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Short communication

Synthesis and antileishmanial profile of some novel terpenyl pyrimidines☆

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Abstract

Some novel terpenyl pyrimidine derivatives **2(a–d)** and **6(a–b)** have been synthesised from α/β-ionone keteneacetals **1** and **5**. The terpenyl pyrimidine **2e** has been synthesised from β-ionone **3** in two steps in quantitative yield. The pyrimidine derivatives were screened for in-vivo antilesihmanial activity. The compounds **2d**, **2e**, **6a** and **6b** showed promising in-vivo antileishmanial activity.

Keywords: Ionones; Terpenyl pyrimidines; Antileishmanial activity

1. Introduction

Leishmaniasis is an infection caused by protozoa of the genus *Leishmania* presenting several forms of the disease such as cutaneous (CL), mucocutaneous (MCL) and visceral leishmaniasis (VL), which can be fatal when untreated. The disease is endemic in some tropical areas of the world and in under developed countries, directly affecting about 2 million people per annum, with approximately 350 million people under the risk of contracting the disease worldwide [1,2]. The incidence for new cases of leishmaniasis is increasing daily and currently is emerging as a common and serious opportunistic infection in human immuno deficiency virus (HIV) infected patients [3]. The current treatment for the leishmaniasis is now based on the pentavalent antimonials, as sodium stibogluconate (pentostam), meglumine antimonate (glucantime). The long course of treatment with antimonials leads to the accumulation of the drug in the liver and spleen. The lengthy treatment with antimonials often causes side effects such as myalgia, pancreatitis, cardiac arrhythmia and hepatitis leading to the reduction or cessation of treatment. Pentamidine is a second line of drug for the treatment of visceral leishmaniasis in patients who failed to respond to antimony therapy [4]. Although pentamidine is less toxic than antimonials but still it is not free from side effects such as hypoglycemia, diabetes, nephrotoxicity and pain at site of infection. Antibiotic amphoterecin-B is the second line of drug for the treatment of visceral leishmaniasis. It shows better response even in cases resistant to the antimonials and diamidines [5], but it is quite toxic such as nephrotoxicity and cardiotoxicity [6]. The development of new antileishmanial agents is extremely important, considering the high toxicity of the existing clinical drugs.

Currently, efforts are being made to search for new molecules from the natural sources and in this endeavour. Diaryl heptanoids [7], oxygenated abietanes [8], diterpene quinones [9] are showing promise as new lead molecules. Randomly designed heterocyclic ionone like molecules [10] and some novel terpenyl 2,4-diamino pyrimidines [11] are showing promising antimicrobial and dihydrofolate reductase inhibitory activities. Rationally designed 2,4-diaminopyrimidines [12] and some computer aided molecules [13] are also giving further inputs in the leishmanial dihydrofoliate reductase activity. Prompted with these literature reports we designed some novel terpenyl pyrimidines and evaluated for their in vivo antileishmanial activity and the results are reported in this communication (Scheme 1).

2. Chemistry

α-oxoketene dithioacetals of aromatic substrates are very useful synthons in the synthesis of variety of heterocyclic and

