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Design and synthesis of C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives via click reactions

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Abstract

The synthesis of C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives at the 4-OH *via* click reactions is accomplished, and a total of 16 novel sinomenine double N-heterocyclic derivatives are obtained in 74%–95% yields. The C-ring is first transformed into a 1,2-diketone structure under the action of hydrochloric acid, and then reacted with *o*-phenylenediamine to obtain a C-ring quinoxaline-substituted structure. The 4-OH of sinomenine reacts with chloropropyne to give an alkynyl sinomenine, and then reacts with sodium azide and various benzyl chlorides to give the target compounds. All the synthesized derivatives are characterized by Fourier-transform infrared spectrometry, high resolution mass spectrometry, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Keywords

1,2,3-triazoles, click reaction, quinoxaline, sinomenine, synthesis

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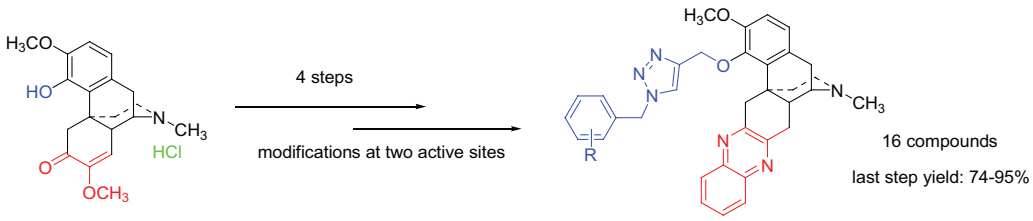

Sinomenine is mainly extracted from the roots and stems of the *Sinomenium acutum*[1,2] and exists mostly in the form of sinomenine hydrochloride. It has been found to have unique effects in the treatment of rheumatoid arthritis with 85% rate total effective.[3,4] It also exhibits pharmacological activities including antiarrhythmic, antineoplastic, analgesic and immunoregulatory effects.[5–8] However, some side effects of sinomenine itself, such as slower duration of action and allergies,[1,6,9–13] have limited the application of sinomenine in some diseases. Hence, structural modification research is inevitable as a preferred means to obtain derivatives with higher biological activity and lower side effects.

Structurally, sinomenine is similar to the morphine skeleton and consists of four fused rings. It contains a number of functional groups, such as aryl, methoxyl, phenolic hydroxy, carbonyl, double bond, and N-methyl. So it is very suitable for modification research. Previous structural modification often focused on only one site. Heterocyclic structures often show better biological activities. Therefore, modifying the heterocyclic components of sinomenine is an

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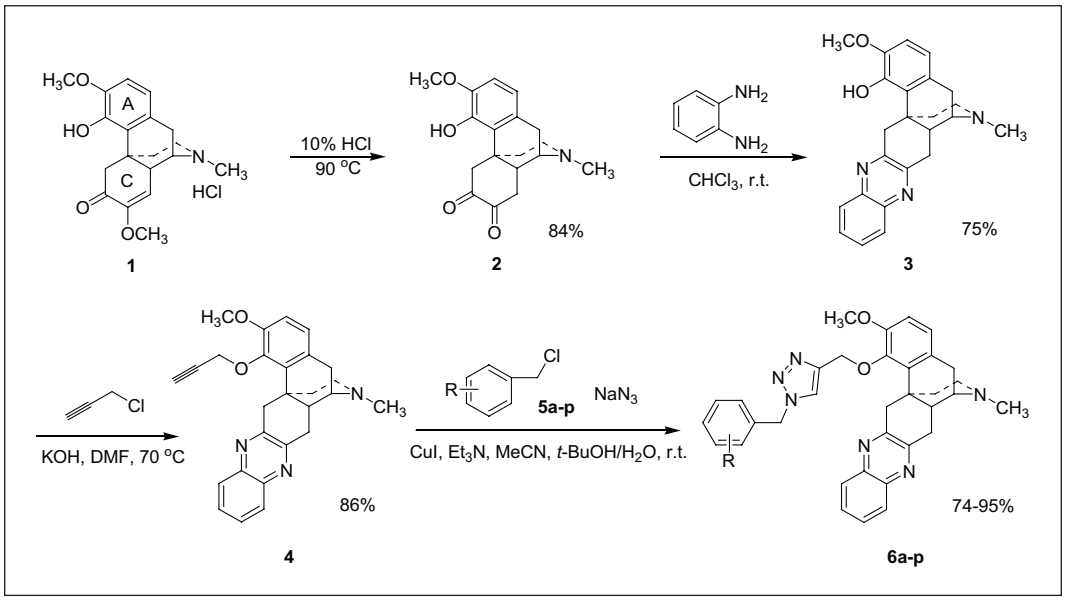
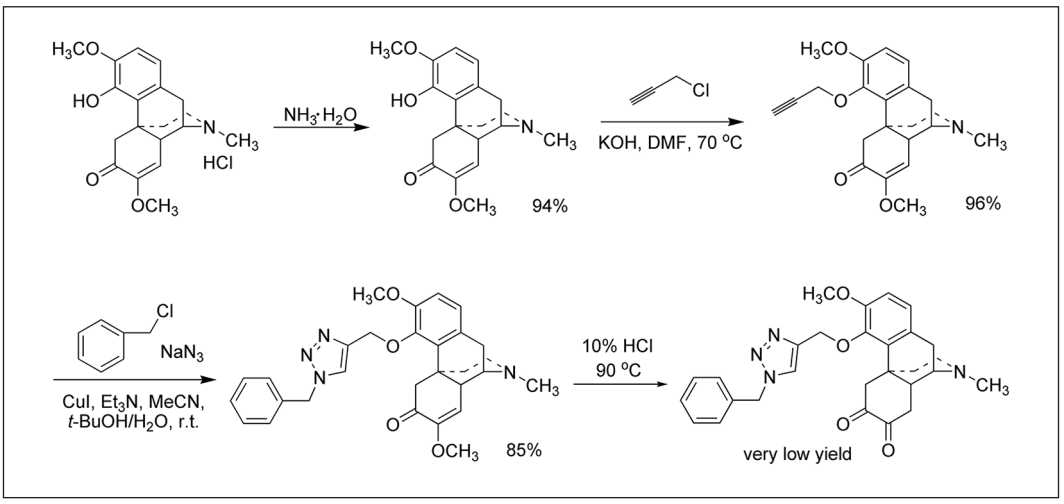


