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Preparation of *N*-Sulfonyl- and *N*-Carbonyl-11-Azaartemisinins with Greatly Enhanced Thermal Stabilities: in vitro Antimalarial Activities

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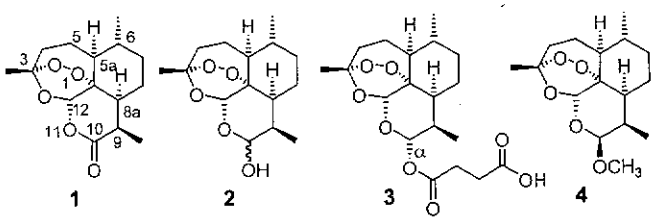
As the clinically used artemisinins do not withstand the thermal stress testing required to evaluate shelf life for storage in tropical countries where malaria is prevalent, there is a need to develop thermally more robust artemisinin derivatives. Herein we describe the attachment of electron-withdrawing arene- and alkanesulfonyl and -carbonyl groups to the nitrogen atom of the readily accessible Ziffer 11-azaartemisinin to provide the corresponding N-sulfonyl- and -carbonylazaartemisinins. Two acylurea analogues were also prepared by treatment of the 11-azaartemisinin with arylisocyanates. Several of the N-sulfonylazaartemisinins have melting points above 200°C and possess substantially greater thermal stabilities than the artemisinins in current clinical use, with the antimalarial activities of several of the arylsulfonyl derivatives being similar to that of artesunate against the drug-sensitive 3D7 clone of the NF54 isolate and the multidrug-resistant K1 strain of P. falciparum. The compounds possess relatively low cytotoxicities. The carbonyl derivatives are less crystalline than the N-sulfonyl derivatives, but are generally more active as antimalarials. The N-nitroarylcarbonyl and arylurea derivatives possess sub-ng ml^{-1} activities. Although several of the azaartemisinins possess log P values below 3.5, the compounds have poor aqueous solubility (< 1 mg L^{-1} at pH 7). The greatly enhanced thermal stability of our artemisinins suggests that strategic incorporation of electron-withdrawing polar groups into both new artemisinin derivatives and totally synthetic trioxanes or trioxolanes may assist in the generation of practical new antimalarial drugs which will be stable to storage conditions in the field, while retaining favorable physicochemical properties.

Introduction

As monotherapy with the current clinically used artemisinins comprising dihydroartemisinin (DHA) **2**, artesunate **3**, and artemether **4** encounters problems of recrudescence, use of the artemisinins in combination therapies (ACT) with drugs that have longer half-lives for treatment of malaria is now mandatory.[1]



1 **2** **3** **4**

Although artesunate and artemether are either hydrolytically or metabolically unstable and, together with the principal metabolite DHA, elicit neurotoxicity in cellular and animal assays, they are the drugs of choice for the treatment of malaria. However, neurotoxicity aside, an issue which markedly complicates production of registered formulations is their thermal instability.[2] The International Conference of Harmonization (ICH) and World Health Organization (WHO) have guidelines prescribing accelerated thermal stress testing by heating the formulated drug at 40 ± 2°C at a relative humidity of 75 ± 5% for six months.[3] The threshold of unknown decomposition products based on a daily dose of 100 mg should not exceed 0.2%, with less than 1.5% decomposition to known degradants the toxicity and efficacy profiles of which have been quantified as for

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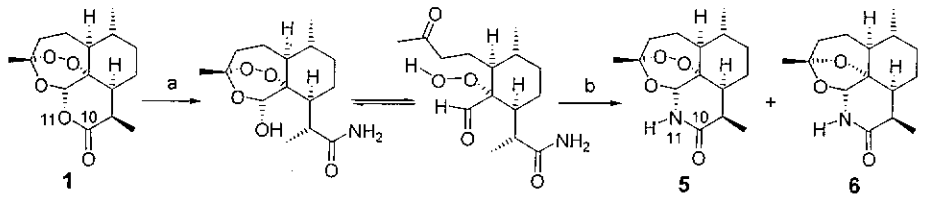
the parent drug. However, thermal stress testing of artesunate at 40 °C for six months results in up to 7.8% decomposition to provide some 3.7% of DHA and other products.[2] Controlled thermal decomposition data for formulated artemisinins appears not to be available in the primary literature, although anecdotal evidence indicates that under thermal stress, artemisinins undergo substantial decomposition. Cases have been recounted verbally of DHA tablets containing less than 50% of the specified active ingredient, and the magnitude of the decomposition problem of formulated artemisinins, especially of DHA and artemether, used in tropical countries is highlighted in recent publications.[4] The thermal sensitivity of the clinically used artemisinins is incompatible with current ICH/WHO requirements, and thus there is an urgent need to develop thermally more robust artemisinin derivatives. At the same time, attention must also be paid to economy of production, efficacy, log *P* and solubility, and metabolism, as has been discussed elsewhere.[5–7] In particular, the compound should not undergo metabolism to DHA, which is the most neurotoxic of all artemisinins.[8]

11-Azaartemisinin **5** and alkyl derivatives first made by Ziffer and co-workers[9,10] have pronounced in vitro activity against *Plasmodium falciparum*. They were prepared from artemisinin **1** by treatment with ammonia or an alkyl amine in methanol followed by treatment with silica gel/H_2SO_4 in the presence of butylated hydroxytoluene or Amberlyst-15 to induce closure of the intermediate open hydroperoxide (Scheme 1). The deoxy compound **6** was also obtained in the presence of the former acid system. Formation of **6** was traced to reduction of the ring-opened hydroperoxide to the tertiary alcohol by the amine, which is thereby oxidized.[11] The tertiary alcohol undergoes cyclization upon treatment with acid to give the deoxy compound **6**. The parent 11-azaartemisinin **5** can be modified by attaching substituents at N11 by reactions with Michael acceptors in the presence of weak bases.[12–15]



Scheme 1. Conversion of artemisinin **1** into 11-azaartemisinin **5**: a) NH_3, MeOH, −5 to −12 °C, 10 h; b) SiO_2–H_2SO_4–butylated hydroxytoluene, CH_2Cl_2, −78→20 °C; overall yield to **5**: 45% (Ref. [9]).

Because 11-azaartemisinins display such good in vitro antimalarial activities, will possess a different metabolic profile, and are likely to have a toxicity profile different from those of the current artemisinins, we sought to prepare thermally stable derivatives bearing polar electron-withdrawing groups attached to the nitrogen atom. We also planned for the eventual removal of the carbonyl group in such azaartemisinins by using reagents that are effective in the removal of the carbonyl group in lactams or amides. Thereby a locus of potential instability—the carbonyl group at C10—is removed, and the resulting and as yet unreported 10-deoxo-11-azaartemisinin becomes of interest from a structure–activity viewpoint.

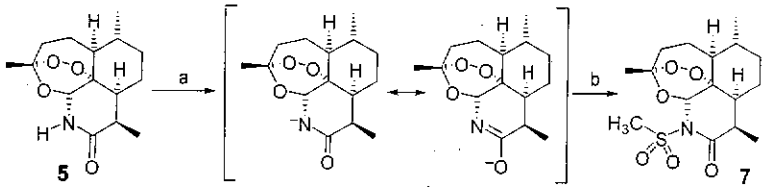
Results

a. Preparation of *N*-sulfonyl- and *N*-carbonylazaartemisinins

i. N-*Methanesulfonyl-11-azaartemisinin 7*

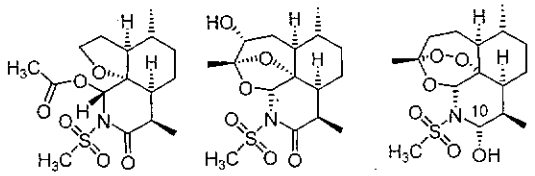
Whilst *N*-benzylated azaartemisinin derivatives may be prepared in acceptable yields according to the Ziffer method,[16] the preparation of the parent 11-azaartemisinin **5** was complicated by the temperature sensitivity of the ammonolysis of artemisinin **1** in methanol. Below −20 °C, no reaction took place, whereas at 0 °C or above, mixtures containing larger amounts of the deoxy derivative **6** were obtained. The best temperature range was found to be between −5 to −12 °C. Cyclization with the sulfuric acid–BHT system (Scheme 1, step b) at higher temperatures and/or with higher concentrations of reactants also resulted in the formation of complex product mixtures. The overall method was therefore modified by treating artemisinin **1** in a THF–methanol mixture (10:3) at −10 to −15 °C with 33% aqueous ammonium hydroxide. After direct evaporation of solvent and treatment of the residue with *p*-toluenesulfonic acid in dichloromethane at room temperature, 11-azaartemisinin **5** was obtained by direct crystallization without chromatography in about 70% yield for multigram-scale reactions.

Although attempts to prepare the *N*-sulfonyl derivative by treatment of **5** with methanesulfonyl chloride or methanesulfonic anhydride in the presence of amine bases were unsuccessful, deprotonation with lithium diisopropylamide (LDA) in THF at −78 °C followed by treatment with methanesulfonyl chloride gave the methanesulfonyl derivative **7** in 62% yield. Sodium hydride in THF was also used to deprotonate the azaartemisinin at 0 °C to give the product in 55% yield, isolated by direct crystallization (Scheme 2). An X-ray crystallographic analysis of **7** is described below.



Scheme 2. Preparation of *N*-methanesulfonyl-11-azaartemisinin **7**: a) i) LDA (1.5 equiv), −78 °C, 3 h, or ii) NaH (1.5 equiv, 60% dispersion in mineral oil), 0 °C, 3 h; b) CH_3SO_2Cl (1.8 equiv), i) −78 °C, 3 h (62%), or ii) 0 °C, 3 h (55%).

Attempts to reduce the carbonyl group of 11-azaartemisinin **5** with reagents normally used both to convert amides to amines[17–19] and artemisinins into the 10-deoxo derivatives[20–22] were ineffective, in that starting material was returned or extensive degradation took place. Surprisingly, attempted removal of the carbonyl group in the methanesulfonyl derivative **7** using these same reagents also failed; the attachment of an electron-withdrawing group to the nitrogen atom was expected to attenuate the deactivating effect of the nitrogen atom on carbonyl reactivity characteristic of amides. Attempted reduction of imidate esters[10] derived from **5** with hydride donors also failed. Treatment of **7** in dichloromethane containing an excess of trimethylsilyl chloride with lithium borohydride in THF[18] resulted in isomerization to the products **8** (24%) and **9** (22%). Compounds were identified by comparison of their spectroscopic data with that of analogous compounds,[23] and the structure of **9** was confirmed by X-ray crystallographic analysis as described below. Reaction with smaller amounts of lithium borohydride resulted in an incomplete reaction with starting material remaining in the reaction mixture. The formation of the products **8** and **9** under these conditions is noteworthy, as the related compounds are obtained from artemisinin derivatives by Fe^{2+}-catalysed isomerization involving Fenton-type cleavage of the peroxide bond to alkoxyl radicals, followed by intramolecular hydrogen atom abstractions to generate C-centered radicals, which rearrange to the products.[23]

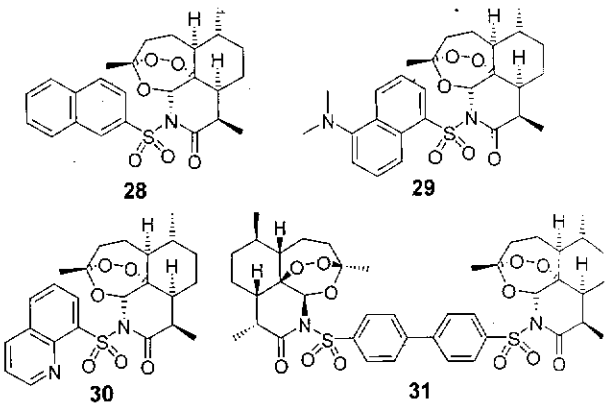


8 **9** **10**

The methanesulfonyl derivative **7** was able to be reduced with an excess of diisobutylaluminum hydride in dichloromethane to the crystalline alcohol **10**, mp: 159 °C, in low yield (22%). The structure of the alcohol was established by X-ray crystallography, which intriguingly shows a twist-boat pyran ring with axial hydroxy group engaged in hydrogen bonding with the peroxide. Thus, the structure is rather different from that of α-dihydroartemisinin, which possesses a chair pyran ring and equatorial hydroxy group.[7] Details of the crystallographic study are given below. However, it was not possible to remove the hydroxy group in **10** by using those reagents which readily effect deoxygenation at C10 of dihydroartemisinin.[22] Thus, attention turned to the preparation and screening for antimalarial activities of *N*-sulfonyl and *N*-carbonyl-11-azaartemisinins.

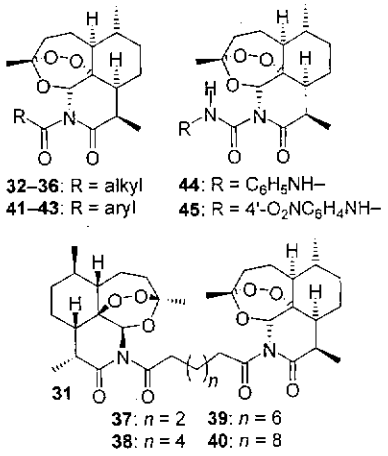
ii. N-*Sulfonyl- and* N-*carbonyl-11-azaartemisinins*

Treatment of 11-azaartemisinin **5** with LDA (conditions i, Scheme 2) or sodium hydride (conditions ii, Scheme 2) followed by treatment with the sulfonyl chloride provided the *N*-sulfonyl derivatives **11–31** (Table 1). In general, aliphatic sulfonyl chlorides gave better yields than their aromatic counterparts. Thus the 2-naphthyl- and 8-quinolinesulfonyl derivatives **28** and **30** were obtained in 35% isolated yields, the dansyl derivative **29** in 5% isolated yield. Biphenyl-4,4′-disulfonyl chloride provided the bis-sulfonyl derivative **31** (entry 22, Table 1), although from benzene-1,3-disulfonyl chloride, no product was obtained. The deprotonated 11-azaartemisinin (Scheme 2) also



28 **29** **30** **31**

reacted with acyl chlorides to give the corresponding *N*-carbonyl derivatives **32–36** (entries 1–5, Table 2) and **41–43** (entries 10–12, Table 2). Reaction with aryl isocyanates gave the acylureas **44** and **45** (entries 13 and 14, Table 2). The dimeric adducts **37–40** were obtained from the corresponding diacid



32–36: R = alkyl **44**: R = C_6H_5NH–
41–43: R = aryl **45**: R = 4′-$O_2NC_6H_4NH$–

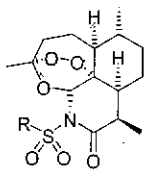
37: *n* = 2 **39**: *n* = 6
38: *n* = 4 **40**: *n* = 8

chlorides (entries 6–9, Table 2). With the oxophilic acid chlorides, there is the possibility of the reaction taking place through the oxygen atom to give an imidate ester. However only the *N*-linked derivatives were formed. The preparation of the acylureas from the arylisocyanates represents a useful extension to the methodology of attaching polar non-metabolizable groups to the artemisinin nucleus.[6]

b. Thermal stabilities

Dihydroartemisinin (DHA) melts at 153–154 °C, artemether at 86–88 °C,[24] and artesunate at 134.7[25] or 135.1–135.2 °C.[7,26] Of

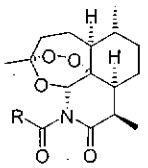
Table 1. *N*-Sulfonylazaartemisinin derivatives and antimalarial activities.



