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An alternate synthesis of mafenide acetate

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ABSTRACT: Mafenide acetate (**1**) is an important antibacterial substance popularly used to treat burn wound infections, especially second- and third-degree infected burns. In this paper, we report a novel, efficient and scalable method for synthesizing mafenide acetate from low-cost materials. This robust synthesis requires minimal purification effort using no column chromatography while affording the final product of high purity (99.18%, HPLC). In addition, we present the spectral data (IR, NMR, and MS) for the key intermediate, N^1,N^4-*bis*(4-sulfamoylbenzyl)succinamide (**3b**), for the first time, providing a valuable reference for future research in the development of more potent mafenide derivatives.

KEYWORDS: mafenide acetate, burn, sulfonamide, chlorosulfonation, sulfoamidation

INTRODUCTION

Mafenide acetate (*p*-aminomethylbenzenesulfonamide monoacetate, **1**) is a member of the synthetic antimicrobial sulfonamides. It is a broad-spectrum antibacterial agent exhibiting inhibitory activity against both Gram-positive and Gram-negative microorganisms, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Clostridium* [1, 2]. Mafenide acetate has been found to effectively inhibit bacterial nucleotide synthesis and widely utilized to treat second- and third-degree infected burns [3–5]. In addition, it possesses some anti-inflammatory and anti-fungal capabilities [6, 7].

The synthesis of mafenide acetate has been popularly described in the literature using many starting materials, including *N*-benzylacetamide [8–10], *N*-benzylformamide [11], methyl *N*-benzylcarbamate [12], *N*-benzylphthalimide [13]. These synthetic approaches shared a similar mechanistic pathway (Scheme 1) comprising the following steps:

a) Chlorosulfonation of *N*-benzyl derivatives (amides, carbamates, and imides) by chlorosulfonic acid to form sulfonyl chloride intermediates.

b) Reaction of the obtained sulfonyl chlorides with ammonia to generate sulfonamide intermediates.

c) Hydrolysis of protecting groups on sulfonamide intermediates to afford mafenide.

d) Reaction of mafenide and acetic acid to form mafenide acetate.

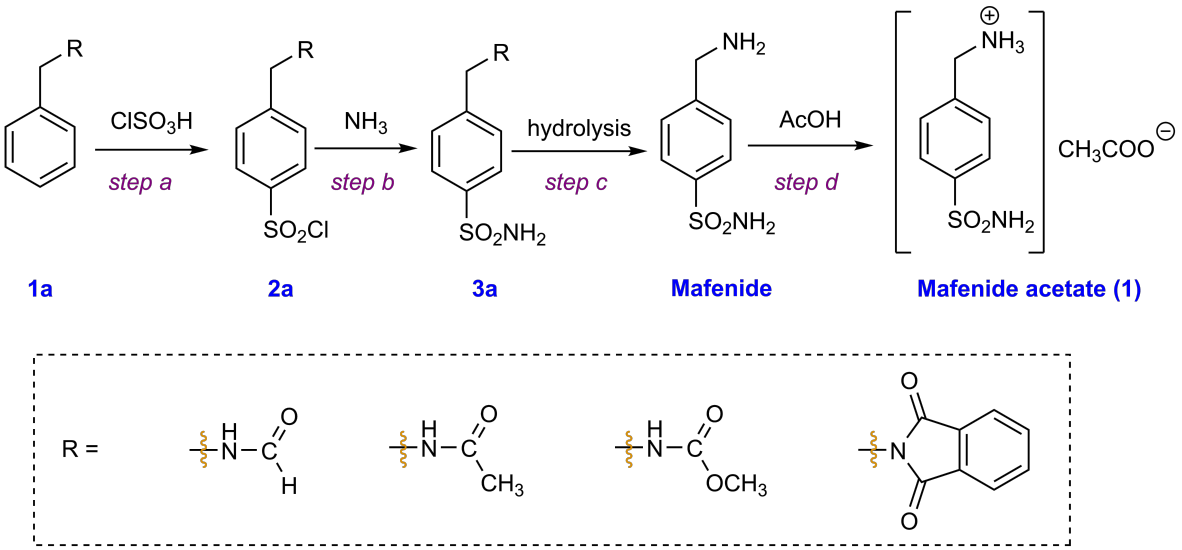
Newer synthetic approaches include the electrochemical reduction of cyano sulfonamides to produce amino sulfonamides, as well as the direct oxidative coupling of thiols and amines to generate sulfonamides [14, 15]. However, these synthetic methods have certain drawbacks, such as the limited availability or challenging preparation of suitable starting materials for making mafenide. Additionally, the high costs associated with these reaction conditions make them less suitable for large-scale synthesis.

Herein, we report an efficient and cost-effective synthetic procedure to obtain the target compound, mafenide acetate, using inexpensive and readily available starting materials including diethyl succinate, benzylamine, acetic acid, ammonia and sodium hydroxide (Scheme 2). This procedure eliminated the need for column chromatography making it suitable for scalable production. Additionally, we present the synthesis and spectral data of intermediate 3b, which is currently unavailable in the literature. This compound belongs to a group of mafenide derivatives with improved antimicrobial activity compared to mafenide, and its synthesis feasibility demonstrates the efficiency and versatility of our method in producing similarly potent derivatives [2].

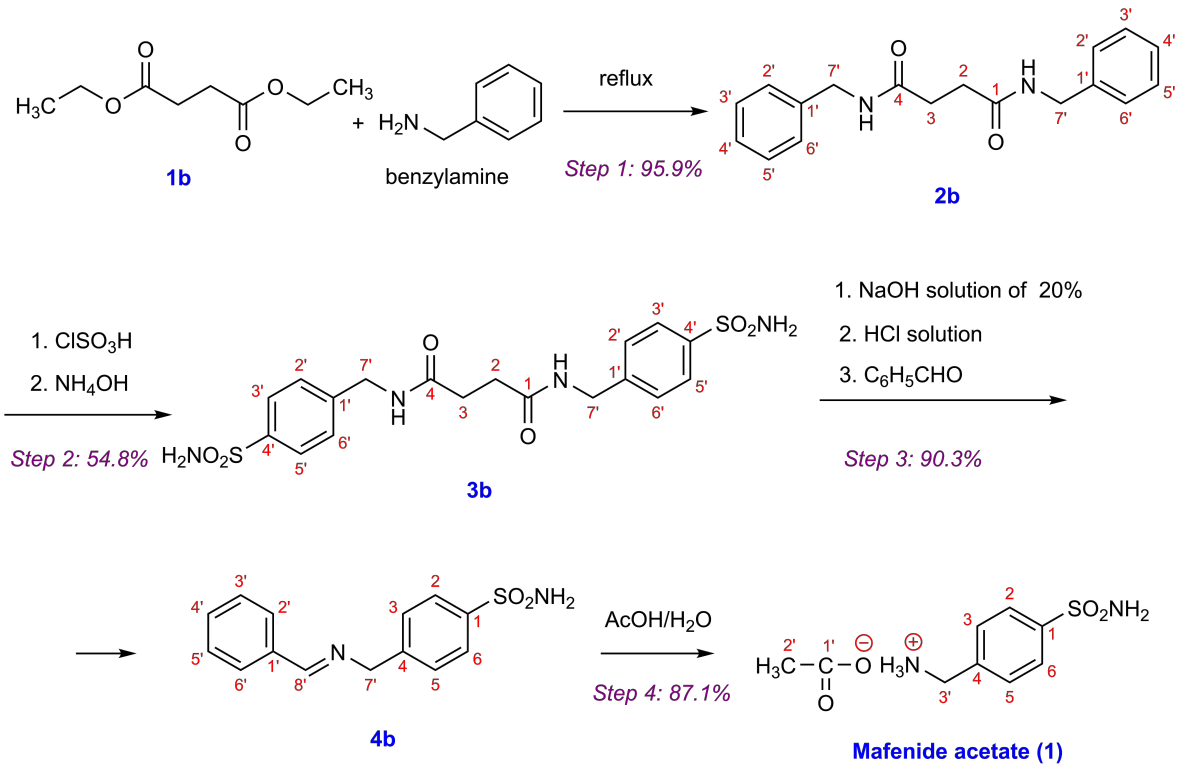
MATERIALS AND METHODS

General Information

All solvents and reagents were purchased from Merck KGaA (Darmstadt, Germany) and Sigma-Aldrich (St. Louis, Missouri, USA) and used as received without further purification. The melting point (m.p) was measured by using the capillary tube method with an SRS EZ-Melt apparatus (Stanford Research Systems, Sunnyvale, CA, USA) and was uncorrected. The FT-IR spectrum was recorded by a Shimadzu spectrometer (Kyoto, Japan). Nuclear magnetic resonance (^{1}H,



Scheme 1 General synthetic route of mafenide acetate from various starting materials.



Scheme 2 A novel and efficient synthesis of mafenide acetate using low-cost starting materials.

^{13}C) experiments were measured on a Bruker Ascend spectrometer (Billerica, MA, USA) at 500 MHz for proton and 125 MHz for carbon-13 using DMSO-d_6 as the solvent and tetramethylsilane (TMS) as an internal standard. MS was performed at an SCIEX X500 QTOF system (AB Sciex Pte. Ltd., Woodlands Central Industrial Estate, Singapore) in an electrospray ionization (ESI) mode. The reaction mixtures were monitored, and the purity of the compounds was checked by thin-layer chromatography (TLC) on silica gel 60 F_{254} plates (Merck). Analytical HPLC traces for the standard and sample of mafenide acetate were obtained using an Agilent system equipped with a UV/vis detector. This system was fitted with an Inertsil™ C18 (5 µm

150 mm × 4.6 mm) column with the mobile phase made of phosphate buffer (pH = 2.5) in acetonitrile (90:10). HPLC traces were acquired at a flow rate of 1.0 ml/min, over 15.0 min, with detection at 267 nm.