Scheme 1. Synthesis of C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives.



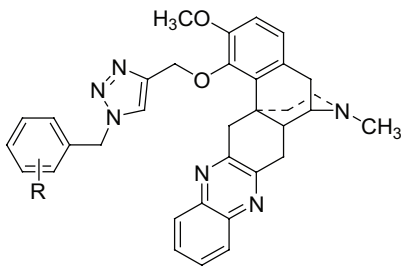
Scheme 2. An inefficient synthesis method of sinomenine 1,2,3-triazole derivatives.

effective means to improve the biological activity of this natural product. Based on our previous research,[14,15] herein we report a new process for double N-heterocyclic structure modifications on the A-ring and C-rings, respectively, in order to obtain potentially improved pharmacologically active derivatives.

Results and Discussion

Scheme 1 demonstrates the synthetic method toward the double N-heterocyclic sinomenine derivatives in four steps, and 16 target compounds are synthesized in this work. 1,4-Quinoxaline is a six-membered benzo N-heterocyclic ring, and 1,2,3-triazole is a five-membered N-heterocyclic ring. Compounds containing these heterocyclic structures often exhibit good biological activity.[16–18] The 1,2-diketone scaffold sinomenine **2** is an important intermediate for the synthesis of C-ring quinoxaline-substituted sinomenine **3**. Commercial sinomenine hydrochloride **1** can be converted into **2** using 10% hydrochloric acid at 90 °C for 5 h,[19] which then reacts with *o*-phenylenediamine in $CHCl_3$ to form compound **3**. This is the first N-heterocyclic structure installed on the C-ring of sinomenine. Another N-heterocyclic structure, that is 1,2,3-triazole, is then installed on the A-ring at the 4-OH position. The hydrogen atom on 4-OH of compound **3** is substituted with chloropropyne to obtain alkynyl sinomenine **4**, which is the key intermediate for synthesizing sinomenine 1,2,3-triazole derivatives. Finally, click reactions of **4** with different benzyl chlorides **5** and NaN_3 yield various C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives substituted at the C-4 position.[20]

Scheme 1 shows the functionalization of the C-ring with a quinoxaline and then A-ring modification with 1,2,3-triazole. We also tried to synthesize the target compounds using another method as shown in Scheme 2, which involves synthesizing the A-ring 1,2,3-triazole first and then the C-ring quinoxaline heterocycle. However, the yield was very low when reducing the C-ring to a 1,2-diketone structure with



6a: R = H	74%	**6i**: R = 3-CH_3O	86%
6b: R = 2-Cl	90%	**6j**: R = 4-CH_3O	85%
6c: R = 3-Cl	90%	**6k**: R = 2-H_3C,6-H_3C	89%
6d: R = 2-Cl,6-Cl	91%	**6l**: R = 4-NC	85%
6e: R = 3-Br	90%	**6m**:R = 2-H_3C	95%
6f: R = 2-F,6-F	92%	**6n**: R = 3-H_3C	95%
6g: R = 2-F,3-F	95%	**6o**: R = 4-H_3C	89%
6h: R = 3-F,4-F	85%	**6p**: R = 4-CF_3O	80%

Figure 1. The prepared C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives.

hydrochloric acid. Hence, the second method was not successful. This may be due to the steric hindrance of the previously synthesized 1,2,3-triazole ring which interferes with the formation of the 1,2-diketone.

We have synthesized 16 sinomenine derivatives (see Figure 1) using the method shown in Scheme 1 by using benzyl chlorides with different substituents. A wide range of derivatives was obtained with the benzyl moiety possessing *ortho, meta*, or *para* substituents, either electron-withdrawing or electron-donating. The derivatives were obtained in 74%–95% yields. The results show that this method is reliable for the synthesis of other sinomenine derivatives.

