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New Orally Active Amino- and Hydroxy-Functionalized 11-Azaartemisinins and Their Derivatives with High Order of Antimalarial Activity against Multidrug-Resistant *Plasmodium yoelii* in Swiss Mice[1]

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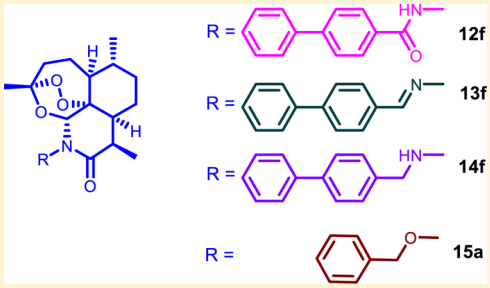
Supporting Information

ABSTRACT: By use of artemisinin **1** as the starting material, two new amino- and hydroxy-functionalized 11-azaartemisinins **9** and **11** and their derivatives **12a−g**, **13a−g**, **14a−g**, and **15a−c** have been prepared and screened for antimalarial activity by oral route against multidrug-resistant *Plasmodium yoelii* in Swiss mice. While azaartemisinins **9** and **11** showed only modest activity, several of their derivatives showed high order of antimalarial activity. Biphenyl-based compound **13f**, the most active compound of the series, provided 100% and 80% protection to the infected mice at 12 mg/kg × 4 days and 6 mg/kg × 4 days, respectively. Compounds **12f**, **13b**, **13e**, **13g**, and **14f** showed 100% protection at 12 mg/kg × 4 days, while compounds **12a−c**, **14a**, **14c−e**, **14g**, and **15a−c** showed similar levels of protection at 24 mg/kg × 4 days. Clinically useful drug β-arteether provided 100% protection at 48 mg/kg × 4 days and 20% protection at 24 mg/kg × 4 days in this model.



INTRODUCTION

Malaria, a vector-borne infectious disease caused by protozoan parasites of the genus *Plasmodium*, affects around 40% of the world population residing in tropical and subtropical regions of America, Asia, and Africa. Around 300−500 million clinical cases of malaria are reported every year. More than a million cases, mostly involving children, result in death due to complicated malaria.[2] The malaria situation is getting worse with the rapid spread of multidrug-resistant *Plasmodium falciparum*. Against this background, discovery of artemisinin **1** as the active principle of the Chinese traditional drug against malaria, *Artemisia annua*, and its conversion to clinically useful derivatives artemether **2**, arteether **3**, and artesunic acid **4** (Figure 1) were major breakthroughs in malaria chemotherapy.[3] These artemisinin derivatives are fast acting and are currently the drugs of choice for the treatment of cerebral/complicated malaria caused by multidrug-resistant *Plasmodium falciparum*.[4] While these drugs show excellent activity by parenteral routes, they are poorly absorbed when administered orally.[5] Therefore, the search for artemisinin derivatives with acceptable activity profile by oral route has been a major objective of several recent studies.[6] Particularly relevant to the present studies is the conversion of artemisinin to its aza derivatives, e.g., **5**−**8** (Figure 2), which are significantly more active than artemisinin.[7,8] In these aza derivatives nitrogen is in the form of an amide group, and only a limited number of derivatives have been made. Herein, we report an efficient conversion of artemisinin **1** into two new 11-azaartemisinin prototypes **9** and **11** with either a free amino or a free hydroxyl group and their subsequent derivatives, several of which

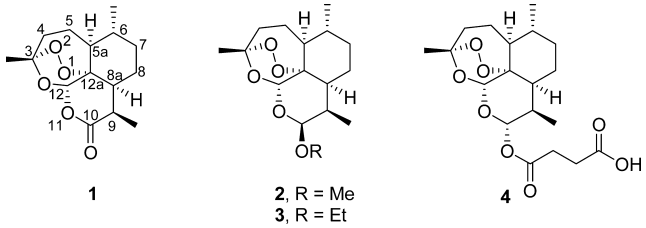


Figure 1. Artemisinin and its derivatives.

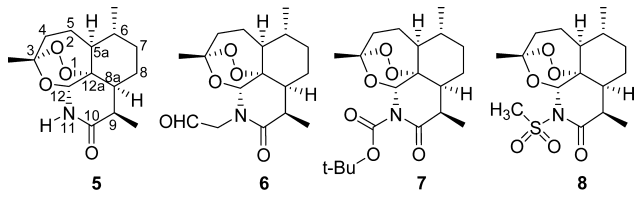


Figure 2. 11-Azaartemisinin and its derivative.

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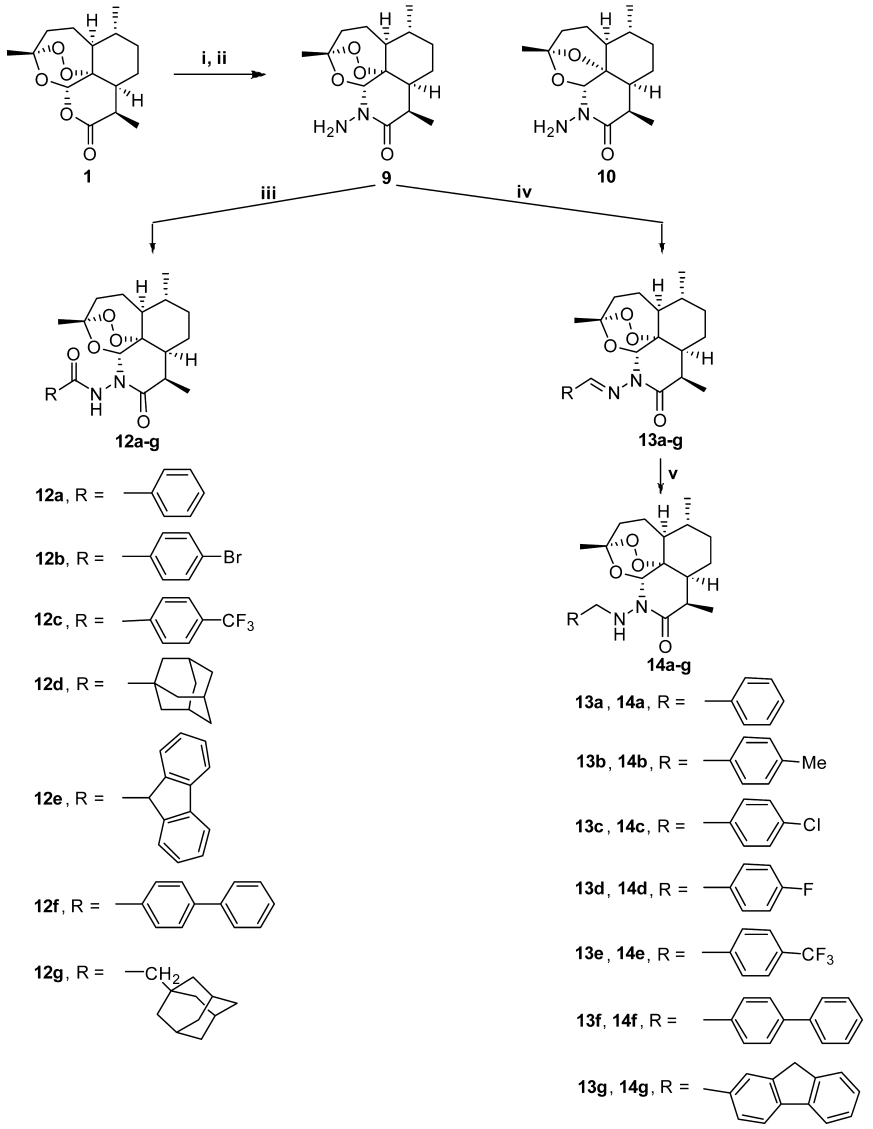
Scheme 1[a]



[a]Reagents and conditions: (i) $N_2H_4.H_2O$, MeOH, rt, 1 h; (ii) SiO_2/20% H_2SO_4, 2,6-di-*tert*-butylphenol, $CHCl_3$, 0 °C to rt, 12 h; (iii) RCOCl, Et_3N, C_6H_6, 0 °C, 2 h; (iv) RCHO, Amberlyst-15, C_6H_6, rt, 2 h; (v) $NaBH_4$, C_6H_6, 0 °C, 4 h.

showed high order of antimalarial activity against multidrug-resistant *P. yoelii* in Swiss mice by oral route.[9]

