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新型取代查尔酮-哌嗪衍生物的合成及其生物活性评价

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摘要 为了寻找结构新颖的活性分子, 采用活性亚结构拼接的方法, 设计合成了 24 个未见文献报道的取代查尔酮-哌嗪衍生物, 其结构经 ^{1}H NMR、^{13}C NMR 和 HRMS 确证. 分别采用小鼠巨噬细胞 Raw 264.7 炎症模型和噻唑蓝(MTT)法对目标化合物的体外抗炎活性和细胞毒活性进行测试, 结果表明, 查尔酮母核和哌嗪环上的取代基对化合物的生物活性有明显影响. 特别是 3,4,5-三甲氧基-4'-[*N*-(2-氧代丙基)-1-哌嗪基]查尔酮(**11**)能有效抑制 NO 的生成(IC_{50}=3.81 μmol/L), 4-溴-4'-[*N*-(4'-甲基-2-氧代苯乙基)-1-哌嗪基]查尔酮(**25**)对三种肿瘤细胞株(Hela, A549 和 sk-ov-3)均表现出良好的体外细胞毒活性(IC_{50} 值分别为 0.54, 0.05 和 9.12 μmol/L).

关键词 查尔酮-哌嗪衍生物; 抗炎活性; 细胞毒活性

Synthesis and Biological Evaluation of Novel Substituted Chalcone-piperazine Derivatives

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Abstract A series of novel substituted chalcone-piperazine derivatives have been synthesized, and screened *in vitro* anti-inflammatory in lipopolysaccharide (LPS)-stimulated RAW-264.7 macrophages and cytotoxic activity against 3 strains human tumor cell lines. The results demonstrated that the substituents of the core ring and the NH group of piperazine ring had obvious influences on biological activities. Especially, 3,4,5-trimethoxy-4'-[*N*-(2-oxopropyl)-1-piperazinyl]chalcone (**11**) showed better inhibitory effect on the generation of NO (IC_{50}=3.81 μmol/L), and 4-bromo-4'-[*N*-(4'-methyl-2-oxophenylethyl)-1-piperazinyl]chalcone (**25**) displayed good cytotoxic activity against A549, Hela and sk-ov-3 (IC_{50}=0.54, 0.05 and 9.12 μmol/L, respectively).

Keywords chalcone-piperazine derivatives; anti-inflammatory activity; cytotoxic activity

1 Introduction

Chalcones, consisting of two aromatic rings through a three-carbon *α*,*β*-unsaturated carbonyl system, is an exceptional chemical template having important biological activities, including antitumor, anti-inflammatory, antioxidant, antimicrobial, anti-tubercular and antiplatelet properties.[1~5] The anti-inflammatory and anticancer activities of chalcones have been investigated extensively for more than several decades.[6~8]

Moreover, there were some reports describing the possible mechanistic basis of the cytotoxic or anti-inflammatory activity. Chalcones exert anticancer activities through multiple mechanisms including cell cycle disruption, inhibition

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of angiogenesis, induction of apoptosis and tubulin polymerization.[9~11] In addition, chalcone derivatives show anti-inflammatory properties by inhibition of secretory phospholipase A2 and COX, proinflammatory cytokines production, and production of reactive oxygen species (ROS).[12~14]

Literature on structure-activity relationship (SAR) analysis of chalcones highlights the employment of pronged strategies including structural modification of both aryl rings, replacement of aryl rings with heteroaryl scaffolds, and molecular hybridization through conjugation with other pharmacologically moieties. Recently, we have reported the synthesis of a series of novel hybrid compounds of chalcone and N-heterocycles and their potential anti-inflammatory and antitumor activities.[15] Especially, the hybrid compounds between chalcone and substituted piperazine displayed potential anti-tumor activities[16] (Figure 1).

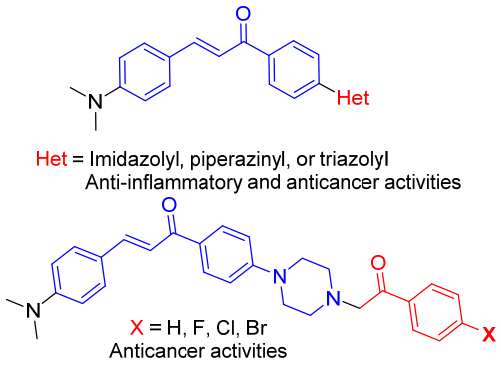
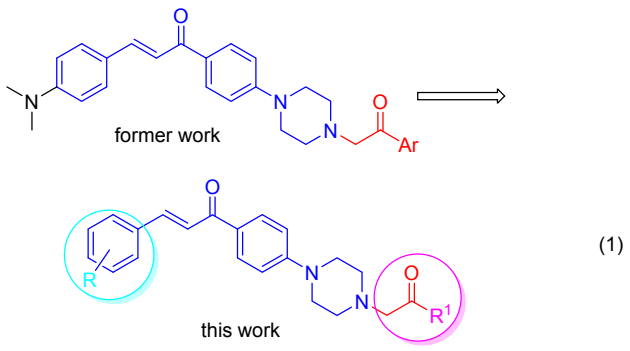


Figure 1 Synthetic biological chalcone compounds

In order to keep in view of the biological importance of chalcone-piperazine hybrids, we were interested in synthesizing a number of novel chalcone derivatives bearing various substituted groups on aryl rings. Herein, we reported the synthesis of a series of novel substituted chalcone-piperazine compounds. The design strategy of new compounds was shown in Eq. 1. These derivatives were evaluated for their *in vitro* anti-inflammatory activity in lipopolysaccharide (LPS)-stimulated RAW-264.7 macrophages and anti-tumor activity against a panel of human tumor cell lines by methyl thiazolyl tetrazolium (MTT) assay, with the aim of developing new potential biological active agents. We also discussed the preliminary SAR of anti-inflammatory and anti-tumor activities.

