Brief Articles

Synthesis and Antimalarial Activity of Artemisinin Derivatives Containing an Amino Group

Ying Li,* Yuan-Ming Zhu, Hong-Jian Jiang, Jian-Ping Pan, Guang-Shao Wu, and Jin-Ming Wu

Department of Synthetic Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China

Yun-Lin Shi,* Jun-De Yang, and Bo-An Wu

Department of Malaria, Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences, Bejing 100071, China

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In search of water-soluble artemisinin derivatives that are more stable than sodium artesunate, over 30 derivatives containing an amino group (compounds **3**−**5**) were synthesized and tested in mice. All products tested (except **5a** and **5b**) are the β isomers. These basic compounds combined with organic acids (oxalic acid, maleic acid, etc.) to yield the corresponding salts. Generally, the maleates have better solubility in water than the corresponding oxalates. The aqueous solutions of these salts can be kept at room temperature for several weeks without any discernible decomposition. Compounds **3f**, **3h**, and **3r** are much more active against *P. berghei* than artesunic acid by oral administration and therefore were further tested in monkeys. However, their oral efficacies are poorer than that of artesunic acid against *P. knowlesi* in rhesus monkeys. It is interesting to note that **3f**, **3h**, and **3r** showed much lower efficacies against *P. berghei* when they were administered subcutaneously than orally.

Introduction

Artemisinin (qinghaosu, **1**) is the antimalarial principle of Chinese traditional medicine qinghao (*Artemisia annua* L.).[1] In the early clinical studies, it showed fast action, low toxicity, and high activity against both drug-resistant and drug-sensitive malaria; however its sparing solubility in water or oil caused difficulty in the rescue of severe patients. This compound also showed a relatively high recrudescence rate.[2] To overcome these shortcomings, a program aiming at modifying the chemical structure of artemisinin was launched in 1976, which led to the new agents: oil-soluble artemether **(2b)** and water-soluble sodium artesunate (sodium of **2c**), approved in China as new antimalarial drugs in 1987, along with artemisinin itself.Artesunic acid **(2c)** is the semisuccinate of dihydroartemisinin. Its sodium salt is freely soluble in water. However, the aqueous solution is so unstable that when kept at room temperature dihydroartemisinin (**2a**) precipitates very rapidly as tiny white solids. The poor stability of the aqueous solution appears to result from the facile hydrolysis of the ester linkage. The carboxylic group in compound **2d**[3] is linked to the artemisinin nucleus via an ethereal, rather than an ester, linkage and thus might be more stable. Two compounds of this type (n = 2, 3) were then prepared and tested against *P. berghei* in mice. The sodium salts of these compounds were more stable in aqueous solution, but their antimalarial activities were much less active than that of sodium artesunate. For this reason, we stopped our effort to synthesize this type of artemisinin derivatives. It should be noted that although Klayman and co-workers reported[3] that artelinic acid **(2e)** had better stability and higher activity than artesunic acid, in our hands **2e** was not even as active as artemisinin in vivo.[4]

Most of the known antimalarials (such as chloroquine, quinine) contain an amino group or/and a basic heterocyclic ring and are used as their salts. Similarly, introducing an amino group into the artemisinin molecule may lead to water-soluble derivatives. In addition, introducing a hydroxyl group into the nucleus or side chain might enhance their hydrophilicity. We report here the synthesis and antimalarial activity of a new type of water-soluble artemisinin derivative (compounds **3**−**5**), in which the amino group is bonded to the artemisinin nucleus still through an ethereal linkage.

Chemistry

Dihydroartemisinin **(2a)** was prepared by sodium borohydride reduction according to the literature procedure.[1] Reaction of **2a** with the bromo alcohol in the presence of boron trifluoride etherate[5] yielded **6**, which was converted to **3** (see Table 1) in good yields by treatment with various amines. Compound **4** (see Table 2) was synthesized from **7** (β isomer).[6] Compound **5** (see Table 2) was obtained from the bromo ether of 9α-

* To whom correspondence should be addressed. Y. Li: tel, 86 21 643 11833; fax, 86 21 643 70269; e-mail, yli@mail.shcnc.ac.cn.

