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Chemistry & Drug Discovery

Supporting Information

Anti-Dengue-Virus Activity and Structure–Activity Relationship Studies of Lycorine Derivatives

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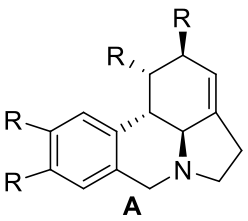
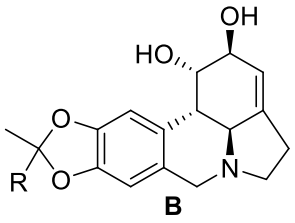
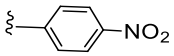
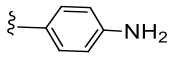
Table S1. The lycorine derivatives containing a modified A-ring, and their in vitro activities against DENV.



A



B

Compound	Structure	R	CC_{50}[a]/μM	EC_{50}[b]/μM
3	A	OAc	>300	>300
4	A	OH	>300	>300
5	B	CH_3	>300	>300
6	B	$(CH_2)_2CH_3$	>300	>300
7	B	$(CH_2)_2CH_2Cl$	>300	>300
8	B		>300	>300
9	B		>300	>300

[a]The molar concentration of a drug that causes 50% reduction in cell viability.

[b]The molar concentration of a drug that inhibits 50% of viral antigen production.

Table S2. Predicted pEC_{50} calculated by 3D-QSAR.

Compound	pEC_{50}[a]	Pred. pEC_{50}[b]	Compound	pEC_{50}[a]	Pred. pEC_{50}[b]
1	6.1	6.1	**27**	4.5	4.5
2	4.6	4.6	**28**	3.6	3.6
10	6.4	6.4	**29**	3.9	3.9
11	4.5	4.5	**30**	4.0	4.0
12	3.9	3.9	**31**	4.7	4.7
13	3.8	3.8	**32**	4.5	4.5
14	4.7	4.7	**33**	4.4	4.4
15	4.3	4.4	**34**	5.1	5.2
16	4.1	4.5	**35**	5.1	5.0
17	3.8	3.8	**36**	5.4	5.4
18	4.0	4.0	**37**	5.3	5.3
19	4.0	4.0	**38**	4.5	4.5
22	5.7	5.7	**39**	4.4	4.4
23	6.3	6.3	**40**	4.2	4.2
25	3.7	3.6	**41**	3.9	3.9
26	3.7	3.7			

[d]Negative logarithm of EC_{50}.

[e]Predicted pEC_{50} is calculated using the 3D-QSAR model for validation.

General procedure for 6-7

To a solution of **4** in 2 mL of methanol, anhydrous ketone (20 eq) and PTSA (0.2 eq) were added, and the mixture was refluxed at 70 ℃ for 20 h. The solvent was removed under reduced pressure followed by the addition of DCM and water. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated, and the crude residue was purified using silica gel chromatography to yield the product.

12-Methyl-12-propyllycorine (6)

Following the previously described general procedure, 129 mg (0.47 mmol) of **4** yielded **6** as a pale solid (146 mg, 90.6%). ^{1}H NMR (400 MHz, CD_3OD): δ=0.84 (t, *J*= 6.8 Hz, 3H), 1.32 (m, 2H), 1.43 (s, 3H), 1.56 (m, 2H), 2.82 (m, 2H), 3.07 (d, *J*=11.2 Hz, 1H), 3.42 (m, 1H), 3.73 (m, 2H), 4.14 (d, *J*=13.6 Hz, 1H), 4.42 (d, *J*=13.6 Hz, 1H), 4.92 (s, 1H), 5.15 (d, *J*=5.2 Hz, 1H), 5.84 (s, 1H), 6.76 (s, 1H), 7.00 ppm (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ=14.6, 17.9, 24.0, 30.4, 42.7, 43.3, 54.5, 54.9, 62.0, 72.2, 75.0, 111.7, 113.4, 115.3, 122.2, 122.9, 129.9, 140.1, 145.8, 147.2 ppm; ESI-MS: *m/z* 344 $[M+H]^+$; HRMS: $[M+H]^+$ calcd. for $C_{20}H_{25}NO_4$: 344.1840, found: 344.1849.

