Tetrahedron 65 (2009) 1276–1280

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of bischromones by deformylative Mannich type reaction on chromone-3-carbaldehyde using α-aminoacid as the source of amine

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ARTICLE INFO

Article history:
Received 4 October 2008
Received in revised form 4 December 2008
Accepted 20 December 2008
Available online 25 December 2008

Keywords:
3-Formylchromone
Mannich reaction
Bischromone
1-Benzopyran
α-Aminoacids
Deformylation

ABSTRACT

Chromone-3-carbaldehyde reacts with *N*-methylglycine or glycine in the presence of excess formaldehyde to produce *N*-(chromone-3-ylmethyl)-*N*-methylglycine or *N*,*N*-di(chromone-3-ylmethyl)glycine, respectively, by a deformylative Mannich type reaction. Use of alanine or leucine or methionine in place of glycine produces *N*-(chromone-3-ylmethyl)alanine/-leucine/-methionine, respectively.

1. Introduction

A large number of HIV-1 integrase inhibitors have common two aryl units separated by a central linker.[1] Majority of the bischromones (Fig. 1) so far synthesized are pharmaceutically important. Bischromones linked through their 5- or 6-position and having ester or carboxylic acid functionalities at their 2,2′-positions are inhibitors of certain types of antigen–antibody reactions and can cure hay fever, urticaria and viral infections. They can be compounded with bronchodilators when used in inhalation preparations.[2] Disodium cromoglycate is a well-known antiasthmatic and antiallergic compound. Its nature of binding to human serum albumin has also been determined.[3] A khellin-based 7,7′-glycerol-bridged bischromone exhibits more effective anaphylactic activity than cromoglycate.[4] 3,3′-Biscoumarin linked through nitrogen of an alkanamide inhibits the activity of the A and B isoforms of monoamine oxidase (MAO).[5] Nebivolol, a 2,2′-bischroman tethered by 3-aza-1,5-pentanediol moiety, is an antihypertensive drug.[6]

It has been observed that activities of bischromones depend on (i) the position of attachment of two rings, (ii) the length and nature of linker and (iii) attainment of coplanarity of the two chromone rings.[7] So synthesis of bischromones having suitable linkers and effective linking sites are of great importance. A few 3,3′-bischromones having a methylene bridge were obtained in the course of Mannich type reaction on 2-(*N*,*N*-dimethylaminonaphthopyrone) in the presence of a large amount of acetic acid or by heating the Mannich base with acetic anhydride for several hours.[8]

In continuation to our earlier studies on the electrocyclic ring closure of azomethine ylide, derived from **1** and **3** (R^1=Me),[9] and 1,3-dipolar cycloaddition of azomethine ylide, derived from **3** and ninhydrin, with the C2–C3 double bond of **1**,[10] acetal **2** was considered to act as dipolarophile. But, on heating an equimolar mixture of acetal **2**, **3** (R^1=Me) and ninhydrin under reflux in methanol for 15 h gave unreacted acetal **2** (80%) and dispiro compound **5**[10] in 25% yield. Compound **5** was obtained by the dimerization of azomethine ylide, generated from **3** (R^1=Me) and ninhydrin. So, to utilize the C_2–C_3 double bond of **1** as a dipolarophile in the presence of suitable azomethine ylide in a one-pot reaction, azomethine ylide must be generated in situ using a carbonyl compound having higher carbonyl group reactivity than **1**. Like ninhydrin, formaldehyde also possesses higher carbonyl group reactivity than **1**. The

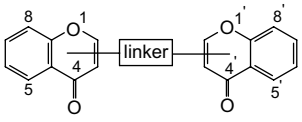

Figure 1. General structure of bischromone.

