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Sinomenine derivatives with embedment of nitrogen-containing heterocycles exhibiting potent TNF-α inhibitory activity

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Inhibitory effect on tumor necrosis factor-α (TNF-α) production by sinomenine derivatives with embedment of small drug-like nitrogen hetereocyclic moieties has been studied in this work. Several new sinomenine derivatives having chlorophenyl substituent have been found to exhibit much more potent TNF-α inhibitory activity than natural sinomenine and other derivatives.

sinomenine, druggability, heterocycle, tumor necrosis factor-α, inhibition

1 Introduction

Improvement of the druggability of bioactive natural products by proper chemical modifications has influenced modern drug discovery across the therapeutic spectrum for many decades [1]. Among numerous naturally occurring compounds, only a small part meet the requirements for further pharmaceutical development. Many easily available natural compounds are insufficiently active to be potential drug candidates. Sinomenine (**1**, Figure 1), an economically available alkaloid extracted from the Chinese medicinal plant *Sinomenium acutum* [2], is distributed widely as an ingredient of traditional Chinese medicines for treatment of rheumatoid arthritis (RA) for centuries. However, sinomenine alone only exhibits very weak immunomodulating activity. Furthermore, the mechanisms associated with its treatment effects to rheumatoid arthritis are still ambiguous [3–5].

For its easy and economic availability, various modifications of the naturally existing functionalities of sinomenine have been conducted in the past several decades [6]. Unfortunately, no achievement has been advanced to the clinical applications yet (Figure 1). Insufficient druggability of sinomenine of plant origin is thought to be a major drawback. Therefore, developing druggable derivatives should be a more promising strategy in further efforts. Our recent study has developed a number of new derivatives by incorporation of certain druggable fragments into the skeleton of sinomenine and examined their inhibitory effect on the growth of T- and B-cells [7]. The modified compounds were found to display more potent inhibitory activity than natural sinomenine in a high hit rate. To exclude possible complicated environment problems involved in the whole-cell model, further study of the effects on the key cytokines associated with the immunomodulating response is necessary. Furthermore, fine tuning and examination of more

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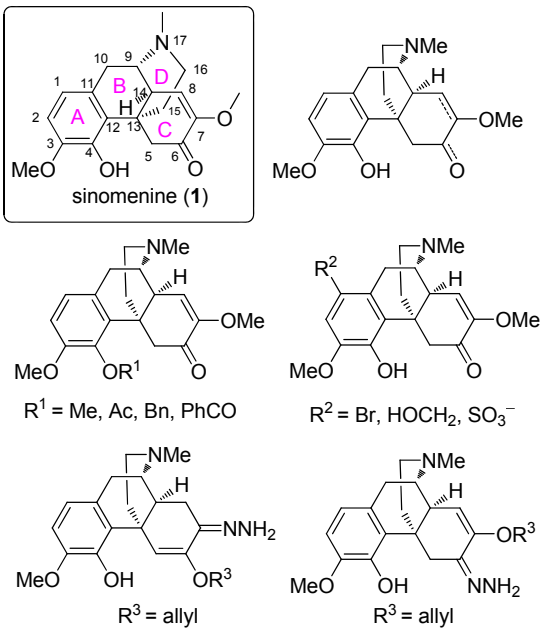


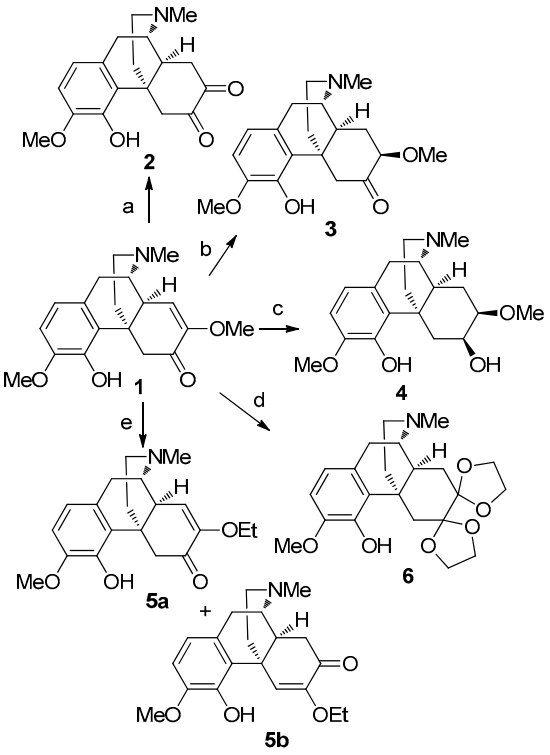
Figure 1 Representative chemical modifications of sinomenine (**1**).

diverse sinomenine derivatives on the basis of our previous findings [7] are also helpful to conclude structure-activity relationships. With these considerations, inhibition of the production of TNF-α (pro-inflammatory cytokine tumor necrosis factor-α), which is generally involved in the pathogenesis of the disease rheumatoid arthritis (RA) [8], was employed in this work as the evaluation platform of the corresponding immunomodulating properties.

2 Results and discussion

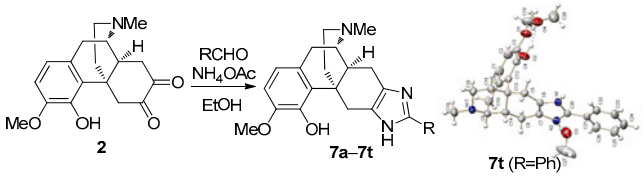
In order to avoid the known modifications [6] and identify a unique modification protocol, we decided to screen a suitable intermediate from scalable transformations as our starting point. We called such a protocol as re-invention. Firstly, a number of available reactions were examined using natural sinomenine (**1**) as the substrate so that we could understand the chemo- and stereoselectivity under protecting-free conditions (Scheme 1). Hydrogenation of **1** afforded a single product **3** (79%) in the presence of 10% Pd/C [9], while that using catalytic amount of PtO_2 gave another single product **4** (70%) [10]. Treatment of **1** with conc. HCl in ethanol provided **5a** (43%) and **5b** (37%), and vicinal diacetal **6** was afforded when ethylene glycol was employed as the solvent [6n]. Simple acid treatment of sinomenine provided a vicinal diketone compound **2** in 86% yield [7, 9a].

Considering the results of the above reactions and available further transformations, vicinal diketone **2** was finally chosen as the starting material for introduction of small heterocycles in its C-ring. Two categories of derivatives **7** (fusing with an imidazole-ring to the C-ring, Table 1) and **8**



Scheme 1 Reagents and conditions: (a) 10% HCl, 80 °C, 86%; (b) 10% Pd-C, H_2O, 79%; (c) PtO_2, EtOH, H_2, rt, 70%; (d) $HOCH_2CH_2OH$, *p*-TsOH, $PhCH_3$, reflux, 59%; (e) HCl/ EtOH, reflux, **5a** (43%) and **5b** (37%).

Table 1 Synthesis of imidazole-fused sinomenine derivatives **7a–7t**



Entry	R	Product	Yield (%) [a]
1	CH_3	**7a**	67
2	*p*-CH_3-C_6H_4	**7b**	53
3	*p*-$CH_3(CH_2)_6$-C_6H_4	**7c**	80
4	*o*-Cl-C_6H_4	**7d**	77
5	*m*-Cl-C_6H_4	**7e**	53
6	*p*-Cl-C_6H_4	**7f**	75
7	*o*-F-C_6H_4	**7g**	75
8	*p*-Br-C_6H_4	**7h**	61
9	*o*-CF_3-C_6H_4	**7i**	71
10	*p*-CH_3O-C_6H_4	**7j**	66
11	*p*-CH_3SO_2-C_6H_4	**7k**	48
12	*o*-HO-C_6H_4	**7*l***	78
13	2,6-Cl_2-C_6H_3	**7m**	56
14	1-naphtyl	**7n**	74
15	2-pyridinyl	**7o**	82
16	3-pyridinyl	**7p**	86
17	2-furanyl	**7q**	85
18	*p*-ph-C_6H_4	**7r**	61
19	2-(5-CH_3-furanyl)	**7s**	72
20 [b]	C_6H_5	**7t**	79

a) Isolated yields. b) Derivative **7t** was confirmed by the X-ray single crystallography analysis.

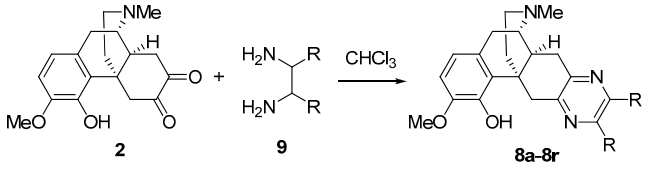
(fusing with a pyrazine-ring to the C-ring, Table 2) were conveniently prepared from **2** by corresponding one-pot reactions, respectively.

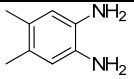
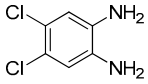
Three-component reactions of **2** with a variety of aldehydes and ammonium acetate in EtOH afforded the corresponding imidazoles **7a–7t** in satisfactory yields. Their structures were determined by NMR methods and further confirmed by an X-ray single crystallographic structure of representative derivative **7t**. According to this evidence, the chemistry nature of two newly introduced nitrogen atoms (positions of NH and N) in derivatives **7** was finally elucidated.