Entry	Compd	R	Method[a]	Yield [%]	mp [°C]	$[\alpha]_D^{22}$ (*c*, $CHCl_3$)	IC_{50} [ng ml^{-1} (nM)] 3D7	K1
1	**7**	CH_3–	i	62	245 (dec)	−103.15 (1.00)	4.1 (11.4)	3.2 (8.9)
			ii	45				
2	**11**	CH_3CH_2–	i	61	136.4–137	−87.9 (1.56)	1.7 (4.6)	3.7 (9.9)
3	**12**	$CH_3CH_2CH_2$–	i	71	127–128	−87.4 (0.58)	–	–
4	**13**	$CH_3(CH_2)_8CH_2$–	i	55	oil	−69.2 (2.23)	1.1 (2.4)	2.1 (4.6)
5	**14**	$CH_3(CH_2)_{14}CH_2$–	i	42	oil	−55.8 (1.51)	–	50
6	**15**	4′-FC_6H_4–	i	11	189–190	−83.4 (3.38)	–	8.0 (18.2)
7	**16**	4′-ClC_6H_4–	ii	56	212 (dec)	−94.52 (1.00)	>50	17
8	**17**	4′-BrC_6H_4–	ii	46	199–200	−81.87 (1.00)	>50	>50
9	**18**	4′-$CH_3C_6H_4$–	ii	43	219	−93.36 (1.00)	>50	37
10	**19**	4′-$O_2NC_6H_4$–	ii	38	186 (dec)	−91.8 (1.00)	17.1	9.1 (19.5)
11	**20**	3′-$O_2NC_6H_4$–	i	49	196–197	−95.3 (0.60)	2.1 (4.5)	2.2 (4.7)
12	**21**	2′-$O_2NC_6H_4$–	ii	14	201 (dec)	−388.9 (1.00)	–	10 (21.4)
13	**22**	3′-N≡CC_6H_4–	i	44	219–220	−109.8 (0.87)	–	>50
14	**23**	4′-Cl-3′-$O_2NC_6H_3$–	i	31	215–216	−75.9 (1.71)	1.5 (3.0)	3.8 (7.6)
15	**24**	3′,4′-$(CH_3O)_2C_6H_3$–	i	17	208–209	−85.4 (1.26)	>50	40
16	**25**	4′-$CH_3SO_2C_6H_4$–	ii	40	201 (dec)	−76.99 (1.00)	–	13 (26)
17	**26**	4′-C_6H_5-C_6H_4–	i	8.0	219–220	−72.7 (1.2)	40	45
18	**27**	5′-Cl-2′-thienyl	i	14	178.6–179	−90.5 (1.26)	–	40
19	**28**	2′-$C_{10}H_7$– (2-naphthyl)	i	35	224–225	−74.4 (2.04)	2.8 (5.9)	0.2 (0.42)
20	**29**	5′-[$(CH_3)_2N$]-1′-$C_{10}H_8$– (dansyl)	i	9.0	gum	−79.7 (1.57)	–	–
21	**30**	8′-quinolinyl	i	35	220–221	−36 (2.61)	1.9 (4.0)	2.0 (4.2)
22	**31**	bis-4′,4″-biphenyl	i	7.0	201 (dec)	−55.5 (1.52)	–	–
23	**3**	artesunate	–	–	–	–	1.5 (3.9)	2.2 (5.7)

[a] See Scheme 2.

Table 2. *N*-Carbonylazaartemisinin derivatives and antimalarial activities.



Entry	Compd	R	Yield [%]	mp [°C]	$[\alpha]_D^{22}$ (*c*, $CHCl_3$)	IC_{50} [ng ml^{-1} (nM)] 3D7	K1
1	**32**	CH_3–	54	127.9–128.5	−5.75 (0.84)	3.0 (9.3)	4.5 (13.9)
2	**33**	CH_3CH_2–	58	121.5–122.4	+10.65 (0.45)	2.0 (5.9)	1.0 (3.0)
3	**34**	$CH_3(CH_2)_2$–	67	gum	+14.59 (1.18)	2.0 (5.7)	2.0 (5.7)
4	**35**	$CH_3(CH_2)_4$–	84	gum	+7.0 (1.02)	1.0 (2.6)	2.0 (5.3)
5	**36**	$CH_3(CH_2)_{14}$–	71	gum	+2.5 (0.99)	>50	>50
6	**37**	–$CH_2(CH_2)_2CH_2$–	35	134.5–134.8	+5.54 (2.11)	2.3 (3.4)	50 (74.3)
7	**38**	–$CH_2(CH_2)_4CH_2$–	32	135.8–136.6	+11.51 (1.19)	9.2 (13.1)	9.0 (12.8)
8	**39**	–$CH_2(CH_2)_6CH_2$–	13	128.5–129.1	+10.45 (0.85)	13 (17.8)	2.0 (2.7)
9	**40**	–$CH_2(CH_2)_8CH_2$–	28	121.5–122.4	+11.61 (3.26)	>50	40
10	**41**	4′-$O_2NC_6H_4$–	60	gum	+100.6 (1.44)	0.45 (1.0)	0.6 (1.4)
11	**42**	3′-$O_2NC_6H_4$–	48	foam	+74.4 (1.28)	0.46 (1.1)	0.6 (1.4)
12	**43**	3′,5′-$(O_2N)_2C_6H_3$–	52	203–204 (dec)	+72.9 (1.07)	–	2.0 (4.2)
13	**44**	C_6H_5NH–	2	gum	−135.9 (1.38)	–	–
14	**45**	4′-$O_2NC_6H_4NH$–	26	foam	−201.7 (2.44)	0.6 (1.3)	0.4 (0.9)
15	**46**	artemisone	–	–	–	0.4 (1.0)	0.4 (1.0)

these compounds, DHA is thermally the least stable. It decomposes completely in solution at 100 °C over the course of 24 h, and at 40 °C at a relative humidity of 70%, solid DHA undergoes 2% decomposition after one month and 2.9% after three months.[2] As explained in the preceding paper, thermogravimetric analysis (TGA) is a technique normally applied to determine the thermal stability of a material by monitoring the temperature increase (*X* axis) as a function of change in weight% (*Y* axis). The onset of loss of volatiles such a solvent of recrystallization, or of decomposition associated with loss of volatile products is thereby recorded. TGA of each of DHA, artemether, and artesunate reflect data obtained from protracted thermal stability studies.[2] DHA commences decomposition at 110 °C, artemether **4** at 116 °C, and artesunate **3** at 152 °C. A plot of weight loss as a function of temperature for artesunate is given in Figure 1; plots for DHA and artemether are given elsewhere.[2]

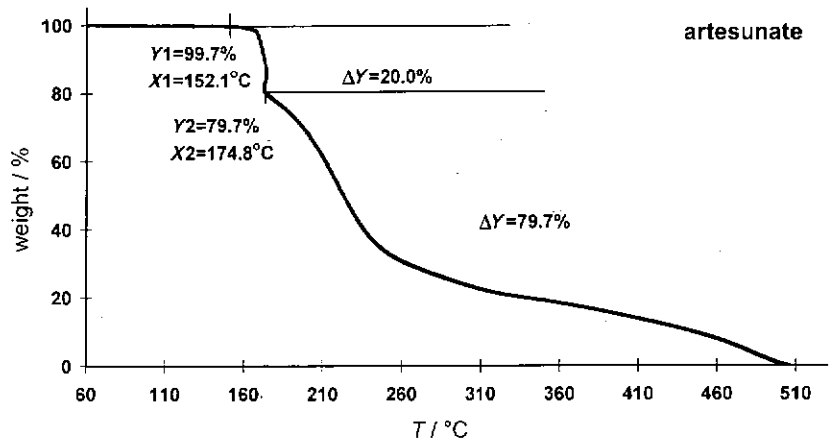


Figure 1. TGA results of artesunate **3** heated at a rate of 10 °C min^{-1} under N_2. *X*1 and *Y*1 respectively refer to temperature and weight of the sample at the incipient decomposition event, and ΔY represents the percent weight loss of sample between the designated temperatures.

11-Azaartemisinin, with a melting point of 143–144.5 °C, appears to possess a thermal stability similar to that of artemisinin **1** (mp: 156–157 °C). In contrast, the highly crystalline methanesulfonylazaartemisinin **7** has a melting point of 245 °C, which appears to be the highest ever recorded for any artemisinin. TGA indicates that whereas artemisinin commences decomposition at 149 °C, 11-azaartemisinin commences decomposition at 132 °C, and the methanesulfonyl derivative **7** commences decomposition at about 185 °C (Figure 2). Similar stabilities are also displayed by arylsulfonylazaartemisinins listed in Table 1. With the exception of the 4′-fluorobenzenesulfonyl derivative **15** and the 4′- and 3′-nitrobenzenesulfonyl derivatives **19** and **20**, the compounds melt at or above 200 °C.

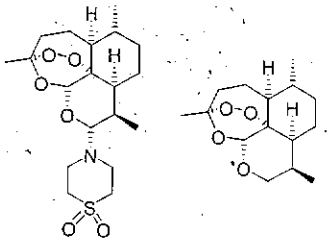
The greatly enhanced stability of the sulfonylazaartemisinins is also dramatically demonstrated in Figure 3, which shows that heating of the methanesulfonyl derivative **7** at 70 °C in [D_3]acetonitrile results in no detectable decomposition over the course of 14 days. Similarly, the 4-chlorobenzensulfonyl derivative **16** (Table 1) showed no detectable decomposition. In contrast, artesunate undergoes >60% decomposition over 4 days to give products for which characterization is described elsewhere.[2] The *N*-carbonyl derivatives listed in Table 2 are generally less crystalline and have lower melting points than the sulfonyl derivatives. The *N*-methylcarbonylazaartemisinin **32** melts at 128 °C and, according to TGA, has a decomposition threshold of 152 °C (Figure 2).

The generally greatly enhanced thermal stabilities of the *N*-sulfonyl compounds are encouraging from a drug-development perspective. Most of these compounds are nicely crystalline and show no detectable signs of decomposition during storage at room temperature over periods of three years or more. Overall, the new compounds are thermally much more stable than the three clinically used artemisinins DHA **2**, artemether **4**, and artesunate **3**.

c. Antimalarial activity and relative cytotoxicities

In vitro parasite growth inhibition was assessed by the incorporation of [^{3}H]hypoxanthine based on the modified Desjardins method described in the Experimental Section.[27] Azaartemisinin **7** itself was screened against W2 (chloroquine-resistant) and D6 (chloroquine-sensitive) strains, with respective IC_{50} values of 1.73 and 2.60 ng mL. Strains/isolates used for the study of sulfonyl- and carbonylazaartemisinins reported herein were the drug-sensitive 3D7 clone of the NF54 isolate and the chloroquine-, pyrimethamine-, and cycloguanil- resistant K1 strain from Thailand. Results are given in Table 1. The alkanesulfonyl derivatives **11** and **13**, the 3′-nitrobenzenesulfonyl derivative **20**, the 2-naphthalenesulfonyl derivative **28**, and the 8′-quinolinyl derivative **30** are approximately equipotent with artesunate in vitro. Whilst an increase in lipophilicity generally enhances antimalarial activity, it also enhances toxicity.[5,7] It has been shown that the attachment of alkyl chains (C_{10-16}) to artemisinins at C10 by an amide linker results in drastic enhancement in cytotoxicity, as gauged by effects in vitro on Hep G2 cancer cell lines.[28] However, such compounds are so toxic they cannot be screened in vivo. In our case, we conducted preliminary screens of the sulfonylazaartemisinins against Hep G2 lines, and at a concentration of 10 μM during a 6-day treatment, only the alkylsulfonyl compounds **14** (C_{16}), **13** (C_8) and the biphenyl bis-sulfonyl compound **19** appreciably depressed cell viability, namely to 75, 50, and 50% of initial values, respectively. Other compounds depressed cell viability to 20% or less of initial values, and therefore can be considered non-cytotoxic. Thus, whereas the alkanesulfonylazaartemisinin **13** displays good antimalarial activity, it is not further considered on the basis of its cytotoxicity.

The carbonylazaartemisinins generally displayed superior antimalarial activities to the sulfonylazaartemisinins (Table 2). The nitroaryl derivatives **41** and **42**, and the acylurea analogue **45**, in displaying in vitro activities against malaria in the sub-ng ml^{-1} range, are approximately equipotent in vitro with artemisone **46**, the new artemisinin development candidate, which in clinical trials is effective at a curative dose one third that of artesunate.[5] However, the general lack of crystallinity of the *N*-carbonyl compounds militates against their further development.



46 **47**

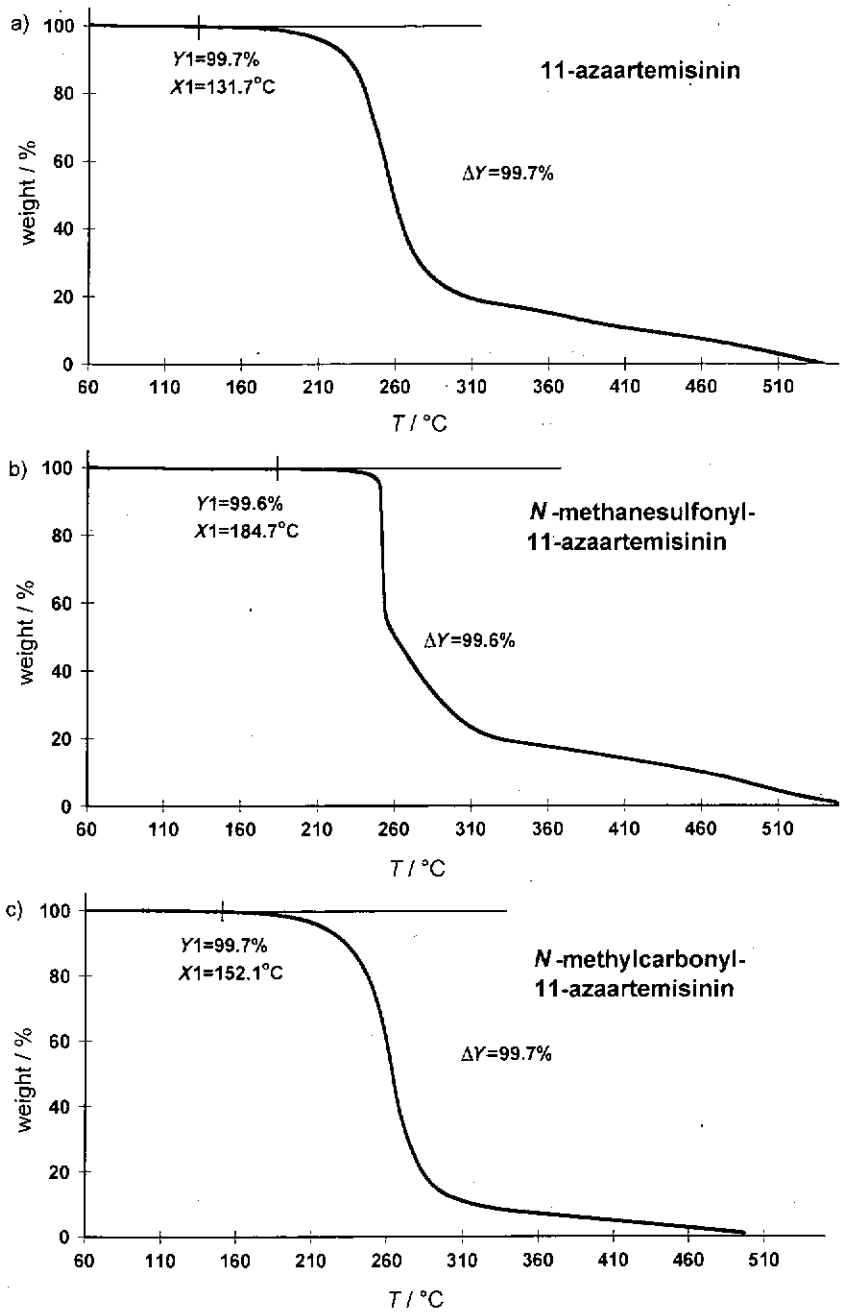


Figure 2. TGA results of a) 11-azaartemisinin **5**, b) *N*-methanesufonyl-11-azaartemisinin **7**, and c) *N*-methylcarbonyl-11-azaartemisinin **32** heated at a rate of 10 °C min^{-1} under N_2. *X*1 and *Y*1 respectively refer to temperature and weight of the sample at the incipient decomposition event, and ΔY represents the percent weight loss of sample between the designated temperatures.

