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Synthesis and anti-inflammatory activity of novel 1,2,3-triazole- derivatives from 7-Oxodehydroabietic acid

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Abstract

Dehydroabietic acid (DHA) is a naturally occurring diterpene with relevant biological activities. 7-Oxodehydroabietic acid as a highly oxidized state derivative from Dehydroabietic acid (DHA) showing good activities. However, the reported compounds did not include triazole derivatives. To discover novel potent anti-inflammatory diterpenoids, a series of hybrids of 7-Oxodehydroabietic acid containing 1,2,3-triazole moiety were designed and synthesized. The anti-inflammatory activity of the new compounds was assessed towards BV2 cell lines using L-NMMA (IC_{50} = 42.36 ± 2.47 μM) as a positive control. Compared with the L-NMMA, anti-inflammatory effect (NO inhibitory activities) was found in these novel molecules, especially compounds **9** (IC_{50} = 8.00 ± 0.83 μM), **10** (IC_{50} = 8.44 ± 0.89 μM), **15** (IC_{50} = 8.13 ± 0.97 μM) and **16** (IC_{50} = 8.84 ± 1.10 μM). The anti-inflammatory activity of compounds **9**, **10**, **15** and **16** in vivo are underway.

Keywords 7-Oxodehydroabietic acid, Triazoles, Anti-inflammatory activity, Click chemistry

Introduction

Natural products are important resources for drug discovery, and the utilization of natural products or their novel structures, in order to discover and develop the final drug entity, is still alive and well [1–2]. Dehydroabietic acid (DHA) is a natural occurring diterpenic resin acid, which can be easily isolated from commercial disproportionated rosin [3]. Recent reports showing DHA and its derivatives exhibited a broad spectrum biological activities, such as antiulcer, antimicrobial, antifungal, anti-inflammatory, anti-pepsin, anxiolytic, antiviral, antitumor, and cytotoxic activities [4–10]. To our surprise, 7-Oxodehydroabietic acid (Fig. 1) as a highly oxidized state derivative from dehydroabietic acid (DHA) has rarely been concerned. So far, the modification of 7-Oxodehydroabietic acid mainly focused on oximation and acylhydrazation of C-7 position to develop new agents against BK channel-opening activity and antibacterial activity [11–13]. Inflammation is closely related to the occurrence of many diseases, for instance, neuroinflammation is a hallmark of brain injury and plays a critical role in the pathogenesis of neurological disorders such as depression, anxiety, Alzheimer's disease, Parkinson's disease, and multiple system atrophy [14–15]. In view of broad spectrum biological activities and limited exploration of 7-Oxodehydroabietic acid, we envisaged

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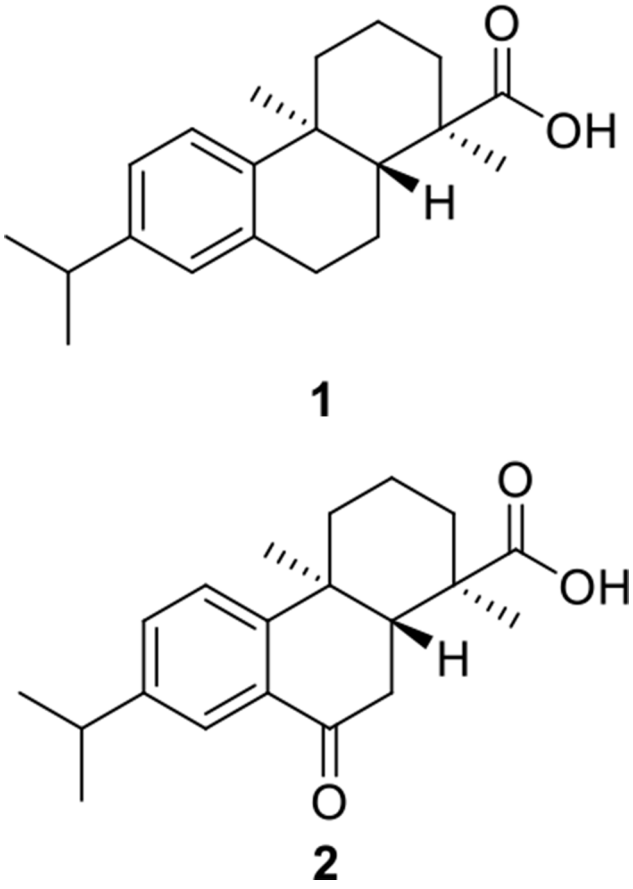


Fig. 1 The structures of dehydroabietic acid (1) and 7-oxodehydroabietic acid (2)

to develop new compounds bearing anti-inflammatory activity based on it.

1,2,3-triazoles are very important heterocyclic structural motifs due to their good solubility and metabolic stability. Consequently, the derivatives of natural products containing a 1,2,3-triazole unit usually showing better pharmacological activities [16–23]. As we all know, click chemistry is considered to be a nearly perfect synthesizing strategy for affording 1,2,3-triazoles derivatives under mild conditions. Therefore, it has been widely applied in many aspects of drug discovery, ranging from the design of lead compounds to tagging of biological systems [24]. Considering the above benefits and our interest in searching for the pharmacological effects of 7-Oxodehydroabietic acid derivatives. We envisioned that the combination of the 7-Oxodehydroabietic acid framework with 1,2,3-triazole unit may play a synergistic role showing better pharmacological activity. With the idea in mind, our goal is to synthesize a series of novel DHA derivatives containing triazole structure to find some molecules with good anti-inflammatory activity.

In this work, a series of novel hybrids of 7-Oxodehydroabietic acid containing 1,2,3-triazole were synthesized and their anti-inflammatory activities were assessed in vitro towards BV2 cell lines (mouse small glioma cells). BV2 cells can produce a series of inflammatory factors and cytokines after infection and inflammatory stimulation, so they are widely used in inflammation-related research [25]. Better anti-inflammatory effect (NO inhibitory activities) was found in promising compounds **9**, **10**, **15** and **16**.

Results and discussion

Synthesis of *O*-propargylated 7-oxodehydroabietic acid (4) and *O*-pentynylated 7-oxodehydroabietic acid (6)

In this manuscript, 7-Oxodehydroabietic acid (**2**) was synthesized according to the reported literature [9]. The key intermediates (**4**) and (**6**) were obtained as shown in Scheme 1. Treatment of 7-Oxodehydroabietic acid (**2**) with 3-bromoprop-1-yne (**3**) or 5-iodopent-1-yne (**5**) in the presence of potassium carbonate yielded the *O*-propargylated 7-oxodehydroabietic (**4**) and *O*-pentynylated 7-oxodehydroabietic (**6**) respectively (Scheme 1).

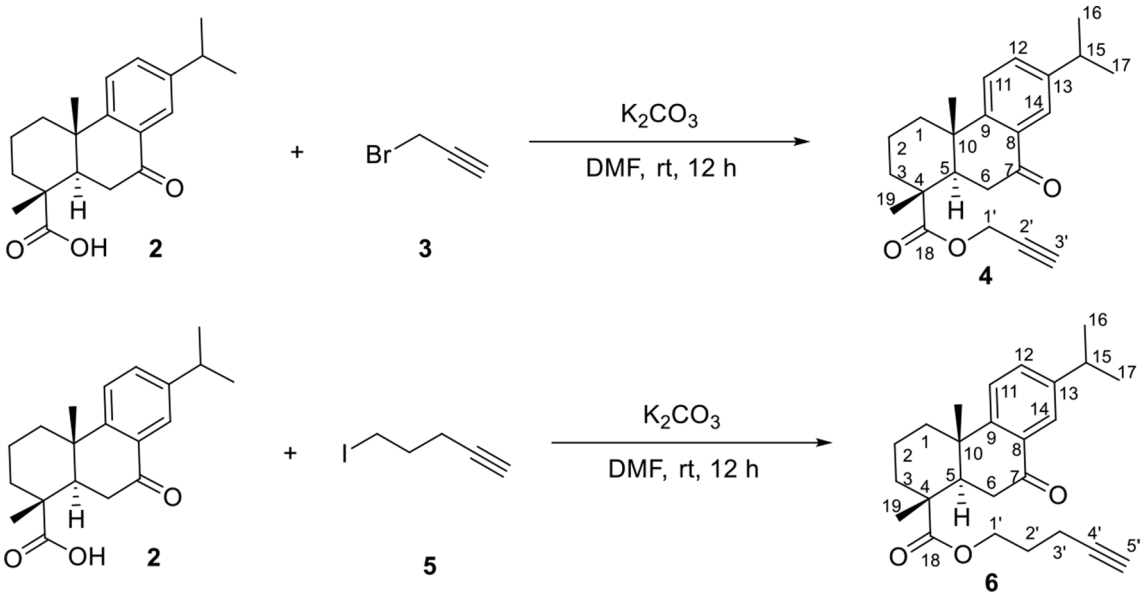
Synthesis of 7-oxodehydroabietic acid-1,2,3-triazole hybrids

The novel derivatives of 7-Oxodehydroabietic acid containing 1,2,3-triazole unit (**8–37**) were synthesized via Cu-catalyzed Huisgen [3 + 2] between *O*-propargylated 7-oxodehydroabietic (**4**) or *O*-pentynylated 7-oxodehydroabietic (**6**) with different substituted aromatic azides (Scheme 2 and Scheme 3) [20, 26, 27]. In addition, all aromatic azides were prepared from corresponding boronic acid with sodium azide in the presence of $CuSO_4$ in methanol (MeOH) without further purification [28, 29].

