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Syntheses and Evaluation of 2- or 3-(*N*-Cyclicamino)chromone Derivatives as Monoamine Oxidase Inhibitors

Koichi Takao,* Tsukasa Sakatsume, Hitoshi Kamauchi, and Yoshiaki Sugita

Laboratory of Bioorganic Chemistry, Department of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Josai University; 1–1 Keyaki-dai, Sakado, Saitama 350–0295, Japan.
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A series of 2-(*N*-cyclicamino)chromone derivatives (1a–4c) and 3-(*N*-cyclicamino)chromone derivatives (5a–8c) were synthesized, and their monoamine oxidase (MAO) A and B inhibitory activities were studied as part of a structure–activity relationship investigation. Compounds 1a–4c showed no remarkable inhibition for MAO-A or MAO-B, whereas compounds 5a–8c (with a few exceptions) showed significant and selective inhibition of MAO-B. Of these compounds, 7c, 7-methoxy-3-(4-phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one inhibited MAO-B the most potently and selectively, having IC_{50} of 15 nM and an MAO-B selectivity index of more than 6700; *c.f*, 50 nM and 2000, respectively, for safinamide. The mode of inhibition of 7c to MAO-B was competitive and reversible. Considering the IC_{50} values and selectivity indices of the other synthetic compounds, the presence of the methoxy group on the chromone ring (R^2) of 7c seemed to increase MAO-B inhibition. Molecular docking analysis also supports this hypothesis. Our results suggest that 3-(*N*-cyclicamino)-chromones are useful lead compounds for the development of MAO-B inhibitors.

Key words 2-(*N*-cycloamino)chromone; 3-(*N*-cycloamino)chromone; monoamine oxidase (MAO); structure–activity relationship; molecular docking analysis

Introduction

Monoamine oxidase (MAO, EC 1.4.3.4), a flavoenzyme bound to the mitochondrial outer membrane of many type of mammalian cells, degrades neurotransmitters and thus, regulates their concentration.[1–3] The two isozymes of MAO, MAO-A and MAO-B, which have about 70% amino acid sequence homology, are identified by their substrate specificity and inhibitor sensitivity. These two enzymes degrade epinephrine, norepinephrine, tyramine, dopamine, and tryptamine, but MAO-A preferentially degrades serotonin and is selectively inhibited by clorgyline, whereas MAO-B preferentially degrades benzylamine, kynuramine, and 2-phenethylamine and is selectively inhibited by deprenyl. MAO inhibition has been actively studied in many laboratories to develop better drugs for the increasing number of patients suffering from age-related neurodegenerative diseases.[4,5]

Naturally occurring flavones and isoflavones containing the chromone skeleton are known to be biologically active.[6,7] Synthetic chromone derivatives (flavonoid analogs) have been reported to have various biological effects, including MAO inhibitory activity.[8–10] In contrast, known MAO inhibitory compounds often contain cyclic amine structures, such as piperidine in piperine or antiepilepsirine,[11] morpholine in moclobemide,[12] and piperazine derivatives.[13] We recently reported 2-azolylchromone derivatives containing the chromone skeleton and cyclic amines that showed potent and selective MAO inhibitory effects.[14] This report is concerned with 2- or 3-(*N*-cyclicamino)chromone derivatives. Some 2-(*N*-cyclicamino)chromone derivatives have been reported to have anti-inflammatory,[15,16] antimicrobial,[16] phosphodiesterase inhibitory,[17] DNA-dependent protein kinase inhibitory,[18,19] and anticancer[20] effects, but reports of the biological effects of 3-(*N*-cyclicamino)chromone derivatives are limited to our recent report.[21] To explore the MAO inhibitory activities of 2- or 3-(*N*-cyclicamino)chromone derivatives further, these compounds were synthesized, and the structure–activity relationship with respect to MAO inhibition was investigated.

Results and Discussion

Chemistry The protocol for the syntheses of 2- or 3-(*N*-cyclicamino)chromone derivatives is shown in Fig. 1. 2-(*N*-Cyclicamino)chromone derivatives (**1**–**4**) were synthesized by the substitution reaction of 2-(1,2,4-triazolyl)-chromone derivatives (**IIa**–**c**) with the corresponding cyclic amine according to the method of Samanta *et al.*[22] with a slight modification. The mechanism of substitution may be the conjugate addition of the cyclic amine at the 2-position of the chromone ring, followed by the elimination of triazole. The key compounds (**IIa**–**c**) were synthesized by the conjugate addition of 3-iodochromone derivatives **Ia**–**c** with 1,2,4-triazole according to the previous method.[14] Next, 3-(*N*-cyclicamino)-chromone derivatives **5**–**8** were synthesized by the condensation reaction of 2,3-epoxychromone derivatives **IVa**–**c** with the corresponding cyclic amine. In the reaction, the first step may be nucleophilic addition of the cyclic amine to the epoxy ring (3-position of the chromone ring) to afford intermediate **A**, followed by dehydration to give 3-(*N*-cyclicamino)-chromone. 2,3-Epoxychromone derivatives (**IVa**–**c**) were synthesized by the epoxidation of chromone derivatives (**IIIa**–**c**) using aqueous H_2O_2 solution under basic conditions.

Biological Activity All the synthesized compounds were evaluated for their MAO inhibitory activity, and the results are summarized in Table 1. Compounds **2b**, **2c**, and **3b** inhibited both MAO-A and MAO-B moderately, showing similar IC_{50} values for the two enzymes. Compounds **6** and **7** showed no inhibitory activity against MAO-A at a concentration of 100 μM, which was expected because the active site of MAO-A is smaller than that of MAO-B.[1] Compounds **6a**, **6c**,