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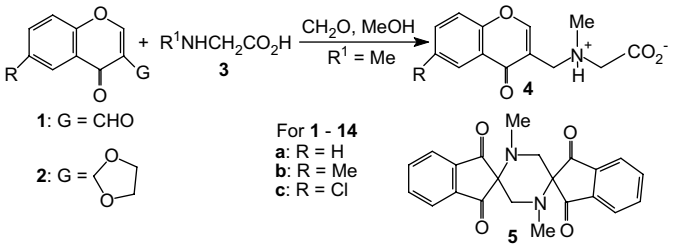
doi:10.1016/j.tet.2008.12.065

Table 1
Results of the reactions between equimolar amounts of **1** and **3** in the presence of excess formaldehyde in methanol

Entry	R	R^1	Source of formaldehyde	Time (h)	Product	Yield (%)	Mp (°C)
1	H	Me	A	25	**4a**	40	196–198
2	Me	Me	A	24	**4b**	42	124–126
3	Cl	Me	A	27	**4c**	35	174–176
4	H	Me	B	5	**4a**	73	196–198
5	Me	Me	B	3	**4b**	60	124–126
6	Cl	Me	B	4.5	**4c**	57	174–176
7[a]	Me	Me	A	40	**4b**	38	124–126
8	H	CH_3CO	B	27	**9a**	25	202–204
9	Me	CH_3CO	B	35	**9b**	15	226–228
10	H	H	B	2	**9a**	20	202–204
11	Me	H	B	2.5	**9b**	18	226–228
12[b]	H	H	B	4	**9a**	62	202–204
13[b]	Me	H	B	4	**9b**	65	226–228
14[b]	Cl	H	B	8	**9c**	50	212–214

A: paraformaldehyde; B: 37% aqueous formaldehyde solution.
[a] Ethanol was used in place of methanol.
[b] 2:1 molar ratio of **1** and **3** was used.



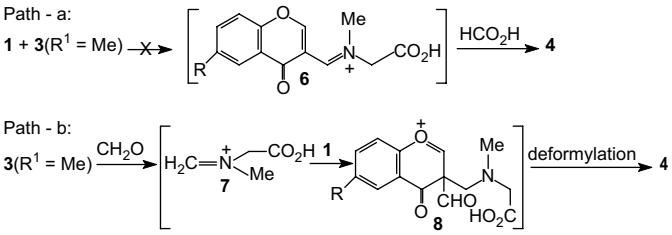
Scheme 1. Synthesis of **4**.

results of the reactions of **1** with **3** in the presence of formaldehyde are reported herein.

2. Results and discussion

A mixture of **1** (1 mmol), **3** (R^1=Me, 1 mmol) and paraformaldehyde (2.5 mmol) in methanol (25 mL) was heated under reflux for several hours (Table 1, entries 1–3). Excess paraformaldehyde was filtered off and solvent was removed under reduced pressure to afford a white solid, which was washed with water and crystallized from methanol to afford **4** (Scheme 1). The structure of compound **4** was established on the basis of IR, NMR and mass spectral analyses. It was further confirmed by single crystal X-ray diffraction (Fig. 2). A few water molecules are present in the crystal structure. ^{1}H NMR spectrum of **4a** corroborates this observation. However, for simplification, structure of an independent molecule of **4a** is displayed in Figure 2 without showing the water molecules.[11] Use of formalin in place of paraformaldehyde improves the yield and reduces the reaction time (entries 4–6). Formation of **4** may be rationalized via the formation of iminium ion **6** and subsequent reduction by HCOOH, which may be present as an impurity with formaldehyde (Scheme 2, path a) or by considering deformylative Mannich type reaction (Scheme 2, path b). To check the feasibility of path a, an equimolar mixture of **1**, **3** (R^1=Me) and HCOOH in methanol was heated under reflux for 20 h, but compound **4** was not formed. So, path a was ruled out. Formation of iminium ion **7** and its interception by **1** using the enol ether moiety leads to the formation of **8**, which on deformylation produces **4** (Scheme 2, path b). Solvent or water molecule may initiate the deformylation. Use of ethanol in place of methanol showed no considerable change (Table 1, entry 7). Literature survey revealed that the use of aminoacid as amine component in Mannich reaction is scarce.[12] Reaction of some aminoacids with kojic acid in the presence of formalin,[13] exchange reactions between Mannich bases and α-aminoacids[14] and use of chiral aminoacids as organocatalyst in the asymmetric Mannich reaction[15] have been reported. To the best of our knowledge it is the first example of deformylative Mannich type reaction.

