

New C-terminal hydrazide L-Leucine derivatives as multi-solvent low molecular weight organogelators

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THREE new low-molecular-weight gelators (LMWGs) based on L-Leucine derivatives bearing different chain lengths (i.e. 9, 12 or 16) were designed and synthesized. The N-terminal carries various alkyl chain lengths while the C-terminal is modified with hydrazide moiety. The prepared gelators **1-3** were fully characterized using ¹H, ¹³C NMR, FTIR and mass spectroscopy. The gelation behavior has also been investigated using different organic solvents and oils with determination of critical gelation concentration (CGC). The self-assembly process was investigated by recording FTIR spectra gel states to investigate the driving forces for gelation process. The morphology of the prepared xerogels was studied using SEM.

Keywords: Low-Molecular-Weight Gelators, L - Leucine, gelation, self-assembly, hydrogen bonding

Introduction

In the last decade gels are focusing intense research interest, thanks to the wide application fields in medicine¹, electronics², catalysis³. Among them, organogels are able to immobilize organic solvents such as aliphatics and aromatics. Several strategies can be considered to develop such soft materials. Indeed, in parallel to macromolecular chemical gels, and because of their smart and versatile architecture, supramolecular low-molecular-weight gelators (LMWGs) have recently gained interest with applications in environmental issues⁴ or drug delivery⁵. LMWGs have the ability to restrict the flow of various fluid phases, thanks to self-assembly process of the pre-designed small molecules (< 2000 g. mol⁻¹), forming three dimensional fibrillar networks. This assembly is achieved via different intermolecular physical interactions such as Hydrogen bonding or van der Waals, hydrophobic interactions.^{6,7} Among the range of bioinspired LMWG, amino acids offers suitably oriented donor and acceptor hydrogen bonding sites promoting self-assembly processes^{8,9}.

Moreover, these gelators provide several advantages such as low price, commercial availability, non-toxicity and are eco-friendly. The use of single amino-acid based molecules for the gelation of organic solvents and oils is less exploited and reported than peptides. For instance, Yu *et al.* have reported L-Leucine dihydrazide derivative that could gel many organic solvents.¹⁰ Zinic *et al.* have proposed the model of bis(leucine) oxalyl-amide¹¹, while Boekhoven *et al.* have selected the same gelator to study the orthogonal self-assembly and the molecular arrangement in gel fiber.¹²

In this context we have developed a new series of L-leucine derivatives **1-3** (Chart 1) bearing hydrazide moiety and alkyl chain (C₉, C₁₂ and C₁₆) at C- and N-terminal positions respectively. The inherent design of this series stands on the C-terminal hydrazide modification which was introduced in order to enhance the hydrogen bonding potentials and finally the gelation efficiency. Thus, our gelators are able to trap various organic solvents and several oils.

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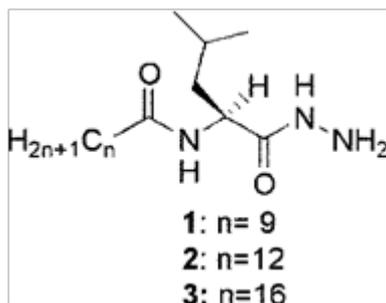


Chart 1. LMWGs 1-3

Experimental

Materials

L-Leucine methylester hydrochloride, decanoic acid, tridecanoic acid and heptadecanoic acid were purchased from TCI. *N,N,N',N'*-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) was purchased from Iris. *N,N*-Diisopropylethyl amine (DIPEA), hydrazine monohydrate and all other chemicals and solvents were purchased from Sigma-Aldrich.

Analysis

All the ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer. Electrospray mass spectrometry (ESI-MS) was performed with a ToF-Q HR spectrometer. The characteristic absorption peaks for solid and gel samples were studied by ATR-FTIR spectroscopy (ATR Pike Miracle equipped with Germanium crystal, Bruker Tensor 27). All spectra were obtained by 164 scans and 2 cm^{-1} resolutions in wavenumbers ranging from 4000 to 1000 cm^{-1} . The morphology of the prepared xerogels were analyzed by scanning electron microscopy (SEM, Quanta FEG 250, FEI). The critical gelation concentration (CGC) is determined by visual checking in various fluids (*i.e.* organic solvents and oils) by test tube inversion.¹³

Synthesis of C_n -Leu-OMe and 1-3

Synthesis of C_n -Leu-OMe

A solution of L-Leucine methylester hydrochloride (5 g, 27.50 mmol), DIPEA (10.0 mL, 2.0 eq, 55.10 mmol) and decanoic acid (5.21 g, 1.1eq, 30.25 mmol), tridecanoic acid (6.48 g, 1.1eq, 30.25 mmol) or heptadecanoic acid (8.18 g, 1.1eq, 30.25 mmol) in case of C_9 -Leu-OMe, C_{12} -Leu-OMe and C_{16} -Leu-OMe, respectively in (50 mL) chloroform, were added to a solution containing HBTU (11.52 g, 1.1eq, 30.25 mmol) and DIPEA (10.0 mL, 2.0 eq, 55.10 mmol) in DMF (20 mL), and the mixture was stirred at room temperature till completion of the reaction (followed by TLC), Then washed two times consequently with 5% HCl, 10% K_2CO_3 , brine and water. The separated organic phase was dried over anhydrous MgSO_4 , and the volatiles were removed using a rotary evaporator. The resultant solids were purified collected by precipitation in diethyl ether, then dried *in vacuo*.

In case of C_9 -Leu-OMe

^1H NMR (300 MHz, CDCl_3 at $25\text{ }^\circ\text{C}$): δ (ppm) = 6.60 (s, 1H), 4.51 (m, 1H), 3.71 (s, 3H), 2.12 (t, 2H), 1.54 (br, 6H), 1.19 (br, 14H), 0.85 (br, 9H). ^{13}C NMR (CDCl_3 at $25\text{ }^\circ\text{C}$): δ (ppm) = 174.41, 94, 41, 37.63, 32.86, 30.01, 25.90, 23.05, 15.08, 9.71. Yield 6.5 g (80.0 %).