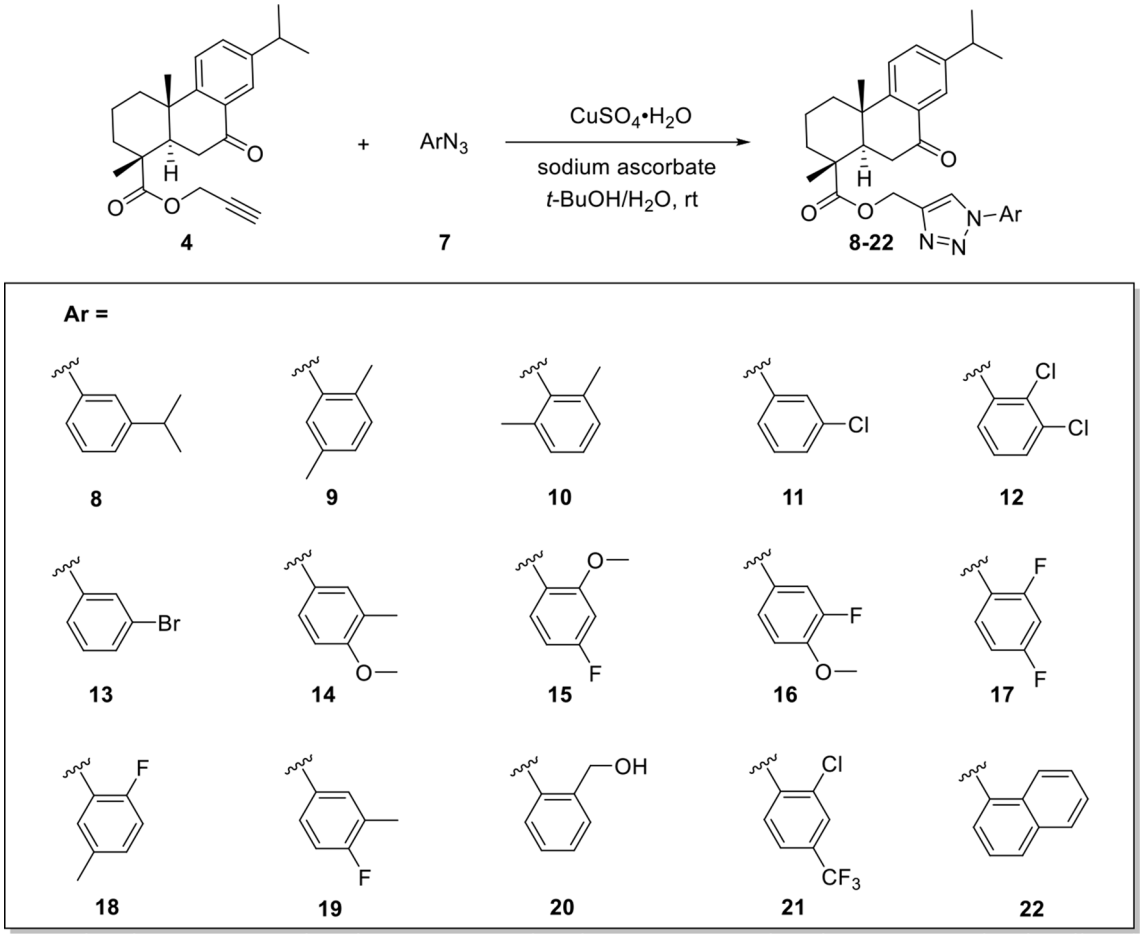
As we can see from Scheme 2 and Scheme 3, 7-oxodehydroabietic acid-1,2,3-triazole hybrids (**8–22**) from *O*-propargylated 7-oxodehydroabietic acid (**4**) and 7-oxodehydroabietic acid-1,2,3-triazole hybrids (**23–37**) from *O*-pentynylated 7-oxodehydroabietic acid (**6**) were obtained via Cu-catalyzed click reaction. The method proved to be suitable to obtain series of derivatives from 7-oxodehydroabietic acid and can be applied to other natural products to increase structural diversity. All the compounds present different substituents at the triazole moiety to evaluate their influence on the anti-inflammatory effect (NO inhibitory activities). Compounds **8–37** are described for the first time. The structures of all the compounds were confirmed by spectroscopic and spectrometric means.

Biological evaluation in vitro anti-inflammatory evaluation

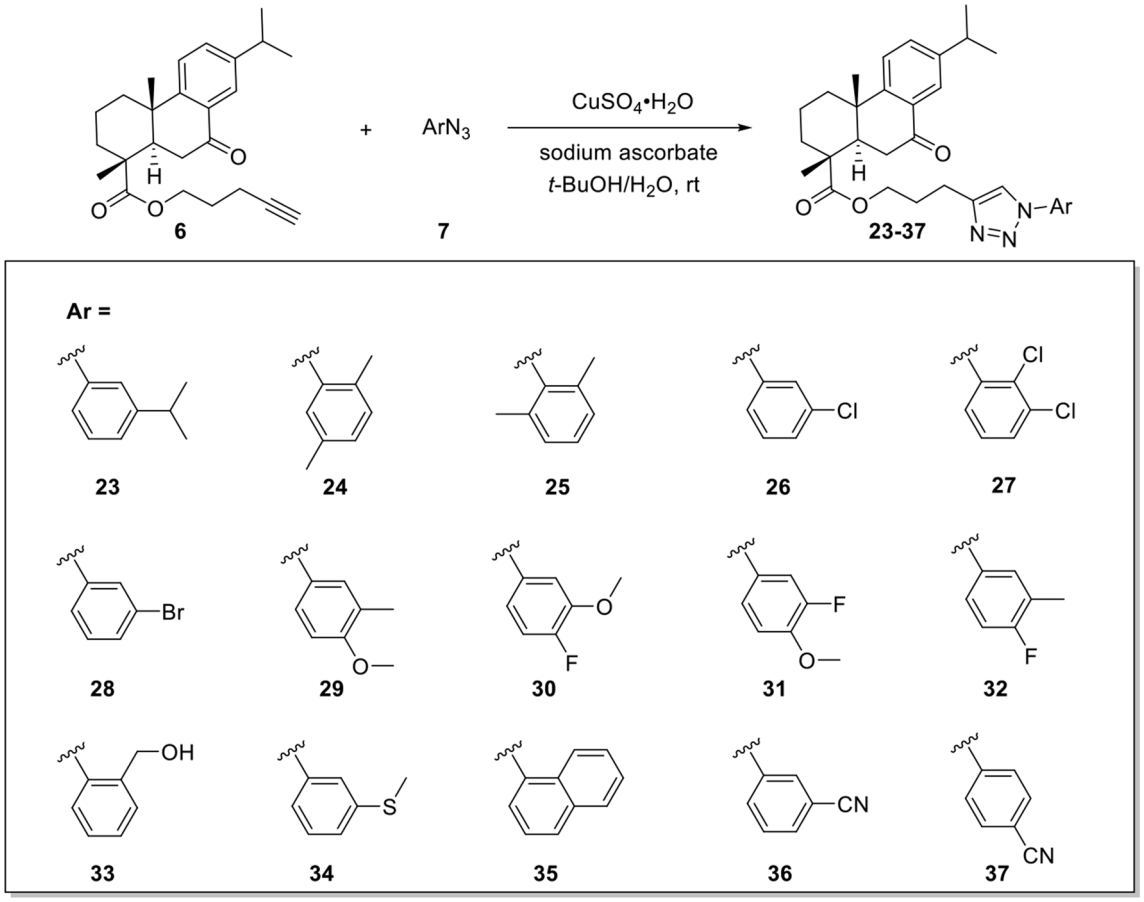
The compounds were then assessed for anti-inflammatory effect (NO inhibitory activities) towards the BV2 cell lines using NG-Methyl-L-arginine acetate salt (L-NMMA) ($IC_{50} = 42.36 \pm 2.47$ μM), a well-known nitric oxide synthase (NOS) inhibitor [30, 31], was used



