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[3+2] Cycloaddition-based one-pot synthesis of 3,9-diazabicyclo[4.2.1]nonane-containing scaffold

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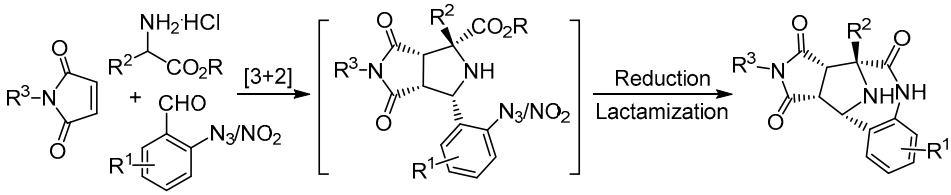
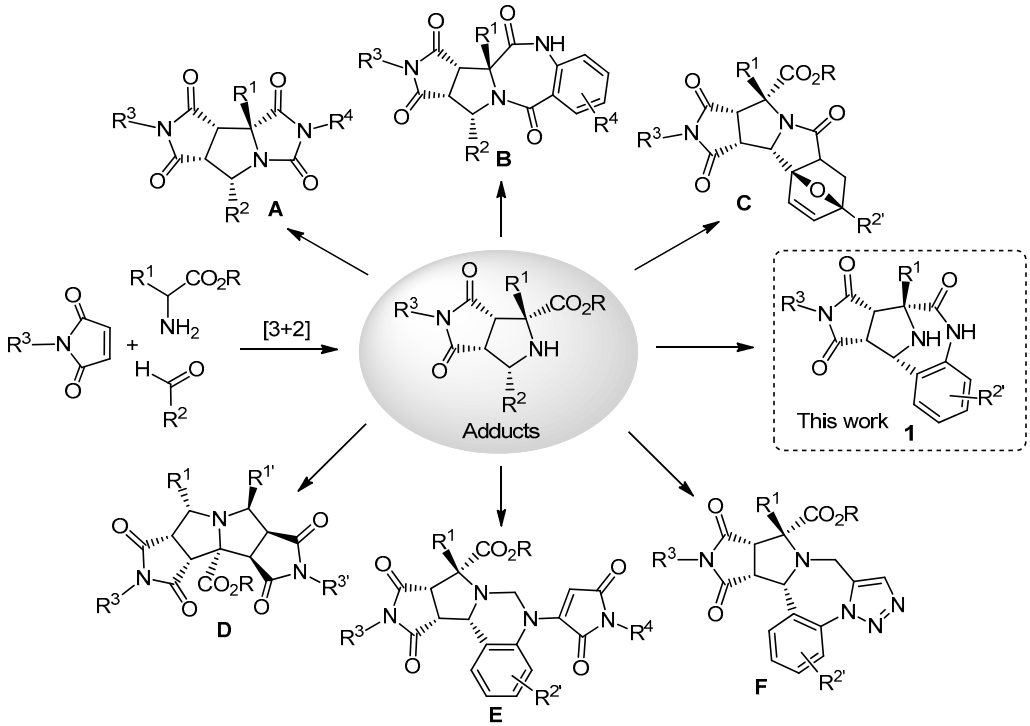


Three-component [3+2] cycloaddition followed by reduction and lactamization has been developed as a one-pot methodology for diastereoselective synthesis of 3,9-diazabicyclo[4.2.1]nonane-containing scaffold.

Keywords: 3,9-diazabicyclo[4.2.1]nonane, [3+2] cycloaddition, 1,3-dipolar cycloaddition, multicomponent reaction, one-pot synthesis.

1,3-Dipolar cycloaddition of azomethine ylides involving aldehyde, amine, and activated alkene is a well-established multicomponent reaction (MCR).[1] Compounds generated by [3+2] cycloaddition are valuable intermediates for post-addition reactions to access diverse heterocyclic scaffolds. Our group has integrated the fluorous technology,[2] MCRs,[3] as well as pot, atom, and step economic (PASE)[4] reaction processes to increase the efficiency of [3+2] cycloaddition-based synthesis of novel heterocyclic compound libraries **A–F** (Scheme 1).[5–11]