Discussion

11-Azaartemisinin is a readily accessible artemisinin that is easily converted into derivatives bearing electron-withdrawing *N*-sulfonyl and *N*-carbonyl groups. Some of the sulfonylazaartemisinins possess thermal stabilities substantially greater than those of the artemisinins in clinical use and are relatively easily prepared. In addition, the preparation of the acylureas **44** and **45** from the arylisocyanates represents a useful extension to the methodology of attaching polar non-metabolizable groups to the artemisinin nucleus.[6] Whilst we have not probed the physical basis for the enhanced thermal stability of the *N*-sulfonyl-11-azaartemisinin derivatives, it is apparent that the peroxide in the artemisinin nucleus is sensitive to remote inductive effects exerted by the electron-withdrawing substituents. Decomposition threshold temperatures for each of 10-deoxoartemisinin **47** and artemisinin **1** as assessed by TGA are 106 and 149 °C, and for each of artemether **4** and artesunate **3** are 116 and 152 °C, respectively. The increased decomposition thresholds for the artemisinins substituted with electron-withdrawing groups may be ascribed to remote inductive effects raising the (homolytic) bond dissociation energy of the peroxide bond. Parallels may be observed in the effect of electron-withdrawing groups raising the activation energy for homolysis of diacyl peroxides[29] or, of

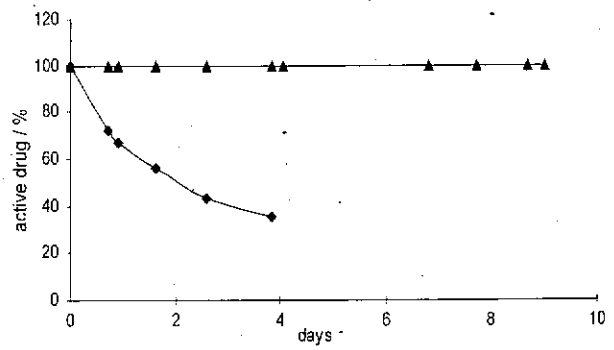


Figure 3. Comparison of the thermal stabilities of artesunate **3** (♦) and *N*-methanesulfonylazaartemisinin **7** (▲) determined by ^{1}H NMR spectroscopy with compound solution concentrations of 0.025 M in [D_3]acetonitrile at 70 °C; the amount of remaining intact artemisinin was determined by comparison of the relative intensity of the signal from H12 in each of **3** at $\delta = 5.44$ ppm and **7** at $\delta = 6.03$ ppm with that of the signal at $\delta = 6.08$ ppm of the internal standard, trimethoxybenzene.

greater relevance to the present case, of peroxy esters.[30] Thus, we have uncovered a simple device to improve thermal stability of artemisinins. In this respect, the difluoromethylene and trifluoromethyl derivatives prepared from artemisinin and DHA by Begue, Bonnet-Delpon, and co-workers[31] are predicted to be thermally more stable than the artemisinins from which they are derived. The compounds possess good antimalarial activities, and therefore appear to be good development candidates.

The sulfonylazaartemisinins are relatively polar. The *N*-methanesulfonylazaartemisinin **7** has a log*P* (*P* = partition coefficient in 1-octanol/water) value of 3.38 at pH 7, and log*P* for the *p*-methanesulfonylbenzenesulfonyl derivative **25** (entry 16, Table 1) is 2.95. However, both compounds have poor aqueous solubility (< 1 mg L^{-1} at pH 7). Notably, 11-azaartemisinin **5**, with log*P* 2.32, has a solubility at pH 7 of > 1000 mg L^{-1}, a value which renders this compound suitable for examination as an intravenous antimalarial, a purpose for which it would be more suited than artesunate, which is unstable at neutral pH. It possesses antimalarial activity similar to that of artemisinin.[10]

Conclusions

With a set of compounds that are thermally very stable and that possess good antimalarial activities, we now aim to prepare thermally stable derivatives with improved solubility in water, and to this end, attention is focused on arenesulfonyl derivatives bearing hydrogen bond donor and acceptor groups at C3′ in the aromatic ring. The paradigm that emerges from the current work is that totally synthetic cyclic peroxides, trioxanes or trioxolanes[32,33] could be prepared through the strategic attachment of polar electron-withdrawing groups whose inductive effects will enhance both the thermal stability of the peroxide and the overall physicochemical properties so as to generate practical antimalarial drugs.

X-Ray Crystallography

Single-crystal structure determinations were carried out on suitable specimens of compounds **7**, **9**, and **10**. The compounds were found to crystallize in chiral space groups *P*2$_1$ or *P*1, consistent with enantiomeric purity. Data were collected at 100 K on a Bruker Smart APEX CCD diffractometer. Structure solution and refinement was carried out using the SHELXTL suite of X-ray programs. Although the radiation used was Mo$_{K\alpha}$, absolute structure determination of the azaartemisinin skeletons was verified for each compound and clearly determined from anomalous dispersion of the single sulfur atom per molecule, with the Flack parameters refining in each case to a small value less than 0.1 with an acceptably low effective SD. All three crystal structures refined successfully to low-discrepancy *R* indices below 3% and with low residual electron-density peaks and holes in the final difference Fourier map. Crystal data and structure determination summaries for the three structures are given in Table 3.

The single-crystal X-ray structure determination of compound **7** confirmed its proposed molecular structure as *N*-methylsulfonyl-11-azaartemisinin, and a thermal ellipsoid plot (40% probability) is shown in Figure 4. The molecular parameters in **7** are similar to those found for other artemisinin derivatives; the O1–O2 peroxy bond length is 1.471(2) Å, whereas in artemisinin itself this is 1.477(2) Å. Other key geometric param-

Table 3. Crystal data and structure refinement for compounds **7**, **9**, and **10**.

	7	**9**	**10**
CSD deposition number	633954	633955	633956
empirical formula	$C_{16}H_{25}NO_6S$	$C_{16}H_{25}NO_6S$	$C_{16}H_{27}NO_6S$
formula weight [Da]	359.43	359.43	361.45
T [K], λ [Å]	100(2), 0.71073	100(2), 0.71073	100(2), 0.71073
crystal system, space group	monoclinic, $P2_1$	triclinic, $P1$	monoclinic, $P2_1$
a [Å]	8.5196(9)	5.9690(7)	8.4655(12)
b [Å]	10.7659(12)	8.0679(9)	10.5713(16)
c [Å]	9.8361(10)	9.4148(10)	10.3061(15)
α [°]	90	68.691(2)	90
β [°]	113.450(2)	79.835(2)	112.024(2)
γ [°]	90	88.215(2)	90
V [Å^3]	827.67(15)	415.50(8)	855.0(2)
Z, D_c [Mgm^{-3}]	2, 1.442	1, 1.436	2, 1.404
μ [mm^{-1}]	0.229	0.228	0.222
crystal size [mm]	0.70×0.60×0.20	0.40×0.10×0.08	0.65×0.28×0.25
$2\Phi_{max}$, completeness [%]	50 (97.7)	50 (96.9)	50 (98.0)
transmission [max/min]	1.00/0.88	1.00/0.83	1.00/0.94
data, restraints, parameters	1967, 1, 217	1902, 3, 221	2837, 1, 217
R_1 (obs), wR_2 (all)	0.0252, 0.0639	0.0278, 0.0710	0.0276, 0.0697
GoF	1.049	1.043	1.052
Flack parameter	0.06(7)	0.07(7)	0.04(6)
peak/hole [e–Å^{-3}]	+0.24/−0.18	+0.33/−0.21	+0.22/−0.16

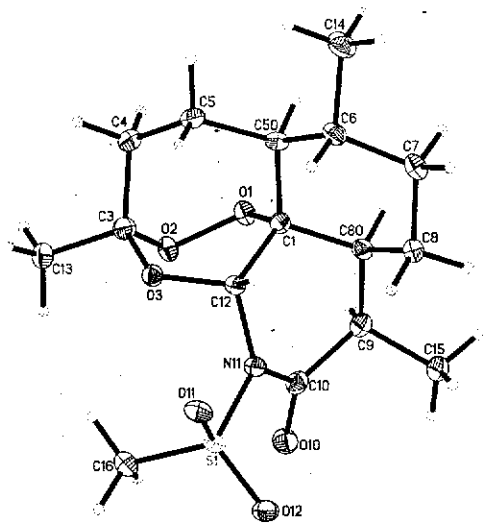


Figure 4. X-ray crystal structure of *N*-methanesulfonyl-11-azaartemisinin **7**.

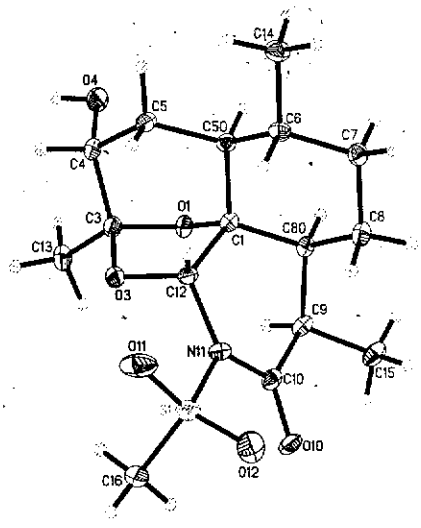


Figure 5. X-ray crystal structure of *N*-methanesulfonyl-11-azaartemisinin degradation product **9**.

Table 4. Additional geometric parameters for compounds 7–10.

	Compound		
	7	**9**	**10**
	Torsion Angles [°]		
C1–O1–O2–C3	45.5	–	41.5
O1–C1–C12–O3	−46.9	−23.1	−43.4
O1–O2–C3–O3	−75.2	–	−73.5
S1–N11–C10–O10	24.2	4.9	80.1
C9–C10–N11–C12	35.9	5.1	48.2
O10–C10–N11–C12	−148.8	−174.7	−80.4
S1–N11–C12–C1	176.3	168.5	175.2
	Ring Displacements [Å]		
C1, C80, C9, C10, N11, C12	+0.35, −0.33, +0.05, +0.21, −0.21, −0.07	+0.18, −0.36, +0.27, −0.01, −0.15, +0.06	+0.36, −0.36, +0.05, +0.26, −0.29, +0.02
Conformation	twist-boat	irregular	twist-boat

eters are given in Table 4. One notable change relative to artemisinin is the effect of the 11-aza substituent on ring conformation; in **7** the lactam ring is best described as having a twist-boat conformation. In contrast, the lactone ring in artemisinin is close to a half-chair conformation in which the C10 carbonyl group is rotated into the plane of its ring neighbors.

Compound **9**, prepared from **7** by action of trimethylchlorosilane and lithium borohydride, is shown by X-ray crystallography to be a rearrangement product isomeric with **7**, with the peroxy oxygen O2 removed and inserted into the α-C–H bond at C4 (Figure 5). The new stereochemical center thus generated at C4 has the *R* configuration. As for 2-deoxyartemisinin compared with artemisinin itself, the removal of the peroxide oxygen atom changes the ring geometries considerably; the 5-membered 1,3-dioxolane ring has an envelope conformation with O1 at the flap. In addition, the geometry of the ring containing the 11-azasulfonyl moiety is slightly modified, with the N11 sulfonyl substituent now almost coplanar with the C1 keto group. The torsion angle O10–C10–N11–S1 is 4.9°, compared with 24.2° in the parent compound **7**. This variability is likely due to solid-state packing effects and probably indicates a low barrier for these conformational changes, with the tendency for better conjugation being offset by increased ring strain.

Compound **10**, the reduction product of **7** using diisobutylaluminum hydride, is confirmed by single-crystal X-ray diffraction as the 10-α-hydroxy epimer, with an absolute configuration of *S* at C10 (Figure 6). Surprisingly, the pyran ring containing the lactam does not exhibit a chair conformation as found for most C10-α-substituted artemisinin derivatives such as α-artesunate[26] or α-DHA,[7] but adopts a twist-boat form similar to that found in **7**. In **10** this conformation is supported by the formation of an intramolecular hydrogen bond from the α-hydroxy group to O2 of the peroxide functionality. As shown in Table 4, the geometric parameters for the peroxide functionality are little perturbed by the H-bond interaction; there is no significant change in the O1–O2 peroxide bond length (1.470(2) Å) and only a slight lengthening of the C–O bond lengths involving the peroxide oxygen atoms.

Experimental Section

General

Artemisinin was obtained either from the Kunming Pharmaceutical Corporation, Kunming, China, or from Haphacen, Hanoi College of Pharmacy, Vietnam, and used without further purification. The following solvents were dried and distilled prior to use: ethyl acetate ($MgSO_4$), hexane ($CaCl_2$), CH_2Cl_2 (CaH), triethylamine (CaH and stored over KOH pellets), THF (sodium in benzophenone), diethyl

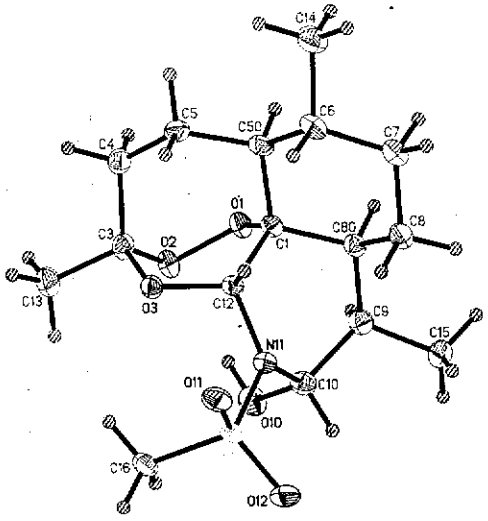


Figure 6. X-ray crystal structure of compound **10**.

ether (sodium in benzophenone), and toluene (sodium in benzophenone). Thin-layer chromatography was performed with Merck Kieselgel 60 F_{254} plates and visualized with UV light (254 nm) and/or heating after treatment with 5% ammonium molybdate in 10% concentrated H_2SO_4. Column chromatography was performed with Merck silica gel 60 (0.04–0.063 mm). ^1H and ^{13}C NMR spectra were obtained on Bruker ARX 300 and Varian Mercury 300 spectrometers operating at 300 and 75 MHz, respectively, with the sample dissolved in $CDCl_3$. Melting points were determined with a Leica Hot Stage DME E compound Microscope and are corrected. MS data were obtained on a Finnigan TSQ 7000 mass spectrometer operating in CI mode and on an API QSTAR high-performance triple-quadrupole time-of-flight mass spectrometer with electrospray ionization. IR spectra were recorded on a PerkinElmer Spectrum One spectrometer. Polarimetry was performed on a PerkinElmer model 241 spectrometer. Elemental analyses were obtained from MEDAC Ltd., Surrey, UK.

Preparation of azaartemisinins

11-Azaartemisinin 5: A solution of artemisinin **1** (10.0 g, 35.42 mmol) in THF (200 mL) and CH_3OH (60 mL) at −10 to −15 °C was treated with NH_4OH (aq, 33%, 100 mL). The resulting mixture was stirred for 10 h at this temperature, during which time the color changed to a very pale yellow. The solution was then evaporated under reduced pressure, without heating, to leave a yellow foam. This was dissolved in CH_2Cl_2 (250 mL), and treated with *p*-toluenesulfonic acid monohydrate (6.8 g, 35.84 mmol) at room temperature. The mixture was stirred for 12 h and then washed with 5% aqueous sodium bicarbonate (400 mL) and water (500 mL). The organic layer was separated and dried ($MgSO_4$). The filtrate was evaporated under reduced pressure to leave the residue as a foam. This was crystallized from ethyl acetate/hexanes to give 11-azaartemisinin **5** (7.3 g, 73%) as colorless needles; mp: 143–144.5 °C (Ref. [9]: 143–145 °C); ^1H NMR: δ = 0.95–1.19 (m, 3H), 0.99 (d, J = 5.94 Hz, 3H, H-15), 1.12 (d, J = 7.38 Hz, 3H, H-16), 1.25–1.56 (m, 4H), 1.38 (s, 3H, H-14), 1.68–1.87 (m, 3H), 1.90–2.05 (m, 2H), 2.30–2.47 (m, 1H), 3.15 (m, 1H, H-9), 5.36 (s, 1H, H-12), 6.20 ppm (brs, 1H, H-11); MS (EI, 70 eV) *m/z* (%) = 282 [M^+ + H] (2), 265 [M^+ − O] (4), 250 (18), 249 [M^+ − O_2] (100), 235 (8), 234 (36), 221 (8), 208 (10), 205 (19).