* To whom correspondence should be addressed. e-mail: ktakao@josai.ac.jp

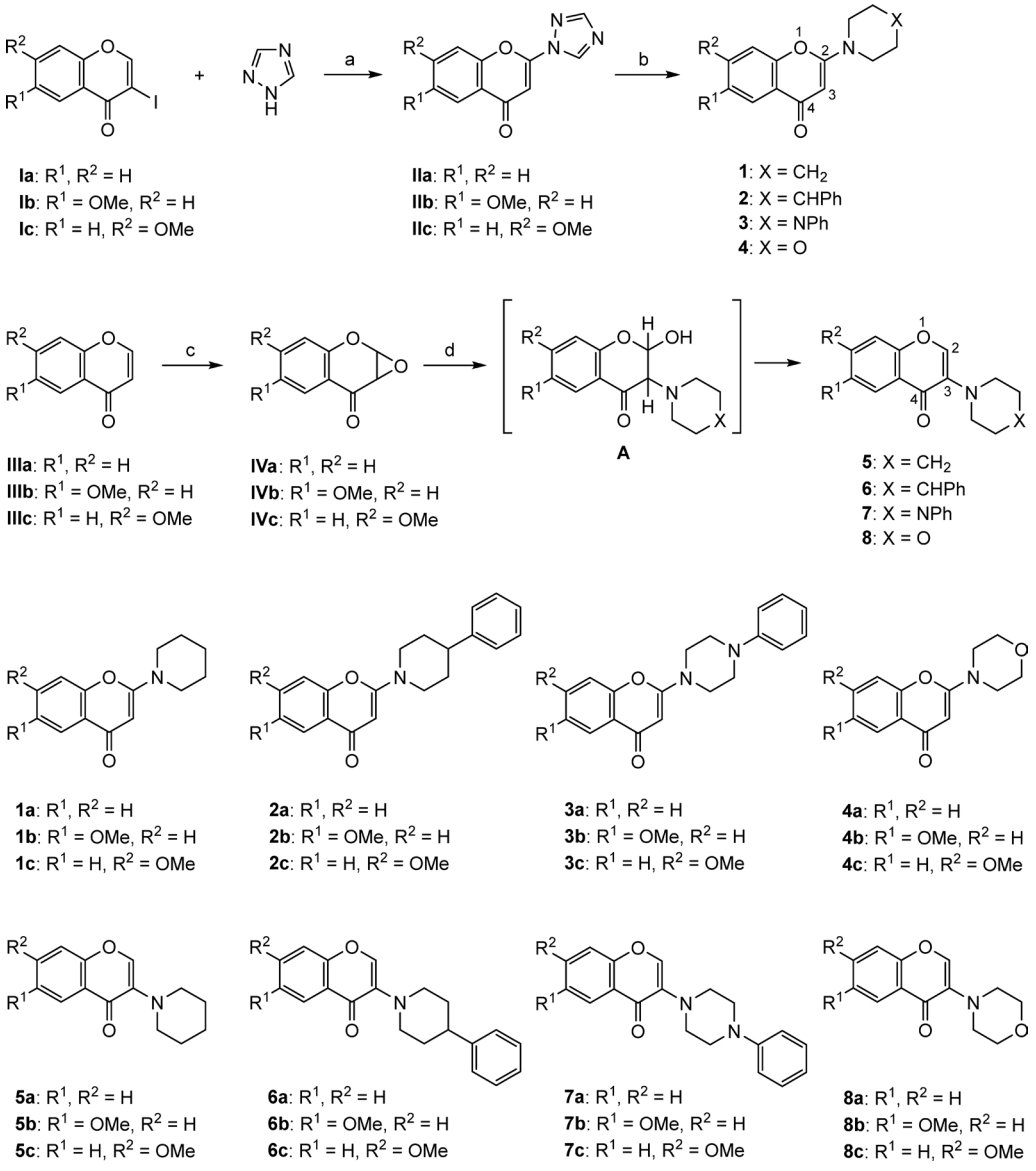

Fig. 1. Synthetic Protocol for 2- or 3-(*N*-Cyclicamino)chromone Derivatives

Reagents and conditions: (a) K_2CO_3, DMF, and 80 °C; (b) cyclic amine, DMF, and 80 °C; (c) H_2O_2, $PhCH_2N^+(CH_3)_3$ OH^-, Et_2O, and 0 °C; and (d) cyclic amine, CH_3CN, and room temperature (r.t.).

7a, and **7c** inhibited MAO-B potently and selectively. Some of the other compounds, such as compounds **5a**, **8b**, and **8c**, showed moderate inhibition of MAO-B. Of these compounds, **7c** showed the most potent inhibition and the highest selectivity for MAO-B. The potency and selectivity were compared with those of safinamide, which was used as a positive control, and it was found that compound **7c** was about three times more effective than safinamide. Generally, the 3-(*N*-cyclicamino)chromone derivatives (with the exception of compounds **6b** and **7b**) inhibited MAO-B selectively, but the 2-(*N*-cyclicamino)chromone derivatives had no such selectivity. The present results show clear differences between the two groups of derivatives, and this is consistent with previous reports concerning chromone carboxylic acid[23] and their amides,[24] as well as recent reports of the MAO inhibitory activities of chrysin (flavone) and genistein (isoflavone).[25,26] All these data show that substitution at the 3-position of the chromone ring increases the MAO-B inhibitory activity.

The results for compounds **6** or **7** indicate a strong structure–activity relationship. The clear difference between compounds **6b** or **7b** and **6c** or **7c**, respectively, in the selective inhibition of MAO-B was caused by the presence of the methoxy group at positions 6 (R^1) or 7 (R^2) of the chromone ring. This may indicate that the presence of a methoxy group at position-6, as in compound **6b** or **7b**, resulted in exclusion from the catalytic site of MAO-B. In contrast, a methoxy group at position 7, *i.e.*, compound **6c** or **7c**, resulted in tight binding in the active site. Thus, moderate MAO-B inhibition by compound **6a** or **7a**, which have no methoxy group, would be expected. These results suggest that the diagonal substituents on the chromone ring increased the MAO-B inhibitory activity, and we have previously discussed the effect of methoxy substitution on the chromone ring.[27]

Kinetic studies were then carried out using compound **7c** as an example. The mode of inhibition of MAO-B was competitive (inhibitor constant (K_i) = 7 nM) (Fig. 2) and reversible compared with the irreversible inhibitor pargyline (Fig. 3). Compound **7c** had a low K_i value and the lowest IC_{50} value

Table 1. IC_{50} Values of 2- or 3-(*N*-Cyclicamino)chromone Derivatives for the Inhibition of MAO-A and MAO-B

Compound	R^1	R^2	IC_{50} values for MAO-A (μM)	IC_{50} values for MAO-B (μM)	MAO-B selectivity
2-(*N*-Cyclicamino)chromone					
1a	H	H	38	59	0.64
1b	OMe	H	16	27	0.59
1c	H	OMe	57	36	1.6
2a	H	H	31	22	1.4
2b	OMe	H	4.1	5.6	0.73
2c	H	OMe	8.8	7.4	1.2
3a	H	H	38	22	1.6
3b	OMe	H	2.6	2.8	0.93
3c	H	OMe	59	12	4.9
4a	H	H	66	58	1.1
4b	OMe	H	36	40	0.90
4c	H	OMe	34	31	1.1
3-(*N*-Cyclicamino)chromone					
5a	H	H	23	2.0	12
5b	OMe	H	23	0.99	23
5c	H	OMe	18	14	1.3
6a	H	H	>100	1.5	>67
6b	OMe	H	>100	>100	—
6c	H	OMe	>100	0.25	>400
7a	H	H	>100	0.72	>140
7b	OMe	H	>100	>100	—
7c	H	OMe	>100	0.015	>6700
8a	H	H	57	23	2.5
8b	OMe	H	34	8.0	4.3
8c	H	OMe	25	7.3	3.4
Positive control					
Pargyline	—	—	4.6	0.22	21
Clorgyline	—	—	0.0049	5.8	0.00085
Safinamide	—	—	100	0.050	2000

MAO-B selectivity is given as the ratio of IC_{50} value of MAO-B to IC_{50} value of MAO-A.