Conclusion

In summary, we have developed a practical approach to synthesize novel C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives in good to excellent yields *via* click reactions. The sinomenine derivatives possess both a five-membered N-heterocycle and a six-membered N-heterocycle, thus enriching the library of sinomenine derivatives. At the same time, we also studied different synthetic methods toward such derivatives. All the products were characterized by ^{1}H NMR, ^{13}C NMR, high resolution mass spectrometry (HRMS), and Fourier-transform infrared spectrometry (FTIR). These new sinomenine derivatives may be beneficial for future drug research and development.

Experimental

Sinomenine and all the reagents are commercially available (Macklin and China National Pharmaceutical Group Corporation) and used directly without further purification. Reactions were monitored by the thin-layer chromatography (TLC) with GF_{254} silica gel plates, and products were purified by the column chromatography over brand 300–400 mesh silica gel with $CH_2Cl_2/CH_3OH/NH_3{\cdot}H_2O$ (200:10:1–400:10:1 v/v) as eluents. Melting points were measured with a Jinke SGWX-4B melting point apparatus and are uncorrected. All NMR spectra were recorded on a Bruker AV-III 400 MHz NMR spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard. FTIR spectra were recorded on a Nicolet 6700 FTIR spectrometer. HRMS measurements were conducted with an Agilent model G6220 mass spectrometer. The optical rotations of six representative target products were recorded on a Rudolph A25829-T polarimeter in CH_3OH. HRMS, FT-IR, 1H NMR, and 13C NMR spectroscopy, please see Supplemental Material.

Synthesis of the 1,2-diketone scaffold of sinomenine (2)

Sinomenine hydrochloride (**1**) (7.31 g, 20 mmol) was dissolved in 10% HCl solution (100 mL), and then refluxed for 5 h. After the reaction was complete (monitored by TLC), the reaction solution was cooled to room temperature and the pH was adjusted to 9–10 with $NH_3{\cdot}H_2O$. The solution was extracted with dichloromethane (3×60 mL), and the combined organic layers were dried over anhydrous sodium sulfate and evaporated to give compound **2** in 84% yield. The intermediate product was used directly without purification and characterization.

Synthesis of C-ring quinoxaline-substituted sinomenine (3)

The 1,2-diketone scaffold sinomenine (**2**) (6.3 g, 20 mmol) and *o*-phenylenediamine (2.38 g, 22 mmol) were dissolved in chloroform (100 mL) and the solution was then stirred for 6 h at room temperature under a nitrogen atmosphere. After the reaction was complete (monitored by TLC), the solvent was evaporated to give a brown powder. The product was further purified by the column chromatography using $CH_2Cl_2/CH_3OH/NH_3{\cdot}H_2O$ (200:10:1 v/v) as eluent to give C-ring quinoxaline-substituted sinomenine (**3**). White powder; yield 75%; m.p.: 240–242 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.00 (1H, m), 7.86 (1H, m), 7.60 (2H, m), 6.59 (2H, q, J=8.4 Hz), 6.09 (1H, s), 5.02 (1H, d, J=17.2 Hz), 3.71 (3H, s), 3.25-2.89 (6H, m), 2.58 (2H, m), 2.48 (3H, s), 2.22 (1H, td, J=12.4, 2.8 Hz), 2.10 (1H, m), 1.97-1.90 (1H, td, J=12.8, 4.8 Hz); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.8, 153.4, 144.7, 144.5, 141.3, 141.2, 130.9, 128.6, 128.6, 128.5, 128.1, 123.1, 118.6, 108.9, 56.6, 55.8, 46.9, 44.5, 42.9, 42.6, 38.0, 36.2, 33.5, 23.3; IR (υ_{max}, cm^{-1}): 2929, 1602, 1578, 1481, 1438, 1274, 1228, 1150, 1052, 758; HRMS: *m/z* calcd for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2025; found: 388.2018.

Synthesis of alkynyl sinomenine (4)

The C-ring quinoxaline-substituted sinomenine (**3**) (3.87 g, 10 mmol), chloropropyne (1.49 g, 20 mmol), and KOH (1.12 g, 20 mmol) were dissolved in DMF (50 mL), and the

solution was refluxed for 8 h at 70 °C. After the reaction was complete (monitored by TLC), the DMF was evaporated and the crude alkynyl sinomenine (**4**) was dissolved in dichloromethane (20 mL), washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate, and then evaporated to give compound **4** as a brown powder. Yield: 86%; m.p.: 56–58 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 7.99 (1H, m), 7.85 (1H, m), 7.60 (2H, m), 6.82 (1H, d, *J*=8.4 Hz), 6.65 (1H, d, *J*=8.4 Hz), 4.93 (1H, d, *J*=17.2 Hz), 4.88-4.65 (2H, m), 3.71 (3H, s), 3.23-2.90 (6H, m), 2.55 (2H, m), 2.47 (3H, s), 2.40 (1H, t, *J*=2.4 Hz), 2.21-2.13 (2H, m), 1.99-1.92 (1H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.7, 153.2, 150.9, 146.2, 141.4, 141.3, 131.0, 130.7, 128.8, 128.6, 128.0, 123.6, 111.0, 79.7, 75.2, 59.7, 56.3, 55.6, 46.8, 45.1, 43.0, 42.9, 39.5, 36.6, 33.6, 23.5; IR (υ_{max}, cm^{-1}): 3283, 2907, 2114, 1600, 1570, 1478, 1435, 1275, 1215, 1152, 1036, 761; HRMS: *m/z* calcd for $C_{27}H_{28}N_3O_2$ $[M+H]^+$: 426.2176; found: 426.2172.