The other category of pyrazines derivatives **8a–8r** were prepared by direct dehydrative condensation reactions of diketone **2** with a variety of symmetrical vicinal diamines in chloroform under mild conditions. Unfortunately, the reactions with unsymmetrical vicinal diamines afforded a mixture of two regioisomers, which were inseparable by chromatographic methods. The structures of few pure single unsymmetrical isomers separated by several times of careful chromatographies could not be clearly elucidated by the NMR methods. For these unambiguous sample problems, we did not further study them in this work.

Though it is weakly active in the cell or pro-inflammatory cytokine models, natural sinomenine has been known to involve in the treatment of rheumatoid arthritis as an ingredient of herb medicines. Modern researches also indicate that TNF-α expression in rheumatoid arthritis (RA) patients is particularly elevated in RA synovial fluid, serum and synovial fibroblasts. More importantly, these enhanced TNF-α levels correlate well with disease pathology and severity. Application of anti TNF-α drugs in the clinic has also proved that blocking TNF-α is an effective way to treat RA [12].

Table 2 Synthesis of pyrazine-fused sinomenine derivatives **8a–8r**



Entry	Diamine/R	Product	Yield (%) [a]
1		**8a**	79
2		**8b**	75
3 [b]	Ph	**8c**	75
4	1-naphthyl	**8d**	65
5	*o*-Cl-C_6H_4	**8e**	59
6	*m*-Cl-C_6H_4	**8f**	66
7	*p*-Cl-C_6H_4	**8g**	62
8	*o*-Br-C_6H_4	**8h**	64
9	*m*-Br-C_6H_4	**8i**	63
10	*p*-Br-C_6H_4	**8j**	61
11	*o*-F-C_6H_4	**8k**	66
12	*m*-F-C_6H_4	**8l**	68
13	*p*-F-C_6H_4	**8m**	69
14	*p*-CH_3-C_6H_4	**8n**	75
15	*p*-CF_3-C_6H_4	**8o**	70
16	*o*-CH_3O-C_6H_4	**8p**	74
17	*m*-CH_3O-C_6H_4	**8q**	71
18	*p*-CH_3O-C_6H_4	**8r**	69

a) Isolated yields. b) Reported in ref. [11].

With the above sinomenine derivatives in hand, the *in vitro* effects on TNF-α production in LPS stimulated mouse macrophage cells (J774) were then evaluated. TNF-α inhibitory and stimulating effects of sinomenine (**1**) and its derivatives **7a–7s** were assayed in LPS stimulated mouse macrophage cells (J774) at 10 μM concentration. All the imidazole derivatives **7a–7s** exhibited TNF-α inhibitory activity with a higher potency than sinomenine (Figure 2). Among these, compound **7e** (R = *m*-ClC_6H_4) bearing a chlorobenzene moiety provided the highest score with a 47% inhibitory rate, while sinomenine **1** displayed only 7% inhibitotion and diketone derivative **2** exhibited 26% inhibition. These imidazoles derived from various aromatic aldehydes (phenyl, naphthyl, pyridinyl, furanyl) were generally found to improve the TNF-α inhibitory activity. This may indicate that introduction of a lipophilic moiety is helpful. Furthermore, introduction of one or two halogens into the phenyl ring is also useful in activity improvement (**7d**, **7e**, **7g**, **7h** and **7m**). Chlorinated derivatives **7d**, **7e** and **7m** are listed in the four compounds (another one is **7j**) exhibiting over 40% inhibition. Minor change of the halogen position can also influence the biological effects. Slight activity difference is found between **7d** (R = *o*-ClC_6H_4) and **7e** (R = *m*-ClC_6H_4), while it is much greater by comparison with compound **7f** (R = *p*-ClC_6H_4, less than 20% TNF-α inhibition). In addition, a smaller substituent at *ortho* position of the phenyl ring of R might be helpful for their *anti*-TNF-α production activity (**7d**, R = *o*-ClC_6H_4; **7g**, R = *o*-FC_6H_4; ***7l***, R = *o*-HOC_6H_4; **7i**, R = *o*-$CF_3C_6H_4$).

Pyrazine derivatives **8a–8r** generally exhibit more potent inhibitory effects on the TNF-α production in LPS stimulated mouse macrophage cells (J774) (Figure 3). Among these, derivatives **8h** (R = *o*-BrC_6H_4) displayed more than 70% inhibitory rate, and **8e** (R = *o*-ClC_6H_4) and **8k** (R = *o*-FC_6H_4) showed over 60% inhibitory rates. The halogen is again found to be helpful in the biological effects. An *ortho* halogen substituent in both newly introduced phenyl rings improves the *anti*-TNF-α production activity. Compared to **8c** (R = Ph, 50% inhibition of TNF-α production), the above three compounds gave higher scores in their inhibitory activity. Other two substitution positions (*meta*, *para*) seem insignificant in improving the bioactivity (**8e** vs. **8f** and **8g**; **8h** vs. **8i** and **8j**; **8k** vs. **8*l*** and **8m**). A *para* substituent in both phenyl rings is again negative to the

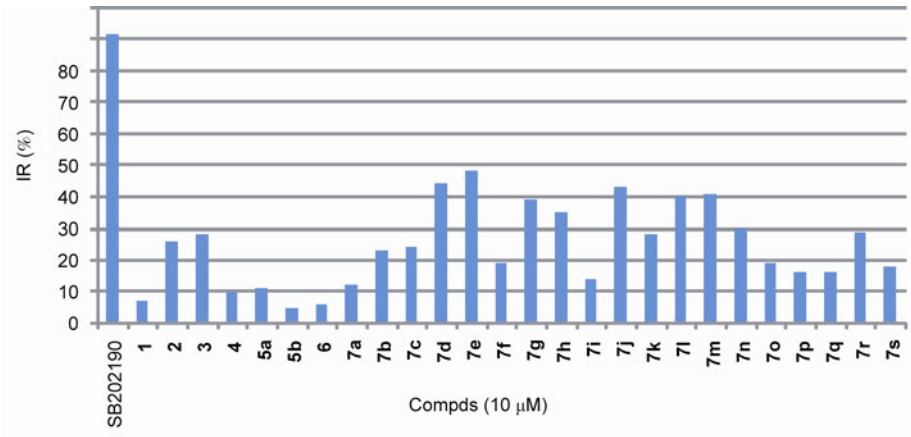


Figure 2 TNF-α inhibitory and stimulating effects of sinomenine **1** and its derivatives **7a–7s** in LPS stimulated mouse macrophage cells (J774). Compounds were assayed at 10 μM concentration. SB202190 (4-(4-fluor- ophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-1*H*-imidazole), a highly selective, potent and cell permeable inhibitor of *p*38 MAP kinase, was used as the positive control [13]. Compound **7t** was not determined. IR: inhibitory rate.

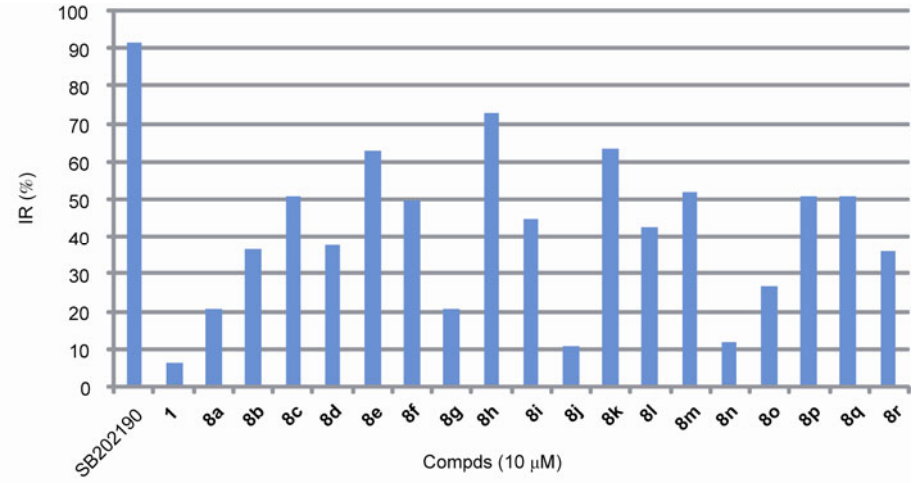


Figure 3 TNF-α inhibitory and stimulating effects of sinomenine **1** and its derivatives **8a–8r** in LPS stimulated mouse macrophage cells (J774). Compounds were assayed in 10 μM concentration. SB202190 was used as the positive control. IR: inhibitory rate.

biological activity (**8g**, **8j**, **8n**, **8o**, and **8r**), and bigger aromatic substituent (or ring system) is harmful (**8a**, **8b**, and **8d**) either.

3 Conclusion

In summary, embedment of drug-like heterocyclic moieties has been employed and proven to be an effective modification protocol for the readily available but poorly active natural alkaloid sinomenine. Most of the newly prepared derivatives are found to exhibit improved anti-TNF-α production activity than natural sinomenine. Derivative **8h** was identified to significantly inhibit *in vitro* TNF-α production in LPS stimulated mouse macrophage cells (J774) with a 73% inhibitory rate. The results also mention that introduction of a halogen atom at the proper position(s) of the newly introduced phenyl ring(s) can significantly improve the immunomodulating activity. Further study on other RA-related immunomodulating cytokines, as well as assessment in animal models, will be reported in due course.

