Supporting information

Amphotericin B Tamed by Salicylic Acid

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1 General information

Amphotericin B (AmB), $N$, $N$, $N'$, $N'$-tetramethyl-O-(3,4-dihydro-4-oxo-1,2,3-benzoazin-3-yl) uranium tetrafluoroborate (TDBTU), 9-fluorenylmethoxycarbonyl N-hydroxysuccinimide (Fmoc-OSu), piperidine (PIP), $N$, $N$-diisopropylethylamine (DIPEA) are obtained from Shanghai Aladdin Biochemical Technology Co., Ltd.China. Salicylic acid, $N$-Boc-Ethylenediamine, $N$-Boc-1,4-butanediamine, $N$-Boc-1,6-Hexanediamine, $N$, $N'$-dicyclohexylcarbodiimide (DCC), Dimethyl Formamide (DMF), dimethyl sulfoxide (DMSO) are provided by Sarn Chemical Technology (Shanghai) Co., Ltd.China. DMEM, MOPS, Cell Counting Kit-8 (CCK-8), Fetal Bovine Serum (FBS) were purchased from Cosmo Mall.China. Unless otherwise specified, all used chemical reagents are commercially available. Available analysis level, can be used directly without further purification.
2 Experimental procedures

2.1 Synthetic procedures

\[ \text{Experimental procedures} \]

\[ \text{2.1 Synthetic procedures} \]

\[ \begin{align*}
\text{O} & \text{O} \\
\text{O} & \text{H} \\
\text{OH} & + \quad \text{H}_2\text{N} - \quad \text{NHBOc} \\
\text{DCC} & \quad \text{THF} \\
\text{O} & \text{O} \\
\text{O} & \text{H} \\
\text{OH} & + \quad \text{H}_2\text{N} - \quad \text{NHBOc} \\
\text{DCC} & \quad \text{THF} \\
\text{O} & \text{O} \\
\text{O} & \text{H} \\
\text{OH} & + \quad \text{H}_2\text{N} - \quad \text{NHBOc} \\
\text{DCC} & \quad \text{THF} \\
\end{align*} \]

\[ \begin{align*}
\text{2a} & \quad \text{NHBOc} \\
\text{TFA} & \\
\text{3a} \\
\text{2b} & \quad \text{NHBOc} \\
\text{TFA} & \\
\text{3b} \\
\text{2c} & \quad \text{NHBOc} \\
\text{TFA} & \\
\text{3c} \\
\end{align*} \]

\[ \begin{align*}
\text{4} & \quad \text{NHBOc} \\
\text{NHBOc} & \\
\text{piperidine} & \\
\text{5a, n=2} \\
\text{5b, n=4} \\
\text{5c, n=6} \\
\end{align*} \]
The Synthesis of compound 3a

Salicylic acid (3.1 mmol, 428.2 mg) and N-Boc-1,2-ethylenediamine (3.1 mmol, 496.7 mg) were dissolved in 8 mL of dry tetrahydrofuran (THF) and stirred for 30 minutes at 0°C. The DCC (3.41 mmol, 703.6 mg) dissolved in 3 mL of dry THF was added. The reaction mixture was slowly raised to room temperature and stirred for 18 hours. After the reaction was completed (monitored by TLC, DCM/MeOH, 25/1, v/v, Rf 0.5), the product was filtered, dropped into 200 mL of saturated sodium chloride solution, extracted (3×15 mL) with ethyl acetate (EA) for three times, and then dried over anhydrous Na₂SO₄. After removing the solvent under reduced pressure, 2a is obtained. The unstable Boc protecting group was hydrolyzed by CF₃COOH, and then the free amine 3a (84%) was produced. The crude product was purified by column chromatography on silica gel.

2a: ¹H NMR (400 MHz, Methanol-d4) δ 7.66 (dd, J = 8.0, 1.6 Hz, 1H), 7.26 (ddd, J = 8.3, 7.2, 1.7 Hz, 1H), 6.85 – 6.73 (m, 2H), 3.39 (dd, J = 6.6, 5.6 Hz, 2H), 3.20 (dd, J = 6.6, 5.6 Hz, 2H), 1.32 (s, 9H).