Scheme 1



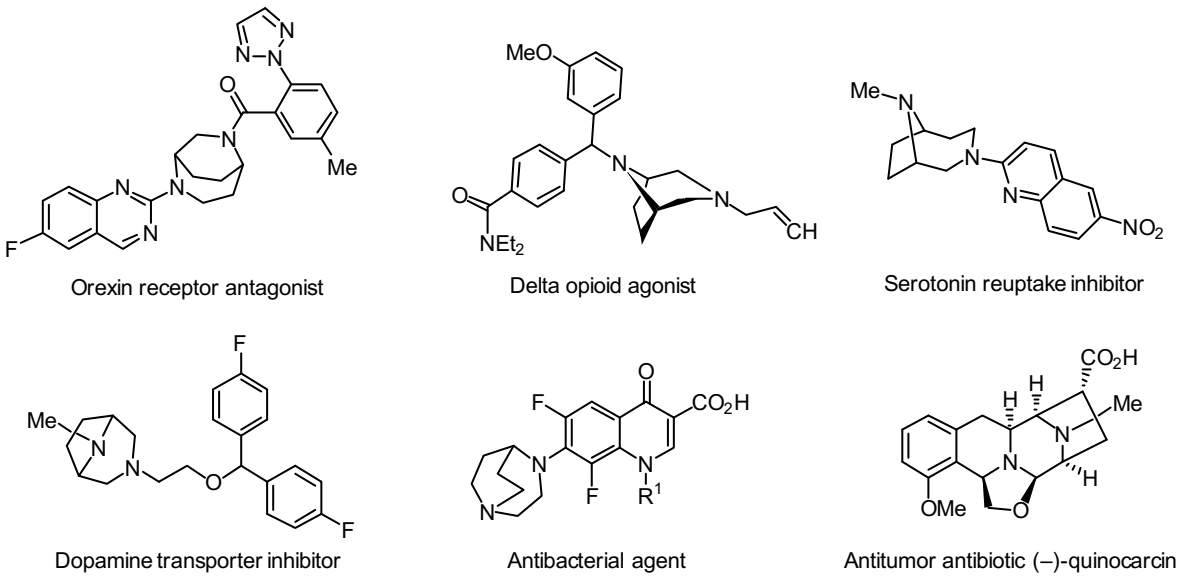
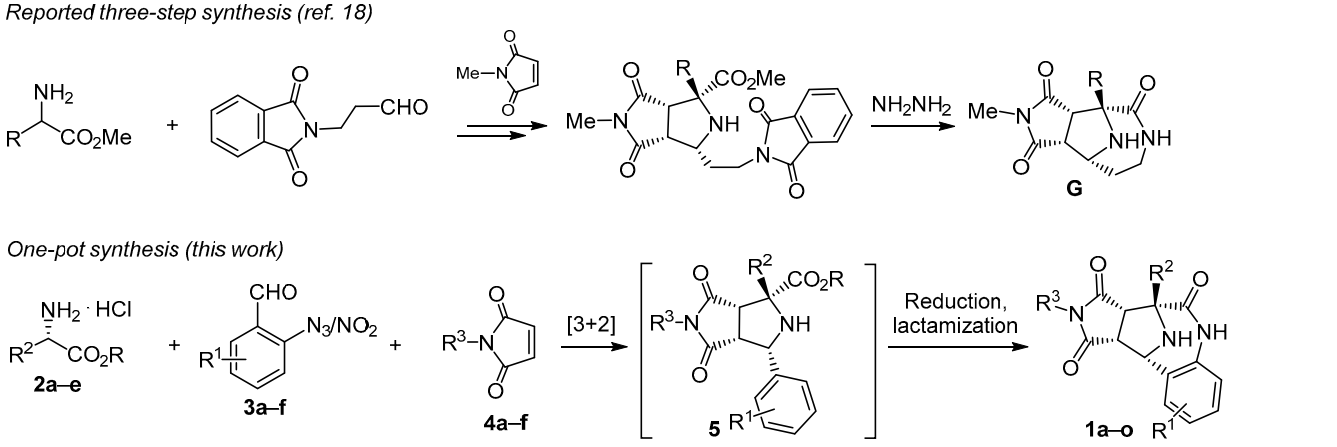


Figure 1. Representative biologically active bridged *N*-cyclic compounds.

Some diazabicyclo[4.2.1]nonane derivatives possess biological activity and have been demonstrated as potential dual orexin receptor antagonists,[12] delta opioid agonists,[13] serotonin reuptake inhibitors,[14] dopamine transporter inhibitors,[15] antibacterial agents,[16] and antitumor antibiotics (Fig. 1).[17] Grigg has reported a three-step protocol for the synthesis of bridged bi- and tricyclic lactams, involving [3+2] cycloaddition of aldimines and activated alkenes and sequential hydrazine-promoted lactamization for 3,9-diazabicyclo[4.2.1]nonane **G** (Scheme 2).[18] To improve the synthetic efficiency and increase the structural diversity of the products **1**, we have designed a one-pot reaction process utilizing 2-azidobenzaldehydes **3a**,**c**,**f** or 2-nitrobenzaldehydes **3b**,**d**,**e** for three-component [3+2] cycloaddition. The azide or nitro group in intermediates **5** may be reduced to amine prior to lactamization without isolation and/or purification of the [3+2] cycloaddition products. Herein, we report a new PASE synthesis involving [3+2] cycloaddition, azide/nitro reduction, and lactamization that allows to obtain bridged polycyclic system **1** bearing tetrahydrobenzoazocinone, pyrrolidine, and pyrrolidine-dione fragments within the 3,9-diazabicyclo[4.2.1]nonane scaffold.