4 Experimental section

4.1 General

All reactions were conducted using oven-dried glassware. All melting points were uncorrected. Dichloromethane was distilled from CaH_2, and tetrahydrofuran was distilled from Na prior to uses. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded at 300, 400 or 500 MHz, and ^{13}C NMR spectra were recorded at 75, 100 or 125 MHz, and assigned in parts per million (δ). Reference peaks for $CDCl_3$ in ^{1}H NMR and ^{13}C NMR spectra were set at

7.26 and 77.0 ppm, respectively. For CD_3OD, the reference peak of ^{13}C NMR spectra was set at 49.00 ppm, respectively. Petroleum ether and ethyl acetate were obtained from commercial suppliers and used without distillation.

4.2 Synthesis of imidazoles 7a–7t

To a solution of NH_4OAc (2.45 g, 31 mmol) in EtOH (30 mL) was successively added diketone **2** (1.0 g, 3.2 mmol) and the corresponding aldehyde (4.8 mmol) at room temperature. The reaction mixture was stirred at this temperature and monitored by TLC. The solvent was concentrated and the residue was then diluted with water and CH_2Cl_2. The separated aqueous layer was basified with 10% aqueous $NaHCO_3$ to pH 8–9 and then extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and the residue was purified by flash chromatography using CH_2Cl_2 and CH_3OH as the eluents to afford the sinomenine derivative **7** (See Table 1 for the yields).

7a: White solid. Mp: 147–149 °C; $[\alpha]_D^{25}$ 113.9 (*c* 0.18, $CHCl_3/CH_3OH$ = 10:1); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.62 (1H, d, *J* = 8.7 Hz), 6.59 (1H, d, *J* = 9.0 Hz), 4.64 (1H, d, *J* = 15.9 Hz), 3.77 (3H, s), 3.05-2.85 (3H, m), 2.54–2.25 (11H, m), 2.14 (1H, dt, *J* = 3.0, 12.3 Hz), 1.98–1.94 (1H, m), 1.84 (1H, dt, *J* = 4.8, 12.6 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$ = 10:1, 125 MHz): δ 148.8, 148.5, 146.1, 134.9, 131.5, 131.1, 128.1, 122.3, 112.6, 61.2, 59.7, 50.8, 46.5, 46.3, 42.0, 41.2, 36.4, 28.3, 27.9, 17.2; IR (KBr): 3200, 2914, 2844, 1671, 1481, 1438, 1379, 1279, 1226, 1105, 1063, 1053, 1024, 795, 753, 662 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{20}H_{26}N_3O_2$ ($M+H^+$): 340.2020, found: 340.2028.

7b: White solid. Mp: 213–214 °C; $[\alpha]_D^{24}$ 175.7 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (2H, d, *J* = 8.4 Hz), 7.11 (2H, d, *J* = 8 Hz), 6.61 (1H, d, *J* = 8 Hz), 6.58 (1H, d, *J* = 8.4 Hz), 5.96 (1H, brs), 4.73 (1H, d, *J* = 16 Hz), 3.75 (3H, s), 3.09 (1H, s), 2.99 (1H, d, *J* = 18.4 Hz), 2.90 (1H, dd, *J* = 6, 18.4 Hz), 2.63 (1H, dd, *J* = 5.2, 15.2 Hz), 2.44– 2.52 (3H, m), 2.44 (3H, s), 2.31–2.36 (1H, m), 2.31 (3H, s), 2.19 (1H, dt, *J* = 4.8, 12 Hz), 1.97 (1H, d, *J* = 12.8 Hz), 1.89 (1H, dt, *J* = 4.4, 12.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.5, 144.4, 144.3, 137.3, 131.0, 129.2, 127.7, 124.7, 124.1, 118.4, 108.4, 57.1, 55.7, 46.8, 42.6, 42.5, 38.2, 37.2, 32.6, 24.5, 23.8, 21.2; IR (KBr): 3419, 2912, 2841, 1622, 1614, 1481, 1437, 1380, 1279, 1225, 1105, 1053, 1022, 823, 728 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{26}H_{30}N_3O_2$ ($M+H^+$): 416.2333, found: 416.2337.

7c: White solid. Mp: 144–146 °C (dec.); $[\alpha]_D^{25}$ 126.5 (*c* 0.52, $CHCl_3/CH_3OH$ = 10:1); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.64 (1H, d, *J* = 8.4 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 4.70 (1H, d, *J* = 15.9 Hz), 3.79 (3H, s), 3.09–2.85 (3H; m), 2.66 (2H, t, *J* = 7.5 Hz), 2.62–2.51 (2H, m), 2.44 (3H, s), 2.46–2.36 (2H, m), 2.32–2.28 (1H, m), 2.17 (1H, dt, *J* = 2.4, 12.0 Hz), 1.99–1.95 (1H, m), 1.85 (1H, dt, *J* = 4.2, 12.6 Hz), 1.67–1.59 (2H, m), 1.23-1.20 (8H, m), 0.83 (3H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.0, 144.6, 144.4, 131.2, 126.64, 126.59, 123.8, 118.7, 108.7, 57.1, 56.0, 46.9, 42.7, 42.5, 38.3, 37.3, 32.0, 31.6, 29.2, 28.9, 28.3, 27.5, 23.8, 23.6, 22.5, 14.0; IR (KBr): 3517, 2926, 2852, 1670, 1482, 1438, 1280, 1226, 1064, 1054, 856, 755 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{26}H_{38}N_3O_2$ ($M+H^+$): 424.2959, found: 424.2957.

7d: Yellow solid. Mp: 158–160 °C; $[\alpha]_D^{26}$ 144.1 (*c* 1.7, $CHCl_3/CH_3OH$ = 10:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.96 (1H, brs), 8.16 (1H, d, *J* = 7.6 Hz), 7.31 (1H, d, *J* = 8 Hz), 7.22 (1H, t, *J* = 7.6 Hz), 7.14 (1H, t, *J* = 7.6 Hz), 6.61 (1H, d, *J* = 8.4 Hz), 6.59 (1H, d, *J* = 8.8 Hz), 6.16 (1H, brs), 4.78 (1H, d, *J* = 16 Hz), 3.73 (3H, s), 3.13 (1H, s), 3.02 (1H, d, *J* = 18.8 Hz), 2.92 (1H, dd, *J* = 6.4, 18.8 Hz), 2.67 (1H, dd, *J* = 5.6, 15.2 Hz), 2.46–2.59 (3H, m), 2.45 (3H, s), 2.30–2.39 (1H, m), 2.19 (1H, dt, *J* = 2.4, 12 Hz), 2.00 (1H, d, *J* = 12.8 Hz), 1.90 (1H, dt, *J* = 4.4, 12.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.4, 144.3 ,141.3, 131.2, 130.3, 130.1, 128.9, 128.6, 128.4, 127.1, 124.0, 118.5, 108.5, 57.2, 55.9, 46.9, 42.8, 42.7, 38.4, 37.4, 32.9, 24.9, 23.8; IR (KBr): 3440, 2910, 2842, 1614, 1481, 1437, 1279, 1225, 1104, 1052, 979, 761, 734 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{25}H_{27}ClN_3O_2$ ($M+H^+$): 436.1786, found: 436.1785.

7e: Yellow solid. Mp: 204–206 °C; $[\alpha]_D^{26}$ 149.3 (*c* 0.80, $CHCl_3/CH_3OH$ = 10:1); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.71 (1H, s), 7.58 (1H, d, *J* = 6 Hz), 7.08–7.19 (2H, m), 6.50–6.63 (2H, m), 6.10 (1H, brs), 4.74 (1H, d, *J* = 15.9 Hz), 3.70 (3H, s), 3.08 (1H, s), 2.98 (1H, d, *J* = 18 Hz), 2.88 (1H, dd, *J* = 5.4, 18.9 Hz), 2.50–2.67 (2H, m), 2.36–2.50 (2H, m), 2.44 (3H, s), 2.26–2.36 (1H, m), 2.09–2.25 (1H, m), 1.80-2.02 (2H, m); ^{13}C NMR ($CDCl_3/CDOD_3$ = 10:1, 75 MHz): δ 144.7, 144.3, 142.8, 134.4, 132.2, 130.2, 129.9, 127.4, 124.4, 123.5, 122.6, 118.4, 108.7, 57.4, 55.8, 46.8, 42.1, 42.0, 37.6, 37.0, 32.4, 24.3, 23.8; IR (KBr): 2916, 2842, 1596, 1481, 1437, 1379, 1279, 1224, 1049, 1021, 979, 790.6, 729, 511 cm^{-1}; HRMS (MALDI, *m/z*) Anal. calcd for $C_{25}H_{27}ClN_3O_2$ ($M+ H^+$): 436.1786, found: 436.1782.