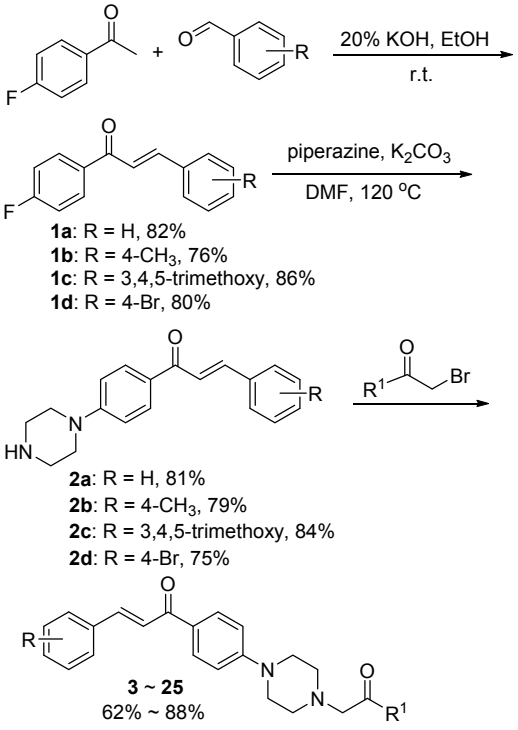


(1)

2 Results and discussion

2.1 Chemistry

The general synthetic route used to synthesize hybrid compounds is outlined in Scheme 1. Treatment of commercially substituted benzaldehyde with 4-fluoro acetophenone gave the chalcone compound **1** in the presence of 20% KOH in EtOH. Then, the key piperazine substituted chalcone intermediate **2** was prepared by substitution with piperazine from compound **1** in the presence of K_2CO_3 at 120 ℃ in *N*,*N*-dimetylformamide (DMF). Starting from desired intermediate **2**, a series of substituted chalcone-piperazine hybrids were synthesized by treatment of compound **2** with a number of available *α*-bromoketone or *α*-bromo ethyl acetate. In order to compare the biological activities and get further discuss toward the structure and activity relationship (SAR), various tertiary amines **3**~**25** were prepared. Comparative data for new hybrid derivatives with respective to structures, melting point and yield were provided in Table 1. All of the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS analysis as well.



Scheme 1 Synthetic routes of chalcone-piperazine compounds

1.2 Biological evaluation

1.2.1 Anti-inflammatory activity

In vitro anti-inflammatory activities of synthetic substituted chalcone-piperazine compounds were investigated in LPS-induced RAW 264.7 on the generation of NO.[17] The results of title compounds were summarized in Table 2. As shown in Table 2, the substituents of the core ring and the NH group of piperazine ring had an obvious influence

Table 1 Structures and yields of compounds

Compd.	R	R^1	m.p.[a]/℃	Yield[b]/%
3	H	Ethoxy	147～149	90
4	H	CH_3	168～170	82
5	H	Phenyl	177～179	76
6	H	4-Fluorophenyl	186～188	69
7	H	4-Chlorophenyl	196～198	73
8	H	4-Bromophenyl	174～176	81
9	H	4-Methylphenyl	172～174	78
10	3,4,5-Trimethoxy	Ethoxy	138～140	92
11	3,4,5-Trimethoxy	CH_3	153～155	84
12	3,4,5-Trimethoxy	Phenyl	168～170	70
13	3,4,5-Trimethoxy	4-Fluorophenyl	181～183	66
14	3,4,5-Trimethoxy	4-Chlorophenyl	169～171	72
15	3,4,5-Trimethoxy	4-Bromophenyl	153～155	83
16	3,4,5-Trimethoxy	4-Methylphenyl	141～143	66
17	3,4,5-Trimethoxy	4-Methoxyphenyl	132～134	84
18	3,4,5-Trimethoxy	2-Naphthyl	177～179	60
19	4-CH_3	Ethoxy	141～143	85
20	4-CH_3	CH_3	165～167	84
21	4-CH_3	Phenyl	173～175	65
22	4-CH_3	4-Methylphenyl	199～201	72
23	4-Br	Ethoxy	182～184	88
24	4-Br	CH_3	204～206	83
25	4-Br	4-Methylphenyl	180～182	76

[a] Melting point was uncorrected. [b] Yields represented isolated yields.

Table 2 Anti-inflammatory activities of compounds[a]

Compd.	IC_{50}/(mol•L^{-1})	Compd.	IC_{50}/(μmol•L^{-1})
3	＞50	**15**	16.38
4	9.43	**16**	6.26
5	32.07	**17**	19.25
6	15.88	**18**	＞50
7	25.58	**19**	＞50
8	＞50	**20**	11.85
9	＞50	**21**	36.04
10	＞50	**22**	＞50
11	3.81	**23**	＞50
12	7.47	**24**	25.24
13	18.30	**25**	13.80
14	9.53		

[a] Values represent the concentration required to produce 50% inhibition of the response.

on anti-inflammatory activities. To our delight, replacement of electron-donating group increased the anti-inflammatory activity (trimethoxy), and the substituents of NH group had an obvious influence against the generation of NO. On the whole, methyl ketone substituent contributed to better activity, but aryl ketone substituents led to weaker activity (CH_3COCH_2＞$ArCOCH_2$). For example, compounds **4**, **11**, **12**, **14** and **16** showed satisfied anti-inflammatory activity on the generation of NO (IC_{50}＜10 μmol/L). In addition, compounds **6**, **13**, **15**, **17**, **20** and **25** displayed potent anti-inflammatory activity (IC_{50}＜20 μmol/L). Among all synthetic compounds, hybrid **11** was found to be the most potent anti-inflammatory agent (IC_{50}＝3.81 μmol/L).

