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SYNTHESIS OF BERBERINE BROMIDE ANALOGS CONTAINING TERTIARY AMIDES OF ACETIC ACID IN THE 9-*O*-POSITION

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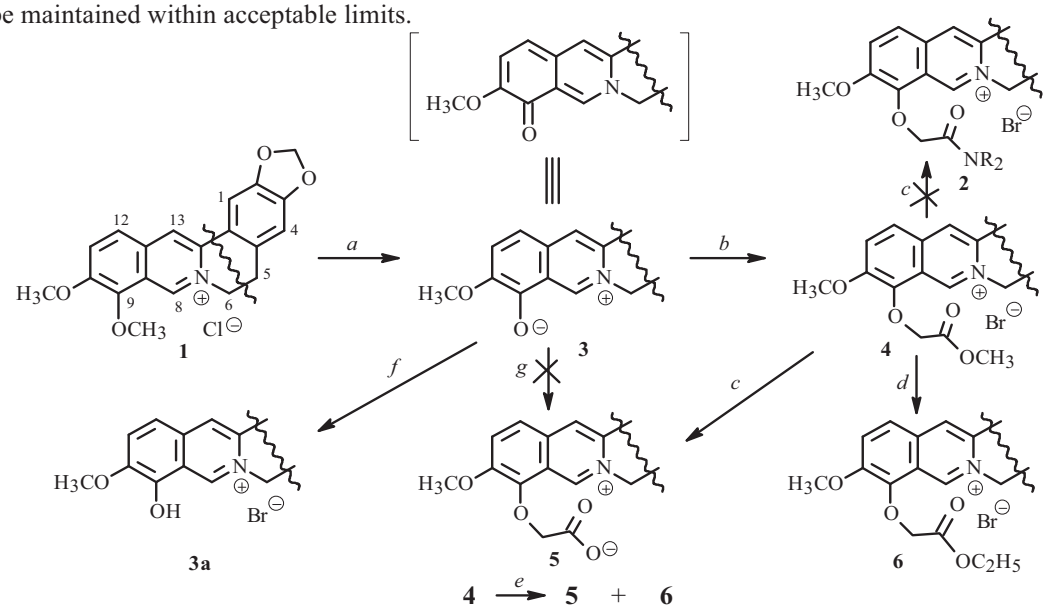
9-O-Acetamide analogs of berberine bromide were prepared in 20–87% yields via reaction of the isoquinoline alkaloid berberrubine with tertiary amides of bromoacetic acid. Aminolysis did not occur during reaction of methyl-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetate with secondary amines. The corresponding acid or its ethyl ester was isolated.

Keywords: berberine, berberine chloride, berberrubine, tertiary amides, isoquinoline alkaloids, hypocholesterolemic activity.

The leading cause of death (greater than 50% of all lethalities) in the majority of economically developed countries remains as before cardiovascular diseases (CVD) of atherosclerotic origin and their complications (acute myocardial infarct, sudden cardiac death). Hyperlipidemia and, in particular, hypercholesterolemia is the principal risk factor of atherosclerotic CVD. Drugs used in medical practice and developed to lower cholesterol can be divided into two classes that differ in principle according to their mechanism of action. The first class includes drugs that inhibit the synthesis of endogenous cholesterol. Such chemical compounds (e.g., statins) interrupt the synthetic pathway of cholesterol *in vivo* by blocking (mostly by a competing mechanism) the activity of the corresponding enzyme. The second class comprises compounds that regulate by one method or another the amounts of cholesterol already synthesized by the body or obtained in food and enable its amount to be maintained within acceptable limits.



a. 190–200°C, 20–30 mm Hg; *b*. $BrCH_2COOCH_3$, CH_2Cl_2, 40°C, 12 h; *c*. Et_2NH or pyrrolidine, EtOH, 78°C, 9.5–12.5 h; *d*. morpholine, EtOH, 78°C, 11 h; *e*. Bu_2NH, EtOH, 78°C, 11 h; *f*. $BrCH_2COOH$, CH_2Cl_2 or CH_3CN or DMF or MeOH, K_2CO_3 or Et_3N or KOH; *g*. $BrCH_2COOH$, DMF, 85°C, 2 h

Scheme 1

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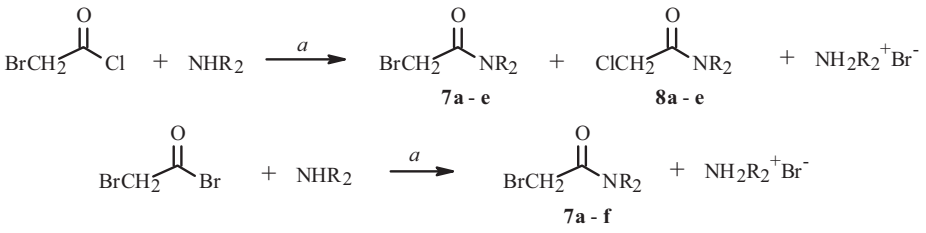
Compounds of just this class have recently attracted more and more attention. One of the most promising of them is the isoquinoline alkaloid berberine chloride (**1**) [1]. Therefore, the synthesis of berberine derivatives, which possess potentially hypolipidemic activity, is extremely critical. Our task was to synthesize previously undescribed compounds of type **2** that contained tertiary amides of acetic acid (Scheme 1). The amide group is a pharmacophore that is frequently encountered, e.g., in cardiovascular and antiviral drugs [2].

