5Y.[35] After incubating the cells with compound **5n** for 48 h, the cell viability was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay. As shown in the Fig. 3, compound **5n** at 2.5–20 μM did not exhibit neurotoxicity. This suggests that

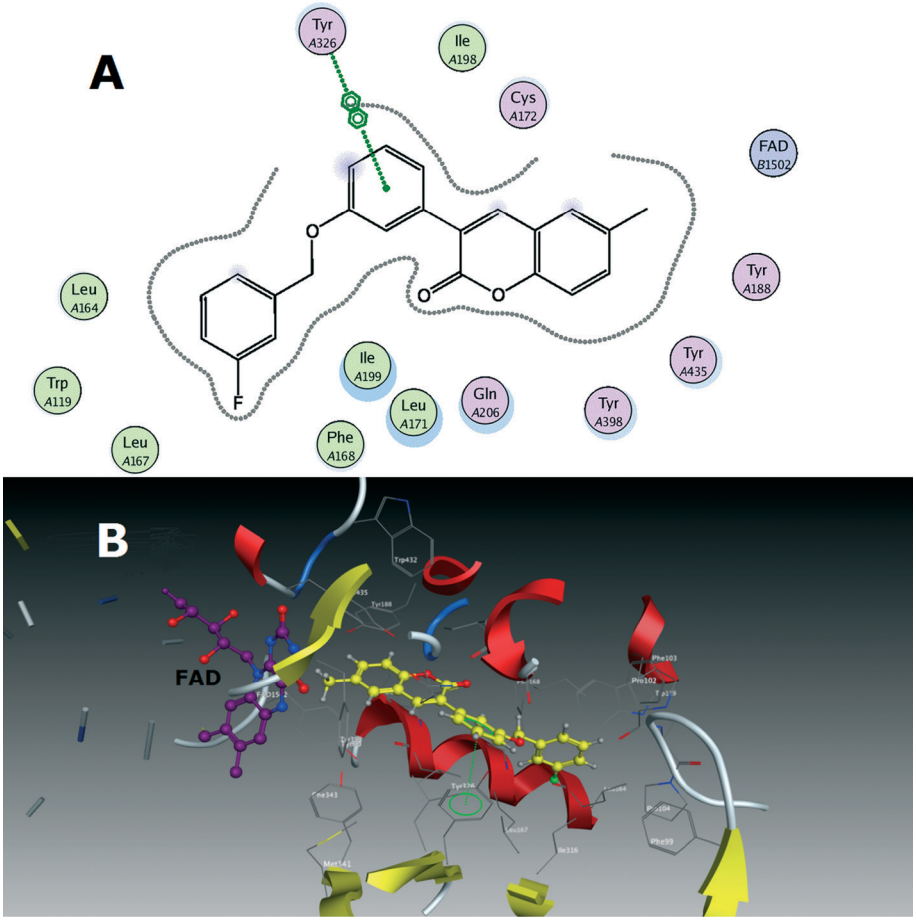


Fig. 2 Molecular docking of the compound **5n** into the ligand binding model site of MAO-B was performed on the binding model based on the MAO-B complex structure (2V61. pdb). The 2D picture of binding is depicted in part A. The 3D picture of binding is depicted in part B.

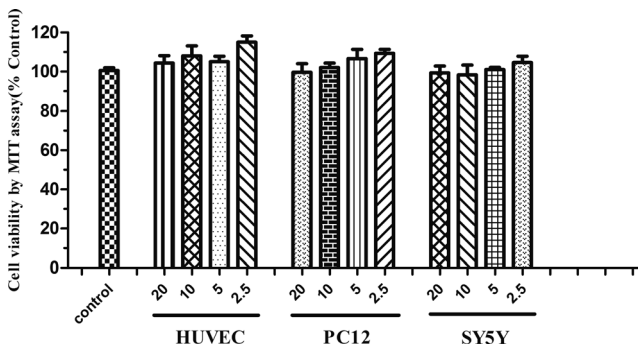


Fig. 3 The toxicity effect of **5n** on the normal cell line HUVEC, neural cell line PC12 and neural cell line SH-SY5Y.

compound **5n** might be used to develop promising drug candidates for the treatment of neurodegenerative diseases.

