Design, Synthesis and Antitumor Activity of Novel Artemisinin Derivatives Using Hybrid Approach

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In an attempt to develop potent and selective anti-tumor agents, two novel series of artemisinin-chalcone hybrids were designed, synthesized and screened for their antitumor activities against HT-29, A549, MDA-MB-231, HeLa and H460 cell lines *in vitro*. Nearly all of the tested compounds showed significantly increased anti-tumor activity compared with the corresponding dihydroartemisinin (DHA). Most of the title compounds displayed good selectivity toward HT-29 and HeLa cell lines with IC_{50} values ranging from 0.09 to 0.85 μM. Among them, the most promising compound 9c (IC_{50} range of 0.09—0.93 μM) was 10.5- to 70-times more active than DHA (IC_{50} range of 5.6—15.6 μM) respectively.

Key words artemisinin; chalcone; hybrid approach; anti-tumor activity; X-ray crystallography

Despite cancer chemotherapy has entered a new era of molecularly targeted therapeutics and some forms of cancer have been successfully treated by modern therapies, the successful treatment of cancer remains a significant challenge in the future because chemotherapy is limited by the drug resistance and adverse side effects.[1)] In order to develop more effective and reliable anticancer agents that circumvent these limitations, the search for novel anti-tumor agents has turned to natural products, in particular plants used in traditional folk medicines.[2)]

In recent years, artemisinin and its derivatives have been widely studied for their anticancer activities. Some of them showed excellent anti-tumor activity toward different cancer cell lines *in vitro*.[3—9)] Also, several studies demonstrated that artemisinin analogues were effective to many drug- and radiation-resistant cancer cell lines due to their multiple mechanisms.[10,11)] The main mode likely involves a similar metal-induced free-radical formation leading to induce apoptosis in cancer cells and inhibit the tumor angiogenesis.[12—16)]

Recently, considerable attention has been focused on chalcones, which are a class of privileged structures that are easily prepared and have a wide range of biological properties,[17—21)] which makes them an attractive pharmacophoric scaffold. An area of particular interest is their potential as antitumor agents, for which several modes of action have been proposed. The key mechanism is the inhibition of tubulin polymerization, while also including the inhibition of angiogenesis and the induction of apoptosis.[22—24)] Chalcones and artemisinin analogues represent two classes of natural products, whose antitumor effects appear to be consistent *via* different molecular mechanisms. As the application of hybrid strategy to synthesize artemisinin analogues are continuously emerging,[9,25)] it is reasonable to combine their structure analogues to form a single molecular framework with a linker, which would allow us to find more potent anti-tumor agents, in which these 'merge' pharmacophore may be addressing the active site of different targets and offering the possibility to overcome drug resistance. Intrigued by these observations, we designed and synthesized two new series of novel artemisinin derivatives by replacement of oxygen at C-10 with nitrogen, in which the substituted chalcone group is bonded to the artemisinin nucleus through an oxyacetyl linkage.

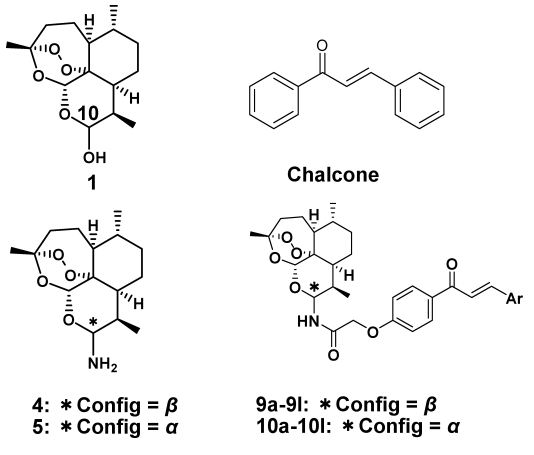

Fig. 1. The Structures of DHA, Chalcone and the Target Compounds

Chemistry The synthetic routes of compounds are outlined in Chart 1. Separable diastereomeric mixture of 10β-azidodihydroartemisinin (**2**) and 10α-azidodihydroartemisinin (**3**) were obtained by treating **1** with trimethylsilyl chloride, sodium azide and sodium iodide at room temperature for 28 h, according to ref 6. The α and β isomers appeared as two distinct spots on TLC and were separated by column chromatography, with β-isomers as the major products. The reduction of azido compounds (**2, 3**) with Staudinger reaction afforded the corresponding 10β-aminodihydroartemisinin (**4**) and 10α-aminodihydroartemisinin (**5**) respectively, which subsequently reacted with chloroacetyl chloride to afford two important intermediates 10β-*N*-chloroacetyl-aminodihydroartemisinin (**7**) and 10α-*N*-chloroacetyl-amino-dihydroartemisinin (**8**) as white solid.

On the side chain, the preparation of the chalcone analogues was carried out *via* Claisen–Schmidt condensation. This method for the preparation of chalcones is attractive since it predominantly generates the (*E*)-isomer from simple building blocks.[26)] Coupling constants (J_{trans}=15—16 Hz) from the proton nuclear magnetic resonance (^{1}H-NMR) spectra of the title compounds clearly indicated that derivatives

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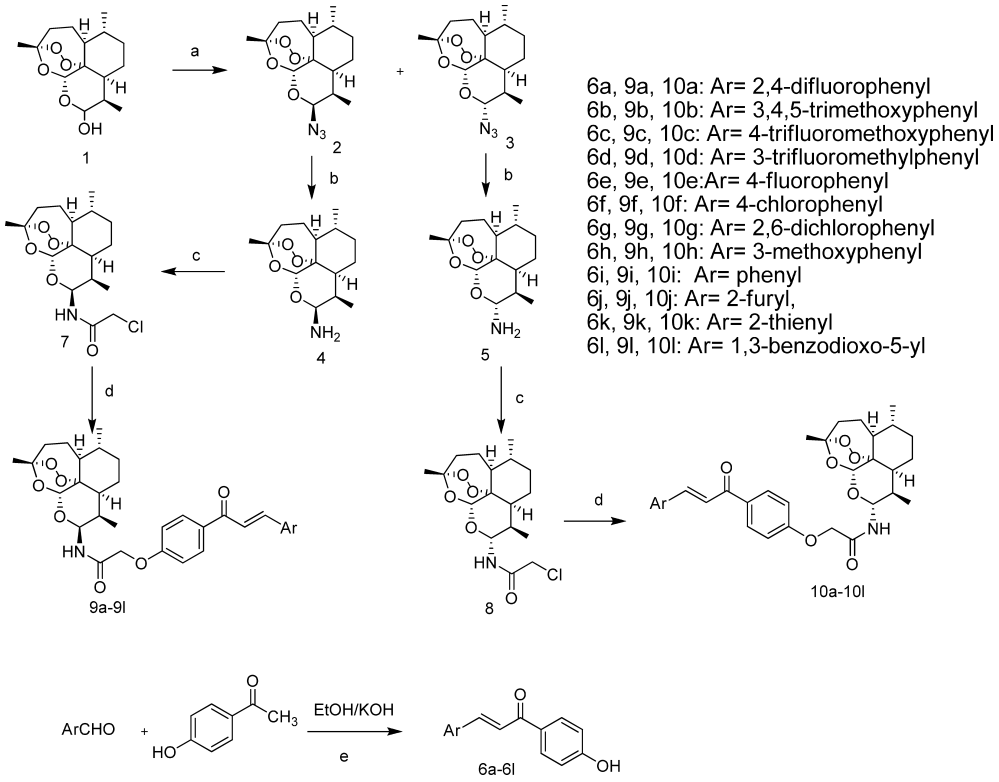

Reagents and conditions: (a) Me_3SiCl, NaN_3, NaI, dichloromethane, r.t., 28 h; (b) PPh_3, H_2O, THF, 60 °C, 6 h; (c) 2-chloroacetyl chloride, Et_3N, 0—10 °C, 3 h; (d) compound **6**, K_2CO_3, NaI, DMF, 60 °C, 5 h; (e) KOH, ethanol, r.t., 24 h.