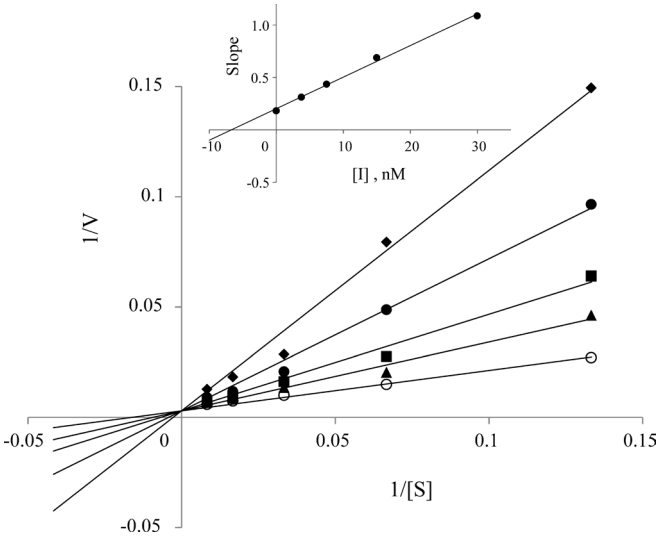

Fig. 2. Lineweaver–Burk Plots for the Inhibition of MAO-B by **7c**

The plots were constructed in the absence (open circles) and presence (other symbols) of various concentrations of **7c**. The inset is a graph of the slopes of the Lineweaver–Burk plots *versus* inhibitor concentration ($K_i = 8$ nM). The rate (V) is expressed as the percentage of control. Kynuramine was used at 30 μM.

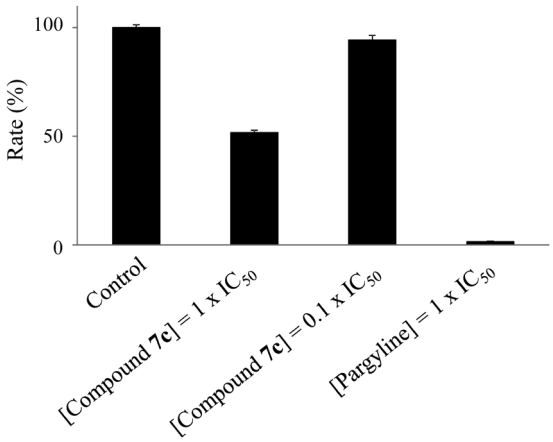

Fig. 3. Reversibility of Inhibition of MAO-B by **7c**

MAO-B was preincubated with compound **7c** at $10 \times IC_{50}$ and $100 \times IC_{50}$ for 30 min and then diluted to $0.1 \times IC_{50}$ and $1 \times IC_{50}$, respectively. For comparison, pargyline, an irreversible MAO-B inhibitor, at $10 \times IC_{50}$ was similarly incubated with MAO-B and diluted to $1 \times IC_{50}$. The residual activity of MAO-B was subsequently measured.

of the tested compounds, including pargyline and safinamide, and could be useful as a potent and selective inhibitor of MAO-B. Kumar *et al.* recently reported phenyl-/benzylpiperazine derivatives as potent and selective MAO inhibitors.[13] They reported that phenylpiperazine derivatives show lower inhibitory activities against MAO-B than pargyline ($IC_{50} = 0.15\,\mu$M, see ref. 13).

Docking Study To elucidate the mechanism of the inhibitory activity of compound **7c**, a molecular docking study with the active site model of MAO-B was carried out using a