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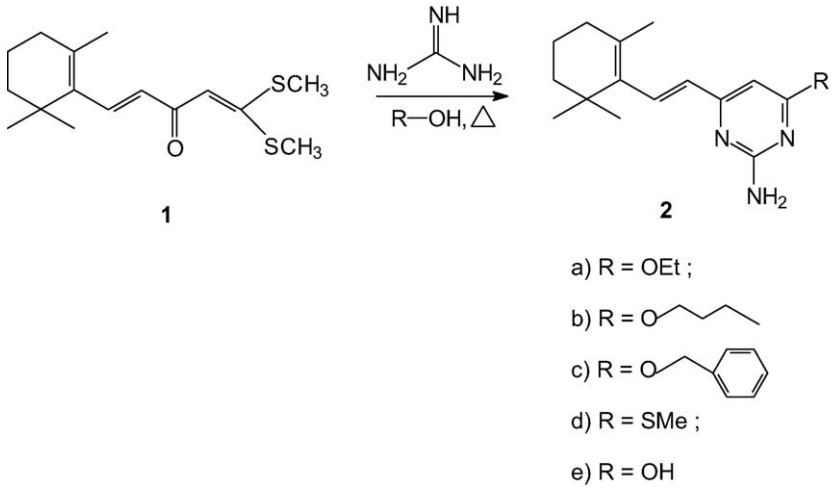
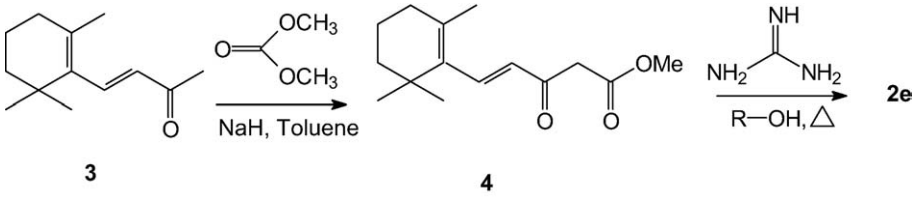


Scheme 1

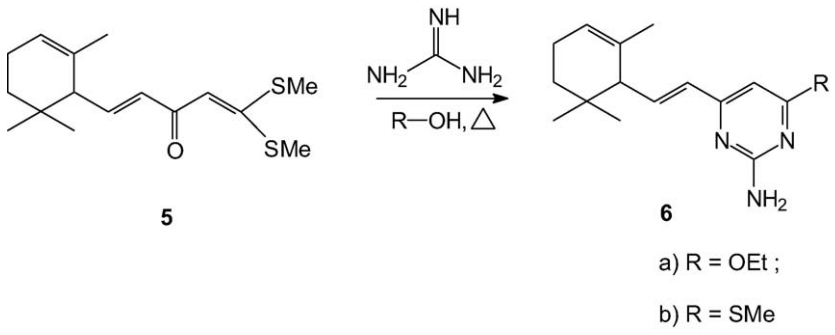
carbocyclic compounds [14]. However, α-oxoketene dithioacetals of terpene substrates are some what more labile but can be realised on a multigram scale [15]. The reaction of α-oxoketene dithioacetal **1** with guanidine in refluxing ethanol furnished **2a** in 50% yield. Similarly, the reaction of α-oxoketene dithioacetal **1** with guanidine in *n*-butanol and or benzyl alcohol under reflux conditions furnished **2b** and or **2c** in good yields. Initially, the preparation of **2d** proved to be problematic. However, after some experimentation the reaction of α-oxoketene dithioacetal **1** with guanidine in isopropyl alcohol at 140 °C (steel bomb, 24 h) furnished **2d** in 50% yield. The terpenyl pyrimidine **2e** was prepared as shown in Scheme 2. The reaction of β-ionone with sodium hydride and dimethyl carbonate in toluene at reflux temperature (6 h) furnished **4** in near quantitative yield [16]. The reaction of ketoester **4** with guanidine in refluxing ethanol furnished **2e** in quantitative yield. α-ionone based α-oxoketene dithioacetal **5** on reaction with guanidine in refluxing ethanol (48 h) furnished **6a** in 52% yield. The reaction of **5** with guanidine in isopropanol (140 °C, steel bomb, 24 h) furnished **6b** in 23% yield (Scheme 3).