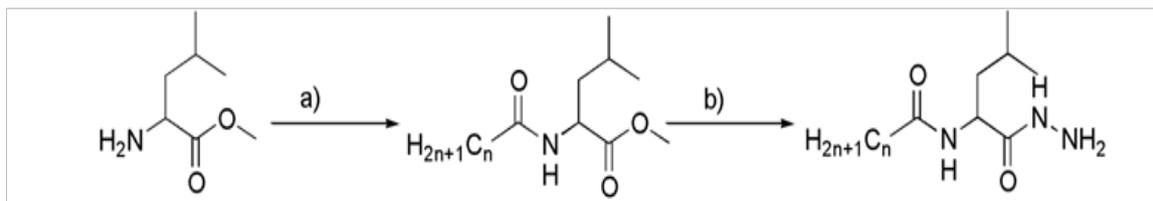
HRMS (ESI): Calcd. for $\text{C}_{17}\text{H}_{33}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 300.25, Found: 300.25.

In case of C_{12} -Leu-OMe

^1H NMR (300 MHz, CDCl_3 at $25\text{ }^\circ\text{C}$): δ (ppm) = 5.81 (s, 1H), 4.66 (m, 1H), 3.71 (s, 3H), 2.20 (t, 2H), 1.64 (br, 6H), 1.25 (br, 14H), 0.87-0.94 (br, 9H). ^{13}C NMR (CDCl_3 at $25\text{ }^\circ\text{C}$): δ (ppm) = 174.79, 173.55, 52.90, 50.94, 42.74, 37.65, 32.87, 30.01, 26.27, 25.57, 23.05, 22.67, 14.78. Yield 7.0 g (75.0 %).

HRMS (ESI): Calcd. for $\text{C}_{20}\text{H}_{39}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 341.29, Found: 341.29.

In case of C_{16} -Leu-OMe



Scheme 1. Reagents and conditions: (a) $\text{C}_n\text{H}_{2n+1}\text{COOH}$, 1 equiv, DIEA in DMF/CHCl_3 , rt; (b) $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$, 2 equiv, MeOH, rt, 18 h.

$^1\text{H NMR}$ (300 MHz, CDCl_3 at 25 °C): δ (ppm) = 5.92 (s, 1H), 4.63 (m, 1H), 3.71 (s, 3H), 2.18 (t, 2H), 1.60 (br, 6H), 1.23 (br, 14H), 0.92 (br, 9H). $^{13}\text{C NMR}$ (CDCl_3 at 25 °C): δ (ppm) = 173.75, 172.90, 52.58, 50.49, 41.71, 36.51, 31.89, 29.47, 25.58, 24.86, 22.77, 22.35, 21.93, 14.06. Yield 8.9 g (82.0 %).

HRMS (ESI): Calcd. for $\text{C}_{24}\text{H}_{47}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 398.36, Found: 398.36.

Synthesis of 1-3

To a solution of C_9 -Leu-OME, C_{12} -Leu-OME or C_{16} -Leu-OME (5 g) in methanol, hydrazine monohydrate (2 eq.) was added at 0-5 °C and stirred at room temperature until a precipitate appeared. The white solid was filtered and washed with diethylether. The precipitate was dried in vacuo.

In case of Gelator 1

$^1\text{H NMR}$ (300 MHz, CDCl_3 at 25 °C): δ (ppm) = 6.60 (s, 1H), 4.51 (m, 1H), 2.12 (t, 2H), 1.54 (br, 6H), 1.19 (br, 14H), 0.85 (br, 9H). $^{13}\text{C NMR}$ (CDCl_3 at 25 °C): δ (ppm) = 174.41, 94, 41, 37.63, 32.86, 30.01, 25.90, 23.05, 15.08, 9.71. Yield 4.0 g (80.0 %).

HRMS (ESI): Calcd. for $\text{C}_{16}\text{H}_{33}\text{N}_3\text{O}_2$ $[\text{M}+\text{Na}]^+$: 322.24, Found: 322.23.

In case of Gelator 2

$^1\text{H NMR}$ (300 MHz, CDCl_3 at 25 °C): δ (ppm) = 5.81 (s, 1H), 4.66 (m, 1H), 2.20 (t, 2H), 1.64 (br, 6H), 1.25 (br, 14H), 0.87-0.94 (br, 9H). $^{13}\text{C NMR}$ (CDCl_3 at 25 °C): δ (ppm) = 174.79, 173.55, 52.90, 50.94, 42.74, 37.65, 32.87, 30.01, 26.27, 25.57, 23.05, 22.67, 14.78. Yield 3.5 g (70.0 %).

HRMS (ESI): Calcd. for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_3$ $[\text{M}+\text{Na}]^+$:

364.30, Found: 364.29.

In case of Gelator 3

$^1\text{H NMR}$ (300 MHz, CDCl_3 at 25 °C): δ (ppm) = 5.92 (s, 1H), 4.63 (m, 1H), 3.71 (s, 3H), 2.18 (t, 2H), 1.60 (br, 6H), 1.23 (br, 14H), 0.92 (br, 9H). $^{13}\text{C NMR}$ (CDCl_3 at 25 °C): δ (ppm) = 173.75, 172.90, 52.58, 50.49, 41.71, 36.51, 31.89, 29.47, 25.58, 24.86, 22.77, 22.35, 21.93, 14.06. Yield 3.25 g (65.0 %).

HRMS (ESI): Calcd. for $\text{C}_{23}\text{H}_{48}\text{N}_3\text{O}_2$ $[\text{M}+\text{Na}]^+$: 420.36, Found: 420.37.

Results and discussion

Organogelation properties

The ability of the three synthesized compounds 1-3 to form gels with various organic solvents and oils (*i.e.* alkanes, aromatics, ester, chlorinated and alcohol) and oils (paraffin, olive and sunflower) were evaluated, as shown in Table 1.

As a general overview, organogels were obtained with alkanes (except for gelator 2 in *i*-Octane), aromatics and oils. In contrast, our compounds are not efficient for other organic solvent such as dichloromethane, chloroform, methanol and ethyl acetate. For all gelators, the lower CGC were obtained with alkanes. Another general trend concerns the decrease of CGC when gelator alkyl chain lengths increase. For instance, in *n*-Octane, CGC decrease of a factor of 1.5 from C_9 to C_{12} and 1.7 from C_{12} to C_{16} . In other words, a longer alkyl chain introduces more hydrophobic interactions and thus increase the gelation number (GN) as shown in Figure 1.