This synthetic method was developed based on related references: Ref. [16] for compound **2b**, Refs. [8–10] for compound **3b**, and Ref. [12] for mafenide acetate.

Experimental section

Preparation of N^1, N^4-dibenzylsuccinamide (2b)

A mixture of diethyl succinate (**1b**) (10.0 g, 0.058 mol) and benzylamine (12.7 ml, 0.116 mol) was heated to reflux and stirred for 2 h. Then, the reaction mixture was cooled to 60 °C, and 100 ml of ethanol was added. The resulting mixture was further stirred at this temperature for 30 min followed by cooling to 0–5 °C for 10 h. A white solid was collected by filtration and then dried under vacuum at 50 °C for 6 h to obtain **2b** (16.4 g, 95.9% yield). m.p 209–210 °C, TLC R_f = 0.59, one spot ($CHCl_3$:MeOH = 9:1, v/v, as the mobile phase). **IR** (KBr), ν_{max} (cm^{-1}): 3289 (N—H_{amide}); 3069 (C—$H_{aromatic}$); 2934 (C—H_{alkane}); 1633 (C=O_{amide}); 1548 (C=C) (Fig. S1). **ESI-MS** (MeOH), m/z: 295.1 $[M-H]^-$, 319.0 $[M+Na]^+$ ($C_{18}H_{20}N_2O_2$, M = 296.37 Dalton) (Fig. S2); ^{1}**H-NMR** (500 MHz, DMSO-d_6), δ (ppm): 2.43 (4H, s, H-2, H-3); 4.27 (4H, d, J = 6.0 Hz, H-7′); 7.23–7.25 (6H, m, H-3′, H-4′, H-5′); 7.30 (4H, d, J = 7.5 Hz, H-2′, H-6′); 8.36 (2H, t, J = 6.0 Hz, 2 —NH—) (Fig. S3). ^{13}**C-NMR** (125 MHz, DMSO-d_6), δ (ppm): 31.32 (2C, C-2, C-3); 42.49 (2C, C-7′); 127.13 (2C, C-4′); 127.61 (4C, C-2′, C-6′); 128.70 (4C, C-3′, C-5′); 140.09 (2C, C-1′); 171.81 (2C, C-1, C-4) (Fig. S4).

Preparation of N^1, N^4-bis(4-sulfamoylbenzyl) succinamide (3b)

3.0 g (10.1 mmol) **2b** was introduced in small fractions to 5.4 ml (81.1 mmol) of chlorosulfonic acid under stirring, with the temperature being kept in a range from 20 to 30 °C. After stirring at this temperature for 1 h, the reaction mixture was slowly warmed to 60–65 °C for 2 h. After cooling to 20 °C, the reaction mixture was gradually added in drops to a mixture of 20 g of water and 20 g of ice at a rate such that the temperature during decomposition did not rise over 30 °C. The resulting precipitate was filtered and washed with water, dried, and introduced into 15.0 ml (∼210 mmol) of 25% ammonia solution with the temperature being kept about 20 °C. The obtained mixture was then heated with stirring to 50 °C for 30 min and cooled to 10 °C for 4 h. The resulting solid was filtered, washed with water, and dried under vacuum at 50 °C for 6 h affording sulfonamide **3b** as a white solid (2.52 g, 54.8% yield). m.p 214–215 °C. **TLC** R_f = 0.64, one spot (n-butanol:acetic acid:water = 9.0:2.0:2.5, v/v/v, as the mobile phase). **IR** (KBr), ν_{max} (cm^{-1}): 3277 (N—H_{amide}); 3093 (C—$H_{aromatic}$); 2923 (C—H_{alkane}); 1623 (C=O_{amide}); 1337 and 1159 (O=S=O) (Fig. S5). **ESI-MS** (MeOH), m/z: 453.0 $[M-H]^-$; 477.0 $[M+Na]^+$ ($C_{18}H_{22}N_4O_6S_2$, M = 454.52 Dalton) (Fig. S6). ^{1}**H-NMR** (500 MHz, MeOD), δ (ppm): 2.63 (4H, s, H-2, H-3); 4.48 (4H, s, H-7′); 7.51 (4H, d, J = 6.0 Hz, H-2′, H-6′); 7.87 (4H, d, J = 6.0 Hz, H-3′, H-5′) (Fig. S7). ^{13}**C-NMR** (125 MHz, MeOD), δ (ppm): 30.64 (C-2, C-3); 42.15 (C-7′); 126.04 (C-2′, C-6′); 127.55 (C-3′, C-5′); 142.62 (C-4′); 143.73 (C-1′); 173.03 (C-1, C-4) (Fig. S8).

Preparation of p-[(benzylidenamino)methyl] benzenesulfonamide (4b)

A solution of 4.54 g (10 mmol) of **3b** in 14.0 ml 20% NaOH (70 mmol) solution was heated with stirring at 90–100 °C for 2 h. After cooling to ambient temperature, the reaction was adjusted to pH 9–10 using 5 M HCl solution. To the obtained solution was added 2.3 ml (0.021 mol) benzaldehyde and the mixture was gradually heated to 60 °C for 2 h. After cooling to 20 °C, a precipitate was formed and isolated by filtration. It was further washed with water and dried under vacuum at 60 °C for 6 h to generate **4b** a white solid (yield: 4.95 g, 90.3%). m.p 149–151 °C. **TLC** R_f = 0.61, one spot (n-hexane:EtOAc = 3:7, v/v, as the mobile phase). **IR** (KBr), ν_{max} (cm^{-1}): 3332 and 3288 (N—$H_{sulfonamide}$); 3182 (C—$H_{aromatic}$); 2981 (C—H_{alkane}); 1639 (C=N); 1328 and 1149 (O=S=O) (Fig. S9). **ESI-MS** (MeOH), m/z: 272.808 $[M-H]^-$ ($C_{14}H_{14}N_2O_2S$, M = 274.34 Dalton) (Fig. S10). ^{1}**H-NMR** (500 MHz, DMSO-d_6), δ (ppm): 4.86 (s, 2H, H-7′); 7.33 (s, 2H, $-SO_2NH_2$); 7.32–7.54 (5H, m, H-3, H-5, H-3′, H-4′, H-5′); 7.80–7.83 (4H, m, H-2, H-6, H-2′, H-6′); 8.55 (s, 1H, H-8′) (Fig. S11). ^{13}**C-NMR** (125 MHz, DMSO-d_6), δ (ppm): 63.14 (C-7′); 125.76 (C-3′, C-5′); 128.02 (C-2′, C-6′); 128.15 (C-2, C-6); 128.70 (C-3, C-5); 130.89 (C-4′); 135.90 (C-1′); 142.63 (C-1); 143.73 (C-4); 162.55 (C-8′) (Fig. S12).

Preparation of mafenide acetate

A mixture of 5.48 g (20.0 mmol) of **4b** and 14.0 ml of 15% acetic acid solution (v/v, ∼245 mmol) was heated and stirred at 60 °C for 2 h. The mixture was cooled to 20 °C and 10.0 ml of CH_2Cl_2 was added. Then, the mixture was stirred vigorously, left to separate and the organic phase was removed using a separatory funnel. The water phase was rewashed with 6.0 ml of CH_2Cl_2 and the same process was repeated. The water phase was then evaporated under reduced pressure at 80 °C to a volume of about 3 ml. To the concentrate was added 12 ml isopropanol (IPA) and the mixture was stirred for 30 min at 75 °C. After cooling to 10 °C for 2 h, a precipitate was formed, filtered, and washed on the filter with 10 ml chilled IPA to get crude mafenide acetate. The crude mafenide acetate was then completely dissolved in 12 ml 95% ethanol (EtOH) at 70 °C. To

this solution was added 0.075 g activated charcoal and the mixture was stirred at 70 °C for 30 min. The hot mixture was filtered to remove charcoal and the filtrate was cooled to room temperature and then chilled to 5 °C for 5 h. The precipitate was formed, filtered, and washed on the filter with chilled IPA. It was dried under vacuum at 60 °C for 6 h to obtain mafenide acetate as a white precipitate (4.28 g, 87.10% yield, 99.18%, HPLC) (Fig. S17 and Fig. S18). m.p 164–166 °C. **TLC** R_f = 0.27, one spot (*n*-butanol:acetic acid:water = 9.0:2.0:2.5, v/v/v, as the mobile phase). **IR** (KBr), ν_{max} (cm^{-1}): 3327 and 3116 ($-NH_2$); 3072 ($C-H_{aromatic}$); 2947 and 2802 ($C-H_{alkane}$); 2085 (N^+-H); 1406 ($C=O_{acetate}$); 1517 ($C=C_{aromatic}$); 1317 and 1139 (O=S=O) (Fig. S13). **ESI-MS** (MeOH), m/z: 187.0 $[M-CH_3COO]^+$ ($C_9H_{14}N_2O_4S$, M = 246.28 Dalton) (Fig. S14). ^{1}**H-NMR** (500 MHz, D_2O), δ (ppm): 1.89 (3H, s, H-2′); 4.30 (2H, s, H-3′); 7.67 (2H, d, J = 8.0 Hz, H-3, H-5); 7.97 (2H, d, J = 8.5 Hz, H-2, H-6) (Fig. S15). ^{13}**C-NMR** (125 MHz, D_2O), δ (ppm): 23.24 (C-2′); 42.43 (C-3′); 126.59 (C-2, C-6); 129.68 (C-3, C-5); 137.82 (C-4); 141.77 (C-1); 181.38 (C-1′) (Fig. S16).

