Supporting Information (1, 2, 3)

Berberine azoles as antimicrobial agents: synthesis, biological evaluation and their interactions with human serum albumin

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Supporting Information 1

1. General methods

Melting points were recorded on X-6 melting point apparatus and uncorrected. TLC analysis was done using pre-coated silica gel plates. FT-IR spectra were carried out on Bruker RFS100/S spectrophotometer (Bio-Rad, Cambridge, MA, USA) using KBr pellets in the 400–4000 cm^{-1} range. NMR spectra were recorded on a Bruker AV 300 or Varian 400 spectrometer using TMS as an internal standard. The chemical shifts were reported in parts per million (ppm), the coupling constants (*J*) were expressed in hertz (Hz) and signals were described as singlet (s), doublet (d), triplet (t), as well as multiplet (m). The following abbreviations were used to designate aryl groups: Tri, triazolyl; Im, imidazolyl; Benim, benzimidazolyl; Bentri, benzotriazolyl; Ph, phenyl; Ber, berberinyl. The mass spectra were recorded on LCMS-2010A and the high-resolution mass spectra (HRMS) were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource.

2. Spectral data of the prepared compounds

*2.1 General procedures for the preparation of intermediates diols (**4a**–**h**) and bromides (**5a**–**h**)*

The intermediates **4** and **5** were prepared according to the previously reported methods [1].

*2.2 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(2,4-difluorobenzyl)ethanamine] (**6a**)*

1,2,4-Triazole (0.59 g, 8.5 mmol) and potassium carbonate (2.32 g, 16.7 mmol) in acetonitrile (5 mL) were stirred at 60 ºC for 1 h, then the mixture was cooled to room temperature, compound **5a** (3.01 g, 8.4 mmol) was added and stirred for 2 h at room temperature. After the reaction was completed (monitored by TLC, eluent, ethyl acetate/petroleum, 1/2, V/V), solvent was removed under reduced pressure, then the residue was extracted with ethyl acetate (3 × 30 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. Subsequently the crude products were purified by column chromatography eluting with ethyl acetate/petroleum (1/2, V/V) to afford the target compound **6a** as oil (1.15 g). Yield: 39.1%; IR (KBr, cm^{-1}) ν: 3042 (Ar-H), 2926, 2857 (CH_2), 1604, 1505, 1480 (aromatic skeleton), 1374, 1232, 1134, 1109, 1039, 873, 814; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H, Tri 3-*H*), 7.86 (s, 1H, Tri 5-*H*), 7.12-6.89 (m, 1H, Ph 3,5,6-*H*), 4.17 (br, 2H, Tri-CH_2), 3.64 (s, 2H, Ph-CH_2), 3.20 (br, 2H, Br-CH_2), 2.95 (br, 2H, Tri-CH_2CH_2), 2.87 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 162.6, 161.3, 161.1, 159.6, 158.4, 150.4, 141.3, 135.7, 132.0, 119.4, 111.6, 104.2, 103.7, 56.2, 53.5, 51.2, 48.4, 29.6 ppm; MS (ESI): m/z 346 $[M+H]^+$.

*2.3 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(3,4-dichlorobenzyl)ethanamine] (**6b**)*

Compound **6b** was prepared according to the procedure described for compound **6a** starting from 1,2,4-triazole (0.69 g, 10.0 mol), potassium carbonate (2.81 g, 20.2 mmol) and compound **5b** (4.00 g, 10.4 mmol). The desired compound **6b** was obtained as oil (2.18 g). Yield: 57.8%; IR (KBr, cm^{-1}) ν: 3077, 3021 (Ar-H), 2943, 2821 (CH_2), 1609, 1511, 1467 (aromatic skeleton), 1343, 1223, 1132, 1108, 1031, 867, 821; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H, Tri 3-*H*), 7.82 (s, 1H, Tri 5-*H*), 7.09–6.77 (m, 3H, Ph 2,5,6-*H*), 4.18 (br, 2H, Tri-CH_2), 3.58 (s, 2H, Ph-CH_2), 3.21 (br, 2H, Br-CH_2), 2.98 (br, 2H, Tri-CH_2CH_2), 2.92 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 142.9, 138.7, 132.6, 131.4, 120.5, 112.3, 107.7, 56.0, 54.2, 51.5, 48.3, 29.8 ppm; MS (ESI): m/z 379 $[M+H]^+$.

*2.4 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(2-chlorobenzyl)ethanamine] (**6c**)*

Compound **6c** was prepared according to the procedure described for compound **6a** starting from 1,2,4-triazole (1.00 g, 14.5 mmol), potassium carbonate (4.18 g, 30.3 mmol) and compound **5c** (5.48 g, 15.4 mmol). The target compound **6c** was obtained as oil (2.13 g). Yield: 42.7%; IR (KBr, cm^{-1}) ν: 3082, 3033 (Ar-H), 2947, 2853 (CH_2), 1603, 1504, 1454 (aromatic skeleton), 1335, 1232, 1115, 1027, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H, Tri 3-*H*), 7.93 (s, 1H, Tri 5-*H*), 7.23–6.76 (m, 4H, Ph 3,4,5,6-*H*), 4.18 (br, 2H, Tri-CH_2), 3.62 (s, 2H, Ph-CH_2), 3.18 (br, 2H, Br-CH_2), 2.96 (br, 2H, Tri-CH_2CH_2), 2.84 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 142.6, 132.3, 122.7, 121.4, 117.4, 113.9, 103.6, 54.7, 52.9, 49.4, 46.4, 29.5 ppm; MS (ESI): m/z 344 $[M+H]^+$.

*2.5 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(3-chlorobenzyl)ethanamine] (**6d**)*

Compound **6d** was prepared according to the procedure described for compound **6a** starting from 1,2,4-triazole (0.69 g, 10.0 mmol), potassium carbonate (2.79 g, 20.2 mmol) and compound **5d** (3.69 g, 10.4 mmol). The target compound **6d** was obtained as oil (1.12 g). Yield: 32.7%; IR (KBr, cm^{-1}) ν: 3054 (Ar-H), 2944, 2821 (CH_2), 1607, 1504, 1445 (aromatic skeleton), 1342, 1226, 1108, 1034, 807, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H, Tri 3-*H*), 7.91 (s, 1H, Tri 5-*H*), 7.23–6.76 (m, 4H, Ph 2,4,5,6-*H*), 4.14 (br, 2H, Tri-CH_2), 3.63 (br, 2H, Ph-CH_2), 3.14 (br, 2H, Br-CH_2), 2.99 (br, 2H, Tri-CH_2CH_2), 2.81 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 142.7, 132.1, 124.7, 121.9, 118.0, 114.7, 103.4, 54.5, 52.6, 49.3, 46.2, 29.5 ppm; MS (ESI): m/z 344 $[M+H]^+$.

*2.6 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(4-chlorobenzyl)ethanamine] (**6e**)*

Compound **6e** was prepared according to the procedure described for compound **6a** starting from 1,2,4-triazole (0.71 g, 10.3 mmol), potassium carbonate (4.14 g, 30.0 mmol) and compound **5e** (3.61 g, 10.0 mmol). The pure compound **6e** was obtained as oil (0.87 g). Yield: 25.4%; IR (KBr, cm^{-1}) ν: 3021 (Ar-H), 2932, 2846 (CH_2), 1605, 1498, 1451 (aromatic skeleton), 1322, 1234, 1112, 1077, 843; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, Tri 3-*H*), 7.86 (s, 1H, Tri 5-*H*), 7.13–6.72 (m, 4H, Ph 2,3,5,6-*H*), 4.19 (br, 2H, Tri-CH_2), 3.59 (br, 2H, Ph-CH_2), 3.25 (br, 2H, Br-CH_2), 2.91 (br, 2H, Tri-CH_2CH_2), 2.85 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 142.2, 133.5, 123.2, 120.7, 116.4, 113.8, 102.6, 54.6, 52.8, 50.4, 46.9, 28.8 ppm; MS (ESI): m/z 344 $[M+H]^+$.