12-Methyl-12-(3-chloro-propyl)lycorine (7)

Following the previously described general procedure, 182 mg (0.58 mmol) of **4** yielded **7** as a pale solid (56 mg, 46.2%). ^{1}H NMR (400 MHz, CD_3OD): δ=1.34 (s, 3H), 1.77-1.64 (m, 4H), 2.63-2.53 (m, 1H), 2.66 (m, 2H), 2.73 (d, *J*=10.4 Hz, 1H), 3.01 (d, *J*=10.4 Hz, 1H), 3.28-3.19 (m, 1H), 3.44 (m, 2H), 3.49 (d, *J*=14.0 Hz, 1H), 3.76 (d, *J*=13.6 Hz, 1H), 4.66 (m, 1H), 4.83 (m, 1H), 5.59 (s, 1H), 6.16 (s, 1H), 6.65 ppm (s, 1H); ^{13}C NMR (400 MHz, CD_3OD): δ=24.2, 26.8, 28.7, 36.8, 43.2, 45.4, 53.6, 55.7, 60.8, 72.0, 75.0, 109.8, 111.8, 113.7, 118.0, 125.6, 126.3, 143.7, 144.0, 144.2 ppm; ESI-MS: *m/z* 378 $[M+H]^+$; HRMS: $[M+H]^+$ calcd. for $C_{20}H_{24}ClNO_4$: 378.1467, found: 378.1469.

General procedure for 11-13 and **16-19**

To a solution of **10** in anhydrous pyridine, acyl chloride or anhydride in anhydrous DCM was slowly added for 15 min at 0 ℃. The solution was stirred at 0 ℃ until TLC analysis indicated that all of the starting material had been consumed. Subsequently, DCM and water were added. The organic layer was washed using an aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was purified using silica gel chromatography to yield the products.

1-Acetyl-2-valeryllycorine (12)

Following the previously described general procedure, 95 mg (0.28 mmol) of **10** yielded **12** as a pale solid (163 mg, 64.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (t, *J*=7.3 Hz, 3H), 1.36 (dd, *J*=15.0, 7.4 Hz, 3H), 1.61 (dd, *J*=15.2, 7.6 Hz, 2H), 1.95 (s, 3H), 2.33 (td, *J*=7.4, 3.3 Hz, 2H), 2.43 (dd, *J*=17.5, 8.7 Hz, 1H), 2.66 (s, 2H), 2.81 (d, *J*=10.5 Hz, 1H), 2.89 (d, *J*=10.5 Hz, 1H), 3.38 (dt, *J*=9.1, 4.7 Hz, 1H), 3.55 (d, *J*=14.0 Hz, 1H), 4.16 (d, *J*=14.1 Hz, 1H), 5.26 (s, 1H), 5.53 (s, 1H), 5.73 (s, 1H), 5.92 (s, 2H), 6.57 (s, 1H), 6.75 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 20.9, 22.2, 26.9, 28.7, 34.1, 40.4, 53.6, 56.7, 61.2, 69.2, 70.6, 101.0, 105.1, 107.3, 114.0, 126.6, 129.3, 145.8, 146.3, 146.5, 170.0, 172.5 ppm; ESI-MS: *m/z* 414 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{28}NO_6$: 414.1917, found: 414.1905.

1-Acetyl-2-hexanoyllycorine (13)

Following the previously described general procedure, 95 mg (0.28 mmol) of **10** yielded **13** as a white solid (99 mg, 75.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (m, 3H), 1.28 (m, 4H), 1.61 (m, 2H), 1.92 (s, 3H), 2.29 (m, 2H), 2.37 (m, 1H), 2.62 (m, 2H), 2.75 (d, *J*=10.4 Hz, 1H), 2.85 (d, *J*=10.0