Methanesulfonylazaartemisinin 7:

With LDA: A solution of 11-azaartemisinin **5** (1.0 g, 3.55 mmol) in THF (20 mL) was added to a stirred solution of LDA (5.35 mmol, 1.5 equiv) in THF (40 mL) at −78 °C. The solution was stirred for 3 h. Methanesulfonyl chloride (0.5 mL, 6.46 mmol, 1.8 equiv) was added, and the resulting mixture was stirred for 3 h. The mixture was concentrated by evaporation under reduced pressure, and the residue was diluted with CH_2Cl_2 (30 mL). This was washed with water (2 × 20 mL) and dried ($MgSO_4$). Filtration and evaporation of the filtrate gave a residue that was purified by chromatography with acetone/CH_2Cl_2 (3:97) to give *N*-methanesulfonyl-11-azaartemisinin **7** as a white finely crystalline powder, which crystallized as large colorless prisms from ethyl acetate (0.79 g, 62%); mp: 245 °C (dec); $[\alpha]_D^{20}$ = −103.15 (c = 1.0, $CHCl_3$); ^1H NMR: δ = 0.99 (d, J = 6 Hz, 3H, H-15), 0.95–1.10 (m, 1H), 1.22 (d, J = 7.8 Hz, 3H, H-16), 1.11–1.29 (m, 1H), 1.47 (s, 3H, H-14), 1.30–1.65 (m, 3H), 1.75–1.80 (m, 3H), 2.00–2.07 (m, 2H), 2.35–2.43 (m, 1H), 3.32–3.38 (m, 1H, H-9), 3.38 (s, 3H), 6.03 ppm (s, 1H, H-12); ^{13}C NMR: δ = 13.39, 19.26, 22.01, 24.48, 25.04, 33.32, 35.75, 36.12, 36.94, 43.83, 44.02, 51.05, 78.43, 79.97, 104.96, 173.67 ppm; IR (film): $\tilde{\nu}_{max}$ = 487, 520, 587, 772, 796, 892, 947, 970, 1024, 1128, 1169, 1214, 1316, 1352, 1447, 1715, 2941 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 359 [M^- + H] (8), 282 (100), 237 (80); anal. calcd for $C_{16}H_{25}NO_6S$: C 53.47, H 7.01, N 3.89; found: C 53.46, H 7.02, N 3.81.

With NaH: 11-Azaartemisinin **5** (5.0 g, 17.8 mmol) was stirred with NaH (60% dispersion in mineral oil, 1.1 g, 27.5 mmol) in THF (100 mL) at 0 °C. After 3 h, methanesulfonyl chloride (2.2 mL, 28.4 mmol) was added. After a further 3 h, the reaction mixture was quenched with water (100 mL), and the volatiles were removed by evaporation under reduced pressure at room temperature. The semi-aqueous residual mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$). Filtration and evaporation of the filtrate under reduced pressure left a semicrystalline residue. This was washed twice with a minimum amount of ethyl acetate to dissolve byproducts, which were removed by decantation. The remaining white crystalline powdery residue was purified directly by recrystallization with hexanes/CH_2Cl_2 by dissolving the residue in a minimum amount of CH_2Cl_2 and then adding the hexanes to dilute the solution. Slow evaporation of most of the solvent resulted in deposition of the product **7** as a white crystalline solid (3.50 g, 55%). Further material was recovered by allowing the mother liquor to concentrate by slow evaporation and collecting the precipitate.

Reduction of methanesulfonyl-11-azaartemisinin 7:

Attempted reduction with TMSCl–LiBH$_4$: Trimethylsilyl chloride (0.145 mL, 1.14 mmol) was added to a stirred solution of lithium borohydride (2 M in THF, 280 µL, 0.56 mmol) at 0 °C to give a mixture containing a white precipitate. A solution of **7** in THF/CH_2Cl_2 (1:1, 6 mL) was then added. After 1 h, the reaction was quenched with water (5 mL), extracted with CH_2Cl_2, and the extracts were dried ($MgSO_4$). After filtration, the solution was evaporated under reduced pressure to leave a semi-solid residue. This was submitted to chromatography with acetone/CH_2Cl_2 (2:98) to give firstly compound **8** as prism (24.3 mg, 24%); mp: 177 °C; $[\alpha]_D^{20}$ = −44.76 (c = 0.95, $CHCl_3$); ^1H NMR: δ = 0.90–1.08 (m, 1H), 0.96 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.09–1.26 (m, 1H), 1.37–1.42 (m, 1H), 1.67–2.00 (m, 6H), 2.10 (s, 3H), 3.09–3.21 (m, 1H), 3.26 (s, 3H), 3.70–3.87 (m, 2H), 6.59 ppm (s, 1H); ^{13}C NMR: δ = 12.00, 19.91, 20.82, 23.37, 25.65, 29.09, 34.16, 37.89, 42.83, 45.57, 55.37, 68.37, 78.95, 81.20, 168.24, 175.09 ppm; IR (film): $\tilde{\nu}_{max}$ = 530, 597, 760, 823, 922, 961, 984, 1018, 1075, 1105, 1132, 1170, 1356, 1460, 1724, 1752, 2887

2939 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 300 (100); anal. calcd for $C_{16}H_{25}NO_6S$: C 53.47, H 7.01, N 3.89; found: C 53.40, H 7.00, N 3.77.

The next fraction consisted of compound **9**, which was obtained as prisms (22 mg, 22%); mp: 201 °C; $[\alpha]_D^{20} = -222.92$ (*c* = 0.91, $CHCl_3$); ^1H NMR: $\delta = 0.90$ (d, *J* = 6.3 Hz, 3H), 0.96–1.1 (m, 2H), 1.17 (d, *J* = 7.5 Hz, 3H), 1.15–1.37 (m, 1H), 1.50 (s, 3H), 1.53–1.68 (m, 2H), 1.71–1.90 (m, 2H), 1.93–2.09 (m, 2H), 2.15–2.17 (brd, 1H), 3.12–3.25 (m, 1H), 3.33 (s, 3H), 3.61 (s, 1H), 5.76 ppm (s, 1H, H-12); ^{13}C NMR: $\delta = 12.13$, 17.98, 20.48, 22.36, 29.96, 33.05, 34.59, 35.15, 41.41, 42.95, 68.81, 82.89, 83.45, 107.90, 172.81 ppm; IR (film): $\tilde{\nu}_{max} = 528$, 549, 666, 757, 799, 834, 872, 892, 928, 951, 970, 1005, 1018, 1032, 1060, 1075, 1116, 1152, 1169, 1352, 1452, 1703, 2930, 3441 (OH) cm^{-1}; MS (CI, CH_4): *m/z* (%) = 360 (100), 299(12), 282 (10); anal. calcd for $C_{16}H_{25}NO_6S$: C 53.47, H 7.01, N 3.89; found: C 53.42, H 7.02, N 3.82.

Reduction with diisobutylaluminum hydride: Diisobutylaluminum hydride (1.0 M in CH_2Cl_2, 1.40 mL, 1.40 mmol) was added to a solution of **7** (0.10 g, 0.278 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred for 6 h with warming to room temperature. It was then quenched by the addition of water (10 mL), and the resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined and dried ($MgSO_4$). Filtration and evaporation of the solution under reduced pressure left the crude product which was purified by chromatography with acetone/CH_2Cl_2 (2:98) to give the product **10** as a fine white powder (22 mg, 22%); mp: 159 °C; $[\alpha]_D^{20} = +15.94$ (*c* = 0.94, $CHCl_3$); ^1H NMR: $\delta = 0.98$ (d, *J* = 5.7 Hz, 3H, H-15), 0.79–1.20 (m, 2H), 1.09 (d, *J* = 7.8 Hz, 3H, H-16), 1.32–1.59 (m, 2H), 1.45 (s, 3H, H-14), 1.55–1.79 (m, 4H), 2.00–2.15 (m, 2H), 5.78 (s, 1H, H-12), 2.30–2.45 (m, 1H), 2.54–2.69 (m, 1H), 3.21 (s, 3H), 4.53 (d, *J* = 12.6 Hz, 1H, OH), 5.05 ppm (dd, *J* = 12.6, 2.16 Hz, 1H, H-10); ^{13}C NMR: $\delta = 16.78$, 19.27, 21.99, 24.59, 25.35, 33.56, 36.44, 37.01, 37.43, 43.89, 44.11, 51.70, 74.78, 81.85, 82.53, 105.15 ppm; IR (film): $\tilde{\nu}_{max} = 487$, 524, 549, 583, 766, 825, 848, 889, 927, 964, 980, 1014, 1043, 1073, 1111, 1132, 1160, 1277, 1339, 1377, 1453, 2877, 2946, 3512 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 344 (100), 221 (20); anal. calcd for $C_{16}H_{27}NO_6S$: C 53.17, H 7.53, N 3.88; found: C 53.00, H 7.61, N 3.74.

Other sulfonyl derivatives:

Ethanesulfonyl ***11***: A solution of 11-azaartemisinin **5** (600 mg, 2.14 mmol) in THF (10 mL) was added to a stirred solution of LDA (3.20 mmol, 1.5 equiv) in THF (15 mL), and the resulting solution was stirred for 3 h at −78 °C. Ethanesulfonyl chloride (304 µL, 412 mg, 3.20 mmol, 1.5 equiv) was added to the reaction mixture, which was subsequently stirred for 3 h at −78 °C, and then for another 30 min at room temperature. The mixture was quenched with saturated aqueous ammonium chloride (20 mL), diluted with water (10 mL), and then extracted with ethyl acetate (3 × 30 mL). The extracts were washed with brine (30 mL), dried ($MgSO_4$), and then filtered. The filtrate was evaporated under reduced pressure to leave the a white solid, which was submitted to chromatography with ethyl acetate/hexanes (40:60) and recrystallization from ethyl acetate/hexanes to give **11** as white rectangular plates (489 mg, 61%); mp: 136.4–137.0 °C; $[\alpha]_D^{22} = -87.9$ (*c* = 1.56, $CHCl_3$); ^1H NMR: $\delta = 1.02$ (d, *J* = 6.3 Hz, 3H, 6-Me), 1.23 (d, *J* = 7.8 Hz, 3H, 9-Me), 1.42 (s, 3H, 3-Me), 1.47 (t, *J* = 7.8 Hz, 3H, 2′-Me), 1.51–1.60 (m, 3H), 1.65–1.82 (m, 4H), 1.97–2.07 (m, 3H), 2.34–2.45 (m, 1H), 3.33–3.42 (m, 1H, H-9), 3.48–3.74 (m, 2H, H-1′), 6.02 ppm (s, 1H, H-12); ^{13}C NMR $\delta = 7.81$, 13.76, 19.90, 22.59, 25.10, 25.68, 33.88, 36.09, 36.81, 37.52, 45.06, 51.67, 51.73, 78.46, 80.51, 105.50, 174.15 ppm; IR (film): $\tilde{\nu}_{max} = 515$, 535, 547, 556, 575, 596, 618, 648, 664, 713, 739, 776, 810, 831, 859, 880, 895, 930, 946, 966, 974, 1005, 1018, 1027, 1051, 1064, 1084, 1115, 1131, 1146, 1164, 1187, 1203, 1215, 1275, 1353, 1377, 1408, 1456, 1705, 2877, 2939, 3064 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 374 (100), 356 (20), 314 (34), 281 (26), 267 (46), 237 (58), 178 (48), 162 (88), 150 (32), 110 (16); exact mass: calcd for $C_{17}H_{28}NO_6S^+ = 374.1632$, found 374.1619; anal. calcd for $C_{17}H_{27}NO_6S$: C 54.67, H 7.29, N 3.75; found: C 53.99, H 7.30, N 3.62.

Propanesulfonyl ***12***: Compound **12** was obtained from **5** (500 mg, 1.78 mmol), LDA and propanesulfonyl chloride (299 µL, 381 mg, 2.67 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 40:60) as white rectangular plates (491.4 mg, 71.3%); mp: 127.8–128.2 °C; $[\alpha]_D^{22} = -87.4$ (*c* = 0.58, $CHCl_3$); ^1H NMR: $\delta = 1.02$ (d, *J* = 6.3 Hz, 3H, 6-Me), 1.08 (t, *J* = 7.5 Hz, 3H, 3′-Me), 1.22 (d, *J* = 7.8 Hz, 3H, 9-Me), 1.43 (s, 3H, 3-Me), 1.46–2.08 (m, 12H), 2.34–2.45 (m, 1H), 3.32–3.41 (m, 1H, H-9), 3.43–3.50 (m, 1H, H-1′), 3.60–3.70 (m, 1H, H-1′), 6.02 ppm (s, 1H, H-12); ^{13}C NMR: $\delta = 13.37$, 13.79, 16.79, 19.91, 22.59, 25.10, 25.65, 33.89, 36.13, 36.81, 37.52, 45.01, 51.73, 58.86, 78.50, 80.53, 105.48, 174.14 ppm; IR (film): $\tilde{\nu}_{max} = 555$, 575, 598, 621, 648, 671, 703, 737, 772, 792, 812, 831, 855, 881, 895, 931, 946, 965, 973, 1006, 1027, 1062, 1082, 1131, 1146, 1163, 1188, 1203, 1216, 1266, 1300, 1360, 1377, 1406, 1456, 1705, 2877, 2931, 2954 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 388 (12)268 (10), 240 (100); exact mass: calcd for $C_{18}H_{30}NO_6S^+ = 388.1788$, found 388.1812; anal. calcd for $C_{18}H_{29}NO_6S$: C 55.79, H 7.54, N 3.61; found: C 55.49, H 7.62, N 3.52.

Octanesulfonyl ***13***: Compound **13** was obtained from **5** (600 mg, 2.14 mmol), LDA and octanesulfonyl chloride (627 µL, 681 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a pale-yellow oil (539 mg, 55%); $[\alpha]_D^{22} = -69.2$ (*c* = 2.23, $CHCl_3$); ^1H NMR: $\delta = 0.85$–0.89 (m, 3H, 8′-Me), 1.01 (d, *J* = 6.3 Hz, 3H, 6-Me), 1.21 (d, *J* = 7.5 Hz, 3H, 9-Me), 1.26–1.39 (m, 12H, H-2′–H-7′), 1.42 (s, 3H, 3-Me), 1.45–2.07 (m, 10H), 2.31–2.44 (m, 1H), 3.31–3.40 (m, 1H, H-9), 3.42–3.51 (m, 1H, H-1′), 3.60–3.70 (m, 1H, H-1′), 6.01 ppm (s, 1H, H-12); ^{13}C NMR: $\delta = 13.77$, 14.45, 19.89, 22.57, 22.87, 22.95, 25.09, 25.64, 28.62, 29.27, 29.35, 32.03, 33.88, 36.11, 36.79, 37.50, 44.99, 51.71, 57.20, 78.48, 80.50, 105.45, 174.11 ppm; IR (film): $\tilde{\nu}_{max} = 577$, 598, 623, 648, 699, 733, 812, 832, 860, 880, 896, 930, 946, 966, 1027, 1063, 1167, 1203, 1276, 1359, 1457, 1709, 2928 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 458 (100), 398 (12), 367 (14), 248 (22), 237 (30), 209 (22); exact mass: calcd for $C_{23}H_{40}NO_6S^- = 458.2571$, found 458.2577; anal. calcd for $C_{23}H_{39}NO_6S$: C 60.37, H 8.59, N 3.06; found: C 60.20, H 8.74, N 2.53.

1-Hexadecanesulfonyl ***14***: Compound **14** was obtained from **5** (600 mg, 2.14 mmol), LDA and 1-hexadecanesulfonyl chloride (1.015 g, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a pale-yellow oil (505 mg, 42%); $[\alpha]_D^{22} = -55.8$ (*c* = 1.51, $CHCl_3$); ^1H NMR: $\delta = 0.87$–0.91 (m, 3H, 16′-Me), 1.02 (d, *J* = 6.3 Hz, 3H, 6-Me), 1.23 (d, *J* = 7.5 Hz, 3H, 9-Me), 1.26 (m, 28H, H-2′–H-15′), 1.43 (s, 3H, 3-Me), 1.46–2.09 (m, 10H), 2.36–2.44 (m, 1H), 3.35–3.43 (m, 1H, H-9), 3.47–3.53 (m, 1H, H-1′), 3.62–3.39 (m, 1H, H-1′), 6.03 ppm (s, 1H, H-12); ^{13}C NMR: $\delta = 13.79$, 14.54, 19.91, 22.59, 22.89, 23.09, 25.11, 25.67, 28.65, 29.42, 29.65, 29.74, 29.87, 29.96, 30.04, 32.30, 33.90, 36.13, 36.82, 37.52, 45.03, 51.74, 57.23, 78.50, 80.53, 105.47, 174.14 ppm; IR (film): $\tilde{\nu}_{max} = 598$, 623, 698, 812, 832, 860, 896, 946, 966, 1027, 1063, 1167, 1202, 1361, 1464, 1710, 2854, 2924 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 570 (8), 510 (12), 362 (6), 334 (82), 267 (6), 237 (100); exact mass: calcd for $C_{31}H_{56}NO_6S^+ = 570.3823$, found 570.3552.