Scheme 1 Preparation of *O*-propargylated 7-oxodehydroabietic acid (**4**) and *O*-pentynylated 7-oxodehydroabietic acid (**6**)



Scheme 2 Synthesis of 7-oxodehydroabietic acid-1,2,3-triazole hybrids from *O*-propargylated 7-oxodehydroabietic acid (**4**)



Scheme 3 Synthesis of 7-oxodehydroabietic acid-1,2,3-triazole hybrids from *O*-pentynylated 7-oxodehydroabietic acid (**6**)

Table 1 IC_{50} value in μM of 7-oxodehydroabietic acid-1,2,3-triazole hybrids on the panel of BV2 cell lines

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
8	> 20	**23**	> 20
9	8.00 ± 0.83	**24**	> 20
10	8.44 ± 0.89	**25**	> 20
11	10.72 ± 5.66	**26**	> 20
12	9.67 ± 1.08	**27**	> 20
13	14.72 ± 1.79	**28**	> 20
14	13.63 ± 2.20	**29**	> 20
15	8.13 ± 0.97	**30**	> 20
16	8.84 ± 1.10	**31**	> 20
17	9.38 ± 0.91	**32**	> 20
18	> 20	**33**	> 20
19	> 20	**34**	> 20
20	> 20	**35**	> 20
21	> 20	**36**	> 20
22	> 20	**37**	> 20

as a positive control. The tested results were shown in Table 1. It was found from Table 1 that some of the newly synthesized compounds had significant anti-inflammatory effect (NO inhibitory activities) towards the BV2 cell lines. Compared with 7-oxodehydroabietic acid-1,2,3-triazole hybrids (**23–37**) from *O*-pentynylated 7-oxodehydroabietic acid (**6**), 7-oxodehydroabietic acid-1,2,3-triazole hybrids (**8–22**) from *O*-propargylated 7-oxodehydroabietic acid (**4**) showing better anti-inflammatory effect (NO inhibitory activities) towards the BV2 cell lines. This fact suggests that the length of the CH_2 linker have an importance influence in the anti-inflammatory activity. Compounds **9–17** exhibited good anti-inflammatory effect (NO inhibitory activities) towards the BV2 cell lines with IC_{50} values from 8.00 ± 0.83 μM to 14.72 ± 1.79 μM. From an overall perspective, all of them containing electron donors such as a methoxy group or methyl group and electron acceptors such as fluorine atom or chlorine atom in the aromatic ring are beneficial for anti-inflammatory activities. Particularly, benzene ring containing bismethyl substitution or both fluorine and methoxy substitution can significantly enhance the activity of the compound (**9**, **10**, **15** and **16**). As for promising initial screening compounds **9**, **10**, **15** and **16**, we are conducting in vivo testing, mechanism exploration and drug properties analysis.

Conclusions

Taken together, a series of 7-oxodehydroabietic acid-1,2,3-triazole hybrids (**8–37**) were synthesized by a convenient Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction from *O*-propargylated 7-oxodehydroabietic (**4**) or *O*-pentynylated 7-oxodehydroabietic (**6**) with different substituted aromatic azides. The synthesized compounds were screened for anti-inflammatory effect (NO inhibitory activities) towards the BV2 cell lines. Among these compounds, compounds **9** ($IC_{50} = 8.00 \pm 0.83$ μM), **10** ($IC_{50} = 8.44 \pm 0.89$ μM), **15** ($IC_{50} = 8.13 \pm 0.97$ μM) and **16** ($IC_{50} = 8.84 \pm 1.10$ μM) were the most promising derivatives. The anti-inflammatory activity in vivo and the mechanism in anti-inflammatory activity of compounds **9**, **10**, **15** and **16** are under investigation.

Experimental

Materials and chemistry

All the reagents and solvents used for purification and synthesis were purchased from Anhui Zesheng Technology Co., Ltd. (Energy, Anqing, China). All synthesized derivatives were purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 10:1 to 1:1 and petroleum ether/acetone, 10:1 to 1:1) and their structures were elucidated by ^{1}H NMR, ^{13}C NMR, high-resolution mass spectrometry (HR-ESIMS). Mass spectra were performed on UPLC-IT-TOF (Shimadzu, Kyoto, Japan) spectrometer. NMR spectra were recorded on Avance III 600 MHz (Bruker, Bremerhaven, Germany) instruments using $CDCl_3$, CD_3OD or acetone-d_6 as the solvent with TMS as the internal standard. Chemical shifts (δ) were reported in parts per million (ppm) and the coupling constants (J) were given in Hertz. Column chromatography was performed on silica gel (200–300 mesh, Qingdao Makall Group CO., Qingdao, China). All chemical reactions were monitored by TLC on silica gel 60 F254 plates and the spots were visualized by UV light and sprayed with $Ce(SO_4)_2$ solution followed by heating. Prepare the $Ce(SO_4)_2$ solution by dissolving 2.5 g $Ce(SO_4)_2$ in 10 mL H_2SO_4 and diluting with water to a final volume of 100 mL. After spraying the plate, controlled heating with a heat gun or hot plate will reveal colored spots. All compounds were named using the ACD40 NamePro program, which is based on IUPAC rules. Azides (**7**) were synthesized according to procedures previously described in the literature [28, 29].

Preparation of *O*-propargylated 7-oxodehydroabietic (4) and *O*-pentynylated 7-oxodehydroabietic acid (6)

O-propargylated 7-oxodehydroabietic (**4**). To a solution of 7-oxodehydroabietic (**2**) (2.00 g, 6.37 mmol, 1.0 eq) in DMF (30 mL) was added K_2CO_3 (1.32 g, 9.55 mmol, 1.5 eq) slowly. The reaction mixture was stirred at rt for 30 min, and 3-bromoprop-1-yne (**3**) (0.67 mL, 7.64 mmol, 1.2 eq) was added dropwise at rt. The reaction mixture was stirred at rt for 24 h before it was quenched by saturated NaCl aqueous solution (30 mL), and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (2 × 40 mL), and dried over Na_2SO_4, and filtered. After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (10:1 to 5:1 petroleum ether/EtOAc) provided *O*-propargylated 7-oxodehydroabietic (**4**) (1.68 g, 75% yield) as a white solid [32].

O-pentynylated 7-oxodehydroabietic acid (**6**). To a solution of 7-oxodehydroabietic (**2**) (2.00 g, 6.37 mmol, 1.0 eq) in DMF (30 mL) was added K_2CO_3 (1.32 g, 9.55 mmol, 1.5 eq) slowly. The reaction mixture was stirred at rt for 30 min, and 5-iodopent-1-yne (**5**) (0.87 mL, 7.64 mmol, 1.2 eq) was added dropwise at rt. The reaction mixture was stirred at rt for 24 h before it was quenched by saturated NaCl aqueous solution (30 mL), and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (2 × 40 mL), and dried over Na_2SO_4, and filtered. After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (10:1 to 5:1 petroleum ether/EtOAc) provided *O*-pentynylated 7-oxodehydroabietic (**6**) (1.70 g, 70% yield) as a white solid.

Preparation of 7-oxodehydroabietic acid-1,2,3-triazole hybrids

To a solution of the corresponding azide (0.2 mmol) in 4 mL mixed solution (t-BuOH/H_2O = 1:1, v/v) was added *O*-propargylated 7-oxodehydroabietic (**4**) or *O*-pentynylated 7-oxodehydroabietic acid (**6**) (0.2 mmol), sodium ascorbate (0.02 mmol), $CuSO_4 \cdot 5H_2O$ (0.02 mmol). The reaction mixture was stirred for 48 h at room temperature before it was quenched by saturated NH_4Cl aqueous solution (5 mL), and the mixture was extracted with ethyl acetate (3 × 6 mL). The combined organic layer was washed with brine (2 × 15 mL), and dried over Na_2SO_4, and filtered [33]. After removal of the solvent under vacuum, the residue was purified by flash column chromatography on silica gel (8/1 to 1/1 petroleum ether/EtOAc) provided compound **8–37**.