CHEMISTRY

N-Amino-11-azaartemisinin **9** and its derivatives **12a–g**, **13a–g**, and **14a–g** were prepared according to the Scheme 1. Thus, artemisinin **1** on reaction with hydrazine hydrate in MeOH at room temperature for 1 h followed by the treatment with silica gel and 20% H_2SO_4 in the presence of 2,6-di-*tert*-butylphenol in $CHCl_3$ furnished a mixture of *N*-amino-11-azaartemisinin **9** and its deoxy analogue **10** in a combined yield of 59% and in a ratio of 3:7, as indicated by ^{1}H NMR spectrum of the mixture. The yield of **9** improved to 70% when the first step of the reaction sequence was conducted in MeOH–$CHCl_3$ (7:3) for 1 h at 0 °C; no deoxy analogue was formed under these conditions. The reaction of **9** with benzoyl chloride in dry benzene in the presence of Et_3N at 0 °C furnished hydrazide derivative **12a** in 93% yield. Similar reaction of **9** with *p*-bromobenzoyl chloride, *p*-trifluoromethylbenzoyl chloride, adamantane-1-carbonyl chloride, 9*H*-fluorene-9-carbonyl chloride, *p*-phenylbenzoyl chloride, and adamantan-1-yl-acetyl chloride furnished the corresponding hydrazides **12b–g** in 60–93% yields. Hydrazones **13a–g** were prepared (76–94% yields) by reacting **9** with benzaldehyde, *p*-methylbenzaldehyde, *p*-chlorobenzaldehyde, *p*-fluorobenzaldehyde, *p*-trifluoromethylbenzaldehyde, *p*-phenylbenzaldehyde, and 9*H*-fluorene-2-carbaldehyde in the presence of Amberlyst-15 in dry benzene at room temperature. Sodium borohydride reduction of hydrazones **13a–g** in dry benzene at 0 °C provided the hydrazines **14a–g** in 62–74% yields. *N*-Hydroxy-11-azaartemisinin **11** and its derivatives **15a–c** were prepared according to Scheme 2. Thus, the reaction of artemisinin **1** with hydroxylamine in MeOH–$CHCl_3$ for 1 h at 0 °C followed by the treatment with SiO_2/20% H_2SO_4 in the presence of 2,6-di-*tert*-butylphenol in $CHCl_3$ furnished *N*-hydroxy-11-azaartemisinin **11** in 45% yield. Compound **11**, when reacted with benzyl bromide/NaH in dry THF, provided ether derivative **15a** in 72% yield. Similar reaction of **11** with *o*-fluorobenzyl bromide and *p*-phenylbenzyl

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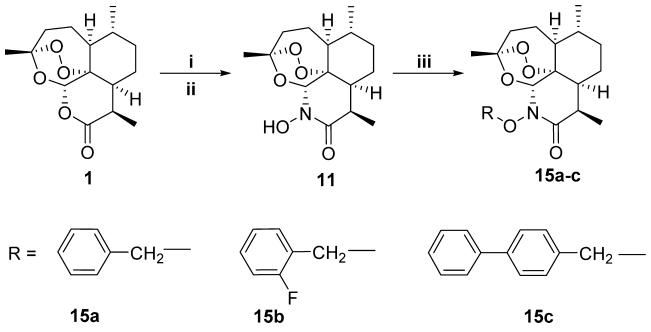
Scheme 2[a]



[a]Reagents and conditions: (i) NH_2OH, MeOH−$CHCl_3$, 0 °C, 1 h; (ii) SiO_2/20% H_2SO_4, 2,6-di-*tert*-butylphenol, $CHCl_3$, 0 °C to rt, 12 h; (iii) NaH, RBr, THF, 0 °C to rt, 12 h.

bromide furnished the corresponding ethers **15b** and **15c** in 65% and 74% yields, respectively.

All the new azaartemisinin derivatives were stable at room temperature and under standard conditions of purification such as column chromatography and crystallization.

ANTIMALARIAL ACTIVITY

Azaartemisinins **9** and **11** and their derivatives **12a−g**, **13a−g**, **14a−g**, and **15a−c** were evaluated for antimalarial activity against multidrug-resistant *Plasmodium yoelii* in Swiss mice by oral route.[10] In this model *β*-arteether provided 100% protection at a dose of 48 mg/kg × 4 days and 20% protection at 24 mg/kg × 4 days. Since the objective of this study was to discover compounds with better activity profile than that of arteether, all the compounds were initially screened at a dose of 24 mg/kg × 4 days. Compounds that provided 100% protection at 24 mg/kg × 4 days were further screened at 12 mg/kg × 4 days and 6 mg/kg × 4 days. The results are summarized in Table 1.

RESULTS AND DISCUSSION

Artemisinin derivatives such as artemether **2**, arteether **3**, and artesunic acid **4** are active against both chloroquine-sensitive and chloroquine-resistant malaria and are currently the drugs of choice for the treatment of malaria caused by chloroquine-resistant *P. falciparum*.[4] These drugs, however, have serious limitations such as short half-life and poor bioavailability when given by oral route.[5] Therefore the main objective of the recent studies on artemisinin has been to produce compound with improved bioavailability by oral route.[6]

We had recently reported the synthesis of several lipophilic ethers and esters of dihydroartemisinin that showed high order of antimalarial activity by oral route.[11] We have observed a similar relationship between lipophilicity and antimalarial activity in our work on synthetic 1,2,4-trioxanes.[12] Therefore, it was heartening to note that several of the lipophilic azaartemisinins reported in this paper showed high order of antimalarial activity against multidrug-resistant *P. yoelii* by oral route.

As can be seen from Table 1, both the parent azaartemisinins **9** and **11** showed poor activity but several of their derivatives, particularly hydrazides, hydrazones, and hydrazine derivatives of **9**, showed very promising antimalarial activity. Among the hydrazides, biphenyl-based derivative **12f** was the most active compound of the series. It provided 100% protection at 12 mg/kg × 4 days. Hydrazides **12a−c** provided 100% protection at 24 mg/kg × 4 days, while hydrazides **12d**, **12e**, **12g** showed only partial protection at 24 mg/kg × 4 days. Among the hydrazones, biphenyl-based derivative **13f** was the most active compound of the series. It showed 100% and 80% protection at 12 mg/kg × 4 days and 6 mg/kg × 4 days, respectively. Hydrazones **13b**, **13e**, and **13g** also provided 100% protection at 12 mg/kg × 4 days. Among hydrazines **14a−g**, biphenyl-based derivative **14f**, the most active compound of this series, showed 100% and 20% protection at 12 mg/kg × 4 days and 6 mg/kg × 4 days, respectively. Hydrazine **14c** showed 100% and 80% protection at 24 mg/kg × 4 days and 12 mg/kg × 4 days, respectively. Hydrazines **14a**, **14d**, **14e**, and **14g** were another four compounds of this series that showed promising activity; these compounds provided 100% protection at 24 mg/kg × 4 days.

All the ether derivatives (**15a−c**) prepared from hydroxy-functionalized azaartemisinin **11** showed 100% protection at 24 mg/kg × 4 days. Ether **15a** was the most active derivative of **11**. It showed 100% and 80% protection at 24 mg/kg × 4 days and 12 mg/kg × 4 days, respectively.

It is clear from this discussion that the compounds derived from amino-functionalized azaartemisinin **9** in general showed better activity profile than the compounds derived from hydroxy-functionalized azaartemisinin **11**. Six of the derivatives of **9** (**12f**, **13b**, **13e−g**, and **14f**) showed 100% protection at dose of 12 mg/kg × 4 days. These compounds are thus 4-fold more potent than *β*-arteether, which showed 100% protection at 48 mg/kg × 4 days.

It is instructive to note that log *P* values of the six most active compounds of the series lie in the range 5.40−6.65. These activity results reinforce our earlier observation that increased lipophilicity generally leads to improved activity by oral route.

CONCLUSION

We have prepared a new series of azaartemisinins, several of which showed excellent antimalarial activity by oral route. Hydrazone **13f**, the most active compound of the series, showed 100% and 80% protection at 12 mg/kg × 4 days and 6 mg/kg × 4 days, respectively. Compounds **12f**, **13b**, **13e**, **13g**, and **14f**, which showed 100% protection at 12 mg/kg × 4 days, are the other promising compounds of this series. All six of these compounds are 4-fold more potent than *β*-arteether by oral route.