Synthesis of C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (*6a–p*); general procedure

Benzyl chloride (**5**) (2 mmol) and NaN_3 (143 g, 2.2 mmol) were dissolved in DMF (10 mL) and reacted for 24 h at room temperature. After the reaction was complete, a solution of compound **4** (425.5 mg, 1 mmol), CuI (38 mg, 0.2 mmol), and Et_3N (202.4 mg, 2 mmol) in a co-solvent of MeCN/*t*-BuOH/H_2O (10 mL, 1:3:6 v/v) was poured into the reaction mixture and stirred for another 10 h at room temperature. After the reaction was complete (monitored by TLC), the solvent was evaporated and the solid residue was dissolved in dichloromethane (20 mL). The solution was washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate, and then evaporated to give the crude target compound **6**. The product was then purified by the column chromatography using CH_2Cl_2/CH_3OH/$NH_3{\cdot}H_2O$ (400:10:1 v/v) on silica gel to give the C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives **6a–p**.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6a**). Brown powder; yield: 74%; m.p.: 87–89 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.22 (1H, s), 7.84 (1H, m), 7.73 (1H, m), 7.58 (2H, m), 7.45-7.38 (5H, m), 6.90 (1H, d, *J*=8.4 Hz), 6.68 (1H, d, *J*=8.4 Hz), 5.65 (2H, dd, *J*=31.6, 14.8 Hz), 5.18 (2H, dd, *J*=17.6, 11.2 Hz), 4.86 (1H, d, *J*=17.2 Hz), 3.67 (3H, s), 3.23-2.93 (6H, m), 2.58 (2H, m), 2.48 (3H, s), 2.21-2.14 (1H, m), 2.00-1.91 (2H, m); ^{13}C NMR (100 MHz; CDCl3; TMS): δ 153.5, 153.0, 151.2, 146.6, 145.7, 141.3, 141.2, 134.9, 130.7, 130.4, 129.1, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 123.7, 123.6, 111.1, 65.6, 56.4, 55.6, 54.3, 46.7, 44.9, 42.9, 42.8, 39.5, 36.5, 33.5, 23.6; IR (υ_{max}, cm^{-1}): 2909, 1602, 1575, 1480, 1435, 1334, 1278, 1213, 1150, 1053, 763; HRMS: *m/z* calcd for $C_{34}H_{35}N_6O_2$ $[M+H]^+$: 559.2821; found: 559.2817.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6b**). Brown powder; yield: 90%; m.p.: 85–86 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.27 (1H, s), 7.85 (1H, m), 7.80 (1H, m), 7.58 (2H, m), 7.47 (1H, m), 7.35-7.28 (3H, m), 6.84 (1H, d, *J*=8.4 Hz), 6.67 (1H, d, *J*=8.4 Hz), 5.78 (2H, s), 5.20 (2H, dd, *J*=15.6, 11.6 Hz), 4.87 (1H, d, *J*=17.2 Hz), 3.69 (3H, s), 3.22-2.90 (6H, m), 2.52 (2H, m), 2.46 (3H, s), 2.17-2.10 (1H, m), 2.01-1.89 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.1, 146.6, 145.6, 141.3, 141.2, 133.5, 132.8, 130.7, 130.6, 130.4, 130.1, 129.9, 128.8, 128.6, 128.5, 128.1, 127.6, 124.0, 123.7, 111.0, 65.6, 56.3, 55.5, 51.5, 46.6, 44.9, 42.9, 42.8, 39.5, 36.5, 33.5, 23.6; IR (υ_{max}, cm^{-1}): 2906, 1595, 1573, 1474, 1433, 1333, 1271, 1208, 1152, 1048, 755; HRMS: *m/z* calcd for $C_{34}H_{34}N_6O_2Cl$ $[M+H]^+$: 593.2432; found: 593.2433.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6c**). Brown powder; yield: 90%; m.p.: 98–100 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.27 (1H, s), 7.85 (1H, m), 7.76 (1H, m), 7.59 (2H, m), 7.38-7.32 (3H, m), 7.26 (1H, s), 6.85 (1H, d, *J*=8.4 Hz), 6.68 (1H, d, *J*=8.4 Hz), 5.63 (2H, q, *J*=15.2 Hz), 5.19 (2H, dd, *J*=21.2, 11.6 Hz), 4.86 (1H, d, *J*=17.6 Hz), 3.68 (3H, s), 3.23-2.91 (6H, m), 2.56 (2H, m), 2.47 (3H, s), 2.20-2.13 (1H, m), 2.00-1.88 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.1, 146.6, 145.6, 141.3, 141.2, 133.5, 132.8, 130.7, 130.6, 130.4, 130.1, 129.9, 128.8, 128.6, 128.5, 128.1, 127.6, 124.0, 123.7, 111.0, 65.6, 56.3, 55.5, 51.5, 46.6, 44.9, 42.9, 42.8, 39.5, 36.5, 33.5, 23.6; IR (υ_{max}, cm^{-1}): 2907, 1602, 1575, 1480, 1435, 1334, 1275, 1209, 1150, 1049, 763; HRMS: *m/z* calcd for $C_{34}H_{34}N_6O_2Cl$ $[M+H]^+$: 593.2432; found: 593.2429.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6d**). Brown powder; yield: 91%; m.p.: 103–104 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.19 (1H, s), 7.83 (2H, m), 7.58 (2H, m), 7.43 (2H, m), 7.32-7.28 (1H, m), 6.82 (1H, d, *J*=8.4 Hz), 6.66 (1H, d, *J*=8.4 Hz), 5.96 (2H, dd, *J*=17.6, 14.4 Hz), 5.17 (2H, dd, *J*=15.2, 11.6 Hz), 4.87 (1H, d, *J*=17.2 Hz), 3.67 (3H, s), 3.21-2.89 (6H, m), 2.52 (2H, m), 2.45 (3H, s), 2.14-2.07 (1H, m), 1.99-1.83 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.7, 153.1, 151.0, 146.7, 145.1, 141.2, 136.9, 131.0, 130.8, 130.7, 130.4, 128.9, 128.8, 128.6, 128.5, 128.0, 123.6, 123.5, 111.0, 65.6, 56.2, 55.5, 49.1, 46.6, 44.8, 43.0, 42.9, 39.5, 36.5, 33.6, 23.5; IR (υ_{max}, cm^{-1}): 2906, 1581, 1566, 1477, 1435, 1335, 1277, 1209, 1151, 1049, 760; HRMS: *m/z* calcd for $C_{34}H_{33}N_6O_2Cl_2$ $[M+H]^+$: 627.2042; found: 627.2038. $[\alpha]_D^{20} = +30.14$ (c 0.16, CH_3OH).