TABLE 1. Selected results of the gelation ability screening for 1-3 in various solvents.

G(x): gel / CGC in wt% / CGC in mM;

OG: opaque gel, TG: transparent gel, PG: partial gel, S: soluble, P: precipitate.

Solvents	1	2	3
Paraffin oil	TG / 1.00 / 30.06	TG / 0.44 / 11.61	TG / 0.10 / 22.70
Olive oil	TG / 1.50 / 46.35	TG / 1.00 / 26.82	TG / 0.45 / 10.38
Sunflower oil	TG / 1.60 / 49.01	TG / 1.20 / 32.10	TG / 0.56 / 12.86
<i>i</i> -Octane	TG / 0.90 / 20.76	PG / N.A. / N.A.	OG / 0.50 / 8.72
<i>n</i> -Octane	OG / 0.80 / 18.78	OG / 0.60 / 12.40	OG / 0.41 / 7.28
Cyclohexane	OG / 0.61 / 15.96	OG / 0.52 / 11.88	OG / 0.31 / 6.08
Toluene	TG / 1.40 / 40.78	TG / 0.72 / 18.40	TG / 0.62 / 13.54
Benzene	TG / 1.80 / 53.19	TG / 0.92 / 23.75	TG / 0.56 / 12.31
<i>p</i> -Xylene	TG / 1.20 / 34.64	TG / 0.80 / 20.17	TG / 0.68 / 14.73
1,2-Dichlorobenzene	TG / 1.20 / 52.30	TG / 0.73 / 27.99	TG / 0.53 / 17.30
Dichloromethane	S	S	S
Chloroform	S	S	S
Methanol	S	S	S
Ethyl Acetate	S	PG / N.A. / N.A.	P

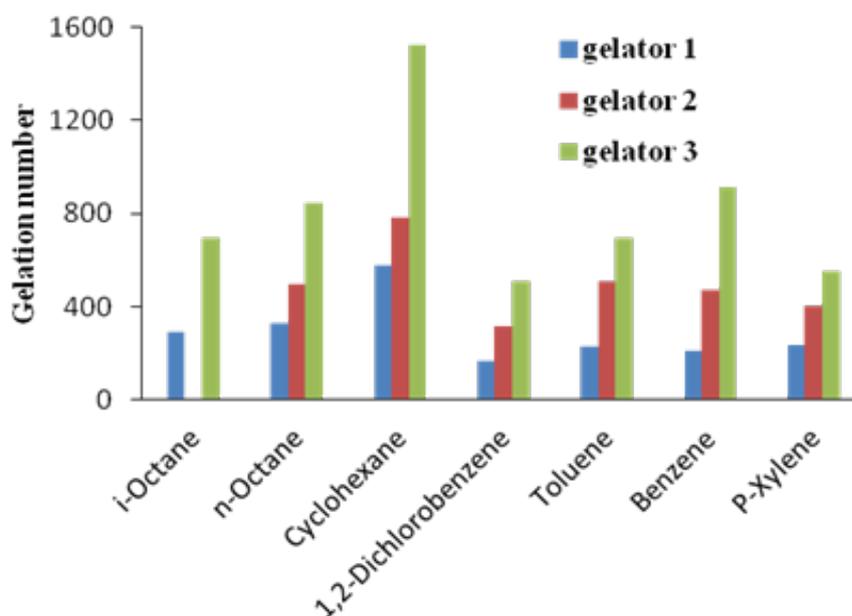


Fig. 1. Gelation number (GN: number of immobilized solvent molecules per gelator molecule) for compounds 1-3 in alkane and aromatic solvents, the GN increase with the length of alkyl chains.

Gelation in aromatic solvents and oils forms transparent gels, when opaque gels are observed in alkanes. Opacity is a consequence of the size of objects found in the gel network. When objects are smaller than light wavelength, gels are transparent. In contrast, gels are more opaque with larger objects.¹⁴

Methyl ester precursors were also evaluated in order to demonstrate the relevance of the hydrazide moiety. Interestingly, no gels were obtained. This indicates that the presence of hydrazide function is essential for additional hydrogen bonding, which is of primary importance for 1D-self assembly process, subsequently leading to the formation of three dimensional fibrillar networks.

Fourier-transform infrared investigation

FTIR spectroscopy have been used to investigate, at molecular level, the weak interactions promoting the self-assembly processes. The area of the stretching vibrations of carbonyls (amide and hydrazide) was studied. Spectra of n-octane (Figure 2) and toluene (Figure 3) organogels were recorded for all three gelators at 20 mM. In the case of n-Octane, study of amide I region shows that gelators 2 and 3 have an extremely similar signature with two major vibrators at 1635 and 1608 cm^{-1} corresponding to hydrazide and amide C=O respectively.

Interestingly, shortening of alkyl chain length provokes slight changes in the self-assembly process at molecular level. Indeed, spectrum of 1 (Figure 2) show the hydrazide carbonyl at 1639 cm^{-1} and the amide one at 1618 cm^{-1} , instead of 1635 and 1608 cm^{-1} in the case of gelators 2 and 3. Moreover, weak bands, attributed to free hydrazide and amide carbonyls (obtained from DMSO solutions), found at 1680 and 1661 cm^{-1} indicates that a small part of gelator molecules is not completely involved in the 3D gel network. Same phenomenon is observed in toluene gels (Figure 3). The spectrum of gelator 1 is different than spectra of 2 and 3.

Morphological study of the prepared xerogels.

SEM was used to investigate the morphology of the obtained materials. The analyzed xerogels were obtained by open air drying the corresponding organogels. The self-assembled nanofibers are entangled leading to formation of three-dimensional network during gel formation as shown in Figure 4. The difference in fibre size are clearly observed, which indicates that the nanofibers are different from a solvent to another.

Further investigations regarding rheological properties and FTIR will be conducted to go further in the understanding of the gelation process.

