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Synthesis of Novel Danshensu Alkamine Derivatives as Potential Anti-Myocardial Ischemia Agents

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Ten novel danshensu alkamine derivatives were synthesized and the preliminary biological activity of these complexes were investigated. The bioassay results indicated that some of derivatives exhibit significant activities on protecting hypoxic H_9C_2 cardiomyocytes.

Keywords: Anti-myocardial ischemia activities, Danshensu alkamine derivatives, Synthesis.

INTRODUCTION

The compounds isolated from *Salvia miltiorrhiza* root, a widly used traditional Chinese medicine, have recently attracted considerable attention owing to their prominent biological activity. Danshensu is one of the major effective component of aqueous extracts and has significant pharmacological activities such as relaxant coronary arteries[1,2], inhibit platelet aggregation and decrease the levels of blood viscosity[3], improve microcirculation[4], protect myocardial ischemia reperfusion injury[5,6]. In addition, danshensu inhibit myocardium cell apoptosis[7], protect the endothelial cells against homocysteinemia[8], radical scavengers and antioxidants[9]. Previously, we reported that sodium DSS showed biphasic effects on vessel tension, low dosage of sodium danshensu produced small contraction, high dosage produced significant vasodilation[10].

However, it has been shown that danshensu has low oral bioavailability[11] and is instability. Therefore, it is necessary for developing new generation drug suit for clinic from molecular modification of danshensu.

Structure-activity relationship studies indicated that phenyllactic acid in the molecule of danshensu might be the active site[12,13]. Present domestic and international research of danshensu derivatives are most about danshensu esters while few are about danshensu alkamines. Many nature products with physiological activity contain alkamine structure which is the critical area in many molecules of medicine[14]. On the basis of this, we retain structure of phenyllactic acid and synthetize danshensu alkamine derivatives (Fig.1) in order to find novel compounds more stability and better activity.

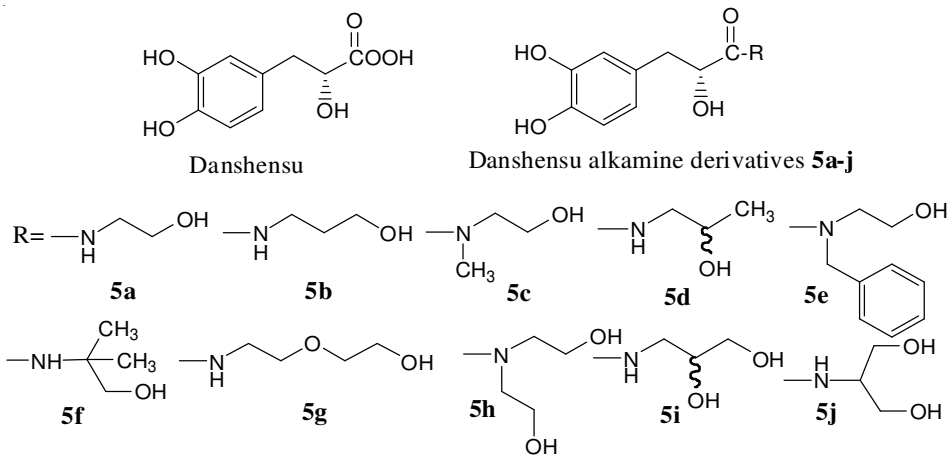
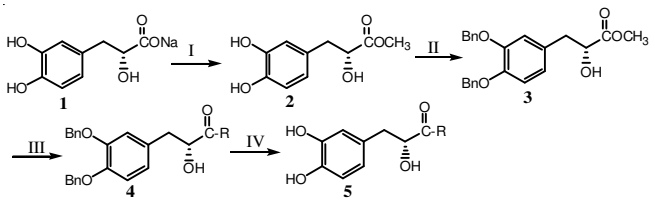


Fig.1. Structures of danshensu and danshensu alkamine derivatives **5a-j**

EXPERIMENTAL

Melting point were conducted on a Yamato MP-21 melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise indicated with a Bruker AC-300P spectrometer or a Bruker Avance II 600 spectrometer, using TMS as internal standard. ESI mass spectra were performed on an API-3000 LC-MS spectrometer. All compounds were routinely checked by thin-layer chromatography (TLC) and ^{1}H NMR. Components were visualized by UV light (254 nm).

