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Original article

Synthesis and evaluation of a novel series of heterocyclic oleanolic acid derivatives with anti-osteoclast formation activity

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ABSTRACT

Oleanolic acid with anti-bone resorption effect was an active component discovered in a medicinal plant of *Achyranthes bidentata*. A series of heterocyclic derivatives of oleanolic acid including indole, pyrazine, quinoxaline, quinoline moieties and their natural amino acid amides were synthesized. Their inhibitory activity on the formation of osteoclast-like multinucleated cells (OCLs) and cytotoxicity of the selected derivatives were evaluated. Among the derivatives, compounds **2a** and **8a** displayed quite a potent activity even at 200 nM. The structure–activity relationships of the derivatives were also discussed.

1. Introduction

Osteoporosis, widely recognized as a major public health problem, particularly among postmenopausal women, is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures [1]. Currently, it is estimated that over 200 million people worldwide have osteoporosis [2] and osteoporosis related fractures accounted for more disability-adjusted life years (DALYs) lost than common cancers except for lung cancer in Europe [3]. Bone is a mechanically optimized connective tissue that is maintained in dynamic equilibrium via bone resorption by osteoclasts and bone formation by osteoblasts. A shift or uncoupling of this dynamic process favoring resorption results in osteoporosis. Increased osteoclastic bone resorption plays a key role in the pathogenesis of osteoporosis. Osteoclast, the only known cell responsible for the bone resorption, is one of the key therapeutical targets for osteoporosis. Inhibitors of the osteoclast may therefore present a potential to prevent the excessive bone resorption associated with osteoporosis [4].

In a research project aiming at new anti-osteoporosis agents, we discovered that the *n*-butanol extract from the root of a medicinal plant, *Achyranthes bidentata* Blume (Amaranthaceae) possesses the anti-osteoporosis activity *in vitro* and *in vivo*, further research revealed that oleanolic acid (OA, **1**, Fig. 1) and its glycosides were the active components of the extract responsible for the activity [5,6]. It has been reported that OA possesses a variety of biological activities, such as anti-inflammatory [7], anti-cancer [8] and hepatoprotective effects [9]. Cognizing oleanolic acid to be a potential anti-osteoporosis lead compound and commercially available, targeting to discover novel structures with a better biological profile, we therefore started a structure modification of OA (**1**). Heterocyclic system has been known to be a very important recognition segment in biologically active molecules and also could produce effective anti-osteoporosis activity [10–12]. It has been reported that conjugates of amino acids and natural product could provide effective bioactivity [13], and our previous results also implied that amino acids might be effective moieties to improve the potency of anti-osteoclast formation of OA [6]. The above information inspired us to incorporate heterocyclic and amino acid segments in the synthesis of oleanolic acid derivatives to improve the inhibitory effect on osteoclast formation. In the present study, we report here the synthesis, activity evaluation of several heterocyclic derivatives in A-ring of oleanolic acid and C_{17}-amides using several natural

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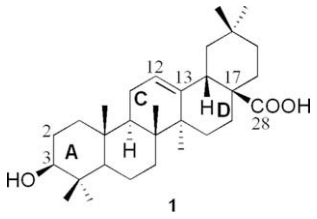


Fig. 1. Chemical structure of oleanolic acid.

amino acids. The structure–activity relationships of these derivatives are also discussed.

2. Results and discussion

2.1. Chemistry

The target molecules are divided into five categories: 3-keto oleanolic acid **2**; indole derivatives **3**–**6**; pyrazine derivatives **7**, **11**; quinoxaline derivatives **8**, **12** and quinoline derivative **9**. Their syntheses are shown in Schemes 1–3.

Scheme 1 describes the synthesis of target compounds **3**–**9**. Compound **2**, 3-keto OA, a key intermediate was prepared by Jones oxidation of **1** in 92% yield [14]. Indole compound **3** was prepared by Fischer indolization of **2** with the phenylhydrazine in the presence of acetic acid [15]. In order to understand the influences on activity of substitution group at phenyl ring, compounds **4**–**6** were synthesized with the same protocol as **3**. It is noteworthy that unprotection of the C-17 carboxyl group of **2** did not impact the Fischer indolization yield.

The synthesis of target compounds pyrazine **7** and quinoxaline **8** was undertaken as depicted in Scheme 1. The reaction of ketone with available 1,2-diamine and sulfur in refluxing morpholine has been applied for the preparation of pyrazine and quinoxaline derivatives [16]. 3-Keto OA (**2**) reacted with ethylenediamine and *o*-phenylenediamine followed by silica gel column chromatography to provide **7** and **8**, respectively.

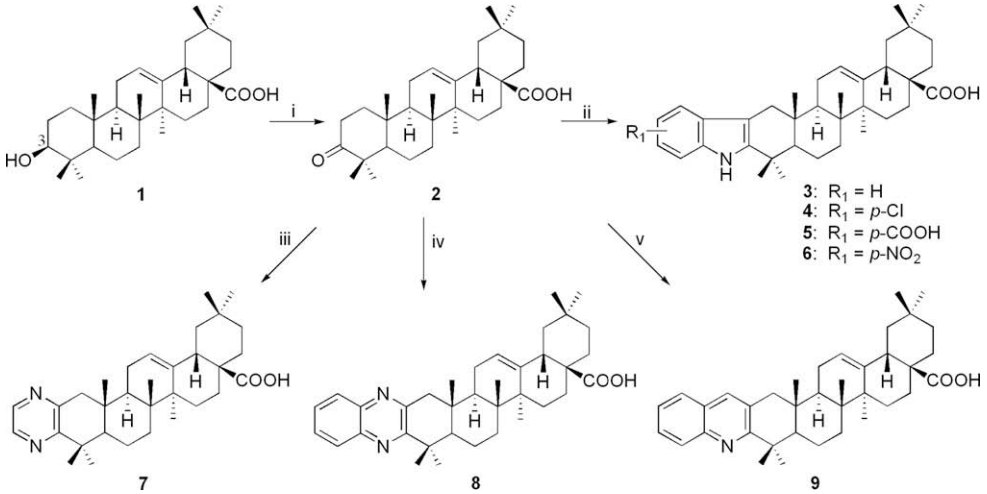
To introduce quinoline moiety, Friedländer reaction was employed. 2-Aminobenzaldehyde obtained by reduction of 2-nitrobenzaldehyde with iron powder in acidic medium [17], reacted with **2** by refluxing in absolute EtOH in the presence of saturated ethanolic KOH to afford target compound **9**.

Scheme 2 characterizes the synthesis of pyrazine and quinoxaline derivatives (**11**, **12**). At first, the same synthetic protocol as that of **7** and **8** was used for the preparation of **11** and **12**, unfortunately no target compounds could be obtained. Thus, an attempt was made to synthesize **11** and **12** via diketone intermediate, 2,3-diketo OA (**10**) obtained by oxidation with SeO_2 in acetic acid reacted with corresponding 1,2-diamine compounds (1.5 mol equiv) in refluxing acetic acid to yield compounds **11** (yield, 53%) and **12** (yield, 44%), respectively. However, the yields were relatively lower compared with those of **7** and **8** (about 70% yield). It should be noted that SeO_2 oxidized the methylene next to the ketone but did not oxidize the allylic methylene next to the olefin, which might be due to the Pummerer-like rearrangement of β-ketoseleninic acids [18].

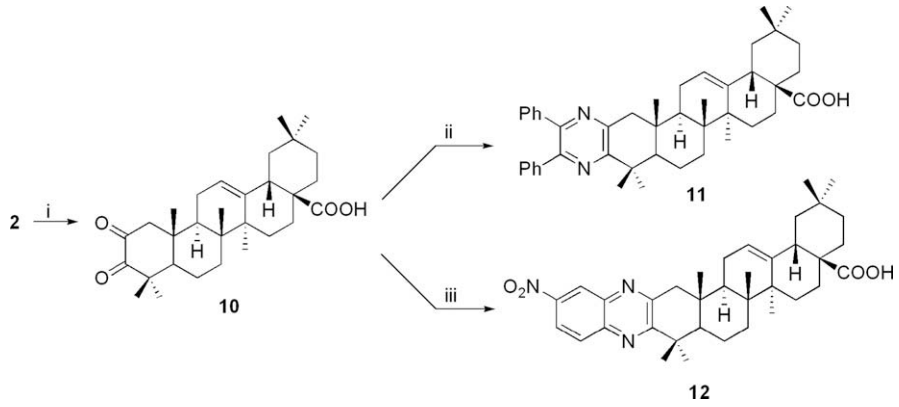
Scheme 3 depicts the synthesis of amino acid derivatives **2a**–**l**, **3a**–**l**, **4a**–**l**, **7a**–**l** and **8a**–**l** from compounds **2**–**4** and **7**, **8**. A general procedure to introduce amino acid moieties was conducted according to the following steps. 17-Acyl chlorides of OA derivatives were prepared by stirring OA derivatives with oxalyl chloride in anhydrous CH_2Cl_2. Treatment with corresponding amino acid methyl esters [19] in the presence of triethylamine afforded amides **2a**–**f**, **3a**–**f**, **4a**–**f**, **7a**–**f** and **8a**–**f**. Hydrolysis of the methyl esters in aqueous sodium hydroxide yielded corresponding compounds **2g**–**l**, **3g**–**l**, **4g**–**l**, **7g**–**l** and **8g**–**l**.

2.2. Biological activity and SAR

Bone resorption is accomplished by the osteoclasts. The most successfully established therapies of osteoporosis with agents such as bisphosphonates are based on osteoclast inhibition [20,21]. Thus, all of the derivatives together with OA (**1**) were tested for their inhibitory activity on 1α,25-dihydroxy vitamin D_3 [1α,25$(OH)_2D_3$] induced TRAP-positive osteoclast-like multinucleated cell (OCL) formation using a co-culture assay system with mouse bone marrow cells and osteoblast-like cells reported by Takahashi [22]. Alendronate sodium, a clinically available bisphosphonate type anti-osteoporosis drug was used as a positive control [23]. In a preliminary screening (see Table 1), out of the 70 compounds at 20 μM, 26 exhibited a better inhibitory activity than OA did. Compound **2**, in which 3-OH of OA was converted to 3-keto showed a much stronger activity compared with OA, the OCL formation was



Scheme 1. (i) Jones oxidation; (ii) phenylhydrazine derivatives, AcOH, reflux; (iii) ethylenediamine, morpholine, S, reflux; (iv) *o*-phenylenediamine, morpholine, S, reflux; (v) *o*-aminobenzaldehyde, saturated ethanolic KOH, absolute EtOH, reflux.



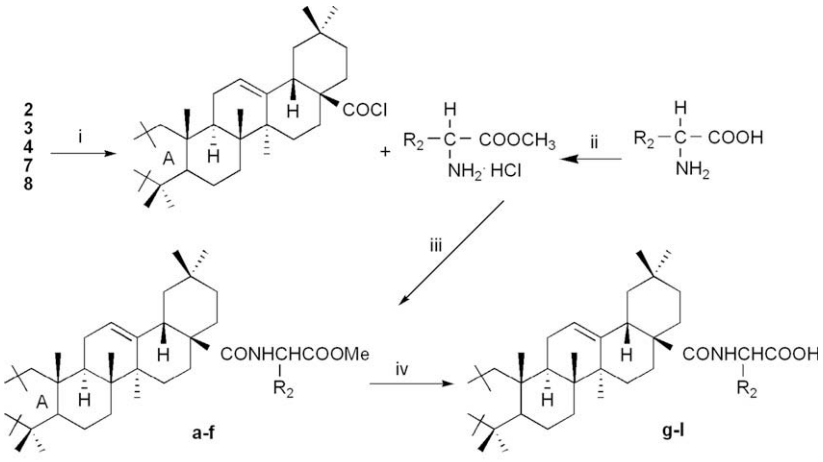
Scheme 2. (i) SeO_2, H_2O, AcOH, reflux; (ii) 1,2-diphenyl-1,2-ethanediamine, AcOH, reflux; (iii) 4-nitro-*o*-phenylenediamine, AcOH, reflux.

only 1.4% compared with control group (100.0%). Compounds **7** (1.8%) and **8** (0%) which contained pyrazine and quinoxaline moieties with two nitrogen atoms displayed a comparable activity with **2**. On the other hand, indole and quinoline moieties (**3** and **9**) containing only one nitrogen atom, negatively impacted the activity. However, substitutions of –Cl, $–NO_2$ and –COOH at phenyl ring of indole moiety (**4**, **5** and **6**) resulted in a much more potent inhibitory effect compared with compound **3**, while substituents of phenyl group at pyrazine ring (**11**) or $–NO_2$ at quinoxaline ring (**12**) lowered the activity.

In addition, all of the derivatives with amino acid methyl ester showed a stronger activity compared with those of amino acid ones except for certain compounds (**3c**–**e** and **3i**–**k**) in compound **3** series, and compound **4** series which was clearly due to their cytotoxicity which will be discussed later. Most of the derivatives with glycine and alanine displayed a better activity than those with other amino acids.

Further evaluation of the compounds with potent activity (OCL% less than 75% was defined as potent activity) was conducted at 2 μM and 200 nM. As shown in Table 2, most of the compounds displayed a weak activity at 2 μM. However, encouragingly, compounds **2a**, **7k**, **8a** and **8i** displayed quite a potent activity even at 200 nM.

It is reasonable to consider that the inhibitory activity of the compounds in this *in vitro* assay is sometimes a result of their cytotoxic effect, and an erroneous conclusion might occur. Thus, to avoid such confusion, a recovery test [24] was conducted (Table 3). The inhibitory activity of compound **4** series was clearly due to their



R_2		2	3	4	7	8
–H	(Gly)	2a, 2g	3a, 3g	4a, 4g	7a, 7g	8a, 8g
$–CH_3$	(Ala)	2b, 2h	3b, 3h	4b, 4h	7b, 7h	8b, 8h
$–CH(CH_3)_2$	(Val)	2c, 2i	3c, 3i	4c, 4i	7c, 7i	8c, 8i
$–CH_2CH(CH_3)_2$	(Leu)	2d, 2j	3d, 3j	4d, 4j	7d, 7j	8d, 8j
$–CH(CH_3)CH_2CH_3$	(Ile)	2e, 2k	3e, 3k	4e, 4k	7e, 7k	8e, 8k
$–CH_2Ph$	(Phe)	2f, 2l	3f, 3l	4f, 4l	7f, 7l	8f, 8l

Scheme 3. (i) ClCOCOCl, CH_2Cl_2, r.t; (ii) $SOCl_2$, MeOH; (iii) Et_3N, CH_2Cl_2; (iv) 4 M NaOH, MeOH, THF.