Chart 1

6a—**l** were both geometrically pure and were exclusively *trans* (*E*) isomers. Thus, appropriate aryl aldehydes were reacted with inexpensive *p*-hydroxyacetophenone in ethanol/KOH at 0—5 °C. Upon completion, the cooled reaction mixture was poured into ice water and treated with HCl (10%) yielded the desired chalcone analogues **(6a**—**l)**.

Finally, the target compounds **9a**—**l** and **10a**—**l** were successfully obtained *via* the reaction of intermediate **7** and **8** with **6a**—**m** in the presence of K_2CO_3 and sodium iodide in *N*,*N*-dimethylformamide (DMF) at 60 °C, respectively. The products obtained were purified by column chromatography on silica gel.

The formation of 10β-azidoartemisinin (**2**) and 10α-azidoartemisinin (**3**) were confirmed by ^{1}H-NMR spectrum and LC-MS data. In our previous report, the stereochemistry of compound **2** had ready been determined by single crystal X-ray diffraction studies.[27] The structure of compound **3** was elucidated by ^{1}H-NMR spectrum and LC-MS analyses. Specifically, the configuration at the C-10 position of compound **3** was assigned based on the vicinal couplings (J=10.1 Hz) between protons at positions 10 and 9, indicating that the relative configuration at the positions 10 and 9 is *trans*.

In addition, the molecular structure of the compound **5** was established by single crystal X-ray diffraction studies. The ORTEP view of the molecular structure shows the spatial atomic positions of compound **5**, as shown in Fig. 2. The stereochemistry of compound **3** was further determined indirectly by the crystal data of compound **5**, because the configuration at the C-10 was not changed when compound **3** was transformed to compound **5** *via* the Staudinger reduction.

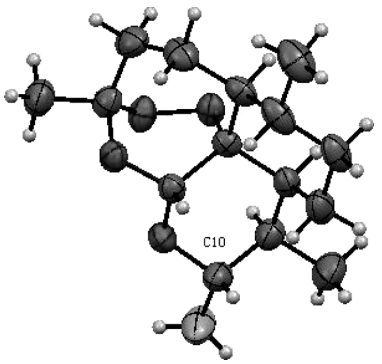

Fig. 2. ORTEP Diagram Showing the X-Ray Crystal Structure of **5**

The formation of two important intermediates (**7**, **8**) were confirmed by ^{1}H-NMR spectral and LC-MS data, The formation of the title compounds, were evidenced by ^{1}H-NMR spectrum, IR, LC-MS and element analysis data, which were explained in experimental part.

Results and Discussion

Biological Evaluation All the compounds **9a**—**l** and **10a**—**l** were evaluated for their anti-tumor activities on human colorectal cancer cell line (HT-29), human non-small-cell lung cancer cell line (A549), human breast cancer cell line (MDA-MB-231), human cervical carcinoma cell line (HeLa) and human lung cancer cell line (H460) by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, using DHA as a control. The results expressed as IC_{50} were summarized in Table 1, and the IC_{50} values are

Table 1. Anti-tumor Activity of the Compounds against HT-29, A549, MDA-MB-231, HeLa and H460 Cell Lines *in Vitro*

Compd. No.	IC_{50} (μM)[a]				
	HT-29[b]	A549[b]	MDA-MB-231[b]	HeLa[b]	H460[b]
9a	0.93	3.2	1.1	1.1	3.3
9b	0.24	3.5	1.3	0.64	0.6
9c	0.36	0.80	0.93	0.09	0.28
9d	0.26	2.0	0.96	0.18	1.2
9e	0.70	4.3	0.87	0.77	4.4
9f	0.50	2.8	0.79	0.4	3.0
9g	0.14	1.2	0.96	0.29	1.3
9h	0.72	2.2	5.4	1.8	1.8
9i	0.65	2.5	1.3	0.46	2.0
9j	2.3	16	2.9	3.8	1.8
9k	1.6	8.3	1.6	1.2	3.0
9l	1.2	23	0.47	0.75	7.2
10a	2.6	3.8	1.3	1.7	2.8
10b	0.70	8.5	1.7	1.1	1.9
10c	0.39	0.68	0.76	0.27	2.4
10d	0.24	0.89	1.0	0.10	1.2
10e	0.76	2.3	1.7	1.2	3.4
10f	0.67	2.4	1.5	0.98	3.1
10g	0.50	1.6	0.72	0.73	1.1
10h	0.67	2.1	1.2	0.74	2.6
10i	0.75	1.8	0.92	0.85	1.7
10j	1.4	13	1.7	2.2	12
10k	2.1	29	23	0.89	4.7
10l	1.7	12	2.6	4.2	19
4	3.6	6.1	2.8	1.5	1.9
5	1.2	4	4.6	3.9	3.3
DHA[c]	5.6	15.6	9.8	6.3	13

a) IC_{50}: concentration of the compound (μM) producing 50% cell growth inhibition after 72 h of drug exposure, as determined by the MTT assay. Each experiment was run at least two times, and the results are presented as average values. *b*) HT-29, human colon cancer cell line; A549, human non-small-cell lung adenocarcinoma cell line; MDA-MB-231, human breast cancer cell line; HeLa, human cervical carcinoma cell line; H460, human lung cancer cell line. *c*) Used as a positive control.

the average of at least two independent experiments.

As shown in Table 1, most of the compounds **9a**—**l** and **10a**—**l** were 2.6- to 40-fold more active than the corresponding dihydroartemisinin (DHA) respectively, suggesting that the presence of a chalcone moiety enhanced their anti-tumor activities significantly toward all five cancer cell lines. In general, most of the prepared compounds showed moderate activity against MDA-MB-231, A549 and H460 cell lines with IC_{50} values ranging from 0.68 to 29 μM, which were several- to tens-fold less potent than against HT-29 and HeLa cell lines respectively. The results demonstrated that the introduction of a chalcone moiety also enhanced their selectivity significantly for HT-29 and HeLa cell lines. The two key intermediates **4** and **5** with amino group at C-10 position caused only a minor improvement in anti-tumor activity against the five cancer cell lines as compared to DHA.

Turning to the effects of **9j** and **9k** containing heteroaromatic chalcone moiety, interestingly, the bioisosteric replacement of phenyl (**9i**) with a thiophene ring (**9k**) and furan (**9j**) ring decreased activity greatly against the five tumor cell lines respectively. It may be concluded that the presence of heteroaromatic ring is detrimental for the activity. The data in Table 1 demonstrated that substitution pattern on the phenyl rings linked to the β-position of the enone system affected their potency significantly. For **9a**—**l**, in most cases, compounds (**9c**, **d**, **g**) bearing electron withdrawing groups (EWG) at the phenyl rings are found to be more active than compounds attached electron releasing groups (**9h**, **l**) with the exception of 3,4,5-trimethoxy derivative **9b**, with IC_{50} values 0.70—1.9 μM. The fluoro substituent (**9a**, **e**) had comparable anti-tumor activity with the unsubstituted analogue **9i**. Specifically with the mono-halogen substituted derivatives (**9e**, **f**), activity increased in the following order: Cl (**9f**)>F (**9e**). Insertion of a second chlorine atom, to yield the 2,6-dichloro derivative **9g**, resulted in about a fourfold increase in activity as compared with **9f**. Ignoring the derivative with a 3-MeO (**9h**) and 3,4-OCH_2O- (**9l**), the greatest enhancement of activity occurred with the bulkier substituents, 3-CF_3 (**9d**) and 4-CF_3O (**9c**).