*2.7 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(2-fluorobenzyl)ethanamine] (**6f**)*

Compound **6f** was prepared according to the procedure described for compound **6a** starting from 1,2,4-triazole (0.69 g, 10.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and compound **5f** (3.63 g, 10.8 mmol). The target compound **6f** was obtained as oil (1.45 g). Yield: 44.3%; IR (KBr, cm^{-1}) ν: 3078 (Ar-H), 2943, 2852 (CH_2), 1609, 1502, 1456 (aromatic skeleton), 1332, 1236, 1117, 1078, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, Tri 3-*H*), 7.87 (s, 1H, Tri 5-*H*), 7.28–7.01 (m, 4H, Ph 3,4,5,6-*H*), 4.18 (br, 2H, Tri-CH_2), 3.72 (s, 2H, Ph-CH_2), 3.19 (br, 2H, Br-CH_2), 2.99 (br, 2H, Tri-CH_2CH_2), 2.89 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 160.6, 151.6, 143.3, 131.5, 131.6, 128.2, 127.9, 115.6, 114.9, 55.4, 53.4, 50.8, 47.0, 28.9 ppm; MS (ESI): m/z 328 $[M+H]^+$.

*2.8 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(3-fluorobenzyl)ethanamine] (**6g**)*

Compound **6g** was prepared according to the procedure described for compound **6a** starting from 1,2,4-triazole (0.69 g, 10.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and compound **5g** (3.29 g, 9.7 mmol). The pure compound **6g** was obtained as oil (1.32 g). Yield: 40.4%; IR (KBr, cm^{-1}) ν: 3071, 3022 (Ar-H), 2943, 2877, 2843 (CH_2), 1611, 1513, 1452 (aromatic skeleton), 1326, 1241, 1105, 1077, 808, 699; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H, Tri 3-*H*), 7.90 (s, 1H, Tri 5-*H*), 7.29–6.80 (m, 4H, Ph 2,4,5,6-*H*), 4.17 (br, 2H, Tri-CH_2), 3.64 (s, 2H, Ph-CH_2), 3.28 (br, 2H, Br-CH_2), 2.99 (br, 2H, Tri-CH_2CH_2), 2.92 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 161.3, 151.1, 142.8, 132.7, 131.6, 127.7, 120.2, 117.9, 107.3, 56.5, 52.3, 49.7, 47.3, 29.3 ppm; MS (ESI): m/z 328 $[M+H]^+$.

*2.9 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-2-bromo-N-(2,4-dichlorobenzyl)ethanamine] (**6h**)*

Compound **6h** was prepared according to the procedure described for compound **6a** starting from 1,2,4-triazole (0.38 g, 5.5 mmol), potassium carbonate (1.52 g, 11.0 mmol) and compound **5h** (1.83 g, 5.4 mmol). The pure compound **6h** was obtained as oil (0.65 g). Yield: 39.3%; IR (KBr, cm^{-1}) ν: 3055 (Ar-H), 2953, 2873 (CH_2), 1606, 1511, 1450

(aromatic skeleton), 1332, 1236, 1107, 1077, 855; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, Tri 3-*H*), 7.82 (s, 1H, Tri 5-*H*), 7.09–6.77 (m, 3H, Ph 3,5,6-*H*), 4.13 (br, 2H, Tri-CH_2), 3.65 (s, 2H, Ph-CH_2), 3.21 (br, 2H, Br-CH_2), 2.97 (br, 2H, Tri-CH_2CH_2), 2.85 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 141.7, 138.2, 130.8, 122.7, 120.3, 112.7, 102.5, 55.6, 53.8, 50.8, 47.9, 29.3 ppm; MS (ESI): m/z 379 $[M+H]^+$.

*2.10 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(2,4-difluorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7a**)*

To a stirred solution of berberrubine (0.70 g, 2.0 mmol) in DMF (5 mL) was added dropwise compound **6a** (0.66 g, 1.9 mmol) in DMF (5 mL). The mixture was stirred for 20 h and monitored by TLC (chloroform/methanol, 20/1, V/V). After the reaction come to the end, the mixture was cooled to room temperature and extracted with chloroform (3 × 30 mL). The organic phase was washed with water and dried over anhydrous sodium sulfate. After the filtrate was concentrated, the crude product was purified by column chromatography eluting with chloroform/methanol (20/1, V/V) to afford the compound **7a** (0.45 g) as yellow solid. Yield: 36.2%; mp: 210–212 ºC. IR (KBr, cm^{-1}) ν: 3073 (Ar-H), 2966, 2847 (CH_2), 1620, 1604, 1569, 1505 (aromatic skeleton), 1480, 1394, 1367, 1338, 1276, 1232, 1134, 1109, 1039, 960, 873; ^{1}H NMR (400 MHz, CD_3OD): δ 9.57 (s, 1H, Ber 8-*H*), 8.70 (s, 1H, Ber 13-*H*), 8.47 (s, 1H, Tri 3-*H*), 8.08 (d, 1H, *J* = 8.8 Hz, Ber 12-*H*), 7.98 (d, 1H, *J* = 8.8 Hz, Ber 11-*H*), 7.86 (s, 1H, Tri 3-*H*), 7.66 (s, 1H, Ber 1-*H*), 7.22–6.82 (m, 3H, Ph 3,5,6-*H*), 6.97 (s, 1H, Ber 4-*H*), 6.11 (s, 2H, OCH_2O), 4.92 (br, 2H, Ber 6-*H*), 4.39 (br, 4H, OC$H_2$$CH_2$N, Tri-C$H_2$), 4.06 (s, 3H, OC$H_3$), 3.79 (s, 2H, Ph-C$H_2$), 3.27 (br, 2H, Ber 5-*H*), 3.06 (br, 4H, OCH_2CH_2N, Tri-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 163.4, 163.1, 161.8, 161.2, 160.8, 159.3, 158.5, 150.4, 149.6, 148.3, 145.4, 142.4, 142.0, 135.7, 132.8, 132.2, 131.6, 131.1, 123.2, 120.5, 119.4, 119.2, 118.9, 118.6, 118.2, 116.8, 112.5, 111.3, 108.9, 105.2, 104.7, 103.4, 102.5, 73.6, 57.9, 56.1, 53.8, 51.9, 47.6, 29.9, 26.5 ppm; MS (ESI): m/z 586 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{30}ClF_2N_5O_4$ $[M–Cl]^+$, 586.2260; found, 586.2252.