Table 1
Effects of target compounds on $1\alpha,25(OH)_2D_3$ induced TRAP(+)-OCL formation.

Compd	OCLs (%)	Compd	OCLs (%)	Compd	OCLs (%)
Control	$100.0 \pm 9.7^{\#}$	Normal	20.0 ± 10.0		
AS	0^{**}	**3a**	0^{**}	**7a**	$41.1 \pm 7.1^{**}$
OA (**1**)	$19.4 \pm 4.8^{**}$	**3b**	0^{**}	**7b**	$3.4 \pm 4.0^{**}$
2	$1.4 \pm 3.4^{**}$	**3c**	99.0 ± 7.6	**7c**	$27.8 \pm 8.3^{**}$
3	$51.1 \pm 6.2^{**}$	**3d**	$96.8 \pm 8.5^{**}$	**7d**	$2.8 \pm 1.7^{**}$
4	0^{**}	**3e**	98.4 ± 10.0	**7e**	$0.7 \pm 1.1^{**}$
5	0^{**}	**3f**	0^{**}	**7f**	$29.6 \pm 4.3^{**}$
6	0^{**}	**3g**	$9.0 \pm 8.3^{**}$	**7g**	$85.1 \pm 5.4^{**}$
7	$1.8 \pm 0.9^{**}$	**3h**	$21.0 \pm 12.4^{**}$	**7h**	$76.5 \pm 13^{**}$
8	0^{**}	**3i**	$6.1 \pm 7.2^{**}$	**7i**	$83.5 \pm 10.9^{**}$
9	$33.2 \pm 23.1^{**}$	**3j**	0^{**}	**7j**	$44.8 \pm 14.4^{**}$
11	$28.1 \pm 8.8^{**}$	**3k**	$84.4 \pm 10.3^{**}$	**7k**	$73.7 \pm 9.1^{**}$
12	$24.1 \pm 5.3^{**}$	**3l**	$58.0 \pm 26.1^{**}$	**7l**	$89.4 \pm 4.6^{**}$
2a	0^{**}	**4a**	0^{**}	**8a**	$20.7 \pm 8.7^{**}$
2b	$29.3 \pm 8.0^{**}$	**4b**	$10.1 \pm 3.8^{**}$	**8b**	$31.2 \pm 4.2^{**}$
2c	100.6 ± 0.7	**4c**	$21.1 \pm 6.0^{**}$	**8c**	$36.3 \pm 14.2^{**}$
2d	$92.9 \pm 6.0^{**}$	**4d**	$86.0 \pm 8.7^{**}$	**8d**	$14.0 \pm 6.1^{**}$
2e	$1.4 \pm 9.4^{**}$	**4e**	$82.4 \pm 18.6^{**}$	**8e**	$78.5 \pm 1.7^{**}$
2f	$82.3 \pm 8.5^{**}$	**4f**	$77.4 \pm 11.7^{**}$	**8f**	$34.2 \pm 10.5^{**}$
2g	103.0 ± 12.8	**4g**	0^{**}	**8g**	$91.9 \pm 6.3^{*}$
2h	100.0 ± 13.6	**4h**	0^{**}	**8h**	$96.5 \pm 8.9^{*}$
2i	99.8 ± 9.2	**4i**	0^{**}	**8i**	$42.8 \pm 6.0^{**}$
2j	100.6 ± 16.8	**4j**	0^{**}	**8j**	$45.9 \pm 10.6^{**}$
2k	100.3 ± 9.6	**4k**	0^{**}	**8k**	$30.6 \pm 7.5^{**}$
2l	$80.7 \pm 13.1^{**}$	**4l**	0^{**}	**8l**	$75.4 \pm 10.2^{**}$

Control: cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M). AS (alendronate sodium): cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M) and AS (20 μM). Normal: cultured without any additions. Samples: cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M) and each compound (20 μM). Each value was expressed as mean ± SD, $n = 4$. The data of control group were pegged as 100%, while other data were calculated relative to it. Data were analyzed by student's t test. Significant differences in TRAP(+)-OCLs compared with control group, * $p < 0.05$, ** $p < 0.01$, $^{\#}$ $p < 0.01$ versus normal group.

Table 2
Effects of selected compounds on $1\alpha,25(OH)_2D_3$ induced TRAP(+)-OCL formation.

Compd	OCLs (%)		Compd	OCLs (%)	
	2 μM	200 nM		2 μM	200 nM
Control	$100.0 \pm 6.2^{\#}$	$100.0 \pm 8.2^{\#}$	Normal	20.0 ± 7.4	20.0 ± 8.6
AS	$3.5 \pm 2.9^{**}$	$47.5 \pm 6.3^{**}$			
OA (**1**)	$89.5 \pm 10.2^{**}$	$97.5 \pm 4.6^{*}$	**4c**	$90.8 \pm 14.2^{**}$	
2	$79.2 \pm 12.0^{**}$		**4g**	$74.2 \pm 4.9^{**}$	
3	$94.6 \pm 9.6^{**}$		**4h**	$1.4 \pm 1.9^{**}$	98.3 ± 13.8
4	$13.0 \pm 3.7^{**}$	99.5 ± 8.3	**4i**	$80.0 \pm 3.2^{**}$	
5	$77.2 \pm 13.4^{**}$		**4j**	$71.6 \pm 3.7^{**}$	
6	$83.0 \pm 10.6^{**}$		**4k**	$86.9 \pm 12.6^{**}$	
7	$16.4 \pm 5.7^{**}$	97.6 ± 15.5	**4l**	$77.8 \pm 3.3^{**}$	
8	$72.7 \pm 8.0^{**}$		**7a**	$93.5 \pm 11.2^{**}$	
9	$39.2 \pm 5.2^{**}$	97.2 ± 15.5	**7b**	$3.8 \pm 6.9^{**}$	$93.7 \pm 12.2^{*}$
11	$76.2 \pm 6.1^{**}$		**7c**	$59.8 \pm 10.8^{**}$	$78.4 \pm 12.5^{**}$
12	$88.7 \pm 12.0^{**}$		**7d**	$1.7 \pm 2.2^{**}$	96.4 ± 10.7
2a	$27.2 \pm 10.9^{**}$	$31.7 \pm 9.1^{**}$	**7e**	$0.7 \pm 1.6^{**}$	101.0 ± 5.9
2b	$68.7 \pm 7.2^{**}$		**7f**	$82.8 \pm 7.9^{**}$	
2e	$94.0 \pm 8.3^{**}$		**7j**	$21.2 \pm 8.6^{**}$	100.2 ± 5.8
3a	$32.3 \pm 2.3^{**}$	$86.3 \pm 6.3^{**}$	**7k**	$16.2 \pm 5.9^{**}$	$52.6 \pm 17.9^{**}$
3b	99.4 ± 2.7		**8a**	$31.9 \pm 6.1^{**}$	$34.1 \pm 2.8^{**}$
3f	$69.2 \pm 4.9^{**}$		**8b**	$25.7 \pm 6.1^{**}$	$77.0 \pm 12.3^{**}$
3g	$95.2 \pm 7.5^{*}$		**8c**	$37.1 \pm 8.9^{**}$	$93.0 \pm 8.0^{**}$
3h	$90.2 \pm 4.6^{**}$		**8d**	$55.1 \pm 7.6^{**}$	$91.2 \pm 14.5^{*}$
3i	$70.8 \pm 6.1^{**}$		**8f**	$53.6 \pm 6.0^{**}$	$93.0 \pm 7.8^{**}$
3j	98.2 ± 4.0		**8i**	$47.3 \pm 5.6^{**}$	$57.5 \pm 4.8^{**}$
4a	$66.6 \pm 2.6^{**}$		**8j**	$58.3 \pm 7.2^{**}$	$86.3 \pm 7.3^{**}$
4b	$79.9 \pm 12.0^{**}$		**8k**	$58.7 \pm 8.7^{**}$	$95.0 \pm 8.0^{*}$

Control: cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M). AS (alendronate sodium): cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M) and AS. Normal: cultured without any additions. Samples: cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M) and each compound. Each value was expressed as mean ± SD, $n = 4$. The data of control group were pegged as 100%, while other data were calculated relative to it. Data were analyzed by student's t test. Significant differences in TRAP(+)-OCLs compared with control group, * $p < 0.05$, ** $p < 0.01$, $^{\#}$ $p < 0.01$ versus normal group.

Table 3
Recovery of TRAP(+)-OCLs from inhibition by selected compounds.

Compd	OCLs (%)		Compd	OCLs (%)	
	20 μM	2 μM		20 μM	2 μM
Control	100.0 ± 13.5	100.0 ± 8.5	**7c**	$73.1 \pm 8.0^{**}$	$77.6 \pm 8.2^{**}$
OA (**1**)	98.0 ± 5.6		**7d**		$95.7 \pm 4.3^{**}$
4	0^{**}	$73.3 \pm 6.8^{**}$	**7e**		$96.2 \pm 2.9^{**}$
7	$93.2 \pm 9.6^{**}$		**7f**	$89.5 \pm 5.3^{**}$	$95.6 \pm 3.9^{**}$
8	$92.6 \pm 5.3^{**}$		**7j**		$93.9 \pm 3.0^{**}$
9	$18.9 \pm 9.0^{**}$	$73.0 \pm 8.9^{**}$	**7k**		$81.3 \pm 3.5^{**}$
11	$94.5 \pm 2.2^{*}$		**8a**	$94.3 \pm 2.5^{*}$	
2a	$41.3 \pm 12.7^{**}$	$73.9 \pm 8.5^{**}$	**8b**	97.7 ± 5.4	
2d	100.2 ± 3.2		**8c**	$94.6 \pm 3.8^{*}$	
2f	99.1 ± 7.2		**8d**	97.3 ± 2.9	
3a	$82.9 \pm 9.0^{**}$	$96.1 \pm 3.2^{**}$	**8f**	$93.5 \pm 2.5^{**}$	
4f	$70.7 \pm 8.5^{**}$	$95.2 \pm 3.2^{**}$	**8i**		$70.6 \pm 8.9^{**}$
4h		$93.4 \pm 3.6^{**}$	**8j**	$92.3 \pm 5.0^{**}$	
7b		$96.1 \pm 5.4^{**}$	**8k**	$94.7 \pm 4.8^{*}$	

Control: cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M). Samples: cultured with $1\alpha,25(OH)_2D_3$ (10^{-8} M) and each compound (20 μM or 2 μM). Each value was expressed as mean ± SD, $n = 4$. The data of control group were pegged as 100%, while other data were calculated relative to it. Data were analyzed by student's t test. Significantly different from $1\alpha,25(OH)_2D_3$ alone, * $p < 0.05$, ** $p < 0.01$.

toxicity at 20 μM (see Supplementary data, Table 2). Most of the tested compounds with strong activity were reversed after removal of the compounds, suggesting that the compounds did not possess irreversible toxicity at 20 μM or 2 μM. However, only partial recovery was observed by removing 2 μM of compounds **2a**, **4**, **7c**, **7k**, **8i** and **9**. Because osteoblastic cells are essential for OCL formation [22], the toxic effect of those compounds (2 μM) on osteoblastic-like cells was examined using MTT assay. As shown in Table 4, no cytotoxicity on osteoblastic-like cells was confirmed, on the contrary, all of the compounds except for **7k** enhanced the differentiation of osteoblastic-like cells. These results suggested that those compounds might affect the differentiation of the bone marrow cells rather than impacting the collaboration of osteoblastic cells in OCL differentiation.

Taking the above results together, a preliminary SAR for OA derivatives could be outlined as follows: (1) A carbonyl group at C-3 of OA could enhance the activity. (2) It seems that a six-membered heterocyclic ring with two nitrogen atoms at C-2 and 3 positions of OA is relevant to the strong activity, while if the heterocyclic ring possessing one nitrogen atom, the compounds become less active. (3) Substituted groups at phenyl ring of indole moiety could promote the activity, while any substituents such as phenyl or NO_2 groups at six-membered heterocyclic moieties with two nitrogen atoms, should be detrimental to the activity. (4) A hydrophobic group (methyl ester) at the amino acid could elevate the activity, compared with those of the derivatives with amino acid. (5) The short chain length of amino acid, such as glycine and alanine seems

Table 4
Effects of compounds on viability of osteoblast-like cell.

Compd	Osteoblasts (%)
Control	100.0 ± 13.1
4	$132.1 \pm 7.4^{**}$
9	$134.0 \pm 13.3^{**}$
2a	$141.1 \pm 6.7^{**}$
7c	$141.6 \pm 6.7^{**}$
7k	109.4 ± 7.7
8i	$128.5 \pm 6.5^{*}$

Control: cultured without compounds. Samples: cultured with each compound (2 μM). Each value was expressed as mean ± SD, $n = 4$. The data of control group were pegged as 100%, while other data were calculated relative to it. Data were analyzed by student's t test. Significant differences compared to control group, * $p < 0.05$, ** $p < 0.01$.

to relate to a stronger activity, in other words, the amino acid with big molecular weights will render the derivative less active or inactive.

3. Conclusion

We have synthesized a novel series of heterocyclic oleanolic acid derivatives with inhibitory effect on OCL formation. Compounds **2a** and **8a** exhibited quite a potent activity even at 200 nM. Carbonyl group at C-3 and introducing heterocyclic ring with two nitrogen atoms enhanced the activity, and glycine and alanine substituents of the derivatives show benefits on improvement of the activity. The *in vivo* tests including PK profiles of **2a** and **8a** are in progress. We deem the oleanolic acid and its derivatives as a promising new class of anti-osteoporosis leads deserving of further studies.

4. Experimental

^{1}H and ^{13}C NMR spectra were taken on a Bruker Avance II 300 spectrometer with tetramethylsilane (TMS) as an internal standard and chemical shifts were recorded in δ values. The splitting pattern abbreviations are as follows: s = singlet, d = doublet, t = triplet and m = multiplet. Melting points were determined using X4 apparatus and uncorrected. ESI-MS spectra were obtained on a Finnigan TSQ-7000 mass spectrometer. All of the materials and reagents were obtained from commercial suppliers and were used without further purifications. Thin layer chromatography (TLC) was carried out on precoated Kieselgel F_{254} plates (0.25 mm), and spots were visualized under a UV lamp or by iodine spray to monitor all of the described reactions. The purities of all of the compounds were analyzed by HPLC methods (see Supplementary data).

ICR mice were used for activity evaluations. All procedures involving animals were approved by the Jiangsu Animal Care and Use Committee, China and followed the national and institutional rules considering animal experiments. Mice were housed in a climate-controlled room, 12 h light/dark photoperiod, water and food *ad libitium*.