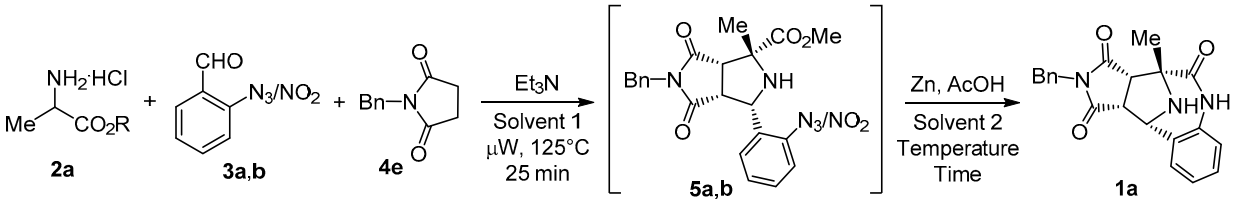
Our initial effort was focused on the development of reaction conditions for the one-pot synthesis of 3,9-diazabicyclo[4.2.1]nonane **1a** using 1.2:1.1:1.0 of L-alanine methyl ester hydrochloride (**2a**), 2-azidobenzaldehyde (**3a**) or 2-nitrobenzaldehyde (**3b**), and *N*-benzylmaleimide (**4e**) as starting materials (Table 1). Following our previously reported conditions for diastereoselective [3+2] cycloaddition[10,11,19] and explored solvents (PhMe, MeCN, MeOH), reaction temperature, and time for sequential reduction and lactamization,[7,8,18] we found that the optimized reaction conditions for the [3+2] cycloaddition involved the use of Et_3N as a base under microwave irradiation at 125°C for 25 min. Without workup, the

Scheme 2



2 a R^2 = Me, **b** R^2 = Et, **c** R^2 = *i*-Bu, **d** R^2 = CH_2OH, **e** R^2 = Bn
3 a R^1 = H, R^4 = N_3; **b** R^1 = H, R^4 = NO_2; **c** R^1 = 4-MeO, R^4 = N_3; **d** R^1 = 4-MeO, R^4 = NO_2; **e** R^1 = 4,5-OCH_2O, R^4 = NO_2; **f** R^1 = 5-Cl, R^4 = N_3
4 a R^3 = Me, **b** R^3 = Et, **c** R^3 = *i*-Bu, **d** R^3 = Cy, **e** R^3 = Bn, **f** R^3 = Ph

