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Design, synthesis and anti-rheumatoid arthritis evaluation of double-ring conjugated enones

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ABSTRACT

Four series of double-ring conjugated enones were designed, synthesized and studied for the inhibition of synovial cell activity through the modification of Dysodensiol K core structure, double-ring, double-bond and double-carbonyl groups. For *in vitro* synovial cell assay of rats, compound **151** and **168** exhibited good inhibitory activities, with IC_{50} values of 2.71 ± 0.18 and 2.68 ± 0.16 μM respectively. At the same time, the LDH release and LD_{50} test results revealed that the target compounds were low cytotoxicity and acute toxicity. For *in vivo* CIA model test through the oral administration, compounds **151** and **168** were exhibited similar effect to positive control group methotrexate.

1. Introduction

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease, and characterized by synovitis of the joints [1–3]. Repeated attacks of synovitis can lead to the destruction of cartilage and bone joints, joint dysfunction, and even disability. Although the RA is not malignant, it imposes a heavy burden on the patient and the family as the patient has recurrent episodes that eventually lead to joint malformations and loss of function. RA not only brings physical unbearable pain, distortion, swelling of joints and trauma to the patients, but also mental devastation [4]. Once the disease is severe, the sufferer will be unbearable pain. So once the body is not must be timely intervention treatment. However, the majority of patients even RA pathogenic factors are not clear, how difficult to talk about treatment. The early clinical manifestations of RA is relate to joint redness, heat, pain, swelling and dysfunction. In late stage, different degrees of deformity and stiffness of joints may occur, accompany by atrophy of the bone and skeletal muscle, which is very likely to cause disability [5]. RA onset age mostly in 20–60 years old age and the incidence of women than men. From the point of view for pathological changes, RA is a major involve synovial membrane of the joint. After the severity of the disease can affect the articular cartilage, joint ligament, bone tissue and muscle bond. It can be further affect by the extensive inflammatory disease of connective tissue such as heart, lung, serous membrane and eye. In addition to joint lesions, RA systemic manifestations of fever, pericarditis, fatigue, pleurisy, subcutaneous nodules, peripheral neuropathy and arteritis, etc [6–8]. The etiology of RA is not completely clear, it is closely related to the environment, genetics, viruses and sex hormones factors [9]. The pathogenesis is not completely clear, but it is generally recognize as an autoimmune disease. Although the tissue changes of the RA may vary slightly due to the location, the basic changes are the same [10–12].

The main purpose of RA treatment is to reduce the inflammatory reaction of joints. Inhibit the development of lesions and irreversible bone destruction, protect the function of muscles and joints as much as possible. Finally, achieve the goal of complete reduction or remission of disease activity [13]. Currently, RA is an incurable disease and the common drugs used are generally divided into five categories: 1) Non-steroidal anti-inflammatory drugs (NSAIs), which have to beanalgesic and anti-inflammatory, which could reduce the symptoms of arthritis, but cannot control the condition. At such a situation, it is suggested to change the anti-rheumatoid drug. 2) Slow-acting anti-rheumatoid drugs (SAARs) can play a role in controlling the course of rheumatoid arthritis.

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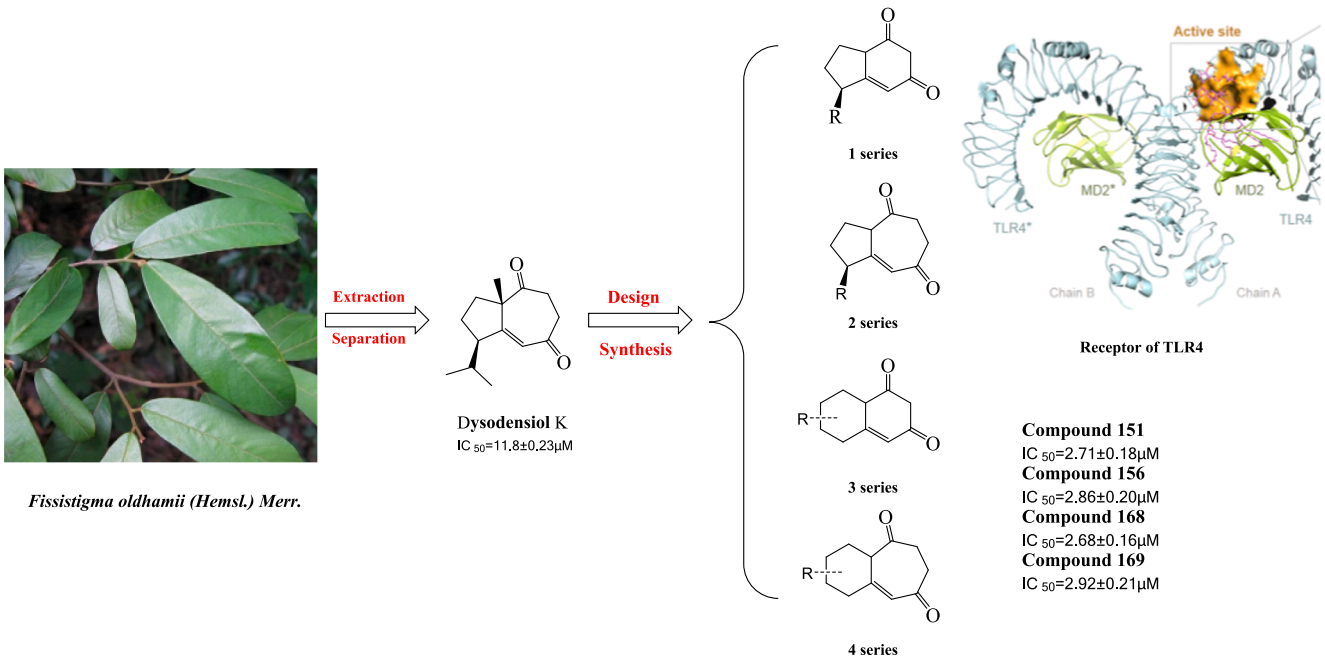
3) Glucocorticoids (GCs) have a powerful anti-inflammatory effect, which can quickly relieve systemic inflammation, joint swelling and pain. 4) Targeted therapy with biological agents. 5) Botanical medicine preparation [14–16]. Clinically, the pain associate with RA is very severe. Therefore, when this happens, the patients should be treated with NSAIs in time, such as dichlorfenic acid, nabumetonen and meloxicam. In addition, SAARs can be treated with RA, such as methotrexate and sulfasalazine. If the patient's condition is more serious, it is recommended to use GCs and biological agents for treatment. At present, there have been a variety of plant drugs for RA, such as sinomenine, tripterygium wilfordii, etc. Some plant drugs are effective with treatment RA, but the mechanism of action needs further study. Dysodensiol K is a monomer compound and isolate from *Fissistigma oldhamii* with anti-rheumatoid arthritis activity. Its inhibitory effect on synovial cells can reach $IC_{50} = 11.8 \pm 0.23$ μM *in vitro* (Fig. 1) [17–19]. In the further study of the mechanism of action, it is found that the Dysodensiol K has a good binding to Toll-like receptor 4 (TLR4). Thus, inhibiting the growth of synovial cells and playing a role in the treatment of RA [20–25]. In this study, Dysodensiol K was used as the lead compound to modify the chemical structure to find a more ideal target compounds with anti-rheumatoid arthritis activity. Four series of double-ring conjugated enones were designed (Fig. 1) and these target compounds (compounds **41**–**78** and compounds **139**–**198**) were screened for anti-rheumatoid arthritis activity tests *in vitro,* including rat synovial inhibitory activity, LDH cell activity tests. On this basis, *in vivo* anti-rheumatoid arthritis activity tests were carried out on the ideal target compounds with anti-rheumatoid arthritis activity *in vitro*. At the same time, the molecular docking simulation studies were used to explain the degree of binding between the target compounds and TLR4. It can be providing a certain theoretical basis for the design of such compounds [26].

2. Results and discussions

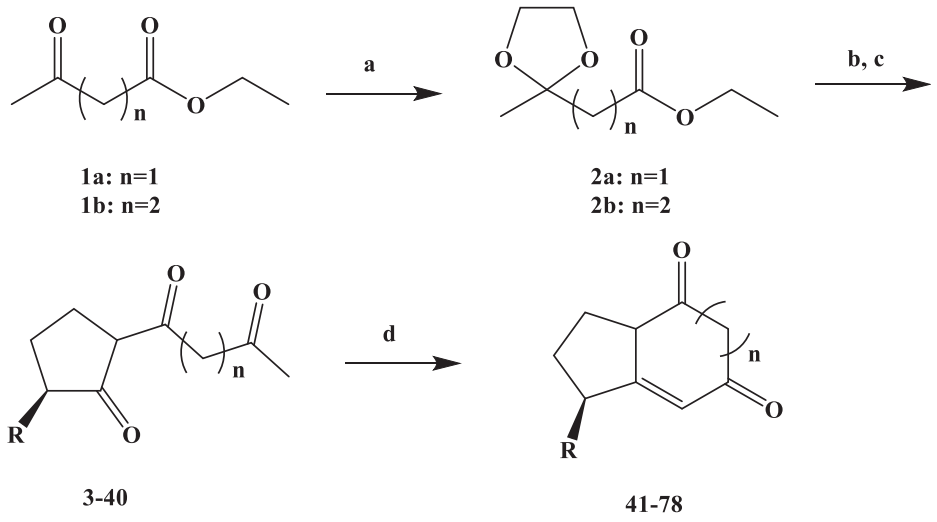
2.1. Design and synthesis

Further separation of small molecule and monomer compounds from active components of phytodrugs was an important part of modern phytodrug chemistry. And as the lead compound, further structural optimization and modification, it could be obtained a more ideal anti-rheumatoid arthritis treatment drugs. Dysodensiol K was a natural product isolated from medicinal plant (*Fissistigma oldhamii*) and it had shown a good inhibitory effect on synovial cells growth during the screening of anti-rheumatoid arthritis activity *in vitro*. Due to the low content of natural products, it also limits the further research and development of drugs [27]. In view of Dysodensiol K was a good anti-rheumatoid arthritis activity, we analyzed its chemical structure and found that it had a double-ring conjugated enone structure (double-ring, double-bond and double-carbonyl groups). In order to find a large number of compounds that could be screened for anti-rheumatoid arthritis activity *in vitro*, we turned to chemical synthesis. We took Dysodensiol K as the lead compound and modified its structure, designed four series of 98 target compounds (Fig. 1). In the design process of the target compounds (**41**–**78** and **139**–**198**), we retained the basic skeleton structure of Dysodensiol K (double-ring conjugated enone structure). So as to ensure the anti-rheumatoid arthritis activity of the designed target compounds to a greater extent. In order to obtain the ideal target compounds with anti-rheumatoid arthritis activity, introduced different substituents at different positions of the aliphatic ring to study the structure–activity relationship (SAR) of the drugs. In the process of synthesis the target compounds, we chose a synthetic route with better synthetic efficiency (Scheme 1 and Scheme 2). Four series of target compounds were synthesized from ethyl acetoacetate (compound **1a**) and ethyl levulinate (compound **1b**) by four steps of carbonyl protection, condensation, hydrolysis and cyclization. First of all, compound **1a** and compound **1b** were placed in benzene and carbonyl protected with ethylene glycol. In this step, *p*-methylbenzenesulfonic acid (*p*-TsOH) was used as catalyst and reflux reaction lasted for 48 h to obtain a relatively ideal yield (more than 98% yield). After the compounds **2a** and **2b** were obtained, it were placed in anhydrous ethanol and treated with different substituted cyclopentanone (Scheme 1, 1 and 2 series target compounds **41**–**78**) or cyclohexanone (**Scheme 2, 3 and 4** series target compounds **139**–**198**). During the treatment, sodium ethanol was used as an alkaline substance and refluxed for 12 h. After the condensation reaction was completed and solvent was removed. The hydrochloric acid solution was directly hydrolyzed to remove the carbonyl protection, and the corresponding intermediates (compounds **3**–**40** and **79**–**138**) could be obtained (56.7%-92.1% yield). Finally, compounds **3**–**40** and compounds **79**–**138** were placed in anhydrous ethanol and

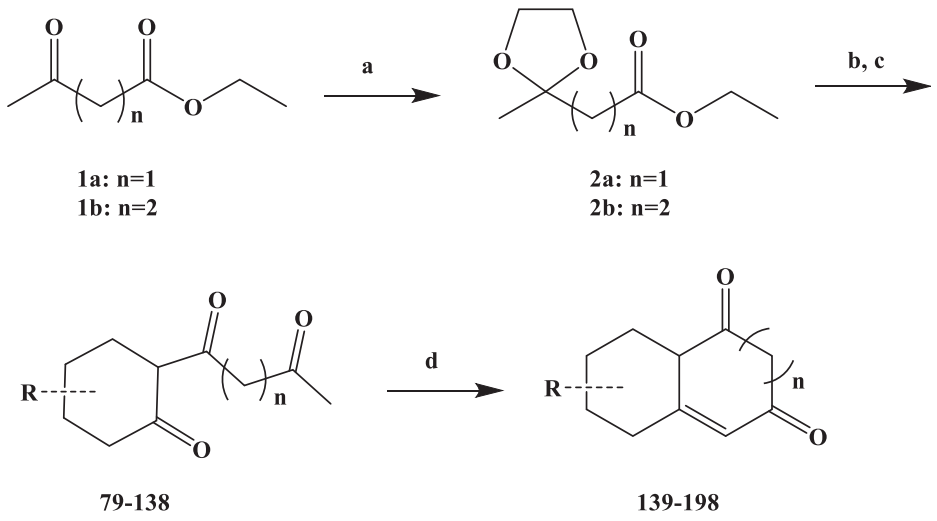


Fissistigma oldhamii (Hemsl.) Merr.

Fig. 1. The design of double-ring conjugated enones.



Scheme 1. Reagents and conditions: (a) ethanediol, benzene, *p*-TsOH, reflux 48 h; (b) substituted cyclopentanone, C_2H_5OH, C_2H_5ONa, reflux 12 h; (c) HCl, H_2O, 60℃, 2 h, (d) KOH, C_2H_5OH, reflux 12 h.



Scheme 2. Reagents and conditions: (a) ethanediol, benzene, *p*-TsOH, reflux 48 h; (b) substituted cyclohexanone, C_2H_5OH, C_2H_5ONa, reflux 12 h; (c) HCl, H_2O, 60℃, 2 h, (d) KOH, C_2H_5OH, reflux 12 h.

refluxed under the condition of potassium hydroxide as an alkaline substance (refluxed for 12 huorus). The target compounds **41**–**78** and compounds **139**–**198** were obtained by silica gel column separation, with an yield of 38.8%-89.2%. Meanwhile, in order to study the presence of enantiomers in the target compounds, we measured the e.e. value of target compound **151**, **156** and **168**. The results showed that the e.e. values of the compounds **151**, **156** and **168** were relatively high, which were 98.8%, 99.1% and 99.3%, respectively, which also indicated that the design of the synthesis route was scientific and reasonable. The synthetic route has relatively conventional operation, the solvents and reagents used were cheap and easy to be obtained, no expensive catalyst was needed, and the total yield of the target compounds were relatively ideal. This synthetic route provides a certain experimental basis for industrialization in the future, and facilitates the subsequent expansion of output.

2.2. Inhibition and morphology study of rat synovial cells in vitro

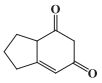
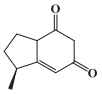
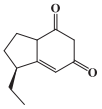
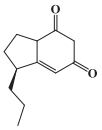
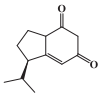
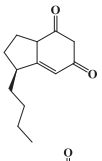
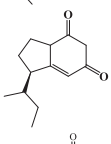
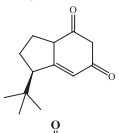
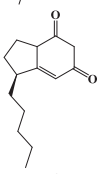
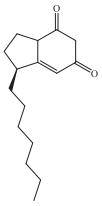
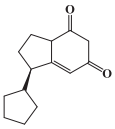
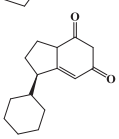
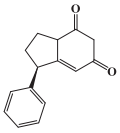
RA is a systemic disease with unknown etiology, and mainly inflammatory synovitis. Synovial cells were important tissue structures to maintain the normal function of joints and the main lesion sites in patients with RA. In the screening process of anti-rheumatoid arthritis activity *in vitro*, the inhibitory activity of target compounds on rat synovial cells was used as the evaluation index. The CKK assay was used to determine the inhibitory effect of the compounds on rat synovial cells, and the IC_{50} value was used to evaluate the anti-rheumatoid arthritis activity of the target compounds *in vitro*. Dysodensiol K was a natural product that had been shown inhibitory rat synovial cells activity. Its inhibitory activity of $IC_{50} = 11.8 \pm 0.23$ μM during *in vitro* screening could be used as a potential treatment for RA or as a lead compound for further structural optimization. Used Dysodensiol K as the lead compound, we designed and synthesized four series of 98 target compounds (1, 2, 3, 3a-tetrahydro-4*H*-indene-4, 6 (5*H*)-dione derivatives, compounds **41**–**59**; 1, 2, 3, 3a, 5, 6-hexahydroazulene-4, 7-dione derivatives, compounds **60**–**78**; 6, 7, 8, 8a-tetrahydronaphthalene-1, 3 (2*H*, 5*H*)-dione derivatives, compounds **139**–**168** and 2, 3, 4, 4a, 6, 7-hexahydro-1*H*-benzo [7] annulene-5, 8-dione derivatives, compounds **169**–**198**) [28]. And screened these compounds to inhibit the activity of rat synovial cells *in vitro*, so as to evaluate the anti-rheumatoid arthritis activity of the target compounds (**41**–**78** and **139**–**198**). *In vitro* screening results showed that the most of target compounds could inhibit the growth of rat synovial cells, with IC_{50} values ranging from 2.68 ± 0.16 to

10.64 ± 0.76 μM (Table 1). Among them, the compounds **44**, **45**, **56**, **57**, **63**, **64**, **66**, **67**, **75**, **78**, **151**, **156**, **166**, **168**, **169**, **171**, **177**, **178** and **195** showed ideal inhibitory activities, with IC_{50} values of 3.04 ± 0.26, 2.93 ± 0.21, 3.04 ± 0.31, 2.93 ± 0.16, 3.19 ± 0.21, 2.95 ± 0.20, 3.21 ± 0.29, 3.05 ± 0.24, 3.19 ± 0.26, 3.26 ± 0.22, 2.71 ± 0.18, 2.86 ± 0.20, 2.98 ± 0.23, 2.68 ± 0.16, 2.92 ± 0.21, 2.97 ± 0.26, 3.12 ± 0.29, 3.07 ± 0.28 and 3.28 ± 0.32 μM, respectively. Among these compounds, the compounds **151** (IC_{50} = 2.71 ± 0.18 μM) and **168** (IC_{50} = 2.68 ± 0.16 μM) showed inhibitory activity close to positive control methotrexate (IC_{50} = 2.36 ± 0.22 μM), which was at the same level as the inhibitory rat synovial cells activity. Drugs generally combine with the receptors on the cells of the body and then play a drug effect. Structure-activity relationship (SAR) refers to the relationship between the chemical structure of drugs or other physiologically active substances and their physiological activities, which was one of the main research contents of pharmacochemistry. Compound **41**, **60**, **139** and **169** has the parent nucleus structure, its has the similar structure of the lead compound Dysodensiol K. On the basis of compounds **41**, **60**, **139** and **169**, the structure of the junction was modified, increasing or decreasing ring, and different substituents (electron-withdrawing group and electron-donating group) were introduced into the aliphatic ring to study the SAR of the compounds. The four series of parent compounds showed good inhibitory activity *in vitro*, and their IC_{50} values were 3.49 ± 0.35, 3.23 ± 0.23, 3.12 ± 0.22 and 2.92 ± 0.21 μM, respectively. After the optimization of the structure of the parent compounds in each series, some compounds with better activity were also obtained, among which the compounds in the third series were better as a whole, especially like compounds **151** and **168**. In order to visualize the inhibitory activity of the target compounds *in vitro*, we studied the morphology of rat synovial cells *in vitro* of target compounds **151**, **156**, **168** and **169** (Fig. 2). Compared with the normal group, the morphology of rat synovial cells in the DMSO group was not abnormal. The damage of rat synovial cells in the positive control methotrexate group was significant, the refractive activity of the cells was decreased, the cytoplasm of the cells became narrow and wrinkled, the fibroblasts were significantly reduced, some cells were broken, and the number of cell fragments increased. Compounds **151**, **156**, **168** and **169** group showed obvious damage to rats synovial cells and different degrees of refraction, with cell cytoplasm becoming narrow and shrunken, fibroblasts decreasing significantly, some cells were broken and cell fragments increased, showing a good effect of destroying synovial cells. Cell morphology studies could be showed that the target compounds inhibit the growth of rat synovial cells *in vitro*.

2.3. LDH release values of rat synovial cells in vitro

Lactate dehydrogenase (LDH) is one of the most important redox enzymes in the glycolytic pathway of organisms. It could reversely catalyze the oxidation of lactic acid to pyruvate[28]. LDH was an extremely stable cytoplasmic enzyme, which mainly exists in the liver, myocardium, skeletal muscle, kidney and lung tissues. LDH was abundant in the cytoplasm, which cannot pass through the cell membrane in normal times. But LDH could be released into the extracellular environment when the cell dead or damage. The number of cell death was in direct proportion to the LDH activity in the supernatant of cell culture. Quantitative analysis of cytotoxicity could be achieved by detecting the activity of LDH released into the culture medium from cell membrane ruptured. LDH release was regarded as an important indicator of cell membrane integrity, which could determine the degree of cell damage and widely used in cytotoxicity detection. Compounds **44**, **45**, **56**, **57**, **63**, **64**, **66**, **67**, **151**, **156**, **166**, **168**, **169**, **171**, **177**, **178** and **195** showed ideal inhibitory activities during the screening process of inhibiting the growth of rat synovial cells *in vitro*. Therefore, these compounds (concentration at 1 μM) were further tested for LDH release to evaluate the degree of damage to rat synovial cells caused by the target compounds (Table 2). Test results showed that the LDH release values of these

Table 1
In vitro inhibition activity of rat synovial cells.

