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Metachromins L–Q, new sesquiterpenoid quinones with an amino acid residue from sponge *Spongia* sp.

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Abstract—Six new sesquiterpenoid quinones with an amino acid residue, metachromins L–Q (**1**–**6**), have been isolated from an Okinawan marine sponge *Spongia* sp. The structures and stereochemistry of **1**–**6** were elucidated on the basis of the spectroscopic data and chemical correlations. Metachromins L (**1**) and M (**2**) showed modest cytotoxicity.

1. Introduction

Marine sponges contain a number of unique secondary metabolites with a diversity of biological activities,[1] and sponges of the genus *Spongia* are known to be a rich source of terpenoids[2] and polyketides.[3] In our continuing search for bioactive compounds from marine organisms, we previously isolated new sesquiterpenoid quinones, metachromins J and K, from an Okinawan sponge *Spongia* sp. (SS-1037).[4] Further investigation of extracts of this sponge resulted in the isolation of six new sesquiterpenoid quinones with an amino acid residue, metachromins L–Q (**1**–**6**). Here we describe the isolation and structure elucidation of **1**–**6**.

2. Results and discussion

The sponge *Spongia* sp. (SS-1037) collected off Gesashi, Okinawa, was extracted with MeOH. The extracts were partitioned between EtOAc and water, and the aqueous phase was further extracted with *n*-BuOH. *n*-BuOH-soluble materials were purified by a silica gel column ($CHCl_3$/MeOH/H_2O) and C_{18} column (MeOH/H_2O/TFA) followed by reversed-phase HPLC (Cosmosil Cholester, CH_3CN/H_2O/TFA) to afford metachromins L (**1**, 0.00007%, wet weight), M (**2**, 0.00009%), N (**3**, 0.00007%), O (**4**, 0.00007%), P (**5**, 0.00004%), and Q (**6**, 0.00004%) together with known related sesquiterpenoids, metachromins A (**7**), C (**8**), D, E, J, and K (Fig. 1).[4–7]

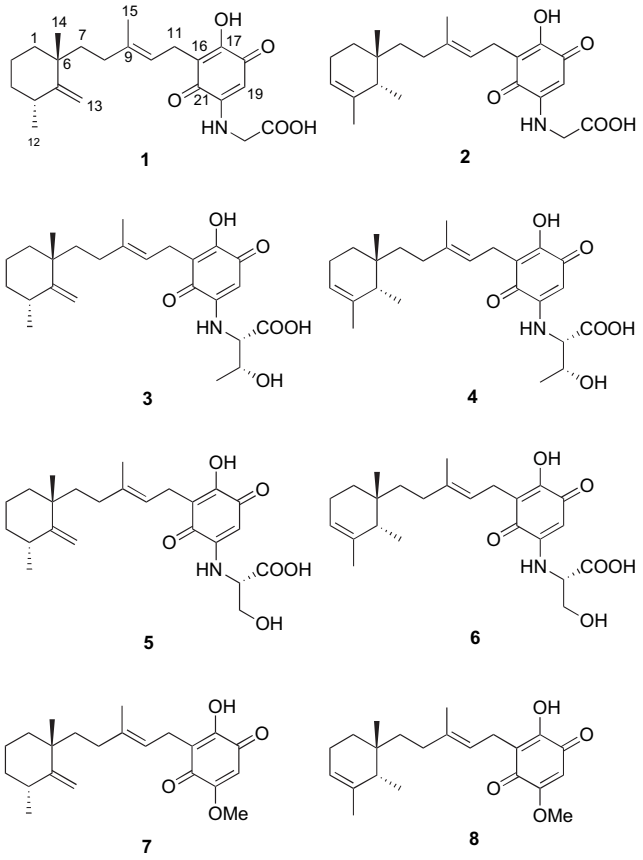

Figure 1. Structures of metachromins L–Q (**1**–**6**), A (**7**), and C (**8**).

