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ARTEMISININ DERIVATIVES WITH 12-ANILINE SUBSTITUTION : SYNTHESIS AND ANTIMALARIAL ACTIVITY

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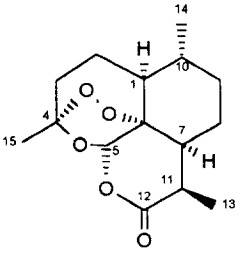
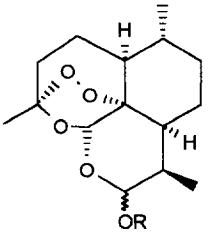
Abstract: 10 New artemisinin derivatives were synthesized by the reaction of dihydroartemisinin and aromatic amines in the presence of acidic catalyst. These compounds showed more effective *in vivo* against *Plasmodium berghei* in mice than artemisinin.

Artemisinin **1**, isolated from the Chinese medicinal herb *Artemisia annua*, is an unusual sesquiterpene bearing endoperoxide linkage[1] . The utility of **1** as antimalarial agents are limited to a great extent by its low solubility in both oil and water . In order to search for more effective and soluble drugs, a number of ether derivatives of dihydroartemisinin such as artemether **2b** and arteether **2c** and other types of derivatives were synthesized by our laboratory[2]. In this communication, we would like to report the chemistry of artemisinin derivatives which contain aromatic amine functions at C_{12} position and their antimalarial activity.

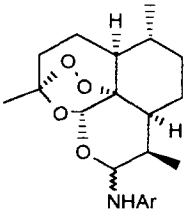


1



2a R = H (α + β)
b R = Me (β)
c R = Et (β)

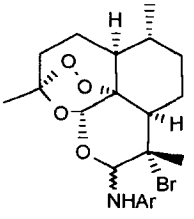
Dihydroartemisinin **2** was prepared by reduction of **1** with sodium borohydride according to a modified literature procedure[1] and treatment of **2** with aromatic amines in the presence of pyridinium sulphate[3] to afford derivatives **3** in good yields (50.7--93.2 %, except $\mathbf{3_K}$). If pyridinium perchlorate or pyridinium chloride was used as acidic catalyst, the yield would be lower . When **2** reacted with aliphatic amines such as ethylamine, butylamine, morpholine and cyclohexylamine under the same conditions, no reactions were observed.



(Q-NHAr)

3 a-j

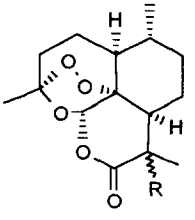
3 k Ar = $C_6H_4SO_3H$ (p)



4

Ar = C_6H_5

C_6H_4F (m)



5

R = OH, Cl, Br

Scheme

Dihydroartemisinin reacted with aromatic amine in pyridine in the presence of a catalytic amount of pyridinium sulphate at room temperature. After finishing of the reaction , the solvent was evaporated to dryness under reduced pressure. Column chromatography of the residue on silica gel with petroleum ether / EtOAc (9:1) or CH_2Cl_2 / EtOH (98:2) as eluent gave the desired products. Petroleum ether / EtOAc (9:1) for **3a-h** and CH_2Cl_2 / EtOH (98:2) for **3i-j** were used as eluent respectively. Recrystallization of these white solids from CH_2Cl_2 / petroleum ether afforded crystal **3a-j** . The major products **3** were identified as α-isomers by their larger coupling constants between C_{11} -H and C_{12} -H (J = 9.2 ~10.0 Hz). The structures of all products were established by ^{1}H-NMR, IR and elemental analysis.

The antimalarial test of compound **3a-j** was carried out according to Peters' procedure. The result (see Table 1) showed that they were more effective *in vivo* than the parent compound **1**. Meanwhile, compounds **4** were reported to have no significant antimalarial activity against *P. berghei* [4]. The great decrease of activity of compounds **4** coincides with the screening results of compounds **5**[5] , thus it could be deduced that any substituent at C_{11} position might impair the antimalarial effect in artemisinin series.