1.2.2 Cytotoxic activity

Cytotoxic activity of novel synthesized derivatives was evaluated against human lung cancer cell line A549, human cervical carcinoma Hela, human ovarian cancer cell line sk-ov-3 and human normal liver cell L02 by MTT assay, using cisplatin as the reference drug.[18] The anti-tumor results of hybrids were summarized in Table 3.

From the activity data, we could observed that the structures of compounds had an obvious influence on anticancer activities. There were four series of substituents of core benzene ring, including H, methyl, trimethoxy and Br. To explore the structure-activity relationships (SAR), various substituents (CH_3COCH_2, $CH_2CO_2C_2H_5$ and $ArCOCH_2$) were introduced into the NH group. In generally, derivatives containing halide exhibited more sensitive to anticancer activities on three tested cancer cell lines. For example, compounds **6**, **7**, **8**, **14**, **15**, **21**, **24** and **25** showed selected anticancer activity against tumor cell lines. Among all synthesized derivatives, compound **8** displayed the best inhibitory activity for A549 (IC_{50}＝0.18 μmol/L), compound **25** showed the most potent cytotoxic activity against Hela (IC_{50}＝0.05 μmol/L) and compound **23** displayed the best antitumor activity for sk-ov-3 (IC_{50}＝0.37 μmol/L), respectively. Moreover, to compare the anticancer activity of cancer cells and normal cells, we evaluated the cytotoxic activity of compounds against human normal liver cell L02. According to the result, it is found that most hybrids were non-sensitive to L02. Compound **25** showed most cytotoxic

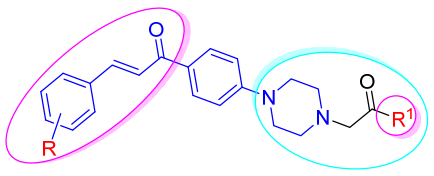
Table 3 *In vitro* cytotoxic activities [IC_{50}/(μmol•L^{-1})] of title compounds[a]

Compd.	A549	Hela	sk-ov-3	L02
3	＞50	＞50	＞50	＞50
4	＞50	＞50	＞50	＞50
5	＞50	＞50	＞50	＞50
6	＞50	14.13±1.22	12.07±1.28	＞50
7	2.35±0.24	0.39±0.02	3.16±0.64	＞50
8	0.18±0.03	＞50	19.74±1.72	＞50
9	＞50	13.76±1.54	＞50	24.27±1.92
10	＞50	＞50	＞50	＞50
11	＞50	＞50	＞50	＞50
12	＞50	8.14±1.16	＞50	＞50
13	＞50	18.23±2.02	19.81±1.86	＞50
14	＞50	0.45±0.04	0.92±0.20	28.08±3.02
15	3.83±0.91	1.06±0.27	12.60±1.32	23.22±1.66
16	＞50	0.06±0.01	34.62±3.85	＞50
17	＞50	18.93±1.82	＞50	＞50
18	＞50	＞50	＞50	＞50
19	＞50	＞50	＞50	＞50
20	＞50	＞50	＞50	＞50
21	5.15±0.57	2.31±0.42	9.55±1.12	＞50
22	＞50	＞50	＞50	＞50
23	＞50	＞50	0.37±0.04	＞50
24	12.36±0.98	1.74±0.34	5.52±0.66	3.82±0.44
25	0.54±0.11	0.05±0.01	9.12±1.26	33.24±2.72
Cisplatin	11.54±1.15	20.52±1.84	5.68±0.82	＞50

[a] Cytotoxicity as IC_{50} values for each cell line, the concentration of compound that inhibit 50% of the cell growth measured by MTT assay.

activity (IC_{50}=3.82 μmol/L), and compounds **9**, **14** and **15** had weak inhibitory activity for L02 (IC_{50}＜30 μmol/L).

The biological results suggested that existence of substituents played an important role in the anti-inflammatory and cytotoxic activity of compounds. On one hand, electron-donating groups of phenyl ring had better inhibitory effect on the generation of NO, and 4-Br substituent exhibited more potent cytotoxic activity. On the other hand, the substituents of the NH group of piperazine ring also had an obvious influence on biological activities. Especially, CH_3COCH_2 group contributed better anti-inflammatory activity, and $ArCOCH_2$ led to potent anticancer activity. On the whole, the compounds bearing 4-Br (R) and Ar (R^1) led to better anticancer activity, and the compounds bearing R (trimethoxy) and methyl (R^1) contributed to better anti-inflammatory activity. The structure-activity relationship (SAR) results were summarized in Figure 2.



R = Br, R^1 = Ar: better cytotoxic activity
R = trimethoxy, R^1 = CH_3: better anti-inflammatory activity

Figure 2 Structure-activity relationship of title compounds

3 Conclusions

In summary, a series of novel substituted chalcone-piperazine derivatives have been synthesized and screened *in vitro* anti-inflammatory and cytotoxic activity. The results demonstrated that the substituents of the core ring and the NH group of piperazine ring had an obvious influence on biological activities. Especially, derivative **11** showed better inhibitory effect on the generation of NO (IC_{50}=3.81 μmol/L), and compound **25** displayed good cytotoxic activity against A549 and Hela (IC_{50}=0.54 and 0.05 μmol/L, respectively), which was considered as the most potent active agents. Further research is currently undergoing and the results will be reported in due course.

4 Experimental

4.1 General considerations

Starting materials were analytically pure. Melting points were measured on a YANACO microscopic melting point meter and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 400 spectrometer (Bruker, Switzerland), using TMS as internal standard and $CDCl_3$ as solvent, respectively. Thin layer chromatographic (TLC) analysis was carried out on silica gel plates GF_{254}. High-resolution mass spectra were performed on an ESI Q-TOF MS spectrometer (Agilent, America).