Metachromin L (**1**) was obtained as a red amorphous solid and the molecular formula was established to be $C_{23}H_{31}NO_5$ by HRFABMS data [*m*/*z* 402.2278

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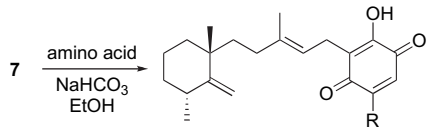
(M+2H−H)$^-$, Δ −0.3 mmu]. The IR spectrum indicated the presence of OH and/or NH (3290 cm^{-1}), carboxy (1730 cm^{-1}), and conjugated carbonyl (1650 and 1590 cm^{-1}) functionalities. UV absorptions (330 and 498 nm) suggested the presence of quinone chromophore. ^{1}H and ^{13}C NMR data of **1** were similar to those of metachromin A (**7**), while in place of a methoxy signal [δ_H 3.86 (s), δ_C 56.8 (q)] in **7**, signals due to a glycine residue [δ_H 3.82 (s), δ_C 45.9 (t), 173.0 (s)] were observed for **1**. Treatment of metachromin A (**7**) with Gly in EtOH containing $NaHCO_3$ afforded compound **1** (Scheme 1), whose spectral data were coincident with those of natural metachromin L (**1**) including optical rotation. Thus, the structure of metachromin L was assigned as **1**.



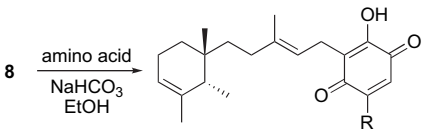
1 : R = Gly
3 : R = L-Thr
5 : R = L-Ser

Scheme 1. Chemical conversion of metachromin A (**7**) to metachromins L (**1**), N (**3**), and P (**5**).

Metachromins N (**3**) and P (**5**) were obtained as red amorphous solids and each molecular formula was established to be $C_{25}H_{35}NO_6$ and $C_{24}H_{33}NO_6$ by HRFABMS data [*m/z* 446.2535 (M+2H−H)$^-$, Δ −0.8 mmu] and [*m/z* 432.2381 (M+2H−H)$^-$, Δ −0.5 mmu], respectively. ^{1}H NMR data of **3** and **5** were similar to those of metachromin L (**1**), except for the amino acid residue. Treatment of metachromin A (**7**) with L-Thr or L-Ser in EtOH containing $NaHCO_3$ afforded compounds **3** and **5** (Scheme 1), respectively. The spectral data and retention times from HPLC column (DAICEL CHIRALCEL AD) of **3** and **5** were coincident with those of natural metachromins N (**3**) and P (**5**), respectively. Thus, the structures of metachromins N and P were assigned as **3** and **5**, respectively.

Metachromins M (**2**), O (**4**), and Q (**6**) were obtained as red amorphous solids and each molecular formula was established to be $C_{23}H_{31}NO_5$, $C_{25}H_{35}NO_6$, and $C_{24}H_{33}NO_6$ by HRFABMS data [*m/z* 402.2285 (M+2H−H)$^-$, Δ +0.4 mmu], [*m/z* 446.2532 (M+2H−H)$^-$, Δ −1.1 mmu], and [*m/z* 432.2393 (M+2H−H)$^-$, Δ 0.0 mmu], respectively. ^{1}H NMR data of **2**, **4**, and **6** were similar to those of metachromin C (**8**), while in place of a methoxy signal [δ_H 3.88 (s), δ_C 56.5 (q)] in **8**, signals due to an amino acid residue (glycine, threonine, and serine, respectively) were observed for **2**, **4**, and **6**. The spectral data and retention times from HPLC column (DAICEL CHIRALCEL AD) of natural metachromins M (**2**), O (**4**), and Q (**6**) were coincident with those of compounds **2**, **4**, and **6**, which were derived from metachromin C (**8**) and amino acids by the same procedure as described above (Scheme 2). Thus, the structures of metachromins M (**2**), O (**4**), and Q (**6**) were assigned as **4**, **5**, and **6**, respectively.

Metachromins L (**1**) and M (**2**) showed cytotoxicity against L1210 murine leukemia (IC_{50}, 4.0 and 3.5 μg/mL, respectively) and KB human epidermoid carcinoma cells (IC_{50}, 4.0 and 5.4 μg/mL, respectively) in vitro, while



2 : R = Gly
4 : R = L-Thr
6 : R = L-Ser

Scheme 2. Chemical conversion of metachromin C (**8**) to metachromins M (**2**), O (**4**), and Q (**6**).

metachromins N (**3**), O (**4**), P (**5**), and Q (**6**) did not show such activity (IC_{50}>10 μg/mL).

3. Experimental section

3.1. General experimental procedures

IR and UV spectra were recorded on JASCO FTIR-5300 and Shimadzu UV-1600PC spectrophotometer, respectively. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JMN-EX 400, Bruker ARX-500, and AMX-600 spectrometers. FABMS spectra were recorded on a JEOL JMS-HX110 using glycerol as a matrix in negative mode.