Compounds	Structure	log*p*	pK_a	IC_{50} (μM)[a] ± *SD*
41		1.35	8.3	3.49 ± 0.35
42		1.66	8.3	4.22 ± 0.30
43		2.11	8.2	3.29 ± 0.34
44		2.56	8.2	3.04 ± 0.26
45		2.43	8.2	2.93 ± 0.21
46		2.90	8.1	4.68 ± 0.35
47		2.83	8.1	3.78 ± 0.32
48		2.88	8.0	5.48 ± 0.041
49		3.15	8.0	4.01 ± 0.36
50		3.91	7.9	3.37 ± 0.28
51		2.78	8.4	6.09 ± 0.51
52		3.12	8.3	4.94 ± 0.50
53		2.98	8.1	5.70 ± 0.53
54		0.89	8.6	3.96 ± 0.37

(*continued on next page*)

Table 1 (*continued*)

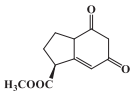
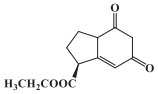
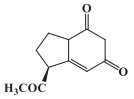
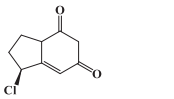
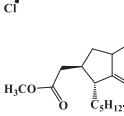
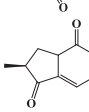
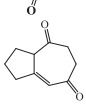
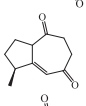
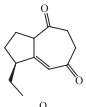
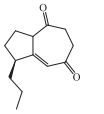
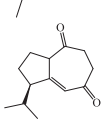
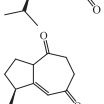
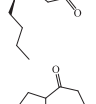
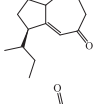
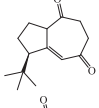
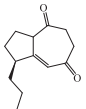
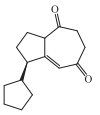
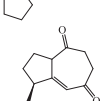
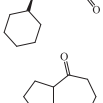
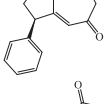
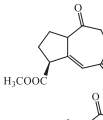
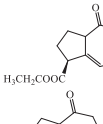
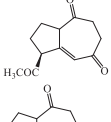
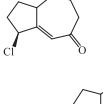
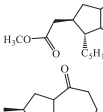
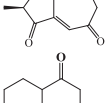
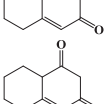
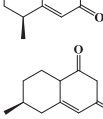
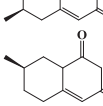
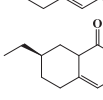
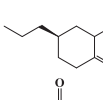
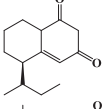
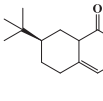
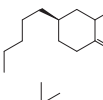
Compounds	Structure	log*p*	pK_a	IC_{50} (μM)[a] ± *SD*
55		1.12	8.5	3.96 ± 0.35
56		0.44	8.5	3.04 ± 0.31
57		1.50	7.3	2.93 ± 0.16
58		2.97	8.0	3.16 ± 0.23
59		0.81	8.3	8.61 ± 0.68
60		1.58	8.4	3.23 ± 0.23
61		1.90	8.4	3.52 ± 0.22
62		2.34	8.2	3.64 ± 0.26
63		2.77	8.3	3.19 ± 0.21
64		2.66	8.3	2.95 ± 0.20
65		3.15	8.1	3.64 ± 0.28
66		3.08	8.2	3.21 ± 0.29
67		3.13	8.1	3.05 ± 0.24
68		3.59	8.0	3.89 ± 0.31
69		4.32	8.0	4.19 ± 0.33
70		3.01	8.5	3.52 ± 0.26

Table 1 (*continued*)

Compounds	Structure	log*p*	pK_a	IC_{50} (μM)[a] ± *SD*
71		3.40	8.3	5.01 ± 0.40
72		3.00	8.3	4.40 ± 0.39
73		1.02	8.5	6.43 ± 0.43
74		1.35	8.5	3.77 ± 0.32
75		0.61	8.5	3.19 ± 0.26
76		1.79	7.3	4.33 ± 0.29
77		3.18	8.0	6.34 ± 0.41
78		0.92	8.3	3.26 ± 0.22
139		1.57	8.2	3.12 ± 0.22
140		1.91	8.0	5.08 ± 0.43
141		1.92	8.0	5.33 ± 0.49
142		1.90	8.0	5.46 ± 0.45
143		2.33	8.0	4.35 ± 0.40
144		2.70	7.9	3.82 ± 0.28
145		3.05	7.8	5.71 ± 0.51
146		3.11	7.8	3.94 ± 0.30
147		3.57	7.9	4.73 ± 0.41
148		3.51	7.9	4.14 ± 0.39

(*continued on next page*)

Table 1 (*continued*)

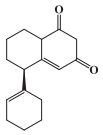
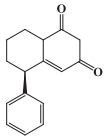
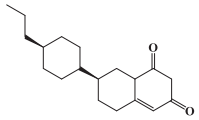
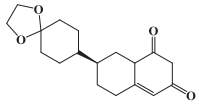
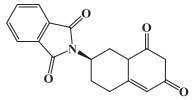
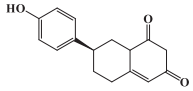
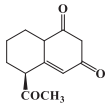
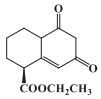
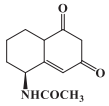
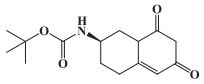
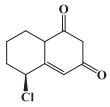
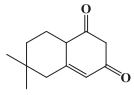
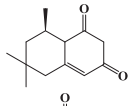
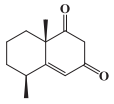
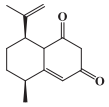
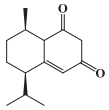
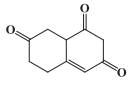
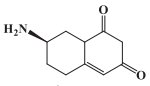
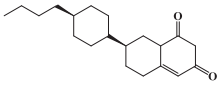
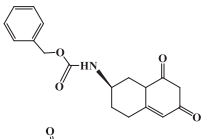
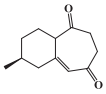
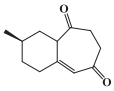
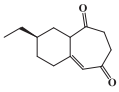
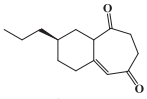
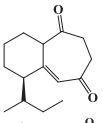
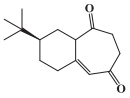
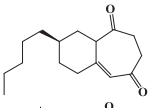
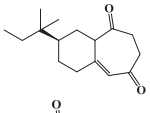
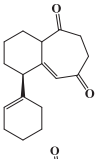
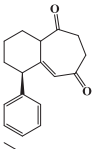
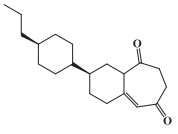
Compounds	Structure	log*p*	pK_a	IC_{50} (μM)[a] ± *SD*
149		2.90	7.7	3.48 ± 0.26
150		3.05	7.8	4.17 ± 0.33
151		3.55	7.9	2.71 ± 0.18
152		2.50	7.8	3.89 ± 0.37
153		1.60	8.5	3.29 ± 0.26
154		0.59	8.0	4.33 ± 0.41
155		1.32	8.1	3.37 ± 0.33
156		1.44	8.0	2.86 ± 0.20
157		0.39	8.3	4.96 ± 0.47
158		1.35	8.6	4.68 ± 0.46
159		1.70	7.6	4.53 ± 0.49
160		2.33	7.7	3.56 ± 0.34
161		2.76	7.7	3.34 ± 0.36
162		2.63	7.8	3.51 ± 0.33
163		2.59	7.6	3.55 ± 0.39
164		2.93	7.8	4.12 ± 0.39
165		0.50	7.9	6.24 ± 0.51

Table 1 (*continued*)

Compounds	Structure	log*p*	pK_a	IC_{50} (μM)[a] ± *SD*
166		0.39	8.9	2.98 ± 0.23
167		3.99	7.9	4.58 ± 0.50
168		2.45	8.8	2.68 ± 0.16
169		1.68	8.1	2.92 ± 0.21
170		1.88	8.0	4.46 ± 0.38
171		1.89	8.0	2.97 ± 0.26
172		1.87	8.0	4.05 ± 0.36
173		2.38	8.1	4.22 ± 0.39
174		2.69	7.9	4.24 ± 0.40
175		3.00	7.9	3.78 ± 0.35
176		3.06	7.8	4.11 ± 0.35
177		3.55	7.9	3.12 ± 0.29
178		3.48	8.0	3.07 ± 0.28
179		2.88	7.7	4.12 ± 0.38
180		3.05	7.8	4.43 ± 0.40
181		4.35	8.0	3.19 ± 0.31
182		2.49	7.8	4.28 ± 0.41

(*continued on next page*)

Table 1 (*continued*)

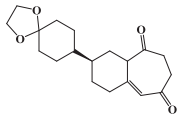
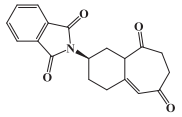
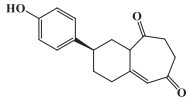
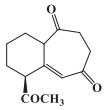
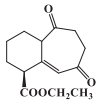
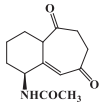
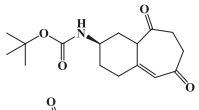
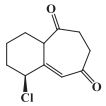
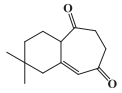
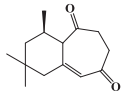
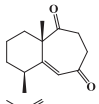
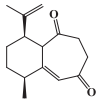
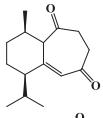
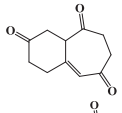
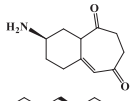
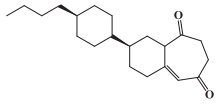
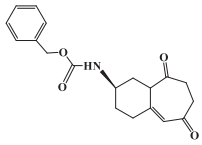
Compounds	Structure	log*p*	pK_a	IC_{50} (μM)[a] ± *SD*
				
183		1.55	8.6	10.64 ± 0.76
184		2.61	8.0	4.76 ± 0.39
185		0.55	8.1	6.65 ± 0.59
186		1.29	8.0	4.26 ± 0.43
187		0.33	8.3	5.18 ± 0.48
188		1.29	8.7	5.10 ± 0.51
189		1.68	7.6	4.81 ± 0.39
190		2.33	7.7	4.23 ± 0.38
191		2.66	7.8	3.78 ± 0.33
192		2.59	7.8	3.76 ± 0.39
193		2.50	7.6	3.89 ± 0.37
194		2.99	7.9	4.37 ± 0.41
195		0.98	7.9	3.28 ± 0.32
196		0.62	9.0	3.78 ± 0.35
197		4.59	7.9	4.01 ± 0.36
198		2.26	8.8	4.09 ± 0.31

Table 1 (*continued*)

Compounds	Structure	log*p*	pK_a	IC_{50} (μM)[a] ± *SD*
				
methotrexate[b]	—	—	—	2.36 ± 0.22

[a] Values are the average of 3 independent experiments run in triplicate.
[b] Methotrexate is use as positive control.

compounds were lower than those of the positive control methotrexate (454.59 ± 19.75 U/L at 1 μM), indicating that these target compounds had better cell membrane damage than the positive control substance. The LDH release value of compound **63** was the lowest, it were 281.22 ± 22.84 U/L at 1 μM. It also showed that the inhibitory activity of the target compounds on rat synovial cells was not caused by cytotoxicity, and these compounds could be showed low cytotoxicity. Therefore, these types of target compounds have further structural modifications, in-depth study, including mechanism of action, pharmacokinetics, acute toxicity and other related studies.

2.4. *In vivo* of anti-rheumatoid arthritis activity

In vitro screening of anti-rheumatoid arthritis activity, most of the target compounds showed a good inhibition of rat synovial cells [29]. *In vitro* activity results combined with LDH release values for the compounds **151**, **156**, **168** and **169**were necessary for anti-rheumatoid arthritis *in vivo* testing. To determine the effectiveness of an animal model for anti-rheumatoid arthritis *in vivo*, we used a collagen-induced arthritis (CIA) model in rats. In a rat CIA model, we evaluated the therapeutic effects of compounds **151**, **156**, **168** and **169**, including paw volume, IL-6 and TNF-α concentrations of serum. During the evaluation, normal group, blank control group, positive control group (methotrexate, 50 mg/kg/day) and target compound groups (50 mg/kg/day and 100 mg/kg/day) were set. In the paw volume evaluation of rats (Fig. 3 and Fig. 4), the test results showed that the paw volume of the induced inflammation rats was basically unchanged before and after the treatment with the compounds **151**, **156**, **168** and **169** for high dose. However, at low dose, compound **151** and **168** remained essentially unchanged before and after treatment, while compound **156** and **169** showed a slight change in paw volume before and after treatment, suggesting that compounds **151** and **168** might be more effective. As could be seen from the real picture of the rat paw in Fig. 4, the blank group (Fig. 4b) showed obvious redness and swelling, the paw became significantly larger, which was caused by inflammation. However, the rats treated with the compounds **151**, **156**, **168** and **169** showed no redness or swelling, the paw volume remained unchanged, reaching the level of the normal group (Fig. 4a). In measuring IL-6 and TNF-α concentrations of serum (Fig. 5), the treatment with high and low doses of compounds **151**, **156**, **168** and **169** showed improvement. Test results show that the compounds **151**, **156**, **168** and **169** with treatment, the concentration of IL-6 basic reached a consistent level. Compared with normal group and positive control products in the same level, the concentration of IL-6 and blank control group has obvious improvement, suggesting that compounds **151**, **156**, **168** and **169** have good anti-rheumatoid arthritis activity *in vitro*. At the same time, the concentrations of TNF-α in serum after treatment of compounds **151**, **156**, **168** and **169** were also improved compared with the blank control group, but there was a dose dependence. The compounds **151** and **168** were relatively most effective after high dose treatment, reaching the treatment level of the positive control methotrexate. The meaning of symbols were ** = P less than 0.01, * = P less than 0.05.

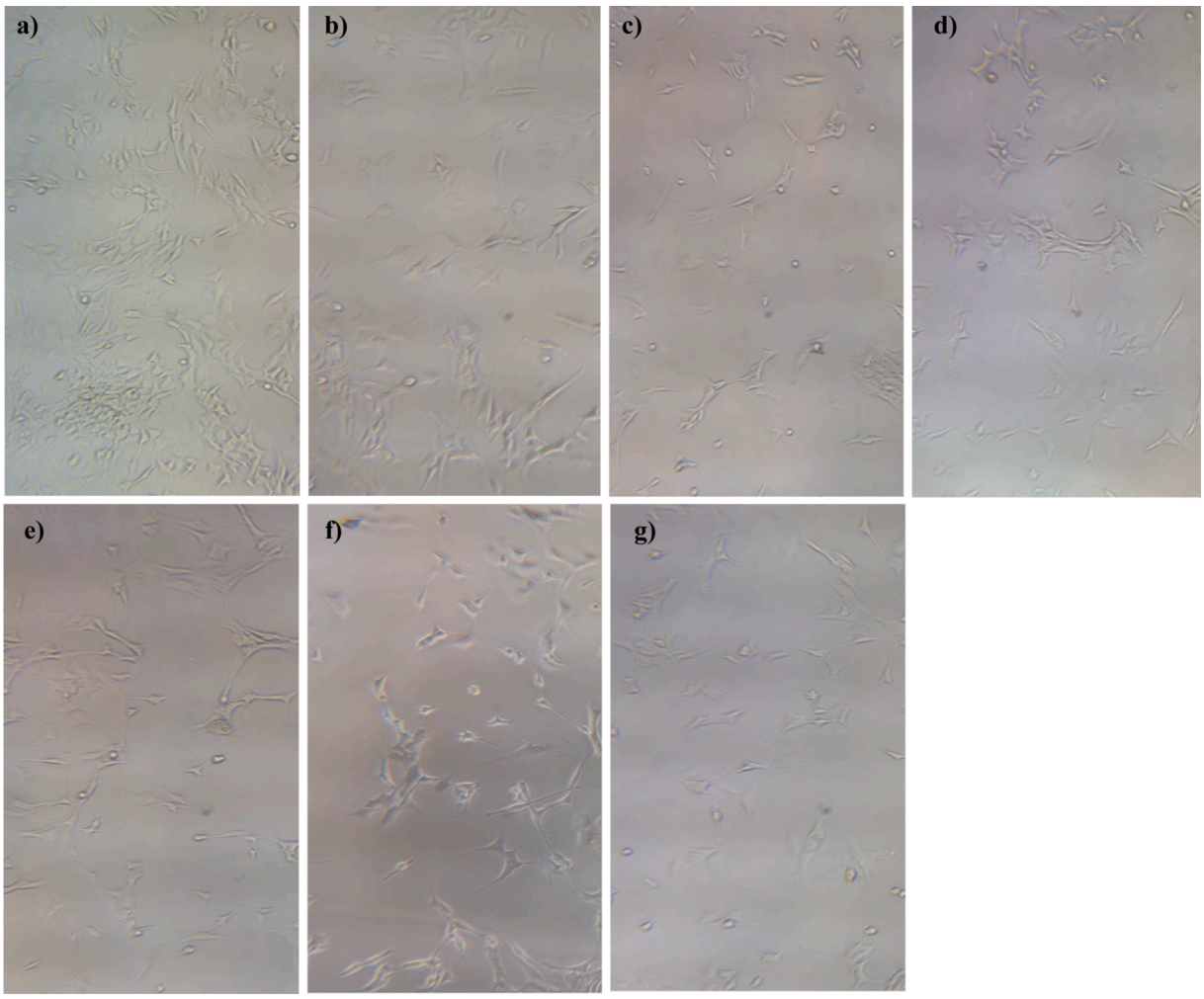


Fig. 2. The morphology of rat synovial cells. a) normal group; b) DMSO group; c) methotrexate group; d) compound **151** group; e) compound **156** group; f) compound **168** group; g) compound **169** group. The rat synovial cells were treated with different concentrations of test substances for 48 h, including the concentration at 5‰ of DMSO group, the concentration at 1 μM of methotrexate group and target groups. Morphological changes of synovial cells were observed on the cell imaging analysis system (x 150).

2.5. *In vivo of LD_{50} test*

Acute toxicity refers to the toxic effects caused by the body after one or more exposure within 24 h to foreign compounds and even death [30]. Acute toxicity test was the fundamental basis for understanding the toxicity of exogenous chemicals on the body and the first step of toxicological safety evaluation. The purpose of the acute toxicity test was to calculate the lethal dose of half (LD_{50}) of the tested substance based on the data obtained from the test [31]. Explain the relative toxicity and toxicity characteristics of the tested substance and the dose–response relationship, and provide guidance for the dose used in other experimental studies. To evaluate the safety of the target compounds, we tested compounds **151**, **156**, **168** and **169** for acute toxicity (Table 3). The *in vivo* safety of the compounds were evaluated by the method of oral intragastric in mice. The acute toxicity test results showed that the acute toxicity of the tested compounds was low *in vivo* and significantly reduced compared with the positive control substance methotrexate. The LD_{50} of compound **168** was 2614.26 ± 9.19 mg/kg and that of methotrexate was 1368.43 ± 5.34 mg/kg. The test of acute toxicity provides the necessary theoretical basis for further toxicological study.

2.6. *Binding modes of TLR4*

In order to make in depth study of the binding modes between TLR4 and target compounds, interaction processes of TLR4 within four representative compounds (**151**, **156**, **168** and **169**) were performed through docking analysis by molecular dock [32]. As shown in Fig. 6a, it could be seen that the binding pocket of co-crystalized antagonist Eritoran was consist of the most of hydrophobic residues of MD-2 and partial interface residues of TLR4. The former pocket mainly combines group with unsaturated and saturated fatty acid chains, while the latter prefer to combine aromatic rings and carbonyl groups [33]. Considering carbon and carbon-carbonyl heterocycles as the main structure of synthetic compounds, binding pocket on TLR4 generated by 5 Å distance from co-crystalized antagonist Eritoran was chosen as the binding drug site to estimate interaction between TLR4-MD-2 complex and target compounds. It could be observed that the protein contact potential and hydrophobic lipophilic potential was asymmetrically distributed in the ligand binding pocked. The lowest energy conformations of target compounds **151**, **156**, **168** and **169** were displayed in Fig. 6b-6e, which reveals small molecules tightly combine to TLR4-MD-2 complex inside the hydrophobic cavity. It could be observed that the hydrogen bonding and electrostatic interactions were the predominant forces to form the protein-drug complexes, which the compound **168** form four H-bonds with Thr319 and Arg262, compound **151** form tow H-bonds with

Table 2
The release values of LDH.

Compounds	Concentration	LDH activity (U/L)[a] ± SD
44	1 μM	351.39 ± 23.02
45	1 μM	334.62 ± 16.98
56	1 μM	309.86 ± 27.12
57	1 μM	367.13 ± 10.92
63	1 μM	281.22 ± 22.84
64	1 μM	363.78 ± 23.78
66	1 μM	333.85 ± 20.87
67	1 μM	380.55 ± 13.63
75	1 μM	316.56 ± 27.04
78	1 μM	291.02 ± 18.96
151	1 μM	370.05 ± 24.69
156	1 μM	352.43 ± 8.15
166	1 μM	333.33 ± 22.89
168	1 μM	385.71 ± 18.30
169	1 μM	352.68 ± 24.87
171	1 μM	343.40 ± 24.87
177	1 μM	332.04 ± 18.07
178	1 μM	337.20 ± 19.68
195	1 μM	324.05 ± 23.22
methotrexate[b]	1 μM	454.59 ± 19.75
DMSO	5‰	236.58 ± 20.61
Normal	—	231.42 ± 19.18

[a] Values are the average of 3 independent experiments run in triplicate.
[b] Methotrexate is use as positive control.

Arg262, compound **156** form tow H-bonds with Thr319 and Lys362 and compound **169** form only one H-bond with Tyr292. Furthermore, the total score (-log (K_D)) of the optimal conformation of compound **168** was calculated to be 6.91. Additionally, the binding modes indicate that the hydrophilic interactions between the host and guest molecules are mainly formed by the carbonyl groups of compounds and charged side chain of residues. Four residues, i.e. Thr319, Lys362, Arg262 and Tyr292 play the important role in the binding site [34].

3. Conclusions

From our structural modification based on Dysodensiol K as lead compound, the compounds **151** and **168** were identified as the potential candidates drug for treatment of RA. Compounds **151** and **168** showed ideal inhibitory activities *in vitro* against rat synovial cells generation. At the same time, compounds **151** and **168** exhibited low cytotoxicity and acute toxicity. In addition, we have demonstrated that, the compounds 151 and 168 can act as *in vivo* therapeutic agents and can show efficacy in the treatment of rheumatoid arthritis, at the same therapeutic level as methotrexate in the CIA rat model. Compounds **151** and **168** can inhibit the production of IL-6 factor and appropriately reduce the production of TNF-α factor during *in vivo* treatment. In the molecular docking studies have found that compounds **151** and **168** have a good affinity for the receptor TLR4 associated with RA. In general, compounds **151** and **168** have satisfactory efficacy as oral anti-rheumatoid arthritis agents. These finding suggest the compounds **151** and **168** may be a candidates drug for treatment of RA.