18-O-(1-(3-(propan-2-yl)phenyl)-1H-1,2,3-triazol-4-yl) methyl-7-oxo-dehydroabietic acid (**8**). Yield: 53%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.63 (s, 1H), 7.52 (dd, J = 8.1, 2.1 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.1, 2.1 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 5.29 (s, 2 H), 3.01 (p, J = 6.9 Hz, 1H), 2.91 (p, J = 6.9 Hz, 1H), 2.67–2.77 (m, 2 H), 2.30–2.35 (m, 2 H), 1.71–1.83 (m, 3 H), 1.71 (q, J = 3.3 Hz, 1H), 1.61 (td, J = 12.6, 3.9 Hz, 1H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.25 (s, 3 H), 1.24 (d, J = 2.0 Hz,

3 H), 1.22 (d, J = 2.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 177.3, 152.9, 151.1, 147.0, 143.4, 136.9, 132.6, 130.7, 129.6, 127.1, 125.0, 123.6, 122.0, 119.0, 118.2, 58.1, 46.7, 43.7, 38.0, 37.4, 37.0, 36.4, 34.2, 33.6, 31.2, 23.8, 23.8, 23.8, 23.7, 8.1, 16.4; HRESIMS: calcd for $C_{32}H_{39}N_3O_3$ $[M+H]^+$ 514.3070, found 514.3171.

18-O-(1-(2,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl) methyl-7-oxo-dehydroabietic acid (**9**). Yield: 44%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 2.0 Hz, 1H), 7.75 (s, 1H), 7.40 (dd, J = 8.1, 2.0 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 5.30 (d, J = 2.2 Hz, 2 H), 2.92 (hept, J = 6.9 Hz, 1H), 2.71 (d, J = 14.4 Hz, 2 H), 2.39 (s, 3 H), 2.32 (m, 2 H), 2.14 (s, 3 H), 1.79 (t, J = 10.2 Hz, 3 H), 1.69–1.74 (m, 1H), 1.60–1.64 (m, 1H), 1.36 (s, 3 H), 1.25 (s, 3 H), 1.25 (d, J = 1.6 Hz, 3 H), 1.23 (d, J = 1.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2, 177.2, 152.8, 146.9, 142.5, 136.8, 136.0, 132.5, 131.2, 130.6, 130.2, 126.5, 125.2, 125.0, 123.4, 58.0, 46.6, 43.6, 37.8, 37.2, 37.0, 36.4, 33.5, 29.6, 23.7, 23.7, 23.6, 22.6, 20.6, 18.0, 17.3, 16.3; HRESIMS: calcd for $C_{31}H_{37}N_3O_3$ $[M+H]^+$ 500.2913, found 500.2914.

18-O-(1-(2,6-dimethylphenyl)-1H-1,2,3-triazol-4-yl) methyl-7-oxo-dehydroabietic acid (**10**). Yield: 51%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 1.9 Hz, 1H), 7.66 (s, 1H), 7.40 (dd, J = 8.1, 1.9 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2 H), 5.24 (d, J = 3.5 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.65–2.77 (m, 2 H), 2.24–2.39 (m, 2 H), 1.97 (s, 6 H), 1.73–1.81 (m, 3 H), 1.68–1.72 (m, 1H), 1.62 (dd, J = 12.2, 3.6 Hz, 1H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2, 177.2, 152.8, 146.9, 142.7, 135.7, 135.3, 132.5, 130.6, 130.0, 130.0, 128.4, 125.5, 124.9, 123.4, 58.0, 46.5, 43.5, 37.8, 37.2, 36.9, 36.4, 36.4, 33.5, 29.6, 23.8, 23.7, 23.6, 18.0, 17.3, 16.3; HRESIMS: calcd for $C_{31}H_{37}N_3O_3$ $[M+H]^+$ 500.2913, found 500.2917.

18-O-(1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**11**). Yield: 50%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.83 (t, J = 2.0 Hz, 1H), 7.67 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.42 (m, 1H), 7.40 (dd, J = 8.2, 2.2 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 5.31 (d, J = 12.8 Hz, 1H), 5.26 (d, J = 12.8 Hz, 1H), 2.91 (hept, J = 6.9 Hz, 1H), 2.73 (dd, J = 7.1, 3.4 Hz, 2 H), 2.26–2.37 (m, 2 H), 1.69–1.82 (m, 4 H), 1.57–1.63 (m, 1H), 1.35 (s, 3 H), 1.26 (s, 3 H), 1.24 (d, J = 2.2 Hz, 3 H), 1.23 (d, J = 2.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.6, 177.2, 152.9, 147.0, 143.8, 137.7, 135.6, 132.8, 130.9, 129.0, 125.0, 123.6, 121.9, 121.0, 118.7, 57.9, 46.7, 43.8, 38.0, 37.4, 37.1, 36.4, 33.6, 23.8, 23.8, 23.6, 18.1, 16.4; HRESIMS: calcd for $C_{29}H_{32}ClN_3O_3$ $[M+H]^+$ 506.2210, found 506.2213.

18-O-(1-(2,3-dichlorophenyl)-1 H-1,2,3-triazol-4-yl) methyl-7-oxo-dehydroabietic acid (**12**). Yield: 52%, yellow oil, 1 H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.84 (d, J = 2.1 Hz, 1 H), 7.64 (dd, J = 8.0, 1.5 Hz, 1 H), 7.59 (dd, J = 8.0, 1.5 Hz, 1 H), 7.43–7.40 (m, 1 H), 7.39 (dd, J = 6.3, 1.8 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 1 H), 5.34 (d, J = 12.8 Hz, 1 H), 5.31 (d, J = 12.8 Hz, 1 H), 2.91 (hept, J = 6.9 Hz, 1 H), 2.64–2.75 (m, 2 H), 2.35 (d, J = 12.0 Hz, 1 H), 2.23 (d, J = 14.7 Hz, 1 H), 1.80 (dt, J = 9.6, 5.8 Hz, 3 H), 1.69–1.73 (m, 1 H), 1.64 (dd, J = 12.4, 4.5 Hz, 1 H), 1.35 (s, 3 H), 1.25 (s, 6 H), 1.24 (d, J = 1.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1, 177.1, 152.8, 146.9, 142.7, 136.2, 134.5, 132.6, 131.7, 130.5, 128.1, 127.9, 125.8, 125.0, 123.4, 60.3, 57.8, 46.6, 43.7, 37.7, 37.2, 37.0, 36.3, 33.5, 23.7, 23.7, 23.6, 18.0, 16.3; HRESIMS: calcd for $C_{29}H_{31}Cl_2N_3O_3$ $[M+H]^+$ 540.1821, found 540.1821.

18-O-(1-(3-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**13**). Yield: 58%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 8.0, 2.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.28 (d, J = 8.2 Hz, 1H), 5.31 (d, J = 12.8 Hz, 1H), 5.26 (d, J = 12.8 Hz, 1H), 2.91 (hept, J = 6.8 Hz, 1H), 2.72 (dd, J = 7.0, 3.2 Hz, 2 H), 2.31 (dq, J = 16.2, 11.0 Hz, 2 H), 1.79 (d, J = 10.7 Hz, 3 H), 1.71 (d, J = 7.6 Hz, 1H), 1.60 (t, J = 11.9 Hz, 1H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.23 (d, J = 2.2 Hz, 3 H), 1.22 (d, J = 2.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 177.1, 152.8, 146.9, 143.5, 137.5, 132.6, 131.8, 131.0, 130.5, 124.9, 123.7, 123.5, 123.2, 121.8, 119.0, 77.2, 57.9, 43.7, 37.9, 37.3, 37.0, 36.3, 33.5, 23.7, 23.7, 23.5, 18.0,16.3; HRESIMS: calcd for $C_{29}H_{32}BrN_3O_3$ $[M+H]^+$ 550.1705, found 550.1707.

18-O-(1-(4-methoxy-3-methylphenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**14**). Yield: 46%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2 H), 7.40 (dd, J = 8.2, 2.0 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 6.92 (dd, J = 8.2 Hz, 1H), 5.28 (s, 2 H), 3.89 (s, 3 H), 2.92 (p, J = 6.9 Hz, 1H), 2.67–2.77 (m, 2 H), 2.34 (td, J = 11.6, 3.0 Hz, 2 H), 2.30 (s, 3 H), 1.76–1.82 (m, 3 H), 1.72 (m, 1H), 1.62 (m, 1H), 1.36 (s, 3 H), 1.26 (s, 3 H), 1.25 (d, J = 2.0 Hz, 3 H), 1.24 (d, J = 2.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 177.3, 158.1, 152.9, 147.0, 143.2, 132.6, 130.7, 129.9, 128.3, 125.0, 123.6, 123.4, 122.1, 119.4, 110.3, 58.1, 55.7, 46.67, 43.7, 38.0, 37.4, 37.0, 36.4, 33.6, 23.8, 23.8, 23.7, 18.1, 16.4, 16.3; HRESIMS: calcd for $C_{31}H_{37}N_3O_4$ $[M+H]^+$ 516.2862, found 516.2867.

