Regular Article

Synthesis and Biological Evaluation of 2-Azolylmethylene-3-(2*H*)-benzofuranone Derivatives as Potent Monoamine Oxidases Inhibitors

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A series of 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives, 2-indolylmethylene-3-(2*H*)-benzofuranone and 2-pyrrolylmethylene-3-(2*H*)-benzofuranone derivatives, were synthesized, and their monoamine oxidase (MAO) A and B inhibitory activities were evaluated. Compounds 1b, 3b, 6b, 7b, and 10b showed strong inhibitory activity against MAO-A, and compound 3b showed the highest potency and selectivity, with an IC_{50} value of 21 nM and a MAO-A selectivity index of 48. Compounds 3c, 4c, 9a, 9c, 10c, 11a, and 11c showed strong inhibitory activity against MAO-B, and compound 4c showed the highest potency and selectivity, with an IC_{50} value of 16 nM and a MAO-B selectivity index of >1100. Further analysis of these compounds indicated that compound 3b for MAO-A and compound 4c for MAO-B were competitive inhibitors, with K_i values of 10 and 6.1 nM, respectively. Furthermore, computational analyses, such as quantitative structure–activity relationship (QSAR) analysis of the 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives conducting their pIC_{50} values with the Molecular Operating Environment (MOE) and Mordred, and molecular docking analysis using MOE-Dock supported that the 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives are a privileged scaffold for the design and development of novel MAO inhibitors.

Key words 2-azolylmethylene-3-(2*H*)-benzofuranone derivative, monoamine oxidase (MAO) A, MAO B, quantitative structure–activity relationship, molecular operating environment (MOE)

Introduction

Monoamine oxidases (MAOs, EC 1.4.3.4) are FAD-containing enzymes bound to the mitochondrial outer membrane in various mammalian cells. Two isozymes, MAO-A and B, are responsible for the oxidative degradation of neurotransmitters such as dopamine, epinephrin, and serotonin. MAO-A and B share approximately 70% amino acid sequence identity but differ in substrate, inhibitor sensitivity, tissue distribution, three-dimensional (3D) structure, and active site size and shape. MAO-A preferentially degrades epinephrine, norepinephrine, and serotonin and is irreversibly inhibited by clorgyline. However, MAO-B preferentially degrades benzylamine, dopamine, and *β*-phenethylamine and is irreversibly inhibited by (*R*)-(−)-deprenyl. MAO inhibitors are effective in treating several neurological diseases; MAO-A inhibitors are used as antidepressants and anxiolytics, while MAO-B inhibitors are used to treat Parkinson's disease and are also expected to affect Alzheimer's disease.[1–3]

Natural products play an important role in drug development.[4,5] Among them, flavonoids are the major natural products, and they are classified as phenolic secondary metabolites. Flavonoids, widely present in the plant kingdom, are an important resource as biologically active compounds that promote human health. Flavonoids are chemically classified into subgroups, such as flavones, isoflavones, flavanes, and isoflavanes, which differ in their oxidation status and heterocyclic saturation. The structural isomer of flavones, 2-benzylidene-benzofuran-3-(2*H*)-ones, known as aurones, are found in vegetables and flowers.[6] Aurones have recently been the subject of intense research because of their broad range of biological activities against neurological diseases.[7] For example, several groups have reported MAO inhibition by naturally occurring or organically synthesized aurones.[8–10] Another important subgroup of heterocycles are the indoles, many of which have been found in natural products and drugs as important scaffold.[11] This evidence suggests that aurone and indole hybrid compounds, 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives, are useful MAO inhibitors. Therefore, we recently synthesized 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives and reported that 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives inhibit MAOs[12] (Fig. 1).

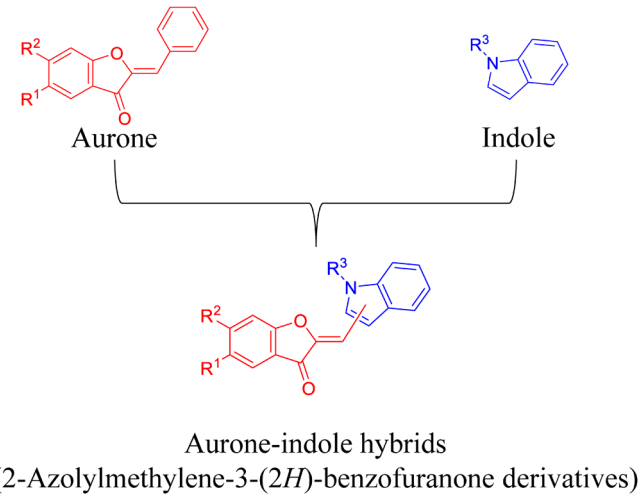

Fig. 1. Design Strategy for the Aurone-Indole Hybrids

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In this study, additional 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives were designed, synthesized, and investigated for their MAO inhibitory activities to further explore promising lead compounds to develop MAO inhibitors.

Results and Discussion

Chemistry The protocol for the synthesis of 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives, 2-indolylmethylene-3-(2*H*)-benzofuranone derivatives and 2-pyrrolylmethilene-3-(2*H*)-benzofuranone derivatives, is shown in Fig. 2. 2-Azolylmethylene-3-(2*H*)-benzofuranone derivatives (compounds **1**–**11**) were synthesized by the Claisen–Schmidt reaction of benzofuranone derivatives (**IIIa**–**d**) and azolecarboxaldehyde derivatives under basic conditions. Satisfactory yields were obtained in all cases. The key compounds (**IIIa-d**, **VII**, and **VIII**) were synthesized as described in Experimental.

Biological Activity All the synthesized 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives (compounds **1**–**11**) were evaluated for their MAO-A and B inhibitory activities (Table 1). The effects of substituting the benzofuranone ring (R^1, R^2) and the corresponding azoles (R^3) on the MAO inhibitory activity revealed some structure–activity relationships.

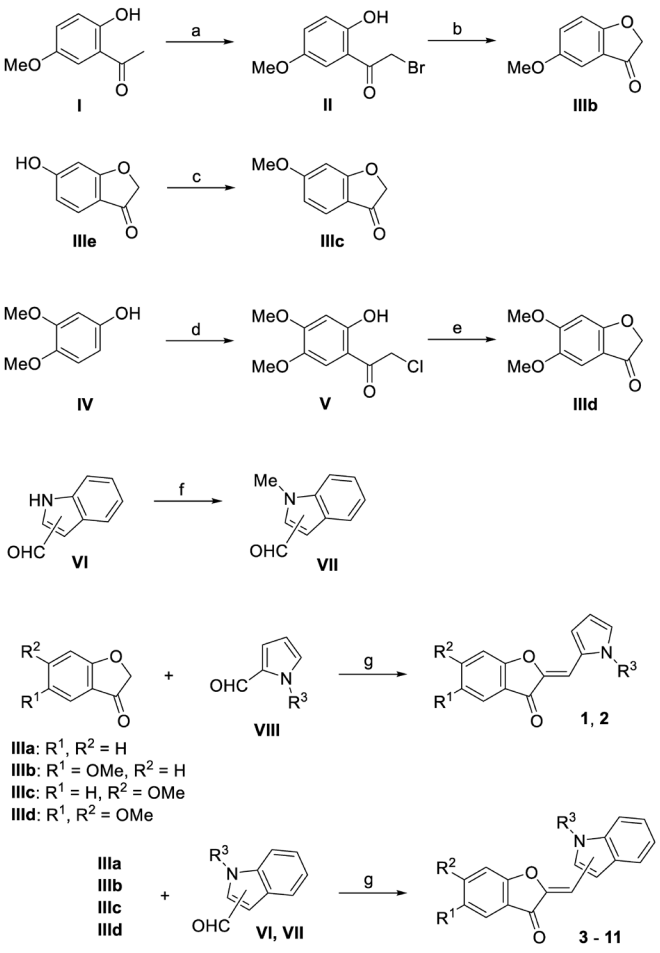


Fig. 2. Synthetic Protocol for 2-Azolylmethylene-3-(2*H*)-benzofuranone Derivatives

Reagents and conditions: (a) $CuBr_2$, $CHCl_3$–AcOEt, reflux; (b) sodium acetate, EtOH, reflux; (c) iodomethane, K_2CO_3, DMF, 80 °C; (d) $ClCH_2COCl$, $AlCl_3$, AcOEt; (e) sodium acetate, MeOH, reflux; (f) iodomethane, NaH, DMF; (g) KOH 50% in water, MeOH, 60 °C.

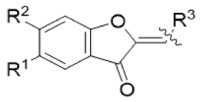
Inhibitory Activities of 2-Azolylmethylene-3-(2*H*)-benzofuranone Derivatives towards MAO-A and B Among the 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives, compounds **1a**, **1c**, **2a**, **2b**, **2c**, **4a**, **5a**, **7c**, **8a**, **8b**, and **11b** showed IC_{50} values against MAO-A of $<10\,\mu$M, and compounds **3a**, **4b**, **6a**, **7a**, and **10a** showed IC_{50} values against MAO-A of $<1\,\mu$M, and compounds **1b**, **3b**, **6b**, **7b**, and **10b** showed IC_{50} values against MAO-A of $<0.1\,\mu$M, suggesting that the substitution of methoxy group on R^1 was effective for MAO-A inhibition. Compound **3b** showed significant MAO-A inhibitory activity, with an IC_{50} value of 21 nM, whereas clorgyline, which was used as a positive control, showed an IC_{50} value of 4.9 nM. Compounds **1a**, **1b**, **2a**, and **3b** showed IC_{50} values against MAO-B of $<10\,\mu$M. Compounds **1c**, **2b**, **2c**, **3a**, **4a**, **4b**, **5a**, **5b**, **5c**, **6a**, **6b**, **6c**, **7a**, **7b**, **7c**, **8a**, **8b**, **8c**, **9b**, **9d**, **10a**, **10b**, and **11b** showed IC_{50} values against MAO-B of $<1\,\mu$M, and compounds **3c**, **4c**, **9a**, **9c**, **10c**, **11a**, and **11c** showed IC_{50} values against MAO-B of $<0.1\,\mu$M, suggesting that the substitution of methoxy group on R^2 was effective for MAO-B inhibition. Compound **4c** showed significant MAO-B inhibitory activity, with an IC_{50} value of 16 nM, whereas safinamide, used as a positive control, showed an IC_{50} value of 50 nM. The substitution of the methoxy group on both R^1 and R^2 in compounds **3d**, **4d**, and **9d** may reduce the inhibitory activity against MAO-A and B.