Table 1. Optimization of the conditions for one-pot synthesis of compound **1a**

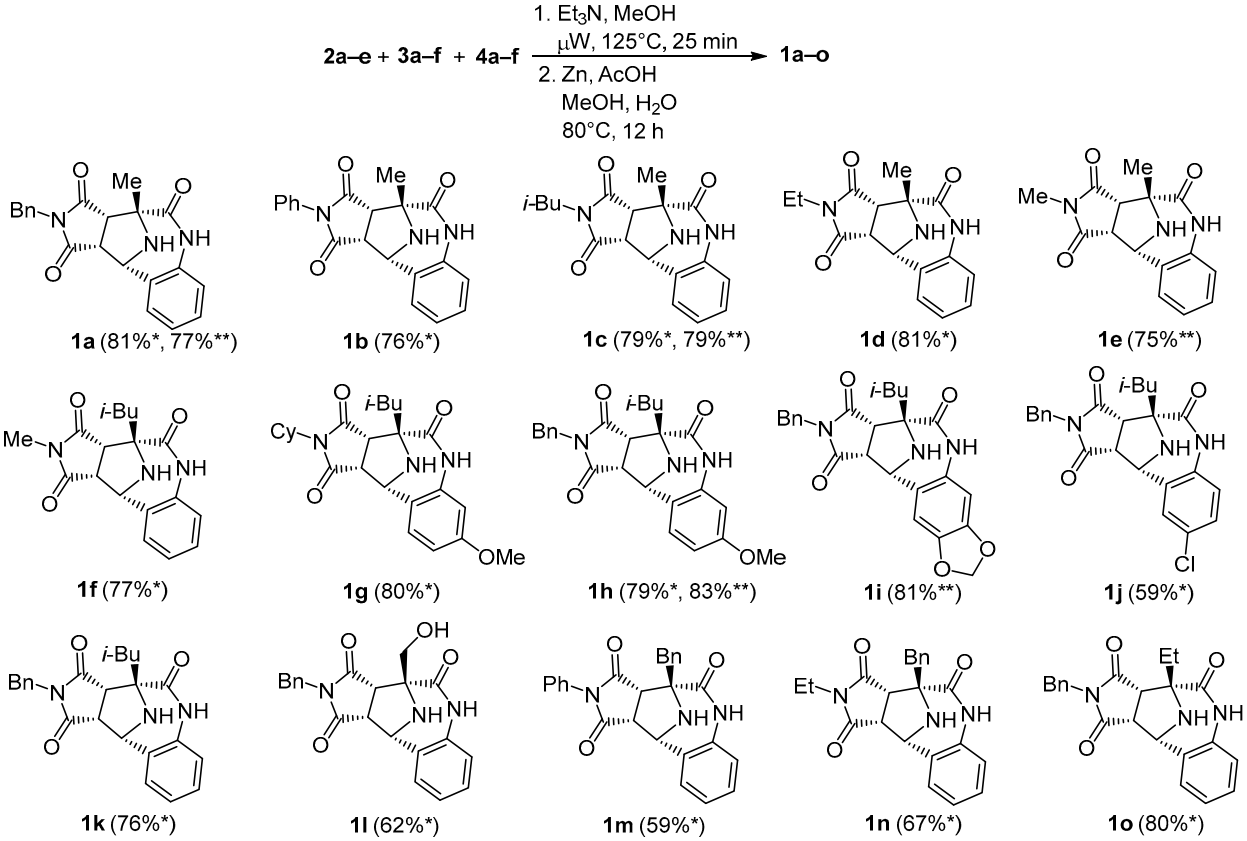


Entry	Aldehyde	Solvent 1	Solvent 2	Time, h	Temperature, °C	Yield, %
1	**3a**	PhMe	PhMe	24	110	Trace
2	**3a**	MeCN	MeCN	24	80	15
3	**3a**	MeOH	MeOH	16	65	43
4	**3a**	MeOH	MeOH–H_2O, 2:1	16	65	57
5	**3a**	MeOH	MeOH–H_2O, 3:1	16	65	68
6	**3a**	MeOH	MeOH–H_2O, 3:1	12	80	81
7	**3b**	MeOH	MeOH–H_2O, 3:1	12	80	77

resulting intermediate **5a** or **5b** as a single diastereomer was reduced with 6.0 equiv of zinc dust in the presence of 4.0 equiv of AcOH under conventional heating at 80°C for 16 h to afford product **1a** in 81% (using aldehyde **3a**) and 77% (aldehyde **3b**) yield (Table 1, entries 6 and 7). MeOH was found to be the appropriate solvent for the first step of the reaction, while MeOH–H_2O, 3:1, was the best choice for the reduction and lactamization steps.

Starting materials bearing different substituents R^1, R^2, and R^3 were employed for the synthesis of 15 analogs of bridged *N*-cyclic products **1** under the optimized reaction conditions (Scheme 3). The yields of 3,9-diazabicyclo-[4.2.1]nonanes **1a–o** obtained by this one-pot three-step synthesis were in the range of 59–83%. The choice of azido or nitro substituents in benzaldehydes **3** had no significant effect on the yields of final products **1a–o**.

Scheme 3



* Using 2-azidobenzaldehydes **3a**,**c**,**f**.
** Using 2-nitrobenzaldehydes **3b**,**d**,**e**.

In conclusion, a PASE synthesis involving three-component [3+2] cycloaddition, reduction, and lactamization has been developed to obtain 3,9-diazabicyclo[4.2.1]-nonanes bearing different substituents. The [3+2] cycloaddition affords a single diastereomer which is reduced with zinc followed by spontaneous lactamization to form the product.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on an Agilent NMR spectrometer (400 and 101 MHz, respectively). ^{1}H and ^{13}C NMR spectra of compounds **1e**,**l** were obtained in DMSO-d_6, all other compounds were analyzed as their $CDCl_3$ solutions. Low-resolution mass spectra were recorded by APCI (atmospheric pressure chemical ionization) method. LC-MS analyses were performed on an Agilent 2100 LC apparatus with a 6130 quadrupole mass spectrometer. A Venusil AQ-C_{18} column (5.0 μm, 6.0 × 50 mm) was used for the separation. The eluents were MeOH and H_2O both containing 0.05% CF_3CO_2H. A linear gradient from 25:75 (v/v) MeOH/H_2O to 100% MeOH over 7.0 min at a flow rate of 0.7 ml/min was applied for the mobile phase. UV detections were conducted at 210, 254, and 365 nm. Final products were purified on an Angela HP-100 pre-LC system with a Venusil PrepG C_{18} column (10 μm, 120 Å, 21.2 × 250 mm). All chemicals and solvents were purchased from commercial suppliers and used as received.

One-pot synthesis of bridged polycyclic compounds 1a–o (General method). To a solution of an amino acid ester hydrochloride **2** (1.2 mmol), 2-azidobenzaldehyde or 2-nitrobenzaldehyde **3** (1.1 mmol), and maleimide **4** (1.0 mmol) in MeOH (3 ml), Et_3N (0.2 ml, 1.5 mmol) was added. After stirring at 25°C for 5 min, the reaction mixture was heated under microwave irradiation at 125°C for 25 min. Upon completion of the reaction, as confirmed by LC-MS, zinc dust (392 mg, 6.0 mmol), AcOH (0.2 ml, 4.0 mmol), and water (1 ml) were added to the reaction mixture and then heated at 80°C for 12 h. After aqueous workup, the concentrated reaction mixture was separated on a semi-prep HPLC C_{18} column to afford the purified product **1** as a single diastereomer.

Compound 1a was obtained using amino acid ester hydrochloride **2a**, aldehyde **3a** or **3b**, and maleimide **4e**. Yield 81% (from aldehyde **3a**), 77% (from aldehyde **3b**), white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.18 (1H, s, C(O)NH); 7.34 (1H, d, *J* = 7.7, H Ar); 7.19–7.00 (6H, m, H Ar); 6.96–6.85 (1H, m, H Ar); 6.78 (1H, d, *J* = 7.4, H Ar); 4.70 (1H, d, *J* = 7.2, 11-CH); 3.90 (2H, dd, *J* = 36.5, *J* =14.2, NCH_2); 3.47 (1H, s, 11a-CH); 3.33 (1H, d, *J* = 10.1, 3a-CH); 2.95 (1H, s, NH); 1.51 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 179.6; 174.2; 168.4; 135.5; 134.9; 129.3; 128.7; 128.6; 127.7; 126.7; 123.8; 122.1; 115.9; 66.2; 58.4; 53.2; 48.4; 42.0; 22.4. Found, *m*/*z*: 361.1529 $[M]^+$. $C_{21}H_{19}N_3O_3$. Calculated, *m*/*z*: 361.1505.