7f: Yellow solid. Mp: 181–183 °C (dec.); $[\alpha]_D^{25}$ 185.0 (*c* 0.49, $CHCl_3/CH_3OH$ = 10:1); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.63 (2H, d, J = 9.0 Hz) 7.20 (2H, d, J = 9.0 Hz), 6.63 (1H, d, J = 8.4 Hz), 6.60 (1H, d, J = 8.4 Hz), 5.91 (1H, brs), 4.71 (1H, d, J = 15.9 Hz), 3.76 (3H, s), 3.06–3.02 (2H, m), 2.87-2.79 (1H, m), 2.66–2.48 (4H, m), 2.42 (3H, s), 2.33-2.26 (1H, m), 2.14(1H, dt, *J* = 3.0, 12.3 Hz), 1.98-1.93 (1H, m), 1.84 (1H, dt, *J* = 4.8, 12.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.4, 144.2, 143.4, 133.1, 131.5, 129.3, 128.7, 125.9, 124.2, 118.6, 108.4, 57.1, 55.9, 46.9, 43.0, 42.8, 38.5, 37.5, 32.9, 24.7, 23.8; IR (KBr): 3508, 2907, 2840, 1621, 1526, 1481, 1437, 1380, 1279, 1225, 1104, 1064, 1053, 1053, 834, 754 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{25}H_{27}N_3O_2Cl$ ($M+H^+$): 436.1786, found: 436.1785.

7g: Yellow solid. Mp: 158–160 °C; $[\alpha]_D^{26}$ 161.8 (*c* 2.0, $CHCl_3/CH_3OH$ = 10:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.49

(1H, brs), 8.14 (1H, s), 6.99–7.22 (3H, m), 6.53–6.63 (2H, m), 6.13 (1H, brs), 4.75 (1H, d, *J* = 15.6 Hz), 3.73 (3H, s), 3.11 (1H, s), 3.01 (1H, d, *J* = 18.4 Hz), 2.90 (1H, dd, *J* = 6, 18.4 Hz), 2.59–2.73 (1H, m), 2.47–2.57 (3H, m), 2.43 (3H, s), 2.28–2.37 (1H, m), 2.17 (1H, dt, *J* = 2.4, 12 Hz), 1.99 (1H, d, *J* = 12.8 Hz), 1.89 (1H, dt, *J* = 4.4, 12.8 Hz); ^{19}F NMR ($CDCl_3$/CD_3OD = 10:1, 300 MHz): δ −118.92; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0 (d, *J* = 242.9 Hz), 144.4, 144.2, 139.3, 131.4, 128.6 (d, *J* = 8.8 Hz), 128.0, 124.7, 124.0, 118.5, 118.2 (d, *J* = 10.5 Hz), 115.6 (d, *J* = 22.7 Hz), 108.4, 57.1, 55.8, 46.9, 42.9, 42.8, 38.4, 37.4, 32.4, 25.3, 23.8; IR (KBr): 3473, 2909, 2841, 1624, 1609, 1581, 1527, 1481, 1465, 1438, 1279, 1225, 1063, 1052, 1023, 759, 733 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{25}H_{27}N_3O_2F$ (M+H$^+$): 420.2082, found: 420.2081.

7h: White solid. Mp: 216–218 °C; $[\alpha]_D^{25}$ 149.7 (*c* 1.4, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 6.62 (1H, d, *J* = 8.4 Hz), 6.59 (1H, d, *J* = 8.4 Hz), 5.99 (1H, brs), 4.72 (1H, d, *J* = 15.6 Hz), 3.74 (3H, s), 3.07 (1H, s), 2.98 (1H, d, *J* = 18.8 Hz), 2.87 (1H, dd, *J* = 6.0, 18.8 Hz), 2.43–2.67 (4H, m), 2.43 (3H, m), 2.26–2.36 (1H, m), 2.09–2.23 (1H, m), 1.95 (1H, d, *J* = 12.4 Hz), 1.87 (1H, dt, *J* = 4, 12.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.4, 144.2, 143.4, 131.7, 131.2, 129.6, 126.1, 124.0, 121.3, 118.6, 108.3, 57.2, 55.9, 46.9, 42.8, 38.3, 37.4, 32.8, 24.7, 23.7; IR (KBr): 3431, 2911, 2841, 1619, 1481, 1437, 1379, 1279, 1225, 1105, 1064, 1023, 831, 727 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{25}H_{27}BrN_3O_2$ (M+H$^+$): 480.1281, found: 480.1372.

7i: White solid. Mp: 164–166 °C (dec.); $[\alpha]_D^{25}$ 142.4 (*c* 0.54, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.15 (1H, brs), 7.96 (1H, d, *J* = 7.2 Hz), 7.68 (1H, d, *J* = 7.8 Hz), 7.53 (1H, t, *J* = 7.5 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 6.65 (1H, d, *J* = 8.1 Hz), 6.61 (1H, d, *J* = 8.1 Hz), 6.06 (1H, brs), 4.74 (1H, d, *J* = 15.3 Hz), 3.78 (3H, s), 3.15–2.84 (3H, m), 2.72–2.51 (4H, m), 2.47 (3H, s), 2.44–2.36 (1H, m), 2.21 (1H, dt, *J* = 3.6, 12.0 Hz), 2.03–1.92 (2H, m); IR (KBr): 3512, 2844, 1606, 1580, 1482, 1493,1315, 1280, 1126, 1054, 755 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{26}H_{27}N_3O_2F_3$ (M+H$^+$): 470.2050, found: 470.2048; Anal calcd. for $C_{26}H_{26}F_3N_3O_2$: C, 66.51; H, 5.58; N, 8.95; found: C, 66.34; H, 5.96; N, 8.60.

7j: Yellow solid. Mp: 186–188 °C; $[\alpha]_D^{26}$ 162.4 (*c* 2.3, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (1H, brs), 7.67 (2H, d, *J* = 8.4 Hz), 6.73 (2H, d, *J* = 8.4 Hz), 6.52–6.61 (2H, m), 5.96 (1H, brs), 4.69 (1H, d, *J* = 16 Hz), 3.72 (3H, s), 3.68 (3H, s), 3.01 (1H, s), 2.95 (1H, d, *J* = 18.4 Hz), 2.81 (1H, dd, *J* = 5.6, 18.4 Hz), 2.58 (1H, dd, *J* = 5.6, 15.6 Hz), 2.38–2.53 (3H, m), 2.38 (3H, s), 2.21–2.31 (1H, m), 2.06–2.18 (1H, m), 1.90 (1H, d, *J* = 12.4 Hz), 1.81 (1H, dt, *J* = 4, 12.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 144.4, 144.2, 131.4, 130.2, 128.6, 126.2, 124.3, 123.4, 118.4, 113.9, 108.2, 57.1, 55.7, 55.1, 46.9, 42.9, 42.7, 38.4, 37.3, 32.6, 24.6, 23.7; IR (KBr): 3429, 2910, 2838, 1624, 1580, 1541, 1481, 1438, 1389, 1280, 1250, 1178, 1063, 1053, 1029, 835, 797, 733 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{26}H_{30}N_3O_3$ (M+H$^+$): 432.2282, found: 432.2281.

7k: Yellow solid. Mp: 242 °C (dec.); $[\alpha]_D^{26}$ 138.5 (*c* 0.80, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.17 (1H, brs), 7.79 (2H, d, *J* = 8 Hz), 7.63 (2H, d, *J* = 7.6 Hz), 6.48–6.66 (2H, m), 6.15 (1H, brs), 4.77 (1H, d, *J* = 12 Hz), 3.67 (3H, s), 3.07 (1H, s), 2.77–3.03 (2H, m), 2.96 (3H, s), 2.55–2.68 (1H, m), 2.40–2.55 (3H, m), 2.41 (3H, s), 2.24–2.35 (1H, m), 2.07–2.21 (1H, m), 1.94 (1H, d, *J* = 12.4 Hz), 1.76-1.89 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.6, 144.2, 142.2, 138.0, 135.5, 131.0, 127.5, 124.8, 123.9, 118.6, 108.5, 57.1, 55.8, 46.8, 44.2, 42.6, 38.2, 37.3, 23.7, 23.6; IR (KBr): 3419, 2913, 2814, 1593, 1481, 1437, 1279, 1149, 1053, 956, 779, 729, 557 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{26}H_{30}N_3O_4S$ (M+H$^+$): 480.1952, found: 480.1914.

7l: Brown solid. Mp: 208–210 °C; $[\alpha]_D^{25}$ 190.0 (*c* 0.50, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.55 (1H, brs), 7.35 (1H, d, *J* = 6.8 Hz), 7.13 (1H, t, *J* = 7.6 Hz), 6.96 (1H, d, *J* = 8 Hz), 6.77 (1H, t, *J* = 7.2 Hz), 6.55–6.65 (2H, m), 4.74 (1H, d, *J* = 16 Hz), 3.74 (3H, s), 3.10 (1H, s), 3.01 (1H, d, *J* = 18.8 Hz), 2.90 (1H, dd, *J* = 5.6, 18.8 Hz), 2.43–2.67 (4H, m), 2.48 (3H, s), 2.23–2.35 (1H, m), 2.09–2.23 (1H, m), 1.98 (1H ,d, *J* = 12.4 Hz), 1.83 (1H, dt, *J* = 4, 12 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 144.5, 144.3, 144.2; 131.1, 129.0, 123.9, 123.0, 118.5, 117.2, 113.8, 108.5, 57.1, 55.8, 46.8, 42.6, 38.2, 37.3, 32.5, 24.6, 23.8; IR (KBr): 3405, 2911, 2842, 1625, 1590, 1483, 1456, 1438, 1381, 1279, 1226, 1052, 755 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{25}H_{28}N_3O_3$ (M+H$^+$): 418.2125, found: 418.2131.