Hz, 1H), 3.34 (m, 1H), 3.50 (d, *J*=14.0 Hz, 1H), 4.13 (d, *J*=14.0 Hz, 1H), 5.23 (s, 1H), 5.49 (s, 1H), 5.70 (s, 1H), 5.88 (s, 2H), 6.54 (s, 1H), 6.71 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.0, 21.0, 22.3, 24.6, 28.7, 31.2, 34.3, 40.5, 53.6, 56.9, 61.2, 69.2, 70.6, 101.0, 105.0, 107.3, 114.0, 126.5, 129.4, 145.9, 146.3, 146.4, 170.0, 172.5 ppm; ESI-MS: *m/z* 428 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{24}H_{30}NO_6$: 428.2073, found: 428.2067.

1-Acetyl-2-pivaloyllycorine (16)

Following the previously described general procedure, 95 mg (0.28 mmol) of **10** yielded **16** as a pale solid (34 mg, 13.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (s, 9H), 1.97 (s, 3H), 2.44 (m, 1H), 2.68 (s, 2H), 2.81 (d, *J*=10.6 Hz, 1H), 2.90 (d, *J*=10.4 Hz, 1H), 3.41 (dt, *J*=9.0, 4.7 Hz, 1H), 3.56 (d, *J*=14.1 Hz, 1H), 4.19 (d, *J*=14.2 Hz, 1H), 5.24 (s, 1H), 5.52 (s, 1H), 5.72 (s, 1H), 5.93 (s, 2H), 6.59 (s, 1H), 6.77 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.9, 27.1, 28.6, 38.7, 40.6, 53.6, 56.8, 61.3, 69.1, 70.6, 101.0, 105.1, 107.3, 113.9, 126.6, 129.3, 145.8, 146.3, 146.5, 169.9, 177.2 ppm; ESI-MS: *m/z* 414 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{28}NO_6$: 414.1917, found: 414.1912.

1-Acetyl-2-(4-nitrobenzoyl)lycorine (18)

Following the previously described general procedure, 120 mg (0.36 mmol) of **10** yielded **18** as a pale yellow solid (121 mg, 69.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.95 (s, 3H), 2.40 (m, 1H), 2.65 (m, 2H), 2.82 (d, *J*=10.0 Hz, 1H), 2.98 (d, *J*=10.4 Hz, 1H), 3.36 (m, 1H), 3.52 (d, *J*=14.0 Hz, 1H), 4.14 (d, *J*=14.4 Hz, 1H), 5.53 (s, 1H), 5.59 (s, 1H), 5.85 (s, 3H), 6.53 (s, 1H), 6.71 (s, 1H), 8.18 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.8, 40.4, 45.1, 53.5, 56.6, 61.1, 68.9, 72.0, 72.0, 101.1, 104.9, 107.4, 113.3, 123.5, 126.2, 129.1, 130.9, 135.3, 146.5, 146.6, 147.0, 150.6, 163.4, 170.0 ppm; ESI-MS: *m/z* 479 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{25}H_{23}N_2O_8$: 479.1449, found: 479.1446.

1-Acetyl-2-(4-chlorobenzoyl)lycorine (19)

Following the previously described general procedure, 200 mg (0.61 mmol) of **10** yielded **19** as a pale yellow solid (180 mg, 72.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.01 (s, 3H), 2.48 (q, *J*=8.8 Hz, 1H), 2.71 (d, *J*=1.8 Hz, 2H), 2.89 (d, *J*=10.4 Hz, 1H), 3.05 (d, *J*=10.4 Hz, 1H), 3.48-3.38 (m, 1H), 3.60 (d, *J*=14.0 Hz, 1H), 4.22 (d, *J*=14.1 Hz, 1H), 5.55 (d, *J*=1.5 Hz, 1H), 5.65 (s, 1H), 5.90 (s, 1H), 5.94 (d, *J*=1.1 Hz, 2H), 6.62 (s, 1H), 6.80 (s, 1H), 7.42 (d, *J*=8.6 Hz, 2H), 7.99 ppm (d, *J*=8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.0, 28.7, 40.6, 53.6, 56.8, 61.3, 69.0, 71.3, 101.0, 105.1, 107.4, 113.7, 126.4, 128.3, 128.7, 129.3, 131.2, 139.6, 146.6, 164.4, 170.0 ppm; ESI-MS: *m/z* 468 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{25}H_{23}ClNO_6$: 468.1208, found: 468.1200.