Conclusions

In conclusion, a new series of 6-methylcoumarins were designed, synthesized and evaluated for their MAO inhibitory activity *in vitro*. Compared with the reference compound iproniazid, most of the studied compounds were highly potent and selective hMAO-B inhibitors. In particular, compound **5n** was the best MAO-B inhibitor (IC_{50} = 0.0601 μM, SI > 1663.9). Both the type and position of the substituents attached to the 3-phenyl group played an important role in the MAO inhibitory activity. It is likely that *meta* and *para* substituents were the most positive positions for the MAO-B inhibitory activity. Due to their potent and selective MAO-B inhibitory activities, these compounds could be used to develop promising drug candidates for the treatment of neurodegenerative diseases.

Experimental

General

All common reagents and solvents were obtained from commercial suppliers and used without further purification. The reaction progress was monitored using analytical thin layer chromatography (TLC) on precoated silica gel GF254 plates (Qingdao Haiyang Chemical Plant, Qingdao, China) and the spots were detected under UV light (254 nm). Column chromatography was performed on silica gel (90–150 μm; Qingdao Marine Chemical Inc.) The purity of all compounds used for biological evaluation was confirmed to be higher than

95% through analytical HPLC, performed with an Agilent 1200 HPLC System. Melting points were measured on an XT-4 micromelting point instrument and are uncorrected. ^{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 the internal standard. Mass spectra were obtained on a MS Agilent 1100 Series LC/MSD Trap mass spectrometer (ESI-MS) and a Mariner ESI-TOF spectrometer (HRESI-MS).

General procedure for the preparation of 3a–c. Triethylamine (4 mL) was added to a solution of 5-methylsalicylaldehyde (**1**, 10 mmol) and substituted phenyl acetic acid (**2a–c**, 10 mmol) in acetic anhydride (6 mL). The mixture was heated to 120 °C and stirred for 8 h. After cooling, it was poured into ice water, stirred, and stored for 4 h. The precipitated yellowish solid was filtered, washed with water, dried, and recrystallized from ethyl acetate to give the target compound (**3a–c**).

*3-(2-Acetoxyphenyl)-6-methylcoumarin (**3a**).* Yield 60%, red solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (s, 1H, CH═CH), 7.60 (br s, 1H, Ar–H), 7.55–7.47 (m, 3H, Ar–H), 7.41–7.36 (m, 2H, Ar–H), 7.31–7.27 (m, 1H, Ar–H), 2.40 (s, 3H, Ar–CH_3), 2.12 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.89, 159.53, 151.91, 148.74, 143.08, 134.44, 133.41, 131.59, 130.17, 128.78, 128.52, 126.26, 124.87, 123.48, 119.20, 116.33, 21.14, 20.74. MS (ESI) m/z 295.1 $[M + H]^+$; m.p. 112–115 °C; HRMS (ESI) m/z 295.0963 $[M + H]^+$ (calcd 295.0965, $C_{18}H_{15}O_4$).

*3-(3-Acetoxyphenyl)-6-methylcoumarin (**3b**).* Yield 85%, colorless solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H, CH═CH), 7.65 (d, J = 8.0 Hz, 1H, Ar–H), 7.59 (br s, 1H, Ar–H), 7.56–7.51 (m, 2H, Ar–H), 7.48 (dd, J = 8.4, 2.0 Hz, 1H, Ar–H), 7.37 (d, J = 8.5 Hz, 1H, Ar–H), 7.22 (dd, J = 8.0, 1.5 Hz, 1H, Ar–H), 2.41 (s, 3H, Ar–CH_3), 2.32 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.96, 158.83, 152.91, 147.32, 143.51, 133.69, 133.46, 131.86, 130.17, 128.78, 128.61, 126.35, 124.78, 123.37, 119.16, 116.54, 21.26, 20.35. MS (ESI) m/z 295.2 $[M + H]^+$; m.p. 138–141 °C; HRMS (ESI) m/z 295.0966 $[M + H]^+$ (calcd 295.0965, $C_{18}H_{15}O_4$).