Synthesis of compounds: All the danshensu derivatives were synthesized according to the route as shown in **Scheme-I**.



Scheme-I: Synthetic route for compounds **5a-j**

Methyl 3-(3,4-Dihydroxyphenyl)-2-hydroxypropanoate (2): Concentrated sulfuric acid (4.6 g, 0.047 mol) was added to sodium DSS (1) (10 g, 0.045 mol) in anhydrous methanol (20 mL) and stirred at refluxed for 7 h. After completion of the reaction, methanol was concentrated to dryness. The residue was purified by recrystallization from methanol and chloroform to give pure products **2** (9.1 g). Yield: 95.4 %; oil. ^{1}H NMR (300 MHz, acetone-d_6): δ 6.67 (s, 1H, 2'-H), 6.65 (d, 1H, *J* = 7.8, 5'-H), 6.52 (d, 1H, *J* = 8.1, 6'-H), 4.14-4.21 (m, 1H, 2-H), 3.68 (s, 3H, $COOCH_3$), 2.96 (dd, 1H, *J* = 14.1, 5.4, 3-H), 2.79 (dd, 1H, *J* = 13.8, 7.5, 3-H); ^{13}C NMR (300 MHz, acetone-d_6): δ 176.37, 146.51, 145.51, 130.34, 122.31, 118.06, 116.66, 73.83, 52.77, 41.61; MS(ESI) *m/z* calc. for $C_{10}H_{12}O_5$ 212.20, found $[M-H]^+$ 211.65.

Methyl 3-[3,4-*bis*(benzyloxy)phenyl]-2-hydroxypropanoate(3): Compound **2** (15 g, 0.071 mol), benzyl bromide (30 g, 0.175 mol), K_2CO_3 (20 g, 0.145 mol) and KI (2 g, 0.012 mol) were added in anhydrous acetone (100 mL), stirring at refluxed for 7 h at 70 °C. After the reaction end and the mixture cool to room temperature, wash the reaction solution with ice water (30 mL), than extract with acetic ether (3 × 40 mL). The combined organic extracts were washed with saturated brine (40 mL) and dried over anhydrous Na_2SO_4, than evaporated *in vacuo*. After filtration and evaporation, the residue was purified by flash column chromatography with a mixture of ligarine/EtOAc (3:1 v/v) as eluent to provide the compound methyl 3-[3,4-*bis*(benzyloxy)phenyl]-2-hydroxypropanoate (**3**). Yield: 69.3 %, white power, m.p. 92-93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.29 (m, 10H, Ar-H), 6.95 (s, 1H, 2'-H), 6.92 (d, 1H, *J* = 8.4, 5'-H), 6.70 (d, 1H, *J* = 7.8, 6'-H), 5.04 (s, 2H, -OCH_2Ph), 5.07 (s, 2H, -OCH_2Ph), 4.17-4.21 (m, 1H, 2-H), 3.56 (s, 3H, $COOCH_3$), 2.91 (dd, 1H, *J* = 10.5, 4.8, 3-H), 2.74 (dd, 1H, *J* = 14.4, 8.1, 3-H); MS (ESI) *m/z* calc. for $C_{10}H_{12}O_5$ 392.44, found $[M-H]^+$ 391.14.

3-[3,4-*Bis*(benzyloxy)phenyl]-2-hydroxy-R-propionamide (4a-j): Compound **3** (0.4 g) and amino alcohol (1.02 mmol) in methanol (20 mL) react in heating reflux. Progress of the reaction was monitored by TLC. After completion of the reaction, the solution was cooled, than the methanol were evaporated *in vacuo*. The residue was purified by flash column chromatography with a mixture of pet. ether:EtOAc (2:1 to 1:4) as eluent to provide 3-[3,4-*bis*(benzyloxy)phenyl]-2-hydroxy-R-propionamide **(4a-j)**.