EXPERIMENTAL SECTION

General Comments on Experimental Data. All glass apparatus were oven-dried prior to use. Melting points were taken in open capillaries on Complab melting point apparatus and are presented uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Supercon Magnet DPX-200 and DRX-300 spectrometers (respectively operating at 200 and 300 MHz for ^{1}H and at 50 and 75 MHz for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR, and $CDCl_3$ (δ 77.23 ppm) was the internal standard in ^{13}C NMR. Chemical shifts are reported in parts per million (ppm). Fast atom bombardment mass spectrometry (FAB-MS) results were obtained on a JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectrometry (ES-MS) results were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectrometry (EI-HRMS) results were obtained on JEOL MS route 600H instrument. Column chromatography was performed over silica gel (particle size, 60−120 mesh)

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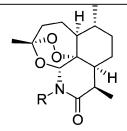
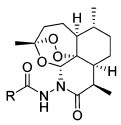
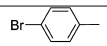
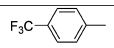
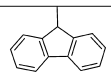
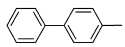
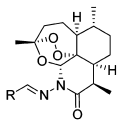
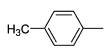
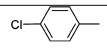
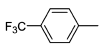
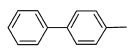
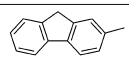
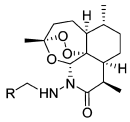
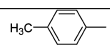
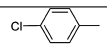
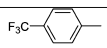
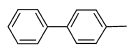
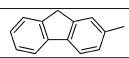
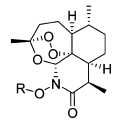
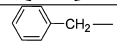
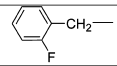
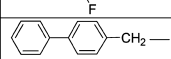
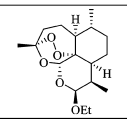
Table 1. Blood Schizontocidal Activity of Compounds 9, 11, 12a–g, 13a–g, 14a–g, and 15a–c against Multidrug-Resistant *P. yoelii* in Swiss Mice via Oral Route

General Structure	Compd	R	Log *P*	Dose mg/kg x 4 days	% Supp. on day 4 [a,b]	Mice alive on day 28
	**9**	-NH_2	2.25	24	100	2/5
	11	-OH	2.66	24	54	0/5
	**12a**		3.85	24	100	5/5
				12	62	0/5
	12b		4.68	24	100	5/5
				12	100	0/5
	12c		4.78	24	100	5/5
				12	100	1/5
	12d		4.63	24	100	3/5
	12e		5.19	24	100	3/5
	12f		5.53	24	100	5/5
				12	100	5/5
				6	94	0/5
	12g		4.57	24	100	3/5
	**13a**		4.92	24	100	2/5
	13b		5.40	24	100	5/5
				12	100	5/5
				6	66	0/5
	13c		5.48	24	100	1/5
	13d		5.07	24	100	2/5
	13e		5.84	24	100	5/5
				12	100	5/5
				6	99	0/5
	13f		6.59	24	100	5/5
				12	100	5/5
				6	100	4/5
	13g		6.65	24	100	5/5
				12	100	5/5
				6	66	0/5
	**14a**		4.21	24	100	5/5
				12	100	0/5
	14b		4.70	24	100	3/5
				12	74	0/5
	14c		4.77	24	100	5/5
				12	100	4/5
	14d		4.37	24	100	5/5
				12	100	1/5
	14e		5.14	24	100	5/5
				12	100	1/5
	14f		5.89	24	100	5/5
				12	100	5/5
				6	100	1/5
	14g		5.95	24	100	5/5
				12	100	2/5
	**15a**		4.66	24	100	5/5
				12	100	4/5
	15b		4.81	24	100	5/5
				12	89	0/5
	15c		6.33	24	100	5/5
				12	100	3/5
	**3**	-	3.84	48	100	5/5
				24	100	1/5

[a]Percent suppression = $[(C - T)/C] \times 100$; where C is parasitemia in control group and T is parasitaemia in treated group. [b]100% suppression of parasitemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[13]

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procured from Qualigens (India). All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used without further purification. Nomenclature and log *P* values of the compounds were assigned using ChemBio Draw Ultra 13.0 software. Elemental analysis results of all the new compounds were recorded on Vario EL-III CHNS analyzer (Germany), and values were within 0.5% of the calculated values for all compounds; therefore, these compounds meet the criteria of ≥95% purity.

Preparation of *N*-Amino-11-azaartemisnin (9). To a stirred solution of $N_2H_4{\cdot}H_2O$ (21.3 mL, 425 mmol, 20 equiv) in a mixture of MeOH−$CHCl_3$ (7:3, 120 mL) at 0 °C was added a solution of artemisinin **1** (6.00 g, 21.3 mmol) in $CHCl_3$ (30.0 mL) gradually over 5 min, and the reaction mixture was allowed to stir for 1 h at the same temperature. The reaction mixture was diluted with water (300 mL) and extracted with $CHCl_3$ (3 × 100 mL). To the combined organic layer, 2,6-di-*tert*-butylphenol (400 mg), 20% H_2SO_4 (40.0 mL) and silica gel (40.0 g) were added, and the mixture was stirred for 12 h at room temperature. The reaction mixture was filtered, and the residue was washed with $CHCl_3$ (2 × 100 mL). The combined filtrate was washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure at room temperature. The crude product was purified by column chromatography over silica gel using 50% EtOAc/hexane as eluent to furnish pure *N*-amino-11-azaartemisinin **9** (4.40 g, yield 70%) as a white solid, mp 122−125 °C. FT-IR (KBr cm^{-1}) 1653, 3315; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86−1.00 (m, 2H), 0.94 (d, 3H, J = 6.2 Hz), 1.10 (d, 3H, J = 7.3 Hz), 1.29−1.44 (m, 3H), 1.33 (s, 3H), 1.59−1.75 (m, 3H), 1.92−2.03 (m, 2H), 2.30−2.41 (m, 1H), 3.24−3.33 (m, 1H), 4.63 (brs, 2H, NH_2), 5.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.64 (CH_3), 19.80 (CH_3), 22.77 (CH_2), 25.06 (CH_2), 25.51 (CH_3), 32.85 (CH), 33.65 (CH_2), 36.56 (CH_2), 37.38 (CH), 46.01 (CH), 51.35 (CH), 80.66 (C), 80.99 (CH), 104.92 (C), 169.68 (C); ESI-MS (m/z) 297 $[M + H]^+$. EI-HRMS calcd for $C_{15}H_{24}N_2O_4$ $[M]^+$: 296.1736. Found: 296.1742. Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79%, H, 8.16%, N, 9.45%. Found: C, 60.92%, H, 8.65%, N, 9.75%.

Preparation of *N*-Hydroxy-11-azaartemisinin (11). Compound **11** was prepared by the above procedure by replacing hydrazine hydrate with hydroxylamine. Yield 45%, white solid, mp 165−167 °C; IR (KBr, cm^{-1}) 1649, 3418; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89−1.02 (m, 2H), 0.97 (d, 3H, J = 5.9 Hz), 1.10 (d, 3H, J = 7.3 Hz), 1.31−1.52 (m, 3H), 1.43 (s, 3H), 1.63−1.77 (m, 3H), 1.94−2.07 (m, 2H), 2.35−2.46 (m, 1H), 3.35−3.44 (m, 1H), 5.40 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.11 (CH_3), 19.88 (CH_3), 22.94 (CH_2), 25.18 (CH_2), 25.47 (CH_3), 32.98 (CH), 33.75 (CH_2), 36.70 (CH_2), 37.52 (CH), 46.64 (CH), 51.49 (CH), 81.22 (CH), 81.52 (C), 105.27 (C), 170.08 (C); ESIMS (m/z) 298 $[M + H]^+$. HRMS [ESI] calcd for $C_{15}H_{24}NO_5$ $[M + H]^+$: 298.1654. Found: 298.1631. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59%, H, 7.80%, N, 4.71%. Found: C, 60.64%, H, 7.89%, N, 4.53%.