4. Experimental section

4.1. Chemistry

All commercially available reagents were purchased from Aladdin (Shanghai, China) and solvents were purchased from Chronchem (Chengdu, China), and when used without further purification. In

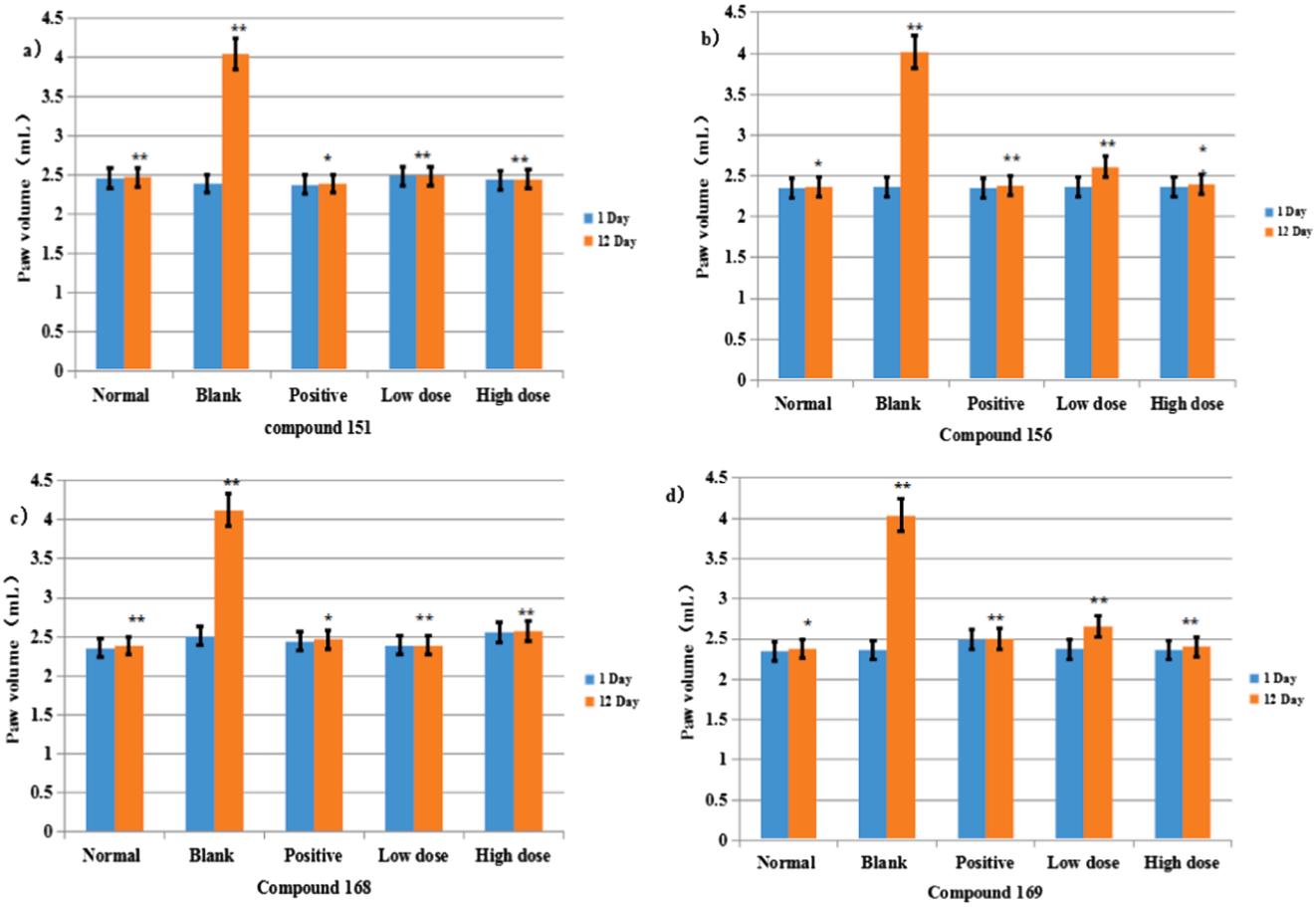


Fig. 3. The rats paw volume.

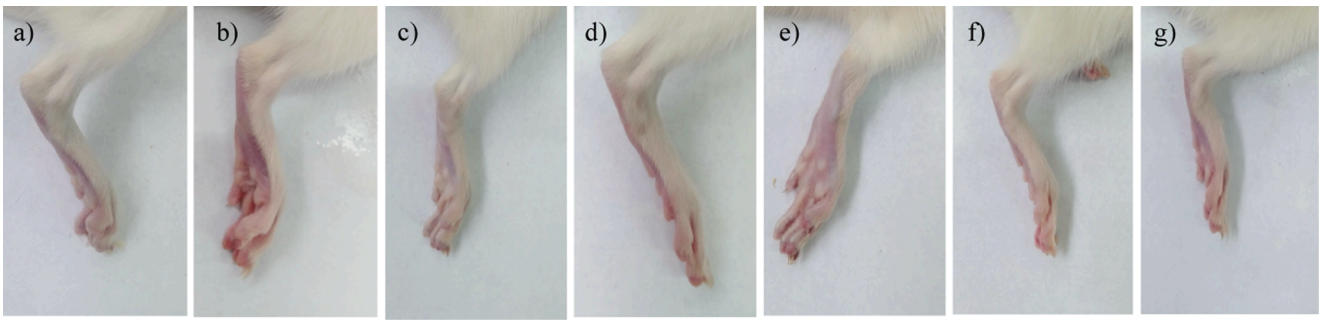


Fig. 4. The rats paw. a) normal group; b) blank group; c) methotrexate group; d) compound **151** group; e) compound **156** group; f) compound **168** group; g) compound **169** group.

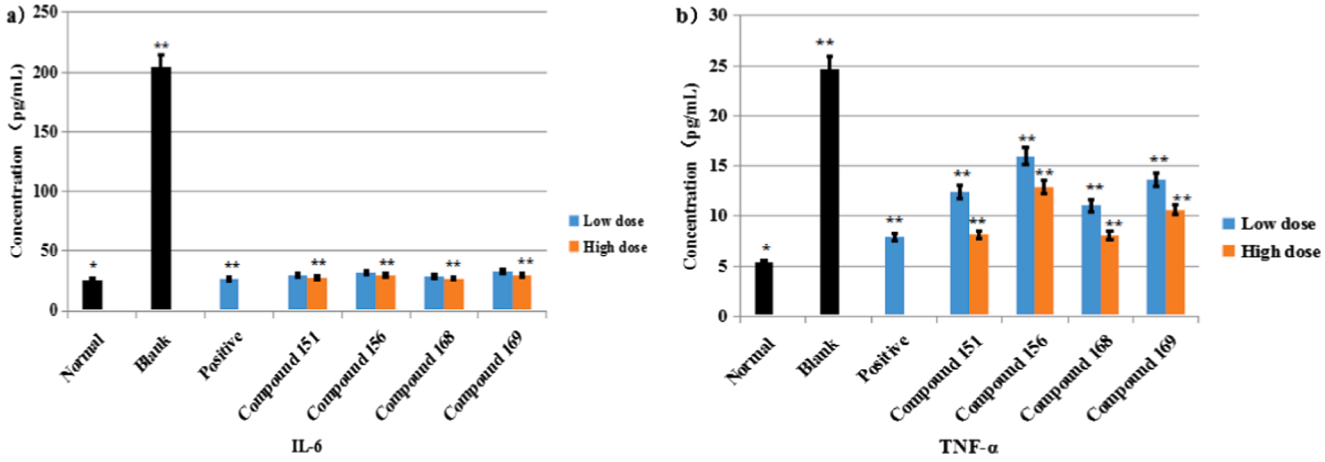


Fig. 5. The IL-6 and TNF-α concentrations.

Table 3
The LD_{50} test of results.

Compounds	Administration	LD_{50} (mg/kg)[a] ± *SD*
151	ig	2530.49 ± 8.60
156	ig	2490.36 ± 7.65
168	ig	2614.26 ± 9.19
169	ig	2593.35 ± 8.33
methotrexate[b]	ig	1368.43 ± 5.34

[a] Values are the average of 1 independent experiments run in triplicate.
[b] Methotrexate is use as positive control.

general, all reactions were performed under normal atmosphere and at room temperature unless otherwise noted. All reactions were monitored for completion by TLC using merck silica gel 60 F254 glass plates. Spots were detected by viewing under UV lamps at 254 nm. ^{1}H NMR spectra were recorded on Bruker NMR spectrometers at 400 MHz and ^{13}C NMR spectra were recorded on Bruker NMR spectrometers at 100 MHz, respectively, tetramethylsilane (TMS) was used as internal standard. Chemical shifts were signified in ppm relative to internal TMS in DMSO-d_6. The purity of the tested compounds was determined using an Agilent 1260 series HPLC system with a C18 column, and that for all the compounds was found to be greater than 95%.

*4.1.1. Synthesis of compounds **2a-2b***

A ethanediol (7.45 g, 120 mmol) and ethyl acetoacetate (compound **1a**, 13.01 g, 100 mmol) were dissolved in 100 mL of anhydrous benzene was placed in a 250 mL round-bottom flask. The *p*-methylbenzene sulfonic acid (*p*-TsOH, 0.5% mol) used as a catalyst for the reaction were added. After the reactants were added, the reaction mixture was lasted for 48 h under refluxing with magnetic stirring. When the refluxing reaction was completed, the mixture was distillation under reduced pressure, removed of reaction solvent benzene, and to obtain crude product ethyl 2-(2-methyl-1, 3-dioxolan-2-yl) acetate (compound **2a**). The crude product was purified to use silica gel column chromatography (petroleum ether: ethyl acetate, 3:1). Removed solvents in vacuum provided and to give the pure product compound **2a** as a colorless liquid (98.6% yield). The general method were used to synthesis ethyl 3-(2-methyl-1, 3-dioxolan-2-yl) propanoate (compounds **2b**) as was of yellow oily liquid (98.9% yield).

*4.1.2. Synthesis of compounds **3–40** and **79–138***

A ethyl 2-(2-methyl-1, 3-dioxolan-2-yl) acetate (compound **2a**, 17.42 g, 100 mmol) and cyclohexanone (9.81 g, 100 mmol) were dissolved in 100 mL of anhydrous ethyl alcohol was placed in a 250 mL round-bottom flask. The sodium ethanolate (CH_3CH_2ONa, 6.81 g, 100 mmol) used as an alkaline substancea for the reaction were added. After the reactants were added, the reaction mixture was lasted for 12 h under refluxing with magnetic stirring. When the refluxing reaction was completed, the mixture was distillation under reduced pressure, removed of reaction solvent ethyl alcohol. The residue mixture was dissolved in 50 mL hydrochloric acid solution (2 mol.L^{-1}) and constant temperature at 60℃ for 2 h with magnetic stirring. After the hydrolysis reaction was completed, it was cooled, extracted with 40 mL ethyl acetate three times and washed with 40 mL saturated sodium bicarbonate ($NaHCO_3$). The combined organic layers were dried with anhydrous sodium sulfate (Na_2SO_4), then filtered and the filtrate was collected. The filtrate was reduced pressure and evaporated to dry, and to obtain crude product 1-(2-oxocyclohexyl)butane-1, 3-dione (compound **3**). The crude product was purified to use silica gel column chromatography (petroleum ether: ethyl acetate, 4:1). Removed solvents in vacuum provided and to give the pure product compound **3** as a colorless liquid (89.2%

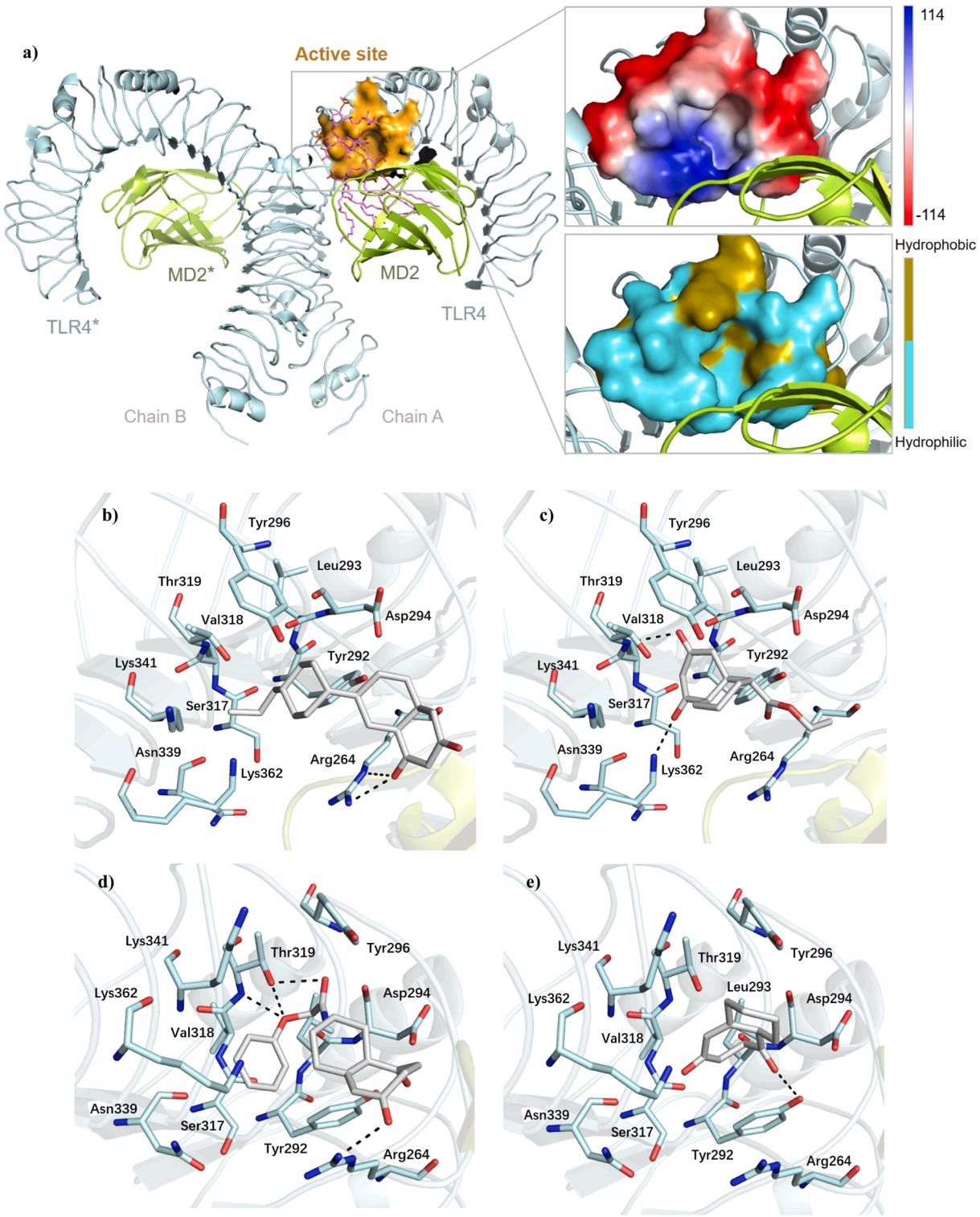


Fig. 6. Binding modes between TLR4 and representative active compounds. (a) The overall structure of TLR4-MD2 dimer in complex with co-crystalized antagonist Eritoran (PDB ID: 3FXI). Putative binding pocket in TLR4 are shown as orange surfaces. Protein contact potential and hydrophobic lipophilic potential distrubutions are shown in red/blue and cyan/brown surfaces, respectively. The binding modes of compound **151** (b), compound **156** (c), compound **168** (d) and compound **169** (e) with the TLR4-MD-2 complex. Residues around binding site with 5 Å are shown as blue stick. Hydrogen bonds interactions are represented as black dotted lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

yield). The general method were used to synthesis compounds **4**–**40** and **79**–**138** as was of yellow oily liquid.

*4.1.3. Synthesis of compounds **41**–**78** and **139**–**198***

A 1-(2-oxocyclohexyl)butane-1, 3-dione (compound **3**, 19.62 g, 100 mmol) anhydrous potassium hydroxide (KOH, 5.61 g, 100 mmol) were dissolved in 100 mL of anhydrous ethyl alcohol was placed in a 250 mL round-bottom flask. After the reactants were added, the reaction mixture was lasted for 12 h under refluxing with magnetic stirring. When the refluxing reaction was completed, the mixture was distillation under

reduced pressure, removed of reaction solvent ethyl alcohol. The residue mixture was dissolved in 50 mL of deionized water, then adjust pH to neutral with 2 mol.L^{-1} hydrochloric acid solution. After the extracted with 40 mL ethyl acetate three times and washed with 40 mL saturated sodium bicarbonate ($NaHCO_3$). The combined organic layers were dried with anhydrous sodium sulfate (Na_2SO_4), then filtered and the filtrate was collected. The filtrate was reduced pressure and evaporated to dry, and to obtain crude product compound **41**. The crude product was purified to use silica gel column chromatography (petroleum ether: ethyl acetate, 4:1). Removed solvents in vacuum provided and to give the pure product compound **41** as a colorless liquid (82.1% yield). The general method were used to synthesis compounds **42**–**78** and **139**–**198** as was of yellow oily liquid.

compound **41**, yellow oily liquid, yield 82.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.1.26 (2H, 1.16 (ddddd, J = 11.7, 8.1, 7.6, 7.0, 4.0 Hz), 1.23 (ddddd, J = 11.7, 8.1, 6.9, 4.3, 1.8 Hz)), 1.85–1.92 (2H, 1.88 (dddd, J = 13.2, 8.1, 6.6, 4.0 Hz), 1.91 (dddd, J = 13.2, 8.1, 8.0, 4.3 Hz)), 2.46 (2H, ddd, J = 13.9, 7.0, 1.8 Hz), 2.72 (1H, d, J = 15.9 Hz), 4.04 (2H, dd, J = 8.0, 6.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.1, 27.1, 34.0, 51.1, 60.0,128.0, 156.7, 20.5.5, 208.9; HR-ESI-MS m/z: calcd for $C_9H_{10}O_2$\{[M + H]$^+$\} 150.1770, found 150.1124; Anal. calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31; found: C, 71.96; H, 6.72; O, 21.32%.

compound **42**, yellow oily liquid, yield 73.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.20 (3H, d, J = 6.7 Hz), 1.41–1.43 (2H, 1.41 (dddd, J = 13.2, 7.0, 5.1, 1.8 Hz), 1.43(dddd, J = 13.2, 9.6, 7.5, 6.9 Hz)), 2.21 (1H, dqd, J = 8.1, 6.7, 3.9 Hz), 2.63–2.76 (2H, 2.63 (d, J = 16.2 Hz), 2.66 (d, J = 16.2 Hz), 3.90 (1H, dd, J = 8.0 Hz), 4.10 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.6, 20.1, 32.5, 34.1, 48.9, 59.8, 128.2, 169.1, 194.7, 206.4; HR-ESI-MS m/z: calcd for $C_{10}H_{12}O_2$\{[M + H]$^+$\}164.2040, found 164.1144; Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; O, 19.49; found: C, 73.10; H, 7.39; O, 19.51%.

compound **43**, yellow oily liquid, yield 72.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (3H, t, J = 6.9 Hz), 1.16–1.21 (2H, 1.16 (dddd, J = 13.3, 8.1, 6.9, 1.8 Hz), 1.20 (dd, J = 6.9, 2.7 Hz)), 1.42 (2H, qd, J = 6.9, 2.7 Hz), 2.00 (1H, dddd, J = 13.7, 7.0, 5.1, 1.8 Hz), 2.09 (2H, ddt, J = 8.1, 3.9, 2.7 Hz), 3.88 (1H, d, J = 16.2 Hz), 4.07 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.6, 17.9, 23.8, 32.7, 34.0, 52.7, 53.9, 55.6, 128.2, 170.6, 206.5, 207.3; HR-ESI-MS m/z: calcd for $C_{11}H_{14}O_2$\{[M + H]$^+$\}178.2310, found 178.0536; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95; found: C, 74.10; H, 7.92; O, 17.96%.

compound **44**, yellow oily liquid, yield 66.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, t, J = 6.5 Hz), 1.14–1.25 (4H, 1.32 (tq, J = 6.6, 6.5 Hz), 1.32 (tq, J = 6.6, 6.5 Hz)), 2.00 (1H, dddd, J = 13.4, 7.5, 7.0, 3.9 Hz), 2.12 (2H, dddd, J = 13.7, 7.0, 5.1, 1.8 Hz, 2.46 (1H, ddt, J = 8.1, 3.9, 2.8 Hz), 2.72 (2H, d, J = 16.2 Hz), 4.06 (1H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.6, 16.8, 27.0, 36.5, 48.9, 53.0, 59.9, 126.2, 169.1, 194.6, 206.3; HR-ESI-MS m/z: calcd for $C_{12}H_{16}O_2$\{[M + H]$^+$\}192.2580, found 192.1013; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.94; H, 8.39; O, 16.67%.

compound **45**, yellow oily liquid, yield 65.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (6H, 0.88, d, J = 6.9 Hz), 1.15–1.31 (4H, 1.17 (dddd, J = 13.1, 8.1, 6.9, 1.8 Hz), 1.22 (dddd, J = 13.1, 7.5, 7.0, 3.9 Hz)), 1.68 (1H, dddd, J = 13.7, 7.0, 5.1, 1.8 Hz), 2.02 (1H, tq, J = 6.9, 2.4 Hz), 2.20–2.35 (2H, 2.23 (ddd, J = 8.1, 3.9, 2.4 Hz), 2.32 (d, J = 16.2 Hz)), 4.08 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.4, 20.1, 27.0, 32.2, 52.7, 55.4, 56.2, 128.2, 169.1, 194.7, 206.3; HR-ESI-MS m/z: calcd for $C_{12}H_{16}O_2$\{[M + H]$^+$\}192.2580, found 192.1460; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.92; H, 8.41; O, 16.66%.

compound **46**, yellow oily liquid, yield 60.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.84 (3H, t, J = 6.5 Hz), 1.17–1.27 (4H, 1.19 (tt, J = 7.6, 6.5 Hz), 1.25 (h, J = 6.5 Hz)), 1.61–1.69 (2H, 1.62 (dddd, J = 13.4, 8.1, 6.9, 1.8 Hz), 1.67 (td, J = 7.6, 2.7 Hz)), 1.81–1.87 (2H, 1.82 (dddd, J = 13.7, 7.0, 5.1, 1.8 Hz), 1.85 (dddd, J = 13.7, 9.6, 7.5, 6.9 Hz)), 2.00 (1H, ddt, J = 8.1, 3.9, 2.7 Hz), 2.19–2.29 (2H, 2.22 (d, J = 16.2 Hz), 2.27 (d, J = 16.2 Hz)), 2.66 (1H, d, J = 16.2 Hz), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 14.5, 25.2, 31.6, 32.4, 34.1, 49.5, 52.7, 60.2, 126.8, 170.7, 206.3, 209.1; HR-ESI-MS m/z: calcd for $C_{13}H_{18}O_2$\{[M + H]$^+$\} 206.2850, found 206.1035; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.65; H, 8.82; O, 15.53%.