A possible variant of the synthesis of amides **2** is preparation of the ester with subsequent aminolysis. Heating berberine chloride (**1**) in vacuum (20–30 mm Hg) led to selective demethylation and formation of berberrubine (**3**) (81% yield) [3]. Compound **3** reacted readily with the methyl ester of bromoacetic acid to form ester **4** of 2-substituted acetic acid in 89% yield. Compound **4** was prepared for the first time. The synthesis of the methyl ester as the chloride via the reaction of **3** with the methyl ester of chloroacetic acid was described before [4]. It was confirmed that the reaction of methyl ester **4** with Et_2NH gave **2a** ($R_2 = Et_2$) [4]. However, we isolated acid **5** in 49% yield upon repeating this method. The reaction of methyl ester **4** with other secondary amines also did not produce the aminolysis products. Thus, reaction with pyrrolidine gave acid **5** (77% yield); with morpholine in EtOH, ethyl ester **6** in 68% yield (Scheme 1). Reaction of ester **4** with Bu_2NH in EtOH afforded ethyl ester **6** and acid **5** in yields of 48 and 41%, respectively.

Apparently, the amines acted as bases under the reaction conditions. Use of less basic morpholine and Bu_2NH led to transesterification; of more basic amines, to hydrolysis of ester **4**. The structure of salt **5** was confirmed by several physicochemical methods. The IR spectrum of **5** contained a band at 1601 cm^{-1} that corresponded to COO^- vibrations. Elemental analysis showed the presence of Br. The mass spectrum contained a peak for $[M + H]^+$ at 380.110. Acid **5** was prepared earlier by hydrolysis of ethyl ester **6** [5]. The literature method for its preparation by reaction of **3** with bromoacetic acid could not be reproduced (Scheme 1). The reaction in neutral solution [4, 6] isolated the protonated form of berberrubine (**3a**) instead of acid **5**. Compound **3** also did not react with bromoacetic acid in the presence of base (K_2CO_3, Et_3N, KOH) in various solvents (CH_2Cl_2, CH_3CN, DMF, MeOH). We isolated starting **3**. Apparently, bromoacetic acid in basic solution is present as a salt. Substitution of the Br atom does not occur because of the large +I-effect of the COO^- group.

An alternative method for preparing amides **2** is the reaction of **3** with amides of bromoacetic acid **7** (Scheme 3). We used secondary amines to synthesize amides **7**. These were special types of compounds such as linear diethyl- and dibutylamine, cyclic pyrrolidine and piperidine, heterocyclic morpholine, and aromatic diphenylamine. Such an assortment of amines enabled trends to be found in the reactivity of the compounds and their biological activity.

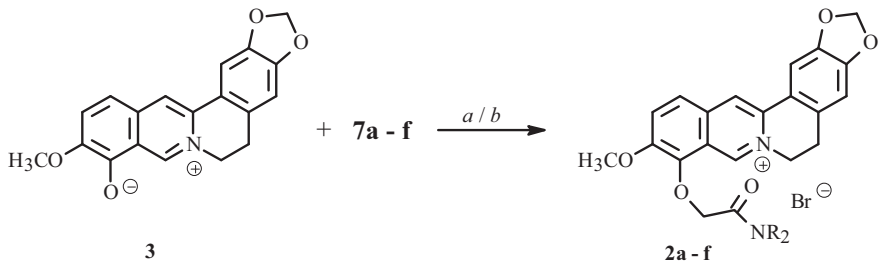


$R_2 = Et_2$ (**a**); Bu_2 (**b**); -$(CH_2)_4$- (**c**); -$(CH_2)_5$- (**d**); -$(CH_2)_2O(CH_2)_2$- (**e**); Ph_2 (**f**)
a. CH_2Cl_2, –25°C (30 min), +20°C (3 h)

Scheme 2

It was observed in repeating the literature method for reaction of bromoacetic acid chloride with secondary amines [7] that the main products were amides of chloroacetic acid **8a**–**e** instead of amides of bromoacetic acid **7a**–**e**, which were present in the mixture only in minor amounts (Scheme 2). Apparently, the reactive Br atom in amide **7** was replaced in this instance by Cl from the amine hydrochloride. Several examples of an analogous substitution of Br by Cl in bromoacetamides have been reported [8]. The reaction of the amines with bromoacetic acid bromide enabled such processes to be avoided and amides **7a**–**f** to be selectively prepared.