RESULTS AND DISCUSSION

Our four-step synthetic pathway starts with an aminolyis of the ester, diethyl succinate, by benzylamine to generate the amide intermediate (**2b**, step 1, 95.9%, Scheme 2). Subsequent chlorosulfonation of **2b** and amidation of the obtained sulfonyl chloride intermediate by ammonia solution generated the sulfonamide intermediate (**3b**, step 2, 54.8%, Scheme 2). Hydrolysis of **3b** by 20% sodium hydroxide solution and subsequent reaction of the obtained primary amine with benzaldehyde afforded the imine derivative of mafenide (**4b**, step 3, 90.3%, Scheme 2). This mafenide derivative was reacted with an excess amount of acetic acid to generate the target product mafenide acetate (**1**, step 4, 87.1%, Scheme 2). In the pharmaceutical industry, either mafenide acetate or chloride can be used as the active pharmaceutical ingredient in the finished products. While the chloride salt was popularly used in the past, the acetate form is preferred in today's formulations. The overall yield for affording mafenide acetate using our protocol is 43.1%. This isolated yield is either comparable to the pathways using methyl *N*-benzylcarbamate (41%, mafenide acetate) [12] and *N*-benzylformamide (45.5%, mafenide hydrochloride) [11], or superior to other pathways using *N*-benzylacetamide (30.8%, mafenide hydrochloride), [9], and *N*-benzylphathalimide (22.5%, mafenide hydrochloride) [13] (Table S1).

Our synthesis commences with the condensation of two low-cost starting materials: diethyl succinate and benzylamine (1:2) under reflux condition to afford diamide **2b** (Scheme 2, step 1). Our preference for forming a diamide rather than a monoamide product was justified by the fact that the diamide facilitates the electrophilic substitution (chlorosulfonation) at the para-position probably due to the increase steric effect in its structure (Scheme 2, step 2). In addition, not only did the formation of the diamide product **2b** afford excellent yield (95.9%), but it was also simple to perform and required no complex purification. More importantly, we found that the chlorosulfonation product of the diamide was a stable compound which could be readily washed by water before reacting with ammonia solution to form the intermediate **3b**. This is a strong advantage in upscaling the synthesis as instability can be a real problem in some sulfonyl chloride derivatives.

Theoretically, from the disulfonamide intermediate **3b** our target compound mafenide acetate (**1**) could be achieved by first hydrolysis of the amide groups to generate mafenide which was then reacted with an excess amount of acetic acid to generate mafenide acetate. However, doing so would create by products that necessitated a column chromatography to purify the target product. With the focus on developing a synthetic pathway that can be feasibly upscaled to industrial production quantities, we have adopted an intervention that does not require chromatography purification [12]. This was achieved by the formation of an imine intermediate (**4b**, Schiff base) which could be easily isolated by filtration and subsequently reacted with acetic acid to afford mafenide acetate (Scheme 2, steps 3 and 4). Imine **4b** was synthesized by first hydrolysis of **3b** in mild conditions (20% sodium hydroxide, 90–100 °C) to form mafenide in the reaction mixture. This reaction mixture, without any purification needed, was directly reacted with benzaldehyde to afford imine **4b**. As this compound is slightly soluble in water and stable at pH 9–11, it can be easily isolated from water soluble by-products including sodium chloride, disodium and monosodium succinate, just by washing with water. In addition, **4b** can be readily hydrolyzed by acetic acid to directly form mafenide acetate.

CONCLUSION

In summary, a novel synthetic route to afford mafenide acetate has been developed from low-cost materials. This synthesis is robust with no chromatography purification required, and thus can be feasibly scalable to industrial quantities.

Appendix A. Supplementary data

Supplementary data associated with this article can be found at https://dx.doi.org/10.2306/scienceasia1513-1874.2025.084.

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Appendix A. Supplementary data

Table S1 The overall yield reported in the literature for producing mafenide in salt form from different starting materials.

No.	Starting materials	Yield (%)			Ref.
		Chlorosulfonation and amidation	Mafenide hydrochloride (popularly used in the past)	Mafenide acetate (currently used in today formulations)	
1	*N*-Benzylformamide	50.5	45.5	—	[11]
2	*N*-benzylacetamide	Not provided	—	—	[10]
3	*N*-benzylacetamide	36.9	30.8	—	[9]
4	*N*-benzylacetamide	47	Not provided	Not provided	[8]
5	Methyl *N*-Benzylcarbamate	50	—	41	[12]
6	*N*-benzylphathalimide	32	22.5	—	[13]
7	N^1,N^4-dibenzylsuccinamide	54.8	—	43.1	Current method

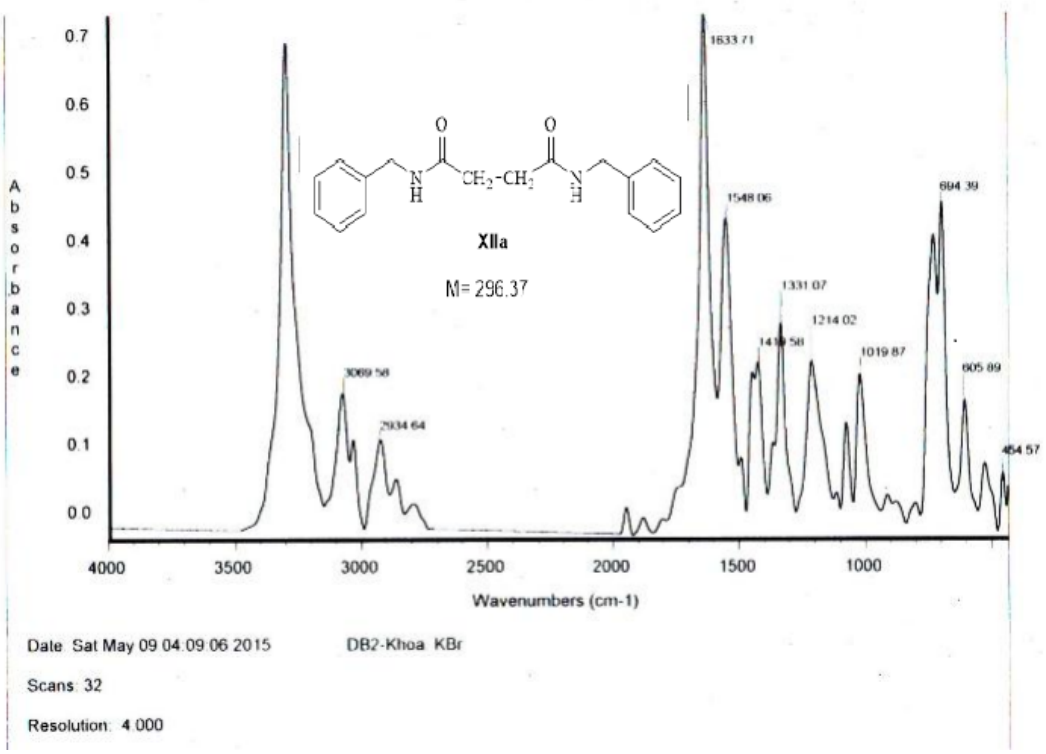


Fig. S1 IR of N^1,N^4-dibenzylsuccinamide (**2b**).

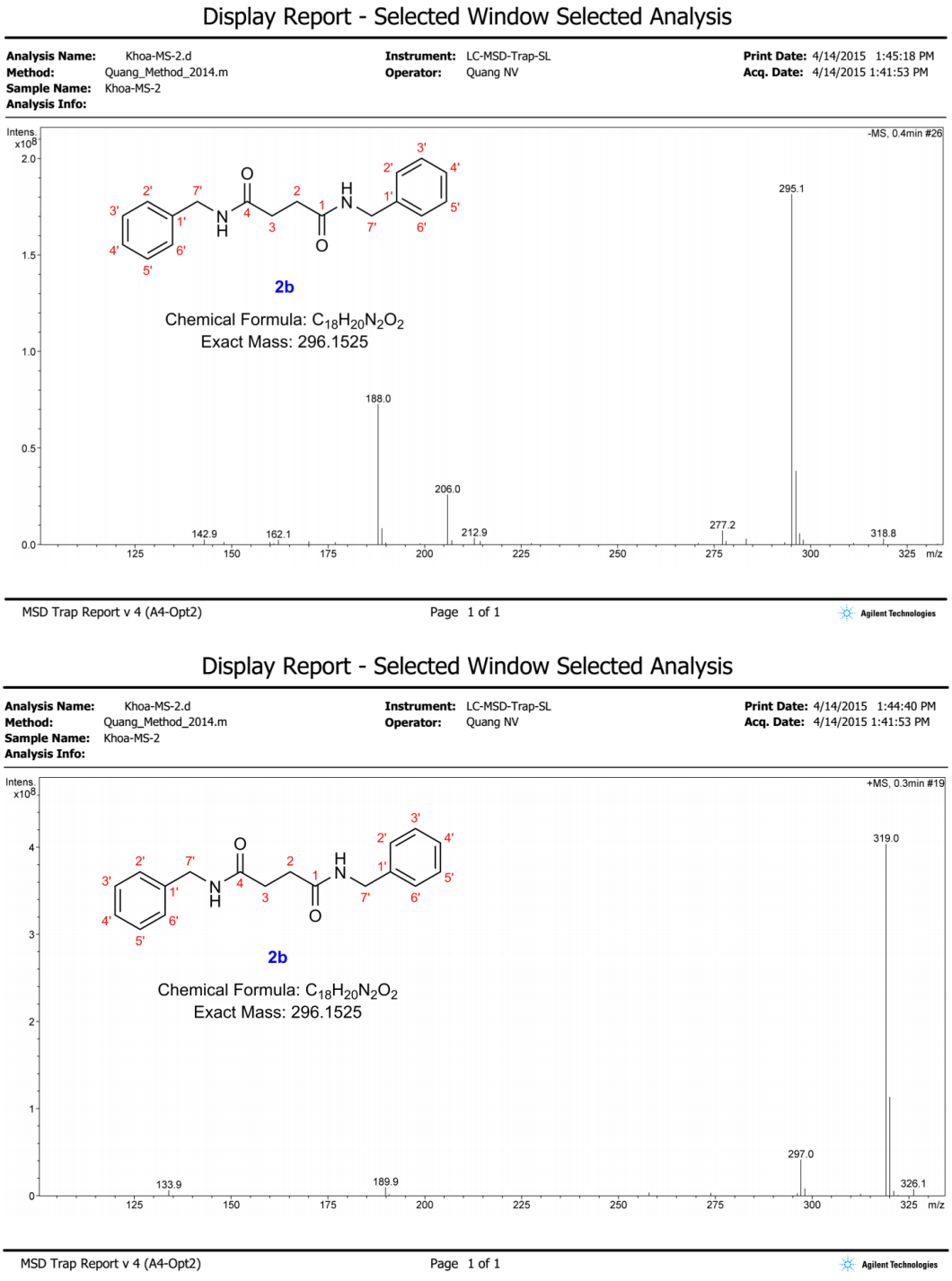


Fig. S2 MS of N^1,N^4-dibenzylsuccinamide (**2b**).