3.2. Sponge material

The sponge *Spongia* sp. (order Dictyoceratida, family Spongiidae) was collected off Gesashi, Okinawa, and kept frozen until used. The voucher specimen (SS-1037) was deposited at the Graduate School of Pharmaceutical Sciences, Hokkaido University.

3.3. Extraction and isolation

The sponge (0.7 kg, wet weight) was extracted with MeOH, and the extract was partitioned between EtOAc (three times) and H_2O (500 mL). The aqueous phase was further extracted with *n*-BuOH (500 mL×3). A part (2.3 g) of *n*-BuOH soluble materials (3.3 g) was purified by a silica gel column ($CHCl_3$/MeOH/H_2O, 6:4:0.5) and C_{18} column (MeOH/H_2O/TFA, 80:20:0.1) followed by reversed-phase HPLC (Cosmosil Cholester, Nacalai Tesque, Inc., 10×250 mm; eluent, CH_3CN/H_2O/TFA, 70:30:0.1; flow rate, 1.5 mL/min; UV detection at 300 nm) to afford metachromins L (**1**, 0.5 mg, t_R 53.6 min), M (**2**, 0.6 mg, t_R 52.4 min), N (**3**, 0.5 mg, t_R 42.4 min), O (**4**, 0.5 mg, t_R 41.6 min), P (**5**, 0.3 mg, t_R 36.0 min), and Q (**6**, 0.3 mg, t_R 35.2 min) and metachromins A (**7**), C (**8**), D, E, J, and K.

3.3.1. Metachromin L (1). Red amorphous solid; $[\alpha]_D^{23}$ +19 (*c* 0.2, MeOH); IR (film) ν_{max} 3290, 1730, 1650, 1590, 1510, 1370, and 1210 cm^{-1}; UV (MeOH) λ_{max} 330 (ε 9700), and 498 nm (640); ^{1}H NMR ($CDCl_3$/CD_3OD, 95:5) δ 0.90 (1H, m, H-2b), 0.93 (1H, m, H-3b), 0.98 (3H, d, *J*=6.3 Hz, H_3-12), 0.98 (3H, s, H_3-14), 1.16 (1H, ddd, *J*=12.8, 12.8, and 4.5 Hz, H-1b), 1.4–1.6 (4H, m, H-1a, H-2a, and H_2-7), 1.70 (1H, m, H-3a), 1.71 (3H, br s, H_3-15), 2.28 (1H, m, H-4), 3.07 (2H, br d, *J*=7.1 Hz, H_2-11), 3.82 (2H, s, H_2-22), 4.64 (1H, s, H-13b), 4.66 (1H, s, H-13a), 5.12 (1H, br t, *J*=7.1 Hz, H-10), and 5.23 (1H, s, H-19); ^{13}C NMR (CD_3OD) δ 17.26 (q, C-15), 20.83 (q, C-12), 23.27 (t,

C-11), 23.65 (t, C-2), 26.11 (q, C-14), 35.98 (d, C-4), 36.07 (t, C-8), 39.19 (t, C-3), 40.74 (t, C-1), 41.16 (s, C-6), 42.23 (t, C-7), 45.88 (t, C-22), 94.43 (d, C-19), 105.08 (t, C-13), 117.60 (s, C-16), 122.18 (d, C-10), 139.04 (s, C-9), 151.57 (s, C-20), 158.28 (s, C-17), 161.53 (s, C-5), 173.01 (s, C-23), 182.20 (s, C-18), and 184.23 (s, C-21); FABMS (negative, glycerol matrix) *m/z* 402 (M+2H−H)$^-$; HRFABMS *m/z* 402.2278 (M+2H−H)$^-$, calcd for $C_{23}H_{32}NO_5$ 402.2281.