Amides of chloroacetic acid **8** were poorly reactive toward substitution. Thus, refluxing a mixture of amides **8a**/**7a** (mole ratio 2:0.32) with berberrubine in CH_2Cl_2 in the presence of K_2CO_3 did not produce the substitution products. However, reaction of amides of bromoacetic acid **7a**–**f** and berberrubine in the presence of Et_3N or without base gave the series of tertiary amides **2a**–**f** in yields from 20 to 87% (Scheme 3).



3 **2a - f**

R_2 = Et_2 (**a**); Bu_2 (**b**); -$(CH_2)_4$- (**c**); -$(CH_2)_5$- (**d**); -$(CH_2)_2O(CH_2)_2$- (**e**); Ph_2 (**f**)
a. MeCN, NEt_3, 100°C, 35–61.5 h; *b*. MeCN, 100°C, 37 h

Scheme 3

This reaction occurred more slowly and required the use of base as opposed to the reaction of **3** with the methyl ester of bromoacetic acid. The decreased reaction rate could be explained by the smaller –I-effect of the amide compared with the –I-effect of the ester. The reaction with diphenylamide **7f** was the fastest and gave the best yield, 87% after 4.5 h (–I-effect of the amide phenyl substituents). Satisfactory yields were achieved in the reactions with diethyl- and dibutylamides **7a** and **7b** (+I-effect of ethyl and butyl groups). The reaction of berberrubine with cyclic amides **7c**–**e** took longer and gave poorer yields. Examples of the synthesis of compounds of type **2** containing tertiary amides of acetic acid were not found in the literature. The synthesis of amides via the reaction of berberrubine with amides of 3-bromopropionic acid was reported. The yields were 55–72% for anilides [9] and 23–33% for secondary amides [10].

The structures of amides **2** were proved using spectral data. Mass spectra contained peaks (*m*/*z*) corresponding to positively charged molecular fragment. Fragmentation of these cations using tandem mass spectrometry gave a unique set of fragment ions with *m*/*z* 334.11, 321.10 (corresponding to berberrubine cation-radical $C_{19}H_{15}NO_4$), 306.08, and 292.10. Elemental analyses confirmed the presence of bromide. The amount of Br agreed with that calculated. IR spectra exhibited vibrations in the range 1653–1664 cm^{-1} that corresponded to the vibrational frequency of a tertiary amide. PMR and ^{13}C NMR spectra showed resonances for the berberine molecule that were similar to those of berberine chloride and indicated that this fragment was unchanged [11]. PMR spectra of **2** exhibited resonances for methylene protons of OCH_2CON as singlet with chemical shifts δ 4.99–5.26 ppm. The methylene protons of $N(CH_2R)_2$ resonated as multiplets with chemical shifts δ 3.21–3.63 ppm. Resonances of chemically identical protons of the alkyl substituents in the amide were nonequivalent. This was indicative of the hindered rotation that is characteristic of tertiary amides [12]. Resonances of amide C atoms, e.g., dibutylamide **2b**, were also nonequivalent in ^{13}C NMR spectra. The corresponding chemical shifts were δ 44.74 and 45.58 ppm ($NCH_2^{1'}$), 29.30 and 30.45 ppm ($CH_2^{2'}$), and 19.46 and 19.58 ppm ($CH_2^{3'}$). This was consistent with the literature data for analogous amides [13].

EXPERIMENTAL

Melting points were measured on a Mettler Toledo FP 900 instrument and on a Kofler stage. UV spectra were recorded in EtOH (*c* 10^{-4} M) on an HP 8453 UV-Vis instrument. IR spectra were taken in KBr on a Vector 22 instrument. PMR and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions (5–10%) on Bruker AV-300 (300.13 and 75.47 MHz) and AM-400 (400.13 and 100.61 MHz) instruments. The standards were the solvent resonances. Empirical formulas of the compounds were determined from elemental analyses using the Brutto Formula Searcher program (AlgorithmSoft) [14]. Elemental analyses of all compounds agreed with those calculated.

Mass spectra were recorded using an HPLC-MS system that included an Agilent 1200 liquid chromatograph and a Bruker micrOTof-Q hybrid quadrupole–time-of-flight mass spectrometer. The operating parameters for mass detection were electrospray ionization at atmospheric pressure (API-ES), positive-ion scanning in the range *m*/*z* 100–3000, drying gas (N_2) flow rate 4 L/min, temperature 220°C, sprayer pressure 1.0 atm. A solution of the compound (2 μL) with concentration 0.1 mg/mL in MeOH was fed into the sprayer chamber of the mass spectrometer by injection using an autosampler into the solvent flow (MeOH, 0.1 mL/min). GC-MS was performed on an Agilent 7890A instrument with an Agilent 5975C quadrupole mass spectrometer as the detector (electron-impact ionization, EI) using an HP-5MS 30000 × 0.25 mm quartz column and He

carrier gas (flow rate 1 mL/min, stream division 10:1). The temperature regime was 50°C for 2 min, heating at 15°C/min to 250°C, 10 min at 250°C, and heating at 20°C/min to 275°C.