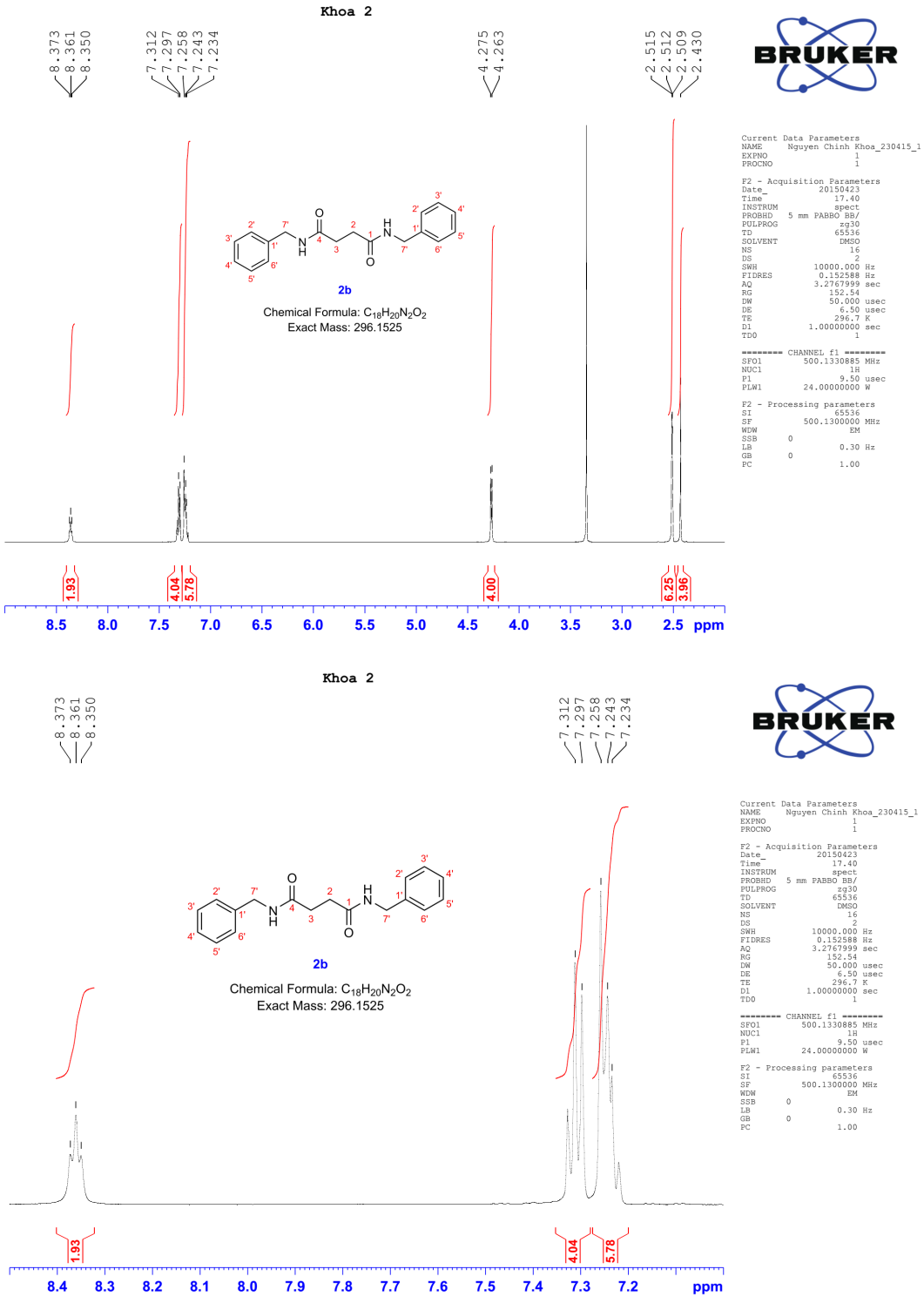


Fig. S3 ^{1}H-NMR of N^1,N^4-dibenzylsuccinamide (**2b**).

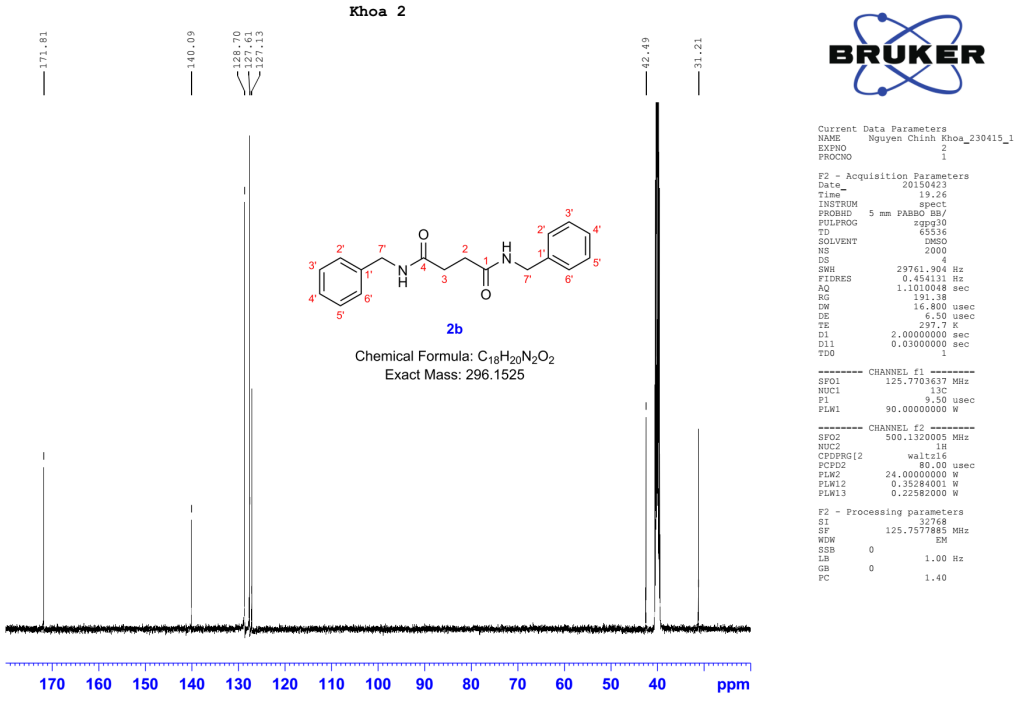


Fig. S4 ^{13}C-NMR of N^1,N^4-dibenzylsuccinamide (**2b**).