The Synthesis of compound 3b

Salicylic acid (3.1 mmol, 428.2 mg) and N-Boc-1,4-butyl diamine (3.2 mmol, 602.5 mg) were dissolved in 8mL of dry THF, and stirred at 0°C for 30 minutes. The DCC (3.41 mmol, 703.6 mg) dissolved in 3 mL of dry THF was added. The reaction mixture was slowly raised to room
temperature and stirred for 18 hours. After the reaction was completed (monitored by TLC, DCM/MeOH, 25/1, v/v, Rf 0.5, the product was filtered, dropped into 200 mL of saturated sodium chloride solution, extracted (3×15 mL) with ethyl acetate (EA) for three times, and then dried over anhydrous Na₂SO₄. After removing the solvent under reduced pressure, 2b is obtained. The unstable Boc protecting group was hydrolyzed by CF₃COOH, and then the free amine 3b (87%) was produced. The crude product was purified by column chromatography on silica gel.

2b: ¹H NMR (400 MHz, Methanol-d4) δ 7.77 (dd, J = 8.0, 1.6 Hz, 1H), 7.35 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 6.88 (ddd, J = 16.7, 8.3, 1.2 Hz, 2H), 3.40 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 6.7 Hz, 2H), 1.64 (dq, J = 11.0, 6.9 Hz, 2H), 1.59 – 1.51 (m, 2H), 1.43 (s, 9H).

**The Synthesis of compound 3c**

Salicylic acid (3.1 mmol, 428.2 mg) and N-Boc-1,6-hexamethylenediamine (3.2 mmol, 691.2 mg) were dissolved in 8 mL of dry THF, and stirred at 0°C for 30 minutes. The DCC (3.41 mmol, 703.6 mg) dissolved in 3 mL of dry THF was added. The reaction mixture was slowly raised to room temperature and stirred for 18 hours. After the reaction was completed (monitored by TLC, DCM/MeOH, 25/1, v/v, Rf 0.5), the product was filtered, dropped into 200 mL of saturated sodium chloride solution, extracted (3×15 mL) with ethyl acetate (EA) for three times, and then dried over anhydrous Na₂SO₄. After removing the solvent
under reduced pressure, \(2c\) is obtained. The unstable Boc protecting group was hydrolyzed by CF\(_3\)COOH, and then the free amine \(3c\) (89%) was produced. The crude product was purified by column chromatography on silica gel.

\(2c\): \(^1\)H NMR (400 MHz, Methanol-d4) \(\delta 7.76 \text{ (dd, } J = 7.9, 1.7 \text{ Hz, } 1\text{H}), 7.36 \text{ (ddd, } J = 8.6, 7.2, 1.7 \text{ Hz, } 1\text{H}), 6.91 – 6.84 \text{ (m, } 2\text{H}), 3.38 \text{ (t, } J = 7.1 \text{ Hz, } 2\text{H}), 3.03 \text{ (t, } J = 6.9 \text{ Hz, } 2\text{H}), 1.62 \text{ (p, } J = 7.2 \text{ Hz, } 2\text{H}), 1.48 \text{ (t, } J = 6.8 \text{ Hz, } 2\text{H}), 1.45 – 1.26 \text{ (m, } 15\text{H}).