HPLC was carried out on a Millichrom A-02 microcolumn chromatograph (EkoNova) using ProntoSIL-120-5-C18AQ reversed-phase sorbent (particle size 5 μm, column 75 × 2 mm) at 35°C, 30–36 atm, and flow rate 150 μL/min with elution by a linear gradient of solvents from 100% A to 100% B over 25 min (solvent A, 0.1% TFA in H_2O; solvent B, MeOH) and simultaneous multiwave detection at six wavelengths (220, 240, 260, 280, 320, and 360 nm).

Column chromatography was performed on neutral Al_2O_3 LL40/250. Berberine chloride was isolated from roots of *Berberis sibirica* growing in Ongudai Region, Republic of Altai, Russia, by the literature method [15]. Berberrubine (**3**) was obtained in 81% yield as the solvate with one EtOH molecule as before [3]. Amides of bromoacetic acid **7a**–**f** were prepared by the literature method [16]. Spectral data agreed with those published [17].

Mixtures of amides of chloroacetic **8a**–**e** and bromoacetic **7a**–**e** acids were obtained by repeating the published methods [7]. The ratio of amides was determined from PMR spectral data; molecular weights, from GC-MS spectral data (EI). The **8a**:**7a** ratio was 2:0.32, partial PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 4.03 (2H, s, $ClCH_2$), 3.81 (2H, s, $BrCH_2$). Mass spectrum (EI, *m*/*z*): **8a**: 149.0; **7a**: 193.0. The **8b**:**7b** ratio was 2:0.66, partial PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 4.03 (2H, s, $ClCH_2$), 3.81 (2H, s, $BrCH_2$). Mass spectrum (EI, *m*/*z*): **8b**: 205.1; **7b**: 249.1. The **8c**:**7c** ratio was 2:0.43, partial PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 4.08 (2H, s, $ClCH_2$), 3.80 (2H, s, $BrCH_2$). Mass spectrum (EI, *m*/*z*): **8c**: 147.0; **7c**: 191.0. The **8d**:**7d** ratio was 2:0.11, partial PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 4.04 (2H, s, $ClCH_2$), 3.83 (2H, s, $BrCH_2$). Mass spectrum (EI, *m*/*z*): **8d**: 161.0; **7d**: 205.0. The **8e**:**7e** ratio was 100:0, partial PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 4.03 (2H, s, $ClCH_2$). Mass spectrum (EI, *m*/*z*): **8e**: 163.0. Other resonances in PMR spectra of **7a**–**e** and **8a**–**e** agreed with those in the literature [17].

Methyl-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetate (4). A solution of **3**·EtOH (3.10 g, 8.45 mmol) in CH_2Cl_2 (50 mL) was treated with the methyl ester of bromoacetic acid (1.60 mL, 16.89 mmol), stirred on a magnetic stirrer, and refluxed for 7.5 h. The yellow precipitate was filtered off, refluxed with EtOH (100 mL), cooled, filtered off, and dried *in vacuo* to afford **4** (3.54 g, 89%), mp 254–256°C (dec.). UV spectrum (EtOH, λ_{max}, nm): 230, 265, 350, 428. IR spectrum (KBr, ν, cm^{-1}): 1758, 1505, 1397, 1273, 1212. Mass spectrum (API-ES, *m*/*z*): 394.124; calcd for $C_{22}H_{20}NO_6^+$, 394.129.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.21 (2H, t, J = 6.2, H-5), 3.72 (3H, s, $COOCH_3$), 4.03 (3H, s, OCH_3), 4.94 (2H, t, J = 6.2, H-6), 5.07 (2H, s, OCH_2CO), 6.17 (2H, s, OCH_2O), 7.09 (1H, s, H-4), 7.79 (1H, s, H-1), 7.99 (1H, d, J = 9.3, H-12), 8.19 (1H, d, J = 9.3, H-11), 8.96 (1H, s, H-13), 9.94 (1H, s, H-8).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 26.69 (C-5), 52.24 ($COOCH_3$), 55.75 (C-6), 57.52 (OCH_3), 69.60 (OCH_2CO), 102.44 (OCH_2O), 105.80 (C-1), 108.80 (C-4), 120.43 (C-13), 120.74 (C-1a), 121.49 (C-8a), 123.92 (C-12), 127.04 (C-11), 131.01 (C-4a), 133.26 (C-12a), 137.88 (C-13a), 141.78 (C-9), 146.06 (C-8), 148.01 (C-2), 149.61 (C-3), 150.19 (C-10), 169.70 (CO).