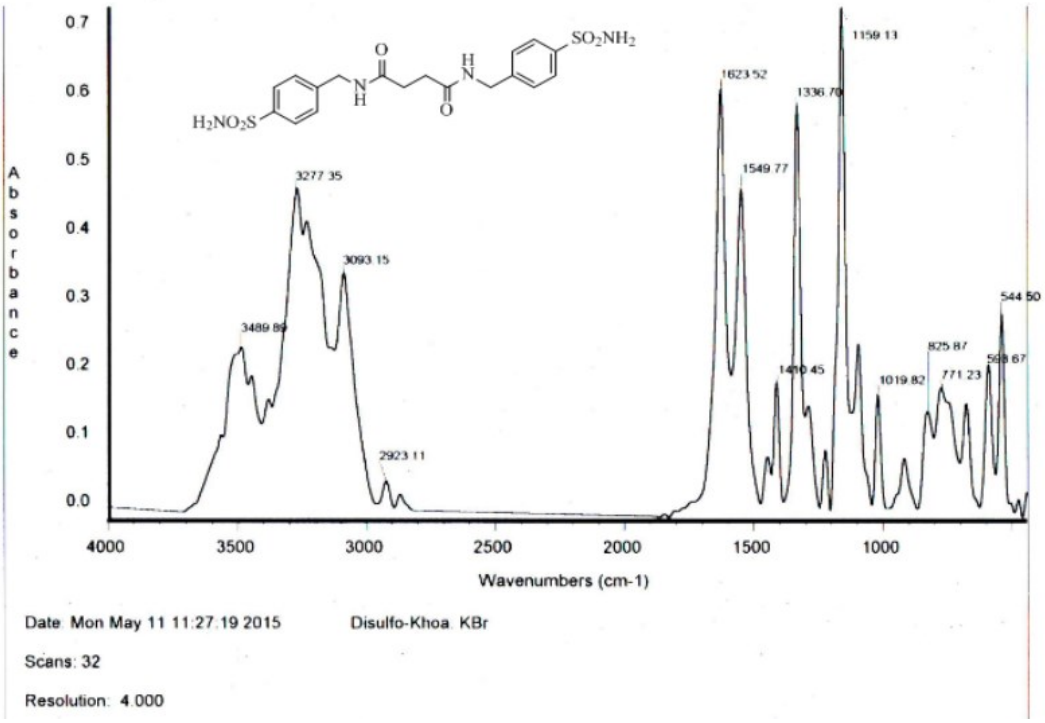
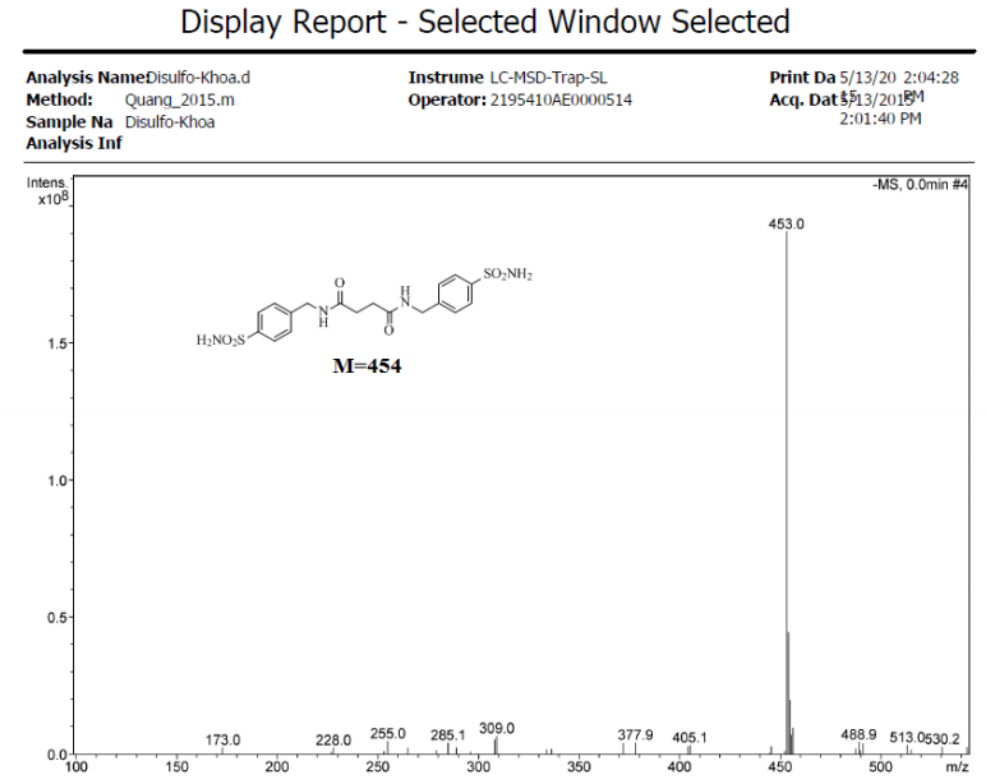


Fig. S5 IR of N^1,N^4-bis(4-sulfamoylbenzyl)succinamide (**3b**).



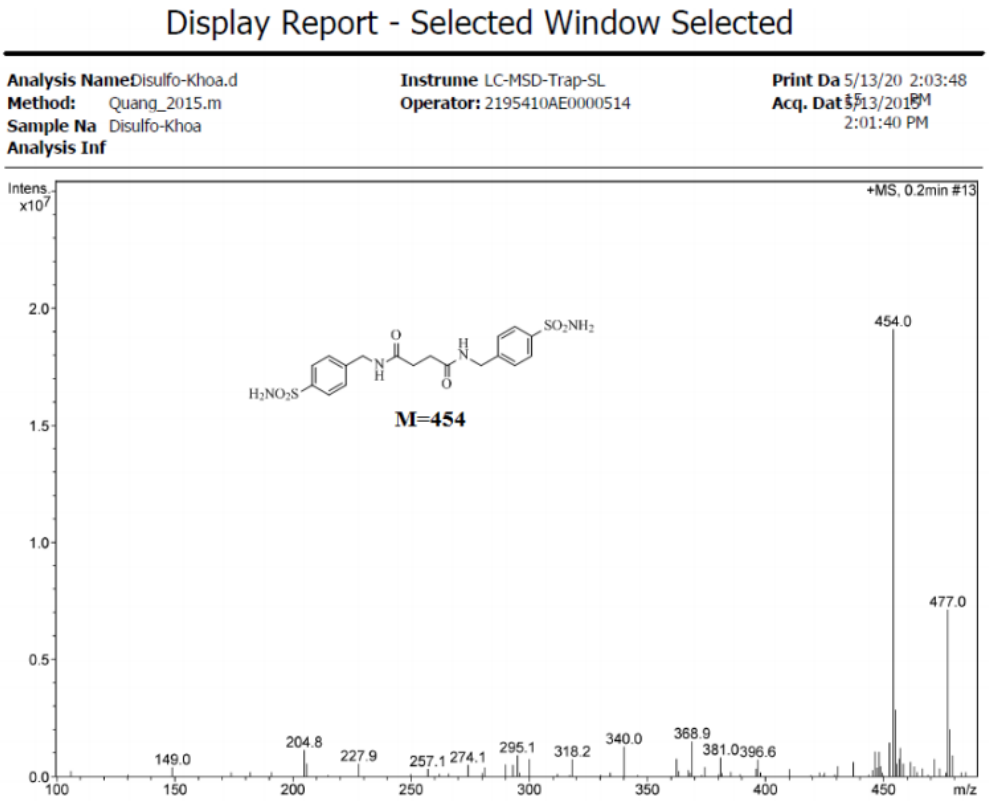


Fig. S6 MS of N^1,N^4-bis(4-sulfamoylbenzyl)succinamide (**3b**).

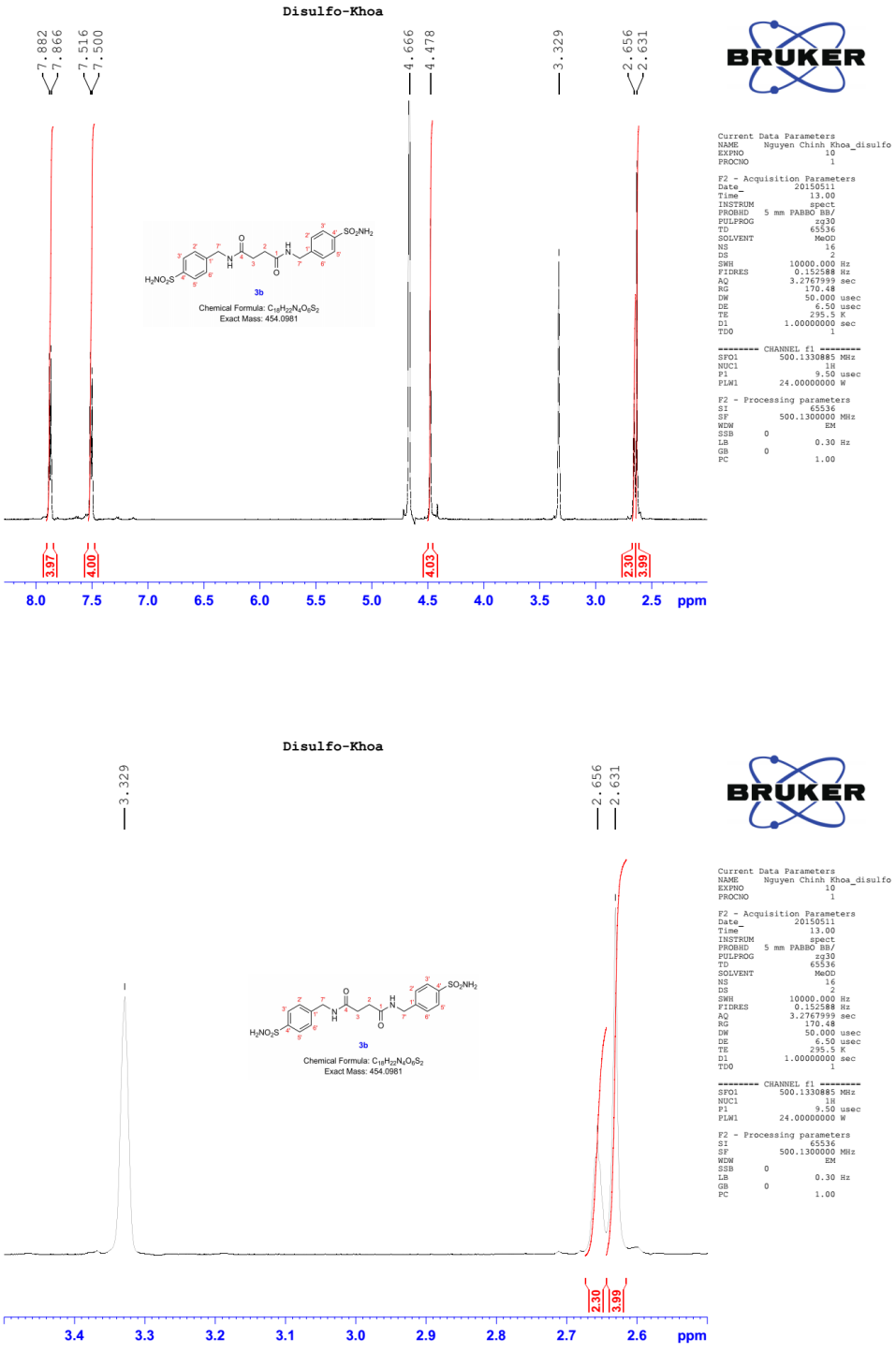


Fig. S7 ^{1}H-NMR of N^1,N^4-bis(4-sulfamoylbenzyl)succinamide (**3b**).