General procedure for 34-41

To a solution of **23** in 5 mL of anhydrous pyridine, chloride was added, and the solution was stirred at 0 ℃ until TLC analysis indicated that all of the starting material had been consumed followed by the addition of DCM and water. The organic layer was washed with an aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was purified using silica gel chromatography to yield the products.

1-Butyryl-2-oxolycorine (35)

Following the previously described general procedure, 200 mg (0.70 mmol) of **23** yielded **35** as a white solid (112 mg, 45.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.78 (t, *J*=7.4 Hz, 3H), 1.51 (dd, *J*=14.7, 7.3 Hz, 2H), 2.18 (td, *J*=7.3, 4.0 Hz, 2H), 2.54 (d, *J*=8.6 Hz, 1H), 2.87 (s, 2H), 3.18 (d, *J*=9.7 Hz, 1H), 3.28 (d, *J*=9.9 Hz, 1H), 3.47 (dd, *J*=8.8, 4.4 Hz, 1H), 3.61 (d, *J*=14.1 Hz, 1H), 4.18

(d, *J*=14.1 Hz, 1H), 5.92 (s, 2H), 6.05–5.97 (m, 2H), 6.58 (s, 1H), 6.73 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.3, 18.4, 30.0, 35.9, 45.5, 53.2, 56.3, 62.4, 68.7, 101.1, 105.6, 107.3, 120.4, 125.3, 128.8, 146.6, 146.7, 169.0, 172.1, 193.1 ppm; ESI-MS: *m/z* 356 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{20}H_{22}NO_5$: 356.1498, found: 356.1496.

1-Valeryl-2-oxolycorine (36)

Following the previously described general procedure, 200 mg (0.70 mmol) of **23** yielded **36** as a white solid (164 mg, 72.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.76 (t, *J*=7.3 Hz, 3H), 1.13 (dd, *J*=12.0, 6.9 Hz, 2H), 1.51-1.38 (m, 2H), 2.19 (dd, *J*=9.4, 4.6 Hz, 2H), 2.53 (dd, *J*=17.2, 8.6 Hz, 1H), 2.86 (s, 2H), 3.17 (d, *J*=9.8 Hz, 1H), 3.27 (d, *J*=9.6 Hz, 1H), 3.52-3.41 (m, 1H), 3.60 (d, *J*=14.1 Hz, 1H), 4.17 (d, *J*=14.1 Hz, 1H), 5.91 (d, *J*=1.4 Hz, 2H), 6.00 (d, *J*=2.8 Hz, 2H), 6.57 (s, 1H), 6.72 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.6, 21.8, 26.9, 30.0, 33.8, 45.5, 53.2, 56.3, 62.4, 68.7, 101.1, 105.6, 107.2, 120.4, 125.2, 128.8, 146.6, 146.7, 169.0, 172.3, 193.1 ppm; ESI-MS: *m/z* 370 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{21}H_{24}NO_5$: 370.1654, found: 370.1649.

1-Hexanoyl-2-oxolycorine (37)

Following the previously described general procedure, 200 mg (0.70 mmol) of **23** yielded **37** as a white solid (182 mg, 68.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.79 (t, *J*=7.2 Hz, 3H), 1.11–1.01 (m, 2H), 1.16 (m, 2H), 1.46 (m, 2H), 2.19 (m, 2H), 2.53 (m, 1H), 2.92-2.82 (m, 2H), 3.17 (d, *J*=9.9 Hz, 1H), 3.27 (d, *J*=10.0 Hz, 1H), 3.47 (m, 1H), 3.60 (d, *J*=14.1 Hz, 1H), 4.17 (d, *J*=14.1 Hz, 1H), 5.92 (s, 2H), 6.00 (dd, *J*=6.4, 2.6 Hz, 2H), 6.57 (s, 1H), 6.73 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.8, 22.2, 24.6, 30.0, 30.9, 34.1, 45.5, 53.2, 56.3, 62.4, 68.7, 101.1, 105.6, 107.3, 120.4, 125.2, 128.8, 146.6, 146.7, 169.0, 172.3, 193.1 ppm; ESI-MS: *m/z* 384 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{22}H_{26}NO_5$: 384.1811, found: 384.1802.