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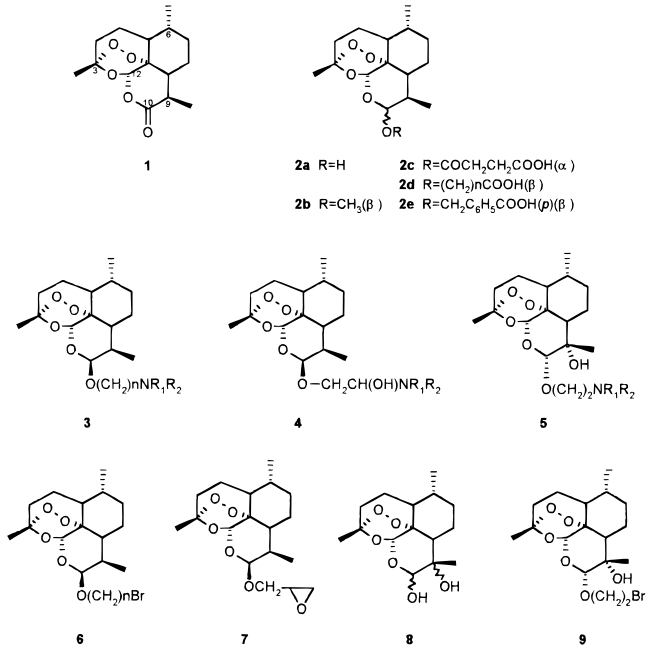
Chart 1



hydroxydihydroartemisinin **(9)** prepared from 9-hydroxydihydroartemisinin **(8)**[7,8] and the bromo alcohol.

Pure free bases of compounds **3**−**5** may be obtained by column chromatography. Most of them are colorless or pale yellow oils, and few products were solid. All products tested (except **5a** and **5b**) are the β isomers as indicated by the small coupling constants ($J = 3-4$ Hz) between 10-H and 9-H in ^{1}H NMR. Due to the close proximity to several asymmetric carbon centers of the artemisinin nucleus, the two methylene protons on the carbon α to the new ether oxygen are nonequivalent and thus appear as an AB pattern.

The free bases combined with organic acids (oxalic acid, maleic acid, etc.) to yield the corresponding salts. Most salts are easily soluble in water. Generally, the maleates have better solubility than the oxalates. The stability of their aqueous solution was monitored by TLC. Usually, they could be kept at room temperature for several weeks without any decomposition.

Biological Results and Discussion

The antimalarial activities of compounds **3**−**5** and artesunic acid **(2c)** were measured in vivo. Mice were infected with 1.5×10^7 *P. berghei* K_{173} strain parasitized cells intraperitoneally on day 0. The compounds to be tested were dissolved (or ground) in water (or peanut oil) and administered orally or subcutaneously 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, and examined under microscope. Based on the preliminary screening results, compound **3** was promising, whereas compounds **4** and **5** were less active than **2c**. The results coincided with that of the previously published work.[8−14] It showed that introduction of a substituent in the 9-position or an OH group in the side chain attached to the 10-position greatly decreased their antimalarial activities.

The results in Table 3 clearly show that these compounds are more active than artesunic acid by oral administration (because of instability of aqueous solution of sodium artesunate, artesunic acid **(2c)** was used as a control). Compounds **3f**, **3h**, and **3r** show 4−5-fold higher activity than artesunic acid **(2c)**, although their activities drastically decreased (30−60 times) when administered via subcutaneous injection (it may be caused by faster excretion). Thus **3f**, **3h**, and **3r** were selected for further evaluation in monkeys. Each monkey was inoculated with 2×10^7 *P. knowlesi* intravenously on D_0. Compounds **3f** , **3h, 3r,** and **2c** in a dose of 3.16 mg/kg/day and compounds **3f** and **2c** in a dose of 10.0 mg/kg/day were given orally from D_0 to D_6. The experimental results are listed in Tables 4 and 5. Compounds **3f**, **3h**, and **3r** reduced parasites more rapidly than artesunic acid **(2c)**, but at a dose of 3.16 mg/kg **3f** did not cleanse all parasites. Compounds **3h** and **3r** showed recrudescence in 5−10 days after administration, whereas artesunic acid **(2c)** can cleanse parasites at a dose of 10.0 or 3.16 mg/kg; no recrudescence within 105 days was observed.