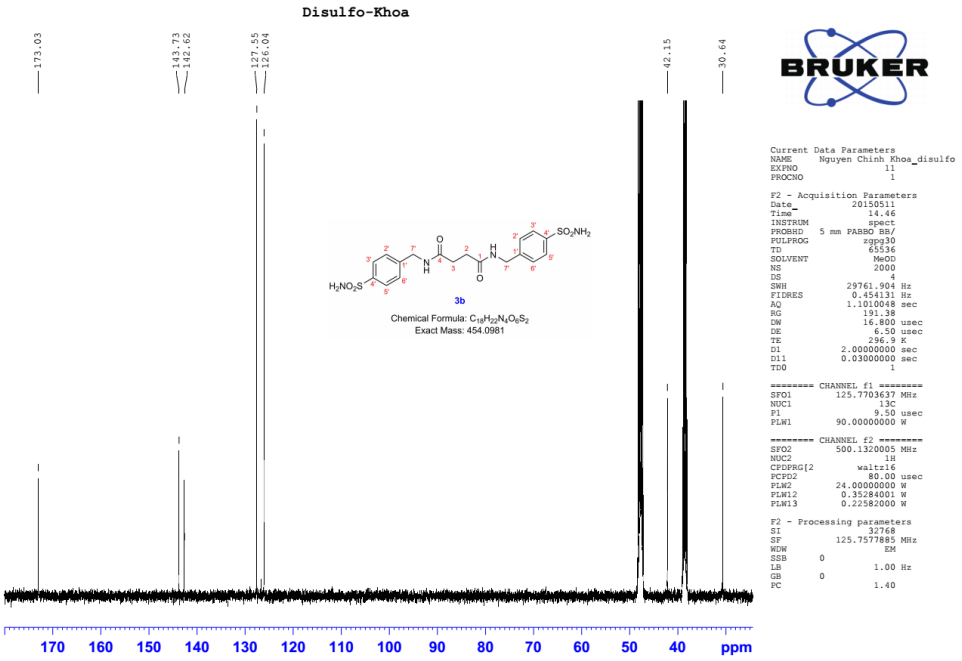


Fig. S8 ^{13}C-NMR of N^1,N^4-bis(4-sulfamoylbenzyl)succinamide (**3b**).

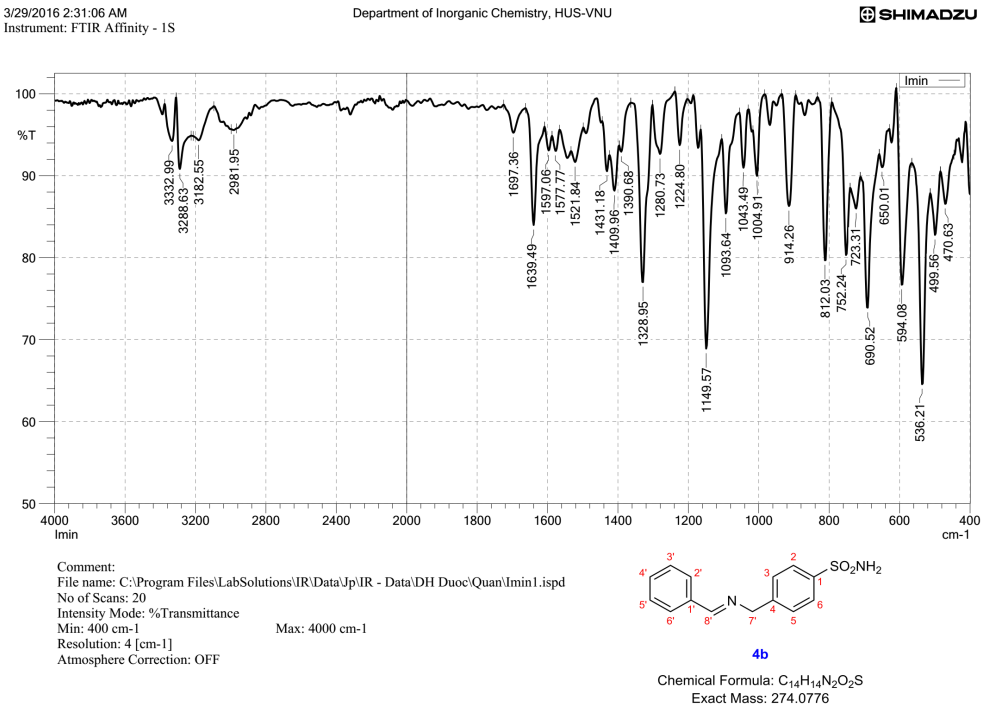


Fig. S9 IR of *p*-[(benzylidenamino)methyl]benzenesulfonamide (**4b**).

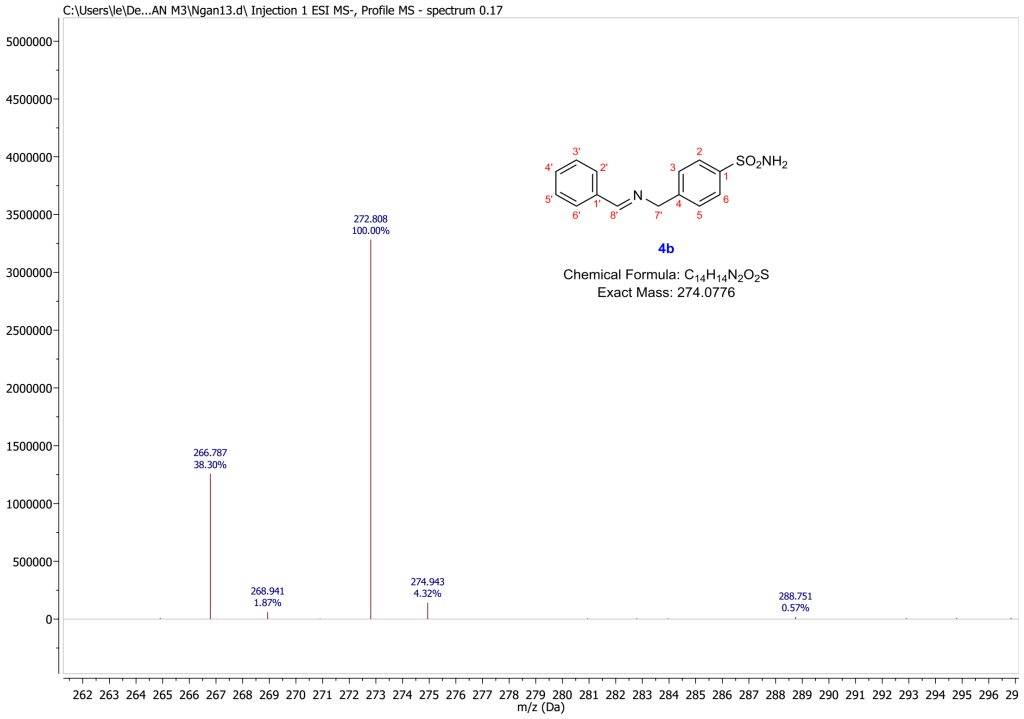


Fig. S10 MS of *p*-[(benzylidenamino)methyl]benzenesulfonamide (**4b**).

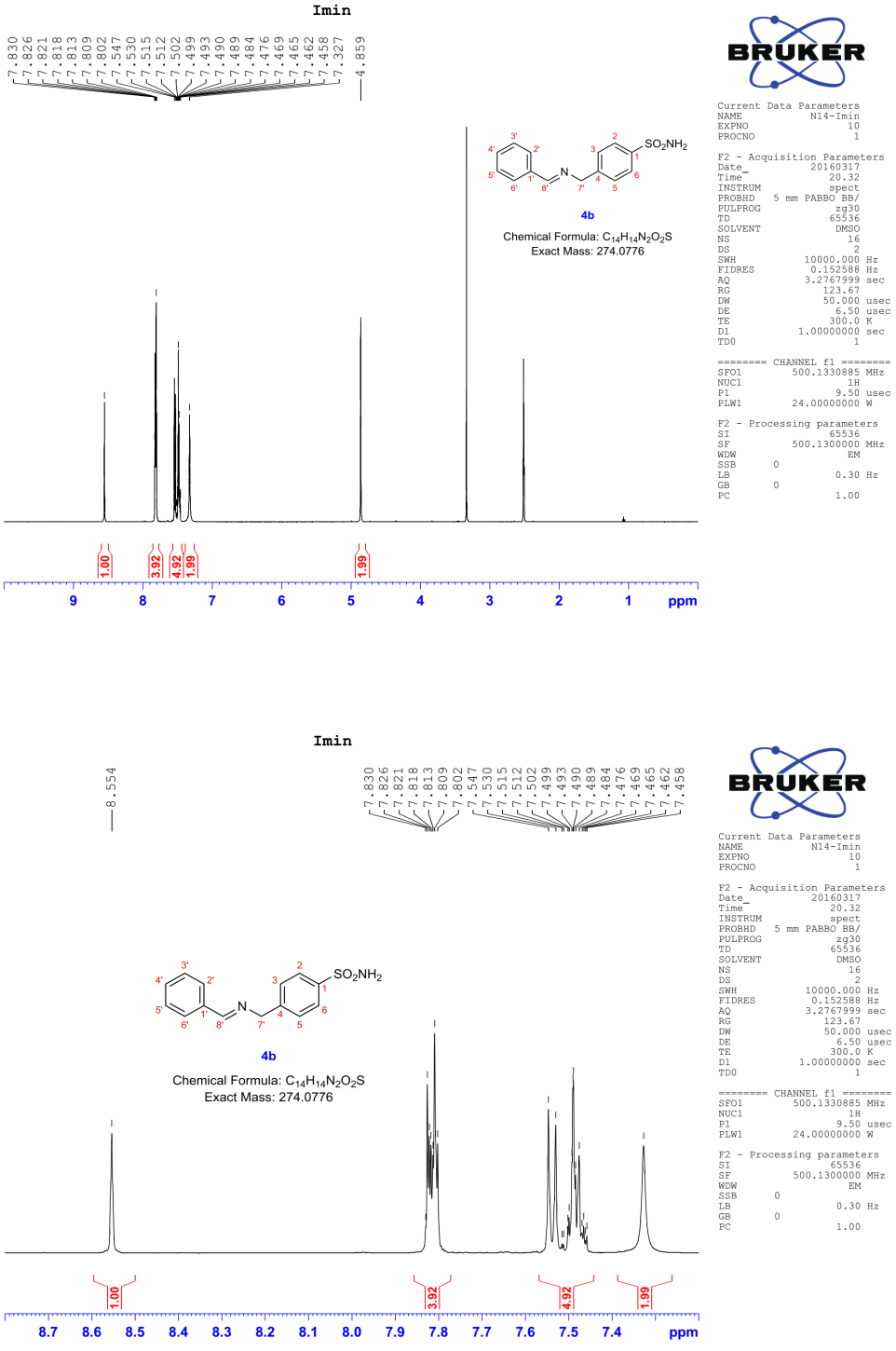


Fig. S11 ^{1}H-NMR of *p*-[(benzylidenamino)methyl]benzenesulfonamide (**4b**).