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6e**). Brown powder; yield: 90%; m.p.: 108–110 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.29 (1H, s), 7.86 (1H, m), 7.76 (1H, m), 7.62-7.50 (4H, m), 7.33-7.28 (2H, m), 6.85 (1H, d, *J*=8.4 Hz), 6.68 (1H, d, *J*=8.4 Hz), 5.63 (2H, q, *J*=15.2 Hz), 5.21 (2H, dd, *J*=21.6, 11.6 Hz), 4.85 (1H, d, *J*=17.6 Hz), 3.68 (3H, s), 3.23-2.90 (6H, m), 2.54 (2H, m), 2.47 (3H, s), 2.19-2.12 (1H, m), 2.00-1.89 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.1, 146.5, 146.0, 141.3, 141.1, 137.2, 131.8, 131.0, 130.8, 130.7, 130.6, 128.8, 128.7, 128.4, 128.1, 126.7, 123.8, 123.7, 123.1, 111.0, 65.6, 56.2, 55.6, 53.5, 46.6, 44.9, 43.0, 42.9, 39.7, 36.5, 33.5, 23.6; IR (υ_{max}, cm^{-1}): 2904, 1597, 1572,

1477, 1432, 1334, 1275, 1210, 1151, 1048, 760; HRMS: *m/z* calcd for $C_{34}H_{34}N_6O_2Br$ $[M+H]^+$: 637.1927; found: 637.1930. $[\alpha]_D^{20} = +28.67$ (c 0.15, CH_3OH).

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6f**). Brown powder; yield: 92%; m.p.: 102–104 °C; ^1H NMR (400 MHz; $CDCl_3$; TMS): δ 8.27 (1H, s), 7.90-7.85 (2H, m), 7.60 (2H, m), 7.42-7.35 (1H, m), 7.01 (2H, m), 6.83 (1H, d, *J*=8.4 Hz), 6.67 (1H, d, *J*=8.4 Hz), 5.74 (2H, dd, *J*=17.6, 14.4 Hz), 5.17 (2H, dd, *J*=18.4, 11.6 Hz), 4.87 (1H, d, *J*=17.6 Hz), 3.68 (3H, s), 3.22-2.90 (6H, m), 2.52 (2H, m), 2.46 (3H, s), 2.16-2.09 (1H, m), 1.99-1.86 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 162.8, 162.7, 160.3, 160.2, 153.7, 153.1, 151.1, 146.7, 145.6, 141.3, 131.5, 131.4, 131.2, 130.8, 130.7, 128.8, 128.6, 128.1, 123.7, 123.6, 112.0, 111.9, 111.8, 111.7, 111.3, 111.1, 111.0, 110.9, 65.6, 56.3, 55.5, 46.6, 44.9, 43.0, 42.9, 41.5, 41.4, 41.3, 39.6, 36.5, 33.6, 23.6; IR (υ_{max}, cm^{-1}): 2906, 1625, 1595, 1473, 1434, 1334, 1274, 1231, 1153, 1047, 763; HRMS: *m/z* calcd for $C_{34}H_{33}N_6O_2F_2$ $[M+H]^+$: 595.2633; found: 595.2630. (13C data assignment for this compound, please see Supplemental Material.)