General Procedure for Preparation of Hydrazide Derivatives (12a−g) of *N*-Amino-11-azaartemisnin (9). *Preparation of N-((3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-10-oxodecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-11(12H)-yl)benzamide (**12a**).* To a stirred solution of compound **9** (500 mg, 1.69 mmol) and Et_3N (1.17 mL, 8.39 mmol) in dry benzene (5.00 mL) at 0 °C was added a solution of benzoyl chloride (0.970 mL, 8.34 mmol) in dry benzene (5.00 mL), and the reaction mixture was allowed to stir at the same temperature for 2 h. The reaction mixture was quenched with water (10.0 mL) and extracted with ether (3 × 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ (3 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure at room temperature. The crude product was purified by column chromatography over silica gel using 20% EtOAc/hexane as eluent to furnish compound **12a** (628 mg, 93% yield) as a white solid, mp 218−220 °C. FT-IR (KBr cm^{-1}) 1654, 1701, 3246; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, 3H, J = 6.3 Hz), 1.05−1.09 (m, 1H), 1.22 (d, 3H, J = 7.3 Hz), 1.32−1.52 (m, 3H), 1.47 (s, 3H), 1.70−2.05 (m, 6H), 2.39−2.50 (m, 1H), 3.41−3.48 (m, 1H), 5.62 (s, 1H), 7.24−7.77 (m, 5H, Ar), 9.33 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.73 (CH_3), 19.88 (CH_3), 22.74 (CH_2), 25.26 (CH_2), 25.49 (CH_3), 33.71 (CH), 34.05 (CH_2), 36.72 (CH_2), 37.58 (CH), 46.28 (CH), 51.51 (CH), 80.25 (C), 81.29 (CH), 105.19 (C), 127.68 (2 × CH), 128.50 (2 × CH), 131.66 (C), 132.04 (CH), 165.94 (C), 172.51 (C); ESI-MS (m/z) 401 $[M + H]^+$. Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98%, H, 7.05%, N, 7.00%. Found: C, 66.06%, H, 7.39%, N, 7.01%.

Compounds **12b−g** were prepared by the above procedure by replacing benzoyl chloride with *p*-bromobenzoyl chloride, *p*-trifluoromethylbenzoyl chloride, adamantane-1-carbonyl chloride, 9*H*-fluorene-9-carbonyl chloride, *p*-phenylbenzoyl chloride, and adamantan-1-ylacetyl chloride, respectively.

*4-Bromo-N-((3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-trimethyl-10-oxodecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-11(12H)-yl)benzamide (**12b**).* Yield 60%, white solid, mp 230−232 °C; FT-IR (KBr cm^{-1}) 1692, 1727, 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97−1.01 (m, 1H), 0.98 (d, 3H, J = 6.0 Hz), 1.21 (d, 3H, J = 7.3 Hz), 1.39−2.04 (m, 9H), 1.48 (s, 3H), 2.39−2.49 (m, 1H), 3.42−3.46 (m, 1H), 5.59 (s, 1H), 7.38 (d, 2H, Ar, J = 8.4 Hz), 7.62 (d, 2H, Ar, J = 8.4 Hz), 9.87 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.79 (CH_3), 19.90 (CH_3), 22.87 (CH_2), 25.29 (CH_2), 25.47 (CH_3), 33.71 (CH), 34.07 (CH_2), 36.70 (CH_2), 37.64 (CH), 46.14 (CH), 51.48 (CH), 80.03 (C), 81.26 (CH), 105.24 (C), 127.09 (C), 129.27 (2 × CH), 130.22 (C), 131.68 (2 × CH), 164.66 (C), 172.99 (C); ESI-MS (m/z) 479 $[M + H]^+$. Anal. Calcd for $C_{22}H_{27}N_2O_5Br$: C, 55.12%, H, 5.68%, N, 5.84%. Found: C, 54.80%, H, 6.06%, N, 5.80%.

*4-(Trifluoromethyl)-N-((3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-trimethyl-10-oxodecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-11(12H)-yl)benzamide (**12c**).* Yield 85%, white solid, mp 217−220 °C; FT-IR (KBr cm^{-1}) 1653, 1702, 3422; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3H, J = 6.1 Hz), 1.03−1.12 (m, 1H), 1.23 (d, 3H, J = 7.3 Hz), 1.37−2.05 (m, 9H), 1.50 (s, 3H), 2.40−2.49 (m, 1H), 3.42−3.51 (m, 1H), 5.60 (s, 1H), 7.43 (d, 2H, Ar, J = 8.2 Hz), 7.84 (d, 2H, Ar, J = 8.2 Hz), 10.35 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.83 (CH_3), 19.90 (CH_3), 22.95 (CH_2), 25.28 (CH_2), 25.40 (CH_3), 33.71 (CH), 34.05 (CH_2), 36.64 (CH_2), 37.66 (CH), 46.02 (CH), 51.42 (CH), 79.87 (C), 81.23 (CH), 105.29 (C), 125.48 (q, C, J_{C-F} = 3.8 Hz), 128.09 (4 × CH), 133.14 (C), 134.34 (CH), 163.81 (C), 173.26 (C); ESI-MS (m/z) 469 $[M + H]^+$. EI-HRMS calcd for $C_{23}H_{27}N_2O_5F_3$ $[M]^+$: 468.1872. Found: 468.1843. Anal. Calcd for $C_{23}H_{27}N_2O_5F_3$: C, 58.97%, H, 5.81%, N, 5.98%. Found: C, 58.82%, H, 5.96%, N, 6.00%.

*(1R,3R)-N-((3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-10-oxodecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-11(12H)-yl)-adamantane-2-carboxamide (**12d**).* Yield 89%, white solid, mp 168−170 °C; FT-IR (KBr cm^{-1}) 1672, 1702, 3018, 3334; ^1H NMR (300 MHz, $CDCl_3$); δ 0.63−0.68 (m, 3H), 0.77 (d, 3H, J = 6.3 Hz), 0.97 (d, 3H, J = 7.3 Hz), 1.32−1.87 (m, 22H), 1.19 (s, 3H), 2.18−2.28 (m, 1H), 3.15−3.23 (m, 1H), 5.26 (s, 1H), 7.16 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.55 (CH_3), 19.86 (CH_3), 22.58 (CH_2), 25.20 (CH_2), 25.73 (CH_3), 28.16 (3 × CH), 33.72 (CH), 33.99 (CH_2), 36.61 (3 × CH_2), 36.76 (CH_2), 37.48 (CH), 39.03 (3 × CH_2), 40.69 (C), 46.48 (CH), 51.51 (CH), 80.76 (CH), 81.35 (C), 104.98 (C), 171.68 (C), 177.23 (C); ESI-MS (m/z) 459 $[M + H]^+$. EI-HRMS calcd for $C_{26}H_{39}N_2O_5$ $[M + H]^+$: 459.2859. Found: 459.2843. Anal. Calcd for $C_{26}H_{38}N_2O_5$: C, 68.10%, H, 8.35%, N, 6.11%. Found: C, 68.45%, H, 8.70%, N, 5.88%.

*N-((3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-10-oxodecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-11(12H)-yl)-9H-fluorene-9-carboxamide (**12e**).* Yield 85%, white solid, mp 217−219 °C; FT-IR (KBr cm^{-1}) 1664, 1706, 3264; ^1H NMR (300 MHz, $CDCl_3$); δ 0.87−1.03 (m, 2H), 0.97 (d, 3H, J = 6.2 Hz), 1.16 (d, 3H, J = 7.3 Hz), 1.25 (s, 3H), 1.28−2.01 (m, 8H), 2.35−2.44 (m, 1H), 3.33−3.37 (m, 1H), 4.88 (s, 1H), 5.49 (s, 1H), 7.34−7.85 (m, 9H including NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.54 (CH_3), 19.86 (CH_3), 22.70 (CH_2), 25.17 (CH_2), 25.47 (CH_3), 33.75 (CH), 33.96 (CH_2), 36.69 (CH_2), 37.52 (CH), 46.34 (CH), 51.45 (CH), 54.46 (CH), 80.35 (CH), 81.20 (C), 104.97 (C), 120.46 (2 × CH), 125.63 (CH), 125.68 (CH), 127.80 (CH), 128.10 (CH), 128.59 (CH), 128.64 (CH), 140.78 (C), 140.88 (C), 141.63 (C), 141.82 (C), 169.71 (C), 171.43 (C); ESI-MS (m/z) 489 $[M + H]^+$. EI-HRMS Calcd for $C_{29}H_{32}N_2O_5$

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$[M]^+$: 488.2311. Found: 488.2312. Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29%, H, 6.60%, N, 5.73%. Found: C, 71.49%, H, 6.34%, N, 5.96%.

