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Complete NMR Assignment of MogrosidesII A_2, II E andIII A_1Isolated from Luo Han Guo

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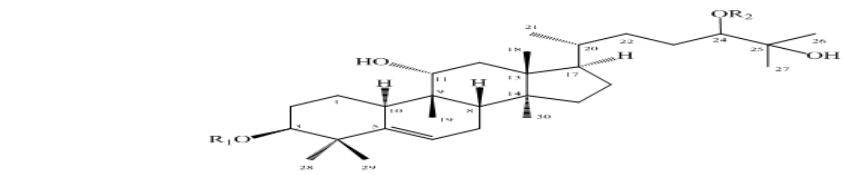
Abstract : *NMR analysis allowed complete assignments of three known mogrol glycosides, Mogroside IIA$_2$ (**1**), II E (**2**)and IIIA$_1$ (**3**), isolated from the extracts of Luo Han Guo. Herein, complete ^{1}H and ^{13}C NMR assignmentsof all threemogrosidesare described based on NMR experiments (^{1}H NMR, ^{13}C NMR, COSY, HSQC-DEPT, HMBC, NOESY and 1DTOCSY) and mass spectral data.*

Keywords:*Mogroside, Structure elucidation, NMR, Luo Han Guo.*

I. Introduction

Due to high demand of non-caloric sweeteners from natural sources, the food industry has been showing great interest in the discovery of high potency sweeteners from plants or fruits. Since the 1970s, steviolglycocidesextracted from the leaves of *Stevia rebaudiana*, such as Rebaudioside A, have been studied extensively and commercialized as zero-calorie high potency sweeteners [1, 2]. By the same token, extracts from the fruit of *Siraitiagrosvenori*mainly grown in southern China, knownas *Luo Han Guo*, have drawn a great deal of attention from the food industry for the development of sweet taste additives [3-7]. More recently, it has been developed into a non-caloric sweetener to compete with other herbal sweeteners such as stevioside [8, 9]. Mogrosideshavebeenused as a traditional medicine for treating conditions such as lung congestion and sore throats [10]. Recently, threeresearch groups reported that mogrosides exhibit antioxidant, antidiabetic and anticancer activities [11-13].The sweet components of *Luo Han Guo*aretriterpene glycosides, known as mogrosides. Mogrosides possess a polycyclic cucurbitane core in common and several derivatives are isolated including Mogroside III, IV, V, II A_2, II E and III A_1. The mixed mogrosides have been estimated to be about 300 times as sweet as sucrose. Among them, Mogroside V is most responsible for sweetness beingabout 400 times sweeter than sucrose. *Luo Han Guo* fruit extracts containing 25 – 55% Mogroside V are a generally recognized as safe (GRAS) non-nutritive sweetener and flavor enhancerin the USA [14], and the purified Mogroside V has been approved as a high-potency sweetening agent in Japan [15].In continuation of our study on the isolation of natural sweeteners from *Lu Han Guo* extracts following Mogroside III A_2 and 11-deoxymogroside III [16], we describe in this report the isolation and full structure elucidation of the three additional mogrosides, II A_2 (**1**), II E (**2**) and III A_1 (**3**) (Figure 1). Compounds **1**, **2** and **3** have been previously reported but their complete NMR assignments have not been published.For Mogroside II A_2 (**1**) the assignments of only the anomeric protons is reported [5] whereas the ^{13}C NMR assignments of Mogroside II E (**2**) are published but the complete ^{1}H NMR assignments are not published [17].For Mogroside III A_1,(**3**) the complete ^{1}H and ^{13}C NMR assignments have been reported [18].Although partial and complete NMR assignments have been reported for Mogroside II E and Mogroside III A_1, respectively, some of the reported assignments arein errorforMogroside II E. In this paper we describe the isolation and complete NMR assignments of compounds**1**, **2** and **3**.



	R_1	R_2
Mogroside II A_2 (1)	β-D-Glc$_V$(1⟶6)-β-D-Glc$_{IV}$-	H
Mogroside II E (2)	β-D-Glc$_{IV}$-	β-D-Glc$_I$-
Mogroside III A_1 (3)	H	[β-D-Glc$_{II}$(1⟶6)]-β-D-Glc$_{III}$(1⟶2)-β-D-Glc$_I$-

Figure 1. Structures ofMogrosides II A_2(**1**), II E (**2**) and III A_1 (**3**)

II. Materials and Methods

The material used for the isolation of Mogroside IIA_2, II E and $IIIA_1$ was *Luo Han Guo* extract (10 g) purchased from Chengdu Biopurify Phytochemicals, China.