For the study of chromone-based β-turn peptidomimetics, aminomethyl group was introduced at the C-3 position of chromone ring.[16] 3-Morpholinomethylchromones are used in cosmetics and dermatological products especially for the treatment of hyperpigmentation.[17] These reports encouraged us to study the reactions for the introduction of an aminomethyl group at the



Scheme 2. Plausible mechanism for the formation of **4**.

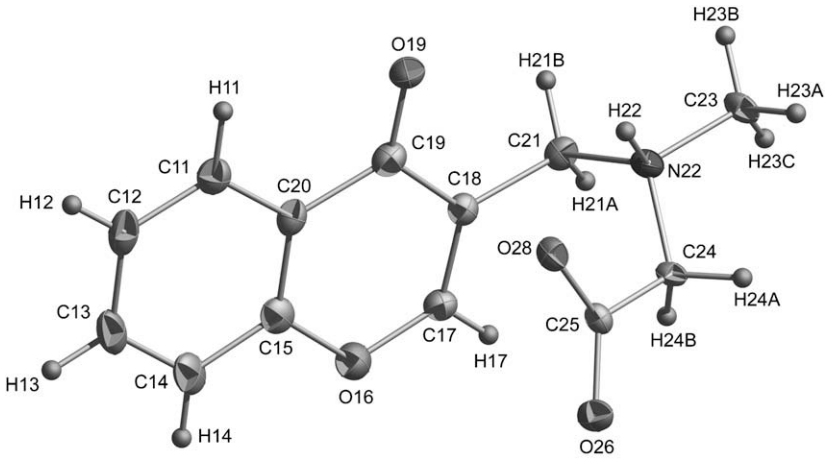
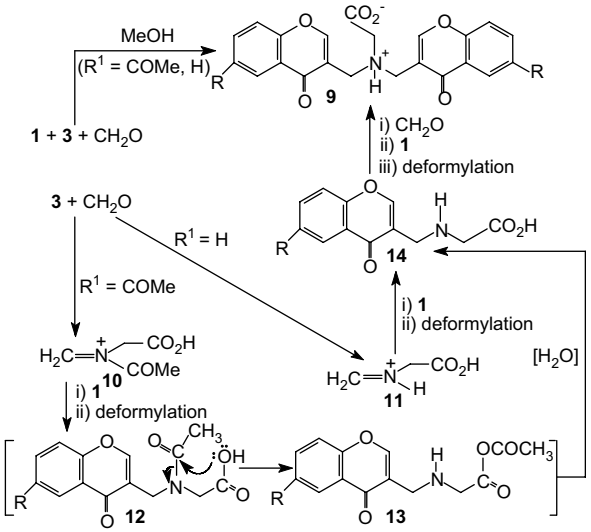


Figure 2. ORTEP drawing of one of the independent molecules of compound **4a** (the compound crystallized in hydrated form with four molecules of **4a** and seven water molecules) in the asymmetric part of the unit cell.