3-[3,4-*Bis*(benzyloxy)phenyl]-2-hydroxy-N-(2-hydroxyethyl)propanamide (4a): White solid, yeld 92.1 %, m.p.120-121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.27 (m, 10H, Ar-H), 6.90-6.73 (m, 3H, 2'-H, 5'-H, 6'-H), 5.16 (s, 2H, -OCH_2Ph), 5.15 (s, 2H, -OCH_2Ph), 4.24-4.21 (m, 1H, 2-H), 3.66-3.62 (m, 2H, -CH_2OH), 3.40-3.34 (m, 2H, -$NHCH_2$-), 3.14 (dd, 1H, *J* = 13.8, 4.2, 3-H), 2.87 (dd, 1H, *J* = 16.8, 8.1, 3-H); MS(ESI) *m/z* calc. for $C_{25}H_{27}NO_5$ 421.49, found $[M-H]^+$ 420.13.

3-[3,4-*Bis*(benzyloxy)phenyl]-2-hydroxy-N-(3-hydroxypropyl)propanamide (4b): White solid, yeld 87.32 %, m.p.124-125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.28 (m, 10H, Ar-H), 6.93-6.88 (m, 2H, 2'-H, 5'-H), 6.78-6.75 (m, 1H, 6'-H), 5.16 (s, 4H, -OCH_2Ph), 4.27-4.24 (m, 1H, 2-H), 3.59-3.55 (m, 2H, $NHCH_2$), 3.41-3.38 (m, 2H, CH_2OH), 3.16 (dd, 1H, *J* = 13.5, 4.2, 3-H), 3.16 (dd, 1H, *J* = 14.1, 8.1, 3-H), 1.64-1.69 (m, 2H, $NHCH_2CH_2$); MS(ESI) *m/z* calc. for $C_{26}H_{29}NO_5$ 435.51, found $[M-H]^+$ 434.50

3-[3,4-*Bis*(benzyloxy)phenyl]2-hydroxy-N-(2-hydroxyethyl)-N-methylpropanamide (4c): White solid, yeld 67.3 %, m.p. 117-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.27 (m, 10H, Ar-H), 6.89 (d, 1H, *J* = 8.7, 5'-H), 6.85 (s, 1H, 2'-H), 6.76 (d, 1H, *J* = 8.1, 6'-H), 5.15 (s, 2H, -OCH_2Ph), 5.14 (s, 2H, -OCH_2Ph), 4.50-4.41 (m, 1H, 2-H), 3.77-3.66 (m, 2H, -CH_2OH), 3.59 (s, 3H, -NCH_3), 3.43-3.50 (m, 2H, -NCH_2-), 3.04-2.81 (m, 2H, 3-H); MS (ESI) *m/z* calc. for $C_{26}H_{29}NO_5$ 435.51, found $[M-H]^+$ 434.23.

3-[3,4-*Bis*(benzyloxy)phenyl]-2-hydroxy-N-(2-hydroxypropyl)propanamide (4d): White solid, yeld 87.32 %, m.p.123-125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.29 (m, 10H, Ar-H), 6.96 (s, 1H, 2'-H), 6.91 (d, 1H, *J* = 8.1 5'-H), 6.72 (d, 1H, *J* = 7.8, 6'-H), 5.07 (s, 4H, -OCH_2Ph), 4.73-4.71 (m, 1H, 2-H), 3.63-3.52 (m, 1H, CHOH), 3.23-3.42 (m, 2H, $NHCH_2$), 2.96 (dd, 1H, *J* = 14.4, 4.2, 3-H), 2.79 (dd, 1H, *J* = 13.8, 7.2, 3-H), 1.02-0.92 (m, 3H, CH_3); MS(ESI) *m/z* calc. for $C_{26}H_{29}NO_5$ 435.51, found $[M-H]^+$ 434.50.

N-Benzyl-3-[3,4-*bis*(benzyloxy)phenyl]-2-hydroxy-N-(2-hydroxyethyl)propanamide(4e): White solid, yeld 61.1 %, m.p.134-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.27 (m, 10H, Ar-H), 7.19 (d, 1H, *J* = 7.5, 5'-H), 7.08 (s, 1H, 2'-H), 7.07 (d, 1H, *J* = 6.3, 6'-H), 6.89-6.70 (m, 5H, Ar-H), 5.17 (s, 2H, -OCH_2Ph), 5.16 (s, 2H, -OCH_2Ph), 5.14 (s, 2H, -NCH_2Ph), 4.55-4.52 (m, 1H, 2-H), 3.68-3.65 (m, 2H, -CH_2OH), 3.60-3.42 (m, 2H, -NCH_2), 3.17-2.89 (m, 2H, 3-H); MS(ESI) *m/z* calc. for $C_{32}H_{33}NO_5$ 511.60, found $[M-H]^+$ 510.54.