compound **47**, yellow oily liquid, yield 54.7%,; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (3H, t, J = 6.5 Hz), 1.14 (3H, d, J = 6.9 Hz), 1.64–1.71 (2H, 1.66 (dq, J = 6.9, 6.5 Hz), 1.69 (dq, J = 6.9, 6.5 Hz)), 1.82 (1H, dddd, J = 13.1, 8.1, 6.9, 1.8 Hz), 2.01 (1H, dddd, J = 13.1, 7.5, 7.0, 3.9 Hz), 2.17–2.31 (2H, 2.20 (dddd, J = 13.7, 7.0, 5.1, 1.8 Hz), 2.26 (dddd, J = 13.7, 9.6, 7.5, 6.9 Hz)), 2.48 (2H, ddd, J = 8.1, 3.9, 2.4 Hz), 2.74 (1H, d, J = 16.2 Hz), 4.06 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.2, 14.3, 19.1, 31.3, 32.3, 37.8, 56.6, 60.2, 60.3, 145.8, 170.7, 192.9, 211.6; HR-ESI-MS m/z: calcd for $C_{13}H_{18}O_2$ {[M + H]$^+$} 206.2850, found 206.1030; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.64; H, 8.83; O, 15.54%.

compound **48**, yellow oily liquid, yield 46.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (9H, s), 1.13–1.21 (2H, 1.16 (dddd, J = 13.0, 7.5, 7.0, 3.9 Hz), 1.18 (dddd, J = 13.0, 8.1, 6.9, 1.8 Hz)), 1.64 (2H, dddd, J = 13.7, 7.0, 5.1, 1.8 Hz), 1.81 (2H, dd, J = 8.1, 3.9 Hz), 2.19–2.29 (2H, 2.20 (d, J = 16.2 Hz), 2.28 (d, J = 16.2 Hz)), 2.71 (1H, dd, J = 13.7, 9.6 Hz), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.3, 27.0, 27.1, 41.3, 54.9, 56.2, 60.2, 128.2, 156.2, 194.9, 206.1; HR-ESI-MS m/z: calcd for $C_{13}H_{18}O_2$\{[M + H]$^+$\}206.2850, found 206.1028; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.65; H, 8.83; O, 15.52%.

compound **49**, yellow oily liquid, yield 50.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.84 (3H, t, J = 6.5 Hz), 1.17–1.28 (4H, 1.25 (tt, J = 7.6, 6.5 Hz), 1.28 (h, J = 6.5 Hz)), 1.61–1.67 (2H, 1.62 (h, J = 6.5 Hz), 1.67 (tt, J = 7.6, 6.5 Hz)), 1.82 (2H, dddd, J = 13.7, 7.0, 5.1, 1.8 Hz), 2.02 (1H, ddt, J = 8.1, 3.9, 2.7 Hz), 2.19–2.30 (2H, 2.22 (d, J = 16.2 Hz), 2.29 (d, J = 16.2 Hz)), 2.50 (2H, dd, J = 13.4, 8.1 Hz) 2.67 (1H, td, J = 7.6, 2.7 Hz), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.3, 14.5, 22.6, 27.0, 32.2, 32.4, 34.1, 49.5, 52.6, 60.3, 126.7, 170.7, 195.7, 206.2; HR-ESI-MS m/z: calcd for $C_{14}H_{20}O_2$[M + H]$^+$ 220.3120, found 220.0936; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.30; H, 9.16; O, 14.54%.

compound **50**, yellow oily liquid, yield 46.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.87 (3H, t, J = 7.0 Hz), 1.17–1.26 (4H, 1.17 (h, J = 7.0 Hz), 1.26 (h, J = 7.0 Hz)), 1.64 (2H, tt, J = 7.0, 6.9 Hz), 1.83–1.88 (4H, 1.83 (tt, J = 7.0, 6.9 Hz), 1.85 (td, J = 7.5, 2.7 Hz)), 2.00 (1H, ddt, J = 8.1, 3.9, 2.7 Hz), 2.20–2.31 (4H, 2.22 (dddd, J = 13.4, 8.1, 6.9, 1.8 Hz), 2.28 (td, J = 7.5, 2.7 Hz)), 2.48 (2H, d, J = 16.2 Hz), 2.67 (1H, d, J = 16.2 Hz), 4.06 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.1, 20.8, 22.8, 27.7, 27.8, 29.4, 29.8, 29.9, 32.0, 37.7, 48.7, 52.1, 128.2, 160.2, 205.1, 206.2; HR-ESI-MS m/z: calcd for $C_{16}H_{24}O_2$\{[M + H]$^+$\}248.3660, found 248.1846; Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74; O, 12.88; found: C, 77.34; H, 9.75; O, 12.89%.

compound **51**, yellow oily liquid, yield 46.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (2H, t, J = 7.0 Hz), 1.16–1.24 (2H, 1.19 (h, J = 7.0 Hz), 1.24 (h, J = 7.0 Hz)), 1.58–1.71 (4H, 1.64 (tt, J = 7.0, 6.9 Hz), 1.70 (tt, J = 7.0, 6.9 Hz)), 1.84 (1H, tt, J = 7.5, 6.5 Hz), 2.14–2.30 (4H, 2.19 (tt, J = 7.5, 6.5 Hz), 2.29 (tt, J = 6.9, 6.5 Hz)), 2.47 (1H, tt, J = 6.9, 6.5 Hz), 2.68 (1H, td, J = 7.5, 2.7 Hz), 4.02 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.7, 24.9, 25.3, 27.7, 29.7, 30.9, 38.4, 52.7, 127.0, 174.3, 203.4, 209.0; HR-ESI-MS m/z: calcd for $C_{14}H_{18}O_2$ {[M + H]$^+$}218.2960, found 218.1618; Anal. calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; O, 14.66; found: C, 77.05; H, 8.33; O, 14.60%.

compound **52**, yellow oily liquid, yield 45.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (2H, dtt, J = 12.8, 10.3, 2.8 Hz), 1.04–1.14 (4H, 1.07 (dtd, J = 12.6, 10.3, 2.8 Hz), 1.14 (dtd, J = 12.6, 10.3, 2.8 Hz)), 1.25 (1H, ddd, J = 10.3, 8.1, 3.9 Hz), 1.57–1.71 (2H, 1.60 (dq, J = 12.6, 2.8 Hz), 1.70 (dt, J = 12.0, 2.8 Hz)), 1.73–1.88 (1H, dtt, J = 12.0, 10.3, 2.8

Hz), 2.14–2.30 (4H, 2.20 (dt, J = 12.8, 2.8 Hz), 2.30 (dt, J = 12.8, 2.8 Hz)), 2.52 (1H, d, J = 16.2 Hz), 2.64–2.76 (2H, 2.64 (dtt, J = 12.8, 10.3, 2.8 Hz), 2.74 (dq, J = 12.6, 2.8 Hz)), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.6, 19.1, 25.9, 33.9, 35.9, 45.2, 53.2, 57.9, 58.9, 127.4, 169.2, 197.5, 208.3; HR-ESI-MS *m/z*: calcd for $C_{15}H_{20}O_2$ {[M + H]$^+$} 232.3230, found 232.1096; Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77; found: C, 77.50; H, 8.69; O, 13.78%.

compound **53**, yellow oily liquid, yield 50.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08–1.25 (2H, 1.18 (dddd, J = 13.5, 8.1, 6.9, 1.8 Hz), 1.22 (dddd, J = 13.5, 7.5, 7.0, 3.9 Hz)), 1.45–1.66 (2H, 1.51 (dddd, J = 13.7, 7.0, 5.1, 1.8 Hz), 1.63 (dddd, J = 13.7, 9.6, 7.5, 6.9 Hz)), 2.25 (1H, d, J = 16.2 Hz), 3.39 (1H, d, J = 16.2 Hz), 4.06 (2H, dddd, J = 7.8, 7.7, 1.9, 0.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 17.6, 21.9, 55.2, 58.1, 58.9, 112.1, 114.7, 124.2, 130.9, 146.0, 169.4, 202.3, 209.6; HR-ESI-MS *m/z*: calcd for $C_{15}H_{14}O_2$ {[M + H]$^+$} 226.2750, found 226.1056; Anal. calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24; O, 14.14; found: C, 79.58; H, 6.26; O, 14.17%.

compound **54**, yellow oily liquid, yield 60.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14–1.18 (2H, 1.16 (dddd, J = 15.9, 7.5, 7.0, 3.9 Hz), 1.18 (dddd, J = 12.8, 9.6, 7.5, 6.9 Hz), 1.52 (3H, s), 1.92 (1H, dddd, J = 12.8, 7.0, 5.1, 1.8 Hz), 2.00 (1H, d, J = 16.2 Hz), 2.19–2.32 (2H, 2.20 (d, J = 16.2 Hz), 2.29 (dd, J = 8.1, 3.9 Hz)), 4.04 (dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.3, 24.4, 51.3, 56.6, 60.0, 60.2, 126.0, 169.0, 172.9, 201.4, 206.6; HR-ESI-MS *m/z*: calcd for $C_{11}H_{12}O_4$ {[M + H]$^+$} 208.21300, found 208.1332; Anal. calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; O, 30.74; found: C, 63.40; H, 5.83; O, 30.76%.

compound **55**, yellow oily liquid, yield 56.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (3H, t, J = 7.1 Hz), 1.50–1.57 (2H, 1.51 (dddd, J = 15.9, 7.5, 7.0, 3.9 Hz), 1.57 (dddd, J = 12.8, 9.6, 7.5, 6.9 Hz)), 1.90 (1H, dddd, J = 12.8, 7.0, 5.1, 1.8 Hz), 1.98 (1H, d, J = 16.2 Hz), 2.19–2.30 (2H, 2.21 (d, J = 16.2 Hz), 2.30 (dd, J = 8.1, 3.9 Hz)), 3.99–4.08 (4H, 3.99 (q, J = 7.1 Hz), 4.08 (q, J = 7.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 20.5, 24.3, 30.5, 56.8, 59.9, 64.3, 125.5, 170.5, 172.9, 203.8, 209.8; HR-ESI-MS *m/z*: calcd for $C_{12}H_{14}O_4$ {[M + H]$^+$} 222.2400, found 222.0518; Anal. calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; O, 28.80; found: C, 64.80; H, 6.36; O, 28.81%.

compound **56**, yellow oily liquid, yield 59.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.13–1.20 (2H, 1.13 (dddd, J = 15.6, 7.5, 7.0, 3.9 Hz), 1.20 (dddd, J = 12.8, 9.6, 7.5, 6.9 Hz)), 1.43 (2H, dddd, J = 12.8, 7.0, 5.1, 1.8 Hz), 2.08 (3H, s), 2.19 (1H, dddd, J = 15.6, 8.1, 6.9, 1.8 Hz)), 2.66 (1H, d, J = 16.2 Hz), 4.04 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.2, 23.1, 24.4, 29.5, 33.8, 42.7, 59.9, 128.0, 170.2, 172.7, 205.6, 207.4; HR-ESI-MS *m/z*: calcd for $C_{11}H_{12}O_3$ {[M + H]$^+$} 192.2140, found 192.0210; Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; O, 24.97; found: C, 68.70; H, 6.29; O, 24.99%.

compound **57**, yellow oily liquid, yield 39.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07–1.27 (2H, 1.08 (dddd, J = 13.8, 8.1, 6.9, 1.8 Hz), 1.26 (dddd, J = 12.8, 9.6, 7.5, 6.9 Hz)), 1.47 (1H, dddd, J = 13.8, 7.5, 7.0, 3.9 Hz), 1.63–1.76 (2H, 1.68 (dddd, J = 12.8, 7.0, 5.1, 1.8 Hz), 1.73 (d, J = 16.2 Hz), 3.36 (1H, d, J = 16.2 Hz), 4.44 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 17.3, 29.5, 36.5, 50.0, 59.4, 128.1, 174.5, 202.9, 206.1; HR-ESI-MS *m/z*: calcd for $C_9H_9ClO_2$ {[M + H]$^+$} 184.6190, found 184.0661; Anal. calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.91; Cl, 19.20; O, 17.33; found: C, 58.50; H, 4.93; Cl, 19.26; O, 17.30%.

compound **58**, yellow oily liquid, yield 53.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (3H, t, J = 6.5 Hz), 1.14–1.34 (4H, 1.18 (tt, J = 6.7, 6.5 Hz), 1.25 (h, J = 6.5 Hz)), 1.37–1.50 (4H, 1.39 (h, J = 6.5 Hz), 1.49 (dt, J = 6.5 Hz)), 1.82 (1H, td, J = 6.7, 3.7 Hz), 2.00 (1H, td, J = 6.7, 3.7 Hz), 2.04–2.30 (4H, 2.08 (ddd, J = 13.8, 5.1, 1.8 Hz), 2.25 (ddd, J = 13.8, 9.6, 6.9 Hz)), 2.52 (2H, d, J = 6.6 Hz), 3.41 (3H, s), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 22.5, 27.2, 27.7, 32.1, 38.1, 39.1, 50.9, 52.3, 53.8, 55.2, 60.2, 130.6, 172.5, 174.0, 207.1, 219.7; HR-ESI-MS *m/z*: calcd for $C_{17}H_{24}O_4$ {[M + H]$^+$} 292.3750, found 292.1035; Anal. calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27; O, 21.89; found: C, 69.81; H, 8.29; O, 21.88%.

compound **59**, yellow oily liquid, yield 45.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (3H, d, J = 6.6 Hz), 1.76–1.90 (2H, 1.79 (ddd, J = 18.2, 7.3, 3.9 Hz), 1.90 (ddd, J = 18.2, 8.1, 7.0 Hz)), 2.27 (1H, dqd, J = 8.1, 6.6, 3.9 Hz), 2.65 (1H, d, J = 16.3 Hz), 4.05 (2H, dd, J = 7.3, 7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.7, 26.9, 32.3, 46.1, 62.2, 144.1, 150.1, 195.7, 202.5, 202.7; HR-ESI-MS *m/z*: calcd for $C_{10}H_{10}O_3$ {[M + H]$^+$} 178.1870, found 178.0096; Anal. calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66; O, 26.94; found: C, 67.37; H, 5.65; O, 26.98%.

compound **60**, yellow oily liquid, yield 84.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.11.09–1.28 (2H, 1.17 (ddddd, J = 12.9, 7.3, 5.4, 1.9, 1.4 Hz), 1.25 (ddtd, J = 12.9, 9.3, 7.1, 5.6 Hz)), 2.00 (1H, dddd, J = 13.3, 5.6, 5.1, 1.4 Hz), 2.12 (2H, dddd, J = 13.3, 9.6, 9.3, 5.4 Hz), 2.43–2.55 (2H, 2.45 (ddd, J = 17.1, 6.1, 1.4 Hz), 2.54 (ddd, J = 12.0, 7.3, 7.1 Hz)), 2.67–2.74 (2H, 2.69 (ddd, J = 14.9, 8.5, 6.1 Hz), 2.73 (ddd, J = 17.1, 8.5, 6.0 Hz), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.1, 25.4, 30.9, 37.6, 41.7, 56.4, 126.2, 157.1, 205.9, 207.9; HR-ESI-MS *m/z*: calcd for $C_{10}H_{12}O_2$ {[M + H]$^+$}164.2040, found 164.0071; Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; O, 19.49; found: C, 73.12; H, 7.38; O, 19.51%.

compound **61**, yellow oily liquid, yield 76.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.01 (3H, d, J = 6.6 Hz), 1.62–1.81 (2H, 1.6.2 (dddd, J = 13.5, 5.4, 1.9, 1.4 Hz), 1.71 (dddd, J = 13.5, 9.3, 7.1, 5.6 Hz)), 2.01 (1H, dddd, J = 13.2, 5.6, 5.1, 1.4 Hz), 2.11–2.33 (2H, 2.17 (dddd, J = 13.2, 9.6, 9.3, 5.4 Hz), 2.27 (ddd, J = 17.1, 6.1, 1.4 Hz)), 2.56 (1H, ddd, J = 14.9, 8.5, 6.1 Hz), 2.70–2.76 (2H, 2.70 (dqd, J = 7.1, 6.6, 1.9 Hz), 2.75 (ddd, J = 17.1, 8.5, 6.0 Hz)), 4.06 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.0, 17.9, 32.2, 34.8, 38.3, 39.6, 52.7, 127.4, 162.2, 206.0, 207.6; HR-ESI-MS *m/z*: calcd for $C_{11}H_{14}O_2$ {[M + H]$^+$} 178.2310, found 178.1429; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95; found: C, 74.10; H, 7.93; O, 17.97%.

compound **62**, yellow oily liquid, yield 74.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, t, J = 6.9 Hz), 1.12–1.31 (2H, 1.19 (dddd, J = 13.0, 5.4, 1.9, 1.4 Hz), 1.26 (qd, J = 6.9, 2.8 Hz)), 1.58–1.68 (2H, 1.60 (qd, J = 6.9, 2.8 Hz), 1.65 (dddd, J = 13.0, 9.3, 7.1, 5.6 Hz)), 1.84 (1H, 2.14 dddd, J = 13.2, 5.6, 5.1, 1.4 Hz), 2.18–2.27 (2H, 2.11 (dddd, J = 13.2, 9.6, 9.3, 5.4 Hz), 2.25 (ddd, J = 17.9, 6.1, 1.4 Hz)), 2.47 (1H, ddd, J = 14.9, 8.5, 6.1 Hz), 2.64–2.76 (2H, 2.65 (dtd, J = 7.1, 2.8, 1.9 Hz), 2.74 (ddd, J = 17.9, 8.5, 6.0 Hz)), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.6, 17.9, 32.2, 36.5, 38.3, 39.6, 51.8, 56.9, 127.9, 161.1, 201.6, 207.3; HR-ESI-MS *m/z*: calcd for $C_{12}H_{16}O_2$ {[M + H]$^+$}192.2580, found 192.1063; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.93; H, 8.40; O, 16.68%.

compound **63**, yellow oily liquid, yield 68.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.87 (3H, t, J = 6.5 Hz), 1.14–1.22 (6H, 1.14 (tq, J = 6.6, 6.5 Hz), 1.17 (tq, J = 6.6, 6.5 Hz), 1.19 (dddd, J = 13.0, 5.4, 1.9, 1.4 Hz), 1.22 (dddd, J = 13.0, 9.3, 7.1, 5.6 Hz)), 2.00 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.12 (1H, dtd, J = 7.1, 2.8, 1.9 Hz), 2.46 (2H, ddd, J = 14.9, 8.5, 6.1 Hz), 2.72 (2H, ddd, J = 17.9, 8.5, 6.0 Hz), 4.06 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 18.9, 21.1, 32.5, 35.7, 36.6, 38.0, 46.4, 60.2, 125.5, 170.8, 207.4, 209.8; HR-ESI-MS *m/z*: calcd for $C_{13}H_{18}O_2$ {[M + H]$^+$}206.2850, found 206.1050; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.64; H, 8.83; O, 15.53%.

compound **64**, yellow oily liquid, yield 67.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14–1.22 (6H, 1.17 (d, J = 6.9 Hz), 1.17(d, J = 6.9 Hz)), 1.80 (1H, dddd, J = 13.2, 9.3, 7.1, 5.6 Hz), 1.90 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 1.98 (1H, dddd, J = 13.2, 5.4, 1.9, 1.4 Hz), 2.09 (2H, dddd, J = 13.5, 5.6, 5.1, 1.4 Hz), 2.33–2.41 (2H, 2.36 (dd, J = 6.9, 2.4 Hz), 2.39 (dddd, J = 13.5, 9.6, 9.3, 5.4 Hz)), 2.63–2.68 (2H, 2.63 (ddd, J = 14.9, 8.5, 6.1 Hz), 2.68 (ddd, J = 7.1, 2.4, 1.9 Hz)), 4.03 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 22.3, 28.0, 29.5, 32.0, 37.9, 57.5, 60.2, 122.6, 174.3, 205.6, 207.4; HR-ESI-MS *m/z*: calcd for $C_{13}H_{18}O_2$ {[M + H]$^+$}206.2850, found 206.1617; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.63; H, 8.83; O, 15.54%.

compound **65**, yellow oily liquid, yield 62.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (3H, t, J = 6.5 Hz), 1.13–1.21 (8H, 1.13 (tt, J = 7.6, 6.5 Hz), 1.16 (h, J = 6.5 Hz), 1.19 (tt, J = 7.6, 6.5 Hz), 1.21 (tt, J = 7.6, 6.5 Hz)), 2.00 (1H, dd, J = 5.4, 1.9 Hz), 2.12 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.40–2.48 (2H, 2.43 (dddd, J = 13.0, 9.3, 7.1, 5.6 Hz), 2.48 (td, J = 7.6, 2.8 Hz)), 2.72 (2H, dddd, J = 13.5, 5.6, 5.1, 1.4 Hz), 4.06 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 14.6, 25.2, 29.5, 31.6, 32.4, 34.1, 38.6, 49.5, 53.9, 126.8, 157.1, 206.3, 209.1; HR-ESI-MS *m/z*: calcd for $C_{14}H_{20}O_2$ {[M + H]$^+$}220.3120, found 220.1062; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.30; H, 9.15; O, 14.56%.

compound **66**, yellow oily liquid, yield 56.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.04 (3H, t, J = 6.5 Hz), 1.16–1.22 (5H, 1.16 (d, J = 6.9 Hz), 1.20 (dq, J = 6.9, 6.5 Hz)), 1.32 (2H, dq, J = 6.9, 6.5 Hz), 1.92 (1H, hd, J = 6.9, 2.4 Hz), 2.01 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.12 (1H, dd, J = 13.2, 5.6 Hz), 2.26–2.43 (2H, 2.27 (dddd, J = 13.5, 5.6, 5.1, 1.4 Hz), 2.38 (dddd, J = 13.5, 9.6, 9.3, 5.4 Hz)), 2.68 (2H, ddd, J = 14.9, 8.5, 6.1 Hz), 4.04 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.2, 17.7, 19.1, 30.7, 31.3, 33.5, 37.8, 41.2, 56.6, 60.2, 125.6, 170.7, 204.2, 209.8; HR-ESI-MS *m/z*: calcd for $C_{14}H_{20}O_2$ {[M + H]$^+$}220.3120, found 220.1056; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.31; H, 9.16; O, 14.54%.

compound **67**, yellow oily liquid, yield 49.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (9H, s), 1.17–1.33 (2H, 1.21 (dddd, J = 14.1, 5.4, 1.9, 1.4 Hz), 1.29 (dddd, J = 14.1, 9.3, 7.1, 5.6 Hz)), 1.84 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 1.90 (1H, dddd, J = 13.5, 5.6, 5.1, 1.4 Hz), 2.25 (2H, ddd, J = 14.9, 8.5, 6.1 Hz), 2.89 (2H, ddd, J = 17.9, 8.5, 6.0 Hz), 4.06 (1H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.1, 27.0, 29.5, 32.4, 38.3, 47.4, 54.2, 60.2, 128.2, 170.8, 206.3, 208.9; HR-ESI-MS *m/z*: calcd for $C_{14}H_{20}O_2$ {[M + H]$^+$}220.3120, found 220.1050; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.30; H, 9.18; O, 14.51%.