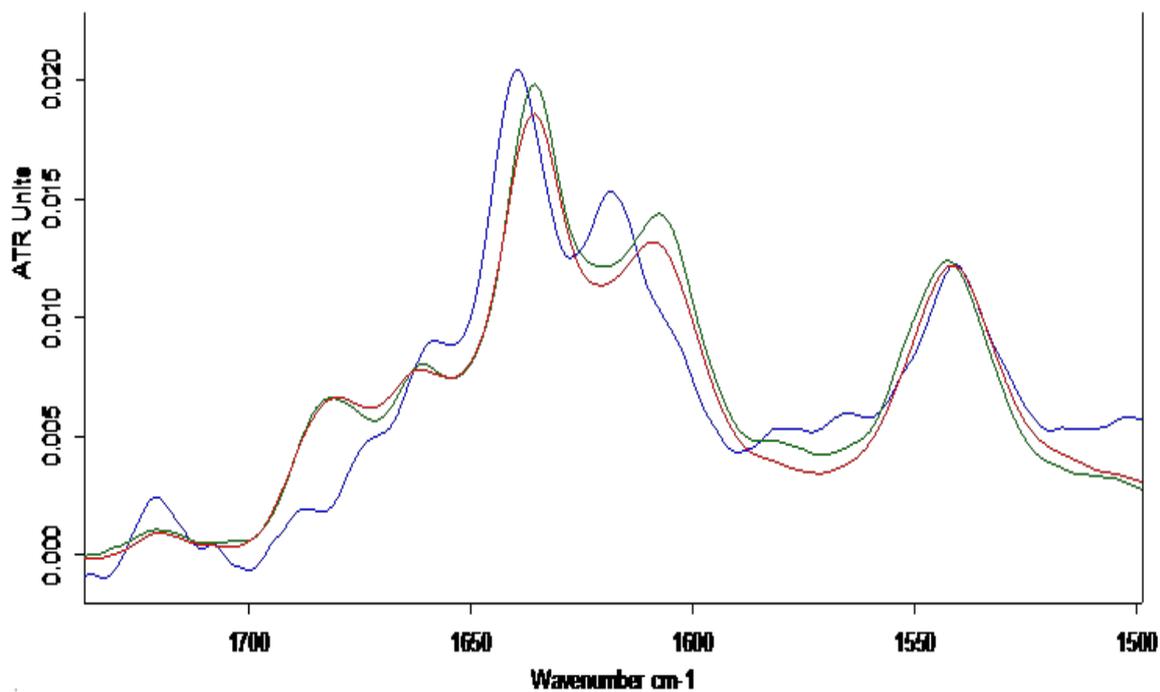


Fig. 2. Amide I region FT-IR spectra of 1 (blue), 2 (red) and 3 (green) in gel state (n-Octane, 20 mM).

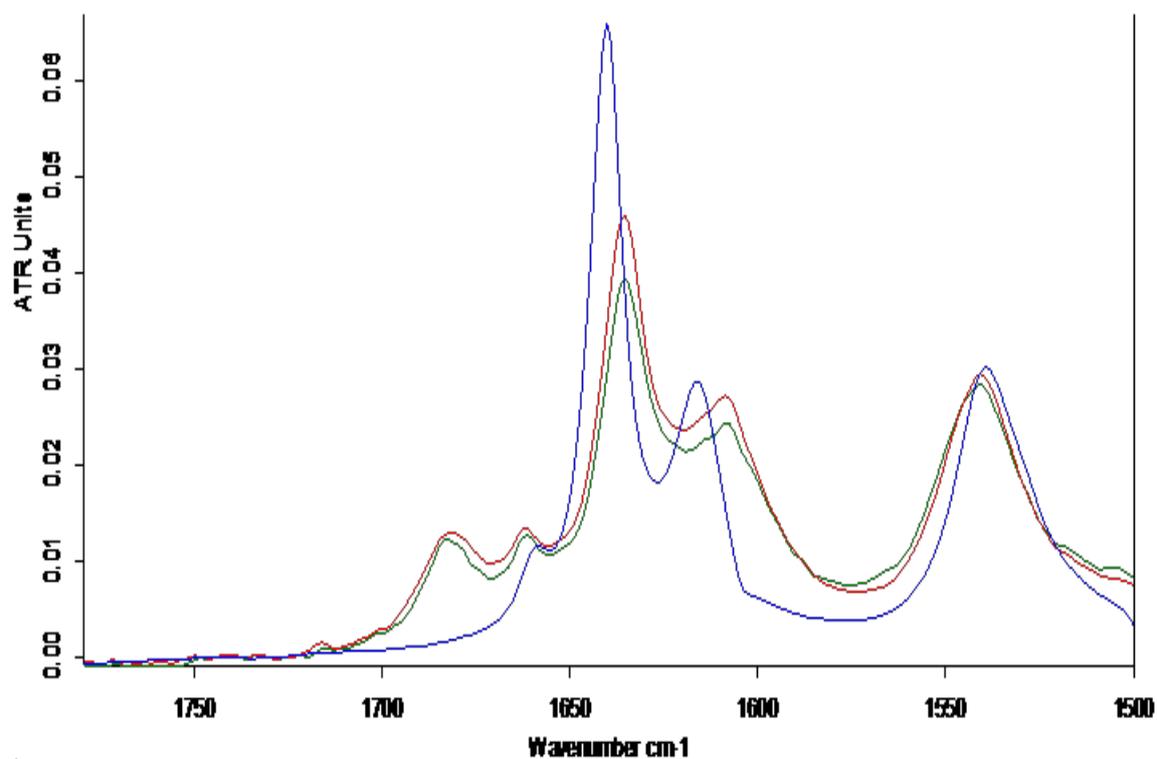


Fig. 3. Amide I region FT-IR spectra of 1 (blue), 2 (red) and 3 (green) in gel state (toluene, 20 mM).

Conclusions

Three new LMWGs based on L-Leucine derivatives 1-3 bearing different alkyl chains (9, 12, or 16 carbons) at their N-term position and an hydrazide moiety at their C-term position were synthesized. The prepared gelators were fully characterized using ^1H , ^{13}C NMR, FTIR and mass spectroscopy. LMWGs 1-3 show good gelation behavior in alkanes, aromatics and oils with low CGC. FT-IR study show the primary importance of hydrogen bonding. The morphology of the prepared xerogels was also investigated using SEM.

The modifications introduced on leucine amino acid derivatives lead to efficient organogels with a wide variety of solvents and oils, pointing the way towards many applications.

Acknowledgements

The authors acknowledge O. Fabre for NMR characterization and Elodie Jeanvoine for FT-IR experiments; M.M. Abdellatif thanks Région Lorraine and Lorraine-Université for funding this research.