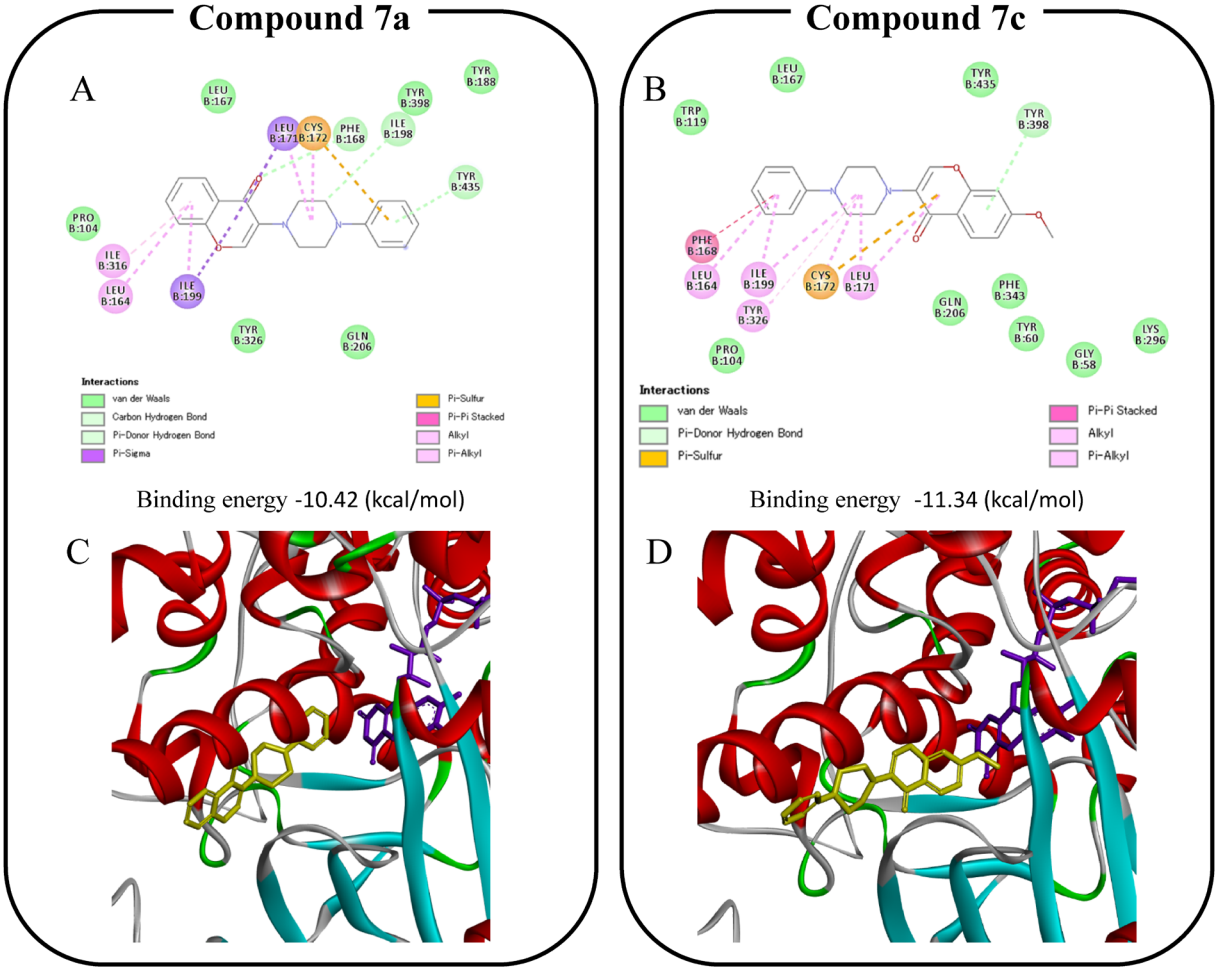

Fig. 4. Most Stable Binding Poses of Compounds **7a** and **7c** in the Active Site of MAO-B (PDB Code: 4A79)

Two dimensional models showing ligand interaction diagrams of MAO-B with **7a** (A) and **7c** (B). Three dimensional models showing the orientations of **7a** (C) and **7c** (D) in the active site. (Color figure can be accessed in the online version.)

binding model based on the MAO-B complex structure (PDB code: 4A79) using AutoDock and compared with that of compound **7a** (Fig. 4).

The ligand interaction diagrams (Figs. 4A, 4B) show that the number of interacting amino acid residues was higher for **7c** than **7a**, and the calculated binding energies were −10.42 and −11.24 kcal/mol for **7a** and **7c**, respectively. These data further support the higher inhibitory activity of compound **7c**. The interacting residues in the two models included the important residues for the binding site in MAO-B recognition: Leu199 and Tyr326, which are important for active site cavity size regulation, and Tyr398 and Tyr435, which are important for the substrate binding in the active site.[1,28] To see any key interacting residues to **7c**, specific residues for **7a** such as Ile198 and Tyr188, and those for **7c** such as Gly58, Tyr60, Trp119, Lys296, and Phe343 were compared on the docking model. It was hard to specify key interacting residue(s), but the residues except for Trp119 seemed to be close to 7-methoxychromone ring of **7c** and to strengthen the binding together. The three-dimensional models showed that, when **7a** and **7c** were docked in the active site of MAO-B, they had opposing orientations. Further, the model showed that compound **7c** was positioned close to flavin adenine dinucleotide (FAD) in the active site. This might strengthen the inhibitory activity *via* methoxy substitution.

Finally, MAO-B inhibitors are potential candidates for the treatment of Parkinson's and Alzheimer's diseases. A recent study of drugs for the treatment of Alzheimer's reported the use of multi-targeted drugs including MAO and cholinesterase inhibitors.[29] Thus, 2- or 3-(*N*-cyclicamino)chromone derivatives were tested for their acetylcholinesterase and butyrylcholinesterase inhibitory activities. Most of the compounds exhibited no or slight inhibitory activity against acetylcholinesterase and butyrylcholinesterase, compound **6a** alone, showing inhibitory activity against butyrylcholinesterase comparable to donepezil (data not shown).

Conclusion

A series of 2- or 3-(*N*-cyclicamino)chromone derivatives were synthesized and evaluated for their MAO inhibitory activity. Of the compounds tested, including safinamide, which was used as a positive control, compound **7c**, 7-methoxy-3-(4-phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one, exhibited the most potent inhibitory activity and the highest selectivity for MAO-B and acted in a reversible and competitive manner. These results indicate that 3-(*N*-cyclicamino)chromone derivatives are promising lead compounds for the development of MAO-B inhibitors.

Experimental

Synthesis All reagents and solvents were purchased from commercial sources. Analytical TLC was performed on silica-coated plates (silica gel 60 F-254; Merck Ltd., Tokyo, Japan) and visualized under UV light. Column chromatography was carried out using silica gel (Wakogel C-200; Wako Pure Chemical Corporation, Osaka, Japan). All melting points were determined using a Yanagimoto micro-hot stage and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 400-MR spectrometer using tetramethylsilane as the internal standard. MS spectra were measured using a JEOL JMS-700 spectrometer. Elemental analyses were carried out on a Yanaco CHN MT-6 elemental analyzer.

Synthesis of 2-(1,2,4-Triazolyl)chromone Derivatives (IIa–c) 2-(1,2,4-Triazolyl)chromone derivatives (**IIa–c**) were synthesized according to a previously reported method.[14] A mixture of 3-iodochromone (1 mmol), 1,2,4-triazole (2 mmol), and K_2CO_3 (10 mmol) in dimethylformamide (DMF, 5 mL) was stirred at 80 °C for 24 h. The reaction mixture was extracted with water and $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt) to give the title compounds. The products (**IIa–c**) were identified from their ^{1}H-NMR spectra.[14]

2-(1*H*-1,2,4-Triazol-1-yl)-4*H*-1-benzopyran-4-one (**IIa**)

Yield 71%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.92 (1H, s, H-5′), 8.27 (1H, dd, J = 7.8, 1.7 Hz, H-5), 8.20 (1H, s, H-3′), 7.78 (1H, ddd, J = 8.5, 7.1, 1.7 Hz, H-6), 7.58 (1H, dd, J = 8.5, 1.0 Hz, H-8), 7.52 (1H, ddd, J = 7.8, 7.1, 1.0 Hz, H-6), 6.91 (1H, s, H-3). MS (electron ionization (EI)) m/z 213 $[M]^+$.

6-Methoxy-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-1-benzopyran-4-one (**IIb**)

Yield 78%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.90 (1H, s, H-5′), 8.19 (1H, s, H-3′), 7.63 (1H, d, J = 3.1 Hz, H-5), 7.51 (1H, d, J = 9.1 Hz, H-8), 7.34 (1H, dd, J = 9.1, 3.1 Hz, H-7), 6.89 (1H, s, H-3), 3.93 (3H, s, OCH_3). MS (EI) m/z 243 $[M]^+$.

7-Methoxy-2-(1*H*-1,2,4-triazol-1-yl)-4*H*-1-benzopyran-4-one (**IIc**)

Yield 95%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.88 (1H, s, H-5′), 8.18 (1H, s, H-3′), 8.16 (1H, d, J = 8.9 Hz, H-5), 7.06 (1H, dd, J = 8.9, 2.3 Hz, H-6), 6.97 (1H, d, J = 2.3 Hz, H-8), 6.83 (1H, s, H-3), 3.95 (3H, s, OCH_3). MS (EI) m/z 243 $[M]^+$.