3-[3,4-*Bis*(benzyloxy)phenyl)-2-hydroxy-N-(1-hydroxy-2-dimethylethyl)propanamide (4f): White solid, yeld 52.5 %, m.p.126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.27 (m, 10H, Ar-H), 6.93-6.82 (m, 2H, 2'-H, 5'-H, 6'-H), 5.15 (s, 4H, -OCH_2Ph), 4.18-4.14 (m, 1H, 2-H), 3.57-3.84 (m, 2H, -CH_2OH), 3.09 (dd, 1H, *J* = 13.8, 7.5, 3-H), 2.87 (dd, 1H, *J* = 14.7, 7.5, 3-H), 1.38 (s, 6H, -$N(CH_3)_2$); MS (ESI) *m/z* calc. for $C_{27}H_{31}NO_5$ 449.54, found $[M-H]^+$ 448.33.

3-[3,4-*Bis*(benzyloxy)phenyl]-2-hydroxy-N-[2-(2-hydroxyethoxy)ethyl]propanamide (4g): White solid, yeld 53.6 %, m.p.128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.27 (m, 10H, Ar-H), 6.89 (d, 1H, *J* = 6.6, 5'-H), 6.86 (s, 1H, 2'-H), 6.76 (d, 1H, *J* = 8.4,6'-H), 5.14 (s, 2H, -OCH_2Ph), 5.13 (s, 2H, -OCH_2Ph), 4.23-4.19 (m, 1H, 2-H), 3.68-3.65 (m, 2H, -CH_2O), 3.51-3.48 (m, 2H, $NHCH_2$), 3.45-3.43 (m, 2H, OCH_2), 3.41-3.47 (m, 2H, CH_2OH), 3.13 (dd, 1H, *J* = 14.1, 4.2, 3-H), 2.82 (dd, 1H, *J* = 13.8, 8.4, 3-H); MS (ESI) *m/z* calc. for $C_{27}H_{31}NO_6$ 465.53, found $[M-H]^+$ 464.19.

3-[3,4-*Bis*(benzyloxy)phenyl]-2-hydroxy-N,N-*bis*(2-hydroxyethyl)propanamide (4h): White solid, yeld 92.1 %, m.p.130-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.27 (m, 10H, Ar-H), 6.87 (d, 1H, *J* = 8.1, 5'-H), 6.75 (s, 1H, 2'-H), 6.72 (d, 1H, *J* = 7.5, 6'-H), 5.14 (s, 4H, -OCH_2Ph), 4.63-4.61 (m, 1H, 2-H), 3.82-3.77 (m, 4H, -CH_2OH), 3.71-3.65 (m, 4H, -NCH_2), 2.97-3.84 (m, 2H, 3-H); MS (ESI) *m/z* calc. for $C_{27}H_{31}NO_6$ 465.54, found $[M-H]^+$ 464.41.

3-[3,4-*Bis*(benzyloxy)phenyl]-N-(2,3-dihydroxypropyl)-2-hydroxypropanamide (4i): White solid, yeld 46.6 %, m.p.133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.27 (m, 10H, Ar-H), 6.88 (d, 1H, *J* = 6.3 5'-H), 6.84 (s, 1H, 2'-H), 6.74 (d, 1H, *J* = 8.1, 6'-H), 5.12 (s, 4H, -OCH_2Ph), 4.22-4.24 (m, 1H, 2-H), 3.67-3.65 (m, 1H, CHOH), 3.47-3.41 (m, 2H, CH_2OH), 3.39-3.35 (m, 2H, $NHCH_2$), 3.11 (dd, 1H, *J* = 14.1, 4.5, 3-H), 2.96 (dd, 1H, *J* = 13.8, 5.7, 3-H); MS(ESI) *m/z* calc. for $C_{26}H_{29}NO_6$ 451.51, found $[M-H]^+$ 450.63.