*N-((3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-10-oxodecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-11(12H)-yl)-[1,1′-biphenyl]-4-carboxamide (**12f**).* Yield 93%, white solid, mp 205−207 °C; FT-IR (KBr cm^{-1}) 1614, 1675, 3396; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3H, J = 6.1 Hz), 1.07−1.11 (m, 1H), 1.25 (d, 3H, J = 7.3 Hz), 1.38−2.06 (m, 9H), 1.51 (s, 3H), 2.41−2.51 (m, 1H), 3.47−3.50 (m, 1H), 5.66 (s, 1H), 7.37−7.88 (m, 9H, Ar), 9.59 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.81 (CH_3), 19.91 (CH_3), 22.85 (CH_2), 25.29 (CH_2), 25.55 (CH_3), 33.74 (CH), 34.09 (CH_2), 36.74 (CH_2), 37.61 (CH), 46.26 (CH), 51.52 (CH), 80.22 (CH), 81.32 (C), 105.20 (C), 127.03 (2 × CH), 127.30 (2 × CH), 128.07 (CH), 128.20 (2 × CH), 128.98 (2 × CH), 130.23 (C), 140.16 (C), 144.55 (C), 165.56 (C), 172.78 (C); ESI-MS (m/z) 477 $[M + H]^+$. EI-HRMS calcd for $C_{28}H_{32}N_2O_5$ $[M]^+$: 476.2311. Found: 476.2310 Anal. Calcd for $C_{28}H_{32}N_2O_5$: C, 70.57%, H, 6.77%, N, 5.88%. Found: C, 70.89%, H, 7.00%, N, 6.15%.

*2-((1R,3R)-Adamantan-2-yl)-N-((3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-trimethyl-10-oxodecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-11(12H)-yl)acetamide (**12g**).* Yield 88%, white solid, mp 166−168 °C; FT-IR (KBr cm^{-1}), 1646, 1702, 3201; ^1H NMR (300 MHz, $CDCl_3$); δ 0.97−1.05 (m, 1H), 0.98 (d, 3H, J = 6.1 Hz), 1.17 (d, 3H, J = 7.2 Hz), 1.30−2.07 (m, 26H), 1.38 (s, 3H), 2.37−2.48 (m, 1H), 3.33−3.41 (m, 1H), 5.49 (s, 1H), 7.43 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.65 (CH_3), 19.87 (CH_3), 22.65 (CH_2), 25.28 (CH_2), 25.59 (CH_3), 28.84 (3 × CH), 33.15 (CH), 33.71 (C), 33.98 (CH_2), 36.75 (CH_2), 36.91 (3 × CH_2), 37.59 (CH), 42.55 (3 × CH_2), 46.44 (CH), 49.35 (CH_2), 51.48 (CH), 80.47 (CH), 81.25 (C), 105.08 (C), 169.75 (C), 171.60 (C); ESI-MS (m/z) 473 $[M + H]^+$. Anal. Calcd for $C_{27}H_{40}N_2O_5$: C, 68.62%, H, 8.53%, N, 5.93%. Found: C, 68.99%, H, 8.66%, N, 5.67%.

General Procedure for Preparation of Hydrazone Derivatives (13a−g) of *N*-Amino-11-azaartemisnin (9). *Preparation of (3R,5aS,6R,8aS,9R,12R,12aR)-11-(((E)-Benzylidene)amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-10(3H)-one (**13a**).* To a stirred solution of **9** (500 mg, 1.69 mmol) in dry benzene (5.00 mL) at room temperature were added benzaldehyde (0.700 mL, 6.86 mmol) and Amberlyst-15 (50.0 mg), and the reaction mixture was allowed to stir for 2 h at the same temperature. The reaction mixture was filtered, and the residue was washed with ether (2 × 50 mL). The combined organic layer was concentrated under reduced pressure at room temperature and the crude product was purified by column chromatography over silica gel using 5% EtOAc/hexane as eluent to furnish compound **13a** (610 mg, 94% yield) as a white solid, mp 178−181 °C. FT-IR (KBr cm^{-1}) 1662, 1603; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, 3H, J = 6.3 Hz), 1.09−1.16 (m, 2H), 1.20 (d, 3H, J = 7.2 Hz), 1.34 (s, 3H), 1.41−2.07 (m, 8H), 2.40−2.49 (m, 1H), 3.50−3.59 (m, 1H), 5.77 (s, 1H), 7.39−7.83 (m, 5H, Ar), 8.61 (s, 1H, imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.67 (CH_3), 19.99 (CH_3), 23.02 (CH_2), 25.23 (CH_2), 25.66 (CH_3), 33.91 (CH_2), 34.36 (CH), 36.74 (CH_2), 37.59 (CH), 46.59 (CH), 51.72 (CH), 81.24 (C), 81.80 (CH), 105.20 (C), 128.48 (2 × CH), 128.78 (2 × CH), 131.30 (C), 133.96 (C), 164.67 (CH), 169.12 (C); ESI-MS (m/z) 385 $[M + H]^+$. EI-HRMS calcd for $C_{22}H_{28}N_2O_4$ $[M]^+$: 384.2049. Found: 384.2024. Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73%, H, 7.34%, N, 7.29%. Found: C, 68.80%, H, 7.16%, N, 7.25%.

Compounds **13b−g** were prepared by the above procedure by replacing benzaldehyde with *p*-methylbenzaldehyde, *p*-chlorobenzaldehyde, *p*-fluorobenzaldehyde, *p*-trifluoromethylbenzaldehyde, *p*-phenylbenzaldehyde, and 9*H*-fluorene-2-carbaldehyde, respectively.