General Methods

NMR sampleswerepreparedin CD_3OD (~1.4-2 mg/130-150 µL) and NMR data were acquired on BrukerAvance 500 MHz instruments with either a 2.5 mm inverse probe or a 5 mm broad band probe. The ^1H and ^{13}C NMR spectra were referenced to the solvent resonance at δ_H 3.30 ppm and δ_C 49.0 ppm, respectively. MS and MS/MS data were generated with a Waters QTof Micro mass spectrometer equipped with an electrospray ionization source. The sampleswereanalyzed by negative ESI. The samples (~0.1 mg) werediluted with 50:50 MeCN:H_2Oeither with or without 0.1% NH_4OH and introduced *via* direct infusion.

Isolation and Purification

Primary preparative processing of *Luo Han Guo*extract was performed by purifying on a pre-packed Waters X-Bridge C-18 column using a Waters Delta Prep LC Model 2000/4000 system(Injection: 1~2 g in 15 mL of DMSO and 25 mL of water Mobile phase of solvent system:0.05% HOAc in water (A), 0.05% HOAc in MeCN (B) and 0.5% HOAc in MeOH (C);gradient: 90:10:0 (A:B:C, 0-15 min), 50:50:0 (55 min), 0:100:0 (60-70 min) and then 25:0:75(71-75 min); flow rate:105 mL/min, Detection: UV at 225 nm). Corresponding combined fractions contained mogrosides were subjected to consecutive secondarypreparative purification processing to afford Mogrosides II A_2, IIE and III A_1.

III. Results and Discussion

Compounds **1**, **2** and **3** were isolated as white solids. The ESI-TOF mass spectrum forMogroside II A_2 (**1**) showed a $[M-H]^-$ ion at *m/z* 799.4817 which upon accurate mass measurement provided the molecular formula $C_{42}H_{72}O_{14}$ (calcd for $C_{42}H_{71}O_{14}$: 799.4844, error: -3.4 ppm). Similarly, the ESI-TOF mass spectrum acquired for Mogroside II E (**2**) showed a $[M-H]^-$ ion at 799.4738 which also corresponded to the molecular formula $C_{42}H_{72}O_{14}$ (calcd for $C_{42}H_{71}O_{14}$: 799.4844, error: -1.6 ppm) indicative of compounds**1** and **2**being isomers. For Mogroside III A_1 (**3**), ESI-TOF mass spectrum showed a $[M-H]^-$ ion at *m/z* 961.5316 and accurate mass measurement provided the molecular formula $C_{48}H_{82}O_{19}$ (calcd for $C_{48}H_{81}O_{19}$: 961.5372, error: -5.8 ppm).