18-O-(1-(4-fluoro-3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**15**). Yield: 55%, brown oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.57 (dd, J = 11.3, 2.6 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.40 (dd, J = 8.2, 2.0 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.09 (t, J = 8.9 Hz, 2 H), 5.33 (d, J = 12.7 Hz, 1H), 5.26 (d, J = 12.7 Hz, 1H), 4.01 (s, 3 H), 2.91 (p, J = 6.9 Hz, 1H), 2.67–2.80 (m, 2 H), 2.32–2.38 (m, 1H), 2.28 (dt, J = 15.0, 11.1 Hz, 1H), 1.73–1.82 (m, 3 H), 1.71 (d, J = 9.4 Hz, 1H), 1.61 (m, 1H), 1.35 (s, 3 H),

1.26 (s, 3 H), 1.24 (d, J = 2.2 Hz, 3 H), 1.23 (d, J = 2.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 177.3, 152.9, 152.3 (d, J = 247.5 Hz, 153.15 and 151.50), 151.5, 148.7 (d, J = 11.7 Hz, 148.70 and 148.62), 147.0, 143.7, 133.3 (d, J = 3.5 Hz, 133.34 and 133.31), 132.7, 130.6, 125.0, 123.7, 122.1, 116.6 (d, J = 19.5 Hz, 116.70 and 116.57), 112.6 (d, J = 7.5 Hz, 112.64 and 112.59), 106.9, 58.0, 56.6, 46.7, 43.9, 38.0, 37.4, 37.1, 36.4, 33.6, 23.8, 23.8, 23.6, 18.1, 16.4; HRESIMS: calcd for $C_{30}H_{34}FN_3O_4$ $[M+H]^+$ 520.2612, found 520.2616.

18-O-(1-(3-fluoro-4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**16**). Yield: 56%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85 (d, J = 1.9 Hz, 1H), 7.57 (dd, J = 11.3, 2.3 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.40 (dd, J = 8.1, 1.9 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.09 (t, J = 8.7 Hz, 1H), 5.30 (d, J = 12.8 Hz, 1H), 5.25 (d, J = 12.8 Hz, 1H), 3.95 (s, 3 H), 2.91 (h, J = 6.9 Hz, 1H), 2.66–2.77 (m, 2 H), 2.24–2.38 (m, 2 H), 1.78 (t, J = 11.5 Hz, 3 H), 1.72 (d, J = 6.2 Hz, 1H), 1.61 (t, J = 12.3 Hz, 1H), 1.35 (s, 3 H), 1.26 (s, 3 H), 1.24 (d, J = 2.2 Hz, 3 H), 1.23 (d, J = 2.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 177.1, 152.8, 152.2 (d, J = 247.5 Hz, 153.03 and 151.38), 148.1 (d, J = 10.7 Hz, 148.15 and 148.08), 146.9, 143.5, 132.6, 130.5, 129.9 (d, J = 8.8 Hz, 129.97 and 129.91), 124.9, 123.5, 121.9, 116.5 (d, J = 3.9 Hz, 116.48 and 116.45), 113.6, 109.8 (d, J = 22.8 Hz, 109.84 and 109.69), 57.9, 56.5, 46.6, 43.7, 37.9, 37.3, 37.0, 36.3, 33.5, 23.7, 23.7, 23.5, 18.0, 16.3; HRESIMS: calcd for $C_{30}H_{34}FN_3O_4$ $[M+H]^+$ 520.2612, found 520.2616.

18-O-(1-(2,4-difluorophenyl)-1H-1,2,3-triazol-4-yl) methyl-7-oxo-dehydroabietic acid (**17**). Yield: 36%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, J = 2.7 Hz, 1H), 7.94 (td, J = 8.6, 5.6 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.39 (dd, J = 8.2, 2.1 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.03–7.11 (m, 2 H), 5.30 (m, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.69 (d, J = 14.8 Hz, 2 H), 2.31–2.38 (m, 1H), 2.26 (d, J = 14.4 Hz, 1H), 1.75–1.83 (m, 3 H), 1.72 (dd, J = 6.7, 2.1 Hz, 1H), 1.62 (m, 1H), 1.35 (s, 3 H), 1.25 (s, 6 H), 1.23 (d, J = 1.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 177.2, 162.6 (dd, J = 252.8, 11.0 Hz, 163.45, 163.38, 163.78 and 161.71), 153.9 (dd, J = 254.2, 12.3 Hz, 154.78, 154.70, 153.10 and 153.01), 152.9, 147.0, 143.3, 132.6, 130.7, 126.5 (d, J = 9.9 Hz, 126.51 and 126.44), 125.1, 125.0 (d, J = 7.4 Hz, 124.98 and 124.93), 123.5, 121.8 (dd, J = 10.8, 4.0 Hz, 121.83, 121.80, 121.76 and 121.73), 112.6 (dd, J = 22.5, 3.8 Hz, 112.7, 112.7, 112.6 and 112.5), 105.4 (dd, J = 27.1, 24.0 Hz, 105.56, 105.40, 105.38 and 105.22), 57.8, 46.7, 43.7, 37.8, 37.3, 37.0, 36.4, 33.6, 29.7, 23.8, 23.8, 23.7, 18.1, 16.4; HRESIMS: calcd for $C_{29}H_{31}F_2N_3O_3$ $[M+H]^+$ 508.2412, found 508.2416.

18-O-(1-(2-fluoro-5-methylphenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**18**). Yield: 33%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.75 (m, 1H), 7.39 (dd, J = 8.1, 2.0 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.22 (m, 1H), 7.16 (dd, J = 10.6, 8.6 Hz, 1H), 5.32 (d, J = 12.7 Hz, 1H), 5.27 (d, J = 12.7 Hz, 1H), 2.92 (p, J = 6.9 Hz, 1H), 2.77–2.65 (m, 2 H), 2.42 (s, 3 H), 2.33 (t, J = 14.8 Hz, 2 H), 1.75–1.81 (m, 3 H), 1.73 (s, 1H), 1.63 (m, 1H), 1.35 (s, 3 H), 1.25 (m, 6 H), 1.24 (d, J = 1.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 177.1, 162.1 (d, J = 250.3 Hz, 162.89 and 161.23), 152.8, 150.7, 146.9, 143.0, 135.2 (d, J = 3.9 Hz, 135.19 and 135.17), 132.5, 130.7 (d, J = 7.4 Hz, 130.73 and 130.68), 130.6, 125.1, 125.0, 124.9 (d, J = 7.5 Hz, 124.93 and 124.88), 123.4, 116.6 (d, J = 19.8 Hz, 116.61 and 116.48), 57.8, 46.6, 43.6, 37.8, 37.2, 36.9, 36.4, 33.5, 23.8, 23.7, 23.7, 20.6, 18.0, 16.3; HRESIMS: calcd for $C_{30}H_{34}FN_3O_3$ $[M+H]^+$ 504.2662, found 504.2661.

18-O-(1-(4-fluoro-3-methylphenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**19**), Yield: 60%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.62 (dd, J = 6.3, 2.3 Hz, 1H), 7.53 (dt, J = 7.3, 3.4 Hz, 1H), 7.40 (dd, J = 8.1, 2.1 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 8.8 Hz, 1H), 5.30 (d, J = 12.8 Hz, 1H), 5.26 (d, J = 12.8 Hz, 1H), 2.91 (hept, J = 6.9 Hz, 1H), 2.77–2.68 (m, 2 H), 2.38 (s, 3 H), 2.36–2.26 (m, 2 H), 1.79 (t, J = 11.7 Hz, 3 H), 1.76–1.70 (m, 1H), 1.65–1.58 (m, 1H), 1.35 (s, 3 H), 1.26 (s, 3 H), 1.24 (d, J = 2.1 Hz, 3 H), 1.23 (d, J = 2.1 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 177.2, 161.0 (d, J = 247.5 Hz, 161.85 and 160.21), 152.8, 146.9, 143.5, 132.6, 130.5, 126.7 (d, J = 19.4 Hz, 126.80 and 126.67), 124.9, 124.0 (d, J = 5.5 Hz, 123.99 and 123.96), 123.5, 122.0, 119.8 (d, J = 8.7 Hz, 119.80 and 119.74), 116.1 (d, J = 24.0 Hz, 116.14 and 115.98), 58.0, 46.6, 43.7, 37.9, 37.3, 37.0, 36.3, 33.5, 23.7, 23.7, 23.5, 18.0, 16.3, 14.6; HRESIMS: calcd for $C_{30}H_{34}FN_3O_3$ $[M+H]^+$ 504.2662, found 504.2661.