4.1. Synthesis of compounds

4.1.1. Preparation of 3-keto OA (**2**)

To a solution of OA (**1**) (456 mg, 1 mmol) in $CHCl_3/CH_3COCH_3$ (2:1, 45 mL) in an ice bath was added Jones reagent dropwise until the color of the solution changed from orange to green, then stirred at room temperature for 10 min. After removal of the solvent, water was added to the resultant mixture. The aqueous mixture was extracted with a mixture of CH_2Cl_2/Et_2O (1:2) (3 × 40 mL). After removal of CH_2Cl_2/Et_2O, the residue was purified by column chromatography (silica gel; EtOAc/petroleum ether) to give **2** (417 mg, 92%). mp 187 °C; ^{1}H NMR ($CDCl_3$) δ 5.32 (1H, s, H-12), 2.85 (1H, dd, J = 3.0 Hz, J' = 15.0 Hz, H-18), 2.62–2.51 (1H, m, H-2), 2.45–2.33 (1H, m, H-2), 1.15 (s, CH_3), 1.10 (s, CH_3), 1.05 (s, CH_3), 1.03 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.82 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 217.7 (C-3), 184.2 (C-28), 143.6 (C-13), 122.3 (C-12), 55.3, 47.4, 46.6, 45.6, 41.7, 41.0, 39.2, 34.1, 30.7, 27.6, 26.4, 25.8, 23.5, 22.9, 21.4, 19.5, 17.0, 15.0; ESI-MS (negative) m/z: 453 $[M-H]^-$.

4.1.2. General method for Fischer indolization of OA (**3**–**6**)

A mixture of 3-keto OA (**2**, 0.19 mmol), phenylhydrazine (1.05 equiv, prepared from aniline [25]) in acetic acid (10 mL) was refluxed for 1 h under nitrogen atmosphere. The reaction mixture was pipetted into distilled water (50 mL) and then extracted with Et_2O (4 × 20 mL). After removing Et_2O, the residue was purified by column chromatography (silica gel; EtOAc/petroleum ether) to provide indole derivative **3**. Compounds **4**–**6** were prepared following the same protocol.

Compound ***3***: Yield 69%; mp 229–230 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (1H, s, N-H), 7.42 (1H, d, J = 6.0 Hz, Ar-H), 7.31–7.26 (1H, m, Ar-H), 7.13–7.03 (2H, m, Ar-H), 5.40 (1H, s, H-12), 2.87 (1H, dd, J = 3 Hz, J' = 15.0 Hz, H-18), 2.75 (1H, d, J = 15.3 Hz, H-1), 2.18 (1H, d, J = 15.3 Hz, H-1), 1.26 (s, CH_3), 1.19 (s, CH_3), 1.17 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.92 (s, CH_3), 0.83 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.5 (C-28), 143.3 (C-13), 140.8 (Ar-C), 136.0 (Ar-C), 128.2 (Ar-C), 122.8 (C-12), 120.9 (Ar-C), 118.8 (Ar-C), 117.9 (Ar-C), 110.3 (Ar-C), 106.8 (Ar-C), 53.1, 46.6, 46.3, 45.8, 41.7, 41.0, 39.4, 38.0, 36.7, 33.9, 33.0, 32.4, 32.1, 30.9, 30.6, 25.8, 23.5, 23.3, 22.9, 19.2, 16.9, 15.5; ESI-MS (negative) m/z: 526 $[M-H]^-$. This compound was already reported by Finlay et al. [15].

Compound ***4***: Yield 60%; mp 173 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (1H, s, N-H), 7.37 (1H, d, J = 3.0 Hz, Ar-H), 7.19 (1H, d, J = 6.0 Hz, Ar-H), 7.07–7.04 (1H, m, Ar-H), 5.40 (1H, s, H-12), 2.88 (1H, dd, J = 3.0 Hz, J' = 16.5 Hz, H-18), 2.70 (1H, d, J = 15.0 Hz, H-1), 1.28 (s, CH_3), 1.18 (s, CH_3), 1.15 (s, CH_3), 0.96 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.85 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.3 (C-28), 143.3 (C-13), 142.5 (Ar-C), 134.4 (Ar-C), 129.4 (Ar-C), 124.6 (Ar-C), 122.8 (C-12), 121.0 (Ar-C), 117.6 (Ar-C), 111.2 (Ar-C), 106.8 (Ar-C), 53.0, 46.6, 45.8, 41.8, 41.1, 39.4, 38.1, 36.5, 35.7, 34.0, 33.0, 32.5, 32.1, 30.9, 27.7, 25.8, 23.5, 23.3, 22.9, 19.2, 16.9, 15.5; ESI-MS (negative) m/z: 560 $[M-H]^-$.

Compound ***5***: Yield 60%; mp 251 °C; ^{1}H NMR ($CDCl_3$) δ 8.27 (1H, s, Ar-H), 7.95 (1H, s, N-H), 7.85 (1H, d, J = 9.0 Hz, Ar-H), 7.29–7.26 (1H, m, Ar-H), 5.41 (1H, s, H-12), 2.95 (1H, d, J = 12.0 Hz, H-18), 2.70 (1H, d, J = 15.2 Hz, H-1), 2.18 (1H, d, J = 15.2 Hz, H-1), 1.27 (s, CH_3), 1.20 (s, CH_3), 1.15 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.85 (s, CH_3), 0.82 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.6 (C-28), 173.3 (Ar-COOH), 143.0 (C-13), 142.3 (Ar-C), 139.3 (Ar-C), 127.9 (Ar-C), 122.8 (C-12), 121.8 (Ar-C), 119.6 (Ar-C), 109.8 (Ar-C), 108.4 (Ar-C), 53.0, 46.6, 41.7, 39.4, 37.9, 33.9, 33.0, 30.6, 27.6, 25.7, 23.5, 19.2, 15.4; ESI-MS (negative) m/z: 570 $[M-H]^-$.

Compound ***6***: Yield 61%; mp 200 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d, J = 2.5 Hz, Ar-H), 8.18 (1H, s, N-H), 8.06–8.02 (1H, m, Ar-H), 7.31–7.26 (1H, m, Ar-H), 5.41 (1H, t, J = 3.0 Hz, H-12), 2.90 (1H, dd, J = 3.0 Hz, J' = 15.0 Hz, H-18), 2.71 (1H, d, J = 15.2 Hz, H-1), 2.18 (1H, d, J = 15.2 Hz, H-1), 1.28 (s, CH_3), 1.19 (s, CH_3), 1.15 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.83 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 183.8 (C-28), 144.2 (Ar-C), 143.3 (C-13), 141.2 (Ar-C), 139.3 (Ar-C), 127.8 (Ar-C), 122.7 (C-12), 116.9 (Ar-C), 115.3 (Ar-C), 110.0 (Ar-C), 109.5 (Ar-C), 53.0, 46.6, 46.3, 45.7, 41.7, 41.1, 39.4, 38.0, 36.3, 33.8, 32.4, 30.7, 27.7, 25.7, 23.5, 23.3, 22.9, 19.2, 16.8, 15.5; ESI-MS (negative) m/z: 571 $[M-H]^-$.

4.1.3. General procedure for pyrazine and quinoxaline derivatives (***7***, ***8***, ***11***–***12***)

To a solution of 3-keto OA (**2**, 2.27 g, 5 mmol) in morpholine (20 mL) were added sulfur (1.50 g, 47 mmol) and each 1,2-diamine compound (25 mmol), and the reaction mixture was refluxed for 2–4 h. The mixture was poured into distilled water and then extracted with CH_2Cl_2 (3 × 80 mL). Organic layer was washed with H_2O, diluted aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, H_2O, dried with anhydrous Na_2SO_4, successively, and then evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc/petroleum ether) to yield the expected products **7** and **8**, respectively.

A mixture of 3-keto OA (**2**, 4.54 g, 10 mmol) and selenium dioxide (1.34 g, 1.2 mmol) in acetic acid (30 mL) was refluxed for 24 h. After cooling to room temperature, the reaction mixture was filtered and evaporated to dryness. The residue was dissolved in Et_2O and washed with brine. The organic layer was dried (anhydrous Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by column

chromatography (silica gel; Et_2OAc/petroleum ether) to get 2,3-diketo OA (**10**).

A mixture of **10** (468 mg, 1 mmol), each 1,2-diamine compound (1.50 mmol) and acetic acid (10 mL) was refluxed under nitrogen atmosphere for 2 h. The reaction solution was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel; Et_2OAc/petroleum ether) to obtain the expected products **11**, **12**, respectively.

Compound ***7***: Yield 70%; mp 267 °C; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, s, Ar-H), 8.28 (1H, s, Ar-H), 5.37 (1H, s, H-12), 3.0 (1H, d, $J = 15.0$ Hz, H-1), 2.87 (1H, dd, $J = 3.0$ Hz, $J' = 15.0$ Hz, H-18), 2.52 (1H, d, $J = 15.0$ Hz, H-1), 1.31 (s, CH_3), 1.28 (s, CH_3), 1.19 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.86 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 183.7 (C-28), 159.8 (Ar-C), 150.4 (Ar-C), 143.5 (C-13), 142.4 (Ar-C), 141.2 (Ar-C), 122.4 (H-12), 53.1, 48.1, 46.7, 45.9, 41.9, 41.3, 39.3, 36.7, 33.2, 31.7, 30.8, 27.8, 25.9, 24.3, 23.7, 20.2, 16.9, 15.6; ESI-MS m/z: 490 $[M + H]^+$.

Compound ***8***: Yield 67%; mp 152 °C; ^{1}H NMR ($CDCl_3$) δ 8.03–7.96 (2H, m, Ar-H), 7.68–7.64 (2H, m, Ar-H), 5.39 (1H, t, $J = 3.0$ Hz, H-12), 3.26 (1H, d, $J = 15.0$ Hz, H-1), 2.88 (1H, dd, $J = 3.0$ Hz, $J' = 15.0$ Hz, H-18), 2.66 (1H, d, $J = 15.0$ Hz, H-1), 1.39 (s, CH_3), 1.38 (s, CH_3), 1.19 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.84 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.0 (C-28), 161.2 (Ar-C), 152.0 (Ar-C), 143.6 (C-13), 142.3 (Ar-C), 140.7 (Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.0 (Ar-C), 122.7 (C-12), 53.6, 49.3, 46.7, 45.7, 42.0, 41.2, 40.5, 39.4, 37.0, 34.0, 33.2, 32.4, 30.8, 27.8, 25.9, 25.5, 23.7, 20.5, 16.9, 15.7; ESI-MS (negative) m/z: 539 $[M - H]^-$.

Compound ***11***: Yield 53%; mp 238 °C; ^{1}H NMR ($CDCl_3$) δ 7.43–7.26 (10H, m, Ar-H), 5.39 (1H, s, H-12), 3.02–2.83 (2H, m, H-1 and H-18), 1.39 (s, CH_3), 1.28 (s, CH_3), 1.19 (s, CH_3), 1.18 (s, CH_3), 0.97 (s, CH_3), 0.93 (s, CH_3), 0.89 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.3 (C-28), 164.9 (Ar-C), 161.8 (Ar-C), 149.7 (Ar-C), 148.7 (Ar-C), 143.2 (C-13), 139.8 (Ar-C), 139.6 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 123.2 (C-12), 46.6, 45.7, 45.5, 43.1, 41.3, 40.8, 33.8, 33.0, 32.4, 30.6, 28.4, 27.8, 26.4, 25.5, 23.5, 22.6, 22.0, 18.4, 18.2, 17.2; ESI-MS (negative) m/z: 641 $[M - H]^-$.

Compound ***12***: Yield 44%; mp 176 °C; ^{1}H NMR ($CDCl_3$) δ 8.96 (1H, s, Ar-H), 8.47–8.41 (2H, m, Ar-H), 5.40 (1H, s, H-12), 3.28 (1H, d, $J = 15.0$ Hz, H-1), 2.90 (1H, dd, $J = 3.0$ Hz, $J' = 15.0$ Hz, H-18), 2.64 (1H, d, $J = 15.0$ Hz, H-1), 1.38 (s, CH_3), 1.28 (s, CH_3), 1.19 (s, CH_3), 1.15 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.83 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.2 (C-28), 164.0 (Ar-C), 155.8 (Ar-C), 147.0 (Ar-C), 143.6 (Ar-C), 143.3 (C-13), 140.8 (Ar-C), 129.6 (Ar-C), 125.4 (Ar-C), 122.4 (C-12), 53.2, 49.5, 46.6, 45.7, 41.8, 40.7, 39.2, 36.9, 33.8, 30.7, 27.6, 25.8, 23.5, 20.3, 16.7, 15.8; ESI-MS (negative) m/z: 584 $[M - H]^-$.

4.1.4. Preparation of 2,3-quinoline OA (*9*)

To a solution of *o*-nitrobenzaldehyde (588 mg, 3.89 mmol) in EtOH/AcOH/H_2O (2:2:1, 25 mL) were added iron powder (650 mg, 11.61 mmol) and concentrated hydrochloric acid (0.2 mL). The reaction mixture was refluxed for 15 min and then stirred at room temperature for 40 min, filtered, and extracted with EtOAc (3×50 mL). The organic layer was washed with saturated $NaHCO_3$ (3×30 mL) and brine (40 mL), dried over Na_2SO_4, and then purified by chromatography to produce *o*-aminobenzaldehyde. To a mixture of *o*-aminobenzaldehyde (250 mg, 1.45 mmol) and **2** (658 mg, 1.45 mmol) in absolute EtOH (15 mL) under nitrogen atmosphere was added saturated ethanolic KOH (0.5 mL) dropwise, and the mixture was refluxed for 24 h. After cooling to room temperature, the solution was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with water and dried over $MgSO_4$, removal of the solvent gave the crude product, further purification of the product by silica gel chromatography with EtOAc/petroleum ether provided compound **9** (72% yield). mp 294 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, d, $J = 3.0$ Hz, Ar-H), 7.71–7.67 (2H, m, Ar-H), 7.61–7.56 (1H, m, Ar-H), 7.44–7.39 (1H, m, Ar-H), 5.38 (1H, t, $J = 3.0$ Hz, H-12), 2.96–2.85 (2H, m, H-1 and H-18), 2.54 (1H, d, $J = 15.0$ Hz, H-1), 1.38 (s, CH_3), 1.28 (s, CH_3), 1.20 (s, CH_3), 0.96 (s, CH_3), 0.95 (s, CH_3), 0.92 (s, CH_3), 0.88 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.1 (C-28), 166.0 (Ar-C), 147.3 (Ar-C), 143.7 (C-13), 135.3 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 128.0 (Ar-C), 126.9 (Ar-C), 126.5 (Ar-C), 125.4 (Ar-C), 122.5 (C-12), 53.9, 46.7, 45.6, 41.9, 41.1, 40.2, 39.2, 36.3, 33.8, 33.1, 30.7, 27.7, 25.8, 23.6, 20.4, 16.7, 15.0; ESI-MS (negative) m/z: 538 $[M - H]^-$.