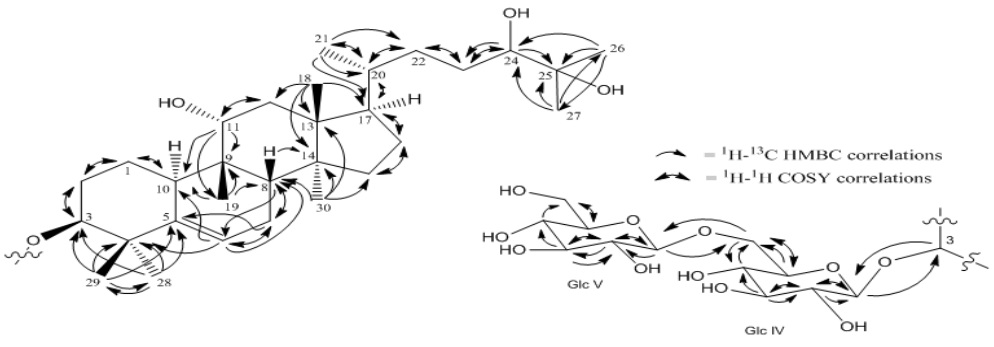
The 1D and 2D NMR data showed that theMogrosides II A_2 (**1**), II E (**2**) and III A_1(**3**) share the same triterpenecentral core with seven methyl singletsbetween δ_H0.86 – 1.18, a methyl doublet betweenδ_H0.96 – 0.97, eight methylenes betweenδ_H1.13 – 2.42, fourmethine protons betweenδ_H1.45 – 2.50, three additional methines between δ_H3.21-3.85, the chemical shifts indicative of these methines being attached to carbons bearing oxygen groups, and a tertiary hydroxyl carbon between δ_c73.6 – 73.9. The three compounds vary by the substituents of secondary alcohols at C-3 and C-24 in the Mogroside core. The triterpenoidaglycone central core for compound **1** was supported by ^1H-^1H COSY correlations of H-1/H-2; H-2/H-3; H-6/H-7; H-7/H-8; H-10/H-1; H-11/H-12; H-15/H-16; H-16/H-17; H-17/H-20; H-20/H-21; H-20/H-22; H-22/H-23 and H-23/H-24 and ^1H-^{13}C HMBC correlations of H-6/C-4, C-8; H-8/C-6, C-14; H-11/C-9, C-10, C-19; H-18/C-12, C-13, C-14, C-17; H-19/C-8, C-9, C-10; H-21/C-17, C-20, C-22; H-24/C-23, C-25; H-26 and H-27/C-24, C-25; H-28 and H-29/C-3, C-4, C-5 and H-30/C-8, C-13, C-14, C-15.The key ^1H-^1H COSY and ^1H-^{13}C HMBC correlations used to assign the aglycone unit of **1** are provided in Figure 2 (A).The COSY and HMBC correlations observed for compounds **2** and **3** were consistent with compound **1**. The complete^1H and ^{13}C NMR assignmentsof the aglycones of all three compounds were madeon the basis of ^1H,^{13}C,COSY, HSQC-DEPTand HMBC dataand aregiven in Table 1.

The relative stereochemistry of the central triterpene core was assigned based on NOE correlations. In the NOESY spectrum of **1**, NOE correlations of H-10/H-28, H-10/H-30 and H-30/H-17 indicated that H-10, H-17, H-28, and H-30 are on the same face of the rings. Similarly, NOE correlations ofH-8/H-18, H-8/H-19, H-11/ H-18, H-11/H-19 indicated that H-8, H-11, H-18 and H-19 are on the same face of the ring.Absence of NOE correlations between H-8/H-11/H-18/H-19 and H-10/H-17/H-28/H-30 indicated that these were on the opposite face of the rings as presented in Figure 2. Also, NOE correlations observed between H-17 and H-21 indicated that they are on the same face. Based on the available NOESY data, the relative stereochemistry of H-3 and H-29 could not be assigned unambiguously. However, based on large coupling constant (7.8 Hz, β-configuration) of Glc_{IV}anomeric proton and its attachment at C-3 of the central triterpene core (discussed below), the H-3 would most likely be in α-orientation. Also, since the relative stereochemistry ofH-28 is assigned as α, the relative stereochemistry ofH-29 would be β as shown in figure 2.The relative stereochemistry for the central triterpene core of compounds**2** and **3** were similarly assigned are consistent with Mogroside II A_2 (**1**) (Figure 2).

Table 1. ^{1}H and ^{13}C NMR (500 and 125 MHz, CD_3OD), assignments foraglycone of **1**, **2**, and **3**.