Table 1 Antimalarial activity of compound **3a-j** against *P. berghei* [K173 strain] in mice(in peanut oil, po)

compound [6]	chemical structure	SD_{50} (mg / kg / day)	SD_{90} (mg / kg / day)
1		5.13	11.50
3 a	Q--NHC_6H_5	2.63	7.30
3 b	Q--NHC_6H_4Cl (m)	1.62	4.80
3 c	Q--NHC_6H_4Cl (p)	1.77	4.50
3 d	Q--NHC_6H_4Br (m)	3.40	5.38
3 e	Q--NHC_6H_4Br (p)	2.70	9.10
3 f	Q--NHC_6H_4I (p)	4.56	11.03
3 g	Q--$NHC_6H_4CH_3$ (p)	2.77	6.08
3 h	Q--$NHC_6H_4OCH_3$ (p)	3.50	11.23
3 i	Q--NHC_6H_4COOH (p)	1.36	6.88
3 j	Q--NHC_6H_4COOH (m)	2.76	8.23

Additionally, some of these new compounds **3** were found to be active *in vitro* against P388. Further antineoplastic studies are in progress.

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6. **3a**: mp. 121.5-122 °C; Yield: 93.2%; ^{1}H-NMR ($CDCl_3$): δ 7.16, 6.73 (5H, m, Ar-H) , 5.42 (1H, s, C_5-H), 4.82 (1H, d, J=9.7Hz, C_{12}-H), 1.38 (3H, s, C_{15}-H), 0.98 (3H, d, J=6.2Hz, C_{13}-H), 0.92 (3H, d, J=7.2Hz, C_{14}-H); IR(KBr): 3000-3590 , 880, 825 cm^{-1} Anal. Calcd. for $C_{21}H_{29}NO_4$: C 70.17 ; H 8.13 ; N 3.90 Found: C69.80 ; H 8.33 ; N 3.89 .

3b: mp. 146-146.5 °C; Yield: 62.4% ^{1}H-NMR($CDCl_3$): δ 6.98, 6.84, 6.61 (4H, m, Ar-H), 5.41 (1H, s, C_5-H), 4.75 (1H, d, J=9.9Hz, C_{12}-H), 1.37 (3H, s, C_{15}-H), 0.96 (3H, d, J=6.4Hz, C_{13}-H), 0.89 (3H, d, J=7.2Hz, C_{14}-H); IR(KBr): 3360 , 1600, 1500 , 882, 830 cm^{-1}. Anal. Calcd. for $C_{21}H_{28}ClNO_4$: C 64.03 ; H 7.16 ; N 3.56 ; Cl 9.00. Found: C 64.14 ; H 7.13 ; N 3.58 ; Cl 8.99 .

3c: mp. 144.5-145 °C; Yield: 72.4%; ^{1}H-NMR($CDCl_3$): δ 7.09, 6.65 (4H, m, Ar-H), 5.39 (1H, s, C_5-H), 4.74 (1H, d, J=9.6Hz, C_{12}-H), 1.37 (3H, s, C_{15}-H), 0.97 (3H, d, J=5.9Hz, C_{13}-H), 0.91(3H, d, J=9.1Hz, C_{14}-H); IR(KBr): 3360, 1600, 1500 , 880, 830 cm^{-1} . Anal. Calcd. for $C_{21}H_{28}ClNO_4$: C 64.03 ; H 7.16 ; N 3.56 ; Cl 9.00. Found: C 63.91; H 7.16 ; N 3.34 ; Cl 8.83 .

3d: mp. 137.5-138 °C; Yield: 52.1%; ^{1}H-NMR($CDCl_3$): δ 6.99, 6.85, 6.62 (4H,m, Ar-H), 5.42 (1H, s, C_5-H), 4.75 (1H, d, J=9.9Hz, C_{12}-H), 1.39 (3H, s, C_{15}-H), 0.97 (3H, d, J=6.5Hz, C_{13}-H), 0.88 (3H, d, J=7.3Hz, C_{14}-H); IR(KBr): 3420 , 1595, 1510, 1482 , 880, 828 cm^{-1} . Anal. Calcd. for $C_{21}H_{28}BrNO_4$: C 57.54 ; H 6.44 ; N 3.20 ; Br 18.20. Found: C 57.61; H 6.38 ; N2.83 ; Br 18.37 .