*3-(4-Acetoxyphenyl)-6-methylcoumarin (**3c**).* Yield 78%, colorless solid; ^{1}H NMR (500 MHz, DMSO) δ 8.23 (s, 1H, CH═CH), 7.79 (d, J = 8.5 Hz, 2H, Ar–H), 7.58 (br s, 1H, Ar–H), 7.49–7.45 (m, 1H, Ar–H), 7.36 (d, J = 8.5 Hz, 1H, Ar–H), 7.25 (d, J = 9.0 Hz, 2H, Ar–H), 2.41 (s, 3H, Ar–CH_3), 2.32 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.61, 160.32, 151.65, 151.15, 141.03, 134.33, 133.13, 132.74, 130.19, 128.73, 128.73, 126.52, 122.14, 122.14, 119.71, 116.15, 21.35, 20.77; MS (ESI) m/z 295.2 $[M + H]^+$; m.p. 171–174 °C; HRMS (ESI) m/z 295.0967 $[M + H]^+$ (calcd 295.0965, $C_{18}H_{15}O_4$).

General procedure for the preparation of compounds 5a–c. To a stirred mixture of **4c** (5 mmol) and K_2CO_3 (1.4 g, 10 mmol) in acetonitrile (15 mL), α,ω-dibromoalkane (25 mmol) was added. After stirring for 4 h at 40 °C, the mixture was filtered and the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography with petroleum ether–ethyl acetate as the eluent to give the target compound (**5a–c**).

*3-(3-(2-Bromoethoxy)phenyl)-6-methyl-2H-chromen-2-one (**5a**).* Yield 88%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (s, 1H, CH═CH), 7.59 (br s, 1H, Ar–H), 7.47 (dd, J = 8.5, 2.0 Hz, 1H, Ar–H), 7.41 (t, J = 8.0 Hz, 1H, Ar–H), 7.38–7.33 (m, 3H, Ar–H), 7.06–7.04 (m, 1H, Ar–H), 4.40 (t, J = 5.5 Hz, 2H, OCH_2), 3.86 (t, J = 5.5 Hz, 2H, $BrCH_2$), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.19, 158.22, 151.65, 141.26, 136.63, 134.29, 133.16, 129.89, 128.78, 126.88, 121.86, 119.68, 116.12, 115.50, 115.28, 68.39, 31.87, 20.78; m.p. 124–126 °C; HRMS (ESI) m/z 381.0098 $[M + Na]^+$ (calcd 381.0097, $C_{18}H_{15}BrNaO_3$).

*3-(3-(3-Bromopropoxy)phenyl)-6-methyl-2H-chromen-2-one (**5b**).* Yield 83%, red solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (s, 1H, CH═CH), 7.59 (br s, 1H, Ar–H), 7.47 (dd, J = 8.5, 2.0 Hz, 1H, Ar–H), 7.43–7.30 (m, 4H, Ar–H), 7.07–7.02 (m, 1H, Ar–H), 4.16 (t, J = 6.0 Hz, 2H, OCH_2), 3.72 (t, J = 6.5 Hz, 2H, $BrCH_2$), 2.41 (s, 3H, Ar–CH_3), 2.33–2.27 (m, 2H, alkyl chains-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.20, 158.64, 151.64, 141.20, 134.28, 133.14, 129.84, 129.75, 128.77, 126.97, 121.54, 121.20, 119.68, 116.12, 115.37, 115.13, 65.93, 65.24, 57.84, 32.66, 32.38, 31.70, 20.78; m.p. 82–84 °C; HRMS (ESI) m/z 395.0254 $[M + Na]^+$ (calcd 395.0253, $C_{19}H_{17}BrNaO_3$).