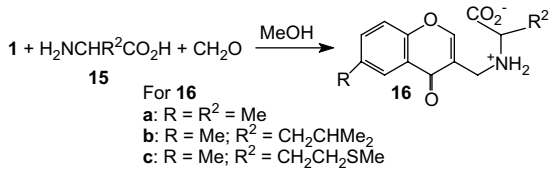
3-position of chromone ring where the amino group is a part of an α-aminoacid. Reaction of **1** with *N*-acetylglycine (**3**, R^1=$COCH_3$) in methanol in the presence of formaldehyde produced a compound, which was found to contain chromone ring but no acetyl group from its ^{1}H NMR spectrum. Considering deacetylation in the reaction medium the above reaction was repeated using glycine in place of acetylglycine. Interestingly, the same compound **9** was obtained in a much shorter reaction time (Table 1, entries 8–11). The structure of the compound was determined on the basis of IR, NMR and mass spectral analyses. Compound **9** was obtained from **1**, glycine and formaldehyde as a result of a double deformylative Mannich type reaction via **11** and **14** (Scheme 3), whereas formation of **9** using acetylglycine may be rationalized as follows. Compound **1** reacts with iminium ion **10**, derived from **3** (R^1=COMe) and formaldehyde, followed by deformylation leads to **12**. It undergoes acyl transfer to produce anhydride **13**, which on subsequent hydrolysis gives **14**. It undergoes further deformylative Mannich type reaction to produce **9** (Scheme 3). The proposed mechanism requires the molar ratios of **1**, **3** and CH_2O to be 2:1:2. Indeed, the reaction afforded better yield when it was carried out using 2:1 molar ratios of **1** and **3** in the presence of excess formalin (entries 12–14). It is to be noted that in ^{1}H NMR spectra of **4**, **9** and **18**, signals corresponding to the protons of carboxylic acid groups or the NH protons of the zwitterions were not obtained. However, the X-ray structure of **4a** proved the zwitterionic structure. Both compounds **4** and **9** can be used as fluorescent markers for peptides.[18]



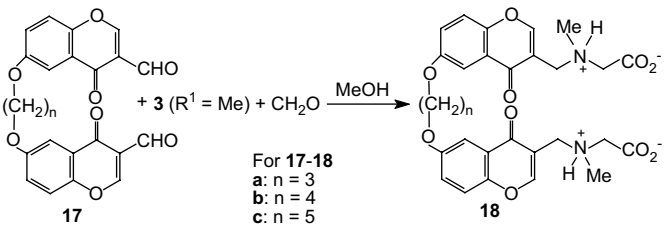
Scheme 3. Reaction and mechanism for the formation of **9**.

On performing similar reactions using α-aminoacids **15** (other than glycine) it was observed that products **16a–c** arise from monodeformylative Mannich type reaction even after using 2:1 molar ratios of **1** and **15** (Scheme 4). Steric interaction may be responsible for inhibiting the formation of bischromones.[13]

Deformylative Mannich type reaction was further extended to 3,3′-diformyl-6,6′-bischromones **17**.[19] Bischromones **17** react with



Scheme 4. Deformylative Mannich type reaction using aminoacids other than glycine.



Scheme 5. Deformylative Mannich type reaction on bischromones.

sarcosine (**3**, R^1=Me) in the presence of formaldehyde to produce bischromone-linked aminoacids **18** (Scheme 5). Like our earlier reports,[9,19,20] here also methylene protons for polymethylenedioxy chain appear as singlet in **18b**, although they appear with their usual multiplicities in **18a** and **18c**. This anomaly could not be explained.

3. Conclusion

In conclusion, we have developed a hitherto unreported deformylative Mannich type reaction on chromone-3-carbaldehyde and this methodology has been utilized for the synthesis of 3,3′-bischromones having α-aminoacid linker. The resulting products are of considerable importance from the pharmaceutical point of view and also can act as fluorescent marker.

4. Experimental

4.1. General

The recorded mps are uncorrected. IR spectra were recorded in KBr on a Beckman IR 20a, ^{1}H NMR/^{13}C NMR spectra on a Bruker 300 MHz/75 MHz spectrometer in DMSO-d_6 unless stated otherwise, mass spectra on a Qtof Micro YA 263 instrument and elemental analysis on a Perkin Elmer 240c elemental analyzer. Light petroleum refers to the fraction with 60–80 °C. All chemicals used are of commercial grade and are used as such. Chromone-3-carbaldehydes **1a–c** were prepared according to the literature procedure.[21]

4.2. General procedure for the synthesis of *N*-(chromon-3-ylmethyl)-*N*-methylglycines (4a–c)

A mixture of aldehyde **1** (1 mmol), sarcosine (**3**, R^1=Me) (90 mg, 1 mmol) and 37% aqueous solution of formaldehyde (0.6 mL) in methanol (25 mL) was heated under reflux for 3–5 h. The reaction mixture on concentration and cooling produced a white solid, which was washed with water and crystallized from methanol to afford **4** as white crystalline solids.