compound **68**, yellow oily liquid, yield 52.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, t, J = 6.5 Hz), 1.17–1.35 (8H, 1.17 (tt, J = 7.5, 6.5 Hz), 1.23 (h, J = 6.5 Hz), 1.28 (h, J = 6.5 Hz), 1.30 (tt, J = 7.5, 6.5 Hz)), 1.53–1.67 (2H, 1.55 (dddd, J = 13.7, 7.3, 5.4, 1.4 Hz), 1.65 (td, J = 7.5, 3.2 Hz)), 2.00 (1H, dddd, J = 13.4, 5.6, 5.1, 1.4 Hz), 2.25 (2H, td, J = 7.5, 3.2 Hz), 2.49 (2H, dddd, J = 13.7, 9.3, 7.1, 5.6 Hz), 2.72 (2H, dddd, J = 13.4, 9.6, 9.3, 5.4 Hz), 4.03 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 17.3, 22.6, 27.0, 32.2, 32.4, 33.8, 34.1, 36.7, 49.5, 53.9, 128.2, 170.7, 206.3, 209.1; HR-ESI-MS *m/z*: calcd for $C_{15}H_{22}O_2$[M + H]$^+$}234.3390, found 234.1158; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.65; found: C, 76.84; H, 9.48; O, 13.66%.

compound **69**, yellow oily liquid, yield 49.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (3H, t, J = 7.0 Hz), 1.13–1.34 (10*H*, 1.14 (h, J = 6.5 Hz), 1.21 (h, J = 7.0 Hz), 1.25 (h, J = 7.0 Hz), 1.31 (tt, J = 7.0, 6.5 Hz)), 1.98 (1H, dddd, J = 13.4, 5.6, 5.1, 1.4 Hz), 2.13 (1H, tt, J = 7.0, 6.5 Hz), 2.24 (2H, dddd, J = 13.7, 7.3, 5.4, 1.4 Hz), 2.35 (2H, td, J = 7.5, 3.2 Hz), 2.62 (2H, dddd, J = 13.7, 9.3, 7.1, 5.6 Hz), 2.84 (2H, dddd, J = 13.4, 9.6, 9.3, 5.4 Hz), 4.04 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 17.3, 22.5, 27.2, 29.6, 30.1, 31.7, 32.6, 32.8, 32.9, 37.6, 50.3, 56.0, 132.3, 173.2, 207.8, 208.6; HR-ESI-MS *m/z*: calcd for $C_{17}H_{26}O_2$[M + H]$^+$}262.3930, found 262.1840; Anal. calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99; O, 12.19; found: C, 77.80; H, 9.98; O, 12.22%.

compound **70**, yellow oily liquid, yield 48.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15–1.21 (4H, 1.16 (ddddd, J = 12.0, 7.0, 5.3, 1.7, 1.4 Hz), 1.21 (dddd, J = 11.7, 9.4, 7.6, 5.4 Hz)), 1.49–1.56 (4H, 1.51 (dddd, J = 10.7, 6.8, 4.1, 1.7 Hz), 1.56 (dddd, J = 10.7, 8.1, 7.6, 7.0 Hz)), 1.92 (1H, dddd, J = 11.7, 7.0, 5.3, 1.4 Hz), 2.00 (1H, dddd, J = 13.4, 5.6, 5.1, 1.4 Hz), 2.12 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.19–2.31 (2H, 2.22 (dddd, J = 13.5, 9.3, 7.1, 5.6 Hz), 2.27 (dddd, J = 13.4, 9.6, 9.3, 5.4 Hz)), 2.45 (2H, ddd, J = 17.9, 8.5, 6.0 Hz), 2.71 (2H, ddd, J = 14.9, 8.5, 6.1 Hz), 4.05 (1H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.7, 24.9, 25.3, 27.6, 29.8, 30.8, 30.9, 38.5, 52.7, 125.9, 174.5, 211.6, 219.3; HR-ESI-MS *m/z*: calcd for $C_{15}H_{20}O_2$[M + H]$^+$} 232.3230, found 232.1411; Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77; found: C, 77.50; H, 8.69; O, 13.79%.

compound **71**, yellow oily liquid, yield 47.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18–1.28 (2H, 1.23 (dtt, J = 12.8, 10.3, 2.8 Hz), 1.28 (dtd, J = 12.6, 10.3, 2.8 Hz)), 1.57–1.70 (4H, 1.61 (dtd, J = 12.6, 10.3, 2.8 Hz), 1.68 (dq, J = 12.6, 2.8 Hz)), 1.75–1.91 (5H, 1.81 (dd, J = 12.8, 2.8 Hz), 1.86 (dtt, J = 12.8, 10.3, 2.8 Hz)), 2.00 (1H, dq, J = 12.6, 2.8 Hz), 2.14–2.34 (3H, 2.14 (dddd, J = 13.5, 7.3, 5.4, 1.4 Hz), 2.19 (tdt, J = 10.3, 10.1, 2.8 Hz), 2.26 (dddd, J = 13.4, 5.6, 5.1, 1.4 Hz)), 2.48 (2H, dddd, J = 13.5, 9.3, 7.1, 5.6 Hz), 2.63–2.76 (2H, 2.65 (dddd, J = 13.4, 9.6, 9.3, 5.4 Hz), 2.12), 2.71 (ddd, J = 17.9, 6.1, 1.4 Hz)), 4.05 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.5, 24.3, 25.9, 27.0, 31.7, 33.0, 35.5, 35.9, 45.2, 55.5, 58.9, 129.1, 169.2, 205.1, 208.1; HR-ESI-MS *m/z*: calcd for $C_{16}H_{22}O_2$[M + H]$^+$} 246.3500, found 246.1486; Anal. calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; O, 12.99; found: C, 78.03; H, 9.01; O, 12.95%.

compound **72**, yellow oily liquid, yield 52.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.54–1.67 (2H, 1.55 (dddd, J = 13.7, 7.3, 5.4, 1.4 Hz), 1.63 (dddd, J = 13.7, 9.3, 7.1, 5.6 Hz)), 1.82 (2H, dddd, J = 13.5, 9.6, 9.3, 5.4 Hz), 1.99 (1H, ddd, J = 15.0, 8.5, 6.1 Hz), 2.23 (2H, dddd, J = 13.5, 5.6, 5.1, 1.4 Hz), 3.40 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 4.04 (2H, dd, J = 9.6, 5.1 Hz), 7.29–7.38 (3H, 7.31 (dddd, J = 7.8, 7.7, 1.9, 0.5 Hz), 7.35 (dddd, J = 7.8, 1.3, 1.2, 0.5 Hz)), 7.56 (2H, tt, J = 7.7, 1.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.1, 20.0, 31.1, 40.1, 58.1, 58.9, 124.1, 130.9, 144.2, 146.0, 149.0, 171.1, 208.5, 209.7; HR-ESI-MS *m/z*: calcd for $C_{16}H_{16}O_2$[M + H]$^+$} 240.3020, found 240.0926; Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71; O, 13.32; found: C, 79.92; H, 6.73; O, 13.35%.

compound **73**, yellow oily liquid, yield 62.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.48–1.57 (2H, 1.50 (dddd, J = 13.3, 9.3, 7.1, 5.6 Hz), 1.57 (dddd, J = 14.2, 5.6, 5.1, 1.4 Hz)), 1.99 (1H, dddd, J = 14.2, 9.6, 9.3, 5.4 Hz), 2.19–2.31 (2H, 2.21 (ddd, J = 14.9, 8.5, 6.1 Hz), 2.29 (ddd, J = 17.9, 8.5, 6.0 Hz)), 2.45 (2H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.71 (1H, dd, J = 7.3, 7.1 Hz), 3.65 (3H, s), 4.04 (2H, dd, J = 9.6, 5.1 Hz; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.1, 20.6, 33.5, 37.6, 52.6, 56.7, 59.9, 125.8, 172.8, 174.7, 206.4, 209.8; HR-ESI-MS *m/z*: calcd for $C_{12}H_{14}O_4$[M + H]$^+$} 222.2400, found 220.1258; Anal. calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; O, 28.80; found: C, 64.80; H, 6.37; O, 28.82%.

compound **74**, yellow oily liquid, yield 58.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (3H, t, J = 7.1 Hz), 1.51 (2H, dddd, J = 13.3, 7.3, 5.4, 1.4 Hz), 1.97 (1H, dddd, J = 14.2, 9.6, 9.3, 5.4 Hz), 2.18–2.30 (2H, 2.18 (dddd, J = 13.3, 9.3, 7.1, 5.6 Hz), 2.29 (dddd, J = 14.2, 5.6, 5.1, 1.4 Hz), 2.38 (2H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.65 (1H, dd, J = 7.3, 7.1 Hz), 4.03 (2H, dd, J = 9.6, 5.1 Hz), 4.21 (2H, q, J = 7.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.0, 18.2, 20.6, 33.5, 37.6, 52.6, 56.7, 59.9, 125.8, 172.4, 174.7, 206.4,209.8; HR-ESI-MS *m/z*: calcd for $C_{13}H_{16}O_4$[M + H]$^+$} 236.2670, found 236.0953; Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; O, 27.09; found: C, 66.04; H, 6.88; O, 27.12%.

compound **75**, yellow oily liquid, yield 61.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.41–1.50 (2H, 1.43 (dddd, J = 13.2, 9.3, 7.1, 5.6 Hz), 1.48 (dddd, J = 14.1, 9.6, 9.3, 5.4 Hz)), 1.99 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.10 (2H, dddd, J = 13.2, 7.3, 5.4, 1.4 Hz), 2.19 (2H, dddd, J = 14.1, 5.6, 5.1, 1.4 Hz), 2.41 (3H, s), 2.66 (1H, ddd, J = 17.9, 8.5, 6.0 Hz), 4.04 (2H, dd, J = 9.6, 5.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.0, 20.5, 29.4, 37.7, 51.2, 60.2, 122.4, 171.0, 206.6, 207.6, 209.3; HR-ESI-MS *m/z*: calcd for $C_{12}H_{14}O_3$[M + H]$^+$} 236.2670, found 236.0953; Anal. calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84; O, 23.27; found: C, 69.84; H, 6.86; O, 23.29%.

compound **76**, yellow oily liquid, yield 42.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15–1.31 (2H, 1.18 (dddd, J = 13.7, 7.3, 5.4, 1.4 Hz), 1.21 (dddd, J = 13.4, 9.6, 9.3, 5.4 Hz)), 2.12 (1H, dddd, J = 13.4, 5.6, 5.1, 1.4 Hz), 2.45 (2H, ddd, J = 14.9, 8.5, 6.1 Hz), 2.71 (2H, ddd, J = 17.9, 8.5, 6.0 Hz), 4.01–4.08 (3H, 4.03 (ddd, J = 17.9, 6.1, 1.4 Hz), 4.08 (dd, J = 9.6, 5.1 Hz)); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 28.1, 35.5, 37.8, 60.3, 65.2, 126.2, 169.1, 202.8, 207.1; HR-ESI-MS *m/z*: calcd for

$C_{10}H_{11}ClO_2$\{[M + H]$^+$\} 198.6460, found 198.1207; Anal. calcd for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58; Cl, 17.85; O, 16.11; found: C, 60.40; H, 5.59; Cl, 17.86; O, 16.14%.

compound **77**, yellow oily liquid, yield 55.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (3H, t, J = 6.5 Hz), 1.15–1.46 (10*H*, 1.17 (tt, J = 6.8, 6.5 Hz), 1.20 (h, J = 6.5 Hz), 1.25 (h, J = 6.5 Hz), 1.29 (tt, J = 6.8, 6.5 Hz), 1.44 (td, J = 6.8, 3.9 Hz)), 1.83 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 1.99 (1H, td, J = 3.9, 1.9 Hz), 2.08 (1H, td, J = 6.8, 3.9 Hz), 2.14–2.25 (2H, 2.14 (ddd, J = 16.9, 5.1, 1.4 Hz), 2.23 (ddd, J = 16.9, 9.6, 5.4 Hz)), 2.35 (2H, tddd, J = 6.4, 5.4, 1.9, 1.4 Hz), 2.54 (2H, d, J = 6.4 Hz), 4.05–4.12 (5H, 4.05 (dd, J = 9.6, 5.1 Hz), 4.12 (s)); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 22.5, 27.7, 28.3, 31.9, 32.1, 37.7, 38.1, 39.1, 509, 52.3, 53.8, 55.2, 130.6, 170.8, 174.0, 205.3, 207.1; HR-ESI-MS *m/z*: calcd for $C_{18}H_{26}O_4$\{[M + H]$^+$\}306.4020, found 306.1296; Anal. calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55; O, 20.89; found: C, 70.50; H, 8.56; O, 20.92%.

compound **78**, yellow oily liquid, yield 47.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (3H, d, J = 6.6 Hz), 1.89 (1H, ddd, J = 17.9, 6.1, 1.4 Hz), 2.00 (1H, ddd, J = 16.1, 8.5, 6.1 Hz), 2.33 (2H, ddd, J = 17.9, 8.5, 6.0 Hz), 2.35 (2H, ddd, J = 16.1, 6.0, 1.4 Hz), 4.05 (2H, dd, J = 8.7, 6.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.7, 26.9, 32.3, 38.0, 42.2, 45.1, 144.1, 150.1, 202.5, 204.4, 208.5; HR-ESI-MS *m/z*: calcd for $C_{11}H_{12}O_3$\{[M + H]$^+$\}192.2140, found 192.0076; Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; O, 24.97; found: C, 68.70; H, 6.30; O, 24.99%.

compound **139**, yellow oily liquid, yield 86.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14–1.24 (2H, 1.16 (ddddd, J = 14.7, 5.8, 4.1, 1.8, 1.4 Hz), 1.21 (ddddd, J = 13.6, 5.6, 4.1, 1.9, 1.4 Hz)), 1.46–1.57 (2H, 1.56 (ddd, J = 13.5, 8.9, 5.6 Hz), 1.54 (ddd, J = 13.5, 5.7, 1.4 Hz)), 1.92 (2H, dddd, J = 13.0, 8.1, 5.8, 1.4 Hz), 2.00 (1H, d, J = 15.9 Hz), 2.19–2.32 (2H, 2.22 (d, J = 15.9 Hz), 2.29 (dd, J = 8.1, 6.3 Hz)), 4.04 (2H, dd, J = 8.6, 5.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.3, 25.9, 27.7, 35.9, 49.1, 56.6, 126.2, 168.0, 200.9, 208; HR-ESI-MS *m/z*: calcd for $C_{10}H_{12}O_2$\{[M + H]$^+$\}164.2040, found 164.0788; Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; O, 19.49; found: C, 73.11; H, 7.38; O, 19.52%.

compound **140**, yellow oily liquid, yield 80.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, d, J = 6.7 Hz), 1.10–1.35 (4H, 1.12 (dddd, J = 13.2, 5.6, 4.1, 1.9 Hz), 1.17 (ddddd, J = 13.0, 10.0, 8.6, 5.8, 1.9 Hz), 1.25 (dddd, J = 13.2, 10.0, 8.9, 1.8 Hz), 1.30 (dddd, J = 13.0, 8.1, 5.8, 1.4 Hz)), 1.43 (2H, dddd, J = 13.0, 8.6, 6.3, 5.8 Hz), 2.00 (1H, dqd, J = 8.9, 6.7, 5.6 Hz), 3.35 (1H, d, J = 15.9 Hz), 4.05 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 27.9, 34.0, 36.2, 41.6, 52.8, 56.6, 126.0, 170.4, 204.2, 209.0; HR-ESI-MS *m/z*: calcd for $C_{11}H_{14}O_2$\{[M + H]$^+$\}178.2310, found 178.1312; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95; found: C, 74.10; H, 7.91; O, 17.97%.

compound **141**, yellow oily liquid, yield 81.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (3H, d, J = 7.0 Hz), 1.17–1.36 (2H, 1.22 (dddd, J = 14.6, 8.6, 5.8, 1.9 Hz), 1.32 (dddd, J = 13.3, 8.1, 5.8, 1.4 Hz)), 1.41 (1H, dddd, J = 14.6, 5.8, 4.1, 1.4 Hz), 2.00 (1H, dddd, J = 13.3, 8.6, 6.3, 5.8 Hz), 2.19 (2H, dd, J = 13.8, 5.6 Hz), 2.38 (2H, dd, J = 13.8, 1.4 Hz), 4.05 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.3, 31.5, 34.6, 35.6, 45.2, 49.8, 56.6, 125.9, 170.1, 200.7, 208.0; HR-ESI-MS *m/z*: calcd for $C_{11}H_{14}O_2$\{[M + H]$^+$\}178.2310, found 178.1308; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95; found: C, 74.10; H, 7.92; O, 17.96%.

compound **142**, yellow oily liquid, yield 82.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (3H, d, J = 6.9 Hz), 1.08–1.22 (2H, 1.10 (ddd, J = 13.0, 8.6, 6.3 Hz), 1.185 (dddd, J = 13.3, 10.0, 8.9, 5.7 Hz)), 1.48 (1H, dddd, J = 13.3, 5.6, 1.9, 1.4 Hz), 1.63–1.76 (4H, 1.66 (dddd, J = 10.0, 8.6, 6.9, 5.8, 1.9 Hz), 1.71 (ddd, J = 13.0, 8.1, 5.8 Hz)), 2.00 (1H, d, J = 16.1 Hz), 4.05 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.5, 29.4, 32.1, 36.0, 40.2, 47.9, 55.0, 126.3, 168.9, 201.3, 208.5; HR-ESI-MS *m/z*: calcd for $C_{11}H_{14}O_2$\{[M + H]$^+$\}178.2310, found 178.1313; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95; found: C, 74.11; H, 7.93; O, 17.95%.

compound **143**, yellow oily liquid, yield 82.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (3H, t, J = 6.9 Hz), 1.05–1.43 (5H, 1.06 (qd, J = 6.9, 4.7 Hz), 1.27 (qd, J = 6.9, 4.7 Hz), 1.42 (dddd, J = 13.6, 5.6, 1.9, 1.4 Hz)), 1.56–1.67 (2H, 1.57 (dddd, J = 13.6, 10.0, 8.9, 5.7 Hz), 1.63 (dddtd, J = 10.0, 8.6, 5.8, 4.7, 1.9 Hz)), 2.01 (1H, ddd, J = 13.0, 8.6, 6.3 Hz), 2.16–2.24 (2H, 2.18 (ddd, J = 13.5, 8.9, 5.6 Hz), 2.23 (ddd, J = 13.5, 5.7, 1.4 Hz)), 4.04 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.0, 27.0, 29.5, 34.7, 35.9, 40.7, 47.8, 57.0, 126.2, 71.7, 200.7, 211.4; HR-ESI-MS *m/z*: calcd for $C_{12}H_{16}O_2$\{[M + H]$^+$\}192.2580, found 192.0031.0034; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.93; H, 8.39; O, 16.66%.

compound **144**, yellow oily liquid, yield 81.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.84 (3H, t, J = 6.5 Hz), 1.04–1.41 (5H, 1.10 (td, J = 6.5, 4.1 Hz), 1.27 (h, J = 6.5 Hz), 1.41 (h, J = 6.5 Hz), 1.64–1.85 (4H, 1.65 (dddd, J = 13.7, 5.6, 1.9, 1.4 Hz), 1.81 (dddtd, J = 10.0, 8.6, 5.8, 4.1, 1.9 Hz)), 1.99 (1H, dd, J = 8.1, 6.3 Hz), 2.49 (2H, ddd, J = 13.4, 8.6, 6.3 Hz), 4.05 (2H, d, J = 16.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.7, 20.2, 27.4, 31.6, 35.9, 36.7, 39.3, 48.0, 57.2, 126.0, 169.6, 199.5, 210.3; HR-ESI-MS *m/z*: calcd for $C_{13}H_{18}O_2$\{[M + H]$^+$\}206.2850, found 206.1618; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.65; H, 8.82; O, 15.54%.

compound **145**, yellow oily liquid, yield 80.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.82–0.89 (6H, 0.82 (t, J = 6.5 Hz), 0.89 (d, J = 6.9 Hz), 1.16–1.21 (4H, 1.16 (dq, J = 6.9, 6.5 Hz), 1.21 (dq, J = 6.9, 6.5 Hz)), 1.40 (1H, dd, J = 10.0, 5.8 Hz), 1.49–1.59 (2H, 1.51 (dddd, J = 13.8, 5.6, 4.1, 1.9 Hz), 1.54 (ddddd, J = 13.5, 5.8, 4.1, 1.8, 1.4 Hz)), 2.00 (1H, dddd, J = 13.8, 10.0, 8.9, 1.8 Hz), 2.26–2.33 (3H, 2.28 (dddd, J = 13.4, 8.6, 6.3, 5.8 Hz), 2.30 (dddd, J = 13.4, 8.1, 5.8, 1.4 Hz), 2.32 (hd, J = 6.9, 2.5 Hz)), 4.03 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.9, 15.5, 24.7, 25.7, 29.3, 32.5, 42.0, 47.9, 54.5, 55.5, 124.9, 171.4, 204.5, 210.7; HR-ESI-MS *m/z*: calcd for $C_{14}H_{20}O_2$\{[M + H]$^+$\}220.3120, found 220.0761; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.29; H, 9.16; O, 14.55%.

compound **146**, yellow oily liquid, yield 80.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (9H, s), 1.18 (1H, dd, J = 10.0, 5.8 Hz), 1.59–1.68 (2H, 1.59 (ddd, J = 13.3, 8.6, 6.3 Hz), 1.64 (dddd, J = 14.2, 10.0, 8.9, 5.7 Hz)), 1.80 (2H, ddd, J = 13.3, 8.1, 5.8 Hz), 1.99 (1H, ddd, J = 13.5, 8.9, 5.6 Hz), 2.13–2.30 (2H, 2.20 (ddd, J = 13.5, 5.7, 1.4 Hz), 2.28 (dddd, J = 14.2, 5.6, 1.9, 1.4 Hz)), 4.05 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.5, 27.6, 31.5, 32.5, 36.1, 46.2, 47.9, 55.5, 125.6, 169.2, 201.8, 210.7; HR-ESI-MS *m/z*: calcd for $C_{14}H_{20}O_2$\{[M + H]$^+$\}220.3120, found 220.1653; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.29; H, 9.17; O, 14.56%.

compound **147**, yellow oily liquid, yield 78.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (3H, t, J = 6.5 Hz), 1.10–1.45 (9H, 1.17 (tt, J = 6.8, 6.5 Hz), 1.24 (td, J = 6.8, 4.3 Hz), 1.32 (td, J = 6.8, 4.3 Hz), 1.36 (tq, J = 6.9, 6.5 Hz), 1.42 (ddd, J = 13.4, 8.6, 6.3 Hz)), 1.66 (2H, tt, J = 6.9, 6.5 Hz), 2.00 (1H, dd, J = 8.9, 5.7 Hz), 2.17 (2H, dddd, J = 10.0, 8.6, 5.8, 4.3, 1.9 Hz), 2.38 (2H, dddd, J = 13.7, 5.6, 1.9, 1.4 Hz), 4.05 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.1, 22.7, 25.3, 27.0, 31.6, 32.3, 34.0, 35.8, 40.6, 48.1, 57.3, 125.7, 168.8, 201.8, 210.0; HR-ESI-MS *m/z*: calcd for $C_{15}H_{22}O_2$\{[M + H]$^+$\}234.3390, found 234.1933; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.65; found: C, 76.83; H, 9.47; O, 13.66%.