*(3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-11-(((E)-4-methylbenzylidene)amino)decahydro-3,12-epoxy[1,2]dioxepino-[4,3-i]isoquinolin-10(3H)-one (**13b**).* Yield 94%, white solid, mp 138−140 °C; FT-IR (KBr cm^{-1}) 1667, 2864, 2936; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 3H, J = 6.0 Hz), 1.08−1.16 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.40−2.04 (m, 8H), 2.39 (s, 3H), 2.39−2.45 (m, 1H), 3.51−3.55 (m, 1H), 5.75 (s, 1H), 7.23 (d, 2H, J = 7.8 Hz), 7.70 (d, 2H, J = 7.8 Hz), 8.54 (s, 1H, imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.64 (CH_3), 19.96 (CH_3), 21.77 (CH_3), 22.99 (CH_2), 25.20 (CH_2), 25.62 (CH_3), 33.90 (CH_2), 34.29 (CH), 36.72 (CH_2), 37.56 (CH), 46.57 (CH), 51.72 (CH), 81.22 (C), 81.65 (CH), 105.14 (C), 128.47 (2 × CH), 129.49 (2 × CH), 131.19 (C), 141.72 (C), 165.18 (C), 169.02 (C); ESI-MS (m/z) 399 $[M + H]^+$. Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32%, H, 7.59%, N, 7.03%. Found: C, 69.55%, H, 7.77%, N, 7.08%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-(((E)-4-Chlorobenzylidene)-amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]-isoquinolin-10(3H)-one (**13c**).* Yield 76%, white solid, mp 170−172 °C; FT-IR (KBr cm^{-1}) 1654, 2931, 3020; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, 3H, J = 6.2 Hz), 1.09−1.13 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.41−2.07 (m, 8H), 2.45−2.49 (m, 1H), 3.50−3.59 (m, 1H), 5.76 (s, 1H), 7.40 (d, 2H, J = 8.5 Hz), 7.74 (d, 2H, J = 8.5 Hz), 8.61 (s, 1H, imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.64 (CH_3), 19.96 (CH_3), 23.01 (CH_2), 25.22 (CH_2), 25.64 (CH_3), 33.88 (CH_2), 34.41 (CH), 36.71 (CH_2), 37.61 (CH), 46.53 (CH), 51.68 (CH), 81.20 (C), 81.91 (CH), 105.25 (C), 129.09 (2 × CH), 129.58 (2 × CH), 132.56 (C), 137.21 (C), 162.48 (CH), 169.26 (C); ESI-MS (m/z) 419 $[M + H]^+$. Anal. Calcd for $C_{22}H_{27}N_2O_4Cl$: C, 63.08%, H, 6.50%, N, 6.69%. Found: C, 62.95%, H, 6.66%, N, 6.50%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-(((E)-4-Fluorobenzylidene)-amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]-isoquinolin-10(3H)-one (**13d**).* Yield 92%, white solid, mp 115−120 °C; FT-IR (KBr cm^{-1}) 1652, 2931, 3017; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 3H, J = 6.2 Hz), 1.07−1.14 (m, 2H), 1.19 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.40−2.06 (m, 8H), 2.40−2.49 (m, 1H), 3.50−3.58 (m, 1H), 5.75 (s, 1H), 7.07−7.83 (m, 4H, Ar), 8.58 (s, 1H, imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.61 (CH_3), 19.94 (CH_3), 22.98 (CH_2), 25.19 (CH_2), 25.62 (CH_3), 33.86 (CH_2), 34.32 (CH), 36.69 (CH_2), 37.58 (CH), 46.54 (CH), 51.66 (CH), 81.18 (C), 81.80 (CH), 105.21 (C), 115.93 (d, 2 × CH, J_{C-F} = 22 Hz), 130.19 (d, C, J_{C-F} = 3.0 Hz), 130.42 (d, 2 × CH, J_{C-F} = 9.0 Hz), 163.26 (CH), 164.77 (d, C, J_{C-F} = 250 Hz), 169.20 (C); ESI-MS (m/z) 403 $[M + H]^+$, 425 $[M + Na]^+$. EI-HRMS calcd for $C_{22}H_{27}N_2O_4F$ $[M]^+$: 402.1955. Found: 402.1982. Anal. Calcd for $C_{22}H_{27}N_2O_4F$: C, 65.66%, H, 6.76%, N, 6.96%. Found: C, 65.79%, H, 6.83%, N, 6.82%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-11-(((E)-4-(trifluoromethyl)benzylidene)amino)decahydro-3,12-epoxy[1,2]-dioxepino[4,3-i]isoquinolin-10(3H)-one (**13e**).* Yield 82%, white solid, mp 170−173 °C; FT-IR (KBr cm^{-1}) 1672; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, 3H, J = 6.2 Hz), 1.09−1.13 (m, 2H), 1.21 (d, 3H, J = 7.2 Hz), 1.33 (s, 3H), 1.41−2.06 (m, 8H), 2.40−2.51 (m, 1H), 3.51−3.60 (m, 1H), 5.79 (s, 1H), 7.67 (d, 2H, Ar, J = 8.1 Hz), 7.91 (d, 2H, Ar, J = 8.1 Hz), 8.74 (s, 1H, imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.62 (CH_3), 19.92 (CH_3), 22.99 (CH_2), 25.19 (CH_2), 25.60 (CH_3), 33.83 (CH_2), 34.51 (CH), 36.67 (CH_2), 37.59 (CH), 46.46 (CH), 51.64 (CH), 81.15 (C), 82.05 (CH), 105.27 (C), 125.71 (q, C, J_{C-F} = 4.0 Hz, CF_3), 128.45 (4 × CH), 137.56 (2 × C), 160.75 (CH), 169.38 (C); ESI-MS (m/z) 453 $[M + H]^+$. EI-HRMS calcd for $C_{23}H_{27}N_2O_4F_3$ $[M]^+$: 452.1923. Found: 452.1922. Anal. Calcd for $C_{23}H_{27}N_2O_4F_3$: C, 61.05%, H, 6.01%, N, 6.19%. Found: C, 61.15%, H, 6.20%, N, 6.14%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-(((E)-[1,1′-Biphenyl]-4-ylmethylene)amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]-dioxepino[4,3-i]isoquinolin-10(3H)-one (**13f**).* Yield 94%, white solid, mp 118−120 °C; FT-IR (KBr cm^{-1}) 1601, 1687; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85−1.13 (m, 2H), 1.05 (d, 3H, J = 6.3 Hz), 1.22 (d, 3H, J = 7.3 Hz), 1.35 (s, 3H), 1.42−1.81 (m, 6H), 2.02−2.08 (m, 2H), 2.41−2.52 (m, 1H), 3.52−3.61 (m, 1H), 5.80 (s, 1H), 7.36−7.91 (m, 9H, Ar), 8.66 (s, 1H, imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.67 (CH_3), 19.97 (CH_3), 23.01 (CH_2), 25.22 (CH_2), 25.66 (CH_3), 33.90 (CH_2), 34.38 (CH), 36.73 (CH_2), 37.58 (CH), 46.58 (CH), 51.72 (CH), 81.23 (C), 81.81 (CH), 105.20 (C), 127.33 (2 × CH), 127.46 (2 × CH), 127.99 (CH), 128.91 (2 × CH), 129.05 (2 × CH), 132.92 (C), 140.55 (C), 143.99 (C), 164.10 (CH), 169.14 (C); ESI-MS (m/z) 461 $[M + H]^+$. Anal. Calcd for $C_{28}H_{32}N_2O_4$: C, 73.02%, H, 7.00%, N, 6.08%. Found: C, 72.95%, H, 6.91%, N, 6.00%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-(((E)-(9H-Fluoren-2-yl)-methylene)amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]-dioxepino[4,3-i]isoquinolin-10(3H)-one (**13g**).* Yield 92%, white solid, mp 205−207 °C; FT-IR (KBr cm^{-1}) 1659, 2930; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88−1.36 (m, 2H), 1.05 (d, 3H, J = 6.2 Hz), 1.21 (d, 3H, J

= 7.2 Hz), 1.36 (s, 3H), 1.44−1.88 (m, 6H), 2.02−2.07 (m, 2H), 2.41−2.51 (m, 1H), 3.55−3.59 (m, 1H), 3.94 (s, 2H), 5.80 (s, 1H), 7.33−7.85 (m, 6H), 8.09 (s, 1H), 8.66 (s, 1H, imine H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.68 (CH_3), 19.99 (CH_3), 23.02 (CH_2), 25.23 (CH_2), 25.68 (CH_3), 33.92 (CH_2), 34.34 (CH), 36.74 (CH_2), 36.99 (CH_2), 37.61 (CH), 46.60 (CH), 51.73 (CH), 81.25 (C), 81.77 (CH), 105.22 (C), 120.07 (CH), 120.67 (CH), 124.39 (CH), 125.36 (CH), 127.13 (CH), 127.68 (CH), 128.31 (CH), 132.37 (C), 141.21 (C), 143.68 (C), 144.27 (C), 144.97 (C), 165.31 (CH), 169.14 (C); ESI-MS (m/z) 473 $[M + H]^+$. Anal. Calcd for $C_{29}H_{32}N_2O_4$: C 73.70%, H 6.83%, N 5.93%. Found: C 73.99%, H 6.95%, N 5.89%.

General Procedure for Preparation of Hydrazine Derivatives (14a−g) of *N*-Amino-11-azaartemisnin (9). *Preparation of (3R,5aS,6R,8aS,9R,12R,12aR)-11-(Benzylamino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-10(3H)-one (**14a**).* To a stirred solution of compound **13a** (500 mg, 1.30 mmol) in benzene (15.0 mL) at 0 °C was added $NaBH_4$ (247 mg, 6.52 mmol), and the reaction mixture was allowed to stir at the same temperature for 4 h. The reaction mixture was quenched with glacial AcOH (3.00 mL), neutralized with saturated $NaHCO_3$ (10.0 mL), and extracted with ether (3 × 25 mL). The combined organic layer was concentrated under reduced pressure at room temperature and the crude product was purified by column chromatography over silica gel using 5% EtOAc/hexane as eluent to furnish compound **14a** (336 mg, 67% yield) as an oil. FT-IR (neat cm^{-1}) 1659; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77−1.00 (m, 2H), 0.99 (d, 3H, J = 5.7 Hz), 1.17 (d, 3H, J = 7.3 Hz), 1.27−2.11 (m, 8H), 1.49 (s, 3H), 2.41−2.51 (m, 1H), 3.43−3.47 (m, 1H), 4.04 (d, 1H, J = 10.9 Hz, benzylic H), 4.15 (d, 1H, J = 10.9 Hz, benzylic H), 5.28 (brs, 1H, NH), 5.36 (s, 1H), 7.28−7.49 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.59 (CH_3), 19.93 (CH_3), 22.88 (CH_2), 25.12 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.78 (CH_2), 36.95 (CH_2), 37.48 (CH), 46.63 (CH), 51.61 (CH), 56.81 (CH_2), 81.11 (C), 82.50 (CH), 105.13 (C), 127.76 (C), 128.67 (2 × CH), 129.43 (2 × CH), 137.69 (C), 172.18 (C); ESI-MS (m/z) 387 $[M + H]^+$, 409 $[M + Na]^+$. Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37%, H, 7.82%, N, 7.25%. Found: C, 68.59%, H 7.96%, N 7.24%.