3-[3,4-*Bis*(benzyloxy)phenyl]-N-(1,3-dihydroxypropan-2-yl)-2-hydroxypropanamide (4j): White solid, yeld 87.6 %, m.p.130-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.28 (m, 10H, Ar-H), 6.86 (d, 1H, *J* = 7.2 5'-H), 6.82 (s, 1H, 2'-H), 6.72 (d, 1H, *J* = 8.1, 6'-H), 5.11 (s, 2H, -OCH_2Ph), 5.08 (s, 2H, -OCH_2Ph), 4.49-4.52 (m, 1H, 2-H), 4.13-4.20 (m, 1H, NHCH), 3.45-3.58 (m, 4H, CH_2OH), 3.11 (dd, 1H, *J* = 14.1, 3.9, 3-H), 2.96 (dd, 1H, *J* = 11.1, 6.5, 3-H); MS (ESI) *m/z* calc. for $C_{26}H_{29}NO_6$ 451.51, found $[M-H]^+$ 450.37.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-R-propionamide 5a-j: Compound **4** (0.53 mol) and Pd/C (20 mg) in acetic ether (20 mL) are refluxed while strring for 24 h at room temperutrue. Then the reaction mixture was filtered, evaporated *in vacuo* and dried to give 3-(3,4-dihydroxyphenyl)-2-hydroxy-R-propionamide **(5a-j)**.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-N-(2-hydroxyethyl)-propanamide (5a): Oil, yeld 96.3 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 7.96 (bar, 1H, NH), 6.74 (d, 1H, *J* = 2.1, 2'-H), 6.71 (d, 1H, *J* = 7.8, 5'-H), 6.62 (dd, 1H, *J* = 7.8, 2.1, 6'-H), 4.25-4.21 (m, 1H, 2-H), 3.65-3.62 (m, 2H, -CH_2OH), 3.37-3.32 (m, 2H, -$NHCH_2$-), 3.01 (dd, 1H, *J* = 14.1, 3.9, 3-H), 2.82 (dd, 1H, *J* = 13.8, 7.5, 3-H); MS(ESI) *m/z* calc. for $C_{11}H_{15}NO_5$ 241.24, found $[M-H]^+$ 240.42.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-N-(3-hydroxypropyl)propanamide (5b): Oil, yeld 95.32 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 7.67 (bar, 1H, NH), 6.77 (d, 1H, *J* = 1.6, 2'-H), 6.72 (d, 1H, *J* = 8.1, 5'-H), 6.59 (dd, 1H, *J* = 8.1, 2.1, 6'-H), 4.32 (dd, 1H, *J* = 7.2, 5.1, 2-H), 3.54-3.47 (m, 2H, CH_2OH), 3.33-3.26 (m, 2H, $NHCH_2$), 3.00 (dd, 1H, *J* = 13.8, 3.6, 3-H), 2.72 (dd, 1H, *J* = 13.8, 7.8, 3-H), 1.69-1.60 (m, 2H, CH_2); MS (ESI) *m/z* calc. for $C_{12}H_{17}NO_5$ 255.26, found $[M-H]^+$ 254.51.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-N-(2-hydroxyethyl)-N-methylpropanamide (5c): Oil, yeld 89.3 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 8.08 (bar, 1H, NH), 6.76-6.69 (m, 2H, 2'-H, 5'-H), 6.59 (dd, 1H, *J* = 8.1, 1.8, 6'-H), 4.65-4.52 (m, 1H, 2-H), 3.71-3.60 (m, 2H, -CH_2OH), 3.52 (s, 3H, -NCH_3), 3.37-3.22 (m, 2H, -NCH_2-), 2.99 (dd, 1H, *J* = 14.1, 4.8, 3-H), 2.82 (dd, 1H, *J* = 13.5, 7.5, 3-H); MS (ESI) *m/z* calc. for $C_{12}H_{17}NO_5$ 255.11, found $[M-H]^+$ 254.31.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-N-(2-hydroxypropyl)propanamide (5d): Oil, yeld 97.58 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 8.02 (bar, 1H, NH), 6.75 (s, 1H, 2'-H), 6.72 (d, 1H, *J* = 6.9, 5'-H), 6.58 (d, 1H, *J* = 8.1, 6'-H), 4.20-4.14 (m, 1H, 2-H), 3.63-3.71 (m, 1H, CHOH), 3.26-3.06 (m, 2H, $NHCH_2$), 2.99 (dd, 1H, *J* = 13.8, 3.6, 3-H), 2.70 (dd, 1H, *J* = 14.4, 4.8, 3-H), 1.25-1.02 (m, 3H, CH_3); MS(ESI) *m/z* calc. for $C_{12}H_{17}NO_5$ 255.26, found $[M-H]^+$ 254.12.