3e; mp. 152-153°C; Yield; 75.3%; ^{1}H-NMR($CDCl_3$): δ 7.23, 6.60 (4H, m, Ar-H), 5.39 (1H, s, C_5-H), 4.74 (1H, d, J=9.9Hz, C_{12}-H), 1.38 (3H, s, C_{15}-H), 0.97 (3H, d, J=6.2Hz, C_{13}-H), 0.88 (3H, d, J=7.2Hz, C_{14}-H); IR(KBr): 3360 , 1590, 1500 , 880, 825 cm^{-1} . Anal. Calcd. for $C_{21}H_{28}BrNO_4$: C 57.54 ; H 6.44 ; N 3.20 ; Br 18.20. Found: C 57.31; H 6.42 ; N 2.98 ; Br 18.50 .

3f: mp. 156.5-158 °C; Yield: 50.7%; ^{1}H-NMR($CDCl_3$): δ 7.39, 6.50 (4H, m, Ar-H), 5.39 (1H, s, C_5-H), 4.74 (1H, d, J=9.2Hz, C_{12}-H), 1.37 (3H, s, C_{15}-H), 0.97 (3H, d, J=6.4Hz, C_{13} -H), 0.89 (3H, d, J=7.9Hz, C_{14}-H); IR(KBr) : 3370 , 1590, 1500, 883, 828 cm^{-1} . Anal. Calcd. for $C_{21}H_{28}INO_4$: C 51.97 ; H 5.81 ; N 2.89 . Found: C 52.06 ; H 5.78 ; N 2.91 .

3g; mp.149-150°C; Yield: 68.6%; ^{1}H-NMR($CDCl_3$): δ 6.97, 6.65 (4H, m, Ar-H), 5.40 (1H, s, C_5-H), 4.77 (1H, d, J=9.9Hz, C_{12}-H), 2.21 (3H, s, Ar-CH_3), 1.37 (3H, s, C_{15}-H), 0.96 (3H, d, J=6.2Hz, C_{13}-H), 0.88 (3H, s , C_{14}-H); IR(KBr): 3360 , 1615, 1518 , 880, 825 cm^{-1} . Anal. Calcd. for $C_{22}H_{31}NO_4$: C 70.75 ; H 8.36 ; N 3.75. Found: C 70.31; H 8.38 ; N 3.57 .

3h: mp. 144.5-146 °C; Yield: 85.0 %; ^{1}H-NMR($CDCl_3$): δ 6.72 (4H, m, Ar-H), 5.39 (1H, s, C_5-H), 4.72 (1H, d, J=10.0Hz, C_{12}-H), 3.72 (3H, s, OCH_3), 1.38 (3H, s, C_{15}-H), 0.95 (3H, d, J=6.0Hz, C_{13}-H), 0.90 (3H, d, J=7.1Hz, C_{14}-H); IR(KBr): 3350 , 1618, 1593, 1513 , 880, 825 cm^{-1} . Anal. Calcd. for $C_{22}H_{31}NO_5$: C 67.84 ; H 8.02 ; N 3.60. Found: C 67.59 ; H 7.94 ; N 3.41 .

3i: mp.155-157°C; Yield; 61.6%; ^{1}H-NMR(DMSO-d_6): δ 7.70, 6.81 (4H, m, Ar-H), 5.58 (1H, s, C_5-H), 4.88 (1H, d, J=9.7Hz, C_{12}-H), 1.22 (3H, s, C_{15}-H), 0.93 (3H, d, J=6.1Hz, C_{13}-H), 0.85 (3H, d, J=6.9Hz, C_{14}-H); IR(KBr): 3490 , 3390 , 1655 , 1610, 1520, 1500, 884, 825 cm^{-1} . Anal. Calcd. for $C_{22}H_{29}NO_6.H_2O$: C 62.64 ; H 7.36 ; N 3.37. Found: C 62.77 ; H 7.39 ; N 3.27 .

3j: mp. 153-153.5 °C; Yield: 77.4%; ^{1}H-NMR($CDCl_3$): δ 7.42, 7.30, 6.99, 6.87 (4H, Ar-H), 5.54 (1H, s, C_5-H), 4.94 (1H, d, J=9.8Hz, C_{12}-H), 1.40 (3H, s, C_{15}-H), 0.98 (3H, d, J=6.3Hz, C_{13}-H); 0.90 (3H, d, J=6.9Hz, C_{14}-H); IR(KBr): 3300-3500 , 3370 , 1650 , 1605, 1520, 1500 , 882, 825 cm^{-1} . Anal. Calcd. for $C_{22}H_{29}NO_6.H_2O$: C 62.64 ; H 7.36 ; N 3.37. Found: C 62.50 ; H 7.57 ; N 3.31 .

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