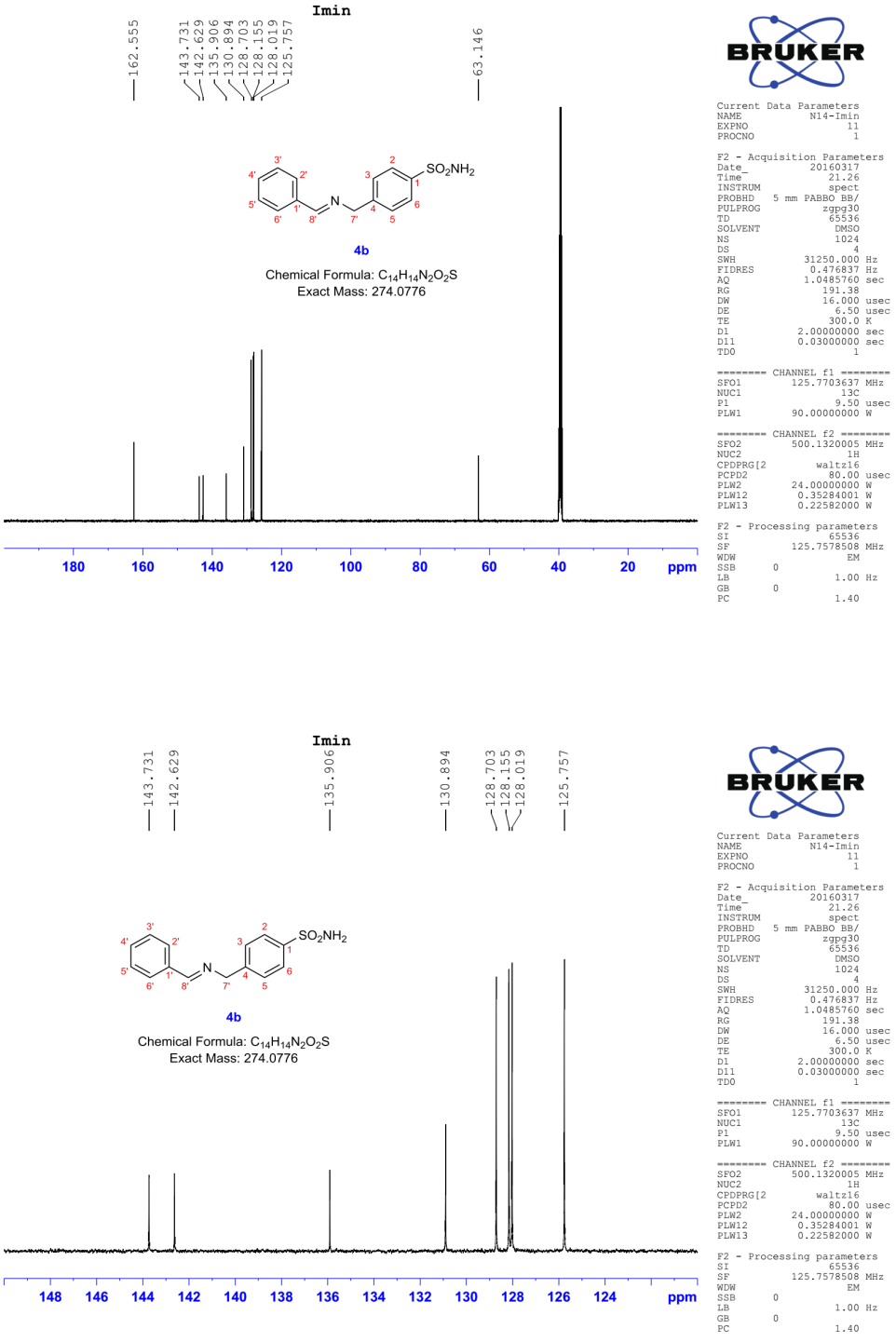


Fig. S12 ^{13}C-NMR of *p*-[(benzylidenamino)methyl]benzenesulfonamide (**4b**).

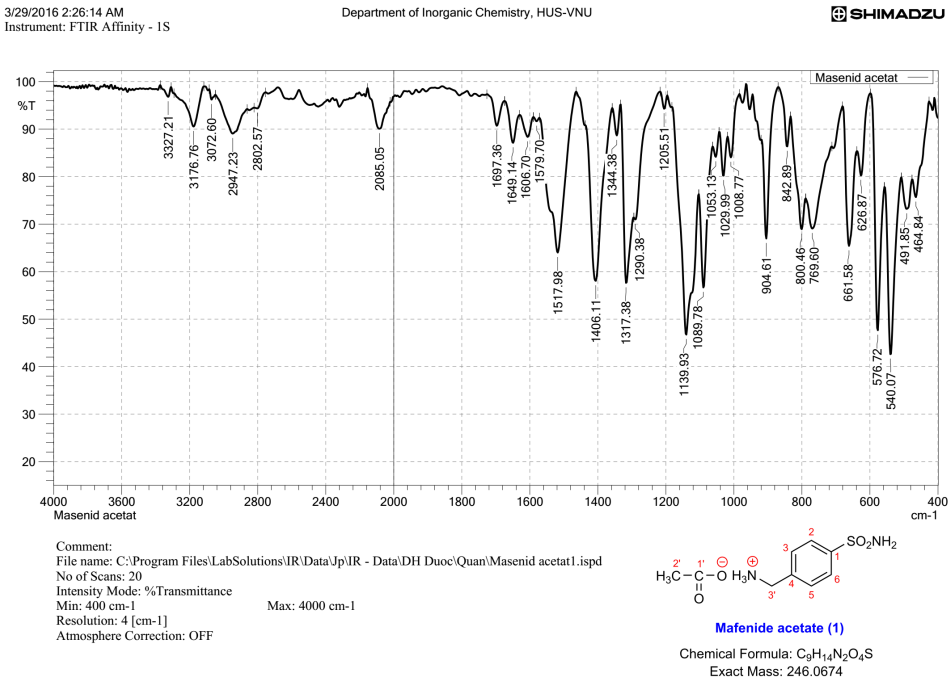


Fig. S13 IR of mafenide acetate.

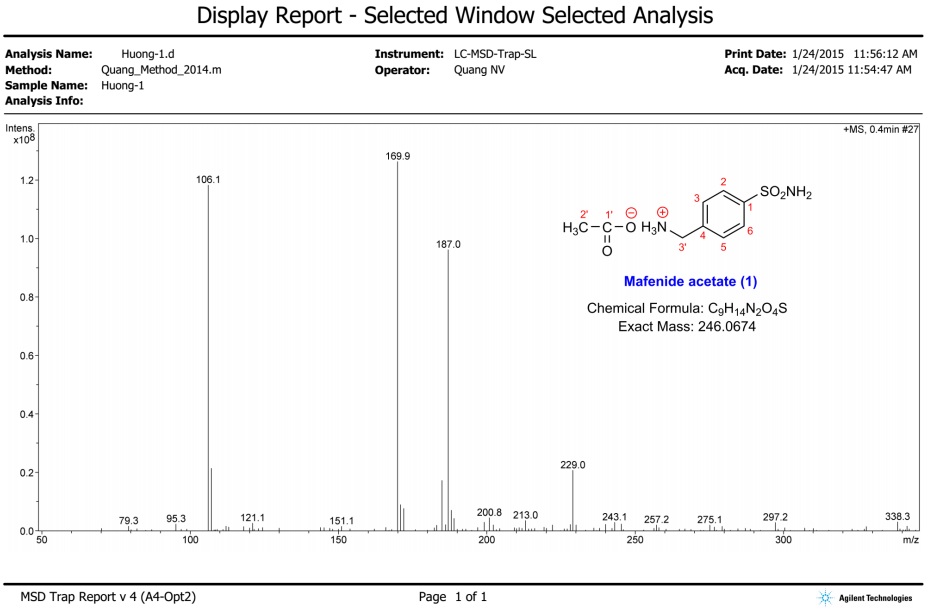


Fig. S14 MS of mafenide acetate.