2-(9-Demethoxyberberin-9-yl)hydroxyacetic Acid (5). a) A suspension of **4** (300 mg, 0.63 mmol) in EtOH (6 mL) was treated with pyrrolidine (0.11 mL, 1.26 mmol), refluxed on a water bath for 9.5 h, and cooled. The yellow precipitate was filtered off and dried *in vacuo* to afford **5**·$2H_2O$ (123 mg). Chromatography of the mother liquor over Al_2O_3 (CH_2Cl_2:MeOH, 10:1→1:1) isolated additional 73 mg of **5**·$2H_2O$ (overall yield 77%).

b) A suspension of **4** (100 mg, 0.21 mmol) in EtOH (5 mL) was treated with Et_2NH (0.22 mL, 2.11 mmol), refluxed on a water bath for 12.5 h, and cooled. The yellow precipitate was filtered off and dried *in vacuo* to afford **5**·$3H_2O$ (45 mg, 49%).

c) A suspension of **4** (300 mg, 0.63 mmol) in anhydrous EtOH (6 mL) was treated with Bu_2NH (0.64 mL, 3.80 mmol), refluxed on a water bath for 11 h, and cooled. The yellow precipitate was filtered off and dried *in vacuo* to afford **6** (149 mg, 48%). Chromatography of the mother liquor over Al_2O_3 (CH_2Cl_2:MeOH, 10:1→1:1) isolated 111 mg of **5**·$3H_2O$ (41%), mp 158–162°C (dec.), $C_{21}H_{17}NO_6$·$2H_2O$. UV spectrum (EtOH, λ_{max}, nm): 230, 268, 350, 429. IR spectrum (KBr, ν, cm^{-1}): 3416, 1601 1504, 1395, 1276, 1224. Mass spectrum (API-ES, *m*/*z*): 380.110; calcd for $C_{21}H_{18}NO_6^+$, 380.113.

PMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 3.25 (2H, t, J = 6.2, H-5), 4.06 (3H, s, OCH_3), 4.93 (2H, t, J = 6.2, H-6), 4.82 (2H, s, OCH_2CO), 6.09 (2H, s, OCH_2O), 6.94 (1H, s, H-4), 7.60 (1H, s, H-1), 7.90 (1H, d, J = 8.8, H-12), 8.03 (1H, d, J = 8.8, H-11), 8.57 (1H, s, H-13), 10.09 (1H, s, H-8).

^{13}C NMR spectrum (100 MHz, CD_3OD, δ, ppm): 28.19 (C-5), 57.21 (C-6), 57.61 (OCH_3), 72.89 (OCH_2CO), 103.60 (OCH_2O), 106.43 (C-1), 109.38 (C-4), 120.93 (C-13), 121.87 (C-1a), 123.60 (C-8a), 123.92 (C-12), 127.74 (C-11), 131.78 (C-4a), 134.85 (C-12a), 139.15 (C-13a), 145.00 (C-9), 148.03 (C-8), 149.81 (C-2), 151.36 (C-3), 151.99 (C-10), 176.40 (CO).

Ethyl-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetate (6). A suspension of **4** (300 mg, 0.63 mmol) in EtOH (10 mL) was treated with morpholine (0.11 mL, 1.27 mmol), refluxed on a water bath for 11 h, and cooled. The yellow

precipitate was filtered off and dried *in vacuo* to afford **6** (209 mg, 68%), mp 276–278°C (dec.). UV spectrum (EtOH, λ_{max}, nm): 230, 265, 350, 429. IR spectrum (KBr, ν, cm^{-1}): 1755, 1504, 1396, 1271, 1215. Mass spectrum (API-ES, *m*/*z*): 408.140; calcd for $C_{23}H_{22}NO_6^+$, 408.144.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.21 (3H, t, J = 7.2, CH_3), 3.21 (2H, t, J = 6.2, H-5), 4.03 (3H, s, OCH_3), 4.18 (2H, q, J = 7.2, $COOCH_2$), 4.94 (2H, t, J = 6.2, H-6), 5.06 (2H, s, OCH_2CO), 6.17 (2H, s, OCH_2O), 7.10 (1H, s, H-4), 7.80 (1H, s, H-1), 8.00 (1H, d, J = 9.2, H-12), 8.20 (1H, d, J = 9.2, H-11), 8.96 (1H, s, H-13), 9.94 (1H, s, H-8).

^{13}C NMR spectrum (75 MHz, DMSO-d_6, δ, ppm): 14.07 (CH_3), 26.39 (C-5), 55.43 (C-6), 57.21 (OCH_3), 60.80 ($COOCH_2$), 69.33 (OCH_2CO), 102.12 (OCH_2O), 105.49 (C-1), 108.46 (C-4), 120.13 (C-13), 120.43 (C-1a), 121.17 (C-8a), 123.51 (C-12), 126.78 (C-11), 130.70 (C-4a), 132.96 (C-12a), 137.59 (C-13a), 141.54 (C-9), 145.75 (C-8), 147.72 (C-2), 149.22 (C-3), 149.90 (C-10), 168.87 (CO).