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6g**). Brown powder; yield: 95%; m.p.: 89–91 °C; ^1H NMR (400 MHz; $CDCl_3$; TMS): δ 8.29 (1H, s), 7.86 (2H, m), 7.60 (2H, m), 7.24-7.11 (3H, m), 6.84 (1H, d, *J*=8.4 Hz), 6.68 (1H, d, *J*=8.4 Hz), 5.73 (2H, d, *J*=1.2 Hz), 5.19 (2H, dd, *J*=26.4, 11.6 Hz), 4.86 (1H, d, *J*=17.2 Hz), 3.68 (3H, s), 3.23-2.90 (6H, m), 2.53 (2H, m), 2.46 (3H, s), 2.17-2.10 (1H, m), 2.00-1.87 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.8, 151.7, 151.0, 149.9, 149.8, 149.3, 149.2, 147.5, 147.3, 146.5, 145.9, 141.3, 141.2, 130.8, 130.7, 128.8, 128.7, 128.5, 128.1, 125.2, 125.2, 125.2, 125.2, 124.9, 124.9, 124.8, 124.8, 124.6, 124.5, 123.8, 123.7, 118.0, 117.8, 111.0, 65.5, 56.2, 55.5, 47.2, 47.2, 47.2, 46.6, 45.0, 43.0, 42.9, 39.7, 36.5, 33.5, 23.5; IR (υ_{max}, cm^{-1}): 2904, 1629, 1600, 1476, 1438, 1335, 1278, 1215, 1150, 1052, 763; HRMS: *m/z* calcd for $C_{34}H_{33}N_6O_2F_2$ $[M+H]^+$: 595.2633; found: 595.2628. $[\alpha]_D^{20} = +26.65$ (c 0.33, CH_3OH).

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6h**). Brown powder; yield: 85%; m.p.: 87–88 °C; ^1H NMR (400 MHz; $CDCl_3$; TMS): δ 8.26 (1H, s), 7.86 (1H, m), 7.75 (1H, m), 7.59 (2H, m), 7.24-7.18 (2H, m), 7.13 (1H, m), 6.85 (1H, d, *J*=8.4 Hz), 6.68 (1H, d, *J*=8.4 Hz), 5.61 (2H, dd, *J*=29.2, 15.2 Hz), 5.20 (2H, dd, *J*=27.6, 11.6 Hz), 4.85 (1H, d, *J*=17.6 Hz), 3.68 (3H, s), 3.23-2.89 (6H, m), 2.54 (2H, m), 2.46 (3H, s), 2.18-2.11 (1H, m), 2.00-1.88 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.2, 151.8, 151.8, 151.7, 151.6, 151.0, 149.3, 149.3, 149.2, 149.1, 146.5, 146.0, 141.3, 141.1, 132.0, 132.0, 132.0, 131.9, 130.8, 130.7, 128.9, 128.7, 128.3, 128.1, 124.3, 124.3, 124.3, 124.2, 123.8, 123.6, 118.0, 117.9, 117.3, 117.2, 111.0, 65.6, 56.2, 55.5, 53.0, 46.5, 44.9, 42.9, 42.8, 39.8, 36.5, 33.5, 23.5; IR (υ_{max}, cm^{-1}): 2907, 1600, 1587, 1480, 1435, 1334, 1264, 1213, 1153, 1048, 763; HRMS: *m/z* calcd for $C_{34}H_{33}N_6O_2F_2$ $[M+H]^+$: 595.2633; found: 595.2631. $[\alpha]_D^{20} = +27.25$ (c 0.21, CH_3OH).

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6i**). Brown powder; yield: 86%; m.p.: 90–91 °C; ^1H NMR (400 MHz; $CDCl_3$; TMS): δ 8.24 (1H, s), 7.85 (1H, m), 7.75 (1H, m), 7.61-7.54 (2H, m), 7.35-7.31 (1H, m), 6.97 (1H, m), 6.92 (2H, m), 6.84 (1H, d, *J*=8.4 Hz), 6.67 (1H, d, *J*=8.4 Hz), 5.61 (2H, dd, *J*=32, 14.8 Hz), 5.18 (2H, dd, *J*=16.4, 12 Hz), 4.86 (1H, d, *J*=17.6 Hz), 3.80 (3H, s), 3.68 (3H, s), 3.22-2.91 (6H, m), 2.55 (2H, m), 2.47 (3H, s), 2.19-2.12 (1H, m), 2.00-1.90 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 160.1, 153.6, 153.1, 151.1, 146.6, 145.7, 141.3, 141.2, 136.4, 130.8, 130.6, 130.2, 128.8, 128.6, 128.5, 128.1, 123.7, 120.3, 114.2, 113.7, 111.1, 65.6, 56.3, 55.5, 55.3, 54.2, 46.6, 44.9, 42.9, 42.8, 39.6, 36.5, 33.5, 23.6; IR (υ_{max}, cm^{-1}): 2903, 1613, 1571, 1477, 1518, 1477, 1437, 1335, 1274, 1210, 1152, 758; HRMS: *m/z* calcd for $C_{35}H_{37}N_6O_3$ $[M+H]^+$: 589.2927; found: 589.2924.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6j**). Brown powder; yield: 85%; m.p.: 92–93 °C; ^1H NMR (400 MHz; $CDCl_3$; TMS): δ 8.19 (1H, s), 7.84 (1H, m), 7.72 (1H, m), 7.61-7.53 (2H, m), 7.35-7.33 (2H, m), 6.94 (2H, d, *J*=8 Hz), 6.83 (1H, d, *J*=8.4 Hz), 6.67 (1H, d, *J*=8.4 Hz), 5.57 (2H, dd, *J*=35.2, 14.8 Hz), 5.17 (2H, dd, *J*=17.2, 11.6 Hz), 4.86 (1H, d, *J*=17.2 Hz), 3.81 (3H, s), 3.67 (3H, s), 3.21-2.88 (6H, m), 2.52 (2H, m), 2.45 (3H, s), 2.17-2.10 (1H, m), 1.99-1.85 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 159.9, 153.6, 153.1, 151.1, 146.6, 145.5, 141.2, 141.1, 130.8, 130.6, 129.7, 128.8, 128.6, 128.5, 128.0, 126.9, 123.7, 123.5, 114.4, 111.1, 65.6, 56.2, 55.5, 55.3, 53.7, 46.6, 44.9, 42.9, 42.8, 39.6, 36.5, 33.5, 23.5 ppm; IR (υ_{max}, cm^{-1}): 2904, 1616, 1587, 1477, 1513, 1477, 1437, 1335, 1277, 1248, 1175, 1156, 1052, 1034, 764; HRMS: *m/z* calcd for $C_{35}H_{37}N_6O_3$ $[M+H]^+$: 589.2927; found: 589.2929. $[\alpha]_D^{20} = +26.97$ (c 0.09, CH_3OH).