*4.2.1. N-(Chromon-3-ylmethyl)-N-methylglycine (**4a**)*

Yield 73%, mp 196–198 °C; IR 3434, 1635, 1475, 1400 cm^{-1}; ^{1}H NMR δ 2.37 (s, 3H, N–CH_3), 3.28 (s, 2H, N–CH_2–COO^-), 3.63 (s, 2H, N–CH_2), 4.50–5.32 (br s, exchangeable, 4H, 2×H_2O),[11] 7.47–7.52 (m, 1H, 6-H), 7.65 (br d, 1H, 8-H, *J*=8.4 Hz), 7.78–7.83 (m, 1H, 7-H), 8.07 (br d, 1H, 5-H, *J*=7.8 Hz), 8.33 (s, 1H, 2-H); ^{13}C NMR δ 41.4, 50.5, 57.7, 118.4, 119.4, 123.3, 125.1, 125.4, 134.2, 155.8, 155.9, 171.2, 176.6; mass *m*/*z* 248 (M^++H), 270 (M^++Na). Anal. Calcd for $C_{13}H_{13}NO_4\cdot 2H_2O$: C, 55.12; H, 6.05; N, 4.94. Found: C, 54.90; H, 6.14; N, 5.01.

*4.2.2. N-(6-Methylchromon-3-ylmethyl)-N-methylglycine (**4b**)*

Yield 60%, mp 124–126 °C; IR 3436,1641, 1485, 1401 cm^{-1}; ^1H NMR δ 2.39 (s, 3H, N–CH_3), 2.41 (s, 3H, $ArCH_3$), 3.28 (s, 2H, N–CH_2COO^-), 3.64 (s, 2H, N–CH_2), 4.25–4.75 (br s, exchangeable, 4H, 2×H_2O), 7.52 (d, 1H, 8-H, J=8.3 Hz), 7.60 (br d, 1H, 7-H, J=8.3 Hz), 7.83 (br s, 1H, 5-H), 8.30 (s, 1H, 2-H); mass m/z 262 (M^++H), 284 (M^++Na). Anal. Calcd for $C_{14}H_{15}NO_4\cdot 2H_2O$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.65; H, 6.33; N, 4.62.

*4.2.3. N-(6-Chlorochromon-3-ylmethyl)-N-methylglycine (**4c**)*

Yield 57%, mp 174–176 °C; IR 3467, 1650, 1611, 1466 cm^{-1}; ^1H NMR δ 2.35 (s, 3H, N–CH_3), 3.27 (s, 2H, N–CH_2COO^-), 3.59 (s, 2H, N–CH_2), 3.66–4.40 (br s, exchangeable, 4H, 2×H_2O), 7.74 (d, 1H, 8-H, J=8.9 Hz), 7.86 (dd, 1H, 7-H, J=8.9, 2.4 Hz), 7.99 (d, 1H, 5-H, J=2.4 Hz), 8.35 (s, 1H, 2-H). Anal. Calcd for $C_{13}H_{12}NClO_4\cdot 2H_2O$: C, 49.14; H, 5.08; N, 4.41. Found: C, 48.92; H, 5.20; N, 4.32.

4.3. General procedure for the synthesis of *N,N*-di-(chromon-3-ylmethyl)glycines (9a–c)

A methanolic solution (25 mL) of **1** (2 mmol), glycine (1 mmol) and 37% aqueous solution of formaldehyde (1 mL) was heated under reflux for 4–8 h. On concentration the reaction mixture afforded a white solid, which was washed with water and crystallized from methanol to produce white crystalline solids **9**.

