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Digest

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Graphical Abstract

Design, Synthesis, and Biological Activity Evaluation of A series of Pleuromutilin Derivatives with New C14 Side Chains

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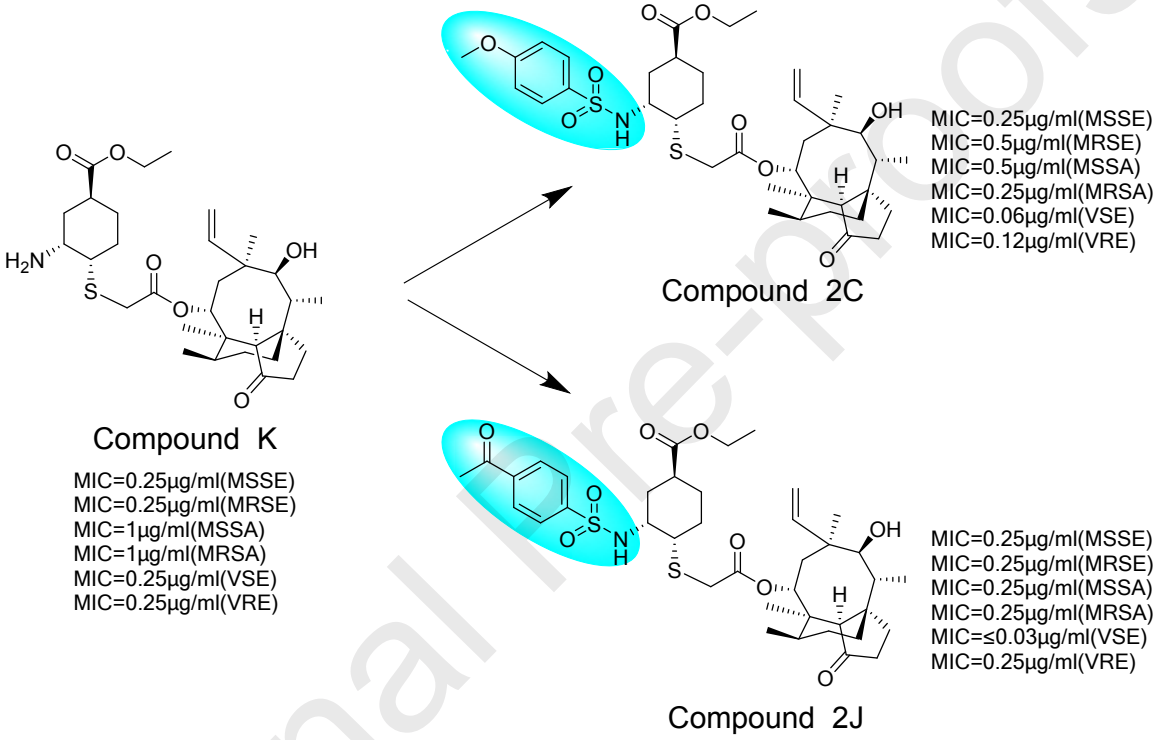

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ABSTRACT

In this work, according to the 'me-too me-better' design strategy, a peculiar side chain different from lefamulin at C14 position of pleuromutilin was introduced. A series of novel thioether pleuromutilin derivatives containing cyclohexane in the C14 chain was synthesized by ten-step synthesis reaction. All derivatives were characterized by Nuclear Magnetic Resonance (NMR) and High Resolution Mass Spectrometer (HRMS). Furthermore, majority of derivatives displayed moderate antibacterial activity *in vitro*.. However, the compound 2C and 2J exhibited comparable or superior antibacterial activity to lefamulin. The summarized structure-activity relationship not only made the variety of pleuromutilin derivatives more diverse, but also provided new ideas for its design and development.

Antibiotics have experienced rapid development since the discovery of penicillin.[1] However, with the widespread use of antibacterial drugs, multi-drug resistant bacteria infection have become an increasingly serious social and medical problem.[2] Therefore, effective antibacterial drugs with novel structure and unique mechanism of actionare urgently needed to be developed.[3, 4]

Pleuromutilin, constituted of 5−6−8 tricyclic carbon skeleton, was a natural product, which was first discovered and isolated in 1951 from *Pleurotus mutilus (Fr.) Sacc.and Pleurotus Passeckerianus Pilat*.[5-7] Pleuromutilin displayed modest antibacterial activity *in vitro*, but pleuromutilin derivatives incorporating substituents in the C14 side chain usually were more efficient against mycoplasmas and drug-resistant Gram-po sitive bacteria, especially *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and methicillin-resistant *Staphylococcus epidermidis* (MRSE).[5, 8-11] To date, only three pleuromutilin derivatives have been marketed : tiamulin, valnemulin, and retapamulin (Figure 1). Tiamulin and Vlnemulin were used as veterinary drugs.[12, 13] Retapamulin was the first new topical antibacterial drug for human skin infections developed by GlaxoSmithKline, which was approved by FDA in April 2007[14, 15].

The target of pleuromutilin and its derivatives was the peptidyl transferase center (PTC) of the bacterial ribosome. The extension of the ternary nucleus and the C14 side chain interfered with the binding of the tRNA to the P-site and the A-site, thereby blocking protein synthesis.[16, 17]

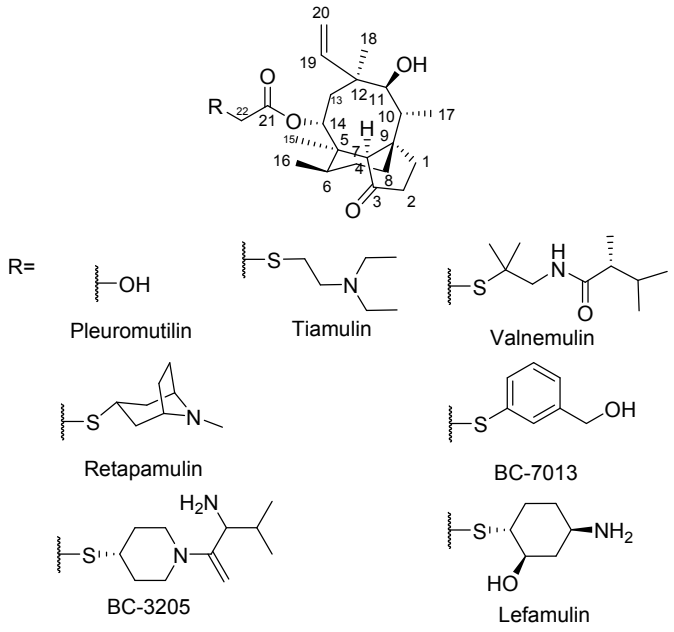


Figure 1. Structures of pleuromutilin and its derivatives

The research on pleuromutilin and its derivatives has never stopped. Many authors realized that the presence of thioether in C-14 position could improve biological activity and enhance water-solubility.[18-20] BC-3205 and BC-7013 (Figure 1) were pleuromutilin derivatives developed by Nabria Therapeutics, which were used to treat acute skin and skin structure infections (ABSSSI) and respiratory infections (RTI) caused by Gram-positive bacteria. Sexual bacterial pneumonia (CABP) could be

adm n is have completed.[21, 22] Lefamulin (Figure 1) was currently the most promising pleuromutilin derivative. February this year, FDA has accepted the New Drug Applications (NDAs) and both applications have been granted priority review. In addition to priority review, lefamulin has been granted Qualified Infectious Disease Product (QIDP) and Fast Track designations by the FDA.[23]