Regarding the anti-tumor activities of **10a**—**l**, bearing a same molecular structure but only different C-10 stereochemistry, showed few differences in inhibitory effect against five cell lines as compared with **9a**—**l**. Among them, the **10c**, **d** and **g** had the best activities toward the five cell lines, which further proved that it was beneficial for enhancing their anti-tumor activities when compounds with bulkier and EWG group on the phenyl ring. The replacement of phenyl with hetero-aryl group would result in a decrease of anti-tumor activity and hence they aren't ideally suited for further modifications.

Conclusion

In summary, two novel series of hybrid artemisinin derivatives conjugated with chalcone moieties were designed and synthesized based on the hybrid strategy. The structures were confirmed by elemental analyses, spectrometry and single crystal X-ray analysis. Through anti-tumor activity screening against five cell lines (HT-29, A549, MDA-MB-231, HeLa and H460), on the basis of the above-described results, the following conclusions could be drawn: (a) most of the prepared compounds displayed the enhanced and selective anti-tumor activities toward HT-29 and HeLa cell lines as compared with DHA; (b) introduction of bulkier and EWG group on the phenyl ring is associated with increased anti-tumor activity. When the phenyl rings were attached by 4-CF_3O (**9c**) or 3-CF_3 (**9d**), the effect was more obvious; (c) the heteroaryl group at β-position of the enone system may be detrimental for the activity; (d) the configuration of compounds **9a**—**l**, **10a**—**l** at C-10 position has little influence on their anti-tumor activities. Moreover, the two important intermediates **4** and **5** reported firstly also show more potent anti-tumor activities than DHA. Taking them as intermediates, many novel arteminin derivatives will be obtained and evaluated for their biological activities. To assess the potentials of these new compounds as cancer chemotherapeutic agents, further *in vivo* activity and toxicity studies are needed. The results obtained from this study can be used as guidelines for further development.

Experimental

Reagents and General Procedures All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. Mass spectra (MS) were taken in electrospray ionization (ESI) mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, U.S.A.). Proton (1H) nuclear magnetic resonance spectroscopy was performed using Bruker ARX-300, 300 MHz spectrometers (Bruker Bioscience, Billerica, MA, U.S.A.) with tetramethylsilane (TMS) as an internal standard. IR spectra (KBr disks) were recorded with a Bruker IFS 55 instrument (Bruker). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). Unless otherwise

noted, all the materials were obtained from commercially available sources and were used without further purification.

Preparation of 10β-Azidodihydroartemisinin (2), 10α-Azidodihydroartemisinin (3) Trimethylchlorosilane (300 mmol, 38.1 ml) was added gradually to the mixture solution of dihydroartemisinin (200 mmol, 56.8 g) and sodium azide (300 mmol, 19.5 g) in dry dichloromethane (300 ml), then sodium iodide (5 mmol, 3.0 g) was added to the reaction mixture at 0—5 °C. The reaction mixture was stirred at room temperature for 28 h. The mixture was quenched with a saturated $NaHCO_3$ solution (100 ml) and diluted with dichloromethane. Two phases were separated and the organic phase was washed with brine, the organic phase was then collected and dried overnight over anhydrous Na_2SO_4. After filtering, the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography (silica, 1—5% EtOAc/hexanes) to furnish the compound **2** (29.0 g, 47%) and compound **3** as white solid (3.0 g, 5%). Compound **2**: mp: 41—43 °C; MS (ESI) *m/z*: 332.2 $(M+Na)^+$; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 5.76 (s, 1H), 5.54 (d, J=3.6 Hz, 1H), 2.46 (m, 1H), 2.26—2.12 (m, 1H), 2.07—1.96 (m, 1H), 1.87—1.78 (m, 1H), 1.77—1.65 (m, 1H), 1.58 (m,2H), 1.48—1.33 (m, 3H), 1.31 (s, 3H), 1.16 (m, 1H), 0.89 (d, J=6.3 Hz, 3H), 0.84 (d, J=7.3 Hz, 3H). Compound **3**: mp: 101—103 °C; MS (ESI) *m/z*: 332.2 $(M+Na)^+$; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 5.53 (s, 1H), 4.86 (d, J=10.1 Hz, 1H), 2.29—2.06 (m, 2H), 2.05—1.94 (m, 1H), 1.87—1.76 (m, 1H), 1.65—1.33 (m, 5H), 1.30 (s, 3H), 1.24—1.10 (m, 1H), 0.89 (d, J=6.2 Hz, 3H), 0.81 (d, J=7.1 Hz, 3H).

Preparation of 10β-Aminodihydroartemisinin (4) A 100 ml round-bottomed flask was charged with compound **2** (16.0 g, 52 mmol) and tetrahydrofuran (THF) (130 ml). To this solution, triphenyl phosphine (20.4 g, 78 mmol) was added slowly, and the reaction mixture was stirred for 2 h at 60 °C. At this time, TLC analysis confirmed that no starting material (compound **2**) remained. Distilled water (160 mmol, 3.0 ml) was added, and the resulting suspension was stirred for 6 h. The mixture was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica, dichloromethane/methanol, 200 : 1) to afford the desired compound **4** (9.1 g, 62%) as yellow oil. MS (ESI) *m/z*: 284.1 $(M+H)^+$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.34 (s, 1H), 4.21 (d, J=9.7 Hz, 1H), 2.44—2.31 (m, 1H), 2.30—2.17 (m, 1H), 2.08—1.94 (m, 4H), 1.94—1.83 (m, 2H), 1.81—1.61 (m, 3H), 1.60—1.46 (m, 2H), 1.44 (s, 3H), 0.97 (d, J=6.2 Hz, 3H), 0.94 (d, J=7.2 Hz, 3H).

Preparation of 10α-Aminodihydroartemisinin (5) This compound was prepared according to compound **4** from compound **3** (5.0 g, 16.2 mmol), triphenyl phosphine (6.4 g, 24.5 mmol) and distilled water (52.0 mmol, 1 ml). Purification of the resulting oil afforded **5** as colorless crystal (3.2 g, 70%); mp: 46 °C; MS (ESI) *m/z*: 284.1 $(M+H)^+$; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 5.31 (s, 1H), 4.08 (d, J=9.6 Hz, 1H), 2.23 (s, 2H, NH_2, D_2O-exchangable), 2.21—2.10 (m, 1H), 2.08—1.89 (m, 2H), 1.86—1.72 (m, 1H), 1.65—1.52 (m, 2H), 1.45—1.29 (m, 4H), 1.26 (s, 3H), 0.89 (d, J=6.3 Hz, 3H), 0.79 (d, J=7.2 Hz, 3H).