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6k**). Brown powder; yield: 89%; m.p.: 99–100 °C; ^1H NMR (400 MHz; $CDCl_3$; TMS): δ 7.96 (1H, s), 7.84 (1H, m), 7.63-7.52 (3H, m), 7.24 (1H, m), 7.15 (2H, d, *J*=7.6 Hz), 6.82 (1H, d, *J*=8.4 Hz), 6.64 (1H, d, *J*=8.4 Hz), 5.70 (2H, q, *J*=14.8 Hz), 5.12 (2H, dd, *J*=28, 11.6 Hz), 4.84 (1H, d, *J*=17.2 Hz), 3.64 (3H, s), 3.20-2.89 (6H, m), 2.52 (2H, m), 2.45 (3H, s), 2.43 (6H, s), 2.15-2.08 (1H, m), 1.99-1.82 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.1, 146.7, 145.0, 141.2, 138.2, 130.8, 130.7, 130.7, 129.1, 129.0, 128.7, 128.6, 128.5, 128.0, 123.6, 123.1, 111.0, 65.6, 56.2, 55.5, 48.5, 46.6, 44.7, 43.0, 42.9, 39.6, 36.5, 33.6, 23.6, 19.9; IR (υ_{max}, cm^{-1}): 2904, 1595, 1573, 1477, 1435, 1334, 1278, 1212, 1153, 1048, 764; HRMS: *m/z* calcd for $C_{36}H_{39}N_6O_2$ $[M+H]^+$: 587.3134; found: 587.3133.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6l**). Brown powder; yield: 85%; m.p.: 110–112 °C; ^1H NMR (400 MHz; $CDCl_3$; TMS): δ 8.30 (1H, s), 7.86 (1H, m), 7.71 (3H, m), 7.63-7.55 (2H, m), 7.46 (2H, m), 6.86 (1H, d, *J*=8.4 Hz), 6.68 (1H, d, *J*=8.4 Hz), 5.73 (2H, dd, *J*=26.8, 15.6 Hz), 5.20 (2H, dd, *J*=35.6, 11.6 Hz),

4.84 (1H, d, J=17.2 Hz), 3.69 (3H, s), 3.23-2.89 (6H, m), 2.54 (2H, m), 2.46 (3H, s), 2.19-2.12 (1H, m), 2.01-1.88 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.2, 151.1, 146.5, 146.2, 141.3, 141.1, 140.2, 132.8, 130.9, 130.8, 128.8, 128.6, 128.5, 128.2, 128.2, 123.8, 118.2, 112.6, 111.1, 65.6, 56.2, 55.5, 53.4, 46.6, 45.0, 43.0, 42.9, 39.8, 36.6, 33.6, 23.6; IR (υ_{max}, cm^{-1}): 2904, 2231, 1610, 1572, 1480, 1434, 1334, 1277, 1207, 1153, 1049, 763; HRMS: *m/z* calcd for $C_{35}H_{34}N_7O_2$ $[M+H]^+$: 584.2774; found: 584.2772.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6m**). Brown powder; yield: 95%; m.p.: 86–88 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.10 (1H, s), 7.84 (1H, m), 7.68 (1H, m), 7.60-7.52 (2H, m), 7.34-7.28 (4H, m), 6.83 (1H, d, J=8.4 Hz), 6.66 (1H, d, J=8.4 Hz), 5.65 (2H, dd, J=35.2, 14.8 Hz), 5.16 (2H, dd, J=13.6, 11.6 Hz), 4.86 (1H, d, J=17.6 Hz), 3.66 (3H, s), 3.21-2.88 (6H, m), 2.51 (2H, m), 2.45 (3H, s), 2.36 (3H, s), 2.16-2.09 (1H, m), 2.01-1.84 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.0, 146.6, 145.3, 141.2, 141.1, 137.0, 132.8, 131.0, 130.8, 130.7, 129.5, 129.0, 128.8, 128.6, 128.5, 128.0, 126.6, 123.7, 123.6, 111.1, 65.6, 56.2, 55.5, 52.4, 46.6, 44.8, 42.9, 42.8, 39.6, 36.5, 33.5, 23.5, 19.1; IR (υ_{max}, cm^{-1}): 2907, 1601, 1572, 1477, 1435, 1334, 1277, 1215, 1153, 1048, 760; HRMS: *m/z* calcd for $C_{35}H_{37}N_6O_2$ $[M+H]^+$: 573.2978; found: 573.2984. $[\alpha]_D^{20}$ = +28.57 (c 0.09, CH_3OH).