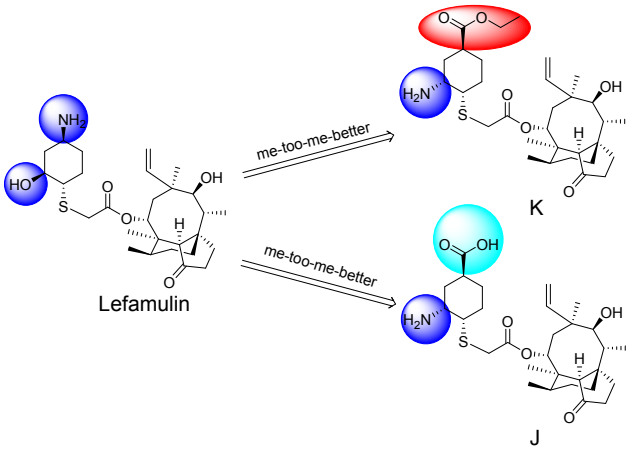
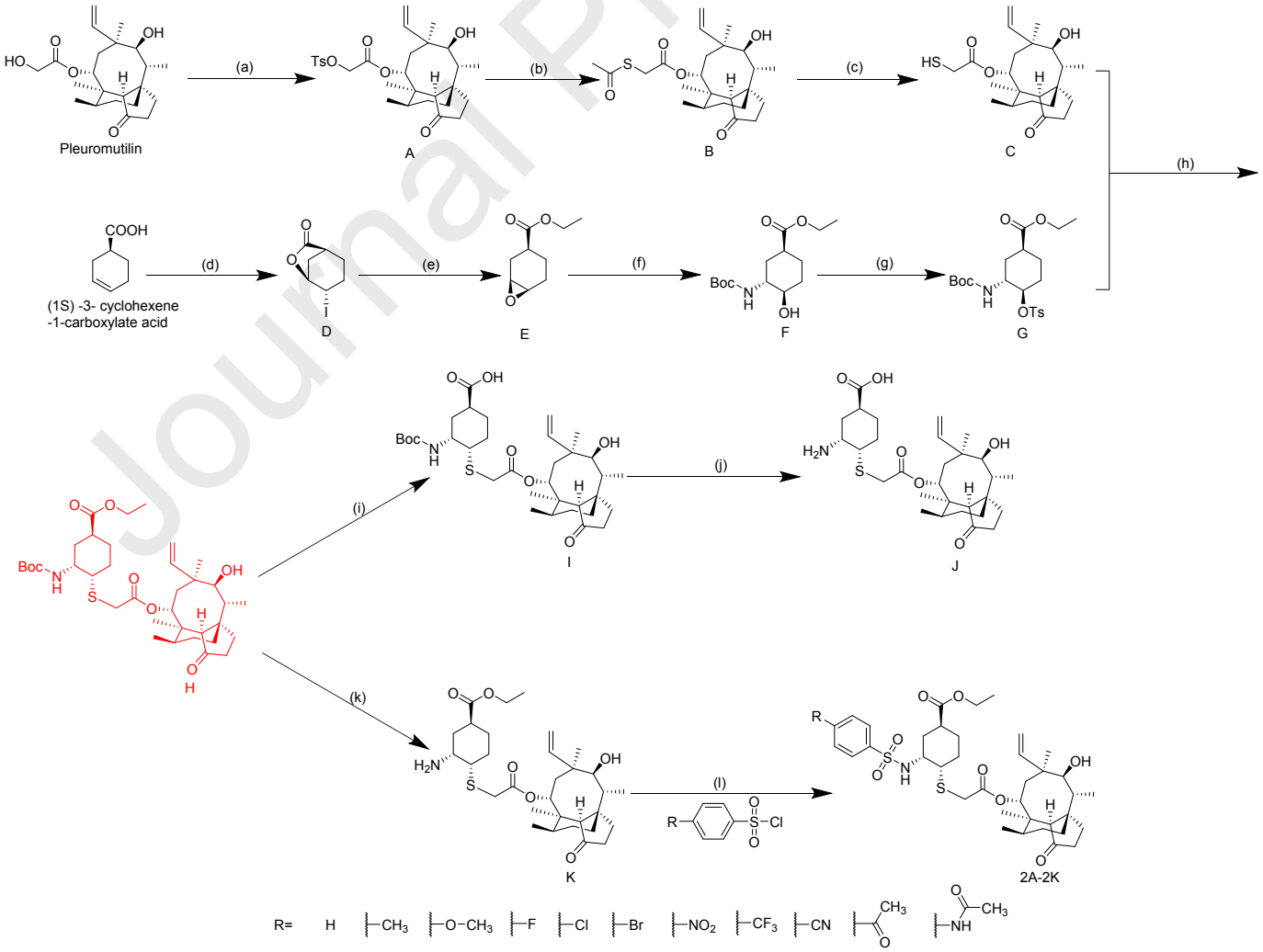


Figure 2 me-too me-better designed strategy

Me-too refers to the original drug pluromutilin, while me-better refers to further changes in the structure of the original drug in the hope of obtaining a more active compound. Base on ‘me-too me-better’ designed strategy, we focused on the chiral thioether structure of lefamulin in this study. This study introduced the core chiral structure of edoxaban at the C14 replaced by its electron isostere amino group. By comparing the antibacterial activity of compounds J and K ， we found that compound K has better antibacterial activity, so we modified it further.

The synthetic route for compound **K, J** and **2A-2K** were showed in Scheme **1**. Intermediate **C** was synthesized by a three-steps reaction with pleuromutilin as starting material, which was esterified by *p*-toluenesulfonyl chloride under basic conditions to give compound **A**, followed by substitution with thioacetic acid to afford compound **B**. Compound **B** was hydrolyzed with hydrazine monohydrate to obtain Compound **C**. on the other hand, the commercially available material (S)-cyclohex-3-ene-1-carboxylic acid was treated with iodine and potassium iodide to provide the iodolactone **D, which was reated with** sodium hydroxide in alcohol to give compound **E**. The three-membered ring of Compound **E** was opened with ammonia water, and then the amino group was protected with di-tert-butyl dicarbonate to afford compound **F**. Compound **G** was synthesized by compound **F** with *p*-toluenesulfonyl chloride under basic conditions. The important intermediate compound **H** was obtained by reation of compound **C** and **G** under basic conditions. At the end, the final products **J, K** and **2A-2K** were sythesized from intermediate **H** by hydrolysis, deprotection and condensation, respectively. All intermediates and final products were confirmed by HRMS, ^{1}H NMR and ^{13}CNMR.



Scheme **1**. Synthesis of compound **J, K** and **2A-2K.** Reagents and conditions: (a). TsCl, NaOH, t-butyl methyl ether/H2O, reflux, 1h. (b). Thioacetic acid, cesium carbonate, DMF, rt. (c). 80% hydrazine monohydrate, DCM, Ar, rt. (d). $NaHCO_3$, I, KI, 0-5℃. (e). NaOH (aq), EtOH. (f). Aqueous ammonia, 45℃. di-tert-butyl dicarbonate, EtOH. (g). P-Toluenesulfonyl chloride, Et_3N, DCM, rt. (h). Sodium ethoxide, THF, Ar, rt. (i). LiOH, MeOH, rt. (j). HCl (gas), DCM, rt. (k). HCl (gas), DCM, rt. (l). DMAP, N-Ethyldiisopropylamine, DCM, Ar, rt.

Anti-gram-positive bacteria activity *in vitro* of compound J 、K and 2A-2K was evaluated with Lefamulin as the positive control and the results were reported in Table 1 and Table 2, respectively. In Table 1, Compound K was found to be significantly superior to Compound J by comparing the *in vitro* antibacterial activity of Compounds J and K, with MIC value of 0.25 μg/ml. Therefore, compound K was chosen as the lead compound for further study. The amino group at C-14 side chain of compound K was modified by substituted benzenesulfonyl to generate compound 2A-2K.

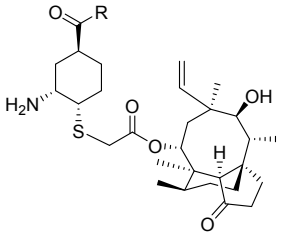
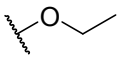


Table 1 Antibacterial activity of J and K against Gram-positive strains *in vitro*

Compound	R=	MIC (μg/ml)					
		MSSE	MRSE	MSSA	MRSA	VSE	VRE
J		2	4	32	32	16	8
K		0.25	0.25	1	1	0.25	0.25

MSSE, methicillin-sensitive Staphylococcus epidermidis ATCC 12228; MRSE, methicillin-resistant Staphylococcus epidermidis 16-5; MSSA, methicillin-sensitive Staphylococcus aureus ATCC 29213; MRSA, methicillin-resistant Staphylococcus aureus ATCC 33591; VSE, vancomycin-sensitive epidermidis 16-5; VRE, vancomycin- resistant epidermidis ATCC 700221.