1-Pivaloyl-2-oxolycorine (38)

Following the previously described general procedure, 200 mg (0.70 mmol) of **23** yielded **38** as a white solid (123 mg, 48.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.99 (s, 9H), 2.53 (q, *J*=8.6 Hz, 1H), 2.87 (s, 2H), 3.14 (d, *J*=9.8 Hz, 1H), 3.28 (d, *J*=9.7 Hz, 1H), 3.51-3.43 (m, 1H), 3.59 (d, *J*=14.1 Hz, 1H), 4.18 (d, *J*=14.1 Hz, 1H), 5.91 (d, *J*=2.6 Hz, 2H), 5.97 (d, *J*=2.6 Hz, 1H), 6.00 (s, 1H), 6.57 (s, 1H), 6.69 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.9, 30.0, 38.9, 45.7, 53.3, 56.4, 62.6, 68.6, 101.1, 105.6, 107.2, 120.4, 125.3, 128.8, 146.5, 168.9, 176.7, 193.1 ppm; ESI-MS: *m/z* 370 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{21}H_{24}NO_5$: 370.1654, found: 370.1652.

1-(4-Chloro-benzoyl)-2-oxolycorine (40)

Following the previously described general procedure, 200 mg (0.70 mmol) of **23** yielded **40** as a white solid (163 mg, 55.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.62 (m, 1H), 2.93 (s, 2H), 3.33 (d, *J*=10.0 Hz, 1H), 3.42 (d, *J*=9.2 Hz, 1H), 3.59-3.48 (m, 1H), 3.65 (d, *J*=14.1 Hz, 1H), 4.22 (d, *J*=14.2 Hz, 1H), 5.88 (d, *J*=10.8 Hz, 2H), 6.06 (s, 1H), 6.23 (d, *J*=2.1 Hz, 1H), 6.56 (s, 1H), 6.80 (s, 1H), 7.33 (d, *J*=8.1 Hz, 2H), 7.81 ppm (d, *J*=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.0, 45.5, 53.2, 56.2, 62.5, 69.7, 101.1, 105.3, 107.4, 120.7, 124.9, 127.7, 128.7, 131.3, 131.4, 139.8, 146.6, 164.2, 168.7, 192.4 ppm; ESI-MS: *m/z* 424 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{19}ClNO_5$: 424.0946, found: 424.0941.

1-(4-Methoxyl-benzoyl)-2-oxolycorine (41)

Following the previously described general procedure, 200 mg (0.70 mmol) of **23** yielded **41** as a white solid (156 mg, 53.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.59 (q, *J*=8.7 Hz, 1H), 2.90 (d, *J*=8.9 Hz, 2H), 3.36 (dd, *J*=20.7, 10.0 Hz, 2H), 3.55-3.47 (m, 1H), 3.63 (d, *J*=14.1 Hz, 1H), 3.81 (s, 3H), 4.20 (d, *J*=14.1 Hz, 1H), 5.87 (d, *J*=12.5 Hz, 2H), 6.04 (s, 1H), 6.22 (s, 1H), 6.54 (s, 1H), 6.84

(m, 3H), 7.84 ppm (d, *J*=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.0, 45.7, 53.3, 55.4, 56.3, 62.6, 69.2, 101.1, 105.5, 107.3, 113.5, 120.6, 121.8, 125.2, 128.6, 132.0, 146.7, 163.5, 164.8, 193.0 ppm; ESI-MS: *m/z* 420 $[M+H]^+$; HRMS: *m/z* $[M+Na]^+$ calcd. for $C_{24}H_{21}NO_6Na$: 442.1261, found: 442.1259.