*3-(3-(4-Bromobutoxy)phenyl)-6-methyl-2H-chromen-2-one (**5c**).* Yield 72%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (s, 1H, CH═CH), 7.59 (s, 1H, Ar–H), 7.47 (dd, J = 8.4, 1.8 Hz, 1H, Ar–H), 7.38 (dd, J = 17.2, 8.5 Hz, 2H, Ar–H), 7.33–7.30 (m, 2H, Ar–H), 7.04–7.01 (m, 1H, Ar–H), 4.08 (t, J = 6.3 Hz, 2H, OCH_2), 3.65 (t, J = 6.7 Hz, 2H, $BrCH_2$), 2.41 (s, 3H, Ar–CH_3), 2.02 (m, 2H, alkyl chains-H), 1.92–1.86 (m, 2H, alkyl chains-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.20, 158.84, 151.64, 141.17, 136.51, 134.28, 133.13, 129.77, 128.76, 127.03, 121.34, 119.68, 116.12, 115.35, 115.07, 67.23, 35.28, 29.62, 27.91, 20.78; MS (ESI) m/z 387.1 $[M + H]^+$; m.p. 124–126 °C; HRMS (ESI) m/z 387.0589 $[M + H]^+$ (calcd 387.0590, $C_{20}H_{20}BrO_3$).

General procedure for the preparation of compounds 5d–f. To a stirred mixture of **5a–c** (0.5 mmol) and K_2CO_3 (0.14 g, 1 mmol) in acetonitrile (10 mL), dimethylamine hydrochloride (0.5 mmol) was added and the mixture was refluxed for 8 h. After cooling to room temperature, the mixture was filtered and the filtrate was evaporated under vacuum. The obtained residue was purified by silica gel chromatography with petroleum ether–acetone as the eluent to give the target compound (**5d–f**).

*3-(3-(2-(Dimethylamino)ethoxy)phenyl)-6-methyl-2H-chromen-2-one (**5d**).* Yield 84%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (s, 1H, CH═CH), 7.59 (br s, 1H, Ar–H), 7.47 (dd, J = 8.5, 2.0 Hz, 1H, Ar–H), 7.41–7.34 (m, 2H, Ar–H), 7.33–7.30 (m, 2H, Ar–H), 7.02 (dd, J = 8.5, 2.0 Hz, 1H, Ar–H), 4.12 (t, J = 6.0 Hz, 2H, OCH_2), 2.67 (t, J = 6.0 Hz, 2H, NCH_2), 2.41 (s, 3H, Ar–CH_3), 2.25 (s, 6H, NCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.19, 158.79, 151.63, 141.16, 136.50, 134.26, 133.12, 129.77, 128.76, 127.01, 121.31, 119.69, 116.11, 115.32, 115.06, 66.42, 58.19, 46.03, 20.78; MS (ESI) m/z 324.2 $[M + H]^+$; m.p. 93–95 °C; HRMS (ESI) m/z 324.1595 $[M + H]^+$ (calcd 324.1594, $C_{20}H_{22}NO_3$).

*3-(3-(3-(Dimethylamino)propoxy)phenyl)-6-methyl-2H-chromen-2-one (**5e**).* Yield 82%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (s, 1H, CH═CH), 7.59 (br s, 1H, Ar–H), 7.47 (dd, J = 8.5, 2.0 Hz, 1H, Ar–H), 7.40–7.35 (m, 2H, Ar–H), 7.30 (dd, J = 4.5, 2.0 Hz, 2H, Ar–H), 7.01 (dd, J = 8.5, 2.0 Hz, 1H, Ar–H), 4.07 (t, J = 6.4 Hz, 2H, OCH_2), 2.42–2.38 (m, 5H, Ar–CH_3, NCH_2), 2.17 (s, 6H, NCH_3), 1.92–1.86 (m, 2H, alkyl chains-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.21, 158.95, 151.64, 141.14, 136.50, 134.26, 133.11, 129.77, 128.77, 127.05, 121.23, 119.70, 116.11, 115.27, 115.09, 66.42, 56.19, 45.69, 27.43, 20.78; m.p. 93–95 °C; HRMS (ESI) m/z 338.1753 $[M + H]^+$ (calcd 338.1751, $C_{21}H_{24}NO_3$).