Compound 1b was obtained using amino acid ester hydrochloride **2a**, aldehyde **3a**, and maleimide **4f**. Yield 76%, off-white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.88 (1H, s, C(O)NH); 7.45 (1H, dd, *J* = 22.7, *J* = 14.1, H Ar); 7.23–7.06 (4H, m, H Ar); 7.02 (1H, dt, *J* = 21.5, *J* = 7.2, H Ar); 6.77 (1H, d, *J* = 8.1, H Ar); 6.52–6.33 (2H, m, H Ar); 4.72 (1H, t, *J* = 8.4, 11-CH); 3.52 (2H, dq, *J* = 11.3, *J* = 7.8, 3a,11a-CH); 1.62 (3H, d, *J* = 4.2, CH_3). ^{13}C NMR spectrum, δ, ppm: 178.9; 173.3; 167.9; 135.7; 131.1; 129.4; 128.7; 128.6; 127.1; 126.2; 124.2; 122.5; 116.1; 66.2; 58.5; 53.4; 48.6; 22.7. Found, *m*/*z*: 347.1301 $[M]^+$. $C_{20}H_{17}N_3O_3$. Calculated, *m*/*z*: 347.1289.

Compound 1c was obtained using amino acid ester hydrochloride **2a**, aldehyde **3a** or **3b**, and maleimide **4c**. Yield 79% (from both aldehydes **3a** and **3b**), white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.70 (1H, s, C(O)NH); 7.42–7.28 (1H, m, H Ar); 7.17–7.07 (1H, m, H Ar); 7.04–6.88 (1H, m, H Ar); 6.76 (1H, d, *J* = 7.9, H Ar); 4.68 (1H, t, *J* = 10.5, 11-CH); 3.46 (1H, dd, *J* = 9.8, *J* = 7.4, 11a-CH); 3.37–3.23 (1H, m, 3a-CH); 2.70–2.55 (2H, m, NCH_2); 1.60 (1H, dd, *J* = 13.6, *J* = 6.9, C<u>H</u>$(CH_3)_2$); 1.55 (3H, s, CH_3); 0.62 (6H, dd, *J* = 8.7, *J* = 3.0, CH(C<u>H</u>$_3)_2$). ^{13}C NMR spectrum, δ, ppm: 180.1; 174.5; 168.1; 135.5; 129.3; 126.8; 123.8; 122.1; 115.8; 65.8; 58.3; 53.1; 48.3; 45.6; 26.8; 22.7; 20.1; 20.0. Found, *m*/*z*: 327.1648 $[M]^+$. $C_{18}H_{21}N_3O_3$. Calculated, *m*/*z*: 327.1662.

Compound 1d was obtained using amino acid ester hydrochloride **2a**, aldehyde **3a**, and maleimide **4b**. Yield 81%, light-yellow solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.94 (1H, s, C(O)NH); 7.41–7.30 (1H, m, H Ar); 7.20–7.05 (1H, m, H Ar); 7.03–6.88 (1H, m, H Ar); 6.84–6.71 (1H, m, H Ar); 4.80–4.63 (1H, m, 11-CH); 3.55–3.42 (1H, m, 11a-CH); 3.37–3.25 (1H, m, 3a-CH); 3.04–2.92 (3H, m, C<u>H</u>$_2$CH$_3$, NH); 1.55 (3H, s, CH_3); 0.42 (3H, t, *J* = 7.2, CH_2C<u>H</u>$_3$). ^{13}C NMR spectrum, δ, ppm: 179.6; 173.9; 168.2; 135.6; 129.3; 126.9; 124.0; 122.4; 115.9; 66.1; 58.4; 53.4; 48.4; 33.8; 22.6; 11.5. Found, *m*/*z*: 299.1283 $[M]^+$. $C_{16}H_{17}N_3O_3$. Calculated, *m*/*z*: 299.1262.

Compound 1e was obtained using amino acid ester hydrochloride **2a**, aldehyde **3b**, and maleimide **4a**. Yield 75%, off-white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.13 (1H, s, C(O)NH); 7.30–7.25 (1H, m, H Ar); 7.06–6.98 (1H, m, H Ar); 6.83 (1H, td, *J* = 7.5, *J* = 0.9, H Ar); 6.73 (1H, d, *J* = 7.2, H Ar); 4.49 (1H, d, *J* = 7.0, 11-CH); 3.22 (1H, d, *J* = 10.0, 11a-CH); 3.15–3.09 (2H, m, 3a-CH, NH); 2.09 (3H, s, NCH_3); 1.37 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 180.0; 175.2; 168.0; 137.2; 128.6; 127.1; 123.6; 122.5; 115.5; 66.7; 58.5; 53.1; 48.8; 24.1; 21.5. Found, *m*/*z*: 285.1351 $[M]^+$. $C_{15}H_{15}N_3O_3$. Calculated, *m*/*z*: 285.1323.