18-O-(1-(2-(hydroxymethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl-7-oxo-dehydroabietic acid (**20**). Yield: 66%, white oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.66 (dd, J = 7.6, 1.5 Hz, 1H), 7.54 (td, J = 7.6, 1.5 Hz, 1H), 7.47 (td, J = 7.6, 1.5 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.41 (dd, J = 8.7, 2.0 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 5.36 (d, J = 12.8 Hz, 1H), 5.31 (d, J = 12.8 Hz, 1H), 4.52 (d, J = 12.3 Hz, 1H), 4.49 (d, J = 12.3 Hz, 1H), 2.91 (hept, J = 7.0 Hz, 1H), 2.65–2.76 (m, 2 H), 2.17–2.42 (m, 2 H), 2.01–2.17 (m, 1H), 1.78–1.88 (m, 3 H), 1.74 (d, J = 7.1 Hz, 1H), 1.63 (td, J = 11.8, 4.5 Hz, 1H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.24 (d, J = 1.4 Hz, 3 H), 1.23 (d, J = 1.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.0, 177.2, 153.0, 147.0, 142.9, 135.7, 135.6, 132.9, 131.1, 130.3, 130.1, 128.9, 125.6, 125.0, 125.0, 123.6, 61.3, 57.8, 46.6, 43.8, 37.7, 37.3, 36.9, 36.3, 33.5, 23.7, 23.7, 23.6, 18.1, 16.3; HRESIMS: calcd for $C_{30}H_{35}N_3O_4$ $[M+H]^+$ 502.2706, found 502.2709.

18-O-(1-(2-chloro-4-(trifluoromethyl)phenyl)-1H-1,2,3-tziazol-4-yl)methyl-7-oxo-dehydroabietic acid (**21**).

Yield: 40%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.83 (d, J = 2.1 Hz, 1H), 7.75 (dd, J = 8.3, 1.9 Hz, 1H), 7.40 (dd, J = 8.1, 2.1 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 5.35 (d, J = 12.8 Hz, 1H), 5.31 (d, J = 12.8 Hz, 1H), 2.91 (hept, J = 6.9 Hz, 1H), 2.64–2.74 (m, 2 H), 2.15–2.39 (m, 2 H), 1.80 (m, 3 H), 1.72 (d, J = 5.2 Hz, 1H), 1.62–1.65 (m, 1H), 1.35 (s, 3 H), 1.25 (s, 6 H), 1.23–1.24 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1, 177.2, 152.8, 146.9, 143.0, 137.3, 133.0, 132.6, 130.5, 129.0, 128.4, 128.1, 125.6, 125.0, 125.0, 123.5, 122.6 (d, J = 273.0 Hz, 123.53 and 121.72), 57.7, 46.6, 43.7, 37.7, 37.3, 37.0, 36.3, 33.5, 23.7, 23.7, 23.6, 18.0, 16.3; HRESIMS: calcd for $C_{30}H_{31}ClF_3N_3O_3$ $[M+H]^+$ 574.2084, found 574.2090.

18-O-(1-(naphthalen-1-yl)-1H-1,2,3-triazol-4-yl) methyl-7-oxo-dehydroabietic acid (**22**). Yield: 51%, colorless oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, J = 7.9 Hz, 1H), 7.96 (d, J = 6.6 Hz, 2 H), 7.85 (d, J = 2.1 Hz, 1H), 7.60 (m, 5 H), 7.40 (dd, J = 8.1, 2.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 5.38 (s, 2 H), 2.91 (hept, J = 6.9 Hz, 1H), 2.68–2.79 (m, 2 H), 2.27–2.39 (m, 2 H), 1.78–1.85 (m, 3 H), 1.75 (d, J = 7.7 Hz, 1H), 1.65 (dt, J = 11.9, 5.7 Hz, 1H), 1.37 (s, 3 H), 1.26 (s, 3 H), 1.24 (d, J = 2.3 Hz, 3 H), 1.23 (d, J = 2.3 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 177.3, 152.9, 147.0, 142.8, 134.1, 133.5, 132.6, 130.7, 130.5, 128.5, 128.3, 128.0, 127.1, 126.4, 125.1, 125.0, 123.8, 123.5, 122.2, 58.1, 46.7, 43.7, 37.9, 37.3, 37.0, 36.4, 33.6, 23.8, 23.8, 23.7, 18.1, 16.4; HRESIMS: calcd for $C_{33}H_{35}N_3O_3$ $[M+H]^+$ 522.2757, found 522.2759.

18-O-(1-(3-isopropylphenyl)-1H-1,2,3-triazol-4-yl) propyl-7-oxo-dehydroabietic acid (**23**). Yield: 65.0%,yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, J = 1.8 Hz, 1H), 7.85 (s, 1H), 7.64 (s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.41 (t, J = 7.9 Hz, 2 H), 7.29 (dd, J = 12.4, 7.9 Hz, 2 H), 4.15 (t, J = 6.3 Hz, 2 H), 3.00 (p, J = 6.9 Hz, 1H), 2.92 (p, J = 6.9 Hz, 1H), 2.83 (t, J = 7.6 Hz, 2 H), 2.74 (d, J = 11.7 Hz, 2 H), 2.36 (m, 2 H), 2.09 (m, 2 H), 1.72–1.83 (m, 4 H), 1.63–1.68 (m, 1H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.27 (s, 3 H), 1.24 (d, J = 2.2 Hz, 3 H), 1.23 (d, J = 2.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.6, 177.4, 153.2, 151.1, 147.4, 147.1, 137.4, 132.8, 130.7, 129.7, 126.8, 125.2, 123.7, 119.6, 118.9, 118.0, 64.2, 46.9, 44.1, 38.1, 37.5, 37.3, 36.7, 34.3, 33.7, 28.4, 24.0, 23.9, 23.9, 23.8, 22.3, 18.3, 16.5; HRESIMS: calcd for $C_{34}H_{44}N_3O_3$ $[M+H]^+$ 542.3383, found 542.3387.

18-O-(1-(2,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl) propyl-7-oxo-dehydroabietic acid (**24**). Yield: 37.3%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 2.1 Hz, 1H), 7.55 (s, 1H), 7.41 (dd, J = 8.1, 2.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 4.17 (t, J = 6.3 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.84 (t, J = 7.6 Hz, 2 H), 2.77–2.69 (m, 2 H), 2.37 (m, 2 H), 2.37 (s, 3 H), 2.17 (s, 3 H), 2.10 (m, 2 H), 1.73–1.85 (m, 4 H), 1.65 (m, 1H), 1.36 (s, 3 H), 1.27 (s, 3 H), 1.25 (d, J = 2.5 Hz, 3 H), 1.23 (d, J = 2.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.7, 177.5, 153.2, 147.1, 136.9, 132.8, 131.4, 130.8, 130.5, 130.4, 126.7, 125.2, 123.8, 64.3, 46.9, 44.0, 38.1, 37.5, 37.3, 36.8, 33.8, 28.4, 24.0, 23.9, 23.9, 22.3, 20.9, 18.4, 17.6, 16.6; HRESIMS: calcd for $C_{33}H_{42}N_3O_3$ $[M+H]^+$ 528.3226, found 528.3228.

18-O-(1-(2,6-dimethylphenyl)-1 H-1,2,3-triazol-4-yl) propyl-7-oxo-dehydroabietic acid (**25**).

Yield: 37.0%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 2.1 Hz, 1H), 7.44 (s, 1H), 7.41 (dd, J = 8.2, 2.1 Hz, 1H), 7.31 (d, J = 7.6 Hz, 2 H), 7.17 (d, J = 7.6 Hz, 2 H), 4.17 (t, J = 6.3 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.86 (t, J = 7.6 Hz, 2 H), 2.77–2.71 (m, 2 H), 2.37 (m, 2 H), 2.11 (m, 2 H), 2.00 (s, 6 H), 1.73–1.87 (m, 4 H), 1.63 (m, 1H), 1.36 (s, 3 H), 1.27 (s, 3 H), 1.25 (d, J = 2.5 Hz, 3 H), 1.24 (d, J = 2.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 177.3, 153.0, 147.0, 146.6, 136.1, 135.5, 132.7, 130.7, 129.9, 128.4, 126.4, 125.1, 123.6, 122.8, 64.0, 46.8, 43.9, 38.0, 37.4, 37.1, 36.6, 33.6, 28.3, 23.8, 23.8, 23.7, 22.2, 18.2, 17.4, 16.4; HRESIMS: calcd for $C_{33}H_{42}N_3O_3$ $[M+H]^+$ 528.3226, found 528.3228.