Synthesis of 2-(*N*-Cyclicamino)chromone Derivatives (1–4) 2-(*N*-Cyclicamino)chromones (**1–4**) were synthesized by modifying a previously reported procedure.[22] A mixture of 2-(1,2,4-triazolyl)chromone (1 mmol) and the cyclic amine (4 mmol) in DMF (10 mL) was stirred at 80 °C for 12 h. The reaction mixture was extracted with water and $CHCl_3$. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt) to give the title compounds.

2-(1-Piperidinyl)-4*H*-1-benzopyran-4-one (**1a**)

Yield 99%. White prism. mp 119–121 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.15 (1H, dd, J = 7.8, 1.7 Hz, H-5), 7.54 (1H, ddd, J = 8.3, 7.2, 1.7 Hz, H-7), 7.33 (1H, ddd, J = 7.8, 7.2, 1.1 Hz, H-6), 7.29 (1H, dd, J = 8.3, 1.1 Hz, H-8), 5.54 (1H, s, H-3), 3.58–3.50 (4H, m, CH_2), 1.78–1.68 (6H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.0, 162.4, 153.7, 131.9, 125.5, 124.5, 123.0, 116.2, 86.8, 45.9, 25.2, 24.1. MS (EI) m/z 229 $[M]^+$. *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.15; H, 6.44; N, 6.27.

6-Methoxy-2-(1-piperidinyl)-4*H*-1-benzopyran-4-one (**1b**)

Yield 86%. Pale brown prism. mp 127–129 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.57 (1H, d, J = 3.1 Hz, H-5), 7.22 (1H, d, J = 9.0 Hz, H-8), 7.11 (1H, dd, J = 9.0, 3.1 Hz, H-7), 5.54 (1H, s, H-3), 3.89 (3H, s, OCH_3), 3.56–3.49 (4H, m, CH_2), 1.75–1.65 (6H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.9, 162.4, 156.5, 148.2, 123.5, 121.1, 117.5, 105.7, 86.6, 55.9, 45.9, 25.2, 24.1. MS (EI) m/z 259 $[M]^+$. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.49; H, 6.58; N, 5.53.

7-Methoxy-2-(1-piperidinyl)-4*H*-1-benzopyran-4-one (**1c**)

Yield 83%. Pale yellow prism. mp 159–161 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.05 (1H, d, J = 8.7 Hz, H-5), 6.89 (1H, dd, J = 8.7, 2.3 Hz, H-6), 6.74 (1H, d, J = 2.3 Hz, H-8), 5.44 (1H, s, H-3), 3.88 (3H, s, OCH_3), 3.53–3.45 (4H, m, CH_2), 1.75–1.64 (6H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.0, 162.8, 162.5, 155.2, 126.7, 116.6, 112.5, 100.0, 86.4, 55.7, 46.0, 25.2, 24.1. MS (EI) m/z 259 $[M]^+$. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.41; H, 6.73; N, 5.16.

2-(4-Phenyl-1-piperidinyl)-4*H*-1-benzopyran-4-one (**2a**)

Yield 99%. Yellow prism. mp 201–202 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.17 (1H, dd, J = 7.8, 1.7 Hz, H-5), 7.56 (1H, ddd, J = 8.3, 7.2, 1.7 Hz, H-7), 7.37–7.30 (4H, m, H-6, H-8, Ph), 7.26–7.20 (3H, m, Ph), 5.60 (1H, s, H-3), 4.27 (2H, m, CH_2), 3.11 (2H, m, CH_2), 2.83 (1H, m, CH), 2.02 (2H, m, CH_2), 1.82 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.2, 162.4, 153.8, 144.6, 132.1, 128.7, 126.71, 126.68, 125.5, 124.7, 123.0, 116.3, 87.2, 45.7, 42.4, 32.6. MS (EI) m/z 305 $[M]^+$. *Anal.* Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.72; H, 6.31; N, 4.79.

6-Methoxy-2-(4-phenyl-1-piperidinyl)-4*H*-1-benzopyran-4-one (**2b**)

Yield 99%. Pale brown prism. mp 248–250 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.59 (1H, d, J = 3.1 Hz, H-5), 7.37–7.31 (2H, m, Ph), 7.27–7.21 (3H, m, Ph), 7.25 (1H, d, J = 9.0 Hz, H-8), 7.13 (1H, dd, J = 9.0, 3.1 Hz, H-7), 5.60 (1H, s, H-3), 4.25 (2H, m, CH_2), 3.90 (3H, s, OCH_3), 3.10 (2H, m, CH_2), 2.82 (1H, m, CH), 2.01 (2H, m, CH_2), 1.81 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.1, 162.4, 156.6, 148.3, 144.7, 128.7, 126.70, 126.68, 123.5, 121.3, 117.6, 105.7, 86.9, 55.9, 45.6, 42.4, 32.6. MS (EI) m/z 335 $[M]^+$. *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.21; H, 6.33; N, 4.36.

7-Methoxy-2-(4-phenyl-1-piperidinyl)-4*H*-1-benzopyran-4-one (**2c**)

Yield 81%. White prism. mp 206–207 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (1H, d, J = 8.7 Hz, H-5), 7.36–7.31 (2H, m, Ph), 7.27–7.21 (3H, m, Ph), 6.92 (1H, dd, J = 8.7, 2.3 Hz, H-6), 6.77 (1H, d, J = 2.3 Hz, H-8), 5.52 (1H, s, H-3), 4.23 (2H, m, CH_2), 3.89 (3H, s, OCH_3), 3.09 (2H, m, CH_2), 2.82 (1H, m, CH), 2.01 (2H, m, CH_2), 1.82 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.1, 162.9, 162.5, 155.2, 144.7, 128.7, 126.8, 126.7 (2C), 116.6, 112.6, 100.0, 86.7, 55.7, 45.7, 42.4, 32.5. MS (EI) m/z 335 $[M]^+$. *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.37; H, 6.36; N, 4.36.

2-(4-Phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one (**3a**)

Yield 83%. Orange powder. mp 155–157 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.17 (1H, dd, J = 7.8, 1.7 Hz, H-5), 7.57 (1H, ddd, J = 8.3, 7.2, 1.7 Hz, H-7), 7.38–7.29 (4H, m, H-6, H-8, Ph), 6.99–6.92 (3H, m, Ph), 5.58 (H, s, H-3), 3.74–3.70 (4H, m, CH_2), 3.35–3.31 (4H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.2, 162.5, 153.8, 150.6, 132.3, 129.3, 125.6,

124.8, 123.0, 120.8, 116.7, 116.3, 87.5, 48.9, 44.6. MS (EI) *m/z* 306 $[M]^+$. *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.64; H, 6.04; N, 9.21.