*2.11 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(3,4-dichlorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7b**)*

Compound **7b** was prepared according to the procedure described for compound **7a** starting from berberrubine (1.09 g, 3.1 mmol) and compound **6b** (1.15 g, 3.0 mmol). The target compound **7b** (0.78 g) was obtained as yellow solid. Yield: 38.6%; mp: 216–218 ºC. IR (KBr, cm^{-1}) ν: 3094, 3033 (Ar-H), 2966, 2814 (CH_2), 1631, 1601, 1573, 1506 (aromatic skeleton), 1476, 1450, 1385, 1349, 1272, 1232, 1170, 1084, 1040, 876, 796; ^{1}H NMR (400 MHz, CD_3OD): δ 9.62 (s, 1H, Ber 8-*H*), 8.75 (s, 1H, Ber 13-*H*), 8.45 (s, 1H, Tri 5-*H*), 8.14 (d, *J* = 8.8 Hz, Ber 12-*H*), 7.93 (d, *J* = 8.8 Hz, Ber 11-*H*), 7.93 (s, 1H, Tri 3-*H*), 7.68 (s, 1H, Ber 1-*H*), 7.40–7.20 (m, 3H, Ph 2,5,6-*H*), 6.93 (s, 1H, Ber 4-*H*), 6.12 (s, 2H, OCH_2O), 4.93 (br, 2H, Ber 6-*H*), 4.35 (br, 2H, OC$H_2$$CH_2$N), 4.29 (s, 2H, Tri-C$H_2$), 4.08 (s, 3H, OC$H_3$), 3.74 (s, 2H, Ph-C$H_2$), 3.21 (br, 2H, Ber 5-*H*), 3.03 (br, 4H, OCH_2CH_2N, Tri-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 151.1, 149.4, 148.7, 146.1, 145.7, 144.5, 142.4, 139.9, 136.7, 134.2, 133.4, 132.5, 131.6, 130.9, 128.3, 125.8, 122.7, 120.5, 119.4, 118.9, 118.5, 116.1, 107.7, 102.3, 72.1, 58.2, 56.1, 53.8, 51.7, 48.5, 28.9, 27.2 ppm; MS (ESI): m/z 619 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{30}Cl_3N_5O_4$ $[M–Cl]^+$, 618.1669; found, 618.1677.

*2.12 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(2-chlorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7c**)*

Compound **7c** was prepared according to the procedure described for compound **7a** starting from berberrubine (0.71 g, 2.2 mmol) and compound **6c** (0.73 g, 2.1 mmol). The target compound **7c** (0.43 g) was obtained as yellow solid. Yield: 31.7%; mp: 191–193 ºC. IR (KBr, cm^{-1}) ν: 3058 (Ar-H), 2966, 2847 (CH_2), 1608, 1599, 1561, 1502 (aromatic skeleton), 1482, 1386, 1365, 1304, 1136, 961, 860; ^{1}H NMR (400 MHz, CD_3OD): δ 9.62 (s, 1H, Ber 8-*H*), 8.79 (s, 1H, Ber 13-*H*), 8.50 (s, 1H, Tri 3-*H*), 8.13 (d, 1H, *J* = 8.8 Hz, Ber 12-*H*), 7.92 (d, 1H, *J* = 8.8 Hz, Ber 11-*H*), 7.83 (s, 1H, Tri 5-*H*), 7.69 (s, 1H, Ber 1-*H*), 7.37–7.02 (m, 4H, Ph 3,4,5,6-*H*), 6.98 (s, 1H, Ber 4-*H*), 6.10 (s, 2H, OCH_2O), 4.91 (br, 2H, Ber 6-*H*), 4.34 (br, 2H, OC$H_2$$CH_2$N), 4.27 (br, 2H, Tri-C$H_2$), 4.04 (s, 3H, OC$H_3$), 3.81 (s, 2H, Ph-C$H_2$), 3.25 (br, 2H, Ber 5-*H*), 3.01 (br, 4H, OCH_2CH_2N, Tri-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 150.9, 149.3, 148.6, 146.2, 145.3, 144.7, 142.3, 141.6, 134.7, 133.4, 132.5, 131.1, 129.4, 128.7, 127.2, 126.5, 123.0, 120.4, 119.4, 118.8, 118.2, 116.4, 108.5, 102.9, 72.4, 57.9, 55.3, 54.2, 52.3, 47.8, 30.2, 27.3 ppm; MS (ESI): m/z 585 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{31}Cl_2N_5O_4$ $[M–Cl]^+$, 584.2059; found, 584.2063.

*2.13 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(3-chlorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7d**)*

Compound **7d** was prepared according to the procedure described for compound **7a** starting from berberrubine (1.06 g, 3.0 mmol) and compound **6d** (1.07 g, 3.1 mmol). The target compound **7d** (0.56 g) was obtained as yellow solid. Yield: 30.1%; mp: 195–197 ºC; IR (KBr, cm^{-1}) ν: 3101, 3027 (Ar-H), 2948, 2845 (CH_2), 1631, 1601, 1506 (aromatic skeleton), 1479, 1430, 1384, 1300, 1274, 1141, 1002, 873; ^{1}H NMR (400 MHz, CD_3OD): δ 9.62 (s, 1H, Ber 8-*H*), 8.84 (s, 1H, Ber 13-*H*), 8.42 (s, 1H, Tri 3-*H*), 8.12 (d, J = 8.8 Hz, 1H, Ber 12-*H*), 7.93 (d, J = 8.8 Hz, 1H, Ber 11-*H*), 7.84 (s, 1H, Tri 5-*H*), 7.74 (s, 1H, Ber 1-*H*), 7.36–7.13 (m, 4H, Ph 2,4,5,6-*H*), 6.93 (s, 1H, Ber 4-*H*), 6.10 (s, 2H, OCH_2O), 4.93 (br, 2H, Ber 6-*H*), 4.39 (br, 2H, OCH_2CH$_2$N), 4.23 (br, 2H, Tri-CH_2), 3.96 (s, 3H, OCH_3), 3.81 (s, 2H, Ph-CH_2), 3.28 (br, 2H, Ber 5-*H*), 3.05 (br, 4H, OCH$_2$CH_2N, Tri-CH$_2$CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 152.1, 151.2, 148.1, 146.8, 145.4, 144.7, 143.4, 142.5, 138.4, 134.3, 133.4, 131.1, 130.7, 126.6, 124.1, 123.0, 120.9, 118.9, 118.6, 117.9, 112.2, 108.9, 102.5, 73.1, 56.8, 55.5, 53.8, 50.9, 47.8, 28.6, 26.5 ppm; MS (ESI): m/z 585 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{31}Cl_2N_5O_4$ $[M–Cl]^+$, 584.2059; found, 584.2067.

*2.14 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(4-chlorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7e**)*

Compound **7e** was prepared according to the procedure described for compound **7a** starting from berberrubine (0.72 g, 2.0 mmol) and compound **6e** (0.70 g, 2.0 mmol). The pure compound **7e** (0.26 g) was obtained as yellow solid. Yield: 21.0%; mp: 198–200 ºC; IR (KBr, cm^{-1}) ν: 3048 (Ar-H), 2925, 2853 (CH_2), 1606, 1597, 1560, 1502 (aromatic skeleton), 1481, 1380, 1365, 1302, 1120, 965, 860; ^{1}H NMR (400 MHz, CD_3OD): δ 9.58 (s, 1H, Ber 8-*H*), 8.84 (s, 1H, Ber 13-*H*), 8.52 (s, 1H, Tri 3-*H*), 8.12 (d, 1H, J = 8.8 Hz, Ber 12-*H*), 7.96 (d, 1H, J = 8.8 Hz, Ber 11-*H*), 7.88 (s, 1H, Tri 5-*H*), 7.67 (s, 1H, Ber 1-*H*), 7.43–7.02 (m, 4H, Ph 2,3,5,6-*H*), 6.98 (s, 1H, Ber 4-*H*), 6.12 (s, 2H, OCH_2O), 4.87 (br, 2H, Ber 6-*H*), 4.29 (br, 2H, OCH_2CH$_2$N), 4.33 (br, 2H, Tri-CH_2), 4.02 (s, 3H, OCH_3), 3.78 (s, 2H, Ph-CH_2), 3.24 (br, 2H, Ber 5-*H*), 3.01 (br, 4H, OCH$_2$CH_2N, Tri-CH$_2$CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 151.7, 150.4, 149.4, 146.6, 145.6, 144.8, 142.4, 140.7, 135.2, 133.4, 132.9, 131.1, 128.7, 127.9, 123.5, 121.3, 119.4, 118.4, 117.9, 116.7, 108.4, 103.1, 72.9, 56.8, 55.5, 53.8, 51.1, 48.7, 28.8, 27.0 ppm; MS (ESI): m/z 584 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{31}Cl_2N_5O_4$ $[M–Cl]^+$, 584.2065; found, 584.2067.