	1		**2**		**3**	
Position	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	27.2	1.48 m 2.22 m	27.2	1.51 m 2.21 m	26.4	1.51 m 2.22 m
2	29.7	1.90 m 1.92 m	29.6	1.92 m 1.94 m	30.5	1.54 m 2.00 m
3	88.2	3.46 m	88.5	3.41 m	77.6	3.41 m
4	42.9	---	42.9	---	42.6	---
5	144.9	---	144.9	---	144.1	---
6	119.6	5.48 brd (5.9)	119.7	5.49 d (5.3)	120.5	5.47 d (6.1)
7	25.1	1.80 m 2.38 dd (18.7, 7.2)	25.1	1.80 m 2.38 m	25.1	1.80 m 2.42 dd (18.0, 6.8)
8	44.7	1.66 d (7.4)	44.7	1.66 brd (7.4)	44.7	1.67 d (7.5)
9	40.9	---	40.9	---	40.9	---
10	37.3	2.48 brd (12.0)	37.5	2.47 brd (11.7)	37.1	2.50 brd (12.4)
11	79.4	3.85 m	79.4	3.84 m	79.4	3.85 m
12	41.1	1.80 m 1.83 m	41.1	1.80 m 1.83 m	41.1	1.81 m 1.86 m
13	48.2	---	48.2	---	48.3	---
14	50.6	---	50.6	---	50.6	---
15	35.3	1.13 m 1.19 m	35.4	1.13 m 1.19 m	35.4	1.14 m 1.21 m
16	29.1	1.34 m 1.96 m	29.1	1.34 m 1.98 m	29.4	1.33 m 1.98 m
17	51.8	1.60 m	51.7	1.62 m	51.8	1.62 m
18	17.1	0.91 s	17.1	0.91 s	17.1	0.91 s
19	26.2	1.10 s	26.2	1.10 m	26.2	1.14 s
20	37.0	1.50 m	37.3	1.47 m	37.5	1.45 m
21	19.1	0.96 d (6.3)	19.1	0.96 d (4.9)	19.3	0.97 d (6.3)
22	34.4	1.27 m 1.48 m	34.2	1.48 m 1.52 m	34.1	1.48 m 1.55 m
23	28.8	1.34 m 1.50 m	29.7	1.47 m 1.59 m	29.9	1.40 m 1.54 m
24	79.7	3.21 m	89.7	3.44 m	93.3	3.39 m
25	73.9	---	73.6	---	73.9	---
26	25.0†	1.12 s†	26.6†	1.14 s†	26.8†	1.10 s†
27	25.6†	1.14 s†	24.7†	1.15 s†	24.1†	1.14 s†
28	27.8	1.06 s	27.8	1.06 s	27.5	1.05 s
29	26.2	1.18 s	26.3	1.18 s	26.4	1.09 s
30	19.8	0.87 s	19.8	0.86 s	20.0	0.88 s

†Assignments can be interchanged.



A. Aglycone unit of Mogroside II A_2 (**1**) B. Glycone unit of Mogroside II A_2 (**1**)

Figure 2. A summary of key ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBC correlations used to assign theaglycone (A) and the C-3 glycoside (B) of Mogroside II A_2 (**1**).

Table 2. ^{1}H and ^{13}C NMR (500 and 125 MHz, CD_3OD), assignments forthe glycosides of **1**, **2**, and **3**.

	1		**2**		**3**	
Position	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
Glc_I-1	---	---	104.9	4.33 d (7.7)	104.2	4.43 d (7.3)
Glc_I-2	---	---	75.3	3.21 m	81.2	3.61 m
Glc_I-3	---	---	78.0 or 78.1 or 78.3	3.35 m	78.7	3.59 m
Glc_I-4	---	---	71.6 or 71.7	3.28 m	71.6	3.33 m
Glc_I-5	---	---	78.0 or 78.1 or 78.3	3.27 m	76.5	3.50 m
Glc_I-6	---	---	62.6	3.64 m 3.84 m	70.1	3.62 m 4.23 dd (10.4, 1.8)
Glc_{II}-1	---	---	---	---	104.4 or 104.5	4.28 d (7.7)
Glc_{II}-2	---	---	---	---	75.2	3.20 m
Glc_{II}-3	---	---	---	---	77.7-78.2[¥]	3.36 m
Glc_{II}-4	---	---	---	---	71.6	3.27 m
Glc_{II}-5	---	---	---	---	77.7-78.2[¥]	3.26 m
Glc_{II}-6	---	---	---	---	62.7	3.65 m 3.85 m
Glc_{III}-1	---	---	---	---	104.4 or 104.5	4.77 d (7.8)
Glc_{III}-2	---	---	---	---	75.7	3.27 m
Glc_{III}-3	---	---	---	---	77.7-78.2[¥]	3.36 m
Glc_{III}-4	---	---	---	---	72.4	3.21 m
Glc_{III}-5	---	---	---	---	77.7-78.2[¥]	3.27 m
Glc_{III}-6	---	---	---	---	63.6	3.63 m 3.86 m
Glc_{IV}-1	106.4	4.28 d (7.8)	106.6	4.27 d (7.8)	---	---
Glc_{IV}-2	75.2 or 75.6	3.19 m	75.6	3.18 m	---	---
Glc_{IV}-3	78.1	3.31 m	78.0 or 78.1 or 78.3	3.31 m	---	---
Glc_{IV}-4	71.6	3.29 m	71.6 or 71.7	3.26 m	---	---
Glc_{IV}-5	77.2	3.40 m	77.7	3.21 m	---	---
Glc_{IV}-6	69.8	3.80 m 4.05 dd (11.8, 1.5)	62.8	3.65 m 3.81 m	---	---
Glc_V-1	104.8	4.42 d (7.8)	---	---	---	---
Glc_V-2	75.2 or 75.6	3.18 m	---	---	---	---
Glc_V-3	77.9 or 78.0	3.35 m	---	---	---	---
Glc_V-4	71.6	3.28 m	---	---	---	---
Glc_V-5	77.9 or 78.0	3.25 m	---	---	---	---
Glc_V-6	62.7	3.66 m 3.85 m	---	---	---	---