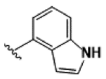
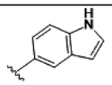
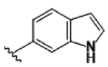
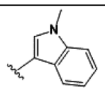
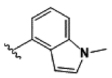
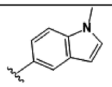
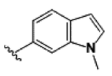
The selectivity index (SI) was expressed as the ratio of the IC_{50} values of MAO-A and MAO-B for each compound. Compounds **1a**, **1b**, **3b**, **4b**, **6b**, **7a**, **7b**, and **10b** showed SI values of >2. Compound **1b** exhibited the highest MAO-A selectivity, with an SI value of 85. Compounds **1c**, **2b**, **2c**, **3c**, **4a**, **5a**, **5b**, **5c**, **6c**, **7c**, **8a**, **8b**, **8c**, **9a**, **9b**, **9c**, **9d**, **10a**, **10c**, **11a**, **11b**, and **11c** showed SI value for MAO-B >2. Compound **3c** showed the highest MAO-B selectivity, with an SI value of >2700.

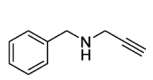
Kinetic Studies of Compounds 3b for MAO-A and 4c for MAO-B Compounds **3b**, the most potent MAO-A inhibitor, and **4c**, the most potent MAO-B inhibitor, were selected for subsequent kinetic studies (Fig. 3). The lines of the Lineweaver–Burk plots for these two compounds intersected on the *y*-axis, suggesting that the 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives were competitive inhibitors. The apparent K_i values were 10 nM for compound **3b** in MAO-A and 6.1 nM for compound **4c** in MAO-B.

Computational Analyses To further understand the inhibitory activities of 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives on MAO-A and B, quantitative structure–activity relationship (QSAR) analyses of 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives were conducted using the Molecular Operating Environment (MOE)[13] and Mordred[14] (1427 descriptors) with pIC_{50} values for MAO-A and MAO-B inhibitory activities. A total of 430 descriptors showed significant correlations ($p<0.05$) with MAO-A inhibitory activity, and 158 descriptors showed significant correlations ($p<0.05$) with MAO-B inhibitory activity. Scatter plots of the top six descriptors of MAO-A and MAO-B inhibitory activities are shown in Fig. 4 and listed in Table 2. These results suggested that the characteristics of the derivatives contributing to the inhibitory activity of MAO-A are associated with their unique molecular shape and electronic properties, including both sigma and pi electrons. Conversely, the characteristics of these derivatives contributing to the inhibitory activity of MAO-B

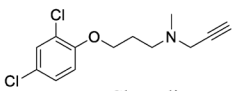
Table 1. IC_{50} Values and Selectivities of 2-Azolylmethylene-3-(2*H*)-benzofuranone Derivatives for Inhibiting MAO-A and MAO-B



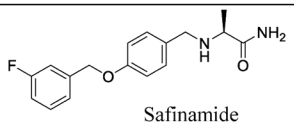
	R^1	R^2	R^3	IC_{50} μM MAO-A	IC_{50} μM MAO-B	SI MAO-A	SI MAO-B
1a	H	H		1.0 ± 0.15	5.4 ± 0.20	5.4	-
1b	MeO	H		0.062 ± 0.0147	5.3 ± 0.58	85	-
1c	H	MeO		3.8 ± 1.05	0.67 ± 0.083	-	5.7
2a	H	H		1.8 ± 0.64	1.1 ± 0.26	-	-
2b	MeO	H		3.9 ± 0.29	0.25 ± 0.109	-	15
2c	H	MeO		2.7 ± 0.08	0.52 ± 0.060	-	5.2
3a	H	H		0.42 ± 0.027	0.26 ± 0.065	-	-
3b	MeO	H		0.021 ± 0.0055	1.0 ± 0.47	48	-
3c	H	MeO		> 100	0.037 ± 0.0063	-	>2700
3d	MeO	MeO		> 100	> 100	-	-
4a	H	H		1.8 ± 0.76	0.37 ± 0.043	-	4.9
4b	MeO	H		0.17 ± 0.079	0.31 ± 0.144	-	-
4c	H	MeO		17 ± 3.0	0.016 ± 0.0033	-	1100
4d	MeO	MeO		> 100	> 100	-	-
5a	H	H		5.7 ± 0.49	0.15 ± 0.044	-	38
5b	MeO	H		65 ± 8.4	0.26 ± 0.097	-	250
5c	H	MeO		25 ± 8.7	0.13 ± 0.022	-	190
6a	H	H		0.18 ± 0.031	0.26 ± 0.068	-	-
6b	MeO	H		0.027 ± 0.0042	0.18 ± 0.039	6.7	-
6c	H	MeO		25 ± 7.7	0.12 ± 0.016	-	210
7a	H	H		0.18 ± 0.059	0.42 ± 0.069	2.3	-
7b	MeO	H		0.023 ± 0.0018	0.41 ± 0.068	18	-
7c	H	MeO		1.8 ± 0.46	0.34 ± 0.036	-	5.3
8a	H	H		7.6 ± 0.50	0.52 ± 0.131	-	15
8b	MeO	H		6.2 ± 0.29	0.66 ± 0.029	-	9.4
8c	H	MeO		> 100	0.48 ± 0.130	-	>210
9a	H	H		> 100	0.046 ± 0.0084	-	>2200
9b	MeO	H		> 100	0.14 ± 0.024	-	>710
9c	H	MeO		60 ± 4.5	0.043 ± 0.0053	-	1400
9d	MeO	MeO		> 100	0.22 ± 0.058	-	>450
10a	H	H		0.94 ± 0.004	0.12 ± 0.045	-	7.8
10b	MeO	H		0.062 ± 0.0104	0.39 ± 0.031	6.3	-
10c	H	MeO		> 100	0.065 ± 0.0067	-	>1500
11a	H	H		45 ± 3.9	0.057 ± 0.0172	-	790
11b	MeO	H		1.0 ± 0.02	0.17 ± 0.069	-	5.9
11c	H	MeO		> 100	0.080 ± 0.0115	-	>1300
Pargyline				4.6 ± 0.27	0.22 ± 0.024	-	21
Clorgyline				0.0049 ± 0.00028	5.8 ± 0.34	1200	-
Safinamide				100	0.050 ± 0.0063	-	2000



Pargyline



Clorgyline



Safinamide

MAO selectivity indices are given as the ratio of IC_{50} values of MAO-A and MAO-B.

are presumably linked to their distinct molecular shape and electronegativity, which differ from those of MAO-A. Although the characteristics of molecules influencing the inhibition of both MAO-A and MAO-B are related to their molecular features and electronic properties, it is inferred that these properties significantly differ depending on the target protein.

To elucidate the mechanism of the inhibitory activities of 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives against MAOs, molecular docking studies were performed using MOE-Dock, and interactions between compound **3b** and MAO-A (PDB code 2Z5X) and between compound **4c** and MAO-B (PDB code 4A79) were investigated. The interaction diagrams are shown in Fig. 5. In the interaction of compound **3b** with MAO-A, Gln215, Ile335, and Tyr407 interacted with the indole moiety by arene-H interaction; Ala111 and Thr336 interacted as backbone donors with the indole moiety; Ile180 interacted with the oxygen atom on the benzofuranone moiety; and the other interacting residues were Tyr69, Leu97, Asn181, Phe208, Val210, Cys323, Ile325, Leu337, Met350, Phe352, and Tyr444. The MAO-A active site had a monopartite cavity of