4-Fluorobenzenesulfonyl ***15***: Compound **15** was obtained from **5** (600 mg, 2.14 mmol), LDA and 4-fluorobenzenesulfonyl chloride (623 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as white rectangular plates (105 mg, 11%);

mp: 189.2–190.0 °C; $[\alpha]_D^{22} = -83.4$ ($c = 3.38$, $CHCl_3$); ^1H NMR: $\delta =$ 1.03 (d, $J = 6.6$ Hz, 3H, 6-Me), 1.18 (s, 3H, 3-Me), 1.19 (d, $J = 7.5$ Hz, 3H, 9-Me), 1.23–1.44 (m, 2H), 1.51–1.85 (m, 6H), 1.99–2.08 (m, 2H), 2.30–2.40 (m, 1H), 3.24–3.33 (m, 1H, H-9), 6.18 (s, 1H, H-12), 7.14 (t, $J = 8.7$ Hz, 2H, ArH-3', ArH-5'), 8.19 ppm (dd, $J = 5.4$ Hz, 9.3 Hz, 2H, ArH-2', ArH-6'); ^{13}C NMR: $\delta = 13.73$, 19.90, 22.65, 25.12, 25.20, 33.90, 36.17, 36.81, 37.58, 45.09, 51.71, 78.91, 80.51, 105.43, 115.68, 115.99, 132.27, 132.40, 164.04, 167.42, 173.01 ppm; ^{19}F NMR: $\delta = -103.88$ ppm; IR (film): $\tilde{\nu}_{max} = 535$, 547, 560, 591, 610, 630, 647, 670, 697, 708, 729, 746, 792, 808, 819, 836, 860, 879, 894, 928, 944, 966, 1007, 1018, 1026, 1035, 1061, 1087, 1098, 1114, 1130, 1143, 1156, 1179, 1202, 1215, 1236, 1273, 1294, 1362, 1406, 1428, 1448, 1465, 1493, 1591, 1708, 2888, 2913, 2956, 2976, 3055, 3114 cm^{-1}; MS (CI, CH_4): m/z (%) = 440 (100), 380 (32), 281 (16), 215 (40), 237 (52), 209 (42); exact mass: calcd for $C_{21}H_{27}FNO_6S^+ = 440.1543$, found 440.1581; anal. calcd for $C_{21}H_{26}FNO_6S$: C 57.39, H 5.96, N 3.19; found: C 57.56, H 6.01, N 3.17.

4'-Chlorobenzenesulfonyl ***16***: A solution of 11-azaartemisinin **5** (5.0 g, 17.8 mmol) was stirred with NaH (60% dispersion in mineral oil, 1.10 g, 27.5 mmol, 1.5 equiv) in THF (100 mL) at 0 °C. After 3 h, 4-chlorobenzenesulfonyl chloride (5.64 g, 26.7 mmol, 1.5 equiv) was added. After a further 3 h, the reaction mixture was quenched with water (50 mL), and the volatiles were removed from the mixture by gentle evaporation under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$). Filtration and evaporation gave the crude product, recrystallization of which from ethyl acetate/hexanes gave **16** as white prisms (4.43 g, 56%); mp: 212 °C (dec); $[\alpha]_D^{20} = -94.52$ ($c = 0.98$, $CHCl_3$); ^1H NMR: $\delta = 1.02$ (d, $J = 6.3$ Hz, 3H, H-15), 0.95–1.10 (m, 1H), 1.11–1.29 (m, 1H), 1.17 (d, $J = 7.14$ Hz, 3H, H-16), 1.20 (s, 3H, H-14), 1.27–1.41 (m, 1H), 1.45–1.62 (m, 2H), 1.65–1.74 (m, 1H), 1.77–1.88 (m, 2H), 1.98–2.09 (m, 2H), 2.29–2.43 (m, 1H), 3.23–3.35 (m, 1H, H-9), 6.19 (s, 1H, H-12), 7.47 (d, $J =$ 8.7 Hz, 2H, ArH-3', ArH-5'), 8.12 ppm (d, $J = 8.76$ Hz, 2H, ArH-2', ArH-6'); ^{13}C NMR: $\delta = 13.05$, 19.25, 22.02, 24.48, 24.57, 33.27, 35.54, 36.21, 36.97, 44.52, 51.12, 78.38, 79.96, 104.98, 128.44, 130.43, 138.22, 139.93, 172.68 ppm; IR (film): $\tilde{\nu}_{max} = 472$, 491, 567, 590, 606, 627, 729, 757, 792, 810, 835, 895, 944, 1017, 1084, 1115, 1169, 1203, 1361, 1377, 1398, 1479, 1569, 1701, 2952 cm^{-1}; MS (CI, CH_4): m/z (%) = 456 [$M^+ + H$] (100), 396 (30), 281 (30), 237 (70); anal. calcd for $C_{21}H_{26}ClNO_6S$: C 55.32, H 5.75, N 3.07; found: C 55.33, H 5.61, N 3.04.

4'-Bromobenzenesulfonyl ***17***: Compound **17** was obtained from **5** (5.0 g, 17.8 mmol) and 4-bromobenzenesulfonyl chloride (6.82 g, 26.7 mmol, 1.5 equiv) according to the procedure used to prepare **16** as fine white prisms (4.05 g, 45.5%); mp: 199 °C (dec); $[\alpha]_D^{20} = -81.87$ ($c = 0.99$, $CHCl_3$); ^1H NMR: $\delta = 1.02$ (d, $J = 6.3$ Hz, 3H, H-15), 0.95–1.12 (m, 1H), 1.11–1.30 (m, 1H), 1.17 (d, $J = 8.1$ Hz, 3H, H-16), 1.20 (s, 3H, H-14), 1.27–1.41 (m, 1H), 1.45–1.62 (m, 2H), 1.65–1.74 (m, 1H), 1.77–1.88 (m, 2H), 1.98–2.09 (m, 2H), 2.29–2.43 (m, 1H), 3.23–3.35 (m, 1H, H-9), 6.19 (s, 1H, H-12), 7.63 (d, $J = 8.7$ Hz, 2H, ArH-3', ArH-5'), 8.04 ppm (d, $J = 8.7$ Hz, 2H, ArH-2', ArH-6'); ^{13}C NMR: $\delta = 13.04$, 19.26, 22.02, 24.48, 24.58, 33.27, 35.54, 36.21, 36.97, 44.53, 51.13, 78.38, 79.96, 129, 130.48, 104.99, 131.44, 138, 173 ppm; IR (film): $\tilde{\nu}_{max} = 602$, 619, 702, 730, 743, 792, 810, 833, 911, 944, 1012, 1036, 1067, 1114, 1131, 1168, 1204, 1216, 1276, 1359, 1377, 1464, 1568, 1700, 2951 cm^{-1}; MS (CI, CH_4): m/z (%) = 501 [$M^+ + H$] (32), 502 (32), 282 (36), 237 (100), 209 (64); anal. calcd for $C_{21}H_{26}BrNO_6S$: C 50.41, H 5.24, N 2.80; found: C 50.34, H 5.26, N 2.79.

p-Toluenesulfonyl ***18***: Compound **18** was obtained from **5** (5.0 g, 17.8 mmol) and *p*-toluenesulfonyl chloride (5.09 g, 26.7 mmol, 1.5 equiv) according to the procedure used to prepare **16** as prisms (3.33 g, 43%); mp: 219 °C (dec); $[\alpha]_D^{20} = -93.36$ ($c = 0.99$, $CHCl_3$); ^1H NMR: $\delta = 1.01$ (d, $J = 6.3$ Hz, 3H, H-15), 0.95–1.12 (m, 1H), 1.16 (d, $J = 7.5$ Hz, 3H, H-16), 1.24 (s, 3H, H-14), 1.12–1.27 (m, 1H), 1.28–1.41 (m, 1H), 1.45–1.72 (m, 3H), 1.75–1.87 (m, 2H), 2.00–2.09 (m, 2H), 2.27–2.43 (m, 1H), 2.42 (s, 3H), 3.24–3.32 (m, 1H), 6.20 (s, 1H, H-12), 7.28 (d, $J = 8.1$ Hz, 2H, ArH-3', ArH-5'), 8.04 ppm (d, $J = 8.4$ Hz, 2H, ArH-2', ArH-6'); ^{13}C NMR: $\delta = 13.00$, 19.28, 21.40, 22.00, 24.49, 24.59, 33.31, 35.44, 36.27, 36.95, 44.64, 51.19, 78.19, 80.00, 104.91, 128.73, 128.93, 136.85, 144.31, 172.56 ppm; IR (film): $\tilde{\nu}_{max} = 546$, 591, 664, 696, 728, 810, 895, 945, 1026, 1130, 1214, 1357, 1697, 2936 cm^{-1}; MS (CI, CH_4): m/z (%) = 436 [$M^+ + H$] (100), 376 (25), 281 (10), 237(43), 209 (30); anal. calcd for $C_{22}H_{29}NO_6S$: C 60.67, H 6.71, N 3.21; found: C 60.61, H 6.70, N 3.20.

4'-Nitrobenzenesulfonyl ***19***: Compound **19** was obtained from **5** (5.0 g, 17.8 mmol) and 4-nitrobenzenesulfonyl chloride (5.97 g, 26.7 mmol, 1.5 equiv) according to the procedure used to prepare **16** as a fine off-white powder that could not be recrystallized (3.13 g, 37.8%); mp: 186 °C (dec); $[\alpha]_D^{20} = -91.79$ ($c = 0.98$, $CHCl_3$); ^1H NMR: $\delta = 1.03$ (d, $J = 6.3$ Hz, 3H, H-15), 0.95–1.12 (m, 1H), 1.13–1.30 (m, 1H), 1.18 (s, 3H, H-14), 1.19 (d, $J = 7.7$ Hz, 3H, H-16), 1.30–1.43 (m, 1H), 1.45–1.63 (m, 2H), 1.65–1.74 (m, 1H), 1.79–1.90 (m, 2H), 1.98–2.11 (m, 2H), 2.29–2.42 (m, 1H), 3.26–3.35 (m, 1H, H-9), 6.21 (s, 1H, H-12), 8.31–8.45 ppm (m, 4H, ArH); ^{13}C NMR: $\delta = 13.04$, 19.24, 22.05, 24.47, 24.56, 33.23, 35.64, 36.15, 37.01, 44.45, 51.07, 78.63, 79.94, 105.10, 123.36, 130.31, 145.25, 150, 172.87 ppm; IR (film): $\tilde{\nu}_{max} = 606$, 624, 682, 743, 831, 895, 944, 1026, 1113, 1176, 1347, 1526, 1706, 2885 cm^{-1}; MS (CI, CH_4): m/z (%) = 467 [$M^+ + H$] (36), 403 (100), 237 (75), 209 (85); anal. calcd for $C_{21}H_{26}N_2O_8S \cdot 2H_2O$: C 50.20, H 5.21, N 5.57; found: C 50.70, H 5.37, N 5.44.

3'-Nitrobenzenesulfonyl ***20***: Compound **20** was obtained from **5** (1 g, 3.56 mmol), LDA and 3-nitrobenzenesulfonyl chloride (1.18 g, 5.34 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 40:60) according to the procedure used to prepare **11** as a white rectangular plates (814 mg, 49%); mp: 196.1–197.0 °C; $[\alpha]_D^{22} = -95.3$ ($c = 0.60$, $CHCl_3$); ^1H NMR: $\delta = 1.05$ (d, $J = 6$ Hz, 3H, 6-Me), 1.20 (d, $J = 7.5$ Hz, 3H, 9-Me), 1.20 (s, 3H, 3-Me), 1.26–1.45 (m, 3H), 1.47–1.63 (m, 2H), 1.67–1.75 (m, 1H), 1.80–1.85 (m, 2H), 2.01–2.10 (m, 2H), 2.31–2.41 (m, 1H), 3.28–3.35 (m, 1H, H-9), 6.21 (s, 1H, H-12), 7.73 (t, $J = 8.1$ Hz, 1H, ArH-5'), 8.45 (d, $J = 8.1$ Hz, 1H, ArH-6'), 8.57 (d, $J = 7.8$ Hz, 1H, ArH-4'), 8.94 ppm (s, 1H, ArH-2'); ^{13}C NMR: $\delta = 13.66$, 19.89, 22.65, 25.11, 25.20, 33.85, 36.21, 36.78, 37.60, 45.16, 51.71, 79.07, 80.37, 105.64, 124.62, 128.20, 129.99, 135.36, 142.11, 147.95, 173.32 ppm; IR (film): $\tilde{\nu}_{max} = 697$, 735, 762, 809, 831, 859, 878, 895, 944, 966, 1027, 1062, 1083, 1126, 1182, 1203, 1274, 1275, 1350, 1372, 1449, 1533, 1639, 1708, 2885, 2932 cm^{-1}; MS (CI, CH_4): m/z (%) = 467 (52), 282 (22), 237 (100), 209 (48); exact mass: calcd for $C_{21}H_{27}N_2O_8S^+ = 467.1488$, found 467.1508; anal. calcd for $C_{21}H_{26}N_2O_8S$: C 54.07, H 5.62, N 6.00; found: C 54.04, H 5.64, N 5.98.

2'-Nitrobenzenesulfonyl ***21***: Compound **21** was obtained from **5** (5.0 g, 17.8 mmol) and 2-nitrobenzenesulfonyl chloride (5.97 g, 26.7 mmol, 1.5 equiv) according to the procedure used to prepare **16** as a pale-yellow powder (1.12 g, 13.5%); mp: 201 °C (dec); $[\alpha]_D^{20} = -388.92$ ($c = 0.94$, $CHCl_3$); ^1H NMR: $\delta = 0.79$–0.92 (m, 1H), 0.94–1.16 (m, 1H), 1.01 (d, $J = 6.3$ Hz, 3H, H-15), 1.02 (d, $J = 8.1$ Hz, 3H, H-16), 1.16–1.34 (m, 1H), 1.33–1.46 (m, 1H), 1.50 (s, 3H, H-14), 1.54–1.87 (m, 4H), 1.95–2.11 (m, 2H), 2.36–2.50 (m, 1H), 3.32–3.47 (m, 1H, H-9), 6.12 (s, 1H, H-12), 7.69–7.85 (m, 3H, ArH), 8.44 ppm (d, $J = 6.9$ Hz, 1H, ArH); ^{13}C NMR: $\delta = 12.52$, 19.36, 21.54, 21.67, 24.37, 24.91, 33.57, 35.10, 36.05, 36.54, 44.53, 51.61, 79.96, 80.77, 105.15, 124.23, 131.98, 133.95, 135.20, 147.75, 171.66 ppm; IR (film): $\tilde{\nu}_{max} = 503$, 518, 561, 593, 613, 655, 700, 734, 783, 832, 85

893, 912, 946, 967, 1037, 1066, 1126, 1146, 1176, 1225, 1276, 1306, 1368, 1443, 1543, 1591, 1698, 2259, 2878, 2930, 3104 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 467 [M^+ − H] (10), 282 (10), 267 (24), 237 (78), 209 (100); anal. calcd for $C_{21}H_{26}N_2O_8S$: C 54.07, H 5.62, N 6.00; found: C 54.39, H 5.75, N 5.88.