*2.15 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(2-fluorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7f**)*

Compound **7f** was prepared according to the procedure described for compound **7a** starting from berberrubine (1.47 g, 4.1 mmol) and compound **6f** (1.35 g, 4.1 mmol). The target compound **7f** (0.77 mg) was obtained as yellow solid. Yield: 31.3%; mp: 211–212 ºC; IR (KBr, cm^{-1}) ν: 3052 (Ar-H), 2923, 2852 (CH_2), 1631, 1593, 1558, 1508 (aromatic skeleton), 1483, 1380, 1346, 1275, 1137, 1101, 973, 870; ^{1}H NMR (400 MHz, CD_3OD): δ 9.59 (s, 1H, Ber 8-*H*), 8.83 (s, 1H, Ber 13-*H*), 8.50 (s, 1H, Tri 3-*H*), 8.13 (d, J = 8.8 Hz, 1H, Ber 12-*H*), 7.99 (d, J = 8.8 Hz, 1H, Ber 11-*H*), 7.88 (s, 1H, Tri 5-*H*), 7.71 (s, 1H, Ber 1-*H*), 7.28–7.10 (m, 4H, Ph 3,4,5,6-*H*), 6.94 (s, 1H, Ber 4-*H*), 6.12 (s, 2H, OCH_2O), 4.90 (br, 2H, Ber 6-*H*), 4.35 (br, 2H, OCH_2CH$_2$N), 4.26 (br, 2H, Tri-CH_2), 4.02 (s, 3H, OCH_3), 3.81 (s, 2H, Ph-CH_2), 3.22 (br, 2H, Ber 5-*H*), 2.98 (br, 4H, OCH$_2$CH_2N, Tri-CH$_2$CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 163.5, 160.8, 151.1, 149.6, 149.3, 146.4, 145.1, 143.2, 141.4, 133.5, 131.9, 131.2, 128.7, 127.2, 123.8, 120.4, 119.5, 118.2, 117.1, 116.2, 114.4, 108.5, 102.7, 74.1, 57.9, 55.6, 54.2, 51.5, 47.8, 28.8, 27.3 ppm. MS (ESI): m/z 568 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{31}ClFN_5O_4$ $[M–Cl]^+$, 568.2355; found, 568.2361.

*2.16 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(3-fluorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7g**)*

Compound **7g** was prepared according to the procedure described for compound **7a** starting from berberrubine (1.28 g, 3.6 mmol) and compound **6g** (1.40 g, 4.3 mmol). The target compound **7g** (0.74 g) was obtained as yellow solid. Yield: 34.1%; mp: 203–205 ºC; IR (KBr, cm^{-1}) ν: 3042 (Ar-H), 2923, 2848 (CH_2), 1632, 1569, 1507 (aromatic skeleton), 1482, 1388, 1372, 1343, 1137, 1101, 973, 870; ^{1}H NMR (400 MHz, CD_3OH): δ 9.64 (s, 1H, Ber 8-*H*), 8.85 (s, 1H, Ber 13-*H*), 8.54 (s, 1H, Tri 3-*H*), 8.12 (d, J = 8.8 Hz, 1H, Ber 12-*H*), 8.00 (d, J = 8.8 Hz, 1H, Ber 11-*H*), 7.90 (s, 1H, Tri 5-*H*), 7.71 (s, 1H, Ber 1-*H*), 7.33–7.08 (m, 4H, Ph 2,4,5,6-*H*), 6.97 (s, 1H, Ber 4-*H*), 6.13 (s, 2H, OCH_2O), 4.88 (br, 2H, Ber 6-*H*), 4.35 (br, 2H, OCH_2CH$_2$N), 4.26 (br, 2H, Tri-CH_2), 4.02 (s, 3H, OCH_3), 3.76 (s, 2H, Ph-CH_2), 3.22 (br, 2H, Ber 5-*H*), 3.00–2.98 (br, 4H, OCH$_2$CH_2N, Tri-CH$_2$CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 162.7, 160.3, 151.1, 150.6, 148.4, 145.4, 145.2, 142.4, 133.2, 131.6, 131.3, 130.5, 128.4, 128.1, 123.6, 120.4, 119.5, 118.7,

118.4, 116.5, 115.1, 114.3, 107.8, 103.1, 73.1, 57.5, 55.2, 53.8, 52.1, 48.5, 29.2, 27.1 ppm; MS (ESI): m/z 568 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{31}ClFN_5O_4$ $[M–Cl]^+$, 568.2355; found, 568.2360.

*2.17 [N-(2-(1,2,4-Triazol-1-yl)ethyl)-N-(2,4-dichlorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**7h**)*

Compound **7h** was prepared according to the procedure described for compound **7a** starting from berberrubine (0.72 g, 2.0 mmol) and compound **6h** (0.76 g, 2.0 mmol). The pure compound **7h** (0.43 g) was obtained as yellow solid. Yield: 32.5%; mp: 217–219 ºC; IR (KBr, cm^{-1}) ν: 3094, 3022 (Ar-H), 2987, 2958, 2838 (CH_2), 1620, 1604, 1570, 1507 (aromatic skeleton), 1479, 1450, 1388, 1362, 1335, 1276, 1232, 1204, 1103, 976, 876, 828; ^{1}H NMR (400 MHz, CD_3OD): δ 9.70 (s, 1H, Ber 8-*H*), 8.83 (s, 1H, Ber 13-*H*), 8.51 (s, 1H, Tri 3-*H*), 8.09 (d, J = 8.8 Hz, 1H, Ber 12-*H*), 7.97 (d, J = 8.8 Hz, 1H, Ber 11-*H*), 7.91 (s, 1H, Tri 5-*H*), 7.84 (s, 1H, Ber 1-*H*), 7.23–7.08 (m, 3H, Ph 3,5,6-*H*), 7.01 (s, 1H, Ber 4-*H*), 6.09 (s, 2H, OCH_2O), 4.92 (br, 2H, Ber 6-*H*), 4.35 (br, 2H, OCH_2CH_2N), 4.29 (br, 2H, Tri-CH_2), 4.00 (s, 3H, OCH_3), 3.76 (s, 2H, Ph-CH_2), 3.22 (br, 2H, Ber 5-*H*), 3.00–2.98 (br, 4H, OCH_2CH_2N, Tri-CH_2CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 150.7, 149.5, 148.4, 146.6, 146.1, 145.4, 142.5, 141.1, 137.4, 134.2, 133.7, 132.2, 131.4, 130.8, 127.5, 125.3, 123.3, 120.4, 119.2, 118.1, 117.4, 116.2, 108.9, 103.1, 72.5, 57.1, 55.8, 54.5, 50.9, 49.1, 30.3, 27.3 ppm; MS (ESI): m/z 619 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{32}H_{30}Cl_3N_5O_4$ $[M–Cl]^+$, 618.1669; found, 618.1674.