The X-ray crystallographic analysis of **5** was determined on a colorless plate crystal, with approximate dimensions of 0.40 mm×0.45 mm×0.48 mm, grown from the slow evaporation of a dilute ethanol solution at room temperature. The crystal structure solution was solved by full matrix least-squares method using SHELXL97. All the atoms were located in different Fourier maps and refined isotropically, using a riding model and all the projections were generated using ORTEP. The details of the crystal data and refinement are shown in Table 2. Crystallographic data (cif file) for **5** have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 796528. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax: +44 1233 336033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

Preparation of (10*R*)-*N*-Chloroacetyl-aminodihydroartemisinin (7) Triethylamine (3.2 g, 31.8 mmol) was added to a solution of compound **4** (6.0 g, 21.2 mmol) in dichloromethane (80 ml) and then 2-chloroacetyl chloride (3.1 g, 27.6 mmol) was added drop-wise to the reaction mixture at 0—10 °C. The reaction mixture was stirred at room temperature for 1—3 h. After completion of reaction as indicated by TLC, the mixture was quenched with H_2O (5 ml) and diluted with dichloromethane (50 ml). The organic layer was washed with brine (200 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resultant solid products were collected by filtration and recrystallized from methanol to give compound **7** (5.9 g, 78%). mp: 171—173 °C; MS (ESI) *m/z*: 382.1 $(M+Na)^+$; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.96 (d, J=9.1 Hz, 1H), 5.47 (s, 1H), 5.08 (t, J=9.8 Hz, 1H), 4.09 (s, 2H), 2.40—2.25 (m, 1H), 2.18 (td, J=14.0, 3.7 Hz, 1H), 2.04—1.93 (m, 1H), 1.87—1.75 (m, 1H), 1.66—1.30 (m, 7H), 1.27 (s, 3H), 1.17 (m, 1H), 0.89 (d, J=6.3 Hz, 3H), 0.72 (d, J=7.1 Hz, 3H).

Table 2. Crystal Data and Measurement Detail for Compound **5**

Crystal data	
Empirical formula	$C_{15}H_{25}NO_4$
Formula weight	283.36
Crystal system	Orthorhombic
Crystal dimension	0.40 mm×0.45 mm×0.48 mm
Space group	$P2_12_12_1$ (No. 19)
a (Å)	9.2901(8)
b (Å)	9.3435(9)
c (Å)	17.2037(16)
Volume (Å^3)	1493.3(2)
Angle α, β, γ	90.00, 90.00, 90.00
Z	4
Crystal density, g/cm^3	1.260
F(000)	616
μ(Mo$K\alpha$) [/mm]	0.090
Absorption coefficient	0.090
Cut-off used in *R*-factor calculations	$F_o^2>2\sigma(F_o^2)$
$R(F_o)$	0.0358
$Rw(F_o^2)$	0.0902
Temperature (T)	298
Radiation wavelength	0.71073
Radiation type	Fine-focus sealed tube
Radiation source	Mo$K\alpha$
Radiation monochromator	Graphite
Dataset	−9: 11; −8: 11; −20: 20
Reflns (F_o)	1323
Structure refinement	SHELXL97

Preparation of (10*S*)-*N*-Chloroacetyl-aminodihydroartemisinin (8) The product was prepared from **4** (3.0 g, 10.6 mmol) in a similar manner as described for the preparation of compound **7**. The resultant solid products were collected by filtration and recrystallized from methanol to give compound **8** (3.1 g, 81%). mp: 175—177 °C; MS (ESI) *m/z*: 382.2 $(M+Na)^+$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.45 (s, 1H), 5.36 (t, J=10.1 Hz, 1H), 4.09 (s, 2H), 2.55—2.41 (m, 1H), 2.41—2.32 (m, 1H), 2.11—2.00 (m, 1H), 1.98—1.86 (m, 1H), 1.85—1.70 (m, 2H), 1.71—1.46 (m, 4H), 1.45 (s, 3H), 1.39—1.24 (m, 2H), 0.99 (d, J=6.0 Hz, 3H), 0.88 (d, J=7.2 Hz, 3H).

General Procedure for Preparation of Compounds (6a—l) A stirred solution of *p*-hydroxyacetophenone (8.1 g, 0.06 mol) in ethanol (200 ml) was added to 60% KOH (6.7 g, 0.12 mol) solution at 0 °C, the mixture was stirred at 0 °C temperature for 1 h. The substituted aryl aldehyde (0.06 mol) was added to the mixture, and the resulting mixture was stirred at room temperature for 24 h. The aqueous mixture was neutralized by the addition of aqueous 10% HCl solution. The light yellow solid thus obtained was filtered, washed with water and dried. The residue was recrystallized from ethanol to afford pure compounds (**6a**—**l**).

General Procedure for Preparation of Compounds (9a—l), Compounds (10a—l) K_2CO_3 (0.12 g, 0.84 mmol) and NaI (0.03 g) were added to a stirred solution of compound **7** or compound **8** (0.2 g, 0.57 mmol) and substituted chalcone (0.57 mmol) in DMF (6.0 ml). The reaction mixture was heated to 60 °C for 3—5 h. The mixture was poured into ice water, stirred for 1h and separated by filtration to give crude compounds, which purified by chromatography on silica gel using (1—5% petroleum ether/ethyl acetate) to obtain **9a**—**l**, **10a**—**l**.

(10*R*)-*N*-{4-[3-(2,4-Difluorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**9a**): This compound was obtained as brown solid in 81% yield. mp: 102—104 °C; MS (ESI) *m/z*: 606.3 $(M+Na)^+$; IR (KBr) cm^{-1}: 3421.9, 2926.6, 2873.8, 1690.1, 1664.2, 1606.0, 1503.1, 1274.8, 1216.9, 1173.0, 1038.2, 846.0, 750.9, 612.2. 489.8; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.9 Hz, 2H), 7.86 (d, J=15.9 Hz, 1H), 7.66 (dd, J=14.9, 8.5 Hz, 1H), 7.60 (d, J=15.9 Hz, 1H), 7.07 (d, J=9.0 Hz, 2H), 7.01—6.86 (m, 2H), 5.52—5.40 (m, 2H), 4.62 (s, 2H), 2.51—2.32 (m, 2H), 2.12—2.00 (m, 1H), 1.99—1.86 (m, 1H), 1.84—1.71 (m, 2H), 1.45 (s, 3H), 0.99 (d, J=6.0 Hz, 3H), 0.82 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{32}H_{35}F_2NO_7$ (in %): C, 65.85; H, 6.04; N, 2.40; Found C, 65.76; H, 6.16 and N, 2.29.

(10*R*)-*N*-{4-[3-(3,4,5-Trimethoxyphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9b**): This compound was obtained as yel-

low solid in 76% yield. mp: 115—117 °C; MS (ESI) *m/z*: 660.5 $(M+Na)^+$; IR (KBr) cm^{-1}: 3422.8, 2937.9, 2874.2, 1691.8, 1659.7, 1603.3, 1579.5, 1504.9, 1281.6, 1127.5, 1038.5, 824.8, 749.4, 596.3; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.94 (d, J=9.3 Hz, 1H), 8.18 (d, J=8.7 Hz, 2H), 7.90 (d, J=15.2 Hz, 1H), 7.67 (d, J=15.3 Hz, 1H), 7.23 (s, 2H), 7.11 (d, J=8.8 Hz, 2H), 5.47 (s, 1H), 5.17 (t, J=9.7 Hz, 1H), 4.72 (s, 2H), 3.87 (s, 6H), 3.71 (s, 3H), 2.46—2.33 (m, 1H), 2.26—2.11 (m, 1H), 2.05—1.93 (m, 1H), 1.89—1.73 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=6.1 Hz, 3H), 0.71 (d, J=7.0 Hz, 3H); *Anal.* Calcd for $C_{35}H_{43}NO_{10}$ (in %): C, 65.92; H, 6.80; N, 2.20; Found C, 65.84; H, 6.86 and N, 2.19.