These results in mice and monkeys seem to be contradictory. The only explanation may be that these water-soluble artemisinin derivatives have different types of absorption, excretion, and metabolism in different species.

In summary, introduction of an amino group into the artemisinin molecule leads to a new type of water-soluble artemisinin derivatives, which show antimalarial activity and other bioactivities such as local anesthetics.[15,16]

Experimental Section

All melting points were determined on a Buchi melting point apparatus and were uncorrected. ^{1}H NMR spectra were taken on a JNM PS-100 or AM 400 spectrophotometer. IR spectra were obtained on a Unicam SP-100 or Perkin-Elmer 599B spectrophotometer. Elemental analysis were performed on a CE 1106 or vario-EL microelemental analyzer.

Preparation of Dihydroartemisinin (2a) and 2-(10β-Dihydroartemisinoxy)ethyl Bromide (6) (n = 2). Dihydroartemisinin **(2a)** and 2-(10β-dihydroartemisinoxy)ethyl bromide **(6)** (n = 2) were prepared according to a reported procedure[1,5] respectively.

Preparation of 3-(10β-Dihydroartemisinoxy)propyl Bromide (6) (n = 3). To a solution of dihydroartemisinin (1.0 g, 3.5 mmol) and 3-bromopropanol (1.0 g, 7.2 mmol) in 20 mL of CH_2Cl_2 was added $BF_3{\cdot}Et_2O$ (5 drops) at 0 °C. The mixture was stirred at room temperature until the reaction completed. The reaction mixture was washed with a saturated $NaHCO_3$ solution, water and brine. The organic layer was dried and concentrated. The residue was recrystallized from petroleum ether to give 0.85 g of white crystals (yield 60%, mp 83−85 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, d, J = 7.4 Hz, 6-CH_3), 0.92 (3H, d, J = 6.2 Hz, 9-CH_3), 1.41 (3H, s, 3-CH_3), 2.07 (2H, m, -CH_2-C**H$_2$**-CH_2-), 3.46 (2H, m, -CH_2Br), 3.46, 3.97 (2H, m, m, -OCH_2-), 4.78 (1H, d, J = 3.3 Hz, 10-H), 5.39 (1H, s, 12-H). Anal. ($C_{18}H_{29}BrO_5$) C, H, Br.

Preparation of 3-(10β-Dihydroartemisinoxy)-1,2-oxopropane (7). Reaction of dihydroatemisinin and acrylic alcohol in the presence of BF_3-Et_2O obtained 3-(10-dihydroartemisinoxy)propene from which the 10β isomer was isolated by column chromatography. A solution of 3-(10β-dihydroartemisinoxy)propene (0.91 g, 2.8 mmol) and *m*-chloroperoxybenzoic acid (0.70 g, 4.0 mmol) in 15 mL of CH_2Cl_2 was heated to reflux until the reaction was complete. The reaction mixture was filtered. The organic layer was washed with aqueous sodium hydrosulfite and water and dried. The crude product was passed through a column of silica gel, eluting with ethyl acetate/petroleum ether (1:9) to give 0.74 g of pure product (yield 78%) as a white solid, mp 92−94 °C (mp 55−57 °C, yield