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6n**). Brown powder; yield: 95%; m.p.: 82–84 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.24 (1H, s), 7.85 (1H, m), 7.73 (1H, m), 7.61-7.53 (2H, m), 7.32-7.29 (1H, m), 7.19 (3H, m), 6.84 (1H, d, J=8.4 Hz), 6.67 (1H, d, J=8.4 Hz), 5.61 (2H, dd, J=33.6, 14.8 Hz), 5.18 (2H, dd, J=16, 11.2 Hz), 4.87 (1H, d, J=17.2 Hz), 3.67 (3H, s), 3.22-2.91 (6H, m), 2.54 (2H, m), 2.47 (3H, s), 2.36 (3H, s), 2.19-2.12 (1H, m), 2.00-1.90 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.2, 146.7, 145.7, 141.3, 141.2, 138.9, 134.9, 130.8, 130.7, 129.4, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 125.3, 123.7, 123.6, 111.2, 65.7, 56.3, 55.6, 54.3, 46.6, 44.9, 43.0, 42.8, 39.6, 36.6, 33.6, 23.6, 21.4; IR (υ_{max}, cm^{-1}): 2904, 1611, 1572, 1476, 1437, 1334, 1277, 1210, 1151, 1050, 762; HRMS: *m/z* calcd for $C_{35}H_{37}N_6O_2$ $[M+H]^+$: 573.2978; found: 573.2971.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6o**). Brown powder; yield: 89%; m.p.: 87–88 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.20 (1H, s), 7.85 (1H, m), 7.73 (1H, m), 7.61-7.53 (2H, m), 7.29 (2H, m), 7.22 (2H, m), 6.83 (1H, d, J=8.4 Hz), 6.67 (1H, d, J=8.4 Hz), 5.60 (2H, dd, J=32.8, 14.8 Hz), 5.17 (2H, dd, J=16.8, 11.6 Hz), 4.86 (1H, d, J=16.8 Hz), 3.67 (3H, s), 3.21-2.89 (6H, m), 2.52 (2H, m), 2.46 (3H, s), 2.37 (3H, s), 2.17-2.10 (1H, m), 1.99-1.89 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.1, 151.1, 146.7, 145.6, 141.3, 141.2, 138.6, 131.9, 130.8, 130.6, 129.8, 128.8, 128.6, 128.5, 128.2, 128.1, 123.7, 123.5, 111.1, 65.6, 56.3, 55.5, 54.1, 46.6, 44.9, 42.9, 42.8, 39.7, 36.5, 33.6, 23.6, 21.2; IR (υ_{max}, cm^{-1}): 2906, 1601, 1572, 1480, 1435, 1335, 1277, 1210, 1151, 1050, 763; HRMS: *m/z* calcd for $C_{35}H_{37}N_6O_2$ $[M+H]^+$: 573.2978; found: 573.2983.

C-ring quinoxaline-substituted sinomenine 1,2,3-triazole derivatives (**6p**). Brown powder; yield: 80%; m.p.: 97–99 °C; ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ 8.29 (1H, s), 7.85 (1H, m), 7.69 (3H, m), 7.61-7.50 (2H, m), 7.49 (2H, m), 6.85 (1H, d, J=8.4 Hz), 6.68 (1H, d, J=8.4 Hz), 5.72 (2H, dd, J=33.2, 15.2 Hz), 5.20 (2H, dd, J=22.8, 11.6 Hz), 4.85 (1H, d, J=17.2 Hz), 3.68 (3H, s), 3.22-2.90 (6H, m), 2.54 (2H, m), 2.46 (3H, s), 2.19-2.12 (1H, m), 2.01-1.91 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$; TMS): δ 153.6, 153.2, 151.1, 146.5, 146.2, 141.3, 141.2, 139.0, 130.8, 130.8, 128.9, 128.6, 128.3, 128.2, 126.2, 126.1, 126.1, 126.1, 123.8, 123.7, 111.0, 65.6, 56.2, 55.5, 53.6, 46.6, 45.0, 43.1, 42.9, 39.8, 36.6, 33.6, 23.6; IR (υ_{max}, cm^{-1}): 2904, 1622, 1573, 1479, 1439, 1421, 1323, 1277, 1210, 1123, 1066, 763; HRMS: *m/z* calcd for $C_{35}H_{34}N_6O_3F_3$ $[M+H]^+$: 643.2644; found: 643.2647.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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