3.2 Synthesis

3.2.1 General procedure for the synthesis of compounds **1a**～**1d**

To a solution of EtOH (20 mL), ArCHO (10 mmol) and 4-fluoroacetophenone (1.38 g, 10 mmol), was added 20% KOH (15 mL), and the mixture was left to react at room temperature overnight. The reaction was quenched by the addition of water (30 mL), the mixture was filtrated and the solid was dried to afford products. The characterization data of compounds **1a**～**1d** was the same to References [19～21].

3.2.2 General procedure for the preparation of compounds **2a**～**2d**

To a stirred solution of the compound **1** (10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in dried *N*,*N*-dimethylformamide (DMF) (30 mL), piperazine (1.72 g, 20 mmol) was added and reaction mixture was stirred for 12 h at 120 ℃. After completion of the reaction as indicated by thin-layer chromatography (TLC), the reaction solution was cooled and quenched by the addition of dichloromethane (DCM) (50 mL). The organic layer was washed with water (20 mL×3) and dried by anhydrous sodium sulfate, concentrated *in vacuo* and purified by column chromatography to afford compounds.

3.2.3 General procedure for the preparation of hybrid derivatives **3**～**25**

To a stirred solution of compound **2** (0.1 g) and K_2CO_3 (0.2 g) in dried DCM (10 mL), RX (1 mmol) was added and the reaction mixture was stirred for 5～24 h at room tem-

perature. After completion of the reaction as indicated by TLC, the reaction was quenched by the addition of 5% NaOH (20 mL) and was extracted with DCM (10 mL×3). The organic layer was dried using anhydrous sodium sulfate, concentrated in vacuo and purified by column chromatography (1% MeOH/DCM) to afford title products.

4'-(1-Piperazinyl)chalcone (**2a**): Pale yellow solid, m.p. 151～153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J=8.9 Hz, 2H), 7.86 (dd, J=3.2, 2.2 Hz, 1H), 7.83 (d, J=15.6 Hz, 1H), 7.66 (d, J=8.0 Hz, 2H), 7.60 (d, J=15.6 Hz, 1H), 7.42 (d, J=8.9 Hz, 2H), 6.93 (d, J=9.0 Hz, 2H), 3.33～3.35 (m, 4H), 3.01～3.03 (m, 4H), 2.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.1, 154.5, 154.1, 143.1, 135.4, 130.7, 130.2, 130.1, 128.9, 128.3, 122.1, 113.5, 50.1, 48.4, 45.8; HRMS (ESI-TOF) calcd for $C_{19}H_{21}N_2O$ $(M+H)^+$ 293.1648, found 293.1648.

4-Methyl-4'-(1-piperazinyl)chalcone (**2b**): Yellow solid, m.p. 159～161 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (dd, J=2.0, 7.1 Hz, 2H), 7.77 (d, J=15.6 Hz, 1H), 7.50～7.54 (m, 3H), 7.20 (d, J=8.0 Hz, 2H), 6.90 (dd, J=1.9, 7.2 Hz, 2H), 3.32 (t, J=5.0 Hz, 4H), 3.02 (t, J=5.2 Hz, 4H), 2.38 (s, 3H), 1.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.3, 154.6, 143.3, 140.6, 132.7, 130.7, 129.7, 128.5, 128.4, 121.1, 113.6, 48.6, 46.0, 21.6; HRMS (ESI-TOF) calcd for $C_{20}H_{23}N_2O$ $(M+H)^+$ 307.1805, found 307.1806.

3,4,5-Trimethoxy-4'-(1-piperazinyl)chalcone (**2c**): Yellow solid, m.p. 162～164 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=8.8 Hz, 2H), 7.69 (d, J=15.5 Hz, 1H), 7.42 (d, J=15.5 Hz, 1H), 6.91 (d, J=8.7 Hz, 2H), 6.85 (s, 2H), 3.91 (s, 9H), 3.90 (s, 3H), 3.89 (s, 3H), 3.34 (t, J=4.8 Hz, 4H), 3.03 (t, J=5.2 Hz, 4H), 2.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.1, 154.6, 153.6, 143.4, 131.0, 130.8, 128.4, 121.5, 113.6, 105.7, 61.1, 56.3, 48.5, 45.9; HRMS (ESI-TOF) calcd for $C_{22}H_{27}N_2O_4$ $(M+H)^+$ 383.1965, found 383.1962.

4-Bromo-4'-(1-piperazinyl)chalcone (**2d**): Pale yellow solid, m.p. 187～189 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (dd, J=1.9, 7.1 Hz, 2H), 7.69 (d, J=15.6 Hz, 1H), 7.46～7.55 (m, 5H), 6.89 (d, J=9.0 Hz, 2H), 3.33 (t, J=5.0 Hz, 4H), 3.01 (t, J=5.1 Hz, 4H), 1.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.7, 154.6, 141.7, 134.4, 132.2, 130.8, 129.7, 128.0, 124.3, 122.7, 113.6, 113.5, 113.4, 48.4, 45.9; HRMS (ESI-TOF) calcd for $C_{19}H_{20}BrN_2O$ $(M+H)^+$ 371.0754, found 371.0754.

4'-[*N*-(2-Oxo-2-ethoxyethyl)-1-piperazinyl]chalcone (**3**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, J=8.6 Hz, 2H), 7.78 (d, J=15.6 Hz, 1H), 7.63 (dd, J=1.6, 7.3 Hz, 2H), 7.55 (d, J=15.6 Hz, 1H), 7.39 (d, J=6.4 Hz, 3H), 6.90 (d, J=8.8 Hz, 2H), 4.23 (q, J=7.1 Hz, 2H), 3.43 (t, J=4.6 Hz, 4H), 3.27 (s, 2H), 2.74 (t, J=4.7 Hz, 4H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.1, 170.1, 154.1, 143.2, 135.4, 130.8, 130.2, 129.0, 128.5, 128.4, 122.2, 113.7, 60.9, 59.4, 52.7, 47.3, 14.4; HRMS (ESI-TOF) calcd for $C_{23}H_{27}N_2O_3$ $(M+H)^+$ 379.2013, found 379.2016.