Table 1. Physical Properties of Compound **3**

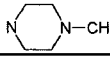
Compd	n	NR_1R_2	Yield(%)	M.P. (°C)	Formula	Elementary Analysis
3a	2	NHMe	47	175-175.5 (oxalate)	$C_{18}H_{31}NO_5 \cdot C_2H_2O_4$	C, H, N
3b	2	NHMe	75	147-148 (maleate)	$C_{18}H_{31}NO_5 \cdot C_4H_4O_4$	C, H, N
3c	2	NHEt	66	143-144.5 (maleate)	$C_{19}H_{33}NO_5 \cdot C_4H_4O_4$	C, H, N
3d	2	$NHC_3H_7(n)$	87	173-5 (oxalate)	$C_{20}H_{35}NO_5 \cdot C_2H_2O_4$	C, H, N
3e	2	$NHC_3H_7(i)$	78	160-161 (maleate)	$C_{20}H_{35}NO_5 \cdot C_4H_4O_4$	C, H, N
3f	2	NMe_2	71	166-168 (oxalate)	$C_{19}H_{33}NO_5 \cdot C_2H_2O_4$	C, H, N
3g	2	NMe_2	78	143-145 (maleate)	$C_{19}H_{33}NO_5 \cdot C_4H_4O_4$	C, H, N
3h	2	NEt_2	88	100-102 (oxalate)	$C_{21}H_{37}NO_5 \cdot C_2H_2O_4$	C, H, N
3i	2	NEt_2	70	124-126 (maleate)	$C_{21}H_{37}NO_5 \cdot C_4H_4O_4$	C, H, N
3j	3	NEt_2	72	142-144 (maleate)	$C_{22}H_{39}NO_5 \cdot C_4H_4O_4$	C, H, N
3k	2	$NH(CH_2)_2OH$	75	140-142 (maleate)	$C_{19}H_{33}NO_6 \cdot C_4H_4O_4$	C, H, N
3l	2	$NH(CH_2)_2NMe_2$	89	146-148 (maleate)	$C_{21}H_{38}N_2O_5 \cdot 2\ C_4H_4O_4$	C, H, N
3m	2	$NH(CH_2)_3NMe_2$	50	151-153 (maleate)	$C_{22}H_{40}N_2O_5 \cdot 2\ C_4H_4O_4$	C, H, N
3n	2	$NH(CH_2)_2CN$	62	146-148 (maleate)	$C_{20}H_{32}N_2O_5 \cdot C_4H_4O_4$	C, H, N
3o	3	$NH(CH_2)_3NMe_2$	35	132-134 (maleate)	$C_{23}H_{42}N_2O_5 \cdot 2\ C_4H_4O_4$	C, H, N
3p	2		92	171-173 (oxalate)	$C_{21}H_{35}NO_6 \cdot C_2H_2O_4$	C, H, N
3q	2		88	158-160 (maleate)	$C_{21}H_{35}NO_6 \cdot C_4H_4O_4$	C, H, N
3r	3		76	145-147 (maleate)	$C_{22}H_{37}NO_6 \cdot C_4H_4O_4$	C, H, N
3s	3		75	138-140 (fumarate)	$C_{22}H_{37}NO_6 \cdot C_4H_4O_4$	C, H, N
3t	2		60	174-176 (oxalate)	$C_{21}H_{36}N_2O_5 \cdot 2C_2H_2O_4$	C, H, N
3u	2		38	159-161 (maleate)	$C_{21}H_{36}N_2O_5 \cdot 2C_4H_4O_4$	C, H, N
3v	2		33	81-83(ref[6]: 71-3) (free base) 147-149.5 (maleate)	$C_{22}H_{36}N_2O_5 \cdot C_4H_4O_4$	C, H, N
3x	2		62	170-171 (maleate)	$C_{34}H_{46}N_2O_5 \cdot C_4H_4O_4$	C, H, N

Table 2. Physical Properties of Compounds **4** and **5**

Compd	NR_1R_2	Yield(%)	M.P. (°C)	Formula	Elementary Analysis
4a	NMe_2	65	140-142 (maleate)	$C_{20}H_{35}NO_6 \bullet C_4H_4O_4$	C, H, N
4b	NEt_2	80	140-142 (maleate)	$C_{22}H_{39}NO_6 \bullet C_4H_4O_4$	C, H, N
4c	$NHC_3H_7(i)$	85	150-152 (maleate)	$C_{21}H_{37}NO_6 \bullet C_4H_4O_4$	C, H, N
4d		83	143-145 (malcatc)	$C_{22}H_{37}NO_7 \bullet C_4H_4O_4$	C, H, N
4e		71	148-150 (maleate)	$C_{22}H_{37}NO_6 \bullet C_4H_4O_4$	C, H, N
5a	NMe_2	94	148-152 (oxalate)	$C_{19}H_{33}NO_6 \bullet C_2H_2O_4$	C, H, N
5b	NEt_2	68	138-140 (maleate)	$C_{21}H_{37}NO_6 \bullet C_4H_4O_4$	C, H, N