(10*R*)-*N*-{4-[3-(4-Trifluoromethoxyphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9c**): This compound was obtained as pale yellow solid in 84% yield. mp: 103—105 °C; MS (ESI) *m/z*: 654.4 $(M+Na)^+$; IR (KBr) cm^{-1}: 3243.4, 2928.0, 2874.8, 1684.5, 1663.8, 1605.3, 1507.4, 1257.8, 1217.0, 1170.2, 1038.3, 878.3, 828.4, 595.7; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.94 (d, J=9.1 Hz, 1H), 8.18 (d, J=8.9 Hz, 2H), 8.04 (d, J=8.8 Hz, 2H), 7.99 (d, J=15.7 Hz, 1H), 7.73 (d, J=15.6 Hz, 1H), 7.45 (d, J=8.6 Hz, 2H), 7.11 (d, J=8.9 Hz, 2H), 5.47 (s, 1H), 5.17 (t, J=9.8 Hz, 1H), 4.72 (s, 2H), 2.46—2.34 (m, 1H), 2.19 (td, J=14.2, 3.6 Hz, 1H), 2.06—1.93 (m, 1H), 1.89—1.73 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=6.2 Hz, 3H), 0.71 (d, J=7.1 Hz, 3H); *Anal.* Calcd for $C_{33}H_{36}F_3NO_8$ (in %): C, 62.75; H, 5.74; N, 2.22; Found C, 62.72; H, 5.78 and N, 2.20.

(10*R*)-*N*-{4-[3-(3-Trifluoromethylphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9d**): This compound was obtained as pale yellow solid in 82% yield. mp: 113—115 °C; MS (ESI) *m/z*: 638.7 $(M+Na)^+$; IR (KBr) cm^{-1}: 3243.8, 2927.5, 2874.3, 2826.3, 1664.4, 1603.5, 1336.1, 1217.3, 1169.7, 1127.3, 1038.3, 878.4, 801.7, 571.3; 1H-NMR (300 MHz, DMSO-d_6) δ: 8.94 (d, J=9.1 Hz, 1H), 8.34 (s, 1H), 8.22 (d, J=8.8 Hz, 2H), 8.13 (d, J=16.1 Hz, 1H), 7.84—7.74 (m, 3H), 7.69 (t, J=7.7 Hz, 1H), 7.12 (d, J=8.8 Hz, 2H), 5.47 (s, 1H), 5.17 (t, J=9.8 Hz, 1H), 4.72 (s, 2H), 2.44—2.34 (m, 1H), 2.19 (td, J=14.9, 4.9 Hz, 1H), 2.05—1.94 (m, 1H), 1.86—1.76 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=6.0 Hz, 3H), 0.71 (d, J=7.0 Hz, 3H); *Anal.* Calcd for $C_{33}H_{36}F_3NO_7$ (in %): C, 64.38; H, 5.89; N, 2.28; Found C, 64.35; H, 6.01 and N, 2.29.

(10*R*)-*N*-{4-[3-(4-Fluorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9e**): This compound was obtained as pale yellow solid in 86% yield. mp: 106—108 °C; MS (ESI) *m/z*: 588.6$(M+Na)^+$; IR (KBr) cm^{-1}: 3241.4, 2926.4, 2873.3, 1685.4, 1662.4, 1599.3, 1535.3, 1507.7, 1218.9, 1172.9, 1038.3, 845.0, 826.3, 514.4; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.94 (d, J=9.2 Hz, 1H), 8.18 (d, J=8.8 Hz, 2H), 7.96 (d, J=15.6 Hz, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.48 (s, 1H),7.46—7.33 (m, 2H), 7.11 (d, J=8.8 Hz, 2H), 7.08—6.97 (m, 1H), 5.47 (s, 1H), 5.17 (t, J=9.8 Hz, 1H), 4.72 (s, 2H), 3.83 (s, 1H), 2.47—2.38 (m, 1H), 2.19 (td, J=13.7, 3.0 Hz, 1H), 2.05—1.93 (m, 1H), 1.87—1.74 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=6.2 Hz, 3H), 0.71 (d, J=7.0 Hz, 3H); *Anal.* Calcd for $C_{32}H_{36}FNO_7$ (in %): C, 67.95; H, 6.42; N, 2.48; Found C, 67.96; H, 6.49 and N, 2.42.

(10*R*)-*N*-{4-[3-(4-Chlorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9f**): This compound was obtained as pale yellow solid in 82% yield. mp: 108—110 °C; MS (ESI) *m/z*: 604.2 $(M+Na)^+$; IR (KBr) cm^{-1}: 3241.7, 2935.9, 2874.8, 1691.8, 1662.6, 1602.5, 1274.2, 1218.8, 1173.5, 1068.1, 1038.3, 841.0, 757.6, 515.9; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.93 (d, J=8.8 Hz, 1H), 8.18 (d, J=8.6 Hz, 2H), 8.06—7.87 (m, 3H), 7.70 (d, J=15.7 Hz, 1H), 7.53 (d, J=8.2 Hz, 2H), 7.11 (d, J=8.7 Hz, 2H), 5.47 (s, 1H), 5.17 (t, J=9.7 Hz, 1H), 4.72 (s, 2H), 2.46—2.34 (m, 1H), 2.29—2.11 (m, 1H), 2.06—1.93 (m, 1H), 1.86—1.75 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=5.9 Hz, 3H), 0.71 (d, J=7.0 Hz, 3H); *Anal.* Calcd for $C_{32}H_{36}ClNO_7$ (in %): C, 66.03; H, 6.23; N, 2.41; Found C, 66.00; H, 6.36 and N, 2.37.

(10*R*)-*N*-{4-[3-(2,6-Dichlorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**9g**): This compound was obtained as yellow solid in 83% yield. mp: 103—105 °C; MS (ESI) *m/z*: 638.2 $(M+Na)^+$; IR (KBr) cm^{-1}: 3420.6, 2925.9, 2872.8, 1665.8, 1599.5, 1532.5, 1508.4, 1428.4, 1256.8, 1220.4, 1171.9, 1038.5, 776.4, 596.3; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.9 Hz, 2H), 7.87 (d, J=16.1 Hz, 1H), 7.68 (d, J=16.1 Hz, 1H), 7.41 (d, J=8.0 Hz, 2H), 7.27—7.19 (m, 1H), 7.07 (d, J=8.9 Hz, 2H), 5.51—5.40 (m, 2H), 4.61 (s, 2H), 2.53—2.32 (m, 2H), 2.11—2.00 (m, 1H), 1.97—1.87 (m, 1H), 1.83—1.72 (m, 2H), 1.44 (s, 3H), 0.99 (d, J=6.0 Hz, 3H), 0.81 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{32}H_{35}Cl_2NO_7$ (in %): C, 62.34; H, 5.72; N, 2.27; Found C, 62.33; H, 5.79 and N, 2.21.

(10*R*)-*N*-{4-[3-(3-Methoxyphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**9h**): This compound was obtained as white solid in 87% yield. mp: 110—112 °C; MS (ESI) *m/z*: 600.4 $(M+Na)^+$; IR (KBr) cm^{-1}: 3423.8, 2926.7, 2873.0, 1684.6, 1657.2, 1603.7, 1254.5, 1172.3, 1038.8, 878.1, 835.6, 784.6, 673.6, 574.3; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.94 (d, J=9.2 Hz, 1H), 8.18 (d, J=8.8 Hz, 2H), 7.96 (d, J=15.6 Hz, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.48 (s, 1H),7.46—7.33 (m, 2H), 7.11 (d, J=8.8 Hz, 2H), 7.08—6.97 (m, 1H), 5.47 (s, 1H), 5.17 (t, J=9.8 Hz, 1H), 4.72 (s, 2H), 3.83 (s, 1H), 2.47—2.38 (m, 1H), 2.19 (td, J=13.7, 3.0 Hz, 1H), 2.05—1.93 (m, 1H), 1.87—1.74 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=6.2 Hz, 3H), 0.71 (d, J=7.0 Hz, 3H); *Anal.* Calcd for $C_{33}H_{39}NO_8$ (in %): C, 68.61; H, 6.80; N, 2.42; Found C, 68.62; H, 6.83 and N, 2.41.