compound **148**, yellow oily liquid, yield 77.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.73–0.80 (9H, 0.75 (t, J = 7.1 Hz), 0.80 (q, J = 7.1 Hz)), 1.00 (1H, ddd, J = 10.0, 8.6, 5.8, 1.9 Hz), 1.16–1.24 (2H, 1.18 (ddd, J = 13.3, 8.1, 5.8 Hz), 1.21 (dddd, J = 14.2, 10.0, 8.9, 5.7 Hz)), 1.91 (2H, dddd, J = 14.2, 5.6, 1.9, 1.4 Hz), 2.02 (1H, ddd, J = 13.3, 8.6, 6.3 Hz), 2.25 (2H, ddd, J = 13.5, 8.9, 5.6 Hz), 4.02 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 8.4, 24.5, 27.1, 32.9, 34.6, 34.8, 35.4, 43.6, 49.1, 60.1, 126.4, 170.5, 200.1, 210.8; HR-ESI-MS *m/z*: calcd for $C_{15}H_{22}O_2$\{[M + H]$^+$\}234.3390, found 234.1083; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.65; found: C, 76.84; H, 9.48; O,

13.65%.

compound **149**, yellow oily liquid, yield 81.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (2H, ddd, J = 14.2, 4.7, 3.9, 1.9 Hz), 1.24 (2H, dddd, J = 14.1, 10.0, 8.9, 1.8 Hz), 1.57–1.70 (4H, 1.60 (dddd, J = 13.4, 8.6, 6.3, 5.8 Hz), 1.68 (dddd, J = 13.4, 8.1, 5.8, 1.4 Hz)), 1.75–1.89 (2H, 1.77 (ddddd, J = 13.5, 10.0, 8.6, 5.8, 1.9 Hz), 1.86 (dddd, J = 14.1, 5.6, 4.1, 1.9 Hz)), 2.00 (1H, dd, J = 13.5, 5.8, Hz), 2.14–2.26 (2H, 2.14 (ddd, J = 14.3, 10.0, 4.0 Hz), 2.24 (ddd, J = 14.3, 3.9, 1.9 Hz)), 2.48 (1H, dd, J = 13.5, 3.9 Hz), 2.63–2.76 (2H, 2.65 (ddddd, J = 13.5, 4.0, 3.5, 2.1, 1.9 Hz), 2.74 (dddd, J = 14.2, 10.0, 4.7, 4.0 Hz)), 4.05 (2H, dd, J = 8.1, 6.3 Hz)), 5.62 (1H, t, J = 4.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.2, 22.6, 23.0, 25.3, 27.2, 27.6, 31.9, 42.1, 49.2, 58.2, 123.0, 128.8, 136.6, 174.9, 198.9, 210.5; HR-ESI-MS *m/z*: calcd for $C_{16}H_{20}O_2${[M + H]$^+$}244.3340, found 244.2134; Anal. calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25; O, 13.10; found: C, 78.61; H, 8.27; O, 13.12%.

compound **150**, yellow oily liquid, yield 80.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85–1.95 (2H, 1.87 (dddd, J = 14.1, 5.6, 4.1, 1.9 Hz), 1.94 (ddddd, J = 13.5, 5.8, 4.1, 1.8, 1.4 Hz)), 2.05 (1H, dddd, J = 14.1, 10.0, 8.9, 1.8 Hz), 2.25 (2H, dddd, J = 13.4, 8.6, 6.3, 5.8 Hz), 2.54–2.65 (2H, 2.54 (dddd, J = 13.4, 8.1, 5.8, 1.4 Hz), 2.63 (ddddd, J = 13.5, 10.0, 8.6, 5.8, 1.9 Hz)), 3.07 (1H, d, J = 15.9 Hz), 3.74 (2H, dd, J = 8.9, 5.6 Hz), 7.21–7.36 (5H, 7.23 (tt, J = 7.7, 1.3 Hz), 7.232 (4H, 7.31 (dddd, J = 7.8, 7.7, 1.9, 0.5 Hz), 7.35 (dddd, J = 7.8, 1.3, 1.2, 0.5 Hz)); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.6, 26.9, 41.3, 50.8, 56.6, 64.2, 126.4, 126.7, 127.2, 128.8, 145.8, 170.3, 204.4, 210.5; HR-ESI-MS *m/z*: calcd for $C_{16}H_{16}O_2${[M + H]$^+$}240.3020, found 240.1956; Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71; O, 13.32; found: C, 79.94; H, 6.73; O, 13.34%.

compound **151**, yellow oily liquid, yield 76.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (3H, t, J = 6.5 Hz), 0.98 (1H, dd, J = 10.3, 5.8 Hz), 1.10–1.32 (13H, 1.10 (dddd, J = 13.9, 5.6, 1.9, 1.4 Hz), 1.16 (dq, J = 12.9, 2.8 Hz), 1.64–1.74 (4H, 1.64 (dddd, J = 13.9, 10.0, 8.9, 5.7 Hz), 1.69 (ddd, J = 13.5, 8.9, 5.6 Hz)), 1.92 (1H, ddd, J = 13.2, 8.1, 5.8 Hz), 2.00 (1H, ddd, J = 13.2, 8.6, 6.3 Hz), 2.51 (2H, ddd, J = 13.5, 5.7, 1.4 Hz), 4.04 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 20.2, 27.4, 30.0, 30.4, 33.6, 33.8, 35.2, 37.7, 37.8, 42.4, 50.2, 64.1, 125.3, 169.6, 200.0, 208.8; HR-ESI-MS *m/z*: calcd for $C_{19}H_{28}O_2${[M + H]$^+$}288.4310, found 288.1799; Anal. calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79; O, 11.09; found: C, 79.10; H, 9.78; O, 11.10%.

compound **152**, yellow oily liquid, yield 73.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06–1.22 (2H, 1.07 (dddd, J = 13.9, 10.0, 8.9, 5.7 Hz), 1.17 (dt, J = 14.2, 2.8 Hz)), 1.35–1.46 (8H, 1.38 (qt, J = 10.3, 2.8 Hz), 1.46 (dtd, J = 13.0, 10.3, 2.8 Hz)), 1.69 (2H, dt, J = 14.1, 2.8 Hz), 2.00 (1H, ddd, J = 14.2, 10.3, 2.8 Hz), 2.18–2.38 (4H, 2.21 (ddd, J = 13.5, 8.9, 5.6 Hz), 2.35 (ddd, J = 13.5, 5.7, 1.4 Hz)), 3.83 (4H, 3.85 (ddd, J = 14.6, 5.6, 1.4 Hz), 4.05 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.2, 30.4, 33.6, 33.8, 35.2, 37.7, 42.4, 52.0, 58.2, 64.1, 119.1, 127.0, 168.7, 196.8, 208.7; HR-ESI-MS *m/z*: calcd for $C_{18}H_{24}O_4${[M + H]$^+$}304.3860, found 304.1028; Anal. calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95; O, 21.02; found: C, 71.00; H, 7.96; O, 21.04%.

compound **153**, yellow oily liquid, yield 70.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16 (2H, dddd, J = 13.8, 10.0, 8.9, 5.7 Hz), 1.91 (2H, dddd, J = 13.8, 5.6, 1.9, 1.4 Hz), 1.99 (1H, ddd, J = 13.1, 8.6, 6.3 Hz), 2.50 (2H, ddd, J = 13.1, 8.1, 5.8 Hz), 3.45 (1H, ddd, J = 13.5, 8.9, 5.6 Hz), 4.04 (2 h, dd, J = 8.1, 6.3 Hz), 7.57–7.70 (4H, 7.60 (ddd, J = 7.8, 1.3, 0.5 Hz), 7.67 (ddd, J = 7.8, 7.6, 1.3 Hz)); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.9, 32.3, 32.8, 48.1, 57.0, 68.3, 123.0, 128.3, 134.5, 140.0, 168.7, 199.0, 200.1, 209.8; HR-ESI-MS *m/z*: calcd for $C_{18}H_{15}NO_4${[M + H]$^+$}309.4001, found 309.2209; Anal. calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53; O, 20.69; found: C, 69.84; H, 4.88; N, 4.56; O, 20.71%.

compound **154**, yellow oily liquid, yield 71.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (2H, dddd, J = 14.2, 5.6, 1.9, 1.4 Hz), 1.93 (1H, dddd, J = 14.2, 10.0, 8.9, 5.7 Hz), 2.01 (1H, ddd, J = 13.4, 8.1, 5.8 Hz), 2.11 (2H, ddd, J = 13.4, 8.6, 6.3 Hz), 2.71 (2H, ddd, J = 13.5, 8.9, 5.6 Hz), 4.05 (2H, dd, J = 8.1, 6.3 Hz), 6.70 (2H, ddd, J = 8.2, 2.6, 0.5 Hz), 7.07 (2H, ddd, J = 8.2, 1.0, 0.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 33.8, 34.8, 37.0, 39.6, 48.7, 60.1, 121.7, 127.6, 132.3, 134.7, 161.1, 162.2, 198.2, 206.2; HR-ESI-MS *m/z*: calcd for $C_{16}H_{16}O_3${[M + H]$^+$}256.3010, found 256.1772; Anal. calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; O, 18.73; found: C, 74.94; H, 6.31; O, 18.76%.

compound **155**, yellow oily liquid, yield 66.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08–1.30 (2H, 1.12 (ddddd, J = 14.8, 10.0, 8.6, 5.8, 1.9 Hz), 1.23 (ddddd, J = 14.8, 5.8, 4.1, 1.8, 1.4 Hz)), 1.47 (2H, dddd, J = 13.2, 8.1, 5.8, 1.4 Hz), 1.63–1.76 (2H, 1.66 (dddd, J = 13.1, 10.0, 8.9, 1.8 Hz), 1.72 (dddd, J = 13.2, 8.6, 6.3, 5.8 Hz)), 2.00 (1H, dddd, J = 13.1, 5.6, 4.1, 1.9 Hz), 2.19 (3H, s), 3.39 (1H, d, J = 16.2 Hz), 4.03 (2H, dd, J = 8.9, 5.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.1, 24.3, 25.9, 29.3, 48.5, 52.8, 59.7, 126.0, 168.7, 199.5, 204.8, 208.3; HR-ESI-MS *m/z*: calcd for $C_{12}H_{14}O_3${[M + H]$^+$}206.2410, found 206.0268; Anal. calcd for $C_{12}H_{14}O_3$: 69.89; H, 6.84; O, 23.27; found: 69.85; H, 6.86; O, 23.28%.

compound **156**, yellow oily liquid, yield 67.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (3H, t, J = 7.1 Hz), 1.48–1.81 (4H, 1.53 (ddddd, J = 13.7, 10.0, 8.6, 5.8, 1.9 Hz), 1.64 (ddddd, J = 13.7, 5.8, 4.1, 1.8, 1.4 Hz), 1.77 (dddd, J = 13.1, 10.0, 8.9, 1.8 Hz)), 2.00 (1H, dddd, J = 13.1, 5.6, 4.1, 1.9 Hz), 2.26 (2H, dddd, J = 13.2, 8.6, 6.3, 5.8 Hz), 3.36 (1H, d, J = 16.2 Hz), 4.00–4.09 (4H, 3.55 (dd, J = 8.1, 6.3 Hz), 4.09 (q, J = 7.1 Hz)); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.0, 14.2, 26.9, 33.7, 41.7, 56.9, 59.9, 64.0, 123.9, 172.9, 174.7, 198.5, 206.0; HR-ESI-MS *m/z*: calcd for $C_{13}H_{16}O_4${[M + H]$^+$}236.2670, found 236.1727; Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; O, 27.09; found: C, 66.05; H, 6.84; O, 27.81%.

compound **157**, yellow oily liquid, yield 53.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14–1.23 (2H, 1.15 (ddddd, J = 13.2, 5.8, 4.1, 1.8, 1.4 Hz), 1.20 (ddddd, J = 13.2, 10.0, 8.6, 5.8, 1.9 Hz)), 1.41 (2H, dddd, J = 15.2, 10.0, 8.9, 1.8 Hz), 1.91 (2H, dddd, J = 15.2, 5.6, 4.1, 1.9 Hz), 1.98 (1H, dddd, J = 13.2, 8.1, 5.8, 1.4 Hz), 2.50 (2H, dddd, J = 13.2, 8.6, 6.3, 5.8 Hz), 3.87 (1H, dd, J = 8.9, 5.6 Hz), 4.04 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 120.4, 24.1, 26.1, 30.2, 43.6, 57.0, 60.1, 125.8, 170.9, 173.3, 204.0, 207.3; HR-ESI-MS *m/z*: calcd for $C_{12}H_{15}NO_3${[M + H]$^+$}221.2560, found 221.1534; Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; O, 21.69; found: C, 65.10; H, 6.85; N, 6.34; O, 21.68%.

compound **158**, yellow oily liquid, yield 56.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (9H, s), 1.42 (2H, dddd, J = 11.4, 10.0, 8.9, 5.7 Hz), 1.92 (2H, ddd, J = 13.4, 8.1, 5.8 Hz), 2.00 (1H, dddd, J = 11.4, 5.6, 1.9, 1.4 Hz), 2.10 (2H, ddd, J = 13.1, 8.9, 5.6 Hz), 3.85 (1H, d, J = 16.1 Hz), 4.03 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.9, 28.9, 29.4, 31.6, 47.5, 60.2, 60.3, 77.2, 124.4, 156.2, 170.6, 201.3, 207.6; HR-ESI-MS *m/z*: calcd for $C_{15}H_{21}NO_4${[M + H]$^+$}279.3360, found 279.0583; Anal. calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01; O, 22.91; found: C, 64.48; H, 7.59; N, 5.01; O, 22.92%.

compound **159**, yellow oily liquid, yield 61.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16 (2H, ddddd, J = 14.7, 10.0, 8.6, 5.8, 1.9 Hz), 1.41 (2H, ddddd, J = 14.7, 5.8, 4.1, 1.8, 1.4 Hz), 1.91 (2H, dddd, J = 12.7, 8.1, 5.8, 1.4 Hz), 1.99 (1H, dddd, J = 14.1, 10.0, 8.9, 1.8 Hz), 3.88 (1H, dd, J = 8.9, 5.6 Hz), 4.03 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.1, 25.8, 37.7, 43.7, 57.4, 64.3, 126.4, 170.5, 202.9, 209.2; HR-ESI-MS *m/z*: calcd for $C_{10}H_{11}ClO_2${[M + H]$^+$}198.6460, found 198.0818; Anal. calcd for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58; Cl, 17.85; O, 16.11; found: C, 60.43; H, 5.59; Cl, 17.86; O, 16.10%.

compound **160**, yellow oily liquid, yield 61.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86–1.00 (6H, 0.86 (s), 0.99 (s)), 1.16–1.27 (2H, 1.19 (ddd, J = 15.0, 8.6, 5.8 Hz), 1.22 (ddd, J = 15.0, 5.8, 1.4 Hz)), 1.47–1.56 (1.50 (dddd, J = 13.4, 8.1, 5.8, 1.4 Hz), 1.52 (ddd, J = 13.4, 8.6, 6.3, 5.8 Hz), 1.93 (2H, d, J = 15.4 Hz), 2.00 (1H, d, J = 15.4 Hz), 4.05 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.5, 28.7, 32.1, 42.5, 46.9, 51.1, 54.8, 124.1, 168.9, 197.6, 209.9; HR-ESI-MS *m/z*: calcd for $C_{12}H_{16}O_2${[M + H]$^+$}192.2580, found 192.1460; Anal. calcd for

$C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.93; H, 8.40; O, 16.65%.

compound **161**, yellow oily liquid, yield 58.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.80–0.89 (6H, 0.0.83 (d, J = 6.9 Hz), 0.87 (s)), 0.98 (3H, s), 1.17–1.28 (2H, 1.24 (dd, J = 15.0, 5.8 Hz), 1.27 (dd, J = 15.0, 1.4 Hz)), 1.56 (1H, ddd, J = 8.1, 6.9, 5.8, 1.4 Hz), 1.93 (2H, d, J = 15.6 Hz), 2.00 (1H, d, J = 15.6 Hz), 4.05 (2H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.0, 26.2, 27.3, 33.7, 45.2, 48.0, 66.1, 125.9, 162.7, 198.9, 207.2; HR-ESI-MS m/z: calcd for $C_{13}H_{18}O_2$\{[M + H]$^+$\}206.2850, found 206.1255; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.65; H, 8.82; O, 15.53%.

compound **162**, yellow oily liquid, yield 53.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (3H, d, J = 6.9 Hz), 1.19–1.65 (7H, 1.22 (3H, s), 1.36 (dddd, J = 13.2, 10.0, 8.9, 1.8 Hz), 1.59 (ddddd, J = 13.4, 5.8, 4.1, 1.8, 1.4 Hz), 1.85 (2H, ddd, J = 13.3, 5.8, 1.4 Hz), 2.00 (1H, ddd, J = 13.3, 8.6, 5.8 Hz), 4.04 (2H, d, J = 16.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.2, 20.2, 27.7, 30.8, 33.5, 34.6, 42.4, 44.9, 126.0, 170.1, 212.7, 215.0; HR-ESI-MS m/z: calcd for $C_{12}H_{16}O_2$\{[M + H]$^+$\}192.2580, found 192.1462; Anal. calcd for $C_{13}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.93; H, 8.41; O, 16.67%.

compound **163**, yellow oily liquid, yield 50.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15 (3H, d, J = 6.9 Hz), 1.41 (3H, s), 1.91 (2H, dddd, J = 13.7, 5.6, 4.1, 1.9 Hz), 2.00 (1H, dddd, J = 13.7, 10.0, 8.9, 1.8 Hz), 2.10 (2H, dddd, J = 13.3, 4.1, 1.8, 1.4 Hz), 2.33 (1H, ddd, J = 13.3, 5.8, 1.9 Hz), 2.58 (2H, ddd, J = 8.1, 5.8, 1.4 Hz), 4.05 (2H, ddd, J = 8.9, 6.9, 5.6 Hz), 4.66 (2H, d, J = 1.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.7, 21.8, 29.4, 34.7, 36.5, 45.4, 60.2, 64.0, 115.5, 127.0, 153.1, 172.6, 197.7, 207.0; HR-ESI-MS m/z: calcd for $C_{14}H_{18}O_2$\{[M + H]$^+$\}218.2960, found 218.1618; Anal. calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; O, 14.66; found: C, 77.00; H, 8.32; O, 14.68%.

compound **164**, yellow oily liquid, yield 51.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.78–0.99 (9H, 0.80 (d, J = 6.9 Hz), 0.89 (d, J = 6.9 Hz)), 1.31–1.36 (4H, 1.32 (dddd, J = 14.2, 5.6, 4.1, 1.9 Hz), 1.36 (dddd, J = 13.8, 4.1, 1.8, 1.4 Hz)), 1.82 (1H, dddd, J = 14.2, 10.0, 8.9, 1.8 Hz), 2.00 (1H, dddd, J = 13.8, 10.0, 5.8, 1.9 Hz), 2.09 (1H, dqdd, J = 8.1, 6.9, 5.8, 1.4 Hz), 2.17 (1H, dd, J = 6.9, 2.5 Hz), 4.05 (1H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.8, 21.1, 25.7, 26.6, 27.9, 33.9, 50.6, 55.2, 56.8, 126.2, 170.0, 203.2, 209.9; HR-ESI-MS m/z: calcd for $C_{14}H_{20}O_2$\{[M + H]$^+$\}220.3120, found 220.1411; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.30; H, 9.17; O, 14.51%.

compound **165**, yellow oily liquid, yield 49.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85 (2H, ddd, J = 14.6, 3.9, 1.9 Hz), 2.00 (1H, ddd, J = 13.4, 10.0, 3.9 Hz), 2.12 (2H, ddd, J = 13.4, 3.9, 1.9 Hz), 2.19 (2H, ddd, J = 14.6, 10.0, 3.9 Hz), 2.48–2.55 (2H, 2.51 (d, J = 16.3 Hz), 2.54 (dd, J = 14.6, 3.6 Hz)), 4.03 (2H, dd, J = 10.1, 3.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.1, 40.0, 41.1, 47.6, 56.6, 126.3, 161.4, 199.9, 204.1, 210.4; HR-ESI-MS m/z: calcd for $C_{10}H_{10}O_3$\{[M + H]$^+$\}178.1870, found 178.0059; Anal. calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66; O, 26.94; found: C, 67.38; H, 5.67; O, 26.96%.

compound **166**, yellow oily liquid, yield 38.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15–1.21 (2H, 1.17 (dddd, J = 13.8, 10.0, 8.9, 5.7 Hz), 1.19 (ddd, J = 13.6, 8.1, 5.8 Hz)), 1.91 (2H, dddd, J = 13.8, 5.6, 1.9, 1.4 Hz), 2.01 (1H, ddd, J = 13.6, 8.6, 6.3 Hz), 2.23–2.30 (2H, 2.25 (ddd, J = 13.1, 8.9, 5.6 Hz), 2.29 (ddd, J = 13.1, 5.7, 1.4 Hz)), 2.58 (1H, dd, J = 8.6, 1.9 Hz), 4.04 (2H, dd, J = 8.1, 6.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.6, 30.0, 35.2, 46.7, 50.1, 60.2, 126.3, 169.2, 194.3, 208.2; HR-ESI-MS m/z: calcd for $C_{10}H_{13}NO_2$\{[M + H]$^+$\}179.2190, found 179.0762; Anal. calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82; O, 17.85; found: C, 67.00; H, 7.33; N, 7.81; O, 17.87%.

compound **167**, yellow oily liquid, yield 71.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, t, J = 6.5 Hz), 0.96–1.35 (11*H*, 0.98 (ddd, J = 14.1, 10.2, 3.4 Hz), 1.07 (ddd, J = 12.9, 10.3, 2.8 Hz), 1.19 (ddd, J = 12.9, 10.3, 2.8 Hz), 1.21 (dq, J = 12.9, 2.8 Hz), 1.26 (dq, J = 12.9, 2.8 Hz), 1.35 (qdd, J = 10.2, 2.6, 2.5 Hz)), 1.60–1.81 (8H, 1.64 (td, J = 6.8, 4.7 Hz), 1.69 (td, J = 6.8, 4.7 Hz), 1.72 (ttt, J = 10.3, 4.7, 2.8 Hz), 1.80 (dddd, J = 14.1, 3.3, 2.5, 2.3 Hz)), 2.00 (1H, qt, J = 10.3, 2.8 Hz), 4.03 (2H, dd, J = 10.3, 3.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 23.0, 24.2, 28.4, 29.3, 30.2, 33.1, 33.7, 36.2, 37.2, 37.9, 42.6, 49.5, 59.4, 128.8, 169.4, 199.8, 207.6; HR-ESI-MS m/z: calcd for $C_{20}H_{30}O_2$\{[M + H]$^+$\}302.4580, found 302.1896; Anal. calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; O, 10.58; found: C, 79.40; H, 10.01; O, 10.59%.