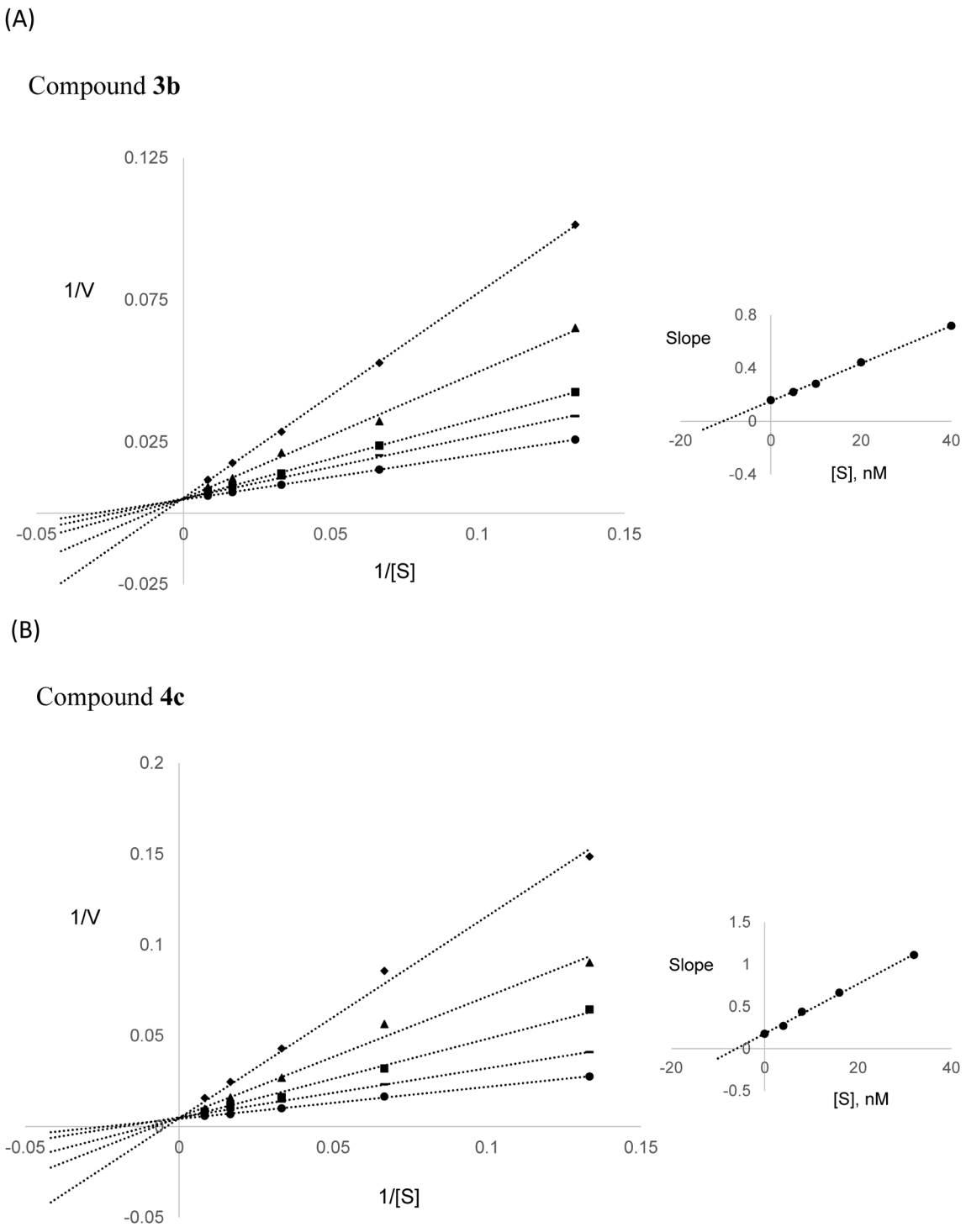


Fig. 3. Kinetic Study on the Mechanism of Inhibition by 2-Azolylmethylene-3-(2*H*)-benzofuranone Derivatives for MAO-A by Compound **3b** (A) and MAO-B by Compound **4c** (B)

The plots were constructed in the absence (filled circles) and presence (other symbols) of various concentrations of the compounds. The sub-graphs of the slopes of these Lineweaver–Burk plots *versus* inhibitor concentration for the compounds. The rate (V) is expressed as % of control. Kynuramine was used at 30 μM.

approximately 550 Å^3 volume; the key residues in the active site for substrate and inhibitor binding were Tyr69, Ile180, Phe177, Asn181, Tyr197, Ile207, Phe208, Gln215, Ile335, Phe352, Tyr407, and Tyr444, respectively.[3] These residues were included in the docking results, suggesting that 2-azolylmethylene-3-(2*H*)-benzofuranone derivative compound **3b** tightly binds to the active site of MAO-A.

In the interaction of compound **4c** with MAO-B, Ile199 interacted with the benzofuranone moiety *via* two arene-H interactions, Leu171 interacted with both benzofuranone and indole moieties *via* arene-H interactions, Cys127 interacted with both ketones on benzofuranone and methylene as side chain acceptors, Phe168 interacted with the ketone as the backbone acceptor, Phe343 interacted with indole by arene-H interactions, and other interacting residues were Tyr60, Pro102, Pro104, Ile198, Gln206, Ile316, Tyr326, Leu328,

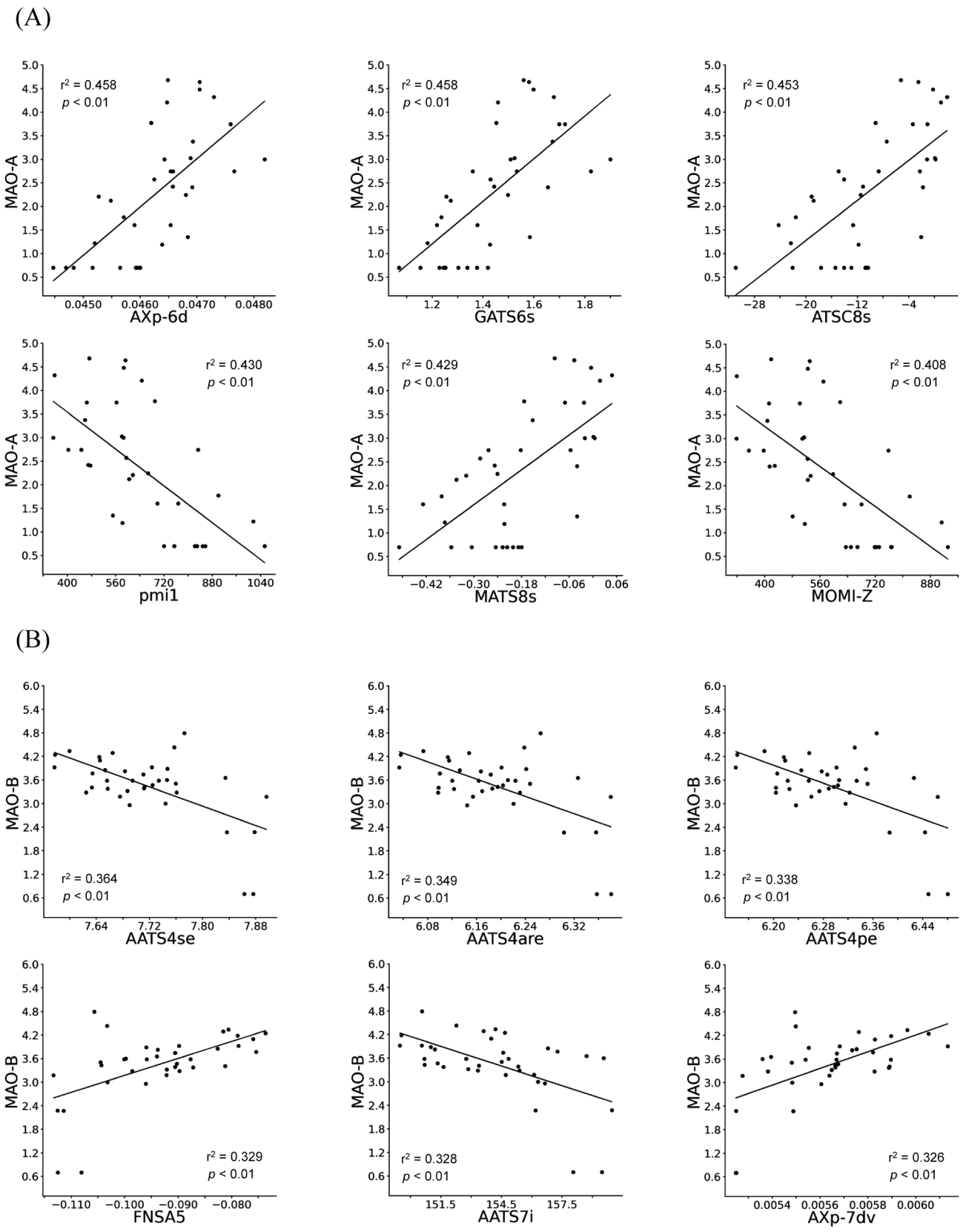


Fig. 4. Determination of the Correlation between the Chemical Descriptors and the pIC_{50} Values of 2-Azolylmethylene-3-(2*H*)-benzofuranone Derivatives, for MAO-A (A) and MAO-B (B)

Tyr398, and Tyr435. MAO-B active site had bipartite cavities, the entrance cavity (approx. 300 Å^3) and the substrate cavity (approx. 400 Å^3), 700 Å^3 volume, and key residues in the active site were Tyr60, Phe168, Leu171, Cys172, Tyr188, Ile198, Ile199, Gln206, Tyr326, Tyr398, and Tyr435 for substrate and inhibitor binding.[3] These residues were included in the

Table 2. Top Six Descriptors in the QSAR Analysis of MAO-A and MAO-B

Objective_variable	Descriptors	Meanings
MAO-A	AXp-6d	6-Ordered averaged Chi path weighted by sigma electrons (topological descriptor)
	GATS6s	Geary coefficient of lag 6 weighted by intrinsic state (topological descriptor)
	ATSC8s	Centered moreau-broto autocorrelation of lag 8 weighted by intrinsic state (topological descriptor)
	pmi1	Principal moment of inertia
	MATS8s	Moran autocorrelation of topological structure of lag 8 atoms weighted by intrinsic state (topological descriptor)
	MOMI-Z	Moment of inertia (axis = Z)
MAO-B	AATS4se	Averaged Moreau-Broto autocorrelation of topological structure of lag 4 atoms weighted by sanderson EN (topological descriptor)
	AATS4are	Averaged Moreau-Broto autocorrelation of topological structure of lag 4 atoms weighted by allred-rocow EN (topological descriptor)
	AATS4pe	Averaged Moreau-Broto autocorrelation of topological structure of lag 4 atoms weighted by pauling EN (topological descriptor)
	FNSA5	Fractional charged partial negative surface area version 5 (molecular surface area descriptor)
	AATS7i	Averaged Moreau-Broto autocorrelation of topological structure of lag 7 atoms weighted by ionization potential (topological descriptor)
	AXp-7dv	7-ordered averaged Chi path weighted by valence electrons (topological descriptor)