7m: Light yellow solid. Mp: 208–210 °C; $[\alpha]_D^{26}$ 72.4 (*c* 1.5, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$/CD_3OD = 10/1, 400 MHz): δ 7.32 (2H, d, *J* = 8 Hz), 7.22 (1H, t, *J* = 8 Hz), 6.65 (1H, d, *J* = 8 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 4.75 (1H, d, *J* = 16 Hz), 3.77 (3H, s), 3.39 (1H, s), 2.87–3.03 (2H, m), 2.34-2.64 (4H, m), 2.44 (3H, s), 2.11–2.34 (2H, m), 2.00 (1H, d, *J* = 12.8 Hz), 1.73-1.92 (1H, m); ^{13}C NMR ($CDCl_3$/CD_3OD = 10/1, 75 MHz): δ 144.6, 144.4, 138.0, 136.3, 130.7, 130.5, 130.4, 127.8, 123.8, 118.4, 108.7, 57.2, 56.0, 46.7, 42.2, 37.8, 37.1, 32.4, 24.4, 23.8; IR (KBr): 3435, 2911, 1614, 1551, 1482, 1435, 1278, 1224, 1059, 784, 501 cm^{-1}; HRMS (MALDI, *m/z*) Anal. calcd for $C_{25}H_{26}Cl_2N_3O_2$ (M+H$^+$) 470.1397, found: 470.1407.

7n: Yellow solid. Mp: 250 °C (dec.); $[\alpha]_D^{26}$ 60.7 (*c* 0.40, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (1H, s), 7.90 (2H, d, *J* = 8.4 Hz), 7.68 (2H, d, *J* = 8.4 Hz), 7.35 (2H, t, *J* = 7.6 Hz), 7.19–7.31 (2H, m), 6.57 (1H, d, *J* = 8 Hz), 6.48 (1H, d, *J* = 8 Hz), 5.83 (1H, brs), 4.22 (1H, d, *J* = 16 Hz), 3.71 (3H, s), 2.79 (1H, d, *J* = 18.4 Hz), 2.46–2.69 (2H, m), 2.34–2.44 (1H, m), 2.31 (3H, s), 1.76–2.13 (5H, m), 1.67 (1H, d, *J* = 12.4 Hz), 1.43–1.61

(1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.4, 144.3, 140.7, 131.5, 128.0, 127.9, 126.4, 125.8, 125.1, 124.0, 118.3, 108.5, 57.0, 56.0, 46.7, 42.4, 42.2, 37.7, 36.9, 32.2, 24.1, 23.6; IR (KBr): 3408, 3048, 2912, 2841, 1623, 1481, 1457, 1437, 1278, 1226, 1053, 735 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{33}H_{32}N_3O_2$ (M+H$^+$): 502.2489, found: 502.2501.

7o: Yellow solid. Mp: 172–174 °C; $[\alpha]_D^{26}$ 182.9 (*c* 2.6, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.85 (1H, brs), 8.39 (1H, d, *J* = 4.4 Hz), 8.01 (1H, d, *J* = 5.2 Hz), 7.63 (1H, t, *J* = 8 Hz), 7.02–7.12 (1H, m), 6.50–6.60 (2H, m), 6.28 (1H, brs), 4.69 (1H, brs), 3.68 (3H, s), 3.09 (1H, s), 2.99 (1H, d, *J* = 18.4 Hz), 2.80–2.93 (1H, m), 2.57–2.76 (1H, m), 2.40–2.57 (3H, m), 2.41 (3H, s), 2.25–2.35 (1H, m), 2.08–2.21 (1H, m), 1.95 (1H, d, *J* = 12 Hz), 1.85 (1H, dt, *J* = 3.6, 12.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.9, 148.4, 144.4, 144.3, 143.8, 136.8, 131.4, 124.1, 122.0, 119.2, 118.4, 108.4, 57.1, 55.8, 46.8, 42.9, 42.7, 38.4, 37.3, 32.6, 25.8, 23.8; IR (KBr): 3445, 2909, 2841, 1589, 1522, 1480, 1457, 1437, 1402, 1278, 1225, 1148, 1101, 1063, 1052, 730 cm^{-1}; HRMS (MALDI, *m/z*) Anal. calcd for $C_{24}H_{27}N_4O_2$ (M+H$^+$): 403.2129, found: 403.2129.

7p: Yellow solid. Mp: 203–205 °C (dec.); $[\alpha]_D^2$ 184.3 (*c* 0.52, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$/CH_3OD = 10:1, 500 MHz): δ 8.91 (1H, s), 8.39 (1H, d, *J* = 4.8 Hz), 8.14 (1H, m), 7.36(1H, dd, J = 4.8, 7.9 Hz), 6.67(1H, d, *J* = 8.3 Hz), 6.62 (1H, d, *J* = 8.3 Hz), 4.90 (1H, *J* = 15.9 Hz), 3.71 (3H, s), 3.16 (1H, s), 3.08–3.04 (2H, m), 2.69–2.65 (1H, m), 2.57–2.47 (3H, m), 2.46 (3H, s), 2.35–2.33 (1H, m), 2.28–2.23 (1H, m), 2.07–2.05 (1H, m), 1.88 (1H, dt, *J* = 5.6, 12.9 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD = 10:1, 125 MHz): δ 146.9, 144.7, 144.6, 144.3, 140.5, 132.2, 130.1, 127.0, 123.6, 123.2, 118.0, 108.5, 56.8, 55.2, 46.3, 41.9, 41.6, 37.4, 36.7, 32.2, 24.0, 23.4; IR (KBr): 3180, 3050, 2900, 1577, 1483, 1439, 1397, 1329, 1281, 1128, 1056, 1022, 851, 813, 755, 709, 653 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{24}H_{27}N_4O_2$ (M+H$^+$): 403.2129, found: 403.2130.

7q: White solid. Mp: 160–162 °C (dec.); $[\alpha]_D^{25}$ 162.9 (*c* 0.56, $CHCl_3$/CH_3OH = 10:1); 1H NMR ($CDCl_3$, 500 MHz): δ 7.18 (1H, s), 6.62 (1H, d, *J* = 3.2 Hz), 6.58 (1H, d, J = 8.9), 6.56 (1H, d, *J* = 9.0 Hz), 6.27 (1H, d, *J* = 1.3 Hz), 4.72(1H, d, *J* = 16.0 Hz), 3.66 (3H, s), 3.08 (1H, s), 2.97 (1H, d, *J* = 18.6 Hz), 2.88 (1H, dd, *J* = 6.1, 18.6 Hz), 2.61–2.53 (2H, m), 2.48–2.43 (2H, m), 2.43 (3H, s), 2.35–2.26 (1H, m), 2.20–2.15 (1H, m), 1.96–1.93 (1H, m), 1.85 (1H, dt, *J* = 4.0, 12.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.5, 143.4, 143.3, 140.1, 136.2, 130.1, 127.1(2C), 123.0, 117.4, 110.4, 107.5, 104.5, 56.1, 54.8, 45.8, 41.6, 41.5, 37.1, 36.3, 31.6, 23.7, 22.9; IR (KBr): 3503, 2909, 2841, 1604, 1481, 1438, 1279, 1224, 1063, 1053, 1013, 753 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{23}H_{26}N_3O_3$ (M+H$^+$): 392.1969, found: 392.1975.

7r: Yellow solid. Mp: 215–217 °C; $[\alpha]_D^{26}$ 175.0 (*c* 2.6, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (2H, d, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 7.6 Hz), 7.46 (2H, d, *J* = 7.6 Hz), 7.37 (2H, t, *J* = 7.2 Hz), 7.29 (1H, t, *J* = 7.2 Hz), 6.44–6.54 (2H, m), 5.99 (1H, brs), 4.74 (1H, d, *J* = 16 Hz), 3.58 (3H, s), 3.03 (1H, s), 2.94 (1H, d, *J* = 18.8 Hz), 2.82 (1H, dd, *J* = 5.2, 18.4 Hz), 2.64 (1H, dd, *J* = 5.6, 15.6 Hz), 2.40–2.56 (3H, m), 2.39 (3H, s), 2.24–2.35 (1H, m), 2.04–2.18 (1H, m), 1.75–1.98 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.3, 144.2, 144.1, 140.3, 139.7, 131.2, 129.6, 128.6, 127.1, 127.0, 126.7, 125.1, 124.1, 118.4, 108.2, 57.1, 55.6, 46.8, 42.8, 42.7, 38.3, 37.3, 32.8, 24.6, 23.7; IR (KBr): 3497, 2908, 2840, 1622, 1581, 1481, 1437, 1279, 1225, 1104, 1063, 1053, 845, 767, 732, 698 cm^{-1}; HRMS (MALDI, *m/z*) Anal. calcd for $C_{31}H_{32}N_3O_2$ (M+H$^+$): 478.2489, found: 478.2485.