**The Synthesis of compound \(5a\)**

To a solution that was made from 270 mg of \(N\)-Fmoc Amphotericin B carbamate-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl) ester (4), 800 mg of amine \(3a\) and 8 mL of anhydrous DMF was added 400 µL of DIPEA. The resulting mixture was stirred at room temperature in a closed flask for 1 hour. After the reaction was completed (monitored by TLC, DCM/MeOH/NH\(_3\)·H\(_2\)O, 60/20/3, v/v/v, \(R_f\) 0.5), 1 ml of piperidine was added and the mixture allowed to stir for an additional 30 minutes. Then, the mixture was dropped into 150 mL cold methyl tert-butyl ether. Then, the product was dissolved in methanol and dichloromethane, and then the solvent was removed under reduced pressure to obtain yellow solid \(5a\) (40%). \(5a\): \(^1\)H NMR (400 MHz, CD\(_3\)OD:CDCl\(_3\)=1:3) \(\delta 7.82 \text{ (dd, } J = 8.0, 1.6 \text{ Hz, } 1\text{H}), 7.38 \text{ (ddd, } J = 8.6, 7.2, 1.7 \text{ Hz, } 1\text{H}), 6.90 \text{ (ddd, } J = 12.3, 5.9, 3.1 \text{ Hz, } 2\text{H}), 6.50 – 5.93 \text{ (m, } 13\text{H}), 5.42 \text{ (d, } J = 6.8 \text{ Hz, } 1\text{H}), 5.32 \text{ (t, } J = 12.2 \text{ Hz, } 1\text{H}), 4.38 \text{ (q, } J = 10.8, 10.2 \text{ Hz, } 2\text{H}), 4.29 \text{ (s, } 1\text{H}), 4.19 \text{ (td, } J = 10.8, 4.8 \text{ Hz, } 2\text{H}), 4.11 \text{ (d, } J = 9.3 \text{ Hz, } 2\text{H}), 4.00 – 3.92 \text{ (m, } 2\text{H}), 3.72 \text{ (t, } J = 10.1 \text{ Hz, } 1\text{H}), 3.65 – 3.52 \text{ (m, } 5\text{H}), 3.40 \text{ (t, } J = 9.6 \text{ Hz, } 1\text{H}), 3.28 – 3.10 \text{ (m, } 4\text{H}), 2.47 – 2.33 \text{ (m, } 1\text{H}), 2.34 – 2.26 \text{ (m, } 1\text{H}), 2.19 \text{ (dd, } J = 16.9, 2.4 \text{ Hz, } 1\text{H}), 1.47 – 0.84 \text{ (m, } 15\text{H}), 0.84 \text{ (s, } 3\text{H}).

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Hz, 1H), 2.11 – 1.95 (m, 2H), 1.90 (d, J = 14.0 Hz, 1H), 1.83 – 1.65 (m, 4H), 1.63 – 1.02 (m, 21H), 0.99 (d, J = 7.1 Hz, 3H), 0.92 – 0.82 (m, 1H). $^{13}$C NMR (151 MHz, CD$_3$OH:CDCl$_3$=1:3) δ 177.83, 176.43, 174.21, 164.64, 140.38, 139.70, 137.76, 137.70, 137.08, 136.94, 136.81, 136.77, 136.66, 135.83, 133.84, 133.76 (2C), 133.62, 133.29, 131.59, 122.61, 121.88, 119.43, 103.22, 101.52, 79.39, 78.41, 77.30, 76.59, 76.38, 73.98, 73.92, 72.93, 72.74, 69.69, 69.12, 61.95, 59.95, 50.17, 47.68, 46.58, 44.72, 44.06, 43.69, 43.21, 42.94, 42.64, 38.80, 35.04, 33.52, 22.34, 21.22, 20.46, 15.73.

HR-MS: for C$_{56}$H$_{83}$N$_3$O$_{18}$, [M+H]$^+$ calculated: 1086.5744; found:1086.5767