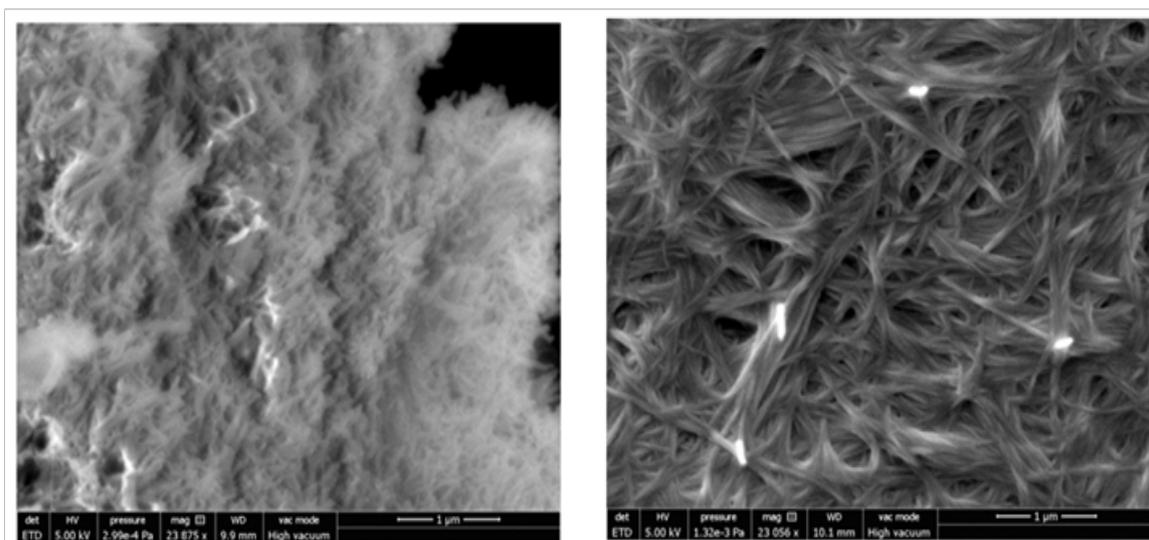


Fig. 4. SEM images of xerogels obtained by open air drying of organogels of 3 (1 wt%) in toluene (left) and in i-Octane (right).

Supporting information

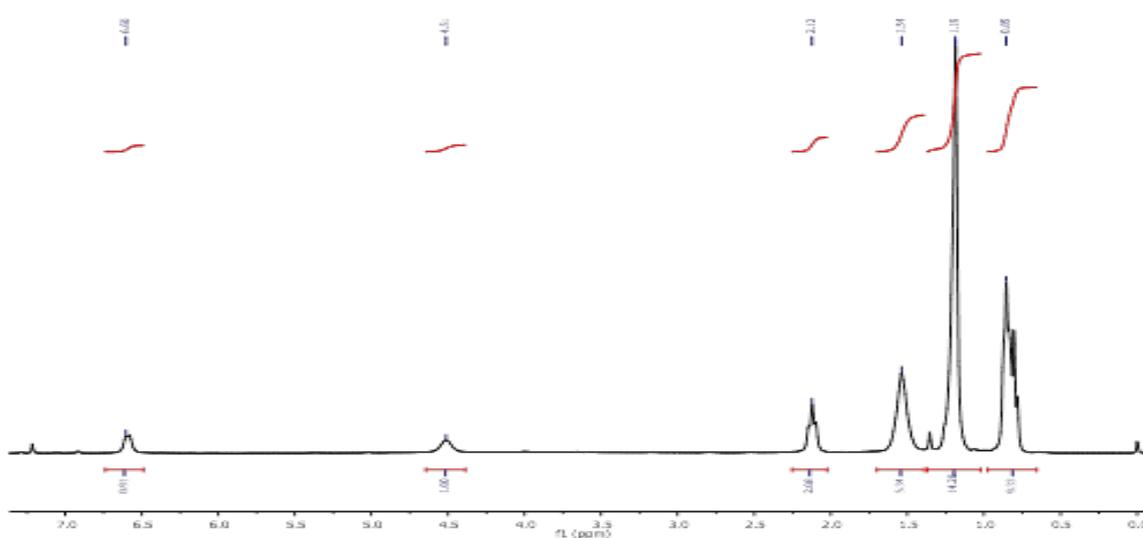


Fig. 1S. ^1H NMR chart of 1 (in CHCl_3 at 25°C).

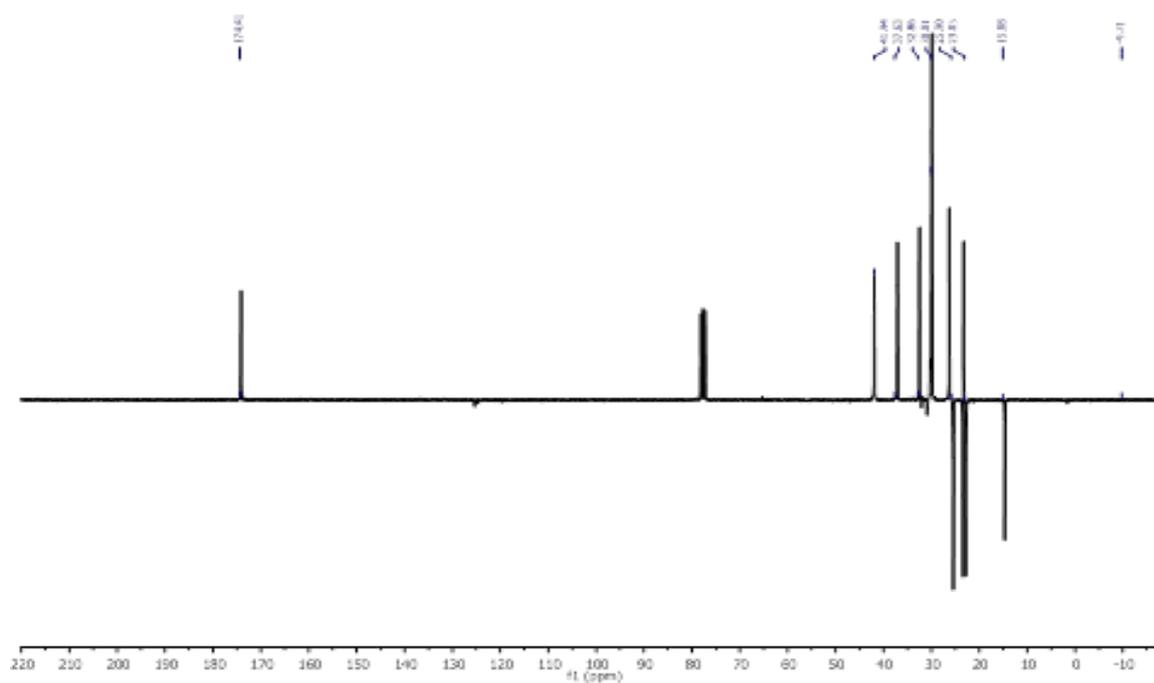


Fig. 2S. ^{13}C NMR chart of 1 (in CHCl_3 at 25°C).