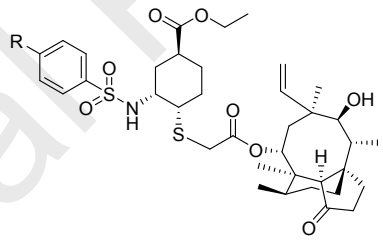
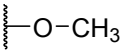
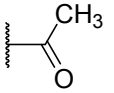
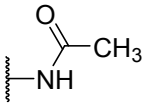


Table 2 In vitro antibacterial activity of 2A-2K against Gram-positive strains

Compound	R=	MIC (μg/ml)					
		MSSE	MRSE	MSSA	MRSA	VSE	VRE
2A	H	0.5	1	1	0.5	2	2
2B		0.25	0.5	1	1	0.5	0.5
2C		0.25	0.5	0.5	0.25	0.06	0.12
2D		0.5	1	1	1	1	1
2E		0.5	0.5	1	0.5	1	1
2F		1	1	1	1	1	1
2G		0.5	0.5	1	1	2	2
2H		0.25	0.5	1	1	0.25	0.25

2I		1	64	64	64	32	32
2J		0.25	0.25	0.25	0.25	≤0.03	0.25
2K		0.5	0.5	0.5	0.5	1	1
Lefamulin		⩽0.03	0.25	0.25	0.5	0.06	0.12

In Table 2, most of the derivatives exhibited potent antibacterial activity *in vitro* against Gram-positive bacteria. In particular, compound 2C had comparable antibacterial efficacy to MRSA, VSE and VRE as the control lefamulin. In addition, the inhibitory potency of compound 2J against MRSE and MSSA was also comparable to that of lefamulin. The MIC values of compound 2J for MRSA and VSE were 0.25μg/ml and ≤0.03μg/ml, respectively, which were better than that of lefamulin.

The substituents on the para position on the benzene ring were divided into electron-donating group and electron-withdrawing group. The results in Table 2 displayed that when the substituent was methoxy, amide or methyl, the antibacterial activity of the corresponding derivative was sequentially decreased. Therefore, it may be considered that the electron donating ability of the substituent on the benzene ring was weakened, and the antibacterial activity was lowered. When the substituent was electron withdrawing group of trifluoromethyl , nitro, cyano or acyl, the antibacterial activity of the corresponding compound was sequentially increased. The compound in which the substituent was a strong electron withdrawing group trifluoromethyl group has the worst antibacterial activity. However, it may be similar to 2C in structure, and 2J has the best activity. When the substituent on the benzene ring is a halogen atom. Although the halogen atom is a weak electron withdrawing group, it forms a P-π conjugate with the benzene ring, so its activity is not much different.

In conclusions, a series of novel pleuromutilin derivatives was designed, synthesized and tested for their anti-gram-positive bacterial activity *in vitro*. Most of these derivatives displayed moderate antibacterial activity. Among them, compound 2C and 2J showed comparable or superior antibacterial activity to lefamulin. The structure-activity relationship obtained from the results of antimicrobial activity: The stronger the electron donating ability of the substituent on the para position of the benzene ring, the better the antibacterial activity of the derivative; the weaker the electron withdrawing ability of the substituent on the para position of the benzene ring, the better the antibacterial activity of the derivative. Which contains oxygen and methyl 2C and 2J have similar structures and the best activity. The summarized structure-activity relationship provided some interesting clues for the exploration and development of such pleuromutilin derivatives.

General Information

Unless otherwise stated, all chemicals were obtained commercially and were used without special treatment. Thin-layerchromatography (TLC) analysis (silica gel 60 GF254 aluminum foil plate, Merck) was used to monitor the reaction process. Column chromatography: silica gel (100–200 mesh and 200–300 mesh; Qingdao Ocean Chemical Factory). 1HNMRand 13CNMR spectra were obtained on Bruker 600 MHz spectrometer (Varian, Palo Alto, CA, USA) in DMSO-d6 or $CDCl_3$ solvents; Chemical shifts (δ) were expressed in parts per million (ppm) relative to TMS (tetramethylsilane) as internal standard, J in Hz. High-resolution mass spectra (HRMS) were obtained using a MicrOTOF-Q II instrument from Bruker (Billerica, MA, USA).

4.1.2. 14-O-({[(4-Methylphenyl)sulfonyl]oxy}acetyl)motilin ***(A).*** Pleuromutilin (15.15 g, 40 mmol) and p-toluenesulfonyl chloride (8.4 g, 44 mmol) were sequentially added to a mixed solution of water (100 mL) and tert-butyl methyl ether (40 mL), and then to the mixture Aqueous NaOH (10 N, 10 mL) was added dropwise. The reaction mixture was stirred at reflux for 1 h and then cooled to rt. The reaction solution was washed with water (100 mL) was diluted and stirred in an ice bath for 30 min, filtered off with suction, washed with water (100 mL × 3) and cold tert-butyl methyl ether (40 mL) and dried to give a white powder. Yield: 92.6%. ^{1}HNMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 6.40 (dd, J = 17.4, 11.0 Hz, 1H), 5.76 (d, J = 8.5 Hz, 1H), 5.32 (d, J = 12.2 Hz, 1H), 5.19 (d, J = 18.8 Hz, 1H), 4.48 (s, 2H), 3.35 (d, J = 6.5 Hz, 1H), 2.45 (s, 3H), 2.28 (p, J = 6.9 Hz, 1H), 2.24 (d, J = 9.7 Hz, 1H), 2.18 (m, 1H), 2.10 – 2.02 (m, 2H), 1.75 (dd, J = 14.5, 2.8 Hz, 1H), 1.64 (m, 2H), 1.56 (s, 1H), 1.53 – 1.42 (m, 2H), 1.40 (s, 3H), 1.34 (dd, J = 14.3, 3.0 Hz, 1H), 1.25 (d, J = 16.1 Hz, 1H), 1.15 (s, 3H), 1.11 (m, 1H), 0.88 (d, J = 7.0 Hz, 3H), 0.62 (d, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.73 , 164.83, 145.28, 132.54, 138.67 , 129.89 , 128.06 , 117.35 , 74.49 , 70.26 , 65.02 , 57.99 , 45.36, 44.46 , 43.94, 41.80, 36.51 , 36.00 , 34.38 , 30.31 , 26.74 , 26.38 , 24.78 , 21.68, 16.51 , 14.74 , 11.47 , HRMS: calcd for $C_{29}H_{40}O_7S$ $[M + Na]^+$： 555.2392， found: 555.2371.

4.1.3. 14-O-[(acetylthio)acetyl] mutilin ***(B).*** Thioacetic acid (0.89ml, 12.5 mmol) was added dropwise cesium carbonate (2.12g, 6.5 mmol) in DMF (25ml) solution, stirred at room temperature for 30 min. A solution of 14-O-({[(4-methylphenyl)sulfonyl)oxy}acetyl) mutilin in DMF (25 ml) was added dropwise to the above reaction and allowed to react at room temperature. After completion of the reaction (confirmed by TLC), 100 ml of water was added to the reaction, which was extracted with EtOH (100 ml). The organic layer was washed with saturated sodium bicarbonate (100ml), dried over anhydrous sodium sulfate overnight. The crude mixture was purified by column chromatography on silica to give a viscous liquid product B 3.5g. Yield: 80.01%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.40 (dd, J = 17.2, 10.8 Hz, 1H), 5.67 (d, J = 8.5 Hz, 1H), 5.29 (d, J = 13.9 Hz, 3H), 5.15 (d, J = 17.4 Hz, 1H), 3.58 (s, 2H), 3.32 (d, J = 6.4 Hz, 1H), 2.34 (s, 3H), 2.27 (p, J = 8.7, 7.6 Hz, 1H), 2.17 (m, 2H), 2.07 (s, 1H), 2.06 – 1.99 (m, 1H), 1.73 (d, J = 14.4 Hz, 1H), 1.61 (q, J = 11.7, 10.9 Hz, 3H), 1.49 (q, J =

13.9 ... 60 , (s, 3H), 1.09 (m, 1H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.89 , 193.42 , 167.23 , 138.87 , 117.07 , 74.48 , 70.00 , 58.03 , 53.47 , 45.37 , 44.60 , 43.92 , 41.81 , 36.66 , 35.93 , 34.39 , 32.13 , 30.34 , 30.03 , 26.77 , 26.41 , 24.75 , 16.68 , 14.74 , 11.41 . HRMS: calcd for $C_{24}H_{36}O_5S$ [M - H]$^-$：435.2205，found: 435.2213.