Table 3. Antimalarial Activity of Seven Compounds against *P. berghei* K_{137}

Compd	Preparation	Route of administration	SD_{50}(mg/kg/day)	SD_{90}(mg/kg/day)
2c	aq. suspension	PO	6.33	23.39
3f	aq. solution	PO	1.61	4.71
		SC	24.57	255.83
3h	aq. solution	PO	1.74	5.08
		SC	27.66	165.96
3k	aq. solution	PO	1.67	19.85
3p	aq. solution	PO	1.61	5.26
3q	aq. solution	PO	1.82	7.29
3r	aq. solution	PO	1.82	5.28
		SC	5.57	302.49
3s	aq. solution	PO	1.33	11.19

25% in ref 6). ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.96 (3H, d, 6-CH_3), 0.98 (3H, d, 9-CH_3), 1.40 (3H, s, 3-CH_3), 3.80−4.30 (5H, m), 4.86 (1H, d, J = 3 Hz, 10-H), 5.43 (1H, s, 12-H). Anal. ($C_{18}H_{28}O_6$) C, H.

Preparation of 9α-Hydroxy-10α-(2′-bromoethyloxy)-artemisinin (9). 9-Hydroxydihydroartemisinin **(8)** (mp 131−133 °C) was prepared according to the reported procedure.[8,9] To a solution of 9-hydroxydihydroartemisinin **(8)** (3.0 g, 10 mmol) and bromoethanol (2.5 g, 20 mmol) in 150 mL of CH_2Cl_2 was added several drops of $BF_3 \cdot Et_2O$ at 0 °C. The mixture was stirred at room temperature until the reaction was complete. The reaction mixture was washed with a saturated $NaHCO_3$ solution, water and brine. The organic layer was dried and concentrated. The residue was recrystallized from petroleum ether−ethyl acetate to give 2.4 g of white crystals (yield 60%, mp 144−146 °C). ^{1}H NMR (100 MHz, $CDCl_3$): δ 0.84 (3H, d, 6-CH_3), 1.08 (3H, s, 9-CH_3), 1.36 (3H, s, 3-CH_3), 3.36 (2H, m, -CH_2Br), 3.80, 3.90 (2H, m, m, -OCH_2-), 4.60 (1H, s, 10-H), 5.44 (1H, s, 12-H). Anal. ($C_{17}H_{27}BrO_6$) C, H.

General Procedure for 3−5. A solution of bromide or **7**

Table 4. Rapidity of Parasite Clearance of **3f**, **3h,** and **3r** Oral Administration on *P. knowlesi* in Rhesus Monkeys (7-day treatment test)

Compd	Dose (mg/kg/day)	Number of monkey	Parasitemia before treatment(%)	Mean time for 50% reduction(h)	Mean time for 90% reduction(h)	Time of parasitemia clearance(h)
2c	10.0	3	35.0	8.21	13.74	50
	3.16	3	42.7	7.84	13.30	54
3f	10.0	2	42.5	6.25	13.98	44
	3.16	2	51.5	5.29	12.09	not
3h	3.16	2	74.0	4.50	11.38	52
3r	3.16	2	70.5	5.19	11.80	40

Table 5. Curative Efficacy of **3f**, **3h,** and **3s** Oral Administration on *P. knowlesi* in Rhesus Monkeys (7-day treatment test)[a]

Compound	Dose(mg/kg/day × 7) 10.0	3.16	Minimal curative dose
2c	3C/3T	3C/3T	3.16
3f	2MS/2T	2I/2T	> 10.0
3h	2MS/2T		> 3.16
3r	2I/2T		> 3.16

[a] T, tested monkey; C, cure; I, inactive; MS, marked suppression.

(1.0 equiv) and amine (2.0−4.0 equiv) in DMF (or alcohol, 50 mL) was heated in an oil bath (50−60 °C). After the reaction was complete, the mixture was evaporated to dryness under reduced pressure. The residue was extracted with CH_2Cl_2. The combined extract was washed with brine and dried. After the solvent was moved, the residue was purified by column chromatography to give the free base which combined with organic acid to yield compounds **3**−**5**. Some compounds were directly prepared from the crude bases and organic acid then recrystallized.