compound **168**, yellow oily liquid, yield 55.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.20 (2H, dtd, J = 14.1, 10.2, 3.4 Hz), 2.01 (1H, dddd, J = 14.1, 3.3, 2.5, 2.3 Hz), 2.25 (2H, ddd, J = 14.1, 3.0, 2.6 Hz), 2.50 (2H, dt, J = 14.1, 10.3 Hz), 3.53 (1H, dd, J = 10.3, 3.0 Hz), 4.07 (2H, tdd, J = 10.2, 2.6, 2.5 Hz), 5.25 (2H, s), 7.26 (1H, tt, J = 7.7, 1.3 Hz), 7.33–7.40 (4H, 7.36 (dddd, J = 7.8, 1.3, 1.0, 0.6 Hz), 7.40 (dddd, J = 7.8, 7.7, 1.6, 0.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 28.2, 29.1, 31.7, 45.3, 56.7, 60.3, 63.6, 126.9, 127.1, 128.5, 128.9, 136.1, 156.2, 170.8, 198.3, 208.5; HR-ESI-MS m/z: calcd for $C_{18}H_{19}NO_4$\{[M + H]$^+$\}313.3530, found 313.1009; Anal. calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47; O, 20.42; found: C, 68.96; H, 6.12; N, 4.49; O, 20.41%.

compound **169** , yellow oily liquid, yield 89.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14–1.24 (2H, 1.16 (ddddd, J = 13.8, 3.1, 2.9, 2.8, 2.4 Hz), 1.18 (dtdd, J = 13.8, 10.2, 3.4, 2.8 Hz)), 1.54 (2H, dtt, J = 13.5, 10.3, 2.8 Hz), 1.92 (2H, dtd, J = 13.5, 2.8, 2.5 Hz), 2.00 (1H, dtd, J = 13.5, 10.2, 2.7 Hz), 2.19–2.32 (4H, 2.22 (ddd, J = 13.9, 3.4, 2.4 Hz), 2.29 (ddd, J = 13.9, 10.2, 3.1 Hz)), 4.07 (2H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 25.4, 26.0, 29.1, 32.9, 36.2, 41.6, 52.8, 125.9, 170.3, 201.9, 211.8; HR-ESI-MS m/z: calcd for $C_{11}H_{14}O_2$\{[M + H]$^+$\}178.2310, found 178.0826; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95; found: C, 74.10; H, 7.93; O, 17.96%.

compound **170**, yellow oily liquid, yield 86.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.87 (3H, d, J = 6.7 Hz), 1.17 (2H, dtt, J = 13.3, 10.3, 2.8 Hz), 1.48–1.58 (2H, 1.51 (dddt, J = 13.3, 2.9, 2.8, 2.7 Hz), 1.56 (dddd, J = 14.1, 2.9, 2.8, 2.4 Hz)), 1.66–1.82 (2H, 1.68 (dddd, J = 14.1, 10.3, 3.4, 2.8 Hz), 1.76 (dtd, J = 13.5, 2.8, 2.5 Hz)), 2.00 (1H, dtd, J = 13.5, 10.2, 2.7 Hz), 2.10 (1H, ddd, J = 16.2, 6.1, 1.4 Hz), 2.27 (2H, dd, J = 6.7, 32.4 Hz), 4.04 (2H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.1, 25.4, 26.0, 32.9, 33.9, 36.2, 40.2, 52.8, 125.8, 172.3, 204.8, 211.8; HR-ESI-MS m/z: calcd for $C_{12}H_{16}O_2$\{[M + H]$^+$\}192.2580, found 192.1100; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.93; H, 8.41; O, 16.66%.

compound **171**, yellow oily liquid, yield 87.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (3H, d, J = 7.0 Hz), 1.19 (1H, dtd, J = 12.8, 2.8, 2.7 Hz), 1.50–1.68 (2H, 1.55 (dtd, J = 12.8, 10.3, 2.9 Hz), 1.63 (dddd, J = 10.2, 7.0, 3.4, 2.8 Hz)), 1.80 (2H, dtd, J = 13.4, 2.8, 2.5 Hz), 1.99 (1H, dtd, J = 13.4, 10.2, 2.7 Hz), 2.09 (2H, dd, J = 14.1, 10.2 Hz), 2.65 (2H, ddd, J = 16.2, 8.5, 6.2 Hz)), 4.03 (2H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.4, 31.5, 33.4, 34.5, 35.8, 42.0, 45.2, 56.3, 125.9, 173.6, 207.3, 201.9; HR-ESI-MS m/z: calcd for $C_{12}H_{16}O_2$\{[M + H]$^+$\}192.2580, found 192.1098; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.93; H, 8.40; O, 16.67%.

compound **172**, yellow oily liquid, yield 87.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, d, J = 7.0 Hz), 1.18 (1H, dddd, J = 14.1, 3.1, 2.9, 2.4 Hz), 1.58–1.78 (2H, 1.60 (dddd, J = 14.1, 10.2, 3.4, 2.8 Hz), 1.77 (qdtd, J = 7.0, 2.9, 2.8, 2.7 Hz)), 2.00 (1H, ddd, J = 14.2, 2.8, 2.5 Hz), 2.11 (2H, ddd, J = 14.2, 10.2, 2.7 Hz), 2.43 (2H, ddd, J = 13.8, 3.4, 2.4 Hz), 2.71 (2H, ddd, J = 13.8, 10.2, 3.1 Hz), 4.03 (2H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.3, 21.1, 29.3, 33.7, 34.8, 35.8, 40.6, 60.1, 125.8, 172.3, 206.2, 210.2; HR-ESI-MS m/z: calcd for $C_{12}H_{16}O_2$\{[M + H]$^+$\}192.2580, found 192.0995; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64; found: C, 74.92; H, 8.41; O, 16.63%.

compound **173**, yellow oily liquid, yield 85.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (3H, t, J = 6.9 Hz), 1.12–1.31 (2H, 1.18 (qd, J = 6.9, 3.7 Hz), 1.24 (qd, J = 6.9, 3.7 Hz)), 1.65–1.84 (2H, 1.67 (dddd, J = 14.1, 3.1, 2.9, 2.4 Hz), 1.80 (dddd, J = 14.1, 10.2, 3.4, 2.8 Hz)), 1.92 (1H, tdtd, J = 3.7, 2.9, 2.8, 2.7 Hz), 1.99 (1H, ddd, J = 13.5, 2.8, 2.5 Hz), 2.11 (2H, ddd, J = 13.5, 10.2, 2.7 Hz), 2.66 (2H, ddd, J = 13.7, 3.4, 2.4 Hz), 2.38 (2H, ddd, J = 13.7, 10.2, 3.1 Hz), 4.05 (2H, dd, J = 10.2, 2.5 Hz);

^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.0, 27.0, 28.1, 32.6, 34.9, 35.9, 38.7, 40.6, 51.6, 125.1, 173.6, 207.8, 211.3; HR-ESI-MS *m/z*: calcd for $C_{13}H_{18}O_2$\{[M + H]$^+$\}206.2850, found 206.1617; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.67; H, 8.81; O, 15.53%.

compound **174**, yellow oily liquid, yield 83.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, t, *J* = 6.5 Hz), 1.04–1.29 (4H, 1.07 (td, *J* = 6.5, 4.5 Hz), 1.12 (h, *J* = 6.5 Hz), 1.19 (h, *J* = 6.5 Hz), 1.26 (td, *J* = 6.5, 4.5 Hz)), 1.41 (1H, dddd, *J* = 14.1, 10.2, 3.4, 2.8 Hz), 1.63–1.85 (4H, 1.65 (dddd, *J* = 14.1, 3.1, 2.9, 2.4 Hz), 1.81 (tdtd, *J* = 4.5, 2.9, 2.8, 2.7 Hz)), 1.99 (1H, ddd, *J* = 13.5, 2.8, 2.5 Hz), 2.08 (2H, ddd, *J* = 13.5, 10.2, 2.7 Hz), 2.38 (2H, ddd, *J* = 13.8, 3.4, 2.4 Hz), 4.05 (2H, dd, *J* = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 20.3, 27.3, 31.6, 32.5, 35.8, 36.7, 40.6, 42.0, 48.1, 125.8, 173.5, 197.2, 206.6; HR-ESI-MS *m/z*: calcd for $C_{14}H_{20}O_2$\{[M + H]$^+$\}220.3120, found 220.1328; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.30; H, 9.16; O, 14.53%.

compound **175**, yellow oily liquid, yield 82.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.77–0.87 (6H, 0.79 (t, *J* = 6.5 Hz), 0.86 (d, *J* = 6.9 Hz), 1.13–1.25 (4H, 1.17 (dq, *J* = 6.9, 6.5 Hz), 1.23 (dq, *J* = 6.9, 6.5 Hz)), 1.41 (1H, dddd, *J* = 14.1, 10.3, 3.4, 2.8 Hz), 1.62 (2H, 1.73 (dddd, *J* = 14.1, 2.9, 2.8, 2.4 Hz), 1.78–2.00 (4H, 1.81 (ddtd, *J* = 13.2, 2.9, 2.8, 2.7 Hz), 1.91 (dtt, *J* = 13.2, 10.3, 2.8 Hz), 2.00 (dtd, *J* = 13.4, 2.8, 2.5 Hz)), 2.25 (2H, dtd, *J* = 13.4, 10.2, 2.7 Hz), 4.05 (2H, dd, *J* = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 20.5, 23.5, 28.0, 28.8, 29.3, 34.0, 37.7, 37.8, 57.5, 60.2, 122.7, 174.3, 202.7, 207.4; HR-ESI-MS *m/z*: calcd for $C_{15}H_{22}O_2$\{[M + H]$^+$\}234.3390, found 234.1333; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.65; found: C, 76.84; H, 9.48; O, 13.67%.

compound **176**, yellow oily liquid, yield 82.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.84 (9H, s), 1.15–1.33 (3H, 1.19 (dddd, *J* = 13.6, 3.2, 2.9, 2.6 Hz), 1.30 (dddd, *J* = 13.6, 10.3, 2.9, 2.4 Hz)), 1.92 (2H, dddd, *J* = 3.8, 3.2, 2.4, 2.2 Hz), 2.00 (1H, ddd, *J* = 14.1, 8.9, 3.8 Hz), 2.09 (2H, ddd, *J* = 14.1, 5.3, 2.2 Hz), 2.48 (2H, ddd, *J* = 13.7, 2.9, 2.6 Hz), 4.05 (2H, dd, *J* = 8.9, 5.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.6, 27.8, 32.2, 32.4, 32.5, 36.4, 41.1, 46.3, 47.5, 126.3, 173.5, 206.5, 210.4; HR-ESI-MS *m/z*: calcd for $C_{15}H_{22}O_2$\{[M + H]$^+$\}234.3390, found 234.0757; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.65; found: C, 76.85; H, 9.48; O, 13.66%.

compound **177**, yellow oily liquid, yield 83.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86 (3H, t, *J* = 6.5 Hz), 1.07–1.44 (9H, 1.08 (tt, *J* = 6.8, 6.5 Hz), 1.12 (td, *J* = 6.8, 4.5 Hz), 1.23 (td, *J* = 6.8, 4.5 Hz), 1.29 (tq, *J* = 6.9, 6.5 Hz), 1.41 (tq, *J* = 6.9, 6.5 Hz)), 1.64 (2H, dddd, *J* = 14.1, 10.2, 3.4, 2.8 Hz), 1.79 (2H, dddd, *J* = 14.1, 3.1, 2.9, 2.4 Hz), 2.08 (1H, ddd, *J* = 13.5, 10.2, 2.7 Hz), 2.38 (2H, ddd, *J* = 13.8, 3.4, 2.4 Hz), 2.66 (2H, ddd, *J* = 16.3, 6.1, 1.4 Hz), 4.05 (2H, dd, *J* = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.1, 22.7, 26.3, 27.0, 31.6, 32.3, 33.2, 35.7, 37.0, 40.6, 41.9, 51.6, 125.0, 174.0, 206.6, 207.1; HR-ESI-MS *m/z*: calcd for $C_{16}H_{24}O_2$\{[M + H]$^+$\}248.3660, found 248.1725; Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74; O, 12.88; found: C, 77.34; H, 9.76; O, 12.90%.

compound **178**, yellow oily liquid, yield 81.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.75–0.86 (9H, 0.76 (t, *J* = 7.1 Hz), 0.85 (q, *J* = 7.1 Hz)), 1.02 (1H, dddd, *J* = 14.1, 3.2, 2.9, 2.6 Hz), 1.18 (2H, dddd, *J* = 14.1, 10.3, 2.9, 2.4 Hz), 1.30 (2H, dddd, *J* = 3.8, 3.2, 2.4, 2.2 Hz), 1.92 (2H, ddd, *J* = 14.1, 5.3, 2.2 Hz), 1.99 (1H, ddd, *J* = 14.1, 8.9, 3.8 Hz), 2.09 (2H, ddd, *J* = 17.9, 6.1, 1.4 Hz), 2.48 (2H, ddd, *J* = 13.7, 10.3, 2.9 Hz), 4.05 (2H, dd, *J* = 8.9, 5.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 8.5, 25.4, 27.1, 32.5, 32.9, 33.8, 34.7, 36.5, 41.2, 43.5, 50.7, 126.2, 172.6, 197.7, 211.3; HR-ESI-MS *m/z*: calcd for $C_{16}H_{24}O_2$\{[M + H]$^+$\}248.3660, found 248.1561; Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74; O, 12.88; found: C, 77.35; H, 9.74; O, 12.91%.

compound **179**, yellow oily liquid, yield 76.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.54 (10*H*,1.18 (dddd, *J* = 14.2, 10.0, 4.7, 4.0 Hz), 1.25 (dtd, *J* = 13.6, 10.1, 2.2 Hz), 1.36 (dddd, *J* = 14.1, 10.3, 4.6, 2.7 Hz), 1.41 (dddd, *J* = 14.1, 3.0, 2.5, 1.6 Hz), 1.50 (dddd, *J* = 13.6, 3.6, 3.5, 2.2 Hz)), 1.78 (2H, ddddd, *J* = 12.9, 3.5, 3.0, 2.7, 2.2 Hz), 1.92 (2H, ddddd, *J* = 12.9, 10.3, 10.1, 2.5, 2.2 Hz), 1.99 (1H, ddd, *J* = 13.9, 10.0, 4.0 Hz), 2.15 (2H, ddd, *J* = 13.9, 3.9, 1.9 Hz), 2.72 (1H, ddd, *J* = 17.9, 8.5, 6.1 Hz), 4.05 (2H, dd, *J* = 10.1, 3.6 Hz), 5.51 (1H, t, *J* = 4.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.2, 22.6, 23.0, 25.3, 27.2, 27.6, 30.7, 31.9, 42.1, 43.5, 49.2, 122.9, 128.8, 136.6, 17.01, 205.0, 210.5; HR-ESI-MS *m/z*: calcd for $C_{17}H_{22}O_2$\{[M + H]$^+$\}258.3610, found 258.1330; Anal. calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; O, 12.38; found: C, 79.00; H, 8.59; O, 12.39%.

compound **180**, yellow oily liquid, yield 75.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.46 (2H, ddddd, *J* = 12.9, 10.3, 10.1, 2.5, 2.2 Hz), 1.79 (2H, dddd, *J* = 14.1, 10.3, 4.6, 2.7 Hz), 1.93 (2H, dtd, *J* = 13.6, 10.1, 2.2 Hz), 1.99 (1H, dddd, *J* = 13.6, 3.6, 3.5, 2.2 Hz), 2.14 (2H, ddd, *J* = 15.5, 8.5, 6.1 Hz), 3.48 (1H, dd, *J* = 10.1, 3.6 Hz), 4.05 (2H, dd, *J* = 4.6, 1.6 Hz), 7.13–7.30 (5H, 7.18 (tt, *J* = 7.7, 1.3 Hz), 7.24 (dddd, *J* = 7.8, 7.7, 1.9, 0.5 Hz), 7.29 (dddd, *J* = 7.8, 1.3, 1.2, 0.5 Hz)); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.0, 26.9, 31.8, 41.2, 42.2, 50.8, 64.2, 126.4, 126.7, 127.2, 128.8, 145.8, 170.3, 202.8, 210.5; HR-ESI-MS *m/z*: calcd for $C_{17}H_{18}O_2$\{[M + H]$^+$\}254.3290, found 254.1606; Anal. calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13; O, 12.58; found: C, 80.25; H, 7.16; O, 12.54%.

compound **181**, yellow oily liquid, yield 78.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, t, *J* = 6.5 Hz), 0.94–1.32 (11*H*, 1.00 (dddd, *J* = 14.1, 3.1, 2.9, 2.4 Hz), 1.13 (ddtd, *J* = 10.3, 2.9, 2.8, 2.7 Hz), 1.16 (dddd, *J* = 14.1, 10.2, 3.4, 2.8 Hz), 1.20 (dq, *J* = 12.9, 2.8 Hz), 1.12 (dtd, *J* = 12.9, 10.3, 2.8 Hz), 1.30 (dtd, *J* = 12.9, 10.3, 2.8 Hz)), 1.71–1.78 (6H, 1.72 (dq, *J* = 12.9, 2.8 Hz), 1.76 (ttt, *J* = 10.3, 4.7, 2.8 Hz)), 1.92 (2H, qt, *J* = 10.3, 2.8 Hz), 2.00 (1H, ddd, *J* = 13.5, 2.8, 2.5 Hz), 2.08 (2H, ddd, *J* = 13.5, 10.2, 2.7 Hz), 2.49 (2H, ddd, *J* = 14.3, 3.4, 2.4 Hz), 4.05 (2H, dd, *J* = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 20.2, 27.4, 30.0, 30.4, 32.9, 33.6, 35.2, 37.7, 37.8, 40.9, 42.4, 50.2, 126.5, 170.1, 204.2, 210.1; HR-ESI-MS *m/z*: calcd for $C_{20}H_{30}O_2$\{[M + H]$^+$\}302.4580, found 302.2018; Anal. calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; O, 10.58; found: C, 79.39; H, 10.01; O, 10.59%.

compound **182**, yellow oily liquid, yield 72.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (1H, dddd, *J* = 14.1, 3.1, 2.9, 2.4 Hz), 1.25 (1H, dq, *J* = 13.0, 2.8 Hz), 1.43 (4H, ddtd, *J* = 10.3, 2.9, 2.8, 2.7 Hz), 1.65 (4H, dtd, *J* = 13.0, 10.3, 2.8 Hz), 1.90 (2H, dtd, *J* = 13.0, 10.3, 2.8 Hz), 2.01 (1H, ddd, *J* = 13.5, 2.8, 2.5 Hz), 2.09 (2H, dddd, *J* = 14.1, 10.2, 3.4, 2.8 Hz), 2.20 (2H, ddd, *J* = 13.5, 10.2, 2.7 Hz), 2.37 (2H, ddd, *J* = 14.3, 3.4, 2.4 Hz), 3.84 (4H, ddd, *J* = 14.6, 5.6, 1.4 Hz),4.05 (2H, dd, *J* = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.0, 30.2, 33.1, 33.5, 33.6, 35.0, 37.5, 40.0, 42.6, 50.2, 64.1, 119.0, 126.7, 172.1, 203.4, 211.5; HR-ESI-MS *m/z*: calcd for $C_{19}H_{26}O_4$\{[M + H]$^+$\}318.4130, found 318.2066; Anal. calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10; found: C, 71.62; H, 8.24; O, 20.13%.

compound **183**, yellow oily liquid, yield 66.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.28 (2H, ddd, *J* = 14.1, 2.8, 2.5 Hz), 1.92 (2H, dddd, *J* = 13.8, 3.1, 2.9, 2.4 Hz), 1.99 (1H, dddd, *J* = 13.8, 10.2, 3.4, 2.8 Hz), 2.39 (2H, ddd, *J* = 14.1, 10.2, 2.7 Hz), 2.66 (2H, ddd, *J* = 14.6, 3.4, 2.4 Hz), 3.59 (1H, ddd, *J* = 14.6, 10.2, 3.1 Hz), 4.04 (2H, dd, *J* = 10.2, 2.5 Hz), 7.56–7.70 (4H, 7.62 (ddd, *J* = 7.8, 1.3, 0.5 Hz), 7.68 (ddd, *J* = 7.8, 7.6, 1.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.9, 32.3, 32.8, 34.4, 41.8, 49.5, 68.3, 123.0, 125.8, 128.3, 134.5, 140.0, 168.1, 202.8, 210.8; HR-ESI-MS *m/z*: calcd for $C_{19}H_{17}NO_4$\{[M + H]$^+$\}323.3480, found 323.2357; Anal. calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33; O, 19.79; found: C, 70.54; H, 5.31; N, 4.35; O, 19.80%.

compound **184**, yellow oily liquid, yield 71.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05–1.20 (2H, 1.09 (dddd, *J* = 14.1, 3.1, 2.9, 2.4 Hz), 1.18 (dddd, *J* = 14.1, 10.2, 3.4, 2.8 Hz)), 1.86 (2H, ddd, *J* = 13.5, 2.8, 2.5 Hz), 2.05 (1H, ddd, *J* = 13.5, 10.2, 2.7 Hz), 2.28 (2H, ddd, *J* = 14.4, 3.4, 2.4 Hz), 2.59 (2H, ddd, *J* = 14.4, 10.2, 3.1 Hz), 2.95 (1H, ddd, *J* = 16.3, 6.1, 1.4 Hz), 4.45 (2H, dd, *J* = 10.2, 2.5 Hz), 6.71 (2H, ddd, *J* = 8.2, 2.6, 0.5 Hz), 7.11 (2H, ddd, *J* = 8.2, 1.1, 0.5 Hz), 9.23 (1H, *s*); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 33.1, 33.4, 34.2, 36.4, 41.4, 42.7, 51.0, 115.5, 1278,

128.0, 136.0, 155.8, 172.5, 201.9, 210.9; HR-ESI-MS *m/z*: calcd for $C_{17}H_{18}O_3$\{[M + H]$^+$\}270.3280, found 270.1093; Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71; O, 17.76; found: C, 75.50; H, 6.72; O, 17.78%.