The Synthesis of compound 5b

To a solution that was made from 270 mg of N-Fmoc Amphotericin B carbamate-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl) ester (4), 800 mg of amine 3b and 8 mL of anhydrous DMF was added 400 µL of DIPEA. The resulting mixture was stirred at room temperature in a closed flask for 1 hour. After the reaction was completed (monitored by TLC, DCM/MeOH/NH$_3$·H$_2$O, 60/20/3, v/v/v, R$_f$ 0.5), 1 mL of piperidine was added and the mixture allowed to stir for an additional 30 minutes. Then, the mixture was dropped into 150 mL cold methyl tert-butyl ether. Then, the product was dissolved in methanol and dichloromethane, and then the solvent was removed under reduced pressure to obtain yellow solid 5b (44%). 5b: $^1$H NMR (400 MHz, CD$_3$OD:CDCl$_3$=1:3) δ 7.81 (dd, J = 8.0, 1.6 Hz, 1H), 7.38 – 7.32 (m, 1H), 6.93 – 6.85 (m, 2H), 6.50 – 5.98 (m, 14H), 5.45 – 5.28 (m, 2H), 4.45 – 4.38 (m, 2H), 4.37 (s, 1H), 4.35 – 4.31 (m, 1H), 4.24 – 4.10 (m, 3H), 4.07 (s, 1H), 4.00 – 3.94 (m, 2H), 3.73 (t, J = 10.0 Hz, 1H), 3.65 – 3.57 (m, 2H), 3.44 – 3.37 (m, 3H), 3.20 (dt, J = 9.1, 6.1 Hz, 4H), 3.05 (dd, J = 10.2, 3.2 Hz, 1H), 2.45 – 1.02 (m,
\( \text{SI-9} \)

39H), 0.99 (d, J = 7.2 Hz, 3H), 0.93 – 0.80 (m, 1H). \(^{13}\text{C NMR} \) (151 MHz, CD\(_3\)OH:CDCl\(_3\)=1:3) \( \delta \) 177.61, 176.51, 173.77, 163.91, 140.45, 139.12, 137.83, 137.70, 137.10, 137.00, 136.90, 136.68, 135.85 (2C), 134.36, 133.76 (2C), 133.60, 133.25, 131.44, 123.00, 121.48, 119.19, 101.72, 100.80, 79.58, 78.45, 77.11, 76.45, 73.98, 73.06, 72.77, 72.72, 71.50, 69.47, 69.06, 61.39, 59.96, 46.65, 44.65, 42.98, 42.77, 33.61, 33.52, 33.36, 33.21, 33.15, 31.03, 30.45, 30.42, 26.51, 26.34, 22.39, 20.95, 20.45, 15.75.

HR-MS: for C\(_{58}\)H\(_{87}\)N\(_3\)O\(_18\), [M+H]\(^+\) calculated:1114.6057; found:1114.6091

The Synthesis of compound 5c

To a solution that was made from 270 mg of N-Fmoc Amphotericin B carbamate-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl) ester (4), 800 mg of amine 3c and 8 mL of anhydrous DMF was added 400 \( \mu \)L of DIPEA. The resulting mixture was stirred at room temperature in a closed flask for 1 hour. After the reaction was completed (monitored by TLC, DCM/MeOH/NH\(_3\)·H\(_2\)O, 60/20/3, v/v/v, \( R_f \) 0.5), 1 mL of piperidine was added and the mixture allowed to stir for an additional 30 minutes. Then, the mixture was dropped into 150 mL cold methyl tert-butyl ether. Then, the product was dissolved in methanol and dichloromethane, and then the solvent was removed under reduced pressure to obtain yellow solid 5c (48%). 5c: \(^1\text{H NMR} \) (400 MHz, CD\(_3\)OD:CDCl\(_3\)=1:3) \( \delta \) 7.76 (dd, J = 8.0, 1.7 Hz, 1H), 7.33 (ddd, J = 8.7, 7.2, 1.7 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.51 – 5.98 (m, 17H), 5.43 (d, J = 6.9 Hz, 1H), 5.31 (dd, J = 14.4, 10.2 Hz, 1H), 4.46 – 4.34 (m, 6H), 4.24 – 4.07 (m, 3H), 4.00 (dd, J = 20.7, 17.5 Hz, 3H), 3.72 (t, J = 10.2 Hz, 1H), 3.66 – 3.56 (m,
2H), 3.47 – 3.40 (m, 1H), 3.38 (dd, J = 7.0, 1.9 Hz, 1H), 3.29 – 3.12 (m, 7H), 3.10 – 3.03 (m, 1H), 2.46 – 2.36 (m, 1H), 2.31 (dd, J = 17.3, 10.2 Hz, 1H), 2.20 (dd, J = 17.1, 2.5 Hz, 1H), 2.06 (dd, J = 12.4, 4.6 Hz, 1H), 1.99 (t, J = 10.3 Hz, 2H), 1.83 – 1.02 (m, 41H), 0.98 (d, J = 7.1 Hz, 3H), 0.86 (dd, J = 16.5, 6.8 Hz, 1H). $^{13}$C NMR (151 MHz, CD$_3$OH:CDCl$_3$=1:3) δ 177.44, 176.52, 173.57, 163.68, 140.38, 139.06, 137.67, 137.59, 137.13, 137.05, 136.99, 136.85, 135.86, 133.68, 131.38, 123.04, 121.44, 119.49, 101.66, 101.06, 79.48, 78.38, 77.14, 76.39, 73.98, 73.00, 72.80, 72.62, 72.01, 71.40, 70.84, 69.50, 69.06, 61.45, 59.96, 50.07, 47.82, 46.61, 44.63, 43.63, 43.31, 43.18, 43.01, 42.01, 38.80, 35.01, 33.53, 32.96, 32.90, 30.27, 30.17, 22.27, 20.95, 20.41, 15.73.