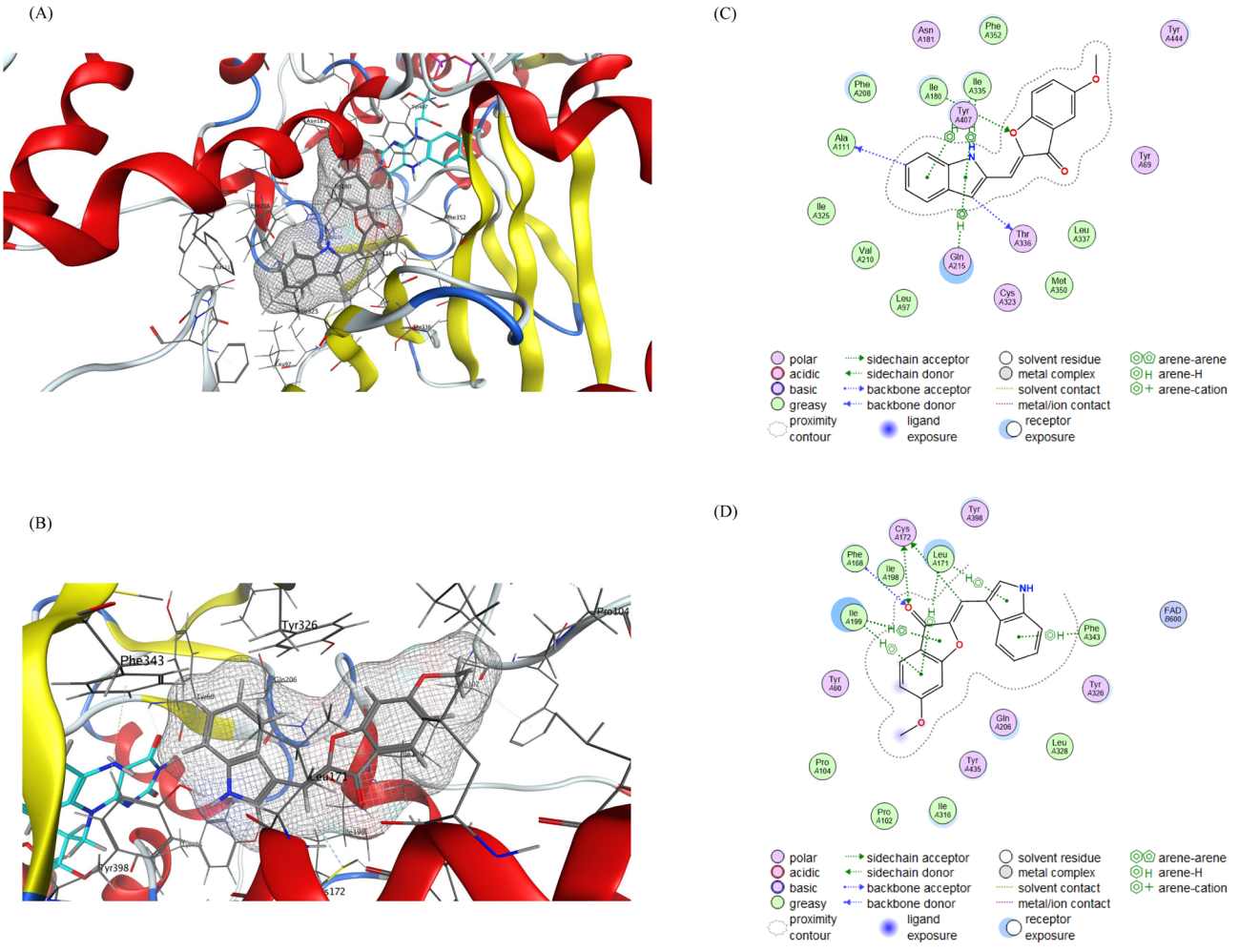


Fig. 5. Docking Outcomes for the 2-Azolylmethylene-3-(2*H*)-benzofuranone Derivative as an Inhibitor of MAO-A and MAO-B

Protein–ligand interaction diagrams of the active site are presented for compounds **3b** and **4c** interacting with MAO-A (A) and MAO-B (B). Additionally, two-dimensional interaction diagrams for compounds **3b** and **4c** with the binding pockets of MAO-A (C) and MAO-B (D) are depicted.

docking results, suggesting that 2-azolylmethylene-3-(2*H*)-benzofuranone derivative compound **4c** is tightly bound to the active site of MAO-B.

Conclusion

A series of 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives were synthesized and evaluated for their MAO

inhibitory activities. Among these compounds, **3b** showed significant inhibitory activity and selectivity against MAO-A and compound **4c** for MAO-B. Computational analyses suggested that 2-azolylmethylene-3-(2*H*)-benzofuranone derivatives are a privileged scaffold for designing and developing novel MAO inhibitors.

Experimental

Chemistry All the reagents and solvents were purchased from commercial sources. Analytical TLC was performed on silica-coated plates (silica gel 60F-254; Merck Ltd., Tokyo, Japan) and visualized under UV light. Column chromatography was performed using silica gel (Wakogel C-200; FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan). All melting points were determined using a Yanagimoto micro-hot stage and were 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 recorded using a JEOL JMS-700 spectrometer. Elemental analyses were performed using a Yanaco CHN MT-6 elemental analyzer.

5-Methoxy-3(2*H*)-benzofuranone (IIIb) 5-Methoxy-3(2*H*)-benzofuranone was synthesized using a previously reported method.[15,16] $CuBr_2$ (40 mmol) was added under an argon atmosphere to a solution of 2′-hydroxy-5′-methoxyacetophenone (**I**, 20 mmol) in AcOEt (10 mL) and $CHCl_3$ (10 mL). $CuBr_2$ (40 mmol) was added under an argon atmosphere. The reaction mixture was refluxed under vigorous stirring for 36 h and then cooled to room temperature. Cuprous bromide was filtered, and the filtrate was evaporated under reduced pressure. The reaction mixture was extracted with AcOEt, and the combined organic layer was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to produce 2-bromo-1-(2-hydroxy-5-methoxyphenyl)ethanone (**II**), which was used without further purification. The crude product (**II**) and sodium acetate (42 mmol) were dissolved in EtOH (20 mL) and heated under reflux for 2 h. The solvent was then evaporated under reduced pressure. The reaction mixture was extracted with AcOEt, and the combined organic layer was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified using silica gel column chromatography (hexane–AcOEt solvent system) to obtain the title compound in 44% yield. mp 89–90 °C (lit. 92 °C[17]). ^{1}H-NMR (dimethyl sulfoxide (DMSO)-d_6, 400 MHz) δ: 7.40 (1H, dd, J = 9.0, 2.8 Hz, H-6), 7.29 (1H, d, J = 9.0 Hz, H-7), 7.14 (1H, d, J = 2.8 Hz, H-4), 4.86 (2H, s, H-2), 3.83 (3H, s, OMe). MS (electron ionization (EI)) m/z: 164 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[16,17]

6-Methoxy-3(2*H*)-benzofuranone (IIIc) 6-Methoxy-3(2*H*)-benzofuranone was synthesized using a modified version of a previously reported method.[18] A mixture of 6-hydroxy-3(2*H*)-benzofuranone (**IIIe**, 10 mmol), iodomethane (15 mmol), and K_2CO_3 (12 mmol) in *N*,*N*-dimethylformamide (DMF) (30 mL) was stirred at 80 °C for 3 h. The reaction mixture was then extracted using $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified using silica gel column chromatography (hexane–AcOEt solvent system) to obtain the title compound in 68% yield. mp 121–122 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.57 (1H, d, J = 8.6 Hz, H-4), 6.65 (1H, dd, J = 8.6, 2.1 Hz, H-5), 6.55 (1H, d, J = 2.1 Hz, H-7), 4.64 (2H, s, H-2), 3.89 (3H, s, OMe). MS (EI) m/z: 164 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[18]

5,6-Dimethoxy-3(2*H*)-benzofuranone (IIId) 5,6-Dimethoxy-3(2*H*)-benzofuranone was synthesized using a previously reported method.[19] $AlCl_3$ (40 mmol) was added to a solution of 3,4-dimethoxyphenol (**IV**, 10 mmol) in AcOEt (25 mL). $AlCl_3$ (40 mmol) was added at room temperature, and the reaction mixture was stirred for 30 min. Chloroacetyl chloride (12 mmol) was added, and the reaction mixture was stirred at room temperature overnight and then heated at 50 °C for 6 h. The reaction was then quenched with ice-cold water. The reaction mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to produce 2-chloro-1-(2-hydroxy-4,5-dimethoxyphenyl)ethanone (**V**), which was used without further purification. The obtained crude product (**V**) and sodium acetate (20 mmol) were dissolved in MeOH (30 mL), and the mixture was refluxed under an argon atmosphere for 7 h. The solvent was then evaporated under reduced pressure. The reaction mixture was then extracted using CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified using silica gel column chromatography (hexane–AcOEt solvent system) to obtain a 73% yield of the title compound. mp 168–169 °C dec. (lit. 164–166 °C[19]). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.03 (1H, s, H-4), 6.60 (1H, s, H-7), 4.62 (2H, s, H-2), 3.97 (3H, s, OMe), 3.87 (3H, s, MeO). MS (EI) m/z: 194 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[20]

Synthesis of 1-Methyl-1*H*-indole-carboxaldehydes (VII) 1-Methyl-1*H*-indole-carboxaldehydes were synthesized by modifying a previously reported procedure.[21] To a stirred solution of the corresponding 1*H*-indole-carboxaldehyde (**VI**, 5 mmol) in DMF (15 mL), and NaH (60% in oil, 20 mmol) was added at 0 °C. After stirring for 15 min, iodomethane (7.5 mmol) was added dropwise to the solution. After stirring for 1 h at room temperature, the reaction was quenched with saturated $NaHCO_3$. The reaction mixture was then extracted using AcOEt. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified *via* silica gel column chromatography (hexane–AcOEt solvent system) to obtain the title compound.

1-Methyl-1*H*-indole-3-carboxaldehyde (VIIa) Yield 97%. mp 69–70 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.89 (1H, s, CHO), 8.27 (1H, s, H-2), 8.10 (1H, brd, J = 7.7 Hz, H-4), 7.58 (1H, brd, J = 8.1 Hz, H-7), 7.33 (1H, ddd, J = 8.1, 7.1, 1.4 Hz, H-6), 7.27 (1H, ddd, J = 7.7, 7.1, 1.2 Hz, H-5), 3.89 (3H, s, CH_3). MS (EI) m/z: 159 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[22]

1-Methyl-1*H*-indole-4-carboxaldehyde (VIIb) Yield 31%. oil. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.20 (1H, s, CHO), 7.85 (1H, dt, J = 8.1, 0.9 Hz, H-7), 7.70 (1H, dd, J = 7.2, 0.9 Hz, H-5), 7.59 (1H, d, J = 3.0 Hz, H-2), 7.37 (1H, dd, J = 8.1, 7.2 Hz, H-6), 7.08 (1H, dd, J = 3.0, 0.9 Hz, H-3), 3.88 (3H, s, CH_3). MS (EI) m/z: 159 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[23]

1-Methyl-1*H*-indole-5-carboxaldehyde (VIIc) Yield 84%. mp 67–68 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.98 (1H, s, CHO), 8.18 (1H, d, J = 1.6 Hz, H-4), 7.69 (1H, dd, J = 8.6,