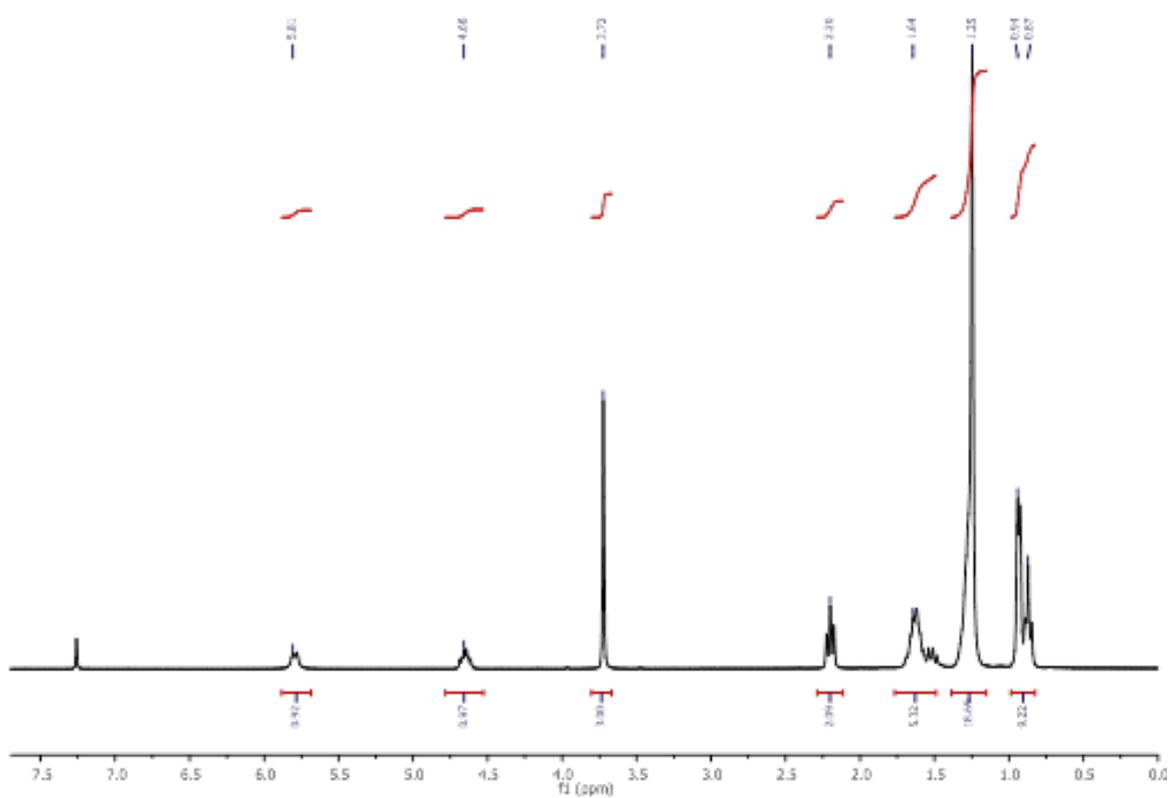


Fig. 3S. ^1H NMR chart of C_{12} -Leu-OMe (in CHCl_3 at 25°C).

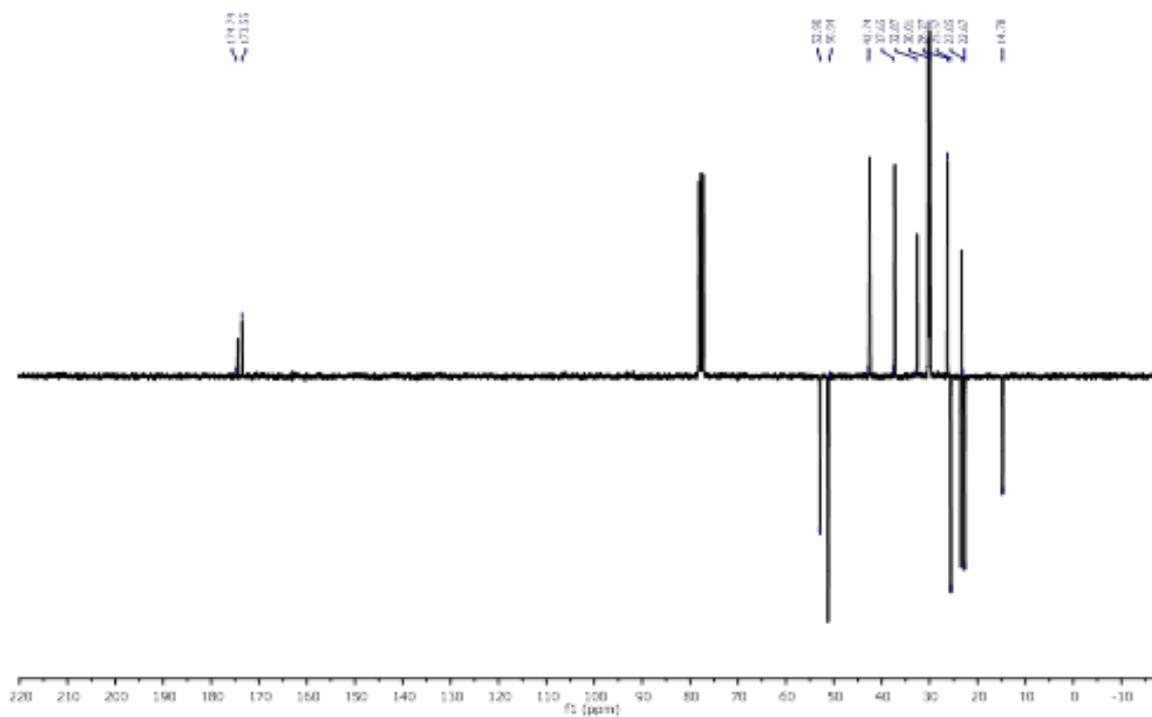


Fig. 4S. ^{13}C NMR chart of C_{12} -Leu-OMe (in CHCl_3 at 25°C).