*2.18 Synthesis procedure of berberrubine (**2**)*

Commercially available berberine (30.0 g) chloride was heated at 190 ºC in a vacuum oven under reduced pressure (20 mm Hg) for 2 h to obtain berberrubine (25.46 g) in 88.2% yield in agreement with the literature [2].

*2.19 [N-(2-(Imidazole-1-yl)ethyl)-2-bromo-N-(2,4-difluorobenzyl)ethanamine] (**8**)*

To a stirred suspension of sodium hydride (1.44 g, 60.0 mmol) in tetrahydrofuran (25 mL) of was added imidazole (1.04 g, 15.3 mmol), and then the mixture was heated at 60 °C for 1 h. Compound **5a** (3.58 g, 10.0 mmol) was added and the mixture was stirred at 60 °C. After the reaction was completed, the reaction system was cooled to room temperature. The residue was extracted with ethyl acetate (3 × 40 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The crude product was purified by column chromatography eluting with acetone/ethyl acetate (1/4, V/V) to afford compound **8** as colorless oil (2.05 g). Yield: 57.3%; IR (KBr, cm^{-1}) ν: 3073, 3021 (Ar-H), 2962, 2913, 2842 (CH_2), 1601, 1542, 1489 (aromatic skeleton), 1420, 1327, 1289, 1234, 1137, 1049, 1031, 975, 853, 826; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H, Im 2-*H*), 7.25–6.95 (m, 3H, Ph 3,5,6-*H*), 6.92 (d, J = 9.0 Hz, 1H, Im 4-*H*), 6.79 (d, J = 9.0 Hz, 1H, Im 4-*H*), 4.22 (t, J = 6.2 Hz, 2H, Im-CH_2), 3.76 (s, 2H, Ph-CH_2), 3.35 (t, J = 6.0 Hz, 2H, Br-CH_2), 2.98 (t, J = 6.2 Hz, 2H, Im-CH_2CH_2), 2.88 (t, J = 6.0 Hz, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 163.3, 160.3, 161.3, 158.9, 157.5, 136.3, 135.2, 132.1, 131.8, 125.1, 119.5, 118.7, 111.4, 104.5, 104.3, 103.8, 54.9, 53.2, 50.7, 46.3, 29.4 ppm; MS (ESI): m/z 344 $[M+H]^+$.

*2.20 [N-(2-(Imidazole-1-yl)ethyl)-N-(2,4-difluorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**9**)*

Compound **9** was prepared according to the procedure described for compound **7a** starting from berberrubine (1.84 g, 5.1 mmol) and compound **8** (1.77 g, 5.1 mmol). The target compound **9** (0.95 g) was obtained as yellow solid. Yield: 30.8%; mp: 195–197 ºC; IR (KBr, cm^{-1}) ν: 3053 (Ar-H), 2928, 2857 (CH_2), 1631, 1600, 1546, 1501, 1483 (aromatic skeleton), 1385, 1366, 1301, 1142, 1098, 955, 837; ^{1}H NMR (300 MHz, CD_3OD): δ 9.57 (s, 1H, Ber 8-*H*), 8.66 (s, 1H, Ber 13-*H*), 8.03 (d, J = 9.0 Hz, 1H, Ber 12-*H*), 7.95 (d, J = 9.0 Hz, 1H, Ber 11-*H*), 7.71 (s, 1H, Ber 1-*H*), 7.28–7.25 (m, 1H, Ph 3-*H*), 7.04 (s, 1H, Ber 4-*H*), 7.13–7.10 (m, 1H, Ph 5-*H*), 6.91 (m, 1H, Ph 6-*H*), 7.31 (s, 1H, Im-2*H*), 7.02 (s, 1H, Im 4-*H*), 6.77 (s, 1H, Im-5*H*), 6.14 (s, 2H, OCH_2O), 4.91 (br, 2H, Ber 6-*H*), 4.30 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 4.08 (t, J = 6.2 Hz, 2H, Im-CH_2), 4.01 (s, 3H, OCH_3), 3.81 (s, 2H, Ph-CH_2), 3.23 (br, 2H, Ber 5-*H*), 3.07 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 2.88 (t, J = 6.2 Hz, 2H, Im-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 163.6, 163.2, 162.3, 161.3, 161.1, 159.1, 158.3, 150.3, 148.1, 145.6, 145.3, 142.9, 139.0, 135.2, 133.4, 132.1, 131.1, 128.1, 123.0, 120.9, 120.5, 119.7, 119.2, 118.6, 118.2, 117.9, 111.9, 111.5, 108.9, 104.1, 104.3, 103.5, 102.6, 72.4, 58.3, 54.2, 53.8, 52.2, 47.4, 29.1, 27.3 ppm; MS (ESI): m/z 586 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{33}H_{31}ClF_2N_5O_6$ $[M–Cl]^+$, 585.2308; found, 585.2305.

*2.21 [N-(2-(Benzimidazole-1-yl)ethyl)-2-bromo-N-(2,4-difluorobenzyl)ethanamine] (**10a**)*

Compound **10a** was prepared according to the procedure described for compound **6a** starting from benzimidazole (1.18 g, 10.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and compound **5a** (4.70 g, 13.2 mmol). The target compound **10a** (1.22 g) was obtained as colorless oil. Yield: 32.9%; IR (KBr, cm^{-1}) ν: 3031 (Ar-H), 2953, 2835 (CH_2), 1615, 1517, 1483 (aromatic skeleton), 1313, 1178, 979, 846, 670; ^{1}H NMR (300 MHz, $CDCl_3$): 8.37 (s, 1H, Benim 2-*H*), 7.71 (s, 2H, Benim 4,7-*H*), 7.32 (m, 2H, Benim 5,6-*H*), 7.10−6.95 (m, 3H, Ph 3,5,6-*H*), 4.11 (t, *J* = 6.2 Hz, 2H, Benim-CH_2), 3.64 (s, 2H, Ph-CH_2), 3.27 (t, *J* = 6.0 Hz, 2H, Br-CH_2), 3.11 (t, *J* = 6.2 Hz, 2H, Benim-CH_2CH_2), 2.92 (t, *J* = 6.0 Hz, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 161.9, 161.2, 159.7, 158.4, 142.6, 135.2, 132.1, 126.9, 125.2, 119.1, 117.7, 111.5, 104.1, 103.2, 55.4, 54.1, 51.9, 46.3, 28.9 ppm; MS (ESI): m/z 395 $[M+H]^+$.

*2.22 [N-(2-(5,6-Dimethyl-benzimidazole-1-yl)ethyl)-2-bromo-N-(2,4-difluorobenzyl) ethanamine] (**10b**)*

Compound **10b** was prepared according to the procedure described for compound **6a** starting from 5,6-dimethyl-benzimidazole (1.46 g, 10.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and compound **5a** (4.78 g, 12.9 mol). The pure compound **10b** (1.47 g) was obtained as white solid. Yield: 40.2%; mp: 167–170 ºC; IR (KBr, cm^{-1}) ν: 3053 (Ar-H), 2988, 2934, 2818 (CH_2, CH_3), 1609, 1523, 1465 (aromatic skeleton), 1321, 1267, 1178, 967, 853, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H, Benim 2-*H*), 7.77 (m, 2H, Benim 4,7-*H*), 7.30 (m, 2H, Benim 5,6-*H*), 7.10−6.95 (m, 3H, Ph 3,5,6-*H*), 4.15 (t, *J* = 6.2 Hz, 2H, Benim-CH_2), 3.64 (s, 2H, PhCH_2), 3.29 (t, *J* = 6.0 Hz, 2H, Br-CH_2), 3.07 (t, *J* = 6.2 Hz, 2H, Benim-CH_2CH_2), 2.89 (t, *J* = 6.0 Hz, 2H, Br-CH_2CH_2), 2.44 (s, 6H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6, 162.3, 159.6, 158.1, 142.6, 135.2, 126.8, 125.2, 119.1, 117.7, 111.5, 104.3, 103.7, 56.2, 54.4, 51.3, 46.1, 37.3, 28.8 ppm; MS (ESI): m/z 423 $[M+H]^+$.