4.1.4. 14-O-[(mercapto)acetyl]motilin ***(C).*** 14-O-[(acetylthio) acetyl]mutilin (3.0 g, 6.87 mmol) was dissolved in 30 mL dichloromethane under argon. Then, 80% hydrazine monohydrate (0.3 g, 1.05 mmol) was added dropwise to the above reaction. The reaction was stirred at room temperature for 3 h. After completion of the reaction (confirmed by TLC).Then concentrated in vacuo to dryness.The residue was purified by column chromatography on silica gel to give a white solid C 2.2g. Yield: 81.5%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.72 (d, *J* = 8.4 Hz, 1H), 5.37 – 5.27 (m, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 3.35 (d, *J* = 6.4 Hz, 1H), 3.22 – 3.11 (m, 2H), 2.35 – 2.29 (m, 1H), 2.21 – 2.20 (m, 2H), 2.10 (s, 1H), 2.09 – 2.04 (m, 1H), 1.89 (t, *J* = 8.2 Hz, 1H), 1.76 (d, *J* = 14.5 Hz, 1H), 1.64 (q, *J* = 11.0 Hz, 2H), 1.54 (dd, *J* = 26.8, 13.0 Hz, 2H), 1.44 (s, 3H), 1.34 (dd, *J* = 25.2, 15.2 Hz, 2H), 1.16 (s, 3H), 1.11 (d, *J* = 14.0 Hz, 1H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.94 , 169.25 , 138.89 , 117.19 , 74.55 , 69.70 , 58.12 , 45.41 , 44.68 , 43.93 , 41.78 , 36.72 , 35.97 , 34.42 , 30.38 , 27.20 , 26.79 , 26.37 , 24.80 , 16.88 , 14.83 , 11.48 . HRMS: calcd for $C_{22}H_{34}O_4S$ [M - H]$^-$：393.2100，found: 393.2109.

4.1.5. (1S, 4S, 5S)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one ***(D).*** 250 ml of a NaHCO3 solution (15.2 g, 181 mmol) was added to (S)-cyclohex-3-ene-1-carboxylic acid (7.6 g, 60.2 mmol) in an ice bath (0-5 °C). After stirring to dissolve the suspension, 150 ml of an aqueous solution of KI (60 g, 361 mmol) and I (16.1 g, 63.3 mmol) was added. After completion of the reaction (confirmed by TLC), 300 ml of dichloromethane was added and the aqueous layer was extracted with CHCl2 (2×50 ml). The organic layer was collected and washed with saturated Na_2SO_3 (250 ml), then dried over anhydrous $MgSO_4$, the solvent was evaporated in vacuo to give a white solid product D 13.05g. Yield:86%, ^{1}H NMR (600 MHz,$CDCl_3$) δ 4.80 (s, 1H), 4.49 (s, 1H), 2.77 (d, *J* = 11.9 Hz, 1H), 2.65 (s, 1H), 2.40 (d, *J* = 21.2 Hz, 2H), 2.09 (d, *J* = 15.6 Hz, 1H), 1.97 – 1.70 (m, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ 177.71 , 80.19 , 38.58 , 34.49 , 29.70 , 23.80 , 23.11 . HRMS: calcd for $C_7H_9IO_2$ [M + H]$^+$：252.9725，found: 252.9735.

4.1.6. (1S, 3S, 6R)-7-oxabicyclo[4.1.0]heptane-3-carboxylate ethyl ***(E).*** (1S, 4S, 5S)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (25.2 g, 0.1 mmol) was added to EtOH (250 ml) and stirred rapidly to disperse in ethanol. Then 50 ml of an aqueous solution of NaOH (4.0 g, 0.1 mmol) was added dropwise to the above solution and the reaction was stirred at room temperature. After completion of the reaction (confirmed by 1H NMR). The reaction was concentrated at 40 ℃, the residue was added 300ml of water, then extracted with 300 ml of dichloromethane layered, aqueous layer was extracted once with 300 ml of methylene chloride, the organic phases were combined and dried overnight over Na_2SO4, and concentrated in vacuo to give the product Yellow liquid E 16.00g. Yield:94.0%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.88 (q, *J* = 7.1 Hz, 2H), 2.91 (s, 2H), 2.01 – 1.99 (m, 1H), 1.98 – 1.91 (m, 2H), 1.87 (dd, *J* = 15.2, 11.0 Hz, 1H), 1.56 (m, 1H), 1.43 – 1.28 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR 26.03 , 23.83 , 20.85 , 13.92 .HRMS: calcd for $C_9H_{14}O_3$ [M + Na]$^+$：193.0841，found: 193.0845.

4.1.7. (1S, 3R, 4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxy cyclohexane-1-carboxylate ethyl ***(F).*** To (1S,3S,6R)-7-oxabicyclo[4.1.0]heptane-3-carboxylate ethyl (17 g, 0.1 mmol) was added 175 ml of aqueous ammonia and the reaction was stirred at 45 °C. After completion of the reaction (confirmed by TLC),concentrated in vacuo and then 175 ml of EtOH was added. A solution of di-tert-butyl dicarbonate (44.0 g, 201 mmol) in ethanol(175ml) was added dropwise to the above reaction and the reaction was stirred at room temperature. After completion of the reaction (confirmed by 1H NMR), concentrated in vacuo. Add 300 ml of water to the residue, and the aqueous layer was extracted twice with EtOH (300 ml). The organic phases were combined and dried over anhydrous sodium sulfate. concentrated in vacuo and the residue was purified by column chromatography on silica gel to give the white solid F 16g. Yield:50.0% ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.15 (m, 2H), 3.58 (s, 1H), 3.43 (t, *J* = 8.3 Hz, 1H), 2.62 (s, 1H), 2.31 (d, *J* = 12.7 Hz, 1H), 2.09 (d, *J* = 10.7 Hz, 1H), 1.86 (d, *J* = 10.1 Hz, 1H), 1.51 (s, 4H), 1.43 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.15 , 156.68 , 85.11, 79.82 , 72.92 , 60.53 , 38.64 , 29.75 , 27.33 , 24.60 , 14.17 .HRMS: calcd for $C_{14}H_{25}NO_5$ [M + Na]$^+$：310.1630，found: 310.1644.

4.1.8. (1S, 3R, 4R)-3-((tert-butoxycarbonyl) amino)-4-(tosyloxy) cyclohexane-1-carboxylate ethyl ***(G).*** Phenylsulfonyl chloride (8.76 g, 46 mmol) and (1S, 3R, 4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclohexane-1-carboxy late ethyl (11 g, 38.3 mmol) were dissolved in 200 ml in methyl chloride. 8 ml of triethylamine was added dropwise to the above reaction at -5 ° C, and after 15 minutes of dropwise addition, the temperature was raised to 25 °C. After completion of the reaction (confirmed by 1H NMR), the reaction solution was washed with citric 200ml 5%, washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate. concentrated in vacuo and the crude mixture was purified by column chromatography on silica gel to give the white solid product G 8g. Yield: 60.0% ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.55 (d, *J* = 29.6 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.78 – 3.70 (m, 1H), 2.53 (td, *J* = 7.7, 7.2, 4.1 Hz, 1H), 2.44 (s, 3H), 2.27 (d, *J* = 18.6 Hz, 1H), 1.96 (d, *J* = 13.0 Hz, 1H), 1.68 – 1.56 (m, 2H), 1.43 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.77, 154.74 , 144.64, 134.08, 129.78 , 127.65 , 79.55, 60.64 , 49.29 , 37.78 , 30.57 , 28.28 , 27.20, 26.99, 23.78 , 21.59, 14.16 . HRMS: calcd for $C_{21}H_{31}NO_7S$ [M + Na]$^+$：464.1719，found: 464.1734.

4.1.9. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-tert-butoxycar bonylamino-cyclohexyl-sulfanyl]acetyl}-mutilin ***(H).*** 14-O-[(mercapto) acetyl] mutilin (C) (1.0 g, 2.53 mmol) and sodium ethoxide (207 mg, 3.04 mmol) were dissolved in THF and stirred for 30 min under argon protection. A solution of (1S, 3R, 4R)-3-((tert-butoxycarbonyl) amino) - 4 - (tosyloxy) cyclohexane-1-carboxylate ethyl (G) (1.3 g, 2.94 mmol) in THF was added dropwise to the above reaction and the reaction was stirred at room temperature. After completion of the reaction (confirmed by TLC), the reaction was concentrated in vacuo and the residue was added 30ml EtOH. The organic phase was washed with 30 ml of saturated sodium chloride and dried over anhydrous sodium sulfate. The crude mixture was purified by column

chro]⁻：
735 mg. Yield: 44.0% ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.76 (d, *J* = 8.4 Hz, 1H), 5.35 (d, *J* = 11.0 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 4.70 (s, 1H), 4.13 – 4.01 (m, 3H), 3.75 (s, 1H), 3.36 (d, *J* = 6.5 Hz, 1H), 3.29 – 3.16 (m, 2H), 2.93 (s, 1H), 2.52 (s, 1H), 2.34 – 2.27 (m, 2H), 2.22 – 2.18 (m, 2H), 2.12 – 2.06 (m, 2H), 2.04 (s, 1H), 1.96 (td, *J* = 9.5, 4.3 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.76 (s, 2H), 1.65 – 1.51 (m, 4H), 1.45 (d, *J* = 4.5 Hz, 12H), 1.39 – 1.32 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 4H), 1.18 (s, 3H), 1.14 – 1.08 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 217.00 , 174.24 , 168.99 , 154.94 , 139.21 , 117.21 , 74.67 , 69.22 , 60.58 , 60.38 , 58.23 , 49.76 , 46.71 , 45.47 , 44.81 , 43.92 , 41.77 , 38.55 , 36.81 , 36.04 , 34.47 , 33.50 , 30.46 , 28.43 , 27.33 , 26.87 , 26.39 , 25.15 , 24.87 , 21.05 , 16.84 , 14.93 , 14.24 , 11.50 . HRMS: calcd for $C_{36}H_{57}NO_8S$ [M - H]⁻： 662.3727， found: 662.3720.