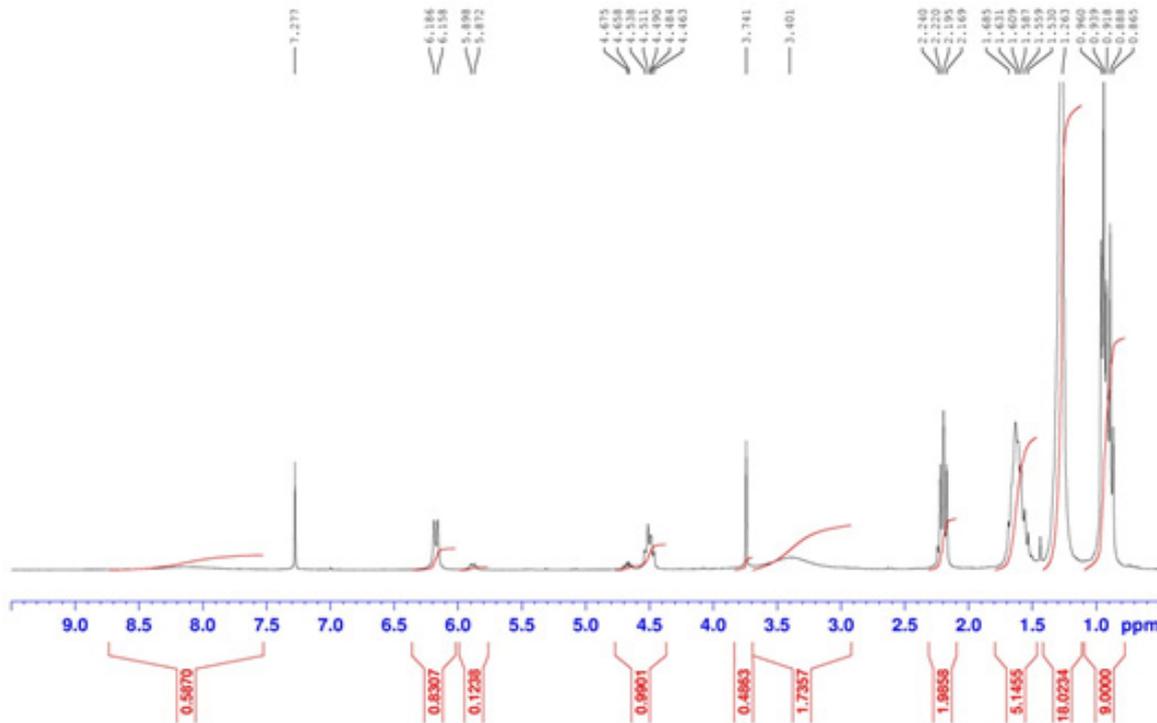


Fig. 5S. ^1H NMR chart of 2 (in CHCl_3 at 25°C).

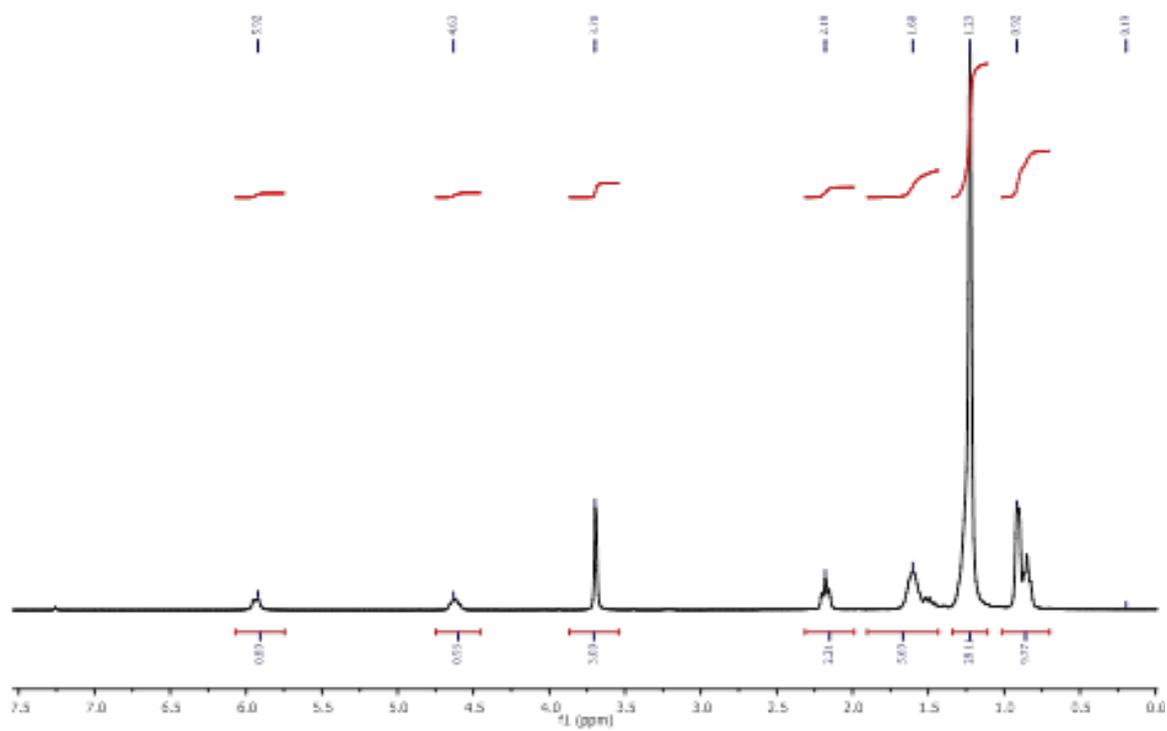


Fig. 6S. ^1H NMR chart of $\text{C}_{16}\text{-Leu-OMe}$ (in CHCl_3 at 25°C).