3. Biological activities

The in vivo leishmanicidal activity against amastigote stage of *Leishmania donovani* was determined in Golden hamsters (*Mesocricotus aurctus*) infected with HOM/IN/80/DD8 strain of *L. donovani* obtained by courtesy of PCC Garnham, Imperial College, London (UK). Male hamsters weighing 35–40 g were infected with 1×10^7 amastigotes and the intensity of infection was assessed by spleen biopsy. Animals with 2^+ infections (5–15 amastigote/100 cell nuclei) were chosen for screening drugs. Usually 4–6 animals were used for each dose of the drug and the same numbers were kept as controls. The treat-



Scheme 2



Scheme 3

Table 1
Antileishmanial activity of compounds against amastigotes of *Leishmania donovani* in hamsters

Sr. no.	Compound number	Dose (mg/kg)	In vivo inhibition (%)	
			Day-7	Day-28
1	**2a**	50	47	–
2	**2b**	50	53	–
3	**2c**	50	40	–
4	**2d**	50	66	–
5	**2e**	50	22	63
6	**6a**	50	64	–
7	**6b**	50	64	–

ment of test animals was carried out by giving injection of the drug suspension daily for 5 days intraperitoneally. The post-treatment spleen biopsies were performed on each animal after 7 and 28 days of drug administration. On the basis of the intensity of infection (number of amastigote/100 spleen cell nuclei) in treated animal in comparison to control animals. The percentage inhibition was calculated in individual treated animals.

The leishmanicidal activity of various screened compounds **2**(**a–e**), **6**(**a–b**) is presented in Table 1. The compounds were screened at 50 mg/kg/day × 5 and the activity found is expressed at the minimum effective dose.

4. Results and discussion

Out of all the compounds screened **2b, 2d, 6a** and **6b** found most active showing 50–65% activity at 50 mg/kg doses. Interestingly, compound **2e** showed 63% activity on day 28, which probably is acting through immunostimulation [17]. Rest of the compounds showed moderate activity.

5. Experimental protocol

The reported melting points (°C) are the uncorrected ones. The infrared spectra were recorded in KBr on a Perkin Elmer model 881. NMR spectra were obtained in $CDCl_3$ (with Me_4Si internal standard, Aldrich) and are reported in ppm downfield from Me_4Si. Proton, carbon NMR spectra were recorded on Bruker Advance DRX 2000 instrument. Electron impact (EI) mass spectra were recorded on a Jeol JMS-D-300 spectrometer with the ionisation potential of 70 eV. Elemental analysis was carried out on a Carlo-Erba EA 1108 instrument, and agrees within ±0.4% with calculated values.

*5.1. 6-(2,6,6-trimethyl-1-cyclohexene-1-yl) ethenyl-2-amino-4-ethoxyl pyrimidine (**2a**)*

To a solution of sodium ethoxide (prepared by dissolving sodium metal 0.72 g, in absolute alcohol (60 ml) was added guanidine hydrochloride (1.04 g, 22 mmol) and stirred the reaction mixture for 0.5 h at room temperature. 1,1-dimethylmercapto-5-(2,6,6-trimethyl-1-cyclohex-2-ene-1-yl)-penta-1,4-(z)-dien-3-one (5.92 g, 20 mmol) was added to the reaction mixture and stirred for 48 h. The reaction mixture was concentrated in vacuo, poured into water and extracted with ethylacetate (100 ml × 3). The combined extract was washed with water (100 ml × 3), brine solution (100 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was chromatographed (SiO_2, 60–120 mesh). Elution with 7% ethylacetate in hexane furnished starting compound (2.00 g). Further elution with 15% ethylacetate in hexane furnished **2a** (2.5 g, 50%) as a white crystalline solid. m.p. 135–138 °C. IR (KBr, cm^{-1}) 3332, 3216, 2926, 1642, 1566, 1448. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (s, 6H), 1.35 (t, J = 7.00 Hz, 3H) 1.50 (m, 2H) 1.60 (m, 2H), 1.75 (s, 3H), 2.05 (m, 2H), 4.30 (q, 2H), 4.90 (m, 2H), 6.05 (s, 1H), 6.20 (d, J = 16.00 Hz, 1H), 7.30 (d, J = 16.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.872 (q), 19.515 (t), 22.130 (q), 2 × 29.300 (q), 33.621 (t), 34.597 (s), 40.083 (t), 62.228 (t), 95.324 (d), 130.774 (d), 132.439 (s), 135.228 (d), 137.343 (s), 163.171 (s), 164.804 (s), 171.471 (s). MS: (m/e), 288 (M^+ + 1) (M^+–CH_3).