Berberrubine Hydrobromide (3a). A solution of bromoacetic acid (227 mg, 1.63 mmol) in DMF (5 mL) was treated with berberrubine (**3**, 200 mg, 0.54 mmol), stirred on a magnetic stirrer at 85°C for 2 h, and cooled. The yellow precipitate was filtered off, washed with CH_2Cl_2, and dried *in vacuo* to afford **3a**·$2H_2O$ (128 mg, 58%), mp 294–298°C (dec.). UV spectrum (EtOH, λ_{max}, nm): 239, 276, 335, 360, 396, 550. IR spectrum (KBr, ν, cm^{-1}): 3429, 1602, 1510, 1338, 1240. Mass spectrum (API-ES, *m*/*z*): 322.110; calcd for $C_{19}H_{16}NO_4^+$, 322.107.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.18 (2H, t, J = 6.0, H-5), 4.03 (3H, s, OCH_3), 4.88 (2H, t, J = 6.0, H-6), 6.16 (2H, s, OCH_2O), 7.06 (1H, s, H-4), 7.68 (1H, d, J = 8.8, H-12), 7.70 (1H, s, H-1), 8.08 (1H, d, J = 8.8, H-11), 8.82 (1H, s, H-13), 9.88 (1H, s, H-8), 11.25 (1H, br.s, OH).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 26.78 (C-5), 55.19 (C-6), 57.34 (OCH_3), 102.35 (OCH_2O), 105.66 (C-1), 108.73 (C-4), 117.94 (C-1a), 118.24 (C-11), 120.13 (C-12), 120.98 (C-8a), 125.77 (C-13), 130.79 (C-4a), 132.72 (C-12a), 136.87 (C-13a), 144.24 (C-9), 145.70 (C-2), 146.13 (C-8), 147.95 (C-10), 149.91 (C-3).

General Methods for Preparing Amides 2a–f. a) A solution of **3**·EtOH (200 mg, 0.544 mmol) in CH_3CN (10 mL) was treated with amide **7a**–**f** (1.5–2.5 equiv.) and Et_3N (0.19 mL, 1.361 mmol) , stirred on a magnetic stirrer at 100°C for a given time, and cooled. The solvent was removed. The residue was separated by chromatography over Al_2O_3 (CH_2Cl_2:MeOH, 100:1→100:2). The product was recrystallized from CH_3CN.

b) The reaction was carried out analogously but without adding Et_3N. The product was isolated by chromatography over Al_2O_3 (CH_2Cl_2:MeOH, 100:1→100:2) and recrystallized from CH_3CN.

***N*,*N*-Diethyl-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetamide (2a).** a) Reaction of **3**·EtOH (200 mg) and amide **7a** (263 mg, 1.36 mmol) for 35 h by general method a) produced amide **2a** (169 mg, 60%).

b) Reaction of **3**·EtOH (200 mg) and amide **7a** (225 mg, 1.14 mmol) for 37 h by general method b) produced amide **2a** (115 mg, 39%), mp 244°C. UV spectrum (EtOH, λ_{max}, nm): 230, 266, 350, 428. IR spectrum (KBr, ν, cm^{-1}): 1655, 1504, 1394, 1271, 1228. Mass spectrum (API-ES, *m*/*z*): 435.189; calcd for $C_{25}H_{27}N_2O_5^+$, 435.191.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.01 (3H, t, J = 7.0, CH_3), 1.14 (3H, t, J = 7.0, CH_3), 3.21 (2H, t, J = 6.3, H-5), 3.27 (4H, m, NCH_2), 4.02 (3H, s, OCH_3), 4.94 (2H, t, J = 6.3, H-6), 5.23 (2H, s, OCH_2CO), 6.17 (2H, s, OCH_2CO), 7.10 (1H, s, H-4), 7.80 (1H, s, H-1), 7.95 (1H, d, J = 9.3, H-12), 8.17 (1H, d, J = 9.3, H-11), 8.92 (1H, s, H-13), 10.01 (1H, s, H-8).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 12.89 (CH_3), 13.91 (CH_3), 26.40 (C-5), 39.38 (NCH_2), 40.04 (NCH_2), 55.40 (C-6), 57.13 (OCH_3), 69.71 (OCH_2CO), 102.06 (OCH_2O), 105.43 (C-1), 108.40 (C-4), 119.95 (C-13), 120.45 (C-1a), 121.45 (C-8a), 122.78 (C-12), 126.69 (C-11), 130.60 (C-4a), 132.92 (C-12a), 137.32 (C-13a), 142.41 (C-9), 146.23 (C-8), 146.23 (C-2), 149.12 (C-3), 149.78 (C-10), 166.54 (CO).