*2.23 [N-(2-(Benzotriazol-1-yl)ethyl)-2-bromo-N-(2,4-difluorobenzyl)ethanamine] (**10c**)*

Compound **10c** was prepared according to the procedure described for compound **6a** starting from benzotriazole (1.19 g, 10.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and compound **5a** (4.78 g, 13.4 mmol). The pure compound **10c** (1.47 g) was obtained as white solid. Yield: 21.9%; mp: 187–188 ºC; IR (KBr, cm^{-1}) ν: 3066 (Ar-H), 2931, 2818 (CH_2), 1605, 1527, 1468 (aromatic skeleton), 1320, 1267, 1176, 967, 853, 702; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87−7.85 (m, 2H, Bentri 4,7-*H*), 7.39−7.34 (m, 2H, Bentri 5,6-*H*), 7.21−6.95 (m, 3H, Ph 3,5,6-*H*), 4.22 (t, *J* = 6.2 Hz, 2H, Bentri-CH_2), 3.66 (s, 2H, Ph-CH_2), 3.29 (t, *J* = 6.0 Hz, 2H, Br-CH_2), 3.11 (t, *J* = 6.2 Hz, 2H, Bentri-CH_2CH_2), 2.89 (t, *J* = 6.0 Hz, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 162.3, 159.7, 157.9, 142.3, 126.8, 125.1, 119.1, 117.7, 111.5, 104.2, 103.9, 56.2, 54.1, 51.6, 46.0, 28.8 ppm; MS (ESI): m/z 423 $[M+H]^+$.

*2.24 [N-(2-(Benzimidazole-1-yl)ethyl)-N-(2,4-difluorobenzyl)-2-(2- berberinoxyethoxy) ethanamine] (**11a**)*

Compound **11a** was prepared according to the procedure described for compound **7a** starting from berberrubine (1.11 g, 3.1 mmol) and compound **10a** (1.13 g, 3.1 mmol). The pure compound **11a** (0.67 g) was obtained as yellow solid. Yield: 32.3%; mp: 162–164 ºC; IR (KBr, cm^{-1}) ν: 3127, 3035 (Ar-H), 2921, 2850 (CH_2), 1631, 1600, 1537, 1504, 1481 (aromatic skeleton), 1385, 1347, 1273, 1229, 1100, 1035, 960, 825; ^{1}H NMR (300 MHz, CD_3OD): δ 9.59 (s, 1H, Ber 8-*H*), 8.72 (s, 1H, Ber 13-*H*), 8.33 (s, 1H, Benim 2-*H*), 8.10 (d, *J* = 9.0 Hz, 1H, Ber 12-*H*), 7.97 (d, *J* = 9.0 Hz, 1H, Ber 11-*H*), 7.71 (s, 1H, Ber 1-*H*), 7.64–7.51 (m, 4H, Benim 4,5,6,7-*H*), 7.12–6.95 (m, 3H, Ph 3,5,6-*H*), 6.89 (s, 1H, Ber 4-*H*), 6.12 (s, 2H, OCH_2O), 4.88 (br, 2H, Ber 6-*H*), 4.39 (t, *J* = 6.0 Hz, 2H, OCH_2CH_2N), 4.22 (t, *J* = 6.2 Hz, 2H, Benim-CH_2), 4.08 (s, 3H, OCH_3), 3.79 (s, 2H, Ph-CH_2), 3.23 (br, 2H, Ber 5-*H*), 3.02 (t, *J* = 6.0 Hz, 2H, OCH_2CH_2N), 2.96 (t, *J* = 6.2 Hz, 2H, Benim-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 163.8, 163.4, 161.1, 159.1, 158.3, 150.3, 148.1, 145.6, 142.9, 135.1, 133.4, 132.1, 131.1, 123.0, 122.1, 120.9, 119.8, 119.3, 118.9, 118.6, 118.2, 117.9, 111.9, 111.5, 108.9, 104.5, 104.3, 103.7, 102.5, 72.5, 57.3, 55.2, 54.3, 51.5, 49.1, 28.4, 26.3 ppm; MS (ESI): m/z 636 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{37}H_{33}ClF_2N_5O_4$ $[M–Cl]^+$, 635.2464; found, 635.2466.

*2.25 [N-(2-(5,6-Dimethyl-benzimidazole-1-yl)ethyl)-N-(2,4-difluorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**11b**)*

Compound **11b** was prepared according to the procedure described for compound **7a** starting from berberrubine

(0.46 g, 1.3 mmol) and compound **10b** (0.53 g, 1.3 mmol). The target compound **11b** (0.28 g) was obtained as yellow solid. Yield: 31.4%; mp: 217–220 ºC; IR (KBr, cm^{-1}) ν: 3037 (Ar-H), 2928, 2855 (CH_2, CH_3), 1631, 1600, 1533, 1504, 1487 (aromatic skeleton), 1383, 1344, 1275, 1228, 1102, 1035, 966, 828; ^{1}H NMR (300 MHz, CD_3OD): δ 9.60 (s, 1H, Ber 8-*H*), 8.83 (s, 1H, Ber 13-*H*), 8.31 (s, 1H, Benim 2-*H*), 8.11 (d, J = 9.0 Hz, 1H, Ber 12-*H*), 7.95 (d, J = 9.0 Hz, 1H, Ber 11-*H*), 7.61 (s, 1H, Ber 1-*H*), 7.59−7.53 (m, 4H, Benim 4,5,67-*H*), 7.15−7.08 (m, 2H, Ph 3,5-*H*), 6.96 (s, 1H, Ber 4-*H*), 6.76 (br, 1H, Ph 6-*H*), 6.19 (s, 2H, OCH_2O), 4.88 (br, 2H, Ber 6-*H*), 4.39 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 4.22 (t, J = 6.2 Hz, 2H, Benim-CH_2), 3.98 (s, 3H, OCH_3), 3.79 (s, 2H, Ph-CH_2), 3.23 (br, 2H, Ber 5-*H*), 3.02 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 2.96 (t, J = 6.2 Hz, 2H, Benim-CH_2CH_2), 2.75 (m, 6H, CH_3) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 163.7, 163.5, 161.3, 159.6, 159.1, 158.3, 150.3, 147.6, 145.6, 145.0, 142.7, 135.2, 133.4, 132.1, 131.7, 131.1, 123.2, 122.1, 121.0, 119.7, 119.2, 118.9, 118.6, 118.2, 117.9, 111.9, 111.5, 108.1, 104.5, 103.7, 102.5, 72.5, 57.3, 55.2, 54.4, 51.4, 49.1, 28.1, 26.2, 23.5 ppm; MS (ESI): m/z 664 $[M–Cl]^+$; HRMS (ESI) calcd. for $C_{39}H_{37}ClF_2N_4O_4$ $[M–Cl]^+$, 663.2777; found, 663.2774.