1.6 Hz, H-6), 7.61 (1H, dd, J = 8.6, 0.9 Hz, H-7), 7.50 (1H, d, J = 3.2 Hz, H-2), 6.66 (1H, dd, J = 3.2, 0.9 Hz, H-3), 3.85 (3H, s, CH_3). MS (EI) m/z: 159 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[24)]

1-Methyl-1*H*-indole-6-carboxaldehyde (VIId) Yield 50%. mp 80–81 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.03 (1H, s, CHO), 8.08 (1H, brs, H-7), 7.72 (1H, brd, J = 8.2 Hz, H-4), 7.66 (1H, d, J = 3.0 Hz, H-2), 7.57 (1H, dd, J = 8.2, 1.4 Hz, H-5), 6.57 (1H, dd, J = 3.0, 0.9 Hz, H-3), 3.85 (3H, s, CH_3). MS (EI) m/z: 159 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[25)]

Synthesis of 2-Azolylmethylene-3(2*H*)-benzofuranones (1–11) 2-Azolylmethylene-3(2*H*)-benzofuranones were synthesized by Claisen–Schmidt condensation of the appropriate 3(2*H*)-benzofuranone with azole-carboxaldehyde under basic conditions and synthesized by modifying a previously reported synthetic procedure for benzylidene-3(2*H*)-benzofuranone (aurones).[26)] To a solution of 3(2*H*)benzofuranone (**III**, 1 mmol) and azole-carboxaldehyde (1 mmol) in MeOH (10 mL), an aqueous solution of potassium hydroxide (50%, 1.5 mL) was added. The mixture was heated at 60 °C for 1 h, and then MeOH was evaporated under reduced pressure. After the reaction mixture was diluted with ice water and acidified to pH 3 using 10% HCl, the sample was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified using silica gel column chromatography (hexane–AcOEt solvent system) to obtain the title compound.

(2*Z*)-2-(1*H*-Pyrrol-2-ylmethylene)-3(2*H*)-benzofuranone (1a) Yield 28%. mp 166–168 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.54 (1H, s, NH), 7.78–7.72 (2H, m, H-4, H-6), 7.51 (1H, dd, J = 8.0, 0.8 Hz, H-7), 7.28 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.21 (1H, m, H-3′ or H-5′), 6.97 (1H, m, H-3′ or H-5′), 6.95 (1H, s, =CH–), 6.34 (1H, m, H-4′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 182.0, 164.2, 142.8, 136.5, 125.1, 125.0, 123.8, 123.5, 122.1, 117.4, 113.1, 111.6, 105.1. MS (EI) m/z: 211 $[M]^+$. The ^{1}H- and ^{13}C-NMR spectra were similar to that previously reported.[27)]

(2*Z*)-2-[(1-Methyl-1*H*-pyrrol-2-yl)methylene]-3(2*H*)-benzofuranone (2a) Yield 49%. mp 171–172 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.78–7.72 (2H, m, H-4, H-6), 7.54 (1H, dd, J = 8.0, 0.8 Hz, H-7), 7.29 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.18 (1H, m, H-3′ or H-5′), 7.14 (1H, m, H-3′ or H-5′), 6.95 (1H, s, =CH–), 6.31 (1H, m, H-4′), 3.80 (3H, s, CH3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.9, 164.3, 143.3, 136.5, 129.1, 125.8, 123.8, 123.5, 122.0, 117.9, 113.1, 110.3, 102.6, 33.8. MS (EI) m/z: 225 $[M]^+$. *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.92; H, 4.99; N, 6.12.

(2*Z*)-2-(1*H*-Indol-2-ylmethylene)-3(2*H*)-benzofuranone (3a) Yield 54%. mp 231–232 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.47 (1H, s, NH), 7.86–7.79 (2H, m, H-4, H-6), 7.66 (1H, brd, J = 8.0 Hz, H-4′), 7.61 (1H, brd, J = 8.2 Hz, H-7), 7.53 (1H, brd, J = 8.3 Hz, H-7′), 7.35 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.27 (1H, brs, H-3′), 7.24 (1H, ddd, J = 8.3, 7.0, 1.2 Hz, H-6′), 7.11–7.04 (1H, m, H-5′), 7.07 (1H, s, =CH–). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 182.6, 164.9, 145.4, 138.2, 137.3, 130.4, 128.2, 124.2 (2C), 123.9, 121.5, 121.2, 120.2, 113.3, 112.0, 109.8, 104.1. MS (EI) m/z: 261 $[M]^+$. *Anal.* Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.97; H, 4.40; N, 5.35.

(2*Z*)-2-(1*H*-Indol-3-ylmethylene)-3(2*H*)-benzofuranone (4a) Yield 30%. mp 244–246 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.15 (1H, s, NH), 8.29 (1H, s, H-2′), 8.08 (1H, brd, J = 7.6 Hz, H-4′), 7.82–7.75 (2H, m, H-4, H-6), 7.59 (1H, dd, J = 8.1, 0.9 Hz, H-7), 7.52 (1H, brd, J = 7.7 Hz, H-7′), 7.38 (1H, s, =CH–), 7.30 (1H, td, J = 7.5, 0.9 Hz, H-5), 7.28–7.18 (2H, m, H-5, H-6′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.7, 164.1, 144.1, 136.4, 136.3, 132.3, 126.7, 123.8, 123.4, 122.8, 122.3, 121.0, 119.1, 113.1, 112.4, 108.5, 107.5. MS (EI) m/z: 261 $[M]_+$. *Anal.* Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.39; H, 4.37; N, 5.30.

(2*Z*)-2-(1*H*-Indol-4-ylmethylene)-3(2*H*)-benzofuranone (5a) Yield 34%. mp 222–224 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.45 (1H, s, NH), 8.03 (1H, d, J = 7.5 Hz, H-5′), 7.85–7.80 (2H, m, H-4, H-6), 7.62 (1H, brd, J = 8.3 Hz, H-7), 7.57–7.53 (2H, m, H-2′, H-7′), 7.34 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.30 (1H, s, =CH–), 7.28 (1H, t, J = 7.8 Hz, H-6′), 6.82 (1H, m, H-3′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.3, 165.3, 146.2, 137.4, 136.1, 129.1, 127.2, 124.3, 123.9, 122.5, 122.4, 121.4, 121.2, 114.1, 113.2, 110.1, 99.6. MS (EI) m/z: 261 $[M]^+$. *Anal.* Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.14; H, 4.34; N, 5.30.

(2*Z*)-2-(1*H*-Indol-5-ylmethylene)-3(2*H*)-benzofuranone (6a) Yield 38%. mp 244–246 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.45 (1H, s, NH), 8.27 (1H, d, J = 1.0 Hz, H-4′), 7.86–7.78 (3H, m, H-4, H-6, H-6′), 7.61 (1H, dd, J = 8.9, 0.8 Hz, H-7), 7.54 (1H, d, J = 8.5 Hz, H-7′), 7.46 (1H, t, J = 2.7 Hz, H-2′), 7.33 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.10 (1H, s, =CH–), 6.58 (1H, m, H-3′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.1, 165.0, 144.8, 137.1, 136.9, 128.2, 127.0, 125.2, 124.8, 124.1, 123.7, 122.8, 121.4, 115.5, 113.2, 112.2, 102.3. MS (EI) m/z: 261 $[M]^+$. *Anal.* Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.17; H, 4.43; N, 5.35.

(2*Z*)-2-(1*H*-Indol-6-ylmethylene)-3(2*H*)-benzofuranone (7a) Yield 18%. mp 234–236 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.51 (1H, s, NH), 8.12 (1H, brs, H-7′), 7.83–7.78 (2H, m, H-4, H-6), 7.70 (1H, dd, J = 8.4, 1.4 Hz, H-5′), 7.66 (1H, d, J = 8.4 Hz, H-4′), 7.57 (1H, dd, J = 8.8, 0.8 Hz, H-7), 7.55 (1H, t, J = 2.7 Hz, H-2′), 7.33 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.11 (1H, s, =CH–), 6.52 (1H, m, H-3′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.1, 165.0, 145.1, 137.2, 136.1, 129.6, 129.0, 124.5, 124.2, 123.8, 122.7, 121.4, 120.6, 115.6, 115.3, 113.1, 101.8. MS (EI) m/z: 261 $[M]^+$. *Anal.* Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.38; H, 4.39; N, 5.36.

(2*Z*)-2-[(1-Methyl-1*H*-indol-3-yl)methylene]-3(2*H*)-benzofuranone (8a) Yield 33%. mp 167–168 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.31 (1H, s, H-2′), 8.08 (1H, brd, J = 7.8 Hz, H-4′), 7.81–7.75 (2H, m, H-4, H-6), 7.60–7.54 (2H, m, H-7, H-7′), 7.36 (1H, s, =CH–), 7.35–7.23 (3H, m, H-5, H-5′, H-6′), 3.96 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.6, 164.1, 144.1, 136.9, 136.4, 135.7, 127.2, 123.9, 123.4, 122.9, 122.3, 121.3, 119.2, 113.0, 110.8, 107.5, 107.0, 33.3. MS (EI) m/z: 275 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.60; H, 4.84; N, 5.07.

(2*Z*)-2-[(1-Methyl-1*H*-indol-4-yl)methylene]-3(2*H*)-benzofuranone (9a) Yield 52%. mp 176–178 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.06 (1H, d, J = 7.5 Hz, H-5′), 7.86–7.79 (2H, m, H-4, H-6), 7.63–7.59 (2H, m, H-7, H-7′), 7.52 (1H, d, J = 3.1 Hz, H-2′), 7.37–7.31 (2H, m, H-5, H-6′), 7.28 (1H, s, =CH–), 6.86 (1H, dd, J = 3.1, 0.9 Hz, H-3′), 3.85 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.3, 165.3, 146.3, 137.4, 136.6, 131.3, 129.4, 124.3, 123.9, 122.8, 122.5,

121.5, 121.1, 113.2, 112.3, 109.7, 98.8, 32.7. MS (EI) *m/z*: 275 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.58; H, 4.86; N, 5.09.