[¥]Four carbon resonances in the range of 77.7-78.2 (77.66, 77.92, 77.05, and 78.16), hence chemical shifts could not be unequivocally assigned.

The ^{1}H and^{1}H-^{13}C HSQC-DEPT data allowed identification of the two anomeric protons inMogroside II A_2 which were well resolved at δ_H 4.42 (δ_C 104.8) and 4.28 (δ_C 106.4) and both protons had large couplings (7.8 Hz) indicating that they had β-configurations. The anomeric proton at δ_H 4.28 showed an HMBC correlation to C-3 (δ_C88.2)which indicated that it corresponded to Glc_{IV} H-1.Glc_{IV}H-2 and H-3 were then assigned based on COSY correlation between Glc_{IV} H-1/Glc_{IV} H-2 and Glc_{IV} H-2/Glc_{IV} H-3.Due to data overlap the COSY spectrum did not allow assignment of remaining Glc_{IV} protons. Therefore, 1D TOCSY experiments were performed to assignGlc_{IV} H-4, H-5 and H-6. HSQC-DEPT data was then used to assign the carbon chemical shift of Glc_{IV} C-1 to C-6.HMBC correlations ofGlc_{IV} H-1/C-2, C-3, C-5; H-2/C-1; H-3/C-2, C-4;H-4/C-6 and H-6/C-4 further confirmed the assignments.The complete^{1}H and ^{13}C assignments for$Glc_{IV}$are presented in Table 2. The downfield carbon chemical shift of C-6 (δ_C 69.8) indicated that the hydroxyl group at C-6 is replaced by a sugar linkage.The anomeric proton of Glc_V at δ_H 4.42 showed an HMBC correlation to the carbon at δ_C 69.8 ppm (Glc_{IV} C-6) and the reciprocal HMBC correlations from the methylene protons of Glc_{IV}(δ_H 3.80 and 4.05) to the anomeric carbon ofGlc_V at δ_C 104.8 confirmedthe 1→6 linkage between Glc_V and Glc_{IV}.The remaining proton and carbon assignments for Glc_Vwasdone as discussed above for Glc_{IV}. The key ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBCcorrelations for theglycone unit of Mogroside II A_2 (**1**) are presented in Figure 2 (B) and the complete proton and carbon assignments are presented in Table 2.

Similarly in Mogroside II E(**2**),the presence of two anomeric protons were confirmed at δ_H 4.33 (δ_C 104.9) and 4.27 (δ_C 106.6), having coupling of 7.7 Hz and 7.8 Hz, respectively, indicating that they hadβ−configurations.The anomeric proton at δ_H 4.27 showed an HMBC correlation to C-3(δ_C 88.5)hence establishing the linkage ofGlc_{IV} to C-3. The anomeric proton at δ_H 4.33 showed an HMBC correlation to C-24 (δ_C 88.7)establishing the linkage ofGlc_I to C-24. The COSY and 1D-TOCSY data allowed the assignments of Glc_I and Glc_{IV} H-2 to H-6 while the carbon assignments were based on HSQC-DEPT data and confirmed by HMBC correlations... The key ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBCcorrelations usedto assign the glucose units and their attachment to the triterpene core in Mogroside II E (**2**) are presented in Figure 3 and the complete proton and carbon assignments are presented in Table 2. Compound **2** is an isomer of compound **1**, differing only in the position of the attachment of glucose units.