4'-[*N*-(2-Oxopropyl)-1-piperazinyl]chalcone (**4**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=8.8 Hz, 2H), 7.78 (d, J=15.6 Hz, 1H), 7.63 (dd, J=2.2 Hz, 7.8 Hz, 2H), 7.55 (d, J=15.6 Hz, 1H), 7.39 (d, J=6.4 Hz, 3H), 6.90 (d, J=8.9 Hz, 2H), 3.42 (t, J=4.9 Hz, 4H), 3.27 (s, 2H), 2.65 (t, J=5.0 Hz, 4H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 188.2, 154.1, 143.3, 135.4, 130.8, 130.2, 129.0, 128.5, 128.4, 122.1, 113.7, 68.0, 53.0, 47.2, 27.9; HRMS (ESI-TOF) calcd for $C_{22}H_{25}N_2O_2$ $(M+H)^+$ 349.1911, found 349.1912.

4'-[*N*-(2-Oxophenylethyl)-1-piperazinyl]chalcone (**5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99～8.03 (m, 4H), 7.79 (d, J=15.6 Hz, 1H), 7.64 (dd, J=2.2, 7.7 Hz, 2H), 7.54～7.59 (m, 2H), 7.47 (t, J=7.9 Hz, 2H), 7.99～8.03 (m, 4H), 7.39～7.41 (m, 3H), 6.92 (d, J=9.1 Hz, 2H), 3.90 (s, 2H), 3.47 (t, J=5.0 Hz, 4H), 2.78 (t, J=5.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.2, 188.2, 154.2, 143.3, 136.1, 135.5, 133.6, 130.8, 130.2, 129.0, 128.8, 128.5, 128.4, 128.2, 122.2, 113.7, 64.4, 53.2, 47.4; HRMS (ESI-TOF) calcd for $C_{27}H_{27}N_2O_2$ $(M+H)^+$ 411.2068, found 411.2067.

4'-[*N*-(4'-Fluoro-2-oxophenylethyl)-1-piperazinyl]chalkone (**6**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04～8.08 (dd, J=5.4, 9.0 Hz, 2H), 7.99 (d, J=9.0 Hz, 2H), 7.78 (d, J=15.6 Hz, 1H), 7.63 (dd, J=2.2, 7.6 Hz, 2H), 7.55 (d, J=15.6 Hz, 1H), 7.38～7.40 (m, 3H), 7.13 (t, J=8.7 Hz, 2H), 6.91 (d, J=9.1 Hz, 2H), 3.84 (s, 2H), 3.44 (t, J=5.0 Hz, 4H), 2.75 (t, J=5.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.7, 188.2, 167.3, 164.7, 154.1, 143.3, 135.4, 132.4, 131.1, 131.0, 130.2, 129.0, 128.5, 128.4, 122.1, 116.0, 115.8, 113.7, 64.4, 53.2, 47.3; HRMS (ESI-TOF) calcd for $C_{27}H_{26}N_2O_2F$ $(M+H)^+$ 429.1973, found 429.1971.

4'-[*N*-(4'-Chloro-2-oxophenylethyl)-1-piperazinyl]chalcone (**7**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94～7.99 (m, 4H), 7.77 (d, J=15.6 Hz, 1H), 7.62 (dd, J=1.5, 7.2 Hz, 2H), 7.54 (d, J=15.6 Hz, 1H), 7.37～7.43 (m, 5H), 6.89 (d, J=8.9 Hz, 2H), 3.82 (s, 2H), 3.41 (t, J=4.3 Hz, 4H), 2.73 (t, J=4.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.1, 188.1, 154.1, 143.3, 140.0, 135.4, 134.2, 130.8, 130.2, 129.8, 129.0, 129.0, 128.5, 128.4, 122.1, 113.7, 64.4, 53.1, 47.3; HRMS (ESI-TOF) calcd for $C_{27}H_{26}ClN_2O_2$ $(M+H)^+$ 445.1677, found 445.1678.

4'-[*N*-(4'-Bromo-2-oxophenylethyl)-1-piperazinyl]chalcone (**8**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, J=8.9 Hz, 2H), 7.88 (d, J=8.6 Hz, 2H), 7.78 (d, J=15.6 Hz, 1H), 7.54～7.64 (m, 5H), 7.37～7.41 (m, 3H), 6.90 (d, J=9.0 Hz, 2H), 3.83 (s, 2H), 3.44 (t, J=4.8 Hz, 4H), 2.75 (t, J=5.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.3, 188.1, 154.1, 143.3, 135.4, 134.6, 132.0, 130.8, 130.2, 129.9, 129.0, 128.7, 128.5, 128.4, 122.1, 113.7, 64.4, 53.1, 47.3; HRMS (ESI-TOF) calcd for $C_{27}H_{25}BrN_2O_2Na$ $(M+Na)^+$ 511.0992, found 511.0996.

4'-[*N*-(4'-Methyl-2-oxophenylethyl)-1-piperazinyl]chalcone (**9**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=9.0 Hz, 2H), 7.91 (d, J=8.2 Hz, 2H), 7.79 (d, J=15.6 Hz, 1H), 7.64 (dd, J=2.2, 7.8 Hz, 2H), 7.56 (d, J=15.6 Hz, 1H), 7.39～7.41 (m, 3H), 7.26 (d, J=8.0 Hz, 2H), 6.92 (d, J=9.0 Hz, 2H), 3.86 (s, 2H), 3.46 (t, J=4.9 Hz, 4H), 2.77 (t, J=5.0 Hz, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 188.2, 154.2, 144.4, 143.2, 135.5, 133.6, 130.8,

130.2, 129.4, 129.0, 128.4, 128.4, 128.3, 122.2, 113.7, 64.2, 53.2, 47.3, 21.8; HRMS (ESI-TOF) calcd for $C_{28}H_{29}N_2O_2$ $(M+H)^+$ 425.2220, found 425.2224.