*4.3.1. N,N-Di-(chromon-3-ylmethyl)glycine (**9a**)*

Yield 62%, mp 202–204 °C; IR 3433, 1660, 1636, 1466 cm^{-1}; ^1H NMR δ 3.45 (s, 2H, N–CH_2COO^-), 3.67 (s, 4H, 2×N–CH_2), 7.41–7.46 [m, 4H, 2×(6-H+8-H)], 7.68 (br t, 2H, 2×7-H, J=7.5 Hz), 8.06 (s, 2H, 2×2-H), 8.23 (br d, 2H, 5-H, J=7.7 Hz); mass m/z 391 (M^+), 414 (M^++Na). Anal. Calcd for $C_{22}H_{17}NO_6$: C, 67.52; H, 4.38; N, 3.58. Found: C, 67.62; H, 4.30; N, 3.50.

*4.3.2. N,N-Di-(6-methylchromon-3-ylmethyl)glycine (**9b**)*

Yield 65%, mp 226–228 °C; IR 3430, 1650, 1635, 1470 cm^{-1}; ^1H NMR δ 2.41 (s, 6H, 2×$ArCH_3$), 3.38 (s, 2H, N–CH_2COO^-), 3.65 (s, 4H, 2×N–CH_2), 7.51 (d, 2H, 2×8-H, J=8.3 Hz), 7.59 (br d, 2H, 2×7-H, J=8.3 Hz), 7.83 (br s, 2H, 2×5-H), 8.38 (s, 2H, 2×2-H); ^{13}C NMR δ 20.4, 48.6, 54.5, 118.1, 120.2, 122.9, 124.2, 134.8, 135.0, 154.2, 155.4, 172.5, 176.6. Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.82; H, 4.92; N, 3.27.

*4.3.3. N,N-Di(6-chlorochromon-3-ylmethyl)glycine (**9c**)*

Yield 50%, mp 212–214 °C; IR 3400, 1645, 1640, 1440 cm^{-1}; ^1H NMR δ 3.52 (s, 2H, N–CH_2COO^-), 3.67 (s, 4H, 2×N–CH_2), 7.70 (d, 2H, 2×8-H, J=8.3 Hz), 7.82 (br d, 2H, 2×7-H, J=8.3 Hz), 7.95 (br s, 2H, 2×5-H), 8.44 (s, 2H, 2×2-H). Anal. Calcd for $C_{22}H_{15}NCl_2O_6$: C, 57.41; H, 3.28; N, 3.04. Found: C, 57.58; H, 3.20; N, 2.95.

4.4. General procedure for the synthesis of *N*-(chromon-3-ylmethyl)-2-substituted glycines (16a–c)

To a methanolic solution (25 mL) of 6-methylchromone-3-carbaldehyde **1b** (188 mg, 1 mmol) and 2-substituted glycine **15** (1 mmol), 37% aqueous solution of formaldehyde (0.6 mL) was added. The reaction mixture was heated under reflux for 2 h. On concentration, the reaction mixture produced a dirty yellow crystalline compound. It was washed with water, dried and digested with $CHCl_3$ and filtered. The residue was crystallized from methanol to produce white solids **16a–c**.

*4.4.1. DL-N-(6-Methylchromon-3-ylmethyl)alanine (**16a**)*

Yield 46%, mp 196–198 °C; IR 3400, 3000, 2850, 1640, 1610 cm^{-1}; ^1H NMR δ 1.25 (d, 3H, CH_3, J=6.5 Hz), 2.43 (s, 3H, $ArCH_3$), 3.24 (q, 1H, C*H*Me, J=6.5 Hz), 3.35–3.57 (br s, exchangeable, 2H, $^+NH_2$), 3.72 (s, 2H, N–CH_2), 7.57 (d, 1H, 8-H, J=8.4 Hz), 7.65 (br d, 1H, 7-H, J=8.4 Hz), 7.86 (br s, 1H, 5-H), 8.38 (s, 1H, 2-H); ^{13}C NMR δ 17.2, 20.4, 41.6, 56.2, 118.3, 119.3, 122.8, 124.2, 135.1, 135.4, 154.2, 155.4, 173.3, 176.4; mass m/z 262 (M^++H), 284 (M^++Na). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.21; H, 5.82; N, 5.22.