***N*,*N*-Dibutyl-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetamide (2b).** a) Reaction of **3**·EtOH (200 mg) and amide **7b** (340 mg, 1.36 mmol) for 35 h by general method a) produced amide **2b** (201 mg, 65%).

b) Reaction of **3**·EtOH (200 mg) and amide **7b** (284 mg, 1.14 mmol) for 37 h by general method b) produced amide **2b** (172 mg, 53%), mp 230°C. UV spectrum (EtOH, λ_{max}, nm): 229, 266, 350, 429. IR spectrum (KBr, ν, cm^{-1}): 1663, 1643, 1506, 1396, 1279, 1271, 1103. Mass spectrum (API-ES, *m*/*z*): 491.256; calcd for $C_{29}H_{35}N_2O_5^+$, 491.254.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.23 (3H, t, J = 7.2, CH_3), 1.30 (3H, t, J = 7.2, CH_3), 1.15–1.55 (8H, m, CH_2), 3.21 (6H, m, H-5, NCH_2), 4.02 (3H, s, OCH_3), 4.95 (2H, t, J = 5.9, H-6), 5.26 (2H, s, OCH_2CO), 6.17 (2H, s, OCH_2O), 7.09 (1H, s, H-4), 7.79 (1H, s, H-1), 7.95 (1H, d, J = 9.3, H-12), 8.16 (1H, d, J = 9.3, H-11), 8.93 (1H, s, H-13), 9.98 (1H, s, H-8).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 13.72 ($2CH_3$), 19.46 (CH_2), 19.58 (CH_2), 26.45 (C-5), 29.30 (CH_2), 30.45 (CH_2), 44.74 (NCH_2), 45.58 (NCH_2), 55.45 (C-6), 57.16 (OCH_3), 69.66 (OCH_2CO), 102.09 (OCH_2O), 105.47

(C-1), 108.42 (C-4), 119.99 (C-13), 120.46 (C-1a), 121.48 (C-8a), 122.77 (C-12), 126.72 (C-11), 130.60 (C-4a), 133.01 (C-12a), 137.36 (C-13a), 142.44 (C-9), 146.18 (C-8), 147.68 (C-2), 49.07 (C-3), 149.81 (C-10), 166.90 (CO).

***N*,*N*-Tetramethylene-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetamide (2c).** Reaction of **3**·EtOH (200 mg) and amide **7c** (270 mg, 1.36 mmol) for 61.5 h by general method a) produced amide **2c** (56 mg, 20%), mp 256–258°C (dec.). UV spectrum (EtOH, λ_{max}, nm): 230, 266, 350, 430. IR spectrum (KBr, ν, cm^{-1}): 1654, 1637, 1506, 1394, 1344, 1272, 1227, 1101. Mass spectrum (API-ES, *m*/*z*): 433.178; calcd for $C_{25}H_{25}N_2O_5^+$, 433.176.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.75 (2H, m, CH_2), 1.89 (2H, m, CH_2), 3.21 (2H, t, J = 6.0, H-5), 3.29 (2H, m, NCH_2), 3.39 (2H, m, NCH_2), 4.04 (3H, s, OCH_3), 4.94 (2H, t, J = 6.0, H-6), 5.11 (2H, s, OCH_2CO), 6.17 (2H, s, OCH_2O), 7.10 (1H, s, H-4), 7.79 (1H, s, H-1), 7.97 (1H, d, J = 9.2, H-12), 8.17 (1H, d, J = 9.2, H-11), 8.93 (1H, s, H-13), 10.07 (1H, s, H-8).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 23.50 (CH_2), 25.66 (CH_2), 26.45 (C-5), 44.43 (NCH_2), 45.56 (NCH_2), 55.52 (C-6), 57.16 (OCH_3), 70.24 (OCH_2CO), 102.10 (OCH_2O), 105.46 (C-1), 108.44 (C-4), 119.98 (C-13), 120.48 (C-1a), 121.64 (C-8a), 123.18 (C-12), 126.66 (C-11), 130.61 (C-4a), 132.87 (C-12a), 137.31 (C-13a), 142.47 (C-9), 146.43 (C-8), 147.69 (C-2), 149.53 (C-3), 149.82 (C-10), 166.14 (CO).

***N*,*N*-Pentamethylene-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetamide (2d).** a) Reaction of **3**·EtOH (200 mg) and amide **7d** (290 mg, 1.36 mmol) for 44.5 h by general method a) produced amide **2d** (102 mg, 35%).

b) Reaction of **3**·EtOH (200 mg) and amide **7d** (234 mg, 1.14 mmol) for 37 h by general method b) produced amide **2d** (66 mg, 22%), mp 241°C. UV spectrum (EtOH, λ_{max}, nm): 230, 266, 350, 428. IR spectrum (KBr, ν, cm^{-1}): 1663, 1504, 1394, 1273, 1227, 1103. Mass spectrum (API-ES, *m*/*z*): 447.190; calcd for $C_{26}H_{27}N_2O_5^+$, 447.191.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.38–1.62 (6H, m, CH_2), 3.21 (2H, t, J = 5.6, H-5), 3.38 (4H, m, NCH_2), 4.03 (3H, s, OCH_3), 4.94 (2H, t, J = 5.6, H-6), 5.23 (2H, s, OCH_2CO), 6.17 (2H, s, OCH_2O), 7.09 (1H, s, H-4), 7.79 (1H, s, H-1), 7.95 (1H, d, J = 9.2, H-12), 8.16 (1H, d, J = 9.2, H-11), 8.92 (1H, s, H-13), 10.02 (1H, s, H-8).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 23.85 (CH_2), 25.17 (CH_2), 25.83 (CH_2), 26.42 (C-5), 42.03 (NCH_2), 44.65 (NCH_2), 55.43 (C-6), 57.18 (OCH_3), 70.02 (OCH_2CO), 102.08 (OCH_2O), 105.44 (C-1), 108.42 (C-4), 119.96 (C-13), 120.46 (C-1a), 121.53 (C-8a), 122.91 (C-12), 126.71 (C-11), 130.61 (C-4a), 132.91 (C-12a), 137.31 (C-13a), 142.52 (C-9), 146.31 (C-8), 147.66 (C-2), 149.31 (C-3), 149.80 (C-10), 165.86 (CO).