Compound 1f was obtained using amino acid ester hydrochloride **2c**, aldehyde **3a**, and maleimide **4a**. Yield 77%, white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.19 (1H, s, C(O)NH); 7.31 (1H, d, *J* = 7.6, H Ar); 7.11 (1H, t, *J* = 7.5, H Ar); 6.99 (1H, td, *J* = 7.6, *J* = 0.8, H Ar); 6.82 (1H, t, *J* = 11.1, H Ar); 4.66 (1H, t, *J* = 8.9, 11-CH); 3.49–3.38 (2H, m, 3a,11a-CH); 2.28 (3H, s, NCH_3); 1.92–1.82 (1H, m, C<u>H</u>$(CH_3)_2$); 1.77–1.60 (2H, m, C<u>H</u>$_2$CH$(CH_3)_2$); 0.92 (3H, t, *J* = 7.9, CH(C<u>H</u>$_3)_2$); 0.87 (3H, d, *J* = 6.5, CH(C<u>H</u>$_3)_2$). ^{13}C NMR spectrum, δ, ppm: 180.2; 174.8; 168.5; 135.5; 129.1; 126.5; 123.8; 122.4; 116.0; 69.4; 57.4; 50.9; 48.5; 43.7; 24.9; 24.4; 24.3; 23.8. Found, *m*/*z*: 327.1648 $[M]^+$. $C_{18}H_{21}N_3O_3$. Calculated, *m*/*z*: 327.1662.

Compound 1g was obtained using amino acid ester hydrochloride **2c**, aldehyde **3c**, and maleimide **4d**. Yield 80%, light-yellow solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.01 (1H, s, C(O)NH); 7.20 (1H, dd, *J* = 17.6, *J* = 5.8, H Ar); 6.56–6.46 (1H, m, H Ar); 6.41–6.28 (1H, m, H Ar); 4.62–4.56 (1H, m, 11-CH); 3.69 (3H, s, OCH_3); 3.54–3.48 (1H, m, 1-CH Cy); 3.41–3.36 (2H, m, 3a,11a-CH); 1.89 (1H, tt, *J* = 13.4, *J* = 6.5, $C\underline{H}_ACH(CH_3)_2$); 1.62 (6H, ddd, *J* = 20.2, *J* = 12.5, *J* = 8.4, H Cy, $C\underline{H}_BCH(CH_3)_2$); 1.47 (1H, d, *J* = 8.8, $C\underline{H}(CH_3)_2$); 1.10–0.95 (3H, m, H Cy); 0.91 (3H, d, *J* = 6.3, $CH(C\underline{H}_3)_2$); 0.88 (3H, d, *J* = 6.3, $CH(C\underline{H}_3)_2$); 0.78 (2H, dd, *J* = 27.2, *J* = 12.3, H Cy). ^{13}C NMR spectrum, δ, ppm: 180.2; 174.3; 168.6; 160.6; 136.7; 128.0; 114.8; 109.4; 101.8; 68.8; 56.9; 55.5; 51.6; 50.8; 48.5; 44.5; 27.9; 27.5; 25.5; 25.4; 25.0; 24.8; 24.1; 23.9. Found, *m*/*z*: 425.2376 $[M]^+$. $C_{24}H_{31}N_3O_4$. Calculated, *m*/*z*: 425.2394.

Compound 1h was obtained using amino acid ester hydrochloride **2c**, aldehyde **3c** or **3d**, and maleimide **4e**. Yield 79% (from aldehyde **3c**), 83% (from aldehyde **3d**), white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.31 (1H, s, C(O)NH); 7.16 (6H, ddd, *J* = 17.6, *J* = 9.4, *J* = 6.0, H Ar); 6.50 (1H, dd, *J* = 8.6, *J* = 2.3, H Ar); 6.26 (1H, s, H Ar); 4.62 (1H, d, *J* = 6.6, 11-CH); 4.04–3.93 (2H, m, NCH_2); 3.73 (3H, s, OCH_3); 3.40 (2H, dt, *J* = 10.1, *J* = 8.4, 3a,11a-CH); 1.86 (1H, dd, *J* = 14.1, *J* = 6.3, $C\underline{H}_ACH(CH_3)_2$); 1.65 (1H, dd, *J* = 14.1, *J* = 6.4, $C\underline{H}_BCH(CH_3)_2$); 1.54 (1H, td, *J* = 13.0, *J* = 6.5, $C\underline{H}(CH_3)_2$); 0.82 (3H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$); 0.75 (3H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 179.6; 174.3; 168.1; 160.2; 136.4; 134.9; 128.7; 128.4; 127.8; 127.8; 114.4; 109.3; 101.3; 69.4; 57.0; 55.3; 51.0; 48.6; 44.1; 42.1; 24.8; 24.1; 23.6. Found, *m*/*z*: 433.2056 $[M]^+$. $C_{25}H_{27}N_3O_4$. Calculated, *m*/*z*: 433.2081.