*4.4.2. L-N-(6-Methylchromon-3-ylmethyl)leucine (**16b**)*

Yield 43%, mp 194–196 °C; IR 3448, 2956, 2870, 1647, 1618 cm^{-1}; ^1H NMR (CD_3OD) δ 0.98 (d, 3H, CH_3, J=6.4 Hz), 1.01 (d, 3H, CH_3, J=6.5 Hz), 1.62–1.72 (m, 1H, C*H*Me_2), 1.76–1.90 (m, 2H, CH_2), 2.50 (s, 3H, $ArCH_3$), 3.54–3.61 (m, 1H, N–CH), 4.12 (s, 2H, N–CH_2), 7.55 (d, 1H, 8-H, J=8.5 Hz), 7.68 (br d, 1H, 7-H, J=8.5 Hz), 8.00 (br s, 1H, 5-H), 8.41 (s, 1H, 2-H). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.20; H, 7.08; N, 4.51.

*4.4.3. L-N-(6-Methylchromon-3-ylmethyl)methionine (**16c**)*

Yield 45%, mp 196–198 °C; IR 3440, 2900, 1650, 1600 cm^{-1}; ^1H NMR δ 1.76–1.90 (m, 2H, CH_2), 2.02 (s, 3H, SCH_3), 2.43 (s, 3H, $ArCH_3$), 2.53–2.63 (m, 2H, CH_2), 3.16–3.28 (m, 1H, N–CH), 3.30–3.50 (br s, exchangeable, 2H, $^+NH_2$), 3.64 (s, 2H, N–CH_2), 7.56 (d, 1H, 8-H, J=8.7 Hz), 7.63 (dd, 1H, 7-H, J=8.7, 1.8 Hz), 7.85 (d, 1H, 5-H, J=1.8 Hz), 8.33 (s, 1H, 2-H). Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.69; H, 5.85; N, 4.30.

4.5. General procedure for the synthesis of 6,6′-(α,ω-polymethylenedioxy)di-(*N*-[chromon-3-ylmethyl]-*N*-methylglycines) (18a–c)

A methanolic suspension (50 mL) of bischromone-3,3′-dicarbaldehyde **17** (0.5 mmol), sarcosine (90 mg, 1 mmol) and 37% aqueous solution of formaldehyde (1 mL) was heated under reflux. After 1.5 h of heating, a clear solution was obtained and disappearance of dialdehyde **17** from the reaction mixture was observed by TLC. On concentration the reaction mixture produced a solid, which was washed with water, dried in air and treated with chloroform under reflux for 10 min and filtered hot. The residue was crystallized from methanol to afford white amorphous solids **18**.

*4.5.1. 6,6′-(α,ω-Trimethylenedioxy)di-(N-[chromon-3-ylmethyl]-N-methylglycine) (**18a**)*

Yield 70%, mp 130–132 °C (decomp.); IR 3074, 1640, 1486, 1468 cm^{-1}; ^1H NMR δ 2.25 (quintet, 2H, CH_2, J=5.8 Hz), 2.35 (s, 6H, 2×N–CH_3), 3.27 (s, 4H, 2×CH_2COO^-), 3.62 (s, 4H, 2×N–CH_2), 4.26 (t, 4H, 2×OCH_2, J=5.8 Hz), 7.43 (dd, 2H, 2×7-H, J=8.8, 2.8 Hz), 7.46 (d, 2H, 2×5-H, J=2.8 Hz), 7.62 (d, 2H, 2×8-H, J=8.8 Hz), 8.31 (s, 2H, 2×2-H). Anal. Calcd for $C_{29}H_{30}N_2O_{10}$: C, 61.48; H, 5.34; N, 4.94. Found: C, 61.35; H, 5.21; N, 4.84.