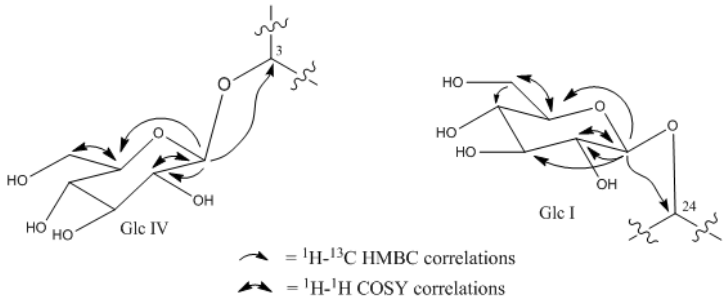


Figure 3. The summary of key ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBCcorrelations used to assign glycoside regions at C-3 and C-24 of Mogroside II E (**2**).

In Mogroside III A_1(**3**), the^{1}H and HSQC-DEPT NMR data confirmed the presence of three glucose units.Theanomeric protons of these glucose units were observed at δ_H 4.77 (δ_C 104.4 or 104.5), 4.43 (δ_C 104.2), and 4.28 (δ_C 104.4 or 104.5) and had large couplings (7.3 – 7.8 Hz) indicating that they had β-configurations. The anomeric proton at δ_H 4.43 showed an HMBC correlation to C-24 (δ_C 93.3)which indicated that it corresponded to the anomeric proton of Glc_I. The COSY and 1D-TOCSY experiments allowed the assignment of Glc_I H-2 to Glc_I H-6 and the HSQC-DEPT data was used to assign Glc_IC-2 to Glc_IC-6. HMBC correlations ofGlc_I H-1/C-3; H-2/C-1, C-3; H-3/C-2; H-4/C-3, C-6 and H-5/C-6 further confirmed the assignments. The complete^{1}H and ^{13}C assignments for$Glc_I$are presented in Table 2. The downfield carbon chemical shifts of C-2 (δ_C81.2) and C-6 (δ_C 70.1) indicated that the hydroxyl groups at C-2 and C-6 arereplaced by sugar linkages which was subsequently confirmed byHMBC correlations. The anomeric proton of Glc_{II} at δ_H 4.28 showed an HMBC correlation to the carbon at δ_C 70.1 ppm (Glc_I C-6) and the reciprocal HMBC correlation from the methylene protons of Glc_I(δ_H 3.62 and 4.23) to the anomeric carbon ofGlc_{II} at δ_C 104.4 or 104.5 confirmed the 1→6 linkage between Glc_{II} and Glc_I. Similarly, HMBC correlation from the anomeric proton of Glc_{III} at δ_H 4.77 to the carbon at δ_C 81.2 ppm (Glc_I C-2) and the reciprocal HMBC correlation from the methine proton of Glc_IH-2 (δ_H 3.61) to the anomeric carbon ofGlc_{III} at δ_C 104.4 or 104.5 confirmed the 1→2 linkage between Glc_{III} and Glc_I.The assignment of remaining protons and carbons of Glc_{II} and Glc_{III} were done based on COSY, HSQC-DEPT, HMBC and 1D-TOCSY data. A summary of the key ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBCcorrelations of Mogroside III A_1 (**3**) used to assign the C-24 glycosides are described in Figure 4 and the complete^{1}H and ^{13}C assignments are presented in Table 2.

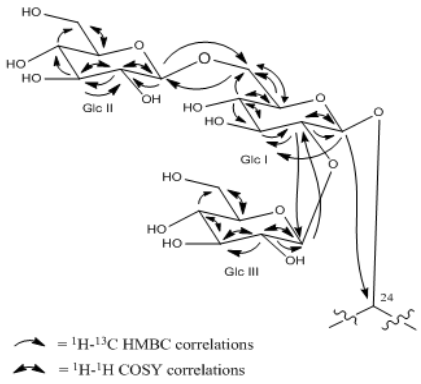


Figure 4. The summary of key ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBCcorrelations used to assign C-24 glycoside region of Mogroside III A_1(**3**).

The ^{13}C NMR assignmentsfor compound **2** reported by Si et al. [15] for position 28 and 30 are incorrect, the assignments are swapped. Similarly, for compound **3**,the ^{13}C NMR assignments reported by Li et al [16] for position 26 and 27 are swapped.

IV. Conclusions

This report describes complete NMR assignments for Mogrosides II A_2, II E and III A_1 through extensive NMR analysis. The structures of Mogrosides II A_2, II E and III $A_1$are disclosed in the literature, however, full NMR assignmentshave not beenreported for Mogroside II A_2 and only partial assignment have been reported for Mogroside II E.

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