*3-(3-(4-(Dimethylamino)butoxy)phenyl)-6-methyl-2H-chromen-2-one (**5f**).* Yield 73%, colorless solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (s, 1H, CH═CH), 7.59 (s, 1H, Ar–H), 7.47 (dd, J = 8.4, 1.6 Hz, 1H, Ar–H), 7.40–7.34 (m, 2H, Ar–H), 7.32–7.29 (m, 2H, Ar–H), 7.01 (dd, J = 8.2, 1.6 Hz, 1H, Ar–H), 4.05 (t, J = 6.5 Hz, 2H, OCH_2), 2.41 (s, 3H, Ar–CH_3), 2.27 (t, J = 7.2 Hz, 2H, NCH_2), 2.15 (s, 6H, NCH_3), 1.80–1.72 (m, 2H, alkyl chains-H), 1.61–1.55 (m, 2H, alkyl chains-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.18, 158.94, 151.61, 141.11, 136.48, 134.25, 133.10, 129.74, 128.75, 127.04, 121.19, 119.68, 116.09, 115.31, 115.06, 67.95, 59.19, 45.61, 27.07, 24.05, 20.77; MS (ESI) m/z 352.3 $[M + H]^+$; m.p. >250 °C; HRMS (ESI) m/z 352.1909 $[M + H]^+$ (calcd 352.1907, $C_{22}H_{26}NO_3$).

General procedure for the preparation of compounds 5g–i. To a stirred mixture of **4b** (0.5 mmol) and K_2CO_3 (0.14 g, 1 mmol) in acetonitrile (10 mL), acyl chloride (1 mmol) was added. After stirring at room temperature for 5 h, the mixture was filtered and the filtrate was evaporated under vacuum. The obtained residue was purified by silica gel chromatography with petroleum ether–acetone as the eluent to give the target compound (**5g–i**).

*3-(6-Methyl-2-oxo-2H-chromen-3-yl)phenyl dimethylcarbamate (**5g**).* Yield 79%, colorless solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H, CH═CH), 7.62–7.60 (m, 2H, Ar–H), 7.54–7.45 (m, 3H, Ar–H), 7.37 (d, J = 8.5 Hz, 1H, Ar–H), 7.20 (dd, J = 8.0, 2.0 Hz, 1H, Ar–H), 3.10 (s, 3H, NCH_3), 2.95 (s, 3H, NCH_3), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.12, 154.45, 151.68, 141.41, 136.30, 134.32, 133.27, 129.51, 128.83, 126.24, 125.70, 122.64, 122.32, 119.63, 116.14, 36.62, 20.78; m.p. 166–168 °C; HRMS (ESI) m/z 346.1052 $[M + Na]^+$ (calcd 346.1050, $C_{19}H_{17}NNaO_4$).

*3-(6-Methyl-2-oxo-2H-chromen-3-yl)phenyl-4-methylbenzenesulfonate (**5h**).* Yield 81%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (s, 1H, CH═CH), 7.81 (d, J = 8.5 Hz, 2H, Ar–H), 7.71 (d, J = 8.0 Hz, 1H, Ar–H), 7.58 (br s, 1H, Ar–H), 7.53–7.48 (m, 5H, Ar–H), 7.37 (d, J = 8.5 Hz, 1H, Ar–H), 7.08–7.06 (m, 1H, Ar–H), 2.45 (s, 3H, Ar–CH_3), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.95, 151.75, 149.38, 146.34, 141.80, 137.01, 134.42, 133.52, 132.04, 130.77, 130.32, 128.89, 128.73, 127.88, 125.57, 122.54, 122.40, 119.47, 116.20, 21.66, 20.76; MS (ESI) m/z 407.2 $[M + H]^+$; m.p. 140–143 °C; HRMS (ESI) m/z 429.0768 $[M + Na]^+$ (calcd 429.0767, $C_{23}H_{18}NaO_5S$).