*4.5.2. 6,6′-(α,ω-Tetramethylenedioxy)di-(N-[chromon-3-ylmethyl]-N-methylglycine) (**18b**)*

Yield 75%, mp 138–140 °C (decomp.); IR 3075, 1650, 1500, 1460 cm^{-1}; ^1H NMR δ 1.94 (s^{19}, 4H, 2×CH_2), 2.36 (s, 6H, 2×N–CH_3), 3.27 (s, 4H, 2×CH_2COO^-), 3.62 (s, 4H, 2×N–CH_2), 4.16 (s^{19}, 4H, 2×OCH_2), 7.41 (br d, 2H, 2×7-H, J=9.0 Hz), 7.43 (br s, 2H, 2×5-H), 7.61 (d, 2H, 2×8-H, J=9.0 Hz), 8.31 (s, 2H, 2×2-H); mass m/z 603 (M^++Na). Anal. Calcd for $C_{30}H_{32}N_2O_{10}$: C, 62.06; H, 5.56; N, 4.82. Found: C, 62.18; H, 5.48; N, 4.76.

*4.5.3. 6,6′-(α,ω-Pentamethylenedioxy)di-(N-[chromon-3-ylmethyl]-N-methylglycine) (**18c**)*

Yield 72%, mp 130–132 °C (decomp.); IR 3000, 1650, 1515, 1470 cm^{-1}; ^1H NMR δ 1.63 (quintet, 2H, CH_2, J=6.8 Hz), 1.82–1.86 (m, 4H, 2×CH_2), 2.36 (s, 6H, 2×N–CH_3), 3.27 (s, 4H, 2×CH_2COO^-), 3.62 (s, 4H, 2×N–CH_2), 4.10 (t, 4H, 2×OCH_2, J=5.9 Hz), 7.40 (dd, 2H, 2×7-H, J=8.7, 2.5 Hz), 7.42 (d, 2H, 2×5-H, J=2.5 Hz), 7.60 (d, 2H,

2×8-H, J=8.7 Hz), 8.30 (s, 2H, 2×2-H); ^{13}C NMR δ 22.1, 28.2, 41.3, 50.5, 57.6, 68.1, 105.4, 118.3, 120.0, 123.6, 123.9, 150.6, 155.7, 155.9, 171.1, 176.3. Anal. Calcd for $C_{31}H_{34}N_2O_{10}$: C, 62.62; H, 5.76; N, 4.71. Found: C, 62.75; H, 5.62; N, 4.65.

Acknowledgements

We gratefully acknowledge CSIR, New Delhi [Project no. 01(2206)/07/EMR-II] for financial assistance; IICB, Jadavpur and R.K. Mission Residential College, Narendrapur for spectral analysis; Dr. Jishnunil Chakraborty and Dr. Tapas Ghosh for helping with the crystallographic presentation and finally the college authority for providing research facilities.

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11. The single crystal X-ray diffractometric study indicates that compound **4a** crystallizes with seven molecules of water in which four structurally very similar but crystallographically distinct **4a** molecules are present. However, all the hydrogen atoms of water molecules could not be located. For these reason there is a discrepancy in the molecular formula of **4a** obtained by crystallographic data and from C, H, N analysis. Crystal data: $C_{52}H_{63}N_4O_{23}$, M=1112.06, monoclinic, space group $P2_1$, a=9.0999(8), b=19.1473(14), c=15.0649(10) Å, β=90.383(6)°, U=2624.8(3) Å^3, D_{calcd}=1.407 g cm^{-3}, Z=2, Mo Kα radiation (λ=0.71073 Å), μ=0.111 mm^{-1}, T=150 K, 18058 measured reflections, 9721 observed reflections (R_{int}=0.043), R_1=0.0730, wR_2=0.2340 (all data). The structure was solved and refined using SHELXL-97 suite of programs.[22] Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre and allocated deposition number is CCDC 700726.
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