HR-MS: for C$_{60}$H$_{91}$N$_3$O$_{18}$, [M+H]$^+$ calculated:1142.6370; found:1142.6399

2.2 In vitro antifungal assays

We used three fungi, Candida albicans (CMCC 98001), Candida glabrata (ATCC 2001) and Cryptococcus neoformans (ATCC 32719), to conduct vitro antifungal assays test. The MIC was determined in RPMI 1640 butter (pH 7.0, adjusted by MOPs). Solutions of 5a-5c and AmB were prepared at a concentration of 1.6 mg/mL, using the serial two-fold dilution method to dilute each drug, with the final concentration of 0.125 to 16 μg/mL. 2000 CFU·mL$^{-1}$ cells were added to each well. After incubation at 37°C for 48 hours and 72 hours, the results were recorded. MIC is defined as the lowest drug concentration that leads to complete inhibition of visible growth.
2.3 In vitro Hemolysis tests

Dilute 4% sheep red blood cells with PBS solution with pH 7.4, centrifuge at 1500 g for 5 minutes, and discard the supernatant. The sheep red blood cells were washed three times until the supernatant was colorless. Solutions of AmB and 5a-5c were prepared at 20.48 mg/mL, using the serial two-fold dilution method to dilute each drug, with the final concentration of 1.6 to 204.8 μg/mL. 200 μL drug solution and 200 μL sheep red blood cells were added to the centrifuge tube. The resulting solution was incubated for 1 hour at 37℃. Then the obtained solution was centrifuged at 1500 g for 5 minutes. The absorbance of supernatant was measured at 540 nm by microplate reader. The percentage of hemolysis was calculated using the formula below.

\[
\text{Hemolysis\%} = \frac{(O. \ D_{540\text{nm}} - O. \ D_{\text{negative control}})}{(O. \ D_{\text{positive control}} - O. \ D_{\text{negative control}})} \times 100\%
\]

2.4 In vitro nephrotoxicity studies

Cell viability and cell proliferation were determined using a Cell Counting Kit-8 (CCK-8) assay. Human embryonic kidney 293T cells (HEK 293T cells) were cultured and passaged in 90% DMEM, 20% fetal bovine serum and 1% double antibody medium. HEK 293T were inoculated into 96-well plates (6 \times 10^4 cells/well) at the best cell viability,
and incubated at 37°C and 5% CO₂ for 12 hours. Solutions of AmB and 
\textbf{5a-5c} were prepared at 20.48 mg/mL, using the serial two-fold dilution 
method to dilute each drug, with the final concentration of 1.6 to 204.8 
μg/mL. After treatment, the culture media was removed, and 100 μL of 
drugs was added to each well. And the background absorption of the 
control group was set. After 24 hours, CCK-8 was added, and OD value 
were measured at 1 hour and 2 hours respectively. The absorbance of 
supernatant was measured at 450 nm by microplate reader.