*3-(6-Methyl-2-oxo-2H-chromen-3-yl)phenyl benzoate (**5i**).* Yield 86%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H, CH═CH), 8.20–8.18 (m, 2H, Ar–H), 7.79–7.60 (m, 7H, Ar–H), 7.48 (dd, J = 8.5, 2.0 Hz, 1H, Ar–H), 7.39 (m, 2H, Ar–H), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.86, 156.52, 151.78, 142.41, 137.57, 134.25, 132.93, 131.27, 130.50, 128.80, 128.47, 128.13, 127.64, 126.89, 126.33, 125.18, 121.08, 119.40, 116.22, 113.39, 70.19, 20.74; MS (ESI) m/z 357.2 $[M + H]^+$; m.p. 140–142 °C; HRMS (ESI) m/z 379.0942 $[M + Na]^+$ (calcd 379.0941, $C_{23}H_{16}NaO_4$).

General procedure for the preparation of compounds 5j–o. To a stirred mixture of **4a–c** (0.5 mmol) and K_2CO_3 (0.14 g, 1 mmol) in acetonitrile (10 mL), benzyl bromide or 3-fluorobenzyl bromide (1 mmol) was added. After stirring for 4 h at room temperature, the mixture was filtered and the filtrate was evaporated under vacuum. The obtained residue was purified by silica gel chromatography with petroleum ether–EtOAc as the eluent to give the target compound (**5j–o**).

*3-(2-(Benzyloxy)phenyl)-6-methyl-2H-chromen-2-one (**5j**).* Yield 82%, red solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (s, 1H, CH═CH), 7.71 (d, J = 8.8 Hz, 2H, Ar–H), 7.56 (s, 1H, Ar–H), 7.50 (d, J = 7.3 Hz, 2H, Ar–H), 7.43 (t, J = 7.5 Hz, 3H, Ar–H), 7.36 (m, 2H, Ar–H), 7.13 (d, J = 8.8 Hz, 2H, Ar–H), 5.20 (s, 2H, OCH_2), 2.40 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.44, 159.14, 151.41, 139.61, 137.45, 134.20, 132.69, 130.29, 128.93, 128.50, 128.33, 128.12, 127.66, 126.81, 119.86, 116.04, 115.09, 69.79, 20.78; MS (ESI) m/z 343.2 $[M + H]^+$; m.p. 108–111 °C; HRMS (ESI) m/z 365.1149 $[M + Na]^+$ (calcd 365.1148, $C_{23}H_{18}NaO_3$).

*3-(3-(Benzyloxy)phenyl)-6-methyl-2H-chromen-2-one (**5k**).* Yield 85%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (s, 1H, CH═CH), 7.59 (br s, 1H, Ar–H), 7.50–7.34 (m, 10H, Ar–H), 7.10 (dd, J = 8.0, 2.5 Hz, 1H, Ar–H), 5.18 (s, 2H, OCH_2), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.18, 158.69, 151.64, 141.20, 137.51, 136.55, 134.29, 133.16, 129.80, 128.94, 128.76, 128.35, 128.22, 126.96, 121.58, 119.67, 116.13, 115.75, 115.32, 69.90, 20.78; MS (ESI) m/z 343.2 $[M + H]^+$; HRMS (ESI) m/z 365.1149 $[M + Na]^+$ (calcd 365.1148, $C_{23}H_{18}NaO_3$).

*3-(4-(Benzyloxy)phenyl)-6-methyl-2H-chromen-2-one (**5l**).* Yield 90%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (s, 1H, CH═CH), 7.71 (d, J = 8.8 Hz, 2H, Ar–H), 7.56 (s, 1H, Ar–H), 7.50 (d, J = 7.3 Hz, 2H, Ar–H), 7.43 (t, J = 7.5 Hz, 3H, Ar–H), 7.36 (dd, J = 12.9, 7.8 Hz, 2H, Ar–H), 7.13 (d, J = 8.8 Hz, 2H, Ar–H), 5.20 (s, 2H, OCH_2), 2.40 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.44, 159.14, 151.41, 139.61, 137.45, 134.20, 132.69, 130.29, 128.93, 128.50, 128.33, 128.12, 127.66, 126.81, 119.86, 116.04, 115.09, 69.79, 20.78; MS (ESI) m/z 343.2 $[M + H]^+$; m.p. 169–172 °C; HRMS (ESI) m/z 365.1149 $[M + Na]^+$ (calcd 365.1148, $C_{23}H_{18}NaO_3$).