6-Methoxy-2-(4-phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one (**3b**)

Yield 90%. Yellow prism. mp 202–203 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.58 (1H, d, J = 3.1 Hz, H-5), 7.35–7.29 (2H, m, Ph), 7.26 (1H, d, J = 9.0 Hz, H-8), 7.15 (1H, dd, J = 9.0, 3.1 Hz, H-7), 6.99–6.92 (3H, m, Ph), 5.58 (1H, s, H-3), 3.89 (3H, s, OCH_3), 3.73–3.68 (4H, m, CH_2), 3.35–3.30 (4H, m, CH_2). MS (EI) *m/z* 336 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[16)]

7-Methoxy-2-(4-phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one (**3c**)

Yield 71%. White powder. mp 166–167 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (1H, d, J = 8.8 Hz, H-5), 7.35–7.29 (2H, m, Ph), 6.99–6.92 (3H, m, Ph), 6.92 (1H, dd, J = 8.8, 2.4 Hz, H-6), 6.77 (1H, d, J = 2.4 Hz, H-8), 5.49 (1H, s, H-3), 3.89 (3H, s, OCH_3), 3.76–3.66 (4H, m, CH_2), 3.34–3.30 (4H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.1, 163.1, 162.6, 155.2, 150.6, 129.3, 126.9, 120.8, 116.7, 116.6, 112.7, 100.0, 87.1, 55.7, 48.9, 44.7. MS (EI) *m/z* 336 $[M]^+$. *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.54; H, 5.99; N, 8.31.

2-(4-Morpholinyl)-4*H*-1-benzopyran-4-one (**4a**)

Yield 95%. White powder. mp 160–163 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.92 (1H, dd, J = 7.8, 1.8 Hz, H-5), 7.66 (1H, ddd, J = 8.3, 7.2, 1.8 Hz, H-7), 7.52 (1H, dd, J = 8.3, 1.1 Hz, H-8), 7.38 (1H, ddd, J = 7.8, 7.2, 1.1 Hz, H-6), 5.51 (1H, s, H-3), 3.74–3.70 (4H, m, CH_2), 3.54–3.50 (4H, m, CH_2). MS (EI) *m/z* 231 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[30)]

6-Methoxy-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (**4b**)

Yield 95%. Pale brown prism. mp 143–145 °C (lit. 16 145–147 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.57 (1H, d, J = 3.0 Hz, H-5), 7.24 (1H, d, J = 8.9 Hz, H-8), 7.14 (1H, dd, J = 8.9, 3.0 Hz, H-7), 5.52 (1H, s H-3), 3.89 (3H, s, OCH_3), 3.86–3.81 (4H, m, CH_2), 3.53–3.49 (4H, m, CH_2). MS (EI) *m/z* 261 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[16,31,32)]

7-Methoxy-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (**4c**)

Yield 97%. White powder. mp 172–174 °C (lit. 32 171–173 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.07 (1H, d, J = 8.8 Hz, H-5), 6.92 (1H, dd, J = 8.8, 2.4 Hz, H-6), 6.75 (1H, d, J = 2.4 Hz, H-8), 5.43 (1H, s, H-3), 3.89 (3H, s, OCH_3), 3.86–3.82 (4H, m, CH_2), 3.51–3.47 (4H, m, CH_2). MS (EI) *m/z* 261 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[30,32)]

Synthesis of 2,3-Epoxychromone Derivatives (IVa–c) 2,3-Epoxychromone derivatives (**IVa**–**c**) were synthesized by modifying a previously reported procedure.[33)] To a solution of chromone (30 mmol) in Et_2O (300 mL), hydrogen peroxide (6 equivalent (equiv), 35% aqueous solution, 21 mL) and benzyltrimethylammonium hydroxide (1.2 equiv, 40% in methanol, 15 mL) were slowly added at 0 °C. After stirring for 4 h at the same temperature, water was added to the mixture, which was extracted with ethyl acetate. The organic layer was washed with 10% $Na_2S_2O_3$ solution and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt) to give the title compounds. The products (**IVa**–**c**) were identified from their ^{1}H-NMR spectra.

1a,7a-Dihydro-7*H*-oxireno[*b*][1]benzopyran-7-one (**IVa**)

Yield 30%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.92 (1H, dd, J = 7.9, 1.7 Hz, H-5), 7.59 (1H, ddd, J = 8.4, 7.2, 1.7 Hz, H-7), 7.18 (1H, ddd, J = 7.9, 7.2, 1.0 Hz, H-6), 7.08 (1H, dd, J = 8.4, 1.0 Hz, H-8), 5.70 (1H, d, J = 2.4 Hz, H-2), 3.73 (1H, d, J = 2.4 Hz, H-3). MS (EI) *m/z* 162 $[M]^+$.

1a,7a-Dihydro-5-methoxy-7*H*-oxireno[*b*][1]benzopyran-7-one (**IVb**)

Yield 46%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.31 (1H, d, J = 3.1 Hz, H-5), 7.18 (1H, dd, J = 9.1, 3.1 Hz, H-7), 7.02 (1H, d, J = 9.1 Hz, H-8), 5.68 (1H, d, J = 2.5 Hz, H-2), 3.83 (3H, s, OCH_3), 3.73 (1H, d, J = 2.5 Hz, H-3). MS (EI) *m/z* 192 $[M]^+$.

1a,7a-Dihydro-4-methoxy-7*H*-oxireno[*b*][1]benzopyran-7-one (**IVc**)

Yield 36%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.86 (1H, d, J = 8.8 Hz, H-5), 6.73 (1H, dd, J = 8.8, 2.3 Hz, H-6), 6.51 (1H, d, J = 2.3 Hz, H-8), 5.67 (1H, d, J = 2.4 Hz, H-2), 3.86 (3H, s, OCH_3), 3.66 (1H, d, J = 2.4 Hz, H-3). MS (EI) *m/z* 192 $[M]^+$.

Synthesis of 3-(*N*-Cyclicamino)chromone Derivatives (5–8) To a solution of 2,3-epoxychromone (1 mmol) in CH_3CN (10 mL), the corresponding cyclic amine (2 mmol) in CH_3CN (2 mL) was added at room temperature. After stirring for 5 min, water was added the mixture and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–AcOEt) to give the title compound.