*5.2. 6-(2,6,6-trimethyl-1-cyclohex-1-yl) ethenyl-2-amino-4-n-butyloxy pyrimidine (**2b**)*

To a solution of sodium butoxide (prepared by dissolving (0.12 g of sodium metal in 80 ml of dry *n*-butanol) was added guanidine hydrochloride (0.32 g, 0.5 mmol) and stirred the reaction mixture for 0.5 h at room temperature. 1,1-dimethylmercapto-5-(2,6,6-trimethyl-1-cyclohex-2-en-1-yl)penta-1,4-(z)-dien-3-one (1.48 gm, 5 mmol)was added to the reaction mixture and stirred at room temperature for 48 h. It was concentrated in vacuo, poured into water and extracted with ethylacetate (50 ml × 3). The combined extract was washed with water (50 ml × 3), brine solution (50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product after column chromatography (SiO_2, 60–120 mesh) furnished colourless thick liquid (0.560 g, 39%) which after crystallisation from ether–hexane furnished **2b** as a colorless crystalline solid. m.p. 105–106 °C, IR (KBr, cm^{-1}) 3388, 3207, 2929, 1647, 1568. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, 3H), 1.00 (s, 6H), 1.50 (m, 2H) 1.70 (m, 2H), 1.75 (s, 3H), 2.00 (t, 2H), 4.20 (t, 2H), 4.80 (m, 2H), 6.00 (s, 1H), 6.15 (d, J = 16.00 Hz, 1H), 7.25 (d, J = 16.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.208 (q), 19.532 (t), 19.577 (t), 22.130 (q), 2 × 29.307 (q), 33.586 (t), 34.588 (s), 40.070 (t), 66.187 (t), 95.257 (d), 131.013 (d), 132.285 (s), 135.054 (d), 137.356 (s), 163.305 (s), 164.986 (s), 171.622 (s). MS: (m/e), 316 (M^+ + 1) 300 (M^+–CH_3), 260 (M^+–$CH_3CH_2CH{=}CH_2$).

*5.3. 6-(2,6,6-trimethyl-cyclohex-1-yl)ethenyl-2-amino-4-n-benzyloxy pyrimidine (**2c**)*

To a solution of sodium benzyloxide (prepared by dissolving sodium metal (0.80 g) in dry benzyl alcohol (20 ml) was added guanidine hydrochloride (0.32 g, 0.5 mmol) and

stirred the reaction mixture for 0.5 h. 1,1-dimethylmercapto-5-(2,6,6-trimethyl-1-cyclohex-2-en-1-yl)penta-1,4-(z)-dien-3-one (1.48 gm, 5.00 mmol) was added. Resulting reaction mixture was magnetically stirred for 36 h at room temperature. It was concentrated in vacuo, poured into water and extracted with ethylacetate (50 ml × 3), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh) to furnish **2c** as a white crystalline solid (0.786 g, 21%), m.p. 120–121 °C. IR (KBr, cm^{-1}) 3328, 3214, 2924, 1636, 1564. ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 6H), 1.50 (m, 2H), 1.65 (m, 2H), 1.85 (s, 3H), 2.10 (m, 2H), 4.90 (bs, 2H), 5.35 (s, 2H), 6.10 (s, 1H), 6.20 (d, J = 16 Hz, 1H), 7.40 (m, 6H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.540 (t), 22.174 (q), 2 × 29.343 (q), 33.644 (t), 34.627 (s), 40.100 (t), 67.925 (t), 95.710 (d), 3 × 128.437 (d), 2 × 128.906 (d), 130.912 (d), 132.482 (s), 135.322 (d), 137.171 (s), 137.354 (s), 163.125 (s), 165.302 (s), 171.254 (s). MS: (m/e), 350 (M^+ + 1), 334 (M^+–CH_3).

5.4. 6-(2,6,6-trimethyl-1-cyclohexene-1-yl) ethenyl-2-amino-4-thiomethyl pyrimidine (**2d**)

To a solution of 1,1-dimethylmercapto-5-(2,6,6-trimethyl-1-cyclohex-1-ene-1-yl) penta-1,4-(z)-diene-3-one (5.92 g, 20 mmol)in dry isopropanol (20 ml) was added guanidine solution in isopropanol (1.90 g, 20 mmol, 20 ml)and the reaction mixture was heated in steel bomb at 120–130 °C for 24 h. It was concentrated in vacuo, poured into water (30 ml) and extracted with ethylacetate (50 ml × 4). Combined extract was washed with water (50 ml × 2), brine solution (50 ml) dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh) to furnish **2d** as a white crystalline solid (2.80 g, 50%). m.p. 98–100 °C. IR (KBr, cm^{-1}) 3314, 2922, 1628, 1516, 1432, 1312, ^1H NNR ($CDCl_3$, 200 MHz) δ 1.07 (s, 6H), 1.60 (m, 2H), 1.63 (m, 2H), 1.66 (s, 3H) 2.08 (m, 2H), 2.50 (s, 3H), 5.00 (s, 2H), 6.27 (d, J = 17.00 Hz, 1H), 6.56 (s, 1H), 7.34 (d, J = 17.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 12.76 (q), 19.49 (t), 22.16 (q), 2 × 29.32 (q), 33.66 (t), 34.61 (s), 40.10 (t), 106.24 (d), 130.53 (d), 132.89 (s), 136.06 (d), 137.34 (s), 162.37 (s), 162.66 (s), 171.63 (s). MS (m/e): 290 (M^+ + 1), 275 (M^+–CH_3). Anal. $C_{16}H_{23}N_3S$ (C,H,N).

5.5. Methyl-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-keto-4-pentenoate (**4**)

Sodium hydride (3.5 g, 50% suspension in oil, 73 mmol) was added to a solution of β-ionone (14.00 g, 72 mmol) and dimethyl carbonate (13.00 g, 144 mmol) in toluene (150 ml) and the stirred reaction mixture was held at 100 °C for 1.5 h. After cooling, a mixture of ether (250 ml), cone. HCl (35 ml), water (85 ml) was carefully added with vigorous stirring. The organic layer and subsequent ether extract of aqueous phase were combined washed with water (50 ml × 2), dried on sodium sulfate, concentrated in vacuo and purified by column chromatography (SiO_2, 60–120 mesh) to furnish **4** as a thick liquid (13.00 g, 90%). IR (neat, cm^{-1}): 2954, 1744, 1650. ^1H NMR (200 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 1.80 (s, 3H), 2.01 (m, 2H), 3.70 (s, 2H), 3.75 (s, 3H), 6.20 (d, J = 16.00 Hz), 7.35 (d, J = 16.00 Hz, 1H). MS: m/e 250 (M^+), 235 (M^+–CH_3).

5.6. 6-(2,6,6-trimethyl-1-cyclohexene-1-yl)-ethenyl-2-amino-pyrimidine-4-one (**2e**)

To a solution of methyl-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-keto-4-pentenoate **4** (5.00 g, 20 mmol) in dry isopropanol (10 ml) was added guanidine solution in isopropanol (3.80 g, 40 mmol, 40 ml) and the reaction mixture was heated in a steel bomb at 130–140 °C for 16 h. It was concentrated in vacuo, poured into water (30 ml) and extracted with dichloromethane (100 ml × 2), brine solution (50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh) to furnish **2e** as white crystalline solid (2.00 g, 40%), m.p. 250–253 °C. IR (KBr, cm^{-1}): 3331, 3171, 2928, 1599. ^1H NMR (200 MHz, $CDCl_3$) δ 1.028 (m, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 1.71 (s, 3H), 2.10 (m, 2H), 5.60 (s, 1H), 6.10 (d, J = 16.00 Hz, 1H), 6.50 (m, 2H), 7.20 (d, J = 16.00 Hz, 1H), 10.69 (m, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 18.327 (t), 21.105 (q), 2 × 28.420 (q), 32.336 (s), 33.470 (t), 39.571 (t), 100.108 (d), 130.520 (s), 130.884 (d), 132.946 (d), 136.235 (s), 154.857 (s), 161.066 (s), 163.054 (s). MS: m/e (259).