7s: Yellow solid. Mp: 194–196 °C; $[\alpha]_D^{26}$ 231.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.51–6.67 (3H, m), 5.97 (1H, d, *J* = 2.8 Hz), 4.70 (1H, d, *J* = 15.6 Hz), 3.75 (3H, s), 3.12 (1H, s), 3.00 (1H, d, *J* = 18.8 Hz), 2.90 (1H, dd, *J* = 6, 18.8 Hz), 2.62 (1H, dd, *J* = 5.6, 14.8 Hz), 2.50–2.57 (1H, m), 2.39–2.49 (2H, m), 2.43 (3H, s), 2.29–2.36 (1H, m), 2.27 (3H, s), 2.18 (1H, dt, *J* = 2.8, 12 Hz), 1.97 (1H, d, *J* = 12.4 Hz), 1.88 (1H, dt, *J* = 4.4, 12.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.1, 144.8, 144.4, 144.3, 137.5, 131.1, 124.1, 118.4, 108.4, 107.5, 106.5, 57.1, 55.8, 46.7, 42.6, 42.5, 38.2, 37.3, 32.6, 24.7, 23.8, 13.4; IR (KBr): 3432, 2916, 2842, 1609, 1580, 1481, 1438, 1279, 1225, 1053, 1022, 788 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{24}H_{28}N_3O_3$ (M+H$^+$): 406.2125, found: 406.2141.

7t: White solid. Mp: 205–208 °C; $[\alpha]_D^{25}$ 190.9 (*c* 0.48, $CHCl_3$/CH_3OH = 10:1); ^{1}H NMR ($CDCl_3$/CD_3OD = 10:1, 300 MHz): δ 7.73–7.70 (2H, m), 7.34–7.31 (2H, m), 7.27–7.22 (1H, m), 6.64 (1H, d, *J* = 8.1 Hz), 6.59 (1H, d, *J* = 8.1 Hz), 4.79 (1H, d, J = 15.6 Hz), 3.77 (3H, s), 3.09–3.08 (1H, m), 2.99–2.97 (2H, m), 2.64–2.59 (1H, m), 2.54– 2.44 (3H, m), 2.42 (3H, s), 2.33-2.28 (1H, m), 2.20 (1H, dt, *J* = 3.0, 12.3 Hz), 2.03–1.99 (1H, m), 1.84 (1H, dt, *J* = 4.8, 12.9 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD=10:1, 125 MHz): δ 144.6, 144.3, 144.2, 130.8, 130.4, 128.4(2C), 127.5, 124.4 (2C), 123.9, 118.3, 108.6, 57.0, 55.7, 46.7, 42.4, 42.2, 37.9, 37.1, 32.5, 24.3, 23.7; IR (KBr): 3508, 2909, 2840, 1623, 1602, 1481, 1458, 1437, 1400, 1278, 1225, 1105, 1063, 1054, 1022, 856, 771, 701, 695 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{25}H_{28}N_3O_2$ (M+H$^+$): 402.2176, found: 402.2179.

4.3 Synthesis of pyrazines 8a–8r

A mixture of diketone **2** and the corresponding diamine **9** in $CHCl_3$ was stirred at room temperature until completion of the reaction by TLC monitoring. After removal of the solvent, the residue was purified by flash chromatography using the mixture of CH_2Cl_2 and CH_3OH as the eluent to afford sinomenine derivative **8** (See Table 2 for the yields).

8a: Yellow solid. Mp: 207–209 °C (dec.); $[\alpha]_D^{20}$ 222.9 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (1H, s),

7.50 (1H, s), 6.60 (1H, d, *J* = 8.3 Hz), 6.54 (1H d, *J* = 8.3 Hz), 5.02 (1H, d, *J* = 17.0 Hz), 3.62 (3H, s), 3.19–2.93 (6H, m), 2.58–2.55 (2H, m), 2.46 (3H, s), 2.36 (3H, s), 2.31 (3H, s), 2.22 (1H, dt, *J* = 3.0, 12.9 Hz), 2.1(1H,d, *J* = 12.9 Hz) 1.91(1H, dt, *J* = 4.8, 13.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.8, 152.4, 145.0, 144.6, 140.4, 140.1, 138.83, 138.77, 131.3, 127.657, 127.2, 123.7, 118.7, 109.0, 77.6, 77.2, 76.8, 56.7, 55.9, 47.0, 44.6, 43.1, 43.0, 38.3, 36.3, 33.6, 23.4, 20.3, 20.2; IR (KBr): 2916, 2802, 1604 1483, 1439, 1335, 1274, 1228, 1153, 1104, 1066, 1054, 1023, 989, 867, 857, 792 cm^{-1}; HRMS (EI, *m/z*): Anal. calcd for $C_{26}H_{30}N_3O_2$ (M^+): 416.2333, found: 416.2345; Anal. calcd for $C_{26}H_{29}N_3O_2$: C, 75.15; H, 7.03; N, 10.11; found: C, 74.84; H, 7.29; N, 10.12.

8b: Yellow soild. Mp: 205–207 °C (dec.); $[\alpha]_D^{20}$ 203.2 (c 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (1H, s), 7.94 (1H, s), 6.62 (1H, d, *J* = 8.4 Hz), 6.58 (1H, d, *J* = 8.4 Hz), 6.21 (1H, brs), 4.99 (1H, d, *J* = 17.4 Hz), 3.71 (3H, s), 3.24–2.88 (6H, m), 2.57–2.50 (2H, m), 2.47 (3H, s), 2.20 (1H, dt, J = 2.4, 12.3 Hz), 2.09(1H, d, *J* = 12.3 Hz) 1.91 (1H, dt, *J* = 4.2, 12.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.3, 155.0, 144.7, 144.4, 140.1, 134.0, 132.82, 132.79, 131.0, 129.2, 128.8, 122.9, 118.7, 109.0, 56.4, 55.9, 46.8, 44.6, 43.0, 42.7, 38.1, 36.2, 33.5, 23.1; IR (KBr): 2910, 1603, 1482, 1453, 1441, 1416, 1328, 1279, 1230, 1175, 1153, 1105, 1053, 879, 854, 731, 429 cm^{-1}; HRMS (EI, *m/z*): Anal. calcd for $C_{24}H_{24}N_3O_2Cl_2$ (M^+): 456.1240, found: 456.1228.

8c [11]: Yellow solid. $[\alpha]_D^{20}$ = +215.0 (*c* = 0.53, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz): δ 8.01–7.98 (1H, m), 7.87-7.84 (1H, m), 7.64–7.57 (2H, m), 6.61 (1H, d, *J* = 8.4 Hz), 6.57 (1H, d, *J* = 8.4 Hz), 6.06 (1H, brs), 5.02 (1H, d, *J* = 17.4 Hz), 3.71 (3H, s), 3.27–2.88 (6H, m), 2.61–2.53 (2H, m), 2.48 (3H, s), 2.22 (1H, dt, *J*=2.4, 12.3 Hz), 2.10 (1H, *J* = 12.9) 1.92 (1H; dt, *J* = 4.5, 12.9 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD = 10:1, 125 MHz): δ 153.6, 153.3, 144.7, 144.3, 140.8, 140.5, 130.2, 128.9 (2C), 127.6, 127.5, 122.3, 118.3, 109.1, 56.3, 55.6, 46.6, 43.7, 42.3, 42.0, 41.9, 37.3, 35.8, 32.9, 23.0; IR (KBr): 2932, 1602, 1483, 1400, 1356, 1276, 1228, 1066, 1053, 836, 761 cm^{-1}; HRMS (EI, *m/z*): Anal. calcd for $C_{24}H_{26}N_3O_2$ (M^+): 388.2020, found: 388.2012.

8d: Yellow solid. Mp: 214–217 °C (dec.); $[\alpha]_D^{25}$ 99.9 (*c* 0.28, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.83 (4H, m), 7.56–7.65 (2H, m), 7.27–7.48 (5H, m), 6.95–7.08 (3H, m), 6.70 (2H, dd, *J*= 8.2, 23.8), 5.09 (1H, d, *J* =17.2), 3.86 (3H, s), 3.34 (1H, s), 3.23 (1H, dd, *J* = 6.6, 18.2), 2.85–3.15 (4H, m), 2.68–2.82 (2H, m), 2.56 (3H, s), 2.30–2.40 (1H, m), 2.02–2.20 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1, 151.0, 150.2, 149.4, 144.9, 144.6, 135.9, 135.8, 133.6, 133.5, 131.9, 131.6, 128.34 (2), 128.33 (2), 128.13, 128.08, 127.5, 126.1, 126.0, 125.6, 125.5, 124.60, 124.58, 123.1, 118.8, 109.1, 57.1, 56.1, 47.1, 42.4 (d), 41.7, 37.4, 36.0, 32.4, 29.7, 23.4; IR (KBr): 3425, 2926, 2845, 1654, 1484, 1439, 1379, 1280, 1151, 1054, 803, 778 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{40}H_{36}N_3O_2$ ($M+H^+$): 590.2808; found: 590.2802.