1-Dimethylamino-2-(10β-dihydroartemisinoxy)ethane oxalate (3f): free base; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.21 (6H, s, NMe_2), 2.44 (2H, t, -CH_2N-), 3.42, 3.82 (2H, m, -OC**H$_2$**CH_2-), 4.72 (1H, d, J = 3.3 Hz, 10-H), 5.36 (1H, s, 12-H). It combined with oxalic acid to yield **3f**.

1-(Hydroxyethylamino)-2-(10β-dihydroartemisinoxy)-ethane maleate (3k): ^{1}H NMR (400 MHz, D_2O) δ 0.94 (3H, d, J = 4.0 Hz, 6-CH_3), 0.96 (3H, d, J = 5.6 Hz, 9-CH_3), 1.42 (3H, s, 3-CH_3), 3.28 (2H, t, J = 5.2 Hz, -NC**H$_2$**CH_2OH), 3.41 (2H, m, O-CH_2C**H$_2$**-N-CH_2-), 3.87 (2H, t, J = 5.2 Hz, -NCH_2C**H$_2$**-OH), 3.72, 4.12 (2H, m, m, -OC**H$_2$**CH_2-), 4.87 (1H, d, J = 3.5 Hz, 10-H), 5.62 (1H, s, 12-H), 6.33 (2H, s, -CH=CH-); IR (KBr) 3500.

1-Morpholino-3-(10β-dihydroartemisinoxy)propane maleate (3r): free base; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, d, J = 7.5 Hz, 6-CH_3), 0.89 (3H, d, J = 6.2 Hz, 9-CH_3), 1.38 (3H, s, 3-CH_3), 1.71 (2H, m, -CH_2-C**H$_2$**-CH_2-), 2.38 {6H, m, -C**H$_2$**N-(C**H$_2$**)$_2$}, 3.36, 3.83 (2H, m, m, -OC**H$_2$**CH_2-CH_2-), 3.66 (4H, t, J = 4.6 Hz, CH_2C**H$_2$**-O-C**H$_2$**CH_2), 4.72 (1H, d, J = 3.4 Hz, 10-H), 5.33 (1H, s, 12-H). Its maleate: ^{1}H NMR (400 MHz, D_2O) δ 0.99 (3H, d, J = 7.4 Hz, 6-CH_3), 1.00 (3H, d, J = 5.8 Hz, 9-CH_3), 1.47 (3H, s, 3-CH_3), 2.14 (2H, m, -CH_2-C**H$_2$**-CH_2-), 3.34 (2H, m, -CH_2N), 3.30, 3.58 (2H, 2H, m, m, -CH_2N-CH_2-), 3.57, 3.97 (2H, m, m, −OC**H$_2$**CH_2CH_2-), 3.88, 4.18 (4H, m, m, CH_2C**H$_2$**-O-C**H$_2$**CH_2), 4.86 (1H, d, J = 4.0 Hz, 10-H), 5.62 (1H, s, 12-H), 6.39 (2H, s, -CH=CH-).

1-Dimethylamino-2-hydroxy-3-(10β-dihydroartemisinoxy)propane maleate (4a): ^{1}H NMR (100 MHz, D_2O) δ 0.95 (6H, d, 6, 9-Me_2), 1.42 (3H, s, 3-CH_3), 2.92, 2.97 (6H, s, s NMe_2), 3.27 (2H, m, -CH_2-N-), 3.48 (1H, m, -CH_2-C**H**-CH_2-) 3.85, 4.26 (2H, m, m, -OC**H$_2$**CH-), 4.82 (1H, d, J = 2.8 Hz, 10-H), 5.60 (1H, s, 12-H), 6.32 (2H, s, -CH=CH-).

9α-Hydroxy-10α-(2′-(dimethylamino)ethyloxy)deoxoartemisinin oxalate (5a): free base; ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.84 (3H, d, 6-CH_3), 1.08 (3H, s, 9-CH_3), 1.36 (3H, s, 3-CH_3), 2.84 (6H, s, NMe_2), 3.36 (2H, t, -CH_2-N-), 3.80, 3.90 (2H, m, m, -OC**H$_2$**CH-), 4.60 (1H, d, J = 3.0 Hz, 10-H), 5.44 (1H, s, 12-H).

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