\textbf{2.5 Spectroscopic properties and self-association}

The self-association of the compounds was monitored by UV – visible 
spectrum. PBS was used to prepare drugs with concentrations of 6.4, 12.8, 
25.6, 51.2 and 102.4 μg/mL, respectively. Methanol was used to prepare 
drugs with concentrations of 6.4 and 102.4 μg/mL, respectively. The 
UV-visible spectrum of each sample was recorded in the range of 
300-450 nm.

a)
Figure SI-1. Absorption spectra of AmB, 5a, 5b and 5c in a) 12.8 μg/mL in PBS, b) 25.6 μg/mL in PBS and, c) 51.2 μg/mL in PBS, d) 102.4 μg/mL in Methanol.
3 NMR and HR-MS spectra of compounds

**Figure SI-2:** $^1$H NMR spectrum of 3a

**Figure SI-3:** $^1$H NMR spectrum of 3b
**Figure SI-4:** $^1$H NMR spectrum of 3c

**Figure SI-5:** $^1$H NMR spectrum of 5a
Figure SI-6: $^1$H NMR spectrum of 5b

Figure SI-7: $^1$H NMR spectrum of 5c
Figure SI-8 High resolution mass spectrum of 5a

Figure SI-9 High resolution mass spectrum of 5b
**Figure SI-10** High resolution mass spectrum of 5c

**Figure SI-11**: $^{13}$C NMR spectrum of 5a
Figure SI-12: $^{13}$C NMR spectrum of 5b

Figure SI-13: $^{13}$C NMR spectrum of 5c
5a:

![IR of 5a](image)

Figure SI-14: IR of 5a

5b:
Figure SI-15: IR of 5b
Figure SI-16: IR of 5c
5a, 5b, 5c were taken and dissolved in DMF (PH 7.4), which analysed by HPLC according to the following analysis conditions.

**Analysis conditions of HPLC:**

Column: Symmetry C18 4.6 x 250 mm, Mobile phase: (A) 0.6% acetic acid in water and (B) methyl alcohol, Flow: 1 mL/min, Temperature: 40°C, Wavelength (nm): 409. 0 min: A: 70%, B: 30%; 3 min: A: 70%, B: 30%; 20 min: A: 30%, B: 70%; 21 min: A: 10%, B: 90%; 25 min: 10%, B: 90%; 26 min: A: 70%, B: 30%; 30 min: A: 70%, B: 30%.

5a:

| Peak# | Ret.Time | Area   | Height   | Area%  | Height%  |
|-------|----------|--------|----------|--------|----------|
| 1     | 27.972   | 5416759| 545572   | 100.000| 100.000  |
| Total |          | 5416759| 545572   | 100.000| 100.000  |

**Figure SI-17: HPLC of 5a**
5b:

![HPLC of 5b](image)

| Peak# | Ret.Time | Area  | Height | Area%  | Height% |
|-------|----------|-------|--------|--------|---------|
| 1     | 27.722   | 6667401 | 697064 | 100.000 | 100.000 |
| Total |          | 6667401 | 697064 | 100.000 | 100.000 |

**Figure SI-18: HPLC of 5b**

5c:

![HPLC of 5c](image)

| Peak# | Ret.Time | Area    | Height  | Area%  | Height% |
|-------|----------|---------|---------|--------|---------|
| 1     | 27.749   | 12547677 | 1220666 | 98.532 | 98.997 |
| 2     | 29.852   | 186884  | 12371   | 100.000 | 1.003  |
| Total |          | 12734561 | 1233036 |        |         |

**Figure SI-19: HPLC of 5c**
Reference:

Zhang, J.; Dong, Y.; Xu, H.; Dong, Y. Z.; Chen, M. W.; Zhang, Y.; Shangguan, W. W.; Zhao W. J.; Feng, J. Design, synthesis and biological evaluation of a novel N-aminoacyl derivative of amphotericin B methyl ester as an antifungal agent. *Eur. J. Med. Chem.* **2021**, *113104.*