4.1.10. 14-O-{[(1R, 2R, 4S)-4-acetate-2-tert-butoxycarbony lamino-cyclohexyl-sulfanyl]acetyl} mutilin ***(I).*** 14-O-{[(1R, 2R,4S)-4-ethylacetate-2-tert-butoxycarbonylamino-cyclohexyl-sulfanyl]acetyl}mutilin (350 mg, 0.53 mmol) was dissolved in 10 mL MeOH. Then 1 ml of LiOH (80 mg, 1.95 mmol) was added dropwise and the reaction was stirred at room temperature. After completion of the reaction (confirmed by TLC), the reaction was concentrated in vacuo and the residue was added 10ml DCM. The organic layer was washed twice with 20 ml of water and dried over anhydrous sodium sulfate. The crude mixture was purified by column chromatography on silica gel to give the white solid product I 135 mg. Yield: 41%.^{1}H NMR (600 MHz, DMSO-d_6) δ 12.12 (s, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.13 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.75 (s, 1H), 5.55 (d, *J* = 8.1 Hz, 1H), 5.11 – 5.00 (m, 2H), 4.52 (d, *J* = 5.2 Hz, 1H), 3.57 (s, 1H), 3.43 (t, *J* = 5.5 Hz, 1H), 3.36 – 3.30 (m, 3H), 3.23 (d, *J* = 15.0 Hz, 1H), 2.79 (s, 1H), 2.65 (s, 1H), 2.50 (s, 1H), 2.41 (s, 1H), 2.19 (t, *J* = 9.7 Hz, 2H), 2.00 – 1.92 (m, 2H), 1.91 (s, 1H), 1.70 – 1.59 (m, 3H), 1.51 (d, *J* = 4.6 Hz, 2H), 1.39 (s, 9H), 1.36 (s, 2H), 1.27 (dd, *J* = 28.6, 15.9 Hz, 5H), 1.06 (s, 3H), 1.04 – 0.98 (m, 1H), 0.94 – 0.84 (m, 1H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.63 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 217.60 , 176.35, 168.88 , 155.34 , 141.20 , 115.63 , 70.09, 73.04 , 69.80 , 57.70 , 55.33, 49.64 , 45.40 , 44.44 , 44.14 , 41.89 , 37.92 , 36.80 , 34.44 , 33.49 , 30.56 , 29.01 , 28.71 , 27.63 , 27.01 , 25.54 , 24.92 , 21.49, 16.55 , 14.99 , 11.97 . HRMS: calcd for $C_{34}H_{53}NO_8S$ [M - H]⁻：634.3414，found: 634.3420.

4.1.11. 14-O-{[(1R, 2R, 4S)-4-acetate-2-amino-sulf anyl]acetyl}-mutilin ***(J).*** 14-O-{[(1R, 2R, 4S)-4-acetate-2-tert-butoxycarbonylamino-cyclohexyl-sulfanyl]acetyl} -mutilin (135 mg, 0.21 mmol) was dissolved in 5 mL DCM. Then, HCl gas was passed through the above reaction for about 1.5 hours. Suction filtration to give a white solid product J 60 mg. Yield: 53%. ^{1}H NMR (600 MHz, DMSO) δ 8.23 (s, 2H), 6.15 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.76 (s, 1H), 5.57 (d, *J* = 8.3 Hz, 1H), 5.12 – 5.05 (m, 2H), 3.53 (d, *J* = 15.7 Hz, 1H), 3.46 – 3.43 (m, 1H), 3.35 (d, *J* = 15.7 Hz, 1H), 3.21 (s, 1H), 2.99 – 2.89 (m, 1H), 2.84 – 2.72 (m, 1H), 2.43 (s, 1H), 2.29 – 2.16 (m, 2H), 2.09 – 1.99 (m, 4H), 1.83 (d, *J* = 7.6 Hz, 1H), 1.65 – 1.62 (m, 3H), 1.60 – 1.47 (m, 3H), 1.38 (s, 3H), 1.35 – 1.22 (m, 4H), 1.07 (s, 3H), 1.02 (td, *J* = 14.0, 4.0 Hz, 1H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.64 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 217.59 , 175.61 , 168.99 , 141.24 , 115.73 , 72.98 , 70.26 , 57.65 , 55.36 , 50.42 , 45.40 , 44.50 , 44.13 , 41.93 , 37.34 , 36.87 , 36.78 , 34.44 , 33.69 , 30.55 , 29.94 , 28.99 , 28.37 , 27.03 , 26.02 , 24.91 , 534.2890，found: 534.2879.

4.1.12. 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin ***(K).*** 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-tert-butoxycarbonylamino-cyclohexyl-sulfanyl]acetyl}-mutilin (200 mg, 0.21 mmol) was dissolved in 5 mL DCM. Then, HCl gas was passed through the above reaction for about 1.5 hours. Suction filtration to give the white solid product K 100 mg. Yield:58%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (s, 2H), 6.34 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.67 (d, *J* = 8.4 Hz, 1H), 5.45 (d, *J* = 10.9 Hz, 1H), 5.24 – 5.08 (m, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.37 (s, 1H), 3.33 – 3.24 (m, 2H), 3.18 (d, *J* = 16.7 Hz, 1H), 3.05 (t, *J* = 9.0 Hz, 1H), 2.79 (s, 1H), 2.67 – 2.61 (m, 1H), 2.27 – 2.22 (m, 1H), 2.20 – 2.06 (m, 2H), 2.04 – 1.92 (m, 5H), 1.67 (dd, *J* = 27.1, 14.3 Hz, 2H), 1.57 – 1.50 (m, 3H), 1.48 – 1.41 (m, 1H), 1.35 (s, 3H), 1.27 (t, *J* = 16.8 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 1.10 (s, 3H), 1.04 – 0.99 (m, 1H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.61 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.92 , 173.76 , 170.68 , 138.59 , 117.91 , 74.63 , 70.41 , 60.73 , 58.06 , 53.42 , 51.17 , 46.74 , 45.39 , 44.86 , 43.89 , 41.73 , 37.97 , 36.65 , 35.95 , 34.42 , 32.51 , 30.72 , 30.38 , 28.45 , 26.84 , 26.33 , 24.82 , 16.85 , 14.83 , 14.23 , 11.59 . HRMS: calcd for $C_{31}H_{49}NO_6S$ [M - H]⁻：562.3201，found: 562.3169.

4.1.13 General Procedure for the Synthesis of ***2A-2J*** *Derivatives*

4.1.13.1. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-benzene sulfonamide-sulfanyl]acetyl}-mutilin ***(2A)***. 14-O-{[(1R, 2R, 4S)-4-ethylacetate -2-amino-sulfanyl]acetyl}-mutilin (200mg, 0.36mmol), Phenylsulfonyl chloride (88mg, 0.5mmol) and DMAP (43 mg, 0.35 mmol) was dissolved in 5 mL DCM under argon. To the reaction, (140 mg, 1.08 mmol) was added dropwise, and the mixture was reacted to completion at 25 °C. The reaction solution was washed twice with 15 ml of water and dried over anhydrous sodium sulfate. Column chromatography gave a white solid product 180 mg.Yield:72%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 6.47 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.72 (d, *J* = 8.5 Hz, 1H), 5.55 (s, 1H), 5.36 (d, *J* = 11.0 Hz, 1H), 5.28 (s, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 2H), 3.35 (d, *J* = 6.4 Hz, 1H), 3.28 (s, 1H), 2.99 (s, 2H), 2.64 (s, 1H), 2.56 (s, 1H), 2.46 (d, *J* = 11.2 Hz, 1H), 2.32 (p, *J* = 6.8 Hz, 1H), 2.21 (dtd, *J* = 28.8, 19.3, 10.1 Hz, 3H), 2.11 – 2.06 (m, 2H), 1.98 – 1.93 (m, 1H), 1.90 – 1.85 (m, 1H), 1.79 – 1.74 (m, 1H), 1.64 (dt, *J* = 18.9, 10.3 Hz, 3H), 1.55 (dd, *J* = 32.5, 12.4 Hz, 4H), 1.43 (s, 3H), 1.38 – 1.33 (m, 1H), 1.29 (d, *J* = 16.1 Hz, 1H), 1.23 (t, *J* = 6.8 Hz, 3H), 1.18 (s, 3H), 1.12 (td, *J* = 14.1, 4.1 Hz, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.98 , 173.93 , 169.03 , 139.86 , 138.96 , 132.63 , 128.98 , 127.30 , 117.43 , 74.55 , 69.70 , 60.57 , 58.08 , 52.77 , 48.20 , 45.41 , 44.81 , 43.91 , 41.71 , 38.16 , 36.66 , 35.96 , 34.42 , 33.69 , 30.37 , 28.32 , 26.85 , 26.31 , 25.70 , 24.79 , 21.03 , 16.84 , 14.84 , 14.21 , 11.50 . HRMS: calcd for $C_{37}H_{53}NO_8S_2$ [M - H]⁻：702.3135，found: 702.3126.