3′-Cyanobenzenesulfonyl ***22***: Compound **22** was obtained from **5** (600 mg, 2.135 mmol), LDA and 3-cyanobenzenesulfonyl chloride (646 mg, 3.20 mmol, 1.5 equiv) according to the procedure used to prepare **11**, followed by direct recrystallization from ethyl acetate, as white rectangular plates (419 mg, 44%); mp: 219–220 °C; $[\alpha]_D^{22}$ = −109.8 (*c* = 0.87, $CHCl_3$); ^{1}H NMR: δ = 1.05 (d, *J* = 6.3 Hz, 3H, 6-Me), 1.22 (d, *J* = 7.5 Hz, 3H, 9-Me) 1.21 (s, 3H, 3-Me), 1.25–1.63 (m, 5H), 1.68–1.76 (m, 1H), 1.81–1.86 (m, 2H), 2.03–2.10 (m, 2H), 2.32–2.42 (m, 1H), 3.29–3.33 (m, 1H, H-9), 6.20 (s, 1H, H-12), 7.66 (t, *J* = 8.1 Hz, 1H, ArH-5′), 7.87 (td, *J* = 1.5, 8.1 Hz, 1H, ArH-6′), 8.44–8.48 ppm (m, 2H, ArH-2′, ArH-4′); ^{13}C NMR: δ = 13.75, 19.90, 22.67, 25.11, 25.17, 33.86, 36.26, 36.78, 37.61, 45.05, 51.67, 79.89, 80.43, 105.60, 113.30, 117.34, 129.69, 133.13, 133.55, 136.67, 141.72, 173.21 ppm; IR (film): $\tilde{\nu}_{max}$ = 625, 678, 701, 739, 800, 832, 857, 895, 928, 944, 966, 1025, 1036, 1060, 1094, 1113, 1129, 1143, 1169, 1207, 1266, 1367, 1421, 1449, 1710, 2888, 2929, 3085 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 447 (100), 429 (16), 387 (50), 282 (22), 265 (16), 237 (82), 209 (44); exact mass: calcd for $C_{22}H_{27}N_2O_6S^+$ = 447.1584, found 447.1583; anal. calcd for $C_{22}H_{26}N_2O_6S$: C 59.18, H 5.87, N 6.27; found: C 58.71, H 5.87, N 6.09.

3′-Nitro-4′-chlorobenzenesulfonyl ***23***: Compound **23** was obtained from **5** (600 mg, 2.14 mmol), LDA and 3-nitro-4-chlorobenzenesulfonyl chloride (820 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as white rectangular plates (332 mg, 31%); mp: 215–216 °C; $[\alpha]_D^{22}$ = −75.9 (*c* = 1.71, $CHCl_3$); ^{1}H NMR: δ = 1.06 (d, *J* = 6.6 Hz, 3H, 6-Me), 1.23 (1×s, 1×d, *J* = 7.5 Hz, 6H, 3-Me, 9-Me), 1.38–1.60 (m, 5H), 1.69–1.76 (m, 1H), 1.82–1.87 (m, 2H), 2.03–2.10 (m, 2H), 2.32–2.41 (m, 1H), 3.30–3.34 (m, 1H, H-9), 6.19 (s, 1H, H-12), 7.72 (d, *J* = 8.4 Hz, 1H, ArH-5′), 8.39 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H, ArH-6′), 8.60 ppm (d, *J* = 1.8 Hz, 1H, ArH-2′); ^{13}C NMR: δ = 13.71, 19.88, 22.66, 25.10, 25.20, 33.83, 36.29, 36.76, 37.61, 45.09, 51.67, 79.16, 80.35, 105.67, 126.71, 132.44, 132.77, 133.71, 140.09, 147.53, 173.34 ppm; IR (film): $\tilde{\nu}_{max}$ = 605, 629, 647, 664, 697, 726, 739, 776, 791, 813, 832, 858, 896, 930, 945, 965, 1018, 1027, 1037, 1052, 1097, 1116, 1130, 1143, 1202, 1214, 1266, 1362, 1371, 1408, 1466, 1541, 1572, 1590, 1712, 2874, 2944, 3076, 3104 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 501 (78), 483 (22), 441 (30), 281 (36), 265 (54), 237 (88), 209 (100); exact mass: calcd for $C_{21}H_{26}ClN_2O_8S^+$ = 501.1093, found 501.1099; anal. calcd for $C_{21}H_{25}ClN_2O_8S$: C 50.35, H 5.03, N 5.59; found: C 50.46, H 5.09, N 5.54.

3′,4′-Dimethoxybenzenesulfonyl ***24***: The crude product was obtained from **5** (600 mg, 2.14 mmol), LDA and 3,4-dimethoxybenzenesulfonyl chloride (758 mg, 3.20 mmol, 1.5 equiv), and stirring of the reaction mixture firstly at −78 °C for 3 h, then at room temperature for 17 h followed by chromatography (ethyl acetate/hexanes 45:55). This was recrystallized from ethyl acetate to give **24** as a white rectangular plates (179 mg, 17%); mp: 208–209 °C; $[\alpha]_D^{22}$ = −85.4 (*c* = 1.26, $CHCl_3$); ^{1}H NMR: δ = 1.04 (d, *J* = 6 Hz, 3H, 6-Me), 1.18 (s, 3H, 3-Me), 1.20 (d, *J* = 7.2 Hz, 3H, 9-Me), 1.33–1.86 (m, 8H), 1.99–2.05 (m, 2H), 2.33–2.37 (m, 1H), 3.28–3.33 (m, 1H, H-9), 3.94 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.20 (s, 1H, H-12), 6.92 (d, *J* = 8.4 Hz, 1H, ArH-5′), 7.70 (d, *J* = 2.1 Hz, 1H, ArH-2′), 7.79 ppm (dd, *J* = 2.4, 8.4 Hz, 1H, ArH-6′); ^{13}C NMR: δ = 13.84, 19.93, 22.67, 25.14, 25.40, 33.95, 36.21, 36.84, 37.60, 45.09, 51.73, 56.54, 56.67, 78.83, 80.64, 105.33, 110.10, 112.01, 123.59, 131.93, 148.48, 153.42, 172.96 ppm; IR (film): $\tilde{\nu}_{max}$ = 523, 535, 544, 559, 579, 625, 668, 699, 748, 808, 831, 859, 880, 896, 930, 966, 946, 1020, 1063, 1092, 1115, 1143, 1166, 1185, 1203, 1216, 1237, 1265, 1359, 1408, 1459, 1509, 1588, 1707, 2874, 2930 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 482 (24), 466 (10), 422 (8), 282 (20), 246 (24), 237 (100), 209 (70), 201 (28); exact mass: calcd for $C_{23}H_{32}NO_8S^+$ = 482.1843, found 482.1866; anal. calcd for $C_{23}H_{31}NO_8S$: C 57.37, H 6.49, N 2.91; found: C 57.57, H 6.57, N 2.89.

4′-(Methanesulfonyl)benzenesulfonyl ***25***: Compound **25** was obtained from **5** (5.0 g, 17.8 mmol) and 4-(methanesulfonyl)benzenesulfonyl chloride (6.80 g, 26.7 mmol, 1.5 equiv) according to the procedure used to prepare **16** as a white microcrystalline solid (3.64 g, 40%); mp: 201 °C (dec); $[\alpha]_D^{20}$ = −76.99° (*c* = 0.9, $CHCl_3$); ^{1}H NMR: δ = 1.02 (d, *J* = 6.3 Hz, 3H, 6-Me), 0.95–1.12 (m, 1H), 1.17 (s, 3H, 3-Me), 1.17 (d, *J* = 8.4 Hz, 3H, 9-Me), 1.12–1.28 (m, 1H), 1.29–1.43 (m, 1H), 1.45–1.76 (m, 3H), 1.75–1.88 (m, 2H), 2.00–2.10 (m, 2H), 2.27–2.43 (m, 1H), 3.08 (s, 3H, $MeSO_2Ar$), 3.27–3.36 (m, 1H, H-9), 6.21 (s, 1H, H-12), 8.07 (d, *J* = 6.9 Hz, 2H, ArH), 8.38 ppm (d, *J* = 8.4 Hz, 2H, ArH); ^{13}C NMR: δ = 13.02, 19.23, 22.04, 24.46, 24.54, 33.24, 35.62, 37.00, 36.16, 44.09, 44.48, 51.09, 78.58, 79.95, 105.10, 127.36, 129.97, 144.67, 144.79, 172.87 ppm; IR (film): $\tilde{\nu}_{max}$ = 570, 589, 606, 624, 742, 780, 832, 895, 947, 1028, 1088, 1154, 1174, 1322, 1364, 1393, 1451, 1710, 2934, 3100 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 500 [M^+ + H] (50), 282 (100); anal. calcd for $C_{22}H_{29}NO_8S_2$: C 52.89, H 5.85, N 2.80; found: C 52.54, H 5.90, N 2.71.

(4′-Phenyl)benzenesulfonyl ***26***: Compound **26** was obtained from **5** (600 mg, 2.14 mmol), LDA and 4-(phenyl)benzenesulfonyl chloride (809 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) followed by recrystallization from ethyl acetate as fine white needles (86 mg, 8%); mp: 219–220 °C; $[\alpha]_D^{22}$ = −72.7 (*c* = 1.2, $CHCl_3$); ^{1}H NMR: δ = 1.03 (d, *J* = 6.3 Hz, 3H, 6-Me), 1.20 (d, *J* = 7.5 Hz, 3H, 9-Me), 1.22 (s, 3H, 3-Me), 1.26–1.42 (m, 2H), 1.51–1.73 (m, 4H), 1.78–1.84 (m, 2H), 2.00–2.07 (m, 2H), 2.31–2.40 (m, 1H), 3.27–3.33 (m, 1H, H-9), 6.22 (s, 1H, H-12), 7.36–7.48 (m, 3H, Ar-H3″, Ar-H4″), 7.56–7.60 (m, 2H, Ar-H2″), 7.67–7.71 (m, 2H, ArH-3′, ArH-5′), 8.20–8.24 (m, 2H, ArH-2′, ArH-6′); ^{13}C NMR: δ = 13.72, 19.94, 22.68, 25.15, 25.24, 33.94, 36.15, 36.88, 37.60, 45.21, 51.77, 78.85, 80.56, 105.47, 127.22, 127.62, 128.73, 129.21, 129.85, 138.76, 139.52, 146.65, 173.05 ppm; IR (film): $\tilde{\nu}_{max}$ = 563, 586, 602, 616, 635, 650, 674, 704, 739, 769, 797, 809, 840, 858, 881, 894, 929, 946, 965, 1005, 1018, 1027, 1062, 1088, 1113, 1127, 1144, 1172, 1218, 1265, 1359, 1447, 1564, 1593, 1699, 2307, 2927, 3056 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 498 (28), 438 (80), 387 (18), 347 (24), 311 (54), 284 (90), 257 (64), 237 (100), 209 (62); exact mass: calcd for $C_{27}H_{32}NO_6S^-$ = 498.1945, found 498.1958; anal. calcd for $C_{27}H_{31}NO_6S$: C 65.17, H 6.28, N 2.81; found: C 64.98, H 6.31, N 2.78.

5′-Chloro-2′-thiophenesulfonyl ***27***: Compound **27** was obtained from **5** (600 mg, 2.14 mmol), LDA and 5-chloro-2-thiophenesulfonyl chloride (431 µL, 700 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) followed by recrystallization from ethyl acetate as a white rectangular plates (142 mg, 14%); mp: 178.6–179.2 °C; $[\alpha]_D^{22}$ = −90.5 (*c* = 1.26, $CHCl_3$); ^{1}H NMR: δ = 1.01 (d, *J* = 6 Hz, 3H, 6-Me), 1.20 (s, 3H, 3-Me), 1.23 (d, *J* = 7.8 Hz, 3H, 9-Me), 1.33–1.85 (m, 8H), 1.98–2.08 (m, 2H), 2.32–2.43 (m, 1H), 3.30–3.39 (m, 1H, H-9), 6.14 (s, 1H, H-12), 6.91 (d, *J* = 4.2 Hz, 1H, ArH-3′), 7.70 ppm (d, *J* = 3.9 Hz, 1H, ArH-4′); ^{13}C NMR: δ = 13.88, 19.91, 22.69, 25.12, 25.15, 33.93, 36.35, 36.77, 37.61, 44.87, 51.64, 79.47, 80.56, 105.51, 126.09, 134.79, 138.25, 139.72, 173.45 ppm; IR (film): $\tilde{\nu}_{max}$ = 624, 679, 698, 745, 811, 832, 858, 895, 945, 994, 1027, 1062, 1115, 1130, 1143, 1173, 1024, 1214, 1266, 1317, 1369, 1407, 1450, 1514, 1708, 2930, 3111 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 462 (38), 402 (22), 264 (24), 237 (100), 209 (62); exact mass: calcd for $C_{19}H_{25}ClNO_6S_2^+$ = 462.0806, found 462.0809; anal. calcd for

$C_{19}H_{24}ClNO_6S_2$: C 49.40, H 5.24, N 3.03; found: C 49.49, H 5.22, N 3.00.

2′-Naphthalenesulfonyl ***28***: Compound **28** was obtained from **5** (600 mg, 2.14 mmol), LDA and 2-naphthalenesulfonyl chloride (726 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a white rectangular plates, from ethyl acetate (347 mg, 35%); mp: 224–225 °C; $[\alpha]_D^{22} = -74.4$ ($c = 2.04$, $CHCl_3$); ^{1}H NMR: $\delta = 1.03$ (d, $J = 6.6$ Hz, 3H, 6-Me), 1.18 (6H, 3-Me, 9-Me), 1.21–1.46 (m, 3H), 1.50–1.75 (m, 3H), 1.51–1.84 (m, 2H), 2.00–2.07 (m, 2H), 2.27–2.39 (m, 1H), 3.26–3.31 (m, 1H, H-9), 6.26 (s, 1H, H-12), 7.53–7.64 (m, 2H, ArH), 7.86–7.96 (m, 3H, ArH), 8.18 (dd, J = 1.8, 8.4 Hz, 1H, ArH-3′), 8.72 ppm (d, $J = 1.5$ Hz, 1H, ArH-1′); ^{13}C NMR: $\delta = 13.72$, 19.93, 22.68, 25.15, 25.26, 33.93, 36.14, 36.88, 37.59, 45.20, 51.76, 78.86, 80.55, 105.47, 124.06, 127.55, 128.08, 128.60, 129.36, 129.69, 131.24, 131.96, 135.48, 137.12, 173.00 ppm; IR (film): $\tilde{\nu}_{max} = 547$, 618, 641, 661, 696, 727, 750, 793, 825, 860, 879, 895, 929, 945, 966, 1027, 1074, 1115, 1132, 1144, 1171, 1201, 1214, 1270, 1352, 1459, 1505, 1590, 1709, 2342, 2874, 2929, 3025 cm^{-1}; MS (CI, CH_4): m/z (%) = 472 (40), 412 (66), 282 (18), 267 (28), 237 (100), 209 (96); exact mass: calcd for $C_{25}H_{30}NO_6S^- = 472.1794$, found 472.1765; anal. calcd for $C_{25}H_{29}NO_6S$: C 63.68, H 6.20, N 2.97; found: C 63.86, H 6.25, N 2.95.

Dansyl ***29***: Compound **29** was obtained from **5** (200 mg, 0.71 mmol), LDA and dansyl chloride (288 mg, 1.07 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a yellow gum (31.3 mg, 8.5%); $[\alpha]_D^{22} = -79.7$ ($c = 1.565$, $CHCl_3$); ^{1}H NMR: $\delta = 0.89$ (d, $J = 7.5$ Hz, 3H, 9-Me), 1.08 (d, $J = 6$ Hz, 3H, 6-Me), 1.47 (s, 3H, 3-Me), 1.62–1.86 (m, 8H), 2.04–2.16 (m, 2H), 2.41–2.46 (m, 1H), 2.88 (s, 6H, Me_2N), 3.29–3.33 (m, 1H, H-9), 6.38 (s, 1H, H-12), 7.49–7.60 (m, 3H, Ar-H), 8.38–8.57 ppm (m, 3H, Ar-H); ^{13}C NMR: $\delta = 13.47$, 20.02, 22.65, 25.16, 25.52, 34.04, 35.99, 36.92, 37.66, 44.99, 45.75, 51.99, 79.23, 80.92, 105.71, 115.18, 119.17, 123.44, 128.23, 129.76, 131.22, 132.05, 135.77, 151.96, 172.85; MS (CI, CH_4): m/z (%) = 515 (8), 473 (42), 429 (24), 387 (100), 347 (20), 321 (16); exact mass: calcd for $C_{27}H_{35}N_2O_6S^+ = 515.2210$, found 515.2244.