(2*Z*)-2-[(1-Methyl-1*H*-indol-5-yl)methylene]-3(2*H*)-benzofuranone (10a) Yield 25%. mp 186–187 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.27 (1H, d, J = 1.6 Hz, H-4′), 7.88 (1H, dd, J = 8.6, 1.6 Hz, H-6′), 7.83–7.77 (2H, m, H-4, H-6), 7.63 (1H, dd, J = 8.0, 0.8 Hz, H-7), 7.58 (1H, brd, J = 8.6 Hz, H-7′), 7.44 (1H, d, J = 3.1 Hz, H-2′), 7.32 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.10 (1H, s, =CH–), 6.59 (1H, dd, J = 3.1, 0.8 Hz, H-3′), 3.84 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.1, 165.1, 144.9, 137.2, 137.1, 131.3, 128.5, 125.3, 124.8, 124.1, 123.7, 122.9, 121.4, 115.3, 113.2, 110.5, 101.7, 32.7. MS (EI) *m/z*: 275 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.81; H, 4.87; N, 5.02.

(2*Z*)-2-[(1-Methyl-1*H*-indol-6-yl)methylene]-3(2*H*)-benzofuranone (11a) Yield 26%. mp 182–183 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.12 (1H, brs, H-7′), 7.84–7.78 (3H, m, H-4, H-5′, H-6), 7.68 (1H, d, J = 8.4 Hz, H-4′), 7.63 (1H, dd, J = 8.8, 0.8 Hz, H-7), 7.54 (1H, d, J = 3.0 Hz, H-2′), 7.33 (1H, td, J = 7.5, 0.8 Hz, H-5), 7.12 (1H, s, =CH–), 6.52 (1H, dd, J = 3.0, 0.9 Hz, H-3′), 3.88 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.1, 165.1, 145.2, 137.2, 136.5, 133.0, 129.8, 124.7, 124.1, 123.8, 122.2, 121.3, 120.9, 115.0, 114.2, 113.3, 101.1, 32.6. MS (EI) *m/z*: 275 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.69; H, 4.86; N, 5.09.

(2*Z*)-5-Methoxy-2-(1*H*-pyrrol-2-ylmethylene)-3(2*H*)-benzofuranone (1b) Yield 50%. mp 192–193 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.53 (1H, s, NH), 7.44 (1H, d, J = 8.9 Hz, H-7), 7.35 (1H, dd, J = 8.9, 2.8 Hz, H-6), 7.21 (1H, m, H-3′ or H-5′), 7.20 (1H, d, J = 2.8 Hz, H-4), 6.95 (1H, m, H-3′ or H-5′), 6.93 (1H, s, =CH–), 6.34 (1H, m, H-4′), 3.81 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 182.0, 159.2, 155.6, 143.6, 125.02, 125.00, 124.9, 122.3, 117.3, 114.0, 111.5, 105.03, 105.00, 55.9. MS (EI) *m/z*: 241 $[M]^+$. *Anal.* Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.82; H, 4.72; N, 5.55.

(2*Z*)-5-Methoxy-2-[(1-methyl-1*H*-pyrrol-2-yl)methylene]-3(2*H*)-benzofuranone (2b) Yield 55%. mp 192–193 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.47 (1H, d, J = 8.9 Hz, H-7), 7.34 (1H, dd, J = 8.9, 2.8 Hz, H-6), 7.23 (1H, d, J = 2.8 Hz, H-4), 7.17 (1H, m, H-3′ or H-5′), 7.12 (1H, m, H-3′ or H-5′), 6.93 (1H, s, =CH–), 6.31 (1H, m, H-4′), 3.82 (3H, s, CH_3), 3.80 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.9, 159.0, 155.4, 143.9, 128.9, 125.6, 124.9, 122.0, 117.7, 113.8, 110.1, 104.9, 102.3, 55.7, 33.6. MS (EI) *m/z*: 255 $[M]^+$. *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.63; H, 5.23; N, 5.20.

(2*Z*)-5-Methoxy-2-(1*H*-indol-2-ylmethylene)-3(2*H*)-benzofuranone (3b) Yield 29%. mp 214–216 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.45 (1H, s, NH), 7.65 (1H, d, J = 8.0 Hz, H-4′), 7.54 (1H, d, J = 9.0 Hz, H-7), 7.52 (1H, brd, J = 8.2 Hz, H-7′), 7.42 (1H, dd, J = 9.0, 2.8 Hz, H-6), 7.26 (1H, d, J = 2.8 Hz, H-4), 7.25 (1H, brs, H-3′), 7.23 (1H, ddd, J = 8.2, 7.0, 1.2 Hz, H-6′), 7.07 (1H, ddd, J = 8.0, 7.0, 1.0 Hz, H-5′), 7.05 (1H, s, =CH–), 3.84 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.1, 160.3, 156.3, 146.6, 138.6, 130.9, 128.7, 126.2, 124.6, 122.2, 121.6, 120.6, 114.6, 112.4, 110.2, 105.9, 104.5, 56.4. MS (EI) *m/z*: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.40; H, 4.62; N, 4.65.

(2*Z*)-5-Methoxy-2-(1*H*-indol-3-ylmethylene)-3(2*H*)-benzofuranone (4b) Yield 10%. mp 248–250 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.13 (1H, s, NH), 8.26 (1H, d, J = 2.9 Hz, H-2′), 8.07 (1H, brd, J = 7.3 Hz, H-4′), 7.52 (1H, d, J = 8.9 Hz, H-7), 7.51 (1H, brd, J = 7.9 Hz, H-7′), 7.36 (1H, dd, J = 8.9, 2.8 Hz, H-6), 7.35 (1H, s, =CH–), 7.28–7.18 (3H, m, H-4, H-5′, H-6′), 3.83 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.6, 158.9, 155.4, 144.7, 136.2, 132.0, 126.5, 124.8, 122.6, 122.3, 120.8, 118.9, 113.8, 112.1, 108.3, 107.3, 104.9, 55.7. MS (EI) *m/z*: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 73.92; H, 4.58; N, 4.60.

(2*Z*)-5-Methoxy-2-(1*H*-indol-4-ylmethylene)-3(2*H*)-benzofuranone (5b) Yield 31%. mp 220–222 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.43 (1H, s, NH), 8.01 (1H, d, J = 7.2 Hz, H-5′), 7.55–7.52 (3H, m, H-2′, H-7, H-7′), 7.39 (1H, dd, J = 8.9, 2.8 Hz, H-6), 7.29 (1H, d, J = 2.8 Hz, H-4), 7.29–7.24 (1H, m, H-6′), 7.26 (1H, s, =CH–), 6.85 (1H, m, H-3′), 3.83 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.4, 160.2, 155.9, 147.0, 136.1, 129.1, 127.1, 125.9, 122.6, 122.5, 121.4, 121.3, 114.2, 114.0, 110.0, 105.5, 99.6, 55.9. MS (EI) *m/z*: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.01; H, 4.60; N, 4.63.

(2*Z*)-5-Methoxy-2-(1*H*-indol-5-ylmethylene)-3(2*H*)-benzofuranone (6b) Yield 22%. mp 237–239 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.42 (1H, s, NH), 8.25 (1H, brs, H-4′), 7.81 (1H, dd, J = 8.6, 1.7 Hz, H-6′), 7.53 (1H, d, J = 8.9 Hz, H-7), 7.52 (1H, d, J = 8.6 Hz, H-7′), 7.44 (1H, t, J = 2.7 Hz, H-2′), 7.37 (1H, dd, J = 8.9, 2.8 Hz, H-6), 7.25 (1H, d, J = 2.8 Hz, H-4), 7.06 (1H, s, =CH–), 6.56 (1H, m, H-3′), 3.83 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.0, 159.9, 155.5, 145.4, 136.7, 128.0, 126.8, 125.4, 125.0, 124.6, 122.7, 121.4, 115.3, 114.0, 112.0, 105.1, 102.1, 55.7. MS (EI) *m/z*: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 73.93; H, 4.56; N, 4.56.

(2*Z*)-5-Methoxy-2-(1*H*-indol-6-ylmethylene)-3(2*H*)-benzofuranone (7b) Yield 37%. mp 254–256 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.56 (1H, s, NH), 8.17 (1H, brs, H-7′), 7.76 (1H, dd, J = 8.3, 1.4 Hz, H-5′), 7.73 (1H, d, J = 8.3 Hz, H-4′), 7.61 (1H, t, J = 2.7 Hz, H-2′), 7.57 (1H, d, J = 8.9 Hz, H-7), 7.45 (1H, dd, J = 8.9, 2.8 Hz, H-6), 7.34 (1H, d, J = 2.8 Hz, H-4), 7.15 (1H, s, =CH–), 6.59 (1H, m, H-3′), 3.90 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.3, 160.0, 155.8, 146.0, 136.1, 129.6, 129.0, 125.7, 124.6, 122.7, 121.6, 120.6, 115.6, 115.4, 114.1, 105.4, 101.9, 56.0. HR-MS (EI) *m/z*: 291 $[M]^+$. Calcd for $C_{18}H_{13}NO_3$ 291.0885, Found 290.0813.

(2*Z*)-5-Methoxy-2-[(1-methyl-1*H*-indol-3-yl)methylene]-3(2*H*)-benzofuranone (8b) Yield 16%. mp 201–202 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.28 (1H, s, H-2′), 8.07 (1H, brd, J = 7.8 Hz, H-4′), 7.57 (1H, brd, J = 8.1 Hz, H-7′), 7.48 (1H, d, J = 8.9 Hz, H-7), 7.36 (1H, dd, J = 8.9, 2.8 Hz, H-6), 7.34 (1H, s, =CH–), 7.34–7.23 (2H, m, H-5′, H-6′), 7.24 (1H, d, J = 2.8 Hz, H-4), 3.95 (3H, s, CH_3), 3.83 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.7, 159.1, 155.6, 144.9, 136.9, 135.7, 127.2, 125.0, 122.9, 122.6, 121.3, 119.2, 114.0, 110.8, 107.6, 107.0, 105.2, 55.9, 33.3. MS (EI) *m/z*: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.67; H, 5.01; N, 4.37.