*3-(2-((3-Fluorobenzyl)oxy)phenyl)-6-methyl-2H-chromen-2-one (**5m**).* Yield 87%, red solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H, CH═CH), 7.52–7.30 (m, 8H, Ar–H), 7.25–7.12 (m, 3H, Ar–H), 5.19 (s, 2H, OCH_2), 2.37 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.45, 159.83, 159.49, 156.29, 151.76, 142.46, 134.25, 132.95, 131.37, 130.55, 128.44,

126.03, 125.30, 124.90, 124.87, 121.42, 119.36, 116.23, 115.82, 115.65, 113.64, 64.54, 20.74; MS (ESI) *m*/*z* 361.0 $[M + H]^+$; m.p. 99–102 °C; HRMS (ESI) *m*/*z* 383.1052 $[M + H]^+$ (calcd 383.1054, $C_{23}H_{17}FNaO_3$).

*3-(3-((3-Fluorobenzyl)oxy)phenyl)-6-methyl-2H-chromen-2-one (**5n**).* Yield 89%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (s, 1H, CH═CH), 7.62 (t, *J* = 7.6 Hz, 2H, Ar–H), 7.46 (dd, *J* = 7.8, 5.6 Hz, 2H, Ar–H), 7.42 (dd, *J* = 8.9, 7.0 Hz, 2H, Ar–H), 7.36 (d, *J* = 8.2 Hz, 2H, Ar–H), 7.28 (dd, *J* = 15.5, 8.1 Hz, 2H, Ar–H), 7.13 (dd, *J* = 8.0, 2.1 Hz, 1H, Ar–H), 5.22 (s, 2H, OCH_2), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.89, 160.17, 159.93, 158.52, 151.65, 141.24, 136.61, 134.29, 133.16, 129.84, 128.76, 126.91, 125.04, 125.02, 121.80, 119.67, 116.12, 115.97, 115.80, 115.62, 115.26, 64.19, 64.16, 20.77. MS (ESI) *m*/*z* 361.0 $[M + H]^+$; m.p. 96–98 °C; HRMS (ESI) *m*/*z* 383.1052 $[M + H]^+$ (calcd 383.1054, $C_{23}H_{17}FNaO_3$).

*3-(4-((3-Fluorobenzyl)oxy)phenyl)-6-methyl-2H-chromen-2-one (**5o**).* Yield 82%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1H, CH═CH), 7.73 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.60 (dd, *J* = 16.5, 8.9 Hz, 2H, Ar–H), 7.48–7.43 (m, 2H, Ar–H), 7.35 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.31–7.26 (m, 2H, Ar–H), 7.15 (d, *J* = 8.8 Hz, 2H, Ar–H), 5.23 (s, 2H, OCH_2), 2.40 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.43, 158.97, 151.42, 139.69, 134.20, 132.71, 131.15, 130.93, 130.34, 128.52, 127.92, 126.78, 125.04, 119.85, 116.05, 115.97, 115.80, 115.00, 64.14, 20.78. MS (ESI) *m*/*z* 361.0 $[M + H]^+$; m.p. 147–140 °C; HRMS (ESI) *m*/*z* 383.1052 $[M + H]^+$ (calcd 383.1054, $C_{23}H_{17}FNaO_3$).

General procedure for the preparation of compounds 5p–s. A solution of 5-methylsalicylaldehyde (**1**, 8 mmol), substituted acetic acid (**2d–g**, 10 mmol) and DCC (12 mmol) in dimethylsulfoxide (DMSO, 10 mL) was heated at 110 °C for 24–48 h. On completion of the reaction, cold water (100 mL) and acetic acid (15 mL) were added. The reaction mixture was stirred at room temperature for 4 h and extracted with diethyl ether. The precipitated dicyclohexylurea was filtered off. The filtrate was extracted with 5% aqueous $NaHCO_3$ (200 mL). The organic phase was stirred for 1 h with 5% aqueous sodium metabisulfite in order to remove the unreacted hydroxybenzaldehyde. The organic phase was washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The obtained residue was purified by silica gel chromatography with petroleum ether–EtOAc as the eluent to give the target compound (**5p–s**).