8-Quinolinesulfonyl ***30***: Compound **30** was obtained from **5** (600 mg, 2.14 mmol), LDA and 8-quinolinesulfonyl chloride (729 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 50:50) as a white rectangular plates (353 mg, 35%), m.p 220–221 °C; $[\alpha]_D^{22} = -36$ ($c = 2.61$, $CHCl_3$); ^{1}H NMR: $\delta = 0.71$ (d, $J = 7.2$ Hz, 3H, 9-Me), 1.10 (d, $J = 6.3$ Hz, 3H, 6-Me), 1.34–1.54 (m, 4H), 1.57 (s, 3H, 3-Me), 1.71–1.91 (m, 4H), 2.01–2.15 (m, 2H), 2.42–2.52 (m, 1H), 3.32–3.41 (m, 1H, H-9), 6.73 (s, 1H, H-12), 7.48 (dd, $J = 4.5$ Hz, 8.7 Hz, 1H, ArH-6′), 7.68 (dd, $J = 7.8$ Hz, 7.8 Hz, 1H, ArH-3′), 8.03 (dd, $J = 1.5$, 8.4 Hz, 1H, ArH-7′), 8.22 (dd, $J = 1.8$, 8.1 Hz, 1H, ArH-5′), 8.64 (dd, $J = 1.5$ Hz, 7.5 Hz, 1H, ArH-2′), 8.87 ppm (dd, J = 1.8 Hz, 3.9 Hz, 1H, ArH-4′); ^{13}C NMR: $\delta = 12.81$, 20.16, 21.94, 25.21, 25.78, 34.28, 35.46, 36.83, 37.39, 45.39, 52.19, 80.07, 81.17, 105.36, 122.22, 126.12, 128.96, 133.99, 134.35, 136.96, 137.80, 143.37, 150.93, 171.90 ppm; IR (film): $\tilde{\nu}_{max} = 553$, 577, 596, 635, 612, 649, 670, 701, 735, 767, 792, 835, 859, 894, 931, 947, 966, 985, 1037, 1055, 1067, 1131, 1147, 1171, 1204, 1215, 1271, 1311, 1356, 1377, 1495, 1563, 1596, 1615, 1694, 2876, 2938, 3063 cm^{-1}; MS (CI, CH_4): m/z (%) = 473 (100), 413 (6), 347 (8), 237 (30), 209 (24); exact mass: calcd for $C_{24}H_{29}N_2O_6S^+ = 473.1746$, found 473.1566; anal. calcd for $C_{24}H_{28}N_2O_6S$: C 61.00, H 5.97, N 5.93; found: C 60.98, H 6.04, N 5.87.

4′,4″-Biphenyl-1′,1″-bis-sulfonyl ***31***: Compound **31** was obtained from **5** (600 mg, 2.14 mmol), LDA and biphenyl-4,4′-disulfonyl chloride (562 mg, 1.60 mmol, 0.75 equiv), and chromatography (ethyl acetate/hexanes 35:65) followed by recrystallization from ethyl acetate as a white fine rectangular plates (66 mg, 7%); mp: 201 °C (dec); $[\alpha]_D^{22} = -55.5$ ($c = 1.52$, $CHCl_3$); ^{1}H NMR: $\delta = 1.05$ (d, $J = 6$ Hz, 6H, 6-Me), 1.20 (d, $J = 7.5$ Hz, 6H, 9-Me), 1.21 (6H, s, 3-Me), 1.46–1.73 (m, 10H), 1.80–1.93 (m, 6H), 2.02–2.07 (m, 4H), 2.32–2.42 (m, 2H), 3.26–3.35 (m, 2H, H-9), 6.22 (s, 2H, H-12), 7.70 (d, $J = 8.4$ Hz, 4H, ArH-3′, ArH-3″, ArH-5′, ArH-5″), 8.26 ppm (d, $J = 8.1$ Hz, 4H, ArH-2′, ArH-2″, ArH-6′, ArH-6″); ^{13}C NMR: $\delta = 13.70$, 19.92, 22.68, 25.13, 25.45, 33.19, 36.17, 36.85, 37.60, 45.18, 51.75, 78.90, 80.53, 105.48, 127.48, 127.50, 127.81, 130.06, 140.06, 144.60, 173.10 ppm; IR (film): $\tilde{\nu}_{max} = 584$, 597, 615, 668, 715, 731, 809, 823, 859, 895, 936, 946, 966, 1003, 1028, 1063, 1090, 1145, 1129, 1172, 1202, 1214, 1273, 1359, 1458, 1594, 1705, 2874, 2930 cm^{-1}; MS (CI, CH_4): m/z (%) = 842 (44), 749 (100), 731 (48), 171 (62), 702 (68), 693 (88), exact mass: calcd for $C_{42}H_{53}N_2O_{12}S_2^- = 841.3040$, found 841.2895; anal. calcd for $C_{42}H_{52}N_2O_{12}S_2$: C 59.98, H 6.23, N 3.33; found: C 59.88, H 6.29, N 3.25.

Carbonylazaartemisinin derivatives:

Methanecarbonyl ***32***: Compound **32** was obtained from **5** (600 mg, 2.135 mmol), LDA and acetyl chloride (228 µL, 251 mg, 3.203 mmol, 1.5 equiv) according to the procedure used to prepare the ethanesulfonyl derivative **11** followed by chromatography (ethyl acetate/hexanes 35:65) as a white microcrystalline solid from ethyl acetate/hexanes (374 mg, 54%); mp: 127.9–128.3 °C; $[\alpha]_D^{22} = -5.75$ ($c = 0.84$, $CHCl_3$); ^{1}H NMR: $\delta = 1.00$ (d, $J = 6.2$ Hz, 3H, 6-Me), 1.16 (d, J = 7.3 Hz, 3H, 9-Me), 1.34 (s, 3H, 3-Me), 1.46–1.79 (m, 8H), 1.95–2.06 (m, 2H), 2.34–2.48 (m, 1H), 2.50 (s, 3H, MeCO), 3.47–3.56 (m, 1H, H-9), 6.08 ppm (s, 1H, H-12); ^{13}C NMR: $\delta = 13.14$, 20.02, 22.99, 25.14, 25.93, 28.77, 33.97, 35.69, 36.68, 37.48, 45.99, 51.76, 77.20, 80.36, 105.10, 174.42, 176.38 ppm; IR (film): $\tilde{\nu}_{max} = 603$, 620, 666, 699, 728, 756, 804, 826, 860, 900, 930, 946, 963, 992, 1029, 1058, 1070, 1118, 1130, 1147, 1156, 1183, 1203, 1244, 1259, 1274, 1361, 1378, 1408, 1443, 1458, 1667, 1740, 2860, 2873, 2928, 2974 cm^{-1}; MS (CI, CH_4): m/z (%) = 324 (30), 297 (20), 283 (17), 282 (28), 281 (100), 267 (11), 264 (74),237 (12), 222 (12); exact mass: calcd for $C_{17}H_{26}NO_5^+ = 324.1811$, found 324.1734.

Ethanecarbonyl ***33***: Compound **33** was obtained from **5** (500 mg, 1.78 mmol), LDA and propionyl chloride (233 µL, 245 mg, 2.67 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 30:70) as white microcrystalline solid from ethyl acetate/hexanes (347 mg, 58%); mp: 121.5–122.4 °C; $[\alpha]_D^{22} = +10.65$ ($c = 0.45$, $CHCl_3$); ^{1}H NMR: $\delta = 1.00$ (d, $J = 6.15$ Hz, 3H, 6-Me), 1.10–1.20 (6H, 9-Me, 2′-Me), 1.34 (s, 3H, 3-Me), 1.49–1.79 (m, 8H), 1.96–2.04 (m, 2H), 2.35–2.45 (m, 1H), 2.68–3.01 (m, 2H, H-1′), 3.48–3.57 (1H, m, H-9), 6.10 ppm (s, 1H, H-12); ^{13}C NMR: $\delta = 9.70$, 12.93, 20.05, 23.00, 25.17, 25.93, 33.97, 34.51, 35.51, 36.70, 37.51, 46.24, 51.75, 80.40, 105.08, 174.15, 181.39 ppm; IR (film): $\tilde{\nu}_{max} = 665$, 760, 813, 837, 862, 899, 947, 1033, 1065, 1146, 1172, 1201, 1233, 1376, 1041, 1459, 1684, 1727, 2875, 2938 cm^{-1}; MS (CI, CH_4): m/z (%) = 338 (100), 305 (39), 282 (41), 264 (34), 209 (36), 191 (28), 178 (10); exact mass: calcd for $C_{18}H_{28}NO_5^+ = 338.1967$, found 338.1997.

Propanecarbonyl ***34***: Compound **34** was obtained from **5** (500 mg, 1.78 mmol), LDA and butyryl chloride (279 µL, 284 mg, 2.67 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 30:70) as a pale-yellow oil (419 mg, 67%); $[\alpha]_D^{22} = +14.59$ ($c = 1.18$, $CHCl_3$); ^{1}H NMR: $\delta = 0.96$ (t, $J = 7.5$ Hz, 3H, 3′-Me), 1.00 (d, $J = 6.6$ Hz, 3H, 6-Me), 1.15 (d, $J = 6.9$ Hz, 3H, 9-Me), 1.33 (s, 3H, 3-Me), 1.41–1.80 (m, 10H), 1.95–2.06 (m, 2H), 2.35–2.45 (m, 1H), 2.70–2.94 (m, 2H, H-1′), 3.51–3.56 (m, 1H, H-9), 6.11 ppm (s, 1H, H-12); ^{13}C NMR: $\delta = 12.87$, 14.11, 18.94, 20.01, 22.95, 25.12, 25.86, 33.92, 35.49, 36.69, 37.47, 42.99, 46.27, 51.73, 77.30, 80.34, 105.04, 174.10, 180.38 ppm; IR (film): $\tilde{\nu}_{max} = 607$, 650, 665, 697, 759, 786, 800, 820, 836, 862, 890,

909, 931, 948, 964, 975, 1033, 1069, 1170, 1203, 1235, 1303, 1377, 1403, 1455, 1644, 1694, 2735, 2875, 2936 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 352 (100), 319 (40), 301 (22), 282 (55), 264 (36), 231 (15), 209 (20), 191 (61), 178 (11); exact mass: calcd for $C_{19}H_{30}NO_5^+$ = 352.2124, found 352.2109.

Pentanecarbonyl ***35***: Compound **35** was obtained from **5** (500 mg, 1.78 mmol), LDA and hexanoyl chloride (367 µL, 359 mg, 2.67 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 30:70) as a pale-yellow oil (565 mg, 84%); $[\alpha]_D^{22} = +7$ (*c* = 1.02, $CHCl_3$); ^{1}H NMR: δ = 0.86–0.96 (overlapping m, 9H, including H-2′, H-3′), 1.00 (d, *J* = 6.6 Hz, 3H, 6-Me), 1.15 (d, *J* = 6.9 Hz, 3H, 9-Me), 1.34 (s, 3H, 3-Me), 1.40–1.80 (m, 8H), 1.95–2.07 (m, 2H), 2.35–2.48 (m, 1H), 2.71–2.95 (m, 2H, H-1′), 3.50–3.56 (1H, m, H-9), 6.11 ppm (s, 1H, H-12); ^{13}C NMR: δ = 12.86, 14.28, 20.01, 22.80, 22.94, 25.12, 25.16, 25.85, 31.64, 33.91, 35.45, 36.68, 37.45, 41.08, 46.27, 51.72, 77.29, 80.33, 105.03, 174.06, 180.58 ppm; IR (film): $\tilde{\nu}_{max}$ = 606, 650, 666, 697, 736, 761, 801, 820, 837, 863, 889, 931, 947, 962, 975, 1031, 1069, 1167, 1203, 1233, 1329, 1377, 1404, 1455, 1644, 1694, 2731, 2873, 2931 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 380 (100), 347 (21), 289 (12), 282 (23), 264 (17), 231 (10), 191 (32), 178 (6); exact mass: calcd for $C_{21}H_{34}NO_5^+$ = 380.2437, found 380.2403.

Pentadecanecarbonyl ***36***: Compound **36** was obtained from **5** (500 mg, 1.78 mmol), LDA and palmitoyl chloride (809 µL, 734 mg, 2.67 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 30:70) as a pale-yellow oil (652 mg, 71%); $[\alpha]_D^{22} = +2.5$ (*c* = 0.99, $CHCl_3$); ^{1}H NMR: δ = 0.88 (t, *J* = 7.2 Hz, 3H, H-15′), 1.00 (d, *J* = 6.3 Hz, 3H, 6-Me), 1.14 (d, *J* = 6.9 Hz, 3H, 9-Me), 1.21–1.30 (m, 26H, H-2′–H-14′), 1.33 (s, 3H, 3-Me), 1.40–1.79 (m, 8H), 1.94–2.05 (m, 2H), 2.35–2.47 (m, 1H), 2.71–2.95 (m, 2H, H-1′), 3.47–3.55 (m, 1H, H-9), 6.11 ppm (s, 1H, H-12); ^{13}C NMR: δ = 12.90, 14.52, 20.04, 22.98, 23.07, 25.14, 25.55, 25.90, 29.51, 29.58, 29.66, 29.73, 29.80, 29.88, 29.99, 30.03, 32.29, 33.95, 35.52, 36.72, 37.49, 41.18, 46.32, 51.77, 80.38, 105.07, 174.11, 180.65 ppm; IR (film): $\tilde{\nu}_{max}$ = 607, 650, 666, 721, 764, 801, 837, 863, 889, 904, 931, 947, 963, 975, 1032, 1070, 1146, 1166, 1203, 1232, 1376, 1405, 1463, 1644, 1694, 2853, 2923 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 520 (100), 518 (69), 487 (38), 469(18), 429 (10), 381 (16), 338 (14), 310 (9), 282 (39), 237 (81); exact mass: calcd for $C_{31}H_{54}NO_5^+$ = 520.4002, found 520.4002.

1′,4′-Butanedicarbonyl ***37***: Compound **37** was obtained from **5** (500 mg, 1.78 mmol), LDA and adipoyl chloride (195 µL, 244 mg, 1.34 mmol, 0.75 equiv), and chromatography (ethyl acetate/hexanes 30:70) followed by precipitation from ethyl acetate by addition of hexanes, as a fine white solid (207 mg, 35%); mp: 134.5–134.8 °C; $[\alpha]_D^{22} = +5.54$ (*c* = 2.11, $CHCl_3$); ^{1}H NMR: δ = 0.99 (d, *J* = 6.0 Hz, 6H, 6-Me), 1.14 (d, *J* = 6.9 Hz, 6H, 9-Me), 1.33 (s, 6H, 3-Me), 1.39–1.61 (m, 8H), 1.63–1.98 (m, 12H), 2.02–2.08 (m, 4H), 2.34–2.44 (m, 2H), 2.74–2.97 (m, 4H, H-1′, H-4′), 3.48–3.56 (m, 2H, H-9), 6.09 ppm (2H, s, H-12); ^{13}C NMR: δ = 12.90, 20.03, 22.97, 24.93, 25.13, 25.97, 33.94, 35.52, 36.70, 37.47, 41.81, 46.24, 51.74, 77.29, 80.33, 105.07, 174.14, 179.95 ppm; IR (film): $\tilde{\nu}_{max}$ = 665, 755, 837, 862, 907, 931, 948, 963, 1032, 1071, 1145, 1167, 1202, 1232, 1377, 1405, 1458, 1686, 1718, 2874, 2937 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 673 (66), 392 (7), 282 (8), 267 (16), 237 (16), 209 (100); exact mass: calcd for $C_{36}H_{53}N_2O_{10}^-$ = 673.3700, found 673.3641.

1′,6′-Hexanedicarbonyl ***38***: Compound **38** was obtained from **5** (600 mg, 2.14 mmol), LDA and suberoyl chloride (288 µL, 338 mg, 1.60 mmol, 0.75 equiv), and chromatography (ethyl acetate/hexanes 30:70) followed by precipitation from ethyl acetate by addition of hexanes, as a fine white solid (238 mg, 32%); mp: 135.8–136.6 °C; $[\alpha]_D^{22} = +11.51$ (*c* = 1.19, $CHCl_3$); ^{1}H NMR: δ = 0.99 (d, *J* = 6.15 Hz, 6H, 6-Me), 1.14 (d, *J* = 7.03 Hz, 6H, 9-Me), 1.34 (s, 6H, 3-Me), 1.36–1.78 (m, 24H), 1.95–2.05 (m, 4H), 2.34–2.44 (m, 2H), 2.69–2.95 (m, 4H, H-1′, H-6′), 3.48–3.54 (m, 2H, H-9), 6.10 ppm (s, 2H, H-12); ^{13}C NMR: δ = 12.90, 20.04, 22.97, 25.14, 25.40, 25.93, 29.41, 33.95, 35.51, 36.70, 37.48, 41.11, 46.30, 51.76, 77.31, 80.36, 105.07, 174.09, 180.44 ppm; IR (film): $\tilde{\nu}_{max}$ = 665, 755, 836, 862, 904, 931, 947, 963, 1031, 1070, 1145, 1167, 1202, 1233, 1377, 1403, 1448, 1690, 2872, 2935 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 701 (100), 669 (25), 635 (13), 558 (17), 519 (16), 376 (6), 319 (10); exact mass: calcd for $C_{38}H_{57}N_2O_{10}^-$ = 701.4008, found 701.3911.