18-O-(1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**26**). Yield: 45.6%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 11.9 Hz, 1H), 7.88 (d, J = 1.5 Hz, 1H), 7.83 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.41 (dd, J = 8.2, 2.1 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 1H), 4.15 (td, J = 6.4, 3.2 Hz, 2 H), 2.93 (p, J = 6.9 Hz, 1H), 2.83 (t, J = 7.2 Hz, 2 H), 2.75 (d, J = 15.6 Hz, 2 H), 2.37 (m, 2 H), 2.09 (m, 2 H), 1.73–1.85 (m, 4 H), 1.64 (m, 1H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.25 (d, J = 2.2 Hz, 3 H), 1.24 (d, J = 2.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.8, 177.5, 153.2, 147.2, 136.9, 135.7, 134.1,132.9, 130.9, 130.7, 129.8,128.7, 125.2, 123.8, 120.8, 119.5, 118.5, 64.1, 47.0, 44.2, 38.2, 37.6, 37.3, 36.7, 33.7, 29.8, 28.3, 23.9, 23.8, 22.2, 18.3, 16.5; HRESIMS: calcd for $C_{31}H_{36}ClN_3O_3$ $[M+H]^+$ 534.2523, found 534.2526.

18-O-(1-(2,3-dichlorophenyl)-1H-1,2,3-triazol-4-yl) propyl-7-oxo-dehydroabietic acid (**27**). Yield: 46.7%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 2.1 Hz, 1H), 7.80 (s, 1H), 7.63 (dd, J = 8.2, 1.6 Hz, 1H), 7.53 (dd, J = 8.2, 1.6 Hz, 1H), 7.42 (dd, J = 8.2, 2.1 Hz, 1H), 7.39 (t, J = 8.2 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 4.17 (t, J = 6.3 Hz, 2 H), 2.92 (h, J = 6.8 Hz, 1H), 2.86 (t, J = 7.6 Hz, 2 H), 2.74 (dd, J = 7.2, 3.6 Hz, 2 H), 2.37 (m, 3 H), 2.11 (m, 2 H), 1.71–1.87 (m, 4 H), 1.63 (m, 1H), 1.36 (s, 3 H), 1.27 (s, 3 H), 1.25 (d, J = 2.4 Hz, 3 H), 1.24 (d, J = 2.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.7, 177.5, 153.2, 147.1, 136.8, 134.7, 132.8, 131.6, 130.8, 128.3, 128.0, 126.5, 126.3, 125.2, 123.7, 123.3, 64.1, 46.9, 44.0, 38.1, 37.6, 37.3, 36.8, 33.7, 28.3, 23.9, 23.9, 23.9, 22.2, 18.4, 16.6; HRESIMS: calcd for $C_{31}H_{35}Cl_2N_3O_3$ $[M+H]^+$ 568.2134, found 568.2136.

18-O-(1-(3-bromophenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**28**).Yield: 63.0%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.89 (d, J = 2.1 Hz, 2 H), 7.72 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.42 (dd, J = 8.1, 2.1 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 4.14 (t, J = 5.7 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.83 (t, J = 7.2 Hz, 2 H), 2.75 (d, J = 15.4 Hz, 2 H), 2.36 (m, 2 H), 2.09 (m, 2 H), 1.71–1.82 (m, 4 H), 1.65 (m, 1H), 1.35 (s, 3 H), 1.27 (s, 3 H), 1.25 (d, J = 1.9 Hz, 3 H), 1.23 (d, J = 1.9 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.1, 177.5, 153.3, 147.1, 137.9, 135.3, 133.8, 133.0, 132.2, 131.3, 129.9, 125.2, 123.8, 123.7, 123.5, 119.1, 63.9, 46.9, 44.2, 38.2, 37.6, 37.2, 36.5, 33.7, 28.3, 23.9, 23.9, 23.7, 22.0, 18.3, 16.5; HRESIMS: calcd for $C_{31}H_{36}BrN_3O_3$ $[M+H]^+$ 578.2018, found 578.2023.

18-O-(1-(4-methoxy-3-methylphenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**29**). Yield: 66.1%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 2.1 Hz, 1H), 7.74 (s, 1H), 7.53–7.46 (m, 2 H), 7.41 (dd, J = 8.1, 2.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 4.15 (t, J = 6.3 Hz, 2 H), 3.88 (s, 3 H), 2.92 (p, J = 6.9 Hz, 1H), 2.82 (t, J = 7.6 Hz, 2 H) 2.79–2.70 (m, 2 H), 2.37 (m, 2 H), 2.29 (s, 3 H), 2.08 (m, 2 H), 1.72–1.85 (m, 4 H), 1.65 (m, 1H), 1.35 (s, 3 H), 1.27 (s, 3 H), 1.25 (d, J = 2.4 Hz, 3 H), 1.23 (d, J = 2.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.6, 177.3, 157.8, 153.1, 147.1, 147.0, 132.7, 130.6, 130.2, 128.2, 125.0, 123.6, 123.2, 119.5, 119.1, 110.2, 64.1, 55.7, 46.8, 43.9, 38.0, 37.4, 37.1, 36.6, 33.6, 28.3, 23.8, 23.8, 23.7, 22.2, 18.2, 16.4, 16.3; HRESIMS: calcd for $C_{32}H_{38}ClN_3O_4$ $[M+H]^+$ 564.2629, found 564.2631.

18-O-(1-(4-fluoro-3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**30**). Yield: 57.9%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.42 (dd, J = 8.2, 2.1 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2 H), 4.14 (t, J = 5.7 Hz, 2 H), 3.98 (s, 3 H), 2.92 (p, J = 6.9 Hz, 1H), 2.82 (h, J = 7.7 Hz, 2 H), 2.75 (d, J = 14.6 Hz, 2 H), 2.36 (m, 2 H), 2.09 (m, 2 H), 1.81 (m, 4 H), 1.64 (m, 1H), 1.35 (s, 3 H), 1.27 (s, 3 H), 1.24 (d, J = 2.7 Hz, 3 H), 1.23 (d, J = 2.7 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.8, 177.5, 153.2, 152.2 (d, J = 248.3 Hz, 153.00 and 151.36), 148.7 (d, J = 11.9 Hz, 148.75 and 148.67), 147.6, 147.1, 133.7, 132.9, 130.7, 127.2 (d, J = 6.9 Hz, 127.25 and 127.21), 125.1, 123.8, 119.9, 116.8 (d, J = 19.7 Hz, 116.76 and 116.63), 112.3 (d, J = 6.9 Hz, 112.29 and 112.25), 106.7, 64.0, 56.7, 46.9, 44.2, 38.2, 37.6, 37.3, 36.6, 33.7, 28.3, 23.9, 23.8, 22.2, 18.3, 16.5; HRESIMS: calcd for $C_{32}H_{38}FN_3O_4$ $[M+H]^+$ 548.2925, found 548.2929.

18-O-(1-(3-fluoro-4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**31**). Yield: 74.5%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 2.1 Hz, 1H), 7.80 (s, 1H), 7.55 (dd, J = 11.5, 2.5 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 8.1, 2.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.07 (t, J = 8.8 Hz, 1H), 4.14 (td, J = 6.4, 2.0 Hz, 2 H), 3.94 (s, 3 H), 2.92 (hept, J = 6.9 Hz, 1H), 2.81 (td, J = 7.4, 3.0 Hz, 2 H), 2.74 (d, J = 13.0 Hz, 2 H), 2.36 (m, 2 H), 2.08 (m, 2 H), 1.70–1.82 (m, 4 H), 1.64 (m, 1H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.24 (d, J = 2.4 Hz, 3 H), 1.23 (d, J = 2.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.6, 177.3, 153.1, 152.3 (d, J = 248.6 Hz, 153.13 and 151.49), 147.9 (d, J = 10.5 Hz, 153.00 and 151.36), 147.5, 147.0, 132.8, 130.6, 130.4 (d, J = 8.7 Hz, 130.45 and 130.39), 125.0, 123.7, 119.5, 116.2 (d, J = 3.3 Hz, 116.17 and 116.15), 113.7, 109.5 (d, J = 22.9 Hz, 109.58 and 109.43), 64.0, 56.5, 46.8, 44.0, 38.0, 37.4, 37.1, 36.5, 33.6, 28.2, 23.8, 23.8, 23.7, 22.1, 18.2, 16.4; HRESIMS: calcd for $C_{32}H_{38}FN_3O_4$ $[M+H]^+$ 548.2925, found 548.2929.