Compound 1i was obtained using amino acid ester hydrochloride **2c**, aldehyde **3e**, and maleimide **4e**. Yield 81%, off-white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.76 (1H, s, C(O)NH); 7.22–7.14 (4H, m, H Ar); 6.76 (1H, s, H Ar); 6.12 (1H, s, H Ar); 5.89 (2H, dd, *J* = 27.4, *J* = 1.1, OCH_2O); 4.55 (1H, d, *J* = 7.3, 11-CH); 4.11 (2H, dd, *J* = 36.7, *J* = 13.8, NCH_2); 3.43 (1H, d, *J* = 10.1, 3a-CH); 3.34 (1H, dd, *J* = 9.9, *J* = 7.4, 11a-CH); 2.71 (1H, s, NH); 1.88 (1H, dd, *J* = 13.9, *J* = 6.3, $C\underline{H}_ACH(CH_3)_2$); 1.69–1.64 (2H, m, $C\underline{H}_BCH(CH_3)_2$, $C\underline{H}(CH_3)_2$); 0.84 (3H, d, *J* = 6.5, $CH(C\underline{H}_3)_2$); 0.78 (3H, d, *J* = 6.5, $CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 179.1; 174.1; 168.3; 147.9; 144.2; 134.8; 129.4; 129.0; 128.3; 127.8; 114.9; 106.5; 101.4; 97.3; 69.6; 57.6; 51.0; 48.6; 44.0; 42.3; 30.9; 24.9; 24.2; 23.6. Found, *m*/*z*: 447.1886 $[M]^+$. $C_{25}H_{25}N_3O_5$. Calculated, *m*/*z*: 447.1873.

Compound 1j was obtained using amino acid ester hydrochloride **2c**, aldehyde **3f**, and maleimide **4e**. Yield 59%, white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.82 (1H, s, C(O)NH); 7.30 (1H, s, H Ar); 7.20–7.05 (5H, m, H Ar); 6.96 (1H, dd, *J* = 8.4, *J* = 2.0, H Ar); 6.61 (1H, d, *J* = 8.4, H Ar); 4.64 (1H, d, *J* = 6.6, 11-CH); 4.02 (2H, dd, *J* = 35.5, *J* = 13.9, NCH_2); 3.49–3.38 (2H, m, 3a,11a-CH); 2.85 (1H, s, NH); 1.90 (1H, dd, *J* = 14.0, *J* = 6.4, $C\underline{H}_ACH(CH_3)_2$); 1.68 (1H, dd, *J* = 14.0, *J* = 6.2, $C\underline{H}_BCH(CH_3)_2$); 1.58 (1H, dt, *J* = 13.1, *J* = 6.5, $C\underline{H}(CH_3)_2$); 0.83 (3H, d, *J* = 6.7, $CH(C\underline{H}_3)_2$); 0.79 (3H, d, *J* = 7.0, $CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 179.0; 174.1; 167.8; 134.4; 133.8; 129.3; 129.0; 128.9; 128.5; 127.9; 126.8; 124.1; 116.9; 69.6; 57.3; 51.0; 48.2; 43.9; 42.3; 24.9; 24.2; 23.6. Found, *m*/*z*: 437.1625 $[M]^+$. $C_{24}H_{24}ClN_3O_3$. Calculated, *m*/*z*: 437.1585.

Compound 1k was obtained using amino acid ester hydrochloride **2c**, aldehyde **3a**, and maleimide **4e**. Yield 76%, white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.97 (1H, s, C(O)NH); 7.32 (1H, d, *J* = 7.7, H Ar); 7.18–7.13 (3H, m, H Ar); 7.11–7.07 (3H, m, H Ar); 6.97 (1H, t, *J* = 7.5, H Ar); 6.78 (1H, d, *J* = 7.8, H Ar); 4.67 (1H, t, *J* = 7.4, 11-CH); 3.87 (2H, d, *J* = 8.4, NCH_2); 3.49–3.43 (2H, m, 3a,11a-CH); 2.97 (1H, s, NH); 1.87 (1H, dd, *J* = 14.1, *J* = 6.3, $C\underline{H}_ACH(CH_3)_2$); 1.66 (1H, dd, *J* = 14.1, *J* = 6.4, $C\underline{H}_BCH(CH_3)_2$); 1.54 (1H, tt, *J* = 13.1, *J* = 6.5, $C\underline{H}(CH_3)_2$); 0.81 (3H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$); 0.74 (3H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 179.6; 174.3; 168.4; 135.4; 134.8; 129.3; 128.7; 128.4; 127.7; 126.5; 123.8; 122.3; 115.9; 69.3; 57.4; 50.8; 48.4; 44.0; 42.0; 24.8; 24.1; 23.6. Found, *m*/*z*: 403.1968 $[M]^+$. $C_{24}H_{25}N_3O_3$. Calculated, *m*/*z*: 403.1975.