Hydrazines **14b−g** were prepared by the above procedure from hydrazones **13b−g**.

*(3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-11-((4-methylbenzyl)amino)decahydro-3,12-epoxy[1,2]dioxepino[4,3-i]-isoquinolin-10(3H)-one (**14b**).* Yield 62%, white solid, mp 125−127 °C; FT-IR (KBr cm^{-1}) 1652, 2928, 3398; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77−1.04 (m, 2H), 0.99 (d, 3H, J = 5.8 Hz), 1.17 (d, 3H, J = 7.2 Hz), 1.28−2.12 (m, 8H), 1.49 (s, 3H), 2.34 (s, 3H), 2.40−2.51 (m, 1H), 3.43−3.47 (m, 1H), 4.01−4.12 (m, 2H), 5.23 (brs, 1H, NH), 5.35 (s, 1H), 7.15 (d, 2H, J = 7.8 Hz), 7.37 (d, 2H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.61 (CH_3), 19.94 (CH_3), 21.34 (CH_3), 22.89 (CH_2), 25.14 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.80 (CH_2), 36.96 (CH_2), 37.49 (CH), 46.64 (CH), 51.63 (CH), 56.55 (CH_2), 81.12 (C), 82.48 (CH), 105.12 (C), 129.34 (2 × CH), 129.39 (2 × CH), 134.66 (C), 137.38 (C), 172.12 (C); ESI-MS (m/z) 401 $[M + H]^+$. Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97%, H, 8.05%, N, 6.99%. Found: C, 69.15%, H, 8.39%, N, 6.77%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-((4-Chlorobenzyl)amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-10(3H)-one (**14c**).* Yield 74%, white solid, mp 118−120 °C; FT-IR (KBr cm^{-1}) 1667, 2923, 3402; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77−1.07 (m, 2H), 1.00 (d, 3H, J = 5.9 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.28−1.80 (m, 6H), 1.47 (s, 3H), 1.98−2.12 (m, 2H), 2.42−2.51 (m, 1H), 3.42−3.46 (m, 1H), 4.01−4.13 (m, 2H), 5.22 (d, 1H, J = 5.4 Hz), 5.35 (s, 1H), 7.31 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.57 (CH_3), 19.94 (CH_3), 22.92 (CH_2), 25.13 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.76 (CH_2), 36.93 (CH_2), 37.53 (CH), 46.63 (CH), 51.59 (CH), 56.07 (CH_2), 81.12 (C), 82.58 (CH), 105.16 (C), 128.81 (2 × CH), 130.79 (2 × CH), 133.60 (C), 136.24 (C), 172.30 (C); ESI-MS (m/z) 421 $[M + H]^+$. Anal. Calcd for $C_{22}H_{29}N_2O_4Cl$: C, 62.77%, H, 6.94%, N, 6.66%. Found: C, 62.80%, H, 6.59%, N, 6.60%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-((4-Fluorobenzyl)amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-10(3H)-one (**14d**).* Yield 72%, oil; FT-IR (neat cm^{-1}) 1655, 2926, 3271; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77−1.07 (m, 2H), 0.99 (d, 3H, J = 5.9 Hz), 1.16 (d, 3H, J = 7.3 Hz), 1.27−2.12 (m, 9H), 1.48 (s, 3H), 2.41−2.51 (m, 1H), 3.43−3.47 (m, 1H), 4.02 (d, 1H, J = 11.0 Hz, benzylic H), 4.11 (d, 1H, J = 11.0 Hz, benzylic H), 5.36 (s, 1H), 6.99−7.05 (m, 2H), 7.42−7.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.57 (CH_3), 19.94 (CH_3), 22.91 (CH_2), 25.13 (CH_2), 25.71 (CH_3), 33.59 (CH), 33.77 (CH_2), 36.93 (CH_2), 37.52 (CH), 46.63 (CH), 51.59 (CH), 56.06 (CH_2), 81.13 (C), 82.55 (CH), 105.17 (C), 115.51 (d, 2 × CH, J_{C-F} = 22 Hz), 131.11 (d, 2 × CH, J_{C-F} = 8.0 Hz), 133.48 (d, C, J_{C-F} = 3.0 Hz), 162.56 (d, C, J_{C-F} = 245 Hz), 172.28 (C); ESI-MS (m/z) 405 $[M + H]^+$, 427 $[M + Na]^+$. EI-HRMS calcd for $C_{22}H_{29}N_2O_4F$ $[M]^+$: 404.2111. Found: 404.2117. Anal. Calcd for $C_{22}H_{29}N_2O_4F$: C, 65.33%, H, 7.23%, N, 6.93%. Found: C, 65.38%, H, 7.29%, N, 6.91%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-3,6,9-Trimethyl-11-((4-(trifluoromethyl)benzyl)amino)decahydro-3,12-epoxy[1,2]-dioxepino[4,3-i]isoquinolin-10(3H)-one (**14e**).* Yield 68%, white solid, mp 137−140 °C; FT-IR (KBr cm^{-1}) 1660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80−1.03 (m, 2H), 1.00 (d, 3H, J = 5.7 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.32−2.11 (m, 8H), 1.46 (s, 3H), 2.41−2.51 (m, 1H), 3.40−3.49 (m, 1H), 4.06−4.25 (m, 2H, benzylic H), 5.29 (d, 1H, NH, J = 5.6 Hz), 5.35 (s, 1H), 7.59 (s, 4H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.55 (CH_3), 19.90 (CH_3), 22.93 (CH_2), 25.13 (CH_2), 25.69 (CH_3), 33.62 (CH), 33.75 (CH_2), 36.92 (CH_2), 37.54 (CH), 46.63 (CH), 51.59 (CH), 56.17 (CH_2), 81.13 (C), 82.64 (CH), 105.18 (C), 125.58 (q, C, J_{C-F} = 3.8 Hz, CF_3), 129.63 (4 × CH), 141.83 (C), 141.85 (C), 172.42 (C); ESI-MS (m/z) 455 $[M + H]^+$. EI-HRMS calcd for $C_{23}H_{29}N_2O_4F_3$ $[M]^+$: 454.2079. Found: 454.2078.. Anal. Calcd for $C_{23}H_{29}N_2O_4F_3$: C, 60.78%, H, 6.43%, N, 6.16%. Found: C, 60.74%, H, 6.46%, N, 6.20%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-(([1,1′-Biphenyl]-4-ylmethyl)-amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]-isoquinolin-10(3H)-one (**14f**).* Yield 62%, white solid, mp 68−70 °C; FT-IR (KBr cm^{-1}) 1652; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82−1.04 (m, 2H), 1.00 (d, 3H, J = 5.8 Hz), 1.19 (d, 3H, J = 7.3 Hz), 1.28−1.80 (m, 6H), 1.51 (s, 3H), 1.99−2.14 (m, 2H), 2.42−2.53 (m, 1H), 3.46−3.49 (m, 1H), 4.12 (d, 1H, J = 11.1 Hz, benzylic H), 4.21 (d, 1H, J = 11.1 Hz, benzylic H), 5.32 (brs, 1H, NH), 5.38 (s, 1H), 7.33−7.62 (m, 9H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.61 (CH_3), 19.94 (CH_3), 22.89 (CH_2), 25.13 (CH_2), 25.73 (CH_3), 33.61 (CH), 33.77 (CH_2), 36.94 (CH_2), 37.49 (CH), 46.61 (CH), 51.60 (CH), 56.41 (CH_2), 81.12 (C), 82.51 (CH), 105.14 (C), 127.27 (2 × CH), 127.43 (3 × CH), 128.91 (2 × CH), 129.87 (2 × CH), 136.77 (C), 140.71 (C), 141.14 (C), 172.22 (C); ESI-MS (m/z) 463 $[M + H]^+$. EI-HRMS calcd for $C_{28}H_{34}N_2O_4$ $[M]^+$: 462.2519. Found: 462.2511. Anal. Calcd for $C_{28}H_{34}N_2O_4$: C, 72.70%, H, 7.41%, N, 6.06%. Found: C, 72.99%, H, 7.02%, N, 5.95%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-(((9H-Fluoren-2-yl)methyl)-amino)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]-isoquinolin-10(3H)-one (**14g**).* Yield 74%, white solid, mp 78−80 °C; FT-IR (KBr cm^{-1}) 1659, 2930, 3456; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87−1.05 (m, 2H), 0.98 (d, 3H, J = 5.7 Hz), 1.19 (d, 3H, J = 7.3 Hz), 1.28−1.74 (m, 6H), 1.53 (s, 3H), 1.99−2.53 (m, 3H), 3.46−3.50 (m, 1H), 3.91 (s, 2H), 4.15 (d, 1H, J = 10.9 Hz, benzylic H), 4.21 (d, 1H, J = 10.7 Hz, benzylic H), 5.31 (brs, 1H, NH), 5.39 (s, 1H), 7.28−7.80 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.61 (CH_3), 19.92 (CH_3), 22.89 (CH_2), 25.13 (CH_2), 25.76 (CH_3), 33.62 (CH), 33.77 (CH_2), 36.96 (CH_2), 37.00 (CH_2), 37.49 (CH), 46.63 (CH), 51.60 (CH), 57.06 (CH), 81.13 (C), 82.50 (CH), 105.16 (C), 120.04 (CH), 120.06 (CH), 125.21 (CH), 126.21 (CH), 126.81 (CH), 126.88 (CH), 128.21 (CH), 136.17 (C), 141.40 (C), 141.69 (C), 143.59 (C), 143.78 (C), 172.21 (C); ESI-MS (m/z) 475 $[M + H]^+$, 497 $[M + Na]^+$. Anal. Calcd for $C_{29}H_{34}N_2O_4$: C, 73.39%, H, 7.22%, N, 5.90%. Found: C, 73.55%, H, 6.99%, N, 5.95%.