3,4,5-Trimethoxy-4'-[*N*-(2-oxo-2-ethoxyethyl)-1-piperazinyl]chalcone (**10**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J=8.2 Hz, 2H), 7.66 (d, J=15.5 Hz, 1H), 7.41 (d, J=15.5 Hz, 1H), 6.88 (d, J=8.5 Hz, 2H), 6.84 (d, J=5.3 Hz, 2H), 4.20 (q, J=7.0 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.40 (t, J=4.4 Hz, 4H), 3.25 (d, J=5.6 Hz, 2H), 2.72 (t, J=4.6 Hz, 4H), 1.26 (t, J=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.0, 170.1, 154.0, 153.5, 143.32, 140.1, 130.9, 130.7, 128.4, 121.5, 113.6, 105.6, 61.0, 60.8, 59.3, 56.3, 52.6, 47.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{33}N_2O_6$ $(M+H)^+$ 469.2333, found 469.2332.

3,4,5-Trimethoxy-4'-[*N*-(2-oxopropyl)-1-piperazinyl]chalcone (**11**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=8.6 Hz, 2H), 7.69 (d, J=15.5 Hz, 1H), 7.42 (d, J=15.5 Hz, 1H), 6.90 (d, J=8.7 Hz, 2H), 6.85 (s, 2H), 3.89 (s, 6H), 3.88 (s, 3H), 3.42 (t, J=4.8 Hz, 4H), 3.27 (s, 2H), 2.65 (t, J=4.7 Hz, 4H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 188.1, 154.1, 153.6, 143.5, 131.0, 130.8, 128.5, 121.5, 113.7, 105.7, 68.0, 61.1, 56.35, 53.1, 47.3, 27.9; HRMS (ESI-TOF) calcd for $C_{25}H_{31}N_2O_5$ $(M+H)^+$ 439.2226, found 439.2227.

3,4,5-Trimethoxy-4'-[*N*-(2-oxophenylethyl)-1-piperazinyl]chalcone (**12**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97～8.00 (m, 4H), 7.69 (d, J=15.5 Hz, 1H), 7.55～7.59 (m, 1H), 7.41～7.47 (m, 3H), 6.90 (d, J=9.0 Hz, 2H), 6.85 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.45 (t, J=5.0 Hz, 4H), 2.77 (t, J=5.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.1, 188.1, 154.1, 153.5, 143.4, 136.0, 133.5, 130.9, 130.7, 128.7, 128.4, 128.2, 122.5, 113.7, 105.6, 64.2, 61.0, 56.3, 53.2, 47.3; HRMS (ESI-TOF) calcd for $C_{30}H_{33}N_2O_5$ $(M+H)^+$ 501.2384, found 501.2380.

3,4,5-Trimethoxy-4'-[*N*-(4'-fluoro-2-oxophenylethyl)-1-piperazinyl]chalcone (**13**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04～8.08 (m, 2H), 8.00 (d, J=8.9 Hz, 2H), 7.70 (d, J=15.5 Hz, 1H), 7.45 (d, J=15.5 Hz, 1H), 7.13 (t, J=8.6 Hz, 2H), 6.91 (d, J=8.9 Hz, 2H), 6.86 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.85 (s, 2H), 3.43 (t, J=4.4 Hz, 4H), 2.76 (t, J=4.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.6, 188.0, 167.1, 164.6, 154.0, 153.5, 143.3, 140.1, 132.3, 131.0, 130.9, 130.8, 130.7, 128.4, 121.4, 115.9, 115.6, 113.6, 105.6, 64.3, 61.0, 56.2, 53.0, 47.2; HRMS (ESI-TOF) calcd for $C_{30}H_{32}FN_2O_5$ $(M+H)^+$ 519.2290, found 519.2285.

3,4,5-Trimethoxy-4'-[*N*-(4'-chloro-2-oxophenylethyl)-1-piperazinyl]chalcone (**14**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92～7.98 (m, 4H), 7.67 (d, J=15.5 Hz, 1H), 7.39～7.44 (m, 3H), 6.88 (d, J=9.0 Hz, 2H), 6.83 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 2H), 3.41 (t, J=4.8 Hz, 4H), 2.72 (t, J=5.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.1, 188.0, 154.0, 153.5, 143.4, 139.9, 134.2, 130.8, 130.7, 129.7, 129.0, 128.4, 121.4, 113.6, 105.6, 64.3, 61.0, 56.3, 53.1, 47.2; HRMS (ESI-TOF) calcd for $C_{30}H_{32}N_2O_5Cl$ $(M+H)^+$ 535.1991, found 535.1994.

3,4,5-Trimethoxy-4'-[*N*-(4'-bromo-2-oxophenylethyl)-1-piperazinyl]chalcone (**15**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=8.7 Hz, 2H), 7.88 (d, J=8.2 Hz, 2H), 7.68 (d, J=15.5 Hz, 1H), 7.59 (d, J=8.2 Hz, 2H), 7.42 (d, J=15.5 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 6.85 (s, 2H), 3.89 (s, 6H), 3.88 (s, 3H), 3.83 (s, 2H), 3.43 (t, J=4.8 Hz, 4H), 2.75 (t, J=4.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.3, 188.1, 154.1, 153.6, 143.5, 134.6, 132.1, 130.9, 130.8, 129.8, 128.8, 128.6, 121.5, 113.7, 105.7, 64.4, 61.1, 56.3, 53.1, 47.3; HRMS (ESI-TOF) calcd for $C_{30}H_{31}N_2O_2BrNa$ $(M+Na)^+$ 601.1309, found 601.1304.