3-(1-Piperidinyl)-4*H*-1-benzopyran-4-one (**5a**)

Yield 54%. Pale yellow prism. mp 141–142 °C (lit. 35 126 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.27 (1H, dd, J = 8.0, 1.7 Hz, H-5), 7.62 (1H, ddd, J = 8.5, 7.8, 1.1 Hz, H-7), 7.56 (1H, s, H-2), 7.42 (1H, dd, J = 8.5, 1.1 Hz, H-8), 7.35 (1H, ddd, J = 8.0, 7.8, 1.1 Hz, H-6), 2.99 (4H, t, J = 5.5 Hz, CH_2), 1.78 (4H, quin, J = 5.5 Hz, CH_2), 1.59 (2H, m, CH_2). MS (EI) *m/z* 229 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[34)]

6-Methoxy-3-(1-piperidinyl)-4*H*-1-benzopyran-4-one (**5b**)

Yield 57%. Pale orange prism. mp 104–105 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.61 (1H, d, J = 3.0 Hz, H-5), 7.56 (1H, s, H-2), 7.35 (1H, d, J = 9.1 Hz, H-8), 7.22 (1H, dd, J = 9.1, 3.0 Hz, H-7), 3.89 (3H, s, OCH_3), 2.99 (4H, t, J = 5.5 Hz, CH_2), 1.78 (4H, quin, J = 5.5 Hz, CH_2), 1.58 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.5, 156.2, 150.5, 144.0, 136.9, 124.4, 123.4, 119.2, 104.8, 55.8, 51.3, 25.9, 24.2. MS (EI) *m/z* 259 $[M]^+$. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.62; H, 6.67; N, 5.56.

7-Methoxy-3-(1-piperidinyl)-4*H*-1-benzopyran-4-one (**5c**)

Yield 78%. White needle. mp 126–127 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.15 (1H, d, J = 9.0 Hz, H-5), 7.47 (1H, s, H-2), 6.92 (1H, dd, J = 9.0, 2.4 Hz, H-6), 6.78 (1H, d, J = 2.4 Hz, H-8), 3.89 (3H, s, OCH_3), 2.97 (4H, t, J = 5.5 Hz, CH_2), 1.78 (4H, quin, J = 5.5 Hz, CH_2), 1.58 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.2, 163.6, 157.3, 143.5, 137.4, 127.6, 118.0, 114.0, 99.5, 55.7, 51.3, 25.9, 24.2. MS (EI) *m/z* 259 $[M]^+$. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.26; H, 6.56; N, 5.49.

3-(4-Phenyl-1-piperidinyl)-4*H*-1-benzopyran-4-one (**6a**)

Yield 80%. Pale yellow prism. mp 163–164 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.29 (1H, dd, J = 8.0, 1.7 Hz, H-5), 7.64 (1H, ddd, J = 8.5, 7.1, 1.7 Hz, H-7), 7.63 (1H, s, H-2),

7.44 (1H, dd, $J=8.5$, 1.1 Hz, H-8), 7.37 (1H, ddd, $J=8.0$, 7.1, 1.1 Hz, H-6), 7.34–7.20 (5H, m, Ph), 3.70 (2H, m, CH_2), 2.72–2.60 (3H, m, CH, CH_2), 2.09 (2H, m, CH_2), 1.95 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.8, 155.6, 146.1, 144.1, 137.1, 133.0, 128.5, 126.9, 126.3, 126.2, 124.3, 123.9, 117.8, 51.0, 42.6, 33.3. MS (EI) *m/z* 305 $[M]^+$. *Anal.* Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.48; H, 6.30; N, 4.81.

6-Methoxy-3-(4-phenyl-1-piperidinyl)-4*H*-1-benzopyran-4-one (**6b**)

Yield 56%. White needle. mp 152–153 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.63 (1H, s, H-2), 7.62 (1H, d, $J=3.1$ Hz, H-5), 7.37 (1H, d, $J=9.1$ Hz, H-8), 7.36–7.20 (5H, m, Ph), 7.24 (1H, dd, $J=7.9$, 3.1 Hz, H-7), 3.90 (3H, s, OCH_3), 3.69 (2H, m, CH_2), 2.72–2.60 (3H, m, CH, CH_2), 2.08 (2H, m, CH_2), 19.5 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.5, 156.3, 150.6, 146.1, 144.1, 136.5, 128.5, 126.9, 126.2, 124.4, 123.5, 119.3, 104.8, 55.9, 51.0, 42.6, 33.3. MS (EI) *m/z* 335 $[M]^+$. *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.41; H, 6.40; N, 4.41.

7-Methoxy-3-(4-phenyl-1-piperidinyl)-4*H*-1-benzopyran-4-one (**6c**)

Yield 60%. White prism. mp 207–208 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.18 (1H, d, $J=8.9$ Hz, H-5), 7.54 (1H, s, H-2), 7.36–7.20 (5H, m, Ph), 6.95 (1H, dd, $J=8.9$, 2.3 Hz, H-6), 6.80 (1H, d, $J=2.3$ Hz, H-8), 3.90 (3H, s, OCH_3), 3.68 (2H, m, CH_2), 2.70–2.58 (3H, m, CH, CH_2), 2.07 (2H, m, CH_2), 1.94 (2H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.2, 163.7, 157.4, 146.1, 143.6, 137.0, 128.5, 127.6, 126.9, 126.2, 118.0, 114.2, 99.6, 55.8, 51.1, 42.6, 33.3. MS (EI) *m/z* 335 $[M]^+$. *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.26; H, 6.31; N, 4.46.

3-(4-Phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one (**7a**)

Yield 80%. Orange prism. mp 193–194 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.28 (1H, dd, $J=8.0$, 1.7 Hz, H-5), 7.65 (1H, ddd, $J=8.5$, 7.1, 1.7 Hz, H-7), 7.62 (1H, s, H-2), 7.45 (1H, dd, $J=8.5$, 1.1 Hz, H-8), 7.38 (1H, ddd, $J=8.0$, 7.1, 1.1 Hz, H-6), 7.30 (2H, dd, $J=7.7$, 7.3 Hz, Ph), 7.00 (2H, dd, $J=7.7$, 1.1 Hz, Ph), 6.90 (1H, tt, $J=7.3$, 1.1 Hz, Ph), 3.40 (4H, m, CH_2), 3.24 (4H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.6, 155.6, 151.3, 143.7, 136.3, 133.2, 129.2, 126.2, 124.5, 123.8, 120.1, 117.9, 116.4, 49.8, 49.3. MS (EI) *m/z* 306 $[M]^+$. *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.20; H, 6.01; N 9.05.

6-Methoxy-3-(4-phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one (**7b**)

Yield 52%. Pale yellow scaly crystal. mp 146–147 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.62 (1H, s, H-2), 7.61 (1H, d, $J=3.0$ Hz, H-5), 7.38 (1H, d, $J=9.1$ Hz, H-8), 7.30 (2H, dd, $J=7.7$, 7.3 Hz, Ph), 7.25 (1H, dd, $J=9.1$, 3.0 Hz, H-7), 7.00 (2H, d, $J=7.7$, 1.1 Hz, Ph), 6.90 (1H, tt, $J=7.3$, 1.1 Hz, Ph), 3.90 (3H, s, OCH_3), 3.40 (4H, m, CH_2), 3.23 (4H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.3, 156.4, 151.3, 150.6, 143.7, 135.7, 129.2, 124.3, 123.7, 120.0, 119.3, 116.4, 104.7, 55.9, 49.8, 49.3. MS (EI) *m/z* 336 $[M]^+$. *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.44; H, 6.06; N, 8.43.