4.1.13.2. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-toluenesul fonamide-sulfanyl]acetyl}-mutilin ***(2B)***. Compound **2B** was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and P-toluenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 200

mg. ... 95 , Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.49 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.75 (d, *J* = 8.5 Hz, 1H), 5.42 – 5.32 (m, 2H), 5.23 (d, *J* = 17.4 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.37 (d, *J* = 6.5 Hz, 1H), 3.26 (s, 1H), 3.01 (s, 2H), 2.65 (s, 1H), 2.57 (s, 1H), 2.50 (d, *J* = 12.3 Hz, 1H), 2.42 (s, 3H), 2.33 (q, *J* = 7.1 Hz, 1H), 2.23 – 2.19 (m, 2H), 2.10 (q, *J* = 8.4 Hz, 2H), 2.00 – 1.94 (m, 1H), 1.94 – 1.87 (m, 1H), 1.81 – 1.75 (m, 1H), 1.70 – 1.60 (m, 4H), 1.57 – 1.49 (m, 3H), 1.45 (s, 3H), 1.40 – 1.35 (m, 1H), 1.31 (d, *J* = 16.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 4H), 1.20 (s, 3H), 1.14 – 1.10 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.93 , 173.92 , 169.01 , 143.39 , 138.94 , 136.82 , 129.58 , 127.39 , 117.47 , 74.57 , 69.69 , 60.57 , 58.10 , 52.69 , 48.25 , 45.42 , 44.82 , 43.91 , 41.72 , 38.20 , 36.67 , 35.96 , 34.42 , 33.60 , 32.83 , 30.38 , 28.38 , 26.86 , 26.28 , 25.78 , 24.80 , 21.55 , 16.84 , 14.85 , 14.21 , 11.50 . HRMS: calcd for $C_{38}H_{55}NO_8S_2$ [M - H]$^-$：716.3291，found: 716.3297.

4.1.13.3. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-methoxy benzenesulfonamide-sulfanyl]acetyl}-mutilin ***(2C).*** Compound 2C was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and P-methoxybenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 210 mg.Yield： 80%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.49 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.74 (d, *J* = 8.5 Hz, 1H), 5.45 (s, 1H), 5.37 (d, *J* = 11.0 Hz, 1H), 5.31 (s, 1H), 5.23 (d, *J* = 17.4 Hz, 1H), 4.12 (q, *J* = 6.7 Hz, 2H), 3.87 (s, 3H), 3.37 (d, *J* = 6.5 Hz, 1H), 3.27 (s, 1H), 3.04 (s, 2H), 2.68 (s, 1H), 2.58 (s, 1H), 2.53 – 2.41 (m, 1H), 2.34 (p, *J* = 6.8 Hz, 1H), 2.23 – 2.20 (m, 2H), 2.14 – 2.07 (m, 2H), 2.05 (s, 1H), 2.01 – 1.95 (m, 1H), 1.92 – 1.86 (m, 1H), 1.78 (d, *J* = 14.3 Hz, 1H), 1.66 (p, *J* = 13.5, 12.7 Hz, 4H), 1.55 (dd, *J* = 14.4, 3.9 Hz, 2H), 1.45 (s, 3H), 1.38 (d, *J* = 14.1 Hz, 1H), 1.32 (d, *J* = 16.1 Hz, 1H), 1.26 (q, *J* = 6.9, 6.2 Hz, 4H), 1.20 (s, 3H), 1.14 (td, *J* = 14.3, 4.4 Hz, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 216.98 , 173.99 , 168.99 , 162.83 , 138.95 , 131.46 , 129.45 , 117.41 , 114.10 , 74.55 , 69.67 , 60.55 , 60.36 , 58.09 , 55.55 , 53.43 , 52.63 , 48.11 , 45.41 , 44.79 , 43.90 , 41.71 , 38.13 , 36.67 , 35.95 , 34.42 , 33.71 , 30.37 , 26.85 , 26.30 , 24.79 , 21.02 , 16.82 , 14.83 , 14.20 , 11.49 . HRMS: calcd for $C_{38}H_{55}NO_9S_2$ [M - H]$^-$：732.3240，found: 732.3219.

4.1.13.4. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-P-fluoro benzenesulfonamide-sulfanyl]acetyl}-mutilin ***(2D).*** Compound 2C was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and *P*-fluorobenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 190 mg.Yield： 74%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 2H), 7.24 – 7.11 (m, 2H), 6.51 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.75 (d, *J* = 8.5 Hz, 1H), 5.66 (s, 1H), 5.40 (dd, *J* = 10.9, 1.6 Hz, 1H), 5.24 (dd, *J* = 17.4, 1.6 Hz, 1H), 4.13 – 4.19 (m, 2H), 3.37 (d, *J* = 6.5 Hz, 1H), 3.27 – 3.24 (m, 1H), 3.06 (s, 2H), 2.97 (s, 1H), 2.89 (s, 1H), 2.61 (s, 2H), 2.54 (d, *J* = 13.0 Hz, 1H), 2.38 – 2.32 (m, 2H), 2.23 – 2.19 (m, 2H), 2.14 – 2.08 (m, 2H), 2.02 – 1.94 (m, 2H), 1.79 (d, *J* = 14.4 Hz, 1H), 1.71 – 1.64 (m, 2H), 1.61 – 1.50 (m, 4H), 1.45 (s, 4H), 1.41 – 1.36 (m, 1H), 1.31 (d, *J* = 16.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 3H), 1.14 – 1.10 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.88 , 173.85 , 169.25 , 165.85 , 164.16 , 138.97 , 130.15 , 130.09 , 117.50 , 116.18 , 116.03 , 77.22 , 74.54 , 69.89 , 60.61 , 58.06 , 52.96 , 34.41 , 33.78 , 31.47 , 30.36 , 28.90 , 26.87 , 26.28 , 26.08 , 24.78 , 16.85 , 14.81 , 14.21 , 11.49 . HRMS: calcd for $C_{37}H_{52}FNO_8S_2$ [M - H]$^-$：720.3040，found: 720.3044.

4.1.13.5. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-P-chlorobenzene sulfonamide-sulfanyl]acetyl}-mutilin ***(2E).*** Compound 2D was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and *P*-chlorobenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 195 mg.Yield：73%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.50 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.75 (d, *J* = 8.5 Hz, 1H), 5.66 (s, 1H), 5.39 (d, *J* = 11.0 Hz, 1H), 5.31 – 5.20 (m, 2H), 4.12 (qt, *J* = 7.6, 3.8 Hz, 2H), 3.36 (d, *J* = 6.5 Hz, 1H), 3.25 (s, 1H), 3.06 (s, 2H), 2.57 (dd, *J* = 26.0, 10.9 Hz, 3H), 2.32 – 2.29 (m, 1H), 2.22 – 2.19 (m, 2H), 2.10 (t, *J* = 12.3 Hz, 2H), 2.01 – 1.92 (m, 2H), 1.80 – 1.75 (m, 1H), 1.66 (q, *J* = 11.2 Hz, 2H), 1.59 – 1.50 (m, 4H), 1.44 (s, 3H), 1.40 – 1.35 (m, 1H), 1.30 (d, *J* = 16.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.13 – 1.10 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.88 , 173.81 , 169.33 , 139.02 , 138.95 , 138.35 , 129.18 , 128.90 , 117.54 , 74.54 , 69.94 , 60.63 , 58.06 , 53.02 , 48.72 , 45.41 , 44.85 , 43.93 , 41.71 , 38.29 , 36.63 , 35.95 , 34.42 , 33.82 , 33.50 , 30.36 , 29.02 , 26.88 , 26.28 , 26.15 , 24.79 , 16.87 , 14.82 , 14.22 , 11.51 . HRMS: calcd for $C_{37}H_{52}ClNO_8S_2$ [M - H]$^-$：736.2745，found: 736.2726.