8e: Yellow soild. Mp: 142–146 °C; $[\alpha]_D^{25}$ 98.2 (*c* 0.91, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.07 (8H, m), 6.70 (2H, dd, *J*= 8.4, 17.1 Hz), 5.06 (1H, d, *J* = 18.0 Hz), 3.82 (3H, s), 3.69 (1H, s), 3.34–2.89 (6H, m), 2.80 (3H, s), 2.64 (1H, m), 2.41 (1H, m), 2.23 (1H, d, *J* = 12.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.1, 149.1, 149.0, 148.8, 145.4, 145.4, 144.7, 136.9, 136.8, 133.1, 133.0, 131.05, 130.98, 129.5 (2C), 129.4 (2C), 127.2, 126.1 (2), 121.5, 118.9, 109.7, 58.1, 56.0, 47.2, 41.3, 39.1, 35.4, 35.1, 31.7, 29.5, 23.9; IR (KBr): 3390, 2923, 2851, 1611, 1484, 1438, 1392, 1280, 1155, 1054, 760, 739, 468 cm^{-1}; HRMS (ESI, m/z) Anal. calcd for $C_{32}H_{30}Cl_2N_3O_2$ ($M+H^+$): 558.1715; found: 558.1713.

8f: Yellow solid. Mp: 121~131 °C; $[\alpha]_D^{25}$ 103.5 (*c* 0.80, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53–7.25 (4H, m), 7.18-7.09 (4H, m), 6.66 (2H, s), 5.05 (1H, d, *J* = 17.5 Hz), 3.79 (3H, s), 3.20 (1H, s), 3.13–3.08 (2H, m), 2.99–2.90 (3H, m), 2.62–2.50 (3H, m), 2.50 (3H, s), 2.24 (1H, t, *J* = 12.0 Hz), 2.12 (1H, d, *J* = 12.5 Hz), 1.94 (1H, m); ^{13}C NMR (CD_3OD, 75 MHz): δ 152.0, 151.0, 149.5, 149.4, 147.2, 146.5, 141.5 (2), 135.15, 135.10, 130.8, 130.64, 130.60, 130.56, 129.9, 129.5 (2), 129.3, 129.2, 123.1, 119.7, 111.1, 58.9, 56.4, 48.0, 42.8, 42.2, 41.8, 37.4, 36.6, 32.8, 24.6; IR (KBr): 3502, 2905, 2836, 1594, 1568, 1482, 1437, 1380, 1279, 1151, 1053, 785, 691, 462 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{32}H_{30}Cl_2N_3O_2$ ($M+H^+$): 558.1715; found: 558.1712.

8g: Yellow solid. Mp: 183–186 °C; $[\alpha]_D^{25}$ 96.1 (*c* 0.93, MeOH); ^{1}H NMR (CD_3OD/$CDCl_3$ = 1:1, 300 MHz): δ 7.27-7.20 (8H, m), 6.69 (2H, dd, *J* = 8.4, 18.6 Hz), 5.11 (1H, d, *J* = 17.4 Hz), 3.77 (3H, s), 3.56 (1H, s), 3.17–2.84 (6H, m), 2.56 (3H, s), 2.34 (1H, m), 2.22 (1H, d, *J* = 12.3 Hz), 2.04 (1H, m); ^{13}C NMR (CD_3OD/$CDCl_3$ = 2:1, 75 MHz): δ 151.0, 150.1, 149.34, 149.29, 146.3, 145.7, 137.3, 135.3, 131.7, 131.6, 129.3, 129.0, 122.6, 119.3, 110.4, 58.0, 56.2, 47.6, 42.1, 41.3, 37.1, 36.0, 32.3, 30.2, 24.2; IR (KBr): 3297, 2934, 2517, 1595, 1485, 1443, 1389, 1279, 1158, 1091, 1013, 840, 462 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{32}H_{30}Cl_2N_3O_2$ ($M+H^+$): 558.1715; found: 558.1711.

8h: Yellow solid. Mp: 102–106 °C; $[\alpha]_D^{25}$ 40.4 (*c* 0.91, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53–7.49 (2H, m), 7.34–7.22 (2H, m), 7.17–7.07 (4H, m), 6.66 (2H, dd, *J*= 8.0, 14.0 Hz), 4.98 (1H, d, *J* = 17.5 Hz), 3.81 (3H, s), 3.69 (1H, s), 3.20–3.08 (3H, m), 2.97–2.91 (3H, m), 2.63–2.58 (2H, m), 2.50 (3H, s), 2.23 (1H, m), 2.10 (1H, m), 1.94 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.2, 150.7, 149.5, 149.3, 144.6, 144.4, 138.9, 138.8, 132.7, 132.7, 131.2, 130.8, 129.5, 129.4, 128.7, 127.6, 126.7, 123.3, 123.1, 118.5, 108.9, 56.5, 56.1, 46.8, 42.8, 42.7, 42.5, 37.8, 36.1, 32.4, 23.2; IR (KBr): 3053, 2907, 2853, 1608, 1482, 1437, 1391, 1279, 1153, 1024, 762, 734, 657 cm^{-1}; HRMS (ESI, *m/z*)

Anal. calcd for $C_{32}H_{30}Br_2N_3O_2$ (M+H$^+$): 648.0684; found: 648.0686.

8i: Yellow solid. Mp: 168–172 °C; $[\alpha]_D^{25}$ 81.9 (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67–7.59 (2H, m), 7.44–7.41 (2H, m), 7.16–7.05 (4H, m), 6.69 (2H, d, *J* = 3.0Hz), 5.06 (1H, d, *J* = 17.7 Hz), 3.81 (3H, s), 3.77 (1H, s), 3.20–3.08 (3H, m), 2.97–2.91 (3H, m), 2.63–2.58 (2H, m), 2.50 (3H, s), 2.23 (1H, m), 2.10 (1H, m), 1.94 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.6, 148.4, 148.21, 148.16, 145.4, 144.6, 140.2 (2), 132.4, 132.3, 131.4, 131.3, 129.5, 129.4, 128.3, 128.1, 126.6, 122.32, 122.27, 121.1, 118.9, 109.5, 58.2, 55.7, 47.2, 41.2, 38.8, 35.2, 34.9, 31.5, 29.6, 23.9; IR (KBr): 3053, 2907, 2853, 1608, 1482, 1437, 1391, 1279, 1153, 1024, 762, 734, 657 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{32}H_{30}Br_2N_3O_2$ (M+H$^+$): 648.0684; found: 648.0682.

8j: Yellow solid. Mp: 207–212 °C; $[\alpha]_D^{25}$ 76.2 (*c* 0.94, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48–7.38 (4H, m), 7.27-7.19 (4H, m), 6.66 (2H, s), 5.03 (1H, d, J = 17.7 Hz), 3.78 (3H, s), 3.77 (1H, s), 3.20–3.08 (3H, m), 2.97–2.91 (3H, m), 2.63–2.58 (2H, m), 2.50 (3H, s), 2.23 (1H, m), 2.10 (1H, m), 1.94 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.6, 149.3, 149.2, 148.8, 144.7, 144.6, 137.6, 137.5, 136.3, 131.1, 129.5, 129.3, 128.7, 128.6, 123.7, 118.4, 108.5, 56.5, 55.7, 46.8, 42.8, 42.5, 38.2, 36.0, 32.5, 23.3, 21.2; IR (KBr): 3383, 2918, 2843, 2521, 1588, 1485, 1442, 1385, 1279, 1159, 1010, 724, 539 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{32}H_{30}Br_2N_3O_2$ (M+H$^+$): 648.0684; found: 648.0682.

8k: Yellow solid. Mp: 188–192 °C; $[\alpha]_D^{25}$ 97.7 (*c* 0.93, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.32 (2H, m), 7.26-7.23 (2H, m), 7.01 (2H, dd, *J* = 7.5, 9.9 Hz), 6.80 (2H, dd, *J* = 7.2, 9.0 Hz), 6.68 (2H, d, *J* = 2.1Hz), 6.12 (1H, brs), 5.09 (1H, d, *J* = 17.7 Hz), 3.81 (3H, s), 3.21–2.91 (6H, m), 2.64–2.59 (2H, m), 2.51 (3H, s), 2.25 (1H, td, *J* = 12.3, 2.4 Hz), 2.10(1H, d, J = 12.3 Hz) 1.94 (1H, td, *J* = 12.6, 4.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.18 (J = 247.6), 159.13 (*J* = 247.6), 150.0, 148.8, 146.7, 131.4, 131.2, 130.22, 130.16, 130.1, 127.1, 126.3, 126.2, 123.7, 121.4, 118.7, 115.4, 115.2, 115.0, 109.4, 57.7, 55.6, 47.0, 41.2, 39.1, 35.6, 35.0, 31.6, 29.4, 23.8; IR (KBr): 3504, 2920, 2838, 1616, 1582, 1496, 1483, 1453, 1438, 1279, 1230, 1153, 1054, 758, 458 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{32}H_{30}F_2N_3O_2$ (M+H$^+$): 526.2301; found: 526.2295.