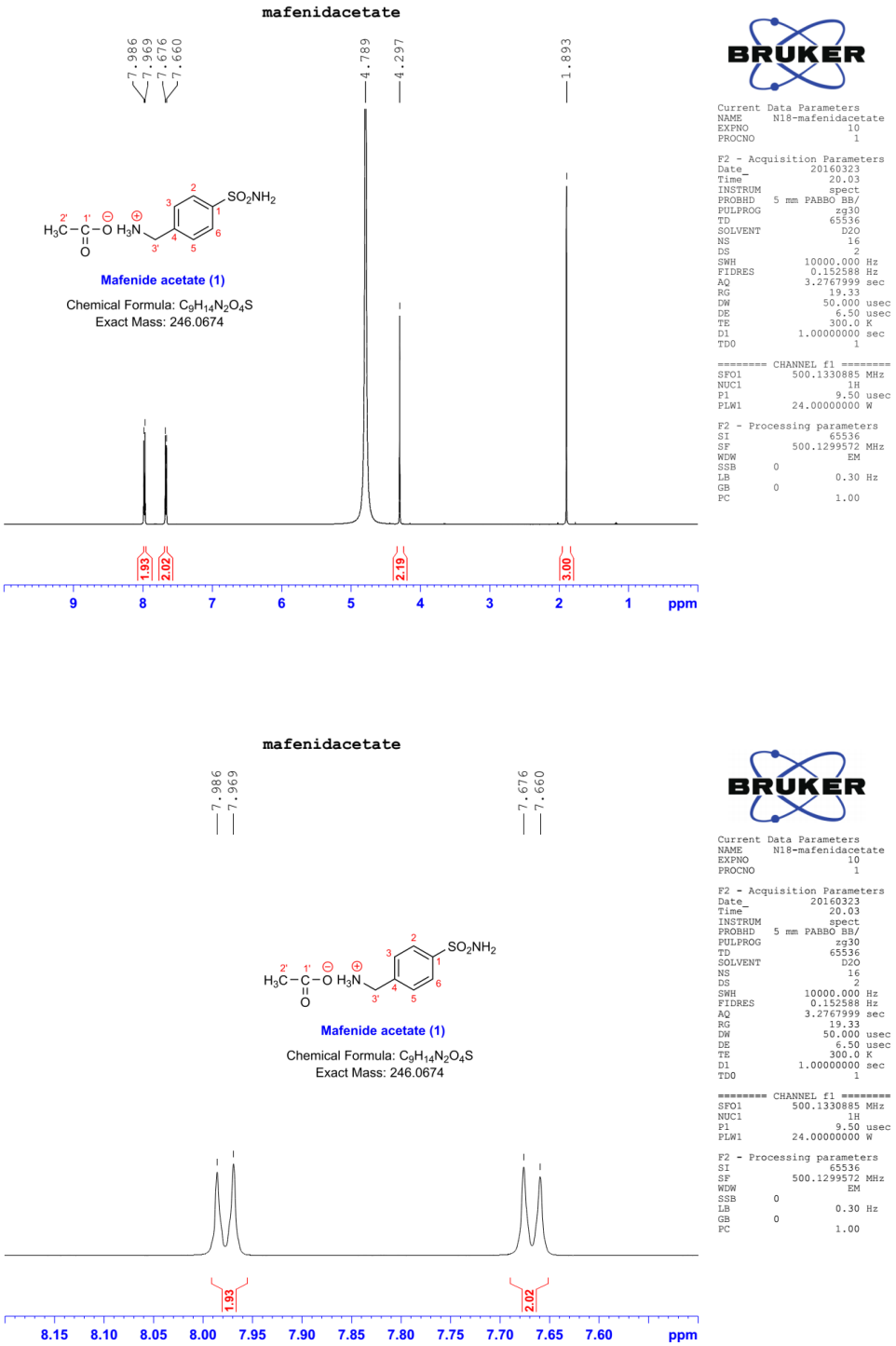
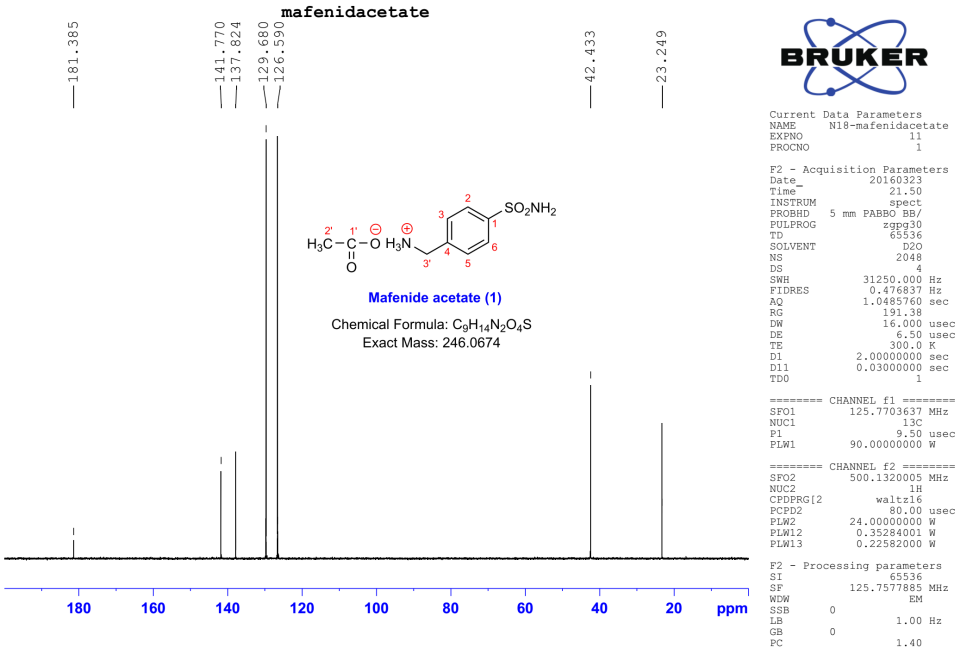


Fig. S15 ^{1}H-NMR of mafenide acetate.



[h]

Fig. S16 ^{13}C-NMR of mafenide acetate.

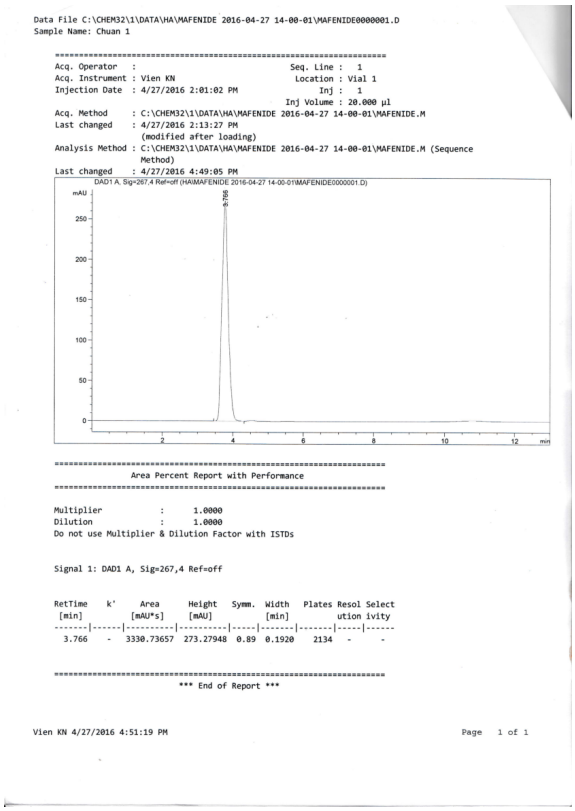
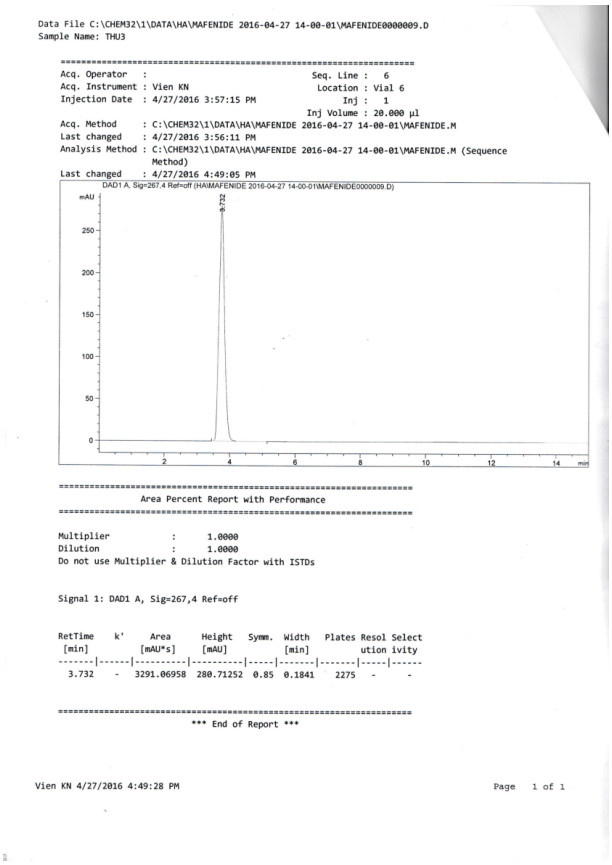


Fig. S17 HPLC of mafenide acetate USP.



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Injection Date : 4/27/2016 3:57:15 PM Inj : 1
Inj Volume : 20.000 µl
Acq. Method : C:\CHEM32\1\DATA\HA\MAFENIDE 2016-04-27 14-00-01\MAFENIDE.M
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Analysis Method : C:\CHEM32\1\DATA\HA\MAFENIDE 2016-04-27 14-00-01\MAFENIDE.M (Sequence Method)
Last changed : 4/27/2016 4:49:05 PM

DAD1 A, Sig=267,4 Ref=off (HA\MAFENIDE 2016-04-27 14-00-01\MAFENIDE0000009.D)

Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=267,4 Ref=off

RetTime [min]	k'	Area [mAU*s]	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
3.732	-	3291.06958	280.71252	0.85	0.1841	2275	-	-

*** End of Report ***

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Fig. S18 HPLC of obtained mafenide acetate.