3.3.2. Metachromin M (2). Red amorphous solid; $[\alpha]_D^{23}$ +25 (*c* 0.2, MeOH); IR (film) ν_{max} 3300, 1720, 1650, 1590, 1510, 1380, and 1210 cm^{-1}; UV (MeOH) λ_{max} 314 (ε 12,800), and 498 nm (970); ^{1}H NMR ($CDCl_3/CD_3OD$, 95:5) δ 0.79 (3H, s, H_3-14), 0.85 (3H, d, *J*=7.0 Hz, H_3-13), 1.07 (1H, m, H-1b), 1.15 (1H, m, H-7b), 1.25 (1H, m, H-7a), 1.37 (1H, m, H-1a), 1.57 (1H, m, H-5), 1.60 (3H, br s, H_3-12), 1.70 (3H, br s, H_3-15), 1.89 (4H, m, H_2-2 and H_2-8), 3.06 (2H, br d, *J*=7.0 Hz, H_2-11), 3.82 (2H, s, H_2-22), 5.10 (1H, br t, *J*=7.0 Hz, H-10), 5.21 (1H, br s, H-3), and 5.23 (1H, s, H-19); ^{13}C NMR (CD_3OD) δ 15.99 (q, C-13), 17.24 (q, C-15), 23.27 (t, C-11), 23.87 (q, C-12), 24.00 (q, C-14), 24.62 (t, C-2), 31.06 (t, C-1), 35.28 (t, C-8), 35.89 (s, C-6), 40.05 (t, C-7), 44.70 (d, C-5), 45.66 (t, C-22), 94.61 (d, C-19), 117.65 (s, C-16), 121.50 (d, C-3), 122.08 (d, C-10), 139.05 (s, C-4), 139.40 (s, C-9), 151.61 (s, C-20), 158.15 (s, C-17), 172.77 (s, C-23), 182.25 (s, C-18), and 184.24 (s, C-21); FABMS (negative, glycerol matrix) *m/z* 402 (M+2H−H)$^-$; HRFABMS *m/z* 402.2285 (M+2H−H)$^-$, calcd for $C_{23}H_{32}NO_5$ 402.2281.

3.3.3. Metachromin N (3). Red amorphous solid; $[\alpha]_D^{24}$ +38 (*c* 0.2, MeOH); IR (film) ν_{max} 3310, 1720, 1650, 1590, 1520, 1380, and 1210 cm^{-1}; UV (MeOH) λ_{max} 326 (ε 10,000), and 492 nm (730); ^{1}H NMR (CD_3OD) δ 1.00 (1H, m, H-2b), 1.02 (1H, m, H-3b), 1.06 (3H, d, *J*=6.3 Hz, H_3-12), 1.08 (3H, s, H_3-14), 1.28 (1H, m, H-1b), 1.28 (3H, d, *J*=5.8 Hz, H_3-25), 1.5–1.7 (4H, m, H-1a, H-2a, and H_2-7), 1.80 (1H, m, H-3a), 1.80 (3H, br s, H_3-15), 2.39 (1H, m, H-4), 3.14 (2H, br d, *J*=6.3 Hz, H_2-11), 4.02 (1H, m, H-22), 4.40 (1H, m, H-24), 4.74 (1H, s, H-13b), 4.75 (1H, s, H-13a), 5.21 (1H, br t, *J*=6.3 Hz, H-10), and 5.37 (1H, s, H-19); ^{13}C NMR (CD_3OD) δ 17.27 (q, C-15), 20.84 (q, C-12), 21.52 (q, C-25), 23.33 (t, C-11), 23.66 (t, C-2), 26.11 (q, C-14), 36.00 (d, C-4), 36.08 (t, C-8), 39.20 (t, C-3), 40.76 (t, C-1), 41.18 (s, C-6), 42.23 (t, C-7), 63.05 (d, C-22), 69.45 (d, C-24), 94.78 (d, C-19), 105.10 (t, C-13), 117.63 (s, C-16), 122.17 (d, C-10), 139.07 (s, C-9), 151.74 (s, C-20), 158.40 (s, C-17), 161.53 (s, C-5), 174.04 (s, C-23), 182.49 (s, C-18), and 184.11 (s, C-21); FABMS (negative, glycerol matrix) *m/z* 446 (M+2H−H)$^-$; HRFABMS *m/z* 446.2535 (M+2H−H)$^-$, calcd for $C_{25}H_{36}NO_6$ 446.2543.