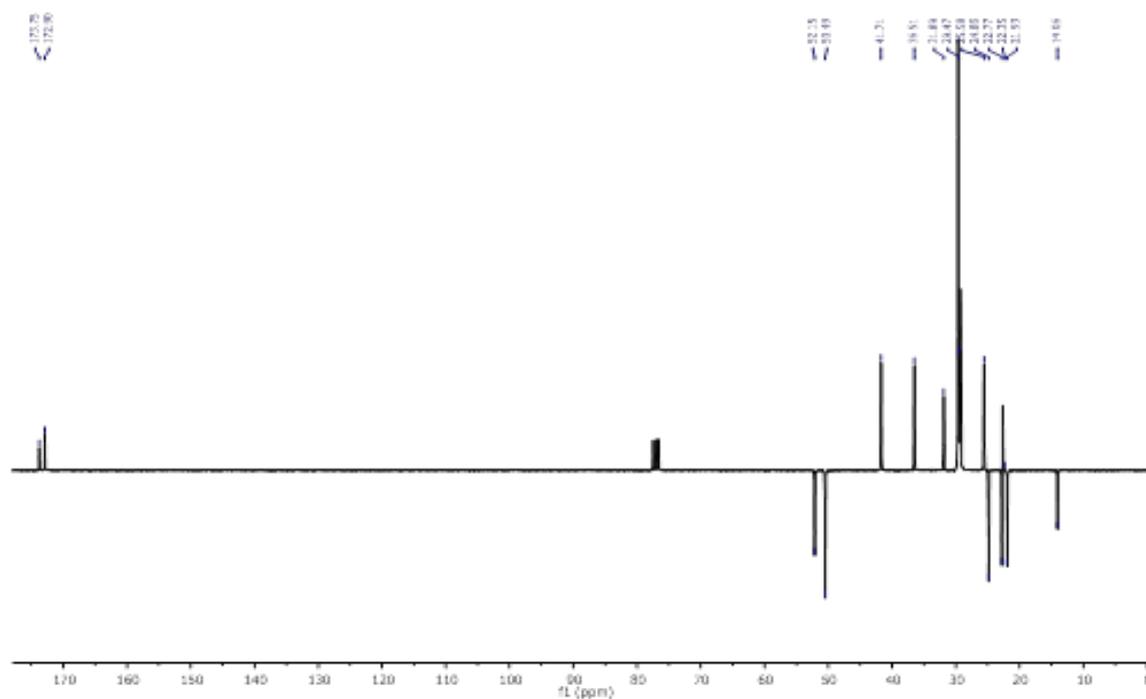


Fig. 7S. ^{13}C NMR chart of $\text{C}_{16}\text{-Leu-OMe}$ (in CHCl_3 at 25°C).

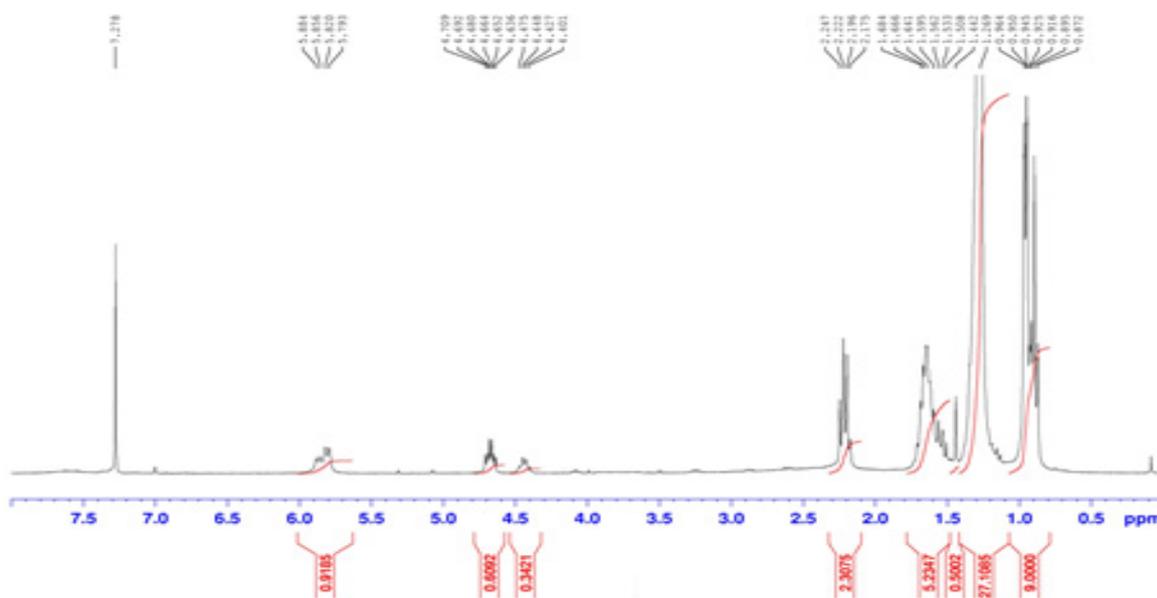


Fig. 8S. ^1H NMR chart of $\mathbf{3}$ (in CHCl_3 at 25°C).

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أستخدام مشتقات الليوسين ذات مجموعة الهيدرازيد الطرفية كمواد مجلنتة للعديد من المذيبات العضوية

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ثلاثة مواد مجلنتة صغيرة الوزن الجزيئي تم تحضيرهم وتصميمهم بأستخدام الليوسين ذات مجموعة 21 أو 21 (. المواد المجلنتة المحضرة تم , الهيدرازيد الطرفية واطوال مختلفة من سلاسل الالكيل) 9 توصيفهم بشكل كامل بأستخدام الاشعة تحت الحمراء, الرنين المغناطيسي و طيف الكتلة. وتم تقييم القدرة الجيلاتينية للمركبات المحضرة بأستخدام مذيبات عضوية وزبوت مع تعيين التركيز الحرج لتكوين الجيلاتين. وتم أستخدام الاشعة تحت الحمراء لدراسة عملية تكوين الجيلاتين ومعرفة القوى المحفزة لتكوينه. كما تم استخدام الميكروسكوب الالكتروني لدراسة الخواص السطحية للجبل الهواني.