8l: Yellow soild. Mp: 184–188 °C; $[\alpha]_D^{25}$ 110.5 (*c* 0.98, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28–6.98 (8H, m), 6.67 (2H, s), 6.11 (1H, brs), 5.05 (1H, d, *J* = 17.4 Hz), 3.80 (3H, s), 3.23–2.90 (6H, m), 2.67–2.62 (2H, m), 2.52 (3H, s), 2.26 (1H, td, *J* = 12.9, 2.4 Hz), 2.11(1H, d, *J* = 10.5 Hz) 1.99 (1H, td, *J* =12.0, 4.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6 (2C) (*J* = 247.0), 149.5, 148.6, 148.5, 145.2, 144.7, 134.6, 131.8, 131.5, 131.4, 131.2, 122.1, 118.7, 115.3, 115.2, 115.0, 114.9, 109.2, 57.5, 55.7, 47.1, 41.6, 40.1, 36.3, 35.3, 31.8, 29.6, 23.7; IR (KBr): 3389, 2930, 2839, 1612, 1586, 1485, 1440, 1390, 1280, 1230, 1153, 1054, 789, 701, 458 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{32}H_{30}F_2N_3O_2$ (M+H$^+$): 526.2301; found: 526.2301.

8m: Yellow solid. Mp: 170–176 °C; $[\alpha]_D^{25}$ 114.3 (*c* 0.94, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.27 (4H, m), 6.99–6.92 (4H, m), 6.70 (2H, dd, *J* = 9.0, 3.3 Hz), 6.21 (1H, brs), 5.04 (1H, d, J = 17.1 Hz), 3.79 (3H, s), 3.69 (1H, s), 3.43 (1H, dd *J* = 6.6, 19.5 Hz), 3.20–2.88 (6H, m), 2.83 (3H, s), 2.64 (1H, m), 2.42 (1H, m), 2.23(1H, d, *J* = 12.9 Hz); ^{13}C NMR ($CD_3OD/CDCl_3$ = 5:1, 75 MHz): δ 163.8 (2C) (*J* = 246.9), 150.6, 149.9, 149.8, 149.5, 147.0, 146.1, 135.3, 132.5, 132.4, 132.3, 128.4, 122.2, 119.6, 116.0, 115.7, 111.0, 59.2, 56.3, 48.0, 42.0, 41.7, 40.8, 36.5, 36.0, 32.2, 24.6; IR (KBr): 3383, 2923, 2850, 1604, 1510, 1484, 1439, 1280, 1225, 1156, 1054, 840, 556 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{32}H_{30}F_2N_3O_2$ (M+H$^+$): 526.2301; found: 526.2300.

8n: Yellow solid. Mp: 155–158 °C; $[\alpha]_D^{25}$ 101.7 (*c* 0.95, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.23 (4H, m), 7.07-7.03 (4H, m), 6.64 (2H, s), 5.03 (1H, d, *J* = 17.7 Hz), 3.78 (3H, s), 3.18 (1H, s), 3.12–2.87 (5H, m), 2.51– 2.49 (2H, m), 2.47 (3H, s), 2.33 (3H, s), 2.31 (3H, s), 2.28–1.85 (3H, m); ^{13}C NMR ($CD_3OD/CDCl_3$ = 1:2, 75 MHz): δ 149.9 (2C), 148.5, 147.5, 145.5 (2), 144.7 (2), 138.0, 135.4, 129.3, 129.1, 128.6 (2), 127.0, 121.3, 118.6, 109.6, 58.0, 55.7, 47.1, 40.9, 40.7, 39.3, 35.4, 34.8, 31.1, 29.4, 23.7, 20.8;IR (KBr): 2909, 2837, 1610, 1482, 1438, 1392, 1278, 1154, 1066, 822, 788, 553 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{34}H_{36}N_3O_2$ (M+H$^+$): 518.2808; found: 518.2806.

8o: Yellow solid. Mp: 144–147 °C; $[\alpha]_D^{25}$ 107.2 (*c* 0.99, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58–7.45 (8H, m), 6.69 (2H, d, *J* = 7.5 Hz), 5.06 (1H, d, *J* = 16.5 Hz), 3.78 (3H, s), 3.20 (1H, s), 3.14–2.89 (5H, m), 2.62–2.49 (2H, m), 2.47 (3H, s), 2.26–1.92 (3H, m); ^{13}C NMR (CD_3OD/ $CDCl_3$ = 5:1, 75 MHz): δ 152.7, 151.9, 149.45, 149.43, 146.8, 146.2, 143.3, 131.5, 131.4 (2), 131.3 (2), 131.1, 130.7, 127.1, 126.0, 123.8, 123.5, 119.5, 110.7, 57.8, 56.3, 47.7, 43.2, 42.8 (2C), 38.3, 36.9, 33.1, 24.3; IR (KBr): 2910, 2841, 1618, 1484, 1440, 1395, 1325, 1166, 1066, 1017, 847, 622 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{34}H_{30}F_6N_3O_2$ (M+H$^+$): 626.2242; found: 626.2238.

8p: Yellow solid. Mp: 123–126 °C; $[\alpha]_D^{25}$ 168.6 (*c* 0.91, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.14 (4H, m), 6.91 (2H, dd, *J* = 7.2, 15.0 Hz), 6.68–6.61 (4H, m), 5.11 (1H, d, *J* = 17.4 Hz), 3.77 (3H, s), 3.35 (3H, s), 3.31 (3H, s), 3.19-2.90 (6H, m), 2.59–2.48 (2H, m), 2.46 (3H, s), 2.20-2.09 (2H, m), 1.90 (1H, m); ^{13}C NMR (CD_3OD, 75 MHz): δ 157.9 (2C), 151.31, 151.26, 151.2, 150.2, 147.0, 146.5, 132.3, 132.2, 131.2, 131.0 (2C), 129.1, 129.0, 123.9, 120.9 (2C), 119.7, 111.5 (2C), 111.0, 58.1, 56.5, 55.3 (2C), 47.9, 42.7 (3C), 38.4, 36.9, 32.9, 24.5; IR (KBr): 2925, 2833, 1601, 1582, 1497, 1482, 1461, 1436, 1280, 1249, 1153, 1023, 751 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for

$C_{34}H_{36}N_3O_4$ ($M+H^+$): 550.2706; found: 550.2709.

8q: Yellow solid. Mp: 125–130 °C; $[\alpha]_D^{25}$ 146.8 (*c* 0.93, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17–7.10 (2H, m), 6.96–6.82 (4H, m), 6.82–6.77(2H, m), 6.64 (2H, s) 5.04 (1H, d, *J* = 17.4 Hz), 3.77 (3H, s), 3.65 (3H, s), 3.63 (3H, s), 3.26 (1H, s), 3.13–2.88 (5H, m), 2.65–2.52 (2H, m), 2.53 (3H, s), 2.28 (1H, t, *J* = 8.7, 21.9 Hz), 2.08 (1H, m), 2.00 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 159.1, 149.9, 149.2 (2), 149.0, 144.9, 144.7, 140.20, 140.16, 130.2, 129.0, 128.9, 123.2, 122.1, 121.9, 118.4, 114.8, 114.4, 114.3, 114.0, 108.7, 56.6, 55.6, 54.98, 54.96, 46.8, 42.4, 42.2, 41.6, 37.6, 35.8, 32.2, 23.4; IR (KBr): 2929, 2834, 1600, 1581, 1483, 1437, 1391, 1279, 1230, 1155, 1050, 753 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{34}H_{36}N_3O_4$ ($M+H^+$): 550.2706; found: 550.2709.

8r: Yellow solid. Mp: 137–141 °C; $[\alpha]_D^{25}$ 189.9 (*c* 0.93, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.27 (4H, m), 6.81–6.67 (4H, m), 6.63 (2H, d, *J* = 2.1 Hz), 5.02 (1H, d, *J* = 17.7 Hz), 3.80 (3H, s), 3.79 (3H, s), 3.78 (3H, s), 3.47 (1H, s), 3.14-2.86 (6H, m), 2.66 (3H, s), 2.43 (1H, brs), 2.08 (2H, m), 2.04 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.9 (2), 150.62, 150.57, 150.4, 149.4, 146.8, 146.1, 131.9, 131.8, 130.2, 123.4, 119.5, 114.4 (2), 114.3 (2), 110.6, 58.3, 56.3, 55.6 (2), 47.8, 42.5, 42.4, 42.2, 37.7, 35.6, 32.6, 22.4; IR (KBr): 2925, 2837, 1608, 1514, 1483, 1438, 1393, 1280, 1250, 1176, 1027, 835, 754 cm^{-1}; HRMS (ESI, *m/z*) Anal. calcd for $C_{34}H_{36}N_3O_4$ ($M+H^+$): 550.2706; found: 550.2709.

4.4 Cell culture

The mouse macrophage cell line J774 was used to evaluate the pro-inflammatory cytokine TNF-α under the lipopolysaccharide (LPS)-stimulation. Cells were grown in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 100 U/mL streptomycin at 37 °C in a humidified atmosphere of 6% CO_2.

Sinomenine and its derivatives were dissolved in dimethyl sulfoxide (DMSO) and added at a DMSO concentration at 0.1%. The same amount of 1% DMSO was added to the control cultures. Immunoassay of TNF-α cells were plated in 48-well plates at 10^5 cells/well and incubated for 12 h. Then 1 μg/mL LPS in the presence or absence of 10 μM of compounds in DMEM culture medium with 10% FBS was added to each and well treated for 6 h. The culture supernatants were collected and used for assaying the inhibitory activity on TNF-α production by ELISA kit (R&D).

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