4.1.5. General synthetic procedure for compounds *2a–l*, *3a–l*, *4a–l*, *7a–l* and *8a–l*

The target compounds were synthesized with the route outlined in Scheme 3. To a solution of **2** (2.72 g, 6 mmol) in anhydrous CH_2Cl_2 (40 mL) was added oxalyl chloride (2.2 mL) and stirred at room temperature for 24 h. The mixture was concentrated to dryness under reduced pressure. Hexane (3×50 mL) was added to the residue, then the solution was concentrated to dryness (this procedure was repeated three times) to give acid chloride. To an anhydrous CH_2Cl_2 (200 mL) solution of each corresponding amino acid methyl ester (6.60 mmol) and triethylamine (3.4 mL) was added the above acid chloride. The reaction mixture was stirred at room temperature for 2 h, and then concentrated and chromatographed to yield compounds **2a–f**.

The above compounds **2a–f** (3 mmol) were treated with 4 M NaOH (16 mL) in CH_3OH–THF (1:1.5, 75 mL) at room temperature overnight. The solutions were neutralized with 2 M HCl, then extracted with CH_2Cl_2 to provide compounds **2g–l**, respectively. Compounds **3a–l**, **4a–l**, **7a–l**, **8a–l** were synthesized with the same protocol as **2a–l** from **3**, **4**, **7** and **8**, respectively. Data of compounds **2a–l**, **3a–l**, **4a–l**, **7a–l** and **8a–l** are summarized in Table 5.

4.2. Formation of OCLs

A co-culture assay using mouse bone marrow cells and osteoblast-like cells was used for the evaluation of the effects of the compounds on OCL formation (Takahashi et al. [22]). Briefly, osteoblast-like cells were prepared from calvaria of 2-day-old ICR mice. Mouse bone marrow cells were obtained from tibiae of 6-week-old male ICR mouse. Osteoblast-like cells (1×10^4/well) and bone marrow cells (1×10^5/well) were co-cultured for 6 days with 1α,25(OH)$_2$D$_3$ (10^{-8} M) and each compound. The medium was replaced every 2 days. After 6 days, adherent cells on the well surface were fixed with 10% formalin-phosphate buffered saline (PBS, pH = 7.2) for 10 min and dehydrated with ethanol–acetone (1:1, v/v) for 1 min. The cells were stained by tartrate-resistant acid phosphatase (TRAP) for 12 min at room temperature and TRAP-positive cells containing three or more nuclei were counted. The percentages of TRAP(+)-OCLs cultured with compounds were compared to that only with 1α,25(OH)$_2$D$_3$ group.

4.3. Recovery assay

Recovery experiment was performed as described above. The cells were treated with 1α,25(OH)$_2$D$_3$ (10^{-8} M) and each compound for the first 2 days. Thereafter each compound was removed from the medium and the cells were cultured with 1α,25(OH)$_2$D$_3$ (10^{-8} M) only.

4.4. Osteoblast viability

The cell viability of osteoblasts was determined by means of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Osteoblast-like cells (5×10^3/well) were cultured with each compound in 96-well. The control group was cultured without

Table 5
Data of compounds **2a–l**, **3a–l**, **4a–l**, **7a–l** and **8a–l**.

No.	Yield (%)	Mp (°C)	ESI-MS m/z	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
				(δ ppm) J = Hz	(δ ppm)
2a	89	101	526 $[M+H]^+$; 548 $[M+Na]^+$	6.52 (1H, t, J = 6.0, N-H), 5.47 (1H, s, H-12), 4.16–4.09 (1H, m, H-2′), 3.86–3.80 (1H, m, H-2′), 3.76 (3H, s, CH_3), 2.66–2.53 (2H, m, H-2 and H-18), 2.40–2.34 (1H, m, H-2), 1.17 (s, CH_3), 1.08 (s, CH_3), 1.04 (s, CH_3), 1.03 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.76 (s, CH_3)	217.6 (C-3), 178.2 (COO), 170.5 (CON), 144.3 (C-13), 123.0 (C-12), 55.3, 52.3, 47.4, 42.4, 42.0, 39.3, 37.5, 34.1, 34.0, 32.9, 32.3, 31.9, 27.2, 26.5, 25.6, 24.6, 23.8, 23.6, 21.4, 19.5, 18.1, 16.3
2b	90	103	540 $[M+H]^+$; 562 $[M+Na]^+$	6.53 (1H, d, J = 6.0, N-H), 5.36 (1H, s, H-12), 4.39–4.35 (1H, m, H-2′), 3.64 (3H, s, CH_3), 2.62 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.54–2.47 (1H, m, H-2), 2.30–2.24 (1H, m, H-2), 1.15 (s, CH_3), 1.10 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.82 (s, CH_3)	217.3 (C-3), 177.2 (COO), 173.4 (CON), 143.6 (C-13), 122.8 (C-12), 55.1, 52.2, 47.4, 47.2, 46.6, 46.2, 42.5, 39.7, 36.5, 33.9, 32.8, 32.6, 30.5, 26.8, 25.9, 23.8, 21.5, 19.8, 17.6, 16.3, 15.4
2c	86	215	568 $[M+H]^+$; 590 $[M+Na]^+$	6.42 (1H, d, J = 6.0, N-H), 5.46 (1H, s, H-12), 4.46 (1H, s, H-2′), 3.72 (3H, s, CH_3), 2.67 (1H, dd, J = 3.0, J' = 13.8, H-18), 2.57–2.49 (1H, m, H-2), 2.40–2.35 (1H, m, H-2), 1.15 (s, CH_3), 1.09 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.78 (s, CH_3)	218.0 (C-3), 178.0 (COO), 172.8 (CON), 144.1 (C-13), 123.4 (C-12), 57.6, 55.6, 52.1, 47.2, 46.8, 42.6, 39.5, 34.5, 33.6, 33.3, 32.5, 32.1, 27.7, 26.8, 24.0, 23.9, 21.8, 19.9, 19.1, 18.6, 17.0, 15.4
2d	85	146	582 $[M+H]^+$; 604 $[M+Na]^+$	6.33 (1H, d, J = 6.0, N-H), 5.44 (1H, t, J = 3.0, H-12), 4.55–4.53 (1H, m, H-2′), 3.71 (3H, s, CH_3), 2.65 (1H, dd, J = 3.0, J' = 13.8, H-18), 2.58–2.50 (1H, m, H-2), 2.39–2.30 (1H, m, H-2), 1.16 (s, CH_3), 1.09 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.95 (s, CH_3), 0.93 (s, CH_3), 0.82 (s, CH_3).	217.6 (C-3), 177.5 (COO), 173.5 (CON), 143.9 (C-13), 122.9 (C-12), 55.2, 52.1, 50.9, 47.4, 46.8, 46.5, 46.3, 42.1, 42.0, 39.3, 39.2, 36.7, 34.1, 32.9, 32.1, 30.7, 27.3, 26.4, 25.5, 25.0, 23.8, 23.6
2e	89	98	582 $[M+H]^+$; 604 $[M+Na]^+$	6.46 (1H, d, J = 6.0, N-H), 5.45 (1H, s, H-12), 4.52 (1H, t, J = 3.0, H-2′), 3.71 (3H, s, CH_3), 2.66 (1H, dd, J = 3.0, J' = 13.8, H-18), 2.58–2.50 (1H, m, H-2), 2.39–2.31 (1H, m, H-2), 1.15 (s, CH_3), 1.08 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.79 (s, CH_3)	217.7 (C-3), 177.4 (COO), 172.3 (CON), 143.8 (C-13), 123.0 (C-12), 56.2, 55.2, 52.0, 51.9, 48.9, 47.6, 47.4, 46.8, 46.5, 46.1, 42.7, 42.2, 41.4, 39.8, 39.4, 39.2, 38.2, 37.5, 36.7, 34.1, 33.1, 32.6, 30.7, 26.6, 25.8, 23.5, 21.5, 19.8, 16.9, 15.3, 11.7
2f	90	82	616 $[M+H]^+$; 638 $[M+Na]^+$	7.28–7.23 (3H, m, Ar-H), 7.11–7.08 (2H, m, Ar-H), 6.38 (1H, d, J = 6.0, N-H), 5.30 (1H, s, H-12), 4.77–4.75 (1H, m, H-2′), 3.70 (3H, s, CH_3), 3.17–3.01 (2H, m, H-3′), 2.59–2.49 (2H, m, H-2 and H-18), 2.39–2.31 (1H, m, H-2), 1.16 (s, CH_3), 1.08 (s, CH_3), 1.05 (s, CH_3), 1.03 (s, CH_3), 0.94 (s, CH_3), 0.89 (s, CH_3), 0.79 (s, CH_3)	217.6 (C-3), 177.5 (COO), 172.0 (CON), 143.7 (C-13), 136.1 (Ar-C), 129.3 (Ar-C), 128.4 (Ar-C), 127.0 (Ar-C), 123.0 (C-12), 55.2, 53.3, 52.1, 47.4, 46.8, 46.4, 42.0, 41.9, 39.3, 36.6, 34.1, 32.9, 32.6, 32.0, 27.2, 26.4, 25.5, 23.7, 23.5, 19.2, 16.8, 15.4