4.1.13.6. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-bromobenzene sulfonamide-sulfanyl]acetyl}-mutilin ***(2F).*** Compound **2E** was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and *P*-bromobenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 200 mg.Yield：72%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 6.48 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.82 (s, 1H), 5.73 (d, *J* = 8.4 Hz, 1H), 5.36 (d, *J* = 10.9 Hz, 1H), 5.30 – 5.18 (m, 1H), 4.12 – 4.08 (m, 2H), 3.36 (d, *J* = 6.1 Hz, 1H), 3.29 (s, 1H), 3.09 – 3.02 (m, 2H), 2.60 (d, *J* = 20.6 Hz, 2H), 2.46 (d, *J* = 10.9 Hz, 1H), 2.32 (p, *J* = 7.7, 7.0 Hz, 1H), 2.20 – 2.15 (m, 2H), 2.12 – 2.06 (m, 2H), 2.02 (s, 2H), 1.97 (dd, *J* = 11.7, 5.3 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.77 (d, *J* = 14.1 Hz, 1H), 1.65 (q, *J* = 11.2, 10.7 Hz, 2H), 1.57 – 1.49 (m, 4H), 1.43 (s, 3H), 1.36 (d, *J* = 13.8 Hz, 1H), 1.29 (d, *J* = 16.1 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 4H), 1.18 (s, 3H), 1.12 – 1.09 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.95 , 173.88 , 171.12 , 169.29 , 138.97 , 132.16 , 128.94 , 127.46 , 117.42 , 74.52 , 69.86 , 60.60 , 60.36 , 58.05 , 52.96 , 48.47 , 45.40 , 44.81 , 43.92 , 41.70 , 38.17 , 36.63 , 35.95 , 34.41 , 33.91 , 30.35 , 26.86 , 26.33 , 25.84 , 24.78 , 21.02 , 16.85 , 14.82 , 14.21 , 11.50 . HRMS: calcd for $C_{37}H_{52}BrNO_8S_2$ [M + H]$^+$：782.2396，found: 782.2221.

4.1.13.7. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-nitrobenzene sulfonamide-sulfanyl]acetyl}-mutilin ***(2G).*** Compound 2F was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and P-nitrobenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 160 mg.Yield：60%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.7 Hz, 2H), 8.08 (d, *J* = 8.7 Hz, 2H), 6.52 (dd, *J* = 17.4, 11.0 Hz, 1H), 6.20 (s, 1H), 5.74 (d, *J* = 8.5 Hz, 1H), 5.42 (d, *J* =

11.0
3.36 (d, *J* = 6.4 Hz, 1H), 3.26 (s, 1H), 3.08 (s, 2H), 2.67 – 2.57 (m, 2H), 2.45 (s, 1H), 2.36 – 2.27 (m, 2H), 2.20 – 2.15 (m, 2H), 2.10 (q, *J* = 8.4 Hz, 2H), 2.03 – 1.94 (m, 3H), 1.80 – 1.75 (m, 1H), 1.65 (q, *J* = 10.9, 10.4 Hz, 2H), 1.49 – 1.44 (m, 4H), 1.42 (s, 3H), 1.39 – 1.34 (m, 1H), 1.24 (p, *J* = 7.4, 6.8 Hz, 4H), 1.19 (s, 3H), 1.12 (td, *J* = 14.2, 4.3 Hz, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.66 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.81 , 173.75 , 169.82 , 149.91 , 145.60 , 138.99 , 128.76 , 124.07 , 117.60 , 74.51 , 70.35 , 60.69 , 60.37 , 57.98 , 53.48 , 49.35 , 45.40 , 44.89 , 43.98 , 41.70 , 38.39 , 36.56 , 35.94 , 34.40 , 34.18 , 30.32 , 29.82 , 26.90 , 26.59 , 26.31 , 24.76 , 16.91 , 14.77 , 14.23 , 11.50 . HRMS: calcd for $C_{37}H_{52}N_2O_{10}S_2$ [M - H]$^-$：747.2895，found: 747.2974.

4.1.13.8. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-cyanobenzene sulfonamide-sulfanyl]acetyl}-mutilin ***(2H).*** Compound **2G** was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and P-cyanobenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 180 mg.Yield：70%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 3.3 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 6.54 – 6.39 (m, 2H), 5.73 (d, *J* = 8.5 Hz, 1H), 5.38 (d, *J* = 11.0 Hz, 1H), 5.31 – 5.18 (m, 2H), 4.11 (p, *J* = 6.9 Hz, 2H), 3.36 (d, *J* = 6.4 Hz, 1H), 3.29 (s, 1H), 3.13 – 3.03 (m, 2H), 2.65 – 2.60 (m, 1H), 2.55 (s, 1H), 2.48 (d, *J* = 13.2 Hz, 1H), 2.34 – 2.26 (m, 2H), 2.20-2.23 (m, 2H), 2.09 (q, *J* = 8.7 Hz, 2H), 2.01 – 1.90 (m, 3H), 1.77 (d, *J* = 12.6 Hz, 1H), 1.65 (q, *J* = 11.8, 10.9 Hz, 2H), 1.52 – 1.49 (m, 4H), 1.39 – 1.34 (m, 1H), 1.28 (d, *J* = 16.2 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.18 (s, 3H), 1.12 – 1.09 (m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.86 , 173.85 , 169.56 , 162.57 , 144.39 , 139.04 , 132.66 , 128.02 , 117.46 , 116.02 , 74.48 , 70.12 , 60.61 , 58.01 , 53.35 , 48.92 , 45.39 , 44.85 , 43.95 , 41.70 , 38.24 , 36.58 , 36.50 , 35.95 , 34.40 , 34.16 , 31.43 , 30.32 , 26.88 , 26.37 , 26.17 , 24.75 , 16.87 , 14.79 , 14.21 , 11.48 . HRMS: calcd for $C_{38}H_{52}N_2O_8S_2$ [M - H]$^-$：727.3081，found: 727.3053.

4.1.13.9. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-trifluoromethyl benzenesulfonamide-sulfanyl]acetyl}-mutilin ***(2I).*** Compound 2H was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and *P*-trifluoromethylbenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 150 mg.Yield：55%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 6.50 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.90 (s, 1H), 5.74 (d, *J* = 8.5 Hz, 1H), 5.37 (d, *J* = 11.0 Hz, 1H), 5.22 (d, *J* = 17.3 Hz, 1H), 4.11 – 4.08 (m, 2H), 3.35 (d, *J* = 6.4 Hz, 1H), 3.28 (s, 1H), 3.05 (s, 2H), 2.57 (d, *J* = 33.8 Hz, 3H), 2.35 – 2.27 (m, 2H), 2.20 – 2.10 (m, 2H), 2.09 (t, *J* = 12.3 Hz, 2H), 2.03 – 1.92 (m, 3H), 1.80 – 1.74 (m, 1H), 1.65 (q, *J* = 11.0, 10.4 Hz, 3H), 1.59 – 1.47 (m, 4H), 1.42 (s, 3H), 1.39 – 1.33 (m, 1H), 1.29 (d, *J* = 16.1 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 4H), 1.18 (s, 3H), 1.12 – 1.09 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.87 , 173.78 , 169.50 , 143.45 , 138.96 , 134.07 , 127.95 , 126.03 , 126.00 , 122.36 , 117.51 , 74.53 , 70.06 , 60.65 , 60.37 , 58.04 , 53.19 , 48.93 , 45.40 , 44.85 , 43.94 , 41.70 , 38.31 , 36.61 , 35.95 , 34.41 , 33.95 , 30.34 , 29.21 , 26.87 , 26.27 , 24.77 , 21.03 , 16.86 , 14.79 , 14.20 , 11.48 . HRMS: calcd for $C_{38}H_{52}F_3NO_8S_2$ [M - H]$^-$：770.3008，found: 770.3004.