1′,8′-Octanedicarbonyl ***39***: Compound **39** was obtained from **5** (500 mg, 1.78 mmol), LDA and sebacoyl chloride (285 µL, 319 mg, 1.34 mmol, 0.75 equiv), and chromatography (ethyl acetate/hexanes 30:70) followed by concentration of the eluate by slow evaporation as a white solid (81 mg, 13%); mp: 128.5–129.1 °C; $[\alpha]_D^{22} = +10.45$ (*c* = 0.85, $CHCl_3$); ^{1}H NMR: δ = 0.99 (d, *J* = 6.3 Hz, 6H, 6-Me), 1.14 (d, 6H, *J* = 6.9 Hz, 9 Me), 1.24–1.28 (m, 12H), 1.33 (s, 6H, 3-Me), 1.40–1.79 (m, 16H), 1.95–2.05 (m, 4H), 2.34–2.45 (m, 2H), 2.69–2.94 (m, 4H, H-1′, H-8′), 3.48–3.55 (m, 2H, H-9), 6.10 ppm (s, 2H, H-12); ^{13}C NMR: δ = 12.91, 20.05, 22.99, 25.15, 25.52, 25.92, 29.55, 29.68, 33.96, 35.52, 36.72, 37.49, 41.15, 46.32, 51.78, 80.38, 105.08, 174.12, 180.61 ppm; IR (film): $\tilde{\nu}_{max}$ = 665, 756, 837, 862, 948, 963, 1031, 1070, 1146, 1166, 1202, 1233, 1376, 1405, 1458, 1689, 1718, 2871, 2929 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 729 (34), 722 (20), 282 (7), 267 (18), 237 (47), 209 (100); exact mass: calcd for $C_{40}H_{61}N_2O_{10}^+$ = 729.4326, found 729.4317.

1′,10′-Decanedicarbonyl ***40***: Compound **40** was obtained from **5** (600 mg, 2.14 mmol), LDA and dodecanedioyl chloride (400 µL, 428 mg, 1.60 mmol, 0.75 equiv), and chromatography (ethyl acetate/hexanes 30:70) followed by concentration of the eluate by slow evaporation as a fine white solid (188 mg, 28%); mp: 121.5–122.4 °C; $[\alpha]_D^{22} = +11.61$ (*c* = 3.26, $CHCl_3$); ^{1}H NMR: δ = 1.00 (d, *J* = 6.6 Hz, 6H, 6-Me), 1.14 (d, *J* = 7.2 Hz, 6H, 9-Me), 1.24–1.30 (m, 16H), 1.33 (s, 6H, 3-Me), 1.40–1.78 (m, 16H), 1.94–2.05 (m, 4H), 2.34–2.45 (m, 2H), 2.70–2.94 (m, 4H, H-1′, H-10′), 3.48–3.57 (m, 2H, H-9), 6.10 ppm (s, 2H, H-12); ^{13}C NMR: δ = 12.90, 20.05, 22.98, 25.15, 25.55, 25.91, 29.57, 29.80, 29.85, 33.96, 35.52, 36.72, 37.49, 41.17, 46.32, 51.77, 77.32, 80.38, 105.07, 174.10, 180.63 ppm; IR (film): $\tilde{\nu}_{max}$ = 650, 666, 697, 723, 738, 764, 796, 837, 862, 889, 905, 931, 948, 963, 975, 1031, 1071, 1168, 1203, 1236, 1328, 1377, 1403, 1455, 1463, 1645, 1682, 1694, 1714, 1729, 1738, 2732, 2855, 2921 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 757 (55), 282 (3), 267 (11), 237 (49), 209 (100); exact mass: calcd for $C_{42}H_{65}N_2O_{10}^-$ = 757.4634, found 757.4549.

4′-Nitrobenzenecarbonyl ***41***: Compound **41** was obtained from **5** (500 mg, 1.78 mmol), LDA and 4-nitrobenzoyl chloride (495 mg, 2.67 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a gum (459 mg, 60%); $[\alpha]_D^{22} = +100.6$ (*c* = 1.44, $CHCl_3$); ^{1}H NMR: δ = 1.04 (d, *J* = 5.7 Hz, 3H, 6-Me), 1.07 (d, *J* = 7.2 Hz, 3H, 9-Me), 1.25 (s, 3H, 3-Me), 1.41–1.71 (m, 6H), 1.78–1.85 (m, 2H), 2.01–2.05 (m, 2H), 2.43–2.28 (m, 1H), 3.60–3.68 (m, 1H, H-9), 6.20 (s, 1H, H-12), 7.97 (d, *J* = 8.1 Hz, 2H, ArH-2′, ArH-6′), 8.27 ppm (d, *J* = 8.1 Hz, 2H, ArH-3′, ArH-5′); ^{13}C NMR: δ = 12.14, 20.12, 23.32, 25.27, 25.84, 34.02, 35.23, 36.60, 37.72, 46.56, 51.60, 78.54, 80.81, 105.56, 124.11, 129.42, 141.62, 150.12, 174.03, 174.42 ppm; IR (film): $\tilde{\nu}_{max}$ = 715, 736, 762, 799, 817, 834, 856, 871, 895, 931, 947, 962, 976, 1003, 1015, 1033, 1071, 1088, 1108, 1114, 1146, 1154, 1174, 1201, 1226, 1265, 1319, 1349, 1379, 1397, 1449, 1527, 1606, 1688, 1715, 2875, 2930, 3079, 3110 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 431 (100), 371 (8), 282 (4), 264 (4), 237 (20), 168 (6); exact mass: calcd for $C_{22}H_{27}N_2O_7^+$ = 431.1818, found 431.1831; anal. calcd for $C_{22}H_{26}N_2O_7$: C 61.39, H 6.09, N 6.50; found: C 61.39, H 6.13, N 6.41.

3'-Nitrobenzenecarbonyl **42**: Compound **42** was obtained from **5** (600 mg, 2.14 mmol), LDA and 3-nitrobenzoyl chloride (594 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a pale-yellow foam that could not be crystallized (438 mg, 48%); $[\alpha]_D^{22} = +74.4$ ($c = 1.28$, $CHCl_3$); ^1H NMR: $\delta = 1.04$ (d, $J = 6$ Hz, 3H, 6-Me), 1.08 (d, $J = 7.2$ Hz, 3H, 9-Me), 1.24 (s, 3H, 3-Me), 1.42–1.67 (m, 4H), 1.80–1.86 (m, 3H), 2.02–2.06 (m, 3H), 2.44–2.53 (m, 1H), 3.62–3.72 (m, 1H, H-9), 6.21 (s, 1H, H-12), 7.63 (t, $J = 7.8$ Hz, 1H, Ar-H5'), 8.13 (d, $J = 7.5$ Hz, 1H, ArH-6'), 8.36 (d, $J = 8.1$ Hz, 1H, ArH-4'), 8.66 ppm (s, 1H, ArH-2'); ^{13}C NMR: $\delta = 12.16$, 20.12, 23.32, 25.28, 25.79, 34.04, 35.17, 36.63, 37.72, 46.57, 51.59, 78.61, 80.75, 105.58, 123.62, 127.16, 129.97, 134.21, 137.98, 148.62, 173.85, 174.39 ppm; IR (film): $\tilde{\nu}_{max} = 716$, 758, 803, 829, 870, 886, 917, 948, 964, 1032, 1071, 1088, 1135, 1146, 1157, 1201, 1225, 1258, 1291, 1351, 1379, 1400, 1438, 1477, 1534, 1616, 1686, 1718, 2875, 2930, 3087 cm^{-1}; exact mass: calcd for $C_{22}H_{27}N_2O_7^+ = 431.1818$, found 431.1826; anal. calcd for $C_{22}H_{26}N_2O_7$: C 61.39, H 6.09, N 6.50; found: C 61.49, H 6.30, N 6.25.

3',5'-Dinitrobenzenecarbonyl **43**: Compound **43** was obtained from **5** (600 mg, 2.14 mmol), LDA and 3,5-dinitrobenzoyl chloride (738 mg, 3.20 mmol, 1.5 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a pale-yellow solid (530 mg, 52%); mp: 203–204 °C (dec); $[\alpha]_D^{22} = +72.9$ ($c = 1.07$, $CHCl_3$); ^1H NMR: $\delta = 1.04$–1.09 (overlapping d, $J = 6.9$ Hz, 7.2 Hz, 6H, 6-Me, 9-Me), 1.27 (s, 3H, 3-Me), 1.45–1.68 (m, 4H), 1.80–1.90 (m, 3H), 2.04–2.09 (m, 3H), 2.46–2.55 (m, 1H), 3.66–3.74 (m, 1H, H-9), 6.23 (s, 1H, H-12), 8.85–8.86 (m, 2H, ArH-2', ArH-6'), 9.13–9.14 ppm (m, 1H, ArH-4'); ^{13}C NMR: $\delta = 12.10$, 20.08, 23.34, 25.26, 25.89, 33.99, 35.30, 36.54, 37.74, 46.46, 51.50, 78.74, 80.65, 105.79, 121.72, 127.95, 140.05, 148.94, 171.84, 174.89 ppm; IR (film): $\tilde{\nu}_{max} = 705$, 719, 729, 756, 829, 861, 886, 921, 948, 1033, 1071, 1135, 1146, 1172, 1201, 1224, 1267, 1345, 1380, 1459, 1546, 1628, 1683, 1719, 2878, 2932, 3106 cm^{-1}; exact mass: calcd for $C_{22}H_{26}N_3O_9^+ = 476.1669$, found 476.1710; anal. calcd for $C_{22}H_{25}N_3O_9$: C 55.58, H 5.30, N 8.83; found: C 55.12, H 5.28, N 9.02.

Isocyanate adducts:

N-Phenyl **44**: Compound **44** was obtained from **5** (600 mg, 2.14 mmol), LDA and phenyl isocyanate (464 μL, 509 mg, 4.27 mmol, 2.0 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a pale-yellow gum (14 mg, 2%); $[\alpha]_D^{22} = -135.9$ ($c = 1.38$, $CHCl_3$); ^1H NMR: $\delta = 1.03$ (d, $J = 6.3$ Hz, 3H, 6-Me), 1.25 (d, $J = 7.5$ Hz, 3H, 9-Me), 1.40 (s, 3H, 3 Me), 1.41–1.82 (m, 7H), 2.00–2.10 (m, 2H), 2.23–2.30 (m, 1H), 2.37–2.49 (m, 1H), 3.52–3.56 (m, 1H, H-9), 6.32 (s, 1H, H-12), 7.27–7.60 (m, 5H, ArH), 10.82 ppm (s, 1H, N-H); ^{13}C NMR: $\delta = 13.62$, 30.02, 22.82, 25.17, 25.09, 33.94, 35.75, 36.74, 37.49, 45.07, 51.79, 80.23, 105.41, 120.30, 124.35, 129.13, 137.79, 151.27, 176.15; MS (CI, CH_4): m/z (%) = 401 (82), 282 (70), 237 (32), 120 (100); exact mass: calcd for $C_{22}H_{29}N_2O_5^+ = 401.2071$, found 401.2190.

4-Nitrophenyl **45**: Compound **45** was obtained from **5** (600 mg, 2.14 mmol), LDA and 4-nitrophenyl isocyanate (701 mg, 4.27 mmol, 2.0 equiv), and chromatography (ethyl acetate/hexanes 35:65) as a pale-yellow foamy solid (248 mg, 26%); $[\alpha]_D^{22} = -201.7$ ($c = 2.44$, $CHCl_3$); ^1H NMR: $\delta = 1.04$ (d, $J = 6$ Hz, 3H, 6-Me), 1.25 (d, $J = 7.2$ Hz, 3H, 9-Me), 1.39 (s, 3H, 3-Me), 1.56–1.82 (m, 8H), 2.02–2.10 (m, 2H), 2.38–2.48 (m, 1H), 3.52–3.61 (m, 1H, H-9), 6.29 (s, 1H, H-12), 7.75 (d, $J = 9$ Hz, 2H, ArH-2', ArH-6'), 8.21 (d, $J = 9$ Hz, 2H, ArH-3', ArH-5'), 11.43 ppm (s, 1H, N-H); ^{13}C NMR: $\delta = 13.58$, 19.98, 22.85, 25.15, 25.88, 33.87, 35.88, 36.68, 37.53, 44.96, 51.71, 77.14, 80.11, 105.58, 119.85, 125.20, 143.74, 151.24, 176.89 ppm; IR (film): $\tilde{\nu}_{max} = 523$, 543, 603, 667, 702, 751, 822, 836, 855, 893, 947, 982, 1031, 1071, 1112, 1134, 1147, 1174, 1212, 1242, 1265, 1305, 1342, 1378, 1415, 1451, 1512, 1553, 1598, 1610, 1665, 1723, 2875, 2929, 3294 cm^{-1}; MS (CI, CH_4): m/z (%) = 446 (6), 282 (34), 237 (54), 209 (24), 165 (100), 154 (38); exact mass: calcd for $C_{22}H_{28}N_3O_7^+ = 446.1922$, found 446.1936; anal. calcd for $C_{22}H_{27}N_3O_7$: C 59.32, H 6.11, N 9.43; found: C 59.70, H 6.29, N 8.96.

In vitro parasite growth inhibition assays

Parasite clones, isolates, and strains were acquired from MR4 (Malaria Research and Reference Reagent Resource Center, Manassas, VA, USA). Strains/isolates used in this study were the drug-sensitive 3D7 clone of the NF54 isolate (The Netherlands) and the chloroquine-, pyrimethamine-, and cycloguanil-resistant K1 strain (Thailand). *P. falciparum* in vitro culture was carried out following the standard method with modifications.[27] Briefly, parasites were maintained in tissue-culture flasks in human A5 Rh+ erythrocytes at 5% hematocrit in RPMI-1640 supplemented with HEPES (25 mM), $NaHCO_3$ (24 mM), glucose (0.2% *w/v*), L-glutamine (0.03%), hypoxanthine (150μM), and Albumax II® (0.5%, Gibco, UK) in a 5% CO_2/95% air mixture at 37 °C; the medium was changed daily. Stock solutions of the azaartemisinins and comparator drug artesunate and artemisone were freshly prepared in 100% DMSO in glass bottles, and serial dilutions of the drugs were carried out in the assay medium RPMI-1640 supplemented with Albumax II (0.5%), glucose (0.2% *w/v*), L-glutamine (0.03%), and hypoxanthine (15μM) in 96-well plates. This was followed by the addition of 50 μL asynchronous (65–75% ring-stage) *P. falciparum* culture (0.5% parasitemia) or uninfected erythrocytes at 5% hematocrit to each well in the assay medium. Thus the final hematocrit and parasitemia were 2.5 and 0.5%, respectively. Plates were incubated at 37 °C in 5% CO_2 for 24 h, followed by the addition of 10 μL (3.7 Bq) of [^{3}H]hypoxanthine to each well. Plates were mixed for 1 min using a plate shaker and returned to the incubator. After an additional 24 h incubation, the experiment was terminated by placing the plates in a freezer at −80 °C. Plates were thawed and harvested onto glass fiber filter mats using a cell harvester (Tomtec, USA) and dried. After the addition of Meltilex (Wallac) solid scintillant, the incorporated radioactivity was measured using a Wallac BetaLux scintillation counter. Data acquired were exported into Microsoft Excel, and the IC_{50} value of each drug was calculated using Excel Fit.

Cell viability assays

Test compounds were dissolved in DMSO at final concentrations of 100 mM and stored at −20 °C. Cytotoxicity was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as described.[34] Hep G2 cells (4000 cells per well) were seeded on 96-well plates. After pre-incubation overnight, cells were treated with 1 or 10 μM of test compounds for 6 days. At the end of the experiment, 10 μL of MTT reagent was added to each well and incubated at 37 °C for 4 h followed by the addition of 100 μL solubilization buffer (10% SDS in 0.01 M HCl) and overnight incubation. A_{585} values were determined from each well the next day. The percentage of viable cells was calculated using the following formula: percent cell viability = $A_{treated}/A_{control} \times 100$.

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