2g	90	140	511 $[M+H]^+$	6.70 (1H, s, N-H), 5.48 (1H, s, H-12), 4.14–3.86 (2H, m, H-2′), 2.62–2.53 (2H, m, H-2 and H-18), 2.41–2.35 (1H, m, H-2), 1.15 (s, CH_3), 1.07 (s, CH_3), 1.04 (s, CH_3), 1.03 (s, CH_3), 0.95 (s, CH_3), 0.91 (s, CH_3), 0.77 (s, CH_3).	218.1 (C-3), 179.8 (COO), 172.0 (CON), 144.2 (C-13), 123.5 (C-12), 57.2, 55.3, 49.7, 47.6, 46.5, 42.3, 41.3, 39.5, 36.8, 34.2, 33.1, 32.3, 30.8, 26.6, 25.8, 23.7, 21.6, 19.7, 18.8, 16.5, 15.2
2h	89	134	526 $[M+H]^+$	6.68 (1H, d, J = 6.0, N-H), 5.46 (1H, s, H-12), 4.47–4.43 (1H, m, H-2′), 2.62–2.52 (2H, m, H-2 and H-18), 2.39–2.30 (1H, m, H-2), 1.16 (s, CH_3), 1.09 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.95 (s, CH_3), 0.91 (s, CH_3), 0.82 (s, CH_3)	218.1 (C-3), 179.4 (COO), 175.3 (CON), 144.0 (C-13), 123.5 (C-12), 55.3, 48.9, 47.5, 46.9, 46.4, 42.2, 39.5, 36.8, 34.2, 33.1, 32.1, 30.8, 26.6, 25.7, 23.7, 21.5, 19.6, 17.9, 16.6, 15.2
2i	91	232	554 $[M+H]^+$; 576 $[M+Na]^+$	6.53 (1H, d, J = 6.0, N-H), 5.46 (1H, t, J = 3.0, H-12), 4.47 (1H, t, J = 3.0, H-2′), 2.62–2.52 (2H, m, H-2 and H-18), 2.39–2.30 (1H, m, H-2), 1.16 (s, CH_3), 1.09 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.98 (s, CH_3), 0.97 (s, CH_3), 0.78 (s, CH_3)	217.9 (C-3), 179.1 (COO), 175.4 (CON), 143.9 (C-13), 123.4 (C-12), 57.4, 55.3, 47.6, 46.9, 42.3, 39.5, 36.8, 34.2, 33.0, 30.8, 26.6, 25.7, 23.6, 21.6, 19.1, 18.1, 16.8, 15.2
2j	86	142	568 $[M+H]^+$	6.33 (1H, d, J = 6.0, N-H), 5.44 (1H, t, J = 3.0, H-12), 4.55–4.53 (1H, m, H-2′), 2.65 (1H, dd, J = 3.0, J' = 13.8, H-18), 2.58–2.50 (1H, m, H-2), 2.39–2.30 (1H, m, H-2), 1.15 (s, CH_3), 1.09 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.82 (s, CH_3)	218.4 (C-3), 179.3 (COO), 175.4 (CON), 143.8 (C-13), 123.4 (C-12), 56.6, 55.3, 42.3, 39.5, 37.6, 36.8, 33.1, 30.8, 26.6, 23.6, 16.8, 15.3, 11.8
2k	88	142	568 $[M+H]^+$	6.55 (1H, d, J = 6.0, N-H), 5.45 (1H, s, H-12), 4.53–4.50 (1H, m, H-2′), 2.67 (1H, dd, J = 3.0, J' = 13.8, H-18), 2.58–2.50 (1H, m, H-2), 2.39–2.31 (1H, m, H-2), 1.16 (s, CH_3), 1.09 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.79 (s, CH_3)	218.1 (C-3), 178.3 (COO), 175.4 (CON), 143.9 (C-13), 123.4 (C-12), 56.6, 55.3, 47.6, 46.9, 42.9, 39.5, 37.6, 36.8, 34.2, 33.1, 30.8, 26.6, 25.7, 23.6, 21.6, 19.7, 16.8, 15.3, 11.8
2l	90	128	602 $[M+H]^+$	7.31–7.17 (5H, m, Ar-H), 6.44 (1H, d, J = 6.0, N-H), 5.23 (1H, s, H-12), 4.71–4.69 (1H, m, H-2′), 3.30–3.06 (2H, m, H-3′), 2.59–2.50 (2H, m, H-2 and H-18), 2.39–2.30 (1H, m, H-2), 1.15 (s, CH_3), 1.08 (s, CH_3), 1.05 (s, CH_3), 1.03 (s, CH_3), 0.94 (s, CH_3), 0.92 (s, CH_3), 0.79 (s, CH_3)	218.2 (C-3), 179.8 (COO), 173.7 (CON), 143.6 (C-13), 135.8 (Ar-C), 129.5 (Ar-C), 128.8 (Ar-C), 127.4 (Ar-C), 123.5 (C-12), 55.2, 53.8, 47.6, 46.5, 42.3, 40.3, 39.4, 36.7, 34.3, 33.0, 30.8, 27.3, 26.5, 25.6, 25.1, 23.5, 23.1, 22.3, 21.6, 16.7, 15.3
3a	84	140	621 $[M+Na]^+$	7.81 (1H, s, N-H), 7.46–7.43 (1H, m, Ar-H), 7.34–7.28 (1H, m, Ar-H), 7.16–7.08 (2H, m, Ar-H), 6.61 (1H, s, N-H), 5.60 (1H, s, H-12), 4.18 (1H, dd, J = 3.0, J' = 15.0, H-2′), 3.90–3.78 (4H, m, CH_3 and H-2′), 2.80 (1H, d, J = 15.0, H-1), 2.72 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.18 (1H, d, J = 15.0, H-1), 1.26 (s, CH_3), 1.20 (s, CH_3), 1.19 (s, CH_3), 1.17 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.83 (s, CH_3)	178.4 (COO), 170.5 (CON), 144.0 (C-13), 140.8 (Ar-C), 136.1 (Ar-C), 128.1 (Ar-C), 123.6 (C-12), 120.9 (Ar-C), 118.8 (Ar-C), 117.9 (Ar-C), 110.4 (Ar-C), 106.7 (Ar-C), 52.4, 47.5, 46.4, 42.1, 41.5, 39.5, 38.0, 36.7, 34.0, 32.3, 31.8, 30.8, 27.3, 25.6, 23.3, 21.5, 16.2, 15.7
3b	87	129	635 $[M+Na]^+$	7.84 (1H, s, N-H), 7.42 (1H, d, J = 6.0, Ar-H), 7.30–7.25 (1H, m, Ar-H), 7.11–7.05 (2H, m, Ar-H), 6.64 (1H, d, J = 6.0, N-H), 5.55 (1H, s, H-12), 4.50–4.46 (1H, m, H-2′), 3.74 (3H, s, CH_3), 2.82 (1H, d, J = 15.0, H-1), 2.74 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.18 (1H, d, J = 15.0, H-1), 1.28 (s, CH_3), 1.18 (s, CH_3), 1.16 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.84 (s, CH_3)	177.6 (COO), 173.6 (CON), 143.6 (C-13), 140.9 (Ar-C), 136.1 (Ar-C), 128.1 (Ar-C), 123.6 (C-12), 120.9 (Ar-C), 118.8 (Ar-C), 117.9 (Ar-C), 110.4 (Ar-C), 106.7 (Ar-C), 52.4, 48.4, 46.3, 42.2, 39.5, 36.0, 34.0, 30.8, 27.4, 25.6, 23.6, 18.7, 16.4, 15.5
3c	89	122	663 $[M+Na]^+$	7.86 (1H, s, N-H), 7.45 (1H, d, J = 6.0, Ar-H), 7.33–7.25 (1H, m, Ar-H), 7.16–7.08 (2H, m, Ar-H), 6.50 (1H, d, J = 6.0, N-H), 5.58 (1H, s, H-12), 4.50 (1H, t, J = 6.0, H-2′), 3.73 (3H, s, CH_3), 2.82 (1H, d, J = 15.0, H-1), 2.74 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.18 (1H, d, J = 15.0, H-1), 1.27 (s, CH_3), 1.19 (s, CH_3), 1.16 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.83 (s, CH_3)	178.2 (COO), 172.7 (CON), 143.9 (C-13), 141.2 (Ar-C), 136.5 (Ar-C), 128.6 (Ar-C), 123.9 (C-12), 121.3 (Ar-C), 119.2 (Ar-C), 118.3 (Ar-C), 110.7 (Ar-C), 107.1 (Ar-C), 57.7, 53.5, 52.3, 47.1, 46.9, 46.7, 42.8, 37.2, 34.5, 33.6, 33.4, 32.6, 32.1, 31.3, 27.8, 25.9, 24.1, 23.9, 23.6, 19.1, 18.7, 16.9, 16.0
3d	82	145	655 $[M+H]^+$; 677 $[M+Na]^+$	7.82 (1H, s, N-H), 7.42 (1H, d, J = 6.0, Ar-H), 7.30–7.25 (1H, m, Ar-H), 7.11–7.05 (2H, m, Ar-H), 6.40 (1H, d, J = 6.0, N-H), 5.54 (1H, s, H-12), 4.56 (1H, d, J = 6.0, H-2′), 3.70 (3H, s, CH_3), 2.85 (1H, d, J = 15.2, H-1), 2.74 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.18 (1H, d, J = 15.2, H-1), 1.26 (s, CH_3), 1.18 (s, CH_3), 1.17 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.85 (s, CH_3)	177.6 (COO), 173.4 (CON), 143.6 (C-13), 140.8 (Ar-C), 136.1 (Ar-C), 128.2 (Ar-C), 123.5 (C-12), 120.9 (Ar-C), 118.8 (Ar-C), 117.9 (Ar-C), 110.3 (Ar-C), 106.7 (Ar-C), 55.2, 53.1, 52.1, 51.0, 46.8, 46.6, 46.3, 42.2, 41.9, 39.5, 39.2, 36.8, 34.1, 33.9, 33.0, 32.9, 30.9, 27.4, 26.4, 25.5, 23.9, 23.6, 22.7, 22.4, 21.4, 19.3, 16.6, 15.6
3e	88	148	655 $[M+H]^+$; 677 $[M+Na]^+$	7.80 (1H, s, N-H), 7.42 (1H, d, J = 6.0, Ar-H), 7.30–7.25 (1H, m, Ar-H), 7.13–7.03 (2H, m, Ar-H), 6.52 (1H, d, J = 6.0, N-H), 5.55 (1H, t, J = 3.0, H-12), 4.53 (1H, t, J = 6.0, H-2′), 3.70 (3H, s, CH_3), 2.82 (1H, d, J = 15.0, H-1), 2.72 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.16 (1H, d, J = 15.0, H-1), 1.23 (s, CH_3), 1.18 (s, CH_3), 1.16 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.84 (s, CH_3)	177.7 (COO), 172.3 (CON), 143.5 (C-13), 140.9 (Ar-C), 136.1 (Ar-C), 128.1 (Ar-C), 123.6 (C-12), 120.9 (Ar-C), 118.8 (Ar-C), 117.9 (Ar-C), 110.4 (Ar-C), 106.7 (Ar-C), 56.3, 53.1, 52.0, 46.7, 42.2, 39.5, 38.2, 36.8, 34.0, 33.1, 32.2, 30.8, 27.5, 25.5, 19.3, 16.5, 15.2, 11.6