(10*R*)-*N*-{4-[3-Phenyl-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9i**): This compound was obtained as pale yellow solid in 88% yield. mp: 102—104 °C; MS (ESI) *m/z*: 570.2 $(M+Na)^+$; IR (KBr) cm^{-1}: 3419.7, 2925.6, 2872.5, 1685.9, 1659.4, 1604.5, 1531.2, 1507.9, 1217.8, 1171.8, 1037.3, 878.1, 841.0, 767.1; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.6 Hz, 2H), 7.83 (d, J=15.8 Hz, 1H), 7.66 (d, J=3.4 Hz, 2H), 7.55 (d, J=15.7 Hz, 1H), 7.44 (d, J=3.3 Hz, 2H), 7.18—7.00 (m, 3H), 5.46 (t, J=10.0 Hz, 2H), 4.61 (s, 2H), 2.54—2.31 (m, 2H), 2.11—2.00 (m, 1H), 1.97—1.86 (m, 1H), 1.44 (s, 3H), 0.99 (d, J=5.7 Hz, 3H), 0.81 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{32}H_{37}NO_7$ (in %): C, 70.18; H, 6.81; N, 2.56; Found C, 70.09; H, 6.88 and N, 2.56.

(10*R*)-*N*-{4-[3-(2-Furyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9j**): This compound was obtained as yellow solid in 70% yield. mp: 115—117 °C; MS (ESI) *m/z*: 560.1 $(M+Na)^+$; IR (KBr) cm^{-1}: 3422.1, 2925.6, 2872.8, 1657.4, 1603.8, 1544.3, 1508.0, 1225.8, 1172.8, 1038.4, 1017.7, 880.0, 826.0, 595.5; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.93 (d, J=9.1 Hz, 1H), 8.08 (d, J=8.9 Hz, 2H), 7.90 (d, J=1.4 Hz, 1H), 7.58 (d, J=15.9 Hz, 1H), 7.52 (d, J=15.8 Hz, 1H), 7.10 (d, J=2.9 Hz, 1H), 7.08 (d, J=2.2 Hz, 2H), 6.69 (dd, J=3.4, 1.8 Hz, 1H), 5.47 (s, 1H), 5.16 (t, J=9.8 Hz, 1H), 4.70 (s, 2H), 2.48—2.36 (m, 1H), 2.19 (td, J=13.9, 3.7 Hz, 1H), 2.04—1.94 (m, 1H), 1.87—1.74 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=6.2 Hz, 3H), 0.71 (d, J=7.1 Hz, 3H); *Anal.* Calcd for $C_{30}H_{35}NO_8$ (in %): C, 67.02; H, 6.56; N, 2.61; Found C, 66.95; H, 6.67 and N, 2.56.

(10*R*)-*N*-{4-[3-(2-Thienyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**9k**): This compound was obtained as pale yellow solid in 73% yield. mp: 101—103 °C; MS (ESI) *m/z*: 576.5 $(M+Na)^+$; IR (KBr) cm^{-1}: 3419.0, 2924.9, 2872.4, 1686.3, 1654.6, 1601.9, 1535.1, 1506.9, 1236.8, 1214.2, 1172.1, 1037.6, 825.0, 747.5; ^{1}H-NMR (300 MHz, CDCl3) δ: 8.07 (d, J=8.8 Hz, 2H), 7.96 (d, J=15.3 Hz, 1H), 7.46—7.31 (m, 3H), 7.14—7.09 (m, 1H), 7.06 (d, J=8.8 Hz, 2H), 5.51—5.40 (m, 1H), 4.62 (s, 1H), 2.53—2.31 (m, 2H), 2.11—2.01 (m, 1H), 1.97—1.87 (m, 1H), 1.84—1.71 (m, 1H), 1.45 (s, 3H), 0.99 (d, J=5.9 Hz, 3H), 0.82 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{30}H_{35}NO_7S$ (in %): C, 65.08; H, 6.37; N, 2.53; Found C, 65.02; H, 6.45 and N, 2.47.

(10*R*)-*N*-{4-[3-(1,3-Benzodioxo-5-yl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**9l**): This compound was obtained as pale yellow solid in 78% yield. mp: 110—112 °C; MS (ESI) *m/z*: 614.6 $(M+Na)^+$; IR (KBr) cm^{-1}: 3421.3, 2936.1, 2883.2, 1680.1, 1655.2, 1606.1, 1513.2, 1254.7, 1216.8, 1153.0, 1108.2, 847.2, 750.6, 623.6. 483.8; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.93 (d, J=9.2 Hz, 1H), 8.16 (d, J=8.7 Hz, 2H), 7.83 (d, J=15.4 Hz, 1H), 7.69—7.59(m, 2H), 7.32 (d, J=7.9 Hz, 1H), 7.09 (d, J=8.8 Hz, 2H), 6.99 (d, J=8.0 Hz, 1H), 6.11 (s, 2H), 5.47 (s, 1H), 5.17 (t, J=9.8 Hz, 1H), 4.71 (s, 2H), 2.47—2.36 (m, 1H), 2.26—2.12 (m, 1H), 2.05—1.94 (m, 1H), 1.86—1.74 (m, 1H), 1.28 (s, 3H), 0.89 (d, J=6.2 Hz, 3H), 0.71 (d, J=7.1 Hz, 3H); *Anal.* Calcd for $C_{33}H_{37}NO_9$ (in %): C, 66.99; H, 6.30; N, 2.37; Found C, 66.97; H, 6.37 and N, 2.34.

(10*S*)-*N*-{4-[3-(2,4-Difluorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**10a**): This compound was obtained as brown powder in 76% yield. mp: 111—113 °C; MS (ESI) *m/z*: 606.2 $(M+Na)^+$; IR (KBr) cm^{-1}: 3416.7, 2927.4, 2874.4, 1664.5, 1606.4, 1534.5, 1503.0, 1338.2, 1216.7, 1172.8, 1101.6, 966.4, 845.6, 464.8; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.9 Hz, 2H), 7.86 (d, J=15.8 Hz, 1H), 7.66 (dd, J=14.9, 8.3 Hz, 1H), 7.60 (d, J=15.9 Hz, 1H), 7.07 (d, J=8.9 Hz, 2H), 7.01—6.87 (m, 2H), 5.53—5.40 (m, 2H), 4.62 (s, 2H), 2.54—2.31 (m, 2H), 2.12—1.99 (m, 1H), 1.98—1.86 (m, 1H), 1.84—1.71 (m, 2H), 1.45 (s, 3H), 0.99 (d, J=5.9 Hz, 3H), 0.81 (d, J=7.1 Hz, 3H); *Anal.* Calcd for $C_{32}H_{35}F_2NO_7$ (in %): C, 65.85; H, 6.04; N, 2.40; Found C, 65.76; H, 6.15 and N, 2.36.