3.3.4. Metachromin O (4). Red amorphous solid; $[\alpha]_D^{24}$ +36 (*c* 0.2, MeOH); IR (film) ν_{max} 3320, 1720, 1650, 1590, 1510, 1380, and 1210 cm^{-1}; UV (MeOH) λ_{max} 328 (ε 8900), and 498 nm (670); ^{1}H NMR ($CDCl_3/CD_3OD$, 95:5) δ 0.76 (3H, s, H_3-14), 0.82 (3H, d, *J*=6.9 Hz, H_3-13), 1.03 (1H, m, H-1b), 1.12 (1H, ddd, *J*=12.8, 12.8, and 5.0 Hz, H-7b), 1.19 (3H, d, *J*=6.0 Hz, H_3-25), 1.22 (1H, ddd, *J*=13.0, 13.0, and 4.9 Hz, H-7a), 1.33 (1H, m, H-1a), 1.54 (1H, q, *J*=7.3 Hz, H-5), 1.57 (3H, br s, H_3-12), 1.67 (3H, br s, H_3-15), 1.85 (4H, m, H_2-2 and H_2-8), 3.03 (2H, br d, *J*=7.1 Hz, H_2-11), 3.81 (1H, m, H-22), 4.29 (1H, m, H-24), 5.07 (1H, br t, *J*=6.6 Hz, H-10), 5.18 (1H, br s, H-3), and 5.25 (1H, s, H-19); ^{13}C NMR (CD_3OD) δ 16.00 (q, C-13), 17.25 (q, C-15), 21.52 (q, C-25), 23.33 (t, C-11), 23.87 (q, C-12), 24.00 (q, C-14), 24.63 (t, C-2), 31.07 (t, C-1), 35.30 (t, C-8), 35.91 (s, C-6), 40.06 (t, C-7), 44.71 (d, C-5), 63.09 (d, C-22), 69.44 (d, C-24), 94.76 (d, C-19), 117.61 (s, C-16), 121.50 (d, C-3), 122.10 (d, C-10), 139.04 (s, C-4), 139.41 (s, C-9), 151.70 (s, C-20), 158.31 (s, C-17), 174.16 (s, C-23), 182.46 (s, C-18), and 184.11 (s, C-21); FABMS (negative, glycerol matrix) *m/z* 446 (M+2H−H)$^-$; HRFABMS *m/z* 446.2532 (M+2H−H)$^-$, calcd for $C_{25}H_{36}NO_6$ 446.2543.

3.3.5. Metachromin P (5). Red amorphous solid; $[\alpha]_D^{23}$ +67 (*c* 0.15, MeOH); IR (film) ν_{max} 3320, 1720, 1680, 1590, 1540, 1380, and 1210 cm^{-1}; UV (MeOH) λ_{max} 336 (ε 7100), and 497 nm (310); ^{1}H NMR (CD_3OD) δ 1.00 (1H, m, H-2b), 1.02 (1H, m, H-3b), 1.06 (3H, d, *J*=6.7 Hz, H_3-12), 1.07 (3H, s, H_3-14), 1.30 (1H, ddd, *J*=12.7, 12.7, and 4.0 Hz, H-1b), 1.4–1.6 (4H, m, H-1a, H-2a, and H_2-7), 1.68 (1H, m, H-3a), 1.79 (3H, br s, H_3-15), 2.38 (1H, m, H-4), 3.12 (2H, br d, *J*=7.1 Hz, H_2-11), 3.95 (2H, m, H_2-24), 4.16 (1H, m, H-22), 4.73 (1H, s, H-13b), 4.75 (1H, s, H-13a), 5.21 (1H, br t, *J*=7.1 Hz, H-10), and 5.37 (1H, s, H-19); ^{13}C NMR (CD_3OD) δ 17.27 (q, C-15), 20.82 (q, C-12), 23.31 (t, C-11), 23.65 (t, C-2), 26.10 (q, C-14), 35.97 (d, C-4), 36.06 (t, C-8), 39.19 (t, C-3), 40.74 (t, C-1), 41.15 (s, C-6), 42.21 (t, C-7), 59.30 (d, C-22), 62.86 (t, C-24), 94.95 (d, C-19), 105.08 (t, C-13), 117.71 (s, C-16), 122.13 (d, C-10), 139.03 (s, C-9), 150.77 (s, C-20), 158.21 (s, C-17), 161.50 (s, C-5), 173.19 (s, C-23), 182.45 (s, C-18), 184.13 (s, C-21); FABMS (negative, glycerol matrix) *m/z* 432 (M+2H−H)$^-$; HRFABMS *m/z* 432.2381 (M+2H−H)$^-$, calcd for $C_{24}H_{34}NO_6$ 432.2386.