*2.26 [N-(2-(2-Thio-benztriazole-1-yl)ethyl)-N-(2,4-difluorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**11c**)*

Compound **11c** was prepared according to the procedure described for compound **7a** starting from berberrubine (0.46 g, 1.3 mmol) and compound **10c** (0.51 g, 1.3 mmol). The target compound **11b** (0.20 g) was obtained as yellow solid. Yield: 22.8%; mp: 217–220 ºC; IR (KBr, cm^{-1}) ν: 3037 (Ar-H), 2945, 2922, 2842 (CH_2), 1625, 1600, 1543, 1504, 1487 (aromatic skeleton), 1381, 1259, 1221, 1102, 1035, 967, 821 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 9.62 (s, 1H, Ber 8-*H*), 8.82 (s, 1H, Ber 13-*H*), 8.09 (d, J = 9.0 Hz, 1H, Ber 12-*H*), 7.96 (d, J = 9.0 Hz, 1H, Ber 11-*H*), 7.87−7.85 (m, 2H, Bentri 4,7-*H*), 7.65 (s, 1H, Ber 1-*H*), 7.42−7.39 (m, 2H, Bentri 5,6-*H*), 7.15−7.11 (m, 2H, Ph 3,5-*H*), 6.95 (s, 1H, Ber 4-*H*), 6.77 (br, 1H, Ph 6-*H*), 6.14 (s, 2H, OCH_2O), 4.91 (br, 2H, Ber 6-*H*), 4.36 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 4.31 (t, J = 6.2 Hz, 2H, Bentri-CH_2), 3.97 (s, 3H, OCH_3), 3.76 (s, 2H, Ph-CH_2), 3.23 (br, 2H, Ber 5-*H*), 3.04 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 3.05 (t, J = 6.2 Hz, 2H, Bentri-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 163.5, 162.9, 161.3, 159.1, 158.6, 150.3, 147.6, 145.6, 142.6, 135.2, 133.4, 132.1, 131.1, 123.2, 122.1, 121.0, 119.7, 118.9, 117.9, 111.9, 111.5, 108.1, 104.5, 103.7, 102.5, 72.5, 57.3, 55.2, 54.4, 51.4, 49.1, 28.1, 26.2 ppm; MS (m/z): 664 $[M–Cl]^+$; HRMS (TOF) calcd for $C_{39}H_{37}ClF_2N_4O_4$: $[M–Cl]^+$, 663.2777; found, 663.2774.

*2.27 [2-(Benzimidazol-2-thio)-N-(2-bromoethyl)-N-(2,4-difluorobenzyl)ethanamine] (**12**)*

Compound **12** was prepared according to the procedure described for compound **6a** starting from 2-mercaptobenzimidazole (1.58 g, 10.0 mmol), potassium carbonate (4.14 g, 30.0 mmol) and compound **5a** (4.37 g, 12.3 mmol). The target compound **12** (2.73 g) was obtained as white solid. Yield: 64.1%; mp: 138–140 ºC; IR (KBr, cm^{-1}) ν: 3074, 3021 (Ar-H), 2934, 2854, 2818 (CH_2), 1609, 1557, 1523, 1465 (aromatic skeleton), 1387, 1323, 1276, 1134, 943, 864, 713; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.48 (m, 4H, Benim 4,5,6,7-*H*), 7.19–6.96 (m, 3H, Ph 3,5,6-*H*), 3.75 (br, 2H, SCH_2), 3.65 (s, 2H, Ph-CH_2), 3.32 (br, 2H, Br-CH_2), 3.09 (br, 2H, Benim-CH_2SCH_2), 2.96 (br, 2H, Br-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 161.8, 161.1, 159.7, 158.4, 142.4, 135.3, 132.1, 126.9, 125.1, 119.1, 117.7, 111.5, 104.2, 103.4, 55.4, 54.1, 51.7, 46.2, 28.7 ppm; MS (ESI): m/z 427 $[M+H]^+$.

*2.28 [N-(2-(2-Thio-benzimidazole-1-yl)ethyl)-N-(2,4-difluorobenzyl)-2-(2-berberinoxyethoxy) ethanamine] (**13**)*

Compound 13 was prepared according to the procedure described for compound 7a starting from berberrubine (0.84 g, 2.35 mmol) and compound 12 (0.99 g, 2.32 mmol). The target compound 13 (552 mg) was obtained as yellow solid. Yield: 33.4%; mp: 187–189 ºC; ^{1}H NMR (300 MHz, CD_3OD): δ 9.61 (s, 1H, 8-*H*), 8.89 (s, 1H, Ber 13-*H*), 8.10 (d, J = 9.0 Hz, 1H, Ber 12-*H*), 7.99 (d, J = 9.0 Hz, 1H, Ber 11-*H*), 7.63 (s, 1H, Ber 1-*H*), 7.54–7.49 (m, 4H, Benim 4,5,6,7-*H*), 7.17 (m, 1H, Ph 3-*H*), 7.02 (s, 1H, Ph 5-*H*), 6.95 (s, 1H, Ber 4-*H*), 6.78 (s, 1H, Ph 6-*H*), 6.11 (s, 2H, OCH_2O), 4.83 (br, 2H, Ber 6-*H*), 4.39 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 4.01 (s, 3H, OCH_3), 3.95 (t, J = 6.2 Hz, 2H, S-CH_2), 3.77 (s, 2H, Ph-CH_2), 3.32 (br, 2H, Ber 5-*H*), 3.18 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 2.95 (t, J = 6.2 Hz, 2H, S-CH_2CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 163.7, 163.4, 162.8, 161.7, 161.1, 160.2, 159.1, 158.4, 150.3, 147.6, 145.4, 142.6, 135.2, 133.4, 132.1, 131.1, 123.2, 122.1, 121.0, 119.7, 118.9, 118.2, 116.8, 112.3, 111.5, 108.1, 104.5,

103.7, 102.5, 72.5, 59.3, 56.1, 55.2, 51.9, 49.7, 28.1, 27.2 ppm; MS (m/z): 668 $[M–Cl]^+$; HRMS (TOF) calcd for $C_{37}H_{33}ClF_2N_4O_4$: $[M–Cl]^+$, 667.2185; found, 667.2182.

Supporting Information 2

1. Biological assays procedures

Minimal inhibitory concentration (MIC, μg/mL) is defined as the lowest concentration of the new compounds that completely inhibited the growth of bacteria, by means of standard two folds serial dilution method in 96-well microtest plates according to the National Committee for Clinical Laboratory Standards (NCCLS). The tested microorganism strains were provided by the School of Pharmaceutical Sciences, Southwest University and the College of Pharmacy, Third Military Medical University. Chloromycin, Norfloxacin and Fluconazole were used as control drugs. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment. All the bacteria and fungi growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimal inhibitory concentration (MIC).

1.1 Antibacterial Assays

The prepared compounds **6–13** were evaluated for their antibacterial activities against *Methicillinresistant staphylococcus aureus* N315, *Staphylococcus aureus* ATCC25923, *Micrococcus luteus* ATCC 4698 and *Bacillus subtilis* as Gram-positive, *Escherichia coli* DH52, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *Proteus vulgaris* as Gram-negative bacteria. The bacterial suspension was adjusted with sterile saline to a concentration of 1×10^5 CFU/mL. The compounds were dissolved in DMSO to prepare the stock solutions. The compounds and reference drugs were prepared in Mueller–Hinton broth (Guangdong huaikai microbial sci.& tech co., Ltd, Guangzhou, Guangdong, China) by twofold serial dilution to obtain the required concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5 μg/mL. These dilutions were inoculated and incubated at 37 ºC for 24 h. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

1.2 Antifungal Assays

The synthesized compounds were also evaluated for their antifungal activities against *Candida albicans*, *Candida mycoderma*, *Candida utilis* and *Beer yeast*. A spore suspension in sterile distilled water was prepared from 1-day old culture of the fungi growing on Sabouraud agar (SA) media. The final spore concentration was $1–5\times10^3$ spore/mL. From the stock solutions of the tested compounds and reference antifungal Fluconazole, dilutions in sterile RPMI 1640 medium (Neuronbc Laboraton Technology CO., Ltd, Beijing, China) were made resulting in eleven wanted concentrations (0.5-512 μg/mL) of each tested compounds. These dilutions were inoculated and incubated at 35 ºC for 24 h. The drug's MIC was defined as the first well with an approximate 80% reduction in growth compared to the growth of the drug-free well.