18-O-(1-(4-fluoro-3-methylphenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**32**). Yield: 57.6%, white oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 2.1 Hz, 1H), 7.80 (s, 1H), 7.61 (dd, J = 6.5, 2.6 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.41 (dd, J = 8.2, 2.1 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.13 (dt, J = 8.7, 3.5 Hz, 1H), 4.14 (t, J = 6.2 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.82 (t, J = 7.4 Hz, 2 H), 2.75 (d, J = 12.7 Hz, 2 H), 2.36 (m, 2 H), 2.36 (s, 3 H), 2.08 (m, 2 H), 1.73–1.82 (m, 4 H), 1.65 (m, 1H), 1.35 (s, 3 H), 1.27 (s, 3 H), 1.25 (d, J = 1.9 Hz, 3 H), 1.24 (d, J = 1.9 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.7, 177.4, 161.0 (d, J = 247.3 Hz, 161.82 and 160.18), 153.2, 147.6, 147.1, 133.3, 132.9, 130.7, 126.8 (d, J = 19.5 Hz, 126.87 and 126.74), 125.2, 123.9 (d, J = 5.5 Hz, 123.88 and 123.84), 123.8, 119.7, 119.6 (d, J = 8.7 Hz, 119.66 and 119.60), 116.2 (d, J = 24.1 Hz, 116.26 and 116.10), 64.1, 46.9, 44.1, 38.2, 37.6, 37.3, 36.7, 33.7, 28.4, 23.9, 23.9, 23.8, 22.3, 18.3, 16.5, 14.8; HRESIMS: calcd for $C_{32}H_{38}FN_3O_3$ $[M+H]^+$ 532.2975, found 532.2977.

18-O-(1-(2-(hydroxymethyl)phenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**33**). Yield: 66.7%, white oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 2.1 Hz, 1H), 7.82 (s, 1H), 7.61 (d, J = 7.1 Hz, 1H), 7.48 (pd, J = 7.4, 1.7 Hz, 2 H), 7.41 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.3 Hz, 1H), 4.48 (s, 2 H), 4.17 (td, J = 6.2, 4.3 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.85 (td, J = 7.4, 2.8 Hz, 2 H), 2.74 (dd, J = 7.2, 3.5 Hz, 2 H), 2.36 (m, 2 H), 2.10 (m, 2 H), 1.72–1.83 (m, 4 H), 1.65 (m, 1H), 1.35 (s, 3 H), 1.27 (s, 3 H), 1.24 (d, J = 2.4 Hz, 3 H), 1.23 (d, J = 2.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.8, 177.5, 153.2, 147.1,147.1, 136.3, 135.6, 132.9, 131.8, 130.7, 129.9, 129.2, 125.2, 124.5, 123.8, 122.9, 68.3, 64.0, 62.0, 46.9, 44.1, 38.2, 37.6, 37.3, 36.7, 33.7, 28.3, 23.9, 23.9, 23.8, 22.2, 18.3, 16.5; HRESIMS: calcd for $C_{32}H_{39}N_3O_4$ $[M+H]^+$ 530.3019, found 530.3022.

18-O-(1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**34**). Yield: 61.3%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 2 H), 7.66 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.41 (m, 2 H), 7.30

(d, J = 8.1, 1H), 7.28 (d, J = 8.1 Hz, 1H), 4.15 (t, J = 6.1 Hz, 2 H), 2.92 (dt, J = 13.8, 6.9 Hz, 1H), 2.83 (t, J = 7.9 Hz, 2 H), 2.74 (d, J = 12.7 Hz, 2 H), 2.55 (s, 3 H), 2.36 (m, 2 H), 2.08 (m, 2 H), 1.72–1.84 (m, 4 H), 1.61–1.66 (m, 1H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.24 (d, J = 2.1 Hz, 3 H), 1.23(d, J = 2.1 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.7, 177.4, 153.2, 147.6, 147.1, 141.3, 137.8, 132.8, 130.7, 130.0, 126.3, 125.2, 123.8, 119.6, 118.0, 116.8, 64.1, 46.9, 44.1, 38.1, 37.6, 37.3, 36.7, 33.7, 29.8, 28.4, 23.9, 23.8, 22.3, 18.3, 16.5, 15.7; HRESIMS: calcd for $C_{32}H_{39}N_3O_3S$ [M + H] + 546.2790, found 546.2791.

18-O-(1-(naphthalen-1-yl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**35**). Yield: 57.0%, white oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (dd, J = 6.0, 3.3 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.75 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.58 (q, J = 3.3 Hz, 3 H), 7.54 (d, J = 7.2 Hz, 1H), 7.42 (dd, J = 8.2, 2.2 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 4.21 (t, J = 6.4 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.92 (t, J = 6.3 Hz, 2 H), 2.75 (d, J = 13.3 Hz, 2 H), 2.38 (m, 2 H), 2.16 (m, 2 H), 1.74–1.85 (m, 4 H), 1.66 (m, 1H), 1.36 (s, 3 H), 1.27 (s, 3 H), 1.23 (d, J = 3.0 Hz, 3 H), 1.22 (d, J = 3.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.6, 177.5, 153.2, 147.7, 146.9, 134.3, 134.0, 132.8, 130.8, 130.4, 128.7, 128.4, 128.0, 127.1, 125.2, 125.1, 124.0, 123.8, 123.7, 122.6, 64.3, 46.9, 44.0, 38.1, 37.5, 37.3, 36.8, 33.7, 28.5, 23.9, 23.9, 23.8, 22.3, 18.3, 16.5; HRESIMS: calcd for $C_{35}H_{39}N_3O_3$ $[M+H]^+$ 550.3070, found 550.3073.

18-O-(1-(3-cyanophenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**36**). Yield: 61.3%, yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 8.01 (s, 1H), 7.87 (d, J = 1.7 Hz, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.42 (dd, J = 8.2, 1.9 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 4.13 (t, J = 6.3 Hz, 2 H), 2.92 (p, J = 6.9 Hz, 1H), 2.83 (td, J = 7.4, 2.2 Hz, 2 H), 2.75 (d, J = 14.8 Hz, 2 H), 2.36 (m, 2 H), 2.10 (m, 2 H), 1.74–1.83 (m, 4 H), 1.65 (m, 1H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.24 (d, J = 2.1 Hz, 3 H), 1.23 (d, J = 2.1 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.8, 177.5, 153.2, 148.2, 147.2, 137.8, 132.9, 131.9, 130.9, 130.6, 125.2, 124.4, 123.8, 123.5, 119.5, 117.6, 114.2, 63.9, 47.0, 44.2, 38.2, 37.6, 37.3, 36.6, 33.7, 28.2, 23.9, 23.9, 23.8, 22.1, 18.3, 16.5; HRESIMS: calcd for $C_{32}H_{36}N_4O_3$ $[M+H]^+$ 525.2866, found 584.2869.

O-(1-(4-cyanophenyl)-1H-1,2,3-triazol-4-yl)propyl-7-oxo-dehydroabietic acid (**37**). Yield: 56.0%, white solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.97 (d, J = 8.6 Hz, 2 H), 7.85 (d, J = 1.9 Hz, 1H), 7.83 (d, J = 8.6 Hz, 2 H), 7.42 (dd, J = 8.2, 1.9 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 4.13 (td, J = 6.4, 2.0 Hz, 2 H), 2.91 (p, J = 6.9 Hz, 1H), 2.83 (h, J = 7.8 Hz, 2 H), 2.73 (d, J = 14.6 Hz, 2 H), 2.35 (m, 2 H), 2.09 (m, 2 H), 1.70–1.84 (m, 4 H), 1.59–1.66 (m, 1H), 1.34 (s, 3 H), 1.27 (s, 3 H), 1.24 (d, J = 2.4 Hz, 3 H), 1.23 (d, J = 2.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.8, 177.4, 153.2, 148.2, 147.1, 140.1, 134.7, 134.0, 133.0, 131.2, 130.6, 125.1, 123.8, 120.5, 119.4, 117.9, 112.1, 77.2, 63.8, 46.9, 44.2, 38.2, 37.6, 37.2, 36.6, 33.7, 28.1, 23.9, 23.9, 23.7, 22.1, 18.3, 16.5; HRESIMS: calcd for $C_{32}H_{36}N_4O_3$ $[M+H]^+$ 525.2866, found 584.2869.

Biological assays

Inoculate BV2 cells into a 96 well plate, induce stimulation with 1μg/mL LPS, and add the test compound (diluted 2-fold starting from 50μM) for treatment. After overnight cell culture, take the culture medium to detect NO production, and measure the absorbance value at 540 nm using an enzyme-linked immunosorbent assay (ELISA) reader. Add CCK-8 to the remaining culture medium for cell survival rate detection to eliminate the toxic effects of the compound on cells.

Inhibition rate of NO generation (%) = (OD_{540mm} of non drug treatment group– OD_{540mm} of sample group)/ OD_{540mm} of non drug treatment group × 100%.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13065-025-01449-7.

Supplementary Material 1

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Author contributions

Y.-F.L. and H.L. were responsible for the experimental design; H.L., H.K. and J.Z performed the experiments; F.-C. R. performed data analysis; Y.-F.L. and H.L. wrote the manuscript; S.-J. L. supervised and revised the manuscript; funding acquisition, H.L. All authors have read and agreed to the published version of the manuscript.

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Data availability

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request. We have presented all data in the form of Tables and Figure.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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