***N*,*N*-(3-Oxapentamethylene)-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetamide (2e).** a) Reaction of **3**·EtOH (200 mg) and amide **7e** (285 mg, 1.36 mmol) for 44.5 h by general method a) produced amide **2e** (123 mg, 43%).

b) Reaction of **3**·EtOH (200 mg) and amide **7e** (236 mg, 1.14 mmol) for 37 h by general method b) produced amide **2e** (92 mg, 30%), mp 241°C. UV spectrum (EtOH, λ_{max}, nm): 229, 266, 350, 430. IR spectrum (KBr, ν, cm^{-1}): 1664, 1506, 1396, 1275, 1229, 1112. Mass spectrum (API-ES, *m*/*z*): 449.170; calcd for $C_{25}H_{25}N_2O_6^+$, 449.171.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.21 (2H, t, J = 6.0, H-5), 3.42 (4H, m, NCH_2), 3.54–3.63 (4H, m, CH_2), 4.04 (3H, s, OCH_3), 4.94 (2H, t, J = 6.0, H-6), 5.24 (2H, s, OCH_2CO), 6.17 (2H, s, OCH_2O), 7.10 (1H, s, H-4), 7.79 (1H, s, H-1), 7.96 (1H, d, J = 9.2, H-12), 8.17 (1H, d, J = 9.2, H-11), 8.93 (1H, s, H-13), 10.01 (1H, s, H-8).

^{13}C NMR spectrum (75 MHz, DMSO-d_6, δ, ppm): 26.45 (C-5), 41.48 (NCH_2), 44.33 (CH_2), 55.51 (C-6), 57.26 (OCH_3), 65.96 (CH_2), 70.04 (OCH_2CO), 102.10 (OCH_2O), 105.48 (C-1), 108.44 (C-4), 120.03 (C-13), 120.47 (C-1a), 121.53 (C-8a), 123.11 (C-12), 126.79 (C-11), 130.64 (C-4a), 132.97 (C-12a), 137.40 (C-13a), 142.46 (C-9), 146.22 (C-8), 147.71 (C-2), 149.41 (C-3), 149.86 (C-10), 166.54 (CO).

***N*,*N*-Diphenyl-2-(9-demethoxyberberine bromide-9-yl)hydroxyacetamide (2f).** Reaction of **3**·EtOH (200 mg) and amide **7f** (239 mg, 0.817 mmol) for 4.5 h by general method a) produced after filtration of the precipitate amide **2f** (290 mg, 87%), mp 232°C. UV spectrum (EtOH, λ_{max}, nm): 231, 265, 350, 427. IR spectrum (KBr, ν, cm^{-1}): 1692, 1506, 1402, 1280, 1232. Mass spectrum (API-ES, *m*/*z*): 531.192; calcd for $C_{33}H_{27}N_2O_5^+$, 531.191.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.20 (2H, t, J = 6.0, H-5), 4.00 (3H, s, OCH_3), 4.93 (2H, t, J = 6.0, H-6), 4.99 (2H, s, OCH_2CO), 6.16 (2H, s, OCH_2O), 7.44 (10H, br.s, 2 Ph), 7.77 (1H, s, H-1), 7.95 (1H, d, J = 9.2, H-12), 8.16 (1H, d, J = 9.2, H-11), 8.94 (1H, s, H-13), 9.97 (1H, s, H-8).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 26.36 (C-5), 55.45 (C-6), 57.23 (OCH_3), 70.19 (OCH_2CO), 102.07 (OCH_2O), 105.43 (C-1), 108.40 (C-4), 119.97 (C-13), 120.38 (C-1a), 121.28 (C-8a), 123.05 (C-12), 126.65 (C-11), 127.13 (br., C-4′), 129.65 (br., C-2′, C-3′, C-5′, C-6′), 130.58 (C-4a), 132.93 (C-12a), 137.41 (C-13a), 141.16 (br., C-1′), 141.90 (C-9), 145.99 (C-8), 147.63 (C-2), 148.98 (C-3), 149.80 (C-10), 167.15 (CO).

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