3,4,5-Trimethoxy-4'-[*N*-(4'-methyl-2-oxophenylethyl)-1-piperazinyl]chalcone (**16**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=9.0 Hz, 2H), 7.91 (d, J=8.2 Hz, 2H), 7.70 (d, J=15.6 Hz, 1H), 7.43 (d, J=15.6 Hz, 1H), 7.27 (t, J=3.7 Hz, 2H), 6.93 (d, J=9.0 Hz, 2H), 6.86 (s, 2H), 3.92 (s, 6H), 3.90 (s, 3H), 3.88 (s, 2H), 3.45～3.48 (m, 4H), 2.77～2.79 (m, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 188.2, 154.2, 153.6, 144.4, 143.4, 133.6, 131.0, 130.8, 129.4, 128.5, 128.3, 121.6, 113.7, 105.7, 64.2, 61.1, 56.4, 53.2, 47.4, 21.8; HRMS (ESI-TOF) calcd for $C_{31}H_{35}N_2O_5$ $(M+H)^+$ 515.2540, found 515.2540.

3,4,5-Trimethoxy-4'-[*N*-(4'-methoxy-2-oxophenylethyl)-1-piperazinyl]chalcone (**17**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99～8.04 (m, 4H), 7.72 (dd, J=5.1, 15.5 Hz, 1H), 7.43 (dd, J=4.0, 15.6 Hz, 1H), 6.90～6.96 (m, 4H), 6.87 (s, 2H), 3.92 (s, 6H), 3.90 (s, 3H), 3.88 (s, 1H), 3.87 (s, 2H), 3.85 (s, 1H), 3.79 (d, J=5.0 Hz, 1H), 3.72 (d, J=3.2 Hz, 1H), 3.55 (t, J=4.8 Hz, 1H), 3.47 (t, J=4.8 Hz, 2H), 3.35～3.42 (m, 2H), 2.81 (t, J=5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.5, 188.2, 163.9, 161.0, 154.1, 153.5, 143.5, 132.2, 130.8, 130.5, 121.5, 114.6, 113.9, 113.7, 105.8, 105.7, 63.9, 61.1, 56.3, 55.6, 55.5, 53.1, 47.2; HRMS (ESI-TOF) calcd for $C_{31}H_{35}N_2O_6$ $(M+H)^+$ 531.2490, found 531.2490.

3,4,5-Trimethoxy-4'-[*N*-(2-oxo-β-naphthalenylethyl)-1-piperazinyl]chalcone (**18**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (s, 1H), 7.93～8.04 (m, 4H), 7.86 (t, J=8.8 Hz, 2H), 7.69 (d, J=15.5 Hz, 1H), 7.53～7.60 (m, 2H), 7.43 (d, J=15.5 Hz, 1H), 6.90 (d, J=9.0 Hz, 2H), 6.84 (s, 2H), 4.04 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.46 (t, J=4.2 Hz, 4H), 2.80 (t, J=4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.0, 188.1, 154.1, 153.5, 143.3, 140.1, 135.8, 133.3, 132.5, 130.9, 130.7, 129.8, 129.6, 128.7, 128.6, 128.4, 127.9, 126.9, 123.8, 121.5, 113.6, 105.6, 64.3, 61.0, 56.3, 53.2, 47.3; HRMS (ESI-TOF) calcd for $C_{34}H_{35}N_2O_5$ $(M+H)^+$ 551.2537, found 551.2540.

4-Methyl-4'-[*N*-(2-oxo-2-ethoxyethyl)-1-piperazinyl]-chalcone (**19**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=8.9 Hz, 2H), 7.75 (d, J=15.6 Hz, 1H), 7.49～7.53 (m, 3H), 7.19 (d, J=8.0 Hz, 2H), 6.89 (d, J=8.9 Hz, 2H), 4.22 (q, J=7.1 Hz, 2H), 3.41 (t, J=4.9 Hz, 4H), 3.26 (s, 2H), 2.73 (t, J=5.0 Hz, 4H), 2.37 (s, 3H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.2, 170.1, 154.0, 143.3, 140.6, 132.6, 130.7, 129.7, 128.6, 128.4, 121.1, 113.7, 60.8, 59.4, 52.6, 47.3, 21.6, 14.3; HRMS (ESI-TOF) calcd for $C_{24}H_{28}N_2O_3Na$ $(M+Na)^+$ 415.1992, found 415.1996.

4-Methyl-4'-[*N*-(2-oxopropyl)-1-piperazinyl]chal-

cone (**20**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J=8.9 Hz, 2H), 7.75 (d, J=15.6 Hz, 1H), 7.48～7.52 (m, 3H), 7.18 (d, J=7.9 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 3.39 (t, J=4.8 Hz, 4H), 3.24 (s, 2H), 2.62 (t, J=5.0 Hz, 4H), 2.35 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 188.2, 154.0, 143.3, 140.6, 132.6, 130.7, 129.7, 128.5, 128.3, 121.1, 113.6, 67.9, 53.0, 47.2, 27.8, 21.5; HRMS (ESI-TOF) calcd for $C_{23}H_{27}N_2O_2$ $(M+H)^+$ 385.1884, found 385.1886.