3.1.13.10. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-acetylbenzene sulfonamide-sulfanyl]acetyl}-mutilin ***(2J).*** Compound 2I was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and P-acetylbenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 160 mg.Yield：60%.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.99 (d, *J* = 8.2 Hz, 2H), 6.49 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.93 (s, 1H), 5.73 (d, *J* = 8.5 Hz, 1H), 5.38 (d, *J* = 11.0 Hz, 1H), 5.34 – 5.18 (m, 2H), 4.13 – 4.08 (m, 2H), 3.36 (d, *J* = 6.4 Hz, 1H), 3.29 (s, 1H), 3.06 (d, *J* = 3.4 Hz, 2H), 2.64 (s, 3H), 2.62 – 2.56 (m, 2H), 2.51 (d, *J* = 12.5 Hz, 1H), 2.32 (p, *J* = 7.0 Hz, 1H), 2.21 – 2.19 (m, 2H), 2.09 (q, *J* = 8.6, 7.9 Hz, 2H), 2.02 (s, 1H), 2.00 – 1.91 (m, 2H), 1.77 (d, *J* = 12.8 Hz, 1H), 1.64 (dd, *J* = 13.6, 7.0 Hz, 2H), 1.56 – 1.50 (m, 3H), 1.42 (s, 3H), 1.40 – 1.34 (m, 1H), 1.29 (d, *J* = 16.1 Hz, 1H), 1.24 (d, *J* = 7.1 Hz, 3H), 1.19 (s, 3H), 1.16 – 1.08 (m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 216.92 , 196.86 , 173.83 , 169.36 , 143.85 , 139.81 , 138.97 , 128.76 , 127.66 , 117.46 , 74.52 , 69.98 , 60.62 , 60.36 , 58.03 , 53.15 , 48.72 , 45.40 , 44.84 , 43.93 , 41.70 , 38.25 , 36.61 , 35.94 , 34.40 , 33.96 , 30.34 , 28.93 , 26.86 , 26.33 , 26.06 , 24.77 , 21.02 , 16.86 , 14.80 , 14.21 , 11.49 . HRMS: calcd for $C_{39}H_{55}NO_9S_2$ [M - H]$^-$：744.3240，found: 744.3212.

4.1.13.11. 14-O-{[(1R, 2R, 4S)-4-ethylacetate-2-p-acetamidoben zenesulfonamide-sulfanyl]acetyl}mutilin ***(2K).*** Compound 2J was prepared according to the general procedure from 14-O-{[(1R, 2R, 4S)-4- ethylacetate -2-amino-sulfanyl]acetyl}-mutilin(K) and P-acetamidobenzenesulfonyl chloride. The crude product was purified over silica gel column chromatography to give white solid 170 mg.Yield：63%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 6.47 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.77 – 5.67 (m, 2H), 5.36 (d, *J* = 11.0 Hz, 1H), 5.30 (s, 1H), 5.22 (d, *J* = 17.4 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.37 (d, *J* = 6.2 Hz, 1H), 3.28 (s, 1H), 3.08 (q, *J* = 15.6 Hz, 2H), 2.71 – 2.64 (m, 1H), 2.59 (s, 1H), 2.44 (d, *J* = 11.9 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.20 (s, 3H), 2.13 – 2.06 (m, 2H), 2.03 – 1.94 (m, 2H), 1.90 (d, *J* = 11.7 Hz, 1H), 1.77 (d, *J* = 12.9 Hz, 1H), 1.69 – 1.61 (m, 2H), 1.59 – 1.49 (m, 4H), 1.43 (d, *J* = 6.1 Hz, 3H), 1.36 (d, *J* = 12.1 Hz, 1H), 1.31 (d, *J* = 16.1 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H), 1.12 – 1.09 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 217.21 , 174.06 , 169.16 , 169.00 , 142.21 , 138.97 , 134.37 , 128.45 , 119.17 , 117.42 , 74.56 , 73.43 , 69.80 , 60.65 , 58.11 , 52.87 , 48.28 , 48.24 , 45.43 , 44.80 , 43.93 , 41.73 , 38.19 , 36.69 , 35.95 , 34.46 , 33.89 , 30.38 , 28.34 , 26.85 , 26.34 , 25.49 , 24.78 , 24.68 , 16.84 , 14.85 , 14.21 , 11.50 . HRMS: calcd for $C_{39}H_{56}N_2O_9S_2$ [M - H]$^-$：759.3349，found: 759.3308.

MIC Testing

Minimum inhibitory concentrations (MIC) of the compounds were determined by using the agar dilution method described by the Clinical Laboratory Standards Institute. The stocks solutions of the compounds were prepared in 0.2%DMSO and the concentrations are 1920 μg/ml. The drug stock solution is diluted twice with the corresponding diluent to various desired concentrations. 1 ml of different concentrations of the dilutions were sequentially taken and added to the well-marked 90 mm

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using a graduated pipette. After thoroughly mixing the drug solution with the culture medium, it was placed on a horizontal test bench. After the agar naturally solidifies, it is ready for use. The final concentrations of compounds ranged from 0.03 to 128 μg/mL. The concentration of the bacterial solution was adjusted to 0.5 turbidity (about 108 CFU/ml) using a turbidimeter. Further, it was diluted 10 times (about 107 CFU/ml), and after mixing, an appropriate amount (about 0.3 ml) was added to the inoculated plate in order. The above-mentioned bacterial solution was inoculated to a series of plates containing different concentrations of the drug using a multi-point inoculation instrument (inoculation needle diameter 3 mm, dispensing amount 1-2 μl) within 30 minutes, and the inoculum amount per inoculation point was about 104 CFU. Culture plates were incubated at 35 ±2°C for 18 h, and MICs were then recorded. The MIC was defined as the lowest concentration that prevented visible growth of the bacteria.

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Author Contribution Statement

Yun-Ge Li, Fan Zhang, and Yu-Cheng Wang designed and planned the experiments. Yun-Ge Li and Mei Zhu synthesized the compounds. Xue-Fu You tested the antibacterial activity. Yun-Ge Li wrote the manuscript with support from Guo-Ning Zhang, Ju-Xian Wang, and Fan Zhang. Yu-Cheng Wang supervised the project.

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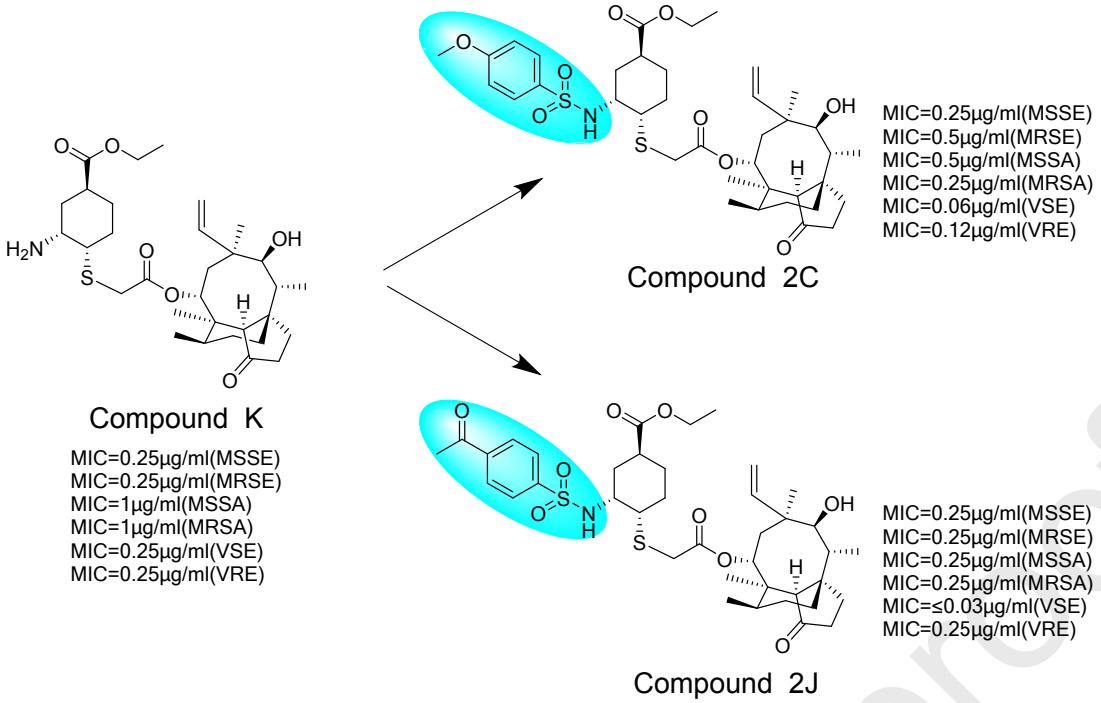

Declaration of interests

☑The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence t √ he work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: