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Michael addition of artemisitene

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Abstract—Michael addition of artemisitene with triazole, benzotriazole or benzimidazole under non- or base-catalyzed conditions yielded compounds **3a–c** and **4a–c**. They showed high antimalarial activity against *Plasmodium berghei* in mice.

Artemisinin (Qinghaosu **1**), a novel sesquiterpene endoperoxide, is the antimalarial constituent of the Chinese medicinal herb qinghao (*Artemisia annua* L.).[1] Due to its outstanding antimalarial activity and insolubility in water or oil, a great number of its derivatives and analogues have been synthesized since 1976.[1–5] However, the overwhelming majority of artemisinin derivatives have concentrated on C-12 derivatives, only few C-13 derivatives were prepared.[6–9] Artemisitene **2**, another sesquiterpene endoperoxide, exists in the same plant in much lower yield and has less antimalarial activity than artemisinin.[6,10] It contains an α,β-unsaturated lactone moiety which can be used as the substrate for some reactions. Recently acid catalyzed Michael additions of artemisitene were published by Ma.[11] We also prepared a new type of C-13 artemisinin derivative by Michael reaction of artemisitene. Here we would like to report their synthesis and antimalarial activity.

According to El-Feraly's procedure,[12] we prepared artemisitene **2** from artemisinin in high yield. It reacted with 1,2,4-triazole, benzotriazole or benzimidazole under different conditions to yield compounds **3a–c** and **4a–c**. Heating 1,2,4-triazole (as its salt) and **2** in acetonitrile at 60°C gave a mixture of **3a** and **4a**.[13] An aqueous ethanol solution of benzotriazole and **2** was refluxed to yield **3b**[14] and **4b**.[15] If the reaction was run in the presence of K_2CO_3 the yield dropped markedly. Reaction of benzimidazole and **2** in THF in the presence of $KF–Al_2O_3$ afforded **3c**[16] and **4c**[17] smoothly. When **2** reacted with imidazole or morpholine under similar conditions, no product was found. Although the reactions of azoles with α,β-unsaturated ketones usually resulted in mixtures of the triazol-1-yl and 4-yl isomers or benzotriazol-1-yl and 2-yl isomers,[18–20] the formation of no triazol-4-yl and benzotriazol-2-yl isomer was found in our experiments. The addition of these hetero-

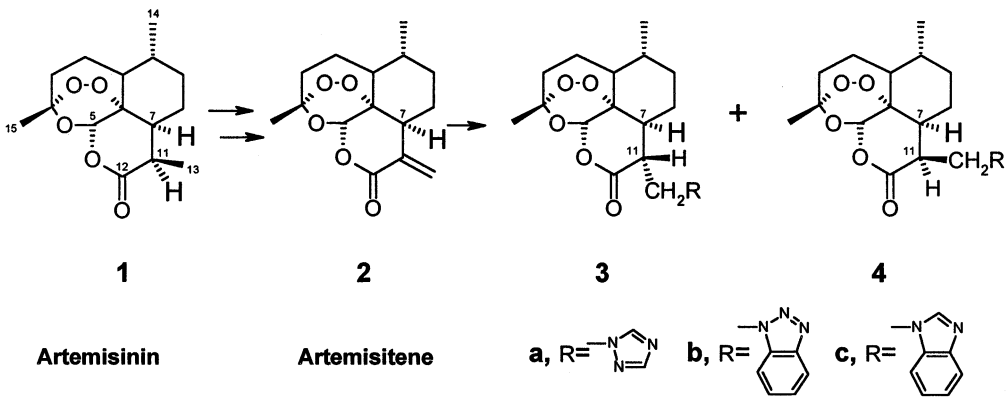

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Table 1. Antimalarial activity of compounds **3** and **4** against *P. bergei* K-173 strain in mice (PO)

Compound	Preparation (suspension)	SD_{50} (mg/kg/day)	SD_{90} (mg/kg/day)
3a+**4a**	In water	2.38	6.52
3b	In oil	5.48	11.41
3c	In water	3.94	10.05
4c	In oil	1.59	56.03
1	In water	18.75	56.66
1	In oil	5.13	11.50

cyclic compounds to artemisitene led to C-11 diastereoisomers **3b**/**4b** and **3c**/**4c** which could be separated by column chromatography. The C-11 configuration of **3** and **4** was determined by two-dimensional NOESY spectra. There was a NOESY cross peak between the C-7 H at δ 1.5 ppm and the C-11 H at δ 4.0 ppm for **4b**, but no cross peak between these two protons for **3b**. Moreover, the coupling constants between C-11 H and C-7 H in **4b** and **4c** were 4.8 and 5.3 Hz, respectively. While artemisinin **1** and 11-epiartemisinin had $J_{11,7}$ of 5.4 and 1.2 Hz.[8] Hence, the 11-CH_2R group in **4** and the 11-CH_3 group in **1** should take the same β-orientation.