*6-Methyl-3-(thiophen-2-yl)-2H-chromen-2-one (**5p**).* Yield 58%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H, CH═CH), 7.89 (d, *J* = 4.0 Hz, 1H, Ar–H), 7.72 (d, *J* = 5.0 Hz, 1H, Ar–H), 7.59 (s, 1H, Ar–H), 7.45 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar–H), 7.37 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.23–7.21 (m, 1H, Ar–H), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.60, 150.85, 136.67, 135.89, 134.58, 132.94, 129.23, 128.50, 127.85, 127.12, 120.99, 119.54, 116.19, 20.80; MS (ESI) *m*/*z* 243.1 $[M + H]^+$; m.p. 177–180 °C; HRMS (ESI) *m*/*z* 265.0925 $[M + Na]^+$ (calcd 265.0924, $C_{14}H_{10}NaO_2S$).

*6-Methyl-3-(pyridin-3-yl)-2H-chromen-2-one (**5q**).* Yield 62%, colorless solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (d, *J* = 2.0 Hz, 1H, CH═CH), 8.63 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar–H), 8.34 (s, 1H, Ar–H), 8.17–8.13 (m, 1H, Ar–H), 7.59 (br s, 1H, Ar–H), 7.54–7.48 (m, 2H, Ar–H), 7.38 (d, *J* = 8.5 Hz, 1H, Ar–H), 2.41 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.23, 151.84, 149.80, 149.48, 141.84, 136.50, 134.46, 133.50, 131.17, 128.86, 124.57, 123.65, 119.57, 116.28, 20.76; MS (ESI) *m*/*z* 238.1 $[M + H]^+$; m.p. 167–170 °C; HRMS (ESI) *m*/*z* 238.0864 $[M + H]^+$ (calcd 238.0863, $C_{15}H_{12}NO_2$).

*6-Methyl-3-(naphthalen-1-yl)-2H-chromen-2-one (**5r**).* Yield 67%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (s, 1H, CH═CH), 8.03 (t, *J* = 7.0 Hz, 2H, Ar–H), 7.79 (d, *J* = 8.5 Hz, 1H, Ar–H), 7.59 (m, 4H, Ar–H), 7.54–7.50 (m, 2H, Ar–H), 7.43 (d, *J* = 8.4 Hz, 1H, Ar–H), 2.42 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.61, 152.19, 143.63, 134.33, 133.21, 131.74, 129.32, 128.73, 128.16, 127.78, 126.87, 126.54, 125.92, 125.87, 119.51, 116.37, 20.76; MS (ESI) *m*/*z* 287.2 $[M + H]^+$; m.p. 131–135 °C; HRMS (ESI) *m*/*z* 287.1065 $[M + H]^+$ (calcd 287.1067, $C_{20}H_{15}O_2$).

*3-(1H-Indol-3-yl)-6-methyl-2H-chromen-2-one (**5s**).* Yield 69%, yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.59 (s, 1H, NH), 8.32 (s, 1H, CH═CH), 8.13 (d, *J* = 2.6 Hz, 1H, Ar–H), 8.04 (d, *J* = 7.8 Hz, 1H, Ar–H), 7.69 (s, 1H, Ar–H), 7.50 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.36 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.32 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.19 (m, 2H, Ar–H), 2.39 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.36, 150.18, 136.90, 134.80, 134.05, 131.50, 128.51, 128.14, 125.62, 122.69, 122.36, 120.61, 120.29, 120.19, 115.87, 112.63, 108.86, 20.86; m.p. 216–219 °C; HRMS (ESI) *m*/*z* 298.0840 $[M + Na]^+$ (calcd 298.0838, $C_{18}H_{13}NNaO_2$).

Abbreviations

MAO	Monoamine oxidase
FAD	Flavin adenine dinucleotide
5-HT	5-Hydroxytryptamine
NE	Norepinephrine
DA	Dopamine
SI	Selectivity index

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