Supporting Information 3

1. Binding experiments

1.1 Material

All fluorescence spectra were recorded at 298, 304, 310 K in the range of 300–450 nm on F-2700 Spectrofluorimeter (Hitachi, Tokyo, Japan) equipped with 1.0 cm quartz cells, the widths of both the excitation and emission slit were set as 2.5 nm, and the excitation wavelength was 295 nm. UV spectra were recorded at room temperature on a TU-2450 spectrophotometer (Puxi Analytic Instrument Ltd. of Beijing, China) equipped with 1.0 cm quartz cells. HSA was obtained from Sigma-Aldrich (St. Louis, MO, USA). Tris, NaCl, HCl were analytical purity. Sample masses were weighed on a microbalance

with a resolution of 0.1 mg. All other chemicals and solvents were commercially available, and used without further purification. Molecular docking was carried out using software eHiTS. The crystal data of HSA was obtained from the Protein Data Bank (PDB ID: 3LU6). Small molecules in HSA-3LU6 were removed prior to the docking by software eHiTS.

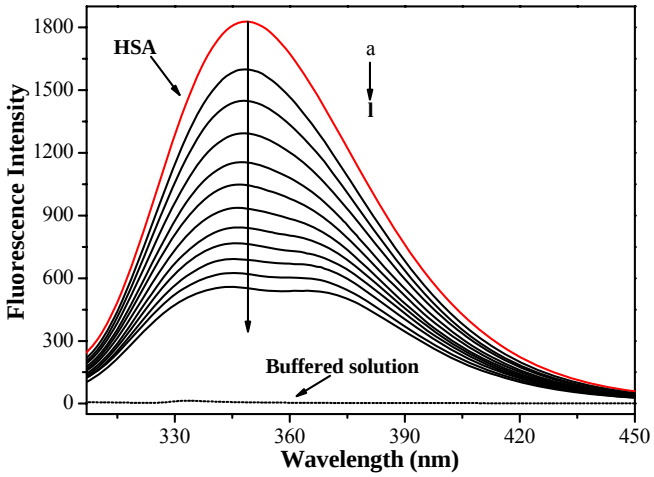

Fig S1 Emission spectra of HSA in the presence of various concentrations of compound **7a**. *c*(HSA) 1.0 × 10^{-5} mol/L; *c*(compound **7a**)/(10^{-5} mol/L), *a*-*l*: from 0.0 to 2.2 at increments of 0.20; dash line shows the emission spectrum of buffered solution only; T = 298 K, λ_{ex} = 295 nm. The Fluorescence of compound **7a** was deducted from spectra.

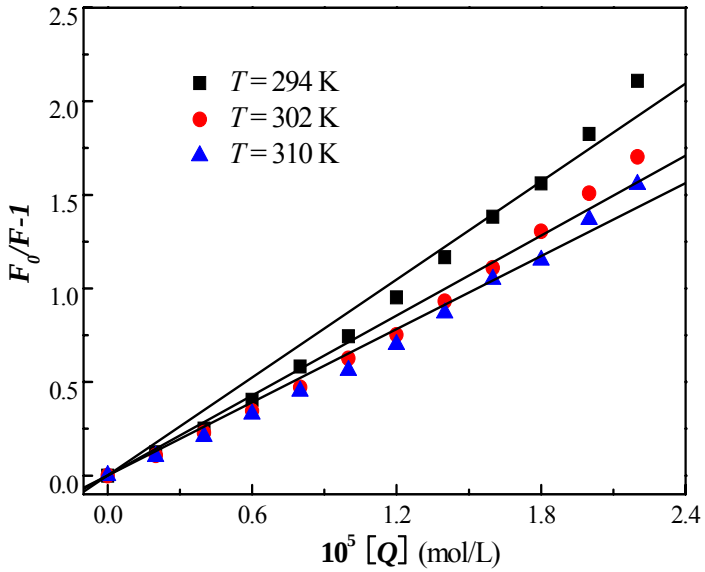

Fig. S2 Stern-Volmer plots of compound **7a**-HSA system at three different temperatures

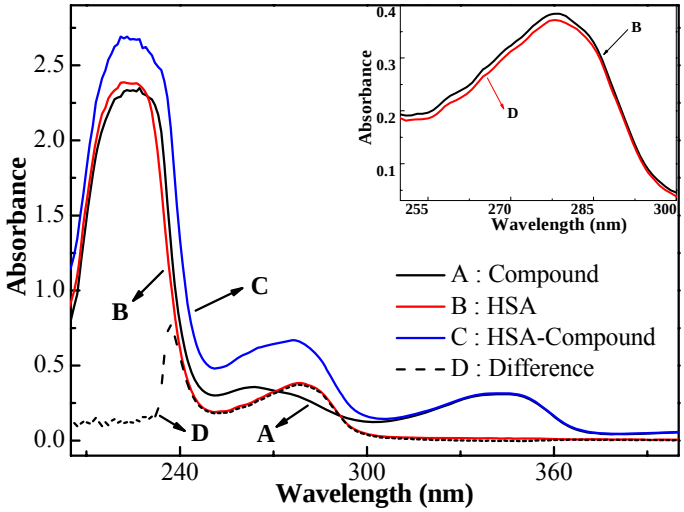

Fig. S3 UV-vis spectra of HSA in the presence of compound **7a**: **A**, absorption spectrum of compound **7a** only; **B**, absorption spectrum of HSA only; **C**, absorption spectrum of compound **7a**/HSA 1:1 complex; **D**, difference between absorption spectrum of compound **7a**/HSA 1:1 complex and compound **7a**, c(HSA) = c(compound **7a**) = 1.0×10^{-5} M. The curves **B** and **D** for the wavelength ranging from 250 to 300 nm were depicted in the inset

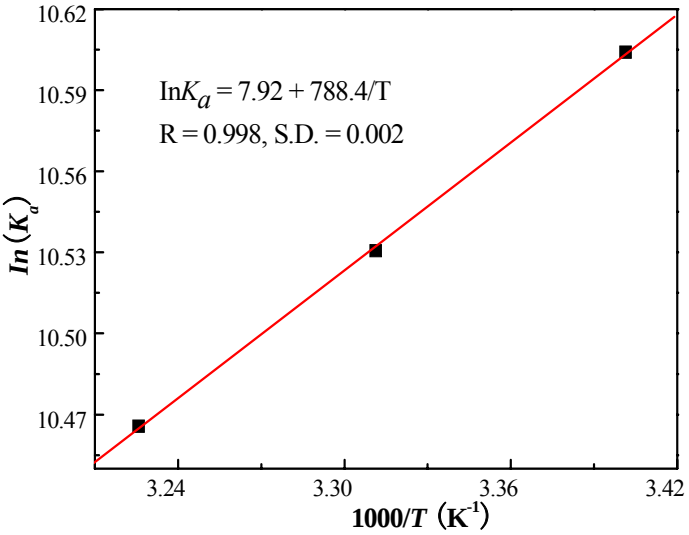

Fig. S4 Van't Hoff plots of the compound **7a**-HSA system

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