Table 5 (*continued*)

No.	Yield (%)	Mp (°C)	ESI-MS *m/z*	^{1}H NMR ($CDCl_3$) (δ ppm) J = Hz	^{13}C NMR ($CDCl_3$) (δ ppm)
3f	89	158	689 $[M+H]^+$	7.79 (1H, s, N-H), 7.41 (1H, d, J = 6.0, Ar-H), 7.30–7.02 (8H, m, Ar-H), 6.44 (1H, d, J = 6.0, N-H), 5.40 (1H, s, H-12), 4.78–4.75 (1H, m, H-2′), 3.70 (3H, s, CH_3), 3.23–3.06 (2H, m, H-3′), 2.75 (1H, d, J = 15.2, H-1), 2.52 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.14 (1H, d, J = 15.2, H-1), 1.26 (s, CH_3), 1.19 (s, CH_3), 1.15 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.83 (s, CH_3)	177.7 (COO), 171.9 (CON), 143.4 (C-13), 140.8 (Ar-C), 136.1 (Ar-C), 129.4 (Ar-C), 128.5 (Ar-C), 127.1 (Ar-C), 123.6 (C-12), 120.9 (Ar-C), 118.8 (Ar-C), 117.9 (Ar-C), 110.4 (Ar-C), 106.7 (Ar-C), 53.5, 53.1, 52.2, 47.4, 46.6, 46.3, 42.1, 39.5, 38.0, 36.8, 34.0, 33.0, 32.6, 32.0, 30.7, 27.3, 25.5, 23.4, 16.2, 15.6, 15.1
3g	86	226	585 $[M+H]^+$; 607 $[M+Na]^+$	7.76 (1H, s, N-H), 7.42 (1H, d, J = 6.0, Ar-H), 7.31–7.26 (1H, m, Ar-H), 7.14–7.05 (2H, m, Ar-H), 6.76 (1H, s, N-H), 5.57 (1H, t, J = 3.0, H-12), 4.11 (1H, dd, J = 3.0, J' = 15.0, H-2′), 3.92 (1H, dd, J = 3.0, J' = 15.0, H-2′), 2.77 (1H, d, J = 15.0, H-1), 2.65 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.20 (1H, d, J = 15.0, H-1), 1.26 (s, CH_3), 1.20 (s, CH_3), 1.19 (s, CH_3), 1.17 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.82 (s, CH_3)	180.0 (COO), 172.1 (CON), 144.0 (C-13), 140.9 (Ar-C), 136.2 (Ar-C), 128.3 (Ar-C), 124.0 (C-12), 121.1 (Ar-C), 119.0 (Ar-C), 118.0 (Ar-C), 110.5 (Ar-C), 106.8 (Ar-C), 53.2, 46.6, 42.3, 39.6, 38.1, 34.1, 33.1, 30.8, 27.4, 25.7, 23.7, 23.4, 19.4, 16.3, 15.8
3h	89	220	599 $[M+H]^+$; 621 $[M+Na]^+$	7.84 (1H, s, N-H), 7.42 (1H, d, J = 6.0, Ar-H), 7.31–7.26 (1H, m, Ar-H), 7.13–7.06 (2H, m, Ar-H), 6.70 (1H, d, J = 6.0, N-H), 5.56 (1H, t, J = 3.0, H-12), 4.47–4.43 (1H, m, H-2′), 2.78 (1H, d, J = 15.0, H-1), 2.62 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.20 (1H, d, J = 15.0, H-1), 1.28 (s, CH_3), 1.22 (s, CH_3), 1.18 (s, CH_3), 1.16 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.81 (s, CH_3)	180.0 (COO), 175.0 (CON), 143.8 (C-13), 140.9 (Ar-C), 136.3 (Ar-C), 128.3 (Ar-C), 124.1 (C-12), 121.1 (Ar-C), 119.0 (Ar-C), 118.0 (Ar-C), 110.5 (Ar-C), 106.8 (Ar-C), 53.2, 49.0, 47.6, 46.5, 42.4, 39.7, 38.1, 36.8, 34.1, 33.1, 30.8, 27.4, 25.7, 23.6, 21.6, 19.4, 17.7, 16.5, 15.8
3i	90	223	627 $[M+H]^+$; 649 $[M+Na]^+$	7.83 (1H, s, N-H), 7.43 (1H, d, J = 6.0, Ar-H), 7.31–7.29 (1H, m, Ar-H), 7.12–7.03 (2H, m, Ar-H), 6.54 (1H, d, J = 6.0, N-H), 5.56 (1H, s, H-12), 4.45 (1H, t, J = 6.0, H-2′), 2.80 (1H, d, J = 15.0, H-1), 2.62 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.18 (1H, d, J = 15.0, H-1), 1.28 (s, CH_3), 1.18 (s, CH_3), 1.17 (s, CH_3), 0.98 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.81 (s, CH_3)	179.6 (COO), 174.9 (CON), 143.7 (C-13), 140.9 (Ar-C), 136.3 (Ar-C), 128.3 (Ar-C), 124.0 (C-12), 121.1 (Ar-C), 119.0 (Ar-C), 118.0 (Ar-C), 110.5 (Ar-C), 106.8 (Ar-C), 57.5, 53.3, 47.1, 46.4, 42.5, 39.7, 38.1, 34.1, 33.0, 31.1, 30.8, 27.5, 25.6, 23.4, 19.2, 18.0, 16.8, 15.8
3j	88	208	641 $[M+H]^+$; 663 $[M+Na]^+$	7.80 (1H, s, N-H), 7.42 (1H, d, J = 6.0, Ar-H), 7.31–7.26 (1H, m, Ar-H), 7.14–7.03 (2H, m, Ar-H), 6.49 (1H, d, J = 6.0, N-H), 5.54 (1H, t, J = 3.0, H-12), 4.49–4.42 (1H, m, H-2′), 2.80 (1H, d, J = 15.0, H-1), 2.60 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.17 (1H, d, J = 15.0, H-1), 1.30 (s, CH_3), 1.21 (s, CH_3), 1.17 (s, CH_3), 0.96 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.82 (s, CH_3)	180.3 (COO), 174.7 (CON), 144.0 (C-13), 140.9 (Ar-C), 136.3 (Ar-C), 128.3 (Ar-C), 124.1 (C-12), 121.1 (Ar-C), 119.0 (Ar-C), 118.0 (Ar-C), 110.5 (Ar-C), 106.8 (Ar-C), 53.2, 51.8, 46.7, 42.5, 40.4, 39.6, 38.1, 36.8, 34.1, 33.0, 30.8, 27.4, 25.6, 25.2, 23.1, 22.3, 19.4, 16.7, 15.8
3k	90	206	641 $[M+H]^+$; 663 $[M+Na]^+$	7.85 (1H, s, N-H), 7.43 (1H, d, J = 6.0, Ar-H), 7.31–7.26 (1H, m, Ar-H), 7.11–7.05 (2H, m, Ar-H), 6.58 (1H, d, J = 6.0, N-H), 5.56 (1H, s, H-12), 4.53 (1H, t, J = 3.0, H-2′), 2.80 (1H, d, J = 15.0, H-1), 2.62 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.16 (1H, d, J = 15.0, H-1), 1.28 (s, CH_3), 1.18 (s, CH_3), 1.16 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.84 (s, CH_3)	178.9 (COO), 175.6 (CON), 143.6 (C-13), 140.8 (Ar-C), 136.3 (Ar-C), 128.3 (Ar-C), 123.9 (C-12), 121.1 (Ar-C), 119.0 (Ar-C), 118.0 (Ar-C), 110.5 (Ar-C), 106.8 (Ar-C), 56.5, 53.3, 47.0, 46.4, 42.4, 39.7, 38.1, 34.1, 33.0, 30.8, 27.5, 25.6, 23.4, 19.4, 16.8, 15.8, 15.5, 11.7
3l	91	205	675 $[M+H]^+$; 697 $[M+Na]^+$	7.77 (1H, s, N-H), 7.41–7.06 (9H, m, Ar-H), 6.40 (1H, d, J = 6.0, N-H), 5.29 (1H, t, J = 3.0, H-12), 4.70–4.64 (1H, m, H-2′), 3.23–3.06 (2H, m, H-3′), 2.76 (1H, d, J = 15.1, H-1), 2.52 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.12 (1H, d, J = 15.1, H-1), 1.28 (s, CH_3), 1.19 (s, CH_3), 1.15 (s, CH_3), 0.89 (s, CH_3), 0.88 (s, CH_3), 0.74 (s, CH_3), 0.73 (s, CH_3)	181.0 (COO), 172.8 (CON), 143.6 (C-13), 140.9 (Ar-C), 136.3 (Ar-C), 135.8 (Ar-C), 129.5 (Ar-C), 129.0 (Ar-C), 128.3 (Ar-C), 127.5 (Ar-C), 124.1 (C-12), 121.1 (Ar-C), 119.0 (Ar-C), 118.0 (Ar-C), 110.5 (Ar-C), 106.8 (Ar-C), 54.1, 53.2, 46.7, 42.0, 39.6, 38.1, 36.3, 34.1, 32.9, 31.1, 30.7, 27.3, 25.6, 23.4, 19.3, 16.4, 15.8
4a	85	162	633 $[M+H]^+$; 678 $[M+2Na]^+$	7.91 (1H, s, N-H), 7.37 (1H, d, J = 3.0, Ar-H), 7.20 (1H, d, J = 6.0, Ar-H), 7.07–7.04 (1H, m, Ar-H), 6.59 (1H, s, N-H), 5.58 (1H, s, H-12), 4.17 (1H, dd, J = 3.0, J' = 15.0, H-2′), 3.84 (1H, dd, J = 3.0, J' = 15.0, H-2′), 3.76 (3H, s, CH_3), 2.75–2.60 (2H, m, H-1 and H-18), 2.16 (1H, d, J = 15.3, H-1), 1.30 (s, CH_3), 1.22 (s, CH_3), 1.21 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.85 (s, CH_3)	178.5 (COO), 170.6 (CON), 144.2 (C-13), 142.6 (Ar-C), 134.5 (Ar-C), 129.4 (Ar-C), 124.6 (Ar-C), 123.6 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.8 (Ar-C), 53.0, 52.5, 46.5, 42.4, 42.2, 41.6, 39.6, 38.1, 36.7, 34.2, 33.1, 32.5, 30.9, 27.4, 25.7, 23.7, 19.4, 16.3, 15.7
4b	83	118	669 $[M+Na]^+$	7.83 (1H, s, N-H), 7.37 (1H, s, Ar-H), 7.21 (1H, d, J = 6.0, Ar-H), 7.06–7.04 (1H, m, Ar-H), 6.64 (1H, d, J = 6.0, N-H), 5.57 (1H, s, H-12), 4.51–4.47 (1H, m, H-2′), 3.74 (3H, s, CH_3), 2.82 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.72 (1H, d, J = 15.0, H-1), 2.12 (1H, d, J = 15.0, H-1), 1.29 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.84 (s, CH_3)	177.7 (COO), 173.7 (CON), 143.7 (C-13), 142.6 (Ar-C), 134.6 (Ar-C), 129.5 (Ar-C), 124.7 (Ar-C), 123.6 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.9 (Ar-C), 53.2, 53.1, 52.5, 48.6, 48.5, 46.6, 46.4, 42.3, 42.1, 41.5, 39.7, 38.2, 36.8, 34.3, 33.1, 32.3, 31.0, 27.5, 25.9, 25.7, 23.7, 17.9, 15.7
4c	87	161	675 $[M+H]^+$; 720 $[M+2Na]^+$	7.84 (1H, s, N-H), 7.37 (1H, d, J = 3.0, Ar-H), 7.20 (1H, d, J = 6.0, Ar-H), 7.07–7.03 (1H, m, Ar-H), 6.47 (1H, d, J = 6.0, N-H), 5.56 (1H, s, H-12), 4.47 (1H, t, J = 3.0, H-2′), 3.71 (3H, s, CH_3), 2.75–2.65 (2H, m, H-1 and H-18), 2.19 (1H, d, J = 15.3, H-1), 1.28 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.84 (s, CH_3)	177.9 (COO), 172.4 (CON), 143.6 (C-13), 142.6 (Ar-C), 134.6 (Ar-C), 129.5 (Ar-C), 124.7 (Ar-C), 123.6 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.9 (Ar-C), 57.4, 53.2, 52.1, 46.9, 42.5, 42.3, 39.6, 38.1, 36.8, 34.3, 33.4, 31.9, 30.9, 27.6, 23.8, 23.4, 18.4, 15.8
4d	89	119	689 $[M+H]^+$; 711 $[M+Na]^+$	7.79 (1H, s, N-H), 7.37 (1H, d, J = 3.0, Ar-H), 7.20 (1H, d, J = 6.0, Ar-H), 7.07–7.04 (1H, m, Ar-H), 6.39 (1H, d, J = 6.0, N-H), 5.54 (1H, t, J = 3.0, H-12), 4.59–4.53 (1H, m, H-2′), 3.71 (3H, s, CH_3), 2.75–2.61 (2H, m, H-1 and H-18), 2.17 (1H, d, J = 15.3, H-1), 1.29 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.83 (s, CH_3)	177.8 (COO), 173.6 (CON), 143.8 (C-13), 142.6 (Ar-C), 134.6 (Ar-C), 129.5 (Ar-C), 124.7 (Ar-C), 123.5 (C-12), 121.2 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.9 (Ar-C), 53.2, 52.2, 51.2, 46.7, 46.6, 42.4, 42.1, 39.6, 38.1, 36.8, 34.3, 33.1, 33.0, 32.2, 31.0, 30.8, 27.5, 25.6, 25.1, 24.0, 23.7, 23.4, 22.5, 20.6, 16.9, 15.8
4e	88	160	711 $[M+Na]^+$	7.95 (1H, s, N-H), 7.37 (1H, d, J = 3.0, Ar-H), 7.20 (1H, d, J = 6.0, Ar-H), 7.07–7.04 (1H, m, Ar-H), 6.54 (1H, d, J = 6.0, N-H), 5.56 (1H, t, J = 3.0, H-12), 4.53 (1H, t, J = 6.0, H-2′), 3.70 (3H, s, CH_3), 2.74–2.69 (2H, m, H-1 and H-18), 2.16 (1H, d, J = 15.3, H-1), 1.29 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.85 (s, CH_3)	177.7 (COO), 172.3 (CON), 143.6 (C-13), 142.6 (Ar-C), 134.5 (Ar-C), 129.4 (Ar-C), 124.6 (Ar-C), 123.6 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.8 (Ar-C), 56.4, 53.1, 52.1, 46.8, 46.4, 42.3, 39.6, 38.3, 38.1, 36.7, 34.2, 33.1, 31.0, 30.9, 27.6, 25.7, 25.6, 23.6, 19.4, 16.6, 15.7, 15.3, 11.7
4f	85	165	745 $[M+Na]^+$	7.78 (1H, s, N-H), 7.39–7.06 (8H, m, Ar-H), 6.46 (1H, d, J = 6.0, N-H), 5.42 (1H, s, H-12), 4.83–4.77 (1H, m, H-2′), 3.72 (3H, s, CH_3), 3.25–3.05 (2H, m, H-3′), 2.75 (1H, d, J = 15.0, H-1), 2.54 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.13 (1H, d, J = 15.0, H-1), 1.29 (s, CH_3), 1.22 (s, CH_3), 1.21 (s, CH_3), 0.96 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.84 (s, CH_3)	177.7 (COO), 171.9 (CON), 143.4 (C-13), 142.5 (Ar-C), 136.1 (Ar-C), 134.6 (Ar-C), 129.3 (Ar-C), 128.5 (Ar-C), 127.1 (Ar-C), 124.5 (Ar-C), 123.5 (C-12), 121.0 (Ar-C), 117.5 (Ar-C), 111.3 (Ar-C), 106.7 (Ar-C), 53.4, 52.2, 46.5, 42.1, 39.5, 37.9, 34.0, 33.0, 32.7, 30.7, 27.3, 25.5, 23.3, 19.2, 16.2, 15.6
4g	88	250	641 $[M+Na]^+$	7.89 (1H, s, N-H), 7.35 (1H, d, J = 3.0, Ar-H), 7.18 (1H, d, J = 6.0, Ar-H), 7.05–7.02 (1H, m, Ar-H), 6.57 (1H, t, J = 6.0, N-H), 5.55 (1H, t, J = 3.0, H-12), 4.15 (1H, dd, J = 3.0, J' = 15.0, H-2′), 3.83 (1H, dd, J = 3.0, J' = 15.0, H-2′), 2.71–2.60 (2H, m, H-1 and H-18), 2.16 (1H, d, J = 15.3, H-1), 1.29 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.96 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.84 (s, CH_3)	179.7 (COO), 171.9 (CON), 144.2 (C-13), 142.6 (Ar-C), 134.5 (Ar-C), 129.4 (Ar-C), 124.6 (Ar-C), 123.6 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.8 (Ar-C), 53.0, 52.5, 46.5, 42.2, 38.1, 34.2, 30.9, 27.4, 25.7, 23.7, 19.4, 16.3

(*continued on next page*)

Table 5 (*continued*)