compound **185**, yellow oily liquid, yield 70.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.13–128 (2H, 1.18 (dtt, J = 16.4, 10.3, 2.8 Hz), 1.25 (ddtd, J = 16.4, 2.9, 2.8, 2.7 Hz)), 1.37–1.66 (2H, 1.46 (dddd, J = 13.8, 2.9, 2.8, 2.4 Hz), 1.57 (dtd, J = 13.5, 10.2, 2.7 Hz)), 2.01 (1H, dtd, J = 13.5, 2.8, 2.5 Hz), 2.10 (2H, dddd, J = 13.8, 10.3, 3.4, 2.8 Hz), 2.19 (3H, s), 2.41 (2H, ddd, J = 16.3, 6.1, 1.4 Hz), 2.68 (1H, ddd, J = 16.7, 8.5, 6.1 Hz), 4.04 (2H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.4, 23.4, 25.8, 28.6, 33.9, 43.0, 56.5, 60.1, 126.3, 174.9, 207.0, 207.2, 208.5; HR-ESI-MS *m/z*: calcd for $C_{13}H_{16}O_3$\{[M + H]$^+$\}220.2680, found 220.0962; Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79; found: C, 70.85; H, 7.34; O, 21.81%.

compound **186**, yellow oily liquid, yield 66.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (3H, t, J = 7.1 Hz), 1.51–1.80 (6H, 1.51 (dtt, J = 13.5, 10.3, 2.8 Hz), 1.66 (ddtd, J = 13.5, 2.9, 2.8, 2.7 Hz), 1.78 (ddd, J = 16.3, 8.5, 6.2 Hz)), 2.00 (1H, dddd, J = 13.9, 10.3, 3.4, 2.8 Hz), 2.27 (2H, dtd, J = 13.5, 10.2, 2.7 Hz), 2.96 (1H, dtd, J = 13.5, 2.8, 2.5 Hz), 4.04 (2H, dd, J = 3.4, 2.4 Hz), 4.16 (2H, q, J = 7.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.9, 14.2, 24.6, 27.0, 33.8, 41.7, 56.9, 59.9, 64.0, 122.8, 169.9, 172.7, 205.6, 209.9; HR-ESI-MS *m/z*: calcd for $C_{14}H_{18}O_4$\{[M + H]$^+$\}250.2940, found 250.0996; Anal. calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; O, 25.57; found: C, 67.14; H, 7.26; O, 25.59%.

compound **187**, yellow oily liquid, yield 58.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.13–1.18 (2H, 1.15 (dddd, J = 14.3, 10.3, 3.4, 2.8 Hz), 1.18 (dtt, J = 13.8, 10.3, 2.8 Hz)), 1.89 (3H, ddd, J = 13.8, 2.9, 2.7 Hz), 1.96 (1H, dddd, J = 14.3, 2.9, 2.8, 2.4 Hz), 2.08 (2H, dtd, J = 13.5, 2.8, 2.5 Hz), 2.38 (2H, dtd, J = 13.5, 10.2, 2.7 Hz), 2.64 (2H, 2.78 (ddd, J = 16.3, 6.1, 1.4 Hz), 4.02 (2H, dd, J = 10.2, 2.5 Hz), 4.57 (1H, dd, J = 3.4, 2.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.0, 20.6, 27.9, 29.3, 33.6, 37.7, 49.7, 60.2, 123.9, 173.1, 174.5, 206.7, 207.7; HR-ESI-MS *m/z*: calcd for $C_{13}H_{17}NO_3$\{[M + H]$^+$\}235.2830, found 235.0876; Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; O, 20.40; found: C, 66.33; H, 7.29; N, 5.98; O, 20.39%.

compound **188**, yellow oily liquid, yield 52.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15 (9H, s), 1.77 (2H, dddd, J = 14.2, 3.1, 2.9, 2.4 Hz), 2.00 (1H, dddd, J = 14.2, 10.2, 3.4, 2.8 Hz), 2.10 (2H, ddd, J = 14.1, 2.8, 2.5 Hz), 2.38 (2H, ddd, J = 14.1, 10.2, 2.7 Hz), 2.66 (2H, ddd, J = 13.9, 3.4, 2.4 Hz), 3.94–4.07 (3H, 3.94 (dtd, J = 2.9, 2.8, 2.7 Hz), 4.04 (dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.9, 28.9, 29.4, 31.6, 33.7, 37.7, 47.5, 60.2, 77.4, 124.0, 156.3, 174.5, 199.6, 207.6; HR-ESI-MS *m/z*: calcd for $C_{16}H_{23}NO_4$\{[M + H]$^+$\}293.3630, found 293.1353; Anal. calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77; O, 21.81; found: C, 65.48; H, 7.91; N, 4.76; O, 21.85%.

compound **189**, yellow oily liquid, yield 53.2%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (2H, ddtd, J = 13.4, 2.9, 2.8, 2.7 Hz), 1.91 (2H, dtt, J = 13.4, 10.3, 2.8 Hz), 1.99 (1H, dddd, J = 14.1, 10.3, 3.4, 2.8 Hz), 2.10 (2H, dtd, J = 13.5, 10.2, 2.7 Hz), 2.36 (2H, dddd, J = 14.1, 2.9, 2.8, 2.4 Hz), 2.66 (1H, dtd, J = 13.5, 2.8, 2.5 Hz), 4.05 (2H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.5, 24.3, 32.9, 37.7, 39.7, 57.0, 65.1, 124.2, 173.3, 205.1, 207.8; HR-ESI-MS *m/z*: calcd for $C_{11}H_{13}ClO_2$\{[M + H]$^+$\}212.6730, found 212.1360; Anal. calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16; Cl, 16.67; O, 15.05; found: C, 62.10; H, 6.15; Cl, 16.68; O, 15.07%.

compound **190**, yellow oily liquid, yield 50.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.86–1.07 (8H, 0.90 (s), 1.03 (ddd, J = 16.2, 8.5, 6.2 Hz)), 1.48–1.58 (2H, 1.49 (ddd, J = 13.8, 2.8, 2.7 Hz), 1.54 (ddd, J = 13.8, 10.3, 2.9 Hz)), 1.81 (2H, d, J = 14.9 Hz), 2.01 (1H, dtd, J = 13.3, 2.8, 2.5 Hz), 2.66 (2H, dtd, J = 13.3, 10.2, 2.7 Hz), 4.05 (2H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.1, 25.9, 32.1, 33.5, 38.8, 44.6, 45.1, 49.0, 128.7, 172.7, 203.6, 209.8; HR-ESI-MS *m/z*: calcd for $C_{13}H_{18}O_2$\{[M + H]$^+$\}206.2850, found 206.0861; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.65; H, 8.82; O, 15.53%.

compound **191**, yellow oily liquid, yield 48.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.82–1.02 (9H, 0.88 (d, J = 6.9 Hz), 0.93 (s), 0.98 (s), 1.07 (2H, ddd, J = 16.3, 8.5, 6.2 Hz), 1.61–1.68 (2H, 1.62 (dd, J = 14.1, 2.7 Hz), 1.67 (dd, J = 14.1, 10.3 Hz)), 1.89 (1H, d, J = 14.1 Hz), 2.00 (1H, ddd, J = 10.2, 6.9, 2.7 Hz), 2.29 (2H, dd, J = 16.3, 6.1, 1.4 Hz), 3.96 (2H, d, J = 10.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.1, 26.0, 29.6, 32.2, 35.2, 42.1, 44.7, 49.1, 63.3, 126.8, 171.4, 204.0, 210.0; HR-ESI-MS *m/z*: calcd for $C_{14}H_{20}O_2$\{[M + H]$^+$\}220.3120, found 220.1174; Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52; found: C, 76.31; H, 9.16; O, 14.53%.

compound **192**, yellow oily liquid, yield 47.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, d, J = 6.6 Hz), 1.16 (3H, s), 1.83 (2H, ddd, J = 13.5, 3.3, 2.6 Hz), 2.00 (1H, ddd, J = 14.1, 3.5, 1.6 Hz), 2.09 (2H, dddd, J = 14.1, 10.1, 4.7, 3.4 Hz), 2.45 (1H, ddd, J = 13.5, 10.2, 3.0 Hz), 2.71 (2H, ddd, J = 14.9, 6.0, 1.4 Hz), 4.05 (2H, ddd, J = 14.9, 8.6, 6.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.8, 20.2, 22.5, 30.8, 31.7, 33.6, 34.6, 37.2, 51.6, 126.4, 169.2, 200.6, 209.9; HR-ESI-MS *m/z*: calcd for $C_{13}H_{18}O_2$\{[M + H]$^+$\}206.2850, found 206.0871; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; O, 15.51; found: C, 75.65; H, 8.81; O, 15.54%.

compound **193**, yellow oily liquid, yield 50.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.95 (3H, d, J = 6.7 Hz), 1.12–1.37 (4H, 1.25 (ddd, J = 16.3, 8.5, 6.2 Hz), 1.37 (dddd, J = 14.1, 10.3, 3.4, 2.8 Hz)), 1.61–1.81 (2H, 1.68 (dtd, J = 14.2, 10.3, 2.8 Hz), 1.80 (dddd, J = 14.1, 2.9, 2.8, 2.4 Hz)), 1.99 (1H, td, J = 10.2, 2.7 Hz), 2.23–2.44 (3H, 2.24 (ddd, J = 16.3, 6.1, 1.4 Hz), 2.40 (qdd, J = 6.7, 3.4, 2.4 Hz)), 3.89 (2H, ddd, J = 16.6, 6.2, 1.4 Hz),), 4.64–4.74 (2H, 4.65 (d, J = 1.3 Hz), 4.73 (d, J = 1.3 Hz)); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.1, 22.4, 28.3, 33.1, 34.2, 41.4, 45.1, 69.3, 115.6.128.0, 156.2, 170.3, 199.7, 210.9; HR-ESI-MS *m/z*: calcd for $C_{15}H_{20}O_2$\{[M + H]$^+$\}232.3230, found 232.1383; Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77; found: C, 77.51; H, 8.69; O, 13.80%.

compound **194**, yellow oily liquid, yield 52.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.79–0.97 (9H, 0.84 (d, J = 6.9 Hz), 0.84 (d, J = 6.9 Hz), 0.92 (d, J = 6.9 Hz)), 1.10–1.31 (4H, 1.15 (dtd, J = 14.6, 10.3, 2.8 Hz), 1.26 (dddd, J = 14.1, 10.3, 3.4, 2.8 Hz)), 1.41 (1H, Hdddd, J = 14.6, 2.9, 2.8, 2.7 Hz), 1.61 (1H, dddd, J = 14.1, 2.9, 2.8, 2.4 Hz), 1.80 (1H, tqd, J = 10.2, 6.9, 2.7 Hz), 2.00 (1H, dd, J = 10.2, 2.7 Hz), 2.53 (2H, ddd, J = 16.3, 6.1, 1.4 Hz), 4.05 (2H, dd, J = 16.3, 8.5, 6.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.2, 21.0, 25.8, 28.0, 29.7, 31.2, 31.7, 37.8, 50.5, 56.7, 126.1, 172.6, 204.4, 209.4; HR-ESI-MS *m/z*: calcd for $C_{15}H_{22}O_2$\{[M + H]$^+$\}234.3390, found 234.1116; Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.65; found: C, 76.84; H, 9.47; O, 13.68%.

compound **195**, yellow oily liquid, yield 43.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.00 (1H, ddd, J = 16.3, 6.1, 1.4 Hz), 2.11 (2H, ddd, J = 13.1, 10.0, 3.8 Hz), 2.19 (2H, ddd, J = 13.1, 4.0, 1.9 Hz), 2.46 (2H, ddd, J = 14.9, 3.8, 1.9 Hz), 2.71 (2H, ddd, J = 14.9, 10.0, 4.0 Hz), 4.04 (2H, dd, J = 16.4, 10.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.9, 31.7, 37.9, 42.5, 45.6, 50.6, 126.1, 172.7, 197.6, 207.0, 210.7; HR-ESI-MS *m/z*: calcd for $C_{11}H_{12}O_3$\{[M + H]$^+$\}192.2140, found 192.0893; Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; O, 24.97; found: C, 68.70; H, 6.31; O, 24.98%.

compound **196**, yellow oily liquid, yield 40.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (2H, dddd, J = 11.5, 10.2, 3.4, 2.8 Hz), 1.91 (1H, dddd, J = 11.5, 3.1, 2.9, 2.4 Hz), 1.98 (1H, ddd, J = 14.1, 2.8, 2.5 Hz), 2.10 (2H, ddd, J = 14.1, 10.2, 2.7 Hz), 2.39 (2H, ddd, J = 13.2, 3.4, 2.4 Hz), 2.63 (2H, ddd, J = 13.2, 10.2, 3.1 Hz), 4.04 (1H, dd, J = 10.2, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 28.1, 29.9, 30.7, 31.5, 37.9, 45.2, 49.8, 126.2, 170.7, 194.7, 207.0; HR-ESI-MS *m/z*: calcd for $C_{11}H_{15}NO_2$\{[M + H]$^+$\}193.2460, found 193.0849; Anal. calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25; O, 16.56; found: C, 68.33; H, 7.83; N, 7.26; O, 16.58%.

compound **197**, yellow oily liquid, yield 70.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.84–1.41 (19H, 0.85 (t, J = 6.5 Hz), 0.95 (dddd, J = 14.1, 3.1, 2.9, 2.4 Hz), 1.16 (ddtd, J = 10.3, 2.9, 2.8, 2.7 Hz), 1.18 (dddd, J =

14.1, 10.2, 3.4, 2.8 Hz), 1.21 (dq, $J = 12.9$, 2.8 Hz), 1.24 (dtd, $J = 12.9$, 10.3, 2.8 Hz), 1.26 (dtd, $J = 12.9$, 10.3, 2.8 Hz), 1.34 (dq, $J = 12.9$, 2.8 Hz), 1.38 (td, $J = 6.8$, 4.7 Hz)), 1.64–1.84 (5H, 1.64 (td, $J = 6.8$, 4.7 Hz), 1.69 (ttt, $J = 10.3$, 4.7, 2.8 Hz), 1.80 (dtd, $J = 12.7$, 10.3, 2.8 Hz)), 2.00 (1H, ddd, $J = 13.5$, 2.8, 2.5 Hz), 2.21 (2H, ddd, $J = 13.5$, 10.2, 2.7 Hz), 2.34 (2H, ddd, $J = 14.3$, 3.4, 2.4 Hz), 4.05 (2H, dd, $J = 10.2$, 2.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 23.0, 24.2, 28.4, 29.2, 30.2, 33.1, 33.6, 33.7, 36.2, 37.2, 37.8, 40.9, 42.6, 50.2, 124.7, 168.3, 200.8, 211.6; HR-ESI-MS *m/z*: calcd for $C_{21}H_{32}O_2$\{[M + H]$^+$\}316.4850, found 316.2496; Anal. calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; O, 10.11; found: C, 79.67; H, 10.21; O, 10.13%.

compound **198**, yellow oily liquid, yield 55.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16 (2H, dddd, $J = 14.2$, 3.1, 2.9, 2.4 Hz), 1.91 (2H, dddd, $J = 14.2$, 10.2, 3.4, 2.8 Hz), 2.09 (1H, ddd, $J = 14.1$, 2.8, 2.5 Hz), 2.39 (2H, ddd, $J = 14.1$, 10.2, 2.7 Hz), 2.65 (2H, ddd, $J = 13.9$, 3.4, 2.4 Hz), 3.44 (1H, ddd, $J = 16.7$, 6.2, 1.4 Hz), 4.04 (2H, dd, $J = 10.2$, 2.5 Hz), 5.06 (2H, s), 7.22–7.36 (5H, 7.23 (tt, $J = 7.7$, 1.3 Hz), 7.31 (dddd, $J = 7.8$, 1.3, 1.0, 0.6 Hz), 7.35 (dddd, $J = 7.8$, 7.7, 1.6, 0.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 28.1, 28.2, 29.8, 31.7, 38.8, 47.4, 60.4, 63.5, 126.9, 127.1, 128.5, 128.8, 136.6, 156.4, 172.9, 207.7, 210.7; HR-ESI-MS *m/z*: calcd for $C_{19}H_{21}NO_4$\{[M + H]$^+$\}327.3800, found 327.1534; Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; O, 19.55; found: C, 69.68; H, 6.46; N, 4.30; O, 19.58%.

4.2. In vitro inhibition test of rat synovial cells

When the synovial cells of rats grew to the confluence level of 70%-80% and were in the logarithmic growth stage, the cell density was adjusted after digestion with 0.25% trypsin. 5×10^3 cells per hole vaccination in 96-well culture plate, let stand train for 24 h, will be randomly divided into groups of cells: normal group, DMSO group (dimethylsulfoxide), positive group group (methotrexate) , target compound groups. After the cells were fully adherent to the wall, the liquid in the pore was discarded. In addition to the normal group, the equivalent medium was added to the other groups, and the test substance with corresponding concentration was added to the other groups (among which the insoluble test substance could be dissolved in DMSO less than 5‰). After 48 h of continuous culture, the liquid in the wells was discarded, and then 200 μL of complete culture medium was added. At the same time, 20 μL CCK8 (cell counting kit-8) solution was added to each well, and the solution was placed in the cell culture tank for another 4 h [35]. Finally, optical density (OD) value of each well was measured with a enzyme-linked immuno sorbent assay (ELISA) at the wavelength of 450 nm, and the cell inhibition rate of each group was calculated. Cell inhibition rate = ($OD_{\text{normal group}}$ - $OD_{\text{administration group}}$)/$OD_{\text{normal group}}$.

4.3. In vitro morphological study of rat synovial cells

When the synovial cells of rats grew to the confluence level of 70%-80% and were in the logarithmic growth stage, the cell density was adjusted after digestion with 0.25% trypsin. 5×10^3 cells per hole vaccination in 96-well culture plate, let stand train for 24 h, will be randomly divided into groups of cells: normal group, DMSO group (dimethylsulfoxide, 1 μM), positive group group (methotrexate, 1 μM) , target compounds group (1 μM). After the cells were fully adherent to the wall, the liquid in the pore was discarded. In addition to the normal group, the equivalent medium was added to the other groups, and the test substance with corresponding concentration was added to the other groups (among which the insoluble test substance could be dissolved in DMSO less than 5‰). After 48 h of continuous culture, it were placed on the cell imaging analysis system to observe the morphological changes of synovial cells in each group.

4.4. In vitro LDH release test of rat synovial cells

When the synovial cells of rats grew to the confluence level of 70%-80% and were in the logarithmic growth stage, the cell density was adjusted after digestion with 0.25% trypsin. 2×10^4 cells per hole vaccination in 96-well culture plate, let stand train for 24 h, will be randomly divided into groups of cells: normal group, DMSO group (dimethylsulfoxide, 5‰), positive group group (methotrexate, 1 μM and 0.1 μM) , target compounds group (1 μM and 0.1 μM). After the cells were fully adherent to the wall, the liquid in the pore was discarded. In addition to the normal group, the equivalent medium was added to the other groups, and the test substance with corresponding concentration was added to the other groups (among which the insoluble test substance could be dissolved in DMSO less than 5‰). After continued culture for 48 h, centrifuged at 1500 r/min for 15 min and the supernatant of the cells in each group was collected. The LDH (lactate dehydrogenase) activity of each group was determined by the LDH assay kit in strict accordance with the kit instructions. The LDH activity of each group was calculated according to the definition of lactate dehydrogenase, and the calculation formula was LDH activity (U/L) = (OD_{measured} - OD_{control})/(OD_{standard} - OD_{blank}) × C × N × 1000.

4.5. In vivo anti-rheumatoid arthritis activity test

Adult male rats (200 ± 20 g, SD, SPF, china) were kept under non-specific therapeutic conditions, and the animals had free access to drinking water and food. After 10 days of acclimation, the 0.1 mL of complete freund's adjuvant (CFA, USA) was injected 2 cm away from the rat tail root to cause inflammation, and 0.1 mL of normal saline was injected into the normal group. After 14 days of immunity, when all the rats showed sign of arthritis, the rats were randomly divided into groups (positive control group, compound test groups), and the rats injected with saline acted as the normal group [36]. All test subjects were given orally once a day at the prescribed dose (normal group and blank control group were not given, positive control group was given methotrexate of 50 mg/kg, compound groups were given two different doses of 50 mg/kg and 100 mg/kg), and continuous gavage treatment was performed for 12 days. The test material was prepared with edible vegetable oil as the solvent, and the specified concentration was prepared as required for testing. The paws volume of the rats were measured with a toe volumetric meter (SA701, China) after administration on one day and twelve day. On thirteen day (a day after the last dose), all the experimental rats were killed and autopsies were performed. The blood samples from the abdominal aorta were treated and the serum cytokine IL-6 and TNF-α were determined by ELISA kit (RAB0307, USA).

4.6. Acute toxicity (half lethal dose, LD_{50}) test in mice

Pretest: It was taken 14 mice (20 ± 2 g, SPF, china), each group of 2 were divided into 7 groups. The sexes were equally divided, they need to stop feeding the 4–6 h and hand water freedom before the experiment. The selection of the different doses of the groups, 0.4 mL of sample solution containing the test substance was given by oral intragastric administration, and dimethyl sulfoxide (DMSO) was used as blank control. After giving the drug, fasting 1–2 h, continuous observation 48 h and hand recorded the symptoms and death number. Found the dose of 100% and 0% death of the mice, and used these doses as the highest and lowest doses of the later test.

Formal test: The 100% and 0% lethal doses obtained in the pretest was converted into common logarithm. The maximum lethal dose and the minimum lethal dose was used for the common logarithmic difference, and according to the equidistant dose group divide into 6 groups. Each dose group used 10 mice, the sexes are equally divided. Before the experiment, it was necessary to stop feeding the 4–6 h and hand water freedom. Each mice was given a 0.4 mL of sample solution containing the test substance, and used as a blank control for the DMSO. After giving the test, fasting 1–2 h hand normal feeding, observed the death rate, death time and poisoning phenomenon of the mice in 14 days.

4.7. Docking simulation

The surflex-dock a semi-flexible of molecular dock method, it was employed to estimate the interaction between Toll-like receptor 4 (TLR4) and representative active the compounds [33]. The surflex-dock employs protomol, an idealized ensemble of CH4, NH and CO probes, to guide the generation of docking conformers of the ligands. Herein, crystal structures of the TLR4-MD-2 dimer in complex with co-crystalized antagonist Eritoran (PDB ID: 3FXI) was used for molecular docking. Before docking, all the ligands were charged by tripos force field with the conjugate gradient minimizer. The maximum iteration step and energy gradient were set to 10 000 times and 0.05 kcal/mol·Å, respectively. In surflex-dock, the protomol was generated based on the residues within the 8 Å distance from co-crystalized antagonist eritoran. The search grid and the number of additional starting conformations were set as 2 Å and 3 Å, respectively. The self-scoring, molecule fragmentation, soft grid, pre- and post-dock minimizations were considered in the docking processes. Total score, which indicates -log (K_D) was used for ligand ranking. Ultimately, the lowest energy conformation was utilized to analyze the binding modes between TLR4 and the representative compounds. The conformer with the lowest binding energy was further analyzed using PyMOL molecular graphics system.

Declaration of Competing Interest

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

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