General Procedure for Preparation of Ether Derivatives of *N*-Hydroxy-11-azaartemisnin (11). *Preparation of (3R,5aS,6-R,8aS,9R,12R,12aR)-11-(Benzyloxy)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-10(3H)-one (**15a**).* To a stirred slurry of NaH (60% dispersion in mineral oil, 0.323 g, 13.4 mmol) in dry THF (10.0 mL) at 0 °C was added *N*-hydroxy-11-azaartemisnin **11** (0.40 g, 1.34 mmol) dissolved in dry THF (10 mL), and the

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reaction mixture was stirred at 0 °C for 2 h. To this reaction mixture was added benzyl bromide (0.960 mL, 8.07 mmol), and the mixture was further stirred at room temperature for 12 h. The reaction mixture was quenched with water (10.0 mL) and extracted with ether (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure at room temperature, and the crude product was purified by column chromatography over silica gel (60−120 mesh) using 5% EtOAc/hexane as eluent to furnish (0.375 g, 72% yield) of pure **15a** as a white solid, mp 120−122 °C. IR (KBr, cm^{-1}) 1731; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86−1.02 (m, 2H), 0.98 (d, 3H, J = 5.4 Hz), 1.15 (d, 3H, J = 7.2 Hz), 1.34−1.57 (m, 3H), 1.50 (s, 3H), 1.64−1.80 (m, 3H), 1.98−2.12 (m, 2H), 2.42−2.53 (m, 1H), 3.43−3.52 (m, 1H), 5.01 (d, 1H, J = 9.1 Hz, benzylic H), 5.20 (d, 1H, J = 9.1 Hz, benzylic H), 5.46 (s, 1H), 7.32−7.39 (m, 3H, Ar), 7.54−7.56 (m, 2H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.00 (CH_3), 19.87 (CH_3), 22.86 (CH_2), 25.06 (CH_2), 25.67 (CH_3), 33.69 (CH_2), 34.07 (CH), 36.77 (CH_2), 37.48 (CH), 46.82 (CH), 51.48 (CH), 79.13 (CH_2), 81.90 (C), 82.65 (CH), 105.05 (C), 128.53 (2 × CH), 128.67 (CH), 129.68 (2 × CH), 135.63 (C), 171.27 (C); ESIMS (m/z) 388 $[M + H]^+$. EI-HRMS calcd For $C_{22}H_{30}NO_5$ $[M + H]^+$: 388.2124. Found: 388.2116. Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20%, H, 7.54%, N, 3.61%. Found: C, 67.84%, H, 7.52%, N, 3.31%.

Compounds **15b,c** were prepared from **11** by the above procedure by replacing benzyl bromide with *o*-fluorobenzyl bromide and *p*-phenylbenzyl bromide, respectively.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-((2-Fluorobenzyl)oxy)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]isoquinolin-10(3H)-one (**15b**).* Yield 65%, oil. IR (neat, cm^{-1}) 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88−1.00 (m, 2H), 0.96 (d, 3H, J = 5.2 Hz), 1.13 (d, 3H, J = 7.2 Hz), 1.18−1.42 (m, 3H), 1.47 (s, 3H), 1.67−1.78 (m, 3H), 1.95−2.09 (m, 2H), 2.39−2.50 (m, 1H), 3.43−3.47 (m, 1H), 5.18 (s, 2H), 5.44 (s, 1H), 7.00−7.68 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.74 (CH_3), 19.60 (CH_3), 22.66 (CH_2), 24.81 (CH_2), 25.32 (CH_3), 33.47 (CH_2), 33.87 (CH), 36.55 (CH_2), 37.23 (CH), 46.58 (CH), 51.25 (CH), 71.43 (d, CH_2, J_{C-F} = 3.9 Hz), 81.65 (C), 82.45 (CH), 104.85 (C), 115.18 (d, CH, J_{C-F} = 21.3 Hz), 122.66 (d, C, J_{C-F} = 15.1 Hz), 124.04 (d, CH, J_{C-F} = 3.7 Hz), 130.22 (d, CH, J_{C-F} = 8.2 Hz), 131.91 (d, CH, J_{C-F} = 3.7 Hz), 160.97 (d, C, J_{C-F} = 248.1 Hz), 171.15 (C); ESIMS (m/z) 406 $[M + H]^+$. HRMS [ESI] calcd for $C_{22}H_{29}NO_5F$: 406.2030 $[M + H]^+$. Found: 406.2020. Anal. Calcd for $C_{22}H_{28}NO_5F$: C, 65.17%, H, 6.96%, N, 3.45%. Found: C, 65.28%, H, 7.00%, N, 3.40%.

*(3R,5aS,6R,8aS,9R,12R,12aR)-11-([1,1′-Biphenyl]-4-ylmethoxy)-3,6,9-trimethyldecahydro-3,12-epoxy[1,2]dioxepino[4,3-i]-isoquinolin-10(3H)-one (**15c**).* Yield 74%, white solid, mp 65−66 °C. IR (KBr, cm^{-1}) 1728; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89−1.01 (m, 2H), 1.00 (d, 3H, J = 5.3 Hz), 1.16 (d, 3H, J = 7.2 Hz), 1.33−1.42 (m, 3H), 1.52 (s, 3H), 1.64−1.80 (m, 3H), 1.98−2.12 (m, 2H), 2.43−2.53 (m, 1H), 3.44−3.53 (m, 1H), 5.04 (d, 1H, J = 9.1 Hz, benzylic H), 5.24 (d, 1H, J = 9.1 Hz, benzylic H), 5.47 (s, 1H), 7.32−7.46 (m, 3H, Ar), 7.57−7.64 (m, 6H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.06 (CH_3), 19.92 (CH_3), 22.93 (CH_2), 25.13 (CH_2), 25.75 (CH_3), 33.76 (CH_2), 34.15 (CH), 36.84 (CH_2), 37.55 (CH), 46.91 (CH), 51.55 (CH), 78.89 (CH_2), 81.98 (C), 82.75 (CH), 105.14 (C), 127.35 (2 × CH), 127.40 (2 × CH), 127.52 (CH), 128.94 (2 × CH), 130.19 (2 × CH), 134.73 (C), 141.13 (C), 141.69 (C), 171.39 (C); ESIMS (m/z) 464 $[M + H]^+$. HRMS [ESI] calcd for $C_{28}H_{34}NO_5$: 464.2437 $[M + H]^+$. Found: 464.2461. Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.55%, H, 7.18%, N, 3.02%. Found: C, 72.48%, H, 7.34%, N, 2.81%.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR and ^{13}C NMR spectra of compounds **9**, **11**, **12a−g**, **13a−g**, **14a−g**, and **15a−c**; table showing degree of purity (elemental analysis) for compounds; and table showng HRMS results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This manuscript is dedicated to Dr. Sukh Dev on the occasion of his 90th birthday.

■ ABBREVIATIONS USED

$N_2H_4·H_2O$, hydrazine hydrate; NaH, sodium hydride; $NaBH_4$, sodium borohydride; NH_2OH, hydroxylamine

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