No.	Yield (%)	Mp (°C)	ESI-MS *m/z*	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
				(δ ppm) J = Hz	(δ ppm)
4h	88	234	633 $[M+H]^+$; 655 $[M+Na]^+$	7.85 (1H, s, N-H), 7.38 (1H, d, J = 3.0, Ar-H), 7.20 (1H, d, J = 6.0, Ar-H), 7.07–7.03 (1H, m, Ar-H), 6.65 (1H, d, J = 6.0, N-H), 5.56 (1H, t, J = 3.0, H-12), 4.55–4.41 (1H, m, H-2′), 2.70 (1H, d, J = 15.0, H-1), 2.58 (1H, dd, J = 3.0, J' = 13.5, H-18), 1.29 (s, CH_3), 1.20 (s, CH_3), 1.19 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.79 (s, CH_3)	180.5 (COO), 174.6 (CON), 144.0 (C-13), 142.5 (Ar-C), 134.5 (Ar-C), 129.4 (Ar-C), 124.6 (Ar-C), 124.0 (C-12), 121.2 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.7 (Ar-C), 53.0, 49.1, 46.5, 46.4, 46.2, 42.3, 39.6, 38.0, 36.8, 34.1, 33.0, 30.8, 27.3, 25.6, 24.1, 23.6, 23.4, 17.4, 16.4, 15.7
4i	89	204	661 $[M+H]^+$	7.83 (1H, s, N-H), 7.36 (1H, d, J = 3.0, Ar-H), 7.19 (1H, d, J = 6.0, Ar-H), 7.06–7.03 (1H, m, Ar-H), 6.46 (1H, d, J = 6.0, N-H), 5.55 (1H, t, J = 3.0, H-12), 4.49–4.45 (1H, m, H-2′), 2.73–2.68 (2H, m, H-1 and H-18), 2.18 (1H, d, J = 15.0, H-1), 1.29 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.96 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.84 (s, CH_3)	180.0 (COO), 173.5 (CON), 143.6 (C-13), 142.6 (Ar-C), 134.6 (Ar-C), 129.5 (Ar-C), 124.7 (Ar-C), 123.6 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.9 (Ar-C), 57.4, 52.1, 46.9, 42.5, 39.6, 38.1, 36.8, 34.4, 33.5, 31.8, 30.9, 27.8, 23.7, 23.4, 18.4, 15.7
4j	90	197	697 $[M+Na]^+$	7.86 (1H, s, N-H), 7.37 (1H, d, J = 3.0, Ar-H), 7.22–7.19 (1H, m, Ar-H), 7.07–7.03 (1H, m, Ar-H), 6.49 (1H, d, J = 6.0, N-H), 5.54 (1H, t, J = 3.0, H-12), 4.48–4.42 (1H, m, H-2′), 2.70 (1H, d, J = 15.0, H-1), 2.60 (1H, dd, J = 3.0, J' = 13.5, H-18), 2.16 (1H, d, J = 15.0, H-1), 1.28 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.96 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.81 (s, CH_3)	180.6 (COO), 174.5 (CON), 144.0 (C-13), 142.5 (Ar-C), 134.5 (Ar-C), 129.4 (Ar-C), 124.6 (Ar-C), 123.5 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.7 (Ar-C), 55.3, 53.0, 51.7, 46.6, 42.4, 39.6, 38.1, 36.7, 34.2, 33.0, 30.8, 25.6, 25.1, 23.1, 22.2, 21.6, 16.7, 15.8, 15.3
4k	90	224	697 $[M+Na]^+$	7.94 (1H, s, N-H), 7.38 (1H, d, J = 3.0, Ar-H), 7.20 (1H, d, J = 6.0, Ar-H), 7.07–7.03 (1H, m, Ar-H), 6.57 (1H, d, J = 6.0, N-H), 5.57 (1H, s, H-12), 4.52 (1H, t, J = 6.0, H-2′), 2.72 (1H, d, J = 15.0, H-1), 2.59 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.16 (1H, d, J = 15.0, H-1), 1.29 (s, CH_3), 1.20 (s, CH_3), 1.19 (s, CH_3), 0.96 (s, CH_3), 0.95 (s, CH_3), 0.94 (s, CH_3), 0.83 (s, CH_3)	179.0 (COO), 175.7 (CON), 143.6 (C-13), 142.5 (Ar-C), 134.6 (Ar-C), 129.4 (Ar-C), 124.6 (Ar-C), 123.8 (C-12), 121.1 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.7 (Ar-C), 56.4, 53.1, 46.9, 42.4, 39.6, 38.1, 34.2, 33.0, 30.8, 25.6, 23.4, 19.4, 16.7, 15.8, 15.4, 11.7
4l	88	223	731 $[M+Na]^+$	7.85 (1H, s, N-H), 7.38–7.04 (8H, m, Ar-H), 6.41 (1H, d, J = 6.0, N-H), 5.28 (1H, s, H-12), 4.69–4.63 (1H, m, H-2′), 3.35–3.03 (2H, m, H-3′), 2.69 (1H, d, J = 15.0, H-1), 2.25 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.12 (1H, d, J = 15.0, H-1), 1.28 (s, CH_3), 1.21 (s, CH_3), 1.20 (s, CH_3), 0.97 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.81 (s, CH_3)	179.5 (COO), 171.4 (CON), 143.5 (C-13), 142.5 (Ar-C), 135.8 (Ar-C), 134.6 (Ar-C), 129.5 (Ar-C), 128.9 (Ar-C), 127.5 (Ar-C), 124.7 (Ar-C), 124.0 (C-12), 121.2 (Ar-C), 117.6 (Ar-C), 111.4 (Ar-C), 106.7 (Ar-C), 54.1, 53.0, 46.7, 42.2, 39.5, 38.0, 36.7, 34.1, 32.9, 30.7, 27.2, 25.6, 23.4, 19.3, 16.3, 15.7
7a	87	116	562 $[M+H]^+$; 584 $[M+Na]^+$	8.42 (1H, d, J = 3.0, Ar-H), 8.27 (1H, d, J = 3.0, Ar-H), 6.54 (1H, d, J = 6.0, N-H), 5.54 (1H, t, J = 3.0, H-12), 4.14 (1H, dd, J = 3.0, J' = 15.0, H-2′), 3.84 (1H, dd, J = 3.0, J' = 15.0, H-2′), 3.76 (3H, s, CH_3), 3.0 (1H, d, J = 15.0, H-1), 2.67 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.52 (1H, d, J = 15.0, H-1), 1.30 (s, CH_3), 1.29 (s, CH_3), 1.21 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.80 (s, CH_3), 0.73 (s, CH_3)	178.4 (COO), 170.7 (CON), 159.9 (Ar-C), 150.5 (Ar-C), 144.3 (C-13), 142.5 (Ar-C), 141.4 (Ar-C), 123.3 (C-12), 52.9, 52.5, 48.3, 46.6, 46.5, 45.8, 42.4, 42.3, 41.6, 39.5, 39.4, 36.6, 34.2, 33.1, 32.5, 31.8, 30.9, 27.4, 25.7, 24.3, 23.7, 23.6, 20.2, 16.1, 15.6
7b	89	107	598 $[M+Na]^+$	8.43 (1H, d, J = 3.0, Ar-H), 8.27 (1H, d, J = 3.0, Ar-H), 6.61 (1H, d, J = 6.0, N-H), 5.52 (1H, t, J = 3.0, H-12), 4.51–4.43 (1H, m, H-2′), 3.73 (3H, s, CH_3), 3.00 (1H, d, J = 15.0, H-1), 2.68 (1H, dd, J = 3.0, J' = 12.0, H-18), 2.53 (1H, d, J = 15.0, H-1), 1.31 (s, CH_3), 1.29 (s, CH_3), 1.21 (s, CH_3), 0.92 (s, CH_3), 0.91 (s, CH_3), 0.90 (s, CH_3), 0.80 (s, CH_3)	177.5 (COO), 173.8 (CON), 160.0 (Ar-C), 150.5 (Ar-C), 143.8 (C-13), 142.5 (Ar-C), 141.2 (Ar-C), 123.2 (C-12), 52.9, 52.5, 48.4, 48.2, 46.4, 45.8, 42.2, 39.5, 36.6, 34.2, 31.8, 30.8, 27.4, 25.7, 24.3, 23.7, 20.2, 18.8, 16.3, 15.6
7c	86	103	604 $[M+H]^+$; 649 $[M+2Na]^+$	8.42 (1H, s, Ar-H), 8.27 (1H, s, Ar-H), 6.43 (1H, d, J = 6.0, N-H), 5.52 (1H, s, H-12), 4.46 (1H, t, J = 6.0, H-2′), 3.70 (3H, s, CH_3), 3.00 (1H, d, J = 15.0, H-1), 2.69 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.50 (1H, d, J = 15.0, H-1), 1.30 (s, CH_3), 1.29 (s, CH_3), 1.21 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.91 (s, CH_3), 0.78 (s, CH_3)	177.9 (COO), 172.5 (CON), 159.8 (Ar-C), 150.6 (Ar-C), 143.7 (C-13), 142.5 (Ar-C), 141.5 (Ar-C), 123.3 (C-12), 57.3, 53.0, 52.1, 48.4, 45.8, 42.4, 39.4, 36.6, 34.3, 31.9, 30.9, 27.5, 25.6, 24.3, 23.6, 20.2, 18.9, 18.4, 16.6, 15.6
7d	83	132	618 $[M+H]^+$; 640 $[M+Na]^+$	8.42 (1H, d, J = 3.0, Ar-H), 8.27 (1H, d, J = 3.0, Ar-H), 6.36 (1H, d, J = 6.0, N-H), 5.51 (1H, t, J = 3.0, H-12), 4.58–4.51 (1H, m, H-2′), 3.70 (3H, s, CH_3), 3.00 (1H, d, J = 15.0, H-1), 2.70–2.63 (1H, m, H-18), 2.50 (1H, d, J = 15.0, H-1), 1.31 (s, CH_3), 1.30 (s, CH_3), 1.21 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.91 (s, CH_3), 0.81 (s, CH_3)	177.7 (COO), 173.6 (CON), 159.8 (Ar-C), 150.5 (Ar-C), 143.9 (C-13), 142.5 (Ar-C), 141.4 (Ar-C), 123.2 (C-12), 53.0, 52.3, 51.1, 48.3, 46.5, 45.8, 42.3, 39.4, 36.6, 33.1, 31.8, 30.8, 27.4, 25.1, 25.6, 24.3, 23.6, 22.5, 20.2, 16.5, 15.8
7e	87	110	640 $[M+Na]^+$	8.41 (1H, d, J = 3.0, Ar-H), 8.27 (1H, d, J = 3.0, Ar-H), 6.48 (1H, d, J = 6.0, N-H), 5.52 (1H, s, H-12), 4.54–4.50 (1H, m, H-2′), 3.69 (3H, s, CH_3), 2.98 (1H, d, J = 15.0, H-1), 2.50 (1H, d, J = 15.0, H-1), 1.30 (s, CH_3), 1.29 (s, CH_3), 1.20 (s, CH_3), 0.92 (s, CH_3), 0.91 (s, CH_3), 0.88 (s, CH_3), 0.77 (s, CH_3)	177.6 (COO), 172.4 (CON), 159.8 (Ar-C), 150.6 (Ar-C), 143.7 (C-13), 142.5 (Ar-C), 141.5 (Ar-C), 123.3 (C-12), 56.3, 53.0, 52.0, 48.3, 46.7, 46.5, 46.2, 45.8, 42.6, 42.4, 39.4, 38.3, 36.6, 34.2, 33.1, 31.7, 30.8, 27.4, 25.6, 24.6, 24.3, 23.8, 20.2, 16.5, 15.3, 11.7
7f	83	127	652 $[M+H]^+$	8.42 (1H, d, J = 3.0, Ar-H), 8.27 (1H, d, J = 3.0, Ar-H), 7.28–7.09 (5H, m, Ar-H), 6.41 (1H, d, J = 6.0, N-H), 5.37 (1H, t, J = 3.0, H-12), 4.80–4.74 (1H, m, H-2′), 3.69 (3H, s, CH_3), 3.21–3.07 (2H, m, H-3′), 2.96 (1H, d, J = 15.0, H-1), 2.72 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.50 (1H, d, J = 15.0, H-1), 1.31 (s, CH_3), 1.30 (s, CH_3), 1.18 (s, CH_3), 0.88 (s, CH_3), 0.87 (s, CH_3), 0.86 (s, CH_3), 0.72 (s, CH_3)	177.7 (COO), 172.1 (CON), 159.8 (Ar-C), 150.6 (Ar-C), 143.6 (C-13), 142.5 (Ar-C), 141.4 (Ar-C), 136.1 (Ar-C), 129.4 (Ar-C), 128.6 (Ar-C), 127.2 (Ar-C), 123.3 (C-12), 53.4, 52.9, 52.3, 48.3, 46.5, 45.8, 45.7, 42.2, 42.1, 41.9, 41.3, 39.5, 39.3, 37.8, 36.7, 36.5, 34.2, 33.9, 32.7, 31.9, 29.8, 27.3, 25.8, 24.3, 23.5, 16.3, 15.9
7g	86	172	548 $[M+H]^+$; 570 $[M+Na]^+$	8.54 (1H, s, Ar-H), 8.13 (1H, s, Ar-H), 7.02 (1H, s, N-H), 5.69 (1H, s, H-12), 4.10–3.94 (2H, m, H-2′), 3.79 (1H, d, J = 15.0, H-1), 2.68 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.50 (1H, d, J = 15.0, H-1), 1.30 (s, CH_3), 1.29 (s, CH_3), 1.21 (s, CH_3), 0.96 (s, CH_3), 0.94 (s, CH_3), 0.85 (s, CH_3), 0.84 (s, CH_3)	178.7 (COO), 172.0 (CON), 161.7 (Ar-C), 150.3 (Ar-C), 144.0 (C-13), 143.3 (Ar-C), 138.7 (Ar-C), 124.1 (C-12), 53.0, 47.0, 46.5, 42.9, 42.4, 39.8, 39.5, 36.2, 33.2, 31.8, 30.9, 27.4, 25.5, 24.3, 20.1, 15.8
7h	88	152	561 $[M+H]^+$	8.52 (1H, d, J = 3.0, Ar-H), 8.14 (1H, d, J = 3.0, Ar-H), 7.12 (1H, d, J = 6.0, N-H), 5.67 (1H, t, J = 3.0, H-2), 4.45–4.41 (1H, m, H-2′), 3.64 (1H, d, J = 15.0, H-1), 2.65 (1H, dd, J = 3.0, J' = 12.0, H-18), 2.49 (1H, d, J = 15.0, H-1), 1.30 (s, CH_3), 1.25 (s, CH_3), 1.24 (s, CH_3), 0.94 (s, CH_3), 0.93 (s, CH_3), 0.80 (s, CH_3), 0.79 (s, CH_3)	178.1 (COO), 175.0 (CON), 161.6 (Ar-C), 150.2 (Ar-C), 143.6 (C-13), 143.3 (Ar-C), 124.0 (C-12), 52.9, 48.5, 46.6, 45.8, 42.3, 39.7, 36.3, 33.2, 31.8, 30.9, 25.7, 24.2, 24.1, 18.8, 15.8
7i	83	172	590 $[M+H]^+$; 612 $[M+Na]^+$	8.50 (1H, s, Ar-H), 8.27 (1H, s, Ar-H), 6.77 (1H, d, J = 6.0, N-H), 5.62 (1H, s, H-12), 4.49 (1H, t, J = 6.0, H-2′), 3.24 (1H, d, J = 15.0, H-1), 2.68 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.53 (1H, d, J = 15.0, H-1), 1.29 (s, CH_3), 1.27 (s, CH_3), 1.21 (s, CH_3), 0.95 (s, CH_3), 0.92 (s, CH_3), 0.80 (s, CH_3), 0.79 (s, CH_3)	178.0 (COO), 173.5 (CON), 161.1 (Ar-C), 149.8 (Ar-C), 143.5 (C-13), 143.2 (Ar-C), 139.7 (Ar-C), 123.6 (C-12), 57.3, 52.8, 47.1, 46.9, 45.7, 42.6, 42.2, 39.6, 39.4, 36.4, 34.1, 33.2, 33.1, 31.7, 30.9, 27.6, 25.7, 24.2, 23.9, 23.2, 20.1, 18.8
7j	83	140	604 $[M+H]^+$; 626 $[M+Na]^+$	8.51 (1H, s, Ar-H), 8.23 (1H, s, Ar-H), 6.83 (1H, d, J = 6.0, N-H), 5.63 (1H, t, J = 3.0, H-12), 4.59–4.53 (1H, m, H-2′), 3.36 (1H, d, J = 15.0, H-1), 2.67–2.63 (1H, m, H-18), 2.52 (1H, d, J = 15.0, H-1), 1.33 (s, CH_3), 1.28 (s, CH_3), 0.91 (s, CH_3), 0.82 (s, CH_3), 0.81 (s, CH_3)	177.9 (COO), 174.6, 161.2 (Ar-C), 149.9 (Ar-C), 143.6 (C-13), 143.3 (Ar-C), 139.5 (Ar-C), 123.7 (C-12), 52.8, 51.3, 46.7, 45.7, 42.3, 39.6, 39.4, 36.3 33.2, 31.8, 30.9, 27.5, 25.1, 24.3, 23.9, 22.9, 16.0, 15.9

Table 5 (*continued*)