N-Benzyl-3-(3,4-dihydroxyphenyl)-2-hydroxy-N-(2-hydroxyethyl)propanamide (5e): Oil, yeld 87.1 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 7.22-7.13 (m, 5H, Ar-H), 6.83 (d, 1H, *J* = 1.8, 2'-H), 6.76 (d, 1H, *J* = 7.8, 5'-H), 6.72 (dd, 1H, *J* = 8.1, 1.5, 6'-H), 4.59-4.54 (m, 1H, 2-H), 4.42 (s, 2H, -NCH_2Ph), 3.70-3.63 (m, 2H, -CH_2OH), 3.29-3.22 (m, 2H, -NCH_2), 2.95 (dd, 1H, *J* = 13.8, 8.4, 3-H), 2.77 (dd, 1H, *J* = 13.8, 7.2, 3-H); MS(ESI) *m/z* calc. for $C_{18}H_{21}NO_5$ 331.36, found $[M-H]^+$ 330.15.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-N-(1-hydroxy-2-dimethylethyl)propanamide (5f): Oil, yeld 92.5 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 7.86 (bar, 1H, NH), 6.16 (s, 1H, 2'-H), 6.71(d, 1H, *J* = 7.8, 5'-H), 6.57(d, 1H, *J* = 7.8, 6'-H), 4.16-4.32 (m, 1H, 2-H), 3.51-3.42 (m, 2H, -CH_2OH), 2.95 (dd, 1H, *J* = 11.1, 4.5, 3-H), 2.70 (dd, 1H, *J* = 13.8, 7.5, 3-H), 1.23 (s, 6H, -$N(CH_3)_2$); MS(ESI) *m/z* calc. for $C_{13}H_{19}NO_5$ 269.13, found $[M-H]^+$ 268.29.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-N-(2-(2-hydroxyethoxy)ethyl)propanamide (5g): Oil, yeld 89.16 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 7.99 (bar, 1H, NH), 6.74 (d, 1H, *J* = 1.8, 2'-H), 6.70 (d, 1H, *J* = 8.1, 5'-H), 6.57 (dd, 1H, *J* = 8.1, 1.8, 6'-H), 4.17 (dd, 1H, *J* = 7.8, 3.9, 2-H), 3.64-3.59 (m, 2H, -CH_2O), 3.52-3.49 (m, 2H, $NHCH_2$), 3.48-3.43 (m, 2H, OCH_2), 3.41-3.34 (m, 2H, CH_2OH), 2.97 (dd, 1H, *J* = 13.8, 3.9, 3-H), 2.69 (dd, 1H, *J* = 13.8, 7.8, 3-H); MS(ESI) *m/z* calc. for $C_{13}H_{19}NO_6$ 285.12, found $[M-H]^+$ 284.32.

3-(3,4-Dihydroxyphenyl)-2-hydroxy-N,N-*bis*(2-hydroxyethyl)propanamide (5h): Oil, yeld 96.32 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 7.96 (bar, 1H, NH), 6.77 (d, 1H, *J* = 2.1, 2'-H), 6.71 (d, 1H, *J* = 8.1, 5'-H), 6.72 (dd, 1H, *J* = 7.8, 1.8, 6'-H), 4.64 (dd, 1H, *J* = 6.6, 5.4, 2-H), 3.70-3.62 (m, 4H, -CH_2OH), 3.40-3.34 (m, 4H, -NCH_2), 2.89 (dd, 1H, *J* = 13.8, 5.1, 3-H), 2.70 (dd, 1H, *J* = 13.8, 7.2, 3-H); MS (ESI) *m/z* calc. for $C_{13}H_{19}NO_6$ 285.29, found $[M-H]^+$ 284.12.