Compound 1l was obtained using amino acid ester hydrochloride **2d**, aldehyde **3a**, and maleimide **4e**. Yield 62%, off-white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.19 (1H, s, C(O)NH); 7.32 (1H, t, *J* = 10.6, H Ar); 7.18–7.11 (3H, m, H Ar); 7.09 (1H, t, *J* = 7.6, H Ar); 6.93–6.80 (3H, m, H Ar); 6.73 (1H, t, *J* = 10.6, H Ar); 5.32–5.26 (1H, m, $CH_2O\underline{H}$); 4.54 (1H, dt, *J* = 13.2, *J* = 6.6, 11-CH); 3.93–3.84 (2H, m); 3.80–3.77 (1H, m); 3.75 (1H, t, *J* = 5.2); 3.58–3.47 (2H, m); 3.18–3.10 (1H, m). ^{13}C NMR spectrum, δ, ppm: 179.1; 175.3; 167.7; 137.1; 135.8; 128.9; 128.7; 127.5; 127.4; 127.2; 123.6; 122.7; 115.5; 71.9; 62.9; 58.3; 49.9; 48.0. Found, *m*/*z*: 377.1432 $[M]^+$. $C_{21}H_{19}N_3O_4$. Calculated, *m*/*z*: 377.1455.

Compound 1m was obtained using amino acid ester hydrochloride **2e**, aldehyde **3a**, and maleimide **4f**. Yield 59%, white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.89 (1H, s, C(O)NH); 7.40 (1H, t, *J* = 11.5, H Ar); 7.34–7.19 (5H, m, H Ar); 7.20–7.08 (4H, m, H Ar); 7.00 (1H, dd, *J* = 16.8, *J* = 9.9, H Ar); 6.72 (1H, d, *J* = 7.8, H Ar); 6.15 (2H, dd, *J* = 8.0, *J* = 1.3, H Ar); 4.69 (1H, d, *J* = 7.3, 11-CH); 3.69 (1H, t, *J* = 8.8, 3a-CH); 3.43 (1H, d, *J* = 13.3, $C\underline{H}_APh$); 3.35 (1H, dd, *J* = 10.2, *J* = 7.3, 11a-CH); 3.05 (1H, d, *J* = 13.3, $C\underline{H}_BPh$). ^{13}C NMR spectrum, δ, ppm: 178.7; 173.2; 167.8; 135.7; 134.2; 131.0; 130.1; 129.4; 128.9; 128.7; 128.6; 127.8; 127.0; 126.2; 124.2; 122.4; 116.2; 70.6; 58.2; 50.0; 48.1; 41.4. Found, *m*/*z*: 423.1672 $[M]^+$. $C_{26}H_{21}N_3O_3$. Calculated, *m*/*z*: 423.1662.

Compound 1n was obtained using amino acid ester hydrochloride **2e**, aldehyde **3a**, and maleimide **4b**. Yield 67%, white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.86 (1H, s, C(O)NH); 7.35 (1H, d, *J* = 7.6, H Ar); 7.28–7.16 (5H, m, H Ar); 7.12 (1H, t, *J* = 7.6, H Ar); 6.97 (1H, t, *J* = 7.5, H Ar); 6.73 (1H, d, *J* = 7.8, H Ar); 4.64 (1H, d, *J* = 7.4, 11-CH); 3.49 (1H, d, *J* = 10.4, 3a-CH); 3.24 (1H, d, *J* = 13.5, $C\underline{H}_APh$); 3.15 (1H, dd, *J* = 10.2, *J* = 7.4, 11a-CH); 3.03 (1H, d, *J* = 13.5, $C\underline{H}_BPh$); 2.86 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 1.83 (1H, s, NH); 0.36 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 179.4; 173.8; 168.0; 135.4; 134.2; 130.0; 129.3; 128.9; 127.7; 126.8; 123.9;

122.4; 115.9; 70.3; 58.0; 49.9; 48.0; 40.9; 33.5; 11.5. Found, *m*/*z*: 375.1678 $[M]^+$. $C_{22}H_{21}N_3O_3$. Calculated, *m*/*z*: 375.1662.

Compound 1o was obtained using amino acid ester hydrochloride **2b**, aldehyde **3a**, and maleimide **4e**. Yield 80%, white solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.26 (1H, s, C(O)NH); 7.33 (1H, d, *J* = 7.7, H Ar); 7.18–7.11 (3H, m, H Ar); 7.11–7.02 (3H, m, H Ar); 6.94 (1H, td, *J* = 7.6, *J* = 0.9, H Ar); 6.80 (1H, d, *J* = 7.3, H Ar); 4.70 (1H, d, *J* = 6.3, 11-CH); 3.97–3.82 (2H, m, NCH_2); 3.44–3.34 (2H, m, 3a,11a-CH); 2.91 (1H, s, NH); 1.94 (1H, dq, *J* = 14.8, *J* = 7.4, $C\underline{H}_ACH_3$); 1.78 (1H, dq, *J* = 14.7, *J* = 7.4, $C\underline{H}_BCH_3$); 0.82 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 179.6; 174.4; 168.4; 135.5; 135.0; 129.3; 128.5; 128.4; 127.7; 126.5; 123.8; 122.4; 116.0; 70.1; 57.9; 50.2; 48.3; 42.0; 28.3; 8.4. Found, *m*/*z*: 375.1678 $[M]^+$. $C_{22}H_{21}N_3O_3$. Calculated, *m*/*z*: 375.1662.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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