No.	Yield (%)	Mp (°C)	ESI-MS *m/z*	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
				(δ ppm) J = Hz	(δ ppm)
7k	86	136	604 $[M+H]^+$; 626 $[M+Na]^+$	8.50 (1H, d, J = 3.0, Ar-H), 8.26 (1H, d, J = 3.0, Ar-H), 6.84 (1H, d, J = 6.0, N-H), 5.62 (1H, t, J = 3.0, H-12), 4.54 (1H, t, J = 3.0, H-2′), 3.26 (1H, d, J = 15.0, H-1), 2.67 (1H, dd, J = 3.0, J' = 12.0, H-18), 2.53 (1H, d, J = 15.0, H-1), 1.26 (s, CH_3), 1.23 (s, CH_3), 0.90 (s, CH_3), 0.89 (s, CH_3), 0.81 (s, CH_3), 0.80 (s, CH_3)	177.7 (COO), 173.4 (CON), 161.1 (Ar-C), 149.8 (Ar-C), 143.6 (C-13), 143.3 (Ar-C), 139.6 (Ar-C), 123.6 (C-12), 56.4, 52.8, 47.0, 45.7, 42.2, 39.6, 39.4, 38.4, 36.4, 31.8, 30.9, 25.7, 24.3, 23.9, 20.1, 16.1, 15.8, 15.3, 12.0
7l	89	151	638 $[M+H]^+$; 660 $[M+Na]^+$	8.53 (1H, s, Ar-H), 8.19 (1H, s, Ar-H), 7.26–7.20 (5H, m, Ar-H), 6.71 (1H, d, J = 6.0, N-H), 5.26 (1H, s, H-12), 4.80 (1H, s, H-2′), 3.47 (1H, d, J = 15.0, H-1), 3.30–3.21 (2H, m, H-3′), 2.40–2.35 (2H, m, H-1 and H-18), 1.31 (s, CH_3), 1.24 (s, CH_3), 1.20 (s, CH_3), 0.93 (s, CH_3), 0.86 (s, CH_3), 0.74 (s, CH_3), 0.72 (s, CH_3)	178.7 (COO), 172.5 (CON), 161.5 (Ar-C), 150.2 (Ar-C), 143.2 (C-13), 143.0 (Ar-C), 139.2 (Ar-C), 136.6 (Ar-C), 129.9 (Ar-C), 128.3 (Ar-C), 127.0 (Ar-C), 124.2 (C-12), 53.4, 53.1, 46.8, 45.8, 42.5, 42.4, 39.7, 39.5, 37.4, 36.3, 34.3, 30.8, 27.5, 25.4, 24.3, 23.6, 16.2, 15.8
8a	85	134	612 $[M+H]^+$; 634 $[M+Na]^+$	8.02–7.94 (2H, m, Ar-H), 7.67–7.63 (2H, m, Ar-H), 6.56 (1H, s, N-H), 5.56 (1H, s, H-12), 4.15 (1H, dd, J = 6.0, J' = 18.0, H-2′), 3.88–3.81 (1H, m, H-2′), 3.75 (3H, s, CH_3), 3.23 (1H, d, J = 15.0, H-1), 2.69–2.63 (2H, m, H-1 and H-18), 1.42 (s, CH_3), 1.30 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.91 (s, CH_3), 0.81 (s, CH_3)	178.4 (COO), 170.6 (CON), 161.1 (Ar-C), 151.9 (Ar-C), 144.2 (C-13), 142.2 (Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.1 (Ar-C), 123.3 (C-12), 53.4, 52.5, 49.4, 46.5, 45.6, 42.2, 41.6, 40.4, 39.3, 36.9, 34.2, 33.1, 32.4, 30.8, 27.3, 25.7, 25.4, 23.6, 20.4, 16.2, 15.8
8b	83	97	626 $[M+H]^+$; 648 $[M+Na]^+$	8.03–7.98 (2H, m, Ar-H), 7.67–7.64 (2H, m, Ar-H), 6.61 (1H, d, J = 6.0, N-H), 5.54 (1H, s, H-12), 4.52–4.45 (1H, m, H-2′), 3.73 (3H, s, CH_3), 3.25 (1H, d, J = 15.0, H-1), 2.71–2.64 (2H, m, H-1 and H-18), 1.42 (s, CH_3), 1.38 (s, CH_3), 1.23 (s, CH_3), 0.92 (s, CH_3), 0.91 (s, CH_3), 0.82 (s, CH_3)	177.6 (COO), 173.8 (CON), 161.2 (Ar-C), 151.9 (Ar-C), 143.8 (C-13), 142.3 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.0 (Ar-C), 123.3 (C-12), 53.5, 52.5, 48.4, 46.4, 45.6, 42.2, 40.5, 39.5, 36.9, 34.2, 33.1, 32.5, 30.9, 25.7, 23.7, 20.5, 18.8, 16.4, 15.8
8c	86	108	654 $[M+H]^+$; 676 $[M+Na]^+$	8.01–7.94 (2H, m, Ar-H), 7.65–7.63 (2H, m, Ar-H), 6.43 (1H, d, J = 6, N-H), 5.54 (1H, s, H-12), 4.46 (1H, t, J = 6, H-2′), 3.68 (3H, s, CH_3), 3.23 (1H, d, J = 15, H-1), 2.71–2.62 (2H, m, H-1 and H-18), 1.42 (s, CH_3), 1.22 (s, CH_3), 0.92 (s, CH_3), 0.91 (s, CH_3), 0.82 (s, CH_3)	177.8 (COO), 172.5 (CON), 161.1 (Ar-C), 152.0 (Ar-C), 143.6 (C-13), 142.2 (Ar-C), 140.8 (Ar-C), 128.9 (Ar-C), 128.9 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 123.3 (C-12), 57.3, 53.8, 53.1, 46.9, 45.6, 42.6, 40.6, 39.5, 36.5, 33.2, 32.5, 30.8, 25.3, 23.7, 20.4, 16.4, 15.9
8d	88	134	668 $[M+H]^+$; 690 $[M+Na]^+$	8.03–7.96 (2H, m, Ar-H), 7.67–7.64 (2H, m, Ar-H), 6.36 (1H, d, J = 6.0, N-H), 5.53 (1H, s, H-12), 4.59–4.52 (1H, m, H-2′), 3.70 (3H, s, CH_3), 3.25 (1H, d, J = 15.0, H-1), 2.69–2.64 (2H, m, H-1 and H-18), 1.43 (s, CH_3), 1.24 (s, CH_3), 0.92 (s, CH_3), 0.90 (s, CH_3), 0.81 (s, CH_3)	177.7 (COO), 173.6 (CON), 163.0 (Ar-C), 161.2 (Ar-C), 151.9 (Ar-C), 143.8 (C-13), 142.3 (Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.0 (Ar-C), 123.3 (C-12), 53.5, 52.3, 51.1, 46.6, 45.6, 42.4, 42.0, 40.5, 39.4, 37.0, 33.1, 32.5, 30.9, 27.4, 25.6, 25.1, 23.6, 22.9, 22.5, 16.5, 15.8
8e	83	98	668 $[M+H]^+$; 690 $[M+Na]^+$	8.02–7.94 (2H, m, Ar-H), 7.67–7.63 (2H, m, Ar-H), 6.49 (1H, d, J = 6.0, N-H), 5.54 (1H, s, H-12), 4.53 (1H, t, J = 6.0, H-2′), 3.69 (3H, s, CH_3), 3.24 (1H, d, J = 15.0, H-1), 2.69–2.63 (2H, m, H-1 and H-18), 1.40 (s, CH_3), 1.23 (s, CH_3), 0.92 (s, CH_3), 0.91 (s, CH_3), 0.86 (s, CH_3), 0.84 (s, CH_3), 0.81 (s, CH_3)	177.6 (COO), 172.4 (CON), 161.1 (Ar-C), 152.0 (Ar-C), 143.7 (C-13), 142.2 (Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.1 (Ar-C), 123.3 (Ar-C), 122.9 (C-12), 56.4, 53.7, 52.1, 46.7, 45.6, 42.4, 40.5, 39.4, 38.3, 36.9, 34.3, 33.1, 32.4, 30.9, 27.5, 25.6, 23.6, 20.5, 16.5, 15.8, 15.3, 11.7
8f	83	101	724 $[M+Na]^+$	8.03–7.95 (2H, m, Ar-H), 7.67–7.65 (2H, m, Ar-H), 7.29–7.09 (5H, m, Ar-H), 6.42 (1H, d, J = 6.0, N-H), 5.39 (1H, s, H-12), 4.81–4.75 (1H, m, H-2′), 3.69 (3H, s, CH_3), 3.25–3.17 (2H, m, H-3′), 3.06 (1H, d, J = 15.0, H-1), 2.64 (1H, d, J = 15.0, H-1), 2.45 (1H, dd, J = 3.0, J' = 15.0, H-18), 1.42 (s, CH_3), 1.20 (s, CH_3), 0.90 (s, CH_3), 0.89 (s, CH_3), 0.88 (s, CH_3), 0.73 (s, CH_3)	177.7 (COO), 172.1 (CON), 161.2 (Ar-C), 151.9 (Ar-C), 143.6 (C-13), 142.3 (Ar-C), 136.2 (Ar-C), 139.4 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 127.2 (Ar-C), 123.4 (C-12), 57.3, 53.5, 52.3, 49.5, 47.2, 46.6, 45.6, 42.2, 40.5, 39.4, 38.0, 36.9, 33.1, 32.4, 30.8, 27.4, 25.6, 23.5, 20.4, 16.3, 15.8
8g	87	159	598 $[M+H]^+$; 620 $[M+Na]^+$	8.02–7.96 (2H, m, Ar-H), 7.70–7.65 (2H, m, Ar-H), 7.15 (1H, s, N-H), 5.75 (1H, s, H-12), 4.26–4.07 (3H, m, H-2′ and H-1), 2.72 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.54 (1H, d, J = 15.0, H-1), 1.42 (s, CH_3), 1.38 (s, CH_3), 1.29 (s, CH_3), 0.98 (s, CH_3), 0.97 (s, CH_3), 0.89 (s, CH_3), 0.85 (s, CH_3), 0.84 (s, CH_3)	178.8 (COO), 171.8 (CON), 162.2 (Ar-C), 152.4 (Ar-C), 143.8 (C-13), 142.5 (Ar-C), 138.7 (Ar-C), 129.7 (Ar-C), 129.1 (Ar-C), 129.1 (Ar-C), 125.8 (Ar-C), 124.5 (C-12), 53.6, 47.1, 46.5, 45.5, 43.1, 42.5, 40.6, 39.6, 36.5, 33.1, 32.5, 30.9, 27.4, 25.5, 25.3, 24.0, 20.3, 15.9
8h	85	172	611 $[M+H]^+$	8.01–7.99 (2H, m, Ar-H), 7.69–7.67 (2H, m, Ar-H), 7.17 (1H, s, N-H), 5.71 (1H, s, H-12), 4.52 (1H, s, H-2′), 4.04 (1H, d, J = 15.0, H-1), 2.65 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.55 (1H, d, J = 15.0, H-1), 1.41 (s, CH_3), 1.38 (s, CH_3), 1.25 (s, CH_3), 0.93 (s, CH_3), 0.91 (s, CH_3), 0.84 (s, CH_3), 0.82 (s, CH_3)	178.4 (COO), 175.0 (CON), 162.1 (Ar-C), 152.4 (Ar-C), 143.5 (C-13), 142.5 (Ar-C), 138.9 (Ar-C), 129.7 (Ar-C), 129.1 (Ar-C), 126.1 (Ar-C), 124.3 (C-12), 53.5, 48.6, 46.7, 45.6, 42.4, 40.6, 39.6, 36.6, 33.2, 32.5, 25.7, 25.3, 24.0, 23.7, 18.7, 16.0
8i	87	160	640 $[M+H]^+$; 662 $[M+Na]^+$	8.01–7.98 (2H, m, Ar-H), 7.68–7.65 (2H, m, Ar-H), 6.88 (1H, d, J = 6.0, N-H), 5.63 (1H, s, H-12), 4.57 (1H, t, J = 6.0, H-2′), 3.82 (1H, d, J = 15.0, H-1), 2.72 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.67 (1H, d, J = 15.0, H-1), 1.40 (s, CH_3), 1.38 (s, CH_3), 1.23 (s, CH_3), 0.95 (s, CH_3), 0.92 (s, CH_3), 0.85 (s, CH_3), 0.84 (s, CH_3)	178.3 (COO), 173.6 (CON), 161.9 (Ar-C), 152.3 (Ar-C), 143.1 (C-13), 142.4 (Ar-C), 139.3 (Ar-C), 129.5 (Ar-C), 129.0 (Ar-C), 126.4 (Ar-C), 124.1 (C-12), 57.0, 53.4, 48.0, 47.0, 45.5, 42.8, 42.3, 40.5, 39.5, 39.0, 36.6, 33.3, 32.5, 31.8, 30.9, 27.6, 25.3, 23.8, 20.4, 18.9, 18.5, 15.9
8j	83	161	654 $[M+H]^+$; 676 $[M+Na]^+$	8.02–7.98 (2H, m, Ar-H), 7.69–7.66 (2H, m, Ar-H), 6.93 (1H, d, J = 6.0, N-H), 5.66 (1H, s, H-12), 4.63–4.57 (1H, m, H-2′), 3.89 (1H, d, J = 15.0, H-1), 2.68–2.55 (2H, m, H-1 and H-18), 1.40 (s, CH_3), 1.35 (s, CH_3), 1.26 (s, CH_3), 1.00 (s, CH_3), 0.98 (s, CH_3), 0.96 (s, CH_3), 0.87 (s, CH_3)	178.3 (COO), 174.6 (CON), 162.0 (Ar-C), 152.3 (Ar-C), 143.4 (C-13), 142.5 (Ar-C), 139.2 (Ar-C), 129.6 (Ar-C), 129.1 (Ar-C), 126.3 (Ar-C), 124.2 (C-12), 53.5, 51.2, 48.0, 46.8, 42.8, 42.4, 40.5, 39.6, 36.6, 33.2, 32.5, 30.9, 25.7, 25.2, 23.9, 22.9, 16.1
8k	88	150	676 $[M+Na]^+$; 708 $[M+2Na]^+$	8.01–7.97 (2H, m, Ar-H), 7.68–7.65 (2H, m, Ar-H), 6.94 (1H, d, J = 6.0, N-H), 5.63 (1H, s, H-12), 4.60 (1H, t, J = 3.0, H-2′), 3.82 (1H, d, J = 15.0, H-1), 2.70 (1H, dd, J = 3.0, J' = 15.0, H-18), 2.58 (1H, d, J = 15.0, H-1), 1.40 (s, CH_3), 1.38 (s, CH_3), 1.23 (s, CH_3), 0.93 (s, CH_3), 0.92 (s, CH_3), 0.81 (s, CH_3)	178.0 (COO), 173.6 (CON), 161.9 (Ar-C), 152.3 (Ar-C), 143.2 (C-13), 142.5 (Ar-C), 139.3 (Ar-C), 129.5 (Ar-C), 129.0 (Ar-C), 126.4 (Ar-C), 124.1 (C-12), 56.3, 53.5, 48.1, 46.9, 45.6, 42.4, 40.5, 39.6, 38.2, 36.7, 33.2, 30.9, 27.7, 25.7, 23.9, 20.4, 16.2, 15.4, 12.1
8l	89	197	688 $[M+H]^+$	8.02–7.93 (2H, m, Ar-H), 7.69–7.66 (2H, m, Ar-H), 7.26–7.23 (5H, m, Ar-H), 6.87 (1H, d, J = 6.0, N-H), 5.23 (1H, s, H-12), 4.95 (1H, s, H-2′), 3.91 (1H, d, J = 15.0, H-1), 3.34–3.19 (2H, m, H-3′), 2.45–2.39 (2H, m, H-1 and H-18), 1.42 (s, CH_3), 1.35 (s, CH_3), 1.30 (s, CH_3), 1.02 (s, CH_3), 1.00 (s, CH_3), 0.74 (s, CH_3), 0.73 (s, CH_3)	178.4 (COO), 172.3 (CON), 162.3 (Ar-C), 152.4 (Ar-C), 142.5 (C-13), 136.9 (Ar-C), 130.0 (Ar-C), 129.7 (Ar-C), 129.1 (Ar-C), 128.0 (Ar-C), 127.0 (Ar-C), 126.1 (Ar-C), 124.8 (C-12), 53.5, 51.2, 48.0, 46.8, 45.6, 42.8, 42.4, 42.2, 40.5, 39.5, 36.6, 34.2, 33.2, 32.8, 32.5, 32.0, 30.9, 27.6, 25.7, 25.3, 25.2, 23.7, 23.0, 20.3, 16.7, 15.8

compounds. After 2 days, each compound was removed and cells were cultured with fresh medium for 2 more days, and then 20 μL of MTT (5 mg/mL) and fresh medium then were added to each well. After incubation for 4 h, the medium was removed and the crystals were solubilized with 150 μL dimethylsulfoxide. The absorbance of each well was recorded at 570 nm using an ELISA plate reader and the percentages of cells' viability cultured with compounds were compared to that of the control group.

In the assays, all of the tested compounds were dissolved in DMSO and added at a DMSO concentration of 0.1%, which did not affect the cells. All of the cultures were performed at 37 °C in a humidified incubator with 5% CO_2 in air.

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2008.12.024.

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