3-(3,4-Dihydroxyphenyl)-N-(2,3-dihydroxypropyl)-2-hydroxypropanamide (5i): Oil, yeld 97.2 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 8.06 (bar, 1H, NH), 6.87 (d, 1H, *J* = 1.5, 2'-H), 6.82 ((d, 1H, *J* = 7.8, 5'-H), 6.72 (d, 1H, *J* = 8.1, 1.8, 6'-H), 4.23 (dd, 1H, *J* = 8.7, 4.5, 2-H), 3.57-3.54 (m, 1H, CHOH), 3.43-3.37 (m, 2H, CH_2OH), 3.36-3.34 (m, 2H, $NHCH_2$), 2.98 (dd, 1H, *J* = 14.1, 4.5, 3-H), 2.81 (dd, 1H, J = 13.8, 7.5, 3-H); MS (ESI) *m/z* calc. for $C_{12}H_{17}NO_6$ 271.11, found $[M-H]^+$ 270.34.

TABLE-1
RELATIVE CELL VIABILITY OF DANSENSU AND ITS DERIVATIVES **5a-j**

Drug	DSS	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**
Relative ratio %	37.5	39.35	-14.91	-8.66	39.42	45.17	40.34	32.46	9.66	33.88	32.88

3-(3,4-Dihydroxyphenyl)-N-(1,3-dihydroxypropan-2-yl)-2-hydroxypropanamide (5j): Oil, yeld 87.6 %; ^{1}H NMR (300 MHz, Acetone-d_6): δ 7.95 (bar, 1H, NH), 6.86 (d, 1H, *J* = 7.8 5'-H), 6.82 (s, 1H, 2'-H), 6.72 (d, 1H, *J* = 8.1, 6'-H), 4.37 (dd, 1H, *J* = 9.6, 4.5, 2-H), 3.75-3.73 (m, 1H, NCH), 3.45-3.42 (m, 4H, CH_2OH), 2.97 (dd, 1H, *J* = 13.8, 3.9, 3-H), 2.78 (dd, 1H, *J* = 14.1, 7.5, 3-H); MS (ESI) *m/z* calc. for $C_{12}H_{17}NO_6$ 271.11, found $[M-H]^+$ 270.25.

Bioassay of danshensu alkamine derivatives: Rat myocardial cell lines H_9C_2 obtained from Institutes of Biochemistry and Cell Biology, CAS, Shanghai, China, was maintained in DMEM medium supplemented with 10 % (v/v) fetal bovine serum at 37 °C in 5 % CO_2 and 95 % air. The cells disassociated by 0.25 % trypsin were seeded at a density of 1×10^4 cells/well in 96-well plates, with a volume of 100 µL in each well. After a period of 24 h, cells were exposed to different compounds (DSS, 5a-j) at 10 µmol/L or vehicle alone for 2 h, respectively and then subjected to hypoxia at 37 °C in 5 % CO_2 and 95 % N_2. After 24 h, the cells were collected and MTT assay was performed as previously described[15]. The viability of normal cell is presumed as 100 %. The relative cell viability rate of the derivatives compare to the model assay was calculated *via* the following equation:

$$\text{Relative ratio \%} = (Ns-Nc)/Nc \times 100\ \%$$

where, Ns is the value of the drug group; and Nc is the value of the model group.

RESULTS AND DISCUSSION

Ten novel danshensu alkamine derivatives were synthesized by DSS with substituted ketones. Reaction mixtures were maintained strring at room temperature, leading to the desired compounds in 87.1-97.2 % yelds. All the compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS.

Anti-myocardial ischemia activities: The result listed in Table-1 showed that **5a**, **5d**, **5e**, **5f** exhibited more potent activities than that of DSS., while **5b**, **5c**, **5h** showed less potent activity. Other three compounds **5g**, **5i**, **5j** were less but close to the DSS. Compound **5e** was found to be the most active anti-myocardial ischemia agent.

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