(10*S*)-*N*-{4-[3-(3,4,5-Trimethoxyphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10b**): This compound was obtained as pale yellow solid in 81% yield. mp: 113—115 °C; MS (ESI) *m/z*: 660.4 $(M+Na)^+$; IR (KBr) cm^{-1}: 3421.2, 2926.1, 1655.3, 1602.3, 1533.8, 1506.7, 1469.9, 1427.3, 1235.3, 1171.8, 1103.8, 1037.8, 927.1, 806.9, 596.7. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.8 Hz, 2H), 7.74 (d, J=15.6 Hz, 1H), 7.42 (d, J=15.6 Hz, 1H), 7.07 (d, J=8.7 Hz, 2H), 6.89 (s, 1H), 6.72 (s, 1H), 4.62 (s, 2H), 3.95 (s, 6H), 3.76 (s, 3H), 2.54—2.30 (m, 2H), 2.13—2.00 (m, 1H), 2.00—1.86 (m, 1H), 1.84—1.70 (m, 2H), 1.45 (s, 3H), 0.99

(d, J=5.6 Hz, 3H), 0.82 (d, J=7.1 Hz, 3H); *Anal.* Calcd for $C_{35}H_{43}NO_{10}$ (in %): C, 65.92; H, 6.80; N, 2.20; Found C, 65.87; H, 6.84 and N, 2.16.

(10*S*)-*N*-{4-[3-(4-Trifluoromethoxyphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10c**): This compound was obtained as pale yellow solid in 89% yield. mp: 101—103 °C; MS (ESI) *m*/*z*: 654.3 $(M+Na)^+$; IR (KBr) cm^{-1}: 3423.5, 2927.7, 2874.5, 1663.4, 1601.8, 1531.2, 1506.5, 1258.4, 1217.5, 1168.7, 1038.5, 828.0, 594.2; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.8 Hz, 2H), 7.99 (d, J=8.7 Hz, 2H), 7.80 (d, J=15.6 Hz, 1H), 7.52 (d, J=15.7 Hz, 1H), 7.46 (d, J=8.7 Hz, 2H), 7.07 (d, J=8.8 Hz, 2H), 5.53—5.39 (m, 2H), 4.62 (s, 2H), 2.52—2.31 (m, 2H), 2.11—2.00 (m, 1H), 1.98—1.85 (m, 1H), 1.85—1.70 (m, 2H), 1.44 (s, 3H), 0.99 (d, J=5.8 Hz, 3H), 0.81 (d, J=8.4 Hz, 3H); *Anal.* Calcd for $C_{33}H_{36}F_3NO_8$ (in %): C, 62.75; H, 5.74; N, 2.22; Found C, 62.71; H, 5.83 and N, 2.21.

(10*S*)-*N*-{4-[3-(3-Trifluoromethylphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10d**): This compound was obtained as white solid in 85% yield. mp: 105—107 °C; MS (ESI) *m*/*z*: 638.1 $(M+Na)^+$; IR (KBr) cm^{-1}: 3423.3, 2927.6, 2874.6, 1664.3, 1602.6, 1531.4, 1438.2, 1335.9, 1217.5, 1169.6, 1127.2, 1038.3, 801.7, 571.3; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J=8.8 Hz, 2H), 7.91 (s, 1H), 7.84 (d, J=15.7 Hz, 1H), 7.72—7.52 (m, 4H), 7.08 (d, J=8.8 Hz, 2H), 5.53—5.41 (m, 2H), 4.62 (s, 1H), 2.54—2.31 (m, 2H), 2.12—2.01 (m, 1H), 1.99—1.86 (m, 1H), 1.84—1.72(m, 2H), 1.45 (s, 3H), 0.99 (d, J=5.9 Hz, 3H), 0.82 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{33}H_{36}F_3NO_7$ (in %): C, 64.38; H, 5.89; N, 2.28; Found C, 64.34; H, 5.99 and 2.23.

(10*S*)-*N*-{4-[3-(4-Fluorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10e**): This compound was obtained as pale yellow solid in 86% yield. mp: 111—113 °C; MS (ESI) *m*/*z*: 588.2 $(M+Na)^+$; IR (KBr) cm^{-1}: 3424.1, 2927.3, 1662.3, 1599.7, 1536.8, 1507.3, 1418.4, 1382.7, 1219.3, 1173.1, 1115.1, 1038.3, 826.9, 515.0; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.8 Hz, 2H), 7.80 (d, J=15.7 Hz, 1H), 7.66 (dd, J=8.7, 5.4 Hz, 2H), 7.48 (d, J=15.6 Hz, 1H), 7.17—7.06 (m, 2H), 7.07 (d, J=8.8 Hz, 2H), 5.53—5.41 (m, 2H), 4.62 (s, 2H), 2.53—2.31 (m, 2H), 2.12—2.00 (m, 1H), 1.99—1.85 (m, 1H), 1.85—1.70 (m, 2H), 1.45 (s, 3H), 0.99 (d, J=6.0 Hz, 3H), 0.82 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{32}H_{36}FNO_7$ (in %): C, 67.95; H, 6.42; N, 2.48; Found C, 67.93; H, 6.46 and N, 2.43.

(10*S*)-*N*-{4-[3-(4-Chlorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10f**): This compound was obtained as pale yellow solid in 82% yield. mp: 109—111 °C; MS (ESI) *m*/*z*: 604.1 $(M+Na)^+$; IR (KBr) cm^{-1}: 3419.2 2926.0, 2873.3, 1692.2, 1661.2, 1604.5, 1532.0, 1337.0, 1217.7, 1172.1, 1114.6, 1037.8, 767.7, 563.5; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, J=8.9 Hz, 2H), 7.84 (d, J=15.7 Hz, 1H), 7.68 (d, J=7.5 Hz, 2H), 7.56 (d, J=15.7 Hz, 1H), 7.44 (d, J=7.5 Hz, 2H), 7.07 (d, J=8.9 Hz, 2H), 5.52—5.42 (m, 2H), 4.62 (s, 2H), 2.53—2.32 (m, 2H), 2.11—2.01 (m, 1H), 1.98—1.86 (m,1H), 1.85—1.71 (m, 2H), 1.45 (s, 3H), 1.00 (d, J=6.0 Hz, 3H), 0.82 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{32}H_{36}ClNO_7$ (in %): C, 66.03; H, 6.23; N, 2.41; Found C, 65.95; H, 6.35 and N, 2.40.

(10*S*)-*N*-{4-[3-(2,6-Dichlorophenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**10g**): This compound was obtained as brown solid in 81% yield. mp: 122—125 °C; MS (ESI) *m*/*z*: 637.9 $(M+Na)^+$; IR (KBr) cm^{-1}: 3422.1, 2925.9, 2873.2, 1666.4, 1599.8, 1533.3, 1508.7, 1221.9, 1172.1, 1114.9, 1039.0, 776.8, 596.3; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.71 (d, J=5.1 Hz, 2H), 8.11—8.05 (m, 3H), 7.67 (d, J=16.8 Hz, 1H), 7.49 (d, J=5.0 Hz, 2H), 7.07 (d, J=8.9 Hz, 2H), 5.52—5.41 (m, 2H), 4.62 (s, 2H), 2.52—2.31 (m, 2H), 2.11—2.00 (m, 1H), 1.97—1.86 (m, 1H), 1.83—1.70 (m, 2H), 1.44 (s, 3H), 0.98 (d, J=5.9 Hz, 3H), 0.81 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{32}H_{35}Cl_2NO_7$ (in %): C, 62.34; H, 5.72; N, 2.27; Found C, 62.31; H, 5.79 and N, 2.26.