3.3.6. Metachromin Q (6). Red amorphous solid; $[\alpha]_D^{23}$ +35 (*c* 0.15, MeOH); IR (film) ν_{max} 3420, 1720, 1680, 1600, 1560, 1380, and 1210 cm^{-1}; UV (MeOH) λ_{max} 336 (ε 6500), and 498 nm (310); ^{1}H NMR (CD_3OD) δ 0.90 (3H, s, H_3-14), 0.95 (3H, d, *J*=7.1 Hz, H_3-13), 1.16 (1H, m, H-1b), 1.25 (1H, m, H-7b), 1.35 (1H, m, H-7a), 1.47 (1H, m, H-1a), 1.68 (1H, m, H-5), 1.68 (3H, br s, H_3-12), 1.78 (3H, br s, H_3-15), 1.98 (4H, m, H_2-2 and H_2-8), 3.12 (2H, br d, *J*=7.1 Hz, H_2-11), 4.00 (2H, m, H_2-24), 4.14 (1H, m, H-22), 5.19 (1H, br t, *J*=7.1 Hz, H-10), 5.29 (1H, br s, H-3), and 5.38 (1H, s, H-19); ^{13}C NMR (CD_3OD) δ 16.00 (q, C-13), 17.25 (q, C-15), 23.31 (t, C-11), 23.87 (q, C-12), 23.99 (q, C-14), 24.62 (t, C-2), 31.07 (t, C-1), 35.27 (t, C-8), 35.89 (s, C-6), 40.05 (t, C-7), 44.70 (d, C-5), 59.39 (d, C-22), 62.91 (t, C-24), 94.93 (d, C-19), 117.71 (s, C-16), 121.50 (d, C-3), 122.07 (d, C-10), 139.05 (s, C-4), 139.39 (s, C-9), 150.82 (s, C-20), 158.19 (s, C-17), 173.28 (s, C-23), 182.43 (s, C-18), 184.17 (s, C-21); FABMS (negative, glycerol matrix) *m/z* 432 (M+2H−H)$^-$; HRFABMS *m/z* 432.2393 (M+2H−H)$^-$, calcd for $C_{24}H_{34}NO_6$ 432.2393.

3.3.7. Metachromin L (1) derived from metachromin A (7). A mixture of **7** (5.6 mg, 16 μmol) and glycine (5.0 mg, 67 μmol) in EtOH (1 mL) was stirred at 35 °C for 72 h in the presence of $NaHCO_3$ (60.3 mg, 718 μmol). After filtration, the filtrate was evaporated to dryness, and the residue was purified by reversed-phase HPLC (Luna 5u phenylhexyl, 5 μm, Phenomenex, 10×250 mm; eluent, MeCN/

H_2O/TFA, 65:35:0.05; flow rate, 3.0 mL/min; UV detection at 300 nm) to afford **1** (0.9 mg, 2.2 μmol, 14%).

3.3.8. Metachromin M (2) derived from metachromin C (8). Metachromin M (**2**, 1.5 mg, 3.7 μmol) was obtained from **8** (5.0 mg, 14 μmol), glycine (4.0 mg, 53 μmol), EtOH (1 mL), and $NaHCO_3$ (54.8 mg, 652 mmol) in 27% yield by the same procedure as described above.

3.3.9. Metachromin N (3) derived from metachromin A (7). Metachromin N (**3**, 3.1 mg, 7.0 μmol) was obtained from **7** (5.2 mg, 15 μmol), L-threonine (5.2 mg, 44 μmol), EtOH (1 mL), and $NaHCO_3$ (56.2 mg, 669 μmol) in 48% yield by the same procedure as described above.

3.3.10. Metachromin O (4) derived from metachromin C (8). Metachromin O (**4**, 3.9 mg, 8.8 μmol) was obtained from **8** (5.7 mg, 16 μmol), L-threonine (4.8 mg, 40 μmol), EtOH (1 mL), and $NaHCO_3$ (54.6 mg, 650 μmol) in 55% yield by the same procedure as described above.

3.3.11. Metachromin P (5) derived from metachromin A (7). Metachromin P (**5**, 1.8 mg, 4.2 μmol) was obtained from **7** (3.2 mg, 8.9 μmol), L-serine (3.3 mg, 31 μmol), EtOH (1 mL), and $NaHCO_3$ (50.3 mg, 599 μmol) in 47% yield by the same procedure as described above.

3.3.12. Metachromin Q (6) derived from metachromin C (8). Metachromin Q (**6**, 1.8 mg, 4.2 μmol) was obtained from **7** (3.9 mg, 37.1 μmol), L-serine (3.9 mg, 37.1 μmol), EtOH (1 mL), and $NaHCO_3$ (55.5 mg, 661 μmol) in 44% yield by the same procedure as described above.

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References and notes

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