5.7. 6-(2,6,6-Trimethyl-1-cyclohexen-1-yl) ethenyl-2-amino-4-ethoxylpyrimidine (**6a**)

To a solution of sodium ethoxide (prepared by the reaction of sodium 6.72 g in absolute alcohol (60 ml) was added guanidine hydrochloride (1.04 g, 22 mmol) and stirred the reaction mixture for 0.5 h at room temperature. 1,1-dimethylmercapto-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-penta-1,4-(z)-dien-3-one (5.92 g, 20 mmol) was added and the resulting reaction mixture was stirred for 48 h at room temperature. The reaction mixture was poured into water (50 ml) and extracted with ethylacetate (50 ml × 4). Combined extract was washed with water (50 ml × 2), brine solution (50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh). Elution with 7% ethylacetate in hexane furnished starting compound (2.00 g, 33%). Continued elution with 15% ethylacetate in hexane furnished **6a** (2.72 g, 52%) as a white crystalline solid. m.p. 109–110 °C. IR (KBr cm^{-1}) 3350, 3176, 2916, 1664, 1579. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 1.00 (s, 3H), 1.60 (s, 3H), 2.00 (bs, 2H), 2.30 (d, J = 8.00 Hz, 1H), 6.20 (d, J = 16.00 Hz, 1H), 6.70 (dd, J = 16.00, 10.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.864 (q), 23.343 (q), 23.495 (t), 27.291 (q), 28.239 (q), 31.757 (s), 32.953 (t), 54.959 (d), 62.139 (t),

95.128 (d), 122.140 (d), 130.273 (d), 133.527 (s), 139.734 (d), 163.259 (s), 164.826 (s), 171.434 (s). MS (m/e): 287 (M^+) 272(M^+–CH_3). Anal. $C_{17}H_{25}ON_3$ (C,H,N).

*5.8. 6-(2,6,6-trimethyl-2-cyclohexen-1-yl) ethenyl-2-amino-4-thiomethyl pyrimidine (**6b**)*

To a solution of 1,1-dimethylmercapto-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-penta-1,4-(z)-dien-3-one (6.53 g, 22 mmol) in dry isopropanol (20 ml) was added guanidine solution in isopropanol (1.90 g, 20 ml, 20 mmol) and the reaction mixture was heated in a steel bomb at 120–130 °C for 24 h. It was concentrated in vacuo, poured into water and extracted with ethylacetate (50 ml × 4). The combined extract was washed with water (50 ml × 2), brine solution (50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh). Elution with 10% ethylacetate in hexane furnished **6b** as a white crystalline solid (2.00 g, 33%). m.p. 74–75 °C. IR (KBr, cm^{-1}) 3510, 3410, 3314, 2940, 1540, 1440. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.75 (s, 3H), 1.15 (m, 1H), 1.40 (m, 1H), 1.55 (s, 3H), 2.00 (m, 2H), 2.25 (d, J = 10.00 Hz, 1H), 2.40 (s, 3H), 4.85 (bs, 2H), 5.40 (bs, 1H), 6.05 (d, J = 16.00 Hz, 1H), 6.50 (s, 1H), 6.65 (dd, J = 16.00, 10.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 12.747 (q), 23.358 (q), 23.504 (t), 27.27 (q), 28.329 (t), 31.692 (s), 33.002 (t), 55.044 (d), 105.926 (d), 122.306 (d), 129.980 (d), 133.378 (s), 140.813 (d), 162.088 (s), 162.668 (s), 171.641 (s). MS: (m/e) 289 (M^+), 274 (M^+–CH_3).

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