(2*Z*)-5-Methoxy-2-[(1-methyl-1*H*-indol-4-yl)methylene]-3(2*H*)-benzofuranone (9b) Yield 37%. mp 219–221 °C.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.12 (1H, brd, J = 7.5 Hz, H-5′), 7.68 (1H, brd, J = 8.2 Hz, H-7′), 7.62 (1H, d, J = 9.0 Hz, H-7), 7.59 (1H, d, J = 3.2 Hz, H-2′), 7.48 (1H, dd, J = 9.0, 2.8 Hz, H-6), 7.42 (1H, t, J = 7.9 Hz, H-6′), 7.37 (1H, d, J = 2.8 Hz, H-4), 7.34 (1H, s, =CH–), 6.94 (1H, dd, J = 3.2, 0.9 Hz, H-3′), 3.93 (3H, s, CH_3), 3.92 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.5, 160.3, 155.9, 147.2, 136.6, 131.4, 129.4, 126.0, 122.9, 122.5, 121.5, 121.4, 114.2, 112.4, 109.7, 105.5, 98.8, 56.0, 32.7. MS (EI) m/z: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.94; H, 4.98; N, 4.44.

(2*Z*)-5-Methoxy-2-[(1-methyl-1*H*-indol-5-yl)methylene]-3(2*H*)-benzofuranone (10b) Yield 12%. mp 162–163 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.26 (1H, d, J = 1.7 Hz, H-4′), 7.85 (1H, dd, J = 8.7, 1.7 Hz, H-6′), 7.58 (1H, brd, J = 8.7 Hz, H-7′), 7.55 (1H, d, J = 9.0 Hz, H-7), 7.44 (1H, d, J = 3.1 Hz, H-2′), 7.38 (1H, dd, J = 9.0, 2.8 Hz, H-6), 7.23 (1H, d, J = 2.8 Hz, H-4), 7.07 (1H, s, =CH–), 6.57 (1H, d, J = 3.1 Hz, H-3′), 3.84 (3H, s, CH_3), 3.83 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.2, 160.1, 155.7, 145.6, 137.2, 131.3, 128.5, 125.6, 125.3, 124.8, 122.9, 121.6, 115.3, 114.2, 110.5, 105.3, 101.7, 55.9, 32.7. MS (EI) m/z: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.44; H, 4.97; N, 4.37.

(2*Z*)-5-Methoxy-2-[(1-methyl-1*H*-indol-6-yl)methylene]-3(2*H*)-benzofuranone (11b) Yield 12%. mp 190–191 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.09 (1H, brs, H-7′), 7.78 (1H, dd, J = 8.4, 1.5 Hz, H-5′), 7.67 (1H, d, J = 8.4 Hz, H-4′), 7.56 (1H, d, J = 9.0 Hz, H-7), 7.54 (1H, d, J = 3.0 Hz, H-2′), 7.40 (1H, dd, J = 9.0, 2.8 Hz, H-6), 7.26 (1H, d, J = 2.8 Hz, H-4), 7.09 (1H, s, =CH–), 6.51 (1H, dd, J = 3.0, 0.9 Hz, H-3′), 3.88 (3H, s, CH_3), 3.84 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 183.2, 160.1, 155.8, 146.0, 136.5, 132.9, 129.7, 125.6, 124.7, 122.3, 121.5, 120.9, 115.0, 114.2, 114.1, 105.4, 101.0, 56.0, 32.6. MS (EI) m/z: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.94; H, 5.00; N, 4.43.

(2*Z*)-6-Methoxy-2-(1*H*-pyrrol-2-ylmethylene)-3(2*H*)-benzofuranone (1c) Yield 43%. mp 198–199 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.48 (1H, s, NH), 7.64 (1H, d, J = 8.6 Hz, H-4), 7.17 (1H, m, H-3′ or H-5′), 7.06 (1H, d, J = 2.2 Hz, H-7), 6.92 (1H, m, H-3′ or H-5′), 6.84 (1H, s, =CH–), 6.83 (1H, dd, J = 8.6, 2.2 Hz, H-5), 6.32 (1H, m, H-4′), 3.91 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 180.5, 166.7, 166.5, 143.7, 124.9, 124.9, 124.3, 116.5, 115.0 112.2, 111.3, 103.8, 96.9, 56.2. MS (EI) m/z: 241 $[M]^+$. *Anal.* Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.81; H, 4.65; N, 5.86.

(2*Z*)-6-Methoxy-2-[(1-methyl-1*H*-pyrrol-2-yl)methylene]-3(2*H*)-benzofuranone (2c) Yield 49%. mp 217–218 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.65 (1H, d, J = 8.6 Hz, H-4), 7.13 (1H, m, H-3′ or H-5′), 7.12 (1H, d, J = 2.2 Hz, H-7), 7.08 (1H, dd, J = 3.9, 1.6 Hz, H-3′ or H-5′), 6.84 (1H, dd, J = 8.6, 2.2 Hz, H-5), 6.83 (1H, s, =CH–), 6.29 (1H, m, H-4′), 3.92 (3H, s, CH_3), 3.79 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 180.5, 166.8, 166.6, 144.2, 128.4, 125.6, 125.0, 117.1, 114.9, 112.3, 110.0, 101.3, 97.0, 56.3, 33.8. MS (EI) m/z: 255 $[M]^+$. *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.60; H, 5.21; N, 4.54.

(2*Z*)-6-Methoxy-2-(1*H*-indol-2-ylmethylene)-3(2*H*)-benzofuranone (3c) Yield 46%. mp 223–224 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.34 (1H, s, NH), 7.75 (1H, d, J = 8.6 Hz, H-4), 7.64 (1H, dd, J = 8.0, 1.0 Hz, H-4′), 7.60 (1H, dd, J = 8.3, 1.0 Hz, H-7′), 7.40 (1H, s, =CH–), 7.27 (1H, ddd, J = 8.3, 7.0, 1.0 Hz, H-6′), 7.15 (1H, s, H-3′), 7.08 (1H, ddd, J = 8.0, 7.0, 1.0 Hz, H-5′), 7.06 (1H, d, J = 2.1 Hz, H-7), 6.88 (1H, dd, J = 8.6, 2.1 Hz, H-5), 3.93 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 180.6, 167.6, 167.1, 147.1, 137.2, 131.5, 128.0, 125.6, 124.9, 121.0, 120.2, 115.4, 113.0, 112.7, 112.1, 111.2, 96.5, 56.5. MS (EI) m/z: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.24; H, 4.59; N, 4.75.

(2*Z*)-6-Methoxy-2-(1*H*-indol-3-ylmethylene)-3(2*H*)-benzofuranone (4c) Yield 33%. mp 214–215 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.07 (1H, s, NH), 8.23 (1H, s, H-2′), 8.06 (1H, brd, J = 8.0 Hz, H-4′), 7.67 (1H, d, J = 8.5 Hz, H-4), 7.51 (1H, brd, J = 8.0 Hz, H-7′), 7.28–7.19 (2H, m, H-5′, H-6′), 7.24 (1H, s, =CH–), 7.17 (1H, d, J = 2.2 Hz, H-7), 6.85 (1H, dd, J = 8.5, 2.2 Hz, H-5), 3.94 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 180.3, 166.7, 166.5, 145.0, 136.3, 131.6, 126.6, 125.0, 122.7, 120.9, 119.1, 115.3, 112.3, 112.2, 108.3, 106.0, 97.0, 56.3. MS (EI) m/z: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.47; H, 4.59; N, 4.77.

(2*Z*)-6-Methoxy-2-(1*H*-indol-4-ylmethylene)-3(2*H*)-benzofuranone (5c) Yield 52%. mp 257–258 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.43 (1H, s, NH), 8.00 (1H, d, J = 7.5 Hz, H-5′), 7.74 (1H, d, J = 8.6 Hz, H-4), 7.56–7.52 (2H, m, H-2′, H-7′), 7.27 (1H, t, J = 7.8 Hz, H-6′), 7.21 (1H, d, J = 2.1 Hz, H-7), 7.19 (1H, s, =CH–), 6.88 (1H, dd, J = 8.6, 2.1 Hz, H-5), 6.85 (1H, m, H-3′), 3.95 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.3, 167.6, 167.0, 147.0, 135.9, 128.7, 126.8, 125.2, 122.4, 121.9, 121.2, 113.9, 113.5, 112.5, 108.6, 99.3, 97.0, 56.2. MS (EI) m/z: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.29; H, 4.54; N, 4.83.

(2*Z*)-6-Methoxy-2-(1*H*-indol-5-ylmethylene)-3(2*H*)-benzofuranone (6c) Yield 35%. mp 243–244 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.41 (1H, s, NH), 8.24 (1H, brs, H-4′), 7.78 (1H, dd, J = 8.5, 1.7 Hz, H-6′), 7.68 (1H, d, J = 8.5 Hz, H-4), 7.51 (1H, d, J = 8.5 Hz, H-7′), 7.44 (1H, m, H-2′), 7.18 (1H, d, J = 2.1 Hz, H-7), 6.97 (1H, s, =CH–), 6.86 (1H, dd, J = 8.5, 2.1 Hz, H-5), 6.56 (1H, m, H-3′), 3.94 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 182.0, 168.2, 167.6, 146.3, 137.4, 128.8, 127.6, 125.9, 125.4, 125.2, 123.5, 115.0, 114.7, 113.2, 112.7, 102.8, 97.7, 57.0. MS (EI) m/z: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.24; H, 4.67; N, 4.59.

(2*Z*)-6-Methoxy-2-(1*H*-indol-6-ylmethylene)-3(2*H*)-benzofuranone (7c) Yield 62%. mp 229–230 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.47 (1H, s, NH), 8.05 (1H, brs, H-7′), 7.73–7.68 (2H, m, H-4, H-5′), 7.65 (1H, d, J = 8.3 Hz, H-4′), 7.53 (1H, t, J = 2.7 Hz, H-2′), 7.13 (1H, d, J = 2.1 Hz, H-7), 7.00 (1H, s, =CH–), 6.88 (1H, dd, J = 8.6, 2.1 Hz, H-5), 6.51 (1H, m, H-3′), 3.95 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.6, 167.8, 167.2, 146.2, 136.3, 129.5, 128.9, 125.5, 124.9, 122.5, 120.7, 115.6, 114.6, 114.1, 112.7, 101.9, 97.2, 56.6. MS (EI) m/z: 291 $[M]^+$. *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.17; H, 4.58; N, 4.90.