(10*S*)-*N*-{4-[3-(3-Methoxyphenyl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**10h**): This compound was obtained as pale yellow solid in 84% yield. mp: 105—107 °C; MS (ESI) *m*/*z*: 600.1 $(M+Na)^+$; IR (KBr) cm^{-1}: 3424.2, 2926.2, 2872.9, 1686.2, 1659.4, 1603.4, 1578.8, 1254.5, 1214.3, 1172.2, 1115.3, 1038.8, 834.7, 574.9; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.18 (d, J=8.9 Hz, 2H), 7.96 (d, J=15.6 Hz, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.48 (s, 1H), 7.44 (d, J=7.8 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.11 (d, J=8.9 Hz, 2H), 7.07—6.99 (m, 1H), 5.47 (s, 1H), 5.17 (t, J=9.8 Hz, 1H), 4.72 (s, 2H), 3.83 (s, 3H), 2.45—2.34 (m, 1H), 2.28—2.12 (m, 1H), 2.04—1.94 (m, 1H), 1.88—1.75 (m, 1H), 1.29 (s, 3H), 0.89 (d, J=6.3 Hz, 3H), 0.71 (d, J=7.1 Hz, 3H); *Anal.* Calcd for $C_{33}H_{39}NO_8$ (in %): C, 68.61; H, 6.80; N, 2.42; Found C, 68.52; H, 6.86 and N, 2.41.

(10*S*)-*N*-{4-[3-Phenyl-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10i**): This compound was obtained as pale yellow solid in 89% yield. mp: 107—109 °C; MS (ESI) *m*/*z*: 570.2 $(M+Na)^+$; IR (KBr) cm^{-1}: 3418.4, 2925.0, 2872.7, 1685.7, 1661.8, 1606.2, 1531.4, 1332.6, 1218.9, 1172.1, 1138.9, 1038.5, 816.9, 472.5; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J=8.9 Hz, 2H), 7.78 (d, J=15.6 Hz, 1H), 7.60 (d, J=8.5 Hz, 2H), 7.52 (d, J=15.7 Hz, 1H), 7.41 (d, J=8.5 Hz, 2H), 7.13—7.02(m, 3H), 5.52—5.41 (m, 2H), 4.62 (s, 2H), 2.54—2.30 (m, 2H), 2.12—1.99 (m, 1H), 1.97—1.86 (m, 1H), 1.85—1.71 (m, 2H), 1.45 (s, 3H), 0.99 (d, J=5.9 Hz, 3H), 0.82 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{32}H_{37}NO_7$ (in %): C, 70.18; H, 6.81; N, 2.56; Found C, 70.18; H, 6.89 and N, 2.53.

(10*S*)-*N*-{4-[3-(2-Furyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10j**): This compound was obtained as brown solid in 76% yield. mp: 110—112 °C; MS (ESI) *m*/*z*: 560.2 $(M+Na)^+$; IR (KBr) cm^{-1}: 3421.5, 2925.8, 2873.2, 1685.9, 1659.3, 1603.5, 1550.2, 1258.0, 1225.7, 1172.7, 1038.5, 1017.7, 880.0, 595.7; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, J=8.9 Hz, 2H), 7.62 (d, J=15.3 Hz, 1H), 7.55 (d, J=1.6 Hz, 1H), 7.47 (d, J=15.3 Hz, 1H), 7.06 (d, J=8.9 Hz, 2H), 6.74 (d, J=3.4 Hz, 1H), 6.54 (dd, J=3.4, 1.8 Hz, 1H), 5.52—5.41 (m, 2H), 4.62 (s, 2H), 2.53—2.31 (m, 2H), 2.12—2.00 (m, 1H), 1.99—1.86 (m, 1H), 1.85—1.71 (m, 2H), 1.45 (s, 3H), 1.36—1.24 (m, 1H), 0.99 (d, J=6.0 Hz, 3H), 0.81 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{30}H_{35}NO_8$ (in %): C, 67.02; H, 6.56; N, 2.61; Found C, 67.01; H, 6.68 and N, 2.53.

(10*S*)-*N*-{4-[3-(2-Thienyl)-2-(*E*)-propenoyl]phenyloxyacetyl}aminodihydroartemisinin (**10k**): This compound was obtained as pale yellow solid in 71% yield. mp: 117—119 °C; MS (ESI) *m*/*z*: 576.1 $(M+Na)^+$; IR (KBr) cm^{-1}: 3421.3, 2924.5, 2870.6, 1662.3, 1601.6, 1521.5, 1438.2, 1325.9, 1212.5, 1169.6, 1137.1, 1038.6, 801.7, 561.3; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.06 (d, J=8.8 Hz, 2H), 7.96 (d, J=15.3 Hz, 1H), 7.44 (d, J=5.0 Hz, 1H), 7.38 (d, J=3.9 Hz, 1H), 7.35 (d, J=15.3 Hz, 1H), 7.16—7.09 (m, 1H), 7.06 (d, J=8.8 Hz, 2H), 5.53—5.41 (m, 2H), 4.61 (s, 2H), 2.53—2.31 (m, 2H), 2.11—2.00 (m, 1H), 1.98—1.86 (m, 1H), 1.83—1.72 (m, 2H), 1.44 (s, 3H), 0.99 (d, J=5.9 Hz, 3H), 0.81 (d, J=7.1 Hz, 3H); *Anal.* Calcd for $C_{30}H_{35}NO_7S$ (in %): C, 65.08; H, 6.37; N, 2.53; Found C, 65.01; H, 6.42 and N, 2.50.

(10*S*)-*N*-{4-[3-(1,3-Benzodioxo-5-yl)-2-(*E*)-propenoyl]phenyloxyacetyl}-aminodihydroartemisinin (**10l**): This compound was obtained as yellow solid in 78% yield. mp: 118—121 °C; MS (ESI) *m*/*z*: 614.1 $(M+Na)^+$; IR (KBr) cm^{-1}: 3420.2, 2925.1, 1657.1, 1601.5, 1529.8, 1504.7, 1489.9, 1447.3, 1249.6, 1171.8, 1113.8, 1037.3, 927.1, 808.9, 598.4; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, J=8.9 Hz, 2H), 7.76 (d, J=15.5 Hz, 1H), 7.39 (d, J=15.5 Hz, 1H), 7.19 (s, 1H), 7.15 (d, J=8.1 Hz, 1H), 7.06 (d, J=8.2 Hz, 2H), 6.87 (d, J=8.1 Hz, 1H), 6.05 (s, 2H), 5.53—5.41 (m, 2H), 4.61 (s, 2H), 2.52—2.31 (m, 2H), 2.11—1.98 (m, 1H), 1.98—1.86 (m, 1H), 1.85—1.70 (m, 2H), 1.45 (s, 3H), 0.99 (d, J=5.9 Hz, 3H), 0.81 (d, J=7.2 Hz, 3H); *Anal.* Calcd for $C_{33}H_{37}NO_9$ (in %): C, 66.99; H, 6.30; N, 2.37; Found C, 66.95; H, 6.42 and N, 2.36.

Anti-tumor Activity Assay *in Vitro* The anti-tumor activities of compounds **9a**—**l** and **10a**—**l** were evaluated with HT-29, A549, MDA-MB-231, HeLa, and H460 cell lines by the standard MTT assay *in vitro*, with DHA as the positive control. The cancer cell lines were cultured in minimum essential medium (MEM) supplement with 10% fetal bovine serum (FBS).

Approximately 4×10^3 cells, suspended in MEM, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The test compounds at indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 μg/ml and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 μl dimethyl sulfoxide (DMSO) each well, and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the enzyme-linked immunosorbent assay (ELISA) reader. All of the compounds were tested twice in each of the cell lines. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of two determinations and calculated by using the Bacus Laboratories Inc. Slide Scanner (Bliss) software.

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