7-Methoxy-3-(4-phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one (**7c**)

Yield 88%. Pale brown scaly crystal. mp 230–231 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.17 (1H, d, $J=9.0$ Hz, H-5), 7.53 (1H, s, H-2), 7.30 (2H, dd, $J=7.7$, 7.3 Hz, Ph), 6.99 (2H, dd, $J=7.7$, 1.1 Hz, Ph), 6.95 (1H, dd, $J=9.0$, 2.4 Hz, H-6), 6.89 (1H, tt, $J=7.3$, 1.1 Hz, Ph), 6.81 (1H, d, $J=2.4$ Hz, H-8), 3.91 (3H, s, OCH_3), 3.39 (4H, m, CH_2), 3.22 (4H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.0, 163.8, 157.4, 151.3, 143.2, 136.2, 129.2, 127.5, 120.0, 117.8, 116.4, 114.3, 99.6, 55.8, 49.9, 49.3. MS (EI) *m/z* 336 $[M]^+$. *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.51; H, 6.02; N, 8.28.

3-(4-Morpholinyl)-4*H*-1-benzopyran-4-one (**8a**)

Yield 61%. Pale yellow scaly crystal. mp 145–146 °C (lit. 34 147 °C). ^{11}H NMR ($CDCl_3$, 400 MHz) δ: 8.26 (1H, dd, $J=8.0$, 1.7 Hz, H-5), 7.65 (1H, ddd, $J=8.5$, 7.0, 1.7 Hz, H-7), 7.57 (1H, s, H-2), 7.44 (1H, dd, $J=8.5$, 1.1 Hz, H-8), 7.37 (1H, ddd, $J=8.0$, 7.0, 1.1 Hz, H-6), 3.91 (4H, m, CH_2), 3.09 (4H, m, CH_2). MS (EI) *m/z* 231 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[34]

6-Methoxy-3-(4-morpholinyl)-4*H*-1-benzopyran-4-one (**8b**)

Yield 90%. Pale yellow scaly crystal. mp 155–156 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.59 (1H, d, $J=3.0$ Hz, H-5), 7.57 (1H, s, H-2), 7.37 (H, d, $J=9.1$ Hz, H-8), 7.24 (1H, dd, $J=9.1$, 3.0 Hz, H-7), 3.91 (4H, m, CH_2), 3.90 (3H, s, OCH_3), 3.08 (4H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.3, 156.4, 150.6, 143.7, 135.6, 124.3, 123.7, 119.3, 104.7, 66.9, 55.9, 50.2. MS (EI) *m/z* 261 $[M]^+$. *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.27; H, 5.77; N, 5.54.

7-Methoxy-3-(4-morpholinyl)-4*H*-1-benzopyran-4-one (**8c**)

Yield 64%. White scaly crystal. mp 181–182 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.15 (1H, d, $J=8.9$ Hz, H-5), 7.48 (1H, s, H-2), 6.94 (1H, dd, $J=8.9$, 2.4 Hz, H-6), 6.79 (1H, d, $J=2.4$ Hz, H-8), 3.90 (4H, m, CH_2), 3.90 (3H, s, OCH_3), 3.07 (4H, m, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 174.0, 163.8, 157.3, 143.1, 136.1, 127.5, 117.8, 114.3, 99.6, 66.9, 55.8, 50.2. MS (EI) *m/z* 261 $[M]^+$. *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.48; H, 5.77; N, 5.49.

MAO Inhibitory Assay MAO inhibitory activity was assayed according to previously reported methods.[14,27] Briefly, 140 μL of 0.1 M potassium phosphate buffer (pH 7.4), 8 μL of 0.75 mM kynuramine, and 2 μL of a dimethyl sulfoxide (DMSO) inhibitor solution (final DMSO concentration of 1% (v/v) and final concentrations of the inhibitors of 0–100 μM) were preincubated at 37 °C for 10 min. Diluted human recombinant enzyme (50 μL) was then added to obtain a final protein concentration of 0.0075 mg/mL (MAO-A) or 0.015 mg/mL (MAO-B) in the assay mixture. The reaction mixture was further incubated at 37 °C and the reaction was stopped after 20 min by the addition of 75 μL of 2 M NaOH. The product generated by MAO, 4-quinolinol, is fluorescent and was measured at an excitation wavelength of 310 nm and emission wavelength of 400 nm using a microplate reader (Molecular Devices SPECTRA MAX M2). Each data point is the average of triplicate experiments. The sample solution was replaced with DMSO to provide a negative control, and pargyline was used as a positive control. The IC_{50} values were calculated from a line drawn through two points, which were obtained from the 50% (IC_{50}) point in the plot of the remaining activity (%) relative to the control (100%) *versus* the logarithm of the inhibitor concentration to obtain a sigmoidal dose–response curve.

Lineweaver–Burk Plots For the inhibition of MAO-B by **7c**, a set of five Lineweaver–Burk plots was constructed. The first plot was constructed in the absence of the inhibitor, whereas the remaining four plots were constructed in

the presence of various concentrations of the test inhibitor: $1/4 \times IC_{50}$, $1/2 \times IC_{50}$, $1 \times IC_{50}$, and $2 \times IC_{50}$ ($IC_{50} = 0.015\,\mu M$). The enzyme substrate kynuramine was used at concentrations ranging from 7.5 to $120\,\mu M$.

Molecular Docking Study The MAO-B crystal structure was retrieved from the Protein Data Bank (PDB code: 4A79) and imported into AutoDock (Version 4.2). The structures of compounds **7a** and **7c** were drawn using ChemBioDrawUltra 11.0 and subjected to energy minimization using molecular mechanics (MM2). AutoGrid was used to calculate the grid maps and the grid was centered on the ligand binding site of MAO-B such that it would totally cover the ligand molecule. The centroid of the grid map was set to *X*: 17, *Y*: 125, *Z*: 29, and the number of grid points was *X*: 55, *Y*: 61, *Z*: 55. The maximum number of energy evaluations was set to 250000. Ligand and receptor docking was performed using the Lamarckian Genetic Algorithm (Runs 20) after using the default parameter settings generated by AutoDock Tools for docking. The binding modes were visualized in Discovery Studio Visualizer (version 19; Accelrys, Inc., San Diego, CA, U.S.A.).

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Conflict of Interest The authors declare no conflict of interest.

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