(2*Z*)-6-Methoxy-2-[(1-methyl-1*H*-indol-3-yl)methylene]-3(2*H*)-benzofuranone (8c) Yield 56%. mp 202–204 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.25 (1H, s, H-2′), 8.06 (1H, brd, J = 7.8 Hz, H-4′), 7.67 (1H, d, J = 8.5 Hz, H-4), 7.57 (1H,

brd, $J=8.1$ Hz, H-7′), 7.31 (1H, ddd, $J=8.1$, 7.0, 1.2 Hz, H-6′), 7.24 (1H, ddd, $J=7.8$, 7.0, 1.1 Hz, H-5′), 7.23 (1H, s, =CH–), 7.13 (1H, d, $J=2.1$ Hz, H-7), 6.85 (1H, dd, $J=8.5$, 2.1 Hz, H-5), 3.94 (6H, CH_3, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 179.5, 166.0, 165.9, 144.3, 136.2, 134.4, 126.5, 124.4, 122.1, 120.5, 118.5, 114.7, 111.6, 110.0, 106.7, 104.9, 96.2, 55.6, 32.6. MS (EI) *m/z*: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.74; H, 5.02; N, 4.34.

(2*Z*)-6-Methoxy-2-[(1-methyl-1*H*-indol-4-yl)methylene]-3(2*H*)-benzofuranone (9c) Yield 72%. mp 207–209 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.02 (1H, brd, $J=7.7$ Hz, H-5′), 7.72 (1H, d, $J=8.6$ Hz, H-4), 7.57 (1H, brd, $J=8.2$ Hz, H-7′), 7.50 (1H, d, $J=3.2$ Hz, H-2′), 7.32 (1H, t, $J=7.8$ Hz, H-6′), 7.19 (1H, d, $J=2.1$ Hz, H-7), 7.16 (1H, s, =CH–), 6.87 (1H, dd, $J=8.6$, 2.1 Hz, H-5), 6.83 (1H, dd, $J=3.2$, 0.9 Hz, H-3′), 3.94 (3H, s, CH_3), 3.84 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.7, 168.1, 167.5, 147.5, 136.8, 131.4, 129.4, 125.7, 123.1, 122.4, 121.6, 114.3, 112.9, 112.2, 108.6, 98.9, 97.4, 56.7, 32.9. MS (EI) *m/z*: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.62; H, 5.03; N, 4.62.

(2*Z*)-6-Methoxy-2-[(1-methyl-1*H*-indol-5-yl)methylene]-3(2*H*)-benzofuranone (10c) Yield 27%. mp 145–146 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.24 (1H, d, $J=1.7$ Hz, H-4′), 7.82 (1H, dd, $J=8.7$, 1.7 Hz, H-6′), 7.69 (1H, d, $J=8.5$ Hz, H-4), 7.56 (1H, brd, $J=8.7$ Hz, H-7′), 7.43 (1H, d, $J=3.1$ Hz, H-2′), 7.19 (1H, d, $J=2.1$ Hz, H-7), 6.97 (1H, s, =CH–), 6.86 (1H, dd, $J=8.5$, 2.1 Hz, H-5), 6.56 (1H, dd, $J=3.1$, 0.9 Hz, H-3′), 3.94 (3H, s, CH_3), 3.84 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.0, 167.2, 166.6, 145.3, 136.6, 130.8, 128.0, 124.8, 124.4, 124.2, 122.5, 113.9, 113.4, 112.1, 110.0, 101.1, 96.6, 55.9, 32.2. MS (EI) *m/z*: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.49; H, 5.00; N, 4.66.

(2*Z*)-6-Methoxy-2-[(1-methyl-1*H*-indol-6-yl)methylene]-3(2*H*)-benzofuranone (11c) Yield 56%. mp 212–214 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.07 (1H, brs, H-7′), 7.77 (1H, dd, $J=8.3$, 1.5 Hz, H-5′), 7.70 (1H, d, $J=8.6$ Hz, H-4), 7.66 (1H, d, $J=8.3$, H-4′), 7.53 (1H, d, $J=3.0$ Hz, H-2′), 7.21 (1H, d, $J=2.1$ Hz, H-7), 7.00 (1H, s, =CH–), 6.86 (1H, dd, $J=8.6$, 2.1 Hz, H-5), 6.51 (1H, dd, $J=3.0$, 0.9 Hz, H-3′), 3.95 (3H, s, CH_3), 3.87 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 188.3, 174.6, 174.0, 153.0, 143.4, 139.6, 136.4, 132.2, 131.7, 129.0, 127.7, 121.2, 120.7, 120.5, 119.5, 107.9, 104.0, 63.3, 39.5. MS (EI) *m/z*: 305 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.77; H, 5.01; N, 4.65.

(2*Z*)-5,6-Dimethoxy-2-(1*H*-indol-2-ylmethylene)-3(2*H*)-benzofuranone (3d) Yield 54%. mp 278–279 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.40 (1H, s, NH), 7.63 (1H, brd, $J=8.0$ Hz, H-4′), 7.50 (1H, brd, $J=8.3$ Hz, H-7′), 7.25–7.19 (4H, m, H-3′, H-4, H-6′, H-7), 7.07 (1H, ddd, $J=8.0$, 7.0, 1.0 Hz, H-5′), 6.94 (1H, s, =CH–), 3.98 (3H, s, CH_3), 3.83 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.1, 162.3, 157.5, 146.6, 146.5, 137.9, 130.6, 128.3, 123.8, 121.0, 120.1, 112.5, 111.8, 108.8, 103.9, 102.6, 96.4, 56.6, 56.1. MS (EI) *m/z*: 321 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.76; H, 4.84; N, 4.07.

(2*Z*)-5,6-Dimethoxy-2-(1*H*-indol-3-ylmethylene)-3(2*H*)-benzofuranone (4d) Yield 27%. mp 277–278 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.06 (1H, s, NH), 8.19 (1H, s, H-2′), 8.05 (1H, brd, $J=7.9$ Hz, H-4′), 7.50 (1H, brd, $J=7.9$ Hz, H-7′), 7.27–7.16 (5H, m, H-4, H-5′, H-6′, H-7, =CH–), 3.95 (3H, s, CH_3), 3.82 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 180.7, 161.4, 156.9, 146.2, 145.1, 136.3, 131.4, 126.6, 122.7, 120.8, 119.1, 113.2, 112.2, 108.4, 105.8, 103.7, 96.4, 56.5, 56.0. MS (EI) *m/z*: 321 $[M]^+$. *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.98; H, 4.81; N, 4.14.

(2*Z*)-5,6-Dimethoxy-2-[(1-methyl-1*H*-indol-4-yl)-methylene]-3(2*H*)-benzofuranone (9d) Yield 51%. mp 232–234 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.01 (1H, brd, $J=7.5$ Hz, H-5′), 7.57 (1H, brd, $J=8.2$ Hz, H-7′), 7.50 (1H, d, $J=3.1$ Hz, H-2′), 7.32 (1H, t, $J=7.8$ Hz, H-6′), 7.28 (1H, s, H-4), 7.22 (1H, s, H-7), 7.16 (1H, s, =CH–), 6.84 (1H, dd, $J=3.1$, 0.9 Hz, H-3′), 3.96 (3H, s, CH_3), 3.85 (3H, s, CH_3), 3.83 (3H, s, CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 181.8, 162.7, 157.6, 147.5, 146.5, 136.6, 131.2, 129.2, 123.0, 122.1, 121.4, 112.1, 111.9, 108.2, 104.0, 98.7, 96.6, 56.7, 56.0, 32.7. MS (EI) *m/z*: 335 $[M]^+$. *Anal.* Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.60; H, 5.15; N, 4.05.

Measurement of MAO Inhibitory Activity The MAO inhibitory activity was assayed according to previously reported methods. 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 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 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 adding 75 μL of 2 M NaOH. The fluorescent product generated by MAO, 4-quinolinol, 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 represents an average of three experiments. The sample solution was replaced with DMSO as a negative 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 Five Lineweaver–Burk plots were constructed to inhibit MAO-A by compound **3b** and MAO-B by compound **4c**. The first plot was constructed in the absence of the inhibitor. In contrast, the remaining four plots were constructed in the presence of various concentrations of the test inhibitor: 1/4× IC_{50}, 1/2× IC_{50}, 1× IC_{50}, and 2× the IC_{50} ($IC_{50}=21$ nM for compound **3b** and 16 nM for compound **4c**). The enzyme-substrate, kynuramine, was used at concentrations ranging from 7.5 to 120 μM.

Calculation of Chemical Descriptors Each three-dimensional chemical structure (Marvin Sketch version 16; ChemAxon, Budapest, Hungary, http://www.chemaxon.com) was optimized using CORINA Classic (Molecular Networks GmbH, Nürnberg, Germany) with force field calculations (amber-10: EHT) in the Molecular Operating Environment (MOE) version 2018.0101 (Chemical Computing Group Inc., Quebec, Canada).[11] Chemical descriptors were calculated using MOE and Mordred version 1.2.0 (Python Library) based on the optimal 3D structures. The numbers of structural descriptors calculated from MOE and Mordred[12] were 354 and

1826, respectively, duplicated and containing missing values and outliers were excluded from this analysis; in total, 1427 descriptors were used for analysis.

Docking Analyses The docking studies were performed on MAO-A (PDB code 2Z5X) and MAO-B (PDB code 4A79) employing the Dock induced-fit methodology within MOE (MOE-Dock). Utilizing the amber 10:eht force field, the binding affinity scoring function was calculated, with triangle matcher for placement and GBVI/WSA dG as the scoring method.[28] For protein preparation, especially concerning charged residues within the binding pocket, the Protonate 3D feature of MOE was invoked to establish ionization states and introduce hydrogens.[29] This Protonate 3D tool aids in designating ionization states and situating hydrogens based on the crystal structure's 3D coordinates.

Statistical Analysis The relationships between the chemical descriptors and MAO-related properties were investigated using Pearson's correlation analysis. Statistical calculations were performed using JMP Pro version 15.0.0 (SAS Institute Inc., Cary, NC, U.S.A.), with significance set at $p < 0.05$.

Conflict of Interest The authors declare no conflict of interest.

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