4-Methyl-4'-[*N*-(2-oxophenylethyl)-1-piperazinyl]chalcone (**21**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98～8.02 (m, 4H), 7.79 (d, J=15.6 Hz, 1H), 7.45～7.58 (m, 6H), 7.22 (d, J=8.0 Hz, 2H), 6.93 (d, J=9.0 Hz, 2H), 3.90 (s, 2H), 3.48 (t, J=5.2 Hz, 4H), 2.80 (t, J=5.0 Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.2, 188.3, 154.1, 143.4, 140.6, 136.1, 133.5, 132.7, 130.7, 129.7, 128.8, 128.7, 128.4, 128.2, 121.2, 113.8, 64.3, 53.2, 47.4, 21.6; HRMS (ESI-TOF) calcd for $C_{28}H_{29}N_2O_2$ $(M+H)^+$ 425.2224, found 425.2227.

4-Methyl-4'-[*N*-(4'-methyl-2-oxophenylethyl)-1-piperazinyl]chalcone (**22**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.7 Hz, 1H), 7.90 (dd, J=2.2, 6.5 Hz, 3H), 7.77 (d, J=15.6 Hz, 1H), 7.54 (t, J=2.2 Hz, 2H), 7.31 (d, J=11.6 Hz, 1H), 7.20～7.27 (m, 4H), 7.03 (d, J=7.5 Hz, 1H), 6.91 (d, J=7.9 Hz, 1H), 6.82 (t, J=7.4 Hz, 1H), 3.87 (d, J=7.0 Hz, 2H), 3.41～3.47 (m, 4H), 2.74～2.79 (m, 4H), 2.41 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 188.4, 154.1, 144.4, 143.4, 140.6, 137.5, 133.6, 132.7, 131.3, 130.8, 129.7, 129.5, 129.4, 129.1, 128.7, 128.4, 128.4, 126.6, 121.2, 113.7, 113.6, 64.2, 53.2, 53.2, 47.4, 47.2, 21.8, 21.6; HRMS (ESI-TOF) calcd for $C_{29}H_{31}N_2O_2$ $(M+H)^+$ 439.2378, found 439.2380.

4-Bromo-4'-[*N*-(2-oxo-2-ethoxyethyl)-1-piperazinyl]-chalcone (**23**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, J=9.0 Hz, 2H), 7.67 (d, J=15.6 Hz, 1H), 7.44～7.53 (m, 5H), 6.87 (d, J=9.1 Hz, 2H), 4.20 (q, J=7.1 Hz, 2H), 3.40 (t, J=4.9 Hz, 4H), 3.25 (s, 2H), 2.71 (t, J=5.0 Hz, 4H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.6, 170.1, 154.1, 141.6, 134.3, 132.1, 130.7, 129.7, 128.1, 124.2, 122.6, 113.6, 60.8, 59.3, 52.55, 47.2, 14.3; HRMS (ESI-TOF) calcd for $C_{23}H_{26}N_2O_3Br$ $(M+H)^+$ 457.1121, found 457.1121.

4-Bromo-4'-[*N*-(2-oxopropyl)-1-piperazinyl]chalcone-(**24**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J=8.8 Hz, 2H), 7.69 (d, J=15.6 Hz, 1H), 7.46～7.54 (m, 5H), 6.88 (d, J=8.9 Hz, 2H), 3.42 (t, J=5.0 Hz, 4H), 3.26 (s, 2H), 2.64 (t, J=5.0 Hz, 4H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 187.7, 154.2, 141.7, 134.3, 132.2, 130.8, 129.9, 128.2, 124.3, 122.7, 113.6, 68.0, 53.0, 47.2, 27.9; HRMS (ESI-TOF) calcd for $C_{22}H_{24}N_2O_2Br$ $(M+H)^+$ 427.1016, found 427.1016.

4-Bromo-4'-[*N*-(4'-methyl-2-oxophenylethyl)-1-piperazinyl]chalcone (**25**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (dd, J=2.6, 8.8 Hz, 2H), 7.90 (d, J=5.3 Hz, 2H), 7.72 (dd, J=2.6, 15.6 Hz, 1H), 7.50～7.56 (m, 4H), 7.25～7.33 (m, 4H), 6.92 (dd, J=2.5, 8.9 Hz, 1H), 3.87 (d, J=2.6 Hz, 2H), 3.47 (s, 4H), 2.78 (s, 3H), 2.41 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 187.9, 154.3, 144.5, 141.8, 134.5, 133.6, 132.2, 131.5, 131.0, 130.9, 130.0, 129.8, 129.5, 128.6, 128.4, 128.3, 122.8, 113.7, 64.2, 53.2, 47.3, 21.8; HRMS (ESI-TOF) calcd for $C_{28}H_{28}N_2O_2Br$ $(M+H)^+$ 503.1329, found 503.1326.

4.3 Biological activity experiments

4.3.1 Anti-inflammatory activity

Murine RAW264.7 macrophages were plated in 96 well plate at a density of 1×10^5 cells/well and stimulated with 1 μg/mL lipopolysaccharides (LPS) in the present or absence of various concentration of compound for 24 h. The production of NO was determined by assaying culture supernatant for NO^{2-}. 100 μL of supernatant was mixed with an equal volume of Griess reagent at room temperature for 10 min. Absorbance was measured at 540 nm in a microplate reader.

4.3.2 Cytotoxic activity

The assay was carried out using the method previously described. About 1×10^4 cell/well were seeded into 96-well microtiter plates. After 24 h post-seeding, cells were treated with vehicle control or various concentrations of samples for 48 h. 20 μL of MTT solution (5 mg/mL) was added to each well and the tumor cells were incubated at 37 ℃ in a humidified atmosphere of 5% CO_2 air for 4 h. Upon removal of MTT/medium, 150 μL of dimethylsulfoxide (DMSO) was added to each well and the plate was agitated at oscillator for 5 min to dissolve the MTT-formazan. The assay plate was read at a wavelength of 570 nm using a microplate reader.

Supporting Information The ^{1}H NMR, ^{13}C NMR and HRMS spectra of compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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