The antimalarial activities of compounds **3** and **4** were measured according to Peters'procedure.[21] Mice were infected with 1.5×10^7 *P. berghei* K-173 strain parasitized cells intraperitoneally on day 0. Compounds **3a**+**4a**, **3b**, **3c** and **4c** were ground in water (or peanut oil) and orally administered once a day for D_0–D_3. The doses of the compounds given were 0.625, 1.25, 2.5, 5 and 10 mg/kg. Blood smears were made on day D_4, stained, examined under a microscope and calculated by a regression equation. All of the new derivatives tested had antimalarial activity in vivo.

As can be seen from Table 1, the mixture of **3a** and **4a** obviously is the most active with nine times the potency of artemisinin. Compound **3b** showed activity comparable to that of the natural artemisinin. However, **3c** with an 11α-benzimidazolyl group had higher activity than the corresponding 11β-isomer **4c**. To our knowledge, this is the first exception to the structure–activity relationship of C-11 substitution in artemisinin.[8,22,23]

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13. Compounds **3a** and **4a** (1:1): mp 144–146°C. Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20, 8.15 (1H, s, s, azolyl-H), 7.93, 7.90 (1H, s, s, azolyl-H), 5.94, 5.88 (1H, s, s, 5–H), 4.81, 4.73 (1H, m, m, 13–H), 4.48, 4.23 (1H, m, m, 13–H), 3.85, 2.91 (1H, m, m, 11–H), 1.44, 1.41 (3H, s, s, 15–H), 0.96, 0.93 (3H, d, d, J=6.1, 5.8 Hz, 14–H); IR (KBr): ν_{max} 1737, 1506, 1400, 1275, 1192, 1119, 880, 845 cm^{-1} Anal. calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.63; N 12.03. Found: C, 58.39; H, 6.49; N, 12.00.
14. Compound **3b** (11α-isomer)**:** mp 176–178°C. Yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (1H, d, J=8.5 Hz, arom-H), 7.62 (1H, d, J=8.1 Hz, arom-H), 7.51 (1H, t, J=7.6 Hz, arom-H), 7.38 (1H, t, J=7.9 Hz, arom-H), 5.98 (1H, s, 5-H), 5.20 (1H, d d, J=14.0, 4.5 Hz, 13-H), 5.02 (1H, d d, J=14.0, 10.2 Hz, 13-H), 3.05 (1H, d d, J=10.20, 4.21 Hz, 11-H), 1.47 (3H, s, 15-H), 0.90 (3H, d, J=6.0 Hz, 14-H); IR (KBr): ν_{max} 1743, 1379, 1269, 1198, 1105, 984, 880, 827 cm^{-1}. Anal. calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 63.01; H, 6.40; N, 10.43.
15. Compound **4b** (11β-isomer): mp 173–174°C. Yield: 20%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (1H, d, J=8.6 Hz, arom-H), 7.60 (1H, d, J=8.3 Hz, arom-H), 7.51 (1H, t, J=7.4 Hz, arom-H), 7.38 (1H, t, J=7.8 Hz, arom-H), 5.93 (1H, s, 5-H), 5.25 (1H, d d, J=14.8, 4.3 Hz, 13-H), 4.89 (1H, dd, J=14.8, 11.3 Hz, 13-H), 3.96 (1H, d t, J=11.2, 4.8 Hz, 11-H), 1.41 (3H, s, 15-H), 0.93 (3H, d, J=6.3 Hz, 14-H); IR (KBr): ν_{max} 1741, 1454, 1193, 1114, 1002, 880, 850 cm^{-1}. Anal. calcd for $C_{21}H_{25}N_3O_5$: C,

63.14; H, 6.31; N, 10.52. Found: C, 63.20; H, 6.30; N, 10.40

16. Compound **3c** (11α-isomer): mp 138–140°C. Yield: 26%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (1H, s, -N-CH=N-), 7.82 (1H, m, arom-H), 7.49 (1H, m, arom-H), 7.31 (2H, m, arom-H), 5.95 (1H, s, 5-H), 4.84 (1H, d d, J=14.3, 4.9 Hz, 13-H), 4.61 (1H, d d, J=14.3, 10.8 Hz, 13-H), 2.87 (1H, d d, J=10.8, 4.9 Hz, 11-H), 1.49 (3H, s, 15-H), 0.91 (3H, d, J=6.1 Hz, 14-H); IR (KBr): ν_{max} 1743, 1495, 1379, 1211, 1105, 989, 880, 830, cm^{-1}. Anal. calcd for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.07; H, 6.73; N, 7.03.
17. Compound **4c** (11β-isomer): mp 156–157°C. Yield: 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (1H, s, -N-CH=N-), 7.80 (1H, m, arom-H), 7.38 (1H, m, arom-H), 7.30 (2H, m, arom-H), 5.89 (1H, s, 5-H), 4.86 (1H, d d, J=14.8, 5.8 Hz, 13-H), 4.22 (1H, d d, J=14.8, 8.7 Hz, 13-H), 3.93 (1H, d t, J=9.5, 5.3 Hz, 11-H), 1.40 (3H, s, 15-H), 0.95 (3H, d, J=6.2 Hz, 14-H); IR (KBr): ν_{max} 1747, 1498, 1290, 1186, 1117, 1002, 974, 883, 830, cm^{-1}. Anal. calcd For $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.25; H, 6.27; N, 6.85.
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